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Stereoselective Synthesis of Steroids and Related Compounds, III[1]

Synthesis of Enantiomerically Pure Hexahydro-1*H*-indenes and Substituted Cyclopentanes as Intermediates for the Synthesis of Steroids

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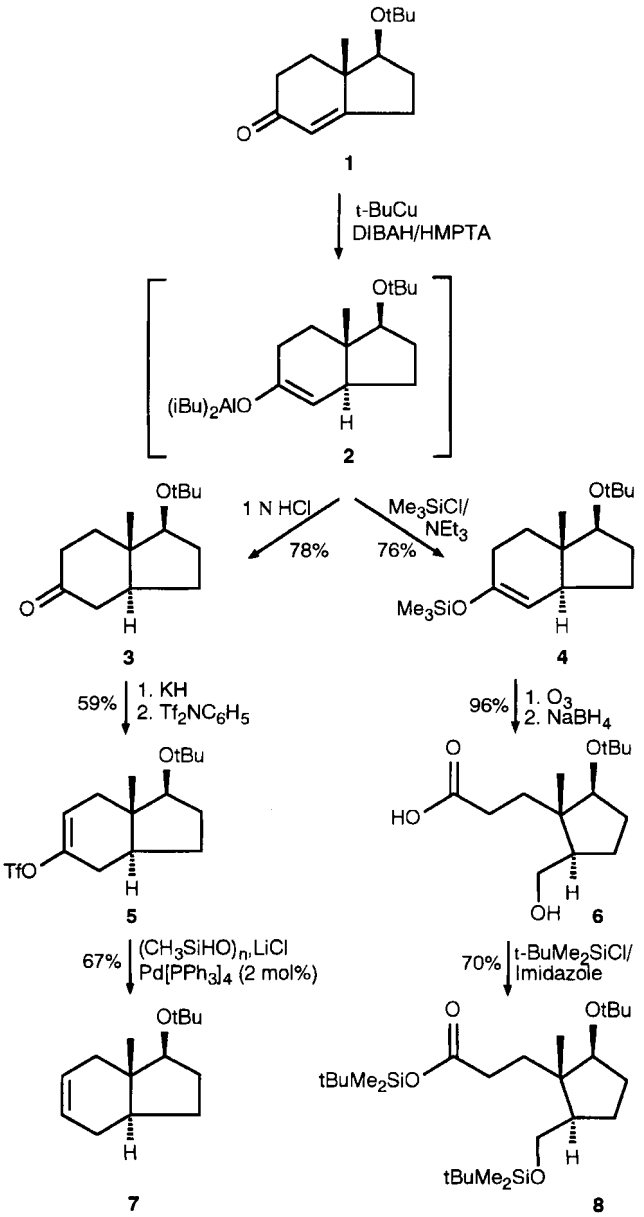
The indene derivative **7** and the 1,2,2,3-tetrasubstituted cyclopentane derivative **8** have been synthesized in three steps starting from the Hajos-Wiechert ketone **1**.

Due to their biological activity and pharmaceutical importance, steroids such as the oral contraceptive component estrone, the corticoids and vitamin D derivatives are attractive target molecules in organic synthesis[2]. Recently, we report on the synthesis of enantiomerically pure estradiol-3-methyl-17-*tert*-butyl diethyl by zinc chloride mediated thioalkylation of the aluminium enolate **2** or the trimethylsilylenol ether **4**[1]. The aluminium enolate **2**, generated by diastereoselective 1,4-reduction[1,3] of the Hajos-Wiechert ketone **1**[4], could be trapped either with trimethylsilyl chloride to the silylenol ether **4** or protonated to give the ketone **3**. In this short communication, we would like to describe the transformation of ketone **3** and the silylenol ether **4** into the indene **7** and the 1,2,2,3-tetrasubstituted cyclopentane derivative **8**, which have proved to be valuable intermediates in steroid synthesis[5].

Ketone **3** was deprotonated regiospecifically with potassium hydride[6] at C-6. Subsequent treatment of this potassium enolate with *N,N*-bis(trifluoromethylsulfonyl)aniline afforded the enol triflate **5** in 59% yield. A palladium(0)-catalyzed reduction of **5** with tributyltin hydride or better with polymethylhydrosiloxane in the presence of lithium chloride[7] gave rise to the *trans*-hydroindene derivative **7** in 62% and 67% yield, respectively. This compound is a key intermediate for the enantioselective synthesis of 11-oxosteroids, used in racemic from by Snider and Kirk[5b].

Another approach to promising precursors for the total synthesis of steroids was achieved by ozonolysis of the silylenol ether **4** followed by reduction with sodium borohydride affording the 1,2,2,3-tetrasubstituted cyclopentane derivative **6** in almost quantitative yield. Any epimerization of the intermediary occuring aldehyde at C-3 could be avoided by the in situ performed reduction. All attempts to isolate this aldehyde failed due to the lability of this compound. Since the cyclopentane derivative **6** is difficult to handle due to the polar hydroxy and carboxylic acid functions, it was converted into the bis(silyloxy) derivative **8**, which could be purified by silica gel chromatography.



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Experimental

General remarks: See preceding paper. – All reactions were carried out under argon. All reagents were purified and dried if necessary before use. THF was freshly distilled from $LiAlH_4$ prior to use.

(1S,3aS,7aS)-1-tert-Butoxy-7a-methyl-octahydro-5H-inden-5-one (**3**): To a slurry of CuBr · SMe_2 (205 mg, 1 mmol) in THF (10 ml) a solution of *tert*-butyllithium in pentane (1.7 N, 0.65 ml, 1.1 mmol) was added with stirring at −50°C. Stirring was continued for 15 min, then HMPTA (0.72 g, 4 mmol) was added, the solution was cooled down to −100°C and a mixture of a solution of diisobutylaluminium hydride (DIBAH) in toluene (1.2 M, 1.25 ml, 1.5 mmol) and HMPTA (0.72 g, 4 mmol) was slowly added during 10 min. A solution of **1** (0.22 g, 1 mmol) in THF (1 ml) was added dropwise with stirring within 15 min. The temperature was allowed to rise to −80°C and stirring was continued for 2 h at this temperature and for 2 h at −40°C. 1 N HCl (5 ml) was added with stirring at 0°C and stirring was continued for 10 min. The THF was removed in vacuo (25°C/20 Torr) and the residue was extracted with pentane (100 ml) in a perforator for 12 h. The solvent was removed in vacuo (25°C/20 Torr) and the residue – the crude ketone **3** – purified by chromatography on silica gel with diethyl ether/pentane (1:2) to yield 0.18 g (78%) of **3** as a colorless oil, R_f = 0.55. – $[\alpha]_D^{20}$ = +81.5 (*c* = 1.5, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 1705 cm^{-1} (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.97 (s; 3H, 7a-CH_3), 1.14 [s; 9H, O-C-$(CH_3)_3$], 1.15–2.55 (m; 11H, CH and CH_2), 3.36 (dd, *J* = 8 and 9 Hz; 1H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.20 (7a-CH_3), 25.80 (C-3), 28.67 [O-C(CH_3)$_3$], 31.78 (C-7), 35.22 (C-2), 37.39 (C-6), 42.02 (C-7a), 42.91 (C-4), 44.60 (C-3a), 72.49 [O-*C*(CH_3)$_3$], 79.37 (C-1), 211.95 (C-5). – MS (70 eV): *m/z* (%) = 224 (2) [M^+], 57 (100) [$C_4H_9^+$]. – $C_{14}H_{24}O_2$ (224.3): calcd. C 74.95, H 10.78; found C 74.85, H 10.77.

(1S,3aS,7aS)-1-tert-Butoxy-7a-methyl-5-trifluoromethylsulfonyloxy-2,3,3a,4,7,7a-hexahydro-1H-indene (**5**): Potassium hydride (0.74 g of a 25% suspension in mineral oil, 4.6 mmol) was washed twice with pentane and twice with THF (10 ml each) and suspended in THF (25 ml). A solution of the ketone **3** (1.03 g, 4.6 mmol) in THF (5 ml) was added at 0°C and the reaction mixture was allowed to warm up to room temp. within 90 min. After the evolution of hydrogen had ceased, the solution was cooled to 0°C, a solution of *N,N*-bis-(trifluoromethylsulfonyl)aniline (1.78 g, 5 mmol) in THF (5 ml) was slowly added and stirring was continued at room temp. for 12 h. The solvent was removed in vacuo (25°C/20 Torr), the residue diluted with diethyl ether (30 ml) and extracted with cold 1 N HCl, an aqueous $NaHCO_3$ solution and water (10 ml each). The organic layer was dried with $MgSO_4$, the solvent evaporated in vacuo (25°C/20 Torr) and the solid residue – the crude yellow enol triflate **5** – purified by chromatography on silica gel with diethyl ether/pentane (1:2) to yield 0.98 g (59%) of the enol triflate **5**, R_f = 0.76. – IR (nujol): $\tilde{\nu}$ = 1670 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.70–2.50 (m; 9H, CH and CH_2), 0.79 (s; 3H, 7a-CH_3), 1.14 [s; 9H, O-C(CH_3)$_3$], 3.50 (t, *J* = 8 Hz; 1H, 1-H), 5.68–5.74 (m; 1H, 6-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.65 (7a-CH_3), 28.71 [O-C(*C*(CH_3)$_3$], 25.39, 30.99, 31.61 and 36.06 (C-2, C-3, C-4 and C-7), 41.27 (C-7a), 41.35 (C-3a), 72.53 [O-*C*(CH_3)$_3$], 79.39 (C-1), 118.36 (C-6), 118.59 (q, J_{C-F} = 318 Hz; CF_3), 148.79 (C-5). – MS (70 eV): *m/z* (%) = 356 (2) [M^+], 57 (100) [$C_4H_9^+$]. – $C_{15}H_{23}O_4SF_3$: calcd. 356.4004, found 356.4004 (MS).

(3S,3aS,7aS)-3-tert-Butoxy-3a-methyl-2,3,3a,4,7,7a-hexahydro-1H-indene (**7**): To a slurry of lithium chloride (0.32 g, 7.5 mmol) and tetrakis(triphenylphosphano)palladium(0) (58 mg, 0.05 mmol) in THF (10 ml) a solution of the enol triflate **5** (0.89 g, 2.5 mmol) in THF (2 ml) and a second solution of polymethylhydrosiloxane (0.33 g, 3 mmol) in THF (1 ml) were added and the mixture was heated under reflux for 18 h. The reaction mixture was diluted with pentane (50 ml) and extracted with water, a 10% aqueous ammonia solution and a concentrated aqueous NaCl solution (30 ml each). The organic layer was dried with $MgSO_4$, the solvent evaporated in vacuo (25°C/20 Torr) and the residue – the crude olefine **7** – purified by chromatography on silica gel with diethyl ether/pentane (1:50) to yield 0.35 g (67%) of **7** as a colorless oil, R_f = 0.52. – $[\alpha]_D^{20}$ = +61.4 (*c* = 1.1, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 1650 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.65–2.20 (m; 9H, CH and CH_2), 0.71 (s; 3H, 7a-CH_3), 1.14 [s; 9H, O-C(CH_3)$_3$], 3.49 (dd, *J* = 7.5 Hz and 9 Hz; 1H, 1-H), 5.61 (t, *J* = 2 Hz; 2H, 5-H and 6-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.62 (7a-CH_3), 28.79 [O-C(*C*H_3)$_3$], 26.14, 28.66, 30.84 and 39.05 (C-2, C-3, C-4 and C-7), 40.36 (C-3a), 41.10 (C-7a), 72.20 (C-1), 80.84 [O-*C*(CH_3)$_3$], 126.31 and 126.41 (C-5 and C-6). – MS (70 eV): *m/z* (%) = 208 (6) [M^+], 57 (100) [$C_4H_9^+$]. – $C_{14}H_{24}O$ (208.3): calcd. C 80.71, H 11.61; found C 80.45, H 11.44.

(1S,2S,3S)-**6** (numbering refers to the cyclopentane ring): At −70°C a stream of ozone and oxygen was bubbled through a stirred solution of the trimethylsilyl enol ether **4**[8] (0.47 g, 1.6 mmol) in dichloromethane (5 ml) and methanol (5 ml) until a slightly blue color indicated an excess of ozone. The ozone was removed with a stream of oxygen, sodium borohydride (61 mg, 1.6 mmol) was added and stirring was continued at −70°C for 1 h. A second portion of sodium borohydride (61 mg, 1.6 mmol) was added and the solution was allowed to warm up to room temp. The solvent was removed in vacuo (30°C/25 Torr) and the residue treated with diethyl ether (10 ml) and 2 N NaOH (30 ml). 2 N HCl was added dropwise to the aqueous layer until the solid compounds were completely dissolved and the aqueous layer was extracted three times with diethyl ether (20 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo (40°C/8 Torr) to afford 0.40 g (96%) of **6** analytically pure as a colorless oil which solidified at −20°C. – $[\alpha]_D^{20}$ = +33.1 (*c* = 1.4, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3300 (OH), 1700 cm^{-1} (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (s; 3H, 2-CH_3), 1.10–2.10 (m; 9H, CH and CH_2), 1.11 [s; 9H, O-C(CH_3)$_3$], 3.30–3.45 (m; 1H, 1-H), 3.50–3.70 (m; 2H, 3-CH_2), 7.10–7.60 (m; 2H, COOH and OH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.18 [O-C(*C*H_3)$_3$], 28.39 (2-CH_3), 23.75, 29.12, 31.28 and 34.06 (CH_2), 45.70 (C-3), 46.35 (C-2), 63.06 (3-CH_2OH), 73.83 [O-*C*(CH_3)$_3$], 77.99 (C-1), 177.77 (COOH). – MS (70 eV): *m/z* (%) = 258 (1) [M^+], 184 (31) [M^+ – C_4H_9OH], 140 (52) [M^+ – C_4H_9OH – CO_2], 57 (100) [$C_4H_9^+$]. – $C_{14}H_{26}O_4$ (258.4): calcd. C 65.09, H 10.14; found C 64.93, H 10.01.

(1S,2S,3S)-**8** (numbering refers to the cyclopentane ring): To a stirred solution of **6** (0.36 g, 1.4 mmol) and *tert*-butylchlorodimethylsilane (0.51 g, 3.4 mmol) in DMF (7 ml) imidazole (0.34 g, 5 mmol) was added at −10°C and stirring was continued at −10°C for 30 min and at room temp. for 12 h. Pentane (100 ml) and a saturated aqueous NH_4Cl solution (15 ml) were added. The layers were separated and the aqueous layer was extracted three times with pentane (30 ml each). The combined organic layers were reextracted three times with water (20 ml each) and dried with $MgSO_4$.

The solvent was removed in vacuo (25°C/20 Torr) and the residue – the crude cyclopentanone derivative **8** – purified by chromatography on silica gel with ethyl acetate/dichloromethane (1:10) to afford 0.48 g (70%) of **8** as a colorless oil, R_f = 0.78. – IR (neat): $\tilde{\nu}$ = 1725 (C=O), 1250 cm^{-1} (Si-O). – ^1H NMR (200 MHz, $CDCl_3$): δ = −0.04 and 0.18 [2 s; 12H, O-SiC(CH_3)$_3$(CH_3)$_2$], 0.68 (s; 3H, 2-CH_3), 0.81 and 0.86 [2 s; 18H, O-SiC(CH_3)$_3$(CH_3)$_2$], 1.00–2.52 (m; 9H, CH and CH_2), 1.08 [s; 9H, 1-O-C(CH_3)$_3$], 3.33–3.63 (m; 3H, 1-H and 3-CH_2-OSi). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.64 and −5.45 [Si(CH_3)$_2$], 13.81 (2-CH_3), 17.61 and 18.25 [Si-C(CH_3)$_3$], 25.58 and 25.95 [Si-C(CH_3)$_3$], 28.81 [O-C(CH_3)$_3$], 24.10, 30.53, 31.33 and 33.57 (CH_2), 44.63 (C-2), 44.77 (C-3), 64.34 (3-CH_2OSi), 72.66 [O-C(CH_3)$_3$], 77.98 (C-1), 174.94 (COOSi). – MS (70 eV): *m/z* (%) = 486 (1) [M^+], 429 (100) [M^+ − C_4H_9], 57 (50) [$C_4H_9^+$]. – $C_{26}H_4O_4Si_2$ (486.9): calcd. C 64.14, H 11.18; found C 64.43, H 11.07.

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