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Syntéza a vlastnosti neuroaktivních steroidů
Synthesis and Properties of Neuroactive Steroids

PhD. Thesis

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Declaration

Prohlašuji, že jsem předloženou doktorskou dizertační práci vypracoval samostatně a uvedl všechny použité literární prameny. Dále prohlašuji, že jsem nepředložil tuto práci ani její podstatnou část k získání jiného nebo stejného akademického titulu.

This work was carried out in years 2009-2015 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.

Prague 29th October 2015 .....

Vojtěch Kapras

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Abstract

Herein is reported the synthesis of molecular probes for action of neuroactive steroids *in vitro* and in living organisms. In the first part, preparation of enantiomeric pregnane steroids is investigated, ultimately resulting into the total synthesis of *ent*-progesterone. The chirality of the target molecule is introduced by a highly effective organocatalytic asymmetric Robinson annulation. A new method for the sequential construction of five-membered carbocyclic ring is introduced as the key step. This is composed of substrate-controlled copper-catalyzed conjugate addition followed by radical oxygenation and subsequent thermal cyclization employing the persistent radical effect. The synthesis of truncated neurosteroid analogs is described and their biological activity at the NMDA receptor is compared with the native hormone.

In the second part, methodology for specific deuterium labeling of both angular methyls of the 5β-pregnane steroid core is explored. Special attention was paid to the Barton-McCombie deoxygenation as the tool for introduction of the last deuterium atom into the methyl group. Both positions were labelled with total of three deuterium atoms in high isotopic purity.

Souhrn

V této práci je popsána syntéza molekulárních sond pro výzkum činnosti neuroaktivních steroidů *in vitro* a v živých organismech. V první části je zkoumána syntéza enantiomerních pregnanových steroidů, vedoucí k přípravě *ent*-progesteronu. Chiralita cílové molekuly je zavedena pomocí vysoce efektivní organokatalytické asymetrické Robinsonovy anelace. Jako klíčový krok je zde prozkoumána nová metoda postupné konstrukce 5-členného karbocyklu. Tato sestává ze substrátem řízené konjugované adice katalyzované mědí, následné radikálové oxygenace a termální cyklizace s využitím efektu perzistentního radikálu. Dále je v práci popsána příprava zkrácených analog neurosteroidů a jejich biologická aktivita na NMDA receptoru je srovnána s přirozeným hormonem.

V druhé části je zkoumána metodologie specifického značení obou angulárních methylů 5β-pregnanového steroidního skeletu deuteriem. Zvláštní pozornost je zde věnována Barton-McCombie deoxygenaci jakožto nástroje pro zavedení posledního atomu deuteria do methylové skupiny. Obě pozice byly značeny celkovým počtem tří atomů deuteria ve vysoké izotopické čistotě.

ABBREVIATIONS

ABCN	1,1'-Azobis(cyclohexanecarbonitrile)
AIBN	1,1'-Azobis(isobutyronitrile)
AMPA	2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid
AMPAR	AMPA receptor
ATD	Amino terminal domain
ATR	Attenuated total reflectance
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAM	1,1'-Binaphthyl-2,2'-diamine
brsm	Based on recovered starting material
CA	Conjugate addition
CAN	Cerium(IV) ammonium nitrate
CNS	Central nervous system
*m*CPBA	3-Chloroperbenzoic acid
CSA	Camphorsulfonic acid
DIPEA	*N*,*N*-Diisopropyl-ethylamine, Hünig's base
DMAP	4-Dimethylaminopyridine
DMS	Dimethyl sulfide
dba	(*E*,*E*)-1,5-Diphenyl-1,4-pentadien-3-one
dppe	1,2-Bis(diphenylphosphino)ethane
EC_{50}	Half-maximal effective concentration
FGI	Functional group interconversion
FGA	Functional group addition
$GABA_A$	Class A γ-aminobutyric acid receptor
HPESW	Hajos-Parrish-Eder-Sauer-Wiechert
IC_{50}	Half-maximal inhibition concentration
IBX	2-Iodoxybenzoic acid
Josiphos	(2*R*)-1-[(1*R*)-1-(Dicyclohexylphosphino)ethyl]-2-diphenylphosphino)ferrocene
LBD	Ligand-binding domain
(*R*)-MTPA	(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic acid, Mosher's acid
n/a	Not available
Nf	Nonaflyl or nonafluorobutanesulfonyl
NHC	*N*-Heterocyclic carbene
NMDA	*N*-Methyl-D-aspartic acid
NMDAR	NMDA receptor
NOE	Nuclear Overhauser effect
PG	Protecting group
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PMHS	Poly(methylhydrosiloxane)
PNS	Peripheral nervous system
PPTS	Pyridinium *p*-toluenesulfonate

PRE	Persistent radical effect
quant.	Quantitative
ROESY	Rotating-frame nuclear Overhauser effect spectroscopy
rt	Room temperature
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TMD	Transmembrane domain
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidin-1-yl

Common abbreviations are adapted from *The ACS Style guide*.[1]

1. INTRODUCTION

1.1. NEUROACTIVE STEROIDS, HISTORY AND TERMINOLOGY

The human brain, one of the most complex organic architectures in Nature, has always attracted the attention of scientists. How does it work? How can people move their body and perceive the surroundings? How are thoughts and memories formed, processed and forgotten? These are some ultimate questions with answers that are so far out of reach of our understanding. However, when divided into properly formulated simpler questions, we might be able to answer them.

The nervous system is a subject of broad scientific discipline called neuroscience. The roots of neuroscience reach far into ancient Egypt and are intertwined with the history of biology and medicine.[2] On the verge of 19th century, pioneering works of Golgi and Ramón y Cajal (discovery of synaptic cleft, among many others, shared Nobel Prize 1906) and later Loewi (discovery of chemical transmission at synapses, Nobel Prize 1936)[3] and Dale (identification of acetylcholine as neurotransmitter, Nobel Prize 1936)[4,5] opened the field to chemical science.[6,7] The second half of 20th century saw the birth of a new subdiscipline of neuroscience – neurochemistry – the specific study of molecules affecting the function of neurons. The natural progress in the field led to a boom in understanding of the elementary processes in the neural system, which was supported by development of new biochemical, genetic, imaging and data processing techniques. Most of the currently known neurotransmitters and neuromodulators were discovered in this era.

Neuronal signal transduction is one of the methods how the brain controls bodily functions. Slower processes, mainly vegetative functions and homeostasis, are controlled through the endocrine system. The hypothalamus, a compartment of brain, releases tropic hormones into blood, triggering a tightly controlled signalling cascade going through several levels of endocrine glands. The cascade ends by the release of non-tropic hormones, which target multiple organs in the body and form a feedback loop. This complex system enables delicate and precise control of bodily functions through the action of chemical messengers.

Steroid hormones form an important class of non-tropic hormones in vertebrates, insects and other organisms. They were amongst the first described and isolated hormones.[8] Estrone was the first gonadal hormone to be isolated and characterized (1929 by Butenandt, Nobel Prize 1939),[9,10] followed by testosterone (1934 by Butenandt),[11,12] the progestational hormone progesterone (1934 by several groups),[13–16] the adrenal hormones cortisone (1936 by Kendall and Reichstein, Nobel Prize 1950),[17,18] and aldosterone (1953 by Reichstein).[19] These steroid hormones are typically biosynthesized in the respective endocrine glands from circulating steroidal precursors and are released into the blood stream. Being highly lipophilic, they easily penetrate cell membranes of target tissue and bind to nuclear receptors, which regulate expression of specific target genes.

In contrast, a rapid inhibitory action of progesterone on the central nervous system was described in 1941 by Selye.[20] This was the precedent for the direct steroid influence on signal transmission in the brain. Practical consequences of this discovery were the general anesthetics alfaxalone and alfadolone. Closer inspection of the phenomenon in the 1980's showed a fundamentally different mechanism of action.[21–23] Alfaxalone was shown by electrophysiological techniques to potentiate the inhibitory action of γ-aminobutyric acid (GABA) receptors, the major inhibitory ion channels of the central nervous system (CNS).[24–26] Moreover, several steroids such as progesterone, dehydroepiandrosterone (DHEA), pregnenolone and their 5-reduced equivalents, were found to be biosynthesized in the brain, independently of gonadal and adrenal glands.[27–29] Therefore, the term neurosteroids was coined for

steroids with neuromodulatory action, directly synthesized in brain, *de facto* paracrine and autocrine hormones. The broader term neuroactive steroids encompasses all steroidal compounds with neuromodulatory function, irrespective of their origin (e.g. synthetic or from systemic circulation).[30]

Since then, neurosteroids have been found to influence a broad variety of receptors, such as $GABA_A$, glutamate, glycine, σ_1-opioid, nicotinic acetylcholine and serotonin receptors ($5\text{-}HT_3$ subtype), as well as T-type Ca^{2+} channels. In addition to these receptors in the CNS, neuroactive steroids also influence the peripheral nervous system (PNS). Both areas are well covered by several reviews.[31–37]

1.2. Neuroactive Steroids at the NMDA Receptor, Structure and Pharmacology

Some neurosteroids affect glutamate receptors. Glutamate mediates most of the fast excitatory neurotransmission in the CNS, and ca. 80-90% of the neurons in the brain are glutamatergic. Repolarization of membranes during glutamatergic activity may account for as much as 80% of the energy consumption of the brain. Glutamate is the principal neurotransmitter of sensory information, motor coordination, cognition, emotions and memory processes.[38]

The family of glutamate receptors is composed of metabotropic glutamate receptors and ion channels, which form three further subclasses: *N*-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and kainate receptors.

NMDARs and AMPARs are the most abundant glutamate receptors in the CNS, usually colocalised at postsynaptic membranes. AMPARs are Na^+ permeable ligand-gated ion channels, responsible for fast depolarization of glutamatergic postsynaptic neurons. The affinity of AMPARs for glutamate is lower ($EC_{50} \approx 400$ μM), the duration of the AMPAR component of postsynaptic current is short (< 10 ms), but its amplitude is high. In contrast, the more abundant ligand-gated NMDARs are permeable both for Ca^{2+} and Na^+ and have a higher affinity for glutamate ($EC_{50} \approx 1$ μM). Their component of postsynaptic current has a slower onset, lower amplitude and significantly longer decay (up to several hundred ms). In addition, they have a unique property, which distinguishes them from other types of ion channels – they are blocked by Mg^{2+} ions in a voltage-dependent manner. Thus at hyperpolarized membranes (< −50 mV), Mg^{2+} at physiological concentration works as an effective blocker of the channel, which is released as the membrane becomes depolarized through the action of other (e.g. AMPA) receptors.[39]

From the structural point of view, NMDARs are heterotetrameric transmembrane proteins, composed of a pair of GluN1 subunits and a pair of GluN2/GluN3 subunits, which largely differ in various areas of the CNS, as well as during ontogenesis. The structures of the extracellular and transmembrane domains of NMDAR were recently determined by X-ray crystallography independently by the groups of Furukawa and Gouaux (**Figure 1**).[40,41] The main agonist glutamate is binding in the ligand binding domain (LBD) of the GluN2 subunit, while the co-agonist glycine has a binding pocket in the LBD of the GluN1 subunit. The binding of two molecules of both agonists is a necessary condition for opening of the channel, which is another speciality of NMDARs. The significance of glycine binding has remained so far uncertain, since the physiological concentration of glycine is well above its EC_{50}. The pore of the ion channel is the binding site for the already mentioned Mg^{2+} and other voltage-dependent uncompetitive antagonists, such as a model compound MK-801, an anesthetic ketamine or an anti-Alzheimer drug memantine. The NMDAR selective non-competitive antagonist ifenprodil has a binding pocket in the N-terminal domain (ATD) of the GluN2 subunit. Moreover, NMDARs are subject to allosteric inhibition by Zn^{2+} and potentiation by

polyamines (e.g. spermine), both occuring in the ATD of the GluN2 subunit.[39] For a more detailed description of other endo- and exogenous ligands of NMDARs see recent reviews.[39,42]

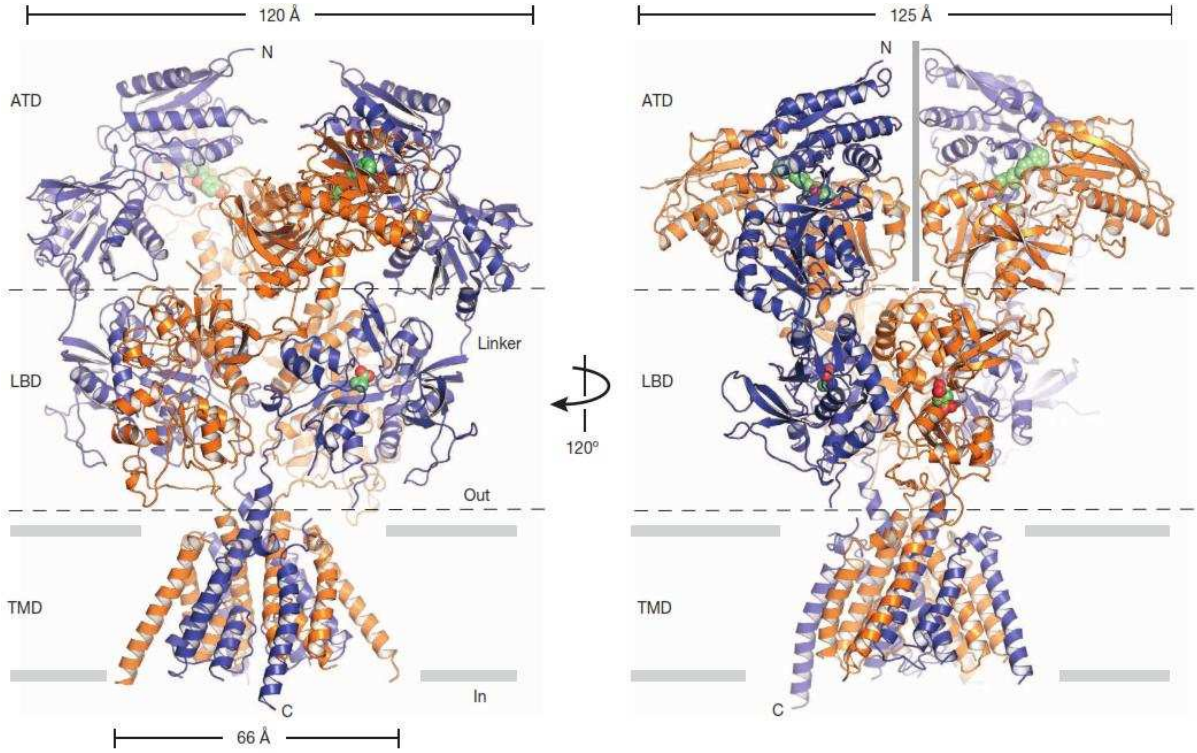
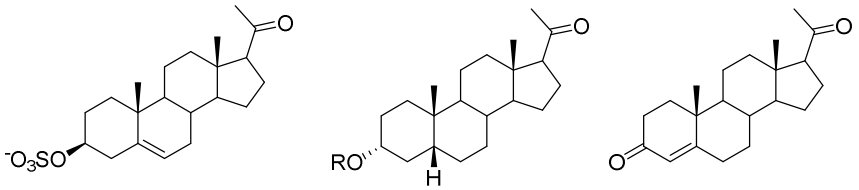


Figure 1: X-ray crystal structure of the NMDAR showing the transmembrane domain (TMD), ligand-binding domain (LBD) and N-terminal domain (ATD). The GluN1 subunit is shown in blue, GluN2B in orange. The right representation shows the structure rotated by 120°. Reproduced without change from Gouaux *et al*.[41]

Several naturally occurring neurosteroids have been shown to affect the activity of NMDARs (**Figure 2**). In contrast to GABA receptors, where uncharged pregnane steroids, for example 3α-hydroxy-5α-pregnan-20-one, also known as allopregnanolone, show nanomolar activites, NMDARs are not effected by uncharged pregnane derivatives.[35] However, sulfatation triggers a marked change of behavior of steroids towards these ion channels.

Pregnenolone sulfate (**1**), a ubiquitous neurosteroid synthesized in the brain from cholesterol, is potentiating NMDA receptors, while inhibiting AMPA, kainate and $GABA_A$ receptors.[43,44] This potentiation is believed to be exerted through allosteric modulation at a binding site distinct from the agonists, noncompetitive antagonists and channel blockers.[35] Experiments with receptors containing a chimeric GluN2 subunit and single point mutation experiments helped to localize the probable binding site of **1** at an extracellular loop between the third and fourth α-helix of the TMD, together with the fourth α-helix of the TMD of GluN2.[44,45]



1 **2**: R = SO_3^- **3**

4: R = $(CO)OCH(NH_2)CH_2CH_2COOH$

Figure 2: Neuroactive steroids

Pregnanolone sulfate (**2**) is a typical member of neurosteroid family showing inhibition of the NMDA receptor.[46] As other 5-reduced pregnane steroids, it is biosynthesized in the brain from progesterone (**3**), and acts similarly by allosteric modulation of the NMDA receptor. Its binding site is, however, different from known agonists, noncompetitive antagonists, channel blockers and also of **1**.[47–49] Pregnanolone sulfate (**2**) is a use-dependent inhibitor, binding only after the channel is opened by agonists. Studies of the binding site suggest a location at subunit GluN2 between the third and fourth α-helix of the TMD.[50] However, the exact shape and position of the neurosteroid binding sites are still unknown.[51]

The NMDA receptor is an interesting pharmacological target because of its functional uniqueness. It is thought to be critical for memory formation and modulation through regulation of synaptic plasticity. The NMDA receptor is directly involved in a phenomenon called long-term potentiation, where a high-frequency pulse triggers a long-lasting augmentation of signals in the connected neurons. The long-term potentiation is hypothesized to be one of the major cellular mechanisms for learning and memory.[39] Overexpression of GluN2B subunits was shown to enhance learning and memory in model animals.[52–54] Pregnenolone sulfate (**1**) has a remarkable ability to enhance mental performance of mice and rats.[55–57]

In contrast, excessive stimulation of glutamate receptors leads to accumulation of intracellular Ca^{2+}, which over time causes irreversible damage and leads ultimately to apoptosis. This phenomenon is called excitotoxicity and is hypothesized to contribute to many neurodegenerative diseases and conditions like stroke, traumatic brain injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and others.[38,39,42] Compounds inhibiting NMDARs may therefore have desirable impact on potential treatment of these conditions. Dissapointingly, most NMDA inhibitors failed in attempted clinical trials because of side effects, with the notable exception of memantine (3,5-dimethyladamantan-1-amine). These failures were ascribed to psychotomimetic effects caused by overinhibition of NMDARs or insufficient ability to reach the target neurons.[39,42] Synthetic neuroactive analogues of **2** were prepared in Chodounská's group and tested for neuroprotective properties.[58–62] Some of these compounds, e.g. pregnanolone glutamate (**4**), show promising *in vitro* and *in vivo* activities. Most importantly, their action appears to be free of psychotomimetic side effects in animal models.[63–66] They are believed to share the same mechanism of action with the native neurosteroid **2**, with improved pharmacological properties.[35]

Steroids active at NMDAR's share some common features. Most importantly, a charged substituent such as sulfate, carboxylic acid or quarternary ammonium salt at C-3 markedly increases their activity.[47,48,51,58] 5β-Reduced neuroactive steroids exert stronger inhibitory effect at NMDARs than 5α-reduced analogs.[47,48] In contrast, the Δ^5-double bond is typical for potentiating neurosteroids, such as **1**. Substitution in positions C-7 and C-11 of **2** are not well tolerated,[60] but substitution at ring D and steroid side chain can lead to more potent inhibition of NMDAR.[62,67,68]

1.3. Nomenclature of Steroids

Since the majority of this work will deal with steroids and their synthetic intermediates, it is useful to summarize briefly the nomenclature rules applying to this class of compounds. Steroids are compounds possessing the skeleton of cyclopenta[*a*]phenanthrene or a skeleton derived therefrom by one or more bond scissions, ring expansions or contractions.[69] The systematic naming conventions are derived from the parent hydrocarbons, the two relevant for this thesis are depicted in **Figure 3**. The basic C19 skeleton **5** is called androstane, the C21 skeleton **6** pregnane. The rings are named A to D

from left to right and the carbon positions are numbered as shown in structure **6**. The absolute stereochemistry is defined by the name of the parent structure for chiral centers at carbons 8, 9, 10, 13 and 14 as shown in the structure of **5**, and for the configuration of the side chain as shown in **6**. Other stereocenters, including the one at C5, have to be declared both in a schematic structure and a name. The stereochemistry of the natural enantiomer can be stressed with the prefix *nat*-. When the rings of steroid are depicted as projections onto the plane of the paper as in **5** and *nat*-**7a**, substituents below the plane of paper are termed α, and above the plane as β. Unknown configurations are denoted with prefix ξ. Thus, pregnanolone (*nat*-**7a**) is systematically named 3α-hydroxy-5β-pregnane-20-one. Descriptors 8β, 9α, 10β, 13β, 14α and 17β can be omitted, since they constitute the natural configuration.

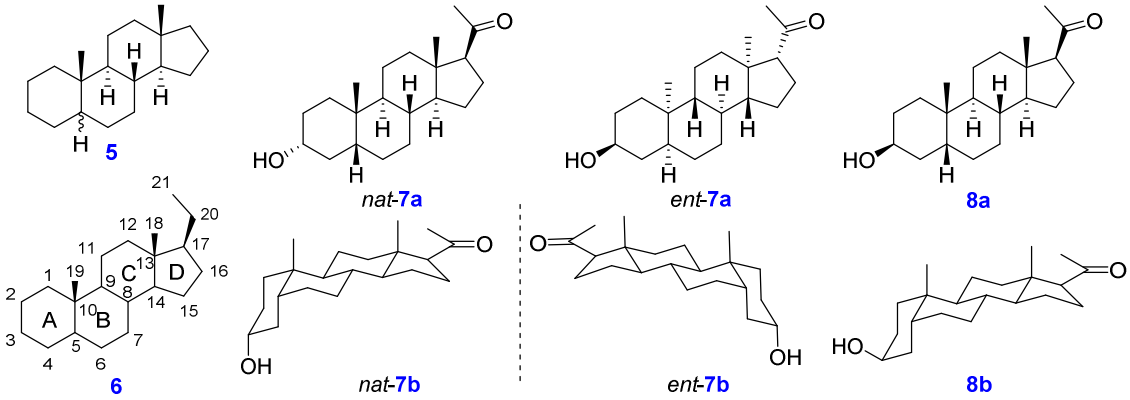


Figure 3: Structure and atom numbering of steroids and their enantiomers

Unnatural enantiomers of steroids are designated by the prefix *ent*-. This implies that **all** stereocenters in the molecule are inverted, no matter whether they are cited separately, what is especially important for relative descriptors α and β, or are implied in the name. For example, the opposite enantiomer of *nat*-**7a** can be named as *ent*-3α-hydroxy-5β-pregnane-20-one (*ent*-**7a**), being the mirror image as can be seen in stereochemical structures *nat*-**7b** and *ent*-**7b**. Inversion of a single stereogenic center leads to a diastereomer – as in 3β-hydroxy-5β-pregnane-20-one (**8**).

Since this thesis deals with the total synthesis of steroids and truncated analogs, it is necessary to define the nomenclature of steroids with an incomplete skeleton (**Figure 4**). Deletion of a methylene group from a steroid is indicated by the prefix nor-, which is preceded by the number of the deleted carbon atom. The remainder of the original steroid numbering is unchanged. The removal of a ring, with substitution at each junction with a hydrogen atom, is indicated by the prefix des-, followed by an italicized capital letter of the missing ring. Finally, fission of a ring, with addition of a hydrogen atom at each terminal group thus created, is indicated by the prefix seco-, with the original steroid numbering retained. Locants preceding the prefix specify the atoms of the deleted bond.[69] The complete and detailed IUPAC nomenclature of steroids is available.[70,71]

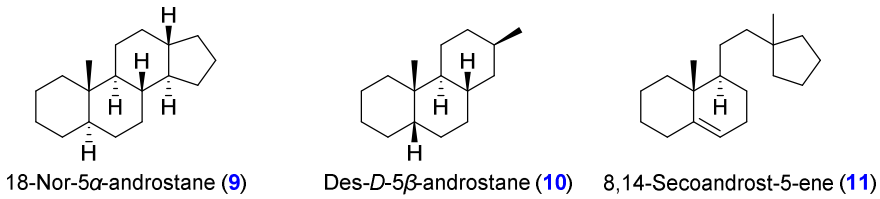


Figure 4: Nomenclature of truncated steroids

1.4. ENANTIOMERS OF NEUROACTIVE STEROIDS

The cell membrane of neurons is a complex environment, composed of a phospholipid bilayer with increased proportion of cholesterol and abundant proteins, including the ion channels mentioned in **Chapter 1.2**. Steroids are lipophilic compounds and as such have a high affinity for the cell membrane. Questions arise whether the effects of neurosteroids are caused by tight binding with the protein structure, blocking of the channel, or are merely a perturbation of the membrane. Some studies suggested localization of the binding site for neurosteroids near to the surface of the cytoplasmic membrane.[44,45] The membrane probably serves as a reservoir for neurosteroids, effectively increasing the concentration in close proximity of the ion channel.[58,72]

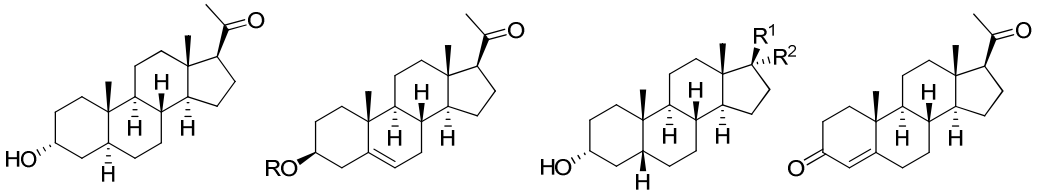
The neurosteroid potentiating binding site for the $GABA_A$ receptor has been recently identified by photoaffinity labeling.[73] The high affinity of neurosteroids for $GABA_A$ receptors in nanomolar range suggests the existence of a defined binding site. This is in contrast with neurosteroids active at the NMDA receptors, displaying activity in micromolar range.[35] It is therefore of interest to distinguish the possible modes of neurosteroid action at the NMDA receptor.

One of the methods to differentiate the specific protein binding from membrane effects is the application of opposite enantiomers of native neurosteroids (*ent*-steroids).[74] It is assumed, that the unnatural enantiomer should exhibit much lower affinity in case of specific binding into a defined pocket in the protein. This process can be compared to fitting a right hand in a left-hand glove. In pharmacology, this concept is known as Pfeiffer's rule: The greater the difference of pharmacological activity between both chiral antipodes, the greater the specificity of the active isomer for the response of the tissue under test.[75,76] In contrast, the environment of cell membranes is fluid and the overall diastereoselective interaction of the chiral substituted diacylglycerols with the substrate will be an average of interaction of all possible mutual orientations. Given that most phospholipids contain only one stereogenic center, the difference of interaction between both diastereomeric pairs will be very low. Therefore, the physicochemical properties and not the absolute configuration will be the main determinant of the behavior of steroids in the cytoplasmic membrane. The experimental support for this hypothesis in steroid-membrane interactions was reviewed by Covey.[74]

In agreement with Pfeiffer's rule, the enantiomers of classical steroid hormones are devoid of activity at nuclear receptors.[77] Racemic steroids usually exhibit 50% effect, which is consistent with the much lower activity of *ent*-steroids. The situation is more complex for the modulation of ligand-gated ion channels by steroids. *ent*-3α-Hydroxy-5α-pregnane-20-one (*ent*-**12**), or *ent*-allopregnanolone, is a significantly weaker potentiator of the $GABA_A$ receptor than *nat*-**12**.[78–80] In contrast, 3α-hydroxy-5β-pregnane-20-one (*nat*-**7**), or pregnanolone, shows a less pronounced difference, both *in vitro* and *in vivo*.[81,82] Interestingly, *ent*-3α-hydroxy-5β-androstan-17-one (*ent*-**13**) shows higher potentiating $GABA_A$ activity than its natural counterpart. It is also worth mentioning that the $GABA_A$ receptor does not discriminate between the enantiomers of inhibitory neurosteroid pregnenolone sulfate (**1**).[83]

Studies of the influence of *ent*-steroids at the NMDA receptor are rarer in the literature. Only *ent*-pregnenolone sulfate (*ent*-**1**) was tested so far and performed as well as its enantiomer *nat*-**1**.[57] In accordance with these results, both enantiomers of **1** were shown to facilitate learning and memory of rats and mice.[57,84] Interestingly, some steroids which are inert to $GABA_A$ or NMDA receptors showed *in vivo* neuroprotective activity. Progesterone (*nat*-**3**), for example, exerts neuroprotective action in a rodent model of traumatic brain injury.[85] The enantiomer *ent*-**3** proved to have identical

neuroprotective properties, but no activity at the progesterone nuclear receptor.[86] The activities are summarized in **Figure 5**.



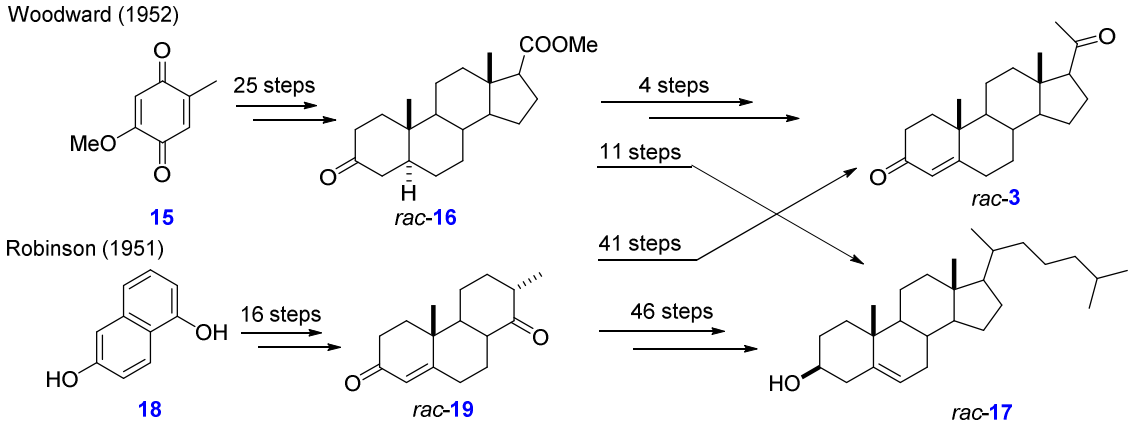
	nat-12	*ent*-12	*nat*-1	*ent*-1	*nat*-7	*ent*-7	*nat*-3	*ent*-3
$GABA_A$	+++	+	- -	- -	++	+	0	n/a
NMDA	0	n/a	++	++	+	n/a	0	n/a

Figure 5: Physiological activities of *ent*-steroids on $GABA_A$ and NMDA receptors

1.5. TOTAL SYNTHESES OF PREGNANE STEROIDS

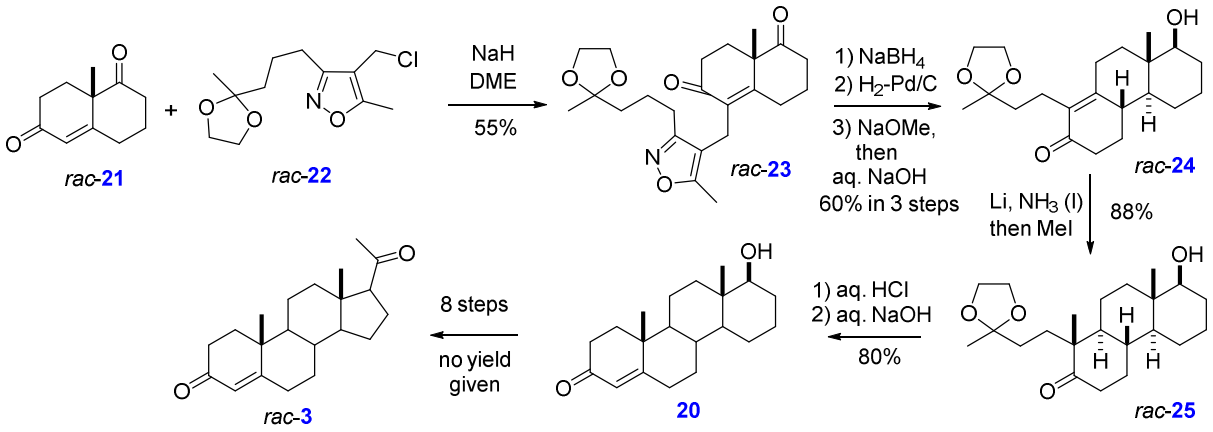
ent-Steroids do not occur in the Nature because of conservative biosynthetic pathways. In mammals, cooperation of squalene monooxygenase and lanosterol synthase leads to the formation of single enantiomer of lanosterol, the precursor of all mammalian steroids. Therefore the only method to obtain *ent*-steroids is total synthesis. In principle, this can be achieved either by preparation of racemic steroids followed by resolution or by enantioselective synthesis. Since the total synthesis of steroids is considered a classic in organic chemistry, many syntheses and successful attempts have been reported in the past 75 years. It is not a goal of this thesis to give detailed and exhausting summary of all past syntheses. The employed strategies were reviewed in numerous monographs and reviews.[77,87–91] Therefore only total syntheses of pregnane steroids – progesterone **3**, pregnenolone **14** and their reduced forms **7**, **8**, and **12** will be reviewed.

The first syntheses of pregnane steroids are intertwined with the "steroid rush" of the 1950's and the race for the first synthesis of cholesterol (**17**).[92] Woodward's famous synthesis of **17** published in 1952 started from hydroquinone **15** and afforded a key intermediate methyl *rac*-3-oxo-etioallocholanate (*rac*-**16**) in 25 steps. This intermediate was converted to *rac*-**3** in 4 steps or to *rac*-**17** in 11 steps. Strategically, the CD rings were constructed first, followed by subsequent annelation of rings B and A; in short CD→BCD→ABCD.[93] Robinson's relay synthesis (1951) started from 1,6-dihydroxynaphthalene **18** and reached pregnenolone *rac*-**14** in 56 steps. This steroid can be either directly oxidized to *rac*-**3**, or continued to *rac*-**17** in 6 steps. The order of ring construction corresponds to BC→ABC→ABCD.[94,95] Both syntheses were linear, but were remarkable milestones in organic synthesis, considering the unavailability of nowadays common structural analysis methods and the early stage of chromatographic techniques.



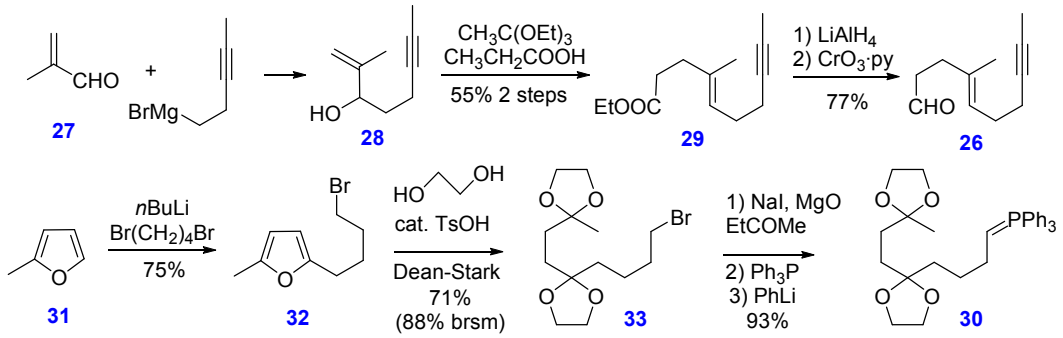
Scheme 1: Woodward's and Robinson's syntheses of *rac*-cholesterol **(***rac*-**17**) and *rac*-progesterone (*rac*-**3**)

Woodward's strategic approach (CD→BCD→ABCD) was followed by Stork in the synthesis of *rac*-**3** via *rac*-17-homotestosterone (*rac*-**20**).[96] Starting from the Wieland-Miescher ketone *rac*-**21** as a precursor for the CD ring system, the alkyl chain **22** was introduced to *rac*-**23** by a thermodynamically controlled alkylation (**Scheme 2**). After two successive reductions, the substrate was prepared for the isoxazole annelation to give tricyclic *rac*-**24**. Importantly, the group found that reduction of the enone by lithium in ammonia followed by direct alkylation with MeI afforded a single diastereomer of *rac*-**25**, which greatly facilitated this and some later syntheses. A deprotection and an intramolecular aldol reaction furnished the target *rac*-**20** in 7 steps from *rac*-**21**. Conversion to *rac*-**3** was possible in 8 steps, although the yields were not stated.



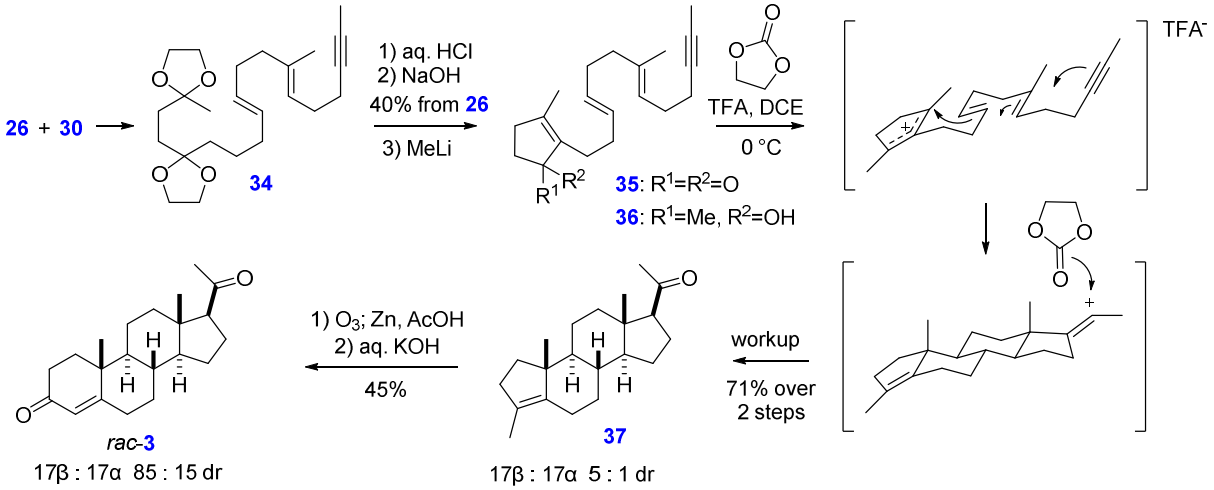
Scheme 2: Stork's synthesis of *rac*-progesterone (*rac*-**3**)

A truly remarkable biomimetic synthesis of *rac*-**3** was published by Johnson *et al.* in 1968 and improved in 1971.[97,98] The core of the synthesis was based on the concept of polyolefinic carbocationic cyclization, developed earlier in the same group. The synthesis itself is highly convergent and the order of ring construction can be summed up as A→ABCD (**Scheme 3**). Fragment **26** is constructed from methacrolein (**27**) by addition of a Grignard reagent, followed by a Johnson-Claisen rearrangement of the resulting alcohol **28** to ester **29**, which underwent a two-step conversion to aldehyde **26**. Wittig reagent **30** was prepared from 2-methylfuran (**31**) by *ortho*-lithiation and alkylation. An acid-catalyzed opening of the furan ring of **32** gave diketal **33**, which was converted to the phosphorane **30** in three steps.



Scheme 3: Johnson's synthesis of *rac*-progesterone (*rac*-**3**)

The fragments **26** and **30** were coupled by Wittig reaction to afford selectively the *E*-alkene **34** (97:3 *E*:*Z*, **Scheme 4**). Deprotection of **34** followed by an aldol condensation gave cyclopentenone **35**, which was methylated to furnish an unstable tertiary alcohol *rac*-**36**. An acid-promoted cyclization gave rise to the tetracyclic ring system *rac*-**37** in high yield, forming five new stereocenters in a single cascade reaction. Intermediate *rac*-**37** was ozonolyzed and cyclized to *rac*-**3** mixed with its 17-epimer, which was separated by crystallization. The longest linear sequence consisted of 11 steps and the overall yield of *rac*-**3** was 5%. Modified procedures were later published by different groups.[99–101]

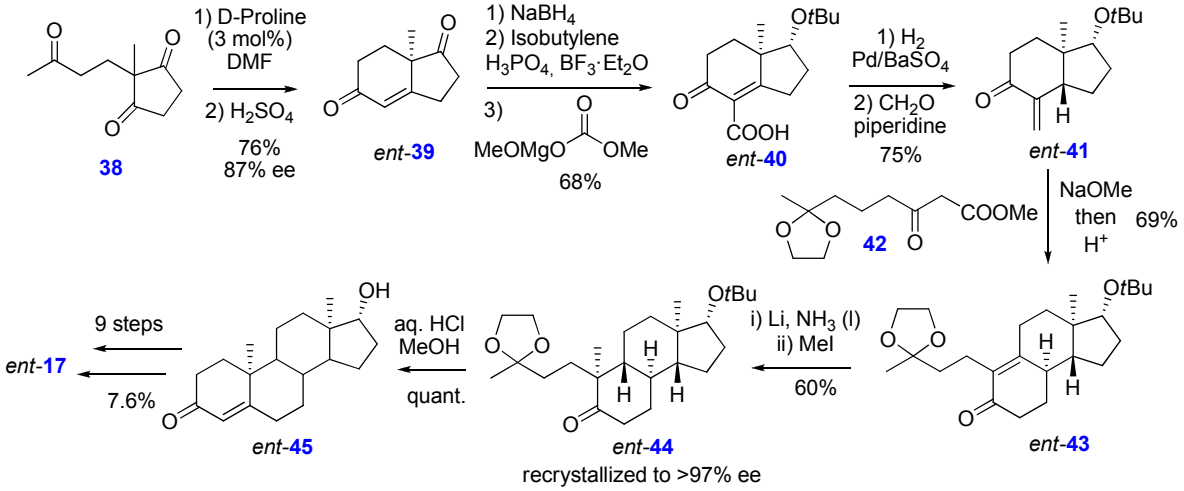


Scheme 4: Johnson's total synthesis of *rac*-progesterone (*rac*-**3**)

Multiple syntheses were based on the strategy CD→BCD→ABCD to synthesize androstane derivatives, which could be converted to the pregnane skeleton by introduction of the side chain. This approach was initially developed at Hoffmann-La Roche as an approach to 19-norsteroids.[88,102,103] Most importantly, one of their syntheses constituted the first synthesis of a steroid with catalytic asymmetric generation of stereocenters. The first chiral center was established by what is now known as Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction, the catalytic asymmetric variant of Robinson annulation (*vide infra*).[104–106] This synthetic approach was later chosen by Ohloff's and Rychnovsky's group to target *ent*-steroids.[107,108]

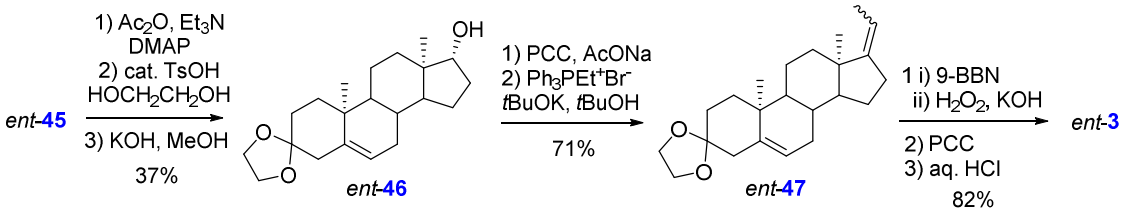
Triketone **38** was cyclized in the above mentioned HPESW reaction with subsequent acidic dehydration of the aldol to give Hajos-Parrish ketone *ent*-**39** with 87% ee (**Scheme 5**). A selective borohydride reduction of the saturated ketone, followed by protection and reaction with the Stiles' reagent afforded acid *ent*-**40** in good overall yield. Hydrogenation established the *trans*-CD configuration and Mannich condensation with formaldehyde yielded enone *ent*-**41**. The Robinson annulation with **42** formed ring B in the tricyclic intermediate *ent*-**43**. Here, Rychnovsky's group

diverted from the Hoffmann-La Roche synthesis and successfully applied Stork's method for the introduction of the 19-methyl group (*vide supra*). The resulting ketone *ent*-**44** was recrystallized to >97% ee and converted to *ent*-testosterone (*ent*-**45**) by treatment with methanolic HCl. The overall yield of *ent*-**45** was 16% over 10 steps from triketone **38**. The conversion to *ent*-cholesterol (*ent*-**17**) took another 9 steps in 7.6% yield from *ent*-**45**.



Scheme 5: Rychnovsky's total synthesis of *ent*-testosterone (*ent*-**45**) and *ent*-cholesterol (*ent*-**17**)

The synthesis of pregnane *ent*-steroids from a common precursor *ent*-**45** was studied in detail by Covey's group.[109] Protection of the enone moiety of *ent*-**45** gave rise to alcohol *ent*-**46**, which was oxidized and converted to ethylidene derivative *ent*-**47** by a Wittig reaction. A hydroboration-oxidation sequence with 9-BBN was regioselective for the side-chain double bond and installed the correct 17β-stereochemistry. Oxidation of the resulting alcohol followed by acidic deprotection afforded *ent*-progesterone (*ent*-**3**) in 7 steps and 21% overall yield from *ent*-**45**. *ent*-Testosterone (*ent*-**45**) served as a precursor to other pregnane derivatives employing a similar methodology: *ent*-Allopregnanolone (*ent*-**12**) was prepared in 6 steps and 10% yield, *ent*-pregnenolone (*ent*-**14**) in 8 steps and 23% yield and *ent*-pregnanolone (*ent*-**7**) was elaborated in 9 steps with 12% overall yield from *ent*-**45**.[83,110]

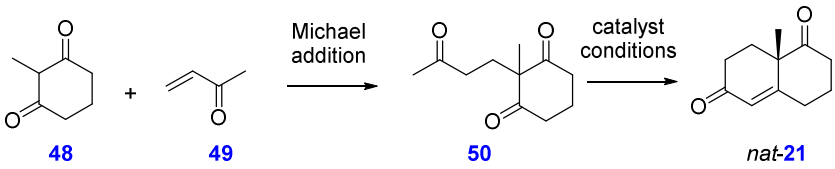


Scheme 6: Covey's synthesis of *ent*-progesterone (*ent*-**3**)

1.6. Asymmetric Robinson Annulation

Modern approaches to the total synthesis of optically active molecules preferably apply either starting materials from the chiral pool, or catalytic asymmetric methods. In such an arrangement, one molecule of the catalyst, which is derived from either the chiral pool or from resolution, gives rise to multiple chiral molecules of the product. In an ideal system, the catalyst should be readily available and cheap, the catalyst loading should be low, and the reaction should be scalable with minimal side products and waste.

With respect to total syntheses of terpenoid natural products, the Robinson annulation is one of the well established and reliable methods to construct six-membered rings. The formation of bicyclic hydrindane **39** or decaline **21** systems is the cornerstone of several successful total syntheses of steroids (*vide supra*). The Wieland-Miescher ketone **21** is easily available from 2-methyl-cyclohexane-1,3-dione (**48**) and methyl vinyl ketone (**49**), both bulk chemicals, by an asymmetric Robinson annulation (**Scheme 7**). It was in fact this reaction, which demonstrated the power of asymmetric organocatalysis. Nowadays, the reaction is named after its inventors Hajos, Parrish (both from Hoffmann-La Roche),[104–106] and Eder, Sauer, Wiechert (all from Schering AG),[111] who have discovered it independently. In the past 40 years, the reaction was optimized several times with respect to yield and enantiomeric excess.[112,113]



Scheme 7: Hajos-Parrish-Eder-Sauer-Wiechert reaction

The original catalyst L-proline (**51**) gave the Wieland-Miescher ketone (*nat*-**21**) from achiral triketone **50** in 81% yield and 70% optical purity (**Figure 6**).[114] L-Proline (30 mol%) was also shown to catalyze the preceding Michael addition step to afford *nat*-**21** in 49% yield and 76% ee in a one-pot sequence by Barbas.[115]

Other proline-derived catalysts were studied with inferior results. The necessity of pyrrolidine and carboxylic acid functionality was postulated for an effective catalyst.[115] Several amino acid catalysts were screened, but most of the substitutions brought no improvement over the original proline, with the notable exception of cispentacin **52**.[116] Diamines **53**-**55** were reported to be very efficient catalysts as salts of a strong acid.[117–121]

One of the highest enantioselectivities for the synthesis of **21** was achieved with isophthalamide **56**.[122] Amides of proline such as **57**-**60** constitute one of the most effective catalyst class employed in asymmetric Robinson annulations.[123–125] Notably, BINAM derived amide **59** allows for very low catalyst loading under solvent-free conditions and afforded **21** in excellent yield and enantiomeric excess.[126–129] Finally, chiral Brønsted acid **61** can also efficiently catalyze the formation of **21**.[130]

Importantly, **21** can be prepared in enantiopure form by fractional crystallization from Et_2O at −20 °C with seeding by enantiopure material,[114] or from Et_2O/EtOAc at −70 °C by spontaneous resolution.[131] Although asymmetric Robinson annulations can be conducted directly from substrates **48** and **49**,[115] the combined yield is better when the process is conducted stepwise.[114,128] The triketone **50** is most efficiently prepared by triethylamine-catalyzed Michael addition.[128]

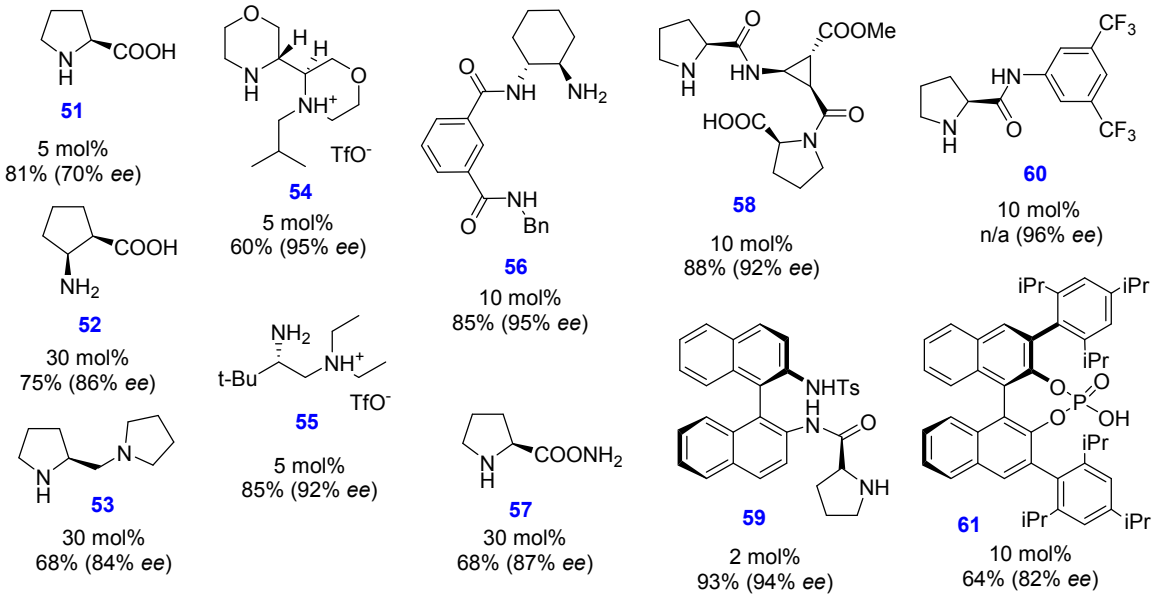


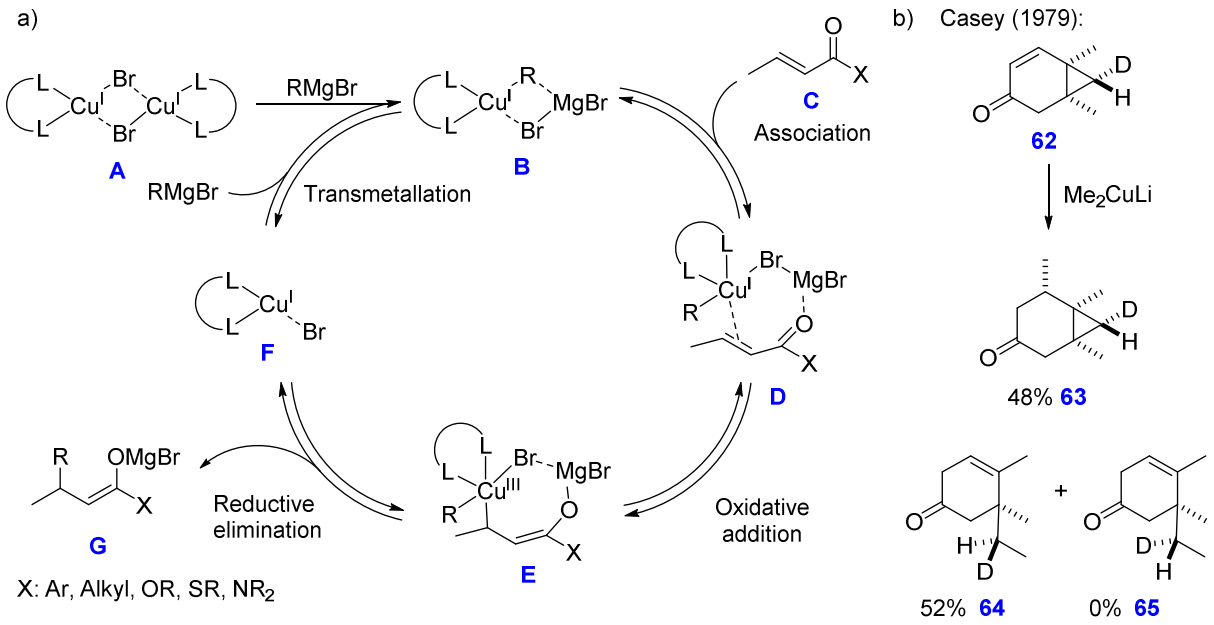
Figure 6: Chiral catalysts for HPESW reaction with the respective catalyst loading, yield of **21** and enantioselectivity achieved.

1.7. Copper-catalyzed Conjugate Addition of Grignard Reagents to Enones

Conjugate additions of carbon nucleophiles are among the most important C-C bond forming reactions. To promote the conjugate addition mode, soft nucleophiles are often used. In contrast, hard carbon nucleophiles, such as organolithium and organomagnesium compounds, often prefer 1,2-addition. The conjugate addition of non-stabilized carbon nucleophiles is a domain of transition metal catalysis with copper being the most investigated element in this respect,[132] the others being rhodium,[133–136] palladium,[133,137,138] and nickel.[139,140]

The history of organocopper chemistry can be backtracked to preparation of phenylcopper by Reich,[141] later expanded by preparation of ethylcopper by Gilman and Straley,[142] who have demonstrated the applicability of organocopper reagents in organic chemistry. In 1941, Kharash and Tawney described the effect of catalytic copper(I) halides on the outcome of conjugate addition (CA) of Grignard reagents to enones.[143] However, it was the introduction of organocuprates by Gilman,[144] followed by works of House[145,146] and Corey,[147] which spreaded the use of organocopper reagents in organic synthesis.

Stoichiometric homoalkyl cuprates suffer from poor atom economy, with one of the alkyl group being lost in the unreactive monoalkylcopper. This issue was alleviated with the introduction of non-transferable groups, such as thiolates, alkynyl or cyano residues.[148,149] Another, perhaps more appealing option is catalysis by copper(I) species, which wastes only substoichiometric amounts of the potentially valuable organometallic reagent. Moreover, it opens a way to effective asymmetric variants of this transformation (**Scheme 8**).[132,148,150–152] This introduction concentrates only on the aspect of diastereoselectivity of the copper-catalyzed CA. It is anticipated that the catalytic cycle doesn't differ significantly for substrate- and reagent-controlled variants and it is based on the same mechanistic foundation as the stoichiometric addition of organocuprates.



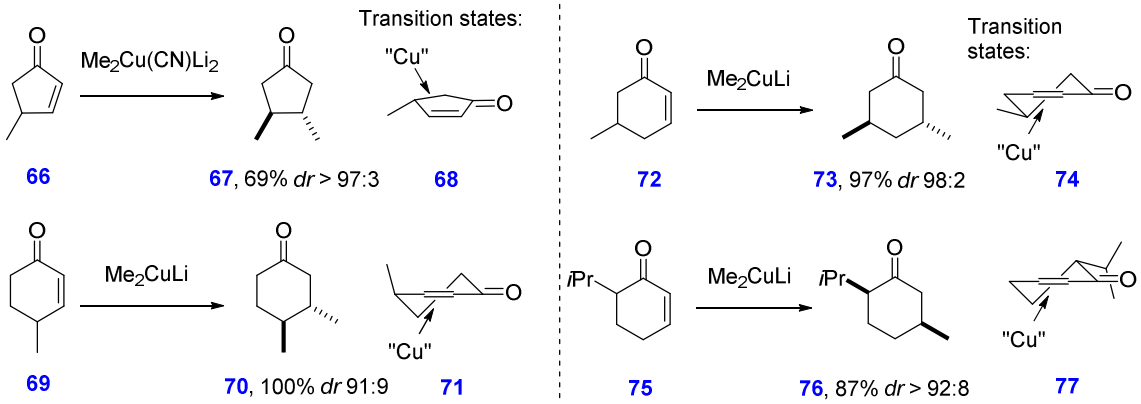
Scheme 8: a) Catalytic cycle of copper(I) catalyzed CA, **b)** Casey's experiment[153]

The cycle begins with transmetallation of the dimeric complex **A** to generate the catalytically active species **B**. The dimer **A** with the Josiphos ligand was isolated and characterized by X-ray crystallography by Feringa *et al.* and the structure of **B** was supported by a detailed NMR study.[154] Coordination of the organometallic complex **B** to α,β-unsaturated carbonyl compound **C** is facilitated by the oxophilic magnesium ion, thus anchoring the copper complex at the C-C double bond through a halogen bridge. Similar bridging effects were described for sulfonamides in Cu-catalyzed CA of organozincs.[155] Oxidative addition of Cu^{I} from the π-complex **D** results in the formation of Cu^{III} σ-complex **E**. A rapid equilibrium occurs between these species, which is supported by *cis-trans* isomerisation of the double bond of (*Z*)-enones during the reaction course.[154] Reductive elimination of Cu^{III} from σ-complex **E** leads to irreversible formation of magnesium enolate g and released Cu^{I}-catalyst **F**. This step is rate-determining for the whole catalytic cycle.[153] Thermodynamic stabilization of complex **E** in the equilibrium **D**/**E** can be achieved by using soft donor ligands (e.g. phosphines), while the kinetic lability in the reductive elimination step is mostly dependent on the geometry of **E**.[154] A hypothetical SET pathway was originally proposed by House,[156,157] but was later disproved in an elegant study by Casey,[158] demonstrating stereospecificity in the vinylic cyclopropane ring-opening during the course of the reaction (**Scheme 8b**).[153]

In principle, all organometallics in which the metal is less electronegative than copper and all organometallic species of similar electronegativity, but with weaker carbon-metal bonds, are potential candidates for transmetalation. Thus, besides organolithiums and Grignard reagents, reaction conditions have been found for transmetalation of organoboron, aluminum, zinc, tin, lead, tellurium, titanium, manganese, zirconium and samarium compounds.[150] The central copper atom can accommodate for variety of ligands: Common are amines, phosphines, phosphoramidites and more recently also NHC ligands, which exhibit a significant accelerating effect and form the basis for asymmetric copper-catalyzed CA.[132] However, no extra ligand is necessary for substrate-controlled CA in more polar solvents such as THF in contrast to Et_2O, MTBE and CH_2Cl_2. LiCl has also been shown to be an efficient cocatalyst, forming a soluble Li_2CuXCl_2 complex in THF.[159] The

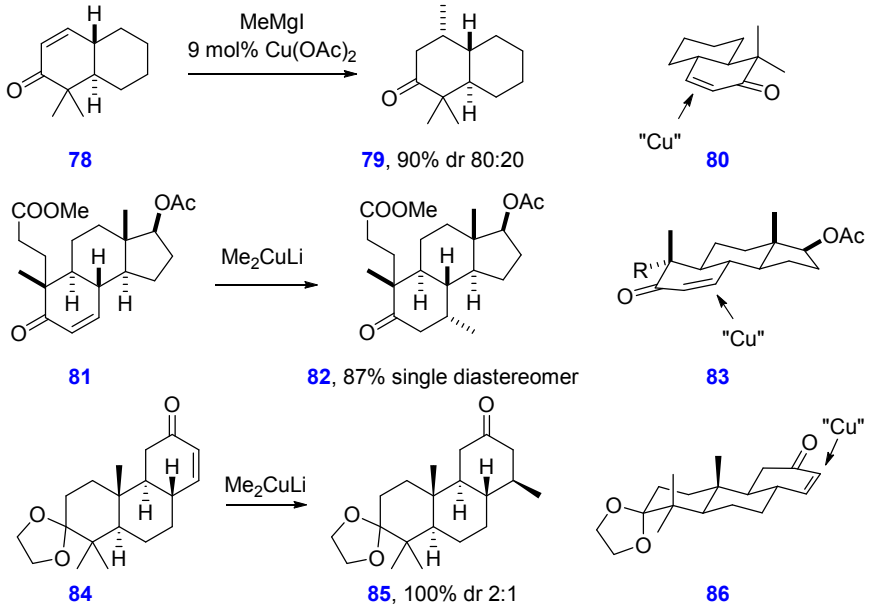
regioselectivity of the addition seems to be dependent on the solubility of the active copper species rather than on the copper source.[146,160]

A distinct advantage of the Cu-catalyzed CA is its generally predictable diastereoselectivity.[150,161,162] The addition of organocuprates to a number of chiral cyclic enones proceeds with high level of stereoselectivity, owing to the existence of a single preferred reactive conformation (**Scheme 9**).[150] Good to excellent *trans*-diastereoselectivity can be reached in 4-substituted cyclopentenones **66** and 4- or 5-substituted cyclohexenones **69** or **72** respectively. In contrast, 6-substituted cyclohexenones **75** give *cis*-adduct **76**.[163–167]



Scheme 9: Diastereoselectivity of Cu-catalyzed CA in monocyclic enones

In more complex fused carbocycles, the level of diastereoselectivity depends on the superposition of all substituent effects (**Scheme 10**). For example, cuprate attacks less hindered α-face in the catalyzed addition of MeMgI to octalone **78**, avoiding a steric clash with the axial methyl group in **80**.[168] A similar selectivity was observed *en route* to 7-substituted androstane analogues during alkylation of enone **81**.[169] On the other hand, the stereoselectivity was found to be surprisingly low for the cuprate addition to decahydrophenanthrenone **84** in the synthesis of (+)-2-deoxyphytocassane A.[170]



Scheme 10: Diastereoselectivity of Cu-catalyzed CA in polycyclic enones

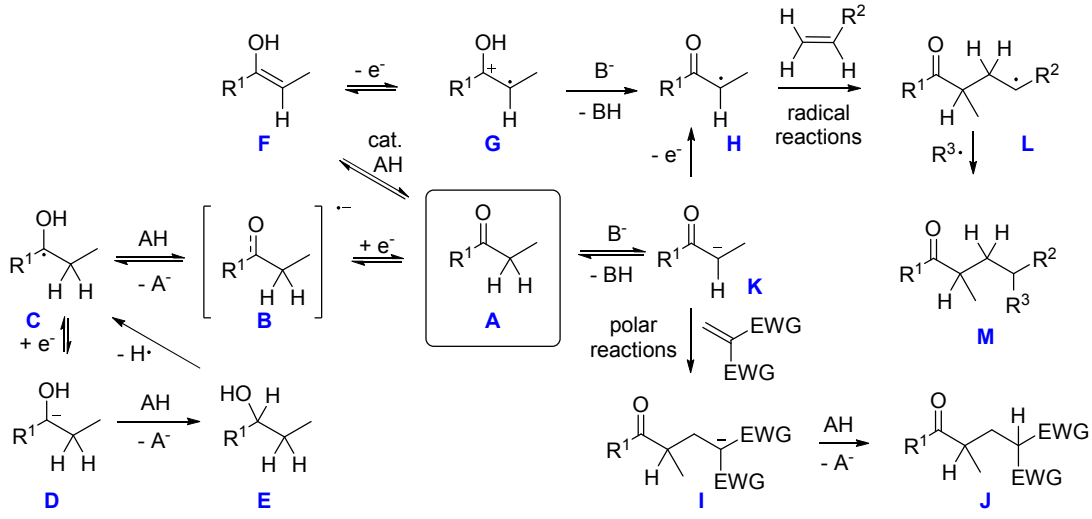
1.8. Redox Processes at the Carbonyl Group

Organic synthesis relies upon reactive intermediates to achieve selective synthetic transformations. Frequently, these transformations include heterolytic processes, which operate with charged species – anions and cations. In contrast, homolytic cleavage of chemical bonds gives rise to radicals, with reactivity different from ions. Switching between these reactive intermediates in one process can lead to an advantageous reactivity pattern, which shares the better of both reactive species.

Charged species and radicals can be interconverted by single electron transfer (SET).[171] These transitions are illustrated for a general carbonyl group **A** (**Scheme 11**). Both neutral and charged species can undergo SET processes.

Direct single electron reduction of **A** is common and leads to a radical anion **B**. Species **B** is a known intermediate in dissolving metal reductions (**A**→**E**), acyloin condensation and pinacol coupling, among others. In this process, alkali metals or SmI_2 are usually used as reductants, because of the need for high reduction potential.[172] Alkyl- or arylhalogen bonds are reducible to the respective carbanions by super-electron-donors such as tetrakis(dimethylamino)ethylene (not shown).[173]

In contrast to reduction **A**→**B**, the carbonyl group itself is quite stable to oxidation. An enol form **F** undergoes more facile single electron oxidation to a radical cation **G**, which rapidly loses the acidic proton, leading to a neutral α-keto radical **H**. Ceric ammonium nitrate (CAN) is an archetypal reagent for this transformation,[174–176] while $Mn(OAc)_3$ is frequently employed in SET oxidation of stabilized enols.[177–181]



Scheme 11: Redox interconversion of carbonyl compound-derived reactive species and their transformations

Deprotonation of the carbonyl compound **A** to enolate **K** leads to an increase of the electron density of the system and therefore its nucleophilicity. Enolate **K** can participate in a multitude of polar reactions, here the Michael addition is depicted as an example (**K**→**J**). Anions can tranfer one electron to a suitable oxidizing agent and thus generate radicals (**K**→**H**), which can then undergo a typical radical reaction. An addition to a double bond (**H**→**L**), followed by an elimination of radical or a recombination (**L**→**M**) is shown as an example. Importantly, this constitutes a method to switch the reactivity of the intermediate, since the radicals and the anions can be viewed as orthogonal reactive species.

Enolates **K** can be oxidized to α-carbonyl radicals **H** by a variety of reagents. SET oxidants can be divided according to Marcus theory to inner- and outer-sphere reagents. Inner-sphere reagents react through a bond formation with the substrate (e.g. **K**), followed by a homolysis of the said bond. Among the more commonly used inner-sphere oxidants of enolates **K** are transition metals in higher oxidation state: Cu(II) salts, Fe(III) salts, Ti(IV) and iodine compounds.[171,174,177,182–185] In contrast to these stand the outer-sphere reagents, where the SET occurs through space (solvent). Anodic oxidation can be employed in this type of reaction.[182] Ferrocenium salts can be used as distinct outer sphere SET oxidants of **K**.[186–190] They are water-soluble intensively blue crystalline non-hygroscopic solids, whereas the reduced ferrocene is orange-colored, highly lipophilic compound soluble in organic solvents, which facilitates their separation from other organic material. Importantly, the redox properties of the ferrocene/ferrocenium couple can be fine-tuned by functionalization of the cyclopentadienyl ring.[191,192]

The synthetic potential of ferrocenium salts has been extensively studied by Jahn *et al*. Among the areas explored are tandem Michael addition-radical cyclizations,[190,193–198] α-oxygenations of carbonyl functions,[189,199] and oxidative homocoupling of enolates.[200] Enantioselective oxidative homocoupling of titanium enolates was studied in the group of Schäfer.[201] It is noteworthy that ferrocenium salts can be employed as a catalytic oxidant with stoichiometric amount of 2,2,6,6-tetramethyl-*N*-oxopiperidinium salts, which generate *in situ* a persistent radical TEMPO.[193]

The synthetic power of these transformations has been demonstrated in several syntheses of natural products (**Figure 7**). Jahn's group has applied the methodology to the total synthesis of monoterpene (±)-dihydronepetalactone (**87**) and 15-F_{2t}-isoprostane (**88**).[202–204] Theodorakis *et al*. have used TEMPO/Ferrocenium couple for the radical cyclization of the ring C of (−)-fusariasetin A (**89**).[205] The stereoselective oxidative dimerization of a ketone enolate mediated by ferrocenium salt was reported by Shair *et al*. in the total synthesis of lomaiviticin A aglycon precursor **90**.[206,207] Finally, the intramolecular cyclization of a seven-membered ring was performed by the Li's group in the synthesis of (+)-subincanadine F (**91**).[208] Baran *et al*. have used a diastereoselective oxidative cyclization mediated by ferrocenium hexafluorophosphate in the synthesis of the analgesic (*S*)-ketorolac (**92**).[209]

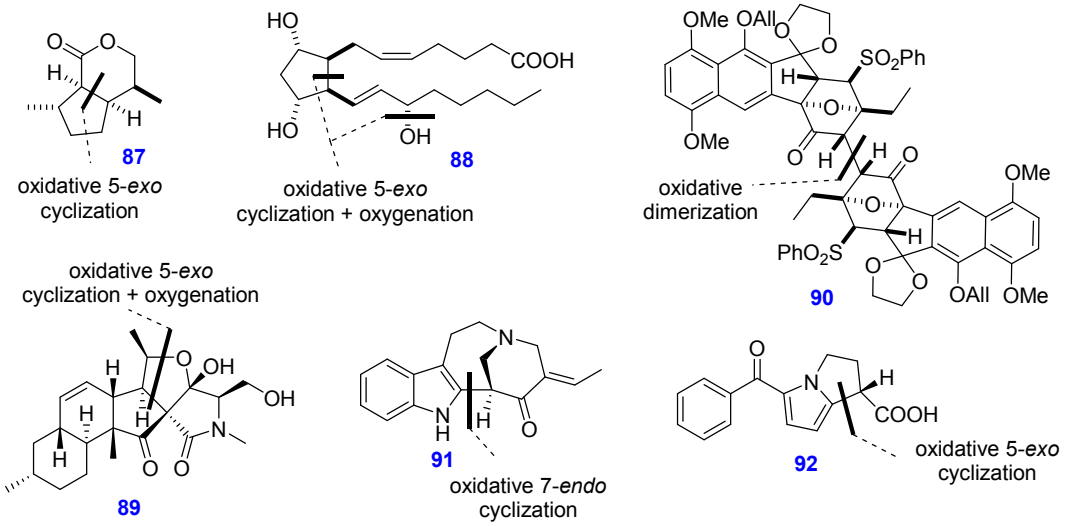
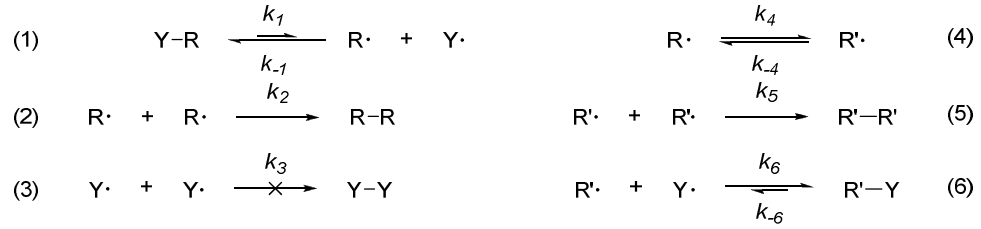


Figure 7: Applications of ferrocenium salts in total syntheses

1.9. THE PERSISTENT RADICAL EFFECT

It has been noted throughout history that radical reactions involving both transient and persistent species sometimes lead to unusually selective and high-yielding cross-coupling reaction of these radicals.[210] The first to observe this phenomenon was probably Bachmann *et al.* in 1936,[211] who noticed a remarkable effectivity in thermolysis-recombination of diphenylmethyl (transient) and triphenylmethyl (persistent) radicals. It was not until 1986, when Fischer and Ingold described the mechanistic rationale of the phenomenon and Finke coined the term persistent radical effect (PRE).[212–214] A simplified kinetic scheme of reactions is shown in **Scheme 12**.

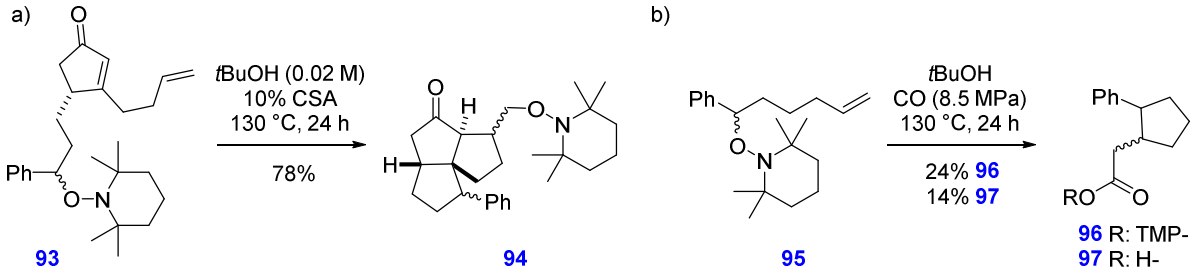
Typically, a homolytic cleavage gives rise to a transient radical R• and a persistent radical Y• (eq. 1). The back-reaction should be faster for the PRE to be operative ($k_1<k_{-1}$), otherwise the rise in the concentration of R• would lead to a product R-R (eq. 2) and accumulation of Y•. This process occurs anyway to a small extent in the beginning of the reaction, resulting in a rapidly rising concentration of the persistent radical Y•, which does not deplete by dimerization (eq. 3). An excess of Y• effectively suppresses the R• dimerization (eq. 2) by accelerating the unproductive back-reaction (eq. 1). If radical R• can undergo a rearrangement, intramolecular hydrogen abstraction, or perhaps a cyclization to radical R'• (eq. 4), the same rules apply for the latter, leading to the homo- or hetero-coupled products (eqs. 5, 6). If the rate of homolytic cleavage of RY exceeds that of R'Y ($k_1>k_{-6}$), the situation results in selective accumulation of the product R'Y in the reaction mixture.



Scheme 12: The persistent radical effect

Strikingly, this may also enable a productive channel for a thermodynamically less stable radical R'• if the kinetic conditions ($k_1>k_{-6}$) are favorable. The most significant applications were found in polymer chemistry in nitroxide mediated polymerization and atom transfer radical polymerization, where the PRE is used to achieve polymers with low molecular weight dispersity.[210]

Besides being a mechanistic curiosity, the PRE has been used only sporadically in organic synthesis of low molecular weight targets. Notable exceptions are copper-catalyzed halogen transfer, radical reactions in the Barton nitrite reaction and reactions involving homolytic cleavage of weak organometallic bonds of transition metals.[210] The thermolysis of nitroxide adducts is a powerful method in polymer chemistry, but remains underinvestigated in the field of organic synthesis. Studer *et al.* have explored its synthetic potential in connection with common radical cyclizations (**Scheme 13**).[213] To demonstrate the scope of this transformation, cyclopentenone **93** was transformed to tricyclic **94** in a domino reaction consisting of two consecutive 5-*exo* radical cyclizations.[215] The same laboratory later demonstrated a possibility of CO incorporation during the sequence.[216]



Scheme 13: Radical cyclizations mediated by the PRE

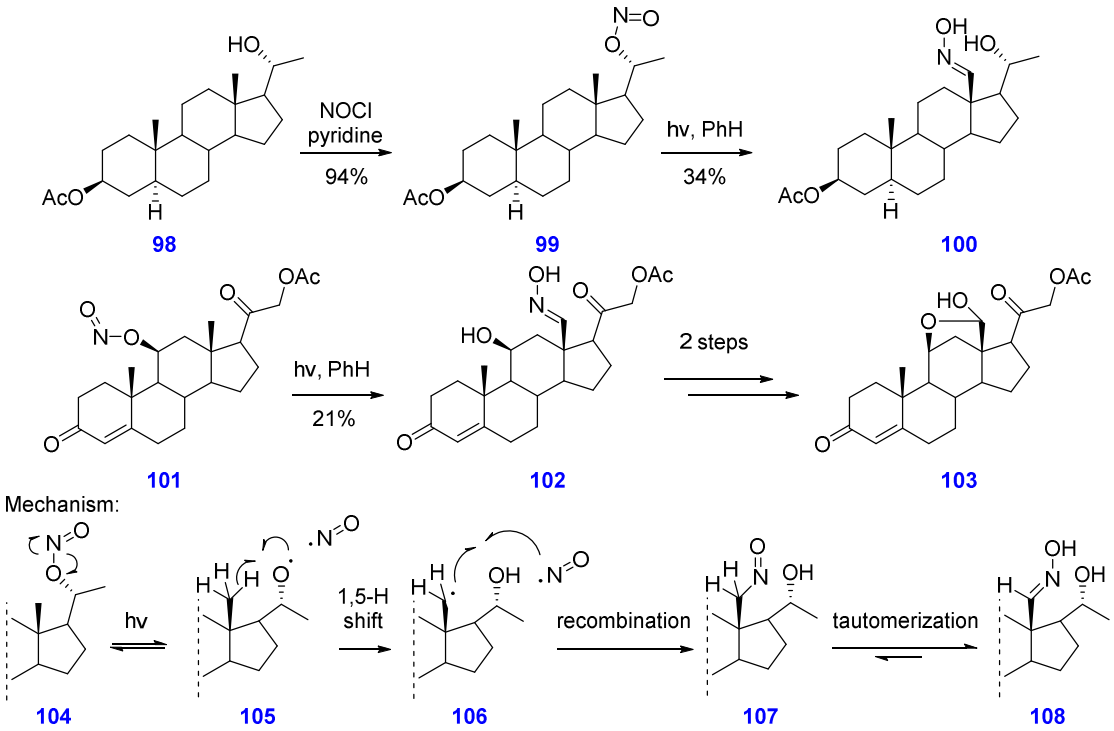
1.10. Deuterium Labeling in Metabolically Stable Positions of Steroids

Considerable effort has been invested into synthetic modifications of native neurosteroids, leading to more effective ligands for membrane receptors. Some of them have shown interesting *in vivo* activity in animal models of diseases. For further development of lead compounds toward possible clinical trials, it is necessary to study their pharmacokinetic properties and metabolism. For this purpose, mass spectrometry and especially the stable isotope dilution LC-MS/MS is the method of choice.[217–219] It combines the extreme sensitivity of mass spectrometric detection with the selectivity of HPLC separation and the possibility of monitoring a specific fragmentation pattern in the MS/MS mode. The limitations of this method are the cost of instrumentation and the availability of isotopically labeled compounds. The tracers should differ from the native compound by 2-4 mass units and the isotope labeling should be introduced with high isotopic purity at metabolically and chemically stable sites.

The most commonly employed nuclei for stable isotopic labeling are ^{2}H and ^{13}C. The incorporation of ^{13}C nuclei into steroids has the advantage of very good chemical and metabolic stability, but is outweighed by the need for breaking and reforming of C-C bonds. Therefore, it is usually only feasible in the last steps of total synthesis.[220,221] Deuterium reagents tend to be more accessible and economical, especially where simple acidobasic equilibrium can introduce deuterium from D_2O. The condition of chemical and metabolic stability, however, excludes positions alpha to existing hydroxy or keto groups, which are the most accessible positions for deuterium exchange. However, these groups may serve as reactive handles at the steroid core and be removed after introduction of the stable isotope.[222] Unfortunately, the parent oxo or hydroxy steroids are limited to a few available positions at the steroid core.

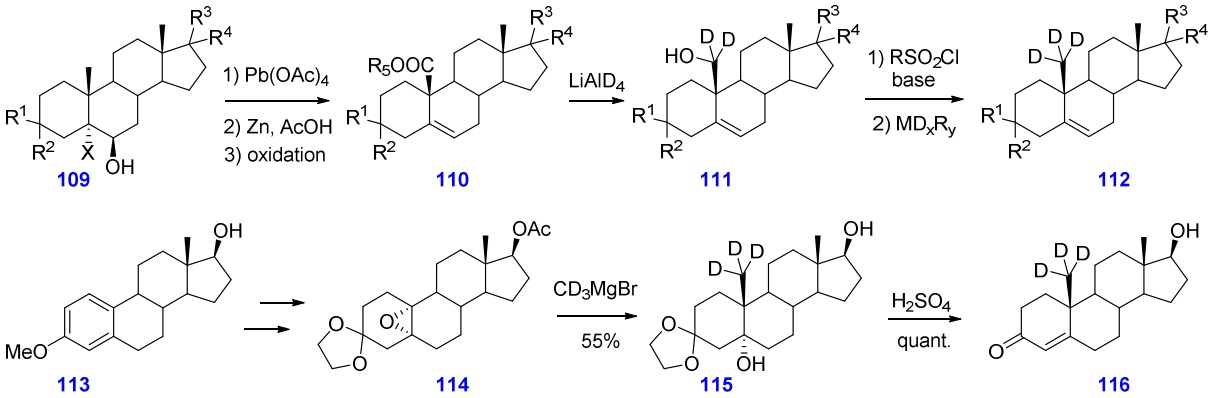
From the point of metabolic stability, angular methyl groups are almost ideal targets for stable isotope labeling. Functionalization of the methyl group poses a challenging synthetic problem, which was nevertheless solved by utilization of remote functionalization strategies. An important precedent was set by Barton in the early 1960's,[223,224] which was successfully employed in the synthesis of aldosterone acetate (**103**).[225] The free hydroxyl group of **98** was esterified with nitrosyl chloride and the resulting nitrite **99** was irradiated with mercury lamp to give oxime **100** (**Scheme 14**). The mechanism of the reaction is as follows: nitrite ester **104** is homolyzed by UV irradiation to give *O*-centered radical **105** and a persistent radical – nitric oxide. Oxyl radical **105** subsequently undergoes a 1,5-hydrogen atom shift to afford thermodynamically more stable *C*-centered radical **106**, which rapidly couples with nitric oxide. Tautomerization of nitrosoalcohol **107** to oxime **108** completes the transformation. The reactions perform well in rigid systems, where the *O*-centered radical **105** is conformationally locked in proximity of the hydrogen atom to be abstracted. The PRE (*vide supra*) is operative here and contributes to the high selectivity of the reaction.[210]

Many variants of this reaction were later introduced, where the nitrite ester was replaced by *in situ* generated labile oxygen-heteroatom bond. Lead tetraacetate and bis(acetoxy)iodobenzene are probably the most used reagents for this purpose. In addition, the *C*-centered radical **106** can undergo reaction with iodine, bromotrichloromethane or tetrachloromethane to afford the respective halogenides, or can even undergo a cascade cyclization to a suitably positioned double bond.[226–228] These variations proceed under milder conditions and often give higher yields than the original procedure.



Scheme 14: Barton reaction and the synthesis of aldosterone acetate (**103**).

Most known methods for introduction of deuterium atoms into position C-19 are based on a variation of the Barton reaction (**Scheme 15**).[229–231] The axial 6β-hydroxy group of halohydrin **109** served as a directing group for this process and zinc reduction reinstated the Δ^5-double bond. Oxidation to carboxy derivative **110**, followed by reduction with a deuterated reagent provided primary dideuteroalcohol **111**, which was transformed into leaving group reducible by alkali metal deuterides. The most comprehensive study was performed by Kirk *et al.*, who prepared [18-$^2H_3$]-progesterone and [19-$^2H_3$]-progesterone by reduction of the corresponding dideutero tosylates of **111** with $LiEt_3BD$.[232] Černý *et al.* prepared [19-$^2H_3$]-pregnenolone by reduction of the mesylate of **111** with Zn in presence of NaI and D_2O.[233] A different approach was chosen by Kasuya *et al.*, who introduced a perdeuterated C-19 methyl group by a regio- and stereoselective ring opening of 4,10-epoxide **114** by trideuteromethylmagnesium iodide (**Scheme 15**).[234,235] Finally, *ent*-[19-$^2H_3$]-testosterone **116** was prepared by Covey *et al.* by total synthesis.[236] None of the 18-d_3 and 19-d_3 steroids were prepared in the 5β-series.



Scheme 15: Preparation of 19-d_3 steroids **112**.

2. AIMS OF THE WORK

Neuroactive steroids are an important class of isoprenoid compounds, affecting the function of mammalian CNS. Their action at NMDA receptors is thought to affect fundamental processes such as memory formation, cognitive functions and neuroprotection. The exact mechanism of action of neuroactive steroids at NMDA receptors is still unknown. Despite some attempts, the binding site of neurosteroids at NMDAR was never fully determined. Questions arise, if the defined binding site exists, or if the effects of neurosteroids are mediated through a different mechanism. Membrane perturbation or blocking of the ion channel are viable alternatives.[51]

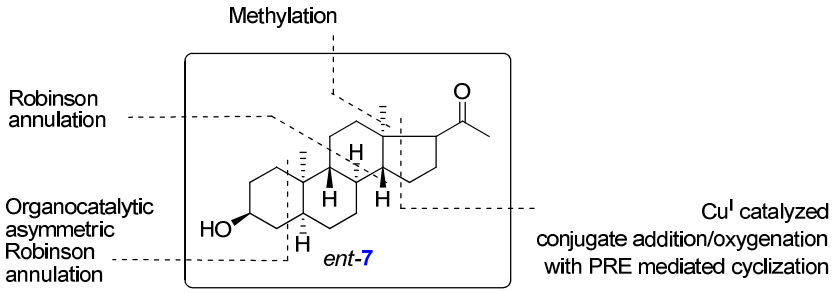
Even less is known about the fate of neuroactive steroids in organisms. Modern analytical methods are capable of pharmacokinetic and metabolic studies with minute amounts of analyte. However, a necessary condition for these methods is the preparation of a tracer molecule. This is achievable only by organic synthesis.

The main topic of this thesis will be to design and elaborate probes for distinguishing the mechanism of action of neurosteroids at the NMDA receptor. Unnatural enantiomers of native neurosteroids will be chosen as the synthetic tool capable of differentiating direct binding site-mediated action from less specific mechanism. The desired pregnane *ent*-steroids will be prepared by total synthesis, which will also enable preparation of truncated mimics of neurosteroids in both enantiopure forms. These mimics will be exploited to identify minimum binding requirements for inhibition of the NMDA receptor.

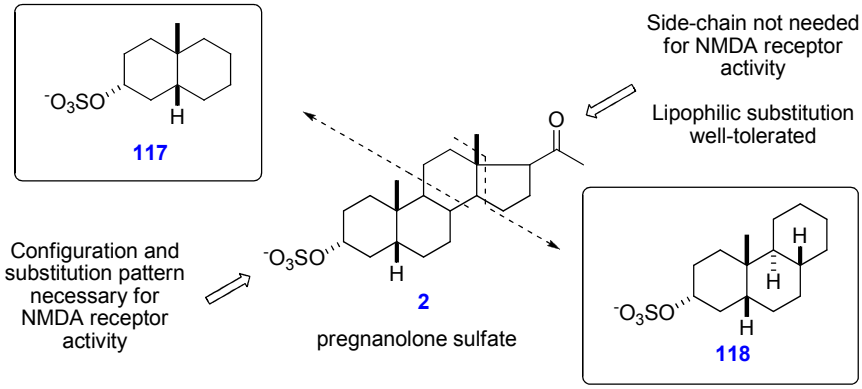
The last part of the thesis reports a study of incorporation of deuterium atoms into metabolically inaccessible positions of steroidal angular methyl groups to provide internal standards for pharmacokinetic measurements and tracing of metabolites by HPLC-MS/MS analysis.

Specific aims are:

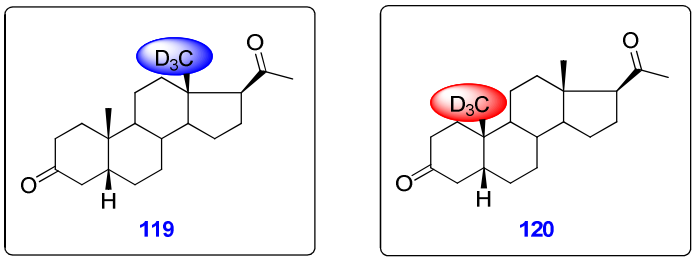
- To design and develop a modular total synthesis of pregnane *ent*-steroids. Strategically, this means assembling rings A and B first to allow for possible modification/deletion of the side chain and rings D and C. *ent*-Pregnanolone (*ent*-**7**) will be chosen as the central intermediate for other pregnane derived *ent*-steroids. An original C-C bond forming methodology will be used for the annelation of the D-ring and its viability will be evaluated.



- To synthesize truncated analogs of neurosteroids, lacking the steroid side chain and ring D or rings CD. These mimics will be prepared in both enantiomeric forms and converted to the corresponding sulfates, suitable for physiological testing.



- To develop methods for incorporation of deuterium atoms into angular methyl groups of the steroid core in 5β-pregnane steroids. Special attention will be paid to radical methods and their applicability for this purpose.



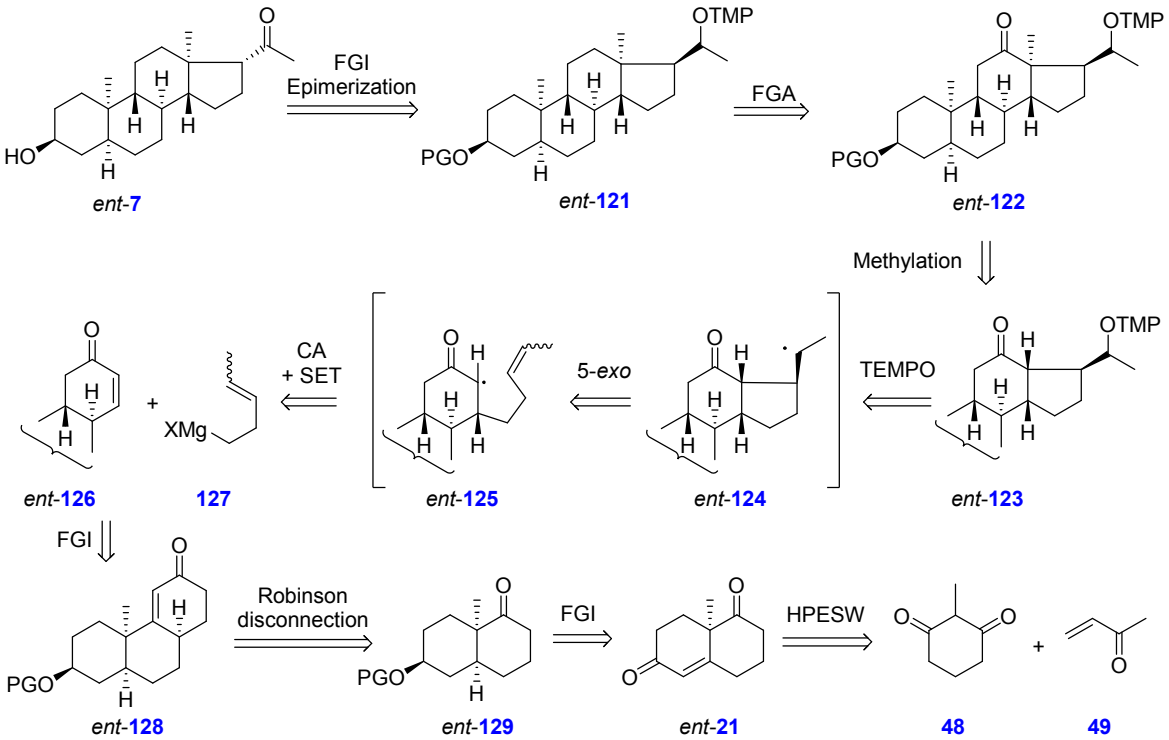
3. Results and Discussion

3.1. Total Synthesis of Pregnane Steroids

3.1.1 Retrosynthetic Analysis

In the retrosynthetic planning, several points were taken into the consideration. First, Chodounská and Vyklický's groups have found that binding of neuroactive steroids to the NMDA receptor can be enhanced by changes in the steroid side-chain (see **Chapter 1.2**). It was therefore desirable to design the retrosynthesis with the late construction of the rings C and D to enable the synthesis of biologically interesting truncated analogs **117** and **118**. Second, since the bent shape of the *cis*-AB junction of the steroid core was responsible for the inhibitory action at the NMDA receptors (see **Chapter 1.2**), *ent*-pregnanolone (*ent*-**7**) was chosen as the target molecule (**Scheme 16**). Third, the D-ring and the oxygen function in position C-20 seemed ideally positioned for a radical 5-*exo* cyclization with oxygenative termination and offered an opportunity to extend the methodology of copper-catalyzed conjugate addition of organometallics with SET oxidation of the resulting enolate (see **Chapters 1.7-1.8**).

A series of functional group interconversions (FGI's) and a functional group addition (FGA) lead from *ent*-**7** through *ent*-**121** to the fully assembled carbon skeleton of *ent*-**122**. The C-18 methyl group is disconnected first to give *ent*-**123**, prepared for the key disconnection of the D-ring. The persistent radical TEMPO can be disconnected from *ent*-**123** to give radical *ent*-**124,** enabling a radical 5-*exo* disconnection to an α-keto radical *ent*-**125**. This is in turn accessible from *ent*-**126** by a SET process and a conjugate retro-addition of a carbon nucleophile **127**. Different carbon nucleophiles **127** can be envisaged to enable the synthesis of various steroid side chains, e.g. cholestane or cholane types, by a unified approach.

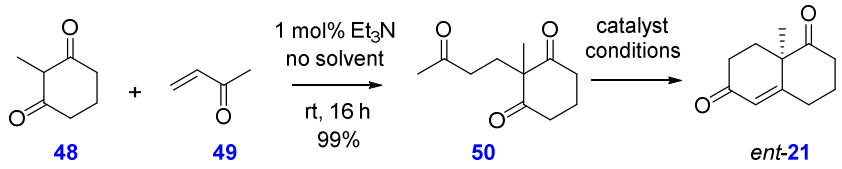


Scheme 16: Retrosynthetic analysis of *ent*-**7**

The double bond in *ent*-**126** is on the other side of the C-ring than would be desirable and has to be repositioned by series of FGI's. This in turn enables the Robinson disconnection of the C-ring of *ent*-**128**, leading to *cis*-decalin *ent*-**129**, which can be traced back to the known Wieland-Miescher ketone *ent*-**21** by a series of redox steps. The Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) disconnection leads to simple diketone **48** and enone **49** (See **Chapter 1.6**).

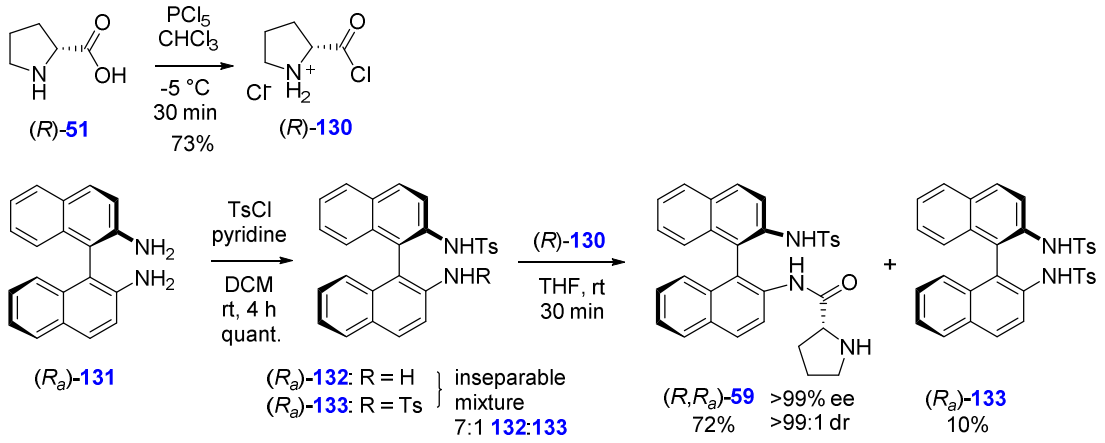
3.1.2 Enantioselective Entry into the Synthesis

The first step of the total synthesis was the HPESW reaction (**Scheme 17**). The described addition of diketone **48** to methyl vinyl ketone (**49**) catalyzed by triethylamine proceeded as reported with quantitative yield to afford triketone **50**.[128] This reaction was scaled up to 100 g of **50** without a decrease in the yield.



Scheme 17: Synthesis of the Wieland-Miescher ketone *ent*-**21**

The catalyst for the asymmetric reaction was chosen on the basis of the highest yield and enantioselectivity published in the literature (see **Chapter 1.6**). None of the reported catalysts was commercially available, with the exception of the unsubstituted amino acids proline **51** and cispentacin **52**, which offered only mediocre yields and enantioselectivity. The synthetic accessibility of the catalyst thus came into play. It was necessary to ensure enough material of the organocatalyst to provide at least multigram amounts of cyclized product *ent*-**21**. Prolinanilides were selected as a first class of catalysts, since they met all the criteria and a small library could be rapidly assembled for screening.



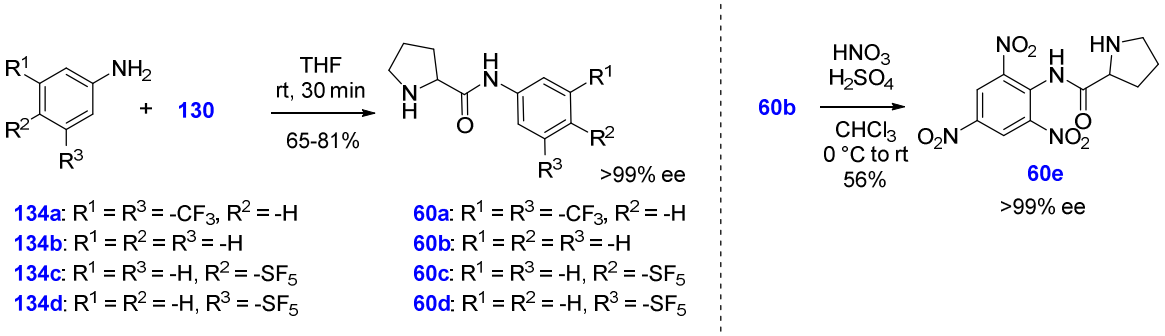
Scheme 18: Synthesis of the catalyst (*R*,R_a)-**59**

Catalyst (*R*,R_a)-**59** was prepared from a commercially available BINAM (R_a)-**131** in 2 steps by modification of the known procedure (**Scheme 18**).[127,128] Instead of using *N*-protected proline, prolinoyl chloride hydrochloride (*R*)-**130**, was employed. It is a crystalline storable reagent, which was pioneered by Fischer[237] and later utilized by Morán *et al.* in their synthesis of various prolinanilides.[125] This reagent was prepared by reaction of (*R*)-proline ((*R*)-**51**) with PCl_5 in chloroform at −5 °C, typically in 70-80% yield. Tosylation of enantiopure (R_a)-**131** afforded an inseparable mixture of mono- and ditosylate (R_a)-**132** and (R_a)-**133**, respectively. Prolination with (*R*)-**130** proceeded

smoothly, affording (*R*,*R*$_a$)-**59** in 72% yield from (*R*$_a$)-**131**. No detectable racemization of the proline chiral center was observed by NMR spectroscopy.

Because of the relatively high price of enantiopure (*R*$_a$)-**131**, it was decided to test Morán's catalyst **60a**, which was prepared according to the literature from (*S*)-**130** or (*R*)-**130** and commercially available aniline **134a** in 77% yield (**Scheme 19**). Because the enantioselectivity and the rate of the HPESW reaction was postulated to be a function of the acidity of the amide hydrogen,[125] a few related catalysts featuring electron withdrawing groups at the aniline ring were prepared. Thus, trinitroanilide **60e** was prepared according to the literature by nitration of **60b** in 56% yield.[238] Anilide **60b** was synthesized in 81% yield from aniline (**134b**) and **130**. Finally *m*- and *p*- substituted (pentafluoro-λ^6-sulfanyl)anilines **60c** and **60d** were prepared from the corresponding anilines **134c** and **134d** in 79% and 65% yield, respectively.

Amides **60a** and **60e** were prepared in both enantiomeric forms. Their enantiomeric purity was confirmed by synthesis of both diastereomers of their Mosher's amides. Comparison of ^{1}H and ^{19}F NMR spectra showed >99% ee. Compounds **60c** and **60d** were prepared only in the (*S*)-series and the NMR spectra of their respective amides with optically pure (*R*)-Mosher's acid revealed single compounds.



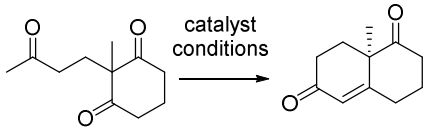
Scheme 19: Synthesis of prolineanilides **60a-e**

All catalysts were tested in the HPESW reaction with substrate **50** (**Table 1**). First, the catalysts were used under the reported conditions (Entries 1–3).[125,126,128] Trinitroanilide **60e** showed rather low enantioselectivity, therefore it was not further optimized (Entry 1). The use of (*R*,*R*$_a$)-**59** afforded results comparable to those reported in the literature (Entry 3).[126,128] In contrast, **60a** gave **21** with 87% ee vs. The reported 96%.[125] This might be caused by unintended deviation from the published procedure, since Morán *et. al.* performed the reaction as an NMR experiment without isolation of product.

Viózquez *et al.* have shown that both the yield and the enantioselectivity of the cyclization with **59** can be enhanced by: a) coapplication of a catalytic amount of benzoic acid, and b) running the reaction under solvent-free conditions.[127] Gratifyingly, employing solvent-free conditions and 5 mol% of **60a** gave the Wieland-Miescher ketone in 94% ee after 3 days, although the crude reaction mixture still contained ca. 25% of starting triketone **50** (Entry 4). Adding 1 mol% of benzoic acid accelerated the reaction and afforded **21** in excellent yield and 96% ee (Entry 5). Lowering the catalyst amount to 3 mol% did not affect the yield, but decreased slightly the enantioselectivity to 92% ee (Entry 6). Decreasing the temperature did not lead to an improvement (Entry 7). Catalysts **60c** and **60d** proved to be as effective as **60a** under these optimized conditions (Entries 8–11). In both cases, addition of 1 mol% of benzoic acid increased the rate of reaction and enantioselectivity (Entry 8 vs. 9, 10 vs. 11). The *p*-SF$_5$ substituted catalyst **60c** proved slightly inferior to the *m*-SF$_5$ substituted catalyst **60d**. The

latter gave almost identical results to **60a**. A kinetic experiment for 5 mol% of **60a** or **60d** showed marked dependence of the reaction rate on the concentration of BzOH (see **Appendix A**). While it took ca. 20 h with 0.5 mol% of BzOH and **60a** (5 mol%), to reach full conversion, cocatalysis with 5 mol% of BzOH reduced the time to 3 h. The enantiomeric excess was slightly worse (93%) in all kinetic experiments (see **Appendix A**). These results are to our knowledge the best so far reported for the preparation of **21**.

Table 1: Screening of catalysts **59** and **60a-e** for the asymmetric Robinson annulation



50 *ent*-**21**

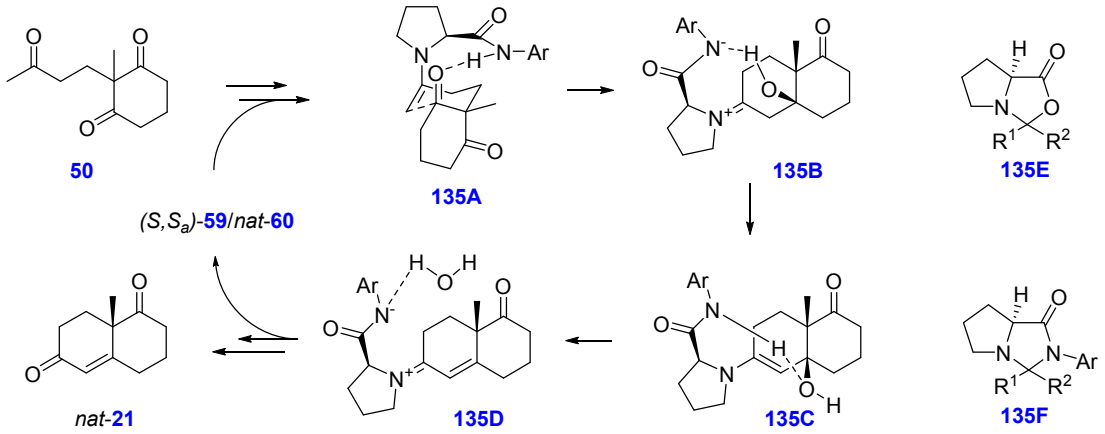
Entry	Catalyst	Solvent	Catalyst Loading (mol%)	BzOH (mol%)	*T* (°C)	*t* (d)	Yield of **21** (%)	ee[a] (%)
1	**60e**	$CHCl_3$[b]	10	–	rt	7	92[c]	39
2	**60a**	$CHCl_3$[b]	10	–	rt	7	70[c]	87
3	**59**	–	2	0.5	rt	7	89[c]	92
4	**60a**	–	5	–	rt	3	72[d,e]	94
5	**60a**	–	5	1	rt	3	98[d]	96
6	**60a**	–	3	0.5	rt	3	98[d]	92
7	**60a**	–	5	1	5	3	98[d]	94
8	**60c**	–	5	1	rt	3	95[d]	95
9	**60c**	–	5	–	rt	5	93[d]	84
10	**60d**	–	5	1	rt	1	98[d]	96
11	**60d**	–	5	–	rt	3	94[d]	95

[a] Determined by HPLC at chiral stationary phase (see **Appendix A**). [b] *c*[**50**] = 1 M. [c] Isolated yield at 5.0 mmol scale. [d] Isolated yield at 1.5 mmol scale.[e] ca. 75% conversion as indicated by ^{1}H NMR spectroscopy.

At preparative scale, the reaction of 8.23 g of **50** with 2 mol% of (R,R_a)-**59** and 1 mol% of benzoic acid afforded 97% of **1** (95% ee) after 7 days. The reaction of 49.5 g **50** with 5 mol% of **60a** and 1 mol% of benzoic acid afforded quantitative yield of **21** (96% ee) after 24 h. A single crystallization from Et_2O/EtOAc at −78 °C afforded 34.2 g (76% yield) of material with >99% ee. The mother liquors were utilized as a model substrate in further syntheses and optimizations. A racemic Robinson annulation catalyzed by pyrrolidine afforded *rac*-**21** in 55% yield.[239] This compound was used as a standard for chiral HPLC analysis.

The observed behavior of catalysts **60a-e** is consistent with the known Houk-List enamine mechanism,[125,240,241] where the proline catalyst **51** is substituted by the respective prolinamide **59** or **60**. The currently accepted mechanism is shown in **Scheme 20**. The anilide CONH group is a much weaker acid than proline COOH group (pK_a = 1.99 in H_2O).[242] For comparison, *N*-[2,4-dinitrophenyl]anilides have pK_a in the range 9.5-10.5.[243] The amide is too weakly acidic to completely protonate the amino group of proline (pK_a = 10.6 in H_2O)[242] and thus to inhibit the reaction, yet strong enough to be capable of forming zwitterions in equilibrium. The rate of the aldol reaction **135A**→**135B** has been shown to increase with more acidic prolinanilides.[125] The same effect was observed for the dehydration step **135C**→**135D**. The acceleration of the reaction in the absence of

solvent is, however, probably just a concentration effect. Small amounts of water, coformed during the condensation, have also been shown to accelerate the reaction by hydrolyzing proline-derived oxazolidinones **135E**.[127,244] Presumably, the same principle applies to imidazolidinones **135F**, which have been observed during the reaction by Morán *et. al.*[125,245] Running the reaction in neat conditions increases the concentration of water, leading to an enhanced rate of hydrolysis.

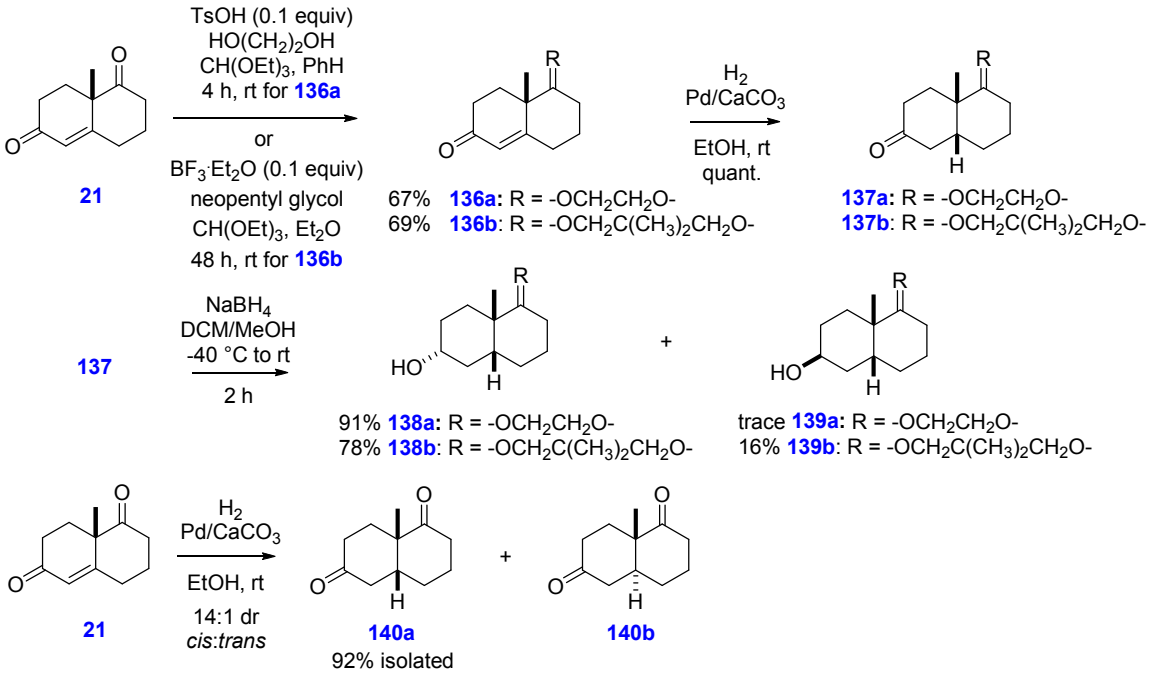


Scheme 20: Mechanism of the HPESW reaction

Benzoic acid catalyzes the formation of enamines **135A,C** and their hydrolysis. Finally, the lowest rates of conversion and enantioselectivities were observed with catalysts **60c** and **60e**, which were the only crystalline compounds, suggesting solubility issues. In contrast, the dependence of the reaction rate or enantioselectivity on the electronic density of the aromatic ring seems to play a minor role.

3.1.3 Stereoselective Reductions of the Decalin System

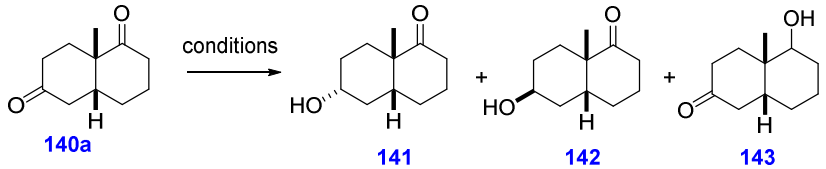
Acetalization of the Wieland-Miescher ketone **21** afforded dioxolane **136a** or 2,2-dimethyl-1,3-dioxane **136b** in moderate yield (**Scheme 21**). Hydrogenation over 5% $Pd/CaCO_3$ at ambient pressure afforded smoothly the *cis*-diastereomers **137a,b** in quantitative yield. The steric effect of 9-dioxolane is responsible for the high selectivity of hydrogenation of **21**.[246] Ketal-protected ketone **137a** was reduced smoothly with $NaBH_4$ to furnish the anticipated equatorial hydroxy derivative **138a** in 91% yield.[247] Isolation of the minor diastereomer **139a** was not attempted. In contrast, reduction of ketal **137** under identical conditions afforded 78% of equatorial alcohol **138b** and 16% of axial alcohol **139b**. This difference in stereoselectivity can be attributed to a different composition of the *cis*-decalin conformers. Compound **138a** showed broadened ^{1}H and ^{13}C NMR spectra of a single diastereomer, indicating slow ring inversion, which somewhat improved by measuring the sample at higher temperature (60 °C, $CDCl_3$). The NMR spectra of alcohols **138b** and **139b** showed clearly the presence of two conformers, which coalesced into one set of signals at 60 °C in $CDCl_3$. Hydrogenation of **21** afforded crude diketone **140** in a 14:1 *cis*:*trans* ratio of **140a**:**140b**, as determined by ^{1}H NMR, which yielded 92% of pure *cis*-decalindione **140a** after column chromatography. The observed selectivity of hydrogenation compares favorably to known methods,[246,248] since hydrogenation over 5% $Pd/CaCO_3$ in pyridine was reported to afford a 6:1 *cis*:*trans* mixture.[246] Similar results were observed with 5% Pd/C in EtOH.[248]



Scheme 21: Preparation and reduction of ketals **137a,b**

The subsequent regioselective reduction of **140a** was possible under several conditions (**Table 2**). Unfortunately, the separation of stereoisomers was difficult, but it was at least possible to separate the fractions containing starting material, keto alcohols **141**-**143** and diols, respectively. This enabled to assess the regio- and stereoselectivity of several reagents by isolating the appropriate fraction and integrating the ^{1}H NMR spectrum. $NaBH_4$ at −40 °C afforded a very good **141**:**142** ratio, while the regioselectivity was mediocre (Entry 1). The best results were obtained under Luche reduction conditions (Entry 2), which afforded very good regio- and stereoselectivity. Surprisingly, bulky $LiAlH(OtBu)_3$ provided the lowest regioselectivity, although the **141**:**142** ratio was the highest reached in the series (Entry 3). For the best isolated yields of alcohols **141**-**143**, it was critical to quench the reaction mixture at low temperature with an excess of acetone, followed by acidification. Omitting acetone led to significant overreduction to diols. All reductions were attempted at the lowest possible temperature and were quenched when TLC showed disappearance of the starting material.

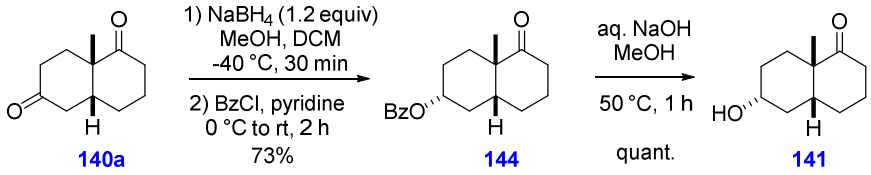
Table 2: Regioselective reduction of **140a**



Entry	Solvent	Reductant (equiv)	Additive (equiv)	*T* (°C)	Time (h)	Yield[a] (%)	Selectivity[b] **141**:**142**:**143**
1	CH_2Cl_2/MeOH 1:1	$NaBH_4$ (1.4)	-	−40	0.5	81	19:1:7
2	CH_2Cl_2/MeOH 1:1	$NaBH_4$ (1.6)	$CeCl_3$ (1.3)	−78	1	72	15:1:1
3	THF	$LiAlH(OtBu)_3$ (1.1)	-	−40	1	95	20:1:10

[a] Reactions were performed on 1 gram scale. Isolated yield of the monoalcohol fraction **141**-**143**. [b] Determined from ^{1}H NMR spectra.

On a larger scale, the crude mixture from reduction of **140a** was benzoylated under standard conditions for the purpose of detection during HPLC separation (**Scheme 22**). The resulting mixture was even easily separable by flash column chromatography affording the desired monobenzoate **144** as a pure compound in 73% yield over two steps. Saponification of **144** by NaOH in methanol afforded quantitatively the desired alcohol **141** as an analytically pure compound.

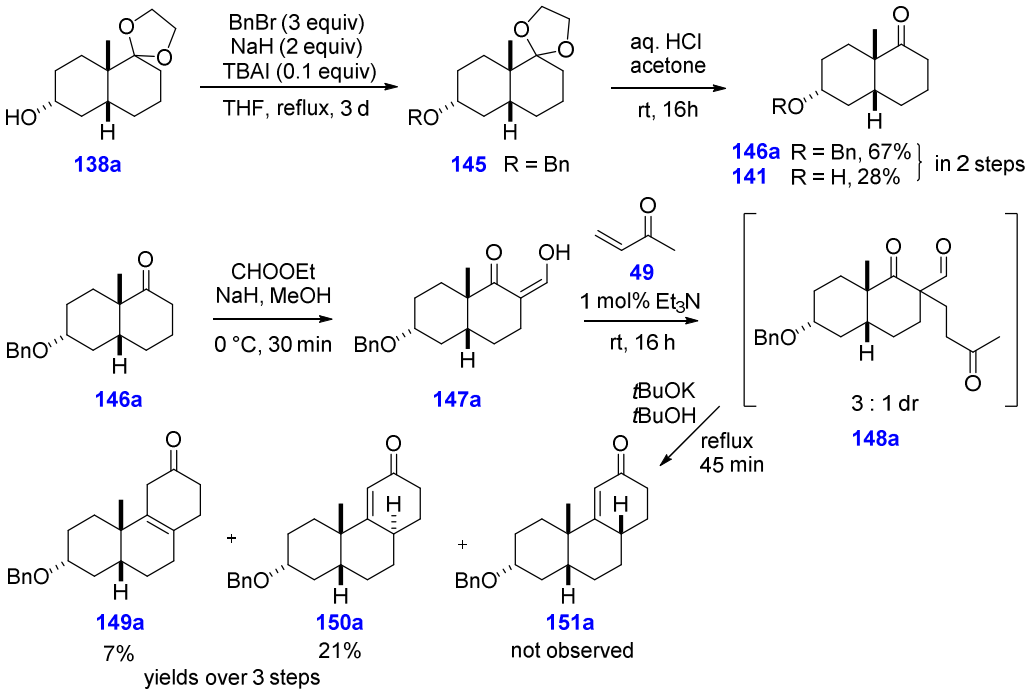


Scheme 22: The preparation of **141**

3.1.4 Substrate-controlled Robinson Annulation

With the three chiral centers successfully established, the Robinson annulation of ring C was explored. While it is possible to conduct the whole Robinson annulation in one flask by reaction with excess of methyl vinyl ketone (**49**) under basic conditions, the yields usually suffer, mainly by oligomerization of **49** and of the intermediates.[249] It was therefore decided to split the reaction sequence into three separate steps: a Claisen condensation, a Michael addition and a Dieckmann condensation with a retro-Claisen condensation; an approach used in the syntheses of many terpenoid natural products.[170,250–254] Activation of the ketone by α-formylation has been reported to facilitate the Michael addition and thus increase the overall yield of the transformation.[250,254]

First, the hydroxy group at C-3 had to be protected with a base-stable protecting group to prevent side reactions. Thus, ketal-protected alcohol **138b** was converted to benzyl ether **145** under standard conditions (**Scheme 23**). Crude **145** was directly hydrolyzed to the free ketone **146a** by acid catalysis in acetone in 67% yield of desired **146a** and 28% of recovered alcohol **141**. The reduced yield was caused by incomplete conversion to benzyl ether **145**.



Scheme 23: Robinson annulation of **146a**

Benzyl ether **146a** was formylated by reaction with sodium methoxide in neat dry ethyl formate to afford β-dicarbonyl intermediate **147a** in essentially quantitative yield. The crude material was subjected to a Michael addition with a slight excess of **49**, catalyzed by 1% of Et_3N in a manner analogous to the first step of the synthesis (**Chapter 3.1.2**, **Scheme 17**). A crude 3:1 mixture of diastereomers **148a** at the newly formed stereocenter was obtained. However, this was irrelevant to the outcome of the Robinson annulation, since this stereocenter was epimerized in the last step of the sequence. The last step proved to be difficult both in terms of yield and stereoselectivity. By employing conditions reported in the literature,[170] a complex reaction mixture was obtained. Chromatographic separation afforded tricyclic compound **150a** in 21% overall yield for all three steps, along with 7% yield of the Δ^8-double bond isomer **149a**. Unfortunately, the desired diastereomer **151a** was not observed.

The stereochemistry of **150a** was suggested by a missing NOE contact between CH_3-19 and H-8 (**Figure 8**). In addition, the benzyloxy substituent at C-3 was in an axial position, which was deducted from small coupling constants in ^{1}H NMR spectrum (^4J = 4.2 Hz, CH-3β). Clearly, conformer **150a'** predominates over the expected conformer **150a"**.

Since the deformylative condensation was performed under equilibrating conditions, a thermodynamically controlled product should be formed preferentially. Assuming that the desired **151a** is thermodynamically less stable than isolated **149a** and **150a**, it was attempted to enforce the desired 8β-configuration by employing a bulkier protecting group, which should prefer the equatorial position. This could twist *cis*-decalin **148** into a more favorable conformation, leading ultimately to tricyclic **151**. *tert*-Butyldimethylsilyl and trityl- groups were chosen as the respective protecting groups.

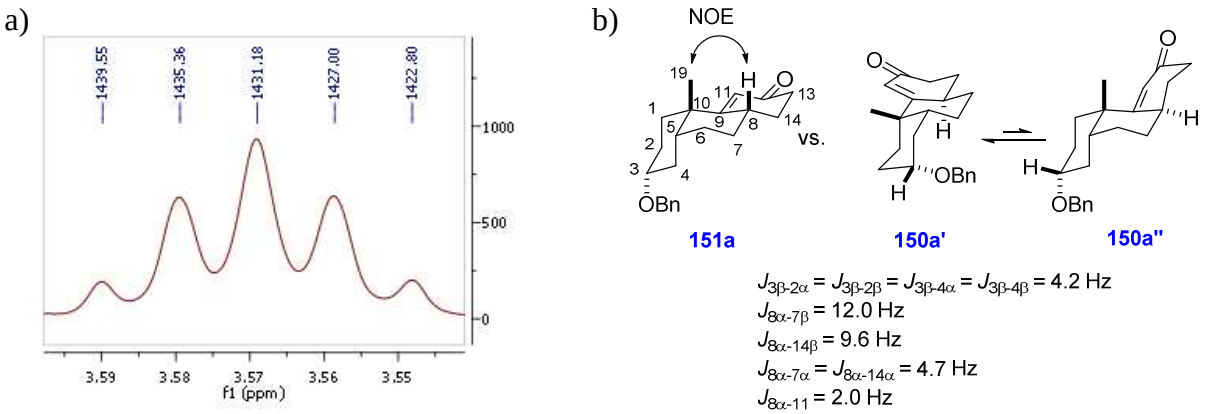
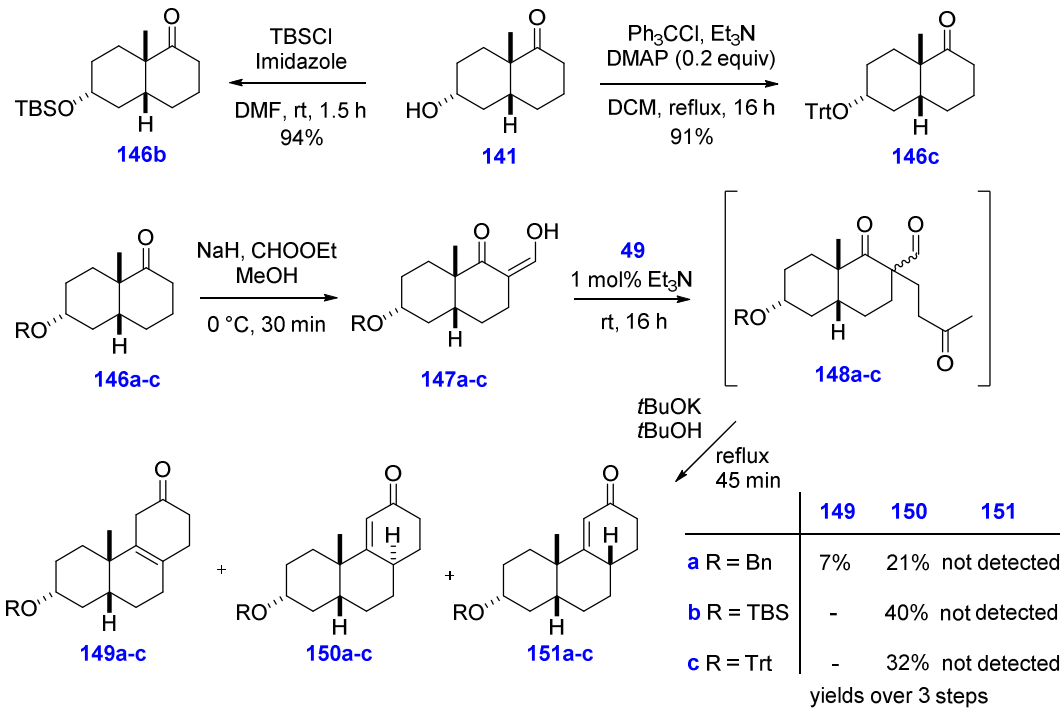


Figure 8: a) Detail of the ^{1}H NMR signal of CH-3β of **150a**, measured at 400 MHz. **b)** Probable conformations of diastereomers **150a** and **151a**. The observed $J_{H,H}$ of crucial hydrogens H-3β and H-8α are displayed below.

Alcohol **141** was easily protected to afford either TBS ether **146b** or trityl ether **146c** in excellent yields (**Scheme 24**). Their Robinson annulation gave similar results. Again, the major products **150b,c** had an undesired 8α-configuration, and the H-3β ^{1}H NMR signal was a quintet as in **150a**. No product with the desired stereochemistry was observed in either of the reactions. At this point, it was decided to abandon the Robinson annulation of *cis*-decalins **148**. Nevertheless, the reaction should proceed with the desired stereoselectivity in case of a flat decalin system, either a *trans*-decalin or a decalin with a double bond at the ring-fusion.[170,251,255]



Scheme 24: Substrate-controlled Robinson annulation with **146a-c**

3.1.5. Second Generation

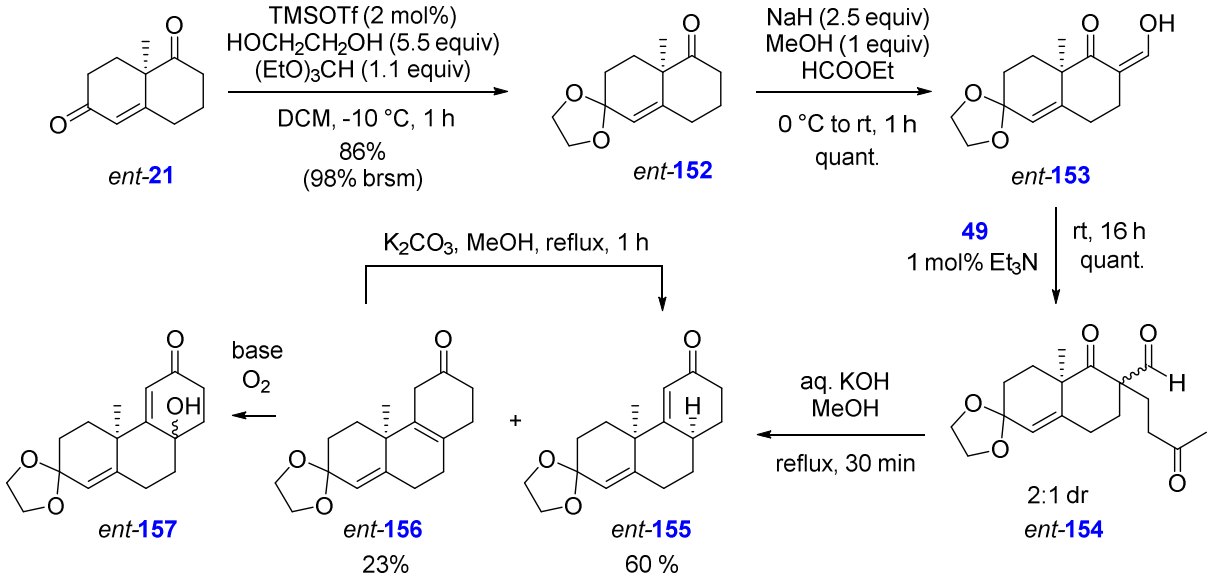
The outcome of the substrate-controlled Robinson annulation called for a change of the *cis*-decalin system to a more rigid *trans*-decalin. However, this would complicate the synthesis of 5β-steroids at late stages of the synthesis. It was therefore decided to accomplish the total synthesis with the Δ^4-double bond preserved in the molecule, leading to *ent*-progesterone *ent*-**3** in the end – a known precursor to both 5α- and 5β-pregnanes.

This approach required the chemoselective protection of the enone in the presence of the simple keto group in *ent*-**21** (**Scheme 25**). Of the known robust protecting groups for ketones, a thioketal was ruled out on the basis of its reactivity with alkali metals in ammonia – a step planned later on in the synthesis (see **Chapter 3.1.1**). The regioselective protection of the 3-keto group of **21** as a dioxolane is possible with bis(trimethylsilyloxy)ethane and TMSOTf as an acid catalyst by employment of non-equilibrating conditions at −78 °C.[256] This method is on one hand highly selective and mild, proceeding with no shift of the conjugated double bond.[256–258] On the other hand, the reaction time of a week for substrate **21** makes this method impractical. Another option for kinetic control is the application of bulky acid collidinium *p*-toluenesulfonate, which leads to a substantial deconjugation of the double bond.[259,260] In contrast, classically employed methods provide selectively thermodynamically more stable monoketal **136a** (cf. **Scheme 21**).[261]

A solution of the ketalization problem was found by serendipity during efforts to produce the thermodynamic ketal **136a**. When the reaction was conducted with dry ethylene glycol in the presence of a slight excess of triethyl orthoformate and 10 mol% of *p*TsOH·H_2O at 25 °C in benzene, the thermodynamic ketal **136a** was formed in 67% yield (78% brsm). Lowering the temperature to −20 °C in toluene led to 72% yield of the kinetic ketal *ent*-**152**. These conditions were optimized to 86% yield in dry CH_2Cl_2 by using 2 mol% of TMSOTf as the catalyst (**Scheme 25**). Moreover, the unreacted starting material *ent*-**21** could be easily recovered in 12% yield. Remarkably, these conditions completely prevented the migration of the double bond from the Δ^4 to the Δ^5-position.

Monoketal *ent*-**152** was subjected to the Robinson annulation conditions. Ketone *ent*-**152** was formylated in virtually quantitative yield, and the resulting Michael donor *ent*-**153** was coupled to **49**, which proceeded smoothly to afford a crude mixture of diastereomers *ent*-**154** in 2:1 ratio. At first attempt, the aldol condensation of this mixture with *t*BuOK/*t*BuOH at 25 °C afforded two separable double bond isomers: 40% of deconjugated enone *ent*-**156** and 26% of desired *ent*-**155**. The ROESY spectrum of *ent*-**155** clearly showed a NOE between CH_3-19 and atoms H-1β, H-6β, H-8β and H-11, thus confirming the desired stereochemistry. The coupling constants were also consistent with an axial position of H-8β: $J_{8\beta\text{-}7\alpha}$ = 12.3, $J_{8\beta\text{-}14\alpha}$ = 10.1, $J_{8\beta\text{-}7\beta}$ = $J_{8\beta\text{-}14\beta}$ = 5.0, $J_{8\beta\text{-}11}$ = 2.2 Hz. Please note that in *ent*-series the α-substituents are above the plane of drawing to maintain the relative stereochemistry (see **Chapter 1.3**).

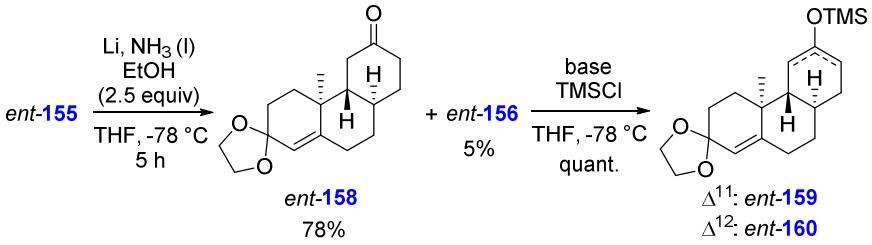
Optimization of the reaction conditions for the last step of Robinson annulation seemed prudent. The main problem was identified as a follow-up reaction of *ent*-**155** and *ent*-**156** with oxygen, leading to formation of 8-hydroxy derivative *ent*-**157**. This oxygenation reaction was also observed with other bases such as aqueous K_2CO_3, KOH or methanolic NaOMe. For example, *ent*-**157** was isolated in 30% yield after 4 h of reflux of *ent*-**154** in 0.25 M nondegassed methanolic KOH. However, performing the reaction in degassed solvents with careful exclusion of air led to satisfactory yield 60% of *ent*-**155** and 23% of *ent*-**156**. Furthermore, the isolated deconjugated ketone *ent*-**156** could be isomerized by refluxing with two equivalents of K_2CO_3 in degassed methanol to afford 46% of desired *ent*-**155** and 45% of recovered *ent*-**156**.



Scheme 25: The substrate-controlled Robinson annulation

Dissolving metal reduction of *ent*-**155** in liquid ammonia smoothly afforded ketone *ent*-**158** in very good yield (**Scheme 26**). The use of EtOH as a proton source and a temperature of −78 °C were crucial for good yield and chemoselectivity of the reduction. Some isomerization of the double bond was observed during the reaction leading to ca. 5% of *ent*-**156**, which was somewhat difficult to separate from *ent*-**158**. The correct stereochemistry was again confirmed by a ROESY spectrum. The CH_3-19 group exhibited a NOE with H-1β, H-6β, H-8β and H-11β, but not with H-9, strongly suggesting a *trans*-BC ring junction. The *trans*-junction of the product is also consistent with the known course of the dissolving metal reduction of bicyclic enones.[170,251,262]

For introduction of the Δ^{13}-double bond the Saegusa-Ito oxidation was chosen, because it offered the possibility of a catalytic reaction. Therefore the kinetic silyl enol ether *ent*-**160** had to be selectively prepared. A number of bases were screened under typical non-equilibrating conditions and consecutive addition of TMSCl. A mixture of isomeric TMS enol ethers *ent*-**159** and *ent*-**160** was isolated in virtually quantitative yield in each case. The ratios detected by ^{1}H NMR of the crude reaction mixture are shown in **Scheme 26**. The steric effects are clearly reflected in the series LDA:LiHMDS:LiTMP (1:3.9 vs. 1:7.4 vs. 1:10 of *ent*-**159**:*ent*-**160**), while the role of counterion is visible in the series LiHMDS:NaHMDS:KHMDS (1:7.4 vs. 1:6.4 vs. 1:5.3 of *ent*-**159**:*ent*-**160**).



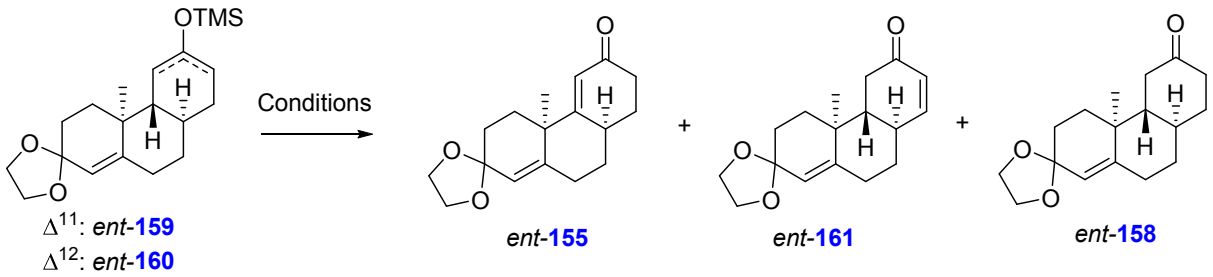
Base	Δ^{11} *ent*-**159**	Δ^{12} *ent*-**160**
LDA	1	3.9
LiHMDS	1	7.4
NaHMDS	1	6.4
KHMDS	1	5.3
LiTMP	1	10

Scheme 26: Dissolving metal reduction of *ent*-**155** and a kinetic deprotonation of *ent*-**158**

After finding satisfactory conditions for the preparation of *ent*-**160**, it was subjected to Saegusa-Ito oxidation (**Table 3**). The original conditions employing 0.5 equivalent of $Pd(OAc)_2$ and benzoquinone as a sacrificial oxidant were attempted,[263] but led to early precipitation of palladium black and incomplete conversion (Entry 1). Nevertheless, it afforded a sample of the desired enone *ent*-**161**. The major side reaction in all experiments was desilylation, leading to saturated ketone *ent*-**158**. The Larock modification of the Saegusa-Ito reaction worked reasonably well,[264] yet some loss of the ketal protecting group was observed during aq. workup (Entry 2). This was presumably caused by the acetic acid released by contact with water, since the allylic ketals are very sensitive to aq. acids, even more so than saturated ketals. This issue was solved by pouring the reaction mixture on ice-cold aq. $NaHCO_3$ (Entries 3–5). Attempts to suppress the desilylative side reaction were also made. Employment of a catalytic amount of NaOAc as a mild acid scavenger led to an increased desilylation to *ent*-**158** (Entry 4). The culprit was found to be fine particles of molecular sieves, suspended in the solvent during drying. Satisfactory yield was achieved by using distilled DMSO without contact with molecular sieves and by prolonging the reaction time (Entry 5).

Finally, an effort was undertaken to decrease the catalyst loading. Tsuji *et al.* reported a procedure which makes use of a stoichiometric amount of allylic carbonate as the hydrogen acceptor.[265] The catalytic species in this variant is Pd^0 supported by dppe or dba ligands. The latter method was successfully applied by Shibasaki *et al.* in their synthesis of strychnine.[266] The yields of enone *ent*-**161** obtained by these methods were inferior to the optimized Larock modification (Entries 7–10). The main problem of the former method was the precipitation of palladium black and loss of the catalytic activity. In some cases, this was accompanied by a significant desilylation of the starting material (Entries 6, 8, 9).

Table 3: Optimization of the reaction conditions for the Saegusa-Ito oxidation

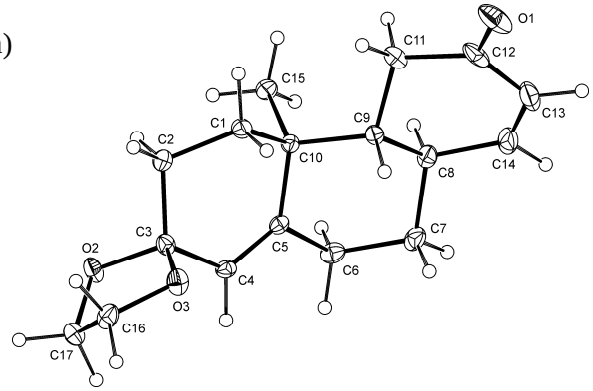


Entry	Catalyst (mol%)	Solvent	Additive (equiv)	*T* (°C)	*t* (h)	Recovered[a] 159+160 (%)	Yield[a] of 161 (%)
1[b]	$Pd(OAc)_2$ (50)	MeCN	Benzoquinone (0.5)	rt	16	14	53
2[b]	$Pd(OAc)_2$ (10)	DMSO[c]	Air (excess)	rt	16	7	63[d]
3[b]	$Pd(OAc)_2$ (10)	DMSO[c]	Air (excess)	rt	11	8	59
4[e]	$Pd(OAc)_2$ (10)	DMSO[c]	Air (excess) NaOAc (0.2)	rt	1	0	24
5[e]	$Pd(OAc)_2$ (10)	DMSO[f]	Air (excess)	rt	48	0	80[g]
6[e]	$Pd(OAc)_2$ (2)	MeCN	Diallyl carbonate (1.4), dppe (0.02)	81	24	11	13
7[b]	$Pd_2dba_3 \cdot CHCl_3$ (2)	MeCN	Diallyl carbonate (3.0)	rt	16	60	17
8[e]	$Pd_2dba_3 \cdot CHCl_3$ (5)	MeCN	Diallyl carbonate (1.4)	rt	24	8	35
9[e]	$Pd_2dba_3 \cdot CHCl_3$ (1)	MeCN	Methyl allyl carbonate (2.0)	40	24	4	38
10[e]	$Pd_2dba_3 \cdot CHCl_3$ (2)	MeCN	Methyl allyl carbonate (2.0)	81	96	63[g]	19[g,h]

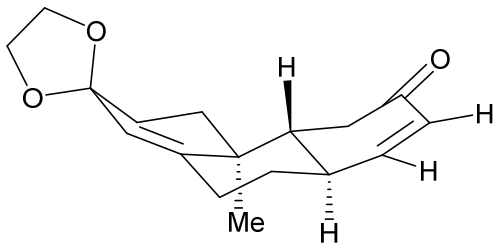
[a] Determined by ^1H NMR. [b] Reactants **159** and **160** in a 1:4 ratio. [c] Dry, stored over 4Å molecular sieves. [d] Ca. 40% deprotection of ketal [e] Reactants **159** and **160** in a 1:10 ratio. [f] Dry, stored without molecular sieves. [g] Isolated yield. [h] Ketone *ent*-**158** isolated in 13% yield.

The enone *ent*-**161** formed crystals suitable for X-ray analysis, which helped to confirm its structure unambiguously (**Figure 9**). The molecule is slightly bent with the C-19 methyl protruding from the convex face. Central ring B adopts chair a conformation and contains C-19, H-8 and H-9 in axial positions. Both the A and C rings are in half-chair conformation, where methyl C-19 and α-O of the ketal occupy pseudoaxial positions of the A-ring. Dioxolane ring is in a half-chair conformation, rather than an envelope.

a)



b)

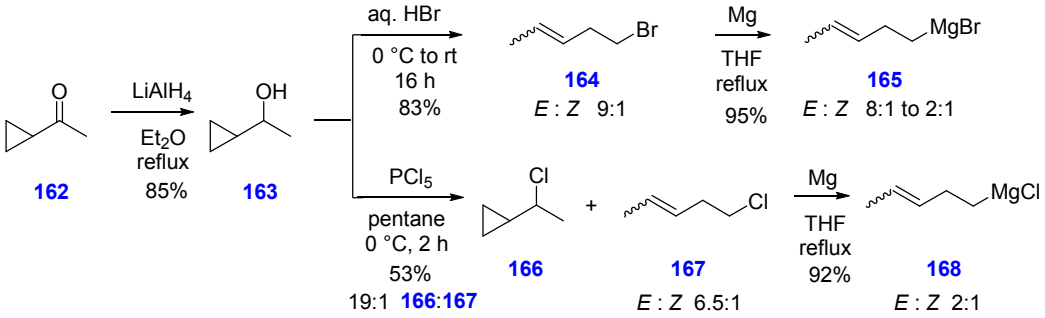


ent-**161**

Figure 9: a) X-ray crystal structure of *ent*-**161**. Thermal ellipsoids are drawn at the 30% probability level. **b)** Schematic representation, side-view

3.1.6. The Tandem Conjugate Addition – Cyclization

For practical reasons, a Grignard reagent was chosen as the stoichiometric organometallic reagent in copper-catalyzed conjugate addition. The main factors in this decision were: a) Precedent of asymmetric copper-catalyzed CA of organomagnesium compounds in the literature (See **Chapter 1.7**), suggesting a larger synthetic potential b) Facile formation of Grignard reagents from the corresponding alkyl halides and magnesium metal. c) Stability during storage and existence of reliable titration procedures.[267–269] d) The ability of magnesium enolates to undergo a single electron oxidation with ferrocenium salts.[270]



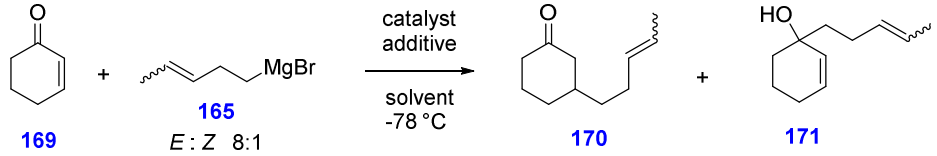
Scheme 27: Preparation of Grignard reagents **165** and **168**

Both Grignard reagents **165** and **168** were prepared in two steps from cyclopropyl methyl ketone (**162**) by reduction to an alcohol **163**, followed by halogenation (**Scheme 27**).[271,272] Alcohol **163** was substituted with bromide with concomittant opening of the cyclopropane ring affording **164**. This procedure can be also performed as a one-pot operation. Chlorination of **163** with PCl_5 proceeded predominantly with retention of the cyclopropyl ring to give secondary chloride **166** with a small amount of the linear **167**. The cyclopropyl ring was opened in the reaction of **166** with magnesium to give pure **168** without detectable amount of the cyclic Grignard reagent. This is in accordance with the known shifted equilibrium between cyclic and linear forms of homoallylic Grignard reagents.[273,274] *E*/*Z*-isomerization of the double bond during the Grignard reagent formation was observed both in **165** and **168**, which is consistent with the well-known SET mechanism of this reaction.[275,276]

The screening of suitable conditions for a substrate-controlled copper-catalyzed CA was performed using cyclohexenone (**169**) (**Table 4**). LiCl was added to every reaction mixture to enhance the solubility of the copper salt.[160] A control experiment in the absence of copper catalyst afforded a mixture of 1,2-adduct **171** and 1,4-adduct **170** in a 3:2 ratio (Entry 1). When the copper catalyst was

present, the regioselectivity was reversed (Entries 2–18). Surprisingly, the regioselectivity was only weakly dependent on copper source (Entries 2–6). Anhydrous $CuCl_2$ was therefore chosen as a shelf-stable convenient precatalyst in the following experiments. Addition of ligands resulted in mild improvement of the regioselectivity (Entries 7–9). Interestingly, HMPA or TMEDA ligands led to deterioration of the *E*/*Z* ratio in the products. Slowing the rate of addition of **165** had a marked effect on the regioselectivity, allowing for a 99:1 ratio **170**:**171** (Entry 5 vs. 10, 11). More polar ethereal solvents THF and DME were more suitable than Et_2O or MTBE (Entries 11–14). Lowering the catalyst loading below 10 mol% resulted in a significant decrease of regiselectivity (Entries 15, 16). Finally, CuCN gave worse regioselectivity even under slow addition conditions (Entry 17), whereas $Cu(OTf)_2$ served as an equally good precatalyst as $CuCl_2$ (Entry 19). The most practical reaction conditions are $CuCl_2$ as the copper source in polar ethereal solvents such as THF or DME (Entries 11, 14).

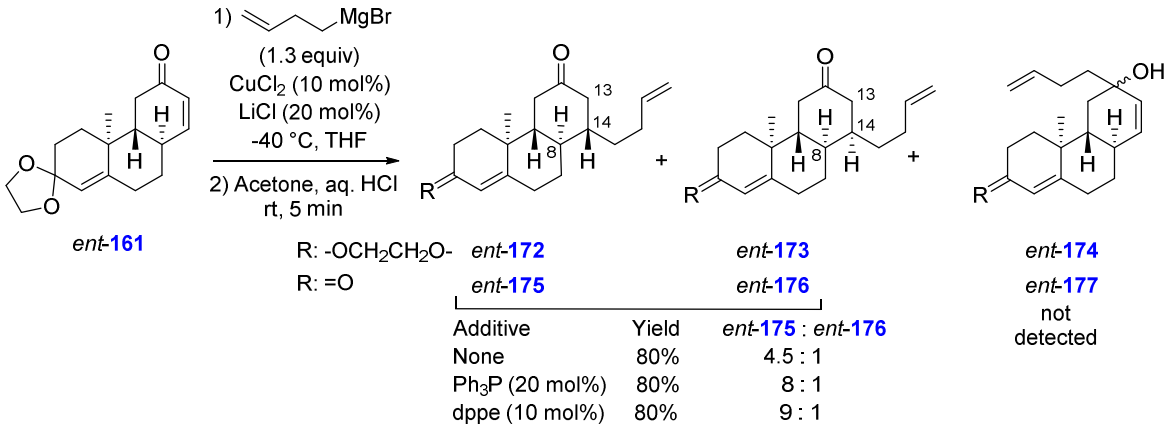
Table 4: Optimization of the reaction conditions for the copper-catalyzed CA



Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Addition of 165 (min) [a]	170 (%) [b]	171 (%) [b]	*E*/*Z* ratio [b]
1	none	LiCl (20)	THF	5[c]	39	61	8.3
2	CuCl (10)	LiCl (20)	THF	5[c]	82	18	7.6
3	CuBr·DMS (10)	LiCl (20)	THF	5[c]	79	21	7.6
4	CuI (10)	LiCl (20)	THF	5[c]	84	16	7.6
5	$CuCl_2$ (10)	LiCl (20)	THF	5[c]	85	15	7.9
6	CuCN (10)	LiCl (20)	THF	5[c]	87	13	7.6
7	$CuCl_2$ (10)	LiCl (20), HMPA (200)	THF	10[c]	94	6	1.7
8	$CuCl_2$ (10)	LiCl (20), Ph_3P (20)	THF	7[c]	93	7	7.8
9	$CuCl_2$ (10)	LiCl (20), TMEDA (20)	THF	5[c]	91	9	1.9
10	$CuCl_2$ (10)	LiCl (20)	THF	30[c]	97	3	7.5
11	**$CuCl_2$ (10)**	**LiCl (20)**	**THF**	**60[d]**	**99**	**1**	**7.3**
12	$CuCl_2$ (10)	LiCl (20)	Et_2O	60[d]	77	23	7.6
13	$CuCl_2$ (10)	LiCl (20)	MTBE	60[d]	71	29	7.9
14	**$CuCl_2$ (10)**	**LiCl (20)**	**DME**	**60[d]**	**99**	**1**	**7.5**
15	$CuCl_2$ (1)	LiCl (20)	THF	60[d]	60	40	7.5
16	$CuCl_2$ (5)	LiCl (20)	THF	60[d]	86	14	7.8
17	CuCN (10)	LiCl (20)	THF	60[d]	80	20	7.7
18	**$Cu(OTf)_2$ (10)**	**LiCl (20)**	**THF**	**60[d]**	**98**	**2**	**8.0**

[a] Grignard reagent **165** (1.3 equiv) was used [b] Ratios determined by GC. [c] Added manually. [d] Added with a syringe pump.

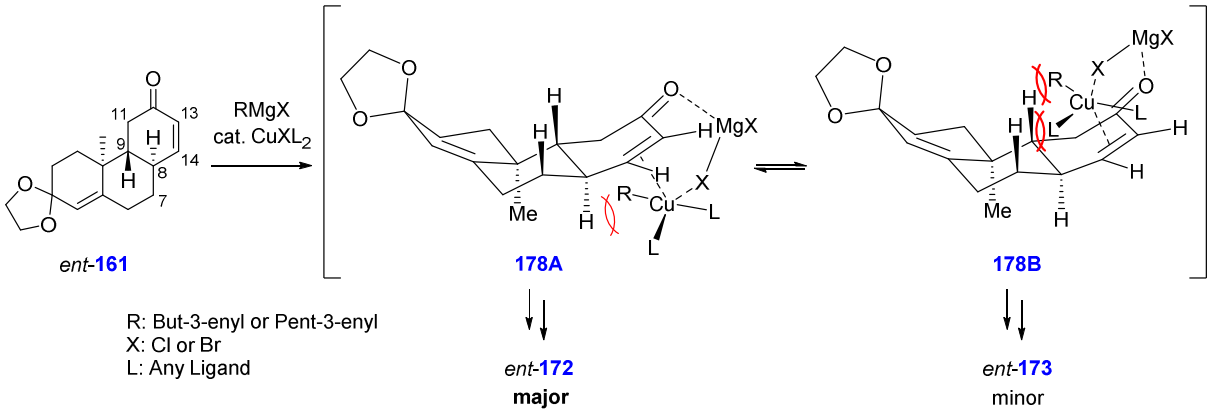
The most convenient reaction conditions found for **169** were applied to the steroid precursor *ent*-**161** (**Scheme 28**). To simplify the NMR analysis of the reaction mixture, but-3-enylmagnesium bromide, prepared from commercially available 4-bromobut-1-ene, was used instead of **165**.



Scheme 28: Copper-catalyzed conjugate addition of 3-butenylmagnesium bromide to *ent*-**161**

Under the optimized conditions (Entry 11 of **Table 4**) at −78 °C the conversion was slow. The reaction was quenched after the addition of Grignard reagent and stirring for additional 30 min at the given temperature. The NMR of the crude reaction mixture showed 25% of the starting material *ent*-**161** and 75% of the expected products *ent*-**172** and *ent*-**173**. When the temperature of the reaction was raised to −40 °C, the conversion reached completion in the same time. The products *ent*-**172** and *ent*-**173** were hydrolyzed to the respective enones *ent*-**175**, *ent*-**176** and isolated in 80% yield in a 4.5:1 ratio. Neither of the diastereomeric pairs *ent*-**172**, *ent*-**173** or *ent*-**175**, *ent*-**176,** respectively, was separable by chromatography. Nevertheless, the stereochemistry of the major isomer could be deduced from a *J*-resolved NMR spectrum measured in a 1:1 mixture of C_6D_6/$CDCl_3$. The coupling constants of H-14 of the major component *ent*-**175** were measured to be $J_{8\beta\text{-}14\alpha}$ = 11.2 Hz, $J_{13\beta\text{-}14\alpha}$ = 12.5 Hz, $J_{13\alpha\text{-}14\alpha}$ = 4.1 Hz, showing clearly the axial position of H-14α. Please note that in *ent*-series the α-substituents are above the plane of drawing to maintain the relative stereochemistry (see **Chapter 1.3**). The minor constituent *ent*-**176** showed identical connectivity of atoms and was therefore assigned as the 14β-diastereomer. None of the 1,2-adducts *ent*-**174** or *ent*-**177** were detected in a measurable quantity.

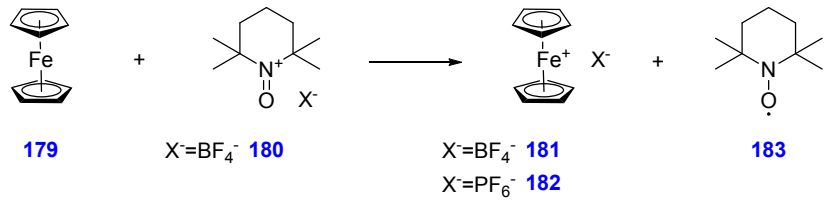
Hypothetical transition states of the reaction are depicted in **Scheme 29**. The cuprate reagent is coordinated through a metal halide bridge to the carbonyl group of enone **178**. The structure of *ent*-**161** is conformationally locked by the *trans*-annelation of rings B and C, forming a bent shape (see **Chapter 3.1.5.**, **Figure 9**). Coordination of the cuprate complex at the convex face (**178A**) leads to the major diastereomer *ent*-**172**, whereas coordination to the Δ^{13}-double bond at the concave face (**178B**) results in minor distereomer *ent*-**173**. Oxidative addition of copper in **178B** is accompanied by a double 1,3-diaxial interaction of the cuprate complex with H-7α and H-9α for the minor pathway. In the major pathway **178A**, the largest contribution comes from steric interaction of cuprate with H-8β. Therefore, it seemed possible that an increase in the steric bulk of the cuprate complex results in a larger difference in transition state energies of **178A** vs. **178B** and thus to an improvement of the diastereoselectivity.



Scheme 29: Proposed transition states for coordination of cuprate to *ent*-**161**

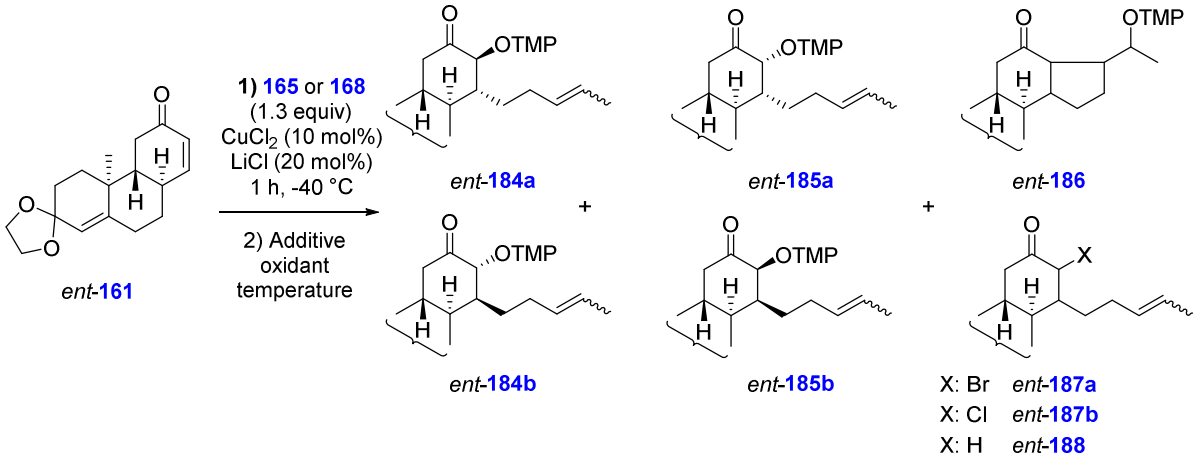
Thus, Ph_3P (20 mol%) or dppe (10 mol%) were added to the reaction mixture and the reaction was performed at −40 °C, followed by acidic hydrolysis. The 1,4-adducts *ent*-**175** and *ent*-**176** were isolated in 80% yield and the diastereomeric ratio improved to 9:1 or 10:1 respectively as estimated by ^{13}C NMR. The PPh_3 ligand afforded a slightly worse diastereoselectivity and was harder to remove from the product. An attempt to reach better selectivity by lowering the temperature to −78 °C in the presence of 10 mol% dppe resulted in isolation of *ent*-**175**:*ent*-**176**:*ent*-**177** in quantitative yield, but in 13:2:5 ratio as estimated by ^{13}C NMR. Presumably, the catalyzed reaction was too slow at −78 °C and the uncatalyzed reaction took place upon warming, lowering both the regio- and the diastereoselectivity considerably.

With the first step of the tandem reaction successfully established, the conditions for oxidation of the enolate were explored. Several SET oxidants were used in this study. Firstly, ferrocenium hexafluorophosphate (**182**) was used to generate the α-keto radical from the respective enolate (see **Chapter 1.8**). The resulting alkyl radical reacted with an added stable radical TEMPO (**183**). In another setup, 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (**180**) was used as the terminal oxidant. The salt **180** has been shown to oxidize ferrocene (**179**) *in situ* to the corresponding ferrocenium salt **181** (**Scheme 30**).[193] Conveniently, this process co-generates the trapping agent **183** and enables catalytic turnover of **179**. Low concentration of **183** in the reaction mixture increases the time-window for an intramolecular reaction of the radical generated from an enolate. It may be therefore advantageous to add or generate **183** slowly.[193] The possibility of oxidative cyclization of the enolate generated by addition of **165** or **168** to *ent*-**161** was probed (**Table 5**).



Scheme 30: SET oxidants employed in the tandem reaction

Table 5: Tandem copper-catalyzed CA–Oxidative cyclization



Entry [a]	Oxidant (equiv)	Additives (equiv)	RMgX	Solvent	T [c] (°C)	Isolated Yield (%)[b] *ent*-184	*ent*-185[d]	*ent*-186[d]	*ent*-187[d]	*ent*-188
1	**182** (1.0)[e]	**183** (1.0)[e]	**165**	THF	0	19	3	10	5	32
2	**182** (1.2)[e]	**183** (1.0),[e] LiCl (7.0), HMPA (6.0)	**165**	THF	0	20	5	3	5	34
3	**180** (1.5)[e]	**179** (0.05), iPr$_2$NH (1.0)	**165**	THF	0	33	4	13	12	29
4	**182** (1.2)[e]	**183** (1.1), iPr$_2$NH (1.0)	**165**	THF	0	42	8	13	3	11
5	**182** (1.2)[e]	**183** (1.15)[e]	**165**	Et$_2$O[f]	0	35	10	trace	0	27
6	**180** (1.1)[e]	**179** (0.05), iPr$_2$NH (0.5)	**165**	DME[f]	0	49	18	8	0	10
7	**182** (1.2)[e]	**183** (1.05),[e] iPr$_2$NH (0.5)	**168**	THF	−40	51	14	16	3	5
8	**180** (1.2)	iPr$_2$NH (0.5)	**168**	THF	−40	78	6	5	2	5
9[g]	**180** (1.2)	iPr$_2$NH (0.5)	**168**	THF	−40	73	8	5	1	5
10[h]	**180** (1.5)	iPr$_2$NH (0.5)	**168**	THF	−60	83	5	5	< 1	5

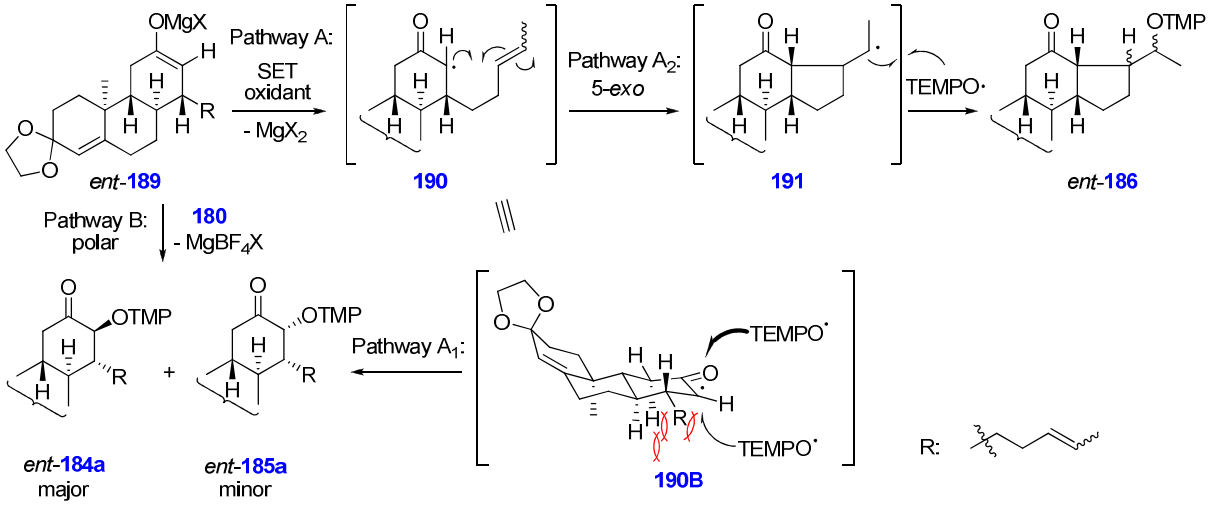
[a] Unless mentioned otherwise, all reactions were performed at 0.5 mmol scale in THF (5 mL) with 10 mol% of Li_2CuCl_4. RMgX (1.3 equiv) was added slowly over 1 h. [b] Inseparable mixture of 14α- and 14β-diastereomers **184-188 a**:**b** 4.5:1. [c] Temperature during the oxidation step. [d] Ratios determined by integration of the ^{1}H NMR spectrum of the isolated mixture of **185-187**. [e] Added slowly. [f] The magnesium enolate was trapped with TMSCl, the resulting silyl enol ether isolated in quantitative yield and redissolved in the respective solvent. The TMS group was transmetalated with MeLi (1.1 equiv) at rt. [g] Performed at 8 mmol scale. [h] Performed at 10 mmol scale, with 10 mol% of dppe ligand. Products obtained as inseparable mixture of 14α- and 14β-diastereomers **184-188 a**:**b** 6.2:1.

Ferrocenium hexafluorophosphate (**182**) was ground to homogeneity with TEMPO **183** and this powder was slowly added to the generated enolate (Entry 1). This approach led to a low isolated yield of *trans*-alkoxyamines *ent*-**184a** and *ent*-**184b**. Although they were chromatographically inseparable, the former crystallized readily, in contrast to the latter. The second fraction contained *cis*-alkoxyamines *ent*-**185a,b**, cyclized steroids *ent*-**186** and a small amount of 13-bromo derivative *ent*-

187a. Repeated chromatography in CH_2Cl_2/MTBE enabled separation of *ent*-**185**-**187**. The very last fraction consisted of simple 1,4-adducts *ent*-**188**. Addition of an excess of LiCl and HMPA before oxidation did not influence the composition of products significantly (Entry 2). Diisopropylamine was added to quench the excess of organometallic reagent (Entries 3,4,6–10). The applied catalytic oxidative conditions led to an increased proportion of halogenated byproducts *ent*-**187a** (Entry 3). Halogenation could be prevented to some extent by adding the TEMPO **183** to the reaction mixture in one portion, followed by a slow addition of the oxidant **182** (Entry 4). Next, the role of halides on the reaction was examined. With organomagnesium chloride **168**, the formation of **187** was supressed in comparison with bromide **165** (Cf. entries 1–4 vs. 7–10).

To examine the influence of enolate counterion and solvent on cyclization, the oxidation of lithium enolates was attempted in Et_2O and DME, respectively (Entries 5, 6). The lithium enolates were prepared by the standard procedure, reported by Stork and Hudrlik,[277,278] and subsequently oxidized by **182** in the presence of TEMPO **183** (Entry 5), or with **180** and a catalytic amount of ferrocene **179** (Entry 6). No halogenated product *ent*-**187a** was observed, yet the yield of cyclic isomers *ent*-**186** remained very low.

When performing the oxidation with a mixture of **182** and **183**, slowly added to the enolate generated from **168**, the cyclized product *ent*-**186** was isolated in the highest observed yield (Entry 7). However, the direct TEMPO trapping products *ent*-**184** and *ent*-**185** were still the major components. Since the cyclization result could not be improved to a useful level, the yields of alkoxyamines *ent*-**184** and **185** were optimized instead. Therefore, the oxoammonium salt **180** was used without ferrocene **179** (Entry 8). This approach was rewarded with 78% yield of *trans*-adduct *ent*-**184** and 6% of *cis*-adduct *ent*-**185**. The cyclized product *ent*-**186** was isolated in mere 5% yield and the chloride *ent*-**187b** was detected only in minute amount. The reaction was scaled-up to a gram-scale synthesis without major change in yield or product ratios (Entry 9). Employing the dppe ligand for the CA step and lowering the temperature of oxidation to −60 °C improved the ratio of *ent*-**184a**:**b** to 6.2:1 and increased the yield (Entry 10).



Scheme 31: Putative mechanism of formation of products *ent*-**184**-**186**

A suggested mechanism of the oxidative part of the tandem reaction is depicted in **Scheme 31**. The first part of the tandem, the CA of the Grignard reagent, results in the enolate *ent*-**189**. In principle, the metal cation in *ent*-**189** can be Li^+, Cu^+ or Mg^{2+}, although the latter is present in excess and is therefore the most probable. The enolate *ent*-**189** is oxidized by a SET oxidant, to afford a

transient α-carbonyl radical **190** (Pathway A). This can be mediated by an outer-sphere oxidant **182** or an inner-sphere oxidant Cu(II), through the formation and homolysis of Cu^{2+} enolate. Whether the oxoammonium salt **180** itself is capable of SET oxidation according to pathway A remains an open question, but polar addition of the enolate *ent*-**189** to **180** seems to be a viable process (Pathway B). Copper(I) maybe oxidized to copper(II), either by the oxoammonium salt **180** or potentially by the ferrocenium salt **182**.

Pathway A_1, which is predominant under all conditions, leads to direct trapping of **190** with **183**. The upper face of intermediate **190B** is less hindered, leading to the major product *ent*-**184a**. 1,3-Diaxial interactions combined with steric hindrance by the β-alkyl substituent are supposedly the key factors for the observed diastereoselectivity.[279] Similar interactions are governing the polar reaction according to pathway B, yet the face-selectivity is superior to pathway A_1 (Entries 7 vs. 8). The α-carbonyl radical **190** undergoes 5-*exo* cyclization to give radical **191** only to a minor extent (Pathway A_2). Radical **191** is trapped by the present persistent radical TEMPO **183**, affording the desired product *ent*-**186** in low yield.

Pathways A_1 and A_2 are directly competing and the distribution of products is determined by the respective rates of reaction. Combination of TEMPO radical with transient radicals occurs with $k \approx 10^8$ to 10^9 $M^{-1}s^{-1}$ at 80 °C, more polar solvents being at the slower end of the range.[280,281] The 5-*exo* cyclization of the 2-(but-3-enyl)cyclohexyl radical has a rate constant $k \approx 4\times10^5$ s^{-1} at 65 °C.[282] This explains the obtained results, however, since the cyclization is a unimolecular reaction, whereas the rate of combination reaction is dependent on the concentration of TEMPO **183**, a larger amount of the cyclized material *ent*-**186** can be isolated when **183** is added or generated slowly (Entries 3,4,7).

Halogenated byproducts *ent*-**187** are probably formed by the reaction of enolate **189** with copper(II) halide, generated by *in situ* oxidation of copper(I). Indeed, no *ent*-**187** is formed in the absence of copper (Entries 5, 6, **Table 5**). Ligand transfer of halogen from copper(II) halide is a facile process, occurring with rate constants $k \approx 1–5\times10^8$ $M^{-1}s^{-1}$ for $CuCl_2$ and about four times faster for $CuBr_2$.[283] It is therefore not surprising that the use of alkyl magnesium chloride **168** instead of bromide **165** led to a diminished amount of *ent*-**187**. Moreover, LiCl has been shown to accelerate the ligand transfer of $X^{\bullet}$.[283] CuX_2 is therefore directly competing with TEMPO (**183**) for the radical **190**. This can be overcome by employing a higher concentration of **183** over the copper catalyst at the price of suppressing the 5-*exo* cyclization (Entry 4, **Table 5**).

The structure of *nat*-**184a** was determined by single-crystal X-ray crystallography (**Figure 10a**). Both tetramethylpiperidinyloxy- (TMPO-) and pentenyl substituents occupy axial positions at the cyclohexane C-ring which exists in the boat conformation. This is consistent with the observed coupling constant $J_{13\beta\text{-}14\alpha}$= 1.6 Hz in $CDCl_3$, corresponding to a dihedral angle of the respective C-H bonds close to 90°. Supposedly, a steric clash between vicinal TMPO-, pentenyl and carbonyl groups forces the cyclohexanone ring into boat conformation. The axial pentenyl substituent also avoids the 1,3-diaxial interaction with H-7α. An anomeric effect might be also contributing, in an analogy to a reported α-halo ketone effect.[284–286]

For the minor isomer *ent*-**184b**, the signal of H-13α was obscured by the multiplet of the ketal OCH_2 signals. However, deprotection in acetone with a catalytic amount of acid afforded diketone *ent*-**192**, which showed a coupling constant of $J_{13\beta\text{-}14\alpha}$= 3.5 Hz in d_6-DMSO. The ROESY spectrum of *ent*-**192** confirmed the *trans*-configuration of the side chain and the TEMPO residue (**Figure 10b**). The constitution of the minor products *ent*-**185** is identical to *nat*-**184a** based on their 2D NMR spectra.

Nevertheless, a conformational equilibrium of ring C caused broadening of the crucial ^{1}H and ^{13}C signals. An exact configurational assignment was therefore impossible at this point.

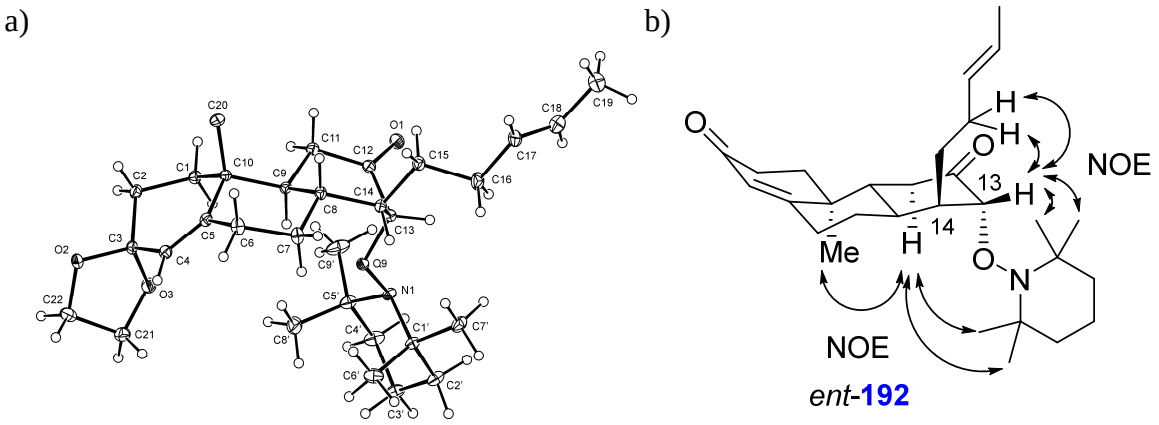
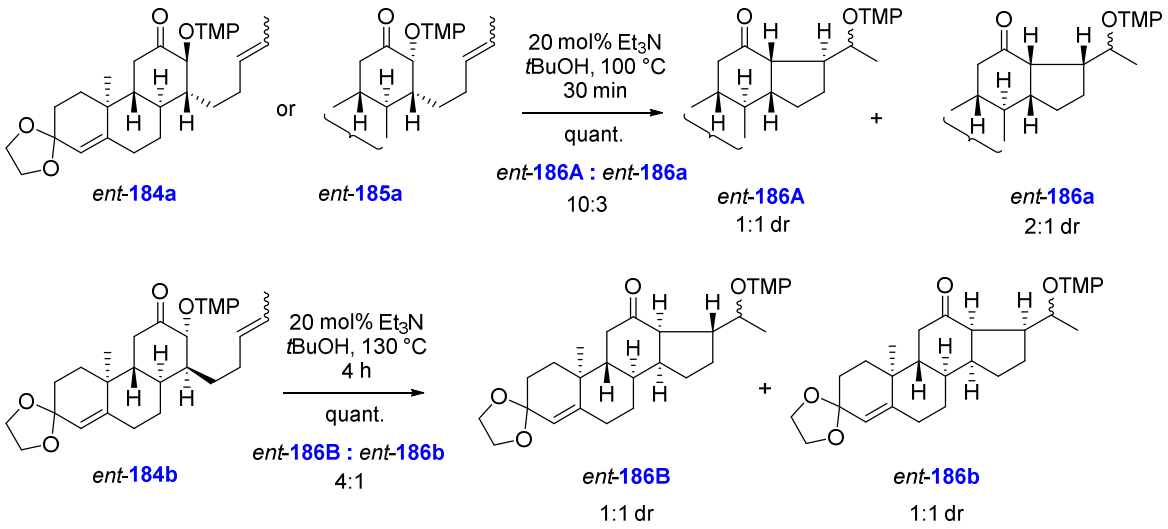


Figure 10: a) X-ray crystal structure of *nat*-**184a**. Thermal ellipsoids are drawn at the 30% probability level. **b)** Configuration and the probable conformation of *ent*-**192**. Arrows show important ROESY crosspeaks.

To conclude, efficient reaction conditions were found for the high-yielding synthesis of acyclic products *ent*-**184-185** with high 16:1 *trans*:*cis* ratio (Entry 10, **Table 5**). Competing halogenation side reactions can be suppressed by choosing proper substrates and reaction conditions, namely oxidant **180** and alkyl magnesium chloride **168**. The direct tandem cyclization is possible, although the maximum obtained yields of *ent*-**186** remained low.

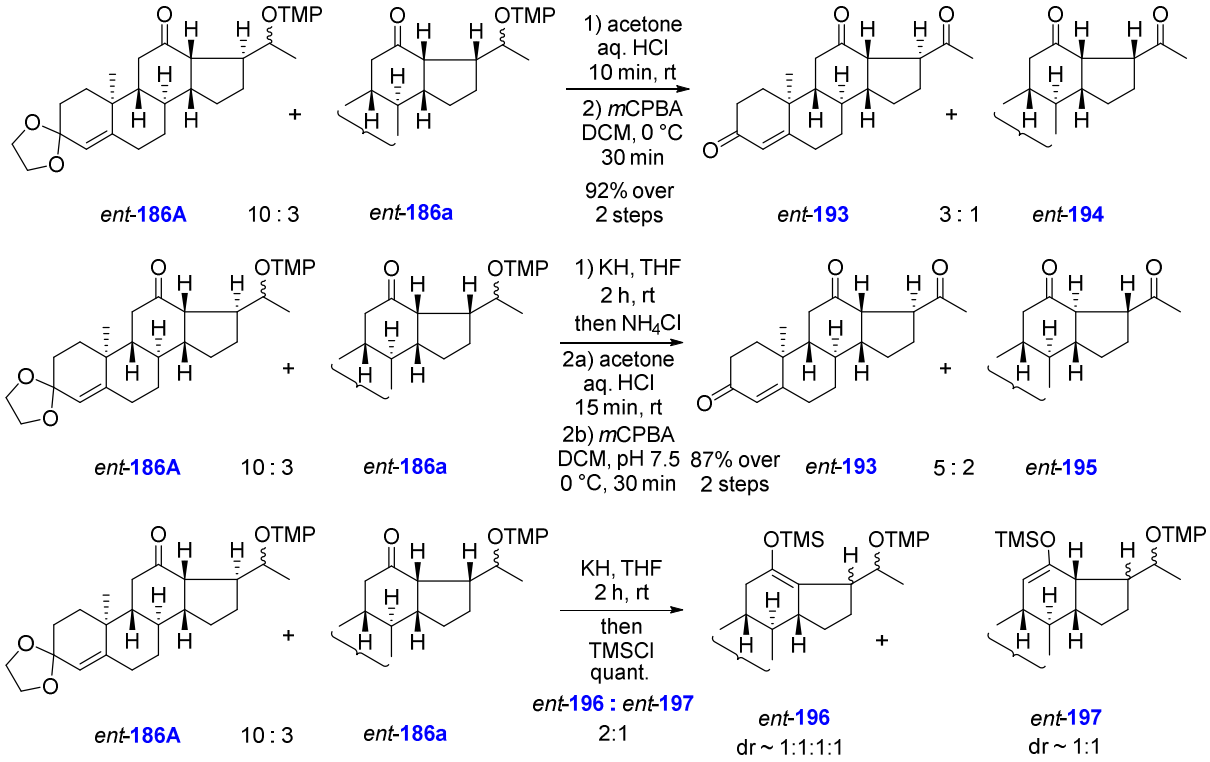
3.1.7. Thermal Cyclization

The potential of alkoxyamines *ent*-**184-185** to undergo thermal cyclization employing the PRE effect was investigated (**Scheme 32**). *t*BuOH was used as the solvent to minimize radical side reactions. Since the applied temperature exceeded the boiling point, a microwave reactor was used. At 100 °C, *trans*-alkoxyamine *ent*-**184a** cyclized in quantitative yield within 30 min. The diastereomeric ratio of the obtained steroids *ent*-**186A,a** was 5:5:2:1. The structure was elucidated after oxidative deprotection of TEMPO (*vide infra*). Addition of a small amount of triethylamine to the reaction mixture was necessary to suppress hydrolysis of the acid-sensitive ketal. The isolated *cis*-alkoxyamine *ent*-**185a** underwent the cyclization under identical conditions, affording exactly the same composition of diastereomers *ent*-**186A,a**. Importantly, this represented a proof of configuration of *ent*-**185a**. The H-14β isomer *ent*-**184b** did not cyclize at all at 100 °C, but required at least 130 °C to react. Even so, the reaction took approximately 4 h to completion and gave rise to a 4:4:1:1 mixture of diastereomers *ent*-**186B,b**. When a mixture of *ent*-**184a** and *ent*-**184b** was subjected to the reaction at 100 °C, *ent*-**184b** was quantitatively recovered by column chromatography. The tetracyclic diastereomers *ent*-**186** were chromatographically inseparable from each other.



Scheme 32: Thermal cyclization to ring D

To assign the stereochemistry at the newly formed stereocenters, the mixture of tetracyclic diastereomers *ent*-**186A,a** was fully deprotected by acidic hydrolysis of the ketal and subsequently by oxidative cleavage of the alkoxyamine (**Scheme 33**).[287] Two diastereomeric triketones **193** and **194** were obtained in a 3:1 ratio and excellent yield. The major compound **193** crystallized after HPLC separation and was characterized by X-ray crystallography (**Figure 11**).



Scheme 33: Structure assignment of diastereomeric 18-norsteroids *ent*-**186A,a**

The minor isomer *ent*-**194** was inseparable from *ent*-**193**. Nevertheless, NMR assignment of the mixture was possible (**Table 6**). Control experiments were performed to confirm the determined stereochemistry. First, the 13-position was epimerized in an attempt to prepare all four diastereomers at C-13 and C-17 for complete comparison. Therefore, the cyclized mixture *ent*-**186A,a** was

deprotonated with potassium hydride in THF and the potassium enolate was quenched with aqueous NH_4Cl. The resulting mixture of diastereomers was deprotected to afford triketones *ent*-**193** and *ent*-**195** in 5:2 ratio and 87% yield. Oxidative alkoxyamine deprotection was in this case performed in a biphasic mixture CH_2Cl_2/H_2O with phosphate buffer of pH 7.5 to prevent possible epimerization at C-17, but even so the expected minor diastereomer possessing H-13β,H-17β could not be found in the reaction mixture. Norsteroid *ent*-**195** was crystalline and was unambiguously characterized by X-ray crystallography (**Figure 11**).

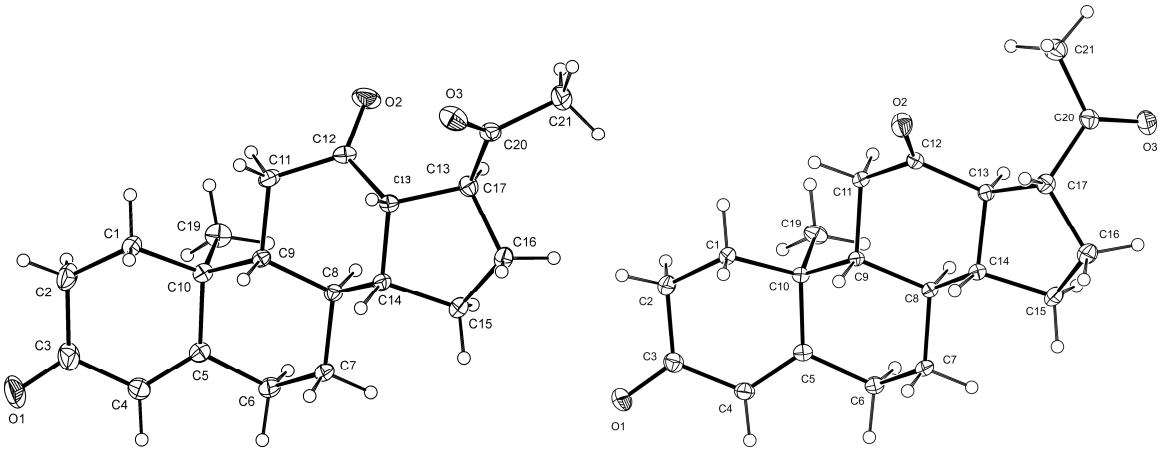


Figure 11: X-ray crystal structure of *ent*-**193** (left) and *ent*-**195** (right). Thermal ellipsoids are drawn at 30% probability level.

The stereochemistry of *ent*-**195** corresponds to the all-*trans* isomer and the structure resembles that of native steroids. Rings B and C are in chair conformation and ring D is in envelope conformation with carbon C-14 in *endo* position. The acetyl side chain resides in pseudoequatorial position. In contrast, the structure of **193** is unexpectedly flat, because of a boat conformation of the C-ring. Rings A and B are in typical half-chair or chair conformation respectively, while the D-ring is again in a nearly perfect envelope conformation with carbon C-16 in *endo* position. The acetyl side chain occupies pseudoequatorial position.

Table 6: D-ring coupling constants of triketones *ent*-**193**-**195** and *ent*-**200**

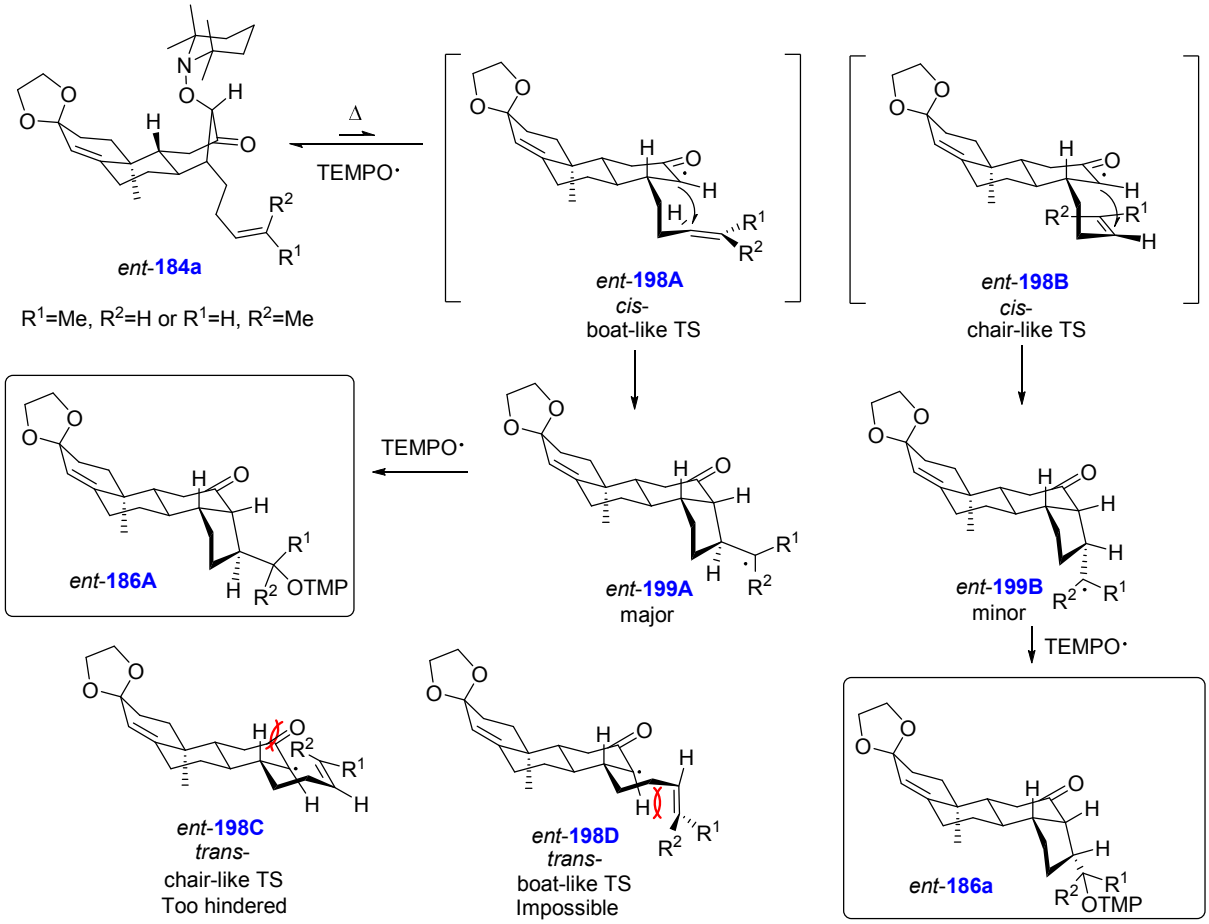
Triketone	Stereochemistry	^{1}H-^{1}H Coupling constants (Hz)			
		$J_{13\text{-}14}$	$J_{13\text{-}17}$	$J_{17\text{-}16a}$	$J_{17\text{-}16b}$
ent-**193**	H-13α, H-14α, H-17β	7.4	11.1	7.7	7.7
ent-**194**	H-13α, H-14α, H-17α	11.1	7.9	2.9	7.9
ent-**195**	H-13β, H-14α, H-17α	10.0	11.2	10.0	6.5
ent-**200**	H-13β, H-14β, H-17α	7.9	2.1	7.3	9.8

The result of the epimerization experiment suggests that the diastereomer *ent*-**195** shares a H-17α configuration with *ent*-**194**, if the 17-stereocenter did not isomerize during manipulation. To validate this, the potassium enolate of *ent*-**186A,a** was quenched with TMSCl and the mixture of TMS enol ethers *ent*-**196** and **197** was isolated in quantitative yield (**Scheme 33**). The ^{13}C NMR spectrum revealed the formation of four thermodynamic Δ^{12}-enol ethers *ent*-**196** and two kinetic Δ^{11}-enol ethers *ent*-**197** in ca. equimolar ratio (see **Chapter 5.2**). Therefore *ent*-**193** and *ent*-**194** must be epimeric at C-17, effectively leading to the proposal of a single possible configuration for *ent*-**194**, as shown in **Scheme 33**.

Based on this assignment, a likely mechanism of the thermal cyclization can be derived (**Scheme 34**). Upon heating, the C-OTMP bond of *ent*-**184a** or *ent*-**185a** homolyze to radicals *ent*-**198** and stable radical TEMPO.[215] An identical stereochemical outcome of both cyclizations strongly suggests an identical intermediate *ent*-**198** (*vide supra*). The thermal homolysis is facilitated by the release of steric strain in the boat-type C-ring. This is supported by the fact that both *ent*-**184a** and *ent*-**185a** homolyze at a by 30 °C lower temperature than *ent*-**184b**. In addition, the neighboring electron-withdrawing keto group is known to lower the homolytic C-OTMP bond dissociation energy.[213]

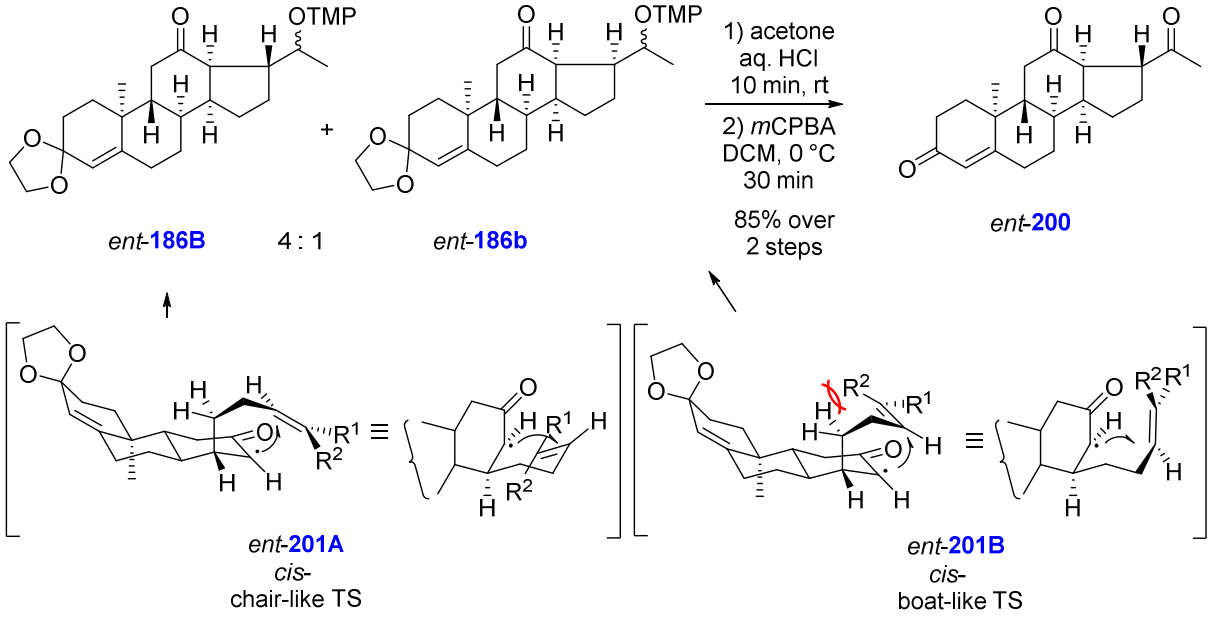
The cyclization process is governed by the equilibrium established according to the persistent radical effect, which is responsible for the virtual absence of side reactions in the process (see **Chapter 1.9**). Radical *ent*-**198** preferentially undergoes a 5-*exo* radical cyclization over a potential 6-*endo* process, which is favored by the angle of attack of about 109°, the geometry of the system and the substitution pattern at the $\Delta^{17(20)}$-double bond.[288]

The stereoselectivity of D-ring formation can be explained by the Beckwith-Houk model.[289–291] Two boat-like and two chair-like transition states *ent*-**198** can be imagined. From the two possible *cis*-transition states, the boat-like *ent*-**198A** display less interaction with the C-ring and is thus preferred over chair-like *ent*-**198B**. The resulting radicals **199** subsequently couple irreversibly with free radical TEMPO, since the C-OTMP bond dissociation energy of *ent*-**186** is too high for homolysis at 100 °C.[213] The coupling is not stereoselective because of free rotation of the side chain in *ent*-**199** bearing the radical and unhindered coupling trajectories of TEMPO. The transition states *ent*-**198C,D** leading to *trans*-annelation are highly disfavored by the geometry of the system.



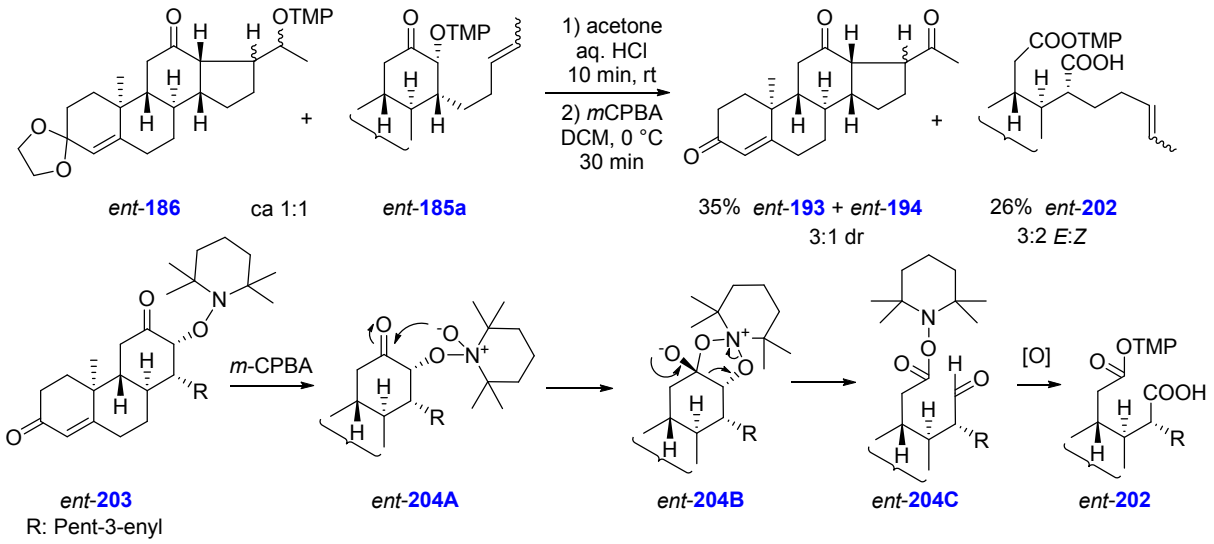
Scheme 34: The suggested cyclization mechanism for the D-ring formation

The 14β-diastereomers *ent*-**186B,b** were also subjected to deprotection, affording triketone *ent*-**200** in 85% yield (**Scheme 35**). The compound crystallized in long needles, which were not suitable for single crystal X-ray analysis. The structure was therefore assigned by its NMR spectrum on the basis of its characteristic coupling constants (**Table 6**). Presumably, the major diastereomer *ent*-**186B** shares the same stereochemistry with *ent*-**200**. Unfortunately, the amount of the sample of triketones was too low to allow reliable detection and analysis of the minor diastereomer. The configuration of *ent*-**186b** was therefore assigned by analogy with *ent*-**186a**. The hypothetical transition states *ent*-**201A** and *ent*-**201B** leading to both isomers *ent*-**186B,b** are shown in **Scheme 35**. The stereochemical preference of *ent*-**201A** vs. *ent*-**201B** is governed by minimalization of the allylic strain in the side chain. The *trans*-annelation of the D-ring is in case of H-14β-diastereomers *ent*-**184b** geometrically impossible, ruling out the 13α-configuration of *ent*-**186B,b**.



Scheme 35: Structure assignment of diastereomeric 18-norsteroids *ent*-**186B,b** and favored transition states of the cyclization

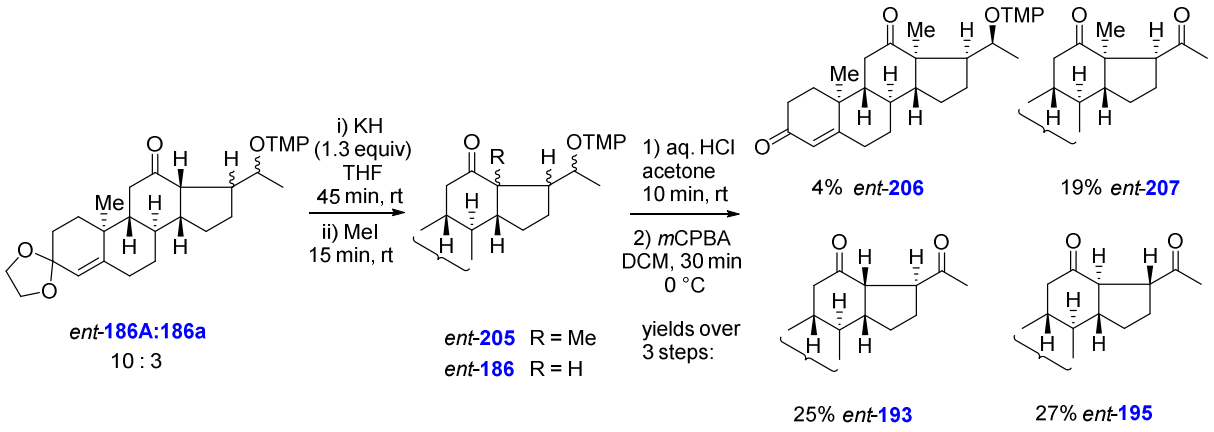
Finally, the mixture *ent*-**186** and *ent*-**185** obtained after the tandem CA-oxygenation reaction was also deprotected (**Scheme 36**). Three compounds were obtained: tetracyclic diastereomers *ent*-**193** and *ent*-**194** in a 3:1 ratio and the bicyclic acid *ent*-**202** in modest yield. The ratio of *ent*-**193**:**194** demonstrates a similar stereoselectivity of the tandem CA-oxidation and the stepwise thermal radical cyclizations. Formation of acid *ent*-**202** is probably a consequence of oxidative cleavage of *ent*-**185a**. A suggested mechanism is drawn in **Scheme 36**. Alkoxyamine *ent*-**203** is converted to its corresponding *N*-oxide *ent*-**204A**, which attacks C-12 carbonyl group to form tetrahedral intermediate *ent*-**204B**. Fragmentation of *ent*-**204B** leads to TMP ester *ent*-**204C**, which is oxidized under the reaction conditions to *ent*-**202**.



Scheme 36: Elucidation of the structure of 18-norsteroids *ent*-**186** formed directly by the tandem conjugate addition – oxidative cyclization (top). A suggested mechanism of the oxidative cleavage of *ent*-**203** (bottom)

3.1.8. Completion of the Steroid Skeleton

For the construction of the last C-C bond of the steroid skeleton (**Scheme 37**), the thermodynamic enolate from *ent*-**186A,a** was generated with a slight excess of KH in THF and subsequently methylated with an excess of methyl iodide. The resulting mixture of products *ent*-**205** and *ent*-**186** was difficult to separate and so it was carried on to global deprotection. The expected steroid *ent*-**207** was isolated in low yield along with a minute amount of some remaining alkoxyamine *ent*-**206**. Non-alkylated triketones *ent*-**193** and *ent*-**195** were isolated in moderate yield and a ca. 1:1 ratio. Importantly, both *ent*-**206** and *ent*-**207** crystallized in sufficient quality to allow a single-crystal diffraction analysis (**Figure 12**). The X-ray structure revealed a classical all-*trans* steroid skeleton, however with the side chain in pseudoaxial position of the D-ring. In *ent*-**206**, the tetramethylpiperidine ring resides over the D-ring, which illustrates the observed stereoselectivity in methylation of *ent*-**186**, provided that the solution conformation of the corresponding enolate is similar.



Scheme 37 Introduction of the C-18 methyl group

In an attempt to improve the synthesis of *ent*-**205**, other methods for generation of the thermodynamic enolate were explored. The use of TMSOTf with an excess of triethylamine or *in situ*

generated TMSI failed to generate silyl enol ether *ent*-**196** in good yield because of competing ring-opening of the allylic ketal. Silyl enol ether *ent*-**196** was therefore generated with KH and TMSCl and transmetalated with MeLi in DME (Cf. **Scheme 33**). The resulting lithium enolate proved to be too unreactive for alkylation with MeI, yielding only epimerized triketones *ent*-**193** and **195** after global deprotection. The same negative result was obtained when the potassium enolate of *ent*-**186A,a** was treated first with anhydrous LiCl in THF and subsequently with MeI. The use of NaH instead of KH at 50 °C also did not lead to an appreciable extent of methylation.

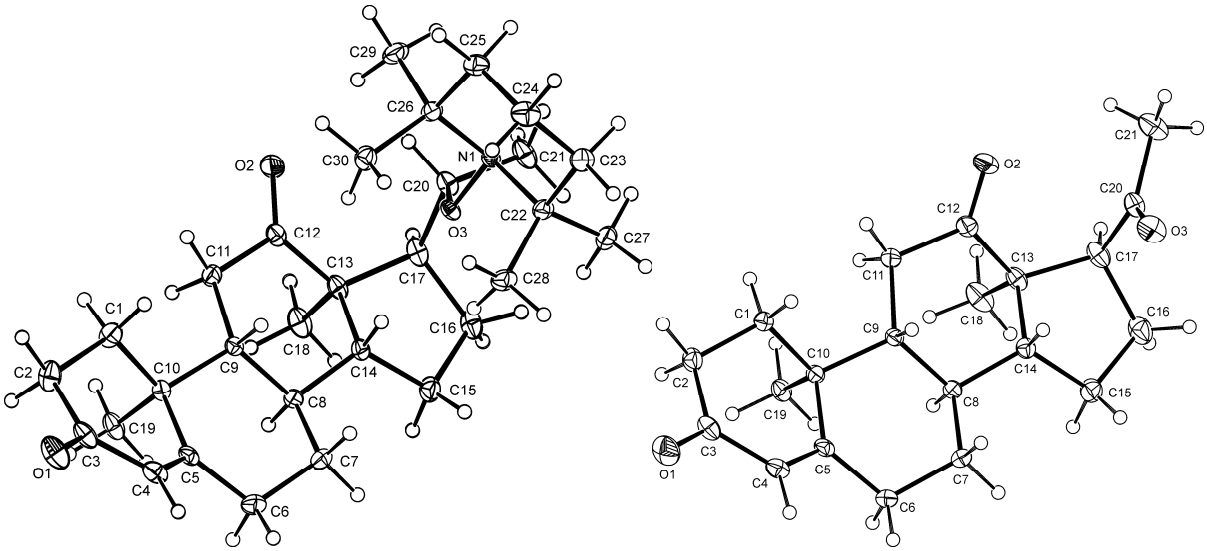
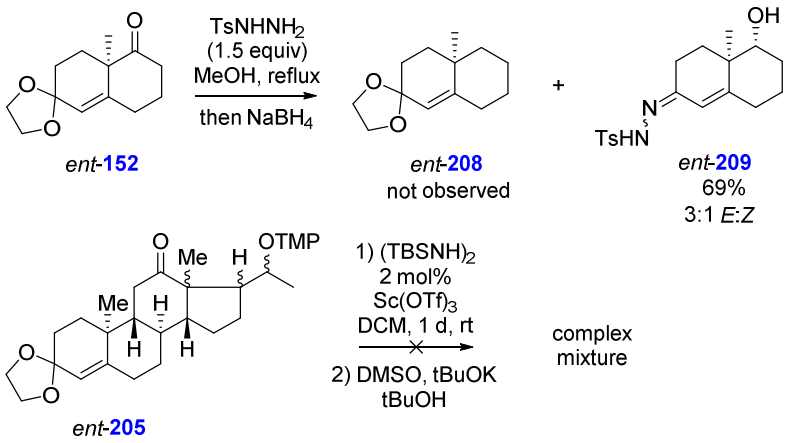


Figure 12: X-ray crystal structure of *ent*-**206** (left) and *ent*-**207** (right). Thermal ellipsoids are drawn at the 30% probability level.

Once KH was identified as the most suitable base, the reaction conditions were modified to improve the yield of alkylated product. The reaction time was prolonged to 2 h and an excess of hydride (3 equiv) was used. After deprotonation, the enolate was transferred to another flask and MeI was added. This approach led to significant overalkylation, resulting in a 4:3 ratio of monoalkylated:dialkylated product as determined by ESI+ mass spectrometry. This was presumably caused by fine KH particles present during the methylation. Therefore, a small amount of dry *t*BuOH (0.1 equiv) was added before MeI, which improved the ratio of monoalkylated:dialkylated steroids to 5:1. The ^{1}H NMR spectrum of the crude mixture of *ent*-**205** also showed the presence of ca. 15% of *O*-methylated products in both cases. Since no method to purify the mixture obtained after methylation was found, the next step was performed with the crude material.

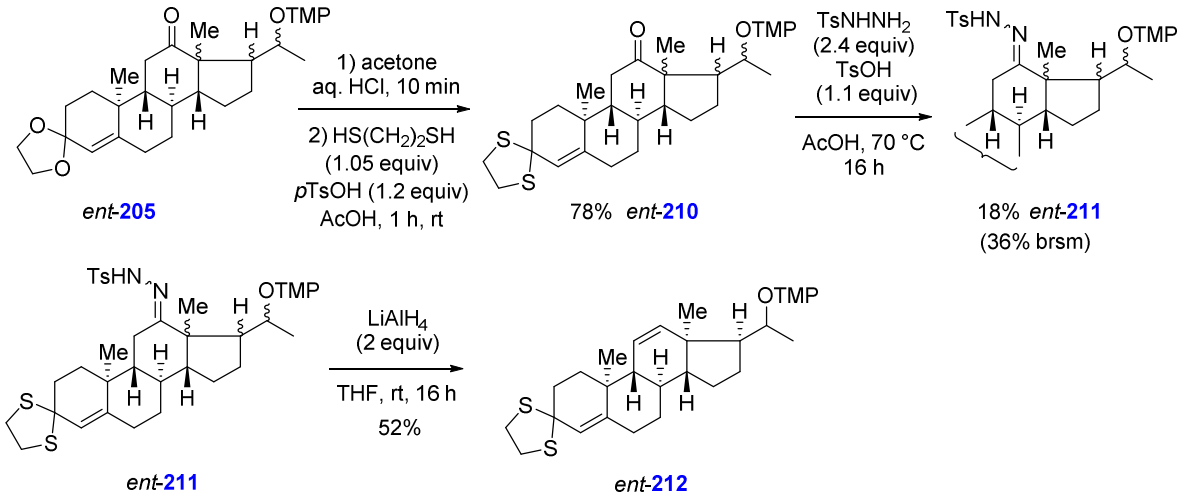
To access the enantiomers of neurosteroid *ent*-**7**, the C-12 carbonyl group had to be reduced to a methylene unit. A number of synthetic methods is available for this operation, yet the two most popular could not be used. The classic Clemmensen reduction is incompatible with the ketal, while Wolff-Kishner reduction requires drastic thermal conditions, which would cause elimination of the alkoxyamine group in the side chain. The latter became apparent during the thermal cyclization of *ent*-**184** at temperatures above 130 °C. The Caglioti reaction was tried on model compound *ent*-**152**,[292,293] but tosylhydrazide reacted preferentially with the allylic ketal and the desired product *ent*-**208** was not formed (**Scheme 38**). Instead, alcohol *ent*-**209** was isolated as the major product. Addition of stoichiometric amount of triethylamine inhibited the tosylhydrazone formation completely. Myers modification of Wolff-Kishner reaction was also attempted at the substrate *ent*-**205**,[294] but led only to intractable mixtures.



Scheme 38: Unsuccessful attempts for hydrazone formation

The labile ketal in *ent*-**205** was therefore exchanged for the more robust thioketal *ent*-**210** in two steps and good overall yield (**Scheme 39**). More than one equivalent of *p*TsOH was necessary to start the reaction. Presumably, the first equivalent is unproductively consumed in salt formation with the nitrogen atom of the piperidine ring. The conversion to tosylhydrazone *ent*-**211**, however, required harsh reaction conditions and the yield was very low. It should be nevertheless noted that the reaction was performed on a mixture of various alkylated products, since the mixtures *ent*-**205** or *ent*-**210** were inseparable. It can be envisaged that doubly alkylated products react more slowly, or even cannot be converted to a tosylhydrazone.

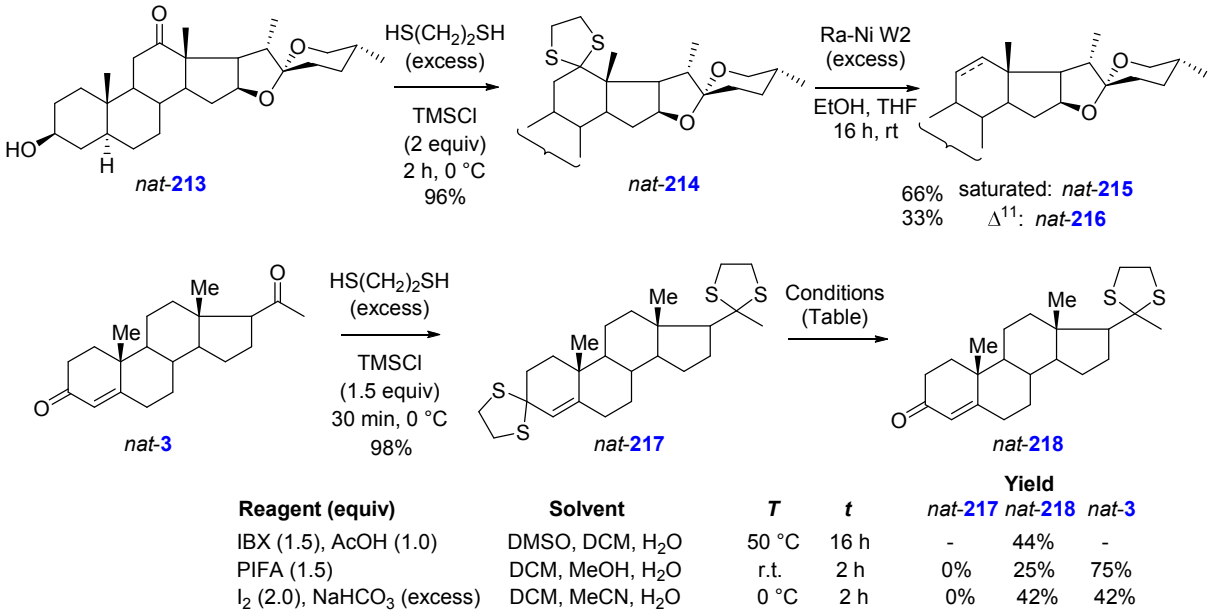
The hydrazone *ent*-**211** proved to be reducible, but only to the stage of Δ^{11}-olefin. Only one diastereomer of *ent*-**212** was isolated. These facts and the low yield of hydrazone formation can be explained by steric hindrance of C-12 in 13-methyl ketones *ent*-**205** and *ent*-**210**. One of the isomers in position C-20 reacts either more slowly or not at all. $LiAlH_4$ apparently serves only as a base instead of a nucleophile in the reduction of *ent*-**211**, and the result is a Bamford-Stevens-Shapiro reaction giving alkene *ent*-**212**.[295,296]



Scheme 39: Formation of hydrazone *ent*-**211** and its reduction

To improve the reduction of the C-12 carbonyl group, thioketal formation and its reduction was investigated (**Scheme 40**). For this study, model compounds hecogenin *nat*-**213** and progesterone *nat*-**3** were employed to simplify interpretation of results and to save valuable synthetic material. Formation of thioketals *nat*-**214** and *nat*-**217** proceeded in neat 1,2-ethanedithiol with TMSCl as the

source of anhydrous HCl in excellent yields. Remarkably, the spiroketal unit of *nat*-**213** remained untouched under these conditions. Desulfurization of the thioketal was successful, provided that fresh Raney nickel of W-2 quality was used. A mixture of tigogenin (*nat*-**215**) and Δ^{11}-unsaturated steroid *nat*-**216** was isolated in 2:1 ratio and good yield.

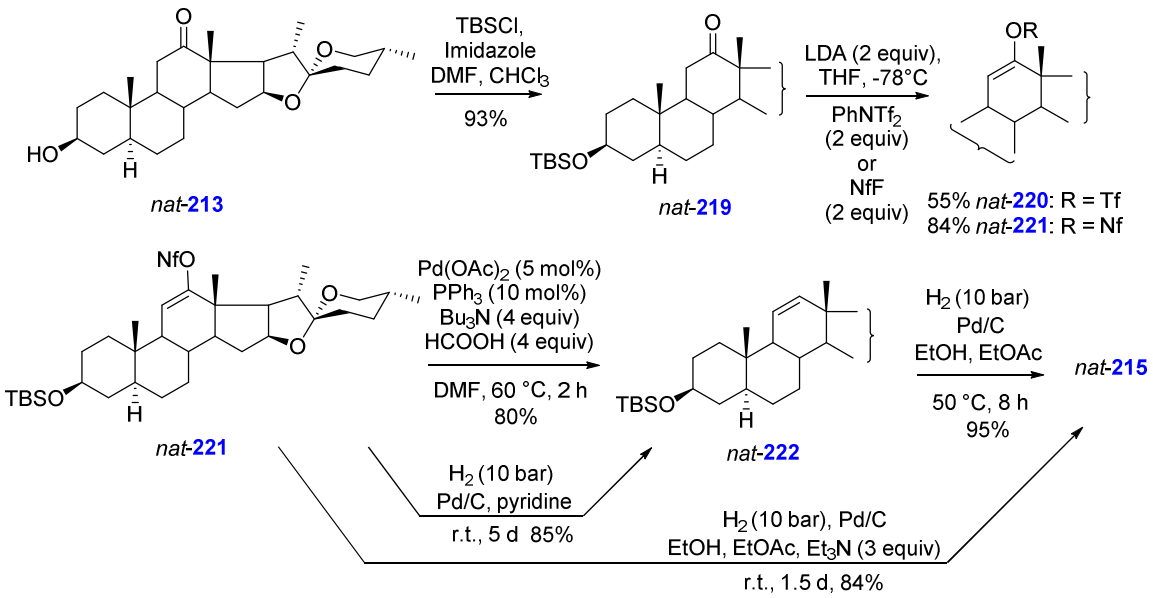


Reagent (equiv)	Solvent	*T*	*t*	Yield *nat*-217	*nat*-218	*nat*-3
IBX (1.5), AcOH (1.0)	DMSO, DCM, H_2O	50 °C	16 h	-	44%	-
PIFA (1.5)	DCM, MeOH, H_2O	r.t.	2 h	0%	25%	75%
I_2 (2.0), $NaHCO_3$ (excess)	DCM, MeCN, H_2O	0 °C	2 h	0%	42%	42%

Scheme 40: Thioketal formation, reduction and deprotection on model systems

Next, selective deprotection of allylic thioketal in the presence of the alicyclic thioketal was investigated (**Scheme 40**). IBX gave the best yield of enone *nat*-**218**, but the mass recovery was poor. In contrast, both bis(trifluoroacetoxy)iodobenzene (PIFA) or iodine gave clean conversions, although substantial amounts of globally deprotected progesterone *nat*-**3** were isolated. Employing a lower amount of oxidant led in all three cases to incomplete conversion (not shown).

In light of the low yields of selective thioketal deprotection and desulfurization, the strategy of carbonyl reduction was changed to conversion of the ketone to a sulfonyl enol ether, followed by catalytic reduction (**Scheme 41**).[297–299] Hecogenin (*nat*-**213**) was protected as TBS ether *nat*-**219** under standard conditions. Ketone *nat*-**219** was deprotonated with a strong base and the enolate was trapped with *N*-phenylbis(trifluoromethanesulfonimide) or nonaflyl fluoride. The corresponding triflate *nat*-**220** or nonaflate *nat*-**221** were isolated in 55% and 84% yields, respectively. Apart from the lower yield, the triflate *nat*-**220** was contaminated with a small amount of the triflimide reagent and was therefore not further used in the synthesis. The nonaflate *nat*-**221** was reduced to alkene *nat*-**222** with tributylammonium formate in the presence of Pd^0 catalyst in good yield. Hydrogenation of *nat*-**222** proceeded with a loss of TBS group to afford tigogenin (*nat*-**215**) in virtually quantitative yield. It is known that molecular hydrogen can be directly used as a reductant of enol sulfonates in the presence of heterogeneous Pd catalyst.[299] Hydrogenation of nonaflate *nat*-**221** over Pd/C in EtOH/EtOAc mixture in the presence of triethylamine gave directly the desired *nat*-**215** in very good yield. When pyridine was employed as the solvent, the reduction of *nat*-**221** stopped in the stage of Δ^{11}-alkene *nat*-**222** and the TBS group was preserved.

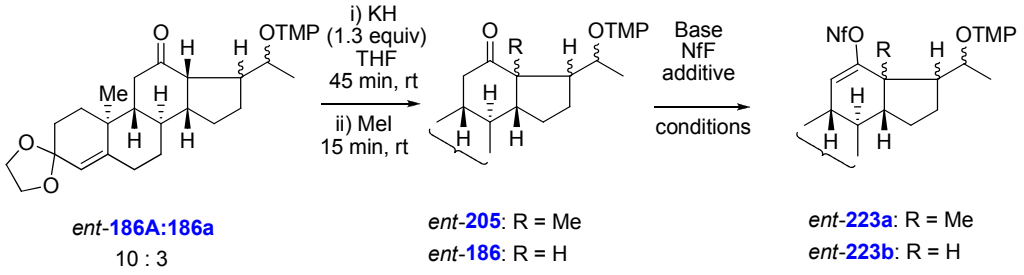


Scheme 41: Formation and reduction of model compound nonaflate *nat*-**221**

3.1.9. Synthesis of *ent*-Progesterone

The results of the model study were applied to the key substrate *ent*-**205** (**Table 7**). The crude mixture of diastereomers *ent*-**205** was deprotonated with strong base and NfF was added to form the respective nonaflate. Lithium diisopropylamide gave a modest yield of the desired nonaflate *ent*-**223**, which was inseparable from side product *N*,*N*-diisopropyl nonafluorobutanesulfonamide (Entry 1).[300] LiHMDS and KHMDS, sterically more hindered bases, led to low conversion (Entries 2, 3). Interestingly, only one diastereomer of **223** was isolated, suggesting a large difference in reactivity of the isomers at C-20, which were both present in the reaction mixture. *t*BuLi or *i*PrMgCl led to full recovery of the starting material (Entries 4, 5). Use of KH resulted in higher yields of the isolated nonaflates (Entries 6–9). Small amounts of protic additives were used to facilitate the deprotonation of the hindered ketone *ent*-**205**. The differences between these additives were nevertheless quite small. The reaction of the respective potassium enolate with NfF is relatively rapid, the composition of the reaction mixture did not change anymore after 30 min since NfF addition. Overall, KH with a sterically hindered additive proved to be the reagent of choice (Entries 6, 8).

Table 7: Synthesis of nonaflate *ent*-**223**



ent-**186A:186a**
10 : 3

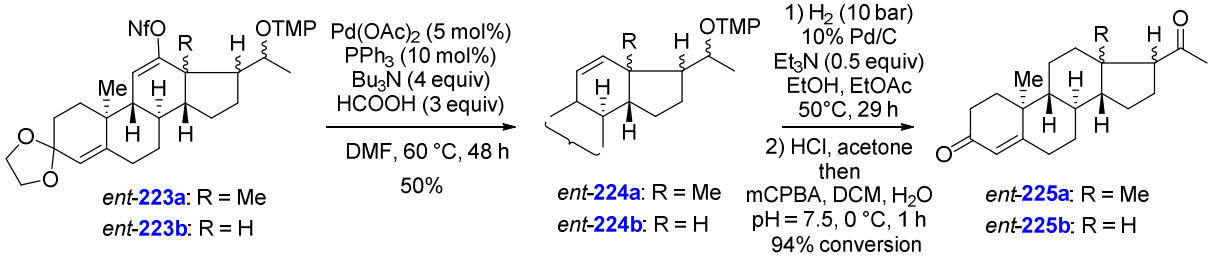
ent-**205**: R = Me
ent-**186**: R = H

ent-**223a**: R = Me
ent-**223b**: R = H

					Yield (%)	
		Additive	**Temperature**[a]		**Recovered**	
Entry	**Base (equiv)**	**(equiv)**	**(°C)**	**Time**[b] **(h)**	***ent*-205**	***ent*-223**
1	LDA (2.0)	-	−78 to 0	1 + 16	55	32[c]
2	LiHMDS (2.0)	-	0	2 + 16	84	13[d]
3	KHMDS (2.4)	-	0 to 25	2 + 16	55	17[d]
4	*i*PrMgCl (1.1)	-	−78 to 0	3 + 16	100	0
5	*t*BuLi (1.1)	-	−78 to 0	3 + 16	100	0
6	KH (3.0)	*t*BuOH (0.2)	25	2 + 1	16	56
7	KH (3.0)	*i*PrOH (1.0)	0	2 + 16	48	32
8	KH (3.0)	HMDS (1.0)	0	5 + 11	52	40[d]
9	KH (1.5)	*i*PrOH (1.0)	0	1.5 + 0.5	42	42

All reactions were performed in THF with 2.0 equiv of NfF. [a] During deprotonation. [b] First number is the duration of deprotonation, the second is the reaction time after addition of NfF. [c] The product contained a large amount of inseparable sulfonamide iPr_2NNf, [300] the yield was calculated from integration of the ^1H NMR spectrum. [d] Single diastereomer.

The mixture of nonaflates *ent*-**223** was subjected to reduction catalyzed by $Pd(PPh_3)_4$, but the reaction was much slower than for *nat*-**221** (**Scheme 42**). After two days, the nonaflate was reduced and a mixture of olefins *ent*-**224a** and *ent*-**224b** was isolated in 50% yield. The mass spectrum of *ent*-**224** showed >80% of non-methylated product *ent*-**224b**. To facilitate interpretation of the NMR spectra, the Δ^{11}-double bond was hydrogenated and the alkoxyamine side chain oxidatively deprotected to afford a complex mixture of diketones *ent*-**225b**. Nevertheless, not a trace of desired *ent*-17-isoprogesterone or *ent*-progesterone (*ent*-**3**) was observed.



ent-**223a**: R = Me
ent-**223b**: R = H

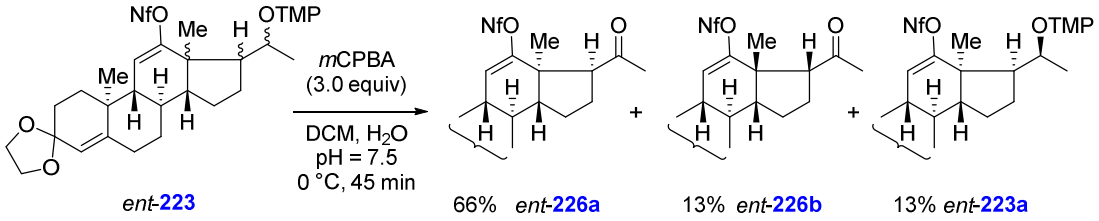
ent-**224a**: R = Me
ent-**224b**: R = H

ent-**225a**: R = Me
ent-**225b**: R = H

Scheme 42: Attempted reduction of nonaflate *ent*-**223**

The slow reduction of nonaflate *ent*-**223** was thought to be caused by steric hindrance of a bulky side chain. This hypothesis was supported by the fact that unsubstituted nonaflates *ent*-**223b** were reduced preferentially, although slowly. To reduce the steric crowding next to C-12, alkoxyamines

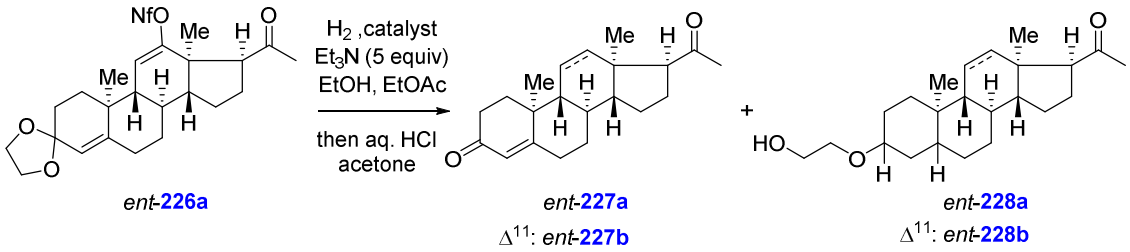
ent-**223** were oxidized first to ketones *ent*-**226** (**Scheme 43**). At slightly basic pH to preserve ketal and enol nonaflate, the oxidation smoothly afforded the expected *ent*-**226a** in 66% yield, diastereomer *ent*-**226b** in 13% yield, and recovered *ent*-**223a** as a single diastereomer in 13% yield.



Scheme 43: Chemoselective deprotection of nonaflate *ent*-**223**

A selective reduction of *ent*-**226a** over heterogeneous palladium catalyst was explored (**Table 8**). Reduction over 10% Pd/C was relatively fast at 50 °C and also at room temperature, with the 12-nonaflyl substituent disappearing in 1 day (Entries 1–4). The conversion was conveniently monitored by the ratio of CF_3 signals in the ^{19}F NMR spectrum. An undesired reaction occurred at the ketal *ent*-**226**, causing reduction of the Δ^4-double bond. At the same time, the dioxolane ring was opened to afford alcohol *ent*-**228**.

Table 8: Reduction of nonaflate *ent*-**226a**



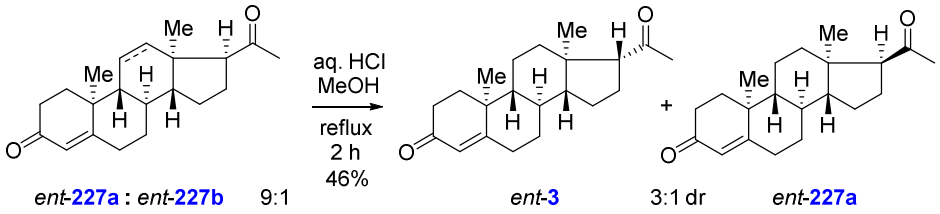
Entry	Catalyst (mol%)	H_2 Pressure (bar)	*T* (°C)	*t* (d)	Conversion[a] (%)	*ent*-**227**: *ent*-**228**[b]	**a** : **b**[b]
1	10% Pd/C (15)	10	50	1	100	0.6 : 1	5 : 1
2	10% Pd/C (30)	10	25	1	100	1.3 : 1 (33% : 31%)[c]	9 : 1
3	10% Pd/C (30)	1	25	1	100	1.7 : 1	6.6 : 1
4	10% Pd/C (30)	1	25	2	100	0.7 : 1 (24% : 26%)[c]	19 : 1
5	5% Pd/$CaCO_3$ (15)[d]	1	25	1 to 6[e]	50	6.8 : 1	8.4 : 1
6	5% Pd/$CaCO_3$ (15)	1	25	2 to 6[e]	66	6.6 : 1	5 : 1
7	5% Pd/$BaSO_4$ (26)	10	25	8	95	3.9 : 1	2.2 : 1
8	5% Pd/Al_2O_3 (22)	1	25	8	85	4.3 : 1	2.1 : 1
9	5% Pd/Al_2O_3 (22)	20	25	1[f]	100	1.2 : 1	2.9 : 1

The reaction was conducted at *c* = 14 mM in EtOH/EtOAc 1:1 and Et_3N (5 equiv). [a] The conversion was determined by integration of the ^{19}F NMR spectra. [b] The ratios were determined by integration of groups of characteristic signals in the ^{1}H NMR spectra. [c] Isolated yield. [d] Lindlar catalyst, poisoned with lead [e] The conversion halted after the first day and the reaction mixture remained unchanged thereafter. [f] The reaction mixture from entry 8 was resubjected to the reaction under stated conditions.

To reach selective hydrogenation, other palladium catalysts were screened. The Lindlar catalyst or 5% $Pd/CaCO_3$ led to the best selectivity, but the reaction stalled once it reached 50% or 66% conversion, respectively (Entries 5, 6). A new portion of catalyst, an aqueous workup or changing the reaction solvent to ethanol with THF, MeCN or DMF instead of EtOAc did not lead to improvement. The use of 5% $Pd/BaSO_4$ resulted in moderate selectivity with respect to ketal opening, but the hydrogenation of the Δ^{11}-double bond was slow (Entry 7). Palladium on alumina proved comparable to $Pd/BaSO_4$ (Entries 8, 9). Under all the investigated conditions, a reduction of Δ^{11}-double bond was slower than that of the vinyl nonaflate. The ketal opening was found to be the slowest of the observed reactions.

The reaction mixtures from entries 2 and 4 were separated by column chromatography to furnish 33% and 24% of *ent*-**227**, respectively. Compounds *ent*-**227a** and *ent*-**227b** were inseparable by standard column chromatography.

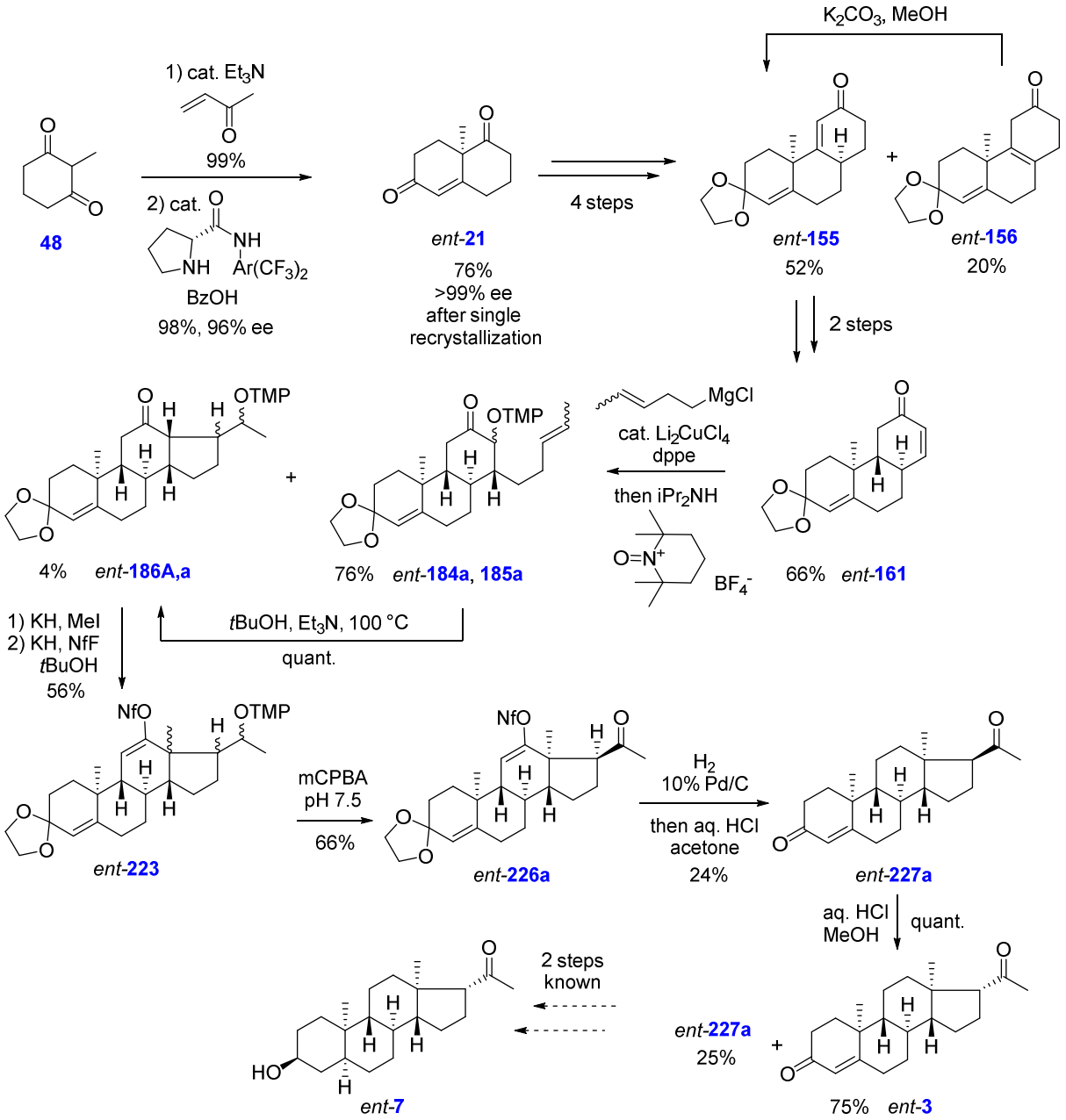
The obtained sample of *ent*-isoprogesterone (*ent*-**227a**) contaminated with *ent*-**227b** was subjected to the known isomerization of the side chain.[301] The diastereomeric ratio of the obtained crude mixture was 3:1 *ent*-**3**:*ent*-**227** as determined from ^{1}H NMR spectrum. Column chromatography on silica gel impregnated with silver(I) nitrate enabled separation of the Δ^{11}-double bond containing impurities, affording a mixture of diastereomers *ent*-**3**:*ent*-**227** in a 3:1 ratio and 46% yield. These compounds are known to be separable by crystallization from EtOH.[301] An enantiomeric sample obtained by isomerization of *nat*-**3** was separable by preparative HPLC on silica gel in $CHCl_3$/hexanes/MTBE 6:3:1. Unfortunately, the amount of *ent*-**3** so far obtained in the last step of the total synthesis did not allow for either of these methods. The identity of prepared *ent*-**3** was confirmed by comparison of ^{1}H and ^{13}C NMR spectra with the natural enantiomer *nat*-**3** (**Appendix D**). It should be noted that low yields in last two steps are in part result of working with less than 10 mg of material.



Scheme 44: Isomerization of the steroid side chain to *ent*-**3**

The summary of the total synthesis of *ent*-**3** is depicted in **Scheme 45**. The first asymmetric center is introduced in the HPESW reaction, which was optimized to afford 98% yield of Wieland-Miescher ketone *ent*-**21** with 96% ee. A single crystallization provided virtually enantiopure material, which was selectively protected and subjected to Robinson annulation to furnish enone *ent*-**155** in 52% overall yield for 4 steps. Deconjugated enone *ent*-**156** was isolated in 20% yield, but could be easily equilibrated to *ent*-**155**. Consecutive Birch reduction and Saegusa oxidation installed the Δ^{13}-double bond in 66% yield. The key tandem conjugate addition-oxygenation followed by a thermal radical cyclization afforded steroid *ent*-**186A,a** in 80% yield from *ent*-**161**. The C-18 methyl group was introduced by methylation of the thermodynamic enolate of *ent*-**186A,a**. Nonaflation and oxidation of the alkoxyamine in the side chain afforded *ent*-**226a** as a single diastereomer in 37% yield over three steps from *ent*-**186A,a**. Hydrogenation of nonaflate followed by acidic workup gave 24% yield of *ent*-17-isoprogesterone (*ent*-**227a**). Epimerization of the side chain provided a sample of *ent*-progesterone (*ent*-**3**), which had identical spectral properties compared to native progesterone. The whole synthesis consisted of 15 steps in the longest linear sequence and provided *ent*-**3** in 2.4% overall yield. The

synthesis of larger amounts of *ent*-**3** for the preparation of *ent*-pregnanolone (*ent*-**7**) and its sulfate as enantiomers of native neurosteroids is underway.



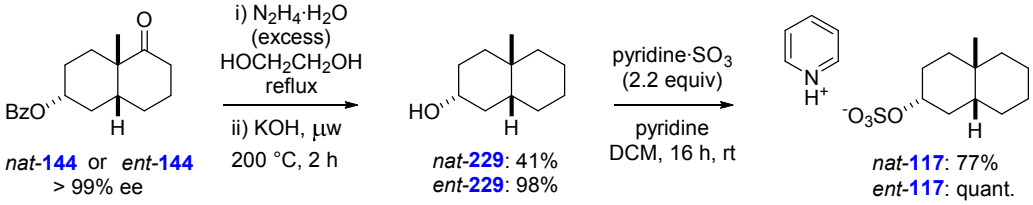
Scheme 45: Summary of the total synthesis of *ent*-progesterone *ent*-**3** and a formal synthesis of *ent*-pregnenolone (*ent*-**7**)

3.2. TRUNCATED STEROID ANALOGS

3.2.1 Synthesis of the Bicyclic and Tricyclic Analogs

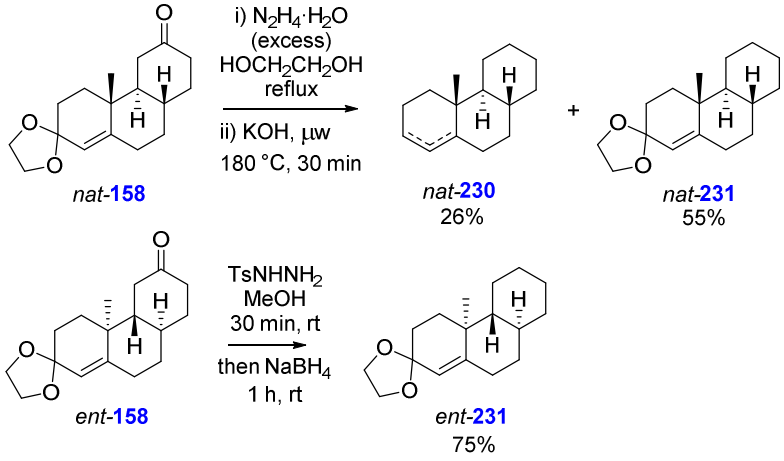
To explore the minimum binding requirements of the NMDA receptor, bicyclic and tricyclic steroid analogs **117** and **118** were synthesized. The rings A and B were preserved together with the relative configuration of the native neurosteroid hormone *nat*-**7**. The potential B-ring and C-ring were left unsubstituted to exclude random polar interactions of the substrate with a surface of the receptor.

The synthesis of **117** started from benzoate **144** (see **Chapter 3.1.3**). Both enantiomers of **144** were subjected to the Huang-Minlon modification of the Wolff-Kishner reduction to afford the respective alcohol **229** in good yield (**Scheme 46**). Decalinol **229** was slightly volatile, which caused lower yield in case of *ent*-**229**, which was synthesized on a smaller scale. Sulfation of **229** with pyridine-sulfur trioxide complex afforded smoothly both enantiomers of **117** in excellent yields.



Scheme 46: Preparation of bicyclic sulfates **117**

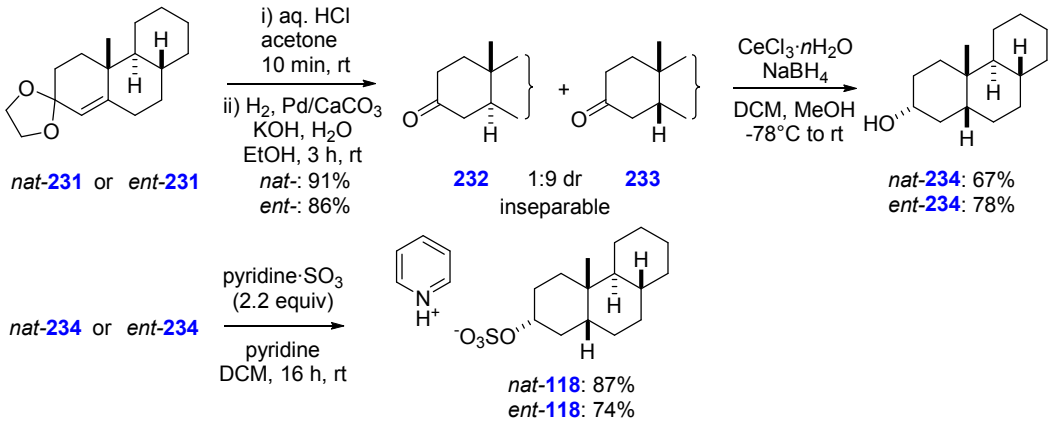
The tricyclic analogs **118** were prepared by taking another synthetic detour from the total synthesis. Ketone *nat*-**158**, which was accessed as shown in **Chapter 3.1.5**, was reduced in a manner analogous to benzoate **144** (**Scheme 47**). The corresponding ketal *nat*-**231** was isolated in a modest yield, along with a small amount of doubly deoxygenated hydrocarbon *nat*-**230**. Apparently, the harsh reaction conditions caused substitution of the ketal for hydrazone, which was then reduced. Partial migration of the Δ^4-double bond to Δ^3-position was observed in *nat*-**230**. Nevertheless, sufficient amounts of material for further synthesis of *nat*-**118** were obtained in this reaction. To reach a higher yield, *ent*-**158** was reduced under Caglioti conditions by $NaBH_4$ reduction of the respective tosylhydrazone. This variant worked better and the desired *ent*-**231** was prepared in one-pot procedure and good yield. Interestingly, the allylic ketal remained untouched under the applied conditions (cf. **Chapter 3.1.8**).



Scheme 47: Deoxygenation of carbonyl C-12

The allylic ketal was deprotected and the Δ^4-double bond was hydrogenated to afford preferentially 5β-isomer **233**, which was inseparable from the minor 5α-isomer **232** (**Scheme 48**).

Luche reduction of the ketones gave the corresponding mixture of equatorial alcohols, from which **234** was separated in pure form. The minor 3β,5α-isomer could not be purified even after repeated chromatography in various solvent systems (not shown). The sulfation of **234** proceeded uneventfully to furnish *nat*-**118** and *ent*-**118** in good yields.



Scheme 48: Preparation of tricyclic sulfates **118**

3.2.1 Biological Activity of the Truncated Analogs

The *in vitro* activity of **117** and **118** at NMDA receptors was evaluated by Mgr. Barbora Krausová in the laboratory of Dr. Ladislav Vyklický, Jr. at the Institute of Physiology of Academy of Sciences of the Czech Republic. For comparison, data of native neurosteroid *nat*-**2**, measured under identical conditions, are displayed.[58] For a more detailed description see **Appendix B**.

The IC_{50} value of native neurosteroid *nat*-**2** and synthetic analogs **117** and **118** is plotted in **Figure 13**. The inhibitory activity of tricyclic analogs **118** approach that of native inhibitory ligand *nat*-**2** of the NMDA receptor. The difference between both enantiomers of **118** is strikingly small, ca. 1.3-fold in favor of the natural enantiomer. In contrast, bicyclic sulfates **117** exhibit a markedly lower inhibitory activity, with *nat*-**117** showing ca. 6-fold decrease and *ent*-**117** ca. 12-fold decrease against *nat*-**2**.

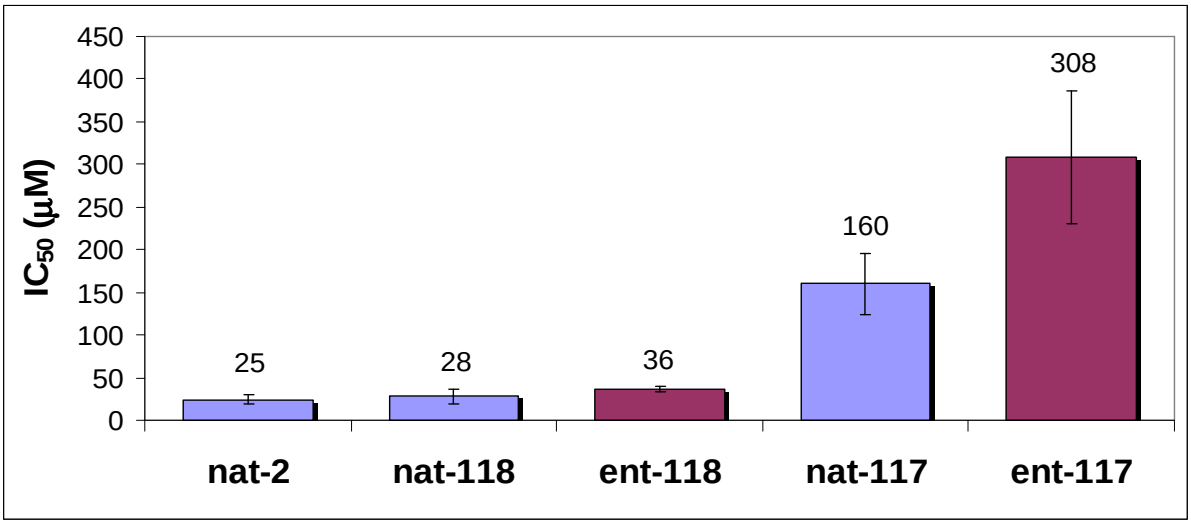


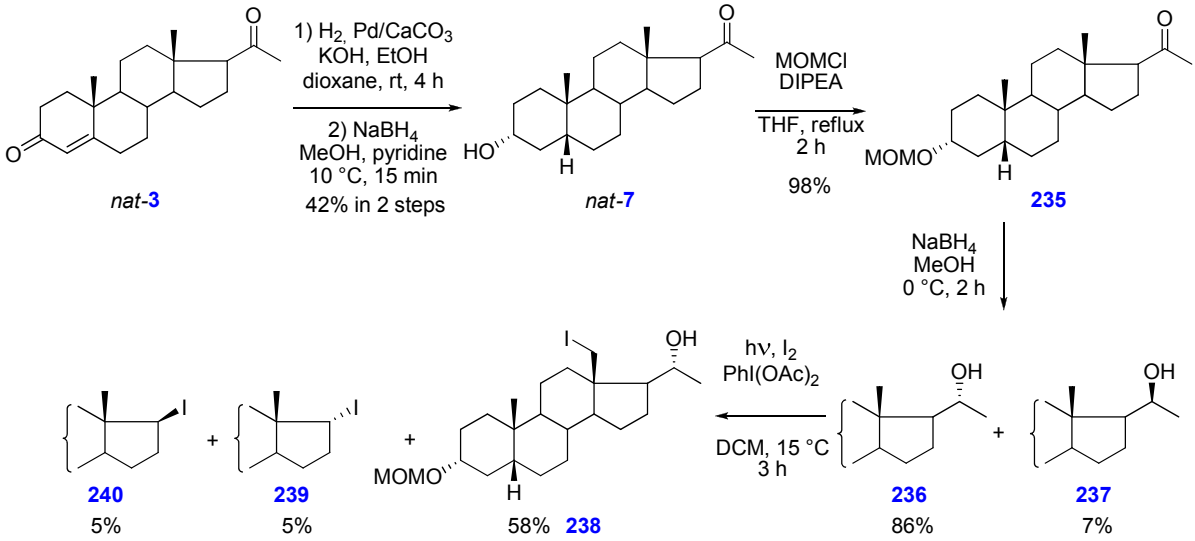
Figure 13: Half-maximal inhibition concentration (IC_{50}) of native neurosteroid *nat*-**2** and truncated analogs **117** and **118** at the NMDA receptor. The values above columns show means, the error bars show the standard deviation.

These results suggest that the interaction of neurosteroids with the NMDA receptor tolerates the loss of D-ring and side chain, whereas *cis*-decalins **117** are already too short for a significant inhibition of the receptor. The small difference between both enantiomers of **118** points to a small binding specificity. This is also supported by the fact that a polar function in the side chain of *nat*-**2** is not a neccessary condition for inhibitory activity. Since a charged polar group is indispensable for the activity at the NMDA receptor,[35,58] it seems probable that this group will prefer an aqueous environment, while the hydrophobic steroid core fits in a lipophilic compartment. In other words, it is likely, that interaction with the membrane or lipophilic transmembrane domain is crucial for the action of steroids at the NMDA receptor. It is unlikely that a highly specific binding site for neurosteroids, known for example in nuclear receptors, exists in the NMDA receptor. It will be interesting to compare the activity of *ent*-**2** with this data set. Currently, the synthesis of *ent*-**2** is underway.

3.3. Synthesis of Deuterated Tracers of Neuroactive Steroids

To gain insight into pharmacokinetics and metabolic fate of neuroactive steroids *in vivo*, methods of specific isotopic labeling were studied. Metabolically non-exchangeable positions of the C-18 and C-19 methyl groups were chosen to provide reliable tracers for physiological testing. Although some methods for deuteration of steroid angular methyls were described (see **Chapter 1.10**), the preparation of specifically labeled 5β-pregnane steroids is unknown in the literature.

From the synthetic point of view it is interesting that while radical chemistry is virtually the only method for functionalization of steroidal methyls, it is underused as a method for deuteration. In the third part of this thesis, a method of specific deuterium labeling of angular methyls C-18 and C-19 with focus on radical chemistry was developed. [18-$^2H_3$]- And [19-$^2H_3$]-5β-pregnane-3,20-dione **119** and **120** were chosen as target compounds, because they are readily convertible into a range of neuroactive steroids.[58,59,62,63,302]



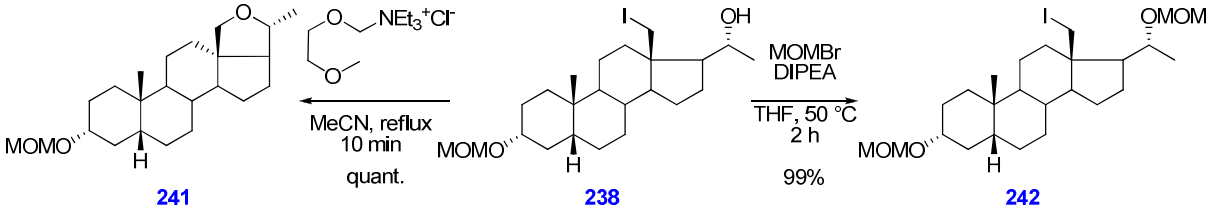
Scheme 49: Functionalization of C-18 methyl group

3.3.1. Synthesis of [18-$^2H_3$]-5β-pregnane-3,20-dione

The synthesis of **119** started from commercially available *nat*-progesterone (*nat*-**3**), which was converted in two known steps to *nat*-pregnanolone (*nat*-**7**) (**Scheme 49**).[222,303,304] The hydroxy group of *nat*-**7** was protected as methoxymethoxy ether **235** and reduced with $NaBH_4$ to afford selectively 20*R*-alcohol **236**, along with a small amount of separable 20*S*-alcohol **237**. Pure **236** was subjected to a

Suárez reaction to afford a slightly unstable 18-iodo steroid **238** in acceptable yield.[305,306] The major side products **239** and **240** were isolated in small amounts. Their formation can be explained by β-fragmentation of the alkoxyl radical generated from **236** to acetaldehyde and secondary C-17 radical, which reacts unselectively with iodine to form **239** and **240**. Similar products were observed by others upon analogous oxidation with $Pb(OAc)_4$ and iodine.[307,308]

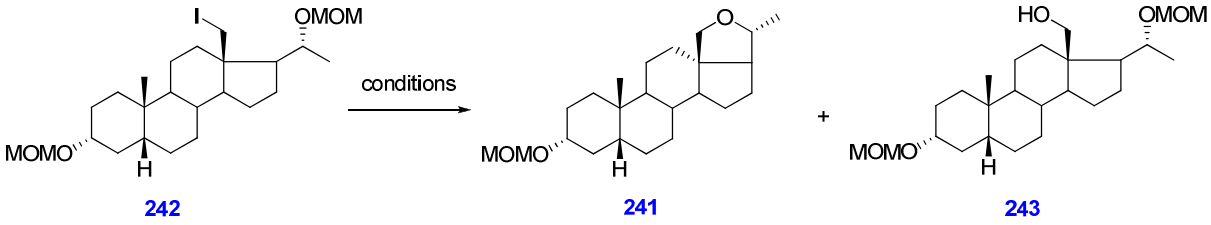
To simplify later transformations, the hydroxy group of **238** was protected (**Scheme 50**). An attempt to introduce a methoxyethoxymethyl (MEM) protecting group failed, leading to cyclized ether **241**. In contrast, switching to more reactive methoxymethyl bromide smoothly afforded ether **242**.



Scheme 50: Protection of the side chain hydroxy group at C-20

In the next step, the oxygenation of iodo derivative **242** was explored (**Table 9**). Simple nucleophilic substitution in the dipolar aprotic solvent HMPA led exclusively to cyclic ether **241** without any trace of desired alcohol **243** (Entry 1). Reductive oxygenation with ABCN as an initiator, and Bu_3SnH as the hydrogen donor afforded **243** in moderate yield (Entry 2).[309,310] A large amount of tributyltin oxide complicated the isolation and therefore a catalytic variant of the reaction was sought. Fu's conditions were tried with little success (Entry 3).[311,312] Changing the hydrogen donor for diphenylsilane led only to recovery of starting material (Entry 4), while tris(trimethylsilyl)silane gave the desired product in satisfactory yield (Entry 5). The addition of base proved beneficial for the stability of the protecting groups. Silyl ethers, which were coformed, were destroyed with a small excess of TBAF, facilitating purification and improving the yield.

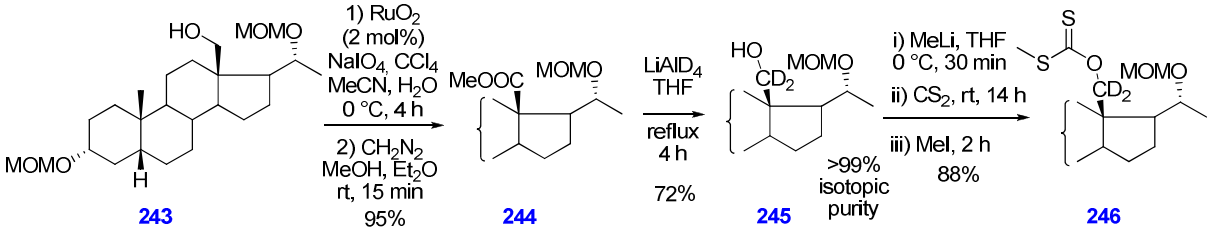
Table 9: Oxygenation of iodide **242**



					Yield (%)		
Entry	**Reagents (equiv)**	**Solvent**	**T (°C)**	Time	**241**	**242**	**243**
1	KOH (5)	HMPA	120	30 min	85	-	0
2	O_2,[a] ABCN (0.2), Bu_3SnH (3.0)	PhMe	90	6 h	-	-	30
3	O_2,[a] ABCN (0.2), Bu_3SnH (0.15), PMHS (5), *n*BuOH (5)	PhMe	90	6 h	-	-	14
4	O_2,[a] ABCN (0.2), Ph_2SiH_2 (3.0)	PhMe	90	6 h	-	99	0
5	O_2,[a] ABCN (0.2), TMS_3SiH (1.5), DIPEA (1.5)	PhMe	90	6 h	-	-	78[b]

[a] Continuous stream of pure O_2 used. [b] The crude reaction mixture was treated with TBAF (1.5 equiv).

The neopentylic alcohol **243** was oxidized by catalytic ruthenium tetroxide to the corresponding carboxylic acid, which was immediately esterified with diazomethane to furnish **244** (**Scheme 51**). Reduction with lithium aluminum deuteride to **245** introduced two deuterium atoms with more than 99% isotopic purity, as shown by mass spectrometry. In preparation for the envisaged Barton-McCombie deoxygenation, **245** was converted to xanthate **246** by a standard procedure in very good yield.

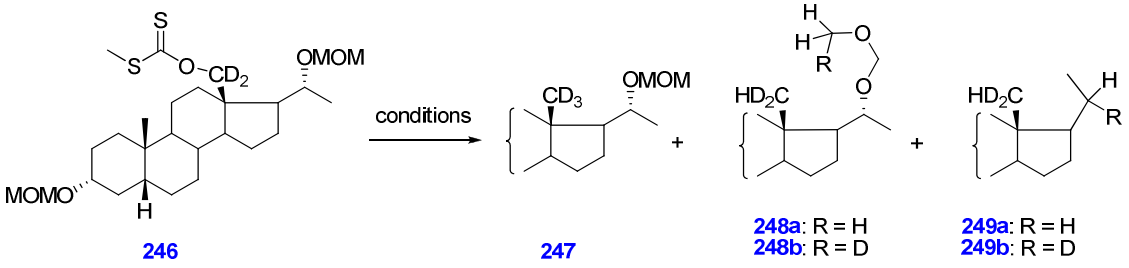


Scheme 51: Introduction of two deuterium atoms to C-18 methyl group

The Barton-McCombie deoxygenation of **246** under standard conditions with commercial tributyltin deuteride led only to recovery of starting material (**Table 10**, entry 1). The use of Et_3B and O_2 as the radical initiator with the Et_3B-D_2O couple as the deuterium donor led to a worse result (Entry 2).[313] A successful deoxygenation was achieved with tris(trimethylsilyl)silyl deuteride, which was prepared by a published procedure and showed >95% isotopic purity by MS (Entry 3).[314] Both isolated products **248** and **249** contained the reduced methyl group C-18, but both contained a hydrogen atom in position C-18, which was clearly observable by the presence of a broad singlet at δ 0.65 ppm in the ^{1}H NMR spectrum. MOM ether **248** was isolated as a mixture of **248a** and **248b** in 1:1 ratio differing by a deuterium atom at the terminal methoxy group. Similarly, the fragmented product **249** was isolated as a 1:1 mixture of **249a** and **249b**. This result prompted us to repeat the deoxygenation with Bu_3SnD (Entry 4), this time using freshly prepared material, since commercial samples are sometimes of dubious quality. Thermally less stable AIBN allowed for the use benzene as a solvent, which has considerably less hydrogen-donating properties. Under these conditions the desired 18-d_3 steroid **247** was isolated in 35% yield. It should be nevertheless mentioned that an improvement of the Bu_3SnD reduction may be possible by increasing the concentration. In the end the optimization was not attempted because the obtained amount of material was insufficient.

The outcome of the Barton-McCombie reaction can be explained by the following mechanism (**Scheme 52**). The reaction is initiated by thermal decomposition of the azoalkane, which abstracts the deuterium atom from TMS_3SiD or Bu_3SnD. Thus generated TMS_3Si or stannyl radicals rapidly add to xanthate **246**, followed by a slower fragmentation to radical **250A**, here shown in one sequence.[315] The next step is deuterium abstraction from another molecule of TMS_3SiD or Bu_3SnD leading to **247**. This pathway dominates when Bu_3SnD is employed as deuterium source (Entry 4). However, TMS_3SiH is about five-times slower hydrogen donor than Bu_3SnH, with rates of approximately 6×10^6 $M^{-1}s^{-1}$ for primary alkyl radicals and Bu_3SnH at 80 °C.[316] The deutero analogs are slower donors because of the primary kinetic isotope effect. For Bu_3SnH/D and primary alkyl radicals the k_H/k_D is approximately 2.[317–319] Moreover, the bulkiness of TMS_3SiD may contribute to lower rates with sterically hindered radicals such as neopentylic **250A**. Therefore a time window exists for competitive processes.[320]

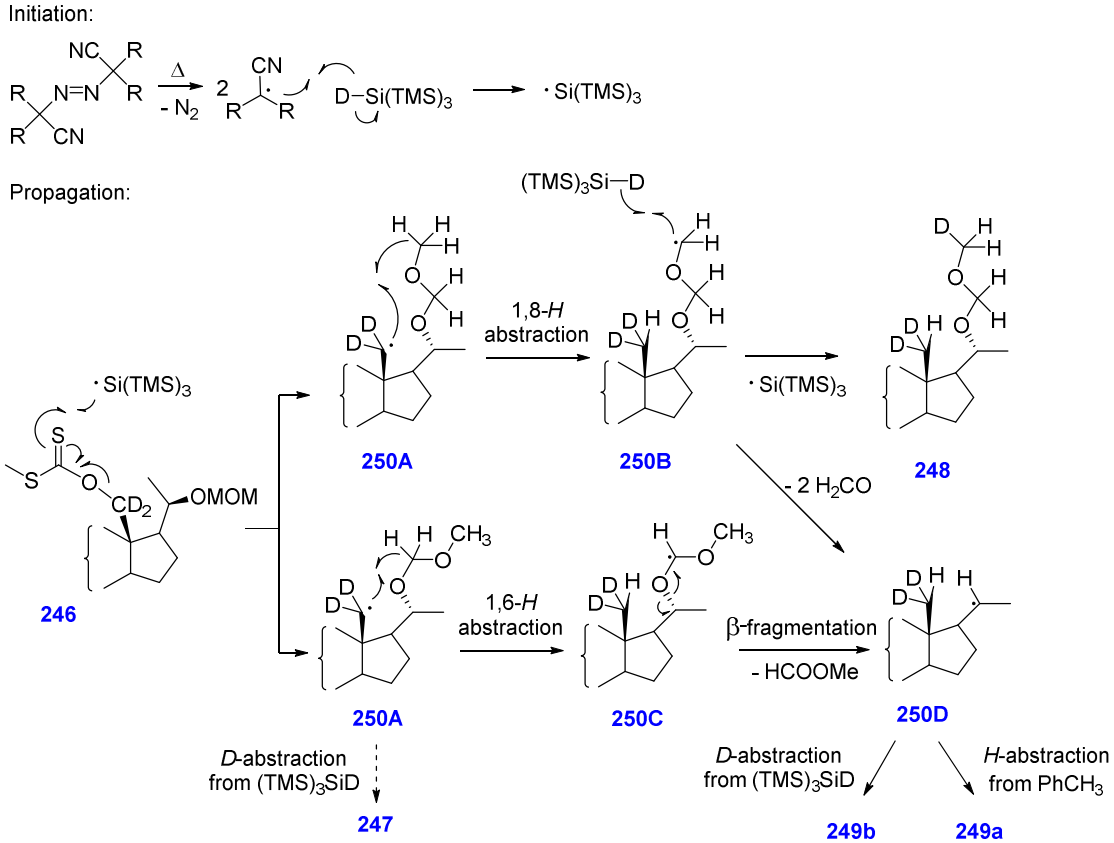
Table 10: Deuteration of xanthate **246**



Entry	Reagents (equiv)	Solvent	*c*[a] (M)	*T* (°C)	*t* (h)	Yield (%) 246	247	248	249
1	Bu_3SnD[b] (1.5), ABCN (0.2)	PhMe	0.09	111	6	64	-	-	-
2	Et_3B[c] (10), D_2O (10), O_2[c] (0.8)	C_6H_6	0.43	25	12	48	-	-	-
3	TMS_3SiD[d] (1.2), ABCN (0.1)	PhMe	0.21	111	5	-	-	26[e]	72[e]
4	Bu_3SnD[d] (1.5), AIBN (0.1)	C_6H_6	0.33	80	2.5	-	35[f]	-	-

[a] Of the deuterium reagent. [b] Commercial. [c] Added with syringe pump over 1 h. [d] Freshly prepared. [e] **a** : **b** in ca. 1:1 ratio as determined by NMR and MS. [f] 88% isotopic purity by MS.

Product **248** is probably formed via intermediate **250B** by 1,8-hydrogen abstraction. Although rare, this process has been observed in carbohydrate chemistry.[321] Deuterium abstraction from TMS_3SiD or hydrogen abstraction from toluene completes the transformation to **248a** or **248b**, respectively. Double β-scission of species **250B** can be envisaged to form two molecules of formaldehyde and radical **250D**, which is transformed to the observed major products **249a** and **249b**.

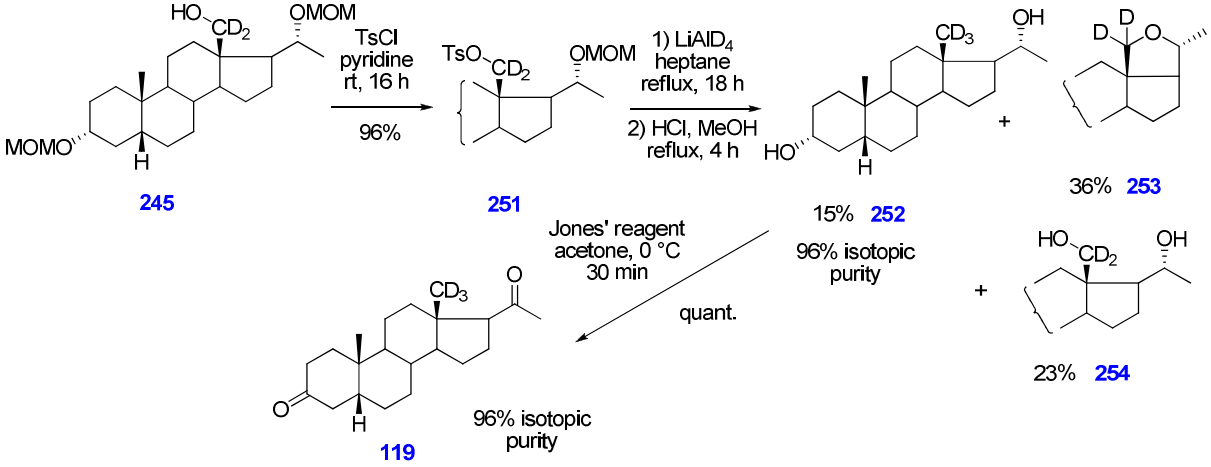


Scheme 52: Proposed mechanism for Barton-McCombie deoxygenation with $(TMS)_3SiD$

An even more likely process is shown in the bottom of **Scheme 52**. Here **250A** undergoes 1,6-hydrogen atom transfer to generate **250C** that fragments to methyl formate and **250D**. Several arguments speak for the contribution of this second mechanism. First, the 1,6-hydrogen atom transfer is geometrically preferred over 1,8-hydrogen atom transfer.[322] And second, the transition state leading to radical **250C** is lower in energy than that leading to **250B** by stabilization with one more alkoxy substituent.

To provide a comparison for the Bu_3SnD reduction of xanthate **246**, alcohol **245** was converted to the corresponing tosylate **251** (**Scheme 53**). Reduction with $LiAlD_4$ in *n*-heptane provided three compounds, which were isolated after acid mediated deprotection as the alcohols **252**, **253** and **254** in modest yields. The yields obtained were inferior to those reported for related pregn-5-ene derivatives, 34% for an analog of **252** and 28% for an analog of **253**.[232] Presumably, the $LiAlD_4$ quality was a factor. Nevertheless, the achieved 96% isotopic purity of **252** was higher than 88% in Bu_3SnD reduction. The diol **252** was quantitatively converted to [18,18,18-$^2H_3$]-5β-pregnane-3,20-dione (**119**) by Jones oxidation.

The synthesis of **119** from pregnanolone *nat*-**7** was 12 steps long and gave 7.3% overall yield for the radical route or 3.7% overall yield for the reduction of tosylate **251**, respectively. The former route afforded diketone **119** of slightly lower isotopic purity. Even so, the xanthate reduction compares favorably in terms of yield with the reduction of tosylate **251**.



Scheme 53: Alternative synthesis of **119**

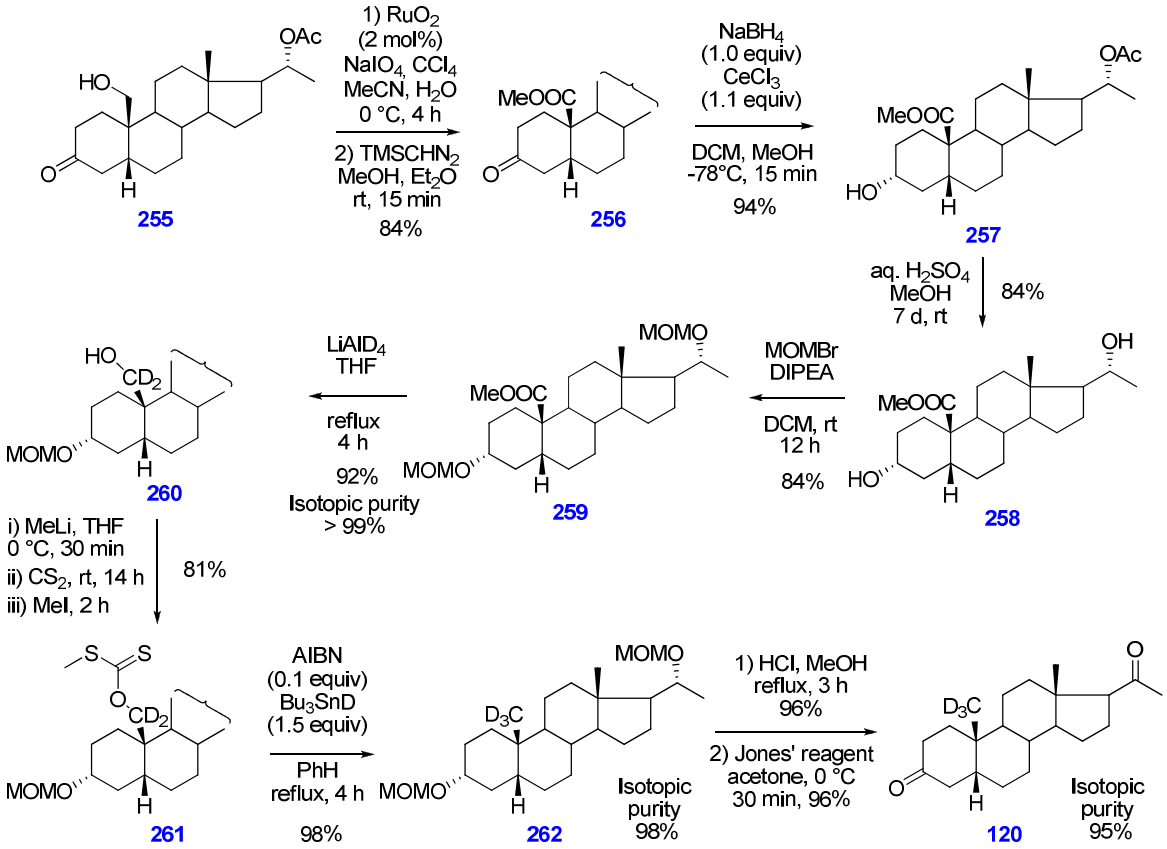
3.3.2. Synthesis of [19-$^2H_3$]-5β-pregnane-3,20-dione

The starting material **255** for synthesis of **120** was prepared in the Dr. Chodounská's laboratory in 8 steps and 26% overall yield from commercially available pregnenolone acetate according to a published procedure.[323] Oxidation by sodium periodate catalyzed by ruthenium dioxide, followed by methylation with trimethylsilyl diazomethane provided ester **256** in good yield (**Scheme 54**). Reduction of **256** by $NaBH_4/CeCl_3$ gave selectively the equatorial alcohol **257**, which was hydrolyzed to diol **258**. Global protection to base-stable MOM diether **259** and subsequent reduction with $LiAlD_4$ afforded d_2-steroid **260** in very good yield and excellent isotopic purity. The alcohol was smoothly converted to xanthate **261** and deoxygenated under the previously optimized conditions, with freshly prepared Bu_3SnD. In contrast to reduction of xanthate **246**, no issues were observed during C-19 reduction and the product **262** was isolated in excellent yield and isotopic purity. Deprotection and Jones oxidation furnished the specifically labeled steroid **120** in almost quantitative yield. The final

isotopic purity was 95% as determined by mass spectrometry. The overall yield of **120** from **255** was 37% over 10 steps.

It should be noted that in case of 5β-pregnane steroids, reduction of the corresponding 19-tosylate with $LiEt_3BD$[232] or $NaI/Zn/D_2O$[233] failed to provide the respective 19-d_3 steroid,[324] probably because of steric hindrance. This problem can nevertheless be circumvented by performing the deuteration with Δ^5-steroid and reducing the double bond later. The synthesis described here offers a high-yielding alternative and employs accessible reagent $LiAlD_4$.

To compare the ease of deuteration of angular methyls C-18 and C-19 by Bu_3SnD, the latter can be obtained in higher isotopic purity. When the whole synthesis from commercially starting material is taken into account, **119** is accessible in 14 steps and 3.1% overall yield from *nat*-progesterone (*nat*- **3**). d_3-Steroid **120** was synthesized in a total of 18 steps and 9.5% overall yield from commercially available pregnenolone acetate.



Scheme 54: Preparation of **120**

4. CONCLUSIONS

A conceptually new synthetic approach to *ent*-progesterone (*ent*-**3**) was investigated. From the strategic point of view, the synthesis started by building chiral A,B-ring system of steroid core, followed by substrate-controlled annelation of ring C. Ring D was formed together with the side chain in a newly developed reaction sequence.

The first chiral center of *ent*-**3** originated in Hajos-Parrish-Eder-Sauer-Wiechert reaction, catalyzed by prolinanilide (*R*)-**60a**. Optimization of the reaction conditions allowed for an extremely effective synthesis of Wieland-Miescher ketone (*ent*-**21**) in high enantiomeric excess. Enantiopure synthetic material was achieved by a single crystallization. Reductions of **21** to the *cis*-decalin system **146** were successfully investigated, leading to a good yield of potential precursor of 5β-saturated steroids. Their synthesis was hampered by unwanted conformation of the substituted *cis*-decalin, leading ultimately to an unnatural relative configuration of the steroid core. In a second generation synthesis, the troublesome *cis*-decalin intermediate was substituted for conformationally stable octalin derivative. A developed chemoselective protection of enone *ent*-**21**, followed by substrate-controlled Robinson annulation enabled rapid high-yielding synthesis of the tricyclic system *ent*-**155** with a correct configuration.

The key step of the synthesis consisted of substrate-controlled copper-catalyzed conjugate addition followed by oxygenation with a TEMPO surrogate. In the investigated system, 10 mol% of Li_2CuCl_4 with the dppe ligand emerged as the best catalyst for the conjugate addition of Grignard reagents. Excellent yields and high diastereoselectivity were achieved. An attempted single electron transfer induced radical cyclization did not lead to a significant extent of cyclization to the D-ring, yet enabled a high-yielding preparation of α-alkoxyamine derivatives *ent*-**184a** and **185a**. The incorporation of the SET oxidant into the product renders the key step highly atom-economic. The α-alkoxyamine derivatives were found to cyclize quantitatively under thermal conditions in a radical process mediated by the persistent radical effect. The diastereoselectivity of the radical cyclization was thoroughly investigated and key intermediates were characterized unambiguously by single crystal X-ray diffraction.

Methylation of the activated C-13 position completed the synthesis of steroid skeleton. However, deoxygenation of the advanced intermediate *ent*-**205** proved difficult. Desulfurization or hydrazone reduction failed to provide the desired saturation of ring C. An acceptable solution was found in hydrogenolysis of a corresponding vinyl nonaflate *ent*-**223a**. Epimerization of the side chain provided *ent*-progesterone (*ent*-**3**) in 2.4% overall yield in the longest linear sequence of 15 steps.

The total synthesis design toward *ent*-**3** enabled the preparation of truncated neurosteroid congeners **117** and **118** in both enantiomeric forms. Bicyclic sulfates *nat*- and *ent*-**117** were prepared in 7 steps and 20 or 42% overall yield, respectively. Tricyclic sulfates *nat*- and *ent*-**118** were prepared in 12 steps and 11 or 18% overall yield, respectively. All four sulfates were tested for inhibitory activity at the NMDA receptor in collaboration with Dr. Vyklický's group at the Institute of Physiology AS CR. While both enantiomers of tricyclic sulfates **118** exhibited activity comparable to native neurosteroid *nat*-**2**, bicyclic enantiomers **117** were significantly less active. This substrate tolerance suggests a lack of specifity of the steroid binding site at the NMDA receptor or possibly a membrane-mediated action of neurosteroids. Comparison with *ent*-**2** is however desirable as more robust evidence.

To provide steroid tracers for pharmacokinetic and metabolic studies of neuroactive steroids, methods of specific perdeuteration of the C-18 and C-19 methyl groups were briefly investigated. The C-18 methyl group was functionalized by a Suárez reaction, followed by radical reductive oxygenation to provide 18-hydroxy steroid in moderate yield. Oxidation to acid, followed by reduction with $LiAlD_4$ was confirmed as an effective method for the introduction of two deuterium atoms into the molecule. Conversion to the corresponding xanthate enabled a study of radical deuterium donors. Bu_3SnD emerged as an acceptable candidate, being fast enough to outcompete undesirable intramolecular hydrogen transfer reactions. D_3-diketone **119** of 88% isotopic purity was prepared in 14 steps and 3.1% yield from *nat*-progesterone. In comparison, an analogous approach for the deuteration of the C-19 methyl group proved to be more successful because of fewer competing side reactions. The introduction of the third deuterium atom proceeded in almost quantitative yield and 95% isotopic purity. Thus d_3-diketone **120** was prepared, albeit from advanced intermediate **255**, in 37% overall yield and 10 steps. Both methods provide the first known access to [18-$^2H_3$]- and [19-$^2H_3$]-labeled 5β-pregnane steroids.

Overall, the described total synthesis of *ent*-progesterone (*ent*-**3**) demonstrates the synthetic utility of tandem copper-catalyzed conjugate addition with oxygenation, followed by thermal cyclization of persistent radical adducts. Although the method itself leaves some space for improvement in terms of step-efficiency, it provides a practical solution for the synthesis of polycyclic natural compunds. Further mechanistic investigation and exploration of scope and limitations of this tandem reaction can be envisaged. Large potential can be seen especially in conjunction with the rapidly developing field of enantioselective copper-catalyzed conjugate additions. Improvement of the Wieland-Miescher ketone synthesis is also worth mentioning, since *ent*-**21** is a common intermediate in numerous syntheses of terpenoids.

The described synthesis of *ent*-**3** also constitutes a formal synthesis of *ent*-pregnanolone (*ent*-**7**) and its sulfate *ent*-**2**. In light of the observed activity of neurosteroid congeners at the NMDA receptor, it will be interesting to see whether the enantiomers of neurosteroids posess the same activity. The synthesis of both *ent*-**7** and *ent*-**2** is in progress. It is noteworthy that the prepared enantiomers of pregnane steroids can be studied in relation to neurosteroid receptors other than NMDAR's.

The tricyclic steroid congeners **118** are intriguing in relation to a known *in vivo* activity of neuroactive steroids. While the neuroactive steroids are subject to an inherent metabolic regulation, the tricyclic congeners or their analogs might provide different pharmacokinetic properties. The topic was covered in a recent patent application from IOCB and Institute of Physiology AS CR.[62] This synthetic study will be followed by structure-activity relationship studies of various tricyclic derivatives at NMDA receptors.

Finally, the investigated method of specific d_3-labeling of angular methyls of 5β-pregnane steroids presents a competitive deuteration strategy. The envisaged metabolic studies are expected in due course.

5. EXPERIMENTAL SECTION

5.1. GENERAL EXPERIMENTAL CONDITIONS

Reactions not involving aqueous conditions were performed in flame-dried glassware under a positive pressure of dinitrogen. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula.

TLC analyses were performed on POLYGRAM SIL G/UV_{254} plates. TLC plates were visualized by exposure to ultraviolet light, then stained by chemical reagent. For this purpose, iodine vapors were used, followed by one of the following solutions: aq. phosphomolybdic acid with ceric sulfate, acidic methanolic anisaldehyde, basic aq. potassium permanganate or methanolic sulfuric acid. The TLC plate was then heated briefly to 200 °C. Chromatographic separations were carried out on silica gel (60 Å pore size, Fluka, 230-400 mesh) or Florisil (60-100 mesh) where specified. Preparative TLC (prep-TLC) was carried out on 200 mm × 200 mm plates coated with a 0.4 mm thick layer of silica gel with $CaSO_4$ as the binder.

Melting points were determined on a micro-melting point apparatus Hund/Wetzlar (Germany). Optical rotations were measured in chloroform using an Autopol IV (Rudolf Research Analytical, Flanders, USA), $[\alpha]_D$ values are given in ° (10^{-1} deg cm^2 g^{-1}). IR spectra of $CHCl_3$ solutions were recorded on a Nicolet 6700 (Thermo Scientific) spectrometer and the characteristic absorptions are given in wavenumbers. Neat samples were measured on Bruker Alpha instrument by the attenuated total reflectance (ATR) method. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 400 or 600 spectrometers. Proton chemical shifts are expressed in ppm (δ scale) downfield from tetramethylsilane and are referenced to this standard. Carbon chemical shifts are expressed in ppm (δ scale) downfield from tetramethylsilane and are referenced to carbon resonance of the NMR solvent ($CDCl_3$ 77.00, C_6D_6 128.06, d_6-DMSO 39.52). Fluorine chemical shifts are expressed in ppm (δ scale) and referenced to internal standard $PhCF_3$ (−63.72 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal), coupling constants (*J*) in Hz, integration, assignment. The connectivity was determined by ^1H-^1H COSY and ^1H-^{13}C HMBC experiments and ^1H-^{13}C assignments were obtained from HSQC measurements. The stereochemistry of critical intermediates of the total synthesis was assigned using ^1H-^1H ROESY experiments. Numbering of the signals in NMR spectra of the steroids, their synthetic analogs and precursors follows the standard IUPAC recommendation for steroid compounds.[69] Non-discernable proton signals in the aliphatic region of steroids, which were not prepared by total synthesis, are omitted for clarity. Mass spectra were obtained with spectrometers Q-TOF micro (Waters), GC/TOF-MS GCT Premier (Waters). Elemental analyses were performed on 2400 Series II CHNS/O System (Perkin Elmer, USA). In case of deuterated analogs, calculated values of hydrogen content were corrected for the method of detection: $x_H = (n_H + n_D) \times 1.00794 / M_w$ Where x_H is weight ratio of hydrogen in sample, n_H and n_D are numbers of hydrogen or respectively deuterium atoms in molecular formula and M_w is molecular weight. Gas chromatography was performed on Agilent 6850 Series GC System equipped with flame-ionization detector and nitrogen as a carrier gas, using Zebron ZB-1 column (L 30m × I.D. 0.32 mm × df 0.25 µm).

X-Ray crystallographic analyses were performed by Dr. Ivana Císařová at the Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague. X-Ray crystallographic data are described separately in Appendix C. Analytical HPLC was performed on Agilent 1200 Series instrument with diode array and light-scattering detectors.

Solvents and additives were dried prior to use according to standard procedures: THF, Et_2O and DME were freshly distilled over Na or K with Ph_2CO added. MeOH was dried with Mg, distilled and stored over 4Å molecular sieves. Toluene was freshly distilled with Na. Dry MTBE, pentane and EtOH were purchased. MeCN, ethyl formate, hexane and DMF were distilled (the latter under reduced pressure) from P_2O_5 and stored over 4Å molecular sieves. CH_2Cl_2, Et_3N, iPr_2NH, HMDS, HMPA, TMEDA, TMSCl, pyridine and DMSO were distilled from CaH_2 and kept over 4Å molecular sieves (except TMSCl, CH_2Cl_2, pyridine). Ethylene glycol, *t*BuOH and benzene were distilled with Na and stored over 4Å molecular sieves.

(20*R*)-19-Hydroxy-3-oxo-5β-pregnan-20-yl acetate (**255**) was prepared from commercial pregnenolone according to the known procedure and its spectral and physical data matched those reported.[323] 3α-Hydroxy-5β-pregnan-20-one (*nat*-**7**) was prepared from commercially available progesterone (*nat*-**3**) according to the previously described procedure.[222,303,304] TMS_3SiD was prepared according to the literature,[314] with D_2O (>99% isotopic purity, Sigma-Aldrich) as a deuterium source. Diazomethane was prepared from *N*-nitroso-*N*-methylurea,[325] by extraction into Et_2O from conc. KOH solution. Tributyltin deuteride was freshly prepared from tributyltin chloride and $LiAlD_4$ (>99% isotopic purity).[326] Jones' reagent,[327] ferrocenium hexafluorophosphate (**182**)[328] and 1-oxo-2,2,6,6-tetramethyl-piperidinium tetrafluoroborate (**180**)[329] were prepared according to the published procedures. Perfluorobutanesulfonyl fluoride (NfF) was purified by the described procedure.[330] SF_5 anilines **134c** and **134d** were a generous gift from George Iacobson (IOCB AS CR). All other reagents were used as purchased.

5.2. Total Synthesis of Pregnane Steroids

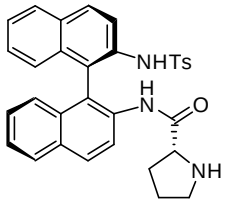
General Procedure A: Prolinanilides

The method is essentially identical to that of Moran and Fischer.[125,237] Phosphorus pentachloride (3.8 g, 18.2 mmol) was suspended in anhydrous chloroform (10 mL) under nitrogen in an ice–salt bath at −5 °C. Finely powdered D-Proline (2.0 g, 17.3 mmol) was added to the reaction mixture in small portions. The white suspension dissolved to a colorless solution. After ca. 30 min at −5 °C, prolinoyl chloride hydrochloride started to crystallize from the solution. The suspension was filtered under an inert atmosphere, the crystals were washed with anhydrous chloroform (2 × 10 mL) and dried *in vacuo* to yield 2.14 g (73%) of prolinoyl chloride hydrochloride (*R*)-**130** as colorless crystals, which were immediately used in the next step.

The appropriate amine (10.1 mmol) was dissolved in dry THF (25 mL) under a N_2 atmosphere. D-Prolinoyl chloride hydrochloride (*R*)-**130** (2.14 g, 12.6 mmol) was added portionwise and the mixture was stirred for 15 min, when TLC showed full conversion of the starting material. The reaction was quenched with 5% aq. HCl (100 mL) and washed with Et_2O (3 × 50 mL). The ethereal layer was discarded. The aqueous layer was made basic by addition of K_2CO_3 and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography (silica gel, 5% to 10% MeOH/CH_2Cl_2) afforded the desired prolinanilides.

(*R*)-Pyrrolidine-2-carboxylic acid (R_a)-[2´-(4-methylphenylsulfonamido)-1,1´-binaphthyl]-2-ylamide ((*R*,R_a)-59)

Prepared according to a modified procedure.[331,127] (R_a)-BINAM (R_a)-**131** (1.02 g, 3.59 mmol) was dissolved in CH_2Cl_2 (27 mL) and pyridine (3.47 mL). A solution of tosyl chloride (1.026 g,

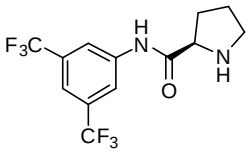


5.39 mmol) in CH_2Cl_2 (9 mL) was added dropwise over 10 min while stirring. After 4 h of stirring at rt, the reaction mixture was poured into 5% aq. HCl (100 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to chromatography on silica gel (30 g) in 15% EtOAc/hexane to afford 1.55 g of the inseparable mixture of monotosylamide (R_a)-**132** and bistosylamide (R_a)-**133**, which was used for the next step according to the General procedure A for the preparation of prolinanilides. Chromatography on silica gel (50 g) in 50% EtOAc/hexanes removed the bistosylamide (R_a)-**133**. Switching to 10% MeOH/EtOAc eluted 1.38 g (72% overall) of (R,R_a)-**59**.
$[\alpha]_D^{20}$ +87.4 (*c* 0.183, $CHCl_3$) for (R,R_a)-**59**; Lit. $[\alpha]_D^{25}$ +93 (*c* 1.0, $CHCl_3$) for (R,R_a)-**59**;
Anal. Calcd for $C_{32}H_{29}N_3O_3S$: C, 71.75; H, 5.46; N, 7.84; S, 5.99; Found: C, 71.79; H, 5.59; N, 7.31; S, 5.41; for (R,R_a)-**59**.
The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.

General Procedure B: Mosher's amides

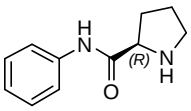
Under inert conditions, oxalyl chloride (90 µL, 1 mmol) was added to a solution of (*R*)-MTPA (24 mg, 0.1 mmol) and DMF (16 µL, 0.2 mmol) in hexane (5 mL) at room temperature. A white precipitate formed immediately. After stirring for 2 h, the reaction mixture was filtered through a glass wool plug in a syringe and the solvent was evaporated *in vacuo* to give a residue of chiral acyl chloride. Solid DMAP (24 mg, 0.2 mmol) was added to the reaction flask and it was evacuated and refilled with argon. A solution of the amine (0.04 mmol) in dichloromethane (2 mL) was transferred to the mixture, which was stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (5 mL) and the product was extracted into Et_2O (20 mL). The organic layer was washed consecutively with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the desired Mosher's amide in quantitative yield. The absence of the starting amine was checked by ^{1}H NMR. The enantiomeric purity was determined according to the literature.[332]

(*R*)-Pyrrolidine-2-carboxylic acid 3,5-bis(trifluoromethyl)phenylamide ((*R*)-60a)



Prepared according to General procedure A in a yield of 1.61 g (77%).
$[\alpha]_D^{20}$ +42.5 (*c* 0.267, $CHCl_3$); Lit. $[\alpha]_D^{25}$ −37.52 (*c* 1.39, $CHCl_3$) for the *S*-enantiomer;[125]
Anal. Calcd for $C_{13}H_{12}F_6N_2O$: C, 47.86; H, 3.71; F, 34.94; N, 8.59; Found: C, 47.45; H, 3.68; F, 34.67; N, 8.30;
The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.[125]
The enantiomeric purity was determined by preparing Mosher's amide according to General procedure B. Comparison of the ^{1}H and ^{19}F NMR spectra of both diastereomers, separately and as a mixture, showed >99% ee. The signals used for quantitative analysis are underlined.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 8.2, 5.9 Hz, 1H, OCC*H*N)^{RR}, 4.78 (dd, *J* = 7.8, 4.9 Hz, 1H, OCC*H*N)^{SR}, 3.95 (q, *J* = 1.5 Hz, 3H, OCH_3)^{RR}, 3.69 (q, *J* = 1.5 Hz, 3H, OCH_3)^{SR}, 3.63 (ddd, *J* = 11.3, 8.1, 6.7 Hz, 1H, CH_aH$_b$N)^{RR}, 3.56 (dt, *J* = 11.5, 7.0 Hz, 1H, CH_aH$_b$N)^{SR}, 3.02 (ddd, *J* = 11.4, 7.5, 4.8 Hz, 1H, CH$_a$$H_b$N)^{RR}, 2.87 (dt, *J* = 11.4, 6.9 Hz, 1H, CH$_a$$H_b$N)^{SR};
^{19}F NMR (376.3 MHz, $CDCl_3$) δ <u>−63.57 (s, 6F, Ar(CF_3)$_2$)^{SR}, −63.70 (s, 6F, Ar(CF_3)$_2$)^{RR}</u>, −70.66 (br s, 3F, CCF_3)^{RR}, −70.98 (br s, 3F, CCF_3)^{SR}.

(*S*)-Pyrrolidine-2-carboxylic acid phenylamide ((*S*)-60b) and (*R*)-pyrrolidine-2-carboxylic acid phenylamide ((*R*)-60b)



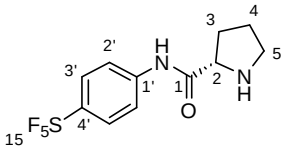
Prepared according to General procedure A in a yield of 1.55 g (81%). (Described for the opposite enantiomer).[125]

(*S*)-**60b**: Mp 77-78 °C (hexane/CH_2Cl_2); Lit. Mp 79-80 °C (Et_2O/hexane);[333] $[\alpha]_D^{20}$ −65.2 (*c* 0.282, $CHCl_3$); Lit. $[\alpha]_D^{22}$ −71.1 (*c* 0.9, $CHCl_3$);[333]

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73; Found: C, 69.34; H, 7.36; N, 14.57;

The ^1H and ^{13}C NMR spectra are in agreement with the literature.

(*S*)-Pyrrolidine-2-carboxylic acid 4-(pentafluoro-λ^6-sulfanyl)phenylamide ((*S*)-60c)



Prepared according to General procedure A in a yield of 250 mg (79%).

$[\alpha]_D^{20}$ −35.2 (*c* 0.270, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 581, 597 (*p*-Ar), 822, 852 (SF), 1102 (Ar), 1317 (Ar), 1405 (CH_2), 1498 (Ar), 1518 (CON), 1595 (Ar), 1691 (CON), 2876 (CH_2), 2979, 3254 (NH).

^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H, N*H*CO), 7.70 (s, 4H, CH-2', CH-3'), 3.88 (dd, *J* = 9.3, 5.2 Hz, 1H, CH-2), 3.10 (dt, *J* = 10.3, 6.8 Hz, 1H, CH-5a), 2.98 (dt, *J* = 10.3, 6.3 Hz, 1H, CH-5b), 2.23 (ddt, *J* = 13.0, 9.2, 7.5 Hz, 1H, CH-3a), 2.04 (dtd, *J* = 13.0, 6.8, 5.3 Hz, 1H, CH-3b), 2.04 (br s, 1H, CHN*H*CH_2), 1.80-1.73 (m, 2H, CH_2-4).

^{19}F NMR (377 MHz, $CDCl_3$) δ 85.78-84.18 (m, 1F), 63.05 (d, *J* = 150.0 Hz, 4F).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C, C-1), ~148.8 (m, C, C-4'), 140.4 (C, C-1'), 126.9 (CH, quint, J_{CF} = 4.6 Hz, C-3'), 118.5 (CH, C-2'), 61.0 (CH, C-2), 47.4 (CH_2, C-5), 30.7 (CH_2, C-3), 26.3 (CH_2, C-4).

MS (CI+) *m/z*, (%): 297 (100, $[M+H-HF]^+$), 317 (51, $[M+H]^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{14}F_5N_2OS$ 317.0747; Found 317.0751;

Anal. Calcd for $C_{11}H_{13}F_5N_2OS$: C, 41.77; H, 4.14; F, 30.03; N, 8.86; S, 10.14; Found: C, 41.62; H, 4.02; F, 30.28; N, 8.60; S, 10.69;

The enantiomeric purity was determined by preparing Mosher's amide according to General procedure B. Comparison of the ^1H and ^{19}F NMR spectra showed >99% ee. The signals used for quantitative analysis are underlined. The (*R*,*R*)-diastereomer was not observed in either of the spectra.

^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (dd, *J* = 7.6, 3.1 Hz, 1H, OCC*H*N)^{SR}, <u>3.68 (d, *J* = 1.5 Hz, 3H, OCH_3)^{SR}</u>, 3.53 (dt, *J* = 11.6, 7.5 Hz, 1H, C$H_a$$H_b$N)^{SR}, 2.73 (ddd, *J* = 11.7, 7.2, 5.1 Hz, 1H, CH_aH_bN)^{SR}.

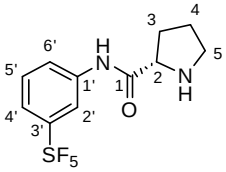
^{19}F NMR (376.3 MHz, $CDCl_3$) <u>δ −70.92 (br s, 3F, CCF_3)^{SR}.</u>

(*S*)-Pyrrolidine-2-carboxylic acid 3-(pentafluoro-λ^6-sulfanyl)phenylamide ((*S*)-60d)

Prepared according to General procedure A in a yield of 206 mg (65%).

$[\alpha]_D^{20}$ −38.7 (*c* 0.527, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 575, 597, 647, 685 (*m*-Ar), 820, 855 (SF), 1098 (Ar), 1420, 1431 (Ar), 1522 (CON), 1587, 1606 (Ar), 1684 (CON), 2876 (CH_2), 2979, 3256 (NH).



^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H, N*H*CO), 8.01 (t, *J* = 2.1 Hz, 1H, CH-2'), 7.84 (d, *J* = 8.1 Hz, 1H, CH-6'), 7.47 (ddd, *J* = 8.3, 2.1, 1.1 Hz, 1H, CH-4'), 7.40 (t, *J* = 8.1 Hz, 1H, CH-5'), 3.88 (dd, *J* = 9.3, 5.1 Hz, 1H, CH-2), 3.11 (dt, *J* = 10.3, 6.8 Hz, 1H, CH-5a), 3.00 (dt, *J* = 10.3, 6.3 Hz, 1H, CH-5b), 2.23 (ddt, *J* =

13.0, 9.3, 7.5 Hz, 1H, CH-3a), 2.18 (br s, 1H, CHN*H*CH_2), 2.05 (dtd, *J* = 13.1, 6.7, 5.2 Hz, 1H, CH-3b), 1.83-1.72 (m, 2H, CH_2-4).

^{19}F NMR (377 MHz, $CDCl_3$) δ 84.62-83.02 (m, 1F), 62.16 (d, *J* = 150.0 Hz, 4F).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C, C-1), 154.2 (m, C, C-3'), 138.3 (C, C-1'), 129.1 (CH, C-5'), 122.1 (CH, C-6'), 121.1 (CH, quint, J_{CF} = 4.7 Hz, C-4'), 116.8 (CH, quint, J_{CF} = 4.9 Hz, C-2'), 61.0 (CH, C-2), 47.4 (CH_2, C-5), 30.7 (CH_2, C-3), 26.3 (CH_2, C-4).

MS (CI+) *m/z*, (%): 297 (85, $[M+H-HF]^+$), 317 (100, $[M+H]^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{14}F_5N_2OS$ 317.0747; Found 317.0748;

Anal. Calcd for $C_{11}H_{13}F_5N_2OS$: C, 41.77; H, 4.14; F, 30.03; N, 8.86; S, 10.14; Found: C, 41.72; H, 4.08; F, 29.51; N, 8.56; S, 9.87;

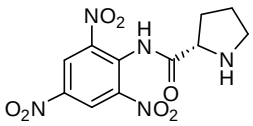
The enantiomeric purity was determined by preparing Mosher's amide according to General procedure B. Comparison of the ^{1}H and ^{19}F NMR spectra showed >99% ee. The signals used for quantitative analysis are underlined. The (*R*,*R*)-diastereomer was not observed in either of the spectra.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 7.5, 3.3 Hz, 1H, OCC*H*N)^{SR}, <u>3.69 (d, *J* = 1.5 Hz, 3H, OCH_3)^{SR}</u>, 3.54 (dt, *J* = 11.6, 7.3 Hz, 1H, C$H_a$$H_b$N)^{SR}, 2.76 (ddd, *J* = 11.8, 7.2, 5.2 Hz, 1H, CH_aH_bN)^{SR}.

^{19}F NMR (376.3 MHz, $CDCl_3$) <u>δ −70.95 (br s, 3F, CCF_3)^{SR}.</u>

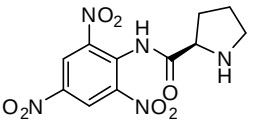
(*R*)-Pyrrolidine-2-carboxylic acid 2,4,6-trinitrophenylamide ((*R*)-60e) and (*S*)-pyrrolidine-2-carboxylic acid 2,4,6-trinitrophenylamide ((*S*)-60e)

The (*S*)-enantiomer was prepared according to the literature[238] from 2.156 g (11.3 mmol) of prolinanilide (*S*)-**60b**. Crystallization from MeCN gave 2.07 g (56%) of bright yellow crystals of trinitroanilide (*S*)-**60e**.



(*S*)-**60e**: Mp 175-180 °C decomp. (MeCN); Lit. Mp 174-178 °C (MeCN);[238]
$[\alpha]_D^{20}$ −138.5 (*c* 0.395, DMSO); Lit. $[\alpha]_D^{18}$ −155. 2 (*c* 1.00, DMSO);[238]
Anal. Calcd for $C_{11}H_{11}N_5O_7$: C, 40.62; H, 3.41; N, 21.53; Found: C, 40.40; H, 3.42; N, 21.41.

(*R*)-**60e**: Mp 176-180 °C decomp. (MeCN);

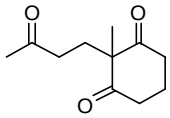


$[\alpha]_D^{20}$ +141.7 (*c* 0.261, DMSO);
Anal. Calcd for $C_{11}H_{11}N_5O_7$: C, 40.62; H, 3.41; N, 21.53; Found: C, 40.49; H, 3.38; N, 21.24;
The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.[238]

The enantiomeric purity was determined by preparing Mosher's amide according to General procedure B. Comparison of the ^{1}H and ^{19}F NMR spectra of both diastereomers, separately and as a mixture, showed >99% ee. The signals used for quantitative analysis are underlined.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 7.6, 4.7 Hz, 1H, OCC*H*N)^{RR}, 4.84 (dd, *J* = 8.2, 3.1 Hz, 1H, OCC*H*N)^{SR}, <u>3.72 (q, *J* = 1.7 Hz, 3H, OCH_3)^{RR}, 3.67 (q, *J* = 1.7 Hz, 3H, OCH_3)^{SR}</u>, 3.49 (dt, *J* = 11.6, 6.7 Hz, 1H, C$H_a$$H_b$N)^{RR}, 3.46 (dt, *J* = 11.3, 7.7 Hz, 1H, C$H_a$$H_b$N)^{SR}, 2.73 (dt, *J* = 11.3, 6.2 Hz, 1H, CH_aH_bN)^{SR}, 2.83 (dt, *J* = 11.5, 6.8 Hz, 1H, CH_aH_bN)^{RR}. ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −70.06 (s, 3F, CF_3)^{MTPA}, −70.80 (br s, 3F, CF_3)^{RR}, −71.04 (br s, 3F, CF_3)^{SR}.

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (50)

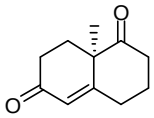


Prepared according to the literature. The crude product was purified by chromatography on silica gel (500 g) in 10% to 50% EtOAc/hexanes to afford 101.6 g (99%) **50** as a colorless liquid.[128,126]

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; Found: C, 67.23; H, 8.23;

The ^1H and ^{13}C NMR spectra are in agreement with the literature.

(*R*)-8a-Methyl-3,4,8,8a-tetrahydro-1,6-(2*H*,7*H*)-naphthalenedione or *ent*-Wieland-Miescher ketone (*ent*-21)



A mixture of triketone **50** (49.50 g, 252.2 mmol), (*R*)-prolinanilide **60a** (4.115 g, 12.61 mmol, 5 mol%) and benzoic acid (308 mg, 2.52 mmol) together with a big magnetic strirring bar to ensure efficient stirring was degassed and refilled with nitrogen. The thick oil was stirred at rt for 24 h. A sample taken from the reaction mixture showed full conversion by ^1H NMR. The reaction mixture was dried by azeotropic distillation with toluene under reduced pressure. The residue was purified by column chromatography on silica gel (600 g) in 20% to 40% EtOAc/hexanes to afford 44.83 g (100%, 96% ee) *ent*-**21** as a brownish oil, which was dissolved in a mixture of Et_2O (480 mL) and EtOAc (48 mL) and cooled to −78 °C for 6 h. The resulting crystals were filtered under nitrogen, warmed to rt and dried *in vacuo*. The yield of *ent*-Wieland-Miescher ketone *ent*-**21** was 34.23 g (76%), with an enantiomeric purity 99.7% ee as determined by HPLC on chiral stationary phase.

Mp 45-47 °C; Lit.[128] mp 49-50 °C.

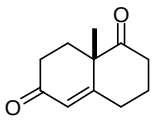
$[\alpha]_D^{20}$ −94.1 (*c* 0.324, benzene) for *ent*-**21**; Lit.[126] $[\alpha]_D^{20}$ +96 (*c* 1.1, benzene) for *nat*-**21**;

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; Found: C, 73.76; H, 7.77.

HPLC was performed with an Eurocel 01 column (Knauer, 250 × 4.6 mm, 5µm particle size, isocratic heptane/*i*PrOH 95:5, 1.0 mL·min^{-1}, detection at 254 nm) and gave retention times t_S = 32.2 min, t_R = 34.4 min.

The spectral properties are in agreement with the literature[126,128].

(±)-8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (*rac*-21)



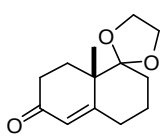
Prepared according to the literature from triketone **50** in 55% yield.[239]

The spectral and physical properties of the product are in agreement with the literature and identical to *ent*-**21**.

Mp 47-50 °C;

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; Found: C, 73.77; H, 7.95.

(±)-5-(Ethylenedioxy)-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (136a)

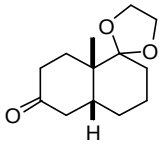


Diketone **21** (4.73 g, 26.5 mmol), triethyl orthoformate (4.12 mL, 24.8 mmol) and ethylene glycol (1.65 mL, 29.6 mmol) were dissolved in benzene (29 mL) and *p*TsOH·H_2O (507 mg, 2.66 mmol) was added with stirring at rt The mixture was stirred for 4 h and quenched with Et_3N (740 µL, 5.3 mmol). The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel (140 g) in 5% to 10% EtOAc/hexanes to afford 3.96 g (67%) of monoketal **136a** as a yellow oil, followed by 658 mg (14%) of recovered starting material.

The ^1H and ^{13}C NMR spectra are in agreement with the literature.[334,247]

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; Found: C, 70.27; H, 8.24.

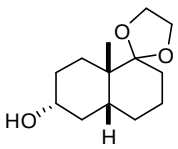
(±)-(4a*S,8a*R**)-5-(Ethylenedioxy)-4a-methyloctahydronaphthalen-2(1*H*)-one (137a)**



Ketal **136a** (3.120 g, 14.04 mmol) was dissolved in EtOH (20 mL) and 5% palladium on $CaCO_3$ (135 mg) was added to the reaction mixture. The mixture was hydrogenated under a slight overpressure of hydrogen for 16 h. The catalyst was filtered off and the solvent evaporated *in vacuo* to afford 3.117 g (99%) of saturated ketone **137a** as a colorless oil, which solidified on standing.

The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.[247,246]

(±)-(2*R,4a*S**,8a*R**)-5-(Ethylenedioxy)-4a-methyldecahydronaphthalen-2-ol (138a)**

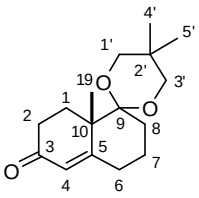


Ketone **137a** (2.976 g, 13.27 mmol) was dissolved in CH_2Cl_2 (15 mL) and MeOH (15 mL), the reaction flask was immersed in −45 °C bath and $NaBH_4$ (784 mg, 20.72 mmol) was added portionwise. The mixture was stirred at −45 °C for 30 min and subsequently warmed slowly to rt The reaction was quenched with 5% aq. citric acid (50 mL), the organic layer separated and the aqueous extracted with $CHCl_3$ (2 × 25 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (50 mL), dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (60 g) in 20% EtOAc/hexanes + 0.2% Et_3N to afford 2.741 g (91%) of alcohol **138a** as a colorless oil.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 68.99; H, 9.80; Found: C, 69.03; H, 9.87.

The IR, MS, ^{1}H NMR and ^{13}C NMR spectra are in agreement with the literature.[247]

(±)-5-(2',2'-Dimethylpropylenedioxy)-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (136b)



Diketone **21** (2.386 g, 13.39 mmol), neopentyl glycol (1.528 g, 14.67 mmol) and trimethyl orthoformate (1.46 mL, 14.18 mmol) were dissolved in Et_2O (33 mL) and $BF_3{\cdot}Et_2O$ (0.168 mL, 1.36 mmol) was added dropwise to the reaction mixture with stirring. The content of the flask was stirred for 48 h, quenched with saturated aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (60 g) in 15% EtOAc/hexanes to afford 2.438 g (69%) of monoketal **136b** as an off-white solid, which was crystallized from Et_2O.

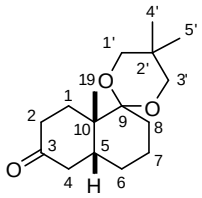
Mp 97-99 °C; Lit.[335] mp 96 °C, for (−)-**136b**.

IR ($CHCl_3$); ν[cm^{-1}]: 873, 913 (COCOC), 1013 (CH_3), 1037, 1049, 1111, 1153, 1233, 1282 (COCOC), 1375, 1396, 1443, 1463, 1472, 1481 (CH_3), 1620 (C=C), 1661 (C=O), 2871 (CH_3), 2959 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (d, *J* = 2.0 Hz, 1H, CH-4), 3.73 (d, *J* = 11.5 Hz, 1H, CH-1'a), 3.58 (d, *J* = 11.5 Hz, 1H, CH-3'a), 3.34 (dd, *J* = 11.5, 2.5 Hz, 1H, CH-1'b), 3.33 (dd, *J* = 11.5, 2.5 Hz, 1H, CH-3'b), 2.76 (td, *J* = 13.8, 5.1 Hz, 1H, CH-1a), 2.68 (ddd, *J* = 10.6, 2.5, 1.5 Hz, 1H, CH-8a), 2.47 (dddd, *J* = 16.7, 5.2, 3.6, 0.8 Hz, 1H, CH-2a), 2.76-2.68 (m, 1H, CH-2b), 2.38 (ddd, *J* = 16.8, 14.1, 5.3 Hz, 1H, CH-6a), 2.31-2.22 (m, 1H, 6b), 1.86 (ddd, *J* = 13.7, 5.3, 3.7 Hz, 1H, CH-1b), 1.76-1.68 (m, 1H, 7a), 1.55-1.46 (m, 2H, CH-7b, CH-8b), 1.27 (s, 3H, CH_3-19), 1.17 (s, 3H, CH_3-4'), 0.73 (s, 3H, CH_3-5').

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (C, C-3), 168.0 (C, C-5), 125.7 (CH, C-4), 100.7 (C, C-9), 70.1 (CH_2, C-1'), 69.9 (CH_2, C-3'), 45.6 (C, C-10), 34.3 (CH_2, C-2), 31.5 (CH_2, C-6), 29.7 (C, C-2'), 26.6 (CH_2, C-1), 23.4 (CH_3, C-4'), 22.2 (CH_3, C-5'), 21.2 (CH_2, C-8), 20.7 (CH_2, C-7), 19.6 (CH_3, C-19).
MS (ESI+) *m/z*, (%): 265 (10, $[M+H]^+$), 287 (100, $[M+Na]^+$), 551 (33, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{25}O_3$ 265.1798; Found 265.1799;
Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; Found: C, 72.66; H, 9.15.

(±)-(4a*S,8a*R**)-5-(2',2'-Dimethylpropylenedioxy)-4a-methyloctahydronaphthalen-2(1*H*)-one (137b)**

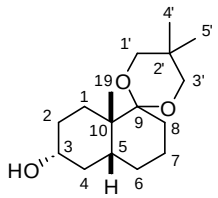


Enone **136b** (4.413 g, 16.69 mmol) was dissolved in EtOH (25 mL) and 5% palladium on $CaCO_3$ (100 mg) was added to the reaction mixture. The mixture was hydrogenated under a slight overpressure of hydrogen for 14 h. The catalyst was filtered off and the solvent evaporated *in vacuo* to afford 4.44 g (100%) of saturated ketone **137b**, crystallizing from hexane.
Mp 87-88 °C;
IR ($CHCl_3$); ν[cm^{-1}]: 876, 911 (COCOC), 1013 (CH_3), 1026, 1041, 1103, 1146, 1236, 1282 (COCOC), 1375, 1395, 1444, 1464, 1472, 1481 (CH_3), 1704 (C=O), 2868 (CH_3), 2931 (CH_2), 2959 (CH_3);
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (d, *J* = 11.1 Hz, 1H, CH-1'a), 3.64 (d, *J* = 11.1 Hz, 1H, CH-3'a), 3.33 (dd, *J* = 11.1, 2.7 Hz, 1H, CH-1'b), 3.29 (dd, *J* = 11.1, 2.7 Hz, 1H, CH-3'b), 2.63 (dd, *J* = 14.8, 5.8 Hz, 1H, CH-4a), 2.46 (ddd, *J* = 15.2, 7.2, 0.8 Hz, 1H, CH-2a), 2.42 (ddd, *J* = 15.3, 7.1, 0.8 Hz, 1H, CH-8a), 2.32 (ddt, *J* = 15.2, 5.1, 2.7 Hz, 1H, CH-2b), 2.15-2.06 (m, 3H, CH-1a, CH-4b, CH-5), 1.77 (dddd, *J* = 13.8, 7.1, 2.8, 1.7 Hz, 1H, CH-1b), 1.62-1.53 (m, 1H, CH-7a), 1.51-1.43 (m, 1H, CH-6a), 1.43-1.32 (m, 2H, CH-7b, CH-8b), 1.39 (s, 3H, CH_3-19), 1.29-1.17 (m, 1H, CH-6b), 1.22 (s, 3H, CH_3-4'), 0.73 (s, 3H, CH_3-5');
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.9 (C, C-3), 100.7 (C, C-9), 69.7 (CH_2, C-1'), 69.4 (CH_2, C-3'), 44.3 (CH_2, C-4), 41.7 (C, C-10), 41.3 (CH, C-5), 37.9 (CH_2, C-2), 29.8 (C, C-2'), 28.5 (CH_2, C-6), 28.3 (CH_2, C-1), 23.6 (CH_3, C-4'), 22.4 (CH_3, C-5'), 21.0 (CH_2, C-7/8), 20.9 (CH_2, C-7/8), 17.5 (CH_3, C-19);
MS (ESI+) *m/z*, (%): 267 (1, $[M+H]^+$), 289 (100, $[M+Na]^+$), 555 (9, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{26}NaO_3$ 289.1774; Found 289.1775;
Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84; Found: C, 72.02; H, 9.77.
The NMR and IR spectral data differ from those reported for the **(±)**-(4a*S**,8a*S**) isomer.[336]

(±)-(2*R,4a*S**,8a*R**)-5-(2',2'-Dimethylpropylenedioxy)-4a-methyldecahydronaphthalen-2-ol (138b) and (±)-(2*S**,4a*S**,8a*R**)-5-(2',2'-Dimethylpropylenedioxy)-4a-methyldecahydronaphthalen-2-ol (139b)**

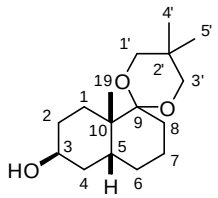
Ketone **137b** (4.553 g, 17.09 mmol) was dissolved in CH_2Cl_2 (25 mL) and MeOH (25 mL), the reaction flask was immersed in −40 °C bath and $NaBH_4$ (775 mg, 20.51 mmol) was added portionwise. The mixture was stirred for 2 h at −40 °C and warmed slowly to rt The reaction was quenched with 5% aq. citric acid (50 mL), the organic layer was separated and the aqueous extracted with CH_2Cl_2 (2 × 25 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (50 mL), dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (100 g) in 15% EtOAc/hexanes to afford 3.586 g (78%) of alcohol **138b**, followed by 0.742g (16%) of alcohol **139b**.

Equatorial alcohol **138b**: colorless oil



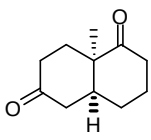
IR ($CHCl_3$); ν[cm^{-1}]: 876, 908 (COCOC), 999 (OH), 1013 (CH_3), 1036, 1105, 1237 (COCOC), 1363, 1380, 1395 (CH_3), 1448, 1472, 1481 (CH_3), 2868 (CH_3), 2931 (CH_2), 2957 (CH_3), 3455 (OH), 3609 (OH);
^{1}H NMR (500 MHz, $CDCl_3$ at 60 °C) δ 3.73 (tt, *J* = 8.6, 4.3 Hz, 1H, CH-3), 3.66 (d, *J* = 11.2 Hz, 1H, CH-1'a), 3.62 (d, *J* = 11.2 Hz, 1H, CH-3'a), 3.30 (dd, *J* = 11.2, 2.7 Hz, 1H, CH-3'b), 3.26 (dd, *J* = 11.2, 2.7 Hz, 1H, CH-1'b), 2.29 (dt, *J* = 14.2, 5.4 Hz, 1H, CH-1a), 2.20-2.10 (br m, 1H, CH-8a), 1.88 (dddd, *J* = 12.9, 10.1, 8.4, 4.7 Hz, 1H, CH-2a), 1.85-1.79 (m, 1H, CH-4a), 1.78-1.71 (m, 1H, CH-2b), 1.75-1.66 (m, 1H, CH-6a), 1.64-1.55 (m, 1H, CH-8b), 1.61-1.49 (m, 5H, CH-4b, CH-6b, CH-5, CH-7a, OH), 1.43-1.36 (m, 1H, CH-7b), 1.19 (s, 3H, CH_3-4'), 1.07 (ddd, *J* = 14.2, 10.2, 5.0 Hz, 1H, CH-1b), 1.03 (s, 3H, CH_3-19), 0.69 (s, 3H, CH_3-5');
^{13}C NMR (126 MHz, $CDCl_3$ at 60 °C) δ 102.0 (C, C-9), 70.3 (CH, C-3), 69.5 (CH_2, C-1'), 69.3 (CH_2, C-3'), 40.9 (CH, C-5), 37.0 (CH_2, C-4), 32.6 (CH_2, C-2), 31.6 (C, C-2'), 29.7 (CH_2 + C, CH_2-1, C-10), 28.6 (CH_2, C-6), 23.5 (2 × CH_3, C-4', C-19), 22.4 (CH_3, C-5'), 22.2 (CH_2, C-8), 19.8 (CH_2, C-7).
MS (ESI+) *m/z*, (%): 291 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{28}NaO_3$ 291.1931; Found 291.1931;
Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52; Found: C, 72.02; H, 10.68.

Axial alcohol **139b**: Mp 110-113 °C (Et_2O/hexane);



IR ($CHCl_3$); ν[cm^{-1}]: 892, 907 (COCOC), 1015 (CH_3), 1037 (COCOC), 1054 (OH), 1104, 1236, 1288 (COCOC), 1364, 1378, 1395 (CH_3), 1443, 1473, 1481 (CH_3), 2865 (CH_3), 2932 (CH_2), 2956 (CH_3), 3463 (OH), 3607 (OH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (tt, *J* = 10.8, 5.4 Hz, 1H, CH-3), 3.69 (d, *J* = 11.6 Hz, 1H, CH-1'a), 3.61 (d, *J* = 11.6 Hz, 1H, CH-3'a), 3.29 (dd, *J* = 11.6, 2.7 Hz, 1H, CH-3'b), 3.26 (dd, *J* = 11.6, 2.7 Hz, 1H, CH-1'b), 2.49 (br d, *J* = 12.0 Hz, 1H, CH-8a), 1.90-1.82 (m, 1H, CH-2a), 1.90-1.79 (m, 1H, CH-5), 1.77-1.66 (m, 1H, CH-1a, CH-6a), 1.69-1.60 (m, 2H, CH_2-4), 1.60-1.50 (m, 5H, CH-7a, CH-6b, CH-2b, CH-1b, OH), 1.36-1.26 (m, 1H, CH-7b), 1.32-1.26 (m, 1H, CH-8b), 1.22 (s, 3H, CH_3-19), 1.19 (s, 3H, CH_3-4'), 0.71 (s, 3H, CH_3-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ 100.9 (C, C-9), 69.7 (CH_2, C-1'), 69.3 (CH_2, C-3'), 66.9 (CH, C-3), 41.8 (C, C-10), 38.9 (CH, C-5), 36.6 (CH_2, C-4), 31.5 (CH_2, C-2), 29.8 (C, C-2'), 27.9 (CH_2, C-6), 25.9 (CH_2, C-1), 23.6 (CH_3, C-4'), 22.4 (CH_3, C-5'), 21.4 (CH_2, C-7), 20.9 (CH_2, C-8), 17.2 (CH_3, C-19);
MS (ESI+) *m/z*, (%): 269 (51, $[M+H]^+$), 291 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{29}O_3$ 269.2111; Found 269.2112; $[M+Na]^+$ Calcd for $C_{16}H_{28}NaO_3$ 291.1931; Found 291.1932;
Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52; Found: C, 71.36; H, 10.53.

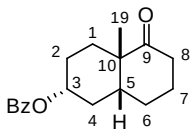
(−)-(4a*R*,8a*S*)-8a-Methylhexahydronaphthalene-1,6(2*H*,7*H*)-dione (*ent*-140a)



Prepared from 3.60 g (20.2 mmol) enone *ent*-**21** by the method published in the literature yielding a 14:1 5β:5α mixture of *ent*-**140a** and *ent*-**140b** in quantitative yield.[248] This mixture was purified by chromatography on silica gel (100 g) in 5% to 10% EtOAc/hexanes to yield 3.36 g (92%) of *ent*-**140a** as colorless crystals.
Mp 50-52 °C; Lit.[337] mp 52-54 °C;
$[\alpha]_D^{20}$ −5.5 (*c* 0.434, benzene) for *ent*-**140a**; Lit.[338] $[\alpha]_D^{25}$ +8.9 (*c* 1.0, benzene) for *nat*-**140a**.

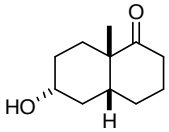
Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; Found: C, 73.21; H, 8.93. *ent*-**140a**;
The ^1H and ^{13}C NMR spectra are in agreement with the literature.[338,246]

(−)-(2*R*,4a*S*,8a*R*)-4a-Methyl-5-oxodecahydronaphthalen-2-yl benzoate (*nat*-144) and (+)-(2*S*,4a*R*,8a*S*)-4a-Methyl-5-oxodecahydronaphthalen-2-yl benzoate (*ent*-144)



Diketone **140a** (5.88 g, 32.6 mmol) was dissolved in CH_2Cl_2 (40 mL) and dry MeOH (40 mL) and the solution was cooled to −78 °C. $NaBH_4$ (1.48 g, 39.1 mmol) was added portionwise with stirring and the mixture was warmed to −40 °C. After 30 min at −40 °C, TLC showed full consumption of the starting material. Acetone (5 mL) was added slowly to the cooled solution and the reaction was quenched with 5% HCl (150 mL). The organic layer was separated and the aqueous was extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was redissolved in dry pyridine (40 mL) and the solution was cooled to 0 °C. Benzoyl chloride (7.64 mL, 65.8 mmol) was added slowly at 0 °C, the mixture was warmed to rt and stirred for 30 min. The reaction mixture was poured on ice (150 mL) and acidified with 35% aq. HCl to pH < 2. The resulting emulsion was extracted with EtOAc (3 × 50 mL) and the combined organic layers were subsequently washed with water (150 mL), saturated aq. $NaHCO_3$ (150 mL) and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. Chromatography of the residue on silica gel (150 g) in 10% EtOAc/hexanes afforded 6.11 g (73%) of the benzoate **144** as a low-melting solid.
$[\alpha]_D^{20}$ +2.4 (*c* 0.246, $CHCl_3$) for *ent*-**144**;
$[\alpha]_D^{20}$ −8.3 (*c* 0.204, $CHCl_3$) for *nat*-**144**;
IR ($CHCl_3$); ν[cm^{-1}]: 713 (C=O), 998, 1026, 1071 (=CH), 1119, 1279 (COC), 1315, 1322, 1382 (CH_3), 1451 (=CH), 1466 (CH_3), 1603 (ring), 1705 (C=O), 2879 (CH_3), 2948 (CH_3);
^1H NMR (400 MHz, $CDCl_3$) δ 8.03-7.99 (m, 2H, CH-3'), 7.57-7.52 (m, 1H, CH-5'), 7.45-7.40 (m, 2H, CH-4'), 4.97 (tt, *J* = 11.2, 4.3 Hz, 1H, CH-3), 2.64-2.54 (m, 1H, CH-8a), 2.37 (dt, *J* = 13.9, 3.7 Hz, 1H, CH-1a), 2.32-2.26 (m, 1H, CH-8b), 2.31-2.19 (m, 1H, CH-6a), 2.06-2.00 (m, 1H, CH-5), 1.99-1.90 (m, 3H, CH_2-7, CH-2a), 1.87 (dtd, *J* = 12.7, 3.8, 2.4 Hz, 1H, CH-4a), 1.67 (dddd, *J* = 13.4, 12.6, 11.3, 4.0 Hz, 1H, CH-2b), 1.57-1.49 (m, 1H, CH-6b), 1.51 (td, *J* = 12.8, 11.0 Hz, 1H, CH-4b), 1.26 (s, 3H, CH_3-19), 1.08 (td, *J* = 13.7, 4.0 Hz, 1H, CH-1b).
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.7 (C, C-9), 166.0 (C, C-1'), 132.7 (CH, C-5'), 130.7 (C, C-2'), 129.5 (CH, C-3'), 128.2 (CH, C-4'), 73.7 (CH, C-3), 48.5 (C, C-10), 43.4 (CH, C-5), 37.8 (CH_2, C-8), 34.4 (CH_2, C-4), 32.6 (CH_2, C-1), 28.6 (CH_2, C-2), 26.4 (CH_3, C-19), 26.2 (CH_2, C-6), 22.1 (CH_2, C-7);
MS (ESI+) *m/z*, (%): 309 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{22}NaO_3$ 309.1461; Found 309.1460;
Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; Found: C, 75.48; H, 7.73 for *ent*-**144**.
Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; Found: C, 74.90; H, 7.82 for *nat*-**144**.

(±)-(4a*R,6*R**,8a*S**)-6-Hydroxy-8a-methyloctahydronaphthalen-1(2*H*)-one (141)**

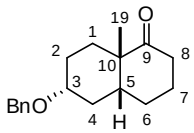


Benzoate **(±)-144** (2.865 g, 10.0 mmol) was dissolved in MeOH (150 mL) and solid KOH (5.6 g, 100 mmol) was added while stirring. The reaction mixture was warmed to 50 °C during 1 h and concentrated *in vacuo* to one third of the volume. The solution was poured into water (150 mL) and extracted with Et_2O (3 × 50 mL). The combined

extracts were washed with saturated aq. $NaHCO_3$ (100 mL) and with brine (100 mL). The organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to afford 1.80 g (99%) of alcohol **141** as a low-melting solid.
The ^1H NMR and ^{13}C NMR spectra are in agreement with the literature.[339]

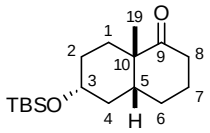
(±)-(4a*R,6*R**,8a*S**)-6-(Benzyloxy)-8a-methyloctahydronaphthalen-1(2*H*)-one (146a) and (±)-(4a*R**,6*R**,8a*S**)-6-hydroxy-8a-methyloctahydronaphthalen-1(2*H*)-one (141)**

Alcohol **138a** (2.648 g, 11.7 mmol) was dissolved in THF (30 mL) and NaH (1.123 g of 50% suspension in paraffin, 23.4 mmol) was added portionwise, followed by tetrabutylammonium iodide (432 mg, 1.16 mmol) and benzyl bromide (4.18 mL, 35.1 mmol). The reaction mixture was refluxed for 3 days, quenched with water (0.5 mL) and concentrated *in vacuo*. The ^1H NMR spectrum of the crude reaction mixture showed ca. 2/3 conversion. The residue was redissolved in acetone (25 mL), water (5 mL) and concentrated aq. HCl (1.0 mL, 35% w/v) and stirred at rt overnight. The reaction mixture was poured into saturated aq. $NaHCO_3$ (150 mL), extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (100 g) in 5% to 30% EtOAc/hexanes to afford 2.144 g (67%) of benzyl ether **146a**, followed by 603 mg (28%) of free alcohol **141**.



146a: colorless oil
IR ($CHCl_3$); ν[cm^{-1}]: 699, 921, 1029, 1070 (Ph), 1090 (COC), 1314 (Ph), 1363 (Ph*C*H_2), 1380 (CH_3), 1423 (CO*C*H_2), 1454, 1496, 1702 (C=O), 2872 (CH_3), 2945 (CH_2), 3011;
^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 4H, Ph), 7.29-7.23 (m, 1H, *p*-Ph), 4.54 (AB system, *J* = 11.9 Hz, 2H, PhCH_2), 3.36 (tt, *J* = 10.8, 4.0 Hz, 1H, CH-3), 2.54 (ddd, *J* = 15.3, 12.7, 7.9 Hz, 1H, CH-8a), 2.32 (dt, *J* = 13.8, 3.7 Hz, 1H, CH-1a), 2.28-2.19 (m, 1H, CH-8b), 2.27-2.14 (m, 1H, CH-7a), 2.00-1.84 (m, 2H, CH_2-6), 1.98-1.89 (m, 1H, CH-2a), 1.90-1.80 (m, 1H, CH-5), 1.85-1.75 (m, 1H, CH-4a), 1.54-1.47 (dqt, *J* = 14.1, 2.6, 1.5 Hz, 1H, CH-7b), 1.46-1.36 (m, 1H, CH-2b), 1.36 (td, *J* = 12.9, 10.7 Hz, 1H, CH-4b), 1.20 (s, 3H, CH_3-19), 0.89 (td, *J* = 13.6, 3.9 Hz, 1H, CH-1b).
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.8 (C, C-9), 139.0 (C, Ph), 128.3 (CH, Ph), 127.5 (CH, Ph), 127.4 (CH, *p*-Ph), 77.4 (CH_2, C-3), 69.7 (CH_2, Ph*C*H_2), 48.8 (C, C-10), 43.5 (CH, C-5), 37.8 (CH_2, C-8), 35.3 (CH_2, C-4), 32.8 (CH_2, C-1), 29.1 (CH_2, C-2), 26.5 (CH_3, C-19), 26.4 (CH_2, C-7), 22.0 (CH_2, C-6);
MS (ESI+) *m/z*, (%): 295 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{24}NaO_2$ 295.1669; Found 295.1670;
Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88; Found: C, 79.04; H, 8.78.

(±)-(4a*R,6*R**,8a*S**)-6-(*tert*-Butyldimethylsilyloxy)-8a-methyloctahydronaphthalen-1(2*H*)-one (146b)**



Alcohol **141** (505 mg, 2.77 mmol) and imidazole (226 mg, 3.32 mmol) were dissolved in DMF (2 mL), cooled to 0 °C and a solution of TBSCl (460 mg, 3.05 mmol) in DMF (1 mL) was added dropwise while stirring. The conversion was complete after 90 min and the mixture was poured into water (25 mL) and extracted with hexane (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents were evaporated *in vacuo*. The residue was purified by chromatography on silica gel (25 g) in 5% EtOAc/hexanes to yield 772 mg (94%) of silyl ether **146b** as a colorless oil.

IR ($CHCl_3$); ν[cm^{-1}]: 837, 864 (Si-CH_3), 1066, 1071, 1095 (C-O), 1257 (Si-CH_3), 1361 (*t*Bu), 1374 (CH_3), 1422 (CO*C*H_2), 1463, 1472 (*t*Bu), 1703 (C=O), 2858 (CH_3), 2883 (*t*Bu), 2903 (Si*C*H_3), 2930, 2949 (*t*Bu);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (tt, *J* = 10.6, 4.2 Hz, 1H, CH-3), 2.52 (ddd, *J* = 15.3, 12.9, 7.5 Hz, 1H, CH-8a), 2.32-2.18 (m, 1H, CH-1a), 2.29-2.18 (m, 1H, CH-8b), 2.25-2.12 (m, 1H, CH-6a), 1.95 (qt, *J* = 13.3, 4.6 Hz, 1H, CH-7a), 1.93-1.79 (m, 1H, CH-7b), 1.91-1.81 (m, 1H, CH-5), 1.72-1.63 (m, 1H, CH-2a), 1.56 (dtd, *J* = 12.9, 3.8, 2.4 Hz, 1H, CH-4a), 1.49 (br d, *J* = 13.8 Hz, 1H, CH-6b), 1.45-1.31 (m, 1H, CH-2b), 1.37-1.25 (m, 1H, CH-4b), 1.18 (s, 3H, CH_3-19), 0.96-0.85 (m, 1H, CH-1b), 0.87 (s, 9H, *t*Bu), 0.03 (m, 6H, 2 × $SiCH_3$).

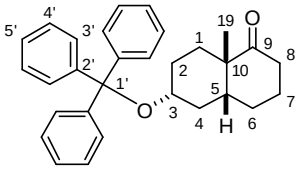
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.8 (C, C-9), 71.5 (CH, C-3), 48.5 (C, C-10), 43.6 (CH, C-5), 38.8 (CH_2, C-4), 37.8 (CH_2, C-8), 32.9 (2 × CH_2, C-1, C-2), 26.5 (CH_2, C-6), 26.4 (CH_3, C-19), 25.9 (CH_3, *t*Bu), 22.0 (CH_2, C-7), 18.1 (C, *t*Bu), −4.6 (CH_3, $SiCH_3$), −4.7 (CH_3, $SiCH_3$).

MS (ESI+) *m/z*, (%): 319 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{32}NaO_2Si$ 319.2064; Found 319.2064;

Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88; Found: C, 68.78; H, 10.83;

(±)-(4a*R,6*R**,8a*S**)-6-(Trityloxy)-8a-methyloctahydronaphthalen-1(2*H*)-one (146c)**



Alcohol **141** (443 mg, 2.43 mmol), DMAP (60 mg, 0.49 mmol) and trityl chloride (1.23 g, 4.40 mmol) were dissolved in CH_2Cl_2 (10 mL) and triethylamine (1.35 mL, 9.69 mmol) and the mixture was refluxed for 16 h. After cooling to rt, the raction mixture was poured into 5% aq. solution of citric acid (50 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed subsequently with 5% aq. citric acid (50 mL), saturated aq. $NaHCO_3$ (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and some trityl alcohol was crystallized off from hot hexane. The mother liquors were subjected to chromatography on silica gel (20 g) in 10% EtOAc/hexanes to afford 934 mg (91%) of trityl ether **146c** as a colorless oil.

IR ($CHCl_3$); ν[cm^{-1}]: 630, 703, 709, 1032 (Ph), 1054, 1083 (C-O), 1152 (Ph), 1371, 1384 (CH_3), 1423 (CO*C*H_2), 1449, 1491 (Ph), 1597 (Ph), 1703 (C=O), 2872, 2881 (CH_3), 2946 (CH_2), 3033, 3061 (C-H);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 6H, CH-3'), 7.37-7.17 (m, 9H, CH-4', CH-5'), 3.42 (tt, *J* = 10.5, 3.8 Hz, 1H, CH-3), 2.49 (ddd, *J* = 15.2, 12.7, 7.9 Hz, 1H, CH-8a), 2.24-2.18 (m, 1H, CH-8b), 2.49 (dt, *J* = 13.7, 3.5 Hz, 1H, CH-1a), 2.08-2.01 (m, 1H, CH-6a), 1.93-1.78 (m, 2H, CH_2-7), 1.54 (dq, *J* = 13.3, 3.3 Hz, 1H, CH-5), 1.40 (tdd, *J* = 13.4, 10.8, 3.7 Hz, 1H, CH-2a), 1.32-1.17 (m, 1H, CH-4a), 1.29-1.22 (m, 1H, CH-2b), 1.27-1.14 (m, 1H, CH-6b), 1.08 (s, 3H, CH_3-19), 0.88 (dq, *J* = 12.6, 3.1 Hz, 1H, CH-4b), 0.64 (td, *J* = 13.7, 4.0 Hz, 1H, CH-1b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0 (C, C-9), 145.4 (C, C-2'), 128.9 (CH, C-3'/C-4'), 127.6 (CH, C-3'/C-4'), 126.8 (CH, C-5'), 86.6 (C, C-1'), 73.2 (CH, C-3), 48.5 (C, C-10), 43.7 (CH, C-5), 37.8 (CH_2, C-8), 36.8 (CH_2, C-4), 33.2 (CH_2, C-1), 31.0 (CH_2, C-2), 26.44 (CH_3, C-19), 26.38 (CH_2, C-6), 22.0 (CH_2, C-7).

MS (ESI+) *m/z*, (%): 447 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{30}H_{32}NaO_2$ 447.2295; Found 447.2295;

Anal. Calcd for $C_{30}H_{32}O_2$: C, 84.87; H, 7.60; Found: C, 85.15; H, 7.60;

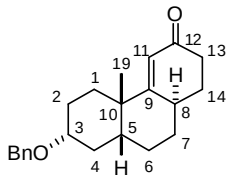
General procedure C: Substrate-controlled Robinson annulation

Ketone **146a-c** (1.686 mmol) was dissolved in dry ethyl formate (5 mL) at 0 °C and sodium hydride (270 mg, 6.75 mmol, 60% suspension in oil) was added portionwise. MeOH (82 µL, 2.03 mmol) was added dropwise while stirring vigorously. The reaction mixture turned into a thick slurry after a few minutes. After 30 min, the reaction was quenched with saturated aq. NH_4Cl (50 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crystalline formyl derivative in essentially quantitative yield. To this neat compound, methyl vinyl ketone (186 µL, 2.23 mmol) is added, followed by triethylamine (2.5 µL, 18 µmol) and the mixture was stirred overnight. The excess of methyl vinyl ketone was evaporated *in vacuo* and the crude mixture was dissolved in *t*BuOH (8 mL). *t*BuOK (378 mg, 3.37 mmol) was added in one portion and the mixture was stirred at rt for 45 min. The reaction was quenched with saturated aq. NH_4Cl (50 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*.

rac-3α-(Benzyloxy)-des-*D*-18-nor-5β,8α-androst-9(11)-en-12-one (150a) and _rac_-3α-(benzyloxy)-des-*D*-18-nor-5β-androst-8-en-12-one (149a)

Prepared according to General procedure C. The crude mixture was purified by column chromatography on silica gel (90 g) in 5% EtOAc/hexanes to afford 180 mg (7%) of ketone **149a**, followed by 575 mg (21%) of conjugated enone **150a** as a colorless oil.

Conjugated enone **150a**:



IR ($CHCl_3$); ν[cm^{-1}]: 698 (Ph), 1028 (Ph), 1068 (Ph), 1090 (COC), 1268 (CH_3), 1330 (CH_2), 1353 (CH_2), 1454 (Ph), 1467 (CH_2), 1496 (Ph), 1598 (C=C), 1660 (C=O), 2865 (CH_2), 2936 (CH_2);

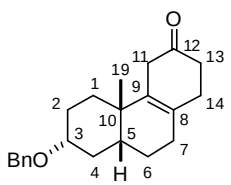
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H, CH-3', CH-4'), 7.31-7.24 (m, 1H, CH-5'), 6.07 (d, *J* = 1.9 Hz, 1H, CH-11), 4.54 (d, *J* = 12.1 Hz, 1H, PhC$H_a$$H_b$O), 4.49 (d, *J* = 12.0 Hz, 1H, PhC$H_a$$H_b$O), 3.57 (quint, *J* = 4.2 Hz, 1H, CH-3), 2.57 (ddtd, *J* = 12.0, 9.6, 4.7, 2.0 Hz, 1H, CH-8), 2.42 (dt, *J* = 16.4, 4.1 Hz, 1H, CH-13a), 2.29 (ddd, *J* = 16.5, 14.0, 5.0 Hz, 1H, CH-13b), 2.24-2.13 (m, 2H, CH-1a, CH-6a), 2.10-2.00 (m, 1H, CH-14a), 1.99-1.88 (m, 1H, CH-4a), 1.89-1.79 (m, 1H, CH-7a), 1.82-1.65 (m, 2H, CH_2-2), 1.80-1.70 (m, 1H, CH-6b), 1.77-1.66 (m, 1H, CH-4b), 1.65-1.50 (m, 1H, CH-14b), 1.60-1.49 (m, 1H, CH-5), 1.27-1.11 (m, 1H, CH-7b), 1.23 (s, 3H, CH_3-19), 1.05-0.94 (m, 1H, CH-1b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (C, C-12), 174.9 (C, C-9), 139.0 (C, C-2'), 128.3 (CH, C-4'), 127.3 (CH, C-5'), 127.2 (CH, C-3'), 123.4 (CH, C-11), 73.7 (CH, C-3), 69.9 (CH_2, PhCH_2O), 40.3 (C, C-10), 39.8 (CH, C-5), 36.7 (CH_2, C-13), 35.1 (CH, C-8), 33.4 (CH_2, C-4), 31.9 (CH_2, C-7), 31.3 (CH_2, C-1), 30.3 (CH_2, C-14), 28.0 (CH_2, C-6), 26.8 (CH_2, C-2), 24.7 (CH_3, C-19).

MS (ESI+) *m/z*, (%): 325 (27, $[M+H]^+$), 347 (100, $[M+Na]^+$), 649 (4, $[2M+H]^+$), 671 (36, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{28}NaO_2$ 347.1982; Found 347.1982;

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70; Found: C, 80.99; H, 8.75;



Deconjugated enone **149a**:

IR ($CHCl_3$); ν[cm^{-1}]: 699 (Ph), 1028 (Ph), 1066, 1076 (Ph), 1089 (COC), 1362 (PhCH_2), 1454 (Ph), 1496 (Ph), 1661 (C=C), 1711 (C=O), 2870 (CH_2), 2937 (CH_2);

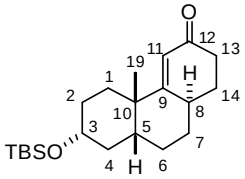
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 4H, C-3', C-4'), 7.30-7.23 (m, 1H, C-5'), 4.57 (d, *J* = 11.8 Hz, 1H, CH-1'a), 4.53 (d, *J* = 11.8 Hz, 1H, CH-1'b), 3.43-3.35 (m, 1H, CH-3), 2.82 (br d, *J* = 20.1 Hz, 1H, CH-11a), 2.70 (br d, *J* = 20.1 Hz, 1H, CH-11b), 2.48 (dddd, *J* = 14.2, 9.3, 7.2, 0.6 Hz, 1H, CH-13a), 2.39 (dddd, *J* = 14.2, 6.2, 5.1, 1.1 Hz, 1H, CH-13b), 2.36-2.20 (m, 2H, CH_2-14), 2.19-2.01 (m, 1H, CH-7a), 2.06-1.91 (m, 1H, CH-6a), 1.97-1.89 (m, 1H, CH-2a), 1.95-1.82 (m, 1H, CH-7b), 1.85-1.73 (m, 1H, CH-1a), 1.84-1.75 (m, 1H, CH-4a), 1.59-1.51 (m, 1H, CH-5), 1.56-1.41 (m, 1H, CH-4b), 1.46-1.38 (m, 1H, CH-6b), 1.12-0.98 (m, 1H, CH-2b), 1.09-1.00 (m, 1H, CH-1b), 0.99 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6 (C, C-12), 138.9 (C, C-2'), 129.4 (C, C-9), 129.1 (C, C-8), 128.3 (CH, C-3'/C-4'), 127.5 (CH, C-3'/C-4'), 127.4 (CH, C-5'), 77.4 (CH, C-3), 71.0 (CH_2, C-1'), 39.5 (CH, C-5), 38.7 (CH_2, C-11), 38.4 (CH_2, C-13), 36.7 (C, C-10), 34.1 (CH_2, C-1), 33.4 (CH_2, C-4), 30.9 (CH_2, C-14), 29.3 (CH_2, C-2), 28.4 (CH_3, C-19), 26.6 (CH_2, C-7), 23.6 (CH_2, C-6).

MS (ESI+) *m/z*, (%): 325 (16, $[M+H]^+$), 347 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{28}NaO_2$ 347.1982; Found 347.1982;

***rac*-3α-(*tert*-Butyldimethylsilyloxy)-des-*D*-18-nor-5β,8α-androst-9(11)-en-12-one (150b)**



Prepared according to General procedure C. The crude mixture was purified by column chromatography on silica gel (30 g) in 5% EtOAc/hexanes to afford 236 mg (40%) of conjugated enone **150b** as a colorless oil.

IR ($CHCl_3$); ν[cm^{-1}]: 837 ($SiCH_3$), 854, 1006 (OTBDMS), 1036, 1062 (C-O), 1256 (CH_3), 1330, 1374 (CH_3), 1455, 1463 (CH_2), 1471 (*t*Bu) 1597 (C=C), 1659 (C=O), 2858 (CH_3), 2930 (CH_2), 2954 (CH_3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, *J* = 2.1 Hz, 1H, CH-11), 3.87 (quint, *J* = 4.0 Hz, 1H, CH-3), 2.56 (ddtd, *J* = 12.3, 9.8, 4.8, 2.2 Hz, 1H, CH-8), 2.42 (dt, *J* = 16.5, 4.1 Hz, 1H, CH-13a), 2.30 (ddd, *J* = 16.5, 14.0, 5.0 Hz, 1H, CH-13b), 2.27-2.17 (m, 1H, CH-6a), 2.18 (ddd, *J* = 14.8, 13.3, 3.7 Hz, 1H, CH-1a), 2.06 (dtd, *J* = 13.3, 4.7, 3.8 Hz, 1H, CH-14a), 1.94-1.84 (m, 1H, CH-4a), 1.88-1.79 (m, 1H, CH-7a), 1.77-1.66 (m, 1H, CH-2a), 1.73-1.63 (m, 1H, CH-6b), 1.64-1.51 (m, 1H, CH-14b), 1.57-1.47 (m, 1H, CH-5), 1.51-1.43 (m, 1H, CH-2b), 1.49-1.39 (m, 1H, CH-4b), 1.20 (s, 3H, CH_3-19), 1.16 (qd, *J* = 12.9, 5.1 Hz, 1H, CH-7b), 1.00-0.90 (m, 1H, CH-1b), 0.90 (s, 9H, *t*Bu), –0.04 (s, 3H, $SiCH_3$), –0.05 (s, 3H, $SiCH_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (C, C-12), 175.3 (C, C-9), 123.3 (CH, C-11), 67.2 (CH, C-3), 40.3 (C, C-10), 40.0 (CH, C-5), 37.2 (CH_2, C-4), 36.8 (CH_2, C-13), 35.3 (CH, C-8), 32.2 (CH_2, C-7), 30.9 (CH_2, C-1), 30.4 (CH_2, C-2), 30.3 (CH_2, C-14), 28.7 (CH_2, C-6), 25.9 (CH_3, *t*Bu), 24.6 (CH_3, C-19), 18.1 (C, *t*Bu), −4.86 (CH_3, $SiCH_3$), –4.89 (CH_3, $SiCH_3$).

MS (ESI+) *m/z*, (%): 349 (16, $[M+H]^+$), 371 (100, $[M+Na]^+$), 697 (4, $[2M+H]^+$), 719 (26, $[2M+Na]^+$);

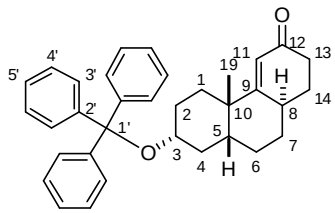
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{36}NaO_2Si$ 371.2377; Found 371.2377;

Anal. Calcd for $C_{21}H_{36}O_2Si$: C, 72.35; H, 10.41; Found: C, 72.04; H, 10.71;

***rac*-3α-(Trityloxy)-des-*D*-18-nor-5β,8α-androst-9(11)-en-12-one (150c)**

Prepared according to General procedure C. The crude mixture was purified by column chromatography on silica gel (30 g) in 5% EtOAc/hexanes to afford 306 mg (32%) of pure conjugated enone **150c** as a colorless oil.

IR ($CHCl_3$); ν[cm^{-1}]: 631, 707, 1029 (Ph), 1053 (C-O), 1151 (Ph), 1372 (CH_3), 1449, 1490 (Ph), 1597 (C=C), 1661 (C=O), 2870 (CH_3), 2939 (CH_2);



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.45 (m, 3H, CH-5'), 7.32-7.18 (m, 12H, CH-3', CH-4'), 6.01 (d, *J* = 2.1 Hz, 1H, CH-11), 3.71 (quint, *J* = 4.8 Hz, 1H, CH-3), 2.62 (ddtd, *J* = 12.3, 9.9, 4.8, 2.2 Hz, 1H, CH-8), 2.43 (dt, *J* = 16.5, 4.0 Hz, 1H, CH-13a), 2.33 (ddd, *J* = 16.5, 14.0, 4.9 Hz, 1H, CH-13b), 2.22-2.09 (m, 1H, CH-6a), 2.19-2.09 (m, 1H, CH-1a), 2.12-2.03 (m, 1H, CH-14a), 1.87-1.81 (m, 1H, CH-7a), 1.70-1.60 (m, 1H, CH-6b), 1.65-1.51 (m, 1H, CH-14b), 1.43 (dt, *J* = 14.1, 4.2 Hz, 1H, CH-4a), 1.38-1.32 (m, 1H, CH-5), 1.28-1.20 (m, 1H, CH-2a), 1.23-1.07 (m, 1H, CH-7b), 1.15-1.07 (m, 1H, CH-4b), 1.10-1.00 (m, 1H, CH-2b), 1.08 (s, 1H, CH_3-19), 0.90-0.80 (m, 1H, CH-1b);

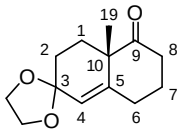
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (C, C-12), 175.1 (C, C-9), 145.3 (C, C-2'), 129.0 (CH, C-3'), 127.7 (CH, C-4'), 126.9 (CH, C-5'), 123.6 (CH, C-11), 87.5 (C, C-1'), 69.2 (CH, C-3), 39.94 (C, C-10), 39.86 (CH, C-5), 36.9 (CH_2, C-13), 35.6 (CH_2, C-4), 35.3 (CH, C-8), 32.3 (CH_2, C-1), 31.4 (CH_2, C-7), 30.5 (CH_2, C-14), 28.4 (CH_2, C-2), 28.1 (CH_2, C-6), 25.2 (CH_3, C-19).

MS (ESI+) *m/z*, (%): 499 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{36}NaO_2$ 499.2608; Found 499.2608;

Anal. Calcd for $C_{34}H_{36}O_2$: C, 85.67; H, 7.61; Found: C, 85.37; H, 7.65;

(*S*)-6-(Ethylenedioxy)-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalen-1(2*H*)-one (*nat*-152) and (*R*)-6-(ethylenedioxy)-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalen-1(2*H*)-one (*ent*-152)



Diketone **21** (7.36 g, 41.3 mmol), triethyl orthoformate (7.58 mL, 45.6 mmol) and ethylene glycol (12.7 mL, 228 mmol) were dissolved in CH_2Cl_2 (50 mL) and the reaction flask was immersed in salt-ice bath kept at −10 °C. TMSOTf (150 µL, 830 µmol) was added with stirring and the temperature was kept at −10 °C for 1 h. Et_3N (200 µL, 1.43 mmol) was added to the reaction mixture, which was subsequently poured into saturated aq. $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (150 g) in 20% EtOAc/hexanes + 0.5% Et_3N to afford 7.88 g (86%) of pure monoketal **152** as an off-white solid, followed by 1.04 g of mixture consisting of ketal **136a** and starting material **21**. This mixture was dissolved in a solution of acetone (5 mL), water (0.7 mL) and conc. HCl (0.4 mL) and stirred overnight at rt. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Distillation of the residue in Kugelrohr at 150 °C and 0.1 mbar afforded 0.88 g (12%) of **21**, showing identical properties with the starting material, including enantiomeric excess.

152:Mp 48-51 °C;

$[\alpha]_D^{20}$ +97.7 (*c* 0.267, $CHCl_3$) for *nat*-**152**;

$[\alpha]_D^{20}$ −82.7 (*c* 0.202, $CHCl_3$) for *ent*-**152**;

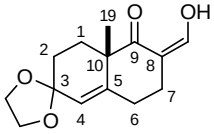
IR ($CHCl_3$); ν[cm^{-1}]: 946, 959, 1003, 1072, 1096 (ring), 1148, 1161, 1234 (COCOC), 1340, 1361, 1378 (CH_3) 1442, 1447, 1461 (CH_2), 1661 (C=C), 1711 (C=O), 2885 (CH_3), 2953 (CH_2), 2975 (CH_3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (dd, *J* = 1.8, 0.9 Hz, 1H, CH-4), 4.02-3.87 (m, 4H, OCH_2CH_2O), 2.64 (ddd, *J* = 15.2, 13.4, 6.3 Hz, 1H, CH-8a), 2.56 (dddd, *J* = 14.0, 13.5, 5.0, 1.9 Hz, 1H, CH-6a), 2.37 (dddd, *J* = 15.2, 4.7, 2.9, 1.8 Hz, 1H, CH-8b), 2.27 (dddd, *J* = 14.1, 4.5, 2.7, 2.1 Hz, 1H, CH-6b),

2.16-2.08 (m, 1H, CH-1a), 2.07-1.99 (m, 1H, CH-7a), 1.86-1.77 (m, 2H, CH_2-2), 1.77-1.69 (m, 1H, CH-1b), 1.65 (qt, *J* = 13.3, 4.6 Hz, 1H, CH-7b), 1.32 (s, 3H, CH_3-19).
^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5 (C, C-9), 146.6 (C, C-5), 123.4 (CH, C-4), 105.4 (C, C-3), 64.6 (CH_2, O*C*$H_2$$CH_2$O), 64.3 ($CH_2$, O$CH_2$*C*$H_2$O), 50.2 (C, C-10), 37.8 (CH_2, C-8), 30.8 (CH_2, C-6), 29.8 (CH_2, C-2), 28.6 (CH_2, C-1), 24.3 (CH_2, C-7), 23.8 (CH_3, C-19).
MS (ESI+) *m/z*, (%): 223 (40, $[M+H]^+$), 245 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{18}NaO_3$ 245.1148; Found 245.1148;
Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; Found: C, 69.86; H, 8.19. for *nat*-**152**;
Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; Found: C, 70.25; H, 8.14. for *ent*-**152**;

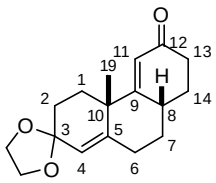
3-(Ethylenedioxy)-des-*D*-18-norandrosta-4,9(11)-dien-12-one (*nat*-155), 3-(ethylenedioxy)-des-*D*-18-norandrosta-4,8-dien-12-one (*nat*-156) and *ent*-3-(ethylenedioxy)-des-*D*-18-norandrosta-4,9(11)-dien-12-one (*ent*-155), *ent*-3-(ethylenedioxy)-des-*D*-18-norandrosta-4,8-dien-12-one (*ent*-156)

Ketone **152** (20.87 g, 93.89 mmol) was dissolved in dry ethyl formate (250 mL) at 0 °C and sodium hydride (9.39 g, 235 mmol, 60% suspension in oil, washed with THF - 3 × 25 mL) suspended in THF (10 mL) was added portionwise. MeOH (3.80 mL, 93.9 mmol) was added dropwise at 0 °C over 15 min. The reaction mixture turned into a thick slurry after a few minutes. After 30 min, the reaction mixture was warmed to rt and after another 30 min quenched with saturated aq. NH_4Cl (400 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crystalline formyl derivative **153** in essentially quantitative yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 14.67 (br s, 1H, OH), 8.54 (s, 1H, C*H*OH), 5.39 (t, *J* = 1.1 Hz, 1H, CH-4), 4.05-3.84 (m, 4H, OCH_2CH_2O), 2.57-2.30 (m, 2H, CH_2-7), 2.43-2.22 (m, 2H, CH_2-6), 2.13-1.82 (m, 4H, CH_2-1, CH_2-2), 1.37 (s, 3H, CH_3-19).



^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2 (C, C-9), 185.8 (CH, CHOH), 145.0 (C, C-5), 122.5 (CH, C-4), 106.8 (C, C-8), 105.3 (C, C-3), 64.7 (CH_2, O*C*$H_2$$CH_2$O), 64.3 ($CH_2$, O$CH_2$*C*$H_2$O), 42.0 (C, C-10), 30.3 (CH_2, C-1), 29.9 (CH_2, C-2), 29.1 (CH_2, C-6), 24.3 (CH_2, C-7), 23.8 (CH_3, C-19).
To the neat compound, methyl vinyl ketone (8.77 mL, 105 mmol) was added, followed by triethylamine (245 µL, 1.75 mmol) and the mixture was stirred overnight. The excess of methyl vinyl ketone was evaporated *in vacuo*, the crude mixture was dissolved in MeOH (320 mL) and degassed by sonication under vacuum, followed by flushing with argon (3 cycles). KOH (15.26 g, 272 mmol) was dissolved in degassed H_2O, the methanolic solution was added via cannula and the mixture was refluxed under N_2 for 30 min. The solution was cooled to rt, quenched with saturated aq. NH_4Cl (400 mL) and extracted with EtOAc (3 × 330 mL). The organic extracts were washed with brine (400 mL), dried over Na_2SO_4 and evaporated *in vacuo.* The residue was purified by chromatography on silica gel (350 g) in 20% EtOAc/hexanes + 0.5% Et_3N to 50% EtOAc/hexanes + 0.5% Et_3N to yield 5.49 g (23%) of **156** and 14.53 g (60%) of **155**.

155: Colorless solid,
$[\alpha]_D^{20}$ +149.8 (*c* 0.259, $CHCl_3$) for *nat*-**155**; Mp 105-108 °C;
$[\alpha]_D^{20}$ −152.1 (*c* 0.353, $CHCl_3$) for *ent*-**155**; Mp 112-113 °C



IR ($CHCl_3$); ν[cm^{-1}]: 883, 946, 1078, 1091 (ring), 1132, 1168, 1361 (CH_2), 1379 (CH_3) 1451, 1454 (CH_2), 1604 (C=C), 1664 (C=O), 2865 (CH_2), 2887 (CH_3), 2941 (CH_2), 2978 (CH_3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J* = 2.1 Hz, 1H, CH-11), 5.36 (d, *J* = 1.3 Hz, 1H, CH-4), 4.06-3.86 (m, 4H, OCH_2CH_2O), 2.68 (ddtd, *J* = 12.3, 10.1, 5.0, 2.2 Hz, 1H, CH-8), 2.47 (tdd, *J* = 14.0, 4.4, 1.9 Hz, 1H, CH-6a), 2.45-2.39 (m, 1H, CH-13a), 2.30 (ddd, *J* = 16.5, 14.1, 5.0 Hz, 1H, CH-13b), 2.21 (ddd, *J* = 14.0, 3.9, 2.8 Hz, 1H, CH-6b), 2.14-2.05 (m, 1H, CH-14a), 2.10-2.00 (m, 1H, CH-1a), 2.00-1.93 (m, 1H, CH-7a), 1.94-1.85 (m, 2H, CH_2-2), 1.91-1.82 (m, 1H, CH-1b), 1.61 (tdd, *J* = 13.8, 10.2, 4.6 Hz, 1H, CH-14b), 1.32 (dtd, *J* = 14.1, 12.8, 4.1 Hz, 1H, CH-7b), 1.31 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3 (C, C-12), 172.4 (C, C-9), 147.2 (C, C-5), 122.7 (CH, C-11), 122.3 (CH, C-4), 105.4 (C, C-3), 64.7 (CH_2, OCH_2CH_2O), 64.3 (CH_2, OCH_2CH_2O), 41.4 (C, C-10), 36.4 (CH_2, C-13), 35.2 (CH, C-8), 34.1 (CH_2, C-7), 32.1 (CH_2, C-1), 31.4 (CH_2, C-6), 30.0 (CH_2, C-2), 29.5 (CH_2, C-14), 27.2 (CH_3, C-19).

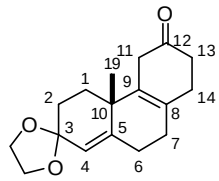
MS (ESI+) *m/z*, (%): 275 (57, $[M+H]^+$), 297 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{23}O_3$ 275.1642; Found 275.1644;

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 74.29; H, 7.98. for *nat*-**155**

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 74.56; H, 7.86. for *ent*-**155.**

156: Oily liquid,



$[\alpha]_D^{20}$ +217.7 (*c* 0.215, $CHCl_3$) for *nat*-**156**;

$[\alpha]_D^{20}$ –245.5 (*c* 0.283, $CHCl_3$) for *ent*-**156**;

IR ($CHCl_3$); ν[cm^{-1}]: 946, 961, 1086 (ring), 1137, 1363 (CH_2), 1380 (CH_3), 1443, 1450 (CH_2), 1674 (C=C), 1713 (C=O), 2855 (CH_2), 2927, 2954 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 1.6 Hz, 1H, CH-4), 4.08-3.81 (m, 4H, OCH_2CH_2O), 2.89 (br d, *J* = 20.1 Hz, 1H, CH-11a), 2.76 (br d, *J* = 20.1 Hz, 1H, CH-11b), 2.46-2.33 (m, 2H, CH_2-13), 2.44-2.34 (m, 1H, CH-2a), 2.36-2.29 (m, 2H, CH_2-14), 2.30-2.19 (m, 1H, CH-1a), 2.23-2.12 (m, 1H, CH-2b), 2.17-2.05 (m, 1H, CH-1b), 1.98-1.74 (m, 2H, CH_2-6), 1.78-1.60 (m, 2H, CH_2-7), 1.18 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2 (C, C-12), 148.4 (C, C-5), 132.4 (C, C-9), 128.6 (C, C-8), 120.2 (CH, C-4), 105.6 (C, C-3), 64.7 (CH, OCH_2CH_2O), 64.2 (CH, OCH_2CH_2O), 38.5 (CH_2, C-11), 38.0 (CH_2, C-13), 37.6 (C, C-10), 32.4 (CH_2, C-7), 32.3 (CH_2, C-1), 30.2 (CH_2, C-6/C-14), 30.1 (CH_2, C-6/C-14), 29.1 (CH_2, C-2), 23.0 (CH_3, C-19).

MS (ESI+) *m/z*, (%): 275 (100, $[M+H]^+$), 297 (42, $[M+Na]^+$);

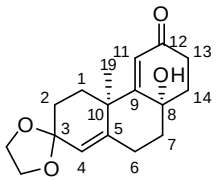
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{23}O_3$ 275.1642; Found 275.1643;

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 74.80; H, 8.82. for *nat*-**156;**

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 73.36; H, 8.05. for *ent*-**156;**

***ent*-3-(Ethylenedioxy)-8β-hydroxy-des-*D*-18-norandrosta-4,9(11)-dien-12-one (*ent*-157)**

The crude triketone *ent*-**154** (105 mg, 383 µmol) was dissolved in nondegassed methanol (4 mL). An aq. KOH solution (2 M, 610 µL, 1.22 mmol) was added to the methanolic solution and the mixture was refluxed for 4 h under air. The solution was cooled to rt, quenched with saturated aq. NH_4Cl (25 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (15 mL) and dried over $MgSO_4$. The solvents were evaporated *in vacuo* and the residue was



purified by chromatography on silica gel (3 g) in 30% EtOAc/hexanes + 1.0% Et_3N to 50% EtOAc/hexanes + 1.0% Et_3N to yield 33 mg (30%) of *ent*-**157**.

IR (ATR); ν[cm^{-1}]: 513, 907, 935, 973, 1017, 1081, 1089 (ring), 1110, 1120, 1198, 1218, 1280, 1328, 1361, 1364 (CH_2), 1382 (CH_3), 1441 (CH_2), 1610 (C=C), 1653 (C=O), 2877 (CH_2), 2947 (CH_2), 2965 (CH_3), 3405 (OH);

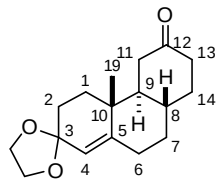
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H, CH-11), 5.37 (br s, 1H, CH-4), 4.06-3.84 (m, 4H, OCH_2CH_2O), 2.84 (dddd, *J* = 14.0, 13.7, 4.1, 1.8 Hz, 1H, CH-6a), 2.81-2.72 (m, 1H, CH-13a), 2.38 (br dt, *J* = 17.4, 3.0 Hz, 1H, CH-13b), 2.20 (br s, 1H, OH), 2.08 (ddd, *J* = 13.7, 3.7, 3.0 Hz, 1H, CH-6b), 2.02-1.95 (m, 3H, CH-7a, CH_2-14), 1.95-1.87 (m, 4H, CH_2-1, CH_2-2), 1.67 (td, *J* = 14.2, 4.0 Hz, 1H, 7b), 1.47 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C, C-12), 168.9 (C, C-9), 147.2 (C, C-5), 124.9 (CH, C-11), 121.9 (CH, C-4), 105.2 (C, C-3), 68.7 (C, C-8), 64.6 (CH_2, OCH_2CH_2O), 64.2 (CH_2, OCH_2CH_2O), 40.6 (C, C-10), 40.2 (CH_2, C-7), 37.9 (CH_2, C-14), 33.0 (CH_2, C-1), 32.4 (CH_2, C-13), 29.8 (CH_2, C-2), 28.0 (CH_3, C-19), 27.4 (CH_2, C-6).

MS (ESI+) *m/z*, (%): 291 (69, $[M_1+H]^+$), 307 (7, $[M_2+H]^+$), 313 (100, $[M_1+Na]^+$), 329 (13, $[M_2+Na]^+$), 603 (48, $[2M_1+Na]^+$), 619 (16, $[M_1+M_2+Na]^+$); Where M_1 is the title compound, M_2 is the analogous hydroperoxide.

HRMS (ESI+) *m/z*: $[M_1+H]^+$ Calcd for $C_{17}H_{23}O_4$ 291.1591; Found 291.1593; $[M_1+Na]^+$ Calcd for $C_{17}H_{22}NaO_4$ 314.1410; Found 314.1410;

3-(Ethylenedioxy)-des-*D*-18-norandrost-4-en-12-one (*nat*-158) and *ent*-3-(ethylenedioxy)-des-*D*-18-norandrost-4-en-12-one (*ent*-158)



Liquid ammonia (ca. 200 mL) was dried with lithium pellets (ca. 0.5 g) and a catalytic amount of $FeCl_3$ (20 mg) at reflux temperature. After the deep blue solution turned colorless, the ammonia was distilled to a three-necked round bottom flask (500 mL) with a stirring bar, nitrogen inlet and a dry-ice cooled condenser. The flask was cooled to −78 °C and a solution of enone **155** (9.074 g, 33.07 mmol) in THF (90 mL) was added, followed by abs. EtOH (4.96 mL, 84.9 mmol). Crushed lithium pellets (2.66 g, 383 mmol) were added portionwise with vigorous stirring at −78 °C. A persistent blue coloration was indicative of a complete reduction. The reaction was quenched with solid NH_4Cl and the excess of ammonia was carefully evaporated. The residue was poured into saturated aq. $NaHCO_3$ (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (150 g) in 30% EtOAc/hexanes + 0.5% Et_3N to give 7.625 g (83%) of **158** as a colorless oil, containing ca 5% of inseparable enone **156**.

$[\alpha]_D^{20}$ +144.7 (*c* 0.409, $CHCl_3$) for *nat*-**158**;

$[\alpha]_D^{20}$ −138.3 (*c* 0.248, $CHCl_3$) for *ent*-**158**;

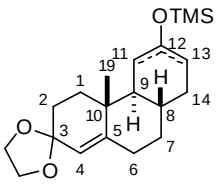
IR ($CHCl_3$); ν[cm^{-1}]: 947, 964, 1009 (ring), 1089, 1113, 1169, 1182, 1233 (COCOC), 1366, 1381 (CH_3), 1440 (CH_2), 1664 (C=C), 1711 (C=O), 2864, 2888 (CH_3), 2938 (CH_2), 2969 (CH_3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (t, *J* = 1.2 Hz, 1H, CH-4), 4.07-3.82 (m, 4H, OCH_2CH_2O), 2.44-2.33 (m, 1H, CH-11a), 2.38-2.28 (m, 2H, CH_2-13), 2.32-2.24 (m, 1H, CH-6a), 2.17-2.09 (m, 1H, CH-11b), 2.14-2.07 (m, 1H, CH-6b), 2.04-1.97 (m, 1H, CH-14a), 1.89-1.81 (m, 1H, CH-7a), 1.85-1.75 (m, 1H, CH-8), 1.82-1.72 (m, 2H, CH_2-2), 1.69-1.64 (m, 1H, CH-1a), 1.61-1.51 (m, 1H, CH-1b), 1.47-1.30 (m, 1H, CH-9), 1.34-1.25 (m, 1H, CH-14b), 1.17-1.10 (m, 1H, CH-7b), 1.07 (s, 3H, CH_3-19).

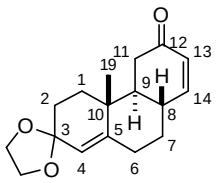
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8 (C, C-12), 149.2 (C, C-5), 121.1 (CH, C-4), 105.8 (C, C-3), 64.6 (CH_2, O*C*H_2CH$_2$O), 64.3 (CH_2, OCH$_2$*C*H$_2$O), 53.0 (CH, C-9), 41.1 (CH_2, C-11), 40.9 (CH_2, C-13), 37.7 (C, C-10), 35.9 (CH, C-8), 34.1 (CH_2, C-1), 33.6 (CH_2, C-7), 33.3 (CH_2, C-14), 31.6 (CH_2, C-6), 29.7 (CH_2, C-2), 17.6 (CH_3, C-19).
MS (ESI+) *m/z*, (%): 277 (23, $[M+H]^+$), 299 (100, $[M+Na]^+$), 575 (21, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{25}O_3$ 277.1798; Found 277.1799; $[M+Na]^+$ Calcd for $C_{17}H_{24}NaO_3$ 299.16177; Found 299.16181;
Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; Found: C, 74.01; H, 8.69. for *nat*-**158.**
Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; Found: C, 73.80; H, 8.82. for *ent*-**158.**

3-(Ethylenedioxy)-des-*D*-18-norandrosta-4,13-dien-12-one (*nat*-161)

2,2,6,6-Tetramethylpiperidine (4.03 mL, 23.88 mmol) was dissolved in THF (30 mL) and the solution was cooled in an ice bath. *n*BuLi (2.25 M in hexane, 10.6 mL, 23.88 mmol) was added dropwise at 0 °C, the homogeneous solution was stirred for 30 min and cooled to −78 °C. A solution of ketone **158** (4.405 g, 15.93 mmol) in THF (50 mL) was added dropwise with stirring and the reaction mixture was kept at −78 °C for 1 h. TMSCl (2.83 mL, 22.3 mmol) diluted with THF (2 mL) was added dropwise and after 30 min of stirring at −78 °C, the reaction mixture was warmed to 0 °C. The content of the reaction flask was poured onto a 1:1 mixture of ice and saturated aq. $NaHCO_3$ (400 mL in total) and extracted with hexane (3 × 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford 6.02 g of crude silyl enol ether **159/160**.

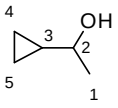


^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H, CH-4), 4.81 (t, *J* = 1.9 Hz, 1H, CH-11)*, 4.78 (br d, *J* = 5.6 Hz, 1H, CH-13), 4.05-3.83 (m, 4H, OCH$_2$CH$_2$O), 2.24 (tdd, *J* = 13.9, 4.8, 1.7 Hz, 1H, CH-6a), 2.13-2.02 (m, 1H, CH-14a), 2.09-2.00 (m, 1H, CH-6b), 1.97-1.91 (m, 2H, CH_2-11), 1.90-1.80 (m, 1H, CH-7a), 1.82-1.73 (m, 2H, CH_2-2), 1.77-1.59 (m, 2H, CH_2-1), 1.70-1.59 (m, 1H, CH-14b), 1.64-1.49 (m, 1H, CH-8), 1.40-1.30 (m, 1H, CH-9), 1.18-1.04 (m, 1H, CH-7b), 1.03 (s, 3H, CH_3-19), 0.95 (s, 3H, CH_3-19)*, 0.19 (s, 9H, TMS)*, 0.18 (s, 9H, TMS). * Denotes the minor Δ^{11} silyl enol ether **159** signals where possible. The ratio of Δ^{11} :Δ^{12} **159**:**160** was found to be 1:10.
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2 (C, C-5), 149.5 (C, C-12), 119.7 (CH, C-4), 106.1 (C, C-3), 102.3 (CH, C-13), 64.5 (CH_2, O*C*H_2CH$_2$O), 64.2 (CH_2, OCH$_2$*C*H$_2$O), 48.5 (CH, C-9), 37.2 (C, C-10), 34.45 (CH_2, C-1/C-7), 34.42 (CH_2, C-1/C-7), 32.2 (CH, C-8), 32.0 (CH_2, C-14), 31.6 (CH_2, C-6), 29.8 (CH_2, C-2), 29.5 (CH_2, C-11), 18.2 (CH_3, C-19), 0.3 (CH_3, SiCH_3).
The crude silyl enol ether **159/160** was dissolved in DMSO (130 mL, fractionally distilled under vacuum) and transferred to a gas washing bottle equipped with a frit and a stirring bar. A gentle flow of air, predried by passing through a plug of KOH pellets, was passed through the solution with stirring. Palladium(II) acetate (360 mg, 1.60 mmol) was added to the solution, resulting in an orange-brown solution. Bubbling and stirring was maintained for 48 h, during which the color remained unchanged. The reaction mixture was poured onto a 1:1 mixture of ice and saturated aq. $NaHCO_3$ (400 mL in total) and extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with brine (400 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford solid crude enone **161**. Crystallization from hexane:Et_2O afforded 2.436 g (56%) of pure **161** as off-white crystals. The mother liquors were evaporated *in vacuo* and the residue was purified by chromatography on silica gel (70 g) in 30% EtOAc/hexanes + 0.5% Et_3N to afford another 1.05 g (24%) of enone **161** as off-white crystals.



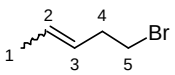
Mp 114-117 °C;
$[\alpha]_D^{20}$ +204.5 (*c* 0.243, $CHCl_3$) for *nat*-**161**;
$[\alpha]_D^{20}$ −243.8 (*c* 0.244, $CHCl_3$) for *ent*-**161**;
IR ($CHCl_3$); ν[cm^{-1}]: 946, 961, 1002 (ring), 1091, 1157, 1233 (COCOC), 1368, 1383, 1389 (CH_3), 1440, 1449 (CH_2), 1618 (C=C), 1676 (C=O), 2863, 2887 (CH_3), 2941 (CH_2), 2972 (CH_3);
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 10.0, 1.8 Hz, 1H, CH-14), 5.96 (ddd, *J* = 10.0, 2.8, 1.0 Hz, 1H, CH-13), 5.33 (s, 1H, CH-4), 4.06-3.83 (m, 4H, OCH_2CH_2O), 2.55-2.47 (m, 1H, CH-8), 2.48 (dd, *J* = 16.0, 3.4 Hz, 1H, CH-11a), 2.39 (tdd, *J* = 13.9, 5.0, 1.9 Hz, 1H, CH-6a), 2.20 (ddd, *J* = 14.0, 4.3, 2.4 Hz, 1H, CH-6b), 2.19 (dd, *J* = 16.1, 14.3 Hz, 1H, CH-11b), 2.01 (dddd, *J* = 12.5, 5.0, 3.9, 2.4 Hz, 1H, CH-7a), 1.82-1.78 (m, 2H, CH_2-2), 1.78-1.67 (m, 1H, CH-1a), 1.74-1.60 (m, 1H, CH-9), 1.61-1.53 (m, 1H, CH-1b), 1.31 (qd, *J* = 13.1, 4.4 Hz, 1H, CH-7b), 1.08 (s, 3H, CH_3-19);
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C, C-12), 154.8 (CH, C-14), 148.2 (C, C-5), 128.6 (CH, C-13), 121.9 (CH, C-4), 105.7 (C, C-3), 64.7 (CH_2, OCH_2CH_2O), 64.3 (CH_2, OCH_2CH_2O), 51.1 (CH, C-9), 38.0 (CH_2, C-11), 37.2 (C, C-10), 36.9 (CH, C-8), 33.8 (CH_2, C-1), 32.4 (CH_2, C-7), 31.9 (CH_2, C-6), 29.6 (CH_2, C-2), 17.6 (CH_3, C-19);
MS (ESI+) *m/z*, (%): 275 (23, $[M+H]^+$), 297 (100, $[M+Na]^+$), 572 (7, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{22}NaO_3$ 297.1461; Found 297.1457;
Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 73.74; H, 8.12. for *nat*-**161**.
Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 74.35; H, 8.27. for *ent*-**161**.
X-ray data are available in Appendix C.

(±)-1-Cyclopropylethanol (163)



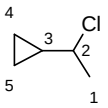
Prepared according to literature.[271]
Bp 121-122 °C (Lit.[272] bp 121-122 °C);
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (dq, *J* = 8.0, 6.2 Hz, 1H, CH-2), 1.96 (s, 1H, OH), 1.28 (d, *J* = 6.2 Hz, 3H, CH_3-1), 0.91 (qt, *J* = 8.1, 5.0 Hz, 1H, CH-3), 0.54-0.45 (m, 2H, CH-4*cis*, CH-5*cis*), 0.33-0.23 (m, 1H, CH-4*trans*), 0.23-0.13 (m, 1H, CH-5*trans*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 72.8 (CH, C-2), 22.4 (CH_3, C-1), 19.1 (CH, C-3), 2.9 (CH_2, C-4), 2.1 (CH_2, C-5).

5-Bromopent-2-ene (164)



Prepared according to the literature as a 9:1 mixture of *E*:*Z* isomers.[271]
Bp 127-128 °C (Lit.[271] bp 125-126 °C)
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66-5.56 (m, 1H, CH-2)*, 5.56 (dqt, *J* = 15.2, 6.3, 1.2 Hz, 1H, CH-2), 5.44-5.35 (m, 1H, CH-3)*, 5.41 (dtq, *J* = 15.2, 6.6, 1.6 Hz, 1H, CH-3), 3.38 (t, *J* = 7.2 Hz, 2H, CH_2-5)*, 3.36 (t, *J* = 7.1 Hz, 2H, CH_2-5), 2.63 (qqd, *J* = 7.2, 1.6, 0.8 Hz, 2H, CH_2-4)*, 2.54 (qquint, *J* = 7.0, 1.2 Hz, 2H, CH_2-4), 1.68 (dq, *J* = 6.3, 1.2 Hz, 3H, CH_3-1), 1.64 (ddt, *J* = 6.8, 1.8, 0.9 Hz, 3H, CH_3-1)*.
^{13}C NMR (101 MHz, $CDCl_3$) δ 128.3 (CH, C-2/C-3), 127.7 (CH, C-2/C-3), 127.0 (CH, C-2/C-3)*, 126.8 (CH, C-2/C-3)*, 36.0 (CH_2, C-4), 32.8 (CH_2, C-5), 32.4 (CH_2, C-5)*, 30.5 (CH_2, C-4)*, 17.9 (CH_3, C-1), 12.9 (CH_3, C-1)*.
Signals of the minor *Z*-isomer are denoted by *.

(±)-(1-Chloroethyl)cyclopropane (166)



Prepared according to literature.[272] The product contained ca. 5% of 5-chloropent-2-ene (**167**).

Bp 99-104 °C (Lit.[272] bp 100-102 °C);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (dq, *J* = 9.1, 6.6 Hz, 1H, CH-2), 1.60 (d, *J* = 6.6 Hz, 3H, CH_3-1), 1.17 (dtt, *J* = 9.1, 8.1, 4.8 Hz, 1H, CH-3), 0.70-0.62 (m, 2H, CH-4*cis*, CH-5*cis*), 0.46-0.37 (m, 1H, CH-4*trans*), 0.37-0.28 (m, 1H, CH-5*trans*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 64.2 (CH, C-2), 25.1 (CH_3, C-1), 20.6 (CH, C-3), 5.9 (CH_2, C-4/C-5), 5.4 (CH_2, C-4/C-5).

General procedure D: Grignard reagent preparation and titration

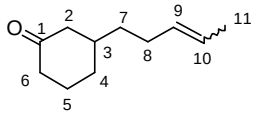
Magnesium powder (2.40 g, 98.9 mmol) was flame-dried in Schlenk flask under vacuum. The flask was refilled with argon and cooled to rt. The powder was stirred dry under argon for 1 h and suspended in THF (22 mL). Neat **164** or **166**/**167** (7.50 mmol) was added dropwise and the mixture was stirred until the exothermic reaction started. In the case of bromide **164**, a drop of dibromoethane was used to start the reaction if necessary. When the mixture ceased to reflux, the rest of **164** or **166**/**167** (22.5 mmol) was added dropwise and the mixture was refluxed for 1 hr. The solution was cooled to rt and diluted with THF (13 mL). The reagent was stored in the reaction flask under argon at rt without the loss of titre for several weeks. Yields varied between 80% and 95%.

Titration was performed with salicylaldehyde phenylhydrazone according to the known protocol.[269]

(±)-3-(Pent-3-en-1-yl)cyclohexanone (170) and (±)-3-(pent-3-en-1-yl)cyclohex-2-en-1-ol (171)

Cyclohexenone (387 µL, 4 mmol) and CuBr·Me_2S (40 mg, 0.20 mmol) were dissolved in THF and the mixture was cooled to −78 °C. A freshly prepared solution of Grignard reagent **165** (0.70 M in THF, 6.25 mL, 4.4 mmol) was added dropwise over 10 min and the mixture was stirred at −78 °C for 30 min. The reaction was quenched with a few drops of saturated aq. NH_4Cl and filtered through a short pad of silica gel. The solvent was evaporated *in vacuo* to ca. 600 mg of liquid, which was purified by flash column chromatography on silica gel (30 g) in 5% EtOAc/hexanes to furnish 78 mg (12%) of ketone **170**, followed by 212 mg (32%) of alcohol **171**.

170: IR ($CHCl_3$); ν[cm^{-1}]: 968 (CH=), 1057, 1314, 1348, 1379 (CH_3), 1426, 1439, 1452 (CH_2), 1650 (C=C), 1707 (C=O), 2853 (CH_2), 2885 (CH_3), 2934 (CH_2);



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.41 (m, 1H, CH-10)*, 5.43-5.36 (m, 2H, CH-9, CH-10), 5.40-5.32 (m, 1H, CH-9)*, 2.45-2.40 (m, 1H, CH-2a), 2.39-2.32 (m, 1H, CH-6a), 2.25 (dddd, *J* = 14.1, 12.3, 6.1, 1.2 Hz, 1H, CH-6b), 2.09-1.97 (m, 1H, CH-5a), 2.05-1.95 (m, 3H, CH_2-8, CH-2b), 1.94-1.86 (m, 1H, CH-4a), 1.84-1.73 (m, 1H, CH-3), 1.70-1.59 (m, 1H, CH-5b), 1.64 (br d, *J* = 5.9 Hz, 3H, CH_3-11), 1.46-1.29 (m, 2H, CH_2-7), 1.38-1.26 (m, 1H, CH-4b).

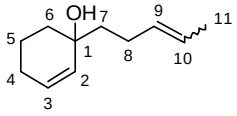
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9 (C, C-1), 130.7 (CH, C-9), 129.9 (CH, C-9)*, 125.2 (CH, C-10), 124.2 (CH, C-10)*, 48.08 (CH_2, C-2)*, 48.03 (CH_2, C-2), 41.47 (CH_2, C-6), 41.46 (CH_2, C-6)*, 38.6 (CH, C-3)*, 38.4 (CH, C-3), 36.4 (CH_2, C-7), 36.3 (CH_2, C-7)*, 31.22 (CH_2, C-4)*, 31.19 (CH_2, C-4), 29.6 (CH_2, C-8), 25.22 (CH_2, C-5), 25.21 (CH_2, C-5)*, 24.0 (CH_2, C-8)*, 17.9 (CH_3, C-11), 12.7 (CH_3, C-11)*. Detectable signals of the minor *Z*-isomer are denoted by an *.

MS (ESI+) *m/z*, (%): 167 (1, $[M+H]^+$), 189 (53, $[M+Na]^+$), 355 (100, $[2M+Na]^+$);

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91; Found: C, 79.17; H, 10.96;

GC (Temperature program: 60 °C for 2 min, followed by linear gradient 10 °C·min^{-1} for 14 min) showed 2 peaks in 89:11 ratio (t_E = 12.94 min, t_Z = 13.01 min). Under identical conditions, cyclohexenone elutes at t = 4.96 min.

171 : IR ($CHCl_3$); ν[cm^{-1}]: 967 (CH=), 1059, 1076 (C-O), 1163, 1231, 1314, 1348, 1379 (CH_3), 1439 (CH_2), 1452 (CH_2), 1646 (C=C), 2856 (CH_2), 2885 (CH_3), 2938 (CH_2), 3467, 3603 (OH);



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddd, J = 10.0, 4.5, 3.1 Hz, 1H, CH-3), 5.62 (br d, J = 10.0 Hz, 1H, CH-2), 5.47-5.33 (m, 2H, CH-9, CH-10), 2.12-2.04 (m, 2H, CH_2-8), 2.09-1.98 (m, 1H, CH-4a), 1.98-1.88 (m, 1H, CH-4b), 1.80-1.65 (m, 7H, CH_2-5, CH_2-6, CH_3-11), 1.65-1.55 (m, 2H, CH_2-7).

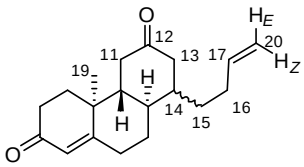
^{13}C NMR (101 MHz, $CDCl_3$) δ 132.58 (CH, C-2), 132.57 (CH, C-2)*, 131.4 (CH, C-9), 130.6 (CH, C-9)*, 129.80 (CH, C-3)*, 129.78 (CH, C-3), 124.8 (CH, C-10), 123.9 (CH, C-10)*, 69.7 (C, C-1), 42.0 (CH_2, C-7), 41.9 (CH_2, C-7)*, 35.49 (CH_2, C-6), 35.45 (CH_2, C-6)*, 26.7 (CH_2, C-8), 25.22 (2 × CH_2, C-4, C-4*), 21.17 (CH_2, C-8)*, 19.0 (2 × CH_2, C-5, C-5*), 17.9 (CH_3, C-11), 14.2 (CH_3, C-11)*. Detectable signals of minor *Z*-isomer are denoted by an *.

MS (ESI+) *m/z*, (%): 189 (11, [M+Na]$^+$), 355 (100, [2M+Na]$^+$);

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91; Found: C, 79.14; H, 10.95;

GC (Temperature program: 60 °C for 2 min, followed by linear gradient 10 °C·min^{-1} for 14 min) showed a single peak at t = 10.7.

ent-17-Methylene-18-nor-13,17-secoandrost-4-ene-3,12-dione (_ent_-175) and _ent_-17-methylene-18-nor-13,17-seco-14β-androst-4-ene-3,12-dione (_ent_-176)



Anhydrous copper(II) chloride (2.5 mg, 18.2 µmol) and lithium chloride (1.5 mg, 36.4 µmol) were flame-dried under vacuum in Schlenk flask with stirring bar. Enone *ent*-**161** (50 mg, 182 µmol) was added as a solution in THF (1.5 mL) and the brown homogeneous solution was cooled to −40 °C, resulting in a yellow homogeneous solution. But-3-enylmagnesium chloride solution (0.48 mL, 237 µmol, 0.49 M in Et_2O) was added at −40 °C via syringe pump over 1 h. The mixture was stirred at −40 °C for 30 min and quenched with saturated aq. NH_4Cl (0.5 mL), followed by saturated aq. $NaHCO_3$ (2 mL) and extracted with hexane (3 × 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated *in vacuo*. The residue was redissolved in acetone (1 mL) and 5 drops of 1 M HCl were added. After 5 min, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (2 mL), extracted with hexane (3 × 2 mL) and the combined organic layers were dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (3 g) in 40% EtOAc/hexanes to afford 41.9 mg (80%) of a 4.5:1 mixture of inseparable diastereomers *ent*-**175** and *ent*-**176** as a colorless oil.

$[\alpha]_D^{20}$ −70.2 (*c* 0.225, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 918, 995 (=CH), 1238, 1356 (CH_2), 1380 (CH_3), 1435, 1450 (CH_2), 1620 (C=C), 1642 (C=CH_2) 1668 (C=O conjug.), 1709 (C=O), 2868, 2921 (CH_3), 2946 (CH_2), 2971, 3013 (=CH), 3080 (=CH_2).

^{1}H NMR (600 MHz, C_6D_6:$CDCl_3$ 1:1) δ 5.69 (ddt, J = 17.0, 10.4, 6.6 Hz, 1H, CH-17), 5.68 (br d, J = 1.9 Hz, 1H, CH-4), 5.00 (br d, J = 17.0 Hz, 1H, CH-20*Z*), 4.96 (br d, J = 10.4 Hz, 1H, CH-20*E*), 2.31 (ddd, J = 13.6, 4.1, 2.2 Hz, 1H, CH-13α), 2.17 (ddd, J = 13.5, 4.9, 2.2 Hz, 1H, CH-11α), 2.16 (m, 2H, CH_2-2), 2.07 (dddd, J = 14.6, 13.6, 5.2, 1.9 Hz, 1H, CH-6β), 2.01 (ddd, J = 14.6, 4.7, 2.8 Hz, 1H, CH-

6α), 1.97 (m, 1H, CH-16a), 1.88 (dddd, *J* = 13.2, 5.2, 3.5, 2.8 Hz, 1H, CH-7β), 1.83 (td, *J* = 13.5, 1.1 Hz, 1H, CH-11β), 1.80 (m, 1H, CH-16b), 1.77 (ddd, *J* = 13.6, 12.5, 1.1 Hz, 1H, CH-13β), 1.57 (ddd, *J* = 13.4, 5.0, 3.4 Hz, 1H, CH-1β), 1.52 (m, 1H, CH-15a), 1.34 (br td, *J* = 13.7, 13.4, 5.6 Hz, 1H, CH-1α), 1.23 (m, 1H, CH-8), 1.17 (m, 1H, CH-14), 1.11 (m, 1H, CH-15b), 1.09 (m, 1H, CH-9), 0.83 (br s, 3H, CH_3-19), 0.70 (dddd, *J* = 13.6, 13.2, 11.5, 4.7 Hz, 1H, CH-7α).

^{13}C NMR (150.9 MHz, C_6D_6:$CDCl_3$ 1:1) δ 210.4 (C, C-12)*, 209.9 (C, C-12), 198.5 (C, C-3)*, 198.4 (C, C-3), 168.3 (C, C-5), 168.1 (C, C-5)*, 138.2 (CH, C-17), 138.1 (CH, C-17)*, 124.6 (CH, C-4)*, 124.4 (CH, C-4), 115.4 (CH_2, C-20)*, 115.2 (CH_2, C-20), 52.5 (CH, C-9), 47.3 (CH, C-9)*, 45.7 (CH_2, C-13), 45.2 (CH_2, C-13)*, 42.3 (CH, C-14), 40.9 (CH_2, C-11), 40.7 (CH_2, C-11)*, 39.8 (2 × CH, C-14*, C-8), 39.2 (CH, C-8)*, 38.7 (2 × C, C-10, C-10*), 35.2 (2 × CH_2, C-1, C-1*), 33.84 (CH_2, C-2), 33.82 (CH_2, C-2)*, 32.6 (CH_2, C-16*), 32.4 (CH_2, C-15), 32.2 (CH_2, C-6), 31.7 (CH_2, C-6)*, 30.4 (CH_2, C-7), 30.1 (CH_2, C-16), 30.0 (CH_2, C-15)*, 26.1 (CH_2, C-7)*, 17.4 (CH_3, C-19)*, 17.1 (CH_3, C-19). Signals of minor 14β-isomer are denoted with an *.

MS (CI+) *m/z*, (%): 287 (100, $[M+H]^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{27}O_2$ 287.2011; Found 287.2012;

Tandem copper-catalyzed conjugate addition – oxygenation

Variant A:

Anhydrous copper(II) chloride (7.4 mg, 54.7 µmol) and lithium chloride (4.6 mg, 109 µmol) were flame-dried under vacuum in a Schlenk flask with a stirring bar. Enone **161** (150 mg, 547 µmol) was added as a solution in THF (6 mL) and the brown homogeneous solution was cooled to −40 °C, resulting in a yellow homogeneous solution. Pent-3-enylmagnesium chloride solution (**168**) (0.925 mL, 712 µmol, 0.77 M in THF) was added at −40 °C via syringe pump over 1 h. During the addition the color changed through red to yellow. The mixture was stirred for 30 min and diisopropylamine (38.5 µL, 275 µmol) was added. 2,2,6,6-Tetramethyl-1-oxopiperidinium tetrafluoroborate (**180**) (160 mg, 657 µmol) was added portionwise at −40 °C during 3 min with vigorous stirring, until the solution attained an orange-brown color. The reaction mixture was warmed to rt, turning the color to green, and the reaction was quenched with few drops of saturated aq. NH_4Cl. The suspension was diluted with Et_2O (20 mL), passed through a plug of silica gel (3 cm), washed with Et_2O (20 mL) and evaporated. The residue was purified by chromatography on silica gel (10 g) in 10% EtOAc/hexanes + 0.5% Et_3N to afford 214 mg (78%) of *trans*-alkoxyamines **184a** and **184b** in 4.5:1 ratio, followed by 37.0 mg (13%) of inseparable *cis*-alkoxyamines **185,** cyclized **186** and **187** in 6:5:2 ratio, and finally 9.4 mg (5%) of **188**. Analytically pure **184a** was obtained by crystallization from hexane as a 9:2 mixture of $\Delta^{17(20)}$-*E* and $\Delta^{17(20)}$-*Z* isomers.

Variant B: Transmetallation to Lithium enolate

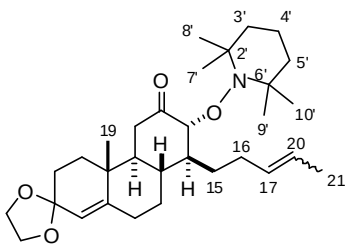
Anhydrous copper(II) chloride (7.4 mg, 54.7 µmol) and lithium chloride (4.6 mg, 109 µmol) were flame-dried under vacuum in Schlenk flask with stirring bar. Enone **161** (150 mg, 547 µmol) was added as a solution in THF (6 mL) and the brown homogeneous solution was cooled to −40 °C, resulting in a yellow homogeneous solution. Pent-3-enylmagnesium bromide solution (**165**) (1.8 mL, 657 µmol, 0.37 M in THF) was added at −40 °C via syringe pump over 1 h. During the addition the color changed through red to yellow. The mixture was stirred for 30 min, cooled to −78 °C and TMSCl (104 µL, 0.82 mmol) was added dropwise, followed by anhydrous Et_3N (114 µL, 0.82 mmol). The reaction mixture was warmed to rt, stirred for 30 min and diluted with hexane (5 mL). The content

of the reaction flask was poured onto a 1:1 mixture of ice and saturated aq. $NaHCO_3$ (40 mL in total) and extracted with hexane (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford 227 mg (99%) of crude silyl enol ether, which was dissolved in anhydrous DME at rt. MeLi (0.41 mL, 656 µmol, 1.60 M in Et_2O) was added dropwise and the mixture was stirred for 15 min, followed by addition of diisopropylamine (38 µL) and ferrocene (5 mg, 27.3 µmol). The mixture was cooled in an ice bath and **180** (146 mg, 601 µmol) was added slowly over 1 h. After another 1 h of stirring at 0 °C, the reaction was quenched with few drops of saturated aq. NH_4Cl. The suspension was diluted with Et_2O (20 mL), passed through a plug of silica gel (3 cm), washed with Et_2O (20 mL) and evaporated. The residue was purified by chromatography on silica gel (10 g) in 10% EtOAc/hexanes + 0.5% Et_3N to afford 133 mg (49%) of *trans*-alkoxyamines **184a** and **184b** in 4.5:1 ratio, followed by 70.6 mg (26%) of inseparable *cis*-alkoxyamines **185** and cyclized **186** in 18:8 ratio, and finally 18.2 mg (10%) of **188**. All corresponding $\Delta^{17(20)}$-*E* and $\Delta^{17(20)}$-*Z* isomers were in 3:1 ratio according to ^{1}H NMR spectra.

Variant C: With dppe ligand

Anhydrous copper(II) chloride (139 mg, 1.03 mmol) and lithium chloride (87.6 mg, 2.06 mmol) were flame-dried under vacuum in 250 mL Schlenk flask with stirring bar. Bis(diphenylphosphino)ethane (411 mg, 1.03 mmol) was added and the catalyst was dissolved in THF (105 mL). Enone **161** (2.84 g, 10.3 mmol) was added neat, dissolved at rt and the nearly colorless homogeneous solution was cooled to −40 °C. Pent-3-enylmagnesium chloride solution (**168**) (14.8 mL, 12.39 mmol, 0.835 M in THF) diluted with THF (15 mL) was added at −40 °C via syringe pump over 1 h. During the addition the color changed to yellow. The mixture was stirred for 30 min, diisopropylamine (0.723 mL, 5.16 mmol) was added and after 15 min of stirring at −40 °C, the reaction mixture was cooled to −60 °C. Solid **180** (3.76 g, 15.5 mmol) was added in four portions during 5 min at −60 °C, turning the mixture to grayish green color, and the mixture was stirred for 2 h after which it was warmed to 0 °C. The reaction was poured into a mixture of saturated aq. NH_4Cl (50 mL) and saturated aq. $NaHCO_3$ (250 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (150 g) in 10% EtOAc/hexanes + 0.5% Et_3N to afford 4.32 g (83%) of *trans*-alkoxyamines **184a** and **184b** in 6.2:1 ratio as determined from ^{1}H NMR spectrum, followed by 559 mg (10%) of inseparable *cis*-alkoxyamines **185** and cyclized **186** in 1:1 ratio, and finally 123 mg (5%) of **188**. All corresponding $\Delta^{17(20)}$-*E* and $\Delta^{17(20)}$-*Z* isomers were in 2:3 ratio according to ^{1}H NMR spectra.

3-(Ethylenedioxy)-13α-(2,2,6,6-tetramethylpiperidin-1-yloxy)-18-nor-13,17-secopregna-4,17(20)-dien-12-one (*nat*-184a) and *ent*-3-(ethylenedioxy)-13α-(2,2,6,6-tetramethylpiperidin-1-yloxy)-18-nor-13,17-secopregna-4,17(20)-dien-12-one (*ent*-184a)



$[\alpha]_D^{20}$ +89.6 (*c* 0.260, $CHCl_3$) for *nat*-**184a**; Mp 144-147 °C;
$[\alpha]_D^{20}$ −101.5 (*c* 0.261, $CHCl_3$) for *ent*-**184a**; Mp 141-143°C;
IR ($CHCl_3$); ν[cm^{-1}]: 947, 1092, 1133, 1162 (COCOC), 1364, 1376, 1381 (CH_3), 1662 (C=C), 1711 (C=O), 2856, 2886 (CH_3), 2936 (CH_2), 2975 (CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47-5.29 (m, 2H, CH-17, CH-20), 5.28 (s, 1H, CH-4), 4.06-3.85 (m, 4H, OCH_2CH_2O), 3.79 (d, *J* = 1.7 Hz, 1H, CH-13)*, 3.75 (d, *J* = 1.6 Hz, 1H, CH-13), 2.60 (dd, *J* = 18.5, 5.3 Hz, 1H, CH-11a), 2.33 (ddd, *J* =

12.9, 12.2, 5.3 Hz, 1H, CH-9), 2.23 (tdd, *J* = 13.8, 4.7, 1.8 Hz, 1H, CH-6a), 2.11 (ddd, *J* = 14.1, 4.1, 2.4 Hz, 1H, CH-6b), 2.08-1.98 (m, 1H, CH-16a), 2.02-1.92 (m, 1H, CH-16b), 2.00-1.90 (m, 1H, CH-7a), 1.96 (dd, *J* = 18.5, 12.9 Hz, 1H, CH-11b), 1.95-1.85 (m, 1H, CH-14), 1.82-1.79 (m, 2H, CH_2-2), 1.71-1.61 (m, 1H, CH-1a), 1.62 (dd, *J* = 5.9, 1.1 Hz, 3H, CH_3-21), 1.66-1.56 (m, 1H, CH-1b), 1.60-1.56 (m, 3H, CH_3-21)*, 1.50-1.36 (m, 4H, CH_2-3', CH_2-5'), 1.49-1.40 (m, 1H, CH-4'a), 1.41-1.26 (m, 1H, CH-7b), 1.37-1.26 (m, 1H, CH-4'b), 1.33-1.18 (m, 2H, CH_2-15), 1.26-1.14 (m, 1H, CH-8), 1.14 (br s, 3H, CH_3-7'), 1.08 (br s, 3H, CH_3-10'), 1.07 (br s, 3H, CH_3-8'), 0.982 (s, 3H, CH_3-19)*, 0.977 (s, 3H, CH_3-19), 0.94 (br s, 3H, CH_3-9').

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6 (C, C-12), 149.9 (C, C-5), 130.5 (CH, C-20), 129.7 (CH, C-20)*, 125.5 (CH, C-17), 124.6 (CH, C-17)*, 120.5 (CH, C-4), 106.0 (C, C-3), 91.5 (CH, C-13), 64.6 (CH_2, O*C*$H_2$$CH_2$O), 64.3 ($CH_2$, OC$H_2$*C*$H_2$O), 60.3 (C, C-2'), 59.1 (C, C-6'), 46.1 (CH, C-14)*, 45.9 (CH, C-14), 45.2 (CH, C-9), 40.0 (2 × CH_2, C-3', C-5'), 39.1 (CH, C-8), 37.9 (CH_2, C-11), 37.4 (C, C-10), 35.7 (CH_2, C-7), 34.5 (CH_2, C-1/C-15), 34.4 (CH_2, C-1/C-15), 34.2 (CH_3, C-7'/C-9'), 33.7 (CH_3, C-7'/C-9'), 32.3 (CH_2, C-6), 30.2 (CH_2, C-16), 29.8 (CH_2, C-2), 24.6 (CH_2, C-16)*, 20.9 (CH_3, C-8'/C-10'), 20.1 (CH_3, C-8'/C-10'), 17.9 (CH_3, C-21), 17.5 (2 × CH_3, C-19, C-19*), 17.1 (CH_2, C-4'), 12.9 (CH_3, C-21)*; Signals of minor *Z*-isomer are denoted with an *.

MS (ESI+) *m/z*, (%): 500 (100, $[M+H]^+$), 522 (6, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{50}NO_4$ 500.3734; Found 500.3727;

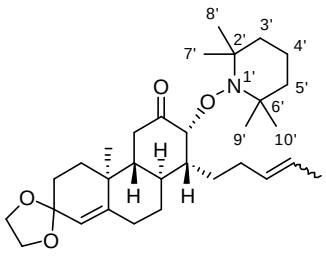
Anal. Calcd for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88; N, 2.80; Found: C, 74.41; H, 9.86; N, 2.75; for *nat*-**184a**;

Anal. Calcd for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88; N, 2.80; Found: C, 74.74; H, 10.05; N, 2.69; for *ent*-**184a**;

X-ray data are available in Appendix C.

ent-3-(Ethylenedioxy)-13β-(2,2,6,6-tetramethylpiperidin-1-yloxy)-18-nor-13,17-secopregna-4,17(20)-dien-12-one (_ent_-185a) and _ent_-13β-bromo-3-(ethylenedioxy)-18-nor-13,17-secopregna-4,17(20)-dien-12-one (_nat_-187a)

Isolated from combined chromatographic fractions of cyclized **186** and **185, 187** from the tandem conjugate addition-oxygenation experiments with pentenylmagnesium bromide **165**. Flash chromatography in 10% MTBE/CH_2Cl_2 afforded 35.2 mg of **187**, followed by 78.8 mg of **185** and 90.0 mg of **186**.

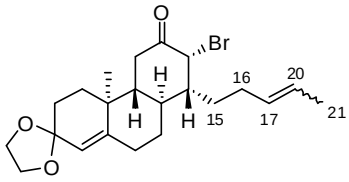


^{1}H NMR (600 MHz, C_6D_6) δ 5.51 (m, 2H, CH-17, CH-20), 5.52 (br s, 1H, CH-4), 4.84 (br d, *J* = 5.3 Hz, 1H, CH-13), 3.77-3.60 (m, 4H, OCH_2CH_2O), 2.32 (m, 1H, CH-11a), 2.17 (m, 1H, CH-2a), 2.11 (m, 1H, CH-6a), 2.08 (m, 1H, CH-2b), 2.06 (m, 1H, CH-8), 1.98 (m, 1H, CH-6b), 1.90 (m, 2H, CH-1a, CH-16a), 1.88 (m, 1H, CH-14), 1.85 (m, 1H, CH-9), 1.83 (m, 2H, CH-1b, CH-16b), 1.74 (m, 1H, CH-7a), 1.68 (m, 3H, CH_3-21), 1.63 (m, 1H, CH-15a), 1.60 (m, 1H, CH-11b), 1.47 (m, 4H, CH_2-3', CH_2-5'), 1.43 (br s, 13H, CH_3-7', CH_3-8', CH_3-9', CH_3-10', CH-4'a), 1.36 (m, 2H, CH-7b, CH-15b), 1.15 (m, 1H, CH-4'b), 0.69 (s, 3H, CH_3-19);

^{13}C NMR (150.9 MHz, C_6D_6) δ 208.2 (C, C-12), 147.3 (C, C-5), 131.0 (CH, C-20), 124.9 (CH, C-17), 121.7 (CH, C-4), 105.7 (C, C-3), 88.2 (CH, C-13), 64.2 (CH_2, O*C*$H_2$$CH_2$O), 63.7 ($CH_2$, OC$H_2$*C*$H_2$O), 60.4 (C, C-2'), 58.7 (C, C-6'), 40.0 (2 × CH_2, C-3', C-5'), 38.6 (CH_2, C-11), 37.1 (C, C-10), 36.5 (CH, C-14), 34.7 (CH_3, C-7'/C-9'), 34.3 (2 × CH_2, C-7, C-15), 34.0 (CH_3, C-7'/C-9'), 31.8 (CH + CH_2, C-6,

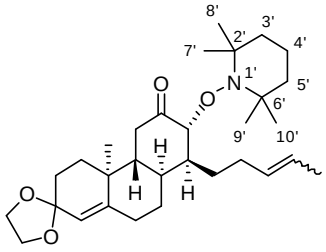
C-8), 30.2 (CH_2, C-2), 29.9 (CH + 2 × CH_2, C-1, C-16, C-9), 20.6 (CH_3, C-8'/C-10'), 20.5 (CH_3, C-8'/C-10'), 17.6 (CH_3, C-21), 17.0 (CH_2, C-4'), 16.2 (CH_3, C-19);
MS (ESI+) *m/z*, (%): 500 (100, $[M+H]^+$), 522 (23, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{50}NO_4$ 500.3734; Found 500.3733;

ent-**187a**: Colorless oil,



^{1}H NMR (400 MHz, C_6D_6) δ 5.53-5.37 (m, 1H, CH-20)*, 5.46-5.37 (m, 1H, CH-17)*, 5.41-5.23 (m, 1H, CH-20), 5.39 (br s, 2H, CH-4, CH-4*), 5.36-5.18 (m, 1H, CH-17), 4.34 (dd, *J* = 2.8, 1.3 Hz, 1H, CH-13)*, 4.30 (dd, *J* = 2.8, 1.3 Hz, 1H, CH-13), 3.65-3.47 (m, 8H, OCH_2CH_2O, OCH_2CH_2O*), 2.85 (t, *J* = 13.8 Hz, 1H, CH-11a), 2.17 (ddd, *J* = 13.8, 3.8, 1.4 Hz, 1H, CH-11b), 1.99-1.85 (m, 1H, CH-16a), 1.96-1.79 (m, 2H, CH_2-6), 1.82-1.66 (m, 2H, CH_2-2), 1.71-1.55 (m, 1H, CH-8), 1.68-1.55 (m, 1H, CH-16b), 1.64-1.49 (m, 1H, CH-7a), 1.59 (br d, *J* = 6.0 Hz, 3H, CH_3-21), 1.57-1.42 (m, 1H, CH-1a), 1.55 (br d, *J* = 6.8 Hz, 3H, CH_3-21)*, 1.49-1.37 (m, 1H, CH-15a), 1.37-1.23 (m, 1H, CH-1b), 1.35-1.21 (m, 1H, CH-15b), 1.05-0.91 (m, 1H, CH-9), 0.90-0.78 (m, 1H, CH-14), 0.71 (s, 6H, CH_3-19, CH_3-19*), 0.48 (qd, *J* = 12.5, 5.3 Hz, 1H, CH-7b).
^{13}C NMR (101 MHz, C_6D_6) δ 203.1 (C, C-12), 147.7 (C, C-5), 130.5 (CH, C-17/C-20), 129.5 (CH, C-17/C-20)*, 125.9 (CH, C-17/C-20), 125.0 (CH, C-17/C-20)*, 122.12 (CH, C-4)*, 122.11 (CH, C-4), 106.0 (C, C-3), 64.7 (CH_2, O*C*H_2CH_2O), 64.2 (CH_2, OCH_2*C*H_2O), 57.88 (CH, C-13)*, 57.86 (CH, C-13), 52.46 (CH, C-9)*, 52.42 (CH, C-9), 45.8 (CH, C-14)*, 45.5 (CH, C-14), 37.8 (C, C-10), 35.60 (CH, C-8), 35.59 (CH, C-8)*, 35.4 (CH_2, C-11), 34.48 (CH_2, C-1)*, 34.45 (CH_2, C-1), 31.6 (CH_2, C-6), 30.4 (CH_2, C-7), 30.3 (CH_2, C-2), 29.7 (CH_2, C-15), 29.6 (CH_2, C-15)*, 29.2 (CH_2, C-16), 23.6 (CH_2, C-16)*, 18.1 (CH_3, C-21), 17.2 (CH_3, C-19, C-19*), 12.6 (CH_3, C-21)*. Signals of minor *Z*-isomer are denoted with an *.
MS (ESI+) *m/z*, (%): 343 (3, $[M-HBr+H]^+$), 365 (12, $[M-HBr+Na]^+$), 423/425 (88, $[M+H]^+$), 445/447 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{32}{}^{79}BrO_3$ 423.1529; Found 423.1528;

ent-3-(Ethylenedioxy)-13β-(2,2,6,6-tetramethylpiperidin-1-yloxy)-18-nor-13,17-seco-14β-pregna-4,17(20)-dien-12-one (_ent_-184b)



trans-Alkoxyamine *ent*-**184** (325 mg, 650 µmol, mixture of *ent*-**184a**/*ent*-**184b** isomers 9:2) and a crystal of TEMPO (ca. 0.1 mg) was dissolved in dry *t*BuOH (5 mL) with heating and triethylamine (9 µL, 65 µmol) was added to the reaction mixture. The solution was degassed by purging with nitrogen at 30 °C for 30 min. The reaction mixture was heated to 100 °C in a closed vessel in a microwave reactor for 2 h. The solution was concentrated *in vacuo*. Flash chromatography of the residue on silica gel (10 g) in 10% EtOAc/hexanes + 0.5% Et_3N afforded 51.6 mg (16%) of *ent*-**184b** as a reddish foam, followed by 273 mg (84%) of the mixture of cyclized isomers *ent*-**186A,a** as a white foam.
$[\alpha]_D^{20}$ −104.1 (*c* 0.243, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 946, 1012, 1091 (ketal), 1133, 1156 (COCOC), 1363, 1376, 1381 (CH_3), 1662 (C=C), 1712 (C=O), 2888 (CH_3), 2936 (CH_2), 2974 (CH_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47-5.33 (m, 2H, CH-20, CH-20*), 5.28 (s, 2H, CH-4, CH-4*), 5.33-5.32 (m, 2H, CH-17, CH-17*), 4.07-3.83 (m, 8H, OCH_2CH_2O, OCH_2CH_2O*), 3.93-3.83 (m, 2H, CH-13, CH-13*), 2.77 (t, *J* = 12.4 Hz, 1H, CH-11a), 2.42-2.29 (m, 1H, CH-8), 2.37-2.26 (m, 1H, CH-6a), 2.32-2.21 (m, 1H, CH-14), 2.22-2.12 (m, 1H, CH-11b), 2.18-2.07 (m, 1H, CH-6b), 2.08-1.99 (m, 1H, CH-16a), 1.87-1.78 (m, 1H, CH-16b), 1.78-1.74 (m, 2H, CH_2-2), 1.69-1.59 (m, 1H, CH-1a), 1.62-1.52 (m, 1H, CH-7a), 1.60 (dq, *J* = 6.0, 1.1 Hz, 3H, CH_3-21), 1.60-1.55 (m, 3H, CH_3-21)*, 1.59-1.49 (m, 1H, CH-1b), 1.57-1.43 (m, 1H, CH-9), 1.50-1.40 (m, 5H, CH_2-3‘, CH_2-5‘, CH-4‘a), 1.42-1.31 (m, 1H, CH-7b), 1.39-1.28 (m, 1H, CH-15a), 1.38-1.25 (m, 1H, CH-4‘b), 1.17-1.08 (m, 9H, CH_3-7‘, CH_3-8‘, CH_3-9‘), 1.12 (s, 3H, CH_3-19), 0.96 (br s, 3H, CH_3-10‘), 0.91-0.75 (m, 1H, CH-15b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7 (C, C-12), 149.3 (C, C-5), 130.4 (CH, C-17), 129.6 (CH, C-17)*, 125.5 (CH, C-20), 124.5 (CH, C-20)*, 120.7 (CH, C-4), 105.7 (C, C-3), 90.7 (CH, C-13), 64.5 (CH_2, O*C*H_2CH_2O), 64.2 (CH_2, OCH_2CH_2O), 60.2 (C, C-2‘, C-2‘*), 59.2 (C, C-6‘, C-6‘*), 48.1 (CH, C-9), 45.8 (CH, C-14)*, 45.5 (CH, C-14), 40.0 (CH_2, C-3‘, C-5‘), 38.3 (CH_2, C-11), 37.9 (C, C-10), 34.2 (CH_2 + CH_3, C-1, C-7‘, C-9‘, C-7‘*, C-9‘*), 33.7 (CH, C-8), 31.9 (CH_2, C-6), 30.4 (CH_2, C-16), 30.0 (CH_2, C-7), 29.6 (CH_2, C-2), 24.8 (CH_2, C-16)*, 23.76 (CH_2, C-15), 23.76 (CH_2, C-15)*, 20.1 (2 × CH_3, C-8‘, C-10‘), 17.71 (CH_3, C-19/C-21), 17.69 (CH_3, C-19/C-21), 16.9 (CH_2, C-4‘), 12.7 (CH_3, C-21)*.

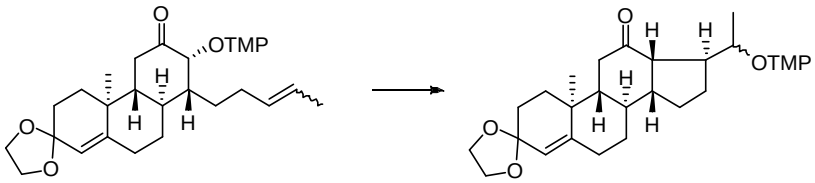
MS (ESI+) *m/z*, (%): 500 (100, $[M+H]^+$), 522 (44, $[M+Na]^+$), 1022 (7, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{50}NO_4$ 500.3734; Found 500.3735; $[M+Na]^+$ Calcd for $C_{31}H_{49}NNaO_4$ 522.3554; Found 522.3554;

Anal. Calcd for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88; N, 2.80; Found: C, 74.21; H, 9.89; N, 2.60;

Thermal Cyclization:

ent-3-(Ethylenedioxy)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-18-nor-17ξ,13α-pregn-4-en-12-one (_ent_-186A,a)



trans-Alkoxyamine *ent*-**184a** (325 mg, 650 µmol, mixture of *Z*/*E* isomers 2:9) and 1 crystal of TEMPO (ca. 0.1 mg) was dissolved in dry *t*BuOH (5 mL) at 40 °C and triethylamine (9 µL, 65 µmol) was added to the reaction mixture. The solution was degassed by purging with nitrogen at 30 °C for 30 min. The reaction mixture was heated to 100 °C in a closed vessel in a microwave reactor for 30 min. The solution was concentrated *in vacuo* to afford 325 mg (99%) of an inseparable mixture of cyclized isomers *ent*-**186A,a** as a white foam.

The mixture composed of 17α20*R* : 17α20*S* : 17β20ξ: 17β20ξ isomers in 5:5:2:1 ratio. NMR signals of the respective 17α-isomers are denoted with A, a, while 17β-isomers are marked with B, b.

HPLC (SUPELCOSIL™ LC-Si Column, 5 µm particle size, L × I.D. 15 cm × 4.6 mm, t = 25 °C, isocratic hexane/CH_2Cl_2/Et_3N = 60:40:0.2 during 20 min, followed by gradient to hexane/CH_2Cl_2/Et_3N = 50:50:0.25 during 10 min, 1.0 mL·min^{-1}; detection at Light Scattering Detector) showed 4 peaks in 9:40:34:17 ratio (t_1 = 14.7 min, t_2 = 17.5 min, t_3 = 19.5 min, t_4 = 25.2 min) of the crude product. Under identical conditions, starting material *ent*-**184a** elutes at t_{trans} = 4.5 min.

IR ($CHCl_3$); ν[cm^{-1}]: 946, 1089 (ketal), 1133, 1174 (COCOC), 1367, 1375 (CH_3), 1440, 1451 (CH_3), 1663 (C=C), 1697 (C=O), 2887 (CH_3), 2937 (CH_2), 2973 (CH_3).

^{1}H NMR (400 MHz, C_6D_6) δ 5.45 (s, 4H, CH-4)^{AaBb}, 4.92 (quint, *J* = 6.5 Hz, 1H, CH-20)^{B}, 4.71 (dq, *J* = 10.1, 6.2 Hz, 1H, CH-20)^{b}, 4.17 (qd, *J* = 6.4, 4.0 Hz, 1H, CH-20)^{A}, 4.01 (quint, *J* = 6.3 Hz, 1H, CH-20)^{a}, 3.69-3.48 (m, 16H, OCH_2CH_2O)^{AaBb}, 2.93 (t, *J* = 8.2 Hz, 1H, CH-13)^{b}, 2.73 (t, *J* = 8.8 Hz, 1H, CH-13)^{A}, 2.55-2.47 (m, 1H, CH-17)^{a}, 2.52-2.44 (m, 2H, CH-13)^{aB}, 2.39-2.31 (m, 1H, CH-17)^{A}, 2.30-1.10 (m, aliphatic region), 1.93-1.83 (m, 1H, CH-17)^{b}, 1.87-1.78 (m, 1H, CH-17)^{B}, 1.35 (d, *J* = 6.5 Hz, 3H, CH_3-21)^{B}, 1.32 (d, *J* = 6.2 Hz, 3H, CH_3-21)^{b}, 1.31 (d, *J* = 6.5 Hz, 3H, CH_3-21)^{A}, 1.28 (d, *J* = 6.3 Hz, 3H, CH_3-21)^{a}, 0.76 (s, 3H, CH_3-19)^{b}, 0.742 (s, 3H, CH_3-19) $^{A/a}$, 0.739 (s, 3H, CH_3-19)^{B}, 0.73 (s, 3H, CH_3-19)$^{A/a}$.

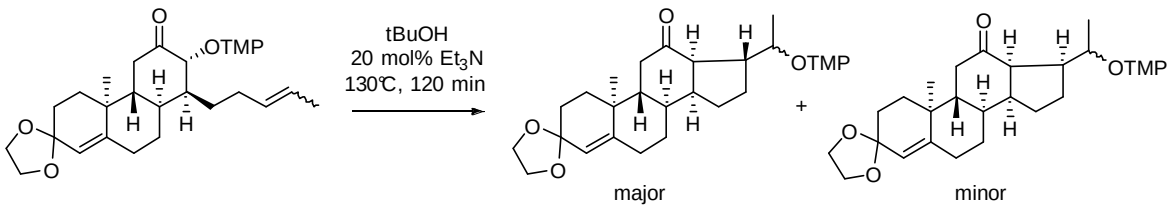
^{13}C NMR (101 MHz, C_6D_6) δ 211.81 (C, C-12)$^{A/a}$, 211.53 (C, C-12)^{B}, 211.27 (C, C-12)^{b}, 211.22 (C, C-12)$^{A/a}$, 148.57 (C, C-5)^{B}, 148.54 (C, C-5)^{b}, 148.39 (C, C-5)$^{A/a}$, 148.33 (C, C-5)$^{A/a}$, 122.17 (CH, C-4)$^{A/a}$, 122.12 (CH, C-4)$^{A/a}$, 121.91 (CH, C-4)^{B}, 121.87 (CH, C-4) ^{b}, 106.33 (C, C-3)^{Bb}, 106.24 (C, C-3)^{Aa}, 80.88 (CH, C-20)^{a}, 78.55 (CH, C-20)^{b}, 78.31 (CH, C-20)^{A}, 77.02 (CH, C-20)^{B}, 64.65 (CH_2, O*C*H_2CH_2O)^{AaBb}, 64.28 (CH_2, OCH_2CH_2O)^{b}, 64.25 (CH_2, OCH_2CH_2O)$^{A/a}$, 64.24 (CH_2, OCH_2CH_2O)$^{A/a}$, 61.14 (C, C-2'/C-6')$^{A/a}$, 60.94 (C, C-2'/C-6')$^{B/b}$, 60.81 (C, C-2'/C-6')$^{A/a}$, 60.63 (C, C-2'/C-6')$^{B/b}$, 59.19 (C, C-2'/C-6')$^{A/a}$, 59.17 (C, C-2'/C-6')$^{A/a}$, 58.81 (C, C-2'/C-6')^{Bb}, 56.47 (CH, C-13)^{a}, 54.47 (CH, C-13)^{A}, 52.25 (CH, C-9)$^{A/a}$, 51.83 (CH, C-13)^{b}, 51.62 (CH, C-13)^{B}, 51.50 (CH, C-9)$^{A/a}$, 50.56 (CH, C-17)^{B}, 50.11 (CH, C-14)$^{A/a}$, 50.03 (CH)^{b}, 49.90 (CH)^{b}, 49.66 (CH, C-14)$^{A/a}$, 49.12 (CH)^{b}, 48.72 (CH, C-9)^{B}, 48.09 (CH, C-17)^{A}, 47.87 (CH, C-14)^{B}, 47.45 (CH, C-17)^{a}, 41.87 (CH_2, C-11)^{b}, 41.48 (CH_2, C-11)^{B}, 41.14 (CH_2, C-3'/C-5'), 41.04 (CH_2, C-3'/C-5'), 40.99 (CH_2, C-3'/C-5'), 40.86 (CH_2, C-3'/C-5'), 40.75 (CH_2, C-3'/C-5'), 40.65 (CH_2, C-3'/C-5'), 40.54 (CH_2, C-3'/C-5'), 39.78 (CH, C-8)^{B}, 39.11 (CH, C-8)^{b}, 38.68 (CH_2, C-11)$^{A/a}$, 38.63 (CH_2, C-11)$^{A/a}$, 38.14 (CH, C-8)$^{A/a}$, 37.92 (C, C-10)$^{A/a}$, 37.80 (C, C-10)$^{A/a}$, 37.72 (CH, C-8)$^{A/a}$, 34.91 (2 × CH_3, C-7', C-9')^{Bb}, 34.81 (CH_2)^{B}, 34.69 (2 × CH_3, C-7', C-9')^{Aa}, 34.58 (CH_2)^{b}, 34.52 (2 × CH_2, C-1)^{Aa}, 34.46 (CH_2)^{B}, 34.25 (CH_2)^{b}, 33.07 (CH_2, C-7)$^{A/a}$, 33.02 (CH_2, C-7)$^{A/a}$, 31.97 (CH_2, C-6)$^{A/a}$, 31.92 (CH_2, C-6)$^{A/a}$, 31.84 (CH_2)^{B}, 31.78 (CH_2)^{b}, 31.65 (CH_2)^{B}, 30.76 (CH_2)^{b}, 30.54 (CH_2)$^{A/a}$, 30.41 (CH_2)$^{A/a}$, 30.39 (CH_2)$^{A/a}$, 30.35 (CH_2)$^{A/a}$, 27.58 (CH_2)^{b}, 27.33 (CH_2)$^{A/a}$, 27.14 (CH_2)^{B}, 25.97 (CH_2)$^{A/a}$, 21.19 (2 × CH_3, C-8', C-10')^{b}, 21.13 (2 × CH_3, C-8', C-10')$^{A/a}$, 20.99 (2 × CH_3, C-8', C-10')$^{A/a}$, 20.87 (2 × CH_3, C-8', C-10')^{B}, 19.66 (CH_3, C-21)^{B}, 19.06 (CH_3, C-21)^{b}, 18.42 (CH_3, C-21)$^{A/a}$, 18.16 (CH_3, C-19)^{b}, 18.01 (CH_3, C-19)^{B}, 17.82 (CH_2, C-4')$^{b/B}$, 17.78 (CH_2, C-4')$^{b/B}$, 17.77 (CH_2, C-4')$^{A/a}$, 17.76 (CH_2, C-4')$^{A/a}$, 17.70 (CH_3, C-19)$^{A/a}$, 17.62 (CH_3, C-19)$^{A/a}$, 17.18 (CH_3, C-21)$^{A/a}$.

MS (ESI+) *m/z*, (%): 500 (100, $[M+H]^+$), 522 (3, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{50}NO_4$ 500.3734; Found 500.3732;

Anal. Calcd for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88; N, 2.80; Found: C, 74.65; H, 9.96; N, 2.62.

ent-3-(Ethylenedioxy)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-18-nor-17ξ,14β-pregn-4-en-12-one (_ent_-186B,b)



trans-Alkoxyamines *ent*-**184b** (61.5 mg, 123 µmol) and 1 crystal of TEMPO (ca. 0.1 mg) was dissolved in dry *t*BuOH (3 mL) and triethylamine (3 µL, 21.5 µmol) was added. The solution was degassed by purging with nitrogen at 30 °C for 30 min. The reaction mixture was heated to 130 °C in a

closed vessel in a microwave reactor for 4 h. The solution was concentrated *in vacuo* to afford 61 mg (99%) of an inseparable mixture of cyclized isomers *ent*-**186B,b** as a white foam.

The mixture composed of 17β20*R* : 17β20*S* : 17α20*R* : 17α20*S* isomers in 4:4:1:1 ratio. NMR signals of the respective 17β-isomers are denoted with A, a, while 17α-isomers are marked with B, b.

HPLC (SUPELCOSIL™ LC-Si Column, 5 μm particle size, L × I.D. 15 cm × 4.6 mm, t = 25 °C, isocratic hexane/CH_2Cl_2/Et_3N = 60:40:0.2 during 20 min, followed by gradient to hexane/CH_2Cl_2/Et_3N = 50:50:0.25 during 10 min, 1.0 mL·min^{-1}; detection at Light Scattering Detector) showed 3 peaks in 7:5:88 ratio (t_1 = 9.1 min, t_2 = 12.1 min, t_3 = 14.7 min) of the crude product. Under identical conditions, starting material *ent*-**184b** elutes at t_{cis} = 6.3 min.

IR ($CHCl_3$); ν[cm^{-1}]: 946, 1089 (ketal), 1133, 1174 (COCOC), 1367, 1375 (CH_3), 1440, 1451 (CH_3), 1663 (C=C), 1697 (C=O), 2887 (CH_3), 2937 (CH_2), 2973 (CH_3).

^{1}H NMR (400 MHz, C_6D_6) δ 5.43 (s, 4H, CH-4)^{AaBb}, 5.23 (dq, *J* = 9.4, 6.1 Hz, 1H, CH-20)^{B}, 5.17 (dq, *J* = 9.6, 6.3 Hz, 1H, CH-20)^{b}, 4.06 (quint, *J* = 6.2 Hz, 1H, CH-20)^{A}, 3.94 (quint, *J* = 6.1 Hz, 1H, CH-20)^{a}, 3.67-3.47 (m, 16H, OCH_2CH_2O)^{AaBb}, 3.21-3.11 (m, 2H, CH-17)^{Aa}, 2.93 (t, *J* = 5.5 Hz, 1H, CH-13)^{b}, 2.79 (dd, *J* = 7.8, 2.1 Hz, 1H, CH-13)^{a}, 2.56 (dd, *J* = 7.1, 2.5 Hz, 1H, CH-13)^{A}, 2.33-2.25 (m, 1H, CH-13)^{B}, 2.30-0.80 (m, aliphatic region), 1.74-1.61 (m, 1H, CH-17)^{B}, 1.69-1.54 (m, 1H, CH-17)^{b}, 1.40 (d, *J* = 6.1 Hz, 3H, CH_3-21)^{B}, 1.33 (d, *J* = 6.3 Hz, 3H, CH_3-21)^{b}, 1.31 (d, *J* = 6.1 Hz, 3H, CH_3-21)^{a}, 1.28 (d, *J* = 6.2 Hz, 3H, CH_3-21)^{A}, 0.76 (s, 3H, CH_3-19) $^{B/b}$, 0.734 (s, 3H, CH_3-19)$^{A/a}$, 0.730 (s, 3H, CH_3-19) $^{B/b}$, 0.70 (s, 3H, CH_3-19)$^{A/a}$.

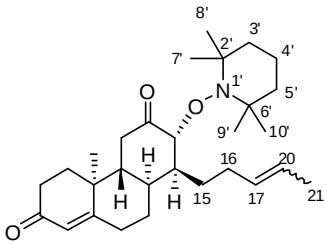
^{13}C NMR (101 MHz, C_6D_6) δ 211.35 (C, C-12)$^{B/b}$, 210.54 (C, C-12)$^{B/b}$, 209.83 (C, C-12)$^{A/a}$, 209.80 (C, C-12)$^{A/a}$, 148.00 (C, C-5)$^{A/a}$, 147.97 (C, C-5)$^{A/a}$, 147.76 (C, C-5)$^{B/b}$, 147.70 (C, C-5)$^{B/b}$, 122.68 (CH, C-4)$^{B/b}$, 122.65 (CH, C-4)$^{B/b}$, 122.47 (CH, C-4)$^{A/a}$, 122.46 (CH, C-4)$^{A/a}$, 106.19 (2 × C, C-3)^{Aa}, 106.16 (2 × C, C-3)^{Bb}, 80.43 (CH, C-20)^{A}, 80.21 (CH, C-20)^{a}, 78.69 (CH, C-20)^{B}, 77.60 (CH, C-20)^{b}, 64.67 (CH_2, OCH_2CH_2O)^{AaBb}, 64.23 (CH_2, OCH_2CH_2O)^{AaBb}, 60.94 (C, C-2'/C-6')$^{A/a}$, 60.92 (C, C-2'/C-6')$^{A/a}$, 60.87 (C, C-2'/C-6')$^{B/b}$, 60.63 (C, C-2'/C-6')$^{B/b}$, 59.20 (C, C-2'/C-6')$^{A/a}$, 59.12 (C, C-2'/C-6')$^{A/a}$, 58.76 (C, C-2'/C-6')$^{B/b}$, 58.65 (C, C-2'/C-6')$^{B/b}$, 56.09 (CH, C-13)^{A}, 55.30 (CH, C-13)^{B}, 53.96 (CH, C-13)^{a}, 53.80 (CH, C-13)^{b}, 50.02 (CH)$^{B/b}$, 49.90 (CH)$^{B/b}$, 49.69 (CH)$^{B/b}$, 49.47 (CH)$^{B/b}$, 48.94 (CH)$^{B/b}$, 48.85 (CH)$^{B/b}$, 48.45 (CH, C-14)$^{A/a}$, 48.14 (CH, C-14)$^{A/a}$, 47.77 (CH, C-9)$^{A/a}$, 47.69 (CH, C-9)$^{A/a}$, 42.61 (CH, C-17)$^{A/a}$, 42.56 (CH, C-17)$^{A/a}$, 42.30 (CH_2, C-11)$^{B/b}$, 41.68 (CH_2, C-11)$^{A/a}$, 41.56 (CH_2, C-11)$^{A/a}$, 41.03 (CH_2, C-11)$^{B/b}$, 41.00 (CH_2, C-3'/C-5')$^{B/b}$, 40.89 (2 × CH_2, C-3'/C-5')$^{A/a}$, 40.58 (CH_2, C-3'/C-5')$^{A/a}$, 40.48 (CH_2, C-3'/C-5')$^{A/a}$, 40.37 (CH_2, C-3'/C-5')$^{B/b}$, 37.90 (C, C-10)$^{B/b}$, 37.77 (C, C-10)$^{B/b}$, 37.70 (C, C-10)^{Aa}, 37.17 (CH, C-8)$^{B/b}$, 36.98 (CH, C-8)$^{B/b}$, 36.93 (2 × CH, C-8)^{Aa}, 35.22 (CH_3, C-7'/C-9')$^{A/a}$, 34.94 (CH_3, C-7'/C-9')$^{A/a}$, 34.86 (CH_2, C-1)$^{B/b}$, 34.83 (CH_2, C-1)$^{B/b}$, 34.72 (CH_2, C-1)$^{A/a}$, 34.71 (CH_2, C-1)$^{A/a}$, 34.67 (CH_3, C-7'/C-9')$^{B/b}$, 34.64 (CH_3, C-7'/C-9')$^{B/b}$, 34.56 (CH_3, C-7'/C-9')$^{A/a}$, 32.40 (4 × CH_2, C-6, C-7)^{Aa}, 31.41 (CH_2)$^{B/b}$, 31.36 (CH_2)$^{B/b}$, 30.40 (CH_2, C-2)^{aA}, 27.07 (CH_2, C-16)^{a}, 26.24 (CH_2)$^{B/b}$, 26.01 (CH_2, C-15)^{a}, 25.89 (CH_2, C-15)^{A}, 25.13 (CH_2, C-16)^{A}, 24.47 (CH_2)$^{B/b}$, 22.99 (CH_2)$^{B/b}$, 22.28 (CH_2)$^{B/b}$, 21.09 (CH_3, C-8'/C-10')$^{A/a}$, 21.03 (CH_3, C-8'/C-10')$^{A/a}$, 20.97 (CH_3, C-8'/C-10')$^{A/a}$, 20.89 (CH_3, C-8'/C-10')$^{A/a}$, 20.77 (CH_3, C-8'/C-10')$^{B/b}$, 19.82 (CH_3, C-21)$^{B/b}$, 19.26 (CH_3, C-21)$^{B/b}$, 18.47 (CH_3, C-21)$^{A/a}$, 18.35 (CH_3, C-21)$^{A/a}$, 17.89 (CH_2, C-4')$^{B/b}$, 17.85 (CH_2, C-4')$^{B/b}$, 17.74 (CH_2, C-4')^{Aa}, 17.61 (CH_3, C-19)$^{A/a}$, 17.59 (CH_3, C-19)$^{A/a}$, 17.56 (CH_3, C-19)$^{B/b}$, 17.54 (CH_3, C-19)$^{B/b}$.

MS (ESI+) *m/z*, (%): 500 (100, $[M+H]^+$), 522 (3, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{50}NO_4$ 500.3734; Found 500.3732;

Anal. Calcd for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88; N, 2.80; Found: C, 74.65; H, 9.96; N, 2.62.

***ent*-13β-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-18-nor-13,17-seco-14β-pregna-4,17(20)-diene-3,12-dione (*ent*-192)**



cis-Alkoxyamine *ent*-**184b** (68 mg, 136 µmol, mixture of *E*/*Z* isomers 3:2) was dissolved in acetone (5 mL) and water (500 µL) and 1 M aq. HCl (250 µL, 250 µmol) was added to the reaction mixture. After 5 min, the reaction was quenched with saturated aq. $NaHCO_3$ (25 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and the solution was concentrated *in vacuo*. Flash chromatography of the residue on silica gel (1 g) in 10% EtOAc/hexanes afforded 59 mg (95%) of *ent*-**192** as a white foam.

Mixture of $\Delta^{17(20)}$-*E* and $\Delta^{17(20)}$-*Z* isomers in 3:2 ratio. NMR signals of minor *Z*-isomer are denoted with an *.

$[\alpha]_D^{20}$ −119.3 (*c* 0.609, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 973 (=C-H), 1011, 1134, 1362, 1376 (CH_3), 1454, 1462 (CH_2), 1618 (C=C), 1667 (C=O), 1715 (C=O), 2871 (CH_3), 2935 (CH_2), 2974 (CH_3).

^{1}H NMR (600 MHz, d_6-DMSO) δ 5.67 (d, *J* = 1.8 Hz, 2H, CH-4, CH-4*), 5.40 (m, 1H, CH-20), 5.37 (m, 1H, CH-20)*, 5.30 (m, 1H, CH-17)*, 5.27 (m, 1H, CH-17), 3.795 (dd, *J* = 3.5, 1.2 Hz, 1H, CH-13α), 3.76 (dd, *J* = 3.5, 1.2 Hz, 1H, CH-13α)*, 2.750 (t, *J* = 12.5 Hz, 1H, CH-11β), 2.745 (t, *J* = 12.5 Hz, 1H, CH-11β)*, 2.50 (m, 2H, CH-6β, CH-6β*), 2.40 (tdd, *J* = 12.4, 4.2, 3.1 Hz, 2H, CH-8β, CH-8β*), 2.376 (ddd, *J* = 16.7, 14.5, 5.1 Hz, 2H, CH-2β, CH-2β*), 2.31 (m, 2H, CH-6α, CH-6α*), 2.30 (dddd, *J* = 8.7, 6.7, 3.5, 3.1 Hz, 1H, CH-14β), 2.29 (dddd, *J* = 8.7, 6.7, 3.5, 3.1 Hz, 1H, CH-14β)*, 2.16 (ddd, *J* = 16.7, 4.4, 3.3 Hz, 2H, CH-2α, CH-2α*), 2.12 (ddd, *J* = 12.5, 4.5, 1.2 Hz, 2H, CH-11α, CH-11α*), 2.03 (m, 1H, CH-16a), 1.96 (m, 1H, CH-16a)*, 1.92 (ddd, *J* = 13.4, 5.1, 3.3 Hz, 2H, CH-1β, CH-1β*), 1.84 (m, 1H, CH-16b), 1.80 (m, 1H, CH-16b)*, 1.65 (m, 2H, CH-7β, CH-7β*), 1.64 (ddd, *J* = 14.5, 13.4, 4.4 Hz, 2H, CH-1α, CH-1α*), 1.57 (m, 3H, CH_3-21), 1.56 (td, *J* = 12.5, 4.5 Hz, 2H, CH-9α, CH-9α*), 1.54 (m, 3H, CH_3-21)*, 1.52 (m, 2H, CH-4'a, CH-4'a*), 1.47 (m, 4H, CH-3'a, CH-5'a, CH-3'a*, CH-5'a*), 1.365 (m, 6H, CH-7α, CH-3'b, CH-5'b, CH-7α*, CH-3'b*, CH-5'b*), 1.36 (m, 2H, CH-15a, CH-15a*), 1.27 (m, 2H, CH-4'b, CH-4'b*), 1.205 (s, 3H, CH_3-19), 1.203 (s, 3H, CH_3-19)*, 1.14 (s, 12H, CH_3-7', CH_3-9', CH_3-7'*, CH_3-9'*), 1.10 (s, 6H, CH_3-10', CH_3-10'*), 0.90 (s, 6H, CH_3-8', CH_3-8'*), 0.76 (m, 2H, CH-15b, CH-15b*).

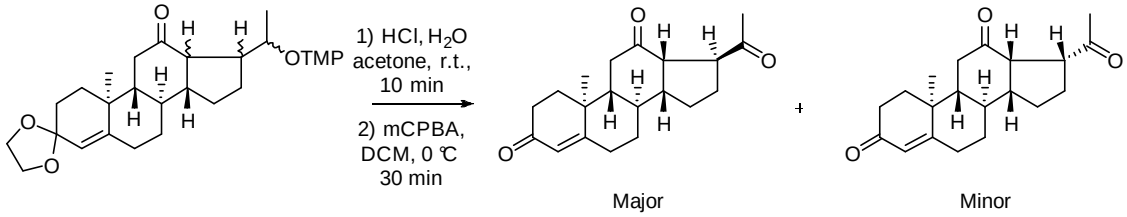
^{13}C NMR (150.9 MHz, d_6-DMSO) δ 211.42 (C, C-12)*, 211.41 (C, C-12), 198.09 (C, C-3)*, 198.08 (C, C-3), 168.93 (C, C-5)*, 168.90 (C, C-5), 130.6 (CH, C-17)*, 129.8 (CH, C-17), 125.49 (CH, C-20), 125.47 (CH, C-20)*, 123.84 (CH, C-4), 123.83 (CH, C-4)*, 90.36 (CH, C-13), 90.34 (CH, C-13)*, 59.8 (C, C-2', C-2'*), 59.0 (C, C-6', C-6'*), 47.6 (CH, C-9, C-9*), 45.2 (CH, C-14), 44.8 (CH, C-14)*, 40.0 (CH_2, C-3', C-5', C-3'*, C-5'*), 38.8 (C, C-10, C-10*), 37.7 (CH_2, C-11, C-11*), 34.5 (CH_2, C-1, C-1*), 33.7 (CH_3, C-8', C-8'*), 33.6 (CH_2, C-2, C-2*), 33.3 (CH_3, C-7', C-7'*), 33.2 (CH, C-8, C-8*), 32.19 (CH_2, C-6)*, 32.18 (CH_2, C-6), 30.0 (CH_2, C-16)*, 29.2 (CH_2, C-7)*, 29.1 (CH_2, C-7), 24.4 (CH_2, C-16), 23.33 (CH_2, C-15), 23.32 (CH_2, C-15)*, 20.1 (CH_3, C-9', C-9'*), 20.0 (CH_3, C-10', C-10'*), 17.9 (CH_3, C-21), 17.0 (CH_3, C-19, C-19*), 16.7 (CH_2, C-4', C-4'*), 12.8 (CH_3, C-21)*.

MS (ESI+) *m/z*, (%): 456 (100, $[M+H]^+$), 478 (21, $[M+Na]^+$), 934 (33, $[2M+Na]^+$), 1389 (12, $[3M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{46}NO_3$ 456.3472; Found 456.3473;

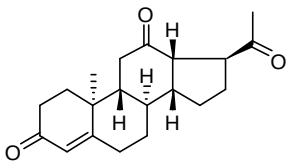
Stereoselectivity of cyclization – control experiments:

***Deprotection of 14α cyclized alkoxyamines* 186A,a**



The cyclization product *ent*-**186A,a** (50 mg, 100 µmol) was dissolved in acetone (1 mL) and 5% aq. HCl (100 µL) was added to the stirred solution. After 10 min at rt, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and the products were extracted into EtOAc (3 × 3 mL). The combined organic fraction was dried over Na_2SO_4 and evaporated *in vacuo* to afford 45 mg of the crude diketone, which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. *m*-CPBA (30 mg, 174 µmol) was added to the stirred solution. The reaction was stirred at 0 °C for 30 min and quenched with 15% aq. ascorbic acid (10 mL). The biphasic mixture was diluted with hexane (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to afford 29.1 mg (92%) of a crude 3:1 mixture *ent*-**193** : *ent*-**194**.

***ent*-18-Nor-13α,17α-pregn-4-ene-3,12,20-trione (*ent*-193)**



Colorless prisms, Mp 90-92 °C.

IR (ATR); ν[cm^{-1}]: 867 (=C-H), 1151, 1188, 1246, 1272, 1360, 1425 (CH_2), 1625 (C=C), 1676 (enone), 1694 (C=O), 1714 (acetyl), 2857 (CH_2), 2869 (CH_3), 2942 (CH_2), 2961 (CH_3).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.79 (br d, *J* = 2.1 Hz, 1H, CH-4), 3.37 (m, 1H, CH-17), 3.18 (dd, *J* = 11.0, 7.4 Hz, 1H, CH-13), 2.52 (m, 1H, CH-11a), 2.40 (m, 1H, CH-6a), 2.39 (m, 2H, CH_2-2), 2.31 (m, 1H, CH-6b), 2.24 (m, 1H, CH-11b), 2.22 (s, 3H, CH_3-21), 2.17 (m, 1H, CH-14), 2.14 (m, 1H, CH-7a), 2.08 (m, 1H, CH-16a), 2.06 (m, 1H, CH-15a), 1.95 (m, 1H, CH-1a), 1.89 (m, 1H, CH-9), 1.76 (m, 1H, CH-1b), 1.60 (m, 1H, CH-16b), 1.32 (m, 1H, CH-15b), 1.31 (m, 1H, CH-8), 1.22 (m, 1H, CH-7b), 1.16 (s, 3H, CH_3-19);

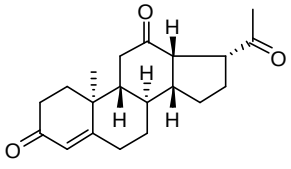
^{13}C NMR (150.9 MHz, $CDCl_3$) δ 212.0 (C, C-20), 209.0 (C, C-12), 198.9 (C, C-3), 168.8 (C, C-5), 124.2 (CH, C-4), 52.2 (CH, C-17), 52.1 (CH, C-13), 49.0 (CH, C-9), 47.7 (CH, C-14), 38.69 (C, C-10), 38.68 (CH+CH_2, C-8, C-11), 35.1 (CH_2, C-1), 33.5 (CH_2, C-2), 32.74 (CH_2, C-7), 32.70 (CH_2, C-15), 31.9 (CH_2, C-6), 29.16 (CH_3, C-21), 29.15 (CH_2, C-16), 17.7 (CH_3, C-19).

MS (ESI+) *m/z*, (%): 315 (44, $[M+H]^+$), 337 (100, $[M+Na]^+$), 629 (1, $[2M+H]^+$), 651 (84, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{27}O_3$ 315.1955; Found 337.1957; $[M+Na]^+$ Calcd for $C_{20}H_{26}NaO_3$ 337.1774; Found 337.1774;

X-ray data are available in Appendix C.

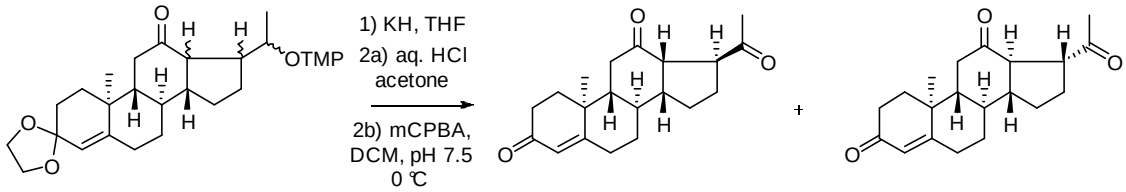
***ent*-18-Nor-13α-pregn-4-ene-3,12,20-trione (*ent*-194)**



^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (br s, 1H, CH-4), 3.60 (td, *J* = 7.9, 2.9 Hz, 1H, CH-17), 2.79 (br dd, *J* = 11.1, 7.9 Hz, 1H, CH-13), 2.44 (m, 2H, CH-6a, CH-11a), 2.39 (m, 3H, CH_2-2, CH-11b), 2.34 (m, 1H, CH-6b), 2.17 (s, 3H, CH_3-21), 2.01 (m, 1H, CH-14), 2.06 (m, 1H, CH-15a), 1.98 (m, 1H,

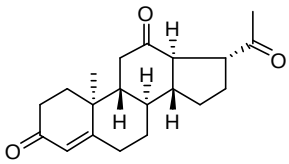
CH-1a), 1.91 (m, 1H, CH-16a), 1.81 (m, 1H, CH-16b), 1.73 (m, 1H, CH-1b), 1.64 (m, 1H, CH-9), 1.45 (m, 1H, CH-15b), 1.23 (s, 3H, CH_3-19); Hydrogen atoms CH_2-7 and CH-8 could not be assigned.
^{13}C NMR (150.9 MHz, $CDCl_3$) δ 213.4 (C, C-12), 210.0 (C, C-20), 199.0 (C, C-3), 169.8 (C, C-5), 123.8 (CH, C-4), 56.5 (CH, C-17), 52.05 (CH, C-13), 48.6 (CH, C-9), 44.6 (CH, C-14), 39.4 (CH_2, C-11), 38.6 (C+CH, C-10, C-8), 35.2 (CH_2, C-1), 33.6 (CH_2, C-2), 32.9 (CH_2, C-7), 32.1 (CH_2, C-6), 31.0 (CH_2, C-15), 29.1 (CH_3, C-21), 28.4 (CH_2, C-16), 17.9 (CH_3, C-19).
Data taken from a mixture with *ent*-**193**.

Isomerization of 14α cyclised alkoxyamines* 186A,a *and deprotection



A suspension of KH (ca. 35% w/v in mineral oil, 60 mg of pure KH; 1.50 mmol) was transferred to a pre-dried Schlenk flask and washed with dry pentane (3 × 2 mL). The remaining solvent was evaporated *in vacuo* and the flask was back-filled with nitrogen. A solution of ketone *ent*-**186A,a** (63 mg, 126 µmol) in THF (7 mL) was added dropwise at rt, which caused immediate foaming of the mixture. The suspension was stirred at rt for 2 h, quenched with saturated aq. NH_4Cl (15 mL) and the products were extracted into EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (15 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in acetone (1 mL) and 5% aq. HCl (300 µL) was added to the stirred solution. After 15 min at rt, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and aq. phosphate buffer (pH 7.5, 0.5 M, 3 mL) and the biphasic mixture was cooled to 0 °C. *m*-CPBA (33 mg, 189 µmol) was added portionwise to the stirred solution. The reaction was stirred at 0 °C for 45 min and was quenched with 10% aq. $Na_2S_2O_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were washed with $NaHCO_3$ (2 × 5 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (0.9 g) in 30% EtOAc/hexanes to afford 34.5 mg (87%) of a 5:2 mixture of *ent*-**193**:*ent*-**195**. Further chromatography on silica gel (0.9 g) in 30% MTBE/hexanes afforded 12 mg of an enriched sample of *ent*-**195**, which was crystallized from Et_2O/hexane to furnish 6 mg of pure *ent*-**195**.

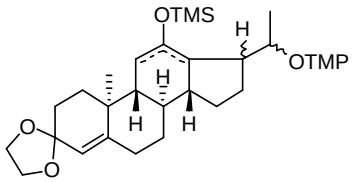
***ent*-18-Norpregn-4-ene-3,12,20-trione (*ent*-195)**
Colorless prisms, Mp 173-175 °C (Et_2O/hexane).
IR ($CHCl_3$); ν[cm^{-1}]: 1176, 1233, 1357, 1377 (CH_3), 1619 (C=C), 1669, 1709 (C=O), 2917, 2943 (CH_2), 2970 (CH_3).



^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (br d, *J* = 2.1 Hz, 1H, CH-4), 3.23 (ddd, *J* = 11.2, 10.0, 6.5 Hz, 1H, CH-17), 2.78 (ddd, *J* = 11.2, 10.0, 1.3 Hz, 1H, CH-13), 2.47 (m, 1H, CH-6a), 2.42 (m, 1H, CH-11a), 2.41 (m, 1H, CH-2a), 2.38 (m, 1H, CH-2b), 2.35 (m, 1H, CH-6b), 2.31 (m, 1H, CH-11b), 2.23 (s, 3H, CH_3-21), 2.06 (m, 1H, CH-7a), 1.99 (m, 2H, CH-16a, CH-15a), 1.94 (m, 1H, CH-1a), 1.82 (m, 2H, CH-8, CH-16b), 1.72 (m, 1H, CH-1b), 1.50 (m, 1H, CH-9), 1.43 (m, 2H, CH-14, CH-15b), 1.24 (s, 3H, CH_3-19), 1.17 (m, 1H, CH-7b);

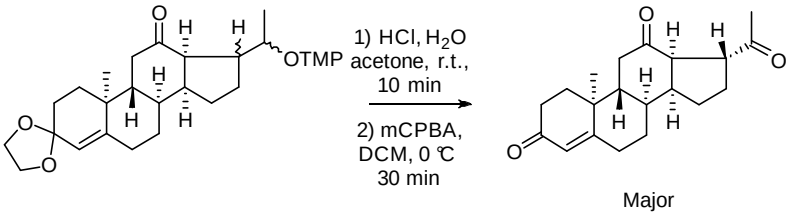
^{13}C NMR (150.9 MHz, $CDCl_3$) δ 209.9 (C, C-20), 208.0 (C, C-12), 198.7 (C, C-3), 168.4 (C, C-5), 124.7 (CH, C-4), 58.3 (CH, C-13), 54.9 (CH, C-9), 53.0 (CH, C-14), 48.3 (CH, C-17), 41.3 (CH, C-8), 41.0 (CH_2, C-11), 38.9 (C, C-10), 35.4 (CH_2, C-1), 33.7 (CH_2, C-2), 32.2 (CH_2, C-6), 31.1 (CH_2, C-7), 29.9 (CH_3, C-21), 29.7 (CH_2, C-15), 26.6 (CH_2, C-16), 17.1 (CH_3, C-19).
MS (CI+) *m/z*, (%): 315 (100, $[M+H]^+$), 343 (19, $[M+C_2H_5]^+$);
HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{27}O_3$ 315.1955; Found 315.1961;
X-ray data are available in Appendix C.

ent-3-(Ethylenedioxy)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-12-(trimethylsilyloxy)-18-nor-17ξ-pregna-4,12-diene (_ent_-196) and _ent_-3-(Ethylenedioxy)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-12-(trimethylsilyloxy)-18-nor-17ξ,13α-pregna-4,11-diene (_ent_-197)



A suspension of KH (ca. 35% w/v in mineral oil, 60 mg of pure KH; 1.50 mmol) was transferred to a pre-dried Schlenk flask and washed with dry pentane (3 × 2 mL). The remaining solvent was evaporated *in vacuo* and the flask was back-filled with nitrogen. A solution of ketone *ent*-**186A,a** (50 mg, 100 µmol) in THF (3 mL) was added dropwise at rt, which caused immediate foaming of the mixture. The suspension was stirred at rt for 2 h, neat TMSCl (25 µL, 200 µmol) was added and the solution was stirred for 30 min. The reaction mixture was diluted with dry pentane (7 mL) and transferred by a syringe to a mixture of saturated aq. $NaHCO_3$ (25 mL) with ice (25 mL). The mixture was subsequently extracted with pentane (3 × 10 mL), the combined organic extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 62.2 mg (108%) of a 2:1 mixture of *ent*-**196**:*ent*-**197** as a colorless oil, contaminated with hexamethyldisiloxane.
^{1}H NMR (400 MHz, $CDCl_3$) δ [5.29, 5.26 (br s, CH-4)], [4.75, 4.59, 4.34, 4.27 (m, CH-20)], [4.68, 4.67 (m, 2H, CH-11)]^K, 4.09-3.82 (m, OCH_2CH_2O), [3.26, 3.19, 2.75, 2.66, 2.58 (m, aliphatic)]^{TK}, 2.34-0.79 (m, aliphatic), [0.21, 0.19, 0.18, 0.15, 0.14, 0.11 ($SiMe_3$)].
^{13}C NMR (101 MHz, $CDCl_3$) δ [155.8, 154.6 (C, C-12)]^K, [151.13, 151.11, 150.78, 150.72, 150.19, 150.18 (C, C-5)], [140.5, 140.4, 139.8, 139.5 (C, C-12)]^T, [122.2, 121.9, 121.6, 121.3 (C, C-13)]^T, [120.14, 120.13, 119.27, 119.24, 2 × 119.06 (CH, C-4)], [105.86, 105.83, 105.81, 2 × 105.79, 105.75 (C, C-3)]^{TK}, [101.3, 100.4 (CH, C-11)]^K, [79.8, 78.7, 78.3, 77.6, 76.6, 75.9 (C, C-20)], [64.26, 64.25, 64.23, 64.22, 64.21, 64.19 (CH_2, OCH_2CH_2O)], [63.92, 2 × 63.88, 63.87, 2 × 63.86 (C, OCH_2CH_2O)], [60.4, 60.1, 59.8, 58.53, 58.46, 58.3 (C, C-2', C-6')], [51.35, 51.31, 49.8, 49.6, 49.4, 48.9, 48.8, 48.45, 48.43, 48.2, 47.8, 47.0, 45.7, 45.6, 45.0, 44.51, 44.47, 43.5, 43.0 (CH)], [40.6, 40.5, 40.4, 40.2, 40.04, 39.98 (CH_2, C-3', C-5')], [38.9, 38.7, 38.5, 38.1, 34.8, 33.2 (CH)], [37.39, 37.34, 37.2, 37.03, 36.96, 36.9 (C, C-10)], [34.36, 34.35, 34.33, 34.25, 34.04, 34.02 (CH_2, C-1)], [34.6, 34.0, 33.8, 33.7 (CH_3, C-7', C-9')], [32.4, 32.3, 32.2, 32.1, 31.9, 31.74, 31.67, 31.5, 31.08, 31.05, 30.95, 30.5, 30.3, 30.01, 29.97, 29.8, 29.52, 29.47, 29.44, 29.42, 29.41, 28.4, 28.2, 25.53, 25.52, 25.3, 24.2, 24.1, 23.7, 22.5 (CH_2)], [21.0, 20.44, 20.39, 20.30, 20.26, 20.2 (CH_3, C-8', C-10')], [19.4, 19.0, 18.4, 17.8, 17.7, 17.19, 17.16, 17.09, 16.8, 15.3, 14.2, 13.3 (CH_3, C-19, C-21)], [17.11, 17.07, 17.01, 17.00, 16.98 (CH_2, C-4')], [0.84, 0.76, 0.72, 0.6, 0.2, 0.1 (CH_3, $SiMe_3$)].
Signals of *ent*-**196** are labeled with T and are in ca. 1:1:1:1 ratio, while those of **197** are labeled K and are in ca. 1:1 ratio. The groups of signals in brackets correspond to the same type of carbon.

Deprotection of 14β cyclic alkoxyamines *ent*-**186B,b**

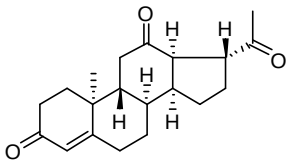


The cyclization product *ent*-**186B,b** (27 mg, 54 µmol) was dissolved in acetone (1 mL) and 5% aq. HCl (100 µL) was added. After 10 min of stirring at rt, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and the products were extracted into EtOAc (3 × 3 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated *in vacuo* to afford 21.2 mg of crude diketone, which was dissolved in CH_2Cl_2 (1.5 mL). The solution was cooled to 0 °C and *m*-CPBA (14 mg, 81 µmol) was added to the stirred solution. The reaction was stirred at 0 °C for 30 min and quenched with 15% aq. ascorbic acid (10 mL). The biphasic mixture was diluted with hexane (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic extracts were washed with sat. aq. $NaHCO_3$ (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to afford 15.1 mg (85%) of *ent*-**200** as a slowly crystallizing oil.

ent-18-Nor-14β-pregn-4-ene-3,12,20-trione (_ent_-200)

Colorless needles, Mp 104-107 °C (Hexane).

$[\alpha]_D^{20}$ −120.8 (*c* 0.187, $CHCl_3$);



IR ($CHCl_3$); ν[cm^{-1}]: 869 (=C-H), 1172, 1186, 1245, 1356, 1380 (CH_3), 1619 (C=C), 1667, 1702 (C=O), 2874 (CH_3), 2935 (CH_2), 2969 (CH_3).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (d, *J* = 2.0 Hz, 1H, CH-4), 3.75 (ddd, *J* = 9.8, 7.3, 2.1 Hz, 1H, CH-17), 3.13 (br d, *J* = 7.9 Hz, 1H, CH-13), 2.47 (dddd, *J* = 14.4, 14.0, 5.1, 2.0 Hz, 1H, CH-6a), 2.44 (m, 1H, CH-11a), 2.42 (m, 1H, CH-2a), 2.41 (m, 1H, CH-14), 2.38 (m, 1H, CH-2b), 2.34 (ddd, *J* = 14.4, 4.2, 2.5, 1H, CH-6b), 2.32 (m, 1H, CH-8), 2.27 (m, 1H, CH-11b), 2.17 (s, 3H, CH_3-21), 2.07 (m, 1H, CH-16a), 2.00 (m, 1H, CH-1a), 1.87 (dddd, *J* = 13.1, 5.1, 3.5, 2.5 Hz, 1H, CH-7a), 1.73 (m, 1H, CH-1b), 1.63 (m, 1H, CH-15a), 1.60 (m, 1H, CH-9), 1.57 (m, 1H, CH-16b), 1.31 (dddd, *J* = 14.4, 13.1, 12.5, 4.2 Hz, 1H, CH-7b), 1.23 (s, 3H, CH_3-19), 1.04 (m, 1H, CH-15b).

^{13}C NMR (150.9 MHz, $CDCl_3$) δ 210.3 (C, C-12), 209.4 (C, C-20), 198.8 (C, C-3), 168.2 (C, C-5), 124.7 (CH, C-4), 53.4 (CH, C-13), 49.1 (CH, C-17), 47.7 (CH, C-9), 47.4 (CH, C-14), 41.0 (CH_2, C-11), 38.6 (C, C-10), 36.0 (CH, C-8), 35.3 (CH_2, C-1), 33.6 (CH_2, C-2), 32.8 (CH_2, C-6), 31.1 (CH_2, C-7), 28.4 (CH_3, C-21), 26.1 (CH_2, C-16), 25.4 (CH_2, C-15), 17.4 (CH_3, C-19).

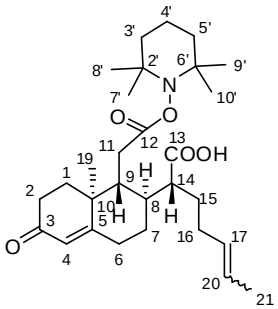
MS (CI+) *m/z*, (%): 315 (100, $[M+H]^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{27}O_3$ 315.1960; Found 315.1962;

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; Found: C, 76.63; H, 8.37;

(*R*)-2-((1*R*,2*S*,8a*S*)-1-(2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-2-oxoethyl)-8a-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)hept-5-enoic acid (*ent*-202)

The cyclized fraction *ent*-**186A,a** and *ent*-**185a** (120 mg, 239 µmol) was dissolved in acetone (3 mL) and 5% aq. HCl (100 µL) was added to the stirred solution. After 30 min of stirring at rt, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 mL) and the aq. layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated *in vacuo*



to afford 109 mg of the intermediate, which was redissolved in CH_2Cl_2 (2 mL) and the solution was cooled to 0 °C. *m*-CPBA (56 mg, 325 µmol) was added portionwise to the stirred cooled solution. The reaction was stirred at 0 °C for 45 min and quenched with 15% aq. ascorbic acid (5 mL). The mixture was extracted with hexane (10 mL) and with EtOAc (2 × 5 mL), the combined organic layers were washed twice with $NaHCO_3$ (2 × 5 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (3 g) in 10% to 40% EtOAc/hexanes to afford 26 mg (35%) of 18-nor steroids *ent*-**193** and *ent*-**194** in 3:1 ratio, followed by 30 mg (26%) of the title compound *ent*-**202**, crystallizing as colorless threads from CH_2Cl_2/hexane:

ent-**202**: Colorless needles, Mp 179-182 °C.

$[\alpha]_D^{20}$ −67.1 (*c* 0.198, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1131 (C-O), 1277 (COH), 1365, 1380 (CH_3), 1420 (CH_2) 1437, 1454, 1462 (piperidin), 1620 (C=C), 1669 (enone), 1705 (COOH dimer), 1761 (COOH, COOR), 2873 (CH_3), 2943 (CH_2), 2967, 2976 (CH_3), 3510 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 1.5 Hz, 2H, CH-4, CH-4*), 5.45-5.35 (m, 2H, CH-20, CH-20*), 5.36-5.27 (m, 2H, CH-17, CH-17*), 2.60-2.49 (m, 1H, CH-14), 2.58-2.49 (m, 2H, CH_2-7), 2.44-2.35 (m, 2H, CH_2-2), 2.33-2.24 (m, 2H, CH_2-6), 2.21-2.09 (m, 1H, CH-8), 2.15-2.03 (m, 1H, CH-9), 2.14-2.03 (m, 1H, CH-16a), 2.04-1.95 (m, 1H, CH-16a)*, 2.01-1.88 (m, 1H, CH-16b), 1.95-1.83 (m, 1H, CH-16b)*, 1.98-1.85 (m, 1H, CH-1a), 1.97-1.87 (m, 1H, CH-11a), 1.72-1.48 (m, 8H, CH_2-3', CH_2-5', CH_2-3'*, CH_2-5'*), 1.70-1.61 (m, 1H, CH-15a), 1.58 (br d, *J* = 5.0 Hz, 3H, CH_3-21)*, 1.56-1.45 (m, 1H, CH-15b), 1.55 (dd, *J* = 6.6, 1.8 Hz, 3H, CH_3-21), 1.50-1..40 (m, 4H, CH_2-4', CH_2-4'*), 1.46-1.33 (m, 1H, CH-11b), 1.21 (s, 3H, CH_3-19), 1.20 (s, 3H, CH_3-19)*, 1.17 (br s, 12H, CH_3-7', CH_3-8', CH_3-7'*, CH_3-8'*), 1.07 (br s, 6H, CH_3-9', CH_3-9'*), 1.07-1.01 (m, 1H, CH-1b), 1.04 (br s, 6H, CH_3-10', CH_3-10'*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1 (C, C-3, C-3*), 180.5 (C, C-12)*, 180.4 (C, C-12), 172.8 (C, C-13, C-13*), 168.9 (C, C-5, C-5*), 130.5 (CH, C-17)*, 129.6 (CH, C-17), 125.4 (CH, C-20)*, 124.6 (CH, C-20), 123.98 (CH, C-4)*, 123.96 (CH, C-4), 60.2 (C, C-2'/C-6'), 60.1 (C, C-2'/C-6'), 46.0 (CH, C-14)*, 45.8 (CH, C-14), 44.67 (CH, C-9), 44.64 (CH, C-9)*, 40.8 (CH, C-8)*, 40.5 (CH, C-8), 39.91 (C, C-10), 39.89 (C, C-10)*, 39.0 (CH_2, C-3', C-5'), 35.19 (CH_2, C-1), 35.16 (CH_2, C-1)*, 33.5 (CH_2, C-2, C-2*), 32.3 (CH_2, C-6, C-6*), 32.2 (CH_3, C-9', C-10')*, 31.9 (CH_3, C-9', C-10'), 31.3 (CH_2, C-16)*, 31.1 (CH_2, C-7)*, 30.9 (CH_2, C-7), 27.5 (CH_2, C-11), 27.4 (CH_2, C-11)*, 25.5 (CH_2, C-16), 24.4 (CH_2, C-15)*, 24.1 (CH_2, C-15), 20.60 (CH_3, C-7', C-8')*, 20.55 (CH_3, C-7', C-8'), 18.20 (CH_3, C-19, C-19*), 18.15 (CH_3, C-21)*, 16.9 (CH_2, C-4', C-4'*), 12.7 (CH_3, C-21).

Mixture of $^{\Delta 17(20)}$-*E* and $\Delta^{17(20)}$-*Z* isomers in 3:2 ratio. Signals of the minor *Z*-isomer are marked by an * where observable.

MS (ESI−) *m/z*, (%): 347 (40, $[M-TMP]^-$), 486 (100, $[M-H]^-$), 974 (21, $[2M-H]^-$), 996 (3, $[2M+Na-2H]^-$);

MS (ESI+) *m/z*, (%): 488 (100, $[M+H]^+$), 510 (10, $[M+Na]^+$), 998 (11, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{46}NO_5$ 488.3371; Found 488.3371;

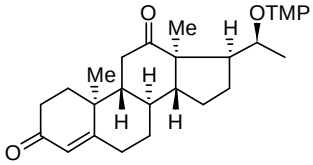
Anal. Calcd for $C_{29}H_{45}NO_5$: C, 71.42; H, 9.30; N, 2.87; Found: C, 71.23; H, 9.71; N, 2.42.

***ent*-17α-Pregn-4-ene-3,12,20-trione (*ent*-207)**

A suspension of KH (20 mg of pure KH, 0.50 mmol, ca. 35% w/v in mineral oil) was transferred to a pre-dried Schlenk flask and washed with dry pentane (3 × 2 mL). The remaining solvent was evaporated *in vacuo* and the flask was back-filled with nitrogen. A solution of ketone *ent*-**186A,a** (170 mg, 336 µmol) in THF (3 mL) was added dropwise at rt, which caused immediate foaming of the mixture. The suspension was stirred at rt for 45 min, neat methyl iodide (63 µL, 1.01 mmol) was added and the solution became cloudy. The reaction mixture was stirred for 1 h and quenched carefully with saturated aq. NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic fractions were evaporated *in vacuo*. The oily residue was redissolved in acetone (3 mL) and 5% aq. HCl (100 µL) was added to the stirred solution. After stirring at rt for 10 min, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 mL) and the products were extracted into CH_2Cl_2 (3 × 3 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated *in vacuo* to afford the crude diketone. After dissolution in CH_2Cl_2 (5 mL), the solution was cooled to 0 °C and *m*CPBA (86 mg, 0.50 mmol) was added portionwise. The reaction mixture was stirred at 0 °C for 45 min and was quenched with 10% aq. $Na_2S_2O_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were washed with $NaHCO_3$ (2 × 5 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (7 g) in 30% hexane/MTBE to afford 8.6 mg (4%) of alkoxyamine *ent*-**206**, followed by 21.2 mg (19%) of the title steroid *ent*-**207**, 27.0 mg (25%) of 18-nor steroid *ent*-**193** and 29.1 mg (27%) of 18-norsteroid *ent*-**195**.

***ent*-20*S*-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-17α-pregn-4-ene-3,12-dione (*ent*-206)**

IR (ATR); ν[cm^{-1}]: 738, 765, 1131 (C-O), 1235, 1273, 1366, 1380 (CH_3), 1427 (CH_2), 1457, 1471 (piperidin), 1623 (C=C), 1674 (enone), 1706 (C=O), 2861 (CH_3), 2934 (CH_2).



^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (br d, *J* = 1.9 Hz, 1H, CH-4), 4.95 (qd, *J* = 6.5, 1.8 Hz, 1H, CH-20), 2.48 (tdd, *J* = 14.4, 5.2, 1.9 Hz, 1H, CH-6a), 2.45 (dd, *J* = 16.6, 13.2 Hz, 1H, CH-11a), 2.45 (m, 1H, CH-14), 2.42 (m, 1H, CH-2a), 2.35 (m, 2H, CH-2b, CH-6b), 2.34 (dd, *J* = 16.6, 5.4 Hz, 1H, CH-11b), 2.02 (m, 1H, CH-7a), 1.98 (m, 1H, CH-16a), 1.95 (m, 1H, CH-17), 1.93 (ddd, *J* = 13.2, 5.0, 3.1 Hz, 1H, CH-1a), 1.83 (m, 1H, CH-15a), 1.80 (m, 1H, CH-8), 1.75 (m, 1H, CH-16b), 1.65 (m, 1H, CH-1b), 1.49 (ddd, *J* = 13.2, 11.1, 5.4 Hz, 1H, CH-9), 1.45 (m, 1H, CH-5'), 1.40 (m, 3H, CH-15b, CH_2-3'), 1.36 (m, 1H, CH-5'), 1.26 (m, 2H, CH_2-4'), 1.24 (s, 3H, CH_3-19), 1.16 (d, *J* = 6.5 Hz, 3H, CH_3-21), 1.15 (s, 3H, CH_3-7'), 1.11 (m, 1H, 7b), 1.08 (s, 3H, CH_3-9'), 1.06 (s, 3H, CH_3-18), 0.97 (s, 3H, CH_3-10'), 0.96 (s, 3H, CH_3-8').

^{13}C NMR (150.9 MHz, $CDCl_3$) δ 212.8 (C, C-12), 198.6 (C, C-3), 169.1 (C, C-5), 124.0 (CH, C-4), 74.2 (CH, C-20), 59.8 (C, C-2'), 58.4 (C, C-6'), 55.0 (C, C-13), 52.5 (CH, C-9), 51.0 (CH, C-17), 48.2 (CH, C-14), 40.6 (CH_2, C-5'), 40.0 (CH_2, C-3'), 38.0 (C, C-10), 37.7 (CH_2, C-11), 35.0 (CH_2, C-1), 34.0 (CH, C-8), 33.4 (CH_3, C-9'), 33.3 (CH_2, C-2), 32.3 (CH_3, C-7'), 32.2 (CH_2, C-6), 31.4 (CH_2, C-7), 23.8 (CH_2, C-15), 21.4 (CH_3, C-18), 20.9 (CH_3, C-8'), 20.5 (CH_3, C-10'), 19.7 (CH_2, C-16), 17.1 (CH_3, C-21), 16.8 (CH_2, C-4'), 16.4 (CH_3, C-19).

MS (ESI+) *m/z*, (%): 313 (6, $[M-TEMPOH+H]^+$), 470 (100, $[M+H]^+$), 492 (26, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{48}NO_3$ 470.3629; Found 470.3628; $[M+Na]^+$ Calcd for $C_{30}H_{47}NNaO_3$ 492.3448; Found 492.3447;

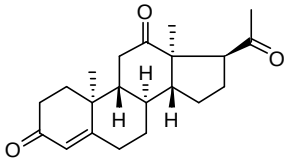
X-ray data are available in Appendix C.

***ent*-17α-Pregn-4-ene-3,12,20-trione (*ent*-207)**

The NMR spectra differ significantly from known 17α-pregn-4-ene-3,12,20-trione.[340]

Mp 224-225 °C (sublimes above 200 °C).

IR ($CHCl_3$); ν[cm^{-1}]: 1175, 1234, 1361, 1377 (CH_3), 1619 (C=C), 1670, 1711 (C=O), 2920, 2943 (CH_2), 2969 (CH_3).



^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (br d, *J* = 2.1 Hz, 1H, CH-4), 2.93 (dd, *J* = 9.3, 2.6 Hz, 1H, CH-17), 2.46 (dddd, *J* = 14.8, 13.8, 5.4, 2.1 Hz, 1H, CH-6a), 2.41 (dd, *J* = 15.5, 13.2 Hz, 1H, CH-11a), 2.38 (m, 2H, CH_2-2), 2.36 (br ddd, *J* = 14.8, 4.4, 2.4 Hz, 1H, CH-6b), 2.33 (ddd, *J* = 12.3, 11.1, 7.1 Hz, 1H, CH-14), 2.29 (s, 3H, CH_3-21), 2.28 (dd, *J* = 15.5, 5.3 Hz, 1H, CH-11b), 2.01 (dddd, *J* = 14.0, 10.6, 9.3, 2.5 Hz, 1H, CH-16a), 1.97 (dddd, *J* = 12.8, 4.4, 3.6, 2.4 Hz, 1H, CH-7a), 1.94 (dddd, *J* = 12.1, 9.1, 7.1, 2.5 Hz, 1H, CH-15a), 1.89 (ddd, *J* = 13.4, 4.8, 3.3 Hz, 1H, CH-1a), 1.87 (dtd, *J* = 11.5, 11.1, 3.6 Hz, 1H, CH-8), 1.70 (dddd, *J* = 13.6, 13.4, 5.7, 0.6 Hz, 1H, CH-1b), 1.64 (dddd, *J* = 14.0, 9.1, 7.5, 2.6 Hz, 1H, CH-16b), 1.54 (ddd, *J* = 13.2, 11.1, 5.3 Hz, 1H, CH-9), 1.53 (dddd, *J* = 12.3, 12.1, 10.6, 7.5 Hz, 1H, CH-15b), 1.24 (d, *J* = 0.6 Hz, 3H, CH_3-19), 1.23 (dddd, *J* = 13.8, 12.8, 11.5, 4.4 Hz, 1H, CH-7b), 1.12 (s, 3H, CH_3-18).

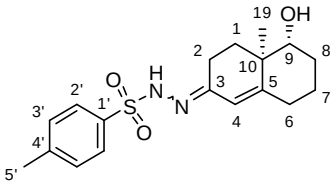
^{13}C NMR (150.9 MHz, $CDCl_3$) δ 212.9 (C, C-20), 211.5 (C, C-12), 198.8 (C, C-3), 168.7 (C, C-5), 124.6 (CH, C-4), 60.6 (C, C-13), 54.8 (CH, C-17), 53.3 (CH, C-9), 49.4 (CH, C-14), 38.5 (C, C-10), 37.2 (CH_2, C-11), 35.2 (CH_2, C-1), 34.5 (CH, C-8), 33.7 (CH_2, C-2), 32.7 (CH_3, C-21), 32.5 (CH_2, C-6), 31.3 (CH_2, C-7), 25.5 (CH_2, C-16), 24.8 (CH_2, C-15), 19.8 (CH_3, C-18), 16.8 (CH_3, C-19).

MS (CI+) *m/z*, (%): 329 (100, $[M+H]^+$), 357 (20, $[M+C_2H_5]^+$);

HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{29}O_3$ 329.2111; Found 329.2118;

X-ray data are available in Appendix C.

***N'*-((4a*R*,5*R*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-ylidene)-4-methylbenzenesulfonohydrazide (*ent*-209)**



Ketone *ent*-152 (222 mg, 1 mmol) was dissolved anhydrous MeOH (5 mL) and Et_3N (14 µL, 0.10 mmol). *p*-Toluenesulfonyl hydrazide (279 mg, 1.50 mmol) was added and the mixture was stirred at rt overnight, causing complete consumption of starting material. $NaBH_4$ (756 mg, 20 mmol) was added portionwise and the mixture was refluxed for 14 h. The reaction was carefully quenched by 5% aq. citric acid (25 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic fractions were washed with saturated aq. $NaHCO_3$ (25 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Crystallization from benzene/hexane afforded 240 mg (69%) of *ent*-209 in 3:1 *E*/*Z* ratio as colorless crystals.

Mp 127-129 °C.

$[\alpha]_D^{20}$ −169.3 (*c* 0.310, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 814, 903, 929, 1035, 1047, 1094 (Ph), 1161 (SO_2), 1308, 1325, 1420 (CH_2), 1603 (Ph), 1633 (C=C), 2840 (CH_2), 2878 (CH_3), 2952 (CH_2), 3080 (NH), 3468 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 4H, CH-2', CH-2'*), 7.56 (br s, NH), 7.31 (d, *J* = 8.2 Hz, 4H, CH-3', CH-3'*), 6.11 (s, 1H, CH-4*), 5.89 (s, 1H, CH-4), 3.32 (dd, *J* = 11.7, 4.0 Hz, 1H, CH-9*), 3.31 (dd, *J* = 11.7, 4.0 Hz, 1H, CH-9), 2.60-2.50 (m, 1H, CH-2a), 2.42 (s, 6H, CH-5', CH-

5'*), 2.35-2.29 (m, 1H, CH-6a*), 2.26-2.17 (m, 1H, CH-6a), 2.19-2.12 (m, 2H, CH-6b, CH-6b*), 2.14-2.08 (m, 1H, CH-2b), 2.10-2.03 (m, 2H, CH-1a, CH-2a*), 2.06-1.99 (m, 1H, CH-1a*), 1.88-1.75 (m, 2H, CH-7a, CH-7a*), 1.84-1.73 (m, 2H, CH-8a, CH-8a*), 1.70-1.57 (m, 2H, CH-8b, CH-8b*), 1.59-1.53 (m, 2H, CH-1b, CH-1b*), 1.37-1.27 (m, 3H, CH-7b, CH-7b*, CH-2b*), 1.09 (s, 3H, CH_3-19*), 1.03 (s, 3H, CH_3-19).

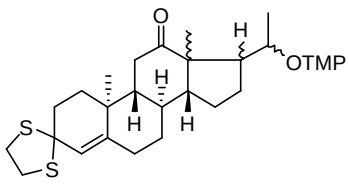
^{13}C NMR (101 MHz, $CDCl_3$) ~154.8 (C, C-5), 144.0 (C, C-4'), 135.4 (C, C-1'), 129.6 (CH, C-3', C-3'*), 128.13 (CH, C-2'*), 128.08 (CH, C-2'), 122.2 (br CH, C-4), 112.64 (br CH, C-4*), 78.5 (CH, C-9), 78.1 (CH, C-9'), ~42.1 (C, C-10*), 40.8 (C, C-10), 34.2 (CH_2, C-1*), 33.1 (CH_2, C-1), 32.6 (CH_2, C-6*), 31.5 (CH_2, C-6), 30.5 (CH_2, C-8), 30.3 (CH_2, C-8*), 27.10 (CH_2, C-2*), 23.7 (CH_2, C-7*), 23.6 (CH_2, C-7), 21.6 (CH_3, C-5', C-5'*), 20.5 (CH_2, C-2*), 16.1 (CH_3, C-19*), 15.3 (CH_3, C-19). Signals of the minor *Z*-diastereomer are marked by an *. Carbons C-3, C-3*, C-5*, C-1'* and C-4'* were lost in signal noise.

MS (ESI+) *m/z*, (%): 349 (57, $[M+H]^+$), 371 (49, $[M+Na]^+$), 697 (12, $[2M+H]^+$), 719 (100, $[2M+Na]^+$), 1067 (27, $[3M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_3S$ 349.1580; Found 349.1582; $[M+Na]^+$ Calcd for $C_{18}H_{25}N_2NaO_3S$ 371.1400; Found 349.1401;

Anal. Calcd for $C_{78}H_{102}N_8O_{12}S_4$ (with 1/4 equiv of benzene): C, 63.65; H, 6.98; N, 7.61; Found: C, 63.95; H, 6.87; N, 7.29.

ent-3-(Ethylenedithio)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-17ξ,13ξ-pregn-4-en-12-one (210)



A suspension of KH (cca 35% w/v in mineral oil, 205 mg of KH; 5.13 mmol) was transferred to a pre-dried Schlenk flask and washed with dry pentane (3 × 2 mL). The remaining solvent was evaporated at low pressure and the flask was back-filled with nitrogen. A solution of ketone *ent*-**186A,a** (500 mg, 1.0 mmol) in THF (10 mL) was added dropwise at rt, which caused immediate foaming of the mixture. The suspension was stirred at rt for 90 min and the supernatant was transferred via cannula to another pre-dried Schlenk flask. Neat methyl iodide (188 µL, 3.02 mmol) was added at once to this solution, turning the solution cloudy. The reaction mixture was stirred for another 30 min and quenched carefully with saturated aq. NH_4Cl (25 mL). The mixture was extracted with EtOAc (3 × 25 mL), the combined organic fractions were dried over Na_2SO_4 and evaporated *in vacuo*. The solution was concentrated *in vacuo* to afford 474 mg (92%) of an inseparable mixture of alkylated products *ent*-**205** as a white foam. The crude mixture was dissolved in acetone (15 mL), 5% aq. HCl (0.5 mL) was added and the mixture was stirred at rt for 10 min. The reaction was quenched with saturated aq. $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (3 × 15 mL). The organic extracts were dried over Na_2SO_4 and evaporated to afford 437 mg of a pale yellow oil, which was dissolved in glacial AcOH (1.42 mL). Ethane-1,2-dithiol (82 µL, 970 µmol) and dried *p*TsOH (191 mg, 1.11 mmol) were added, the mixture was stirred at rt for 1 h and poured carefully into 10% aq. Na_2CO_3 (150 mL). The emulsion was extracted with EtOAc (3 × 25 mL), the organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 50 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (15 g) in 5% to 20% EtOAc/hexanes to afford 352.7 mg (64%) of a first fraction of thioketals *ent*-**210a**, followed by 76.0 mg (14%) of a second fraction of thioketals *ent*-**210b**, both isolated as a white foam.

ent-**210a**: IR ($CHCl_3$); ν[cm^{-1}]: 1132, 1364, 1375 (CH_3), 1440, 1457 (CH_2), 1645 (C=C), 1696 (C=O), 2872 (CH_3), 2934 (CH_2), 2973 (CH_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (m, 1H, CH-4), 4.94 (m, CH-20), 4.67 (m, CH-20), 4.09 (m, CH-20), 4.09 (m, CH-20), 3.98 (m, CH-20), 3.92 (m, CH-20), 3.41-3.31 (m, 3H, SCH_2CH_2S), 3.28-3.18 (m, 1H, SCH_2CH_2S), 2.50-0.80 (m, aliphatic).

MS (ESI+) *m/z*, (%): 546 (100, $[M+H]^+$), 560 (87, $[M^2+H]^+$); Where M^2 is doubly alkylated product.

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{52}NO_2S_2$ 546.3434; Found 546.3436;

The complex mixture *ent*-**210a** consisted of at least six compounds, as is apparent from number of signals of CH-20. In all compounds, a thioketal at C-3 was present, while C-12 was carbonyl.

ent-**210b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (br s, 1H, CH-4), 5.54 (br s, 1H, CH-4), 4.31 (qd, *J* = 6.6, 4.3 Hz, 1H, CH-20), 4.31 (quint, *J* = 6.1 Hz, 1H, CH-20), 3.41-3.31 (m, 6H, SCH_2CH_2S), 3.28-3.18 (m, 2H, SCH_2CH_2S), 2.50-0.80 (m, aliphatic), 1.17 (d, *J* = 6.1 Hz, 3H, CH_3-21), 1.11 (br s, CH_3-7', CH_3-8', CH_3-9', CH_3-10'), 1.09 (s, 3H, CH_3-18), 1.05 (s, 3H, CH_3-19), 1.04 (s, 3H, CH_3-19), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3-21).

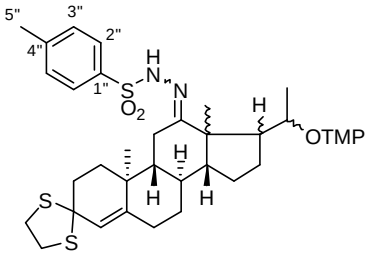
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0 (C, C-12), 213.1 (C, C-12), 144.6 (C, C-5), 144.5 (C, C-5), 125.05 (CH, C-4), 125.03 (CH, C-4), 80.4 (CH, C-20), 76.3 (CH, C-20), 65.3 (2 × C, C-3), 60.4 (br C, C-2'), 58.7 (br C, C-6'), 56.9 (CH, C-13), 55.8 (C, C-13), 53.4 (CH, C-9) 53.0 (CH, C-9), 50.4 (CH), 50.0 (CH), 48.8 (CH, CH-17), 47.6 (CH, CH-17), 40.3 (2 × CH_2, C-3', C-5'), 40.05 (CH_2), 39.99 (CH_2), 39.97 (CH_2), 39.52 (CH_2), 39.47 (CH_2), 38.4 (CH_2), 37.62 (CH_2), 37.59 (CH), 37.0 (C, C-10), 36.60 (CH_2), 36.53 (C, C-10), 36.48 (CH_2), 34.8 (CH), 34.2 (2 × CH_3, C-7', C-9'), 32.7 (CH_2), 32.2 (CH_2), 31.61 (CH_2), 31.57 (CH_2), 29.87 (CH_2), 26.8 (CH_2), 24.5 (CH_2), 22.5 (CH_2), 21.0 (CH_2), 20.6 (2 × CH_3, C-8', C-10'), 18.5 (CH_3, C-19), 17.8 (CH_3, C-19), 17.23 (CH_2, C-4'), 17.19 (CH_2, C-4'), 16.9 (CH_3, C-21), 16.5 (CH_3, C-21).

The mixture *ent*-**210b** consisted of two major compounds, one with 18-Me, one without (1:1, forming ca 80% of the mixture, based on integration of ^{1}H NMR spectra).

MS (ESI+) *m/z*, (%): 532 (47, $[M^0+H]^+$), 546 (100, $[M+H]^+$); M^0 is 18-norsteroid *ent*-**186**.

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{52}NO_2S_2$ 546.3434; Found 546.3433;

ent-3-(Ethylenedithio)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-17ξ,13ξ-pregn-4-en-12-one _N'_-(4-methylbenzenesulfonyl)hydrazone (_ent_-211)



Ketone *ent*-**210a** (100 mg, 183 μmol) was dissolved in glacial acetic acid (1.0 mL), dry *p*TsOH (33 mg, 192 μmol) and *p*-toluenesulfonyl hydrazide (41 mg, 220 μmol) were added and the solution was warmed to 70 °C overnight. The reaction mixture was slowly poured into 1 M aq. Na_2CO_3 (25 mL), diluted with saturated aq. $NaHCO_3$ to 50 mL and the suspension was extracted with EtOAc (3 × 25 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (3 g) in 6% to 10% EtOAc/hexanes to afford 49.4 mg (49%) of recovered starting material *ent*-**210a**, followed by 24.1 mg (18%) of 2:1 mixture of diastereomers *ent*-**211** as a colorless oil.

IR ($CHCl_3$); ν[cm^{-1}]: 1093 (Ph), 1165 (SO_2), 1363, 1379 (CH_3), 1440, 1458 (CH_2), 1599 (Ph), 2855 (CH_2), 2872 (CH_3), 2930 (CH_2), 3295 (NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 4H, CH-2”, CH-2”*), 7.28 (d, *J* = 8.2 Hz, 4H, CH-3”, CH-3”*), 7.27 (br s, 2H, NH), 5.50 (br s, 1H, CH-4), 5.46 (br s, 1H, CH-4)*, 4.66 (q, *J* = 6.4 Hz, 1H, CH-20), 3.68 (quint, *J* = 6.3 Hz, 1H, CH-20)*, 3.40-3.31 (m, 6H, SCH_2CH_2S, SCH_2CH_2S*), 3.27-3.18 (m, 2H, SCH_2CH_2S, SCH_2CH_2S*), 2.49 (dd, *J* = 16.8, 5.9 Hz, 1H, CH-11a), 2.43 (s, 6H, CH_3-5”, CH_3-5”*), 2.35-0.80 (m, aliphatic), 1.29 (d, *J* = 6.3 Hz, 3H, CH_3-21)*, 1.16 (s, 3H, CH_3-18)*, 1.09 (d, *J* = 6.5 Hz, 3H, CH_3-21), 1.05 (s, 3H, CH_3-7’), 1.02 (s, 3H, CH_3-19)*, 1.01 (s, 3H, CH_3-19), 0.94 (s, 3H, CH_3-8’/CH_3-10’), 0.92 (s, 3H, CH_3-8’/CH_3-10’), 0.82 (s, 3H, CH_3-18), 0.60 (s, 3H, CH_3-9’).

^{13}C NMR (101 MHz, $CDCl_3$) δ ~167.8 (C, C-12)*, 164.0 (C, C-12), 145.2 (C, C-5)*, 145.1 (C, C-5), 143.7 (2 × C, C-1”, C-1”*), 135.3 (2 × C, C-4”, C-4”*), 129.2 (2 × CH, C-2”, C-2”*), 128.3 (2 × CH, C-3”, C-3”*), 124.7 (CH, C-4), 123.9 (CH, C-4)*, 79.4 (CH, C-20)*, 74.5 (CH, C-20), 65.6 (C, C-3)*, 65.3 (C, C-3), 60.0 (CH, C-17)*, 59.8 (2 × C, C-2’, C-2’*), 58.6 (2 × C, C-6’, C-6’*), 56.8 (C, C-13)*, 52.3 (CH, C-17), 52.1 (CH, C-9), 50.7 (CH, C-14)*, 50.4 (C, C-13), 47.8 (CH, C-14), 40.6 (2 × CH_2, C-3’, C-3’*), 40.3 (2 × CH_2, C-5’, C-5’*), 40.0 (CH_2, S*C*H$_2$CH$_2$S), 39.9 (CH_2, S*C*H$_2$CH$_2$S)*, 39.48 (CH_2, S*C*H$_2$CH$_2$S)*, 39.43 (CH_2, SCH$_2$*C*H$_2$S), 38.0 (CH)*, 37.8 (CH_2, C-1)*, 37.6 (CH_2, C-1), 37.07 (CH)*, 37.02 (CH_2), 36.54 (C, C-10), 36.46 (C, C-10)*, 34.4 (CH, C-8), 33.9 (2 × CH_3, C-7’, C-7’*), 33.8 (2 × CH_3, C-9’, C-9’*), 33.4 (CH_2)*, 32.5 (CH_2), 32.4 (CH_2), 31.8 (CH_2, C-6)*, 31.6 (CH_2, C-6), 31.3 (CH_3, C-21)*, 30.3 (CH_2)*, 27.3 (CH_2)*, 24.4 (CH_2), 24.0 (CH_3, C-18), 23.9 (CH_3, C-18)*, 23.3 (CH_2, C-11), 22.6 (CH_2)*, 21.5 (2 × CH_3, C-5”, C-5”*), 21.20 (2 × CH_3, C-8’/C-10’, C-8’/C-10’*), 21.14 (CH_3, C-8’/C-10’*), 21.07 (CH_3, C-8’/C-10’), 20.1 (CH_2), 18.92 (CH_3, C-21), 18.88 (CH_3, C-19)*, 17.9 (CH_3, C-19), 17.2 (2 × CH_2, C-4’, C-4’*).

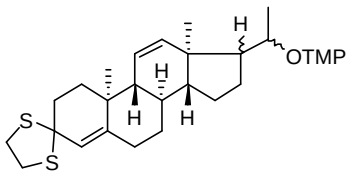
Signals of the minor diastereomer are marked by an *.

MS (ESI+) *m/z*, (%): 557 (36, $[M-TEMPOH+H]^+$), 714 (100, $[M+H]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{39}H_{60}N_3O_3S_3$ 714.3791; Found 714.3794;

ent-3-(Ethylenedithio)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-17ξ-pregna-4,11-diene (_ent_-212)

Hydrazone *ent*-**211** (23 mg, 32.2 µmol) was dissolved in THF (1.0 mL), a solution of $LiAlH_4$ (1.8 M in THF, 36 µL, 64.8 µmol) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was quenched with a few drops of saturated aq. Na_2SO_4, diluted with Et_2O (5 mL), dried over Na_2SO_4 and filtered through a pad of celite, which was washed with Et_2O (3 × 2 mL). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (1.5 g) in 5% EtOAc/hexanes to afford 8.9 mg (52%) of a single diastereomer *ent*-**212** as a colorless oil.

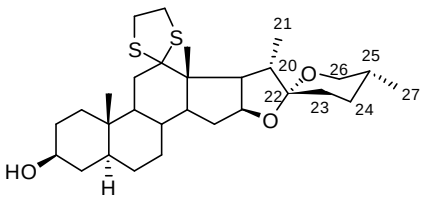


IR (ATR); ν[cm^{-1}]: 968, 1085, 1135, 1190, 1367, 1380 (CH_3), 1463 (CH_2), 2862 (CH_3), 2931 (CH_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 10.2, 2.7 Hz, 1H, CH-12), 5.53 (s, 1H, CH-4), 5.45 (dd, *J* = 10.3, 1.6 Hz, 1H, CH-11), 4.06 (br q, *J* = 6.4 Hz, 1H, CH-20), 3.41-3.33 (m, 3H, SCH_2CH_2S), 3.27-3.19 (m, 1H, SCH_2CH_2S), 2.28-2.22 (m, 1H, CH-6a), 2.24-2.14 (m, 2H, CH_2-2), 2.14-2.08 (m, 2H, CH-6b, CH-14), 1.92-1.85 (m, 2H, CH-1a, CH-16a), 1.79-1.71 (m, 2H, CH-7a, CH-17), 1.75-1.65 (m, 1H, CH-8), 1.69-1.61 (m, 3H, CH-9, CH-15a, CH-16b), 1.64-1.54 (m, 1H, CH-1b), 1.57-1.48 (m, 1H, CH-4’a), 1.49-1.29 (m, 4H, CH_2-3’, CH_2-5’), 1.32-1.22 (m, 1H, CH-4’b), 1.29-1.16 (m, 1H, CH-15b), 1.18-1.02 (m, 1H, CH-7b), 1.16 (d, *J* = 6.5 Hz, 3H, CH_3-21), 1.11 (s, 3H, CH_3-7’), 1.08 (s, 3H, CH_3-9’), 1.06 (s, 3H, CH_3-8’), 1.00 (s, 3H, CH_3-10’), 0.98 (s, 3H, CH_3-19), 0.80 (s, 3H, CH_3-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C, C-5), 137.8 (CH, C-12), 125.2 (CH, C-4), 124.5 (CH, C-11), 78.2 (CH, C-20), 65.9 (C, C-3), 60.5 (C, C-2'), 58.9 (C, C-6'), 57.1 (CH, C-9), 53.3 (CH, C-17), 48.3 (CH, C-14), 45.9 (C, C-13), 40.8 (CH_2, C-3'), 40.5 (CH_2, C-5'), 40.1 (CH_2, S*C*$H_2$$CH_2$S), 39.5 ($CH_2$, S$CH_2$*C*$H_2$S), 38.0 ($CH_2$, C-2), 37.0 (C, C-10), 36.8 (CH_2, C-1), 34.9 (CH, C-8), 34.1 (2 × CH_3, C-7', C-9'), 32.9 (CH_2, C-6), 29.4 (CH_2, C-7), 25.4 (CH_3, C-18), 24.3 (CH_2, C-15), 22.2 (CH_2, C-16), 21.0 (2 × CH_3, C-8', C-10'), 19.0 (CH_3, C-19), 18.6 (CH_3, C-21), 17.4 (CH_2, C-4').
MS (ESI+) *m/z*, (%): 530 (100, $[M+H]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{52}NOS_3$ 530.3485; Found 530.3485;
Commercial $LiAlH_4$ solution was titrated on salicylaldehyde phenylhydrazone according to the known protocol.[269]

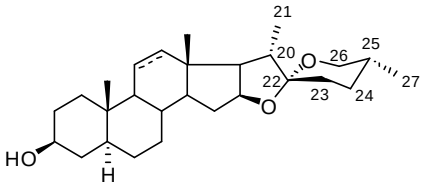
(25*R*)-12-(Ethylenedithio)-5α-spirostan-3β-ol (*nat*-214)



Hecogenin (*nat*-**213**) (1.00 g, 2.32 mmol) was suspended in ethanedithiol (4.0 mL, 47.7 mmol) and the mixture was cooled to 0 °C. Trimethylsilyl chloride (0.59 mL, 4.64 mmol) was added dropwise and the mixture was stirred in an ice bath for 2 h. The reaction mixture was poured into 10% aq. NaOH (150 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with another portion of 10% aq. NaOH (150 mL), brine (150 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford 1.13 g (96%) of thioketal *nat*-**214** as a colorless powder, which was crystallized from hot EtOAc.
$[\alpha]_D^{20}$ −43.4 (*c* 0.304, $CHCl_3$); (Lit.[341] $[\alpha]_D^{20}$ −32.0, $CHCl_3$),
Mp 254-255 °C (Lit.[341] Mp 255-257 °C, EtOH),
IR ($CHCl_3$); ν[cm^{-1}]: 981, 1041, 1054 (C-O-C), 1241, 1371, 1382 (CH_3), 1458 (CH_2), 2861 (CH_2), 2930 (CH_2), 2956 (CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (ddd, *J* = 8.5, 7.8, 6.2 Hz, 1H, CH-16), 3.59 (tt, *J* = 11.1, 4.6 Hz, 1H, CH-3), 3.49 (ddd, *J* = 10.8, 4.1, 1.9 Hz, 1H, CH-26eq), 3.37 (t, *J* = 10.9 Hz, 1H, CH-26ax), 3.30-3.10 (m, 4H, SCH_2CH_2S), 2.61 (dd, *J* = 8.7, 6.3 Hz, 1H, CH-17), 2.17 (t, *J* = 13.1 Hz, 1H, CH-11ax), 2.10-2.01 (m, 2H, CH-11eq, CH-15a), 1.88 (quint, *J* = 6.9 Hz, 1H, CH-20), 1.08 (d, *J* = 7.0 Hz, 3H, CH_3-21), 1.03 (s, 3H, CH_3-18), 0.83 (s, 3H, CH_3-19), 0.79 (d, *J* = 6.3 Hz, 3H, CH_3-27).
^{13}C NMR (101 MHz, $CDCl_3$) δ 109.3 (C, C-22), 80.1 (CH, C-16), 79.3 (C, C-12), 71.2 (CH, C-3), 66.8 (CH_2, C-26), 57.2 (CH, C-17), 55.8 (CH, C-14), 52.9 (CH, C-9), 50.4 (C, C-13), 44.6 (CH, C-5), 42.9 (CH, C-20), 42.0 (CH_2, C-11), 39.5 (CH_2, *C*H_2-S), 38.2 (CH_2, *C*H_2-S), 38.0 (CH_2, C-4), 36.7 (CH_2, C-1), 35.4 (C, C-10), 34.8 (CH, C-8), 31.8 (CH_2, C-15), 31.63 (CH_2), 31.58 (CH_2), 31.4 (CH_2), 30.3 (CH, C-25), 28.8 (CH_2), 28.5 (CH_2), 17.1 (CH_3, C-27), 16.8 (CH_3, C-18), 15.0 (CH_3, C-21), 12.5 (CH_3, C-19).
MS (ESI+) *m/z*, (%): 507 (7, $[M+H]^+$), 529 (100, $[M+Na]^+$), 545 (5, $[M+K]^+$), 1036 (4, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{47}O_3S_2$ 507.2961; Found 507.2961;
Anal. Calcd for $C_{29}H_{46}O_3S_2$: C, 68.73; H, 9.15; S, 12.65; Found: C, 68.77; H, 8.91; S, 12.29.

(25*R*)-5α-Spirostan-3β-ol or tigogenin (*nat*-215) and (25*R*)-5α-spirost-11-en-3β-ol (*nat*-216)

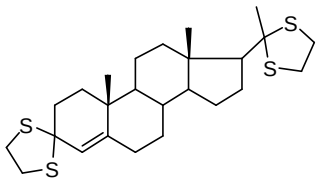
Steroid *nat*-**214** (50.0 mg, 99 μmol) was dissolved in a mixture of abs. EtOH (3 mL) and THF (1 mL), Raney nickel (500 μL of a settled suspension in EtOH, W-2 quality)[342] was suspended in the solution and the mixture was stirred at rt for 16 h. The catalyst was filtered off and the solvent was removed *in*



vacuo to afford 42.3 mg (99%) of 2:1 mixture of tigogenin (*nat*-**215**) and *nat*-**216** as a colorless powder.

The ^{1}H and ^{13}C NMR spectra of both compounds were in agreement with the literature.[294,343] The ^{1}H and ^{13}C NMR spectrum of tigogenin was identical to the sample prepared by hydrogenation of nonaflate *nat*-**221** (*vide infra*).

3,12-Bis(ethylenedithio)-pregn-4-ene (*nat*-217)



Progesterone (*nat*-**3**) (1.05 g, 3.34 mmol) was dissolved in ethanedithiol (4.0 mL, 47.7 mmol) and the mixture was cooled to 0 °C. Trimethylsilyl chloride (0.61 mL, 4.8 mmol) was added dropwise and the mixture was stirred in ice bath for 1 h. The reaction mixture was poured into 10% aq. NaOH (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with another portion of 10% aq. NaOH (50 mL), brine (50 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford crude bis(dithiolane) *nat*-**217** as a colorless powder, which was recrystallized from hexane/CH_2Cl_2 to afford 1.52 g (98%) of colorless crystals.

Mp 173-175 °C,

$[\alpha]_D^{20}$ +99.0 (*c* 0.306, $CHCl_3$);

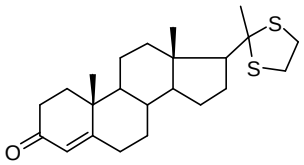
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 1H, CH-4), 3.40-3.33 (m, 4H, CH_2-S), 3.29-3.13 (m, 4H, CH_2-S), 1.86 (s, 3H, CH_3-21), 1.01 (s, 3H, CH_3-19), 0.82 (s, 3H, CH_3-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 (C, C-5), 124.0 (CH, C-4), 71.3 (C, C-20), 65.8 (C, C-3), 60.7 (CH, C-17), 55.9 (CH, C-14), 53.9 (CH, C-9), 44.2 (C, C-13) 41.4 (CH_2, CH_2-S), 40.0 (CH_2, CH_2-S), 39.9 (CH_2, C-12), 39.5 (CH_2, CH_2-S), 38.1 (CH_2, C-2), 37.33 (CH_2, CH_2-S), 37.25 (CH_2, C-1), 36.6 (C, C-10), 35.6 (CH, C-8), 35.4 (CH_3, C-21), 32.5 (CH_2, C-7), 32.1 (CH_2, C-6), 27.0 (CH_2, C-16), 24.0 (CH_2, C-15), 21.2 (CH_2, C-11), 18.5 (CH_3, C-19), 13.2 (CH_3, C-18).

The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.[344]

Anal. Calcd for $C_{25}H_{38}S_4$: C, 64.32; H, 8.21; Found: C, 64.58; H, 8.33;

12-(Ethylenedithio)-pregn-4-en-3-one (*nat*-218)



Steroid *nat*-**217** (100 mg, 214 µmol) was dissolved in a mixture of DMSO (1.8 mL), CH_2Cl_2 (1.0 mL) and H_2O (0.2 mL) and the solution was warmed to 50 °C. Acetic acid (12 µL, 210 µmol) was added with stirring, followed by IBX (90 mg, 321 µmol). The mixture was stirred at 50 °C overnight, followed by quenching with saturated aq. $NaHCO_3$ (12 mL) and 10% aq. $Na_2S_2O_3$ (12 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (3 g) in 10% EtOAc/hexanes to afford 36.6 mg (44%) of enone *nat*-**218** as colorless crystals, which were recrystallized from hexane.

Mp 220-222 °C (Hexane);

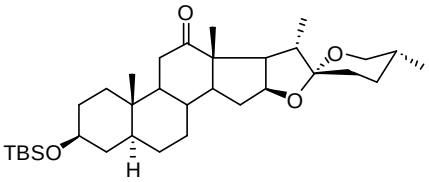
$[\alpha]_D^{20}$ +70.3 (*c* 0.182, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 867 (=C-H), 1231, 1375 (CH_3), 1435, 1450 (CH_2), 1615 (C=C), 1662 (C=O), 2857 (CH_2), 2874 (CH_3), 2942 (CH_2), 2968 (CH_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H, CH-4), 3.38 (dt, *J* = 10.4, 5.2 Hz, 1H, CH-S), 3.30-3.13 (m, 3H, CH_2-S), 1.87 (s, 3H, CH_3, C-21), 1.18 (s, 3H, CH_3, C-19), 0.86 (s, 3H, CH_3, C-18);

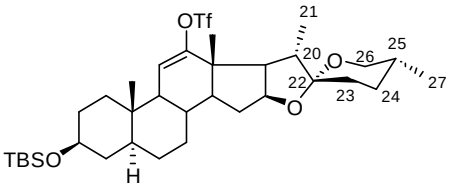
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5 (C, C-3), 171.3 (C, C-5), 123.8 (CH, C-4), 71.2 (C, C-20), 60.6 (CH, C-17), 55.7 (CH, C-14), 53.6 (CH, C-9), 44.0 (C, C-13), 41.4 (CH_2, CH_2-S), 39.7 (CH_2, C-12), 38.5 (C, C-10), 37.4 (CH_2, CH_2-S), 35.7 (CH_2, C-1), 35.6 (CH, C-8), 35.3 (CH_3, C-21), 34.0 (CH_2, C-2), 32.8 (CH_2, C-6), 31.8 (CH_2, C-7), 26.9 (CH_2, C-16), 23.9 (CH_2, C-15), 20.9 (CH_2, C-11), 17.4 (CH_3, C-19), 13.2 (CH_3, C-18);
MS (CI+) *m/z*, (%): 319 (100, $[M+H]^+$);
HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{35}OS_2$ 391.2129; Found 391.2132;
Anal. Calcd for $C_{23}H_{34}OS_2$: C, 70.72; H, 8.77; S, 16.41; Found: C, 70.30; H, 8.83;

(25*R*)-3β-(*tert*-Butyldimethylsilyloxy)-5α-spirostan-12-one (*nat*-219)



Prepared according to literature[345] as 1.17 g (93%) of colorless plates.
Mp 287-289 °C (EtOH), sublimes from 230 °C (Lit.[345] Mp 187-189 °C, EtOH);
$[\alpha]_D^{20}$ +0.3 (*c* 0.315, $CHCl_3$);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37-4.31 (m, 1H, CH-16), 3.54 (tt, *J* = 10.8, 4.8 Hz, 1H, CH-3), 3.48 (dd, *J* = 10.8, 3.9 Hz, 1H, CH-26eq), 3.35 (t, *J* = 10.9 Hz, 1H, CH-26ax), 2.51 (dd, *J* = 8.5, 6.9 Hz, 1H, CH-17), 2.39 (t, *J* = 13.9 Hz, 1H, CH-11β), 2.21 (dd, *J* = 14.1, 5.0 Hz, 1H, CH-11α), 2.14-2.08 (m, 1H), 1.90 (qd, *J* = 11.1, 3.6 Hz, 1H, CH-8), 1.06 (d, *J* = 7.0 Hz, 3H, CH_3-21), 1.04 (s, 3H, CH_3-18), 0.89 (s, 3H, CH_3-19), 0.88 (s, 9H, *t*Bu), 0.79 (d, *J* = 6.3 Hz, 3H, CH_3-27), 0.04 (s, 6H, $Si(CH_3)_2$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 213.7 (C, C-12), 109.2 (C, C-22), 79.2 (CH, C-16), 71.7 (CH, C-3), 66.9 (CH_2, C-26), 55.8 (CH, C-14), 55.6 (CH, C-9), 55.1 (C, C-13), 53.5 (CH, C-17), 44.8 (CH, C-5), 42.2 (CH, C-20), 38.4 (CH_2, C-4), 37.8 (CH_2, C-11), 36.7 (CH_2, C-1), 36.1 (C, C-10), 34.4 (CH, C-8), 31.66 (CH_2), 31.61 (CH_2), 31.4 (CH_2), 31.2 (CH_2), 30.2 (CH, C-25), 28.8 (CH_2, C-24), 28.4 (CH_2), 25.9 (CH_3, *t*Bu), 18.2 (CH_3, Si*C*$(CH_3)_3$), 17.1 (CH_3, C-27), 16.0 (CH_3, C-18), 13.3 (CH_3, C-21), 12.0 (CH_3, C-19), −4.6 (CH_3, $Si(CH_3)_2$).
Anal. Calcd for $C_{33}H_{56}O_3Si$: C, 72.74; H, 10.36; Si, 5.15; Found: C, 72.69; H, 10.43.
The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.[345]

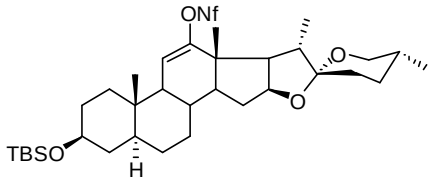
(25*R*)-3β-(*tert*-Butyldimethylsilyloxy)-12-(trifluoromethanesulfonyloxy)-5α-spirost-11-ene (*nat*-220)



Diisopropylamine (163 µL, 1.16 mmol) was dissolved in THF (3 mL), the solution was cooled to −78 °C, *n*BuLi (516 µL, 1.16 mmol, 2.25 M in hexane) was added dropwise and the mixture was stirred at −78 °C for 30 min. A solution of steroid *nat*-219 (300 mg, 0.55 mmol) in THF (7 mL) was added dropwise and the mixture was stirred at −78 °C for 1 h. *N*-Phenyl bis(trifluoromethanesulfonimide) (393 mg, 1.1 mmol) in THF (2 mL) was added at −78 °C and the mixture was allowed to slowly warm to rt overnight. The excess of base was quenched with saturated aq. NH_4Cl (50 mL) and the mixture was extracted with chloroform (3 × 10 mL). The combined organic layers were washed with saturated aq. solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (15 g) in 4% EtOAc/hexanes to afford 281 mg of crude triflate *nat*-220, followed by 104 mg (35%) of recovered *nat*-219. The crude material was purified by crystallization from hexane to obtain 204 mg (55%) of triflate *nat*-220 as a colorless powder.

Mp 148-151 °C,
$[\alpha]_D^{20}$ −36.8 (*c* 0.261, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 836 (SiMe), 1009 (C-F, C-OS), 1055, 1067 (C-O-C), 1078 (C-F, C-O-Si), 1141 (CF_3), 1246 (SO_2), 1382, 1387 (CH_3), 1413 (SO_2), 1463 (CH_2), 2858 (CH_2), 2931 (CH_2), 2956 (CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, *J* = 1.5 Hz, 1H, CH-11), 4.47 (td, *J* = 7.8, 6.2 Hz, 1H, CH-16), 3.58 (tt, *J* = 10.8, 5.2 Hz, 1H, CH-3), 3.47 (dd, *J* = 10.8, 4.2 Hz, 1H, CH-26eq), 3.34 (t, *J* = 11.0 Hz, 1H, CH-26ax), 2.13 (dd, *J* = 8.2, 6.1 Hz, 1H, CH-17), 2.05 (ddd, *J* = 11.9, 7.3, 5.8 Hz, 1H, CH-15), 1.87 (quint, *J* = 6.7 Hz, 1H, CH-20), 1.02 (s, 3H, CH_3-18), 1.02 (d, *J* = 7.0 Hz, 3H, CH_3-21), 0.88 (s, 9H, *t*Bu), 0.80 (s, 3H, CH_3-19), 0.79 (d, *J* = 6.4 Hz, 3H, CH_3-27), 0.05 (s, 6H, $Si(CH_3)_2$).
^{19}F NMR (376 MHz, $CDCl_3$) δ −74.30 (s, 3F, CF_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (C, C-12), 114.3 (CH, C-11), 109.3 (C, C-22), 80.4 (CH, C-16), 71.8 (CH, C-3), 66.9 (CH_2, C-26), 57.8 (CH, C-17), 56.4 (CH, C-9), 54.4 (CH, C-14), 45.8 (C, C-13), 44.7 (CH, C-5), 41.9 (CH, C-20), 38.3 (CH_2, C-4), 36.3 (CH_2, C-1), 36.2 (C, C-10), 33.0 (CH, C-8), 31.6 (CH_2), 31.4 (CH_2), 30.2 (CH_2), 30.1 (CH, C-25), 29.7 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 25.9 (CH_3, *t*Bu), 18.2 (C, Si*C*(CH_3)$_3$), 17.9 (CH_3, C-18), 17.1 (CH_3, C-27), 13.3 (CH_3, C-21), 13.0 (CH_3, C-19), −4.57 (CH_3, $SiCH_3$), −4.60 (CH_3, $SiCH_3$).
MS (ESI+) *m/z*, (%): 401 (100, [M−TfOH−$C_8H_{14}O$+H]$^+$), 527 (91, [M−TfOH+H]$^+$), 545 (11, [M−TBSOH+H]$^+$), 549 (85, [M−TfOH+Na]$^+$), 567 (73, [M−TBSOH+Na]$^+$), 677 (40, [M+H]$^+$), 699 (48, [M+Na]$^+$); Fragment $C_8H_{14}O$ corresponds to (*R*)-2-ethylidene-5-methyltetrahydro-2*H*-pyran.
HRMS (ESI+) *m/z*: [M+H]$^+$ Calcd for $C_{34}H_{56}F_3O_6S_1Si_1$ 677.3514; Found 677.3514;

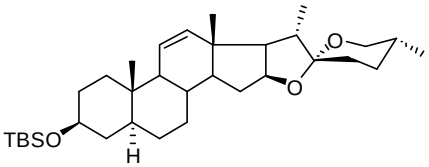
(25*R*)-3β-(*tert*-Butyldimethylsilyloxy)-12-(nonafluorobutanesulfonyloxy)-5*α*-spirost-11-ene (*nat*-221)



Diisopropylamine (163 µL, 1.16 mmol) was dissolved in THF (3 mL), the solution was cooled to −78 °C, *n*BuLi (516 µL, 1.16 mmol, 2.25 M in hexane) was added dropwise and the mixture was stirred at −78 °C for 30 min. A solution of steroid *nat*-**219** (300 mg, 0.55 mmol) in THF (7 mL) was added dropwise and the solution was stirred at −78 °C for 1 h. Nonaflyl fluoride (198 µL, 1.1 mmol) was added neat at −78 °C and the mixture was allowed to slowly warm to rt overnight. The excess of base was quenched with saturated aq. NH_4Cl (50 mL) and the mixture was extracted with chloroform (3 × 10 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (15 g) in 5% EtOAc/hexanes to afford 384 mg (84%) of nonaflate *nat*-**221** as colorless solid, followed by 47 mg (15%) of recovered *nat*-**219**.
Mp 164-167 °C (hexane),
$[\alpha]_D^{20}$ −27.6 (*c* 0.221, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 588 (SO_2), 837 (SiMe), 1010 (C-F, C-OS), 1056, 1067 (C-O-C), 1145 (CF_3), 1242 (SO_2), 1352 (C-F), 1382, 1387 (CH_3), 1414 (SO_2), 2858 (CH_2), 2930 (CH_2), 2956 (CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (d, *J* = 1.4 Hz, 1H, CH-11), 4.47 (td, *J* = 8.0, 6.0 Hz, 1H, CH-16), 3.57 (tt, *J* = 10.8, 4.9 Hz, 1H, CH-3), 3.47 (dd, *J* = 10.8, 3.9 Hz, 1H, CH-26eq), 3.34 (t, *J* = 10.9 Hz, 1H, CH-26ax), 2.13 (dd, *J* = 8.2, 6.1 Hz, 1H, CH-17), 2.05 (ddd, *J* = 11.9, 7.3, 5.8 Hz, 1H, CH-15), 1.91-1.84 (m, 1H, CH-20), 1.03 (s, 3H, CH_3-18), 1.02 (d, *J* = 7.0 Hz, 3H, CH_3-21), 0.88 (s, 9H, *t*Bu), 0.80 (s, 3H, CH_3-19), 0.79 (d, *J* = 6.3 Hz, 3H, CH_3-27), 0.05 (s, 6H, $Si(CH_3)_2$).

^{19}F NMR (376 MHz, $CDCl_3$) δ −80.64 (t, *J* = 9.7 Hz, 3F, CF_3), −109.57 (dt, *J* = 261.2, 13.9 Hz, 1F, $CF_aF_bSO_2$), −110.69 (dt, *J* = 261.5, 14.1 Hz, 1F, $CF_aF_bSO_2$), −121.02 (m, 2F, $CF_2CF_2CF_3$), −125.78 (tdt, *J* = 14.0, 6.1, 3.1 Hz, 2F, $CF_2CF_2CF_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (C, C-12), 114.6 (CH, C-11), 109.4 (C, C-22), 80.4 (CH, C-16), 71.8 (CH, C-3), 66.9 (CH_2, C-26), 57.8 (CH, C-17), 56.5 (CH, C-9), 54.5 (CH, C-14), 45.9 (C, C-13), 44.7 (CH, C-5), 41.9 (CH, C-20), 38.3 (CH_2, C-4), 36.3 (CH_2, C-1), 36.2 (C, C-10), 33.0 (CH, C-8), 31.6 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 30.16 (CH_2), 30.14 (CH, C-25), 28.9 (CH_2), 28.7 (CH_2), 25.9 (CH_3, *t*Bu), 18.2 (CH_3, $SiC(CH_3)_3$), 17.9 (CH_3, C-18), 17.1 (CH_3, C-27), 13.2 (CH_3, C-21), 13.0 (CH_3, C-19), −4.57 (CH_3, $SiCH_3$), −4.60 (CH_3, $SiCH_3$).
MS (ESI+) *m/z*, (%): 401 (41, $[M-NfOH-C_8H_{14}O+H]^+$), 527 (100, $[M-NfOH+H]^+$), 549 (53, $[M-NfOH+Na]^+$), 695 (5, $[M-TBSOH+H]^+$), 827 (30, $[M+H]^+$), 849 (28, $[M+Na]^+$); Fragment $C_8H_{14}O$ corresponds to (*R*)-2-ethylidene-5-methyltetrahydro-2*H*-pyran;
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{37}H_{56}F_9O_6SSi$ 827.3418; Found 827.3420;

(25*R*)-3β-(*tert*-Butyldimethylsilyloxy)-5α-spirost-11-ene (*nat*-222)

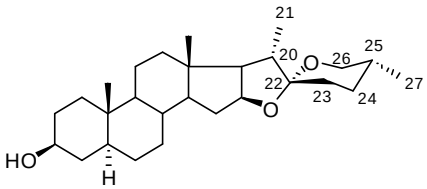


Steroid nonaflate *nat*-**221** (200 mg, 242 µmol), palladium(II) acetate (2.7 mg, 12.1 µmol), triphenylphosphine (6.3 mg, 24.2 µmol) and tributylamine (57 µL, 242 µmol) weredissolved in dry DMF (3 mL) at rt. In a separate flask, formic acid (99%, 36.6 µL, 0.97 mmol) was slowly added to a solution of tributylamine (230 µL, 0.97 mmol) in DMF (2 mL) and the resulting solution was transferred dropwise to the warm reaction mixture (60 °C), and stirred at 60 °C for 2 h. The black reaction mixture was quenched with saturated aq. NH_4Cl (25 mL) and extracted with hexane (3 × 10 mL). The combined extracts were washed subsequently with saturated aq. $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5 g) in hexanes to 4% EtOAc/hexanes to afford 102 mg (80%) of olefin *nat*-**222**, followed by 10 mg (8%) of recovered ketone *nat*-**219**. The product crystallized from CH_2Cl_2/EtOH as colorless plates.
Mp 221-224 °C,
$[\alpha]_D^{20}$ −33.0 (*c* 0.203, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 836 (SiMe), 1052, 1063 (C-O-C), 1093 (C-O-Si), 1251 (SiMe), 1376 (CH_3), 1463 (CH_2), 2858 (CH_2), 2930 (CH_2), 2957 (CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 10.0, 2.8 Hz, 1H, CH-12), 5.45 (br d, *J* = 9.9 Hz, 1H, CH-11), 4.42 (q, *J* = 7.4 Hz, 1H, CH-16), 3.57 (tt, *J* = 10.5, 4.8 Hz, 1H, CH-3), 3.47 (br dd, *J* = 10.9, 4.0 Hz, 1H, CH-26eq), 3.37 (t, *J* = 10.9 Hz, 1H, CH-26ax), 1.00 (d, *J* = 6.8 Hz, 3H, CH_3-21), 0.88 (s, 9H, *t*Bu), 0.81 (s, 3H, CH_3-18), 0.79 (d, *J* = 6.3 Hz, 3H, CH_3-27), 0.77 (s, 3H, CH_3-19), 0.05 (s, 6H, $Si(CH_3)_2$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (CH, C-12), 124.9 (CH, C-11), 109.3 (C, C-22), 80.9 (CH, C-16), 72.0 (CH, C-3), 66.8 (CH_2, C-26), 58.7 (CH, C-17), 56.9 (CH, C-9), 53.0 (CH, C-14), 44.9 (CH, C-5), 42.9 (C, C-13), 41.5 (CH, C-20), 38.6 (CH_2, C-4), 36.3 (CH_2, C-1), 36.0 (C, C-10), 34.0 (CH, C-8), 31.8 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 30.8 (CH_2), 30.3 (CH, C-25), 29.3 (CH_2), 28.8 (CH_2), 25.9 (CH_3, *t*Bu), 20.5 (CH_3, C-18), 18.3(C, $SiC(CH_3)_3$), 17.1 (CH_3, C-27), 14.5 (CH_3, C-21), 12.9 (CH_3, C-19), −4.6 (CH_3, 2 × $SiCH_3$).

MS (ESI+) *m/z*, (%): 253 (6, $[M-H_2O-C_8H_{14}O-TBSOH+H]^+$), 385 (5, $[M-H_2O-C_8H_{14}O+H]^+$), 529 (99, $[M+H]^+$), 551 (100, $[M+Na]^+$); Fragment $C_8H_{14}O$ corresponds to (*R*)-2-ethylidene-5-methyltetrahydro-2*H*-pyran;
HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{57}O_3Si_1$ 529.4072; Found 529.4071;
Anal. Calcd for $C_{33}H_{56}O_3Si$: C, 74.94; H, 10.67; Found: C, 74.79; H, 10.89.

Alternative procedure: Steroid nonaflate *nat*-**221** (30.0 mg, 36 µmol) was dissolved in dry pyridine (2 mL) and 10% palladium on carbon (30 mg) was suspended in the solution. The mixture was hydrogenated at rt with 10 bar H_2 for 5 d, when the starting material was completely consumed. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (1 g) in 5% EtOAc/hexanes to afford 16.3 mg (85%) of olefin *nat*-**222** as colorless crystals.

(25*R*)-5α-Spirostan-3β-ol or tigogenin (*nat*-215)

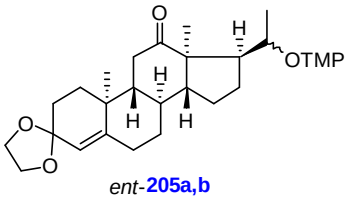


Steroid *nat*-**222** (20.0 mg, 37.8 µmol) was dissolved in a mixture of EtOH (1 mL), EtOAc (2.0 mL) and 10% palladium on carbon (3.0 mg) was suspended in the solution. The mixture was hydrogenated at 50 °C with 10 bar H_2 for 8 h, when the starting material was completely consumed. The catalyst was filtered off and the solvent was removed *in vacuo* to afford 15.5 mg (95%) of tigogenin *nat*-**215** as colorless crystals.
Mp 206-208 °C (EtOH), Lit.[346] Mp 209-211 °C (EtOH),
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (ddd, *J* = 8.6, 7.6, 6.5 Hz, 1H, CH-16), 3.58 (tt, *J* = 11.1, 4.8 Hz, 1H, CH-3), 3.47 (ddd, *J* = 10.8, 4.7, 1.9 Hz, 1H, CH-26eq), 3.37 (t, *J* = 10.8 Hz, 1H, CH-26ax), 1.98 (ddd, *J* = 11.9, 7.5, 5.4 Hz, 1H, CH-15a), 0.96 (d, *J* = 7.0 Hz, 3H, CH_3-21), 0.82 (s, 3H, CH_3-19), 0.79 (d, *J* = 6.3 Hz, 3H, CH_3-27), 0.76 (s, 3H, CH_3-18), 0.65 (ddd, *J* = 12.3, 10.6, 4.2 Hz, 1H, CH-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ 109.2 (C, C-22), 80.8 (CH, C-16), 71.3 (CH, C-3), 66.8 (CH_2, C-26), 62.2 (CH, C-17), 56.3 (CH, C-14), 54.3 (CH, C-9), 44.8 (CH, C-5), 41.6 (CH, C-20), 40.6 (C, C-13), 40.1 (CH_2, C-12), 38.2 (CH_2, C-4), 39.0 (CH_2, C-1), 35.6 (C, C-10), 35.1 (CH, C-8), 32.2 (CH_2), 31.8 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 30.3 (CH, C-25), 28.8 (CH_2), 28.6 (CH_2), 21.1 (CH_2, C-11), 17.1 (CH_3, C-27), 16.5 (CH_3, C-18), 14.5 (CH_3, C-21), 12.4 (CH_3, C-19).
The ^{1}H and ^{13}C NMR spectra are in agreement with the literature.[294]

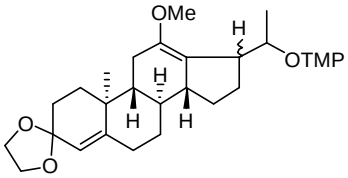
Alternative procedure: Steroid nonaflate *nat*-**221** (70.0 mg, 85 µmol) was dissolved in mixture of EtOH (1.75 mL), EtOAc (3.5 mL), Et_3N (35 µL, 250 µmol) and 10% palladium on carbon (17.5 mg) was suspended in the solution. The mixture was hydrogenated at rt with 10 bar H_2 for 33 h, after which the starting material was completely consumed. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (3 g) in 20% EtOAc/hexanes to afford 29.7 mg (84%) of steroid *nat*-**215** as a colorless solid. Recrystallization from EtOH gave 21.1 mg (60%) of analytically pure tigogenin.

***ent*-3-(Ethylenedioxy)-12-(nonafluorobutanesulfonyloxy)-20ξ-(2,2,6,6-tetramethylpiperidin-1-yloxy)-17ξ,13ξ-pregna-4,11-diene (*ent*-223)**

A suspension of KH (42 mg of KH; 1.05 mmol, ca 35% w/v in mineral oil) was transferred to a pre-dried Schlenk flask and washed with dry pentane (3 × 2 mL). The remaining solvent was evaporated *in vacuo* and the flask was back-filled with nitrogen. A solution of ketone *ent*-**186A,a** (348 mg, 700 µmol) in THF (3 mL) was added dropwise at rt, which caused immediate foaming of the mixture. The suspension was stirred at rt for 1 h, the supernatant was transferred via cannula to a new pre-dried Schlenk flask followed by addition of *t*BuOH (7 µL, 70 µmol). Neat methyl iodide (130 µL, 2.09 mmol) was added at once, turning the solution cloudy. The reaction mixture was stirred for another hour and quenched carefully with saturated aq. NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic fractions were evaporated *in vacuo* to afford 360 mg (100%) of an inseparable mixture of isomers *ent*-**205** as a white foam. The mixture consisted ca. 50% from the major isomers *ent*-**205a,b** in a 1:1 ratio, which were assigned based on the consumed material for the preparation of nonaflates *ent*-**223** and *ent*-**226** (*vide infra*). A 3:1 mixture of *O*-Methylated products *ent*-**205d**:*ent*-**205e** formed ca. 15% of the composition.



ent-**205a,b**



ent-**205d,e**

IR ($CHCl_3$); ν[cm^{-1}]: 946, 1087 (ketal), 1132, 1178 (COCOC), 1366, 1375 (CH_3), 1440, 1456 (CH_3), 1661 (C=C), 1700 (C=O), 2886 (CH_3), 2936 (CH_2), 2974 (CH_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (s, 6H, CH-4)[a-f], 4.96 (qd, *J* = 6.6, 1.6 Hz, 1H, CH-20)[a], 4.77-4.67 (m, 1H, CH-20)[b], 4.51 (qd, *J* = 6.4, 4.1 Hz, 1H, CH-20)[c], 4.36 (qd, *J* = 6.3, 5.0 Hz, 1H, CH-20)[d], 4.34 (qd, *J* = 6.4, 3.3 Hz, 1H, CH-20)[e], 4.09 (qd, *J* = 6.5, 3.6 Hz, 1H, CH-20)[f], 4.04-3.85 (m, 24H, OCH_2CH_2O)[a-f], 3.53 (s, 3H, OMe)[e], 3.48 (s, 3H, OMe)[d], 3.27-3.18 (m, 1H, CH-17)[d], 2.80-2.74 (m, 1H, CH-17)[e], 2.57-0.71 (m, aliphatic region).

Selected characteristic regions from ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.1 (C, C-12)[b], 219.6 (C, C-12)[c/f], 218.2 (C, C-12)[c/f], 214.1 (C, C-12)[a], 151.6 (C, C-5)[e], 151.2 (C, C-5)[d], 150.8 (C, C-5)[b], 150.3 (C, C-5)[a], 145.2 (C, C-12)[d], 143.7 (C, C-12)[e], 123.0 (C, C-13)[d], 122.9 (C, C-13)[e], 120.5 (CH, C-4)[a], 120.2 (CH, C-4)[b], 119.6 (CH, C-4)[d], 119.4 (CH, C-4)[e], 106.2 (C, C-3)[e], 106.1 (C, C-3)[d], 105.93 (C, C-3)[b], 105.86 (C, C-3)[a], 79.2 (CH, C-20)[d], 77.6 (CH, C-20)[e], 74.5 (CH, C-20)[a], 74.4 (CH, C-20)[b]. Signals of isomers *ent*-**205** are marked with the respective letter of alphabet. Structure of *ent*-**205c**, *ent*-**205f** remained undetermined because of low concentration in the sample and overlapping signals.

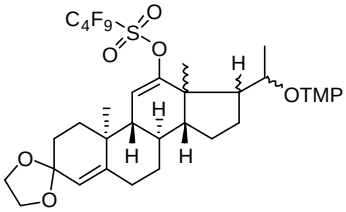
(ESI+) *m/z*, (%): 158 (4, $[TEMPOH+H]^+$), 329 (10, $[M-TEMPOH-C_2H_4+H]^+$), 357 (4, $[M-TEMPOH+H]^+$), 514 (100, $[M+H]^+$), 536 (8, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{52}NO_4$ 514.3891; Found 514.3890;

Anal. Calcd for $C_{32}H_{51}NO_4$: C, 74.81; H, 10.01; N, 2.73; Found: C, 74.44; H, 10.21; N, 2.49.

A suspension of KH (77 mg of KH; 1.92 mmol, ca 35% w/v in mineral oil) was transferred to a pre-dried Schlenk flask and washed with dry pentane (3 × 2 mL). The remaining solvent was evaporated *in vacuo* and the flask was back-filled with nitrogen. A solution of ketone *ent*-**205** (171.5 mg, 334 µmol) in THF (7 mL) was added dropwise at rt, followed by dry *t*BuOH (7 µL, 73 µmol). The reaction mixture was stirred at rt for 2 h and nonaflyl fluoride (200 µL, 1.11 mmol) was added at rt. After another hour at rt, the mixture was carefully quenched with saturated aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine and dried

over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography on silica gel (11 g) in 5% EtOAc/hexanes + 1% Et_3N to furnish 148.2 mg (56%) of 1:1.5 mixture of nonaflates *ent*-**223**, followed by 27.5 mg (16%) of recovered ketone *ent*-**205**, both isolated as colorless oils.



ent-**223**: IR ($CHCl_3$); ν[cm^{-1}]: 946, 1086, 1132, 1145 (CF_3), 1201, 1228, 1242 (CF_3, SO_2), 1353 (C-F), 1365, 1375 (CH_3), 1411 (SO_2), 1440, 1456 (CH_2), 1660, 1689 (C=C), 2874, 2885 (CH_3), 2935 (CH_2), 2973 (CH_3), 3028 (=CH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, *J* = 1.9 Hz, 1H, CH-11), 5.53 (d, *J* = 1.8 Hz, 1H, CH-11)*, 5.32 (t, *J* = 1.3 Hz, 1H, CH-4), 5.31 (t, *J* = 1.3 Hz, 1H, CH-4)*, 4.31 (qd, *J* = 6.6, 1.3 Hz, 1H, CH-20), 4.17 (qd, *J* = 6.5, 4.4 Hz, 1H, CH-20)*, 4.05-3.85 (m, 8H, OCH_2CH_2O, OCH_2CH_2O*), 2.53 (ddd, *J* = 12.8, 11.5, 7.0 Hz, 1H, CH-14), 2.42-0.95 (m, aliphatic region), 2.37-2.29 (m, 1H, CH-17)*, 1.99-1.89 (m, 1H, CH-9), 1.91-1.81 (m, 2H, CH-9*, CH-17), 1.87-1.77 (m, 1H, CH-14)*, 1.55-1.30 (m, 10H, CH_2-3', CH_2-5', CH_2-3'*, CH_2-5'*, CH-4'a, CH-4'a*), 1.32-1.25 (m, 2H, CH-4'b, CH-4'b*), 1.15 (d, *J* = 6.5 Hz, 3H, CH_3-21), 1.093 (s, 3H, CH_3-18*), 1.087 (d, *J* = 6.5 Hz, 3H, CH_3-21)*, 1.08 (br s, 9H, CH_3-7'/CH_3-9', CH_3-7'*, CH_3-9'*), 1.07 (br s, 6H, CH_3-7'/CH_3-9', CH_3-8'/CH_3-10'*), 1.06 (s, 3H, CH_3-8'/CH_3-10'*), 1.05 (s, 3H, CH_3-19), 1.04 (s, 3H, CH_3-18), 1.02 (s, 3H, CH_3-19)*, 1.01 (s, 3H, CH_3-8'/CH_3-10'), 0.97 (s, 3H, CH_3-8'/CH_3-10');

^{19}F NMR (376 MHz, $CDCl_3$) δ −81.59 to −81.69 (m, 6F, CF_3, CF_3*), −109.94 to −110.74 (m ,1F, $CF_aF_bSO_2$), −110.73 to −111.56 (m ,1F, $CF_aF_bSO_2$)*, −111.24 to −112.04 (m ,1F, $CF_aF_bSO_2$), −111.56 to −112.37 (m ,1F, $CF_aF_bSO_2$)*,−121.88 to −122.02 (m, 4F, $CF_2CF_2CF_3$, $CF_2CF_2CF_3$*), −126.78 to −126.93 (m, 4F, $CF_2CF_2CF_3$, $CF_2CF_2CF_3$*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C, C-12), 156.2 (C, C-12)*, 149.3 (C, C-5), 148.7 (C, C-5)*, 122.0 (CH, C-4)*, 121.8 (CH, C-4), 116.2 (CH, C-11), 115.6 (CH, C-11)*, 105.81 (C, C-3)*, 105.78 (C, C-3), 77.4 (CH, C-20)*, 76.6 (CH, C-20), 64.71 (CH_2, OCH_2CH_2O), 64.66 (CH_2, OCH_2CH_2O)*, 64.3 (CH_2, OCH_2CH_2O), 64.2 (CH_2, OCH_2CH_2O)*, 60.3 (C, C-2'/C-6', C-2'/C-6'*), 58.9 (C, C-2'/C-6', C-2'/C-6'*), 56.2 (CH, C-9), 56.1 (CH, C-9)*, 52.6 (CH, C-17), 49.95 (CH, C-14)*, 49.50 (CH, C-17)*, 49.21 (C, C-13), 49.15 (CH, C-14), 47.8 (C, C-13), [40.7, 40.43, 2×40.35 (CH_2, C-3',C-5', C-3'*,C-5'*)], 38.1 (C, C-10), 38.0 (C, C-10)*, 34.3 (CH_2, C-1), 34.2 (CH_2, C-1)*, 33.89 (CH, C-8)*, 33.85 (CH, C-8), [33.7, 33.6 (CH_3, C-7',C-9', C-7'*,C-9'*)], 32.5 (CH_2, C-6), 32.3 (CH_2, C-6)*, 30.7 (CH_2, C-7)*, 30.6 (CH_2, C-7), 29.7 (CH_2, C-2), 29.6 (CH_2, C-2)*, 24.0 (2×CH_2, C-15, C-15*), 23.2 (CH_3, C-18)*, 22.5 (CH_2, C-16)*, 22.2 (CH_3, C-18), [21.4, 21.09 (CH_3, C-8',C-10', C-8'*,C-10'*)], 21.07 (CH_2, C-16), 18.7 (CH_3, C-21), 18.1 (CH_3, C-19), 18.0 (CH_3, C-19)*, 17.3 (CH_2, C-4', C-4'*), 16.5 (CH_3, C-21)*. Signals of minor diastereomer are marked with an asterisk.

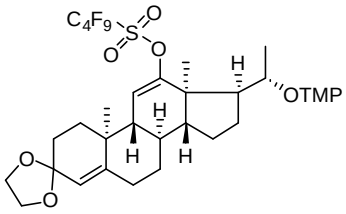
MS (ESI+) *m/z*, (%): 796 (100, $[M+H]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{36}H_{51}F_9NO_6S$ 796.3288; Found 796.3290;

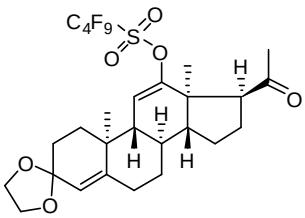
ent-3-(Ethylenedioxy)-12-(nonafluorobutanesulfonyloxy)-17α-pregna-4,11-dien-20-one (_ent_-226a) and _ent_-3-(ethylenedioxy)-12-(nonafluorobutanesulfonyloxy)-13α-pregna-4,11-dien-20-one (_ent_-226b)

Alkoxyamine *ent*-**223** (153.8 mg, 193 μmol) was dissolved in a mixture of CH_2Cl_2 (5 mL) and aq. phosphate buffer (pH 7.5, 0.5 M, 10 mL) and the biphasic mixture was cooled to 0 °C. *m*-CPBA (100 mg, 580 μmol) was added portionwise to the stirred solution. The reaction was stirred at 0 °C for

45 min and was quenched with 10% aq. $Na_2S_2O_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were washed with $NaHCO_3$ (2 × 5 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5 g) in 5% to 20% EtOAc/hexanes to afford 19.4 mg (13%) of recovered alkoxyamine *ent*-**223a** as a single diastereomer, followed by 16.0 mg (13%) of *ent*-**226b** and 83.3 mg (66%) of *ent*-**226a**, all of them isolated as colorless oils.



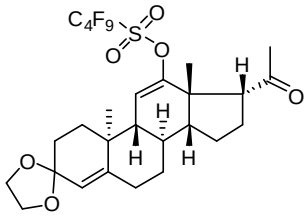
ent-**223a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, *J* = 1.9 Hz, 1H, CH-11), 5.31 (t, *J* = 1.3 Hz, 1H, CH-4), 4.31 (qd, *J* = 6.5, 1.3 Hz, 1H, CH-20), 4.05-3.85 (m, 4H, OCH_2CH_2O), 2.53 (ddd, *J* = 12.8, 11.5, 7.0 Hz, 1H, CH-14), 2.36-2.27 (m, 1H, CH-6a), 2.19 (br ddd, *J* = 14.0, 3.9, 1.8 Hz, 1H, CH-6b), 2.13-2.03 (m, 1H, CH-16a), 1.95 (dd, *J* = 10.2, 2.1 Hz, 1H, CH-9), 1.89-1.83 (m, 1H, CH-17), 1.83-1.73 (m, 1H, CH-16b), 1.82-1.73 (m, 1H, CH-7a), 1.80-1.68 (m, 1H, CH-8), 1.77-1.67 (m, 1H, CH-15a), 1.63-1.51 (m, 1H, CH-1a), 1.55-1.42 (m, 1H, CH-4'a), 1.53-1.32 (m, 4H, CH_2-3', CH_2-5'), 1.45-1.31 (m, 1H, CH-7b), 1.43-1.33 (m, 1H, CH-15b), 1.30-1.22 (m, 3H, CH_2-2, CH-4'b), 1.29-1.15 (m, 1H, CH-1b), 1.15 (d, *J* = 6.5 Hz, 3H, CH_3-21), 1.08 (s, 3H, CH_3-7'/CH_3-9'), 1.07 (s, 3H, CH_3-7'/CH_3-9'), 1.05 (s, 3H, CH_3-19), 1.04 (s, 3H, CH_3-18), 1.01 (s, 3H, CH_3-8'/CH_3-10'), 0.97 (s, 3H, CH_3-8'/CH_3-10');
^{19}F NMR (376 MHz, $CDCl_3$) δ −81.65 (tquint, *J* = 9.8, 2.0 Hz, 3F, CF_3), −111.44 to −111.68 (m, 2F, CF_2SO_2), −121.90 to −122.04 (m, 2F, $CF_2CF_2CF_3$), −126.78 to −126.93 (m, 2F, $CF_2CF_2CF_3$);
MS (ESI+) *m/z*, (%): 796 (100, $[M+H]^+$);
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C, C-12), 149.3 (C, C-5), 121.7 (CH, C-4), 116.2 (CH, C-11), 105.8 (C, C-3), 76.6 (CH, C-20), 64.7 (CH_2, OCH_2CH_2O), 64.3 (CH_2, OCH_2CH_2O), 60.3 (C, C-2'/C-6'), 58.9 (C, C-2'/C-6'), 56.2 (CH, C-9), 52.6 (CH, C-17), 49.21 (C, C-13), 49.15 (CH, C-14), 40.7 (CH_2, C-3'/C-5'), 40.4 (CH_2, C-3'/C-5'), 38.1 (C, C-10), 34.3 (CH_2, C-1), 33.90 (CH_3, C-7'/C-9'), 33.85 (CH, C-8), 33.7 (CH_3, C-7'/C-9'), 32.5 (CH_2, C-6), 30.6 (CH_2, C-7), 29.7 (CH_2, C-2), 24.0 (CH_2, C-15), 22.2 (CH_3, C-18), 21.4 (CH_3, C-8'/C-10'), 21.09 (CH_3, C-8'/C-10'), 21.08 (CH_2, C-16), 18.7 (CH_3, C-21), 18.1 (CH_3, C-19), 17.3 (CH_2, C-4').
Other spectral characteristics are identical to the mixture of diastereomers *ent*-**223**.



ent-**226a**: IR ($CHCl_3$); ν[cm^{-1}]: 568 (SO_2), 907, 946 (COCOC), 1090, 1125, 1145 (CF_3), 1179 (COCOC), 1228, 1242 (CF_3, SO_2), 1354 (C-F), 1365 (CH_2), 1382 (CH_3), 1414 (SO_2), 1660 (C=C), 1710 (C=O), 2858 (CH_2), 2883 (CH_3), 2936 (CH_2), 2973 (CH_3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, *J* = 2.2 Hz, 1H, CH-11), 5.31 (br s, 1H, CH-4), 4.04-3.85 (m, 4H, OCH_2CH_2O), 2.87 (dd, *J* = 9.6, 2.7 Hz, 1H, CH-17), 2.33-2.22 (m, 1H, CH-6a), 2.31-2.19 (m, 1H, CH-14), 2.21-2.08 (m, 2H, CH-6b, CH-16a), 2.13 (s, 3H, CH_3-21), 2.04-1.97 (m, 1H, CH-9), 1.88-1.77 (m, 2H, CH_2-2), 1.86-1.74 (m, 1H, CH-15a), 1.80-1.68 (m, 4H, CH-1a, CH-7a, CH-8, CH-16b), 1.68-1.55 (m, 1H, CH-1b), 1.52-1.38 (m, 1H, CH-15b), 1.25-1.10 (m, 1H, CH-7b), 1.08 (s, 3H, CH_3-18), 1.02 (s, 3H, CH_3-19).
^{19}F NMR (376 MHz, $CDCl_3$) δ −80.66 (m, 3F, CF_3,), −109.95 (dtq, *J* = 262.2, 14.2, 2.3 Hz, 1F, $CF_aF_bSO_2$), −110.98 (dtq, *J* = 262.3, 14.1, 2.3 Hz, 1F, $CF_aF_bSO_2$), −121.02 to −121.15 (m, 2F, $CF_2CF_2CF_3$), −125.77 to −125.88 (m, 2F, $CF_2CF_2CF_3$);
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6 (C, C-20), 154.9 (C, C-12), 148.3 (C, C-5), 122.1 (CH, C-4), 115.1 (CH, C-11), 105.6 (C, C-3), 64.6 (CH_2, OCH_2CH_2O), 64.1 (CH_2, OCH_2CH_2O), 56.1 (CH, C-17),

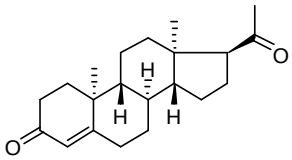
55.7 (CH, C-9), 49.1 (CH, C-14), 48.8 (C, C-13), 37.9 (C, C-10), 34.0 (CH_2, C-1), 33.5 (CH, C-8), 32.3 (CH_2, C-6), 30.48 (CH_2, C-7), 30.45 (CH_3, C-21), 29.6 (CH_2, C-2), 26.2 (CH_2, C-16), 24.1 (CH_2, C-15), 21.5 (CH_3, C-18), 18.0 (CH_3, C-19).
MS (ESI+) *m/z*, (%): 655 (100, $[M+H]^+$), 677 (40, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{31}F_9NaO_6S$ 677.1590; Found 677.1594;

Minor diastereomer *ent*-**226b**:



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (d, *J* = 1.4 Hz, 1H, CH-11), 5.31 (d, *J* = 1.3 Hz, 1H, CH-4), 4.06-3.83 (m, 4H, OCH_2CH_2O), 2.93 (dd, *J* = 8.0, 4.0 Hz, 1H, CH-17), 2.35-2.08 (m, 2H, CH_2-6), 2.17 (s, 3H, CH_3-21), 2.13-1.97 (m, 1H, CH-16a), 1.95-1.85 (m, 1H, CH-8), 1.89-1.82 (m, 2H, CH-9, CH-16b), 1.83-1.56 (m, 2H, CH_2-1), 1.62-1.54 (m, 1H, CH-14), 1.26 (s, 3H, CH_3-18), 1.07 (s, 3H, CH_3-19). Complete assignment of CH_2 groups in positions 2,7 and 15 was not possible due to overlapping signals in the aliphatic region.
^{19}F NMR (376 MHz, $CDCl_3$) δ −80.66 (m, 3F, CF_3), −110.17 (dtq, *J* = 262.1, 14.2, 2.3 Hz, 1F, $CF_aF_bSO_2$ −111.07 (dtq, *J* = 262.3, 14.1, 2.3 Hz, 1F, $CF_aF_bSO_2$), −121.02 to −121.15 (m, 2F, $CF_2CF_2CF_3$*), −125.77 to −125.88 (m, 2F, $CF_2CF_2CF_3$*);
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7 (C, C-20), 154.4 (C, C-12), 149.1 (C, C-5), 121.3 (CH, C-4), 115.4 (CH, C-11), 105.9 (C, C-3), 64.7 (CH_2, OCH_2CH_2O), 64.2 (CH_2, OCH_2CH_2O), 59.8 (CH, C-17), 53.8 (CH, C-14), 51.0 (CH, C-9), 48.8 (C, C-13), 37.5 (C, C-10), 36.1 (CH, C-8), 34.1 (CH_2, C-1), 31.7 (CH_2, C-6), 31.4 (CH_2, C-7), 30.9 (CH_3, C-21), 29.5 (CH_2, C-2/C-15/C-16), 29.3 (CH_3, C-18), 29.1 (CH_2, C-2/C-15/C-16), 28.6 (CH_2, C-2/C-15/C-16), 18.0 (CH_3, C-19).
Stereochemistry of C-13 and C-17 was assigned based on the expected *anti*- stereoselectivity of the methylation of minor diastereomer *ent*-**186a**.

***ent*-17α-Pregn-4-ene-3,20-dione or *ent*-17-isoprogesterone (*ent*-227a)**



Steroid *ent*-**226a** (23 mg, 35 µmol) was dissolved in a mixture of EtOH (1 mL), EtOAc (1 mL) and Et_3N (35 µL, 0.25 mmol) and the mixture was hydrogenated over 10% Pd/C (10 mg, 9.4 µmol) at a slight overpressure of hydrogen baloon at rt for a total of 39 h. The catalyst was filtered off and solvents were evaporated. The residue was dissolved in a mixture of acetone (1 mL) and 1 M aq. HCl (150 µL), stirred at rt for 10 min, diluted with more 1 M aq. HCl (3 mL) and extracted with $CHCl_3$ (3 × 1 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (3 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (1 g) in 20% to 40% EtOAc/hexanes to afford 2.6 mg (24%) of the 19:1 mixture *ent*-**227a** and *ent*-**227b**, followed by 3.3 mg (26%) of a 1:1 mixture of alcohols *ent*-**228**.
ent-**227a**:
$[\alpha]_D^{20}$ 0 (*c* 0.037, EtOH); Lit. $[\alpha]_D^{20}$ 0 (*c* not given, EtOH) For *nat*-**227a**;[301]
IR (ATR); ν[cm^{-1}]: 868, 1113, 1168, 1232, 1357, 1383 (CH_3), 1454, 1616 (C=C), 1671, 1706 (C=O), 2861, 2930 (CH_2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 10.3, 2.1 Hz, 1H, CH-11*), 5.74 (br s, 1H, CH-4*), 5.72 (br s, 1H, CH-4), 5.51 (br d, *J* = 10.2 Hz, 1H, CH-12*), 2.82 (dd, *J* = 8.3, 2.6 Hz, 1H, CH-17β*), 2.82 (dd, *J* = 8.5, 2.7 Hz, 1H, CH-17β), 2.40 (ddd, *J* = 16.9, 14.4, 5.0 Hz, 1H, CH-2β), 2.37 (m, 1H, CH-6β), 2.33 (m, 1H, CH-2α), 2.265 (m, 1H, CH-6α), 2.126 (s, 3H, CH_3-21), 1.99 (m, 1H, CH-1β), 1.91

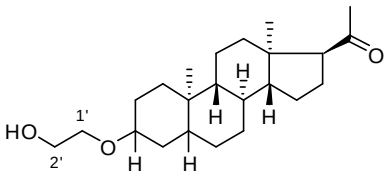
(m, 1H, CH-16β), 1.86 (m, 1H, CH-7β), 1.83 (m, 1H, CH-15α), 1.78 (m, 1H, CH-12β), 1.75 (m, 1H, CH-16α), 1.67 (m, 1H, CH-1α), 1.59 (m, 1H, CH-11α), 1.51 (m, 1H, CH-8β), 1.45 (m, 1H, CH-11β), 1.29 (m, 1H, CH-14α), 1.27 (m, 1H, CH-15β), 1.18 (m, 1H, CH-12α), 1.17 (s, 3H, CH_3-19), 1.11 (m, 1H, CH-7α), 0.96 (s, 3H, CH_3-18), 0.91 (m, 1H, CH-9α).

^{13}C NMR (150.9 MHz, $CDCl_3$) δ 212.6 (C, C-20), 199.4 (C, C-3), 171.0 (C, C-5), 123.9 (CH, C-4), 61.0 (CH, C-17), 53.1 (CH, C-9), 49.7 (CH, C-14), 45.5 (C, C-13), 38.5 (C, C-10), 35.8 (CH, C-8), 35.7 (CH_2, C-1), 34.9 (CH_2, C-12), 33.9 (CH_2, C-2), 32.84 (CH_2, C-6), 32.82 (CH_3, C-21), 32.1 (CH_2, C-7), 25.8 (CH_2, C-15), 24.4 (CH_2, C-16), 21.0 (CH_2, C-11), 20.7 (CH_3, C-18), 17.4 (CH_3, C-19);

MS (ESI+) *m/z*, (%): 315 (97, $[M+H]^+$), 337 (100, $[M+Na]^+$), 629 (33, $[2M+H]^+$), 651 (68, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{31}O_2$ 315.2319; Found 315.2322;

The ^{1}H NMR matched those reported for *nat*-enantiomer.[347] ^{1}H NMR signals of minor component ***ent*-227b** are marked by an *.



***ent*-228**:

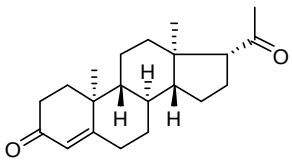
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76-3.67 (m, 4H, CH-2', CH-2'*), 3.61-3.55 (m, 4H, CH-1', CH-1'*), 3.34-3.22 (m, 2H, CH-3, CH-3*), 2.53-0.68 (m, aliphatic region), 2.14 (s, 3H, CH_3-21), 2.12 (s, 3H, CH_3-21*), 0.91 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.76 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5 (C, C-20*), 211.6 (C, C-20), 79.3 (CH, C-3), 78.9 (CH, C-3*), 68.8 (CH_2, C-1'), 68.7 (CH_2, C-1'*), 62.15 (CH_2, C-2'), 62.10 (CH_2, C-2'*), 61.3 (CH, C-17*), 57.4 (CH, C-17), 53.2 (CH), 53.0 (CH), 50.3 (CH), 48.5 (C), 45.9 (C), 44.6 (CH), 41.92 (CH), 41.89 (CH), 39.9 (CH), 37.0 (2 × C, C-10, C-10*), 36.0 (CH), 35.5 (CH_2), 35.3 (2 × CH_2), 34.83 (CH_2), 34.75 (CH_2), 33.0 (CH_2), 32.8 (CH_3, C-21*), 32.3 (CH_2), 30.4 (CH_2), 29.6 (CH_3, C-21), 28.6 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 23.34 (CH_3), 23.27 (CH_3), 20.9 (CH_3), 12.2 (CH_3). Two compounds present in a ca. 1:1 ratio. Low amount of the sample did not allow complete assignment.

MS (ESI+) *m/z*, (%): 385 (100, $[M+Na]^+$), 748 (34, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{38}O_3Na$ 385.2714; Found 385.2713;

ent-Pregn-4-ene-3,20-dione or _ent_-progesterone (_ent_-3)



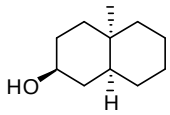
A solution of 9:1 mixture of steroid ***ent*-227a**:***ent*-227b** (3.7 mg, 11.7 μmol) in EtOH (1.5 mL) and concentrated aq. HCl (35%, 0.3 mL) was refluxed for 1.5 h. The solution was diluted with water (1.5 mL) and extracted with CH_2Cl_2 (3 × 1 mL). The organic extracts were washed with saturated aq. $NaHCO_3$ (3 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (1 g, impregnated by washing with 3% w/v $AgNO_3$ in MeOH, drying by air at rt, then 10 min at 110 °C) in 6:3:1 CH_2Cl_2/hexane/MTBE to afford 1.7 mg (46%) of *ent*-progesterone (***ent*-3**) and *ent*-17-isoprogesterone ***ent*-227a** in 3:1 ratio.

The ^{1}H, ^{13}C NMR, IR and MS spectra are in agreement with the literature,[109] as well as with the spectra of commercial *nat*-progesterone (***nat*-3**). Comparison of ^{1}H and ^{13}C NMR spectra is available in **Appendix D**.

When the reaction was performed wtihout purification on a 19:1 mixture of steroid *ent*-**227a**:*ent*-**227b** (2.5 mg, 8.0 µmol), the corresponding mixture 3:1 *ent*-**3**:*ent*-**227a** impure with 5% of Δ^{11}-olefins was obtained in quantitative yield.

5.3. Synthesis of the Truncated Steroid Analogs

(2*S*,4a*R*,8a*S*)-4a-Methyldecahydronaphthalen-2-ol (*ent*-229) and (2*R*,4a*S*,8a*R*)-4a-methyldecahydronaphthalen-2-ol (*nat*-229)



Benzoate **144** (451 mg, 1.57 mmol) was suspended in hydrazine monohydrate (5 mL) and dry ethylene glycol (2 mL) and the solution heated to 150 °C (oil bath) for 2.5 h. A part of liquid (5 mL) was distilled off, the remains were transferred into microwave vial with the help of dry ethylene glycol (2 × 0.5 mL). Powdered KOH (265 mg, 4.71 mmol) was added and the reaction mixture was irradiated in a microwave reactor at 200 °C for 15 min, the solution was cooled to rt and the pressure was released for safety reasons. The mixture was again irradiated in a microwave reactor at 200 °C for 2 h and subsequently poured into water (50 mL). The resulting emulsion was extracted with pentane (3 × 15 mL) and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents afforded 260 mg (98%) of the alcohol **229** as a low-melting solid.

Mp 40-42 °C;

$[\alpha]_D^{20}$ −43.9 (*c* 0.339, $CHCl_3$) for *ent*-**229**;

$[\alpha]_D^{20}$ +47.5 (*c* 0.297, $CHCl_3$) for *nat*-**229**;

IR ($CHCl_3$); ν[cm^{-1}]: 1005, 1029, 1054 (C-OH), 1366, 1378 (CH_3), 1448, 1467 (CH_2), 2865 (CH_2), 2931 (CH_2), 2978 (CH_3), 3449, 3609 (OH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (tt, *J* = 10.8, 4.5 Hz, 1H, CH-3), 1.85-1.71 (m, 1H, CH-6a), 1.82-1.70 (m, 1H, CH-1a), 1.78-1.68 (m, 1H, CH-2a), 1.64 (td, *J* = 12.6, 10.8 Hz, 1H, CH-4a), 1.59-1.49 (m, 1H, CH-4b), 1.58-1.45 (m, 2H, CH_2-7), 1.51-1.37 (m, 1H, CH-2b), 1.47-1.37 (m, 1H, CH-9a), 1.46-1.33 (m, 2H, CH_2-8), 1.43-1.34 (m, 1H, CH-5), 1.33-1.22 (m, 1H, CH-6b), 1.25 (td, *J* = 13.7, 3.9 Hz, 1H, CH-9b), 0.96 (d, *J* = 0.5 Hz, 3H, CH_3-19), 0.88 (br dt, *J* = 13.3, 3.3 Hz, 1H, CH-1b).

^{13}C NMR (101 MHz, $CDCl_3$) δ 71.7 (CH, C-3), 39.6 (CH, C-5), 39.4 (CH_2, C-9), 36.8 (CH_2, C-4), 31.9 (C, C-10), 31.3 (CH_2, C-2), 30.0 (br s, CH_2, C-1), 27.7 (CH_2, C-6), 27.1 (CH_3, C-19), 22.1 (CH_2, C-7), 20.6 (br s, CH_2, C-8).

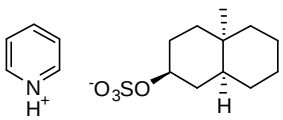
MS (CI+) *m/z*, (%): 149 (30, $[M-H_2O-H^-]^+$), 151 (100, $[M-H_2O+H^+]^+$), 167 (5, $[M-H^-]^+$);

HRMS (CI+) *m/z*: $[M-H^-]^+$ Calcd for $C_{11}H_{19}O$ 167.1436; Found 167.1439;

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98; Found: C, 78.72; H, 12.05. for *ent*-**229**.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98; Found: C, 78.47; H, 12.17. for *nat*-**229**.

Pyridinium (2*S*,4a*R*,8a*S*)-4a-methyldecahydronaphthalen-2-yl sulfate (*ent*-117) and pyridinium (2*R*,4a*S*,8a*R*)-4a-methyldecahydronaphthalen-2-yl sulfate (*nat*-117)

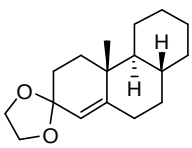


Alcohol **229** (50 mg, 297 µmol) was dissolved in CH_2Cl_2 (5 mL) and a drop of pyridine. The pyridine-sulfur trioxide complex (104 mg, 0.65 mmol) was added and the resulting suspension was stirred overnight. The mixture was cooled to −18 °C, filtered and the filtrate was evaporated *in vacuo* and redissolved in dry CH_2Cl_2 (1 mL). The solution was again cooled to −18 °C and the resulting precipitate filtered off. The filtrate is evaporated *in vacuo* to afford 98.5 mg (99%) sulfate **117** as a colorless solid.

Mp 97-100 °C for *ent*-**117**;

Mp 96-99 °C for *nat*-**117**;
$[\alpha]_D^{20}$ −38.3 (*c* 0.175, $CHCl_3$) for *ent*-**117**;
$[\alpha]_D^{20}$ +27.5 (*c* 0.225, $CHCl_3$) for *nat*-**117**;
IR ($CHCl_3$); ν[cm^{-1}]: 621 (SO_3^-), 682 (=CH), 821 (COS), 837, 935, 959, 964 (COS), 1042 (SO_3^-), 1176, 1262 (SO_3^-), 1371 (CH_3), 1449, 1469 (CH_2), 1490, 1548, 1637 (ring), 2137 (NH^+), 2450-2750 (NH^+), 2866 (CH_2), 2936 (CH_2), 2978 (CH_3), 3072, 3100 (=CH) ;
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.73 (br s, 1H, NH^+), 9.00 (dd, *J* = 6.6, 1.5 Hz, 2H, CH-2'), 8.47 (tt, *J* = 7.9, 1.6 Hz, 1H, CH-4'), 8.01 (dd, *J* = 7.9, 6.7 Hz, 2H, CH-3'), 4.48-4.39 (m, 1H, CH-3), 2.01 (dqd, *J* = 12.6, 3.9, 1.7 Hz, 1H, CH-2a), 1.91-1.80 (m, 2H, CH_2-4), 1.80-1.70 (m, 2H, CH-9a, CH-6a), 1.65 (qd, *J* = 12.6, 3.9 Hz, 1H, CH-2b), 1.56-1.43 (m, 2H, CH_2-7), 1.48-1.38 (m, 1H, CH-5), 1.46-1.36 (m, 1H, CH-1a), 1.43-1.29 (m, 2H, CH_2-8), 1.33-1.23 (m, 2H, CH-1b, CH-6b), 0.95 (s, 3H, CH_3-19), 0.88 (dt, *J* = 13.4, 3.1 Hz, 1H, CH-9b).
^{13}C NMR (150.9 MHz, $CDCl_3$ at 50 °C) δ 145.4 (CH, C-4'), 142.6 (CH, C-2'), 127.1 (CH, C-3'), 79.3 (CH, C-3), 39.8 (CH, C-5), 39.0 (br s, CH_2, C-1), 33.8 (CH_2, C-4), 31.9 (C, C-10), 30.5 (br s, CH_2, C-9), 28.6 (CH_2, C-2), 27.7 (CH_2, C-6), 27.1 (CH_3, C-19), 22.2 (CH_2, C-7), 20.8 (br s, CH_2, C-8).
MS (ESI−) *m/z*, (%): 247 (100, $[M-C_5H_6N^+]^-$);
HRMS (ESI−) *m/z*: $[M-C_5H_6N^+]^-$ Calcd for $C_{11}H_{19}O_4S$ 247.1010; Found 247.1007;
Anal. Calcd for $C_{16}H_{25}NO_4S$: C, 58.69; H, 7.70; N, 4.28; S, 9.79; Found: C, 57.66; H, 7.70; N, 4.28; for *nat*-**117**;
Anal. Calcd for $C_{16}H_{25}NO_4S$: C, 58.69; H, 7.70; N, 4.28; S, 9.79; Found: C, 58.18; H, 7.72; N, 4.16; for *ent*-**117**;

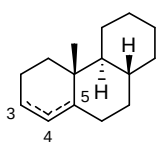
3-(Ethylenedioxy)-des-*D*-18-norandrost-4-ene (*nat*-231)



Ketone *nat*-**158** (1.73 g, 6.32 mmol), ethylene glycol (2 mL) and hydrazine monohydrate (5.0 mL, 103 mmol) were heated to 140 °C for 5 h. Approximately 3.5 mL of liquid was distilled off and the concentrated residue was transferred to a microwave reaction vial. Powdered KOH (1.06 g, 18.9 mmol) was added to the vial and the mixture was heated to 180 °C for 30 min. The reaction mixture was poured in water (100 mL) and extracted with pentane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Chromatography on silica gel (45 g) in 3% EtOAc/*n*-pentane afforded 333 (26%) of olefins *nat*-**230**, followed by 908 mg (55%) of ketal *nat*-**231** as a colorless oil.
$[\alpha]_D^{20}$ +123.2 (*c* 0.574, $CHCl_3$) for *nat*-**231**;
IR ($CHCl_3$); ν[cm^{-1}]: 947, 954, 1014, 1086 (C-O-C), 1113, 1170 (ketal), 1233 (COCOC), 1364, 1380 (CH_3), 1451 (CH_2), 1659 (C=C), 2855, 2886 (CH_3), 2927 (CH_2), 2970 (CH_3);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (d, *J* = 1.4 Hz, 1H, CH-4), 4.04-3.85 (m, 4H, OCH_2CH_2O), 2.22 (tdd, *J* = 13.7, 4.7, 1.6 Hz, 1H, CH-6a), 2.02 (ddd, *J* = 13.7, 4.3, 2.4 Hz, 1H, CH-6b), 1.80-1.70 (m, 4H, CH-1a, CH_2-2), 1.75-1.65 (m, 1H), 1.70-1.61 (m, 3H, CH-7a, CH-14a), 1.61-1.52 (m, 1H, CH-1b), 1.35 (qt, *J* = 11.2, 3.6 Hz, 1H, CH-8), 1.23-1.12 (m, 2H), 1.15-1.01 (m, 1H, CH-7b), 1.04-0.95 (m, 1H), 0.99 (s, 3H, CH_3-19), 0.97-0.87 (m, 1H, CH-14b), 0.94-0.83 (m, 1H, CH-9);
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C, C-5), 119.6 (CH, C-4), 106.3 (C, C-3), 64.5 (CH_2, OCH_2CH_2O), 64.2 (CH_2, OCH_2CH_2O), 53.5 (CH, C-9), 37.6 (C, C-10), 37.1 (CH, C-8), 35.2 (CH_2, C-7), 34.7 (CH_2, C-14), 34.6 (CH_2, C-1), 32.1 (CH_2, C-6), 29.9 (CH_2, C-2), 26.8 (CH_2), 26.3 (CH_2), 25.6 (CH_2), 17.9 (CH_3, C-19);
MS (ESI+) *m/z*, (%): 263 (100, $[M+H]^+$), 285 (13, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{26}NaO_2$ 285.1825; Found 285.1824;
Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99; Found: C, 77.94; H, 10.08. for *nat*-**231**;

nat-**230**: 1:1.7:1.6 Mixture of 5α:5β:Δ^4 isomers as determined by ^{1}H NMR spectrum.

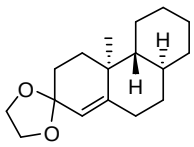


^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70-5.63 (m, 1H, CH-3)$^{\beta}$, 5.57-5.52 (m, 1H, CH-3)$^{\alpha}$, 5.36 (dq, *J* = 10.0, 2.0 Hz, 1H, CH-4)$^{\beta}$, 5.31-5.29 (m, 1H, CH-4)*, 5.28 (dq, *J* = 10.0, 2.0 Hz, 1H, CH-4)$^{\alpha}$, 2.27-0.68 (m, aliphatic region), 0.97 (s, 3H, CH_3-19)*, 0.90 (s, 3H, CH_3-19)$^{\beta}$, 0.72 (s, 3H, CH_3-19)$^{\alpha}$.

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C, C-5*), 132.3 (CH, C-3$^{\beta}$/C-4$^{\beta}$), 131.5 (CH, C-4*), 126.9 (CH, C-3$^{\beta}$/C-4$^{\beta}$), 125.5 (CH, C-3$^{\alpha}$/C-4$^{\alpha}$), 119.0 (CH, C-3$^{\alpha}$/C-4$^{\alpha}$), 54.0 (CH, C-9*), 52.7 (CH, C-9$^{\alpha}$), 45.9 (CH, C-5$^{\alpha}$), 43.6 (CH, C-5$^{\beta}$), 40.5 (CH, C-9$^{\beta}$), 37.5 (CH_2, C-1*), 37.4 (CH, C-8*), 37.3 (CH, C-8$^{\alpha}$), 36.9 (CH, C-8$^{\beta}$), 36.1 (CH_2), 35.3 (CH_2)$^{\alpha}$, 35.1, 35.02, 34.98 (CH_2)$^{\alpha}$, 33.8 (CH_2)$^{\alpha}$, 33.4 (CH_2), 32.7 (CH_2), 30.3 (CH_2), 27.6 (CH_2), 27.45 (CH_2), 27.44 (CH_2)$^{\alpha}$, 27.1 (CH_2)$^{\alpha}$, 27.0 (CH_2), 26.7 (CH_2), 26.6 (CH_2)$^{\alpha}$, 26.5 (CH_2), 26.02 (CH_2), 26.00 (CH_2), 25.9 (CH_2), 25.5 (CH_2)$^{\alpha}$, 23.5 (CH_2)$^{\alpha}$, 23.0 (CH_3, C-19$^{\beta}$), 22.5 (CH_2), 19.8 (CH_3, C-19*), 19.3 (CH_2), 11.7 (CH_3, C-19$^{\alpha}$). Signals of minor 5α-isomer are denoted with α, signals of major 5β-isomer with β and signals of Δ^4-double bond isomer * where possible. Quarternary carbons C-10 were lost in signal noise.

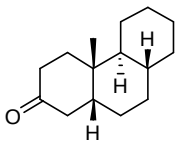
ent-3-(Ethylenedioxy)-des-*D*-18-norandrost-4-ene (*ent*-231)

Ketone *ent*-**158** (1.00 g, 3.62 mmol) was dissolved in MeOH (25 mL) and tosyl hydrazide (1.01 g, 5.42 mmol) was added to the stirred solution at rt. After 30 min, the conversion to hydrazone was complete, as shown by TLC. Solid $NaBH_4$ (2.74 g, 72.4 mmol) was added to the stirred mixture with cooling to 25 °C over 1 h. The resulting mixture was stirred overnight, poured in water (100 mL) and extracted with pentane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Chromatography on silica gel (30 g) in 3% EtOAc/*n*-pentane afforded 708 mg (75%) of ketal *ent*-**231**.



The spectral data were identical to enantiomer *nat*-**231**.

Des-*D*-18-nor-5β-androstan-3-one (*nat*-233)



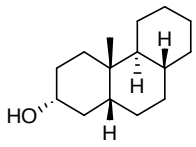
Ketal **231** (380 mg, 1.45 mmol) was dissolved in acetone (10 mL) and water (0.5 mL), 3 drops of concentrated aq. HCl (35%) were added and the mixture was stirred at rt overnight. The solution was concentrated *in vacuo*, poured into 5% HCl (30 mL) and extracted with pentane (3 × 20 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in EtOH (20 mL), a solution of KOH (45 mg) in water (120 µL) was added, followed by 5% $Pd/CaCO_3$ catalyst (40 mg). The mixture was hydrogenated using a slight overpressure of hydrogen gas for 3 h. The catalyst was filtered off and the solvents partially evaporated. The residue was poured into water and extracted with pentane (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo* to afford 291 mg (91%) of ketone **233** as a 1 : 9 mixture of 5α- and 5β-isomers.

$[\alpha]_D^{20}$ +27.8 (*c* 0.431, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1382 (CH_3), 1448, 1455 (CH_2, CH_3), 1707 (CO), 2856 (CH_2), 2929 (CH_2), 2981 (CH_2);

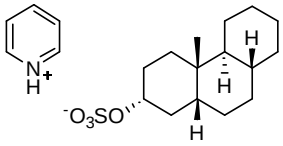
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (ddd, *J* = 14.6, 6.0, 1.0 Hz, 1H, CH-4a)*, 2.72 (ddd, 1H, *J* = 14.9, 13.3, 0.8 Hz, CH-4a), 2.37 (tdd, *J* = 14.7, 5.5, 0.9 Hz, 1H, CH-2a), 2.16 (dddd, *J* = 14.7, 4.3, 3.1, 2.4 Hz, 1H, CH-2b), 2.06 (ddd, *J* = 14.5, 5.5, 3.1 Hz, 1H, CH-1a), 2.02 (ddd, *J* = 14.9, 4.7, 2.4 Hz, 1H, CH-4b), 1.96-1.85 (m, 1H, CH-6a), 1.86-1.77 (m, 2H, CH-5), 1.72-1.65 (m, 4H, CH-14a), 1.49-1.42 (m, 2H, CH-7a, CH-9), 1.41-1.31 (m, 2H, CH-1b, CH-8) 1.27-1.15 (m, 4H, CH-6b, CH-7b, CH-14b), 1.07-0.98 (m, 1H), 0.97 (s, 3H, CH_3-19), 0.96 (s, 3H, CH_3-19)*.
^{13}C NMR (101 MHz, $CDCl_3$) δ 213.4 (C, C-3), 53.2 (CH)*, 46.6 (CH)*, 44.7 (CH_2)*, 44.5 (CH, C-5), 42.3 (CH_2, C-4), 40.4 (CH, C-9), 38.2 (CH_2)*, 38.1 (CH_2)*, 37.3 (CH_2, C-2), 36.9 (CH, C-8), 36.8 (CH)*, 36.5 (CH_2, C-1), 35.1 (CH_2, C-14), 35.0 (C, C-10), 34.5 (CH_2)*, 28.9 (CH_2)*, 28.4 (CH_2, C-7), 27.3 (CH_2), 27.0 (CH_2)*, 26.51 (CH_2), 26.49 (CH_2)*, 26.45 (CH_2), 26.41 (CH_2)*, 25.9 (CH_2)*, 25.6 (CH_2), 22.7 (CH_3, C-19), 11.4 (CH_3, C-19)*.
Signals of minor 5α-isomer are denoted with asterisk. Signal of CH_2-14 was assigned by comparison with alcohol **234** and sulfate **118**.
MS (EI+) *m/z*, (%): 149 (100, $[M-C_4H_5O]^+$), 220 (66, $[M]^{+\bullet}$);
HRMS (EI+) *m/z*: $[M]^{+\bullet}$ Calcd for $C_{15}H_{24}O$ 220.1822; Found 220.1825;
Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; Found: C, 81.61; H, 11.03.

Des-*D*-18-nor-5β-androstan-3α-ol (*nat*-234) and *ent*-des-*D*-18-nor-5β-androstan-3α-ol (*ent*-234)



Ketone **233** (274 mg, 1.24 mmol) was dissolved in CH_2Cl_2 (5 mL) and dry MeOH (5 mL) and the solution was cooled to −78 °C. Dried $CeCl_3$ (337 mg, 1.37 mmol) was added to the stirred solution, followed by $NaBH_4$ (52 mg, 1.37 mmol). After 15 min of stirring at −78 °C, the reaction mixture was warmed slowly to rt and quenched with 5% aq. HCl (25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with saturated aq. $NaHCO_3$, dried over $MgSO_4$ and evaporated *in vacuo*. Multiple chromatography on silica gel (10 g) in 10% Et_2O/*n*-pentane afforded 186.6 mg (78%) of single diastereomer of 3α,5β-alcohol **234** as a colorless amorphous solid.
$[\alpha]_D^{20}$ +21.8 (*c* 0.294, $CHCl_3$) for *nat*-**234**;
$[\alpha]_D^{20}$ −34.0 (*c* 0.209, $CHCl_3$) for *ent*-**234**;
IR ($CHCl_3$); ν[cm^{-1}]: 1015, 1035 (C-OH), 1364, 1380 (CH_3), 1450 (CH_2), 2858 (CH_2), 2927 (CH_2), 2977 (CH_2), 3452, 3609 (OH);
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (tt, *J* = 11.1, 4.7 Hz, 1H, CH-3), 2.18 (br s, 1H, OH), 1.91-1.84 (m, 1H, CH-6a), 1.87-1.77 (m, 1H, CH-14a), 1.84-1.72 (m, 1H, CH-4a), 1.80-1.71 (m, 1H, CH-13a), 1.70-1.62 (m, 1H, CH-2a), 1.70-1.60 (m, 1H, CH-11a), 1.66-1.58 (m, 2H, CH-1a, CH-7a), 1.50 (dddd, *J* = 12.6, 4.7, 3.8, 2.4 Hz, 1H, CH-4b), 1.46-1.39 (m, 1H, CH-9), 1.44-1.31 (m, 1H, CH-2b), 1.42-1.35 (m, 1H, CH-5), 1.39-1.32 (m, 1H, CH-12a), 1.33-1.24 (m, 1H, CH-8), 1.29-1.15 (m, 2H, CH-6b, CH-12b), 1.24-1.14 (m, 2H, CH-13b, CH-11b), 1.04-0.90 (m, 2H, CH-1b, CH-14b), 0.96-0.84 (m, 1H, CH-7b), 0.87 (s, 3H, CH_3-19).
^{13}C NMR (150.9 MHz, $CDCl_3$) δ 71.7 (CH, C-3), 42.2 (CH, C-5), 40.0 (CH, C-9), 37.3 (CH, C-8), 36.2 (CH_2, C-4), 35.2 (CH_2, C-1), 34.6 (CH_2, C-14), 34.5 (C, C-10), 30.5 (CH_2, C-2), 29.1 (CH_2, C-12), 27.3 (CH_2, C-13), 27.0 (CH_2, C-6), 26.5 (CH_2, C-11), 25.3 (CH_2, C-7), 23.3 (CH_3, C-19).
MS (ESI+) *m/z*, (%): 245 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{26}NaO$ 245.1876; Found 245.1875;
Anal. Calcd for $C_{15}H_{26}O$: C, 81.07; H, 11.79; Found: C, 81.11; H, 11.98. for *nat*-**234**.
Anal. Calcd for $C_{15}H_{26}O$: C, 81.07; H, 11.79; Found: C, 81.19; H, 11.70. for *ent*-**234**.

Pyridinium *ent*-des-*D*-18-nor-5β-androstan-3α-yl sulfate (*ent*-118) and pyridinium des-*D*-18-nor-5β-androstan-3α-yl sulfate (*nat*-118)



Alcohol **234** (166 mg, 747 µmol) was dissolved in CH_2Cl_2 (5 mL) and three drops of pyridine. The pyridine-sulfur trioxide complex (262 mg, 1.65 mmol) was added and the resulting suspension was stirred overnight. The mixture was cooled to −18 °C and filtered. The filtrate was evaporated *in vacuo* and redissolved in dry CH_2Cl_2 (3 mL). The solution was again cooled to −18 °C and the resulting precipitate filtered off. The filtrate was evaporated *in vacuo* to afford 248 mg (87%) of sulfate **118** as a colorless crystalline solid.

$[\alpha]_D^{20}$ +22.6 (*c* 0.230, $CHCl_3$) for *nat*-**118**;

$[\alpha]_D^{20}$ −24.1 (*c* 0.311, $CHCl_3$) for *ent*-**118**;

IR ($CHCl_3$); ν[cm^{-1}]: 624 (SO_3^-), 682 (=CH), 828 (COS), 953, 970 (COS), 1047 (SO_3^-), 1171, 1255 (SO_3^-), 1380 (CH_3), 1450 (CH_2), 1490 (ring), 2135 (NH^+), 2450-2750 (NH^+), 2856 (CH_2), 2927 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01-8.99 (m, 2H, CH-2'), 8.48 (tt, *J* = 7.9, 1.6 Hz, 1H, CH-4'), 8.03-7.99 (m, 2H, CH-3'), 4.47 (tt, *J* = 11.3, 4.9 Hz, 1H, CH-3), 2.03-1.90 (m, 2H, CH-4a, CH-2a), 1.88-1.79 (m, 3H, CH-4b, CH-14a, CH-6a), 1.78-1.71 (m, 1H, CH-13a), 1.66-1.56 (m, 2H, CH-1a, CH-11a), 1.63-1.54 (m, 1H, CH-7a), 1.60-1.52 (m, 1H, CH-2b), 1.48-1.38 (m, 2H, CH-5, CH-9), 1.38-1.30 (m, 1H, CH-12a), 1.35-1.22 (m, 1H, CH-8), 1.30-1.20 (m, 2H, CH-12b, CH-6b), 1.20-1.12 (m, 2H, CH-13b, CH-11b), 1.04-0.95 (m, 1H, CH-14b), 1.00-0.90 (m, 1H, CH-1b), 0.93-0.83 (m, 1H, CH-7b), 0.86 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (CH, C-4'), 142.4 (CH, C-2'), 127.1 (CH, C-3'), 79.7 (CH, C-3), 42.3 (CH, C-5), 40.1 (CH, C-9), 37.3 (CH, C-8), 35.3 (CH_2, C-1), 34.7 (CH_2, C-14), 34.5 (C, C-10), 33.3 (CH_2, C-4), 29.19 (CH_2, C-12), 27.9 (CH_2, C-2), 27.4 (CH_2, C-13), 26.9 (CH_2, C-6), 26.6 (CH_2, C-11), 25.4 (CH_2, C-7), 23.3 (CH_3, C-19).

Signals of CH_2-6, CH_2-7, CH_2-11, CH_2-12, CH_2-13 and CH_2-14 were assigned by comparison with alcohol **234**.

MS (ESI−) *m/z*, (%): 301 (100, $[M-C_5H_6N^+]^-$);

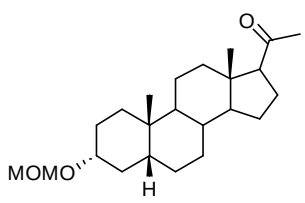
HRMS (ESI−) *m/z*: $[M-C_5H_6N^+]^-$ Calcd for $C_{15}H_{25}O_4S$ 301.1479; Found 301.1479;

Anal. Calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H, 8.19; N, 3.67; Found: C, 60.82; H, 8.09; N, 3.61; for *nat*-**118**.

Anal. Calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H, 8.19; N, 3.67; Found: C, 62.71; H, 8.40; N, 2.81; for *ent*-**118**.

5.4. SYNTHESIS OF [18,18,18]-D_3 PREGNANE STEROIDS

3α-(Methoxymethoxy)-5β-pregnan-20-one (235)

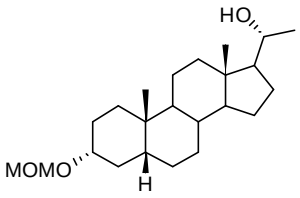


To a stirred solution of pregnanolone *nat*-**7** (10.00 g, 31.4 mmol) and *N*,*N*-diisopropylethylamine (13.67 mL, 78.5 mmol) in THF (70 mL), chloromethylmethylether (4.77 mL, 62.8 mmol) was added dropwise. The reaction mixture was refluxed for 2 h. After this time, the conversion was complete as indicated by TLC (hexanes:acetone 8:2). The reaction mixture was cooled to rt and quenched with saturated aq. NH_4Cl (150 mL). The mixture was extracted with Et_2O (3 × 50 mL), the combined organic extracts were washed with brine (100 mL) and dried with

$MgSO_4$. Evaporation *in vacuo* afforded 11.15 g (98%) of **235** as an amber oil, which was crystallized from EtOAc/heptane.
Mp 72-73 °C;
$[\alpha]_D^{20}$ +105.8 (*c* 0.257, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 1039, 1047, 1103, 1145 (COCOC), 1359, 1373, 1385 (CH_3), 1698 (C=O), 2869, 2889, 2940 (CH_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 3.54 (tt, *J* = 11.2, 4.7 Hz, 1H, CH-3), 3.38 (s, 3H, OCH_3), 2.53 (t, *J* = 9.0 Hz, 1H, CH-17), 2.11 (s, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19), 0.59 (s, 3H, CH_3-18);
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 94.6, 76.8, 63.9, 56.7, 55.2, 44.3, 42.0, 40.3, 39.2, 35.8, 35.3, 34.7, 33.5, 31.5, 27.7, 27.1, 26.3, 24.4, 23.3, 22.8, 20.8, 13.4;
MS (ESI+) *m/z*, (%): 385 (100, $[M+Na]^+$), 748 (7, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{38}NaO_3$: 385.2713; Found 385.2713.
Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56; Found: C, 76.12; H, 10.52.

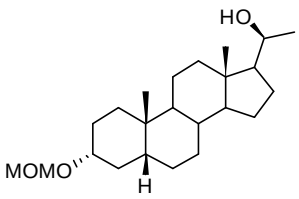
(20*R*)-3α-(Methoxymethoxy)-5β-pregnan-20-ol (236) and (20*S*)-3α-(methoxymethoxy)-5β-pregnan-20-ol (237)

Ketone **235** (11.15 g, 30.8 mmol) was dissolved in MeOH (250 mL) and the solution was cooled to 0 °C. Sodium borohydride (1.78 g, 47.05 mmol) was added slowly with stirring. The mixture was kept at 0 °C for 2 h, after which it was concentrated *in vacuo*, poured into 5% aq. citric acid (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed consecutively with saturated aq. $NaHCO_3$ (100 mL), brine (100 mL) and dried with $MgSO_4$. Evaporation *in vacuo* afforded mixture of stereoisomers, which were separated by chromatography on a column of silica gel (300 g) in hexanes/EtOAc 9:1 to yield 9.84 g (86%) of compound **236** as a colorless oil and 619 mg (7%) of minor *S*-isomer **237** as colorless crystals.
236*:* Mp 95-96 °C (Et_2O/hexanes);



$[\alpha]_D^{20}$ +27.9 (*c* 0.287, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 1039, 1046 (C-OH), 1103, 1145 (CH_2, OCH_2O), 1235, 1450 (OCH_3), 2934 (OCH_2O), 3471, 3615 (OH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O), 3.69 (dq, *J* = 8.4, 6.2 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.2, 4.7 Hz, 1H, CH-3), 3.37 (s, 3H, OCH_3), 1.22 (d, *J* = 6.2 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19), 0.64 (s, 3H, CH_3-18);
^{13}C NMR (101 MHz, $CDCl_3$) δ 94.5, 76.8, 70.3, 58.5, 56.3, 55.1, 42.1, 41.9, 40.4, 39.2, 35.4, 35.3, 34.7, 33.5, 27.7, 27.2, 26.4, 25.7, 24.1, 23.44, 23.36, 20.5, 12.6;
MS (ESI+) *m/z*, (%): 387 (100, $[M+Na]^+$), 752 (3, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{40}NaO_3$ 387.2870; Found 387.2870.
Anal. Calcd for $C_{23}H_{40}O_3$: C, 75.77; H, 11.06; Found: C, 75.94; H, 11.19.

237*:* $[\alpha]_D^{20}$ +17.9 (*c* 0.190, $CHCl_3$);

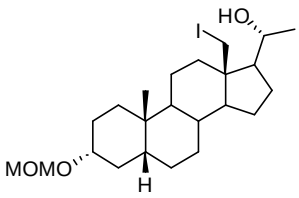


IR ($CHCl_3$); ν[cm^{-1}]: 1040 (C-OH), 1102, 1145 (CH_2, OCH_2O), 1377, 1450 (CH_3), 2869, 2890, 2933, 2942 (CH_2), 3611 (OH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O), 3.72 (dq, *J* = 9.5, 6.0 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.2, 4.5 Hz, 1H, CH-

3), 3.37 (s, 3H, OCH_3), 1.13 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19), 0.73 (s, 3H, CH_3-18);
^{13}C NMR (101 MHz, $CDCl_3$) δ 94.6, 76.9, 70.6, 58.7, 56.0, 55.1, 42.6, 42.2, 40.5, 40.3, 35.7, 35.4, 34.8, 33.6, 27.7, 27.2, 26.5, 25.7, 24.5, 23.6, 23.4, 20.7, 12.5;
MS (ESI+) *m/z*, (%): 387 (67, $[M+Na]^+$), 752 (100, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{40}NaO_3$ 387.2870; Found 387.2870.
Anal. Calcd for $C_{23}H_{40}O_3$: C, 75.77; H, 11.06; Found: C, 75.77; H, 11.08.

(20*R*)-18-Iodo-3α-(methoxymethoxy)-5β-pregnan-20-ol (238), 17α-iodo-3α-(methoxymethoxy)-5β-androstane (239) and 17β-iodo-3α-(methoxymethoxy)-5β-androstane (240)

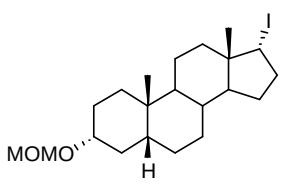
In 500 mL jacketed flask, alcohol **236** (9.85 g, 27.0 mmol) together with iodine (6.90 g, 27.2 mmol) and bis(acetoxy)iodobenzene (9.95 g, 30.9 mmol) were dissolved in CH_2Cl_2 (750 mL) and the mixture was cooled to 15 °C. The reaction vessel was irradiated by a halogen floodlight (500 W) for 3 h and the reaction was quenched with an aq. solution (200 mL) of $Na_2S_2O_3$ (20 g) and $NaHCO_3$ (10 g). The colorless organic layer was washed with brine (200 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting oil was dissolved in a minimal amount of hexanes and crystallized at 5°C to yield 4.19 g of colorless crystals **238**. The mother liquor was concentrated *in vacuo*, adsorbed on a column of Florisil (4 × 30 cm) and eluted with 5% to 15% EtOAc in hexanes to afford 1.54 g (13%) of 17-iodo derivatives **239** and **240** as a colorless oil, followed by 3.49 g of **238** (58% overall) as an off-white solid.



238*:* Mp 124-125.5 °C (Hexanes);
$[\alpha]_D^{20}$ +9.4 (*c* 0.233, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 1045 (C-OH), 1102, 1145 (CH_2, OCH_2O), 1376 (CH_3), 1423 (CH_2I), 2887, 2932, 2944 (CH_2), 3600 (OH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.06 (dqd, *J* = 10.1, 6.1, 4.1 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.2, 4.6 Hz, 1H, CH-3), 3.37 (s, 3H, OCH_3), 3.32 (dd, *J* = 10.6, 1.3 Hz, 1H, CH-18a), 3.13 (dd, *J* = 10.6, 1.1 Hz, 1H, CH-18b), 2.39 (dt, *J* = 13.4, 3.0 Hz, 1H, CH-12β), 2.25 (d, *J* = 4.2 Hz, 1H, OH), 1.14 (d, *J* = 6.2 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19);
^{13}C NMR (101 MHz, $CDCl_3$) δ 94.6, 76.7, 68.4, 58.8, 56.3, 55.2, 44.5, 41.9, 40.8, 40.3, 36.4, 35.3, 34.7, 33.6, 27.7, 27.1, 26.3, 25.4, 24.4, 23.3, 22.2, 20.2, 11.2;
MS (ESI+) *m/z*, (%): 513 (98, $[M+Na]^+$), 1004 (100, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{39}INaO_3$ 513.1836; Found 513.1836.

The fraction of 17-iododerivatives was purified by silica gel (45 g) column chromatography in 2% to 5% EtOAc/hexanes to afford 630 mg (5%) of **239** as a colorless oil, followed by 654 mg (5%) of **240** as a colorless oil.

17α-Iodo-3α-(methoxymethoxy)-5β-androstane (239)



$[\alpha]_D^{20}$ −36.0 (*c* 0.314, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 576 (C-I), 911, 1042, 1104, 1145 (COCOC), 1376 (CH_3), 1469 (CH_2), 2826, 2887 (CH_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (AB system, *J* = 6.8 Hz, 2H, OCH_2O), 4.35 (dd, *J* = 7.0, 1.0 Hz, 1H, CH-17), 3.54 (tt, *J* = 11.3, 4.8 Hz, 1H, CH-3),

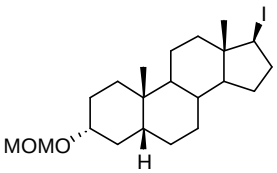
3.38 (s, 3H, OCH_3), 2.77 (dddd, *J* = 16.0, 11.0, 7.0, 3.7 Hz, 1H, CH-16a), 2.42 (dddd, *J* = 16.3, 9.6, 6.0, 1.0 Hz, 1H, CH-16b), 0.94 (s, 3H, CH_3-19), 0.81 (s, 3H, CH_3-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 94.6, 76.8, 55.2, 49.2, 48.2, 45.6, 42.1, 41.0, 40.0, 36.9, 36.6, 35.5, 34.8, 33.6, 27.7, 27.2, 26.6, 25.1, 23.4, 21.6, 15.7.

MS (ESI+) *m/z*, (%): 257 (81, $[M+H-HI-CH_3OCH_2OH]^+$), 341 (100, $[M+Na-HI]^+$), 385 (17, $[M+H-CH_3OCH_2OH]^+$), 469 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{35}INaO_2$ 469.1574; Found 469.1574.

17β-Iodo-3α-(methoxymethoxy)-5β-androstane (240)



$[\alpha]_D^{20}$ +88.5 (*c* 0.287, $CHCl_3$).

IR ($CHCl_3$); ν[cm^{-1}]: 606 (C-I), 915 (COCOC), 1036, 1047, 1102, 1145, 1376 (CH_3),
2869, 2940 (CH_2);

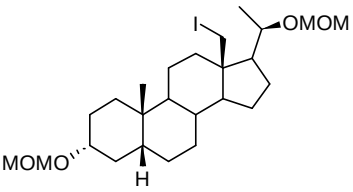
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O), 3.76 (t, *J* = 9.5 Hz, 1H, CH-17), 3.53 (tt, *J* = 11.3, 4.8 Hz, 1H, CH-3), 3.37 (s, 3H, OCH_3), 2.29 (dtd, *J* = 14.0, 9.3, 5.7 Hz, 1H, CH-16a), 2.08 (dddd, *J* = 13.9, 11.7, 10.0, 3.7 Hz, 1H, CH-16b), 0.93 (s, 3H, CH_3-19), 0.79 (s, 3H, CH_3-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 94.6, 76.8, 55.2, 50.0, 44.2, 42.2, 42.1, 40.6, 37.3, 37.0, 35.4, 34.8, 34.3, 33.6, 27.7, 27.1, 26.3, 25.4, 23.4, 20.5, 17.0.

MS (ESI+) *m/z*, (%): 469 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{35}INaO_2$ 469.1574; Found 469.1574.

(20*R*)-18-Iodo-3*α*,20-bis(methoxymethoxy)-5β-pregnane (242)



To a stirred solution of alcohol **238** (1.808 g, 3.69 mmol) and *N*,*N*-diisopropylethylamine (1.28 mL, 7.35 mmol) in THF (25 mL), bromomethyl methyl ether (500 μL, 6.12 mmol) was added dropwise at rt and the mixture was warmed to 50 °C for 2 h. The mixture was quenched with water (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (100 mL) and dried with $MgSO_4$. Evaporation *in vacuo* afforded 1.95 g (99%) compound **242** as a pale yellow oil.

$[\alpha]_D^{20}$ +57.6 (*c* 0.264, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 591 (CH_2I), 1041 (C-O), 1103, 1145 (CH_2, OCH_2O), 1375 (CH_3), 1165 (CH_2I), 2886 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (d, *J* = 6.6 Hz, 1H, OCH_aH_bO-20), 4.70 (d, *J* = 6.6 Hz, 1H, OCH_aH_bO-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 3.89 (dq, *J* = 9.5, 6.0 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.2, 4.6 Hz, 1H, CH-3), 3.38 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.32 (dd, *J* = 10.9, 1.0 Hz, 1H, CH-18a), 3.13 (dd, *J* = 10.9, 0.9 Hz, 1H, CH-18b), 2.42 (dt, *J* = 13.5, 3.11 Hz, 1H, CH-12β), 1.18 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19);

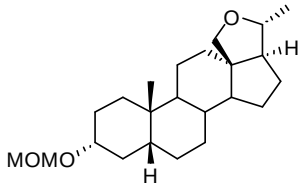
^{13}C NMR (101 MHz, $CDCl_3$) δ 97.0, 94.6, 76.8, 76.5, 57.1, 56.3, 55.5, 55.1, 43.7, 41.9, 40.43, 40.41, 36.4, 35.3, 34.7, 33.6, 27.7, 27.1, 26.2, 25.0, 24.0, 23.4, 20.6, 20.4, 9.5;

MS (ESI+) *m/z*, (%): 557 (100, $[M+Na]^+$), 1092 (10, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{43}INaO_4$ 557.2098; Found 557.2095.

Anal. Calcd for $C_{25}H_{43}IO_4$: C, 56.18; H, 8.11; I, 23.74; Found: C, 56.69; H, 8.21; I, 22.71.

(20*R*)-18,20-Epoxy-3α-(methoxymethoxy)-5β-pregnane (241) and (20*R*)-18,20-epoxy-5β-pregnan-3α-ol (253b)

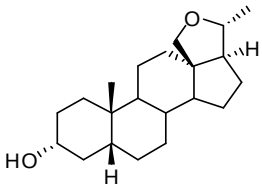


Steroid **242** (175 mg, 327 µmol) and KOH (92 mg, 1.6 mmol) were dissolved in anhydrous HMPA (6 mL) and heated to 120 °C for 2 h. The reaction mixture was cooled to rt, poured into water (40 mL) and extracted with 1:4 CH_2Cl_2/hexane (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. Preparative TLC in 20% EtOAc/hexanes afforded 101 mg (85%) of **241**.

241: 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O), 3.72 (qd, *J* = 6.3, 3.0 Hz, 1H, CH-20), 3.68 (d, *J* = 9.1 Hz, 1H, CH-18a), 3.53 (tt, *J* = 11.3, 4.8 Hz, 1H, CH-3), 3.41 (dd, *J* = 9.0, 1.1 Hz, 1H, CH-18b), 3.37 (s, 3H, OCH_3), 2.05-2.00 (m, 1H, CH-12β), 1.21 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.87 (s, 3H, CH_3-19).

Steroid **241** (101 mg, 279 µmol) was dissolved in MeOH (3 mL) and conc. aq. HCl (60 µL, 35% w/v) and the homogeneous solution was refluxed for 2 h. The reaction mixture was then poured into saturated aq. $NaHCO_3$ (40 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo* to furnish 89 mg (99%) of **253b**.

253b: Mp 183-184.5 °C (Hexanes);



$[\alpha]_D^{20}$ +11.0 (*c* 0.310, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1030, 1036 (C-O), 1377 (CH_3), 1449, 2868, 2934 (CH_2), 3430, 3610 (OH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (qd, *J* = 6.3, 3.0 Hz, 1H, CH-20), 3.68 (d, *J* = 9.0 Hz, 1H, CH-18a), 3.68-3.59 (m, 1H, CH-3), 3.41 (dd, *J* = 9.0, 1.7 Hz, 1H, CH-18b), 2.00 (ddd, *J* = 12.4, 4.1, 2.7 Hz, 1H, CH-12β), 1.22 (d, *J* = 6.3 Hz, 3H, CH_3-21), 0.87 (s, 3H, CH_3-19);

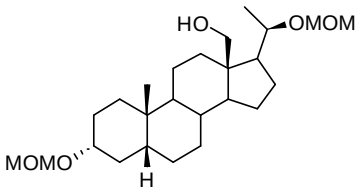
^{13}C NMR (101 MHz, $CDCl_3$) δ 84.5, 71.82, 71.77, 55.9, 55.2, 55.1, 42.0, 40.1, 37.9, 37.1, 36.4, 35.3, 34.6, 32.1, 30.6, 26.93, 26.91, 26.0, 23.3, 22.8, 21.6;

MS (ESI+) *m/z*, (%): 341 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{34}NaO_2$ 341.2451; Found 341.2449.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; Found: C, 79.14; H, 10.64.

(20*R*)-3α,20-Bis(methoxymethoxy)-5β-pregnan-18-ol (243)



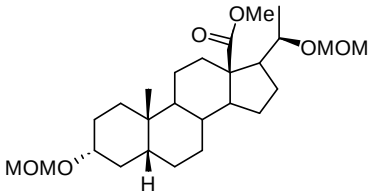
A stirred solution of iodide **242** (4.04 g, 7.56 mmol), *N*,*N*-diisopropylethylamine (1.96 mL, 11.3 mmol), 1,1′-azobis(cyclohexanecarbonitrile) (380 mg, 1.56 mmol) and tris(trimethylsilyl)silane (3.42 mL, 11.08 mmol) in dry toluene (50 mL) was heated to 90 °C and continuous stream of oxygen was bubbled through the solution with vigorous stirring. After 6 h, the reaction mixture was concentrated *in vacuo* and redissolved in THF (20 mL). A solution of TBAF (1 M in THF, 11 mL) was added dropwise while stirring. After 10 minutes, the mixture was poured into water (50 mL), extracted with Et_2O (3 × 30 mL), washed with saturated aq. $NaHCO_3$ (100 mL) and dried with $MgSO_4$. Evaporation in vacuum afforded a crude oil, which was purified by column chromatography on silica gel (150 g) in 5% acetone/hexanes to yield 2.49 g (78%) of compound **243** as a brownish oil.

$[\alpha]_D^{20}$ +20.0 (*c* 0.060, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1041 (C-O), 1102, 1145 (CH_2, OCH_2O), 1377 (CH_3), 2888 (CH_2), 3465 (OH);

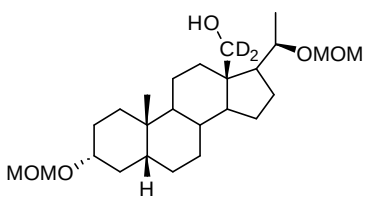
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, *J* = 6.5 Hz, 1H, OC*H*$_a$H$_b$O-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.64 (d, *J* = 6.5 Hz, 1H, OCH$_a$*H*$_b$O-20), 3.86 (quint, *J* = 6.5 Hz, 1H, CH-20), 3.60 (d, *J* = 11.3 Hz, 1H, CH-18a), 3.54 (tt, *J* = 11.2, 4.6 Hz, 1H, CH-3), 3.49 (d, *J* = 11.3 Hz, 1H, CH-18b), 3.40 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.42 (dt, *J* = 12.9, 3.2 Hz, 1H, CH-12β), 1.26 (d, *J* = 6.3 Hz, 3H, CH_3-21), 0.93 (s, 3H, CH_3-19);
^{13}C NMR (101 MHz, $CDCl_3$) δ 94.9, 94.5, 76.8, 76.3, 59.4, 56.2, 56.01, 56.00, 55.1, 47.3, 42.0, 40.6, 35.8, 35.3, 34.8, 34.7, 33.6, 27.7, 27.1, 26.6, 25.8, 24.1, 23.4, 20.4, 19.6;
MS (ESI+) *m/z*, (%): 447 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{44}NaO_5$ 447.3081; Found 447.3080;
Anal. Calcd for $C_{25}H_{44}O_5$: C, 70.72; H, 10.44; Found: C, 70.46; H, 10.03.

Methyl (20*R*)-3α,20-bis(methoxymethoxy)-5β-pregnan-18-oate (244)



A stirred solution of alcohol **243** (2.11 g, 4.97 mmol) in acetonitrile (12.5 mL), CCl_4 (12.5 mL) and water (19 mL) was cooled to 0 °C and $RuO_2 \cdot nH_2O$ (60% Ru, 16.8 mg, 2 mol%) was added. $NaIO_4$ (3.60 g, 16.84 mmol) was added portionwise and the heterogeneous reaction mixture was stirred vigorously for 4 h, until the conversion was complete. The reaction was quenched by addition of solid Na_2SO_3 (1 g) and after discoloration the solution was poured into 5% aq. citric acid (100 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried with $MgSO_4$ and evaporated *in vacuo*. The resulting oil was dissolved in MeOH (30 mL) and a diazomethane solution in Et_2O was added slowly until the conversion to ester was complete, as monitored by TLC in hexanes/acetone 8:2. The solvents were evaporated *in vacuo* and the crude product was purified on a column of silica gel (60 g) in hexanes/EtOAc (8:2) to afford 2.147 g (95%) of ester **244** as a colorless oil.
$[\alpha]_D^{20}$ +59.9 (*c* 0.157, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 1038 (C-O), 1103, 1145 (CH_2, OCH_2O), 1172 (CO-OMe), 1375 (CH_3), 1714 (COOMe), 2884 (CH_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.65 (d, *J* = 6.9 Hz, 1H, OC*H*$_a$H$_b$O-20), 4.61 (d, *J* = 6.9 Hz, 1H, OCH$_a$*H*$_b$O-20), 3.66 (s, 3H, COOMe), 3.54 (tt, *J* = 11.2, 4.6 Hz, 1H, CH-3), 3.373 (s, 3H, OCH_3), 3.370 (s, 3H, OCH_3), 3.86 (dq, *J* = 8.9, 6.1 Hz, 1H, CH-20), 2.73-2.68 (m, 1H, CH-12β), 1.15 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.82 (s, 3H, CH_3-19);
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 96.6, 94.6, 77.6, 76.8, 56.89, 56.88, 56.75, 55.6, 55.1, 50.7, 42.0, 40.4, 37.6, 36.5, 35.3, 34.7, 33.5, 27.7, 27.0, 26.6, 26.2, 24.9, 23.3, 22.6, 20.4;
MS (ESI+) *m/z*, (%): 475 (100, $[M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{44}NaO_6$ 475.3030; Found 475.3027;
Anal. Calcd for $C_{26}H_{44}O_6$: C, 68.99; H, 9.80; Found: C, 69.50; H, 9.81.

(20*R*)-3α,20-Bis(methoxymethoxy)-[18,18-$^2H_2$]-5β-pregnan-18-ol (245)



A solution of ester **244** (2.147 g, 4.74 mmol) in THF (10 mL), was added dropwise to a refluxing solution of $LiAlD_4$ (610 mg, 14.53 mmol) in THF (60 mL). After 4 h of reflux, the reaction mixture was cooled to rt, quenched with saturated aq. Na_2SO_4, dried with anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in*

vacuo and the oily residue was purified by column chromatography on silica gel (60 g) in 15% EtOAc/hexanes to afford 141 mg (7%) of starting material **244**, followed by 1.453 g (72%) of the desired product **245** as a colorless oil.

$[\alpha]_D^{20}$ +4.7 (c 0.255, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1025, 1044 (C-O), 1101, 1145 (CH_2, OCH_2O), 1377 (CH_3), 2109, 2219 (CD_2), 2889 (CH_2), 3469 (OH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, *J* = 6.5 Hz, 1H, OCH_aH_bO-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.64 (d, *J* = 6.5 Hz, 1H, OCH_aH_bO-20), 3.86 (quint, *J* = 6.5 Hz, 1H, CH-20), 3.54 (tt, *J* = 11.2, 4.6 Hz, 1H, CH-3), 3.40 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.32 (br s, 1H, OH), 2.52 (dt, *J* = 12.9, 3.4 Hz, 1H, CH-12β), 1.26 (d, *J* = 6.3 Hz, 3H, CH_3-21), 0.93 (s, 3H, CH_3-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ 95.0, 94.6, 76.8, 76.3, 56.1, 56.00, 55.96, 55.1, 47.1, 42.0, 40.6, 35.9, 35.4, 34.8, 34.7, 33.6, 27.7, 27.1, 26.6, 25.8, 24.1, 23.4, 20.4, 19.6;

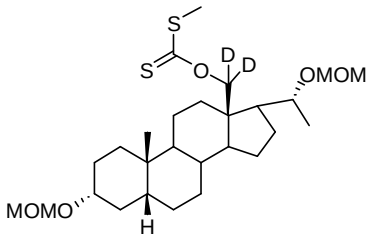
MS (ESI+) *m/z*, (%): 448 (1), 449 (100, $[M(D_2)+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{42}D_2NaO_5$ 449.3203; Found 449.3207;

Anal. Calcd for $C_{25}H_{44}O_5$: C, 70.38; H, 10.40; Found: C, 70.35; H, 10.37.

Isotopic purity >99%.

(20*R*)-3*α*,20-Bis(methoxymethoxy)-[18,18-$^2H_2$]-5β-pregnan-18-yl *O*-(*S*-methyl-dithiocarbonate) (246)



A solution of alcohol **245** (820 mg, 1.92 mmol) and 1,10-phenanthroline (1 mg) in THF (10 mL) was cooled in an ice bath and a solution of methyllithium (1.6 M in Et_2O, 1.20 mL) was added dropwise until a persistent red coloration. The solution was warmed to rt, dry carbon disulfide (355 μL, 5.88 mmol) was added and the mixture was stirred overnight. Methyl iodide (180 μL, 2.88 mmol) was added to the solution and after 2 h of stirring, the reaction was quenched with saturated aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 15 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated. Chromatography of the residue on silica gel (40 g) in 15% EtOAc/hexanes afforded 872 mg (88%) of xanthate **246** as a yellow oil.

$[\alpha]_D^{20}$ +67.5 (*c* 0.080, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1049 (C-O), 1062 (C=S), 1103 (OCH_2O), 1117 (C=S), 1144 (CH_2, OCH_2O), 1241 (CSOC), 1374 (CH_3), 2241 (CD_2), 2884 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, *J* = 6.7 Hz, 1H, OCH_aH_bO-20), 4.71 (d, 1H, *J* = 6.7 Hz, 1H, OCH_aH_bO-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 3.60-3.49 (m, 2H, CH-20, CH-3), 3.39 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.59 (s, 3H, SCH_3), 2.37 (ddd, *J* = 12.8, 3.2, 2.5 Hz, 1H, CH-12β), 1.19 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7, 96.9, 94.6, 77.7, 76.8, 56.3, 55.8, 55.7, 55.2, 45.8, 42.0, 40.6, 36.0, 35.5, 35.3, 34.8, 33.6, 27.7, 27.1, 26.5, 25.8, 24.4, 23.4, 20.8, 20.8, 19.3;

MS (ESI+) *m/z*, (%): 539.4 (1.5), 539.4 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{44}D_2NaO_5S_2$ 539.2804; Found 539.2803;

Anal. Calcd for $C_{27}H_{44}D_2O_5S_2$: C, 62.75; H, 8.97; S, 12.41; Found: C, 63.02; H, 9.12; S, 12.20.

Isotopic purity >99%.

(20*R*)-3α,20-Bis(methoxymethoxy)-5β-pregnan-18-yl *O*-(*S*-methyl-dithiocarbonate) (246b)

IR ($CHCl_3$); ν[cm^{-1}]: 1039, 1044 (C-O), 1067 (C=S), 1103, 1144 (CH_2, OCH_2O), 1374 (CH_3), 2870, 2886 (CH_2), 2933;

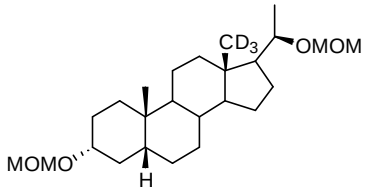
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, *J* = 6.7 Hz, 1H, OCH_aH_bO-20), 4.76 (d, 1H, *J* = 11.6 Hz, CH-18a), 4.71 (d, 1H, *J* = 6.7 Hz, 1H, OCH_aH_bO-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.50 (d, 1H, *J* = 11.6 Hz, CH-18b), 3.60-3.49 (m, 2H, CH-20, CH-3), 3.39 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.59 (s, 3H, SCH_3), 2.36 (ddd, 1H, *J* = 12.8, 3.2, 2.5 Hz, CH-12β), 1.19 (d, 3H, *J* = 6.0 Hz, CH_3-21), 0.92 (s, 3H, CH_3-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7, 96.8, 94.6, 77.6, 76.8, 73.8, 56.4, 55.8, 55.7, 55.2, 46.0, 42.0, 40.7, 36.0, 35.5, 35.4, 34.8, 33.6, 27.7, 27.1, 26.6, 25.8, 24.5, 23.4, 20.82, 20.77, 19.3.

MS (ESI+) *m/z*, (%): 537 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{46}NaO_5S_2$ 537.2679; Found 537.2676.

(20*R*)-3α,20-Bis(methoxymethoxy)-[18,18,18-$^2H_3$]-5β-pregnane (247)



A stirred solution of xanthate **246** (57 mg, 110 µmol), 1,1′-azobis(2-methylpropionitrile) (1.8 mg, 11 µmol) and tributyltin deuteride (45 µL, 167 µmol) in dry benzene (0.5 mL) was heated to reflux under a nitrogen atmosphere. After 2.5 h, the reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (2.5 g) in 10% EtOAc/hexanes to afford 16 mg (35%) of compound **247** as a colorless oil.

$[\alpha]_D^{20}$ +30.0 (c 0.563, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 913, 1045, 1103, 1144 (COCOC), 1374 (CH_3), 1448 (CH_2), 2226 (C^2H_3), 2869 (CH_2), 2887 (CH_3), 2932 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.8 Hz, 1H, OCH_aH_bO-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.61 (d, *J* = 6.8 Hz, 1H, OCH_aH_bO-20), 3.58 (dq, *J* = 10.0, 6.1 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.2, 4.8 Hz, 1H, CH-3), 3.39 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.06 (dd, *J* = 9.1, 2.8 Hz, 1H, CH-12a), 1.13 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 95.4, 94.5, 76.9, 76.5, 56.6, 56.02, 56.00, 55.1, 42.3, 42.1, 40.5, 39.7, 35.8, 35.4, 34.8, 33.6, 29.7, 27.7, 27.2, 26.5, 25.8, 24.3, 23.4, 20.7, 19.8.

MS (ESI+) *m/z*, (%): 431 (8, $[M(D_0)+Na]^+$), 432 (4, $[M(D_1)+Na]^+$), 433 (4, $[M(D_2)+Na]^+$), 434 (100, $[M(D_3)+Na]^+$), 846 (22, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{41}D_3NaO_4$ 434.3320; Found 434.3320.

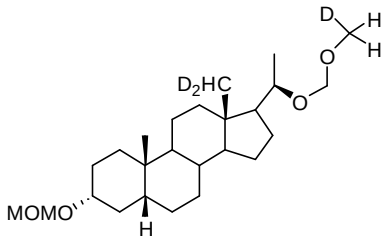
Anal. Calcd for $C_{25}H_{41}D_3O_4$: C, 72.95; H, 10.77; Found: C, 73.08; H, 10.87.

Isotopic purity 88%.

(20*R*)-3α-(Methoxymethoxy)-20-([^{2}H]-methoxymethoxy)-[18,18-$^2H_2$]-5β-pregnane (248) and (20*ξ*)-3α-methoxymethoxy-[20,18,18-$^2H_3$]-5β-pregnane (249)

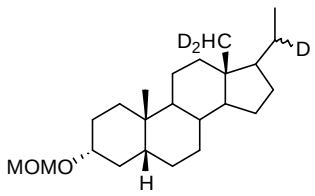
A stirred solution of xanthate **246** (1.33 g, 2.58 mmol), ABCN (63 mg, 0.26 mmol) and tris(trimethylsilyl)silyl deuteride (960 µL, 3.09 mmol) in dry toluene (15 mL) was heated to reflux under a nitrogen atmosphere. After 5 h, the reaction mixture was concentrated *in vacuo* and treated with a solution of TBAF (3.5 mL, 3.5 mmol, 1 M in THF). The solution was evaporated again and purified by column chromatography on silica gel (60 g) in 10% EtOAc/hexanes to afford 654 mg (72%) of **249** as a colorless oil, followed by 273 mg (26%) of **248**.

248: 1:1 Mixture of [18,18-$^2H_2$]-steroid **248a** and [$^2H_3$]-steroid **248b**.



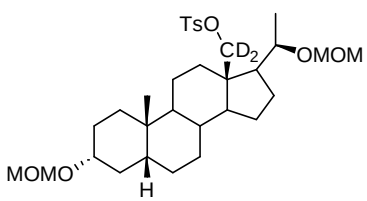
IR (ATR); ν[cm^{-1}]: 841, 918, 1042, 1107, 1148 (COCOC), 1376 (CH_3), 1451 (CH_2), 2875, 2939 (CH_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.8 Hz, 1H, OC*H*$_a$H$_b$O-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.61 (d, *J* = 6.8 Hz, 1H, OCH_aH_bO-20), 3.58 (dq, *J* = 10.0, 6.1 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.2, 4.8 Hz, 1H, CH-3), 3.39 (s, 2H, 20-OCH_2OCH_3), 3.37 (br s, 4H, 3-OCH_2OCH_3, 20-OCH_2OCH_2D*), 2.06 (dd, *J* = 9.1, 2.8 Hz, 1H, CH-12a), 1.89-0.91 (m, aliphatic region), 1.13 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.92 (s, 3H, CH_3-19), 0.65 (br s, 1H, CH_3-18).
^{13}C NMR (101 MHz, $CDCl_3$) δ 95.4 (CH_2, 20-OCH_2O), 94.6 (CH_2, 3-OCH_2O), 76.9 (CH, C-3), 76.4 (CH, C-20), 56.7 (CH_3), 56.04 (CH_3), 55.99 (CH), 55.1 (CH), 42.4 (C, C-13), 42.2 (CH, C-5), 40.5 (CH, C-9), 39.7 (CH_2, C-12), 35.8 (CH, C-8), 35.4 (CH_2, C-1), 34.8 (C, C-10), 33.6 (CH_2, C-4), 27.7 (CH_2, C-2), 27.3 (CH_2, C-6), 26.5 (CH_2, C-7), 25.8 (CH_2, C-15/C-16), 24.3 (CH_2, C-15/C-16), 23.4 (CH_3, C-19), 20.7 (CH_2, C-11), 19.8 (CH_3, C-21), 11.9 (quint, $^2J_{C\text{-}D}$ = 19.1 Hz, CH, C-18). Signals of **248b** are marked with an asterisk, when they are discernable from **248a**.
MS (ESI+) *m/z*, (%): 432 (3, [M(D_1)+Na]$^+$), 433 (79, [M(D_2)+Na]$^+$), 434 (100, [M(D_3)+Na]$^+$);

249: 1:1 Mixture of [18,18-$^2H_2$]-steroid **249a** and [20,18,18-$^2H_3$]-steroid **249b**.



IR ($CHCl_3$); ν[cm^{-1}]: 918, 1047, 1106, 1149 (COCOC), 1377 (CH_3), 1452 (CH_2), 2874, 2939 (CH_2);
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.69 (d, *J* = 6.2 Hz, 1H, OC*H*$_a$H$_b$O), 4.67 (d, *J* = 6.2 Hz, 1H, OCH_aH_bO), 3.52 (tt, *J* = 11.1, 4.7 Hz, 1H, CH-3), 3.36 (s, 3H, OCH_3), 1.85 (m, 1H, CH-6a), 1.84 (m, 1H, CH-16a), 1.80 (m, 2H, CH-1a, CH-4a), 1.72 (m, 2H, CH-2^a, CH-12a), 1.59 (m, 1H, CH-15a), 1.55 (m, 1H, CH-4b), 1.44 (m, 1H, CH-9), 1.42 (m, 1H, CH-7a), 1.41 (m, 1H, CH-11a), 1.39 (m, 2H, CH_2-20), 1.37 (m, 2H, CH-5, CH-8), 1.35 (m, 1H, CH-2b), 1.24 (m, 1H, CH-6b), 1.20 (m, 1H, CH-11b), 1.16 (m, 1H, CH-17), 1.15 (m, 1H, CH-16b), 1.11 (m, 1H, CH-7b), 1.06 (m, 1H, CH-15b), 1.04 (t, *J* = 19 Hz, 1H, CH-20)*, 1.00 (m, 1H, CH-14), 0.99 (m, 1H, CH-12b), 0.94 (m, 1H, CH-1b), 0.92 (s, 3H, CH_3-19), 0.865 (t, *J* = 7.3 Hz, 3H, CH-21), 0.855 (d, *J* = 7.3 Hz, 3H, CH-21)*, 0.50 (br s, 1H, CH-18).
^{13}C NMR (150.9 MHz, $CDCl_3$) δ 94.5 (CH_2, OCH_2O), 76.9 (CH, C-3), 56.0 (CH, C-14), 55.1 (CH_3, OCH_3), 53.1 (CH, C-17), 53.0 (CH, C-17)*, 42.2 (CH, C-5), 42.1 (C, C-13), 40.8 (CH, C-9), 38.2 (CH_2, C-12), 35.9 (CH, C-8), 35.5 (CH_2, C-1), 34.8 (C, C-10), 33.6 (CH_2, C-4), 28.20 (CH_2, C-16), 28.16 (CH_2, C-16)*, 27.7 (CH_2, C-2), 27.2 (CH_2, C-6), 26.6 (CH_2, C-7), 24.6 (CH_2, C-15), 23.4 (CH_3, C-19), 23.1 (CH_2, C-20), 22.7 (t, $J_{C\text{-}D}$ = 19 Hz, CH, C-20)*, 20.6 (CH_2, C-11), 13.3 (CH_3, C-21), 13.2 (CH_3, C-21)*, 11.9 (quint, $^2J_{C\text{-}D}$ = 19.1 Hz, CH, C-18). Signals of **249b** are marked with an asterisk, when they are discernable from **249a**.

(20*R*)-3*α*,20-Bis(methoxymethoxy)-[18,18-$^2H_2$]-5β-pregnan-18-yl *p*-toluenesulfonate (251)



A solution of compound **245** (530 mg, 1.24 mmol), 4-(dimethylamino)pyridine (15 mg, 0.12 mmol), and *p*TsCl (1.19 g, 6.22 mmol) in anhydrous pyridine (3 mL) was stirred at rt overnight. The reaction mixture was poured into ice-cold water and extracted with Et_2O (3 × 20 mL). The combined extracts were washed consecutively with 5% aq. citric acid (50 mL), saturated aq. $NaHCO_3$ (50 mL) and dried over

anhydrous Na_2SO_4. After solvent evaporation, the oily residue was purified by column chromatography on silica gel (25 g) in 20% EtOAc/hexanes to give 691 mg (96%) tosylate **251** as a white foam:

$[\alpha]_D^{20}$ +38.4 (*c* 0.229, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 961 (COS), 1042 (C-O), 1101, 1144 (CH_2, OCH_2O), 1178, 1190, 1364 (SO_2), 2246, 2342, 2360 (CD_2), 2870, 2885 (CH_2), 2933;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H, Ar), 7.36 (d, *J* = 8.0 Hz, 2H, Ar), 4.73 (d, *J* = 6.6 Hz, 1H, OC$H_a$$H_b$O-20), 4.67 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.61 (d, *J* = 6.6 Hz, 1H, OCH_aH_bO-20), 3.86 (dq, *J* = 9.9, 6.0 Hz, 1H, CH-20), 3.49 (tt, *J* = 11.2, 4.6 Hz, 1H, CH-3), 3.360 (s, 3H, OCH_3), 3.357 (s, 3H, OCH_3), 2.45 (s, 3H, Ar-CH_3), 2.25 (dt, *J* = 13.3, 3.1 Hz, 1H, CH-12β), 1.15 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.60 (s, 3H, CH_3-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 132.6, 129.8, 128.2, 96.7, 94.6, 77.3, 76.8, 56.2, 55.7, 55.5, 55.1, 45.5, 41.9, 40.4, 35.8, 35.3, 34.8, 34.6, 33.5, 27.6, 27.0, 26.4, 25.6, 24.3, 23.0, 21.6, 20.8, 20.1;

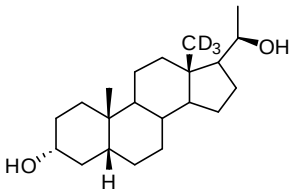
MS (ESI+) *m/z*, (%): 602 (1), 603 (100, $[M+Na]^+$), 604 (36), 605 (7), 606 (3), 1183 (10, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{48}D_2NaO_7S$ 603.3295; Found 603.3294;

Anal. Calcd for $C_{32}H_{48}D_2O_7S$: C, 66.17; H, 8.67; S, 5.52; Found: C, 66.30; H, 8.78; S, 5.62.

Isotopic purity >99%.

(20*R*)-[18,18,18-$^2H_3$]-5β-Pregnane-3α,20-diol (252)



Solid $LiAlD_4$ (430 mg, 10.24 mmol) was added to a solution of tosylate **251** (664 mg, 1.14 mmol) in dry *n*-heptane (10 mL) and the reaction mixture was refluxed for 18 h. The reaction mixture was cooled to rt, quenched with saturated aq. Na_2SO_4, dried with anhydrous Na_2SO_4 and filtered. The filtrate was evaporated *in vacuo*, the oily residue redissolved in MeOH (10 mL), mixed with 6 M HCl (0.10 mL) and refluxed for 4 h. The reaction mixture was concentrated *in vacuo*, poured into saturated aq. $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (3 × 15 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated. Chromatography of the residue on silica gel (15 g) in 10% acetone/hexanes yielded consecutively 131 mg (36%) of ether **253**, 55 mg (15%) of the desired diol **252** and finally 87 mg (23%) of triol **254**.

Diol **252**:

Mp 233-235 °C; Lit.[348] 233.5-234.5 °C for the nondeuterated compound;

$[\alpha]_D^{20}$ +9.9 (*c* 0.262, $CHCl_3$), [Lit.[348] +12 (*c* 0.86, EtOH)];

IR ($CHCl_3$); ν[cm^{-1}]: 1031 (CO), 1044 (CO), 1378 (CH_3), 1449 (CH_2), 2227, 2343, 2361 (CD_3), 2868, 2934 (CH_2), 3609 (OH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dq, *J* = 9.9, 6.1 Hz, 1H, CH-20), 3.63 (tt, *J* = 11.0, 4.7 Hz, 1H, CH-3), 2.03 (dd, *J* = 8.3, 2.4 Hz, 1H, CH-12β), 1.14 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.93 (s, 3H, CH_3-19);

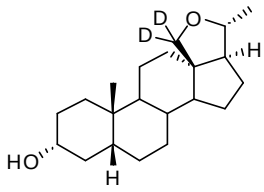
^{13}C NMR (101 MHz, $CDCl_3$) δ 71.9, 70.6, 58.7, 56.0, 42.4, 42.1, 40.5, 40.3, 36.5, 35.8, 35.4, 34.6, 30.6, 27.2, 26.5, 25.7, 24.5, 23.6, 23.4, 20.7.

MS (ESI+) *m/z*, (%): 343 (0, $[M(D_0)+Na]^+$), 344 (0, $[M(D_1)+Na]^+$), 345 (4, $[M(D_2)+Na]^+$), 346 (100, $[M(D_3)+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{33}D_3NaO_2$ 346.2796; Found 346.2795;

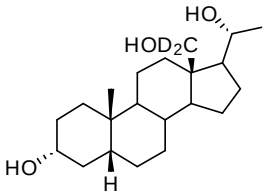
Isotopic purity 96%.

(20*R*)-18,20-Epoxy-[18,18-$^2H_2$]-5β-pregnan-3α-ol (253)



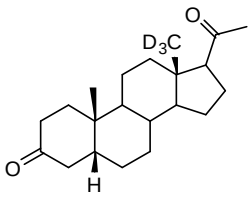
Mp 183-185 °C (CH_2Cl_2/hexanes);
$[\alpha]_D^{20}$ +17.3 (*c* 0.324, $CHCl_3$);
IR (ATR); ν[cm^{-1}]: 831, 935, 981, 1047 (CO), 1069, 1095, 1381 (CH_3), 1449 (CH_2), 2240 (CD_3), 2865, 2933 (CH_2), 3351 (OH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (qd, *J* = 6.3, 3.0 Hz, 1H, CH-20), 3.64 (tt, *J* = 11.0, 4.7 Hz, 1H, CH-3), 2.00 (ddd, *J* = 12.4, 4.1, 2.7 Hz, 1H, CH-12β), 1.22 (d, *J* = 6.3 Hz, 3H, CH_3-21), 0.87 (s, 3H, CH_3-19);
^{13}C NMR (101 MHz, $CDCl_3$) δ 84.5, 71.7, 55.7, 55.2, 55.1, 42.0, 40.1, 37.9, 37.0, 36.4, 35.3, 34.6, 32.1, 30.6, 26.92, 26.90, 26.0, 23.3, 22.8, 21.6.
Anal. Calcd for $C_{21}H_{32}D_2O_2$: C, 78.70; H, 10.69; Found: C, 78.02; H, 10.53.

(20*R*)-[18,18-$^2H_2$]-5β-Pregnane-3α,18,20-triol (254)



Mp 214-217 °C ($CHCl_3$);
$[\alpha]_D^{20}$ +17.4 (*c* 0.046, $CHCl_3$);
IR (ATR); ν[cm^{-1}]: 674, 727, 973, 1038 (CO), 1065, 1099, 1116, 1360, 1375 (CH_3), 1453 (CH_2), 2218, 2207 (CD_2), 2873, 2936, 2953 (CH_2), 3341, 3388, 3445 (OH);
^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$ 1:9) δ 3.77 (qd, *J* = 9.5, 6.3 Hz, 1H, CH-20), 3.60 (tt, *J* = 10.9, 4.7 Hz, 1H, CH-3), 2.45 (br d, *J* = 13.1, 4.1, 2.7 Hz, 1H, CH-12β), 1.17 (d, *J* = 5.9 Hz, 3H, CH_3-21), 0.94 (s, 3H, CH_3-19);
^{13}C NMR (101 MHz, $CDCl_3$) δ 71.4, 71.3, 57.6, 55.7, 47.0, 41.8, 40.5, 36.0, 35.8, 35.2, 34.8, 34.5, 30.1, 27.0, 26.6, 26.2, 24.7, 23.2, 21.9, 20.2.
MS (ESI+) *m/z*, (%): 359 (0, $[M(D_0)+Na]^+$), 360 (0, $[M(D_1)+Na]^+$), 361 (100, $[M(D_2)+Na]^+$), 700 (7, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{34}D_2NaO_3$ 361.2682; Found 361.2681;
Anal. Calcd for $C_{21}H_{34}D_2O_3$: C, 74.51; H, 10.72; Found: C, 73.83; H, 10.54.

[18,18,18-$^2H_3$]-5β-Pregnane-3,20-dione (119)



Steroid **252** (5.0 mg, 15.5 μmol) was dissolved in acetone (3 mL) and $CHCl_3$ (1.5 mL) and the mixture was cooled in an ice bath. Jones' reagent[327] (100 μL, 3 M aq. solution, 0.3 mmol) was added dropwise with stirring and the suspension was stirred at 0 °C for 30 min. The excess of the reagent was quenched with *i*PrOH (0.1 mL) and the mixture was concentrated *in vacuo*. The mixture was diluted with 2 mL of water and extracted with CH_2Cl_2 (3 × 2 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (5 mL), dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (0.5 g) in 0 % to 10% EtOAc/hexanes to afford 5.0 mg (quant.) of diketone **119** as colorless crystalline solid.
Mp 114-117 °C, Lit.[222] 118-119 °C (EtOAc/heptane) for nondeuterated compound;
$[\alpha]_D^{20}$ +93.8 (*c* 0.097, $CHCl_3$);
IR ($CHCl_3$); ν[cm^{-1}]: 1357, 1380 (CH_3), 1446, 1453 (CH_2), 1703 (C=O), 2220, 2234 (C^2H_3), 2857, 2876, 2937 (CH_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 15.0, 13.4 Hz, 1H, CH-4a), 2.55 (t, *J* = 9.0 Hz, 1H, CH-17), 2.34 (tdd, *J* = 14.6, 5.3, 0.7 Hz, 1H, CH-2a), 2.23-2.14 (m, 1H, CH-2b), 2.23-2.11 (m, 1H, CH-

16a), 2.13 (s, 3H, CH_3-21), 2.11-2.02 (m, 1H, CH-12a), 2.09-1.99 (m, 2H, CH-1a, CH-4b), 1.96-1.82 (m, 1H, CH-6a), 1.89-1.78 (m, 1H, CH-5), 1.76-1.66 (m, 1H, CH-15a), 1.72-1.60 (m, 1H, CH-16b), 1.61-1.51 (m, 1H, CH-11a), 1.58-1.50 (m, 1H, CH-7a), 1.58-1.48 (m, 1H, CH-9), 1.56-1.45 (m, 1H, CH-8), 1.51-1.41 (m, 1H, CH-12b), 1.49-1.34 (m, 1H, CH-11b), 1.41 (td, *J* = 14.4, 4.3 Hz, 1H, CH-1b), 1.32-1.20 (m, 1H, CH-6b), 1.30-1.20 (m, 2H, CH-14, CH-15b), 1.20-1.07 (m, 1H, CH-7b), 1.03 (s, 3H, CH_3-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.1 (C, C-3), 209.5 (C, C-20), 63.7 (CH, C-17), 56.6 (CH, C-14), 44.2 (CH, C-5), 44.1 (br s, C, C-13), 42.3 (CH_2, C-4), 40.7 (CH, C-9), 39.0 (CH_2, C-12), 37.2 (CH_2, C-2), 36.9 (CH_2, C-1), 35.5 (CH, C-8), 34.9 (C, C-10), 31.5 (CH_3, C-21), 26.5 (CH_2, C-6), 25.8 (CH_2, C-7), 24.4 (CH_2, C-15), 22.9 (CH_2, C-16), 22.6 (CH_3, C-19), 21.2 (CH_2, C-11);

MS (ESI+) *m/z*, (%): 320 (14, $[M(D_3)+H]^+$), 339 (1, $[M(D_0)+Na]^+$), 340 (0, $[M(D_1)+Na]^+$), 341 (1, $[M(D_3)+Na]^+$), 342 (100, $[M(D_3)+Na]^+$), 661 (4, $[2M+Na]^+$);

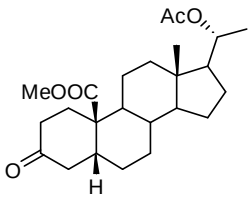
HRMS (CI+) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{30}{}^2H_3O_2$ 320.2669, found 320.2667;

Anal. Calcd for $C_{21}H_{29}D_3O_2$: C, 78.94; H, 10.10; Found: C, 78.43; H, 10.55;

Isotopic purity 96%.

5.5. SYNTHESIS OF [19,19,19]-D_3 PREGNANE STEROIDS

Methyl (20*R*)-20-acetoxy-3-oxo-5β-pregnan-19-oate (256)



A stirred solution of alcohol **255** (564 mg, 1.50 mmol) in acetonitrile (3.75 mL), tetrachloromethane (3.75 mL) and water (5.7 mL) was cooled to 0 °C and $RuO_2{\cdot}nH_2O$ (60% Ru, 5.0 mg, 2 mol%) was added. $NaIO_4$ (1.08 g, 5.05 mmol) was added portionwise and the heterogenous reaction mixture was stirred vigorously for 4 h, until the conversion was complete. The reaction was quenched by addition of solid Na_2SO_3 (0.5 g) which caused discoloration of the solution. The solution was acidified by addition of concentrated hydrochloric acid to pH 1-2. The steroid was extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. The resulting oil was dissolved in MeOH (5 mL) with Et_2O (25 mL) and trimethylsilyldiazomethane solution (0.8 mL, 2 M in THF) was added. After 2 h, the esterification was complete and the reaction mixture was quenched by addition of acetic acid (0.2 mL). The solvents were evaporated *in vacuo* and the crude product was purified on a column of silica gel (20 g) in hexanes/EtOAc (8:2) to afford 507 mg (84%) of ester **256** as a colorless solid.

Mp 113-116 °C (Et_2O);

$[\alpha]_D^{20}$ +17.1 (*c* 0.610, $CHCl_3$);

IR (ATR); ν[cm^{-1}]: 1027 (C-O, acetate), 1205 (C-O, ester), 1251, 1263, 1372 (CH_3), 1462 (CH_2), 1721, 1732 (C=O), 2840, 2882 (CH_2), 2939;

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (dq, *J* = 10.4, 6.1 Hz, 1H, CH-20), 3.70 (s, 3H, OCH_3), 2.01 (s, 3H, OAc), 1.16 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.79 (s, 3H, CH_3-18);

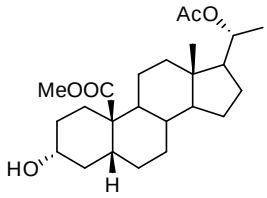
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4, 176.0, 170.4, 72.9, 56.1, 54.9, 51.6, 48.3, 42.6, 42.1, 41.4, 39.6, 39.1, 36.3, 36.1, 31.7, 27.7, 25.9, 25.5, 24.2, 21.7, 21.5, 19.9, 12.5.

MS (ESI+) *m/z*, (%): 345 (10, $[M–AcOH+H]^+$), 367 (10, $[M–AcOH+Na]^+$), 427 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{36}NaO_5$ 427.2455; Found 427.2456.

Anal. Calcd for $C_{24}H_{36}O_5$: 71.26 C, 8.97 H; Found: 71.35 C, 9.05 H;

Methyl (20*R*)-20-acetoxy-3α-hydroxy-5β-pregnan-19-oate (257)



Anhydrous cerium(III) chloride (136 mg, 0.55 mmol) was added to a stirred solution of ketone **256** (203 mg, 0.50 mmol) in methanol:tetrahydrofuran (2:1, 10 mL). The mixture was allowed to stir at room temperature until homogeneous solution resulted. Sodium borohydride (19 mg, 0.50 mmol) was added in small portions over 5 min. After 10 min of stirring, acetic acid (0.2 mL) was added and the solvent was evaporated *in vacuo*. The residue was partitioned between water (50 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). The organic layers were collected, washed subsequently with saturated aq. $KHCO_3$ (50 mL) and water (50 mL), dried, and the solvent was evaporated. Preparative TLC of the residue in a mixture of benzene/EtOAc (8:2) afforded 191 mg (94%) of **257** as a colorless solid.

Mp 94-96 °C (acetone/hexane);

$[\alpha]_D^{20}$ +13.8 (*c* 0.650, $CHCl_3$);

IR (ATR); ν[cm^{-1}]: 1042 (C-O, acetate), 1088, 1117, 1140, 1217 (C-O, ester), 1244, 1372 (CH_3), 1460 (CH_2), 1735 (C=O), 2880, 2955 (CH_2), 3278 (O-H);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (dq, *J* = 10.4, 6.1 Hz, 1H, CH-20), 3.72 (tt, *J* = 10.8, 4.8 Hz, 1H, CH-3), 3.66 (s, 3H, OCH_3), 2.01 (s, 3H, OAc), 1.15 (d, *J* = 6.1 Hz, 1H, CH_3-21), 0.71 (s, 3H, CH_3-18);

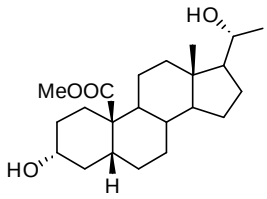
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 170.4, 72.9, 70.4, 56.1, 54.8, 51.2, 48.7, 42.4, 39.5, 39.1, 37.7, 36.5, 35.8, 30.4, 29.4, 28.3, 26.5, 25.4, 24.2, 21.4, 20.9, 19.8, 12.3.

MS (ESI+) *m/z*, (%): 269 (26, $[M–AcOH–HCOOMe–H_2O+H]^+$), 287 (26, $[M–AcOH–HCOOMe+H]^+$) 329 (11, $[M–AcOH–H_2O+H]^+$), 347 (36, $[M–AcOH+H]^+$), 407 (10, $[M+H]^+$), 429 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{38}NaO_5$ 429.2612; Found: 429.2612;

Anal. Calcd for $C_{24}H_{38}O_5$: 70.90 C, 9.42 H; Found: 70.84 C, 9.45 H.

Methyl (20*R*)-3α,20-dihydroxy-5β-pregnan-19-oate (258)



Aq. sulfuric acid (3 M, 3 mL) was added to a solution of acetate **257** (271 mg, 0.67 mmol) in methanol (30 mL) and the reaction mixture was stirred at room temperature. After 7 days, methanol was evaporated *in vacuo*. The residue was partitioned between Et_2O (250 mL) and water (50 mL) and the aqueous phase was extracted with Et_2O (2 × 50 mL). The organic layers were collected, washed subsequently with saturated aq. $KHCO_3$ (2 × 100 mL) and water (100 mL), dried, and the solvent was evaporated. Preparative TLC of the residue in a mixture of benzene/EtOAc (1:1) afforded 206 mg (84%) of **258** as a colorless solid,

Mp 235-238 °C (acetone/hexane);

$[\alpha]_D^{20}$ +7.2 (*c* 0.570, $CHCl_3$);

IR (ATR); ν[cm^{-1}]: 1044 (C-OH), 1099, 1117, 1139, 1223, 1278, 1373 (CH_3), 1460 (CH_2), 1727 (C=O), 2878 (CH_2), 2940, 3299, 3356 (O-H);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77-3.70 (m, 2H, CH-20, CH-3), 3.67 (s, 3H, OCH_3), 1.14 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.84 (s, 3H, CH_3-18);

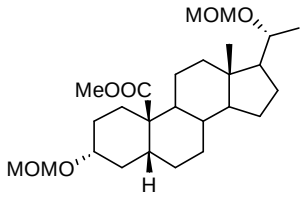
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 70.7, 70.6, 58.4, 56.3, 51.3, 48.9, 42.7, 40.4, 39.3, 37.8, 36.6, 36.0, 30.5, 29.7, 28.5, 26.6, 25.7, 24.6, 23.6, 21.0, 12.5.

MS (ESI+) *m/z*, (%): 365 (6, $[M+H]^+$), 387 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{36}NaO_4$ 387.2506; Found: 387.2506;

Anal. Calcd for $C_{22}H_{36}O_4$ (364.5): 72.49 C, 9.95 H; Found: 72.34 C, 9.87 H.

Methyl (20*R*)-3α,20-bis(methoxymethoxy)-5β-pregnan-19-oate (259)



Diol **258** (255 mg, 0.70 mmol) was dissolved in dry dichloromethane (12 mL), the resulting solution was cooled in an ice bath, and *N*,*N*-diisopropylethylamine (1.46 mL, 8.4 mmol) and bromomethyl methyl ether (90%, 0.38 mL, 4.2 mmol) were added. The mixture was stirred at room temperature for 12 h, poured into ice water (100 mL) and extracted with Et_2O (2 × 100 mL). The collected extracts were washed sequentially with 5% aq. citric acid (2 × 100 mL), water (100 mL), saturated aq. $KHCO_3$ (100 mL) and water (100 mL), dried and the solvent was evaporated. Preparative TLC of the residue in a mixture of benzene/Et_2O (4:1) afforded 266 mg (84%) of derivative **259** as a colorless oil,

$[\alpha]_D^{20}$ +4.6 (*c* 0.550, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 913 (C-OCH_2OCH_3), 1036, 1103, 1142, 1193 (C-O, ester), 1718 (C=O), 2826, 2889 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, *J* = 6.9 Hz, 1H, OC$H_a$$H_b$O-20), 4.70 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.62 (d, *J* = 6.9 Hz, 1H, OCH_aH_bO-20), 3.66 (s, 3H, $COOCH_3$), 3.64-3.56 (m, 1H, CH-3), 3.60 (dq, *J* = 9.8, 6.0 Hz, 1H, CH-20), 3.40 (s, 3H, CH_2OCH_3), 3.38 (s, 3H, CH_2OCH_3), 1.13 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.73 (s, 3H, CH_3-18);

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 95.4, 94.7, 76.4, 75.8, 56.5, 56.4, 56.1, 55.2, 51.3, 49.0, 42.6, 39.9, 39.3, 37.8, 36.7, 33.3, 30.5, 28.6, 27.0, 26.6, 25.8, 24.4, 21.0, 19.8, 12.4.

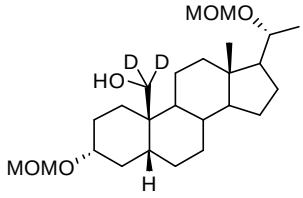
MS (ESI+) *m/z*, (%): 391 (23, $[M–CH_3OCH_2OH+H]^+$), 475 (100%, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{44}NaO_6$ 475.3030; Found 475.3031.

Anal. Calcd for $C_{26}H_{44}O_6$: 68.99 C, 9.80 H; Found: 68.74 C, 9.78 H.

(20*R*)-3α,20-Bis(methoxymethoxy)-[19,19-$^2H_2$]-5β-pregnan-19-ol (260)

Protected ester **259** (500 mg, 1.11 mmol) in THF (15 mL) was refluxed with $LiAlD_4$ (140 mg, 3.33 mmol) under argon for 4 h. The reaction mixture was chilled in an ice bath, the remaining deuteride was destroyed with saturated aq. Na_2SO_4, and the mixture was diluted with Et_2O (15 mL).



The solids were filtered off on a celite column (3 cm), which was washed with Et_2O (50 mL). The resulting solution was washed sequentially with cold 5% aq. citric acid, water, saturated aq. $KHCO_3$ (2×50 mL), and water. After drying, the solvents were evaporated, leaving 435 mg (92%) of **260** as a colorless oil.

$[\alpha]_D^{20}$ +39.5 (*c* 0.299, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 912 (COCOC, methoxymethoxy), 1038, 1056 (C-OH), 1102, 1144, 1376 (C-CH_3), 2120, 2243 (CD_2), 2826, 2889 (CH_2), 3479, 3624 (OH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, *J* = 7.0 Hz, 1H, OC$H_a$$H_b$O-20), 4.70 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.60 (d, *J* = 6.9 Hz, 1H, OCH_aH_bO-20), 3.61-3.51 (m, 2H, CH-3, CH-20), 3.39 (s, 3H, CH_2OCH_3), 3.38 (s, 3H, CH_2OCH_3), 1.12 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.67 (s, 3H, CH_3-18);

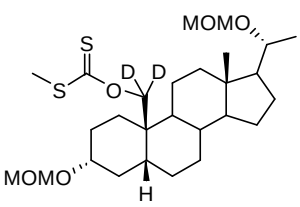
^{13}C NMR (101 MHz, $CDCl_3$) δ 95.4, 94.7, 76.5, 76.4, 56.7, 56.5, 56.0, 55.2, 42.5, 40.1, 40.0, 38.8, 35.7, 34.2, 33.4, 28.4, 27.3, 26.8, 26.0, 25.8, 24.2, 20.8, 19.8, 12.5;

MS (ESI+) *m/z*, (%): 449 (100, $[M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{42}{}^2H_2NaO_5$ 449.3206, found 449.3205.

Isotopic purity >99%.

(20*R*)-3α,20-Bis(methoxymethoxy)-[19,19-$^2H_2$]-5β-pregnan-19-yl *O*-(*S*-methyldithiocarbonate) (261)



Hydroxy derivative **260** (400 mg, 0.94 mmol) in THF (10 mL) was cooled to 0 °C under argon and *n*-BuLi in THF (1.6 M, 0.88 mL, 1.55 mmol) was added dropwise. The reaction mixture was stirred for 7 h at room temperature followed by addition of carbon disulfide (228 mg, 3.00 mmol) and the stirring was continued for 15 h. Iodomethane (254 mg, 1.79 mmol) was added in a single portion and the reaction mixture was stirred for another 3 h. The red solution was quenched with water, the product was extracted with Et_2O (3 × 10 mL), washed sequentially with cold 5% aq. citric acid (25 mL), water, saturated aq. $KHCO_3$ (2 × 25 mL), and water (25 mL). After drying over $MgSO_4$, the solvents were evaporated. The residue was purified by preparative TLC on silica gel in toluene/EtOAc 7:3, to afford 394 mg (81%) of **261** as a yellow oil.

$[\alpha]_D^{20}$ +30.6 (*c* 0.346, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 912, 1038, 1057 (C=S), 1102, 1144, 1242 (COC, xanthate), 1376 (CH_3), 1412 (S-CH_3), 2120, 2243 (CD_2), 2826, 2889 (CH_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$O-20), 4.70 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.61 (d, *J* = 6.8 Hz, 1H, OCH_aH_bO-20), 3.62-3.54 (m, 2H, CH-3, CH-20), 3.393 (s, 3H, CH_3O), 3.385 (s, 3H, CH_3O), 2.57 (s, 3H, CH_3S), 1.12 (d, *J* = 6.0 Hz, 3H, H-21), 0.70 (s, 3H, H-18);

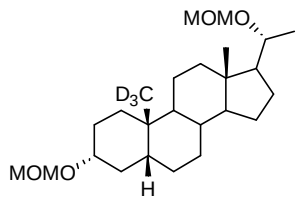
^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2, 95.5, 94.7, 76.4, 76.1, 56.7, 56.5, 56.0, 55.2, 42.5, 40.04, 39.95, 38.6, 35.9, 35.6, 33.4, 29.2, 27.2, 26.9, 25.9, 25.8, 24.2, 21.0, 19.8, 18.9, 12.6.

MS (ESI+) *m/z*, (%): 539 (42, $[M+Na]^+$), 1055 (100, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{44}{}^2H_2NaO_5S_2$ 539.2804, found 539.2793.

Isotopic purity >99%.

(20*R*)-3α,20-Bis(methoxymethoxy)-[19,19,19-$^2H_3$]-5β-pregnane (262)



A reaction mixture of tributyltin deuteride (312 µL, 1.16 mmol), 2,2'-azobis(2-methylpropionitrile) (12.5 mg, 77.4 µmol), xanthate **261** (400 mg, 0.774 mmol) in dry benzene (20 mL) was refluxed under argon for 4 h. After cooling to room temperature, the solvent was evaporated, and the oily residue was purified by chromatography on silica gel (25 g) in 15% EtOAc/hexanes to afford 312 mg (98%) of steroid **262** as a colorless oil.

$[\alpha]_D^{20}$ +28.6 (*c* 0.342, $CHCl_3$);

IR ($CHCl_3$); ν[cm^{-1}]: 1038, 1102 (COCOC), 1144, 1376 (CH_3), 2126, 2211, 2225 (CD_3), 2826, 2889 (CH_2);

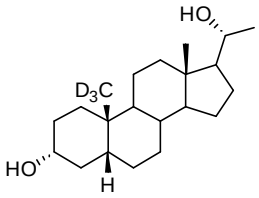
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$O-20), 4.69 (AB system, *J* = 6.8 Hz, 2H, OCH_2O-3), 4.61 (d, *J* = 6.8 Hz, 1H, OCH_aH_bO-20), 3.58 (dq, *J* = 9.9, 6.0 Hz, 1H, CH-20), 3.53 (tt, *J* = 11.1, 4.7 Hz, 1H, CH-3), 3.39 (s, 3H, CH_3O), 3.37 (s, 3H, CH_3O), 1.12 (d, *J* = 6.0 Hz, 3H, CH_3-21), 0.68 (s, 3H, CH_3-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 95.4, 94.5, 76.8, 76.4, 56.7, 56.02, 55.99, 55.1, 42.5, 42.1, 40.4, 39.7, 35.8, 35.3, 34.5, 33.5, 27.6, 27.2, 26.4, 25.8, 24.3, 20.7, 19.8, 12.4.

MS (ESI+) *m/z*, (%): 431 (0, $[M(D_0)+Na]^+$), 432 (0.6, $[M(D_1)+Na]^+$), 433 (1.3, $[M(D_2)+Na]^+$), 434 (100, $[M(D_3)+Na]^+$), 846 (40, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{41}{}^2H_3NaO_4$ 434.3320, found 434.3319;
Anal. Calcd for $C_{25}H_{41}D_3O_4$: C, 72.95; H, 10.77; Found: C, 73.23; H, 11.40;
Isotopic purity: 98%.

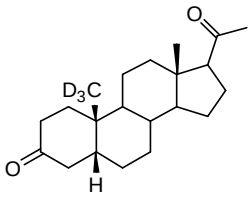
(20*R*)-[19,19,19-$^2H_3$]-5β-Pregnane-3α,20-diol (263)



Steroid **262** (324 mg, 788 µmol) was dissolved in MeOH (10 mL) and conc. aq. HCl (100 µL, 35% w/v) was added dropwise with stirring. The reaction mixture was refluxed for 3 h, followed by quenching with saturated aq. $NaHCO_3$ (50 mL). The suspension was extracted with $CHCl_3$/*n*BuOH (20:1, 3 × 10 mL), dried with $MgSO_4$ and evaporated *in vacuo* to afford 245 mg (96%) of diol **263** as colorless crystals.

Mp 232-234 °C (EtOH); Lit.[348] 233.5-234.5 °C for the nondeuterated compound;
$[\alpha]_D^{20}$ +2.8 (*c* 0.216, EtOH); Lit.[348] +12 (*c* 0.86 in EtOH);
IR ($CHCl_3$); ν[cm^{-1}]: 1033 (C-OH), 1378 (CH_3), 1452 (CH_2), 2203, 2221, 2225 (CD_3), 2867 (CH_2), 2887 (CH_3), 2930 (CH_2), 3279, 3342, 3609 (OH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dd, *J* = 9.8, 6.1 Hz, 1H, CH-20), 3.63 (tt, *J* = 11.0, 4.7 Hz, 1H, CH-3), 2.08-2.00 (m, 1H, CH-12a), 1.14 (d, *J* = 6.1 Hz, 3H, CH_3-21), 0.74 (s, 3H, CH_3-18);
^{13}C NMR (101 MHz, $CDCl_3$) δ 71.9, 70.6, 58.7, 56.0, 42.6, 42.1, 40.5, 40.3, 36.4, 35.7, 35.4, 34.6, 30.6, 27.2, 26.5, 25.7, 24.5, 23.6, 20.7, 12.5.
MS (ESI+) *m/z*, (%): 339 (0), 340 (0), 341 (5), 346 (100, $[M(D_3)+Na]^+$), 668 (54, $[2M+Na]^+$);
HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{33}{}^2H_3NaO_2$ 346.2796, found 346.2796;
Anal. Calcd for $C_{21}H_{33}D_3O_2$: C, 77.96; H, 11.21;Found: C, 78.92; H, 11.54;
Isotopic purity: 95%.

[19,19,19-$^2H_3$]-5β-Pregnane-3,20-dione (120)



Steroid **263** (285 mg, 881 µmol) was suspended in acetone (60 mL) and the mixture was cooled in an ice bath. Jones' reagent (0.9 mL, 3 M aq. solution, 2.7 mmol) was added dropwise with stirring and the suspension was stirred at 0 °C for 2 h. The excess of the reagent was quenched with *i*PrOH and the mixture was concentrated *in vacuo*. The mixture was diluted with 30 mL of 5% aq. HCl and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (25 mL), dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10 g) in 10% EtOAc/hexanes to afford 271 mg (96%) of diketone **120** as colorless crystals.

Mp 116-119 °C, Lit.[222] 118-119 °C (EtOAc/heptane) for the nondeuterated compound;
$[\alpha]_D^{20}$ +105.7 (*c* 0.280, $CHCl_3$);
IR (ATR); ν[cm^{-1}]: 1186, 1204, 1356, 1392 (CH_3), 1461 (CH_2), 1703, 1724 (C=O), 2211, 2230 (C^2H_3), 2860, 2935 (CH_2);
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 15.0, 13.4 Hz, 1H, CH-4a), 2.56 (t, *J* = 9.0 Hz, 1H, CH-17), 2.34 (tdd, *J* = 14.6, 5.3, 0.7 Hz, 1H, CH-2a), 2.23-2.14 (m, 1H, CH-2b), 2.23-2.11 (m, 1H, CH-16a), 2.13 (s, 3H, CH_3-21), 2.11-2.02 (m, 1H, CH-12a), 2.09-1.99 (m, 2H, CH-1a, CH-4b), 1.96-1.82 (m, 1H, CH-6a), 1.89-1.78 (m, 1H, CH-5), 1.76-1.66 (m, 1H, CH-15a), 1.72-1.60 (m, 1H, CH-16b), 1.61-1.51 (m, 1H, CH-11a), 1.58-1.50 (m, 1H, CH-7a), 1.58-1.48 (m, 1H, CH-9), 1.56-1.45 (m, 1H, CH-8), 1.51-1.41 (m, 1H, CH-12b), 1.49-1.34 (m, 1H, CH-11b), 1.41 (td, *J* = 14.4, 4.3 Hz, 1H, CH-

1b), 1.32-1.20 (m, 1H, CH-6b), 1.30-1.20 (m, 2H, CH-14, CH-15b), 1.20-1.07 (m, 1H, CH-7b), 0.64 (s, 3H, CH_3-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0 (C, C-3), 209.4 (C, C-20), 63.8 (CH, C-17), 56.6 (CH, C-14), 44.3 (C, C-13), 44.1 (CH, C-5), 42.3 (CH_2, C-4), 40.7 (CH, C-9), 39.1 (CH_2, C-12), 37.1 (CH_2, C-2), 36.9 (CH_2, C-1), 35.5 (CH, C-8), 34.7 (C, C-10), 31.5 (CH_3, C-21), 26.5 (CH_2, C-6), 25.8 (CH_2, C-7), 24.4 (CH_2, C-15), 22.9 (CH_2, C-16), 21.2 (CH_2, C-11), 13.4 (CH_3, C-18).

MS (ESI+) *m/z*, (%): 320 (3, $[M(D_3)+H]^+$), 339 (0), 340 (0), 341 (5), 342 (100, $[M(D_3)+Na]^+$), 661 (35, $[2M+Na]^+$);

HRMS (ESI+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{29}{}^2H_3NaO_2$ 342.2483, found 342.2483;

Anal. Calcd for $C_{21}H_{29}D_3O_2$: C, 78.94; H, 10.10; Found: C, 78.72; H, 10.34;

Isotopic purity: 95%.

6. Appendix A: Kinetic Data of the Hajos-Parrish-Eder-Sauer-Wiechert Reaction

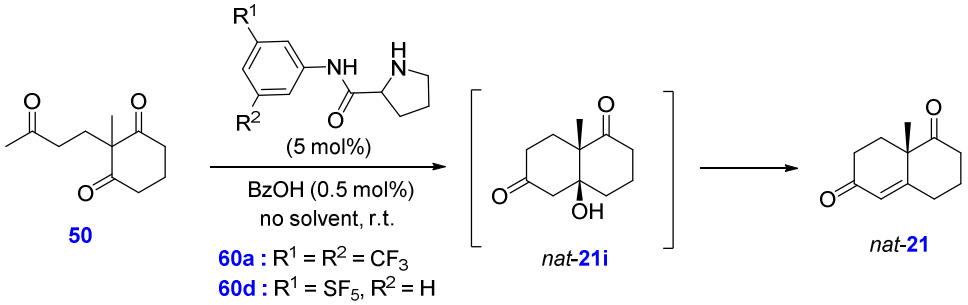
Reaction catalyzed by 5 mol% of prolinanilides 60 and 0.5 mol% of benzoic acid

Methodology:

Prolinanilide **60** (0.10 mmol, 5 mol%) was weighted in a conical 2 mL reaction vial, followed by addition of benzoic acid (1.2 mg, 10 µmol, 0.5 mol%), triketone **50** (392.5 mg, 2.00 mmol) and a V-shaped stir bar. The mixture was stirred at 700 rpm at rt in the closed vessel. At time given in the table, ca 3 mg aliquots were taken from the homogeneous mixture. The samples were immediately diluted with 10% iPrOH/hexane (1.5 mL, HPLC grade). Ca. 15 µL of the diluted sample was analyzed by HPLC (isocratic 50% EtOAc/hexane on Hibar® RT 250-4 LiChrospher® Si 100 Column (Merck Millipore, 5 µm particle size, L × I.D. 25 cm × 4 mm) t = 25 °C, 1.0 mL·min^{-1}). Detection was performed by a light scattering detector (1.60 SLM of nitrogen, evaporator T = 40 °C and nebuliser T = 40 °C). Retention times were: t_{21} = 6.93 min, t_{50} = 7.40 min, t_{21i} = 10.59 min.

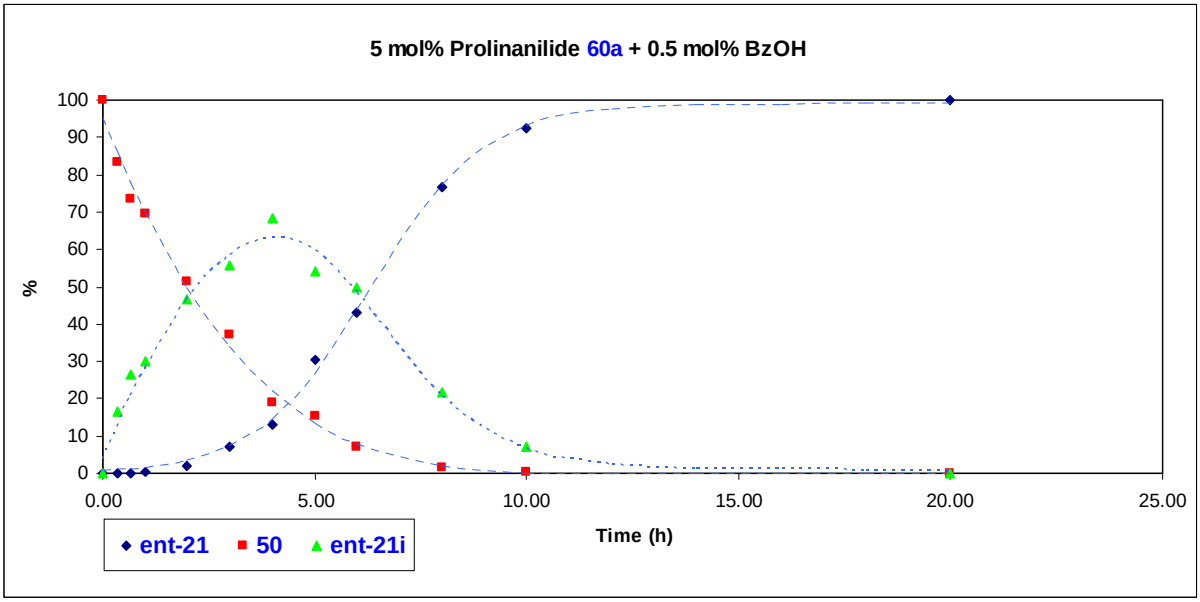
Analysis of the final product **21** was performed on a Chiralcel® OD column (Daicel, 250 × 4.6 mm, 10µm particle size, isocratic hexane/*i*PrOH 90:10, 1.0 mL·min^{-1}, detection at 254 nm) and gave retention times t_S = 16.0 min, t_R = 16.7 min.

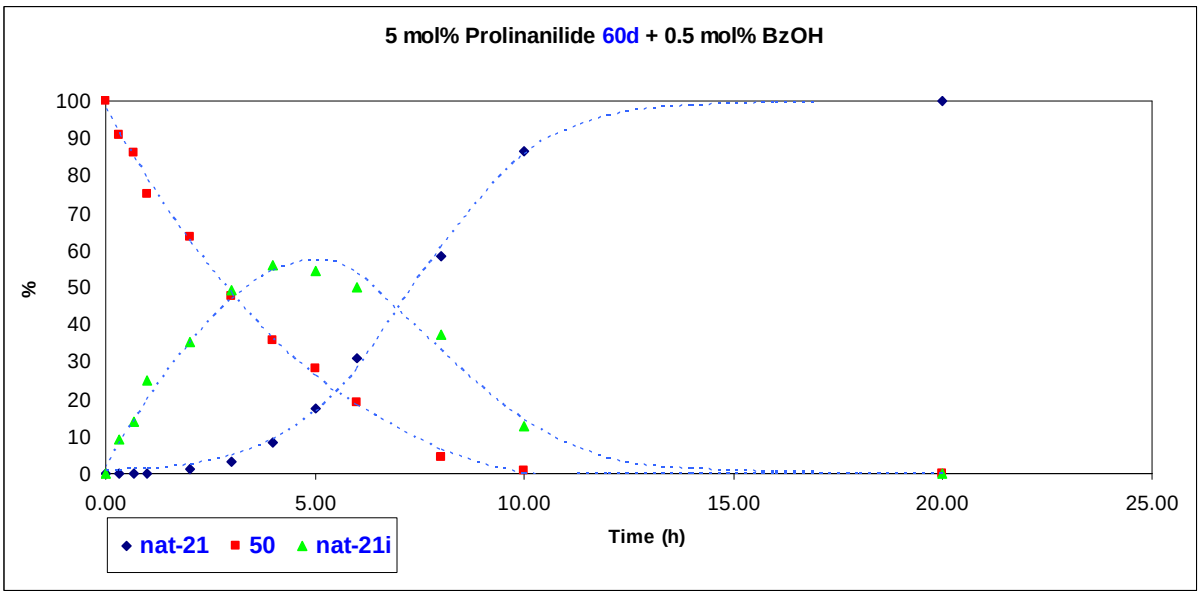
Table 11: HPESW reaction co-catalyzed by 0.5 mol% of benzoic acid



	Composition (%)					
	Catalyst: (*R*)-**60a**			Catalyst: (*S*)-**60d**		
Time (h)	**50**	**21i**	**21**	**50**	**21i**	**21**
0.00	100	0.0	0.0	100	0.0	0.0
0.33	83.5	16.5	0.0	90.7	9.3	0.0
0.67	73.4	26.6	0.0	85.9	14.1	0.0
1.00	69.6	30.2	0.2	74.9	24.9	0.2
2.00	51.5	46.5	2.1	63.5	35.5	1.0
3.00	37.0	55.8	7.2	47.7	49.3	3.0
4.00	18.9	68.2	12.8	35.8	56.1	8.2
5.00	15.5	54.2	30.3	28.3	54.2	17.5
6.00	7.2	49.8	43.0	19.1	49.8	31.1
8.00	1.6	21.7	76.7	4.3	37.3	58.5
10.00	0.3	7.1	92.6	0.8	12.7	86.5
20.00	0.0	0.0	100[a]	0.0	0.0	100[b]

Linear proportionality was assumed between the amount of compounds **50, 21i, 21** and the detector response. The composition of the reaction mixture was calculated as percentual ratio of these 3 compounds. The principal retention times were obtained by analysis of pure compounds. [a] Final product *ent*-**21** had ee = 93.4%. [b] Final product *nat*-**21** had ee = 92.8%.

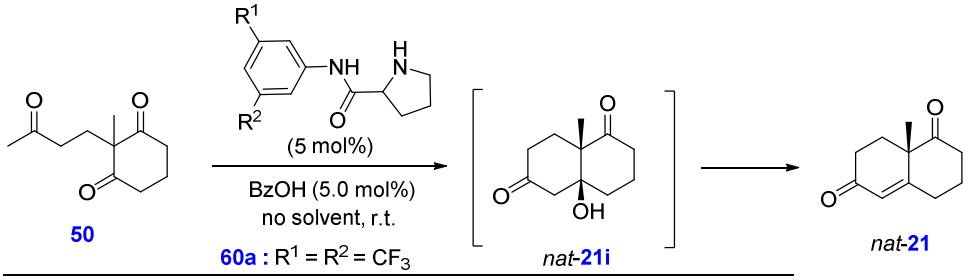

5 mol% Prolinanilide 60a + 0.5 mol% BzOH
%
Time (h)
ent-21
50
ent-21i


5 mol% Prolinanilide 60d + 0.5 mol% BzOH
%
Time (h)
nat-21
50
nat-21i

Reaction catalyzed by 5 mol% of prolinanilide 60a and 0.5 mol% of benzoic acid

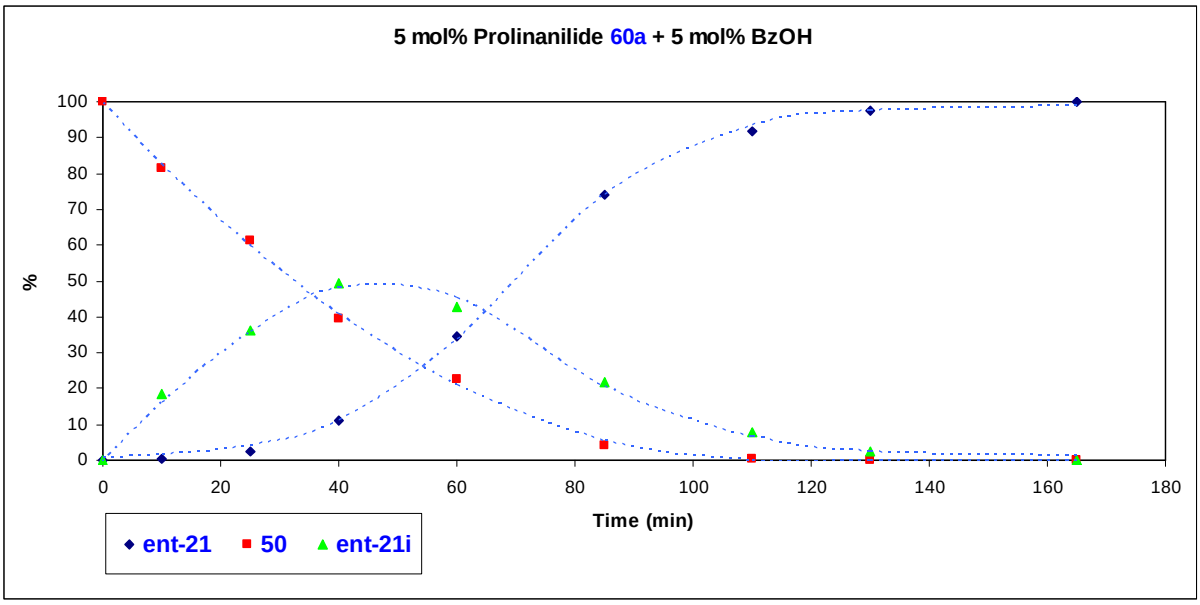
Methodology: Identical to the previous case, but higher amount of benzoic acid (12.2 mg, 100 µmol, 5.0 mol%) was used.

Table 12: HPESW reaction co-catalyzed with 5.0 mol% of benzoic acid



	Composition (%)		
Time (min)	**50**	**21i**	**21**
0	100	0.0	0.0
10	81.3	18.5	0.2
25	61.2	36.4	2.4
40	39.6	49.4	10.9
60	22.5	42.8	34.6
85	3.9	21.8	74.3
110	0.4	8.0	91.6
130	0.0	2.3	97.7
165	0.0	0.0	100[a]

Linear proportionality was assumed between the amount of compounds **50, 21i, 21** and the detector response. Composition of the reaction mixture was calculated as percentual ratio of the 3 compounds. The principal retention times were obtained by analysis of pure compounds. [a] Final product *ent*-**21** had ee = 93.6%.



7. APPENDIX B: BIOLOGICAL ACTIVITIES

7.1. NMDA RECEPTOR ACTIVITY

The *in vitro* activity of **117** and **118** at NMDA receptors was tested by Mgr. Barbora Krausová in the laboratory of Dr. Ladislav Vyklický, Jr. at the Institute of Physiology of Academy of Sciences of the Czech Republic. The currents triggered by 100 μM glutamate were recorded from HEK293 cells, voltage-clamped at a holding potential of −60 mV, which expressed recombinant GluN1/GluN2 receptors. All compounds were tested at single concentrations (50-200 μM). The inhibition of responses to fast application of glutamate was measured and the IC_{50} was determined using the formula $IC_{50} = c \times [(1 - I) / I]^{1/h,}$ where c is the concentration of a steroid analog, I is the relative degree of inhibition and h = 1.2 or 1.0 is the apparent Hill coefficient.[50,58] Full experimental details are provided elsewhere.[58]

Table 13: Inhibitory activity of selected compounds at NMDA receptor[a]

Compound	Relative Inhibition[b]	*SD*[c]	*c* (μM)[d]	IC_{50} (μM)	*SD*[c]	*h*	*n*[e]
nat-**2**	84%	± 3%	100	25	± 5	1.2	5
nat-**117**	56%	± 6%	200	160	± 36	1.0	4
ent-**117**	40%	± 6%	200	308	± 78	1.0	7
nat-**118**	78%	± 6%	50	28	± 9	1.0	5
ent-**118**	58%	± 2%	100	36	± 3	1.0	7

[a] The data are courtesy of Ms. B. Krausová from Dr. L. Vyklický's group at Physiological Institute AS CR. [b] Change of current induced by 100 μM glutamate. [c] Standard deviation. [d] Concentration of applied steroid analog. [e] Number of cells studied.

7.2. Antiviral Activity

All compounds synthesized during the total synthesis of *ent*-progesterone, including the bicyclic and tricyclic steroid analogs (**Chapters 3.1, 3.2**), were tested for potential antiviral activity. A high-throughput screening for hepatitis-C virus (HCV) replicons 1A, 1B and 2A was performed at Gilead Sciences (California, USA), the results of most active compounds are summarized in **Table 14**. Some low micromolar activities were detected, yet the gap between EC_{50} and CC_{50} was very narrow in all active compounds. These compounds were also tested in human immunodeficiency virus (HIV) and human rhinovirus assays at Gilead Sciences, but none of the compounds showed any appreciable activity. An identical set of compounds was tested for activity against the dengue virus in Vero cells, by Dr. Jan Weber's group (IOCB AS CR, Praha). Two genotypes were included in the assay – DENV-1 and DENV-2. Only compound *ent*-**150c** exhibited detectable activity, but also considerable cytotoxicity.

Table 14: Antiviral activity and cytotoxicity of selected compounds

Sample	HCV Replicon 1B		HCV Replicon 2A		HCV Replicon 1A		DENV-1	DENV-2	Dengue
	EC_{50} (μM)	CC_{50} (μM)	EC_{50} (μM)	CC_{50} (μM)	EC_{50} (μM)	CC_{50} (μM)	$EC50$ (μM)	EC_{50} (μM)	CC_{50} (μM)
ent-**172**	3.7	33.0	31.5	18.4	n/a	n/a	> 50	> 50	> 50
nat-**150b**	4.7	23.2	14.2	8.4	n/a	n/a	< 50	< 50	< 50
ent-**186A,a**	7.3	19.9	21.8	16.0	n/a	n/a	> 50	> 50	> 50
ent-**184b**	8.2	36.1	21.2	39.4	n/a	n/a	> 50	> 50	> 50
nat-**161**	8.6	26.8	29.0	26.2	n/a	n/a	> 50	> 50	> 50
ent-**186B,b**	9.2	15.2	27.4	≥ 44	n/a	n/a	n/a	n/a	n/a
ent-**161**	10.8	≥ 44	31.0	28.8	n/a	n/a	n/a	n/a	n/a
ent-**150c**	3.5	≥ 44	29.2	≥ 44	3.4	28.0	3	7	26

8. APPENDIX C: X-RAY DATA SHEETS

Single-crystal X-ray diffraction data for all compounds were obtained on a Bruker Apex II CCD diffractometer applying monochromatic Mo *K*α radiation (λ = 0.71073 Å) at 150 K. The structures were solved by direct methods and refined by full-matrix least squares based on F^2.[349] The hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors $H_{iso}(H)$ = 1.2 U_{eq}(pivot atom). The crystallographic data are summarized in Tables S1-S3. Crystallographic data (excluding structure factors) for structures *ent*-**161** **(CCDC 1048883)**, *nat*-**184a** **(CCDC 1048884),** *ent*-**193** **(CCDC 1048885),** *ent*-**206** **(CCDC 1048886),** *ent*-**195** **(CCDC 1048887)** and *ent*-**207** **(CCDC 1048888)** have been deposited at the Cambridge Crystallographic Data Centre with their respective CCDC numbers given in parentheses. Copies of the data can be obtained, free of charge by application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 15: Crystal data, data collection and refinement parameters for *ent*-**161,** *nat*-**184a** and *ent*-**193**

Compound		*ent*-**161** **(CCDC 1048883)**	*nat*-**184a** **(CCDC 1048884)**	*ent*-**193** **(CCDC 1048885)**
Empirical formula		$C_{17}H_{22}O_3$	$C_{31}H_{46}NO_4$	$C_{20}H_{26}O_3$
M_r		274.35	496.69	314.41
Crystal habit		Prism, colorless	Prism, colorless	Prism, colorless
Crystal size [mm]		0.54 × 0.48 × 0.33	0.71 × 0.64 × 0.61	0.47 × 0.42 × 0.41
Crystal system		Orthorhombic	Monoclinic	Orthorhombic
Space group		$P2_12_12_1$	$P2_1$	$P2_12_12_1$
Unit cell dimensions	a [Å]	11.0475 (4)	7.6957 (2)	6.5649 (2)
	b [Å]	11.1351 (4)	11.4919 (3)	10.1206 (2)
	c [Å]	11.7203 (3)	16.0817 (4)	25.5592 (6)
	β [°]	90	99.676 (1)	90
Volume [Å^3]		1441.77 (8)	1402.00 (6)	1698.17 (7)
Z		4	2	4
D_x [Mg m^{-3}]		1.264	1.177	1.230
μ [mm^{-1}]		0.09	0.08	0.08
θ_{max} [°]		27.5	27.5	27.5
Reflections measured		10226	20924	11011
Unique reflections/observed reflections		3314/3074 [$I > 2\sigma(I)$]	6417/6185 [$I > 2\sigma(I)$]	3907/3672 [$I > 2\sigma(I)$]
R_{int} [a]		0.022	0.019	0.017
Parameters refined		182	330	210
$R(F)$ [b], [$F^2 > 2\sigma(F^2)$]		0.033	0.044	0.037
$wR(F^2)$ [c]		0.081	0.123	0.097
S [d]		1.06	1.03	1.06
$\Delta\rho_{max}$; $\Delta\rho_{min}$ [e Å^{-3}]		0.20; −0.17	0.83; −0.23	0.26; −0.19

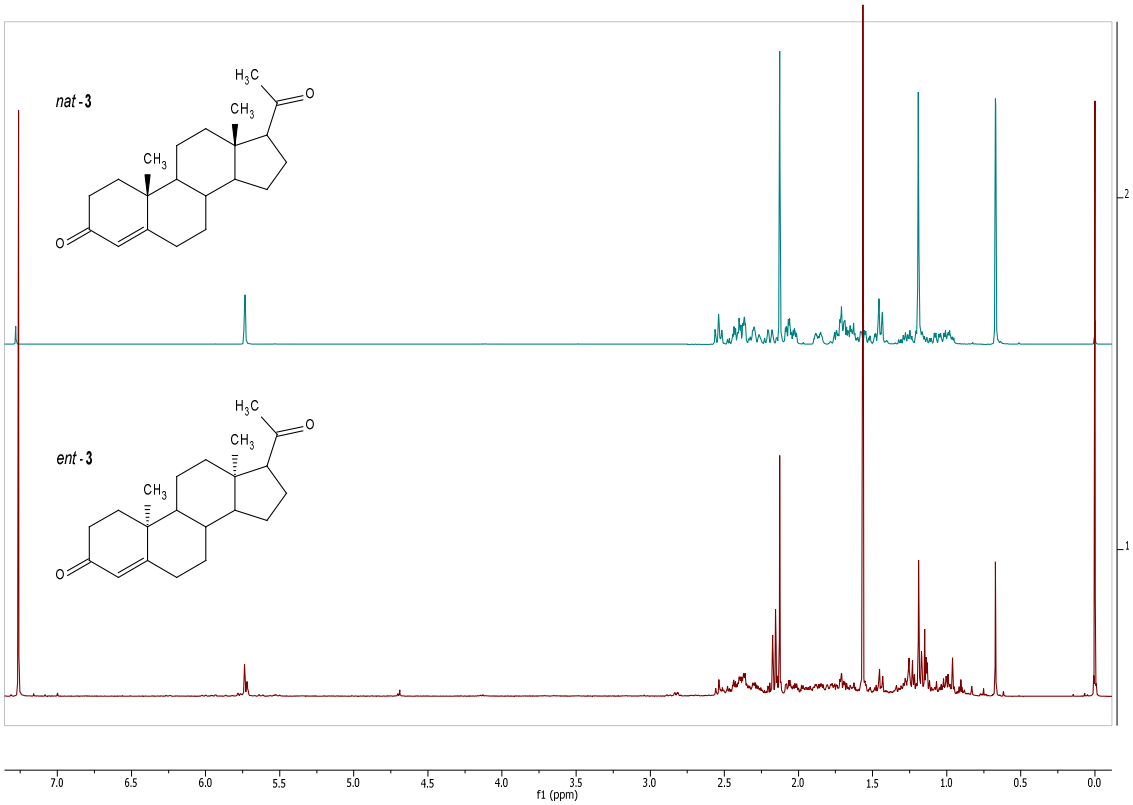
[a] $R_{int} = \Sigma \left| F_o^2 - F_{o,mean}^2 \right| / \Sigma F_o^2$, [b] $R(F) = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$, [c] $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$, weighting scheme: $w = [\sigma^2(F_o^2) + (w_1P)^2 + w_2P]^{-1}$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$., [d] $S = [\Sigma (w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$.

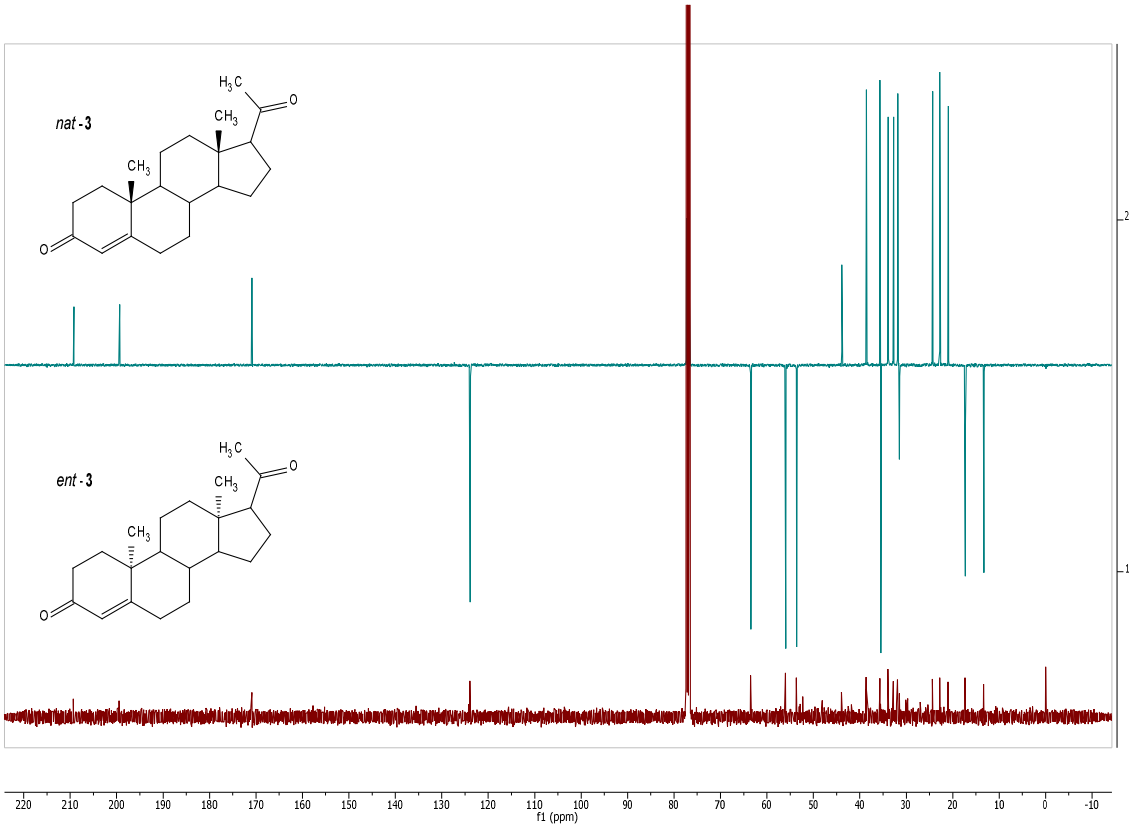
Table 16: Crystal data, data collection and refinement parameters for *ent*-**206,** *ent*-**195** and *ent*-**207**

Compound		*ent*-**206** (CCDC **1048886)**	*ent*-**195** (CCDC **1048887)**	*ent*-**207** (CCDC **1048888)**
Empirical formula		$C_{30}H_{47}NO_3$	$C_{20}H_{26}O_3$	$C_{21}H_{28}O_3$
M_r		469.69	314.41	328.43
Crystal habit		Plate, colorless	Prism, colorless	Prism, colorless
Crystal size [mm]		0.65 × 0.38 × 0.12	0.48 × 0.36 × 0.20	0.46 × 0.32 × 0.32
Crystal system		Orthorhombic	Monoclinic	Orthorhombic
Space group		$P2_12_12_1$	$P2_1$	$P2_12_12_1$
Unit cell dimensions	a [Å]	12.6414 (4)	6.7969 (1)	6.3502 (2)
	b [Å]	13.8253 (5)	18.2803 (4)	12.3688 (3)
	c [Å]	15.1716 (5)	7.4784 (2)	22.0325 (7)
	β [°]	90	116.557 (1)	90
Volume [Å^3]		2651.56 (15)	831.15 (3)	1730.53 (9)
Z		4	2	4
D_x [Mg m^{-3}]		1.177	1.256	1.261
μ [mm^{-1}]		0.07	0.08	0.08
θ_{max} [°]		27.5	27.5	27.5
Reflections measured		23544	12879	14978
Unique reflections/observed reflections		6093/5083 [$I > 2\sigma(I)$]	3829/3627 [$I > 2\sigma(I)$]	3970/3725 [$I > 2\sigma(I)$]
R_{int} [a]		0.034	0.021	0.023
Parameters refined		314	210	220
$R(F)$ [b], [$F^2 > 2\sigma(F^2)$]		0.041	0.032	0.034
$wR(F^2)$ [c]		0.090	0.083	0.088
S [d]		1.02	1.04	1.02
$\Delta\rho_{max}$; $\Delta\rho_{min}$ [e Å^{-3}]		0.20; −0.19	0.22; −0.17	0.26; −0.15

[a] $R_{int} = \Sigma \left| F_o^2 - F_{o,mean}^2 \right| / \Sigma F_o^2$, [b] $R(F) = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$, [c] $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$, weighting scheme: $w = [\sigma^2(F_o^2) + (w_1P)^2 + w_2P]^{-1}$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$., [d] $S = [\Sigma (w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$.

9. APPENDIX D: NMR SPECTRA OF *ENT*-PROGESTERONE





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11. PUBLICATIONS, PATENTS AND SCIENTIFIC PRESENTATIONS

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