Vitamin D: Enantioselective Synthesis of (3a*R*,4*R*,7a*S*)-4-Hydroxy-7a-methylperhydro-1-indenone, a Suitable CD-Ring Fragment

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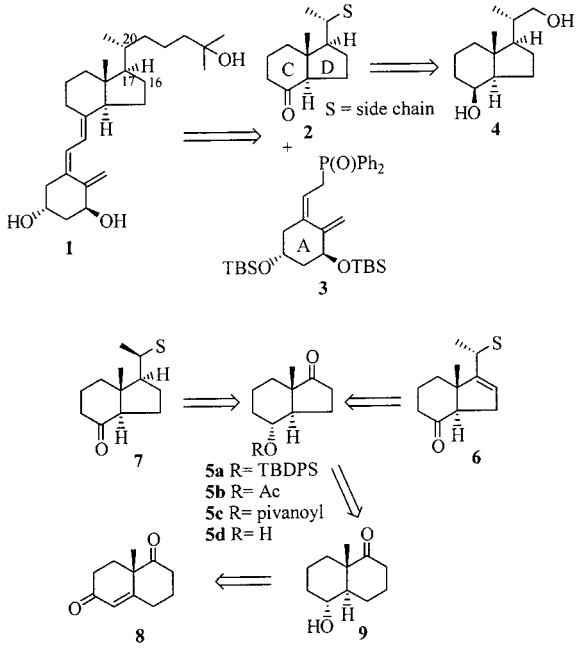
A practical synthesis of *trans*-hydrindanone **5a** from (+)-Wieland–Miescher ketone **8** is described. The target molecule **5a** is a suitable precursor for the synthesis of analogues of 1α,25-dihydroxyvitamin D_3 modified at C-16, C-17 or C-20. During the total synthesis it was found that hydroboration of (1,1)-ethylenedioxy-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene **(11)** leads to a *cis*-decalin **13** instead of the literature reported *trans*-fusion.

Introduction

The observation that the metabolite 1α,25-dihydroxyvitamin D_3 (**1**, calcitriol) is active in the regulation of cell proliferation and differentiation, in addition to its classical role in calcium-bone homeostasis, has led in recent years to the development of analogues capable of dissociating cell differentiating effects from calcemic effects.[1−3]

In general,[4] the synthesis of vitamin D metabolites and analogues follows a modular strategy whereby a side chain (S) is first attached to the central CD-ring followed by coupling of the upper fragment with an A-ring precursor. This final step is frequently based on the Lythgoe coupling[5] of hydrindanone **2** with phosphane oxide **3** (Scheme 1).[6]



Scheme 1

The upper fragment is usually constructed from the Inhoffen−Lythgoe diol **4**[7] obtained upon ozonolysis of vitamin D_2 (with the ergosterol side chain). However, this partial synthesis requires complete removal of the side chain in order to obtain analogues modified at positions C-16, C-17 or C-20. A number of very potent analogues are based on such modifications, for example, 16-ene[8] (see structure **6**) and 20-*epi*[9] (see structure **7**).

It is therefore of interest to develop a total synthesis that can circumvent these problems. An obvious approach should involve the intermediate *trans*-fused hydrindan-17-one (steroid numbering) **5a**, since the synthetic flexibility of the 17-carbonyl function is well documented.[4a]

Extensive research directed towards the total synthesis of Inhoffen−Lythgoe diol derivatives or related key-intermediates has been reported in the literature.[4] The construction of the *trans*-fusion rings with a suitable function at C-8 is the main problem associated with the synthesis of the CD-ring fragments. Usually a large number of steps are required, and all reported approaches involve a cyclization to form a hydrindan skeleton. Furthermore, a full or truncated side chain is usually incorporated in the early stages; the Daniewski synthesis[10] is one of the most efficient. Only a few approaches involve a protected hydroxy-group derivative (**5b**,[11] **5c**[12]) of 4-hydroxy-7a-methylperhydro-1-indenone **(5d).**[13]

Results and Discussion

We want to report an alternative approach based on a D-ring contraction of a *trans*-fused decalone intermediate **9**. In contrast to the hydrindan system, a *trans*-fused decalin is readily accessible. We decided to explore this strategy, and aimed to provide a simple and practical synthetic approach, from the readily available (+)-Wieland−Miescher ketone **8.**[14] The optical purity of **8**[15,16] (m.p. 50 °C), with $[\alpha]_D^{r.t.}$ = +99.2 (*c* = 1.51, benzene), is 99.0% *ee* as determined by subcritical fluid chromatography (SFC).[17]

Selective thioacetalization of the conjugated carbonyl function in **8** led to **10** (Scheme 2). Protection of the remaining carbonyl function in **10**, and desulfurization by re-

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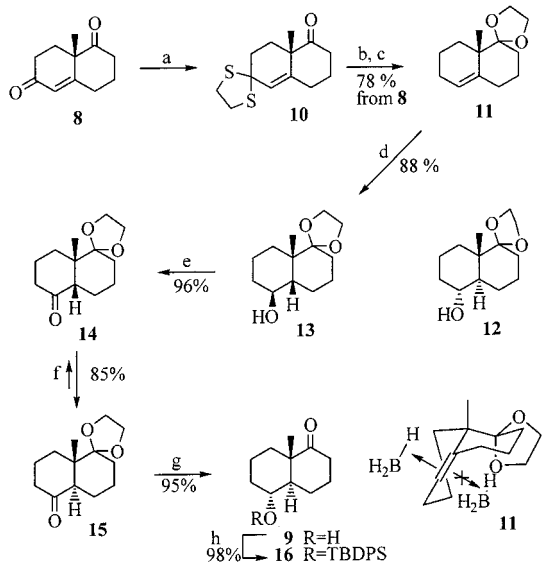
duction with sodium in liquid ammonia afforded **11** in 78% overall yield from **8,**[18] without purification of the intermediates.



Scheme 2. (a) $(CH_2SH)_2$, AcOH, PTSA, room temp., 5 h; (b) $(CH_2OH)_2$, PTSA, toluene, reflux, 12 h; (c) Na, *liq.* NH_3, THF, reflux, 1 h; (d) (i) BH_3 THF, 0 °C, 3 h then room temp., 12 h; (ii) NaOH, H_2O_2, reflux, 4 h. (e) TPAP, NMO, mol. sieves (4Å), CH_2Cl_2, room temp., 3 h; (f) NaOMe, MeOH, room temp., 2 d; (g) Li, *liq.* NH_3, THF, MeOH, −78 °C, 2 h, then PTSA, Me_2CO-H_2O, room temp., 10 h; (h) TBDPSCl, imid., DMAP, room temp., 2 days

Our total synthesis was based on an observation of Bosch et al.[18] who claimed that hydroboration of **11** leads to the *trans*-decalinol **12**. However, we found that the *cis*-fused product **13** is formed in 88% *de*. The stereochemistry was easily proven by oxidation of **13** to **14,** and base-catalyzed equilibration to the thermodynamically more stable *trans*-decalone **15**. Full proof was provided by the eventual synthesis of **5d** (from **15**), which has also been independently obtained by an unambiguous formation of the *trans*-fusion intermediate.[19]

Bosch and Meinwald[18] assigned *trans*-fusion of the ketone obtained after oxidation (presumed **15**) on the basis of the width at half height ($\Delta W_{h/2}$) of its angular methyl ^1H NMR absorption which is characteristically broader in *trans*-decalins than in *cis*-decalins. This rule, proposed by Williamson et al.,[20] is based on the presence of more "W-couplings" for the angular methyl protons in a *trans*-fused system. Our measurements for **14** and **15** on a 500 MHz instrument (60 MHz in refs.[18,19]) show no significant difference in $\Delta W_{h/2}$. The rule is seemingly not valid for compounds with this particular substitution pattern. In retrospect, the outcome of the hydroboration of **11** is logical with regard to the steric congestion of the *endo*-face.

Although a further three steps were required for the stereochemical correction, we nevertheless decided to pursue this route. Indeed, these three steps (e, f, g in Scheme 2) represent easy and high yielding transformations. Reduction of **15** was performed with lithium in liquid ammonia and led solely to the equatorial hydroxy function. It is worthy of note that the epimer with an axial C-8 hydroxy group was obtained as the major product (ratio 85:15) upon reduction with sodium borohydride, and could not be easily protected due to the 1,3 diaxial interaction with the angular methyl group.

Finally, hydrolysis of the acetal group and protection of the hydroxy function afforded decalone **16**, the key-intermediate for the ring contraction (Scheme 3). As we planned to use the half-ester **18b** (vide infra), ring cleavage had to be carried out on the α-hydroxy ketone **17**. Several methods for the formation of **17** from **16** were explored, and the most practical was epoxidation of the TMS-enolether of **16** followed by acid-catalyzed hydrolysis.[21] The yield of pure **17** from **16** was 94%.

For the overall transformation of **16** to **5a** we decided to develop a protocol without purification of the intermediates. Thus, crude α-hydroxy ketone **17** was cleaved with lead(IV) acetate in the presence of methanol; the resulting solution was filtered over a short silica-gel pad, and the solvents were evaporated. The resulting residue **18a** was oxidized with sodium chlorite in the presence of 2-methyl-2-butene. The crude half-ester **18b**, obtained from extraction and drying, was treated at 0 °C with LDA (5 equiv.), and subsequent decarboxylation of **19a** was affected upon workup with acetic acid and reflux for 1 h. The target molecule **5a** was obtained in 70% overall yield from **16**.

The overall yield, from Wieland−Miescher ketone **8**, with five purifications (compounds **11**, **15**, **9**, **16** and **5a**) is 30%. The overall procedure is practical because no cooling below 0 °C is needed [except for reduction steps (c) and (g) in Scheme 2], most reagents are fairly common and the number of purifications is minimal. It therefore compares favourably with the two described approaches.[11,12]

We have also carried out the Dieckmann cyclization of di-ester **18c** which afforded the intermediate β-keto-ester **19b** in 99% yield. However the subsequent decarbomethoxylation gave **5a** in only 34% yield due to substantial cleavage of the silyl ether.

The parent hydroxy-hydrindanone **5b,** already synthesized by Uskokovic et al.,[11] has been transformed by this research group into vitamin D metabolites and analogues.

Experimental Section

General: All reactions were carried out under an argon atmosphere with magnetic stirring. All solvents were purified or dried according to standard literature procedures. Solutions were dried over $MgSO_4$ (unless otherwise specified) and solvent evaporations were carried out in a Rotavapor at 16 Torr. Column chromatography was performed on SiO_2. HPLC separations were performed on a Knauer 64 or a Kontron 420 delivery system with RI detection. Optical rotations were measured with a Perkin−Elmer 421 polarimeter. IR spectra were recorded on a Perkin−Elmer FTIR-1600 spectrometer, mass spectra on a HP-5988 spectrometer. The ^1H NMR spectra were recorded at 500 MHz (Bruker AN-500), the ^{13}C NMR spectra at 50 MHz (Varian Gemini-200). The chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz. Elemental analyses were carried out by ICHOR, Université Pierre et Marie Curie (Paris, France).

(8a*S*)-1,1-(Ethylenedioxy)-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (11):[18] To a solution of **8** (3.00 g, 16.8 mmol) in glacial HOAc (8 mL) were added 1,2-ethanedithiol (1.74 g, 18.5 mmol), PTSA (1.5 g) and glacial HOAc (18 mL). The mixture was stirred at room temp. for 5 h, poured into water, and stirred for another 15 min. The white solid was filtered off, washed successively with water, dilute $NaHCO_3$ solution and water, and dried to afford crude **10** (4.53 g) used as such in the next step. An analytical sample was obtained upon crystallisation from EtOH; m.p. 144 °C, R_f = 0.40 (isooctane/EtOAc, 4:1), $[\alpha]_D^{r.t.}$ = +112.3 (*c* = 1.2, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 2930, 1701, 1640, 1460, 1420, 1234, 1028, 850, 825 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 5.67 (s, 1 H), 3.39−3.33 (m, 3 H), 3.28−3.23 (m, 1 H), 2.63 (ddd, *J* = 15.04, 13.59, 6.33 Hz, 1 H), 2.52 (ddd, *J* = 13.91, 4.86, 1.70 Hz, 1 H), 2.36 (m, 1 H), 2.25−2.11 (m, 4 H), 2.02 (m, 1 H), 1.76 (m, 1 H), 1.61 (qt, *J* = 13.32, 4.57 Hz, 1 H), 1.30 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 213.0 (C), 141.3 (C), 128.1 (CH), 64.9 (C), 49.5 (C), 40.2 (CH_2), 39.7 (CH_2), 38.0 (CH_2), 37.6 (CH_2), 30.9 (CH_2), 30.7 (CH_2), 24.8 (CH_2), 24.6 (CH_3). − MS: *m*/*z* = 254 [M^+], 239, 211, 193, 179, 161, 137, 118, 105, 91. − $C_{13}H_{18}OS_2$: C 61.37, H 7.13; found C 61.57, H 7.03.

A solution of crude **10** (4.53 g, 16.8 mmol), ethylene glycol (10 mL, 168 mmol) and a small amount of PTSA in toluene (70 mL) was refluxed in a Dean−Stark apparatus. The reaction was quenched with a saturated $NaHCO_3$ solution (70 mL), and the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The organic layers were combined, washed with brine, and dried to give the crude acetal (5.33 g). This residue in THF (60 mL) was added over a period of 5 min to sodium (4.0 g, 170 mmol) in *liq*. ammonia (300 mL). After 1 h the mixture was quenched by careful addition of EtOH until the colour disappeared. The ammonia was allowed to evaporate and water-Et_2O (1:1, 100 mL) was added. The aqueous layer was extracted with Et_2O (3×). The combined fractions were dried and concentrated. The residual oil was purified by column chromatography (isooctane/EtOAc, 100:4) to afford olefin **11** (2.72 g; 78% from **8**); $[\alpha]_D^{r.t.}$ = +78.6 (*c* = 1.08, $CHCl_3$) and R_f = 0.34 (pentane/EtOAc, 20:1). − IR (film): $\tilde{\nu}$ = 2934, 2874, 1456, 1339, 1178, 1049, 1121, 1090, 1059, 1027, 956, 917 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 5.49 (m, 1 H), 3.94 (m, 4 H), 2.25 (ttd, *J* = 13.9, 5.4, 3.0 Hz, 1 H), 2.05−1.32 (m, 11 H), 1.21 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 141.1 (C), 122.1 (CH), 113.1 (C), 65.1 (CH_2), 64.8 (CH_2), 43.6 (C), 30.9 (CH_2), 30.5 (CH_2), 28.8 (CH_2), 25.4 (CH_2), 23.1 (CH_2), 22.5 (CH_3), 19.0 (CH_2); MS: *m*/*z* = 208 [M^+], 198, 149, 118, 99, 93, 91, 79.

(4a*S*,5*S*,8a*S*)-1,1-(Ethylenedioxy)-8a-methylperhydro-5-naphthalenol (13): To a stirred solution of **11** (310 mg, 1.49 mmol) in dry THF (6.7 mL), cooled to 0 °C, was added a BH_3·THF solution (2.06 mL, 2.06 mmol). The mixture was kept at 0 °C for 3 h and then room temp. overnight. A mixture of NaOH (3 N, 0.47 mL) and H_2O_2 (30% , 0.47 mL) was added and was stirred for 4 h. The mixture was diluted with Et_2O, washed with brine, and dried, and the solvents were evaporated. Column chromatography (isooctane/EtOAc, 7:3), and HPLC (isooctane/EtOAc, 7:3) gave alcohol **13** (280 mg, 83%), as a white crystalline solid; m.p. 67 °C and R_f = 0.14 (pentane/EtOAc, 4:1). − IR (film): $\tilde{\nu}$ = 3406, 2938, 2868, 1462, 1450, 1377, 1335, 1295, 1230, 1105, 1126, 1087, 1056, 1020, 1006, 953, 928, 906, 880, 857, 844, 806, 740 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.97−3.84 (m, 5 H), 1.92 (m, 1 H), 1.84 (m, 1 H), 1.75−1.21 (m, 10 H), 1.12 (s, 3 H), 1.02 (m, 1 H). − MS: *m*/*z* = 226 [M^+], 208, 164, 149, 146, 125, 99, 86.

(4a*S*,8a*S*)-1,1-(Ethylenedioxy)-8a-methylperhydro-5-naphthalenone (14): To a solution of **13** (68 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) were added molecular sieves (4Å, 150 mg), NMO (120 mg, 1.02 mmol) and a trace of TPAP. After stirring for 3 h at room temp. the mixture was poured onto a SiO_2 column; elution (isooctane/Me_2CO, 9:1) afforded **14** (65 mg, 96%); R_f = 0.29 (isooctane/Me_2CO, 9:1). − IR (film): $\tilde{\nu}$ = 2953, 2877, 1710, 1473, 1444, 1426, 1375, 1334, 1255, 1233, 1189, 1170, 1141, 1109, 1089, 1023, 1004, 950, 919, 880, 823, 772 cm^{-1}. − MS: *m*/*z* (%) = 224 (4) [M^+], 181 (1), 153 (2), 139 (3), 126 (5), 112 (74), 99 (100), 86 (40), 55 (13). − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.97−3.88 (m, 4 H), 2.48 (ddd, *J* = 19.1, 11.8, 7.2 Hz, 1 H), 2.34 (dd, *J* = 11.0, 4.4 Hz, 1 H), 2.18 (m, 1 H), 2.09 (m, 1 H), 1.97 (m, 1 H), 1.87−1.70 (m, 4 H), 1.63−1.51 (m, 4 H), 0.94 (s, 3 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 213.9 (C), 111.2 (C), 64.8 (CH_2), 64.8 (CH_2), 56.7 (CH), 44.8 (C), 37.2 (CH_2), 29.9 (CH_2), 27.1 (CH_2), 24.8 (CH_2), 22.1 (CH_2), 21.9 (CH_2), 19.2 (CH_3).

(4a*R*,8a*S*)-1,1-(Ethylenedioxy)-8a-methylperhydro-5-naphthalenone (15): A solution of **14** (102 mg, 0.45 mmol) in MeOH (3 mL), containing a trace of MeONa was stirred for 24 h at room temp. Evaporation and HPLC separation (isooctane/Me_2CO, 9:1) gave **15** (87 mg, 85%, conversion 99%) and **14** (14 mg, 14%); R_f = 0.23 (isooctane/Me_2CO, 9:1), m.p. 45 °C. − IR (KBr): $\tilde{\nu}$ = 2942, 2882, 1706, 1459, 1442, 1370, 1314, 1277, 1214, 1190, 1176, 1124, 1081, 1023, 950, 924, 875, 830, 797, 742 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.98 (m, 4 H), 2.62 (m, 1 H), 2.29 (m, 2 H), 1.98 (m, 2 H), 1.86−1.38 (m, 8 H), 0.92 (s, 3 H). − ^{13}C NMR DEPT (50 MHz, $CDCl_3$): δ = 212.6 (C), 111.7 (C), 65.2 (CH_2), 65.1 (CH_2), 54.7 (CH), 47.3 (C), 41.0 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 21.9 (CH_2), 21.2 (CH_2), 19.5 (CH_2), 15.4 (CH_3). − MS: *m*/*z* = 224 [M^+], 195, 126, 112, 99, 86, 67, 55.

(4a*R*,5*R*,8a*S*)-5-Hydroxy-8a-methylperhydro-1-naphthalenone (9): A solution of **15** (200.4 mg, 0.89 mmol) in MeOH (1 mL) was added to a solution of Li (60 mg, 8.60 mmol) in *liq.* ammonia (25 mL) at −78 °C. After the addition of NH_4Cl until the blue colour disappeared, the ammonia was evaporated. Et_2O (40 mL) was added, the mixture was filtered, and the solvent was evaporated. To a solution of the above crude residue in Me_2CO (10 mL) was added a small amount of PTSA and a few drops of water. The mixture was stirred overnight at room temp. The reaction mixture was purified by flash chromatography (isooctane/EtOAc, 1:1) affording ketone **9** (155 mg, 95%), as a white crystalline solid; m.p. 69 °C, $[\alpha]_D^{r.t.}$ = −54.25 (*c* = 1.18, $CHCl_3$) and R_f = 0.14 (isooctane/Me_2CO, 8:2). − IR (KBr): $\tilde{\nu}$ = 3430, 2934, 2866, 1695, 1450, 1428, 1377, 1309, 1254, 1150, 1092, 1057, 1002, 939 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.61 (ddd, *J* = 14.9, 10.3, 4.6 Hz, 1 H), 2.64 (td, *J* = 13.9, 6.5 Hz, 1 H), 2.24 (m, 1 H), 2.10 (m, 2 H), 2.02 (m, 1 H), 1.74−1.14 (m, 8 H), 1.11 (s, 3 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 215.3 (C), 69.7 (CH), 52.8 (CH), 49.4 (C), 37.3 (CH_2), 36.0 (CH_2), 31.8 (CH_2), 25.8 (CH_3), 21.9 (CH_2), 19.5 (CH_2), 16.8 (CH_2). − MS: *m*/*z* = 164 [M^+], 149, 135, 125, 111, 95, 81, 79, 67, 55.

(4a*R*,5*R*,8a*S*)-5-[1-(*tert*-Butyl)-1,1-diphenylsilyl)oxy]-8a-methylperhydro-1-naphthalenone (16): To a solution of alcohol **9** (1.82 g, 9.99 mmol) in DMF (30 mL) was added TBDPSCl (5.3 mL, 20 mmol) and imidazole (2.75 g, 40 mmol). The mixture was stirred for 2 days at room temp., poured into water (100 mL) and extracted with pentane (3 × 120 mL). Drying, filtration, solvent evaporation and purification by column chromatography (pentane/Me_2CO, 50:1) provided **16** (4.11 g, 98%) as white crystals; m.p. 75 °C. $[\alpha]_D^{r.t.}$ −12.0 (*c* = 1.1, $CHCl_3$), R_f = 0.27 (pentane/Me_2CO, 40:1) − IR (KBr): $\tilde{\nu}$ = 3070, 2933, 2858, 1708, 1472, 1427, 1361, 1308, 1259, 1111, 1072, 1008, 936, 904, 869, 822, 741, 703, 610 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (m, 4 H), 7.41 (m, 6 H),

3.70 (td, J = 10.2, 4.3 Hz, 1 H), 2.21 (m, 2 H), 2.05 (m, 1 H), 1.69 (m, 1 H), 1.61 (qt, J = 13.5, 4.7 Hz, 1 H), 1.54−1.13 (m, 7 H), 1.05 (s, 9 H), 0.92 (s, 3 H). − ^{13}C NMR/DEPT (500 MHz, $CDCl_3$): δ = 215.6 (C), 135.9 (4 × CH), 134.8 (C), 134.0 (C), 129.6 (CH), 129.5 (CH), 127.5 (2 × CH), 127.3 (2 × CH), 71.8 (CH), 53.1 (CH), 49.6 (C), 37.3 (CH_2), 36.1 (CH_2), 31.8 (CH_2), 27.1 (3 × CH_3), 25.8 (CH_2), 22.5 (CH_2), 19.4 (CH_2 + C), 16.7 (CH_3). − MS: m/z = 363 [M^+], 199, 147, 135, 77, 41. − $C_{27}H_{36}O_2Si$: calcd. C 77.09, H 8.63; found C 76.99, H 8.62.

(3a*R*,4*R*,7a*S*)-4-[(1-(*tert*-Butyl)-1,1-diphenylsilyl)oxy]-7a-methylperhydro-1-indenone (5a): To a stirred solution of ketone **16** (516 mg, 1.23 mmol) in MeCN (2.5 mL), Et_3N (0.341 mL, 2.45 mmol) and chlorotrimethylsilane (0.281 mL, 2.22 mmol), was added dropwise, at room temp., NaI (333 mg, 2.22 mmol) in MeCN (2.5 mL), and stirring was continued overnight. Water (10 mL) and pentane (15 mL) were added and after separation, the aqueous layer was extracted with pentane (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated, giving the crude TMS-enolether.

A solution of this TMS-enolether in pentane (5 mL) was added dropwise to a stirred suspension of MCPBA (363 mg, 1.5 mmol, calculated as 70% purity) in pentane (5 mL) at 0 °C. After stirring for 25 min, MeOH (2 mL) and HCl (12N, 0.12 mL) were added and stirring was continued for 5 min at the same temperature. The mixture was than poured into a saturated $NaHCO_3$ solution (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 × 10 mL), and dried, and the solvents were evaporated, to afford crude α-hydroxy ketone **17**.

To a stirred solution of the crude **17** in a mixture of MeOH (3 mL) and CH_2Cl_2 (1 mL), cooled to 0 °C, was added $Pb(OAc)_4$ (1.09 g, 2.45 mmol). After stirring for 30 min, the mixture was filtered through a short pad of silica gel. The pad was rinsed with EtOAc (80 mL) and the solvents were evaporated to give the crude aldehyde **18a**.

This residue was dissolved in 2-methyl-2-butene (2.2 mL) in *t*BuOH (18 mL). The flask was placed in an ice bath before the dropwise addition of a solution of $NaClO_2$ (1.0 g, 8.85 mmol) and $NaH_2PO_4{\cdot}H_2O$ (1.08 g, 7.7 mmol) in water (6.2 mL). The mixture was stirred at 0 °C for 15 min and at room temp. for 2 h. Most of the *t*BuOH was evaporated, and Et_2O (40 mL), water (5 mL) and saturated NH_4Cl (25 mL) were added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried and evaporated, to afford the crude acid **18b**.

Crude **18b** in dry THF (10 mL) was added dropwise to a cooled (0 °C) solution of 2M LDA (3 mL, 6 mmol) and the reaction was allowed to warm overnight to room temp. Glacial HOAc (0.88 mL, 15.4 mmol) and THF (5 mL) were added and the reaction mixture was refluxed for 1 h. Water (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried and the solvents were evaporated. Purification of the residue by column chromatography (isooctane/EtOAc, 15:1) provided pure ketone **5a** (349 mg, 70%) as white crystals; m.p. 62 °C. $[\alpha]^{r.t.}$ = +27.2 (c = 1.2, $CHCl_3$) and R_f = 0.22 (pentane/Me_2CO, 4:1). − IR (film): $\tilde{\nu}$ = 3070, 2933, 2857, 1741, 1589, 1472, 1460, 1427, 1390,1361,1250, 1182, 1112, 1084, 1040, 1008, 909, 870, 823, 799, 740, 703 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (m, 4 H), 7.41 (m, 6 H), 3.81 (td, J = 10.2, 4.4 Hz, 1 H), 2.35 (dd, J = 19.0, 8.9 Hz, 1 H), 2.15 (m, 2 H), 1.82 (m, 1 H), 1.61 (m, 3 H), 1.37−1.11 (m, 4 H), 1.07 (s, 9 H), 0.64 (s, 3 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 220.4 (C), 135.9 (4 × CH), 134.6 (C), 134.0 (C), 129.7 (CH), 129.5 (CH), 127.5 (2 × CH), 127.4 (2 × CH), 71.7 (CH), 52.5 (CH), 49.5 (C), 36.5 (CH_2), 35.4 (CH_2), 30,9 (CH2), 27.0 (3 × CH_3), 21.9 (CH_2), 20.8 (CH_2), 19.3 (C), 13.5 (CH_3). − MS: m/z = 349 [M^+], 271, 243, 199, 181, 139, 105, 77, 41. − $C_{26}H_{34}O_2$: calcd. C 76.80, H 8.43; found C 76.81, H 8.45.

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