On the Unexpected Stereochemical Outcome of the Magnesium in Methanol – Conjugate Reduction of an Exocyclic α,β-Unsaturated Ester

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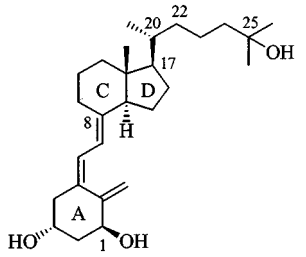
The conjugate reduction of the *exo*cyclic α,β-unsaturated ester **9** with magnesium in methanol gives a mixture of diastereoisomers containing predominantly the less stable **10a**. Eventual structural identification rests on the X-ray diffraction analysis of tosylate **18**.

Next to its role in calcium homeostasis, the *seco*steroid hormone 1α,25-dihydroxyvitamin D_3 (**1**), the physiologically active form of vitamin D_3, has been shown to induce cellular differentiation and to inhibit cellular proliferation.[1] Its therapeutic utility in the treatment of certain cancers and skin diseases is, however, limited because effective doses provoke hypercalcemia. As a consequence in recent years analogs of vitamin D that would possess a high cell differentiating ability but a low calcemic activity have been actively sought.[2]



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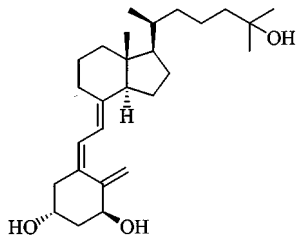
In a first approximation the structure of **1** consists of a central rigid hydrophobic CD-ring system to which are connected two flexible moieties, the side chain at C17 and the *seco*-B,A-ring part at C8, each carrying one of the hydroxy groups, i.e. the 1α-OH and 25-OH groups, that have been shown to be essential for recognition by the receptor protein.[3] With regard to the flexible parts of the molecule successful structural modifications that led to the desired dissociation of activities include e.g. 19-nor derivatives, 22-oxa, 23-yne, 24-homo, 26,27-bishomo, 20-*epi*, and combinations thereof.[4] In contrast our laboratory has focussed in recent years on the development of analogs that are characterized by profound structural modifications in the central part.[5]



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In the context of structure-function relationship it has become clear from several studies that the relative orientation of the side chain is important.[6] In this respect the natural hormone **1** and its (20*S*)-epimer **2** are of particular interest since the latter has been shown to be more efficient than **1** in the inhibition of cellular proliferation and induction of cell differentiation.[7] A representation of the conformational behaviour of the side chain of both derivatives is shown in Figure 1. In this approach force field calculations are performed so as to generate within a given energy window all possible local minimum energy conformations that the side chain may adopt; the orientation in space is further defined by a dot that corresponds to the position of the 25-oxygen atom in that particular conformation.[8] The respective top views nicely show how in **1** the side chain is oriented in a "north-east" direction and in **2** in the "north-west" region.

The present work aims at the development of 6D-analogs in which, as a consequence of a particular substitution pattern on the six-membered D-ring, specific orientations are enforced on the side chain.[5f] 6D-analogs as e.g. **3** are characterized by the absence of a C-ring and by the presence of a conformationally well defined chair six-membered D-ring. In particular analog **4** is designed so as to enforce the above north-west orientation of the side chain. This conformational preference, as illustrated in the dot map of Figure 2, is the result of the absence of the *gem*-dimethyl

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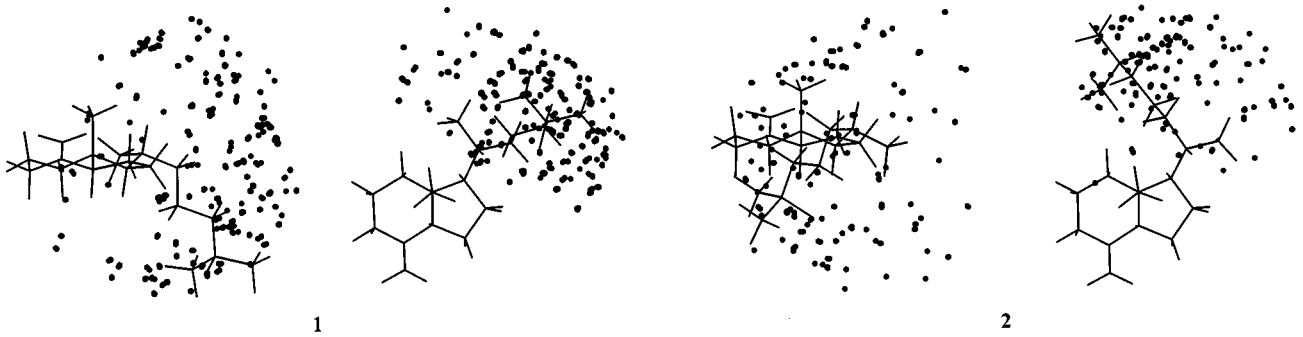

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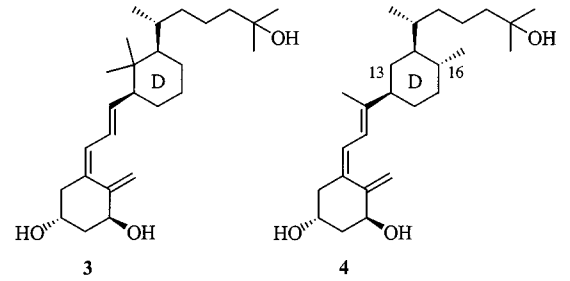
Figure 1. Dot-map representation of the side-chain conformation of **1** (left) and **2** (right) in side and perpendicular views (the line drawing represents the global energy minimum conformation)



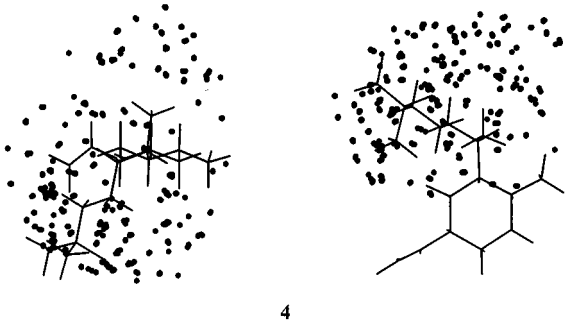


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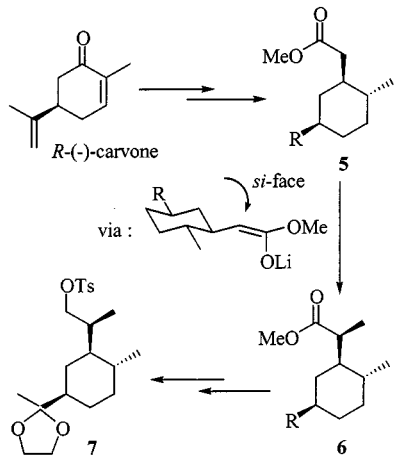
Figure 2. Dot-map representation of the side-chain conformation of **4** in side and perpendicular views (the line drawing represents the global energy minimum conformation)

substitution at C13 (compare **3**) and the presence of the α-oriented methyl group at C16.



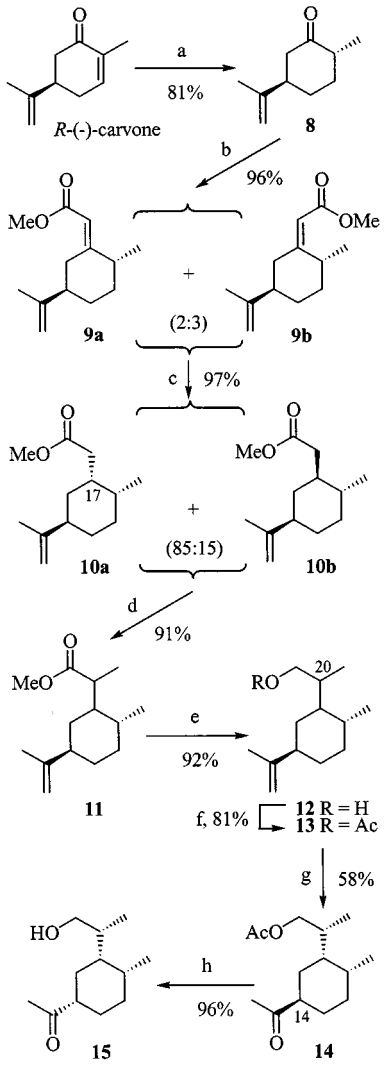
Scheme 1. Synthesis plan

Tosylate **7** is a key intermediate in the synthesis of **4**. Indeed, using known methodology[9] both the classical side chain (substitution process) and the *seco*-B,A-ring part (Horner reaction) can be introduced. The projected enantioselective synthesis of **7** is summarized in Scheme 1. Starting from (*R*)-(−)-carvone a derivative as **5** is first developed in which the three substituents in the six-membered D-ring possess the more stable equatorial orientation. Subsequent introduction of the 20-methyl group in the required (*S*)-configuration as in **6** occurs via stereoselective alkylation of the corresponding enolate from the least hindered *si*-face. Subsequent standard transformations would lead to tosylate **7**, and further to analog **4**.

We now wish to describe the synthesis of tosylate **18**, a derivative that, compared with the desired **7**, is epimeric at C14 and C17,[10] and was obtained because of the unexpected stereochemical outcome of the magnesium in methanol conjugate reduction of the α,β-unsaturated ester **9**.

The synthesis of **18** is shown in Schemes 2 and 3. The route that was expected to lead uneventfully to a 1,2,4-trisubstituted *all*-equatorial derivative, with absolute and relative configurations as shown for **6** and **7**, in practice led to the *all-cis* derivative **15**. The conjugate reduction of (*R*)-(−)-carvone with sodium dithionite under phase transfer conditions led, as described, to *trans*-cyclohexanone **8**.[11a] The corresponding *cis*-isomer (not shown) was isolated as the minor isomer and found to isomerize in base (sodium methoxide) to the more stable **8**.[11b]

In a following stage the methoxycarbonylmethyl substituent was introduced. First a Peterson olefination gave an unseparable mixture of the (*E*,*Z*)-isomers **9a** and **9b** (ratio 2:3, respectively). The preferred formation of the (*Z*)-derivative is in line with the result obtained for 2-methylcyclohexanone.[12] The identification of both isomers rests on ^{1}H-NMR analysis.[13] The subsequent conjugate reduction of the α,β-unsaturated ester **9** (both isomers) with magnesium in methanol was expected to yield ester **10b** with the more stable *all*-equatorial-stereochemistry. Magnesium in methanol has been promoted as reducing agent for the C−C double bond in α,β-unsaturated nitriles, amides, and esters.[14] To the best of our knowledge there are only a few examples in which the stereochemical outcome at the β-centre (i.e., C17) has been addressed, and, not unexpectedly,

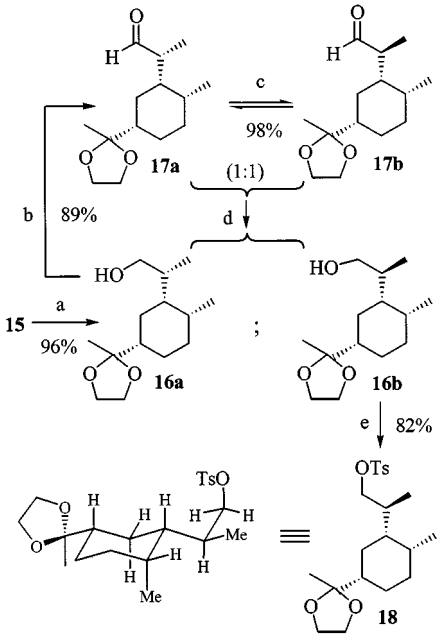


Scheme 2. Synthesis of **15**

the more stable orientation was obtained.[15] However when the mixture of **9a** and **9b** was subjected to the same reduction conditions (Mg, MeOH, reflux), a very high yield of a 85:15 mixture of the two saturated esters **10a** and **10b**, isomeric at C17, was obtained in which we expected the *all*-equatorial isomer **10b** to be the major isomer. This presumption however turned out to be erroneous and was only discovered after the X-ray structural determination of tosylate **18** (see later)! Reinvestigation of this particular reduction step using other dissolving metal conditions, i.e., lithium in liquid ammonia (ether/dimethoxyethane), led to a 3:7 mixture of **10a** and **10b**, respectively, now in favour of the more stable isomer (56% yield).

In the illusion that the major isomer possessed the *all*-equatorial-configuration, the further sequence was pursued. This involved alkylation of the ester enolate (obtained from the mixture of **10a** and **10b** with lithium diisopropylamide in THF) with iodomethane which led to **11** as an unseparable mixture of three diastereomers in high yield (ratio 5:4:1 of unidentified isomers).[16] Subsequent reduction with lithium aluminum hydride gave alcohol **12** which was directly converted into acetate **13**. At this point a 7:3 mixture (from ^{1}H-NMR analysis) of isomers is obtained.

The further sequence calls for the oxidative cleavage of the double bond in **13** so that in a subsequent step the A-ring and *s*-trans diene may be introduced in a classical way via Horner reaction.[17] Cleavage using osmium tetraoxide and potassium periodate led to ketone **14** as an isomericaly pure compound, in isolated yield of 58%; presumably the minor isomer in **13** was also converted into the corresponding ketone and was discarded through the chromatographical process. Ketone **14** was then further converted into alcohol **15**. During this step occurred the isomerization at C14 leading to the *cis*-relation of the two larger equatorial substituents. Indeed, careful analysis of the ^{1}H-NMR spectra reveals an axial orientation of the acetyl group in **14** [δ(H14) = 2.59 (ΣJ_{vic} = 16 Hz)] and an equatorial orientation in **15** [δ(H14) = 2.32 (tt, J = 12.2, 3.6 Hz)].



Scheme 3. Synthesis of **18**

The final conversion of **15** into **18** is shown in Scheme 3. Acetalisation led to **16a**, the tosylate of which did not give adequate crystals for X-ray analysis. After oxidation to the corresponding aldehyde **17a**, isomerization in base led to a ca 1:1 mixture of aldehydes isomeric at C20. After reduction of this mixture, alcohol **16b** could be isolated (47%), which upon tosylation afforded **18**. By slow evaporation from dichloromethane/isooctane (1:1) solutions of **18** crystals (m.p. 93 °C) appropriate for crystal structure analysis were obtained. The X-ray molecular structure[18] is shown in Figure 3, together with the adopted atomic label-

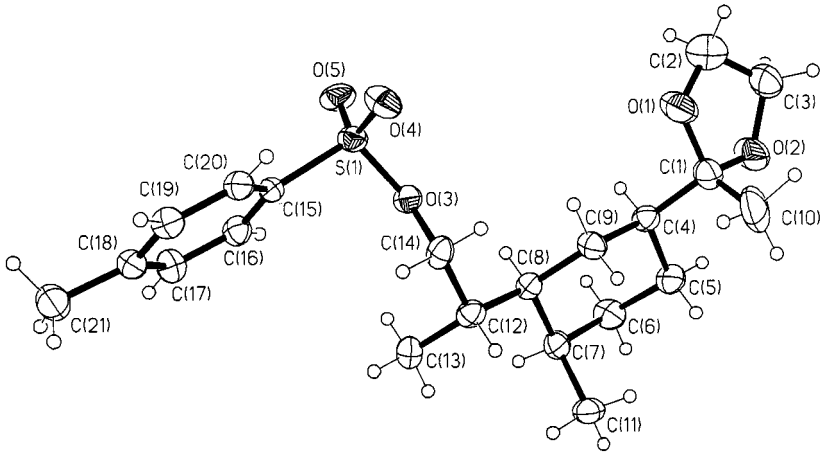


Figure 3. X-ray crystal structure of tosylate **18** with atomic labeling

ing scheme. It may be clearly seen that in tosylate **18** all three cyclohexane substituents point towards the same face (*all-cis*), with equatorial acetal and the tosylated propanol moieties and axial methyl group. Needless to say that great was our surprise when the relative configuration of the derivative appeared to correspond to the one shown for **18**. Clearly, an in depth study of the magnesium in methanol reduction of *exo*cyclic α,β-unsatured esters is in order.

Experimental Section

General: Thin-layer chromatography was performed on Merck silica gel 60F-254 TLC plates. All products were purified by flash chromatography (Merck silica gel 60F254) or High Performance Liquid Chromatography (HPLC): Waters 4000, Kontron 420/422. − $[\alpha]_D^{20}$($CHCl_3$): Perkin−Elmer 241. − IR (NaBr): Perkin−Elmer 1600 series. − ^{1}H NMR ($CDCl_3$): 500 MHz - Bruker AN-500 (internal TMS as reference). − ^{13}C NMR ($CDCl_3$): 50 MHz - Varian Gemini-200 (with DEPT program.). − MS: Finnigan 4000 or Hewlett−Packard 5988A.

X-Ray Crystal Structure Analysis. − Crystal Data: $C_{21}H_{32}O_5S$; M = 396.53 g/mol; orthorombic space group $P2_12_12_1$, a = 8.035(2), b = 8.274(2), c = 32.025(9) Å, V = 2129(1) Å^3, Z = 4, $d_{calcd.}$ = 1.237 Mg/m^3. − **Data Collection:** Siemens P4 diffractometer, Mo-$K\alpha$ radiation (λ = 0.71069 Å), graphite monochromator; crystal size 0.6 × 0.3 × 0.3 mm^3, μ = 0.180 mm^{-1}; ω scan mode, θ range: 1.3−25°, index ranges $0 \le h \le 9$, $0 \le k \le 9$, $0 \le l \le 38$, reflections collected: 2185, independent reflections: 2185, observed reflections[$I > 2\sigma(I)$]: 1414. − **Structure Solution and Refinement:** solution by direct methods; refinement by full-matrix least-squares on F^2, non-H atoms with anisotropic displacement parameters, H atoms could be located in a difference Fourier map, but were geometrically positioned and treated as riding atoms; data/parameters ratio in the final refinement: 2185/244; R = 0.0546 (observed data), $R_w(F^2)$ = 0.1784 (all data). Programs used: P3/PC,[19] SIR92,[20] SHELXL/PC IRIS,[21] SHELXL-97,[22] MOLDRAW.[23]

Conformational Analysis and Molecular Modeling: Conformational analysis of the side chain of compounds **1**, **2**, and **4** was carried out using the MacroModel molecular modeling program of Still[24] run on a Digital VAXstation 4000−90A or SiliconGraphics Octane. Molecular mechanics calculations were carried out on model compounds in which the A-ring and diene system up to C6 were replaced by a H atom. Rotations with 60° increments were applied to the rotatable C−C bonds of the side chain, while the 25-OH was rotated with increments of 120°. The so generated starting conformations were minimized using the MM2* force field implementation of MacroModel and the conformations within 20 kJ/mol of the minimum energy form were retained. Using a PC computer program all conformations of each compound were then overlaid using C13 as common origin (x, y, z = 0), C14 was positioned in the yz-plane (x = 0) and C18 was made to coincide with the positive y-axis (x, z = 0). A line drawing was generated of the minimum energy conformation and the position of O25 in each of the local energy minima within the given energy window was represented by a dot to obtain the dot maps shown in Figures 1 and 2.

(2*R*,5*R*)-5-Isopropenyl-2-methylcyclohexanone (8): A mixture of *R*-(−)-carvone (10 g, 66.569 mmol), phase transfer catalyst (Adogen 464®, 3.59 g, 19.974 mmol) and sodium bicarbonate (100.66 g) in toluene (500 mL) and water (500 mL) was stirred vigorously under argon. Sodium dithionite (104.306 g, 559.116 mmol) was added and the mixture heated in an oil bath at 110 °C for 3 h. After cooling, the aqueous layer was separated and extracted with diethyl ether. The combined organic extracts were washed with water, dried ($MgSO_4$), and the solvent removed in vacuo. Flash chromatography (hexane/diethyl ether, 85:15) and HPLC (hexane/ethyl acetate, 96:4) of the residue afforded **8** (8.209 g, 81%). − R_f = 0.38 (hexane/diethyl ether, 8:2). − $[\alpha]_D^{20}$ +15.87, (c = 1.21, $CHCl_3$), ref.[11b] +17.5. − IR (NaBr): $\tilde{\nu}$ = 2968 cm^{-1}, 2931, 1713, 1646, 1449, 1376, 1218, 1184, 1142, 1057, 891, 730. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.75 (1 H, m), 4.73 (1 H, m), 2.45 (1 H, dt, J = 11.3, 2.4 Hz), 2.25−2.40 (3 H), 2.13 (1 H, dq, J = 13.3, 2.8 Hz), 1.94 (1 H, dq, J = 13.2, 3.2 Hz), 1.73 (3 H, s), 1.62 (1 H, tq, J = 12.3, 1.7 Hz), 1.37 (1 H, qd, J = 12.3, 1.7 Hz), 1.03 (3 H, d, J = 6.5 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 212.5 (C=O), 147.5 (C=), 109.5 (CH_2=), 46.9 (CH), 46.8 (CH_2), 44.7 (CH), 34.8 (CH_2), 30.7 (CH_2), 20.4 (CH_3), 14.2 (CH_3). − MS; m/z (%): 152 (13) [M$^+$], 137 (9), 123 (3), 110 (16), 109 (28), 95 (63), 82 (44), 79 (13), 67 (100), 55 (44), 41 (58). − $C_{10}H_{16}O$ (152.24): calcd. C 78.89, H 10.60; found C 78.85, H 10.61.

Methyl [(2*R*,5*R*)-5-Isopropenyl-2-methylcyclohexylidene]acetate (9a, b): To a solution of diisopropylamine (5.53 mL, 42.186 mmol) in tetrahydrofuran (60 mL) was added a 2.5 molar solution of *n*-butyllithium in hexane (26.37 mL, 42.186 mmol) at 0 °C under argon atmosphere. The solution of lithium diisopropylamide was stirred at 0 °C for 10 min, cooled to −78 °C and treated dropwise with ethyl (trimethylsilyl)-acetate (6.93 mL, 42.186 mmol). The resultant

mixture was stirred at −78 °C for 30 min, treated dropwise with ketone **8** (5.340 g, 35.155 mmol) and then stirred for an additional 2 h at −78 °C. On warming to room temperature the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The combined ether extracts were dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (hexane/diethyl ether, 98:2) and HPLC (hexane/ethyl acetate, 98:2) afforded **9** (**a/b**, 2:3) (7.038 g, 96%). − R_f = 0.23 (hexane/ethyl acetate, 98:2). − IR (NaBr): $\tilde{\nu}$ = 2934 cm^{-1}, 1720, 1644, 1434, 1387, 1336, 1237, 1192, 1161, 1140, 1014, 891, 668. − ^1H NMR (500 MHz, $CDCl_3$): δ = 5.62 (1 H of **9b**, m), 5.59 (1 H of **9a**, m), 4.83 (1 H of **9b**, m), 4.78 (1 H of **9b**, m), 4.74 (1 H of **9a**, m), 4.73 (1 H of **9a**, m), 4.00 (1 H of **9a**, ddd, *J* = 12.6, 9.0, 2.4), 3.85 (1 H of **b**, m), 3.70 (3 H of **9a**, s), 3.67 (3 H of **9b**, s), 2.64 (1 H of **9b**, ddd, *J* = 14.8, 6.7, 2.1 Hz), 2.47 (1 H of **9b**, m), 2.32 (1 H of **9b**, d, *J* = 14.8 Hz), 2.16 (1 H of a, m), 2.04 (1 H of **9a**, tt, *J* = 12.3, 3.3 Hz), 1.97 (1 H of **9a**, ddd, *J* = 13.0, 7.2, 4.0 Hz), 1.76 (3 H of **9a**, s), 1.70 (3 H of **9b**, s), 1.48 (1 H of **9b**, qd, *J* = 12.7, 3.9 Hz), 1.33 (1 H of **9b**, ddd, *J* = 13.8, 7.9, 3.6 Hz), 1.17 (3 H of **9b**, d, *J* = 7.1 Hz), 1.06 (3 H of **9a**, d, *J* = 6.5 Hz). − MS; *m/z* (%): 208 (52) [M^+], 193 (18), 176 (64), 135 (100), 148 (52), 133 (61), 119 (41), 93 (71), 67 (54), 55 (63). − $C_{13}H_{20}O_2$ (208.30): calcd. C 74.95, H 9.68; found C 74.93, H 9.51.

Methyl [(2*R*,5*R*)-5-Isopropenyl-2-methylcyclohexyl]acetate (10a, b): To a stirred solution of **9a**,**b** (2.911 g, 13.975 mmol) in dry methanol (60 mL) was added magnesium powder (0.798 g, 32.836 mmol) through a reflux condenser. After a short time, an exothermic reaction occurred which resulted in boiling of the reaction mixture. When the metal was consumed, a second portion of magnesium (0.798 g, 32.836 mmol) was added and then the addition was repeated twice (total consumption of Mg: 3.193 g, 131.365 mmol). After all the magnesium had been consumed, the reaction mixture was cooled to room temperature and HOAc (15 mL) was added in one portion (exothermic reaction) followed by water (70 mL). The reaction mixture was extracted with diethyl ether and the ether layer washed with brine, dried with magnesium sulfate, and concentrated in vacuo. Flash chromatography (hexane/ethyl acetate, 97:3) and HPLC (isooctane, 97:3) of the residue afforded **10** (**a/b**, 85:15) (2.854 g, 97%). − R_f = 0.38 (hexane/ethyl acetate, 96:4). IR (NaBr): $\tilde{\nu}$ = 2922 cm^{-1}, 2848, 1740, 1644, 1436, 1376, 1286, 1254, 1158, 887. − ^1H NMR (500 MHz, $CDCl_3$) (only signals of the major isomer are given): δ = 4.67 (2 H, m), 3.67 (3 H, s), 1.69 (3 H, s), 0.87 (3 H, d, *J* = 6.9 Hz). − MS; *m/z* (%): 210 (4) [M^+],195 (2), 167 (8), 150 (12), 136 (100), 121 (38), 93 (65), 81 (36), 67 (47), 41 (63). − $C_{13}H_{22}O_2$ (210.32): calcd. C 74.24, H 10.54; found C 74.12, H 10.53.

Methyl 2-[(2*R*,5*R*)-5-Isopropenyl-2-methylcyclohexyl]propionate (11): The ester **10a**, **b** (2.439 g, 11.600 mmol) was added to a 1 molar tetrahydrofuran solution of lithium diisopropylamide [prepared by treatment of diisopropylamine (1.52 mL, 11.600 mmol) with *n*-butyllithium (7.25 mL, 11.600 mmol) at 0 °C for 15 min] at −78 °C. The ester enolate was allowed to form over a period of 30 min and iodomethane (0.79 mL, 12.760 mmol) dissolved in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1.4 mL, 11.600 mmol) was added at −78 °C. After stirring for 30 min, the mixture was treated with aqueous ammonium chloride and extracted with diethyl ether. The ether solution was washed with water, saturated aqueous sodium chloride, and dried with magnesium sulfate. After concentration in vacuo, flash chromatography (hexane/ethyl acetate, 96:4) and HPLC (isooctane/ethyl acetate, 97:3) of the residue afforded **11** as a mixture of three isomers (ratio 5:4:1, 2.370 g, 91%). − R_f = 0.26 (hexane/ethyl acetate, 96:4). − IR (NaBr): $\tilde{\nu}$ = 2924 cm^{-1}, 2857, 2359, 1739, 1644, 1453, 1376, 1264, 1194, 1159, 1082, 887. − MS; *m/z* (%): 224 (3) [M^+], 209 (1), 181 (6), 164 (4), 149 (6), 136 (87), 107 (24), 88 (100), 67 (47), 41 (63). − $C_{14}H_{24}O_2$ (224.34): calcd. C 74.94, H 10.79; found C 75.00, H 10.94.

2-[(2*R*,5*R*)-5-Isopropenyl-2-methylcyclohexyl]propan-1-ol (12): To a solution of **11** (1.333 g, 5.942 mmol) in dry tetrahydrofuran (15 mL) at 0 °C under an argon atmosphere was added lithium aluminum hydride (0.450 g, 11.883 mmol). After being stirred for 4 h at room temperature, the suspension was cooled in an ice bath and water (0.45 mL) was added dropwise followed by a 15% aqueous solution of sodium hydroxide (0.45 mL) and water (1.35 mL). After 15 min, the granular suspension was filtered and the filter cake washed with diethyl ether. The combined filtrates were evaporated under reduced pressure. Flash chromatography (pentane/acetone, 9:1) and HPLC (isooctane/acetone, 85:15) afforded **12** as a mixture of three isomers (1.076 g, 92%). − R_f = 0.28 (hexane/ethyl acetate, 6:4). − IR (NaBr): $\tilde{\nu}$ = 3312 cm^{-1}, 2922, 2875, 1644, 1454, 1376, 1031, 887. − MS; *m/z* (%): 196 (3) [M^+], 165 (6), 153 (5), 137 (42), 109 (26), 82 (100), 67 (71), 41 (91). − $C_{13}H_{24}O$ (196.33): calcd. C 79.53, H 12.32; found C 79.53, H 12.34.

A solution of **12** (3.528 g, 17.970 mmol) in anhydrous pyridine (30 mL) and acetic anhydride (13.34 mL, 141.140 mmol) was stirred at room temperature for 15 h. The reaction mixture was then evaporated to dryness in vacuo. The residue, dissolved in ethyl acetate, was successively washed with 1 N hydrochloric acid, water, 2 N potassium bicarbonate and finally with brine. After the mixture was dried ($MgSO_4$) and the solvent was evaporated, flash chromatography and HPLC (hexane/ethyl acetate, 85:15) of the residue afforded **13** as a 7:3 mixture of two isomers (3.470 g, 81%). R_f = 0.45 (pentane/ethyl acetate, 96:4). − IR (NaBr): $\tilde{\nu}$ = 2928 cm^{-1}, 1742, 1453, 1372, 1236, 1033, 886. − ^1H NMR (500 MHz, $CDCl_3$) (signals of the major isomer are printed in italics): δ = 4.83 (1 *H*, m), 4.76 (1 *H*, m), 4.66 (2 H, m), 4.15 (1 *H*, dd, *J* = 10.8, 4.0 Hz), 3.95 (2 H), 3.80 (1 *H*, dd, *J* = 10.8 Hz, 7.6 Hz), 2.06 (3 H, s), 2.05 (3 *H*, s), 1.72 (3 *H*, s), 1.70 (3 H, s), 0.98 (3 *H*, d, *J* = 6.7 Hz), 0.94 (3 *H*, d, *J* = 7.1 Hz), 0.89 (3 H, d, *J* = 6.3 Hz), 0.80 (3 H, d, *J* = 7.0 Hz). − MS; *m/z* (%): 238 (< 1) [M^+], 223 (1), 194 (1), 178 (15), 163 (7), 149 (4), 135 (35), 121 (20), 93 (42), 82 (67), 67 (34), 43 (100). − $C_{15}H_{26}O_2$ (238.37): calcd. C 75.57, H 11.00; found C 75.52, H 11.11.

Acetate of 1-{(1*R*,3*S*,4*R*)-3-[(1*R*)-2-hydroxy-1-methylethyl]-4-methylcyclohexyl}ethanone (14): A solution of **13** (0.258 g, 1.082 mmol) in a 1:1 mixture of tetrahydrofuran/water (18 mL) was combined with a 1% aqueous solution of osmium tetraoxide (0.25 mL) and finely pulverized potassium periodate (0.800 g, 3.478 mmol) and stirred vigorously for 24 h at 45 °C. Most of the tetrahydrofuran was then evaporated in vacuo and the residue diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with 1 N aqueous sodium bisulfite, followed by water, 2 N aqueous sodium bicarbonate, and brine. After the mixture was dried ($MgSO_4$) and the solvents were evaporated, flash chromatography and HPLC (pentane/ethyl acetate, 9:1) afforded **14** (0.151 g, 58%). − R_f = 0.26 (pentane/ethyl acetate, 9:1). − $[\alpha]_D^{20}$ −27.14 (*c* = 1.05, $CHCl_3$). − IR (NaBr): $\tilde{\nu}$ = 2939 cm^{-1}, 1737, 1708, 1441, 1367, 1238, 1174, 1032. − ^1H NMR (500 MHz, $CDCl_3$): δ = 4.13 (1 H, dd, *J* = 10.9, 3.9 Hz), 3.80 (1 H, dd, *J* = 10.9, 7.2 Hz), 2.59 (1 H, m), 2.15 (3 H, s), 2.05 (3 H, s), 2.02 (1 H, m), 1.89 (2 H, m), 1.68 (1 H, tdd, *J* = 13.5, 5.4, 4.0 Hz), 1.56 (2 H, m), 1.40 (3 H, m), 0.99 (3 H, d, *J* = 6.7 Hz), 0.90 (3 H, d, *J* = 7.1 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 211.1 (C=O), 171.2 (O−C=O), 67.6 (CH_2), 47.5 (CH), 38.5 (CH), 34.0 (CH), 29.8 (CH_2), 29.4 (CH), 27.7 (CH_3), 24.6 (CH_2), 21.0 (CH_2), 20.8

(CH_3), 15.4 (CH_3), 12.3 (CH_3). − MS; *m/z* (%): 180 (6), 165 (3), 137 (23), 123 (5), 107 (5), 95 (19), 67 (10), 43 (100). − $C_{14}H_{24}O_3$ (240.34): calcd. C 69.96, H 10.07; found C 69.80, H 10.07.

1-{(1*S*,3*S*,4*R*)-3-[(1*R*)-2-Hydroxy-1-methylethyl]-4-methylcyclohexyl}ethanone (15): To a solution of **14** (0.985 g, 4.098 mmol) in dry methanol (14 mL) was added potassium carbonate (0.680 g, 4.918 mmol). After stirring for 40 h at room temperature, diethyl ether was added, the mixture filtered over silica and the solvents evaporated. HPLC (pentane/acetone, 8:2) afforded **15** (0.780 g, 96%). − R_f = 0.31 (pentane/acetone, 8:2). − $[\alpha]_D^{20}$ −3.51 (*c* = 1.26, $CHCl_3$). − IR (NaBr): $\tilde{\nu}$ = 3428 cm^{-1}, 2933, 1704, 1464, 1381, 1357, 1175, 1032. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.65 (1 H, dd, *J* = 10.7, 3.7 Hz), 3.50 (1 H, dd, *J* = 10.5, 5.6 Hz), 2.32 (1 H, tt, *J* = 12.2, 3.6 Hz), 2.14 (3 H, s), 2.01 (1 H, m), 1.73 (1 H, dm, *J* = 13.2 Hz), 1.66 (2 H, m), 1.20−1.60 (6H), 0.98 (3 H, d, *J* = 6.7 Hz), 0.86 (3 H, d, *J* = 7.2 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 212 (C=O), 65.7 (CH_2−O), 52.1 (CH), 41.3 (CH), 37.1 (CH), 33.0 (CH_2), 28.9 (CH), 27.9 (CH_3), 25.2 (CH_2), 22.4 (CH_2), 15.1 (CH_3), 12.1 (CH_3). − MS; *m/z* (%): 198 (2) [M^+], 180 (3), 168 (5), 151 (3), 137 (12), 136 (7), 110 (7), 97 (16), 95 (49), 81 (40), 55 (38), 43 (100). − $C_{12}H_{22}O_2$ (198.31): calcd. C 72.68, H 11.18; found C 72.75, H 11.32.

(2*R*)-2-[(1*S*,2*R*,5*S*)-2-Methyl-5-(2-methyl[1,3]dioxolan-2-yl)-cyclohexyl]propan-1-ol (16a): To a solution of **15** (0.236 g, 1.190 mmol) in toluene (10 mL) was added 1,2-ethanediol (0.66 mL, 11.900 mmol) and pyridinium tosylate (0.060 g, 0.238 mmol). The mixture was refluxed with water separation by a Dean−Stark trap until the starting ketone had been completely used (12 h). The solvent was then removed in vacuo, diethyl ether was added and the mixture was washed with sodium bicarbonate and saturated aqueous sodium chloride solution. The organic phase was dried with magnesium sulfate and the solvent removed under reduced pressure. HPLC (pentane/acetone, 86:14) afforded **16a** (0.277 g, 96%). − R_f = 0.38 (pentane/acetone, 8:2). − $[\alpha]_D^{20}$ −7.20 (*c* = 0.96, $CHCl_3$). − IR (NaBr): $\tilde{\nu}$ = 3415 cm^{-1}, 2939, 1467, 1382, 1217, 1174, 1114, 1042, 949, 862. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.92 (4 H, m), 3.66 (1 H, dd, *J* = 10.7, 3.6 Hz), 3.48 (1 H, dd, *J* = 10.6, 6.1 Hz), 1.96 (1 H, m), 1.70 (1 H, dm, *J* = 13.0 Hz), 1.26 (3 H, s), 1.20−1.60 (9H), 0.98 (3 H, d, *J* = 6.7 Hz), 0.86 (3 H, d, *J* = 7.1 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 111.7 (O−C−O), 66.0 (CH_2−O), 64.6 (O−CH_2−CH_2−O), 47.0 (CH), 41.8 (CH), 37.5 (CH), 33.4 (CH_2), 29.2 (CH), 24.4 (CH_2), 21.1 (CH_2), 21.0 (CH_3), 15.2 (CH_3), 12.4 (CH_3). − MS *m/z* (%): 227 (2), 212 (1), 180 (1), 165 (1), 149 (1), 137 (2), 107 (1), 87 (100), 67 (4), 43 (28). − $C_{14}H_{26}O_3$ (242.36): calcd. C 69.38, H 10.81; found C 69.36, H 10.88.

(2*R*)-2-[(1*S*,2*R*,5*S*)-2-Methyl-5-(2-methyl[1,3]dioxolan-2-yl)cyclohexyl]propionaldehyde (17a): To a solution of **16a** (0.643 g, 2.653 mmol) and DMSO (20 mL) in dichloromethane (12 mL) at −12 °C was slowly added a solution of SO_3/pyridine (1.056 g, 6.633 mmol), triethylamine (1.12 mL) and DMSO (10.08 mL) in dichloromethane (5 mL). After 2 h stirring (temperature slowly increased to −6 °C), the reaction mixture was poured into a brine/diethyl ether mixture, and the water phase was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and the solvents were evaporated. Flash chromatography and HPLC (pentane/acetone, 93:7) afforded **17a** (0.568 g, 89%). − R_f = 0.35 (pentane/acetone, 93:7). − $[\alpha]_D^{20}$ −11.81 (*c* = 1.41, $CHCl_3$). − IR (NaBr): $\tilde{\nu}$ = 2943 cm^{-1}, 2877, 1724, 1459, 1384, 1219, 1112, 1043, 872. − ^1H NMR (500 MHz, $CDCl_3$): δ = 9.58 (1 H, d, *J* = 4.0 Hz), 3.93 (4 H, m), 2.24 (1 H, dqd, *J* = 9.5, 6.9, 4.0 Hz), 1.87 (1 H, m), 1.73 (1 H, ddt, *J* = 12.5, 9.4, 3.6 Hz), 1.70 (1 H, dm, *J* = 11.6 Hz), 1.30 (1 H), 1.26 (3 H, s), 1.02−1.64 (5H), 1.07 (3 H, d, *J* = 6.9 Hz), 0.87 (3 H, d, *J* = 7.1 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 205.8 (C=O), 111.9 (O−C−O), 65.1 (O−CH_2−CH_2−O), 49.7 (CH), 47.3 (CH), 41.9 (CH), 33.6 (CH_2), 30.4 (CH), 24.1 (CH_2), 21.4 (CH_2), 21.3 (CH_3), 12.8 (CH_3), 12.7 (CH_3). − MS *m/z* (%): 225 (1), 200 (1), 182 (1), 169 (1), 149 (1), 129 (2), 128 (2), 95 (3), 87 (100), 67 (3), 43 (30). − $C_{14}H_{24}O_3$ (240.34).

(2*S*)-2-[(1*S*,2*R*,5*S*)-2-Methyl-5-(2-methyl[1,3]dioxolan-2-yl)cyclohexyl]propan-1-ol (16b): To a solution of **17a** (0.533 g, 2.218 mmol) in dry methanol (20 mL) and dry tetrahydrofuran (20 mL) was added sodium methoxide (0.300 g, 5.554 mmol). After stirring for 24 h, the reaction mixture was poured into saturated aqueous sodium chloride, extracted with diethyl ether, dried with magnesium sulfate, and concentrated in vacuo. Flash chromatography and HPLC (pentane/acetone, 93:7) of the residue afforded a 1:1 mixture **17a**, **b** (0.522 g, 2.172 mmol, 98%) which was then subjected to reduction as described for **12**. The desired epimeric alcohol **16b** (0.247 g, 47%) could be isolated by flash chromatography and HPLC (pentane/acetone, 85:15). − R_f = 0.42 (pentane/acetone, 8:2). − $[\alpha]_D^{20}$ −4.91 (*c* = 1.13, $CHCl_3$). − IR (NaBr): $\tilde{\nu}$ = 2433 cm^{-1}, 2876, 1446, 1382, 1216, 1165, 1115, 1042, 992, 948, 864. − ^1H NMR (500 MHz, $CDCl_3$): δ = 3.91 (4 H, m), 3.70 (1 H, dd, *J* = 10.5, 2.4 Hz), 3.54 (1 H, dd, *J* = 10.3, 6.2 Hz), 1.98 (1 H, m), 1.73 (1 H, dm, *J* = 13.8 Hz), 1.64 (1 H, dq, *J* = 13.0, 2.9 Hz), 1.00−1.65 (7H), 0.97 (3 H, d, *J* = 6.7 Hz), 0.82 (3 H, d, *J* = 7.1 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 111.7 (O−C−O), 66.3 (CH_2−O), 64.6 (O−CH_2−CH_2−O), 46.8 (CH), 41.5 (CH), 37.7 (CH), 33.3 (CH_2), 28.2 (CH), 24.7 (CH_2), 21.1 (CH_2), 20.9 (CH_3), 14.9 (CH_3), 11.9 (CH_3). − MS *m/z* (%): 227 (2), 202 (1), 181 (1), 165 (1), 141 (2), 128 (2), 107 (2), 87 (100), 67 (4), 43 (32). − $C_{14}H_{26}O_3$ (242.36).

(2*S*)-[(1*S*,2*R*,5*S*)-2-Methyl-5-(2-methyl[1,3]dioxolan-2-yl)cyclohexyl]propyl Toluene-4-sulfonate (18): To a solution of **16b** (0.247 g, 1.019 mmol) in dichloromethane (4.5 mL) at 0 °C was added triethylamine (0.57 mL, 4.110 mmol), a solution of *p*-tosyl chloride (0.392 g, 2.055 mmol) in dichloromethane (2.7 mL) and a trace of 4-dimethylaminopyridine (DMAP). After stirring for 20 h at room temperature, the reaction mixture was concentrated partially, filtered and then evaporated in vacuo. Flash chromatography and HPLC (pentane/acetone, 86:14) afforded **18** (0.331 g, 82%), colorless crystals, m.p. 93 °C. − R_f = 0.32 (pentane/acetone, 9:1). − $[\alpha]_D^{20}$ +9.07 (*c* = 0.70, $CHCl_3$). − IR (NaBr): $\tilde{\nu}$ = 2944 cm^{-1}, 1467, 1360, 1177, 1098, 1042, 960, 837, 815, 668. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 (2 H, d, *J* = 8.2 Hz), 7.3 (2 H, d, *J* = 8.2 Hz), 4.08 (1 H, dd, *J* = 9.4, 3.3 Hz), 3.90 (5 H), 2.44 (3 H, s), 1.92 (1 H, m), 1.61 (1 H, dq, *J* = 13.2, 2.9 Hz), 1.50−1.58 (4 H), 1.45 (1 H, tt, *J* = 12.2, 3.5 Hz), 1.42 (1 H, tt, *J* = 13.8, 3.8 Hz), 1.20−1.30 (2 H), 1.20 (3 H, s), 0.91 (3 H, d, *J* = 6.8 Hz), 0.76 (3 H, d, *J* = 7.11 Hz). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 144.5 (Ar−C), 133.2 (Ar−C), 129.8 (Ar−CH), 127.9 (Ar−CH), 111.5 (O−C−O), 74.1 (CH_2−O), 64.7 (2 × CH_2−O), 46.6 (CH), 41.4 (CH), 35.4 (CH), 33.1 (CH_2), 28.1 (CH_2), 24.5 (CH_2), 21.6 (CH_3), 21.1 (CH_3), 20.8 (CH_2), 14.9 (CH_3), 11.7 (CH_3). − MS *m/z* (%): 381 (3), 366 (1), 278 (1), 259 (1), 209 (1), 155 (3), 88 (22), 87 (100). − $C_{21}H_{32}O_5S$ (396.54). − Relevant torsion angles [°] of tosylate **18** (for the atomic numbering, see Figure 3): O(1)−C(1)−C(4)−C(5) 168.1, O(1)−C(1)−C(4)−C(9) −65.6, O(1)−C(1)−C(4)−H(4) 51, O(2)−C(1)−C(4)−C(5) 53.4, C(10)−C(1)−C(4)−C(5) −71.4, C(10)−C(1)−C(4)−H(4) 172, C(10)−C(1)−O(1)−C(2) 117.4, C(4)−C(9)−C(8)−C(7) 54.6, C(9)−C(8)−C(7)−C(6) −53.9, C(8)−C(7)−C(6)−C(5) 57.2, C(5)−C(4)−C(9)−C(8) −55.1, C(7)−C(6)−C(5)−C(4) −59.1, C(6)−C(5)−C(4)−C(9) 56.5, C(9)−C(8)−C(7)−C(11) 71.0, C(5)−C(6)−C(7)−C(11) −70.1,

C(12)−C(8)−C(7)−C(11) −55.6, C(13)−C(12)−C(8)−C(7) −545, C(14)−C(12)−C(8)−C(7) 179.4, C(14)−C(12)−C(8)−C(9) 53.5, C(13)−C(12)−C(8)−C(9) 179.6, H(8)−C(8)−C(12)−H(12) 179, C(13)−C(12)−C(8)−H(8) 63, C(12)−C(8)−C(7)−H(7) 63, O(3)−C(14)−C(12)−C(8) 61.6, O(3)−C(14)−C(12)−C(13) −66.6.

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[1] H. F. DeLuca, *Endocrinology* **1992**, *130*, 1763; M. R. Walters, *Endocr. Rev.* **1992**, *13*, 419−764; D. D. Bikle, *Endocr. Rev.* 765−784.
[2] R. Bouillon, W. H. Okamura, A. W. Norman, *Endocr. Rev.* **1995**, *16*, 200−257.
[3] W. H. Okamura, M. M. Midland, M. W. Hammond, N. A. Rahman, M. C. Dormanen, I. Nemere, A. W. Norman, *J. Steroid Biochem. Molec. Biol.* **1995**, *53*, 603−613.
[4] [4a] L. Binderup, S. Latini, E. Binderup, C. Bretting, M. Calverley, K. Hansen, *Biochem. Pharmacol.* **1991**, *42*, 1569−1575. − [4b] K. L. Perlman, R. R. Sicinski, H. K. Schnoes, H. F. DeLuca, *Tetrahedron Lett.* **1990**, *31*, 1823−1824. − [4c] S. J. Jung, Y. Y. Lee, S. De Vos, E. Elstner, A. W. Norman, J. Green, M. Uskokovic, H. P. Koeffler, *Leuk. Res.* **1994**, *101*, 713−718.
[5] [5a] C. D′Halleweyn, D. Van Haver, J. Van der Eycken, P. J. De Clercq, M. Vandewalle, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 477−480. − [5b] G. D. Zhu, D. Van Haver, H. Juriaans, P. J. De Clercq, *Tetrahedron* **1994**, *50*, 7049−7060. − [5c] K. Sabbe, C. D′Halleweyn, P. J. De Clercq, M. Vandewalle, R. Bouillon, A. Verstuyf, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1697−1702. − [5d] G. D. Zhu, Y. Chen, X. Zhou, M. Vandewalle, P. J. De Clercq, R. Bouillon, R. Verstuyf, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1703−1708. − [5e] W. Yong, S. Ling, C. D′Halleweyn, D. Van Haver, P. J. De Clercq, M. Vandewalle, R. Bouillon, A. Verstuyf, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 923−928. − [5f] B. Linclau, P. J. De Clercq, M. Vandewalle, R. Bouillon, A. Verstuyf, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1461−1464 and 1465−1468.
[6] K. Yamamoto, W. Y. Sun, M. Ohta, K. Hamada, H. F. DeLuca, S. Yamada, *J. Med. Chem.* **1996**, *39*, 2727−2737; S. Yamada, K. Yamamoto, H. Masuno, M. Ohta, *J. Med. Chem.* **1998**, *41*, 1467−1475.
[7] L. Binderup, S. Latini, E. Binderup, C. Bretting, M. Calverley, K. Hansen, *Biochem. Pharmacol.* **1991**, *42*, 1569−1575.
[8] W. H. Okamura, J. A. Palenzuela, J. Plumet, M. M. Midland, *J. Cell. Biochem.* **1992**, *49*, 10−18; M. M. Midland, J. Plumet, W. H. Okamura, *Bioorg. Med. Chem. Lett.* **1993**, 3, 1799−1804.
[9] G-D Zhu, W. H. Okamura, *Chem. Rev.* **1995**, *95*, 1877−1952.
[10] For the sake of clarity, the classical steroid numbering is used throughout the paper. Numbering of the extra carbon atom in the six-membered D-ring is however omitted.
[11] [11a] F. Camps, J. Coll, J. Gitart, *Tetrahedron* **1986**, *42*, 4603−4609. − For other reduction methods on (*R*)-(−)-carvone, see: [11b] M. Yamashita, Y. Tanaka, A. Arita, M. Nishida, *J. Org. Chem.* **1994**, *59*, 3500−3502; G. Solladié, J. Hutt, *Bull. Soc. Chim. Fr.* **1986**, *4*, 643−644; P. G. Gassman, D. P. Gilbert, S. M. Cole, *J. Org. Chem.* **1977**, *42*, 3233−3236.
[12] L. Strekowski, M. Visnick, M. A. Battiste, *Tetrahedron Lett.* **1984**, *25*, 5603−5606.
[13] In an NOE experiment the equatorial methyl groups [δ = 1.06 (3 H of **9a**, d, *J* = 6.5 Hz), 1.17 (3 H of **9b**, d, *J* = 7.1 Hz)] were irradiated. Response was observed only from the vinylic hydrogen (α to the carboxyl) of the (*E*) isomer **9a**.
[14] J. A. Profitt, D. S. Watt, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 127; P. J. Garratt, C. W. Doecke, J. C. Weber, L. A. Paquette, *J. Org. Chem.* **1986**, *51*, 449.
[15] Y. J. Chen, P. J. De Clercq, M. Vandewalle, *Tetrahedron Lett.* **1996**, *37*, 9361−9364; A. Zarecki, J. Wicha, *Synthesis* **1996**, 455.
[16] J. Wicha, K. Bal, *J. Chem. Soc., Perkin Trans. 1* **1978**, 1282.
[17] B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, J. Tideswell, P. W. Wright, *J. Chem. Soc., Perkin Trans. 1* **1978**, 590; P. J. Kocienski, V. Lythgoe, *J. Chem. Soc., Perkin Trans. 1* **1978**, 1290.
[18] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114258. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. Code +44 (1223) 336-033, E-mail: deposit@ccdc.cam.ac.uk].
[19] Siemens, *P3/PC Diffractometer Program*, Version 3.13 (**1989**), Siemens Analytical X-Ray Instruments Inc., Madison, Winsconsin, USA.
[20] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435−436.
[21] G. M. Sheldrick, *SHELXTL/IRIS* (**1990**), Siemens Analytical X-Ray Instruments Inc., Madison, Winsconsin, USA.
[22] G. M. Sheldrick, *SHELXL-97* (**1997**), University of Gottingen, Germany.
[23] P. Ugliengo, D. Viterbo, G. Chiari, *Z. Kristallog.* **1993**, *207*, 9−23. Available at http://www.ch.unito.it/ifm/fisica/moldraw/moldraw.html
[24] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *MacroModel - An Integrated Software System for Modeling Organic and Bioorganic Molecules using Molecular Mechanics. J. Comput. Chem.* **1990**, *11*, 440−467.

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