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# Studies Towards a Total Synthesis of the Antiprogestine Onapristone

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Dedicated to Professor E. Winterfeldt on the occasion of his 65th birthday

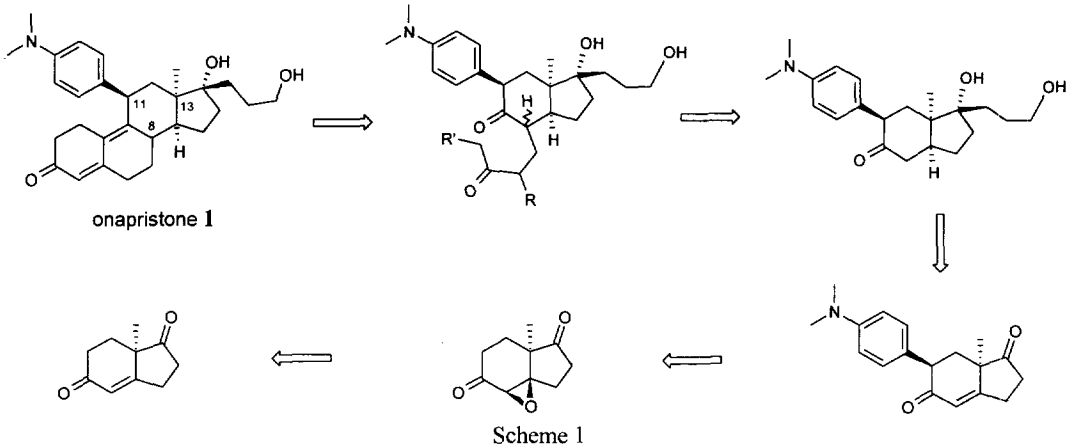
***Abstract:*** *Starting from the readily available Eder-Hajosh ketone* **2** *a stereoselective method for synthesis of arylated hydrindenone* **14** *was developed. One pot Li/$NH_3$ reduction and trapping of the generated enolate with activated Michael acceptor gave a properly substituted BCD-ring precursor* **22**. *Attempted B ring closure with the model compound* **22** *failed under various conditions*.


Onapristone **1** is a highly potent antiprogestin with low antiglucocorticoid activity, which can be potentially used for the treatment of hormone-dependent breast cancer[1]. The most prominent structural features of **1** are the 11-aryl substituent and the inverted (unnatural) configuration of the quaternary C-13. Onapristone was prepared according to a semisynthetic protocol, developed by Neef[2] and based on the general method of Teutsch[3] for synthesis of 11-arylated 19-norsteroids. Because of the small structural similarity to the natural steroids eleven chemical steps are necessary to obtain the structural features of onapristone starting with estradiol methyl ether. The efficiency of the synthesis is additionally limited by the low yield and stereoselectivity of the key transformation - introduction of the 11-aryl substituent and photochemical inversion of the C-13 chiral centre.

Contrary to the semisynthetic route, a total synthesis of onapristone could lead to a shorter and more cost-effective manufacturing process if an efficient assembly of the five chiral centres, concentrated in the CD-unit could be accomplished in a short way. Here we would like to present our first results towards this synthetic strategy.

According to the retrosynthetic analysis (Scheme 1) we contemplated combining the very efficient Roche-Schering route for synthesis of 19-norsteroids with the Marino-Wender umpolung protocol for α'-arylation of enones[4,5]. Starting with Eder-Hajosh diketone **2**#, which is readily available in both enantiomerically pure forms[6], the key steps of our approach include: introduction of the 11-aryl substituent (steroid numbering), introduction of the steroid side chain, reduction to *cis*-hydrindane, coupling with the AB unit precursor and AB rings closure by stereoconvergent Robinson annulation. The single stereogenic centre of **2** is expected to control the construction of the remaining four stereogenic centres, all concentrated in the hydrindane moiety.

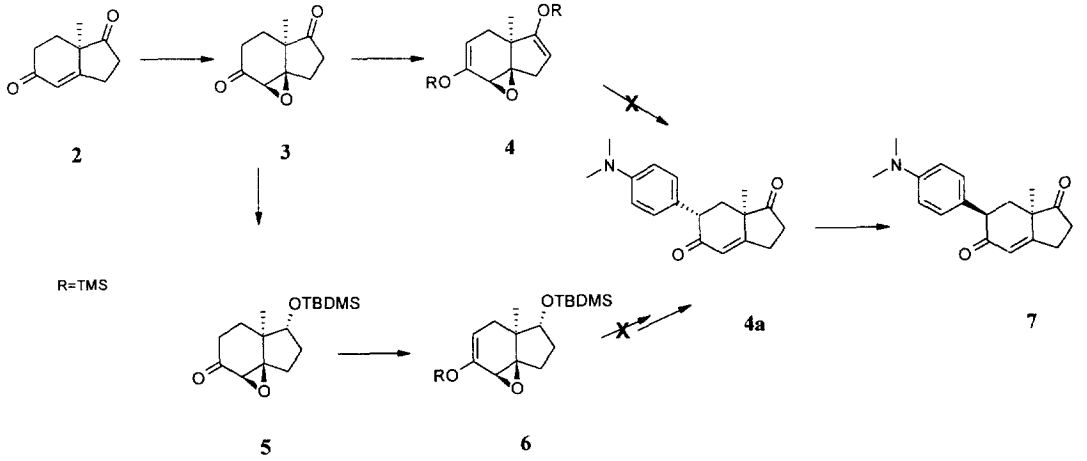
# *All compounds decribed in this article are racemic. In the schemes a single enantiomer is shown for simplicity.*




Scheme 1

The stereochemically most crucial step in this concept is the annulation of the A/B rings. Both, C-8 and C-11 chiral centres (steroid numbering) are adjacent to a ketofunction and should equilibrate under basic or acidic conditions. Based on Dreiding model considerations the most sterically favoured reactive conformation of the ring-closing aldol reaction should fix to the desired C-11 and C-8 configurations.

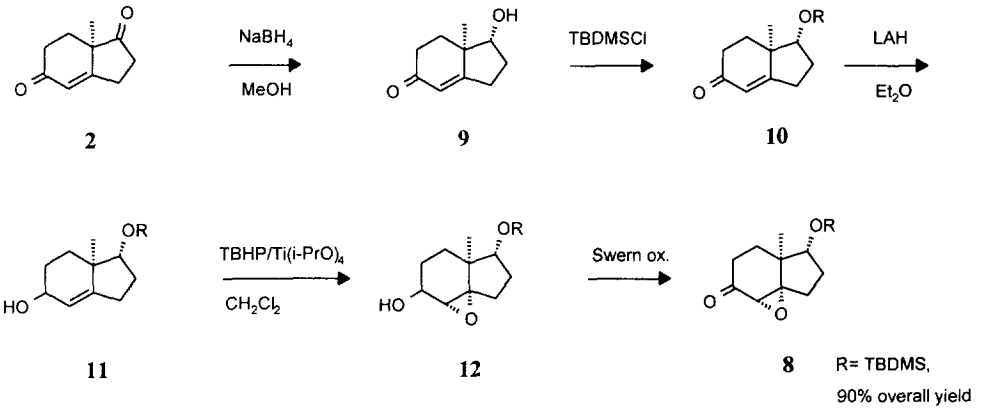
The starting ketone **2** was easily converted to the crystalline epoxide **3**[7]. Enolization of **3** and subsequent treatment of bis-silyl enol ether **4** with an aryl cuprate[5] should give the desired C-6 substituted intermediate **4a** in a short way. It is worth noting that from mechanistic considerations[5] the $S_N2'$ opening of the enol epoxyde **4** will result in the formation of *cis* arylated product with a "wrong" stereochemistry at C-11 (steroid numbering). Nevertheless, one can expect that the compound **4a** should be easily equilibrated to the more stable *trans* product **7**.




Scheme 2

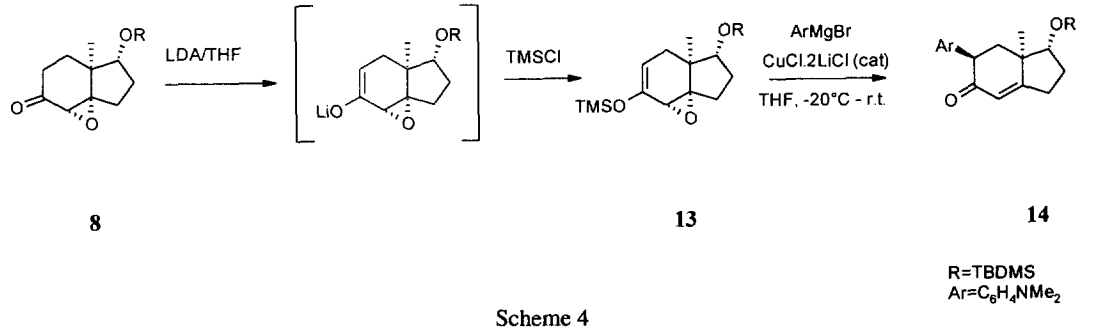
Our first attempts to prepare the bis-silyl enol ether **4** failed. After treatment of **3** with LDA (2.2 equiv), a precipitate was formed, most probably from the corresponding di-Li-salt, which was inert in the further reactions. All our efforts to avoid this problem including Corey's procedure[8] were unsatisfactory. In order to

prevent formation of the insoluble di-Li salt, the keto group in the five-membered ring of **3** was reduced and further protected to yield the epoxy-ketone **5**. Treatment of **5** with a mixture of LDA/TMSCl at -78°C brought a clear solution of the corresponding bis-silyl ether **6** which was used directly in the next step. However, when the latter was exposed to various aryl cuprates (LiArCuBr, LiArCuCN, MgArCuCN, Ar= p-$(Me)_2NC_6H_4$) only the starting material was recovered after acidic work up. It is reasonable to assume that the lack of reaction is rooted in the stereochemistry of the starting epoxide. Most probably, the stereoelectronically required α-attack of the aryl group is sterically hindered by the angular methyl group. Interestingly, this effect was previously not observed in related steroid systems[2]. In order to overcome this problem, we decided to prepare the isomeric *cis* epoxide **8**. The opposite configuration of the oxirane should allow attack from the sterically less hindered face of the molecule. The synthesis of **8** was accomplished according to Scheme 3.




Scheme 3

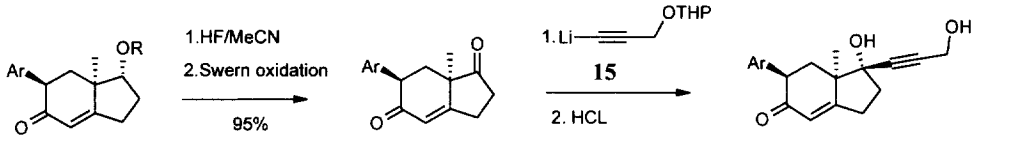
Chemoselective reduction of dienone **2** gave the ketoalcohol **9**[7] which was protected as a TBDMS ether **10** and further reduced to the allylic alcohol **11**. Subsequent epoxidation[9] followed by Swern oxidation[10] resulted in a 90% total yield of the target compound **8**. With the epoxide **8** in hand we undertook a study of its arylation. According to Scheme 4, **8** was converted to silyl enol ether **13** which could be either isolated and purified, or directly used in the next step. The crude TMS enol ether **13** was treated with different organometalic reagents. The best results - an 86% yield of the desired C-6 arylated compound **14** - were obtained with ArMgBr (Ar= p-$(Me)_2NC_6H_4$) and catalytic amount of CuCl.2LiCl. Gilmann or higher order cuprates gave less satisfactory results. The stereochemistry of **14** was confirmed by NOE experiments.




Scheme 4

Thus, our first goal, the stereoselective introduction of the aryl substituent was accomplished with an overall 72% yield, based on the starting material.

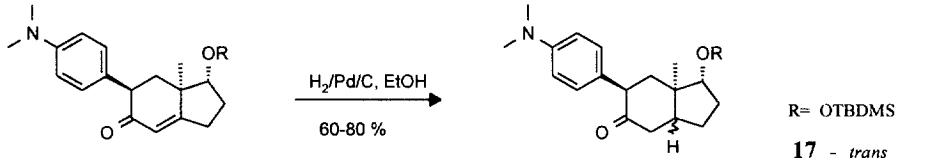
The next target in our synthetic strategy was the introduction of the side chain which was performed according to Scheme 5. Compound **14** was deprotected with HF/MeCN and oxidized to diketone **7** in a 95% yield. Chemo- and stereoselective propargylation of **7** with the lithiathed propargyl ether **15** (0°C, 30 min) yielded, after removal of the THP group, the diol **16** as a single isomer in a 92% yield. In this manner three asymmetric centres with desired stereochemistry were built up in nine steps in a 62% overall yield.




**14** **7** **16** R=TBDMS Ar=$C_6H_4NMe_2$

Scheme 5

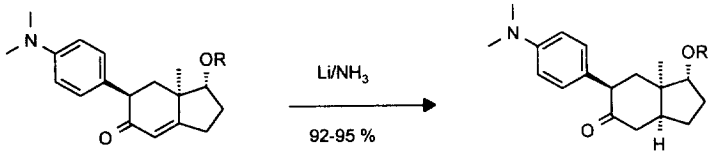
Before continuing the synthesis, we focused our attention on the reduction of the double bond in enone **14**. First we tried catalytic hydrogenation, but the result was disappointing. Exposure of the mixture of **14** and Pd/C (10 mol %) in EtOH to hydrogen at atmospheric pressure resulted in the formation of *cis* and *trans* isomers **17** and **18** in a 1:1 ratio in 82% yield (Scheme 6).




**14**

Scheme 6

In contrast, the reduction of **14** under Birch conditions was highly stereoselective giving only the target *cis* hydrindane **18** in a 98% yield (Scheme 7). The stereochemistry of **18** was confirmed by NOESY experiments.

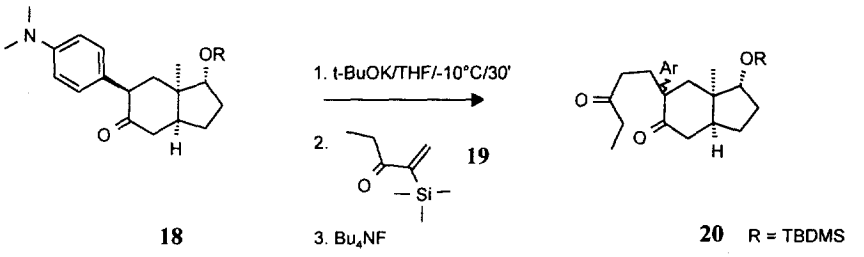



**14** **18**

R= OTBDMS

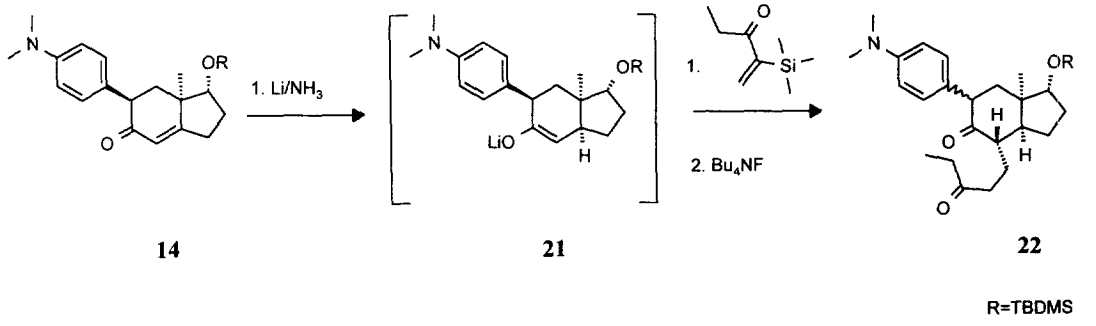
Scheme 7

Having shown that introduction of the side chain as well as reduction to a *cis* hydrindane are highly effective and stereoselective reactions, we turned our attention to the introduction of the AB unit. Following the retrosynthetic scheme, the shortest way for achieving this should be the Robinson annulation. To test the concept we selected a model reaction between ketone **18** and enone **19**. The last one is known to be a very efficient Michael acceptor for non activated donors[11]. Treatment of **18** with vinyl ketone **19** and t-BuOK at -10°C for 30 min furnished after desilylation ($Bu_4NF$) the alkylated product **20** in an 80% yield.




Scheme 8

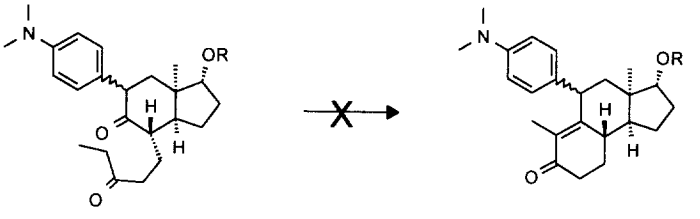
The exclusive C-6 alkylation is most probably due to the higher acidity of the centre bearing the aryl substituent. To avoid this problem we used the regioselective generation of the desired C-4 enolate under the Birch reduction conditions. The enone **14** was allowed to react with Li in liquid ammonia and aniline as a proton donor. The resulting enolate **21** was quenched with **19** to give after desilylation ($Bu_4NF$) the desired C-4 alkylated product **22** as mixture of two diastereomers in a 62% yield. In this way reduction and introduction of the B unit were performed as a one pot reaction and the second and third goal of our investigation was met with a 32% overall yield starting from **2**.




Scheme 9

The last phase of the synthesis plan, required annulation of the B ring. Unfortunately most starting material was recovered when **22** (a mixture of diastereomers) was treated with NaOH (10%) in boiling methanol. Similar results were obtained using other bases such as MeONa or t-BuOK (catalytic or stochiometric amounts) in

MeOH or toluene (rt or reflux). Attempts to achieve cyclization using p-TsOH in toluene at reflux or with pyperidine in acetic acid were also unsuccessful.



**22**

Scheme 10

Our inability to effect B-ring annulation under a variety of basic or acidic conditions was contrary to the general efficacy of this process. Both *trans*[12]- and *cis*-fused[13] C-6 unsubstituted hyndrindanes are known to easily undergo ring closure reactions. Obviously, the problem rises from the presence of the aryl group. Increased acidity of C-6 as well as sterical repulsion in the transition state of the aldol reaction could be the reason for the lack of reactivity.

In summary a highly efficient approach to C-6 substituted *cis*-fused hydrindanes was developed. Additionally, the general possibility for stereoselective introduction of the steroid side chain and an AB ring precursor were proved.

## EXPERIMENTAL

All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was oven-dried (200°C). Tetrahydrofuran was distilled from sodium benzophenone ketyl, DMF from calcium hydride. Flash column chromatography was performed on Merck silica gel (grade 60, 230-400 mesh); TLC were performed on Merck Alufolien 60 F 254. Infrared (IR) spectra were recorded on a Nicolet 20 SBX spectrophotometer. Mass spectral analyses were recorded on a Vacuum Generator TRIO2. $^1H$ (300 MHz) and $^{13}C$ (75 MHz) NMR spectra were recorded on a General Electric QE 300 in $CDCl_3$ using TMS or the solvent as internal standard. $^{13}C$ DEPT: $CH_3$/CH (+), $CH_2$ (-), C (*), J in Hz.

**(3aR*,4R*,7aR*)-3a,4-Epoxy-7a-methylperhydroindene-1,5-dione (3).** Hydrogen peroxide (30%, 3.26 ml, 28.8 mmol) was added dropwise to a solution of **2**[6] (4g, 24 mmol) and NaOH (10%, 1ml) in MeOH (50 ml) at 0°C. The reaction was monitored by TLC. At the end of the reaction the mixture was neutralized with 10% HCl. The mixture was diluted with water (50 ml) and extracted with diethyl ether (3 X 10 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product (4.1 g, 95%) was purified by recrystallization (hexane:ethyl acetate-5:1) to give **3** (3.8 g, 90%), mp 75.8°C. The spectral dates are identical with ref. 7.

**(1R*,3aR*,4R*,7aS*)-1-[(tert-Butyldimethylsilyl)oxy]-3a,4-epoxy-7a-methylperhydroinden-5-one (5).** To a solution of **3** (5.75 g, 32 mmol) in methanol (100 ml) $NaBH_4$ (0.31 g, 8 mmol) was added in small portions with stirring at -30°C. At the end of the reaction (TLC monitoring) the mixture was neutralized with 10% HCl

and diluted with diethyl ether (30 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product (5.6 g) was separated by chromatography (silica gel - 60 g, hexane:diethyl ether 10:1) and the corresponding alcohol was isolated as a second fraction (1.10 g, oil, 20%), IR($CHCl_3$): 3520, 2980, 2960, 1710, 1180, 1020 $cm^{-1}$; $^1H$ NMR: 4.20 (1H, t, J=9.0 ), 3. 42 (1H, s), 2.5-1.5 (8H, m), 1.00 (3H, s); $^{13}C$ NMR: 206.2 (s, C=O), 88.0 (d, C-1), 74.2 (s, C-7), 58.8 (d, C-6), 42.3 (s, C-7a), 32.1, 28.5, 26.0, 24.4 (each t), 12.5 (s, $CH_3$); MS-CI: 200 (100, $M^+ + 1 + NH_3$); 183 (50, $M^+ + 1$), 167 (20). To the solution of crude alcohol in DMF (30 ml) triethylamine (2 ml, 18 mmol), N-ethyldiisopropylamine (2 ml, 13 mmol) and TBDMSCl (2 g, 13 mmol) were added and the mixture was stirred for a 12 hs. The reaction mixture was diluted with water (30 ml) and extracted with toluene (3 X 30 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was filtered trough silica gel ( 50 g) to yield:

**5,** (1.18, 92%), oil, IR($CHCl_3$) 2980, 2960, 1710, 1180, 1020 $cm^{-1}$; $^1H$ NMR: 4.10 (1H, t, J=9.0 ), 3. 42 (1H, s), 2.5-1.5 (8H, m), 0.98 (3H, s), 0.85 (9H, s), 0.02 (6H, s); $^{13}C$ NMR: 206.2 (s, C=O), 86.0 (d, C-1), 74.9 (s, C-7), 57.8 (d, C-6), 42.0 (s, C-7a), 33.1, 28.0, 26.0, 22.4 (each t), 17.5 (s, t-Bu), 12.8 (s, $CH_3$), 5.2 (q, Si-*$CH_3$*); MS-CI: 314 ($M^+ + 1 + NH_3$); MS-EI: 296 (6), 267 (58), 239 (70), 129 (55).

**(1R*,7aR*)-1-Hydroxy-7a-methyl-7,7a-dihydroindan-5(6H)-one (9).** To a solution of **2** (4 g, 24 mmol) in methanol (100 ml) $NaBH_4$ (0.2 g, 6 mmol) was added in small portions and stirred at -5°C. At the end of the reaction (TLC monitoring) the mixture was neutralized with 10% HCl and diluted with diethyl ether (30 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was purified by recrystallization (hexane:ethyl acetate-5:1) to give: **9** (4.0 g, 99%), mp 65°C. The spectral dates are identical with ref. 7.

**(1R*,7aR*)-1-[(tert-Butyldimethylsilyl)oxy]-7a-methyl-7,7a-dihydroindan-5(6H)-one (10).**

To a solution of **9** (3 g, 18 mmol) in DMF (60 ml) triethylamine (4.3 ml, 29 mmol), N-ethyl-diisopropylamine (4.5 ml, 27 mmol) and TBDMSCl (4.1 g, 27 mmol) were added and the mixture was stirred for a 12 hours. The reaction mixture was diluted with water (60 ml) and extracted with toluene (3 X 100 ml).The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was filtered trough silica gel (silica gel - 50 g, diethyl ether : hexane 1:5) to give:

**10**, (5.0 g, 98%), Oil, IR(film): 2950, 1660, 1620, 1110 $cm^{-1}$; $^1H$ NMR: 5.70 (1H, brs), 3.65 (1H, dd, J= 8, 14), 1.10 (3H, s), 0.85 (9H, s), 0.03 (3H, s), 0.02 (3H. s); $^{13}C$ NMR: 198.6 (s, C=O), 174.4 (s, C-3a), 122.9 (d, C-4), 80.5 (d, C-1), 45.2 (s, C-7a), 34.2, 33.1, 29.1, 26.1 (t, C2, C-3, C-6, C-7), 25.2 (q, t-Bu ), 17.5 (s, t-Bu), 14.7 (q, C-*$CH_3$* ), -6.00 (q, Si-*$CH_3$*); MS-CI: 298 ($M^+ + 1 + NH_3$); MS-EI: 280 ($M^+$, 25), 265 (25), 237 (70), 223 (100), 131 (25).

**(1R*,7aR*)-1-[(tert-Butyldimethylsilyl)oxy]-7a-methyl-5,6,7,7a-tetrahydroindan-5-ol (11).** The ketone **10** (4 g, 14 mmol) was reduced with $LiAlH_4$ in ether (100 ml) to give after work up:

**11**, (4g, 99%), Oil, IR(film): 3560, 2950, 1650, 1150, 1080 $cm^{-1}$; $^1H$ NMR: 5.25 (1H, brs), 4.15 (1H, brs), 3.45 (1H, dd, J= 7.0, 14.0), 0.90 (3H, s), 0.85 (9H, s), 0.03 (3H, s), 0.02 (3H. s); $^{13}C$ NMR: 148.3 (s, C-3a), 122.3 (d, C-4), 81.0 (d, C-1), 68.1 (d, C-5), 43.6 (s, C-3), 33.9, 29.1, 25.2 (t, C2, C-6, C-7), 25.5 (q, t-Bu), 17.5 (s, t-Bu), 16.4 (q, C-*$CH_3$* ), -5.3 (q, Si-*$CH_3$*); MS:CI: 283 ($M^+ + 1$).

**(1R*,3aS*,4R*,7aS*)-1-[(tert-Butyldimethylsilyl)oxy]-3a,4-epoxy-7a-methylperhydroinden-5-ol (12).** To a stirred solution of **11** (3 g, 11 mmol) in dichloromethane (60 ml), $Ti(i\text{-}PrO)_4$ (4.25 ml, 12.8 mmol) and (at the same time) *t*-butylhydroperoxide (4.25 ml 3M in toluene) were added dropwise over period of 30 min. The reaction mixture was diluted with water (60 ml) and extracted with dichloromethane (3 X 60 ml). The organic

layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (silica gel - 50 g, diethyl ether : hexane 1:5) to afford:

**12**, (3 g, 98%), Oil, IR(film): 3500, 3010, 2950,2890, 1160, 1080, 1010 $cm^{-1}$; $^1H$ NMR: 3.92 (1H, dd, J= 6.0, 11.2), 3.72 (1H, t, J=7.5), 3.13 (1H, s), 1.90-1.00 (9H, m), 0.92 (3H, s), 0.85 (9H, s), 0.03 (3H, s), 0.02 (3H. s); $^{13}C$ NMR: 80.9 (d, C-1), 70.6 (s, C-3a), 69.0 (d, C-4), 63.0 (d, C-5), 40.1 (s, C-7a), 39.9, 29.5, 26.8, 24.5 ( t, C-2, C-3, C-6, C-7), 25.5 (q, t-Bu), 17.6 (s, t-Bu), 13.7 (q, C-*CH*$_3$), 5.0 (q, Si-*CH*$_3$); MS-CI: 299 ($M^+$ + 1); MS-EI: 298 ($M^+$, 5), 265 (6), 223 (100), 131 (25), 75 (65).

**(1R*,3aS*,4S*,7aS*)-1-[(tert-Butyldimethylsilyl)oxy]-3a,4-epoxy-7a-methylperhydroinden-5-one (8).** To a cooled (-50°C) solution of oxalyl chloride (0.74 ml, 8.8 mmol) in dichloromethane (25 ml) a solution of DMSO (1.35 ml, 17.7 mmol) in dichloromethane (5 ml) was added dropwise. After 10 min a solution of **12** (2.2g, 7.4 mmol) in dichloromethane (10 ml) was added. After 15 min triethylamine (7 ml) was added and the mixture was stirred for additional 15 min. The reaction mixture was diluted with water (60 ml) and extracted with dichloromethane (3 X 50 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (silica gel - 50 g, diethyl ether : hexane 1:10) to give;

**8**, (2.1 g, 94%), mp 71.6°C (Hexane), IR(KBr): 3010, 2850,1700, 1180, 1010, $cm^{-1}$; $^1H$ NMR: 3.87 (1H, t, J=8.5), 3.01 (1H, s), 2.65 (1H, td, J=4, 14), 2.00-1.50 (8H, m), 1.10 (3H, s), 0.85 (9H, s), 0.02 (3H, s) 0.01 (3H, s); $^{13}C$ NMR: 209.0 (s, C=O), 80.0 (d, C-1), 75.7 (s, C-3a), 61.3 (d, C-4), 41.0 (s, C-7a), 37.6, 31.9, 26.6 (t, C-2, C-3, C-6, C-7), 25.5 (q, t-Bu.), 17.8 (s, t-Bu), 13.9 (q, C-*CH*$_3$), -5.0 (q, Si-*CH*$_3$); MS-CI: 314 ($M^+$ + 1+ $NH_3$); MS-EI: 296 (1), 267 (38), 239 (70), 221 (40), 197 (45) 129 (55) 119 (100).

**(1R*,6R*,7aR*)-1-[(tert-Butyldimethylsilyl)oxy]-6-[4-(dimethylamino)phenyl]-7a-methyl-7,7a-dihydroindan-5(6H)-one (14).**

To a solution of LDA (9.5 mmol) in THF (20 ml) a solution of ketone **8** (2g, 6.8 mmol) in THF (5 ml) was added at -78°C. After the mixture had been stirred for 1.5 h, TMSCl (1.5 ml, 10 mmol) was added, with the temperature kept below -70°C. The mixture was stirred for a further 2 h while the temperature rose to -40°C and then was partitioned between toluene (100 ml) and saturated $NaHCO_3$ (20 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated to give crude enolate **13** which was used without further purification.

To a solution of CuCl (0.100 g, 1 mmol) and LiCl (0.085 g, 2 mmol) in THF (15 ml) a solution. of ArMgBr (15 ml, 0.55 M in THF, Ar= p-$(Me)_2NC_6H_4$) was added at -10°C and the mixture was stirred for a 5 min. Then a solution of **13** in toluene (10 ml) was added and the mixture was stirred for an additional 30 min. The reaction was quenched with saturated $NH_4Cl$. The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated to give a dark oil which was dissolved in ether (30 ml) and was treated with 20% HCl (10 ml) for 30 min. The reaction mixture was neutralized with $NaHCO_3$ (pH=9). After separation the organic layer was washed with brine, dried and evaporated. The crude product was chromatographied (silica gel - 60 g, hexane : diethyl ether 5:1) to give:

**14**, (2.3 g, 86%), mp 161°C (hexane), IR(KBr): 3440, 2980, 2830, 1660, 1620, 1520, 1100 $cm^{-1}$; $^1H$ NMR: 7.00 (2H, d, J= 8.5), 6.72 (2H, d, J=8.5), 5.88 (1H, brs), 3.83 (1H, dd, J= 7.5, 10.0), 3.60 (1H, dd, J=5.0, 14.0), 2.92 (6H, s), 1.20 (3H, s), 0.87 (9H, s), 0.04 (3H, s), 0.01(3H, s); $^{13}C$ NMR: 199 (s, C=O), 173.0 (s, C-3a ), 149 (s, Ar), 128.9 (d, Ar), 128.4 (s, Ar), 123.2 (d, C-4), 112.5 (d, Ar), 80.6 (d, C-1), 48.0 (d, C-6), 46.0 (s, C-7a), 40.3 (q, N*Me*$_2$), 43.4, 29.3, 26.2 (t, C-2, C-3, C-6, C-7) 25.4 (q, t-Bu), 17.6 (s, t-Bu), 15.4 (q, C-*CH*$_3$), -4.2 (q, Si-*CH*$_3$); MS-CI: 400 ($M^+$+1); MS-EI: 399 (20), 342 (18), 224 (15), 147 (100).

**(6R*,7aR*)-6-[4-(Dimethylamino)phenyl]-7a-methyl-7,7a-dihydroindane-1,5(6H)-dione (7).** To a solution of **14** (0.4 g, 1 mmol) in acetonitrile (10 ml) HF (3 ml, 30%) was added and the mixture was stirred for 6 hs. The reaction mixture was diluted with water (60 ml) and extracted with diethyl ether (3 X 10 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was oxidized in the same manner as **12** (0.15 ml oxalyl chloride, 0.22 ml DMSO and 1.2 ml TEA) to afford:

**7**, (0.15 g), Oil, IR(film): 3010, 2850,1720, 1689, 1620, 1520, 1180, 1010 $cm^{-1}$; $^1H$ NMR: 7.00 (2H, d, J= 8.5), 6.72 (2H, d, J=0 8.5), 6.10 (1H, brs), 3.60 (1H, dd, J=5.0, 14.0), 2.92 (6H, s), 1.42 (3H, s); MS-CI: 284 ($M^+$+1)

**(1S*,6R*,7aR*)-6-[4-(Dimethylamino)phenyl]-1-hydroxy-7a-methyl-1-(3-hydroxypropynyl)-7,7a-dihydro indan-5(6H)-one (16).** To a solution of **15** (prepared from 1-proryn-3-OTHP 0.2 g and BuLi 0.9 ml 1.6 M) in THF (5 ml) a solution of 7 (0.2 g, 0.7 mmol) in THF (2 ml) was added at -10°C. After 30 min the reaction was quenched with $NH_4Cl$ . The reaction mixture was extracted with diethyl ether (3 X 10 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude product was dissolved in MeOH and 0.1 ml HCl (10%) was added. The solution was stirred for 2 h and after work up the crude product was filtered trough silica gel (20 g) to give:

**16**, (0.16 g), Oil, IR(film): 3010, 2850, 1689, 1620, 1520, 1180, 1010 $cm^{-1}$; $^1H$ NMR: 7.10 (2H, d, J= 8.5), 6.82 (2H, d, J=0 8.5), 5.92 (1H, brs), 4.28 (2H, s), 3.62 (1H, dd, J=5.0, 14.0), 2.92 (6H, s), 1.35 (3H, s); MS-CI 340 ($M^+$+1)

**(1R*,6R*,7aR*)-1-[(tert-Butyldimethylsilyl)oxy]-6-[4-(dimethylamino)phenyl]-7a-methylperhydroinden-5-one (18).** To a solution of lithium (0.009 g, 0.57 mmol) in liquid ammonia (15 ml) a solution of **14** (0.1 g, 0.25 mmol) and *t*-BuOH (0.02 g) in THF (5 ml) was added and the mixture was stirred for 20 min at -70°C. The excess of lithium was destroyed by isoprene. Removal of the ammonia gave a crude product which was purified by crystallization (hexane : ethylacetate: 5:1) to yield:

**18**, (0.1 g, 95%) mp 124.3°C (Hexane); IR(film): 3010, 2850, 1700, 1520, 1180, 1010 $cm^{-1}$; $^1H$ NMR: 7.10 (2H, d, J= 8.5), 6.82 (2H, d, J=0 8.5), 3.80 (H, dd, J= 3.5, 7), 3.63 (1H, dd, J=5.0, 14.0), 2.95 (6H, s), 1.32 (3H, s) 0.87 (9H, s), 0.04 (3H, s), 0.01(3H, s); MS-EI: 401 ($M^+$, 100), 373 (20), 344 (18), 242 (22), 134 (18).

**Synthesis of 20**. To a solution of *t*-BuOK (0.03 g, 0.27 mmol) in THF (5 ml) a solution of **18** (0.1 g, 0.25 mmol) in THF (1 ml) was added at -10 °C the mixture was stirred for 5 min. Then a solution of **19** (0.12 g, 0.3 mmol) was added and stirred for an additional 30 min at same temperature. The reaction mixture was diluted with 10 % solution of $NH_4Cl$ (5 ml) and extracted with diethyl ether (3 X 5 ml).The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude mixture was treated with $Bu_4NF$ and separated on a silica gel (silica gel -30 g, hexane: diethyl ether-2:1) to give:

**20**, Oil (0.095 g, 80%), IR(film): 3010, 2850, 1710, 1690, 1510, 1080, 1010 $cm^{-1}$; $^1H$ NMR: 6.98 (2H, d, J= 8.5), 6.70 (2H, d, J=0 8.5), 3.88 (H, dd, J= 3.5, 5), 2.95 (6H, s), 0.98 (3H, t, J=7.0), 0.87 (9H, s),0.72 (3H, s), 0.04 (3H, s), 0.01(3H, s); MS-CI: 486 ($M^+$+1)

**Synthesis of 22.**[**] To a solution of lithium (0.009 g, 0.57 mmol) in liquid ammonia (15 ml) a solution of **14** (0.1g, 0.25mmol) and aniline (0.026g) in THF (5ml) was added and the mixture was stirred for 15 min at -70°C. The excess of lithium was destroyed by isoprene. Removal of the ammonia finally under oil pump vacuum at 30°C for a *ca.* 10 min, gave a residual white solid. The solid was dissolved in THF at r.t, cooled to -30°C and treated with **19** (0.12 g, 0.3 mmol mmol). The mixture was stirred for additional 20 min and allowed to warm up

[**] *It has to be mentioned that this procedure was tricky and any deviation from the described procedure led to a significantly lower yield.*

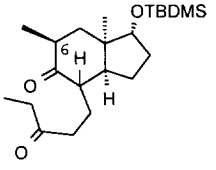
to 10°C. The reaction mixture was extracted with diethyl ether (3 X 10 ml). The organic layer was washed with brine, dried with $Na_2SO_4$ and the solvent was evaporated. The crude mixture was treated with $Bu_4NF$ and then separated on a silica gel to give:

**22a**, Oil (0.054 g, 41%), , IR(film): 3010, 2850, 1710, 1700, 1520, 1180, 1010 $cm^{-1}$; $^1H$ NMR: 7.08 (2H, d, J= 8.5), 6.72 (2H, d, J=0 8.5), 3.78 (H, dd, J= 3.5, 7), 3.41 (1H, dd, J=6.0, 14.0), 2.95 (6H, s), 1.08 (3H, t, J=7.0) 1.05 (3H, s), 0.87 (9H, s), 0.04 (3H, s), 0.01(3H, s); MS-CI: 486 ($M^+$+1)

**22b**, Oil, (0.028 g, 21%), $^1H$ NMR: 6.98 (2H, d, J= 8.5), 6.79 (2H, d, J=0 8.5), 3.72 (H, dd, J= 3.5, 7), 3.62 (1H, dd, J=6.0, 14.0), 2.95 (6H, s), 1.25 (3H, s) 1.04 (3H, t, J=7.0), 0.87 (9H, s), 0.04 (3H, s), 0.01(3H, s); MS-CI: 486 ($M^+$+1)

## REFERENCES AND NOTES


1. G. Neef, S. Beier, W. Efger, D. Handerson, R. Wiechert, *Steroids*, **1984**, 349.
2. G. Neef, G. Sauer, A. Seeger, R. Wiechert; *Tetrahedron Lett.*, **1984**, 25, 3425
3. A. Belanger, D. Philibert, G. Teutsch, *Steroids*, **1981**, 361.
4. J. Marino, N. Hatanaka, *J. Org. Chem,* **1979**, *44*, 4467. J. Marino, J. C. Jaen, *J.Am.Chem.Soc.* **1982**, *104*, 3165.
5. P. Wender, J. Erhardt, L. Letendre, *J.Am.Chem.Soc.,* **1981**, *103*, 2114.
6. a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492.; b)G. Hajos, D. Parrish, *J. Org. Chem.*, **1974**, *39*, 1615.; c) G. Hajos, R. Parrish, *Org. Synth.*, **1984**, 26.
7. B. Trost and T. Salzmann, *J. C. S. Chem. Commun.*, **1975,** 571.
8. E. Corey and A. Gross, *Tetrahedron Lett.*, **1984**, *25*, 495.
9. K. Sharpless, R. Michaelson, *J. Am. Chem. Soc.*, **1973**, *95*, 6136.
10. S. Huang, D. Swern, *J. Org. Chem.*, **1978**, *43*, 2482.
11. G. Stork, J. Singh, *J.Am.Chem.Soc.* **1974**, *96*, 6181.
12. F. Zigler, T. Wang, *ibid.*, **1984**, *106*, 708.
13. **23** undergoes smooth cyclization by treatment with catalytic amount of NaOH in boiling methanol: V. Enev, O. Petrov, unpublished results.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