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Ph.D. study program:
Doktorský studijní program:

Summary of the Ph.D. Thesis
Autoreferát disertační práce

Total Synthesis of (-)-Methoxyestrone
Totální syntéza (-)-methoxyestronu

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1. Abstracts

1.1 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.

1.2 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.

2. Introduction

This dissertation is devoted mainly to synthesis estrone, one of the estrogenic human sex hormones. The work is mainly focused on the total syntheses of this compound. 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 at the same time challenging synthetic target. The attractiveness is strengthened by the fact that estrone and many of its derivatives possesses biological activity and have been a major component of many pharmaceutical drugs. Moreover, recent discoveries[1] suggest that *ent*-steroids (non natural enantiomers of steroids) could possess different and potentially useful biological properties, than their natural equivalents.

3. Aims of the Work

The main objective of this work was 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 preparation of (-)-methoxyestrone.

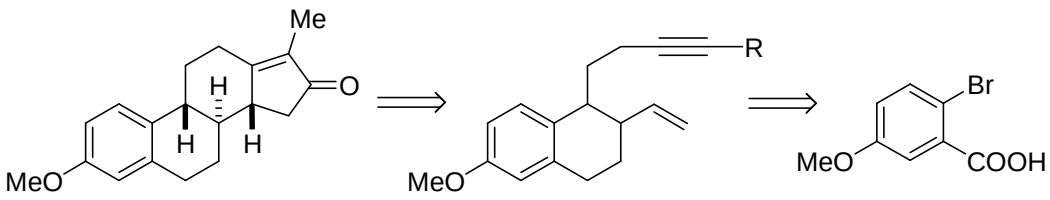
4. Results and discussion

4.1 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 new 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 dibutyl zirconocene.[2][3][4] His work utilized the C-O bond activation in a benzyl ether and various cyclizations of dienes. 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 is shown in the Figure 4.1.1. The tetracyclic estrone precursor 17-methyl-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.

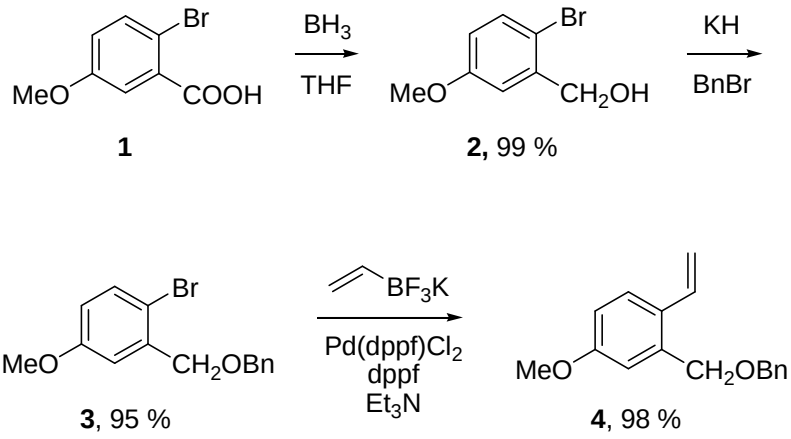
Figure 4.1.1



17-methyl-16-ketoestratetraene enyne

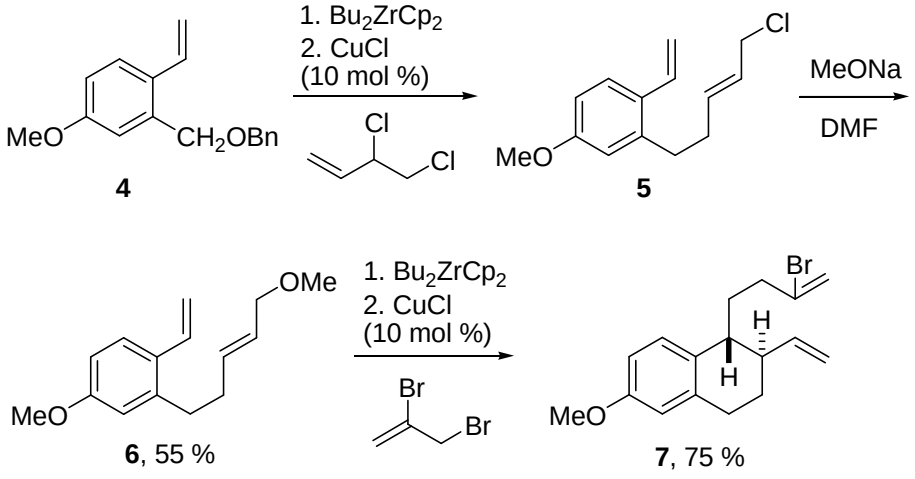
The work began with the preparation of the styrene derivative **4** (Scheme 4.1.1). The commercially available 2-bromo-6-methoxybenzoic acid **1** was used as a starting material. Its reduction with BH_3 in THF afforded 2-bromo-6-methoxybenzyl alcohol **2** in almost quantitative (99 %) yield. Subsequent 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; Phenyl bromide **3** was treated with potassium vinyltrifluoroborate in the presence of catalytic amount of $Pd(dppf)Cl_2$ (5 mol %) and dppf (2 mol %) along with excess of triethylamine, which gave styrene **4** in very nice 98 % yield.

Scheme 4.1.1. Synthesis of styrene **4**.



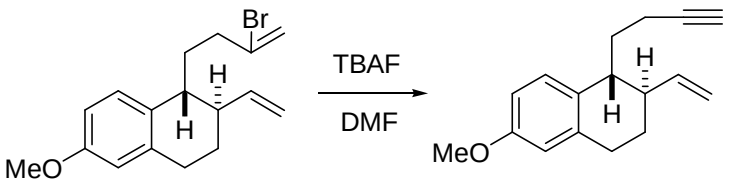
As outlined in Scheme 4.1.2 dibutylzirconocene, also known as Negishi's reagent, was used for transformation of styrene **4** into bromodiene **7**. In the first step, the reaction of a stoichiometric amount of dibutylzirconocene with **4** followed by alkylation with 3,4-dichlorobutene in the presence of a catalytic amount of the CuCl (10 mol %) provided chlorodiene **5**, which was immediately converted to methoxydiene **6** by reaction with MeONa in DMF. The overall yield of the reaction sequence starting from styrene **4** to methoxydiene **6** was 55 %. In the second step, treatment of methoxydiene **6** with a stoichiometric amount of dibutylzirconocene and successive alkylation of with 2,3-dibromopropene catalyzed with 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 4.1.2. Preparation of the methoxydiene **6**.



The synthesis was continued with dehydrobromination of bromodiene **7**. Treatment of **7** with tetrabutylamonium fluoride in DMF[5] gave enyne **13** in 95 % yield (Scheme 4.1.3). 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 4.1.3. Dehydrobromination of bromodiene **7**.

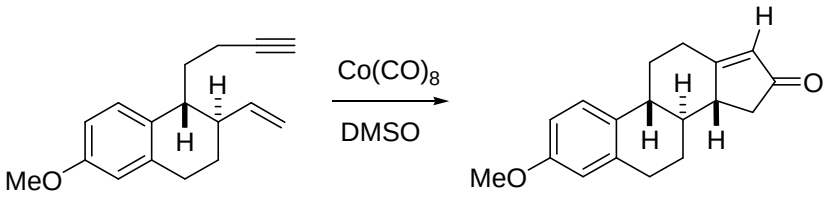


7 **13**, 95 %

With enyne **13** on hand the synthesis was continued with Pauson-Khand reaction. This reaction is formaly [2+2+1] cycloaddition between alkene, alkyne and carbon monooxide to form the α,β-cyclopentenone ring. I envisioned that compound **13**, possessing both the alkyne and the alkene moiety, could constitute 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 the C and D steroid rings in one step.

The most successful out several tested methods was the original procedure, which relied on use of stoichiometric amount of $Co_2(CO)_8$ to mediate the reaction.[6] As shown in Scheme 4.1.4 the enyne **13** was treated with stoichiometric amount of $Co_2(CO)_8$ and subsequently the reaction mixture was exposed to the excess of DMSO (5 eq.) at 80 °C, which led to formation of the tetracyclic compound **22** in very nice 95 % yield. It is important to note that the product was obtained as pure *trans-anti* diastereoisomer, which was the desired configuration! The formation of tetracyclic products with different configuration was not observed.

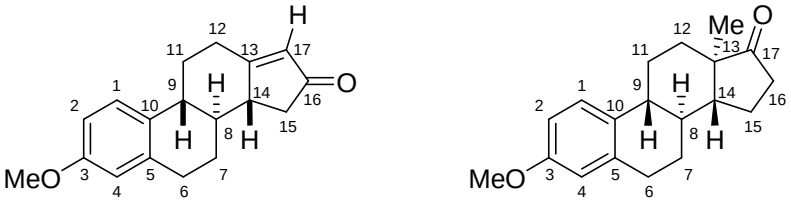
Scheme 4.1.4 Pauson-Khand reaction.



22, 95 %

To continue the synthesis towards the estrone framework, methyl in position 13 had to be introduced (Figure 4.1.2). I expected that conjugate addition to ketone **22** could be utilized to accomplish this transformation.

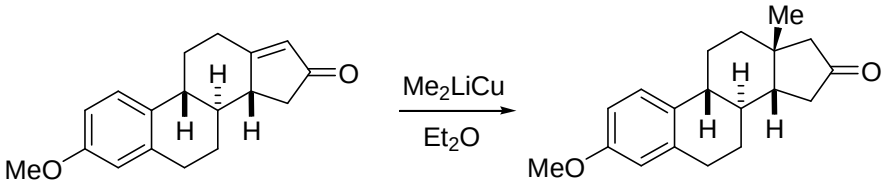
Figure 4.1.2.



22 (-)-methoxyestrone

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 4.1.5); 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 4.1.5. Conjugate addition to ketone **22**.

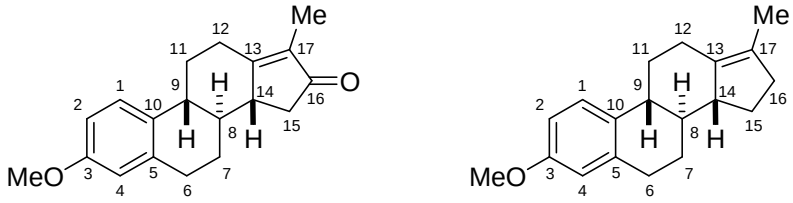


22 **33,** 80 %

Several other commonly applied methods for conjugate addition were tested, unfortunately, in neither case any product with desired *trans-anti-trans* configuration was obtained.

Since conjugate addition failed to give a 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 4.1.3), which is a known intermediate in estrone synthesis (can be converted to methoxyestrone diastereoselectively with simple two step transformation).[7] Reduction of 16-keto group in the derivative **26** could provide the estrone precursor **34**.

Figure 4.1.3.

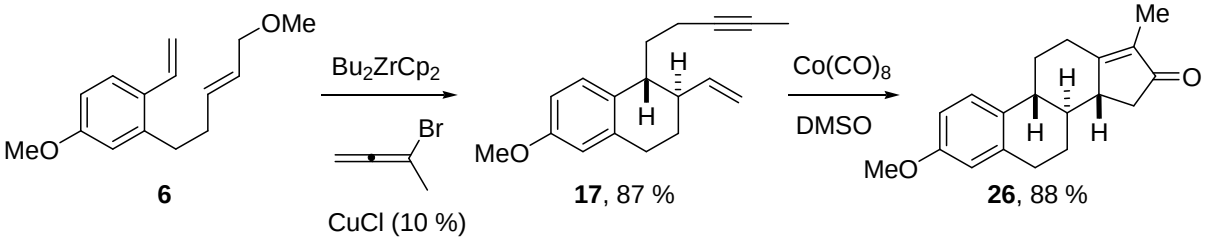


26

34, 17-methylestratetraene

Preparation of 17-methyl-16-ketoestratetraene **26** was accomplished using analogous reaction as were used in the preparation of ketone **22** (Scheme 4.1.6). Methoxydiene **6** was treated with stoichiometric amount of dibutylzirconocene and succesive alkylation with 3-bromobuta-1,2-diene in the presence of the catalytic amount of CuCl (10 mol %) afforded methylenyne **17** in 87 % yield. Pauson-Khand reaction of **17**, under the same conditions as described in the Scheme 4.1.4, afforded the desired 17-methyl-16-ketoestratetraene **26** in 88 % yield with the desired *trans-anti* configuration exclusively.

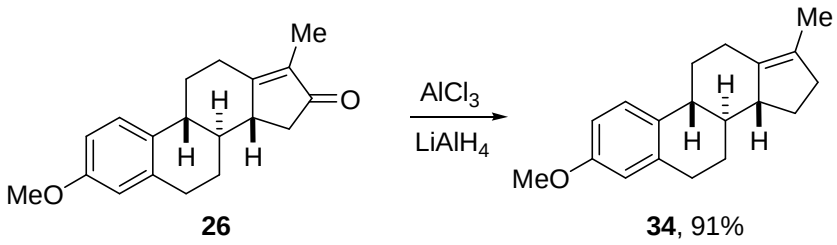
Scheme 4.1.6. Short synthesis of ketone **26**.



6 **17**, 87 % **26**, 88 %

The final step of the diastereoselective synthesis was reduction of the keto group in estratetraene **26**. 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[8], including the keto group in a conjugated system.[9] Treatment of **26** with the solution of aluminum hydride, freshly prepared from $AlCl_3$ (4.8 eq.) and $LiAlH_4$ (1.2 eq.), at 0 °C resulted in the formation of the desired estratetraene **34** in very nice 91 % yield. In conclusion I managed to prepare the direct estrone precursor- 17-methylestratetraene **34** - in 7 steps from commercially available materials with overall yield of 34 %.

Scheme 4.1.7. Reduction of **26** with Al_xH_y.

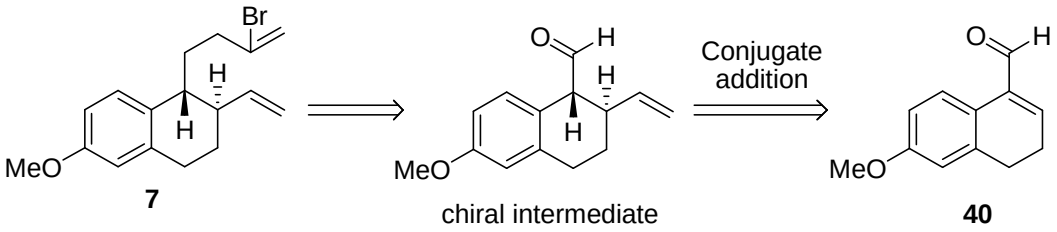


26 **34**, 91%

4.2 Enantioselective Synthesis of (-)-Methoxyestrone.

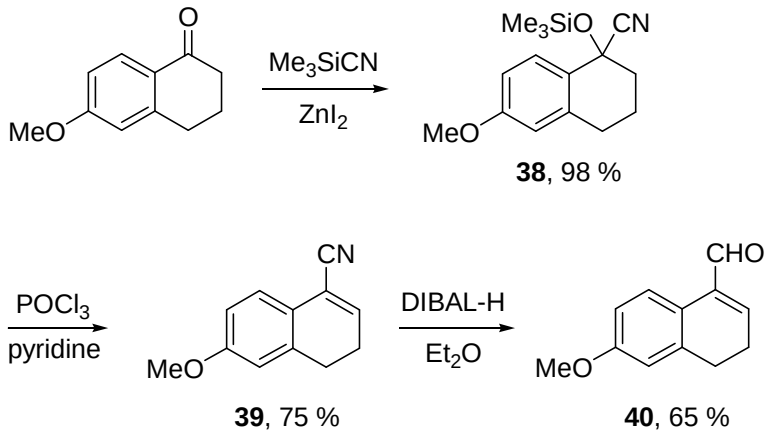
In the previous chapter I described the new synthesis of estrone precursor. The new strategy was very efficient, in terms of yield and diastereoselectivity, therefore I wanted to explore whether it could be modified to achieve enantioselective synthesis as well. I presumed that if I could introduce chirality 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. Unfortunately, after tedious experimentation with various different approaches to this problem we were not successful in the preparation of the enantioenriched bromodiene **7** using zirconocene cyclization. I had to look for a different strategy that would allow preparation of the crucial chiral intermediate. One of the possibilities could be enantioselective conjugate addition, which is 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 4.2.1, which could be subsequently converted to the desired chiral bromodiene **7**. Suitable starting material could be aldehyde **40**.

Figure 4.2.1.



Synthesis began with the preparation of the aldehyde **40**.[10][11][12] The commercially available 6-methoxy tetralone was used as a starting material for the preparation. Addition of trimethylsilylcyanide to 6-methoxytetralone catalyzed with ZnI_2 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.

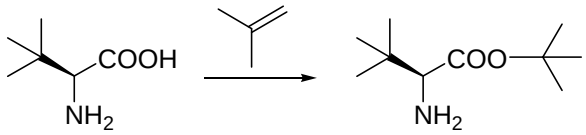
Scheme 4.2.1. Synthesis of conjugated aldehyde **40**.



Having the aldehyde **40** on hand the synthesis was continued with the enantioselective conjugated addition. Initially it was envisioned that the addition of vinylboronic acid ester to **40** under Miyaura-Hayashi catalytic conditions (Rh catalyst with (*S*)-BINAP ligand)[13] could yield the desired chiral precursor. Unfortunately, after tedious experimentation it was discovered that catalytic conjugate addition is not a suitable method for preparation of chiral precursor **45**.

Inspired by work of H. Kogen and K. Koga[14], 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 stoichiometric approach on my substrate **40** (Scheme 4.2.3). According to Koga, the best results in terms of enantioselectivity were achieved when (L)-*t*-leucine *t*-butyl ester (**51**) was used as aminoacid. However, ester **51** is not commercially available so this work had begun with its preparation (Scheme 4.2.2). Esterification of (L)-*t*-leucine with 2-methylpropene in the presence of 20 % oleum (1 eq.)[15] yielded **51** in nice 91 %. It's worth mentioning that the reaction was carried out in a pressure reaction tube.

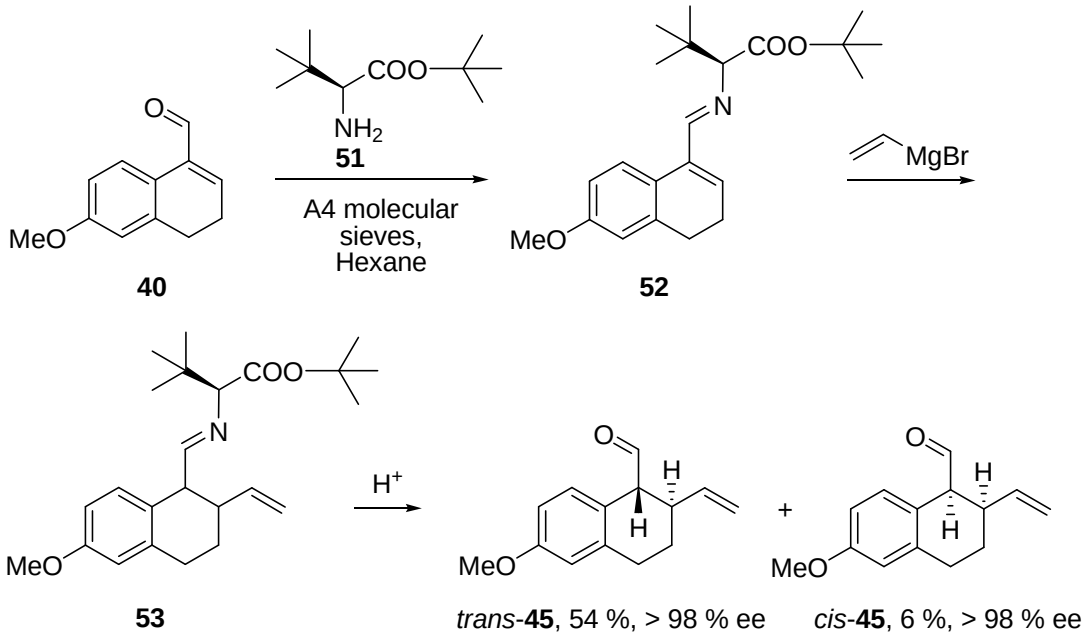
Scheme 4.2.2. Synthesis of (L)-*t*-leucine *t*-butyl ester.



51, 92 %

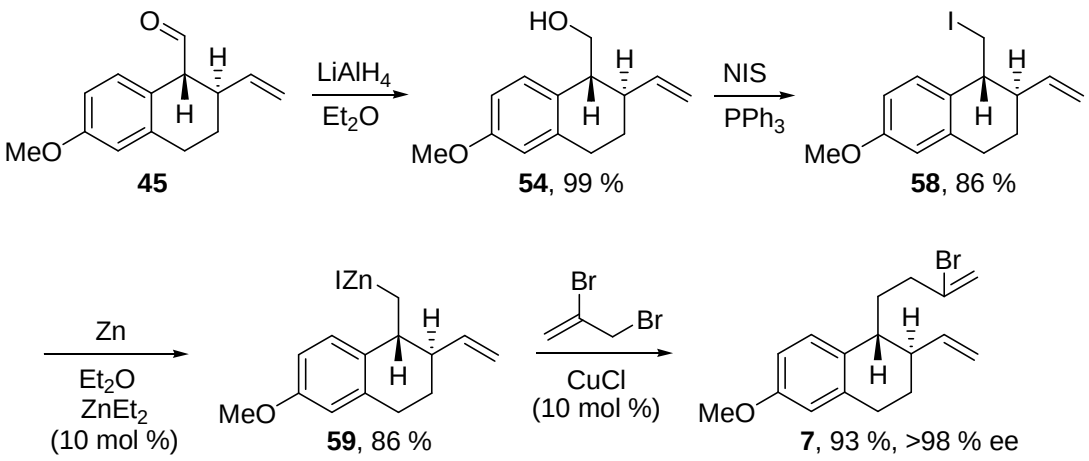
What followed was the preparation of a chiral imine and the conjugated addition itself. Condensation of aldehyde **40** with ester **51** in the presence of molecular sieves A4 proceeded uneventfully, yielding chiral imine **52**. Addition of vinylmagnesium bromide to **52** led to formation of vinyl 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 4.2.3. Stoichiometric conjugate addition.



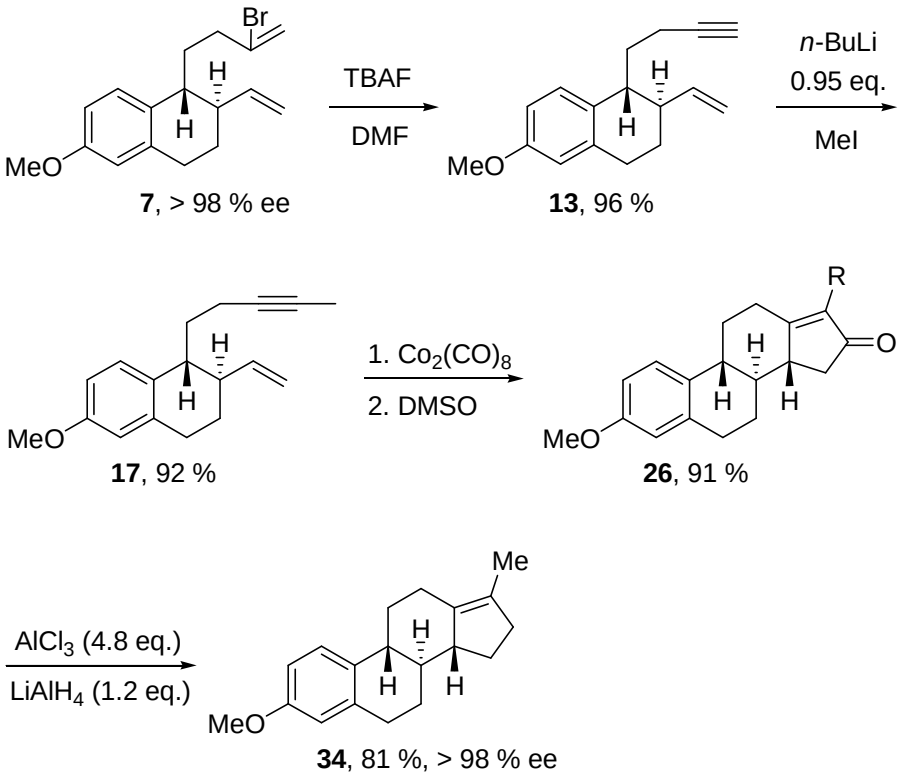
After securing the crucial chiral intermediate **45** the next step of the synthesis was the conversion of **45** to chiral bromodiene **7**. Aldehyde **45** was reduced with $LiAlH_4$ to give alcohol **54** almost quantitatively (99 %) and the following substitution with NIS in the presence of PPh_3 afforded the iodide **58** in 86 % yield. What followed was metallation of the iodide **58** using Rieke® zinc in the presence of a Et_2Zn (10 mol %) to the corresponding organozinc compound **59** and finally, the CuCl catalyzed (10 mol %) reaction between **59** and 1,2-dibromopropene, which gave the desired chiral bromodiene **7** in 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. 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 a mixture of *cis* and *trans* diastereomers in 1/8 ratio. The most importantly, bromodiene **7** 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 4.2.4. Synthesis of chiral bromodiene 7.



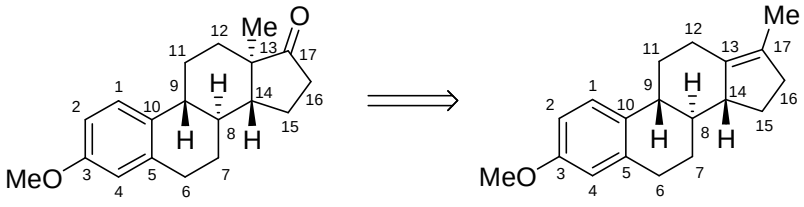
With chiral bromodiene **7** on hand the synthesis was continued with a sequence of reactions developed earlier in the diastereoselective synthesis of the estrone precursor (Scheme 4.2.5). Dehydrobromination of **7** with TBAF in DMF afforded enyne **13** in 96 % yield, subsequent lithiation of the terminal 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 previous results, only 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 4.2.5. Synthesis of chiral 17-methylestratetraene **34**.



The prepared 17-methylestratetraene is a known precursor of synthesis of estrone. According to Bartlet and Johnson[7] 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 4.2.2).

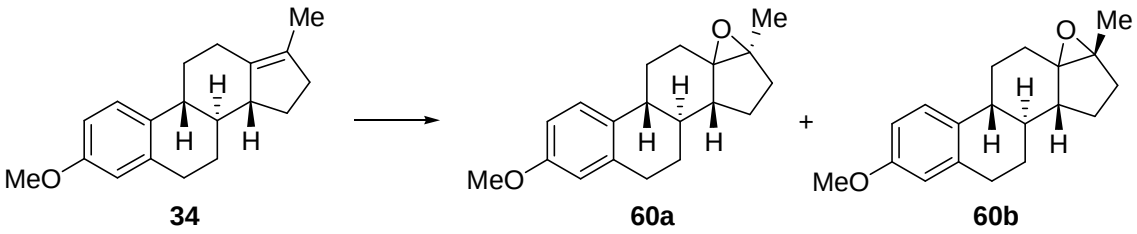
Figure 4.2.2.



The epoxidation was first attempted by the protocol 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 4.2.6). 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.[16] 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 pure **60a** was obtained in 71 % isolated yield.

Scheme 4.2.6. Epoxidation of **34**.



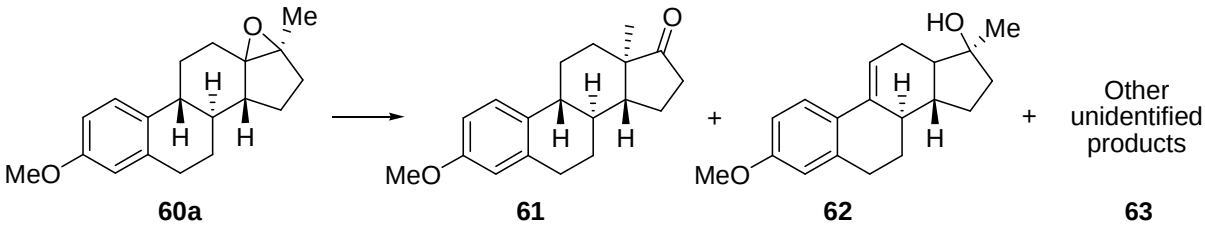
34 **60a** **60b**

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 the 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 the described conditions. The starting epoxide was converted to a complex mixture of compounds that I was not able to further identify **63** (Scheme 4.2.7) during the course of the reaction. 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 4.2.2). 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. $Bi(OTf)_3$,[17] $Cu(BF_4)_2$[18] and $IrCl_3$[19] 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.

Scheme 4.2.7. Rearrangement of epoxide **60a**.



Entry	Lewis Acid	solvent	temperature	**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 %

5. Conclusion

The project described in this dissertation was undertaken to design and develop new diastereoselective as well as enantioselective synthesis of estrone.

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 summary the diastereoselective synthesis was accomplished in 7 steps from commercially available 2-bromo-5-methoxybenzoic acid with overall yield of 37 %.

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 %.

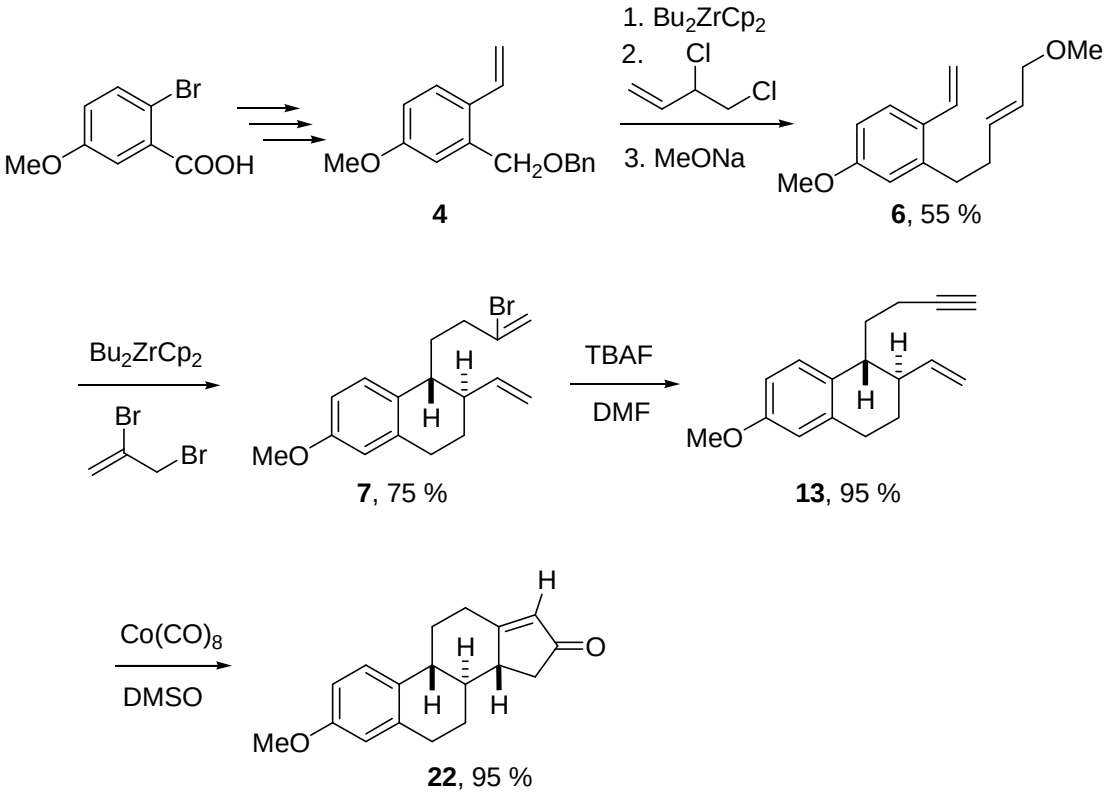
Finally, it was shown that using the described methodology it was possible to synthesize (-)-methoxyestone in 13 steps from commercially available materials with 3 % overall yield.

6. Czech Summary

Tato disertační práce je zaměřena především na totální syntézu estronu a jeho prekurzoru 17-methylestratetraenu. Totální syntézy patří obecně mezi nejatraktivnější oblasti organické chemie. Estron diky své komplexní tetracyklické struktuře se čtyřmi stereogenními centry představuje zajímavý syntetický cíl. Navíc nedávno publikovaná studie ukazuje, že nepřírodní enantiomery steroidních sloučenin by mohly mít praktické terapeutické použití.[1] Hlavním cílem, který si tato disertační práce kladla, bylo vyvinutí nové enantioselektivní syntézy estronu a pomocí této metody připravit nepřírodní (-)-estron. K dosažení tohoto komplexního cílu bylo nutné rozdělit práci na několik dílčích úkolů. Prvním z nich bylo vyvinout novou diastereoselektivní syntézu estronu, ve které byl hlavní důraz kladen na dosažení *trans-anti-trans* konfigurace výsledného tetracyklického skeletu. V další části práce byla pak tato nová diastereoselektivní syntéza modifikována tak, aby bylo docíleno enantioselektivní totální syntézy.

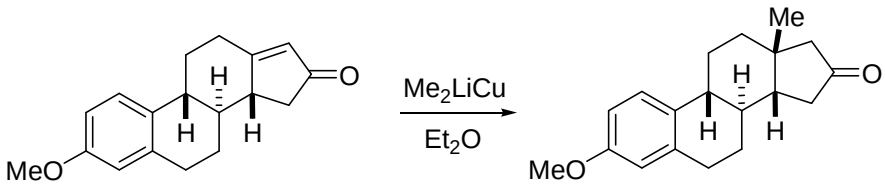
Ve skupině prof. Kotory se problematikou syntézy steroidního skeletu zabýval Pavel Herrmann, který ve své disertační práci popsal velmi elegantní metodiku přípravy tetracyklického skeletu pomocí aktivace C-O benzylové vazby a několikanásobnými cyklizacemi α,ω-dienů zprostředkovanými dibutylzirkonocenem.[2][3][4] Moje práce se snažila zkombinovat výše zmíněnou metodiku s Pauson-Khandovou reakcí a tím vyvinout efektivnější diastereoselektivní totální syntézu estronu. Prvním krokem nové syntézy byla reakce benzyletheru **4**, který byl připraven z komerčně dostupné 2-brom-5-methoxybenoové kyseliny sledem standardních reakcí, s dibutylzirkonocenem následovaná alkylací s 3,4-dichlorbut-1-enem katalyzovanou CuCl (10 mol %) a substitucí s MeONa. Tato sekvence reakcí poskytla methoxydien **6** ve výtěžku 55 %. Následovala klíčová cyklizace dienu **6** zprostředkovaná dibutylzirkonocenem následovaná reakcí s 2,3-dibromprop-1-enem katalyzovanou CuCl (10 mol %), která vedla ke vzniku bicyklického bromdienu **7** v celkovém výtěžku 75 %. Tato cyklizace byla vysoce stereoselektivní a bromdien **7** byl získán výhradně jako *trans* diastereomer. Dehydrobromace dienu **7**, provedena za mírných podmínek použitím TBAF jako báze[5], poskytla enyn **13** ve výtěžku 95 %. Díky vhodnému uspořádáni dvojné a trojné vazby je enyn **13** ideálním substrátem pro intramolekulární Pauson-Khandovu reakci, při které by v tomto případe docházelo k tvorbě C a D steroidních kruhů v jediném kroku. Cyklokarbonylace enynu **13** zprostředkovaná $Co_2(CO)_8$[6] poskytla očekávaný tetracyklický produkt **22** s velmi dobrým výtěžkem 95 % a navíc byla tato reakce diastereoselektiní a vzniklý produkt byl získán takřka výhradně jako požadovaný *trans-anti* diastereomer.

Schéma 6.1 Příprava estratetraenu **22**.



Abych se v syntéze dále přiblížil struktuře estronu, bylo nutné v derivátu **22** zavést methylovou skupinu do polohy 13. O to jsem se pokoušel konjugovanou adicí různými činidly za různých podmínek. Nejlepšího výsledku co se týče celkového výtěžku reakce bylo dosaženo použitím klasického Me_2LiCu v Et_2O (Schéma 6.2), v tomto případě vznikal methylovaný produkt **33** s výtěžkem 80 %. Bohužel látka **33** nemá požadovanou přírodní konfiguraci *trans* na spojeni C a D kruhů. Za všech zkoušených podmínek se nepodařilo připravit ani stopové množství produktu se správnou konfiguraci pomocí konjugované adice. A proto jsem se rozhodl změnit strategii a místo látky **33** připravit látku **34** (Schéma 6.3), která je známým prekurzorem syntézy estronu.[7]

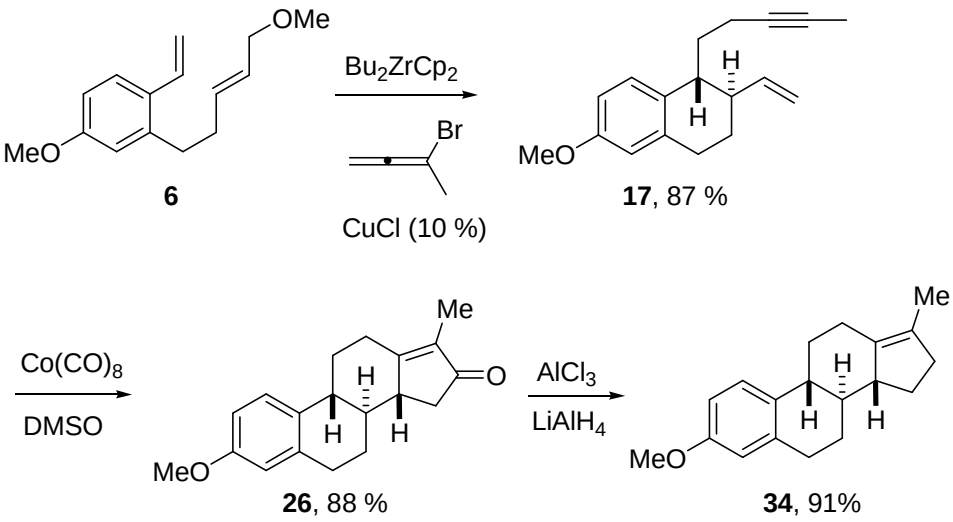
Schéma 6.2 Příprava látky **33** konjugovanou adicí.



22 **33,** 80 %

Syntetický postup přípravy tetracyklické látky **34** byl podobný výše popsanému. Jako výchozí látka byl použit methoxydien **6**, který po cyklizaci zprostředkované dibutylzirkonocenem a alkylaci 3-brombuta-1,2-dienem katalyzované CuCl (10 mol %) poskytl v jediném kroku enyn **17** (jako čistý *trans* diastereomer) ve výtěžku 87 %. Následovala Pauson-Khandova reakce, která vedla ke vzniku tetracyklického derivátu **26** ve výtěžku 88 %. Stejně jako v předchozím případě vznikal takřka výhradně *trans-anti* diastereomer. Posledním krokem této syntézy byla chemoselektivní redukce 16-keto skupiny v derivátu **26**. Tuto reakci jsem zkoušel různými metodami a jako nejlepší se ukázala metoda založená na použití směsi $AlCl_3$ a $LiAlH_4$. Redukce tetraenu **26** 1,2 ekvivalenty $LiAlH_4$ v přítomnosti 4,8 ekvivalentu $AlCl_3$[8][9] poskytla žádaný tetraen **34** s velmi dobrým výtěžkem 91 %. Tímto byla završena diastereoselektivni totální syntéza estronového prekurzoru **34**, který byl připraven z komerčně dostupné kyseliny 2-brom-5-methoxy benzoové v 7 krocích s celkovým výtěžkem 37 %

Schéma 6.3 Syntéza estronového prekurzoru.

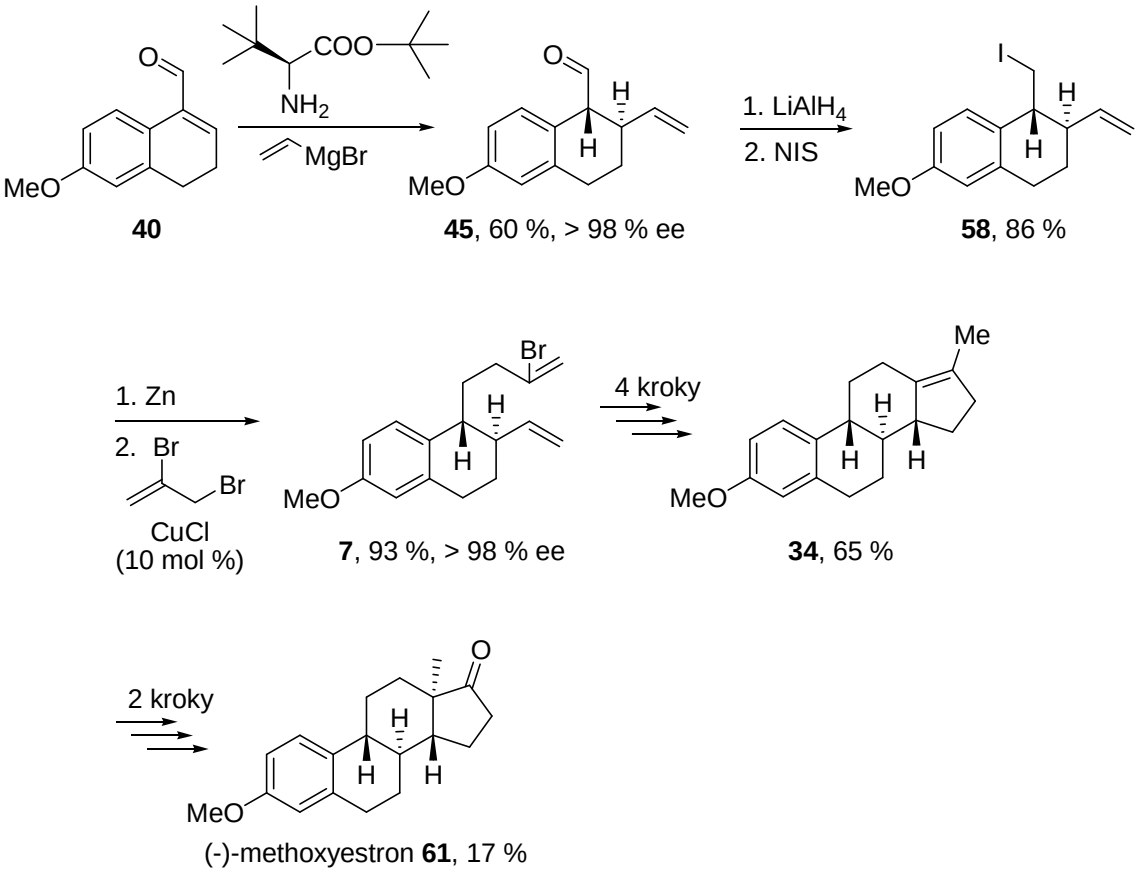


6 **17**, 87 %

26, 88 % **34**, 91%

V následující části práce byla výše popsaná syntéza modifikována tak, aby bylo docíleno enantioselektivní syntézy. Vzhledem k diastereoselektivitě s jakou probíhaly Pauson-Khandova reakce a další transformace popsané v literature[7] vedoucí k methoxyestronu jsem předpokládal, že pokud by byl použit pro syntézu chirální enyn **17** bylo by možné připravit methoxyestron enantioselektivně. Enantioselektivní syntéza bromdienu **7** probíhala následovně. Jako výchozí látka byl použit aldehyd **40**, který byl připraven z komerčně dostupného 6-methoxytetralonu standardními reakcemi.[10][11][12] Konjugovaná adice vinylmagnesium bromidu na aldimín připravený z aldehydu **40** a *t*-butyl esteru (L)-*t*-leucinu[14] poskytla vinyl aldehyd **45** ve výtěžku 60 % s vynikající enantioselektivitou, více než 98 % ee. Převedení aldehydu **45** na chirální bromdien **7** bylo provedeno následujícím sledem reakcí. Nejprve redukce aldehydu **45** použitím $LiAlH_4$ jako redukčního činidla a následná substituce vzniklého alkoholu N-iodsukcinimidem poskytla iodid **58** ve výtěžku 86 %. Reakce iodidu **58** s Riekeho® zinkem vedla ke vzniku organozinečnaté sloučeniny, která po substituci s 2,3-bromprop-1-enem katalyzované CuCl (10 mol %) poskytla kýžený chirální bromdien **7** ve výtěžku 93 %. Enantiomerní čistota se těmito reakcemi nezměnila a bromdien **7** byl získán ve více než 98 % enantiomerním přebytku. Následující část syntézy byla obdobná diastereoselektivní strategii. Dehydrobromace bromdienu **7** poskytla enyn **13**, jehož acetylenový vodík byl nahrazen methylovou skupinou za vzniku enynu **17**. Pauson-Khandova reakce enunu **17** vedla, podle očekávání, ke vzniku opticky čistého tetraenu **26** a konečně chemoselektivní redukce 16-keto skupiny v derivátu **26** poskytla 17-methylestratetraen **34** v celkovém výtěžku 65 %. Tetraen **34** je známým prekurzorem syntézy estronu[7] a podle literatury je možné převést jej na estron ve dvou krocích. Prvním z nich je epoxidace dvojné vazby a následně přesmyk vzniklého epoxidu katalyzovaný Lewisovou kyselinou, který je zároveň doprovázen migrací methylové skupiny z pozice 17 na 13. Po provedení obou reakcí s tetraenem **34** byl připraven (-)-methoxyestron ve výtežku 17 %. Absolutní konfigurace připraveného methoxyestronu byla zjištěna na chirálním HPLC srovnáním s přírodním methoxyestronem.[20] Celkově byl touto novou chirální totální syntézou připraven (-)-methoxyeston ve 13 krocích z komerčně dostupného 6-methoxytetralonu s celkovým výtěžkem 3 %.

Schéma 6.4 Enantioselektivní syntéza estronu.



40

45, 60 %, > 98 % ee

58, 86 %

7, 93 %, > 98 % ee

34, 65 %

(-)-methoxyestron **61**, 17 %

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