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Enantioselective Synthesis of γ-Cyclohomocitral, Pallescensone, and Ancistrodial

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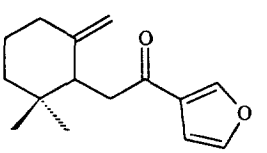
Abstract: A simple and efficient enantioselective synthesis of γ-cyclohomocitral, a key and versatile intermediate for the synthesis of some monocyclofarnesane terpenoids, is described. This features a highly sitoselective Sharpless asymmetric dihydroxylation of a homomonoterpene diolefin. The first enantioselective synthesis of (-)-ancistrodial and (-)-pallescensone were accomplished. The (*S*)- configuration was then assigned to natural pallescensone.

In 1987, R.C. Cambie and his collaborators reported the isolation and identification on spectroscopic evidence of (+)-pallescensone **1** which was obtained from the sponge *Dictyodendrilla cavernosa* Lendenfeld collected from New Zealand coastal waters.[1] Curiously, two years previous to the isolation of the natural product, **1** in its racemic form had been prepared[2] as a key intermediate in the synthesis of (±)-ancistrofuran and its stereoisomers, but the absolute configuration of (+)-**1** has not yet been established.[3] The sesquiterpene ancistrodial **2**, biosynthetically related to **1**, was isolated by R. Baker and his co-workers as the major component in the defensive secretion of minor soldiers of the West African termite *Ancistrotermes cavithorax*.[4] A synthesis of (±)-**2** has been reported; however, the absolute configuration as well as the geometry of the conjugated double bond in the natural product have remained unknown.[4] Moreover, the limited amount of available natural material precluded establishment of the relationship between absolute configuration and specific rotation of **2**.



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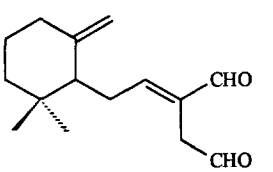

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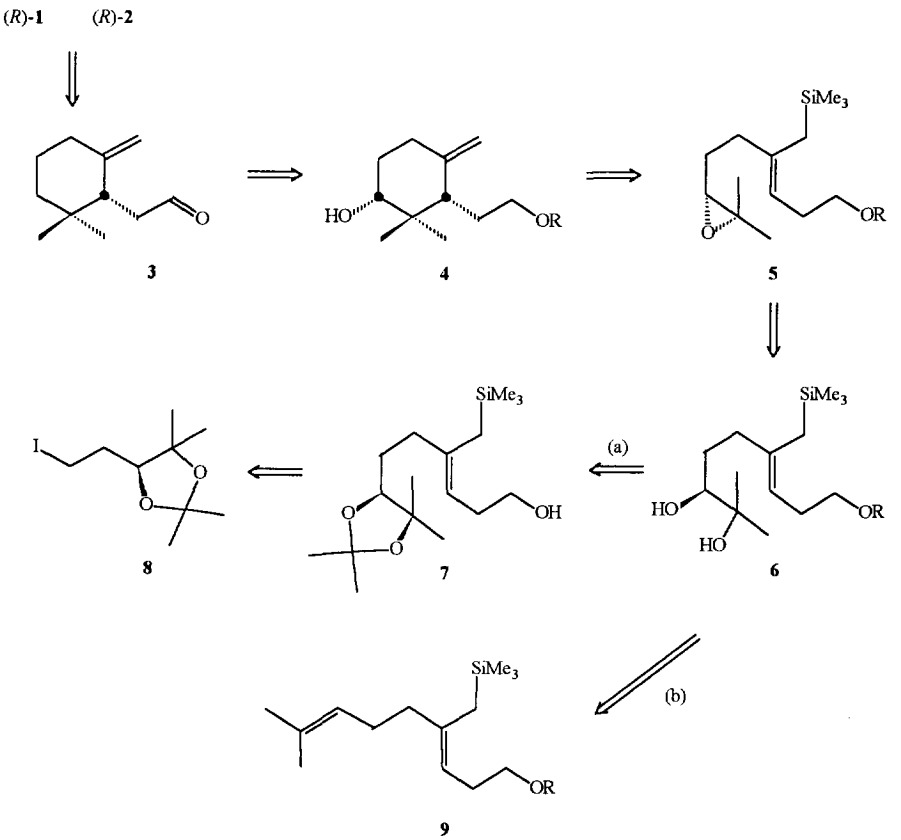
In this paper we describe the first enantioselective synthesis of (-)-(*R*)-**1** which enables us to assign the (*S*)- configuration to naturally occurring pallescensone. Moreover, we accomplished the synthesis of (-)-(*R*)-**2** and established the *E* configuration for the double bond of natural ancistrodial.

The synthesis of (*R*)-**1** and (*R*)-**2** is based on the retrosynthetic analysis illustrated in Scheme 1 which is centered on the preparation of γ-cyclohomocitral **3** as the key intermediate. Several strategies have been reported for the synthesis of **3** or the immediate alcohol precursor **4**, including alkylation of an enolate anion,[3] classic Claisen,[4,5] and aza-Claisen[6] rearrangements. In these approaches appropriate substituted cyclohexane moieties have been used as convenient precursors to **3** or **4**. However, these routes either lead to racemic material or are poorly diastereoselective. In our studies we relied on a different strategy (Scheme 1) which is based on a biomimetic electrophilic olefin cyclization[7] of optically active epoxy-allylsilane **5** to give alcohol **4**.[8]

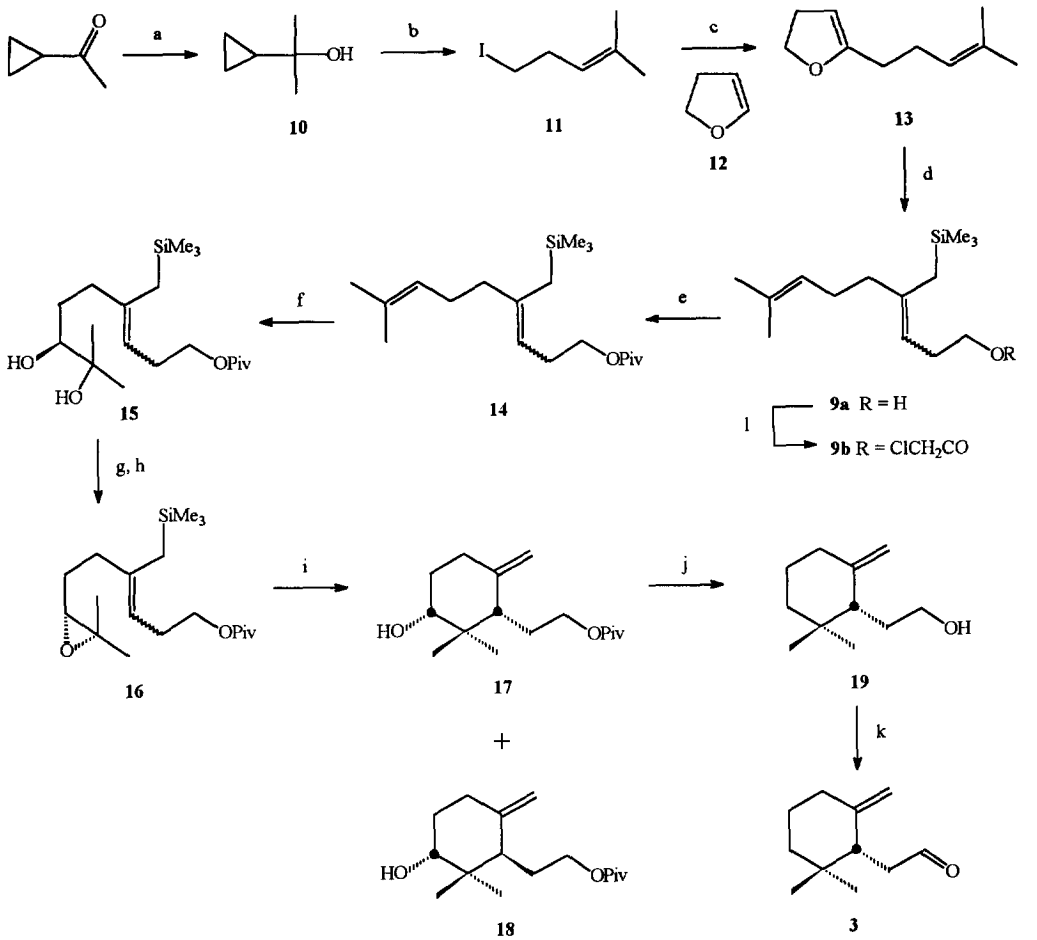


Scheme 1

In our previous synthesis of **4**,[9] the chiral information was encoded in the building block **8** (Scheme 1, route a); unfortunately, this route suffered from a severe drawback, since unmasking acetal **7** to afford diol **6** succeeded in very poor yields (34% at best).[9] Therefore, we explored the feasibility of obtaining diol **6**, in the desired absolute configuration, by a regioselective Sharpless asymmetric dihydroxylation[10] of a suitably protected dienol **9**. In this paper we report the results obtained pursuing this second approach.

RESULTS AND DISCUSSION

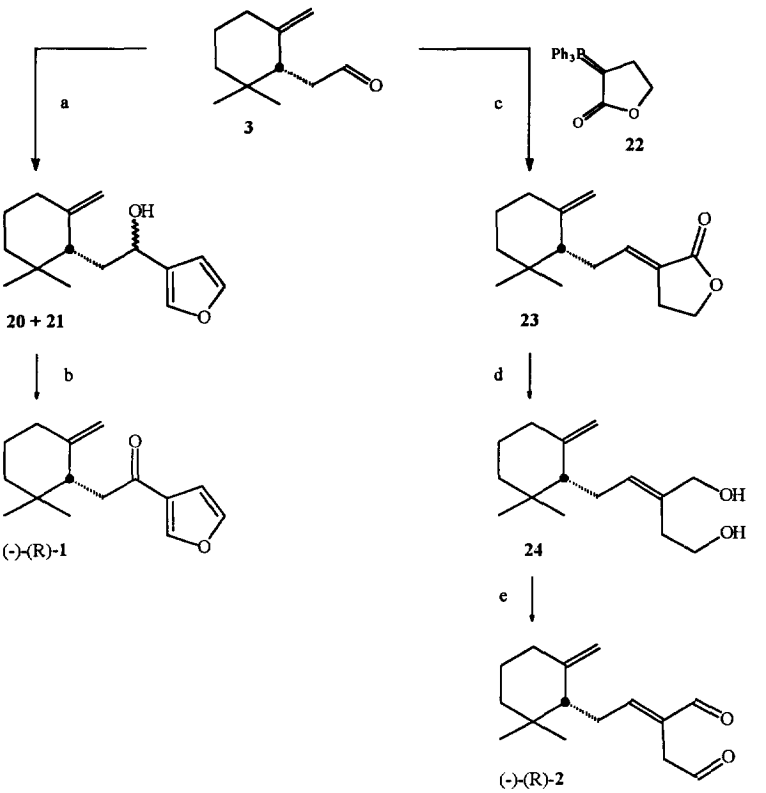
Scheme 2 shows the synthetic route leading to the desired homoallylic alcohol **9a**. Iodine **11** was obtained from readily available tertiary cyclopropyl carbinol **10** according to a slightly modified Julia procedure,[11] and then it was coupled efficiently with 5-lithio-2,3-dihydrofuran by using the Boeckman and Bruza protocol.[12] The unstable cyclic α-alkylvinylether **13** was immediately submitted to the Wenkert-Kocienski reaction[13] which delivered diene **9a** in satisfactory yields. Kocienski already observed[13b] that rapid and efficient stirring in the work up of this reaction is essential to destroy a low-valent nickel catalyst which may be generated and rapidly promotes rearrangement and isomerization of double bonds in the homoallylic alcohol. In our hands, satisfactory retention of stereochemistry at the C-3–C-4 double bond of **9a** could be reproduced when **13** was converted in up to 5-6 g.[14] The two diastereomers were unseparable by preparative silica gel column chromatography and then were submitted as a mixture to the following osmylation reaction. Recently, several reports[15] showed that polyenes with isolated double bonds may be mono-dihydroxylated in good to excellent yields, if the double bonds are electronically and sterically different. Generally, the osmylation of unsymmetrical polyenes preferentially occurs at the most electron-rich and sterically accessible double bond. We anticipated that steric effects should favor the osmylation of **9a** at the 7,8-double bond, since the 3,4-double bond is severely congested by the bulky trimethylsilanylmethyl group.[16] In addition, the electron withdrawing inductive effect of an appropriate homoallylic oxygen substituent in **9a** was expected to increase the preference for the remote double bond oxidation. Relevant to this point, our previous studies on related acyclic terpenes[15c,d] proved that the presence of an allylic ester group has a deleterious effect on the rate of AD of adjacent double bonds. Therefore, alcohol **9a** was converted to the corresponding monochloroacetate **9b**, which was immediately submitted to AD using the $(DHQ)_2$-PHAL ligand (AD-mix-α).[10] Gratifyingly, the ^{1}H-NMR spectrum of the crude reaction mixture showed the 7,8-diol to contain ≤5% of the regioisomeric diol and undetectable tetrols. However, the above protective group was expected not to survive under the basic conditions employed for installing the 7,8-epoxide in the following step of the synthesis (see Scheme 2). Therefore, we decided to protect alcohol **9a** with a pivaloyl group which could compensate its minor electron-withdrawing properties, as compared to the $ClCH_2CO_2$- group, with a greater steric hindrance. In the event, the AD-mix-α reaction on pivaloate **14** gave diol **15** (as a mixture of two diastereomers at C-3, see above) as the only isolable product; if present, the 3,4-diol and tetrols were ≤3%. Conversion of compound **15** into **17** and **18** was executed according to a previously developed procedure,[9] and then the two diastereomers were obtained in a pure state by chromatographic separation. The configurational assignments at the stereogenic carbon atoms C-1 and C-3 of **17** and **18** followed from the mnemonic device described by Sharpless *et al.*[10] for the AD of olefins, and from the mode of concerted cyclization of the epoxy-allylsilane **16**, which proceeds *via* a chair-like transition state.[7] They were confirmed by the NMR data of **17** and **18** (see the Experimental part). In conclusion, the major diastereomer **17** was derived from (*Z*)-**9a**, while its stereoisomer **18** was synthesized from (*E*)-**9a**. An enantiomeric excess of 92% was determined for both alcohols **17** and **18** by ^{1}H-NMR (300 MHz) upon separate conversion to the corresponding Mosher ester derivatives, using *in situ* prepared (-)- and (+)-MTPA-Cl.[17] Thus, both the Sharpless AD of olefin **14** and the subsequent synthetic steps must have taken place in satisfactory stereoselective manner. Conversion of **17** to **3** was executed as described previously for the corresponding primary *O*-acetate,[9] except the pivaloate group was cleaved with $LiEt_3BH$.



Scheme 2

Reagents and conditions: a) MeMgBr, Et_2O, reflux, 30 min, 83%; b) 57% HI, 0°C, 20 min, 79%; c) **12**, *t*BuLi, THF, -50° →0°C, 30 min; then **11**, THF, -30°→25°C, 18 h; d) Me_3SiCH_2MgCl, [1,3-*bis*(diphenylphosphine)propane]nickel(II)chloride, C_6H_6, 25°C, 20 min; then **13**, C_6H_6, reflux, 18 h, 66% from **11**; e) Me_3CCOCl, NEt_3, CH_2Cl_2, 25°C, 3 h, 75%; f) AD-mix-α, $CH_3SO_2NH_2$, *t*BuOH:H_2O (1:1), 0°C, 8 h, 66%; g) MsCl, Py, CH_2Cl_2, -30°C, 6 h; h) K_2CO_3, MeOH, 0°C, 45 min, 82% from **15**; i) BF_3OEt_2, CH_2Cl_2, -78°C, 1 h, 83%; j) 1) phenoxythiocarbonyl chloride, Py, CH_2Cl_2, 25°C, 4 h; 2) *n*Bu_3SnH, AIBN, THF, reflux, 5 h; 3) $LiEt_3BH$, THF, reflux, 2 h, 75% from **17**; k) tetrapropylammonium perruthenate(VII), 4-methylmorpholine-N-oxide, 4Å MS, CH_2Cl_2, 25°C, 3 h, 75%; l) $(ClCH_2CO)_2O$, NEt_3, CH_2Cl_2, 25°C, 2 h, 80%.

(-)-γ-Cyclohomocitral **3** was straightforwardly converted into (-)-pallescensone (*R*)-**1** in two steps (Scheme 3). Addition of **3** to a solution of 3-furyllithium, according to the procedure originally reported by Baker,[2] yielded the diastereomeric alcohols **20** and **21** in 70% yield, and they were smoothly oxidized to the target ketone (*R*)-**1**, $[\alpha]_D^{20}$ = -31.8 (CH_2Cl_2), with Ley's tetrapropylammonium perruthenate(VII) (TPAP) reagent.[18] The IR, ^{1}H- and ^{13}C-NMR spectroscopic data of synthetic (*R*)-**1** were identical with those reported[1] for naturally occurring pallescensone, $[\alpha]_D^{20}$ = +36 ($CHCl_3$), which, therefore, must possess the (*S*)- absolute configuration.



Scheme 3

Reagents and conditions: a) 3-bromofuran, *n*BuLi, THF, -78°C, 15 min; then **3**, THF, -78°C, 15 min, 70%; b) tetrapropylammonium perruthenate(VII), 4-methylmorpholine-N-oxide, 4Å MS, CH_2Cl_2, 25°C, 2 h, 70%; c) α-(triphenyl-phosphoranylidene)-γ-butyrolactone, THF, 50°C, 24 h, 90%; d) DIBAL-H, THF, -10° → 0°C, 3 h, 72%; e) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -60°C, 30 min, 65%.

To achieve ancistrodial, (*R*)-**3** was condensed[9] with the stable ylide **22**[19] to give the desired *E*-lactone **23** as the only stereoisomer (NOE studies). Compound **23** was easily converted into (-)-ancistrodial ((*R*)-**2**), [$\alpha]_D^{20}$ -15.8 (CH_2Cl_2), using standard reactions (Scheme 3). NOE experiments pointed out that the conjugated double bond of synthetic **2** had maintained the *E* configuration. The ^{1}H-NMR spectrum of the synthetic enantiomer of **2** was identical to the data reported for natural ancistrodial.[4] Unfortunately, a direct comparison was not possible since a sample of naturally occurring ancistrodial was not available. Therefore, the absolute configuration of the natural stereoisomer is still to be determined; however, the *E* configuration was firmly established by our synthesis, as well as the relationship between the absolute configuration and the sign of the optical rotation. The enantiomeric purities of (*R*)-**1** and (*R*)-**2** could not be established directly; however, they were assumed to be ca. 92% e.e. because none of the steps of the synthesis arising from aldehyde **3** should cause racemization.

Acknowledgment. This work was supported by the Italian Consiglio Nazionale delle Ricerche and the Ministero dell'Università e della Ricerca Scientifica. We thank Dr. Mariella Mella and Dr. Giorgio Mellerio, Università di Pavia, for NMR and MS spectra determination, respectively.

EXPERIMENTAL

IR spectra were recorded (film or KBr pellets) with a Perkin-Elmer Model 257 spectrometer. ^{1}H-(300 MHz) and ^{13}C-NMR (75.47 MHz) spectra were recorded in $CDCl_3$ solution, using a Bruker CXP 300 spectrometer. Chemical shifts are reported in δ units with Me_4Si or $CHCl_3$, in case of silylated compounds, as internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and b=broad are used throughout. Coupling constants (J) are reported in Hz. The number in parentheses in the ^{13}C-NMR spectra indicates the number of hydrogens attached to each carbon and was established by DEPT experiments. Mass spectra were determined with a Finnigan MAT 8222 instrument at 70 eV (0.5 mA) using a direct inlet system. Merck Kieselgel 60 (0.043-0.060 mm) was used for column chromatography. Analytical GF_{254} TLC plates (250 nm) were obtained from Merck. The spots were visualized under UV light or by spraying the plates with an EtOH sulphuric acid-vanillin solution and then heating to 120°C for few minutes. Optical activity was measured with a Perkin-Elmer 241 polarimeter. All solvents were purified and dried by standard techniques just before use. All reactions were routinely carried out under an inert atmosphere of dry, oxygen free, N_2 or argon.Yields are reported for chromatographically and spectroscopically pure isolated compounds. Actually, the high volatility of **1**, **2**, **3**, **14**, **16**, **19**, and **23** gave rise to considerable losses of these compounds during evaporation of their organic solutions, even under atmospheric pressure. Compounds were named following IUPAC rules as applied by AUTONOM, a PC software for systematic names in Organic Chemistry, Beilstein Institut and Springer Verlag.

2-Cyclopropyl-propan-2-ol 10. A solution of 1-cyclopropylethanone (13.5 mL, 134.6 mmol) in Et_2O (35 mL) was added to a solution of MeMgBr (3M in Et_2O, 50 mL, 150 mmol), at a rate suitable to maintain a gentle reflux of the solvent, to afford the expected alcoholate as a white precipitate; reflux was maintained for an additional 30 min. Stirring was continued overnight at room temperature; then the reaction was quenched by adding aqueous NH_4Cl until dissolution of the solid. Aqueous layer was exhaustively extracted with ether, then the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under atmospheric pressure to give pure compound **10** as a pale yellow oil (11.372 g, 83%). IR ν (cm^{-1}): 3410; 3010; 2980; 1465; 1360; 1230; 1200; 1155; 1050; 1020; 960; 910; 845; 820; 690. ^{1}H-NMR δ: 0.3 (m, 4H, CH_2-CH_2); 0.9 (m, 1H, *CH*); 1.12 (s, 6H, Me_2C).

5-Iodo-2-methyl-2-pentene 11. 57% HI (17 mL) was added to cyclopropyl alcohol **10** (4.48 g, 44.8 mmol) cooled to 0°C; the mixture was vigorously stirred for 20 min, diluted with hexane and extracted with the same solvent; the organic layer was washed with aqueous Na_2SO_3, 5% aqueous $NaHCO_3$ to neutrality, and brine. Drying (K_2SO_4) and evaporation of the solvent by distillation under atmospheric pressure gave compound **11** as an oil (7.43 g, 79%), pure enough to avoid further purification. IR ν (cm^{-1}): 2970; 2930; 2860; 1670; 1450; 1375; 1295; 1250; 1210; 1165; 830. ^{1}H-NMR δ: 1.61 and 1.71 (2s, 2x3H, Me_2C(2)); 2.58 (m, 2H, C(4)H_2); 3.12 (t, J=7, 2H, C(5)H_2); 5.1 (m, 1H, =C(3)*H*). EIMS *m/z* (% rel. int.): 210 (M^+, 16); 155 (13); 127 (20); 83 (67); 55 (100); 39 (80).

5-(4'-Methyl-3'-pentenyl)-2,3-dihydrofuran 13. A solution of *t*BuLi (1.5 M in pentane, 82 mL, 123 mmol) was added dropwise to a solution of 2,3-dihydrofuran (9.32 mL, 123 mmol) in dry THF (17.2 mL) at -50°C. The resulting pale yellow suspension was allowed to warm to 0°C and stirred for an additional 30 min. The mixture was recooled to -30°C and a solution of **11** (7.43 g, 35 mmol) in dry THF (17.2 mL) was added. The mixture was allowed to warm to 25°C and stirring was continued for 18 h. The resulting suspension was poured into a mixture of 28% aqueous NH_4OH (40 mL) and saturated aqueous NH_4Cl (370 mL) under vigorous stirring, and the organic layers were exhaustively extracted with Et_2O. The combined extracts were dried over Na_2CO_3 and evaporated to leave a yellow oil (quantitative yield), submitted to the next step without further purification. IR ν (cm^{-1}): 2970; 2930; 2860; 1665; 1600; 1450; 1370; 1170; 1160; 1000; 930; 720.

(3*Z*)-8-Methyl-4-(trimethylsilanylmethyl)-nona-3,7-dien-1-ol 9a. Me_3SiCH_2MgCl, prepared from Me_3SiCH_2Cl (24.4 mL, 176 mmol) and Mg (4.7 g, 193.6 mmol) in dry Et_2O (150 mL), was added to a stirred suspension of [1,3-*bis*(triphenylphosphine)propane]$NiCl_2$ (3.8 g, 7.04 mmol) in dry benzene (55 mL); the resulting red solution was stirred at 25°C for 20 min until turned dark. Et_2O was removed under reduced pressure and dry benzene (70 mL) was added, followed by a solution of **13** (5.36 g, 35.2 mmol) in dry benzene (11.4 mL). The mixture was heated under reflux for 18 h, cooled to 0 °C, and poured into saturated aqueous NH_4Cl (500 mL) under vigorous stirring and air bubbling. The mixture was stirred until decolorized and exhaustively extracted with Et_2O. Drying ($MgSO_4$) and evaporation of the combined extracts left a residue that was purified by column chromatography (AcOEt-hexane, 1:50 to 1:2) to afford (3*Z*)-**9a** (5.61 g, 66% from **11**) in a mixture with 10% (3*E*)- diastereomer that was impossible to separate by preparative column chromatography. IR ν (cm^{-1}): 3335; 2960; 2930; 1375; 1105; 1045; 855; 665. ^{1}H-NMR ((3*Z*)-diastereomer) δ : 0.02 (s, 9H, Me_3Si); 1.435 (bs, 1H, O*H*); 1.58 (s, 2H, CH_2-$SiMe_3$); 1.61 and 1.69 (2s, 2x3H, C(8)Me_2); 1.98 (m, 2H, C(5)H_2); 2.095 (bt, J=7.0, 2H, C(6)H_2); 2.22 (q, J=6.7, 2H, C(2)H_2); 3.6 (t, J=6.5, 2H, C(1)H_2OH); 4.97 (bt, J=7.2, 1H, C(3)*H*); 5.07 (tsept, J's=7.0 and 1.4, 1H, C(7)*H*). ^{13}C-NMR ((3*Z*)-diastereomer) δ: -0.83 (3x3, SiMe_3); 17.57 (3, C(8)*Me*); 21.28 (2, CH_2Si); 25.59 (3, C(8)*Me*); 26.67 (2, *C*(6)); 31.77 (2, *C*(2)); 39.12 (2, *C*(5)); 62.39 (2, *C*(1)); 116.58 (1, *C*(3)); 124.14 (1, *C*(7)); 131.61 (0, *C*(8)); 140.80 (0, *C*(4)). EIMS *m/z* (% rel. int.): 240 (M^+, 2); 223 (5); 149 (65); 135 (16); 121 (17); 107 (86); 95 (100); 81 (48); 73 (55).

(3*Z*)-8-Methyl-1-*O*-(trimethylacetyl)-4-(trimethylsilanylmethyl)-nona-3,7-dien-1-ol 14. Et_3N (19.5 mL, 140.4 mmol), followed by pivaloyl chloride (7.2 mL, 58.5 mmol), was added to **9a** (5.61 g, 23.4 mmol) in dry CH_2Cl_2 (117 mL). The mixture was stirred at 25°C for 3 h, then quenched by the sequential addition of MeOH and 5% aqueous $NaHCO_3$ after 15 min. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (AcOEt-hexane, 5:95) gave **14** (5.69 g, 75%). IR ν (cm^{-1}): 2960; 1735; 1660; 1640; 1480; 1375; 1155; 1065; 1030; 850; 700. ^{1}H-NMR ((3*Z*)-diastereomer) δ: 0.02 (s, 9H, Me_3Si); 1.2 (s, 9H, Me_3CO); 1.55 (s, 2H, CH_2-$SiMe_3$); 1.60 and 1.70 (2s, 2x3H, C(8)Me_2); 1.95 (m, 2H, C(5)H_2); 2.07 (bt, J=7.0, 2H, C(6)H_2); 2.26 (q, J=6.7, 2H, C(2)H_2); 4.03 (t, J=6.5, 2H, C(1)H_2OR); 5.0 (bt, J=7.2, 1H, C(3)*H*); 5.1 (tsept, J's=7.0 and 1.4, 1H, C(7)*H*). ^{13}C-NMR ((3*Z*)-diastereomer) δ: -0.80 (3x3, SiMe_3); 17.56 (3, C(8)*Me*); 21.44 (2, CH_2Si); 25.57 (3, C(8)*Me*); 26.81 (2, *C*(6)); 27.09 (3x3, Me_3CCO); 27.84 (2, *C*(2)); 38.61 (0, CMe_3); 39.05 (2, *C*(5)); 64.07 (2, *C*(1)); 116.15 (1, *C*(3)); 124.13 (1, *C*(7)); 131.35 (0, *C*(8)); 139.61 (0, *C*(4)); 178.52 (0, *C*=O). EIMS *m/z* (% rel. int.): 324 (M^+, 6); 222(18); 179 (38); 107 (12); 73 (100); 57 (20); 41 (17).

(3*Z*)-(7*S*)-8-Methyl-1-*O*-(trimethylacetyl)-4-(trimethylsilanylmethyl)-non-3-en-1,7,8-triol 15. AD-mix-α (31.75 g) was added to a stirred 1:1 mixture of *t*BuOH-H_2O (240 mL), and stirring was continued at 25°C until two bright yellow phases were obtained. $MeSO_2NH_2$ (1.8 g, 18.9 mmol) was added, followed by **14**, (6.14 g, 18.9 mmol) at 0°C. The heterogeneous mixture was stirred vigorously at 0°C for 8 h, then quenched with solid Na_2SO_3 (35 g); stirring was continued for 30 min, until decoloration, allowing the mixture to warm to room temperature. AcOEt was added, and after separation of the layers the aqueous phase was further extracted with the same organic solvent. The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (hexane-AcOEt 1:2) to afford (3*Z*)-**15** in a mixture with ca. 10% (3*E*)-diastereomer, as a colorless oil (4.48 g, 66%), and recovered starting compound **14** (0.214 g). $[\alpha]_D^{20}$ = -7.5 (c=2.87, CH_2Cl_2). IR ν (cm^{-1}): 3440; 2960; 1730; 1660; 1640; 1480; 1365; 1285; 1250; 1160; 1075; 940; 850; 770. ^{1}H-NMR ((3*Z*)-diastereomer) δ: 0.03 (s, 9H, Me_3Si); 1.19 (s, 9H, Me_3CCO); 1.16 and 1.20 (2s, 2x3H, C(8)Me_2); 1.35-1.50 and 1.50-1.65 (2m, 4H, C(6)H_2 and CH_2-$SiMe_3$); 1.90-2.10 and 2.16-2.32 (2m, 4H, C(5)H_2 and C(2)H_2); 3.36 (dd, J's=10.5 and 2, 1H, C(7)*H*OH); 4.02 (bt, J=6.5, 2H, C(1)H_2OR); 5.03 (t, J=7.1, 1H, C(3)*H*). ^{13}C-NMR ((3*Z*)-diastereomer) δ: -0.81 (3x3, SiMe_3);

21.35 (2, CH_2Si); 23.16 and 26.36 (3 and 3, C(8)Me_2); 27.09 (3x3, Me_3CCO); 27.90 (2, C(2)); 29.86 (2, C(6)); 36.10 (2, C(5)); 38.63 (0, CMe_3); 64.03 (2, C(1)); 72.90 (0, C(8)); 78.12 (1, C(7)); 116.94 (1, C(3)); 139.66 (0, C(4)); 178.57 (0, C=O). EIMS *m/z* (% rel. int.): 256 (10); 195 (8); 154 (90); 144 (16); 107 (16); 95 (18); 79 (18); 73 (100); 67 (18); 57 (38); 41 (17); CIMS (methane) *m/z* (% rel. int.): 359 ($M+H^+$, 5); 149 (100).

(3*Z*)-(7*R*)-7,8-Epoxy-8-methyl-1-*O*-(trimethylacetyl)-4-(trimethylsilanylmethyl)-non-3-en-1-ol 16. Pyridine (3 mL, 37.5 mmol) and freshly distilled MsCl (1.26 mL, 16.25 mmol) were sequentially added to **15** (4.48 g, 12.5 mmol) in dry CH_2Cl_2 (28.5 mL) at -30°C. The mixture was stirred for 6 h and allowed to gradually warm to room temperature to complete the reaction, then recooled to 0°C, diluted with MeOH (90 mL) and treated with solid K_2CO_3. Stirring was continued for an additional 45 min, then the reaction was quenched with brine and the mixture extracted with hexane. The organic layer was sequentially washed with aqueous $CuSO_4$ and brine, dried ($MgSO_4$), and evaporated under atmospheric pressure. The residue was purified by column chromatograpy on silica gel (hexane-AcOEt, 99:1 to 7:3) to afford (3*Z*)-**16** in a mixture with ca. 10% (3*E*) diastereomer as a colorless oil (3.46 g, 82%). $[\alpha]_D^{20}$ = -0.73 (c=2.04, CH_2Cl_2). IR ν (cm^{-1}): 2960; 1730; 1480; 1380; 1285; 1250; 1160; 1030; 850; 770; 700. ^{1}H-NMR ((3*Z*)-diastereomer) δ: 0.03 (s, 9H, Me_3Si); 1.18 (s, 9H, Me_3CCO); 1.25 and 1.30 (2s, 2x3H, C(8)Me_2); 1.543 (s, 2H, CH_2-$SiMe_3$); 1.582-1.673 (m, 2H, C(6)H_2); 1.983-2.175 (m, 2H, C(5)H_2); 2.263 (q, J=6.9, 2H, C(2)H_2); 2.70 (t, J=6.1, 1H, C(7)*H*); 4.01 (t, J=6.9, 2H, C(1)H_2OR); 5.03 (bt, J=7.1, 1H, C(3)*H*). ^{13}C-NMR ((3*Z*)-diastereomer) δ: -0.84 (3x3, $SiMe_3$); 18.60 and 24.74 (3 and 3, C(8)Me_2); 21.48 (2, CH_2Si); 27.05 (3x3, Me_3CCO); 27.57 (2, C(6)); 27.85 (2, C(2)); 35.61 (2, C(5)); 38.57 (0, CMe_3); 58.18 (0, C(8)); 63.92 (2, C(1)); 64.07 (1, C(7)); 116.71 (1, C(3)); 138.83 (0, C(4)); 178.42 (0, C=O). EIMS *m/z* (% rel. int.): 133 (12); 105 (13); 73 (100); 67 (10); 57 (30); 41 (19). CIMS (methane) *m/z* (% rel. int.): 341 ($M+H^+$).

(1'*S*, 3'*R*)-2-(3'-Hydroxy-2',2'-dimethyl-6'-methylene-cyclohexyl)-ethyl trimethylacetate 17 and (1'*R*, 3'*R*)-2-(3'-Hydroxy-2',2'-dimethyl-6'-methylene-cyclohexyl)-ethyl trimethylacetate 18. BF_3Et_2O (5.15 mL, 40.8 mmol) was added dropwise to a solution of **16** (3.46 g, 10.2 mmol) in dry CH_2Cl_2 (70 mL) at -78°C. The solution was stirred at -78°C for 1 h, then quenched with 5% aqueous $NaHCO_3$, and allowed to warm to 25°C (~30 min). The mixture was extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (hexane-AcOEt, 99:1 to 1:1) to afford **17** (1.755 g, 64%), **18** (0.174 g, 6.4%), and a mixture of **17** and **18** (0.336 g, 12%). Data for **17**: $[\alpha]_D^{20}$ = + 19.5 (c=2.05, CH_2Cl_2). IR ν (cm^{-1}): 3500; 3080; 2970; 2875; 1730; 1645; 1480; 1290; 1035; 890; 770; 735. ^{1}H-NMR δ: 0.76 and 1.02 (2s, 2x3H, C(2')Me_2); 1.19 (s, 9H, Me_3CCO); 1.47-1.60, 1.77-1.92, 1.96-2.07, 2.32-2.41 (4m, 2H, 4H, 1H, and 1H respectively, C(2)H_2, C(1')*H*, C(4')H_2-C(5')H_2, C(3')HO*H*); 3.45 (dd, J's=4.2 and 9.4, 1H, C(3')*H*OH); 3.88 and 4.15 (2m, 2x1H, C(2)H_2OR); 4.65 and 4.89 (2bs, 2x1H, C=CH_2). ^{13}C-NMR δ: 16.13 and 25.94 (3 and 3, C(2')Me_2); 24.90 (2, C(4')); 27.11 (3x3, Me_3CCO); 31.78 and 31.95 (2 and 2, C(5') and C(2)); 38.59 (0, CMe_3); 39.98 (0, C(2')); 48.03 (1, C(1')); 63.64 (2, C(1)); 76.80 (1, C(3')); 108.90 (2, C(6')=CH_2); 146.52 (0, C(6')); 178.48 (0, C=O). EIMS *m/z* (% rel. int.): 166 (28); 148 (85); 133 (100); 122 (44); 95 (33); 81 (23); 71 (30); 57 (80); 41 (45).CIMS (methane) *m/z* (% rel. int.): 269 ($M+H^+$). Data for **18**: $[\alpha]_D^{20}$ = - 5.06 (c=2.29, CH_2Cl_2). ^{1}H-NMR δ: 0.92 and 1.00 (2s, 2x3H, C(2')Me_2); 1.20 (s, 9H, Me_3CCO); 1.40-1.73, 1.77-1.90, 2.07, 2.30 (4m, 3H, 2H, 1H, 2H respectively, C(2)H_2, C(1')*H*, C(4')H_2-C(5')H_2, C(3')HO*H*); 3.45 (dd, J's=4.5 and 10, 1H, C(3')*H*OH); 3.86 and 4.06 (2m, 2x1H, C(2)H_2OR); 4.63 and 4.82 (2bs, 2x1H, C=CH_2). ^{13}C-NMR δ: 14.00 and 21.32 (3 and 3, C(2')Me_2); 24.07 (2, C(4')); 27.08 (3x3, Me_3CCO); 29.71 and 31.17 (2 and 2, C(5') and C(2)); 38.57 (0, CMe_3); 38.61 (0, C(2')); 50.06 (1, C(1')); 63.23 (2, C(1)); 73.61 (1, C(3')); 110.91 (2, C(6')=CH_2); 146.40 (0, C(6')); 178.48 (0, C=O).

Determination of the enantiomeric excess of alcohols 17 and 18. General procedure.[17] DMF (0.3 mmol), followed by oxalyl chloride (1.5 mmol), was added dropwise at room temperature under argon to a stirred solution of MTPA acid (0.05M in dry hexane, 0.3 mmol) and stirring was continued for 1 h. A white precipitate was filtered off, washed with dry hexane and the solution was evaporated to afford the corresponding Mosher acyl chloride, (*S*)-(+)-MTPA-Cl from (*R*)-(+)-MTPA acid, and (*R*)-(-)-MTPA-Cl from (*S*)-(-)-MTPA acid, respectively. Et_3N (0.3 mmol) was added to two separate solutions of alcohol **17** or **18** (0.05M in dry CH_2Cl_2, 0.1 mmol) under argon, followed by DMAP (catalytic amount) and freshly prepared (+)- or (-)- MTPA-Cl, (0.05M in CH_2Cl_2 0.3 mmol). Stirring was continued for 1 h, then the mixture was evaporated and the residue filtered through a silica gel pad to afford the desired diastereomer MTPA ester. An e.e.=92% was established for both alcohols by integration of the ^{1}H-NMR signals at δ 3.537 and 3.562 (2xq, O*Me*) for **17**, and at δ 0.845 and 0.900, 0.918 and 0.937 (2x2s, C*Me*$_2$) for **18**, respectively.

2-(2',2'-Dimethyl-6'-methylene-cyclohexyl)-ethanol; (a) (1'*R*)-Isomer (-)-19. Dry pyridine (250 μL, 2.98 mmol), followed by phenoxythiocarbonylchloride (200 μL, 1.43 mmol), was added to a solution of **17** (0.200 g, 0.746 mmol) in dry CH_2Cl_2 (6 mL). The mixture was stirred at 25°C for 4 h, then quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with aqueous $CuSO_4$, dried ($MgSO_4$) and evaporated to afford a residue which was redissolved in dry THF (6 mL) without purification. To this solution was added AIBN (0.001g, 0.006 mmol) in dry THF (0.5 mL), followed by *n*Bu_3SnH (400 μL, 1.47 mmol). After the solution had refluxed for 5 h, it was cooled to 0°C and excess $LiEt_3BH$ (1M in THF, 4 mL, 4 mmol) was added to carry out one pot cleavage of the primary pivaloyloxy group. After stirring under reflux for 2 h, the reaction mixture was recooled to room temperature, quenched with aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated under atmospheric pressure to afford a residue which was purified by column chromatography (hexane to hexane-AcOEt, 9:1) to give (-)-**19**[9] as a colorless oil (0.094 g, 75% from **17**). $[\alpha]_D^{20}$ = -24.4 (c=2, CH_2Cl_2). IR ν (cm^{-1}): 3340; 3070; 2935; 2870; 1645; 1450; 1385; 1365; 1050; 1030; 890; 750; 690; 630. ^{1}H-NMR δ: 0.85 and 0.92 (2s, 2x3H, C(2')*Me*$_2$); 1.15-1.80 (m, 7H, C(2)*H*$_2$, C(3')*H*$_2$, C(4')*H*$_2$, and O*H*); 1.90 (bdd, J's=7.5 and 4.0, C(1')*H*); 2.05 (m, 2H, C(5')*H*$_2$); 3.6 (m, 2H, C(1)*H*$_2$); 4.64 (bd, J=2.5, 1H, C=C*H*H); 4.78 (m, J=1.3, 1H, C=CH*H*). EIMS *m/z* (% rel. int.): 168 (M^+, 10); 167 (57); 149 (33); 123 (100); 107 (90); 93 (82); 81 (82); 69 (96); 55 (63); 41 (97). CIMS (methane) *m/z* (% rel. int.): 169 (M^++1, 36); 151 (53); 135 (9); 125 (100); 113 (21).

(b) (1'*S*)-Isomer (+)-19. In the same manner as described above, **18** (0.100 g, 0.373 mmol) gave (+)-**19** (0.035 g, 55%). $[\alpha]_D^{20}$ = +24.0 (c=0.025, CH_2Cl_2). Its IR and NMR spectra were identical with those of (-)-**19**.

(2',2'-Dimethyl-6'-methylene-cyclohexyl)-acetaldehyde; (a) (1'*R*)-Isomer (-)-3. 4-Methylmorpholine-N-oxide (0,210 g, 1.79 mmol), tetrapropylammonium perruthenate(VII) (catalytic amount), and powdered activated 4Å molecular sieves (0.400 g) were added to a solution of compound (-)-**19** (0.094 g, 0.56 mmol) in dry CH_2Cl_2 (14 mL). The mixture was stirred at 25°C for 3 h, then diluted with CH_2Cl_2 and filtered through a silica gel and celite layer, to remove ruthenium salts. After distillation of solvent, the residue was purified by column chromatography on silica gel (hexane-AcOEt, 99:1) to afford (-)-**3** as a colorless oil (0,070 g, 75%). $[\alpha]_D^{20}$ = -32.8 (c=1.05, CH_2Cl_2). IR ν (cm^{-1}): 3075; 2955; 2935; 2870; 2715; 1730; 1645; 1450; 1385; 1365; 1245; 1045; 900. ^{1}H-NMR δ: 0.80 and 0.98 (2s, 2x3H, C*Me*$_2$); 1.15-2.05 (m, 9H, *aliphatic* C*H*$_2$ and C*H*); 4.52 (bs, 1H, C=C*H*H); 4.80 (bs, 1H, C=CH*H*);, 9.65 (t, J=2.5, 1H, C*H*O). EIMS *m/z* (% rel. int.): 150 (52); 135 (48); 123 (28); 107 (47); 95 (68); 81 (68); 69 (100); 55 (58); 41 (96). CIMS (isobutane) *m/z* (% rel. int.): 183 (50); 167 (M^++1, 55); 149 (65); 131 (81).

(b) (1'*S*)-Isomer (+)-3. In the same manner as described above, (+)-**19** (0.035 g, 0.21 mmol) gave (+)-**3** (0.025 g, 72%). $[\alpha]_D^{20}$ = +29.0 (c=0.35, CH_2Cl_2). Its IR and NMR spectra were identical with those of (-)-**3**.

(1*R*, 1'*R*)-2-(2',2'-Dimethyl-6'-methylene-cyclohexyl)-1-(3''-furyl)-ethanol 20 and (1*S*, 1'*R*)-2-(2',2'-dimethyl-6'-methylene-cyclohexyl)-1-(3''-furyl)-ethanol 21. To a solution of 3-bromofuran (50 μL, 0.60 mmol) in dry THF (0.8 mL) at -78°C was added *n*BuLi (1.6M in hexane, 370 μL, 0.60 mmol). After 15 min aldehyde (-)-**3** (0.037 g, 0.23 mmol) in dry THF (2 mL) was added and the mixture was stirred at -78°C for 15 min. The reaction was quenched by adding saturated aqueous NH_4Cl (4 mL) and the mixture was allowed to warm to room temperature. The mixture was extracted with Et_2O and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated by distillation under atmospheric pressure. The residue was purified by column chromatography (hexane-AcOEt, 98:2) to give a mixture of diastereomers **20** and **21** (0.036 g, 70% overall yield). IR ν (cm^{-1}): 3500; 2900; 1450; 1380; 1100; 875. ^{1}H-NMR δ: 0.85 and 0.95 (2bs, 2x3H, C (2')*Me*$_2$); 1.20-1.80 (m, 6H, 3x*CH*$_2$); 1.90 (bs, 1H, O*H*); 2.00-2.40 (m, 3H, *allylic H*); 4.50 (m, 1H, C(1)*H*); 4.65 and 4.80 (2bs, 2x1H, C=C*H*$_2$); 6.30 (bs, 1H, C(4")*H*); 7.28 (bs, 2H, C(2")*H* and C(5")*H*).

(1'*R*)-2-(2',2'-Dimethyl-6'-methylene-cyclohexyl)-1-(3''-furyl)-ethanone (*R*)-1. 4-Methylmorpholine-N-oxide (0.100 g, 0.852 mmol), tetrapropylammonium perruthenate(VII) (catalytic amount), and powdered activated 4Å molecular sieves (0.090 g) were added to a solution of compounds **20** and **21** (0.030 g, 0.128 mmol) in dry CH_2Cl_2 (3 mL). The mixture was stirred at 25°C for 2 h, then diluted with CH_2Cl_2 and filtered through a silica gel and celite pad to remove ruthenium salts. After distillation of solvent, the residue was purified by column chromatography on silica gel (hexane to hexane-AcOEt, 99:1) to afford (*R*)-**1** (0,021 g, 70%). $[\alpha]_D^{20}$ = -31.78 (c=0.57, CH_2Cl_2). IR ν (cm^{-1}): 2950; 1683; 1560; 1510; 1209; 1152; 868. ^{1}H-NMR δ: 0.88 and 0.98 (2s, 2x3H, C(2')*Me*$_2$); 1.20-1.90 (m, 4H, -*CH*$_2$-*CH*$_2$-); 2.07 and 2.20 (2m, 2x1H, C(5')*H*); 2.66 (dd, J's=9.5 and 4.15, 1H, C(1')*H*); 2.80 (dd, J's=15.9 and 4.4, 1H, C(2)*H*H); 2.92 (dd, J's=15.9 and 9.5, 1H, C(2)H*H*); 4.44 and 4.71 (2bs, 2H, C=C*H*$_2$); 6.77 (dd, J's=1.95 and 0.74, 1H, C(4")*H*); 7.43 (dd, J's=1.95 and 1.47, 1H, C(5")*H*); 8.06 (dd, J's=1.47 and 0.98, 1H, C(2")*H*). ^{13}C-NMR δ: 23.42 and 28.75 (3 and 3, C(2')*Me*$_2$); 23.60 (2, *C*(4')); 34.195 (2, *C*(3')); 34.85 (0, *C*(2')); 38.40 and 38.59 (2 and 2, *C*(5') and *C*(2)); 48.47 (1, *C*(1')); 108.28 (2, *C*H$_2$=C); 108.60 (1, *C*(4")); 127.90 (0, *C*(3")); 143.90 (1, *C*(5")); 146.56 (1, *C*(2")); 148.66 (0, *C*(6')); 194.39 (0, *C*=O). EIMS *m/z* (% rel. int.): 232 (M^+, 14); 217 (6); 189 (4); 176 (4); 163 (3); 137 (5); 123 (10); 122 (27); 107 (25); 95 (100); 81 (13); 69 (16); 67 (10).

(1"*R*)-(1'*E*)-3-[2'-(2",2"-Dimethyl-6"-methylene-cyclohexyl)-ethylidene]-dihydrofuran-2-one 23. A solution of aldehyde (-)-**3** (0.048 g, 0.289 mmol) and α-(triphenylphosphoranylidene)-γ-butyrolactone[19] **22** (0.134 g, 0.387 mmol) in dry THF (8 mL) was stirred at 50°C for 24 h, then the mixture was diluted with CH_2Cl_2 and filtered to remove insoluble excess ylide and triphenylphosphine oxide. The organic layer was evaporated and the residue was purified by column chromatography on silica gel (hexane-AcOEt, 95:5) to afford **23**[9] as a colorless oil (0.060 g, 90%). $[\alpha]_D^{20}$ = -20.1 (c=0.7, CH_2Cl_2). IR ν (cm^{-1}): 3070; 2960; 2925; 2865; 1763; 1680; 1645; 1465; 1378; 1365; 1220; 1180; 1030; 1010; 890. ^{1}H-NMR δ: 0.87 and 0.99 (2s, 2x3H, C(2")*Me*$_2$); 1.2-1.6 (m, 4H, C(3")*H*$_2$ and C(4")*H*$_2$); 1.9-2.45 (m, 5H, C(2')*H*$_2$, C(1")*H*, and C(5")*H*$_2$); 2.85 (m, 2H, C(4)*H*$_2$); 4.37 (t, J=7.5, 2H, C(5)*H*$_2$); 4.51 (bs, 1H, C=C*H*H); 4.78 (bs, 1H, C=CH*H*); 6.69 (m, 1H, C(1')*H*). ^{13}C-NMR δ: 15.15 and 24.76 (3 and 3, C(2")*Me*$_2$); 23.42 (2); 25.08 (2); 27.68 (2); 33.25 (2); 37.23 (2); 34.94 (0, *C*(2")); 52.98 (1, *C*(1")); 65.15 (2, *C*(5)); 109.54 (2, C=*C*H$_2$); 124.61 (0, *C*(3)); 141.27 (1, *C*(1')); 147.89 (0, *C*(6")); 171.11 (0, *C*=O). EIMS *m/z* (% rel. int.): 234 (M^+,18); 219 (16); 148 (22); 133 (19); 123 (100); 112 (57); 105 (17); 91 (28); 81 (82); 69 (37); 55 (33); 41 (62).

(1"*R*)-(1'*E*)-2-[2'-(2",2"-Dimethyl-6"-methylene-cyclohexyl)-ethylidene]-butane-1,4-diol 24. To a solution of **23** (0.059 g, 0.25 mmol) in dry THF (5 mL) cooled to -10°C was added DIBAL-H (1M in THF, 1.350 mL, 1.35 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h, then it was recooled to 0°C, quenched with 1.2N HCl and diluted with CH_2Cl_2; after extraction of aqueous layer with CH_2Cl_2, the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue

was purified by column chromatography (hexane-AcOEt, 1:1) to afford pure **24** as a colorless oil (0.043 g, 72%). $[\alpha]_D^{20}$ = -15.16 (c=0.6, CH_2Cl_2). IR ν (cm^{-1}): 3327; 3082; 2934; 2869; 1643; 1437; 1384; 1363; 1042; 886; 738. ^{1}H-NMR δ: 0.83 and 0.95 (2s, 2x3H, C(2")*Me*$_2$); 1.40-1.60 (2m, 2x2H, C(3")*H*$_2$ and C(4")*H*$_2$); 1.79 (dd, J's=4.0 and 11, 1H, C(1")*H*), 1.95-2.18 (m, 3H, C(2')H*H* and C(5")*H*$_2$), 2.27 (ddd, J's=4.0, 7.0, and 15.0, 1H, C(2')*H*H); 2.43 (dt, J's=4 and 5.9, 2H C(3)*H*$_2$); 2.80 (bs, 2H, 2 O*H*); 3.72 (t, J=5.9, 2H, C(4)*H*$_2$OH); 4.01 (d, J=1.0, 2H, C(1)*H*$_2$OH); 4.51 and 4.78 (2bs, 2x1H, C=C*H*$_2$); 5.45 (t, J=7.0, 1H, C(1')*H*). ^{13}C-NMR δ: 25.01 and 28.54 (3 and 3, C(2")*Me*$_2$); 23.54 and 24.55 (2 and 2, *C*(3") and *C*(4")); 32.57, 33.29, and 37.13 (2, 2, and 2, *C*(3), *C*(2'), and *C*(5")); 34.97 (0, *C*(2")); 53.98 (1, *C*(1")); 61.50 (2, *C*(4)); 68.45 (2, *C*(1)); 109.05 (2, *C*H$_2$=C); 131.53 (1, *C*(1')); 135.53 (0, *C*(6")); 148.78 (0, *C*(2)). EIMS *m/z* (% rel. int.): 238 (M^+); 220 (11); 205 (15); 189 (37); 175 (8); 161 (6); 149 (11); 133 (12); 123 (56); 109 (35); 95 (29); 81 (100); 67 (45); 55 (42); 41 (67).

(1"*R*)-(1'*E*)-2-[2'-(2",2"-Dimethyl-6"-methylene-cyclohexyl)-ethylidene]-succinaldehyde (*R*)-2. To a solution of oxalyl chloride (30 μL, 0.315 mmol) in dry CH_2Cl_2 (0.7 mL) cooled to -60°C, DMSO (45 μL, 0.630 mmol) in dry CH_2Cl_2 (0.3 mL) was added dropwise under stirring. After 5 min, a solution of **24** (0.025 g, 0.105 mmol) in dry CH_2Cl_2 (0.4 mL) was added dropwise over 5 min and the mixture was stirred at -60°C for 30 min; then Et_3N was added (145 μL, 3.51 mmol) and the mixture was allowed to warm to room temperature. The reaction was quenched by adding water and the mixture was extracted with CH_2Cl_2. The organic layer was washed with 1.2N HCl, 5% aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (hexane-AcOEt, 7:3) to afford pure compound (*R*)-**2** as a colorless oil (0.016 g, 65%). $[\alpha]_D^{20}$ = -15.83 (c=0.6, CH_2Cl_2). IR ν (cm^{-1}): 3070; 2932; 2870; 2720; 1727; 1684; 1642; 1450; 1384; 1364; 1160; 892. ^{1}H-NMR δ: 0.88 and 0.98 (2s, 2x3H, C(2")*Me*$_2$); 1.22-1.37, 1.42-1.61, and 1.94-2.16 (3m, 7H, -C*H*$_2$- and *allylic H*); 2.37-2.47 (m, 2H, C(2')*H*$_2$); 3.41 (dd, J's=1.5 and 7.5, 2H, C(3)*H*$_2$); 4.55 and 4.85 (2bs, 2H, C=C*H*$_2$); 6.75 (t, J=7.0, 1H, C(1')*H*); 9.45 (s, 1H, C(1)*H*O); 9.64 (t, J=2.0, 1H, C(4)*H*O). ^{13}C-NMR δ: 24.88 and 28.36 (3 and 3, C(2")*Me*$_2$); 23.33 and 26.65 (2 and 2, *C*(3") and *C*(4")); 33.11 and 36.99 (2 and 2, *C*(2') and *C*(5")); 39.17 (2, *C*(3)); 53.25 (1, *C*(1")); 35.03 (0, *C*(2")); 109.86 (2, *C*H$_2$=C); 134.83 (0, *C*(6")); 147.86 (0, *C*(2)); 158.50 (1, *C*(1')); 193.51 and 197.28 (1 and 1, *C*H=O). EIMS *m/z* (% rel. int.): 234 (M^+, 4); 219 (6); 190 (11); 175 (8); 159 (5); 149 (17); 133 (12); 123 (56); 109 (33); 95 (41); 81 (100); 69 (89); 57 (81); 41 (99).

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