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Enantioselective Synthesis of (–)-Methoxyestrone

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Enantioselective synthesis of unnatural (–)-methoxyestrone in 12 steps from the commercially available tetralone based on the formation of a chiral bicyclic intermediate having the A–B steroid ring framework was accomplished. The crucial synthetic step comprised the enantioselective conjugate addition of vinylmagnesium bromide to a chiral imine formed from a trisubstituted cyclic α,β-unsaturated aldehyde with >98 % *ee*, giving rise to the stereoselectively substituted building block possessing the A–B steroid rings. Further steps included the construction of the side chain containing the triple bond, and the obtained enyne was subjected to a Pauson–Khand reaction that furnished stereoselectively an intermediate tetracyclic ketone. Further functional group transformations yielded the target compound.

Introduction

The total synthesis of compounds possessing the steroid framework is attractive, as the target may possess biological activity, and the process serves as a probing stone for synthetic methodology. In this regard, estrone, thanks to its rather complex structure, has constituted an ideal and favorable target molecule. Development of new synthetic pathways[1] for its enantioselective synthesis[2] has also been fuelled by a recent interest in *ent*-steroids (not produced by Nature), which are presumed to have biological activities different from those of the natural ones.[3]

Recently, we reported two new procedures for the diastereoselective synthesis of an advanced steroid intermediate bearing the required tetracyclic skeleton including the correct relative stereochemistry. The first approach was based on threefold consecutive use of Cp_2ZrBu_2-mediated reactions (Negishi reagent) to construct the steroid A–C rings, and finally the D ring was assembled by a Ru complex catalyzed ring-closing metathesis.[4] The second one utilized two previous Cp_2ZrBu_2-mediated reactions for the construction of the A and B rings followed by a Co-mediated Pauson–Khand reaction that allowed the C and D rings to be assembled in one step.[5] These procedures led to the straightforward synthesis of the known tetracyclic intermediate over nine steps from the commercially available starting material; nonetheless, attempts to develop an enantioselective variant of this procedure were not met with success. Although the key synthetic step, the closing of the B ring, could furnish a substituted tetrahydronaphthalene intermediate with the correct relative stereochemistry under racemic conditions by using Cp_2ZrBu_2, the use of a chiral zirconocene derivative under catalytic or stoichiometric conditions did not lead to the expected intermediates; moreover, loss of stereoselectivity was observed.[6] Obviously this led to the conclusion that a different methodology should be applied to fulfil the desired goal. In this report we would like to outline an approach for the enantioselective construction of the estrone framework that is based on the initial introduction of chirality on the B steroid ring (positions 8 and 9).

Results and Discussion

Because we wanted to apply some parts of the previously used methodology in a new approach, we decided to modify early steps of the synthesis. The overall retrosynthetic analysis is outlined in Scheme 1. It was presumed that the crucial step along the synthetic pathway – the preparation of a chiral intermediate with the tetrahydronaphthalene moiety – could be accomplished by enantioselective conjugate addition of a vinyl nucleophile to α,β-unsaturated carbonyl compound **2a**, which would introduce functional groups (directly or after additional transformation) suitable for a metal-mediated cyclization reaction.

Interestingly, conjugate additions to trisubstituted enals with a similar framework to that of **2a** have not been reported yet. Because the conjugate additions of various nucleophiles to sterically hindered enals constitute interesting synthetic and theoretical problems, we decided to explore its scope. We envisioned three candidates as acceptors and potential synthetic intermediates for conjugate addition: aldehyde **2a**, ketone **2b**, and ester **2c**, which were prepared from commercially available 6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (**1**) by using previously described methodology (see the Supporting Information).[7–10]

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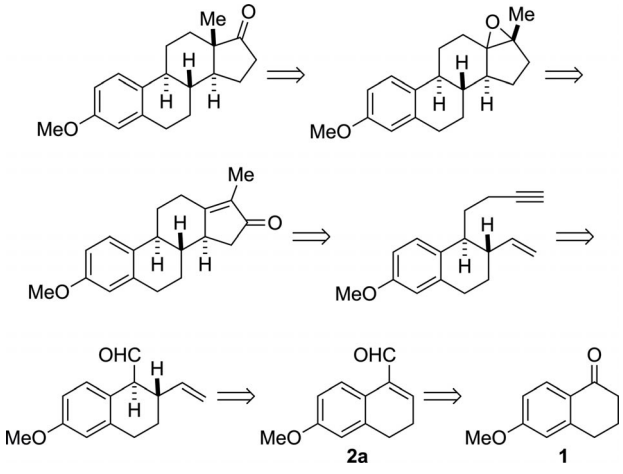
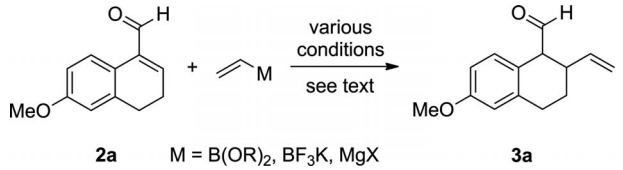


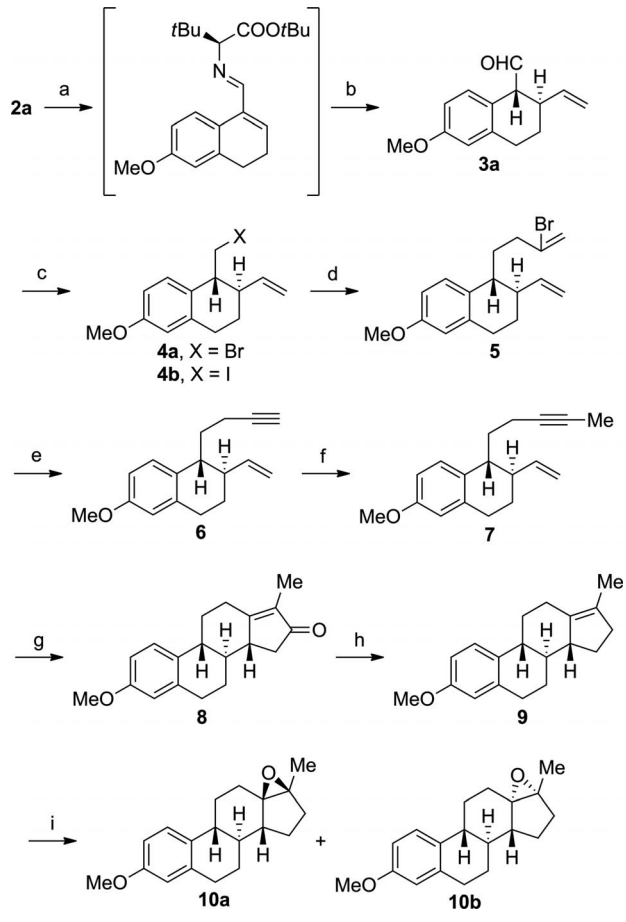
Scheme 1. Retrosynthetic analysis of methoxyestrone synthesis.

After securing compounds **2a**–**c**, conjugate additions with various vinyl nucleophiles were tried under various catalytic and stoichiometric conditions (Scheme 2). Initially, it was expected that the addition of vinylboronic acid ester under Miyaura–Hayashi conditions [a Rh catalyst in combination with (*S*)-BINAP][11] could yield desired chiral intermediate **3a**. Although this step seemed not to pose any problem, because several synthetic procedures for enantioselective conjugate additions of boronic acid derivatives to trisubstituted olefins have been reported,[12] our subsequent studies proved otherwise. Attempts to carry out conjugate addition of CH_2=CHB(OBn)$_2$ catalyzed by Rh(acac)(CO)$_2$, Rh(acac)(cod), or Rh(acac)(CH_2=CH_2) in combination with (*S*)-BINAP did not give rise to expected product **3a**. The conjugate addition of vinylmagnesium bromide catalyzed by CuCN (10 mol-%) was somewhat more successful. It gave **3a** in 5% yield along with 50% of the 1,2-addition product. Although we tried to improve the 1,4-selectivity by changing the reaction conditions (e.g., combination of vinylmagnesium bromide with $AlCl_3$[13] alone or in the presence of HMPA, etc.),[14] only complex reaction mixtures were usually obtained. Finally, a stoichiometric method based on the addition of vinylmagnesium bromide to the in situ formed imine[15] (from **2a** and L-*tert*-leucine *tert*-butyl ester[16]) gave rise to **3a** in 60% yield as an 8:1 mixture of *S*,*S*-/*S*,*R*-diastereoisomers (*trans*/*cis* isomers) with high asymmetric induction of 98%*ee* (it refers to the configuration on the C2 carbon atom). Conjugate additions to **2b** and **2c** resulted in inferior results only (for details, see the Supporting Information).



Scheme 2. Conjugate addition to **2a**.

Having secured chiral aldehyde **3a** (Scheme 3), a two step reaction sequence was required to convert it into halides **4**. Reduction of the aldehyde to an alcohol with $LiAlH_4$ followed by reaction with PPh_3/NBS or PPh_3/NIS furnished corresponding bromide **4a** or iodide **4b** in 73 and 86% yield, respectively. It should be noted that although aldehyde **3a** was obtained as an 8:1 *trans*/*cis* mixture, after conversion into the halides only the corresponding *trans* diastereoisomers were obtained. An attempt to convert bromide **4a** into the corresponding Grignard reagent followed by its coupling with 2,3-dibromopropene was not met with success. A mixture of the starting bromide, the dehydrohalogenated product, and a dimer was obtained without any desired product **5**. Then we turned our attention to iodide **4b**, which was treated with Rieke zinc (3 equiv.) in the presence of Et_2Zn (5 mol-%) to form an organozinc reagent. The presence of Et_2Zn was indispensable for the full conversion of the iodide into the corresponding organozinc compound. In its absence, the conversions were in the 20–80% range.

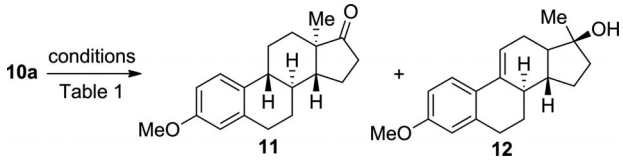


Scheme 3. Reagents and conditions: (a) *tert*-Butyl-*tert*-leucine, hexane, 3 Å molecular sieves; (b) CH_2=CHMgBr, THF, –20 °C (60%, 98%*ee*); (c) 1. $LiAlH_4$, THF, 0 °C; 2. PPh_3/NBS, THF (73%) or PPh_3/NIS, THF (86%); (d) 1. Zn, Et_2Zn (5 mol-%), THF, 40 °C; 2. CH_2=$CBrCH_2Br$, CuCl (3 equiv.), 0 °C (93%); (e) TBAF, DMF (96%); (f) 1. *n*BuLi, THF, –78 °C; 2. MeI (92%); (g) 1. $Co_2(CO)_8$, toluene; 2. DMSO, 80 °C (91%); (h) $LiAlH_4$/$AlCl_3$, Et_2O (81%); (i) *m*-CPBA, CH_2Cl_2, 0 °C (91%).

The formed organozinc compound was immediately reacted with 2,3-dibromopropene in the presence of CuCl to form bromodiene **5** in 93% yield.

In the next four steps, bromodiene **5** was converted into a tetracyclic estrone precursor in an analogous manner to our previously reported racemic synthesis.[5] Firstly, dehydrobromination of **5** with TBAF yielded enyne **6** (96%), its terminal triple bond was metalated with *n*BuLi, and the formed acetylide was treated with MeI to give enyne **7** in 92% yield. Then, the Pauson–Khand reaction of **7** with Co_2CO_8 proceeded diastereoselectively to give rise to a single stereoisomer of tetracyclic ketone **8** in 95% yield. Finally, chemoselective reduction of the keto group with a mixture of $LiAlH_4/AlCl_3$ furnished chiral tetracycle **9** in 81% yield. It should be emphasized that during all these steps no racemization was observed.

As it had been shown that tetracycle **9** can be easily converted into estrone,[17] we decided to follow the described procedure. Initially, tetracycle **9** was transformed into a 3.5:1 mixture of epoxides **10a/10b** by reaction with *m*-CPBA in 91% yield.[18] For the last step, that is, a Lewis acid catalyzed rearrangement of the epoxy group to the carbonyl group, only epoxide **10a** with the desired stereochemistry was used. This step proved to be more complicated than reported and envisioned. In our hands it usually resulted in the formation of a mixture of methoxyestrone **11**, tetracyclic alcohol **12**, and a mixture of unknown nonpolar compounds **13** (Scheme 4). Some typical examples are displayed in Table 1. When the rearrangement was carried out according to the previously published procedure ($BF_3{\cdot}Et_2O$, benzene, 20 °C) only a mixture of nonpolar compounds **13** was formed, not even trace amounts of **11** or **12** were observed. Carrying out the reaction at –20 °C gave rise only to a minor amount of **11** (4%); the major product was found to be tetracyclic alcohol **12** (70%) along with **13** (<20%). The highest yield of (–)-methoxyestrone (**11**, 25%) was obtained at –78 °C. Interestingly, the application of other frequently utilized Lewis acids for the rearrangement of epoxides to carbonyl compounds such as $Bi(OTf)_3$,[19] $Cu(BF_4)$,[20] or $IrCl_3$[21] did not give rise to the desired product; only complex mixtures of compounds were obtained.



Scheme 4. Rearrangement of **10**.

Table 1. Rearrangement of **10** catalyzed by various Lewis acids.

Lewis acid	Solvent	*T*	Yield [%]		
			11[a]	**12**[b]	**13**[b]
$BF_3{\cdot}Et_2O$[c]	benzene	20	0	0	>95
$BF_3{\cdot}Et_2O$[c]	benzene	–20	4	70	<20
$BF_3{\cdot}Et_2O$[c]	toluene	–78	25	55	<20
$Bi(OTf)_3$[d]	CH_2Cl_2	–20	0	0	>95
$Cu(BF_4)_2$[d]	MeCN	–20	0	0	>95
$IrCl_3$[d]	CH_2Cl_2	–20	0	0	>95

[a] Isolated yield. [b] A mixture of unknown nonpolar compounds. [c] 4 equiv. of the Lewis acid was used. [d] 1 equiv. of the Lewis acid was used.

Conclusions

In conclusion, we have outlined a potentially versatile steroid construction strategy based on the synthesis of a chiral synthon having defined configurations at C8 and C9 of the steroid B ring. The synthetic utility was validated with the synthesis of (–)-estrone in 12 steps starting from commercially available tetralone. It is fair to admit that the presented synthesis is longer than those starting from tetralone, such as the classical Torgov's approach (6[22] steps) or the recently reported enantioselective approaches based on the use of Dane's diene[23] in a Diels–Alder reaction (five[1g,1i] or seven[1e] steps) or hydrometalation reactions (nine[1f] steps). The number of steps in this procedure is comparable to that of the recently reported 11-step procedure based on a conjugate addition/allylation sequence.[1h] However, the crucial difference in comparison with the above-mentioned syntheses is that they all initially introduced chirality on the D ring (positions 13 and 14), whereas our approach relies on the introduction of chirality on the B ring (positions 8 and 9). In this respect, it was shown that conjugate addition to trisubstituted α,β-unsaturated aldehyde led to the desired chiral intermediate with high enantioselectivity by using the recyclable chiral auxiliary. We think that this methodology could be useful for the synthesis of a wide range of natural and unnatural steroids as well as their analogues. Further work regarding this goal is in progress.

Experimental Section

Synthesis of (1*R*,2*R*)-1-Formyl-6-methoxy-3,4-dihydro-2-vinylnaphthalene (3a) as a Representative Procedure for Stoichiometric Conjugate Additions: L-*tert*-Leucine *tert*-butyl ester (5.67 mmol, 1.06 g) was added to a solution of **2a** (5.32 mmol, 1 g) in hexane (15 mL) at 20 °C. To this solution was added 3 Å molecular sieves (1 g), 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 by cannula to another flask and the volatiles were removed under reduced pressure to yield a crude aldimine that was used for the next step without further purification. Vinylmagnesium bromide (1 M in THF, 17 mmol, 17 mL) 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 warm up to –20 °C and kept at this temperature for 3 h. the solution was then diluted with HCl (1%, 100 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic fractions were dried with anhydrous $MgSO_4$, the volatiles were removed under reduced pressure, and column chromatography of the residue on silica gel (CH_2Cl_2/hexane, 1:1) yielded the title compound (0.7 g, 61%, >98% *ee*) as a mixture of *trans*/*cis* isomers in a 8:1 ratio. Enantiomeric ratios were determined by GC (HP-Chiral β column, 30 m × 0.25 mm, oven: 70 °C for 0 min, then 0.5 °C/min to 170 °C): $t_{(1S2S)}$ = 176.0 min, $t_{(1R2R)}$ =

176.6 min. Recrystallization (MeOH) yielded the pure *trans* isomer (0.55 g) as a white crystal. Data for the *trans* isomer: M.p. 46–47 °C. $[\alpha]_D$ = –9 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.75 (m, 1 H, C*H*H), 1.94–2.04 (m, 1 H, CH*H*), 2.78–2.88 (m, 3 H, ArCH_2 + CH_2=CHC*H*), 3.44 (dd, *J* = 7.6, 3.2 Hz, 1 H, ArC*H*), 3.79 (s, 3 H, OCH_3), 5.05–5.10 (m, 1 H, CH=CH_2), 5.08–5.14 (m, 1 H, CH=CH_2), 5.84 (ddd, *J* = 17.6, 10.6, 7.4 Hz, 1 H, C*H*=CH_2), 6.68–6.74 (m, 1 H, Ar-*H*), 6.75–6.80 (m, 1 H, Ar-*H*), 6.98–7.02 (m, 1 H, Ar-*H*), 9.47 (d, *J* = 3.2 Hz, 1 H, C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.64 (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) ppm. IR (KBr): $\tilde{\nu}$ = 3082, 3008, 2962, 2939, 2859, 2804, 2714, 1719, 1642, 1607, 1499, 1257, 1004, 919, 839, 919 cm^{-1}. 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. $C_{14}H_{16}O_2$: calcd. C 77.74, H 7.47, found C 74.84, H 7.19, these values correspond to $2C_{14}H_{16}O_2$ + MeOH. R_f (CH_2Cl_2/hexane, 1:1) = 0.4.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data.

Acknowledgments

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