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Synthesis of (+)-Strigol and (+)-Orobanchol, the Germination Stimulants, and Their Stereoisomers by Employing Lipase-Catalyzed Asymmetric Acetylation as the Key Step

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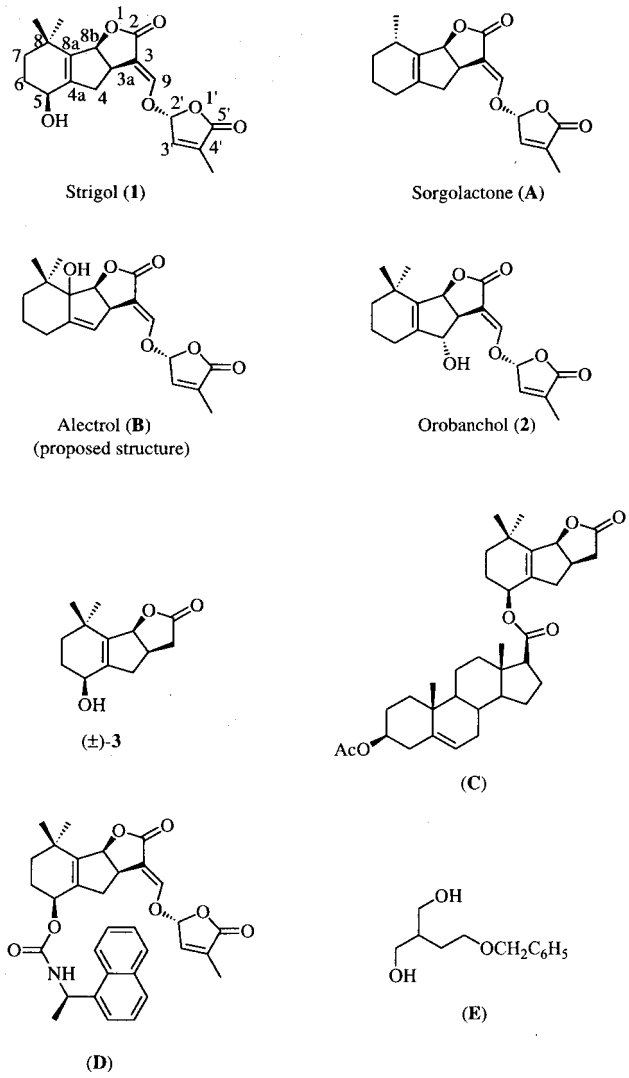
The potent seed germination stimulants (+)-strigol (**1**), (+)-orobanchol (**2**) and their stereoisomers [2′-epistrigol (**1′**), *ent*-**1**, *ent*-**1′**, 2′-epiorobanchol (**2′**), 4-epiorobanchol (**2′′**) and 4, 2′-bisepiorobanchol (**2′′′**)] were prepared from the enantiomers of **3**, which were obtainable by lipase-catalyzed enantiomer separation of (±)-**3**.

Parasitic weeds of the genera *Orobanche* and *Striga* are known to cause severe yield losses in grains and legumes in Africa, Asia and the U.S.A.[1][2] The seeds of such weeds remain dormant in soil until exudates from their host plant induce germination. Four active principles of the exudates have been isolated to date (Scheme 1), and are called under the general name strigolactones. Strigol (**1**) was the first strigolactone to be isolated from cotton root in 1972 as a strong stimulant for the germination of parasitic weeds, although cotton is not a host plant.[3] It was recently reisolated from the host plants like maize, proso millet and sorghum.[4] Two decades later in 1992, sorgolactone (**A**) was isolated from *Sorghum bicolor*, a genuine host plant,[5] and synthesized.[6][7] The isolation and structure proposal in 1992 of alectrol (**B**), the germination stimulant from *Vigna unguiculata*,[8] was followed by synthetic disproof of the correctness of the proposed structure **B**.[9] Orobanchol was most recently isolated together with alectrol as the germination stimulant for *Orobanche minor* from its host red clover, *Trifolium pratense*,[10] and the structure **2** was proposed on the basis of its GC-MS comparison with a synthetic sample of (±)-**2**.[11]

Although the first synthesis of the naturally occurring (+)-enantiomer of strigol (**1**) was executed by Sih and his co-workers over twenty years ago by resolving (±)-**3** via its 3β-acetoxyetienate (**C**)[12] followed by the conversion of (+)-**3** into (+)-**1**, its absolute configuration remained unknown until 1985 when it was clarified by Brooks et al.[13] They resolved (±)-**1** via the corresponding *N*-[(*R*)-1-(1-naphthyl)ethyl]carbamate (**D**), whose structure was solved by an X-ray crystallographic analysis.[13]

Recently substantial efforts were made to prepare (+)-strigol enantioselectively, especially by the groups of Welzel[14] and Zwanenburg.[6][15] It is, however, still difficult to prepare gram quantities of (+)-strigol (**1**) by enantioselective synthesis. The practical way to obtain (+)-**1** must therefore depend on enantiomer separation of (±)-**1** or one of its synthetic intermediates. Indeed Sih's separation of (±)-**3** via



Scheme 1. Structures of strigol and related compounds

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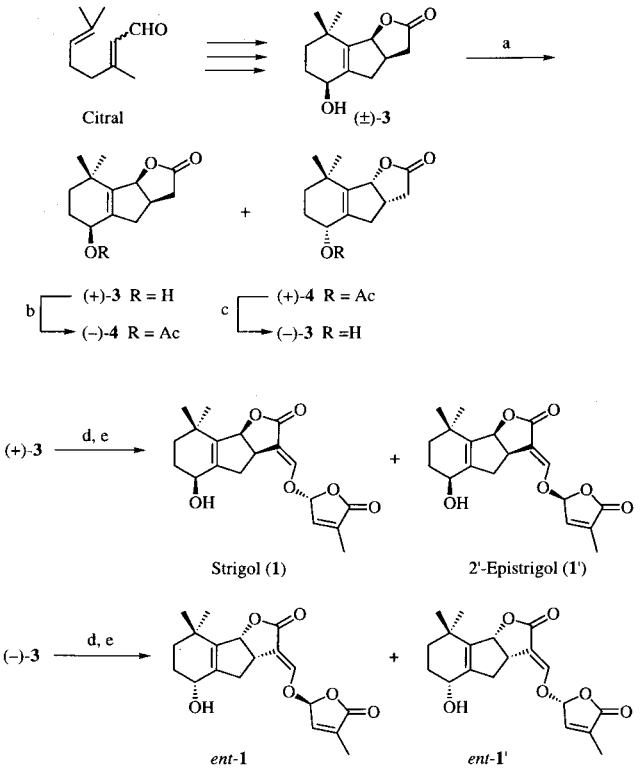
C gave 25 mg of (+)-**1**,[12] while Brooks′ resolution gave 67 mg of (+)-**1**.[13] (±)-Strigol (**1**) itself was resolved by preparative HPLC on a cellulose triacetate column, but the amount of (±)-**1** resolved was only 140 μg.[16] Welzel and his co-workers separated the hydroxylactone (±)-**3** (Scheme 2) by cellulose triacetate column chromatography, and prepared 45.5 mg of (+)-**1** from (+)-**3**.[17] Our experience in enzyme-assisted enantioselective synthesis[18] made us to examine enzymatic resolution of (±)-**3** and its subsequent conversion into the enantiomers of **1**. Although bioactivities of the enantiomers of strigol (**1**) were already known to confirm the extremely high activity of (+)-**1**, we thought it necessary to provide sufficient amount of the samples to clarify the matter thoroughly. It should be added that a *meso*-diol **E** had previously been converted into a chiral and nonracemic intermediate for the synthesis of (+)-strigol (**1**) by means of lipase-catalyzed asymmetric acetylation.[19] The present paper describes our synthesis of (+)-strigol (**1**) and (+)-orobanchol (**2**) based on enzymatic resolution of (±)-**3**.

Scheme 2 shows our synthesis of the stereoisomers (**1**, *ent*-**1**, **1**′ and *ent*-**1**′) of strigol. The racemic hydroxylactone **3** was prepared according to the known methods.[12][20] We then screened hydrolytic enzymes to resolve (±)-**3**. As we expected, enzymatic acetylation of (±)-**3** with vinyl acetate in the presence of lipase AK (Amano) yielded a readily separable mixture of the known hydroxylactone (+)-**3** and the (+)-acetate **4** of the known opposite enantiomer (−)-**3**. The enantiomeric purity of (+)-**3** and that of (+)-**4** could be estimated by HPLC analysis on Chiralcel-OD®. The hydroxylactone (+)-**3** (98.2−99.2% e.e.) was obtained in 47−48% yield, while the acetate (+)-**4** (86.8−87.3% e.e.) was secured in 52−53% yield. Although it was difficult to enhance the enantiomeric purity of (+)-**3** further by recrystallization, the acetate (+)-**4** could be purified by recrystallization to give ca. 100% pure (+)-**4**. A sample of (−)-**4** was prepared by acetylation of (+)-**3**. It should be added that (±)-**3** was more easily purified by recrystallization than (+)-**3** or (−)-**3**. The acetate (+)-**4** gave back the hydroxylactone (−)-**3**, when treated with potassium carbonate in methanol.

Finally, the (+)-lactone (**3**) and its antipode (−)-**3** were converted into the target molecules, (+)-strigol (**1**, 99.0% e.e.), (+)-2′-epistrigol (**1**′, ca. 100% e.e.), (−)-strigol (*ent*-**1**, ca. 99.9% e.e.) and (−)-2′-epistrigol (*ent*-**1**′, 98.8% e.e.) by the known method.[12,13,21] These strigolactones could be purified by recrystallization, and their enantiomeric purities were estimated by HPLC on Chiralcel-OD®. Their physical (m.p. and $[\alpha]_D$) and spectral (IR, ^{1}H NMR, ^{13}C NMR and CD) properties were in good accord with those reported earlier (see Experimental Section). By the present procedure, about 1 g of (+)-strigol (**1**) and about 0.1 g of its antipode *ent*-**1** were prepared and forwarded to biologists for their studies.

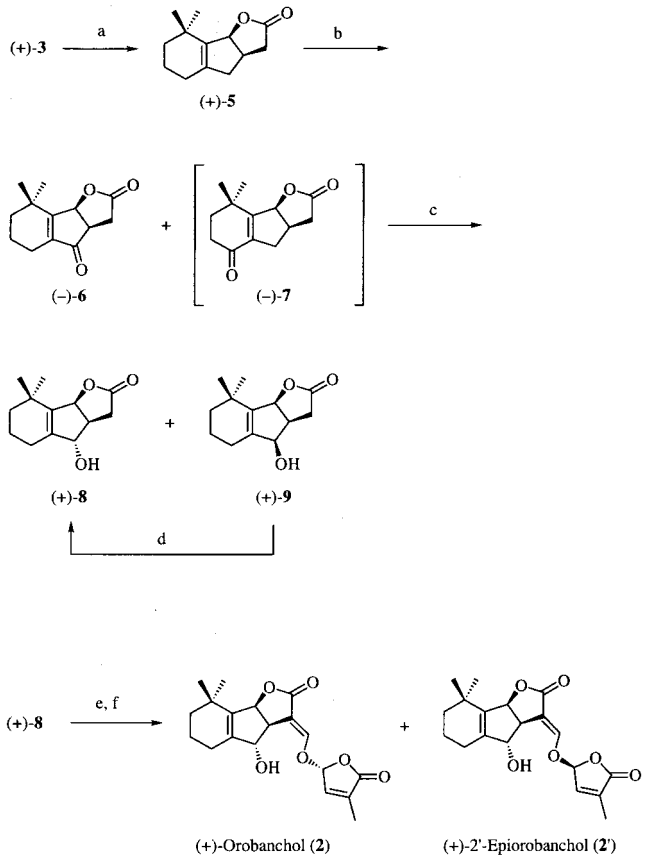
Our synthesis of (+)-orobanchol (**2**) also started from the resolved (+)-hydroxylactone (**3**) as summarized in Scheme 3. The lactone (+)-**3** was converted into the deoxylactone (+)-**5** by the method developed by Welzel and his co-workers for the synthesis of (±)-**5**.[22] Subsequent conversion of



Scheme 2. Synthesis of (+)-strigol (**1**) and its stereoisomers; reagents: (a) CH_2=CHOAc, lipase AK, THF, room temp., 28 h; SiO_2 chromatography [47−48% of (+)-**3** (98.2−99.2% e.e.) and 52−53% of (+)-**4** (86.8−87.3% e.e.)]; (b) Ac_2O, C_5H_5N (95%); (c) K_2CO_3, MeOH (99%); (d) NaH, HCO_2Et, Et_2O; (e) 1) K_2CO_3, 4-bromo-2-methyl-2-buten-4-olide, *N*-methylpyrrolidone; 2) SiO_2 chromatography (26% of **1**, 37% of **1**′, 27% of *ent*-**1** and 29% of *ent*-**1**′)

(+)-**5** to (+)-**2** and (+)-**2**′ was executed in the same manner as was employed in our previous conversion of (±)-**5** to (±)-**2** and (±)-**2**′.[11] Accordingly, (+)-**5** was oxidized to give a mixture of (−)-**6** and (−)-**7**, which could be separated by chromatography. The minor product (−)-**6** was reduced to give the alcohols (+)-**8** and (+)-**9**. These structures could be assigned to the alcohols by comparing the spectral data of (+)-**9** with those of (±)-**9**, whose structure had been solved by X-ray analysis.[11] The major reduction product (+)-**9** could be converted into the minor product (+)-**8** by Mitsunobu inversion. Although our attempt to formylate (+)-**9** was unsuccessful (cf.·ref.[11]), the stereoisomer (+)-**8** could be formylated and converted into a mixture of (+)-orobanchol (**2**) and (+)-2′-epiorobanchol (**2**′). The latter showed the chromatographic and spectral behaviors identical to those of (±)-**2**′, whose structure had been solved by X-ray analysis.[11]

The remaining two possible stereoisomers of (+)-orobanchol-series are (+)-4-epiorobanchol (**2**′′) and (+)-4,2′-bisepiorobanchol (**2**′′′). Because we were unabled to formylate (+)-**9**, we prepared these two isomers by modifying (+)-**2** and (+)-**2**′ as shown in Scheme 4. Oxidation of (+)-orobanchol (**2**) with pyridinium dichromate (PDC) gave the ketolactone (+)-**10**, whose reduction with sodium borohydride in the presence of cerium chloride furnished (+)-**2**′′ in 21% yield. Similarly, oxidation of (+)-2′-epiorobanchol (**2**′) was

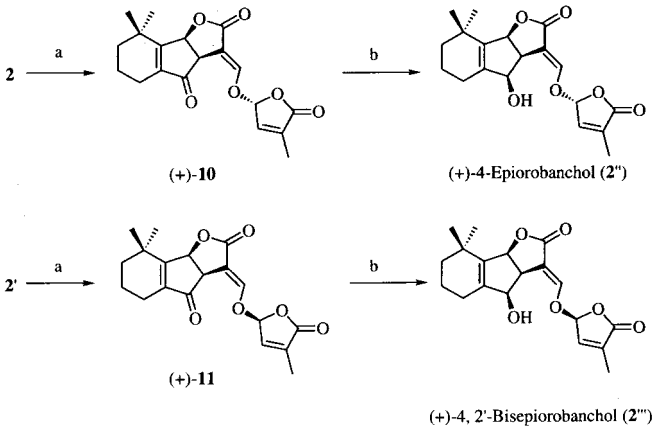


Scheme 3. Synthesis of (+)-orobanchol (**2**) and (+)-2′-epiorobanchol (**2′**); reagents: (a) 1) $P(C_6H_5)_3$, CBr_4, CH_2Cl_2; 2) Zn-Cu, THF; 3) (+)-10-camphorsulfonic acid (CSA), CH_2Cl_2 (76%); (b) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2 (18% of **6**, 51% of **7**); (c) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, EtOH (4% of **8**, 81% of **9**); (d) 1) $P(C_6H_5)_3$, $C_6H_5CO_2$ H, $EtO_2CN{=}NCO_2Et$, THF (95%); 2) K_2CO_3, MeOH (95%); (e) NaH, HCO_2Et, Et_2O; (f) 1) K_2CO_3, (±)-4-bromo-2-methyl-2-buten-4-olide, *N*-methylpyrrolidone; 2) SiO_2 chromatography [30% of (+)-**2** and 30% of (+)-**2′**]

followed by reduction of the resulting ketone (+)-**11** to give (+)-4, 2′-bisepiorobanchol (**2′′′**) in 8% yield. The very low yield in this reduction step was due to the side-reactions to give highly polar by-products.

We compared the ^{1}H-NMR spectra (at 400 or 500 MHz) of these four stereoisomers of orobanchol (**2**, **2′**, **2′′** and **2′′′**) with the reported δ values (at 600 MHz) of the natural product. Due to the scarcity of the isolated material, Yokota et al. could report only four signals due to orobanchol at δ = ca. 1.1 (s, 3 H, 8-Me), 1.1 (s, 3 H, 8-Me), 2.03 (3 H, 4′-Me) and 7.45 (1 H, 9-H).[10] Our synthetic (+)-**2** showed signals at δ = 1.12 (s, 3 H), 1.14 (s, 3 H), 2.01−2.03 (t, 3 H, *J* = 1.5 Hz) and 7.46−7.48 (d, 1 H, *J* = 2.4 Hz). The signal due to 9-H was found to be characteristic to each isomers. The isomer (+)-**2′** showed it at δ = 7.63−7.65, the isomer (+)-**2′′** at δ = 7.50−7.52, and the isomer (+)-**2′′′** at δ = 7.58−7.60. We therefore conclude that the germination stimulant orobanchol is (+)-**2**, considering the known absolute configuration of the related strigolactones such as strigol (**1**)[13] and sorgolactone (**A**).[6]

In conclusion, the facile asymmetric preparation of (+)-hydroxylactone (**3**) enabled us to provide a gram quantity



Scheme 4. Synthesis of (+)-4-epiorobanchol (**2′′**) and (+)-4, 2′-bisepiorobanchol (**2′′′**); reagents: (a) PDC, CH_2Cl_2 (85% for **10** and 77% for **11**); (b) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, EtOH (21% of **2′′** based on the consumed **10** and 8% of **2′′′** based on the consumed **11**)

of (+)-strigol (**1**) and also (+)-orobanchol (**2**) and its stereoisomers.

Experimental Section

General: Melting points: uncorrected values. − IR: Jasco IRA-102. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 400 (400 MHz), Jeol JNM-LA 500 (500 MHz) $CDCl_3$ at δ_H = 7.26 as an internal standard. − ^{13}C NMR: Jeol JNM-LA 400 (100 MHz), Jeol JNM-LA 500 (125 MHz) $CDCl_3$ at δ_C = 77.0 as an internal standard. − Optical rotation: Jasco DIP-1000. − CC: Merck Kieselgel 60 Art 1.07734. − CD spectrum: Jasco J-725. − MS: Jeol JMS-SX 102A and Hitachi M-80B. − M.p.: Yanaco MP-S3. − TLC: 0.25 mm Merck silica gel plates (60F-254). − PTLC: 0.5 mm Merck silica gel plates (60F-254).

(+)-(3a*R*,5*S*,8b*S*)-5-Hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(+)-3] and (+)-(3a*S*,5*R*,8b*R*)-5-Acetoxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]-furan-2-one [(+)-4]: According to the reported procedures,[12][20] hydroxylactone (±)-**3** was synthesized from citral in 7 steps (6.6%) as a white solid. To a solution of hydroxylactone (±)-**3** (9.30 g, 41.9 mmol) in THF (200 mL) was added lipase AK (1.88 g = 20 wt%) and vinyl acetate (20 mL). The mixture was stirred for 28 h at room temp. under argon, and filtered throuth Celite. Evaporation of the filtrate gave the crude product, which was chromatographed on silica gel (hexane/ethyl acetate, 3/1) to afford 4.34 g (47%) of (+)-**3** as a white solid and 5.49 g (52%) of (+)-**4** also as a white solid. − **Hydroxylactone (+)-3**, m.p. 98−100°C [ref.[12] m.p. 103−104°C]. − $[\alpha]_D^{22}$ = +8.39 (*c* = 0.15, $CHCl_3$) [ref.[12] $[\alpha]_D^{25}$ = +8.28 (*c* = 1.3, $CHCl_3$), ref.[17] $[\alpha]_D^{20}$ = +8.10 (*c* = 0.39, $CHCl_3$)]. − Its IR ($CHCl_3$) and ^{1}H-NMR (90 MHz, $CDCl_3$) spectra were identical with those of (±)-**3**. − The acetate (−)-**4** obtained by chemical acetylation of hydroxylactone (+)-**3** was recrystallized from diethyl ether/pentane to give colorless needles, m.p. 84−85°C. − $[\alpha]_D^{23}$ = −94.9 (*c* = 0.97, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1770 cm^{-1} (s, C=O), 1730 (s, C=O), 1250 (s, C−O), 1170 (s, C−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.09 (s, 3 H, 8-Me), 1.17 (s, 3 H, 8-Me), 2.07 (s, 3 H, 5-OAc), 1.30−3.30 (m, 9 H, 3-CH_2 and 3a-H and 4-CH_2 and 6-CH_2 and 7-CH_2), 5.15−5.55 (m, 2 H, 5-H and 8b-H). − $C_{15}H_{20}O_4$ (264.3) calcd. C 68.16, H 7.63; found. C 68.05, H 7.79. − **Acetate (+)-4**, m.p. 77−78°C. − $[\alpha]_D^{23}$ +81.4 (*c* = 1.20,

$CHCl_3$). – This was purified by recrystallization from diethyl ether/pentane to give colorless needles, m.p. 84–85°C. – $[\alpha]_D^{23} = +94.8$ (c = 0.45, $CHCl_3$). – Its IR ($CHCl_3$) and ^{1}H-NMR (90 MHz, $CDCl_3$) spectra were identical with those of (–)-**4**. – $C_{15}H_{20}O_4$ (264.3) calcd. C 68.16, H 7.63; found. C 68.06, H 7.51.

Determination of the Enantiomeric Purity of (+)-3 and (+)-4: HPLC [column: Chiralcel-OD®, 4.6 mm × 25 cm; solvent: hexane/^{i}PrOH (5/1), flow rate: 0.5 mL/min; detector: 205 nm; temperature: 15°C], t_R = 14.6 min [0.4%, (–)-**3**], t_R = 20.2 min [99.6%, (+)-**3**]. The enantiomeric purity of (+)-**3** was estimated to be 99.2% e.e. t_R = 18.4 min [93.4%, ca. 100% (analytical sample), (+)-**4**], t_R = 20.9 min [6.6%, undetectable (analytical sample), (–)-**4**]. The enantiomeric purities of (+)-**4** and its analytical sample were estimated to be 86.8% and ca. 100% e.e., respectively.

(–)-(3a*S*,5*R*,8b*R*)-5-Hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(–)-3]: A mixture of acetate (+)-**4** (1.21 g, 4.58 mmol) and K_2CO_3 (888 mg, 6.43 mmol) in MeOH (30 mL) was stirred for 30 min at room temp., and acidified with 1 M HCl. The reaction mixture was poured into water, and after adding NaCl, it was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to afford the crude product, which was purified by silica-gel chromatography (hexane/ethyl acetate, 2/1) to give 1.01 g (99%) of (–)-**3** as a white solid, m.p. 99–100°C [ref.[12] m.p. 102–104°C]. – $[\alpha]_D^{25} = -7.31$ (c = 0.71, $CHCl_3$) [ref.[12] $[\alpha]_D^{25} = -8.61$ (c = 1.4, $CHCl_3$), ref.[17] $[\alpha]_D^{20} = -8.58$ (c = 0.71, $CHCl_3$)]. – Its IR ($CHCl_3$) and ^{1}H-NMR (90 MHz, $CDCl_3$) spectra were identical with those of (±)-**3**.

(+)-(3a*R*,5*S*,8b*S*,2′*R*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-5-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (1) [(+)-Strigol] and (+)-(3a*R*,5*S*,8b*S*,2′*S*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-5-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (1′) [(+)-2′-Epistrigol]: According to Brooks′ procedure,[20] to a stirred suspension of NaH [60% suspension in oil (551 mg, 13.8 mmol), washed with dry diethyl ether several times] in dry diethyl ether (15 mL) at room temp. under argon, was added a solution of hydroxylactone (+)-**3** (988 mg, 4.45 mmol) in dry diethyl ether (45 mL). Then ethyl formate (5.0 mL, ca. 62 mmol) was added. After stirring for 20 h at room temp., the mixture was acidfied with 1 M HCl and then extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the filtrate gave a pale orange solid (1.10 g), which was used directly in the subsequent transformation without purification. To a stirred mixture of hydroxymethylene lactone (ca. 4.40 mmol) obtained above and K_2CO_3 (1.24 g, 8.97 mmol) in anhydrous *N*-methylpyrrolidone (25 mL) at room temp. under argon, was added a solution of (±)-4-bromo-2 methyl-2-buten-4-olide (1.41 g, 7.96 mmol)[21] in anhydrous *N*-methylpyrrolidone (10 mL). After stirring for 1.5 h at room temp., the reaction mixture was poured into 1 M HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate = 2/1) to afford first 570 mg (37%) of **1′** as a white solid and then 398 mg (26%) of **1** as a white solid. The crystalline **1** was recrystallized from CH_2Cl_2/pentane to give, in sum total after repetition, 1.05 g of pure **1** as colorless needles, m.p. 194–195°C [ref.[12] m.p. 200–202°C (from benzene/pentane), ref.[17] m.p. 191–192°C (from CH_2Cl_2/pentane) 183–186°C (from ethanol/water)]. – CD (c = 0.00023, MeOH) Δε (λ, nm) = +31.1 (231), –24.1 (206) [ref.[12] +28.8 (229), –20.9 (204), ref.[22] –2.25 (263), +27.39 (228)]. – For the CD of strigol and its relatives see also ref.[23]. – $[\alpha]_D^{25} = +271$ (c = 0.50, $CHCl_3$) [ref.[12] $[\alpha]_D^{25} = +293.0$ (c = 0.15, $CHCl_3$), ref.[13] $[\alpha]_D = +270$ (c = 0.2, $CHCl_3$), ref.[17] $[\alpha]_D^{20} = +244.6$ (c = 0.40, $CHCl_3$) $[\alpha]_D^{20} = +262.7$ (c = 0.69, $CHCl_3$)]. – IR ($CHCl_3$): $\tilde{\nu}$ = 3620 cm^{-1} (w, O–H), 1790 (s, C=O), 1745 (s, C=O), 1685 (s, C=O), 1340 (m), 1180 (m), 1100 (s), 1030 (s), 965 (m). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 8-Me), 1.17 (s, 3 H, 8-Me), 1.42–1.49 (ddd, 1 H, J = 13.5, $J′$ = 11.3, $J′′$ = 2.8 Hz, 7-H), 1.52–1.60 (ddd, 1 H, J = 13.5, $J′$ = 7.1, $J′′$ = 3.1 Hz, 7-H′), 1.58–1.62 (bs, 1 H, OH), 1.64–1.73 (m, 1 H, 6-H), 1.95–2.01 (ddd, 1 H, J = 13.4, $J′$ = 7.1, $J′′$ = 3.1 Hz, 6-H′), 2.00–2.03 (t, 3 H, J = 1.5 Hz, 4′-Me), 2.64–2.76 (m, 2 H, 4-CH_2), 3.61–3.67 (dtd, 1 H, J = 11.9, $J′$ = 4.0, $J′′$ = 2.5 Hz, 3a-H), 4.08–4.15 (bs, 1 H, 5-H), 5.48–5.52 (d, 1 H, J = 8.2 Hz, 8b-H), 6.15–6.18 (s, 1 H, 2′-H), 6.92–6.94 (t, 1 H, J = 1.5 Hz, 3′-H), 7.44–7.46 (d, 1 H, J = 2.4 Hz, 9-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 27.5, 27.6, 29.7, 32.4, 36.6, 37.0, 37.8, 67.3, 87.9, 100.6, 113.7, 135.8, 140.9, 142.51, 142.54, 150.6, 170.3, 171.4. – These spectral data were in good accord with those reported in refs.[12,17,20,21] – $C_{19}H_{22}O_6$ (346.4) calcd. C 65.88, H 6.40; found C 65.87, H 6.44. The crystalline **1′** was recrystallized from CH_2Cl_2/pentane to give white plates, m.p. 146–148°C, and from benzene/pentane to give colorless needles, 158–159°C. – CD (c = 0.00024, MeOH) Δε (λ, nm) = +2.86 (248), –6.06 (206) [ref.[22] +5.68 (241)]. – $[\alpha]_D^{24}$ +145 (c = 1.24, $CHCl_3$) [ref.[17] $[\alpha]_D^{20} = +94.0$ (c = 1.24, $CHCl_3$)]. – IR ($CHCl_3$): $\tilde{\nu}$ = 3620 cm^{-1} (w, O–H), 1790 (s, C=O), 1745 (s, C=O), 1680 (s, C=O), 1340 (m), 1180 (m), 1100 (s), 1030 (s), 960 (m). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, 8-Me), 1.14 (s, 3 H, 8-Me), 1.39–1.47 (ddd, 1 H, J = 13.5, $J′$ = 11.0, $J′′$ = 3.5 Hz, 7-H), 1.52–1.58 (ddd, 1 H, J = 13.5, $J′$ = 6.5, $J′′$ = 3.0 Hz, 7-H′), 1.63–1.72 (m, 1 H, 6-H), 1.78–1.86 (bs, 1 H, OH), 1.92–2.20 (m, 1 H, 6-H′, t, 3 H, J = 1.5 Hz, 4′-Me), 2.62–2.74 (m, 2 H, 4-CH_2), 3.58–3.66 (m, 1 H, 3a-H), 4.04–4.10 (t, 1 H, J = 6.5 Hz, 5-H), 5.46–5.52 (d, 1 H, J = 8.0 Hz, 8b-H), 6.14–6.18 (s, 1 H, 2′-H), 6.90–6.95 (t, 1 H, J = 1.5 Hz, 3′-H), 7.40–7.44 (d, 1 H, J = 2.5 Hz, 9-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 27.5, 27.6, 29.6, 32.3, 36.5, 37.0, 37.9, 67.2, 88.0, 100.4, 113.8, 135.8, 141.1, 142.2, 142.8, 150.3, 170.2, 171.5. – These spectral data were in good accord with those reported in refs.[12,17,20,21]. – $C_{19}H_{22}O_6$ (346.4) calcd. C 65.88, H 6.40; found C 65.72, H 6.70.

Determination of the Enantiomeric Purity of 1 and 1′: HPLC [column: Chiralcel-OD®, 4.6 mm × 25 cm; solvent: hexane/^{i}PrOH (1/1), flow rate: 0.5 mL/min; detector: 240 nm; temperature: room temp.], t_R = 10.2 min [0.50%, *ent*-**1**], t_R = 20.5 min [99.5%, **1**]. The enantiomeric purity of **1** was estimated to be 99.0% e.e. t_R = 8.9 min [undetectable, *ent*-**1′**], t_R = 10.5 min [ca. 100%, **1′**]. The enantiomeric purity of **1′** was estimated to be ca. 100% e.e.

(–)-(3a*S*,5*R*,8b*R*,2′*S*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-5-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (ent-1)] [(–)-Strigol] and (–)-(3a*S*,5*R*,8b*R*,2′*R*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-5-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-b]furan-2-one (ent-1′)] [(–)-2′-Epistrigol]: In the same manner as described for **1** and **1′**, hydroxymethylene lactone (ca. 3.28 mmol), prepared from hydroxylactone (–)-**2** (729 mg, 3.28 mmol) by using NaH (427 mg, 10.7 mmol) and ethyl formate (5.0 mL, ca. 62 mmol), was alkylated with 4-bromo-2-methyl-2-buten-4-olide (1.03 g, 5.82 mmol) in the presence of K_2CO_3 (899 mg, 6.50 mmol) in anhydrous *N*-methylpyrrolidone (22 mL). Silica-gel chromatography (hexane/ethyl acetate, 2/1) gave first 333 mg (29%) of *ent*-**1′** as a white solid and then 311 mg (27%) of *ent*-**1** also as a white solid. The crystalline *ent*-**1** was recrystallized twice from CH_2Cl_2/pentane to give colorless needles, m.p.

194−196°C [ref.[12] m.p. 193−194°C (from benzene/pentane), ref.[17] m.p. 192−194°C (from CH_2Cl_2/pentane) 181−184°C (from ethanol/water)]. − CD (c = 0.00020, MeOH) Δε (λ, nm) = −26.0 (232), +21.0 (205) [ref.[12] −27.0 (229), +19.1 (204), ref.[22] +2.55 (262), −24.15 (229)]. − $[\alpha]_D^{25}$ = −277 (c = 0.37, $CHCl_3$) [ref.[12] $[\alpha]_D^{25}$ = −279 (c = 0.11, $CHCl_3$), ref.[13] $[\alpha]_D$ = −272 (c = 0.18, $CHCl_3$), ref.[17] $[\alpha]_D^{20}$ = −244.3 (c = 0.36, $CHCl_3$) $[\alpha]_D^{20}$ = −249.5 (c = 0.51, $CHCl_3$)]. − Its IR ($CHCl_3$), ^{1}H-NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$) spectra were identical with those of (+)-**1**. − $C_{19}H_{22}O_6$ (346.4) calcd. C 65.88, H 6.40; found C 65.62, H 6.57. The crystalline *ent*-**1′** was recrystallized from CH_2Cl_2/pentane to give white plates, m.p. 146−148°C, and from benzene/pentane to give colorless needles, 155−156°C [ref.[12] m.p. 165−166°C (from benzene/pentane)]. − CD (c = 0.00024, MeOH) Δε (λ, nm) = −3.53 (247), +7.71 (206) [ref.[12] −11.8 (242), +33.0 (204), ref.[22] −4.78 (245), +9.62(207)]. − $[\alpha]_D^{24}$ = −141 (c = 1.38, $CHCl_3$) [ref.[12] $[\alpha]_D^{25}$ = +145 (c = 0.09, $CHCl_3$), ref.[17] $[\alpha]_D^{20}$ = −85.9 (c = 1.38, $CHCl_3$)]. − Its IR ($CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra were identical with those of (+)-**1′**. − $C_{19}H_{22}O_6$ (346.4) calcd. C 65.88, H 6.40; found C 65.59, H 6.36.

Determination of the Enantiomeric Purity of *ent*-1 and *ent*-1′: HPLC [column: Chiralcel-OD®, 4.6 mm × 25 cm; solvent: hexane/^{i}PrOH (1/1), flow rate: 0.5 mL/min; detector: 240 nm; temperature: room temp.], t_R = 10.2 min [99.97%, *ent*-**1**], t_R = 20.9 min [0.03%, **1**]. The enantiomeric purity of *ent*-**1** was estimated to be ca. 99.9% e.e. t_R = 8.9 min [99.4%, *ent*-**1′**], t_R = 10.5 min [0.6%, **1′**]. The enantiomeric purity of *ent*-**1′** was estimated to be 98.8% e.e.

(+)-(3a*R*,8b*S*)-8,8-Dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(+)-5]: According to the procedure of Welzel,[22] hydroxylactone (+)-**3** was transformed to deoxylactone (+)-**5** (76%) in 3 steps. The crystalline (+)-**5** was recrystallized from hexane to give colorless needles, m.p. 61−62°C. − CD (c = 0.00032, MeOH) Δε (λ, nm) = +0.041 (244), −2.72 (209). − $[\alpha]_D^{21}$ = +45 (c = 0.63, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1760 cm^{-1} (s, C=O), 1175 (m, C−O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, 8-Me), 1.10 (s, 3 H, 8-Me), 1.33−1.42 (m, 1 H, 7-H), 1.45−1.54 (m, 1 H, 7-H′), 1.61−1.76 (m, 2 H, 6-CH_2), 1.87−2.05 (m, 2 H, 5-CH_2), 2.11−2.19 (dd, 1 H, J = 16.6, $J′$ = 1.5 Hz, 4-H), 2.29−2.36 (dd, 1 H, J = 18.0, $J′$ = 4.9 Hz, 3-H), 2.57−2.65 (dd, 1 H, J = 16.6, $J′$ = 8.6 Hz, 4-H′), 2.75−2.84 (dd, 1 H, J = 18.0, $J′$ = 10.2 Hz, 3-H′), 2.96−3.06 (m, 1 H, 3a-H), 5.45−5.49 (d, 1 H, J = 7.6 Hz, 8b-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 26.4, 27.7, 28.1, 31.9, 34.5, 36.2, 38.9, 42.3, 90.2, 134.0, 141.5, 177.6. − $C_{13}H_{18}O_2$ (206.3) calcd. C 75.69, H 8.80; found C 75.28, H 8.88.

(−)-(3a*R*,8b*S*)-8,8-Dimethyl-4-oxo-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(−)-6] and (−)-(3a*R*,8b*S*)-8,8-Dimethyl-5-oxo-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(−)-7]: To a suspension of chromium trioxide (93.7 g, 0.94 mol) in dry dichloromethane (700 mL) was added 3,5-dimethylpyrazole (90.1 g, 0.94 mol) in one portion at −20°C under argon. The mixture was stirred for 30 min at −20°C and then a solution of (+)-**5** (1.93 g, 9.4 mmol) in dry dichloromethane (60 mL) was added. After stirring for 4 h at −20°C, 5 M NaOH (440 mL) was added in one portion with cooling. The mixture was stirred for 30 min at 0°C and extracted with dichloromethane. The organic layer was washed successively with water, 1 M HCl, water and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate, 10/1) to afford 376 mg (18%) of (−)-**6** as a white solid and 1.05 g (51%) of (−)-**7** as a white solid. The crystalline (−)-**6** was recrystallized from hexane/diethyl ether to give colorless needles, m.p. 84−85°C. − CD (c = 0.00029, MeOH) Δε (λ, nm) = +1.62 (319), −12.7 (232). − $[\alpha]_D^{20}$ = −4.7 (c = 0.52, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1780 cm^{-1} (s, C=O), 1710 (s, C−O), 1700 (s, C−O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H, 8-Me), 1.26 (s, 3 H, 8-Me), 1.48−1.51 (m, 1 H, 7-H), 1.59−1.66 (m, 1 H, 7-H′), 1.69−1.78 (m, 2 H, 6-CH_2), 2.07−2.18 (dtd, 1 H, J = 18.3, $J′$ = 7.1, $J′′$ = 2.2 Hz, 5-H), 2.19−2.28 (dt, 1 H, J = 18.3, $J′$ = 5.6 Hz, 5-H), 2.62−2.69 (dd, 1 H, J = 19.0, $J′$ = 4.4 Hz, 3-H), 2.86−2.96 (dd, 1 H, J = 19.0, $J′$ = 12.4 Hz, 3-H′), 3.16−3.24 (ddd, 1 H, J = 12.6, $J′$ = 6.1, $J′′$ = 4.4 Hz, 3a-H), 5.53−5.57 (dd, 1 H, J = 6.1, $J′$ = 2.2 Hz, 8b-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 20.5, 27.3, 27.4, 30.6, 34.4, 38.3, 43.5, 79.3, 142.0, 173.6, 174.9, 204.7. − $C_{13}H_{16}O_3$ (220.3) calcd. C 70.89, H 7.32; found C 70.50, H 7.14. − The crystalline (−)-**7** was recrystallized from hexane/diethyl ether to give colorless needles, m.p. 101−102°C. − $[\alpha]_D^{20}$ = −53 (c = 1.0, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1765 cm^{-1} (s, C=O), 1670 (s, C=O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, 8-Me), 1.29 (s, 3 H, 8-Me), 1.84−1.97 (m, 2 H, 7-CH_2), 2.26−2.37 (dd, 1 H, J = 18.3, $J′$ = 5.8 Hz, 3-H), 2.40−2.51 (m, 2 H, 4-H and 6-H), 2.53−2.63 (ddd, 1 H, J = 17.6, $J′$ = 10.0, $J′′$ = 5.9 Hz, 6-H), 2.79−2.89 (dd, 1 H, J = 17.1, $J′$ = 8.5 Hz, 4-H′), 2.81−2.90 (dd, 1 H, J = 18.3, $J′$ = 10.2 Hz, 3-H), 3.10−3.20 (m, 1 H, 3a-H), 5.61−5.65 (dd, 1 H, J = 7.6, $J′$ = 1.5 Hz, 8b-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 26.6, 33.3, 34.3, 35.0, 35.2, 35.4, 38.8, 89.0, 137.8, 162.8, 176.2, 198.0. − $C_{13}H_{16}O_3$ (220.3) calcd. C 70.89, H 7.32; found C 70.51, H 7.05.

(+)-(3a*R*,4*S*,8b*S*)-4-Hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(+)-8] and (+)-(3a*R*,4*R*,8b*S*)-4-Hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]-furan-2-one [(+)-9]: To a stirred solution of α,β-unsaturated ketone (−)-**6** (376 mg, 1.71 mmol) in ethanol (30 mL) was added $CeCl_3 \cdot 7\ H_2O$ (640 mg, 1.72 mmol) followed by slow addition of $NaBH_4$ (65 mg, 1.71 mmol). After stirring for 10 min, the reaction mixture was quenched by dropwise addition of 1 M HCl and then extracted with dichloromethane. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (hexane/ethyl acetate = 3/1) to afford first 308 mg (81%) of (+)-**9** as a white solid and then 16 mg (4%) of (+)-**8** as a white solid. The crystalline (+)-**8** was recrystallized from hexane/diethyl ether to give colorless needles, m.p. 77−78°C. − $[\alpha]_D^{20}$ = +1.3 (c = 0.52, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3100−3600 cm^{-1} (w, O−H), 1770 (s, C=O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 8-Me), 1.12 (s, 3 H, 8-Me), 1.39−1.54 (m, 2 H, 7-CH_2), 1.68−1.76 (m, 2 H, 6-CH_2), 1.73−1.77 (d, 1 H, 6-CH_2), 1.94−2.03 (dt, 1 H, J = 17.8, $J′$ = 5.6 Hz, 5-H), 2.14−2.22 (dtd, 1 H, J = 17.8, $J′$ = 7.3, $J′′$ = 2.4 Hz, 5-H′), 2.39−2.51 (dd, 1 H, J = 23.9, $J′$ = 9.8 Hz, 3-H), 2.79−2.90 (m, 1 H, 3a-H, dd, 1 H, J = 23.9, $J′$ = 11.0 Hz, 3-H′), 4.43−4.47 (d, 1 H, J = 6.6 Hz, 4-H), 5.54−5.58 (d, 1 H, J = 6.3 Hz, 8b-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9, 23.4, 27.3, 27.8, 32.0, 33.6, 38.6, 45.4, 84.1, 87.6, 143.3, 143.8, 177.0. − $C_{13}H_{18}O_3$ (222.3) calcd. C 70.25, H 8.16; found C 70.27, H 7.99. − The crystalline (+)-**9** was recrystallized from hexane/diethyl ether to give colorless needles, m.p. 100−102°C. − CD (c = 0.00014, MeOH) Δε (λ, nm) = +0.063 (242). − $[\alpha]_D^{21}$ = +68 (c = 0.86, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (w, O−H), 1760 (s, C=O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 8-Me), 1.14 (s, 3 H, 8-Me), 1.29−1.42 (m, 1 H, 7-H), 1.49−1.61 (m, 1 H, 7-H′), 1.68−1.76 (m, 2 H, 6-CH_2), 1.91−2.02 (m, 1 H, 5-H), 2.22−2.31 (dt, 1 H, J = 17.8, $J′$ = 5.1 Hz, 5-H′), 2.48−2.57 (dd, 1 H, J = 18.6, $J′$ = 10.8 Hz, 3-H), 2.83−2.91 (dd, 1 H, J = 18.6, $J′$ = 5.1 Hz, 3-H), 3.09−3.18 (dtd, 1 H, J = 10.8, $J′$ = 7.3 Hz, $J′′$ = 5.4 Hz, 3a-H), 4.52−4.58 (t, 1 H, J = 7.1 Hz, 4-H), 5.24−5.29 (dd, 1 H, J = 7.1,

J' = 2.0 Hz, 8b-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 23.6, 27.7, 28.1, 28.5, 31.9, 38.8, 40.2, 75.7, 86.4, 143.2, 143.3, 177.9. − $C_{13}H_{18}O_3$ (222.3) calcd. C 70.25, H 8.16; found C 70.25, H 7.91.

Convertion of (+)-9 to (+)-8 Utilizing Mitsunobu Reaction:[24] To a stirred mixture of alcohol (+)-**9** (95 mg, 0.43 mmol), triphenylphosphane (415 mg, 1.58 mmol) and benzoic acid (193 mg, 1.58 mmol) in THF (10 mL) was added a solution of diethyl azodicarboxylate (DEAD, 40% toluene solution, 680 mg, 1.56 mmol) in THF (5 mL). The mixture was stirred for 16.5 h and then concentrated under reduced pressure. Silica-gel chromatography (hexane/ethyl acetate, 15/1) of the residue gave 133 mg (95%) of the benzoate of (+)-**8** as a colorless and amorphous solid, $[\alpha]_D^{21}$ = −55 (*c* = 1.2, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2950 cm^{-1} (w, aromatic H), 1780 (s, C=O), 1730 and 1720 (s, C=O), 1610 and 1460 (m), 720 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.15 (s, 3 H, 8-Me), 1.17 (s, 3 H, 8-Me), 1.20−1.90 (m, 4 H, 6-CH_2 and 7-CH_2), 2.00−2.20 (m, 2 H, 5-CH_2), 2.80−2.92 (m, 3 H, 3-CH_2 and 3a-H), 5.45−5.60 (m, 2 H, 4-H and 8b-H), 7.36−7.60 (m, 3 H, aromatic H), 7.96−8.06 (m, 2 H, aromatic H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9, 23.8, 27.3, 27.8, 32.3, 33.6, 38.5, 43.5, 86.9, 86.9, 128.4, 129.6, 129.7, 133.3, 139.9, 146.6, 166.6, 176.5. − A mixture of the above benzoate (110 mg, 0.34 mmol) and K_2CO_3 (67 mg, 0.48 mmol) in MeOH (10 mL) was stirred for 1.5 h, acidified with 1 M HCl and then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica-gel column chromatography (hexane/ethyl acetate, 2/1) to afford 71 mg (95%) of (+)-**8** as a white solid.

(+)-(3a*R*,4*S*,8b*S*,2′*R*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-4-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (2) [(+)-Orobanchol] and (+)-(3a*R*,4*S*,8b*S*,2′*S*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-4-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (2′) [(+)-2′-Epiorobanchol]: In the same manner as described for **1** and **1**′, to a stirred suspension of NaH (60% suspension in oil, 36 mg, 0.90 mmol), washed with dry diethyl ether several times, in dry diethyl ether (1 mL), at room temperature under argon, was added a solution of the hydroxylactone (+)-**8** (37 mg, 0.17 mmol) in dry diethyl ether (2 mL). Then ethyl formate (0.14 mL, ca. 9 mmol) was added. After stirring for 4 h, the mixture was acidfied with 1 M HCl and then extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the filtrate gave a pale orange solid (42 mg), which was used directly in the subsequent transformation without purification. To the stirred mixture of hydroxymethylenelactone (ca. 0.17 mmol) obtained above and K_2CO_3 (49 mg, 0.35 mmol) in anhydrous *N*-methylpyrrolidone (1.5 mL), at room temp. under argon, was added a solution of (±)-4-bromo-2-methyl-2-buten-4-olide (62 mg, 0.35 mmol) in anhydrous *N*-methylpyrrolidone (1.5 mL). After stirring for 5 h at room temperature, the reaction mixture was poured into 1 M HCl (3 mL) and extracted with ethyl acetate. The organic layer was washed with water twice and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/ethyl acetate, 1/2) to give 17 mg (30%) of **2** as a colorless amorphous solid and 17 mg (30%) of **2**′ also as a colorless amorphous solid. − **(+)-Orobanchol (2):** CD (*c* = 0.00029, MeOH) Δε (λ, nm) = +0.14 (266), +11.2 (231). − $[\alpha]_D^{25}$ = +158 (*c* = 0.38, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3600 cm^{-1} (w, O−H), 1790 (s, C=O), 1750 (s, C=O), 1680 (s, C=O), 1340 (m), 1180 (m), 1100 (s), 1030 (s), 965 (m). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 8-Me), 1.14 (s, 3 H, 8-Me), 1.37−1.52 (m, 2 H, 7-CH_2), 1.66−1.74 (m, 2 H, 6-CH_2), 1.91−2.02 (dt, 1 H, *J* = 18.0, *J*′ = 5.4 Hz, 5-H), 2.01−2.04 (t, 3 H, *J* = 1.5 Hz, 4′-Me), 2.09−2.22 (dtd, 2 H, *J* = 18.0, *J*′ = 7.8, *J*′′ = 2.2 Hz, 5-H′ and OH), 3.39−3.44 (dt, 1 H, *J* = 7.3, *J*′ = 2.2 Hz, 3a-H), 4.56−4.60 (s, 1 H, 4-H), 5.59−5.63 (d, 1 H, *J* = 7.3 Hz, 8b-H), 6.20−6.23 (s, 1 H, 2′-H), 6.94−6.96 (t, 1 H, *J* = 1.5 Hz, 3′-H), 7.46−7.48 (d, 1 H, *J* = 2.4 Hz, 9-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 18.9, 23.6, 27.4, 27.9, 32.1, 38.7, 48.3, 83.0, 85.9, 100.3, 111.3, 136.3, 140.9, 143.0, 144.1, 150.5, 170.1, 171.0. − HRMS $C_{19}H_{22}O_6$: calcd. 346.1400; found 346.1407. − **(+)-2′-Epiorobanchol (2′):** CD (*c* = 0.00023, MeOH) Δε (λ, nm) = +4.84 (266), −2.75 (203). − $[\alpha]_D^{24}$ = +71 (*c* = 0.30, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3600 cm^{-1} (w, O−H), 1790 (s, C=O), 1740 (s, C=O), 1680 (s, C=O), 1340 (m), 1180 (m), 1100 (s), 1030 (s), 960 (m). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 8-Me), 1.13 (s, 3 H, 8-Me), 1.35−1.51 (m, 2 H, 7-CH_2), 1.63−1.73 (m, 2 H, 6-CH_2), 1.91−2.00 (dt, 1 H, *J* = 18.0, *J*′ = 5.4 Hz, 5-H), 2.01−2.03 (t, 3 H, *J* = 1.5 Hz, 4′-Me), 2.10−2.20 (dtd, 1 H, *J* = 18.0, *J*′ = 7.8, *J*′′ = 2.2 Hz, 5-H′), 3.39−3.43 (dt, 1 H, *J* = 7.3, *J*′ = 2.2 Hz, 3a-H), 4.53−4.57 (s, 1 H, 4-H), 5.58−5.63 (dt, 1 H, *J* = 7.3, *J*′ = 1.9 Hz, 8b-H), 6.17−6.20 (t, 1 H, *J* = 1.3 Hz, 2′-H), 6.95−6.98 (p, 1 H, *J* = 1.5 Hz, 3′-H), 7.50−7.52 (d, 1 H, *J* = 2.7 Hz, 9-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 18.9, 23.5, 27.4, 27.9, 32.1, 38.8, 48.2, 83.0, 85.9, 100.6, 111.2, 136.0, 141.0, 143.0, 144.1, 151.1, 170.2, 171.0. − HRMS $C_{19}H_{22}O_6$: calcd. 346.1400; found 346.1410.

(+)-(3a*R*,8b*S*,2′*R*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-4-oxo-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(+)-10]: To a solution of **2** (39 mg, 0.11 mmol) in dichloromethane (5 mL) was added pyridinium dichromate (PDC, 64 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 7 h, diluted with ether, and filtered through Celite. Solvent was evaporated and the residue was chromatographed on silica gel (hexane/ethyl acetate, 3/1) to give 33 mg (85%) of (+)-**10** as a colorless and amorphous solid. − $[\alpha]_D^{18}$ = +336 (*c* = 0.66, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1785 cm^{-1} (s, C=O), 1755 (s, C=O), 1710 (s, C=O), 1680 (s, C=O). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, 8-Me), 1.26 (s, 3 H, 8-Me), 1.46−1.53 (m, 1 H, 7-H), 1.57−1.63 (m, 1 H, 7-H′), 1.67−1.74 (m, 2 H, 6-CH_2), 1.98−2.02 (t, 3 H, *J* = 1.5 Hz, 4′-Me), 2.05−2.13 (m, 1 H, 5-H), 2.13−2.20 (dt, 1 H, *J* = 18.3, *J*′ = 5.5 Hz, 5-H′), 3.82−3.85 (m, 1 H, 3a-H), 5.48−5.52 (m, 1 H, 8b-H), 6.17−6.20 (m, 1 H, 2′-H), 7.03−7.06 (t, 1 H, *J* = 1.5 Hz, 3′-H), 7.63−7.66 (d, 1 H, *J* = 2.5 Hz, 9-H). − HRMS $C_{19}H_{20}O_6$: calcd. 344.1300; found 344.1250.

(+)-(3a*R*,4*R*,8b*S*,2′*R*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-4-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (2′′) [(+)-4 -Epiorobanchol]: To a solution of (+)-**10** (26 mg, 0.047 mmol) and $CeCl_3 \cdot 7\ H_2O$ (73 mg, 0.20 mmol) in EtOH (5 mL) was slowly added $NaBH_4$ (22 mg, 0.58 mmol) at 5°C. The reaction mixture was stirred for 9 h at 5°C to room temperature, then quenched by water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/ethyl acetate, 1/2) to give 5.0 mg (31%) of (+)-**10**, and 2.3 mg [21% based on consumed (+)-**10**] of **2**′′ as a white solid. The crystalline **2**′′ was recrystallized from hexane/ethyl acetate to give colorless needles, m.p. 204−205°C − CD (*c* = 0.00020, MeOH) Δε (λ, nm) = −2.62 (270), +27.2 (233), −6.38 (206). − $[\alpha]_D^{18}$ = +290 (*c* = 0.18, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3600 cm^{-1} (w, O−H), 1785 (s, C=O), 1740 (s, C=O), 1680 (s, C=O), 1340 (m), 1180 (s), 1100 (s), 1020 (s), 960 (s). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 8-Me), 1.16 (s, 3 H, 8-Me), 1.35−1.42 (m, 1 H, 7-H), 1.49−1.55 (m, 1 H, 7-H′), 1.68−1.74 (m, 2 H, 6-CH_2), 1.92−2.00 (m, 1 H, 5-H),

2.01−2.03 (t, 3 H, *J* = 1.5 Hz, 4′-Me), 2.23−2.30 (dt, 1 H, *J* = 18.0, *J*′ = 5.5 Hz, 5-H′), 3.76−3.81 (dt, 1 H, *J* = 7.3, *J*′ = 2.4 Hz, 3a-H), 4.63−4.67 (d, 1 H, *J* = 7.9 Hz, 4-H), 5.25−5.29 (dd, 1 H, *J* = 7.3, *J*′ = 1.5 Hz, 8b-H), 6.16−6.19 (t, 1 H, *J* = 1.5 Hz, 2′-H), 6.94−6.96 (t, 1 H, *J* = 1.5 Hz, 3′-H), 7.63−7.65 (d, 1 H, *J* = 2.5 Hz, 9-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 19.1, 23.9, 27.9, 28.1, 32.1, 38.9, 43.4, 77.3, 84.6, 100.7, 108.3, 135.9, 140.9, 143.3, 143.4, 152.1, 170.1, 171.2. − HRMS $C_{19}H_{22}O_6$: calcd. 346.1400; found 346.1408.

(+)-(3a*R*,8b*S*,2′*S*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-4-oxo-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one [(+)-11]: To a solution of **2′** (65 mg, 0.19 mmol) in dichloromethane (5 mL) was added pyridinium dichromate (PDC, 110 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for 7 h, diluted with ether and filtered through Celite. The solvent was evaporated and the residue was chromatographed on silica gel (hexane/ethyl acetate, 3/1) to give 50 mg (77%) of (+)-**11** as a colorless and amorphous solid. − $[\alpha]_D^{18}$ = +222 (*c* = 0.34, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1780 cm^{-1} (s, C=O), 1750 (s, C=O), 1710 (s, C=O), 1680 (s, C=O). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, 8-Me), 1.28 (s, 3 H, 8-Me), 1.47−1.54 (m, 1 H, 7-H), 1.58−1.64 (m, 1 H, 7-H′), 1.68−1.75 (m, 2 H, 6-CH_2), 2.00−2.05 (t, 3 H, *J* = 1.6 Hz, 4′-Me), 2.06−2.14 (dtd, 1 H, *J* = 18.3, *J*′ = 7.0, *J*′′ = 2.2 Hz, 5-H), 2.15−2.23 (dt, 1 H, *J* = 18.3, *J*′ = 5.5 Hz,5-H), 3.91−3.94 (dd, 1 H, *J* = 6.1, *J*′ = 2.5 Hz, 3a-H), 5.50−5.54 (dd, 1 H, *J* = 6.1, *J*′ = 1.6 Hz, 8b-H), 6.47−6.50 (t, 1 H, *J* = 1.5 Hz, 2′-H), 6.99−7.02 (quintet, 1 H, *J* = 1.6 Hz, 3′-H), 7.51−7.53 (d, 1 H, *J* = 2.5 Hz, 9-H). − HRMS $C_{19}H_{20}O_6$: calcd. 344.1300; found 344.1252.

(+)-(3a*R*,4*R*,8b*S*,2′*S*)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-4-hydroxy-8,8-dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno[1,2-*b*]furan-2-one (2′′′) [(+)-4, 2′-Bisepiorobanchol]: To a solution of (+)-**11** (34 mg, 0.099 mmol) and $CeCl_3 \cdot 7H_2O$ (148 mg, 0.40 mmol) in EtOH (5 mL) was slowly added $NaBH_4$ (15 mg, 0.40 mmol) at 5°C. The reaction mixture was stirred for 2 h at 5°C to room temperature, then quenched by water and extracted with dichloromathane. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/ethyl acetate = 1/2) to give 7.6 mg (22%) of (+)-**11** and 2.2 mg [8.3% based on consumed (+)-**11**] of **2′′′** as a colorless oil. − CD (*c* = 0.00038, MeOH) Δε (λ, nm) = +2.62 (242), −2.60 (220). − $[\alpha]_D^{18}$ = +156 (*c* = 0.065, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3600 cm^{-1} (w, O−H), 1790 (s, C=O), 1745 (s, C=O), 1680 (s, C=O), 1340 (w), 1200 (s), 1100 (s), 1010 (s), 960 (m). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 8-Me), 1.16 (s, 3 H, 8-Me), 1.34−1.41 (m, 1 H, 7-H), 1.49−1.55 (m, 1 H, 7-H′), 1.67−1.74 (m, 2 H, 6-CH_2), 1.90−1.99 (m, 1 H, 5-H), 2.01−2.04 (t, 3 H, *J* = 1.5 Hz, 4′-Me), 2.24−2.31 (dt, 1 H, *J* = 18.0, *J*′ = 5.5 Hz, 5-H′), 3.79−3.83 (dt, 1 H, *J* = 7.4, *J*′ = 2.5 Hz, 3a-H), 4.64−4.68 (d, 1 H, *J* = 7.9 Hz, 4-H), 5.26−5.30 (dd, 1 H, *J* = 7.3, *J*′ = 1.9 Hz, 8b-H), 6.18−6.20 (t, 1 H, *J* = 1.6 Hz, 2′-H), 6.92−6.95 (t, 1 H, *J* = 1.6 Hz, 3′-H), 7.58−7.60 (d, 1 H, *J* = 2.5 Hz, 9-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 19.0, 23.8, 27.9, 28.1, 32.1, 38.9, 43.3, 77.3, 84.6, 100.3, 108.5, 136.2, 141.0, 143.2, 143.3, 151.3, 169.9, 171.2. − HRMS $C_{19}H_{22}O_6$: calcd. 346.1400; found 346.1417.

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