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ZINC(II)-CHLORIDE INDUCED THIOALKYLATION OF ALUMINIUM ENOLATES; ENANTIOSELECTIVE SYNTHESIS OF ESTRADIOL-3-METHYL-17-*tert*-BUTYL DIETHER

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Abstract - Zinc(II)-chloride induced thioalkylation of the aluminium enolate **6** generated by conjugate reduction of the enone **5** leads - directly or via its trimethylsilylenol ether **6** - to alkylated hydrindanones **10** which are important intermediates in the synthesis of 19-norsteroids such as the title compound estradiol-3-methyl-17-*tert*-butyl diether **12**

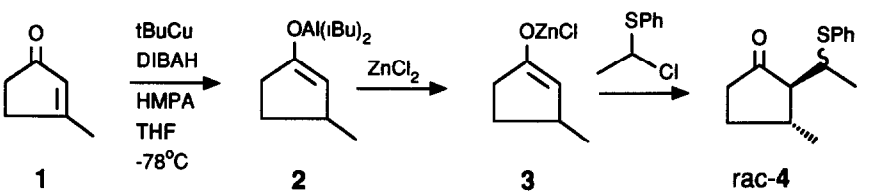
I. Introduction

19-Norsteroids such as estrone are attractive target molecules in organic synthesis because of their biological activity and pharmaceutical importance [1] In this communication a total synthesis of enantiomerically pure estradiol-3-methyl-17-*tert*-butyl diether **12** - a precursor of (+)-estrone - is described This synthesis follows the CD -> ACD -> ABCD approach Establishing the desired *trans* fusion of rings C and D and alkylation of the aluminium enolate **6** to incorporate the missing part of the seco-steroidal skeleton are the two main aims of this synthesis Recently Daniewski and Kiegiel reported[2] about the diastereoselective conjugate reduction[3] of the enone **5** using a *tert*-butylcopper(I) / HMPA / DIBAH / reagent which afforded the saturated *trans*-aluminium enolate **6** This enolate reacts in moderate yields only with very reactive electrophiles such as aldehydes, acyl chlorides or allyl bromides [4] In the present studies alkylation of the aluminium enolate **6** and its corresponding silylenol ether[5] **7** is performed using the thioalkylation method α-Thiophenylcarbenium-ions formed from

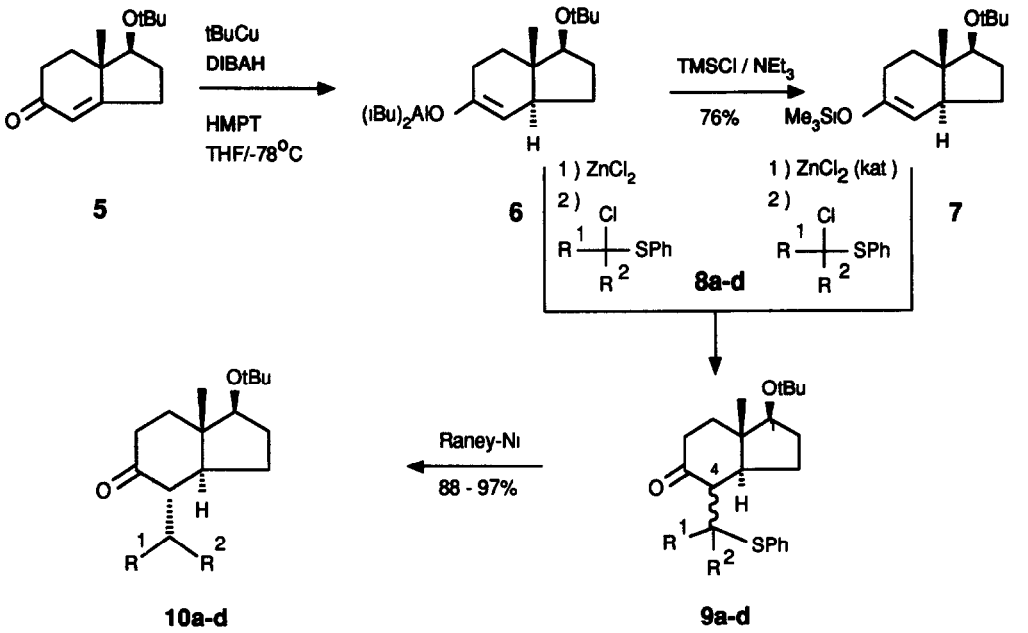
α-chloro-α-thiophenylalkanes with Lewis acids are very strong electrophiles and able to thioalkylate various enolates[6] and silylenol ethers [7]

II. Results and Discussion

The zinc enolate **3** was generated by the ^{t}BuCu(I) / HMPA / DIBAH - catalyzed conjugate reduction of 3-methyl-2-cyclopenten-1-one (**1**) and consecutive transmetallation with 2 equivalents zinc chloride Thioalkylation of the zinc enolate **3** afforded in 67% yield an 80 20 mixture of rac-**4** and the corresponding racemic *cis* isomer In view of this result the thioalkylation of the zinc enolate from enone **5** formed by transmetallation of the aluminium enolate **6** with 2 equivalents of zinc chloride was investigated



The conjugate reduction of the enone **5** to the aluminium enolate **6** was performed by DIBAH in the presence of one equivalent *tert*-butylcopper and 8 equivalents of HMPA which were necessary as a ligand for the copper or aluminium in this reaction It turned out to be of importance to work under extreme exclusion of oxygen in order to achieve the desired products in respectable yields of about 80% with a diastereomeric excess of > 98% Otherwise the 1,2-reduction of the starting enone becomes the predominant reaction and the diastereoselectivity of this reaction decreases dramatically This can be explained by a rapid decomposition of the in situ generated reducing agent Allylic alcohol as the result of 1,2-reduction was also the main product when cosolvents other than HMPA were used Tetramethylethylenediamine (TMEDA), 1,3-dimethyltetrahydro-2-(1H)-pyrimidinone (DMPU),[8] tetraethylsulfamide (TES) and tripiperidinophosphine oxide (TPPO) instead of the toxic and carcinogenic HMPA were tried as cosolvents



5 **6** **7** **10a-d** **9a-d**

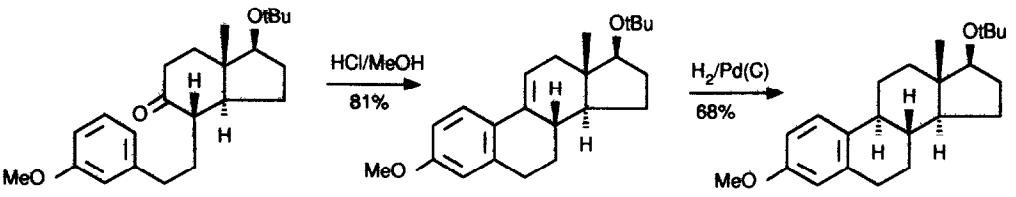
Table 1. Alkylation of the aluminium enolate **6** and the silylenol ether **7**

			yield(%)	
8-10	R^1	R^2	via **6**	via **7**
a	CH_3	H	35	71
b	CH_3	CH_3		60
c	$CH_2C_6H_5$	H		56
d	$CH_2(m\text{-}OCH_3)C_6H_4$	H	27	65

Transmetallation of the aluminium enolate **6** with 11 equivalents of zinc chloride afforded the corresponding zinc enolate, which was subsequently thioalkylated with the α-chloro-α-phenylthioalkanes **8a-d** yielding the β-phenylthioalkanes **9a-d** in 27-35% yield Due to the 11 equivalents of zinc chloride the products **9a-d** partly decomposed under these reaction conditions The large amount of zinc chloride was necessary, because the HMPA which had to be used for the conjugate reduction of the enone **5** had already formed a complex with the zinc chloride

To avoid the presence of great amounts of inorganic salts which possibly initiated the decomposition of the β-phenylthioalkanes **9a-d**, the enolate **6** was trapped as its trimethylsilylenol ether **7** Therefore trimethylsilyl chloride was added to the reaction mixture at -40°C after the conjugate reduction of **5** was completed Then the reaction mixture was allowed to warm up to room temperature After 3 hours triethylamine was added before the work-up procedure to prevent the hydrolysis of the trimethylsilylenol ether which was isolated in 76% yield with > 98% d e (determined by ^{1}H NMR and ^{13}C NMR spectroscopy on the signals of the 7a-methyl group at δ = 0 76 ppm and δ = 10 74 ppm for the *trans*-isomer and at δ = 1.02 ppm and δ = 20 71 ppm for the *cis*-isomer)

This silylenol ether could be converted with the α-chloro-α-phenylthioalkanes **8a-d** into the compounds **9a-d** mediated by catalytic amounts of zinc chloride in respectable yields from 56% to 71% (see Table 1) as 3 1 mixtures of epimers at C-4 and 1 1 mixtures at C-1' (determined by ^{13}C NMR spectroscopy on the signals for C-5, C-4 and C-1') Desulfurization and simultaneous equilibration of **9a-d** with Raney nickel in ethanol yielded the saturated ketones **10a-d** with the substituents at C-4 in equatorial position enantiomerically and diastereomerically pure



10d **11** **12**

The seco-steroidal ketone **10d** was converted into the unsaturated steroid **11** by Friedel-Crafts cyclization with dry hydrochloric acid in methanol at 0°C [9,10] Subsequent hydrogenation with palladium on charcoal in ethyl acetate at room temperature yielded the title compound **12** The optical rotations of **11** and of **12** were in agreement with the values reported by Wiechert et al [9] and Cohen et al [10] The 3,17 - protected estrone derivative **12** can be easily converted by known methodology into pharmaceutically important 19-norsteroids such as norethindrone [11]

Starting from the CD building block **5**, which was prepared enantiomerically pure in a *S*-proline catalyzed asymmetric aldol condensation according to the procedure reported by Eder, Sauer and Wiechert[12] and by Hajos and Parrish,[13] the title compound **12** was synthesized in 5 steps in an overall yield of 24% This synthesis opens a very short and efficient route towards estrone and other 19-norsteroids and uses easily available and inexpensive starting materials

EXPERIMENTAL

NMR spectra were taken on Varian VXR 200, 500 and XL 200 spectrometers IR spectra were taken on a Perkin Elmer Mod 298 spectrometer Mass spectra were recorded on Varian MAT 731 and 311 A spectrometers Optical rotations were measured on a Perkin Elmer Mod 141 polarimeter TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates Silica gel 60 (240-400 mesh) from E Merck Darmstadt was used for flash chromatography Combustion analyses were carried out by the microanalytical laboratory of the University of Gottingen All reactions were carried out under dry and oxygen-free argon CuBr SMe_2 was recrystallized from dimethyl sulfide/pentane and dried under argon All reagents and solvents were dried and purified before using THF, HMPT and the 1 2M DIBAH solution in toluene were degassed by the freeze-pumping method The starting enone **5** was prepared according to the described procedure [12,13] or afforded by the Schering AG The phenylsulfides, used for the synthesis of the α-chlorophenylsulfides **8a-d** were prepared from the corresponding mesylates or halides by S_N2-replacement with thiophenol/K_2CO_3 in acetone

Preparation of the aluminium enolates 2 and 6, general procedure: To a slurry of CuBr SMe_2 (205 mg, 1 mmol) in THF (10 ml) a *tert*-butyllithium solution (1 7M in pentane, 0 65 ml, 1 1 mmol) was added at -50°C and stirred for 15 min Hexamethylphosphoric triamide (HMPA) (716 mg, 4 mmol) was added to the solution and cooled down to -100°C A mixture of diisobutylaluminium hydride (DIBAH) (1 2M in toluene, 1 25 ml, 1 5 mmol) and HMPA (716 mg, 4 mmol) was slowly added during 10 min A solution of **1** (1 mmol, 96 mg) or **5** (1 mmol, 222 mg) in THF (1 ml) was added dropwise during 15 min The temperature was allowed to rise up to -80°C and the reaction mixture was stirred for 2h During two further hours the temperature was allowed to warm up to -40°C

Preparation of the α-chloroalkylphenylsulfides 8a-d, general procedure: To a slurry of N-chlorosuccinimide (1 47g, 11 0 mmol) in CCl_4 (20 ml) the alkylphenylsulfide (10 mmol) was added dropwise at -2 °C and the mixture was stirred for 16h at this temperature The solution was separated by filtration from succinimide, the solvent was evaporated and the crude products **8a-d** were used without further purification

***trans*-3-Methyl-2-(1'-phenylthioethyl)cyclopentanone (4):** The enolate **2** was prepared from CuBr SMe_2 (377 mg, 1 84 mmol), *tert*-butyllithium (1 7M in pentane, 1 13 ml, 1 92 mmol), HMPA (2 54 g, 14 2 mmol), DIBAH (1 2M in toluene, 8 3 ml, 10 mmol) and 3-methyl-2-cyclopenten-1-one (**1**) (0 77 g, 8 mmol) A $ZnCl_2$ solution (1 0M in ether, 25 ml, 25 mmol) was added at -40°C and stirring was continued for 30 min Finally α-chloroethylphenylsulfide (1 72 g, 10 mmol) was added dropwise and the reaction mixture was stirred for 4h at -20°C Within 8h the solution was allowed to warm up to roomtemp , extracted five times with Et_2O (50 ml each time) and the combined organic phases were washed with 1M HCl (40 ml), saturated aqueous $NaHCO_3$ (40 ml) and 3 times with H_2O (20 ml each time) The organic phase was dried over $MgSO_4$ and the solvent evaporated in vacuo Chromatography on silica gel with ether/pentane 1 4 afforded **4** (1 26 g, 5 4 mmol, 67%) as a pale yellow oil (R_f = 0 29 and 0 36) - ratio of diastereomers 4 4 1 1 - **IR (neat):** ν = 3040 (C-H/phenyl), 1730 (C=O), 1580 (C=C/phenyl), 735 and 685 cm^{-1} (C-H/monosub phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 85 - 2 50 (m, 12H,), 3 87 (dq, J = 2 5 Hz and 7 Hz, 1H, C_1'-H), 7 15 - 7 50 (m, 5H, -SC_6H_5) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 17 70 (20 62) (C_1'-CH_3), 20 71 (21 08) (C_3-CH_3), 29 43 (29 71) (C-4), 33 31 (34 45) (C-3), 38 44 (38 50) (C-5), 41 82 (43 93) (C-2), 59 98 (61 32) (C'-1), 126 63 (126 93), 128 92 (128 78) and 130 95 (131 95) (C-H/phenyl), 135 68 (135 32) (C/phenyl), 218 00 (218 31) (C-1) signals in brakets for the minor diastereomer - **MS (70 eV):** (m/z) = 55 (100%, $C_3H_3O^+$), 97 (80%, M^+ -

SC_6H_5 -C_2H_4), 125 (80%, M^+ -SC_6H_5), 234 (95%, M^+) - **HRMS (70 eV):** calculated for $C_{13}H_{18}OS$ 234 1078, found 234 1078

[1S,3aS,7aS]-1-*tert*-Butoxy-2,3,3a,6,7,7a-hexahydro-7a-methyl-5-trimethylsiloxy-1H-indene (7): The enolate **6** was prepared according to the general procedure from CuBr SMe_2 (0 62 g, 3 mmol), *tert*-butyllithium (1 88 ml, 3 2 mmol), HMPA (4 23 g, 24 mmol), DIBAH (3 75 ml, 4 5 mmol) and **5** (0 67 g, 3 mmol) To the reaction mixture chlorotrimethylsilane (0 65 g, 6 mmol) was added at -40°C After stirring for 3h triethylamine (2 42 g, 24 mmol) was added at this temperature and the reaction mixture was allowed to warm up to room temp and was extracted with pentane (200 ml) in a perforator for 4h After solvent evaporation and silica gel chromatography (ether/pentane 1 4, R_f =0 74) **7** (0 68 g, 76%) was obtained as colourless oil that solidified when refrigerated, $[\alpha]_D^{20}$ = + 23.2° (c = 1 0, $CHCl_3$) - **IR (neat):** ν = 1650 cm^{-1} (C=C/olefine) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 14 (s, 9H, $Si(CH_3)_3$), 0 75 - 2 50 (m, 9H, CH, CH_3), 0 76 (s, 3H, C_{7a}-CH_3), 1 08 (s, 9H, $C(CH_3)_3$), 3 41 (t, J = 8Hz, 1H, C_1-H), 4 70 (d, J = 4Hz, 1H, C_4-H) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 0 20 ($Si(CH_3)_3$), 10 74 (C_{7a}-CH_3), 28 55 ($C(\underline{C}H_3)_3$), 25 10, 28 25, 32 04 and 33 22 (C-2,C-3,C-6,C-7), 42 21 (C-7a), 42 79 (C-3a), 71 91 ($\underline{C}(CH_3)_3$), 78 80 (C-1), 104 86 (C-4), 150 20 (C-5) - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 73 (85%, $Si(CH_3)_3^+$), 296 (8%, M^+) - **$C_{17}H_{32}O_2Si$ (296.5)** calc C,68 86, H,10 88, found C,69 06, H,11 02%

Thioalkylation of the silylenol ether 7, general procedure: The silylenol ether **7** (0 30 g, 1 mmol) was dissolved in CH_2Cl_2 (4 ml), cooled to -78 °C and 1 1 mmol of the α-chloroalkylphenylsulfides **8** were added dropwise A catalytic amount of $ZnCl_2$ (2 - 25 mol%) was added and the mixture was stirred for 0 5h at -78 °C and was allowed to warm up to -20 °C within 4h A saturated $NaHCO_3$ solution (25 ml) was added, the aqueous phase was extracted twice with ether (20 ml each time) and the combined organic phases were dried over $MgSO_4$ After the solvent was removed in vacuo the crude product **9** was purified by chromatography on silica gel

(1S,1'RS,3aS,4RS,7aS)-1-*tert*-Butoxy-4-(1'-phenylthioethyl)-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (9a): α-Chloroethylphenylsulfide **8a** (1 566 g, 9 1 mmol, 91%) was prepared from N-chlorosuccinimide (1 47 g, 11 mmol) and ethylphenylsulfide (1 38 g, 10 mmol) The β-phenylthioketone **9a** (225 mg, 0 62 mmol, 71%) was prepared according to the general procedure from the silylenol ether **7** (260 mg, 0 88 mmol), the α-Chloro-ethylphenylsulfide **8a** (167 mg, 0 97 mmol) and $ZnCl_2$ (1 0 M in ether, 0 02 ml, 0 02 mmol) , purified by chromatography on 150 g silica gel with ether/pentane/triethylamine 1 6 0 01 and obtained a an colourless oil (R_f = 0 39 and 0 33 for four diastereomers) - ratio of diastereomers 5 2 2 1 - **IR (neat):** ν = 3050 and 3030 (C-H/phenyl), 1695 (C=O), 1570 cm^{-1} (C=C/phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 98 (s, 3H, C_{7a}-CH_3), 1 18 (s, 9H, $C(CH_3)_3$), 1 38 (d, J = 7Hz, 3H, CH_3CHSPh), 0 75-2 60 (m, 9H, CH and CH_2), 2 64 (dd, J = 2 9 and 12 8 Hz, 1H, C_4-H), 3 49 (dd, J = 7 5 Hz and 8 5 Hz, 1H, C_1-H), 3 62 (dq, J = 2 9 Hz and 7 Hz, 1H, CH-SPh), 7 14 - 7 52 (m, 5H, SC_6H_5) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 27 (C_{7a}-CH_3), 18 95 ($\underline{C}H_3$-CH-SPh), 28 68 (O-C($\underline{C}H_3)_3$), 25 38, 31 89, 35 41, 38 00 (C-2, C-3, C-6, C-7), 42 99 (C-7a), 42 06 and 46 50 (C-3a and C-1'), 56 11 (C-4), 72 58 (C-9), 126 41 (C-4/phenyl), 128 93 (C-2/phenyl), 130 64 (C-3/phenyl), 136 96 (C-1/phenyl), 210 62 (C-5), only signals for the major diastereomer - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 194 (60%, M^+ -SPh -$C_4H_9^+$), 360 (24%, M^+) - **HRMS (70 eV):** calculated for $C_{22}H_{32}O_2S$ 360 2123, found 360 2123 - **$C_{22}H_{32}O_2S$** (360 6) calc C,73 29, H,8 95, found C,74 45, H,9 11%

(1S,3aS,4S,7aS)-1-*tert*-Butoxy-4-(1'-methyl-1'-phenylthioethyl)-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (9b) : α-Chloro-α-methylethylphenylsulfide **8b** (315 mg, 1 69 mmol, 85%) was

prepared from N-chlorosuccinimide (300 mg, 2.25 mmol) and iso-propylphenylsulfide (305 mg, 2 0 mmol) According to the general procedure β-phenylthioketone **9b** was prepared from the silylenol ether **7** (260 mg, 0 88 mmol), α-chloro-α-methylethylphenylsulfide **8b** (180 mg, 0 97 mmol) and $ZnCl_2$ (1.0 M in ether, 0 02 ml, 0.02 mmol) After purification by flash chromatography on 28 g silica gel (desactivated with 3 g H_2O) with ether/pentane/triethylamine 1 20 0 01 **9b** (197 mg, 0 53 mmol, 60%) was obtained as a colourless solid (R_f = 0 17) - d e > 95% - **m.p.** 78 - 81°C - **IR (nujol):** ν = 3050 (C-H/phenyl), 1685 (C=O), 740 and 690 cm^{-1} (C-H/monosub phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 91 (s, 3H, C_{7a}-CH_3), 1 15 (s, 9H, $C(CH_3)_3$), 1 30 (s, 6H, PhS-$C(CH_3)_2$), 0 80 - 2 63 (m, 11H; CH and CH_2), 3 51 (dd, J = 8Hz and 8 5Hz, C_1-H), 7 20 - 7 56 (m, 5H, SC_6H_5) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 12 22 (C_{7a}-CH_3), 28 72 ($C(\underline{C}H_3)_3$), 28 82 (C-3), 27 83 and 29 62 (PhS-$C(\underline{C}H_3)_2$), 32 03 (C-7), 34 72 (C-2), 38 86 (C-6), 43 66 (C-7a), 46 97 and 51 01 (C-3a and C-1'), 61 33 (C-4), 72 54 ($\underline{C}(CH_3)_3$), 79 10 (C-1), 128 49 (C-2/phenyl), 128 88 (C-4/phenyl), 131,43 (C-1/phenyl), 137 95 (C-3/phenyl), 213 79 (C-5) - **MS (70 eV) :** (m/z) = 57 (59%, $C_4H_9^+$), 209 (100%, M^+ - $C_4H_9^+$ -SPh), 265 (30%, M^+ -SPh), 374 (24%, M^+), - **HRMS (70 eV):** calculated for $C_{23}H_{34}O_2S$ 374 2280, found 374 2279 - **$C_{23}H_{34}O_2S$ (374.6)** calc C,73 75, H,9 15, found C,73 74, H,9 01%

(1S,1'RS,3aS,4RS,7aS)-1-*tert*-Butoxy-4-(2'-phenyl-1'-phenylthioethyl)-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (9c) : The α-chloro-β-phenylethylphenylsulfide **8c** (425 mg, 1 71 mmol, 85%) was prepared from N-chlorosuccinimide (294 mg, 2 2 mmol) and ß-phenylethylphenylsulfide (429 mg, 2 0 mmol) The thioalkylation of silylenol ether **7** (200 mg, 0 68 mmol) with **8c** (195 mg, 0 74 mmol) and $ZnCl_2$ (1 0 M in ether, 0 03 ml, 0 03 ml) according to the general procedure yielded the β-thiophenylketone **9c** (165 mg, 0 38 mmol, 56%) After chromatography on 65 g silica gel (desactivated with 6 g H_2O) with ether/pentane/triethylamine 1 6 0 01 **9c** was obtained as a colourless oil (R_f = 0 40 and 0 36 for four diastereomers) - ratio of diastereomers 8 4 1 1 - **IR (neat):** ν = 3040 (C-H/phenyl), 1695 (C=O), 1595 and 1575 (C=C/phenyl), 740 and 690 cm^{-1} (C-H/monosub phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 87 (s, 3H, C_{7a}-CH_3), 1 12 (s, 9H, $C(CH_3)_3$), 2 66 (dd, J = 3 Hz and 13 Hz, 1H, C_4-H), 0 85 - 2 52 and 3 00 - 3 40 (m, 12H, CH and CH_2), 3 46 (dd, J = 7 5 Hz and 8 5 Hz, 1H, C_1-H), 7 10 - 7 38 (m, 10H, phenyl-H) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 11 (C_{7a}-CH_3), 28 65 ($C(\underline{C}H_3)_3$), 24 66, 31 68, 35 29, 38 23, 40 92 and 42 80 (C-2,C-3,C-6,C-7,C-7a,C-2'), 46 87 and 51 15 (C-3a and C-1'), 53 71 (C-4), 72 56 (C-9), 79 26 (C-1), 126 37 and 126 41 (C-4/phenyl), 128 39, 128 79, 129 26 and 130 72 (C-2,C-3/phenyl), 137 61 and 139 84 (C-1/phenyl), 210 91 (C-5), only signals for the major diastereomer - **MS (70 eV):** (m/z) = 57 (88%, $C_4H_9^+$), 91 (100%, CH_2-Ph), 270 (41%, M^+ -SPh - $C_4H_9^+$), 327 (20%, M^+ -SPh), 426 (50%, M^+) - **HRMS (70 eV):** calculated for $C_{28}H_{36}O_2S$ 436 2436, found 436 2436 - **$C_{28}H_{36}O_2S$ (436,7)** calc C,77 02, H,8 31, found C,78 08, H,8 47%

(1S,1'RS,3aS,4RS,7aS)-1-*tert*-Butoxy-4-(2'-m-methoxyphenyl-1'-phenylthioethyl)-7a-methyl-3a,4,7,7a-tetrahydro5(6)-indan-5-one (9d) : α-Chloro-β-(m-methoxyphenyl)ethylphenylsulfide **8d** (797 mg, 2 86 mmol, 95%) was prepared by chlorination of β-(m-methoxyphenyl)ethylphenylsulfide (733 mg, 3 0 mmol) with N-chlorosuccinimide (440 mg, 3 3 mmol) According to the general procedure the β-phenylthioketone **9d** was prepared from the silylenol ether **7** (250 mg, 0 85 mmol), **8d** (259 mg, 0 93 mmol) and $ZnCl_2$ (1 0 M in ether, 0 2 ml, 0 2 mmol) Purification by flash chromatography on 29 g silica gel (desactivated with 3 g H_2O) with ether/pentane/triethylamine 1 6 0 01 yielded **9d** (256 mg, 0 55 mmol, 65%) as a colourless oil with R_f = 0 22 and 0 27 - ratio of diastereomers 12 4 2 1 - **IR (neat):** ν = 3050 (C-H/phenyl), 1705 (C=O), 1595 and 1575 (C=C/phenyl), 775 and 745 cm^{-1} (C-H/disubs phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 88 (s, 3H, C_{7a}-CH_3), 1 13 (s, 9H, $C(C\underline{H}_3)_3$), 2 68 (dd, J = 2 2 Hz and 13 Hz, 1H, C_4-H), 0 80 - 2 60 and 2 65 - 3 19 (m, 11H, CH and CH_2), 3 36 (td, J = 2 2 Hz and 8 Hz, 1H, C_1-H), 3 47 (dd, J = 7 2 Hz and 8 0 Hz, 1H, C_1-H), 3 76 (s, 3H, OCH_3), 6 62 - 6 81 (m, 3H, phenyl-CH), 7 09 - 7 39 (m, 6H, -SC_6H_5 and C_5-phenyl) **^{13}C NMR (50 MHz,$CDCl_3$)**

δ = 11 15 (C_{7a}-CH_3), 28 65 (C($\underline{C}H_3)_3$), 24 64, 31 68, 35 31, 38 26 and 41 00 (C-2,C-2',C-3,C-6,C-7), 42 80 (C-7a), 46 90 and 50 87 (C-1',C-3a), 53 64 (C-4), 55 17 (OCH_3), 72 57 ($\underline{C}(CH_3)_3$), 79 26 (C-1), 111 86, 114 87, 121 60, 126 36, 128 79, 129 34, 130 71, 137 60, 141 39, 159 62, (C-phenyl), 210 89 (C-5), signals for the major diastereomer. - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 357 (10%, M^+ -SPh), 466 (20%, M^+) - **HRMS (70 eV):** calculated for $C_{29}H_{38}O_3S$ 466.2541 found 466 2542 - **$C_{29}H_{38}O_3S$ (466.7)** calc C,74 64, H,8 21, found C,74 66, H,8 37%

Reductive desulfurization of 9, general procedure: 5g Raney nickel were washed 10 times with 10 ml 96% ethanol , 5 more times with 10 ml dry ethanol and suspended in 10 ml dry ethanol A solution of β-phenylthioketones **9a-d** (0 5 mmol) in 8 ml ethanol was added at roomtemp After 3h the Raney nickel was removed by filtration and washed 5 times with 15 ml Et_2O After evaporation of the solvent the crude ketones **10a-d** were purified by chromatography

(1S,3aS,4S,7aS)-(+)-1-*tert*-Butoxy-4-ethyl-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (10a) *:* The desulfurization was carried out according to the general procedure with β-phenylthioketone **9a** (150 mg, 0 42 mmol) and Raney nickel (2 g) After purification by flash chromatography with ether/pentane - 1 6 the ketone **10a** (98 mg, 0 39 mmol, 93%) was obtained as a colourless solid (R_f = 0 52) - d e > 95% - $[\alpha]_D^{20}$ = + 48 75° (c = 0 8, $CHCl_3$) - **m.p.** 44 - 46°C - **IR (neat):** ν = 1695 cm^{-1} (C=O) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 88 (t, J = 7 3 Hz, 3H, CH_2-$C\underline{H}_3$), 1 03 (s, 3H, C_{7a}-CH_3), 1 14 (s, 9H, C($C\underline{H}_3)_3$), 0 75 - 2 58 (m, 12H, CH and CH_2), 3 45 (dd, J = 7 4 Hz and 8 8 Hz, 1H, C_1-H) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 13 (CH_2-$\underline{C}H_3$), 11 48 (C_{7a}-CH_3), 19 28 ($\underline{C}H_2$-CH_3), 24 53 (C-3), 28.66 (C($\underline{C}H_3)_3$), 31 81 (C-7), 35 86 (C-2), 38 00 (C-6), 42 65 (C-7a), 48 96 (C-3a), 51 60 (C-4), 72 48 ($\underline{C}(CH_3)_3$), 79 48 (C-1), 212 97 (C-5) - **MS (70 eV):** (m/z) = 41 (50% $C_3H_5^+$), 57 (100%, M^+ -C_4H_8 - C_2H_4), 196 (40%, M^+ -C_4H_8), 252 (23%, M^+) - **HRMS (70 eV):** calculated for $C_{16}H_{28}O_2$ 252 2089, found 252 2089 - **$C_{16}H_{28}O_2$ (252.4)** calc C,76 14, H,11 18, found C,76 17, H,11 26%

(1S,3aS,4S,7aS)-(+)-1-*tert*-Butoxy-4-iso-propyl-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (10b) : According to the general procedure **10b** was prepared from **9b** (80 mg, 0 22 mmol) by treatment with Raney nickel (1 5 g) The ketone **10b** (51 mg, 0 19 mmol, 90%) was obtained after flash chromatography on 27 g silica gel with ether/pentane 1 20 as a colourless solid (R_f = 0 20) - d e > 95% . - $[\alpha]_D^{20}$ = + 70 1° (c = 0 9, $CHCl_3$) - **m.p.** 34°C - **IR (nujol):** ν = 1695 cm^{-1} (C=O) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 92 (s, 3H, C_{7a}-CH_3), 0 97 (d, J = 7 Hz, 6H, CH($C\underline{H}_3)_2$), 1 14 (s, 9H, C($C\underline{H}_3)_3$), 0 85 - 2 53 (m, 11H, CH and CH_2), 3 45 (dd, J = 8 Hz and 8 5 Hz, 1H, C_1-H) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 28 (C_{7a}-CH_3), 19 07 and 19 60 (CH($\underline{C}H_3)_2$), 25 46 (C-3), 26 55 ($\underline{C}H(CH_3)_2$), 28 71 (C($\underline{C}H_3)_3$), 31 88 (C-7), 35 37 (C-2), 38 39 (C-6), 42 87 (C-7a), 46 60 (C-3a), 55 51 (C-4), 72 50 ($\underline{C}(CH_3)_3$), 79 44 (C-1), 212 83 (C-5) - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 167 (14%, M^+ -C_4H_8 -C_3H_7), 195 (40%, M^+ -C_4H_8 -CH_3), 210 (48%, M^+ -C_4H_8), 266 (34%, M^+) - **HRMS (70 eV):** calculated for $C_{17}H_{30}O_2$ 266 2246, found 266 2245 - **$C_{17}H_{30}O_2$ (266.4)** calc C,76 64, H,11 35, found C,76 52, H,11 31%

(1S,3aS,4S,7aS)-(+)-1-*tert*-Butoxy-4-(2'-phenylethyl)-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (10c) : Treatment of **9c** (132 mg, 0 30 mmol) with Raney nickel (2 g) afforded after purification by flash chromatography on 29 g silica gel with ether/pentane 1 6 the ketone **10c** (88 mg, 0 27 mmol, 88%) as an colourless solid (R_f = 0 42) - d e > 95% - $[\alpha]_D^{20}$ = +28 42° (c = 1 0, $CHCl_3$) - **m.p. :** 70°C - **IR (nujol):** ν = 3040 (C-H/phenyl), 1695 (C=O), 740 and 690 cm^{-1} (C-H/monosubs phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1 02 (s, 3H, C_{7a}-CH_3), 1 13 (s, 9H, C($C\underline{H}_3)_3$), 0 80 - 2 06 (m, 9H, CH and CH_2), 2 25 - 2 58 (m, 4H, CH_2-CH_2-Ph), 2 73 (ddd, J = 5 2 Hz, 10 8 Hz and 13 4 Hz, 1H, C_4-H), 3 45 (dd, J = 7 6 Hz and 8 6 Hz, 1H, C_1-H), 7 11 - 7 32 (m, 5H, phenyl) - **^{13}C NMR (50**

MHz,$CDCl_3$): δ = 11 14 (C_{7a}-CH_3), 28.66 ($C(\underline{C}H_3)_3$), 24 58, 28 61, 31 78, 33 50, 35 98 and 38 09 (C-2,C-3,C-6,C-7,C-1' and C-2'), 42 81 (C-7a), 49 69 (C-3a), 50 05 (C-4), 72 52 ($\underline{C}(CH_3)_3$), 79.41 (C-1), 125 66 (C-4/phenyl), 128 27 and 128 38 (C-2 and C-3/phenyl), 142 81 (C-1/phenyl), 212.80 (C-5) - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 167 (93%, M^+ -$C_4H_9^+$ -CH_2Ph), 181 (85%, M^+ -$C_4H_9^+$ - CH_2CH_2Ph), 272 (4%, M^+ -$C_4H_9^+$), 329 (4% M^+) - **HRMS (70 eV):** calculated for $C_{22}H_{33}O_2$ 328 2402, found 328 2402 - **$C_{22}H_{33}O_2$ (328.5)** calc C,80 44, H,9 82, found, C,80 72, H,9 87%

(1S,3aS,4S,7aS)-(+)-1-*tert*-Butoxy-4-(2'-m-methoxyphenylethyl)-7a-methyl-3a,4,7,7a-tetrahydro-5(6)-indan-5-one (10d) : The seco-steroid **10d**[9,10] was obtained as a colourless oil (130 mg, 0 36 mmol, 97%, R_f = 0 28) from the β-phenylthioketone **9d** (175 mg = 0 375 mmol) and Raney nickel (3 g) after purification by flash chromatography on 29 g silica gel with ether/pentane 1 6 diastereomerically and enantiomerically pure $[\alpha]_D^{20}$ = + 31 63° (c = 1 0, $CHCl_3$), lit [10] $[\alpha]_D^{25}$ = + 27 46° (c = 1 0, $CHCl_3$) - **IR (neat):** ν = 3040 (C-H/phenyl), 1705 (C=O), 1595 and 1575 (C=C/phenyl), 775 cm^{-1} (C-H/1 3-disubs phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1 02 (s, 3H, C_{7a}-CH_3), 1 14 (s, 9H, $C(CH_3)_3$), 0 80 - 2 63 (m, 13H, C_{3a}-H and CH_2), 2 71 (ddd, J = 5 2 Hz, 10 8 Hz and 13 4 Hz; 1H, C_4-H), 3 45 (dd, J = 7 5 Hz and 8 5 Hz, 1H, C_1-H), 3 80 (s, 3H, -OCH_3), 6 67 - 6 86 (m, 3H, CH/phenyl), 7 19 (dt, $^3J_{ortho}$ = 7 6 Hz, $^5J_{para}$ = 0 9 Hz, 1H, C_5-H/phenyl) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 17 (C_{7a}-CH_3), 28 68 ($C(\underline{C}H_3)_3$), 24 61, 28 50, 31 81, 33 58, 36 01 and 38 10 (C-2,C-3,C-6,C-7,C-1' and C-2'), 42 84 (C-7a), 49 74 (C-3a), 50 06 (C-4), 55 14 (OCH_3), 72 53 ($\underline{C}(CH_3)_3$), 79 43 (C-1), 111 13 (C-6/phenyl), 114 04 (C-2/phenyl), 120 83 (C-4/phenyl), 129 23 (C-5/phenyl), 144 48 (C-3/phenyl), 159 62 (C-1/phenyl), 212 85 (C-5) - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 167 (82%, M^+ -C_4H_8 - CH_3O-C_6H_4-$C_2H_4^+$), 181 (40%, M^+ - CH_3O-C_6H_4-CH_2^+), 301 (4%, M^+ -$C_4H_9^+$), 358 (23%, M^+) - **HRMS (70 eV):** calculated for $C_{23}H_{34}O_3$ 358 2508, found 358 2507

(8S,13S,14S,17S)-(+)-17-*tert*-Butoxy-3-methoxyestra-1,3,5(10),9(11)-tetraene (11) : The seco-steroid **10d** (80 mg, 0 22 mmol) was dissolved at 0 °C in MeOH (2 ml) and 10 N HCl (0 2 ml) was added The solution was stirred for 4h at 0 °C, allowed to warm up to roomtemp and stirred for additional 4h The mixture was kept overnight at -28 °C to complete the crystallization The crude product was separated by filtration and recrystallization from MeOH afforded the unsaturated steroid **11**[9,10] (60 mg, 0 18 mmol, 81%) as a colourless solid - $[\alpha]_D^{20}$ = + 107 8° (c = 1 0, $CHCl_3$), lit [9] $[\alpha]_D^{RT}$ = + 102 3° (c = 0 5, $CHCl_3$), lit [10] $[\alpha]_D^{25}$ = + 101 27° (c =1 0, $CHCl_3$) - **m.p.** 129 °C, lit[9] m.p 131-133°C, lit [10] m p 133-134°C - **IR (nujol):** ν = 1625 (C=C/olefine), 1605 and 1585 cm^{-1} (C=C/phenyl) - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0 78 (s, 3H, C_{13}-CH_3), 1 17 (s, 9H, $C(CH_3)_3$), 1 21 - 2 25 (m, 10H, CH and CH_2), 2 75 - 2 98 (m, 2H, C_6-H), 3 54 (dd, J = 7 5 Hz and 8 5 Hz, 1H, C_{17}-H), 3 78 (s, 3H, OCH_3), 6 12 (m, 1H, C_{11}-H), 6 59 (d, $^4J_{meta}$ = 3 Hz, 1H, C_4-H), 6 71 (dd, $^3J_{ortho}$ = 8 Hz, $^4J_{meta}$ = 3 Hz,, 1H, C_2-H), 7 54 (d, $^3J_{ortho}$ = 8 Hz, 1H, C_1-H) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 68 (C_{13}-CH_3), 28 80 ($C(\underline{C}H_3)_3$), 24 42, 28 26, 30 21, and 31 28 (C-7,C-12,C-15,C-16), 38 99 (C-8), 39 58 (C-6), 41 17 (C-13), 47 38 (C-14), 55 21 (OCH_3), 72 25 ($\underline{C}(CH_3)_3$), 80 82 (C-17), 112 60 (C-2), 113 25 (C-4), 117 97 (C-11), 125 09 (C-1), 127 64 (C-9), 134 99 (C-10), 137 48 (C-5), 158 22 (C-3) - **MS (70 eV):** (m/z) = 57 (44%, $C_4H_9^+$), 267 (30%, M^+ -$OC(CH_3)_3^+$), 283 (45%, M^+ -$C_4H_9^+$), 340 (100%, M^+) - **HRMS (70 eV):** calculated for $C_{23}H_{32}O_2$ 340 2402, found 340 2402 - **$C_{23}H_{32}O_2$ (340,5)** calc C,81 13, H,9 47, found C,81 21, H,9 50%

(8S,9S,13S,14S,17S)-(+)-17-*tert*-Butoxy-3-methoxyestra-1,3,5(10)-triene (12) : A mixture of **11** (34 mg, 0 10 mmol), palladium (5 mg, 10% on carbon) and ethyl acetate (1 2 ml) was stirred under hydrogen for 3 h The catalyst was filtered off with suction on Celite and the Celite was washed with ethyl acetate (20 ml) The ethyl acetate was evaporated in vacuo and the crude product purified by flash chromatography on 5 g silica gel with ether/pentane 1 6 to yield **12** [9,10,14] (23 mg, 68%) as a

colourless solid (R_f = 0 53) - $[\alpha]_D^{20}$ = + 63.3° (c = 0.9, $CHCl_3$), lit [10] $[\alpha]_D^{25}$ = + 62 20° (c = 1.0, $CHCl_3$) - **m.p.** 89-91°C; lit.[10] m.p 90-92° - **IR (nujol):** ν = 1605 and 1580 cm-1 (C=C/phenyl) - **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 0 75 (s, 3H, C_{13}-CH_3), 1 15 (s, 9H; $C(CH_3)_3$), 0.80 -2 20 (m, 11H, CH_2 and C_8-H), 2.18 (ddd, J = 4 Hz, 11 5 Hz and 11 5 Hz, 1H, C_9-H), 2 28 (ddd, J = 4 Hz, 7 Hz and 13 Hz, 1H, C_{14}-H), 2 85 (dd, J = 7 5 Hz and 8 Hz, 2H, C_6-H), 3.45 (dd, J = 7 5 Hz and 8 Hz, 1H, C_{17}-H), 3 78 (s, 3H, OCH_3), 6.63 (d, $^4J_{meta}$ = 3 Hz, 1H, C_4-H), 6 71 (dd, $^4J_{meta}$ = 3 Hz, $^3J_{ortho}$ = 9 Hz, 1H; C_2-H), 7 22 (d, $^3J_{ortho}$ = 9 Hz, 1H, C_1-H) - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 11 62 (C_{13}-CH_3), 28 77 ($C(\underline{C}H_3)_3$), 23.50, 26 40, 27 29, 29.91, 31.23 and 37.24 (C-6,C-7,C-11,C-12,C-15,C-16), 42 74 (C-13), 38 75, 44 13 and 50 02 (C-8,C-9,C-14), 55 18 (OCH_3), 72 19 ($\underline{C}(CH_3)_3$), 80 84 (C-17), 111 41 and 113.74 (C-2,C-4), 126.35 (C-1), 132 90 (C-10), 138 06 (C-5), 157 36 (C-3) - **MS (70 eV):** (m/z) = 57 (100%, $C_4H_9^+$), 286 (68%, M^+ -C_4H_8), 342 (80%, M^+) - **HRMS (70 eV)** calculated for $C_{23}H_{34}O_2$ 342 2559, found 342 2559

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