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**Tandem Anionic Sigmatropic Rearrangement/Radical Reactions and Their Application
Toward the Total Synthesis of Natural Products**

Tandem anionický sigmatropní přesmyk/radikálové reakce a jeho využití
v totální syntéze přírodních látek

Doctoral thesis

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Prague, 2022

DECLARATION

This work was carried out in years 2015-2022 at the IOCB AS CR, v.v.i. I declare that I have done the Ph.D. thesis independently, noting all used resources. I also declare that I did not use this work to get the same or another university degree.

Tato práce probíhala v letech 2015-2022 na ÚOCHB AV ČR, v.v.i. Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

Prague, 28th February 2022

Mgr. Michal Šimek

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ABSTRACT

The thesis describes the development of unprecedented tandem reactions merging anionic oxy-Cope rearrangement with single-electron transfer oxidation of thus generated metal enolates by ferrocenium hexafluorophosphate. The formed α -carbonyl radicals were utilized in oxygenation reactions by coupling them with persistent radical TEMPO, furnishing rearranged α -aminoxy carbonyl compounds. Suitable reaction conditions and factors influencing the rearrangement aptitudes were determined. The obtained polyfunctional products proved versatile in diversifications by polar reactions producing diverse scaffolds. Furthermore, rearranged α -aminoxy carbonyls with a double bond located in the δ -position of the carbonyl group are applicable in *all-carbon 5-endo-trig* radical cyclizations governed by the persistent radical effect. Despite the low kinetic rate, this rare cyclization mode furnished a number of substituted cyclopentanes. The reaction scope, including competitive cyclization modes, was studied.

The developed methodology was utilized as a key reaction step to synthesize appropriately substituted cyclopentane core in a divergent approach to meroterpenoid fungal metabolites isolated from *Ganoderma applanatum*. The accomplished synthesis of applanatumols V and W and their epimers enabled the correction of the initially proposed stereochemistry of applanatumol V. The total synthesis of applanatumol B was successfully achieved. Spirocyclization reaction at the carbon skeleton permitted the synthesis of 1-*epi*-spiroapplanatamine O. Branching the synthetic route enabled the total synthesis of meroterpenoids applanatumols X and Y. Biological activity studies of prepared natural products and their synthetic precursors revealed high cytotoxicity of particular compounds against various human cancer cell lines with good tumor-selectivity indexes.

SOUHRN

Disertační práce popisuje vývoj bezprecedentních tandemových reakcí, spojujících anionický sigmatropní přesmyk s jednoelektronovou oxidací vzniklého enolátu pomocí ferrocenium hexafluorofosfátu. Generované radikály v α -pozici karbonylové skupiny byly oxygenovány jejich kaplingem s perzistentním radikálem TEMPO a poskytnuly přesmyknuté karbonylové sloučeniny s aminoroxi skupinou v α -pozici. Byly nalezeny vhodné reakční podmínky a stanoveny faktory ovlivňující tendenci k přesmyku. Získané polyfunkční produkty se ukázaly jako všestranné při diverzifikaci polárními reakcemi poskytující různé struktury. Přesmyknuté α -aminooxy karbonylové sloučeniny s dvojnou vazbou v δ -pozici karbonylové skupiny jsou použitelné v celouhlíkaté 5-*endo*-trig cyklizaci řízené perzistentním radikálovým efektem. Byl studován rozsah reakce, včetně kompetitivních cyklizačních režimů.

Vyvinutá metodologie byla využita při klíčovém reakčním kroku v syntéze vhodně substituovaného cyklopentanového jádra v divergentním přístupu k meroterpenoidním metabolitům izolovaným z houby *Ganoderma applanatum*. Provedená syntéza applanatumolů V a W a jejich epimerů umožnila korekci původně navržené stereochemie applanatumolu V. Dále bylo úspěšně dosaženo totální syntézy applanatumolu B. Spirocyclizační reakce na uhlíkatém skeletu umožnila syntézu 1-*epi*-spiroapplanatuminu O. Větvení původní syntetické cesty vedlo k totální syntéze meroterpenoidů applanatumolů X a Y. Studie biologické aktivity připravených přírodních látek a jejich syntetických prekurzorů odhalila vysokou cytotoxicitu konkrétních sloučenin proti různým rakovinným buněčným liniím s dobrými indexy nádorové selektivity.

LIST OF ABBREVIATIONS

Å	Ångström
AOC	anionic oxy-Cope rearrangement
APCI	atmospheric pressure chemical ionization
ATR	attenuated total reflection
9-BBN	9-borabicyclo(3.3.1)nonane
BDE	bond dissociation energy
Bn	benzyl
br	broad
CI	chemical ionization
COSY	correlation spectroscopy
COX	cyclooxygenase
CYPs	cytochromes P450
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPA	diisopropylamine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNPH	dinitrophenylhydrazine
E1cB	elimination unimolecular conjugate base
EI	electron ionization
ESI	electron-spray ionization
equiv.	equivalent
FAD	flavin adenine dinucleotide
FGI	functional group interconversion
FPP	farnesyl pyrophosphate
GM	<i>Ganoderma</i> meroterpenoid
GPP	geranyl pyrophosphate
HAT	hydrogen atom transfer

HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IBX	2-iodoxybenzoic acid
IC ₅₀	half-maximal inhibitory concentration
IOCB	Institute of Organic Chemistry and Biochemistry
IR	infra red
JAK	Janus kinase
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
MBH	Morita–Baylis–Hillman reaction
m.p.	melting point
MS	mass spectrometry
MW	microwave
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NOE	nuclear Overhauser effect
NP	natural product
PE	petrol ether
PIDA	phenyliodo diacetate
PIFA	phenyliodo bis(trifluoroacetate)
PPTS	pyridinium <i>para</i> -toluenesulfonate
PRE	persistent radical effect
<i>R</i> _F	retention factor (in chromatography)
ROESY	rotating frame Overhauser enhancement spectroscopy

ROS	reactive oxygen species
r.t.	room temperature
SD	standard deviation
SET	single-electron transfer
SI	selectivity index
TBAF	tetrabutylammonium fluoride
TBPB	<i>tert</i> -butyl peroxybenzoate
TBS	<i>tert</i> -butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidin-1-yl
TMS	trimethylsilyl
TS	transition state
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
n.d.	not determined
n.r.	no reaction
<i>p</i> TsOH	<i>para</i> -toluensulfonic acid

COMMON LATIN ABBREVIATIONS

<i>cf.</i>	<i>confer/conferatur</i> - compare
<i>de novo</i>	a new, again from the beginning
<i>et al.</i>	<i>et alia</i> - and others
<i>e.g.</i>	<i>exempli gratia</i> - for example
<i>i.e.</i>	<i>id est</i> – that is
<i>in situ</i>	in its original place or position
<i>in vitro</i>	outside the living body, in an artificial environment
<i>infra</i>	below
<i>supra</i>	above
<i>vide</i>	see, consult

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1. INTRODUCTION

1.1. FUNGAL SECONDARY METABOLITES

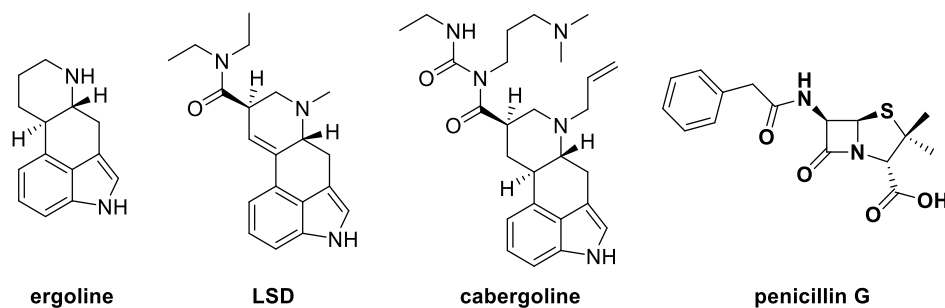
Fungi is a kingdom of fascinating living eukaryotic organisms with 150 000 species known, including yeasts, rusts, smuts, mildews, molds, and mushrooms (**Figure 1**). It is estimated that the vast majority of species are hitherto unknown and that the total number lies between 2.2-3.8 million.^[1] Although around 2000 new species of fungi are discovered every year, the fungal kingdom is significantly less studied than the plant kingdom.^[2] Fungi are worldwide-abundant; their members can be free-living in water or soil or form parasitic or symbiotic relationships with plants or animals. Nevertheless, their ability to break down organic matter and thus provide nutrients for other organisms together with mycorrhizal moderation of ecosystems makes fungi essential for life on Earth.

Figure 1: *Saccharomyces cerevisiae*, Raspberry yellow rust, mold on Petri-dish, fruiting mushrooms.



Fungal secondary metabolites have played an essential role in human history. Fruiting bodies of large fungi are collected as edibles, delicacies, or remedies; yeast is used to ferment beverages and leavening bread; colorful pigment-containing mushrooms are used as natural dyes; psychoactive alkaloid-containing mushrooms are used in religious rituals. However, the most pronounced use of fungi by humans is their use as medicinal agents. During the long history of humankind, fungal extracts and dried materials were utilized based on empirical observations. The improvement of isolation and analytical techniques in the 19th century led to the discovery that particular fungal secondary metabolites are responsible for the corresponding biological effects. Not all interactions of fungi with a human have been positive. For example, the grain disease caused by poisoning by ergot alkaloids such as ergoline (**Figure 2**) produced by the genus *Claviceps* was mentioned already in the Old Testament of the Bible (800-550 BC). In the Middle ages, epidemics of ergotism have killed half of the population of Aquitaine in France (around 60 000 people) between 944-1000 AD.^[3] However, harmful secondary metabolites can be turned into medicines, as documented by the use of ergot alkaloids to accelerate childbirth in 1582.^[4] The further investigation of those natural products (NPs) led to the discovery of a highly potent psychedelic drug, lysergic acid diethylamide, in 1938 and later to its derivatives such as cabergoline for treating Parkinson's disease (**Figure 2**).

Figure 2: Fungal secondary metabolites: natural/semisynthetic ergot alkaloids and antibiotic penicillin.



Fungal secondary metabolites are usually low-molecular-weight NPs with restricted taxonomic distribution, often biosynthesized after active growth of the fungal organisms has ceased.^[5] Although their role in producer species is still a point of debate, evidence for regulatory, defensive, (UV)-protective and interspecies communication purposes has been found.^[6] Although some fungal natural product investigations were already performed at the end of the 19th century, a systematic study began in 1923 by Harold Raistrick, who ultimately isolated and characterized more than 200 mold metabolites.^[7]

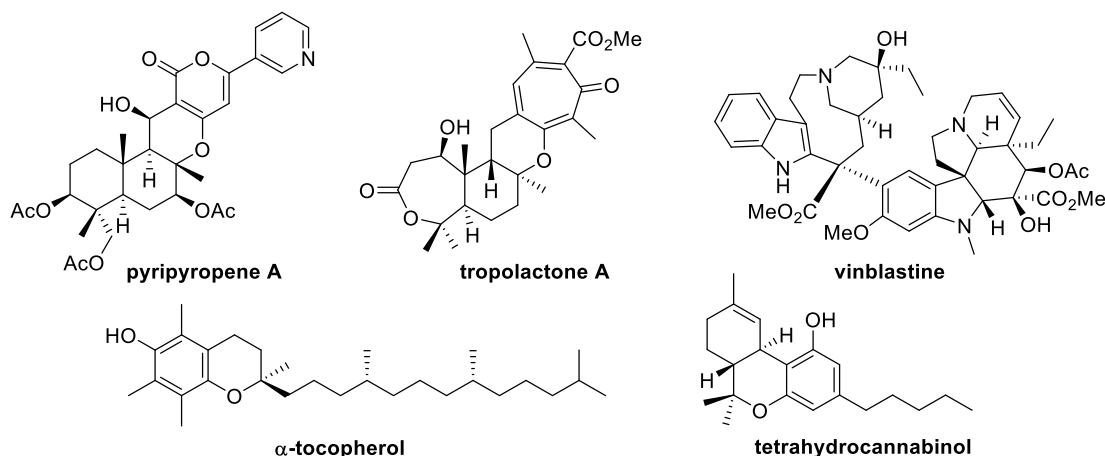
One of the most important discoveries in the history of fungal natural products was made by Alexander Fleming in 1928 with the observation that a fungal strain *Penicillium notatum* effectively inhibits the growth of *Staphylococcus aureus* on a Petri dish.^[8] The small-molecular substance responsible for the antibiotic effects, he gave the name penicillin (**Figure 2**). Although its potential was not fully appreciated in the 1930s, the war-times sparked intensive research leading to rapid mass-production. It is estimated that penicillin saved till nowadays over 82 million lives. In 1942 it was shown that *S. Aureus* and other strains of Staphylococci develop antibiotic resistance under prolonged exposure to lower concentrations of penicillin.^[9] Already in the 1940s, Fleming himself cautioned about the unadvised use of penicillin causing bacterial resistance. This fact, together with terrifying viral epidemics, motivates pharmaceutical companies and academia to search for new pharmaceutical ingredients, and fungal metabolites act as a frequent treasure-trove for drug discovery.

1.2. MEROTERPENOID NATURAL PRODUCTS

The term meroterpenoids was coined by Cornforth in 1968 as “*Compounds containing terpenoid elements along with structures of different biosynthetic origin.*”^[10] As the prefix derived from the Greek word *merus* = part, partial-suggests, meroterpenoids are hybrid natural products partially derived from the mevalonate biosynthetic pathway.^[11] The other part of meroterpenoids can be formed by various biosynthetic pathways, but mostly polyketides and, to a lesser extent, non-polyketides such as amino acids have been described.^[12] They are ubiquitous and can be found in terrestrial plants as well as in marine organisms, microorganisms, invertebrates, and fungi. Fungi are possibly one of the most prominent producers of meroterpenoids, biosynthesizing structurally variable compound classes with

a broad array of biological activities, making them attractive targets for medicinal and organic chemists. Several members are known as pharmaceutical ingredients, drug leads, or commercial pesticides. For example, pyripyropene A (**Figure 3**), isolated from *Aspergillus fumigatus*, is being developed to treat atherosclerosis and is the most potent known inhibitor of acyl-CoA:cholesterol acyltransferase.^[13] Tropolactone A, isolated from marine *Aspergillus* species, is a cytotoxic agent against human colon carcinoma.^[14] Vinblastine isolated from plant species *Catharanthus roseus* is a potent anticancer chemotherapeutic.^[15] Well-known natural products α -tocopherol and tetrahydrocannabinol (**Figure 3**) also belong to the class of meroterpenoids. The classification to meroterpenoids describes the biosynthetic origin primarily, although different designations classifying the nature of the natural product (*e.g.*, alkaloids, *etc.*) can be used as well.

Figure 3: Examples of meroterpenoid natural products.



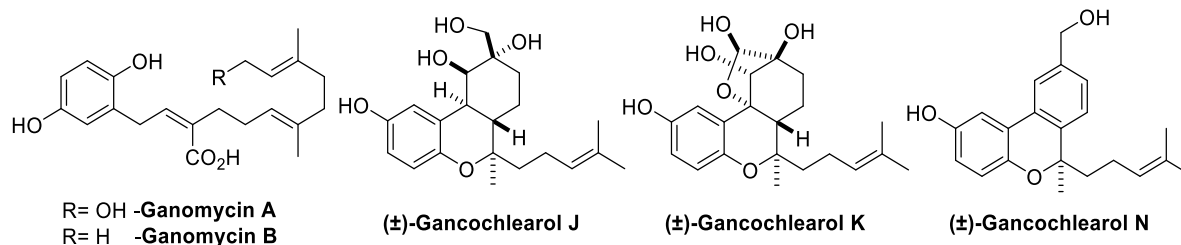
1.3. GANODERMA FUNGI

Ganoderma is a genus of polypore white-rot fungi from the Ganodermataceae (basidiomycete) family growing on rotting woody substrates and logs. It has a worldwide distribution but is highly valued mainly in traditional folk medicine in South-East Asia to treat and prevent various diseases in conjunction with overall well-being and longevity.^[16] The fruiting bodies of *Ganoderma* fungi are usually not edible but are consumed as broths or dried and powdered for their high mycochemical content. The genus consists of about 78 species, and *G. sinense* and *G. lucidum* are even recorded in the 2010 and 2015 editions of Chinese Pharmacopoeia, an official compendium of drugs and pharmacological ingredients, covering Traditional Chinese and western medicines.^[17]

Although this fungal family is highly diverse, only 22 species have been analyzed for their bioactive mycochemical content until now. Before 2006, the focus was mostly put on polysaccharides, fatty acids, steroids, triterpenoids, and proteins. Despite the fact that polysaccharides constitute the most prominent part of its bioactive content, meroterpenoids have drawn considerable attention in recent years.^[18] Since the isolation of Ganomycin A and B (**Figure 4**) in 2000,^[19] more than 250 new phenolic meroterpenoids

from *Ganoderma* were isolated. New members of this family of intriguing NPs are characterized every year with (±)-Gancochlearols J-N as the latest newcomers disclosed in July 2021.^[20]

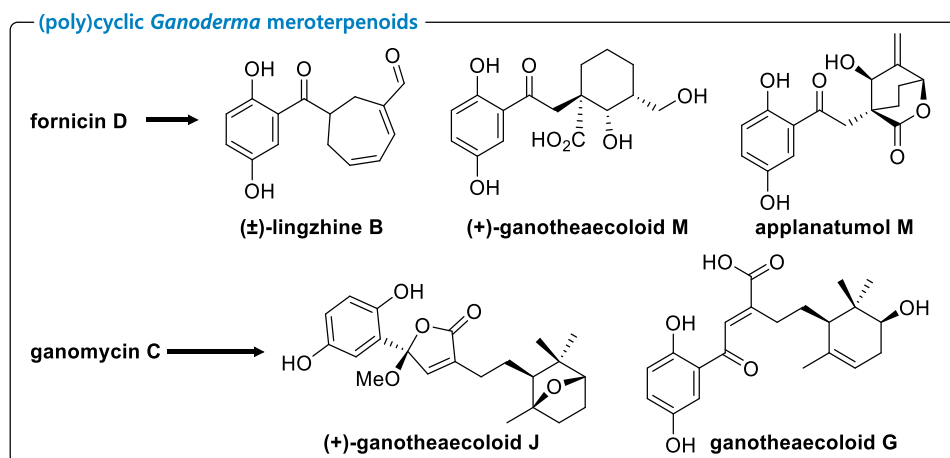
Figure 4: Examples of *Ganoderma* meroterpenoids.



1.4 GANODERMA MEROTERPENOIDS

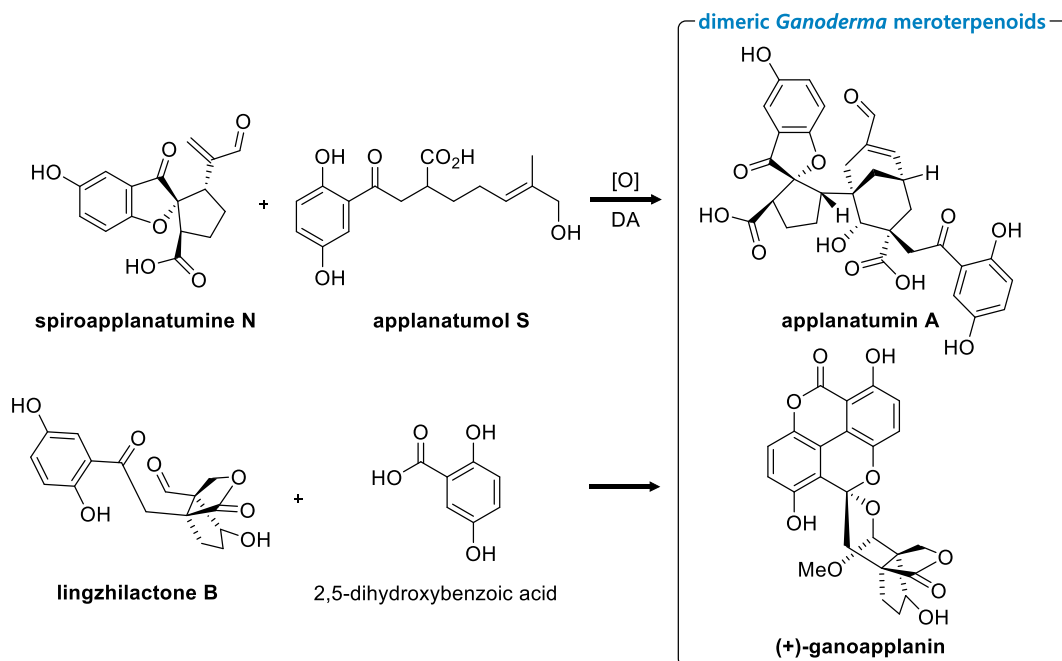
In *Ganoderma*, all known meroterpenoids contain a 1,2,4-trisubstituted phenyl ring that originates most likely from the biosynthetic precursor 4-hydroxybenzoic acid (**Scheme 1**) resulting from the degradation of lignin by ligninolytic enzymes of *Ganoderma* or the shikimic acid pathway.^[17] The terpenoid part assembled by prenyltransferases regularly undergoes further cyclizations leading to metabolites with (poly)cyclic ring systems. Based on the composition of the terpenoid part, *Ganoderma* meroterpenoids (GMs) can be divided into three categories: acyclic, polycyclic, and dimeric GMs.

Acyclic meroterpenoids (**Scheme 1**) are the biosynthetic precursors for more complex polycyclic and dimeric metabolites. Their biosynthesis starts with the attachment of a C10- or C15- oligo-unsaturated side chain from geranyl pyrophosphate (GPP) or farnesyl pyrophosphate (FPP) to 4-hydroxybenzoic acid by prenyltransferases. The prenylated hydroxybenzoic acid is presumably enzymatically hydroxy-decarboxylated through an initial attack of the *ipso*-C1-atom of the activated substrate to the electrophilic flavin hydroperoxide of the FAD-binding monooxygenase.^[21] The formed tetrahedral intermediate eliminates carbon dioxide forming the prenylated hydroquinone (not shown). Subsequent enzymatic redox reactions occurring in the allylic position presumably by proteins of the cytochrome P450 superfamily (CYPs) give oxygenated functionalization in the form of alcohols, ketones, aldehydes, carboxylic acids, or its methyl esters.^[22] The generated carboxylic acid functions can undergo intramolecular ketalizations leading to α,β -unsaturated γ -lactones as exemplified by lucidolactone B and fornicin E, isolated from *G. lucidum* and *G. cochlear* (**Scheme 1**).



Scheme 2: Biosynthetic origin and examples of (poly)cyclic *Ganoderma* meroterpenoids.

In contrast to intramolecular cyclizations, dimeric GMs (**Scheme 3**) are formed by intermolecular cyclizations with either another meroterpenoid or with another polyketide portion. The first case is demonstrated by applanatumin A, originating from spiroapplanatamine N and applanatumol S that were connected by an intermolecular Diels-Alder reaction (**Scheme 3**). In the second case, ganoapplanin was formed by cyclization of the meroterpenoid lingzhilactone B with 2,5-dihydroxybenzoic acid. Interestingly, applanatumin A is found in Nature as an optically active compound, whereas the precursor spiroapplanatamine N was isolated as a racemic mixture. It can be hypothesized that the Diels-Alder reaction proceeds enzymatically only with the matching enantiomer of the meroterpenoid.



Scheme 3: Biosynthetic origin and examples of dimeric *Ganoderma* meroterpenoids.

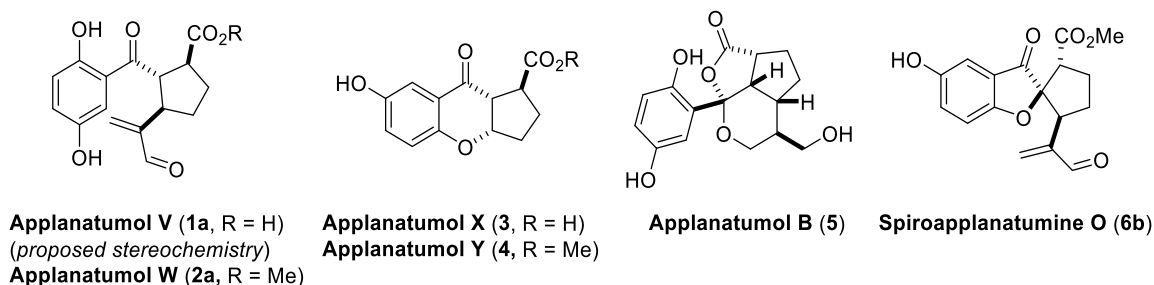
1.4. MEROTERPENOIDS FROM *GANODERMA APPLANATUM*

Between 2016-2017 Cheng et al. isolated 50 new phenolic meroterpenoids from the fungal species *Ganoderma applanatum* called applanatumols and (spiro)applanatumines exhibiting interesting biological activities.^[27] The vast majority of them was isolated as racemic mixtures.

Applanatumol V (**1a**) and X (**3**) (**Figure 5**), and their methyl esters applanatumols W (**2a**) and Y (**4**) bear a common cyclopentyl (2,5-dihydroxyphenyl)methanone motif.^[27b] Despite the fact that one compound from the isolation series, namely applanatumol C, showed active in COX-2 inhibition, with the IC₅₀ value of 25.5 μ M, applanatumols V, W, X, Y did not exhibit any activity in these essays.

During the search for new renoprotective compounds from natural sources, a new meroterpenoid with a unique dioxacyclopenta[cd]indene motif called applanatumol B (**5**, **Figure 5**) possessing five stereogenic centers was isolated as a racemic mixture.^[27a] This compound showed anti-renal fibrotic activity in rat proximal tubular epithelial cells.

Figure 5: Meroterpenoids from *Ganoderma applanatum*.



In 2017 Cheng et al. isolated a series of 17 spiroapplanatumines, including spiroapplanatumine O (**6b**, **Figure 5**), having an interesting spirocyclic 6/5/7 or 6/5/5 ring system.^[27e] Two of the compounds displayed inhibitory properties on JAK3 kinase with the potential to become a new lead structure for the development of drugs for JAK3-overexpressed disorders.

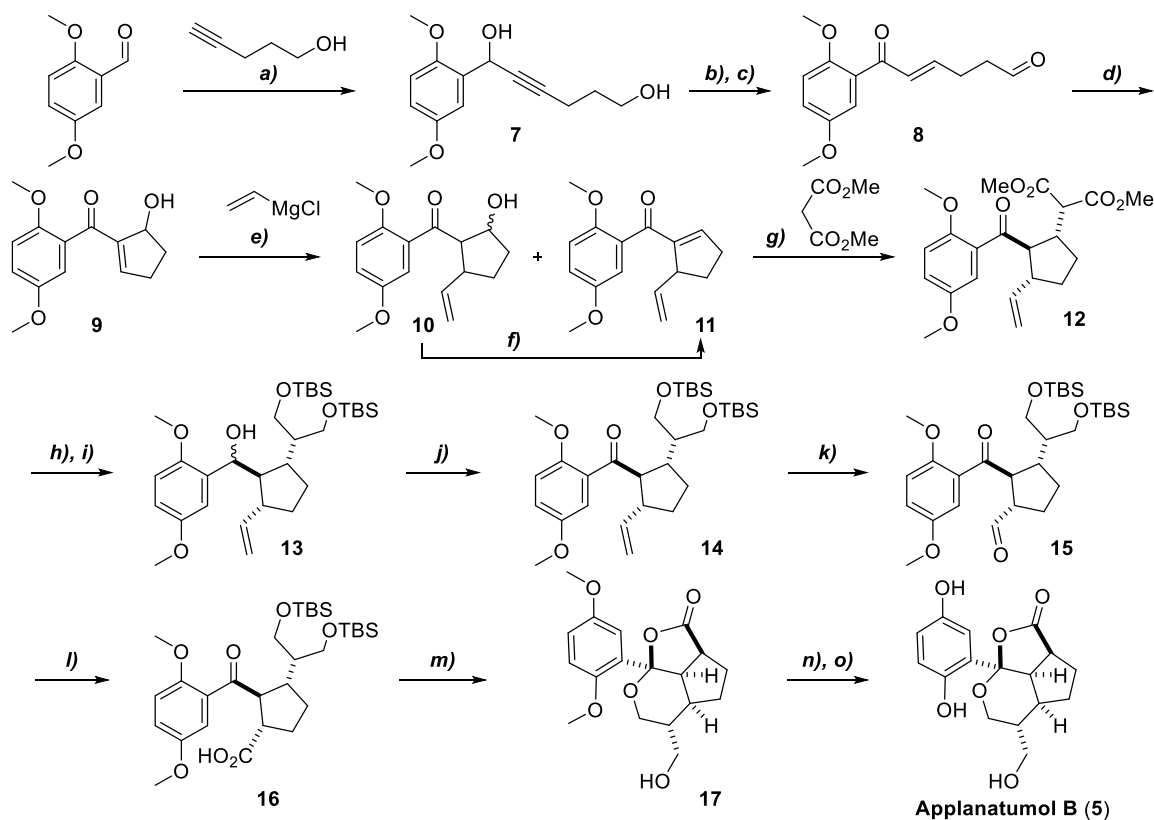
The fact that structurally identical natural products were isolated in the form of free carboxylic acids and their methyl esters poses a frequently-asked question, whether the methyl esters are isolation artifacts or actual natural products.^[28] The isolation protocol that included chromatographic separations with MeOH/H₂O system displays a potential for acid-catalyzed methyl ester formation. No attempts to verify the originality of the natural products were performed by the authors.

1.5. TOTAL SYNTHESSES OF *GANODERMA* MEROTERPENOIDS

GMs have received considerable attention from synthetic chemists resulting in around 20 total syntheses between 2014-2021. Concerning *G. applanatum*, only applanatumols Z5,^[29] F,^[30] B (**5**),^[31] X (**3**), and Y (**4**)^[32] have been synthesized so far.

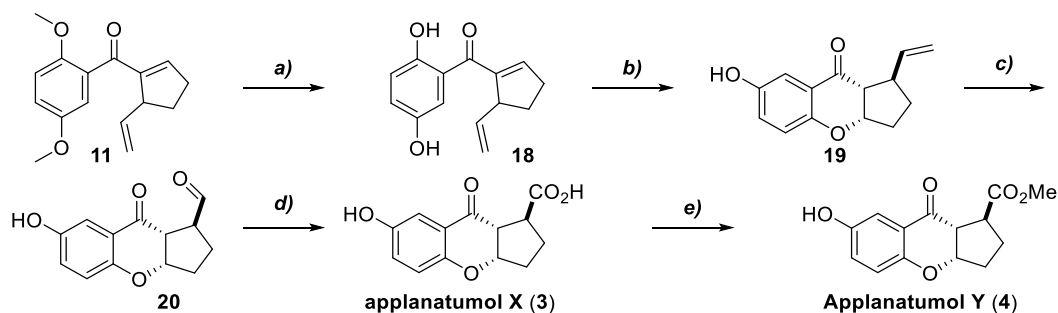
In 2018, Ito et al. published a total synthesis of applanatumol B (**5**, **Scheme 4**) in 14 steps that relied on an intramolecular Morita-Baylis-Hillman (MBH) reaction, stereoselective Michael addition, and an acidic epimerization/ketalization as the crucial reaction steps.^[31] The total synthesis commenced with a nucleophilic addition of pentynol acetylide to 2,5-dimethoxybenzaldehyde, giving diol **7**. Two-step redox manipulation led to aldehyde **8** that was submitted to a phosphine-mediated MBH reaction giving cyclopentenol derivative **9**. Copper-catalyzed conjugate addition of vinylmagnesium chloride to α,β -unsaturated ketone **9** produced a mixture of β -hydroxy ketone **10** and α,β -unsaturated ketone **11**. A Michael addition of dimethyl malonate to enone **11** formed ketone **12** that, after reduction by LiAlH₄ and silyl protection, furnished the protected diol **13**. Oxidation of the benzylic alcohol to phenone **14**, Johnson-Lemieux oxidation of the alkene unit to the aldehyde **15**, and ultimately Pinnick oxidation formed the cyclization precursor **16**. In the crucial ketalization step, the authors performed a thorough optimization to achieve a reasonable degree of diastereoselectivity and yield. *p*TsOH in boiling THF proved optimal, giving ketal **17** as a 3:1 diastereoisomeric mixture with concomitant epimerization of the C2 stereocenter. Oxidative deprotection of the aromatic portion resulted in a low yield of quinone that was subsequently reduced by H₂ on Pd/C, furnishing a single diastereoisomer of applanatumol B (**5**) as a racemic mixture.

Syntheses of applanatumols X and Y (**3,4**, **Scheme 5**) developed by the same authors in 2020 employ identical five initial steps.^[32] The α,β -unsaturated ketone **11** from the synthesis of applanatumol B was deprotected by boron tribromide giving free hydroquinone **18** and then intramolecularly cyclized to chromanone **19**. Johnson-Lemieux oxidative cleavage of the alkene unit and Pinnick oxidation furnished applanatumol X (**3**). Treatment of the free carboxylic acid with TMSCHN₂ gave the corresponding methyl ester applanatumol Y (**4**) in 10 synthetic steps.



Conditions: **a)** *n*BuLi, THF, -78°C to r.t., 6 h, 90%; **b)** Red-Al, Et₂O, r.t., 6 h; **c)** IBX, MeCN, 80°C , 1 h, 73% over 2 steps; **d)** PPh₃, *t*BuOH, 30°C , 3 days, 85%; **e)** CuBr·Me₂S, THF, -78°C , 30 min, 95% **10:11** = 2:1; **f)** POCl₃, DMAP, pyridine, 81%; **g)** NaOMe, MeOH, reflux, 3 h, 95% 25:5:2 *dr*; **h)** LiAlH₄, Et₂O, 0°C to r.t., 1 h; **i)** TBSCl, imidazole, DMF, r.t., 30 min, 73% over 2 steps; **j)** AZADOL, PhI(OAc)₂, CH₂Cl₂, phosphate buffer, r.t., 5 h, quant.; **k)** OsO₄, NaIO₄, 2,6-lutidine, *t*BuOH/H₂O, r.t., 2 h, 80%; **l)** NaClO₂, NaH₂PO₄, 2-methylbut-2-ene, *t*BuOH/H₂O, r.t., 15 min, 82%; **m)** *p*TsOH·H₂O, THF, reflux, 2 h, 88%, 3:1 *dr*; **n)** CAN, MeCN/H₂O, 0°C , 30 min, 35%; **o)** H₂, Pd/C, THF, r.t., 5 min, 64%.

Scheme 4: Total synthesis of applanatumol B by Ito et al.



Conditions: **a)** BBr₃, CH₂Cl₂, -20°C , 3 h, 86%; **b)** K₂CO₃, MeOH, 50°C , 12 h, 96%, 8:1 *dr*; **c)** OsO₄, NaIO₄, 2,6-lutidine, 1,4-dioxane/H₂O, r.t., 12 h, 99%; **d)** NaClO₂, NaH₂PO₄, 2-methylbut-2-ene, *t*BuOH/H₂O, r.t., 1 h, 78%; **e)** TMSCHN₂, toluene/MeOH, r.t., 30 min, 76%.

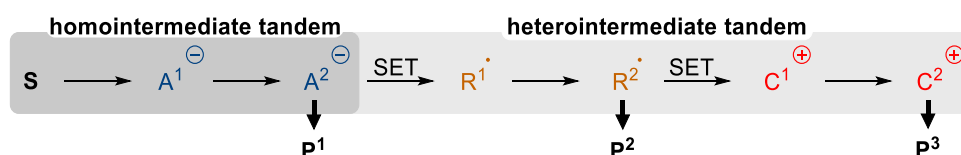
Scheme 5: Total synthesis of applanatumol X and Y by Ito et al.

1.6. TANDEM REACTIONS AND NATURAL PRODUCT SYNTHESIS

The total synthesis of NPs remains an integral part of chemical research.^[33] The motivation to synthesize diverse product classes frequently lies in the preparation of relevant quantities of products that are scarcely occurring in the natural material to be thoroughly biologically investigated.^[34] The synthesis of natural product congeners serves to elucidate the active molecular sites responsible for the biological effects and can ideally lead to activity increase.^[35] The motivation is not only biologically oriented; preparation and precise stereochemical analyses serve the structural and stereochemical verification and potential revision of the initially proposed three-dimensional structure. Frequently, the total synthesis of natural products is a purely academic endeavor to test the applicability and limitations of newly developed synthetic methodologies, to explore new synthetic strategies, or to better understand the reactivity of particular compound classes. Furthermore, unexpected reaction outcomes within the planned synthesis help discover new chemical transformations without any previous rational design.

Nevertheless, irrespective of the motivation, the planned total synthesis campaign should be as practical, efficient, resource and atom economic as possible.^[36] In this sense, tandem reactions (*e.g.*, cascade, domino, or *one-pot*) in which a reactive intermediate from one reaction is utilized in subsequent reaction steps play a dominant role in the rapid increase of molecular complexity.^[37] Their advantage lies in limiting reaction steps and waste production and requiring less time and effort.^[38]

The tandem processes can be classified based on the type of intermediates involved to homointermediate or heterointermediate reactions. In homointermediate tandem reactions, the charged species, be it anion, cation, or radical, stays in an unchanged oxidation state performing multiple transformations (**Scheme 6**). On the other hand, in heterointermediate reactions, the oxidation state of species can repeatedly change, and, therefore, they benefit from diverse inherent reactivity patterns.

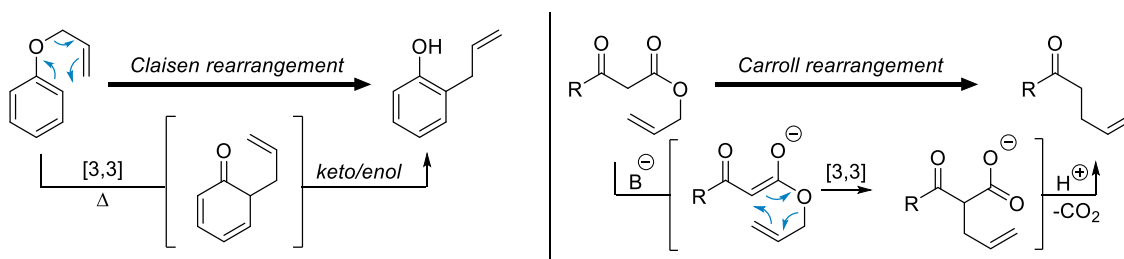


Scheme 6: Illustration of homo- and heterointermediate tandem reactions.

In an exemplary process (**Scheme 6**), a substrate **S** undergoes deprotonation, forming a negatively charged species **A**¹ that undergoes an anionic reaction forming species **A**² that might be protonated to product **P**¹ in a homointermediate process or can be further oxidized by the addition of a SET oxidant to radical intermediate **R**¹. A radical species displays a different array of reactivity undergoing cyclizations, additions, atom transfer reactions, or other processes generating a new radical species **R**² that might terminate to product **P**² or is further oxidized to carbocation **C**¹ reacting further to product **P**³ in heterointermediate reactions. Such tandem processes offer flexible combinations of distinct intermediate reactivities allowing effective multiple bond formations.

1.7. [3,3]-SIGMATROPIC REARRANGEMENTS

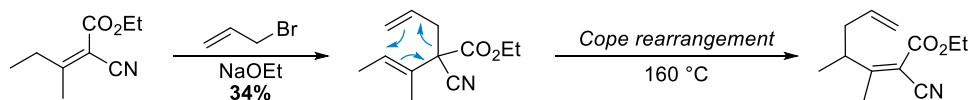
[3,3]-Sigmatropic rearrangements belong to the most fundamental reactions in organic synthesis with the advantage of predictably forming new stereodefined carbon-carbon or carbon-heteroatom bonds. In contrast to other methods that form new bonds between two subunits in an intermolecular fashion, the advantage of sigmatropic rearrangements lies in a controllable reorganization of a well-defined skeleton and a transposition of a substituent of choice or a stereocenter.^[39] The rapid gain in complexity by rearrangements has been used in the total synthesis of natural products and was frequently merged into creatively orchestrated tandem processes.^[37d, 40] To the best known [3,3]-sigmatropic rearrangements belong Claisen,^[41] Carroll,^[42] and Cope rearrangement (**Scheme 7**).^[43]



Scheme 7: Example of Claisen and a base-mediated Carroll rearrangement.

1.8. COPE REARRANGEMENT

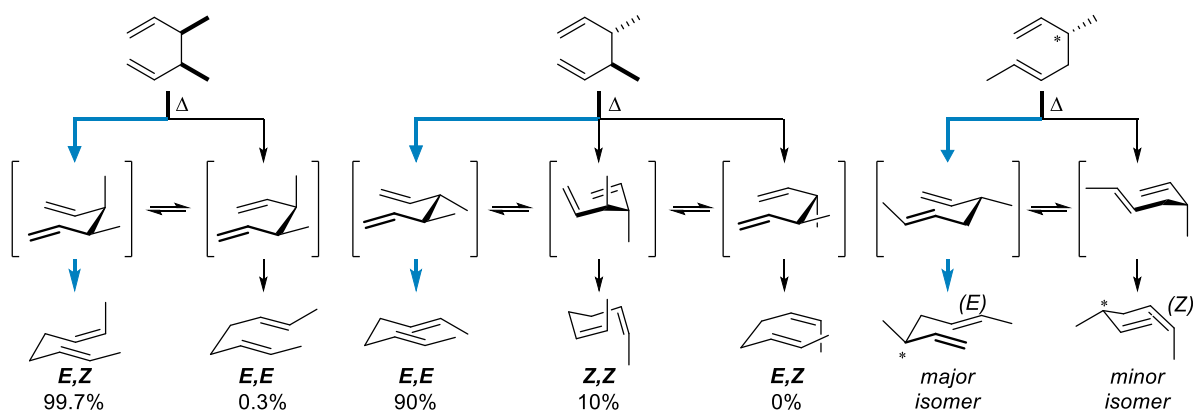
In 1940 Cope and coworkers serendipitously discovered that an allylated cyano ester during vacuum distillation at $\sim 160^\circ C$ underwent a thermal migration of the allyl unit along the second allyl fragment with a coordinated reorganization of the σ - and π -bonds (**Scheme 8**).^[44] Already in the first publication disclosing the rearrangement, Cope describes the similarities with Claisen-rearrangements observed back in 1912, suggesting that these two types of rearrangements follow a “*similar mechanism*”.



Scheme 8: Allylation of a cyano ester and its rearrangement observed by Cope.

In contrast to the Claisen rearrangement that benefits on thermodynamic grounds from the formation of a carbonyl group, the Cope rearrangement is a thermoneutral and potentially reversible process. It proceeds for simple hexa-1,5-diene through a cyclic, concerted transition state with an activation enthalpy of $33.5 \text{ kcal}\cdot\text{mol}^{-1}$ and an activation entropy of $-13.8 \text{ cal}\cdot\text{mol}^{-1}$.^[39] Experimental evidence showed that the Cope rearrangement of acyclic 1,5-dienes stereospecifically proceeds through a chair-like transition state prevailing over the competing boat-like TS by more than $5.7 \text{ kcal}\cdot\text{mol}^{-1}$ (**Scheme 9**).^[39] In contrast, the boat-like TS may be energetically accessible for geometrically constrained cyclic substrates. The power of the Cope rearrangement rests on the predictable formation

of a geometrically defined double bond as well as the transposition of existing stereocenters that is enabled by the preferential orientation of the substituents in an energetically favorable equatorial position of the chair-like TS, typically resulting in the formation of a single stereoisomer of the product (Scheme 9).

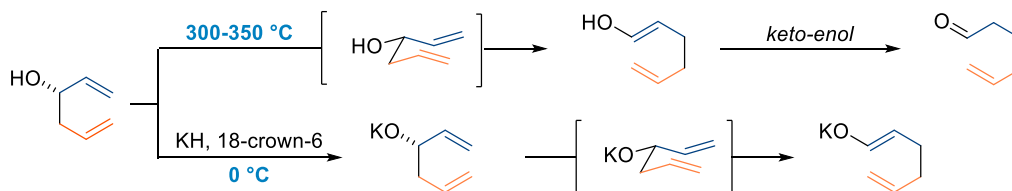


Scheme 9: Transition states of Cope rearrangement for acyclic 3,4- and 3,6-dimethylhexa-1,5-dienes.

1.9. OXY-COPE REARRANGEMENT

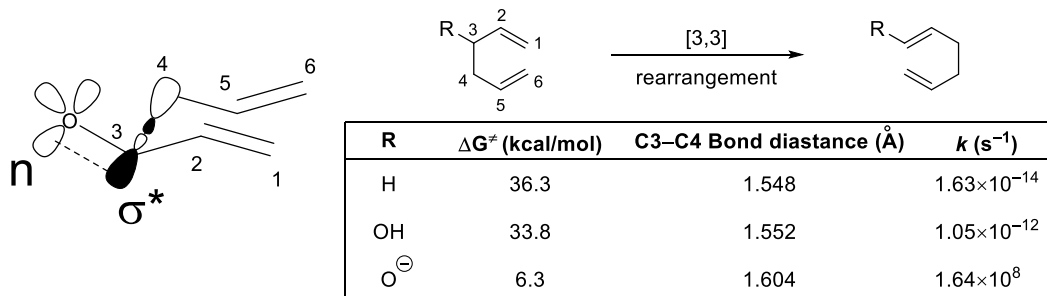
The rearrangement of 1,5-dien-3-ols coined as the oxy-Cope rearrangement in 1964 benefits from a spontaneous and irreversible keto-enol tautomerism, after the rearrangement step, shifting the equilibrium to the side of the product.^[45] Although this variation is of high synthetic value, mainly because of the simple preparation of the starting materials, the high reaction temperatures regularly above 300 °C (Scheme 10), necessary to overcome the activation barrier, seriously limited the use of thermally-labile substrates.

In 1975 Evans and Golob disclosed the observation that a negatively charged alkoxide on the rearranging skeleton tremendously enhances the reaction rate by 10^{10} - 10^{17} .^[46] This anionic variant (Scheme 10) is usually performed at mild reaction temperatures and is, therefore, considerably more tolerable towards functional groups. Despite the presence of a negatively charged heteroatom on the rearranging skeleton, the TS of the anionic oxy-Cope variant remains identical to the parent Cope rearrangement orienting substituents in a pseudo-equatorial orientation in a chair-like conformation.^[47]



Scheme 10: Reaction conditions difference in oxy-Cope and anionic oxy-Cope rearrangement.

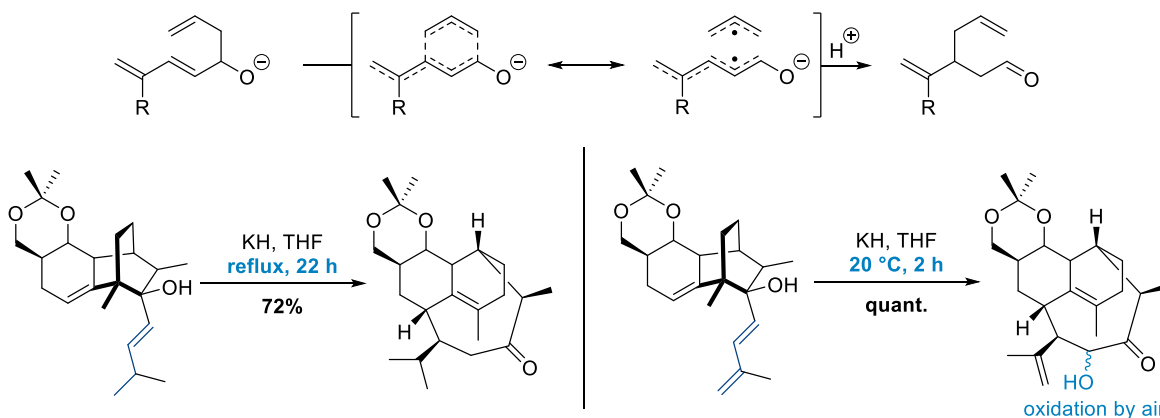
The drastic rate enhancement was theoretically rationalized by DFT calculations by Baumann and Chen in 2001.^[48] The $n \rightarrow \sigma^*$ orbital interaction of the oxygen lone pair with σ^* -orbital of the neighboring C3–C4 bond destabilizes the 3,4- σ -bond, causing bond elongation and lowering of the activation enthalpy for the rearrangement to occur (**Scheme 11**).



Scheme 11: Reactivity order of Cope, oxy- and anionic oxy-Cope rearrangement.

A strong dependence of the rate acceleration on the alkoxide counter ion indicated increasing reactivity for more dissociated ion pairs. Although examples employing lithium or sodium alkoxides are known, the potassium ion proved to be optimal with an additional 180-fold increase in the reaction rate if ionophores such as 18-crown-6 are used.^[39]

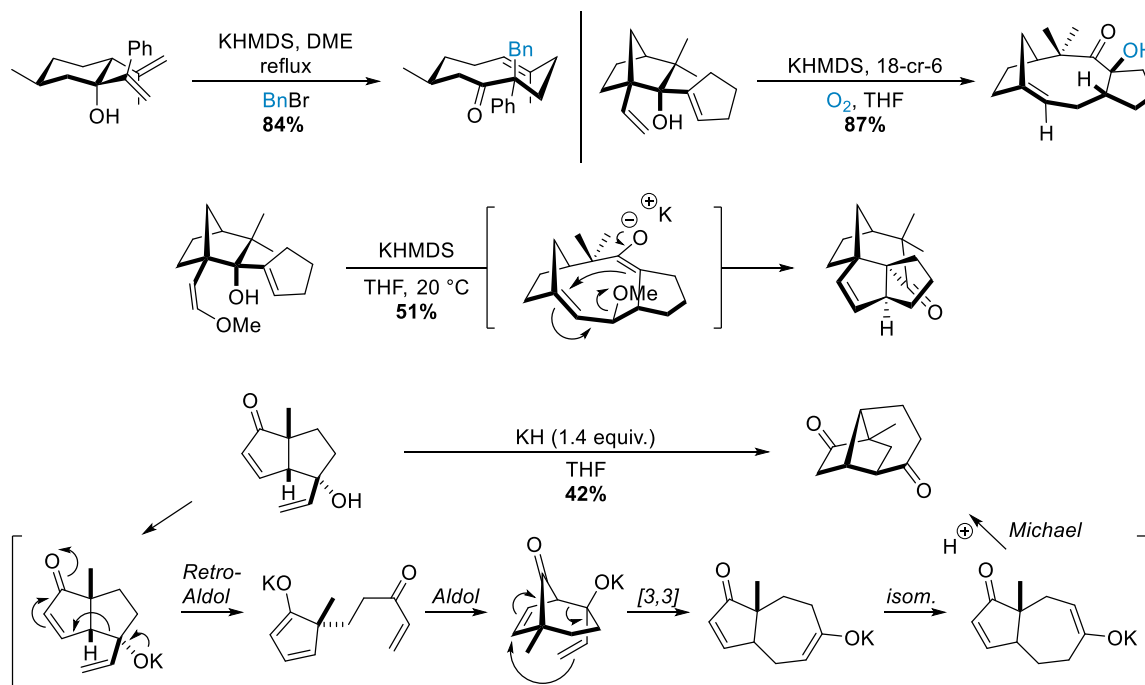
It was shown that the extension of the unsaturated chain to a conjugated diene facilitates the anionic oxy-Cope resulting in further rate acceleration, lowering the reaction temperature and time.^[49] This effect was rationalized by stabilization of the transition state by the additional unsaturation at the terminal position (**Scheme 12**).



Scheme 12: Anionic oxy-Cope rate enhancement by an additional unsaturation and its stabilization rationale.

The formation of an α -hydroxy ketone in the last example by over-oxidation of the resulting enolate by molecular oxygen demonstrates the power of the anionic oxy-Cope rearrangement to be engaged in subsequent reaction steps. The metal enolates resulting from AOC rearrangement have been shown to undergo further polar reactions such as α -alkylation,^[50] α -selenylation or hydroxylation,^[51]

O-acetylation, and silylation, transannular aldol reaction,^[52] or other transformations in tandem processes (**Scheme 13**).^[37d, 53]

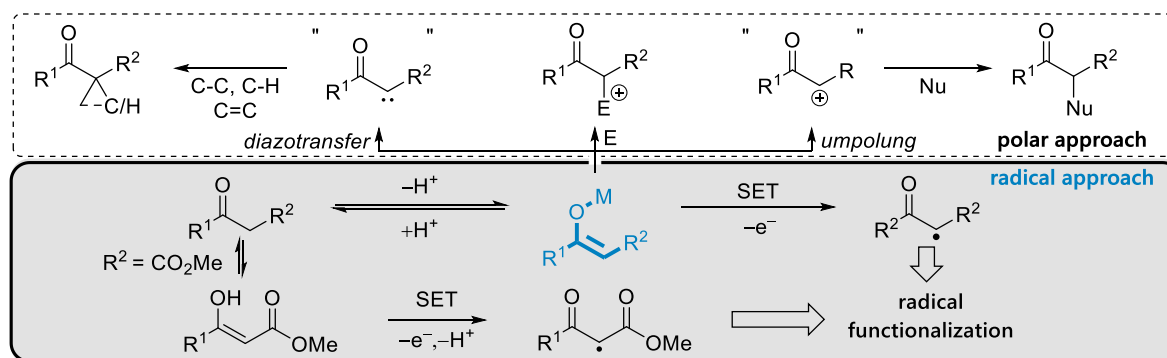


Scheme 13: Examples of anionic oxy-Cope rearrangement coupled with subsequent reaction steps.

1.10. RADICAL α -FUNCTIONALIZATION OF METAL ENOLATES

The α -functionalization of carbonyl or carboxyl derivatives is one of the most fundamental reactions in organic synthesis. Traditional α -functionalization is achieved by employing metal enolates or their surrogates, such as silyl enol ethers or enol ethers in polar reactions with electrophiles.^[54] More recently, *umpolung* reactions converting the α -position of carbonyls into electrophiles or carbenes allowing the reactions with nucleophiles, multiple or C–C, C–H bonds were successfully developed (**Scheme 14**).^[55]

Radical functionalization presents a complementary and attractive method that tolerates a number of otherwise incompatible functional groups, offering a variety of intra/intermolecular C–C bond-forming processes that traditional methods can not achieve (**Scheme 14**). Furthermore, radical functionalization can be performed under relatively mild reaction conditions and frequently in protic solvents.



Scheme 14: Strategic α -functionalization of a carbonyl or carboxyl derivatives by polar and radical reactions.

α -Carbonyl radicals can be formed from α -functionalized carbonyls based on photo-, electro- or chemical methods; in this sense α -halocarbonyl, α -stannylcarbonyl, or α -selenocarbonyl compound are typically employed.^[56] However, α -unfunctionalized carbonyl compounds rely on single-electron transfer (SET) oxidation of either neutral or anionic carbonyl species.^[57]

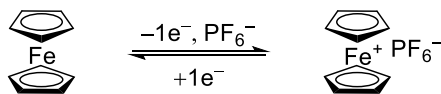
In case of neutral carbonyl compounds, SET oxidation is typically performed on inherently acidic and enolized substrates such as 1,3-diketones, acetoacetates, malonates, and α -sulfinyl or α -nitroketones. Less acidic substrates such as aliphatic ketones can be used but require higher temperatures and an additional acid catalyzing its enolization. Typical SET oxidants in these transformations are high-valent metal salts such as $Mn^{(III)}$, $Ce^{(IV)}$, $V^{(V)}$.

On the other hand, the oxidation of enolates is considerably more facile because of their high electron density. It can be achieved by weaker oxidants even at cryogenic conditions. Typical oxidants used are $Cu^{(II)}$, $Fe^{(III)}$, $Ti^{(IV)}$ salts.

SET oxidizing agents can be distinguished by the Marcus theory as outer- or inner-sphere oxidants.^[58] The latter forms a bond with the substrate that subsequently undergoes a bond homolysis delivering the radical and a reduced metal species. This mechanism applies to the oxidation of neutral, acidic carbonyls. In contrast to these, the outer sphere oxidants remove an electron through space with the potential participation of the solvent.

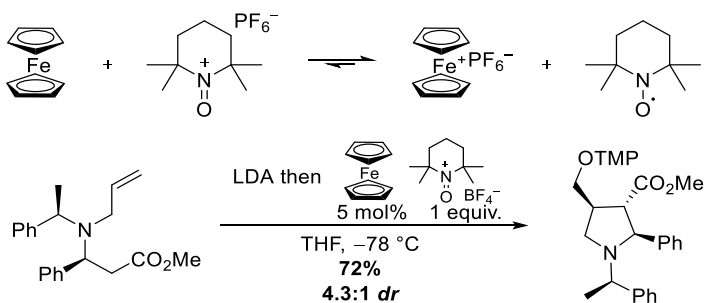
Ferrocenium salts are convenient bench stable reagents operating as outer-sphere SET oxidants (**Scheme 15**).^[59] The Cp_2Fe/Cp_2Fe^+ standard potential is 0.665 V^[60] vs. the normal hydrogen electrode in acetonitrile and can be further fine-tuned by substitution at the cyclopentadienyl ring.^[61] The fact that ferrocenium salts are stable, easily handled, mildly Lewis acidic SET-oxidants makes them suitable for application in organic synthesis in a catalytic or stoichiometric manner.^[59a] It was shown that ferrocenium salts or their derivatives act as catalysts in ring-opening of epoxides,^[62] aldol reactions,^[63] Friedel–Crafts alkylation reactions,^[64] asymmetric alkylation reactions,^[65] cyanosilylations,^[66] aromatic iodinations,^[67] the Strecker reaction,^[68] or in ring expansions.^[69] The application of ferrocenium cations as photoinitiators in polymer chemistry was also demonstrated.^[70] Furthermore, the Cp_2Fe/Cp_2Fe^+

redox couple emerges as a mediator in electrocatalytic transformations in which Cp_2Fe^+ acts as a primary oxidant that is electrochemically recovered.^[71]



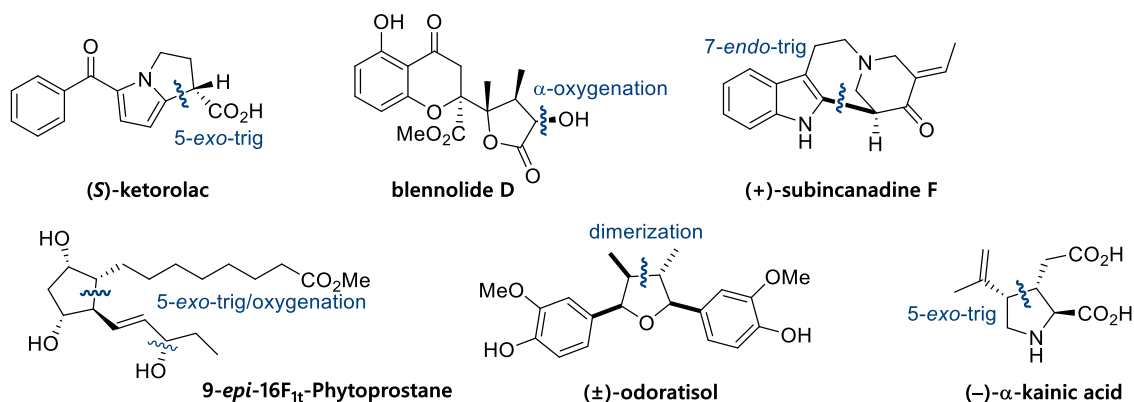
Scheme 15: $\text{Cp}_2\text{Fe}/\text{Cp}_2\text{Fe}^+$ redox couple.

The synthetic potential of ferrocenium hexafluorophosphate in the stoichiometric SET oxidation of diverse carbonyl- or carboxyl-derived metal enolates has been thoroughly investigated by Jahn et al. for almost two decades.^[72] It was shown that $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ oxidizes metal enolates resulting in transient α -carbonyl radicals undergoing intramolecular cyclizations, dimerizations, or α -oxygenation by the persistent radical TEMPO. Ferrocene, resulting from the reduction of the ferrocenium salt, is highly lipophilic, can be easily separated by column chromatography or sublimation from products and can be easily re-oxidized electrochemically or by oxidizing acids. Interestingly, oxidative radical cyclizations of unsaturated enolates can be performed with a catalytic amount of ferrocene and 2,2,6,6-tetramethyl-*N*-oxopiperidinium salts as the stoichiometric oxidant making a redox pair that generates the TEMPO radical *in situ* to be ultimately incorporated into the cyclic substrate (**Scheme 16**).^[73]



Scheme 16: $\text{Cp}_2\text{Fe}/2,2,6,6\text{-tetramethyl-}N\text{-oxopiperidinium}$ salt redox pair and its synthetic application.

The potential of the described oxidative methodology was demonstrated by various groups in the setting of the total synthesis of natural products. In 2005, Baran et al. used $\text{FeCp}_2^+\text{PF}_6^-$ in an enantioselective radical cyclization of analgesic (*S*)-ketorolac.^[74] In 2018, Tietze et al. used radical α -oxygenation in the synthesis of the fungal metabolite blennolide D.^[75] In 2010, Li et al. made use of $\text{FeCp}_2^+\text{PF}_6^-$ in a 7-*exo*-trig ring closure in the synthesis of the alkaloid (+)-subincanadine F.^[76] Jahn et al. used the enolate oxidative methodology to synthesize phytoprostanes,^[77] lignans,^[78] and kainic acid (**Scheme 17**). Other compound classes were synthesized by Jahn et al. through the enolate oxygenation methodology coupled with persistent radical effect-based cyclizations (*vide infra*).



Scheme 17: Examples of the application of SET oxidation by $\text{FeCp}_2^+\text{PF}_6^-$ in the total synthesis of natural products.

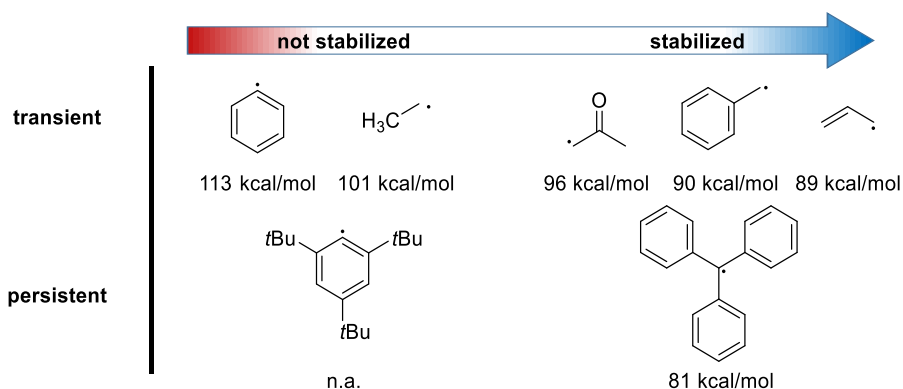
1.11. FREE RADICALS IN ORGANIC SYNTHESIS

Free radicals are usually highly reactive and, therefore, very short-lived species. However, a few radicals are long-lived and can be handled under non-inert conditions. From the point of view of their kinetic stability, radicals can be classified as transient and persistent, from the perspective of the thermodynamic stability divided into destabilized, stabilized, and stable species (**Scheme 18**).^[79]

A transient radical is a species with a lifetime of less than 10^{-3} s and, if not immobilized in a solid matrix, very quickly decays either by disproportionation, self-recombination resulting in a dimer or by atom abstraction from the surrounding environment. Radicals derived from hydrocarbons with a homolytic C–H bond dissociation energy of around 105 kcal/mol or higher (*e.g.*, methyl, vinyl, phenyl C–H) are considered transient and destabilized. In contrast, radicals derived from compounds with a lower C–H BDE (*e.g.*, tolyl, allyl, cyclohexadienyl, α-carbonyl, etc.) caused by the stabilization by a neighboring π -system or a heteroatom can be seen as stabilized transient species. Despite the thermodynamic stabilization by resonance, their reactivity is analogous to unstabilized species, and they rapidly decay in solution or the gas phase. The radical “stabilization energy” has been defined by Benson et al. as the difference between the strength of the appropriate (*i.e.*, primary, secondary, or tertiary) alkane C–H bond and the C–H bond to the radical in question.^[80] For example, the stabilization energy of a tolyl radical is defined as $D[\text{CH}_3\text{CH}_2\text{-H}] - D[\text{C}_6\text{H}_5\text{CH}_2\text{-H}] = 13$ kcal/mol. Transient radicals can not be defined as stable.^[81]

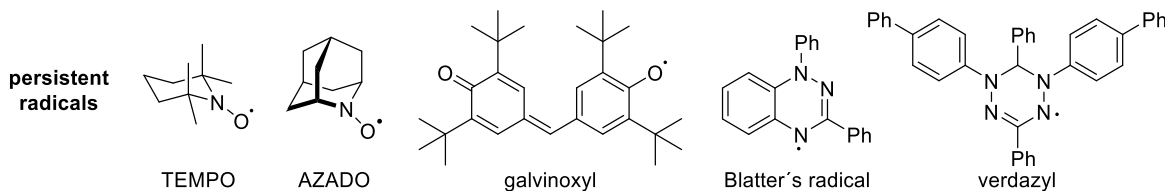
For persistent radicals, Ingold proposed that “the adjective ”persistent“ is to be used to describe a radical that has a lifetime significantly greater than methyl under the same conditions.”^[81] Carbon-centered persistent radicals do not need to be thermodynamically, resonance-stabilized by additional groups but sterically shielding groups in close proximity to the radical center. The term persistent rather describes their kinetic stability, and the reactivity is distinct from that of transient radicals.

As a demonstration, the stabilized $\text{Ph}_3\text{C}\cdot$ radical (Gomberg's radical) exists in a solution in equilibrium with its dimer.^[82] Because it is unreactive towards hydrogen atom abstraction and C=C bonds, a solution of this radical in the absence of oxygen can survive for days. Gomberg's radical can be seen as persistent and stabilized on thermodynamic grounds thanks to the high degree of stabilization by neighboring phenyl rings.^[83] The 2,4,6-tri-*tert*-butyl phenyl radical, on the other hand, lacks resonance stabilization, but because of sterically shielding *t*Bu groups, the radical neither dimerizes, abstracts hydrogen atoms, nor undergoes other reactions typical for transient radicals. This radical can be classified as persistent and destabilized. These two examples demonstrate that steric hindrance around the radical center dramatically decreases the reaction rate towards typical radical reactions despite its thermodynamic instability and thus makes them persistent. However, it must be noted that most of the C-centered radicals in organic synthesis are transient.



Scheme 18: Examples of C-centered transient and persistent radicals and the BDE of the parent hydrocarbon.

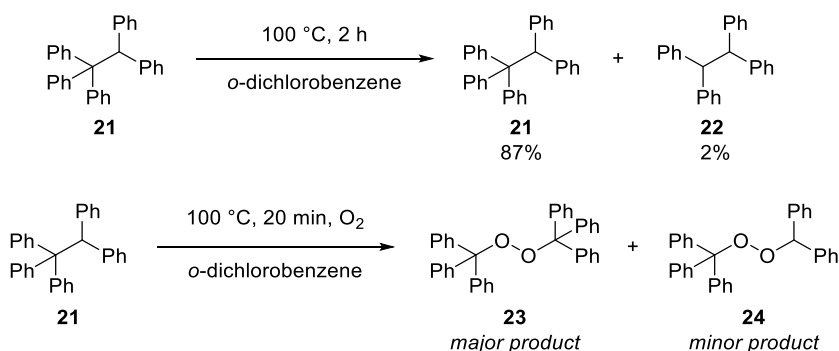
In synthesis, the majority of persistent radicals are heteroatom-centered, bringing extra stabilization. The best known examples are: TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical), AZADO (2-azaadamantane *N*-oxyl radical), galvinoxyl (4-[(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl]-2,6-di-*tert*-butylphenoxyl radical), Blatter's and verdazyl radicals (**Scheme 19**). These compounds are bench-stable, can be handled under standard ambient conditions, and purchased from chemical vendors. Although they do not tend to dimerize and abstract hydrogen atoms from the surroundings, they quickly undergo coupling with transient radicals giving stable compounds. Some low valent 17-electron transition metal complexes of Co^{II} , Ir^{II} , Ni^{I} , Cu^{II} can be considered as persistent radicals as well.



Scheme 19: Examples of common persistent radicals used in organic synthesis.

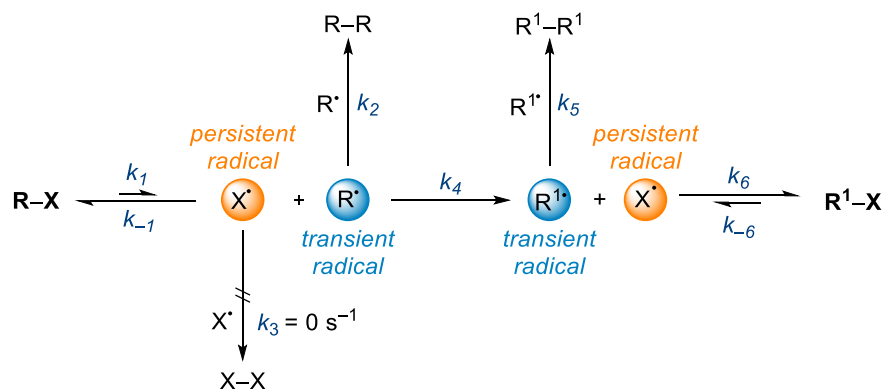
1.12. THE PERSISTENT RADICAL EFFECT

In 1936 Wiselogle and Bachmann documented an experiment in which pentaphenylethane **21** was heated in *o*-dichlorobenzene for two hours at 100 °C and 87% of the starting material **21** was recovered together with 2% of tetraphenylethane **22** (Scheme 20).^[84] In contrast, heating under air provided peroxide **23** and a low amount of compound **24** within minutes. The experiment revealed that the C–C bond in **21** was homolyzed to Gomberg's radical and diphenyl methyl radical. The presence of oxygen proved the bond homolysis and, therefore, a radical mechanism. These preliminary studies posed a question of what causes this selectivity in radical recombination.



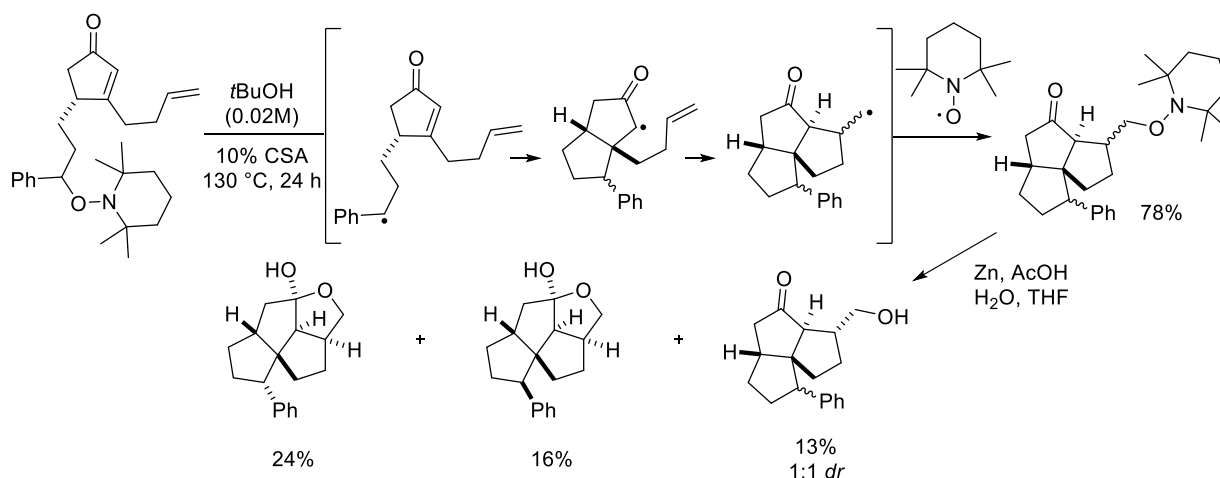
Scheme 20: Early observations of the persistent radical effect by Wiselogle and Bachmann.

This phenomenon was explained by the persistent radical effect, a principle that describes the selective cross-coupling of two radical species produced at equal rates, one being persistent the other transient. The kinetics of such a process can be illustrated on an example of a compound **RX** (Scheme 21).^[85] The **R–X** bond is homolyzed with a rate constant k_1 resulting in the generation of an equal amount of a persistent radical $X\cdot$ and a transient radical $R\cdot$. These two species recombine rapidly with the rate constant k_{-1} , which must be higher than the rate of homolysis ($k_1 < k_{-1}$) in order to achieve a selective transformation. If this requirement is not fulfilled, the concentration of radical $R\cdot$ will rise dramatically and result in homodimerization forming the dimer **R–R**. A small extent of homodimerization is, however, the initiation process in a PRE-governed transformation that generates a slight excess of persistent free radical $X\cdot$, increasing the rate of k_{-1} and of the ultimate coupling k_6 . The persistent radical can only react with a transient species with a diffusion- or a near diffusion-controlled rate constant (ca $10^9 \text{ M}^{-1}\text{s}^{-1}$), and its rate for homodimerization equals zero ($k_3 = 0 \text{ M}^{-1}\text{s}^{-1}$). The formed transient radical $R\cdot$ can undergo intramolecular cyclization, rearrangement, or intramolecular atom abstraction with the rate constant k_4 creating a new transient species $R^1\cdot$ behaving identically as radical $R\cdot$. The newly formed radical $R^1\cdot$ rapidly recombines with the persistent radical $X\cdot$, and the selective accumulation of the product **R^1X** is achieved if the rate of homolytic cleavage k_1 exceeds the reverse reaction rate k_{-6} ($k_1 > k_{-6}$).



Scheme 21: Kinetic rationale of the persistent radical effect.

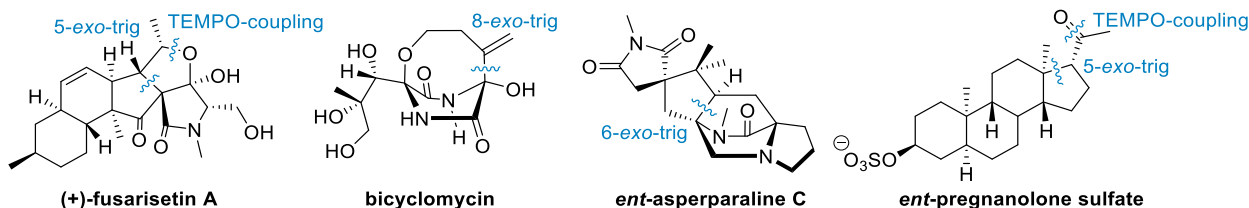
The application of the PRE was thoroughly investigated in nitroxide-mediated polymerizations, where fast recombination of the persistent and transient species prevents the formation of high-molecular-weight homodimers and, therefore, narrow molecular dispersity is achieved.^[86] The PRE in synthetic organic chemistry remained underinvestigated until 2000 when Studer et al. showed in their seminal works the application of nitroxide mediated PRE-based tin-free cyclizations leading to functionalized carbocycles (**Scheme 22**).^[87] TEMPO can be considered as a protected alcohol derivative and can be cleaved by reduction with zinc in acetic acid giving free alcohols or oxidized to a carbonyl group by *m*CPBA. Studer utilized TEMPO reduction to converge tricyclic aminoxy ketones into diastereoisomeric lactols or γ -hydroxy ketone.



Scheme 22: Example of Studer's PRE-based cascade cyclization and subsequent reduction of the aminoxy group.

In the last decade, the application of alkoxyamines in PRE-based cyclizations has been investigated in the context of the total synthesis of natural products. Theodorakis et al. reported the total synthesis of the potent cancer migration inhibitor (+)-fusarisetin A by a PRE-based 5-*exo*-trig cyclization/TEMPO coupling.^[88] Jahn et al. disclosed a formal total synthesis of the diketopiperazine alkaloids bicyclomycin

and *ent*-asperparaline C by PRE-based 8-*exo*-trig or 6-*exo*-trig cyclizations, respectively, as well as a strategy to *ent*-pregnanolone sulfate by a 5-*exo*-trig cyclization (**Scheme 23**).^[89]



Scheme 23: Examples of natural products synthesized by TEMPO-mediated PRE-based cyclizations.

1.13. KINETICS OF RADICAL CYCLIZATIONS

In 1976 Baldwin described on empirical basis rules allowing the prediction of the relative facility of ring-forming reactions. Such a process can be described with the prefix *exo* when the reacting bond is exocyclic to the smallest so formed ring and *endo* when the reacting bond results as a part of this ring. A numerical prefix describes the ring size of the formed ring, and a suffix *tet*, *trig*, *dig* characterizes the geometry of the atom undergoing a ring-closing reaction.^[90]

The rules for tetrahedral, trigonal, and digonal systems can be summarized as follows:

- Tetrahedral systems:
3 to 7-*exo*-tet are all favored, 4 to 6-*endo*-tet are disfavored.
- Trigonal systems:
3 to 7-*exo*-trig are all favored, 3 to 5-*endo*-trig are disfavored, 6 to 7-*endo*-trig are favored.^[a]
- Digonal systems:
3 to 4-*exo*-dig are disfavored, 5 to 7-*exo*-dig are favored, 3 to 7-*endo*-dig are favored.^[a]

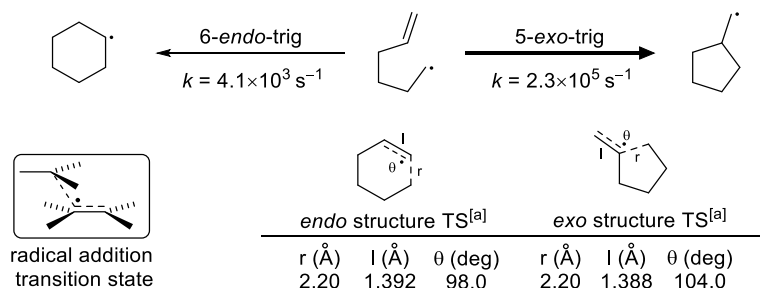
^[a] If multiple favored, kinetically competing *exo/endo* processes are possible, regioisomeric mixtures are formed.

The physical principle of these empirical observations lies in the stereochemical requirement of the transition state.^[91] An effective orbital overlap resulting in bond formation is favored only in a certain combination of the ring size and the geometrical parameters of the interacting atoms. It must be mentioned that the described observations are valid only for second-row elements because the larger atomic radii and bond lengths of higher-row elements can result in bypassing the geometrical restraints. Although Baldwin's rules are generally applicable to predict the outcome of many transformations, several exceptions violating the rules have been observed mainly in the chemistry of carbocations. Based on increasing experimental evidence and computations, the rules have been recently revised and extended.^[92] Radical cyclizations are frequently utilized to synthesize hetero- or carbocyclic compounds and obey the same rules for ring closures as reactions of polar, charged intermediates.

If the cyclization of the most synthetically useful intermediate hex-5-enyl radical gets analyzed (**Scheme 24**), the two ends of the double bond constitute two possible reactive sites for a radical

attack.^[93] Cyclization in the 5-*exo*-trig fashion leads to a cyclopentylmethyl radical, and the 6-*endo*-trig mode leads to a cyclohexyl radical. Although the latter is thermodynamically preferred, the product distribution found is 98:2 in the advantage of the five-membered ring. The striking difference in rate constants $2.3 \times 10^5 \text{ s}^{-1}$ for the *exo* mode and $4.1 \times 10^3 \text{ s}^{-1}$ for the *endo* mode was explained by the energetic difference of the transition states being 1.7 kcal/mol.

There is a general agreement that the transition state in which a carbon-centered radical adds to a double bond comprises a triangular array of centers lying in the same plane as the original π bond. When the two possible transition states of a hex-5-enyl radical were computationally examined, it was revealed that the bond lengths r and l of a forming and a breaking bond were almost identical (**Scheme 24**).^[91] The angle Θ in between these two bonds, however, differed and for the *exo* transition state was closer to that of a 109.5° found in a tetrahedral geometry after complete rehybridization.^[94]



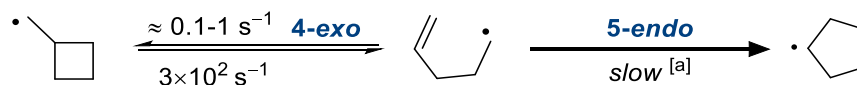
Scheme 24: Cyclization possibilities of a hex-5-enyl radical and its transition states parameters. ^[a] Both *exo* and *endo* structures resemble a distorted chair form of cyclohexane.

The situation gets more complex if substituents are attached to one or both termini of the cyclizing double bond; the transition state energies can be leveled off, and regiochemical mixtures of products are produced.^[95] The rate constants of common radical cyclizations and fragmentations are summarized in **Table 1**.^[91, 94, 96] The last example of cyclopropylcarbinyl radical fragmentation demonstrates the difficulty of forming three-membered rings by radical methods.

Table 1: Rate constants of common radical cyclizations and fragmentations. n.a.-not available.

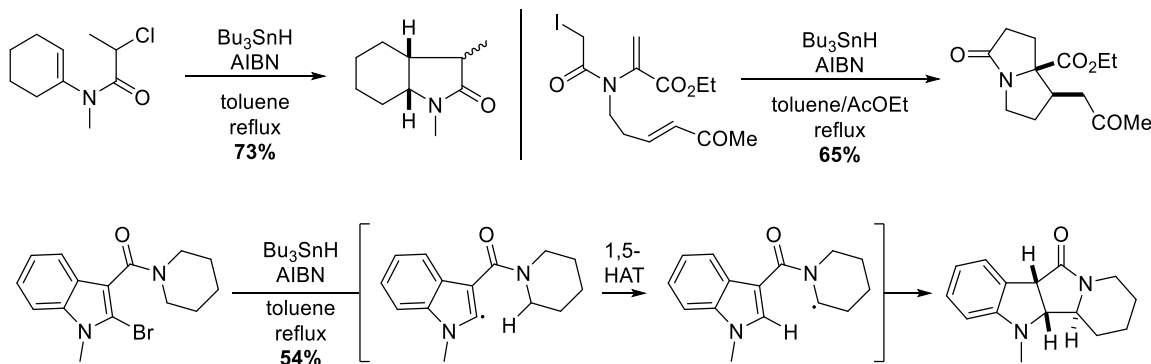
substrate	$k_{exo} \text{ (s}^{-1}\text{)}$	$k_{endo} \text{ (s}^{-1}\text{)}$	substrate	$k_{exo} \text{ (s}^{-1}\text{)}$	$k_{endo} \text{ (s}^{-1}\text{)}$
	2.3×10^5	4.1×10^3		5×10^8	$< 6 \times 10^6$
	5.4×10^3	7.5×10^2		2.8×10^4	$< 6 \times 10^2$
	$< 7 \times 10^1$	1.2×10^2		8×10^3	n.a.
	5.3×10^3	9.0×10^3	substrate	$k_{opening} \text{ (s}^{-1}\text{)}$	
	5.1×10^6	$< 1 \times 10^5$		7.8×10^7	

The situation of pent-4-enyl radical offers similarly two cyclization modes that are both kinetically disfavored (**Scheme 25**).^[97] The 4-*exo*-trig cyclization leads to the formation of a cyclobutylcarbinyl radical that is kinetically as well as thermodynamically unfavorable and reversible, and the equilibrium lies on the side of the starting material. The 5-*endo*-trig cyclization gives a cyclopentyl radical that is favorable on thermodynamic grounds. However, because of the low rate constant faster processes such as hydrogen atom transfer to the parent radical are often observed, and therefore the reaction may be low yielding, or no product is formed at all.



Scheme 25: Cyclization possibilities of a pent-4-enyl radical. ^[a] No precise kinetic data for 5-*endo*-trig cyclization of an unsubstituted pent-4-enyl radical is available.

Although the formation of five-membered rings by 5-*endo*-trig mode seemed synthetically unsuitable, a number of applications of constraint carbamoylmethyl or α -amidoyl radicals in the synthesis of five-membered heterocycles were found (**Scheme 26**).^[98]

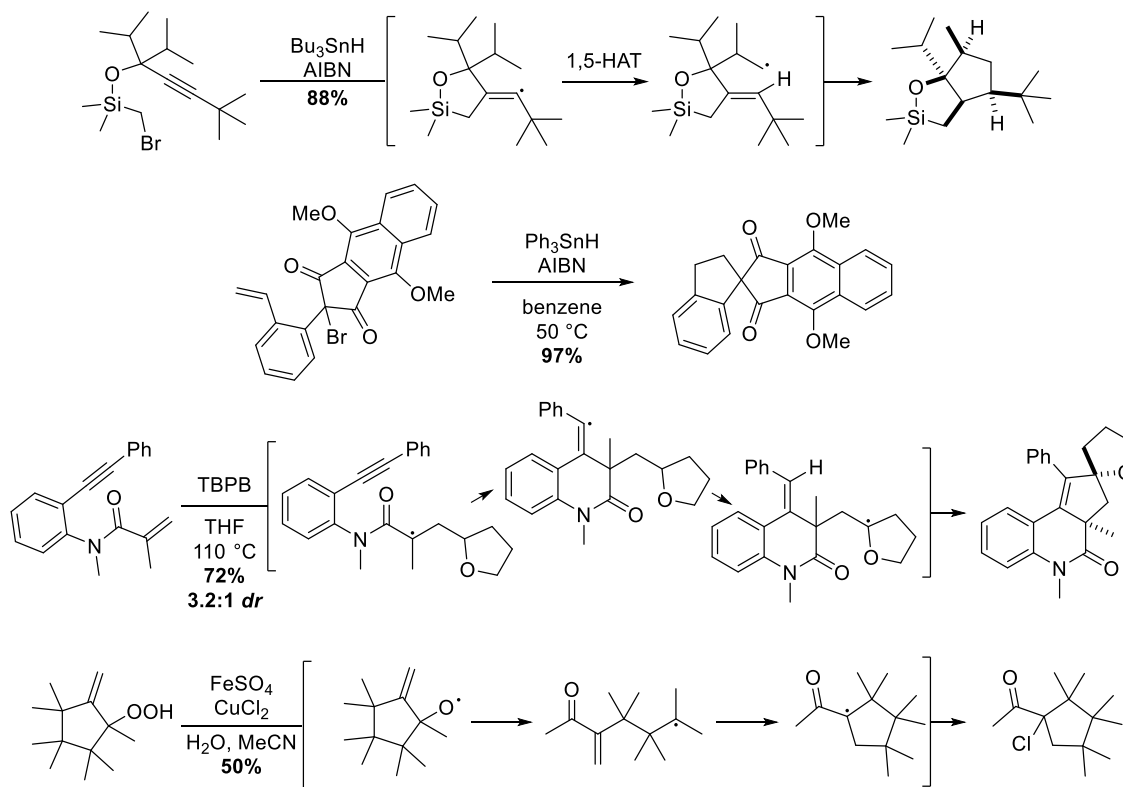


Scheme 26: Application of radical 5-*endo*-trig cyclizations in the synthesis of heterocyclic compounds.

Because of their unrestricted rotation, the synthesis of *all-carbon* five-membered rings by 5-*endo*-trig radical cyclization is considerably more difficult. However, it can be achieved if the following prerequisites increasing the reaction rate are fulfilled: A high degree of substitution around the radical center; strong radical stabilizing group adjacent to the forming cyclized radical; geometrical fixation of the carbon skeleton; sp^2 units incorporated into the cyclizing skeleton.

In 1996, Bogen et al. reported a successful 5-*exo*-dig/1,5-HAT/5-*endo*-trig cyclization sequence in the synthesis of cyclopentanes and diquinanes (**Scheme 27**).^[99] In 1993, Rao et al. applied a 5-*endo*-trig cyclization in the synthesis of the frederamycin A skeleton.^[100] In 2015, Hu et al. developed a formal [2+2+1] carbocyclization through a radical addition/6-*exo*-dig/1,5-HAT/5-*endo*-trig cyclization sequence.^[101a] In 1999, Nonami et al. reported a 5-*endo*-trig cyclization of highly methylated 2-methylenecycloalkyl hydroperoxides upon reduction with $FeSO_4$.^[101b] These examples fulfill

and combine the abovementioned prerequisites. However, the *all-carbon 5-endo-trig* cyclization of unrestrained substrates remains challenging.



Scheme 27: Examples of *all-carbon 5-endo-trig* radical cyclizations.

2. STATE OF THE ART, HYPOTHESIS, AND MOTIVATION

The enolate oxidation methodology is an efficient tool to synthesize carbo- or heterocyclic compounds to be applied as scaffolds for further elaboration. In order to achieve high structural complexity with the lowest step count possible, a number of tandem processes combining the oxidative methodology with initial enolate-generating reaction steps have been developed in Jahn's group. In this sense, tandem transformations coupling aza-,^[102] oxa-,^[72f] Michael-,^[72h] or copper-catalyzed conjugate addition to α,β -unsaturated carbonyl compounds,^[89c] or 1,2-nucleophilic addition/redox isomerization^[78] with subsequent oxidation of the generated enolate have been developed.

The anionic oxy-Cope rearrangement is a powerful tool to synthesize complex molecules. The connectivity of a molecule is fundamentally changed in a single step, and because of the concerted mechanism, the reaction often proceeds with a high degree of diastereoselectivity. The fact that the oxy-Cope rearrangement results in a metal enolate makes it a great candidate to be coupled with subsequent radical steps in a tandem process.

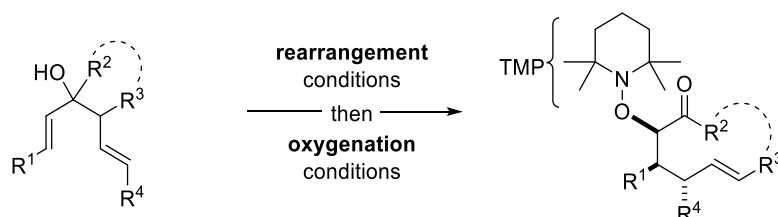
We hypothesized that the enolate generated by an anionic oxy-Cope rearrangement may be SET-oxidized with $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ to generate an α -carbonyl radical applicable in radical α -oxygenation with TEMPO or in intramolecular cyclizations with present double bonds. The fact that the anionic oxy-Cope rearrangement inherently installs a double bond into the δ -position to the carbonyl group raises the question of whether kinetically disfavored 5-*endo*-trig cyclization upon oxidation of the enolate can be induced. Furthermore, installing a double bond at the ε -position of the carbonyl group would most likely cause a 5-*exo*-trig cyclization giving a distinct type of functionalized cyclopentanes applicable as key intermediates in the synthesis of natural products.

Ganoderma fungi, traditionally applied in folk mycotherapy, got into the scientific spotlight as a broad source of new potentially medicinally relevant bioactive scaffolds in recent years. Its mycochemical content, including meroterpenoids, gets analyzed and tested, displaying diverse bioactivities. However, the limited amount of fungal material and the scarce occurrence of meroterpenoids seriously limit their investigation. The structural similarities between applanatumols and spiroapplanatumines isolated from *Ganoderma applanatum*, bearing diversely substituted cyclopentane cores, drew our attention. The facility to construct cyclopentanes by radical methods motivated for testing the applicability of the envisioned tandem processes on a real synthetic challenge. Furthermore, successful total synthesis would allow the thorough biological evaluation of the targeted compounds, analogs as well as their stereochemical verification.

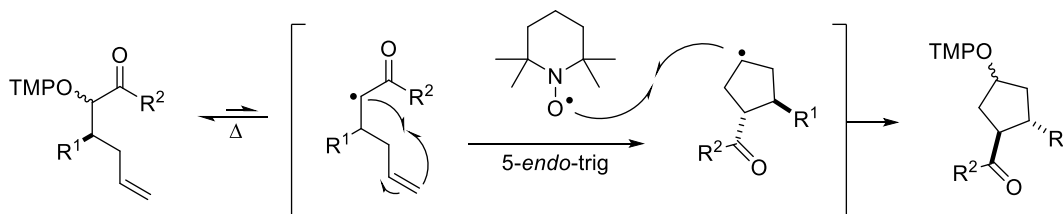
3. AIMS OF THE WORK

We specify the following aims:

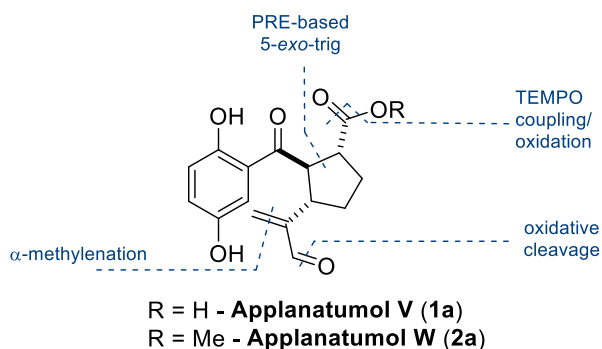
- To develop a tandem process merging anionic oxy-Cope rearrangement/SET/ α -oxygenation by persistent radical TEMPO. Compatible reaction conditions for the rearrangement and the oxidative step must be investigated.



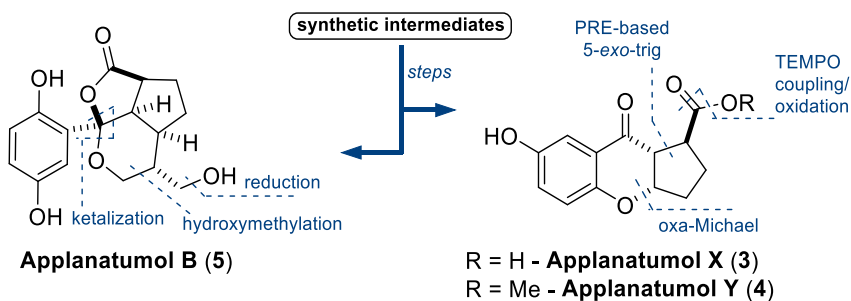
- To study the substrate scope of the tandem AOC/SET/ α -oxygenation on polyunsaturated, cyclic, and rigid hexa-1,5-dien-3-ols to test their rearrangement aptitudes and any potential competing side reactions.
- To study further elaboration possibilities of the prepared α -aminoxy carbonyl compounds by polar reactions. Emphasis will be placed on *one-pot* transformations.
- To study the application of rearranged α -aminoxy carbonyl compounds in PRE-based synthesis of cyclopentanes by 5-*endo*-trig and 5-*exo*-trig cyclization modes.



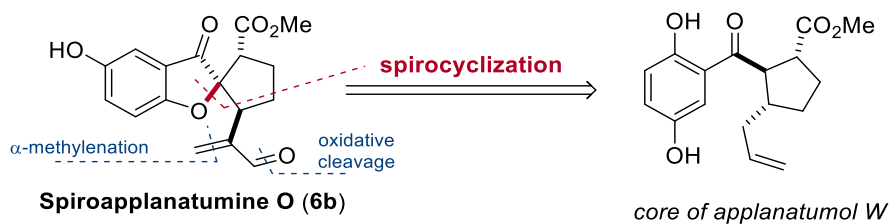
- To study the substrate scope of PRE-based 5-*endo*-trig cyclizations and to test competing cyclization possibilities.
- To design and develop a racemic synthetic route to *Ganoderma* meroterpenoids applanatumols V and W based on the tandem AOC/SET/ α -oxygenation and PRE-based cyclization sequences.



- To diversify the developed synthetic approach to related meroterpenoids applanatumols B, X, and Y utilizing synthetic intermediates from the synthesis of applanatumol W.



- To provide access to spiroapplanatumine meroterpenoids by spiroether bond-formation on the carbocyclic core of applanatumol W. Developed spirocyclization reaction will be utilized toward the synthesis of spiroapplanatumine O.



4. RESULTS AND DISCUSSION

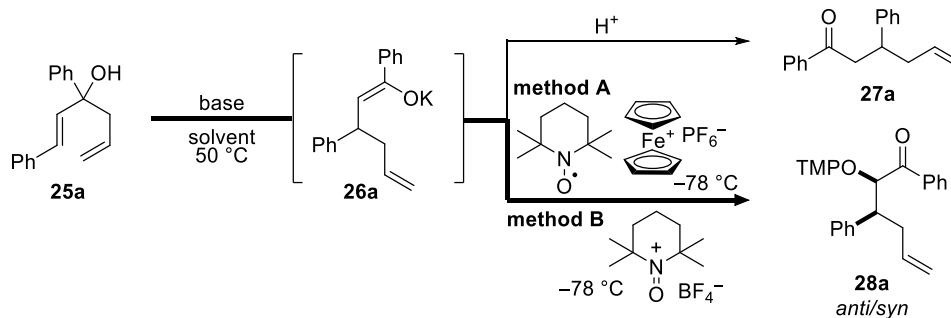
4.1. TANDEM ANIONIC OXY-COPE REARRANGEMENT/SET/ α -OXYGENATION

4.1.1. Optimization of the conditions for the AOC/oxygenation sequence

The first focus of the study was to explore the potential to merge the anionic oxy-Cope rearrangement and SET oxidation of the produced metal enolate with α -oxygenation by radical coupling with the persistent radical TEMPO. The investigation commenced by finding suitable conditions for the anionic oxy-Cope rearrangement step (**Table 2**). Allylated chalcone derivative **25a** was chosen as the initial substrate for the prospected study.

Bases, such as potassium hydride, potassium *tert*-butoxide, and potassium hexamethyldisilazide (KHMDs), were tested to accelerate the rearrangement step (*cf.* [Chapter 1.9](#)). All proved to be equally effective, and alcohol **25a** was cleanly rearranged to enolate **26a** over an hour upon heating to 50 °C in THF and furnished nearly quantitative yields of ketone **27a** upon quenching (**Table 2**, entries 1-3).

Table 2: Optimization of the AOC/oxygenation sequence.



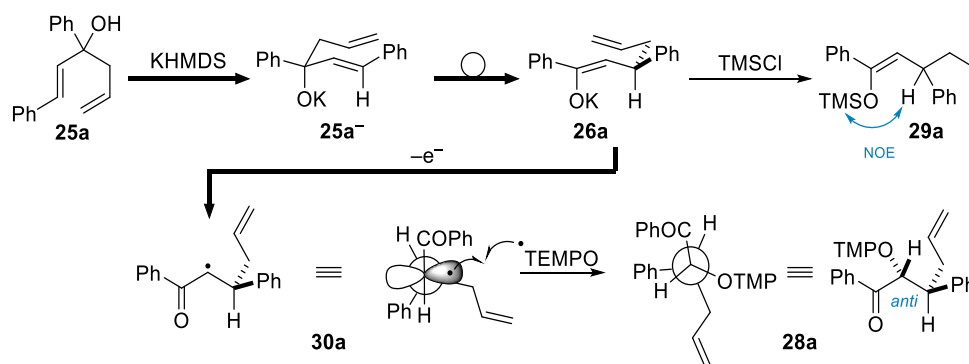
Entry	Base	Solvent	27a	Method ^[a]	28a (%)	28a (<i>anti/syn</i>) ^[b]
1	KH	THF	99			
2	<i>t</i> BuOK	THF	99			
3	KHMDs	THF	99			
4	<i>t</i> BuOK	THF		A	99	4.7:1
5	KHMDs	THF		A	97	4.5:1
6	KH	THF		A	53	4.4:1
7	KHMDs	DME		A	99	4.7:1
8	KHMDs	DME		B	92	3.2:1

^[a] Conditions: Method A: TEMPO (1.1 equiv.), then $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$, -78 °C; Method B: 2,2,6,6-tetramethyl-*N*-oxopiperidinium tetrafluoroborate (1.1 equiv.), -78 °C. ^[b] Determined by ¹H NMR spectroscopy of isolated products.

The promising outcome of the rearrangement step allowed the resulting potassium enolate to be engaged in subsequent oxidative step in a tandem set-up. The THF solution of enolate **26a** was cooled to $-78\text{ }^{\circ}\text{C}$, TEMPO, and $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ was then added in a portion-wise fashion (entries 4-7). *t*BuOK and KHMDS furnished the rearranged α -aminoxy ketone **28a** in an excellent yield as an *anti*/*syn* diastereoisomeric mixture (entries 4,5). KH proved less effective, and the conversion to the product **28a** was not complete (entry 6). Changing the solvent to 1,2-dimethoxyethane (DME) with KHMDS as base slightly improved the yield and diastereoselectivity (entry 7). 2,2,6,6-Tetramethyl-*N*-oxopiperidinium tetrafluoroborate furnished the product **28a** in a somewhat lower yield and diastereoselectivity (entry 8). The mechanism of such oxygenation is still a point of debate and proceeds either through a polar nucleophilic addition or by a SET/radical coupling. Although *t*BuOK and KHMDS performed equally well in the tandem reaction, KHMDS in DME was chosen as the base of choice for further studies. Hence, its higher basicity guarantees irreversible deprotonation of less acidic, aliphatic carbonyl compounds.

The potassium enolate **26a** formed during the rearrangement step was expected to have *Z*-configuration resulting from the preferred transition state of the rearranging alkoxide **25a**⁻, orienting the phenyl groups in a pseudo-equatorial orientation of a chair-like TS (**Scheme 28**).^[39] This was indeed the case as determined by trapping it as its trimethyl silyl ether **29a**. Nuclear Overhauser effect (NOE) measurements showed contact between the TMS group and the benzylic proton, revealing *Z*-configuration.

Oxidation of enolate **26a** by $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ leads to α -carbonyl radical **30a** that couples with TEMPO from the sterically least hindered face in a preferred conformation enforced by 1,3-allylic strain.^[103] This model explains the *anti*-configuration of the major diastereoisomer of **28a**. For the experimental stereochemical evidence of products **28**, see [Chapter 4.1.7](#).



Scheme 28: Stereochemical rationale of the AOC/oxygenation sequence.

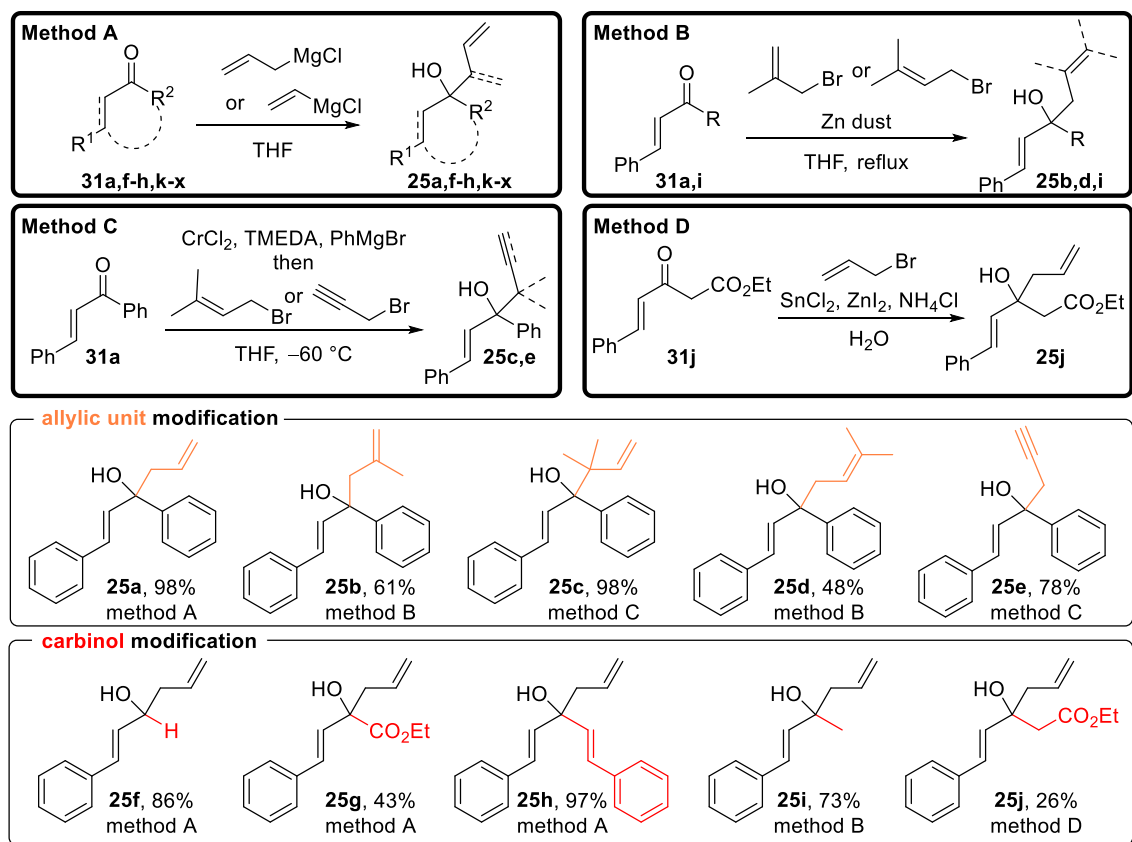
The results show that the anionic oxy-Cope rearrangement can be effectively coupled with a subsequent radical oxygenation step. The fact that no 5-*endo*-trig cyclized, reduced, or dimerized side-products

were detected demonstrates that the near to diffusion-controlled rate of coupling of the transient radical **30a** with the persistent radical TEMPO outperforms other competitive reaction modes.

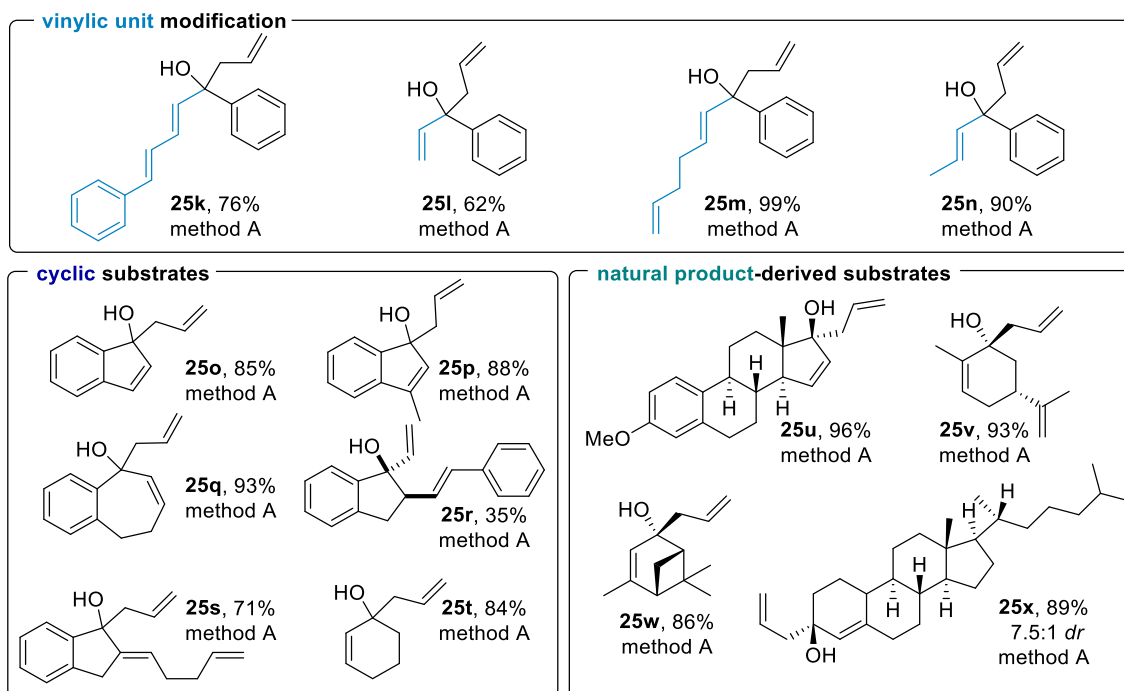
4.1.2. Preparation of carbinols for the substrate scope of the AOC/oxygenation sequence

To prove the generality of the developed tandem sequence, the substrate scope was prospected. The substrates were designed to show the rearrangement aptitudes, the functional group compatibility, and whether fast intramolecular radical cyclization processes can interfere with the oxygenation sequence. For these reasons, substrates **25a-x**, with modified allylic, vinylic, and carbinol substitution together with cyclic and natural product-derived substrates, were prepared.

Substrates **25a,f-h,k-x** were obtained by standard nucleophilic addition of allylic or vinylic Grignard reagents to the corresponding unsaturated carbonyl compounds **31a,f-h,k-x** (Method A, **Scheme 29**). In the case of compounds **25b,d,i** allylic zinc reagents, ensuring the α -addition of the substituted allylic unit were applied (Method B).^[104] Substrates **25c,e** were prepared by the addition of allylic organochromium reagents to chalcone **31a** (Method C).^[105] Unsaturated β -keto ester **31j** was allylated by allylic tin reagent in water yielding substrate **25j** (Method D).^[106]



Scheme 29: Preparation of substrates **25a-j** by 1,2-nucleophilic addition of organometallic reagents.

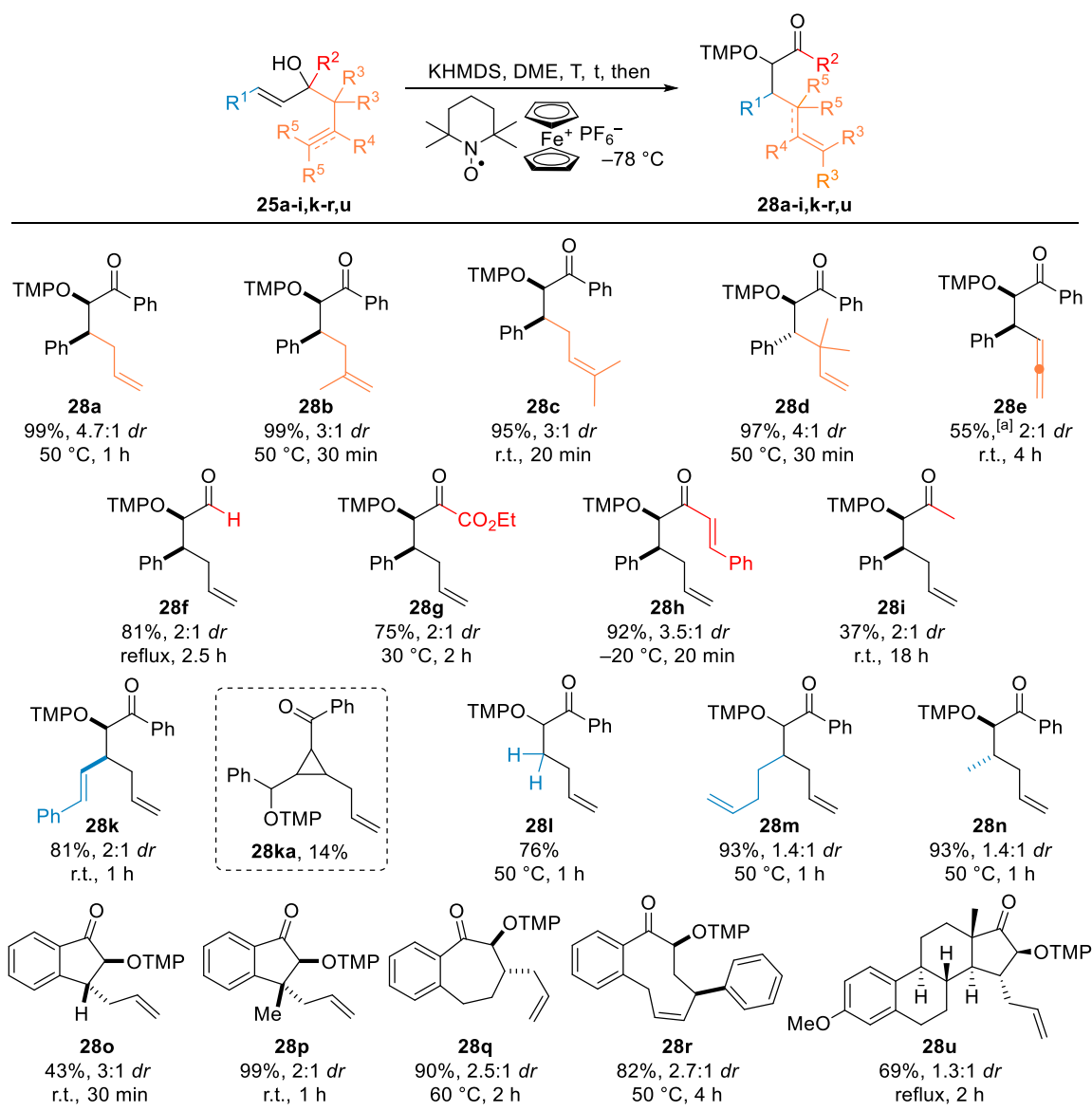


Scheme 29-continuation: Preparation of substrates **25k-x** by 1,2-nucleophilic addition of organometallic reagents.

4.1.3. Substrate scope of the AOC/oxygenation sequence

Substrates **25a-x** were submitted to the optimized AOC/oxygenation conditions (**Scheme 30**). All substrates except **25e** were deprotonated by KHMDS in DME, typically at 0 °C. The temperature was gradually increased until the conversion of the starting material was observed and kept at this temperature until judged finished by TLC analysis. Subsequently, TEMPO was added at room temperature, and after cooling to -78 °C, $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ was added portion-wise until the mixture remained deep-blue, indicating that no more oxidant was consumed.

Chalcone-derived allylated, methallylated, and reverse prenylated alcohols **25a-c** smoothly underwent the AOC/oxygenation sequence providing α -aminoxy ketones **28a-c** in excellent yields and moderate *anti*-selectivity (**Scheme 30**). Interestingly, the congested reverse-prenyl derivative **25c** showed a high rearrangement aptitude and fully reacted already at room temperature in 20 min. Prenylated chalcone derivative **25d** provided an excellent yield of the product **28d** with a reversed *syn*-diastereoselectivity of the major diastereoisomer as a result of higher sterical demand of the *gem*-dimethyl group compared to phenyl (for stereochemical assignment cf. [Chapter 4.1.7](#)).



Scheme 30: Substrate scope of the AOC/oxygenation sequence. Stereochemistry of the major diastereoisomer is displayed

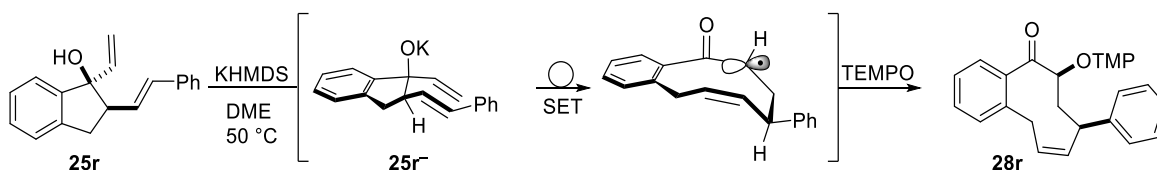
^[a] KH was used as a base.

The reaction is not limited to phenones, as demonstrated for substrates with various carbinol substituents. Rearrangement of compounds **25f-i** generated oxygenated aldehyde **28f**, α -ketoester **28g**, α,β -unsaturated or methyl ketone, **28h** and **28i** respectively. Remarkably, the rearrangement of substrate **25h** proceeded already at cryogenic conditions. Compound **25i** provided the lowest yield of the whole series because of undefined side reactions.

The vinylic position of the rearranging hexa-1,5-dien-3-ol system can be modified as well. An additional unsaturation in the substrate **25k** accelerated the rearrangement proceeding already at room temperature. Interestingly, the product **28k** was accompanied by an unknown diastereoisomer of cyclopropane **28ka** resulting from radical 3-*exo*-trig cyclization/radical coupling with TEMPO.

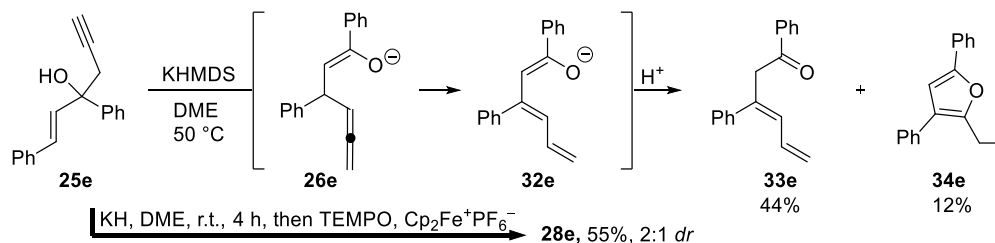
This compound proved very unstable and converted to product **28k** upon standing. Substrates **25l-n** with aliphatic or no substitution at the vinylic end also effectively provided the rearranged α -aminoxy ketones **28l-n**. No cyclic products were detected in the case of substrate **25m**, capable of 5-*exo*-trig radical cyclization. This result demonstrates that even reasonably fast cyclization processes cannot kinetically compete with coupling with a persistent radical. A small methyl substituent of **25n** reversed the diastereoselectivity, and the product **28n** with *syn*-configuration was formed in the tandem sequence.

Cyclic and natural product-derived substrates could also be engaged in the tandem sequence. Indenol derivatives **25o,p** rearranged smoothly and provided high yields of oxygenated products **28o,p**. However, unsubstituted indanone derivative **28o** gave a moderate isolated yield because of partial decomposition on silica gel during purification. The benzosuberone example **28q** shows that larger rings can also be effectively rearranged. The estrone derivative **28u** reacted well in the tandem sequence and demonstrated the potential for late-stage modification of complex scaffolds by the rearrangement/oxygenation sequence. Vinylated β,γ -unsaturated carbonyl compounds undergo a ring expansion during the rearrangement step. Indeed this was the case of substrate **25r** that smoothly expanded at elevated temperature, furnishing oxygenated 9-membered carbocycle **28r** with exclusive *Z*-configuration of the double bond, suggesting that the rearrangement of alkoxide **25r⁻** proceeds through a boat-like TS (Scheme 31).



Scheme 31: Stereochemical explanation of the ring expansion during the AOC/oxygenation sequence of substrate **25r**.

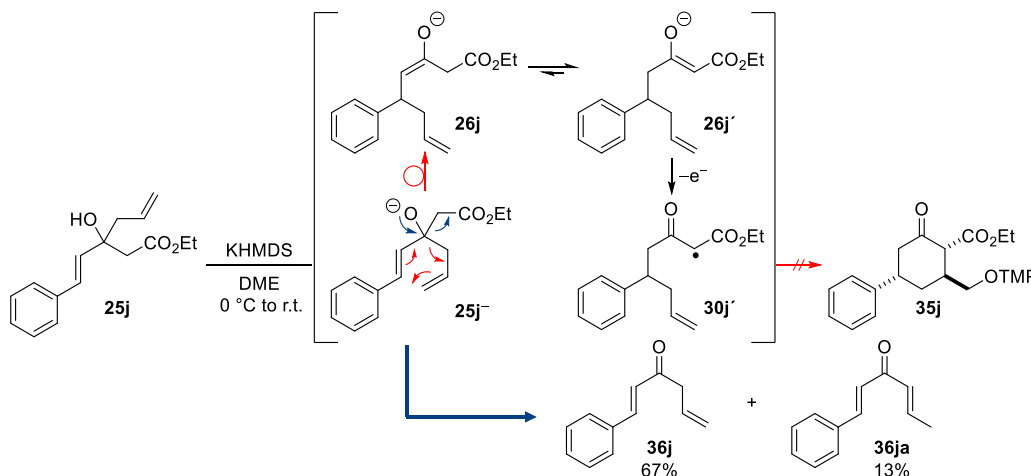
The propargylated chalcone derivative **25e** needed more optimization. Under the influence of KHMDS, the rearranged allene enolate **26e** underwent a double bond shift resulting in a conjugated trienolate **32e** (Scheme 32). The rearrangement step after aqueous workup yielded a dienone **33e** and a furan **34e**. The elementary steps leading to furan **34e** are, however, not known. For these reasons, the applied base was changed to KH, and the desired rearranged aminoxy allene **28e** was isolated in moderate yield and low diastereoselectivity.



Scheme 32: Competing reaction pathways during the rearrangement of **25e** under KHMDS conditions.

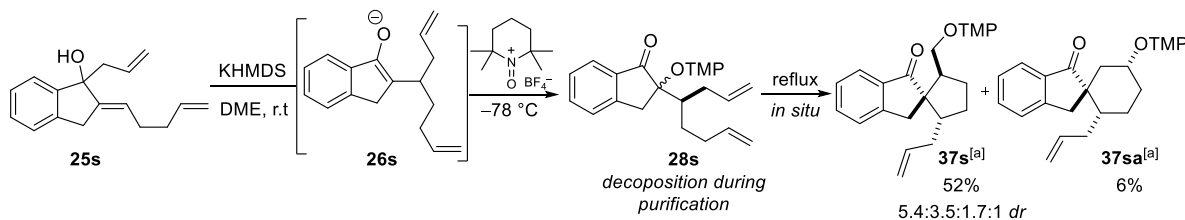
4.1.4. Limitations of the AOC/oxygenation sequence

The substrate scope revealed some limitations of the AOC/oxygenation sequence. The substrate **25j** was designed to generate, after the rearrangement step, enolate **26j** that would likely equilibrate to β -ketoester enolate **26j'** (Scheme 33). Such enolate has the potential to undergo a 6-*exo*-trig radical cyclization upon the oxidation with $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ giving cyclohexanone derivative **35j**. However, this reactivity was not observed. Instead, deprotonation with KHMDS caused a fast *retro*-aldol reaction giving enone **36j** and a dienone **36ja**.



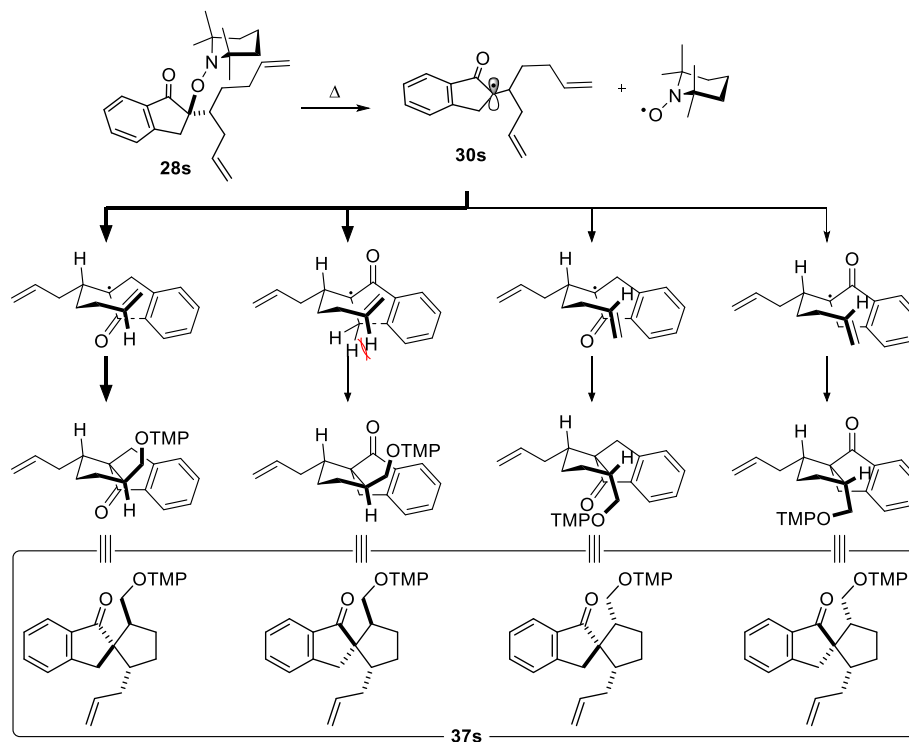
Scheme 33: Retro-aldol pathway during the rearrangement of substrate **25j**.

The situation of the AOC/oxygenation sequence of substrate **25s** is more complex (Scheme 34). The rearrangement of **25s** proceeded well and resulted in an enolate **26s** that was oxygenated by 2,2,6,6-tetramethyl-*N*-oxopiperidinium tetrafluoroborate giving α -aminoxy ketone **28s**. Here, TEMPO is bound to a quaternary carbon atom, with a lower C–O BDE compared to most other adducts **28a-i,k-r,u** (Scheme 30). All isolation attempts resulted in decomposition during purification on silica gel or alumina. Therefore, the solution of **28s** was immediately immersed into a preheated oil bath and refluxed for 30 min. Thermal conditions induced a controlled C–O bond homolysis promoting radical 5-*exo*/6-*endo*-trig cyclizations based on the persistent radical effect. The reaction resulted in a moderate yield of approximately 5.4:3.5:1.7:1 diastereoisomeric mixture of 5-*exo* cyclized spirocycles **37s** and 6-*endo* cyclized spirocycle **37sa**. The relative configuration of formed products was not assigned.



Scheme 34: AOC/oxygenation sequence of **25s** and PRE-based cyclization leading to spirocycles **37s,sa**. ^[a] Predicted stereochemistry of the major diastereoisomer is displayed.

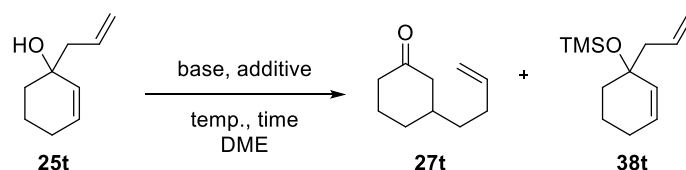
However, a prediction based on the standard Beckwith-Houk TS model can be devised (**Scheme 35**).^[107] It can be predicted that the two major 5-*exo* cyclized diastereoisomers originate from a chair-like transition state in which the carbonyl group orients in the most preferred conformation to avoid a steric clash between the reacting alkenyl group and benzylic hydrogen atoms. The two minor diastereoisomers are predicted to arise from the boat-like TS orienting the carbonyl group similarly in the preferred conformation. The TS for cyclohexane derivatives **37sa** is analogous, trapping TEMPO axially from the sterically less-hindered side (not shown). Spirocyclic scaffolds **37s** structurally remind of natural products spiroapplanatumines isolated from *Ganoderma applanatum* (c.f. [Chapter 4.3.5](#)) and could be potentially used to synthesize their carba analogs.



Scheme 35: Predicted transition state models for the thermal cyclization of α -aminoxy ketone **28s** forming spirocycles **37s**. Axial-chair conformations were omitted for clarity.

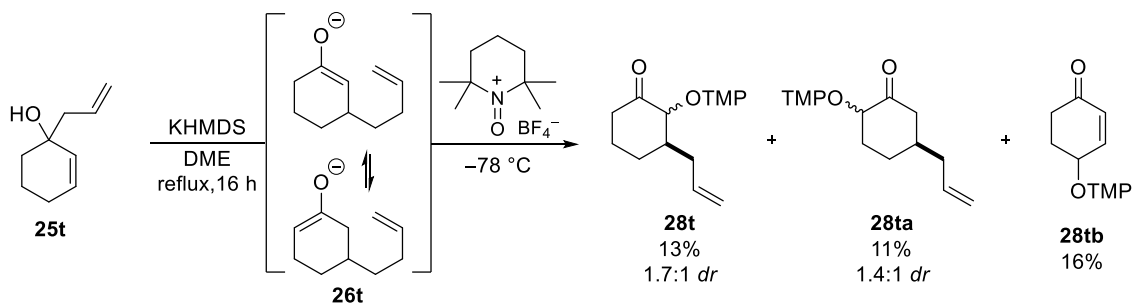
The rearrangement of cyclohexanone derivative **25t** was not facile and needed optimization (**Table 3**). KHMDS at elevated temperature did not induce the rearrangement (entry 1). The addition of an ionophore 18-crown-6 resulted in a silyl transfer to the potassium alkoxide forming silylated alcohol **38t**, and only a low yield of the rearranged product **27t** was obtained (entry 2). The product was cleanly formed at short reaction times if KH together with 18-crown-6 or KHMDS with HMPA at high temperature was used (entries 3,4). Smooth rearrangement of **25t** was observed when KMHDS and prolonged reflux conditions were applied (entry 5).

Table 3: Optimization of rearrangement conditions for an allylated cyclohexenol derivative **25t**.



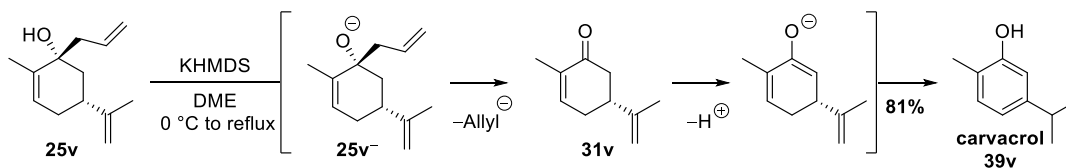
Entry	Base	Additive	Temp. (°C)	Time (h)	27t (%)	38t (%)
1	KHMDS	--	70	1	n.r.	--
2	KHMDS	18-crown-6	50	1	13	46
3	KH	18-crown-6	50	3	95	--
4	KHMDS	HMPA	Reflux	4	99	--
5	KHMDS	--	Reflux	16	99	--

The alcohol **25t** was submitted to the optimized rearrangement conditions, and the formed enolate was oxygenated by 2,2,6,6-tetramethyl-*N*-oxopiperidium tetrafluoroborate (**Scheme 36**). The reaction sequence furnished low yields of regioisomers **28t** and **28ta** as diastereoisomeric mixtures and product **28tb**, lacking the allylic unit. The formation of **28t** and **28ta** can be rationalized by an equilibration/oxygenation of the enolate **26t**. However, the reaction mechanism leading to product **28tb** is not known.



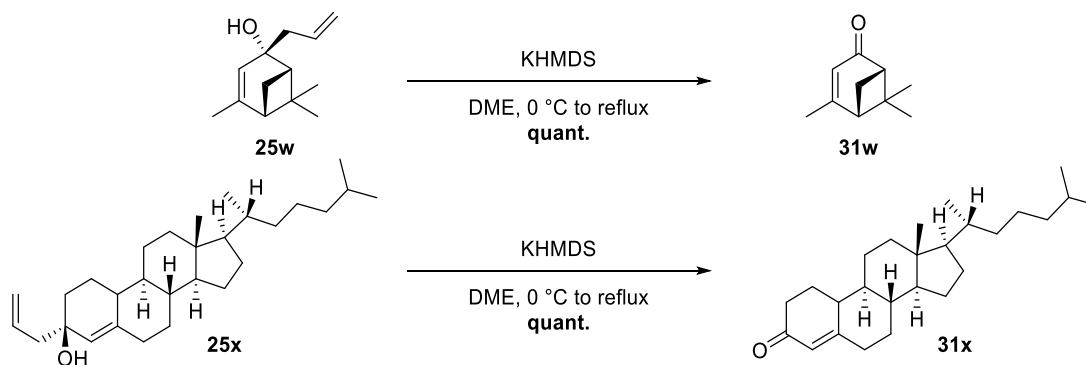
Scheme 36: AOC/oxygenation sequence of allylated cyclohexenol derivative **25t**.

The allylated carvone derivative **25v** showed a different reactivity (**Scheme 37**). The alkoxide **25v⁻** did not undergo the AOC even at elevated temperatures. At reflux, alkoxide **25v⁻** fragments into allyl anion and carvone **31v**. Under the reaction conditions, the propenyl double bond of **31v** migrates into the aromatizing cycle, giving a natural product carvacrol **39v** as determined by the ¹H NMR of the crude reaction mixture.



Scheme 37: Fragmentation pathway during the rearrangement of substrate **25v**.

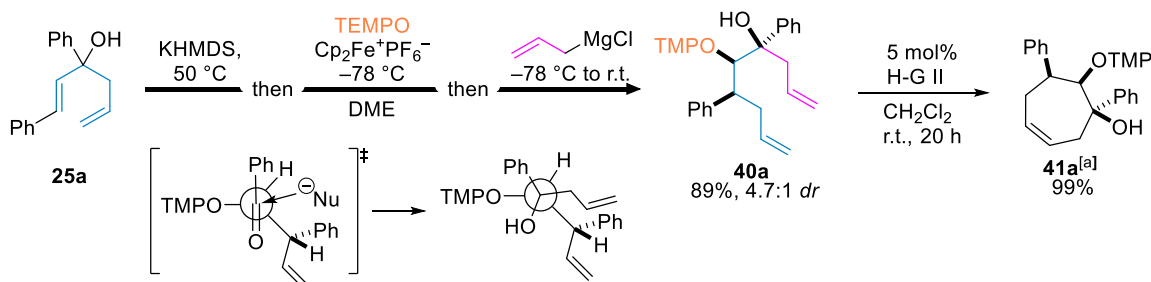
Because of their high rigidity, allylated verbenol and cholesterol derivatives **25w,x** did not exhibit any rearrangement tendency. Upon deprotonation, both eliminated the allyl anion at reflux temperature, providing the parent α,β -unsaturated ketones **31w,x** (Scheme 38).



Scheme 38: Fragmentation pathways during the rearrangement of substrates **25w,x**.

4.1.5. Extension of the AOC/oxygenation sequence by polar reactions

The AOC/oxygenation sequence rapidly increases molecular complexity. In order to gain diverse polyfunctional scaffolds applicable in the target-oriented synthesis, we hypothesized that the tandem process may be further coupled with polar, diastereoselective reaction steps. To verify this hypothesis, substrate **25a** was submitted to the standard AOC/oxygenation sequence producing α -aminoxy ketone **28a**. The *in situ* addition of 1.6 equiv. of allylmagnesium chloride led to clean nucleophilic addition furnishing a 4.7:1 diastereoisomeric mixture of diols **40a** produced during the oxygenation step (Scheme 39). The high selectivity can be rationalized by the Felkin-Anh model, where the alkoxyamine substituent serves as the large group. To demonstrate the synthetic potential of the formed product, the diene **40a** was engaged in ring-closing metathesis, efficiently forming a cycloheptene derivative **41a** by the action of the Hoveyda-Grubbs 2nd generation catalyst.



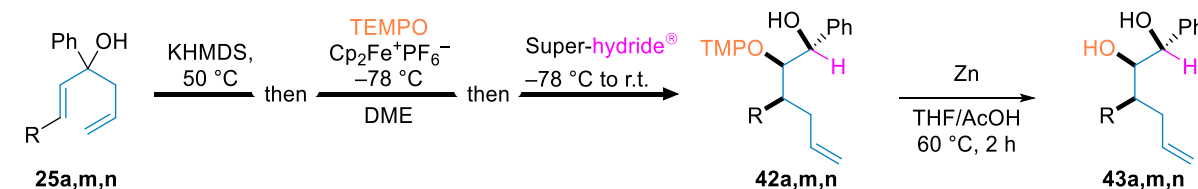
Scheme 39: Extension of the AOC/oxygenation sequence by diastereoselective *in situ* allylation and its application.

^[a] Separated major diastereoisomer was used.

In situ reduction can be applied to extend the AOC/oxygenation sequence as well (Table 4). Superhydride[®] proved to be the most selective hydride donor furnishing protected diols **42a,m,n** as single diastereoisomers at the newly formed, stereogenic center. In comparison, LiAlH₄ and L-Selectride[®]

showed higher reactivity but lower selectivity, producing complex mixtures of isomers. Similarly, the stereochemical outcome can be rationalized by the Felkin-Anh TS model (*vide supra*). The TMP-protected diols can be cleaved with ease by reduction with zinc in a THF/AcOH mixture providing free diols **43a,m,n**.

Table 4: Extension of the AOC/oxygenation sequence by diastereoselective *in situ* reduction and the TMP group removal.



Entry	R	Product	Yield (%)	<i>dr</i> ^[a]	Product	Yield (%)	<i>dr</i> ^[c]
1	Ph	42a	85	4.7:1	43a	80 ^[b]	--
2	Homoallyl	42m	94	1.4:1	43m	97	1.4:1
3	Me	42n	99	1.4:1	43n	83	1.4:1

^[a] Diastereoisomeric mixture formed during the oxygenation step. ^[b] Separated major diastereoisomer was used. ^[c] Determined by ¹H NMR spectroscopy of the isolated product.

It was previously shown that the formation of α,α -dicarbonyl substituted C-centered radicals having a double bond in a cyclizing distance results in spontaneous cyclization even in the presence of TEMPO.^[72b, 73] This can be explained by the additional decrease of electron density at the radical center, making it more electrophilic towards electron-rich double bonds, thus increasing the cyclization rate. Another explanation lies in radical coupling forming a tertiary TEMPO adduct with a low BDE that homolyses and cyclizes based on the PRE already at low temperatures.

The formation of such β -dicarbonyl compounds in a tandem set-up can be achieved by incorporating an additional acylation step after the AOC. An extra equivalent of the base would induce immediate deprotonation of formed β -diketone, opening the opportunity to promote a spontaneous radical cyclization with a present double bond.

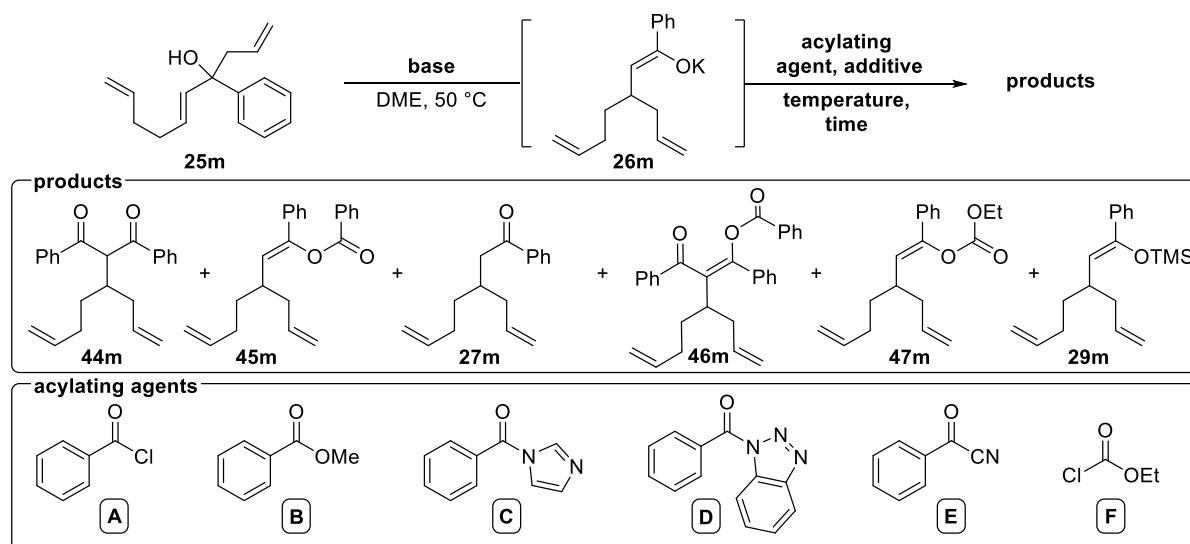
The benzoylation forming a symmetrical β -diketone in a tandem set-up proved to be difficult and needed thorough optimization (**Table 5**). The carbinol **25m** was deprotonated by KHMDS and rearranged at 50 °C over an hour. The resulting enolate **26m** was subsequently subjected to benzoylating conditions exploiting various reagents in the presence of additives.

Benzoyl chloride (**A**) did not provide diketone **44m**; instead, the enolate was *O*-benzoylated resulting in enol ester **45m** (entry 1, **Table 5**). Methyl benzoate (**B**) did not show any reactivity towards the enolate, and only rearranged product **27m** was obtained (entry 2). Similar reactivity was observed with benzoyl imidazole (**C**) or benzotriazole (**D**), respectively, providing very low or no conversion of the starting enolate (entries 3,4). Benzoyl cyanide (**E**) showed effectiveness; however, only low conversion of the starting material was observed even at extended reaction times (entries 5,6). The change to KH

did not lead to better conversion of the enolate (entry 7); therefore, additives were introduced. The addition of 6 equiv. of HMPA did not exhibit any conversion improvement (entry 8). LiCl improved the conversion to 73% when benzoyl cyanide was added at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was warmed to r.t. (entry 9).

Interestingly, keeping the temperature low during the whole reaction course with KHMDs as base and LiCl as an additive led to significant silyl transfer from KHMDs, resulting in a silyl enol ether **29m** (entry 10). The change of the base to KH, together with LiCl as an additive, led to clean benzoylation, and β -diketone **44m** was obtained in 91% isolated yield (entry 11). Noteworthy, because of poor solubility, adding LiCl at elevated temperature is beneficial to achieve a good enolate transmetallation and desaggregation; otherwise, poor conversion and reproducibility were observed. The treatment of enolate **26m** by ethyl chloroformate (**F**) at a slightly elevated temperature formed a high yield of enol carbonate **47m**, and no C-carboxylation was observed (entry 12).

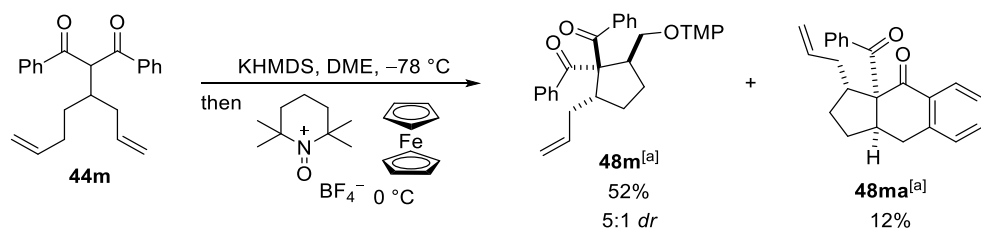
Table 5: Optimization of the AOC/acylation sequence.



Ent.	Base/Additive (equiv.)	Reagent (equiv.)	Temp. (°C)	Time (h)	44m (%)	45m (%)	27m (%)	46m (%)	47m (%)	29m (%)
1 ^[a]	KHMDS (2.0)	A (1.1)	0 to r.t	2.5	--	61	--	--	--	--
2 ^[b]	KHMDS (2.0)	B (1.2)	0 to 60	20	--	--	100	--	--	--
3 ^[b]	KHMDS (1.2)	C (1.2)	0 to r.t	15	2	--	98	--	--	--
4 ^[b]	KHMDS (3.0)	D (1.3)	0 to r.t.	15	--	--	100	--	--	--
5 ^[a]	KHMDS (2.0)	E (1.8)	0 to r.t	2.5	42	--	37	9	--	--
6 ^[b]	KHMDS (2.0)	E (1.1)	−78 to r.t	22	41	--	41	--	--	--
7 ^[b]	KH (3.0)	E (1.1)	−78 to r.t	3	52	--	48	--	--	--
8 ^[b]	KHMDS (3), HMPA (6)	E (1.3)	−78 to r.t	24	36	--	64	--	--	--
9 ^[b]	KHMDS (3), LiCl (6)	E (1.2)	−78 to r.t	3	73	--	27	--	--	--
10 ^[b]	KHMDS (3), LiCl (6)	E (2.0)	−61	3	39	--	--	--	--	48
11 ^[a]	KH (3), LiCl (6)	E (1.5)	−61	3.5	91	--	--	--	--	--
12 ^[a]	KHMDS (3)	F (2.0)	0 to 50	3	--	--	--	--	83	15

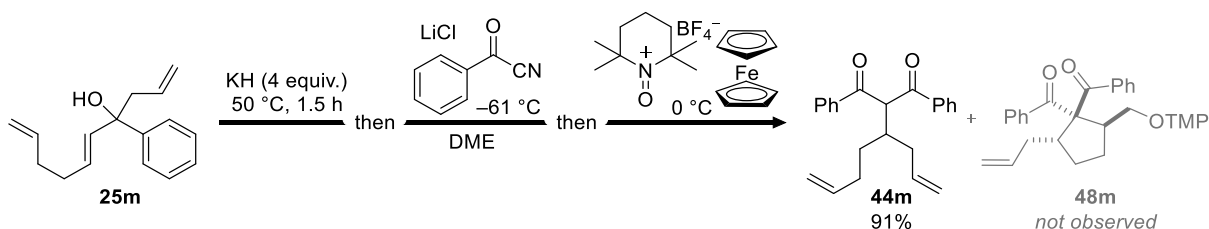
^[a] Isolated yields after column chromatography purification. ^[b] Determined by ¹H NMR spectroscopy of the crude reaction mixture.

The isolated product **44m** was deprotonated by KHMDS at −78 °C, and oxidized by an oxopiperidinium salt with catalytic Cp₂Fe (**Scheme 40**). Indeed the 5-*exo*-trig cyclization was induced, and no coupling of the formed α,α-dicarbonyl radical with TEMPO was observed. The reaction yielded the cyclopentane **48m** as a 5:1 diastereoisomeric mixture and the product of 5-*exo*/6-*exo* double-cyclization with one of the aromatic rings **48ma**. The configuration of the obtained products was not assigned.



Scheme 40: Radical cyclization of the isolated product **44m**. ^[a] Predicted stereochemistry of the major diastereoisomer.

In the tandem set-up, alcohol **25m** was subjected to the optimized benzoylation conditions with an excess of base and similarly oxidized by $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ in the presence of TEMPO or under catalytic conditions employing ferrocene and *N*-oxopiperidinium tetrafluoroborate (**Scheme 41**). The benzoylation conditions proved incompatible with the SET oxidation step. In all cases, the reaction mixture turned black and inhomogenous, and only β -diketone **44m** was isolated.

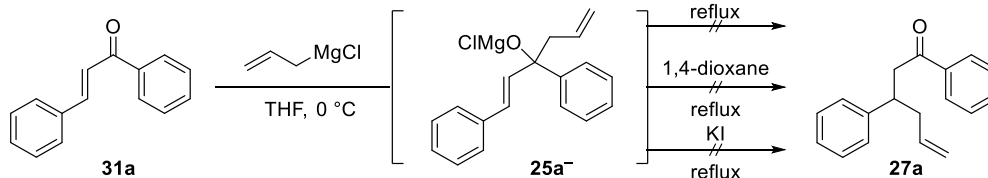


Scheme 41: Unsuccessful tandem AOC/benzoylation/radical cyclization.

4.1.6. Coupling of the tandem sequence with initial nucleophilic addition

The fact that oxy-Cope rearrangement is tremendously accelerated by the presence of an anionic alkoxide unit opens the attractive possibility to perform a 1,2-addition of an allylic organometallic reagent to an α,β -unsaturated carbonyl compound resulting in a rearrangement-undergoing alkoxide. The fact that other alkali metal counterions show much lower rate acceleration compared to potassium makes the situation difficult because of the complicated preparation of allyl potassium reagents.

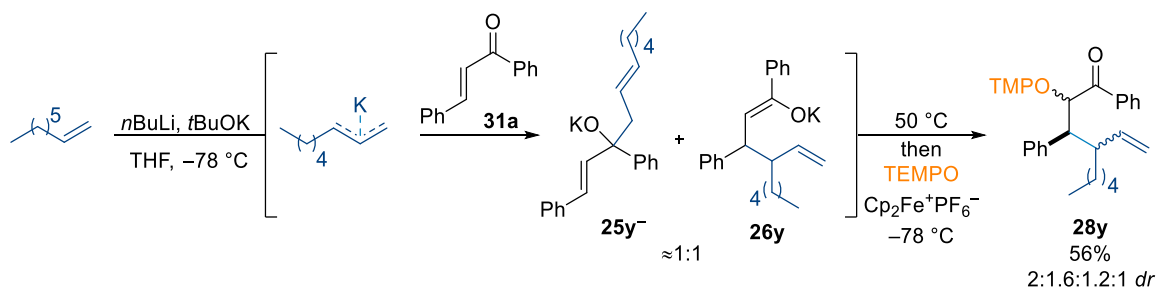
To test if a magnesium alkoxide **25a⁻**, produced by 1,2-addition of allylmagnesium chloride to chalcone **31a** could be rearranged, **25a⁻** was refluxed overnight in THF (**Scheme 42**); however, no conversion of the starting material was observed. The addition of 1,4-dioxane, known to precipitate inorganic magnesium salts, resulted in complete precipitation of the alkoxide, and no acceleration of the rearrangement occurred. An attempt to induce the AOC by transmetallating the magnesium alkoxide with potassium iodide turned out unsuccessful, and no rearrangement was observed. This example demonstrates the thermodynamic unfavorability of transmetalation of less electropositive metal alkoxides to more electropositive potassium alkoxides.



Scheme 42: Attempted AOC rearrangement of a magnesium alkoxide **25a⁻**.

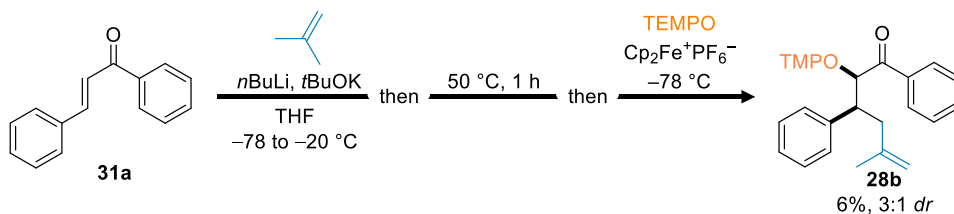
The Lochmann-Schlosser base, also denoted as the *LICKOR superbases*, describes the super basic mixture of alkyl lithium and potassium alkoxide reagents. The previously thought *in situ* generation of *n*-butylpotassium was disproved, and the formation of a highly basic mixed aggregate is generally accepted.^[108] The most commonly utilized 1:1 mixture of *n*BuLi with *t*BuOK is known to be basic enough to deprotonate benzylic or allylic protons of olefins forming benzyl or allyl potassium reagents.^[109] Allylic potassiums prepared by the direct deprotonation of olefins showed synthetically valuable in alkylations,^[110] preparation of allyl boronates for carbonyl allylations,^[111] and 1,2- or 1,4-addition to unsaturated carbonyl or sulfonyl compounds.^[112] The tandem 1,2-addition/AOC has never been reported to the best of our knowledge.

To test if such transformation can be achieved, oct-1-ene, as a simple non-volatile alkene, was deprotonated by the Schlosser-Lochmann base forming allylic potassium that compared to σ -bonded allyl magnesium, has a symmetrical π -complexed, η^3 -structure (**Scheme 43**).^[113] This reagent added to chalcone **31a** in both 1,2- and 1,4-fashion forming potassium alkoxide **25y⁻** and enolate **26y** in a 1:1 ratio as determined by a separate experiment. Heating to 50 °C over an hour resulted in the convergence of both products to enolate **26y** by AOC that was oxygenated by standard protocol resulting in a reasonable yield of a diastereoisomeric mixture of the product **28y**.



Scheme 43: Tandem 1,2-/1,4-addition/AOC/oxygenation sequence.

Next, we examined if organometallic nucleophiles formed from gaseous alkenes can be applied as well. For this purpose, isobutylene was condensed, deprotonated by the *LICKOR superbases*, and added to chalcone **31a** (**Scheme 44**). The unoptimized nucleophilic addition/AOC/oxygenation sequence provided a low yield of the desired product **28b** but served as a proof of principle that such tandem sequences are manageable.



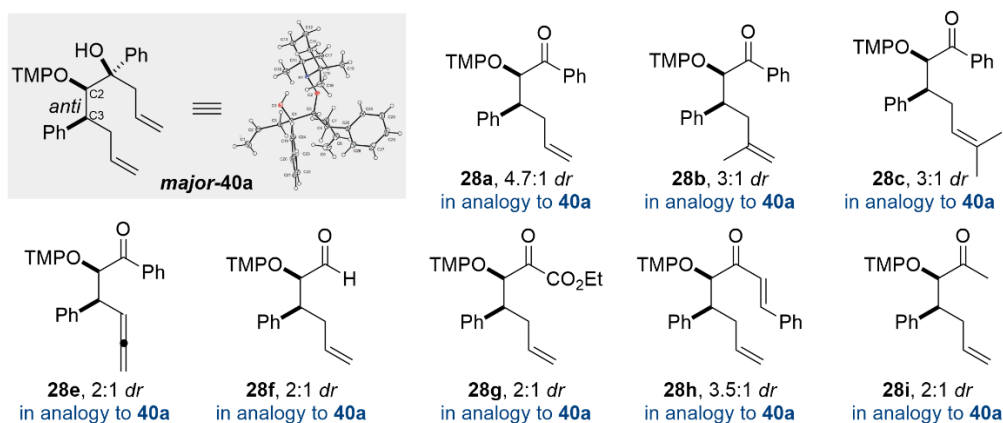
Scheme 44: Tandem nucleophilic addition/AOC/oxygenation sequence.

4.1.7. Stereochemical assignment of α -aminoxy carbonyl compounds

The AOC/oxygenation sequence results in moderate to low diastereomeric ratios of *anti/syn* α -aminoxy carbonyl compounds **28a-i,k-r,u** (Scheme 30). The low diastereoselectivity is typical for fast, radical recombination processes with near to diffusion-controlled reaction rates. The stereochemical outcome can be predicted based on a stereochemical model in which the radicals **30a-i,k-r,u** formed upon oxidation of enolates **26a-i,k-r,u** recombine from the sterically least hindered face with TEMPO (Scheme 28, *c.f.* Chapter 4.1.1). To verify this model, a thorough stereochemical analysis was performed, ensuring the unequivocal assignment of the tandem products.

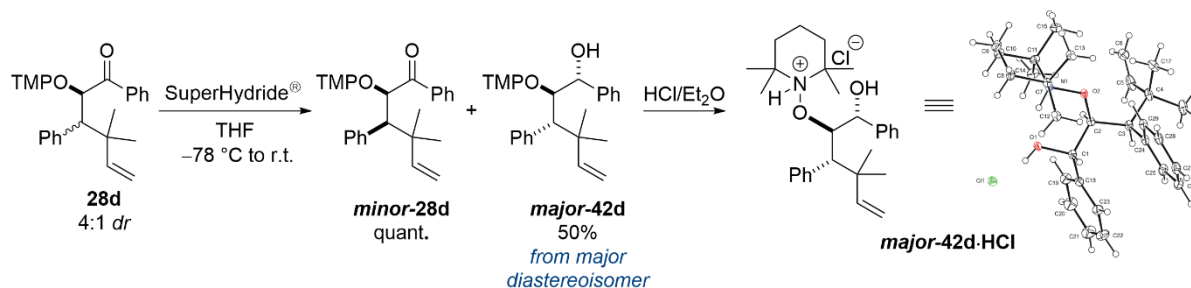
Compounds **28a-c,e-i** did not crystallize, and their assignment had to rely on derivatization. The separated major diastereoisomer of **40a** (*major-40a*) resulting from the AOC/oxygenation/allylation sequence (Scheme 39) crystallized, and its X-ray crystallographic analysis displayed a C2-C3 *anti*-configuration. This undoubtedly confirmed the configuration of the parent ketone **28a**. Furthermore, compounds **28b,c,e-i** having similar or the same allyl and phenyl C3-substitution pattern were assigned analogously to have C2-C3 *anti*-configuration of the major diastereoisomer (Figure 6).

Figure 6: Stereochemical determination of C2-C3 *anti*-configured products **28a-c,e-i**.



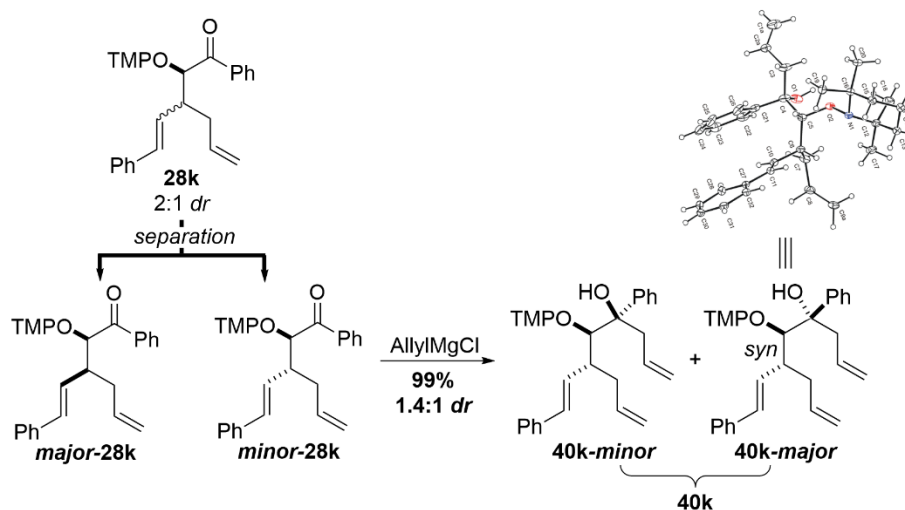
The 4:1 diastereoisomeric mixture of α -aminoxy ketone **28d** was reduced by SuperHydride[®], and only the major diastereoisomer reacted to alcohol *major-42d*, whereas the minor diastereoisomer *minor-28d* was recovered (Scheme 45). The separated alcohol *major-42d* was subsequently treated with an ethereal HCl solution, and formed salt *major-42d*·HCl was crystallized from CH₂Cl₂/hexane mixture.

X-ray crystallography showed reversed C2-C3 *syn*-configuration resulting from the radical coupling from the opposite side to the sterically hindering *gem*-dimethyl group. This unequivocally confirmed the C2-C3 *syn*-configuration for the major diastereoisomer of **28d**.



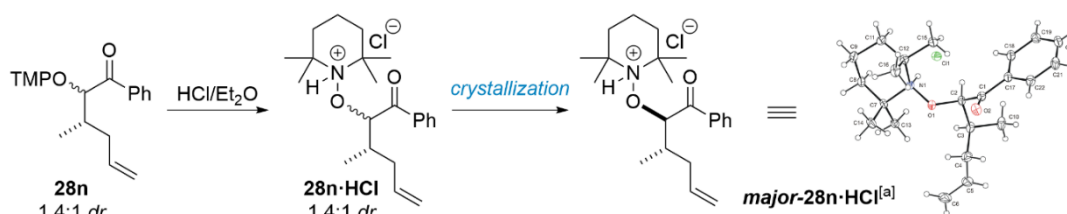
Scheme 45: Derivatization and a stereochemical assignment of α -aminoxy ketone **28d**.

For the assignment of compound **28k** its diastereoisomeric mixture was tediously separated (**Scheme 46**). The minor diastereoisomer **minor-28k** was unselectively allylated, providing separable *syn* and *anti* diols **40k-minor** and **40k-major**. The major, allylated diastereoisomer crystallized from hexane, and its X-ray crystallography revealed its *syn* C2-C3 configuration. The major diastereoisomer **major-28k** of the parent compound **28k** has, therefore, a C2-C3-*anti* configuration.



Scheme 46: Allylation and X-ray stereochemical assignment of α -aminoxy ketone **28k**.

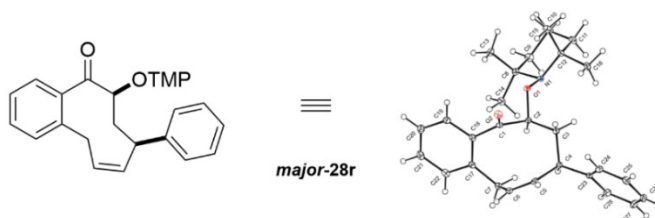
For the configuration determination of substrate **28n** its 1.4:1 diastereoisomeric mixture was treated with ethereal HCl solution (**Scheme 47**). The diastereoisomeric mixture of hydrochlorides **28n·HCl** was crystallized from CH₂Cl₂/hexane mixture, giving crystals of a single diastereoisomer, whose X-ray crystallography revealed a *syn* C2-C3 configuration. The measured single-crystal **major-28n·HCl** was further analyzed by ¹H NMR to confirm the *syn* configuration for the major diastereoisomer of **28n**.



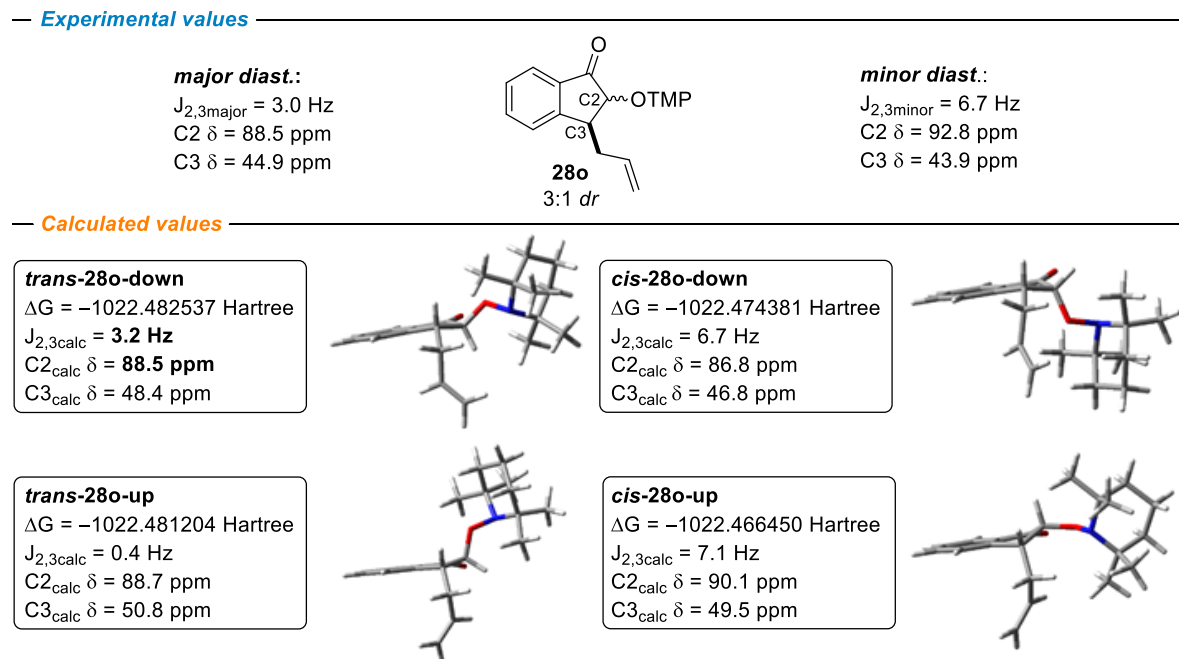
Scheme 47: Derivatization and X-ray crystallographic stereochemical assignment of α -aminoxy ketone **28n**. ^[a] Single-crystal analyzed by X-ray crystallography was remeasured by ¹H NMR to confirm the major diastereoisomer of **28n·HCl**.

The structure and configuration of the separate major crystalline diastereoisomer of **28r** (*major-28r*) were analyzed by X-ray crystallography showing the *Z*-double bond and a C2-C4 *cis* configuration of the major diastereoisomer (**Figure 7**).

Figure 7: X-ray structure of the major diastereoisomer of α -aminoxy ketone **28r**.



The ketone **28o** did not crystallize, and the NOE experiments of the major diastereoisomer showed an intense cross peak between H2-H3, implying a *cis* configuration. This configuration seemed very improbable based on the stereochemical model, suggesting TEMPO coupling from the opposite side to the residual allyl group. Therefore the geometry was optimized, using the DFT B3LYP functional with a 6-31+G(d,p) basis set in the Gaussian09 program package,^[114] and coupling constants and ¹³C NMR chemical shifts were calculated. The calculations were performed in a vacuum at 298.15 K for both diastereoisomers and their possible conformers (**Scheme 48**). The conformer *trans-28o-down* possessed the lowest Gibbs energy. The calculated coupling constant of 3.2 Hz for *trans-28o-down* is in good agreement with the experimental value of 3.0 Hz for the major diastereoisomer. Both *cis* conformers of **28o** possessed coupling constants around 7 Hz, which correspond well to the experimental value of 6.7 Hz for the minor diastereoisomer. The calculated ¹³C NMR chemical shift for C2 of *trans-28o-down* is 88.5 ppm, which agrees with the observed chemical shift of 88.5 ppm. For *cis-28o-down*, the calculated chemical shift for C2 is 86.8 ppm, deviating more strongly from the observed value of 92.8 ppm. The calculated ¹³C NMR chemical shifts for C3 differ for all diastereoisomeric conformers relatively strongly from the experimental values. The calculation results thus indicate that a *trans* configuration is more likely for the major diastereoisomer *major-28o*. Thus, it remains problematic to rely only on NOE experiments for the configuration determination of five-membered rings. In contrast, cyclic compounds **28p,q,u** were accurately assigned to have the *trans* configuration based on NOE experiments.

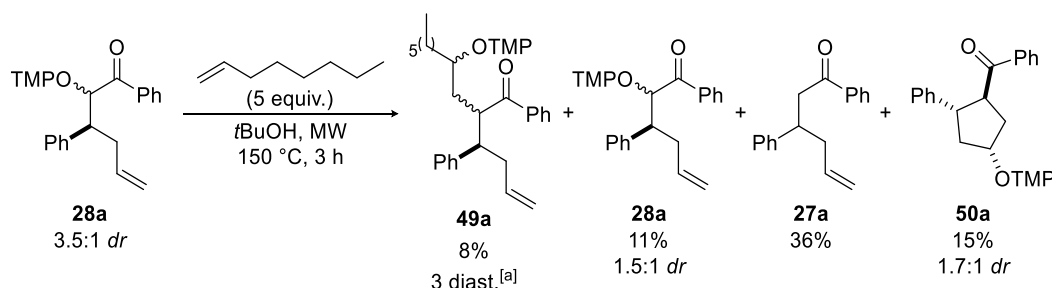


Scheme 48: Observed and calculated geometries, coupling constants, and chemical shifts for the major and minor diastereoisomer of **28o**. Calculations performed at the IOCB NMR department.

The relative configuration of compound **28m** could not be assigned because of the same polarity of *anti/syn* diastereoisomers during column chromatography and the small steric difference between allylic and homoallylic units. Various crystalline derivatives displayed crystal disorders, preventing the determination of the relative configuration.

4.2. PRE-BASED CYCLIZATIONS OF α -AMINOXY CARBONYL COMPOUNDS

Rearranged α -aminoxy carbonyl compounds **28** proved to be versatile polyfunctional compounds that can be diversified by polar reactions. However, the nature of the weak TEMPO–C bond predestines them to be engaged in radical transformations. To test their synthetic potential in intermolecular PRE-based radical additions to C=C bonds, the α -aminoxy ketone **28a** was heated to 150 °C in a microwave reactor in the presence of five equiv. of oct-1-ene (**Scheme 49**). The generated electrophilic, transient α -carbonyl radical was expected to perform the intermolecular addition with subsequent radical coupling with TEMPO based on the PRE giving ketone **49a**. Product **49a** was isolated only to a minor extent. Some starting material **28a** was recovered together with reduced product **27a** formed by a hydrogen atom transfer (HAT) from the solvent or the allylic position of octene. Surprisingly, another constituent of the reaction mixture was identified as the 5-*endo*-trig cyclized cyclopentane **50a** isolated in 15% yield. The presence of this carbocycle revealed the potential for α -aminoxy carbonyl compounds **28** to be applied in the synthesis of substituted cyclopentanes by a kinetically disfavored 5-*endo*-trig cyclization mode.



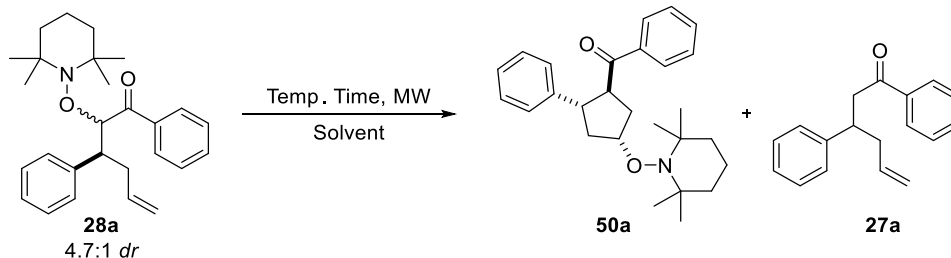
Scheme 49: Intermolecular PRE-based addition of **28a** to a C=C bond of octene. ^[a] Indecipherable ratio from ¹H NMR.

4.2.1. Optimization of the PRE-based 5-*endo*-trig radical cyclization

The PRE-based 5-*endo*-trig cyclization of α -aminoxy ketone **28a** was optimized in terms of solvent, temperature, and reaction time (**Table 6**). Trifluorotoluene, an inert solvent suitable for radical reactions and microwave irradiation in a sealed tube, allowing the heating above the boiling point, was used. Gradual increase of the reaction temperature (entries 1-7) showed that the reaction reaches synthetically applicable rates above 130 °C, where α -aminoxy ketone **28a** entirely converted within a reasonable reaction time. Noteworthy, the diastereoisomeric ratio slightly improved with increasing temperature. Heating to 150 °C in PhCF₃ for 45 min proved optimal, and the product **50a** was isolated in 81% isolated yield together with 9% of reduced product **27a** whose formation could not be prevented (entry 6). The origin of the hydrogen atom necessary for the reduction of the α -carbonyl radical is not known. However, it is hypothesized that it may arise from another molecule of the substrate, as indicates the ratio between the mass balance, isolated yield of product **50a**, and the reduced product **27a**. Other inert solvents frequently applied in radical transformations can be used as well. Chlorobenzene gave

the product in comparable yield but with a slightly decreased diastereoisomeric ratio (entry 8). The reaction in *t*BuOH was not as clean as in PhCF₃, resulting in a lower isolated yield of the product **50a** (entry 9).

Table 6: Optimization of the PRE-based 5-*endo*-trig radical cyclization of alkoxyamine **28a**.

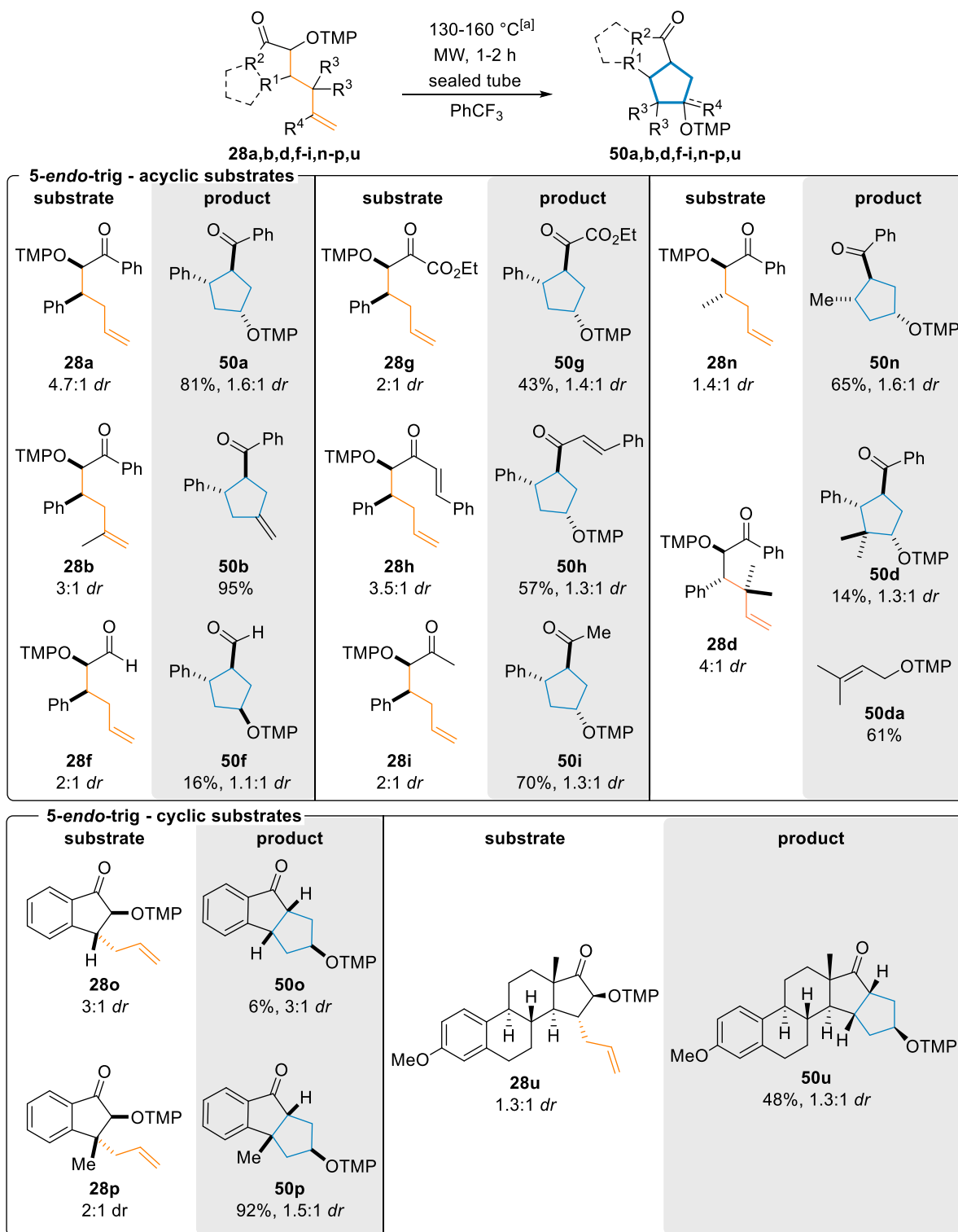


Entry	Solvent	Temp (°C)	Time (h)	Conversion (%) ^[a]	28a (%) ^[b]	50a (%)	50a <i>dr</i> ^[a]	27a (%)
1	PhCF ₃	100	15	46	54	10	1.3:1	n.d. ^[c]
2	PhCF ₃	110	15	73	27	36	1.3:1	14
3	PhCF ₃	120	15	95	5	57	1.5:1	13
4	PhCF ₃	130	6	100	0	74	1.6:1	10
5	PhCF ₃	140	1	100	0	76	1.6:1	9
6	PhCF₃	150	0.75	100	0	81	1.6:1	9
7	PhCF ₃	160	0.5	100	0	80	1.6:1	9
8	PhCl	140	1.25	100	0	76	1.3:1	10
9	<i>t</i> BuOH	140	1	100	0	70	1.6:1	7

^[a] Determined by ¹H NMR spectroscopy of the crude reaction mixture after evaporation of the solvent. ^[b] Recovered starting material. ^[c] Not determined.

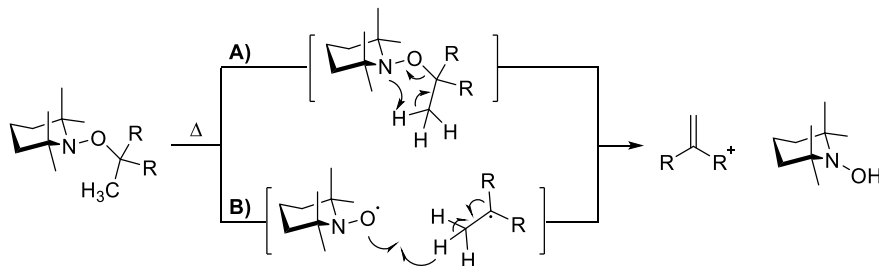
4.2.2. Substrate scope of the 5-*endo*-trig radical cyclization

To test the functional group compatibility, competing cyclization modes, and substitution-based cyclization aptitudes, the substrate scope was performed. The diastereoisomeric mixtures of α -aminoxy carbonyl compounds **28**, resulting from the AOC/oxygenation sequence, were submitted to the optimized cyclization conditions with variable reaction temperatures and times (**Scheme 50**).



Scheme 50: Substrate scope of the PRE-based 5-*endo*-trig radical cyclization of α -aminoxy carbonyls **28**. ^[a] The precise temperature used is stated at the individual compound in the experimental part.

The cyclization of methallylated derivative **28b** was facilitated by the additional radical-stabilizing methyl group and proceeded efficiently, giving a high yield of cyclopentane **50b** (Scheme 50). However, the formation of a tertiary TEMPO adduct resulted in a spontaneous elimination of TEMPOH, forming an exocyclic methylene group. This elimination proceeds at hindered positions either by polar mechanism (A, Scheme 51) or through a hydrogen atom abstraction pathway (B, Scheme 51). Noteworthy, in some cases, tertiary TEMPO-adducts are stable at low temperatures and isolable.^[72g]



Scheme 51: Mechanism of thermal TEMPOH elimination from sterically hindered positions.

The cyclization of aldehyde **28f** afforded a low yield of the cyclopentyl carboxaldehyde **50f**. The substitution of the carbonyl group by an ethyl carboxylate, styryl, or methyl group in **28g**, **28h**, and **28i** respectively did not affect the cyclization, and good yields of products **50g**, **50h**, and **50i** were obtained. An aliphatic methyl group at the cyclizing skeleton in **28n** was tolerated, and the cyclization proceeded smoothly, giving the cyclopentane derivative **50n** in good yield.

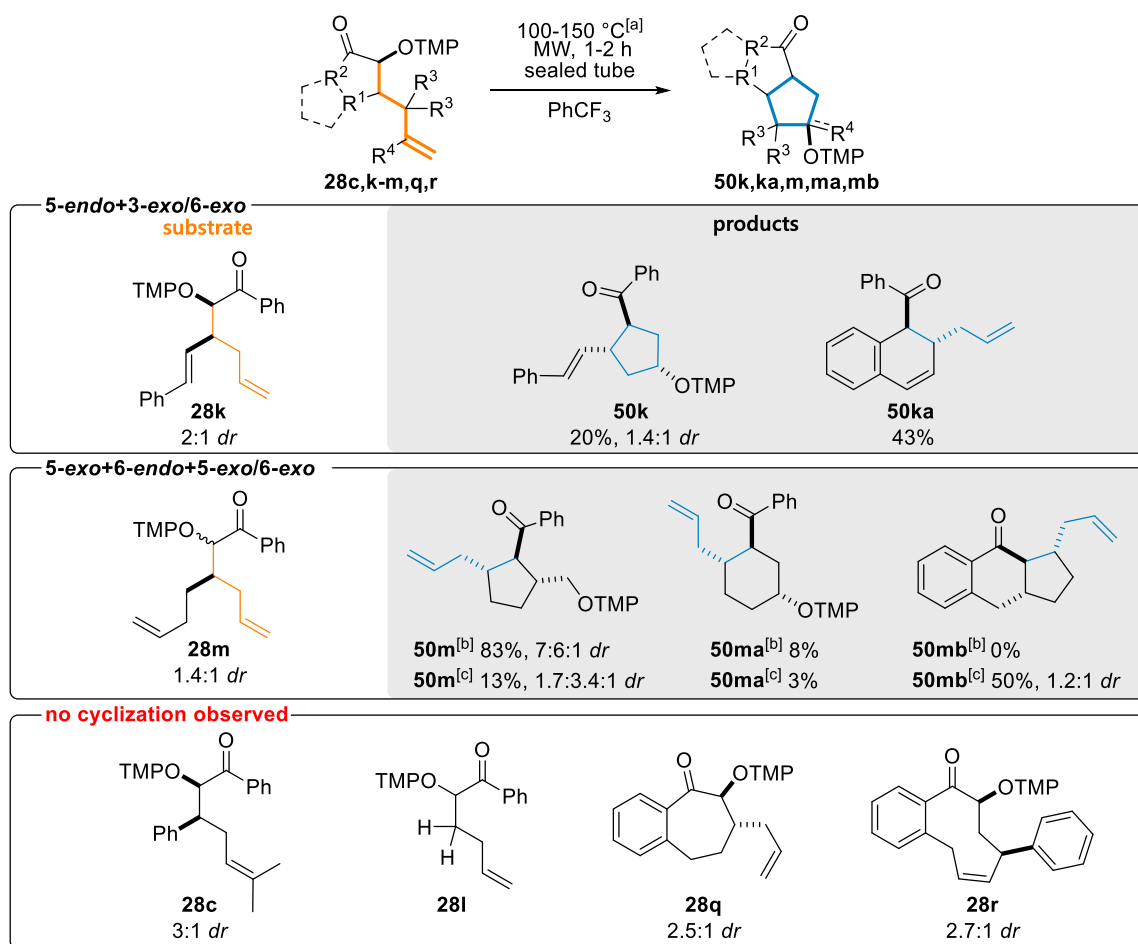
The cyclization of **28d** was expected to proceed well because of the Thorpe-Ingold effect caused by the two geminal methyl substituents.^[115] However, only a low yield of cyclopentane **50d** was obtained. β -Fragmentation was the dominant reaction pathway resulting in the formation of prenyl TEMPO **50da**.

The indanone derivative **28o**, prone to TEMPOH elimination, underwent further side reactions giving the cyclic product **50o** in a meager yield (Scheme 50). On the other hand, the exchange of the C-3 hydrogen by a methyl group in **28p** led to very clean cyclization giving the condensed cyclopentane **50p** in an excellent yield. The estrone derivative **28u** efficiently cyclized in a 5-*endo*-trig fashion furnishing the steroid **50u** with an additional condensed E-ring in moderate yield.

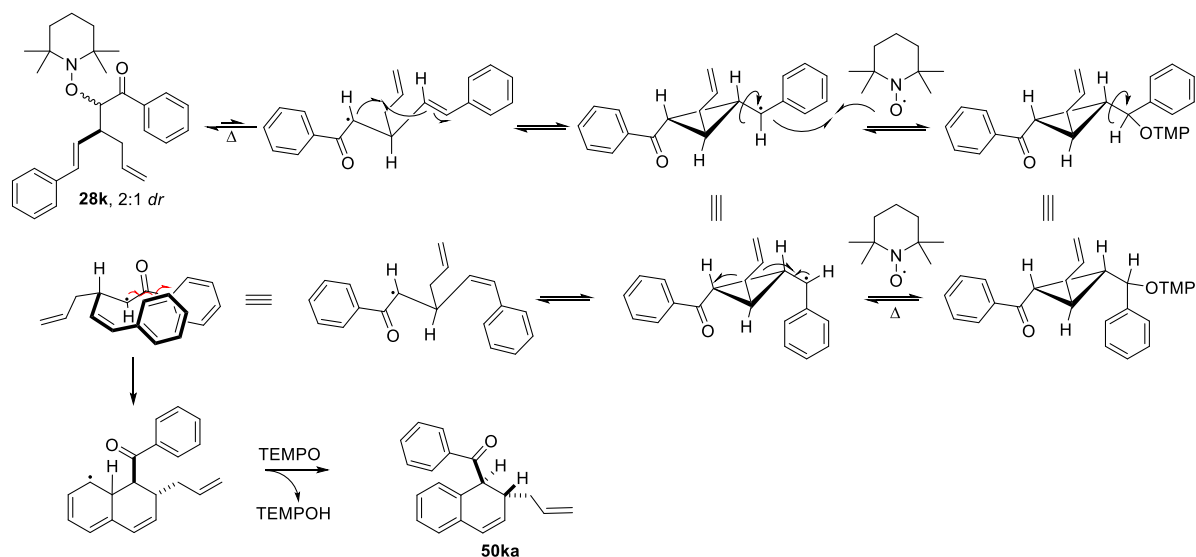
The reaction mixtures of 5-*endo*-trig cyclized products **50** were in some cases complex, containing uncyclized alkenes as byproducts poorly chromatographically separable from the desired cyclopentanes. In such cases, the Upjohn dihydroxylation after the cyclization step was performed. All acyclic alkene-containing byproducts were dihydroxylated, thus increasing their polarity and facilitating the column chromatography purification.

4.2.3. Deviations from the 5-endo-trig cyclization mode

Substrates **28c,k-m,q,r** showed deviations from the standard reactivity that deserve additional comments (Scheme 52). Alkoxyamine **28k** cyclized to cyclopentane **50k** only in a low yield. The dominant reaction pathway turned out to be a 6-*exo*-trig cyclization with the styrenic phenyl ring. However, this reaction is geometrically not possible because of the *E* double bond configuration. For this reason, we hypothesize that a 3-*exo*-trig cyclization leading to benzylic radical occurs at the first stage (Scheme 53). The benzylic radical can either rotate the neighboring σ -bond or recombine with TEMPO and rotate subsequently. Both cases, nevertheless, lead to cyclopropane ring opening forming the starting material with *Z* double bond configuration. At this stage, the 6-*exo*-trig pathway is feasible. The cyclized radical aromatizes, giving dihydronaphthalene derivative **50ka** in a moderate yield.



Scheme 52: Substrate scope of the PRE-based thermal cyclization of alkoxy ketones **28**. ^[a] The precise temperature used is stated at the individual compound in the experimental part. ^[b] 50 mol% of TEMPO as an additive. ^[c] 100 mol% of ascorbic acid as an additive.

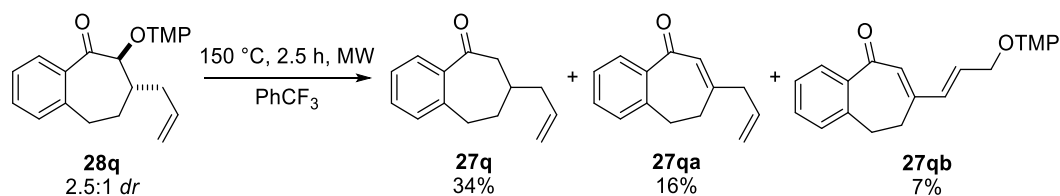


Scheme 53: 3-Exo-trig/cyclopropane opening/6-exo-trig cyclization pathway of the substrate **28k**.

The substrate **28m** offers competitive 5-*exo*/6-*endo* or 5-*endo* cyclization modes. Expectedly, the faster 5-*exo* and 6-*endo* outperformed the kinetically much slower 5-*endo* cyclization mode that was not observed. The heating of substrate **28m** to 100 °C in PhCF₃ furnished a high yield of a 7:6:1 diastereoisomeric mixture of 5-*exo* cyclized cyclopentanes **50m** and a single diastereoisomer of cyclohexane **50ma** (for stereochemical determination cf. [Chapter 4.2.5](#)). Interestingly, the product of 5-*exo*/6-*exo* double-cyclization with the aromatic ring **50mb** was also isolated from the reaction mixture.

Adding 50 mol% TEMPO into the reaction mixture increased the rate of the ultimate radical coupling, preventing the formation of **50mb**. Under such conditions, the cyclopentane **50m** was obtained in 83% yield together with cyclohexane **50ma** in 8% yield. On the other hand, the addition of one equiv. ascorbic acid, capable of TEMPO-reduction, prevented the TEMPO-coupling and diminished the formation of cyclopentane **50m** to 13% and cyclohexane **50ma** to 3%. The double cyclized product **50mb** was isolated in this case in 50% yield as a mixture of 2 diastereoisomers. These results show that the selectivity toward the desired product can be tuned by reaction conditions.

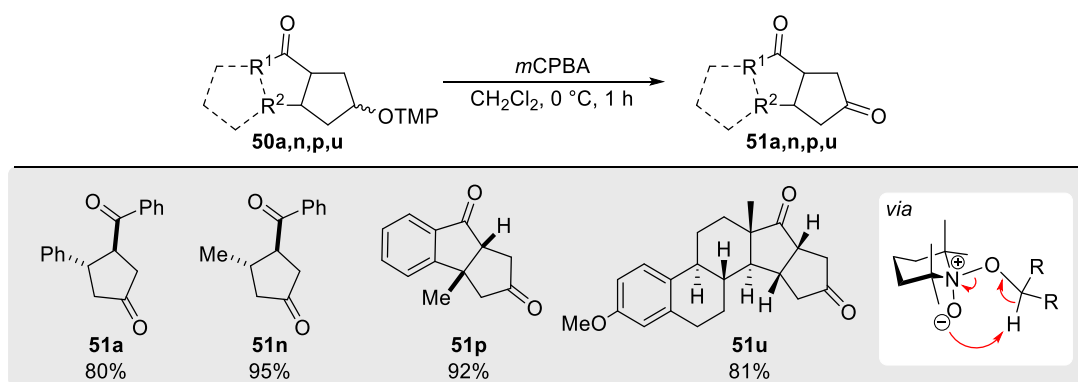
Substrates **28c**, **l**, **q**, **r**, did not provide any cyclic products. Prenyl substituted α -aminoxy ketone **28c** fragmented similarly to substrate **28d**, and only a TEMPO-coupled prenyl radical **50da** was obtained. Unsubstituted substrate **28l** having a high degree of rotational freedom resulted in a complex reaction mixture with no identifiable product. The benzosuberone derivative **28q** with apparently a high-energy transition state for the 5-*endo* cyclization disproportionated upon heating, giving reduced product **27q**, an enone **27qa**, and an unsaturated TEMPO adduct **27qb** (**Scheme 54**). The 9-membered α -aminoxy ketone **28r**, capable of a transannular cyclization, upon heating partially shifted the internal double bond into conjugation with the benzo ring. Subsequent radical cyclizations led to an indecipherable mixture of products.



Scheme 54: A disproportionation pathway during an attempted cyclization of the benzosuberone derivative **28q**.

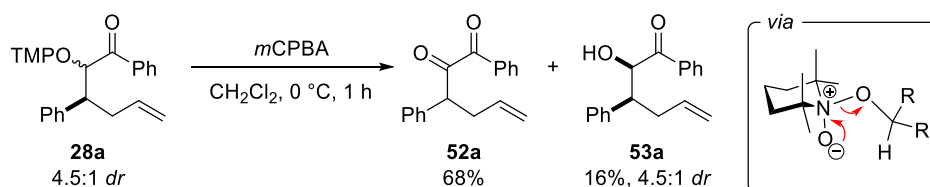
4.2.4. Oxidation of the aminoxy unit

The low diastereoisomeric ratio of 5-*endo*-trig cyclized cyclopentanes **50**, resulting from unselective TEMPO coupling, can be corrected by oxidation of the OTMP group by *m*CPBA resulting in a single diastereoisomer of diones **51**. This was demonstrated for diastereoisomeric mixtures of carbocycles **50a,n,p,u** that upon oxidation provided high yields of diones **51a,n,p,u** (Scheme 55). Mechanistically, the aminoxy unit is oxidized to an *N*-oxide removing the α -proton and eliminating in the form of TEMPOH.



Scheme 55: Oxidative convergence of substituted cyclopentanes into a single diastereoisomer of dione.

Similarly, the α -aminoxy ketone **28a** was converted by treating with *m*CPBA to the α -diketone **52a** in a good isolated yield (Scheme 56). Interestingly, a small amount of the ketol **53a** was isolated in an unchanged diastereoisomeric ratio as well. The ketol is likely formed by the elimination of an oxoammonium salt and protonation of the alkoxide by chlorobenzoic acid.

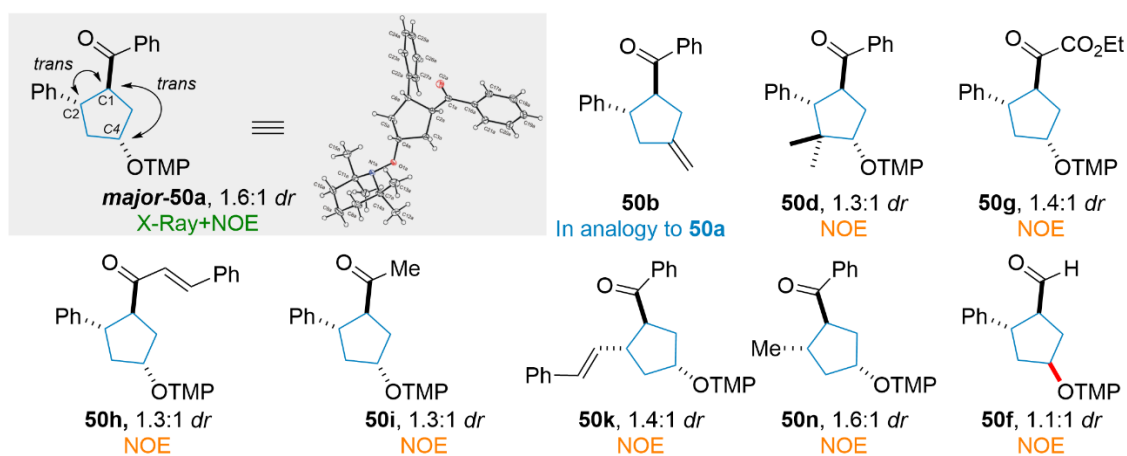


Scheme 56: Oxidation of α -aminoxy ketone **28a** to α -dione.

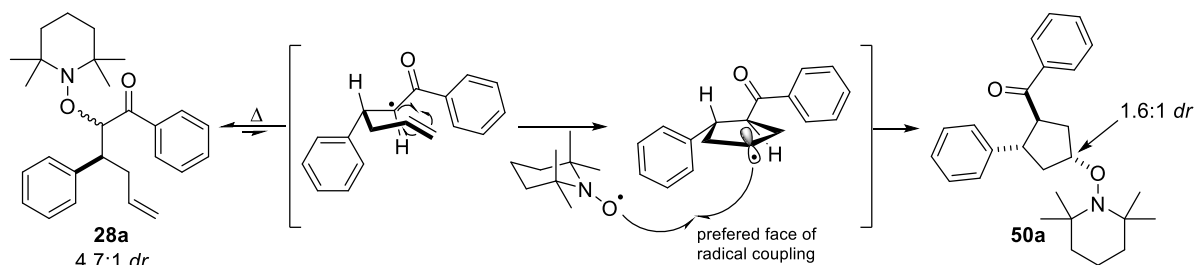
4.2.5. Stereochemical assignment of cyclic products

The relative configuration of the separated major diastereoisomer of cyclopentane **50a** (*major-50a*) was determined by NOE experiments and further verified by X-ray crystallography. The analysis showed the C1-C2 *trans* and C1-C4 *trans* configurations for the major diastereoisomer (**Figure 8**). The stereochemistry of the minor diastereoisomer follows the same trend at C1-C2 and reverses for C1-C4. The NOE experiments of substrates **50b,d,g-i,k,n** showed the same stereochemical pattern except for compound **50f** where the configuration at C4 for the major diastereoisomer reverses as a result of sterically less demanding formyl group in comparison to the neighboring phenyl.

Figure 8: Configuration assignment of the major diastereoisomers of cyclopentanes **50a,b,d,f-i,k,n** formed by PRE-based 5-*endo*-trig cyclization.



From the obtained data, a stereochemical model for the 5-*endo*-trig cyclization of substrates **28** leading to substituted cyclopentanes **50** can be devised (**Scheme 57**). Residing substituents of the pent-4-enyl radical orient in a pseudo-equatorial position of the envelope-like transition state. TEMPO couples with the newly formed secondary radical from the sterically less-hindered face. However, the low steric difference between the residing substituents causes poor selectivity.

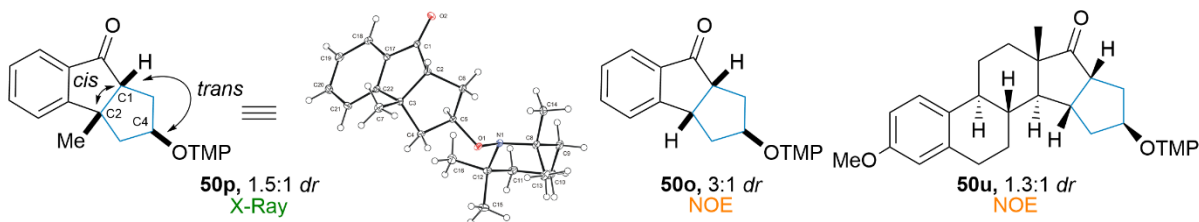


Scheme 57: Stereochemical rationale of the 5-*endo*-trig radical cyclization of **28a** leading to cyclopentane **50a**.

The major diastereoisomer of the indanone derivative **50p** was crystallized from *i*PrOH, and its relative configuration was analyzed by X-ray crystallography showing a C1-C2 *cis* and C1-C4 *trans* configuration (**Figure 9**). The indanone and estrone derivatives **50o** and **50u** were investigated by NOE

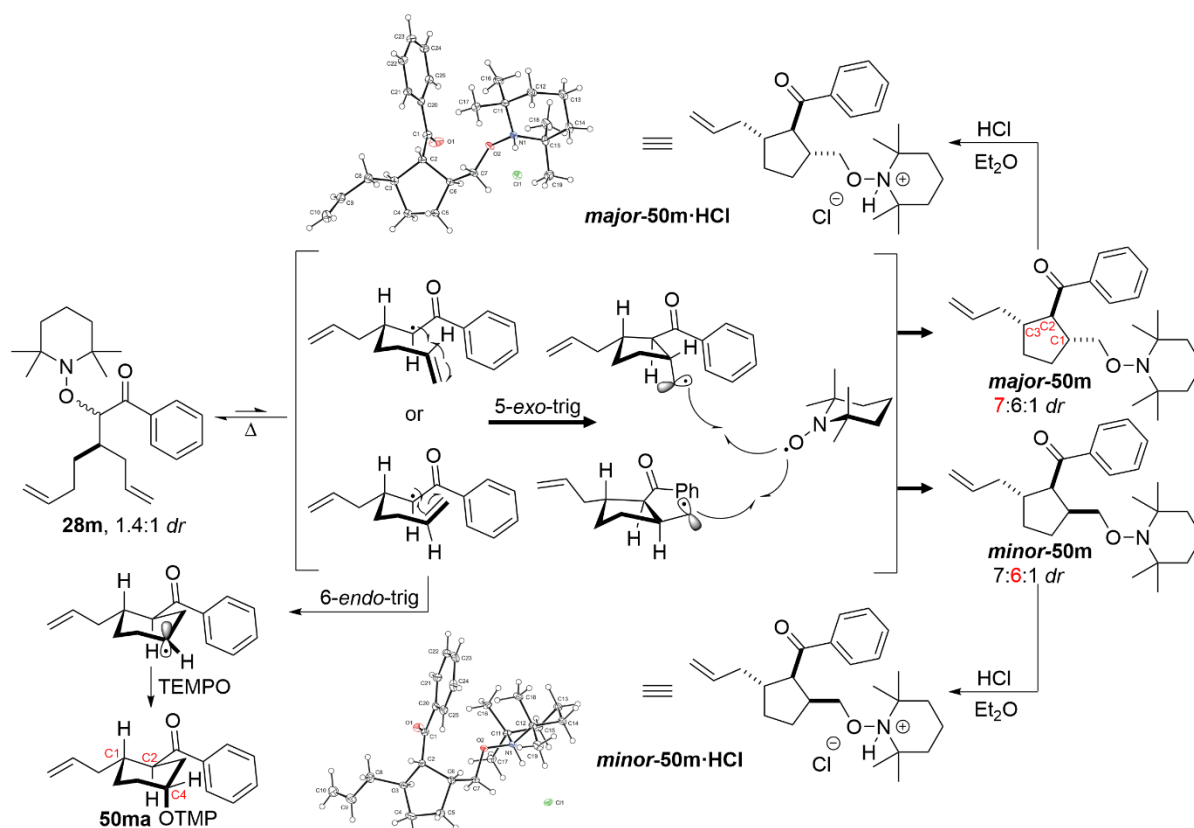
experiments, and the stereochemistry was analogous to substrate **50p** displaying C1-C2 *cis* and C1-C4 *trans* relationships for the major diastereoisomer. The minor diastereoisomer has, as in the previous cases, reversed configuration at C4.

Figure 9: Configuration assignment of carbocycles **50o,p,u** formed by PRE-based 5-*endo*-trig cyclization.



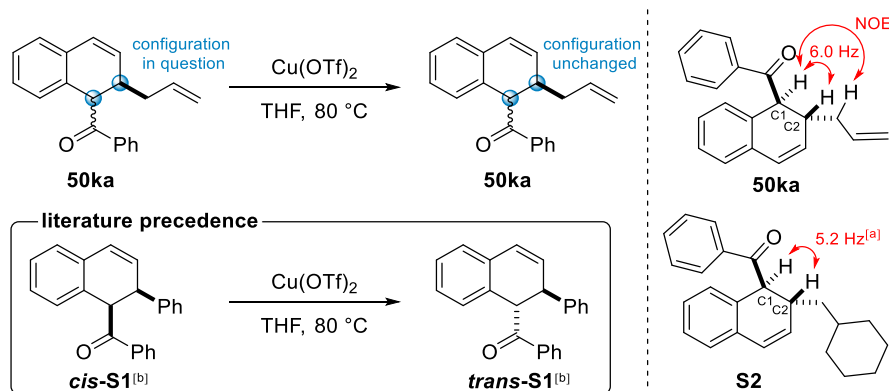
The NOE analysis of the 5-*exo*-trig cyclized cyclopentanes **50m** was unreliable because of the close spatial proximity on the cyclopentane rings. For this reason, both diastereoisomers *major-50m* and *minor-50m* were tediously separated by multiple column chromatography and converted by treating with HCl to their corresponding hydrochlorides *major-50m*·HCl and *minor-50m*·HCl (Scheme 58). The major diastereoisomer crystallized from THF and the minor from a CH₂Cl₂/hexane mixture. The X-ray analysis of *major-50m*·HCl showed a C1-C2 *trans* and C2-C3 *trans* configuration, whereas *minor-50m*·HCl displayed a C1-C2 *cis*, C2-C3 *trans* configuration. This configuration can be rationalized based on the Beckwith-Houk transition state model (Scheme 58),^[95] in which the reacting conformer typically adopts a chair-like transition state orienting the reacting double bond into a pseudo-equatorial orientation. However, under the thermal conditions, the chair- and boat-like transition states are very similar in energy, and a 1.2:1 mixture of 1,2-*trans*/2,3-*trans* and 1,2-*cis*/2,3-*trans* diastereoisomers is produced. The least abundant diastereoisomer of **50m** was not analyzed but most likely has the C1-C2 *trans*, C2-C3 *cis* configuration as the radical formation of the *all-cis* stereoisomer is not likely.

Both diastereoisomers of the tricyclic products **50mb** formed by a double 5-*exo*/6-*exo* cyclization were assigned in analogy to cyclopentanes **50m**, as they originated from the same radical precursor and were isolated in identical diastereoisomeric ratio. The co-formed cyclohexane derivative **50ma** was analyzed by NOE experiments and showed a C1-C2 *trans* and C1-C4 *cis* configuration that was in agreement with the observed coupling-constants suggesting that cyclohexane adopts a chair conformation orienting TEMPO into an axial position and allyl and benzoyl groups equatorially (Scheme 58).



Scheme 58: Stereochemical rationale of the 5-*exo*-trig radical cyclization leading to cyclopentanes **50m** and the way of its stereochemical determination.

The assignment of the dihydronaphthalene derivative **50ka** was difficult. NOE contacts between H1 and H2 were not conclusive since geometry optimization showed that both diastereoisomers would exhibit NOE contacts. Calculations of the coupling constants and chemical shifts were also not definitive. An epimerization experiment of **50ka** with Cu(OTf)₂ based on literature precedence,^[116] where a similar *cis* isomer of dihydronaphthalene *cis*-**S1** was isomerized to *trans*-**S1**, did not lead to a change in the configuration (**Scheme 59**). Therefore, it is concluded that the *trans* isomer is formed by 6-*exo* radical cyclization. This assignment is further strengthened by comparing the ¹H NMR data of **50ka** with the *trans* diastereoisomer of the literature-known dihydronaphthalene derivative **S2** (**Scheme 59**).^[117] The 5.2 Hz H1–H2 coupling constant of **S2** agrees with the 6.0 Hz value of **50ka**. Furthermore, a weak H1–CH₂^{allyl} NOE contact of **50ka** supports the *trans* configuration assignment.



Scheme 59: Epimerization experiment and coupling constant comparison of dihydronaphthalene **50ka**. ^[a] The H1–H2 coupling constant of the *cis* diastereoisomer of **S2** is not available. ^[b] The H1–H2 coupling constant is not available.

4.3. DIVERGENT TOTAL SYNTHESIS OF *GANODERMA* MEROTERPENOIDS

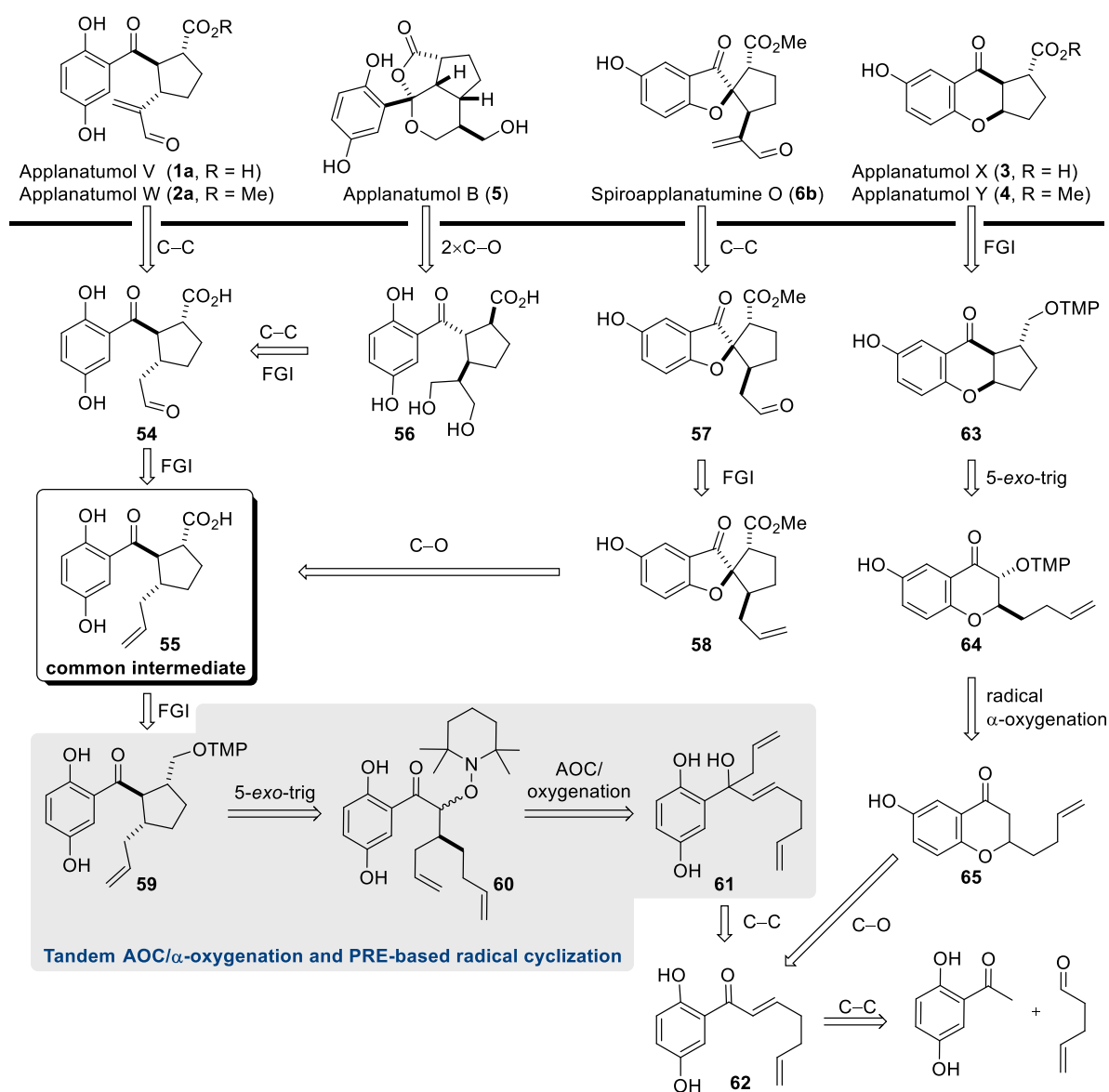
4.3.1. Retrosynthetic analysis

Applanatumols V (**1a**) and W (**2a**) consist of a 1,2,3-trisubstituted cyclopentane ring with a 2',5'-dihydroxylated phenone unit in position 2. In applanatumol B (**5**), the phenone moiety is ketalized into a tricyclic, bridged, dioxacyclopenta[cd]indene system. In the spiroapplanatamine family represented by spiroapplanatamine O (**6b**), the *ortho*-phenolic oxygen closes a spiroether with position 2 of the carbocycle. Structurally similar applanatumols X (**3**) and Y (**4**) consist of a chromanone motif that, compared to the previous meroterpenoids, lacks the three-carbon substitution at position C3 of the cyclopentane ring.

The structural similarities between those *Ganoderma* meroterpenoids motivated to develop a divergent synthetic approach sharing a common synthetic intermediate applicable for all mentioned natural products. The carbocyclic skeleton of such intermediate was planned to originate from the tandem AOC/ α -oxygenation sequence and PRE-based radical cyclization.

The retrosynthetic analysis (**Scheme 60**) revealed that applanatumols V, W can be traced by C–C bond cleavage to the aldehyde **54** and further by functional group interconversion (FGI) to central cyclopentane-carboxylate **55** serving as the common synthetic intermediate.

The fundamental disconnection of the ketal function in applanatumol B (**5**) leads to the diol **56** and further to the abovementioned aldehyde **54**, showing the synthetic link between those meroterpenoids.



Scheme 60: Retrosynthetic analysis of meroterpenoids **1-6** from *Ganoderma applanatum*.

Analogously spiroapplanatumine O (**6b**) could be traced by C–C bond cleavage and FGI to spirocycle **58**. The disconnection of the C–O spiroether bond of **58** leads to the central cyclopentane carboxylate **55**, synthetically linking those compound classes.

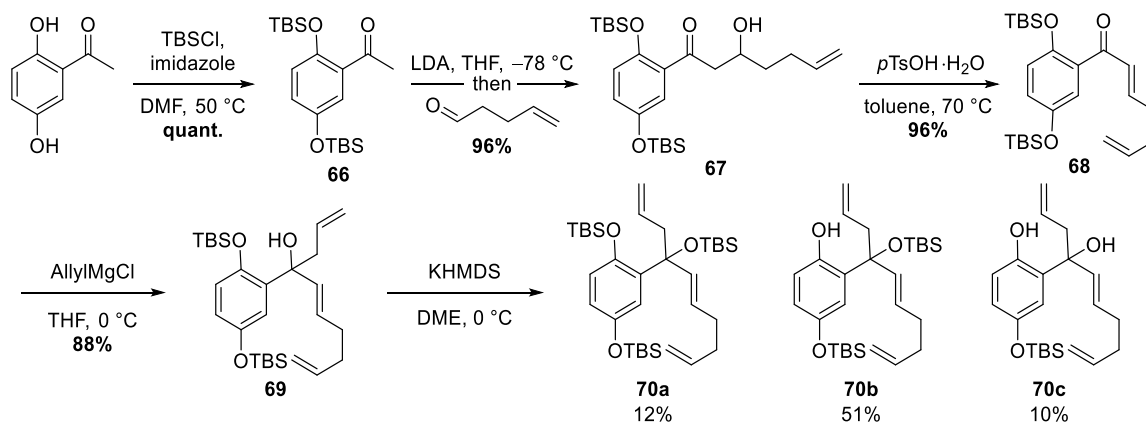
Scission of the cyclopentane core of the intermediate **55** results in α -aminoxy ketone **60**, invoking a radical 5-*exo-trig* cyclization as the key step. This synthetic intermediate retrosynthetically provides aryl carbinol **61** by the developed tandem AOC/ α -oxygenation sequence and further α,β -unsaturated ketone **62** traceable to commercially available 2',5'-dihydroxyacetophenone, and pent-4-enal as available starting materials.

The five-membered ring in applanatumols X (**3**) and Y (**4**) can be similarly envisaged on the basis of a radical 5-*exo*-trig cyclization reaction, whereas the chromanone unit **65** can be disconnected by the retro-oxa-Michael reaction to aldol condensation product **62**, making the ultimate synthetic connection between depicted meroterpenoid compound classes.

4.3.2. Preparation of the common synthetic intermediate

Free phenolic hydroxyls are considered problematic because of their acidity. Therefore, the initial part of the projected total synthesis campaign was to determine the optimal protecting group for the 2',5'-dihydroxyphenone moiety. The deprotection is planned at the ultimate stage, and a deprotection strategy compatible with sensitive enal or ketal functions must be developed. A *tert*-butyldimethylsilyl (TBS) group is reasonably stable under acidic and basic conditions and relatively mildly deprotected by several methods, predominately by fluoride anions. Their risk, however, lies in silyl transfer reactions. Benzyl protecting groups are typically stable under basic conditions and can be cleaved reductively or by Lewis acids. Their risk may lie in hydrogen atom abstraction from the activated benzylic position during radical transformations.

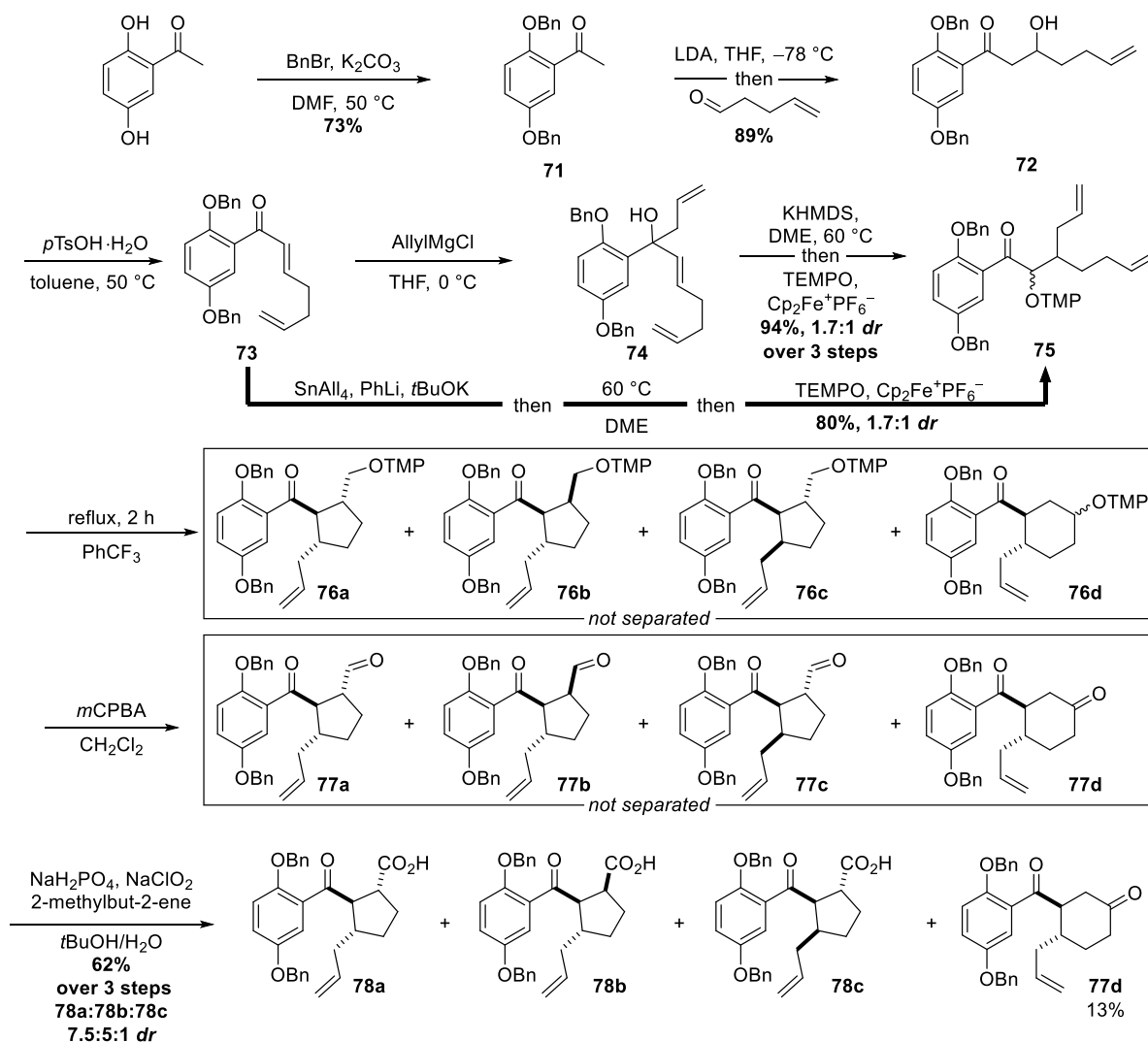
2',5'-Dihydroxyacetophenone was initially silylated by TBSCl, giving the diprotected ketone **66** (**Scheme 61**). Enolization with *in situ* prepared LDA and subsequent aldol condensation with pent-4-enal efficiently provided the aldol product **67** that was smoothly dehydrated to the α,β -unsaturated ketone **68**. Allylation by allylmgCl generated a magnesium alkoxide that, after aqueous workup, provided carbinol **69**, without any silyl transfer observed. However, the subsequent deprotonation by KHMDS at 0 °C, giving a loose ion-pair, immediately induced silyl transfer reactions, forming compounds **70a**, **70b**, and **70c** that prohibited further synthetic attempts.



Scheme 61: Initial synthetic steps using TBS protecting groups.

The subsequent synthetic endeavor was undertaken with benzyl protecting groups (**Scheme 62**). Analogously, 2',5'-dihydroxyacetophenone was treated with benzyl bromide, giving 2',5'-dibenzloxyacetophenone **71** that smoothly condensed with pent-4-enal providing β -hydroxy ketone

72 in high yield. The aldol product was cleanly dehydrated to α,β -unsaturated ketone **73**, and further subjected to allylation by Grignard reagent providing tertiary alcohol **74** without the need for column chromatography purification. The deprotonation of alcohol **74** by KHMDS and heating to 60 °C for an hour smoothly promoted the AOC rearrangement; subsequent SET oxidation and radical α -oxygenation by TEMPO provided an excellent yield of the rearranged α -aminoxy ketone **75**. Noteworthy, a potential competing 1,6-hydrogen atom abstraction from the activated benzylic position was not observed. In order to increase the synthetic efficiency and reduce the step count, the tandem nucleophilic addition/AOC/oxygenation sequence was realized. Tetraallyltin was transmetalated by phenyl lithium and further by *t*BuOK producing allyl potassium that was added to α,β -unsaturated ketone **73**. Heating to 60 °C promoted the AOC rearrangement, and the generated potassium enolate was oxygenated by the standard procedure, providing the α -aminoxy ketone **75** in 80% isolated yield as a 1.7:1 diastereoisomeric mixture.

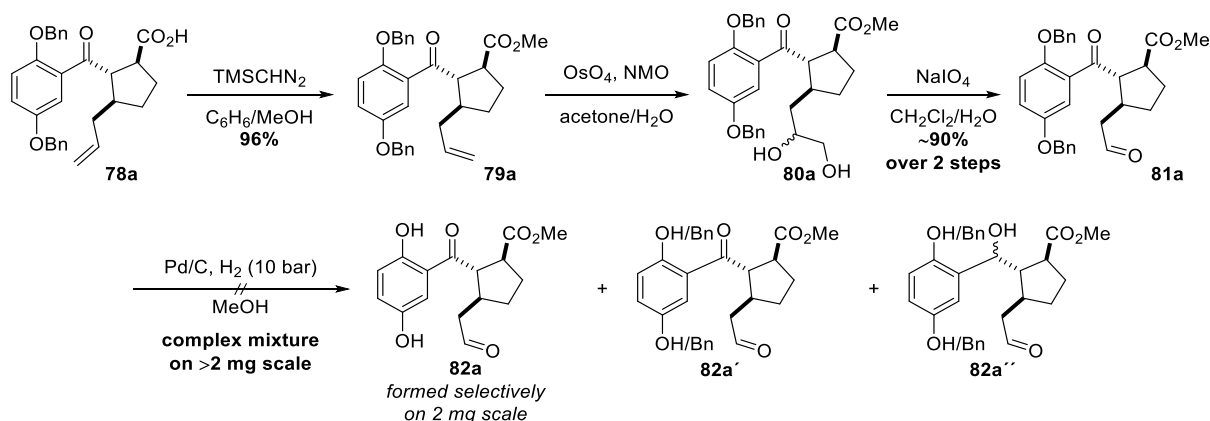


Scheme 62: Synthesis of the common synthetic intermediates **78**.

The cyclization precursor **75** was refluxed in PhCF₃ for two hours, inducing a thermal radical cyclization resulting in a 7.5:5:1 diastereoisomeric mixture of 5-*exo*-trig cyclized cyclopentanes **76a,b,c** together with two diastereoisomers of the 6-*endo*-trig cyclization products **76d** in a 1.2:1 diastereoisomeric ratio. The mixture was not separable, thus prohibiting the isolated yield determination at this stage. Therefore, the crude cyclized mixture was oxidized by *m*CPBA to a diastereoisomeric mixture of corresponding aldehydes **77a,b,c**, and ketone **77d**. Because of the typical aldehyde lability, the mixture was not separated but further converted by the Pinnick oxidation to the corresponding cyclopentane carboxylic acids **78a,b,c** in total 62% yield over three steps as a partially separable 7.5:5:1 diastereoisomeric mixture accompanied by 13% of ketone **77d** formed by the oxidation of cyclohexanes **76d**. The stereochemical outcome of the radical cyclization could be improved by the introduction of an epimerization step at the stage of aldehydes **77a,b,c** by DBU. The overall reaction sequence, in this case, provided carboxylic acids **78a,b,c** in 56% yield as a 10:1.5:1 diastereoisomeric ratio (not shown). The stereochemical analysis of the formed products proved the *1,2-trans/2,3-trans* relative configuration for the major diastereoisomer **78a**, *1,2-cis/2,3-trans* configuration for the minor diastereoisomer **78b**, and *1,2-trans/2,3-cis* for the least abundant diastereoisomer **78c** (cf. [Chapter 4.3.3.1](#)). The separated major *1,2-trans/2,3-trans*-diastereoisomer **78a**, prepared in 7 steps, represents the common intermediate for further elaboration towards applanatumols and spiroapplanatumines.

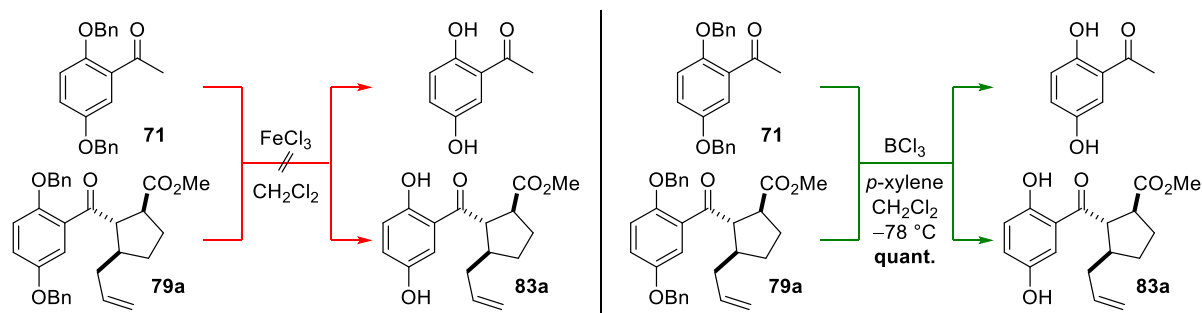
4.3.3. Synthesis of applanatumols V and W

With the *1,2-trans/2,3-trans* diastereoisomer **78a** in hand, the first approach towards applanatumol W was performed (**Scheme 63**). The carboxylic acid **78a** was converted into methyl ester **79a** by treatment with TMSCHN₂ in a MeOH/benzene mixture.^[118] Interestingly, if methanol as a co-solvent was omitted, a mixture of the trimethylsilylmethyl and methyl ester was obtained. The alkene unit of ester **79a** was dihydroxylated to diol **80a** and oxidatively cleaved by NaIO₄ into the aldehyde **81a** in a two-step procedure. The removal of both benzyl groups was attempted by hydrogenolysis on 10% Pd/C before introducing the reducible methylene unit. On a low milligram scale, under 10 bars of H₂, both the benzyl groups were successfully reduced, giving the free hydroquinone **82a**; however, repetition on a larger scale resulted in a complex mixture of partially deprotected phenols **82a'**, together with reduced phenones **82a''**. The risk of phenone reduction and poor reproducibility of this deprotection method led to the investigation of other, reliable deprotection methods.



Scheme 63: Initial attempts toward the synthesis of applanatumol W.

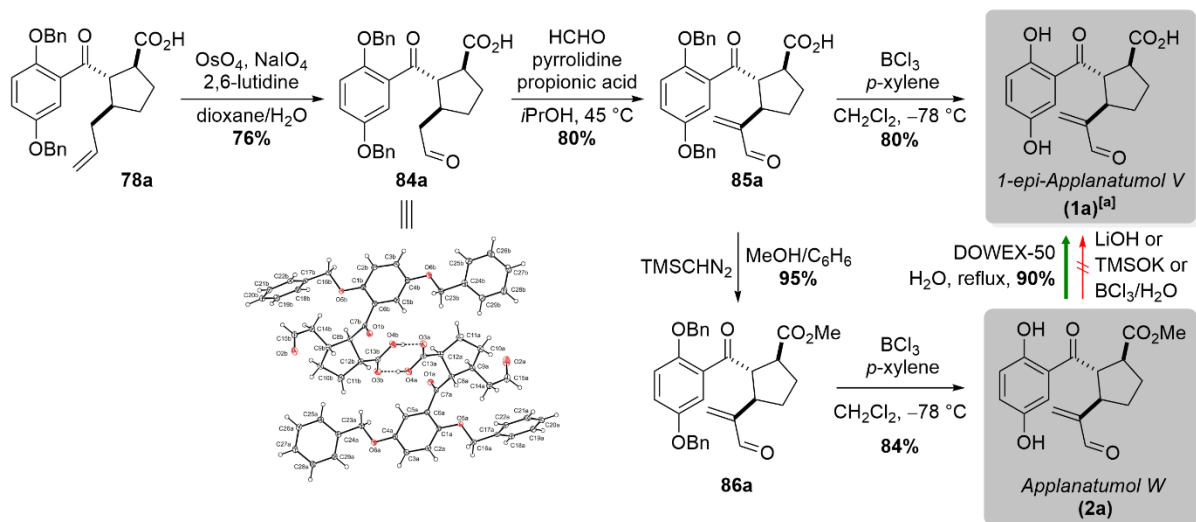
Literature-based deprotection by FeCl_3 in CH_2Cl_2 performed on model substrates **71** and **79a** resulted in complex reaction mixtures (**Scheme 64**).^[119] To our delight, treatment of substrates **71** and **79a** by BCl_3 in the presence of a cation scavenger *p*-xylene at -78°C cleanly provided both the deprotected acetophenone and cyclopentane **83a**.^[120]



Scheme 64: Deprotection of phenolic benzyl groups by Lewis acids.

With an appropriate deprotection strategy established, a second-generation synthesis of applanatumol V (**1a**) and W (**2a**), consisting of a *one-pot* Johnson-Lemieux alkene cleavage on the free carboxylic acid **78a**, was performed (**Scheme 65**). The carboxylic acid **78a** was cleaved to aldehyde **84a** by catalytic OsO_4 and NaIO_4 in the presence of 2,6-lutidine, reportedly improving the reaction outcome.^[121] The α -methylenation of aldehyde **84a** by condensation with formaldehyde under organocatalytic conditions smoothly formed the α,β -unsaturated aldehyde **85a**.^[122] Deprotection by BCl_3 at low temperature removed both the benzyl groups giving 1-*epi*-applanatumol V (**1a**) in high yield (for stereochemical explanation *vide infra*). In order to prepare applanatumol W (**2a**), the carboxylic acid **85a** was converted into methyl ester **86a** by treatment with TMSCHN_2 and further deprotected under the same Lewis acidic conditions giving applanatumol W (**2a**) in high yield. To examine the methyl ester hydrolysis possibilities, applanatumol W (**2a**) was treated either by LiOH , potassium trimethyl silanolate,^[123] or by BCl_3 with aqueous quenching,^[124] however, all attempts ended unsuccessfully. Nevertheless, reflux in water with DOWEX-50 resin cleanly resulted in methyl ester

hydrolysis giving the corresponding carboxylic acid **1a**, thus verifying that no epimerization occurred during this reaction step.^[125]

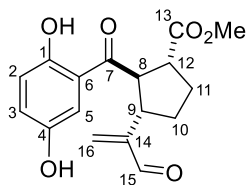


Scheme 65: Synthesis of 1-*epi*-applanatumol V (**1a**) and applanatumol W (**2a**). ^[a] Proposed stereochemistry of applanatumol V by Cheng et al.

The ¹H and ¹³C NMR spectra of the isolated applanatumol W by Cheng et al. ^[27b] and the synthetic material **2a** in methanol-*d*₄ were in an absolute match, confirming the relative stereochemistry of the natural product (**Table 7**).

In contrast, a comparison of both ¹H and ¹³C NMR spectra of the synthetic product **1a** with the isolated material by Cheng et al. showed considerable differences raising the question about the correctness of the original stereochemical assignment (**Table 8**).^[27b] Although no single-crystal suitable for X-ray analysis verifying the 1,2-*trans*/2,3-*trans* configuration of the synthetic product **1a** could be obtained, the crystal structure of aldehyde **84a** (**Scheme 65**), NOE experiments as well as the hydrolysis of the methyl ester **2a** (**Scheme 65**), provided additional evidence for the exactness of the 1,2-*trans*/2,3-*trans* assignment.

Table 7: ^1H and ^{13}C NMR spectral comparison of synthetic and isolated applanatumol W (**2a**).

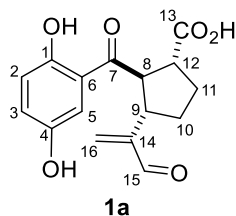


2a
Applanatumol W

No.	synthetic product ^[a]			isolated product ^[b]	
	δ_{H}	δ_{C}	$\Delta \delta_{\text{C}}$	δ_{H}	δ_{C}
1		157.1	0		157.1
2	6.79 (d, 8.9)	119.7	0	6.78 (d, 8.9)	119.7
3	7.01 (dd, 8.9, 2.9)	126.2	0	7.00 (dd, 8.9, 2.9)	126.2
4		150.6	0.1		150.7
5	7.10 (d, 2.9)	115.9	0	7.09 (d, 2.9)	115.9
6		120.8	0		120.8
7		207.9	0		207.9
8	4.25 (t, 8.4)	53.9	0	4.24 (t-like, 8.4)	53.9
9	3.31 (m)	45.3	0.1	3.32 (m)	45.4
10^a	2.08 (m)	32.4	0	2.08 (m)	32.4
10^b	1.85 (dq, 12.5, 8.2)			1.85 (m)	
11^a	2.16 (m)	30.0	0	2.14 (m)	30.0
11^b					
12	3.31 (m)	49.9	0	3.31 (m)	49.9
13		176.3	0		176.3
14		152.2	0.1		152.3
15	9.45 (s)	195.9	0	9.45 (s)	195.9
16^a	6.48 (s)	136.1	0	6.48 (brs)	136.1
16^b	6.15 (s)			6.14 (brs)	
OMe	3.63 (s)	52.5	0	3.63 (s)	52.5

For multiplets the central value is stated. ^[a] Measured on 400 MHz Bruker Avance in $\text{MeOH-}d_4$. ^[b] Q. Luo, X.-H. Yang, Z.-L. Yang, Z.-C. Tu, Y.-X. Cheng, *Tetrahedron* **2016**, 72, 4564-4574.

Table 8: ^1H and ^{13}C NMR spectral comparison of synthetic product **1a** and isolated applanatumol V.

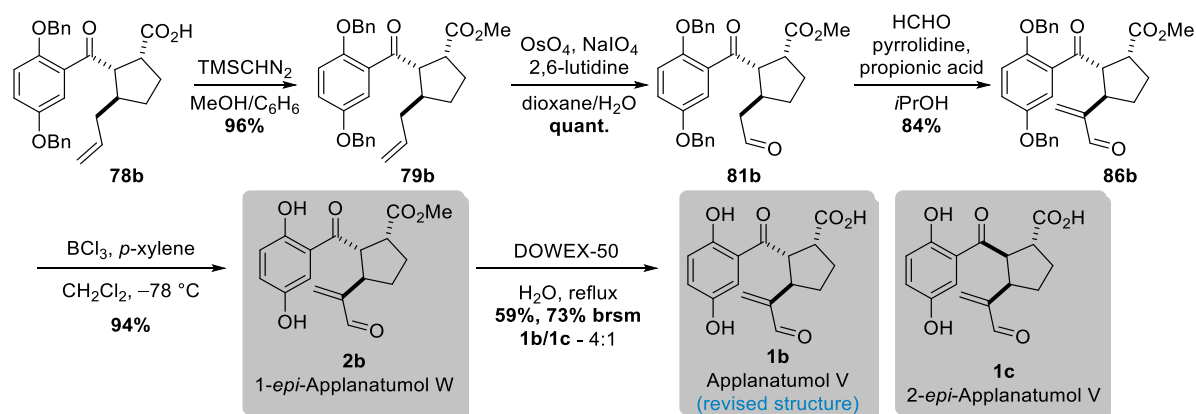


originally proposed structure of
Applanatumol V

No.	synthetic product ^[a]			isolated product ^[b]	
	δ_{H}	δ_{C}	$\Delta \delta_{\text{C}}$	δ_{H}	δ_{C}
1		157.2	0.4		156.8
2	6.78 (d, 8.9)	119.6	0.1	6.76 (d, 8.9)	119.5
3	6.99 (dd, 8.9, 2.9)	126.2	0.6	6.98 (dd, 8.9, 2.9)	125.6
4		150.6	0.1		150.5
5	7.15 (dd, 2.9, 0.5)	116.0	0	7.20 (d, 2.9)	116.0
6		120.7	0.4		121.1
7		208.3	0.6		207.7
8	4.25 (dd, 8.7, 7.7)	53.9	0.4	4.19 (t-like, 8.3)	53.5
9	3.30 (m)	45.3	1.6	3.41 (m)	43.6
10^a	2.08 (m)	32.5	0.4	2.14 (m)	32.1
10^b	1.85 (m)			1.72 (m)	
11^a	2.17 (m)	30.3	0	2.21 (m)	30.3
11^b				2.14 (m)	
12	3.30 (m)	50.0	0.1	3.45 (m)	50.1
13		177.7	0.1		177.8
14		152.5	0.5		153.0
15	9.45 (s)	195.9	0.3	9.53 (s)	196.2
16^a	6.50 (d, 1.0)	136.0	0.1	6.41 (br s)	135.9
16^b	6.15 (s)			6.15 (br s)	

For multiplets the central value is stated ^[a] Measured on 500 MHz Bruker Avance in $\text{MeOH}-d_4$. ^[b] Q. Luo, X.-H. Yang, Z.-L. Yang, Z.-C. Tu, Y.-X. Cheng, *Tetrahedron* **2016**, 72, 4564-4574.

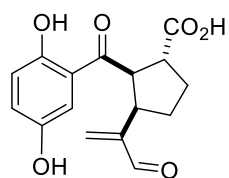
To correct the proposed stereochemistry of applanatumol V, we decided to take advantage of the low-diastereoselectivity of the key thermal cyclization and synthesize epimers of applanatumol V. The *1,2-cis/2,3-trans* diastereoisomer of cyclopentane carboxylic acid **78b** was converted to the methyl ester **79b** and further oxidatively cleaved to aldehyde **81b** under improved Johnson-Lemieux conditions (Scheme 66). The aldehyde was organocatalytically methylenated, providing the enal **86b** and deprotected by BCl_3 , giving a high yield of 1-*epi*-applanatumol W (**2b**). The spectral data of this unnatural epimer **2b** contrasted the previously prepared applanatumol W (**2a**), confirming that no epimerization into the *1,2-trans/2,3-trans* isomer occurred during the deprotection step. The methyl ester **2b** was hydrolyzed by DOWEX-50, resulting in a 4:1 diastereoisomeric mixture of applanatumol V (**1b**) and 2-*epi*-applanatumol V (**1c**). It is assumed that the minor diastereoisomer **1c** results from the epimerization of the acidic α -phenone stereogenic center due to the low steric bias between the two neighboring substituents. Comparison of the spectral data of the *1,2-cis/2,3-trans* diastereoisomer of applanatumol V (**1b**) with the isolated material exhibited a precise match of all resonances, except for the carboxylic acid resonance that deviates by 0.5 ppm in the ^{13}C NMR spectrum (Table 9). The deviation is possibly caused by the involvement of the carboxylic acid in intermolecular hydrogen bonding, and the chemical shift might be concentration-dependent.



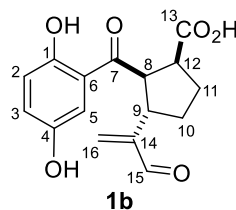
Scheme 66: Synthesis of 1-*epi*-applanatumol W (**2b**), applanatumol V (**1b**) and 2-*epi*-applanatumol V (**1c**).

The fact that racemic structurally related applanatumols in stereoisomeric forms are apparently present in Nature leads to the hypothesis that ring-forming processes during their biosynthesis occur spontaneously in the absence of enzymes. This means that probably more epimers of applanatumols V, W and other meroterpenoids might be discovered in *Ganoderma* fungi in the future.

Table 9: ^1H and ^{13}C NMR spectral comparison of synthetic products **1b,c** and isolated applanatumol V.



1c
2-epi-Applanatumol V



1b
revised structure of
Applanatumol V

No.	synthetic product ^[a]			synthetic product ^[a]			isolated product ^[b]	
	δ_{H}	δ_{C}	$\Delta \delta_{\text{C}}$	δ_{H}	δ_{C}	$\Delta \delta_{\text{C}}$	δ_{H}	δ_{C}
1		156.8	0		156.9	0.1		156.8
2	6.72 (d, 8.9)	119.5	0	6.76 (d, 8.9)	119.5	0	6.76 (d, 8.9)	119.5
3	6.96 (dd, 8.9, 3.0)	126.1	0.5	6.98 (dd 8.9, 2.9)	125.6	0	6.98 (dd, 8.9, 2.9)	125.6
4		150.5	0		150.5	0		150.5
5	7.19 (dd, 3.0, 1.6)	116.3	0.3	7.19 (d, 2.9)	116.0	0	7.20 (d, 2.9)	116.0
6		120.9	0.2		121.0	0.1		121.1
7		208.2	0.5		207.6	0.1		207.7
8	4.51 (dd, 9.4, 7.2)	52.6	0.9	4.20 (dd, 9.1, 7.7)	53.5	0	4.19 (t-like, 8.3)	53.5
9	3.58 (m)	42.6	1.0	3.40 (m)	43.7	0.1	3.41 (m)	43.6
10^a	2.02 (m)	32.2	0.1	2.14 (m)	32.1	0	2.14 (m)	32.1
10^b				1.72 (dtd, 12.2, 9.0, 8.0)			1.72 (m)	
11^a	2.33 (m)	30.2	0.1	2.19 (m)	30.3	0	2.21 (m)	30.3
11^b	1.94 (m)						2.14 (m)	
12	3.43 (m)	48.8	1.3	3.45 (dt, 9.2, 8.1)	50.0	0.1	3.45 (m)	50.1
13		178.1	0.3		177.3	0.5		177.8
14		151.5	1.5		153.0	0		153.0
15	9.20 (s)	195.7	0.5	9.54 (d, 0.5)	196.1	0.1	9.53 (s)	196.2
16^a	6.29 (s)	136.6	0.7	6.42 (d, 1.0)	135.9	0	6.41 (br s)	135.9
16^b	6.06 (s)			6.15 (s)			6.15 (br s)	

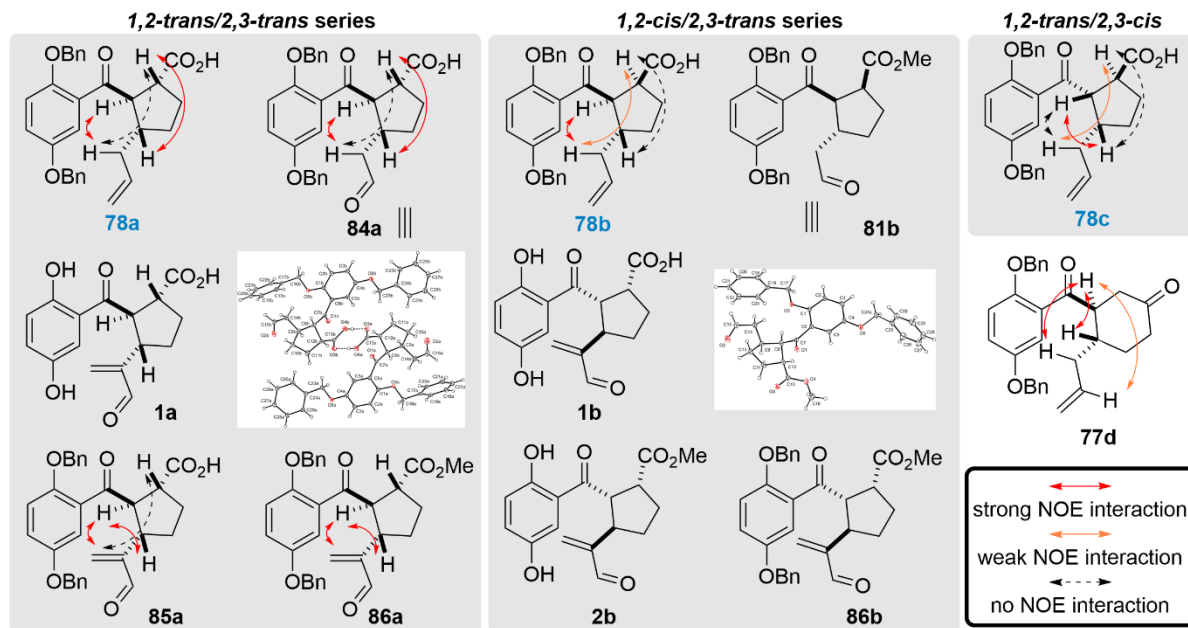
For multiplets the central value is stated ^[a] Measured on 600 MHz Bruker Avance in $\text{MeOH}-d_4$. ^[b] Q. Luo, X.-H. Yang, Z.-L. Yang, Z.-C. Tu, Y.-X. Cheng, *Tetrahedron* **2016**, 72, 4564-4574.

4.3.3.1. Stereochemical assignment of cyclic intermediates

The stereochemical determination of carboxylic acids **78a,b,c** resulting from the thermal cyclization/oxidation sequence (Scheme 62) was at the first stage performed by NOE experiments revealing the *1,2-trans/2,3-trans* configuration for the major (**78a**), *1,2-cis/2,3-trans* for the minor (**78b**), and *1,2-trans/2,3-cis* configuration for the least abundant diastereoisomer **78c** (Scheme 67). The configurations, diastereoisomeric ratios, and transition states involved during the thermal cyclization step are identical to the cyclization of substrate **28m** differing from substrate **75** in the two benzyloxy groups on the aromatic portion (Scheme 58, cf. Chapter 4.2.5).

Compounds **1a**, **84a-86a** prepared from the abovementioned carboxylic acid **78a** were analogously analyzed by NOE experiments, exhibiting the same relative configuration as their parent compound. However, a high degree of uncertainty in NOE analysis of five-membered rings called for the unambiguous determination by X-ray crystallography. The aldehyde **84a** prepared from the carboxylic acid **78a** crystallized, and the X-ray crystallography showed the correct *1,2-trans/2,3-trans* configuration, thus confirming the stereochemistry for the whole series. In analogy, the X-ray structure of methyl ester **81b** prepared from the minor diastereoisomer of carboxylic acid **78b** displayed *1,2-cis/2,3-trans* configuration, thus confirming this configuration for all its synthetic congeners **1b**, **2b**, **86b**.

The configuration of the cyclohexanone derivative **77d** was assigned analogously to cyclohexanone **50ma** (Scheme 58) as *trans* based on NOE experiments. The H3-H4 coupling constant of 9.5 Hz points to the coupling of two protons in an axial orientation.

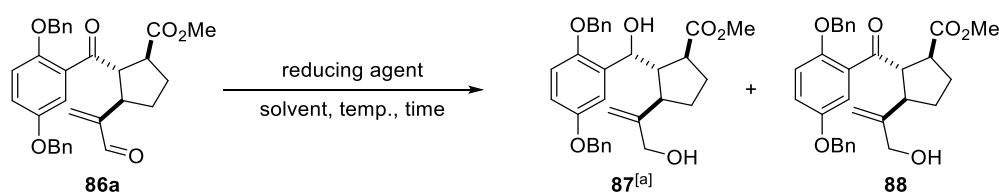


Scheme 67: Stereochemical assignment of synthetic congeners of carboxylic acids **78a,b,c**, and ketone **77d** by NOE experiments and X-ray crystallography.

4.3.4. Synthesis of applanatumol B

The successful synthesis of configurationally defined intermediate **78a** allowed to progress towards applanatumol B. The synthesis commenced with 1,2-reduction of the α,β -unsaturated aldehyde **86a**, which needed some optimization (**Table 10**). Sodium borohydride in methanol rapidly reduced both the aldehyde and the ketone function, furnishing the diol **87** with an unknown configuration at the benzylic stereocenter (entry 1). A weaker reducing agent, triacetoxyborohydride, did not show any reactivity at room temperature; however, led to an unselective reduction at 60 °C (entries 2,3). Gratifyingly, lithium tri-*sec*-butylborohydride (L-Selectride®) smoothly reduced only the aldehyde at –78 °C, providing allylic alcohol **88** in high yield (entry 4).

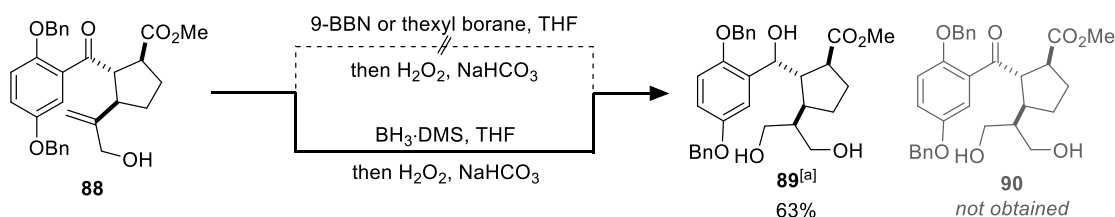
Table 10: Optimization of the 1,2-reduction of the α,β -unsaturated aldehyde **86a**.



Entry	Reducing agent (equiv.)	Solvent	Temp. (°C)	Time (h)	Crude ¹ H NMR ratio 86a : 87 : 88		
1	NaBH ₄ (1.1)	MeOH	–50	1.5	–	100	–
2	NaBH(OAc) ₃ (3.0) ^[b]	THF	60	overnight	30	70	–
3	NaBH(OAc) ₃ (3.0)	THF	60	5	33	40	27
4	L-Selectride® (1.0)	THF	–78	1	–	–	100 ^[c]

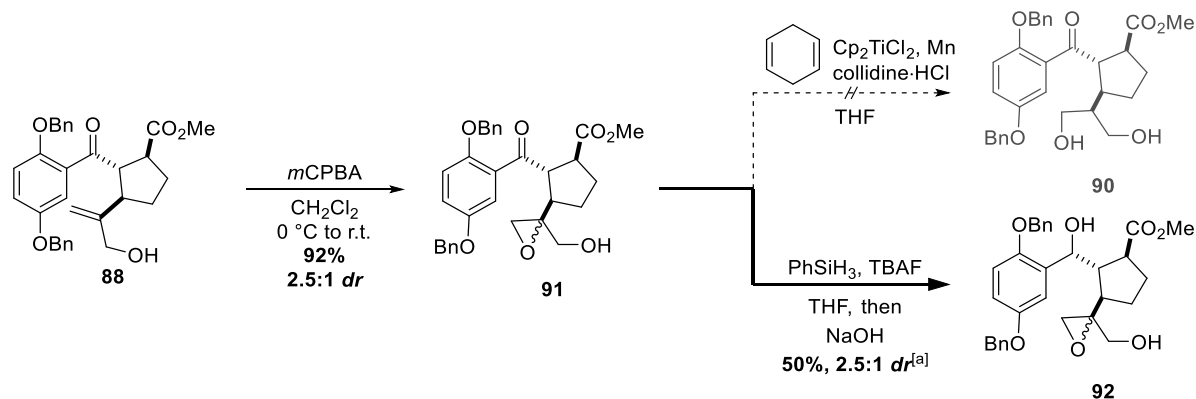
^[a] Unknown configuration at the benzylic stereocenter. ^[b] Stepwise addition of the reducing agent. ^[c] Isolated yield after column chromatography purification is 89%.

Hydroboration/oxidation of the allylic alcohol **88** providing a 1,3-diol **90** necessary for further elaboration towards the tricyclic skeleton of applanatumol B was planned (**Scheme 68**). Bulky boranes such as 9-borabicyclo[3.3.1]nonane (9-BBN) or freshly prepared hexyl borane did not show any reactivity. In contrast, the borane dimethylsulfide complex hydroborated the alkene unit and simultaneously reduced the phenone moiety, giving the triol **89**. The configuration of the newly formed stereocenter was not analyzed.



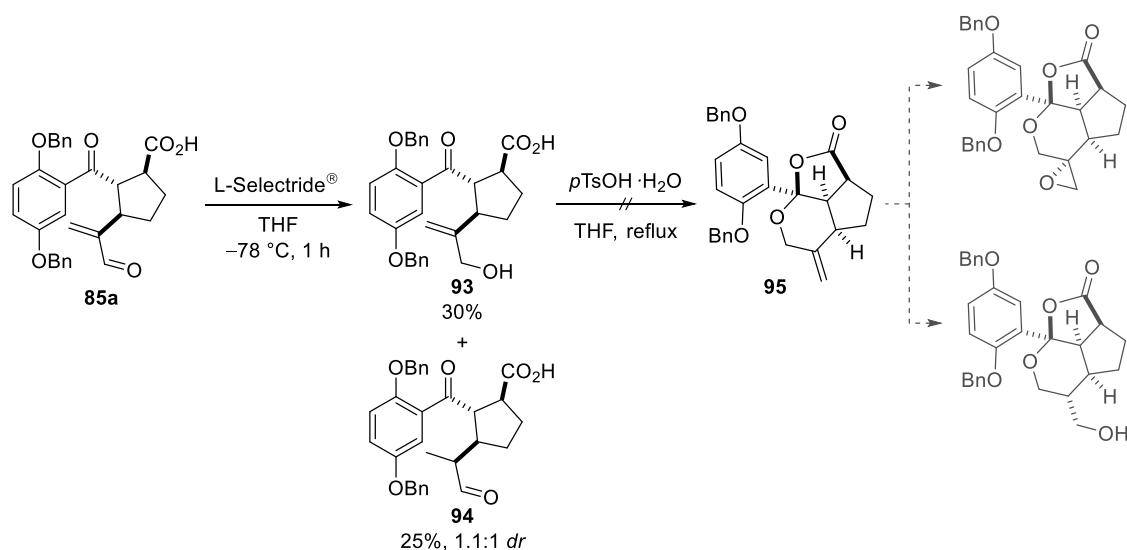
Scheme 68: Attempted hydroboration of allylic alcohol **88**. ^[a] Unknown configuration at the benzylic stereocenter.

The undesired reduction of the benzylic ketone led to a change in the adopted strategy. The allylic alcohol **88** was epoxidized by *m*CPBA, efficiently forming oxiranes **91** as a 2.5:1 diastereoisomeric mixture with an unknown configuration (**Scheme 69**). It is known that epoxides can be reductively opened by Ti(III) in the more radical-stabilizing position.^[126] However, in our case, this reaction proved unsuccessful, and only a complex mixture of products lacking the methyl ester was obtained. A literature preceded opening of epoxy alcohol by phenyl silane in the presence of TBAF resulted in the undesirable reduction of the benzylic ketone giving compound **92**.^[127]



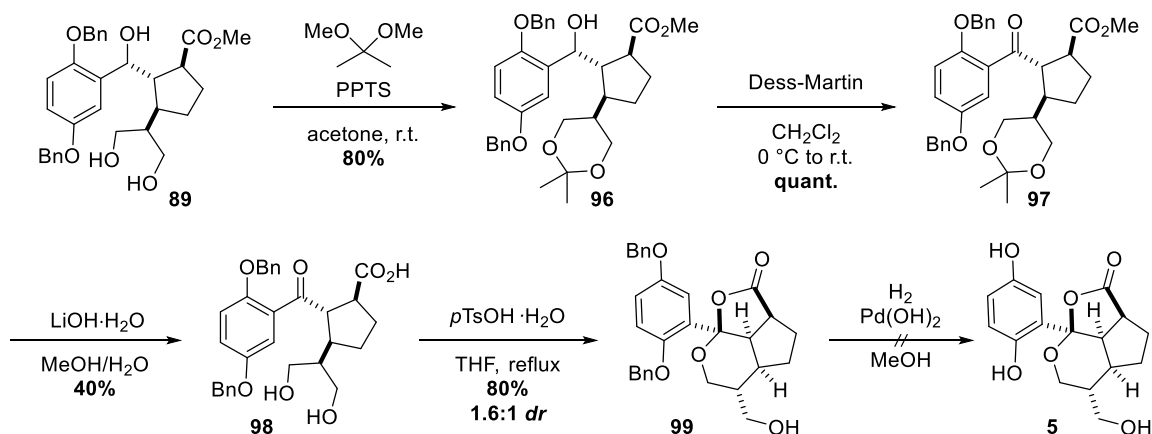
Scheme 69: Epoxidation of allylic alcohol **88** and an attempted oxirane opening to 1,3-diol. ^[a] Unknown configuration of the benzylic stereocenter.

In order to test if allylic alcohol **93** with the free carboxylic acid function could be directly ketalized to tricycle **95** with subsequent double bond elaboration possibilities, the α,β -unsaturated aldehyde **85a** was reduced by L-Selectride[®] (**Scheme 70**). A partial 1,4-reduction giving saturated aldehyde **94** was observed, and only a low yield of the desired allylic alcohol **93** was obtained. An attempted ketalization of the allylic alcohol **93** proved unsuccessful, thus hindering further modification possibilities.



Scheme 70: Reduction of α,β -unsaturated aldehyde **85a** and an attempted ketalization of allylic alcohol **93**.

With a low milligram amount of the triol **89** resulting from the over-reduction by borane in hand (**Scheme 68**), a model reaction sequence, testing the feasibility of the planned total synthesis, was performed (**Scheme 71**). The displayed yields of this small-scale synthesis are approximate, illustrating their workability. The 1,3-diol **89** was protected as an acetonide yielding protected alcohol **96**, and the remaining benzylic alcohol was then oxidized by the Dess-Martine periodinane resulting in ketone **97**. The methyl ester hydrolysis proceeded smoothly with lithium hydroxide providing the carboxylic acid **98** with simultaneous hydrolysis of the acetonide, most likely as a result of acidic quenching. The crucial literature precedented ketalization of diol **98**, cleanly formed the desired tricyclic skeleton **99** in high yield as a 1.6:1 diastereoisomeric mixture at the stereocenter bearing the exocyclic hydroxymethyl substituent.^[31] It must be stated that the acidic epimerization of the C2-stereogenic center allowing the closure of the tricyclic core occurs during this reaction step. The final deprotection step was attempted by hydrogenolysis on Pearlman's catalyst to prevent the acid-catalyzed ketal opening and the reduction of the benzylic position. Nonetheless, the deprotection resulted in an indecipherable mixture of partially deprotected phenols and products of ketal reduction.

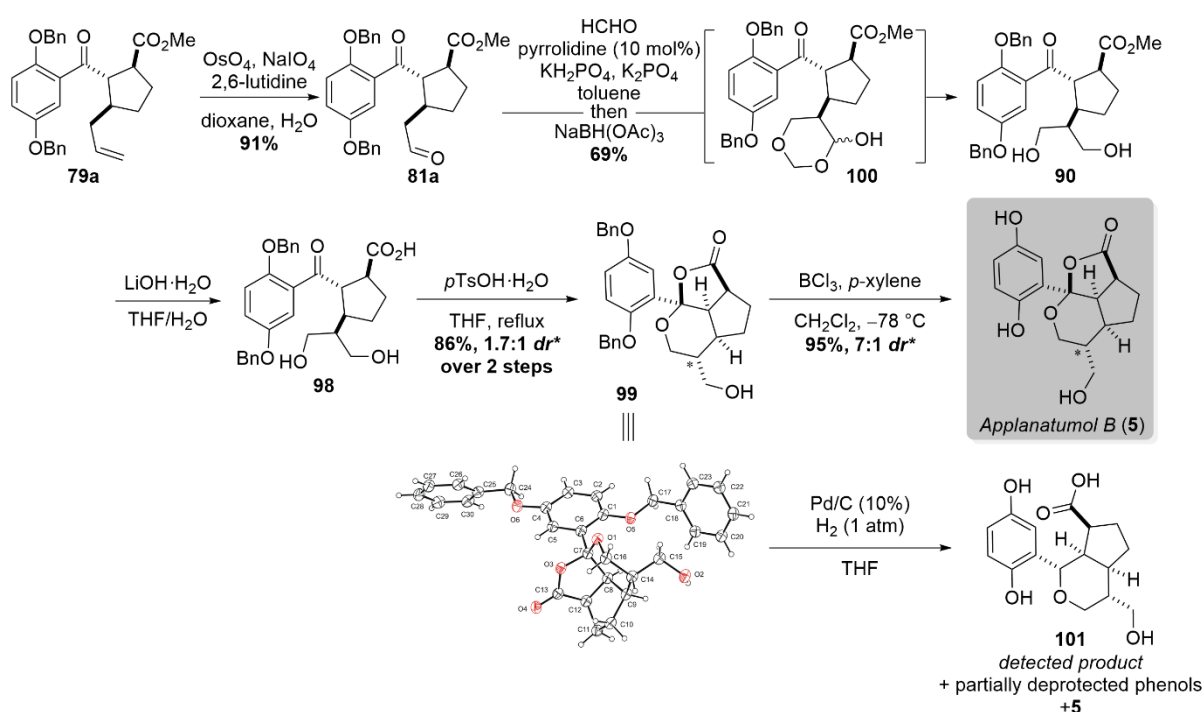


Scheme 71: A small-scale model reaction sequence towards applanatumol B.

The ineffectiveness and a high step count of the latter synthetic route led to redesigning the approach to the 1,3-diol **90**. Aliphatic aldehydes can be α -hydroxymethylated to labile β -hydroxy aldehydes prone to dehydration under acidic or basic conditions to α,β -unsaturated aldehydes. It was shown that buffered pyrrolidine-catalyzed treatment of enolizable aldehydes by formaldehyde forms relatively stable 1,3-dioxan-4-ols applicable in Wittig olefination or Pinnick oxidation.^[122] We hypothesized that such intermediate could be *in situ* reduced, directly providing the desired 1,3-diol.

To test this hypothesis, the methyl ester **79a**, utilized in the synthesis of applanatumol W (**Scheme 63**), was cleaved under Johnson-Lemieux conditions (**Scheme 72**). The obtained aldehyde **81a** was treated with formaldehyde and pyrrolidine in the presence of a phosphate buffer. The formed intermediate **100** was *in situ* reduced by $\text{NaBH}(\text{OAc})_3$ giving a good yield of the diol **90** without over-reduction. The diol **90** was cleanly hydrolyzed to carboxylic acid **98** using the previously established LiOH conditions

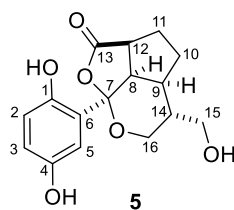
without the necessity for chromatographic purification. The cyclization precursor **98** was submitted to acid-catalyzed epimerization/ketalization, providing a high yield of a 1.7:1 diastereoisomeric mixture of the tricycle **99** separable by preparative TLC in a $\text{CHCl}_3/\text{MeOH}$ mixture. The major diastereoisomer of the ketal **99** crystallized, and a match of its relative configuration with that of the natural product was proven by X-ray crystallography. Attempts to remove the benzyl protecting groups by 1 atm H_2 on Pd/C in THF or EtOAc resulted in a complex mixture of **5**, partially deprotected products together with ether **101** formed by ketal reduction. To our delight, the tricyclic scaffold of **99** proved reasonably stable under acidic conditions, and treatment by BCl_3 at -78°C resulted in deprotection giving applanatumol B (**5**) and *epi*-applanatumol B with the reversed configuration at the hydroxymethyl group bearing stereocenter in high yield as a partially separable 7:1 diastereoisomeric mixture.



Scheme 72: Final synthetic approach to applanatumol B (**5**).

Comparison of the ^1H and ^{13}C NMR spectra of synthetic applanatumol B with material isolated by Cheng et al. and synthesized by Ito et al. showed an agreement, thus confirming the relative stereochemistry of the natural product (**Table 11**).^[27a, 31] Interestingly, during NMR measurements in methanol- d_4 , the acidified proton in the α -position of the ketal function was slowly exchanged for deuterium resulting in the disappearance of its NMR resonance and a change of the splitting of the neighboring proton resonances.

Table 11: ^1H and ^{13}C NMR spectral comparison of synthetic product **5** and isolated applanatumol B.

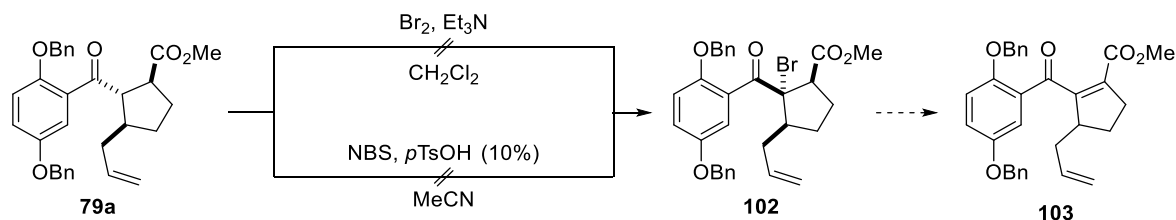


	synthetic material ^[a]			isolated material ^[b]		lto-synthetic material ^[c]	
No.	δ_{H}	δ_{C}	$\Delta \delta_{\text{C}}$	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1		148.5	0		148.5		148.6
2	6.67 (d, 8.7)	118.4	0.1	6.67 (d, 8.6)	118.5	6.67 (d, 8.8)	118.5
3	6.63 (dd, 8.6, 2.8)	117.6	0	6.64 (dd, 8.6, 2.8)	117.6	6.64 (dd, 8.8, 2.8)	117.6
4		150.9	0.1		150.8		150.9
5	6.87 (d, 2.8)	114.0	0	6.87 (d, 2.8)	114.0	6.87 (d, 2.8)	114.0
6		129.7	0		129.7		129.7
7		108.8	0.1		108.9		108.9
8	3.14 (dd, 10.5, 8.4)	41.9	0	3.14 (dd, 10.4, 8.6)	41.9	3.14 (dd, 10.8, 8.8)	41.9
9	2.28 (m)	37.9	0	2.28 (m)	37.9	2.28 (m)	38.0
10^a	1.90 (m)	32.5	0	1.90 (m)	32.5	1.90 (m)	32.6
10^b	1.51 (qd, 12.8, 5.9)			1.51 (m) ^e		1.51 (m)	
				1.51 (qd, 12.8, 6.0) ^[f]			
11^a	2.19 (dd, 12.5, 6.0)	29.9	0	2.18 (m) ^e	29.9	2.18 (m)	29.9
				2.18 (dd, 12.6, 5.9) ^[f]			
11^b	1.74 (m)			1.73 (m)		1.73 (m)	
12	3.28 (m)	50.7	0.1	3.28 (t-like, 8.1)	50.6	3.28 (t-like, 8.4)	50.7
13		181.3	0		181.3		181.4
14	1.68 (m)	38.5	0	1.69 (m)	38.5	1.69 (m)	38.5
15^a	4.02 (dd, 10.8, 8.4)	64.1	0	4.02 (dd, 10.7, 3.9) ^[e]	64.1	4.02 (dd, 10.4, 3.9)	64.2
				4.02 (dd, 10.8, 8.4) ^[f]			
15^b	3.77 (dd, 10.8, 6.6)			3.77 (dd, 10.7, 2.9) ^[e]		3.77 (dd, 10.4, 6.4)	
				3.77 (dd, 10.8, 6.6) ^[f]			
16^a	3.98 (dd, 12.2, 2.6)	59.0	0	3.98 (dd, 12.1, 2.4)	59.0	3.98 (dd, 12.2, 2.0)	59.1
16^b	3.90 (dt, 12.1, 1.4)			3.91 (dd, 12.1, 3.5) ^[e]		3.91 (d, 8.0)	
				3.91 (dt, 12.2, 1.6) ^[f]			
1-OH^[d]	9.15 (s)			9.17 (s)			
4-OH^[d]	8.78 (s)			8.80 (s)			
15-OH^[d]	4.67 (s)			4.68 (s)			

For multiplets the central value is stated. ^[a] Measured on 500 MHz Bruker Avance in MeOH- d_4 . ^[b] Q. Luo, L. Di, X.-H. Yang, Y.-X. Cheng, *RSC Adv.* **2016**, 6, 45963-45967. ^[c] K. Uchida, Y. Kawamoto, T. Kobayashi, H. Ito, *Org. Lett.* **2019**, 21, 6199-6201. ^[d] In DMSO- d_6 . ^[e] Original assignment. ^[f] Reassigned from the original ^1H NMR kindly provided by Prof. Yong-Xian Cheng (Institute for Inheritance-Based Innovation of Chinese Medicine, School of Pharmaceutical Sciences, Health Science Center, Shenzhen University, Shenzhen 518060, People's Republic of China, yxcheng@szu.edu.cn)

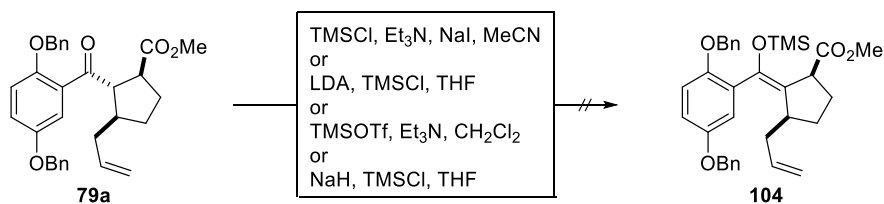
4.3.5. Synthesis of spiroapplanatuminines

The formation of a C–O spirocyclic bond between the *ortho*-phenolic hydroxyl and C2 of the carbocycle **79a** would enable access to the family of spiroapplanatuminines structurally related meroterpenoids from *Ganoderma applanatum*. The first approach to close the spirocycle was based on the introduction of a double bond to the α -position of the ketone forming intermediate **103** (Scheme 73) and subsequent intramolecular oxa-Michael addition of the deprotected *ortho*-phenol. To introduce the unsaturation, α -bromination of the keto function and subsequent E1cB elimination was envisioned. Nevertheless, the bromination of the common intermediate **79a** under basic or acidic conditions did not show any conversion of the starting material (Scheme 73).



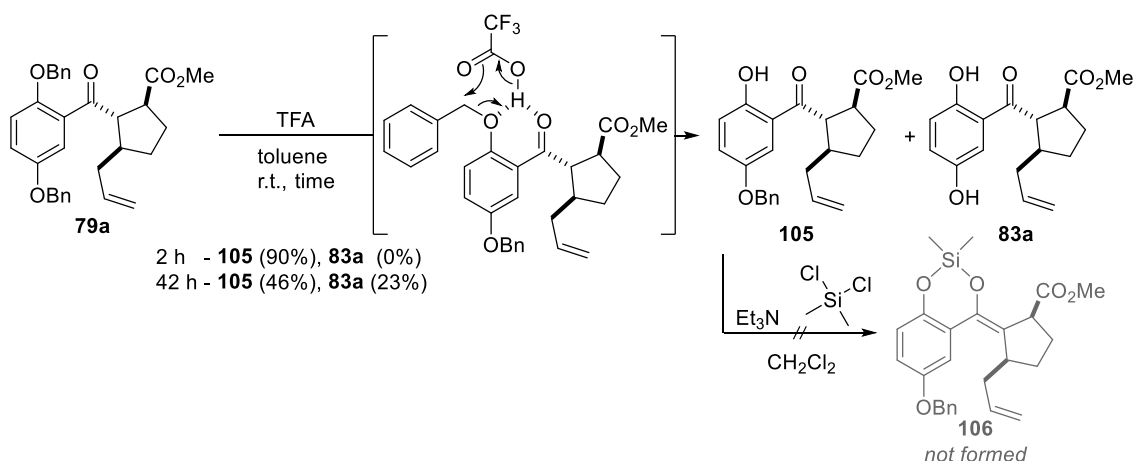
Scheme 73: Unsuccessful bromination/elimination strategy as a tool for the double bond introduction.

For this reason, conversion of the ketone **79a** into silyl enol ether **104** applicable in α -hydroxylation, halogenation, selenylation, or Saegusa-Ito reaction was attempted (Scheme 74). Enolization of the sterically hindered ketone proved problematic, and no conversion of the starting material was observed even with strong bases.



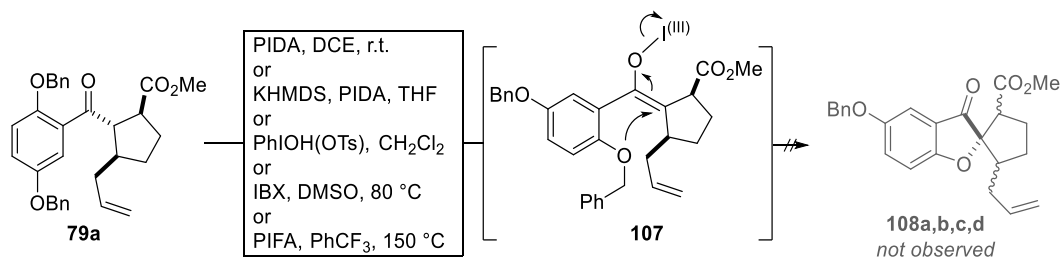
Scheme 74: Unsuccessful silyl enol ether formation.

It was shown that *O*-benzylated, allylated, or *iso*-propylated phenols bearing an *ortho*-EWG can be deprotected by trifluoroacetic acid.^[128] In this sense, compound **79a** was smoothly mono-deprotected by TFA over 2 hours, giving a high isolated yield of phenol **105** (Scheme 75). Interestingly, by extension of the reaction time, the entirely deprotected hydroquinone **83a** was slowly formed. With the mono-deprotected phenol **105** in hand, the formation of cyclic silyl enol ether **106** was attempted. However, the formation of the desired cyclic product **106** was not observed.



Scheme 75: Monodebenzylation of intermediate **79a** and attempted formation of the cyclic silyl enol ether **106**.

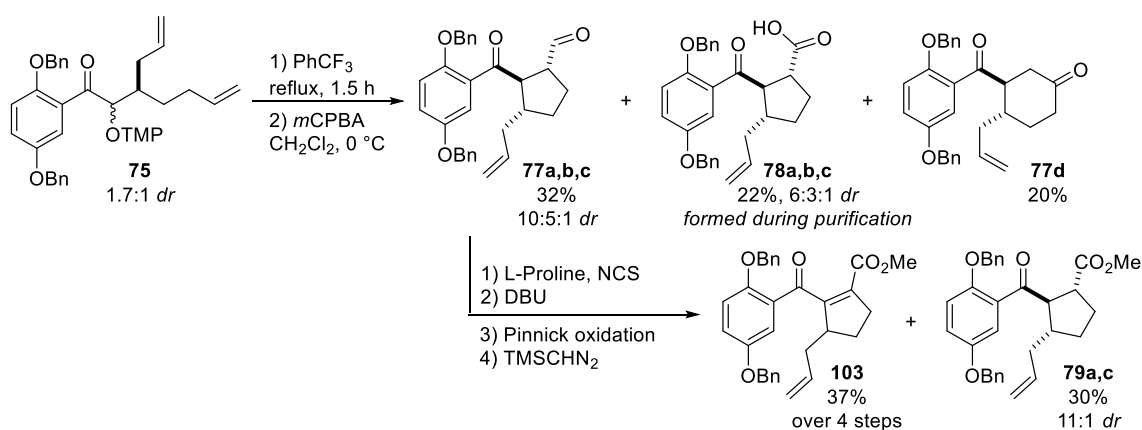
It was shown that ketones react in their enol or enolate form with hypervalent iodine reagents forming iodanyl enol ethers that get attacked by nucleophiles forming α -substituted ketones.^[55b, 129] In the case of compound **79a**, enol ether **107** could intramolecularly cyclize with the *ortho*-phenolic hydroxyl forming spirocycles **108a-d** while losing the protecting group (**Scheme 76**). The compound **79a** submitted to the reaction with (diacetoxyiodo)benzene (PIDA) under neutral or basic conditions, Koser's reagent, PIFA or IBX, potentially introducing a double bond, did not show any conversion. These results correspond to the previous observation that ketone **79a** is very difficult to enolize.



Scheme 76: Attempted oxidative spirocyclization by hypervalent iodine reagents.

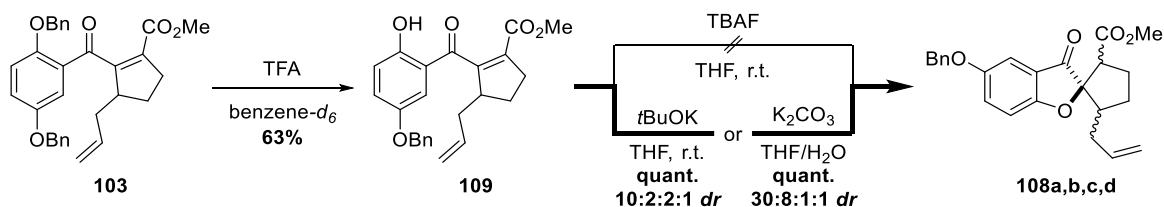
As a result of the inability to modify the sterically hindered α -keto position at C2, we decided to reverse the strategy and modify the α -ester position at C1. In order to achieve a selective transformation, the acidity of this position needed to be increased. For this purpose, a compound bearing a formyl group instead of the ester function was prepared. This was achieved by a *de novo* carbocycle formation through decoupling the cyclization/oxidation sequence leading to the central intermediate **78a** (**Scheme 62**).

α -Aminoxy ketone **75** was cyclized under standard thermal conditions (Scheme 62, cf. Chapter 4.3.2), forming carbocycles **76a,b,c**. The inseparable diastereoisomeric mixture was oxidized by *m*CPBA providing a 10:5:1 diastereoisomeric mixture of aldehydes **77a,b,c**, ketone **77d**, and a 6:3:1 diastereoisomeric mixture of carboxylic acids **78a,b,c** that was formed by undesired oxidation during chromatographic purification (Scheme 77). The diastereoisomeric mixture of aldehydes **77a,b,c** was organocatalytically α -chlorinated by L-Proline/NCS system and, without purification, submitted to elimination by DBU converging all diastereoisomers into an α,β -unsaturated aldehyde. The unsaturated aldehyde was oxidized under Pinnick conditions and treated with TMSCHN₂, giving the desired α,β -unsaturated methyl ester **103** in 37% yield over four steps together with an 11:1 diastereoisomeric mixture of the saturated esters **79a,c** in 32% yield resulting from poor conversion during the chlorination step.



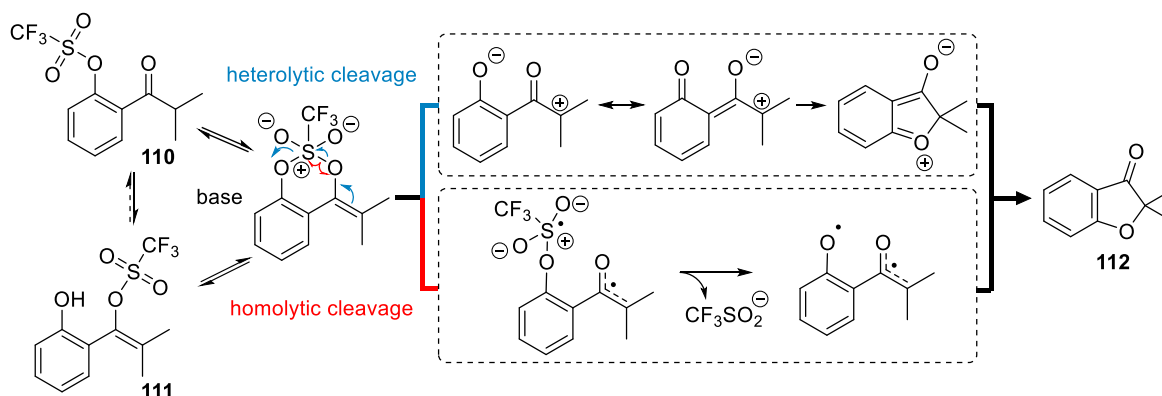
Scheme 77: PRE-based thermal cyclization/oxidation of ketone **75** and a sequence leading to α,β -unsaturated ester **103**. Major diastereoisomers are displayed.

The obtained α,β -unsaturated ester **103** was dissolved in benzene-*d*₆ and treated with TFA (Scheme 78). *In situ* NMR measurements showed that the mono-debenzylation was finished in 4.5 h, but no acid-mediated cyclization leading to spirocycles **108a-d** was observed. For this reason, the deprotected phenol was purified and cyclized under basic reaction conditions. Tetrabutylammonium fluoride did not provide the spirocycle, but the allylic double bond-shift was detected (not shown). *t*BuOK in THF cleanly formed a 10:2:2:1 diastereoisomeric mixture of spirocycles **108a-d**. K₂CO₃ in a THF/H₂O mixture was also effective and yielded spirocycles **108a-d** as a 30:8:1:1 diastereoisomeric mixture (for stereochemical explanation *vide infra*).



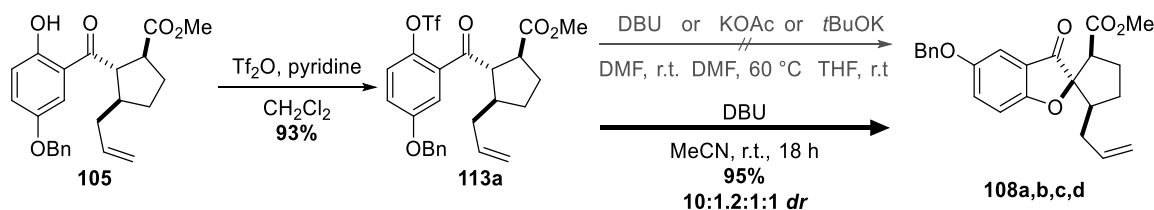
Scheme 78: Mono-debenzylation of unsaturated ester **103** and an intramolecular oxa-Michael addition forming spirocycles **108a-d**.

In 2003, Vetelino et al. showed that α -alkyl-substituted 2'-hydroxy acetophenone triflates **110** undergo under basic conditions triflate migration giving enol triflates **111** that oxidatively cyclize to benzofuranones **112** (Scheme 79).^[130] This oxidative cyclization proceeds either by a polar mechanism through a quinone methide intermediate or a radical mechanism through a biradical intermediate. In both cases, the reduced trifluoromethane sulfinate ion is eliminated.



Scheme 79: Mechanism of triflate migration/oxidative cyclization leading to benzofuranones reported by Vetelino et al.

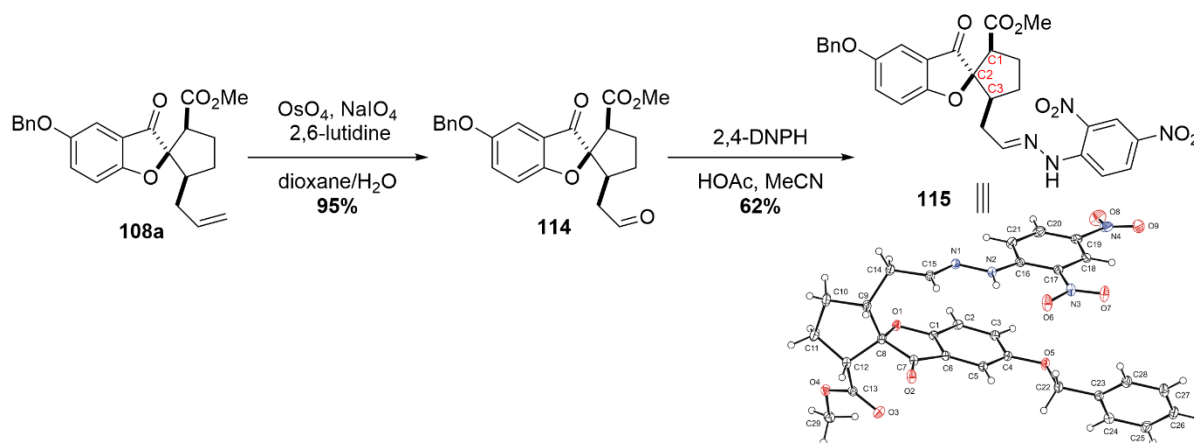
To test the applicability of this oxidative spirocyclization approach, phenol **105** (Scheme 75) was treated with $\text{ Tf}_2\text{O}$, providing a high yield of triflate **113a** that was submitted to oxidative cyclization conditions (Scheme 80). DBU or KOAc in DMF or $t\text{BuOK}$ in THF resulted in complex reaction mixtures with only traces of the product detectable. Other detectable compounds were products of triflate removal and allylic double bond-shift. To our delight, DBU in acetonitrile smoothly promoted oxidative spirocyclization giving a high isolated yield of a 10:1.2:1:1 diastereoisomeric mixture of products **108a-d**. The major diastereoisomer **108a** was chromatographically separable from minor diastereoisomers and utilized as an individual compound. NOE experiments could not be applied to determine the relative configuration of products **108a-d** because of a lack of hydrogen atoms around the spirocyclic center. Furthermore, product **108a** did not crystallize; thus, synthetic transformations were needed to determine the configuration unambiguously (*vide infra*).



Scheme 80: Triflation of phenol **105** and a base-mediated oxidative spirocyclization.

The successful formation of the spirocyclic ring enabled further elaboration towards the spiroapplanatamine skeleton (Scheme 81). The double bond of the major diastereoisomer **108a** was cleaved under Johnson-Lemieux conditions providing aldehyde **114**, which was further transformed

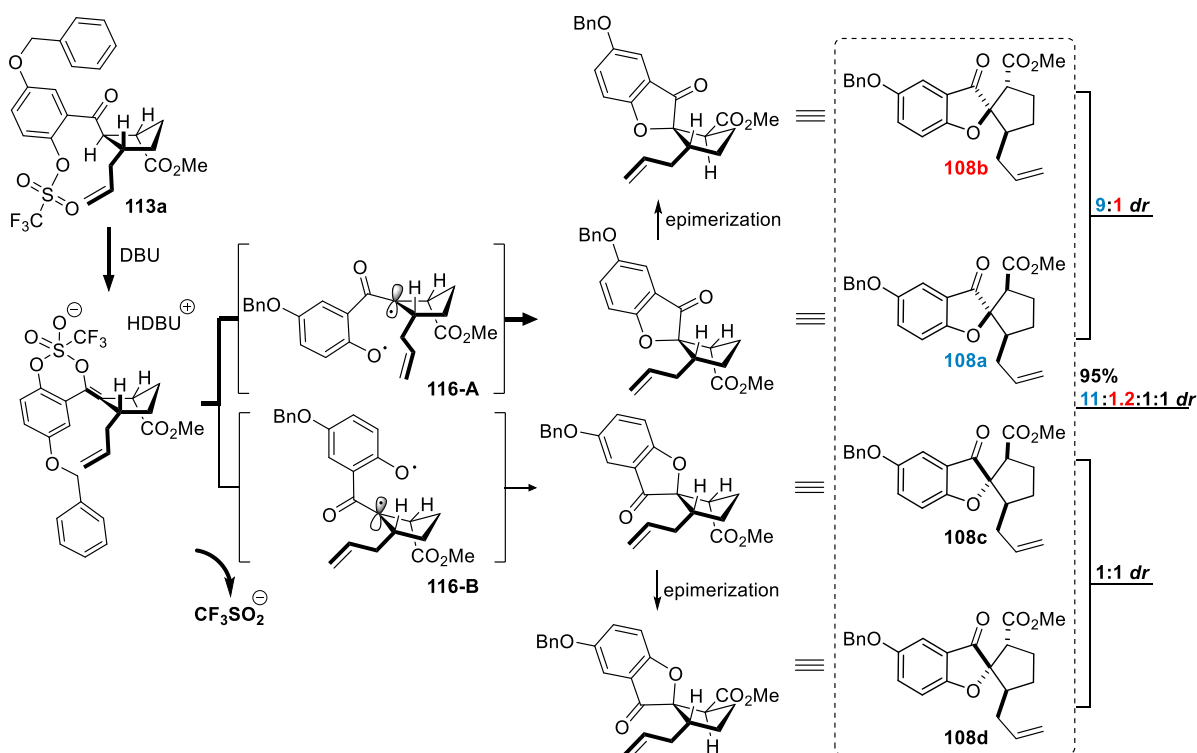
to the 2,4-dinitrophenyl hydrazone derivative **115** that displayed good crystallinity. The X-ray crystallographic analysis showed a *1,2-cis/2,3-cis* configuration of all three substituents of the cyclopentane ring.



Scheme 81: Oxidative cleavage of the alkene unit and the stereochemical determination of the hydrazone derivative **115**.

The numbering of the prepared spirocyclic compounds needs a comment. The standard heterocyclic nomenclature would number the heterocycle as the group with the higher priority and the spiro-attached cyclopentane ring with primed numerals accordingly as lower priority substituents. For clarity of this work, the spirocyclic compounds are numbered as substituted cyclopentanes similarly to previous applanatumols. In this sense, the carboxylate-substituted position is numbered as C1, spirocyclic center as C2, and allyl-bearing carbon atom as C3.

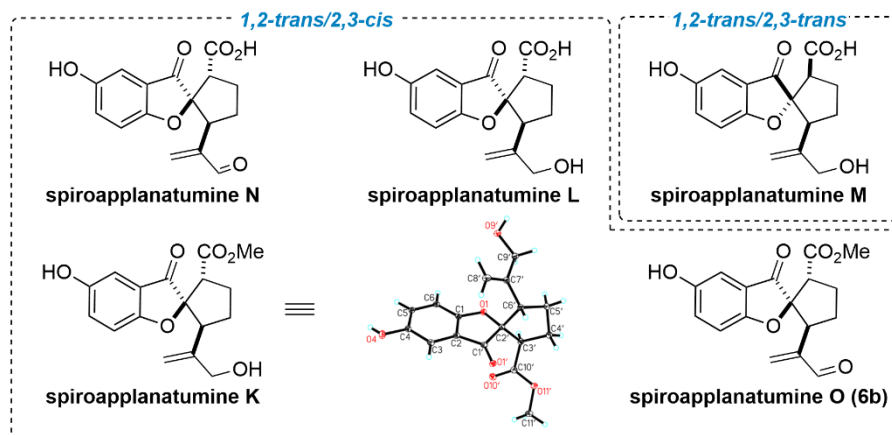
The formation of the diastereoisomeric mixture **108a-d** can be rationalized based on a stereochemical model (**Scheme 82**). The triflate migration/elimination of the CF_3SO_2^- anion under basic conditions at the triflated carbocycle **113a** leads to biradical conformers **116-A** and **116-B**. In the conformer **116-A** the phenoxy radical orients *cis* to the residing substituents of the carbocycle. In the conformer **116-B**, the phenoxy radical orients *trans*. The orientation in **116-A** is, based on the experimental evidence, more preferred, and the radical coupling leads to the major diastereoisomer **108a** with *1,2-cis/2,3-cis* configuration. Under basic reaction conditions, the neighboring α -ester stereocenter at C1 undergoes epimerization, giving rise to the diastereoisomer **108b**. The less preferred biradical conformer **116-B** identically gives rise to the two minor diastereoisomers **108c** and **108d**. However, it must be stated that a complex situation consisting of *retro*-Michael elimination/oxa-Michael addition or epimerization prior to the oxidative spirocyclization step can not be excluded.



Scheme 82: Stereochemical rationale of oxidative spirocyclization forming a diastereoisomeric mixture of **108a-d**.

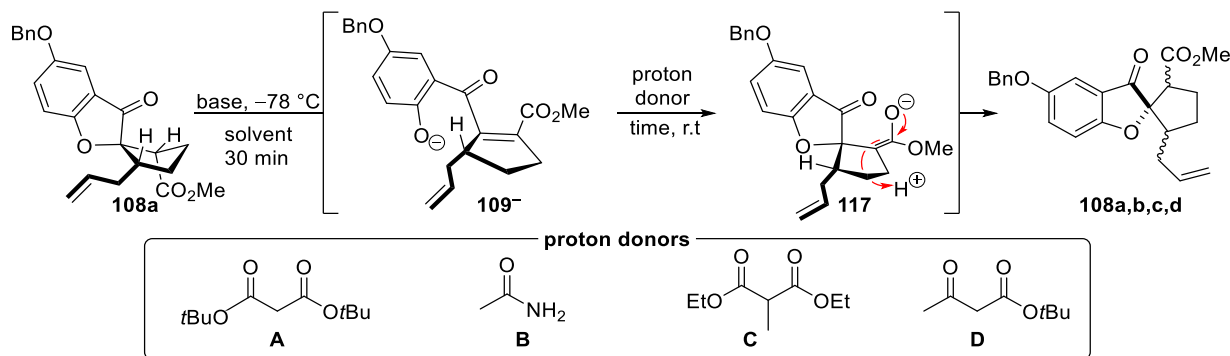
The *1,2-cis/2,3-cis* stereochemical relationship of the major diastereoisomer **108a** does not correspond to the configuration of any spiroapplanatumine isolated from *Ganoderma applanatum* typically having the *1,2-trans/2,3-cis* or *1,2-trans/2,3-trans* configuration (**Figure 10**). The DBU-mediated triflate migration/oxidative cyclization performed on the *1,2-cis/2,3-trans* precursor **113b** was not as clean as on **113a**, and a similar stereochemical outcome was observed (not shown). For this reason, epimerization experiments, potentially converting the major diastereoisomer **108a** into minor diastereoisomers **108b-d** were performed.

Figure 10: Structures and configurations of spiroapplanatumines isolated from *Ganoderma applanatum* by Cheng et al.^[27e]



The major diastereoisomer **108a** was deprotonated by lithium or potassium bases, rapidly inducing E1cB elimination, giving unsaturated phenolate **109⁻** even at low temperatures (**Table 12**) as determined by TLC analysis and further confirmed by ¹H NMR spectroscopy. The phenolate was treated by a proton donor quenching the ester enolate **117** after the ring-closing step. After the addition of the proton donor, the reaction mixture was stirred for a given time, and subsequently, ¹H NMR spectra of the crude reaction mixture were measured. Di-*tert*-butyl malonate, acetamide, or diethyl methylmalonate (entries 1-3) did not improve the ratio in favor of one of the minor diastereoisomers **108b-c**, and the formation of the parent spirocycle **108a** was observed as the dominant process. However, *tert*-butyl acetoacetate with KHMDS as a base increased the ratio towards the *1,2-trans*/*2,3-cis* diastereoisomer **108b** that was found together with the parent *1,2-cis*/*2,3-cis* isomer **108a** in a 1:1.1 ratio in favor of the parent compound (entry 4). A change of the base to LDA led to a worse ratio (entry 5). However, the change of the solvent to toluene gave rise to one of the minor diastereoisomers **108c** or **108d** (entry 6). These experiments show that the kinetic protonation is partially effective, but no selective epimerization was achieved.

Table 12: Epimerization experiments of spirocycle **108a** by E1cB elimination/oxa-Michael addition/protonation.



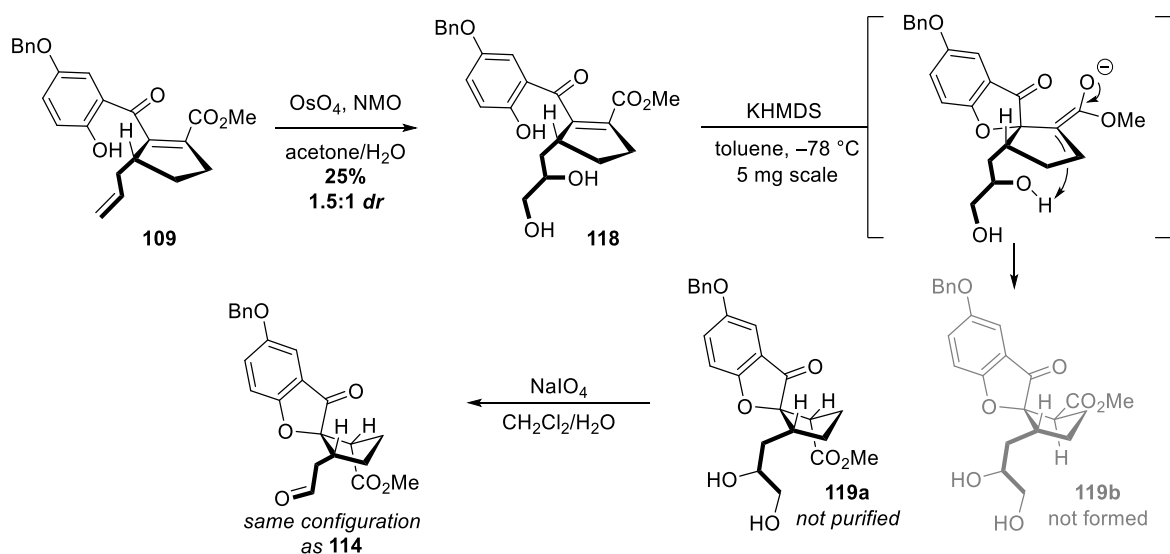
Entry	Base ^[a]	Solvent	Proton donor ^[b]	Time (h) ^[c]	<i>dr</i> ^[d] 108a:b:c:d	109 (mol%) ^[e]
1	KHMDS	THF	A	120	28:3:3:1	0
2	KHMDS	THF	B	24	16:2:1:1	0
3	KHMDS	THF	C	24	22:3:2:1	0
4	KHMDS	THF	D	40	33:29:2:1	15
5	LDA	THF	D	120	27:1:0:0	22
6	KHMDS	Toluene	D	24	28:4:1:10	0

^[a] 1.3 equiv. of the base used. ^[b] 1.5 equiv. of the proton donor used. ^[c] Reaction time after the addition of the proton donor.

^[d] Determined by ¹H NMR spectroscopy of the crude reaction mixture. ^[e] Molar percentage of the acyclic product **109** in the ¹H NMR of the crude reaction mixture.

The fact that the intermolecular protonation was not entirely selective led to the exploration of the intramolecular protonation possibilities. α,β -Unsaturated ketone **109** was dihydroxylated on a small scale giving a poor yield of the diol **118** with a free phenolic function (**Scheme 83**). The compound

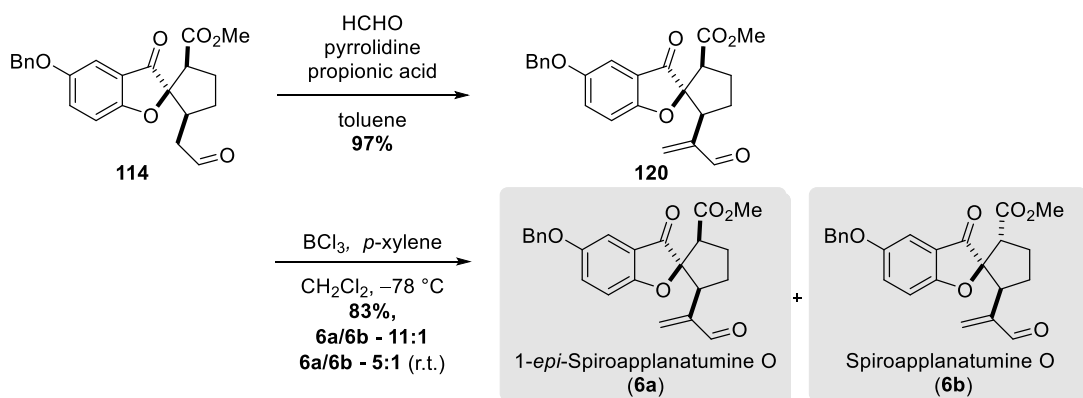
was treated with one equivalent KHMDS in toluene at $-78\text{ }^{\circ}\text{C}$, supposedly deprotonating only the phenolic portion. The phenolate underwent intramolecular oxa-Michael addition forming an ester enolate that was expected to be intramolecularly protonated by the present diol function, thus forming the *1,2-trans/2,3-cis* spirocyclic diol **119b**. However, this was not the case, and the *1,2-cis/2,3-cis* diastereoisomer **119a** was obtained as determined by its oxidative cleavage to aldehyde **114** and comparison of its crude ^1H NMR spectrum with that of compound **114** known from the previous synthesis (**Scheme 81**). Probably an intermolecular protonation or epimerization was operating, and therefore, further epimerization attempts were abandoned.



Scheme 83: Dihydroxylation of the α,β -unsaturated ketone **109** and an attempted cyclization/internal protonation.

The stereochemical outcome of the oxidative spirocyclization, forming the *1,2-cis/2,3-cis* diastereoisomer **108a**, and the inability to selectively epimerize present stereocenters led to the decision to execute the synthesis of the unnatural 1-*epi*-spiroapplanatamine O (**6a**). The aldehyde **114** was efficiently α -methylated, providing the α,β -unsaturated aldehyde **120** (**Scheme 84**). The removal of benzyl protecting groups by BCl_3 at $-78\text{ }^{\circ}\text{C}$ smoothly furnished 1-*epi*-spiroapplanatamine O (**6a**). Interestingly, minor epimerization at C1 occurred, and the product **6a** was isolated together with the naturally configured spiroapplanatamine O (**6b**) in an 11:1 diastereoisomeric ratio in 83% yield as an inseparable mixture. Warming the reaction mixture during the deprotection step from $-78\text{ }^{\circ}\text{C}$ to r.t. led to the formation of a 5:1 diastereoisomeric mixture.

The ^1H and ^{13}C NMR spectra of 1-*epi*-spiroapplanatamine O (**6a**) expectedly differed from spiroapplanatamine O isolated by Cheng et al. (**Table 13**). However, multiple resonances of the co-formed spiroapplanatamine O (**6b**) clearly showed a spectroscopic agreement with the natural product.



Scheme 84: The synthesis of 1-*epi*-spiroapplanatamine O (**6a**) and spiroapplanatamine O (**6b**).

Table 13: ¹H and ¹³C NMR spectral comparison of synthetic products **6a**, **6b**, and isolated spiroapplanatamine O.

6a 1-<i>epi</i>-Spiroapplanatamine O				6b Spiroapplanatamine O			
synthetic product [a]				synthetic product [a,b]		isolated product [c]	
No.	δ _H	δ _C	Δ δ _C	δ _H	δ _C	δ _H	δ _C
1		166.6	0		166.6		166.6
2	6.89 (dd, 8.9, 0.6)	114.4	0		114.4	6.85 (d, 8.8)	114.4
3	7.11 (dd, 8.9, 2.7)	128.4	0.2	7.11 (dd, 8.9, 2.7)	128.2	7.11 (dd, 8.8, 2.7)	128.2
4		154.1	0		154.0		154.1
5	6.87 (dd, 2.8, 0.5)	108.0	0		108.0	6.87 (d, 2.7)	108.0
6		123.6	0.6		123.0		123.0
7		202.3	1.6		203.9		203.9
8		97.5	1.1				96.4
9	3.55 (m)	46.1	1.1	3.40 (m)	47.2	3.40 (m)	47.2
10 ^a	2.22 (m)	31.1	0.9		30.2	2.11 (m)	30.2
10 ^b	2.13 (m)					2.08 (m)	
11 ^a	2.50 (m)	25.6	2.1		27.7	2.21 (m)	27.7
11 ^b	2.13 (m)					2.15 (m)	
12	3.59 (dd, 9.9, 7.3)	54.1	1.6	3.43 (m)	55.7	3.43 (m)	55.7
13		171.6	1.2		172.8		172.8
14		147.0	0.6		147.6		147.6
15	9.21 (s)	194.9	0.1	9.25 (s)	195.0	9.25 (s)	195.0
16 ^a	6.56 (d, 0.8)	138.9	0.7	6.52 (d, 1.1)	138.2	6.52 (s)	138.2
16 ^b	6.13 (s)			6.21 (s)		6.20 (s)	
OMe	3.32 (s)	51.9	0.3	3.48 (s)	52.2	3.48 (s)	52.2

For multiplets the central value is stated. [a] Measured on 600 MHz Bruker Avance in MeOH-*d*₄. [b] Only individually observed values are displayed. [c] Q. Luo, X.-Y. Wei, J. Yang, J.-F. Luo, R. Liang, Z.-C. Tu, Y.-X. Cheng, *J. Nat. Prod.* **2017**, *80*, 61-70.

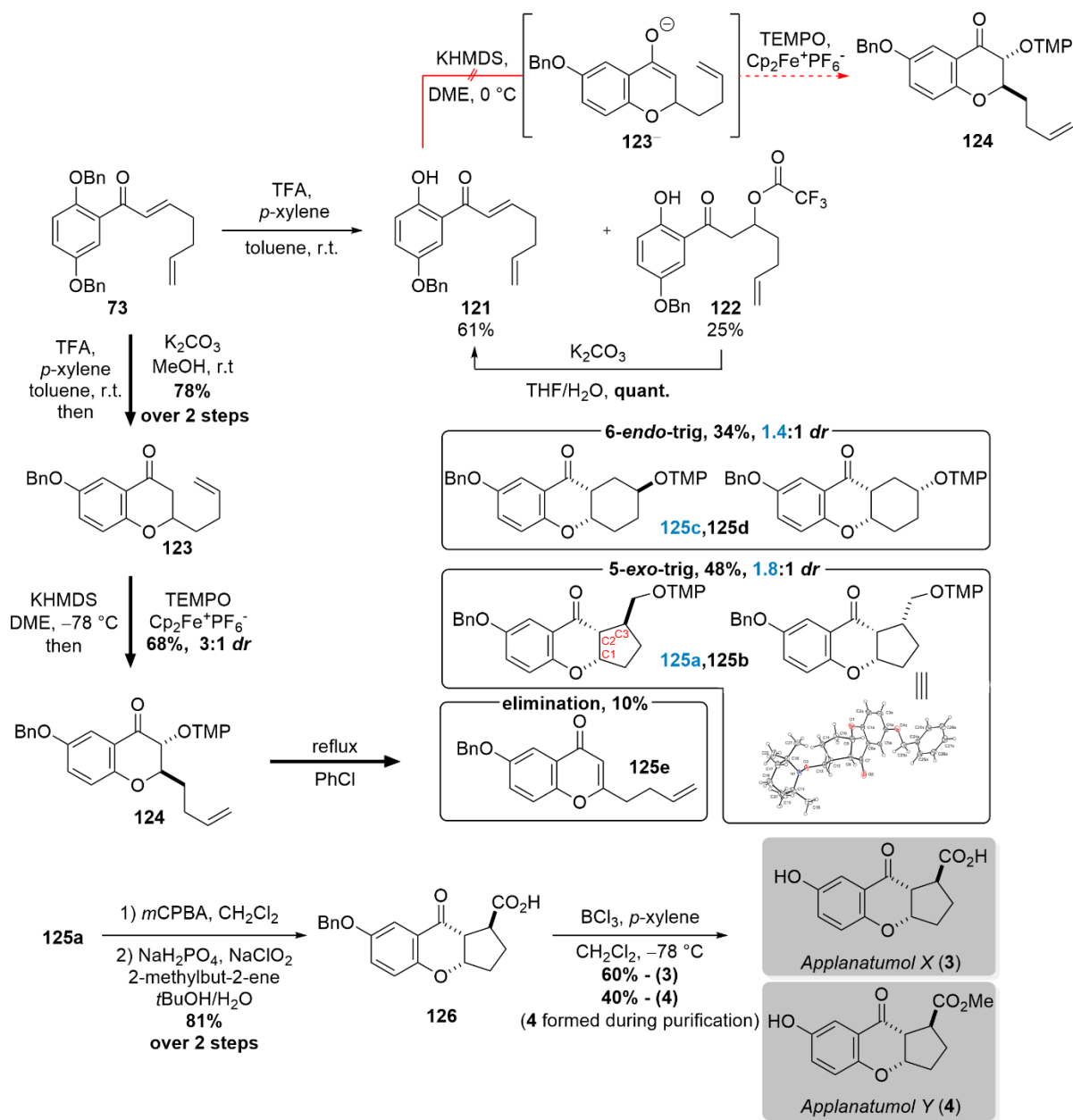
4.3.6. Synthesis of applanatumols X and Y

In comparison to applanatumols V, W, B, and spiroapplanatumines, applanatumol X (**3**) and its methyl ester applanatumol Y (**4**) lack the three-carbon unit at the position C3 of the cyclopentane ring. In contrast, this position is bonded to the *ortho*-phenolic hydroxyl forming a chromanone core. For this reason, our approach towards these natural products starts from α,β -unsaturated ketone **73**, and no introduction of the three-carbon unit by allylation was necessary.

The α,β -unsaturated ketone **73** was mono-deprotected by TFA, giving 61% yield of the phenol **121** and 25% yield of the deprotected β -trifluoroacetoxy ketone **122** (Scheme 85). This product rapidly eliminated upon treatment with K_2CO_3 , giving the parent compound **121** in quantitative yield. It was anticipated that the intramolecular oxa-Michael addition of the phenol **121**, forming a chromanone enolate **123⁻**, might be coupled with SET oxidation and oxygenation by TEMPO, directly giving α -aminoxy ketone **124** in a single step. This sequence proved unsuccessful, and phenol **121** upon deprotonation with KHMDS resulted in a mixture of unspecified phenolic products. For this reason, the tandem sequence was abandoned, and the reactions were performed sequentially.

The chromanone ring-closure was achieved under the same reaction conditions as the elimination of compound **122**; therefore, after TFA-mediated benzyl group removal, the reaction mixture was treated with K_2CO_3 in MeOH, directly forming chromanone **123** in a good yield. The deprotonation of the chromanone **123** at $-78\text{ }^\circ\text{C}$ by KHMDS and subsequent radical α -oxygenation with TEMPO provided α -aminoxy ketone **124** in moderate yield as a 3:1 *trans/cis* diastereoisomeric mixture without any ring-opening observed.

The thermal cyclization of **124**, performed in refluxing PhCl, formed a 1.8:1 diastereoisomeric mixture of cyclopentanes **125a,b** in 48% yield by 5-*exo*-trig cyclization, 1.4:1 diastereoisomeric mixture of cyclohexanes **125c,d** in 34% yield by 6-*endo*-trig cyclization, and a product of TEMPOH elimination **125e** in 10% yield. Optimization of the cyclization conditions in terms of temperature and concentration did not significantly improve the ratio between 5-*exo* and 6-*endo* cyclization products (not shown).

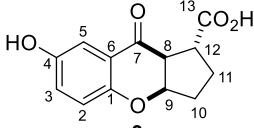


Scheme 85: Synthesis of applanatumols X and Y.

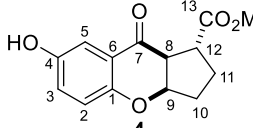
The relative configuration of formed products was analyzed by NOE experiments showing the *1,2-cis/2,3-trans* configuration for the major diastereoisomers **125a** and *1,2-cis/2,3-cis* configuration for the minor diastereoisomer **125b**. Furthermore, the minor diastereoisomer **125b** crystallized, and the X-ray crystallography confirmed its *1,2-cis/2,3-cis* relative configuration. The configuration of co-formed cyclohexane derivatives **125c,d** by 6-*endo*-trig cyclization was analyzed by NOE experiment showing *1,2-cis/1,4-trans* configuration for the major diastereoisomer **125c** and *1,2-cis/1,4-cis* for the minor diastereoisomer **125d**.

The synthesis of applanatumol X was continued with the oxidation of the major diastereoisomer **125a** by *m*CPBA, providing an aldehyde that was without purification submitted to Pinnick oxidation generating the free carboxylic acid **126** in high yield over two steps. Removal of the benzyl protecting group was achieved by BCl₃ at low temperature, smoothly forming applanatumol X (**3**) in a quantitative yield. However, during the chromatographic purification in CH₂Cl₂/MeOH, the carboxylic acid was partially esterified, resulting in the formation of applanatumol X (**3**) in 60% and applanatumol Y (**4**) in 40% yield. The ¹H and ¹³C NMR spectra of both products were identical to those isolated by Cheng et al., thus confirming the relative configuration of both natural products (**Table 14**).

Table 14: ¹H and ¹³C NMR spectral comparison of synthetic and isolated applanatumols X and Y.



3
Applanatumol X



4
Applanatumol Y

No.	synthetic material ^[a]			isolated material ^[b]			synthetic material ^[a]			isolated material ^[b]		
	δ _H	δ _C	Δ δ _C	δ _H	δ _C		δ _H	δ _C	Δ δ _C	δ _H	δ _C	
1		155.7	0		155.7			155.7	0		155.7	
2	6.84 (d, 8.9)	120.2	0	6.83 (d, 8.9)	120.2		6.84 (dd, 8.9, 0.4)	120.2	0.1	6.83 (d, 8.9)	120.3	
3	7.02 (dd, 8.9, 3.1)	126.3	0	7.02 (dd, 8.9, 2.9)	126.3		7.02 (dd, 8.9, 3.1)	126.3	0	7.03 (dd, 8.9, 2.9)	126.3	
4		153.0	0		153.0			153.2	0.1		153.1	
5	7.16 (d, 3.1)	111.4	0.1	7.16 (d, 2.9)	111.3		7.15 (dd, 3.0, 0.4)	111.3	0	7.15 (d, 2.9)	111.3	
6		120.5	0		120.5			120.5	0		120.5	
7		194.7	0.1		194.8			194.4	0.1		194.5	
8	3.09 (dd, 9.7, 4.3)	55.2	0	3.08 (m)	55.2		3.06 (m)	55.4	0	3.03 (m)	55.4	
9	4.96 (m)	84.6	0	4.95 (dd, 6.3, 3.2)	84.6		4.96 (m)	84.5	0	4.95 (dd, 6.3, 3.2)	84.5	
10 ^a	2.13 (m)	33.0	0	2.09 (m)	33.0		2.13 (m)	33.0	0	2.12 (m)	33.0	
10 ^b												
11 ^a	2.33 (m)	29.0	0	2.32 (m)	29.0		2.31 (m)	28.7	0	2.31 (m)	28.7	
11 ^b	2.03 (m)			2.02 (m)			2.02 (m)			2.02 (m)		
12	3.03 (td, 9.9, 6.5)	47.0	0.1	3.03 (m)	47.1		3.06 (m)	46.7	0	3.07 (m)	46.7	
13		178.0	0.2		178.2			176.5	0.1		176.6	
OMe							3.71 (s)	52.7	0	3.66 (s)	52.7	

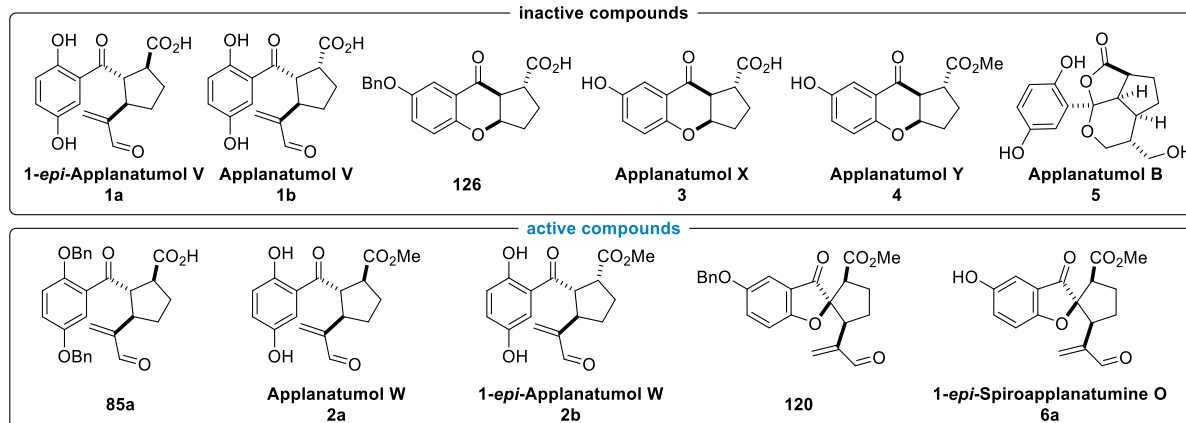
For multiplets the central value is stated. ^[a] Measured on 600 MHz Bruker Avance in MeOH-*d*₄. ^[b] Q. Luo, X.-H. Yang, Z.-L. Yang, Z.-C. Tu, Y.-X. Cheng, *Tetrahedron* **2016**, 72, 4564-4574.

4.3.7. Biological investigation of meroterpenoids

Various types of α,β-unsaturated carbonyl compounds have been described as potential anticancer agents, exhibiting cytotoxic properties by acting as Michael acceptors for biogenic nucleophiles.^[131] To investigate if *Ganoderma* meroterpenoids show cytotoxic activity, selected meroterpenoids and their benzyl-protected precursors **1a,b,2a,b,3,4,5,6a,85a,120,126** (**Figure 11**) were tested *in vitro* against various human cancer cell-lines in cytotoxicity assays. Cervix cancer (HeLa), breast cancer

(MCF-7, T47-D), colorectal cancer (RKO, HCT-116, LoVo), hepatocellular carcinoma (Hep G2), acute promyelocytic leukemia (HL-60), and acute lymphoblastic leukemia (CCRF-CEM) cell-lines were used. For the tumor-selectivity index (SI) determination, the compounds were tested against primary normal human dermal fibroblasts (NHDF).

Figure 11: Meroterpenoids tested in cytotoxicity studies.



All compounds were tested in triplicate, and the compound concentrations required for 50% cell-viability reduction (IC_{50}) are expressed as mean $\pm$ standard deviation (SD). The tumor-selectivity indexes (SI) were calculated by the following equation: $SI = \text{mean } IC_{50} \text{ against normal cells} / \text{mean } IC_{50} \text{ against tumor cells}$. Compounds **1a,b,3,4,5,126** did not show any significant cytotoxicity. Compounds **2a,b,6a,85a,120** showed high IC_{50} against cancerous cells ($IC_{50} \sim 0.4\text{--}29 \mu\text{M}$) with low to high selectivities ($SI \sim 1.5\text{--}30$, **Table 15**). The results show that the α -methylene carbaldehyde structural motif is crucial for cytotoxic properties of tested meroterpenoids. Compounds with free carboxylic acid functions or with corresponding methyl esters are both active; free phenolic hydroxyls are not essential. However, the complete deprotection in **1a,b** leads to full activity loss. In conclusion, *Ganoderma* meroterpenoids bearing the α -methylene carbaldehyde pharmacophore may serve as promising candidates to be further investigated in anticancer research.

Table 15: Cytotoxic activities (IC_{50}) and selectivity indexes (SI) of compounds **2a,b,6a,85a,120** against selected human cancer cells and normal human primary fibroblasts (NHDF) expressed as $\mu\text{M} \pm \text{SD}$. Experiments performed by Dr. Miroslav Hájek.

	HELA	MCF-7	RKO	HCT-116	HEP G2	HL-60	CCRF-CEM	T47-D	LOVO	NHDF
85a	4.3 ± 0.8	11.3 ± 6.0	5.4 ± 0.3	4.9 ± 0.2	10.2 ± 3.3	4.4 ± 0.5	2.9 ± 0.1	10.1 ± 6.0	4.9 ± 1.5	21.1 ± 4.7
SI	4.9	1.9	3.9	4.3	2.1	4.8	7.3	2.1	4.3	
2a	2.7 ± 0.8	1.9 ± 0.2	1.6 ± 0.5	1.1 ± 0.1	4.8 ± 1.7	1.8 ± 0.03	0.6 ± 0.02	3.1 ± 1.8	1.6 ± 0.6	8.3 ± 1.3
SI	3.0	4.3	5.4	7.7	1.7	4.5	15.0	2.7	5.2	
2b	1.8 ± 0.5	1.7 ± 0.4	1.3 ± 0.4	0.8 ± 0.06	3.8 ± 2.0	1.6 ± 0.2	0.4 ± 0.04	2.4 ± 0.8	1.1 ± 0.7	7.3 ± 2.2
SI	4.0	4.4	5.6	9.0	1.9	4.6	16.5	3.0	6.6	
120	2.6 ± 0.8	2.8 ± 0.9	1.4 ± 0.3	1.8 ± 0.07	7.1 ± 4.3	2.6 ± 0.4	1.0 ± 0.2	2.8 ± 1.0	2.8 ± 1.4	10.5 ± 0.6
SI	4.0	3.7	7.3	5.9	1.5	4.0	10.1	3.8	3.7	
6a	28.8 ± 30.6	10.7 ± 2.5	5.6 ± 1.2	5.6 ± 0.5	15.1 ± 4.6	12.4 ± 1.2	3.0 ± 0.4	8.0 ± 3.0	8.2 ± 5.0	88.8 ± 39.8
SI	3.1	8.3	16.0	15.8	5.9	7.2	29.8	11.1	10.9	

5. CONCLUSIONS AND PERSPECTIVES

Merging sigmatropic rearrangements with radical reactions in tandem processes presents an attractive approach to rapidly increase molecular complexity by combining two distinct reactivity patterns. In the presented work, the anionic oxy-Cope rearrangement was successfully coupled with the single-electron oxidation of the generated metal enolate. The formed α -carbonyl radicals were converted into corresponding rearranged α -aminoxyl carbonyl compounds by coupling them with the persistent radical TEMPO.

Optimization of the tandem sequence revealed that acceleration of the AOC by KHMDS applied as a base is compatible with the subsequent oxygenation of the formed potassium enolate by oxidation with ferrocenium hexafluorophosphate in the presence of TEMPO. Testing the developed tandem sequence on a spectrum of substrates proved its generality and reliability. A diverse range of rearranged α -aminoxyl carbonyl compounds was obtained in mostly high yields with moderate to low *anti/syn* (*cis/trans*) diastereoselectivity from corresponding hexa-1,5-dien-3-ols.

The AOC/oxygenation sequence can be extended by subsequent polar processes as shown by *in situ* allylation or reduction of the phenone moiety, providing protected diols with exclusive diastereoselectivity. Coupling of the AOC/oxygenation sequence with initial nucleophilic addition of generated allyl potassium to α,β -unsaturated ketones was also demonstrated.

Accordingly to our initial hypothesis, it was confirmed that rearranged α -aminoxyl carbonyl compounds with the inherently placed double bond in the δ -position of the carbonyl group undergo thermal *all-carbon 5-endo-trig* cyclizations governed by the persistent radical effect. The reaction outcomes and product yields are, however, highly substrate-dependent. Faster competitive cyclization modes outperform the kinetically slow *5-endo-trig* cyclization as exemplified by the *5-exo-trig* cyclization of a β -homoallyl unit-containing substrate producing structurally distinct cyclopentane derivatives.

The applicability of the AOC/oxygenation and PRE-based *5-exo-trig* cyclization sequence was challenged on total syntheses of applanatumols and spiroapplanatumines, meroterpenoid metabolites isolated from fungal species *Ganoderma applanatum*. The developed synthetic methodology allowed the preparation of a stereodefined carbocyclic intermediate modifiable to targeted meroterpenoids. The preparation of the central intermediate was achieved in seven steps from 2',5'-dihydroxyacetophenone, and pent-4-enal as accessible starting materials.

The total synthesis of applanatumols V and W was accomplished in 10 and 11 steps, respectively; however, the comparison of the spectral data with the isolated material revealed that the initially proposed 1,2-*trans*/2,3-*trans* stereochemistry of applanatumol V was misassigned. For this reason, the 1,2-*cis*/2,3-*trans* diastereoisomers of applanatumols V and W were synthesized, correcting the applanatumol's V stereochemistry.

Modification of the common carbocycle enabled the total synthesis of applanatumol B accomplished in 13 synthetic steps. Early-stage diversification of the main synthetic route by intramolecular oxa-Michael addition, radical α -oxygenation/PRE-based cyclization formed the carbocyclic core of applanatumols X and Y. Their total syntheses were accomplished in a total of 9 steps and confirmed the proposed relative configuration.

Access to the spiroapplanatumine family of meroterpenoids was provided by a triflate migration/oxidative spirocyclization reaction performed on the common carbocyclic core. This highly diastereoselective step furnished an unnatural *1,2-cis/2,3-cis* epimer of the spiroapplanatumine core, and the synthetic endeavor resulted in the total synthesis of 1-*epi*-spiroapplanatumine O in a total of 14 reaction steps.

The prepared natural products and their congeners were ultimately submitted to biological activity studies. Particular α,β -unsaturated aldehyde-containing natural products, and their benzyl-protected precursors revealed cytotoxicities in the ranges of $IC_{50} \sim 0.4\text{--}29 \mu\text{M}$ against various human cancer cell lines with good tumor-selectivity indexes (SI $\sim 1.5\text{--}30$). For this reason, applanatumols and spiroapplanatumines bearing the electrophilic α -methylene carbaldehyde structural motif seem to be promising candidates for further development as anti-cancer agents.

The described work presents one of the first mergers of sigmatropic rearrangements with radical reactions that so far remained elusive and brings significant improvements into the well-established repertoire of free radical methods. It shows that *all-carbon 5-endo-trig* cyclization is achievable and applicable in the synthesis of cyclopentanes if the persistent radical effect is employed. The developed methodology offers the first synthetically useful application of this rare cyclization mode on *all-carbon* systems without significant substrate preorganization. The possible preparation of the cyclization precursor in a single-step from α,β -unsaturated carbonyl compounds represents a straightforward and a step-economic strategy, well suited for the late-stage modification of complex molecules. Overall the developed methodologies serve as a versatile approach to diverse polyfunctional scaffolds with high-synthetic utility as demonstrated by the developed unified approach to *Ganoderma* meroterpenoids. This synthetic challenge demonstrates that the frequently low diastereoselectivity of radical cyclization steps can be beneficially used in preparing natural product epimers allowing their stereochemical verification and revision.

Further improvements and extensions can be foreseen. The application of allylpotassium in the AOC/oxygenation tandem sequence has been demonstrated; however, a practical preparation of allylic potassium nucleophiles from gaseous alkenes, allyl halides, allyl silanes, or other precursors remains to be developed. Although methods for asymmetric 1,2-allylation reactions of α,β -unsaturated carbonyl compounds are known, and the AOC proceeds with a stereo-retention, the preparation of enantiomerically enriched carbocyclic rings by these methodologies awaits to be realized.^[132] Other attractive possibilities might be envisaged in applying α -aminoxy carbonyls in transition metal-

catalyzed cross-coupling reactions by coupling the thermally generated transient α -carbonyl radical to a metal center forming diverse C–C or C–Het bonds upon the reductive elimination.^[133]

We believe that the results presented in this work will form a sound basis for developing new powerful synthetic methodologies merging sigmatropic rearrangements with radical reaction steps. It is expected that the kinetically slow 5-*endo*-trig cyclization mode will no longer be perceived as impractical and that target-oriented syntheses exploiting this cyclization mode will be disclosed in the future. Furthermore, the acquired data from the synthetic campaign towards *Ganoderma* meroterpenoids will be beneficial for synthetic chemists to prepare other members of this diverse family of natural products, shed light on their biological activity and eventually find ways to benefit from them.

6. EXPERIMENTAL PART

6.1. GENERAL EXPERIMENTAL INFORMATION

Reactions not involving aqueous conditions were performed in flame-dried glassware under an argon atmosphere. Solvents and additives were dried before use according to standard procedures. TLC analyses were performed on POLYGRAM SIL G/UV254 plates. Chromatographic separations were carried out on silica gel 60 (Fluka, 230-400 mesh) manually or on a CombiFlash® NextGen 300+ instrument. IR spectra were measured on Bruker ALPHA-FT-IR spectrometer as neat samples using an ATR device. Combustion and optical rotation analyses were performed at the Microanalytical Laboratories of the IOCB ASCR. Microwave-assisted reactions were performed using a CEM Discover® SP instrument. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 400, 500, or 600 spectrometers at working frequencies of 400, 500, or 600 MHz for ¹H NMR spectra and 100.1, 125.7, or 150.9 MHz for ¹³C NMR spectra. Connectivity was determined by ¹H-¹H COSY and ¹H-¹³C HMBC experiments, ¹³C NMR assignments were obtained from APT and HSQC measurements. Relative configurations of cyclic compounds were determined by ¹H, ¹H-ROESY experiments. In inseparable mixtures of diastereoisomers, the major diastereoisomer is displayed; their ¹H and ¹³C spectra are assigned separately in two sets of signals.

6.2. GENERAL REACTION PROCEDURES

A) Allylation of α,β -unsaturated ketones by allylic Grignard reagents

In a 250 mL flame-dried Schlenk flask, the α,β -unsaturated ketone **31** (4.8 mmol) was dissolved in dry THF (48 mL) under an argon atmosphere. At 0 °C allylmagnesium chloride (3.12 mL, 6.24 mmol, 2M in THF) was dropwise added by syringe. The mixture was stirred at this temperature for 1 h. After the reaction was complete as judged by TLC analysis, the mixture was quenched by saturated NH₄Cl solution (25 mL) and extracted by Et₂O (3×25 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc) to yield alcohol **25**.

B) Allylation of α,β -unsaturated ketones by allylic zinc reagents

In a 50 mL flame-dried Schlenk flask, Zn dust (<10 μ m-Sigma-Aldrich, 941 mg, 14.4 mmol) was suspended in dry THF (1 mL) under an argon atmosphere. 1,2-Dibromoethane (50 μ L, 0.58 mmol) was added by syringe at r.t. The mixture was immersed into a preheated oil bath (65 °C) for 2 min, cooled to r.t. and TMSCl (75 μ L, 0.6 mmol) was added. The mixture was stirred for 15 min, and allylic bromide (7.2 mmol) was dropwise added by syringe. The mixture was stirred for 1 h, diluted with additional THF (24 mL), and a solution of α,β -unsaturated ketone **31** (4.8 mmol) in THF (5 mL) was dropwise added. The mixture was refluxed for 2 h, cooled to r.t., quenched by saturated NH₄Cl solution (10 mL), and extracted by Et₂O (3×10 mL). The combined organic layers were dried over MgSO₄, filtered, and

evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc, 10:1) to yield alcohol **25**.

C) Allylation of α,β -unsaturated ketones by allylic chromium reagents^[105]

In a 100 mL flame-dried Schlenk flask, CrCl_2 (451 mg, 3.67 mmol) was heated to 50 °C at 1 mbar for 15 min, suspended in dry THF (15 mL), and TMEDA (0.55 mL, 3.67 mmol) was added. After stirring at r.t. for 1 h, the mixture was cooled to -35 °C, and PhMgBr (7.5 mL, 7.5 mmol, 1M in THF) was added slowly. After stirring for 30 min, the mixture was cooled to -60 °C, and a solution of allylic bromide (1.83 mmol) in THF (15 mL) was dropwise added by a syringe pump over 30 min. At -60 °C, a solution of α,β -unsaturated ketone **31** (0.92 mmol) in THF (15 mL) was added. After stirring for 20 min, the reaction was quenched by the addition of 5% HCl solution (40 mL). The mixture was extracted by Et_2O (4×25 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and evaporated. The crude product was purified by column chromatography (hexane/EtOAc, 20:1, gradient to 10:1) to yield alcohol **25**.

D) Tandem AOC/ α -oxygenation by TEMPO/ $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ system

In a flame-dried Schlenk flask, alcohol **25** (1.0 mmol) was dissolved in DME (20 mL). At 0 °C, KHMDs (1.3 mL, 1.3 mmol, 1M in THF) was dropwise added. The mixture was warmed to the appropriate temperature and stirred until complete as judged by TLC analysis. After cooling to r.t., TEMPO (1.1 mmol) was added in one portion. The mixture was cooled to -78 °C, and $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ (1.6 mmol) was added in small portions (~50 mg/30 s) until the mixture remained dark blue. The mixture was stirred for additional 20 min, quenched by saturated NH_4Cl solution (10 drops), diluted with Et_2O (25 mL), and filtered through a plug of silica gel, which was washed by Et_2O . The solution was evaporated, and the crude product was purified by column chromatography (neat hexane, gradient to 10:1 hexane/ Et_2O) to yield α -aminoxy carbonyl compound **28** as a mixture of *syn/anti* (*cis/trans*) diastereoisomers.

E) Microwave-assisted radical cyclization

In a microwave reaction tube, α -aminoxy carbonyl compound **28** (0.2 mmol) was dissolved in degassed PhCF_3 (4.0 mL) under an argon atmosphere. The mixture was heated in a microwave reactor to the appropriate temperature for 45-120 min. After cooling, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc, 30:1, gradient to 10:1) to yield cyclopentane **50** as a mixture of diastereoisomers.

F) Microwave-assisted radical cyclization with purification by Upjohn dihydroxylation

In a microwave reaction tube, α -aminoxy carbonyl compound **28** (0.20 mmol) was dissolved in degassed PhCF_3 (4.0 mL) under an argon atmosphere. The mixture was heated in a microwave reactor to the appropriate temperature for 45-120 min. After cooling, the solvent was removed under reduced pressure, and the residue was dissolved in a 10:1 acetone/ H_2O mixture (1 mL). OsO_4 (137 μL ,

0.01 mmol, 2.5% solution in *t*BuOH) and NMO (23 mg, 0.20 mmol) were subsequently added. The mixture was stirred at r.t. for 1 h until complete as judged by TLC analysis, evaporated, and directly separated by column chromatography (hexane/EtOAc, 10:1) to yield cyclopentane **50** as a mixture of diastereoisomers.

G) Oxidative deprotection of the aminoxy unit

In a round-bottomed flask, cyclopentane **50** (0.13 mmol, mixture of diastereoisomers) was dissolved in dry CH₂Cl₂ (2.6 mL). *m*CPBA (75%, 39 mg, 0.17 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h, warmed to r.t., and diluted by Et₂O (10 mL). The solution was filtered through a plug of silica gel, which was washed by Et₂O. The solvent was evaporated, and the crude product was purified by column chromatography (hexane/EtOAc, 10:1, gradient to 5:1) to yield a single diastereoisomer of cyclopentanone **51**.

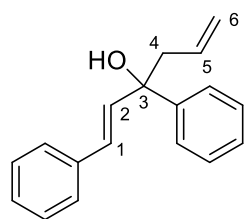
6.3. EXPERIMENTAL DETAILS AND CHARACTERIZATIONS OF COMPOUNDS

Compounds are ordered as they appear in the section Results and discussion.

TANDEM AOC/RADICAL REACTIONS

6.3.1. Preparation of carbinols

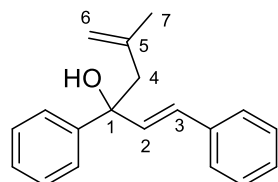
(*E*)-1,3-Diphenylhexa-1,5-dien-3-ol (**25a**)



Prepared according to general procedure **A** from (*E*)-1,3-diphenylprop-2-en-1-one (1.0 g, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 7:1, gradient to 5:1) gave 1.18 g (98%) of **25a** as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.53-7.49 (m, 2H, CH_{Ar}), 7.40-7.34 (m, 4H, CH_{Ar}), 7.33-7.26 (m, 3H, CH_{Ar}), 7.25-7.18 (m, 1H, CH_{Ar}), 6.65 (d, *J* = 16.0 Hz, 1H, CH-1), 6.53 (d, *J* = 16.0 Hz, 1H, CH-2), 5.72 (ddt, *J* = 17.4, 10.1, 7.3 Hz, 1H, CH-5), 5.24-5.17 (m, 2H, CH₂-6), 2.86-2.75 (m, 2H, CH₂-4), 2.29 (s, 1H, OH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 145.3 (C_{Ar}), 136.7 (C_{Ar}), 135.2 (C-2), 133.1 (C-5), 128.5 (CH_{Ar}), 128.32 (C-1), 128.30 (CH_{Ar}), 127.6 (CH_{Ar}), 127.0 (CH_{Ar}), 126.5 (CH_{Ar}), 125.4 (CH_{Ar}), 120.2 (C-6), 75.6 (C-3), 47.1 (C-4). The spectral data match those reported in the literature.^[134]

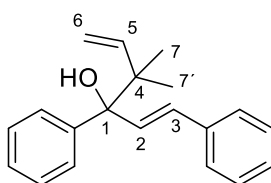
(*E*)-5-Methyl-1,3-diphenylhexa-1,5-dien-3-ol (**25b**)



Prepared according to general procedure **B** from (*E*)-1,3-diphenylprop-2-en-1-one (1.0 g, 4.8 mmol) and methylallene bromide (972 mg, 7.2 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 768 mg (61%) of **25b** as a colorless oil.

R_F = 0.34 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.53-7.48 (m, 2H, CH_{Ar}), 7.37-7.14 (m, 8H, CH_{Ar}), 6.66 (d, J = 15.9 Hz, 1H, CH-3), 6.55 (d, J = 15.9 Hz, 1H, CH-2), 4.93 (dq, J = 2.1, 1.5 Hz, 1H, CH₂-6), 4.81 (dq, J = 1.8, 0.8 Hz, 1H, CH₂-6), 2.79-2.71 (m, 2H, CH₂-4), 2.61 (s, 1H, OH), 1.54 (dd, J = 1.5, 0.8 Hz, 3H, CH₃-7). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 145.9 (C_{Ar}), 142.2 (C-5), 137.1 (C_{Ar}), 136.0 (C-2), 128.7 (CH_{Ar}), 128.4 (CH_{Ar}), 127.7 (C-3), 127.6 (CH_{Ar}), 127.0 (CH_{Ar}), 126.7 (CH_{Ar}), 125.5 (CH_{Ar}), 116.7 (C-6), 75.1 (C-1), 51.2 (C-4), 24.6 (C-7). **MS** (CI⁺) m/z (%) 265 ([M+H⁺], 10), 264 ([M]⁺, 15), 247 ([M-OH]⁻, 40), 246 ([M-H₂O]⁺, 40), 209 ([M-methallyl]⁺, 100), 208 ([PhCOCH=CHPh]⁺, 50). **HRMS** (CI⁺) m/z [M+H⁺] calcd for C₁₉H₂₁O: 265.1592; found: 265.1589. **IR** (neat): ν_{max} = 3534, 3026, 2946, 1640, 1599, 1493, 1446, 1347, 1071, 1028, 967, 893, 743, 692 cm⁻¹.

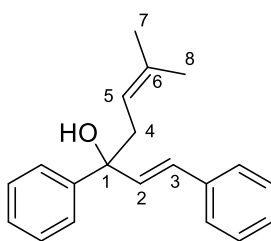
(*E*)-4,4-Dimethyl-1,3-diphenylhexa-1,5-dien-3-ol (25c)



Prepared according to general procedure **C** from (*E*)-1,3-diphenylprop-2-en-1-one (192 mg, 0.92 mmol) and prenyl bromide (273 mg, 1.83 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 20:1, gradient to 10:1) gave 251 mg (98%) of **25c** as a colorless oil.

$^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.52 (dt, J = 8.2, 1.0 Hz, 2H, CH_{Ar}), 7.40 (d, J = 7.1 Hz, 2H, CH_{Ar}), 7.34-7.30 (m, 4H, CH_{Ar}), 7.28-7.19 (m, 2H, CH_{Ar}), 7.08 (d, J = 15.8 Hz, 1H, CH-3), 6.70 (d, J = 15.8 Hz, 1H, CH-2), 5.95 (dd, J = 17.5, 10.8 Hz, 1H, CH-5), 5.15 (dd, J = 10.9, 1.4 Hz, 1H, CH₂-6), 5.10 (dd, J = 17.5, 1.4 Hz, 1H, CH₂-6), 1.82 (bs, 1H, OH), 1.09 (s, 3H, CH₃-7 or 7'), 1.04 (s, 3H, CH₃-7 or 7'). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 144.8 (CH-5), 143.5 (C_{Ar}), 137.4 (C_{Ar}), 133.6 (C-2), 129.5 (C-3), 128.7 (CH_{Ar}), 127.60 (CH_{Ar}), 127.58 (CH_{Ar}), 127.4 (CH_{Ar}), 126.9 (CH_{Ar}), 126.7 (CH_{Ar}), 114.6 (C-6), 79.5 (C-1), 45.5 (C-4), 23.3 (C-7 or 7'), 21.9 (C-7 or 7'). The spectral data match those reported in the literature.^[135]

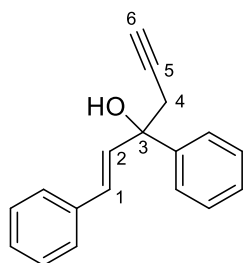
(*E*)-6-Methyl-1,3-diphenylhepta-1,5-dien-3-ol (25d)



Prepared according to general procedure **B** from (*E*)-1,3-diphenylprop-2-en-1-one (1.0 g, 4.8 mmol) and prenyl bromide (1.07 g, 7.2 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 30:1, gradient to 10:1) gave 641 mg (48%) of **25d** as a colorless oil.

$^1\text{H NMR}$ (401 MHz, Chloroform- d) δ 7.55-7.50 (m, 2H, CH_{Ar}), 7.41-7.19 (m, 8H, CH_{Ar}), 6.65 (d, J = 16.0 Hz, 1H, CH-3), 6.53 (d, J = 16.0 Hz, 1H, CH-2), 5.10 (ddq, J = 8.9, 5.7, 1.4 Hz, 1H, CH-5), 2.82-2.69 (m, 2H, CH₂-4), 2.26 (bs, 1H, OH), 1.72 (s, 3H, CH₃-8), 1.66 (s, 3H, CH₃-7). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 145.9 (C_{Ar}), 137.6 (C-6), 137.1 (C_{Ar}), 135.7 (C-2), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.2 (C-3), 127.6 (CH_{Ar}), 127.0 (CH_{Ar}), 126.7 (CH_{Ar}), 125.6 (CH_{Ar}), 118.2 (C-5), 76.6 (C-1), 41.4 (C-4), 26.2 (C-8), 18.3 (C-7). The spectral data match those reported in the literature.^[136]

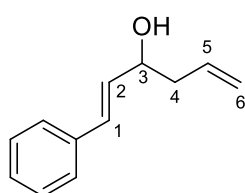
(*E*)-1,3-Diphenylhex-1-en-5-yn-3-ol (**25e**)



Prepared according to general procedure **C** from (*E*)-1,3-diphenylprop-2-en-1-one (192 mg, 0.92 mmol) and propargyl bromide (0.20 mL, 1.83 mmol, 80% in toluene). Purification of the crude product by column chromatography (hexane/Et₂O, 15:1, gradient to 7:1) gave 178 mg (78%) of **25e** as a colorless oil.

¹H NMR (401 MHz, Chloroform-*d*) δ 7.56-7.52 (m, 2H, CH_{Ar}), 7.43-7.22 (m, 8H, CH_{Ar}), 6.71 (d, *J* = 16.0 Hz, 1H, CH-1), 6.54 (d, *J* = 16.0 Hz, 1H, CH-2), 2.95 (d, *J* = 2.6 Hz, 2H, CH₂-4), 2.67 (s, 1H, OH), 2.08 (t, *J* = 2.6 Hz, 1H, CH-6). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 144.2 (C_{Ar}), 136.6 (C_{Ar}), 133.8 (C-2), 129.5 (C-1), 128.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (CH_{Ar}), 126.8 (CH_{Ar}), 125.7 (CH_{Ar}), 79.9 (C-5), 75.6 (C-3), 72.5 (C-6), 33.6 (C-4). The spectral data match those reported in the literature.^[137]

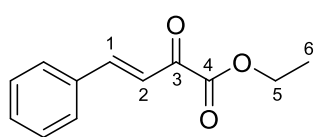
(*E*)-1-Phenylhexa-1,5-dien-3-ol (**25f**)



Prepared according to general procedure **A** from cinnamaldehyde (634 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1, gradient to 5:1) gave 719 mg (86%) of **25f** as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.43-7.35 (m, 2H, CH_{Ar}), 7.35-7.28 (m, 2H, CH_{Ar}), 7.27-7.19 (m, 1H, CH_{Ar}), 6.61 (dd, *J* = 15.9, 1.2 Hz, 1H, CH-1), 6.24 (dd, *J* = 15.9, 6.3 Hz, 1H, CH-2), 5.86 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H, CH-5), 5.22-5.15 (m, 2H, CH₂-6), 4.39-4.34 (m, 1H, CH-3), 2.49-2.35 (m, 2H, CH-4), 1.71 (s, 1H, OH). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 136.6 (C_{Ar}), 134.0 (C-2), 131.5 (C-5), 130.4 (C-1), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 126.5 (CH_{Ar}), 118.5 (C-6), 71.7 (C-3), 42.0 (C-4). The spectral data match those reported in the literature.^[138]

Ethyl (*E*)-2-oxo-4-phenylbut-3-enoate (**31g**)



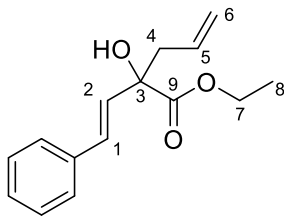
In a 50 mL round-bottomed flask, benzaldehyde (2.54 mL, 25 mmol) and pyruvic acid (1.76 mL, 25 mmol) were dissolved in MeOH (2.0 mL). At 0 °C, a solution of KOH (2.1 g, 37.5 mmol) in MeOH (7.5 mL) was dropwise added, the mixture was stirred at 40 °C for 40 min and at r.t.

overnight. The mixture was cooled to 0 °C, and the formed precipitate was filtered on a sintered glass filter. The obtained solid was successively washed by cold MeOH and Et₂O, collected, and dried at reduced pressure to give 4.02 g (75%) of the potassium carboxylate. In a 50 mL round-bottomed flask, the carboxylate (1.0 g, 4.66 mmol) was dissolved in 10 mL EtOH, and at 0 °C concentrated H₂SO₄ (2.5 mL) was dropwise added. The mixture was stirred at 0 °C for 1 h and at r.t. overnight. The mixture was quenched by saturated NH₄Cl solution and extracted with Et₂O (3×20 mL). The combined organic layers were washed by saturated NH₄Cl solution (2×20 mL), brine (2×20 mL), dried by MgSO₄, filtered,

and evaporated at reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 10:1, gradient to 5:1) to give 577 mg (61%) of **31g** as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, J = 16.1 Hz, 1H, CH-1), 7.67-7.61 (m, 2H, CH_{Ar}), 7.49-7.40 (m, 3H, CH_{Ar}), 7.37 (d, J = 16.1 Hz, 1H, CH-2), 4.40 (q, J = 7.2 Hz, 2H, CH₂-5), 1.42 (t, J = 7.1 Hz, 3H, CH₃-6). The spectral data match those reported in the literature.^[139]

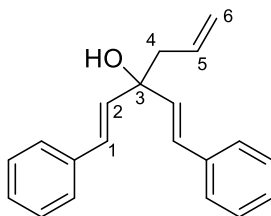
Ethyl (*E*)-2-hydroxy-2-styrylpent-4-enoate (**25g**)



Prepared according to general procedure **A** from ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **31g** (980 mg, 4.8 mmol). Purification of the crude product by column chromatography (neat toluene) gave 508 mg (43%) of **25g** as a colorless oil.

R_F = 0.35 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Benzene-*d*₆) δ 7.37-7.32 (m, 2H, CH_{Ar}), 7.21-7.09 (m, 3H, CH_{Ar}), 7.18 (d, J = 15.8 Hz, 1H, CH-1), 6.53 (d, J = 15.8 Hz, 1H, CH-2), 6.13-6.01 (m, 1H, CH-5), 5.23-5.13 (m, 2H, CH₂-6), 4.04 (dq, J = 10.7, 7.1 Hz, 1H, CH₂-7), 3.91 (dq, J = 10.8, 7.1 Hz, 1H, CH₂-7), 3.72 (s, 1H, OH), 2.75 (dd, J = 13.9, 7.7 Hz, 1H, CH₂-4), 2.67 (ddt, J = 13.8, 6.5, 1.3 Hz, 1H, CH₂-4), 0.95 (t, J = 7.1 Hz, 3H, CH₃-8). **¹³C NMR** (101 MHz, Benzene-*d*₆) δ 174.7 (C-9), 136.9 (C_{Ar}), 132.7 (C-5), 130.7 (C-2), 130.2 (C-1), 128.8 (CH_{Ar}), 127.9 (CH_{Ar}), 127.1 (CH_{Ar}), 118.9 (C-6), 77.4 (C-3), 62.1 (C-7), 44.5 (C-4), 14.0 (C-8). **MS** (ESI+) m/z (%) 515 ([2M+Na⁺], 25), 269 ([M+Na⁺], 100), 229 ([M-H₂O+H⁺], 20). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₁₅H₁₈O₃Na: 269.1148; found: 269.1148. **IR** (neat): ν_{max} = 3506, 3026, 2981, 2914, 1726, 1448, 1218, 1159, 1092, 1027, 971, 919, 859, 745, 691 cm⁻¹.

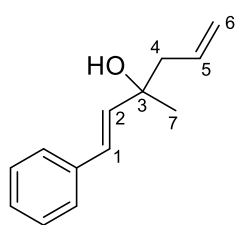
(*E*)-1-Phenyl-3-((*E*)-styryl)hexa-1,5-dien-3-ol (**25h**)



Prepared according to general procedure **A** from dibenzylideneacetone (1.12 g, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1, gradient to 5:1) gave 1.29 g (97%) of **25h** as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.44-7.37 (m, 4H, CH_{Ar}), 7.34-7.28 (m, 4H, CH_{Ar}), 7.26-7.20 (m, 2H, CH_{Ar}), 6.69 (d, J = 16.0 Hz, 2H, CH-1), 6.37 (d, J = 16.0 Hz, 2H, CH-2), 5.90-5.82 (m, 1H, CH-5), 5.25-5.20 (m, 2H, CH₂-6), 2.59 (d, J = 7.3 Hz, 2H, CH₂-4), 2.09 (s, 1H, OH). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 136.9 (C_{Ar}), 133.8 (C-2), 133.0 (C-5), 128.9 (C-1), 128.7 (CH_{Ar}), 127.7 (CH_{Ar}), 126.7 (CH_{Ar}), 120.1 (C-6), 74.8 (C-3), 46.5 (C-4). The spectral data match those reported in the literature.^[140]

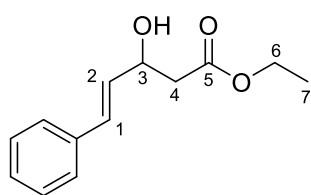
(*E*)-3-Methyl-1-phenylhexa-1,5-dien-3-ol (**25i**)



Prepared according to general procedure **B** from (*E*)-4-phenylbut-3-en-2-one (702 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 15:1, gradient to 3:1) gave 660 mg (73%) of **25i** as a colorless oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, J = 7.5 Hz, 2H, CH_{Ar}), 7.31 (t, J = 7.5 Hz, 2H, CH_{Ar}), 7.27-7.22 (m, 1H, CH_{Ar}), 6.60 (d, J = 16.1 Hz, 1H, CH-1), 6.30 (d, J = 16.0 Hz, 1H, CH-2), 5.91-5.78 (m, 1H, CH-5), 5.23-5.10 (m, 2H, CH₂-6), 2.45 (dd, J = 13.6, 6.7 Hz, 1H, CH₂-4), 2.36 (dd, J = 13.6, 8.2 Hz, 1H, CH₂-4), 1.90 (bs, 1H, OH), 1.39 (s, 3H, CH₃-7). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.0 (C_{Ar}), 136.4 (C-2), 133.7 (C-5), 128.7 (CH_{Ar}), 127.6 (CH_{Ar}, C-1), 126.6 (CH_{Ar}), 119.5 (C-6), 72.5 (C-3), 47.5 (C-4), 28.1 (C-7). The spectral data match those reported in the literature.^[135]

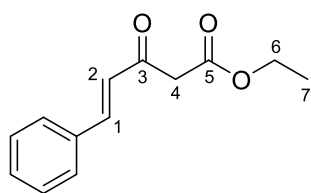
Ethyl (*E*)-3-hydroxy-5-phenylpent-4-enoate (**S31j**)



In a 250 mL Schlenk flask, DIPA (3.85 mL, 27.5 mmol) was dissolved in THF (100 mL). The mixture was cooled to -78 °C, and BuLi (1.6 M in THF, 17.2 mL, 27.5 mmol) was dropwise added. The mixture was stirred for 15 min, and dry EtOAc (2.45 mL, 25 mmol) was dropwise added. The mixture was stirred and warmed to -55 °C over 1 h, and subsequently, cinnamaldehyde (3.30 g, 25 mmol) in THF (15 mL) was added over 5 min. The resulting mixture was stirred for 5 min, quenched with saturated NH₄Cl solution (20 mL), and extracted by Et₂O (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried with MgSO₄, filtered, and evaporated at reduced pressure to give 5.25 g (95%) of **S31j** as a colorless oil that was used without further purification.

R_F = 0.15 (hexanes/EtOAc, 5:1). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.36 (m, 2H, CH_{Ar}), 7.35-7.29 (m, 2H, CH_{Ar}), 7.28-7.22 (m, 1H, CH_{Ar}), 6.66 (d, J = 15.9 Hz, 1H, CH-1), 6.23 (dd, J = 15.9, 6.1 Hz, 1H, CH-2), 4.76-4.70 (m, 1H, CH-3), 4.20 (q, J = 7.1 Hz, 2H, CH₂-6), 3.05 (d, J = 4.3 Hz, 1H, OH), 2.71-2.58 (m, 2H, CH₂-4), 1.28 (t, J = 7.1 Hz, 3H, CH₃-7). The spectral data match those reported in the literature.^[141]

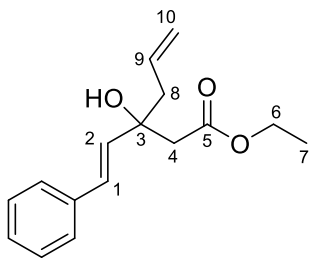
Ethyl (*E*)-3-oxo-5-phenylpent-4-enoate (**31j**)



In a 100 mL round-bottomed flask, alcohol **S31j** (5.23 g, 23.7 mmol) was dissolved in CH₂Cl₂ (24 mL). MnO₂ (41 g, 475 mmol) was added, the resulting suspension was refluxed for 2 h and stirred at r.t. overnight. The resulting mixture was filtered twice over a fresh plug of layered celite, silica gel, and sand. The solvents were evaporated at reduced pressure to give 3.40 g (66%) of **31j** as a yellow oil that was used in the next step without further purification.

R_F = 0.50 (hexanes/EtOAc, 5:1). ^1H NMR (400 MHz, Chloroform- d) 1.5:1 *keto/enol* δ 11.99 (d, J = 1.5 Hz, 1H, OH^{enol}), 7.64-7.29 (m, 10H, CH_{Ar}^{enol}, CH_{Ar}^{keto}), 7.42 (d, J = 16.1 Hz, 1H, CH-1^{keto}), 7.40 (d, J = 15.9 Hz, 1H, CH-1^{enol}), 6.81 (dd, J = 16.1 Hz, 1H, CH-2^{keto}), 6.44 (dd, J = 15.9, 1.5 Hz, 1H, CH-2^{enol}), 5.17 (s, 1H, CH-4^{enol}), 4.24 (q, J = 6.9 Hz, 2H, CH₂-6^{enol}), 4.23 (q, J = 7.2 Hz, 2H, CH₂-6^{keto}), 3.70 (s, 2H, CH₂-4^{keto}), 1.32 (t, J = 7.2 Hz, 3H, CH₃-7^{enol}), 1.29 (t, J = 7.1 Hz, 3H, CH₃-7^{keto}). The spectral data match those reported in the literature.^[142]

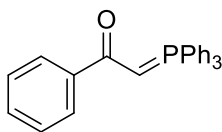
Ethyl (*E*)-3-hydroxy-3-styrylhex-5-enoate (**25j**)



Preparation in analogy to conditions published in the literature.^[106] In a 25 mL round-bottomed flask, β -ketoester **31j** (500 mg, 2.29 mmol) and allyl bromide (0.28 mL, 3.21 mmol) were mixed with water (6.9 mL). ZnI₂ (584 mg, 1.83 mmol) and NH₄Cl (98 mg, 1.83 mmol) were added and after stirring for 1 min, SnCl₂·H₂O (651 mg, 3.44 mmol) was added. The mixture was stirred at 30 °C overnight, diluted with brine (20 mL), and extracted by Et₂O (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/EtOAc, 10:1) to yield 156 mg (26%) of **25j** as a colorless oil.

R_F = 0.20 (hexanes/EtOAc, 5:1). ^1H NMR (400 MHz, Benzene- d_6) δ 7.27-7.22 (m, 2H, CH_{Ar}), 7.13-7.07 (m, 2H, CH_{Ar}), 7.06-7.00 (m, 1H, CH_{Ar}), 6.83 (d, J = 15.9 Hz, 1H, CH-1), 6.20 (d, J = 16.0 Hz, 1H, CH-2), 5.94 (ddt, J = 17.4, 10.3, 7.3 Hz, 1H, CH-9), 5.07-4.96 (m, 2H, CH₂-10), 4.22 (s, 1H, OH), 3.86-3.85 (m, 2H, CH₂-6), 2.50 (d, J = 15.4 Hz, 1H, CH₂-4^a), 2.44 (d, J = 15.4 Hz, 1H, CH₂-4^b), 2.43-2.31 (m, 2H, CH₂-8), 0.83 (t, J = 7.1 Hz, 3H, CH₃-7). ^{13}C NMR (101 MHz, Benzene- d_6) δ 172.6 (C-5), 137.4 (C_{Ar}), 134.4 (C-2), 133.9 (C-9), 129.3 (C-1), 128.8 (CH_{Ar}), 127.7 (CH_{Ar}), 126.9 (CH_{Ar}), 118.5 (C-10), 73.3 (C-3), 60.6 (C-6), 46.4 (C-8), 43.8 (C-4), 14.1 (C-7). **MS** (ESI⁺) m/z (%) 543 ([2M+Na⁺], 30), 283 ([M+Na⁺], 100). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₁₆H₂₀O₃Na: 283.1305; found: 283.1305. **IR** (neat): ν_{max} = 3497, 3079, 3026, 2980, 2936, 1711, 1640, 1371, 1333, 1186, 1062, 1025, 999, 970, 916, 745, 693 cm⁻¹.

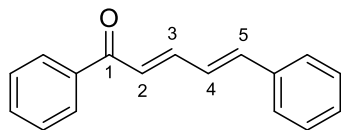
1-Phenyl-2-(triphenyl- λ^5 -phosphaneylidene)ethan-1-one (**S31k**)



In a 100 mL round-bottomed flask, 2-bromoacetophenone (2.99 g, 15 mmol) and triphenylphosphine (4.32 g, 16.5 mmol) were dissolved in THF (30 mL). The mixture was refluxed for 4 h, evaporated at reduced pressure, and dissolved in CH₂Cl₂ (40 mL). The solution was transferred to a separatory funnel and thoroughly extracted with NaOH solution (20% in H₂O, 60 mL). The organic layer was washed with brine (2×20 mL), dried by Na₂SO₄, filtered, and evaporated at reduced pressure to give the crude product that was adsorbed on silica gel and purified by column chromatography (hexane/EtOAc, 4:1, gradient to 2:1) to yield 4.78 g (84%) of **S31k** as a brown powder.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.02-7.93 (m, 2H, CH_{Ar}), 7.78-7.64 (m, 6H, CH_{Ar}), 7.60-7.42 (m, 9H, CH_{Ar}), 7.39-7.32 (m, 3H, CH_{Ar}), 4.43 (d, J = 24.5 Hz, 1H, CH). The spectral data match those reported in the literature.^[139]

(2*E*,4*E*)-1,5-Diphenylpenta-2,4-dien-1-one (31k)

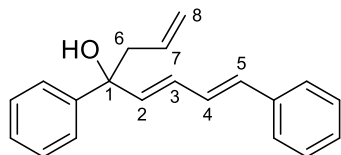


In a 100 mL round-bottomed flask, Wittig reagent **S31k** (1.90 g, 4.99 mmol) was dissolved in CH₂Cl₂ (20 mL). Cinnamaldehyde (600 mg, 4.54 mmol) was added, and the reaction mixture was refluxed for 42 h.

After cooling, the mixture was adsorbed on silica gel and purified by column chromatography (hexane/EtOAc, 20:1) to give 654 mg (62%) of **31k** as a yellow solid.

¹H NMR (401 MHz, Chloroform-*d*) δ 8.01-7.95 (m, 2H, CH_{Ar}), 7.65-7.55 (m, 2H, CH_{Ar}, CH-3), 7.53-7.47 (m, 4H, CH_{Ar}), 7.41-7.30 (m, 3H, CH_{Ar}), 7.10 (d, J = 14.9 Hz, 1H, CH-4), 7.05-7.02 (m, 2H, CH-2, CH-5). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 190.7 (C-1), 145.0 (C-3), 142.1 (C-5), 138.4 (C_{Ar}), 136.3 (C_{Ar}), 132.8 (CH_{Ar}), 129.4 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.5 (CH_{Ar}), 127.4 (CH_{Ar}), 127.1 (C-2), 125.6 (C-4). The spectral data match those reported in the literature.^[143]

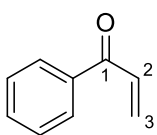
(1*E*,3*E*)-1,5-Diphenylocta-1,3,7-trien-5-ol (25k)



Prepared according to general procedure **A** from dienone **31k** (1.13 g, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1, gradient to 5:1) gave 1.01 g (76%) of **25k** as a colorless oil.

R_F = 0.45 (hexanes/EtOAc, 5:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.52-7.45 (m, 2H, CH_{Ar}), 7.42-7.33 (m, 4H, CH_{Ar}), 7.33-7.17 (m, 4H, CH_{Ar}), 6.78 (dd, J = 15.6, 10.5 Hz, 1H, CH-4), 6.54 (d, J = 15.6 Hz, 1H, CH-5), 6.44 (dd, J = 15.3, 10.5 Hz, 1H, CH-3), 6.13 (d, J = 15.2 Hz, 1H, CH-2), 5.70 (ddt, J = 17.4, 10.1, 7.3 Hz, 1H, CH-7), 5.25-5.15 (m, 2H, CH₂-8), 2.79 (dd, J = 13.9, 7.3 Hz, 1H, CH-6), 2.72 (dd, J = 13.8, 7.3 Hz, 1H, CH-6), 2.24 (s, 1H, OH). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 145.4 (C_{Ar}), 139.5 (C-2), 137.4 (C_{Ar}), 133.2 (C-7), 133.0 (C-5), 129.1 (C-3), 128.7 (CH_{Ar}), 128.5 (C-4), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 127.1 (CH_{Ar}), 126.5 (CH_{Ar}), 125.5 (CH_{Ar}), 120.3 (C-8), 75.7 (C-1), 47.2 (C-6). **MS** (ESI+) m/z (%) 575 ([2M+Na⁺], 10), 299 ([M+Na⁺], 100), 259 ([M-H₂O+H⁺], 30). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₀H₂₀ONa: 299.1406; found: 299.1407. **IR** (neat): $\nu_{\max}$ = 3439, 3058, 3024, 1638, 1596, 1493, 1446, 1347, 1250, 1157, 1071, 1029, 988, 914, 746, 690 cm⁻¹.

1-Phenylprop-2-en-1-one (31l)

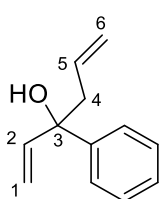


In a flame-dried Schlenk flask, benzaldehyde (2.0 g, 18.8 mmol) was dissolved in dry THF (60 mL). At 0 °C, vinylmagnesium chloride (1.6M in THF, 14.2 mL, 22.7 mmol) was added, the mixture was stirred for 30 min, quenched by saturated NH₄Cl solution, and extracted by Et₂O (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude allylic

alcohol. The allylic alcohol was dissolved in CH₂Cl₂ (10 mL), MnO₂ (11.0 g, 126 mmol) was added, the mixture was refluxed for 4 h and stirred at r.t. overnight. The suspension was filtered through a plug of layered celite, silica gel, and sand. Evaporation of the solvent at reduced pressure gave the crude product that was purified by column chromatography (hexane/EtOAc, 10:1, gradient to 5:1) to yield 1.39 g (56%) of **31i** as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.97-7.92 (m, 2H, CH_{Ar}), 7.60-7.55 (m, 1H, CH_{Ar}), 7.51-7.45 (m, 2H, CH_{Ar}), 7.16 (dd, *J* = 17.1, 10.6 Hz, 1H, CH-2), 6.44 (dd, *J* = 17.1, 1.7 Hz, 1H, CH₂-3), 5.93 (dd, *J* = 10.6, 1.7 Hz, 1H, CH₂-3). The spectral data match those reported in the literature.^[144]

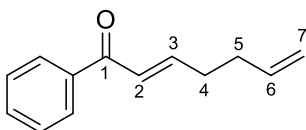
3-Phenylhexa-1,5-dien-3-ol (**25i**)



Prepared according to general procedure A from α,β -unsaturated ketone **31i** (634 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 20:1, gradient to 10:1) gave 519 mg (62%) of **25i** as a colorless oil.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.48-7.44 (m, 2H, *o*-CH_{Ar}), 7.37-7.32 (m, 2H, *m*-CH_{Ar}), 7.27-7.22 (m, 1H, *p*-CH_{Ar}), 6.19 (dd, *J* = 17.2, 10.6 Hz, 1H, CH-2), 5.68 (ddt, *J* = 17.6, 10.4, 7.3 Hz, 1H, CH-5), 5.30 (dd, *J* = 17.2, 1.1 Hz, 1H, CH₂-1), 5.21-5.12 (m, 3H, CH₂-6, CH₂-1), 2.76-2.64 (m, 2H, CH₂-4), 2.17 (s, 1H, OH). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 145.3 (C_{Ar}), 143.7 (C-2), 133.3 (C-5), 128.4 (*m*-CH_{Ar}), 127.1 (*p*-CH_{Ar}), 125.5 (*o*-CH_{Ar}), 120.1 (C-6), 113.2 (C-1), 75.9 (C-3), 46.8 (C-4). The spectral data match those reported in the literature.^[145]

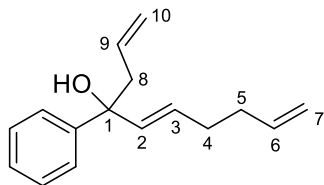
(*E*)-1-Phenylhepta-2,6-dien-1-one (**31m**)



In a 100 mL round-bottomed flask, Wittig reagent **S31k** (2.49 g, 6.55 mmol) was dissolved in CH₂Cl₂ (30 mL). Pent-4-enal (0.59 mL, 5.98 mmol) was added, and the reaction mixture was refluxed for 3 days. After cooling, the mixture was adsorbed on silica gel and purified by column chromatography (hexane/EtOAc, 10:1) to give 942 mg (85%) of **31m** as a colorless oil.

R_F = 0.48 (hexanes/EtOAc, 10:1). **¹H NMR** (401 MHz, Chloroform-*d*) δ 7.95-7.90 (m, 2H, CH_{Ar}), 7.59-7.53 (m, 1H, CH_{Ar}), 7.50-7.44 (m, 2H, CH_{Ar}), 7.05 (dt, *J* = 15.4, 6.7 Hz, 1H, CH-3), 6.89 (dt, *J* = 15.4, 1.4 Hz, 1H, CH-2), 5.84 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H, CH-6), 5.09 (dq, *J* = 17.1, 1.6 Hz, 1H, CH₂-7), 5.06-5.01 (m, 1H, CH₂-7), 2.47-2.39 (m, 2H, CH₂-4), 2.34-2.26 (m, 2H, CH₂-5). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 191.0 (C-1), 149.0 (C-3), 138.1 (C_{Ar}), 137.3 (C-6), 132.8 (CH_{Ar}), 128.69 (CH_{Ar}), 128.66 (CH_{Ar}), 126.5 (C-2), 115.8 (C-7), 32.4 (C-5), 32.3 (C-4). The spectral data match those reported in the literature.^[146]

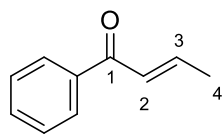
(E)-4-Phenyldeca-1,5,9-trien-4-ol (25m)



Prepared according to general procedure **A** from α,β -unsaturated ketone **31m** (894 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 1.09 g (99%) of **25m** as a colorless oil.

R_F = 0.30 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.44 (d, J = 7.6 Hz, 2H, *o*-CH_{Ar}), 7.34 (t, J = 7.6 Hz, 2H, *m*-CH_{Ar}), 7.29-7.19 (m, 1H, *p*-CH_{Ar}), 5.89-5.73 (m, 2H, CH-6, CH-2), 5.73-5.58 (m, 2H, CH-9, CH-3), 5.20-5.10 (m, 2H, CH₂-10), 5.01 (d, J = 17.3 Hz, 1H, CH₂-7), 4.96 (d, J = 10.3 Hz, 1H, CH₂-7), 2.76-2.57 (m, 2H, CH₂-8), 2.25-2.05 (m, 4H, CH₂-4, CH₂-5), 1.55 (s, 1H, OH). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 145.9 (C_{Ar}), 138.3 (C-6), 136.2 (C-2), 133.6 (C-9), 129.0 (C-3), 128.3 (*m*-CH_{Ar}), 126.9 (*p*-CH_{Ar}), 125.6 (*o*-CH_{Ar}), 119.9 (C-10), 115.0 (C-7), 75.5 (C-1), 47.3 (C-8), 33.6 (C-5), 31.8 (C-4). **MS** (ESI+) m/z (%) 251 ([M+Na⁺], 100), 211 ([M-H₂O+H⁺], 90). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₁₆H₂₀ONa: 251.1406; found: 251.1406. **IR** (neat): ν_{max} = 3473, 3076, 2978, 2923, 1639, 1492, 1446, 1341, 972, 910, 762, 699 cm⁻¹.

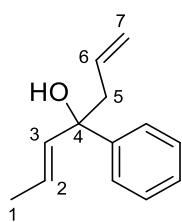
(E)-1-Phenylbut-2-en-1-one (31n)



In a flame-dried Schlenk flask, crotonaldehyde (1.18 mL, 14.24 mmol) was dissolved in dry THF (70 mL). At 0 °C, phenylmagnesium bromide (2.0 M in THF, 8.56 mL, 17.12 mmol) was added, the mixture was stirred for 60 min, quenched by saturated NH₄Cl solution, and extracted with Et₂O (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude allylic alcohol. The allylic alcohol was dissolved in CH₂Cl₂ (20 mL), and MnO₂ (8.60 g, 100 mmol) was added. The suspension was refluxed for 3 h, another portion of MnO₂ (5.0 g, 57.5 mmol) was added, refluxing was continued for another 30 min, and the mixture was stirred at r.t. overnight. The resulting suspension was filtered through a plug of layered celite, silica gel, and sand. Evaporation of the solvent at reduced pressure gave the crude product that was purified by column chromatography (hexane/EtOAc, 10:1, gradient to 7:1) to yield 1.43 g (69%) of **31n** as a colorless oil.

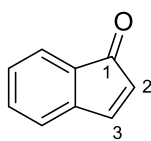
R_F = 0.36 (hexanes/EtOAc, 5:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.95-7.90 (m, 2H, CH_{Ar}), 7.59-7.52 (m, 1H, CH_{Ar}), 7.50-7.43 (m, 2H, CH_{Ar}), 7.08 (dq, J = 15.3, 6.8 Hz, 1H, CH-3), 6.91 (dq, J = 15.3, 1.6 Hz, 1H, CH-2), 2.00 (dd, J = 6.8, 1.6 Hz, 3H, CH₃-4). The spectral data match those reported in the literature.^[147]

(*E*)-4-Phenylhepta-1,5-dien-4-ol (**25n**)



Prepared according to general procedure **A** from α,β -unsaturated ketone **31n** (702 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 20:1, gradient to 10:1) gave 813 mg (90%) of **25n** as a colorless oil. R_F = 0.26 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.48-7.42 (m, 2H, *o*-CH_{Ar}), 7.34 (dd, J = 8.5, 6.9 Hz, 2H, *m*-CH_{Ar}), 7.29-7.19 (m, 1H, *p*-CH_{Ar}), 5.83 (dq, J = 15.4, 1.5 Hz, 1H, CH-3), 5.74-5.59 (m, 2H, CH-2, CH-6), 5.19-5.11 (m, 2H, CH₂-7), 2.73 (ddt, J = 13.8, 7.0, 1.2 Hz, 1H, CH₂-5^a), 2.64 (ddt, J = 13.8, 7.4, 1.1 Hz, 1H, CH₂-5^b), 2.15 (bs, 1H, OH), 1.72 (dd, J = 6.4, 1.5 Hz, 3H, CH₃-1). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 146.0 (C_{Ar}), 137.1 (C-3), 133.6 (C-6), 128.2 (*m*-CH_{Ar}), 126.8 (*p*-CH_{Ar}), 125.6 (*o*-CH_{Ar}), 124.6 (C-2), 119.8 (C-7), 75.5 (C-4), 47.3 (C-5), 17.9 (C-1). **MS** (CI⁺) m/z (%) 189 ([M+H⁺], 50), 171 ([M-H₂O+H⁺], 60), 170 ([M-H₂O]⁺, 40), 147 ([M-CH₂CH=CH₂]⁺, 70), 129 ([M-H₂O-CH₂CH=CH₂]⁺, 30). **HRMS** (ESI⁺) m/z [M+H⁺] calcd for C₁₃H₁₇O: 189.1279; found: 189.1278. **IR** (neat): ν_{max} = 3462, 3075, 3027, 2916, 2855, 1639, 1492, 1446, 1343, 1031, 968, 913, 762, 698 cm⁻¹.

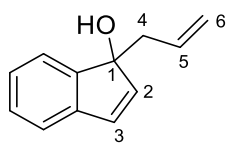
1H-Inden-1-one (**31o**)



In a 50 mL round-bottomed flask, indanone (2.64 g, 20 mmol) was dissolved in CCl₄ (8.0 mL), NBS (3.9 g, 22 mmol), and AIBN (40 mg, 0.24 mmol) were added. The mixture was refluxed for 3 h and filtered through a plug of celite, which was washed by a small amount of CCl₄. Et₃N (5.6 mL, 40.0 mmol) was added to the filtrate, and the mixture was stirred for 3 days, diluted with H₂O (20 mL), and extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were dried by Na₂SO₄, filtered, and evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/EtOAc, 30:1, gradient to 10:1) to yield 1.56 g (60%) of **31o** as a pale yellow oil.

R_F = 0.45 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.57 (dd, J = 5.9, 0.9 Hz, 1H, CH-3), 7.43 (dq, J = 7.1, 0.9 Hz, 1H, CH_{Ar}), 7.34 (ddd, J = 7.7, 7.1, 1.2 Hz, 1H, CH_{Ar}), 7.23 (ddt, J = 8.1, 7.0, 0.7 Hz, 1H, CH_{Ar}), 7.06 (dt, J = 7.2, 0.9 Hz, 1H, CH_{Ar}), 5.89 (d, J = 6.0 Hz, 1H, CH-2). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 198.6 (C-1), 150.0 (C-3), 144.8 (C_{Ar}), 133.8 (CH_{Ar}), 130.5 (C_{Ar}), 129.3 (CH_{Ar}), 127.4 (C-2), 122.8 (CH_{Ar}), 122.4 (CH_{Ar}). The spectral data match those reported in the literature.^[148]

1-Allylinden-1-ol (**25o**)

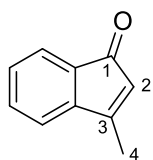


Prepared according to general procedure **A** from indenone **31o** (624 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 15:1, gradient to 7:1) gave 703 mg (85%) of **25o** as an off-white solid.

R_F = 0.30 (hexanes/EtOAc, 5:1). **m.p.** 65-67 °C. $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.48-7.43 (m, 1H, CH_{Ar}), 7.35-7.22 (m, 3H, CH_{Ar}), 6.70 (d, J = 5.6 Hz, 1H, CH-3), 6.38 (d, J = 5.7 Hz, 1H, CH-2),

5.87 (ddt, $J = 17.3, 10.2, 7.3$ Hz, 1H, CH-5), 5.23-5.12 (m, 2H, CH₂-6), 2.80 (ddt, $J = 13.7, 7.5, 1.1$ Hz, 1H, CH₂-4), 2.62 (ddt, $J = 13.7, 7.0, 1.2$ Hz, 1H, CH₂-4), 1.98 (s, 1H, OH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 148.2 (C_{Ar}), 142.1 (C_{Ar}), 141.3 (C-2), 133.6 (C-5), 131.5 (C-3), 128.7 (CH_{Ar}), 126.4 (CH_{Ar}), 122.3 (CH_{Ar}), 121.7 (CH_{Ar}), 118.9 (C-6), 84.1 (C-1), 42.4 (C-4). MS (EI) m/z (%) 172 ([M]⁺, 30), 131 ([M⁺-CH₂CH=CH₂], 100). HRMS (EI⁺) m/z [M]⁺ calcd for C₁₂H₁₂O: 172.0888; found: 172.0889. IR (neat): $\nu_{\max} = 3277, 3073, 2978, 1642, 1466, 1432, 1378, 1090, 1034, 985, 909, 790, 756, 640$ cm⁻¹.

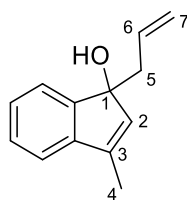
3-Methyl-1H-inden-1-one (31p)



In a flame-dried Schlenk flask, 3-methylindanone (300 mg, 2.05 mmol) was dissolved in dry MeCN (5.0 mL). At r.t. Et₃N (0.71 mL, 5.13 mmol), anhydrous NaI (614 mg, 4.1 mmol) and TMSCl (0.52 mL, 4.1 mmol) were successively added. The mixture was stirred for 45 min, quenched by NaHCO₃ solution (5% in H₂O, 10 mL), and extracted with hexane (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried by Na₂SO₄, filtered, and evaporated at reduced pressure to give 442 mg (99%) of the crude silyl enol ether. The silyl enol ether was dissolved in MeCN (5.0 mL), and Pd(OAc)₂ (460 mg, 2.05 mmol) was added. The reaction mixture was stirred for 1 h, and filtered through a plug of layered celite and silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc, 20:1) to yield 210 mg (71%) of **31p** as a yellow solid.

$R_F = 0.28$ (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.43-7.35 (m, 2H, CH_{Ar}), 7.29-7.23 (m, 1H, CH_{Ar}), 7.11 (dt, $J = 7.1, 0.9$ Hz, 1H, CH_{Ar}), 5.70 (q, $J = 1.7$ Hz, 1H, CH-2), 2.24 (d, $J = 1.7$ Hz, 3H, CH₃-4). MS (CI) m/z (%) 145 ([M+H]⁺, 100), 144 ([M]⁺, 20). HRMS (CI) m/z [M]⁺ calcd for C₁₀H₉O: 145.0653; found: 145.0655. The spectral data match those reported in the literature.^[149]

1-Allyl-3-methylinden-1-ol (25p)

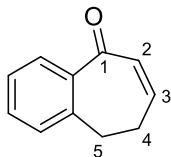


Prepared according to general procedure A from 3-methylinden-1-one **31p** (692 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 787 mg (88%) of **25p** as an orange solid.

$R_F = 0.15$ (hexanes/EtOAc, 10:1). m.p. 50-52 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 (d, $J = 7.3$ Hz, 1H, CH_{Ar}), 7.31-7.23 (m, 1H, CH_{Ar}), 7.20 (td, $J = 7.5, 1.2$ Hz, 1H, CH_{Ar}), 7.14 (d, $J = 7.3$ Hz, 1H, CH_{Ar}), 5.98 (q, $J = 1.6$ Hz, 1H, CH-2), 5.82 (ddt, $J = 17.3, 10.2, 7.2$ Hz, 1H, CH-6), 5.16-5.02 (m, 2H, CH₂-7), 2.74 (dd, $J = 13.7, 7.4$ Hz, 1H, CH₂-5^a), 2.55 (dd, $J = 13.7, 7.0$ Hz, 1H, CH₂-5^b), 2.06 (d, $J = 1.6$ Hz, 3H, CH₃-4), 1.88 (s, 1H, OH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 148.9 (C_{Ar}), 143.6 (C_{Ar}), 140.1 (C-3), 135.8 (C-2), 133.9 (C-6), 128.6 (CH_{Ar}), 126.4 (CH_{Ar}), 121.9 (CH_{Ar}), 119.4 (CH_{Ar}), 118.6 (C-7), 82.9 (C-1), 42.5 (C-5), 12.9 (C-4). MS (CI⁺) m/z (%) 187 ([M+H]⁺, 10), 169 ([M-H₂O+H]⁺, 100), 168 ([M-H₂O]⁺, 30), 145 ([M-CH₂CH=CH₂]⁺, 50).

HRMS (CI⁺) m/z [M+H⁺] calcd for C₁₃H₁₅O: 187.1123; found: 187.1118. **IR** (neat): ν_{max} = 3351, 3070, 2976, 2912, 1639, 1430, 1380, 1346, 1041, 995, 913, 815, 752 cm⁻¹.

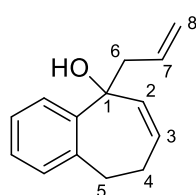
8,9-Dihydro-5H-benzo[7]annulen-5-one (**31q**)



In a flame-dried Schlenk flask, benzosuberone (300 mg, 1.87 mmol), Pd(TFA)₂, and DMSO (2 drops) were dissolved in dry toluene (10 mL). Oxygen was bubbled through the mixture for 5 min by a balloon fitted with a needle. The needle was raised above the solution level, and the mixture was heated to 60 °C for 24 h and to 80 °C for another 24 h. The mixture was evaporated, and the crude product was purified by column chromatography (hexane/EtOAc, 50:1, gradient to 10:1) to give 96 mg (32%) of **31q** as a colorless oil and 175 mg (58%) of recovered starting material. The yield based on the recovered starting material is 78%.

R_F = 0.39 (hexanes/EtOAc, 5:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.75 (dd, J = 7.8, 1.5 Hz, 1H, CH_{Ar}), 7.41 (td, J = 7.5, 1.5 Hz, 1H, CH_{Ar}), 7.30 (td, J = 7.6, 1.3 Hz, 1H, CH_{Ar}), 7.19 (d, J = 7.5 Hz, 1H, CH_{Ar}), 6.74 (dt, J = 12.1, 4.9 Hz, 1H, CH-3), 6.27 (dt, J = 12.1, 1.9 Hz, 1H, CH-2), 3.13-3.02 (m, 2H, CH₂-5), 2.65-2.54 (m, 2H, CH₂-4). The spectral data match those reported in the literature.^[150]

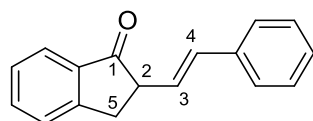
5-Allylbenzocyclohept-6-en-5-ol (**25q**)



Prepared according to general procedure **A** from α,β -unsaturated ketone **31q** (759 mg, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 30:1, gradient to 10:1) gave 894 mg (93%) of **25q** as a colorless oil.

¹H NMR (401 MHz, Chloroform-*d*) δ 7.64 (dd, J = 7.6, 1.7 Hz, 1H, CH_{Ar}), 7.22 (td, J = 7.5, 1.9 Hz, 1H, CH_{Ar}), 7.18 (td, J = 7.3, 1.6 Hz, 1H, CH_{Ar}), 7.13 (dd, J = 7.3, 1.8 Hz, 1H, CH_{Ar}), 5.77-5.62 (m, 3H, CH-2, CH-3, CH-7), 5.15-5.09 (m, 2H, CH₂-8), 3.33 (td, J = 13.4, 3.3 Hz, 1H, CH₂-5^a), 2.80-2.72 (m, 3H, CH₂-6, CH₂-5^b), 2.40 (dtd, J = 18.5, 5.1, 3.3 Hz, 1H, CH₂-4^a), 2.27 (s, 1H, OH), 2.25-2.18 (m, 1H, CH₂-4^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 145.6 (C_{Ar}), 139.0 (C_{Ar}), 135.8 (C-7), 133.7 (C-2), 130.0 (CH_{Ar}), 129.8 (C-3), 127.5 (CH_{Ar}), 126.4 (CH_{Ar}), 125.8 (CH_{Ar}), 119.3 (C-8), 76.1 (C-1), 48.4 (C-6), 34.6 (C-5), 29.0 (C-4). The spectral data match those reported in the literature.^[132b]

(*E*)-2-Styrylindan-1-one (**31r**)

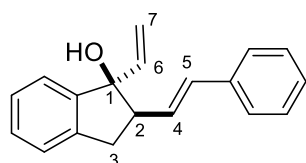


Preparation in analogy to conditions published in the literature.^[151] In a flame-dried Schlenk flask, *t*BuOK (1.68 g, 15 mmol) was suspended in DMSO (38 mL). Indanone (1.98 g, 15 mmol) and phenylacetylene (1.53 g, 15 mmol) were subsequently dropwise added at r.t. The mixture was stirred at 100 °C for 40 min, cooled to r.t. and H₂O (20 mL) was added. The mixture was extracted by Et₂O (4×25 mL), the combined organic layers were washed with brine, dried over Na₂SO₄, filtered,

and evaporated at reduced pressure. The crude product was purified by column chromatography (neat toluene) to yield 1.27 g (36%) of **31r** as an off-white crystalline solid.

R_F = 0.33 (toluene). **m.p.** 76-78 °C. ^1H NMR (401 MHz, Chloroform- d) δ 7.79 (dt, J = 7.6, 1.0 Hz, 1H, CH_{Ar}), 7.61 (td, J = 7.5, 1.3 Hz, 1H, CH_{Ar}), 7.49 (d, J = 7.7 Hz, 1H, CH_{Ar}), 7.42-7.35 (m, 3H, CH_{Ar}), 7.32-7.26 (m, 2H, CH_{Ar}), 7.24-7.17 (m, 1H, CH_{Ar}), 6.63 (dd, J = 15.9, 1.2 Hz, 1H, CH-4), 6.29 (dd, J = 15.9, 7.0 Hz, 1H, CH-3), 3.58-3.46 (m, 2H, CH₂-5^a, CH-2), 3.20-3.10 (m, 1H, CH₂-5^b). ^{13}C NMR (101 MHz, Chloroform- d) δ 205.8 (C-1), 153.4 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 135.1 (CH_{Ar}), 132.9 (C-4), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 126.8 (CH_{Ar}), 126.7 (C-3), 126.4 (CH_{Ar}), 124.5 (CH_{Ar}), 51.0 (C-2), 33.3 (C-5). **MS** (ESI⁺) m/z (%) 491 ([2M+Na⁺], 20), 257 ([M+Na⁺], 100), 235 ([M+H⁺], 10). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₁₇H₁₄ONa: 257.0937; found: 257.0936. **IR** (neat): ν_{max} = 3057, 3027, 2921, 2846, 1709, 1608, 1494, 1464, 1325, 1293, 1270, 1207, 1151, 1072, 1000, 963, 755, 734, 694 cm⁻¹.

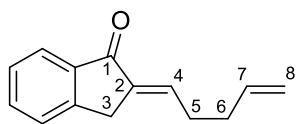
(1*S**,2*R**,*E*)-2-Styryl-1-vinylindan-1-ol (**25r**)



In a flame-dried Schlenk flask, β,γ -unsaturated ketone **31r** (400 mg, 1.71 mmol) was dissolved in THF (20 mL). At -60 °C vinylmagnesium chloride (1.4 mL, 2.21 mmol, 1.6 M in THF) was dropwise added. The mixture was warmed to r.t. over 1.5 h and quenched by saturated NH₄Cl solution (20 mL). The layers were separated, and the aqueous was extracted by Et₂O (3×25 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated at reduced pressure. The crude product was purified by column chromatography (neat toluene) to yield 157 mg (35%) of **25r** as a colorless oil.

R_F = 0.33 (toluene). ^1H NMR (400 MHz, Chloroform- d) δ 7.40-7.34 (m, 2H, CH_{Ar}), 7.31-7.14 (m, 7H, CH_{Ar}), 6.54 (d, J = 16.0 Hz, 1H, CH-5), 6.34 (dd, J = 16.1, 7.1 Hz, 1H, CH-4), 6.04 (dd, J = 17.2, 10.7 Hz, 1H, CH-6), 5.42 (dd, J = 17.2, 1.4 Hz, 1H, CH₂-7), 5.28 (dd, J = 10.6, 1.5 Hz, 1H, CH₂-7), 3.18-3.00 (m, 3H, CH₂-3, CH-2), 1.80 (s, 1H, OH). ^{13}C NMR (101 MHz, Chloroform- d) δ 146.0 (C_{Ar}), 143.0 (C_{Ar}), 141.5 (C-6), 137.2 (C_{Ar}), 133.2 (C-5), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.5 (C-4), 127.3 (CH_{Ar}), 127.0 (CH_{Ar}), 126.4 (CH_{Ar}), 125.0 (CH_{Ar}), 124.1 (CH_{Ar}), 114.7 (C-7), 84.3 (C-1), 54.3 (C-2), 35.7 (C-3). **MS** (EI) m/z (%) 262 ([M]⁺, 40), 244 ([M-H₂O]⁺, 100), 229 ([M-H₂O-CH₃]⁺, 50), 167 ([M-H₂O-C₆H₅]⁺, 30), 91 ([C₇H₇]⁺, 30). **HRMS** (EI) m/z [M]⁺ calcd for C₁₉H₁₈O: 262.1358; found: 262.1360. **IR** (neat): ν_{max} = 3565, 3449, 3025, 2923, 2848, 1645, 1600, 1493, 1475, 1327, 1166, 991, 964, 907, 766, 732, 693 cm⁻¹.

(*E*)-2-(Pent-4-en-1-ylidene)-2,3-dihydro-1H-inden-1-one (**31s**)

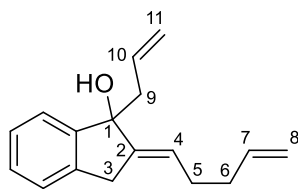


In a 250 mL Schlenk flask, DIPA (1.54 mL, 11.0 mmol) was dissolved in THF (50 mL). The mixture was cooled to -78 °C, and BuLi (1.6 M in THF, 6.88 mL, 11.0 mmol) was dropwise added. The mixture was stirred for 45 min, and indanone (1.45 g, 11 mmol) in THF (5 mL) was dropwise added. The mixture was stirred

for 1 h, and pent-4-enal (1.0 mL, 10 mmol) was dropwise added. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and at $0\text{ }^{\circ}\text{C}$ for 15 min, diluted with Et_2O (50 mL), quenched with HCl solution (1M in H_2O , 10 mL) and stirred overnight. The resulting mixture was extracted by Et_2O ($3\times 20\text{ mL}$), the combined organic layers were washed with brine ($2\times 20\text{ mL}$), dried by MgSO_4 , filtered, and evaporated at reduced pressure. The formed β -hydroxy ketone was dissolved in toluene, and $p\text{TsOH}\cdot\text{H}_2\text{O}$ (1.90 g, 10 mmol) was added. The reaction mixture was stirred at $40\text{ }^{\circ}\text{C}$ for 4 h and filtered through a plug of silica gel, which was washed by Et_2O . Evaporation of the solvent and column chromatography (hexane/ EtOAc , 10:1) gave 1.0 g (51%) of **31s** as a colorless oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.86 (ddt, $J = 7.7, 1.3, 0.7\text{ Hz}$, 1H, CH_{Ar}), 7.59 (ddd, $J = 7.6, 7.2, 1.3\text{ Hz}$, 1H, CH_{Ar}), 7.50 (dq, $J = 7.7, 1.0\text{ Hz}$, 1H, CH_{Ar}), 7.42-7.37 (m, 1H, CH_{Ar}), 6.88 (tt, $J = 7.5, 2.2\text{ Hz}$, 1H, CH-4), 5.85 (ddt, $J = 16.8, 10.2, 6.5\text{ Hz}$, 1H, CH-7), 5.09 (dq, $J = 17.1, 1.6\text{ Hz}$, 1H, CH_2 -8), 5.02 (ddt, $J = 10.2, 1.8, 1.2\text{ Hz}$, 1H, CH_2 -8), 3.68-3.66 (m, 2H, CH_2 -3), 2.46-2.39 (m, 2H, CH_2 -5), 2.34-2.27 (m, 2H, CH_2 -6). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 193.5 (C-1), 149.5 (C-4), 139.0 (C_{Ar}), 137.4 (C-7), 137.3 (C-2), 136.9 (C_{Ar}), 134.6 (CH_{Ar}), 127.6 (CH_{Ar}), 126.5 (CH_{Ar}), 124.5 (CH_{Ar}), 115.8 (C-8), 32.6 (C-3), 30.1 (C-6), 29.5 (C-5). **MS** (APCI) m/z (%) 199 ($[\text{M}+\text{H}^+]$, 100). **HRMS** (APCI) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{14}\text{H}_{15}\text{O}$: 199.1117; found: 199.1118. **IR** (neat): $\nu_{\text{max}} = 3075, 2977, 2918, 1700, 1641, 1604, 1466, 1418, 1326, 1295, 1266, 1201, 1183, 1152, 1095, 993, 911, 735, 701, 674, 627\text{ cm}^{-1}$.

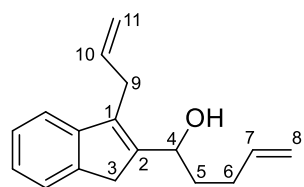
(*E*)-1-Allyl-2-(pent-4-en-1-ylidene)-2,3-dihydro-1H-inden-1-ol (25s)



Prepared according to general procedure **A** from α,β -unsaturated ketone **31s** (992 mg, 5.0 mmol). Purification of the crude product by column chromatography on neutral alumina (hexane/ EtOAc , 20:1, gradient to 3:1) gave 851 mg (71%) of **25s** as a colorless oil. During column chromatography on silica gel, the product **25s** rearranges to alcohol **25sa**.

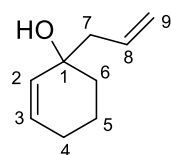
$R_F = 0.36$ (hexanes/ EtOAc , 10:1). **^1H NMR** (400 MHz, Chloroform-*d*) δ 7.42-7.36 (m, 1H, CH_{Ar}), 7.15-7.09 (m, 2H, CH_{Ar}), 7.09-7.02 (m, 1H, CH_{Ar}), 5.86-5.64 (m, 3H, CH-7, CH-10, CH-4), 5.05 (dt, $J = 17.1, 1.7\text{ Hz}$, 1H, CH_2 -8), 5.00 (dd, $J = 10.0, 2.0\text{ Hz}$, 1H, CH_2 -8), 4.95-4.87 (m, 2H, CH_2 -11), 3.34 (dd, $J = 20.1, 2.1\text{ Hz}$, 1H, CH_2 -3^a), 3.16 (dd, $J = 20.1, 2.7\text{ Hz}$, 1H, CH_2 -3^b), 2.73-2.55 (m, 2H, CH_2 -9), 2.12-1.98 (m, 4H, CH_2 -5, CH_2 -6), 1.52 (s, 1H, OH). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 147.9 (C-2), 147.1 (C_{Ar}), 140.0 (C_{Ar}), 138.5 (C-7), 134.0 (C-10), 128.4 (CH_{Ar}), 127.2 (CH_{Ar}), 124.7 (CH_{Ar}), 124.4 (CH_{Ar}), 123.9 (C-4), 118.1 (C-11), 115.1 (C-8), 82.4 (C-1), 48.1 (C-9), 33.90 (C-6), 33.88 (C-3), 28.9 (C-5). **MS** (APCI) m/z (%) 255 ($[\text{M}+\text{CH}_3]^+$, 100), 223 ($[\text{M}-\text{H}_2\text{O}+\text{H}^+]$, 55). **HRMS** (APCI) m/z $[\text{M}-\text{H}^+]$ calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2$: 239.1430; found: 239.1430. **IR** (neat): $\nu_{\text{max}} = 3360, 3074, 2977, 2925, 1640, 1435, 1416, 1364, 1294, 1040, 994, 913, 753, 635\text{ cm}^{-1}$.

1-(3-Allyl-1H-inden-2-yl)pent-4-en-1-ol (25sa)



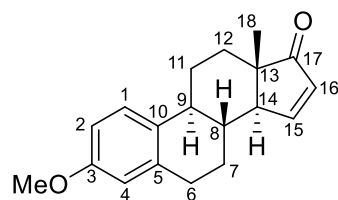
R_F = 0.18 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.46 (d, J = 7.4 Hz, 1H, CH_{Ar}), 7.35 (dt, J = 7.6, 1.0 Hz, 1H, CH_{Ar}), 7.29 (td, J = 7.4, 1.1 Hz, 1H, CH_{Ar}), 7.21 (td, J = 7.3, 1.3 Hz, 1H, CH_{Ar}), 6.00-5.80 (m, 2H, CH-7, CH-10), 5.17-4.97 (m, 4H, CH₂-8, CH₂-11), 4.85 (dd, J = 7.5, 6.4 Hz, 1H, CH-4), 3.56 (d, J = 22.8 Hz, 1H, CH₂-3^a), 3.39-3.34 (m, 2H, CH₂-9), 3.38 (d, J = 22.1 Hz, 1H, CH₂-3^b), 2.24-2.04 (m, 2H, CH₂-6), 1.95 (dddd, J = 13.7, 8.8, 7.5, 6.2 Hz, 1H, CH₂-5^a), 1.86-1.66 (m, 2H, CH₂-5^b, OH). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 145.6 (C_{Ar}), 144.6 (C_{Ar}), 142.8 (C-2), 138.2 (C-7), 136.9 (C-1), 135.8 (C-10), 126.3 (CH_{Ar}), 124.9 (CH_{Ar}), 123.9 (CH_{Ar}), 119.7 (CH_{Ar}), 116.0 (C-11), 115.2 (C-8), 67.9 (C-4), 36.2 (C-5), 36.1 (C-3), 30.3 (C-6), 29.8 (C-9). **MS** (EI) m/z (%) 240 ([M]⁺, 20), 222 ([M-H₂O]⁺, 40), 185 ([M-homoallyl]⁺, 50), 181 ([M-H₂O-allyl]⁺, 50), 167 ([M-H₂O-homoallyl]⁺, 100), 83 ([pentenyl]⁺, 65). **HRMS** (EI) m/z [M]⁺ calcd for C₁₇H₂₀O₂: 240.1514; found: 240.1511. **IR** (neat): ν_{max} = 3378, 3075, 2976, 2929, 1639, 1459, 1434, 1394, 1050, 993, 909, 769, 747, 720, 605 cm⁻¹.

1-Allylcyclohex-2-en-1-ol (25t)



Prepared according to general procedure A from cyclohexenone (500 mg, 5.20 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 7:1, gradient to 1:1) gave 601 mg (84%) of the product **25t** as a colorless oil. R_F = 0.59 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 5.87 (ddt, J = 16.8, 10.5, 7.4 Hz, 1H, CH-8), 5.86-5.79 (m, 1H, CH-3), 5.66-5.59 (m, 1H, CH-2), 5.16-5.09 (m, 2H, CH₂-9), 2.30 (dt, J = 7.4, 1.2 Hz, 2H, CH₂-7), 2.10-2.00 (m, 1H, CH₂-4^a), 1.99-1.88 (m, 1H, CH₂-4^b), 1.78-1.58 (m, 5H, CH₂-5, CH₂-6, OH). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 133.8 (C-8), 132.3 (C-2), 130.3 (C-3), 118.7 (C-9), 69.3 (C-1), 46.8 (C-7), 35.7 (C-6), 25.3 (C-4), 19.1 (C-5). The spectral data match those reported in the literature.^[152]

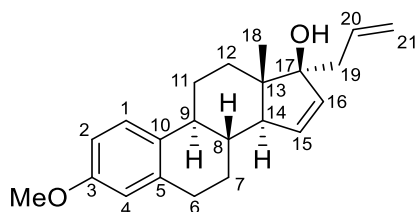
(8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-6,7,8,9,11,12,13,14-octahydro-17H-cyclopenta[a]phenanthren-17-one (31u)



In a flame-dried Schlenk flask, estrone 3-methyl ether (288 mg, 1.01 mmol) was dissolved in dry MeCN (2.0 mL). At r.t. Et₃N (195 μ L, 1.40 mmol), anhydrous NaI (210 mg, 1.40 mmol) and TMSCl (178 μ L, 1.40 mmol) were successively added. The mixture was refluxed for 2 h, quenched by NaHCO₃ solution (5% in H₂O, 10 mL), and extracted with hexane (3 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude silyl enol ether. The silyl enol ether was dissolved in MeCN (15 mL), and Pd(OAc)₂ (674 mg, 3.0 mmol) was added. The reaction mixture was stirred for 30 min filtered through a plug of layered celite and silica gel, which was washed by Et₂O.

The solvents were evaporated at reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc, 10:1, gradient to 3:1) to yield 192 mg (67%) of **31u** as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, J = 6.0, 1.8 Hz, 1H, CH-15), 7.21 (d, J = 8.6 Hz, 1H, CH-1), 6.73 (dd, J = 8.6, 2.8 Hz, 1H, CH-2), 6.66 (d, J = 2.7 Hz, 1H, CH-4), 6.09 (dd, J = 6.0, 3.1 Hz, 1H, CH-16), 3.79 (s, 3H, OMe), 2.99-2.92 (m, 2H, CH₂-6), 2.51 (ddd, J = 11.5, 3.0, 1.9 Hz, 1H, CH-14), 2.48-2.40 (m, 1H, CH₂-11^a), 2.39-2.30 (m, 1H, CH₂-12^a), 2.24-2.16 (m, 1H, CH-7^a), 2.07-1.99 (m, 1H, CH-9), 1.89-1.77 (m, 1H, CH-8), 1.77-1.66 (m, 2H, CH₂-11^b, CH₂-12^b), 1.56 (tdd, J = 12.2, 10.1, 8.1 Hz, 1H, CH-7^b), 1.11 (s, 3H, CH₃-18). The spectral data match those reported in the literature.^[153]

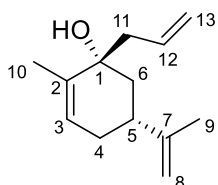
17 α -Allyl-3-*O*-methylestra-1,3,5(10),15-tetraen-17 β -ol (**25u**)



Prepared according to general procedure **A** from 15,16-dehydroestrone methyl ether **31u** (1.34 g, 4.8 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 1.50 g (96%) of **25u** as a colorless solid.

R_F = 0.25 (hexanes/EtOAc, 10:1). **m.p.** 111-113 °C. $[\alpha]_D^{20} = -74.6$ (c 0.29; CHCl₃). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.19 (d, J = 8.6 Hz, 1H, CH_{Ar}-1), 6.71 (dd, J = 8.6, 2.8 Hz, 1H, CH_{Ar}-2), 6.64 (d, J = 2.7 Hz, 1H, CH_{Ar}-4), 6.01-5.87 (m, 2H, CH-20, CH-16), 5.66 (dd, J = 6.0, 3.2 Hz, 1H, CH-15), 5.22-5.07 (m, 2H, CH₂-21), 3.77 (s, 3H, OMe), 2.99-2.80 (m, 2H, CH₂-6), 2.45-2.30 (m, 2H, CH₂-19^a, CH₂-12^a), 2.30-2.19 (m, 2H, CH₂-19^b, CH-9), 2.15 (ddd, J = 11.5, 3.3, 1.7 Hz, 1H, CH-14), 2.09 (ddt, J = 12.8, 5.8, 2.8 Hz, 1H, CH₂-7^a), 1.87 (s, 1H, OH), 1.77-1.54 (m, 4H, CH-8, CH₂-12^b, CH₂-11), 1.50-1.36 (m, 1H, CH₂-7^b), 0.95 (s, 3H, CH₃-18). ¹³C NMR (101 MHz, Chloroform-*d*) δ 157.7 (C-3), 137.9 (C-5), 137.7 (C-15), 135.1 (C-20), 132.7 (C-10), 130.9 (C-16), 126.1 (C-1), 118.7 (C-21), 114.0 (C-4), 111.6 (C-2), 86.1 (C-17), 56.4 (C-14), 55.3 (OMe), 51.5 (C-13), 44.6 (C-9), 38.0 (C-19), 36.8 (C-8), 30.7 (C-11), 29.7 (C-6), 27.9 (C-7), 26.1 (C-12), 15.1 (C-18). **MS** (EI) m/z (%) 324 ([M]⁺, 10), 306 ([M-H₂O]⁺, 60), 282 ([M-CH₃CH=CH₂]⁺, 50), 186 ([M-CH₄-MeOC₆H₄CH₃]⁺, 100), 174 ([M-CH₃CH=CH₂-MeOC₆H₅]⁺, 30). **HRMS** (EI) m/z [M]⁺ calcd for C₂₂H₂₈O₂: 324.2089; found: 324.2092. **IR** (neat): ν_{max} = 3449, 2994, 2927, 2854, 1609, 1576, 1464, 1431, 1375, 1278, 1256, 1150, 1034, 999, 909, 791, 733 cm⁻¹.

(1*R*,5*R*)-1-Allyl-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ol (**25v**)

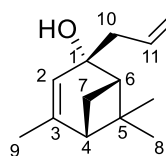


Prepared according to general procedure **A** from (*R*)-carvone (1.0 g, 6.66 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 1.19 g (93%) of **25v** as a colorless oil.

R_F = 0.17 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 5.87 (ddt, J = 17.5, 10.3, 7.4 Hz, 1H, CH-12), 5.50-5.45 (m, 1H, CH-3), 5.22-5.07 (m, 2H, CH₂-13), 4.76-4.70 (m, 2H, CH₂-8), 2.47 (ddd, J = 14.1, 7.4, 1.4 Hz, 1H, CH₂-11^a), 2.42-2.30 (m, 2H, CH₂-11^b, CH-5), 2.17-2.03 (m, 2H, CH₂-4^a, CH₂-6^a), 2.01-1.91 (m, 1H, CH₂-4^b), 1.78-1.71 (m, 6H,

CH₃-9, CH₃-10), 1.63 (bs, 1H, OH), 1.50 (t, J = 12.4 Hz, 1H, CH₂-6^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 149.1 (C-7), 138.2 (C-2), 133.9 (C-12), 124.1 (C-3), 118.8 (C-13), 109.3 (C-8), 73.7 (C-1), 43.0 (C-11), 40.6 (C-6), 39.3 (C-5), 31.0 (C-4), 20.9 (C-9), 17.2 (C-10). The spectral data match those reported in the literature.^[154]

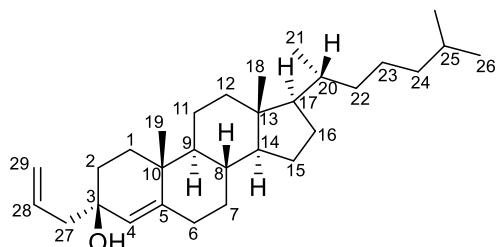
(1*S*,2*S*,5*S*)-2-Allyl-4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-ol (25w)



Prepared according to general procedure A from (*S*)-verbenone (500 mg, 3.33 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 20:1) gave 550 mg (86%) of **25w** as a single diastereoisomer as a colorless oil.

R_F = 0.15 (hexanes/EtOAc, 10:1). $[\alpha]^{20}_{589} = -24.6$ (c 0.60; CHCl₃). ¹H NMR (401 MHz, Chloroform-*d*) δ 5.93 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H, CH-11), 5.22 (dq, J = 3.1, 1.6 Hz, 1H, CH-2), 5.14 (ddt, J = 10.1, 2.0, 0.9 Hz, 1H, CH₂-12), 5.08 (ddt, J = 17.1, 2.6, 1.4 Hz, 1H, CH₂-12), 2.44 (ddd, J = 9.3, 6.1, 5.2 Hz, 1H, CH₂-7^a), 2.37-2.24 (m, 2H, CH₂-10), 2.10 (td, J = 6.0, 2.1 Hz, 1H, CH-4), 1.99-1.95 (m, 1H, CH-6), 1.84 (bs, 1H, OH), 1.72 (d, J = 1.6 Hz, 3H, CH₃-9), 1.43 (d, J = 9.2 Hz, 1H, CH₂-7^b), 1.35 (s, 3H, CH₃-8), 1.09 (s, 3H, CH₃-8). ¹³C NMR (101 MHz, Chloroform-*d*) δ 146.5 (C-3), 133.9 (C-11), 122.1 (C-2), 118.5 (C-12), 76.8 (C-1), 51.6 (C-4), 48.0 (C-6), 45.2 (C-10), 42.6 (C-5), 35.5 (C-7), 27.3 (C-9), 23.7 (C-8), 22.9 (C-8). MS (ESI+) m/z (%) 215 ([M+Na⁺], 20), 175 ([M-H₂O+H⁺], 100). HRMS (CI) m/z [M+H⁺] calcd for C₁₃H₂₁O: 193.1592; found: 193.1590. IR (neat): $\nu_{\max}$ = 3449, 3074, 2973, 2920, 2869, 1639, 1471, 1434, 1382, 1366, 1330, 1253, 1218, 1140, 1048, 1001, 988, 910, 845, 818, 761, 661 cm⁻¹.

3-Allylcholest-4-en-3 β -ol (25x)

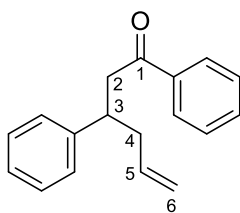


Prepared according to general procedure A from cholest-4-en-3-one (826 mg, 2.15 mmol). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1, gradient to 5:1) gave 95 mg (10%) of the minor α -diastereoisomer followed by 717 mg (79%) of the major β -diastereoisomer **25x** as colorless oils. In total, 812 mg (89%) were obtained as a 7.5:1 diastereoisomeric mixture.

R_F = 0.32 (hexanes/EtOAc, 5:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 5.90 (ddt, J = 17.4, 10.3, 7.4 Hz, 1H, CH-28), 5.18-5.08 (m, 3H, CH₂-29, CH-4), 2.33 (dd, J = 13.8, 7.0 Hz, 1H, CH₂-27^a), 2.24 (dd, J = 13.7, 7.6 Hz, 1H, CH₂-27^b), 2.24-2.14 (m, 1H, CH₂-6^a), 2.02-1.98 (m, 1H, CH₂-6^b), 1.97-0.70 (m, 31H), 1.04 (s, 3H, CH₃-19), 0.90 (d, J = 6.5 Hz, 3H, CH₃-21), 0.862 (d, J = 6.6 Hz, 3H, CH₃-26), 0.858 (d, J = 6.6 Hz, 3H, CH₃-26), 0.68 (s, 3H, CH₃-18). The spectral data match those reported in the literature.^[154]

6.3.2. Tandem AOC/ α -oxygenation

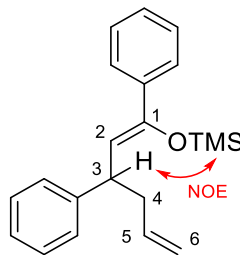
1,3-Diphenylhex-5-en-1-one (27a)



In a flame-dried Schlenk flask, alcohol **25a** (150 mg, 0.6 mmol) was dissolved in THF (12 mL). At 0 °C, KHMDS (1M in THF, 0.78 mL, 0.78 mmol) was dropwise added. The mixture was warmed to 50 °C and stirred for 1 h. The reaction was quenched by saturated NH₄Cl solution (10 drops), diluted by Et₂O, and filtered through a plug of silica gel, which was washed by Et₂O. The solvent was evaporated to give 149 mg (99%) of essentially pure **27a** as a colorless oil.

R_F = 0.74 (hexanes/EtOAc, 5:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.93-7.87 (m, 2H, CH_{Ar}), 7.58-7.50 (m, 1H, CH_{Ar}), 7.47-7.39 (m, 2H, CH_{Ar}), 7.32-7.14 (m, 5H, CH_{Ar}), 5.69 (ddt, J = 17.2, 10.1, 7.0 Hz, 1H, CH-5), 5.05-4.93 (m, 2H, CH₂-6), 3.48 (quint, J = 7.1 Hz, 1H, CH-3), 3.35-3.24 (m, 2H, CH₂-2), 2.53-2.40 (m, 2H, CH₂-4). ¹³C NMR (101 MHz, Chloroform-*d*) δ 199.1 (C-1), 144.5 (C_{Ar}), 137.4 (C_{Ar}), 136.4 (C-5), 133.1 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 127.7 (CH_{Ar}), 126.5 (CH_{Ar}), 116.9 (C-6), 44.7 (C-2), 40.9 (C-3), 40.8 (C-4). The spectral data match those reported in the literature.^[155]

(*Z*)-1,3-Diphenyl-1-(trimethylsilyloxy)hexa-1,5-diene (29a)



In a flame-dried Schlenk flask, alcohol **25a** (212 mg, 0.85 mmol) was dissolved in DME (8.5 mL). At 0 °C, KHMDS (1.1 mL, 1.1 mmol, 1M in THF) was dropwise added. The mixture was warmed to 50 °C and stirred at this temperature for 1 h. The mixture was cooled to -78 °C, and TMSCl (140 μ L, 1.1 mmol) was dropwise added. The mixture was stirred for 1 h, diluted with hexane (30 mL), and washed by diluted NaHCO₃ solution and brine. The

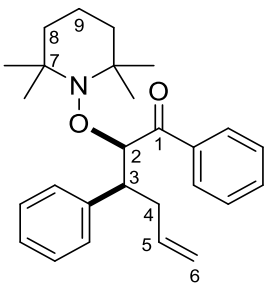
organic layer was dried over MgSO₄ and filtered. The solvent was evaporated at reduced pressure to give 289 mg of crude **29a** that was pure enough for NMR analysis but slowly decomposed in CDCl₃ solution.

R_F = 0.66 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.44 (dt, J = 6.4, 1.5 Hz, 2H, CH_{Ar}), 7.30-7.13 (m, 8H, CH_{Ar}), 5.74 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H, CH-5), 5.38 (d, J = 9.7 Hz, 1H, CH-2), 5.00 (dq, J = 17.1, 1.7 Hz, 1H, CH₂-6), 4.94 (ddt, J = 10.2, 2.3, 1.2 Hz, 1H, CH₂-6), 3.88 (dt, J = 9.7, 7.3 Hz, 1H, CH-3), 2.55-2.39 (m, 2H, CH₂-4), 0.05 (s, 9H, OSiMe₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 149.5 (C-1), 145.2 (C_{Ar}), 139.4 (C_{Ar}), 136.9 (C-5), 128.5 (CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 126.1 (CH_{Ar}), 126.0 (CH_{Ar}), 116.2 (C-6), 114.4 (C-2), 42.2 (C-3), 42.0 (C-4), 0.9 (OSiMe₃).

(2*R**,3*S**)- and (2*R**,3*R**)-1,3-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one
(**28a**)

Prepared according to general procedure **D** from **25a** (313 mg, 1.25 mmol). The rearrangement was performed at 50 °C for 1 h. Purification of the crude product by column chromatography (neat hexane, gradient to 10:1 hexane/EtOAc) gave 503 mg (99%) of **28a** as a 4.7:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.38 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.66-7.60 (m, 2H, CH_{Ar}), 7.38-7.35 (m, 1H, CH_{Ar}), 7.26-7.21 (m, 2H, CH_{Ar}), 7.10-6.97 (m, 5H, CH_{Ar}), 5.61 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, CH-5), 5.38 (d, J = 6.6 Hz, 1H, CH-2), 4.97-4.84 (m, 2H, CH_2 -6), 3.46-3.31 (m, 1H, CH-3), 3.18-3.03 (m, 1H, CH_2 -4^a), 2.61-2.44 (m, 1H, CH_2 -4^b), 1.73-1.41 (m, 6H, CH_2 -9^a, CH_2 -8, $\text{CH}_3^{\text{TEMPO}}$), 1.39-1.22 (m, 6H, CH_2 -9^b, CH_2 -8, $\text{CH}_3^{\text{TEMPO}}$), 1.07 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.78 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 203.3 (C-1), 139.5 (C_{Ar}), 139.2 (C_{Ar}), 136.6 (C-5), 132.1 (CH_{Ar}), 129.4 (CH_{Ar}), 128.18 (CH_{Ar}), 128.12 (CH_{Ar}), 127.9 (CH_{Ar}), 126.7 (CH_{Ar}), 116.5 (C-6), 86.9 (C-2), 61.3 (C-7), 59.8 (C-7), 49.1 (C-3), 41.2 (C-8), 40.8 (C-8), 36.8 (C-4), 34.6 ($\text{CH}_3^{\text{TEMPO}}$), 34.2 ($\text{CH}_3^{\text{TEMPO}}$), 20.8 ($\text{CH}_3^{\text{TEMPO}}$), 20.5 ($\text{CH}_3^{\text{TEMPO}}$), 17.1 (C-9). **MS** (ESI+) m/z (%) 428 ($[\text{M}+\text{Na}^+]$, 30), 406 ($[\text{M}+\text{H}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_2\text{Na}$: 428.2560; found: 428.2559; $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{27}\text{H}_{36}\text{NO}_2$: 406.2741; found: 406.2741. **IR** (neat): ν_{max} = 3063, 2974, 2931, 1687, 1597, 1448, 1362, 1250, 1180, 1132, 972, 909, 758, 697, 637 cm^{-1} .

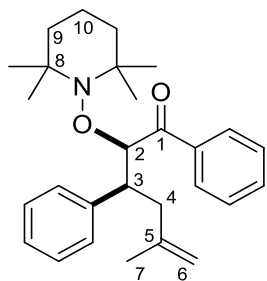
Minor diastereoisomer:

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.66-7.60 (m, 2H, CH_{Ar}), 7.38-7.35 (m, 1H, CH_{Ar}), 7.26-7.21 (m, 2H, CH_{Ar}), 7.10-6.97 (m, 5H, CH_{Ar}), 5.61 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, CH-5), 5.40 (d, J = 8.4 Hz, 1H, CH-2), 4.97-4.84 (m, 2H, CH_2 -6), 3.69-3.58 (m, 1H, CH-3), 2.78-2.65 (m, 1H, CH_2 -4^a), 2.62-2.43 (m, 1H, CH_2 -4^b), 1.73-1.47 (m, 6H, CH_2 -9^a, CH_2 -8, $\text{CH}_3^{\text{TEMPO}}$), 1.39-1.22 (m, 6H, CH_2 -9^b, CH_2 -8, $\text{CH}_3^{\text{TEMPO}}$), 1.01 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.78 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 202.0 (C-1), 139.3 (C_{Ar}), 138.9 (C_{Ar}), 136.8 (C-5), 132.5 (CH_{Ar}), 129.3 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.15 (CH_{Ar}), 126.8 (CH_{Ar}), 116.1 (C-6), 86.9 (C-2), 60.5 (C-7), 59.9 (C-7), 48.5 (C-3), 40.8 (C-8), 40.5 (C-8), 34.5 ($\text{CH}_3^{\text{TEMPO}}$), 34.2 ($\text{CH}_3^{\text{TEMPO}}$), 31.8 (C-4), 20.36 ($\text{CH}_3^{\text{TEMPO}}$), 20.33 ($\text{CH}_3^{\text{TEMPO}}$), 17.2 (C-9).

(2*R,3*S**)- and (2*R**,3*R**)-5-Methyl-1,3-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one (28b)**

Prepared according to general procedure **D** from **25b** (132 mg, 0.5 mmol). The rearrangement step was performed at 50 °C for 30 min. Purification of the crude product by column chromatography (hexane/Et₂O, 30:1) gave 209 mg (99%) of **28b** as a 3:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.63 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63-7.55 (m, 2H, CH_{Ar}), 7.43-7.31 (m, 1H, CH_{Ar}), 7.29-7.17 (m, 2H, CH_{Ar}), 7.15-6.92 (m, 5H, CH_{Ar}), 5.36 (d, J = 8.9 Hz, 1H, CH-2), 4.60 (bs, 1H, CH₂-6), 4.50 (bs, 1H, CH₂-6), 3.54 (ddd, J = 11.8, 9.0, 4.0 Hz, 1H, CH-3), 3.09 (dd, J = 13.4, 4.0 Hz, 1H, CH₂-4^a), 2.51 (dd, J = 13.6, 11.6 Hz, 1H, CH₂-4^b), 1.65 (s, 3H, CH₃-7), 1.59-1.49 (m, 6H, CH₃^{TEMPO}, CH₂-10^a, CH₂-9), 1.40-1.21 (m, 6H, CH₃^{TEMPO}, CH₂-10^b, CH₂-9), 1.07 (bs, 3H, CH₃^{TEMPO}), 0.79 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 203.5 (C-1), 143.3 (C-5), 139.5 (C_{Ar}), 139.3 (C_{Ar}), 132.0 (CH_{Ar}), 129.4 (CH_{Ar}), 128.6 (CH_{Ar}), 127.97 (CH_{Ar}), 127.9 (CH_{Ar}), 126.6 (CH_{Ar}), 112.8 (C-6), 86.6 (C-2), 59.9 (C-8), 59.8 (C-8), 47.4 (C-3), 41.2 (C-9), 40.73 (C-9), 40.66 (C-4), 34.5 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 22.5 (C-7), 20.8 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 17.1 (C-10). MS (ESI+) m/z (%) 861 ([2M+Na⁺], 40), 442 ([M+Na⁺], 100), 420 ([M+H⁺], 10), 286 ([M-TEMPO+Na⁺], 20). HRMS (ESI+) m/z [M+Na⁺] calcd for C₂₈H₃₇NO₂Na: 442.2717; found: 442.2713. IR (neat): ν_{max} = 3063, 3004, 2968, 2931, 1687, 1597, 1448, 1362, 1252, 1132, 1027, 974, 887, 758, 698 cm⁻¹.

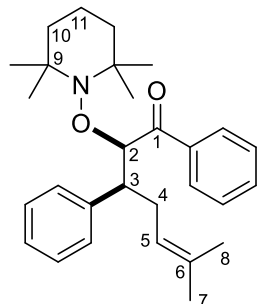
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.70-7.63 (m, 2H, CH_{Ar}), 7.43-7.32 (m, 1H, CH_{Ar}), 7.29-7.18 (m, 2H, CH_{Ar}), 7.15-6.92 (m, 5H, CH_{Ar}), 5.39 (d, J = 7.0 Hz, 1H, CH-2), 4.58 (bs, 1H, CH₂-6), 4.52 (bs, 1H, CH₂-6), 3.80 (ddd, J = 11.0, 6.9, 3.5 Hz, 1H, CH-3), 2.68-2.44 (m, 2H, CH₂-4), 1.61 (s, 3H, CH₃-7), 1.59-1.49 (m, 3H, CH₂-10^a, CH₂-9), 1.40-1.21 (m, 6H, CH₃^{TEMPO}, CH₂-10^b, CH₂-9), 1.09 (bs, 3H, CH₃^{TEMPO}), 0.97 (bs, 3H, CH₃^{TEMPO}), 0.79 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.3 (C-1), 143.4 (C-5), 139.4 (C_{Ar}), 139.0 (C_{Ar}), 132.5 (CH_{Ar}), 129.3 (CH_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.00 (CH_{Ar}), 126.7 (CH_{Ar}), 112.3 (C-6), 86.6 (C-2), 61.3 (C-8), 60.6 (C-8), 46.7 (C-3), 40.73 (C-9), 40.5 (C-9), 35.2 (C-4), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 22.7 (C-7), 20.4 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 17.2 (C-10).

(2*R**,3*S**)- and (2*R**,3*R**)-6-Methyl-1,3-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hept-5-en-1-one (**28c**)

Prepared according to general procedure **D** from **25c** (113 mg, 0.41 mmol). The rearrangement step was performed at r.t. for 20 min. Purification of the crude product by column chromatography (hexane/Et₂O, 30:1) gave 167 mg (95%) of **28c** as a 3:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.55 (hexanes/EtOAc, 10:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 7.64-7.57 (m, 2H, CH_{Ar}), 7.40-7.32 (m, 1H, CH_{Ar}), 7.29-7.19 (m, 2H, CH_{Ar}), 7.15-7.09 (m, 1H, CH_{Ar}), 7.07-6.95 (m, 4H, CH_{Ar}), 5.39 (d, J = 8.7 Hz, 1H, CH-2), 4.95 (ddq, J = 7.6, 5.2, 1.4 Hz, 1H, CH-5), 3.29 (ddd, J = 10.8, 8.8, 4.4 Hz, 1H, CH-3), 3.06 (ddd, J = 13.0, 7.4, 4.5 Hz, 1H, CH₂-4^a), 2.49-2.31 (m, 1H, CH₂-4^b), 1.58 (s, 3H, CH₃-8), 1.58-1.46 (m, 5H, CH₃^{TEMPO}, CH₂-10), 1.53 (s, 3H, CH₃-7), 1.32-1.14 (m, 7H, CH₃^{TEMPO}, CH₂-10, CH₂-11), 0.91 (bs, 3H, CH₃^{TEMPO}), 0.71 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.2 (C-1), 140.1 (C_{Ar}), 139.9 (C_{Ar}), 133.0 (C-6), 132.0 (CH_{Ar}), 129.41 (CH_{Ar}), 128.7 (CH_{Ar}), 128.13 (CH_{Ar}), 127.9 (CH_{Ar}), 126.5 (CH_{Ar}), 122.2 (C-5), 87.1 (C-2), 61.3 (C-9), 59.8 (C-9), 49.6 (C-3), 41.2 (C-10), 40.8 (C-10), 34.5 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 31.2 (C-4), 25.8 (C-7), 20.8 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 18.0 (C-8), 17.16 (C-11). **MS** (ESI+) m/z (%) 456 ([M+Na⁺], 15), 434 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₉H₃₉O₂NNa: 456.2873; found: 456.2874. **IR** (neat): $\nu_{\max}$ = 2968, 2928, 1687, 1597, 1448, 1362, 1250, 1133, 1043, 971, 843, 754, 697, 618 cm⁻¹.

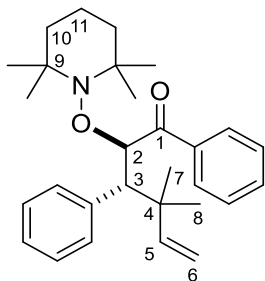
Minor diastereoisomer:

¹H NMR (401 MHz, Chloroform-*d*) δ 7.74-7.65 (m, 2H, CH_{Ar}), 7.40-7.32 (m, 1H, CH_{Ar}), 7.29-7.19 (m, 2H, CH_{Ar}), 7.15-7.09 (m, 1H, CH_{Ar}), 7.07-6.95 (m, 4H, CH_{Ar}), 5.37 (d, J = 6.9 Hz, 1H, CH-2), 4.92-4.86 (m, 1H, C-5), 3.54 (ddd, J = 11.1, 6.9, 3.8 Hz, 1H, C-3), 2.70-2.59 (m, 1H, CH₂-4^a), 2.49-2.31 (m, 1H, CH₂-4^b), 1.58 (s, 3H, CH₃-7), 1.58-1.46 (m, 5H, CH₃^{TEMPO}, CH₂-10), 1.50 (s, 3H, CH₃-8), 1.32-1.14 (m, 7H, CH₃^{TEMPO}, CH₂-10, CH₂-11), 0.91 (bs, 3H, CH₃^{TEMPO}), 0.71 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 203.3 (C-1), 139.5 (C_{Ar}), 139.1 (C_{Ar}), 132.38 (CH_{Ar}), 132.34 (C-6), 129.36 (CH_{Ar}), 128.6 (CH_{Ar}), 128.13 (CH_{Ar}), 128.05 (CH_{Ar}), 126.6 (CH_{Ar}), 122.6 (C-5), 87.1 (C-2), 60.6 (C-9), 59.8 (C-9), 49.1 (C-3), 40.8 (C-10), 40.6 (C-10), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 26.3 (C-4), 25.9 (C-7), 20.33 (CH₃^{TEMPO}), 20.28 (CH₃^{TEMPO}), 18.1 (C-8), 17.20 (C-11).

(2*R**,3*R**)- and (2*R**,3*S**)-4,4-Dimethyl-1,3-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one (**28d**)

Prepared according to general procedure **D** from **25d** (75 mg, 0.27 mmol). The rearrangement step was performed at 50 °C for 30 min. Purification of the crude product by column chromatography (hexane/Et₂O, 20:1) gave 113 mg (97%) of **28d** as a 4:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.55 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 7.6 Hz, 2H, CH_{Ar}), 7.62-7.41 (m, 3H, CH_{Ar}), 7.41-7.11 (m, 5H, CH_{Ar}), 5.96 (dd, J = 17.4, 10.7 Hz, 1H, CH-5), 5.75 (d, J = 8.1 Hz, 1H, CH-2), 4.87 (dd, J = 10.8, 1.2 Hz, 1H, CH₂-6), 4.80 (dd, J = 17.5, 1.2 Hz, 1H, CH₂-6), 3.41 (d, J = 8.1 Hz, 1H, CH-3), 1.55-1.29 (m, 4H, CH₂-11^a, CH₃^{TEMPO}), 1.28-1.15 (m, 2H, CH₂-10), 1.14-1.05 (m, 3H, CH₂-11^b, CH₂-10), 1.02 (s, 3H, CH₃-7 or 8), 0.85 (s, 3H, CH₃-7 or 8), 0.78 (bs, 3H, CH₃^{TEMPO}), 0.75 (bs, 3H, CH₃^{TEMPO}), 0.64 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.0 (C-1), 146.7 (C-5), 139.4 (C_{Ar}), 139.2 (C_{Ar}), 131.9 (CH_{Ar}), 128.7 (CH_{Ar}), 127.8 (CH_{Ar}), 127.17 (CH_{Ar}), 126.7 (CH_{Ar}), 125.7 (CH_{Ar}), 111.7 (C-6), 78.7 (C-2), 61.0 (C-9), 59.5 (C-9), 58.1 (C-3), 40.6 (C-10), 40.0 (C-10), 39.0 (C-4), 33.9 (CH₃^{TEMPO}), 33.3 (CH₃^{TEMPO}), 29.1 (C-7 or 8), 24.7 (C-7 or 8), 20.1 (CH₃^{TEMPO}), 20.0 (CH₃^{TEMPO}), 16.5 (C-11). **MS** (ESI⁺) m/z (%) 456 ([M+Na⁺], 10), 434 ([M+H⁺], 100). **HRMS** (ESI⁺) m/z [M+H⁺] calcd for C₂₉H₄₀NO₂: 434.3054; found: 434.3054. **IR** (neat): $\nu_{\max}$ = 3062, 2971, 2929, 2871, 1687, 1448, 1378, 1363, 1256, 1217, 1179, 1133, 1010, 967, 909, 766, 731, 699 cm⁻¹. **Anal. Calcd.** for C₂₉H₃₉NO₂ (433.64): C, 80.33; H, 9.07; N, 3.23; Found: C, 80.06; H, 9.03; N, 2.99.

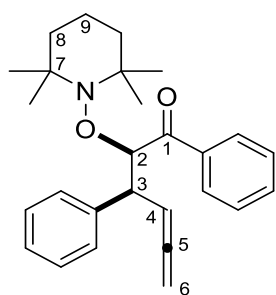
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 7.6 Hz, 2H, CH_{Ar}), 7.59-7.29 (m, 4H, CH_{Ar}), 7.14-7.00 (m, 4H, CH_{Ar}), 6.33 (dd, J = 17.5, 10.8 Hz, 1H, CH-5), 5.72 (d, J = 8.4 Hz, 1H, CH-2), 5.02 (dd, J = 10.8, 1.4 Hz, 1H, CH₂-6), 4.95 (dd, J = 17.5, 1.4 Hz, 1H, CH₂-6), 3.46 (d, J = 8.7 Hz, 1H, CH-3), 1.50-1.28 (m, 3H, CH₂-11^a, CH₂-10), 1.33-1.20 (m, 6H, CH₃-7 or 8, CH₃^{TEMPO}), 1.14-1.04 (m, 3H, CH₂-11^b, CH₂-10), 1.04-0.99 (m, 6H, CH₃^{TEMPO}), 1.03 (s, 3H, CH₃-7 or 8), 0.64 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.0 (C-1), 147.0 (C-5), 139.4 (C_{Ar}), 139.0 (C_{Ar}), 130.9 (CH_{Ar}), 130.8 (CH_{Ar}), 130.3 (CH_{Ar}), 127.9 (CH_{Ar}), 127.18 (CH_{Ar}), 126.2 (CH_{Ar}), 110.9 (C-6), 78.7 (C-2), 60.8 (C-9), 60.0 (C-9), 58.6 (C-3), 40.4 (C-10), 39.6 (C-10), 39.2 (C-4), 34.3 (CH₃^{TEMPO}), 33.3 (CH₃^{TEMPO}), 29.2 (C-7 or 8), 25.6 (C-7 or 8), 21.4 (CH₃^{TEMPO}), 20.9 (CH₃^{TEMPO}), 16.6 (C-11).

(2*R**,3*S**)- and (2*R**,3*R**)-1,3-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexa-4,5-dien-1-one (**28e**)

In a flame-dried Schlenk flask, KH (23 mg, 0.29 mmol, 50% suspension in wax) was washed by hot DME (4×) and subsequently suspended in DME (1.5 mL). At −30 °C, **25e** (65 mg, 0.26 mmol) was added in DME (3.5 mL). The mixture was warmed to r.t. and stirred for 4 h. After cooling to −78 °C, KHMDS (0.26 mL, 0.26 mmol, 1M in THF) and TEMPO (45 mg, 0.29 mmol) was added. The mixture was stirred for 10 min, and Cp₂Fe⁺PF₆[−] (152 mg, 0.46 mmol) was added portion-wise (~30 mg/30 s) until the mixture remained dark blue. The mixture was stirred for another 20 min, quenched by saturated NH₄Cl solution (5 drops), diluted by Et₂O (10 mL), and filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated, and the crude product was purified by column chromatography (hexane/Et₂O, 20:1) to yield 58 mg (55%) of **28e** as an inseparable 2:1 mixture of diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.54 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.95-7.85 (m, 2H, CH_{Ar}), 7.64-7.40 (m, 5H, CH_{Ar}), 7.32-7.18 (m, 3H, CH_{Ar}), 5.97 (dt, J = 7.7, 6.6 Hz, 1H, CH-4), 5.74 (d, J = 9.8 Hz, 1H, CH-2), 4.95-4.78 (m, 2H, CH₂-6), 4.25 (ddt, J = 10.1, 7.6, 2.6 Hz, 1H, CH-3), 1.85-1.67 (m, 6H, CH₃^{TEMPO}, CH₂-9^a, CH₂-8), 1.63-1.40 (m, 6H, CH₃^{TEMPO}, CH₂-9^b, CH₂-8), 1.33 (bs, 3H, CH₃^{TEMPO}), 1.00 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 209.1 (C-1), 202.8 (C-5), 139.3 (C_{Ar}), 138.5 (C_{Ar}), 132.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.14 (CH_{Ar}), 128.08 (CH_{Ar}), 126.9 (CH_{Ar}), 92.2 (C-4), 86.0 (C-2), 76.2 (C-6), 61.6 (C-7), 59.8 (C-7), 48.6 (C-3), 41.1 (C-8), 40.7 (C-8), 34.14 (CH₃^{TEMPO}), 34.12 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.1 (C-9). MS (ESI+) m/z (%) 829 ([2M+Na⁺], 10), 426 ([M+Na⁺], 100), 270 ([M-TEMPO+Na⁺], 65). HRMS (ESI+) m/z [M+Na⁺] calcd for C₂₇H₃₃NO₂Na: 426.2404; found: 426.2405. IR (neat): ν_{max} = 2973, 2931, 1956, 1686, 1449, 1362, 1252, 1180, 1132, 1030, 972, 843, 759, 697 cm^{−1}.

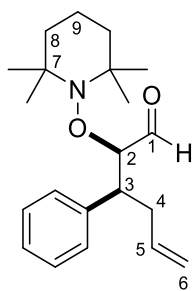
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 8.20-8.11 (m, 2H, CH_{Ar}), 7.73-7.33 (m, 5H, CH_{Ar}), 7.32-7.17 (m, 3H, CH_{Ar}), 5.70-5.63 (m, 1H, CH-4), 5.62 (d, J = 9.1 Hz, 1H, CH-2), 4.93-4.80 (m, 1H, CH₂-6), 4.48 (ddd, J = 10.6, 6.7, 2.2 Hz, 1H, CH₂-6), 4.42-4.31 (m, 1H, CH-3), 1.85-1.67 (m, 6H, CH₃^{TEMPO}, CH₂-9^a, CH₂-8), 1.63-1.41 (m, 3H, CH₂-9^b, CH₂-8), 1.26 (bs, 3H, CH₃^{TEMPO}), 0.98 (bs, 3H, CH₃^{TEMPO}), 0.94 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 209.3 (C-1), 202.7 (C-5), 140.0 (C_{Ar}), 139.5 (C_{Ar}), 132.5 (CH_{Ar}), 129.7 (CH_{Ar}), 129.1 (CH_{Ar}), 128.2 (CH_{Ar}), 128.04 (CH_{Ar}), 127.0 (CH_{Ar}), 89.3 (C-4), 84.6 (C-2), 76.6 (C-6), 61.0 (C-7), 59.8 (C-7), 47.3 (C-3), 40.9 (C-8), 40.5 (C-8), 34.0 (CH₃^{TEMPO}), 33.7 (CH₃^{TEMPO}), 20.0 (CH₃^{TEMPO}), 19.4 (CH₃^{TEMPO}), 17.1 (C-9).

(2*R,3*S**)- and (2*R**,3*R**)-3-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-enal (28f)**

Prepared according to general procedure **D** from **25f** (87 mg, 0.5 mmol). The rearrangement step was performed at reflux temperature for 2.5 h. Purification of the crude product by column chromatography (hexane/Et₂O, 10:1) gave 133 mg (81%) of **28f** as a 2:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.60 (hexanes/EtOAc, 10:1). **¹H NMR** (401 MHz, Chloroform-*d*) δ 9.65 (d, J = 5.1 Hz, 1H, CHO-1), 7.33-7.16 (m, 5H, CH_{Ar}), 5.74-5.59 (m, 1H, CH-5), 5.06 (dq, J = 17.1, 1.6 Hz, 1H, CH₂-6), 4.98 (ddt, J = 10.2, 2.1, 1.2 Hz, 1H, CH₂-6), 4.27 (dd, J = 5.9, 5.2 Hz, 1H, CH-2), 3.23 (dt, J = 8.9, 6.1 Hz, 1H, CH-3), 2.73-2.59 (m, 1H, CH₂-4^a), 2.58-2.47 (m, 1H, CH₂-4^b), 1.48-1.40 (m, 4H, CH₂-8), 1.35-1.22 (m, 2H, CH₂-9), 1.18 (bs, 3H, CH₃^{TEMPO}), 1.14 (bs, 3H, CH₃^{TEMPO}), 1.13 (bs, 3H, CH₃^{TEMPO}), 0.87 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 204.7 (C-1), 139.0 (C_{Ar}), 135.96 (C-5), 129.0 (*m*-CH_{Ar}), 128.4 (*o*-CH_{Ar}), 127.2 (*p*-CH_{Ar}), 117.3 (C-6), 89.3 (C-2), 61.4 (C-7), 60.0 (C-7), 47.6 (C-3), 40.4 (C-8), 40.2 (C-8), 35.3 (C-4), 34.3 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.73 (CH₃^{TEMPO}), 20.67 (CH₃^{TEMPO}), 17.2 (C-9). **MS** (ESI+) m/z (%) 352 ([M+Na⁺], 100), 330 ([M+H⁺], 30). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₁H₃₁NO₂Na: 352.2248; found: 352.2247. **IR** (neat): $\nu_{\max}$ = 3029, 2974, 2872, 1721, 1454, 1375, 1361, 1258, 1182, 1132, 1043, 912, 759, 699 cm⁻¹. **Anal.** Calcd. for C₂₁H₃₁NO₂ (329.48): C, 76.55; H, 9.48; N, 4.25; Found: C, 76.48; H, 9.48; N, 4.26.

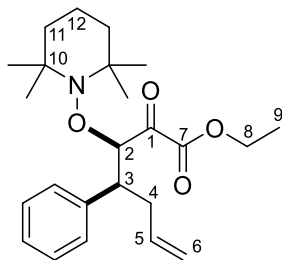
Minor diastereoisomer:

¹H NMR (401 MHz, Chloroform-*d*) δ 9.76 (d, J = 4.8 Hz, 1H, CHO-1), 7.33-7.16 (m, 5H, CH_{Ar}), 5.74-5.59 (m, 1H, CH-5), 5.06 (dq, J = 17.1, 1.6 Hz, 1H, CH₂-6), 4.98 (ddt, J = 10.2, 2.1, 1.2 Hz, 1H, CH₂-6), 4.38 (t, J = 5.0 Hz, 1H, CH-2), 3.09 (ddd, J = 9.0, 6.6, 5.2 Hz, 1H, CH-3), 2.73-2.59 (m, 1H, CH₂-4^a), 2.58-2.47 (m, 1H, CH₂-4^b), 1.48-1.40 (m, 4H, CH₂-8), 1.35-1.22 (m, 2H, CH₂-9), 1.13 (bs, 3H, CH₃^{TEMPO}), 1.09 (bs, 3H, CH₃^{TEMPO}), 1.05 (bs, 3H, CH₃^{TEMPO}), 1.02 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 206.3 (C-1), 139.2 (C_{Ar}), 136.03 (C-5), 129.4 (*m*-CH_{Ar}), 128.2 (*o*-CH_{Ar}), 127.0 (*p*-CH_{Ar}), 117.2 (C-6), 88.4 (C-2), 61.6 (C-7), 60.2 (C-7), 47.9 (C-3), 40.6 (C-8), 40.3 (C-8), 35.7 (C-4), 34.5 (CH₃^{TEMPO}), 34.0 (CH₃^{TEMPO}), 20.59 (CH₃^{TEMPO}), 20.55 (CH₃^{TEMPO}), 17.1 (C-9).

(2*R,3*S**)- and (2*R**,3*R**)-Ethyl 2-oxo-4-phenyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hept-6-enoate (**28g**)**

Prepared according to general procedure **D** from **25g** (49 mg, 0.2 mmol). The rearrangement step was performed at 30 °C for 2 h. Purification of the crude product by column chromatography (hexane/Et₂O, 10:1) gave 60 mg (75%) of **28g** as a 2:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.55 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.31-7.17 (m, 3H, CH_{Ar}), 7.17-7.07 (m, 2H, CH_{Ar}), 5.66-5.53 (m, 1H, CH-5), 5.62 (d, J = 9.8 Hz, 1H, CH-2), 5.02-4.85 (m, 2H, CH₂-6), 4.19 (dq, J = 10.8, 7.1 Hz, 1H, CH₂-8^a), 4.10 (dq, J = 10.9, 7.1 Hz, 1H, CH₂-8^b), 3.25 (td, J = 10.3, 4.0 Hz, 1H, CH-3), 3.00 (ddd, J = 14.1, 6.5, 4.2 Hz, 1H, CH₂-4^a), 2.54-2.44 (m, 1H, CH₂-4^b), 1.59-1.33 (m, 8H, CH₂-12^a, CH₂-11, CH₃^{TEMPO}), 1.32-1.27 (m, 1H, CH₂-12^b), 1.25 (bs, 3H, CH₃^{TEMPO}), 1.23 (t, J = 7.1 Hz, 3H, CH₃-9), 1.10 (bs, 3H, CH₃^{TEMPO}), 0.93 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 195.8 (C-1), 161.2 (C-7), 139.0 (C_{Ar}), 136.0 (C-5), 129.1 (*m*-CH_{Ar}), 128.4 (*o*-CH_{Ar}), 126.9 (*p*-CH_{Ar}), 116.6 (C-6), 82.6 (C-2), 62.0 (C-8), 61.7 (C-10), 60.2 (C-10), 47.5 (C-3), 40.7 (C-11), 40.2 (C-11), 36.9 (C-4), 34.0 (CH₃^{TEMPO}), 33.7 (CH₃^{TEMPO}), 20.9 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.0 (C-12), 14.0 (C-9). **MS** (ESI⁺) m/z (%) 424 ([M+Na⁺], 40), 402 ([M+H⁺], 100), 268 ([M-TEMPO+Na⁺], 10), 227 ([M-TEMPO-CH₂CH=CH₂+Na⁺], 30). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₂₄H₃₅NO₄Na: 424.2458; found: 424.2458. **IR** (neat): $\nu_{\max}$ = 3063, 2977, 2931, 1727, 1468, 1454, 1378, 1364, 1270, 1240, 1183, 1132, 1096, 1033, 990, 957, 911, 876, 762, 699, 648 cm⁻¹. **Anal.** Calcd. for C₂₄H₃₅NO₄ (401.55): C, 71.79; H, 8.79; N, 3.49; Found: C, 71.85; H, 8.77; N, 3.41.

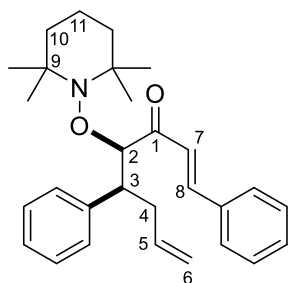
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.31-7.17 (m, 3H, CH_{Ar}), 7.17-7.07 (m, 2H, CH_{Ar}), 5.68-5.52 (m, 1H, CH-5), 5.50 (d, J = 7.3 Hz, 1H, CH-2), 5.02-4.85 (m, 2H, CH₂-6), 4.06-3.93 (m, 2H, CH₂-8), 3.56 (ddd, J = 11.4, 7.3, 4.0 Hz, 1H, CH-3), 2.63 (ddd, J = 15.1, 6.6, 4.2 Hz, 1H, CH₂-4^a), 2.54-2.44 (m, 1H, CH₂-4^b), 1.59-1.33 (m, 5H, CH₂-12^a, CH₂-11), 1.32-1.27 (m, 1H, CH₂-12^b), 1.25 (bs, 3H, CH₃^{TEMPO}), 1.22 (t, J = 7.2 Hz, 3H, CH₃-9), 1.03 (bs, 3H, CH₃^{TEMPO}), 0.95 (bs, 3H, CH₃^{TEMPO}), 0.89 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 196.5 (C-1), 160.8 (C-7), 138.3 (C_{Ar}), 135.9 (C-5), 129.0 (*m*-CH_{Ar}), 128.4 (*o*-CH_{Ar}), 127.0 (*p*-CH_{Ar}), 116.5 (C-6), 85.7 (C-2), 62.1 (C-8), 60.5 (C-10), 60.2 (C-10), 47.0 (C-3), 40.4 (C-11), 40.2 (C-11), 34.3 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 31.4 (C-4), 20.3 (CH₃^{TEMPO}), 20.2 (CH₃^{TEMPO}), 17.1 (C-12), 13.9 (C-9).

(4*R,5*S**,*E*)- and (4*R**,5*R**,*E*)-1,5-Diphenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)octa-1,7-dien-3-one (28h)**

Prepared according to general procedure **D** from **25h** (62 mg, 0.22 mmol). Deprotonation and rearrangement were performed at $-20\text{ }^{\circ}\text{C}$ for 20 min. Purification of the crude product by column chromatography (hexane/Et₂O, 50:1 gradient to 30:1) gave 67 mg of the major diastereoisomer of **28h**, followed by 22 mg of 10:1 mixture of minor and major diastereoisomer. Yield: 89 mg (92%) of **28h** as a partially separable 3.5:1 diastereoisomeric mixture as thick colorless oils.

Major diastereoisomer:



R_F = 0.48 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.34-7.15 (m, 11H, CH_{Ar}, CH-8), 6.33 (d, J = 16.1 Hz, 1H, CH-7), 5.81 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, CH-5), 5.16 (dd, J = 17.1, 1.9 Hz, 1H, CH₂-6), 5.06 (dd, J = 10.2, 2.0 Hz, 1H, CH₂-6), 4.63 (d, J = 5.1 Hz, 1H, CH-2), 3.65 (ddd, J = 8.6, 7.2, 5.1 Hz, 1H, CH-3), 2.79 (ddt, J = 14.5, 7.2, 1.2 Hz, 1H, CH₂-4^a), 2.63-2.53 (m, 1H, CH₂-4^b), 1.67-1.42 (m, 8H, CH₂-11^a, CH₃^{TEMPO}, CH₂-10), 1.42-1.23 (m, 4H, CH₂-11^b, CH₃^{TEMPO}), 1.09 (bs, 3H, CH₃^{TEMPO}), 0.98 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 200.3 (C-1), 140.3 (C-8), 139.34 (C_{Ar}), 136.3 (C-5), 135.2 (C_{Ar}), 130.1 (CH_{Ar}), 129.4 (CH_{Ar}), 128.8 (CH_{Ar}), 128.35 (CH_{Ar}), 128.0 (CH_{Ar}), 126.90 (CH_{Ar}), 125.3 (C-7), 117.2 (C-6), 92.8 (C-2), 60.17 (C-9), 60.1 (C-9), 47.4 (C-3), 40.8 (C-10), 35.3 (C-4), 35.1 (CH₃^{TEMPO}), 34.06 (CH₃^{TEMPO}), 20.9 (CH₃^{TEMPO}), 20.6 (CH₃^{TEMPO}), 17.2 (C-11). **MS** (ESI+) m/z (%) 885 ([2M+Na⁺], 40), 454 ([M+Na⁺], 100), 432 ([M+H⁺], 5), 298 ([M-TEMPO+Na⁺], 30). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₉H₃₇NO₂Na: 454.2717; found: 454.2719. **IR** (neat): ν_{max} = 3011, 2982, 2941, 1688, 1611, 1499, 1454, 1335, 1310, 1264, 1185, 1137, 1033, 990, 879, 758, 733 cm⁻¹.

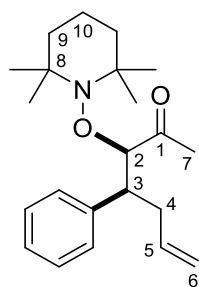
Minor diastereoisomer:

R_F = 0.43 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.54-7.33 (m, 6H, CH-8, CH_{Ar}), 7.32-7.23 (m, 2H, CH_{Ar}), 7.23-7.15 (m, 3H, CH_{Ar}), 6.61 (d, J = 16.0 Hz, 1H, CH-7), 5.66 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, CH-5), 5.00 (dd, J = 17.1, 1.9 Hz, 1H, CH₂-6), 4.89 (dd, J = 10.2, 1.9 Hz, 1H, CH₂-6), 4.71 (d, J = 6.1 Hz, 1H, CH-2), 3.65 (ddd, J = 12.1, 6.0, 3.6 Hz, 1H, CH-3), 2.88-2.68 (m, 1H, CH₂-4^a), 2.62-2.42 (m, 1H, CH₂-4^b), 1.62-1.36 (m, 5H, CH₂-11^a, CH₂-10), 1.36-1.24 (m, 4H, CH₃^{TEMPO}, CH₂-11^b), 1.14-1.00 (m, 6H, CH₃^{TEMPO}), 0.93 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 199.5 (C-1), 141.7 (C-8), 139.26 (C_{Ar}), 136.8 (C-5), 135.0 (C_{Ar}), 130.4 (CH_{Ar}), 129.2 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 128.39 (CH_{Ar}), 126.91 (CH_{Ar}), 125.9 (C-7), 116.3 (C-6), 92.6 (C-2), 60.21 (C-9), 47.9 (C-3), 40.7 (C-10), 35.0 (CH₃^{TEMPO}), 34.13 (CH₃^{TEMPO}), 31.5 (C-4), 20.5 (CH₃^{TEMPO}), 17.3 (C-11).

(3*R**,4*S**)- and (3*R**,4*R**)-4-Phenyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hept-6-en-2-one
(**28i**)

Prepared according to general procedure **D** from **25i** (200 mg, 1.06 mmol). The rearrangement step was performed at r.t. for 18 h. Purification of the crude product by column chromatography (hexane/EtOAc, 50:1 gradient to 10:1) gave 89 mg of the major diastereoisomer, followed by an impure fraction of 44 mg of the minor diastereoisomer of **28i**. Yield: 133 mg (37%) of **28i** as a separable 2:1 diastereoisomeric mixture as a thick colorless oil.

Major diastereoisomer:



R_F = 0.58 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 7.30-7.24 (m, 2H, CH_{Ar}), 7.22-7.16 (m, 3H, CH_{Ar}), 5.66 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H, CH-5), 5.02 (dq, J = 17.1, 1.6 Hz, 1H, CH_2 -6), 4.95 (ddt, J = 10.1, 2.2, 1.1 Hz, 1H, CH_2 -6), 4.51 (d, J = 6.7 Hz, 1H, CH-2), 3.37 (dt, J = 9.5, 6.4 Hz, 1H, CH-3), 2.85 (dddt, J = 14.3, 7.2, 5.9, 1.3 Hz, 1H, CH_2 -4^a), 2.48 (dddt, J = 14.1, 9.5, 6.8, 1.3 Hz, 1H, CH_2 -4^b), 1.67 (s, 3H, CH_3 -7), 1.54-1.38 (m, 8H, CH_2 -9, CH_2 -10^a, $\text{CH}_3^{\text{TEMPO}}$), 1.35-1.19 (m, 4H, CH_2 -10^b, $\text{CH}_3^{\text{TEMPO}}$), 1.12 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.93 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$).

$^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 210.9 (C-1), 139.9 (C_{Ar}), 136.4 (C-5), 128.94 (CH_{Ar}), 128.4 (CH_{Ar}), 126.91 (CH_{Ar}), 116.9 (C-6), 92.0 (C-2), 60.5 (C-8), 60.1 (C-8), 47.2 (C-3), 40.9 (C-9), 35.9 (C-4), 35.4 ($\text{CH}_3^{\text{TEMPO}}$), 34.0 ($\text{CH}_3^{\text{TEMPO}}$), 31.1 (C-7), 20.8 ($\text{CH}_3^{\text{TEMPO}}$), 20.4 ($\text{CH}_3^{\text{TEMPO}}$), 17.15 (C-10). **MS** (ESI+) m/z (%) 366 ($[\text{M}+\text{Na}^+]$, 80), 344 ($[\text{M}+\text{H}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{22}\text{H}_{34}\text{NO}_2$: 344.2584; found: 344.2585. **IR** (neat): ν_{max} = 3063, 3004, 2973, 2931, 2871, 1725, 1707, 1493, 1467, 1452, 1375, 1299, 1240, 1182, 1133, 988, 876, 760, 699 cm^{-1} .

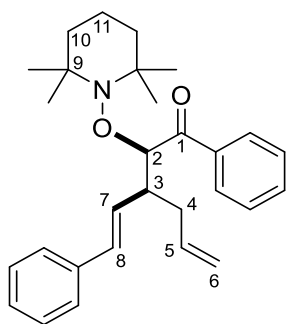
Minor diastereoisomer:

R_F = 0.50 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 7.34-7.24 (m, 2H, CH_{Ar}), 7.24-7.16 (m, 3H, CH_{Ar}), 5.64 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H, CH-5), 5.00 (dq, J = 17.1, 1.7 Hz, 1H, CH_2 -6), 4.89 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H, CH_2 -6), 4.53 (d, J = 6.6 Hz, 1H, CH-2), 3.52 (ddd, J = 11.7, 6.6, 3.6 Hz, 1H, CH_2 -3), 2.68 (dddt, J = 14.8, 6.7, 3.5, 1.5 Hz, 1H, CH_2 -4^a), 2.52 (dddt, J = 14.6, 11.7, 6.9, 1.3 Hz, 1H, CH_2 -4^b), 1.86 (s, 3H, CH_3 -7), 1.54-1.36 (m, 4H, CH_2 -9), 1.33-1.19 (m, 5H, CH_2 -10, $\text{CH}_3^{\text{TEMPO}}$), 1.09 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.99 (s, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.93 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 209.9 (C-1), 139.3 (C_{Ar}), 136.6 (C-5), 128.89 (CH_{Ar}), 128.5 (CH_{Ar}), 126.94 (CH_{Ar}), 116.3 (C-6), 91.9 (C-2), 60.2 (C-8), 47.1 (C-3), 40.63 (C-9), 40.57 (C-9), 34.8 ($\text{CH}_3^{\text{TEMPO}}$), 33.9 ($\text{CH}_3^{\text{TEMPO}}$), 32.7 (C-7), 31.3 (C-4), 20.3 ($\text{CH}_3^{\text{TEMPO}}$), 17.19 (C-10).

(2*R**,3*S**)- and (2*R**,3*R**)-1-Phenyl-3-((*E*)-styryl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one (**28k**) and 2-allyl-1-benzoyl-3-(phenyl((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)cyclopropane (**28ka**)

Prepared according to general procedure **D** from **25k** (138 mg, 0.5 mmol). The rearrangement step was performed at r.t. for 1 h. Purification of the crude product by column chromatography (hexane/Et₂O, 20:1) gave 174 mg (81%) of **28k** as a 2:1 mixture of inseparable diastereoisomers as a thick colorless oil followed by 30 mg (14%) of an impure fraction containing a mixture of an unknown diastereoisomer of cyclopropane **28ka** and both diastereoisomers (1.3:1 *dr*) of **28k** in 1.25:1 ratio. The cyclopropane containing fraction rearranges upon standing to product **28k** as a 1:1 diastereomeric mixture.

Major diastereoisomer:



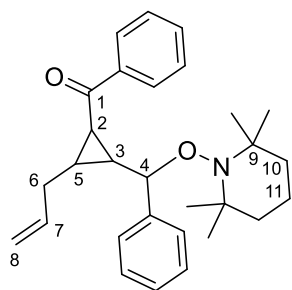
R_F = 0.49 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, J = 7.7 Hz, 2H, CH_{Ar}), 7.55-7.35 (m, 3H, CH_{Ar}), 7.27-7.12 (m, 4H, CH_{Ar}), 7.07-7.02 (m, 1H, CH_{Ar}), 6.37 (d, J = 15.8 Hz, 1H, CH-8), 5.92 (dd, J = 15.8, 9.2 Hz, 1H, CH-7), 5.81-5.61 (m, 1H, CH-5), 5.13 (d, J = 6.3 Hz, 1H, CH-2), 5.03-4.86 (m, 2H, CH₂-6), 3.25-3.05 (m, 1H, CH-3), 2.48 (dt, J = 13.2, 6.2 Hz, 1H, CH₂-4^a), 2.16-2.01 (m, 1H, CH₂-4^b), 1.66-1.46 (m, 3H, CH₂-11^a, CH₂-10), 1.46-1.31 (m, 5H, CH₃^{TEMPO}, CH₂-10), 1.31-1.21 (m, 4H, CH₂-11^b, CH₃^{TEMPO}), 1.00 (bs, 3H, CH₃^{TEMPO}), 0.84 (bs, 3H, CH₃^{TEMPO}). ¹³C

NMR (101 MHz, Chloroform-*d*) δ 202.0 (C-1), 138.5 (C_{Ar}), 137.6 (C_{Ar}), 136.4 (C-5), 133.7 (CH_{Ar}), 132.4 (C-8), 129.7 (CH_{Ar}), 129.0 (C-7), 128.43 (CH_{Ar}), 128.3 (CH_{Ar}), 127.1 (CH_{Ar}), 126.3 (CH_{Ar}), 116.6 (C-6), 89.0 (C-2), 60.5 (C-9), 60.0 (C-9), 46.4 (C-3), 40.7 (C-10), 40.6 (C-10), 35.9 (C-4), 34.5 (CH₃^{TEMPO}), 34.1 (CH₃^{TEMPO}), 20.8 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.1 (C-11). MS (ESI+) m/z (%) 454 ([M+Na⁺], 50), 432 ([M+H⁺], 100). HRMS (ESI+) m/z [M+H⁺] calcd for C₂₉H₃₈NO₂: 432.2897; found: 432.2898. IR (neat): ν_{max} = 3011, 2982, 2941, 1688, 1611, 1499, 1454, 1335, 1310, 1264, 1185, 1137, 1033, 990, 913, 758, 733 cm⁻¹.

Minor diastereoisomer:

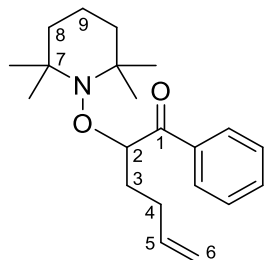
¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, J = 7.7 Hz, 2H, CH_{Ar}), 7.53-7.35 (m, 3H, CH_{Ar}), 7.27-7.12 (m, 4H, CH_{Ar}), 7.05-7.03 (m, 1H, CH_{Ar}), 6.44 (d, J = 15.8 Hz, 1H, CH-8), 5.80-5.63 (m, 2H, CH-5, CH-7), 5.34 (d, J = 6.8 Hz, 1H, CH-2), 5.01-4.88 (m, 2H, CH₂-6), 3.24-3.05 (m, 1H, CH-3), 2.59 (ddd, J = 14.7, 7.3, 3.0 Hz, 1H, CH₂-4^a), 2.16-1.99 (m, 1H, CH₂-4^b), 1.62-1.46 (m, 3H, CH₂-11^a, CH₂-10), 1.41-1.32 (m, 5H, CH₃^{TEMPO}, CH₂-10), 1.31-1.22 (m, 4H, CH₂-11^b, CH₃^{TEMPO}), 1.00 (bs, 3H, CH₃^{TEMPO}), 0.84 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.8 (C-1), 138.4 (C_{Ar}), 137.3 (C_{Ar}), 136.6 (C-5), 132.9 (CH_{Ar}), 132.3 (C-8), 130.4 (C-7), 129.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.39 (CH_{Ar}), 127.2 (CH_{Ar}), 126.2 (CH_{Ar}), 116.2 (C-6), 87.1 (C-2), 60.6 (C-9), 59.9 (C-9), 46.5 (C-3), 40.8 (C-10), 40.5 (C-10), 34.6 (CH₃^{TEMPO}), 34.1 (CH₃^{TEMPO}), 33.4 (C-4), 20.5 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 17.2 (C-11).

2-Allyl-1-benzoyl-3-(phenyl((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)cyclopropane (28ka)



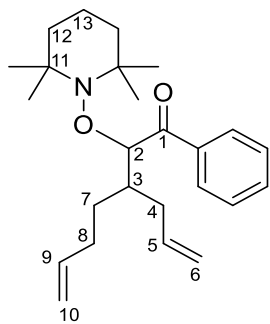
R_F = 0.36 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 8.09 (d, J = 7.6 Hz, 2H, CH_{Ar}), 7.63-7.01 (m, 8H, CH_{Ar}), 5.65-5.54 (m, 1H, CH-7), 4.99-4.82 (m, 2H, CH-8), 4.66 (d, J = 10.0 Hz, 1H, CH-4), 2.86 (t, J = 4.6 Hz, 1H, CH-2), 2.44 (td, J = 9.9, 4.8 Hz, 1H, CH-3), 2.16-2.08 (m, 1H, $\text{CH}_2\text{-6}^{\text{a}}$), 1.97-1.86 (m, 1H, $\text{CH}_2\text{-6}^{\text{b}}$), 1.71 (tt, J = 9.6, 4.7 Hz, 1H, CH-5), 1.58-1.07 (m, 9H, $\text{CH}_2\text{-10}$, $\text{CH}_2\text{-11}$, $\text{CH}_3^{\text{TEMPO}}$), 1.05 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.98 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.78 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 199.7 (C-1), 141.9 (C_{Ar}), 138.0 (C_{Ar}), 136.6 (C-7), 132.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (CH_{Ar}), 126.0 (CH_{Ar}), 115.1 (C-8), 84.8 (C-4), 60.0 (C-9), 40.3 (C-C-10), 40.0 (C-10), 35.6 (C-3), 34.3 ($\text{CH}_3^{\text{TEMPO}}$), 34.1 ($\text{CH}_3^{\text{TEMPO}}$), 33.1 (C-2), 32.3 (C-6), 28.5 (C-5), 20.3 ($\text{CH}_3^{\text{TEMPO}}$), 20.2 ($\text{CH}_3^{\text{TEMPO}}$), 17.1 (C-11). **MS** (ESI+) m/z (%) 454 ($[\text{M}+\text{Na}^+]$, 50), 432 ($[\text{M}+\text{H}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{29}\text{H}_{38}\text{NO}_2$: 432.2897; found: 432.2896.

1-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one (28l)



Prepared according to general procedure **D** from **25l** (80 mg, 0.46 mmol). The rearrangement step was performed at 50 °C for 1 h. Purification of the crude product by column chromatography (hexane/Et₂O, 10:1) gave 116 mg (76%) of **28l** as a thick colorless oil. R_F = 0.50 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 8.13-8.05 (m, 2H, $o\text{-CH}_{\text{Ar}}$), 7.59-7.51 (m, 1H, $p\text{-CH}_{\text{Ar}}$), 7.50-7.42 (m, 2H, $m\text{-CH}_{\text{Ar}}$), 5.72 (ddt, J = 16.7, 10.3, 6.4 Hz, 1H, CH-5), 4.99-4.82 (m, 3H, $\text{CH}_2\text{-6}$, CH-2), 2.15-2.04 (m, 2H, $\text{CH}_2\text{-3}$), 2.04-1.96 (m, 1H, $\text{CH}_2\text{-4}^{\text{a}}$), 1.96-1.82 (m, 1H, $\text{CH}_2\text{-4}^{\text{b}}$), 1.62-1.43 (m, 3H, $\text{CH}_2\text{-9}^{\text{a}}$, $\text{CH}_2\text{-8}$), 1.43-1.33 (m, 2H, $\text{CH}_2\text{-8}$), 1.33-1.23 (bs, 4H, $\text{CH}_2\text{-9}^{\text{b}}$, $\text{CH}_3^{\text{TEMPO}}$), 1.19 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.03 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.85 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 201.4 (C-1), 137.6 (C-5), 136.1 (C_{Ar}), 133.1 ($p\text{-CH}_{\text{Ar}}$), 129.3 ($o\text{-CH}_{\text{Ar}}$), 128.5 ($m\text{-CH}_{\text{Ar}}$), 115.1 (C-6), 88.9 (C-2), 60.0 (C-7), 59.8 (C-7), 40.4 (C-8), 34.1 ($\text{CH}_3^{\text{TEMPO}}$), 33.8 ($\text{CH}_3^{\text{TEMPO}}$), 32.1 (C-3), 29.0 (C-4), 20.4 ($\text{CH}_3^{\text{TEMPO}}$), 20.3 ($\text{CH}_3^{\text{TEMPO}}$), 17.2 (C-9). **MS** (ESI+) m/z (%) 352 ($[\text{M}+\text{Na}^+]$, 20), 330 ($[\text{M}+\text{H}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_2\text{Na}$: 352.2247; found: 352.2242. **IR** (neat): ν_{max} = 3070, 2972, 2931, 2871, 1680, 1597, 1448, 1361, 1261, 1209, 1182, 1133, 1044, 1022, 989, 973, 957, 912, 777, 699 cm^{-1} .

(2*S**,3*R**)- and (2*S**,3*S**)-3-Allyl-1-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hept-6-en-1-one (**28m**)



Prepared according to general procedure **D** from **25m** (400 mg, 1.75 mmol). The rearrangement step was performed at 50 °C for 1 h. Purification of the crude product by column chromatography (hexane/Et₂O, 30:1, gradient to 10:1) gave 623 mg (93%) of **28m** as a 1.4:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:

R_F = 0.65 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ = 7.98 (d, J = 7.7 Hz, 2H, *o*-CH_{Ar}), 7.57-7.51 (m, 1H, *p*-CH_{Ar}), 7.48-7.41 (m, 2H, *m*-CH_{Ar}), 5.82-5.59 (m, 2H, CH-5, CH-9), 5.24 (d, J = 5.5 Hz, 1H, CH-2), 4.98-4.84 (m, 4H, CH₂-6, CH₂-10), 2.34-2.24 (m, 1H, CH-3), 2.20-2.08 (m, 1H, CH₂-8^a), 2.07-1.95 (m, 2H, CH₂-8^b, CH₂-4^a), 1.92-1.75 (m, 2H, CH₂-4^b, CH₂-7^a), 1.63-1.43 (m, 3H, CH₂-13^a, CH₂-12), 1.44-1.25 (m, 6H, CH₂-12, CH₃^{TEMPO}, CH₂-13^b), 1.25-1.15 (m, 4H, CH₃^{TEMPO}, CH₂-7^b), 1.08 (bs, 3H, CH₃^{TEMPO}), 0.83 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.9 (C-1), 139.4 (C_{Ar}), 139.2 (C-9), 137.1 (C-5), 132.78 (*p*-CH_{Ar}), 128.9 (*o*-CH_{Ar}), 128.5 (*m*-CH_{Ar}), 116.6 (C-6), 114.5 (C-10), 85.8 (C-2), 60.6 (C-11), 59.7 (C-11), 41.5 (C-3), 40.7 (C-12), 40.6 (C-12), 35.2 (C-4), 34.5 (CH₃^{TEMPO}), 34.3 (CH₃^{TEMPO}), 31.9 (C-8), 28.9 (C-7), 20.6 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.2 (C-13). MS (ESI+) m/z (%) 406 ([M+Na⁺], 20), 384 ([M+H⁺], 100). HRMS (ESI+) m/z [M+H⁺] calcd for C₂₅H₃₈NO₂: 384.2897; found: 384.2897. IR (neat): ν_{max} = 3083, 2983, 2939, 1694, 1645, 1452, 1380, 1223, 1137, 1081, 995, 961, 912, 706, 634 cm⁻¹.

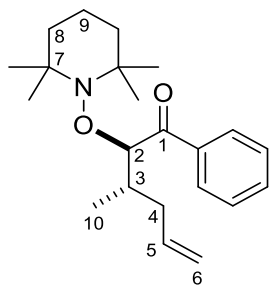
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, J = 7.7 Hz, 2H, *o*-CH_{Ar}), 7.57-7.51 (m, 1H, *p*-CH_{Ar}), 7.48-7.41 (m, 2H, *m*-CH_{Ar}), 5.82-5.59 (m, 2H, CH-5, CH-9), 5.24 (d, J = 5.5 Hz, 1H, CH-2), 5.06-4.82 (m, 3H, CH₂-10, CH₂-6), 4.75 (dq, 1H, J = 17.0, 1.6 Hz, 1H, CH₂-6), 2.62 (dt, J = 14.8, 4.8 Hz, 1H, CH₂-4^a), 2.33-2.23 (m, 1H, CH-3), 2.20-2.08 (m, 1H, CH₂-8^a), 2.07-1.95 (m, 1H, CH₂-8^b), 1.92-1.75 (m, 2H, CH₂-4^b, CH₂-7^a), 1.63-1.43 (m, 3H, CH₂-13^a, CH₂-12), 1.44-1.25 (m, 6H, CH₂-12, CH₃^{TEMPO}, CH₂-13^b), 1.25-1.15 (m, 4H, CH₃^{TEMPO}, CH₂-7^b), 1.08 (bs, 3H, CH₃^{TEMPO}), 0.83 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.8 (C-1), 139.3 (C_{Ar}), 138.4 (C-9), 137.5 (C-5), 132.82 (*p*-CH_{Ar}), 129.0 (*o*-CH_{Ar}), 128.6 (*m*-CH_{Ar}), 116.2 (C-6), 114.7 (C-10), 86.0 (C-2), 60.6 (C-11), 59.8 (C-11), 41.1 (C-3), 40.7 (C-12), 40.6 (C-12), 34.6 (CH₃^{TEMPO}), 34.3 (CH₃^{TEMPO}), 34.1 (C-4), 31.9 (C-8), 29.3 (C-7), 20.7 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.2 (C-13).

(2*R,3*S**)- and (2*R**,3*R**)-3-Methyl-1-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one (28n)**

Prepared according to general procedure **D** from **25n** (100 mg, 0.53 mmol). The rearrangement was performed at 50 °C for 1 h. Purification of the crude product by column chromatography (hexane/EtOAc, 30:1, gradient to 20:1) gave 169 mg (93%) of **28n** as a 1.4:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.50 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 7.7 Hz, 2H, *o*-CH_{Ar}), 7.53 (td, J = 7.3, 1.6 Hz, 1H, *p*-CH_{Ar}), 7.45 (td, J = 7.6, 1.9 Hz, 2H, *m*-CH_{Ar}), 5.76-5.66 (m, 1H, CH-5), 5.14 (d, J = 6.6 Hz, 1H, CH-2), 4.97-4.85 (m, 2H, CH₂-6), 2.54-2.48 (m, 1H, CH₂-4^a), 2.44-2.33 (m, 1H, CH-3), 1.74-1.64 (m, 1H, CH₂-4^b), 1.60-1.42 (m, 3H, CH₂-8, CH₂-9^a), 1.42-1.27 (m, 6H, CH₂-8, CH₂-9^a, CH₃^{TEMPO}), 1.22 (bs, 3H, CH₃^{TEMPO}), 1.08 (bs, 3H, CH₃^{TEMPO}), 0.87 (d, J = 7.1 Hz, 3H, CH₃-10), 0.84 (bs, 3H, CH₃^{TEMPO}).

$^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 202.46 (C-1), 139.08 (C_{Ar}), 137.2 (C-5), 132.9 (CH_{Ar}), 129.0 (CH_{Ar}), 128.53 (CH_{Ar}), 116.2 (C-6), 88.0 (C-2), 60.5 (C-7), 59.9 (C-7), 40.7 (C-8), 40.6 (C-8), 36.3 (C-3), 35.9 (C-4), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.7 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.2 (C-9), 16.5 (C-10). **MS** (ESI+) m/z (%) 709 ([2M+Na⁺], 35), 366 ([M+Na⁺], 100), 344 ([M+H⁺], 10). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₂H₃₃NO₂Na: 366.2404; found: 366.2400; [M+H⁺] calcd for C₂₂H₃₄NO₂: 344.2584; found: 344.2581. **IR** (neat): ν_{max} = 2970, 2931, 2873, 1687, 1596, 1376, 1361, 1257, 1181, 1133, 1042, 990, 911, 840, 702, 630 cm⁻¹.

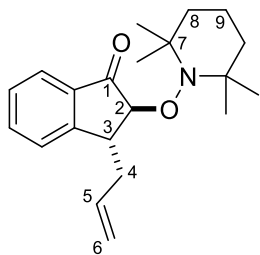
Minor diastereoisomer:

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 7.7 Hz, 2H, *o*-CH_{Ar}), 7.53 (td, J = 7.3, 1.6 Hz, 1H, *p*-CH_{Ar}), 7.45 (td, J = 7.6, 1.9 Hz, 2H, *m*-CH_{Ar}), 5.76-5.66 (m, 1H, CH-5), 5.09 (d, J = 6.4 Hz, 1H, CH-2), 4.97-4.85 (m, 2H, CH₂-6), 2.44-2.33 (m, 1H, CH-3), 2.27 (dt, J = 13.7, 5.8 Hz, 1H, CH₂-4^a), 1.75-1.63 (m, 1H, CH₂-4^b), 1.60-1.42 (m, 3H, CH₂-8, CH₂-9^a), 1.42-1.27 (m, 6H, CH₂-8, CH₂-9^a, CH₃^{TEMPO}), 1.22 (bs, 3H, CH₃^{TEMPO}), 1.08 (bs, 3H, CH₃^{TEMPO}), 0.92 (d, J = 6.8 Hz, 3H, CH₃-10), 0.84 (bs, 3H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 202.48 (C-1), 139.11 (C_{Ar}), 137.1 (C-5), 132.8 (CH_{Ar}), 129.2 (CH_{Ar}), 128.46 (CH_{Ar}), 116.4 (C-6), 88.1 (C-2), 60.5 (C-7), 59.9 (C-7), 40.7 (C-8), 40.6 (C-8), 38.1 (C-3), 36.5 (C-4), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.7 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.2 (C-9), 14.7 (C-10).

(2*S,3*R**)- and (2*S**,3*S**)-3-Allyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)indan-1-one (28o)**

Prepared according to general procedure **D** from **25o** (178 mg, 1.03 mmol). The rearrangement step was performed at r.t. for 30 min. Purification of the crude product by column chromatography (hexane/Et₂O, 20:1) gave 144 mg (43%) of **28o** as a 3:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.65 (hexanes/EtOAc, 5:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.73-7.69 (m, 1H, CH_{Ar}), 7.61-7.49 (m, 2H, CH_{Ar}), 7.39-7.34 (m, 1H, CH_{Ar}), 5.76-5.64 (m, 1H, CH-5), 5.13 (dd, J = 17.2, 1.7 Hz, 1H, CH₂-6), 5.07 (d, J = 10.2 Hz, 1H, CH₂-6), 4.54 (d, J = 2.9 Hz, 1H, CH-2), 3.60 (td, J = 5.8, 2.7 Hz, 1H, CH-3), 2.80-2.74 (m, 1H, CH₂-4^a), 2.66-2.59 (m, 1H, CH₂-4^b), 1.64-1.42 (m, 5H, CH₂-9^a, CH₂-8), 1.41-1.28 (m, 4H, CH₂-9^b, CH₃^{TEMPO}), 1.23 (bs, 6H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 202.6 (C-1), 154.8 (C_{Ar}), 135.5 (C_{Ar}), 135.3 (CH_{Ar}), 135.1 (C-5), 127.8 (CH_{Ar}), 125.9 (CH_{Ar}), 124.1 (CH_{Ar}), 118.1 (C-6), 88.4 (C-2), 61.2 (C-7), 60.0 (C-7), 44.8 (C-3), 41.1 (C-8), 40.5 (C-8), 38.1 (C-4), 34.3 (CH₃^{TEMPO}), 33.6 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.3 (C-9). **MS** (ESI+) m/z (%) 350 ([M+Na⁺], 30), 328 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₁H₃₀NO₂: 328.2271; found: 328.2271. **IR** (neat): $\nu_{\max}$ = 3075, 2973, 2929, 2871, 2847, 1721, 1606, 1465, 1360, 1292, 1260, 1182, 1131, 1045, 989, 915, 699 cm⁻¹.

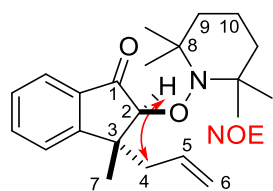
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.73-7.69 (m, 1H, CH_{Ar}), 7.61-7.49 (m, 2H, CH_{Ar}), 7.39-7.34 (m, 1H, CH_{Ar}), 5.76-5.64 (m, 1H, CH-5), 5.02-4.95 (m, 2H, CH-2, CH₂-6), 4.87 (dd, J = 17.1, 1.8 Hz, 1H, CH₂-6), 3.65 (ddd, J = 9.8, 6.7, 3.3 Hz, 1H, CH-3), 2.87 (ddd, J = 14.3, 7.0, 3.1 Hz, 1H, CH₂-4^a), 1.95 (ddd, J = 14.1, 9.5, 7.0 Hz, 1H, CH₂-4^b), 1.64-1.42 (m, 5H, CH₂-9^a, CH₂-8), 1.41-1.28 (m, 4H, CH₂-9^b, CH₃^{TEMPO}), 1.28-1.15 (m, 6H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 202.5 (C-1), 151.9 (C_{Ar}), 134.9 (C-5), 134.3 (CH_{Ar}), 134.0 (C_{Ar}), 128.0 (CH_{Ar}), 126.5 (CH_{Ar}), 123.9 (CH_{Ar}), 117.8 (C-6), 92.7 (C-2), 61.2 (C-7), 60.0 (C-7), 43.8 (C-3), 41.1 (C-8), 40.5 (C-8), 37.3 (C-4), 34.3 (CH₃^{TEMPO}), 33.6 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.1 (C-9).

(2*S**,3*R**)- and (2*S**,3*S**)-3-Allyl-3-methyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)indan-1-one
(**28p**)

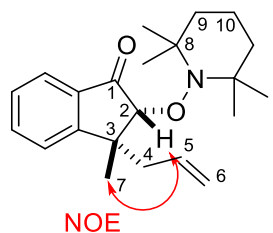
Prepared according to general procedure **D** from **25p** (93 mg, 0.5 mmol). The rearrangement step was performed at r.t. for 1 h. Purification of the crude product by column chromatography (hexane/EtOAc, 30:1, gradient to 10:1) gave 169 mg (99%) of **28p** as a 2:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.35 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.67 (dt, J = 7.6, 1.0 Hz, 1H, CH_{Ar}), 7.62-7.55 (m, 1H, CH_{Ar}), 7.40 (dt, J = 7.7, 0.9 Hz, 1H, CH_{Ar}), 7.36 (td, J = 7.4, 1.0 Hz, 1H, CH_{Ar}), 5.54 (dddd, J = 16.8, 10.3, 7.6, 7.1 Hz, 1H, CH-5), 5.09-4.97 (m, 2H, $\text{CH}_2\text{-6}$), 4.33 (s, 1H, CH-2), 2.34 (ddt, J = 13.8, 7.6, 1.1 Hz, 1H, $\text{CH}_2\text{-4}^a$), 2.27 (ddt, J = 13.8, 7.1, 1.2 Hz, 1H, $\text{CH}_2\text{-4}^b$), 1.55-1.27 (m, 9H, $\text{CH}_2\text{-10}$, $\text{CH}_2\text{-9}$, $\text{CH}_3^{\text{TEMPO}}$), 1.50 (s, 3H, $\text{CH}_3\text{-7}$), 1.18 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.98 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.85 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 203.8 (C-1), 159.0 (C_{Ar}), 135.2 (C_{Ar}), 134.64 (CH_{Ar}), 133.6 (C-5), 127.9 (CH_{Ar}), 123.94 (CH_{Ar}), 123.86 (CH_{Ar}), 119.3 (C-6), 88.4 (C-2), 61.3 (C-8), 60.0 (C-8), 47.1 (C-4), 40.9 (C-3), 40.3 (C-9), 40.2 (C-9), 34.8 ($\text{CH}_3^{\text{TEMPO}}$), 33.9 ($\text{CH}_3^{\text{TEMPO}}$), 20.8 ($\text{CH}_3^{\text{TEMPO}}$), 20.7 ($\text{CH}_3^{\text{TEMPO}}$), 20.6 (C-7), 17.2 (C-10). **MS** (ESI+) m/z (%) 705 ($[\text{2M}+\text{Na}^+]$, 60), 364 ($[\text{M}+\text{Na}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_2\text{Na}$: 364.2247; found: 364.2246. **IR** (neat): ν_{max} = 3075, 2974, 2930, 2871, 1724, 1605, 1467, 1376, 1361, 1240, 1132, 990, 917, 763, 697 cm^{-1} .

Minor diastereoisomer:

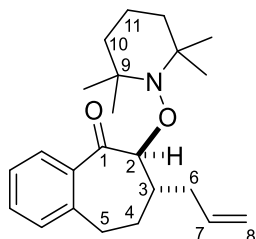


$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.67 (dt, J = 7.6, 1.0 Hz, 1H, CH_{Ar}), 7.62-7.55 (m, 1H, CH_{Ar}), 7.40 (dt, J = 7.7, 0.9 Hz, 1H, CH_{Ar}), 7.35 (td, J = 7.4, 1.0 Hz, 1H, CH_{Ar}), 5.71 (ddt, J = 17.4, 10.2, 7.3 Hz, 1H, CH-5), 5.00-4.95 (m, 1H, $\text{CH}_2\text{-6}$), 4.91 (ddt, J = 17.0, 2.5, 1.4 Hz, 1H, $\text{CH}_2\text{-6}$), 4.54 (s, 1H, CH-2), 2.62 (ddt, J = 13.8, 7.2, 1.3 Hz, 1H, $\text{CH}_2\text{-4}^a$), 2.52 (ddt, J = 13.8, 7.3, 1.1 Hz, 1H, $\text{CH}_2\text{-4}^b$), 1.60-1.29 (m, 9H, $\text{CH}_2\text{-9}$, $\text{CH}_2\text{-10}$, $\text{CH}_3^{\text{TEMPO}}$), 1.48 (s, 3H, $\text{CH}_3\text{-7}$), 1.25 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.09 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.85 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 203.1 (C-1), 157.3 (C_{Ar}), 134.69 (C-5), 134.66 (CH_{Ar}), 134.4 (C_{Ar}), 127.8 (CH_{Ar}), 124.1 (CH_{Ar}), 123.6 (CH_{Ar}), 118.4 (C-6), 92.9 (C-2), 61.3 (C-8), 61.0 (C-8), 46.9 (C-3), 41.9 (C-4), 40.3 (C-9), 40.2 (C-9), 35.3 ($\text{CH}_3^{\text{TEMPO}}$), 33.4 ($\text{CH}_3^{\text{TEMPO}}$), 25.9 (C-7), 20.8 ($\text{CH}_3^{\text{TEMPO}}$), 20.7 ($\text{CH}_3^{\text{TEMPO}}$), 17.1 (C-10).

(6*S**,7*S**)- and (6*S**,7*R**)-7-Allyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)benzocycloheptan-5-one (**28q**)

Prepared according to general procedure **D** from **25q** (94 mg, 0.47 mmol). The rearrangement step was performed at 60 °C for 2 h. Purification of the crude product by column chromatography (hexane/EtOAc, 40:1 gradient to 10:1) gave 150 mg (90%) of **28q** as 2.5:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.45 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.70 (dt, J = 7.7, 2.1 Hz, 1H, CH_{Ar}), 7.35 (td, J = 7.5, 1.5 Hz, 1H, CH_{Ar}), 7.30-7.22 (m, 1H, CH_{Ar}), 7.22-7.18 (m, 1H, CH_{Ar}), 5.87-5.74 (m, 1H, CH-7), 5.13-4.98 (m, 2H, CH₂-8), 4.93 (d, J = 7.2 Hz, 1H, CH-2), 3.06-2.98 (m, 2H, CH₂-5), 2.84-2.76 (m, 1H, CH₂-6^a), 2.71-2.58 (m, 1H, CH-3), 2.37-2.28 (m, 1H, CH₂-4^a), 1.80 (ddd, J = 14.1, 11.1, 8.3 Hz, 1H, CH₂-6^b), 1.58-1.50 (m, 1H, CH₂-11^a), 1.47-1.43 (m, 4H, CH₂-10), 1.33-1.26 (m, 1H, CH₂-11^b), 1.24 (bs, 3H, CH₃^{TEMPO}), 1.22 (bs, 3H, CH₃^{TEMPO}), 1.11-1.01 (m, 1H, CH₂-4^b), 0.88 (bs, 3H, CH₃^{TEMPO}), 0.52 (bs, 3H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 203.1 (C-1), 143.7 (C_{Ar}), 139.1 (C_{Ar}), 137.0 (C-7), 131.18 (CH_{Ar}), 130.0 (CH_{Ar}), 128.2 (CH_{Ar}), 126.5 (CH_{Ar}), 116.3 (C-8), 91.2 (C-2), 60.2 (C-9), 59.8 (C-9), 40.56 (C-10), 40.5 (C-10), 39.2 (C-3), 34.5 (CH₃^{TEMPO}), 33.7 (C-6), 33.4 (CH₃^{TEMPO}), 32.7 (C-5), 30.8 (C-4), 20.8 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.3 (C-11). **MS** (ESI+) m/z (%) 378 ([M+Na⁺], 100), 356 ([M+H⁺], 60). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₃H₃₃NO₂Na: 378.2404; found: 378.2407. **IR** (neat): ν_{max} = 3071, 3001, 2971, 2930, 1697, 1600, 1448, 1374, 1361, 1278, 1260, 1232, 1206, 1133, 962, 914, 762, 737 cm⁻¹.

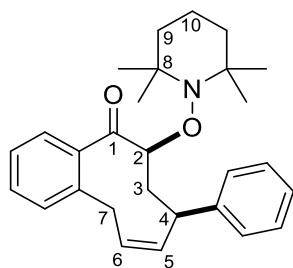
Minor diastereoisomer:

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.70 (dt, J = 7.7, 2.1 Hz, 1H, CH_{Ar}), 7.35 (td, J = 7.5, 1.5 Hz, 1H, CH_{Ar}), 7.30-7.22 (m, 1H, CH_{Ar}), 7.22-7.18 (m, 1H, CH_{Ar}), 5.87-5.74 (m, 1H, CH-7), 5.13-4.98 (m, 2H, CH₂-8), 4.38 (bs, 1H, CH-2), 3.50 (dd, J = 16.6, 11.8 Hz, 1H, CH₂-5^a), 2.89-2.80 (m, 1H, CH₂-5^b), 2.62-2.53 (m, 1H, CH-3), 2.25-2.11 (m, 2H, CH₂-4^a, CH₂-6^a), 2.07-1.99 (m, 1H, CH₂-6^b), 1.49-1.27 (m, 7H, CH₂-11, CH₂-10, CH₂-4^b), 1.13-1.00 (m, 6H, CH₃^{TEMPO}), 0.88 (bs, 3H, CH₃^{TEMPO}), 0.78 (bs, 3H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 203.7 (C-1), 145.2 (C_{Ar}), 137.7 (C_{Ar}), 136.2 (C-7), 131.21 (CH_{Ar}), 130.4 (CH_{Ar}), 129.5 (CH_{Ar}), 125.9 (CH_{Ar}), 117.3 (C-8), 97.6 (C-2), 60.2 (C-9), 59.8 (C-9), 41.8 (C-3), 40.60 (C-10), 40.5 (C-10), 37.6 (C-6), 34.5 (CH₃^{TEMPO}), 33.4 (CH₃^{TEMPO}), 32.64 (C-5), 32.55 (C-4), 20.8 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.2 (C-11).

(6*S**,8*R**,*Z*)- and (6*S**,8*S**,*Z*)-8-Phenyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)benzocyclonon-9-en-5-one (**28r**)

Prepared according to general procedure **D** from **25r** (68 mg, 0.26 mmol). The rearrangement step was performed at 50 °C for 4 h. Purification of the crude product by column chromatography (hexane/Et₂O, 30:1, gradient to 10:1) gave 65 mg of the major diastereoisomer as an off-white solid followed by 24 mg of the minor diastereoisomer of **28r** as a colorless oil. Yield 89 mg (82%) in a 2.7:1 diastereoisomeric ratio. The major diastereoisomer was recrystallized from *i*PrOH for X-ray diffraction analysis.

Major diastereoisomer:



R_F = 0.45 (hexanes/EtOAc, 10:1). **m.p.** 120-122 °C. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.39-7.09 (m, 9H, CH_{Ar}), 5.40-5.31 (m, 2H, CH-5, CH-6), 5.05 (dd, J = 10.1, 3.0 Hz, 1H, CH-2), 4.16-4.09 (m, 1H, CH₂-7^a), 3.89 (ddd, J = 11.7, 7.8, 4.1 Hz, 1H, CH-4), 3.13 (dd, J = 14.8, 3.4 Hz, 1H, CH₂-7^b), 2.52-2.40 (m, 2H, CH₂-3), 1.49-1.34 (m, 1H, CH₂-10^a), 1.39-1.11 (m, 5H, CH₂-10^b, CH₂-9), 1.06 (bs, 3H, CH₃^{TEMPO}), 0.98 (bs, 3H, CH₃^{TEMPO}), 0.90 (bs, 3H, CH₃^{TEMPO}), 0.79 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz,

Chloroform-*d*) δ 206.0 (C-1), 144.6 (C_{Ar}), 143.1 (C_{Ar}), 137.3 (C_{Ar}), 134.5 (C-5), 130.9 (CH_{Ar}), 130.4 (CH_{Ar}), 129.5 (CH_{Ar}), 128.80 (CH_{Ar}), 128.4 (C-6), 127.31 (CH_{Ar}), 126.9 (CH_{Ar}), 126.6 (CH_{Ar}), 85.4 (C-2), 60.6 (C-8), 60.3 (C-8), 41.4 (C-4), 40.4 (C-9), 37.0 (C-3), 34.34 (CH₃^{TEMPO}), 34.28 (C-7), 33.7 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 20.22 (CH₃^{TEMPO}), 17.2 (C-10). **MS** (ESI+) m/z (%) 440 ([M+Na⁺], 50), 418 ([M+H⁺], 100), 284 ([M-TEMPO+Na⁺], 20). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₈H₃₅NO₂Na: 440.2560; found: 440.2560. **IR** (neat): $\nu_{\max}$ = 3061, 2971, 2929, 2871, 1703, 1597, 1494, 1361, 1258, 1216, 1132, 962, 914, 741, 699 cm⁻¹.

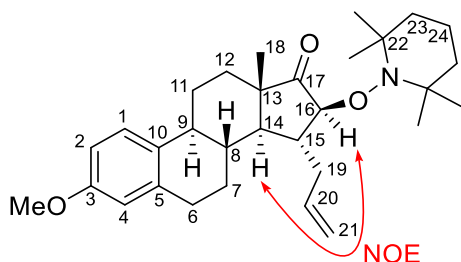
Minor diastereoisomer:

R_F = 0.38 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.39-7.09 (m, 9H, CH_{Ar}), 5.41-5.31 (m, 2H, CH-5, CH-6), 4.72-4.55 (m, 2H, CH-2, CH₂-7^a), 4.20 (td, J = 8.4, 4.6 Hz, 1H, CH-4), 3.03 (dd, J = 13.9, 3.1 Hz, 1H, CH₂-7^b), 2.57-2.37 (m, 2H, CH₂-3), 1.48-1.19 (m, 5H, CH₂-10^a, CH₂-9), 1.20-0.96 (m, 7H, CH₂-10^b, CH₃^{TEMPO}), 0.83 (bs, 3H, CH₃^{TEMPO}), 0.27 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 211.4 (C-1), 142.9 (C_{Ar}), 141.1 (C_{Ar}), 138.4 (C_{Ar}), 132.0 (C-5), 129.2 (CH_{Ar}), 128.75 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (C-6), 127.33 (CH_{Ar}), 126.1 (CH_{Ar}), 125.0 (CH_{Ar}), 124.8 (CH_{Ar}), 89.8 (C-2), 59.5 (C-8), 57.7 (C-8), 39.3 (C-9), 36.9 (C-4), 36.4 (C-3), 33.2 (CH₃^{TEMPO}), 32.3 (C-7), 32.2 (CH₃^{TEMPO}), 20.23 (CH₃^{TEMPO}), 17.4 (CH₃^{TEMPO}), 15.4 (C-10).

(15 α ,16 β)- and (15 α ,16 α)-16-Allyl-15-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3-*O*-methylestra-1,3,5(10),15-trien-17-one (**28u**)

Prepared according to general procedure **D** from **25u** (53 mg, 0.16 mmol). The rearrangement step was performed at reflux temperature for 2 h. Purification of the crude product by column chromatography (hexane/EtOAc, 20:1, gradient to 10:1) gave 31 mg of the major diastereoisomer followed by 23 mg of the minor diastereoisomer as thick colorless oils. Yield 54 mg (69%) of **28u** in a 1.3:1 diastereoisomeric ratio.

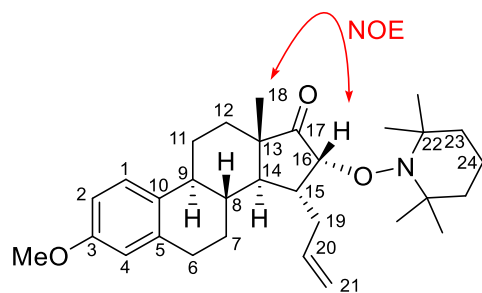
Major diastereoisomer:



R_F = 0.53 (hexanes/EtOAc, 5:1). $[\alpha]^{20}_{589}$ = +138.0 (c 0.20; CHCl₃). ¹H NMR (500.0 MHz, Chloroform-*d*) δ 7.21 (dd, J = 8.6, 1.0 Hz, CH_{Ar}-1), 6.72 (dd, J = 8.6, 2.8 Hz, 1H, CH_{Ar}-2), 6.63 (d, J = 2.8 Hz, 1H, CH_{Ar}-4), 5.84 (dddd, J = 17.2, 10.2, 7.7, 6.6 Hz, 1H, CH-20), 5.21-5.06 (m, 2H, CH₂-21), 4.10 (d, J = 6.6 Hz, 1H, H-16), 3.78 (s, 3H, OMe), 2.96-2.83 (m, 3H, CH₂-6, CH₂-19^a), 2.61 (dddt, J = 14.7, 6.6, 5.1, 1.3

Hz, 1H, CH₂-19^b), 2.46-2.36 (m, 2H, CH₂-11^a, CH-15), 2.35-2.29 (m, 1H, CH-9), 2.26 (ddt, J = 12.6, 5.6, 2.6 Hz, 1H, CH₂-7^a), 1.92-1.87 (m, 1H, CH₂-12^a), 1.82 (dtd, J = 12.2, 10.4, 2.6 Hz, 1H, CH-8), 1.64-1.39 (m, 8H, CH₂-7^b, CH₂-11^b, CH₂-12^b, CH₂-23, CH₂-24^a), 1.35-1.19 (m, 8H, CH-14, CH₂-24^b, CH₃^{TEMPO}), 1.13 (bs, 3H, CH₃^{TEMPO}), 1.11 (bs, 3H, CH₃^{TEMPO}), 1.08 (s, 3H, CH₃-18). ¹³C NMR (125.7 MHz, Chloroform-*d*) δ 214.9 (C-17), 157.4 (C-3), 137.3 (C-5), 134.6 (C-20), 131.8 (C-10), 126.7 (C-1), 118.5 (C-21), 113.40 (C-4), 111.7 (C-2), 86.8 (C-16), 60.8 (C-22), 60.0 (C-22), 55.1 (OMe), 54.1 (C-14), 48.7 (C-13), 45.1 (C-9), 42.7 (C-15), 40.4 (C-23), 40.3 (C-23), 39.3 (C-8), 36.1 (C-19), 34.0 (CH₃^{TEMPO}), 31.7 (C-12), 30.1 (C-6), 27.4 (C-7), 26.3 (C-11), 20.2 (CH₃^{TEMPO}), 17.1 (C-24), 14.2 (C-18). MS (ESI+) m/z (%) 981 ([2M+Na⁺], 20), 502 ([M+Na⁺], 100), 480 ([M+H⁺], 60), 311 ([M-TMPH-CO+H⁺], 20). HRMS (ESI+) m/z [M+H⁺] calcd for C₃₁H₄₅NO₃Na: 502.3292; found: 502.3298. IR (neat): ν_{max} = 2971, 2930, 2870, 1747, 1610, 1501, 1464, 1361, 1255, 1238, 1132, 1045, 989, 910, 812, 731, cm⁻¹.

Minor diastereoisomer:



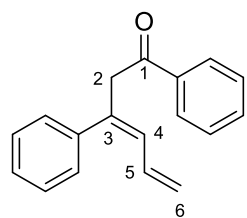
R_F = 0.48 (hexanes/EtOAc, 5:1). $[\alpha]^{20}_{589}$ = +137.0 (c 0.20; CHCl₃). ¹H NMR (500.0 MHz, Chloroform-*d*) δ 7.19 (d, J = 8.6 Hz, 1H, CH_{Ar}-1), 6.72 (dd, J = 8.6, 2.8 Hz, 1H, CH_{Ar}-2), 6.64 (d, J = 2.8 Hz, 1H, CH_{Ar}-4), 5.84 (dtd, J = 17.0, 9.4, 4.6 Hz, 1H, CH-20), 5.09 (dt, J = 10.1, 1.6 Hz, 1H, CH₂-21), 5.03 (dt, J = 17.0, 1.7 Hz, 1H, CH₂-21), 4.95 (d, J = 10.1 Hz, 1H, CH-16), 3.79 (s, 3H, OMe), 2.93-2.86 (m, 2H, CH₂-6), 2.78 (dt, J = 14.3, 4.4 Hz, 1H, CH₂-19^a), 2.61 (dddd, J = 10.7, 10.1, 5.3, 4.2 Hz, 1H, CH-15), 2.41-2.28 (m, 3H, CH-9, CH₂-11^a, CH₂-19^b), 2.15 (ddt, J = 12.8, 4.4, 2.6 Hz, 1H, CH₂-7^a), 1.81-1.72 (m, 1H, CH₂-12^a), 1.71 (dtd, J = 11.4, 10.7, 2.6 Hz, 1H, CH-8), 1.68 (t, J = 10.7 Hz, 1H, CH-14),

1.62-1.43 (m, 8H, CH₂-7^b, CH₂-11^b, CH₂-12^b, CH₂-23, CH₂-24^a), 1.30-1.17 (m, 13H, CH₂-24^b, CH₃^{TEMPO}), 1.05 (s, 3H, CH₃-18). ¹³C NMR (125.7 MHz, Chloroform-*d*) δ 215.6 (C-17), 157.3 (C-3), 137.2 (C-5), 136.8 (C-20), 131.9 (C-10), 126.3 (C-1), 117.6 (C-21), 113.38 (C-4), 111.5 (C-2), 85.3 (C-16), 60.1 (C-22), 55.0 (MeO), 48.4 (C-14), 45.4 (C-13), 44.0 (C-9), 40.7 (C-23), 38.7 (C-8), 37.0 (C-15), 34.5 (C-19), 33.9 (CH₃^{TEMPO}), 30.5 (C-12), 29.8 (C-6), 27.1 (C-7), 25.8 (C-11), 20.1 (CH₃^{TEMPO}), 18.0 (C-18), 16.7 (C-24).

Rearrangement of alcohol **25e** by KHMDS

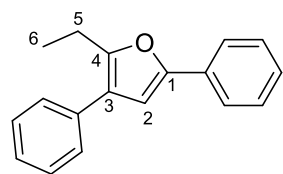
In a flame-dried Schlenk flask, alcohol **25e** (500 mg, 2.0 mmol) was dissolved in DME (12.0 mL). At 0 °C, KHMDS (1M in THF, 2.2 mL, 2.2 mmol) was added. The mixture was warmed to 50 °C, stirred for 2 h, and after cooling, quenched by saturated NH₄Cl solution (10 mL). The mixture was extracted with Et₂O (3×20 mL), the combined organic layers were washed with brine (2×20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure. The crude products were separated by column chromatography (neat hexane, gradient to 10:1 hexane/EtOAc) to give 60 mg (12%) of furan **34e** and 222 mg (44%) of dienone **33e** as colorless oils.

(*Z*)-1,3-Diphenylhexa-3,5-dien-1-one (**33e**)



R_F = 0.48 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.02-7.97 (m, 2H, CH_{Ar}), 7.60-7.55 (m, 1H, CH_{Ar}), 7.49-7.44 (m, 2H, CH_{Ar}), 7.39-7.34 (m, 2H, CH_{Ar}), 7.32-7.27 (m, 2H, CH_{Ar}), 7.26-7.20 (m, 1H, CH_{Ar}), 6.72-6.60 (m, 2H, CH-4, CH-5), 5.42 (dd, J = 15.8, 1.8 Hz, 1H, CH₂-6), 5.26 (dd, J = 9.5, 1.8 Hz, 1H, CH₂-6), 4.33 (s, 2H, CH₂-2). ¹³C NMR (101 MHz, Chloroform-*d*) δ 196.7 (C-1), 142.1 (C-3), 136.8 (C_{Ar}), 134.6 (C_{Ar}), 133.4 (CH_{Ar}), 132.9 (C-5), 131.4 (C-4), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 127.5 (CH_{Ar}), 126.2 (CH_{Ar}), 119.9 (C-6), 40.9 (C-2). The spectral data match those reported in the literature.^[156] HRMS (APCI) m/z [M+H⁺] calcd for C₁₈H₁₇O: 249.1274; found: 249.1278.

2-Ethyl-3,5-diphenylfuran (**34e**)

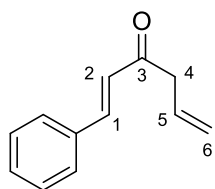


R_F = 0.78 (hexanes/EtOAc, 10:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 7.72-7.66 (m, 2H, CH_{Ar}), 7.45-7.36 (m, 6H, CH_{Ar}), 7.33-7.22 (m, 2H, CH_{Ar}), 6.77 (s, 1H, CH-2), 2.88 (q, J = 7.5 Hz, 2H, CH₂-5), 1.36 (t, J = 7.5 Hz, 3H, CH₃-6). ¹³C NMR (101 MHz, Chloroform-*d*) δ 152.8 (C-1), 151.7 (C-4), 134.3 (C_{Ph}), 131.1 (C_{Ph}), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 127.8 (CH_{Ph}), 127.1 (CH_{Ph}), 126.6 (CH_{Ph}), 123.6 (CH_{Ph}), 122.6 (C-3), 106.7 (C-2), 20.7 (C-5), 13.2 (C-6). IR (neat): ν_{max} = 3057, 2971, 2934, 1702, 1595, 1533, 1494, 1487, 1449, 1316, 1211, 1135, 1072, 1032, 1002, 988, 930, 909, 755, 690, 664, 637 cm⁻¹. MS (APCI) m/z (%) 265 ([M+H₂O-H⁺], 100), 247 ([M-H⁺], 5). HRMS (APCI) m/z [M-H⁺] calcd for C₁₈H₁₅O: 247.1117; found: 247.1120. The spectral data match those reported in the literature.^[152]

Rearrangement of alcohol **25j**

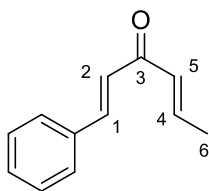
In a flame-dried Schlenk flask, alcohol **25j** (78 mg, 0.3 mmol) was dissolved in DME (6.0 mL). At 0 °C, KHMDS (1M in THF, 0.45 mL, 0.45 mmol) was dropwise added. The mixture was stirred at 0 °C for 20 min and at r.t. for 1 h, quenched by saturated NH₄Cl solution (10 mL), and extracted with Et₂O (3×10 mL). The combined organic layers were washed with brine (20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude products that were separated by column chromatography (hexane/EtOAc, 10:1) to give 35 mg (67%) of **36j** and 7 mg (13%) of **36ja** as colorless oils.

(*E*)-1-Phenylhexa-1,5-dien-3-one (**36j**)



R_F = 0.40 (hexanes/EtOAc, 5:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, J = 16.2 Hz, 1H, CH-1), 7.58-7.51 (m, 2H, CH_{Ar}), 7.43-7.36 (m, 3H, CH_{Ar}), 6.77 (d, J = 16.1 Hz, 1H, CH-2), 6.02 (ddt, J = 17.1, 10.4, 6.8 Hz, 1H, CH-5), 5.28-5.16 (m, 2H, CH₂-6), 3.44 (dt, J = 7.0, 1.5 Hz, 2H, CH₂-4). ¹³C NMR (101 MHz, Chloroform-*d*) δ 197.9 (C-3), 143.3 (C-1), 134.5 (C_{Ar}), 131.0 (C-5), 130.7 (CH_{Ar}), 129.1 (CH_{Ar}), 128.4 (CH_{Ar}), 125.6 (C-2), 119.0 (C-6), 46.0 (C-4). MS (EI) m/z (%) 172 ([M]⁺, 95), 171 ([M-H]⁺, 100), 131 ([M-allyl]⁺, 60). The spectral data match those reported in the literature.^[157]

(*1E,4E*)-1-Phenylhexa-1,4-dien-3-one (**36ja**)



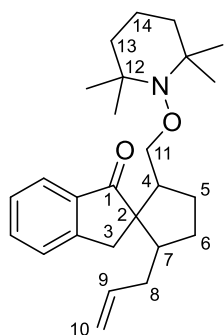
R_F = 0.29 (hexanes/EtOAc, 5:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, J = 16.0 Hz, 1H, CH-1), 7.30-7.53 (m, 2H, CH_{Ar}), 7.43-7.36 (m, 3H, CH_{Ar}), 7.03 (dq, J = 15.6, 6.9 Hz, 1H, CH-4), 6.97 (d, J = 16.0 Hz, 1H, CH-2), 6.47 (dq, J = 15.4, 1.6 Hz, 1H, CH-5), 1.97 (dd, J = 6.9, 1.6 Hz, 3H, CH₃-6). MS (EI) m/z (%) 172 ([M]⁺, 100), 171 ([M-H]⁺, 90), 131 ([M-allyl]⁺, 60). HRMS (CI) m/z [M]⁺ calcd for C₁₂H₁₂O: 172.0888; found: 172.0887. The spectral data match those reported in the literature.^[158]

AOC/oxygenation/PRE-based cyclization sequence of alcohol **25s**

In a flame-dried Schlenk flask, alcohol **25s** (135 mg, 0.56 mmol) was dissolved in DME (9.5 mL). At 0 °C, KHMDS (1M in THF, 0.74 mL, 0.74 mmol) was added. The cooling bath was removed, the reaction mixture was stirred at r.t. for 1 h and cooled to -78 °C. 2,2,6,6-Tetramethyl-*N*-oxopiperidinium tetrafluoroborate (208 mg, 0.86 mmol) was added, and the reaction mixture was stirred for 30 min, during which the color changed from dark orange to light yellow. The mixture was immersed into a preheated oil bath (120 °C) and refluxed for 30 min. After cooling, saturated NH₄Cl solution (20 mL) was added, and the resulting mixture was extracted with Et₂O (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure. The crude products were separated by column chromatography (neat hexane, gradient to 10:1 hexane/Et₂O), giving 11 product-containing fractions with a diverse product distribution that were separately analyzed by NMR spectroscopy and used for the calculation of yields and diastereoisomeric ratios. In total, 116 mg (52%) of the 5-*exo* products **37s** as a partially separable 5.4:3.5:1.7:1 diastereoisomeric mixture and

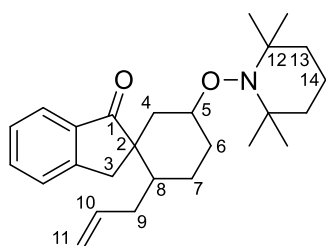
14 mg (6%) of the 6-*endo* cyclized product **37sa** were obtained as colorless oils. Traces of another minor diastereoisomer of the 6-*endo* cyclized cyclohexane **37sa** were also detected. Because of the formation of a complex diastereoisomeric mixture and a poor separation during column chromatography, only the major diastereoisomers were characterized. The overlap of ^1H NMR signals prevented the stereochemical assignment by NOE experiments.

2-Allyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)spiro[cyclopentane-1,2'-inden]-1'(3'H)-one (37s)



$R_F = 0.52$ (hexanes/EtOAc, 10:1). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.53 (td, $J = 7.4, 1.2$ Hz, 1H, CH_{Ar}), 7.41 (d, $J = 7.7$ Hz, 1H, CH_{Ar}), 7.32 (t, $J = 7.4$ Hz, 1H, CH_{Ar}), 5.59 (ddt, $J = 16.4, 10.2, 6.5$ Hz, 1H, CH-9), 4.93-4.81 (m, 2H, CH₂-10), 3.81-3.68 (m, 2H, CH₂-11), 3.56 (d, $J = 17.3$ Hz, 1H, CH₂-3^a), 2.87-2.73 (m, 1H, CH-4), 2.80 (d, $J = 17.4$ Hz, 1H, CH₂-3^b), 2.13-1.82 (m, 5H, CH-7, CH₂-8, CH₂-6^a, CH₂-5^a), 1.74-1.60 (m, 1H, CH₂-5^b), 1.52-1.18 (m, 7H, CH₂-13, CH₂-14, CH₂-6^b), 1.08 (bs, 3H, CH₃^{TEMPO}), 1.00 (bs, 3H, CH₃^{TEMPO}), 0.88 (bs, 3H, CH₃^{TEMPO}), 0.58 (bs, 3H, CH₃^{TEMPO}). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.6 (C-1), 153.3 (C_{Ar}), 137.8 (C-9), 137.6 (C_{Ar}), 134.4 (CH_{Ar}), 127.2 (CH_{Ar}), 126.1 (CH_{Ar}), 123.7 (CH_{Ar}), 115.7 (C-10), 78.5 (C-11), 60.5 (C-2), 59.9 (C-12), 59.6 (C-12), 52.0 (C-4), 45.8 (C-7), 39.8 (C-13), 39.7 (C-13), 38.0 (C-3), 35.6 (C-8), 33.4 (CH₃^{TEMPO}), 32.8 (CH₃^{TEMPO}), 30.2 (C-5), 28.1 (C-6), 20.0 (CH₃^{TEMPO}), 19.7 (CH₃^{TEMPO}), 17.2 (C-14). **MS** (ESI+) m/z (%) 418 ([M+Na⁺], 20), 396 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₆H₃₈O₂N: 396.2897 found: 396.2898. **IR** (neat): $\nu_{\text{max}} = 3074, 2972, 2928, 2868, 1704, 1639, 1607, 1464, 1373, 1359, 1279, 1210, 1186, 1132, 1046, 994, 969, 957, 910, 883, 790, 737, 711$ cm⁻¹.

Allyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (37sa)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.62-7.53 (m, 1H, CH_{Ar}), 7.46 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.41-7.34 (m, 1H, CH_{Ar}), 5.61 (dddd, $J = 16.4, 10.2, 8.2, 5.9$ Hz, 1H, CH-10), 4.84 (d, $J = 10.1$ Hz, 1H, CH₂-11), 4.78 (dq, $J = 16.7, 1.5$ Hz, 1H, CH₂-11), 3.78 (tt, $J = 11.5, 4.1$ Hz, 1H, CH-5), 3.07 (d, $J = 17.6$ Hz, 1H, CH₂-3^a), 2.83 (d, $J = 17.6$ Hz, 1H, CH₂-3^b), 2.28-2.20 (m, 1H, CH₂-6^a), 1.96-1.86 (m, 3H, CH-8, CH₂-4^a, CH₂-7^a), 1.73-1.61 (m, 2H, CH₂-4^b, CH₂-9^a), 1.56-1.49 (m, 2H, CH₂-9^b, CH₂-14^a), 1.47-1.34 (m, 4H, CH₂-13), 1.35-1.22 (m, 2H, CH₂-6^b, CH₂-14^b), 1.16 (bs, 3H, CH₃^{TEMPO}), 1.12-1.10 (m, 1H, CH₂-7^b), 1.07 (bs, 6H, CH₃^{TEMPO}), 1.03 (bs, 3H, CH₃^{TEMPO}). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.7 (C-1), 153.5 (C_{Ar}), 137.04 (C-10), 136.98 (C_{Ar}), 135.0 (CH_{Ar}), 127.6 (CH_{Ar}), 126.7 (CH_{Ar}), 124.3 (CH_{Ar}), 116.2 (C-11), 79.8 (C-5), 59.7 (C-12), 54.8 (C-2), 41.9 (C-8), 41.1 (C-4), 40.3 (C-13), 35.4 (C-9), 34.8 (CH₃^{TEMPO}), 34.7 (C-3), 34.6 (CH₃^{TEMPO}), 32.6 (C-6), 27.5 (C-7), 20.4 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 17.4 (C-14). **MS** (ESI+) m/z (%) 396 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for

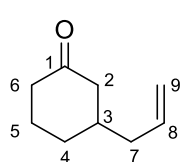
C₂₆H₃₈O₂N: 396.2897 found: 396.2898. **IR** (neat): ν_{max} = 3074, 2928, 2869, 1710, 1640, 1607, 1464, 1374, 1359, 1283, 1243, 1208, 1184, 1132, 1065, 1012, 992, 957, 912, 741 cm⁻¹.

Rearrangement of alcohol **25t** by KHMDS/18-crown-6 system

In a flame-dried Schlenk flask, alcohol **25t** (83 mg, 0.6 mmol) was dissolved in DME (12 mL). At 0 °C, KHMDS (1M in THF, 0.78 mL, 0.78 mmol) was added. The reaction mixture was gradually warmed to 70 °C and stirred at this temperature for 1 h. No reaction occurred as judged by TLC analysis. The mixture was cooled to 0 °C, and 18-crown-6 (222 mg, 0.84 mmol) was added. The mixture was warmed to 50 °C, stirred for 1 h, cooled to r.t., and quenched by 10 drops of saturated NH₄Cl solution. The resulting mixture was diluted with Et₂O (20 mL) and filtered through a plug of silica gel, which was washed by Et₂O. Evaporation of the solvents at reduced pressure gave the crude products that were separated by column chromatography on silica gel (hexane/EtOAc, 10:1) to give 58 mg (46%) of the silylated product **38t** and 11 mg (13%) of **27t** as colorless oils.

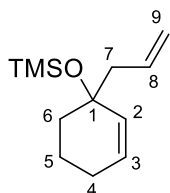
Deprotonation by KHMDS and reflux for 16 h in the absence of 18-crown-6 by the same procedure provides a quantitative yield of the rearranged product **27t**.

3-Allylcyclohexan-1-one (**27t**)



R_F = 0.39 (hexanes/EtOAc, 10:1). ¹³C NMR (101 MHz, Chloroform-*d*) δ 211.8 (C-1), 135.8 (C-8), 116.9 (C-9), 47.8 (C-7), 41.5 (C-2), 40.9 (C-6), 38.9 (C-3), 31.0 (C-4), 25.2 (C-5). The spectral data match those reported in the literature.^[159]

((1-Allylcyclohex-2-en-1-yl)oxy)trimethylsilane (**38t**)



R_F = 0.80 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 5.85 (ddt, J = 16.9, 10.4, 7.2 Hz, 1H, CH-8), 5.81-5.74 (m, 1H, CH-3), 5.67 (dtd, J = 10.1, 2.1, 1.0 Hz, 1H, CH-2), 5.08-5.00 (m, 2H, CH₂-9), 2.35-2.22 (m, 2H, CH₂-7), 2.09-1.85 (m, 2H, CH₂-4), 1.82-1.49 (m, 4H, CH₂-5, CH₂-6), 0.11 (s, 9H, TMS). ¹³C NMR (101 MHz, Chloroform-*d*) δ 135.0 (C-8), 133.2 (C-2), 129.8 (C-3), 117.1 (C-9), 72.6 (C-1), 48.2 (C-7), 36.2 (C-6), 25.3 (C-4), 19.1 (C-5), 2.7 (Si(CH₃)₃).

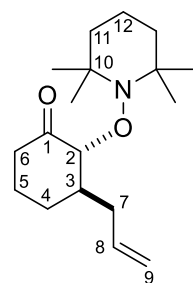
AOC/oxygenation sequence of alcohol **25t**

In a flame-dried Schlenk flask, alcohol **25t** (85 mg, 0.62 mmol) was dissolved in DME (12 mL). At r.t., KHMDS (1M in THF, 0.45 mL, 0.45 mmol) was dropwise added. The mixture was refluxed for 16 h, cooled to -78 °C, and 2,2,6,6-tetramethyl-*N*-oxopiperidinium tetrafluoroborate (180 mg, 0.74 mmol) was added at once. The mixture was stirred for 1 h, quenched by saturated NH₄Cl solution (10 mL), and extracted with Et₂O (3×10 mL). The combined organic layers were washed with a solution of ascorbic acid (10% in H₂O, 3×10 mL), brine (2×20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure. The crude products were separated by column chromatography (hexane/EtOAc, 50:1,

gradient to 10:1) to give 16 mg of the major diastereoisomer **28t**, followed by 11 mg of the major diastereoisomer of the regioisomer **28ta**, followed by 8 mg of the minor diastereoisomer **28ta**, followed by 8 mg of the minor diastereoisomer **28t**, followed by 25 mg (16%) of the α,β -unsaturated ketone **28tb** as colorless oils. In total, 24 mg (13%) of the product **28t** were obtained as a 1.7:1 diastereoisomeric mixture and 19 mg (11%) of regioisomer **28ta** as a 1.4:1 diastereoisomeric mixture.

(2*R**,3*R**) and (2*R**,3*S**)-3-Allyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclohexan-1-one (**28t**)

Major diastereoisomer:



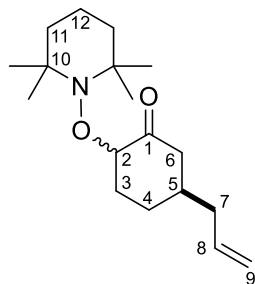
R_F = 0.50 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 5.78-5.61 (m, 1H, CH-8), 5.08-4.95 (m, 2H, CH₂-9), 3.79 (bs, 1H, CH-2), 2.97 (td, J = 12.9, 6.6 Hz, 1H, CH₂-6^a), 2.55 (bs, 1H, CH-3), 2.26-2.18 (m, 1H, CH₂-6^b), 2.08 (tt, J = 13.8, 4.5 Hz, 1H, CH₂-4^a), 2.02-1.84 (m, 3H, CH₂-7, CH₂-5^a), 1.75 (tt, J = 13.9, 4.3 Hz, 1H, CH₂-5^b), 1.57-1.36 (m, 6H, CH₂-4^b, CH₂-12^a, CH₂-11), 1.37-1.21 (m, 1H, CH₂-12^b), 1.12 (s, 9H, CH₃^{TEMPO}), 0.94 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 213.2 (C-1), 135.8 (C-8), 117.1 (C-9), 91.8 (C-2), 60.6 (C-10), 60.2 (C-10), 42.4 (C-3), 40.3 (C-11), 39.9 (C-6), 34.0 (C-7), 33.4 (CH₃^{TEMPO}), 24.4 (C-4), 23.4 (C-5), 20.2 (CH₃^{TEMPO}), 17.2 (C-12). **MS** (EI) m/z (%) 293 ([M]⁺, 20), 278 ([M-CH₃]⁺, 100). **HRMS** (EI) m/z [M]⁺ calcd for C₁₈H₃₁NO₂: 293.2355; found: 293.2357. **IR** (neat): $\nu_{\max}$ = 2981, 2941, 2881, 1724, 1647, 1468, 1380, 1365, 1312, 1264, 1187, 1137, 1088, 1015, 991, 975, 916, 789, 704, 616 cm⁻¹.

Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 5.76-5.63 (m, 1H, CH-8), 5.08-4.96 (m, 2H, CH₂-9), 4.62 (d, J = 5.5 Hz, 1H, CH-2), 2.74 (ddt, J = 12.6, 5.8, 3.4 Hz, 1H, CH-3), 2.47-2.37 (m, 2H, CH₂-6^a, CH₂-7^a), 2.32-2.21 (m, 1H, CH₂-6^b), 1.92-1.68 (m, 5H, CH₂-7^b, CH₂-4, CH₂-5), 1.66-1.52 (m, 1H, CH₂-12^a), 1.51-1.37 (m, 4H, CH₂-11), 1.36-1.28 (m, 1H, CH₂-12^b), 1.25 (bs, 3H, CH₃^{TEMPO}), 1.17 (bs, 3H, CH₃^{TEMPO}), 1.15 (bs, 3H, CH₃^{TEMPO}), 1.01 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 209.8 (C-1), 136.5 (C-8), 116.5 (C-9), 92.3 (C-2), 59.3 (C-10), 42.62 (C-3), 42.57 (C-6), 40.7 (C-11), 34.7 (CH₃^{TEMPO}), 32.7 (CH₃^{TEMPO}), 29.7 (C-7), 26.5 (C-4), 22.7 (C-5), 20.7 (CH₃^{TEMPO}), 20.1 (CH₃^{TEMPO}), 17.2 (C-12).

(2*S**,5*R**) and (2*S**,5*S**)-5-Allyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclohexan-1-one (**28ta**)

Major diastereoisomer:



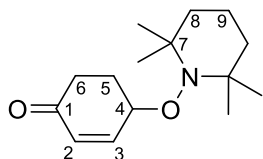
R_F = 0.40 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 5.81-5.68 (m, 1H, CH-8), 5.09-4.99 (m, 2H, CH₂-9), 3.99 (bs, 1H, CH-2), 2.63 (t, J = 11.8 Hz, 1H, CH₂-6^a), 2.45-2.26 (m, 2H, CH₂-6^b, CH₂-3^a), 2.19-2.02 (m, 2H, CH₂-7), 1.87-1.84 (m, 1H, CH-5), 1.71-1.53 (m, 3H, CH₂-4, CH₂-3^b), 1.52-1.38 (m, 5H, CH₂-11, CH₂-12^a), 1.36-1.23 (m, 1H, CH₂-12^b), 1.13 (bs, 9H, CH₃^{TEMPO}), 0.95 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 212.7 (C-1), 135.9 (C-8), 116.9 (C-9), 88.5 (C-2), 60.1 (C-10), 46.0 (C-6),

41.2 (C-7), 40.8 (C-5), 40.3 (C-11), 33.7 (CH₃^{TEMPO}), 32.6 (C-3), 26.9 (C-4), 20.3 (CH₃^{TEMPO}), 17.2 (C-12). **IR** (neat): $\nu_{\max}$ = 3069, 3006, 2982, 2940, 2880, 1726, 1455, 1380, 1365, 1266, 1212, 1186, 1137, 1085, 1047, 996, 974, 917 cm⁻¹.

Minor diastereoisomer:

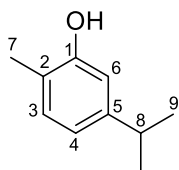
R_F = 0.38 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 5.72 (ddt, J = 14.8, 10.8, 7.4 Hz, 1H, CH-8), 5.09-4.96 (m, 2H, CH₂-9), 4.36 (dd, J = 11.2, 5.8 Hz, 1H, CH-2), 2.59-2.48 (m, 2H, CH₂-3^a, CH₂-6^a), 2.15-1.99 (m, 3H, CH₂-6^b, CH₂-7), 1.99-1.91 (m, 1H, CH₂-4^a), 1.91-1.82 (m, 1H, CH-5), 1.71-1.52 (m, 2H, CH₂-3^b, CH₂-12^a), 1.52-1.27 (m, 6H, CH₂-12^b, CH₂-11, CH₂-4^b), 1.23 (bs, 3H, CH₃^{TEMPO}), 1.16 (bs, 3H, CH₃^{TEMPO}), 1.12 (bs, 3H, CH₃^{TEMPO}), 1.02 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 209.3 (C-1), 135.9 (C-8), 117.0 (C-9), 89.4 (C-2), 61.2 (C-10), 47.6 (C-6), 40.6 (C-11), 40.3 (C-7), 39.9 (C-5), 33.2 (C-3), 33.1 (CH₃^{TEMPO}), 29.9 (C-4), 20.5 (CH₃^{TEMPO}), 17.3 (C-12).

4-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)cyclohex-2-en-1-one (28tb)



R_F = 0.24 (hexanes/EtOAc, 10:1, 2 elutions). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.29 (ddd, J = 10.5, 2.7, 1.6 Hz, 1H, CH-3), 5.95 (ddd, J = 10.4, 2.0, 1.0 Hz, 1H, CH-2), 4.63-4.57 (m, 1H, CH-4), 2.62-2.55 (m, 1H, CH₂-6^a), 2.45-2.27 (m, 2H, CH₂-5^a, CH₂-6^b), 2.07-1.97 (m, 1H, CH₂-5^b), 1.66-1.38 (m, 5H, CH₂-8, CH₂-9^a), 1.38-1.23 (m, 1H, CH₂-9^b), 1.12 (bs, 12H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 199.4 (C-1), 152.0 (C-3), 128.8 (C-2), 77.4 (C-4), 60.1 (C-7), 59.8 (C-7), 40.1 (C-8), 35.7 (C-6), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 30.0 (C-5), 20.5 (CH₃^{TEMPO}), 20.2 (CH₃^{TEMPO}), 17.1 (C-9). **MS** (APCI) m/z (%) 252 ([M+H⁺], 75), 156 ([TEMPO], 100). **HRMS** (APCI) m/z [M+H⁺] calcd for C₁₅H₂₆O₂N: 252.1958 found: 252.1960. **IR** (neat): $\nu_{\max}$ = 2970, 2929, 2871, 1687, 1455, 1375, 1361, 1257, 1242, 1208, 1182, 1132, 1037, 988, 974, 956, 942, 912, 873, 789, 752, 705 cm⁻¹.

5-Isopropyl-2-methylphenol - Carvacrol (39v)



In a flame-dried Schlenk flask, allylated carvone derivative **25v** (116 mg, 0.60 mmol) was dissolved in DME (10 mL). At 0 °C, KHMDS (1M in THF, 0.78 mL, 0.78 mmol) was dropwise added. The mixture was refluxed for 18 h, quenched by 10 drops of saturated NH₄Cl solution, and filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give 73 mg (81%) of the crude mixture that was analyzed by NMR spectroscopy showing essentially pure carvacrol **39v** with traces of the starting material detectable.

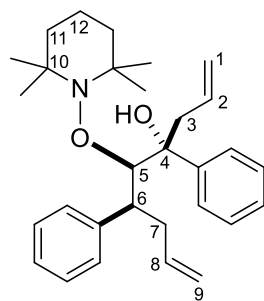
¹H NMR (400 MHz, Chloroform-*d*) δ 7.06 (d, J = 7.7 Hz, 1H, CH-3), 6.75 (dd, J = 7.6, 1.8 Hz, 1H, CH-4), 6.69 (d, J = 1.7 Hz, 1H, CH-6), 5.24 (bs, 1H, OH), 2.84 (sept, J = 7.0 Hz, 1H, CH-8), 2.24 (s, 3H, CH₃-7), 1.24 (d, J = 6.9 Hz, 6H, CH₃-9). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 153.8 (C-1), 148.5 (C-5), 130.9 (C-3), 121.0 (C-2), 118.8 (C-4), 113.1 (C-6), 33.8 (C-8), 24.1 (C-9), 15.5 (C-7). The spectral data match those reported in the literature.^[160]

6.3.3. Extensions of the tandem sequence

(4*R**,5*R**,6*S**)- and (4*R**,5*R**,6*R**)-4,6-Diphenyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)nona-1,8-dien-4-ol (**40a**)

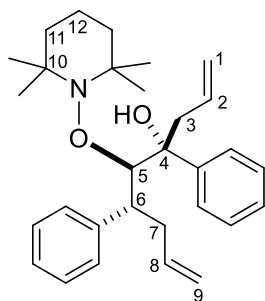
In a flame-dried Schlenk flask, alcohol **25a** (58 mg, 0.23 mmol) was dissolved in DME (4.6 mL). KHMDS (0.3 mL, 0.3 mmol, 1M in THF) was dropwise added at 0 °C. The mixture was warmed to 50 °C and stirred at this temperature for 1 h. After cooling to r.t., TEMPO (40 mg, 0.25 mmol) was added at once. The mixture was cooled to -78 °C, and Cp₂Fe⁺PF₆⁻ (130 mg, 0.39 mmol) was added in small portions (~20 mg/30 s) until the mixture remained dark blue. The mixture was stirred for additional 20 min, and allylmagnesium chloride (0.15 mL, 0.3 mmol, 2M in THF) was dropwise added. After the mixture turned orange, the cooling bath was removed, and the mixture was warmed to r.t. over 1 h. The mixture was quenched by saturated NH₄Cl solution (5 drops), diluted with Et₂O (10 mL), and filtered through a plug of silica gel, which was washed by Et₂O. The solvent was evaporated, and the crude product was purified by column chromatography (neat hexane, gradient 20:1 to 10:1 hexane/Et₂O) to yield 17 mg of the minor diastereoisomer *minor-40a* as a thick yellow oil followed by 76 mg of the major diastereoisomer *major-40a* as an off-white solid. Yield 93 mg (89%) of **40a** as a 4.7:1 diastereoisomeric mixture. The major diastereoisomer was crystallized from *i*PrOH for X-ray diffraction analysis.

Major diastereoisomer:



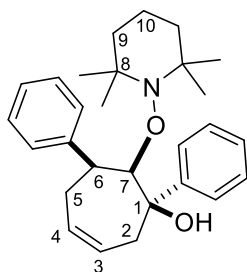
R_F = 0.35 (hexanes/EtOAc, 10:1). **m.p.** 105-107 °C. **¹H NMR** (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H, OH), 7.59 (dd, J = 7.7, 1.7 Hz, 2H, CH_{Ar}), 7.36 (t, J = 7.6 Hz, 2H, CH_{Ar}), 7.30-7.22 (m, 1H, CH_{Ar}), 7.08-7.03 (m, 3H, CH_{Ar}), 6.59 (dd, J = 7.4, 2.2 Hz, 2H, CH_{Ar}), 5.82 (ddt, J = 17.1, 10.3, 6.6 Hz, 1H, CH-8), 5.61 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H, CH-2), 5.14 (dq, J = 17.3, 1.6 Hz, 1H, CH₂-9), 5.10-4.97 (m, 2H, CH₂-9, CH₂-1), 4.89 (dd, J = 10.2, 1.8 Hz, 1H, CH₂-1), 4.45 (d, J = 1.3 Hz, 1H, CH-5), 3.39 (ddt, J = 14.5, 7.0, 1.3 Hz, 1H, CH₂-3^a), 3.06 (ddt, J = 14.4, 6.4, 1.5 Hz, 1H, CH₂-3^b), 2.99-2.94 (m, 1H, CH-6), 2.90-2.80 (m, 1H, CH₂-7^a), 2.77-2.72 (m, 1H, CH₂-7^b), 1.61 (bs, 3H, CH₃^{TEMPO}), 1.60-1.50 (m, 4H, CH₂-11, CH₂-11^a, CH₂-12^a), 1.39-1.31 (m, 2H, CH₂-11^b, CH₂-12^b), 1.29 (bs, 3H, CH₃^{TEMPO}), 1.05 (bs, 3H, CH₃^{TEMPO}), 1.02 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 144.8 (C_{Ar}), 143.6 (C_{Ar}), 137.6 (C-2), 135.0 (C-8), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.1 (CH_{Ar}), 126.1 (CH_{Ar}), 117.4 (C-9), 115.8 (C-1), 89.6 (C-5), 82.9 (C-4), 62.6 (C-10), 62.0 (C-10), 44.4 (C-6), 42.0 (C-11), 40.8 (C-11), 36.7 (C-7), 35.3 (CH₃^{TEMPO}), 34.7 (CH₃^{TEMPO}), 21.3 (CH₃^{TEMPO}), 20.8 (CH₃^{TEMPO}), 17.1 (C-12). **MS** (ESI⁺) m/z (%) 917 ([2M+Na⁺], 20), 470 ([M+Na⁺], 25), 448 ([M+H⁺], 100). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₃₀H₄₁NO₂Na: 470.3030; found: 470.3031; [M+H⁺] calcd for C₃₀H₄₂NO₂: 448.3210; found: 448.3211. **IR** (neat): $\nu_{\max}$ = 3218, 3071, 2977, 2932, 2872, 1639, 1440, 1366, 1240, 1132, 1047, 908, 758, 730, 701 cm⁻¹.

Minor diastereoisomer:



$R_F = 0.55$ (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.16-7.02 (m, 5H, CH_{Ar}), 7.00-6.92 (m, 3H, CH_{Ar}), 6.67-6.55 (m, 2H, CH_{Ar}), 5.41-5.27 (m, 2H, CH-2, CH-8), 4.91-4.71 (m, 4H, CH_2 -1, CH_2 -9), 4.57 (bs, 1H, CH-5), 3.81 (bs, 1H, CH-6), 3.37 (bs, 1H, CH_2 -3^a), 3.03-2.87 (m, 1H, CH_2 -7^a), 2.72-2.64 (m, 1H, CH_2 -7^b), 2.61-2.54 (m, 1H, CH_2 -3^b), 2.53 (bs, 1H, OH), 1.74-1.38 (m, 6H, CH_2 -11, CH_2 -12), 1.36 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.34 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.32 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.25 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (126 MHz, Chloroform- d) δ 142.7 (2C_{Ar}), 138.1 (C-8), 134.1 (C-2), 129.2 (CH_{Ar}), 127.63 (CH_{Ar}), 127.55 (CH_{Ar}), 126.7 (CH_{Ar}), 126.5 (CH_{Ar}), 125.1 (CH_{Ar}), 117.8 (C-1), 115.5 (C-9), 90.4 (C-5), 79.9 (C-4), 62.3 (C-10), 60.6 (C-10), 47.8 (C-3), 44.0 (C-6), 41.7 (C-11), 41.2 (C-11), 35.1 ($\text{CH}_3^{\text{TEMPO}}$), 34.2 ($\text{CH}_3^{\text{TEMPO}}$), 29.9 (C-7), 21.9 ($\text{CH}_3^{\text{TEMPO}}$), 21.5 ($\text{CH}_3^{\text{TEMPO}}$), 17.4 (C-12).

(1R*,2R*,3S*)-1,3-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclohept-5-en-1-ol (41a)



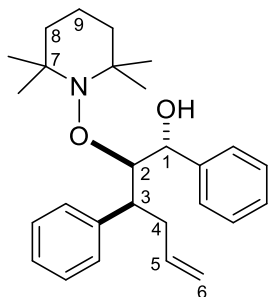
In a round-bottomed flask, protected diol **major-40a** (46 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL). The Hoveyda-Grubbs II catalyst (3.8 mg, 0.005 mmol) was added at r.t. and the mixture was stirred for 20 h. The solvent was removed by a stream of nitrogen, and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to yield 43 mg (99%) of **41a** as a thick colorless oil.

$R_F = 0.28$ (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 8.25 (s, 1H, OH), 7.75 (dd, $J = 8.4, 1.4$ Hz, 2H, CH_{Ar}), 7.38 (dd, $J = 8.3, 6.9$ Hz, 2H, CH_{Ar}), 7.33-7.26 (m, 1H, CH_{Ar}), 7.18 (dd, $J = 8.1, 6.7$ Hz, 2H, CH_{Ar}), 7.13-7.07 (m, 1H, CH_{Ar}), 6.92-6.89 (m, 2H, CH_{Ar}), 5.92 (ddt, $J = 11.5, 7.7, 2.9$ Hz, 1H, CH-3), 5.84 (ddt, $J = 11.5, 8.5, 3.0$ Hz, 1H, CH-4), 4.93 (bs, 1H, CH-7), 3.59 (dq, $J = 17.1, 3.2$ Hz, 1H, CH_2 -2^a), 3.24 (ddq, $J = 15.3, 12.2, 3.1$ Hz, 1H, CH_2 -5^a), 2.88 (dt, $J = 12.3, 1.8$ Hz, 1H, CH-6), 2.82 (dd, $J = 17.2, 7.9$ Hz, 1H, CH_2 -2^b), 2.11 (ddd, $J = 15.6, 8.4, 1.9$ Hz, 1H, CH_2 -5^b), 1.59 (s, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.58-1.48 (m, 4H, CH_2 -10^a, CH_2 -9, CH_2 -9^a), 1.34-1.26 (m, 2H, CH_2 -10^b, CH_2 -9^b), 1.25 (s, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.16 (s, 3H, $\text{CH}_3^{\text{TEMPO}}$), 0.55 (s, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 147.6 (C_{Ar}), 146.0 (C_{Ar}), 130.1 (C-4), 128.5 (C-3), 128.01 (CH_{Ar}), 127.98 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.2 (CH_{Ar}), 126.0 (CH_{Ar}), 88.6 (C-7), 80.8 (C-1), 62.4 (C-8), 61.9 (C-8), 42.5 (C-6), 42.3 (C-9), 40.9 (C-9), 38.7 (C-2), 35.8 ($\text{CH}_3^{\text{TEMPO}}$), 35.3 ($\text{CH}_3^{\text{TEMPO}}$), 25.9 (C-5), 21.0 ($\text{CH}_3^{\text{TEMPO}}$), 20.0 ($\text{CH}_3^{\text{TEMPO}}$), 17.1 (C-10). **MS** (ESI+) m/z (%) 442 ($[\text{M}+\text{Na}^+]$, 5), 420 ($[\text{M}+\text{H}^+]$, 100), 279 ($[\text{M}-\text{TMPH}+\text{H}^+]$, 35). **HRMS** (ESI+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{28}\text{H}_{38}\text{NO}_2$: 420.2897; found: 420.2898. **IR** (neat): $\nu_{\text{max}} = 3223, 2974, 2870, 1493, 1447, 1381, 1366, 1255, 1238, 1181, 1132, 1056, 1023, 940, 760, 700, 685, 605 \text{ cm}^{-1}$.

(1R,2R*,3S*)*- and *(1R*,2R*,3R*)*-**1,3-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-ol (42a)**

In a flame-dried Schlenk flask, alcohol **25a** (501 mg, 2.0 mmol) was dissolved in DME (40 mL). At 0 °C KHMDS (2.6 mL, 2.6 mmol, 1M in THF) was dropwise added. The mixture was warmed to 50 °C and stirred at this temperature for 1 h. After cooling to r.t., TEMPO (343 mg, 2.2 mmol) was added at once. The mixture was cooled to -78 °C, and $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ (1.06 g, 3.2 mmol) was added in small portions (~100 mg/30 s) until the mixture remained dark blue. The mixture was stirred for additional 20 min, and Super-Hydride[®] solution (6.0 mL, 6.0 mmol, 1M in THF) was added slowly. The mixture was warmed to r.t. and stirred overnight. The mixture was quenched by MeOH (1 mL) and H₂O (0.5 mL), diluted by Et₂O (100 mL), filtered through a thick plug of silica gel, which was washed by Et₂O. The solvent was evaporated at reduced pressure to give the crude product, which was purified by column chromatography (neat hexane, gradient 50:1 to 10:1 hexane/EtOAc) to yield 115 mg (14%) of unreacted ketone **28a** followed by 568 mg of the major diastereoisomer as a thick colorless oil that crystallized very slowly upon standing to an off-white solid, followed by 121 mg of the minor diastereoisomer of **42a** as a thick colorless oil. Yield 689 mg (85%) of **42a** as a separable 4.7:1 mixture of diastereoisomers.

Major diastereoisomer:



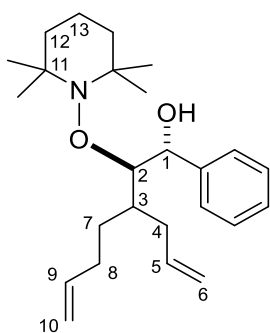
R_F = 0.49 (hexanes/EtOAc, 10:1). **m.p.** 65-67 °C. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H, OH), 7.49-7.31 (m, 5H, CH_{Ar}), 7.25-7.11 (m, 3H, CH_{Ar}), 7.07-7.00 (m, 2H, CH_{Ar}), 5.46 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H, CH-5), 5.26 (d, J = 9.0 Hz, 1H, CH-1), 4.94 (dq, J = 17.1, 1.6 Hz, 1H, CH₂-6), 4.81 (ddt, J = 10.2, 2.2, 1.2 Hz, 1H, CH₂-6), 4.24 (dd, J = 9.2, 1.7 Hz, 1H, CH-2), 2.89 (dddt, J = 14.6, 12.0, 6.6, 1.2 Hz, 1H, CH₂-4^a), 2.66-2.58 (m, 1H, CH₂-4^b), 2.35 (ddd, J = 12.1, 3.4, 1.6 Hz, 1H, CH-3), 1.63-1.45 (m, 7H, CH₂-8, CH₂-8^a, CH₂-9^a, CH₃^{TEMPO}), 1.40-1.31 (m, 2H, CH₂-8^b, CH₂-9^b), 1.27 (bs, 3H, CH₃^{TEMPO}), 0.99 (bs, 3H, CH₃^{TEMPO}), 0.87 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 142.4 (C_{Ar}), 141.7 (C_{Ar}), 137.1 (C-5), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.23 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 126.2 (CH_{Ar}), 116.0 (C-6), 88.5 (C-2), 78.1 (C-1), 62.15 (C-7), 60.8 (C-7), 46.4 (C-3), 40.61 (C-8), 40.2 (C-8), 33.9 (CH₃^{TEMPO}), 32.1 (CH₃^{TEMPO}), 30.6 (C-4), 21.3 (CH₃^{TEMPO}), 20.6 (CH₃^{TEMPO}), 17.24 (C-9). **MS** (ESI+) m/z (%) 430 ([M+Na⁺], 10), 408 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₇H₃₈NO₂: 408.2897; found: 408.2899. **IR** (neat): ν_{max} = 3182, 3066, 2974, 2927, 1494, 1378, 1363, 1181, 1130, 1022, 995, 911, 759, 729, 696 cm⁻¹.

Minor diastereoisomer:

R_F = 0.44 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 8.10 (s, 1H, OH), 7.48-7.11 (m, 10H, CH_{Ar}), 5.46 (dddd, J = 16.0, 10.2, 7.9, 5.6 Hz, 1H, CH-5), 4.99-4.87 (m, 2H, CH₂-6), 4.66-4.57 (m, 2H, CH-1, CH-2), 2.70-2.60 (m, 1H, CH₂-4^a), 2.56-2.48 (m, 1H, CH₂-4^b), 2.35 (td, J = 7.7, 1.8 Hz, 1H, CH-3), 1.65-1.42 (m, 9H, CH₂-8, CH₂-9, CH₃^{TEMPO}), 1.35 (s, 3H, CH₃^{TEMPO}), 1.25 (s, 3H, CH₃^{TEMPO}), 1.10 (s, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 141.4 (C_{Ar}), 140.1 (C_{Ar}),

137.2 (C-5), 130.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.15 (CH_{Ar}), 127.6 (CH_{Ar}), 126.7 (CH_{Ar}), 116.6 (C-6), 84.8 (C-2), 78.1 (C-1), 62.24 (C-7), 60.8 (C-7), 46.7 (C-3), 41.0 (C-8), 40.62 (C-8), 38.7 (C-4), 34.6 (CH₃^{TEMPO}), 31.2 (CH₃^{TEMPO}), 21.2 (CH₃^{TEMPO}), 20.9 (CH₃^{TEMPO}), 17.19 (C-9).

(1*R**,2*R**,3*S**)- and (1*R**,2*R**,3*R**)-3-Allyl-1-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hept-6-en-1-ol (**42m**)



In a flame-dried Schlenk flask, alcohol **25m** (105 mg, 0.46 mmol) was dissolved in DME (9.2 mL). At 0 °C KHMDS (0.6 mL, 0.6 mmol, 1M in THF) was dropwise added. The mixture was warmed to 50 °C and stirred at this temperature for 1 h. After cooling to r.t., TEMPO (79 mg, 0.51 mmol) was added at once. The mixture was cooled to –78 °C, and Cp₂Fe⁺PF₆[–] (244 mg, 0.74 mmol) was added in small portions (~50 mg/30 s) until the mixture remained dark blue. The mixture was stirred for additional 20 min, and Super-Hydride[®] solution (1.4 mL, 1.4 mmol, 1M in THF) was slowly added. The mixture was warmed to r.t. and stirred overnight. The mixture was quenched by MeOH (1 mL) and H₂O (0.5 mL), diluted by Et₂O (30 mL), and filtered through a thick plug of silica gel, which was washed by Et₂O. The solvent was evaporated at reduced pressure to give the crude product, which was purified by column chromatography (hexane/EtOAc, neat hexane, gradient to 10:1) to yield 167 mg (94%) of an inseparable 1.4:1 diastereoisomeric mixture of **42m** as a thick colorless oil.

Major diastereoisomer:

R_F = 0.35 (hexanes/EtOAc, 10:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 7.90 (s, 1H, OH), 7.38-7.23 (m, 5H, CH_{Ar}), 5.67-5.39 (m, 2H, CH-5, CH-9), 5.20 (d, *J* = 9.4 Hz, 1H, CH-1), 5.02-4.89 (m, 3H, CH₂-6, CH₂-10), 4.80-4.73 (m, 1H, CH₂-10), 4.21 (dd, *J* = 9.0, 1.5 Hz, 1H, CH-2), 2.46 (dddt, *J* = 14.5, 6.1, 3.3, 1.8 Hz, 1H, CH₂-4^a), 2.25-1.95 (m, 2H, CH₂-4^b, CH₂-8^a), 1.78-1.51 (m, 7H, CH₂-8^b, CH₂-7^a, CH₂-12, CH₂-13^a), 1.50 (bs, 3H, CH₃^{TEMPO}), 1.48 (bs, 3H, CH₃^{TEMPO}), 1.42-1.30 (m, 2H, CH₂-13^b, CH₂-7^b), 1.24 (bs, 3H, CH₃^{TEMPO}), 1.20 (bs, 3H, CH₃^{TEMPO}), 1.12-1.00 (m, 1H, CH-3). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.6 (C_{Ar}), 138.1 (C-5), 137.9 (C-9), 128.43 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 116.0 (C-6), 114.7 (C-10), 84.2 (C-2), 77.8 (C-1), 62.1 (C-11), 60.84 (C-11), 40.8 (C-12), 40.36 (C-12), 38.8 (C-3), 34.6 (CH₃^{TEMPO}), 33.7 (C-4), 32.0 (CH₃^{TEMPO}), 31.8 (C-8), 29.8 (C-7), 20.80 (CH₃^{TEMPO}), 20.68 (CH₃^{TEMPO}), 17.24 (C-13). MS (ESI⁺) *m/z* (%) 386 ([M+H⁺], 100). HRMS (ESI⁺) *m/z* [M+H⁺] calcd for C₂₅H₄₀NO₂: 386.3054; found: 386.3055. IR (neat): ν_{max} = 3146, 3075, 2974, 2930, 2872, 1640, 1452, 1381, 1338, 1240, 1182, 1131, 1066, 1029, 993, 957, 909, 841, 760, 729, 700, 622 cm^{–1}.

Minor diastereoisomer:

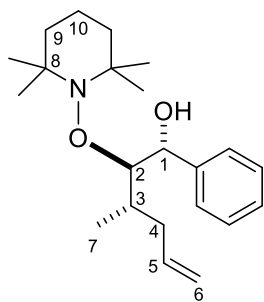
¹H NMR (401 MHz, Chloroform-*d*) δ 7.94 (s, 1H, OH), 7.38-7.23 (m, 5H, CH_{Ar}), 5.75 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 1H, CH-5), 5.54-5.39 (m, 1H, CH-9), 5.18 (d, *J* = 9.6 Hz, 1H, CH-1), 5.02-4.89 (m, 4H, CH₂-6, CH₂-10), 4.16 (dd, *J* = 9.2, 1.5 Hz, 1H, CH-2), 2.25-1.95 (m, 3H, CH₂-4, CH₂-8^a), 1.86-1.51 (m, 7H, CH₂-8^b, CH₂-7^a, CH₂-12, CH₂-13^a), 1.49 (bs, 3H, CH₃^{TEMPO}), 1.45 (bs, 3H, CH₃^{TEMPO}), 1.43 (bs,

3H, CH₃^{TEMPO}), 1.42-1.30 (m, 3H, CH-3, CH₂-13^b, CH₂-7^b), 1.19 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.7 (C_{Ar}), 138.9 (C-5), 138.4 (C-9), 128.37 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 116.4 (C-6), 114.7 (C-10), 84.3 (C-2), 77.8 (C-1), 62.0 (C-11), 60.77 (C-11), 40.9 (C-12), 40.39 (C-12), 39.5 (C-3), 35.2 (C-4), 34.2 (CH₃^{TEMPO}), 32.13 (C-8), 32.1 (CH₃^{TEMPO}), 28.0 (C-7), 20.75 (CH₃^{TEMPO}), 20.65 (CH₃^{TEMPO}), 17.20 (C-13).

(1*R**,2*R**,3*S**)- and (1*R**,2*R**,3*R**)-3-Methyl-1-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-ol (**42n**)

In a flame-dried Schlenk flask, alcohol **25n** (303 mg, 1.61 mmol) was dissolved in DME (32 mL). At 0 °C KHMDS (2.1 mL, 2.1 mmol, 1M in THF) was dropwise added. The mixture was warmed to 50 °C and stirred at this temperature for 1 h. After cooling to r.t., TEMPO (277 mg, 1.77 mmol) was added at once. The mixture was cooled to -78 °C, and Cp₂Fe⁺PF₆⁻ (852 mg, 2.57 mmol) was added in small portions (~100 mg/30 s) until the mixture remained dark blue. The mixture was stirred for additional 20 min, and Super-Hydride[®] solution (4.8 mL, 4.8 mmol, 1M in THF) was added slowly. The mixture was warmed to r.t. and stirred overnight. The mixture was quenched by MeOH (1 mL) and H₂O (0.5 mL), diluted by Et₂O (80 mL) and filtered through a thick plug of silica gel, which was washed by Et₂O. The solvent was evaporated at reduced pressure to give the crude product, which was purified by column chromatography (hexane/EtOAc, neat hexane, gradient to 10:1) to yield 548 mg (99%) of an inseparable 1.4:1 diastereoisomeric mixture of **42n** as a thick colorless oil.

Major diastereoisomer:



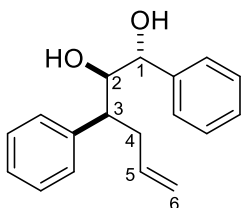
R_F = 0.37 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H, OH), 7.39-7.24 (m, 5H, CH_{Ar}), 5.55-5.45 (m, 1H, CH-5), 5.12 (d, *J* = 9.2 Hz, 1H, CH-1), 5.02-4.89 (m, 2H, CH₂-6), 4.14-4.06 (m, 1H, CH-2), 2.21 (dt, *J* = 14.8, 7.5 Hz, 1H, CH₂-4^a), 2.08-1.96 (m, 1H, CH₂-4^b), 1.72-1.51 (m, 5H, CH₂-9, CH-10^a), 1.52 (s, 3H, CH₃^{TEMPO}), 1.49 (s, 3H, CH₃^{TEMPO}), 1.44-1.35 (m, 1H, CH-10^b), 1.26-1.19 (m, 1H, CH-3), 1.24 (s, 3H, CH₃^{TEMPO}), 1.21 (s, 3H, CH₃^{TEMPO}), 0.99 (d, *J* = 6.9 Hz, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.78 (C_{Ar}), 137.8 (C-5), 128.4 (CH_{Ar}), 127.87 (CH_{Ar}), 127.5 (CH_{Ar}), 116.2 (C-6), 85.0 (C-2), 78.0 (C-1), 62.1 (C-8), 60.79 (C-8), 40.8 (C-9), 40.4 (C-9), 39.5 (C-4), 34.7 (C-3), 34.4 (CH₃^{TEMPO}), 32.01 (CH₃^{TEMPO}), 20.9 (CH₃^{TEMPO}), 20.67 (CH₃^{TEMPO}), 17.2 (C-10), 13.4 (C-7). **MS** (ESI+) *m/z* (%) 368 ([M+Na⁺], 50), 346 ([M+H⁺], 100). **HRMS** (ESI+) *m/z* [M+H⁺] calcd for C₂₂H₃₆NO₂: 346.2741; found: 346.2738. **IR** (neat): ν_{max} = 3182, 3066, 2974, 2927, 1493, 1378, 1363, 1181, 1130, 1022, 995, 911, 759, 729, 696 cm⁻¹.

Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H, OH), 7.39-7.24 (m, 5H, CH_{Ar}), 5.66-5.55 (m, 1H, CH-5), 5.17 (d, *J* = 9.0 Hz, 1H, CH-1), 5.02-4.89 (m, 2H, CH₂-6), 4.14-4.06 (m, 1H, CH-2), 2.46-2.39 (m, 1H, CH₂-4^a), 2.10-1.96 (m, 1H, CH₂-4^b), 1.72-1.51 (m, 5H, CH₂-9, CH₂-10^a), 1.49 (s, 3H, CH₃^{TEMPO}), 1.45 (s, 3H, CH₃^{TEMPO}), 1.44-1.35 (m, 1H, CH₂-10^b), 1.24 (s, 3H, CH₃^{TEMPO}), 1.21 (s, 3H,

CH₃^{TEMPO}), 1.13-1.06 (m, 1H, CH-3), 0.94 (d, $J = 7.0$ Hz, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.80 (C_{Ar}), 137.9 (C-5), 128.4 (CH_{Ar}), 127.90 (CH_{Ar}), 127.5 (CH_{Ar}), 115.8 (C-6), 88.2 (C-2), 77.7 (C-1), 62.3 (C-8), 60.81 (C-8), 40.7 (C-9), 40.3 (C-9), 34.6 (CH₃^{TEMPO}), 34.5 (C-4), 31.98 (CH₃^{TEMPO}), 20.9 (CH₃^{TEMPO}), 20.74 (CH₃^{TEMPO}), 20.69 (C-3), 18.0 (C-7), 17.3 (C-10).

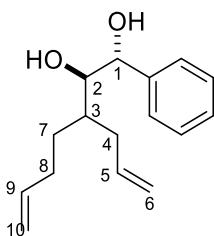
(1*R,2*R**,3*S**)-1,3-Diphenylhex-5-ene-1,2-diol (43a)**



In a 25 mL round-bottomed flask, the major diastereoisomer of **42a** (85 mg, 0.21 mmol) was dissolved in a 1:1 THF/H₂O mixture (3 mL). Acetic acid (4.7 mL) and Zn dust (523 mg, 8 mmol) were added. The mixture was stirred at 60 °C for 1 h. After cooling to r.t., the mixture was diluted with Et₂O (20 mL) and filtered through a plug of silica gel, which was washed by Et₂O. After evaporation of the solvents, the resulting crude mixture was redissolved in EtOAc, preadsorbed on silica gel (5 g), purified by column chromatography (hexane/EtOAc, 5:1), and recrystallized from hot hexanes to yield 45 mg (80%) of **43a** as a colorless solid.

$R_F = 0.68$ (hexanes/EtOAc, 1:1). **m.p.** 106-108 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.31-7.08 (m, 10H, CH_{Ar}), 5.55 (ddt, $J = 17.1, 10.1, 7.0$ Hz, 1H, CH-5), 4.89 (dd, $J = 17.1, 2.0$ Hz, 1H, CH₂-6), 4.81 (dd, $J = 10.0, 2.1$ Hz, 1H, CH₂-6), 4.37 (d, $J = 3.0$ Hz, 1H, CH-1), 3.77 (dd, $J = 8.1, 3.1$ Hz, 1H, CH-2), 2.85 (ddd, $J = 10.2, 8.0, 4.2$ Hz, 1H, CH-3), 2.71 (ddd, $J = 14.1, 7.1, 4.4$ Hz, 1H, CH₂-4^a), 2.52-2.42 (m, 2H, CH₂-4^b, OH), 2.15 (bs, 1H, OH). ¹³C NMR (101 MHz, Chloroform-*d*) δ 142.2 (C_{Ar}), 142.0 (C_{Ar}), 137.0 (C-5), 128.8 (CH_{Ar}), 128.62 (CH_{Ar}), 128.56 (CH_{Ar}), 127.8 (CH_{Ar}), 126.9 (CH_{Ar}), 126.1 (CH_{Ar}), 116.3 (C-6), 79.6 (C-2), 73.2 (C-1), 48.6 (C-3), 36.1 (C-4). **MS** (ESI+) m/z (%): 291 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₁₈H₂₀O₂Na: 291.1356; found: 291.1352. **IR** (neat): $\nu_{max} = 3340, 3064, 3023, 2907, 1492, 1451, 1398, 1329, 1260, 1203, 1102, 1074, 1037, 1025, 996, 909, 761, 723, 670, 654, 609$ cm⁻¹.

(1*R,2*R**,3*S**)- and (1*R**,2*R**,3*R**)-3-Allyl-1-phenylhept-6-ene-1,2-diol (43m)**



In a 25 mL round-bottomed flask, the 1.4:1 diastereoisomeric mixture of **42m** (108 mg, 0.28 mmol) was dissolved in a 1:1 THF/H₂O mixture (4.0 mL). Acetic acid (6.3 mL) and Zn dust (712 mg, 10.9 mmol) were added. The mixture was stirred at 60 °C for 2 h. After cooling to r.t., the mixture was diluted with Et₂O (20 mL) and filtered through a plug of silica gel, which was washed by Et₂O. After evaporation of the solvents, the crude product was purified by column chromatography (hexane/EtOAc, 5:1, gradient to 1:1) to yield 67 mg (97%) of an inseparable 1.4:1 diastereoisomeric mixture of **43m** as a thick colorless oil.

Major diastereoisomer:

$R_F = 0.50$ (hexanes/EtOAc, 1:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.39-7.27 (m, 5H, CH_{Ar}), 5.82-5.59 (m, 2H, CH-5, CH-9), 5.07-4.83 (m, 4H, CH₂-6, CH₂-10), 4.68 (d, $J = 6.7$ Hz, 1H, CH-1), 3.79-3.72 (m, 1H, CH-2), 2.96 (bs, 2H, OH), 2.37-2.23 (m, 1H, CH₂-4^a), 2.21-1.85 (m, 3H, CH₂-4^b, CH₂-8

), 1.56-1.33 (m, 3H, CH-3, CH₂-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.40 (C_{Ar}), 138.5 (C-5), 137.5 (C-9), 128.68 (CH_{Ar}), 128.2 (CH_{Ar}), 126.90 (CH_{Ar}), 116.4 (C-6), 114.8 (C-10), 77.1 (C-2), 75.4 (C-1), 38.06 (C-3), 33.3 (C-4), 31.2 (C-8), 29.7 (C-7). **MS** (ESI+) *m/z* (%): 269 ([M+Na⁺], 100). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₁₆H₂₂O₂Na: 269.1512; found: 269.1509. **IR** (neat): ν_{max} = 3371, 3075, 2975, 2924, 2856, 1640, 1454, 1197, 1049, 995, 910, 845, 761, 701, 637 cm⁻¹.

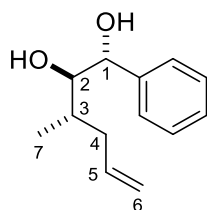
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.39-7.27 (m, 5H, CH_{Ar}), 5.82-5.59 (m, 2H, CH-5, CH-9), 5.07-4.83 (m, 4H, CH₂-6, CH₂-10), 4.66 (d, *J* = 6.7 Hz, 1H, CH-1), 3.79-3.72 (m, 1H, CH-2), 2.96 (bs, 2H, OH), 2.20-1.85 (m, 4H, CH₂-4, CH₂-8), 1.61 (tdd, *J* = 10.1, 7.1, 3.5 Hz, 1H, CH₂-7^a), 1.46-1.34 (m, 1H, CH₂-7^b), 1.27-1.18 (m, 1H, CH-3). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.37 (C_{Ar}), 138.8 (C-5), 136.9 (C-9), 128.66 (CH_{Ar}), 128.2 (CH_{Ar}), 126.93 (CH_{Ar}), 116.6 (C-6), 114.7 (C-10), 77.2 (C-2), 75.2 (C-1), 38.14 (C-3), 35.2 (C-4), 31.5 (C-8), 27.6 (C-7).

(1*R,2*R**,3*S**)- and (1*R**,2*R**,3*R**)-3-Methyl-1-phenylhex-5-ene-1,2-diol (43n)**

In a 25 mL round-bottomed flask, the 1.4:1 diastereoisomeric mixture of **42n** (100 mg, 0.29 mmol) was dissolved in a 1:1 THF/H₂O mixture (4.4 mL). Acetic acid (7.0 mL) and Zn dust (758 mg, 11.6 mmol) were added. The mixture was stirred at 60 °C for 1 h. After cooling to r.t., the mixture was diluted with Et₂O (20 mL) and filtered through a plug of silica gel, which was washed by Et₂O. After evaporation of the solvents, the crude product was purified by column chromatography (hexane/EtOAc, 2:1) to yield 50 mg (83%) of **43n** as an inseparable 1.4:1 diastereoisomeric mixture as a thick colorless oil.

Major diastereoisomer:

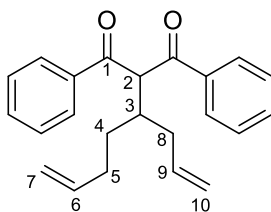


R_F = 0.54 (hexanes/EtOAc, 1:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.27 (m, 5H, CH_{Ar}), 5.65 (ddt, *J* = 17.4, 10.4, 7.1 Hz, 1H, CH-5), 5.05-4.93 (m, 2H, CH₂-6), 4.60 (d, *J* = 7.6 Hz, 1H, CH-1), 3.67 (dd, *J* = 7.6, 3.0 Hz, 1H, CH-2), 2.96 (bs, 1H, OH), 2.62 (bs, 1H, OH), 2.14 (dt, *J* = 13.9, 6.9 Hz, 1H, CH₂-4^a), 2.04-1.93 (m, 1H, CH₂-4^b), 1.40 (sextd, *J* = 6.9, 3.0 Hz, 1H, CH-3), 0.93 (d, *J* = 6.9 Hz, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 141.2 (C_{Ar}), 137.1 (C-5), 128.72 (CH_{Ar}), 128.68 (CH_{Ar}), 127.0 (CH_{Ar}), 116.40 (C-6), 78.1 (C-2), 75.8 (C-1), 39.0 (C-4), 33.6 (C-3), 13.2 (C-7). **MS** (ESI+) *m/z* (%): 229 ([M+Na⁺], 100). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₁₃H₁₈O₂Na: 229.1199; found: 229.1197. **IR** (neat): ν_{max} = 3384, 3065, 3030, 2970, 2928, 2912, 1640, 1494, 1455, 1378, 1198, 1062, 989, 911, 841, 762, 701 cm⁻¹.

Minor diastereoisomer:

¹H NMR (401 MHz, Chloroform-*d*) δ 7.40-7.27 (m, 5H, CH_{Ar}), 5.76 (dddd, *J* = 16.7, 10.1, 8.0, 6.3 Hz, 1H, CH-5), 5.05-4.93 (m, 2H, CH₂-6), 4.72 (d, *J* = 5.1 Hz, 1H, CH-1), 3.52 (t, *J* = 5.4 Hz, 1H, CH-2), 2.79 (bs, 1H, OH), 2.49 (bs, 1H, OH), 2.39-2.28 (m, 1H, CH₂-4^a), 2.08-1.94 (m, 1H, CH₂-4^b), 1.72-1.62 (m, 1H, CH-3), 0.97 (d, *J* = 6.9 Hz, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 142.0 (C_{Ar}), 137.3 (C-5), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 126.6 (CH_{Ar}), 116.35 (C-6), 79.8 (C-2), 74.4 (C-1), 36.1 (C-4), 34.6 (C-3), 16.7 (C-7).

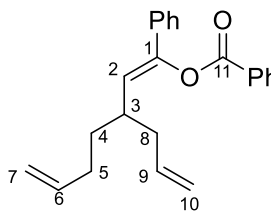
2-(Octa-1,7-dien-4-yl)-1,3-diphenylpropane-1,3-dione (**44m**)



In a flame-dried Schlenk flask, KH (50% wax suspension, 96 mg, 1.20 mmol) was washed by hot DME (3x) and suspended in DME (20 mL). At r.t., alcohol **25m** (69 mg, 0.3 mmol) was dropwise added. The mixture was stirred at 50 °C for 1.5 h, and LiCl (76 mg, 18 mmol) was added. The mixture was stirred for 10 min, cooled to –61 °C in a dry ice/CHCl₃ cooling bath, and benzoyl cyanide (59 mg, 0.45 mmol) was added. The mixture was stirred for 3 h, quenched by saturated NH₄Cl solution (10 mL), and extracted with Et₂O (3×10 mL). The combined organic layers were washed with brine (20 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/EtOAc, 20:1) to give 91 mg (91%) of **44m** as a colorless oil.

R_F = 0.28 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.84-7.77 (m, 4H, CH_{Ar}), 7.58-7.50 (m, 2H, CH_{Ar}), 7.31-7.24 (m, 4H, CH_{Ar}), 5.79 (ddt, J = 17.2, 10.2, 7.2 Hz, 1H, CH-9), 5.67 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H, CH-6), 5.44 (d, J = 8.0 Hz, 1H, CH-2), 5.08-4.84 (m, 4H, CH₂-7, CH₂-10), 2.81-2.71 (m, 1H, CH-3), 2.33-2.19 (m, 2H, CH₂-8), 2.18-1.96 (m, 2H, CH₂-5), 1.63-1.42 (m, 2H, CH₂-4). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 196.1 (C-1), 195.8 (C-1), 138.3 (C-9), 137.3 (C_{Ar}), 137.0 (C_{Ar}), 135.8 (C-6), 133.54 (CH_{Ar}), 133.51 (CH_{Ar}), 128.95 (CH_{Ar}), 128.93 (CH_{Ar}), 128.73 (CH_{Ar}), 128.70 (CH_{Ar}), 117.9 (C-10), 115.0 (C-7), 59.8 (C-2), 38.7 (C-3), 35.4 (C-8), 31.4 (C-4), 30.1 (C-5).

(*Z*)-3-Allyl-1-phenylhepta-1,6-dien-1-yl benzoate (**45m**)

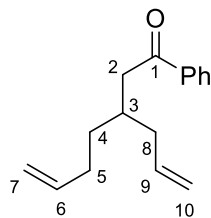


In a flame-dried Schlenk flask, alcohol **25m** (23 mg, 0.1 mmol) was dissolved in DME (2.0 mL). At 0 °C, KHMDS (1M in THF, 0.2 mL, 0.2 mmol) was dropwise added. The mixture was stirred at 50 °C for 1.5 h, cooled to 0 °C, and benzoyl chloride (13 μ L, 0.11 mmol) was added. The mixture was stirred at r.t. for 2.5 h, quenched by 10 drops of saturated NH₄Cl solution, diluted with Et₂O, filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/EtOAc, 20:1) to give 20 mg (61%) of **45m** as a colorless oil. The *Z*-double bond configuration results from the AOC transition state.

R_F = 0.77 (toluene). **¹H NMR** (400 MHz, Chloroform-*d*) δ 8.23-8.16 (m, 2H, CH_{Ar}), 7.65 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.52 (t, J = 7.6 Hz, 2H, CH_{Ar}), 7.49-7.43 (m, 2H, CH_{Ar}), 7.37-7.28 (m, 3H, CH_{Ar}), 5.88-5.72 (m, 2H, CH-6, CH-9), 5.68 (d, J = 10.1 Hz, 1H, CH-2), 5.10-4.85 (m, 4H, CH₂-7, CH₂-10), 2.63-2.48 (m, 1H, CH-3), 2.29-2.11 (m, 3H, CH₂-8, CH₂-5^a), 2.10-1.98 (m, 1H, CH₂-5^b), 1.69-1.37 (m, 2H, CH₂-4). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 166.5 (C-11), 146.9 (C-1), 138.8 (C-9), 136.5 (C-6), 135.2 (C_{Ar}), 133.7 (CH_{Ar}), 130.3 (CH_{Ar}), 129.6 (C_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (CH_{Ar}), 124.7 (CH_{Ar}), 122.3 (C-2), 116.4 (C-10), 114.6 (C-7), 39.6 (C-8), 36.3 (C-3), 34.0 (C-4), 31.7 (C-5). **MS** (ESI+) m/z (%) 355 ([M+Na⁺], 80), 333 ([M+H⁺], 30), 211 ([M-PhCO₂H+H⁺], 100). **HRMS** (ESI+)

m/z $[M+Na^+]$ calcd for $C_{23}H_{24}O_2Na$: 355.1669; found: 355.1671. **IR** (neat): ν_{max} = 3074, 2976, 2922, 2852, 1686, 1639, 1600, 1494, 1449, 1239, 1176, 1086, 1066, 1025, 993, 909, 757, 708, 690 cm^{-1} .

3-Allyl-1-phenylhept-6-en-1-one (27m)

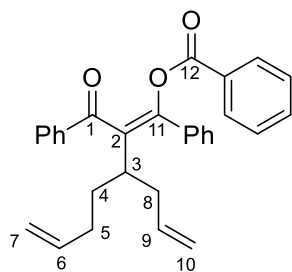


In a flame-dried Schlenk flask, alcohol **25m** (46 mg, 0.2 mmol) was dissolved in DME (4.0 mL). At 0 °C, KHMDS (1M in THF, 0.4 mL, 0.4 mmol) was dropwise added. The mixture was stirred at 50 °C for 1 h, quenched by 10 drops of saturated NH_4Cl solution, diluted with Et_2O , filtered through a plug of silica gel, which was washed by Et_2O . The solvents were evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/ $EtOAc$, 20:1)

to give 45 mg (99%) of **27m** as a colorless oil.

R_F = 0.53 (hexanes/ $EtOAc$, 10:1). **^1H NMR** (400 MHz, Chloroform- d) δ 7.97-7.92 (m, 2H, CH_{Ar}), 7.58-7.53 (m, 1H, CH_{Ar}), 7.49-7.43 (m, 2H, CH_{Ar}), 5.86-5.71 (m, 2H, CH-6, CH-9), 5.08-4.90 (m, 4H, CH_2 -7, CH_2 -10), 2.96 (dd, J = 16.5, 6.4 Hz, 1H, CH_2 -2^a), 2.85 (dd, J = 16.5, 6.5 Hz, 1H, CH_2 -2^b), 2.32-2.15 (m, 2H, CH-3, CH_2 -8^a), 2.15-2.04 (m, 3H, CH_2 -8^b, CH_2 -5), 1.52-1.40 (m, 2H, CH_2 -4). **^{13}C NMR** (101 MHz, Chloroform- d) δ 200.3 (C-1), 138.7 (C-9), 137.6 (C_{Ar}), 136.5 (C-6), 133.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (CH_{Ar}), 117.0 (C-10), 114.7 (C-7), 42.7 (C-2), 38.3 (C-8), 33.5 (C-3), 33.3 (C-4), 31.2 (C-5). **MS** (ESI+) m/z (%) 251 ($[M+Na^+]$, 100), 229 ($[M+H^+]$, 50). **HRMS** (ESI+) m/z $[M+H^+]$ calcd for $C_{16}H_{21}O$: 229.1587; found: 229.1587. **IR** (neat): ν_{max} = 3038, 2985, 2932, 2863, 1688, 1645, 1603, 1453, 1372, 1283, 1218, 998, 913, 753, 692, 601 cm^{-1} .

(Z) or (E)-3-Allyl-2-benzoyl-1-phenylhepta-1,6-dien-1-yl benzoate (46m)



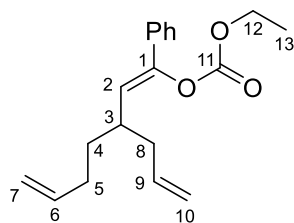
In a flame-dried Schlenk flask, alcohol **25m** (46 mg, 0.2 mmol) was dissolved in DME (4.0 mL). At 0 °C, KHMDS (1M in THF, 0.4 mL, 0.4 mmol) was dropwise added. The mixture was stirred at 50 °C for 1.5 h, cooled to 0 °C, and benzoyl cyanide (31 mg, 0.24 mmol) was added. The mixture was stirred at r.t. for 2.5 h, and another portion of benzoyl cyanide (16 mg, 0.12 mmol) was added. The mixture was stirred at r.t. for 2 h, quenched by 10 drops of saturated NH_4Cl solution, diluted with Et_2O ,

filtered through a plug of silica gel, which was washed by Et_2O . The solvents were evaporated at reduced pressure to give the crude product that was separated by column chromatography (hexane/ $EtOAc$, 20:1) to give 17 mg (37%) of the rearranged ketone **27m**, followed by 8 mg (9%) of the dibenzoylated product **46m**, followed by 28 mg (42%) of the monobenzoylated product **44m** as colorless oils. Double bond configuration was not assigned but is presumably *E* because of potassium chelation between the two carbonyl groups.

R_F = 0.33 (hexanes/ $EtOAc$, 10:1). **^1H NMR** (400 MHz, Chloroform- d) δ 8.23-8.18 (m, 2H, CH_{Ar}), 8.00-7.95 (m, 2H, CH_{Ar}), 7.70-7.64 (m, 1H, CH_{Ar}), 7.54 (dd, J = 8.4, 7.1 Hz, 2H, CH_{Ar}), 7.36-7.19 (m, 5H, CH_{Ar}), 7.10-7.03 (m, 3H, CH_{Ar}), 5.88-5.78 (m, 1H, CH-9), 5.78-5.69 (m, 1H, CH-6), 5.06-4.80 (m, 4H,

CH₂-7, CH₂-10), 2.90 (dtd, $J = 8.8, 7.4, 5.9$ Hz, 1H, CH-3), 2.57-2.43 (m, 1H, CH₂-8^a), 2.35-2.05 (m, 3H, CH₂-8^b, CH₂-5), 1.86-1.71 (m, 1H, CH₂-4^a), 1.68-1.51 (m, 1H, CH₂-4^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 197.6 (C-1), 165.2 (C-12), 149.2 (C-11), 138.6 (C-9), 137.4 (C_{Ar}), 137.1 (C-6), 135.3 (C_{Ar}), 134.0 (CH_{Ar}), 133.0 (CH_{Ar}), 132.2 (C-2), 130.4 (CH_{Ar}), 130.0 (CH_{Ar}), 129.3 (CH_{Ar}), 129.3 (C_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 116.7 (C-10), 114.8 (C-7), 40.9 (C-3), 37.9 (C-8), 32.2 (C-5), 32.1 (C-4). IR (neat): $\nu_{\max} = 3074, 2976, 2922, 2852, 1686, 1639, 1560, 1494, 1449, 1239, 1176, 1086, 1066, 1024, 993, 909, 757, 708, 690$ cm⁻¹.

(Z)-3-Allyl-1-phenylhepta-1,6-dien-1-yl ethyl carbonate (47m)

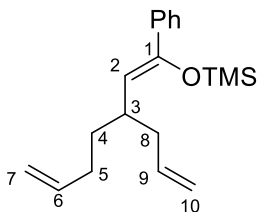


In a flame-dried Schlenk flask, alcohol **25m** (46 mg, 0.2 mmol) was dissolved in DME (4.0 mL). At 0 °C KHMDS (1M in THF, 0.6 mL, 0.6 mmol) was dropwise added. The mixture was stirred at 50 °C for 1.5 h, cooled to r.t. and LiCl (50 mg, 1.18 mmol) was added. The mixture was stirred for 30 min, cooled to 0 °C, and ethyl chloroformate (40 μ L, 0.42 mmol) was added. The mixture was stirred at 50 °C for 3 h, quenched by

10 drops of saturated NH₄Cl solution, diluted with Et₂O, and filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/toluene, 4:1, gradient to 1:1) to yield 50 mg (83%) of **47m** followed by 9 mg (15%) of the silyl enol ether **29m** as colorless oils.

$R_F = 0.50$ (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.47-7.41 (m, 2H, CH_{Ar}), 7.38-7.27 (m, 3H, CH_{Ar}), 5.88-5.75 (m, 2H, CH-6, CH-9), 5.53 (d, $J = 10.1$ Hz, 1H, CH-2), 5.11-4.92 (m, 4H, CH₂-7, CH₂-10), 4.24 (q, $J = 7.1$ Hz, 2H, CH₂-12), 2.72-2.58 (m, 1H, CH-3), 2.31-1.99 (m, 4H, CH₂-5, CH₂-8), 1.70-1.57 (m, 1H, CH₂-4^a), 1.50-1.37 (m, 1H, CH₂-4^b), 1.33 (t, $J = 7.1$ Hz, 3H, CH₃-13). ¹³C NMR (101 MHz, Chloroform-*d*) δ 153.1 (C-11), 147.0 (C-1), 138.7 (C-9), 136.4 (C-6), 135.1 (C_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 124.7 (CH_{Ar}), 122.3 (C-2), 116.5 (C-10), 114.6 (C-7), 64.8 (C-12), 39.5 (C-8), 36.0 (C-3), 33.9 (C-4), 31.6 (C-5), 14.3 (C-13). MS (ESI+) m/z (%) 323 ([M+Na⁺], 30), 211 ([M-EtOCO₂H+H⁺], 100). HRMS (ESI+) m/z [M+Na⁺] calcd for C₁₉H₂₄O₃Na: 323.1617; found: 323.1619. IR (neat): $\nu_{\max} = 3076, 2978, 2925, 1758, 1686, 1640, 1447, 1370, 1224, 1185, 995, 909, 767, 751, 691$ cm⁻¹.

(Z)-((3-Allyl-1-phenylhepta-1,6-dien-1-yl)oxy)trimethylsilane (29m)



In a flame-dried Schlenk flask, alcohol **25m** (69 mg, 0.3 mmol) was dissolved in DME (6.0 mL). At 0 °C, KHMDS (1M in THF, 1.0 mL, 1.0 mmol) was dropwise added. The mixture was stirred at 50 °C for 1.5 h, and LiCl (76 mg, 1.8 mmol) was added. The mixture was stirred for 20 min, cooled to -61 °C in a dry ice/CHCl₃ cooling bath, and benzoyl cyanide (79 mg, 0.6 mmol) was added. The mixture was stirred for 3 h, quenched by H₂O (20 mL), warmed to r.t., and extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were washed with brine (20 mL),

dried by MgSO₄, filtered, and evaporated at reduced pressure to give the crude product that was separated by column chromatography (hexane/EtOAc, 20:1) to give 43 mg (48%) of the silyl enol ether **29m** and 39 mg (39%) of the diketone **44m** as colorless oils. *Z*-double bond configuration results from the AOC transition state.

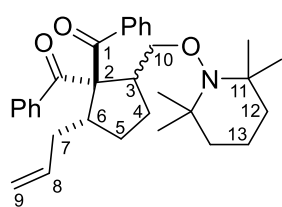
*R*_F = 0.80 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.47 (dt, *J* = 6.3, 1.4 Hz, 2H, CH_{Ar}), 7.36-7.22 (m, 3H, CH_{Ar}), 5.86 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 2H, CH-6, CH-9), 5.11-4.92 (m, 5H, CH₂-7, CH₂-10, CH-2), 2.77-2.63 (m, 1H, CH-3), 2.27-2.01 (m, 4H, CH₂-5, CH₂-8), 1.68-1.53 (m, 1H, CH₂-4^a), 1.43-1.30 (m, 1H, CH₂-4^b), 0.14 (s, 9H, TMS). ¹³C NMR (101 MHz, Chloroform-*d*) δ 149.6 (C-1), 139.6 (C_{Ar}), 139.4 (C-9), 137.3 (C-6), 128.1 (CH_{Ar}), 127.6 (CH_{Ar}), 125.8 (CH_{Ar}), 115.9 (C-10), 115.7 (C-2), 114.3 (C-7), 40.1 (C-8), 35.6 (C-3), 34.6 (C-4), 31.8 (C-5), 0.9 (TMS). MS (EI) *m/z* (%) 300 ([M]⁺, 20), 259 ([M-allyl]⁺, 100), 120 ([acetophenone]⁺, 95). HRMS (EI) *m/z* [M]⁺ calcd for C₁₉H₂₈OSi: 300.1909; found: 300.1911. IR (neat): ν_{max} = 3077, 2958, 2923, 2852, 1640, 1492, 1446, 1356, 1315, 1283, 1251, 1065, 1026, 993, 908, 886, 837, 754, 695 cm⁻¹.

Radical cyclization of 1,3-dione **44m**

In a flame-dried Schlenk flask, diketone **44m** (83 mg, 0.25 mmol) was dissolved in DME (5.0 mL). The mixture was cooled to -78 °C, and KHMDS (1M in THF, 0.3 mL, 0.3 mmol) was dropwise added. The mixture was stirred for 20 min, warmed to 0 °C, and ferrocene (9 mg, 0.05 mmol) was added. The mixture was stirred for 10 min, and 2,2,6,6-tetramethyl-*N*-oxopiperidinium tetrafluoroborate (117 mg, 0.48 mmol) was added portion-wise. The mixture was stirred for 30 min, quenched by 13 drops H₂O, diluted with Et₂O (10 mL), and filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated to give the crude mixture that was purified by multiple column chromatography (hexane/Et₂O, 30:1) and (toluene/hexane, 5:1) to give in total 63 mg (52%) of **48m** as a 5:1 mixture of inseparable diastereoisomers as a thick colorless oil and 15 mg (12%) of **48ma** as a single diastereoisomer as a colorless solid. The configuration of formed products was not analyzed. Because of signal overlaps and a low ratio in the diastereoisomeric mixture, the minor isomer of cyclopentane **48m** was not characterized.

(2*R**,5*S**)- and (2*R**,5*R**)-2-Allyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)cyclopentane-1,1-diylbis(phenylmethanone) (**48m**)

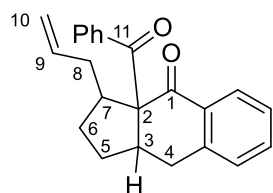
Major diastereoisomer:



*R*_F = 0.33 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 7.7 Hz, 2H, CH_{Ar}), 7.50 (d, *J* = 8.1 Hz, 2H, CH_{Ar}), 7.16-6.92 (m, 6H, CH_{Ar}), 5.50 (dddd, *J* = 16.4, 10.3, 8.1, 5.7 Hz, 1H, CH-8), 4.77-4.62 (m, 2H, CH₂-9) 3.37 (dd, *J* = 8.5, 5.1 Hz, 1H, CH₂-10^a), 3.28-3.18 (m, 1H, CH-3), 3.09 (t, *J* = 8.9 Hz, 1H, CH₂-10^b), 2.99-2.87 (m, 1H, CH-6), 2.16-2.02 (m, 2H, CH₂-7^a, CH₂-4^a), 1.89-1.76 (m, 1H, CH₂-5^a), 1.50-1.38 (m, 1H, CH₂-4^b), 1.31-0.92 (m, 8H, CH₂-7^b, CH₂-5^b, CH₂-12, CH₂-13), 0.78 (bs, 3H, CH₃^{TEMPO}), 0.70 (bs, 3H, CH₃^{TEMPO}), 0.65 (bs, 3H,

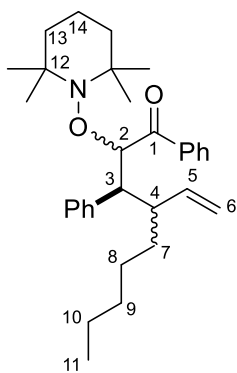
CH₃^{TEMPO}), 0.59 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 198.7 (C-1), 198.0 (C-1), 137.8 (C_{Ar}), 137.7 (C_{Ar}), 137.2 (C-8), 132.3 (2CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 128.0 (CH_{Ar}), 128.0 (CH_{Ar}), 115.6 (C-9), 77.6 (C-10), 74.1 (C-2), 59.4 (C-11), 59.2 (C-11), 46.6 (C-3), 45.2 (C-6), 39.2 (C-12), 36.8 (C-7), 32.7 (CH₃^{TEMPO}), 32.3 (CH₃^{TEMPO}), 28.0 (C-5), 27.7 (C-4), 19.8 (CH₃^{TEMPO}), 19.7 (CH₃^{TEMPO}), 16.7 (C-13). **MS** (ESI+) *m/z* (%) 488 ([M+H⁺], 100), 331 ([M-TEMPOH+H⁺], 65). **HRMS** (ESI+) *m/z* [M+H⁺] calcd for C₃₂H₄₂O₃N: 488.3159; found: 488.3160.

(3*R,3*aS**,9*aS**)-3-Allyl-3*a*-benzoyl-1,2,3,3*a*,9,9*a*-hexahydro-4*H*-cyclopenta[*b*]naphthalen-4-one (48ma)**



R_F = 0.33 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.93-7.87 (m, 2H, CH_{Ar}), 7.76 (dd, *J* = 8.2, 1.5 Hz, 1H, CH_{Ar}), 7.50-7.42 (m, 2H, CH_{Ar}), 7.34 (dd, *J* = 8.5, 7.0 Hz, 2H, CH_{Ar}), 7.23-7.16 (m, 2H, CH_{Ar}), 5.71 (dddd, *J* = 16.4, 10.4, 7.9, 5.7 Hz, 1H, CH-9), 5.04-4.94 (m, 2H, CH₂-10), 3.52 (dd, *J* = 18.1, 6.5 Hz, 1H, CH₂-4^a), 3.50-3.45 (m, 1H, CH-7), 3.31 (dtd, *J* = 10.5, 6.9, 3.3 Hz, 1H, CH-3), 2.93 (dd, *J* = 18.1, 3.3 Hz, 1H, CH₂-4^b), 2.16-1.85 (m, 4H, CH₂-8, CH₂-5^a, CH₂-6^a), 1.73-1.62 (m, 1H, CH₂-6^b), 1.48-1.36 (m, 1H, CH₂-5^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 197.6 (C-11), 196.9 (C-1), 141.6 (C_{Ar}), 137.0 (C-9), 136.7 (C_{Ar}), 134.1 (CH_{Ar}), 132.8 (CH_{Ar}), 132.3 (C_{Ar}), 129.6 (CH_{Ar}), 129.5 (CH_{Ar}), 128.4 (CH_{Ar}), 127.9 (CH_{Ar}), 126.6 (CH_{Ar}), 116.4 (C-10), 72.5 (C-2), 44.1 (C-7), 41.5 (C-3), 35.9 (C-8), 29.2 (C-4), 28.3 (C-5), 27.7 (C-6). **MS** (ESI+) *m/z* (%) 353 ([M+Na⁺], 100), 331 ([M+H⁺], 30). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₂₃H₂₂O₂Na: 353.1512; found: 353.1512.

(2*S,3*S**,4*S**) and (2*S**,3*S**,4*R**) and (2*S**,3*R**,4*S**) and (2*R**,3*S**,4*S**)-1,3-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-4-vinylnonan-1-one (28y)**

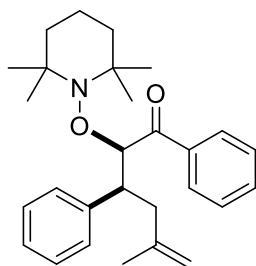


In a flame-dried Schlenk flask, oct-1-ene (0.39 mL, 2.5 mmol) was dissolved in THF (2.0 mL). At -78 °C *n*BuLi (1.6M in hexane, 0.34 mL, 0.54 mmol) and *t*BuOK (1M in THF, 0.58 mL, 0.58 mmol) were dropwise added. The mixture was warmed to -25 °C over 30 min, cooled back to -78 °C, and diluted by THF (8.0 mL). Chalcone (104 mg, 0.5 mmol) was added in small portions, which led to a color change from orange via green to colorless and yellow. The mixture was warmed to r.t. over 1 h then to 50 °C for 20 min. After cooling to -78 °C, TEMPO (86 mg, 0.55 mmol) was added, and after complete dissolution, Cp₂Fe⁺PF₆⁻ (200 mg, 0.60 mmol) was added in small portions (~30 mg/30 s) until the mixture remained dark blue. The mixture was stirred for an additional 10 min, quenched by 10 drops of saturated NH₄Cl solution, diluted with Et₂O (25 mL), filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give the crude products that were purified by column chromatography (neat hexane, gradient to 10:1 hexane/Et₂O) to yield 133 mg (56%)

of **28y** as an inseparable approximately ~2:1.6:1.2:1 diastereoisomeric mixture. Traces of the linear oct-2-en-1-yl group in the β -position were detectable.

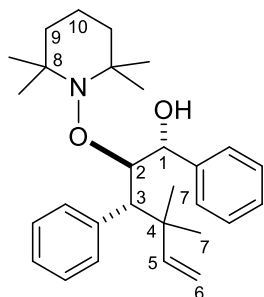
$R_F = 0.59$ (hexanes/EtOAc, 10:1). ^{13}C NMR (101 MHz, Chloroform- d) δ 202.82 (C-1), 202.80 (C-1), 202.2 (C-1), 202.1 (C-1), 141.8 (C-5), 141.4 (C-5), 140.6 (C-5), 140.4 (C-5), 139.9 (C_{Ar}), 139.84 (C_{Ar}), 139.80 (C_{Ar}), 139.78 (C_{Ar}), 139.75 (C_{Ar}), 139.6 (C_{Ar}), 139.5 (C_{Ar}), 139.0 (C_{Ar}), 132.9-126.4 (24 $\times$ CH_{Ar}), 116.44 (C-6), 116.38 (2C-6), 115.7 (C-6), 86.99 (C-2), 86.96 (C-2), 83.5 (C-2), 83.00 (C-2), 61.24 (C-12), 61.16 (C-12), 60.5 (C-12), 60.1 (C-12), 59.8 (C-12), 59.6 (C-12), 53.7 (C-3), 53.3 (C-3), 49.6 (C-3), 49.5 (C-3), 45.9 (C-4), 44.5 (C-4), 44.1 (C-4), 43.6 (C-4), 41.12 (C-13), 41.08 (C-13), 40.94 (C-13), 40.90 (C-13), 40.73 (C-13), 40.66 (C-13), 40.5 (C-13), 40.4 (C-13), 34.5 (CH₃^{TEMPO}), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 34.0 (CH₃^{TEMPO}), 33.9 (CH₃^{TEMPO}), 33.2 (CH₂), 32.5 (CH₂), 32.3 (CH₂), 31.91 (CH₂), 31.86 (CH₂), 31.6 (CH₂), 31.2 (CH₂), 30.4 (CH₂), 27.5 (CH₂), 27.1 (CH₂), 27.0 (CH₂), 26.7 (CH₂), 22.8 (CH₂), 22.7 (CH₂), 22.64 (CH₂), 22.55 (CH₂), 21.0 (CH₃^{TEMPO}), 20.7 (CH₃^{TEMPO}), 20.6 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 20.33 (CH₃^{TEMPO}), 20.29 (CH₃^{TEMPO}), 19.9 (CH₃^{TEMPO}), 19.7 (CH₃^{TEMPO}), 17.2 (C-14), 17.11 (C-14), 17.08 (C-14), 17.0 (C-14), 14.3 (C-11), 14.2 (C-11), 14.11 (C-11), 14.08 (C-11). Characteristic and detectable resonances of the diastereoisomeric mixture are displayed. Because of overlapping signals, the ^1H NMR spectrum of the diastereoisomeric mixture is indecipherable. MS (ESI+) m/z (%) 498 ([M+Na⁺], 5), 476 ([M+H⁺], 100). HRMS (ESI+) m/z [M+H⁺] calcd for C₃₂H₄₆O₂N: 476.3523; found: 476.3525. IR (neat): $\nu_{\text{max}} = 3063, 3005, 2927, 2870, 1687, 1597, 1466, 1449, 1377, 1362, 1255, 1206, 1180, 1029, 1012, 971, 957, 912, 758, 698, 620\text{ cm}^{-1}$.

(2*S**,3*S**) and (2*S**,3*R**)-5-Methyl-1,3-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-one (**28b**)



Unoptimized procedure: A flame-dried Schlenk flask charged with THF (2.0 mL) was weighed and cooled to $-78\text{ }^{\circ}\text{C}$. Isobutylene was bubbled through the solvent for 30 s, and the flask was weighed, showing approximately 5 g of isobutylene. At $-78\text{ }^{\circ}\text{C}$ $n\text{BuLi}$ (1.6M in hexane, 0.34 mL, 0.54 mmol) and $t\text{BuOK}$ (1M in THF, 0.58 mL, 0.58 mmol) were successively dropwise added. The mixture was warmed to $-20\text{ }^{\circ}\text{C}$ over 20 min, cooled back to $-78\text{ }^{\circ}\text{C}$, and chalcone (104 mg, 0.5 mmol) was added in small portions. A color change from orange via green and colorless to yellow was observed. The mixture was gradually warmed to r.t. over 1 h and finally stirred at $50\text{ }^{\circ}\text{C}$ for 1 h. At r.t. TEMPO (86 mg, 0.55 mmol) was added, the mixture was cooled to $-78\text{ }^{\circ}\text{C}$, and $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ (265 mg, 0.80 mmol) was added in small portions (~50 mg/30 s) until the mixture remained dark blue. The mixture was stirred for additional 10 min, quenched by 10 drops of saturated NH_4Cl solution, diluted with Et_2O (25 mL), filtered through a plug of silica gel, which was washed by Et_2O . The solvents were evaporated at reduced pressure to give the crude product that was purified by column chromatography (neat hexane, gradient to 10:1 hexane/ Et_2O) to yield 13 mg (6%) of **28b** as an inseparable 3:1 diastereoisomeric mixture as a colorless oil. For compound characterization *vide supra*.

(1*R,2*R**,3*R**)-4,4-Dimethyl-1,3-diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-5-en-1-ol (*major-42d*)**



In a flame-dried Schlenk flask, α -aminoxy ketone **28d** (4:1 *dr*, 16 mg, 0.04 mmol) was dissolved in THF (2 mL). At $-78\text{ }^{\circ}\text{C}$ Super-Hydride[®] solution (0.16 mL, 0.16 mmol, 1M in THF) was added slowly. The mixture was warmed to r.t. and stirred overnight. The mixture was quenched by MeOH (0.1 mL) and H₂O (0.1 mL), diluted by Et₂O (20 mL), filtered through a thick plug of silica gel, which was washed by Et₂O. The solvent was evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/Et₂O, 20:1, gradient to 5:1) to yield 3.2 mg (quant.)

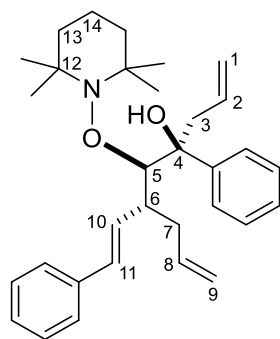
of unreacted minor diastereoisomer **minor-28d** followed by 8 mg (50%) of a single diastereoisomer of the reduced major diastereoisomer **major-42d** as a colorless oil.

R_F = 0.30 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.61 (s, 1H, OH), 7.42-7.14 (m, 10H, CH_{Ar}), 5.85 (dd, J = 17.4, 10.8 Hz, 1H, CH-5), 4.97 (dd, J = 10.8, 1.3 Hz, 1H, CH₂-6), 4.92 (dd, J = 17.5, 1.4 Hz, 1H, CH₂-6), 4.80 (dd, J = 9.4, 1.4 Hz, 1H, CH-2), 4.62 (d, J = 9.4 Hz, 1H, CH-1), 2.18 (d, J = 1.3 Hz, 1H, CH-3), 1.71-1.40 (m, 6H, CH₂-9, CH₂-10), 1.61 (s, 3H, CH₃^{TEMPO}), 1.37 (s, 3H, CH₃^{TEMPO}), 1.25 (s, 3H, CH₃^{TEMPO}), 1.07 (s, 3H, CH₃^{TEMPO}), 1.01 (s, 3H, CH₃-7), 0.71 (s, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 148.3 (C-5), 142.2 (C_{Ar}), 137.8 (C_{Ar}), 128.6 (2CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 127.0 (CH_{Ar}), 126.6 (CH_{Ar}), 111.6 (C-6), 84.0 (C-2), 79.0 (C-1), 62.0 (C-8), 60.7 (C-8), 56.9 (C-3), 41.3 (C-9), 41.0 (C-9), 40.6 (C-4), 34.0 (CH₃^{TEMPO}), 31.3 (CH₃^{TEMPO}), 29.1 (C-7), 24.1 (C-7), 21.44 (CH₃^{TEMPO}), 21.40 (CH₃^{TEMPO}), 17.1 (C-10). MS (ESI+) m/z (%): 458 ([M+Na⁺], 50), 436 ([M+H⁺], 100). HRMS (ESI+) m/z [M+H⁺] calcd for C₂₉H₄₂NO₂: 436.3210; found: 436.3209. IR (neat): ν_{max} = 3420, 3083, 3061, 3027, 2931, 1492, 1453, 1413, 1382, 1365, 1339, 1257, 1179, 1132, 1027, 908, 761, 701 cm⁻¹.

(4*R,5*R**,6*R**)- and (4*S**,5*R**,6*R**)-4-Phenyl-6-((*E*)-styryl)-5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)nona-1,8-dien-4-ol (**40k**)**

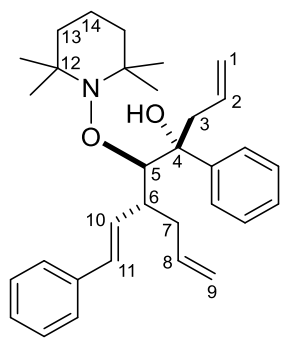
In a flame-dried Schlenk flask, the separated minor diastereoisomer **minor-28k** (12 mg, 0.027 mmol) was dissolved in THF (1 mL). At $-78\text{ }^{\circ}\text{C}$ allylmagnesium bromide (0.1 mL, 0.1 mmol, 1M in Et₂O) was dropwise added. The mixture was stirred for 10 min, quenched by saturated NH₄Cl solution (5 drops), diluted with Et₂O (10 mL), and filtered through a plug of silica gel, which was washed by Et₂O. The solvent was evaporated, and the crude product was purified by column chromatography (neat hexane, gradient to 10:1 hexane/EtOAc) to yield 7.5 mg of the major diastereoisomer **40k-major** as an off-white solid followed by 5.3 mg of the minor diastereoisomer **40k-minor** as a colorless oil. Yield 12.8 mg (99%) of **40k** in a 1.4:1 diastereoisomeric ratio. The major diastereoisomer was recrystallized from hexane for X-ray diffraction analysis.

Major diastereoisomer:



$R_F = 0.42$ (hexanes/EtOAc, 10:1). **m.p.** 116-118 °C. **$^1\text{H NMR}$** (401 MHz, Chloroform-*d*) δ 7.43-7.38 (m, 2H, CH_{Ar}), 7.36-7.30 (m, 2H, CH_{Ar}), 7.30-7.21 (m, 3H, CH_{Ar}), 7.18-7.13 (m, 1H, CH_{Ar}), 7.09-7.04 (m, 2H, CH_{Ar}), 6.19 (d, $J = 15.9$ Hz, 1H, CH-11), 5.55-5.38 (m, 2H, CH-2, CH-8), 4.99 (bs, 1H, CH-10), 4.98-4.76 (m, 4H, CH₂-1, CH₂-9), 4.45 (d, $J = 1.5$ Hz, 1H, CH-5), 3.48-3.25 (m, 2H, CH-6, CH₂-3^a), 2.83 (dd, $J = 14.8, 6.8$ Hz, 1H, CH₂-7^a), 2.67 (ddt, $J = 14.1, 6.4, 1.4$ Hz, 1H, CH₂-3^b), 2.12 (dddt, $J = 15.0, 11.8, 6.4, 1.5$ Hz, 1H, CH₂-7^b), 1.58 (bs, 6H, CH₂-13, CH₂-14), 1.30 (bs, 12H, CH₃^{TEMPO}). **$^{13}\text{C NMR}$** (126 MHz, Chloroform-*d*) δ 141.7 (C_{Ar}), 138.5 (C-2), 137.7 (C_{Ar}), 135.4 (C-10), 134.1 (C-8), 129.6 (C-11), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 126.89 (CH_{Ar}), 126.85 (CH_{Ar}), 126.76 (CH_{Ar}), 126.1 (CH_{Ar}), 118.0 (C-1), 115.0 (C-9), 90.1 (C-5), 79.5 (C-4), 61.9 (C-12), 60.2 (C-12), 47.5 (C-3), 41.8 (C-6), 41.6 (C-13), 40.8 (C-13), 35.6 (CH₃^{TEMPO}), 33.9 (CH₃^{TEMPO}), 29.8 (C-7), 21.6 (CH₃^{TEMPO}), 21.3 (CH₃^{TEMPO}), 17.3 (C-14). **MS** (ESI⁺) m/z (%) 474 ([M+H⁺], 100). **HRMS** (ESI⁺) m/z [M+H⁺] calcd for C₃₂H₄₄NO₂: 474.3367; found: 474.3364. **IR** (neat): $\nu_{\text{max}} = 3582, 3073, 2975, 2931, 2871, 1639, 1560, 1494, 1377, 1362, 1256, 1179, 1132, 967, 909, 748, 719, 693, 648$ cm⁻¹.

Minor diastereoisomer:



$R_F = 0.21$ (hexanes/EtOAc, 10:1). **$^1\text{H NMR}$** (400 MHz, Chloroform-*d*) δ 8.16 (bs, 1H, OH), 7.64-7.57 (m, 2H, CH_{Ar}), 7.43-7.31 (m, 5H, CH_{Ar}), 7.29-7.21 (m, 3H, CH_{Ar}), 6.52-6.37 (m, 2H, CH-11, CH-10), 5.66 (ddt, $J = 17.2, 10.2, 6.8$ Hz, 1H, CH-2), 5.21 (ddt, $J = 17.1, 10.4, 6.7$ Hz, 1H, CH-8), 5.03-4.90 (m, 2H, CH₂-1), 4.83-4.68 (m, 2H, CH₂-9), 4.42 (s, 1H, CH-5), 3.08 (dd, $J = 15.0, 7.3$ Hz, 1H, CH₂-3^a), 3.00 (dd, $J = 15.0, 6.3$ Hz, 1H, CH₂-3^b), 2.61 (q, $J = 6.5$ Hz, 1H, CH-6), 2.32-2.16 (m, 2H, CH₂-7), 1.73-1.46 (m, 5H, CH₂-13, CH₂-14^a), 1.54 (bs, 6H, CH₃^{TEMPO}), 1.43-1.35 (m, 1H, CH₂-14^b), 1.31 (bs, 3H, CH₃^{TEMPO}), 1.28 (bs, 3H, CH₃^{TEMPO}). **$^{13}\text{C NMR}$** (101 MHz, Chloroform-*d*) δ 145.0 (C_{Ar}), 138.0 (C_{Ar}), 136.6 (C-8), 135.2 (C-2), 131.3 (C-11), 130.6 (C-10), 128.7 (CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (CH_{Ar}), 127.2 (CH_{Ar}), 127.0 (CH_{Ar}), 126.2 (CH_{Ar}), 117.2 (C-1), 116.4 (C-9), 86.3 (C-5), 82.4 (C-4), 62.3 (C-12), 61.9 (C-12), 43.3 (C-6), 42.1 (C-13), 40.9 (C-13), 39.7 (C-7), 38.0 (C-3), 35.9 (CH₃^{TEMPO}), 34.9 (CH₃^{TEMPO}), 20.98 (CH₃^{TEMPO}), 20.96 (CH₃^{TEMPO}), 17.1 (C-14).

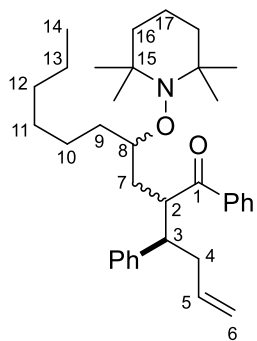
Formation of alkoxyamine·HCl salts for X-ray crystallography

Compound **major-42d**, **major-28n**, **major-50m**, or **minor-50m** (0.2 mmol) was dissolved in a round-bottomed flask in Et₂O (5 mL). The solution was cooled to 0 °C, and an HCl solution (2M in Et₂O, 0.5 mL, 1.0 mmol) was dropwise added. The mixture was stirred for 10 min until a white precipitate appeared. The solvent was removed carefully under reduced pressure to give a quantitative yield of the HCl salt as an off-white solid. The solid materials of **major-42d·HCl**, **major-28n·HCl** and **minor-50m·HCl** were crystallized from CH₂Cl₂/hexane mixture, and the solid of **major-50m·HCl** was

crystallized from THF to give *major-42d*·HCl, *major-28n*·HCl, *major-50m*·HCl, and *minor-50m*·HCl respectively as crystals suitable for X-ray diffraction analysis.

6.3.4. PRE-based radical cyclizations

1-Phenyl-2-(1-phenylbut-3-en-1-yl)-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)decan-1-one (49a)



In a microwave reaction tube, α -aminoxy ketone **28a** (81 mg, 0.2 mmol) and oct-1-ene (157 μ L, 1.0 mmol) were dissolved in dry *t*BuOH (1.0 mL). The mixture was heated to 140 °C for 2 h under microwave irradiation and at 150 °C for 1 h. The resulting mixture was evaporated at reduced pressure and separated by column chromatography (hexane/Et₂O, 20:1) to yield 8 mg (8%) of **49a** as an inseparable approximately 4:2:1 diastereoisomeric mixture as determined by the integration of the ¹³C NMR spectrum, followed by 9 mg (11%) of the starting material **28a**, followed by 18 mg (36%) of the reduced product **27a**,

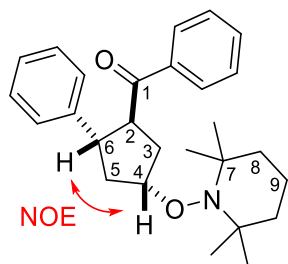
followed by 12 mg (15%) of cyclopentane **50a** as a 1.7:1 diastereoisomeric mixture.

R_F = 0.73 (hexanes/EtOAc, 10:1, 2 elutions). Only characteristic and detectable resonances of the diastereoisomeric mixture are displayed. Indecipherable ¹H NMR. ¹³C NMR (101 MHz, Chloroform-*d*) δ 205.1 (C-1), 204.8 (C-1), 142.4 (C_{Ar}), 140.8 (C_{Ar}), 140.6 (C_{Ar}), 139.0 (C_{Ar}), 136.5 (C-5), 133.1 (C-5), 132.1 (C-5), 129.4-126.4 (15×CH_{Ar}), 117.5 (C-6), 116.5 (C-6), 116.4 (C-6), 80.5 (C-8), 80.4 (C-8), 79.7 (C-8), 60.01 (C-15), 58.9 (C-15), 50.2 (C-2), 50.0 (C-2), 49.1 (C-2), 48.3 (C-3), 47.3 (C-3), 46.3 (C-3), 40.4 (C-16), 40.2 (C-16), 39.8 (C-16), 39.0 (C-16), 38.6 (C-16), 36.8-22.8 (21×CH₂), 34.1 (CH₃^{TEMPO}), 33.7 (CH₃^{TEMPO}), 20.7 (CH₃^{TEMPO}), 20.6 (CH₃^{TEMPO}), 17.4 (C-17), 17.3 (C-17), 17.2 (C-17), 14.24 (C-14), 14.23 (C-14), 14.20 (C-14). MS (ESI+) m/z (%) 540 ([M+Na⁺], 20), 518 ([M+H⁺], 100), 383 ([M-TEMPOH+Na⁺], 20). HRMS (ESI+) m/z [M+H⁺] calcd for C₃₅H₅₂O₂N: 518.3993; found: 518.3994. IR (neat): ν_{max} = 3063, 3028, 2927, 2870, 2857, 1679, 1641, 1597, 1580, 1494, 1448, 1375, 1360, 1257, 1240, 1208, 1181, 1132, 1027, 1001, 991, 957, 913, 758, 670 cm⁻¹.

(1*S**,2*S**,4*R**)- and (1*S**,2*S**,4*S**)-1-Benzoyl-2-phenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane (**50a**)

Prepared according to general procedure **E** from **28a** (90 mg, 0.22 mmol) in PhCF₃ (4.2 mL) at 150 °C for 45 min. Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 73 mg (81%) of **50a** as a 1.6:1 mixture of partially separable diastereoisomers as a thick colorless oil. The major diastereoisomer solidifies very slowly to an off-white solid upon standing.

Major diastereoisomer:

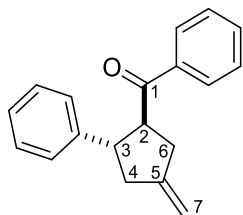


R_F = 0.43 (hexanes/EtOAc, 10:1). **m.p.** 93-95 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.84-7.79 (m, 2H, CH_{Ar}), 7.65-7.34 (m, 4H, CH_{Ar}), 7.29-7.12 (m, 4H, CH_{Ar}), 4.50 (tt, J = 8.3, 6.5 Hz, 1H, CH-4), 3.94 (td, J = 9.7, 7.9 Hz, 1H, CH-2), 3.51 (ddd, J = 11.7, 9.3, 7.0 Hz, 1H, CH-6), 2.73-2.62 (m, 1H, CH₂-5^a), 2.38-2.26 (m, 2H, CH₂-3), 2.07-1.97 (m, 1H, CH₂-5^b), 1.65-1.38 (m, 6H, CH₂-9, CH₂-8), 1.38-1.02 (m, 12H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.9 (C-1), 143.9 (C_{Ar}), 136.9 (C_{Ar}), 133.03 (CH_{Ar}), 128.7 (CH_{Ar}), 128.59 (CH_{Ar}), 128.56 (CH_{Ar}), 127.6 (CH_{Ar}), 126.5 (CH_{Ar}), 86.6 (C-4), 59.6 (C-7), 52.2 (C-2), 45.5 (C-6), 42.3 (C-5), 40.27 (C-8), 40.25 (C-8), 38.0 (C-3), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.4 (C-9). **MS** (ESI+) m/z (%) 428 ([M+Na⁺], 30), 406 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₇H₃₅NO₂Na: 428.2560; found: 428.2560, [M+H⁺] calcd for C₂₇H₃₆NO₂: 406.2741; found: 406.2742. **IR** (neat): $\nu_{\max}$ = 3059, 2995, 2970, 2931, 1682, 1597, 1494, 1448, 1359, 1261, 1133, 1013, 754, 699 cm⁻¹.

Minor diastereoisomer:

R_F = 0.37 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.03-8.01 (m, 2H, CH_{Ar}), 7.65-7.34 (m, 4H, CH_{Ar}), 7.29-7.12 (m, 4H, CH_{Ar}), 4.63 (quint, J = 7.1 Hz, 1H, CH-4), 3.86 (q, J = 9.0 Hz, 1H, CH-6), 3.71 (ddd, J = 10.8, 9.1, 7.6 Hz, 1H, CH-2), 2.71-2.62 (m, 1H, CH₂-5^a), 2.48-2.37 (m, 1H, CH₂-3^a), 2.29-2.21 (m, 1H, CH₂-3^b), 2.07-1.97 (m, CH₂-5^b), 1.65-1.38 (m, 6H, CH₂-9, CH₂-8), 1.38-1.02 (m, 12H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.1 (C-1), 144.8 (C_{Ar}), 137.1 (C_{Ar}), 132.99 (CH_{Ar}), 128.61 (CH_{Ar}), 128.59 (CH_{Ar}), 128.57 (CH_{Ar}), 127.4 (CH_{Ar}), 126.3 (CH_{Ar}), 86.8 (C-4), 59.6 (C-7), 53.2 (C-2), 44.9 (C-6), 40.6 (C-5), 40.4 (C-8), 39.8 (C-3), 34.4 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.4 (C-9).

(1*S**,2*S**)-1-Benzoyl-2-phenyl-4-methylenecyclopentane (**50b**)



Prepared according to general procedure **E** from **28b** (69 mg, 0.16 mmol) in PhCF₃ (3.3 mL) at 150 °C for 1.5 h. Purification of the crude product by column chromatography (hexane/EtOAc, 20:1) gave 40 mg (95%) of **50b** as a colorless solid.

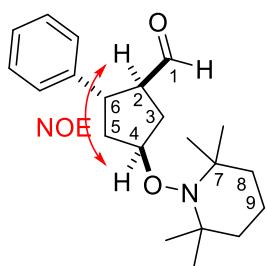
R_F = 0.30 (hexanes/EtOAc, 10:1). **m.p.** 72-74 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dd, J = 8.3, 1.4 Hz, 2H, CH_{Ar}), 7.51-7.47 (m, 1H, CH_{Ar}), 7.37 (t, J = 7.7 Hz, 2H, CH_{Ar}), 7.27-7.20 (m, 4H, CH_{Ar}), 7.18-7.13 (m, 1H, CH_{Ar}), 4.97 (bs, 1H, CH₂-

7), 4.94 (bs, 1H, CH₂-7), 3.97 (q, $J = 9.0$ Hz, 1H, CH-2), 3.72 (q, $J = 9.3$ Hz, 1H, CH-3), 2.97-2.88 (m, 2H, CH₂-4^a, CH₂-6^b), 2.72-2.61 (m, 2H, CH₂-4^b, CH₂-6^a). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.4 (C-1), 149.4 (C-5), 143.5 (C_{Ar}), 137.0 (C_{Ar}), 133.1 (CH_{Ar}), 128.63 (CH_{Ar}), 128.62 (CH_{Ar}), 128.5 (CH_{Ar}), 127.4 (CH_{Ar}), 126.6 (CH_{Ar}), 106.6 (C-7), 54.3 (C-2), 48.1 (C-3), 41.1 (C-4), 38.5 (C-6). **MS** (EI) m/z (%) 262 ([M]⁺, 30), 157 ([M-PhCO]⁺, 100). **HRMS** (EI) m/z [M]⁺ calcd for C₁₉H₁₈O: 262.1358; found: 262.1357. **IR** (neat): $\nu_{\max} = 3079, 3027, 2982, 2950, 1673, 1595, 1492, 1449, 1286, 1231, 1205, 1019, 872, 757, 699, 683$ cm⁻¹.

(1*S**,2*S**,4*S**)- and (1*S**,2*S**,4*R**)-2-Phenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane-1-carbaldehyde (**50f**)

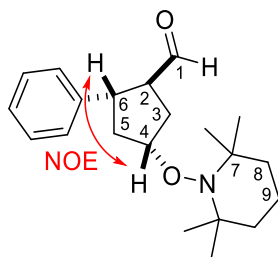
Prepared based on general procedure **F** from **28f** (107 mg, 0.32 mmol) in PhCF₃ (6.5 mL) at 150 °C for 1 h. Purification of the crude product by column chromatography (hexane/Et₂O, 20:1, gradient to 5:1) gave 17 mg (16%) of **50f** as an inseparable 1.1:1 mixture of diastereoisomers as a thick colorless oil.

Major diastereoisomer:



$R_F = 0.39$ (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.67 (d, $J = 2.6$ Hz, 1H, CH-1), 7.36-7.25 (m, 3H, CH_{Ar}), 7.25-7.15 (m, 2H, CH_{Ar}), 4.54 (qd, $J = 6.3, 4.3$ Hz, 1H, CH-4), 3.55 (q, $J = 8.9$ Hz, 1H, CH-6), 2.78 (qd, $J = 8.7, 2.6$ Hz, 1H, CH-2), 2.51-2.41 (m, 2H, CH₂-5^a, CH₂-3^a), 2.21-2.00 (m, 2H, CH₂-5^b, CH₂-3^b), 1.63-1.51 (m, 1H, CH₂-9^a), 1.50-1.44 (m, 4H, CH₂-8), 1.38-1.30 (m, 1H, CH₂-9^b), 1.21-1.10 (m, 12H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.2 (C-1), 143.0 (C_{Ar}), 128.2 (CH_{Ar}), 126.7 (CH_{Ar}), 126.2 (CH_{Ar}), 85.9 (C-4), 59.1 (C-7), 57.2 (C-2), 43.1 (C-6), 40.8 (C-5), 39.65 (C-8), 34.5 (C-3), 33.7 (CH₃^{TEMPO}), 19.8 (CH₃^{TEMPO}), 16.72 (C-9). **MS** (ESI-) m/z (%) 344 ([M+OH-H], 100), 328 ([M-H]⁺, 10). **HRMS** (ESI+) m/z [M+H]⁺ calcd for C₂₁H₃₂NO₂: 330.2428; found: 330.2427. **IR** (neat): $\nu_{\max} = 2970, 2929, 1723, 1456, 1374, 1360, 1261, 1243, 1182, 1133, 1061, 958, 758, 699$ cm⁻¹.

Minor diastereoisomer:

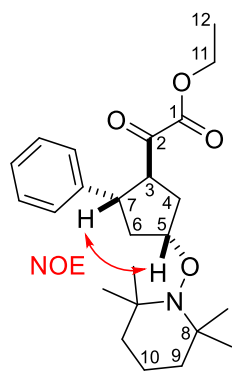


¹H NMR (400 MHz, Chloroform-*d*) δ 9.62 (d, $J = 2.1$ Hz, 1H, CH-1), 7.42-7.26 (m, 3H, CH_{Ar}), 7.25-7.15 (m, 2H, CH_{Ar}), 4.38 (tt, $J = 8.2, 6.4$ Hz, 1H, CH-4), 3.18 (ddd, $J = 11.3, 9.6, 7.2$ Hz, 1H, CH-6), 3.10-2.94 (m, 1H, CH-2), 2.62 (dt, $J = 13.1, 6.7$ Hz, 1H, CH₂-5^a), 2.39-2.32 (m, 1H, CH₂-3^a), 2.18-2.10 (m, 1H, CH₂-3^b), 1.93 (ddd, $J = 12.8, 11.2, 8.2$ Hz, 1H, CH₂-5^b), 1.63-1.51 (m, 1H, CH₂-9^a), 1.50-1.44 (m, 4H, CH₂-8), 1.38-1.30 (m, 1H, CH₂-9^b), 1.21-1.10 (m, 12H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.0 (C-1), 142.4 (C_{Ar}), 128.2 (CH_{Ar}), 126.8 (CH_{Ar}), 126.1 (CH_{Ar}), 85.5 (C-4), 59.1 (C-7), 56.3 (C-2), 43.4 (C-6), 41.8 (C-5), 39.63 (C-8), 33.7 (CH₃^{TEMPO}), 32.4 (C-3), 19.8 (CH₃^{TEMPO}), 16.74 (C-9).

(1*S,2*S**,4*R**)- and (1*S**,2*S**,4*S**)-Ethyl 2-oxo-2-(2-phenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopent-1-yl)acetate (50g)**

Prepared according to general procedure **E** from **28g** (42 mg, 0.10 mmol) in PhCF₃ (3.7 mL) at 140 °C for 1.5 h. Purification of the crude product by column chromatography (hexane/Et₂O, 10:1) gave 18 mg (43%) of **50g** as an inseparable 1.4:1 mixture of diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.18 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.33-7.25 (m, 3H, CH_{Ar}), 7.22-7.16 (m, 2H, CH_{Ar}), 4.42 (tt, J = 7.9, 6.2 Hz, 1H, CH-5), 4.21-4.10 (m, 2H, CH₂-11), 3.80 (td, J = 9.8, 8.1 Hz, 1H, CH-3), 3.28 (ddd, J = 11.3, 9.7, 7.3 Hz, 1H, CH-7), 2.63 (td, J = 13.7, 7.3 Hz, 1H, CH₂-6^a), 2.40-2.30 (m, 1H, CH₂-4^a), 2.27-2.17 (m, 1H, CH₂-4^b), 2.02-1.90 (m, 1H, CH₂-6^b), 1.62-1.40 (m, 5H, CH₂-9, CH₂-10^a), 1.37-1.28 (m, 1H, CH₂-10^b), 1.25 (t, J = 7.0 Hz, 3H, CH₃-12), 1.21-1.03 (m, 12H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 196.0 (C-2), 161.5 (C-1), 143.0 (C_{Ar}), 128.65 (*m*-CH_{Ar}), 127.6 (*o*-CH_{Ar}), 126.8 (*p*-CH_{Ar}), 86.0 (C-5), 62.43 (C-11), 59.7 (C-8), 53.2 (C-3), 45.3 (C-7), 42.6 (C-6), 40.26 (C-9), 35.9 (C-4), 34.3 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.37 (C-10), 14.00 (C-12). **MS** (ESI+) m/z (%) 825 ([2M+Na⁺], 20), 424 ([M+Na⁺], 30), 402 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₄H₃₆NO₄: 402.2639; found: 402.2635. **IR** (neat): $\nu_{\max}$ = 2972, 2930, 2871, 1726, 1454, 1360, 1258, 1133, 1095, 1044, 758, 700 cm⁻¹.

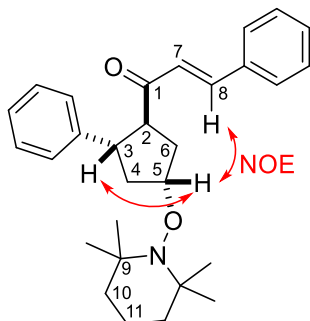
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.33-7.25 (m, 3H, CH_{Ar}), 7.22-7.16 (m, 2H, CH_{Ar}), 4.56 (qd, J = 6.8, 5.0 Hz, 1H, CH-5), 4.21-4.10 (m, 2H, CH₂-11), 3.64 (q, J = 9.0 Hz, 1H, CH-7), 3.56 (td, J = 9.5, 8.0 Hz, 1H, CH-3), 2.67-2.59 (m, 1H, CH₂-4^a), 2.45-2.35 (m, 1H, CH₂-6^a), 2.17-2.06 (m, 1H, CH₂-6^b), 2.04-1.95 (m, 1H, CH₂-4^b), 1.62-1.40 (m, 5H, CH₂-9, CH₂-10^a), 1.37-1.28 (m, 1H, CH₂-10^b), 1.24 (t, J = 7.0 Hz, 3H, CH₃-12), 1.21-1.03 (m, 12H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 195.3 (C-2), 161.7 (C-1), 143.7 (C_{Ar}), 128.68 (*m*-CH_{Ar}), 127.4 (*o*-CH_{Ar}), 126.7 (*p*-CH_{Ar}), 86.4 (C-5), 62.42 (C-11), 59.7 (C-8), 54.0 (C-3), 44.6 (C-7), 41.2 (C-6), 40.28 (C-9), 37.5 (C-4), 34.3 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.36 (C-10), 14.02 (C-12).

(1*S**,2*S**,4*R**)- and (1*S**,2*S**,4*S**)-1-Cinnamoyl-2-phenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane (**50h**)

Prepared according to general procedure **E** from **28h** (70 mg, 0.16 mmol) in PhCF₃ (3.2 mL) at 160 °C for 1 h. Purification of the crude product by column chromatography (hexane/EtOAc, 20:1, gradient to 10:1) gave 40 mg (57%) of **50h** as a 1.3:1 mixture of inseparable diastereoisomers as an off-white solid, which was recrystallized from hot EtOH giving a 1.4:1 diastereoisomeric mixture.

Major diastereoisomer:



R_F = 0.38 (hexanes/EtOAc, 10:1). **m.p.** 114-116 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46-7.13 (m, 11H, CH_{Ar}, CH-8), 6.53 (d, J = 16.1 Hz, 1H, CH-7), 4.48 (quint, J = 7.1 Hz, 1H, CH-5), 3.48 (td, J = 9.6, 7.9 Hz, 1H, CH-2), 3.27 (ddd, J = 11.3, 9.5, 7.3 Hz, 1H, CH-3), 2.65 (dt, J = 13.8, 7.1 Hz, 1H, CH₂-4^a), 2.41-2.21 (m, 2H, CH₂-6), 2.04-1.86 (m, 1H, CH₂-4^b), 1.56-1.46 (m, 5H, CH₂-11^a, CH₂-10), 1.39-0.85 (m, 13H, CH₂-11^b, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.4 (C-1), 144.1 (C_{Ar}), 143.0 (C-8), 134.7 (C_{Ar}), 130.5 (CH_{Ar}), 129.0 (CH_{Ar}), 128.69

(CH_{Ar}), 128.38 (CH_{Ar}), 127.6 (CH_{Ar}), 126.6 (CH_{Ar}), 126.2 (C-7), 86.5 (C-5), 59.66 (C-9), 55.3 (C-2), 46.4 (C-3), 42.8 (C-4), 40.27 (C-10), 36.5 (C-6), 34.5 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.4 (C-11). **MS** (ESI+) m/z (%) 885 ([2M+Na⁺], 80), 454 ([M+Na⁺], 75), 432 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₉H₃₈NO₂: 432.2897; found: 432.2894. **IR** (neat): ν_{max} = 2970, 2931, 1686, 1657, 1610, 1495, 1449, 1359, 1181, 1133, 1031, 975, 761, 699 cm⁻¹.

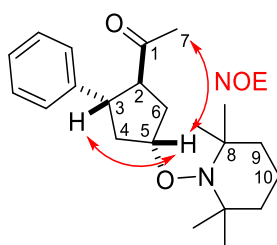
Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.46-7.13 (m, 11H, CH_{Ar}, CH-8), 6.63 (d, J = 16.1 Hz, 1H, CH-7), 4.60 (quint, J = 7.0 Hz, 1H, CH-5), 3.62 (q, J = 9.2 Hz, 1H, CH-3), 3.18 (ddd, J = 10.8, 9.4, 7.6 Hz, 1H, CH-2), 2.60-2.54 (m, 1H, CH₂-6^a), 2.46-2.37 (m, 1H, CH₂-4^a), 2.24-2.14 (m, 1H, CH₂-4^b), 2.14-2.07 (m, 1H, CH₂-6^b), 1.56-1.46 (m, 5H, CH₂-11^a, CH₂-10), 1.39-0.85 (m, 13H, CH₂-11^b, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 200.6 (C-1), 144.8 (C_{Ar}), 142.8 (C-8), 134.8 (C_{Ar}), 130.5 (CH_{Ar}), 129.0 (CH_{Ar}), 128.71 (CH_{Ar}), 128.41 (CH_{Ar}), 127.5 (CH_{Ar}), 126.5 (CH_{Ar}), 125.7 (C-7), 86.8 (C-5), 59.73 (C-9), 56.6 (C-2), 45.5 (C-3), 41.1 (C-4), 40.29 (C-10), 38.2 (C-6), 34.5 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.4 (C-11).

(1*S**,2*S**,4*R**)- and (1*S**,2*S**,4*S**)-1-Acetyl-2-phenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane (**50i**)

Prepared according to general procedure **F** from **28i** (37 mg, 0.11 mmol) in PhCF₃ (2.2 mL) at 150 °C for 2 h. Purification of the crude product by column chromatography (hexane/Et₂O, 10:1) gave 26 mg (70%) of **50i** as a 1.3:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.20 (hexanes/EtOAc, 10:1). **¹H NMR** (401 MHz, Chloroform-*d*) δ 7.25-7.18 (m, 3H, CH_{Ar}), 7.16-7.10 (m, 2H, CH_{Ar}), 4.34 (tt, J = 7.8, 6.2 Hz, 1H, CH-5), 3.15-2.99 (m, 2H, CH-2, CH-3), 2.52 (dt, J = 12.5, 6.5 Hz, 1H, CH₂-6^a), 2.22-2.08 (m, 2H, CH₂-4), 1.88 (s, 3H, CH₃-7), 1.88-1.77 (m, 1H, CH₂-6^b), 1.55-1.43 (m, 1H, CH₂-10^a), 1.43-1.34 (m, 4H, CH₂-9), 1.30-1.20 (m, 1H, CH₂-10^b), 1.13 (bs, 3H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}), 1.06 (bs, 3H, CH₃^{TEMPO}), 1.02 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 209.5 (C-1), 143.8 (C_{Ar}), 128.72 (CH_{Ar}), 127.5 (CH_{Ar}), 126.7 (CH_{Ar}), 86.2 (C-5), 59.6 (C-8), 57.7 (C-2), 46.4 (C-3), 43.1 (C-4), 40.24 (C-9), 36.0 (C-6), 34.2 (CH₃^{TEMPO}), 30.3 (C-7), 20.4 (CH₃^{TEMPO}), 17.4 (C-10). **MS** (ESI+) m/z (%), 366 ([M+Na⁺], 40), 344 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₂H₃₄NO₂: 344.2584; found: 344.2585. **IR** (neat): $\nu_{\max}$ = 2969, 2929, 2870, 1710, 1453, 1358, 1208, 1169, 1132, 1065, 1032, 992, 957, 755, 699 cm⁻¹.

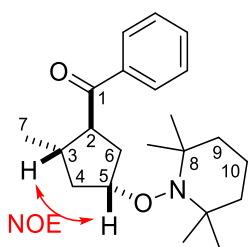
Minor diastereoisomer:

¹H NMR (401 MHz, Chloroform-*d*) δ 7.25-7.18 (m, 3H, CH_{Ar}), 7.16-7.10 (m, 2H, CH_{Ar}), 4.49-4.41 (m, 1H, CH-5), 3.41 (q, J = 9.3 Hz, 1H, CH-3), 2.81 (ddd, J = 10.8, 9.6, 7.5 Hz, 1H, CH-2), 2.49-2.42 (m, 1H, CH₂-6^a), 2.29 (ddd, J = 14.5, 9.4, 5.5 Hz, 1H, CH₂-4^a), 2.08-1.97 (m, 1H, CH₂-4^b), 1.93 (s, 3H, CH₃-7), 1.92-1.83 (m, 1H, CH₂-6^b), 1.55-1.43 (m, 1H, CH₂-10^a), 1.43-1.34 (m, 4H, CH₂-9), 1.30-1.20 (m, 1H, CH₂-10^b), 1.13 (bs, 3H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}), 1.06 (bs, 3H, CH₃^{TEMPO}), 1.02 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 210.2 (C-1), 144.6 (C_{Ar}), 128.74 (CH_{Ar}), 127.3 (CH_{Ar}), 126.5 (CH_{Ar}), 86.5 (C-5), 59.7 (C-8), 58.7 (C-2), 45.3 (C-3), 41.4 (C-4), 40.25 (C-9), 37.8 (C-6), 34.4 (CH₃^{TEMPO}), 29.7 (C-7), 20.4 (CH₃^{TEMPO}), 17.4 (C-10).

(1*S**,2*S**,4*R**)- and (1*S**,2*S**,4*S**)-1-Benzoyl-2-methyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane (**50n**)

Prepared according to general procedure **F** from **28n** (72 mg, 0.21 mmol) in PhCF₃ (4.2 mL) at 150 °C for 1 h. Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 47 mg (65%) of **50n** as a 1.6:1 mixture of inseparable diastereoisomers as a thick colorless oil.

Major diastereoisomer:



R_F = 0.63 (hexanes/EtOAc, 5:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 8.01-7.90 (m, 2H, *o*-CH_{Ar}), 7.58-7.52 (m, 1H, *p*-CH_{Ar}), 7.50-7.42 (m, 2H, *m*-CH_{Ar}), 4.41-4.33 (m, 1H, CH-5), 3.43 (q, *J* = 9.1 Hz, 1H, CH-2), 2.40 (dt, *J* = 12.7, 6.6 Hz, 1H, CH₂-4^a), 2.32-2.23 (m, 1H, CH-3), 2.24-2.16 (m, 2H, CH₂-6), 1.57-1.29 (m, 7H, CH₂-4^b, CH₂-9, CH₂-10), 1.17-0.98 (m, 12H, CH₃^{TEMPO}), 0.96 (d, *J* = 6.5 Hz, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.7 (C-1), 137.4 (C_{Ar}), 133.02 (*p*-CH_{Ar}), 128.69 (*m*-CH_{Ar}), 128.53 (*o*-CH_{Ar}), 86.8 (C-5), 59.5 (C-8), 51.9 (C-2), 42.9 (C-4), 40.2 (C-9), 38.1 (C-6), 35.6 (C-3), 34.3 (CH₃^{TEMPO}), 34.1 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 19.7 (C-7), 17.4 (C-10). **MS** (ESI+) *m/z* (%) 709 ([2M+Na⁺], 30), 366 ([M+Na⁺], 75), 344 ([M+H⁺], 100). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₂₂H₃₃NO₂Na: 366.2404; found: 366.2405. **IR** (neat): ν_{max} = 2928, 2869, 1678, 1597, 1448, 1373, 1359, 1221, 1133, 1005, 991, 787, 698, 662 cm⁻¹.

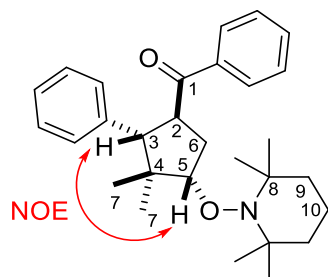
Minor diastereoisomer:

¹H NMR (401 MHz, Chloroform-*d*) δ 8.01-7.90 (m, 2H, *o*-CH_{Ar}), 7.58-7.52 (m, 1H, *p*-CH_{Ar}), 7.50-7.42 (m, 2H, *m*-CH_{Ar}), 4.48-4.41 (m, 1H, CH-5), 3.17 (dt, *J* = 10.8, 7.8 Hz, 1H, CH-2), 2.60-2.46 (m, 1H, CH-3), 2.48-2.39 (m, 1H, CH₂-6^a), 2.03 (ddd, *J* = 13.3, 8.8, 5.9 Hz, 1H, CH₂-4^a), 1.83 (ddd, *J* = 12.9, 10.8, 7.9 Hz, 1H, CH₂-6^b), 1.63 (dt, *J* = 13.3, 8.0 Hz, 1H, CH₂-4^b), 1.57-1.29 (m, 6H, CH₂-9, CH₂-10), 1.17-0.98 (m, 12H, CH₃^{TEMPO}), 0.91 (d, *J* = 6.8 Hz, 3H, CH₃-7). ¹³C NMR (101 MHz, Chloroform-*d*) δ 202.0 (C-1), 137.5 (C_{Ar}), 132.97 (*p*-CH_{Ar}), 128.67 (*m*-CH_{Ar}), 128.47 (*o*-CH_{Ar}), 86.7 (C-5), 59.7 (C-8), 52.7 (C-2), 40.6 (C-4), 40.2 (C-9), 39.3 (C-6), 34.6 (C-3), 34.3 (CH₃^{TEMPO}), 34.1 (CH₃^{TEMPO}), 20.4 (C-7), 20.3 (CH₃^{TEMPO}), 17.4 (C-10).

(1*S**,2*S**,4*R**)- and (1*S**,2*S**,4*S**)-1-Benzoyl-2-phenyl-3,3-dimethyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane (**50d**) and 2,2,6,6-tetramethyl-1-((3-methylbut-2-en-1-yl)oxy)piperidine (**50da**)

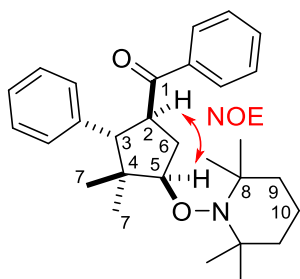
Prepared according to general procedure **E** from **28d** (135 mg, 0.31 mmol) in PhCF₃ (6.2 mL) at 130 °C for 2 h. Purification of the crude product by column chromatography (hexane/EtOAc, 20:1) gave 45 mg (61%) of volatile product **50da** followed by 29 mg (45%) of (*E*)-1,3-diphenylprop-2-en-1-one, followed by 25 mg of a mixed fraction containing (*E*)-1,3-diphenylprop-2-en-1-one and **50d** in a 1.3:1 diastereoisomeric ratio. The product containing fraction was repurified by semi-preparative HPLC (hexane/EtOAc, 50:1) to give 19 mg (14%) of **50d** as partially separable 1.3:1 mixture of diastereoisomers as colorless oils and 6 mg (9%) of (*E*)-1,3-diphenylprop-2-en-1-one.

Major diastereoisomer:



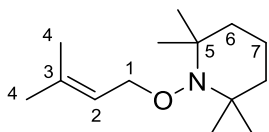
R_F = 0.51 (hexanes/Et₂O, 5:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.88-7.83 (m, 2H, CH_{Ar}), 7.53-7.47 (m, 1H, CH_{Ar}), 7.42-7.35 (m, 2H, CH_{Ar}), 7.28-7.22 (m, 2H, CH_{Ar}), 7.20-7.15 (m, 3H, CH_{Ar}), 4.32 (dd, J = 8.1, 6.0 Hz, 1H, CH-5), 4.00 (dt, J = 10.1, 8.7 Hz, 1H, CH-2), 3.47 (d, J = 8.9 Hz, 1H, CH-3), 2.55 (ddd, J = 12.9, 8.5, 6.0 Hz, 1H, CH₂-6^a), 2.29 (ddd, J = 13.0, 10.1, 8.2 Hz, 1H, CH₂-6^b), 1.66-1.36 (m, 6H, CH₂-9, CH₂-10), 1.23 (bs, 3H, CH₃^{TEMPO}), 1.18 (s, 3H, CH₃-7), 1.15 (bs, 3H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}), 1.08 (bs, 3H, CH₃^{TEMPO}), 0.77 (s, 3H, CH₃-7). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 201.0 (C-1), 142.0 (C_{Ar}), 137.0 (C_{Ar}), 132.9 (CH_{Ar}), 129.1 (CH_{Ar}), 128.60 (CH_{Ar}), 128.57 (CH_{Ar}), 128.2 (CH_{Ar}), 126.4 (CH_{Ar}), 89.2 (C-5), 61.3 (C-8), 59.4 (C-8), 55.8 (C-3), 48.6 (C-2), 45.7 (C-4), 40.82 (C-9), 40.5 (C-9), 34.92 (C-6), 34.87 (CH₃^{TEMPO}), 34.64 (CH₃^{TEMPO}), 25.3 (C-7), 24.1 (C-7), 20.7 (CH₃^{TEMPO}), 17.4 (C-10). **MS** (ESI+) m/z (%) 434 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₉H₄₀NO₂: 434.3054; found: 434.3049. **IR** (neat): $\nu_{\max}$ = 2969, 2930, 2870, 1683, 1597, 1449, 1376, 1360, 1278, 1257, 1230, 1180, 1132, 1097, 1021, 915, 745, 701 cm⁻¹.

Minor diastereoisomer:



R_F = 0.49 (hexanes/Et₂O, 5:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.89-7.83 (m, 2H, CH_{Ar}), 7.51-7.46 (m, 1H, CH_{Ar}), 7.41-7.36 (m, 2H, CH_{Ar}), 7.28-7.21 (m, 5H, CH_{Ar}), 4.24 (dd, J = 10.0, 7.4 Hz, 1H, CH-5), 4.17 (ddd, J = 12.3, 9.7, 4.1 Hz, 1H, CH-2), 3.41 (d, J = 9.7 Hz, 1H, CH-3), 2.50 (td, J = 12.6, 10.0 Hz, 1H, CH₂-6^a), 2.21 (ddd, J = 12.9, 7.5, 4.0 Hz, 1H, CH₂-6^b), 1.50-1.29 (m, 6H, CH₂-9, CH₂-10), 1.26 (bs, 3H, CH₃^{TEMPO}), 1.18 (bs, 6H, CH₃^{TEMPO}), 1.12 (s, 3H, CH₃-7), 1.11 (bs, 3H, CH₃^{TEMPO}), 0.82 (s, 3H, CH₃-7). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 201.6 (C-1), 139.5 (C_{Ar}), 136.8 (C_{Ar}), 132.9 (CH_{Ar}), 129.5 (CH_{Ar}), 128.7 (CH_{Ar}), 128.56 (CH_{Ar}), 128.0 (CH_{Ar}), 126.6 (CH_{Ar}), 88.3 (C-5), 61.2 (C-8), 60.6 (C-8), 54.2 (C-3), 46.5 (C-2), 46.4 (C-4), 40.79 (C-9), 40.5 (C-9), 35.1 (CH₃^{TEMPO}), 34.57 (CH₃^{TEMPO}), 33.8 (C-6), 26.5 (C-7), 20.6 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.4 (C-10), 16.9 (C-7).

2,2,6,6-Tetramethyl-1-((3-methylbut-2-en-1-yl)oxy)piperidine (50da)

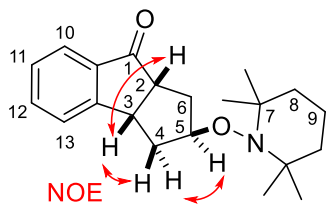


R_F = 0.38 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 5.35 (tt, J = 7.0, 1.8 Hz, 1H, CH-2), 4.27 (d, J = 7.0 Hz, 2H, CH-1), 1.74 (d, J = 1.3 Hz, 3H, CH₃-4), 1.66 (d, J = 1.3 Hz, 3H, CH₃-4), 1.49-1.27 (m, 6H, CH₂-6, CH₂-7), 1.19 (s, 6H, CH₃^{TEMPO}), 1.10 (s, 6H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 136.1 (C-3), 120.6 (C-2), 74.4 (C-1), 59.8 (C-5), 39.9 (C-6), 33.2 (CH₃^{TEMPO}), 26.0 (C-4), 20.4 (CH₃^{TEMPO}), 18.4 (C-4), 17.3 (C-7). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₁₄H₂₈NO: 226.2165; found: 226.2166.

(2*S**,3*aS**,8*aR**)- and (2*R**,3*aS**,8*aR**)-2-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)-2,3,3*a*,8*a*-tetrahydrocyclopenta[*a*]inden-8(1*H*)-one (**50o**)

Prepared according to general procedure **F** from **28o** (202 mg, 0.62 mmol) in PhCF₃ (6.2 mL) at 160 °C for 45 min. Upjohn dihydroxylation was performed for 18 h. Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 9 mg of the major diastereoisomer followed by 3 mg of the minor diastereoisomer as thick yellow oils. Yield 12 mg (6%) of **50o** in a 3:1 diastereomeric ratio.

Major diastereoisomer:



R_F = 0.25 (hexanes/EtOAc, 10:1). **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.68 (d, J = 7.7 Hz, 1H, CH_{Ar}-10), 7.61 (td, J = 7.5, 1.2 Hz, 1H, CH_{Ar}-12), 7.47 (dd, J = 7.7, 1.0 Hz, 1H, CH_{Ar}-13), 7.35 (t, J = 7.5 Hz, 1H, CH_{Ar}-11), 3.89 (tt, J = 9.9, 6.1 Hz, 1H, CH-5), 3.76 (ddd, J = 9.4, 7.1, 2.0 Hz, 1H, CH-3), 3.09 (ddd, J = 11.0, 7.1, 2.2 Hz, 1H, CH-2), 2.41 (ddt, J = 12.9, 6.3, 1.9 Hz, 1H, CH₂-6^a), 2.24 (ddt, J = 12.6, 6.0, 1.7 Hz, 1H, CH₂-4^a), 2.13-1.97 (m, 2H, CH₂-6^b, CH₂-4^b), 1.57-1.44 (m, 1H, CH₂-9^a), 1.44-1.22 (m, 5H, CH₂-9^b, CH₂-8), 1.08 (bs, 3H, CH₃^{TEMPO}), 1.04 (bs, 9H, CH₃^{TEMPO}). **¹³C NMR** (126 MHz, Chloroform-*d*) δ 209.8 (C-1), 158.8 (C_{Ar}), 136.8 (C_{Ar}), 135.4 (CH_{Ar}-12), 127.7 (CH_{Ar}-11), 126.1 (CH_{Ar}-13), 123.6 (CH_{Ar}-10), 85.2 (C-5), 59.68 (C-7), 59.6 (C-7), 49.4 (C-2), 40.9 (C-3), 40.1 (C-8), 38.3 (C-4), 36.0 (C-6), 34.0 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 17.3 (C-9). **MS** (ESI+) m/z (%), 350 ([M+Na⁺], 20), 328 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₁H₃₀NO₂: 328.2271; found: 328.2272. **IR** (neat): ν_{max} = 2966, 2927, 2870, 1710, 1605, 1464, 1374, 1360, 1332, 1291, 1243, 1133, 1072, 973, 758 cm⁻¹.

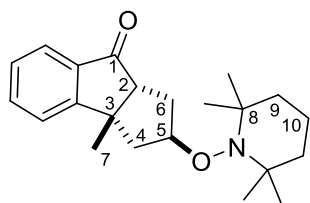
Minor diastereoisomer:

R_F = 0.10 (hexanes/EtOAc, 10:1). **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.70 (d, J = 7.7 Hz, 1H, CH-10), 7.57 (td, J = 7.4, 1.2 Hz, 1H, CH-12), 7.48 (d, J = 7.7 Hz, 1H, CH-13), 7.32 (t, J = 7.4 Hz, 1H, CH-11), 4.30 (quint, J = 4.6 Hz, 1H, CH-5), 3.74 (ddd, J = 10.1, 7.3, 3.8 Hz, 1H, CH-3), 3.08 (ddd, J = 10.6, 7.2, 4.0 Hz, 1H, CH-2), 2.32-2.16 (m, 3H, CH₂-6, CH₂-4^a), 2.08 (dtd, J = 13.4, 4.1, 1.7 Hz, 1H, CH₂-4^b), 1.41-1.17 (m, 6H, CH₂-8, CH₂-9), 1.11 (bs, 3H, CH₃^{TEMPO}), 0.94 (bs, 3H, CH₃^{TEMPO}), 0.76 (bs, 3H, CH₃^{TEMPO}), 0.47 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (126 MHz, Chloroform-*d*) δ 209.7 (C-1), 159.3 (C_{Ar}), 136.6 (C_{Ar}), 134.8 (C_{Ar}-12), 127.3 (C_{Ar}-11), 126.2 (C_{Ar}-13), 124.0 (C_{Ar}-10), 89.1 (C-5), 59.67 (C-7), 59.3 (C-7), 50.7 (C-2), 42.3 (C-3), 40.2 (C-8), 39.1 (C-4), 36.8 (C-6), 34.4 (CH₃^{TEMPO}), 20.0 (CH₃^{TEMPO}), 19.6 (CH₃^{TEMPO}), 17.2 (C-9).

(2*R**,3*aS**,8*aR**)- and (2*S**,3*aS**,8*aR**)-3a-Methyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2,3,3a,8a-tetrahydrocyclopenta[a]inden-8(1H)-one (**50p**)

Prepared according to general procedure **E** from **28p** (93 mg, 0.27 mmol) in PhCF₃ (5.4 mL) at 150 °C for 1 h. Purification of the crude product by column chromatography (hexane/EtOAc, 30:1, gradient to 10:1) gave 52 mg of the major diastereoisomer as a colorless solid followed by 34 mg of the minor diastereoisomer of **50p** as a colorless oil. Yield 86 mg (92%) of **50p** in a 1.5:1 diastereomeric ratio. The major diastereoisomer was recrystallized from *i*PrOH for X-ray diffraction analysis.

Major diastereoisomer:



R_F = 0.45 (hexanes/EtOAc, 10:1). **m.p.** 120-122°C. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.59-7.53 (m, 2H, CH_{Ar}), 7.41 (d, J = 7.7 Hz, 1H, CH_{Ar}), 7.27 (t, J = 7.4 Hz, 1H, CH_{Ar}), 3.74 (tt, J = 10.3, 6.1 Hz, 1H, CH-5), 2.56 (dd, J = 11.0, 1.7 Hz, 1H, CH-2), 2.37-2.33 (m, 2H, CH₂-4^a, CH₂-6^a), 2.02 (dt, J = 12.9, 10.8 Hz, 1H, CH₂-6^b), 1.76 (dd, J = 12.5, 10.2 Hz, 1H, CH₂-4^b), 1.48-1.37 (m, 1H, CH₂-10^a), 1.44 (s, 3H, CH₃-7), 1.33-1.13 (m, 5H, CH₂-10^b, CH₂-9), 1.02-0.91 (m, 12H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 208.7 (C-1), 162.4 (C_{Ar}), 135.5 (C_{Ar}), 135.2 (CH_{Ar}), 127.2 (CH_{Ar}), 123.82 (CH_{Ar}), 123.0 (CH_{Ar}), 85.2 (C-5), 59.1 (C-8), 56.6 (C-2), 46.7 (C-3), 45.8 (C-4), 39.7 (C-9), 36.0 (C-6), 33.6 (CH₃^{TEMPO}), 28.0 (C-7), 19.9 (CH₃^{TEMPO}), 16.9 (C-10). **MS** (ESI+) m/z (%) 705 ([2M+Na⁺], 15), 364 ([M+Na⁺], 40), 342 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₂H₃₁NO₂Na: 364.2247; found: 364.2245. **IR** (neat): $\nu_{\max}$ = 2927, 2868, 1710, 1604, 1464, 1326, 1221, 1134, 962, 764 cm⁻¹.

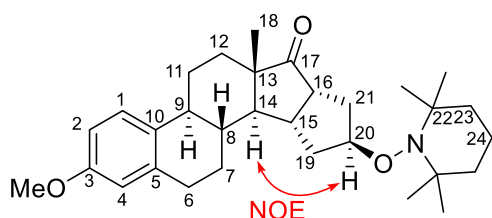
Minor diastereoisomer:

R_F = 0.18 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.67 (d, J = 7.6 Hz, 1H, CH_{Ar}), 7.58 (td, J = 7.4, 1.2 Hz, 1H, CH_{Ar}), 7.48 (d, J = 7.7 Hz, 1H, CH_{Ar}), 7.33-7.29 (m, 1H, CH_{Ar}), 4.33 (quint, J = 4.7 Hz, 1H, CH-5), 2.64 (dd, J = 9.6, 4.6 Hz, 1H, CH-2), 2.39-2.25 (m, 2H, CH₂-6), 2.21 (dd, J = 13.3, 4.4 Hz, 1H, CH₂-4^a), 2.00 (dd, J = 13.3, 5.2 Hz, 1H, CH₂-4^b), 1.48 (s, 3H, CH₃-7), 1.40-1.16 (m, 6H, CH₂-9, CH₂-10), 1.10 (bs, 3H, CH₃^{TEMPO}), 0.92 (bs, 3H, CH₃^{TEMPO}), 0.77 (bs, 3H, CH₃^{TEMPO}), 0.48 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 209.0 (C-1), 163.3 (C_{Ar}), 135.6 (C_{Ar}), 135.0 (CH_{Ar}), 127.3 (CH_{Ar}), 124.3 (CH_{Ar}), 123.77 (CH_{Ar}), 89.5 (C-5), 59.6 (C-8), 59.4 (C-8), 58.6 (C-2), 48.6 (C-3), 46.9 (C-4), 40.2 (C-9), 37.0 (C-6), 34.3 (CH₃^{TEMPO}), 27.9 (C-7), 20.0 (CH₃^{TEMPO}), 19.7 (CH₃^{TEMPO}), 17.2 (C-10).

(4*bS*,6*aS*,7*aR*,9*S*,10*aR*,10*bR*,10*cR*)- and (4*bS*,6*aS*,7*aR*,9*R*,10*aR*,10*bR*,10*cR*)-2-Methoxy-6*a*-methyl-9-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-4*b*,6,6*a*,7*a*,8,9,10,10*a*,10*b*,10*c*,11,12-dodecahydropentaleno[1,2-*a*]phenanthren-7(5*H*)-one (**50u**)

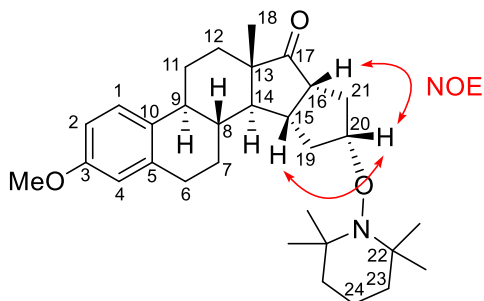
Prepared according to general procedure **F** from **28u** (78 mg, 0.16 mmol) in PhCF₃ (3.3 mL). Reaction performed at 160 °C for 1 h. Purification of the crude product by column chromatography (hexane/EtOAc, 20:1, gradient to 5:1) gave 21 mg of the major diastereoisomer of **50u** followed by 16 mg of the minor diastereoisomer. Yield 37 mg (48%) of **50u** as a separable 1.3:1 diastereoisomeric mixture as colorless oils.

Major diastereoisomer:



R_F = 0.47 (hexanes/EtOAc, 5:1). $[\alpha]^{20}_{589} = +107.0$ (c 0.20; CHCl₃). ¹H NMR (600.1 MHz, Chloroform-*d*) δ 7.20 (dd, J = 8.6, 1.0 Hz, 1H, CH_{Ar}-1), 6.72 (dd, J = 8.6, 2.8 Hz, 1H, CH_{Ar}-2), 6.63 (d, J = 2.8 Hz, 1H, CH_{Ar}-4), 4.16 (tt, J = 8.5, 6.0 Hz, 1H, CH-20), 3.78 (s, 3H, OMe), 3.08 (ddd, J = 11.2, 10.0, 3.9 Hz, 1H, CH-16), 2.97-2.86 (m, 2H, CH₂-6), 2.61 (dddd, J = 10.7, 10.0, 8.5, 2.0 Hz, 1H, CH-15), 2.29-2.19 (m, 2H, CH-9, CH₂-21^a), 2.41-2.35 (m, 1H, CH₂-11^a), 2.12 (ddt, J = 12.6, 5.4, 2.5 Hz, 1H, CH₂-7^a), 2.04 (ddt, J = 12.9, 6.0, 2.0 Hz, 1H, CH₂-19^a), 1.91 (dt, J = 12.9, 8.5 Hz, 1H, CH₂-19^b), 1.85 (dd, J = 9.0, 2.5 Hz, 1H, CH₂-12^a), 1.80 (ddd, J = 13.1, 11.2, 8.5 Hz, 1H, CH₂-21^b), 1.69 (dtd, J = 12.2, 10.7, 2.5 Hz, 1H, CH-8), 1.57-1.41 (m, 8H, CH₂-7^b, CH₂-11^b, CH₂-12^b, CH₂-23, CH₂-24^a), 1.37-1.28 (m, 1H, CH₂-24^b), 1.18 (bs, 3H, CH₃^{TEMPO}), 1.16 (bs, 3H, CH₃^{TEMPO}), 1.06 (bs, 6H, CH₃^{TEMPO}), 1.03 (t, J = 10.7 Hz, 1H, CH-14), 1.01 (s, 3H, CH₃-18). ¹³C NMR (150.9 MHz, Chloroform-*d*) δ 221.1 (C-17), 157.51 (C-3), 137.5 (C-5), 131.8 (C-10), 126.6 (C-1), 113.7 (C-4), 111.69 (C-2), 86.8 (C-20), 59.6 (C-22), 59.4 (C-22), 55.17 (OMe), 54.1 (C-14), 50.4 (C-13), 47.8 (C-16), 44.2 (C-9), 40.0 (C-23), 39.4 (C-8), 38.4 (C-19), 37.5 (C-15), 34.2 (CH₃^{TEMPO}), 33.9 (CH₃^{TEMPO}), 32.9 (C-21), 31.3 (C-12), 29.96 (C-6), 27.5 (C-7), 26.2 (C-11), 20.2 (CH₃^{TEMPO}), 20.1 (CH₃^{TEMPO}), 17.18 (C-24), 15.8 (C-18). **MS** (ESI⁺) m/z (%) 480 ([M+H⁺], 100). **HRMS** (ESI⁺) m/z [M+H⁺] calcd for C₃₁H₄₆NO₃: 480.3472; found: 480.3472. **IR** (neat): $\nu_{\max}$ = 2929, 2868, 1736, 1610, 1501, 1454, 1374, 1258, 1094, 1035, 909, 801, 730 cm⁻¹.

Minor diastereoisomer:

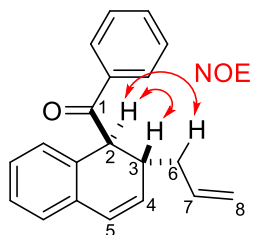


R_F = 0.34 (hexanes/EtOAc, 5:1). $[\alpha]^{20}_{589} = +112.0$ (c 0.20; CHCl₃). ¹H NMR (600.1 MHz, Chloroform-*d*) δ 7.22 (dd, J = 8.7, 1.1 Hz, 1H, CH_{Ar}-1), 6.73 (dd, J = 8.7, 2.8 Hz, 1H, CH_{Ar}-2), 6.65 (d, J = 2.8 Hz, 1H, CH_{Ar}-4), 4.28 (qd, J = 6.4, 5.3 Hz, 1H, CH-20), 3.78 (s, 3H, OMe), 2.97 (td, J = 10.1, 7.5 Hz, 1H, CH-16), 2.96-2.86 (m, 2H, CH₂-6), 2.50 (tdd, J = 10.1, 8.3, 4.4 Hz, 1H, CH-15), 2.41-2.36 (m, 1H, CH₂-11^a), 2.29-2.20 (m, 2H, CH-9, CH₂-19^a), 2.14-2.05 (m, 2H, CH₂-7^a, CH₂-21^a), 1.96 (ddd, J = 13.1, 7.5, 6.4, Hz, 1H, CH₂-21^b), 1.88 (ddd, J = 11.9, 3.4, 2.2 Hz, 1H, CH₂-12^a), 1.75 (ddd, J = 13.3, 6.4, 4.4

Hz, 1H, CH₂-19^b), 1.63 (t, J = 10.1 Hz, 1H, CH-14), 1.71-1.60 (m, 1H, CH-8), 1.60-1.45 (m, 4H, CH₂-7^b, CH₂-11^b, CH₂-12^b, CH₂-24^a), 1.45-1.42 (m, 4H, CH₂-23), 1.32-1.27 (m, 1H, CH₂-24^b), 1.19 (bs, 6H, CH₃^{TEMPO}), 1.04 (bs, 3H, CH₃^{TEMPO}), 1.01 (s, 6H, CH₃-18, CH₃^{TEMPO}). ¹³C NMR (150.9 MHz, Chloroform-*d*) δ 220.7 (C-17), 157.53 (C-3), 137.6 (C-5), 132.0 (C-10), 126.6 (C-1), 113.8 (C-4), 111.68 (C-2), 89.5 (C-20), 59.9 (C-22), 59.1 (C-22), 55.21 (OMe), 55.0 (C-14), 50.9 (C-13), 48.4 (C-16), 44.3 (C-9), 40.2 (C-23), 40.1 (C-23), 39.3 (C-8), 39.2 (C-19), 38.1 (C-15), 34.5 (CH₃^{TEMPO}), 34.0 (CH₃^{TEMPO}), 33.2 (C-21), 31.5 (C-12), 30.04 (C-6), 27.6 (C-7), 26.1 (C-11), 20.31 (CH₃^{TEMPO}), 20.25 (CH₃^{TEMPO}), 17.15 (C-24), 15.9 (C-18). MS (ESI⁺) m/z (%) 480 ([M+H⁺], 100).

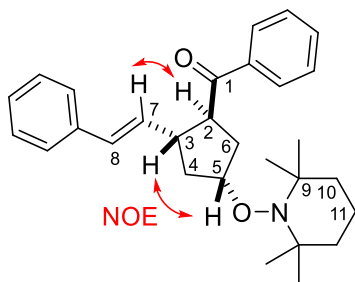
***trans*-2-Allyl-1-benzoyl-1,2-dihydronaphthalene (50ka) and (1*S**,2*R**,4*R**)- and (1*S**,2*R**,4*S**)-1-benzoyl-2-(*E*)-styryl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclopentane (50k)**

Prepared according to general procedure E from **28k** (55 mg, 0.13 mmol) in PhCF₃ (6.3 mL) at 140 °C for 90 min. Purification of the crude product by column chromatography (hexane/EtOAc, 20:1) gave 25 mg of a mixture containing dihydronaphthalene product **50ka** and the product of reduction followed by 11 mg (20%) of **50k** as an inseparable 1.4:1 diastereomeric mixture. The first fraction was repurified by second column chromatography (hexane/benzene, 2:1) to give 15 mg of **50ka** (43%) as a single diastereoisomer as a colorless oil.



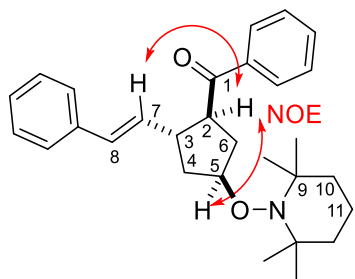
R_F = 0.37 (hexane/benzene, 1:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.01-7.95 (m, 2H, *o*-CH_{Ar}), 7.61-7.54 (m, 1H, *p*-CH_{Ar}), 7.48 (dd, J = 8.4, 6.9 Hz, 2H, *m*-CH_{Ar}), 7.23-7.18 (m, 1H, CH_{Ar}), 7.14-7.06 (m, 2H, CH_{Ar}), 6.91 (d, J = 7.4 Hz, 1H, CH_{Ar}), 6.50 (d, J = 9.9 Hz, 1H, CH-5), 5.89 (dd, J = 9.5, 4.6 Hz, 1H, CH-4), 5.86-5.78 (m, 1H, CH-7), 5.16-5.10 (m, 1H, CH₂-8), 5.03 (dd, J = 17.0, 1.8 Hz, 1H, CH₂-8), 4.73 (d, J = 6.2 Hz, 1H, CH-2), 3.03-2.93 (m, 1H, CH-3), 2.27-2.16 (m, 2H, CH₂-6). ¹³C NMR (126 MHz, Chloroform-*d*) δ 201.1 (C-1), 137.0 (C_{Ar}), 135.7 (C-7), 134.0 (C_{Ar}), 133.2 (CH_{Ar}), 132.1 (C_{Ar}), 130.1 (C-4), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.5 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.3 (CH_{Ar}), 126.6 (C-5), 118.1 (C-8), 49.8 (C-2), 37.9 (C-6), 37.0 (C-3). MS (EI) m/z (%) 274 ([M]⁺, 30), 233 ([M-CH₂CH=CH₂]⁺, 20), 169 ([M-COPh]⁺, 75), 141 ([M-COPh-CH₂CH=CH₂]⁺, 50), 128 ([M-PhCO-CH₂CH=CH₂]⁺, 60), 105 ([PhCO]⁺, 100). HRMS (EI) m/z [M]⁺ calcd for C₂₀H₁₈O: 274.1358; found: 274.1360. IR (neat): ν_{max} = 3062, 3031, 2924, 1683, 1596, 1447, 1277, 1208, 1000, 918, 783, 696 cm⁻¹.

Major diastereoisomer:



$R_F = 0.35$ (hexane/benzene, 1:1). $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 7.91-7.86 (m, 2H, CH_{Ar}), 7.50-7.34 (m, 3H, CH_{Ar}), 7.24-7.15 (m, 4H, CH_{Ar}), 7.13-7.06 (m, 1H, CH_{Ar}), 6.29 (d, $J = 15.8$ Hz, 1H, CH-8), 6.13 (dd, $J = 15.8, 7.9$ Hz, 1H, CH-7), 4.40 (quint, $J = 7.1$ Hz, 1H, CH-5), 3.66 (q, $J = 8.9$ Hz, 1H, CH-2), 3.05-2.96 (m, 1H, CH-3), 2.43 (dt, $J = 12.9, 6.6$ Hz, 1H, CH₂-4^a), 2.22-2.14 (m, 2H, CH₂-6), 1.78-1.67 (m, 1H, CH₂-4^b), 1.52-1.46 (m, 1H, CH₂-11^a), 1.42-1.35 (m, 4H, CH₂-10), 1.31-1.20 (m, 1H, CH₂-11^b), 1.17-0.98 (m, 12H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 201.8 (C-1), 137.5 (C_{Ar}), 137.1 (C_{Ar}), 133.2 (CH_{Ar}), 132.7 (C-7), 130.0 (C-8), 128.7 (2CH_{Ar}), 128.57 (CH_{Ar}), 127.2 (CH_{Ar}), 126.2 (CH_{Ar}), 86.7 (C-5), 59.7 (C-9), 50.5 (C-2), 43.9 (C-3), 40.8 (C-4), 40.3 (C-10), 37.6 (C-6), 34.42 (CH₃^{TEMPO}), 34.1 (CH₃^{TEMPO}), 20.5 (CH₃^{TEMPO}), 17.39 (C-11). **MS** (ESI+) m/z (%) 454 ([M+Na⁺], 10), 432 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₉H₃₈NO₂: 432.2897; found: 432.2894. **IR** (neat): $\nu_{\text{max}} = 3026, 2927, 2868, 1682, 1661, 1599, 1584, 1448, 1373, 1358, 1258, 1179, 1072, 1017, 965, 800, 748, 696 \text{ cm}^{-1}$.

Minor diastereoisomer:



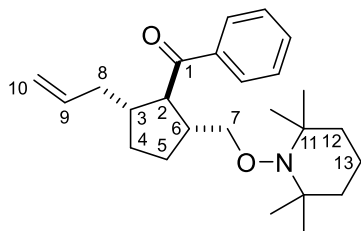
$^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.97-7.92 (m, 2H, CH_{Ar}), 7.56-7.50 (m, 1H, CH_{Ar}), 7.47-7.40 (m, 2H, CH_{Ar}), 7.29-7.20 (m, 5H, CH_{Ar}), 6.36 (dd, $J = 15.8, 1.0$ Hz, 1H, CH-8), 6.12 (dd, $J = 15.8, 8.0$ Hz, 1H, CH-7), 4.56-4.46 (m, 1H, CH-5), 3.49 (dt, $J = 10.5, 8.0$ Hz, 1H, CH-2), 3.38 (quint, $J = 8.2$ Hz, 1H, CH-3), 2.57 (dt, $J = 12.9, 7.3$ Hz, 1H, CH₂-6^a), 2.29-2.18 (m, 1H, CH₂-4^a), 2.08-1.94 (m, 2H, CH₂-4^b, CH₂-6^b), 1.64-1.51 (m, 1H, CH₂-11^a), 1.50-1.38 (m, 4H, CH₂-10), 1.34-1.17 (m, 1H, CH₂-11^b), 1.13 (bs, 3H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}), 1.06 (bs, 3H, CH₃^{TEMPO}), 1.05 (bs, 3H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 201.1 (C-1), 137.4 (C_{Ar}), 137.2 (C_{Ar}), 133.1 (CH_{Ar}), 132.9 (C-7), 129.8 (C-8), 128.7 (CH_{Ar}), 128.62 (CH_{Ar}), 128.57 (CH_{Ar}), 127.2 (CH_{Ar}), 126.2 (CH_{Ar}), 86.6 (C-5), 59.8 (C-9), 51.2 (C-2), 43.1 (C-3), 40.2 (C-10), 38.9 (C-4), 38.8 (C-6), 34.40 (CH₃^{TEMPO}), 34.2 (CH₃^{TEMPO}), 20.4 (CH₃^{TEMPO}), 17.38 (C-11).

PRE-based cyclization of α -aminoxy ketone 28m in the presence of TEMPO

Prepared according to general procedure E from **28m** (65 mg, 0.17 mmol) in PhCF₃ (3.4 mL) at 100 °C for 1 h. TEMPO (13 mg, 0.08 mmol) was added to the reaction mixture prior to heating. Purification of crude products by column chromatography (hexane/Et₂O, 10:1) gave 54 mg (83%) of a mixed fraction containing 3 diastereoisomers of **50m** in a 7:6:1 diastereoisomeric ratio followed by 5 mg (8%) of **50ma** as a single diastereoisomer. The first mixed fraction was purified for analytical purposes by semipreparative HPLC (hexane/EtOAc, 100:1). The least abundant diastereoisomer of 5-*exo*-trig cyclization was not obtained in a pure form and, therefore not characterized.

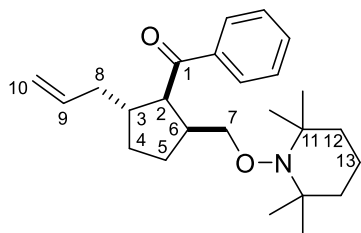
(1*S**,2*S**,3*S**)- and (1*S**,2*S**,3*R**)-1-Allyl-2-benzoyl-3-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)cyclopentane (50m)

Major diastereoisomer:



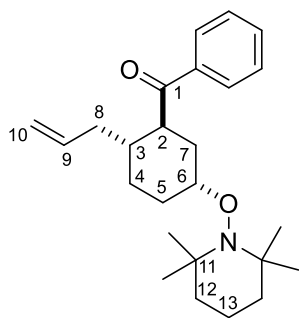
R_F = 0.37 (hexane/EtOAc, 10:1). $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 8.05-7.98 (m, 2H, *o*-CH_{Ar}), 7.56-7.50 (m, 1H, *p*-CH_{Ar}), 7.47-7.41 (m, 2H, *m*-CH_{Ar}), 5.68 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H, CH-9), 4.94 (dq, J = 17.1, 1.6 Hz, 1H, CH₂-10), 4.89 (ddt, J = 10.2, 2.2, 1.1 Hz, 1H, CH₂-10), 3.74-3.68 (m, 2H, CH₂-7), 3.37 (t, J = 7.7 Hz, 1H, CH-2), 2.67-2.57 (m, 1H, CH-6), 2.42 (quintd, J = 8.1, 6.0 Hz, 1H, CH-3), 2.18 (dddt, J = 14.1, 7.1, 5.9, 1.4 Hz, 1H, CH₂-8^a), 2.10 (dddt, J = 13.9, 8.4, 7.1, 1.3 Hz, 1H, CH₂-8^b), 2.02-1.84 (m, 2H, CH₂-4^a, CH₂-5^a), 1.65-1.52 (m, 1H, CH₂-5^b), 1.51-1.22 (m, 7H, CH₂-4^b, CH₂-12, CH₂-13), 1.05 (bs, 6H, CH₃^{TEMPO}), 0.96 (bs, 3H, CH₃^{TEMPO}), 0.80 (bs, 3H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 203.9 (C-1), 138.2 (C_{Ar}), 137.2 (C-9), 132.9 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 116.1 (C-10), 80.0 (C-7), 59.9 (C-11), 59.8 (C-11), 55.2 (C-2), 45.3 (C-3), 44.9 (C-6), 39.8 (C-12), 39.73 (C-12), 39.58 (C-8), 33.2 (CH₃^{TEMPO}), 33.0 (CH₃^{TEMPO}), 31.6 (C-4), 28.6 (C-5), 20.2 (CH₃^{TEMPO}), 20.1 (CH₃^{TEMPO}), 17.2 (C-13). **MS** (ESI+) m/z (%) 406 ([M+Na⁺], 50), 384 ([M+H⁺], 40), 227 ([M-TEMPO]⁺, 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₅H₃₈NO₂: 384.2897; found: 384.2894. **IR** (neat): ν_{max} = 3066, 2973, 2929, 2869, 1678, 1580, 1469, 1448, 1373, 1359, 1261, 1234, 1207, 1182, 1133, 1046, 994, 913, 789, 699, 666 cm⁻¹.

Minor diastereoisomer:



R_F = 0.36 (hexane/EtOAc, 10:1). $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 8.00-7.96 (m, 2H, *o*-CH_{Ar}), 7.53-7.48 (m, 1H, *p*-CH_{Ar}), 7.47-7.40 (m, 2H, *m*-CH_{Ar}), 5.74 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H, CH-9), 4.94 (dq, J = 17.1, 1.6 Hz, 1H, CH₂-10), 4.88 (ddt, J = 10.1, 2.2, 1.1 Hz, 1H, CH₂-10), 3.62 (dd, J = 9.2, 8.0 Hz, 1H, CH₂-7^a), 3.49-3.42 (m, 2H, CH₂-7^b, CH-2), 2.84-2.73 (m, 1H, CH-6), 2.60 (ttt, J = 9.3, 7.6, 5.9 Hz, 1H, CH-3), 2.18 (dddt, J = 12.9, 7.1, 5.8, 1.3 Hz, 1H, CH₂-8^a), 2.05-1.90 (m, 3H, CH₂-8^b, CH₂-5^a, CH₂-4^a), 1.61-1.48 (m, 1H, CH₂-5^b), 1.41-1.16 (m, 7H, CH₂-4^b, CH₂-12, CH₂-13), 1.05 (bs, 3H, CH₃^{TEMPO}), 0.84 (bs, 3H, CH₃^{TEMPO}), 0.79 (bs, 3H, CH₃^{TEMPO}), 0.61 (bs, 3H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 201.3 (C-1), 138.5 (C_{Ar}), 137.5 (C-9), 132.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 115.8 (C-10), 77.7 (C-7), 59.7 (C-11), 59.6 (C-11), 54.1 (C-2), 43.5 (C-6), 41.8 (C-3), 39.71 (C-12), 39.65 (C-12), 39.4 (C-8), 32.9 (CH₃^{TEMPO}), 30.7 (C-4), 29.6 (C-5), 20.0 (CH₃^{TEMPO}), 19.9 (CH₃^{TEMPO}), 17.2 (C-13). **IR** (neat): ν_{max} = 3064, 2972, 2929, 2869, 1677, 1598, 1469, 1448, 1373, 1359, 1261, 1243, 1209, 1133, 1046, 993, 846, 790, 763, 693, 663 cm⁻¹.

(1*R,3*S**,4*R**)-1-Allyl-2-benzoyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclohexane (50ma)**



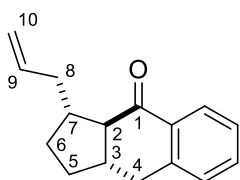
R_F = 0.28 (hexane/EtOAc, 10:1). $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.97-7.92 (m, 2H, *o*-CH_{Ar}), 7.52-7.46 (m, 1H, *p*-CH_{Ar}), 7.39 (t, J = 7.6 Hz, 2H, *m*-CH_{Ar}), 5.68 (dddd, J = 16.5, 10.1, 8.2, 6.1 Hz, 1H, CH-9), 4.88-4.80 (m, 2H, CH₂-10), 3.96 (quint, J = 3.5 Hz, 1H, CH-6), 3.54 (ddd, J = 11.9, 10.0, 3.2 Hz, 1H, CH-2), 2.13-2.02 (m, 3H, CH₂-8^a, CH₂-7^a, CH₂-5^a), 1.98-1.89 (m, 1H, CH-3), 1.80 (dt, J = 13.6, 8.3 Hz, 1H, CH₂-8^b), 1.63 (dq, J = 12.8, 3.6 Hz, 1H, CH₂-4^a), 1.48-1.23 (m, 9H, CH₂-12, CH₂-7^b, CH₂-5^b, CH₂-4^b, CH₂-13), 1.15-0.98 (m, 12H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 203.9 (C-1), 136.5 (C_{Ar}), 136.0 (CH-9), 132.4 (*p*-CH_{Ar}), 128.0 (*m*-CH_{Ar}), 127.7 (*o*-CH_{Ar}), 115.8 (C-10), 77.0 (C-6), 59.6 (C-11), 58.7 (C-11), 44.2 (C-2), 39.7 (C-12), 38.5 (C-8), 37.3 (C-3), 34.6 (C-7), 33.9 (CH₃^{TEMPO}), 33.5 (CH₃^{TEMPO}), 28.9 (C-5), 24.9 (C-4), 19.7 (CH₃^{TEMPO}), 19.5 (CH₃^{TEMPO}), 16.5 (C-13). **MS** (ESI+) m/z (%) 406 ([M+Na⁺], 20), 384 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₅H₃₈NO₂: 384.2897; found: 384.2898. **IR** (neat): ν_{max} = 3072, 3001, 2971, 2930, 2871, 1680, 1640, 1597, 1446, 1373, 1360, 1256, 1207, 1181, 1133, 968, 912, 715, 698 cm⁻¹.

PRE-based cyclization of α -aminoxy ketone 28m in the presence of ascorbic acid

A flame-dried microwave reaction tube was filled with **28m** (75 mg, 0.2 mmol) and dissolved in a 3:1 *t*BuOH/H₂O mixture (4.0 mL). Ascorbic acid (34 mg, 0.2 mmol) was added, and the reaction mixture was sonicated until homogeneous. The mixture was heated at 100 °C for 1 h. After cooling to r.t., the mixture was diluted with Et₂O (20 mL), washed with saturated NaHCO₃ solution (2×10 mL) and brine. The organic layer was dried over MgSO₄, filtered, and evaporated at reduced pressure. Purification of the crude products by column chromatography (hexane/Et₂O, 20:1) gave 10 mg of the minor diastereoisomer followed by 12 mg of the major diastereoisomer of **50mb** as colorless oils (yield 22 mg (50%)) followed by 10 mg (13%) of a mixed fraction containing three diastereoisomers of **50m** in 1.7:3.4:1 diastereoisomeric ratio followed by 2.3 mg (3%) of **50ma**.

(3*S**,3*aS**,9*aR**)- and (3*S**,3*aS**,9*aS**)-3-Allyl-1,2,3,3*a*,9,9*a*-hexahydro-4*H*-cyclopenta[*b*]naphthalen-4-one (**50mb**)

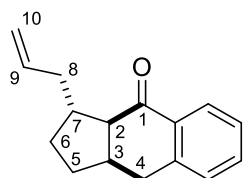
Major diastereoisomer:



R_F = 0.45 (hexane/EtOAc, 10:1). $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 7.99 (dd, J = 7.9, 1.5 Hz, 1H, CH_{Ar}), 7.46 (td, J = 7.5, 1.5 Hz, 1H, CH_{Ar}), 7.30 (td, J = 7.5, 1.2 Hz, 1H, CH_{Ar}), 7.23-7.19 (m, 1H, CH_{Ar}), 5.83 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, CH-9), 5.07 (ddd, J = 17.1, 2.5, 1.2 Hz, 1H, CH₂-10), 5.00 (ddt, J = 10.2, 2.2, 1.1 Hz, 1H, CH₂-10), 2.97 (dd, J = 16.2, 5.8 Hz, 1H, CH₂-4^a), 2.87-2.71 (m, 2H, CH₂-4^b, CH-3), 2.56-2.46 (m, 2H, CH₂-8^a, CH-2), 2.44-2.32 (m, 1H, CH-7), 2.17-2.07 (m, 1H, CH₂-8^b), 1.95 (dddd, J = 13.7, 8.4, 6.6, 4.9 Hz, 1H, CH₂-6^a), 1.90-1.78 (m, 1H, CH₂-5^a), 1.55-1.37 (m, 2H, CH₂-6^b, CH₂-5^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 200.6 (C-1), 142.6 (C_{Ar}), 137.3 (C-9),

133.6 (CH_{Ar}), 132.3 (C_{Ar}), 129.1 (CH_{Ar}), 127.3 (CH_{Ar}), 126.8 (CH_{Ar}), 116.1 (C-10), 55.3 (C-2), 41.7 (C-7), 39.6 (C-8), 38.7 (C-3), 31.4 (C-4), 30.8 (C-5), 30.1 (C-6). **MS** (EI) *m/z* (%) 226 ([M]⁺, 100), 158 ([M–pentadiene], 100). **HRMS** (EI) *m/z* [M]⁺ calcd for C₁₆H₁₈O: 226.1358; found: 226.1356. **IR** (neat): $\nu_{\max}$ = 3071, 2945, 2869, 1674, 1640, 1600, 1454, 1438, 1293, 1232, 1156, 995, 912, 754, 736 cm⁻¹.

Minor diastereoisomer:

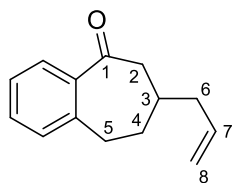


R_F = 0.38 (hexane/EtOAc, 10:1). **¹H NMR** (401 MHz, Chloroform-*d*) δ 8.02 (dd, J = 7.9, 1.5 Hz, 1H, CH_{Ar}), 7.49-7.42 (m, 1H, CH_{Ar}), 7.33-7.28 (m, 1H, CH_{Ar}), 7.26-7.21 (m, 1H, CH_{Ar}), 5.93-5.82 (m, 1H, CH-9), 5.05 (ddt, J = 17.1, 2.2, 1.5 Hz, 1H, CH₂-10), 5.00 (ddt, J = 10.2, 2.2, 1.1 Hz, 1H, CH₂-10), 3.17 (dd, J = 16.1, 3.4 Hz, 1H, CH₂-4^a), 2.84 (dd, J = 16.2, 10.8 Hz, 1H, CH₂-4^b), 2.59 (dddt, J = 13.9, 6.3, 4.6, 1.5 Hz, 1H, CH₂-8^a), 2.50-2.39 (m, 1H, CH-7), 2.22-2.06 (m, 3H, CH₂-8^b, CH-2, CH-3), 2.01-1.85 (m, 2H, CH₂-5^a, CH₂-6^a), 1.52-1.42 (m, 2H, CH₂-5^b, CH₂-6^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 199.8 (C-1), 144.3 (C_{Ar}), 137.4 (C-9), 134.0 (C_{Ar}), 133.0 (CH_{Ar}), 129.2 (CH_{Ar}), 127.2 (CH_{Ar}), 126.7 (CH_{Ar}), 115.9 (C-10), 59.7 (C-2), 44.9 (C-3), 40.4 (C-8), 37.12 (C-4), 37.07 (C-7), 31.1 (C-5), 29.1 (C-6).

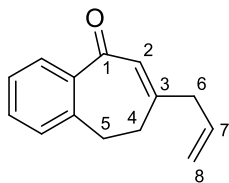
PRE-based cyclization of benzosuberone derivative 28q

In a microwave reaction tube, α -aminoxy ketone **28q** (125 mg, 0.35 mmol) was dissolved in dry PhCF₃ (7.0 mL). The mixture was heated to 150 °C for 2.5 h under microwave irradiation. The resulting mixture was evaporated at reduced pressure and separated by column chromatography (hexane/EtOAc, 40:1, gradient to 10:1) to yield 24 mg (34%) of the reduced product **27q**, followed by 11 mg (16%) of the α,β -unsaturated ketone **27qa**, followed by 9 mg (7%) of **27qb** as colorless oils.

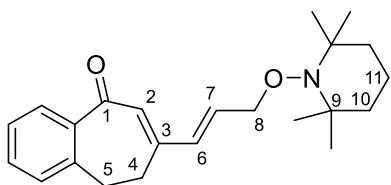
7-Allyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (27q)



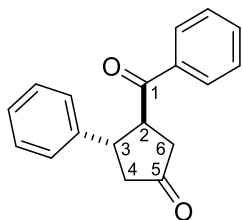
R_F = 0.30 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (dd, J = 7.6, 1.5 Hz, 1H, CH_{Ar}), 7.40 (td, J = 7.5, 1.5 Hz, 1H, CH_{Ar}), 7.29 (td, J = 7.5, 1.2 Hz, 1H, CH_{Ar}), 7.20 (d, J = 7.5 Hz, 1H, CH_{Ar}), 5.75 (ddt, J = 17.3, 10.4, 7.1 Hz, 1H, CH-7), 5.10-5.02 (m, 2H, CH₂-8), 3.02 (ddd, J = 14.9, 10.4, 4.1 Hz, 1H, CH₂-5^a), 2.88 (ddd, J = 15.5, 6.1, 3.5 Hz, 1H, CH₂-5^b), 2.80 (dd, J = 15.1, 3.5 Hz, 1H, CH₂-2^a), 2.60 (dd, J = 15.1, 9.3 Hz, 1H, CH₂-2^a), 2.19-2.08 (m, 2H, CH₂-6), 2.05-1.93 (m, 2H, CH-3, CH₂-4^a), 1.64-1.53 (m, 1H, CH₂-4^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 204.6 (C-1), 142.3 (C_{Ar}), 138.9 (C_{Ar}), 136.3 (C-7), 132.1 (CH_{Ar}), 129.9 (CH_{Ar}), 128.6 (CH_{Ar}), 126.7 (CH_{Ar}), 117.1 (C-8), 46.7 (C-2), 40.4 (C-6), 33.3 (C-3), 32.3 (C-4), 32.1 (C-5). **MS** (APCI) *m/z* (%) 201 ([M+H]⁺, 100). **HRMS** (APCI) *m/z* [M+H]⁺ calcd for C₁₄H₁₇O: 201.1274; found: 201.1276. **IR** (neat): $\nu_{\max}$ = 3070, 2924, 1674, 1640, 1599, 1448, 1289, 1253, 1239, 1022, 994, 958, 913, 766, 749, 604 cm⁻¹.

7-Allyl-8,9-dihydro-5H-benzo[7]annulen-5-one (27qa)

R_F = 0.22 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.76 (dd, J = 7.7, 1.5 Hz, 1H, CH_{Ar}), 7.40 (td, J = 7.4, 1.5 Hz, 1H, CH_{Ar}), 7.30 (td, J = 7.6, 1.3 Hz, 1H, CH_{Ar}), 7.17 (dd, J = 7.5, 1.3 Hz, 1H, CH_{Ar}), 6.23 (quint, J = 1.2 Hz, 1H, CH-2), 5.86-5.75 (m, 1H, CH-7), 5.17-5.11 (m, 2H, CH₂-8), 3.06-3.01 (m, 2H, CH₂-5), 2.99-2.94 (m, 2H, CH₂-6), 2.58-2.52 (m, 2H, CH₂-4). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 193.8 (C-1), 160.1 (C-3), 140.0 (C_{Ar}), 139.5 (C_{Ar}), 134.2 (CH-7), 132.1 (CH_{Ar}), 130.0 (CH_{Ar}), 129.7 (C-2), 128.7 (CH_{Ar}), 126.9 (CH_{Ar}), 118.4 (C-8), 44.9 (C-6), 34.2 (C-5), 33.6 (C-4). **MS** (APCI) m/z (%) 199 ([M+H⁺], 100). **HRMS** (APCI) m/z [M+H⁺] calcd for C₁₄H₁₅O: 199.1117; found: 199.1118. **IR** (neat): ν_{max} = 3069, 2919, 1680, 1630, 1448, 1304, 1231, 1161, 1111, 1072, 1036, 994, 968, 918, 872, 749, 616 cm⁻¹.

(*E*)-7-(3-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)prop-1-en-1-yl)-8,9-dihydro-5H-benzo[7]annulen-5-one (27qb)

R_F = 0.16 (hexanes/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.79 (dd, J = 7.7, 1.5 Hz, 1H, CH_{Ar}), 7.41 (td, J = 7.4, 1.5 Hz, 1H, CH_{Ar}), 7.31 (td, J = 7.6, 1.3 Hz, 1H, CH_{Ar}), 7.20 (dd, J = 7.6, 1.2 Hz, 1H, CH_{Ar}), 6.41 (dt, J = 15.9, 1.8 Hz, 1H, CH-6), 6.33 (s, 1H, CH-2), 6.19 (dt, J = 16.0, 5.4 Hz, 1H, CH-7), 4.43 (dd, J = 5.2, 1.6 Hz, 2H, CH₂-8), 3.12-3.07 (m, 2H, CH₂-5), 2.79-2.74 (m, 2H, CH₂-4), 1.64-1.53 (m, 1H, CH₂-11^a), 1.49-1.41 (m, 4H, CH₂-10), 1.38-1.28 (m, 1H, CH₂-11^b), 1.16 (bs, 6H, CH₃^{TEMPO}), 1.12 (bs, 6H, CH₃^{TEMPO}). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 193.9 (C-1), 154.0 (C-3), 140.2 (C_{Ar}), 139.3 (C_{Ar}), 134.0 (C-6), 132.3 (C-2), 132.2 (CH_{Ar}), 131.9 (C-7), 129.7 (CH_{Ar}), 128.7 (CH_{Ar}), 127.0 (CH_{Ar}), 77.5 (C-8), 60.0 (C-9), 39.8 (C-10), 33.8 (C-5), 33.1 (CH₃^{TEMPO}), 29.2 (C-4), 20.3 (CH₃^{TEMPO}), 17.2 (C-11). **MS** (ESI+) m/z (%) 707 ([2M+H⁺], 30), 354 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+H⁺] calcd for C₂₃H₃₂O₂N: 354.2428; found: 354.2431. **IR** (neat): ν_{max} = 2974, 2930, 2867, 1678, 1625, 1596, 1448, 1375, 1359, 1350, 1306, 1244, 1151, 1116, 1075, 1036, 960, 752 cm⁻¹.

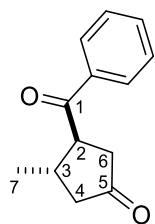
(3*S,4*S**)-3-Benzoyl-4-phenylcyclopentan-1-one (51a)**

Prepared according to general procedure **G** from **50a** (52 mg, 0.13 mmol, 1.6:1 mixture of diastereoisomers). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 27 mg (80%) of **51a** as a single diastereoisomer as an off-white solid.

R_F = 0.20 (hexanes/EtOAc, 5:1). **m.p.** 109-111°C. $^1\text{H NMR}$ (401 MHz, Chloroform-*d*) δ 7.73 (dd, J = 8.4, 1.4 Hz, 2H, CH_{Ar}), 7.48-7.43 (m, 1H, CH_{Ar}), 7.34-7.30 (m, 2H, CH_{Ar}), 7.23-7.11 (m, 5H, CH_{Ar}), 4.14 (dt, J = 9.5, 8.3 Hz, 1H, CH-2), 3.80 (dt, J = 10.1, 8.4 Hz, 1H, CH-3), 2.81 (dd, J = 18.6, 8.3 Hz, 1H, CH₂-4^a), 2.73-2.57 (m, 2H, CH₂-6), 2.53 (dd, J = 18.7, 10.0 Hz, 1H, CH₂-4^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 215.0 (C-5), 200.2 (C-1), 141.7

(C_{Ar}), 136.3 (C_{Ar}), 133.7 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.5 (CH_{Ar}), 127.3 (CH_{Ar}), 127.2 (CH_{Ar}), 50.8 (C-2), 45.5 (C-4), 45.2 (C-3), 43.0 (C-6). **MS** (CI⁺) *m/z* (%) 265 ([M+H]⁺, 100), 264 ([M]⁺, 50), 161 ([M-PhCH=CH₂+H]⁺, 60), 160 ([M-PhCO+H]⁺, 15), 159 ([M-PhCO]⁺, 20), 105 ([PhCO]⁺, 30). **HRMS** (CI⁺) *m/z* [M+H]⁺ calcd for C₁₈H₁₇O₂: 265.1229; found: 265.1230. **IR** (neat): $\nu_{\max}$ = 3061, 3030, 2910, 1744, 1677, 1596, 1495, 1449, 1364, 1232, 1187, 1145, 1014, 765, 698 cm⁻¹.

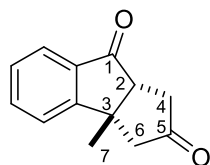
(3*S,4*S**)-3-Benzoyl-4-methylcyclopentan-1-one (51n)**



Prepared according to general procedure **G** from **50n** (34 mg, 0.10 mmol, 1.6:1 mixture of diastereoisomers). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1, gradient to 3:1) gave 19 mg (95%) of **51n** as a single diastereoisomer as a thick colorless oil.

R_F = 0.30 (hexanes/EtOAc, 3:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 8.02-7.94 (m, 2H, *o*-CH_{Ar}), 7.64-7.56 (m, 1H, *p*-CH_{Ar}), 7.50 (t, *J* = 7.7 Hz, 2H, *m*-CH_{Ar}), 3.76 (q, *J* = 8.1 Hz, 1H, CH-2), 2.76-2.63 (m, 1H, CH-3), 2.61-2.52 (m, 3H, CH₂-6, CH₂-4^a), 1.98 (dd, *J* = 18.1, 8.7 Hz, 1H, CH₂-4^b), 1.17 (d, *J* = 6.6 Hz, 3H, CH₃-7). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 216.0 (C-5), 200.7 (C-1), 136.7 (C_{Ar}), 133.7 (*p*-CH_{Ar}), 129.0 (*m*-CH_{Ar}), 128.5 (*o*-CH_{Ar}), 50.1 (C-2), 46.0 (C-4), 42.4 (C-6), 35.0 (C-3), 20.0 (C-7). **MS** (CI⁺) *m/z* (%) 203 ([M+H]⁺, 100), 202 ([M]⁺, 20), 160 ([M-CH₃CH=CH₂]⁺, 20). **HRMS** (CI⁺) *m/z* [M+H]⁺ calcd for C₁₃H₁₅O₂: 203.1072; found: 203.1074. **IR** (neat): $\nu_{\max}$ = 2960, 2928, 2873, 1744, 1674, 1596, 1448, 1402, 1220, 1198, 1019, 982, 916, 846, 776, 698 cm⁻¹.

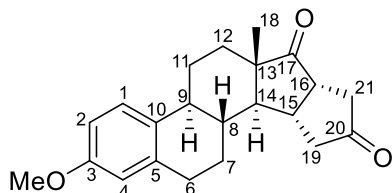
(3*aS,8*aR**)-3a-Methyl-1,3,3a,8a-tetrahydrocyclopenta[a]indene-2,8-dione (51p)**



Prepared according to general procedure **G** from **50p** (8.8 mg, 0.03 mmol, 1.5:1 mixture of diastereoisomers). Purification of the crude product by column chromatography (hexane/EtOAc, 5:1, gradient to 1:1) gave 4.8 mg (92%) of **51p** as a single diastereoisomer as a thick colorless oil.

R_F = 0.57 (hexanes/EtOAc, 1:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 7.69 (td, *J* = 7.5, 1.3 Hz, 1H, CH_{Ar}), 7.54 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 7.46-7.42 (m, 1H, CH_{Ar}), 3.04 (dd, *J* = 11.7, 4.5 Hz, 1H, CH-2), 2.87 (ddd, *J* = 19.5, 11.6, 1.7 Hz, 1H, CH₂-4^a), 2.68 (ddd, *J* = 19.6, 4.5, 1.5 Hz, 1H, CH₂-4^b), 2.61 (dd, *J* = 18.7, 1.8 Hz, 1H, CH₂-6^a), 2.46 (dd, *J* = 18.6, 1.5 Hz, 1H, CH₂-6^b), 1.63 (s, 3H, CH₃-7). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 215.6 (C-5), 206.0 (C-1), 161.0 (C_{Ar}), 136.0 (C_{Ar}), 134.7 (CH_{Ar}), 128.5 (CH_{Ar}), 124.5 (CH_{Ar}), 124.3 (CH_{Ar}), 56.3 (C-2), 52.2 (C-6), 46.4 (C-3), 40.3 (C-4), 27.6 (C-7). **MS** (CI⁺) *m/z* (%) 201 ([M+H]⁺, 100), 200 ([M]⁺, 20), 185 ([M-CH₄+H]⁺, 10). **HRMS** (CI⁺) *m/z* [M+H]⁺ calcd for C₁₃H₁₃O₂: 201.0916; found: 201.0916. **IR** (neat): $\nu_{\max}$ = 2958, 2922, 2851, 1742, 1710, 1603, 1465, 1402, 1326, 1292, 1257, 1213, 1170, 938, 769 cm⁻¹.

(4*bS*,6*aS*,7*aR*,10*aR*,10*bR*,10*cR*)-2-Methoxy-6*a*-methyl-4*b*,5,6,6*a*,7*a*,8,10,10*a*,10*b*,10*c*,11,12-dodecahydropentaleno[1,2-*a*]phenanthrene-7,9-dione (**51u**)



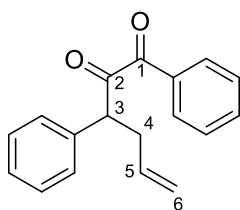
Prepared according to general procedure **G** from **50u** (28 mg, 0.06 mmol, 1.3:1 mixture of diastereoisomers). Purification of the crude product by column chromatography (hexane/EtOAc, 5:1, gradient to 1:1) gave 16 mg (81%) of **51u** as a single diastereoisomer as an off-white solid.

R_F = 0.43 (hexanes/EtOAc, 1:1). **m.p.** 195-197 °C. $[\alpha]^{20}_{589} = +92.0$ (c 0.20; CHCl₃). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.21 (d, J = 8.6 Hz, 1H, CH-1), 6.73 (dd, J = 8.7, 2.8 Hz, 1H, CH-2), 6.63 (d, J = 2.8 Hz, 1H, CH-4), 3.78 (s, 3H, OMe), 3.39 (ddd, J = 12.6, 10.0, 7.3 Hz, 1H, CH-16), 3.00-2.84 (m, 3H, CH-15, CH₂-6), 2.77-2.54 (m, 2H, CH₂-19^a, CH₂-21^a), 2.47-2.32 (m, 3H, CH₂-19^b, CH₂-21^b, CH₂-11^a), 2.32-2.20 (m, 1H, CH-9), 2.06-1.91 (m, 2H, CH₂-7^a, CH₂-12^a), 1.79 (dtd, J = 13.0, 10.7, 2.5 Hz, 1H, CH-8), 1.57-1.45 (m, 3H, CH₂-11^b, CH₂-12^b, CH₂-7^b), 1.33-1.21 (m, 1H, CH-14), 1.09 (s, 3H, CH₃-18). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 219.0 (C-17), 217.6 (C-20), 157.8 (C-3), 137.3 (C-5), 131.4 (C-10), 126.9 (C-1), 113.9 (C-4), 112.0 (C-2), 55.3 (OMe), 55.1 (C-14), 50.3 (C-13), 45.7 (C-16), 44.4 (C-19), 44.2 (C-9), 39.6 (C-8), 37.8 (C-21), 36.1 (C-15), 31.7 (C-12), 30.0 (C-6), 27.6 (C-7), 26.3 (C-11), 15.6 (C-18). **MS** (EI) m/z (%) 338 ([M]⁺, 100), 336 ([M-H₂]⁺, 40). **HRMS** (EI) m/z [M]⁺ calcd for C₂₂H₂₆O₃: 338.1882; found: 338.1884. **IR** (neat): $\nu_{\max}$ = 2928, 2857, 1735, 1609, 1501, 1456, 1280, 1256, 1237, 1167, 1144, 1041, 909, 730 cm⁻¹.

Oxidation of the α -aminoxy ketone **28a by *m*CPBA**

Prepared according to general procedure **G** from **28a** (56 mg, 0.14 mmol, 4.5:1 mixture of diastereoisomers). Purification of the crude product by column chromatography (hexane/EtOAc, 10:1) gave 25 mg (68%) of **52a** as a colorless oil followed by 6 mg (16%) of **53a** as an inseparable 4.5:1 diastereoisomeric mixture as a colorless oil.

1,3-Diphenylhex-5-ene-1,2-dione (52a**)**

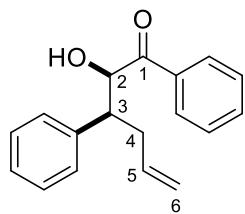


R_F = 0.55 (hexanes/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.76 - 7.71 (m, 2H, CH_{Ar}), 7.55-7.49 (m, 1H, CH_{Ar}), 7.40-7.33 (m, 2H, CH_{Ar}), 7.31-7.17 (m, 5H, CH_{Ar}), 5.74 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H, CH-5), 5.10 (dq, J = 17.0, 1.6 Hz, 1H, CH₂-6), 5.00 (dq, J = 10.2, 1.3 Hz, 1H, CH₂-6), 4.64 (t, J = 7.5 Hz, 1H, CH-3), 2.96 (dtt, J = 14.4, 7.1, 1.3 Hz, 1H, CH₂-4^a), 2.63 (dddt, J = 14.5, 8.0, 6.7, 1.4 Hz, 1H, CH₂-4^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 199.9 (C-2), 192.6 (C-1), 135.3 (C_{Ar}), 135.1 (C-5), 134.4 (CH_{Ar}), 132.4 (C_{Ar}), 130.2 (CH_{Ar}), 129.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 127.9 (CH_{Ar}), 117.3 (C-6), 53.1 (C-3), 35.1 (C-4). **MS** (ESI⁺) m/z (%) 319 ([M+MeOH+Na⁺], 30), 287 ([M+Na⁺], 100). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₁₈H₁₆O₂Na:

287.1043; found: 287.1041. **IR** (neat): $\nu_{\max}$ = 3064, 3030, 3006, 2918, 1804, 1710, 1670, 1596, 1580, 1492, 1450, 1273, 1236, 1182, 1128, 1096, 999, 919, 699 cm^{-1} .

(2*R,3*S**)- and (2*R**,3*R**)-2-hydroxy-1,3-diphenylhex-5-en-1-one (53a)**

Major diastereoisomer:



R_F = 0.28 (hexanes/EtOAc, 10:1). **^1H NMR** (400 MHz, Chloroform-*d*) δ 7.93-7.87 (m, 2H, CH_{Ar}), 7.66-7.60 (m, 1H, CH_{Ar}), 7.54-7.47 (m, 2H, CH_{Ar}), 7.38-7.28 (m, 4H, CH_{Ar}), 7.28-7.14 (m, 1H, CH_{Ar}), 5.50-5.35 (m, 1H, CH-5), 5.25-5.21 (m, 1H, CH-2), 4.84 (dd, J = 17.1, 1.7 Hz, 1H, CH_2 -6), 4.79 (dd, J = 10.2, 1.8 Hz, 1H, CH_2 -6), 3.83 (d, J = 6.4 Hz, 1H, OH), 3.11 (ddd, J = 10.3, 4.9, 2.7 Hz, 1H, CH-3), 2.58-2.47 (m, 1H, CH_2 -4^a), 2.30-2.21 (m, 1H, CH_2 -4^b). **^{13}C**

NMR (101 MHz, Chloroform-*d*) δ 201.7 (C-1), 141.9 (C_{Ar}), 136.0 (C-5), 134.1 (C_{Ar}), 134.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.7 (CH_{Ar}), 128.54 (CH_{Ar}), 128.46 (CH_{Ar}), 127.0 (CH_{Ar}), 116.7 (C-6), 77.1 (C-2), 49.7 (C-3), 32.9 (C-4). **MS** (ESI+) m/z (%) 289 ($[\text{M}+\text{Na}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Na}$: 289.1199; found: 289.1197. **IR** (neat): $\nu_{\max}$ = 3462, 3063, 3029, 3004, 2977, 2919, 1679, 1598, 1493, 1450, 1267, 1097, 985, 915, 753, 699 cm^{-1} .

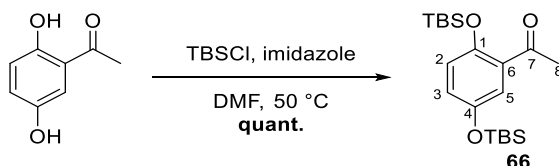
Minor diastereoisomer:

^1H NMR (400 MHz, Chloroform-*d*) δ 7.83-7.77 (m, 2H, CH_{Ar}), 7.66-7.60 (m, 1H, CH_{Ar}), 7.54-7.47 (m, 2H, CH_{Ar}), 7.38-7.28 (m, 4H, CH_{Ar}), 7.28-7.14 (m, 1H, CH_{Ar}), 5.94-5.82 (m, 1H, CH-5), 5.38-5.35 (m, 1H, CH-2), 5.28-5.12 (m, 2H, CH_2 -6), 3.53 (d, J = 7.0 Hz, 1H, OH), 3.18-3.13 (m, 1H, CH-3), 2.88 (dt, J = 15.9, 8.4 Hz, 1H, CH_2 -4^a), 2.67-2.58 (m, 1H, CH_2 -4^b). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 202.7 (C-1), 141.9 (C_{Ar}), 136.2 (C-5), 134.4 (C_{Ar}), 133.8 (CH_{Ar}), 129.0 (CH_{Ar}), 128.6 (CH_{Ar}), 128.49 (CH_{Ar}), 128.0 (CH_{Ar}), 127.2 (CH_{Ar}), 117.8 (C-6), 74.6 (C-2), 49.6 (C-3), 36.7 (C-4).

TOTAL SYNTHESIS OF *GANODERMA* MEROTERPENOIDS

6.3.5. Synthesis of the common intermediate

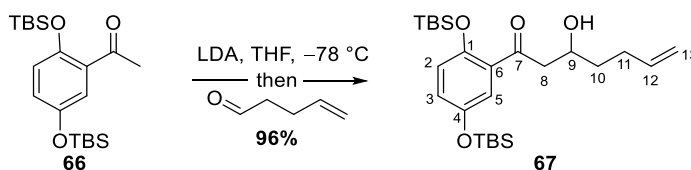
1-(2',5'-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)ethan-1-one (**66**)



In a 100 mL round-bottomed flask, 1-(2',5'-dihydroxyphenyl)ethan-1-one (3.0 g, 19.7 mmol) and imidazole (4.03 g, 59.2 mmol) were dissolved in DMF (50 mL). TBSCl (6.69 g, 44.4 mmol) was added, and the resulting mixture was stirred at 50 °C for 28 h. The mixture was diluted with hexane (100 mL) and Et₂O (20 mL), washed by brine (3×30 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure to give 7.49 g (quant.) of **66** as a colorless oil that was used without further purification.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.05 (d, *J* = 3.1 Hz, 1H, CH-5), 6.83 (dd, *J* = 8.8, 3.1 Hz, 1H, CH-3), 6.73 (d, *J* = 8.8 Hz, 1H, CH-2), 2.58 (s, 3H, CH₃-8), 0.99 (s, 9H, *t*Bu), 0.97 (s, 9H, *t*Bu), 0.23 (s, 6H, SiCH₃), 0.17 (s, 6H, SiCH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 200.7 (C-7), 149.6 (C-1), 149.1 (C-4), 131.8 (C-6), 124.6 (C-3), 121.1 (C-2), 120.4 (C-5), 31.4 (C-8), 26.0 (C(CH₃)₃), 25.8 (C(CH₃)₃), 18.6 (C(CH₃)₃), 18.3 (C(CH₃)₃), -3.9 (CH₃), -4.4 (CH₃). The spectral data match those reported in the literature.^[161]

1-(2',5'-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)-3-hydroxyhept-6-en-1-one (**67**)

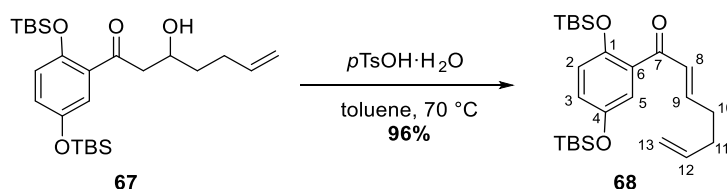


In a flame-dried Schlenk flask, DIPA (0.2 mL, 1.42 mmol) was dissolved in dry THF (2.0 mL). After cooling to -78 °C, BuLi (1.6M in hexanes, 0.9 mL, 1.44 mmol) was dropwise added. The mixture was stirred for 20 min, and **66** (500 mg, 1.31 mmol) in THF (5 mL) was dropwise added. The resulting mixture was stirred at -78 °C for 30 min and pent-4-enal (0.15 mL, 1.52 mmol) in THF (3.0 mL) was dropwise added. The mixture was stirred for 30 min and quenched by saturated NH₄Cl solution (20 mL). The layers were separated, and the aqueous was extracted with Et₂O (3×20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure to give 588 mg (96%) of essentially pure product **67** that was used without further purification.

*R*_F = 0.27 (hexanes/Et₂O, 5:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.07 (d, *J* = 3.0 Hz, 1H, CH-5), 6.85 (dd, *J* = 8.8, 3.1 Hz, 1H, CH-3), 6.73 (d, *J* = 8.6 Hz, 1H, CH-2), 5.84 (ddt, *J* = 16.9, 10.2, 6.7 Hz,

1H, CH-12), 5.04 (dq, $J = 17.1, 1.7$ Hz, 1H, CH₂-13), 4.97 (ddt, $J = 10.2, 2.2, 1.2$ Hz, 1H, CH₂-13), 4.20-4.11 (m, 1H, CH-9), 3.33 (bs, 1H, OH), 3.23 (dd, $J = 18.1, 2.3$ Hz, 1H, CH₂-8^a), 3.01 (dd, $J = 18.1, 9.4$ Hz, 1H, CH₂-8^b), 2.32-2.11 (m, 2H, CH₂-11), 1.65 (dddd, $J = 13.8, 9.2, 8.3, 5.7$ Hz, 1H, CH₂-10^a), 1.52 (dddd, $J = 13.7, 9.4, 6.6, 4.4$ Hz, 1H, CH₂-10^b), 0.99 (s, 9H, *t*Bu), 0.97 (s, 9H, *t*Bu), 0.25 (s, 3H, SiCH₃), 0.24 (s, 3H, SiCH₃), 0.18 (s, 6H, SiCH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 203.6 (C-7), 149.7 (C-1), 149.2 (C-4), 138.5 (C-12), 130.9 (C-6), 125.1 (C-3), 121.2 (C-2), 120.3 (C-5), 114.9 (C-13), 67.5 (C-9), 50.2 (C-8), 35.8 (C-10), 29.9 (C-11), 26.1 (C(CH₃)₃), 25.8 (C(CH₃)₃), 18.6 (C(CH₃)₃), 18.3 (C(CH₃)₃), -3.78 (SiCH₃), -3.80 (SiCH₃), -4.3 (SiCH₃). MS (ESI+) m/z (%) 951 ([2M+Na⁺], 10), 503 ([M+K⁺], 20), 487 ([M+Na⁺], 70), 465 ([M+H⁺], 30), 447 ([M-H₂O+H⁺], 20), 365 ([M-H₂O-hexadiene+H⁺], 30). HRMS (ESI+) m/z [M+Na⁺] calcd for C₂₅H₄₄O₄NaSi₂: 487.2670; found: 487.2671. IR (neat): $\nu_{\max} = 3502, 2955, 2930, 2859, 1670, 1483, 1408, 1255, 1214, 1161, 1006, 904, 836, 801, 779, 686$ cm⁻¹.

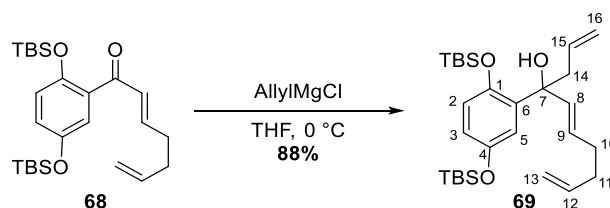
(E)-1-(2',5'-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)hepta-2,6-dien-1-one (68)



In a 25 mL round-bottomed flask, β -hydroxy ketone **67** (288 mg, 0.62 mmol) was dissolved in toluene (6.5 mL). At r.t. *p*TsOH·H₂O (10 mg, 0.05 mmol) was added, and the mixture was stirred at 70 °C for 1 h. After cooling to r.t., the mixture was diluted with Et₂O (30 mL) filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give 265 mg (96%) of essentially pure product **68** that was used in the next step without further purification.

$R_F = 0.68$ (hexanes/Et₂O, 5:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 6.91 (d, $J = 3.0$ Hz, 1H, CH-5), 6.87-6.83 (m, 1H, CH-9), 6.81 (dd, $J = 8.7, 3.1$ Hz, 1H, CH-3), 6.71 (d, $J = 8.2$ Hz, 1H, CH-2), 6.68 (dt, $J = 15.4, 1.4$ Hz, 1H, CH-8), 5.81 (ddt, $J = 16.7, 10.2, 6.5$ Hz, 1H, CH-12), 5.05 (dq, $J = 17.1, 1.6$ Hz, 1H, CH₂-13), 5.00 (ddt, $J = 10.2, 1.9, 1.2$ Hz, 1H, CH₂-13), 2.41-2.29 (m, 2H, CH₂-10), 2.28-2.19 (m, 2H, CH₂-11), 0.96 (s, 9H, *t*Bu), 0.94 (s, 9H, *t*Bu), 0.17 (s, 6H, SiCH₃), 0.14 (s, 6H, SiCH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 193.8 (C-7), 149.7 (C-1), 148.1 (C-4), 147.8 (C-9), 137.4 (C-12), 132.5 (C-6), 131.1 (C-8), 123.8 (C-3), 121.2 (C-2), 120.7 (C-5), 115.6 (C-13), 32.3 (C-11), 32.1 (C-10), 25.9 (C(CH₃)₃), 25.8 (C(CH₃)₃), 18.30 (C(CH₃)₃), 18.28 (C(CH₃)₃), -4.2 (SiCH₃), -4.4 (SiCH₃). MS (CI+) m/z (%) 447 ([M+H⁺], 95), 431 ([M-CH₃]⁺, 40), 389 ([M-butane+H⁺], 100). HRMS (CI+) m/z [M+H⁺] calcd for C₂₅H₄₃O₃Si₂: 447.2751; found: 447.2751. IR (neat): $\nu_{\max} = 2955, 2930, 2887, 2858, 1666, 1620, 1482, 1410, 1255, 1212, 1173, 907, 837, 800, 778, 684$ cm⁻¹.

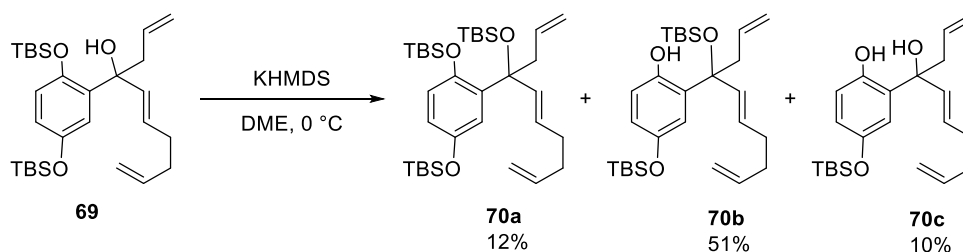
(E)-4-(2',5'-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)deca-1,5,9-trien-4-ol (69)



In a flame-dried Schlenk flask, α,β -unsaturated ketone **68** (250 mg, 0.56 mmol) was dissolved in THF (11 mL) under an argon atmosphere. At $-30\text{ }^{\circ}\text{C}$ allylmagnesium chloride (2M in THF, 0.36 mL, 0.72 mmol) was dropwise added by syringe. The mixture was stirred at this temperature for 5 min, quenched by saturated NH_4Cl solution (25 mL), and extracted by Et_2O ($3\times 25\text{ mL}$). The combined organic layers were washed with brine ($2\times 25\text{ mL}$), dried over MgSO_4 , filtered, and evaporated at reduced pressure. The crude product was purified by column chromatography (hexane/ Et_2O , 10:1) to yield 240 mg (88%) of **69** as a colorless oil.

$R_F = 0.32$ (hexanes/ Et_2O , 5:1). $^1\text{H NMR}$ (400 MHz, CHCl_3 - d) δ 6.83 (d, $J = 3.0\text{ Hz}$, 1H, CH-5), 6.68 (d, $J = 8.7\text{ Hz}$, 1H, CH-2), 6.60 (dd, $J = 8.7, 3.0\text{ Hz}$, 1H, CH-3), 5.86 (dt, $J = 15.6, 1.3\text{ Hz}$, 1H, CH-8), 5.85–5.74 (m, 2H, CH-12, CH-15), 5.53 (dt, $J = 15.5, 6.3\text{ Hz}$, 1H, CH-9), 5.13–4.91 (m, 4H, CH_2 -13, CH_2 -16), 4.43 (s, 1H, OH), 2.83 (dd, $J = 14.2, 7.0\text{ Hz}$, 1H, CH_2 -14^a), 2.64 (ddt, $J = 14.2, 7.0, 1.4\text{ Hz}$, 1H, CH_2 -14^b), 2.17–2.08 (m, 4H, CH_2 -10, CH_2 -11), 1.01 (s, 9H, *t*Bu), 0.97 (s, 9H, *t*Bu), 0.31 (s, 3H, SiCH₃), 0.28 (s, 3H, SiCH₃), 0.16 (s, 6H, SiCH₃). $^{13}\text{C NMR}$ (101 MHz, CHCl_3 - d) δ 149.1 (C-4), 147.3 (C-1), 138.2 (C-15), 135.9 (C-8), 135.3 (C-6), 134.4 (C-12), 128.7 (C-9), 119.9 (C-5), 118.7 (C-2), 118.6 (C-3), 117.7 (C-16), 114.7 (C-13), 76.1 (C-7), 45.2 (C-14), 33.4 (C-11), 31.8 (C-10), 26.0 ($\text{C}(\text{CH}_3)_3$), 25.8 ($\text{C}(\text{CH}_3)_3$), 18.3 ($\text{C}(\text{CH}_3)_3$), 18.2 ($\text{C}(\text{CH}_3)_3$), -3.7 (SiCH₃), -3.8 (SiCH₃), -4.43 (SiCH₃), -4.44 (SiCH₃). **MS** (ESI+) m/z (%) 527 ($[\text{M}+\text{K}^+]$, 15), 511 ($[\text{M}+\text{Na}^+]$, 30), 471 ($[\text{M}-\text{H}_2\text{O}+\text{H}^+]$, 100), 415 ($[\text{M}-\text{H}_2\text{O}-\text{butene}+\text{H}^+]$, 75). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{28}\text{H}_{48}\text{O}_3\text{NaSi}_2$: 511.3034; found: 511.3033. **IR** (neat): $\nu_{\text{max}} = 3517, 3076, 2955, 2930, 2897, 2858, 1640, 1607, 1577, 1483, 1411, 1254, 1210, 992, 906, 836, 802, 777, 685\text{ cm}^{-1}$.

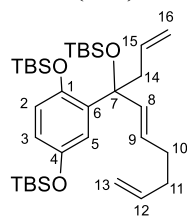
Rearrangement of alcohol 69



In a flame-dried Schlenk flask, alcohol **69** (65 mg, 0.13 mmol) was dissolved in DME (3.0 mL). At $0\text{ }^{\circ}\text{C}$, KHMDS (1M in THF, 0.17 mL, 0.17 mmol) was dropwise added. The mixture was stirred for 15 min, quenched by 10 drops of saturated NH_4Cl solution, diluted with Et_2O , and filtered through a plug of silica gel, which was washed with Et_2O . The solvents were evaporated to give the crude

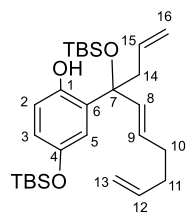
products that were separated by column chromatography (hexane/EtOAc, 50:1, gradient to 10:1) to yield 9 mg (12%) of trisilylated product **70a**, followed by 33 mg (51%) of phenol **70b**, and 5 mg (10%) of the alcohol **70c** as colorless oils.

(E)-4-(tert-Butyldimethylsilyl)oxy-4-(2',5'-bis((tert-butyldimethylsilyl)oxy)phenyl)deca-1,5,9-trien (70a)



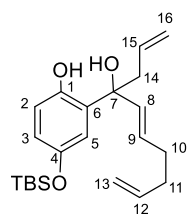
R_F = 0.84 (hexanes/Et₂O, 10:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 7.23 (dd, J = 2.1, 1.4 Hz, 1H, CH-5), 6.56-6.55 (m, 2H, CH-2, CH-3), 5.85-5.74 (m, 1H, CH-12), 5.73 (d, J = 15.7 Hz, 1H, CH-8), 5.69-5.57 (m, 1H, CH-15), 5.38-5.30 (m, 1H, CH-9), 5.03-4.79 (m, 4H, CH₂-13, CH₂-16), 3.19 (ddt, J = 14.2, 7.2, 1.4 Hz, 1H, CH₂-14^a), 2.58 (ddt, J = 14.1, 6.5, 1.4 Hz, 1H, CH₂-14^b), 2.13-2.05 (m, 4H, CH₂-10, CH₂-11), 0.971 (s, 9H, *t*Bu), 0.968 (s, 9H, *t*Bu), 0.965 (s, 9H, *t*Bu), 0.23 (s, 3H, SiCH₃), 0.19 (s, 3H, SiCH₃), 0.15 (s, 3H, SiCH₃), 0.14 (s, 6H, SiCH₃), 0.06 (s, 3H, SiCH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 148.6 (C-4), 146.2 (C-1), 138.4 (C-12), 136.4 (C-6), 136.0 (C-8), 135.3 (C-15), 130.1 (C-9), 121.1 (C-5), 118.4 (C-2), 118.1 (C-3), 116.2 (C-16), 114.8 (C-13), 78.4 (C-7), 43.8 (C-14), 32.9 (C-11), 32.2 (C-10), 26.5 (C(CH₃)₃), 26.3 (C(CH₃)₃), 25.8 (C(CH₃)₃), 19.0 (C(CH₃)₃), 18.7 (C(CH₃)₃), 18.3 (C(CH₃)₃), -1.3 (SiCH₃), -1.4 (SiCH₃), -3.5 (SiCH₃), -3.7 (SiCH₃), -4.45 (SiCH₃), -4.47 (SiCH₃).

(E)-4-(tert-Butyldimethylsilyl)oxy-4-(5'-((tert-butyldimethylsilyl)oxy)-2'-(hydroxy)phenyl)deca-1,5,9-trien (70b)



R_F = 0.59 (hexanes/Et₂O, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H, OH), 6.67 (d, J = 8.6 Hz, 1H, CH-2), 6.62 (dd, J = 8.7, 2.8 Hz, 1H, CH-3), 6.43 (d, J = 2.7 Hz, 1H, CH-5), 5.91-5.63 (m, 4H, CH-12, CH-15, CH-8, CH-9), 5.12-4.93 (m, 4H, CH₂-13, CH₂-16), 2.81 (ddt, J = 14.3, 7.2, 1.3 Hz, 1H, CH₂-14^a), 2.70 (ddt, J = 14.2, 6.6, 1.5 Hz, 1H, CH₂-14^b), 2.32-2.18 (m, 4H, CH₂-10, CH₂-11), 0.95 (s, 9H, *t*Bu), 0.93 (s, 9H, *t*Bu), 0.17 (s, 3H, SiCH₃), 0.14 (s, 3H, SiCH₃), 0.13 (s, 6H, SiCH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 150.9 (C-1), 147.7 (C-4), 137.9 (C-12), 135.1 (C-8), 133.5 (C-15), 131.3 (C-9), 128.2 (C-6), 120.3 (C-3), 119.1 (C-5), 118.3 (C-2), 117.6 (C-16), 115.5 (C-13), 83.1 (C-7), 45.2 (C-14), 33.3 (C-11), 32.0 (C-10), 26.2 (C(CH₃)₃), 25.9 (C(CH₃)₃), 18.5 (C(CH₃)₃), 18.4 (C(CH₃)₃), -1.5 (SiCH₃), -1.8 (SiCH₃), -4.3 (SiCH₃).

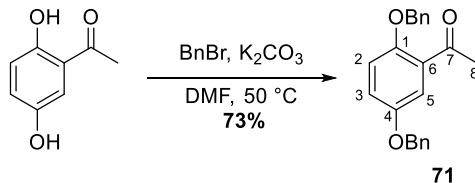
(E)-4-(5'-((tert-Butyldimethylsilyl)oxy)-2'-(hydroxy)phenyl)-1,5,9-trien-4-ol (70c)



R_F = 0.05 (hexanes/Et₂O, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (s, 1H, OH), 6.72 (d, J = 8.7 Hz, 1H, CH-2), 6.65 (dd, J = 8.7, 2.8 Hz, 1H, CH-3), 6.54 (d, J = 2.8 Hz, 1H, CH-5), 5.86-5.62 (m, 3H, CH-12, CH-15, CH-9), 5.73 (d, J = 15.7 Hz, 1H, CH-8), 5.29-5.20 (m, 2H, CH₂-16), 5.05-4.94 (m, 2H, CH₂-13), 2.82 (dd, J = 14.0, 7.5 Hz, 1H, CH₂-14^a), 2.72 (s, 1H, OH), 2.63 (dd, J = 14.0, 7.1 Hz, 1H, CH₂-14^b), 2.22-2.09 (m, 4H, CH₂-10, CH₂-11), 0.97 (s, 9H, *t*Bu), 0.15 (s, 6H, SiCH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 150.5 (C-1), 148.0 (C-4), 138.0 (C-12), 134.2 (C-8), 132.7 (C-15), 130.4 (C-9), 128.0

(C-6), 121.4 (C-16), 120.4 (C-3), 118.4 (C-5), 118.2 (C-2), 115.2 (C-13), 78.3 (C-7), 45.7 (C-14), 33.4 (C-11), 31.7 (C-10), 25.9 (C(CH₃)₃), 18.4 (C(CH₃)₃), -4.3 (SiCH₃).

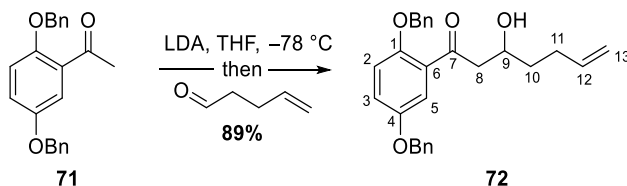
2',5'-Bis(benzyloxy)acetophenone (**71**)



In a 100 mL round-bottomed flask, 2',5'-dihydroxyacetophenone (2.0 g, 13.14 mmol) was dissolved in DMF (13 mL). Benzyl bromide (3.43 mL, 28.84 mmol) was added by syringe, and NaI (50 mg, 0.33 mmol) was subsequently added at once. The mixture was stirred at 50 °C for 6 h, diluted with brine (50 mL), and extracted with Et₂O (3×30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated to give the crude product (4.46 g) as a brown solid, which was recrystallized from hexane/Et₂O mixture to give 3.20 g (73%) of **71** as thin beige needles.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.47-7.30 (m, 11H, CH_{Ph}, CH-5), 7.08 (dd, *J* = 9.0, 3.3 Hz, 1H, CH-3), 6.97 (d, *J* = 9.0 Hz, 1H, CH-2), 5.12 (s, 2H, CH₂Ph), 5.05 (s, 2H, CH₂Ph), 2.62 (s, 3H, CH₃-8). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 199.5 (C-7), 152.9 (C-1), 152.8 (C-4), 137.0 (C_{Ph}), 136.6 (C_{Ph}), 129.1 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.3 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (2CH_{Ph}), 121.2 (C-3), 115.3 (C-5), 114.7 (C-2), 71.5 (CH₂Ph), 70.8 (CH₂Ph), 32.2 (C-8). The spectral data match those reported in the literature.^[162]

1-(2',5'-Bis(benzyloxy)phenyl)-3-hydroxyhept-6-en-1-one (**72**)

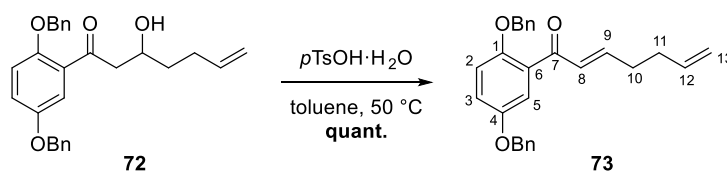


In a flame-dried Schlenk flask, DIPA (6.0 mL, 42.8 mmol) was dissolved in dry THF (62 mL). After cooling to -78 °C, BuLi (1.6 M in hexanes, 27.0 mL, 43.2 mmol) was dropwise added. The mixture was stirred for 30 min, and **71** (12.35 g, 37.15 mmol) in THF (124 mL) was dropwise added. The resulting mixture was stirred at -78 °C for 30 min, and pent-4-enal (4.4 mL, 44.56 mmol) in THF (37 mL) was dropwise added. The mixture was stirred for 1 h and quenched by saturated NH₄Cl solution (50 mL). The layers were separated, and the aqueous was extracted by Et₂O (3×50 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure to give the crude product as a brown solid, which was recrystallized from hexane/CH₂Cl₂ mixture (5:1, 200 mL) to give 11.16 g of **72** as off-white crystals. The mother liquor was further purified

by column chromatography (neat hexane, gradient to 3:1 hexane/EtOAc), yielding another 2.62 g of **72**. Overall yield 13.78 g (89%) of **72** as an off-white solid.

R_F = 0.30 (hexanes/EtOAc, 3:1). **m.p.** 85-87 °C. $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.46-7.30 (m, 11H, CH_{Ph} , CH-5), 7.11 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.98 (d, J = 9.0 Hz, 1H, CH-2), 5.77 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H, CH-12), 5.10 (s, 2H, CH_2Ph), 5.05 (s, 2H, CH_2Ph), 5.03-4.91 (m, 2H, CH_2 -13), 4.15-4.07 (m, 1H, CH-9), 3.26-3.20 (m, 2H, CH_2 -8^a, OH), 2.99 (dd, J = 18.0, 9.4 Hz, 1H, CH_2 -8^b), 2.16-1.96 (m, 2H, CH_2 -11), 1.59-1.49 (m, 1H, CH_2 -10^a), 1.44-1.34 (m, 1H, CH_2 -10^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 202.4 (C-7), 153.00 (C-1), 152.98 (C-4), 138.5 (C-12), 136.9 (C_{Ph}), 136.2 (C_{Ph}), 128.9 (CH_{Ph}), 128.7 (CH_{Ph}), 128.6 (CH_{Ph}), 128.3 (C-6), 128.2 (CH_{Ph}), 128.0 (CH_{Ph}), 127.7 (CH_{Ph}), 121.8 (C-3), 115.2 (C-5), 114.8 (C-13), 114.7 (C-2), 71.6 (CH_2Ph), 70.8 (CH_2Ph), 67.6 (C-9), 50.8 (C-8), 35.6 (C-10), 29.7 (C-11). **MS** (ESI+) m/z (%) 855 ([2M+Na⁺], 40), 439 ([M+Na⁺], 100), 417 ([M+H⁺], 5). **HRMS** (ESI+) m/z [M+Na⁺] calcd for $\text{C}_{27}\text{H}_{28}\text{O}_4\text{Na}$: 439.1880; found: 439.1878; [M+H⁺] calcd for $\text{C}_{27}\text{H}_{29}\text{O}_4$: 417.2060; found: 417.2060. **IR** (neat): ν_{max} = 3522, 3066, 3037, 2979, 2935, 1650, 1491, 1455, 1416, 1377, 1278, 1222, 1164, 999, 906, 738, 696 cm^{-1} .

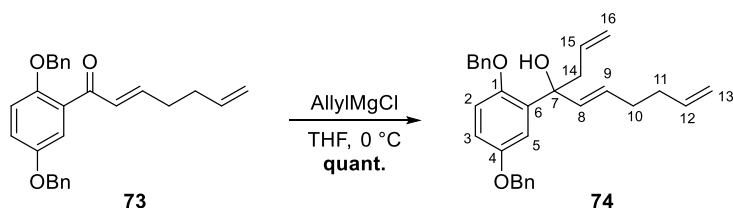
(*E*)-1-(2',5'-Bis(benzyloxy)phenyl)hepta-2,6-dien-1-one (73)



In a 50 mL round-bottomed flask, β -hydroxy ketone **72** (500 mg, 1.20 mmol) was dissolved in toluene (10 mL). $p\text{TsOH} \cdot \text{H}_2\text{O}$ (10 mg, 0.05 mmol) was added, and the mixture was stirred at 50 °C for 1.5 h. After cooling, the mixture was diluted with Et_2O (30 mL) and filtered through a plug of silica gel, which was washed by Et_2O . The solvents were removed at reduced pressure to give 479 mg (quant.) of essentially pure **73** as an off-white solid that can be recrystallized from CH_2Cl_2 /hexane mixture but was used as such in the next reaction step.

R_F = 0.54 (hexanes/EtOAc, 3:1). **m.p.** 56-58 °C. $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.44-7.29 (m, 10H, CH_{Ph}), 7.22 (d, J = 3.2 Hz, 1H, CH-5), 7.04 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.95 (d, J = 9.0 Hz, 1H, CH-2), 6.88 (dt, J = 15.6, 6.4 Hz, 1H, CH-9), 6.79 (dt, J = 15.5, 1.2 Hz, 1H, CH-8), 5.76 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H, CH-12), 5.07 (s, 2H, CH_2Ph), 5.04 (s, 2H, CH_2Ph), 5.04-4.95 (m, 2H, CH_2 -13), 2.31-2.24 (m, 2H, CH_2 -10^a, CH_2 -11^a), 2.17-2.10 (m, 2H, CH_2 -10^b, CH_2 -11^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 192.7 (C-7), 153.2 (C-1), 151.8 (C-4), 147.6 (C-9), 137.4 (C-12), 137.0 (C_{Ph}), 136.8 (C_{Ph}), 131.0 (C-8), 130.4 (C-6), 128.74 (CH_{Ph}), 128.66 (CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 127.5 (CH_{Ph}), 119.9 (C-3), 115.8 (C-5), 115.5 (C-13), 115.2 (C-2), 71.7 (CH_2Ph), 70.8 (CH_2Ph), 32.2 (C-11), 31.9 (C-10). **MS** (ESI+) m/z (%) 819 ([2M+Na⁺], 20), 421 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for $\text{C}_{27}\text{H}_{26}\text{O}_3\text{Na}$: 421.1774; found: 421.1772. **IR** (neat): ν_{max} = 3064, 3033, 2978, 2927, 1661, 1619, 1492, 1454, 1417, 1382, 1279, 1222, 1173, 1025, 913, 847, 809, 781, 737, 696 cm^{-1} .

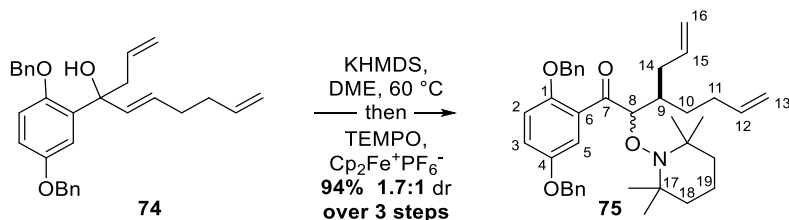
(E)-4-(2',5'-Bis(benzyloxy)phenyl)deca-1,5,9-trien-4-ol (74)



In a flame-dried Schlenk flask, α,β -unsaturated ketone **73** (479 mg, 1.20 mmol) was dissolved in dry THF (6.0 mL). The mixture was cooled to 0 °C, and allylmagnesium chloride (2M in THF, 0.78 mL, 1.56 mmol) was dropwise added. The mixture was stirred at 0 °C for 1 h, quenched with saturated NH_4Cl solution (25 mL) diluted with brine, and extracted with Et_2O (3×25 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and evaporated at reduced pressure to give 528 mg (quant.) of essentially pure product **74** as a colorless oil that was used without further purification in the next step.

R_F = 0.64 (hexanes/ EtOAc , 3:1). ^1H NMR (400 MHz, Chloroform- d) δ 7.46–7.30 (m, 10H, CH_{Ph}), 7.11 (d, J = 3.0 Hz, 1H, CH-5), 6.89 (d, J = 8.9 Hz, 1H, CH-2), 6.81 (dd, J = 8.8, 3.0 Hz, 1H, CH-3), 5.88 (dt, J = 15.5, 1.3 Hz, 1H, CH-8), 5.85–5.68 (m, 2H, CH-12, CH-15), 5.63 (dt, J = 15.7, 6.3 Hz, 1H, CH-9), 5.11–5.02 (m, 2H, CH_2 -16), 5.06 (s, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph), 5.02–4.91 (m, 2H, CH_2 -13), 3.85 (s, 1H, OH), 2.90 (ddt, J = 14.1, 7.2, 1.3 Hz, 1H, CH_2 -14^a), 2.67 (ddt, J = 14.0, 7.1, 1.4 Hz, 1H, CH_2 -14^b), 2.17–2.06 (m, 4H, CH_2 -10, CH_2 -11). ^{13}C NMR (101 MHz, Chloroform- d) δ 153.1 (C-1), 150.4 (C-4), 138.4 (C-12), 137.3 (C_{Ph}), 136.8 (C_{Ph}), 135.22 (C-6), 135.17 (C-8), 134.4 (C-15), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.6 (C-9), 128.3 (CH_{Ph}), 128.0 (CH_{Ph}), 127.7 (CH_{Ph}), 127.6 (CH_{Ph}), 118.2 (C-16), 115.3 (C-5), 114.8 (C-13), 113.5 (C-2), 113.3 (C-3), 75.8 (C-7), 71.1 (CH_2Ph), 70.8 (CH_2Ph), 45.1 (C-14), 33.5 (C-11), 31.8 (C-10). MS (ESI+) m/z (%) 903 ($[\text{2M}+\text{Na}^+]$, 25), 463 ($[\text{M}+\text{Na}^+]$, 100), 423 ($[\text{M}-\text{H}_2\text{O}+\text{H}^+]$, 30). HRMS (ESI+) m/z [$\text{M}+\text{Na}^+$] calcd for $\text{C}_{30}\text{H}_{32}\text{O}_3\text{Na}$: 463.2244; found: 463.2243. IR (neat): ν_{max} = 3528, 3069, 3032, 2976, 2917, 1639, 1586, 1496, 1454, 1420, 1380, 1280, 1206, 1026, 912, 801, 736, 696 cm^{-1} .

Tandem AOC/ α -oxygenation sequence of carbinol 74



In a flame-dried Schlenk flask, alcohol **74** (240 mg, 0.54 mmol) was dissolved in DME (11 mL). The mixture was cooled to 0 °C, and KHMDS (1M in THF, 0.71 mL, 0.71 mmol) was dropwise added. The mixture was warmed to 60 °C and stirred at this temperature for 1 h. After cooling to r.t., TEMPO (111 mg, 0.71 mmol) was added at once. The mixture was cooled to –78 °C, and $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ (286 mg, 0.86 mmol) was added in small portions (~30 mg/30 s) until the mixture remained dark blue. The

mixture was stirred for additional 20 min, diluted with Et₂O (20 mL), and filtered through a plug of silica gel, which was washed by Et₂O. The solution was evaporated, and the crude product was purified by column chromatography (neat hexane, gradient to 15:1 hexane/Et₂O) to yield 306 mg (94%) of α -aminoxyl ketone **75** as an inseparable 1.7:1 *anti/syn* diastereoisomeric mixture.

anti- and *syn*-**3-Allyl-1-(2',5'-bis(benzyloxy)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hept-6-en-1-one (75)**

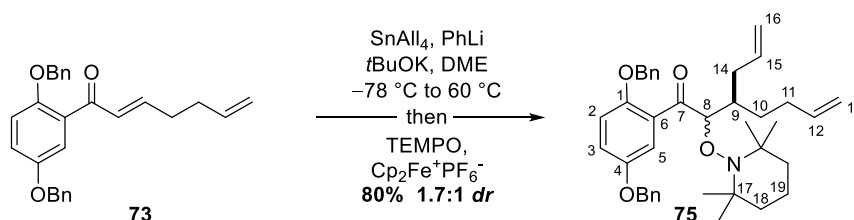
Major diastereoisomer:

R_F = 0.50 (hexanes/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.49-7.27 (m, 11H, CH_{Ph}, CH-5), 7.02 (dd, J = 9.0, 3.0 Hz, 1H, CH-3), 6.90 (d, J = 9.0 Hz, 1H, CH-2), 5.82-5.48 (m, 2H, CH-12, CH-15), 5.38 (d, J = 4.8 Hz, 1H, CH-8), 5.17-4.77 (m, 7H, CH₂Ph, CH₂-16, CH₂-13), 4.63-4.55 (m, 1H, CH₂-13), 2.39-2.12 (m, 1H, CH-9), 2.12-1.63 (m, 6H, CH₂-10, CH₂-11, CH₂-14), 1.61-1.50 (m, 1H, CH₂-19^a), 1.45-1.20 (m, 5H, CH₂-19^b, CH₂-18), 1.14 (bs, 9H, CH₃^{TEMPO}), 0.98 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.80 (C-7), 151.19 (C-1), 150.0 (C-4), 137.9 (C-15), 135.8 (C-12), 135.5 (C_{Ph}), 135.3 (C_{Ph}), 129.9 (C-6), 127.3 (CH_{Ph}), 127.21 (CH_{Ph}), 126.7 (CH_{Ph}), 126.56 (CH_{Ph}), 126.3 (CH_{Ph}), 126.1 (CH_{Ph}), 118.6 (C-3), 114.8 (C-5), 114.6 (C-16), 113.3 (C-2), 112.9 (C-13), 86.9 (C-8), 69.93 (CH₂Ph), 69.4 (CH₂Ph), 59.0 (C-17), 58.15 (C-17), 40.6 (C-9), 39.3 (C-18), 34.0 (C-11), 32.9 (CH₃^{TEMPO}), 30.5 (C-14), 27.6 (C-10), 19.0 (CH₃^{TEMPO}), 15.79 (C-19). MS (ESI+) m/z (%) 618 ([M+Na⁺], 15), 596 ([M+H⁺], 100). HRMS (ESI+) m/z [M+H⁺] calcd for C₃₉H₅₀NO₄: 596.3734; found: 596.3732. IR (neat): $\nu_{\max}$ = 3068, 2973, 2930, 2870, 1684, 1640, 1580, 1490, 1454, 1413, 1376, 1279, 1217, 1171, 1025, 909, 811, 734, 695 cm⁻¹.

Minor diastereoisomer:

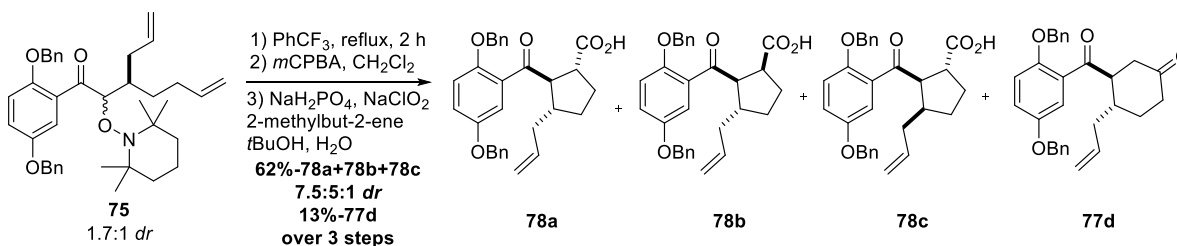
¹H NMR (400 MHz, Chloroform-*d*) δ 7.49-7.27 (m, 11H, CH_{Ph}, CH-5), 7.03 (dd, J = 9.0, 3.0 Hz, 1H, CH-3), 6.91 (d, J = 9.0 Hz, 1H, CH-2), 5.82-5.48 (m, 2H, CH-12, CH-15), 5.44 (d, J = 5.4 Hz, 1H, CH-8), 5.17-4.77 (m, 7H, CH₂Ph, CH₂-16, CH₂-13), 4.76 (dt, J = 17.0, 1.7 Hz, 1H, CH₂-13), 2.56-2.46 (m, 1H, CH₂-14^a), 2.39-2.12 (m, 1H, CH-9), 2.12-1.63 (m, 5H, CH₂-10, CH₂-11, CH₂-14^b), 1.61-1.50 (m, 1H, CH₂-19^a), 1.45-1.20 (m, 5H, CH₂-19^b, CH₂-18), 1.14 (bs, 9H, CH₃^{TEMPO}), 0.98 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.75 (C-7), 151.23 (C-1), 150.0 (C-4), 137.2 (C-15), 136.6 (C-12), 135.4 (C_{Ph}), 135.2 (C_{Ph}), 129.7 (C-6), 127.3 (CH_{Ph}), 127.24 (CH_{Ph}), 126.7 (CH_{Ph}), 126.61 (CH_{Ph}), 126.2 (CH_{Ph}), 126.1 (CH_{Ph}), 118.9 (C-3), 114.7 (C-5), 114.3 (C-16), 113.4 (C-2), 113.0 (C-13), 86.3 (C-8), 69.95 (CH₂Ph), 69.4 (CH₂Ph), 59.0 (C-17), 58.16 (C-17), 40.5 (C-9), 39.3 (C-18), 32.9 (CH₃^{TEMPO}), 32.7 (C-11), 30.3 (C-14), 28.0 (C-10), 19.0 (CH₃^{TEMPO}), 15.81 (C-19).

Tandem allylation/AOC/ α -oxygenation sequence of α,β -unsaturated ketone **73**



In a flame-dried Schlenk flask, tetraallyltin (30 μL , 0.12 mmol) was dissolved in DME (1.6 mL). At r.t. PhLi (1.8 M in THF , 0.27 mL, 0.49 mmol) was dropwise added. The mixture was stirred for 30 min, cooled to $-78\text{ }^\circ\text{C}$, $t\text{BuOK}$ (1M in THF , 0.58 mL, 0.58 mmol) was added, and the mixture was stirred for additional 30 min. α,β -Unsaturated ketone **73** (100 mg, 0.25 mmol) in DME (1.5 mL) was dropwise added at $-78\text{ }^\circ\text{C}$. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 15 min, warmed to r.t., and stirred at $60\text{ }^\circ\text{C}$ for 2 h. The mixture was cooled to r.t., and TEMPO (47 mg, 0.30 mmol) was added. The mixture was cooled to $-78\text{ }^\circ\text{C}$, and $\text{Cp}_2\text{Fe}^+\text{PF}_6^-$ (300 mg, 0.91 mmol) was added in small portions ($\sim 50\text{ mg}/30\text{ s}$) until the mixture remained dark blue. The mixture was stirred for an additional 20 min, quenched by seven drops of saturated NH_4Cl solution, diluted with Et_2O (20 mL), and filtered through a plug of silica gel, which was washed by Et_2O . The solution was evaporated, and the crude product was purified by column chromatography (neat cyclohexane, gradient to 15:1 cyclohexane/ EtOAc) to yield 117 mg (80%) of α -aminoxy ketone **75** as an inseparable 1.7:1 *anti/syn* diastereoisomeric mixture. For compound characterization *vide supra*.

PRE-based cyclization/oxidation sequence of aminoxy ketone **75**



In a 100 mL round-bottomed flask fitted with a reflux condenser, α -aminoxy ketone **75** (4.36 g, 7.32 mmol) was dissolved in dry PhCF_3 (36 mL). The solution was degassed by five gentle vacuum/argon cycles and immersed into a preheated $120\text{ }^\circ\text{C}$ oil bath. The mixture was refluxed for 2 h, cooled to room temperature, and evaporated at reduced pressure.

The residue was dissolved in CH_2Cl_2 (36 mL), cooled to $0\text{ }^\circ\text{C}$, and $m\text{CPBA}$ (70-75%, 2.34 g, 9.51 mmol) was added. The mixture was stirred at $0\text{ }^\circ\text{C}$ for 1 h, diluted with Et_2O (100 mL) and washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution ($2\times 25\text{ mL}$), saturated NaHCO_3 solution ($5\times 25\text{ mL}$), and brine ($2\times 25\text{ mL}$). The organic layer was dried over MgSO_4 , filtered, and evaporated under reduced pressure to give crude aldehydes **77a,b,c** as a 7.5:5:1 mixture of diastereoisomers together with cyclohexanone **77d** resulting from radical 6-*endo* cyclization/oxidation.

The mixture of aldehydes **77a,b,c**, and cyclohexanone **77d** was dissolved in *t*BuOH (37 mL) and H₂O (24 mL). 2-Methylbut-2-ene (7.8 mL), NaH₂PO₄·H₂O (5.05 g, 36.6 mmol) and NaClO₂ (1.99 g, 22.0 mmol) were successively added. The mixture was stirred at r.t. for 15 min, diluted with brine, and extracted by Et₂O (3×25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure to give the crude mixture of products that were separated by column chromatography (neat PE, gradient to 3:1 PE/EtOAc+1% AcOH) to yield 446 mg (13%) of ketone **77d**, 2.13 g (62%) of carboxylic acids **78a,b,c** as a 7.5:5:1 diastereoisomeric mixture. The diastereoisomers were separated by multiple column chromatography (neat PE, gradient to 3:1 PE/Et₂O+1% AcOH) to afford pure **78a** and **78b** in a 1.5:1 ratio. Diastereoisomer **78b** was contaminated with a trace amount of diastereoisomer **78c**.

Optional epimerization step at the stage of aldehydes **77a,b,c**

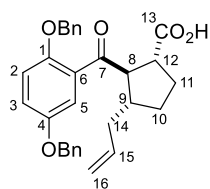
In order to increase the diastereoisomeric ratio of acids **78a/78b**, an epimerization step can be introduced at the stage of aldehydes **77a,b,c**.

In a 100 mL round-bottomed flask fitted with a reflux condenser, α -aminoxyl ketone **75** (1.80 g, 3.02 mmol) and TEMPO (47 mg, 0.30 mmol) were dissolved in PhCF₃ (30 mL). The solution was degassed by five gentle vacuum/argon cycles and immersed into a preheated 120 °C oil bath. The mixture was refluxed for 2 h, cooled to room temperature, and evaporated at reduced pressure.

The residue was dissolved in CH₂Cl₂ (30 mL), cooled to 0 °C, and *m*CPBA (70-75%, 819 mg, 3.32 mmol) was added. The mixture was stirred at 0 °C for 30 min, and DBU (0.81 mL, 5.44 mmol) was added. The mixture was warmed to r.t., stirred for 18 h, diluted with Et₂O (150 mL), and washed with water (1×25 mL), saturated NaHCO₃ solution (5×25 mL), saturated NH₄Cl solution (2×25 mL), and brine (2×25 mL). The organic layer was dried over MgSO₄, filtered, and evaporated under reduced pressure to give crude aldehydes **77a,b,c** as a 10.4:1.5:1 mixture of diastereoisomers together with cyclohexanone **77d** resulting from radical 6-*endo* cyclization/oxidation.

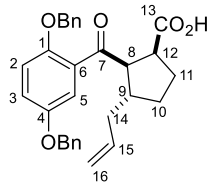
The mixture of aldehydes **77a,b,c**, and cyclohexanone **77d** was dissolved in *t*BuOH (15 mL) and H₂O (10 mL). 2-Methylbut-2-ene (3.3 mL), NaH₂PO₄·H₂O (2.08 g, 15.1 mmol) and NaClO₂ (820 mg, 9.06 mmol) were successively added. The mixture was stirred at r.t. for 15 min, diluted with brine, and extracted by Et₂O (3×25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure to give the crude mixture of products that were separated by column chromatography (neat PE, gradient to 3:1 PE/EtOAc+1% AcOH) to yield 248 mg (18%) of ketone **77d**, 798 mg (56%) of carboxylic acids **78a,b,c** as a 10.4:1.5:1 diastereoisomeric mixture. The diastereoisomers were separated by multiple column chromatography (neat PE, gradient to 3:1 PE/Et₂O+1% AcOH) to afford pure **78a** and **78b** in a 7:1 ratio. Diastereoisomer **78b** was contaminated with a trace amount of diastereoisomer **78c**.

(±)-1,2-trans/2,3-trans-3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carboxylic acid (78a)



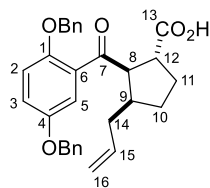
R_F = 0.36 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 11.11 (bs, 1H, COOH), 7.44-7.27 (m, 10H, CH_{Ph}), 7.18 (d, J = 3.1 Hz, 1H, CH-5), 6.99 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.87 (d, J = 9.0 Hz, 1H, CH-2), 5.64-5.51 (m, 1H, CH-15), 5.09 (d, J = 12.0 Hz, 1H, CH₂Ph), 5.05 (d, J = 12.0 Hz, 1H, CH₂Ph), 5.02 (s, 2H, CH₂Ph), 4.87-4.80 (m, 2H, CH₂-16), 4.01 (t, J = 7.1 Hz, 1H, CH-8), 3.33 (dt, J = 8.9, 6.7 Hz, 1H, CH-12), 2.35-2.24 (m, 1H, CH-9), 2.12-1.88 (m, 4H, CH₂-11, CH₂-14), 1.83 (dtd, J = 12.9, 7.3, 5.6 Hz, 1H, CH₂-10^a), 1.51-1.40 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 204.3 (C-7), 181.5 (C-13), 152.9 (C-1), 151.5 (C-4), 136.93 (C_{Ph}), 136.91 (C-15), 136.6 (C_{Ph}), 130.1 (C-6), 128.7 (2CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 127.6 (CH_{Ph}), 120.1 (C-3), 116.1 (C-16), 115.7 (C-5), 114.8 (C-2), 71.4 (CH₂Ph), 70.8 (CH₂Ph), 58.5 (C-8), 47.1 (C-12), 44.5 (C-9), 38.7 (C-14), 31.4 (C-10), 29.3 (C-11). **MS** (ESI⁻) m/z (%) 469 ([M-H⁺], 100). **HRMS** (ESI⁻) m/z [M-H⁺] calcd for C₃₀H₂₉O₅: 469.2021; found: 469.2018. **IR** (neat): ν_{max} = 3500-2400 (v br), 3065, 3032, 2942, 2870, 1700, 1606, 1579, 1490, 1454, 1414, 1381, 1278, 1217, 1170, 1008, 914, 849, 811, 736, 696 cm⁻¹.

(±)-1,2-cis/2,3-trans-3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carboxylic acid (78b)



R_F = 0.36 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (600 MHz, Chloroform-*d*) δ 9.88 (bs, 1H, COOH), 7.44-7.29 (m, 10H, CH_{Ph}), 7.25 (d, J = 3.2 Hz, 1H, CH-5), 7.02 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.91 (d, J = 9.0 Hz, 1H, CH-2), 5.58 (ddt, J = 16.5, 10.7, 7.1 Hz, 1H, CH-15), 5.09 (d, J = 11.3 Hz, 1H, CH₂Ph), 5.06 (d, J = 11.4 Hz, 1H, CH₂Ph), 5.00 (s, 2H, CH₂Ph), 4.87-4.82 (m, 2H, CH₂-16), 3.84 (dd, J = 8.3, 6.9 Hz, 1H, CH-8), 3.00 (q, J = 8.2 Hz, 1H, CH-12), 2.47-2.40 (m, 1H, CH-9), 2.10-1.98 (m, 2H, CH₂-14^a, CH₂-11^a), 1.91-1.82 (m, 2H, CH₂-14^b, CH₂-10^a), 1.81-1.74 (m, 1H, CH₂-11^b), 1.26-1.19 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (151 MHz, Chloroform-*d*) δ 202.2 (C-7), 178.6 (C-13), 153.0 (C-1), 151.9 (C-4), 137.0 (C_{Ph}), 136.8 (C-15), 136.5 (C_{Ph}), 129.3 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.4 (CH_{Ph}), 128.1 (CH_{Ph}), 127.9 (CH_{Ph}), 127.7 (CH_{Ph}), 120.9 (C-3), 116.1 (C-16), 115.8 (C-5), 114.7 (C-2), 71.7 (CH₂Ph), 70.7 (CH₂Ph), 58.7 (C-8), 46.7 (C-12), 41.9 (C-9), 39.4 (C-14), 29.9 (C-10), 27.8 (C-11).

(±)-1,2-trans/2,3-cis-3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carboxylic acid (78c)



R_F = 0.36 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 9.87 (bs, 1H, COOH), 7.45-7.29 (m, 11H, CH_{Ph}, CH-5), 7.07 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.95 (d, J = 9.0 Hz, 1H, CH-2), 5.46 (dddd, J = 16.9, 10.2, 7.9, 5.7 Hz, 1H, CH-15), 5.09 (s, 2H, CH₂Ph), 5.03 (s, 2H, CH₂Ph), 4.88-4.79 (m, 2H, CH₂-16), 4.29 (t, J = 8.5 Hz, 1H, CH-8), 3.42 (q, J = 8.9 Hz, 1H, CH-12), 2.37-2.29 (m, 1H, CH-9), 2.12-2.05 (m, 1H, CH₂-11^a), 1.93-1.84 (m, 1H, CH₂-14^a), 1.79-1.67 (m, 2H, CH₂-14^b, CH₂-11^b), 1.66-1.56 (m, 1H, CH₂-10^a), 1.51-1.43 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 202.1 (C-7), 179.8 (C-13), 152.9 (C-1), 152.6 (C-4), 137.1 (C-15), 136.9 (C_{Ph}), 136.2 (C_{Ph}), 129.1 (C-6), 128.8

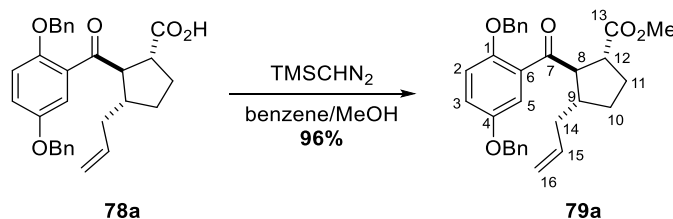
(CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 121.4 (C-3), 116.0 (C-16), 115.8 (C-5), 114.8 (C-2), 71.7 (CH₂Ph), 70.8 (CH₂Ph), 57.5 (C-8), 45.0 (C-12), 41.9 (C-9), 35.5 (C-14), 30.5 (C-10), 27.9 (C-11).

(±)-trans-4-Allyl-3-(2',5'-bis(benzyloxy)benzoyl)cyclohexan-1-one (77d)

*R*_F = 0.28 (hexanes/EtOAc, 3:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45-7.29 (m, 10H, CH_{Ph}), 7.25 (d, *J* = 3.2 Hz, 1H, CH-5), 7.07 (dd, *J* = 9.0, 3.2 Hz, 1H, CH-3), 6.95 (d, *J* = 9.0 Hz, 1H, CH-2), 5.60 (dddd, *J* = 16.5, 10.1, 8.3, 6.1 Hz, 1H, CH-15), 5.09 (s, 2H, CH₂Ph), 5.04 (s, 2H, CH₂Ph), 4.90 (dq, *J* = 10.1, 1.4 Hz, 1H, CH₂-16), 4.81 (dq, 1H, *J* = 17.0, 1.6 Hz, 1H, CH₂-16), 3.78 (td, *J* = 9.4, 5.7 Hz, 1H, CH-8), 2.50-2.37 (m, 2H, CH₂-13), 2.37-2.26 (m, 2H, CH₂-11), 2.26-2.17 (m, 1H, CH-9), 2.17-2.07 (m, 1H, CH₂-14^a), 2.04-1.93 (m, 1H, CH₂-10^a), 1.81-1.72 (m, 1H, CH₂-14^b), 1.35-1.21 (m, 1H, CH₂-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 210.0 (C-12), 204.2 (C-7), 153.0 (C-1), 152.2 (C-4), 136.8 (C_{Ph}), 136.07 (C-15), 136.05 (C_{Ph}), 129.0 (C-6), 128.9 (CH_{Ph}), 128.7 (CH_{Ph}), 128.6 (CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 121.2 (C-3), 117.0 (C-16), 115.9 (C-5), 114.5 (C-2), 71.6 (CH₂Ph), 70.8 (CH₂Ph), 53.2 (C-8), 42.6 (C-13), 39.9 (C-11), 37.4 (C-14), 37.3 (C-9), 29.2 (C-10). MS (ESI+) *m/z* (%) 477 ([M+Na⁺], 100), 455 ([M+H⁺], 10). HRMS (ESI+) *m/z* [M+Na⁺] calcd for C₃₀H₃₀O₄Na: 477.2036; found: 477.2034. IR (neat): ν_{max} = 3065, 3033, 2928, 1713, 1669, 1489, 1454, 1414, 1380, 1278, 1217, 1166, 999, 914, 848, 810, 733, 695 cm⁻¹.

6.3.6. Total synthesis of applanatumols V and W

(±)-Methyl 1,2-trans/2,3-trans-3-allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carboxylate (79a)

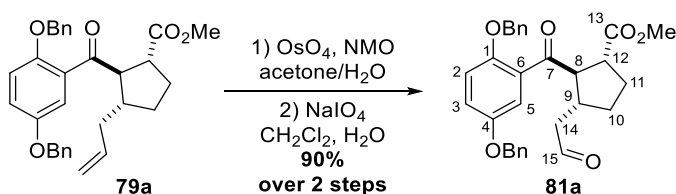


In a 50 mL round-bottomed flask, carboxylic acid **78a** (444 mg, 0.94 mmol) was dissolved in a benzene/MeOH mixture (2:1, 9.0 mL). At r.t. TMSCHN₂ (2M in hexanes, 0.94 mL, 1.88 mmol) was dropwise added. The mixture was stirred for 15 min, quenched by 6 drops of AcOH, and evaporated at reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc, 10:1) to give 438 mg (96%) of methyl ester **79a** as a thick colorless oil.

*R*_F = 0.55 (hexanes/EtOAc, 3:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45-7.28 (m, 10H, CH_{Ph}), 7.16 (d, *J* = 3.1 Hz, 1H, CH-5), 6.99 (dd, *J* = 9.0, 3.2, Hz, 1H, CH-3), 6.88 (d, *J* = 9.0 Hz, 1H, CH-2), 5.64-5.51 (m, 1H, CH-15), 5.09 (s, 2H, CH₂Ph), 5.03 (s, 2H, CH₂Ph), 4.87-4.79 (m, 2H, CH₂-16), 3.96 (t, *J* = 7.5 Hz, 1H, CH-8), 3.47 (s, 3H, OMe), 3.23 (dt, *J* = 8.7, 7.2 Hz, 1H, CH-12), 2.37-2.26 (m, 1H, CH-

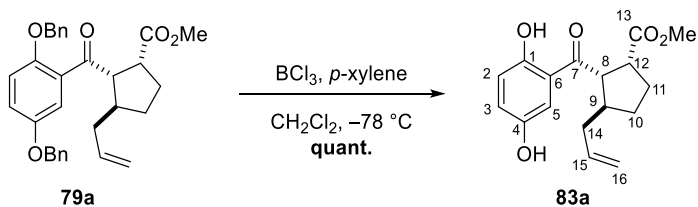
9), 2.12-1.78 (m, 5H, CH₂-14, CH₂-11, CH₂-10^a), 1.42 (dq, *J* = 12.1, 7.6 Hz, 1H, CH₂-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 204.6 (C-7), 175.9 (C-13), 152.9 (C-1), 151.5 (C-4), 137.1 (C-15), 137.0 (C_{Ph}), 136.7 (C_{Ph}), 130.4 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.19 (CH_{Ph}), 128.17 (CH_{Ph}), 127.7 (CH_{Ph}), 127.6 (CH_{Ph}), 119.9 (C-3), 116.0 (C-16), 115.7 (C-5), 114.8 (C-2), 71.4 (CH₂Ph), 70.8 (CH₂Ph), 58.9 (C-8), 51.7 (OMe), 47.5 (C-12), 44.4 (C-9), 38.8 (C-14), 31.3 (C-10), 29.1 (C-11). **MS** (ESI⁺) *m/z* (%) 507 ([M+Na⁺], 100), 485 ([M+H⁺], 10). **HRMS** (ESI⁺) *m/z* [M+Na⁺] calcd for C₃₁H₃₂O₅Na: 507.2142; found: 507.2138. **IR** (neat): ν_{max} = 3065, 3032, 2950, 2871, 1731, 1676, 1491, 1454, 1415, 1379, 1279, 1214, 1170, 1014, 913, 851, 811, 785, 737, 697 cm⁻¹.

(±)-Methyl 1,2-*trans*/2,3-*trans*-2-(2',5'-bis(benzyloxy)benzoyl)-3-(2-oxoethyl)cyclopentane-1-carboxylate (**81a**)



In a 25 mL round-bottomed flask, methyl ester **79a** (29 mg, 60 μmol) was dissolved in a acetone/H₂O mixture (10:1, 1.0 mL). At r.t., OsO₄ (2.5% in *t*BuOH, 50 μL, 4 μmol) and NMO (14 mg, 0.12 mmol) were added. The mixture was stirred for 1 h, diluted with Et₂O (10 mL), and washed with brine (3×10 mL). The ethereal layer was filtered through a plug of silica gel, which was washed by Et₂O, and the solvent was evaporated at reduced pressure. The residue was dissolved in a CH₂Cl₂/H₂O mixture (1:1, 6.0 mL), NaIO₄ (275 mg, 1.29 mmol) was added, and the mixture was stirred for 2.5 h. The mixture was diluted with water (20 mL) and extracted by CH₂Cl₂ (4×10 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated at reduced pressure to give 26 mg (90%) of the aldehyde **81a** that was directly used in the next step. For compound characterization, see Chapter 6.3.7.

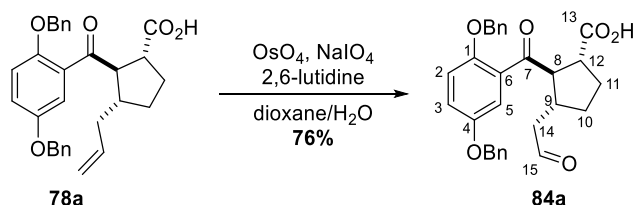
(±)-Methyl 1,2-*cis*/2,3-*trans*-3-allyl-2-(2',5'-dihydroxybenzoyl)cyclopentane-1-carboxylate (**83a**)



In a flame-dried Schlenk flask, ester **79a** (12.0 mg, 25 μmol) was dissolved in dry CH₂Cl₂ (0.5 mL). *p*-Xylene (50 μL, 0.4 mmol) was added, the mixture was cooled to −78 °C and BCl₃ (1M in CH₂Cl₂, 100 μL, 100 μmol) was dropwise added. The mixture was stirred at −78 °C for 5 min and quenched by slow addition of a CHCl₃/MeOH mixture (5:1, 2.0 mL). The reaction mixture was slowly warmed to r.t., and evaporated at reduced pressure. The crude product was purified by column chromatography (hexanes/EtOAc, 3:1, gradient to 1:1) to yield 8.0 mg (quant.) of **83a** as a pale yellow oil.

R_F = 0.21 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 11.80 (s, 1H, OH), 7.20 (d, J = 3.0 Hz, 1H, CH-5), 7.01 (dd, J = 8.9, 3.0 Hz, 1H, CH-3), 6.86 (d, J = 8.9 Hz, 1H, CH-2), 5.77 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H, CH-15), 5.20-5.00 (m, 3H, CH₂-16, OH), 3.77 (dd, J = 8.8, 6.1 Hz, 1H, CH-8), 3.49 (s, 3H, OMe), 3.21 (q, J = 8.5 Hz, 1H, CH-12), 2.51 (sext, J = 6.8 Hz, 1H, CH-9), 2.29-2.19 (m, 2H, CH₂-14^a, CH₂-11^a), 2.18-2.11 (m, 1H, CH₂-14^b), 2.11-2.00 (m, 2H, CH₂-11^b, CH₂-10^a), 1.49-1.39 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 206.8 (C-7), 174.3 (C-13), 157.1 (C-1), 147.6 (C-4), 136.3 (C-15), 125.0 (C-3), 119.5 (C-2), 119.2 (C-6), 117.2 (C-16), 115.1 (C-5), 53.3 (C-8), 51.9 (OMe), 48.0 (C-12), 43.2 (C-9), 39.4 (C-14), 30.7 (C-10), 27.9 (C-11). **MS** (ESI+) m/z (%) 631 ([2M+Na⁺], 20), 343 ([M+K⁺], 15), 327 ([M+Na⁺], 100), 305 ([M+H⁺], 10). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₁₇H₂₀O₅Na: 327.1203; found: 327.1204. **IR** (neat): ν_{max} = 3394, 2953, 2925, 2855, 1732, 1716, 1639, 1616, 1588, 1483, 1437, 1348, 1289, 1211, 1183, 998, 917, 833, 791 cm⁻¹.

(±)-1,2-*trans*/2,3-*trans*-2-(2',5'-Bis(benzyloxy)benzoyl)-3-(2-oxoethyl)cyclopentane-1-carboxylic acid (**84a**)

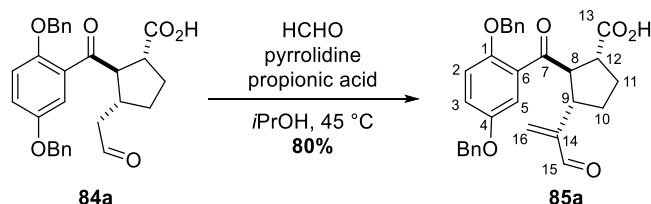


In a 100 mL round-bottomed flask, olefin **78a** (490 mg, 1.04 mmol) was dissolved in dioxane (7.7 mL) and H₂O (2.6 mL). 2,6-Lutidine (0.24 mL, 2.08 mmol), NaIO₄ (891 mg, 4.16 mmol) and OsO₄ (2.5% in *t*BuOH, 170 μ L, 21 μ mol) were successively added. The inhomogeneous mixture was stirred at r.t. for 2 h, quenched with saturated Na₂S₂O₃ solution (5 mL), diluted with brine (20 mL), and extracted with Et₂O (3×25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure to give the crude product that was purified by column chromatography (neat PE, gradient to 1:1 PE/Et₂O) to yield 372 mg (76%) of **84a** as a colorless oil that very slowly crystallizes. X-ray quality crystals were obtained by slow evaporation of a hexane/Et₂O solution.

R_F = 0.59 (PE/EtOAc, 1:1). **m.p.** 103-105 °C. $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 10.36 (bs, 1H, COOH), 9.46 (dd, J = 2.0, 1.3 Hz, 1H, CH-15), 7.43-7.27 (m, 10H, CH_{Ph}), 7.21 (d, J = 3.1 Hz, 1H, CH-5), 7.02 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.89 (d, J = 9.1 Hz, 1H, CH-2), 5.09-4.95 (m, 4H, CH₂Ph), 4.03 (dd, J = 7.6, 6.5 Hz, 1H, CH-8), 3.32-3.19 (m, 1H, CH-12), 2.77-2.63 (m, 1H, CH-9), 2.34 (ddd, J = 17.1, 5.2, 1.3 Hz, 1H, CH₂-14^a), 2.19 (ddd, J = 17.3, 8.9, 2.1 Hz, 1H, CH₂-14^b), 2.07-1.89 (m, 3H, CH₂-11, CH₂-10^a), 1.37-1.29 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 203.3 (C-7), 201.4 (C-15), 180.3 (C-13), 153.0 (C-1), 151.7 (C-4), 136.9 (C_{Ph}), 136.3 (C_{Ph}), 129.3 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.2 (CH_{Ph}), 128.0 (CH_{Ph}), 127.7 (CH_{Ph}), 120.7 (C-3), 115.7 (C-5), 114.8 (C-2), 71.5 (CH₂Ph), 70.8 (CH₂Ph), 58.4 (C-8), 48.4 (C-14), 47.0 (C-12), 38.3 (C-9), 32.0 (C-10), 29.4 (C-11). **MS** (ESI+) m/z (%) 527 ([M+MeOH+Na⁺], 15), 495 ([M+Na⁺], 100). **HRMS** (ESI+)

m/z $[M+Na^+]$ calcd for $C_{29}H_{28}O_6Na$: 495.1784; found: 495.1782. **IR** (neat): ν_{max} = 3500-2400 (v br), 3064, 3033, 2926, 2872, 1720, 1702, 1579, 1491, 1415, 1281, 1221, 1172, 1080, 1016, 917, 849, 739, 697 cm^{-1} .

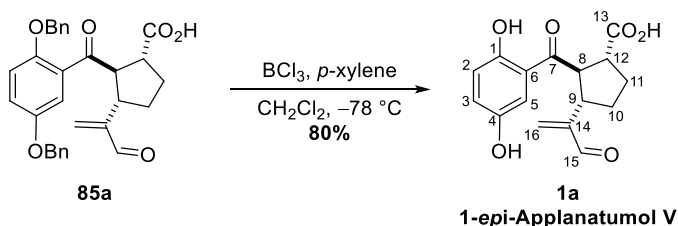
(±)-1,2-*trans*/2,3-*trans*-2-(2',5'-Bis(benzyloxy)benzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylic acid (**85a**)



In a 25 mL round-bottomed flask, aldehyde **84a** (690 mg, 1.47 mmol) was dissolved in *i*PrOH (7.25 mL). Formaldehyde (37% in H_2O , 0.5 mL, 6.7 mmol), pyrrolidine (12 μ L, 0.15 mmol) and propionic acid (11 μ L, 0.15 mmol) were successively added at r.t. The mixture was stirred at 45 °C for 14 h and evaporated at reduced pressure to give the crude product that was purified by column chromatography (neat hexane, gradient to 1:1 hexane/EtOAc) to afford 566 mg (80%) of **85a** as a colorless oil.

R_F = 0.57 (PE/EtOAc, 1:1). **^1H NMR** (400 MHz, Chloroform-*d*) δ 9.29 (s, 1H, CH-15), 7.42-7.27 (m, 10H, CH_{Ph}), 7.17 (d, J = 3.2 Hz, 1H, CH-5), 6.96 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.81 (d, J = 9.0 Hz, 1H, CH-2), 6.07 (d, J = 1.0 Hz, 1H, CH_2 -16), 5.69 (s, 1H, CH_2 -16), 5.00 (s, 2H, CH_2Ph), 4.99 (s, 2H, CH_2Ph), 4.44 (dd, J = 8.0, 6.8 Hz, 1H, CH-8), 3.36 (dt, J = 8.9, 6.4 Hz, 1H, CH-12), 3.28 (q, J = 7.8 Hz, 1H, CH-9), 2.14-1.94 (m, 3H, CH_2 -11, CH_2 -10^a), 1.67-1.53 (m, 1H, CH_2 -10^b). The carboxylic acid resonance is not detectable. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 202.8 (C-7), 193.9 (C-15), 180.3 (C-13), 152.9 (C-1), 151.6 (C-4), 151.3 (C-14), 136.9 (C_{Ph}), 136.5 (C_{Ph}), 134.1 (C-16), 129.3 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.3 (CH_{Ph}), 128.2 (CH_{Ph}), 127.70 (CH_{Ph}), 127.68 (CH_{Ph}), 120.5 (C-3), 115.7 (C-5), 114.6 (C-2), 71.3 (CH_2Ph), 70.8 (CH_2Ph), 57.0 (C-8), 46.7 (C-12), 42.5 (C-9), 32.1 (C-10), 29.6 (C-11). **MS** (ESI⁻) m/z (%) 483 ($[M-H^+]$, 100). **HRMS** (ESI⁻) m/z $[M-H^+]$ calcd for $C_{30}H_{27}O_3$: 483.1813; found: 483.1812. **IR** (neat): ν_{max} = 3500-2400 (v br), 3032, 2950, 2874, 1730, 1691, 1607, 1579, 1492, 1454, 1416, 1381, 1282, 1220, 1173, 1017, 951, 812, 738, 697 cm^{-1} .

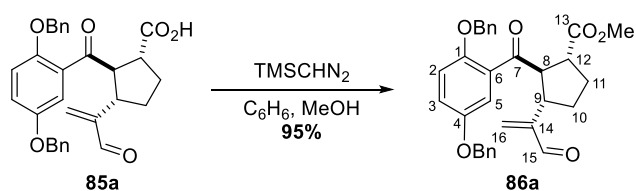
(±)-1,2-*trans*/2,3-*trans*-2-(2',5'-Dihydroxybenzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylic acid - 1-*epi*-Applanatumol V (**1a**)



In a flame-dried Schlenk flask, α,β -unsaturated aldehyde **85a** (42 mg, 86.7 μ mol) and *p*-xylene (110 μ L, 0.89 mmol) were dissolved in dry CH_2Cl_2 (1.8 mL) under an argon atmosphere. The mixture was cooled to -78°C , and BCl_3 (1M in CH_2Cl_2 , 0.35 mL, 0.35 mmol) was dropwise added. The mixture was stirred at -78°C for 1 h, and another portion of BCl_3 (1M in CH_2Cl_2 , 0.35 mL, 0.35 mmol) was dropwise added. The mixture was stirred at -78°C for an additional hour, warmed to 0°C , stirred for 20 min, and finally at r.t. for 15 min. The mixture was quenched by H_2O (0.3 mL) and filtered through a plug of silica gel, which was washed by EtOAc. Evaporation of the solvents at reduced pressure gave the crude product that was adsorbed on celite and purified by column chromatography (PE/EtOAc, 2:1) to yield 21 mg (80%) of **1a** as a yellow oil.

R_F = 0.22 (PE/EtOAc, 1:1). ^1H NMR (500 MHz, Methanol- d_4) δ 9.45 (s, 1H, CH-15), 7.15 (dd, J = 2.9, 0.5 Hz, 1H, CH-5), 6.99 (dd, J = 8.9, 2.9 Hz, 1H, CH-3), 6.78 (d, J = 8.9 Hz, 1H, CH-2), 6.50 (d, J = 1.0 Hz, 1H, CH₂-16), 6.15 (s, 1H, CH₂-16), 4.25 (dd, J = 8.7, 7.7 Hz, 1H, CH-8), 3.35-3.25 (m, 2H, CH-9, CH-12), 2.21-2.12 (m, 2H, CH₂-11), 2.12-2.04 (m, 1H, CH₂-10^a), 1.89-1.80 (m, 1H, CH₂-10^b). ^{13}C NMR (101 MHz, Methanol- d_4) δ 208.3 (C-7), 195.9 (C-15), 177.7 (C-13), 157.2 (C-1), 152.5 (C-14), 150.6 (C-4), 136.0 (C-16), 126.2 (C-3), 120.7 (C-6), 119.6 (C-2), 116.0 (C-5), 53.9 (C-8), 50.0 (C-12), 45.3 (C-9), 32.5 (C-10), 30.3 (C-11). MS (ESI[−]) m/z (%) 303 ([M-H⁺], 100). HRMS (ESI[−]) m/z [M-H⁺] calcd for $\text{C}_{16}\text{H}_{15}\text{O}_6$: 303.0874; found: 303.0876. IR (neat): ν_{max} = 3600-2700 (v br), 3025, 2922, 2855, 1705, 1640, 1602, 1494, 1451, 1378, 1220, 1180, 1113, 1074, 1030, 994, 939, 883, 807, 769, 724, 696, 635, 521 cm^{-1} .

(±)-Methyl *1,2-trans/2,3-trans-2-(2',5'-bis(benzyloxy)benzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylate (86a)*

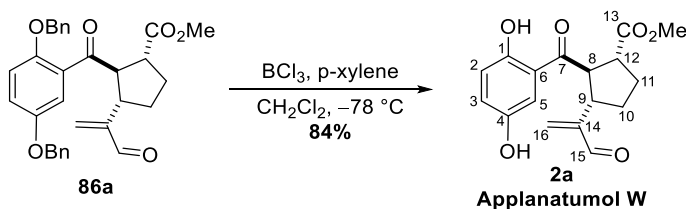


In a 25 mL round-bottomed flask, carboxylic acid **85a** (106 mg, 0.22 mmol) was dissolved in a benzene/MeOH mixture (2:1, 6.0 mL). TMSCHN_2 (2M in hexanes, 0.22 mL, 0.44 mmol) was added. The mixture was stirred at r.t. for 15 min, quenched by 4 drops AcOH and evaporated at reduced pressure to give the crude methyl ester that was purified by column chromatography (neat PE, gradient to 3:1 PE/EtOAc) to yield 105 mg (95%) of **86a** as a colorless oil.

R_F = 0.30 (hexanes/EtOAc, 3:1). ^1H NMR (400 MHz, Chloroform- d) δ 9.30 (s, 1H, CH-15), 7.45-7.28 (m, 10H, CH_{Ph}), 7.16 (d, J = 3.2 Hz, 1H, CH-5), 6.98 (dd, J = 9.1, 3.2 Hz, 1H, CH-3), 6.84 (d, J = 9.0 Hz, 1H, CH-2), 6.10 (s, 1H, CH₂-16), 5.69 (s, 1H, CH₂-16), 5.04 (s, 2H, CH₂Ph), 5.02 (s, 2H, CH₂Ph), 4.42 (t, J = 7.8 Hz, 1H, CH-8), 3.48 (s, 3H, OMe), 3.32 (q, J = 7.8 Hz, 1H, CH-9), 3.29-3.22 (m, 1H, CH-12), 2.09-1.95 (m, 3H, CH₂-10^a, CH₂-11), 1.66-1.54 (m, 1H, CH₂-10^b). ^{13}C NMR (101 MHz, Chloroform- d) δ 203.0 (C-7), 194.0 (C-15), 175.6 (C-13), 152.9 (C-1), 151.6 (C-4), 151.4 (C-14), 136.9

(C_{Ph}), 136.6 (C_{Ph}), 134.0 (C-16), 129.6 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.8 (CH_{Ph}), 127.7 (CH_{Ph}), 120.3 (C-3), 115.7 (C-5), 114.5 (C-2), 71.3 (CH₂Ph), 70.8 (CH₂Ph), 57.3 (C-8), 51.8 (OMe), 47.3 (C-12), 42.2 (C-9), 31.9 (C-10), 29.5 (C-11). **MS** (ESI+) *m/z* (%) 1019 ([2M+Na⁺], 80), 521 ([M+Na⁺], 100), 499 ([M+H⁺], 30). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₃₁H₃₀O₆Na: 521.1935; found: 521.1930. **IR** (neat): $\nu_{\max}$ = 3032, 2950, 2922, 2852, 1732, 1688, 1491, 1454, 1434, 1415, 1379, 1279, 1212, 1172, 1080, 1019, 946, 915, 848, 811, 784, 737, 697 cm⁻¹.

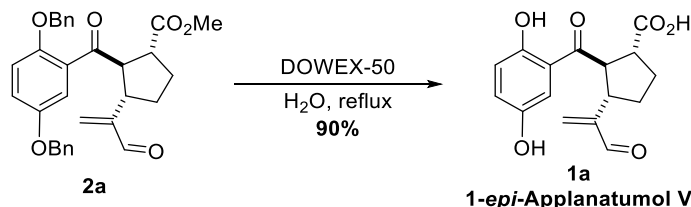
(±)-Methyl 1,2-*trans*/2,3-*trans*-2-(2',5'-dihydroxybenzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylate - **Applanatumol W (2a)**



In a flame-dried Schlenk flask, α,β -unsaturated aldehyde **86a** (60 mg, 0.12 mmol) and *p*-xylene (0.15 mL, 1.2 mmol) were dissolved in dry CH₂Cl₂ (2.4 mL) under an argon atmosphere. The mixture was cooled to -78 °C, and BCl₃ (1M in CH₂Cl₂, 0.48 mL, 0.48 mmol) was dropwise added. The mixture was stirred for 1 h, quenched by CHCl₃/MeOH (2:1, 5 mL), warmed to r.t. and evaporated at reduced pressure to give the crude product that was purified by column chromatography (PE/EtOAc, 2:1) to yield 32 mg (84%) of **2a** as a yellow oil.

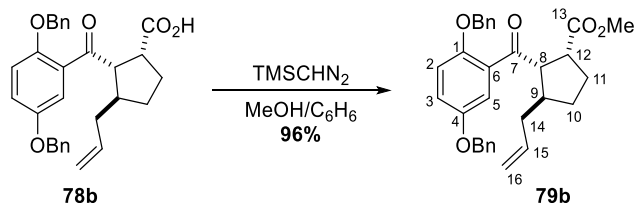
R_F = 0.27 (PE/EtOAc, 2:1). **¹H NMR** (401 MHz, Methanol-*d*₄) δ 9.45 (s, 1H, CH-15), 7.10 (d, *J* = 2.9 Hz, 1H, CH-5), 7.01 (dd, *J* = 8.9, 2.9 Hz, 1H, CH-3), 6.79 (d, *J* = 8.9 Hz, 1H, CH-2), 6.48 (s, 1H, CH₂-16), 6.15 (s, 1H, CH₂-16), 4.25 (t, *J* = 8.4 Hz, 1H, CH-8), 3.63 (s, 3H, OMe), 3.37-3.26 (m, 2H, CH-9, CH-12), 2.21-2.11 (m, 2H, CH₂-11), 2.11-2.03 (m, 1H, CH₂-10^a), 1.85 (dq, *J* = 12.5, 8.2 Hz, 1H, CH₂-10^b). **¹³C NMR** (101 MHz, Methanol-*d*₄) δ 207.9 (C-7), 195.9 (C-15), 176.3 (C-13), 157.1 (C-1), 152.2 (C-14), 150.6 (C-4), 136.1 (C-16), 126.2 (C-3), 120.8 (C-6), 119.7 (C-2), 115.9 (C-5), 53.9 (C-8), 52.5 (OMe), 49.9 (C-12), 45.3 (C-9), 32.4 (C-10), 30.0 (C-11). **MS** (ESI+) *m/z* (%) 341 ([M+Na⁺], 100), 319 ([M+H⁺], 20). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₁₇H₁₈O₆Na: 341.0996; found: 341.0989. **IR** (neat): $\nu_{\max}$ = 3406, 2953, 2875, 1729, 1688, 1641, 1615, 1483, 1437, 1345, 1290, 1218, 1178, 1005, 942, 831, 791, 686 cm⁻¹.

(±)-1,2-*trans*/2,3-*trans*-2-(2',5'-Dihydroxybenzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylic acid - **1-*epi*-Applanatumol V (1a)**



In a 25 mL round-bottomed flask, applanatumol W **2a** (2.0 mg, 6.3 μ mol) was mixed with H₂O (1.0 mL). DOWEX-50 (6 mg) was added, the reaction mixture was refluxed for 16 h, diluted with H₂O (10 mL), and extracted with Et₂O (3 $\times$ 5 mL). The combined organic layers were washed with brine (2 $\times$ 5 mL), dried by MgSO₄, filtered, and evaporated at reduced pressure. The crude product was purified by column chromatography (EtOAc) to yield 1.7 mg (90%) of **1a** as a yellow oil. For compound characterization *vide supra*.

(±)-Methyl 1,2-*cis*/2,3-*trans*-3-allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carboxylate (**79b**)

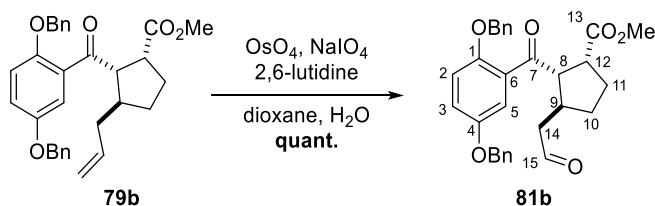


In a 25 mL round-bottomed flask, carboxylic acid **78b** (180 mg, 0.38 mmol) was dissolved in a benzene/MeOH mixture (2:1, 9.0 mL) and TMSCHN₂ (2M in hexanes, 0.38 mL, 0.76 mmol) was added. The mixture was stirred at r.t. for 15 min, quenched by 4 drops AcOH and evaporated at reduced pressure to give the crude methyl ester that was purified by column chromatography (neat PE, gradient to 3:1 PE/EtOAc) to yield 177 mg (96%) of **79b** as a colorless oil.

R_F = 0.30 (hexane/EtOAc, 3:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.46-7.29 (m, 10H, CH_{Ph}), 7.27 (d, J = 3.4 Hz, 1H, CH-5), 7.05 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.94 (d, J = 9.0 Hz, 1H, CH-2), 5.74-5.52 (m, 1H, CH-15), 5.10 (s, 2H, CH₂Ph), 5.04 (s, 2H, CH₂Ph), 4.92-4.82 (m, 2H, CH₂-16), 3.83 (t, J = 8.0 Hz, 1H, CH-8), 3.43 (s, 3H, OMe), 3.05 (td, J = 8.3, 6.7 Hz, 1H, CH-12), 2.53-2.41 (m, 1H, CH-9), 2.15-2.05 (m, 1H, CH₂-14^a), 2.05-1.98 (m, 1H, CH₂-11^a), 1.98-1.82 (m, 2H, CH₂-10^a, CH₂-14^b), 1.76 (dtd, J = 12.2, 8.2, 4.2 Hz, 1H, CH₂-11^b), 1.28-1.17 (m, 1H, CH₂-10^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 202.2 (C-7), 174.8 (C-13), 152.9 (C-1), 152.0 (C-4), 137.0 (C_{Ph}), 136.9 (C-15), 136.5 (C_{Ph}), 129.5 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.4 (CH_{Ph}), 128.1 (CH_{Ph}), 127.9 (CH_{Ph}), 127.7 (CH_{Ph}), 120.6 (C-3), 116.0 (C-16), 115.9 (C-5), 114.6 (C-2), 71.7 (CH₂Ph), 70.7 (CH₂Ph), 58.8 (C-8), 51.5 (OMe), 47.2 (C-12), 41.7 (C-9), 39.3 (C-14), 30.1 (C-10), 27.9 (C-11). **MS** (ESI⁺) m/z (%) 507 ([M+Na⁺], 100), 485 ([M+H⁺], 15). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₃₁H₃₂O₅Na: 507.2142;

found: 507.2140. **IR** (neat): $\nu_{\max}$ = 3065, 3033, 2948, 2872, 1733, 1670, 1491, 1454, 1434, 1415, 1279, 1212, 1172, 1017, 914, 849, 811, 784, 738, 697 cm^{-1} .

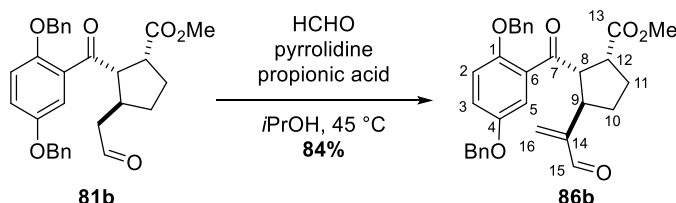
(±)-Methyl 1,2-*cis*/2,3-*trans*-2-(2',5'-bis(benzyloxy)benzoyl)-3-(2-oxoethyl)cyclopentane-1-carboxylate (**81b**)



In a 10 mL round-bottomed flask, olefin **79b** (32 mg, 0.066 mmol) was dissolved in dioxane (2.0 mL) and H_2O (0.2 mL). 2,6-Lutidine (35 μL , 0.13 mmol), OsO_4 (2.5% in *t*BuOH, 40 μL , 4 μmol) and NaIO_4 (282 mg, 1.32 mmol) were successively added. The inhomogeneous mixture was stirred for 2 h, quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (5 mL), diluted with brine (20 mL), and extracted with Et_2O (3×25 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and evaporated at reduced pressure to give 32 mg (quant.) of aldehyde **81b** as an off-white solid that was used without purification in the next step. X-ray quality crystals were obtained by slow evaporation of a hexane/ Et_2O solution.

R_F = 0.17 (PE/ EtOAc , 3:1). **^1H NMR** (400 MHz, Chloroform-*d*) δ 9.57 (dd, J = 2.6, 1.7 Hz, 1H, CH-15), 7.45-7.30 (m, 10H, CH_{Ph}), 7.29 (d, J = 3.2 Hz, 1H, CH-5), 7.08 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.96 (d, J = 9.0 Hz, 1H, CH-2), 5.11 (d, J = 11.1 Hz, 1H, CH_2Ph), 5.07 (d, J = 11.1 Hz, 1H, CH_2Ph), 5.05 (s, 2H, CH_2Ph), 3.73 (t, J = 8.6 Hz, 1H, CH-8), 3.39 (s, 3H, OMe), 3.11 (td, J = 8.5, 6.0 Hz, 1H, CH-12), 2.95-2.84 (m, 1H, CH-9), 2.42 (ddd, J = 16.3, 4.8, 1.7 Hz, 1H, $\text{CH}_2\text{-14}^{\text{a}}$), 2.12 (ddd, J = 16.2, 8.9, 2.5 Hz, 1H, $\text{CH}_2\text{-14}^{\text{b}}$), 2.10-1.94 (m, 2H, $\text{CH}_2\text{-10}^{\text{a}}$, $\text{CH}_2\text{-11}^{\text{a}}$), 1.82-1.71 (m, 1H, $\text{CH}_2\text{-11}^{\text{b}}$), 1.21-1.07 (m, 1H, $\text{CH}_2\text{-10}^{\text{b}}$). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 201.8 (C-15), 201.0 (C-7), 174.5 (C-13), 153.0 (C-1), 152.1 (C-4), 137.0 (C_{Ph}), 136.2 (C_{Ph}), 128.92 (CH_{Ph}), 128.89 (C-6), 128.73 (CH_{Ph}), 128.72 (CH_{Ph}), 128.23 (CH_{Ph}), 128.15 (CH_{Ph}), 127.7 (CH_{Ph}), 121.2 (C-3), 115.8 (C-5), 114.5 (C-2), 71.8 (CH_2Ph), 70.7 (CH_2Ph), 59.3 (C-8), 51.6 (OMe), 48.9 (C-14), 46.8 (C-12), 36.0 (C-9), 30.7 (C-10), 28.1 (C-11). **MS** (ESI+) m/z (%) 541 ($[\text{M}+\text{MeOH}+\text{Na}^+]$, 100), 509 ($[\text{M}+\text{Na}^+]$, 20). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{30}\text{H}_{30}\text{O}_6\text{Na}$: 509.1935; found: 509.1932. **IR** (neat): $\nu_{\max}$ = 3032, 2924, 2854, 2729, 1724, 1668, 1491, 1434, 1415, 1380, 1279, 1211, 1171, 1080, 1021, 918, 848, 813, 784, 739, 698 cm^{-1} .

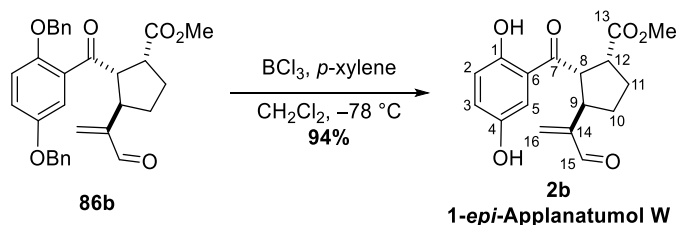
(±)-Methyl 1,2-*cis*/2,3-*trans*-2-(2',5'-bis(benzyloxy)benzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylate (**86b**)



In a 10 mL round-bottomed flask, aldehyde **81b** (29 mg, 0.06 mmol) was dissolved in *i*PrOH (1.0 mL). Formaldehyde (37% in H₂O, 60 μL, 0.72 mmol), pyrrolidine (5 μL), and propionic acid (5 μL) were successively added. The mixture was stirred at 45 °C for 18 h and evaporated under reduced pressure. The crude product was purified by column chromatography (neat cyclohexane, gradient to 5:1 cyclohexane/EtOAc) to yield 25 mg (84%) of **86b** as a colorless oil.

R_F = 0.30 (hexanes/EtOAc, 3:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.38 (s, 1H, CH-15), 7.45-7.28 (m, 10H, CH_{Ph}), 7.25 (d, *J* = 3.2 Hz, 1H, CH-5), 7.04 (dd, *J* = 9.0, 3.2 Hz, 1H, CH-3), 6.92 (d, *J* = 9.0 Hz, 1H, CH-2), 6.05 (s, 1H, CH₂-16), 5.77 (s, 1H, CH₂-16), 5.09 (d, *J* = 11.6 Hz, 1H, CH₂Ph), 5.06 (d, *J* = 11.6 Hz, 1H, CH₂Ph), 5.03 (s, 2H, CH₂Ph), 4.31 (t, *J* = 8.8 Hz, 1H, CH-8), 3.50-3.33 (m, 1H, CH-9), 3.41 (s, 3H, OMe), 3.25-3.19 (m, 1H, CH-12), 2.14-2.05 (m, 1H, CH₂-10^a), 2.05-1.95 (m, 1H, CH₂-11^a), 1.93-1.82 (m, 1H, CH₂-11^b), 1.57-1.45 (m, 1H, CH₂-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 200.9 (C-7), 194.3 (C-15), 174.5 (C-13), 152.9 (C-1), 152.0 (C-4), 151.6 (C-14), 137.0 (C_{Ph}), 136.4 (C_{Ph}), 134.5 (C-16), 129.0 (C-6), 128.9 (CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.1 (CH_{Ph}), 128.0 (CH_{Ph}), 127.7 (CH_{Ph}), 121.0 (C-3), 115.7 (C-5), 114.5 (C-2), 71.7 (CH₂Ph), 70.7 (CH₂Ph), 57.2 (C-8), 51.5 (OMe), 47.2 (C-12), 41.7 (C-9), 30.6 (C-10), 28.8 (C-11). MS (ESI+) *m/z* (%) 1019 ([2M+Na⁺], 80), 521 ([M+Na⁺], 100), 499 ([M+H⁺], 30). HRMS (ESI+) *m/z* [M+Na⁺] calcd for C₃₁H₃₀O₆Na: 521.1935; found: 521.1930. IR (neat): $\nu_{\max}$ = 3032, 2950, 2922, 2852, 1732, 1688, 1491, 1454, 1434, 1415, 1379, 1279, 1212, 1172, 1080, 1019, 946, 915, 848, 811, 784, 737, 697 cm⁻¹.

(±)-Methyl 1,2-*cis*/2,3-*trans*-2-(2',5'-dihydroxybenzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylate - **1-*epi*-Applanatumol W (2b)**

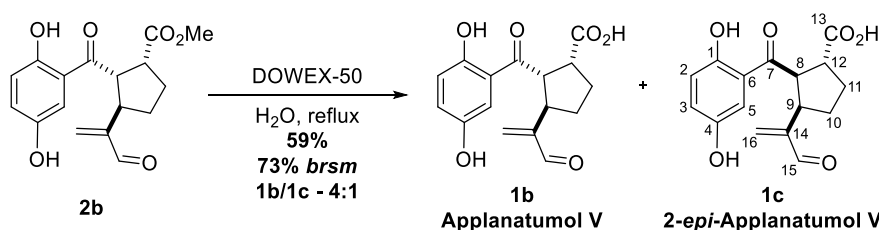


In a flame-dried Schlenk flask, α,β-unsaturated aldehyde **86b** (25 mg, 0.05 mmol) and *p*-xylene (62 μL, 0.5 mmol) were dissolved in dry CH₂Cl₂ (3.0 mL) under an argon atmosphere. The mixture was cooled to -78 °C, and BCl₃ (1M in CH₂Cl₂, 0.25 mL, 0.25 mmol) was dropwise added. The mixture was stirred for 75 min, quenched by a CHCl₃/MeOH mixture (2:1, 3 mL), warmed to r.t., and evaporated at reduced

pressure. The crude product was purified by column chromatography (neat cyclohexane, gradient to 1:1 cyclohexane/EtOAc) to yield 15.0 mg (94%) of **2b** as a yellow oil.

R_F = 0.40 (PE/EtOAc, 1:1). $^1\text{H NMR}$ (600 MHz, Methanol- d_4) δ 9.53 (d, J = 0.6 Hz, 1H, CH-15), 7.16 (d, J = 3.0 Hz, 1H, CH-5), 7.00 (dd, J = 8.9, 2.9 Hz, 1H, CH-3), 6.78 (d, J = 8.9 Hz, 1H, CH-2), 6.41 (d, J = 1.0 Hz, 1H, CH₂-16), 6.16 (s, 1H, CH₂-16), 4.26 (dd, J = 9.2, 7.9 Hz, 1H, CH-8), 3.47 (dt, J = 9.2, 8.0 Hz, 1H, CH-12), 3.42 (s, 3H, OMe), 3.42-3.36 (m, 1H, CH-9), 2.21-2.12 (m, 3H, CH₂-11, CH₂-10^a), 1.79-1.69 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (151 MHz, Methanol- d_4) δ 207.4 (C-7), 196.1 (C-15), 175.5 (C-13), 156.8 (C-1), 152.7 (C-14), 150.6 (C-4), 136.1 (C-16), 125.9 (C-3), 120.8 (C-6), 119.6 (C-2), 115.9 (C-5), 53.5 (C-8), 52.0 (OMe), 49.5 (C-12), 43.6 (C-9), 32.0 (C-10), 29.9 (C-11). **MS** (ESI⁺) m/z (%) 341 ([M+Na⁺], 100), 319 ([M+H⁺], 15). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₁₇H₁₈O₆Na: 341.0996; found: 341.0997. **IR** (neat): ν_{max} = 3392, 2954, 2853, 1733, 1687, 1642, 1618, 1589, 1484, 1437, 1351, 1293, 1211, 1183, 942, 791, 735, 686 cm⁻¹.

Acidic methyl ester hydrolysis of 1-*epi*-applanatumol W



In a 25 mL round-bottomed flask, 1-*epi*-applanatumol W **2b** (8.0 mg, 25 μmol) was dissolved in H₂O (2.0 mL). DOWEX-50 (16 mg) was added, and the mixture was refluxed (120 °C oil bath temperature) for 16 h. The mixture was filtered through a sintered glass filter and extracted with Et₂O (3 $\times$ 25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure to give the crude mixture of products that were separated by column chromatography (pentane/EtOAc, 2:1+1% AcOH) to yield 1.5 mg (19%) of the starting material **2b**, 0.9 mg (12%) of **1c**, and 3.6 mg (47%) of **1b** as pale yellow oils.

($\pm$)-1,2-*cis*/2,3-*trans*-2-(2',5'-Dihydroxybenzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylic acid - Applanatumol V (**1b**)

R_F = 0.45 (PE/EtOAc, 1:1+1% AcOH). $^1\text{H NMR}$ (600 MHz, Methanol- d_4) δ 9.54 (d, J = 0.5 Hz, 1H, CH-15), 7.19 (d, J = 2.9 Hz, 1H, CH-5), 6.98 (dd, J = 8.9, 2.9 Hz, 1H, CH-3), 6.76 (d, J = 8.9 Hz, 1H, CH-2), 6.42 (d, J = 1.0 Hz, 1H, CH₂-16), 6.15 (s, 1H, CH₂-16), 4.20 (dd, J = 9.1, 7.7 Hz, 1H, CH-8), 3.45 (dt, J = 9.2, 8.1 Hz, 1H, CH-12), 3.43-3.38 (m, 1H, CH-9), 2.22-2.16 (m, 2H, CH₂-11), 2.16-2.11 (m, 1H, CH₂-10^a), 1.72 (dtd, J = 12.2, 9.0, 8.0 Hz, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (151 MHz, Methanol- d_4) δ 207.6 (C-7), 196.1 (C-15), 177.3 (C-13), 156.9 (C-1), 153.0 (C-14), 150.5 (C-4), 135.9 (C-16), 125.6 (C-3), 121.0 (C-6), 119.5 (C-2), 116.0 (C-5), 53.5 (C-8), 50.0 (C-12), 43.7 (C-9), 32.1 (C-10), 30.3 (C-11). **MS** (ESI⁻) m/z (%) 303 ([M-H⁺], 100). **HRMS** (ESI⁻) m/z [M-H⁺] calcd for C₁₆H₁₅O₆: 303.0874;

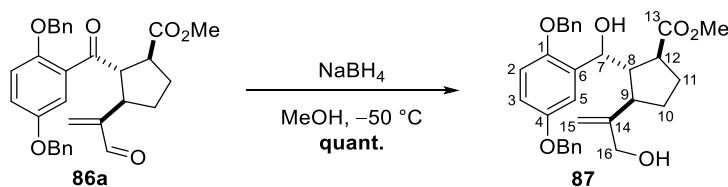
found: 303.0873. **IR** (neat): $\nu_{\max}$ = 3500-2500 (v br), 3266, 2959, 1708, 1687, 1641, 1617, 1588, 1484, 1444, 1352, 1286, 1227, 1185, 1005, 958, 831, 789, 686, 666 cm^{-1} .

(±)-*1,2-trans/2,3-cis*-2-(2',5'-Dihydroxybenzoyl)-3-(3-oxoprop-1-en-2-yl)cyclopentane-1-carboxylic acid – **2-*epi*-Applanatumol V (1c)**

R_F = 0.50 (PE/EtOAc, 1:1+1% AcOH). **^1H NMR** (600 MHz, Methanol- d_4) δ 9.20 (s, 1H, CH-15), 7.19 (dd, J = 3.0, 1.6 Hz, 1H, CH-5), 6.96 (dd, J = 8.9, 3.0 Hz, 1H, CH-3), 6.72 (d, J = 8.9 Hz, 1H, CH-2), 6.29 (s, 1H, CH₂-16), 6.06 (s, 1H, CH₂-16), 4.51 (dd, J = 9.4, 7.2 Hz, 1H, CH-8), 3.61-3.55 (m, 1H, CH-9), 3.46-3.39 (m, 1H, CH-12), 2.36-2.29 (m, 1H, CH₂-11^a), 2.08-1.99 (m, 2H, CH₂-10), 1.97-1.90 (m, 1H, CH₂-11^b). **^{13}C NMR** (151 MHz, Methanol- d_4) δ 208.2 (C-7), 195.7 (C-15), 178.1 (C-13), 156.8 (C-1), 151.5 (C-14), 150.5 (C-4), 136.6 (C-16), 126.1 (C-3), 120.9 (C-6), 119.5 (C-2), 116.3 (C-5), 52.6 (C-8), 48.8 (C-12), 42.6 (C-9), 32.2 (C-10), 30.2 (C-11). **MS** (ESI[−]) m/z (%) 303 ([M-H⁺], 100). **HRMS** (ESI[−]) m/z [M-H⁺] calcd for C₁₆H₁₅O₆: 303.0874; found: 303.0873. **IR** (neat): $\nu_{\max}$ = 3500-2500 (v br), 3311, 2926, 2854, 1709, 1689, 1637, 1614, 1483, 1445, 1334, 1284, 1191, 954, 830, 790, 684, 665 cm^{-1} .

6.3.7. Total synthesis of applanatumol B

(±)-Methyl *1,2-trans/2,3-trans*-2-((2',5'-bis(benzyloxy)phenyl)(hydroxy)methyl)-3-(3-hydroxyprop-1-en-2-yl)cyclopentane-1-carboxylate (**87**)

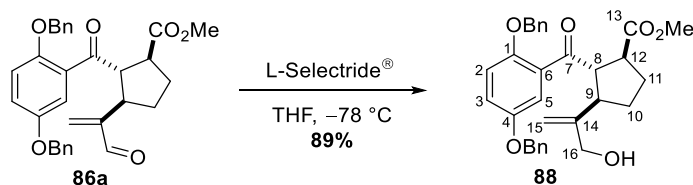


In a flame-dried Schlenk flask, α,β -unsaturated aldehyde **86a** (4.5 mg, 9.0 μmol) was dissolved in dry MeOH (2.0 mL). At $-50\text{ }^\circ\text{C}$ NaBH₄ (0.4 mg, 10 μmol) was added. The reaction mixture was stirred for 20 min, and another portion of NaBH₄ (0.3 mg, 8 μmol) was added. The mixture was stirred for 1 h, and water (0.1 mL) was added. The mixture was diluted with Et₂O filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give 4.5 mg (quant.) of **87** as the only detectable component as a colorless oil.

R_F = 0.39 (hexanes/EtOAc, 1:1). **^1H NMR** (400 MHz, Chloroform- d) δ 7.47-7.29 (m, 10H, CH_{Ph}), 7.09 (bs, 1H, CH-5), 6.79 (bs, 2H, CH-2, CH-3), 5.04-4.98 (m, 4H, CH₂Ph), 4.98-4.94 (m, 1H, CH₂-7), 4.86 (bs, 2H, CH₂-15), 3.86 (bs, 2H, CH₂-16), 3.34 (s, 3H, OMe), 2.98-2.83 (m, 2H, CH-8, CH-9), 2.58 (q, J = 8.7 Hz, 1H, CH-12), 2.49 (bs, 1H, OH), 1.96-1.75 (m, 3H, CH₂-11, CH₂-10^a), 1.66-1.57 (m, 2H, OH, CH₂-10^b). **^{13}C NMR** (101 MHz, Chloroform- d) δ 177.2 (C-13), 153.1 (C-4), 150.14 (C-1), 150.07 (C-14), 137.5 (C_{Ph}), 137.1 (C_{Ph}), 132.6 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 128.0 (CH_{Ph}), 127.6 (CH_{Ph}), 114.5 (C-5), 114.0 (C-3), 112.4 (C-2), 110.4 (C-15), 71.0 (CH₂Ph), 70.7 (CH₂Ph), 69.7 (C-7), 65.3 (C-16), 52.3 (C-8), 51.5 (OMe), 45.7 (C-12), 44.2 (C-9), 32.8 (C-10), 30.0

(C-11). **MS** (ESI+) m/z (%) 541 ([M+K⁺], 20), 525 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₃₁H₃₄O₆Na: 525.2253; found: 525.2249. **IR** (neat): $\nu_{\max}$ = 3447, 3065, 3033, 2948, 2871, 1728, 1590, 1495, 1454, 1434, 1379, 1278, 1203, 1164, 1039, 1026, 909, 802, 737, 697 cm⁻¹.

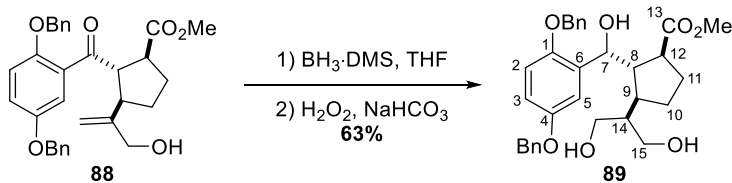
(±)-Methyl *1,2-trans/2,3-trans*-2-(2',5'-bis(benzyloxy)benzoyl)-3-(3-hydroxyprop-1-en-2-yl)cyclopentane-1-carboxylate (**88**)



In a flame-dried Schlenk flask, α,β -unsaturated aldehyde **86a** (4.5 mg, 9.0 μ mol) was dissolved in dry THF (1.8 mL). At -78 °C, L-Selectride[®] (1M in THF, 9 μ L, 9 μ mol) was added. The reaction mixture was stirred for 1 h and, after the complete conversion of the starting material as judged by TLC analysis, quenched by the addition of a drop of saturated NH₄Cl solution. The mixture was diluted with Et₂O and filtered through a plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure to give the crude product that was purified by column chromatography (neat pentane, gradient to 3:1 pentane/EtOAc), providing 4.0 mg (89%) of **88** as a colorless oil.

R_F = 0.52 (hexanes/EtOAc, 1:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.47-7.29 (m, 10H, CH_{Ph}), 7.16 (d, J = 3.1 Hz, 1H, CH-5), 6.99 (dd, J = 9.0, 3.1 Hz, 1H, CH-3), 6.87 (d, J = 9.0 Hz, 1H, CH-2), 5.07 (s, 2H, CH₂Ph), 5.02 (s, 2H, CH₂Ph), 4.87 (s, 1H, CH₂-15), 4.82 (s, 1H, CH₂-15), 4.32 (dd, J = 9.0, 7.3 Hz, 1H, CH-8), 3.90 (bs, 2H, CH₂-16), 3.46 (s, 3H, OMe), 3.14 (q, J = 7.1 Hz, 1H, CH-12), 3.00 (q, J = 8.8 Hz, 1H, CH-9), 2.06-1.88 (m, 3H, CH₂-11, CH₂-10^a), 1.79-1.65 (m, 1H, CH₂-10^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 204.1 (C-7), 175.8 (C-13), 152.9 (C-1), 151.6 (C-4), 149.7 (C-14), 136.9 (C_{Ph}), 136.6 (C_{Ph}), 129.9 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.3 (CH_{Ph}), 128.2 (CH_{Ph}), 127.71 (CH_{Ph}), 127.69 (CH_{Ph}), 120.2 (C-3), 115.7 (C-5), 114.8 (C-2), 110.3 (C-15), 71.5 (CH₂Ph), 70.8 (CH₂Ph), 65.4 (C-16), 58.2 (C-8), 51.8 (OMe), 47.8 (C-12), 46.7 (C-9), 31.9 (C-10), 29.7 (C-11). **MS** (ESI+) m/z (%) 539 ([M+K⁺], 20), 523 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₃₁H₃₂O₆Na: 523.2097; found: 523.2093. **IR** (neat): $\nu_{\max}$ = 3507, 3065, 3032, 2950, 2925, 2873, 1731, 1679, 1607, 1581, 1492, 1454, 1435, 1415, 1380, 1282, 1219, 1172, 1080, 1022, 907, 811, 739, 697 cm⁻¹.

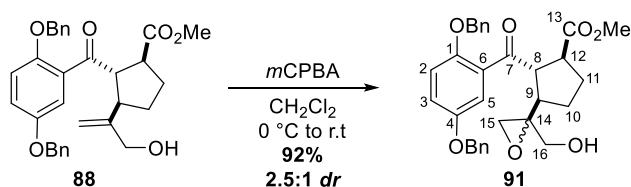
(±)-Methyl *1,2-trans/2,3-trans*-2-(2',5'-bis(benzyloxy)phenyl)(hydroxy)methyl)-3-(1,3-dihydroxypropan-2-yl)cyclopentane-1-carboxylate (**89**)



In a flame-dried Schlenk flask, allylic alcohol **88** (20 mg, 40 μ mol) was dissolved in dry THF (0.8 mL). At 0 °C, $\text{BH}_3 \cdot \text{DMS}$ complex (1M in THF, 13 μ L, 13 μ mol) was added, the reaction mixture was stirred at r.t. for 30 min and another portion of $\text{BH}_3 \cdot \text{DMS}$ complex (1M in THF, 6 μ L, 6 μ mol) was added. The reaction mixture was stirred at r.t. for 1 h, and after cooling to 0 °C, a 1:1 mixture of saturated NaHCO_3 solution and 30% H_2O_2 solution (0.25 mL) was added. The mixture was stirred at 0 °C for 15 min, warmed to r.t., stirred for additional 15 min, and extracted by EtOAc (3 $\times$ 20 mL). The combined organic layers were washed by brine (1 $\times$ 20 mL), dried by MgSO_4 , filtered, and evaporated at reduced pressure. The crude product was purified by column chromatography (neat pentane, gradient to 3:1 pentane/EtOAc) to yield 13.0 mg (63%) of **89** as a colorless oil.

R_F = 0.02 (hexanes/EtOAc, 3:1). ^1H NMR (401 MHz, Chloroform- d) δ 7.50-7.29 (m, 10H, CH_{Ph}), 7.13 (d, J = 2.8 Hz, 1H, CH-5), 6.85 (d, J = 8.8 Hz, 1H, CH-2), 6.82 (dd, J = 8.8, 2.8 Hz, 1H, CH-3), 5.04 (s, 2H, CH_2Ph), 5.00 (s, 2H, CH_2Ph), 4.97 (t, J = 4.6 Hz, 1H, CH-7), 3.74-3.66 (m, 1H, CH_2 -15), 3.62-3.50 (m, 3H, CH_2 -15), 3.37 (s, 3H, OMe), 2.93 (dt, J = 8.8, 6.3 Hz, 1H, CH-12), 2.69 (td, J = 6.9, 4.7 Hz, 1H, CH-8), 2.47 (d, J = 5.1 Hz, 1H, OH), 2.11 (quint, J = 7.4 Hz, 1H, CH-9), 2.05 (bs, 1H, OH), 1.90-1.79 (m, 1H, CH_2 -11^a), 1.77-1.65 (m, 3H, CH_2 -11^b, CH_2 -10^a, OH), 1.53-1.45 (m, 2H, CH_2 -10^b, CH-14). ^{13}C NMR (101 MHz, Chloroform- d) δ 177.3 (C-13), 153.1 (C-4), 150.0 (C-1), 137.4 (C_{Ph}), 137.1 (C_{Ph}), 132.7 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.6 (CH_{Ph}), 128.4 (CH_{Ph}), 128.0 (CH_{Ph}), 127.6 (CH_{Ph}), 114.4 (C-5), 114.1 (C-3), 112.3 (C-2), 71.1 (CH_2Ph), 70.7 (CH_2Ph), 70.6 (C-7), 65.8 (C-15), 64.9 (C-15), 51.6 (OMe), 50.8 (C-8), 45.0 (C-14), 44.7 (C-12), 39.5 (C-9), 30.5 (C-11), 29.6 (C-10). MS (ESI+) m/z (%) 559 ($[\text{M}+\text{K}^+]$, 15), 543 ($[\text{M}+\text{Na}^+]$, 100). HRMS (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{31}\text{H}_{36}\text{O}_7\text{Na}$: 543.2353; found: 543.2357. IR (neat): ν_{max} = 3392, 3063, 3032, 2950, 2927, 2872, 1726, 1589, 1493, 1454, 1433, 1379, 1277, 1202, 1164, 1119, 1079, 1025, 914, 858, 804, 737, 697, 618 cm^{-1} .

($\pm$)-Methyl 1,2-*trans*/2,3-*trans*-2-(2',5'-bis(benzyloxy)benzoyl)-3-(2-(hydroxymethyl)oxiran-2-yl)cyclopentane-1-carboxylate (**91**)



In a 10 mL round-bottomed flask, allylic alcohol **88** (10 mg, 20 μ mol) was dissolved in CH_2Cl_2 (1.0 mL). At 0 °C, $m\text{CPBA}$ (70-75%, 10 mg, 40 μ mol) was added, and the mixture was stirred at r.t. for 1 h. Another portion of $m\text{CPBA}$ (70-75%, 5 mg, 20 μ mol) was added, the mixture was stirred for additional 30 min and directly separated by column chromatography (neat cyclohexane, gradient to 1:1 cyclohexane/EtOAc) to yield 9.5 mg (92%) of **91** as an inseparable 2.5:1 diastereoisomeric mixture as a colorless oil.

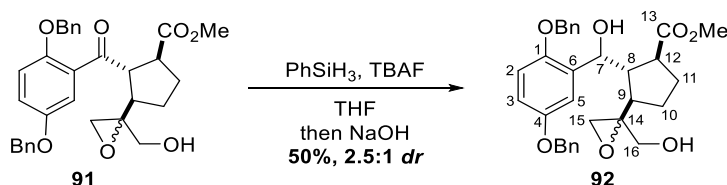
Major diastereoisomer:

$R_F = 0.53$ (hexanes/EtOAc, 1:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.45-7.29 (m, 10H, CH_{Ph}), 7.22 (d, $J = 3.2$ Hz, 1H, CH-5), 7.01 (dd, $J = 9.0, 3.2$ Hz, 1H, CH-3), 6.89 (d, $J = 9.0$ Hz, 1H, CH-2), 5.10 (s, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph), 4.18 (dd, $J = 8.7, 6.9$ Hz, 1H, CH-8), 3.57 (s, 2H, $\text{CH}_2\text{-16}$), 3.44 (s, 3H, OMe), 3.01 (q, $J = 7.2$ Hz, 1H, CH-12), 2.88-2.79 (m, 1H, CH-9), 2.65 (d, $J = 4.4$ Hz, 1H, $\text{CH}_2\text{-15}^a$), 2.54 (d, $J = 4.5$ Hz, 1H, $\text{CH}_2\text{-15}^b$), 1.99-1.90 (m, 2H, $\text{CH}_2\text{-11}$), 1.90-1.81 (m, 1H, $\text{CH}_2\text{-10}^a$), 1.75 (bs, 1H, OH), 1.68-1.59 (m, 1H, $\text{CH}_2\text{-10}^b$). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 203.2 (C-7), 175.4 (C-13), 152.9 (C-1), 151.72 (C-4), 136.92 (C_{Ph}), 136.6 (C_{Ph}), 129.3 (C-6), 128.83 (CH_{Ph}), 128.7 (CH_{Ph}), 128.3 (CH_{Ph}), 128.2 (CH_{Ph}), 127.72 (CH_{Ph}), 127.70 (CH_{Ph}), 120.5 (C-3), 115.84 (C-5), 114.8 (C-2), 71.5 (CH_2Ph), 70.80 (CH_2Ph), 62.7 (C-14), 60.2 (C-16), 54.4 (C-8), 51.9 (OMe), 48.6 (C-15), 48.0 (C-12), 43.9 (C-9), 30.1 (C-10), 28.1 (C-11). **MS** (ESI+) m/z (%) 555 ($[\text{M}+\text{K}^+]$, 10), 539 ($[\text{M}+\text{Na}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{31}\text{H}_{32}\text{O}_7\text{Na}$: 539.2040; found: 539.2033.

Minor diastereoisomer:

$^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.45-7.29 (m, 10H, CH_{Ph}), 7.19 (d, $J = 3.2$ Hz, 1H, CH-5), 7.02 (dd, $J = 9.0, 3.2$ Hz, 1H, CH-3), 6.90 (d, $J = 9.1$ Hz, 1H, CH-2), 5.08 (s, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph), 4.22 (dd, $J = 8.5, 7.2$ Hz, 1H, CH-8), 3.63-3.56 (m, 2H, $\text{CH}_2\text{-16}$), 3.41 (s, 3H, OMe), 2.95-2.89 (m, 2H, CH-9, CH-12), 2.49 (d, $J = 4.3$ Hz, 1H, $\text{CH}_2\text{-15}^a$), 2.48 (d, $J = 4.3$ Hz, 1H, $\text{CH}_2\text{-15}^b$), 1.99-1.90 (m, 2H, $\text{CH}_2\text{-11}$), 1.91-1.79 (m, 1H, $\text{CH}_2\text{-10}^a$), 1.75 (bs, 1H, OH), 1.58-1.50 (m, 1H, $\text{CH}_2\text{-10}^b$). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 203.8 (C-7), 175.2 (C-13), 152.9 (C-1), 151.73 (C-4), 136.88 (C_{Ph}), 136.4 (C_{Ph}), 129.3 (C-6), 128.92 (CH_{Ph}), 128.86 (CH_{Ph}), 128.4 (CH_{Ph}), 128.2 (CH_{Ph}), 128.0 (CH_{Ph}), 127.70 (CH_{Ph}), 120.6 (C-3), 115.81 (C-5), 114.6 (C-2), 71.5 (CH_2Ph), 70.82 (CH_2Ph), 63.1 (C-16), 60.4 (C-14), 55.9 (C-8), 51.8 (OMe), 49.1 (C-12), 48.2 (C-15), 42.5 (C-9), 29.8 (C-10), 26.8 (C-11).

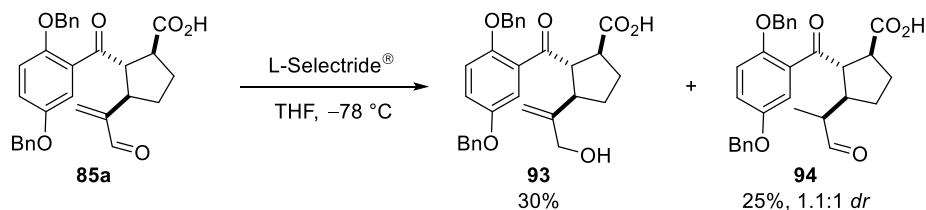
(±)-Methyl 1,2-trans/2,3-trans-2-(2',5'-bis(benzyloxy)phenyl)(hydroxy)methyl-3-(2-(hydroxymethyl)oxiran-2-yl)cyclopentane-1-carboxylate (92)



In a flame-dried Schlenk flask, epoxide **91** (3.0 mg, 5.8 μmol) was dissolved in THF (0.5 mL). At r.t., PhSiH_3 (3.6 μL , 29 μmol) and TBAF (1M in THF, 3.0 μL , 3 μmol) were successively added. The mixture was stirred for 30 min, diluted with Et_2O , and filtered through a plug of silica gel, which was washed by Et_2O . The solvents were evaporated at reduced pressure to give the crude product that was purified by column chromatography (hexane/EtOAc, 10:1, gradient to 3:1) to yield 1.5 mg (50%) of **92** as an inseparable 2.5:1 diastereoisomeric mixture as a colorless oil. Because of a low amount of the diastereoisomeric material, only the $^1\text{H NMR}$ spectrum of the major diastereoisomer is stated.

R_F = 0.27 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.49-7.29 (m, 10H, CH_{Ph}), 7.05 (d, J = 2.8 Hz, 1H, CH-5), 6.85 (d, J = 8.9 Hz, 1H, CH-2), 6.81 (dd, J = 9.0, 2.9 Hz, 1H, CH-3), 5.04-5.00 (m, 4H, CH_2Ph), 4.88 (d, J = 5.7 Hz, 1H, CH-7), 3.65-3.50 (m, 2H, CH_2 -16), 3.41 (s, 3H, OMe), 2.92 (q, J = 7.2 Hz, 1H, CH-12), 2.80-2.70 (m, 2H, CH-8, CH-9), 2.56 (d, J = 4.3 Hz, 1H, CH_2 -15^a), 2.41 (d, J = 4.3 Hz, 1H, CH_2 -15^b), 1.93-1.62 (m, 4H, CH_2 -10, CH_2 -11), 1.22 (bs, 1H, OH). **MS** (ESI+) m/z (%) 557 ($[\text{M}+\text{K}^+]$, 10), 541 ($[\text{M}+\text{Na}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{31}\text{H}_{34}\text{O}_7\text{Na}$: 541.2197; found: 541.2191. **IR** (neat): ν_{max} = 3447, 3032, 2928, 2872, 1728, 1590, 1493, 1454, 1434, 1380, 1276, 1202, 1163, 1111, 1039, 1025, 916, 799, 735, 696 cm^{-1} .

Reduction of α,β -unsaturated aldehyde **85a** by L-Selectride®

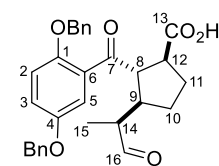


In a flame-dried Schlenk flask, α,β -unsaturated aldehyde **85a** (6.0 mg, 12.4 μmol) was dissolved in dry THF (0.5 mL). At -78°C , L-Selectride® (1M in THF, 26 μL , 26 μmol) was added. The reaction mixture was stirred for 1.5 h and quenched by 2 drops of saturated NH_4Cl solution and 1 drop of 1M HCl solution. The mixture was diluted with Et_2O and filtered through a plug of silica gel, which was washed by Et_2O . The solvents were evaporated at reduced pressure to give the crude products that were separated by column chromatography (neat pentane, gradient to 1:1 pentane/EtOAc) to give 1.5 mg (25%) of the 1,4-reduced product **94** as an inseparable 1.1:1 diastereoisomeric mixture, followed by 1.8 mg (30%) of allylic alcohol **93** as colorless oils.

($\pm$)-1,2-*trans*/2,3-*trans*-2-(2',5'-Bis(benzyloxy)benzoyl)-3-(3-hydroxyprop-1-en-2-yl)cyclopentane-1-carboxylic acid (**93**)

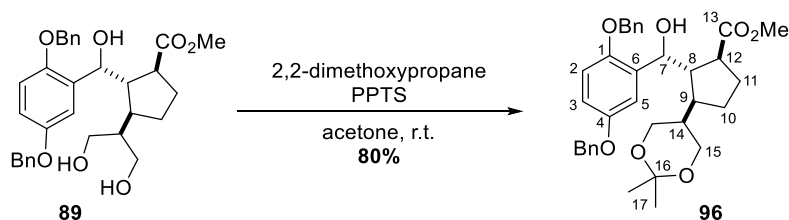
R_F = 0.15 (hexanes/EtOAc, 1:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 9.48 (bs, 1H, COOH), 7.43-7.29 (m, 10H, CH_{Ph}), 7.15 (d, J = 3.2 Hz, 1H, CH-5), 6.99 (dd, J = 9.0, 3.1 Hz, 1H, CH-3), 6.86 (d, J = 9.0 Hz, 1H, CH-2), 5.05 (s, 2H, CH_2Ph), 5.01 (s, 2H, CH_2Ph), 4.88 (q, J = 1.2 Hz, 1H, CH_2 -15), 4.81 (quint, J = 1.0 Hz, 1H, CH_2 -15), 4.32 (dd, J = 8.7, 6.7 Hz, 1H, CH-8), 3.94-3.84 (m, 2H, CH_2 -16), 3.23 (q, J = 6.7 Hz, 1H, CH-12), 2.97 (q, J = 9.1 Hz, 1H, CH-9), 2.07-1.65 (m, 4H, CH_2 -10, CH_2 -11). **MS** (ESI-) m/z (%) 485 ($[\text{M}-\text{H}^+]$, 100). **HRMS** (ESI-) m/z $[\text{M}-\text{H}^+]$ calcd for $\text{C}_{30}\text{H}_{29}\text{O}_6$: 485.1970; found: 485.1969.

(±)-1,2-trans/2,3-trans-2-(2',5'-Bis(benzyloxy)benzoyl)-3-(1-oxopropan-2-yl)cyclopentane-1-carboxylic acid (94)



R_F = 0.23 (hexanes/EtOAc, 1:1). Resonances of the major diastereoisomer are labeled with an asterisk. Only distinguishable, resonances are stated. $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 9.50 (d, J = 2.4 Hz, 1H, CH-16*), 9.42 (d, J = 1.6 Hz, 1H, CH-16), 7.50-7.30 (m, 20H, CH_{Ph} , CH_{Ph} *), 7.23 (d, J = 3.2 Hz, 1H, CH-5), 7.21 (d, J = 3.1 Hz, 1H, CH-5*), 7.04 (dd, J = 9.1, 3.2 Hz, 1H, CH-3), 7.02 (dd, J = 9.1, 3.2 Hz, 1H, CH-3*), 6.91 (d, J = 9.1 Hz, 1H, CH-2*), 6.90 (d, J = 9.1 Hz, 1H, CH-2), 4.26 (dd, J = 7.7, 6.0 Hz, 1H, CH-8*), 4.18 (dd, J = 8.1, 5.8 Hz, 1H, CH-8), 3.19-3.13 (m, 1H, CH-12*), 3.12-3.04 (m, 1H, CH-12), 2.81-2.66 (m, 2H, CH-9, CH-9*), 0.96 (d, J = 7.1 Hz, 3H, CH_3 -15), 0.88 (d, J = 7.0 Hz, 3H, CH_3 -15*). **MS** (ESI-) m/z (%) 485 ($[\text{M}-\text{H}^+]$, 100). **HRMS** (ESI-) m/z $[\text{M}-\text{H}^+]$ calcd for $\text{C}_{30}\text{H}_{29}\text{O}_6$: 485.1970; found: 485.1968. **IR** (neat): ν_{max} = 3500-2500 (v br), 3063, 3033, 2921, 2852, 2760, 1703, 1607, 1581, 1491, 1454, 1415, 1379, 1281, 1219, 1171, 1015, 842, 812, 737, 697 cm^{-1} .

(±)-Methyl 1,2-trans/2,3-trans-2-(2',5'-bis(benzyloxy)phenyl)(hydroxy)methyl)-3-(2,2-dimethyl-1,3-dioxan-5-yl)cyclopentane-1-carboxylate (96)

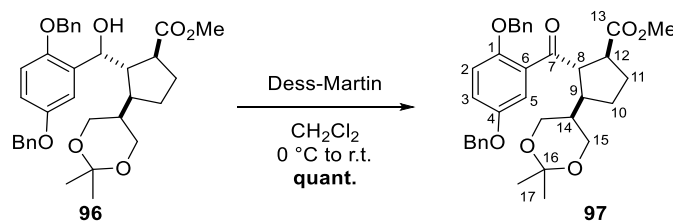


In a 25 mL round-bottomed flask, triol **89** (7.0 mg, 13.4 μmol) was dissolved in acetone (2.0 mL). 2,2-Dimethoxypropane (0.3 mL, 2.44 mmol), and PPTS (5 mg, 20 μmol) were successively added at r.t. The reaction mixture was stirred for 15 min, evaporated at reduced pressure, and the crude product was directly purified by column chromatography (hexane/EtOAc, gradient 5:1, to 3:1) to yield 6.0 mg (80%) of **96** as a colorless oil.

R_F = 0.21 (hexanes/EtOAc, 3:1). $^1\text{H NMR}$ (401 MHz, Chloroform- d) δ 7.47-7.28 (m, 10H, CH_{Ph}), 7.04 (d, J = 2.8 Hz, 1H, CH-5), 6.82 (d, J = 8.5 Hz, 1H, CH-2), 6.79 (dd, J = 8.9, 2.7 Hz, 1H, CH-3), 5.08-5.04 (m, 2H, CH_2Ph), 5.02 (s, 2H, CH_2Ph), 4.76 (t, J = 5.7 Hz, 1H, CH-7), 3.73 (ddd, J = 11.6, 4.6, 1.5 Hz, 1H, CH_2 -15), 3.60 (ddd, J = 11.8, 4.6, 1.6 Hz, 1H, CH_2 -15), 3.52 (dd, J = 11.7, 9.1 Hz, 1H, CH_2 -15), 3.39 (s, 3H, OMe), 3.28 (dd, J = 11.7, 9.2 Hz, 1H, CH_2 -15), 2.95 (dt, J = 7.8, 6.4 Hz, 1H, CH-12), 2.68 (q, J = 5.9 Hz, 1H, CH-8), 2.48 (d, J = 6.0 Hz, 1H, OH), 1.92-1.79 (m, 2H, CH-9, CH_2 -11^a), 1.79-1.66 (m, 2H, CH_2 -11^b, CH_2 -10^a), 1.65-1.59 (m, 1H, CH-14), 1.56-1.46 (dq, J = 12.9, 6.7, 5.9 Hz, 1H, CH_2 -10^b), 1.32 (s, 3H, CH_3 -17), 1.29 (s, 3H, CH_3 -17). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 176.8 (C-13), 153.1 (C-4), 150.1 (C-1), 137.4 (C_{Ph}), 136.9 (C_{Ph}), 132.5 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.2 (CH_{Ph}), 128.0 (CH_{Ph}), 127.8 (CH_{Ph}), 127.6 (CH_{Ph}), 114.9 (C-5), 114.1 (C-2), 112.8 (C-3), 97.6 (C-16), 72.4 (C-7), 71.0 (CH_2Ph), 70.7 (CH_2Ph), 63.5 (C-15), 63.2 (C-15), 51.6 (OMe), 51.0 (C-8), 45.5 (C-

12), 40.7 (C-9), 37.9 (C-14), 30.4 (C-11), 29.4 (C-10), 27.1 (C-17), 21.0 (C-17). **MS** (ESI+) m/z (%) 583 ([$M+Na^+$], 100). **HRMS** (ESI+) m/z [$M+Na^+$] calcd for $C_{34}H_{40}O_7Na$: 583.2666; found: 583.2660. **IR** (neat): ν_{max} = 3478, 3034, 2991, 2947, 2872, 1729, 1494, 1455, 1434, 1378, 1277, 1255, 1199, 1163, 1066, 1027, 823, 737, 697 cm^{-1} .

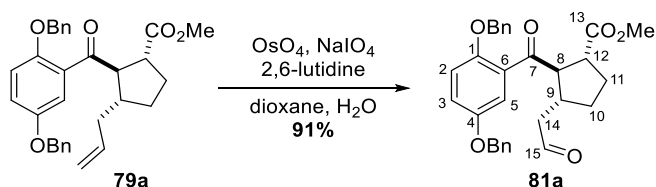
(±)-Methyl 1,2-trans/2,3-trans-2-(2',5'-bis(benzyloxy)benzoyl)-3-(2,2-dimethyl-1,3-dioxan-5-yl)cyclopentane-1-carboxylate (**97**)



In a 25 mL round-bottomed flask, alcohol **96** (5.3 mg, 9.4 μ mol) was dissolved in CH_2Cl_2 (2.0 mL). At 0 °C, Dess-Martin periodinane (6.8 mg, 16.0 μ mol) was added. The reaction mixture was stirred at 0 °C for 10 min and at r.t. for 45 min. The mixture was diluted with Et_2O (10 mL) and washed by saturated $Na_2S_2O_3$ solution (2×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (2×10 mL). The organic layers were dried by $MgSO_4$, filtered, and evaporated at reduced pressure to yield 5.3 mg (quant.) of **97** as a colorless oil.

R_F = 0.32 (hexanes/ $EtOAc$, 3:1). **^1H NMR** (400 MHz, $CHCl_3-d$) δ 7.44-7.29 (m, 10H, CH_{Ph}), 7.21 (d, J = 3.2 Hz, 1H, CH-5), 7.00 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.88 (d, J = 9.1 Hz, 1H, CH-2), 5.13 (d, J = 12.1 Hz, 1H, CH_2Ph), 5.08 (d, J = 12.1 Hz, 1H, CH_2Ph), 5.02 (s, 2H, CH_2Ph), 4.10 (dd, J = 8.2, 6.6 Hz, 1H, CH-8), 3.72 (ddd, J = 11.6, 4.8, 1.9 Hz, 1H, CH_2-15), 3.60-3.55 (m, 1H, CH_2-15), 3.57 (dd, J = 11.6, 10.2 Hz, 1H, CH_2-15), 3.424 (dd, J = 11.8, 10.0 Hz, 1H, CH_2-15), 3.421 (s, 3H, OMe), 2.96 (q, J = 6.8 Hz, 1H, CH-12), 2.37-2.24 (m, 1H, CH-9), 1.96-1.88 (m, 2H, CH_2-11), 1.83 (td, J = 12.0, 6.8 Hz, 1H, CH_2-10^a), 1.71-1.60 (m, 1H, CH_2-10^b), 1.47-1.38 (m, 1H, CH-14), 1.43 (m, 3H, CH_3-17), 1.33 (m, 3H, CH_3-17). **MS** (ESI+) m/z (%) 581 ([$M+Na^+$], 100). **HRMS** (ESI+) m/z [$M+Na^+$] calcd for $C_{34}H_{38}O_7Na$: 581.2509; found: 581.2502.

(±)-Methyl 1,2-trans/2,3-trans-2-(2',5'-bis(benzyloxy)benzoyl)-3-(2-oxoethyl)cyclopentane-1-carboxylate (**81a**)

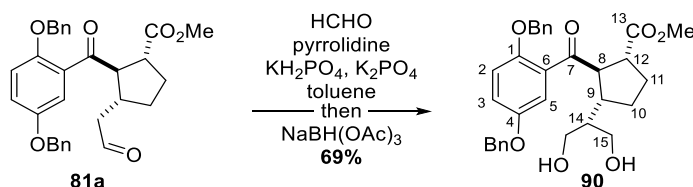


In a 100 mL round-bottomed flask, olefin **79a** (370 mg, 0.76 mmol) was dissolved in dioxane (6.0 mL) and H_2O (2.0 mL). 2,6-Lutidine (0.18 mL, 1.53 mmol), OsO_4 (2.5% in $tBuOH$, 154 μ L, 15 μ mol) and $NaIO_4$ (653 mg, 3.1 mmol) were successively added. The inhomogeneous mixture was stirred for 2 h,

diluted with brine (20 mL), and extracted with Et₂O (3×25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated at reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc, 3:1) to yield 337 mg (91%) of aldehyde **81a** as a colorless oil that slowly solidified to a sticky amorphous solid.

R_F = 0.38 (hexanes/EtOAc, 3:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 9.47 (dd, J = 2.1, 1.3 Hz, 1H, CH-15), 7.45-7.29 (m, 10H, CH_{Ph}), 7.19 (d, J = 3.2 Hz, 1H, CH-5), 7.03 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.92 (d, J = 9.0 Hz, 1H, CH-2), 5.07 (s, 2H, CH₂Ph), 5.03 (s, 2H, CH₂Ph), 4.00 (t, J = 7.6 Hz, 1H, CH-8), 3.47 (s, 3H, OMe), 3.16 (dt, J = 8.2, 6.3 Hz, 1H, CH-12), 2.77-2.64 (m, 1H, CH-9), 2.35 (ddd, J = 17.1, 5.2, 1.4 Hz, 1H, CH₂-14^a), 2.16 (ddd, J = 17.2, 8.9, 2.1 Hz, 1H, CH₂-14^b), 2.06-1.88 (m, 3H, CH₂-11, CH₂-10^a), 1.38-1.23 (m, 1H, CH₂-10^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 203.7 (C-7), 201.5 (C-15), 175.6 (C-13), 153.0 (C-1), 151.7 (C-4), 136.9 (C_{Ph}), 136.4 (C_{Ph}), 129.7 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.2 (CH_{Ph}), 128.0 (CH_{Ph}), 127.7 (CH_{Ph}), 120.4 (C-3), 115.7 (C-5), 114.7 (C-2), 71.6 (CH₂Ph), 70.8 (CH₂Ph), 58.8 (C-8), 51.8 (OMe), 48.5 (C-14), 47.7 (C-12), 38.1 (C-9), 31.8 (C-10), 29.3 (C-11). **MS** (ESI⁺) m/z (%) 541 ([M+MeOH+Na⁺], 100), 509 ([M+Na⁺], 20). **HRMS** (ESI⁺) m/z [M+Na⁺] calcd for C₃₀H₃₀O₆Na: 509.1935; found: 509.1932. **IR** (neat): $\nu_{\max}$ = 3032, 2924, 2854, 2721, 1726, 1680, 1492, 1454, 1435, 1416, 1380, 1280, 1221, 1170, 1018, 813, 738, 698 cm⁻¹.

(±)-Methyl 1,2-*trans*/2,3-*trans*-2-(2',5'-bis(benzyloxy)benzoyl)-3-(1,3-dihydroxypropan-2-yl)cyclopentane-1-carboxylate (**90**)

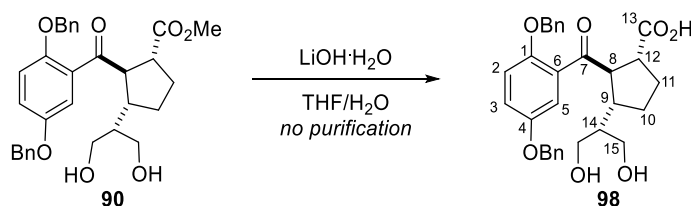


In a 10 mL round-bottomed flask, pyrrolidine (2.3 μ L, 27 μ mol) was dissolved in toluene (0.54 mL), phosphate buffer* (135 mg), and formaldehyde (37% in H₂O, 81 μ L, 1.10 mmol) were successively added. The mixture was stirred for 15 min, and aldehyde **81a** (135 mg, 82 μ mol) was added. The flask was closed with a hard plastic cap, stirred for 5 days, cooled to 0 °C, and subjected to mild vacuum (70 mbar) for 30 min. The resulting mixture was diluted with toluene (2.0 mL), and NaBH(OAc)₃ (309 mg, 1.46 mmol) was added. The mixture was stirred for 6 h, quenched by MeOH (0.5 mL), stirred for additional 30 min, diluted by Et₂O, and filtered through a plug of silica gel, which was washed by EtOAc. The solvent was evaporated at reduced pressure, and the crude product was purified by column chromatography (cyclohexane/EtOAc, 1:2) to yield 99 mg (69%) of **90** as a colorless oil.

*Phosphate buffer was prepared by homogenizing solid K₂HPO₄ (1.0 equiv.) and KH₂PO₄ (1.1 equiv.) using a mortar and pestle.^[122]

R_F = 0.15 (hexanes/EtOAc, 1:1). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.44-7.30 (m, 10H, CH_{Ph}), 7.14 (d, J = 3.1 Hz, 1H, CH-5), 7.04 (dd, J = 9.0, 3.1 Hz, 1H, CH-3), 6.92 (d, J = 9.0 Hz, 1H, CH-2), 5.10-5.04 (m, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph), 4.11 (dd, J = 8.9, 6.6 Hz, 1H, CH-8), 3.75 (dd, J = 10.9, 3.3 Hz, 1H, CH_2 -15), 3.69-3.53 (m, 2H, CH_2 -15), 3.45 (dd, J = 12.0, 3.9 Hz, 1H, CH_2 -15), 3.41 (s, 3H, OMe), 2.88 (q, J = 6.6 Hz, 1H, CH-12), 2.81-2.70 (m, 1H, CH-9), 2.68 (bs, 1H, OH), 2.50 (bs, 1H, OH), 2.03-1.94 (m, 1H, CH_2 -10^a), 1.94-1.86 (m, 2H, CH_2 -11), 1.53-1.39 (m, 1H, CH_2 -10^b), 1.24-1.16 (m, 1H, CH-14). $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 206.1 (C-7), 175.8 (C-13), 153.0 (C-1), 151.6 (C-4), 136.8 (C_{Ph}), 136.4 (C_{Ph}), 129.4 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.2 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 120.5 (C-3), 115.7 (C-5), 114.5 (C-2), 71.5 (CH_2Ph), 70.8 (CH_2Ph), 65.6 (C-15), 65.5 (C-15), 57.9 (C-8), 51.9 (OMe), 49.2 (C-12), 46.3 (C-14), 39.2 (C-9), 30.3 (C-10), 30.2 (C-11). **MS** (ESI+) m/z (%) 541 ($[\text{M}+\text{Na}^+]$, 100), 519 ($[\text{M}+\text{H}^+]$, 20), 501 ($[\text{M}-\text{H}_2\text{O}+\text{H}^+]$, 80). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{31}\text{H}_{34}\text{O}_7\text{Na}$: 541.2197; found: 541.2191. **IR** (neat): ν_{max} = 3607, 3032, 2948, 2881, 1731, 1672, 1492, 1454, 1416, 1380, 1281, 1221, 1170, 1023, 739, 697 cm^{-1} .

(±)-1,2-trans/2,3-trans-2-(2',5'-Bis(benzyloxy)benzoyl)-3-(1,3-dihydroxypropan-2-yl)cyclopentane-1-carboxylic acid (**98**)

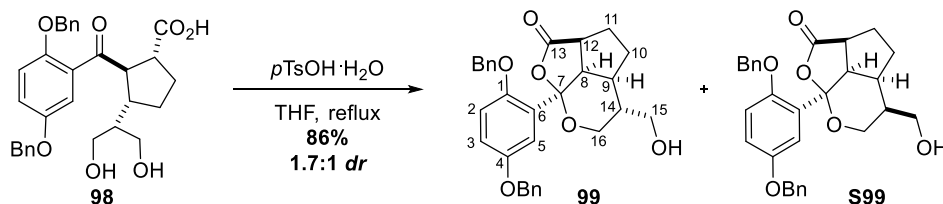


In a 10 mL round-bottomed flask, diol **90** (15 mg, 29 μmol) was dissolved in THF (0.5 mL) and H_2O (0.5 mL). At 0 $^\circ\text{C}$ $\text{LiOH}\cdot\text{H}_2\text{O}$ (12 mg, 0.29 mmol) was added, the cooling bath was removed, and the mixture was stirred at r.t. for 15 h. The mixture was diluted by H_2O (5 mL), acidified by 1M HCl solution (0.35 mL), and extracted by EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and evaporated at reduced pressure to give 16 mg (quant.) of free carboxylic acid **98** as a thick colorless oil that was used in the next step without further purification.

R_F = 0.25 (hexanes/EtOAc, 1:2). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.43-7.28 (m, 10H, CH_{Ph}), 7.15 (d, J = 3.2 Hz, 1H, CH-5), 7.01 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.87 (d, J = 9.1 Hz, 1H, CH-2), 5.11-4.93 (m, 4H, CH_2Ph), 4.17-4.06 (m, 1H, CH-8), 3.74 (dd, J = 11.0, 3.2 Hz, 1H, CH_2 -15), 3.68-3.56 (m, 2H, CH_2 -15), 3.43 (dd, J = 11.9, 4.6 Hz, 1H, CH_2 -15), 2.94 (dt, J = 9.0, 4.9 Hz, 1H, CH-12), 2.70 (quint, J = 9.6 Hz, 1H, CH-9), 2.03-1.83 (m, 3H, CH_2 -11, CH_2 -10^a), 1.52-1.38 (m, 1H, CH_2 -10^b), 1.32-1.23 (m, 1H, CH-14). Carboxylic acid resonance is not detectable. $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 205.8 (C-7), 179.9 (C-13), 153.0 (C-1), 151.5 (C-4), 136.8 (C_{Ph}), 136.4 (C_{Ph}), 129.1 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.2 (CH_{Ph}), 128.0 (CH_{Ph}), 127.7 (CH_{Ph}), 120.7 (C-3), 115.6 (C-5), 114.7 (C-2), 71.4 (CH_2Ph), 70.8 (CH_2Ph), 65.24 (C-15), 65.21 (C-15), 57.5 (C-8), 48.5 (C-12), 46.3 (C-14), 39.3 (C-9), 30.5 (C-10), 30.4 (C-11). **MS** (ESI+) m/z (%) 527 ($[\text{M}+\text{Na}^+]$, 100), 505 ($[\text{M}+\text{H}^+]$, 20), 487

[M-H₂O+H⁺], 70). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₃₀H₃₂O₇Na: 527.2040; found: 527.2035. **IR** (neat): $\nu_{\max}$ = 3600-2500 (v br), 3401, 3033, 2925, 2855, 1702, 1491, 1454, 1415, 1379, 1281, 1221, 1171, 1019, 909, 809, 734, 697 cm⁻¹.

Acidic epimerization/ketalization of diol **98**



In a 25 mL round-bottomed flask, diol **98** (16 mg, 29 μ mol) was dissolved in THF (1.4 mL), and *p*TsOH·H₂O (2.8 mg, 15 μ mol) was added. The mixture was refluxed for 2.5 h, cooled to r.t., and evaporated. The crude product was purified by column chromatography (PE/EtOAc, 2:1) to yield 12 mg (86%) of **99** and **S99** as a 1.7:1 diastereoisomeric mixture as a white solid. The diastereoisomeric mixture was separated by preparative TLC (CHCl₃/MeOH, 50:1, 5 elutions) to yield pure major diastereoisomer **99** and a 1:5 **99**:**S99** diastereoisomeric mixture. The major diastereoisomer was crystallized from a toluene/DCM mixture for X-ray diffraction analysis.

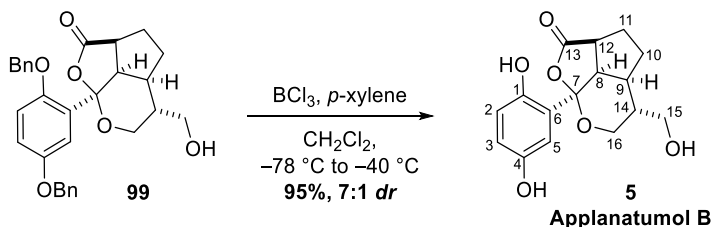
(2*aS**,2*a*1*R**,4*aS**,5*R**,7*aR**)-7*a*-(2',5'-Bis(benzyloxy)phenyl)-5-(hydroxymethyl)octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-2-one (**99**)

*R*_F = 0.42 (hexanes/EtOAc, 1:2). **m.p.** 158-160 °C. **¹H NMR** (600 MHz, Chloroform-*d*) δ 7.46-7.35 (m, 9H, CH_{Ph}), 7.33-7.29 (m, 1H, CH_{Ph}), 7.27-7.25 (m, 1H, CH-5), 6.92 (dd, *J* = 9.0, 0.5 Hz, 1H, CH-2), 6.89 (dd, *J* = 8.9, 3.0 Hz, 1H, CH-3), 5.08 (d, *J* = 11.1 Hz, 1H, CH₂Ph), 5.05 (d, *J* = 11.2 Hz, 1H, CH₂Ph), 5.01 (bs, 2H, CH₂Ph), 3.98 (dd, *J* = 12.3, 2.7 Hz, 1H, CH₂-16^a), 3.78 (dt, *J* = 12.2, 1.6 Hz, 1H, CH₂-16^b), 3.56 (ddd, *J* = 10.4, 7.7, 4.8 Hz, 1H, CH₂-15^a), 3.29 (ddd, *J* = 10.4, 7.5, 4.9 Hz, 1H, CH₂-15^b), 3.19 (dd, *J* = 10.5, 8.3 Hz, 1H, CH-8), 3.06 (t, *J* = 7.8 Hz, 1H, CH-12), 2.25 (dd, *J* = 12.6, 5.8 Hz, 1H, CH₂-11^a), 2.15-2.06 (m, 1H, CH-9), 1.86 (ddd, *J* = 12.8, 7.1, 5.9 Hz, 1H, CH₂-10^a), 1.63 (tdd, *J* = 12.6, 7.4, 6.0 Hz, 1H, CH₂-11^b), 1.59-1.53 (m, 2H, CH-14, OH), 1.49 (qd, *J* = 12.8, 5.9 Hz, 1H, CH₂-10^b). **¹³C NMR** (151 MHz, Chloroform-*d*) δ 178.3 (C-13), 152.8 (C-1), 149.9 (C-4), 137.1 (C_{Ph}), 136.7 (C_{Ph}), 130.3 (C-6), 129.0 (CH_{Ph}), 128.9 (CH_{Ph}), 128.7 (CH_{Ph}), 128.6 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 116.4 (C-3), 114.4 (C-5), 114.1 (C-2), 106.9 (C-7), 71.4 (CH₂Ph), 70.8 (CH₂Ph), 63.8 (C-15), 58.5 (C-16), 48.9 (C-12), 40.2 (C-8), 36.7 (C-14), 36.3 (C-9), 31.7 (C-10), 29.2 (C-11). **MS** (ESI+) *m/z* (%) 509 ([M+Na⁺], 100), 487 ([M+H⁺], 10). **HRMS** (ESI+) *m/z* [M+Na⁺] calcd for C₃₀H₃₀O₆Na: 509.1935; found: 509.1931. **IR** (neat): $\nu_{\max}$ = 3492, 2940, 2884, 1764, 1495, 1425, 1378, 1282, 1222, 1186, 1024, 938, 742, 698 cm⁻¹.

(2*aS,2*a*1*R**,4*aS**,5*S**,7*aR**)-7*a*-(2',5'-bis(benzyloxy)phenyl)-5-(hydroxymethyl)octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-2-one (S99)**

R_F = 0.42 (hexanes/EtOAc, 1:2). ^1H NMR (600 MHz, Chloroform-*d*) δ 7.49-7.35 (m, 9H, CH_{Ph}), 7.33-7.29 (m, 1H, CH_{Ph}), 7.19 (dd, J = 3.0, 0.4 Hz, 1H, CH-5), 6.94 (dd, J = 8.9, 0.4 Hz, 1H, CH-2), 6.91 (dd, J = 8.9, 2.9 Hz, 1H, CH-3), 5.05 (d, J = 10.5 Hz, 1H, CH₂Ph), 5.01 (d, J = 10.5 Hz, 1H, CH₂Ph), 5.01 (bs, 2H, CH₂Ph), 3.68 (ddd, J = 11.6, 3.8, 1.2 Hz, 1H, CH₂-16^a), 3.55 (t, J = 11.7 Hz, 1H, CH₂-16^b), 3.29-3.25 (m, 2H, CH₂-15), 3.24 (dd, J = 10.5, 8.6 Hz, 1H, CH-8), 3.02 (t, J = 8.3 Hz, 1H, CH-12), 2.33-2.27 (m, 1H, CH₂-11^a), 2.21-2.12 (m, 1H, CH-9), 1.82-1.75 (m, 1H, CH-14), 1.70-1.54 (m, 2H, CH₂-11^b, CH₂-10^a), 1.35-1.26 (m, 1H, CH₂-10^b). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 178.3 (C-13), 152.8 (C-1), 150.0 (C-4), 137.2 (C_{Ph}), 137.1 (C_{Ph}), 131.5 (C-6), 129.0 (CH_{Ph}), 128.71 (CH_{Ph}), 128.68 (CH_{Ph}), 128.4 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 116.2 (C-3), 114.5 (C-5), 113.5 (C-2), 107.1 (C-7), 71.8 (CH₂Ph), 70.8 (CH₂Ph), 62.5 (C-15), 59.2 (C-16), 47.7 (C-12), 43.4 (C-8), 38.2 (C-9), 36.5 (C-14), 29.9 (C-11), 25.1 (C-10).

(2*aS,2*a*¹*R**,4*aS**,5*R**,7*aR**)-7*a*-(2',5'-Dihydroxyphenyl)-5-(hydroxymethyl)octahydro-2*H*-1,7-dioxacyclopenta[*cd*]inden-2-one - Applanatumol B (5)**



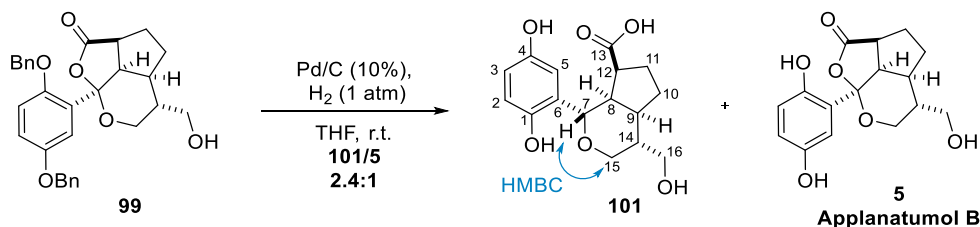
In a flame-dried Schlenk flask, ketal **99** (5.0 mg, 10 μmol) was dissolved in dry CH₂Cl₂ (1.0 mL), and *p*-xylene (13 μL , 100 μmol) was added. The mixture was cooled to $-78\text{ }^\circ\text{C}$, and BCl₃ (1M in CH₂Cl₂, 100 μL , 100 μmol) was dropwise added. The reaction mixture was stirred and gradually warmed to $-30\text{ }^\circ\text{C}$ over 5 h. After completed as judged by TLC analysis, the mixture was cooled to $-78\text{ }^\circ\text{C}$, quenched by slow addition of a CHCl₃/MeOH mixture (2:1, 0.5 mL). The cooling bath was removed, the solvents were evaporated by a stream of N₂ while still cold, and the residue was thoroughly dried under vacuum. The crude product was dissolved in MeOH, adsorbed on celite, and purified by column chromatography (EtOAc) to yield 3.0 mg (95%) of **5** as a 7:1 diastereoisomeric mixture as a white solid. The diastereoisomers were separated by subsequent multiple column chromatography (pentane/*i*PrOH, 10:1) to yield pure applanatumol B (**5**) as a white amorphous solid. The calculated yield of the naturally occurring diastereoisomer **5** after the first column chromatography is 83%.

Note: With trace acid, the CH-8 is slowly deuterated in MeOH-*d*₄ as manifested by a disappearance of the ^1H NMR signal at 3.14 ppm, ^{13}C NMR signal at 41.9 ppm, and a change of the CH-9 splitting to 2.28 (dd, J = 12.6, 7.0 Hz, 1H).

R_F = 0.18 (PE/EtOAc, 1:3). ^1H NMR (500 MHz, Methanol-*d*₄) δ 6.87 (d, J = 2.8 Hz, 1H, CH-5), 6.67 (d, J = 8.7 Hz, 1H, CH-2), 6.63 (dd, J = 8.6, 2.8 Hz, 1H, CH-3), 4.02 (dd, J = 10.8, 8.4 Hz, 1H, CH₂-

15^a), 3.98 (dd, $J = 12.2, 2.6$ Hz, 1H, CH₂-16^a), 3.90 (dt, $J = 12.1, 1.4$ Hz, 1H, CH₂-16^b), 3.77 (dd, $J = 10.8, 6.6$ Hz, 1H, CH₂-15^b), 3.30-3.26 (m, 1H, CH-12), 3.14 (dd, $J = 10.5, 8.4$ Hz, 1H, CH-8), 2.32-2.24 (m, 1H, CH-9), 2.19 (dd, $J = 12.5, 6.0$ Hz, 1H, CH₂-11^a), 1.94-1.87 (m, 1H, CH₂-10^a), 1.78-1.70 (m, 1H, CH₂-11^b), 1.70-1.66 (m, 1H, CH-14), 1.51 (qd, $J = 12.8, 5.9$ Hz, 1H, CH₂-10^b). ¹³C NMR (126 MHz, Methanol-*d*₄) δ 181.3 (C-13), 150.9 (C-4), 148.5 (C-1), 129.7 (C-6), 118.4 (C-2), 117.6 (C-3), 114.0 (C-5), 108.8 (C-7), 64.1 (C-15), 59.0 (C-16), 50.7 (C-12), 41.9 (C-8), 38.5 (C-14), 37.9 (C-9), 32.5 (C-10), 29.9 (C-11). MS (ESI⁺) m/z (%) 329 ([M+Na⁺], 35), 307 ([M+H⁺], 100). HRMS (ESI⁺) m/z [M+Na⁺] calcd for C₁₆H₁₈O₆Na: 329.0996; found: 329.0996; [M+H⁺] calcd for C₁₆H₁₉O₆: 307.1176; found: 307.1177. IR (neat): $\nu_{\max} = 3356, 2925, 2854, 1745, 1599, 1500, 1448, 1324, 1285, 1211, 1127, 1091, 1023, 939, 883, 820, 789, 772, 724, 653, 620$ cm⁻¹.

(1*S,4*R**,4*aS**,7*S**,7*aR**)-1-(2',5'-Dihydroxyphenyl)-4-(hydroxymethyl)octahydrocyclopenta[*c*]pyran-7-carboxylic acid (**101**)**

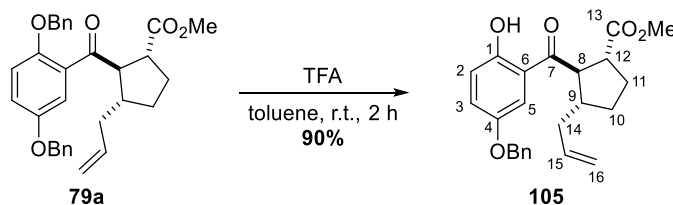


In a small vial, ketal **99** (1.4 mg, 2.9 μ mol) and Pd/C (10%, 1.0 mg) were mixed in dry THF (1.0 mL) under a nitrogen atmosphere. At r.t., a balloon filled with H₂ was attached, and the mixture was stirred for 30 min, showing a low conversion of the starting material as judged by TLC analysis. The mixture was ventilated, another portion of Pd/C (10%, 1.0 mg) was added, a balloon filled with H₂ was attached, and the mixture was stirred for another 30 min. The mixture was filtered through a plug of celite and evaporated at reduced pressure to give 0.8 mg of the crude material that was analyzed by ¹H NMR showing a 2.4:1 mixture of product **101** and applanatumol B (**5**) together with other unidentified phenols. For analytical purposes, **101** was purified by column chromatography (PE/EtOAc, 1:2), providing an analytical sample.

¹H NMR (600 MHz, Methanol-*d*₄) δ 6.83 (d, $J = 3.0$ Hz, 1H, CH-5), 6.55 (d, $J = 8.6$ Hz, 1H, CH-2), 6.50 (dd, $J = 8.6, 2.9$ Hz, 1H, CH-3), 4.92 (d, $J = 4.1$ Hz, 1H, CH-7), 4.28 (dd, $J = 11.3, 4.9$ Hz, 1H, CH₂-15^a), 3.67-3.61 (m, 1H, CH₂-16^a), 3.35-3.31 (m, 2H, CH₂-15^b, CH₂-16^b), 2.89 (td, $J = 8.0, 4.0$ Hz, 1H, CH-8), 2.55-2.51 (m, 1H, CH-12), 2.45-2.36 (m, 1H, CH-14), 2.06-1.96 (m, 2H, CH-9, CH₂-11^a), 1.86-1.76 (m, 2H, CH₂-10^a, CH₂-11^b), 1.38-1.27 (m, 1H, CH₂-10^b). Carboxylic acid resonance not visible. ¹³C NMR (151 MHz, Methanol-*d*₄) δ 180.4 (C-13), 150.5 (C-4), 148.1 (C-1), 128.9 (C-6), 116.4 (C-2), 115.5 (C-5), 114.9 (C-3), 78.1 (C-7), 73.0 (C-15), 63.7 (C-16), 46.5 (C-8), 45.5 (C-12), 40.9 (C-14), 39.9 (C-9), 31.3 (C-11), 30.5 (C-10). MS (ESI⁻) m/z (%) 307 ([M-H⁺], 100). HRMS (ESI⁻) m/z [M-H⁺] calcd for C₁₆H₁₉O₆: 307.1187; found: 307.1186. IR (neat): $\nu_{\max} = 3600-3000$ (v br), 2922, 2852, 1736, 1560, 1503, 1456, 1414, 1377, 1260, 1239, 1205, 1152, 1083, 1024, 805, 731, 699, 615 cm⁻¹.

6.3.8. Total synthesis of spiroapplanatumines

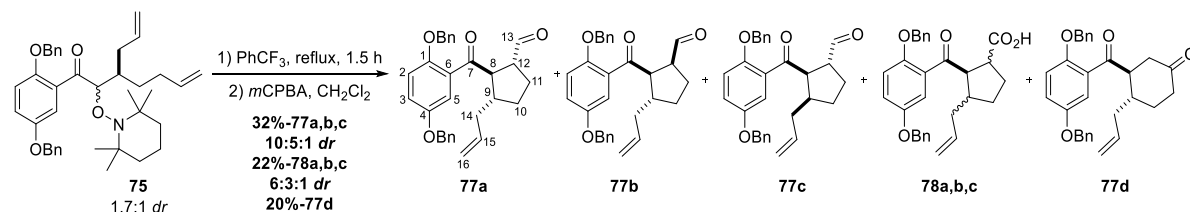
(±)-Methyl 1,2-*trans*/2,3-*trans*-3-allyl-2-(5'-(benzyloxy)-2'-hydroxybenzoyl)cyclopentane-1-carboxylate (**105**)



In a 25 mL round-bottomed flask, methyl ester **79a** (376 mg, 0.78 mmol) was dissolved in dry toluene (4.0 mL) under an inert atmosphere, and TFA (2.0 mL) was added. The mixture was stirred at r.t. for 2 h and evaporated under reduced pressure to give the crude product that was purified by column chromatography (neat cyclohexane, gradient to 10:1 cyclohexane/EtOAc) to yield 275 mg (90%) of **105** as a yellow oil.

R_F = 0.71 (PE/EtOAc, 3:1). ^1H NMR (400 MHz, Chloroform- d) δ 12.06 (s, 1H, OH), 7.51-7.30 (m, 6H, CH_{Ph} , CH-5), 7.19 (dd, J = 9.1, 3.0 Hz, 1H, CH-3), 6.93 (d, J = 9.1 Hz, 1H, CH-2), 5.66 (ddt, J = 17.1, 10.2, 7.1 Hz, 1H, CH-15), 5.08 (d, J = 12.2 Hz, 1H, CH_2Ph), 5.06 (d, J = 11.9 Hz, 1H, CH_2Ph), 5.01-4.89 (m, 2H, CH_2 -16), 3.80 (t, J = 7.9 Hz, 1H, CH-8), 3.62 (s, 3H, OMe), 3.26-3.19 (m, 1H, CH-12), 2.45 (sext, J = 7.6 Hz, 1H, CH-9), 2.20-1.93 (m, 5H, CH_2 -11, CH_2 -10^a, CH_2 -14), 1.60-1.47 (m, 1H, CH_2 -10^b). ^{13}C NMR (101 MHz, Chloroform- d) δ 207.8 (C-7), 175.5 (C-13), 157.7 (C-1), 151.0 (C-4), 136.9 (C_{Ph}), 136.4 (C-15), 128.8 (CH_{Ph}), 128.2 (CH_{Ph}), 127.7 (CH_{Ph}), 126.0 (C-3), 119.4 (C-2), 119.3 (C-6), 116.8 (C-16), 114.4 (C-5), 71.1 (CH_2Ph), 53.7 (C-8), 52.1 (OMe), 48.7 (C-12), 45.2 (C-9), 38.7 (C-14), 31.6 (C-10), 29.4 (C-11). **MS** (ESI+) m/z (%) 417 ($[\text{M}+\text{Na}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{24}\text{H}_{26}\text{O}_5\text{Na}$: 417.1673; found: 417.1674. **IR** (neat): ν_{max} = 3300-2700 (v br), 3069, 3033, 2951, 1731, 1639, 1612, 1485, 1454, 1436, 1421, 1381, 1325, 1280, 1240, 1213, 1179, 1025, 917, 833, 790, 738, 698 cm^{-1} .

PRE-based radical cyclization/oxidation of α -aminoxy ketone **75**



In a flame-dried Schlenk flask, α -aminoxy ketone **75** (500 mg, 0.84 mmol) was dissolved in PhCF_3 (6.0 mL). The solution was refluxed under an inert atmosphere for 1.5 h and evaporated at reduced pressure. The resulting mixture was dissolved in CH_2Cl_2 (10 mL), and $m\text{CPBA}$ (70-75%, 229 mg, 1.0 mmol) was added at 0 °C. The mixture was stirred for 1 h, diluted with cyclohexane (20 mL), washed with saturated NaHCO_3 solution (3 $\times$ 20 mL) and brine (1 $\times$ 20 mL), dried with MgSO_4 , filtered, and evaporated at reduced pressure. The crude products were separated by column chromatography

(hexane/EtOAc, 10:1, gradient to 3:1) to yield 122 mg (32%) of **77a,b,c** as an inseparable 10:5:1 diastereoisomeric mixture as a colorless oil, followed by 76 mg (20%) of the cyclohexanone **77d** as a crystalline solid, followed by 88 mg (22%) of the carboxylic acid **78a,b,c** as a 6:3:1 diastereoisomeric mixture as a colorless oil.

(±)-1,2-trans/2,3-trans-3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carbaldehyde (77a)

R_F = 0.70 (cyclohexane/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 9.42 (d, J = 1.5 Hz, 1H, CH-13), 7.44-7.29 (m, 10H, CH_{Ph}), 7.15 (d, J = 3.1 Hz, 1H, CH-5), 7.02 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.91 (d, J = 9.0 Hz, 1H, CH-2), 5.67-5.51 (m, 1H, CH-15), 5.07 (s, 2H CH₂Ph), 5.03 (s, 2H, CH₂Ph), 4.90-4.80 (m, 2H, CH₂-16), 3.97 (t, J = 6.5 Hz, 1H, CH-8), 3.22-3.11 (m, 1H, CH-12), 2.47-2.30 (m, 1H, CH-9), 2.12-1.76 (m, 5H, CH₂-14, CH₂-11, CH₂-10^a), 1.34-1.14 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 204.5 (C-7), 202.1 (C-13), 153.0 (C-1), 151.4 (C-4), 136.9 (C_{Ph}), 136.8 (C-15), 136.4 (C_{Ph}), 130.0 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.4 (CH_{Ph}), 128.2 (CH_{Ph}), 127.9 (CH_{Ph}), 127.73 (CH_{Ph}), 120.1 (C-3), 116.2 (C-16), 115.70 (C-5), 114.7 (C-2), 71.5 (CH₂Ph), 70.84 (CH₂Ph), 55.7 (C-8), 55.3 (C-12), 44.0 (C-9), 38.7 (C-14), 31.4 (C-10), 25.8 (C-11). **MS** (ESI+) m/z (%) 931 ([2M+Na⁺], 20), 493 ([M+K⁺], 25), 477 ([M+Na⁺], 100), 455 ([M+H⁺], 15). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₃₀H₃₀O₄Na: 477.2036; found: 477.2034.

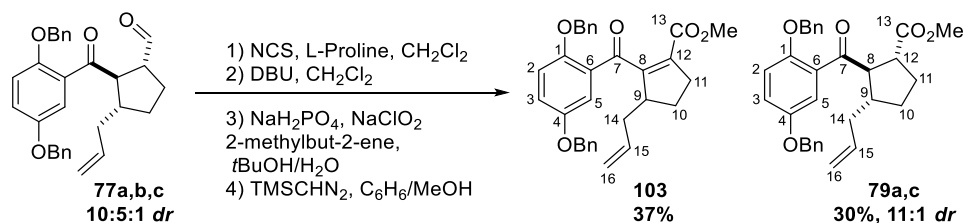
(±)-1,2-cis/2,3-trans-3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carbaldehyde (77b)

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 9.56 (d, J = 1.9 Hz, 1H, CH-13), 7.44-7.29 (m, 10H, CH_{Ph}), 7.15 (d, J = 3.1 Hz, 1H, CH-5), 7.07 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.95 (d, J = 9.0 Hz, 1H, CH-2), 5.67-5.51 (m, 1H, CH-15), 5.10 (s, 2H, CH₂Ph), 5.02 (s, 2H, CH₂Ph), 4.90-4.80 (m, 2H, CH₂-16), 3.89 (t, J = 8.2 Hz, 1H, CH-8), 2.84-2.77 (m, 1H, CH-12), 2.47-2.30 (m, 1H, CH-9), 2.10-1.91 (m, 4H, CH₂-14, CH₂-10^a, CH₂-11^a), 1.70 (dtd, J = 13.0, 8.4, 4.4 Hz, 1H, CH₂-11^b), 1.34-1.14 (m, 1H, CH₂-10^b). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 203.1 (C-7), 202.8 (C-13), 153.1 (C-1), 152.1 (C-4), 136.9 (C_{Ph}), 136.7 (C-15), 136.2 (C_{Ph}), 129.4 (C-6), 128.9 (CH_{Ph}), 128.6 (CH_{Ph}), 128.4 (CH_{Ph}), 128.1 (CH_{Ph}), 127.9 (CH_{Ph}), 127.70 (CH_{Ph}), 121.1 (C-3), 116.3 (C-16), 115.67 (C-5), 114.5 (C-2), 71.7 (CH₂Ph), 70.82 (CH₂Ph), 59.2 (C-8), 54.0 (C-12), 43.2 (C-9), 39.0 (C-14), 30.2 (C-10), 25.1 (C-11).

(±)-1,2-trans/2,3-cis-3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopentane-1-carbaldehyde (77c)

Detectable and identifiable resonances: $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 9.50 (d, J = 1.2 Hz, 1H, CH-13), 6.96 (d, J = 9.0 Hz, 1H, CH-2), 4.27 (t, J = 7.5 Hz, 1H, CH-8), 3.39 (q, J = 7.8 Hz, 1H, CH-12), 2.27-2.17 (m, 1H, CH-9).

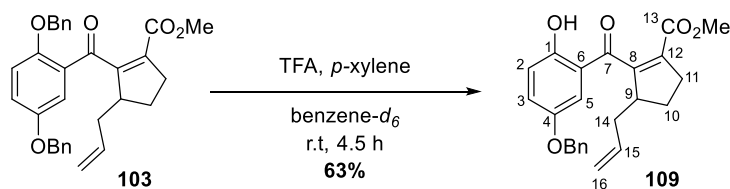
3-Allyl-2-(2',5'-bis(benzyloxy)benzoyl)cyclopent-1-ene-1-carbaldehyde (**103**)



In a 10 mL round-bottomed flask, aldehydes **77a,b,c** (10:5:1 *dr*, 60 mg, 0.13 mmol) were dissolved in CH₂Cl₂ (1.5 mL) under an inert atmosphere. At r.t. L-proline (15 mg, 0.13 mmol) was added, the reaction mixture was stirred for 1 h, and NCS (21 mg, 0.16 mmol) was added. The mixture was stirred at r.t. for 15 h, diluted with Et₂O, filtered through a plug of silica gel, which was washed with Et₂O. The solvent was evaporated at reduced pressure, the crude material was dissolved in CH₂Cl₂ (3.0 mL), cooled to 0 °C, and DBU (30 µL, 0.2 mmol) was added. The cooling bath was removed, the mixture was stirred for 3 h, diluted with Et₂O (20 mL), and washed with saturated NH₄Cl solution (2×10 mL), saturated NaHCO₃ solution (2×10 mL), and brine (2×10 mL). The organic layers were dried with MgSO₄, filtered, and evaporated at reduced pressure. The crude material was dissolved in *t*BuOH (8.0 mL), H₂O (3.0 mL), and 2-methylbut-2-ene (0.3 mL) was added. The mixture was cooled to 0 °C, NaH₂PO₄·H₂O (240 mg, 1.74 mmol) and NaClO₂ (190 mg, 2.1 mmol) were successively added. The cooling bath was removed, the reaction mixture was stirred for 30 min, diluted with Et₂O (20 mL), and washed with brine (2×10 mL). The organic layer was dried with MgSO₄, filtered, and evaporated at reduced pressure. The crude carboxylic acid was dissolved in benzene/MeOH mixture (3:1, 4.0 mL) and at r.t. TMSCHN₂ (2M in hexanes, 0.3 mL, 0.6 mmol) was dropwise added. The mixture was stirred for 20 min, a spoon of solid NH₄Cl was added, and stirring was continued for additional 15 min. The mixture was filtered and evaporated at reduced pressure to give the crude mixture that was separated by column chromatography (hexanes/EtOAc, 10:1) to yield 19 mg (30%) of saturated cyclopentanes **79a,c** as an 11:1 diastereoisomeric mixture, followed by 23 mg (37%) of **103** as colorless oils.

R_F = 0.53 (cyclohexane/EtOAc, 3:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 2.1 Hz, 1H, CH-5), 7.47-7.28 (m, 10H, CH_{Ph}), 7.13 (dd, *J* = 9.0, 2.1 Hz, 1H, CH-3), 6.97 (d, *J* = 9.1 Hz, 1H, CH-2), 5.69-5.55 (m, 1H, CH-15), 5.09 (s, 2H, CH₂Ph), 4.96 (s, 2H, CH₂Ph), 4.94-4.83 (m, 2H, CH₂-16), 3.44 (s, 3H, OMe), 3.17-3.07 (m, 1H, CH-9), 2.49-2.38 (m, 1H, CH₂-11^a), 2.30-2.11 (m, 2H, CH₂-11^b, CH₂-14^a), 2.00-1.88 (m, 1H, CH₂-14^b), 1.71-1.59 (m, 1H, CH₂-10^a), 1.33-1.28 (m, 1H, CH₂-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 194.8 (C-7), 165.2 (C-13), 158.1 (C-8), 153.4 (C-1), 152.9 (C-4), 137.0 (C_{Ph}), 136.5 (C-15), 136.1 (C_{Ph}), 131.2 (C-6), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.6 (2×CH_{Ph}), 128.2 (CH_{Ph}), 127.7 (CH_{Ph}), 127.1 (C-12), 122.5 (C-3), 116.3 (C-16), 115.3 (C-5), 114.4 (C-2), 71.6 (CH₂Ph), 70.8 (CH₂Ph), 51.4 (OMe), 48.7 (C-9), 37.2 (C-14), 31.6 (C-11), 28.4 (C-10). MS (ESI+) *m/z* (%) 987 ([2M+Na⁺], 10), 505 ([M+Na⁺], 100). HRMS (ESI+) *m/z* [M+Na⁺] calcd for C₃₁H₃₀O₅Na: 505.1986; found: 505.1981. IR (neat): $\nu_{\max}$ = 3066, 3033, 2924, 2855, 1714, 1639, 1492, 1455, 1434, 1417, 1381, 1331, 1280, 1210, 1155, 1126, 1023, 1005, 915, 812, 738, 697 cm⁻¹.

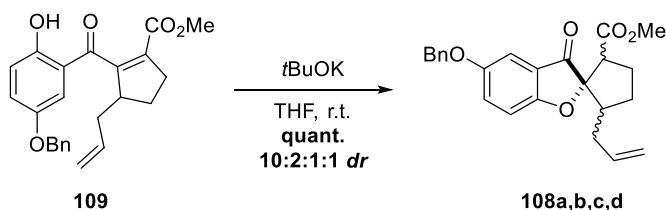
Methyl 3-allyl-2-(5'-(benzyloxy)-2'-hydroxybenzoyl)cyclopent-1-ene-1-carboxylate (**109**)



In an NMR tube, methyl ester **103** (5.0 mg, 10.3 μ mol) was dissolved in benzene- d_6 (0.6 mL). *p*-Xylene (10 μ L, 0.081 mmol) and TFA (0.2 mL) were added at r.t. The reaction mixture was thoroughly mixed, left to stand at r.t. and monitored by ^1H NMR spectroscopy every hour. After 4.5 h, the reaction mixture was transferred to a round-bottomed flask, evaporated at reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc, 10:1 cyclohexane/EtOAc) to yield 2.5 mg (63%) of **109** as a colorless oil.

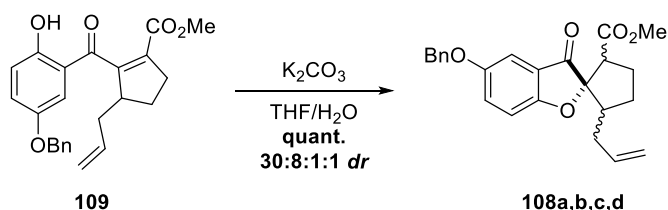
R_F = 0.58 (cyclohexane/EtOAc, 3:1). ^1H NMR (400 MHz, Chloroform- d) δ 11.45 (s, 1H, OH), 7.47-7.29 (m, 5H, CH_{Ph}), 7.19 (dd, J = 9.1, 3.1 Hz, 1H, CH-3), 6.95 (d, J = 9.1 Hz, 1H, CH-2), 6.87 (d, J = 3.1 Hz, 1H, CH-5), 5.62 (ddt, J = 13.9, 10.4, 6.9 Hz, 1H, CH-15), 5.09-4.89 (m, 4H, CH-16, CH_2Ph), 3.52 (s, 3H, OMe), 3.19-3.06 (m, 1H, CH-9), 2.87-2.74 (m, 1H, CH_2 -11^a), 2.73-2.62 (m, 1H, CH_2 -11^b), 2.28-2.13 (m, 2H, CH_2 -14^a, CH_2 -10^a), 2.01-1.89 (m, 1H, CH_2 -14^b), 1.72 (ddd, J = 16.0, 13.4, 7.7 Hz, 1H, CH_2 -10^b). ^{13}C NMR (101 MHz, Chloroform- d) δ 201.8 (C-7), 164.3 (C-13), 157.0 (C-1), 153.6 (C-8), 150.9 (C-4), 137.0 (C_{Ph}), 135.4 (C-15), 134.5 (C-6), 132.1 (C-12), 128.9 (CH_{Ph}), 128.2 (CH_{Ph}), 127.3 (CH_{Ph}), 125.8 (C-3), 119.4 (C-2), 117.2 (C-16), 116.0 (C-5), 71.2 (CH_2Ph), 51.9 (OMe), 50.0 (C-9), 37.5 (C-14), 31.8 (C-11), 29.0 (C-10). MS (ESI⁺) m/z (%) 415 ($[\text{M}+\text{Na}^+]$, 100). HRMS (ESI⁺) m/z $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{24}\text{H}_{24}\text{O}_5\text{N}$: 415.1516; found: 415.1514. IR (neat): ν_{max} = 3340, 3068, 3032, 2951, 2859, 1719, 1635, 1609, 1587, 1482, 1454, 1436, 1375, 1342, 1322, 1284, 1267, 1223, 1196, 1148, 1122, 1026, 918, 832, 793, 738, 698 cm^{-1} .

*t*BuOK-mediated intramolecular oxa-Michael additions of phenol **109**



In a flame-dried Schlenk flask, phenol **109** (3.6 mg, 9.2 μ mol) was dissolved in dry THF (0.5 mL). After cooling to 0 $^{\circ}\text{C}$, *t*BuOK (1M in THF, 15 μ L, 15 μ mol) was dropwise added. The mixture was warmed to r.t., stirred for 4 days, quenched by saturated NH_4Cl solution (5 mL), and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over MgSO_4 , filtered, and evaporated at reduced pressure to give 3.6 mg (quant.) of essentially pure spirocycles **180a,b,c,d** as a 10:2:2:1 diastereoisomeric mixture. For the characterization of spirocycle **108a** *vide infra*.

K₂CO₃-mediated intramolecular oxa-Michael additions of phenol **109**

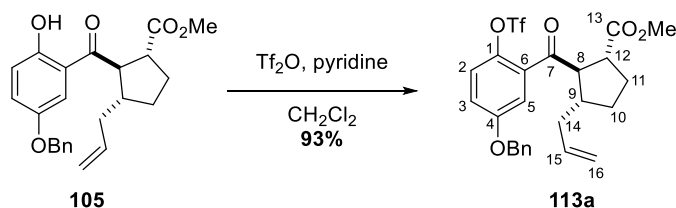


In a 10 mL round-bottomed flask, phenol **109** (3.3 mg, 8.4 μ mol) was dissolved in a THF/H₂O mixture (1:1, 1 mL). After cooling to 0 °C, K₂CO₃ (2.3 mg, 17 μ mol) was added, the mixture was warmed to r.t., stirred for 1.5 h, diluted with brine (5 mL), and extracted with petrol ether (3 $\times$ 10 mL). The combined organic layers were washed with brine (2 $\times$ 5 mL), dried over MgSO₄, filtered, and evaporated at reduced pressure to give 3.3 mg (quant.) of essentially pure spirocycles **180a,b,c,d** as a 30:8:1:1 diastereoisomeric mixture. For the characterization of spirocycle **108a** *vide infra*.

($\pm$)-Methyl

1,2-*trans*/2,3-*trans*-3-allyl-2-(5'-(benzyloxy)-2'-

(((trifluoromethyl)sulfonyl)oxy)benzoyl)cyclopentane-1-carboxylate (**113a**)

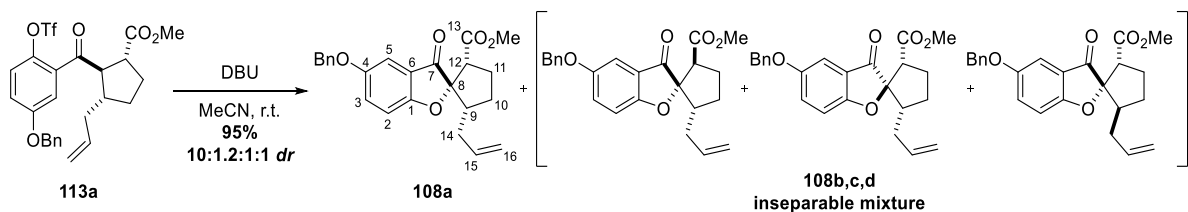


In a flame-dried Schlenk flask, phenol **105** (260 mg, 0.66 mmol) was dissolved in dry CH₂Cl₂ (6.6 mL) under an inert atmosphere, and pyridine (106 μ L, 1.32 mmol) was added. The mixture was cooled to –78 °C, and Tf₂O (1M in CH₂Cl₂, 0.73 mL, 0.73 mmol) was added. The cooling bath was removed, the mixture was gradually warmed to r.t. and stirred for 23 h. The reaction was quenched by the addition of saturated NaHCO₃ solution (200 μ L), diluted with Et₂O, and filtered through a plug of silica gel, which was washed by Et₂O. Evaporation of the solvent at reduced pressure gave the crude product that was purified by column chromatography (neat cyclohexane, gradient to 10:1 cyclohexane/EtOAc) to yield 324 mg (93%) of **113a** as a colorless oil.

R_F = 0.62 (PE/EtOAc, 3:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, J = 3.1 Hz, 1H, CH-5), 7.46–7.33 (m, 5H, CH_{Ph}), 7.22 (d, J = 9.0 Hz, 1H, CH-2), 7.11 (dd, J = 9.0, 3.1 Hz, 1H, CH-3), 5.64 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H, CH-15), 5.13 (bs, 2H, CH₂Ph), 4.97–4.86 (m, 2H, CH₂-16), 3.69 (t, J = 7.5 Hz, 1H, CH-8), 3.63 (s, 3H, OMe), 3.32 (dt, J = 9.0, 7.0 Hz, 1H, CH-12), 2.45–2.34 (m, 1H, CH-9), 2.19–1.87 (m, 5H, CH₂-11, CH₂-14, CH₂-10^a), 1.52–1.44 (m, 1H, CH₂-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 200.6 (C-7), 175.6 (C-13), 158.0 (C-4), 140.4 (C-1), 136.5 (C-15), 135.9 (C_{Ph}), 133.2 (C-6), 128.9 (CH_{Ph}), 128.6 (CH_{Ph}), 127.7 (CH_{Ph}), 124.0 (C-2), 119.3 (C-3), 118.8 (q, J_{C-F} = 320.6 Hz, CF₃), 116.77 (CH-5), 116.76 (C-16), 70.9 (CH₂Ph), 56.8 (C-8), 52.1 (OMe), 47.6 (C-12), 44.3 (C-9), 38.9 (C-14), 31.5 (C-10), 29.3 (C-11). ¹⁹F NMR (376 MHz, Chloroform-*d*) δ –73.5. MS (ESI+) m/z

(%) 1075 ([2M+Na⁺], 15), 549 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₅H₂₅O₇F₃NaS: 549.1165; found: 549.1162. **IR** (neat): $\nu_{\max}$ = 3034, 2952, 1735, 1694, 1581, 1486, 1455, 1423, 1282, 1248, 1205, 1140, 1023, 913, 875, 830, 739, 698, 609 cm⁻¹.

Base-mediated oxidative spirocyclization of triflate **113a**

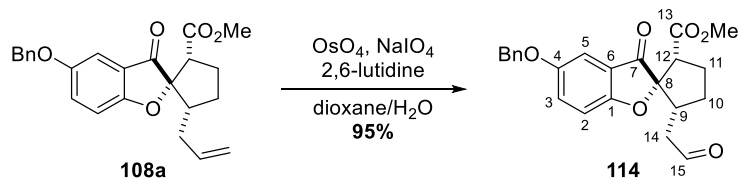


In a flame-dried Schlenk flask, triflate **113a** (320 mg, 0.61 mmol) was dissolved in dry MeCN (3.0 mL) under an inert atmosphere. The mixture was cooled to 0 °C, and DBU (364 μ L, 2.43 mmol) was added. The mixture was gradually warmed to r.t., stirred for 18 h, diluted with Et₂O, and filtered through a plug of silica gel, which was washed by Et₂O. The solvent was evaporated at reduced pressure, and the crude products were purified by column chromatography (hexane/EtOAc, 10:1) to yield 9 mg (3%) of recovered starting material, 56 mg (24%) of a 1.2:1:1 diastereoisomeric mixture of **108b,c,d**, and 170 mg (71%) of pure diastereoisomer **108a**, corresponding to 226 mg (95%) as a 10:1.2:1:1 diastereoisomeric mixture as pale yellow oils. Diastereoisomers **108b,c,d** were not obtained in a pure form and, therefore, not characterized.

(2*S**,2'*R**,5'*R**)-Methyl 2'-allyl-5-(benzyloxy)-3-oxo-3H-spiro[benzofuran-2,1'-cyclopentane]-5'-carboxylate (**108a**)

R_F = 0.52 (PE/EtOAc, 3:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.46-7.32 (m, 5H, CH_{Ph}), 7.30 (dd, J = 9.0, 2.8 Hz, 1H, CH-3), 7.16 (d, J = 2.8 Hz, 1H, CH-5), 7.02 (d, J = 9.0 Hz, 1H, CH-2), 5.53 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H, CH-15), 5.05 (s, 2H, CH₂Ph), 4.82-4.68 (m, 2H, CH₂-16), 3.47 (t, J = 9.1 Hz, 1H, CH-12), 3.30 (s, 3H, OMe), 2.51-2.38 (m, 2H, CH-9, CH₂-11^a), 2.15-2.02 (m, 2H, CH₂-11^b, CH₂-10^a), 2.02-1.86 (m, 2H, CH₂-14), 1.84-1.69 (m, 1H, CH₂-10^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 202.1 (C-7), 170.4 (C-13), 167.1 (C-1), 154.0 (C-4), 136.5 (C_{Ph}), 135.9 (C-15), 128.8 (CH_{Ph}), 128.30 (CH_{Ph}), 128.29 (C-3), 127.7 (CH_{Ph}), 122.7 (C-6), 116.6 (C-16), 113.7 (C-2), 105.8 (C-5), 98.2 (C-8), 71.0 (CH₂Ph), 53.1 (C-12), 51.5 (OMe), 49.6 (C-9), 32.6 (C-14), 30.0 (C-10), 24.5 (C-11). **MS** (ESI+) m/z (%) 807 ([2M+Na⁺], 15), 415 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₄H₂₄O₅Na: 415.1516; found: 415.1516. **IR** (neat): $\nu_{\max}$ = 3072, 3033, 2952, 1741, 1709, 1683, 1641, 1620, 1484, 1453, 1435, 1337, 1276, 1207, 1004, 915, 825, 791, 739, 697 cm⁻¹.

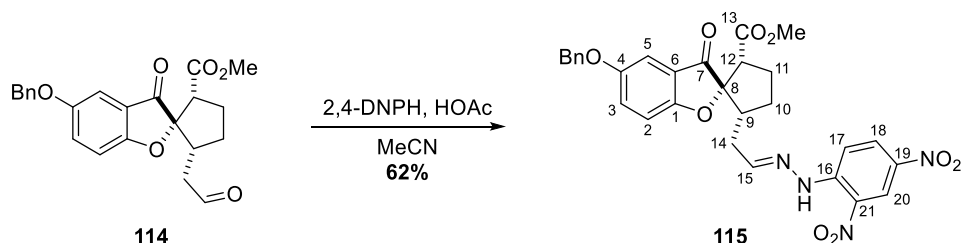
(2*S**,2'*R**,5'*R**)-Methyl 5-(benzyloxy)-3-oxo-5'-(2-oxoethyl)-3*H*-spiro[benzofuran-2,1'-cyclopentane]-2'-carboxylate (**114**)



In a 25 mL round-bottomed flask, alkene **108a** (61 mg, 0.16 mmol) was dissolved in dioxane (3.0 mL) and H₂O (1.0 mL). 2,6-Lutidine (36 μ L, 0.31 mmol), OsO₄ (2.5% in *t*BuOH, 32 μ L, 0.02 mmol) and NaIO₄ (133 mg, 0.62 mmol) were successively added. The mixture was stirred at r.t. for 2 h, diluted with H₂O (20 mL), and extracted with Et₂O (3 $\times$ 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated to give the crude product that was purified by column chromatography (neat cyclohexane, gradient to 1:1 cyclohexane/Et₂O) to yield 58 mg (95%) of **114** as a pale yellow oil.

R_F = 0.57 (PE/EtOAc, 3:1). ¹H NMR (401 MHz, Chloroform-*d*) δ 9.57 (t, J = 1.4 Hz, 1H, CH-15), 7.46-7.34 (m, 5H, CH_{Ph}), 7.32 (dd, J = 9.0, 2.8 Hz, 1H, CH-3), 7.18 (d, J = 2.8 Hz, 1H, CH-5), 7.02 (dd, J = 8.9, 0.5 Hz, 1H, CH-2), 5.05 (s, 2H, CH₂Ph), 3.49 (dd, J = 10.1, 8.3 Hz, 1H, CH-12), 3.32 (s, 3H, OMe), 2.86 (dtd, J = 10.9, 8.3, 4.9 Hz, 1H, CH-9), 2.53-2.44 (m, 1H, CH₂-11^a), 2.41 (ddd, J = 17.8, 8.6, 1.7 Hz, 1H, CH₂-14^a), 2.34-2.23 (m, 2H, CH₂-14^b, CH₂-10^a), 2.15 (dddd, J = 13.5, 10.2, 8.4, 7.2 Hz, 1H, CH₂-11^b), 1.77 (dtd, J = 12.6, 10.7, 7.3 Hz, 1H, CH₂-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 201.1 (C-7), 199.7 (C-15), 170.1 (C-13), 166.8 (C-1), 154.3 (C-4), 136.4 (C_{Ph}), 128.8 (CH_{Ph}), 128.7 (CH_{Ph}), 128.4 (C-3), 127.8 (CH_{Ph}), 122.3 (C-6), 113.8 (C-2), 105.7 (C-5), 97.9 (C-8), 70.9 (CH₂Ph), 52.7 (C-12), 51.7 (OMe), 43.4 (C-9), 42.7 (C-14), 30.2 (C-10), 25.1 (C-11). MS (ESI+) m/z (%) 449 ([M+MeOH+Na⁺], 60), 417 ([M+Na⁺], 100), 395 ([M+H⁺], 15). HRMS (ESI+) m/z [M+H⁺] calcd for C₂₃H₂₃O₆: 395.1489; found: 395.1489. IR (neat): ν_{max} = 2952, 2728, 1742, 1713, 1484, 1453, 1385, 1336, 1277, 1225, 1208, 1147, 1009, 848, 825, 788, 744, 699 cm⁻¹.

(2*S**,2'*R**,5'*R**)-Methyl 5-(benzyloxy)-5'-((*E*)-2-(2-(2,4-dinitrophenyl)hydrazinylidene)ethyl)-3-oxo-3*H*-spiro[benzofuran-2,1'-cyclopentane]-2'-carboxylate (**115**)

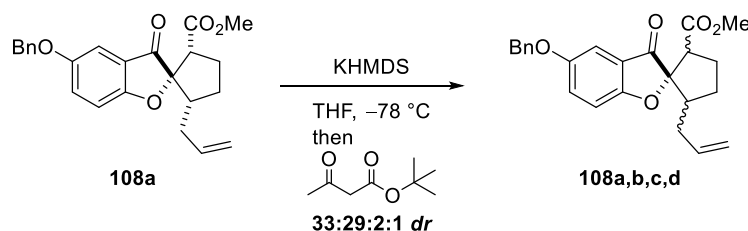


In a vial, aldehyde **114** (10.0 mg, 25 μ mol) was dissolved in MeCN (0.5 mL). 2,4-Dinitrophenylhydrazine (5.7 mg, 29 μ mol) and acetic acid (40 μ L, 0.63 mmol) were added successively. The mixture was stirred overnight, adsorbed on celite, and purified by column

chromatography (hexane/EtOAc, 3:1, then neat MeCN) to yield 9.0 mg (62%) of **115** as an orange solid that was crystallized by slow evaporation of a CH₂Cl₂/hexane solution for X-ray diffraction analysis.

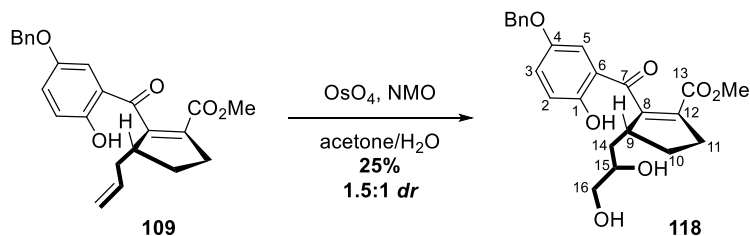
R_F = 0.21 (PE/EtOAc, 3:1). **¹H NMR** (401 MHz, Chloroform-*d*) δ 10.76 (s, 1H, NH), 9.02 (d, J = 2.6 Hz, 1H, CH-20), 8.21 (ddd, J = 9.6, 2.6, 0.7 Hz, 1H, CH-18), 7.47 (d, J = 9.6 Hz, 1H, CH-17), 7.40-7.22 (m, 6H, CH_{Ph}, CH-3), 7.20 (t, J = 5.3 Hz, 1H, CH-15), 7.04 (d, J = 8.9 Hz, 1H, CH-2), 7.00 (d, J = 2.8 Hz, 1H, CH-5), 4.87 (d, J = 11.4 Hz, 1H, CH₂Ph), 4.70 (d, J = 11.4 Hz, 1H, CH₂Ph), 3.51 (dd, J = 9.9, 8.2 Hz, 1H, CH-12), 3.32 (s, 3H, OMe), 2.81 (dq, J = 11.2, 7.4 Hz, 1H, CH-9), 2.56-2.46 (m, 1H, CH₂-11^a), 2.45-2.37 (m, 2H, CH₂-14), 2.28-2.12 (m, 1H, CH₂-11^b, CH₂-10^a), 1.97-1.84 (m, 1H, CH₂-10^b). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 201.6 (C-7), 170.0 (C-13), 167.0 (C-1), 154.3 (C-4), 149.0 (C-15), 144.7 (C-16), 138.1 (C-19), 136.0 (C_{Ph}), 129.9 (C-18), 129.0 (C-21), 128.8 (CH_{Ph}), 128.43 (CH_{Ph}), 128.42 (C-3), 127.5 (CH_{Ph}), 123.4 (C-20), 122.6 (C-6), 116.6 (C-17), 113.9 (C-2), 105.2 (C-5), 97.5 (C-8), 70.8 (CH₂Ph), 53.2 (C-12), 51.7 (OMe), 47.3 (C-9), 31.8 (C-14), 30.4 (C-10), 24.8 (C-11). **MS** (ESI+) m/z (%) 1171 ([2M+Na⁺], 15), 613 ([M+K⁺], 10), 597 ([M+Na⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₉H₂₆O₉N₄Na: 597.1592; found: 597.1591.

Epimerization of spirocycle **108a** by E1cB elimination/oxa-Michael addition



In a flame-dried Schlenk flask, spirocycle **108a** (2.5 mg, 6.4 μ mol) was dissolved in dry THF. At -78°C , KHMDS (1M in THF, 8 μ L, 8 μ mol) was added. After stirring for 15 min, the E1cB elimination was finished as indicated by TLC analysis, and *tert*-butyl acetoacetate (1.5 mg, 9.6 μ mol) in THF (0.5 mL) was added. The mixture was warmed to r.t., stirred for 40 h, diluted with Et₂O, and filtered through a plug of silica gel. Evaporation of the solvents gave 2.5 mg of a crude mixture that was analyzed by ¹H NMR spectroscopy showing spirocycles **108a,b,c,d** in a 33:29:2:1 diastereoisomeric ratio as determined by the integration of the corresponding methyl ester resonances at 3.67, 3.57, 3.41, and 3.30 ppm. Another 15% of the eliminated product **109** were also detected. For the characterization of spirocycle **108a** *vide supra*. Diastereoisomers **108b,c,d** were not obtained in a pure form and, therefore, not characterized.

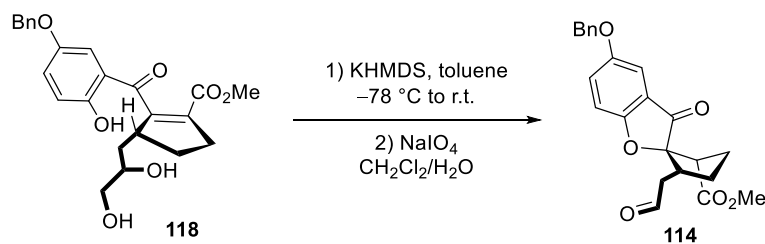
(2''*R**,3*R**)- and (2''*S**,3*R**)-Methyl 2-(5'-(benzyloxy)-2'-hydroxybenzoyl)-3-(2'',3''-dihydroxypropyl)cyclopent-1-ene-1-carboxylate (**118**)



In a 25 mL round-bottomed flask, methyl ester **109** (18 mg, 0.11 mmol) was dissolved in an acetone/H₂O mixture (10:1, 1 mL). At r.t., OsO₄ (2.5% in *t*BuOH, 50 μ L, 4 μ mol) and NMO (26 mg, 0.22 mmol) were added. The mixture was stirred for 1.5 h, diluted with Et₂O, and filtered through a plug of silica gel, which was washed by EtOAc. Evaporation of the solvents gave the crude product that was purified by column chromatography (cyclohexane/EtOAc, 1:1) to yield 5 mg (25%) of **118** as a 1.6:1 diastereoisomeric mixture as a colorless oil.

R_F = 0.11 (PE/EtOAc, 1:1). Resonances of the major diastereoisomer are labeled with an asterisk. Only individual distinguishable, resonances are listed. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.43 (s, 1H, OH*), 11.36 (s, 1H, OH*), 7.40-7.30 (m, 10H, CH_{Ph}*, CH_{Ph}), 7.21 (dd, J = 9.1, 3.1 Hz, 1H, CH-3), 7.19 (dd, J = 9.1, 3.1 Hz, 1H, CH-3*), 6.95 (d, J = 9.1 Hz, 1H, CH-2), 6.94 (d, J = 2.9 Hz, 1H, CH-2*), 6.85 (d, J = 3.1 Hz, 2H, CH-5*, CH-5), 5.05-4.95 (m, 4H, CH₂Ph*, CH₂Ph), 3.73-3.47 (m, 6H, CH-15*, CH-15, CH₂-16*, CH₂-16), 3.523 (s, 3H, OMe*), 3.517 (s, 3H, OMe). **MS** (ESI+) m/z (%) 875 ([2M+Na⁺], 30), 449 ([M+Na⁺], 100), 427 ([M+H⁺], 25). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₄H₂₆O₇Na: 449.1571; found: 449.1568.

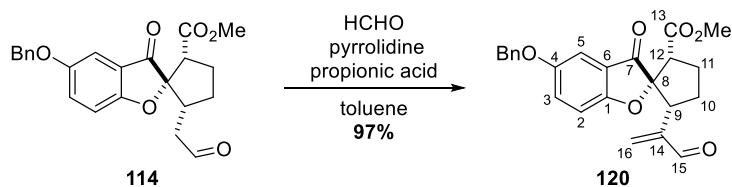
Intramolecular oxa-Michael addition and oxidative cleavage of diol **118**



In a flame-dried Schlenk flask, diol **118** (5.0 mg, 11 μ mol) was dissolved in dry toluene (0.1 mL). At -78 $^{\circ}$ C, KHMDS (1M in THF, 11 μ L, 11 μ mol) was added, the mixture was warmed to r.t. and stirred overnight. After the cyclization was finished as judged by TLC analysis, the mixture was diluted with Et₂O (10 mL) and filtered through a plug of silica gel, which was washed by EtOAc. The solvents were evaporated at reduced pressure, and the residue was dissolved in a CH₂Cl₂/H₂O mixture (1:1, 2 mL). At r.t., NaIO₄ (265 mg, 1.24 mmol) was added, the mixture was vigorously stirred for 1.5 h, diluted with Et₂O, and filtered through a plug of silica gel, which was washed by EtOAc. Evaporation of the

solvents gave the crude aldehyde that was analyzed by ^1H NMR spectroscopy showing a precise match with aldehyde **114**. For compound characterization *vide supra*.

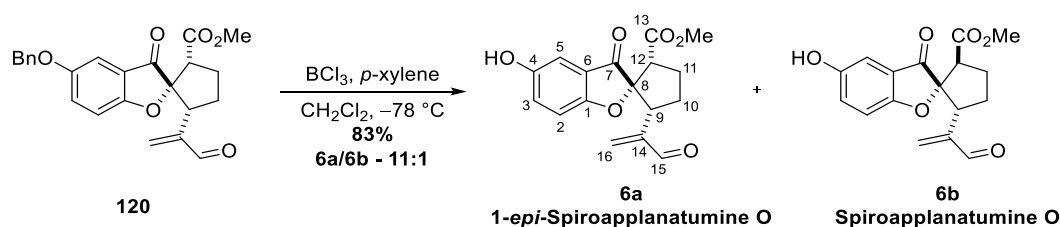
(2*S,2'*R**,5'*R**)-Methyl 5-(benzyloxy)-3-oxo-5'-(3-oxoprop-1-en-2-yl)-3H-spiro[benzofuran-2,1'-cyclopentane]-2'-carboxylate (**120**)**



In a 10 mL round-bottomed flask, aldehyde **114** (28 mg, 0.072 mmol) was dissolved in toluene (1.4 mL). Formaldehyde (37% in H_2O , 30 μL , 0.36 mmol), pyrrolidine (5 μL), and propionic acid (5 μL) were successively added. The mixture was stirred at r.t. overnight and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ Et_2O , 1:1) to yield 28 mg (97%) of **120** as a pale yellow oil.

R_F = 0.50 (PE/ EtOAc , 3:1). ^1H NMR (400 MHz, CHCl_3 - d) δ 9.27 (s, 1H, CH-15), 7.46-7.33 (m, 5H, CH_{Ph}), 7.26 (dd, J = 9.0, 2.9 Hz, 1H, CH-3), 7.17 (d, J = 2.8 Hz, 1H, CH-5), 6.93 (dd, J = 8.9, 0.5 Hz, 1H, CH-2), 6.50 (d, J = 0.9 Hz, 1H, CH_2 -16), 6.03 (s, 1H, CH_2 -16), 5.02 (s, 2H, CH_2 Ph), 3.70-3.58 (m, 2H, CH-12, CH-9), 3.34 (s, 3H, OMe), 2.63-2.51 (m, 1H, CH_2 -11^a), 2.32-2.10 (m, 3H, CH_2 -11^b, CH_2 -10). ^{13}C NMR (101 MHz, CHCl_3 - d) δ 200.0 (C-7), 193.0 (C-15), 170.3 (C-13), 166.3 (C-1), 154.2 (C-4), 145.3 (C-14), 137.5 (C-16), 136.4 (C_{Ph}), 128.8 (CH_{Ph}), 128.36 (CH_{Ph}), 128.34 (CH-3), 127.8 (CH_{Ph}), 122.3 (C-6), 113.5 (C-2), 105.9 (C-5), 96.5 (C-8), 70.9 (CH_2 Ph), 53.0 (C-12), 51.7 (OMe), 45.0 (C-9), 30.3 (C-10), 24.8 (C-11). MS (ESI+) m/z (%) 835 ($[\text{2M}+\text{Na}^+]$, 20), 429 ($[\text{M}+\text{Na}^+]$, 90), 407 ($[\text{M}+\text{H}^+]$, 100). HRMS (ESI+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{24}\text{H}_{22}\text{O}_6\text{Na}$: 429.1309; found: 429.1305. IR (neat): ν_{max} = 3034, 2951, 1741, 1717, 1692, 1484, 1384, 1336, 1277, 1222, 1151, 1026, 1007, 956, 849, 825, 787, 745, 699 cm^{-1} .

Debenzylation of 1-*epi*-spiroapplanatumine O



In a flame-dried Schlenk flask, enal **120** (6.0 mg, 14.8 μmol) was dissolved in dry CH_2Cl_2 (0.75 mL). *p*-Xylene (18 μL , 148 μmol) was added, the mixture was cooled to -78°C , and BCl_3 (1M in CH_2Cl_2 , 44 μL , 44 μmol) was dropwise added. The mixture was stirred at -78°C for 45 min and quenched by slow addition of a $\text{CHCl}_3/\text{MeOH}$ mixture (2:1, 0.5 mL). The cooling bath was removed, the solvent was evaporated by a stream of N_2 while still cold and subsequently dried in high-vacuum. The crude

product was purified by column chromatography (pentane/EtOAc, 3:1) to yield 3.9 mg (83%) of an inseparable 11:1 diastereoisomeric mixture of **6a** and spiroapplanatumine O (**6b**), as a pale yellow oil.

(2*S,2*R**,5*R**)-Methyl 5-hydroxy-3-oxo-5'-(3-oxoprop-1-en-2-yl)-3H-spiro[benzofuran-2,1'-cyclopentane]-2'-carboxylate – 1-*epi*-Spiroapplanatumine O (**6a**)**

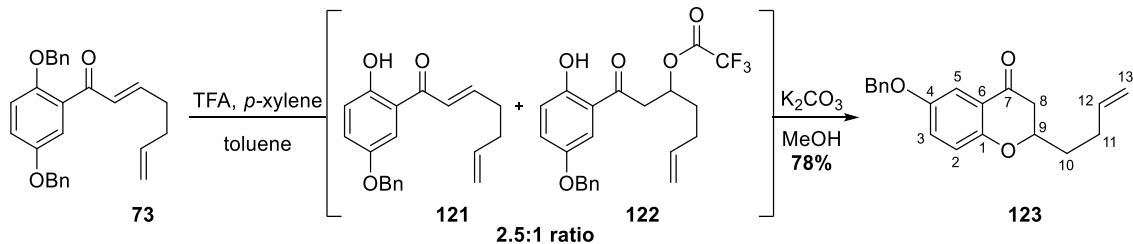
R_F = 0.43 (PE/EtOAc, 1:1). ^1H NMR (600 MHz, Methanol- d_4) δ 9.21 (s, 1H, CH-15), 7.11 (dd, J = 8.9, 2.7 Hz, 1H, CH-3), 6.89 (dd, J = 8.9, 0.6 Hz, 1H, CH-2), 6.87 (dd, J = 2.8, 0.5 Hz, 1H, CH-5), 6.56 (d, J = 0.8 Hz, 1H, CH₂-16), 6.13 (s, 1H, CH₂-16), 3.59 (dd, J = 9.9, 7.3 Hz, 1H, CH-12), 3.57-3.53 (m, 1H, CH-9), 3.32 (s, 3H, OMe), 2.53-2.47 (m, 1H, CH₂-11^a), 2.27-2.18 (m, 1H, CH₂-10^a), 2.17-2.08 (m, 2H, CH₂-11^b, CH₂-10^b). ^{13}C NMR (151 MHz, Methanol- d_4) δ 202.3 (C-7), 194.9 (C-15), 171.6 (C-13), 166.6 (C-1), 154.1 (C-4), 147.0 (C-14), 138.9 (C-16), 128.4 (C-3), 123.6 (C-6), 114.4 (C-2), 108.0 (C-5), 97.5 (C-8), 54.1 (C-12), 51.9 (OMe), 46.1 (C-9), 31.1 (C-10), 25.6 (C-11). **MS** (ESI+) m/z (%) 655 ([2M+Na⁺], 20), 339 ([M+Na⁺], 100), 317 ([M+H⁺], 20). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₁₇H₁₆O₆Na: 339.0839; found: 339.0839; [M+H⁺] calcd for C₁₇H₁₇O₆: 317.1020; found: 317.1020. **IR** (neat): ν_{max} = 3368, 2954, 1742, 1714, 1627, 1607, 1487, 1436, 1348, 1305, 1215, 1139, 1073, 1030, 990, 961, 863, 961, 863, 826, 781 cm⁻¹.

(2*S*,2'*S*,5'*R*)-Methyl 5-hydroxy-3-oxo-5'-(3-oxoprop-1-en-2-yl)-3H-spiro[benzofuran-2,1'-cyclopentane]-2'-carboxylate - Spiroapplanatumine O (6b**)**

R_F = 0.43 (PE/EtOAc, 1:1). *Detectable characteristic NMR resonances in the diastereoisomeric mixture:* ^1H NMR (600 MHz, Methanol- d_4) δ 9.25 (s, 1H, CH-15), 7.11 (dd, J = 8.9, 2.7 Hz, 1H, CH-3), 6.52 (d, J = 1.1 Hz, 1H, CH-16), 6.21 (s, 1H, CH-16), 3.48 (s, 3H, OMe), 3.46-3.40 (m, 1H, CH-12), 3.42-3.38 (m, 1H, CH-9). ^{13}C NMR (151 MHz, Methanol- d_4) δ 203.9 (C-7), 195.0 (C-15), 172.8 (C-13), 166.6 (C-1), 154.0 (C-4), 147.6 (C-14), 138.2 (C-16), 128.2 (C-3), 123.0 (C-6), 114.4 (C-2), 108.0 (C-5), 55.7 (C-12), 52.2 (OMe), 47.2 (C-9), 30.2 (C-10), 27.7 (C-11).

6.3.9. Total synthesis of applanatumols X and Y

6-(Benzyloxy)-2-(but-3-en-1-yl)chroman-4-one (**123**)



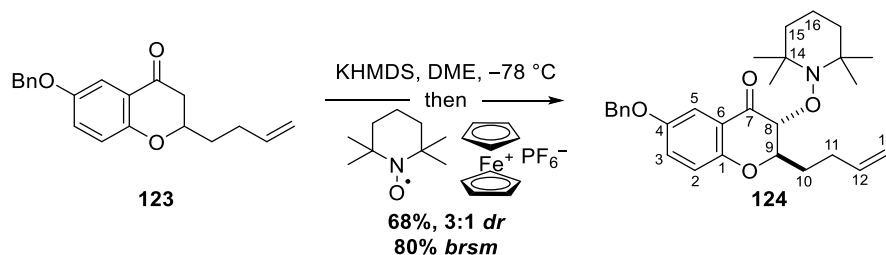
In a 25 mL round-bottomed flask, α,β -unsaturated ketone **73** (440 mg, 1.10 mmol) was dissolved in toluene (1.2 mL) and *p*-xylene (1.3 mL) under an inert atmosphere. The mixture was cooled to 0 °C, and TFA (0.84 mL) was added. The mixture was warmed to r.t., stirred for 2 h, and evaporated under

reduced pressure to give a mixture of mono-deprotected products **121** and **122** that was directly used in the next step.

The crude mixture was dissolved in MeOH (11 mL), and K₂CO₃ (1.53 g, 11.0 mmol) was added. The solution was stirred at r.t. for 30 min, diluted with Et₂O (80 mL), and filtered through a thick plug of silica gel, which was washed by Et₂O. The solvents were evaporated at reduced pressure, and the crude product was purified by column chromatography (neat cyclohexane, gradient to 10:1 cyclohexane/EtOAc) to yield 265 mg (78%) of **123** as an off-white solid that can be crystallized from hexanes.

*R*_F = 0.35 (PE/EtOAc, 10:1). **m.p.** 56-58 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45-7.30 (m, 6H, CH_{Ph}, CH-5), 7.16 (dd, *J* = 9.0, 3.2 Hz, 1H, CH-3), 6.93 (d, *J* = 9.0 Hz, 1H, CH-2), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH-12), 5.09 (dq, *J* = 17.1, 1.6 Hz, 1H, CH₂-13), 5.05-4.99 (m, 3H, CH₂Ph, CH₂-13), 4.48-4.36 (m, 1H, CH-9), 2.70-2.65 (m, 2H, CH₂-8), 2.35-2.20 (m, 2H, CH₂-11), 1.99 (dddd, *J* = 13.9, 8.7, 7.8, 6.1 Hz, 1H, CH-10^a), 1.78 (dddd, *J* = 13.9, 9.0, 6.7, 4.8 Hz, 1H, CH-10^b). ¹³C NMR (101 MHz, Chloroform-*d*) δ 192.6 (C-7), 156.6 (C-1), 153.3 (C-4), 137.4 (C-12), 136.8 (C_{Ph}), 128.7 (CH_{Ph}), 128.2 (CH_{Ph}), 127.7 (CH_{Ph}), 126.0 (C-3), 121.0 (C-6), 119.4 (C-2), 115.7 (C-13), 108.9 (C-5), 77.4 (C-9), 70.7 (CH₂Ph), 43.0 (C-8), 34.2 (C-10), 29.2 (C-11). **MS** (EI) *m/z* (%) 308 ([M]⁺, 50), 218 ([M-C₆H₅CH₂+H]⁺, 45), 163 ([M-Bn-homoallyl+H]⁺, 45), 91 ([C₇H₇]⁺, 100). **HRMS** (EI) *m/z* [M]⁺ calcd for C₂₀H₂₀O₃: 308.1412; found: 308.1409. **IR** (neat): ν_{max} = 3068, 2925, 2862, 1682, 1614, 1485, 1432, 1279, 1223, 1192, 1025, 908, 833, 744, 695 cm⁻¹.

(±)-*trans*- and *cis*-6-(Benzyloxy)-2-(but-3-en-1-yl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)chroman-4-one (**124**)



In a flame-dried Schlenk flask, chromanone **123** (754 mg, 2.45 mmol) was dissolved in dry DME (25 mL) under an argon atmosphere. The mixture was cooled to -78 °C, and KHMDS (1M in THF, 3.1 mL, 3.1 mmol) was dropwise added. The mixture was stirred for 30 min, and TEMPO (420 mg, 2.70 mmol) was added at once. The mixture was stirred until TEMPO was dissolved, and Cp₂Fe⁺PF₆⁻ (1.30 g, 3.91 mmol) was added in small portions (~100 mg/30 s) until the mixture remained dark blue. The mixture was stirred for an additional 20 min, diluted with Et₂O (20 mL), and filtered through a thick plug of silica gel, which was washed by Et₂O. The solution was evaporated, and the crude product was purified by column chromatography (neat hexane, gradient to 10:1 hexane/Et₂O) to yield 772 mg (68%) of α-aminoxy chromanone **124** as an inseparable 3:1 mixture of *trans*/*cis* diastereoisomers, and 113 mg (15%) of the starting material **123**. The yield based on recovered starting material is 80%.

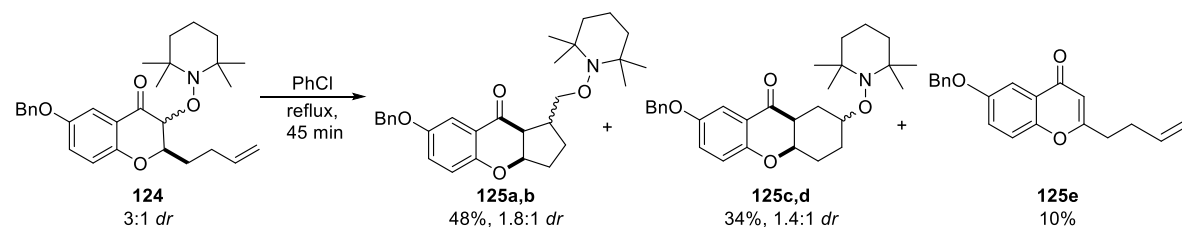
Major diastereoisomer:

$R_F = 0.54$ (PE/EtOAc, 10:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.50-7.30 (m, 6H, CH_{Ph}, CH_{Ar}-5), 7.19 (dd, $J = 9.0, 3.1$ Hz, 1H, CH-3), 6.91 (d, $J = 9.0$ Hz, 1H, CH-2), 5.78 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H, CH-12), 5.12-4.98 (m, 4H, CH₂Ph, CH₂-13), 4.89 (ddd, $J = 9.8, 5.2, 1.7$ Hz, 1H, CH-9), 4.07 (d, $J = 1.7$ Hz, 1H, CH-8), 2.25-2.10 (m, 2H, CH₂-11), 1.81-1.66 (m, 1H, CH₂-10^a), 1.61-1.36 (m, 6H, CH₂-10^b, CH₂-15, CH₂-16^a), 1.34-1.30 (m, 1H, CH₂-16^b), 1.27 (bs, 3H, CH₃^{TEMPO}), 1.14 (bs, 3H, CH₃^{TEMPO}), 0.96 (bs, 3H, CH₃^{TEMPO}), 0.95 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 189.9 (C-7), 153.1 (C-1), 152.8 (C-4), 136.8 (C-12), 136.6 (C_{Ph}), 128.5 (CH_{Ph}), 127.9 (CH_{Ph}), 127.54 (CH_{Ph}), 125.9 (C-3), 119.8 (C-6), 119.2 (C-2), 115.7 (C-13), 108.8 (C-5), 82.9 (C-8), 79.1 (C-9), 70.50 (CH₂Ph), 60.7 (C-14), 59.9 (C-14), 40.0 (C-15), 33.8 (CH₃^{TEMPO}), 29.5 (C-11), 27.9 (C-10), 20.1 (CH₃^{TEMPO}), 17.0 (C-16). **MS** (ESI+) m/z (%) 486 ([M+Na⁺], 15), 464 ([M+H⁺], 100). **HRMS** (ESI+) m/z [M+Na⁺] calcd for C₂₉H₃₇O₄NNa: 486.2610; found: 486.2615. **IR** (neat): $\nu_{\max} = 3067, 2974, 2931, 2871, 1692, 1613, 1485, 1435, 1377, 1278, 1184, 1132, 1025, 910, 823, 730, 695, 558$ cm⁻¹.

Minor diastereoisomer:

¹H NMR (400 MHz, Chloroform-*d*) δ 7.50-7.30 (m, 6H, CH_{Ph}, CH_{Ar}-5), 7.16 (dd, $J = 9.0, 3.1$ Hz, 1H, CH-3), 6.91 (d, $J = 9.0$ Hz, 1H, CH-2), 5.78 (ddt, $J = 16.9, 10.2, 6.5$ Hz, 1H, CH-12), 5.12-4.98 (m, 4H, CH₂Ph, CH₂-13), 4.62 (bs, 1H, CH-8), 4.53 (bd, $J = 10.1$ Hz, 1H, CH-9), 2.44-2.31 (m, 1H, CH₂-11^a), 2.25-2.13 (m, 1H, CH₂-11^b), 1.92-1.82 (m, 1H, CH₂-10^a), 1.82-1.69 (m, 1H, CH₂-10^b), 1.61-1.36 (m, 5H, CH₂-15, CH₂-16^a), 1.35-1.26 (m, 1H, CH₂-16^b), 1.27 (bs, 3H, CH₃^{TEMPO}), 1.14 (bs, 3H, CH₃^{TEMPO}), 0.95 (bs, 3H, CH₃^{TEMPO}), 0.81 (bs, 3H, CH₃^{TEMPO}). **¹³C NMR** (101 MHz, Chloroform-*d*) δ 191.5 (C-7), 153.0 (C-1), 152.8 (C-4), 137.2 (C-12), 136.5 (C_{Ph}), 128.5 (CH_{Ph}), 127.9 (CH_{Ph}), 127.49 (CH_{Ph}), 125.3 (C-3), 120.8 (C-6), 118.8 (C-2), 115.5 (C-13), 109.0 (C-5), 82.9 (C-8), 79.6 (C-9), 70.46 (CH₂Ph), 60.7 (C-14), 59.9 (C-14), 40.0 (C-15), 33.8 (CH₃^{TEMPO}), 29.6 (C-11), 27.9 (C-10), 20.1 (CH₃^{TEMPO}), 16.9 (C-16).

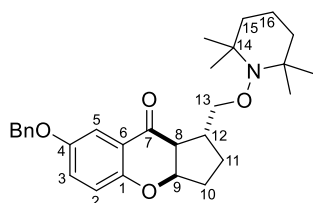
PRE-based cyclization of α -alkoxyamine **124**



In a 250 mL round-bottomed flask fitted with a reflux condenser, α -aminoxy chromanone **124** (350 mg, 0.75 mmol) was dissolved in PhCl (75 mL) under an inert atmosphere. The mixture was submitted to five gentle vacuum/N₂ cycles and immersed into a preheated oil bath (160 °C) for 45 min. The solvent was evaporated under reduced pressure, and the crude products were purified by column chromatography (neat hexane, gradient to 3:1 hexane/EtOAc) to yield 178 mg of a 1.5:1 mixture of **125c** and **125a**, 61 mg of pure **125b**, 49 mg of pure **125d**, and 24 mg of **125e**. The first mixed fraction

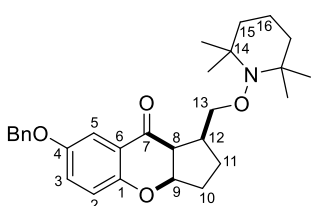
was repurified by second column chromatography (neat hexane, gradient to 3:1 hexane/Et₂O) to give in total 168 mg (48%) of separated **125a** and **125b** as a 1.8:1 diastereomeric mixture, 120 mg (34%) of separated **125c** and **125d** as a 1.4:1 diastereomeric mixture and 24 mg (10%) of **125e**. X-ray quality crystals of **125b** were obtained by slow crystallization of pure oil in the freezer.

(1*R,3*aR**,9*aS**)-7-(Benzyloxy)-1-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-2,3,3*a*,9*a*-tetrahydrocyclopenta[*b*]chromen-9(1*H*)-one (125a)**



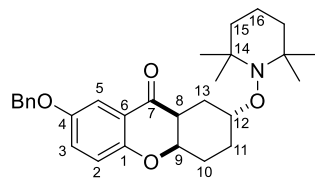
R_F = 0.33 (PE/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.48-7.29 (m, 6H, CH_{Ph}, CH-5), 7.15 (dd, J = 9.0, 3.1 Hz, 1H, CH-3), 6.87 (d, J = 9.0 Hz, 1H, CH-2), 5.03 (s, 2H, CH₂Ph), 4.94 (td, J = 4.2, 1.2 Hz, 1H, CH-9), 3.91 (dd, J = 8.9, 3.7 Hz, 1H, CH-13^a), 3.86 (dd, J = 8.9, 5.3 Hz, 1H, CH-13^b), 2.75 (dd, J = 10.2, 4.1 Hz, 1H, CH-8), 2.55-2.43 (m, 1H, CH-12), 2.22-2.11 (m, 2H, CH₂-10^a, CH₂-11^a), 2.03-1.87 (m, 2H, CH₂-10^b, CH₂-11^b), 1.61-1.41 (m, 5H, CH₂-15, CH₂-16^a), 1.37-1.30 (m, 1H, CH₂-16^b), 1.29 (bs, 3H, CH₃^{TEMPO}), 1.15 (bs, 3H, CH₃^{TEMPO}), 1.12 (bs, 3H, CH₃^{TEMPO}), 1.10 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 193.9 (C-7), 155.5 (C-1), 153.2 (C-4), 136.8 (C_{Ph}), 128.7 (CH_{Ph}), 128.1 (CH_{Ph}), 127.7 (CH_{Ph}), 125.9 (C-3), 119.4 (C-2), 119.2 (C-6), 108.8 (C-5), 83.9 (C-9), 77.3 (C-13), 70.6 (CH₂Ph), 60.1 (C-14), 52.3 (C-8), 41.3 (C-12), 39.8 (C-15), 39.1 (C-15), 33.3 (CH₃^{TEMPO}), 33.2 (CH₃^{TEMPO}), 32.5 (C-10), 26.8 (C-11), 20.4 (CH₃^{TEMPO}), 20.3 (CH₃^{TEMPO}), 17.2 (C-16). MS (ESI+) m/z (%) 486 ([M+Na⁺], 15), 464 ([M+H⁺], 100). HRMS (ESI+) m/z [M+Na⁺] calcd for C₂₉H₃₇O₄NNa: 486.2612; found: 486.2615. IR (neat): ν_{max} = 2970, 2931, 1682, 1615, 1486, 1357, 1282, 1230, 1198, 1133, 1025, 828, 697 cm⁻¹.

(1*S,3*aR**,9*aS**)-7-(Benzyloxy)-1-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-2,3,3*a*,9*a*-tetrahydrocyclopenta[*b*]chromen-9(1*H*)-one (125b)**



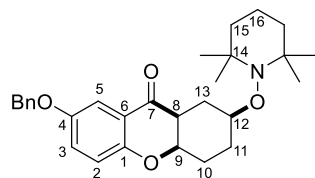
R_F = 0.22 (PE/EtOAc, 10:1). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.47-7.30 (m, 6H, CH_{Ph}, CH-5), 7.11 (dd, J = 8.9, 3.2 Hz, 1H, CH-3), 6.86 (d, J = 9.0 Hz, 1H, CH-2), 5.04 (s, 2H, CH₂Ph), 4.90-4.85 (m, 1H, CH-9), 3.71 (dd, J = 9.0, 6.5 Hz, 1H, CH-13^a), 3.58 (dd, J = 9.0, 7.6 Hz, 1H, CH-13^b), 2.95-2.85 (m, 1H, CH-12), 2.82 (dd, J = 10.2, 4.5 Hz, 1H, CH-8), 2.29-2.16 (m, 1H, CH₂-10^a), 2.07-1.87 (m, 3H, CH₂-10^b, CH₂-11), 1.52-1.39 (m, 1H, CH₂-16^a), 1.39-1.27 (m, 4H, CH₂-15), 1.26-1.18 (m, 1H, CH₂-16^b), 1.03 (bs, 3H, CH₃^{TEMPO}), 0.91 (bs, 3H, CH₃^{TEMPO}), 0.89 (bs, 3H, CH₃^{TEMPO}), 0.83 (bs, 3H, CH₃^{TEMPO}). ¹³C NMR (101 MHz, Chloroform-*d*) δ 193.1 (C-7), 156.3 (C-1), 153.3 (C-4), 137.0 (C_{Ph}), 128.7 (CH_{Ph}), 128.2 (CH_{Ph}), 127.7 (CH_{Ph}), 125.7 (C-3), 121.4 (C-6), 119.5 (C-2), 109.1 (C-5), 83.5 (C-9), 77.8 (C-13), 70.7 (CH₂Ph), 59.8 (C-14), 59.7 (C-14), 52.7 (C-8), 41.4 (C-12), 39.7 (C-15), 32.94 (CH₃^{TEMPO}), 32.86 (C-10), 32.8 (CH₃^{TEMPO}), 27.9 (C-11), 20.2 (CH₃^{TEMPO}), 20.1 (CH₃^{TEMPO}), 17.1 (C-16).

(2*R,4*aR**,9*aS**)-7-(Benzyloxy)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-1,2,3,4,4*a*,9*a*-hexahydro-9*H*-xanthen-9-one (125c)**



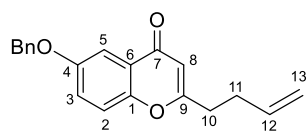
R_F = 0.49 (PE/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.47-7.32 (m, 6H, CH_{Ph} , CH-5), 7.17 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.92 (d, J = 9.0 Hz, 1H, CH-2), 5.05 (s, 2H, CH_2Ph), 4.59 (q, J = 3.6 Hz, 1H, CH-9), 4.05-3.99 (m, 1H, CH-12), 2.98-2.89 (m, 1H, CH-8), 2.07-1.83 (m, 6H, CH_2 -10, CH_2 -11, CH_2 -13), 1.58-1.47 (m, 5H, CH_2 -15, CH_2 -16^a), 1.41-1.33 (m, 1H, CH_2 -16^b), 1.18 (bs, 12H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 192.9 (C-7), 155.8 (C-1), 152.8 (C-4), 136.5 (C_{Ph}), 128.3 (CH_{Ph}), 127.8 (CH_{Ph}), 127.3 (CH_{Ph}), 125.4 (C-3), 119.2 (C-6), 118.9 (C-2), 108.8 (C-5), 76.2 (C-12), 75.9 (C-9), 70.3 (CH_2Ph), 59.6 (C-14), 43.3 (C-8), 40.1 (C-15), 34.1 ($\text{CH}_3^{\text{TEMPO}}$), 28.7 (C-13), 28.2 (C-11), 24.7 (C-10), 20.0 ($\text{CH}_3^{\text{TEMPO}}$), 16.8 (C-16). **MS** (ESI+) m/z (%) 486 ($[\text{M}+\text{Na}^+]$, 15), 464 ($[\text{M}+\text{H}^+]$, 100). **HRMS** (ESI+) m/z $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{29}\text{H}_{38}\text{O}_4\text{N}$: 464.2795; found: 464.2795. **IR** (neat): ν_{max} = 2929, 2871, 1686, 1616, 1486, 1434, 1376, 1279, 1229, 1188, 1132, 1025, 982, 826, 735, 696 cm^{-1} .

(2*S,4*aR**,9*aS**)-7-(Benzyloxy)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-1,2,3,4,4*a*,9*a*-hexahydro-9*H*-xanthen-9-one (125d)**



R_F = 0.16 (PE/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.46-7.30 (m, 6H, CH_{Ph} , CH-5), 7.17 (dd, J = 9.0, 3.2 Hz, 1H, CH-3), 6.93 (d, J = 9.0 Hz, 1H, CH-2), 5.05 (s, 2H, CH_2Ph), 4.41 (q, J = 2.9 Hz, 1H, CH-9), 3.78 (tt, J = 11.2, 4.0 Hz, 1H, CH-12), 2.43 (ddd, J = 13.4, 4.3, 2.6 Hz, 1H, CH-8), 2.29-2.15 (m, 2H, CH-10^a, CH-13^a), 2.14-2.06 (m, 1H, CH-10^b), 1.79-1.65 (m, 1H, CH-13^b), 1.63-1.22 (m, 7H, CH_2 -11, CH_2 -15, CH_2 -16^a), 1.22-1.14 (m, 1H, CH_2 -16^b), 1.12 (bs, 6H, $\text{CH}_3^{\text{TEMPO}}$), 1.09 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$), 1.06 (bs, 3H, $\text{CH}_3^{\text{TEMPO}}$). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 195.1 (C-7), 156.2 (C-1), 153.2 (C-4), 136.7 (C_{Ph}), 128.6 (CH_{Ph}), 128.1 (CH_{Ph}), 127.6 (CH_{Ph}), 125.9 (C-3), 119.3 (C-2), 119.2 (C-6), 109.0 (C-5), 79.9 (C-12), 74.8 (C-9), 70.6 (CH_2Ph), 59.8 (C-14), 47.5 (C-8), 40.2 (C-15), 34.5 ($\text{CH}_3^{\text{TEMPO}}$), 29.9 (C-13), 29.2 (C-11), 26.6 (C-10), 20.1 ($\text{CH}_3^{\text{TEMPO}}$), 17.3 (C-16).

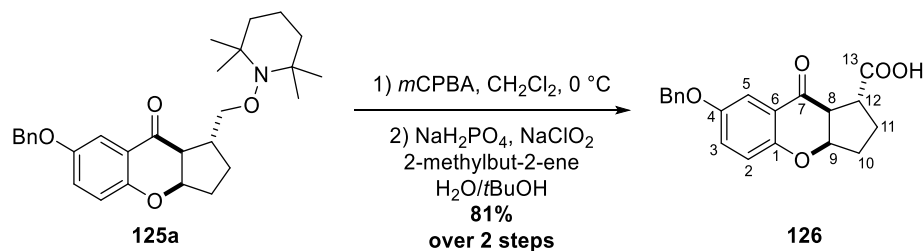
6-(Benzyloxy)-2-(but-3-en-1-yl)-4*H*-chromen-4-one (125e)



R_F = 0.07 (PE/EtOAc, 10:1). $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.66 (d, J = 3.0 Hz, 1H, CH-5), 7.49-7.27 (m, 7H, CH_{Ph} , CH-2, CH-3), 6.17 (s, 1H, CH-8), 5.85 (ddt, J = 16.9, 10.2, 6.5 Hz, 1H, CH-12), 5.14 (s, 2H, CH_2Ph), 5.11 (dt, J = 17.1, 1.6 Hz, 1H, CH-13), 5.05 (dq, J = 10.2, 1.3 Hz, 1H, CH-13), 2.77-2.68 (m, 2H, CH_2 -10), 2.55-2.45 (m, 2H, CH_2 -11). $^{13}\text{C NMR}$ (101 MHz, Chloroform-*d*) δ 178.2 (C-7), 168.6 (C-9), 156.0 (C-1), 151.5 (C-4), 136.4 (C_{Ph}), 136.1 (C-12), 128.8 (CH_{Ph}), 128.3 (CH_{Ph}), 127.8 (CH_{Ph}), 124.4 (C-6), 124.0 (C-3), 119.4 (C-2), 116.5 (C-13), 109.5 (C-8), 106.2 (C-5), 70.7 (CH_2Ph), 33.8 (C-10), 30.9 (C-11). **MS** (ESI+) m/z (%) 329 ($[\text{M}+\text{Na}^+]$, 100), 307

([M+H]⁺, 60). **HRMS** (ESI⁺) *m/z* [M+Na⁺] calcd for C₂₀H₁₈O₃Na: 329.1149; found: 329.1148. **IR** (neat): $\nu_{\max}$ = 3077, 2925, 1641, 1610, 1581, 1481, 1371, 1354, 1286, 1238, 1194, 1124, 1006, 962, 835, 723, 697 cm⁻¹.

(1*R,3*aR**,9*aS**)-7-(Benzyloxy)-9-oxo-1,2,3,3*a*,9,9*a*-hexahydrocyclopenta[*b*]chromene-1-carboxylic acid (**126**)**

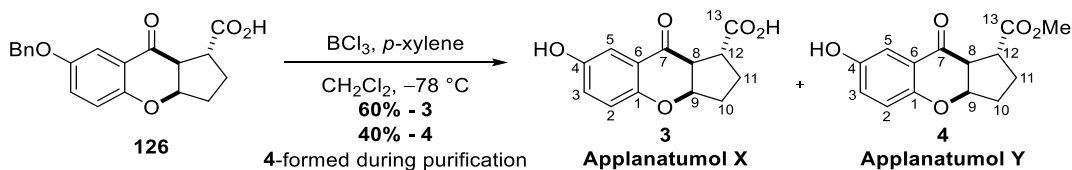


In a 25 mL round-bottomed flask, cyclopentane **125a** (148 mg, 0.32 mmol) was dissolved in CH₂Cl₂ (3.2 mL), cooled to 0 °C and *m*CPBA (70-75%, 102 mg, 0.42 mmol) was added. The mixture was stirred at 0 °C for 30 min, diluted with Et₂O (25 mL), and washed with saturated NaHCO₃ (5×25 mL) and brine (2×25 mL). The organic layer was dried over MgSO₄, filtered, and evaporated at reduced pressure to give the crude aldehyde that was directly used in the next step.

The crude aldehyde was dissolved in *t*BuOH (2.0 mL) and H₂O (1.5 mL). 2-Methylbut-2-ene (0.35 mL, 3.10 mmol), NaH₂PO₄·H₂O (214 mg, 1.55 mmol) and NaClO₂ (84 mg, 0.93 mmol) were successively added. The mixture was stirred at r.t. for 30 min, diluted with brine, and extracted by Et₂O (3×25 mL). The combined organic layers were washed with brine (2×25 mL), dried over MgSO₄, filtered, and evaporated at reduced pressure. The crude product was purified by column chromatography (neat hexane, gradient to 3:1 hexane/Et₂O) to yield 87 mg (81%) of **126** as a colorless oil.

*R*_F = 0.22 (hexane/EtOAc, 3:1). **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.46-7.30 (m, 6H, CH_{Ph}, CH-5), 7.18 (dd, *J* = 9.0, 3.2 Hz, 1H, CH-3), 6.89 (d, *J* = 9.0 Hz, 1H, CH-2), 5.04 (s, 2H, CH₂Ph), 5.02-4.98 (m, 1H, CH-9), 3.25-3.13 (m, 2H, CH-8, CH-12), 2.42-2.31 (m, 1H, CH₂-11^a), 2.23-2.07 (m, 3H, CH₂-11^b, CH₂-10). The carboxylic acid resonance was not detected. **¹³C NMR** (101 MHz, Chloroform-*d*) δ 193.3 (C-7), 177.3 (C-13), 155.6 (C-1), 153.4 (C-4), 136.5 (C_{Ph}), 128.6 (CH_{Ph}), 128.1 (CH_{Ph}), 127.6 (CH_{Ph}), 126.7 (C-3), 119.5 (C-2), 119.0 (C-6), 108.8 (C-5), 82.9 (C-9), 70.6 (CH₂Ph), 53.0 (C-8), 45.6 (C-12), 32.1 (C-10), 27.2 (C-11). **MS** (ESI⁻) *m/z* (%) 337 ([M-H]⁺, 100), 293 ([M-CO₂-H]⁺, 35). **HRMS** (ESI⁻) *m/z* [M-H]⁺ calcd for C₂₀H₁₇O₅: 337.1079; found: 337.1082. **IR** (neat): $\nu_{\max}$ = 3100-2800 (v br), 2932, 1731, 1710, 1680, 1615, 1484, 1455, 1437, 1351, 1281, 1228, 1194, 1145, 1025, 827, 737, 696, 638 cm⁻¹.

Debenzylation of applanatumol X



In a flame-dried Schlenk flask, carboxylic acid **126** (14 mg, 0.041 mmol) was dissolved in dry CH_2Cl_2 (0.82 mL) and *p*-xylene (51 μL , 0.41 mmol) under an inert atmosphere. The mixture was cooled to -78°C , and BCl_3 (1M in CH_2Cl_2 , 0.16 mL, 0.16 mmol) was dropwise added. The mixture was stirred for 30 min, quenched by H_2O (0.2 mL), and warmed to 0°C . The solvents were removed by a stream of N_2 , and the residue was thoroughly dried at a high vacuum. The crude carboxylic acid was separated by column chromatography (neat CH_2Cl_2 , gradient to 10:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield 11 mg of a mixture of **3** and **4** that was separated by second column chromatography (neat hexane, gradient to 1:1 hexane/EtOAc) to yield 6.0 mg (60%) of **3**, and 4.3 mg (40%) of **4** as pale yellow oils.

(1*R**,3*aR**,9*aS**)-7-Hydroxy-9-oxo-1,2,3,3*a*,9,9*a*-hexahydrocyclopenta[*b*]chromene-1-carboxylic acid - **Applanatumol X (3)**

R_F = 0.15 (hexane/EtOAc, 3:1). ^1H NMR (600 MHz, Methanol- d_4) δ 7.16 (d, J = 3.1 Hz, 1H, CH-5), 7.02 (dd, J = 8.9, 3.1 Hz, 1H, CH-3), 6.84 (d, J = 8.9 Hz, 1H, CH-2), 4.98-4.95 (m, 1H, CH-9), 3.09 (dd, J = 9.7, 4.3 Hz, 1H, CH-8), 3.03 (td, J = 9.9, 6.5 Hz, 1H, CH-12), 2.37-2.29 (m, 1H, CH-11^a), 2.15-2.10 (m, 2H, CH-10), 2.06-2.00 (m, 1H, CH-11^b). ^{13}C NMR (151 MHz, Methanol- d_4) δ 194.7 (C-7), 178.0 (C-13), 155.7 (C-1), 153.0 (C-4), 126.3 (C-3), 120.5 (C-6), 120.2 (C-2), 111.4 (C-5), 84.6 (C-9), 55.2 (C-8), 47.0 (C-12), 33.0 (C-10), 29.0 (C-11). **MS** (ESI⁻) m/z (%) 517 ([2M-2H⁺+Na⁺], 25), 247 ([M-H⁺], 100). **HRMS** (ESI⁻) m/z [M-H⁺] calcd for $\text{C}_{13}\text{H}_{11}\text{O}_5$: 247.0612; found: 247.0608. **IR** (neat): ν_{max} = 3600-2500 (v br), 3339, 2946, 1710, 1666, 1619, 1491, 1460, 1351, 1313, 1257, 1223, 1197, 877, 830, 631 cm^{-1} .

(1*R**,3*aR**,9*aS**)-Methyl 7-hydroxy-9-oxo-1,2,3,3*a*,9,9*a*-hexahydrocyclopenta[*b*]chromene-1-carboxylate - **Applanatumol Y (4)**

R_F = 0.40 (hexane/EtOAc, 3:1). ^1H NMR (600 MHz, Methanol- d_4) δ 7.15 (dd, J = 3.1, 0.4 Hz, 1H, CH-5), 7.02 (dd, J = 8.9, 3.1 Hz, 1H, CH-3), 6.84 (dd, J = 8.9, 0.4 Hz, 1H, CH-2), 4.97-4.95 (m, 1H, CH-9), 3.71 (s, 3H, OMe), 3.10-3.02 (m, 2H, CH-8, CH-12), 2.35-2.28 (m, 1H, CH-11^a), 2.15-2.11 (m, 2H, CH-10), 2.06-1.98 (m, 1H, CH-11^b). ^{13}C NMR (151 MHz, Methanol- d_4) δ 194.4 (C-7), 176.5 (C-13), 155.7 (C-1), 153.2 (C-4), 126.3 (C-3), 120.5 (C-6), 120.2 (C-2), 111.3 (C-5), 84.5 (C-9), 55.4 (C-8), 52.7 (OMe), 46.7 (C-12), 33.0 (C-10), 28.7 (C-11). **MS** (ESI⁺) m/z (%) 285 ([M+Na⁺], 100), 263 ([M+H⁺], 15). **HRMS** (ESI⁺) m/z [M+H⁺] calcd for $\text{C}_{14}\text{H}_{15}\text{O}_5$: 263.0915; found: 263.0914. **IR** (neat): ν_{max} = 3391, 2952, 1732, 1667, 1618, 1490, 1456, 1351, 1310, 1255, 1226, 1193, 1127, 1086, 1021, 943, 926, 881, 830, 769, 634 cm^{-1} .

6.4. X-RAY CRYSTALLOGRAPHY

The diffraction experiments for *major-28r*, *major-28n·HCl*, *major-50p*, *major-50a*, *major-50m·HCl*, *minor-50m·HCl*, *major-40a*, *40k-major* and *major-42d·HCl* were performed on Bruker D8 VENTURE Kappa Duo PHOTON 100 (PHOTON III for *major-50m·HCl*) by I μ S micro-focus sealed tube either with MoK α (0.71073) for *major-28r*, *major-50p*, *major-50m·HCl*, *minor-50m·HCl* and *major-40a*, or CuK α (λ = 1.54178) for *major-28n·HCl*, *major-50a*, *40k-major* and *major-42d·HCl*. Radiation at a temperature 120(2) K except for *major-40a* at 150 K and *40k-major* at 130 K. The data for **81b**, **84a**, **115**, **99**, and **125b** were collected on a Bruker D8 VENTURE Kappa Duo PHOTON III with I μ S micro-focus sealed tube CuK α (λ = 1.54178 Å) radiation at low temperature.

The structures were solved by direct methods (XT)^[163] and refined by full-matrix least-squares based on F^2 (SHELXL2018)^[163]. The hydrogen atoms on carbon atoms were fixed into idealized positions (riding model) and assigned temperature factors either $H_{iso}(H) = 1.2 U_{eq}(\text{pivot atom})$ or $H_{iso}(H) = 1.5 U_{eq}(\text{pivot atom})$ for the methyl groups; the hydrogen atoms on oxygens or in N-H groups were found on the difference Fourier maps and refined under a rigid body assumption with assigned temperature factors $H_{iso}(H) = 1.2 U_{eq}(\text{pivot atom})$.

X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers stated in **Tables 16-19** and can be obtained free of charge from the Centre via its website (www.ccdc.cam.ac.uk/getstructures). A summary of the crystallographic data is given in **Tables 16-19**.

Some structures require additional comments:

In **81b**, the 5'-OCH₂Ph carbon atom is disordered into two positions and was refined accordingly.

The crystal of **84a** broke under flash cooling at 120K because of a phase transition from a disordered to an ordered structure. By slow cooling, it was possible to obtain the ordered structure presented in this thesis. The high-temperature phase is not included because of less precise data.

Severe disorder of almost half of the molecule hampered the structure determination of **125b**; however, splitting of the atom positions leads to satisfactory results with sufficient precision.

Table 16: Crystal data, data collection, and refinement parameters for *major-28n*·HCl, *major-28r*, *major-50p*.

Compound	<i>major-28n</i> ·HCl	<i>major-28r</i>	<i>major-50p</i>
CCDC	1968538	1968537	1968539
Formula	C ₂₂ H ₃₄ NO ₂ ·Cl	C ₂₈ H ₃₅ NO ₂	C ₂₂ H ₃₁ NO ₂
M.w.	379.95	417.57	341.48
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> [Å]	13.7908 (5)	11.6529 (5)	7.9405 (5)
<i>b</i> [Å]	10.1414 (4)	19.4223 (9)	40.140 (3)
<i>c</i> [Å]	15.2678 (6)	11.2650 (4)	6.5656 (4)
α [°]			
β [°]	94.141 (2)	112.666 (1)°	112.019 (2)
γ [°]			
<i>Z</i>	4	4	4
<i>V</i> [Å ³]	2129.75 (14)	2352.65 (17)	1940.0 (2)
<i>D_x</i> [g cm ⁻³]	1.185	1.179	1.169
Crystal size [mm]	0.19 × 0.19 × 0.16	0.42 × 0.13 × 0.12	0.98 × 0.25 × 0.17
Crystal color, shape	Prism, colorless	Bar, yellow	Bar, colorless
μ [mm ⁻¹]	1.69	0.07	0.07
<i>T</i> _{min} , <i>T</i> _{max}	0.63, 0.77	0.94, 0.99	0.93, 0.99
Measured reflections	23556	31478	23623
Independent diffractions (<i>R</i> _{int} ^{<i>a</i>})	4038, (0.043)	5414, (0.031)	4464, (0.022)
Observed diffract. [<i>I</i> > 2σ(<i>I</i>)]	3798	4575	3993
No. of parameters	261	284	231
<i>R</i> ^{<i>b</i>}	0.052	0.041	0.041
<i>wR</i> (<i>F</i> ²) for all data	0.118	0.102	0.103
GOF ^{<i>c</i>}	1.19	1.04	1.06
Residual electron density [e/Å ³]	0.31, -0.22	0.37, -0.21	0.31, -0.25

^{*a*} $R_{\text{int}} = \sum |F_o^2 - F_{o,\text{mean}}^2| / \sum F_o^2$; ^{*b*} $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR(F^2) = [\sum (w(F_o^2 - F_c^2)^2) / (\sum w(F_o^2)^2)]^{1/2}$;

^{*c*} $\text{GOF} = [\sum (w(F_o^2 - F_c^2)^2) / (N_{\text{diffs}} - N_{\text{params}})]^{1/2}$

Table 17: Crystal data, data collection, and refinement parameters for *major-40a*, *40k-major*, *major-42d·HCl*.

Compound	<i>major-40a</i>	<i>40k-major</i>	<i>major-42d·HCl</i>
CCDC	1968543	1968544	1968545
Formula	C ₃₀ H ₄₁ NO ₂	C ₃₂ H ₄₃ NO ₂	C ₂₉ H ₄₂ NO ₂ ·Cl
M.w.	447.64	473.67	472.08
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$
<i>a</i> [Å]	8.3980 (4)	9.3606 (4)	10.4310 (5)
<i>b</i> [Å]	10.3094 (5)	10.9019 (5)	14.8714 (8)
<i>c</i> [Å]	16.4454 (7)	27.3286 (12)	17.5269 (9)
α [°]	73.559 (2)		
β [°]	77.155 (2)	98.508 (2)	99.998 (2)
γ [°]	78.526 (2)		
<i>Z</i>	2	4	4
<i>V</i> [Å ³]	1317.27 (11)	2758.1 (2)	2677.5 (2)
<i>D_x</i> [g cm ⁻³]	1.129	1.141	1.171
Crystal size [mm]	0.36 × 0.30 × 0.16	0.41 × 0.18 × 0.11	0.31 × 0.17 × 0.09
Crystal color, shape	Prism, colorless	Prism, colorless	Prism, colorless
μ [mm ⁻¹]	0.07	0.54	1.44
<i>T_{min}</i> , <i>T_{max}</i>	0.95, 0.99	0.83, 0.94	0.76, 0.89
Measured reflections	26823	24711	31279
Independent diffractions (<i>R_{int}</i> ^a)	6047, (0.027)	5156, (0.035)	5263, (0.032)
Observed diffract. [<i>I</i> > 2σ(<i>I</i>)]	5237	4601	4898
No. of parameters	302	339	309
<i>R</i> ^b	0.041	0.046	0.036
<i>wR</i> (<i>F</i> ²) for all data	0.110	0.114	0.095
GOF ^c	1.03	1.04	1.05
Residual electron density [e/Å ³]	0.35, -0.19	0.56, -0.27	0.39, -0.32

^a $R_{\text{int}} = \sum |F_o^2 - F_{o,\text{mean}}^2| / \sum F_o^2$; ^b $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR(F^2) = [\sum (w(F_o^2 - F_c^2)^2) / (\sum w(F_o^2)^2)]^{1/2}$;

^cGOF = $[\sum (w(F_o^2 - F_c^2)^2) / (N_{\text{diffs}} - N_{\text{params}})]^{1/2}$

Table 18: Crystal data, data collection, and refinement parameters for *major-50a*, *major-50m·HCl*, *minor-50m·HCl*.

Compound	<i>major-50a</i>	<i>major-50m·HCl</i>	<i>minor-50m·HCl</i>
CCDC	1968540	1968541	1968542
Formula	C ₂₇ H ₃₅ NO ₂	C ₂₅ H ₃₈ NO ₂ ·Cl	C ₂₅ H ₃₈ NO ₂ ·Cl
M.w.	405.56	420.01	420.01
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> [Å]	17.7096 (4)	10.8249 (4)	9.6821 (5)
<i>b</i> [Å]	14.5534 (4)	18.6036 (8)	25.9329 (14)
<i>c</i> [Å]	18.7458 (5)	11.9705 (5)	9.8846 (5)
α [°]			
β [°]	108.168 (1)	104.204 (2)	108.074 (2)
γ [°]			
<i>Z</i>	8	4	4
<i>V</i> [Å ³]	4590.6 (2)	2336.95 (17)	2359.4 (2)
<i>D_x</i> [g cm ⁻³]	1.174	1.194	1.182
Crystal size [mm]	0.26 × 0.22 × 0.10	0.50 × 0.18 × 0.17	0.41 × 0.25 × 0.24
Crystal color, shape	Prism, colorless	Prism, colorless	Plate, colorless
μ [mm ⁻¹]	0.56	0.18	0.18
<i>T</i> _{min} , <i>T</i> _{max}	0.87, 0.95	0.93, 0.97	0.90, 0.96
Measured reflections	60525	55296	31273
Independent diffractions (<i>R</i> _{int} ^a)	7790, (0.053)	5343, (0.030)	5402, (0.039)
Observed diffract. [<i>I</i> > 2σ(<i>I</i>)]	6859	5042	5003
No. of parameters	550	266	268
<i>R</i> ^b	0.059	0.036	0.055
<i>wR</i> (<i>F</i> ²) for all data	0.155	0.091	0.129
GOF ^c	1.07	1.06	1.11
Residual electron density [e/Å ³]	1.09, -0.38	0.44, -0.21	0.58, -0.31

^a $R_{\text{int}} = \sum |F_o^2 - F_{o,\text{mean}}^2| / \sum F_o^2$; ^b $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR(F^2) = [\sum (w(F_o^2 - F_c^2)^2) / (\sum w(F_o^2)^2)]^{1/2}$;
^cGOF = $[\sum (w(F_o^2 - F_c^2)^2) / (N_{\text{diffs}} - N_{\text{params}})]^{1/2}$

Table 19: Crystal data, data collection, and refinement parameters for **81b**, **84a**, **99**, **115**, **125b**.

Compound	81b	84a	99	115	125b
CCDC	2097881	2097882	2097884	2097883	2097885
Formula	C ₃₀ H ₃₀ O ₆	C ₂₉ H ₂₈ O ₆	C ₃₀ H ₃₀ O ₆ ·C ₇ H ₈	C ₂₉ H ₂₆ N ₄ O ₉	C ₂₉ H ₃₇ NO ₄
M.w.	486.54	472.51	578.67	574.54	463.59
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Triclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁	<i>P</i> [−] 1	<i>P</i> [−] 1
<i>a</i> [Å]	25.7632 (9)	9.8209 (2)	6.4941 (5)	10.2040 (5)	6.6148 (2)
<i>b</i> [Å]	9.0340 (3)	14.8475 (3)	24.4989 (17)	11.6005 (6)	10.9968 (4)
<i>c</i> [Å]	10.7066 (4)	32.6469 (7)	9.5579 (7)	11.6065 (6)	17.6496 (6)
α [°]				91.516 (2)	88.149 (1)°
β [°]	95.171 (1)°	94.744 (1)°	103.083 (3)°	100.676 (2)	88.033 (1)°
γ [°]				103.672 (2)	75.855 (1)°
<i>Z</i>	4	8	2	2	2
<i>V</i> [Å ³]	2481.76 (15)	1940.0 (2)	1481.17 (19)	1308.29 (12)	1243.82 (7)
D _x [g cm ^{−3}]	1.302	1.323	1.297	1.458	1.238
Crystal size [mm]	0.30 × 0.21 × 0.08	0.53 × 0.25 × 0.08	0.29 × 0.14 × 0.05	0.33 × 0.21 × 0.07	0.41 × 0.21 × 0.05
Crystal color, shape	Prism, colorless	Prism, colorless	Plate, colorless	Prism, yellow	Prism, colorless
μ [mm ^{−1}]	0.73	0.75	0.70	0.93	0.65
<i>T</i> _{min} , <i>T</i> _{max}	0.88, 0.95	0.84, 0.94	0.61, 0.97	0.83, 0.94	0.85, 0.97
Measured reflections	24179	70256	21617	17133	30876
Independent diffractions (<i>R</i> _{int} ^a)	4861, (0.001)	9320, (0.021)	5754, (0.081)	5078, (0.021)	4882, (0.025)
Observed diffract. [I > 2σ(I)]	4677	9084	5265	4881	4543
No. of parameters	336	631	389	380	426
<i>R</i> ^b	0.037	0.038	0.071	0.036	0.048
<i>wR</i> (<i>F</i> ²) for all data	0.092	0.097	0.189	0.094	0.136
GOF ^c	1.02	1.05	1.02	1.04	1.06
Residual electron density [e/Å ³]	0.38, −0.19	0.44, −0.24	0.38, −0.29	0.33, −0.24	0.35, −0.20

^a*R*_{int} = $\Sigma |F_o^2 - F_{o,\text{mean}}^2| / \Sigma F_o^2$; ^b*R*(*F*) = $\Sigma ||F_o| - |F_c|| / \Sigma |F_o|$; *wR*(*F*²) = $[\Sigma (w(F_o^2 - F_c^2)^2) / (\Sigma w(F_o^2)^2)]^{1/2}$;

^cGOF = $[\Sigma (w(F_o^2 - F_c^2)^2) / (N_{\text{diffs}} - N_{\text{params}})]^{1/2}$

Figure 12: X-ray crystallographic view on α -aminoxy ketone *major-28n*·HCl. Displacement ellipsoids are at a 30% probability level.

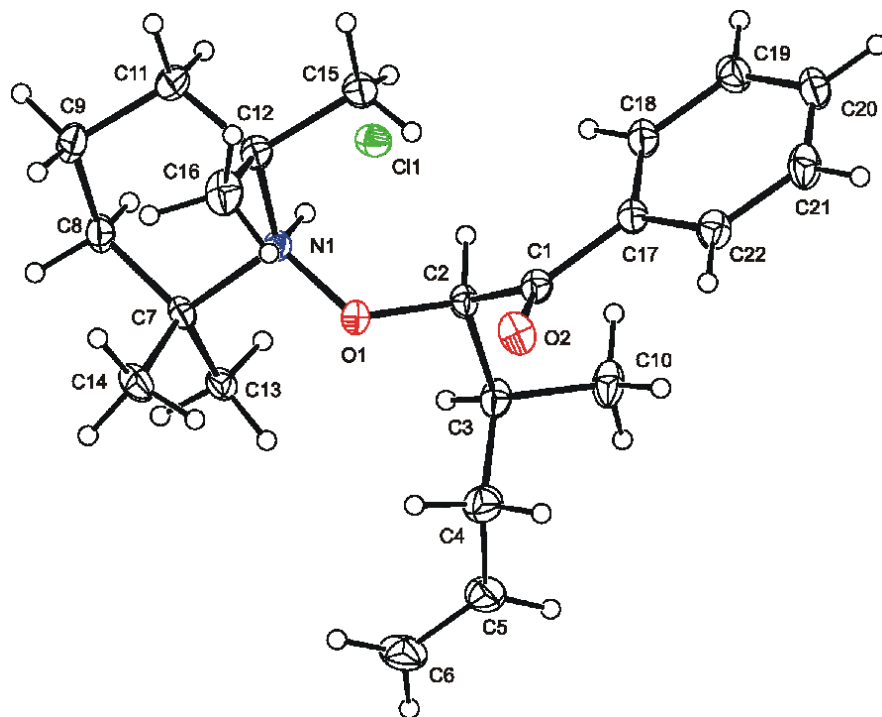


Figure 13: X-ray crystallographic view on α -aminoxy ketone *major-28r*. Displacement ellipsoids are at a 30% probability level.

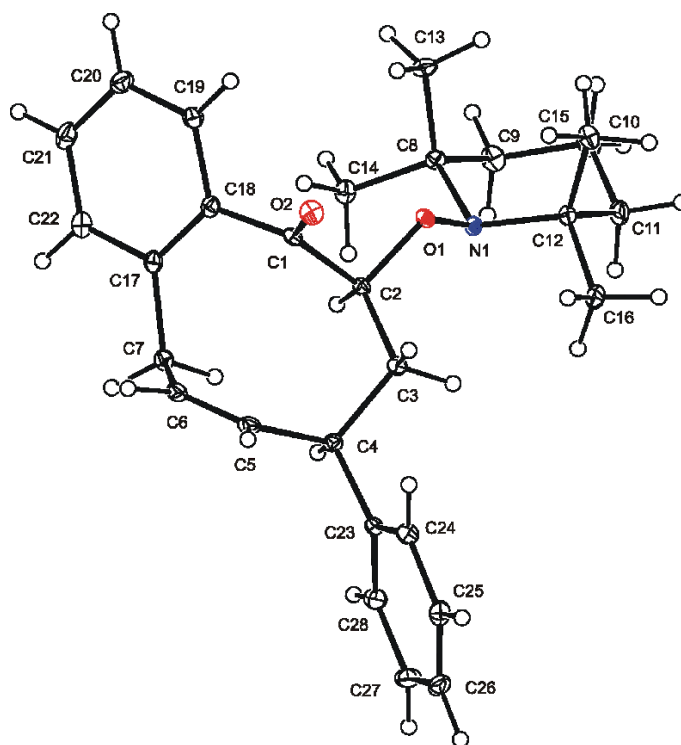


Figure 14: X-ray crystallographic view on cyclopentane *major-50p*. Displacement ellipsoids are at a 30% probability level.

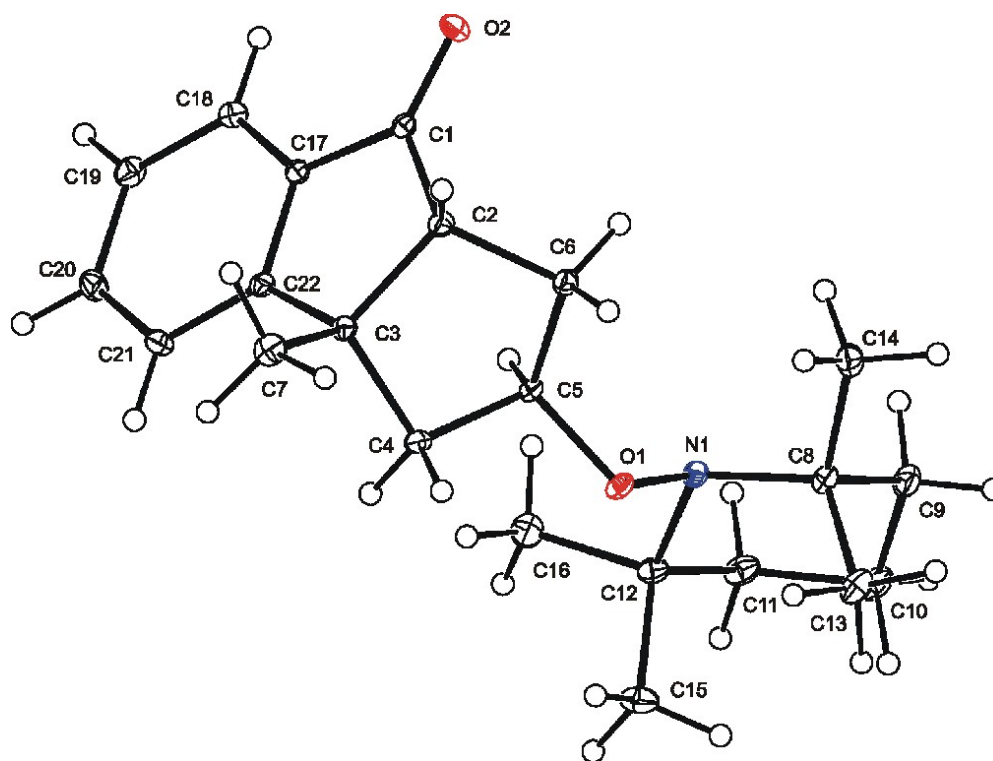


Figure 15: X-ray crystallographic view on protected diol *major-40a*. Displacement ellipsoids are at a 30% probability level.

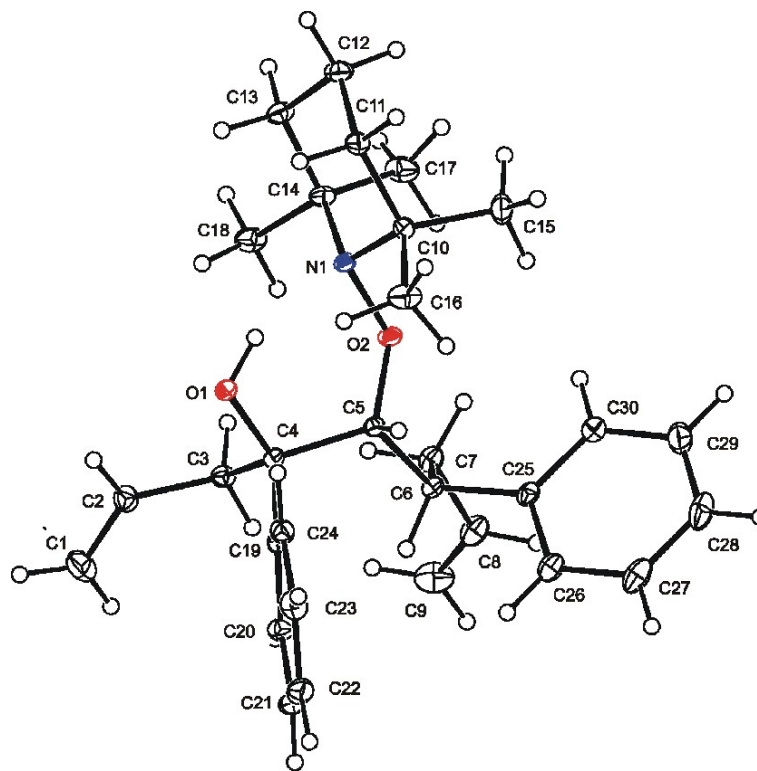


Figure 16: X-ray crystallographic view on protected diol **40k-major**. Displacement ellipsoids are at a 30% probability level.

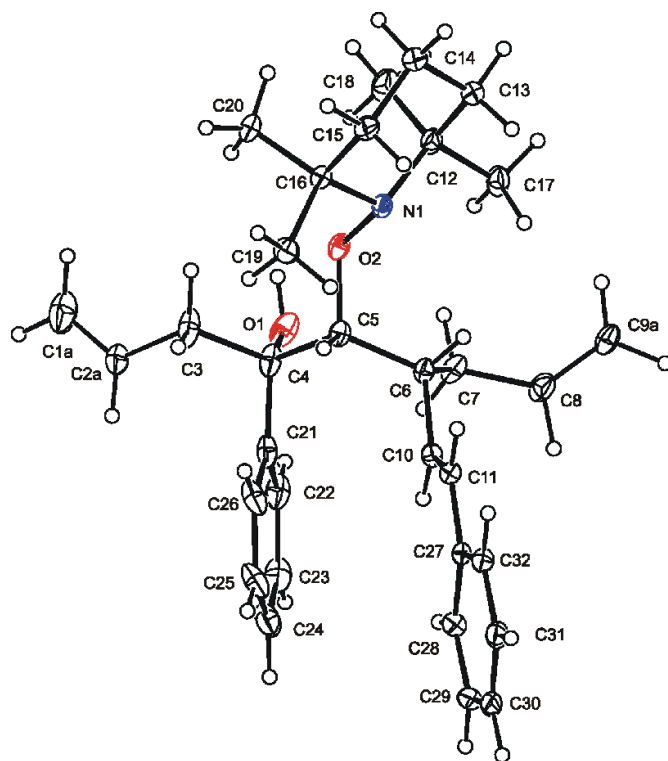


Figure 17: X-ray crystallographic view on protected diol **major-42d-HCl**. Displacement ellipsoids are at a 30% probability level.

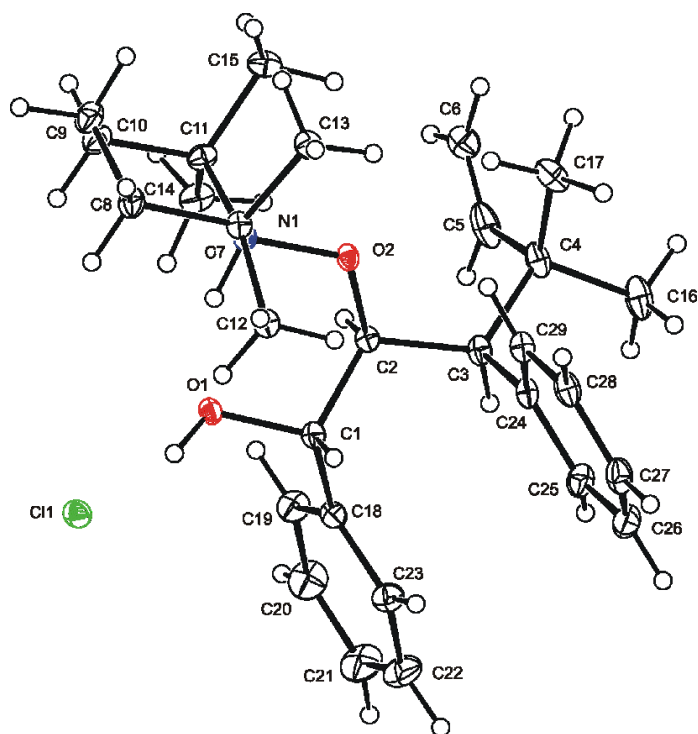


Figure 18: X-ray crystallographic view on cyclopentane *major-50a*. Displacement ellipsoids are at a 30% probability level.

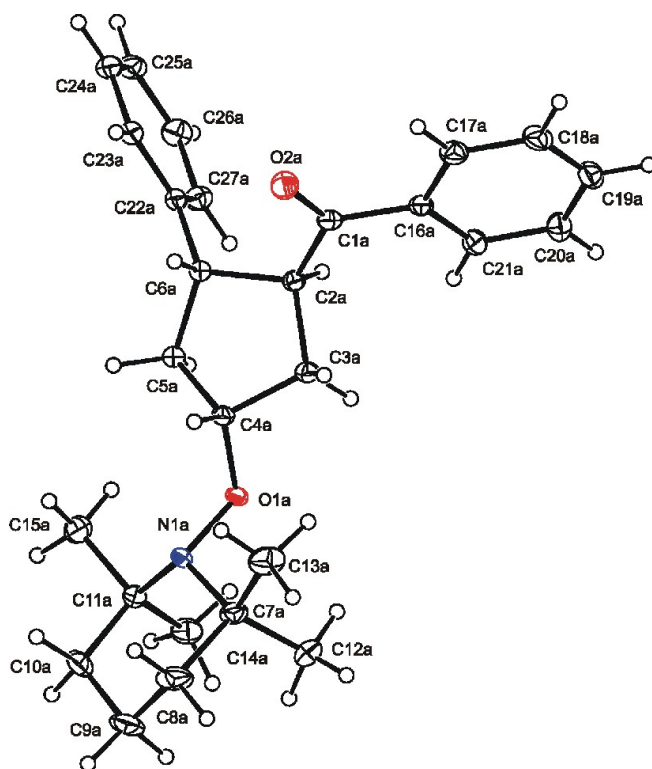


Figure 19: X-ray crystallographic view on cyclopentane *major-50m*·HCl. Displacement ellipsoids are at a 30% probability level.

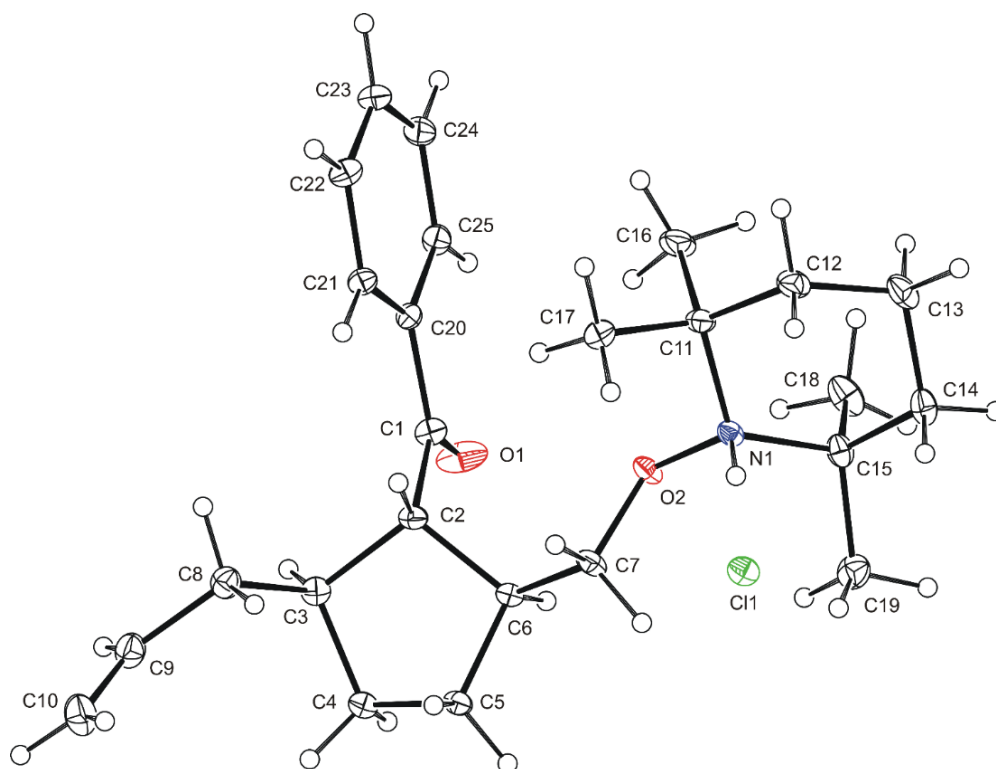


Figure 20: X-ray crystallographic view on cyclopentane *minor*-50m-HCl. Displacement ellipsoids are at a 30% probability level.

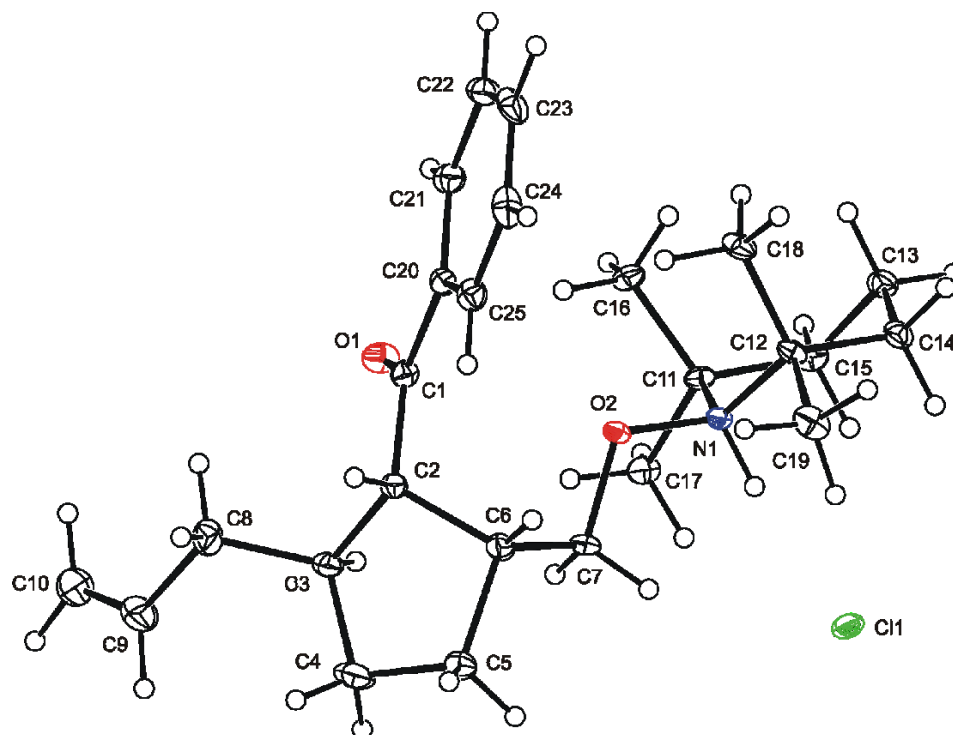


Figure 21: X-ray crystallographic view on molecule **81b**. The displacement ellipsoids are at a 30% probability level.

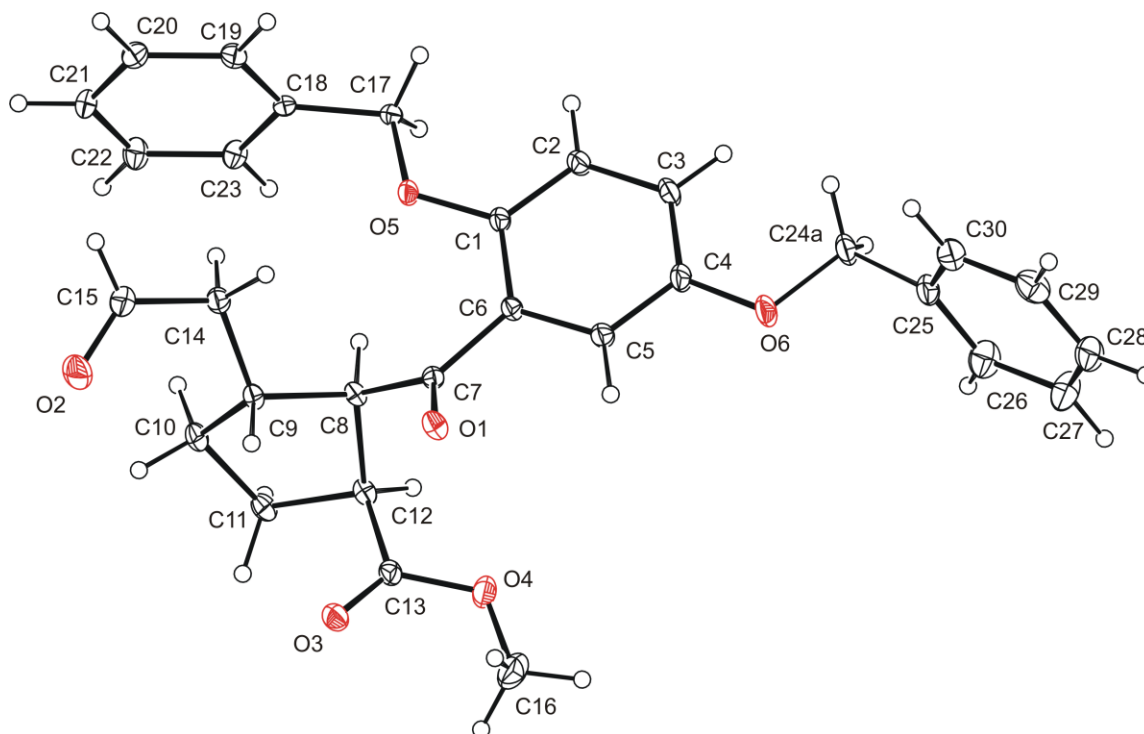


Figure 22: X-ray crystallographic view on molecule **84a**. Displacement ellipsoids are at a 30% probability level.

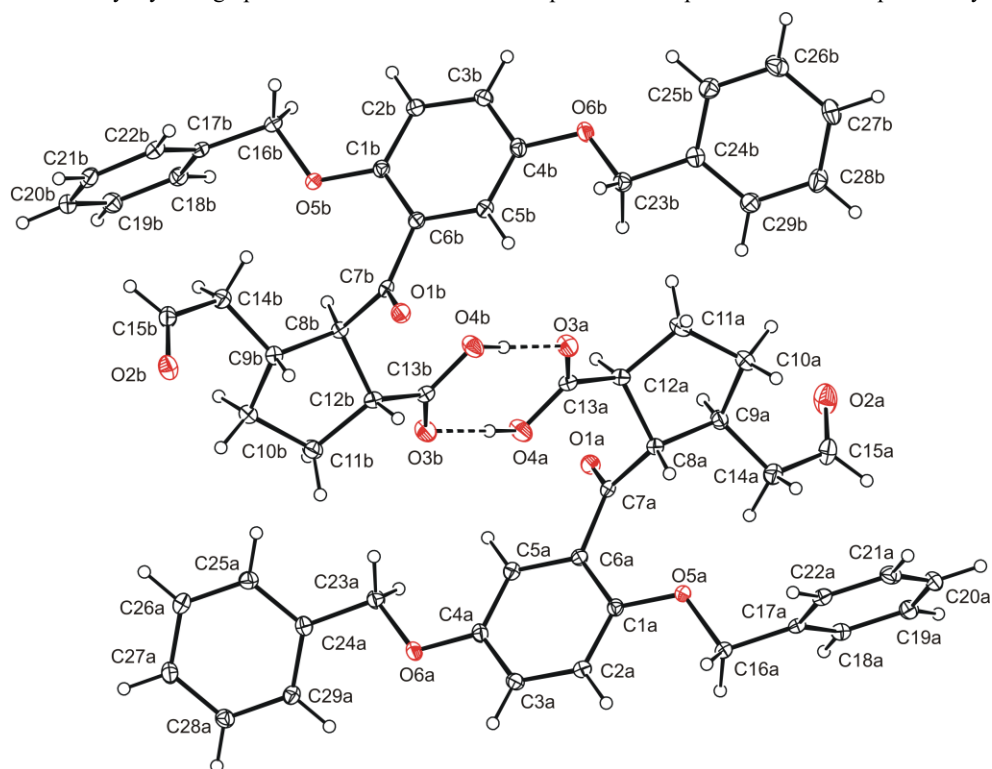


Figure 23: X-ray crystallographic view on molecule **99**. Displacement ellipsoids are at a 30% probability level. A toluene solvate molecule was omitted for clarity.

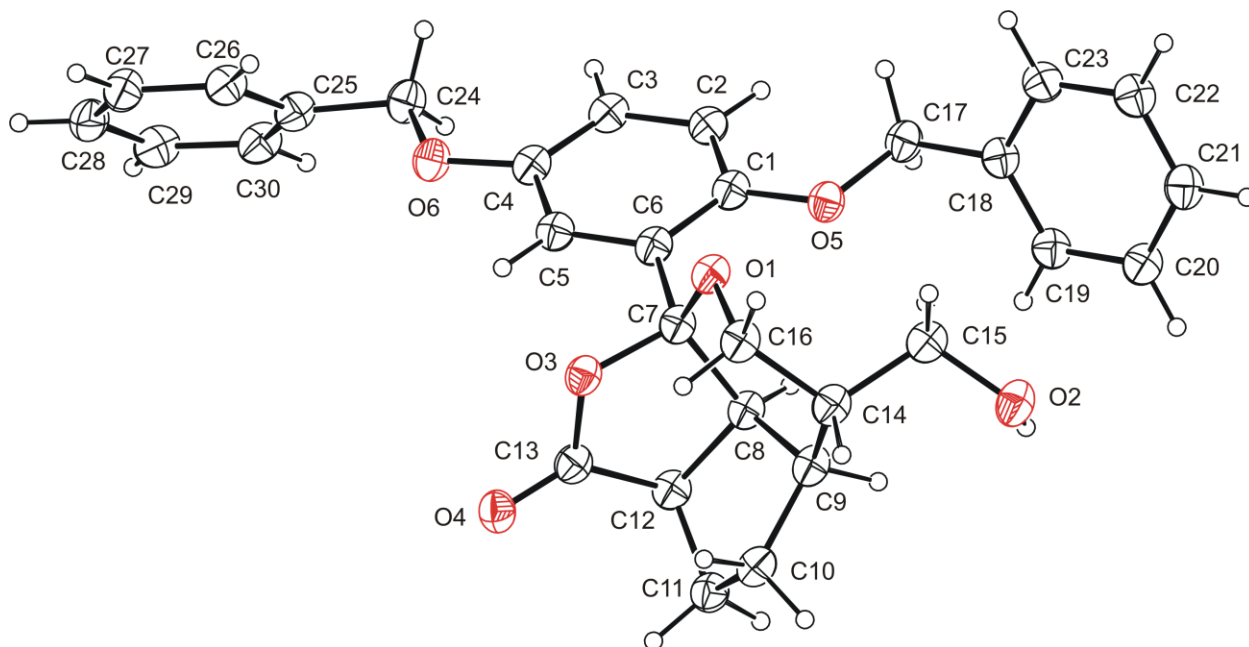


Figure 24: X-ray crystallographic view on molecule **115**. Only one arrangement of the disordered C-24 atom is displayed for clarity. Displacement ellipsoids are at a 30% probability level.

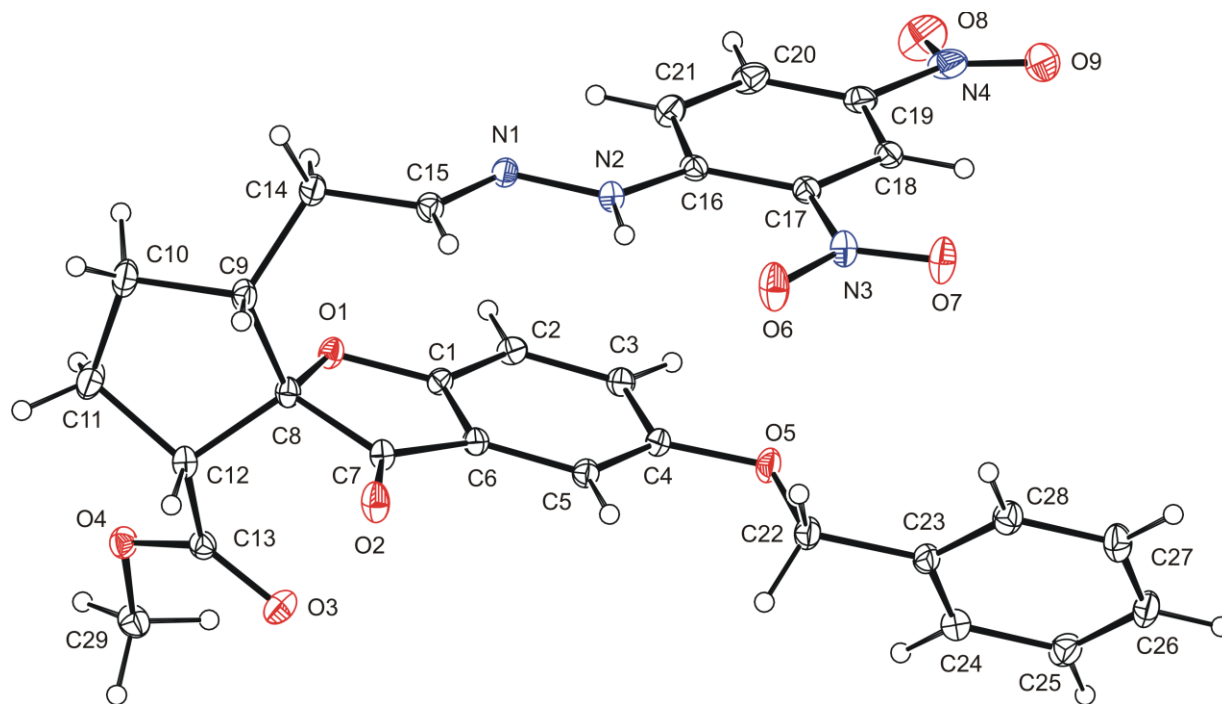
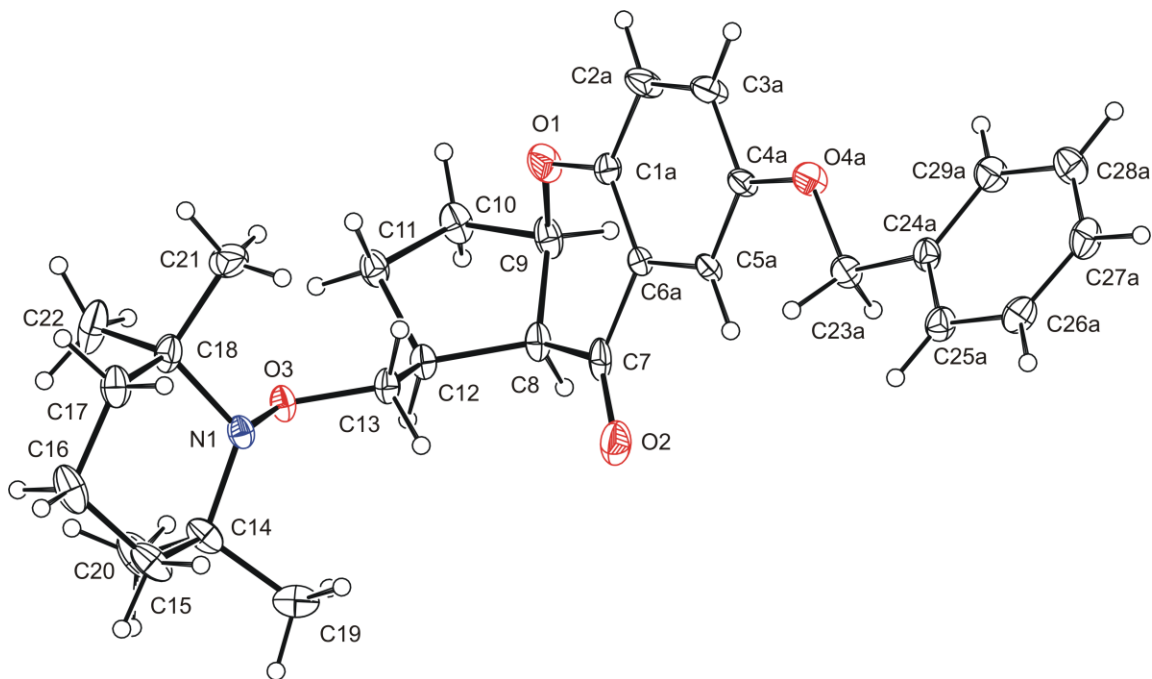


Figure 25: X-ray crystallographic view on molecule **125b**. Displacement ellipsoids are at a 30% probability level.



6.5. BIOLOGICAL INVESTIGATION

Cell culture

Cervix cancer (HeLa), hepatocellular carcinoma (Hep G2), acute lymphoblastic leukemia (CCRF-CEM), acute promyelocytic leukemia (HL-60), colon cancer (HCT-116, LoVo, RKO), breast cancer (T-47D, MCF-7) human cell lines and primary normal human dermal fibroblasts (NHDF) were purchased from ATCC (LGC Standards Sp. z o.o., Poland). RKO, MCF-7, NHDF, and HeLa were cultured in DMEM High Glucose medium (cat. No. D5796), T-47D, CCRF-CEM and HL-60 cells in RPMI-1640 medium (Dutch modification, cat. No. R7638), HCT-116 in McCoy's medium (cat. No. M4892), LoVo in DMEM/F12 (cat. No. D8437) medium and Hep G2 cells in α MEM (cat. No. M4526) medium. All media were supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS) and 2 mM glutamine (all purchased from Sigma-Aldrich) at 37 °C in a humidified atmosphere containing 5% CO₂. Twice a week, when the cells reached up to 80–90% of confluency, they were sub-cultured using 0.25% trypsin/1 mM EDTA solution for further passage.

Cytotoxicity assays

CellTiter-Glo[®] Luminescent Cell Viability Assay (Promega) was used to ascertain the intrinsic cytotoxicity of tested compounds **1a,b,2a,b,3,4,5,6a,85a,120**, and **126**. Cells were cultivated as described above. After seeding into white 384-well plates (Thermo Scientific Nunc[™]), the cells (20 μ L) were grown for 24 h before adding compounds or DMSO (vehicle control) into each well. After 72 h of treatment, CellTiter-Glo[®] reagent (20 μ L) was added to each well, and the 384-well plate was mixed for 2 min at 400 rpm on an orbital shaker in the dark. Subsequently, the luminescent signal was allowed to stabilize for 10 min at room temperature. Luminescence was recorded using a microplate luminometer reader (Cytation 3, BioTek, USA). In this assay, the luminescence directly correlates with the cell number. The cytotoxicity (**Table 20**) is expressed using IC₅₀ values, which is the concentration of a tested compound where the number of viable cells is reduced by half. The data obtained were normalized, and IC₅₀ values were calculated by nonlinear regression analysis, assuming a sigmoidal concentration-response curve with variable Hill slope (GraphPadPRISM[®] 7 software).

Table 20: Raw cytotoxicity data for compounds **1a,b,2a,b,3,4,5,6a,85a,120**, and **126** in μM against selected human cancer cell lines and normal human primary fibroblasts in 3 or 4 separate experiments. After 72 h of treatment, the IC_{50} values were determined using CellTiter-Glo® Luminiscent Cell Viability Assay as described above. For elaborated cytotoxicity data, see Table 15. If no value is stated, no considerable cell viability-reduction was observed. Experiments performed by Dr. Miroslav Hájek.

	HeLa	MCF-7	RKO	HCT-116	Hep G2	HL-60	CCRF-CEM	T47-D	LoVo	NHDF
1a	--	--	--	--	--	--	--	--	--	--
1b	--	--	502	393	--	--	--	--	--	--
2a	2.44	1.76	2.07	0.96	3.48	1.84	0.58	2.36	1.90	6.944
	2.10	2.20	1.12	1.13	4.16	1.87	0.55	5.16	2.32	8.442
	3.68	1.80	1.23	1.17	6.69	1.80	0.53	1.78	1.22	9.5
			1.77						0.99	
2b	1.83	2.00	1.72	0.76	2.02	1.64	0.49	2.75	0.81	9.849
	1.31	1.82	1.33	0.81	3.43	1.42	0.41	2.95	2.08	5.644
	2.33	1.17	0.77	0.87	5.91	1.72	0.43	1.53	0.94	6.452
			1.43						0.62	
3	--	--	532	534	--	--	--	--	--	--
4	688	--	--	--	--	--	--	--	--	--
5	--	--	--	--	--	--	--	--	--	--
6a	63.99	13.19	7.18	6.01	10.53	12.26	3.38	7.30	7.97	133.8
	8.10	8.13	5.08	5.76	15.05	11.31	2.52	11.28	15.28	74.24
	14.27	10.75	4.25	5.12	19.69	13.59	3.06	5.45	4.03	58.27
			5.75						5.30	
85a	4.82	16.49	5.41	5.09	6.74	3.94	2.84	11.33	5.64	16.16
	3.44	12.63	5.47	4.86	10.57	4.45	2.85	15.39	6.57	25.45
	4.68	4.77	5.10	4.80	13.33	4.91	2.93	3.67	3.58	21.6
			5.79						3.62	
120	2.90	3.81	1.69	1.79	3.47	2.40	1.08	2.82	3.60	10.52
	1.70	2.66	1.32	1.70	5.93	2.46	0.87	3.74	4.31	11.07
	3.28	2.04	1.05	1.84	11.76	3.04	1.16	1.69	2.19	9.9
			1.70						1.27	
126	177	133	--	--	--	--	--	--	498	--

7. REFERENCES

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8. AUTHOR'S PUBLICATIONS AND SCIENTIFIC PRESENTATIONS

PUBLICATIONS RELEVANT TO THIS WORK

- *Tandem Anionic oxy-Cope Rearrangement/Oxygenation Reactions as a Versatile Method for Approaching Diverse Scaffolds*

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- *Unified Total Synthesis of Diverse Meroterpenoids from Ganoderma Applanatum*

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OTHER AUTHOR'S PUBLICATIONS

- *Organocatalytic Allylic Amination of Morita-Baylis-Hillman Carbonates*

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PRESENTATIONS

- M. Šimek, U. Jahn: *Unified Radical Approach to Ganoderma Meroterpenoids*. Advances in Organic, Bioorganic and Pharmaceutical Chemistry (Liblice 2021), Špindlerův mlýn, Czech Republic, November 3-6, 2021. *poster presentation* (Otakar Červinka Award for the best poster)
- M. Šimek, U. Jahn: *Tandem Anionic Oxy-Cope Rearrangement/Single-electron Oxidation/Oxygenation Reactions as a Versatile Method for Approaching Functionalized Carbocycles*. Pacific Symposium on Radical Chemistry (PSRC 2019), Pacific Grove, USA, June 16-21, 2019, *poster presentation*
- M. Šimek, U. Jahn: *Approaching Functionalized Carbocycles by Tandem Anionic Oxy-Cope Rearrangement/Oxygenation Reactions - Toward Total Syntheses of Applanatumols*. Advances in Organic, Bioorganic and Pharmaceutical Chemistry (Liblice 2019), Špindlerův mlýn, Czech Republic, November 6-8, 2019. *oral communication* (Otakar Červinka Award for the best oral communication)
- M. Šimek, U. Jahn: *Tandem Anionic Oxy-Cope Rearrangement/Radical Reactions for Approaching Functionalized Carbocycles*, Balticum Syntheticum Organicum (BOS 2018), Tallinn, Estonia, July 1-4, 2018. *poster presentation*
- M. Šimek, U. Jahn: *Tandem Anionic Oxy-Cope Rearrangement/Single-Electron Oxidation/Oxygenation Reactions as a Versatile Method for Approaching Functionalized Carbocycles*. Advances in Organic, Bioorganic and Pharmaceutical Chemistry (Liblice 2018), Lázně Bělohrad, Czech Republic, November 2-4, 2018. *oral communication*
- M. Šimek, U. Jahn: *Tandem Anionic Sigmatropic Rearrangements/Radical reactions*. European Symposium on Organic Chemistry (ESOC 2017), Cologne, Germany, July 2-6, 2017. *poster presentation*
- M. Šimek, U. Jahn: *Tandem Anionic Sigmatropic Rearrangements/Radical Reactions*. Advances in Organic, Bioorganic, and Pharmaceutical Chemistry (Liblice 2017), Lázně Bělohrad, Czech Republic, November 3-5, 2017. *poster presentation*
- M. Šimek, U. Jahn: *Tandem Anionic Sigmatropic Rearrangements/Radical Reactions*. Advances in Organic, Bioorganic, and Pharmaceutical Chemistry (Liblice 2016), Lázně Bělohrad, Czech Republic, November 11-13, 2017. *poster presentation*