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TOTAL SYNTHESIS OF (-)-METHOXYESTRONE

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Ph.D Thesis

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Prohlašuji, že jsem tuto práci vypracoval samostatně pod vedením školitele Prof. RNDr. Martina Kotory, CSc. a řádně ocitoval všechny použité prameny. Dále prohlašuji, že jsem tuto práci ani její části nepředložil k získání stejného nebo jiného akademického titulu.

V Praze dne 1.12.2012 .....

Robert Betík

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First and foremost I would like to express my gratitude to my supervisor Prof. RNDr. Martin Kotora CSc. for the interesting topic of my Ph.D work as well as valuable consultations throughout the work.

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1. Introduction

This dissertation is devoted to synthesis of estrone, one of the estrogenic human sex hormones. Total syntheses of natural compounds are, in general, among the most intriguing parts of organic chemistry and have served as a probing stone of synthetic methodology since the dawn of organic chemistry until today. Estrone itself, due to its rather complex tetracyclic terpenoid structure, constitutes an attractive and challenging synthetic target at the same time. The attractiveness is strengthened by the fact that estrone and many of its derivatives possesses biological activities and have been a major component of many pharmaceutical drugs. Moreover, recent discoveries[1] suggest that *ent*-steroids (non natural enantiomers of steroids) possesses different and potentially useful biological properties, than their natural equivalents.

In this work I would like to briefly introduce how the estrone was first discovered and isolated and show several total syntheses of the hormone that are, in my humble opinion, either important from the historical point of view or interesting from the synthetic point of view. Finally, I'd like to present my new diastereoselective and enantioselective synthesis of (±)-methoxyestrone and (-)-methoxyestrone respectively.

2. Discovery of Estrone

The isolation of estrone (theelin) was first reported in 1930 by Edward Albert Doisy. [2] His work began with the study of the mice estrous cycle. He determined that ovarian follicles precede the appearance of cornified cells in the vagina and showed that extracts from sow ovaries, when injected into ovarectomized mice, resulted in the production of cornified cells in the vagina. Based on this observation attempts to isolate the hormone from liquor folliculi were made, unfortunately, those efforts were futile. Later inspired by work of Aschheim and Zondek in 1927, who had discovered that the pregnant women urine possesses the estrogenic activity, the work on isolating the hormone from pregnancy urine began.[3]

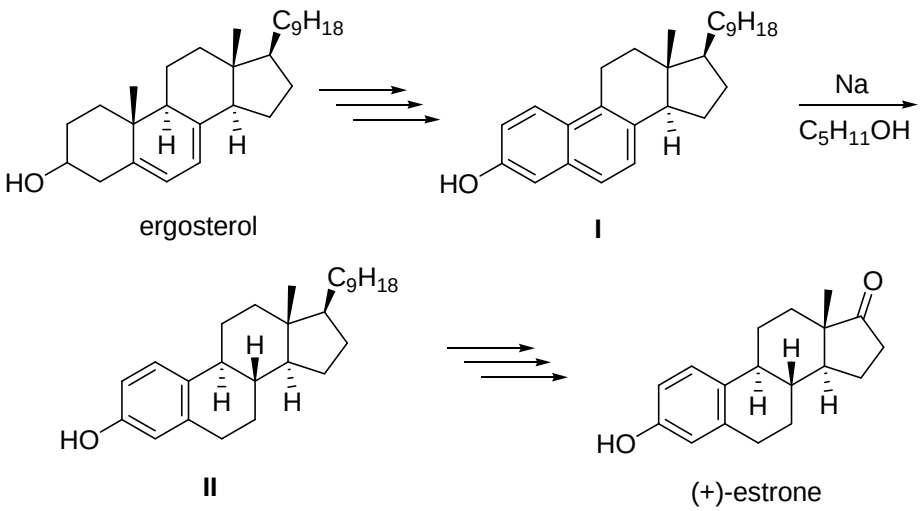
The methodology, which led to extraction of pure estrone was based on multiple extraction steps followed by several recrystalizations. As Doisy said himself, the key step of the procedure was the first extraction of the urine and the choice of the olive oil as an extraction agent proved to be essential. The estrone was successively extracted from the olive oil with ethanol and since it was known that estrone was insoluble in petrolether, the extraction with petrolether was used to remove the remains of the olive oil as well as other non-polar compounds. Distillation of the solvents followed by recrystalization afforded estrone crystals.

3. Selected Syntheses of Estrone

3.1 Marker's Synthesis of Estrone.

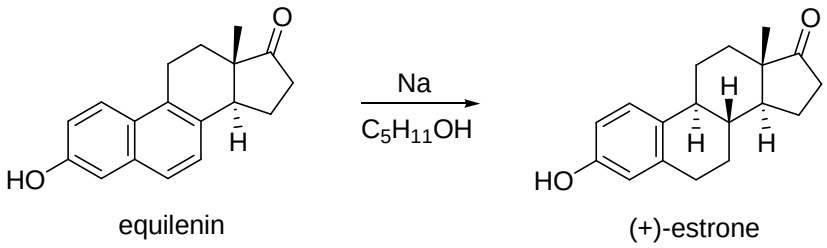
The first synthesis of estrone was reported by Marker *et al*.[4] His synthesis began with dehydrogenation of ergosterol, which is male sex hormone, yielding dehydro-neo-ergosterol **I** (Scheme 3.1.1). Reduction of **I** with sodium in amyl alcohol afforded tetrahydro-dehydro-neo-ergosterol **II**. The reduction proceeded diastereoselectively yielding only the product with the desired *trans-anti-trans* configuration. **II** was further converted to (+)-estrone by protection of phenolic group with acetic anhydride followed by oxidative cleavage of alkyl side chain by exposure to chromic acid and finally, alkaline deprotection of phenolic group.

Scheme 3.1.1 Marker's synthesis of estrone.



The above mentioned work was later followed by synthesis of estrone from equilenin[5] (also a natural hormone) (Scheme 3.1.2), which also utilized the stereoselective reduction of naphthalene scaffold. Both syntheses served as the proof of connection between male and female sex hormones for the first time.

Scheme 3.1.2 Synthesis of estrone from equilenin.

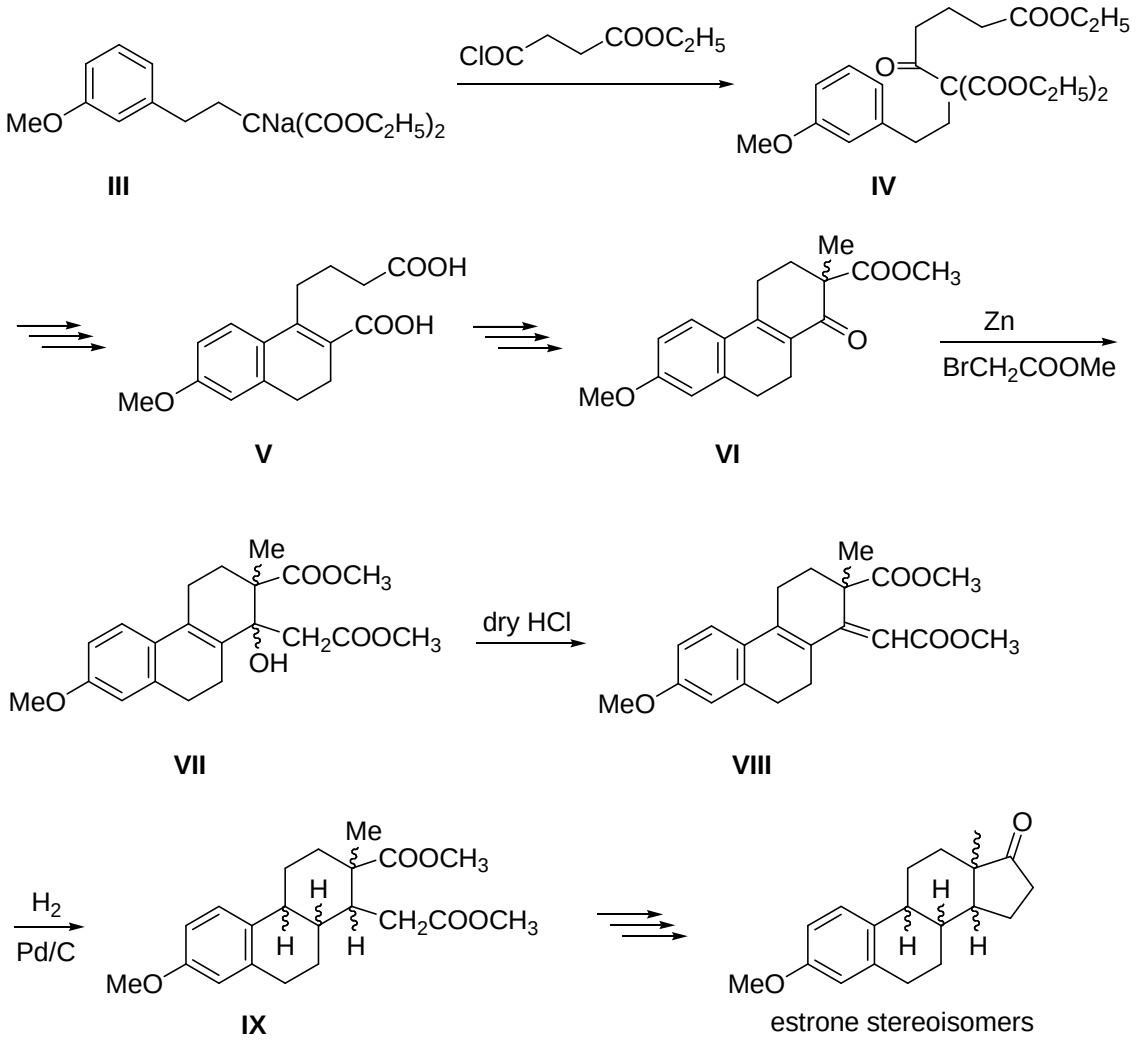


equilenin (+)-estrone

3.2 Syntheses Based on Condensation Reactions

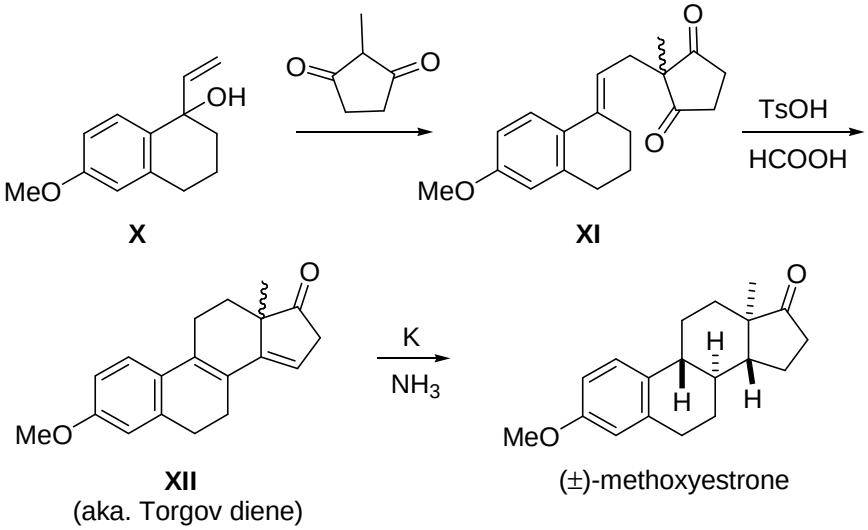
Bachmann's and Stevenson's synthesis[6] could be considered the first total synthesis of estrone scaffold in general. The strategy was based on successive condensation reactions (Scheme 3.2.1). Triester **IV**, which was prepared by condensation of sodium salt of anisoethylmalonic ester **III** with ethyl hydrogenglutarate chloride, was used as a starting material. Cyclization of **IV** in the presence of phosphoric acid followed by decarboxylation yielded naphthalene derivative **V**. Successive esterification, sodium methoxide induced condensation and reaction with methyl iodide gave phenanthrene derivative **VI**. Following the Reformansky reaction of **VI** with methyl bromoacetate, which gave the compound **VII**, the dehydratation with dry HCl in benzene provided unsaturated ester **VIII**. Finally, the reduction of **VIII** with H_2 catalyzed by Pd/C yielded saturated ester **IX**, which was converted to estrone by procedures previously used in his synthesis of equilenin.[7] In this manner an unseparable mixture of all possible stereoisomers of estrone was obtained, the mixture possessed the estrogenic activity proving that it contained the (+)-estrone.

Scheme 3.2.1 Bachmann's synthesis of estrone stereoisomers



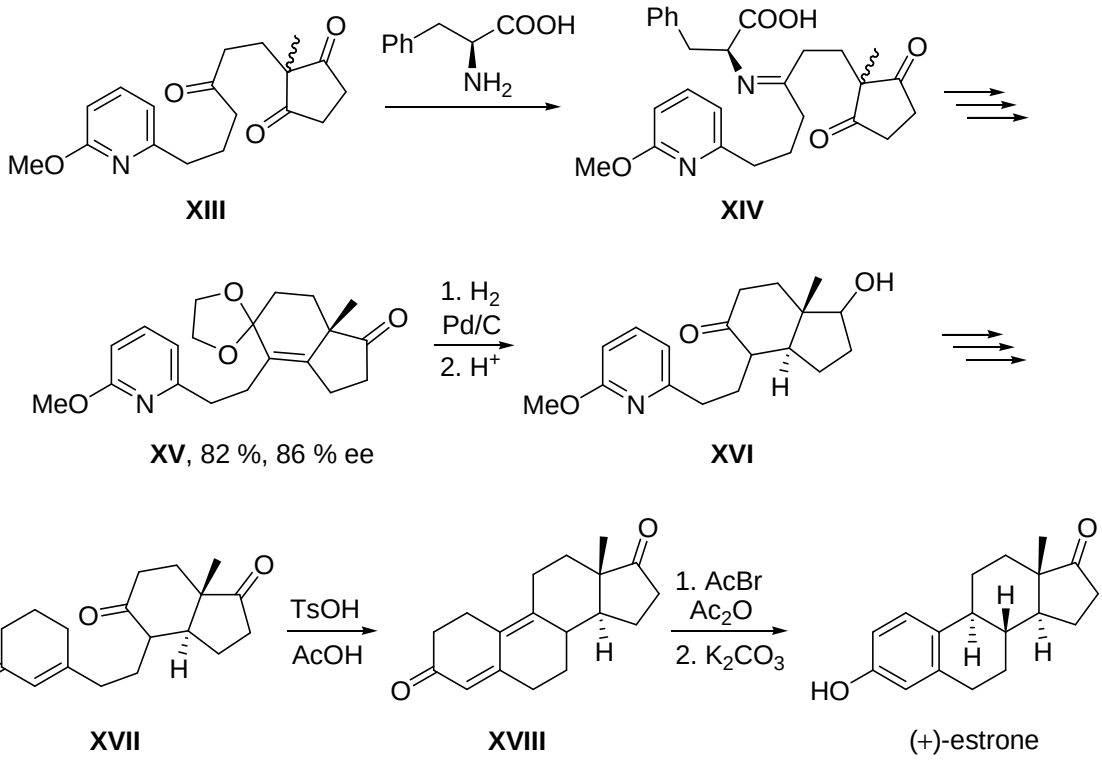
A different synthetic strategy, which also relied on a condensation reaction was introduced by Windholz and Patchett[8] (Scheme 3.2.2). Reaction of vinyltetralone **X** with methylcyclopentadione gave the crucial intermediate **XI**. TsOH catalyzed cyclization and immediate dehydratation led to tetracyclic compound **XII**. The key to the successful preparation of methoxyestrone diastereoselectively was the reduction of **XII** with potassium in liquid ammonia. Ananchenko and Torgov[9] as well as Wendler[10] applied the similar synthetic strategy and were also able to prepare estrone diastereoselectively.

Scheme 3.2.2 Windholz's synthesis.



An interesting synthetic strategy based on intramolecular condensation of a chiral imine, which led to optically pure estrone, was published by Danishefski and Cain.[11] The outline of the synthesis is shown in the Scheme 3.2.3. The chiral imine **XIV** was obtained by reaction of triketone **XIII** with L-proline. Subsequent cyclization of **XIV** induced with perchloric acid, hydrolysis and chemoselective protection of keto-group on the six-membered ring afforded the crucial intermediate **XV** in 82 % yield with 86 % ee. Hydrogenation with H_2 catalyzed by Pd/C proceeded diastereoselectively giving, after the deprotection of ketal, exclusively the intermediate **XVI** with the correct configuration. In the next few steps the pyridine ring was converted to the cyclohexanone ring yielding **XVII**, which was cyclized with TsOH (similarly to the Windholz synthesis) affording dienone **XVIII**. Finally, isomerization of **XVIII** by the action of acetyl bromide/acetic anhydride mixture, followed by cleavage of phenolic acetate with potassium carbonate in methanol gave enantioenriched (+)-estrone.

Scheme 3.2.3 Danishefski's enantioselective synthesis.

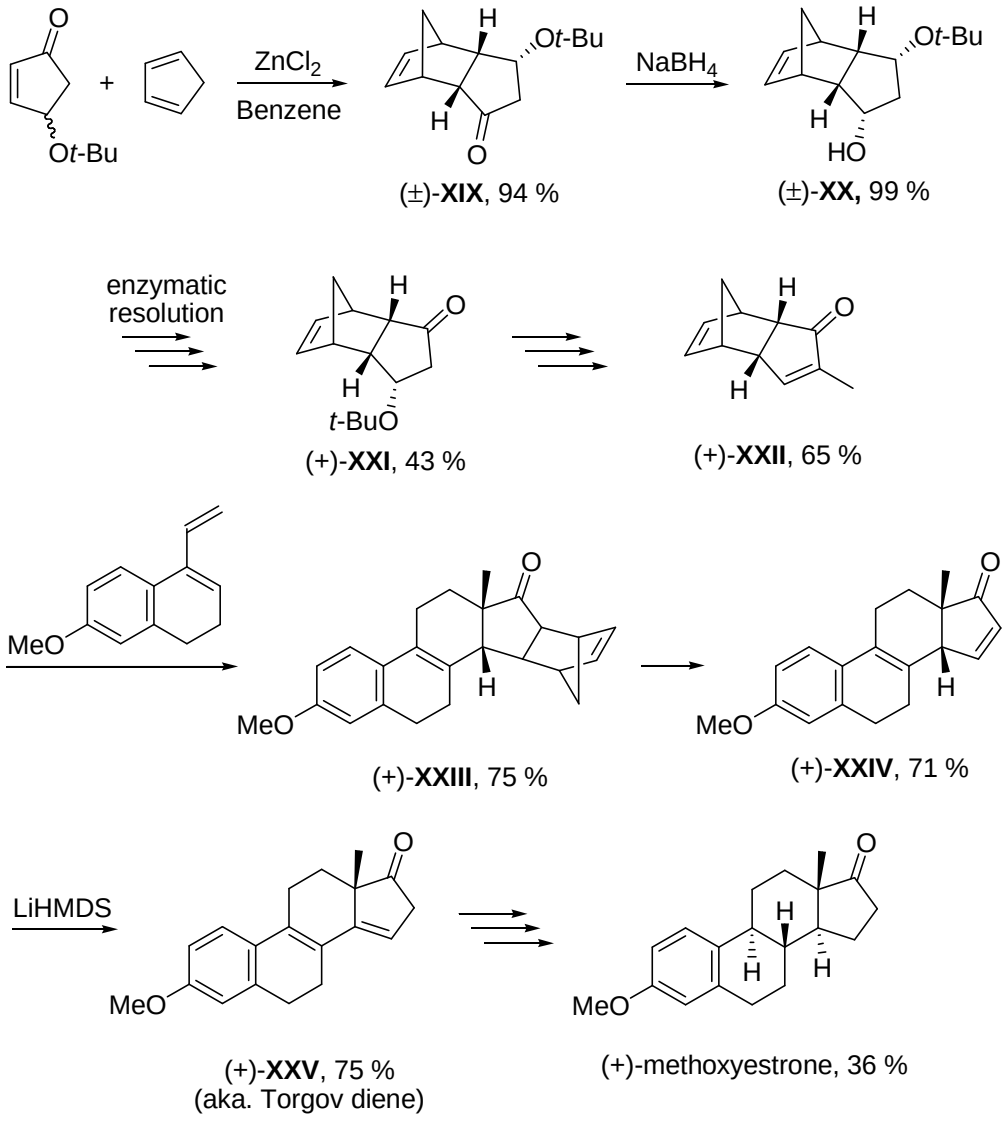


3.3 Syntheses Utilizing Diels-Alder Cycloaddition.

In this paragraph I would like to introduce the Sugahara and Ogasawara[12] synthesis of estrone (Scheme 3.3.1). In addition to being a nice example of synthesis utilizing the Diels-Alder reaction in total synthesis of natural compound in question, it also serves as an example of an enantioselective synthesis based on enzymatic resolution of an early intermediate enantiomers. The synthesis started with the Diels-Alder addition of cyclopentadiene to the cyclopentenone giving racemic tricycloketone **XIX** in 94 % yield, which was reduced to alcohol **XX** in almost quantitative, 99 %, yield. In the next step the racemic alcohol **XX** was exposed to vinyl acetate in the presence of lipase enzyme. This led to selective acetylation of (+)-**XX** only, resulting in the formation of a mixture of (+)-**XX** acetate and unchanged (-)-**XX**. After separation of (+)-**XX** acetate and successive hydrolysis the oxidation yielded optically pure ketone **XXI** in 42 % yield. Methylation of **XXI** followed by elimination of *t*-BuOH gave the crucial intermediate **XXII** in 65 % yield, whose Diels-Alder reaction with Dane's diene resulted in the formation of estrone precursor **XXIII** in 75 % yield. Retro Diels-Alder reaction of **XXIII** afforded the unsaturated tetracyclic compound **XXIV** in 71 % yield, which was isomerized to **XXV** in 75 % yield by the action of LiHMDS. Finally, chemoselective and stereoselective reduction of the cyclopentene double bond with H_2 catalyzed by Pd/C

followed by the stereoselective reduction of the B and C rings junction double bond with Et_3SiH gave the (+)-methoxyestrone in 36 % yield.

Scheme 3.3.1 Ogasawara's synthesis.

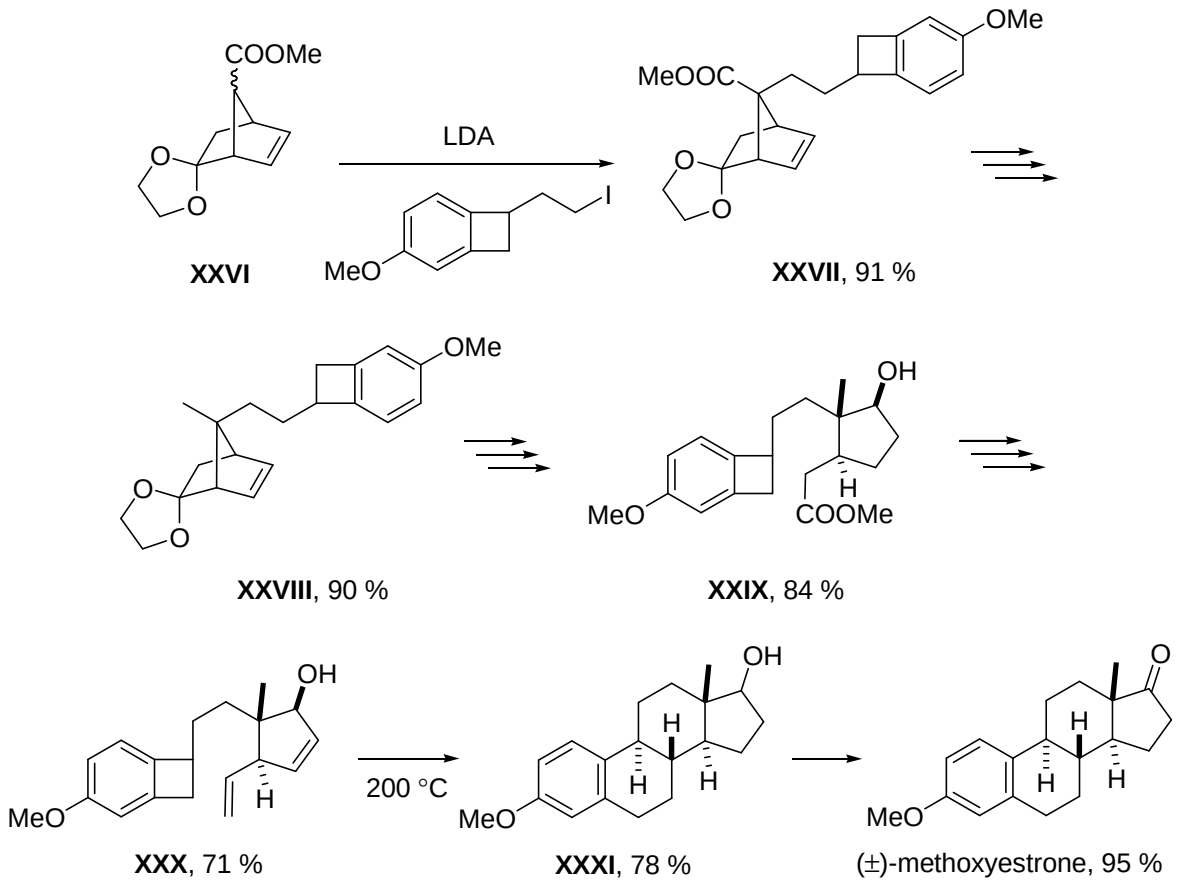


3.4 Syntheses Based on Cleavage of the Cyclobutane Ring.

A cleavage of a cyclobutane ring, particularly the cyclobutane ring annulated to aromatic ring, is well known synthetic tool in the syntheses of the compounds with steroid framework. Therefore it is no surprise, that total syntheses of estrone, based on this reaction, has been published. The first synthesis of this type was reported by Kametani *et al.* in 1976[13] followed by the work of Grieco *et al.* in 1980.[14] The latter approach is shown in the Scheme 3.4.1. The starting ester **XXVII** was prepared by the substitution reaction of **XXVI** with the

commercially available 2-(4-methoxybenzocyclobutenyl)ethyl iodide in the presence of LDA. Interestingly, **XXVII** was obtained as a single product of the reaction in 91 % yield despite the fact, that ester **XXVI** was used as a mixture of diastereomers. Sequence of the reduction of the carboxylic group with $LiAlH_4$, mesylation of the newly formed alcohol and the reduction of the mesylate with $LiEt_3BH$ led to formation of intermediate **XXVIII** in 90 % yield. Several common reactions were used to convert **XXVIII** into **XXIX** in 84 % yield. Finally, reduction of the carboxylic group to alcohol followed by dehydration afforded crucial intermediate **XXX** in 71 % and set the stage for the title step. Thermal cleavage of the cyclobutane ring in combination with intramolecular cycloaddition afforded the tetracyclic compound **XXXI** diastereoselectively in 78 % yield and after oxidation with Jones' reagent (±)-methoxyestrone was obtained in 95 % yield.

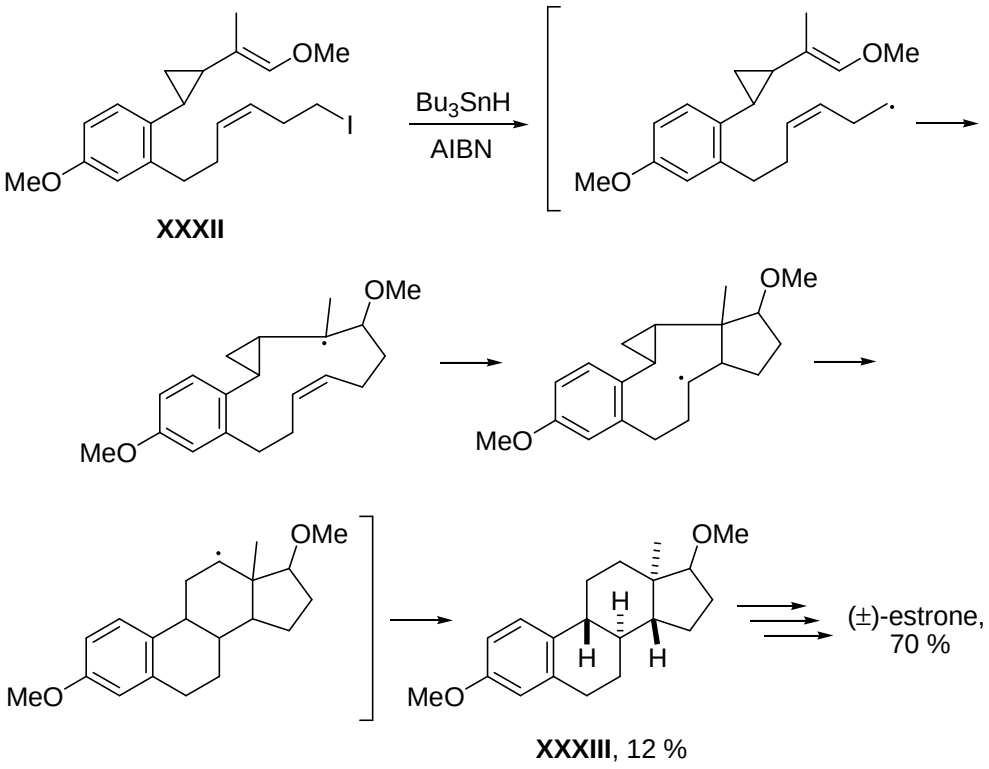
Scheme 3.4.1 Grieco's synthesis of (±)methoxyestrone.



3.5 Pattenden's Radical Cascade Synthesis of Estrone.

Highly inspirative approach to a synthesis of steroid compounds was reported by Pattenden *et al.*[15] His strategy was based on the radical macrocyclization of an alkene possessing multiple double bonds, followed by a number of radical transannulations. This led to the formation of the tetracyclic framework from linear compound in single step. How the strategy was utilized in the total synthesis of estrone is shown in Scheme 3.5.1. Iodide **XXXII** was used as a suitable starting material. Its treatment with Bu_3SnH and AIBN started the radical reaction cascade and after quenching with diluted HCl the tetracyclic intermediate **XXXIII** was obtained in 12 % yield. It is worth mentioning that the tetracyclic compound **XXXIII** was obtained with the correct *trans-anti-trans* configuration on ring junctions. Oxidation of **XXXIII** with CrO_3 and demethylation with BBr_3 gave (±)-estrone in 70 % yield.

Scheme 3.5.1 Pattenden's synthesis of (±)-estrone.

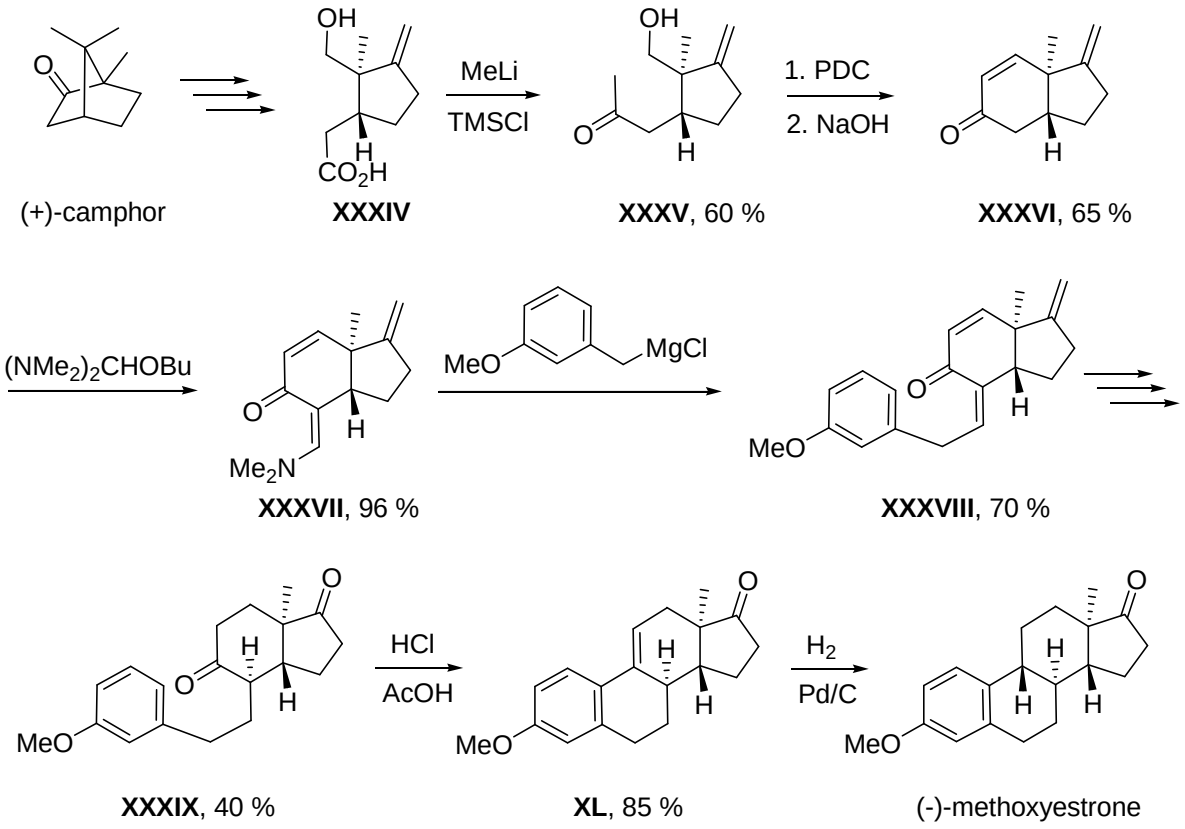


3.6 Syntheses Based on Friedel-Crafts Alkylation.

In the Bryson's[16], Daniewski's[17] and Hutchinson's[18] syntheses of estrone advanced intermediate undergoes the Friedel-Crafts reaction to furnish the tetracyclic estrone precursor. The last named work is worth deeper investigation. The synthesis begun with conversion of

starting (+)-camphor to the cyclopentane derivative **XXXIV.** Subjection of **XXXIV** to MeLi and quenching the reaction with TMSCl provided ketone **XXXV** in 60 % yield. Oxidation of the alcohol group in **XXXV** to ketone with PDC and subsequent base catalyzed intramolecular condensation, which formed the six-membered ring, followed by dehydratation with DBU gave the bicyclic compound **XXXVI** in 65 % yield. Exposure of **XXXVI** to $(NMe_2)_2CHOBu$, which provided dimethylamine derivative **XXXVII** in 96 % yield, and reaction with benzylmagnesium chloride gave the tricyclic intermediate **XXXVIII** in 70 % yield. Both double bonds conjugated to keto group were chemoselectively reduced with Li in NH_3 and subsequent ozonolysis of the *exo*-double bond yielded the crucial intermediate **XXXIX** in 40 %. Intramolecular Friedel-Crafts reaction of **XXXIX** in HCl/AcOH furnished tetracyclic **XL** and finally, reduction with H_2 catalyzed by Pd/C gave (-)-methoxyestrone in 85 % yield.

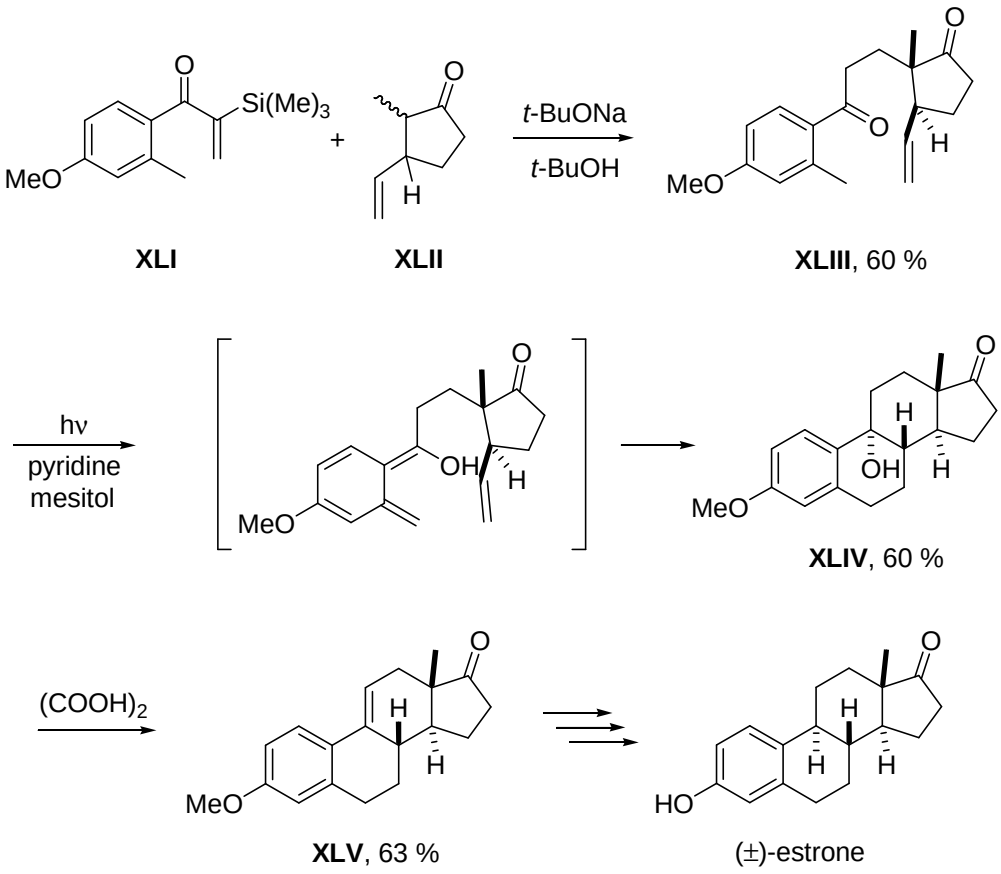
Scheme 3.6.1 Hutchinson's synthesis of (-)-methoxyestrone.



3.7 Synthesis Utilizing Photochemically Induced [4 + 2] Cycloaddition.

Quinkert's et al.[19] strategy of estrone synthesis was based on a photochemically induced intramolecular cycloaddition, which led to the tetracyclic estrone precursor (Scheme 3.7.1). The suitable starting material **XLIII** was prepared by a base catalyzed reaction of α,β-unsaturated ketone **XLI** and cyclopentanone derivative **XLII** in 60 % yield. Irradiation of **XLIII** with UV light (λ = 340 nm) led to the [4+2] cycloaddition furnishing tetracyclic compound **XLIV** in 60 % yield. The cycloaddition proceeded highly diastereoselectively and only the formation of the *trans-anti-trans* diastereomer was observed. To finalize the (±)-estrone synthesis **XLIV** was treated with $(COOH)_2$ to give unsaturated **XLV** in 60 % yield, in which the double bond was reduced with H_2 catalyzed by Pd/C and the methoxy group was demethylated with BBr_3.

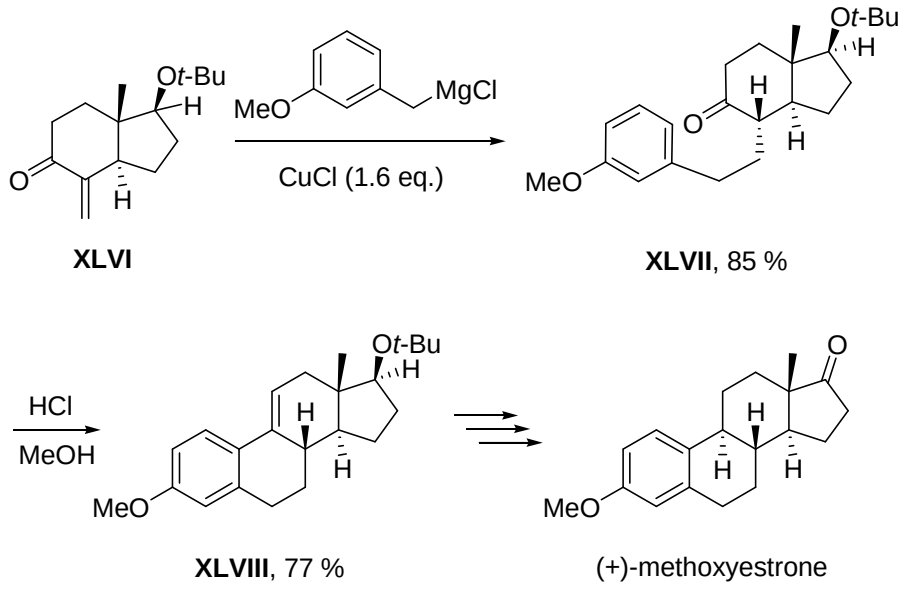
Scheme 3.7.1 Quinkert's synthesis of (±)-estrone.



3.8 Syntheses Based on Transition Metal Mediated Reactions.

As the first example I would like to introduce Cohen's et al.[20] synthesis of (+)-methoxyestrone. The key reaction of the synthesis was Cu-mediated conjugated addition of 2-methoxybenzylmagnesium chloride to the bicyclic ketone **XLVI** as shown in the Scheme 3.8.1, which yielded tricyclic ketone **XLVII** in 85 %. What's worth noticing is that conjugated addition proceeded highly diastereoselectively and the ketone was obtained as pure *trans-anti* diastereomer. In the next step the intramolecular Friedel-Crafts reaction gave the tetracyclic intermediate **XLVIII** in 77 %, which was converted to (+)-methoxyestrone using several common transformations.

Scheme 3.8.1 Cohen's synthesis of (+)-methoxyestrone.



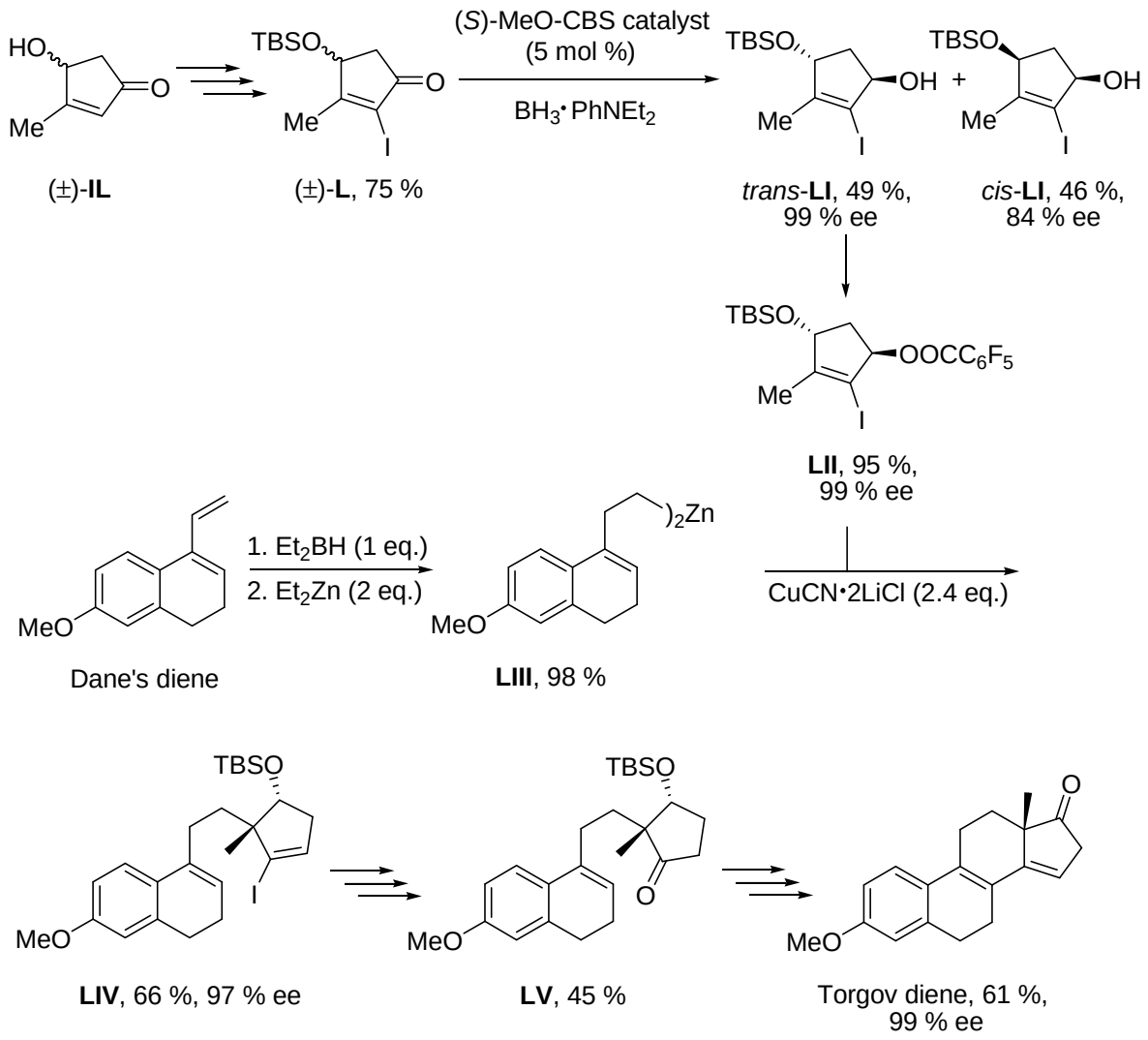
XLVI **XLVII**, 85 %

XLVIII, 77 % (+)-methoxyestrone

Another nice enantioselective synthesis of (+)-estrone, shown in Scheme 3.8.2, was accomplished by Knochel et al.[21] via Torgov diene (Scheme 3.2.2 and 3.3.1). One of the key reactions used in a later stage of the synthesis was the Cu-mediated *anti*-$S_N2`$ allylic substitution. The chirality was introduced in the early steps of the synthesis by means of the enantioselective organocatalytic Corey-Bakashi-Shibata[22] (CBS) reduction. The starting chiral cyclopentenyl iodide **LII** was prepared in the following way. The protection of the free alcohol group in racemic cyclopentanone derivative **IL** with TBSCl and successive iodination afforded cyclopentenonyl iodide **L** in 75 % yield. The reduction of **L** with $BH_3 \cdot PhNEt_2$ in the presence of (*S*)-MeO-CBS catalyst (5 mol %) led to formation of a mixture of separable *cis* and *trans* **LI** in approximately 1:1 ratio. After the separation the desired *trans*-**LI** was

obtained in 49 % yield with excellent enantioselectivity of 99 % ee. A simple protection of the alcohol group in *trans*-**LI** as perfluorobenzoate ester gave **LII** in 95 % with unchanged ee of 99 %. The formal synthesis of estrone itself started with preparation of the organozinc compound **LIII** from Dane's diene by treatment with 1 eq of Et_2BH and successively with 2 eq. of Et_2Zn. What followed was the key step; alkylation of cyclopentenyl iodide **LII** with organozinc **LIII** in the presence of CuCN·2LiCl (2.4 eq), which afforded tricyclic intermediate **LIV** in nice 66 % yield with very good enantioselectivity of 97 % ee. The synthesis was continued with conversion of the iodide **LIV** to ketone **LV** in 45 % yield by one pot procedure based on the treatment of **LIV** successively with *t*-BuLi, $B(OMe)_3$ and $NaBO_3$. Subsequent exposure of **LV** to TsOH in benzene led to the ring closure and removal of the TBS protecting group with TBAF followed by oxidation of the deprotected alcohol group with CrO_3 on Celite furnished Torgov's diene in 61 % yield with 99 % ee. The diene can be converted to (+)-methoxyestroene (as shown in the Scheme 3.3.1).

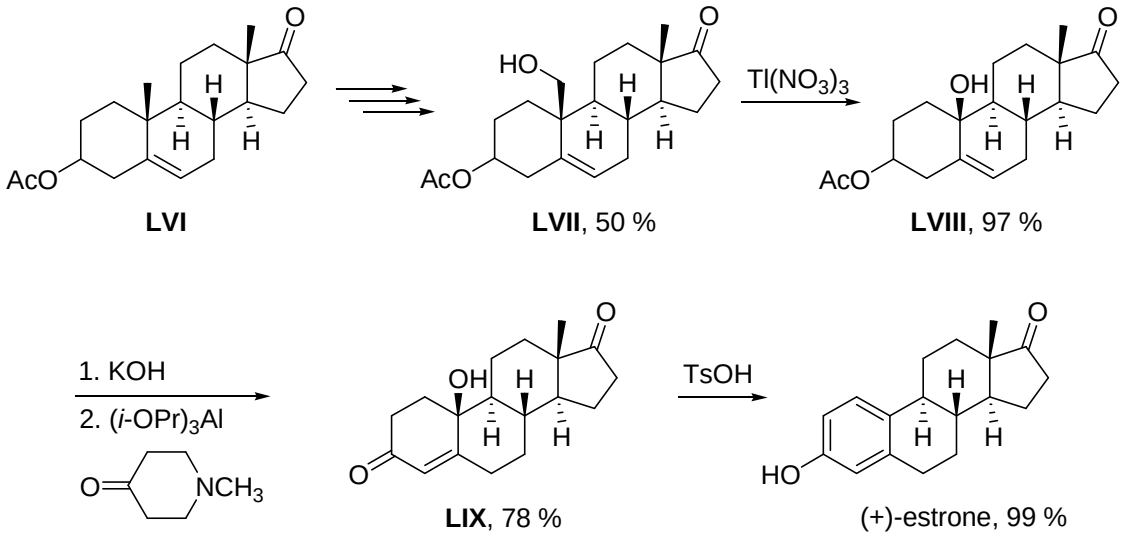
Scheme 3.8.2 Knochel's synthesis of (+)-estrone precursor.



Another nice example was published by Kočovský *et al.* (Scheme 3.8.3).[23] Their synthesis started from androstane derivative **LVI** and the strategy of it's conversion to estrone is based on cleavage of the methyl group on A and B steroid ring junction. Prior to the cleavage itself the methyl group in question had to be functionalized to hydroxymethyl by oxidation with $Pb(AcO)_4$ and successive reduction with Zn, which gave alcohol **LVII** in 50 % yield. The key step, removal of CH_2OH group, was done by the treatment of **LVII** with stoichiometric amount of $Tl(NO_3)_3$. This led to the cleavage of the hydroxymethyl group and furnished one-carbon-shorter alcohol **LVIII** in impressive 97 % yield. What followed was the deprotection of the hydroxy group on the A aromatic ring with KOH and the Oppenauer oxidation of that alcohol group provided ketone **LIX** in 78 % yield. Synthesis was completed

by aromatization of the A ring accomplished by exposure of **LIX** to TsOH, which yielded (+)-estrone almost quantitatively.

Scheme 3.8.3 Kočovksý's synthesis of (+)-estrone.

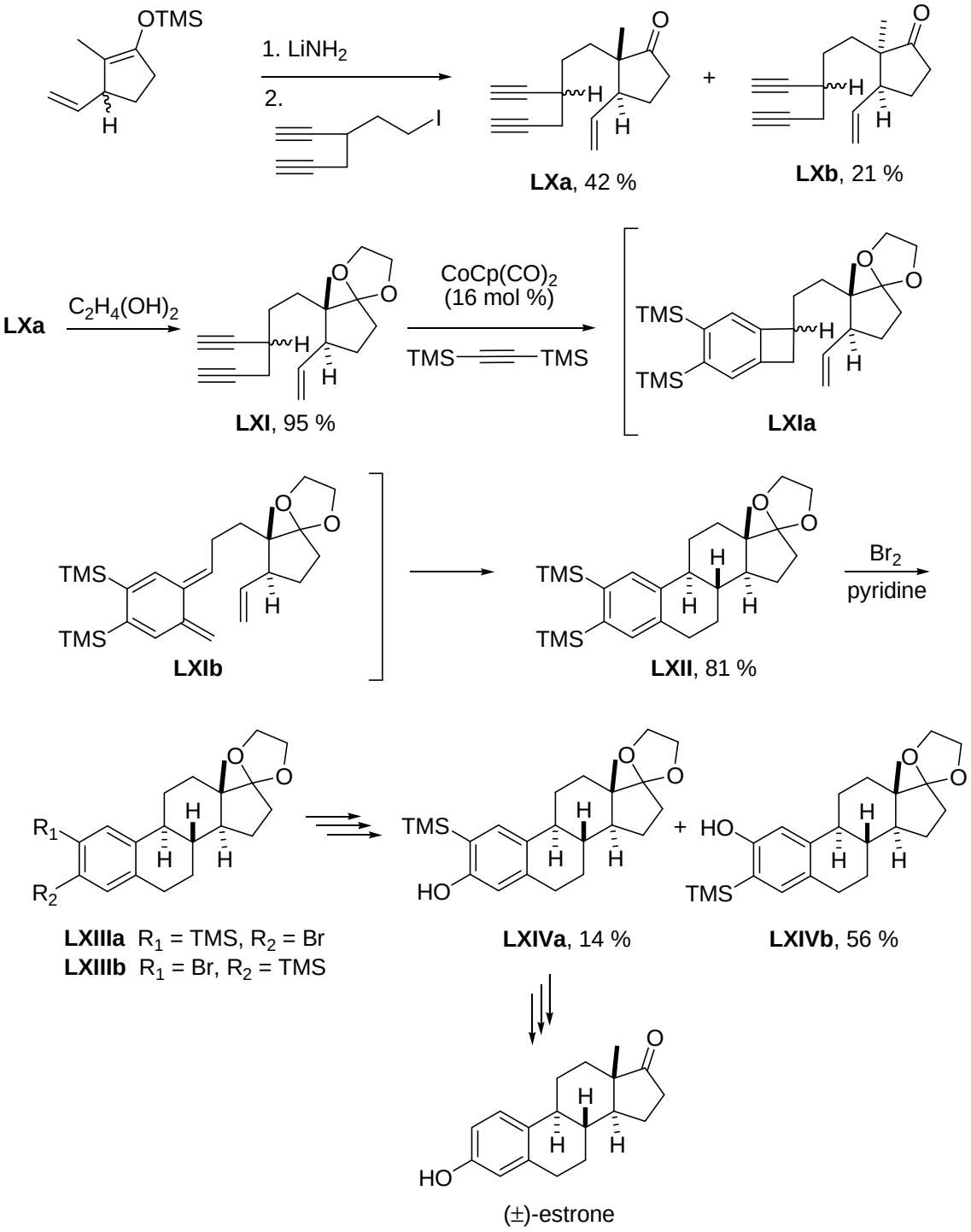


3.9 Syntheses Based on Transition Metal Catalyzed Reactions.

Intramolecular cyclotrimerization of triynes or cyclotrimerization of diyne with alkyne are widely used reactions in the syntheses of steroid compounds with the aromatic B steroid ring. Nevertheless, Vollhardt et al.[24][25] reported total synthesis of several steroid compounds with the aromatic A ring, including estrone, based on cyclotrimerization of advanced diyne intermediate with bistimethylsilylacetylene (Scheme 3.9.1). The diyne **LXa** was prepared by the alkylation of diyne iodide with corresponding TMS-enolate. This led to the formation of the mixture of diynes **LXa** and **LXb** with desired **LXa** being the major component, obtained in 42 % yield. Following the smooth protection of the keto group in **LXa**, which yielded ketal **LXI** in 95 % yield the cyclotrimerization reaction of **LXI** with trimethylsilylacetylene catalyzed by $CoCp(CO)_2$ afforded benzenocyclobutane intermediate **LXIa**, which underwent rearrangement forming **LXIb,** and finally, intramolecular Diels-Alder cycloaddition afforded **LXII** in very nice 81 % total yield. It is worth noticing that the Diels-Alder reaction proceeded highly diastereoselectively and yielded the desired *trans-anti-trans* product. Treatment of **LXII** with Br_2 in pyridine at the room temperature led to substitution of the TMS groups forming the mixture of **LXIIIa** and **LXIIIb** in 19:79 ratio. Unfortunately, the desired **LXIIIa** was only formed as a minor product. Exposure of the mixture of **LXIIIa** and **LXIIIb** successively to *n*-BuLi, trimethyl borate, acetic acid and H_2O_2 followed by separation

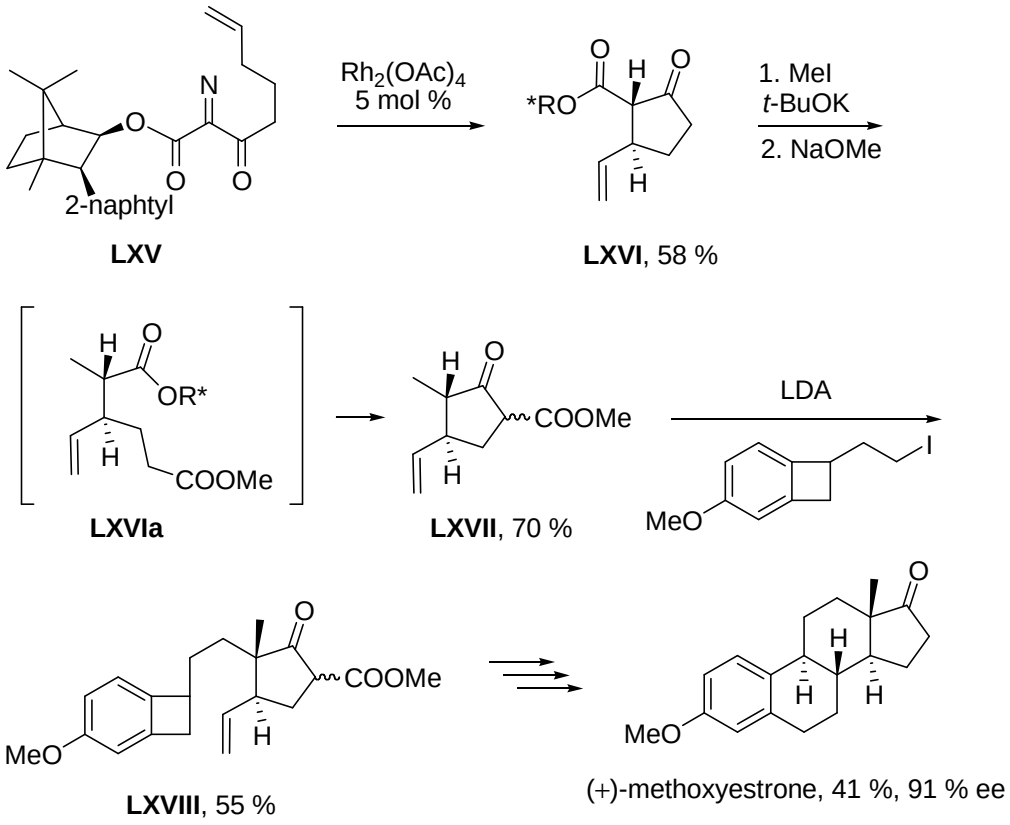
of the formed products **LXIVa** and **LXIVb** gave the desired **LXIVa**, albeit only in 14 % yield. Finally, **LXIVa** was converted to estrone by exposure to H_3O^+.

Scheme 3.9.1 Vollhardt's synthesis of (±)-estrone.



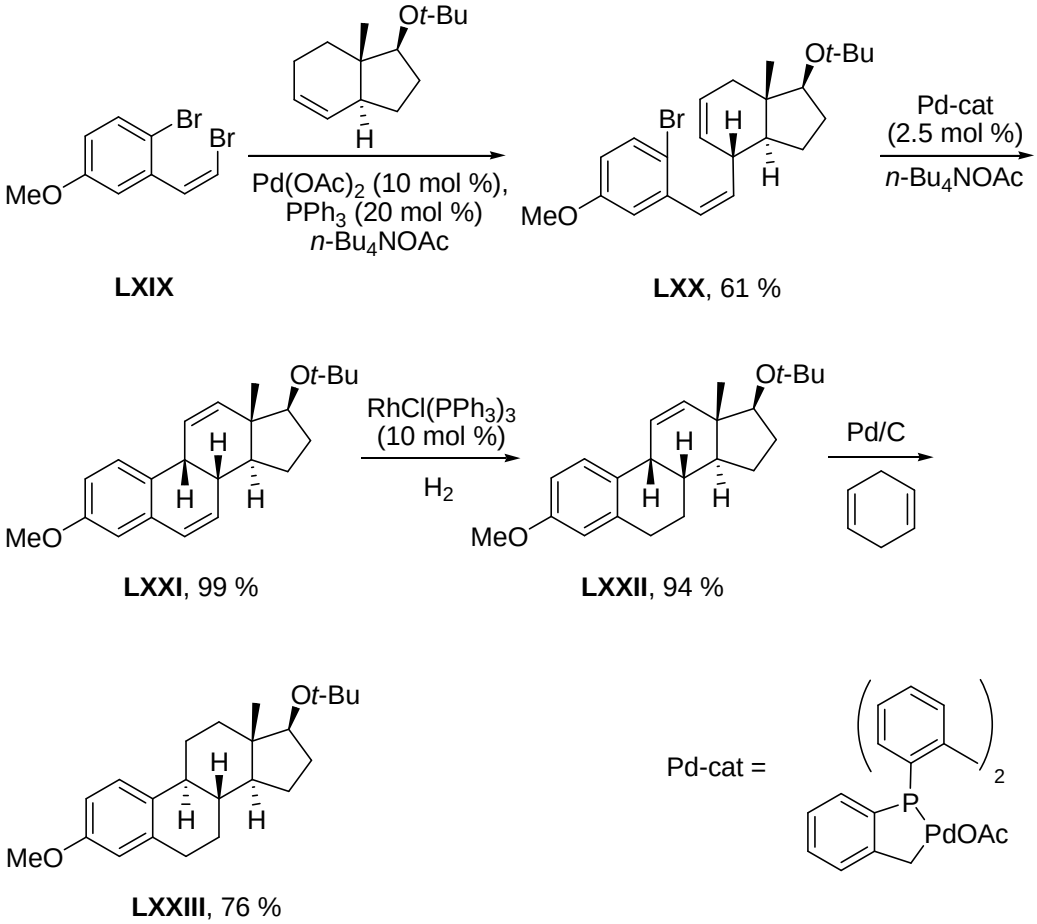
Taber et al.[26] published enantioselective synthesis of (+)-methoxyestrone, in which the key step was accomplished by the rhodium catalyzed C-H activation reaction (Scheme 3.9.2). Diazoketoester of chiral alcohol derived from (+)-camphor **LXV** was used as a starting material. Intramolecular cyclization of **LXV** in the presence of $Rh_2(AcO)_4$ (5 mol %) yielded the mixture of *trans* and *cis* diastereomers of the cyclopentanone derivative **LXVI** in 92:8 ratio in combined yield of 61 %. After separation of diastereomers the desired *trans*-**LXVI** was obtained in 58 % yield. Treatment of *trans*-**LXVI** successively with MeI/*t*-BuOK and NaOMe gave the cyclopentanone methylester **LXVII** in 70 % yield (the reaction proceeds via linear intermediate **LXVIa**)[27]. Following steps of the synthesis were similar to Grieco's synthesis (Scheme 3.4.1). Alkylation with 2-(4-methoxybenzocyclobutenyl)ethyl iodide gave the cyclobutane intermediate **LXVIII** in 55 % yield and it's decarboxymethylation and thermolysis accompanied with the cleavage of the cyclobutane ring gave (+)-methoxyestrone in 41 % with 91 % ee.

Scheme 3.9.2 Taber's synthesis of (+)-methoxyestrone.



This work couldn't be considered complete if I didn't present at least one synthesis, which utilizes Pd catalyzed reaction. In this regard I would like to present Tietze's synthesis of estrone[28] based on two consecutive Pd catalyzed Heck reaction (Scheme 3.9.3). In the first step the dibromide **LXIX** underwent the intermolecular Heck reaction with a chiral cyclohexene derivative to yield intermediate **LXX** in 61 %. The second step was intramolecular Heck reaction catalyzed by Pd catalyst shown in the Scheme 3.9.3, which led to cyclization and formation of the tetracyclic estrone precursor **LXXI** in impressive 99 % yield. The very high chemo- and stereoselectivity for both steps was achieved after tedious experimentation with different starting materials (bearing other halogens instead of bromine) as well as different Pd catalyst and reaction conditions. The synthesis was continued with chemoselective reduction of the B ring double bond in **LXXI** with H_2 in the presence of $RhCl(PPh_3)_3$ to give **LXXII** in 94 % yield. Finally, the reduction of the C ring double bond in **LXXII** catalyzed by Pd/C in the presence of the excess of cyclohexadiene as source of hydrogen afforded the (+)-estrone precursor **LXXIII** in 76 % yield. The interesting change of configuration on C9 can be explained, as claimed by the authors, by isomerization of $\Delta^{11,12}$ double bond to $\Delta^{9,11}$ under the reaction conditions and subsequent hydrogenation. The obtained **LXIII** can be converted to estrone in few steps as shown in the Scheme 3.8.1.

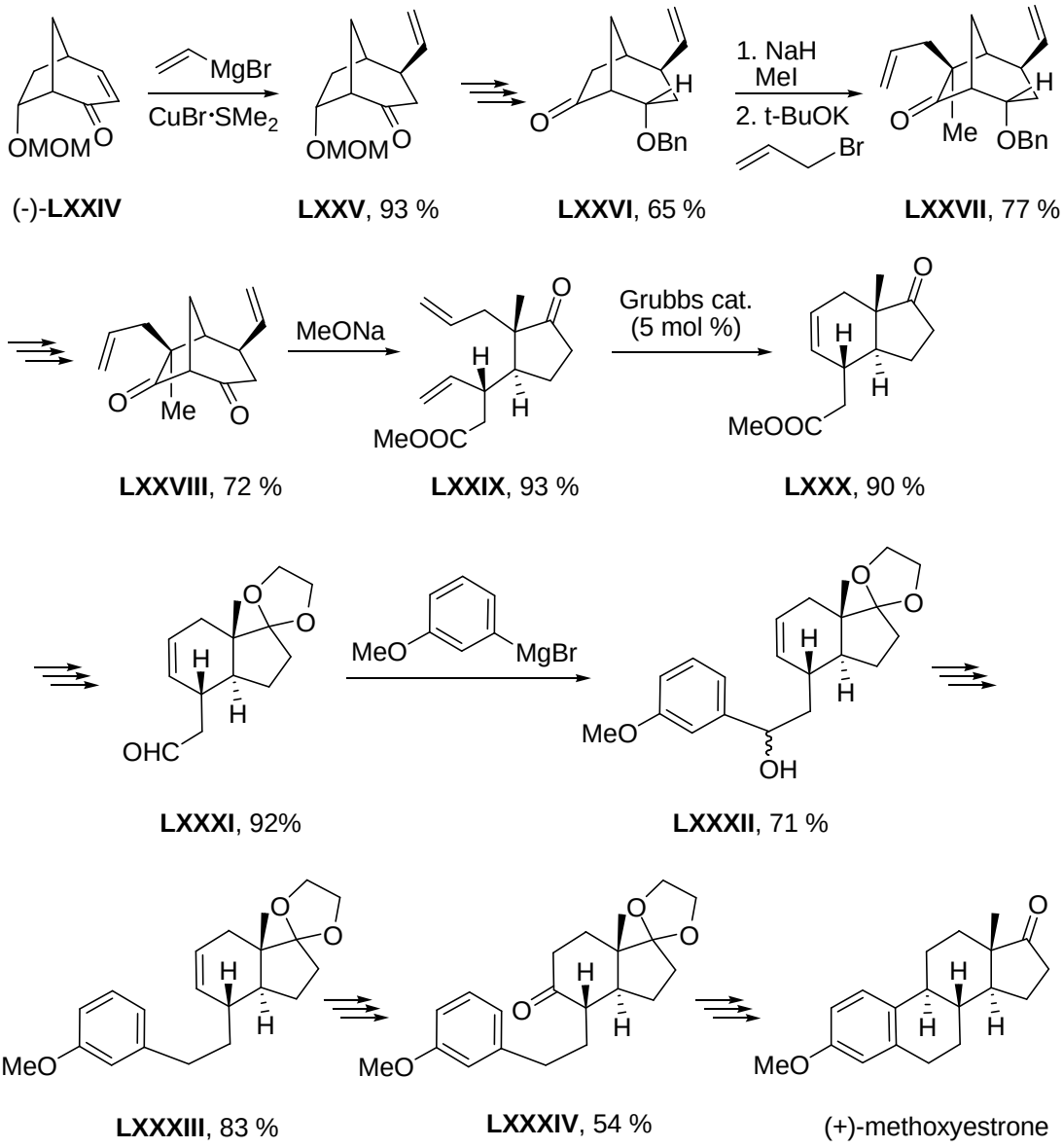
Scheme 3.9.3 Tietze's synthesis of (+)-estrone precursor.



As the last example I would like to describe the Ogasawara's[29] strategy for enantioselective synthesis of (+)-methoxyestrone which started from chiral ketone (-)-**LXXIV**. One of the key reactions was a Ru-complex catalyzed (Grubb's catalyst 1st generation) metathesis of diene; however, the synthesis is rather complex and features several interesting steps. In view of that I decided to describe it in more detail (Scheme 3.9.4). The synthesis began with addition of vinylmagnesium brominde to (-)-**LXXIV** in the presence of $CuBr \cdot Me_2S$ and HMPA, which gave diastereoselectively vinyl derivative **LXXV** in 93 % yield. What followed was the reduction of the keto group in **LXXV**, benzylation of the formed alcohol group on the six-membered ring, deprotection of MOM protective group to free the alcohol on the five-membered ring and the oxidation of alcohol on the five-membered ring with PCC, which gave ketone **LXXVI** in total yield of 65 %. Treatment of the enolate formed from **LXXVI** with MeI and successively with allylic bromide gave diene **LXXVII** in 77 % yield. Surprisingly, the two consecutive alkylations proceeded highly diastereoselectively and the diene **LXXVII** with the desired configuration was obtained as the

major product. The synthesis was continued with deprotection of the benzyl group with DDQ and oxidation of the formed alcohol with PCC, which furnished diketone **LXXVIII** in 73% yield. Cleavage of the six-membered ring induced with MeONa led to the formation of diene **LXXIX** in 93 % yield. The obtained diene is an ideal candidate for the intramolecular diene metathesis reaction, therefore its exposure to Grubbs catalyst (5 mol %) gave the expected product **LXXX** in 90 % yield. Protection of the free keto group in **LXXX** with $(TMSOCH_2)_2$ and subsequent transformation of the methylcarboxy group to the aldehyde group by reduction with $LiAlH_4$ and oxidation with PCC sequence formed compound **LXXXI** in 92 % yield. Reaction of aldehyde **LXXXI** with 3-methoxyphenylmagnesium bromide gave the epimeric mixture of alcohols **LXXXII** in 71 %; however, this formation of the epimeric mixture was not a problem because in the next step the alcohol group was removed. The alkoxide prepared from **LXXXII** was treated with CS_2 and MeI to give xantate, which upon reduction with Bu_3SnH in the presence of AIBN gave compound **LXXXIII** in 83 % yield. Epoxidation of the double bond in **LXXXIII** with MCPBA, opening of formed epoxide with DIBAL and finally, oxidation with PCC, furnished ketone **LXXXIV** in combined yield of 53 %. Conversion of ketone **LXXXIV** to (+)-methoxyestrone was accomplished using the same approach as already presented in the Scheme 3.6.1.

Scheme 3.9.4 Ogasawara's synthesis of (+)-methoxyestrone utilizing diene metathesis.



(-)-**LXXIV**

LXXV, 93 %

LXXVI, 65 %

LXXVII, 77 %

LXXVIII, 72 %

LXXIX, 93 %

LXXX, 90 %

LXXXI, 92%

LXXXII, 71 %

LXXXIII, 83 %

LXXXIV, 54 %

(+)-methoxyestrone

4. Aims of the Work

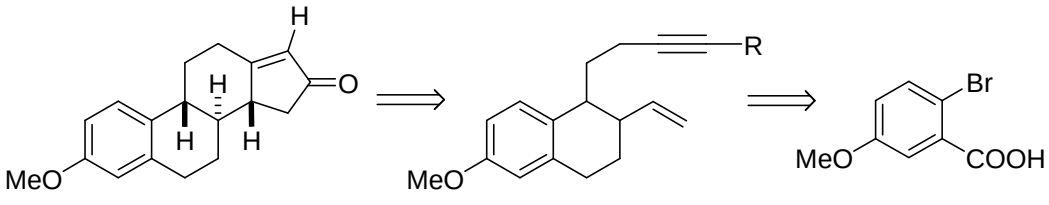
The main objectives of this work were to develop a new enantioselective total synthesis of methoxyestrone and to prepare its unnatural enantiomer (-)-methoxyestrone using the new methodology. In order to accomplish this complex goal the work had to be divided into several more specific tasks. The first one was to develop a new diastereoselective strategy of estrone framework synthesis. This task was mainly focused on designing the synthetic strategy so that the *trans-anti-trans* configuration at ring junctions could be achieved. The second task was to modify the developed diastereoselective synthesis to achieve enantioselective synthesis. And finally, to test the new methodology by the preparation of (-)-methoxyestrone.

5. Results and Discussion

5.1 Diastereoselective Synthesis of Estrone Precursor.

In this chapter I would like to discuss one of the goals of my work the design and development of a diastereoselective strategy for synthesis of the estrone framework. The core idea for the synthesis was the Pauson-Khand reaction. This cyclocarbonylation reaction between a double bond, a triple bond and carbon monoxide is very powerful tool in synthesizing compounds with the cyclopentanone ring. Before this work had begun, Pavel Herrmann (the former member of our group) had developed a synthesis of an estrone precursor based on the repetitive use of Bu_2ZrCp_2.[30][31][32] His work utilized the C-O bond activation in a benzyl ether and various cyclizations of dienes and enynes. However, enynes, possessing both double and triple bond, could constitute ideal substrate for Pauson-Khand reaction, therefore I presumed that combining both approaches could result in more efficient synthesis of tetracyclic estrone framework. The outline of the strategy I envisioned is shown in the Figure 5.1.1. The tetracyclic estrone precursor 16-ketoestratetraene could be prepared from a suitable bicyclic enyne using the Pauson-Khand reaction. The preparation of enyne could be accomplished using modified methodology developed earlier by Pavel Herrmann.

Figure 5.1.1

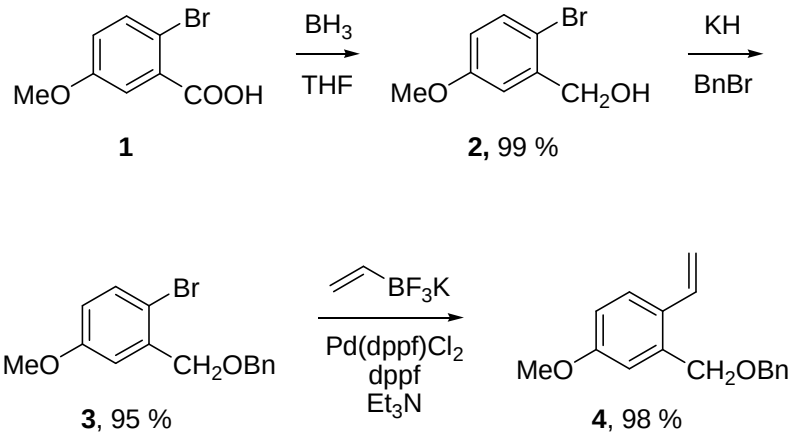


16-ketoestratetraene enyne

The work had began with the preparation of the styrene derivative **4** (Scheme 5.1.1). The commercially available 2-bromo-6-methoxybenzoic acid **1** was used as a starting material. Its reduction with BH_3 in THF afforded 2-bromo-6-methoxybenzyl alcohol **2** in almost quantitative yield. Subsequent protection of the hydroxyl group by exposure to KH followed by the reaction of the formed alcoholate with benzyl bromide furnished benzyl ether **3** in 95 % yield. Introduction of a vinyl moiety into the molecule was achieved by means of the Suzuki coupling reaction; however, under standard Suzuki conditions[30] the reaction was plagued by the formation of debromination product from **3** (3-methoxybenzyl)benzyl ether,

thus lowering the yield of the desired styrene derivative **4**. In order to circumvent this problem the reaction had to be carried out under modified conditions. The reaction of phenyl bromide **3** with potassium vinyltrifluoroborate in the presence of a catalytic amount of $Pd(dppf)Cl_2$ (5 mol %) and dppf (2 mol %) along with excess of triethylamine provided styrene **4** in very nice 98 % yield (Scheme 5.1.1). The use of an additional amount of the dppf ligand was necessary to ensure a good yield of the coupling. It should be noted that without additional dppf ligand the palladium complex decomposed during the course of the reaction and lost its catalytic activity.

Scheme 5.1.1. Synthesis of styrene **4**.

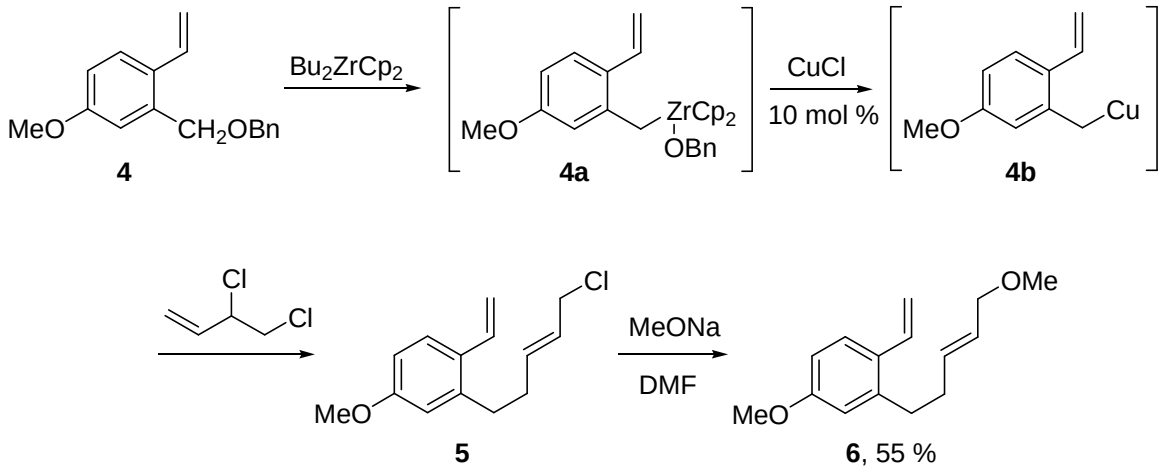


1 **2,** 99 % **3**, 95 % **4**, 98 %

As outlined in Scheme 5.1.2 Bu_2ZrCp_2, also known as Negishi's reagent, was used for transformation of styrene **4** into the methoxydiene **6**. In the first step, the reaction of a stoichiometric amount of Bu_2ZrCp_2 with **4** afforded exclusively the benzylzirconium compound **4a**, in which the zirconium is inserted into the C-O benzylic bond from the styrene side. This selectivity could be explained by coordination of the Bu_2ZrCp_2 to the styrene double bond prior to the oxidative addition to the C-O bond.[33] Exposure of the organozirconium intermediate **4a** to 3,4-dichlorobutene in the presence of a catalytic amount of the CuCl (10 mol %) provided chlorodiene **5**. This reaction proceeded by transmetalation of **4a** with CuCl to the organocopper compound **4b** and the subsequent reaction with 3,4-dichlorobutene, which proceeded via S_N2' mechanism. Unfortunately, chlorodiene **5** was unstable and easily decomposed, therefore its preparation was immediately followed, without any purification, by the reaction with MeONa in DMF, which provided the stable

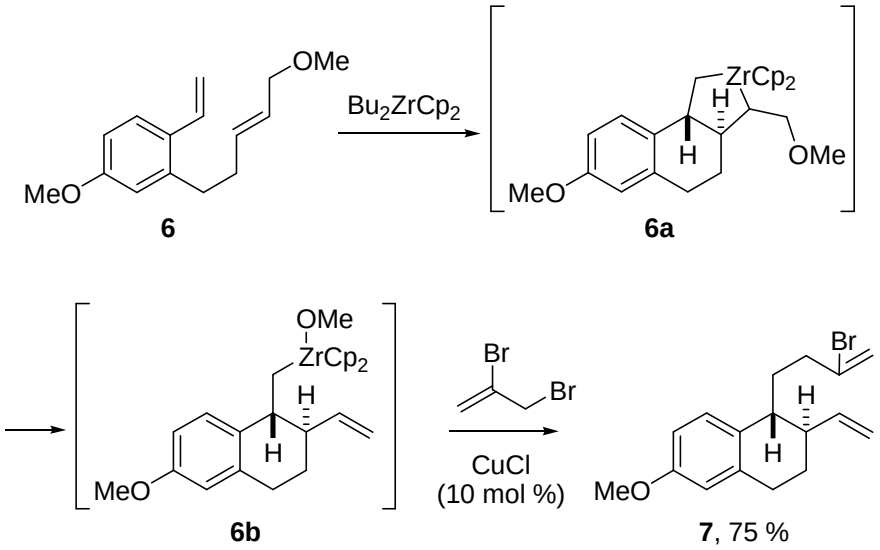
methoxydiene **6**. The overall yield of the reaction sequence starting from styrene **4** to methoxydiene **6** was 55 %.

Scheme 5.1.2. Preparation of the methoxydiene **6**.



In the next step, the Negishi's reagent was used to mediate the cyclization reaction of **6** (Scheme 5.1.3). Methoxydiene **6** upon treatment with a stoichiometric amount of Bu_2ZrCp_2 provided zirconacyclopentane intermediate **6a**, which immediately underwent irreversible *ß*-elimination of the methoxy group forming organozirconium compound **6b**. Successive alkylation of **6b** with 2,3-dibromopropene catalyzed by CuCl (10 mol %) furnished bromodiene **7**. The cyclization was highly diastereoselective and only the *trans* diastereoisomer was obtained as the final product. The yield of this one pot sequence was 75 %.

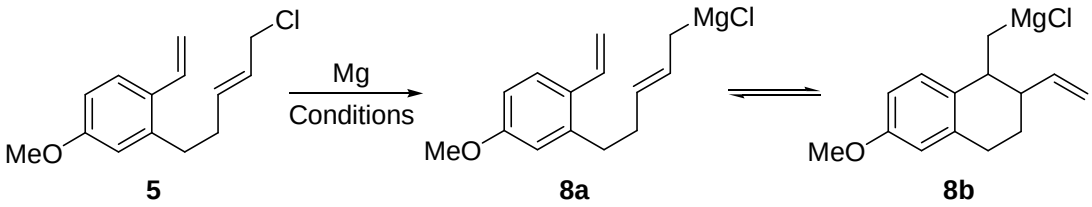
Scheme 5.1.3. Cyclization of methoxydiene **6**.



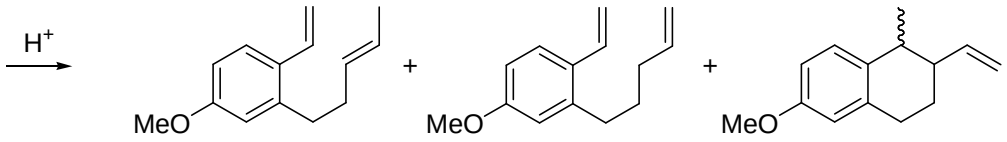
Although the Bu_2ZrCp_2 mediated cyclization of methoxydiene **6** proved to be efficient in both stereoselectivity and yield, I wanted to look for an alternative method that would enable cyclization under simpler or catalytic conditions. Inspired by the Oppolzer's cyclization of ene-allylic Grignards,[34] I decided to try this metallo-ene reaction on my substrates.

As the first suitable starting material for the Oppolzer's cyclization allylmagnesium chloride **8a**, prepared by the reaction of chlorodiene **5** with Rieke® Mg was chosen (Scheme 5.1.4). Initially, the metallo-ene reaction was run at 60 °C for 24h. After hydrolysis inseparable mixture composed of **10** (31 %), **11** (31 %), *cis*-**12** (15 %) and *trans*-**12** (11 %) was obtained. Carrying out the reaction at 100 °C for 24h gave, after hydrolysis, a mixture composed of the previously mentioned products. However, their distribution was strongly shifted towards the cyclized compounds *cis*-**12** (45 %) and *trans*-**12** (21 %) as oppose to the uncyclized dienes **10** (< 2 %) and **11** (< 2 %).

Scheme 5.1.4. Oppolzer's magnesio-ene reaction of **5**.



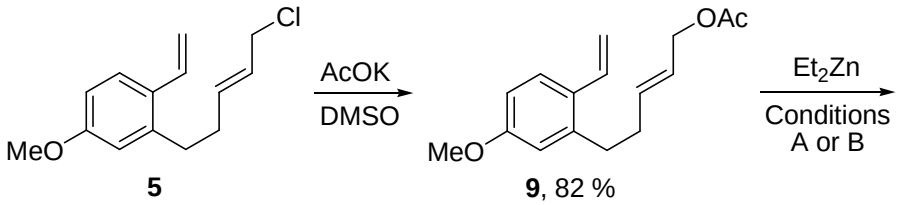
5 **8a** **8b**



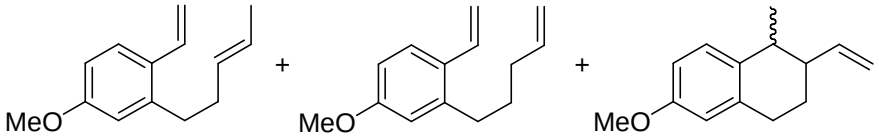
Conditions :	**10**	**11**	**12**
THF, 60 °C, 24h	31 %	31 %	15 % (*cis*)
			11 % (*trans*)
THF, 100 °C, 24h	< 2 %	< 2%	45 % (*cis*)
			21 % (*trans*)

Next the palladium catalyzed variant of the Oppolzer's reaction was explored.[35] In this regard, reaction of chlorodiene **5** with potassium acetate in DMSO provided the starting acetate **9** in 82 % yield (Scheme 5.1.5.). The cyclization reaction was attempted at two different conditions *A* and *B*. Under conditions *A* acetate **9** was exposed to a catalytic amount of $Pd(OAc)_2$ (10 mol %) and PBu_3 (10 mol %) in the presence of an excess of Et_2Zn. Unfortunately, under those conditions only the minor amounts of the cyclized products *cis*-**12** (14 %) and *trans*-**12** (< 1 %) were obtained, the major products were the uncyclized dienes **10** (39 %) and **11** (39 %). Under conditions *B* $Pd(PPh_3)_4$ (10 mol %) was used as the catalyst in the presence of an excess of Et_2Zn. Under those conditions no cyclization was observed, only the uncyclized compounds **10** (50 %) and **11** (46 %) were formed. From the obtained results it was clear, that Oppolzer's metallo-ene cyclization could not provide synthetic advantage over the zirconocene mediated cyclization reaction.

Scheme 5.1.5. Palladium catalyzed metallo-ene cyclization of **9**.



5 **9**, 82 %



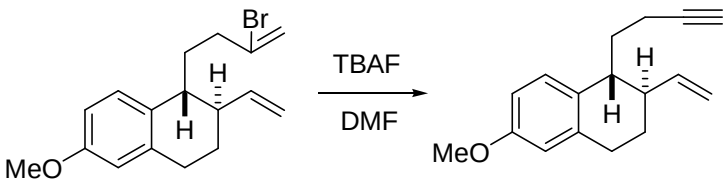
10 **11** **12**

A	39 %	39 %	14 % (*cis*)
B	50 %	46 %	0 %

A: $Pd(OAc)_2$ (10 mol %), PBu_3 (10 mol %), Et_2O
B: Pd(PPh3)4 (10 mol %), toluene

The synthesis was continued with dehydrobromination of bromodiene **7**, prepared by cyclization of methoxydiene **6** with Negishi's reagent (Scheme 5.1.3). Treatment of **7** with tetrabutylamonium fluoride in DMF[36] gave enyne **13** in 95 % yield (Scheme 5.1.6). Using the described methodology it was possible to prepare the desired enyne **13** in six steps from the commercially available materials with overall yield of 36 %.

Scheme 5.1.6. Dehydrobromination of bromodiene **7**.



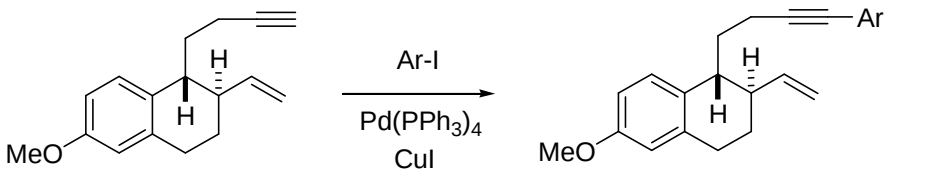
7 **13**, 95 %

In the following part of the synthesis several derivatives of the enyne **13** bearing different functional groups on the terminal triple bond were prepared. Several different synthetic strategies for this functionalization were used.

Attachment of various aryl groups was accomplished by using the standard Sonogashira protocol: 1.1 eq. of the corresponding aryl iodide, 1 mol % of $Pd(PPh_3)_4$, 2 mol

% of CuI, Et_3N (Scheme 5.1.7.). Reactions under those conditions proceeded uneventfully yielding enynes substituted with the phenyl group **14** and the 4-methoxycarbonylphenyl group **15** in nice 78 % and 80 % yields respectively. The 3-pyridinyl substituted enyne **16** was obtained in slightly lower, but still acceptable, 68 % yield.

Sheme 5.1.7. Arylation of enyne **13**.

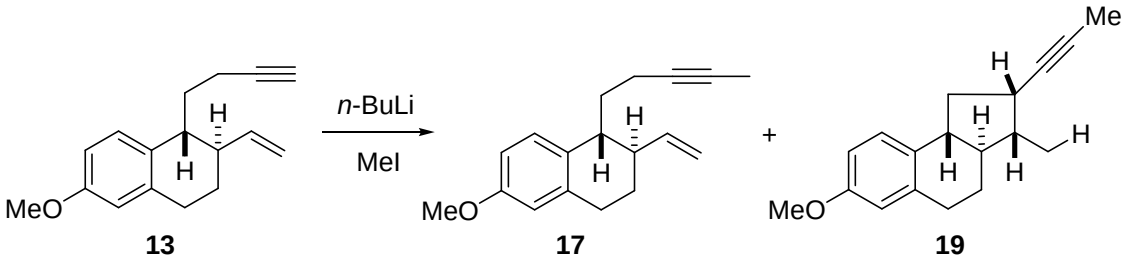


13

14, Ar = Ph 79 %
15, Ar = 4-MeCOOPh 80 %
16, Ar = 3-C_3H_5N 68 %

Next, enynes bearing methyl and trimethylsilyl groups on the triple bonds (**17** and **18** respectively) were prepared. I envisioned that functionalization of enyne **13** with the methyl group could have been done according to the standard procedure for methylation of the terminal triple bond, which is based on lithiation of the acidic hydrogen on the triple bond with *n*-BuLi and alkylation of the formed acetylide with MeI. Surprisingly, this simple transformation proved to be more troublesome than I originally presumed. After lithiation and methylation not only the expected enyne **17,** but also variable amount of the cyclized compound **19** were found in the reaction mixture (Scheme 5.1.8). Ratios in which both products were formed were highly dependant on reaction conditions as well as on the amount of the used *n*-BuLi.

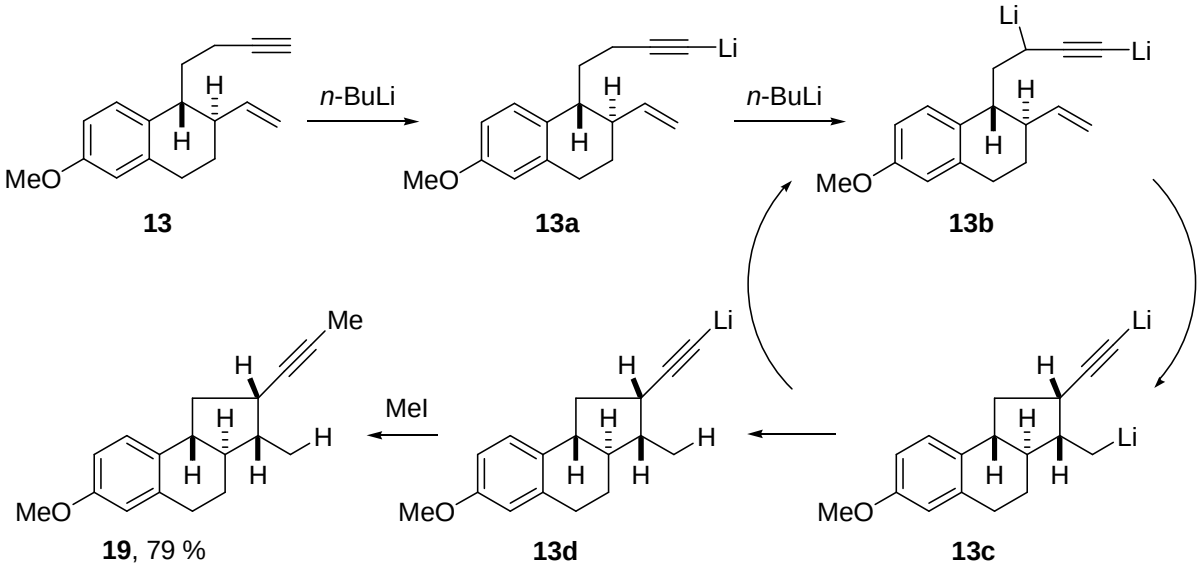
Scheme 5.1.8. Methylation of enyne **13**.



13 **17** **19**

When the starting compound **13** was treated with 1.1 eq. of *n*-BuLi (excess of *n*-BuLi was used to ensure quantitative lithiation of the terminal triple bond) at -78 °C and then the reaction mixture was allowed to warm up to 20 °C before addition of MeI, tedious separation of products provided the cyclized alkyne **19** in 79 % and the methylated enyne **17** in only 20 % yields. The formation of the five-membered ring could be explained in the following terms (Scheme 5.1.9). Lithiation of the propargylic position in **13a** by the excess of *n*-BuLi led to formation of intermediate **13b**, which further underwent the intramolecular cyclization furnishing the cyclopentane derivative **13c**. This would not be surprising, both lithiation of the propargylic position in the presence of the excess of *n*-BuLi[37] and intramolecular carbolithiation of unsaturated organolithium compounds[38] have been observed. However, the described reactions were stoichiometric. In my case the reaction clearly proceeded catalytically. To explain the catalytic nature of the cyclization following mechanism based on the fact that *iso*-alkyllithiums are stronger bases than propargyl lithiums[39] could be suggested. After the tricyclic alkyllithium compound **13c** was formed it acted as a base and intermolecularly lithiated the propargylic position in **13a** via H-Li exchange forming new **13b** as well as **13d**, which after alkylation with MeI gave the tricyclic alkyne **19**.

Scheme 5.1.9. Catalytic cyclization of enyne **13**.

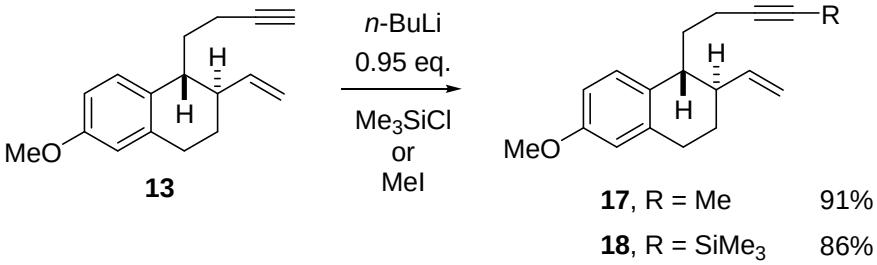


To avoid the above described cyclization, the methylation procedure had to be modified in the following way. Initially, lithiation of the acetylene had been carried out at -10 °C and only 0.95 eq. of *n*-BuLi was used prior to addition of MeI. Under the modified

conditions methylation of the triple bond proceeded smoothly and yielded the desired methylated enyne **17** in very nice 91 % isolated yield (Scheme 5.1.10.).

An approach similar to methylation was also applied for the preparation of the trimethylsilyl derivative **18**. The lithiation of **13** with 0.95 eq. of *n*-Buli at -10 °C, followed by alkylation of formed lithium acetylide with trimethylsilyl chloride afforded, after isolation, enyne **18** in 86 % yield.

Scheme 5.1.10. Methylation and silylation of enyne **13**.



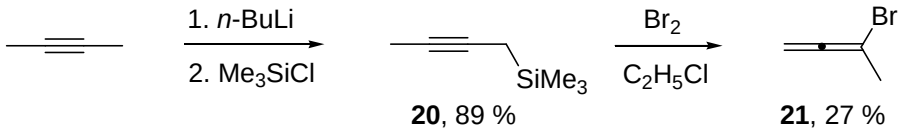
Out of those several bicyclic enynes **13-18** bearing different substituents on the triple bond the methylated enyne **17** was particularly important, because it later served as the crucial intermediate in the total synthesis of estrone. Because of that I wanted to look for another and possibly more efficient pathway for its synthesis.

In this regard, the S_N2' substitution of organotitanium compounds with bromoallene (in the presence of catalytic amount of CuCl), which affords directly derivatives with the triple bond[40] provided us with the necessary hint. This reaction is similar to the alkylation of organozirconium compounds with 2,3-dibromopropene I describer earlier (Scheme 5.1.3). Based on this similarity I presumed that reaction of diene **6** with Bu_2ZrCp_2 followed by alkylation with an appropriately substituted allene could yield enyne **17** directly in one step as opposed to the above described three step procedure (cyclization shown in Scheme 5.1.3, dehydrobromination in 5.1.6 and methylation in 5.1.10).

As a suitable candidate for alkylation 3-bromo-1,2-butadiene was chosen. There are several described syntheses of 3-bromo-1,2-butadiene **21**. The shortest (in terms of reaction steps) is based on usage of organomercury compounds.[41] Another relies on the reaction of trimethylsilylbutyne, prepared by trimethylsilylation of 2-butyne[42], with elemental bromine.[43] To avoid working with hazardous organomercury substances I opted for the latter approach. As shown in Scheme 5.1.11 treatment of 2-butyne with n-BuLi and subsequent

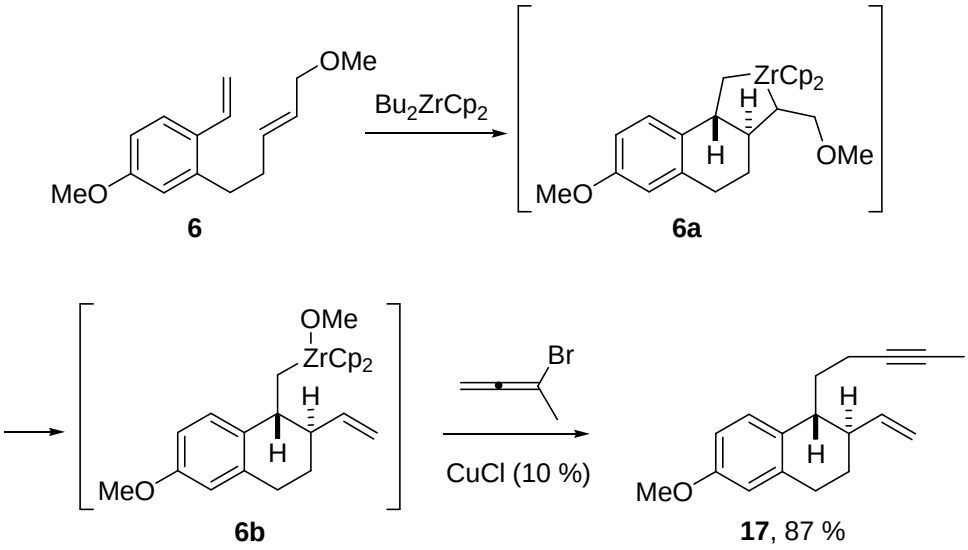
silylation of the formed propargylic lithium with Me_3SiCl provided 1-trimethylsilyl-2-butyne **20** in 89 % yield. In the next step the silylated butyne underwent S_N2' reaction with elemental bromine forming desired 3-bromo-1,2-butadiene **21** in 27 % yield. At this point I would like to note that handling of 3-bromo-1,2-diene was rather difficult. The major difficulty was caused by the allene's boiling point. Initially, the reaction of 1-trimethylsilyl-2-butyne **20** with bromine was carried out in CH_2Cl_2 and allene **21** was supposed to be isolated from the reaction mixture by distillation. However, it turned out that the boiling point of the allene is similar to that of CH_2Cl_2 (40 °C) and as a result I was not able to separate the allene from the solvent. In order to circumvent this problem, the reaction had to be carried out in a solvent with a lower boiling point. As a promising candidate C_2H_5Cl (b.p. 12 °C) was chosen. The final separation of the C_2H_5Cl from the allene was done at 12 °C under atmospheric pressure. Using this approach I was able to obtain the **21** of suitable purity for further synthesis. It should be also noted, that the allene decomposed rapidly at room temperature (20 °C) therefore all manipulation had to be done as swiftly as possible. To prevent its decomposition during long term storage, the allene was stored at -195 °C (submerged in liquid nitrogen).

Scheme 5.1.11. Synthesis of allene **21**.



With bromoallene **21** secured, Negishi's cyclization-alkylation sequence of methoxydiene **6** was attempted. Fortunately, as shown below in Scheme 5.1.12, the reaction of diene **6** with Negishi's reagent followed by CuCl catalyzed (10 mol %) alkylation of the organozirconium intermediate **6b** with 3-bromo-1,2-butadiene proceeded as envisioned giving the expected enyne **17** in very nice 87 % isolated yield, which constitute a significant shortcut in the synthesis of enyne **17** in terms of steps as well as overall yield.

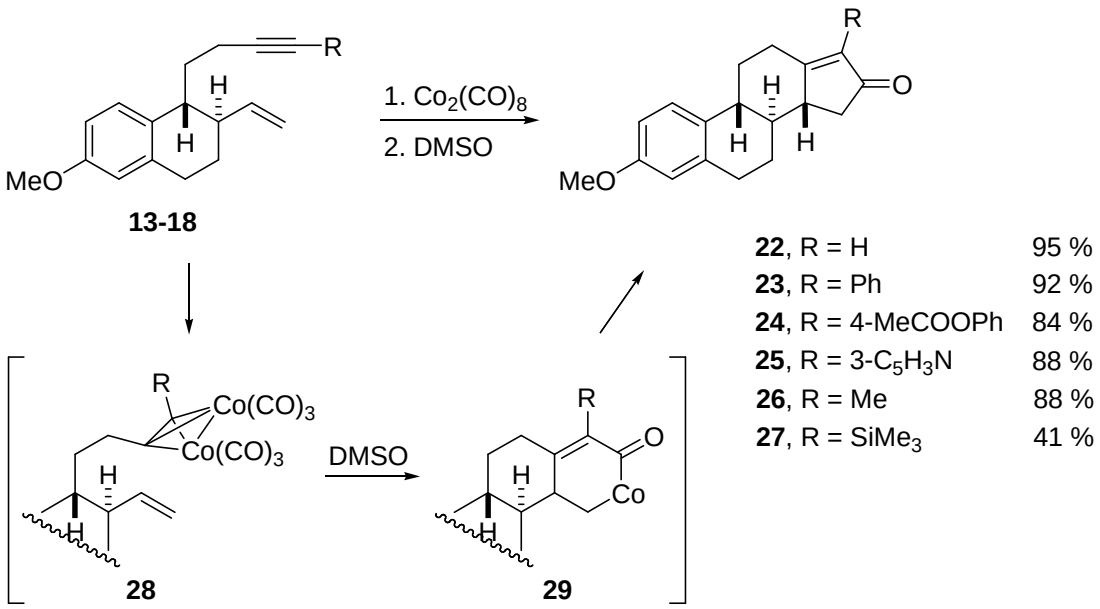
Scheme 5.1.12. Short synthesis of enyne **17**.



The synthesis was continued with Pauson-Khand reaction. This reaction is formally [2+2+1] cycloaddition between alkene, alkyne and carbon monooxide to form the α,β-cyclopentenone ring. I envisioned that compounds **13-18**, possessing both the alkyne and the alkene moiety, could constitute an ideal candidates for intramolecular variant of this reaction. In this particular case the cyclization would results in the formation of the α,β-cyclopentenone ring (steroid D ring) as well as formation of the six-membered (steroid C) ring thus furnishing compound with the tetracyclic steroid framework. This would allow to assembly both C and D steroid rings in one step.

The first tested method was the original procedure, which relied on use of stoichiometric amount of $Co_2(CO)_8$ to mediate the reaction.[44] As shown in Scheme 5.1.13 the enynes **13-18** reacted with $Co_2(CO)_8$ (1.1 eq.) to form the Co-complexes **28**. Following the decomposition of **28** with excess DMSO (5 eq.) at 80 °C, which led to formation of the cobaltocyclohexene compounds **29**, the reductive elimination of cobalt gave the corresponding tetracyclic ketones **22-27**. For enynes bearing hydrogen **13**, aryl groups **14-16** or methyl **17** as a substituent on the triple bond the cyclocarbonylation proceeded with very good yields ranging between 84 and 95 % isolated yields. Only for enyne **18** possessing trimethylsilyl moiety the reaction furnished desired tetracyclic product in mediocre yield of 41 %. It is important to note that all the products were obtained as pure *trans-anti* diastereoisomers, which was the desired configuration! The formation of tetracyclic products with different configuration was not observed.

Scheme 5.1.13 Pauson-Khand reaction.



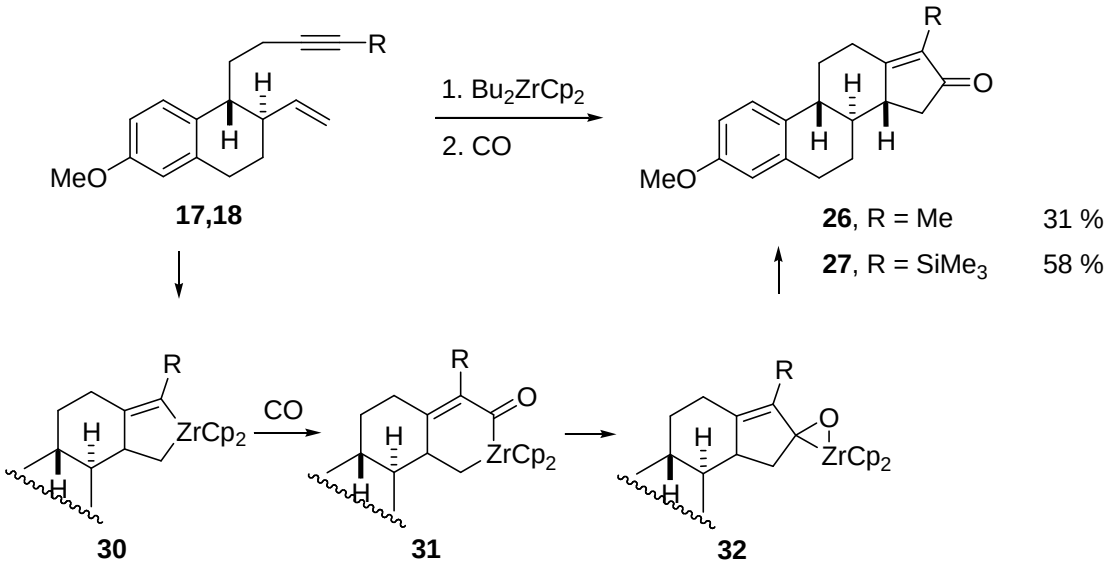
Another commonly applied stoichiometric method for Pauson-Khand reaction is based on the use of $Mo(CO)_6$.[45] The described reaction conditions are similar to the conditions used in the cobalt mediated reaction. However, when I attempted cyclocarbonylation of enyne **13** with $Mo(CO)_6$ the reaction did not proceed. Not even traces of cyclopentenone **22** were detected.

It is worth mentioning that catalytic versions of the Pauson-Khand reaction had been reported as well. Perhaps the most successful among them were those based on catalytic use of rhodium complexes along with either gaseous CO[46] or suitably substituted benzaldehydes (mainly 2-naphtaldehyde or 4-trifluoromethylbenzaldehyde[47]) as an alternative source of CO. Particularly, the later approach seemed tempting. Disappointingly, cyclocarbonylations of **13** with catalytic amount of $Rh(BF_4)(cod)_2$ (10 mol %) and dppp (20 mol %) in the presence of 4-trifluoromethylbenzaldehyde or 2-naphthaldehyde (2 eq.) did not proceed at all and the unchanged starting enyne **13** was recovered from the reaction mixtures. The reactions were attempted several times with variations in the reaction conditions (different solvents, amount of catalyst and temperature), unfortunately, the results were the same, the reactions did not proceed at all.

The last tested method was Negishi's protocol for cyclocarbonylation (Scheme 5.1.14).[48] Treatment of the enynes **17** and **18** with stoichiometric amount of Bu_2ZrCp_2 (1.1 eq.) at -78 °C and subsequent exposure of *in-situ* formed zirconacyclopentenes **30** to gaseous CO at 0 °C led to formation of compounds with the zirconacyclohexene ring **31**, which further

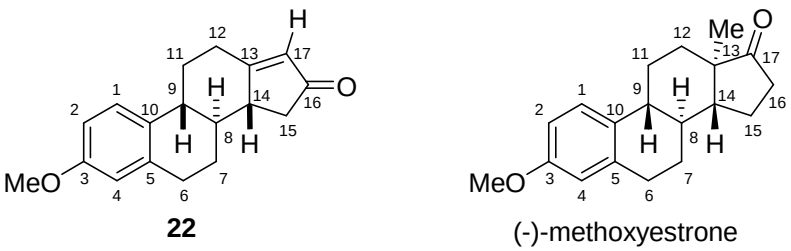
underwent rearrangement to form spirocompounds **32** and finally, acidic decomposition afforded desired tetracyclic ketones **26** or **27**. Reaction with enyne **17** proceeded with rather low yield of 31 %. However, in case of the enyne substituted with trimethylsilyl group **18** this protocol proved to be superior to that of classical Pauson-Khand and furnished product in nice 58 % yield. Similarly to classical Pauson-Khand conditions, only the products with desired *trans-anti* configuration were obtained and tetracyclic compounds with different configuration were not formed in this reaction.

Scheme 5.1.14. Negishi's cyclocarbonylation.



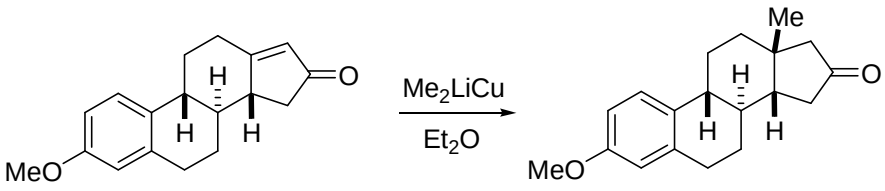
To continue the synthesis towards the estrone framework, methyl in position 13 had to be introduced (Figure 5.1.2). I expected that conjugate addition could be utilized to accomplish this transformation. The α,β-unsaturated tetracyclic ketone **22** seemed like an ideal substrate for this purpose.

Figure 5.1.2.



Experimentation began with one of the most classical approaches to conjugate addition, which is based on organolithium cuprates. Treatment of the tetracyclic ketone **22** with the stoichiometric amount of the Me_2LiCu in Et_2O led to methylation of the position 13 as envisioned (Scheme 5.1.15); however, a product with the undesired *trans-anti-cis* configuration on rings junctions **33** was formed in 80 % yield. Sadly, not even traces of the compound with the desired *trans-anti-trans* configuration were obtained.

Scheme 5.1.15. Conjugate addition to ketone **22**.

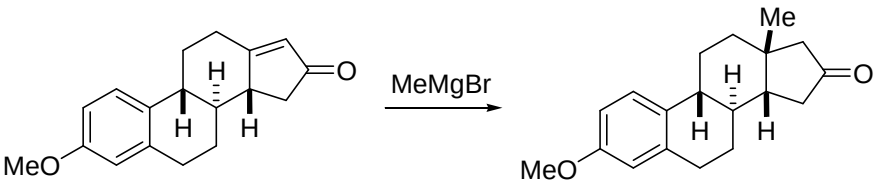


22 **33,** 80 %

In order to explore the possibility of preparation of the product with the correct *trans-anti-trans* configuration, several different commonly applied methods for the conjugate addition of the methyl group were tested.

When ketone **22** was exposed to MeMgBr in the presence of the catalytic amount of CuOTf (10 mol %) in THF and $BF_3 \cdot Et_2O$ product **33** was obtained in 5 % yield (Scheme 5.1.16). Switching the catalyst from CuOTf (10 mol %) to CuI (10 mol %) led to improvement, in THF as well as in Et_2O reaction provided **33** in 30 % yield. Surprisingly, increasing the amount of CuI from catalytic (10 mol %) to stoichiometric (1 eq.) did not lead to increase of the yield and under stoichiometric conditions ketone **33** was obtained in 25 %. Unfortunately, in neither case any product with correct *trans-anti-trans* configuration was obtained.

Scheme 5.1.16. Conjugate addition under various conditions.



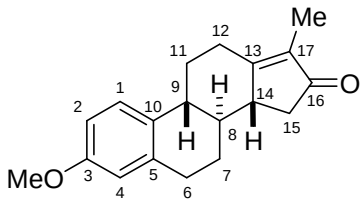
22 **33**

Entry	catalyst	solvent	additive	**33**
1	CuOTf (10 %)	THF	$BF_3 \cdot Et_2O$ (1 eq.)	5 %
2	CuI (10 %)	THF	$BF_3 \cdot Et_2O$ (1 eq.)	30 %
3	CuI (10 %)	Et_2O	$BF_3 \cdot Et_2O$ (1 eq.)	30 %
4	CuI (1 eq.)	Et_2O	$BF_3 \cdot Et_2O$ (1 eq.)	25 %

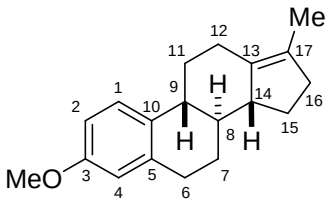
Attempts to introduce methyl with Me_3Al/Ni-cat[49], Me_3Al/Cu-cat[50] or Me_2Zn/Cu-cat[51] systems under various conditions failed. In all of the cases no products of conjugate addition were obtained and starting material remained intact.

Since the conjugate addition failed to give the product with the correct stereochemistry, I decided to look for an alternative approach for synthesis of the compound with the steroid framework. In this regard I turned my attention to 17-methylestratetraene **34** (figure 5.1.3), which is a known intermediate in estrone synthesis (can be converted to methoxyestrone diastereoselectively with simple two step transformation).[52] I presumed that reduction of 16-keto group in the derivative **26** could provide the estrone precursor **34**.

Figure 5.1.3.



26



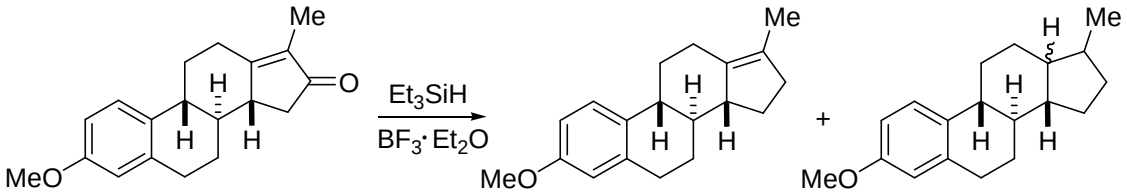
34, 17-methylestratetraene

.

The reduction of **26** was attempted using several different methods. The first tested method, based on the use of mixture of Et_3SiH and $BF_3 \cdot Et_2O$[53], is shown in Scheme 5.1.17. Various different conditions in terms of reaction temperature, solvent and amount of Et_3SiH and $BF_3 \cdot Et_2O$ were tested with the following results. The reduction of **26** resulted in formation

of mixture of the desired compound **34** and saturated compound **35**. Unfortunately, **34** was only formed in low yields (5-20 %), **35** was major product of this reaction (50 - 70 %). It is worth mentioning that classical Kishner-Wolf reaction (or its modification[54]) proceeded with similar results as the above mentioned procedure. Inseparable mixtures of **34**, **35** and other unidentified products were obtained with **34** being the minor component.

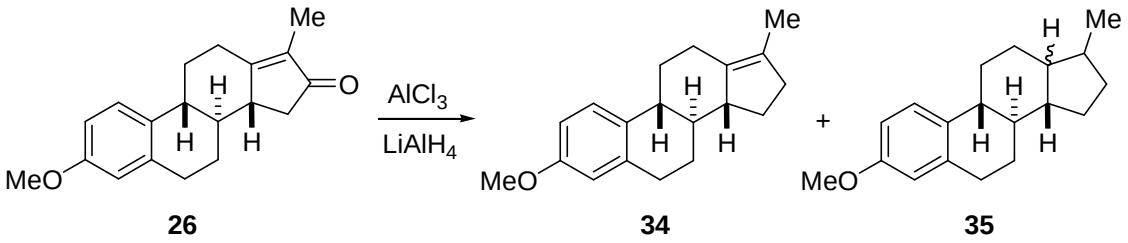
Scheme 5.1.17. Reduction of the **26** with Et_3SiH.



26 **34,** 5-20 % **35,** 50-70 %

The most successful method for the reduction that I tested was based on aluminum hydrides, which are known to be capable of reduction of a keto group directly to methylene group[55], including a keto group in a conjugate system.[56] Treatment of **26** with a solution of aluminum hydride, freshly prepared from $AlCl_3$ and $LiAlH_4$, at 0 °C resulted in formation of the mixture of the **34** and **35**. The ratio in which both products were formed was highly dependant on the ratio of $AlCl_3$ to $LiAlH_4$ as shown in Scheme 5.1.18. When 4.8 eq. of $AlCl_3$ and 1.2 eq. of $LiAlH_4$ were used with respect to the starting ketone **26** the desired 17-methylestratetraene **34** was obtained in very nice 91 % yield. In this manner I managed to complete the formal total synthesis of (±)-estrone.

Scheme 5.1.18. Reduction of **26** with Al_xH_y.



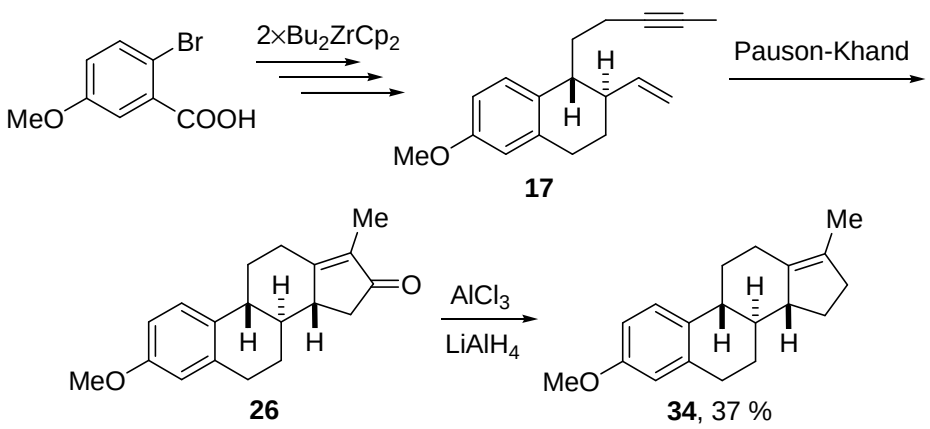
26 **34** **35**

Entry	$AlCl_3/LiAlH_4$*	**34**	**35**
1	0.75/1.5	47 %	40 %
2	4.5/1.5	83 %	13 %
3	6/1.5	87 %	8 %
4	4.8/1.2	91 %	5 %

* Molar ratios with respect to **26**

To conclude this chapter I would like to say that I managed to develop new formal total synthesis of methoxyestrone that was highly diastereoselective (Scheme 5.1.19). The approach was based on two successive zirconocene mediated reactions followed by Pauson-Khand cyclocarbonylation and finally, chemoselective reduction of the keto group in the conjugated system. Using this approach the direct precursor of estrone **34** was obtained in 37 % total yield from commercially available 2-bromo-5-methoxybenzoic acid. I would like to emphasize, that the both crucial cyclization reactions proceeded diastereoselectively yielding the final product **34** with the *trans-anti* configuration, which is the correct relative stereochemistry.

Scheme 5.1.19. Outline of new total synthesis of estrone precursor **34**.



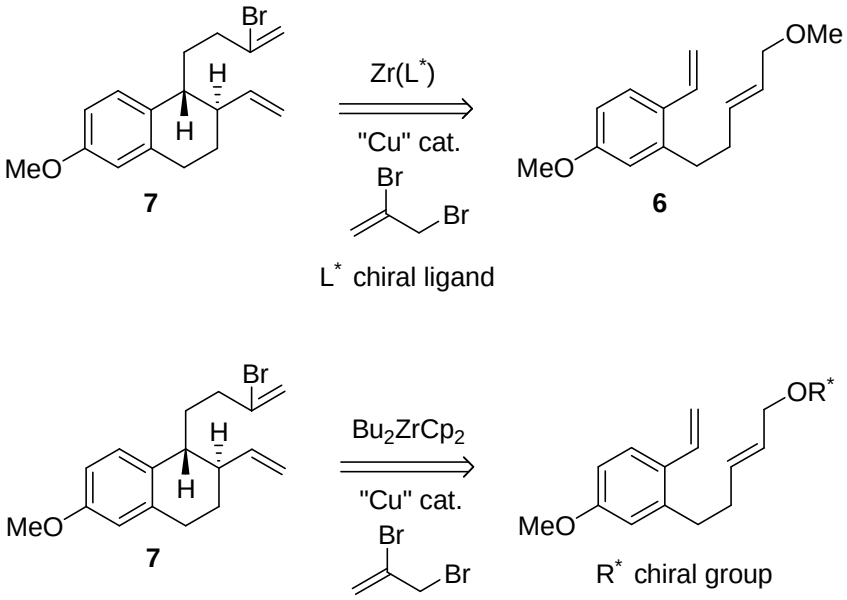
17

26 **34**, 37 %

5.2 Enantioselective Synthesis of (-)-Methoxyestrone.

In the previous chapter I described the new synthesis of estrone precursor. The new strategy was very efficient, in terms of the overall yield and diastereoselectivity, therefore I wanted to explore whether it could be modified to achieve enantioselective synthesis as well. I presumed that if I could introduce chirality early in the synthesis, namely if I could prepare bicyclic diene **7** enantioselectively, it could lead to enantiomericaly pure estrone precursor **34** due to high diastereoselectivity in later steps. In this regard the most obvious choice would be to attempt to modify the zirconocene mediated cyclization of methoxydiene **6** itself. Two different approaches could be utilized; either to carry the cyclization out with a zirconocene bearing chiral ligands or to attempt to cyclize a diene bearing chiral alkoxy group (Figure 5.2.1).

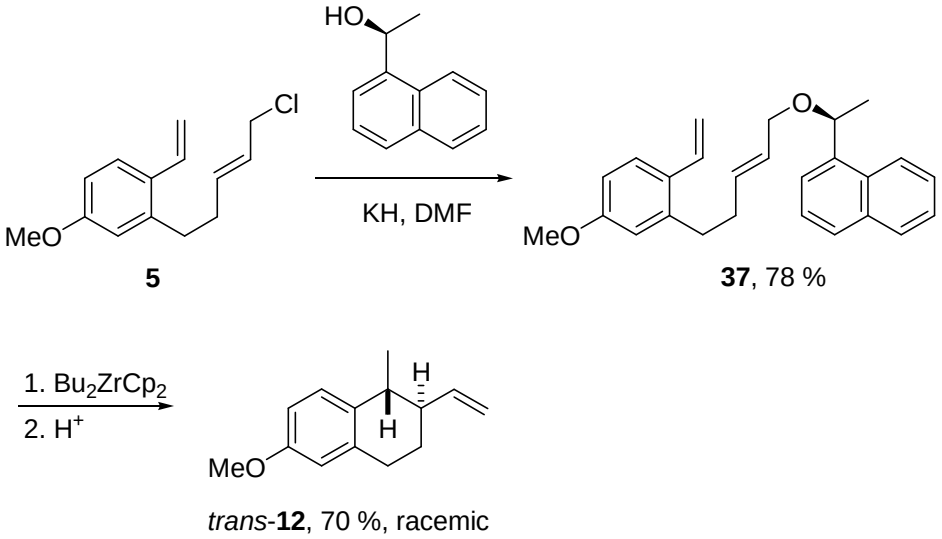
Figure 5.2.1.



The former approach has been explored in the previous work done by Pavel Herrmann (former member of our group).[57] Unfortunately, the cyclization of the methoxydiene **6** with the zirconocene bearing chiral ligands failed to give the product with any optical induction. I explored the latter approach that was based on the zirconocene mediated cyclization of the diene bearing chiral ether moiety **37** (Scheme 5.2.1). Ether **37** was prepared in 78 % yield by the reaction of chlorodiene **5** with potassium (*S*)-1-(1-naphthyl)ethanolate, generated by

exposure of (*S*)-1-(1-naphthyl)ethanol to KH. Cyclization of **37** with a stoichiometric amount of Bu_2ZrCp_2 gave, after quenching the reaction with acid, expected *trans*-**12** in nice 70 % yield. However, no chiral induction was observed, *trans*-**12** was obtained as a racemic mixture.

Scheme 5.2.1. Zirconocene mediated cyclization of chiral ether **37**.

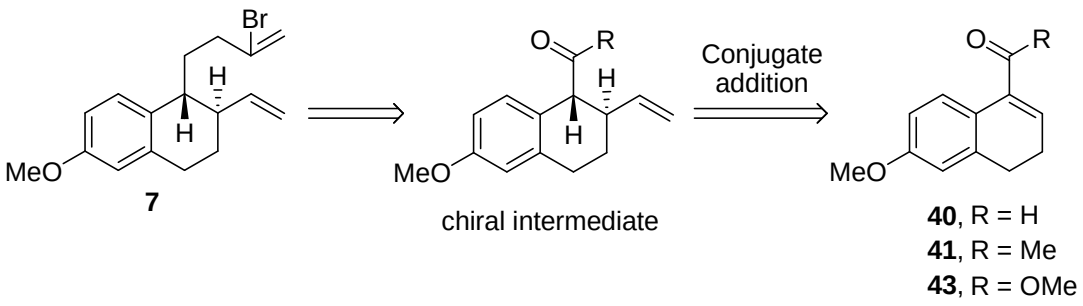


5 **37**, 78 %

trans-**12**, 70 %, racemic

Since the zirconocene mediated cyclization of dienes **6** and **37** failed to give chiral products I decided to look for a different synthetic strategy that would allow preparation of enantiomerically enriched bromodiene **7**. One of the possibilities could be enantioselective conjugate addition, which is a widely used synthetic tool in construction of quartery chiral centers. I envisioned that using this protocol I could be able to prepare the chiral intermediate shown in the Figure 5.2.2, which could be subsequently converted to the desired chiral bromodiene **7**. Aldehyde **40**, ketone **41** or ester **43** seemed as suitable starting materials.

Figure 5.2.2.

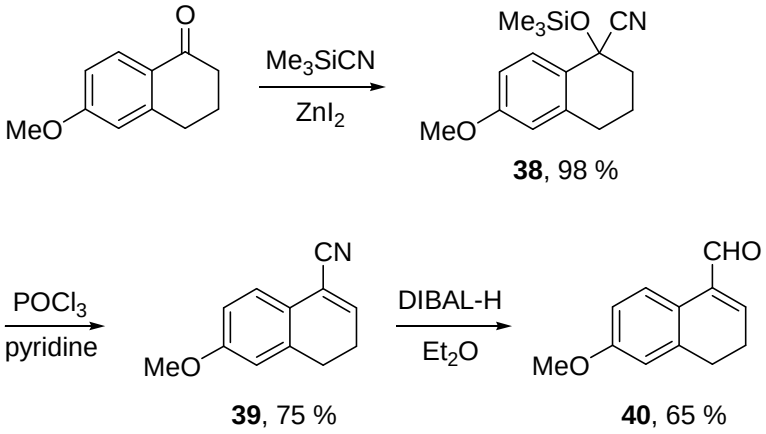


7 chiral intermediate

40, R = H
41, R = Me
43, R = OMe

Synthesis began with the preparation of the **40**, **41** and **43** according to the described methodology.[58][59][60] The commercially available 6-methoxytetralone was used as a starting material for the preparation of the derivatives. As shown in Scheme 5.2.2 synthesis of aldehyde **40** started with addition of trimethylsilylcyanide to 6-methoxytetralone catalyzed by ZnI_2. It led to the formation of silylated cyanohydrine **38** in almost quantitative (98 %) yield. Exposure of **38** to $POCl_3$ in pyridine led to elimination of the trimethylsilyl group and yielded conjugated cyanide **39** in 75 % yield, which was subsequently reduced with diisobutylaluminium hydride to give aldehyde **40** in 65 % yield.

Scheme 5.2.2. Synthesis of conjugated aldehyde **40**.



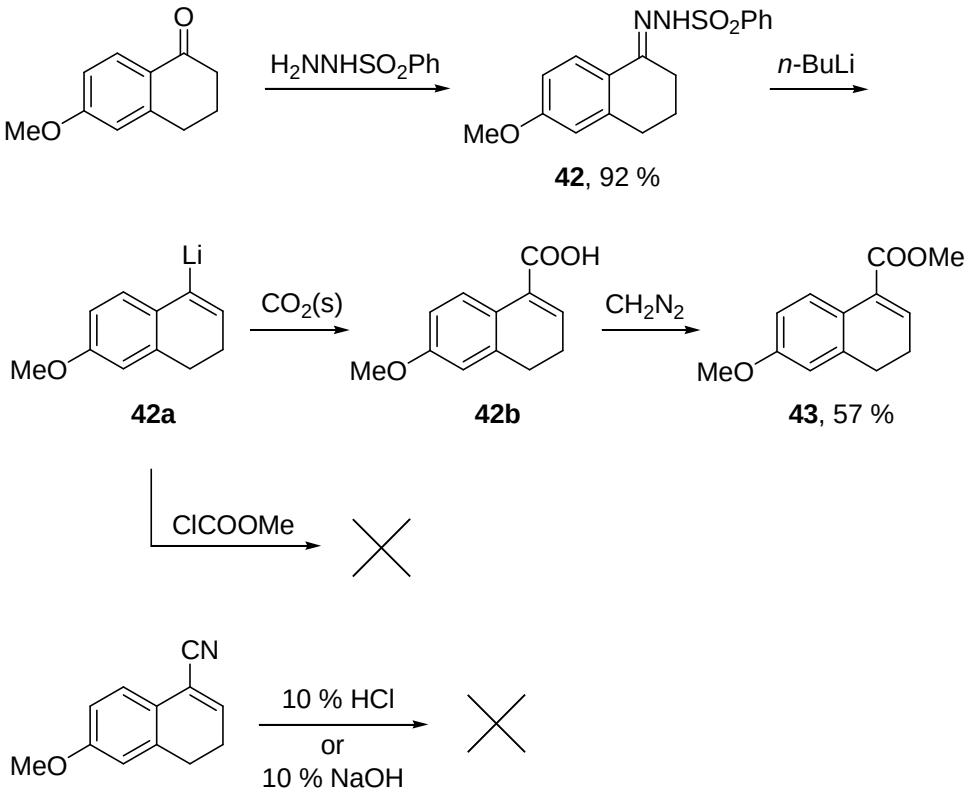
Preparation of ketone **41** (Scheme 5.2.3) was based on the addition of MeLi to cyanohydrine **38** and subsequent treatment with HCl. Conjugated ketone **41** was obtained in 85 % yield.

Scheme 5.2.3. Preparation of conjugated ketone **41**.

The synthesis of ester **43** was accomplished with the following sequence of reactions. Condensation of 6-methoxytetralone with phenylsulfohydrazone afforded hydrazide **42** in 92

% yield. Lithiation of **42** with *n*-BuLi and treatment of the formed organolithium **42a** with solid CO_2 gave crude acid **42b**, which was subsequently converted to its methyl ester **43** by the reaction with diazomethane in 57 % overall yield. It is worth mentioning that synthesis of the ester **43** was also attempted by direct alkylation of the organolithium compound **42a** with methyl chloroformate. However, in this case reaction resulted in formation of a complex mixture, which did not contain any traces of the product. Attempts to prepare acid **42b** by hydrolysis of nitrile **39** were also futile as the nitrile proved to be resiliant to both 10 % NaOH solution and 10 % HCl solution at 90 °C.

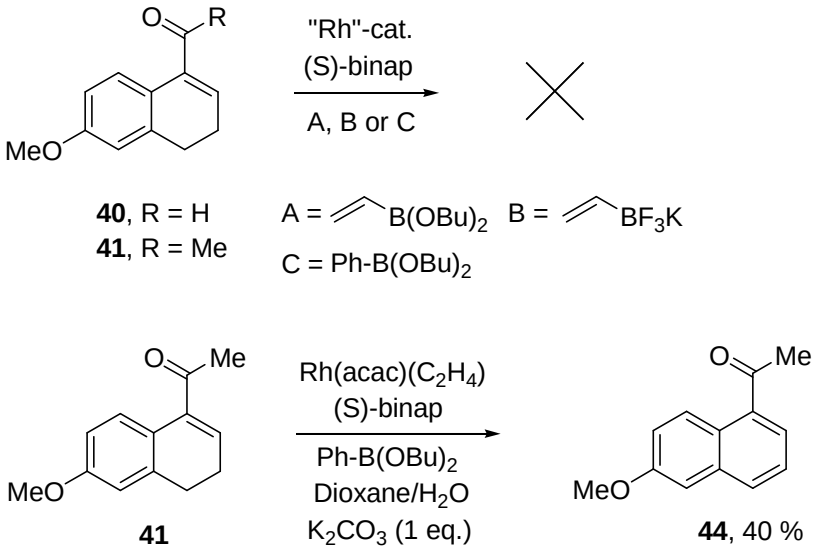
Scheme 5.2.4. Synthesis of the ester **43**.



Having the carbonyl compounds **40**, **41** and **43** on hand the synthesis was continued with the enantioselective conjugated addition. Initially it was envisioned that the addition of vinylboronic acid ester to carbonyl compounds **40**, **41** and **43** under Miyaura-Hayashi conditions (Rh catalyst with (*S*)-BINAP ligand)[61] could yield the chiral precursors (Fig. 5.2.2, page 44.).

The work began with attempts to prepare the desired compounds with the addition of vinylboronic acid ester to aldehyde **40** and ketone **41** in the presence of various rhodium catalysts ($Rh(acac)(CO)_2$, Rh(acac)(cod), $Rh(acac)(CH_2{=}CH_2)$) under various conditions (Scheme 5.2.2). Unfortunately, in neither case any product of conjugate addition was obtained. The starting carbonyl compound remained intact during the course of the reaction. Since I wanted to know why the addition did not proceed, I decided to try addition of different substrate, namely phenylboronic acid ester, to **40** and **41** under the above mentioned conditions. The results were similar, the unreacted starting aldehyde or ketone were recovered from the reaction mixture. There was one exception, when **41** was exposed to phenylboronic acid ester in dioxane/water with $Rh(acac)(CH_2{=}CH_2)$ (10 mol %) (*S*)-BINAP (20 mol %) and K_2CO_3 (1 eq.) the naphthyl derivative **44** was obtained in 40 % yield (no product of conjugate addition was observed). The attempts to introduce vinyl group by addition of potassium vinyltrifluoroborate catalyzed by $Rh(cod)(BF_4)$[62] to **40** or **41** were also made. However, they failed as well, no reaction occurred and the starting material was recovered from the reaction mixture.

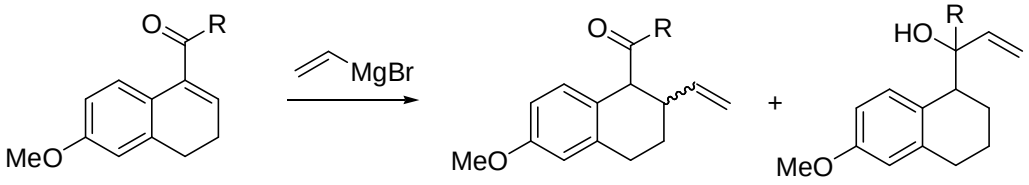
Scheme 5.2.5. Conjugate additions with rhodium catalyst.



The above mentioned procedures not only failed in furnishing the chiral products, they did not even yield expected products of 1,4-addition, therefore I decided to try different approach; the conjugated addition of vinylmagnesium bromide catalyzed by copper salts

(Scheme 5.2.6). Initially, reactions were carried out under racemic conditions to see whether it will be possible to obtain the products of 1,4-addition in the first place. After tedious experimentation some partially successful results were obtained. Treatment of aldehyde **40** with vinylmagnesium bromide in the presence of CuCN (10 mol %) and HMPA (1 eq.)[63] yielded the desired product of 1,4-addition **45**, albeit only in 5 % yield. The major product of reaction under the described conditions was alcohol **46** (50 % yield). The addition of vinylmagnesium bromide to ester **43** in the presence of CuCN (10 mol %) proceeded with a low yield (10 %) of the 1,4-product **48** as well. The most successful, in terms of 1,4-selectivity, was the addition of vinylmagnesium bromide to ketone **41**. When the addition was catalyzed by CuCl (10 mol %) in the presence of HMPA (1 eq.) the product of 1,4-addition **47** was obtained in 40 % (ratio of *cis*/*trans* was 1/5). Switching catalyst to CuCN (10 %) and increasing amount of HMPA to 3 eq. led to improvement of the yield to 60 % (ratio of *cis*/*trans* remained unchanged 1/5). Under the last described conditions no product of 1,2-addition was observed.

Scheme 5.2.6. Conjugate addition by copper catalyst.

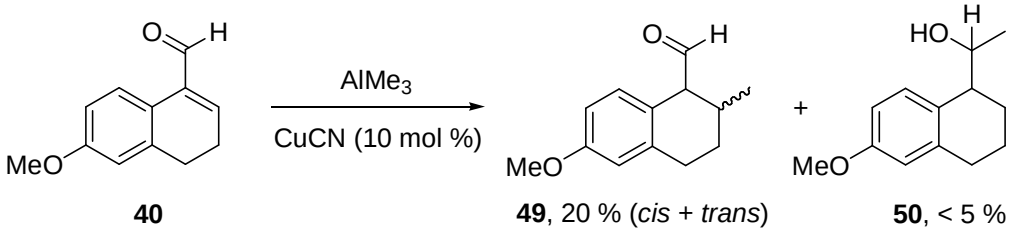


Entry	R	catalyst	additive	1,4-product	*trans*/*cis*	1,2-product
1	H	CuCN (10 mol %)	HMPA (3 eq.)	**45**, 5 %	3/1	**46**, 50 %
2	Me	CuCl (10 mol %)	HMPA (1 eq.)	**47**, 40 %	5/1	
3	Me	CuCN (10 mol %)	HMPA (3 eq.)	**47**, 60 %	5/1	
4	MeO	CuCN (10 mol %)		**48**, 10 %	1/0	

Another suitable method that could provide the desired products of 1,4-addition (either **45**, **46** or **47**) is the addition of organoaluminum and organozinc compounds catalyzed by copper salts. I decided to try this approach on my substrates **40**, **41** and **43** as well. Addition of an Et_2Zn in the presence of CuCN (10 mol %) was tested first. Unfortunately, all three substrates proved to be resilient towards the tested nucleophile and in neither case any reaction was observed. Next, the addition of $AlMe_3$ was tested. In this case ketone **40** and ester **43** did not react; however, aldehyde **40** upon treatment with $AlMe_3$ in the presence of CuCN (10 %) afforded 1,4-product **49** in 20 % yield (along with small amount of 1,2-product

50 (< 5 %)) (Scheme 5.2.7). Encouraged by this result I decided to try the addition of mixture of vinylmagnesium bromide and $AlCl_3$ to **41** in the presence of CuCN (10 mol %)[64]. Sadly, this attempt resulted in formation of a complex reaction mixture without any traces of the desired compound **45**.

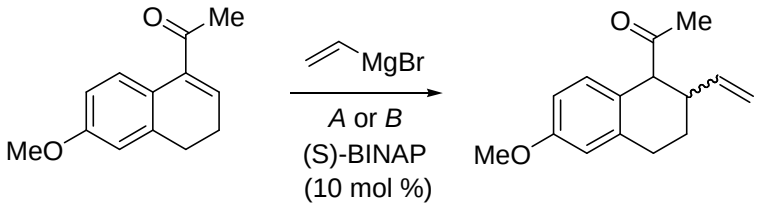
Scheme 5.2.7. Conjugate addition of $AlMe_3$.



40 **49**, 20 % (*cis* + *trans*) **50**, < 5 %

From the above presented results, the addition of vinylmagnesium bromide to ketone **41** catalyzed by CuCN (10 mol %) in the presence of HMPA (3 eq.) proceeded with the best 1,4-selectivity (60 % yield) (Scheme 5.2.6). Consequently, this reaction was attempted under enantioselective conditions. The racemic conditions were modified by addition of (*S*)-BINAP (10 mol %) (conditions *A*, Scheme 5.2.8). Under the new conditions addition proceeded with 60 % yield of product **47** (*trans*/*cis* was 5/1) (the same result as in racemic conditions). Unfortunately, no optical induction occurred. Many different reaction conditions were tested (different solvents: THF, DCM, Et_2O, toluene, Me-THF; different copper salts: $CuBr{\cdot}SMe_2$, CuOTf; different temperatures ranging from -78 °C to 20 °C; and the most importantly the speed of the addition of vinylmagnesium bromide into the reaction mixture). The best result in terms of optical induction was achieved when the reaction was carried out in Me-THF using $CuBr{\cdot}SMe_2$ (10 mol %) and (*S*)-BINAP (10 mol %) as the catalyst,[65] in this case the **47** was obtained in 60 % yield (as a mixture of *cis*/*trans* in 1/5 ratio) with 20 % ee.

Scheme 5.2.8. Enantioselective conjugate addition by copper catalyst.

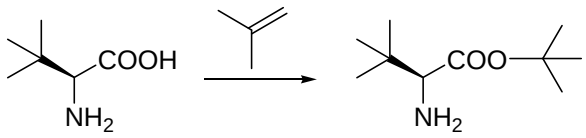


A: CuCN (10 mol %), HMPA(3 eq.), -40 °C — **47**, 60 %, *trans*/*cis* 5/1,racemic

B: $CuBrSMe_2$ (10 mol %), Me-THF, -40 °C — **47**, 60 %, *trans*/*cis* 5/1, 20 % ee

Since I was not able to find suitable catalytic conditions that would enable to prepare the desired chiral intermediate **45** with a reasonable enantiomeric excess I attempted the stoichiometric conjugate addition. Inspired by work of H. Kogen and K. Koga[66], who had successfully attached the vinyl group to various (cycloalken-1-yl)carbaldehydes via 1,4-addition of vinylmagnesium bromide to imines formed from the carbaldehydes by condensation with chiral aminoacid esters, I decided to use their approach on my substrate **40** (Scheme 5.2.10). According to Koga, the best results in terms of enantioselectivity were achieved when *t*-butyl ester of (L)-*t*-leucine (**51**) was used as aminoacid. However, ester **51** is not commercially available so this work had begun with its preparation (Scheme 5.2.9). Esterification of (L)-*t*-leucine with 2-methylpropene in the presence of 20 % oleum (1 eq.)[67] yielded **51** in nice 91 %. It's worth mentioning that the reaction was carried out in a pressure reaction tube.

Scheme 5.2.9. Synthesis of (L)-*t*-leucine *t*-butyl ester.

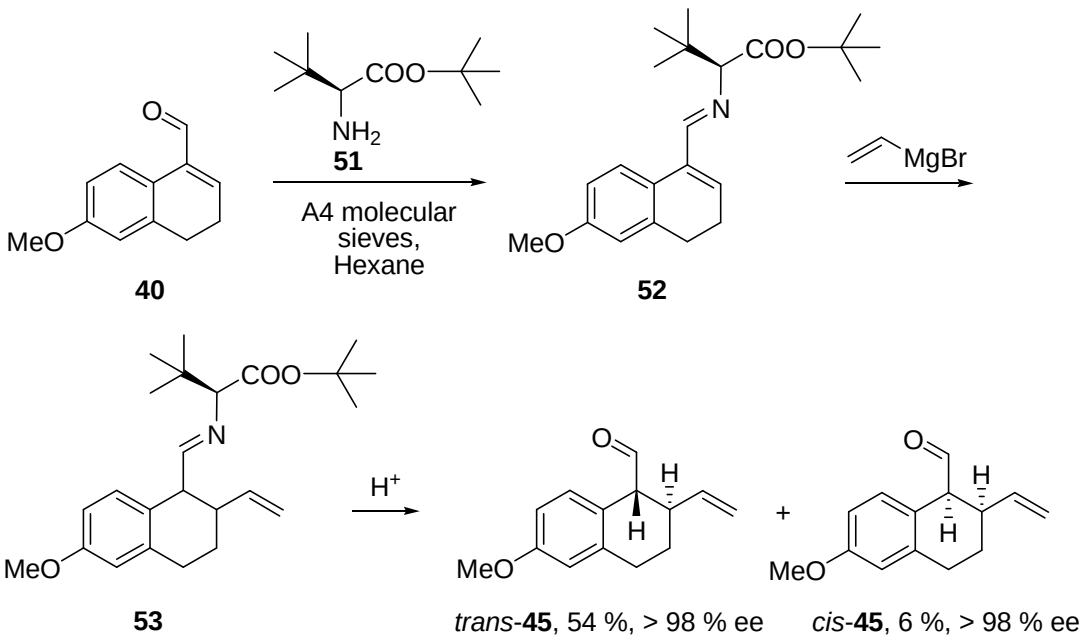


51, 92 %

What followed was the preparation of a chiral imine and the conjugated addition itself. Condensation of aldehyde **40** with amine **51** in the presence of molecular sieves A4 proceeded uneventfully, yielding chiral imine **52**. Addition of vinylmagnesium bromide to **52** led to formation of vinyl imine **53**, which upon treatment with a diluted acid afforded the desired vinylaldehyde **45** in 60 % yield (as a mixture of *cis* and *trans* diastereomers in 1/8 ratio) with

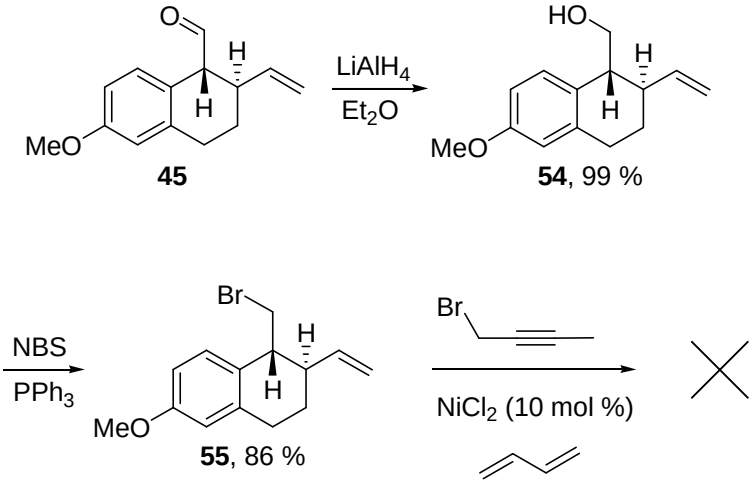
very high > 98 % ee. Enantiomeric excess was determined by chiral GC and absolute configuration was assessed after synthesis of methoxyestrone was completed by comparison of the prepared methoxyestrone with the natural sample.

Scheme 5.2.10. Stoichiometric conjugate addition.



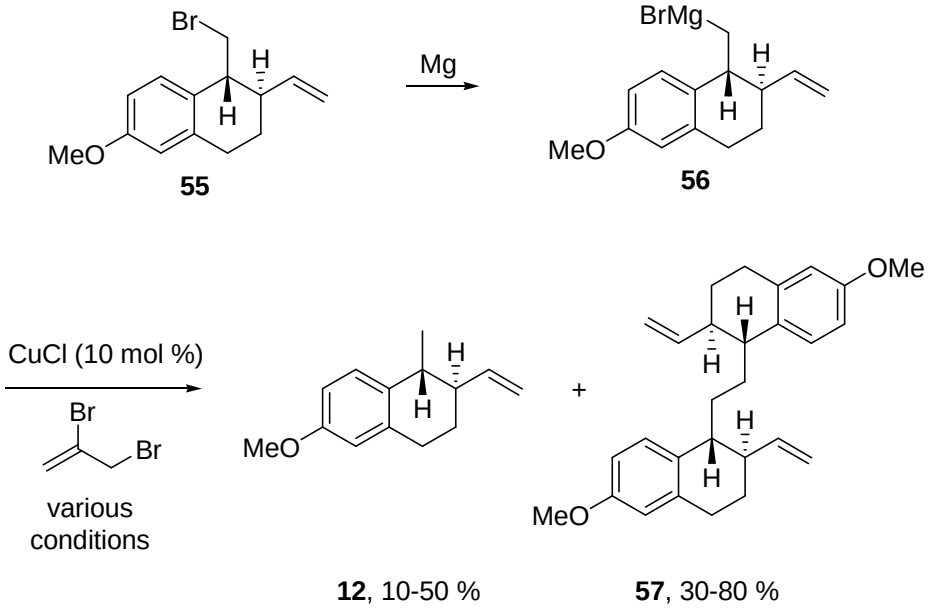
After securing the crucial chiral intermediate **45** the next step of the synthesis was the conversion of **45** to chiral bromodiene **7**. In this regard several different synthetic strategies were tested. The first tested approach relied on $NiCl_2$ catalyzed coupling reaction between alkyl bromide with propargylic bromide (Scheme 5.2.11).[68] Bromide **55**, required for this coupling, was prepared from **45** in 86 % yield by the reduction of **45** with diisobutylaluminium hydride and subsequent substitution of the hydroxy group in the formed vinylalcohol **54** for bromine by treatment with NBS in the presence of PPh_3. With bromide **55** the coupling was attempted; unfortunately, the reaction with propargylic bromide catalyzed by $NiCl_2$ (10 mol %)/1,3-butadiene system did not proceed at all, the unreacted starting material was recovered from the reaction mixture.

Scheme 5.2.11. Preparation of vinyl bromide 55.



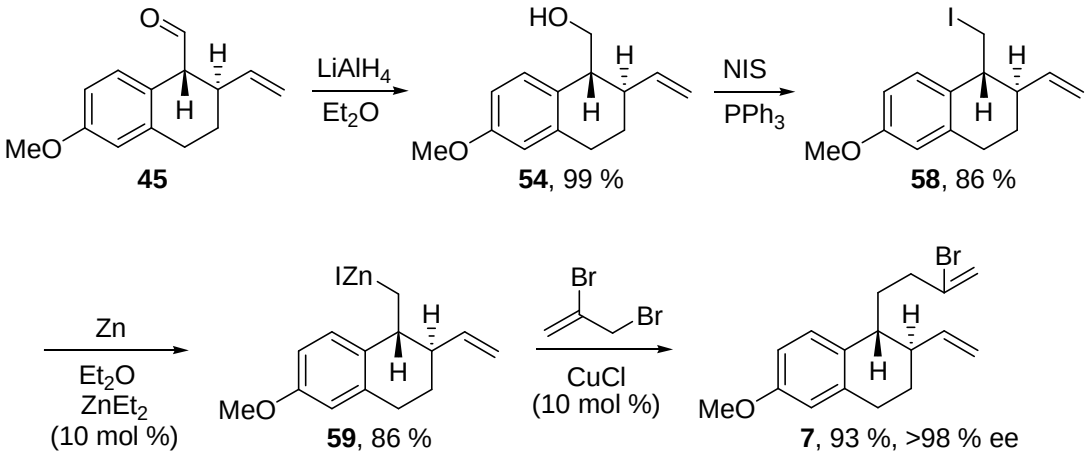
Next attempt to prepare the chiral bromodiene **7** from **45**, based on the copper catalyzed reaction between organomagnesium compounds and *α*,*β*-unsaturated alkyl halides, is shown in Scheme 5.2.12. Reaction of bromide **55** with magnesium gave the organomagnesium compound **56**, which was subsequently exposed to 2,3-dibromopropene in the presence of CuCl (10 mol %). The reaction was attempted under several different conditions; however, only various amoutns of compound **12**, dimer **57** and unreacted bromide **55** were obtained after the reaction. Not even traces of the expected bromodiene **7** were detected.

Scheme 5.2.12. Attempted synthesis of **7** via organomagnesium **56**.



Since the above described attempts of synthesizing bromodiene **7** via the organomagnesium compound **56** failed, we turned our attention towards the organozinc compound **59** (Scheme 5.2.13). However, the organozinc compound **59** could not be prepared from bromide **55**, thus it was necessary to change the starting bromide **55** to iodide **58**. To prepare **58** analogous reactions to above described preparation of bromide **55** were used. The reduction of aldehyde **45** with $LiAlH_4$ gave alcohol **54** almost quantitatively (99 %) and the following substitution with NIS in the presence of PPh_3 afforded iodide **58** in 86 % yield. Conversion of the iodide **58** to the corresponding organozinc **59** was accomplished using Rieke® zinc in the presence of a Et_2Zn (10 mol %). Finally, the CuCl catalyzed (10 mol %) reaction between **59** and 1,2-dibromopropene, which proceeded via S_N2' substitution mechanism, gave the desired chiral bromodiene **7** in a very nice 93 % yield. The presence of diethyl zinc during the formation of the organozinc compound **59** was necessary in order to ensure smooth metallation. Without Et_2Zn the yield of bromodiene **7** was in 20-60 % range, and the reaction was plagued by formation of **12** and dimer **57**. Furthermore, it is important to note that iodide **58** and bromodiene **7** were obtained as pure *trans* diastereomers despite the fact that starting aldehyde **45** was used as a mixture of *cis* and *trans* diastereomers in 1/8 ratio and the most importantly the bromodiene was obtained in optical purity > 98 % ee (determined by chiral GC), meaning that there was no loss of optical purity during the described transformation.

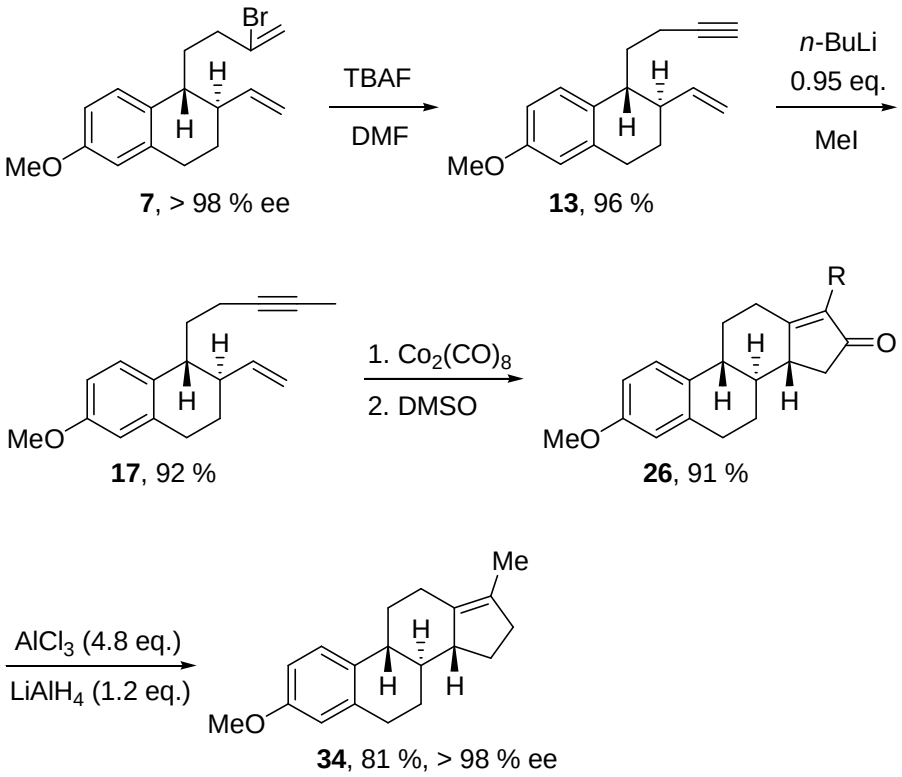
Scheme 5.2.13. Synthesis of chiral bromodiene 7.



With the chiral bromodiene **7** on hand the synthesis was continued with a sequence of reactions developed earlier in the diastereoselective synthesis of the estrone precursor

(Scheme 5.2.14). Dehydrobromination of **7** with TBAF in DMF afforded enyne **13** in 96 % yield, subsequent lithiation of the terminal triple bond with *n*-BuLi followed by methylation of formed acetylide with MeI gave the methylated enyne **17** in 92 % yield. The Pauson-Khand cyclocarbonylation of **17**, which was done by using stoichiometric amount of $Co_2(CO)_8$ yielded 17-methyl-16-ketoestratetraene **26** in 91 %. As expected from the previous results, only the single diastereomer was obtained after the cyclization the desired *trans-anti* **26**. Finally, subjecting **26** to a mixture of $AlCl_3$ (4.8 eq.) and $LiAlH_4$ (1.2 eq.) led to chemoselective reduction of the keto group, thus furnishing 17-methylestratetraene **34** in 81 % isolated yield with ee > 98 %.

Scheme 5.2.14. Synthesis of chiral 17-methylestratetraene **34**.



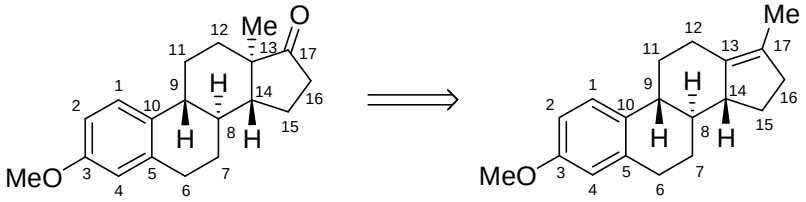
7, > 98 % ee **13**, 96 %

17, 92 % **26**, 91 %

34, 81 %, > 98 % ee

The prepared 17-methylestratetraene is a known precursor of synthesis of estrone. According to Bartlet and Johnson[52] it can be converted to estrone in two steps. The firs step is epoxidation of the double bond and the second one is a Lewis acid mediated rearrangement, which includes the shift of the methyl group from position 17 to 13. (Figure 5.2.3).

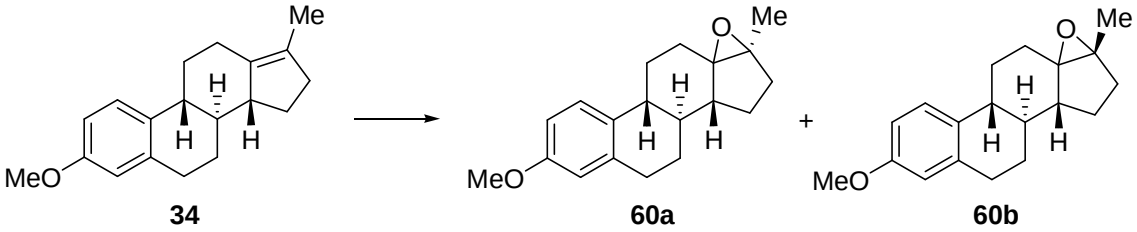
Figure 5.2.3.



(-)-methoxyestrone 17-methylestratetraene

The epoxidation step was first attempted using the procedure suggested by Bartlet and Johnson which relied on conversion of estratetraene **34** to chlorohydrine with *p*-$TsNCl_2$ followed by reaction with Me_4NOH to yield epoxide **60a** (Scheme 5.2.15). The reaction under the described conditions furnished the desired **60a** with 40 % yield (only single diastereomer was obtained). I also tried epoxidation of estratetraene **34** with *m*-CPBA in CH_2Cl_2.[69] In this case the epoxide was formed in 91 % yield, however, both diastereomers, the desired **60a** as well as undesired **60b,** were formed in 3.5/1 ratio. After separation of the diastereomers the pure **60a** was obtained in 71 % isolated yield.

Scheme 5.2.15. Epoxidation of **34**.



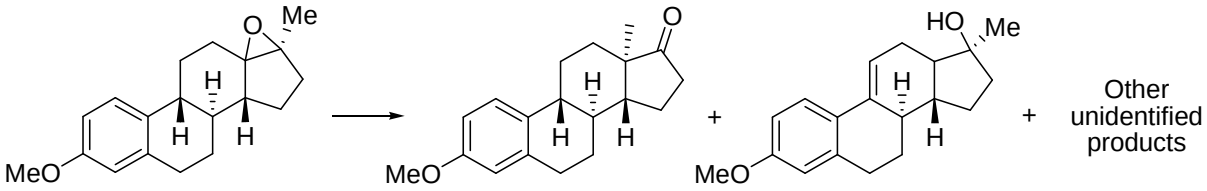
34 **60a** **60b**

1. *p*-$TsNCl_2$, DME/H_2O; 2. Me_4NOH	40 %	
m-CPBA, CH_2Cl_2	71 %	20 %

The final step of the synthesis of methoxyestrone was the Lewis acid mediated rearrangement of the epoxide **60a**. At first I attempted the reaction under Bartlet's and Johnson's conditions. As Lewis acid $BF_3 \cdot Et_2O$ was used in toluene at 20 °C. Surprisingly, in my hands, no methoxyestrone was formed under these conditions. The starting epoxide was converted to a complex mixture of compounds that I was not able to further identify (**63**) (Scheme 5.2.16). When the reaction was carried out at -20 °C, the expected estrone **61** was formed, albeit only in 4 % yield, the major product of the reaction was alcohol **62**, which was

the product of the hydrogen shift from position 8 to 13 (Figure 5.2.3). Switching the solvent from benzene to toluene led to improvement of the yield of methoxyestrone **61**, at -20 °C it was 8 %, at -78 °C the product was obtained in 25 %. In all of the above described cases the major product of the rearrangement was the alcohol **62**. The attempts to improve the yield of methoxyestrone by using different Lewis acids were also made. $Bi(OTf)_3$,[70] $Cu(BF_4)_2$[71] and $IrCl_3$[72] were tested; unfortunately, as can be seen from the table below, in neither case any methoxyestrone was formed. Nevertheless, optical rotation of prepared methoxyestrone was $[\alpha]_D$= -150°, while the value reported for the natural (+)-methoxyestrone is $[\alpha]_D$= +159°.[20] Additionally, absolute configuration was also confirmed by chiral HPLC (the sample of the prepared methoxyestrone was compared to the purchased (+)-methoxyestrone).

Scheme 5.2.16. Rearrangement of epoxide **60a**.

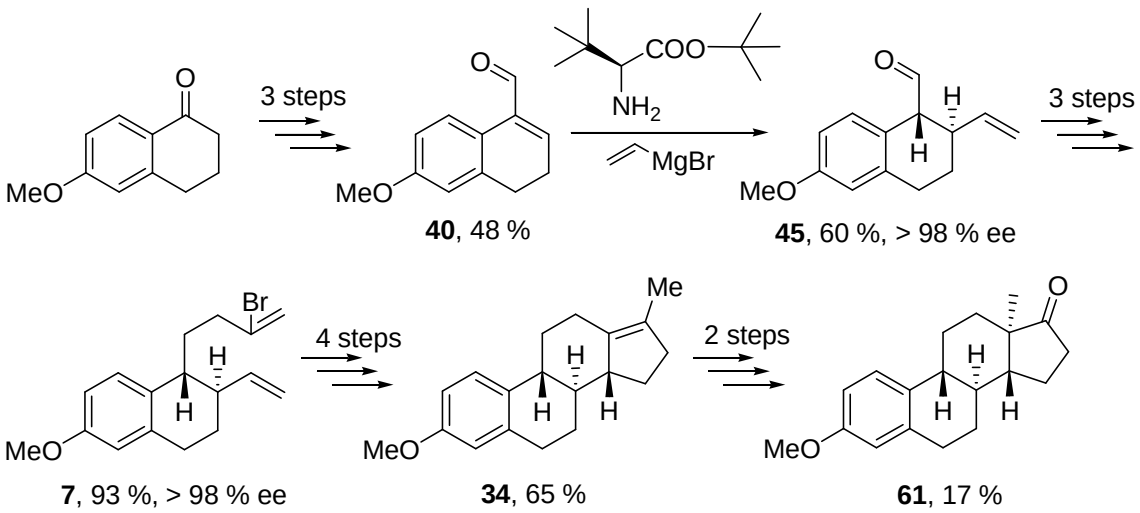


Entry	Lewis Acid	solvent	T (℃)	**61**	**62**	**63**
1	$BF_3{\cdot}Et_2O$ (4. eq)	benzene	20	0 %	0 %	> 95 %
2	$BF_3{\cdot}Et_2O$ (4. eq)	benzene	- 20	4 %	70 %	25 %
3	$BF_3{\cdot}Et_2O$ (4. eq)	toluene	- 20	8 %	60 %	< 20 %
4	$BF_3{\cdot}Et_2O$ (4. eq)	toluene	- 78	25 %	55 %	< 20 %
5	$Bi(OTf)_3$ (1 eq.)	CH_2Cl_2	- 20	0 %	0 %	> 95 %
6	$Cu(BF_4)_2$ (1 eq.)	MeCN	- 20	0 %	0 %	> 95 %
7	$IrCl_3$ (1 eq.)	CH_2Cl_2	- 20	0 %	0 %	> 95 %

The summary of this synthesis is shown in the Scheme 5.2.17. The key step, in which the chirality was introduced, was the stoichiometric conjugated addition of vinylmagnesium bromide to chiral imine formed from aldehyde **40** and (L)-*t*-leucine *t*-butyl ester in 65 % yield. The enantioselectivity of the addition was excellent, exceeding 98 % ee. Another challenge of this synthesis posed by conversion of vinyl aldehyde **45** to chiral bromodiene **7** was solved by conversion of the aldehyde moiety to iodide and subsequent Cu catalyzed reaction with 2,3-dibromoprop-1-en, which proceeded via organozoninc compound. In this

manner I managed to prepare bromodiene **7** from aldehyde **45** in 93 % yield with unchanged optical purity > 98 % ee. The rest of the synthesis was based on previously developed diastereoselective synthesis. The bromodiene **7** was converted to chiral enyne and subsequently, with the use of Pauson-Khand reaction, to 16-keto-17-methylestratetraene, which after reduction furnished estrone precursor **34** in the total yield of 65 %. Finally, epoxidation of the double bond in **34** and Lewis acid catalyzed rearrangement of formed epoxide according to procedure developed by Bartlet and Johnson[52] gave (-)-methoxyestrone in 17 % yield. In conclusion the (-)-methoxyestrone was prepared in 13 steps from the commercially available 6-methoxytetralone with total 3 % yield.

Scheme 5.2.17. Summary of the (-)-methoxyestrone synthesis.



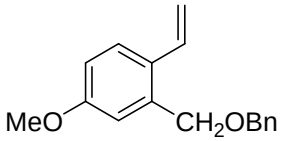
6. Experimental Section

6.1 General Methods

All solvents unless otherwise stated were used as obtained. THF and Et_2O were distilled from $LiAlH_4$, DCM and Et_3N from CaH_2, toluene from sodium benzophenone ketyl. All other reagents were obtained from commercial sources. ^1H and ^{13}C NMR spectra were recorded on a Varian UNITY 400 (^1H at 400 MHz, ^{13}C at 100.6 MHz) and Varian UNITY 300 (^1H at 300 MHz, ^{13}C at 75 MHz as solutions in $CDCl_3$ or C_6D_6 at 25 °C. Chemical shifts are given in δ-scale, coupling constants J are given in Hz. Melting points (uncorrected) were determined using a Kofler apparatus. Mass spectra were recorded on a ZAB-SEQ (VG-Analytical) instrument. Infrared spectra were recorded on a Bruker IFS 55 spectrometer as THF solutions and are reported in wave numbers (cm^{-1}). Fluka 60 silica gel was used for flash chromatography. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets (Merck). All reactions were carried out under an argon atmosphere using flasks. **3** was prepared by the previously reported procedure.[32]

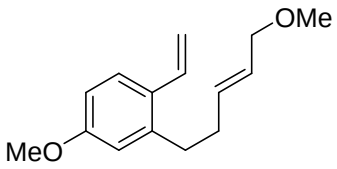
6.2 Diastereoselective Synthesis Synthetic procedures.

1-[(Benzyloxy)methyl]-2-ethenyl-5-methoxybenzene (4). 1-[(Benzyloxy)methyl]-2-bromo-5-methoxybenzene **3** (3 mmol, 0.92 g) was added to stirred solution of $PdCl_2$(dppf) (0.015 mmol, 11 mg), dppf (0.06 mmol, 3 mg) and Et_3N (15 mmol, 1.5 g) in THF (60 mL). To this solution potassium vinyltrifluoroborate (3.6 mmol, 460 mg) was added at 20 °C. The reaction mixture was stirred at 60 °C for 2 h. Then water (150 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 0.76 g (98 %) of the title compound as a colorless viscous liquid. ^{1}H NMR and ^{13}C NMR spectra were in agreement with the previously reported.[32]



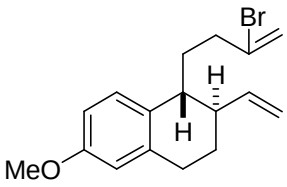
R_f (1/1 hexane/CH_2Cl_2) = 0.6

***E*-1-Ethenyl-2-[(5-methoxy-5-pent-2-enyl)]-4-methoxybenzene (6).** *n*-BuLi (1.6 M solution in hexane, 12.6 mmol, 8 mL) was added to a stirred solution of Cp_2ZrCl_2 (6.3 mmol, 1.84 g) in THF (30 mL) at –78 °C. After 1 h **4** (6 mmol, 0.76 g) was added as a solution in THF (10 mL), the reaction mixture was warmed gradually to 20 °C and stirred for 3 h. To this solution was added 3,4-dichlorobut-1-ene (9 mmol, 1.1 g) and CuCl (0.6 mmol, 60 mg). The reaction mixture was stirred for 4 h. Then hexane (50 mL) was added, which caused formation of precipitate. The solution was filtered through Celite. The volatiles from the filtrate were partially removed under reduced pressure and to the residue the fresh hexane (50 mL) was added, which caused formation of additional precipitate. The filtration through Celite and removal of volatiles under reduced pressure afforded chlorodiene **5** as a yellow oil. The chlorodiene **5** was dissolved in DMF (30 mL) and to this solution sodium methoxide (12.3 mmol, 660 mg) was added. The reaction mixture was stirred at 20 °C for 12 h. Then the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (3×20 mL), and dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 0.38 g (55 %) of the title compound as a colorless viscous liquid. ^{1}H NMR and ^{13}C NMR spectra were in agreement with the previously reported.[32]



R_f (1/1 hexane/CH_2Cl_2) = 0.5.

***anti*-1-[(3-Bromo-but-3-en-1-yl)]-2-ethenyl-6-methoxy-1,2,3,4-tetrahydronaphtalene (7).**



n-BuLi (3.4 mmol, 2.13 mL of 1.6M solution in hexanes) was added to a stirred solution of Cp_2ZrCl_2 (1.7 mmol, 498 mg) in THF (15 mL) at -78 °C. After 1 h methoxydiene **6** (1.63 mmol, 377 mg) in THF (1 mL) was added and the reaction mixture was warmed gradually to 20 °C within 2 h. To this solution 2,3-dibromoprop-1-en (2.44 mmol, 490 mg) and CuCl (0.16 mmol, 16 mg) were added and the reaction mixture was stirred for 2 h. Then solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (5 mL) and hexanes (20 mL) and filtered through Celite. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexanes/CH_2Cl_2) afforded 308 mg (75 %) of the title compound as a colorless viscous liquid. ^{1}H NMR and ^{13}C NMR spectra were in agreement with the previously reported.[32]

R_f (1/1 hexane/CH_2Cl_2) = 0.6.

Magnesio-metallo-ene reaction.

Chlorodiene **5** (0.5 mmol, 118 mg) was added to a suspension of Rieke Mg (0.6 mmol, 15 mg) in THF (3 mL) in a pressure tube. The reaction mixture was heated while stirring to 60 °C for 24 h. Then HCl (1 %, 20 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 88 mg (88 %) of the mixture of products as a colorless liquid. According to ^{1}H NMR the mixture was composed of *cis*- and *trans*-**10** (35 %), **11** (35 %), and a mixture *cis*- and *trans*-**12** (18 and 12 %).

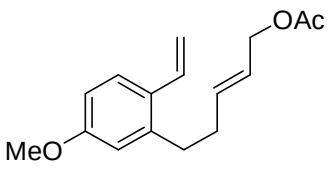
Characteristic signals of *cis*- and *trans*- **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ1.65-1.72 (m, 3H), 5.45-5.52 (m, 2H).

Characteristic signals of **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ5.79-5.92 (ddt, J = 17.2, 10.4, 7.1 Hz, 1H)

Characteristic signals of *trans*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ1.30 (d, J = 6.8 Hz, 3H),

Characteristic signals of *cis*-**12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ1.15 (d, J = 6.4 Hz, 3H).

5-(Ethynyl-5-methoxyfen-1-yl)pent-2-en-1-yl acetate (9). To a suspension of anhydrous AcOK (6 mmol, 588 mg) in DMSO (20 mL) chlorodiene **5** (3 mmol, 708 mg) was added at 20 °C. The reaction mixture was



heated to 120 °C and stirred for 15 min at this temperature. Then water (200 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 640 mg (82 %) of the title compound as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H, OOCC*H*$_3$), 2.29-2.36 (m, 2H, C*H*$_2$), 2.70-2.77 (m, 2H, C*H*$_2$), 3.80 (s, 3H, OC*H*$_3$), 4.50-4.53 (m, 2H, C*H*$_2$O), 5.16-5.21 (m, 1H, CH=C*H*$_2$), 5.52-5.57 (m, 1H, CH=C*H*$_2$), 5.56-5.65 (m, 1H, CH=C*H*), 5.78-5.86 (m, 1H, C*H*=CH), 6.66-6.68 (m, 1H, Ar-H), 6.73-6.76 (m, 1H, Ar-H), 6.84-6.91 (m, 1H, C*H*=CH$_2$), 7.42-7.45 (m, 1H, Ar-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.96 (CH_3), 32.83 (CH_2), 33.43 (CH_2), 55.16 (OCH_3), 65.04 (OCH_2), 111.83 (CH, Ar), 113.57 (CH=*C*H$_2$), 114.71 (CH, Ar), 124.44 (CH=CH), 126.92 (CH, Ar), 129.14 (C, Ar), 133.77 (*C*H=CH$_2$), 135.19 (CH=CH), 140.33 (C, Ar), 159.18 (C, Ar), 170.79 (COO);

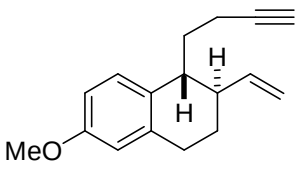
R_f (CH_2Cl_2) = 0.7.

Pd-catalyzed metallo-ene reaction.

Conditions A. Neat Et_2Zn (5 mmol, 615 mg) was added to the solution of acetyldiene **9** (0.5 mmol, 130 mg), $Pd(OAc)_2$ (0.05 mmol, 11 mg) and PBu_3 (0.05 mmol, 10mg) in Et_2O (5 mL) in a pressure tube. The reaction mixture was stirred at 40 ° for 12 h. It was then carefully quenched with HCl (1 %, 30 mL), extracted with Et_2O (3 × 10 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 92 mg (91 %) of the mixture of products as a colorless liquid. According to ^{1}H NMR the mixture was composed of *cis*- and *trans*-**10** (42 %), **11** (43 %), and a *cis*-**12** (15 %).

Conditions B. Et_2Zn (1.5 mmol, 1M in toluene 1.5 mL) was added to the solution of acetyldiene **20** (0.5 mmol, 130 mg) and $Pd(PPh_3)_4$ (0.01 mmol, 11 mg) in toluene (10 mL). The reaction mixture was stirred at 40 ° for 12 h. It was then quenched with HCl (1 %, 30 mL), extracted with Et_2O (3 × 10 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 95 mg (95 %) of the mixture of products as a colorless liquid. According to ^{1}H NMR the mixture was composed of *cis*- and *trans*-**10** (53 %) and **11** (47 %).

***anti*-1-[(But-3-yn-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydronaphtalene (13).** Tetrabutyl-

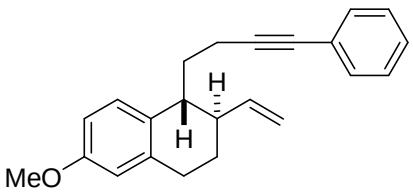


ammonium fluoride (15.5 mmol, 4.9 g) was added to stirred solution of *anti*-1-[(3-bromobut-3-en-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydrona-phtalene **7** (3.1 mmol, 1 g) in DMF (20 mL) and the reaction mixture was stirred at 60 °C for 2 h. Then DMF was removed under reduced pressure and water (150 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 0.7 g (94 %) of the title compound as a colorless viscous liquid. ^{1}H NMR and ^{13}C NMR spectra were in agreement with the previously reported data.[32]

General method for the Sonogashira reaction of 13 with arylhalides.

To a stirred solution of **13** (1 mmol, 239 mg), $Pd(PPh_3)_4$ (0.01 mmol, 11 mg) and CuI (0.02 mmol, 5 mg) in THF (6 mL) and Et_3N (2 mL) the corresponding substituted phenyl iodide (1.1 mmol) was added. The reaction was stirred for 10 h, then it was filtrated through a short pad of Celite, and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel afforded the desired products.

***anti*-1-[(4-Phenylbut-3-yn-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydronaphtalene (14).**



Iodobenzene (1.1 mmol, 224 mg) was used. Column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 249 mg (79 %) of the title compound as a colorless viscous liquid:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.7 (m, 1H, C*H*$_2$), 1.94-2.04 (m, 3H, C*H*$_2$ + C*H*), 2.38-2.52 (m, 3H, C*H*$_2$ + C*H*), 2.70-2.78 (m, 2H, C*H*$_2$), 2.82-2.90 (m, 1H, C*H*$_2$), 3.77 (s, 3H, OC*H*$_3$), 4.98-5.02 (m, 1H, CH=C*H*$_2$), 5.06-5.14 (m, 1H, CH=C*H*$_2$), 5.83 (ddd, *J* = 17.6, 10.4, 7.4 Hz, 1H, C*H*=CH$_2$), 6.58-6.62 (m, 1H, Ar-*H*), 6.70-6.75 (m, 1H, Ar-*H*), 7.10-7.16 (m, 1H, Ar-*H*), 7.23-7.29 (m, 3H, Ar-*H*), 7.36-7.40 (m, 2H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.80 (CH_2), 25.72 (CH_2), 27.13 (CH_2), 35.03 (CH_2), 40.99(CH), 41.22 (CH), 55.14 (OCH_3), 80.99 (C≡C), 90.23 (C≡C), 112.15 (CH, Ar), 113.35 (CH, Ar), 114.36 (C=C), 123.99 (C, Ar), 127.51 (CH, Ar), 128.18 (2×CH, Ar), 130.04 (CH, Ar), 130.88 (C, Ar), 131.53 (2×CH, Ar), 137.98 (C, Ar), 142.09 (C=C), 157.45 (COMe, Ar);

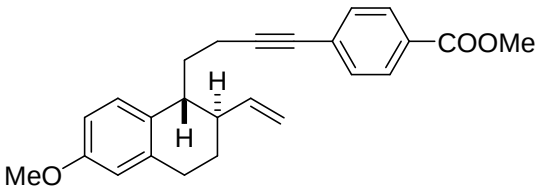
IR (KBr) ν 2955, 2886, 1720, 1442, 1342, 1183, 1060, 1036, 987, 923, 857;

MS-EI (m/z) 316 (85 %) (M^+), 262 (40 %), 187 (100 %), 171 (20 %), 158 (25 %), 146 (30 %), 128 (25 %), 115 (65 %), 83 (45 %);

HRMS (EI+) calcd. for $C_{20}H_{28}OSi$ 316.1827, found 316.1832.

R_f (1/1 hexane/CH_2Cl_2) = 0.6.

***anti*-1-{[4-(4-Methoxycarbonylphenyl)but-3-yn-1-yl]-2-vinyl-6-methoxy}-1,2,3,4-tetrahydronaphtalene (15).**



4-Iodomethoxybenzoate (1.1 mmol, 288 mg) was used. Column chromatography on silica gel (CH_2Cl_2) afforded 298 mg (80 %) of the title compound as a colorless viscous liquid:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61-1.72 (m, 1H, CH2), 1.96-2.08 (m, 3H, C*H* + C*H*2), 2.34-2.54 (m, 3H, C*H* + CH_2), 2.70-2.78 (m, 2H, CH_2), 2.82-2.88 (m, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.91 (s, 3H, COOCH_3), 4.98-5.04 (m, 1H, CH=CH_2), 5.06-5.14 (m, 1H, CH=CH_2), 5.83 (ddd, *J* = 17.5, 10, 7.3 Hz, 1H, C*H*=CH_2), 6.58-6.62 (m, 1H, Ar-*H*), 6.70-6.76 (m, 1H, Ar-*H*), 7.10-7.16 (m, 1H, Ar-*H*), 7.40-7.46 (m, 2H, 2×Ar-*H*), 7.92-7.98 (m, 2H, 2×Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 16.80 (CH_2), 25.85 (CH_2), 27.21 (CH_2), 34.68 (CH_2), 41.01 (CH), 41.31 (CH), 52.12 (COO*C*H_3), 55.13 (OCH_3), 80.50 (C≡C), 93.76 (C≡C), 112.17 (CH, Ar), 113.38 (CH, Ar), 114.41 (C=C), 128.80 (C, Ar), 128.86 (C, Ar), 129.38 (2×CH, Ar), 129.92 (CH, Ar), 130.64 (C, Ar), 131.44 (2×CH, Ar), 138.03 (C, Ar), 142.03 (C=C), 157.49 (COMe, Ar), 166.63 (COOMe);

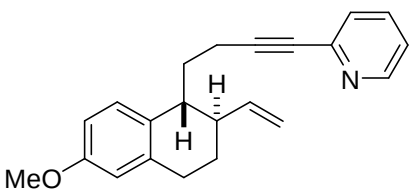
IR (KBr) ν 2956, 2887, 2170, 1757, 1720, 1441, 1247, 1182, 1061, 1035, 987, 923, 844;

MS-EI (m/z) 374.2 (100 %) (M^+), 345 (40 %), 320 (85 %), 261 (50 %), 187 (100 %), 158 (50 %), 146 (30 %), 128 (20 %), 115 (25 %), 91 (15 %);

HRMS (EI+) HRMS calcd. for $C_{25}H_{26}O_3$ 374.1882, found 374.1878.

R_f (1/1 hexane/CH_2Cl_2) = 0.65.

***anti*-1-[(4-(3-Pyridyl)but-3-yn-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydronaphtalene (16).** 3- Iodopyridine (1.1 mmol, 225 mg) was used. Column chromatography on silica gel (20/1 CH_2Cl_2/Et_2O) afforded 215 mg (68 %) of the title compound as a colorless viscous liquid:



^{1}H NMR (400 MHz, C_6D_6) δ 1.40-1.52 (m, 1H, C*H*$_2$), 1.70-1.80 (m, 1H, C*H*), 1.85-1.93 (m, 2H, C*H*$_2$), 2.21-2.32 (m, 3H, C*H* + C*H*$_2$), 2.46-2.64 (m, 2H, C*H*$_2$), 2.72-2.79 (m, 1H, C*H*$_2$), 3.38 (s, 3H, OC*H*$_3$), 4.92-4.98 (m, 1H, CH=C*H*$_2$), 5.00-5.06 (m, 1H, CH=C*H*$_2$), 5.72 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H, C*H*=CH$_2$), 6.52-6.58 (m, 1H, pyr-*H*), 6.60-6.62 (m, 1H, Ar-*H*), 6.70-6.75 (m, 1H, Ar-*H*), 7.00-7.04 (m, 1H, Ar-*H*), 7.35-7.40 (m, 1H, pyr-*H*), 8.32-8.38 (m, 1H, pyr-*H*), 8.95 (bs, 1H, pyr-*H*);

^{13}C NMR (100 MHz, C_6D_6) δ 17.84 (CH_2), 27.19 (CH_2), 28.42(CH_2), 35.90(CH_2), 42.32 (CH), 42.71 (CH), 55.66 (OCH_3), 79.5 (C≡C), 94.97 (C≡C), 113.63 (CH, Ar), 114.89 (CH, Ar), 115.37 (C=C), 123.81 (CH, pyr), 122.21 (C, pyr), 131.12 (CH, Ar), 131.56 (C, Ar), 138.89 (C, Ar), 139.02 (CH, pyr), 143.27 (C=C), 149.41 (CH, pyr), 153.85 (CH, pyr), 159.25 (C, Ar);

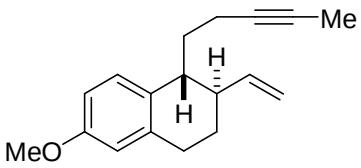
IR (KBr) *ν* 3352, 2951, 2886, 2224, 1769, 1721, 1607, 1440, 1343, 1183, 1061, 1035, 989, 924, 858, 706;

MS-EI (m/z) 317.1 (100 %) (M^+), 263.1 (45 %), 187.1 (90 %), 158 (30 %), 146 (40 %), 128 (25 %), 115 (45 %), 103 (25 %), 91 (30 %), 77 (25 %);

HRMS (EI+) HRMS calcd. for $C_{22}H_{23}NO$ 317.1780, found 317.1783.

R_f (20/1 CH_2Cl_2/Et_2O) = 0.25.

***anti*-1-[(Pent-3-yn-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydronaphtalene (17).**



Alkylation of 13 with MeI. *n*-BuLi (1.13 mmol, 0.7 mL of 1.6M solution in hexanes) was added to a stirred solution of **13** (1 mmol, 240 mg) in THF (5 mL) at -78 °C. The reaction mixture was warmed gradually to -30 °C and stirred for 1 h at this temperature, than it was cooled again to -78 °C followed by the addition of MeI (dried with anhydrous $MgSO_4$ prior to use)(1.5 mmol, 213 mg). Mixture was warmed to 20 °C and stirred for 5 h. Then water (100 mL) and HCl (10 %, 5 mL) were added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure, the residue was dissolved in toluene (5 mL), and the solvent was evaporated under reduced pressure (repeated 2×) to remove residual MeI. Column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 230 mg (91 %) of the title compound as a colorless viscous liquid.

Alkylation of 6 with 3-bromobuta-1,2-diene (21). *n*-BuLi (3.4 mmol, 2.13 mL of 1.6M solution in hexanes) was added to a stirred solution of Cp_2ZrCl_2 (1.7 mmol, 498 mg) in THF

(15 mL) at -78 °C. After 1 h methoxydiene **6** (1.63 mmol, 377 mg) in THF (1 mL) was added and the reaction mixture was warmed gradually to 20 °C within 2 h. To this solution 3-bromobuta-1,2-diene **21** (2.44 mmol, 325 mg) and CuCl (0.16 mmol, 16 mg) were added and the reaction mixture was stirred for 2 h. Then solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (5 mL) and hexanes (20 mL) and filtered through celite. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexanes/CH_2Cl_2) afforded 358 mg (87 %) of the title compound as a colorless viscous liquid:

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61-1.7 (d, *J* = 6 Hz, 1H, C*H*$_2$), 1.79 (t, *J* = 2.4 Hz, 3 H, C≡C-C*H*$_3$), 1.8-1.9 (m, 2H, C*H*$_2$), 1.91-2.00 (m, 1H, C*H*), 2.08-2.16 (m, 2H, C*H*$_2$), 2.38-2.46 (m, 1H, C*H*), 2.66-2.80 (m, 3H, 2×C*H*$_2$), 3.77 (s, 3H, OC*H*$_3$), 4.96-5.02 (m, 1H, CH=C*H*$_2$), 5.04-5.10 (m, 1H, CH=C*H*$_2$), 5.82 (ddd, *J* = 17.4, 10.4, 7.6 Hz, 1H, C*H*=CH2), 5.98-6.02 (m, 1H, Ar-*H*), 6.10-6.14 (m, 1H, Ar-*H*), 7.08-7.12 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 3.49 (CH_3), 16.03 (CH_2), 25.67 (CH_2), 27.08 (CH_2), 35.38 (CH_2), 40.88 (CH), 41.20 (CH), 55.11 (OCH_3), 75.78 (C≡C), 79.17 (C≡C), 112.07 (CH, Ar), 113.26 (CH, Ar), 114.21 (C=C), 130.01 (CH, Ar), 130.99 (C, Ar), 137.89 (C, Ar), 142.15 (C=*C*), 157.39 (COMe, Ar) ;

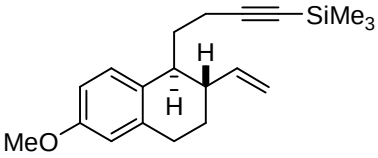
IR (KBr) *ν* 2953, 2885, 1721, 1442, 1183, 1062, 1035, 988, 923;

MS-EI (*m/z*) 254.2 (35 %) (M^+), 225 (40 %), 200 (50 %), 187.1 (100 %), 185.1 (55 %), 159.1 (25 %), 115 (25 %);

HRMS (EI+) calcd. for $C_{18}H_{22}O$ 254.1671, found 254.1677.

R_f (1/1 hexanes/CH_2Cl_2) = 0.65.

***anti*-1-[(4-Trimethylsilylbut-3-yn-1-yl)-2-vinyl-6-methoxy]-1,2,3,4-tetrahydronaphtalene (18).** *n*-BuLi (1.65 mmol, 1.03 ml of 1.6M solution in hexanes) was added to a stirred solution of **13** (1.5 mmol, 359 mg) in Et_2O (10 mL) at -78 °C. After 1 h TMSCl (3 mmol, 327 mg) was added and the reaction mixture was allowed to warm gradually to 20 °C and kept for 3 h at this temperature. Then volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 401 mg (86 %) of the title compound as a colorless viscous liquid:



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H, -Si(C*H*$_3$)$_3$), 1.60-1.70 (m, 1H, C*H*$_2$), 1.84-2.00 (m, 3H, C*H*$_2$ + C*H*), 2.18-2.26 (m, 2H, C*H*$_2$), 2.4-2.5 (m, 1H, C*H*), 2.68-2.82 (m, 3 H, 2×C*H*$_2$),

3.76 (s, 3H, OCH_3), 4.96-5.01 (m, 1H, CH=CH_2), 5.03-5.10 (m, 1H, CH=CH_2), 5.81 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H, C*H*=CH_2), 6.57-6.6 (m, 1H. Ar-*H*), 6.68-6.74 (m, 1H, Ar-*H*), 7.06-7.10 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 0.14 (Si(CH3)3), 17.35 (CH_2), 25.55 (CH_2), 27.02 (CH_2), 35.09 (CH_2), 40.92 (CH), 40.96 (CH), 55.12 (OCH3), 84.84 (C≡C), 107.51 (C≡C), 112.12 (CH, Ar), 113.30 (CH,Ar), 114.27 (C=C), 130.021 (CH, Ar), 130.92 (C, Ar), 137.91 (C, Ar), 142.02 (C=C), 157.43 (C, Ar);

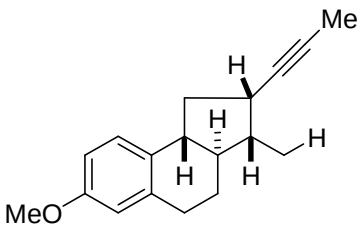
IR (KBr) ν 2954, 2886, 1720, 1439, 1275, 1180, 1061, 1035, 988, 857;

MS-EI (m/z) 312 (50 %) (M^+), 297 (30 %), 200 (65 %), 187 (100 %), 73 (55 %);

HRMS (EI+) calcd. for $C_{20}H_{28}OSi$ 312.1909, found 312.1917.

R_f (1/1 hexane/CH_2Cl_2) = 0.7.

***trans-anti-cis*-2-(Prop-1-yn-1-yl)-7-methoxy-3-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopen-ta[a]naftalene (19)** *n*-BuLi (1.1 mmol, 0.68 mL of 1.6M solution in hexanes) was added to a stirred solution of **13** (1 mmol, 239 mg) in THF (3 mL) at -78 °C. The reaction mixture was warmed gradually to 20 °C and stirred for 1 h at this temperature, then it was cooled again to -78 °C followed by the addition of MeI (dried with anhydrous $MgSO_4$ prior to use) (1.5 mmol, 213 mg). After that it was warmed to 20 °C and stirred for 5 h. It was quenched with water (100 mL) and HCl (10 %, 5 mL), extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure, the residue was dissolved in toluene (5 mL), and the solvent was evaporated under reduced pressure (repeated 2×) to remove residual MeI. Column chromatography of the residue on silica gel (1/1 hexane/CH_2Cl_2) afforded 200 mg (79 %) of the title compound as a colorless viscous liquid:



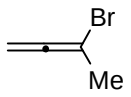
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09-1.14 (d, *J* = 7 Hz, 3H, CH_3), 1.25-1.35 (m, 1H, C*H*), 1.40-1.48 (m, 1H, CH_2), 1.60-1.75 (m, 2H, C*H* + CH_2), 1.79-1.81 (m, 3H, C≡C-CH_3), 2.04-2.09 (m, 1H, CH_2), 2.37-2.45 (m, 1H, C*H*), 2.65-2.73 (m, 1H, CH_2), 2.89-2.96 (m, 2H, CH_2), 3.03-3.12 (m, 1H, C*H*-C≡C), 3.79 (s, 3H, OCH_3), 6.66-6.68 (m, 1H, Ar-*H*), 6.68-6.70 (m, 1H, Ar-*H*) 6.96-7.0 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 3.52 (C≡C-*C*H3), 15.22 (CH_3), 26.56 (CH_2), 30.22 (CH_2), 33.44 (*C*H-C≡C), 37.71 (CH_2), 41.06 (CH), 45.30 (CH), 49.72 (CH), 55.22 (OCH_3), 77.67

(C≡C), 81.71 (C≡C), 111.15 (CH, Ar), 113.67 (CH, Ar), 126.60 (CH, Ar), 133.27 (C, Ar), 137.89 (C, Ar), 157.63 (C, Ar);

R_f (1/1 CH_2Cl_2/hexane) = 0.4.

3-Bromobuta-1,2-diene (21). A solution of Br_2 (15.5 mmol, 2.5 g) in chloroethane (10 ml) was dropwise added to stirred solution of 1-trimethylsilylbut-2-yne (16.2 mmol, 2 g)[39] in chloroethane (30 ml) at -78 °C. Reaction was stirred for 1h at -78 °C. Then silica gel (2 g) was added at -78 °C and the suspension was filtrated through silica gel (5 g). Chloroethane was allowed to evaporate at room temperature and the residue was further purified by distillation under reduced pressure to afford product 0.5 g (24 %) as a colorless liquid:



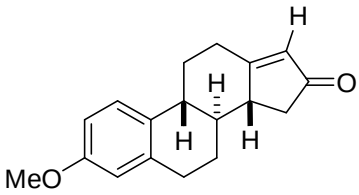
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (t, J = 3.3 Hz, 3H, C*H*$_3$), 4.79 (q, J = 3.3 Hz, 2H, C=C*H*$_2$);

^{13}C NMR (75 MHz, $CDCl_3$) δ 37.94 (CH_3), 80.54 (=CH_2), 87.42(=CBrMe), 204.53(=C=).

General method for the Pauson-Khand reaction.

To a solution of enynes **13-18** (1 mmol) in toluene (5 mL) $Co_2(CO)_8$ (1.3 mmol, 445 mg) was added and the reaction mixture was stirred at 20 °C for 4 h. Then DMSO (5 mmol, 354 μL, 390 mg) was added and the reaction mixture was stirred at 80 °C for 5h. It was quenched with HCl (1 %, 100 mL), extracted with CH_2Cl_2 (3 × 15 mL), combined organic fractions were dried over anhydrous $MgSO_4$, and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel afforded desired products.

(±)-3-Methoxy-16-ketoestra-1,3,5(10),13(17)-tetraene (22).



Enyne **13** (1 mmol, 239 mg) was used. Column chromatography of the residue on silica gel (50/1 CH_2Cl_2/MeOH) followed by recrystalization (MeOH) afforded 254 mg (95 %) of the title compound as a colorless crystals.

m.p. 114-115 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.30 (m, 1H, C*H*), 1.36-1.48 (m, 1H, C*H*$_2$), 1.52-1.66 (m, 1H, C*H*$_2$), 1.96-2.04 (m, 1H, C*H*$_2$), 2.12-2.22 (m, 1H, C*H*$_2$), 2.44-2.74 (m, 5H, 2×C*H* + 2×C*H*$_2$), 2.82-2.90 (m, 2H, C*H*$_2$), 2.98-3.04 (m, 1H, C*H*$_2$), 3.78 (s, 3H, OC*H*$_3$), 5.89 (s, 1H, C=C*H*), 6.61-6.65 (m, 1H, Ar-*H*), 6.71-6.77 (m, 1H, Ar-*H*), 7.19-7.25 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 28.47 (CH_2), 30.11 (CH_2), 30.63 (CH_2), 31.58 (CH_2), 40.65

(CH_2), 41.75 (CH), 47.16 (CH), 48.06 (CH), 55.19 (OCH_3), 112.04 (CH, Ar), 113.72 (CH, Ar), 126.91 (CH, Ar), 127.04 (C=C), 130.50 (C, Ar), 137.86 (C, Ar), 157.72 (C, Ar), 183.15 (C=C), 208.81 (C=O);

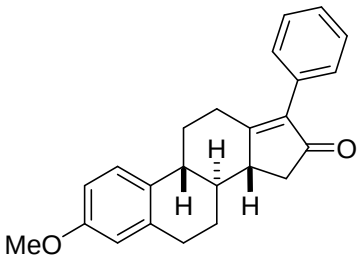
IR (KBr) ν 3014, 2952, 2933, 2865, 2854, 2836, 1699,1674, 1616, 1498, 1449, 1434, 1278, 1256, 1198, 1145, 1045, 1027, 863, 845;

MS-EI (m/z) 268 (100 %) (M^+), 239 (10 %), 211 (10 %), 173 (35 %), 159 (15 %), 147 (30 %), 115 (20 %), 91 (15 %);

HRMS (EI+) calcd. for $C_{18}H_{20}O_2$ 268.1463, found 268.1459.

R_f (50/1 CH_2Cl_2/MeOH) = 0.3.

(±)-3-Methoxy-17-phenyl-16-ketoestra-1,3,5(10),13(17)-tetraene (23). Enyne **14** (1 mmol, 315 mg) was used. Column chromatography of the residue on silica gel (100/1 CH_2Cl_2/MeOH) followed by recrystalization (MeOH) afforded 315 mg (92 %) of the title compound as a colorless solid:



m.p. 178-181 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.50 (m, 2H, C*H* + CH_2), 1.55-1.72 (m, 1H, CH_2), 2.01-2.10 (m, 1H, CH_2), 2.25-2.35 (m, 1H, CH_2), 2.46-2.57 (m, 1H, C*H*), 2.62-2.95 (m, 6H, 3×CH_2 + C*H*), 3.18-3.27 (m, 1H, CH_2), 3.79 (s, 3H, OCH_3), 6.63-6.67 (m, 1H, Ar-*H*), 6.71-6.77 (m, 1H, Ar-*H*), 7.19-7.24 (m, 1H, Ar-*H*), 7.27-7.37 (m, 3H, 3×Ph-*H*), 7.38-7.46 (m, 2H, 2×Ph-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 28.55 (CH_2), 28.94 (CH_2), 30.09 (CH_2), 31.50 (CH_2), 40.14 (CH_2), 41.95 (CH), 45.60 (CH), 48.08 (CH), 55.16 (OCH_3), 112.00 (CH, Ar), 113.70 (CH, Ar), 126.84 (CH, Ar), 127.67 (CH, Ph), 128.28 (2×CH, Ph), 129.23 (2×CH, Ph), 130.61 (C, Ar), 131.32 (C=C), 137.87 (C, Ar), 157.70 (C, Ar), 176.03 (C=C), 206.42 (C=O);

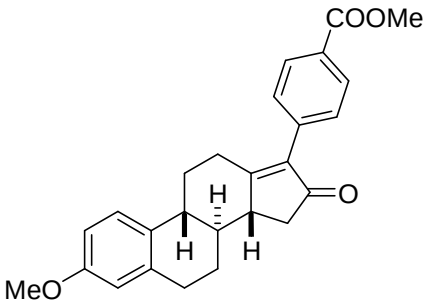
IR (KBr) ν 3054, 2925, 2856, 2836, 1696, 1608, 1499, 1443, 1366, 1234, 1137, 1043, 698;

MS-EI (m/z) 344.1 (100 %) (M^+), 173 (60 %), 147 (80 %), 128 (30 %), 115 (50 %), 91 (25 %), 69 (40 %), 57 (50 %), 43 (55 %);

HRMS (EI+) calcd. For $C_{24}H_{24}O_2$ 344.1776, found 344.1780.

R_f (100/1 CH_2Cl_2/MeOH) = 0.5.

(±)-3-Methoxy-17-(4-methoxycarbonylphenyl)-16-ketoestra-1,3,5(10),13(17)-tetraene



(24). Enyne **15** (1 mmol, 373 mg) was used. Column chromatography of the residue on silica gel (100/1 CH_2Cl_2/MeOH) followed by recrystalization (MeOH) afforded 336 mg (84 %) of the title compound as a colorless solid:

m.p. 182-185 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.50 (m, 2H, C*H* + CH_2), 1.60-1.72 (m, 1H, CH_2), 2.02-2.10 (m, 1H, CH_2), 2.28-2.36 (m, 1H, CH_2), 2.48-2.61 (m, 1H, C*H*), 2.64-2.84 (m, 4H, C*H* + 2×CH_2), 2.84-2.92 (m, 2H, CH_2), 3.15-3.22 (m, 1H, CH_2), 3.78 (s, 3H, OCH_3), 3.93 (s, 3H, COOCH_3), 6.62-6.66 (m, 1H, Ar-*H*), 6.71-6.77 (m, 1H, Ar-*H*), 7.18-7.24 (m, 1H, Ar-*H*), 7.36-7.42 (m, 2H, 2×Ar-*H*), 8.04-8.12 (m, 2H, 2× Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 28.58 (CH_2), 29.05 (CH_2), 30.08 (CH_2), 31.52 (CH_2), 40.15 (CH_2), 41.94 (CH), 45.81 (CH), 48.15 (CH), 52.12 (COO*C*H$_3$), 55.19 (OCH_3), 112.05 (CH, Ar), 113.74 (CH, Ar), 126.84 (CH, Ar), 129.27 (2×CH, Ar), 129.54 (2×CH, Ar), 130.42 (C, Ar), 136.11 (C, Ar), 136.63 (C=C), 137.82 (C, Ar), 157.76 (C, Ar), 166.86 (COO), 177.33 (C=C), 205.77 (C=O);

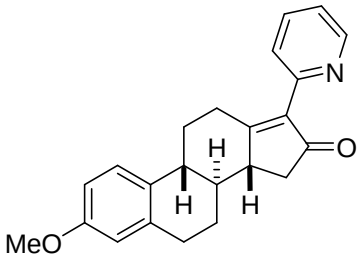
IR (KBr) ν 3001, 2930, 2857, 1719, 1695, 1607, 1497, 1433, 1285, 1108, 1031, 927, 776, 706;

MS-EI (m/z) 402 (45 %) (M^+), 344 (5 %), 256 (5 %), 173 (30 %), 147 (35 %), 97 (40 %), 83 (45 %), 69 (65 %), 55 (90 %), 43 (100 %);

HRMS (EI+) calcd. for $C_{26}H_{26}O_4$ 402.1831, found 402.1838.

R_f (100/1 CH_2Cl_2/MeOH) = 0.3.

(±)-3-Methoxy-17-(3-pyridyl)-16toestra-1,3,5(10),13(17)-tetraene (25). Enyne **16** (1 mmol, 316 mg) was used. Column chromatography of the residue on silica gel (50/1 CH_2Cl_2/MeOH) followed by recrystalization (MeOH/petrolether) afforded 302 mg (88 %) of the title compound as a colorless solid:



m.p. 48-51 °C;

^{1}H NMR (400 MHz, C_6D_6) δ 0.61-0.72 (m, 1H, C*H*), 0.87-0.99 (m, 1H, CH_2), 1.05-1.17 (m, 1H, CH_2), 1.42-1.50 (m, 1H, CH_2), 1.77-1.90 (m, 3H, 2×CH_2+C*H*), 2.10-2.20 (m, 2H,

C*H*+C*H*$_2$), 2.27-2.37 (m, 1H, C*H*$_2$), 2.52-2.59 (m, 2H, C*H*$_2$), 2.75-2.84 (m, 1H, C*H*$_2$), 3.41 (s, 3H, OC*H*$_3$), 6.64-6.68 (m, 1H, Ar-*H*), 6.76-6.80 (m, 1H, Ar-*H*), 6.88-6.98 (bs, 1H, pyr-*H*), 6.98-7.03 (m, 1H, Ar-*H*), 7.72-7.79 (m, 1H, pyr-*H*), 8.50-9.00 (bd, 2H, 2×pyr-*H*);

^{13}C NMR (100 MHz, C_6D_6) δ 29.29 (CH_2), 29.47 (CH_2), 30.87 (CH_2), 32.11 (CH_2), 40.62 (CH_2), 42.57 (CH), 46.18 (CH), 48.31 (CH), 55.46 (OCH_3), 113.00 (CH, Ar), 114.76 (CH, Ar), 127.75 (CH, Ar), 131.51 (C, Ar), 134.79 (C=C), 137.26 (CH, pyr), 138.56 (C, Ar), 159.15 (C, Ar), 176.39 (C=C), 204.81 (C=O);

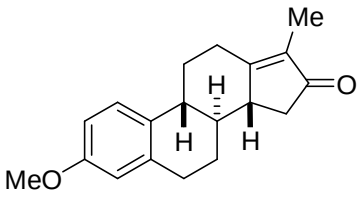
IR (KBr) ν 3031, 2951, 2921, 2858, 1702, 1692, 1608, 1501, 1414, 1252, 1237, 1141, 1043, 927, 808, 713;

MS-EI (m/z) 345 (100 %) (M^+), 316 (10 %), 175 (45 %), 159 (10 %), 147 (35 %), 115 (5 %);

HRMS (EI+) calcd. for $C_{23}H_{23}O_2N$ 345.1729, found 345.1729.

R_f (50/1 CH_2Cl_2/MeOH) = 0.4.

(±)-3-Methoxy-17-methyl-16-ketoestra-1,3,5(10),13(17)-tetraene (26). Enyne **17** (1 mmol, 253 mg) was used. Column chromatography of the residue on silica gel (100/1 CH_2Cl_2/MeOH) followed by recrystalization (MeOH) afforded 247 mg (88 %) of the title compound as a colorless solid:



m.p. >220 °C decomposition;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.20 (m, 1H, CH), 1.30-1.42 (m, 1 H, C*H*$_2$), 1.50-1.64 (m, 1 H, C*H*$_2$), 1.72 (s, 3H, C*H*$_3$), 1.96-2.04 (m, 1H, C*H*$_2$), 2.08-2.18 (m, 1H, C*H*$_2$), 2.32-2.44 (m, 1H, C*H*), 2.44-2.52 (m, 1H, C*H*$_2$), 2.58-2.74 (m, 3H, C*H* + 2×C*H*$_2$), 2.82-2.88 (m, 2H, C*H*$_2$), 2.98-3.08 (m, 1H, C*H*$_2$), 3.78 (s, 3H, OC*H*$_3$), 6.62-6.64 (m, 1H, Ar-*H*), 6.72-6.76 (m, 1H, Ar-*H*), 7.21-2.25 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 7.68 (CH_3), 28.25 (CH_2), 28.52 (CH_2), 30.13 (CH_2), 31.22 (CH_2), 39.48 (CH_2), 42.10 (CH), 45.67 (CH), 47.92 (CH), 55.19 (OCH_3), 111.99 (CH, Ar), 113.70 (CH, Ar), 126.88 (CH, Ar), 130.79 (C, Ar), 133.15(C=C), 137.98 (C, Ar), 157.67 (C, Ar), 174.17 (C=C), 208.87 (C=O);

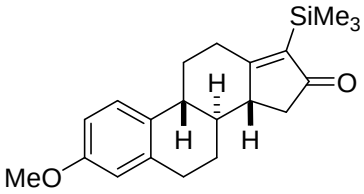
IR (KBr) ν 3013, 2936, 2858, 1690, 1694, 1607, 1498, 1447, 1264, 1148, 1042, 866, 819, 789;

MS-EI (m/z) 282.2 (100 %) (M^+), 253.1 (25 %), 219 (20 %), 173.1 (75 %), 159.1 (35 %), 147.1 (90 %), 115.1 (25 %);

HRMS (EI+) calcd. for $C_{19}H_{22}O_2$ 282.1620, found 282.1617.

R_f (50/1 CH_2Cl_2/MeOH) = 0.4.

(±)-3-Methoxy-17-trimethylsilyl-16-ketoestra-1,3,5(10),13(17)-tetraene (27). Enyne **18** (1 mmol, 312 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 139 mg (41 %) of the title compound as a colorless viscous liquid:



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 9H, 3×SiCH_3), 1.20-1.27 (m, 1H, CH), 1.35-1.46 (m, 1H, CH_2), 1.53-1.64 (m, 1H, CH_2), 1.95-2.00 (m, 1H, CH_2), 2.07-2.15 (m, 1H, CH_2), 2.40-2.75 (m, 5H, 2×CH + 2×CH_2), 2.82-2.87 (m, 2H, CH_2), 3.15-3.23 (m, 1H, CH_2), 3.78 (s, 3H, OCH_3), 6.62-6.64 (m, 1H, Ar-H), 6.70-6.76 (m, 1H, Ar-H), 7.20-7.24 (m, 1H, Ar-H);

^{13}C MR (100 MHz, $CDCl_3$) δ -0.33 ($SiCH_3$), 28.81 (CH_2), 30.14 (CH_2), 31.22 (CH_2), 31.87 (CH_2), 41.04 (CH_2), 41.85 (CH), 48.39 (CH), 48.92 (CH), 55.19 (OCH_3), 111.96 (CH, Ar), 113.69 (CH, Ar), 126.74 (CH, Ar), 130.80 (C, Ar), 136.56 (C=C), 137.88 (C, Ar), 157.69 (C, Ar), 189.96 (C=C), 212.12 (C=O);

IR (KBr) ν 2948, 2912, 2858, 2833, 1686, 1591, 1499, 1449, 1279, 1246, 1198, 1140, 1044, 841;

MS-EI (m/z) 340.2 (100 %) (M^+), 325.2 (90 %), 174.1 (45 %), 147.1 (35 %), 115 (20 %), 73 (70 %);

HRMS (EI+) calcd. for $C_{21}H_{28}O_2Si$ 340.1859, found 340.1859;

R_f (CH_2Cl_2) = 0.2.

General method for cyclocarbonylation with Cp_2ZrBu_2 (Negishi protocol).

n-BuLi (2.1 mmol, 1.36 mL of 1.6M solution in hexanes) was added to a stirred solution of Cp_2ZrCl_2 (1.05 mmol, 306 mg) in THF (10 mL) at -78 °C. After 1 h enyne **17** or **18** (1 mmol) in THF (1 mL) was added and the reaction mixture was warmed gradually to 20 °C within 2 h followed by CO bubbling through the reaction mixture for 20 min at 20 °C. Then it was quenched with HCl (1%, 30 mL), extracted with CH_2Cl_2 (3 × 15 mL), the combined organic fractions were dried over anhydrous $MgSO_4$, and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel afforded desired products.

(±)-3-Methoxy-17-methyl-16-ketoestra-1,3,5(10),13(17)-tetraene (26). Enyne **17** (1 mmol, 253 mg) was used. Column chromatography of the residue on silica gel (100/1

CH_2Cl_2/MeOH) afforded 87 mg (31 %) of the title compound as a colorless solid.

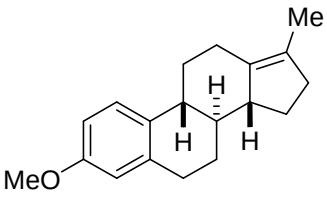
(±)-3-Methoxy-17-trimethylsilyl-16-ketoestra-1,3,5(10),13(17)-tetraene (27). Enyne **18** (1 mmol, 312 mg) was used. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 196 mg (58 %) of the title compound as a colorless viscous liquid.

Stoichiometric conjugated addition with Me_2CuLi.

***rac*-3-Methoxy-8α,9β,13β, 14β-1,3,5(10)-estratrien-16-one (33).** MeLi (1.3 mmol, 0.81 mL of 1.6 M solution in Et_2O) was added to a suspension of CuI (0.65 mmol, 123 mg) in Et_2O (1 mL) at 0 °C and mixture was stirred at this temperature for 10 min. This solution was added to a stirred solution of ketone **22** (0.5 mmol, 133 mg) in Et_2O (5 mL) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 2h. Then water (50 mL) and HCl (10 %, 2 mL) were added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (100/1 CH_2Cl_2/MeOH) afforded 113 mg (80 %) of the title compound as a colorless solid. The spectral characteristics were in agreement with the previously reported data.[32]

R*f* (50/1 CH_2Cl_2/MeOH) = 0.3.

(±)-3-Methoxy-17-methylestra-1,3,5(10),13(17)-tetraene (34). To solution of $LiAlH_4$ (0.6 mmol, 23 mg) in Et_2O (2 mL) $AlCl_3$ (2.4 mmol, 319 mg) was added at 20 °C. The resulting suspension was stirred for 15 min at 20 °C and then it was left to stand for 10 min allowing the insolubilities to sediment. The solution was separated and added dropwise to a solution of **26** (0.5 mmol, 140 mg) in Et_2O (8 mL) at -10 °C. The reaction mixture was stirred at 20 °C for 30 min and then it was quenched with HCl (5 %, 3 mL). Water (100 mL) was added and mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over anhydrous $MgSO_4$, and volatiles were removed under reduced pressure. The filtration over a short pad of silica gel (5 g) in CH_2Cl_2 afforded 126 mg of title compound (95 %) as colorless solid. Spectral characteristics were in agreement with the previously reported data.[52]



R*f* (2/1 CH_2Cl_2/hexane) = 0.6.

6.3. Enantioselective Synthesis of Methoxyestrone Synthetic Procedures

(*S*)-1-Ethynyl-2-(5-(1-(2-naftyl)ethoxy)-pent-3-en-1-yl)-4-methoxybenzene (37). KH (1.6 mmol, 213 mg of 30 % wt. suspension in mineral oil) was washed with hexane (3 × 5 mL), then DMF (5mL) was added. To this suspension (*S)*-1-(2-naphthyl)-ethan-1-ol (1.5 mmol, 258 mg) was added at 20 °C. After stirring the suspension for 1 h, chlorodiene **5** (1 mmol, 236 mg) was added and stirring continued for 3h. Then water (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (CH_2Cl_2) afforded 290 mg (78 %) of the title compound as a colorless liquid:

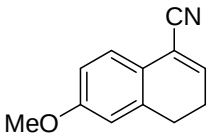
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 2.27-2.35 (m, 2H, C*H*$_2$), 2.70-2.75 (m, 2H, C*H*$_2$), 3.76-3.91 (m, 2H, OC*H*$_2$), 3.79 (s, 3H, OC*H*$_3$), 4.6 (q, *J* = 6.4 Hz, 1H, OC*H*), 5.16-5.20 (m, 1H, CH=C*H*$_2$), 5.50-5.58 (m, 1H, CH=C*H*$_2$), 5.58-5.74 (m, 2H, C*H*=C*H*), 6.67-6.69 (m, 1H, Ar-*H*), 6.79-6.77 (m, 1H, Ar-*H*), 6.88 (dd, *J* = 17.6, 11.2 Hz, 1H, C*H*=CH$_2$), 7.42-7.52 (m, 4H, Ar-*H* + 3×Naph-*H*) 7.72-7.74 (m, 1H, Naph-*H*), 7.80-7.87 (m, 3H, 3×Naph-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 24.09 (CH_3), 33.00 (CH_2), 33.53 (CH_2), 55.19 (OCH_3), 69.17 (OCH_2), 77.16 (OCH), 111.75 (CH, Ar), 113.49 (CH=*C*H$_2$), 114.75 (CH, Ar), 124.26, 125.14, 125.70, 126.05, 126.89 (Ar, H), 127.15, 127.69, 127.81, 128.33, 129.18 (C, Ar), 133.01, 133.23, 133.28, 133.86 (*C*H=CH2), 140.66 (C, Ar), 141.28, 159.18 (C, Ar);

R_f (CH_2Cl_2) = 0.7.

1-Cyano-1-trimethylsilyloxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (38). 6-Methoxy-tetralone (30 mmol, 5.28 g) and ZnI_2 (0.6 mmol, 0.2 g) were dissolved in DME (15 mL). The reaction mixture was heated to 60 °C and TMSCl (35 mmol, 4.6 mL) was added, reaction was stirred for 2h. Then 5% $NaHCO_3$ solution (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure to yield 7.87 g (98 %) of the title compound as viscous liquid that was used for next step without further purification. Spectral characteristics were in agreement with the previously reported data.[73]

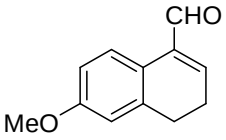
1-Cyano-6-methoxy-3,4-dihydronaphthalene (39). $POCl_3$ (22 mmol, 3.34 g) was added to a stirred solution of **38** (7.2 mmol, 2g) in pyridine (10 mL). The reaction mixture was refluxed overnight and then quenched carefully with H_2O (100 mL). The reaction mixture was extracted with CH_2Cl_2 (3×30 mL), the combined organic fractions were washed with 5% HCl (50 mL), and dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and crystalization from ether/petrolether yielded 1.05 g (75 %) of the title compound as yellow crystals. Spectral characteristics were in agreement with the previously reported data.[73]



^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42-2.53 (m, *2*H, C*H*$_2$), 2.78-2.86 (m, 2 H, ArC*H*$_2$), 3.80 (s, 3H, OC*H*$_3$), 6.70-6.83 (m, 3 H, 2Ar-*H* + C=C*H*), 7.38-7.42 (m, 1H, Ar-*H*);

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.51 (CH_2), 26.54 (CH_2), 55.29 (OCH_3), 111.54 (Ar), 113.77 (Ar), 114.20 (Ar), 117.28 (C=C), 121.76 (Ar), 126.05 (Ar), 136.02 (Ar), 140.81 (C=C), 160.10 (Ar).

1-Formyl-6-methoxy-3,4-dihydronaphthalene (40). DIBAL-H (8.1 mmol, 8.1 mL of 1 M solution in hexanes) was added to a stirred solution of **39** (5.4 mmol, 1 g) in Et_2O (30 mL) at -60 °C. The reaction mixture was allowed to warm gradually to 20 °C and kept for 1 h at this temperature. Then H_2O (100 mL) was added, the reaction mixture was extracted with CH_2Cl_2 (3×15 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (CH_2Cl_2) yielded 0.65 g (65 %) of the title compound as colorless viscous liquid. Spectral characteristics were in agreement with the previously reported data.[74]

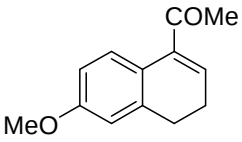


^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52-5.60 (m, 2H, C*H*$_2$), 2.74-2.82 (m, 2 H, ArC*H*$_2$), 3.80 (s, 3H, OC*H*$_3$), 6.70-6.80 (m, 2H, Ar-*H* + C=C*H*), 6.84-6.90 (m, 1H, Ar-*H*), 8.12-8.20 (m, 1H, Ar-*H*), 9.63 (s, 1H, C*H*O);

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.17 (CH_2), 27.37 ($ArCH_2$), 55.13 (OCH_3), 110.99 (Ar), 113.78 (Ar), 122.29 (Ar), 127.12 (Ar), 137.66 (Ar), 137.73 (C=CH), 150.57 (C=CH) 159.31 (Ar), 192.72 (CHO).

R_f (CH_2Cl_2) = 0.5.

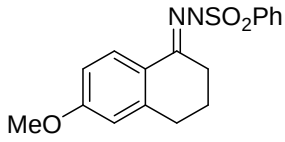
Methyl (3,4-dihydro-6-methoxynaphth-1-yl)ketone (41). MeLi (35.5 mmol, 22.2 mL of 1.6 M solution in hexanes) was added to a stirred solution of **38** (28 mmol, 7.7 g) in DME (15 mL) at 0 °C. The reaction mixture was allowed to warm gradually to 20 °C and kept for 24 h at this temperature. Then water was added (100 mL) and the reaction mixture was extracted with CH_2Cl_2 (3×15 mL). Volatiles were removed from the combined organic fractions under reduced pressure, 10% HCl (40 mL) was added to the residue, and mixture was refluxed for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3×30 mL), the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and crystalization of the residue from MeOH yielded 4.85 g (85 %) of the title compound as yellow crystals. Spectral characteristics were in agreement with the previously reported data.[75]



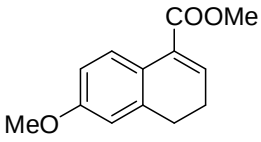
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35-2.47 (m, 5H, C*H*$_3$ + C*H*$_2$), 2.65-2.75 (m, 2 H, C*H*$_2$), 3.80 (s, 3H, OC*H*$_3$), 6.67-6.77 (m, 2H, Ar-*H* +C=C*H*), 6.85-6.93 (m, 1H, Ar-*H*), 7.63-7.70 (m, 1H, Ar-*H*);

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.88 (*C*H$_3$), 27.94 (*C*H$_2$), 28.18 (*C*H$_2$), 55.46 (O*C*H$_3$), 111.26 (Ar), 113.91 (Ar), 124.06 (Ar), 128.22 (Ar), 137.44 (C=CH), 138.64 (C=CH), 138.92 (Ar), 159.14 (Ar), 199.83 (C=O).

1-Benzenesulfonylhydrazo-6-methoxy-3,4-dihydronaphthalene (42). 35% HCl (3 mL) was added to a stirred solution of 6-methoxytetralone (45 mmol, 8 g) and benzenesulphonyl hydrazide (50 mmol, 8.6 g) in absolute ethanol (100 mL). The reaction mixture was refluxed for 2 h, then H_2O (30 mL) was added, and mixture was allowed to cool slowly to 0 °C. At this temperature formed crystals were filtered off and dried under reduced pressure at 50 °C to yield 13.8 g (92 %) of title compound as white crystals. Spectral characteristics were in agreement with the previously reported data.[76]



1-Carboxymethyl-3,4-dihydro-6-methoxynaphthalene (43). *n*-BuLi (15.15 mmol, 9.5 mL of 1.6 M solution in hexanes) was added to a stirred solution of hydrazone **42** (6.06 mmol, 2 g) in THF (40 mL) at -78 °C. The reaction mixture was stirred at this temperature for 1 h, then it was allowed to warm gradually to 20 °C and kept at this temperature until the release of nitrogen ceased (approx. 0.5 h). It was cooled to -78 °C again and solid CO_2 (36 mmol, 1.6 g) was added. The reaction mixture was allowed to warm gradually to 20 °C during 1h, then 5% K_2CO_3 solution



(20 mL) was added, and reaction mixture was extracted with CH_2Cl_2 (30 mL). This organic fraction was discarded, the aqueous phase was acidified with 35% HCl (10 mL), and extracted with CH_2Cl_2 (3×30 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and volatiles were removed under reduced pressure to yield crude carboxylic acid (Spectral characteristics were in agreement with the previously reported data.[77]), which was dissolved in THF (15 mL) and freshly prepared diazomethane was bubbled through this solution at -5 °C. (Diazomethane was prepared in a following way: 20% KOH solution (5 mL) was added to a stirred solution of diazalt (3.8 mmol, 0.81 g) in EtOH (20 mL), argon was bubbled through this solution and formed diazomethane was carried with argon to the reaction mixture). Then CH_3COOH (0.05 mL) was added to dispose of excess of diazomethane. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (CH_2Cl_2) yielded 0.76 g (57 %) of the title compound as a viscous liquid:

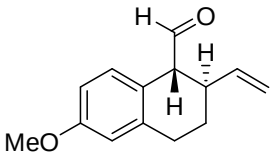
mp 4-5 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32-2.45 (m, 2H, C*H*$_2$), 2.70-2.78 (m, 2H, C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 6.68-6.80 (m, 2H, Ar-*H* + C=C*H*), 7.00-7.08 (m, 1H, Ar-*H*), 7.74-7.78 (m, 1H, Ar-*H*);

^{13}C NMR (75 MHz, $CDCl_3$) δ 23.41 (CH_2), 27.97 (CH_2), 51.70 (OCH_3), 55.21 (OCH_3), 111.10 (Ar), 113.65 (Ar), 123.89 (C=C), 127.31 (Ar), 130.28 (Ar), 137.28 (C=C), 138.09 (Ar), 158.88 (Ar), 167.14 (COOMe). R_f (1/1 CH_2Cl_2) = 0.6.

(1*R*,2*R*)-1-Formyl-6-methoxy-3,4-dihydro-2-vinylnaphthalene (45).

Catalytic conjugated addition. A solution of vinylmagnesium bromide (1.1 mmol, 11 mL of 0.1M solution in THF) was added slowly with syringe pump to the solution of **40** (1 mmol, 188 mg), CuCN (0.1 mmol, 9 mg) and HMPA (3 mmol, 537 mg) in THF (5 mL) at -78 °C during 3 h. Then it was allowed to warm up to 0 °C during 12 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, volatiles were removed under reduced pressure, and column chromatography of the residue on silica gel (CH_2Cl_2/hexane 1/1) yielded 10 mg (5 %) of the title compound as a mixture of cis and trans isomers in 2/1 ratio as a colorless viscous liquid.



Stoichiometric conjugated addition. (L)-*t*-Leucine *t*-butyl ester (5.67 mmol, 1.06 g) was added to a solution of **40** (5.32 mmol, 1 g) in hexane (15 mL) at 20 °C. To this solution molecular sieves A4 (1 g) were added and the reaction mixture was stirred overnight. Then it was left to stand without stirring for 10 min for the molecular sieves to sediment. The solution

over the sieves was transferred via cannula to another flask and volatiles were removed under reduced pressure to yield a crude aldimine that was used for the next step without further purification. Vinylmagnesium bromide (17 mmol, 17 mL of 1 M solution in THF) was added to the stirred solution of the crude aldimine in THF (60 mL) at -40 °C over a period of 2 h. The reaction mixture was then allowed to worm up to -20 °C and kept at this temperature for 3 h then diluted HCl (1 %, 100 mL) was added and the mixture was extracted with CH_2Cl_2 (3×60 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 CH_2Cl_2/hexane) yielded 0.7 g (61 %, ee > 98 %) of the title compound as a mixture of *trans/cis* isomers in 8/1 ratio.Ees were determinated by GC (HP-Chiral ß column, 30m × 0.25mm, oven: 70° C for 0 min, then 0.5° C/min to 170 °C): t_{1S2S} = 176.0 min, t_{1R2R} = 176.6 min. Recrystalization from MeOH yielded 0.55 g of the pure *trans* isomer as a white crystal.

Trans isomer:

mp 46-47 °C;

$[\alpha]_D$= -9° ($CHCl_3$, c = 0.5);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.75 (m, 1H, C*H*H), 1.94-2.04 (m, 1H, CH*H*), 2.78-2.88 (m, 3H, ArCH_2 + CH_2=CHC*H*), 3.44 (dd, *J* = 7.6, 3.2 Hz, 1H, ArC*H*), 3.79 (s, 3H, OCH_3), 5.05-5.10 (m, 1H, CH=CH_2), 5.08-5.14 (m, 1H, CH=CH_2), 5.84 (ddd, *J* = 17.6, 10.6, 7.4 Hz, 1H, C*H*=CH_2), 6.68-6.74 (m, 1H, Ar-*H*), 6.75-6.80 (m, 1H, Ar-*H*), 6.98-7.02 (m, 1H, Ar-*H*), 9.47 (d, *J* = 3.2 Hz, 1H, C*H*O);

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.64 δ (CH_2), 27.98 (CH_2), 37.90 (CH), 55.21 (OCH_3), 56.22 (ArCH), 112.54 (Ar), 114.41 (Ar), 115.40 (C=C), 121.62 (Ar), 130.42 (Ar), 138.75 (Ar), 139.83 (C=C), 158.68 (Ar), 201.06 (C=O).

IR (KBr) ν 3082, 3008, 2962, 2939, 2859, 2804, 2714, 1719, 1642, 1607, 1499, 1257, 1004, 919, 839, 919;

MS-EI (m/z) 216.1 (15 %) (M^+), 187.1 (100 %), 159.1 (25 %), 146.1 (25 %), 128.1 (10 %), 115.1 (15 %);

HRMS (EI+) calcd. for $C_{14}H_{16}O_2$ 216.1150, found 216.1152.

EA calcd. for $C_{14}H_{16}O_2$: C, 77.74 %, H, 7.47 %, found: C, 74.84 %, H, 7.19 %, these values correspond to 2×$C_{14}H_{16}O_2$+MeOH.

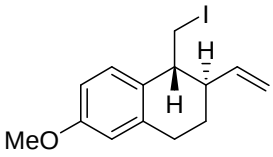
R_f (1/1 CH_2Cl_2/hexane) = 0.4.

Characteristic signals of *cis* isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61-3.66 (dd, 1H, Ar-C*H*), 5.98-6.08 (ddd, J = 17.5, 10.5, 7.2,

1H, C*H*=CH_2), 9.62 (d, J = 2.1, 1H, C*H*O).

(1*R*,2*R*)-1-Iodomethyl-6-methoxy-2-vinyl-1,2,3,4-tetrahydronaphthalene (58). A



suspension of $LiAlH_4$ (0.8 mmol, 30 mg) in THF (2 mL) was added to the stirred solution of **45** (2 mmol, 432 mg) in THF (10 mL) at -78 °C. The reaction mixture was allowed to warm to 20 °C and stirred for 2 h. Then 5% HCl (2 mL) and H_2O (50 mL) were added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and volatiles were removed under reduced pressure. The residue was dissolved in THF (10 mL), PPh_3 (2.2 mmol, 576 mg) was added, and the solution was cooled to -40 °C. A solution of NIS (2.2 mmol, 492 mg) in THF (5 mL) was added at -40 °C and the reaction mixture was allowed to warm to 20 °C and stirred for 30 min. Then H_2O (20 mL) was added and mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 CH_2Cl_2/hexane) yielded 560 mg (86 %) of the title compound as a colorless viscous liquid:

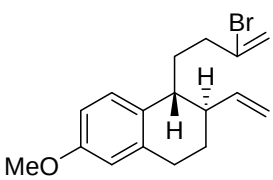
$[\alpha]_D$= +58° ($CHCl_3$, c = 0.5);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.78 (m, 1H, C*H*H), 1.87-1.96 (m, 1H, CH*H*), 2.60-2.68 (m, 2H, CH_2), 2.70-2.78 (m, 2H, CH_2), 3.50-3.62 (m, 2H, ArC*H* + CH_2=CHC*H*), 3.79 (s, 3H, OCH_3), 5.08 (dd, *J* = 10.4, 1.7 Hz, 1H, CH=C*H*H), 5.18 (dd, *J* = 17.2, 1.7 Hz, 1H, CH=CH*H*), 5.76 (ddd, *J* = 17.2, 10.4, 7.3 Hz, 1H, C*H*=CH2), 6.60-6.62 (m, 1H, Ar-*H*), 6.70-6.78 (m, 1H, Ar-*H*), 7.07-7.12 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.45 (CH_2), 26.03 (CH_2), 27.92 (CH), 42.66 (ArCH), 42.87(CH_2I), 55.13 (OCH_3), 112.57 (Ar), 113.43 (Ar), 115.45 (C=C), 129.10 (Ar), 129.25 (Ar), 138.45 (Ar), 141.08 (C=C), 157.95 (Ar).

R_f (1/1 CH_2Cl_2/hexane) = 0.5.

(1*R*,2*R*)-1-(3-Brom-but-3-en-1-yl)-6-methoxy-2-vinyl-1,2,3,4-tetrahydronaphthalene (7).



A solution of **58** (1 mmol, 328 mg) in THF (2 mL) was added to a suspension of Rieke zinc (4 mmol, 260 mg) in THF (5 mL). To this mixture Et_2Zn (0.05 mmol, 0.05 mL of 1M solution in toluene) was added, the reaction was heated to 40 °C, and stirred at this temperature for 30 min. Then the reaction mixture was cooled to 0 °C, 2,3-dibromoprop-1-ene (3 mmol, 600 mg) and CuCl (3 mmol, 300 mg) were added, and stirred at room temperature overnight.

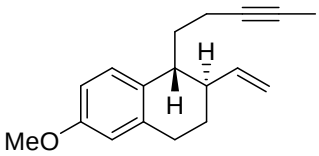
Then it was diluted with CH_2Cl_2 (50 mL) and filtered. To the clear solution diluted 1% HCl (50 mL) was added, extracted with CH_2Cl_2 (3×30 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (CH_2Cl_2/hexane 1/1) yielded 295 mg (93 %) of the title compound as a colorless viscous liquid. Spectral characteristics were in agreement with the previously reported data.[32]

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.69 (m, 1H, C*H*H), 1.93-1.99 (m, 3H, CH_2 + C*H*H), 2.34-2.47 (m, 3H, C*H* + CH_2), 2.69-2.78 (m, 3H, CH_2 + C*H*), 3.77 (s, 3H, OCH_3), 5.00 (ddd, *J* = 10.3, 1.8, 0.9 Hz, 1H, CH=CH_2), 5.07 (ddd, *J* = 17.2, 1.8, 1.2 Hz, 1H, CH=CH_2), 5.38 (dt, *J* = 1.7, 0.5 Hz, 1H, CBr=CH*H*), 5.55 (dt, *J* = 1.7, 0.5 Hz, 1H, CBr=C*H*H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H, C*H*=CH_2), 6.58-6.62 (m, 1H, Ar-H), 6.70-6.75 (m, 1H, Ar-H), 7.08-7.11 (m, 1H, Ar-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.10 (CH_2), 27.4 (CH_2), 33.77 (CH_2), 38.24 (CH_2), 40.71 (CH), 41.25 (CH), 55.14 (OCH_3), 112.26 (Ar), 113.25 (Ar), 114.41 (CH=*C*H_2), 116.48(CBr=*C*H_2), 129.73 (Ar), 130.86 (Ar), 134.81 (*C*Br=CH_2) 138.05 (Ar), 142.09 (*C*H=CH_2), 157.41 (Ar).

R_f (1/1 CH_2Cl_2/hexane) = 0.5.

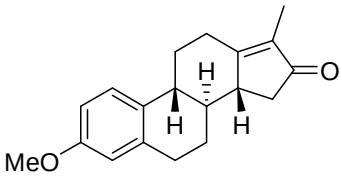
(1*R*,2*R*)-1-(Pent-3-yn-1-yl)-6-methoxy-2-vinyl-1,2,3,4-tetrahydronaphtalene (17). The



compound was prepared from chiral (1*R*, 2*R*)-**7** in the exactly same fashion as in the racemic synthesis. **7** was subjected to dehydrobromination with TBAF, which afforded chiral enyne **13** and subsequent methylation of terminal triple bond by the action of *n*-BuLi and MeI furnished chiral **17**.

$[\alpha]_D$= +31° ($CHCl_3$, c = 0.5).

(-)-3-Methoxy-17-methyl-16-ketoestra-1,3,5(10),13(17)-tetraene (26). To a solution of

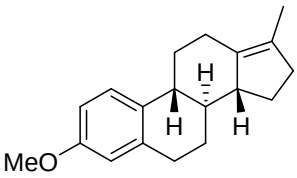


chiral enyne **7** (6 mmol, 1.51 g) in toluene (120 mL) $Co_2(CO)_8$ (7.8 mmol, 2.66 g) was added and the reaction mixture was stirred at 20 °C for 4 h. Then DMSO (60 mmol, 4.2 mL) was added and the reaction mixture was stirred at 80 °C for 12 h. 1% HCl (300 mL) was added, the reaction mixture was extracted with CH_2Cl_2 (3×75 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (10/1

CH_2Cl_2/AcOEt) followed by recrystalization (MeOH) yielded 1.53 g (91 %) of the title compound as white crystals:

$[\alpha]_D$= +165° ($CHCl_3$, c = 0.5).

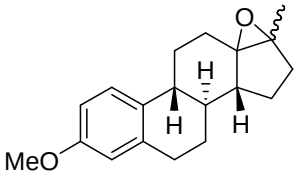
(-)-3-Methoxy-17-methylestra-1,3,5(10),13(17)-tetraene (34).



To solution of $LiAlH_4$ (0.3 mmol, 12 mg) in Et_2O (1 mL) $AlCl_3$ (1.2 mmol, 160 mg) was added at 20 °C. The resulting suspension was stirred for 15 min at 20 °C and then it was left to stand for 10 min allowing the insolubilities to sediment. The solution was separated and added dropwise to a solution of **26** (0.25 mmol, 70 mg) in Et_2O (3 mL) at -10 °C. The reaction mixture was stirred at 20 °C for 30 min and then it was quenched with HCl (5 %, 1 mL). Water (100 mL) was added and mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried over anhydrous $MgSO_4$, and volatiles were removed under reduced pressure. The chromatography on silica gel (20 g) in CH_2Cl_2 afforded 58 mg of title compound (81 %) as colorless solid. Spectral characteristics were in agreement with the previously reported data.[52]

$[\alpha]_D$= +80° ($CHCl_3$, c = 0.5).

(-)-3-Methoxy-17-methyl-13,17-epoxyestra-1,3,5(10),13(17)-tetraene (60a and 60b).

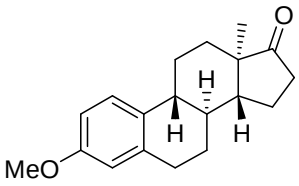


Solution of MCPBA (1.1 mmol, 270 mg of 70 % cont.) in CH_2Cl_2 (3 mL) was added to solution of **34** (1 mmol, 267 mg) in CH_2Cl_2 at 0 °C. Reaction was stirred at this temperature for 30 min and then 5% K_2CO_3 solution (20 mL) was added and mixture was extracted with CH_2Cl_2 (3×10 mL), combined organic fractions were dried over anhydrous $MgSO_4$ and volatiles were removed under reduced pressure. The filtration of the residue over a short pad of silica gel (5 g) in CH_2Cl_2/EtOAc (10/1) followed by crystalization from dry Et_2O afforded 142 mg (51 %) of pure **60a** as white crystals, evaporation of volatiles under reduced pressure from mother liquor afforded 110 mg (40 %) of mixture of **60a**/**60b** in 1/1 ratio.

60a:

$[\alpha]_D$= +74 ° ($CHCl_3$, c = 0.5). Spectral characteristics were in agreement with the previously reported data.[52][78]

(-)-Methoxyestrone (61). Freshly distilled $BF_3 \cdot Et_2O$ (1 mmol, 0.125 mL) was added to a solution of **60a** (0.25 mmol, 70 mg) in toluene (4 mL) at -78 °C. The reaction mixture was stirred at this temperature for 30 min and then it was allowed to warm up gradually over the period of 8 h to 0 °C. Then H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×10 mL), combined organic fractions were dried over anhydrous $MgSO_4$, and volatiles were removed under reduced pressure. Preparative TLC chromatography of the residue on silica gel (10/10/1 hexane/CH_2Cl_2/AcOEt) yielded 17 mg (25 %) of the title compound as white crystals. Spectral characteristics were in agreement with the previously reported data.[19]



$[\alpha]_D$= -150° ($CHCl_3$, c = 0.5);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3 H, C*H*$_3$), 1.40-1.67 (m, 8H), 1.96-2.00 (m, 2H, CH*H*), 2.01-2.10 (m, 2H, 2×CH*H*), 2.14-2.18 (m, 1H, C*H*H), 2.16 (ddd, *J* = 10.3, 6.5, 3.8 Hz, 1H, C*H*), 2.39-2.44 (m, 1H, CH*H*), 2.48-2.52 (m, 1H, CH*H*), 2.90-2.93 (m, 2H, ArC*H*$_2$), 3.79 (s, 3H, OC*H*$_3$), 6.64-6.68 (m, 1H, Ar-*H*), 6.70-6.78 (m, 1H Ar-*H*), 7.18-7.21 (m, 1H, Ar-*H*);

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.84 (CH_3), 21.58 (CH_2), 25.93 (CH_2), 26.55 (CH_2), 29.66 (CH_2), 31.58 (CH_2), 35.87 (CH_2), 38.38 (CH), 43.99 (CH), 48.01 (CH), 50.42 (C), 55.21 (OCH_3), 111.56 (Ar), 113.88 (Ar), 126.27 (Ar), 132.02 (Ar), 137.74 (Ar), 157.59 (Ar), 220.10 (C=O).

R_f (10/10/1 hexane/CH_2Cl_2/AcOEt) = 0.2.

7. Conclusion

The project described in this dissertation was undertaken to design and develop new total synthesis of (-)-methoxyestrone. Since the detailed summary of each part of the work is included at the end of subchapters 5.1 and 5.2 I will only briefly conclude the most important points of the work.

New formal total synthesis of estrone has been developed. The synthesis was based on 2 zirconocene mediated reactions and Pauson-Khand intramolecular cyclocarbonylation. The synthesis was highly diastereoselective and furnished the desired estrone precursor with correct *trans-anti* relative stereochemistry.

In the following part of the work early steps of the diastereoselective synthesis were modified in order to achieve enantioselective total synthesis of estrone. The key step of the modified synthesis, in which the chirality was introduced, was conjugated addition of vinylmagnesium bromide to chiral imine, which provided the crucial chiral intermediate with ee > 98 %.

Finally, it was shown that using the described methodology it was possible to synthesize (-)-methoxyestone in 13 steps from commercially available materials with 3 % overall yield.

8. Abstracts

8.1 English Abstract

The new diastereoselective synthesis of an estrone precursor and enantioselective synthesis of (-)-methoxyestrone are described in this work. The diastereoselective synthesis was based on two Bu_2ZrCp_2–mediated cyclization reactions followed by a Pauson-Khand cyclocarbonylation. The sequence of reactions yielded 16-keto-17-methylestratetraene, compound with the tetracyclic steroid framework, with excellent diastereoselectivity. The synthesis was finished with chemoselective reduction of the keto group in 16-keto-17-methylestratetraene to furnish 17-methylestratetraene, which is a known precursor of estrone. The enantioselective synthesis was based on a conjugate addition of vinylmagnesium bromide to aldimine formed from 1-formyl-3,4-dihydro-6-methoxynaphthalene and (L)-*t*-leucine *t*-butyl ester, which afforded the crucial chiral intermediate – 1-formyl-3,4-dihydro-6-methoxy-2-vinyl-naphthalene – with very high ee > 98 %. Further transformations led to the construction of alkyl side chain containing triple bond and finally, the Pauson-Khand cyclocarbonylation followed by chemoselective reduction of carbonyl group gave estrone precursor, which was converted to (-)-methoxyestrone according the previously reported procedure.

8.2 Czech Abstract

Tato práce popisuje novou diastereoselektivní syntézu prekurzoru estronu a novou enantioselektivní syntézu (-)-methoxyestronu. Diastereoselektivní syntéza byla založena na dvou cyklizačních reakcích zprostředkovaných Bu_2ZrCp_2 a Pauson-Khandově cyklokarbonylaci. Tímto postupem byl diastereoselektivně připraven 17-methyl-16-ketoestratetraen, jehož chemoselektivní redukce ve finálním kroku syntézy poskytla známý prekurzor estronu – 17-methylestratetraen. Klíčovým krokem enantioselektivní syntézy byla konjugovaná adice vinylmagnesiumbromidu na aldimín připravený z 1-formyl-3,4-dihydo-6-methoxynaftalenu a *t*-butyl-esteru (L)-*t*-leucinu, která poskytla klíčový chirální intermediát – 1-formyl-3,4-dihydro-6-methoxy-2-vinylnaftalen – s vynikající enantioselektivitiou > 98 % ee. Následné transformace vedly k vytvoření bicyklického enynu, který byl převeden Pauson-Khandovou cyklokarbonylací na tetracyklický keton. Chemoselektivní redukcí keto skupiny ve vzniklém intermediátu byl získán 17-methylestratetraen, který byl převeden na (-)-methoxyestron publikovaným postupem.

9. List of Abbreviations

Ac	acetyl
AIBN	azoisobutylonitril
aka	also known as
b	broad
Bn	benzyl
Bu	butyl
calcd	calculated
cat	catalyst
Cp	cyclopentadienyl
d	dublet
δ	chemical shift
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamid
EI-MS	electron impact mass spectrometry
ESI-MS	electrospray ionization mass spectrometry
eq	equivalent
Et	ethyl
FAB	fast atom bombardment
h	hour
HMPA	hexamethylphosphotriamide
HR-MS	high resolution mass spectrometry
HPLC	high pressure liquid chromatography
i-	*iso*-
IR	infrared spectroscopy
J	coupling constant
m	multiplet
mp	melting point
Me	methyl
MOM	methoxymethyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance

PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
Py	pyridine
q	quartet
r.t.	room temperature
s	singlet
t	triplet
t-	*tert*-
TBSCl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet

10. References

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