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Synthesis of a chiral steroid ring D precursor starting from carvone

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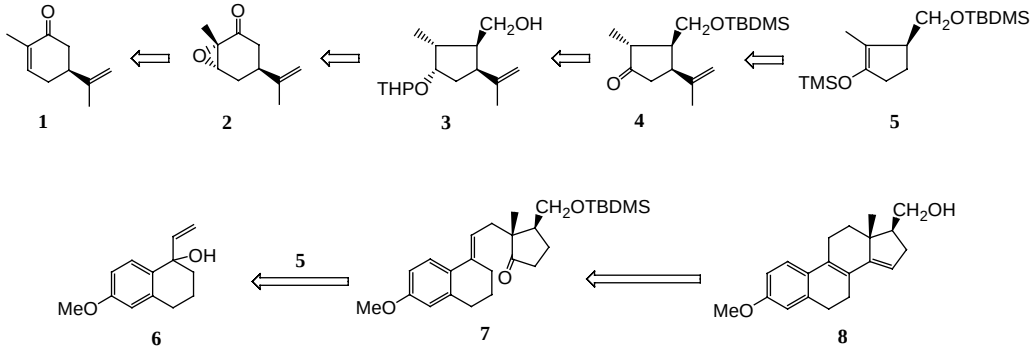
Abstract—A chiral five-membered, silyl enol ether containing, steroid ring D precursor has been synthesized from carvone. This silyl enol ether has been applied in the synthesis of a chiral C17 functionalized steroid skeleton using the addition of a carbocation, generated with $ZnBr_2$ from a Torgov reagent, followed by cyclization of the adduct by treatment with acid.

1. Introduction

An ultimate goal in steroid synthesis is the development of short and efficient routes to enantiomerically pure compounds. The encouraging results obtained in the coupling reactions of the Torgov reagent **6** with silyl enol ether derivatives of five-membered ring D precursors,[1] seems to offer a good prospect for a chiral approach. On the other hand, suitably functionalised optically active five-membered ring ketones or their silyl enol ethers, with the right configuration for steroid synthesis, are not over-abundant. Most efforts were developed to obtain ring D precursors for the synthesis of vitamin D analogs[2–10] and some for steroids.[9–13] Three such routes starting from a chiral natural product have been published,[3,8–10,14,15] next to several routes using a chiral auxiliary during synthesis.[2,4,5,11,16–19] In one route a chiral starting material obtained through biotransformation has been applied.[6,7]

Compounds from the chiral pool seemed to offer good opportunities to access a chiral steroid ring D precursor and based on our experience it was decided to explore a synthesis starting from carvone (**1**). A sequence involving a ring contraction of carvone using a Favorskii rearrangement has been reported in the literature and leads, in five steps, to the selectively protected diol **3** in 36% overall yield.[20] Further transformation could lead in a few more steps to silyl enol ether **5** as the chiral steroid ring D precursor. Coupling with the Torgov reagent **6** and ring closure should lead to the chiral steroid skeleton **8** with a functionalised substituent at C17 (see Scheme 1). To obtain the correct stereochemistry at C17 in the final steroid skeleton, C5 in carvone **1** should have the *S* configuration.



Scheme 1.

Keywords: Mukaiyama–Michael addition; Carvone; Chiral silyl enol ethers; C,D-trans steroid synthesis.
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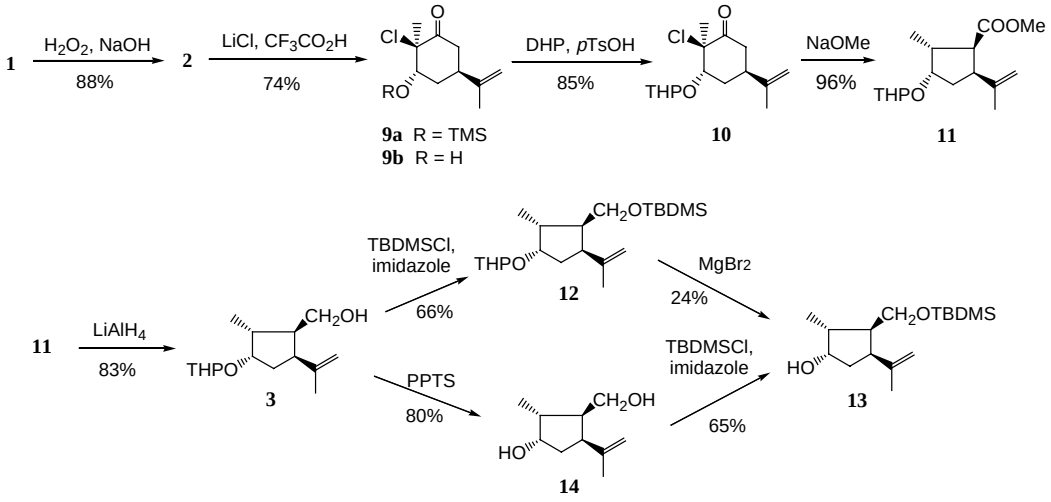
2. Results and discussion

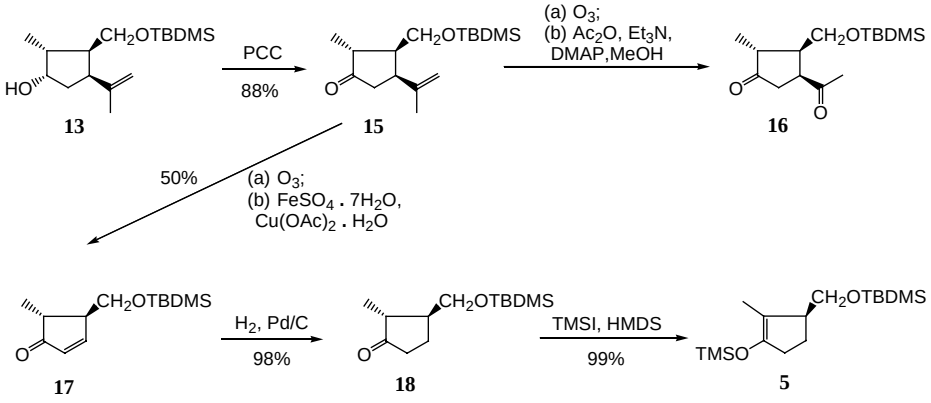
Epoxidation of the double bond of the enone in carvone using hydrogenperoxide in basic solution, leads to epoxide **2** in 88% yield, and in principle this epoxide should be a substrate for the required Favorskii rearrangement. Unfortunately, this rearrangement does not give only the desired ring contraction product, but also a regioisomer and opening of the epoxide.[20–23] For a more selective result, the epoxide ring has to be opened first stereoselectively to compound **9b** and then converted to THP ether **10** (Scheme 2). In the literature an opening of epoxide **2** to the silylated alcohol **9a** was reported using TMSCl.[20] In our hands better results were obtained using LiCl in combination with trifluoroacetic acid,[24] giving directly the free alcohol **9b**. Protection of the alcohol as a diastereomeric mixture of THP ethers **10** was necessary for complete stereo- and regioselectivity in the Favorskii rearrangement,[20,24] the use of silyl protecting groups on the alcohol moiety did not give as good results.[25] Coordination of the oxygen in the THP ring with the alcohol that donates its proton during the rearrangement could be a possible explanation for the desired regioselective opening of the cyclopropane ring.

Reduction of the rearranged ester **11** gave the selectively protected diol **3**.[24] Our attempts to first protect the primary alcohol in **3** and then selectively remove the THP group using $MgBr_2$[26] gave only 24% of **13**, and treatment with Et_2AlCl[27] failed completely. Diol **13**, with a protected primary hydroxyl group, was obtained in a better 65% yield via deprotection to diol **14**, followed by selective reprotection of the primary alcohol. Although this yield is still not very high, the remaining products consist of unreacted diol **14** (21%) and the double protected diol (12.5%), which can be separated easily from **13** and used again.

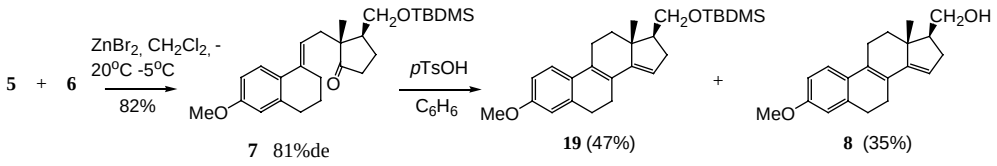
Oxidation of the secondary hydroxyl group in **13** opens up the possibility for regioselective elimination of the isopropenyl group to compound **17** (Scheme 3). Ozonolysis followed by Criegee rearrangement, using triethylamine, aceticanhydride and DMAP in methanol,[28,29] was troublesome in our hands and usually gave diketone **16**, in which normal ozonolysis of the double bond to the ketone had taken place. Only with the use of $FeSO_4$ and $CuSO_4$ salts for decomposition of the intermediate a fair yield (50%) of the desired enone **17** could be obtained.[30] Catalytic reduction of the double bond to **18** and regioselective formation of the silyl enol ether, both in near quantitative yields, finally led to the desired chiral steroid ring D precursor **5** in 10% overall yield starting from (*S*)-(+)-carvone.



Scheme 2.



Scheme 3.



Scheme 4.

Silyl enol ether **5** was put into reaction with the Torgov reagent **6**, which yielded secosteroid **7** in 82% yield as a mixture of two C13 diastereomers, with a diastereomeric excess of 81% (Scheme 4). No crystals could be obtained to prove the configuration of the main product using X-ray crystallography, and also NOE experiments failed to show any effect between the C13 methyl group or the C12 methylene group with the hydrogen atom on C17 or the methylene group bearing the OTBDMS group. However, based on experience with similar reactions,[1] it may be assumed that this main product has the desired *S*-configuration on C13.

Subsequent cyclisation of **7** gave the steroidal diene **19** in 47% yield, next to the deprotected compound **8**, in 35% yield. The protected diene **19** appeared to be unstable upon storage, decomposing to a complex mixture of products, even when kept at −18 °C. Better results were obtained with diene **8**, which remained stable upon storage and complete deprotection of the alcohol moiety in the side chain (e.g., using TBAF in THF) directly after the cyclisation, is therefore the best procedure. Selective reduction (e.g., using H_2, $Pd/CaCO_3$) then can be carried out to afford the C,D trans coupled steroid skeleton.

Although the overall yield of optically active steroid ring D precursor **5** from (*S*)-(+)-carvone is only 10% and requires 11 steps, the applicability of this approach for the preparation of enantiomerically pure steroid skeletons has been shown. The development of straightforward, easy and high yielding syntheses for chiral steroid ring D precursors is, however, essential to make this route to a good method for the synthesis of optically active steroid skeletons.

3. Experimental

3.1. General procedure. See[31]

3.1.1. 3-Hydroxymethyl-4-isopropenyl-2-methyl-cyclopentanol (14). To a cooled solution (at −15 °C) of (*S*)-(+)-carvone (10 g, 0.066 mol) in methanol (66 ml) and 22 ml of H_2O_2 (30%, 0.198 mol), 5 ml of 6.6 M NaOH solution in H_2O was added dropwise over a period of 5 min. During the addition the temperature was carefully kept below 0 °C. The mixture was stirred for 2 h at 0 °C and then the solution was allowed to warm to room temperature over a period of 1 h. The reaction mixture was poured in water (400 ml) and the water solution was extracted four times with diethyl ether (100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 9.8 g of crude product **2**, which was used without any further purification in the next step. ^{1}H NMR (C_6D_6) δ: 1.31 (s, 3H), 1.62 (s, 3H), 1.75–2.05 (m, 2H), 2.28 (br d, J=14.6 Hz, 1H), 2.38–2.75 (m, 2H), 3.37 (d, J=2.8 Hz, 1H), 4.63 (br s, 1H), 4.70 (br s, 1H); ^{13}C NMR (C_6D_6) δ: 15.2 (q), 20.5 (q), 28.6 (t), 34.9 (d), 41.7 (t), 58.6 (s), 61.2 (d), 110.4 (d), 146.3 (s), 205.3 (s).

To an ice-cooled solution of **2** (4.3 g, 26 mmol) in dry THF (100 ml), LiCl (1.8 g, 43 mmol) and CF_3COOH (4.9 g, 43 mmol) were added. The mixture was stirred for 20 min at 0 °C and during 2 h at room temperature. Water (500 ml) was added and the reaction mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (100 ml), water (100 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product (5.2 g) was used without any further purification in the next step. ^{1}H NMR (C_6D_6) δ: 1.63 (s, 3H), 1.73 (s, 3H), 1.87 (ddt, J_1=2.1 Hz, J_2=3.6 Hz, J_3=14.2 Hz, 1H), 2.28–3.10 (m, 5H), 4.23 (dd, J_1=3.7 Hz, J_2=6.3 Hz, 1H), 4.75 (br s, 1H), 4.78 (br s, 1H); ^{13}C NMR (C_6D_6) δ: 20.3 (q), 22.1 (q), 32.8 (t), 38.9 (d), 41.1 (t), 67.9 (s), 76.8 (d), 110.6 (t), 146.4 (s), 205.3 (s).

A solution of product **9b** (5.2 g) from the former reaction in dry CH_2Cl_2 (100 ml) was cooled on ice and DHP (dihydropyran, 6.4 g, 76 mmol) was added, followed by a catalytic amount of *p*TsOH (50 mg). The mixture was stirred for 2 h during, which the temperature was allowed to rise to room temperature (the reaction mixture became green). After evaporation of CH_2Cl_2 under reduced pressure, the residue was dissolved in light petroleum and purified over a short plug of silica (5 g), yielding 4.7 g of crude product **10** as a mixture of diastereomers, which were used without any further purification in the next step.

To 20 ml of an ice-cooled solution of NaOMe (1.2 M) in methanol, 4.7 g of **10**, from the former experiment, in 10 ml of dry methanol was added drop wise over a period of 10 min. During the addition, a precipitate started to form and it appeared necessary to keep the temperature of the reaction below 15 °C. The reaction mixture was stirred for a further 15 min before water (300 ml) was added. The mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 4.43 g of crude product **11** as a slightly yellow oil as a mixture of two diastereomers. The crude product was used without any further purification in the next step.

To an ice-cooled mixture of $LiAlH_4$ (1 g, 26 mmol) in dry diethyl ether (20 ml) was added drop wise a solution of **11** (4.43 g) in dry diethyl ether (10 ml), over a period of 10 min. The reaction mixture was stirred for a 2 h at room temperature. Then 1 ml of water was carefully added under cooling with ice, followed by 4 ml of a 4 M NaOH solution and again 4 ml of water. After stirring for 30 min

the reaction mixture was filtered to remove the inorganic precipitate, which was carefully washed with ether (20 ml). The filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product **3** (3.31 g, slightly yellow oil) was used without any further purification in the next step. ^{1}H NMR (C_6D_6) δ: 0.98 and 1.09 (2d, J= 6.6 Hz, 3H), 1.30–2.15 (m, 10H), 2.78–3.10 (m, 1H), 3.47 (q, J=5.5 Hz, 2H), 3.80–3.93 (m, 1H), 4.00–4.15 (m, 1H), m 4.52–4.67 (m, 1H), 4.76 (br s, 1H), 4.85 (br s, 1H).[24]

The crude product **3** from the former experiment (3.1 g) in 35 ml of methanol and a catalytic amount of pyridinium *para*-toluenesulfonic acid (PPTS, 10 mol%) were stirred at 50 °C during 2 h. After evaporation of the methanol under reduced pressure, the residue (2.35 g) was purified by rapid column chromatography (PE/EtOAc 10:1), yielding 1.5 g of pure **14** (32% overall yield from (*S*)-(+)-carvone). $[\alpha]_D^{20}$ 13.6 (*c* 12.0 in $CHCl_3$); IR (film) cm^{-1}: 3356 (br), 3081, 2957, 2932, 1646, 1453, 1375, 1080, 1041, 891; ^{1}H NMR ($CDCl_3$) δ: 1.01 (d, J=6, 7 Hz, 3H), 1.65–2.23 (m, 9H), 2.94–3.04 (m, 1H), 3.44 (d, J=5 Hz, 2H), 4.11 (m, 1H), 4.72 (s, 1H), 4.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0 (q), 23.83 (q), 38.8 (t), 41.6 (d), 44.8 (d), 49.0 (d), 63.6 (t), 74.47 (d), 110.6 (t), 147.0 (s). HRMS: M^+, found 170.1308. $C_{10}H_{18}O_2$ requires 170.1307. MS *m/e* (%) 170 (M^+, <1), 155 (3), 152 (4), 121 (81), 99 (55), 81 (100), 72 (64), 71 (66), 55 (69), 43 (56).

3.1.2. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropenyl-2-methyl-cyclopentanol (13). A solution of **14** (3.8 g, 22 mmol) in dimethylformamide (DMF, 70 ml) was cooled to 5 °C and TBDMSCl (3.7 g, 24 mmol) in DMF (20 ml) was added by rapid dropping (5 min), followed by a solution of imidazole (3.8 g, 56 mmol) in DMF (10 ml). The reaction mixture was stirred for 20 min at 5 °C and then for 3 h at 30 °C. Water was added (500 ml) and the water layer was extracted with Et_2O (4×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EA 15:1), yielding 4.15 g of **13** (65%) as a colourless oil, 1.1 g of the diprotected compound (12.5%) as a colourless oil, and 0.46 g of unreacted material **14** (12%).

Compound **13**. $[\alpha]_D^{20}$ −3.1 (*c* 5.0 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 3631, 3491 (br), 3083, 2951, 2894, 2858, 1647, 1471, 1459, 1255, 1093, 1003, 889; ^{1}H NMR (C_6D_6) δ: 0.16 (s, 6H), 0.86 (s, 9H), 1.08 (d, J=6.9 Hz, 3H), 1.75 (s, 3H), 1.64–2.04 (m, 5H), 2.89–2.98 (m, 1H), 3.28 (dd, J_1= 7.6 Hz, J_2=10.1 Hz, 1H), 3.47 (dd, J_1=5.3 Hz, J_2= 10.1 Hz, 1H), 4.17 (dd, J_1=3.6 Hz, J_2=4.4 Hz, 1H), 4.62 (s, 1H), 4.77 (s, 1H); ^{13}C NMR (C_6D_6) δ: −5.5 (2q), 14.7 (q), 18.2 (s), 23.8 (q), 25.9 (3q), 38.8 (t), 42.5 (d), 44.8 (d), 47.5 (d), 64.1 (t), 74.6 (d), 110.1 (t), 145.2 (s). HRMS: $[M-tBu]^+$, found 227.1470. $C_{12}H_{23}O_2Si$ requires 227.1467. MS *m/e* (%) 251 ($[M-CH_3-H_2O]^+$, 2), 227 (32), 209 (76), 185 (20), 95 (18), 93 (14), 75 (100), 73 (29).

Diprotected compound. ^{1}H NMR (C_6D_6) δ: 0.07 (s, 6H), 0.09 (s, 6H), 0.89 (s, 18H), 1.02 (d, J=6.6 Hz, 3H), 1.60 (dd, J_1=6.4 Hz, J_2=12.4 Hz, 1H), 1.77 (s, 3H), 1.70–1.97 (m, 3H), 2.89–3.02 (m, 1H), 3.28 (dd, J_1=7.1 Hz, J_2= 10.0 Hz, 1H), 3.47 (dd, J_1=5.1 Hz, J_2=10.0 Hz, 1H), 4.09–4.13 (m, 1H), 4.62 (s, 1H), 4.77 (s, 1H); ^{13}C NMR (C_6D_6) δ: −5.4 (2q), −4.7 (q), −4.6 (q), 15.5 (q), 18.2 (s), 23.9 (q), 25.9 (6q), 39.5 (t), 43.2 (d), 43.7 (d), 47.5 (d), 64.2 (t), 74.8 (d), 109.7 (t), 145.7 (s).

3.1.3. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropenyl-2-methyl-cyclopentanone (15). To a solution of **13** (4.1 g, 14.4 mmol) in dry CH_2Cl_2 (120 ml), to which 4 g of molecular sieves (3 Å) were added, 4.5 g of pyridinium chlorochromate (PCC, 21.6 mmol) was added in three portions over a period of 3 h. The reaction mixture was stirred for 2 h more, filtered over a short plug of silica and evaporated under reduced pressure. The residue was dissolved in Et_2O (200 ml) washed with water and brine, dried ($MgSO_4$) and evaporated again under reduced pressure. The crude product was purified by flash chromatography (PE/EtOAc 15:1), yielding 3.6 g of **15** (88%), next to some minor unidentified products. $[\alpha]_D^{20}$ 21.2 (*c* 1.25 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2958, 2931, 2859, 1743, 1471, 1254, 1091; ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 6H), 0.83 (s, 9H), 1.13 (d, J=7.5 Hz, 3H), 1.77 (s, 3H), 2.05–2.60 (m, 5H), 2.97 (br q, J=8.0 Hz, 1H), 3.57 (d, J=7.9 Hz, 2H), 4.69 (s, 1H), 4.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: −5.7 (2q), 15.9 (q), 18.1 (s), 22.6 (q), 25.7 (3q), 41.7 (t), 42.6 (d), 45.6 (d), 47.9 (d), 62.8 (t), 111.5 (t), 143.9 (s), 221.2 (s). HRMS: $[M-CH_3]^+$, found 267.1782. $C_{15}H_{27}O_2Si$ requires 267.1780. MS *m/e* (%) 282 (M^+, 0.03), 267 (2.7), 225 (100), 195 (8), 133 (20), 131 (15), 75 (59), 73 (22).

3.1.4. 4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-methyl-cyclopent-2-enone (17). A stirred solution of **15** (1.0 g, 3.54 mmol) in CH_2Cl_2 (24 ml) and MeOH (20 ml) was cooled to −78 °C and purged with ozone until a pale blue colour appeared (~15 min). Nitrogen was then bubbled through for 30 min to remove the excess of ozone and $FeSO_4\cdot 7H_2O$ (0.98 g, 3.54 mmol) and $Cu(OAc)_2\cdot H_2O$ (1.4 g, 7.10 mmol) were added. The reaction mixture was allowed to warm to room temperature overnight, after which the solvents were evaporated under reduced pressure. The residue was dissolved in water and extracted with Et_2O (4×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 15:1), yielding 0.43 g of **17** (50%), next to some unidentified products and **16**. $[\alpha]_D^{20}$ 122.4 (*c* 6.6 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.02 (s, 6H), 0.75 (s, 9H), 1.17 (d, J=7.4 Hz, 3H), 2.09 (dq, J_1=2.5 Hz, J_2=7.5 Hz, 1H), 2.65 (m, 1H), 3.68 (m, 2H), 6.15 (dd, J_1= 2.0 Hz, J_2=5.8 Hz, 1H) 7.56 (dd, J_1=2.3 Hz, J_2=5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: −5.5 (2q), 14.9 (q), 18.9 (s), 25.8 (3q), 43.2 (d), 52.9 (d), 64.3 (t), 133.7 (d), 163.9 (d), 212.1 (s). HRMS: $[M-CH_3]^+$, found 225.1311. $C_{12}H_{21}O_2Si$ requires 225.1311. $[M-C_4H_9]^+$, found 183.00842, $C_9H_{15}O_2Si$ requires 183.0841. MS *m/e* (%) 225 ($M-CH_3^+$, 3), 210 (2), 183 ($M-C_4H_9^+$, 100), 153 (15), 139 (15), 126 (9), 75 (32).

3.1.5. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-cyclopentanone (18). To a solution of **17** (200 mg, 0.83 mmol) in *t*BuOMe (10 ml) was added Pd on C (10%, 20 mg) had the suspension was shaken under hydrogen atmosphere pressure (50 psi [3.45 bar]) during 1 h. The reaction mixture was filtered over a short plug of

Hyflo, which was then carefully washed with ether. The filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure yielding pure **18** (198 mg, 98%), which needed no further purification. $[\alpha]_D^{20}$ −46.3 (*c* 1.7 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2957, 2925, 2876, 2858, 1743, 1470, 1255, 1107; ^1H NMR ($CDCl_3$) δ: 0.03 (s, 6H), 0.88 (s, 9H), 1.16 (d, $J=7$ Hz, 3H), 1.61–2.44 (m, 6H), 3.7 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: −5.1 (2q), 12.8 (q), 23.6 (t), 25.8 (3q), 37.2 (t), 46.2 (d), 46.8 (d), 64.3 (t). HRMS: $[M-CH_3]^+$, found 227.1471. $C_{12}H_{23}O_2Si$ requires 227.1467. MS *m/e* (%) 227 ($[M-CH_3]^+$, 2.6), 185 (100), 141 (13), 129 (18), 75 (58), 73 (11).

3.1.6. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-1-trimethylsilanyloxy-cyclopentene (5). Compound **18** (174 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (5 ml) and hexamethyl disilazane (HMDS, 0.550 ml, 2.6 mmol) was added, followed by TMSI (312 µl, 2.2 mmol). The reaction mixture was stirred overnight at room temperature, diluted with Et_2O (15 ml) and washed with a saturated solution of $NaHCO_3$ and brine. After drying (Na_2SO_4) the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:Et_2O/Et_3N 98:1:1) giving 225 mg of pure product **5** (99%). $[\alpha]_D^{20}$ 15.4 (*c* 5.5 in *n*-C_6H_{12}); IR (CCl_4 sol.) cm^{-1}: 2958, 2924, 2898, 2857, 1685, 1329, 1253, 1205, 1107, 1065, 1006, 920; ^1H NMR (C_6D_6) δ: 0.03 (s, 6H), 0.14 (s, 9H), 0.97 (s, 9H), 1.67 (s, 3H), 1.64–1.93 (m, 2H), 2.15–2.34 (m, 2H), 2.50–2.67 (m, 1H), 3.44 (dd, $J_1=6.3$ Hz, $J_2=9.7$ Hz, 1H), 3.59 (dd, $J_1=4.8$ Hz, $J_2=9.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −5.4 (2q), 0.6 (3q), 10.8 (q), 18.4 (s), 24.0 (t), 26.0 (3q), 32.8 (t), 47.9 (d), 66.1 (t), 113.4 (s), 148.3 (s). HRMS: M^+, found 314.2095. $C_{16}H_{34}O_2Si_2$ requires 314.2097. MS *m/e* (%) 314 (M^+, 2), 299 (2), 257 (2), 169 (100), 147 (2), 73 (20).

3.1.7. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (7). 6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (**6**, 68 mg, 0.33 mmol) and compound **5** (314 mg, 1 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to −20 °C. $ZnBr_2$ (a few crystals, approx. 20 mg) was added as the catalyst and the reaction mixture was stirred for 4 h at −5 °C. When all of compound **6** had disappeared (TLC), EtOAc (25 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding compound **7** as a colourless oil in 82% yield (116 mg). $[\alpha]_D^{20}$ −16.5 (*c* 2.34 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2953, 2932, 2896, 2859, 1740, 1606, 1496, 1464, 1255, 1100; ^1H NMR (C_6D_6) δ: 0.02 (s, 6H), 0.94 (s, 9H), 0.97 (s, 3H), 1.10–1.34 (m, 1H), 1.60–1.95 (m, 4H), 2.05–2.26 (m, 2H), 2.30–2.64 (m, 6H), 3.33 (s, 3H), 3.35–3.62 (m, 2H), 6.00 (br t, $J=7.8$ Hz, 1H), 6.57 (d, $J=2.7$ Hz, 1H), 7.72 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.60 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −5.7 (2q), 17.2 (q), 18.1 (s), 22.8 (t), 23.5 (t), 25.8 (q), 26.9 (t), 30.8 (t), 35.9 (t), 36.8 (t), 44.6 (d), 51.1 (s), 54.5 (q), 64.4 (t), 112.7 (d), 113.3 (d), 117.3 (d), 125.3 (d), 129.3 (s), 136.6 (s), 138.6 (s), 159.0 (s), 220.1 (s). HRMS: M^+, found 428.2755. $C_{26}H_{40}O_3Si$ requires 428.2747. MS *m/e* (%) 428 (M^+, 8.1), 187 (100), 174 (3.2), 161 (3.1), 159 (3.5), 75 (2.6), 73 (3.4).

3.1.8. *tert*-Butyl-(3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]-phenanthren-17-ylmethoxy)-dimethyl-silane (19) and (3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-methanol (8). Compound **7** (108 mg, 0.25 mmol) was dissolved in benzene (5 ml) and a crystal of *para*-toluene sulfonic acid (*p*TsOH) was added. The reaction mixture was stirred at 40 °C for 6 h, then the reaction mixture was diluted with Et_2O (15 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding 47% of **19** (48 mg) and 35% of **8** (26 mg).

Compound **19**. $[\alpha]_D^{20}$ −9.3 (*c* 2.89 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2858, 1607, 1464, 1255; ^1H NMR (C_6D_6) δ: 0.10 (s, 6H), 1.00 (s, 3H), 1.02 (s, 9H), 1.20–1.38 (m, 1H), 1.55–1.78 (m, 2H), 2.10–2.80 (m, 8H), 3.38 (s, 3H), 3.65–3.88 (m, 2H), 5.53 (br s, 1H), 6.68–6.79 (m, 2H), 7.19 (d, $J=9.3$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −5.5 (2q), 16.1 (q), 18.2 (s), 23.8 (t), 24.0 (t), 25.9 (3q), 28.8 (t), 33.8 (t), 36.1 (t), 44.9 (s), 53.6 (q), 54.5 (d), 63.7 (t), 111.2 (d), 113.6 (d), 119.3 (d), 124.2 (d), 125.7 (s), 129.1 (s), 129.5 (s), 138.0 (s), 149.8 (s), 158.8 (s). HRMS: M^+, found 410.2639. $C_{26}H_{38}O_2Si$ requires 410.2641. MS *m/e* (%) 410 (M^+, 100), 395 (4), 353 (8), 278 (43), 263 (33), 89 (9), 75 (17), 73 (23).

Compound **8**. $[\alpha]_D^{20}$ −34.0 (*c* 1.08 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2933, 2835, 1606, 1561, 1498, 1248, 1216, 1044; ^1H NMR (C_6D_6) δ: 0.91 (s, 3H), 1.01 (br, 1H), 1.50–1.70 (m, 1H), 1.95–2.73 (m, 10H), 3.37 (s, 3H), 3.45–3.70 (m, 2H), 5.50 (br s, 1H), 6.68–6.75 (m, 2H), 7.17 (d, $J=9.8$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 16.1 (q), 23.8 (t), 24.0 (t), 28.8 (t), 34.1 (t), 35.9 (t), 44.8 (s), 53.7 (d), 54.5 (q), 63.2 (t), 111.3 (d), 113.6 (d), 119.3 (d), 124.3 (d), 125.7 (s), 129.1 (s), 129.5 (s), 138.1 (s), 149.7 (s), 158.8 (s). HRMS: M^+, found 296.1774. $C_{20}H_{24}O_2$ requires 296.1776. MS *m/e* (%) 296 (M^+, 100), 265 (7), 263 (9), 249 (3), 225 (3), 165 (4), 139 (3).

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References and notes

1. Saraber, F. C. E.; de Groot, A. *Tetrahedron Lett.* **2004**, *45*, 9431.
2. Pan, L. R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1473.
3. Daniewski, A. R.; Warchol, T. *Liebigs Ann. Chem.* **1992**, 965.

4. Nagasawa, K.; Matsuda, N.; Noguchi, Y.; Yamanashi, M.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 1483.
5. He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307.
6. Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1998**, *39*, 885.
7. Gorobets, E.; Urbanczyk-Lipowska, Z.; Stepanenko, V.; Wicha, J. *Tetrahedron Lett.* **2001**, *42*, 1135.
8. Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944.
9. Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 724.
10. Suzuki, T.; Sato, E.; Unno, K. *Chem. Pharm. Bull.* **1993**, *41*, 244.
11. Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W. D.; Adam, F.; Baier, H.; Frank, G.; Dürner, G. *Liebigs Ann. Chem.* **1982**, 1999.
12. Trudeau, S.; Deslongchamps, P. *J. Org. Chem.* **2004**, *69*, 832.
13. Jiang, X.; Covey, D. F. *J. Org. Chem.* **2002**, *67*, 4893.
14. Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.
15. Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2263.
16. Pan, L. R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469.
17. Shimizu, I.; Matsuda, N.; Noguchi, Y.; Zako, Y.; Nagasawa, K. *Tetrahedron Lett.* **1990**, *31*, 4899.
18. Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032.
19. Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036.
20. Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479.
21. Kametani, T.; Suzuki, Y.; Ban, C.; Honda, T. *Heterocycles* **1987**, *26*, 1491.
22. Kametani, T.; Honda, T.; Ishizone, H.; Kanada, K.; Naito, K.; Suzuki, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 646.
23. Asaka, Y.; Kamikawa, T.; Kubota, T. *Tetrahedron* **1974**, *30*, 3257.
24. Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996.
25. A lower yield and selectivity was reported in the literature for the TBDPS-protected alcohol [Ref. 22]. In our case, the Favorskii rearrangement was also attempted with the TMS-protected alcohol, but this yielded a mixture of several products, which were not identified.
26. Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439.
27. Ogava, J.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 663.
28. Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363.
29. Daniewski, A. R.; Garofalo, L. M.; Hutchings, S. D.; Kabat, M. M.; Liu, W.; Okabe, M.; Radinov, R.; Yiannikouros, G. P. *J. Org. Chem.* **2002**, *67*, 1580.
30. Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165.
31. Sarabèr, F.C.E.; Drach, S.; Bosselaar, G.; Jansen, B.J.M.; de Groot, A. *Tetrahedron* **2005**, *62*, see doi: 10.1016/j.tet.2005.11.056.