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Total Synthesis of Both Enantiomers of Copalol via Optical Resolution of a General Synthetic Intermediate for Drimane Sesquiterpenes and Labdane Diterpenes

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Abstract—The total synthesis of both enantiomers of copalol (**6**) was accomplished via the optical resolution of a racemic diol [(±)-**4**] which is a general synthetic intermediate for drimane sesquiterpenes and labdane diterpenes. Esterification between (±)-**4** and Boc-L-proline gave the diastereomeric pair of monoesters (**5a** and **5b**) which could be readily separated by flash column chromatography. PDC-oxidation of the resolved **5a** and **5b**, and subsequent β-elimination gave optically active enones (**9** and ***ent*-9**). Both enones were respectively converted into (+)-**6** in 36% yield and (−)-**6** in 26% yield in five steps: (1) Sakurai reaction ($TiCl_4$-promoted conjugate addition of allylsilane), (2) Wittig methylenation, (3) Wacker oxidation, (4) Horner–Emmons reaction, and (5) DIBAL-H reduction.

Introduction

Labdane and biosynthetically related polycyclic diterpenes are a major group of diterpenes.[1] Recent progress on cloning of terpene cyclase (synthase) allows us to study the detailed stereochemical course of enzymatic cyclizations.[2] Although labda-8(17),13-dien-15-yl diphosphate [(+)-**2**] and its enantiomer [also known as copalyl diphosphate (CDP), (−)-**2**] are general biosynthetic intermediates of such diterpenoids,[3] no practical synthesis for both enantiomers of the corresponding alcohol, copalol [(+)-**6**, (−)-**6**], has been reported.[4] In the incorporation study, both (+)-**6** and (−)-**6** are conventionally prepared from structurally related natural products which originated from different natural sources.[5] Purifying the required natural product as the starting material is a serious disadvantage in the preparation of copalol. In order to study the stereochemical course of the polycyclic diterpene cyclization, we required both (+)-**6** and (−)-**6**. This requirement prompted us to develop a practical synthetic method for both (+)-**6** and (−)-**6** (Scheme 1).

An achiral substrate, geranylgeranyl diphosphate (GGDP, **1**) is enzymatically cyclized into one of the chiral intermediates, (+)-**2** or (−)-**2** in the biosynthesis of diterpenes. On the other hand, the application of optical resolution is favorable for preparing both (+)-**6** and (−)-**6** from the viewpoint of chemical synthesis. Therefore, a new synthetic route from racemic diol [(±)-**4**] to both (+)-**6** and (−)-**6** was designed via the optical resolution of appropriate diastereomeric hydroxyesters (**5A** and **5B**). β-Keto ester (±)-**3**, a precursor of (±)-**4**, which has been used for syntheses of drimane sesquiterpenes,[6] labdane diterpenes,[7] and others,[8] can be obtained as crystals via alkylation of methyl acetoacetate with geranyl bromide[7b] (or methoxycarbonylation of geranylacetone[8a]) and subsequent cyclization with $SnCl_4$.[7b] Several methods for optical resolution of (±)-**3** and its related compounds have been also reported: (1) via (*R*)-naphthylethylcarbamate derivatives of (±)-β-hydroxyester [C-2β-OH in (±)-**3**],[8a] (2) via (−)-α-phenylethylamine or (−)-ephedrine salts of (±)-albicanic acid [C-1-COOH, C-2-methylene in (±)-**3**],[6b] (3) via lipase-catalyzed transesterification of (±)-ketoalcohol [C-2-ketone in (±)-**4**],[6c] (4) via lipase-catalyzed transesterification of (±)-drimanediol,[6e] (5) via (2*R*,3*R*)-threitol acetal derivatives of (±)-**3**,[8c] and (6) via (2*R*,3*R*)-butanediol acetal derivatives of (±)-keto-alcohol.[8d] However, no separable diastereomeric pair of hydroxyesters **5A/5b** has been reported.

Results and Discussion

According to the condition reported by Nair et al.,[6c,6d] reduction of (±)-**3** with $LiAlH_4$ in THF gave (±)-**4** as a single diastereomer after recrystallization. In the ^1H NMR spectrum of (±)-**4**, the C-2 equatorial proton was observed δ 4.25 (1H, m, $W_{1/2}$=5.0 Hz).[8a] A commercially available Boc-L-proline, which is usually utilized in the field of peptide synthesis, was chosen as a chiral auxiliary. In

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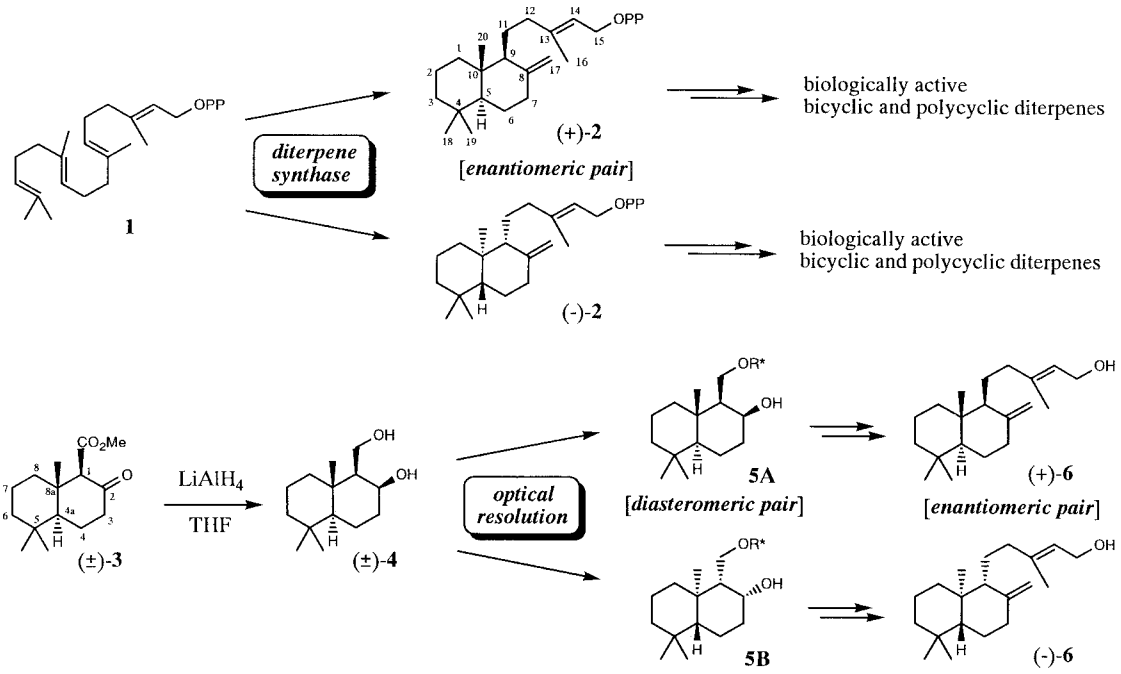
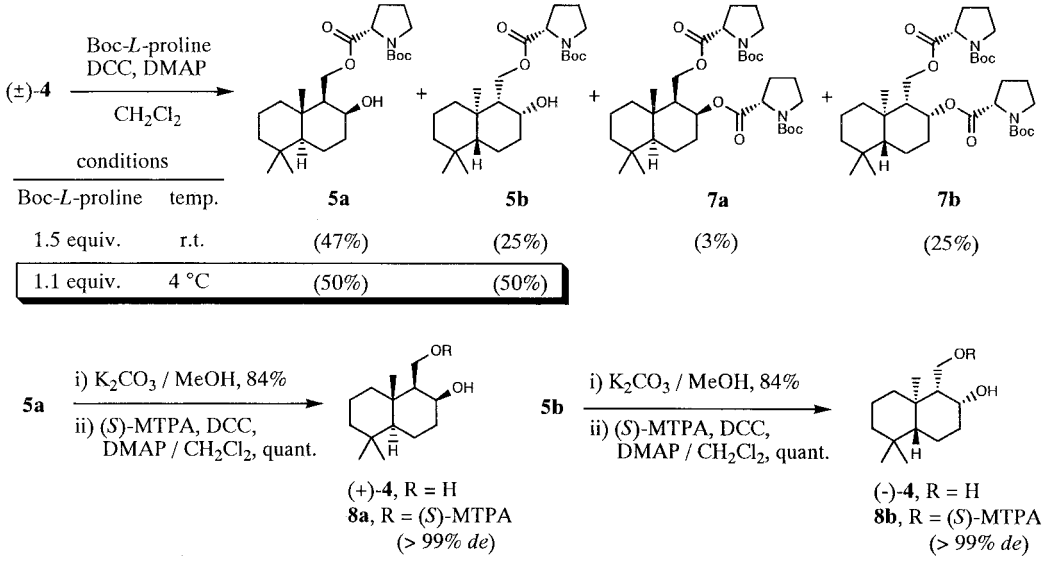


Scheme 1. Brief biosynthetic route of polycylic diterpenes and synthetic plan on both enantiomers of copalol.

order to examine the reactivity of esterification for (±)-**4**, 1.5 equiv. of Boc-L-proline was first used with DCC (1.5 equiv.) and DMAP (0.1 equiv.) in CH_2Cl_2 at room temperature. The spot of (±)-**4** entirely disappeared on silica gel TLC (*n*-hexane/EtOAc=2:1) after 2 h, and two separable spots (R_f=0.32, 0.39) newly appeared. Separation by silica gel PLC gave unbalanced yields of a minor product (**5b**, less polar, R_f=0.39) and a major product (**5a/7a/7b** mixture, more polar, R_f=0.32). By using another solvent-system (toluene/EtOAc=3:2), **5a/7a/7b** mixture could be separated to **5a** (R_f=0.35) and **7a/7b** (R_f=0.43) mixture by silica gel PLC. Diesters (**7a/7b**) could not be further separated. The absolute configurations of monoesters (**5a/5b**) and diesters (**7a/7b**) were confirmed after conversion to a diol (vide infra). While **5a** and **5b** could be entirely separated as a single spot on TLC, each of them looked like a ca. 1:1 mixture of isomers in the ^{1}H NMR spectrum. One pair of *t*-butyl signals (ca. 4.5H×2) and some signals corresponding to ca. 0.5H were clearly detected. In the ^{13}C NMR spectra of **5a** and **5b**, more than 24 ^{13}C signals which are not identical to that based on the molecular formula ($C_{24}H_{41}NO_4$) were observed. Three pairs of ca. 1:1 ^{13}C signals based on methyl in the *t*-butyl group, ester- and carbamate carbonyl and other duplication were clearly detected in each monoester. It seems that both **5a** and **5b** occur as a ca. 1:1 mixture of rotational isomers due to the steric hindrance of the *t*-butyl carbamate part. The mixture of **7a** and **7b** gave a more complex ^{1}H NMR spectrum.

Thus, **5a** and **5b** were respectively converted into diols



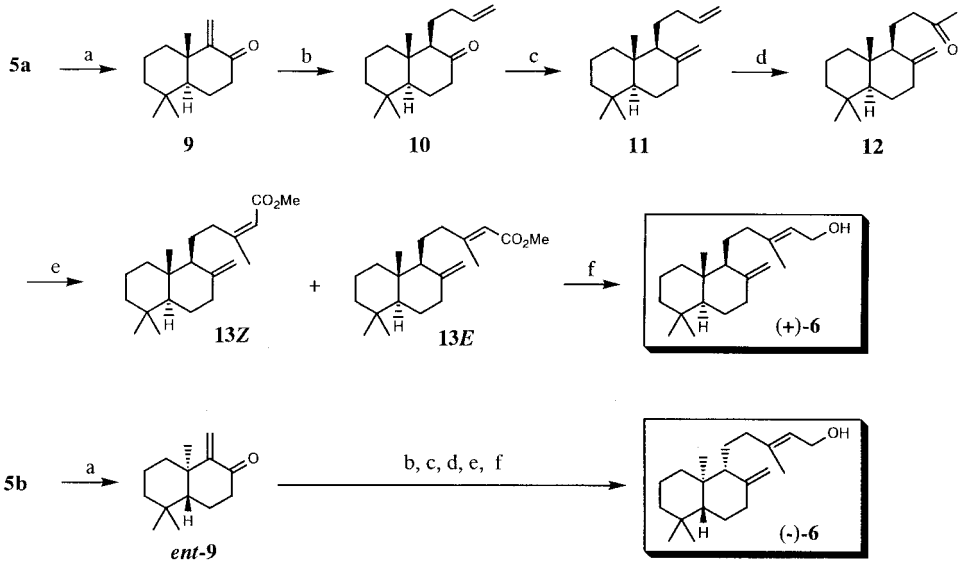
Scheme 2. Optical resolution of racemic diol and determination of optical purity.

(+)-**4** and (−)-**4** by methanolysis with potassium carbonate. Specific rotation of (+)-4; $[\alpha]_D^{23}=+25.5°$ (*c* 0.93, $CHCl_3$), was in good corresponding to that reported by Mori and Komatsu.[8a] Specific rotation of (−)-**4**; $[\alpha]_D^{24}=-26.1°$ (*c* 0.94, $CHCl_3$), was the opposite sign to that of (+)-**4**. Methanolysis of the mixture of **7a** and **7b** gave a diol, whose specific rotation exhibited a negative sign. Therefore, absolute configurations of monoesters (**5a/5b**) and diesters (**7a/7b**) were determined as shown in Scheme 2. Optical purity of the diol was determined as the corresponding (*S*)-MTPA ester. Both (+)-**4** and (−)-**4** without recrystallization were respectively treated with (*S*)-MTPA, DCC, and DMAP in CH_2Cl_2 at room temperature to give quantitatively **8a** and **8b**. Although both spots of **8a** and **8b** exhibited the same R_f value on TLC, both ^{1}H NMR spectra were obviously distinguishable from each other. While the unequivalent acyloxymethylene protons of **8a** were observed at δ 4.52 (1H, t, J=10.6 Hz) and 4.56 (1H, dd, J=10.6, 5.3 Hz), those of **8b** were observed at δ 4.45 (1H, dd, J=10.6, 4.0 Hz) and 4.64 (1H, t, J=10.6 Hz). In the identification limit of the ^{1}H NMR (270 MHz) spectrum, both **8a** and **8b** were regarded as pure diastereomers (>99% *de*). Therefore, enantiomeric purity of both (+)-**4** and (−)-**4** is >99% *ee*, and diastereomeric purity of both **5a** and **5b** is >99% de. The diol obtained from the mixture **7a** and **7b** was determined as ca. 80% *ee* of (−)-**4** from the corresponding (*S*)-MTPA ester mixture. The proportion of **5a/5b/7a/7b** in this esterification was 47/25/3/25 (%). Both **5a** and **5b** tend to isomerize to the corresponding secondary acyl derivatives via 1,3-acyl migration when they are allowed to stand at least overnight in $CDCl_3$ at room temperature. This fact suggests that diester formation would occur after 1,3-acyl migration. Although it is an interesting phenomenon that the diester formation from **5b** kinetically predominates over that from **5a**, it lacks efficiency from a practical point of view.

In order to avoid the diester formation, (±)-**4** was next treated with 1.1 equiv. of Boc-L-proline, DCC (1.1 equiv.) and DMAP (0.1 equiv.) in CH_2Cl_2 at 4°C for 2 h with upscaling of the reaction. Monoesters (**5a/5b**), judged from the TLC-analysis and ^{1}H NMR spectrum of its crude mixture, were obtained without the diester formation. The mixture could be entirely separated by silica gel flash chromatography (*n*-hexane/EtOAc=3:1) to give **5a** and **5b** in almost quantitative yields. In this way, optical resolution of (±)-**4** via hydroxyester derivatives has been first accomplished.

In order to synthesize copalol (**6**), introduction of the prenol part (C-12–C-16: labdane-numbering) at the C-11 position and methylene at the C-8 position is required. While no alkylation is known to proceed at the C-11 position, Michael addition for enone (acceptor) such as **9** is known to stereoselectively proceed by using some donors, namely, methyl acetoacetate,[7b,8e] diethyl malonate,[7b] aryl Grignard reagent,[8a] nitromethane,[6d] and sodium cyanide[8d] under basic conditions. Thus, **5a** was oxidized with PDC in the presence of molecular sieves (MS) 4 Å in CH_2Cl_2 to give a keto ester which was not isolated as such and applied to alumina-mediated β-elimination. This procedure for β-elimination has been reported for the corresponding keto acetate.[9] The reaction mixture was adsorbed on dry alumina column, kept to stand for 1 h, and then eluted with Et_2O to give an almost pure enone **9**[8a] in 87% yield. The efficiency from a practical point of view was increased because removal of the chiral auxiliary with functionalization was accomplished through PDC-oxidation and subsequent β-elimination in an easy manner such as work-up.

Two prenol synthon (C_5-unit); 4-*tert*-butyldiphenylsilyloxy-2-methyl-3-trimethylsilyl-1-butene[10] and (*E*)-1-*p*-toluenesulfonyl-2-methyl-4-hydroxy-2-butene,[11] were synthesized as donors, and Michael addition for **9** was examined. The Sakurai reaction,[12] $TiCl_4$-promoted Michael addition of the former silyloxyallylsilane gave no desired product because the silyloxyallylsilane would be unstable under the reaction



Scheme 3. *Reagents and conditions:* (a) PDC, MA 4 Å/CH_2Cl_2, 4°C–rt, overnight, then adsorption on alumina for 1 h, **9** (87%), ***ent*-9** (84%); (b) $TiCl_4$, allyltrimethylsilane/CH_2Cl_2, −78°C, 30 min, **10** (62%), ***ent*-10** (54%); (c) Ph_3PCH_3Br, *n*-BuLi/toluene, as salt-free ylide/toluene-*t*-BuOH, rt, 3 h, **11** (80%), ***ent*-11** (80%); (d) $PdCl_2$, CuCl, O_2/DMF–H_2O, rt, overnight, **12** (88%), ***ent*-12** (89%); (e) $(EtO)_2P(O)CH_2CO_2Me$, NaH/THF, 4°C–rt, 24 h, **13*E*** (84%), ***ent*-13*E*** (78%); (f) DIBAL-H/Et_2O, 4 °C–rt, 2 h, (+)-**6** (97%), (−)-**6** (87%).

conditions (−78°C to 4°C). Decomposition of both **9** and the silyloxyallylsilane was confirmed from the ^{1}H NMR spectrum after work-up. On the other hand, Michael addition of the dianion of the latter hydroxysulfone gave the desired product, 17-nor-8-oxo-12-*p*-toluenesulfonyl-labdan-15-ol as a mixture of diastereomers at the C-12 position in moderate yields (53–69%). However, results of reductive desulfonylation under several conditions were extremely poor: (1) Na(Hg), Na_2HPO_4 in MeOH, (2) Li in $EtNH_2$–THF, (3) $Pd(PPh_3)_4$, $NaBH_4$ in *i*-PrOH-THF, (4) $Pd(PPh_3)_4$, $NaBH_4$ in EtOH, (5) $PdCl_2$(dppp), $LiHBEt_3$ in THF, to give 17-nor-8-oxo (or -8-hydroxy)-labdan-15-ol in the range of 5–17% yields. Several by-products, which underwent migration and isomerization of the double bond and conjugated diene-formation with reductive desulfonylation and also reduction of ketone, were structurally elucidated from the ^{1}H NMR spectra. Although methylene introduction at the C-8 position by the Wittig or Tebbe reagent was also carried out prior to reductive desulfonylation, no desired product was obtained. Only unknown decomposed products were obtained with recovery of the starting material.

Thus, the Sakurai reaction using allyltrimethylsilane (C_3)[12] as a more simple donor was carried out for **9**. The reaction smoothly proceeded at −78°C for 30 min to give **10** in 62% yield. The stereochemistry at the C-9 position could not be determined by the spectral method at this stage. By considering the reaction mechanism, protonation for the intermediate (titanium enolate) from the axial direction reasonably gives **10** which is also a thermodynamically stable isomer. From the other examples of Michael addition for **9**,[6d,7b,8a] the validity of stereochemistry at the C-9 position is supported and confirmed after conversion into a known compound or copalol itself.

Methylene introduction at the C-8 position by the Wittig reagent was achieved on **10**. When the ylide (Ph_3P^+–CH_2^-) solution containing LiBr in Et_2O was used, the reaction proceeded to give diene **11** in low yields (15–30%) with recovery of the starting material. Using excess ylide (5–10 equiv.) and prolongation of reaction time did not contribute to increasing the yield. The presence of LiBr would promote the enolate formation from **10** when the ylide plays the role of a base but not of a nucleophile in the initial stage of the reaction. Because the partially produced enolate of **10** does not undergo the Wittig reaction, adding a proton source in order to equilibrate **10** and the enolate is considered to be effective. Adding *t*-BuOH to the Wittig reaction mixture exhibited a remarkable effect, namely, that most of **10** disappeared within 12 h. Although the ylide might partially undergo protonation with *t*-BuOH, the resulting phosphonium alkoxide and ylide might be at equilibrium from the fact that the orange color of the ylide remained during the Wittig reaction. Furthermore, by using the roughly prepared salt-free ylide solution[6a] (see Experimental section) and *t*-BuOH as a co-solvent, the reaction was completed in 3 h at room temperature to give **11** in 80% yield without epimerization at the C-9 position.

The Wacker oxidation[13] of the terminal double bond in **11** would give methylketone **12** which corresponds to the degradation product of natural manool and its related compounds.[5d,14] Under the usual Wacker conditions with $PdCl_2$ (0.1 equiv.), CuCl (1.0 equiv.) in DMF–H_2O under oxygen atmosphere, **11** was converted into **12** at room temperature overnight in 88% yield. The spectral data including specific rotation; $[\alpha]_D^{23}=+35.8°$ (*c* 0.91, $CHCl_3$), were identical to those derived from natural products.[5d,14] Therefore, the stereochemistry at the C-9 position in **10**, **11**, and **12** was unambiguously confirmed.

Conversion from **12** into (+)-**6** essentially followed the known procedure. The Horner–Emons reaction of **12** with methyl diethylphosphonoacetate and NaH in THF gave methyl (+)-copalate **13*E***[15] in 84% yield with **13*Z*** in 15% yield. DIBAL-H reduction of **13*E*** in Et_2O gave (+)-copalol [(+)-**6**] in 97% yield; $[\alpha]_D^{24}=+31.2°$ (*c* 1.14, $CHCl_3$), whose spectral data were completely identical to those reported by Yee and Coates.[4]

PDC oxidation for another diastereomer **5b** and subsequent β-elimination gave enone ***ent*-9**[6d,8a] in 84% yield. According to the entirely same manner that for (+)-**6**, (−)-copalol [(−)-**6**] was synthesized in 26% yield in five steps from ***ent*-9**. The spectral data of (−)-**6** were completely identical to those of (+)-**6** and the specific rotation; $[\alpha]_D^{22}=-35.5°$ (*c* 1.02, $CHCl_3$), was the opposite sign to that of (+)-**6**.

Conclusion

The total synthesis of both enantiomers of copalol (**6**) was accomplished via the optical resolution of racemic diol (±)-**4**. The diastereomeric pair of Boc-L-proline-monoesters (**5a/5b**) could be readily separated by flash column chromatography. Removal of the chiral auxiliary was achieved by two methods: (1) methanolysis and (2) oxidation-β-elimination sequence. Methanolysis of **5a** and **5b** gave optically active diols (+)-**4** and (−)-**4** which were converted into (*S*)-MTPA esters **8a** and **8b** in order to determine optical purity. Satisfactory resolution was confirmed on **5a** and **5b**. PDC-oxidation for **5a** and **5b** and subsequent β-elimination, which are regarded as a one-step operation, made it possible to remove the chiral auxiliary with functionalization to give optically active enones **9** and ***ent*-9**. Two pairs of chiral building blocks, (+)-**4**/(−)-**4** and **9**/***ent*-9**, which are useful for syntheses of drimane sesquiterpenes and labdane diterpenes, could be readily prepared. The total synthesis of both enantiomers of copalol (**6**) is a quite appropriate example for labdane diterpenes. Application to the synthesis of drimane sesquiterpenes will be reported elsewhere. Both enones **9** and ***ent*-9** were respectively converted into (+)-copalol [(+)-**6**] in 36% yield and (−)-copalol [(−)-**6**] in 26% yield in five steps: (1) Sakurai reaction ($TiCl_4$-promoted conjugate addition of allylsilane), (2) Wittig methylenation, (3) Wacker oxidation, (4) Horner–Emmons reaction, and (5) DIBAL-H reduction. This synthesis is advantageous in some points in contrast to the known syntheses:[4,5] (1) practical method, (2) short-step synthesis (10 steps) even from the basic starting materials, and (3) giving both enantiomers.

Experimental

General methods

^{1}H- and ^{13}C NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer (^{1}H at 270 MHz; ^{13}C at 67.5 MHz). In the ^{1}H NMR spectra, chemical shifts are reported as δ (ppm) values relative to the residual proton (δ 7.26 ppm) of $CDCl_3$. In the ^{13}C NMR spectra, chemical shifts are reported as δ (ppm) values relative to the carbon signal (δ 77.0 ppm) of $CDCl_3$. IR spectra were measured with a Perkin Elmer System 2000 FT-IR spectrometer, and mass spectra were recorded with a JEOL JMS-AX500 or JEOL JMS-SX102A spectrometer. Specific rotation values were measured with a JASCO DIP-370 digital polarimeter. Melting point values were obtained with Yanaco micro-melting point apparatus and are uncorrected. Analytical and preparative TLC was performed on precoated silica gel 60 F_{254} plates of Merck Art. 5715 and Art. 5744, respectively. Flash column chromatography was carried out with Silica gel 60N (spherical, neutral, 46–50 mm) of Kanto Chemical Co., Inc. Aluminiumoxid 90 active (neutral, 63–200 mm) of Merck Art. 1077 was used for elimination on dry alumina column.

(1*S*,2*S*,4a*S*,8a*S*)-2-Hydroxy-5,5,8a-trimethyldecahydronaphthalen-1-ylmethyl (*S*)-1-*tert*-butoxycarbonyl-pyrrolidine-2-carboxylate (5a) and (1*R*,2*R*,4a*R*,8a*R*)-2-hydroxy-5,5,8a-trimethyldecahydronaphthalen-1-ylmethyl (*S*)-1-*tert*-butoxycarbonyl-pyrrolidine-2-carboxylate (5b). A mixture of (±)-4 (1.00 g, 4.42 mmol), Boc-L-proline (1.05 g, 4.86 mmol), DCC (1.00 g, 4.86 mmol) and DMAP (53.8 mg, 0.44 mmol) in dry CH_2Cl_2 (30 ml) was stirred for 4 h at 4°C. The resulting dicyclohexylurea was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc=3:1) to give **5a** (912 mg, 49%) as a colorless oil and **5b** (915 mg, 49%) as a colorless oil.

Data for ***5a***. More polar, R_f 0.32 on TLC (*n*-hexane/EtOAc=2:1); $[\alpha]_D^{22}=-31.1°$ (*c* 1.27, $CHCl_3$); FDMS *m/z*: 424 (68.0, MH^+), 423 (100, M^+), 57 (18.2); HRMS *m/z* (M^+): calcd for $C_{24}H_{41}NO_5$, 423.2985; found, 423.3002; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.86 (3H, s), 0.87 (1H, m), 0.88 (3H, s), 0.95–1.24 (2H, m), 1.06 (3H, s), 1.28–2.04 (13H, m), 1.42 (4.5H, s), 1.46 (4.5H, s), 2.20 (1H, m), 3.33–3.58 (2H, m), 3.89 (1H, m), 4.10–4.33 (2H, m), 4.49 (0.5H, t, *J*=10.6 Hz), 4.58 (0.5H, t, *J*=10.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 16.9, 17.1, 18.2, 21.7, 23.6, 24.4, 28.3, 28.4, 30.0, 31.0, 33.2, 33.6, 34.5, 34.7, 37.0, 37.1, 39.58, 39.64, 41.8, 46.3, 46.6, 52.8, 53.2, 55.7, 59.1, 59.2, 62.6, 65.6, 66.2, 77.2, 79.9, 153.8, 154.5, 173.7, 174.1; IR ν_{max} (film) cm^{-1}: 3480, 2976, 2927, 2846, 1739, 1694, 1477, 1456, 1404, 1367, 1348, 1281, 1257, 1164, 1125, 1089, 1067, 1040, 1000, 981, 963, 928, 887, 856, 756.

Data for ***5b***. Less polar, R_f 0.39 on TLC (*n*-hexane/EtOAc=2:1); $[\alpha]_D^{23}=-35.4°$ (*c* 1.12, $CHCl_3$); FDMS *m/z*: 424 (74.7, MH^+), 423 (100, M^+), 57 (17.3); HRMS *m/z* (M^+): calcd for $C_{24}H_{41}NO_5$, 423.2985; found, 423.3004; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.86 (3H, s), 0.87 (1H, m), 0.88 (3H, s), 0.98–1.22 (2H, m), 1.07 (3H, s), 1.26–2.02 (13H, m), 1.42 (4.5H, s), 1.44 (4.5H, s), 2.20 (1H, m), 3.32–3.60 (2H, m), 3.89 (0.5H, m), 4.03 (0.5H, m), 4.12–4.39 (2H, m), 4.53 (0.5H, t, *J*=10.6 Hz), 4.57 (0.5H, t, *J*=10.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 16.4, 16.5, 16.9, 17.1, 18.2, 21.7, 21.8, 23.5, 24.4, 28.3, 28.4, 29.8, 30.9, 33.2, 33.7, 34.6, 37.0, 37.1, 39.6, 39.7, 41.8, 46.3, 46.6, 52.9, 53.2, 55.7, 59.0, 59.2, 62.6, 65.6, 66.1, 77.2, 78.0, 153.8, 154.5, 174.0, 174.1; IR ν_{max} (film) cm^{-1}: 3495, 2977, 2928, 2847, 1739, 1694, 1477, 1456, 1404, 1367, 1348, 1280, 1257, 1164, 1125, 1089, 1068, 1046, 999, 979, 963, 928, 887, 855, 757.

(1*S*,2*S*,4a*S*,8a*S*)-2-Hydroxy-1-hydroxymethyl-5,5,8a-trimethyldecahydronaphthalene [(+)-4]. A mixture of **5a** (175 mg, 413 μmol) and K_2CO_3 (100 mg, 723 μmol) in MeOH (2.0 ml) was stirred overnight at room temperature. The mixture was diluted with water (5 ml) and extracted with EtOAc (5 ml×3). The combined organic layers were washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from EtOAc-*n*-hexane to give (+)-**4** (80.3 mg, 86%) as colorless needles; mp 132–134°C; $[\alpha]_D^{23}=+26.1°$ (*c* 0.93, $CHCl_3$) [lit.[8a] $[\alpha]_D^{24}=+24.7°$ (*c* 1.00, $CHCl_3$)]; EIMS *m/z*: 226 (1.5, M^+), 211 (1.3, M^+-CH_3), 208 (59.4, M^+-H_2O), 41 (100); HRMS *m/z* (M^+): calcd for $C_{14}H_{26}O_2$, 226.1933; found, 226.1949; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.86 (3H, s), 0.88 (3H, s), 0.91 (1H, m), 0.99 (1H, m), 1.12 (3H, s), 1.16 (1H, m), 1.20 (1H, m), 1.38 (1H, m), 1.42 (1H, m), 1.47–1.67 (6H, m), 1.74 (1H, m), 1.94 (1H, m), 3.85 (1H, dd, *J*=10.6, 4.3 Hz), 3.97 (1H, dd, *J*=10.6, 7.3 Hz), 4.25 (1H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 17.1, 17.2, 18.3, 21.9, 33.3, 33.8, 35.4, 37.3, 39.7, 42.0, 55.4, 55.9, 61.0, 68.6; IR ν_{max} (KBr) cm^{-1}: 3306, 2977, 2933, 2869, 2845, 1456, 1429, 1368, 1340, 1188, 1169, 1090, 1025, 977, 948, 926.

(1*R*,2*R*,4a*R*,8a*R*)-2-Hydroxy-1-hydroxymethyl-5,5,8a-trimethyldecahydronaphthalene [(−)-4]. According to the same manner as described above, **5b** (55.0 mg, 130 μmol) was treated with K_2CO_3 (18.0 mg, 130 μmol) in MeOH (1.0 ml) to give (−)-**4** (24.7 mg, 84%) as colorless needles; mp 132–134°C; $[\alpha]_D^{24}=-25.5°$ (*c* 0.94, $CHCl_3$) [lit.[8a] $[\alpha]_D^{24}=-23.8°$ (*c* 1.00, $CHCl_3$)]; HRMS *m/z* (M^+): calcd for $C_{14}H_{26}O_2$, 226.1933; found, 226.1960. The other spectral data were identical to those of (+)-**4**.

(4a*S*,8a*S*)-1-Methylene-2-oxo-5,5,8a-trimethyldecahydronaphthalene (9). To a mixture of **5a** (500 mg, 1.18 mmol) and molecular sieves 4 Å (750 mg) in dry CH_2Cl_2 (6.0 ml) was added PDC (886 mg, 2.36 mmol) at 4°C. The mixture was stirred overnight at room temperature, adsorbed on dry alumina column (30 g), kept for 1 h, and then eluted with Et_2O. The eluate was concentrated under reduced pressure to give **9** (213 mg, 87%) as a colorless oil; $[\alpha]_D^{23}=-68.7°$ (*c* 1.22, $CHCl_3$) [lit.[8a] $[\alpha]_D^{23}=-69.6°$ (*c* 0.500, $CHCl_3$)]; EIMS *m/z*: 207 (20.0, MH^+), 206 (100, M^+), 191 (18.8, M^+-CH_3); HRMS *m/z* (M^+): calcd for $C_{14}H_{22}O$, 206.1671; found, 206.1678; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.92 (3H, s), 0.96 (3H, s), 1.02 (3H, s), 1.23 (1H, m), 1.36–1.85 (7H, m), 1.97 (1H, m), 2.33 (1H, ddd, *J*=16.5, 12.5, 7.9 Hz), 2.66 (1H, ddd, *J*=16.5, 5.6, 2.0 Hz), 5.00 (1H, d, *J*=1.3 Hz), 5.53 (1H, d, *J*=1.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 18.9, 20.8, 21.4, 22.1, 33.3, 33.9, 37.6, 40.6, 41.0, 41.9, 50.5, 113.4, 158.9, 204.0; IR ν_{max} (film) cm^{-1}: 3097,

2948, 2930, 2868, 2845, 1697, 1612, 1461, 1443, 1415, 1389, 1377, 1367, 1326, 1293, 1278, 1236, 1203, 1174, 1112, 1100, 1059, 1037, 993, 977, 969, 930, 884, 872, 848.

(4a*R*,8a*R*)-1-Methylene-2-oxo-5,5,8a-trimethyldecahydronaphthalene (*ent*-9). According to the same manner as described above, **5b** (260 mg, 614 μmol) was treated with molecular sieves 4 Å (300 mg) and PDC (462 mg, 1.23 mmol) in dry CH_2Cl_2 (3.0 ml) to give ***ent*-9** (106 mg, 84%) as a colorless oil after elimination on alumina; $[\alpha]_D^{23}=+71.7°$ (*c* 0.84, $CHCl_3$) [lit.[6d] $[\alpha]_D^{24}=+73.6°$ (*c* 1.00, $CHCl_3$), lit.[8a] $[\alpha]_D^{23}=+71.9°$ (*c* 0.695, $CHCl_3$)]; HRMS *m*/*z* (M^+): calcd for $C_{14}H_{22}O$, 206.1671; found, 206.1689. The other spectral data were identical to those of **9**.

(1*S*,4a*S*,8a*S*)-1-(But-3-enyl)-2-methylene-5,5,8a-trimethyldecahydronaphthalene (10). To a solution of **9** (146 mg, 708 μmol) in dry CH_2Cl_2 (5.0 ml) were successively added $TiCl_4$ (0.5 M solution in CH_2Cl_2, 1.51 ml, 779 μmol) and allyltrimethylsilane (124 μl, 779 μmol) at −78°C under argon atmosphere. The mixture was stirred for 30 min at the same temperature. The mixture was diluted with water (5 ml) and extracted with CH_2Cl_2 (5 ml×3). The combined organic layers were washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PLC (*n*-hexane/EtOAc=10:1) to give **10** (108 mg, 62%) as a colorless oil; $[\alpha]_D^{24}=-54.0°$ (*c* 0.93, $CHCl_3$); EIMS *m*/*z*: 248 (31.2, M^+), 233 (78.9, M^+-CH_3), 207 (6.8), 194 (50.3), 179 (100), 55 (30.4), 41 (35.5); HRMS *m*/*z* (M^+): calcd for $C_{17}H_{28}O$, 248.2140; found, 248.2159; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.70 (3H, s), 0.83 (3H, s), 0.95 (3H, s), 1.07–1.31 (3H, m), 1.38–1.90 (8H, m), 1.97–2.17 (3H, m), 2.28 (1H, dt, *J*=6.8, 13.0 Hz), 2.42 (1H, ddd, *J*=13.0, 4.9, 2.2 Hz), 4.91 (1H, dq, *J*=9.2, 1.3 Hz), 4.93 (1H, dq, *J*=17.1, 1.3 Hz), 5.73 (1H, ddt, *J*=17.1, 9.2, 6.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.8, 19.1, 20.9, 21.7, 24.1, 33.2, 33.5, 33.7, 39.3, 42.0, 42.7, 54.3, 63.2, 114.5, 138.8, 211.8 (one ^{13}C-signal is overlapping); IR ν_{max} (film) cm^{-1}: 3076, 2949, 2868, 2848, 1713, 1640, 1461, 1447, 1389, 1366, 1327, 1293, 1277, 1256, 1234, 1218, 1204, 1185, 1149, 1105, 1067, 1036, 995, 971, 949, 909, 869, 832, 757.

(1*R*,4a*R*,8a*R*)-1-(But-3-enyl)-2-methylene-5,5,8a-trimethyldecahydronaphthalene (*ent*-10). According to the same manner as described above, ***ent*-9** (100 mg, 485 μmol) was treated with $TiCl_4$ (0.5 M solution in CH_2Cl_2, 1.07 ml, 533 μmol) and allyltrimethylsilane (84.6 μl, 533 μmol) in dry CH_2Cl_2 (3.0 ml) to give ***ent*-10** (65.6 mg, 54%) as a colorless oil; $[\alpha]_D^{22}=+57.7°$ (*c* 1.20, $CHCl_3$); HRMS *m*/*z* (M^+): calcd for $C_{17}H_{28}O$, 248.2140; found, 248.2150. The other spectral data were identical to those of **10**.

(1*S*,4a*S*,8a*S*)-1-(But-3-enyl)-2-methylene-5,5,8a-trimethyldecahydronaphthalene (11). To a suspension of Ph_3PCH_3Br (1.00 g, 2.80 mmol) in dry toluene (7.5 ml) was added dropwise *n*-BuLi (1.5 M *n*-hexane solution, 1.87 ml, 2.80 mmol) at room temperature under argon atmosphere. The mixture was stirred for 1 h at room temperature to give ca. 0.3 M ylide-solution, whose supernatant was used for the Wittig reaction after standing. To a solution of **10** (105 mg, 423 μmol) in dry toluene (2.0 ml) and *t*-BuOH (0.2 ml) was added the prepared ylide-solution (4.23 ml, 1.27 mmol) at room temperature under argon atmosphere. After being stirred for 3 h, the mixture was diluted with EtOAc (10 ml), washed with water (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane) to give **11** (83.4 mg, 80%) as a colorless oil; $[\alpha]_D^{25}=+29.8°$ (*c* 0.61, $CHCl_3$); EIMS *m*/*z*: 246 (10.2, M^+), 231 (65.4, M^+-CH_3), 218 (8.6), 205 (11.9), 137 (100), 55 (30.1), 41 (37.0); HRMS *m*/*z* (M^+): calcd for $C_{18}H_{30}$, 246.2347; found, 246.2345; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.69 (3H, s), 0.81 (3H, s), 0.88 (3H, s), 0.95–2.05 (14H, m), 2.18 (1H, m), 2.38 (1H, m), 4.51 (1H, d, *J*=1.3 Hz), 4.83 (1H, d, *J*=1.3 Hz), 4.93 (1H, dq, *J*=9.2, 1.3 Hz), 4.98 (1H, dq, *J*=17.1, 1.3 Hz), 5.81 (1H, ddt, *J*=17.1, 9.2, 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.6, 19.5, 21.8, 23.0, 24.5, 32.8, 33.6, 33.7, 38.4, 39.1, 39.6, 42.3, 55.6, 56.1, 106.2, 113.9, 139.4, 148.5; IR ν_{max} (film) cm^{-1}: 3079, 2940, 2867, 2845, 1642, 1460, 1443, 1414, 1388, 1366, 1283, 1255, 1202, 1150, 1112, 1080, 1039, 993, 968, 944, 909, 889.

(1*R*,4a*R*,8a*R*)-1-(But-3-enyl)-2-methylene-5,5,8a-trimethyldecahydronaphthalene (*ent*-11). According to the same manner as described above, ***ent*-10** (55.0 mg, 221 μmol) was treated with the prepared ylide solution (2.11 ml, 633 μmol) in dry toluene (1.0 ml) and *t*-BuOH (0.1 ml) to give ***ent*-11** (43.4 mg, 80%) as a colorless oil; $[\alpha]_D^{23}=-32.2°$ (*c* 0.99, $CHCl_3$); HRMS *m*/*z* (M^+): calcd for $C_{18}H_{30}$, 246.2347; found, 246.2375. The other spectral data were identical to those of **11**.

(1*S*,4a*S*,8a*S*)-2-Methylene-1-(3-oxobutyl)-5,5,8a-trimethyldecahydronaphthalene (12). A mixture of **11** (82.0 mg, 333 μmol), $PdCl_2$ (5.92 mg, 33.3 μmol), and CuCl (33.1 mg, 333 μmol) in DMF (1.75 ml) and H_2O (0.25 ml) was stirred overnight under oxygen atmosphere. The reaction mixture was acidified with 1 M HCl (5 ml) and extracted with EtOAc (5 ml×2). The combined organic layers were washed with water (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PLC (*n*-hexane/EtOAc=15:1) to give **12** (77.3 mg, 88%) as a colorless oil; $[\alpha]_D^{23}=+35.8°$ (*c* 0.91, $CHCl_3$) [lit.[5d] $[\alpha]_D^{19}=+36.5°$ ($CHCl_3$), lit.[14b] $[\alpha]_D^{25}=+38°$ (*c* 0.9, $CHCl_3$)]; EIMS *m*/*z*: 262 (15.5, M^+), 247 (13.1, M^+-CH_3), 244 (14.1), 229 (13.1), 204 (16.9), 137 (43.7), 43 (100); HRMS *m*/*z* (M^+): calcd for $C_{18}H_{30}O$, 262.2297; found, 262.2280; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.68 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 0.98–2.02 (13H, m), 2.09 (3H, s), 2.23–2.42 (2H, m), 2.57 (1H, ddd, *J*=16.9, 9.5, 4.0 Hz), 4.42 (1H, d, *J*=1.3 Hz), 4.81 (1H, d, *J*=1.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.4, 17.6, 19.4, 21.8, 24.5, 30.1, 33.6, 33.7, 38.4, 39.0, 39.8, 42.1, 42.9, 55.5, 56.3, 106.2, 148.2, 209.2; IR ν_{max} (film) cm^{-1}: 3079, 2939, 2868, 2844, 1718, 1643, 1460, 1442, 1410, 1388, 1364, 1314, 1272, 1255, 1202, 1193, 1161, 1114, 1082, 1057, 1039, 994, 975, 946, 889.

(1*R*,4a*R*,8a*R*)-2-Methylene-1-(3-oxobutyl)-5,5,8a-trimethyldecahydronaphthalene (*ent*-12). According to the same manner as described above, ***ent*-11** (39.0 mg, 158 μmol) was treated with $PdCl_2$ (2.81 mg, 15.8 μmol), and CuCl

(15.7 mg, 158 μmol) in DMF (1.75 ml) and H_2O (0.25 ml) under oxygen atmosphere to give ***ent*-12** (37.0 mg, 89%) as a colorless oil; $[\alpha]_D^{23}=-35.3°$ (*c* 1.32, $CHCl_3$) [lit.[5d] $[\alpha]_D^{19}=-32.8°$ ($CHCl_3$), lit.[14c] $[\alpha]_D^{20}=-32.2°$ (*c* 1.25, $CHCl_3$)]; HRMS *m/z* (M^+): calcd for $C_{18}H_{30}O$, 262.2297; found, 262.2323. The other spectral data were identical to those of **12**.

Methyl (+)-copalate (13*E*). To a solution of $(EtO)_2P(O)CH_2CO_2Me$ (181 mg, 858 μmol) in dry THF (3.0 ml) was added NaH (60% in oil, 34.3 mg, 858 μmol) at 4°C. The mixture was stirred at room temperature for 30 min under argon atmosphere. To the resulting solution was added a solution of **12** (75.0 mg, 286 μmol) in dry THF (2.0 ml) at 4°C. The temperature was gradually allowed to warm to room temperature, and the mixture was stirred for 24 h. After being diluted with sat. aq. NH_4Cl (5 ml) and water (5 ml), the reaction mixture was extracted with EtOAc (5 ml×2). The combined organic layers were washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PLC (*n*-hexane/EtOAc=20:1) to give **13*Z*** (13.3 mg, 15%) and **13*E*** (76.1 mg, 84%) as a colorless oil; $[\alpha]_D^{23}=+46.1°$ (*c* 1.25, $CHCl_3$) [lit.[14b] $[\alpha]_D^{25}=+47°$ (*c* 2.2, $CHCl_3$), lit.[15b] $[\alpha]_D^{22}=+46°$ (*c* 0.5, $CHCl_3$)]; EIMS *m/z*: 318 (29.9, M^+), 303 (82.9, M^+-CH_3), 287 (9.6, M^+-CH_3O), 244 (28.7), 205 (30.5), 137 (98.7), 114 (100); HRMS *m/z* (M^+): calcd for $C_{21}H_{34}O_2$, 318.2559; found, 318.2566; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.68 (3H, s), 0.80 (3H, s), 0.87 (3H, s), 0.93–1.78 (12H, m), 1.85–2.03 (2H, m), 2.15 (3H, d, *J*=1.0 Hz), 2.23–2.43 (2H, m), 3.68 (3H, s), 4.49 (1H, d, *J*=1.3 Hz), 4.84 (1H, d, *J*=1.3 Hz), 5.64 (1H, q, *J*=1.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.6, 19.0, 19.4, 21.6, 21.8, 24.5, 33.63, 33.65, 38.3, 39.1, 39.7, 39.8, 42.1, 50.8, 55.5, 56.1, 106.3, 114.8, 148.2, 161.0, 167.1; IR ν_{max} (film) cm^{-1}: 3079, 2944, 2867, 2844, 1721, 1648, 1459, 1435, 1387, 1365, 1329, 1277, 1255, 1148, 1114, 1072, 1057, 1061, 1037, 994, 967, 922, 888.

Methyl (−)-copalate (*ent*-13*E*). According to the same manner as described above, ***ent*-12** (35.0 mg, 133 μmol) in dry THF (1.0 ml) was treated with $(EtO)_2P(O)CH_2CO_2Me$ (140 mg, 665 μmol) and NaH (60% in oil, 26.6 mg, 665 μmol) in dry THF (2.0 ml) to give ***ent*-13*Z*** (8.2 mg, 19%) ***ent*-13*E*** (33.1 mg, 78%) as a colorless oil; $[\alpha]_D^{24}=-47.4°$ (*c* 1.08, $CHCl_3$) [lit.[5e] $[\alpha]_D^{20}=-42.0°$ (*c* 1.0, $CHCl_3$)]; HRMS *m/z* (M^+): calcd for $C_{21}H_{34}O_2$, 318.2559; found, 318.2554. The other spectral data were identical to those of **13*E***.

(+)-Copalol [(+)-6]. To a solution of **13*E*** (71.0 mg, 223 μmol) in dry Et_2O (3.0 ml) was added DIBAL-H (0.96 M, *n*-hexane solution, 0.70 ml, 670 μmol) at 4°C under argon atmosphere. The mixture was stirred at room temperature for 2 h. The reaction was quenched by adding aq. Rochelle salt (5 ml), and the mixture was extracted with EtOAc (5 ml×2). The combined organic layers were washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PLC (*n*-hexane/EtOAc=3:1) to give (+)-**6** (62.6 mg, 97%) as a colorless oil; $[\alpha]_D^{24}=+31.2°$ (*c* 1.14, $CHCl_3$) [lit.[4] $[\alpha]_D^{24}=+29.8°$ (*c* 1.36, $CHCl_3$)]; EIMS *m/z*: 290 (26.0, M^+), 275 (100, M^+-CH_3), 272 (26.2, M^+-CH_3O), 257 (42.7), 205 (18.1), 137 (72.2); HRMS *m/z* (M^+): calcd for $C_{20}H_{34}O$, 290.2610; found, 290.2598; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.68 (3H, s), 0.80 (3H, s), 0.87 (3H, s), 0.99 (1H, dt, *J*=4.3, 12.7 Hz), 1.07 (1H, dd, *J*=2.7, 12.5 Hz), 1.16 (1H, dt, *J*=4.5, 13.2 Hz), 1.30 (1H, dt, *J*=4.3, 12.7 Hz), 1.35–1.87 (10H, m), 1.67 (3H, br. s), 1.96 (1H, dt, *J*=5.2, 13.0 Hz), 2.15 (1H, m), 2.38 (1H, ddd, *J*=13.0, 4.3, 2.4 Hz), 4.14 (2H, d, *J*=6.9 Hz), 4.51 (1H, d, *J*=1.5 Hz), 4.82 (1H, d, *J*=1.5 Hz), 5.38 (1H, tq, *J*=6.9, 1.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.6, 16.4, 19.5, 21.8, 21.9, 24.6, 33.66, 33.68, 38.4, 38.5, 39.2, 39.7, 42.3, 55.6, 56.4, 59.5, 106.2, 123.0, 140.5, 148.5; IR ν_{max} (film) cm^{-1}: 3316, 3079, 2938, 2867, 2845, 1668, 1643, 1460, 1443, 1409, 1387, 1367, 1343, 1272, 1224, 1201, 1100, 998, 888, 758.

(−)-Copalol [(−)-6]. According to the same manner as described above, ***ent*-13*E*** (32.0 mg, 100 μmol) in dry Et_2O (2.0 ml) was treated with DIBAL-H (0.96 M, *n*-hexane solution, 0.31 ml, 300 μmol) to give (−)-**6** (25.4 mg, 87%) as a colorless oil; $[\alpha]_D^{22}=-35.5°$ (*c* 1.02, $CHCl_3$) [lit.[5d] $[\alpha]_D^{17}=-31.7°$ ($CHCl_3$)]; HRMS *m/z* (M^+): calcd for $C_{20}H_{34}O$, 290.2610; found, 290.2631. The other spectral data were identical to those of (+)-**6**.

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