Bioscience, Biotechnology, and Biochemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb20

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Published online: 22 May 2014.

To cite this article: Hiroaki TOSHIMA, Hideaki OIKAWA, Hiroshi YADA, Hiroshi ONO, Tomonobu TOYOMASU & Takeshi SASSA (2002) Total Synthesis of (±)-syn-Copalol, Bioscience, Biotechnology, and Biochemistry, 66:11, 2504-2510, DOI: 10.1271/bbb.66.2504

To link to this article: http://dx.doi.org/10.1271/bbb.66.2504

Biosci. Biotechnol. Biochem., **66** (11), 2504–2510, 2002

Note

Total Synthesis of (±)-*syn*-Copalol

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Received May 23, 2002; Accepted June 26, 2002

The labdane diterpene derivative, *syn*-copalol [(+)-5] is the alcohol part of *syn*-copalyl diphosphate [(+)-4]. In this paper, racemic (±)-5 was synthesized from a known racemic lactone in 8 steps. The current and our previous syntheses provide all four copalol derivatives [(+)-3, (−)-3 and (±)-5] which are required for the biosynthetic study of polycyclic diterpenes.

Key words: labdane; diterpene; biosynthesis; *syn*-copalyl diphosphate; *syn*-copalol

We have recently reported the preparation of both enantiomers of the labdane diterpene derivative, copalol [(+)-**3** and (−)-**3**] (Fig. 1),[1)] whose diphosphates [copalyl diphosphate, (+)-**2** and (−)-**2**] are known as biosynthetic intermediates of polycyclic diterpenes. Geranylgeranyl diphosphate (**1**) was enzymatically converted to (+)-**2** and (−)-**2** *via* the chair-chair transition state, whereas **1** was also cyclized to *syn*-copalyl diphosphate [(+)-**4**] *via* the chair-boat transition state by the other diterpene cyclase (synthase).[2)] The C-9 epimer of (+)-**2** (labdane numbering) is also a biosynthetic intermediate of polycyclic diterpenes. To study the stereochemical course of the polycyclic diterpene cyclization, we required (+)-**4** in addition to (+)-**2** and (−)-**2**.[3)]

To date, Yee and Coates have only reported a versatile total synthesis of (+)-*syn*-copalol [(+)-**5**] which required relatively long steps.[4)] Our need for the enzymatic conversion of (+)-**5** to polycyclic diterpenes prompted us to develop a more concise route to racemic **5**. *syn*-Copalyl diphosphate (±)-**4** has been used in the biosynthetic study of aphidicolin (**7**), a specific inhibitor of DNA polymerase α.[5)] It has been proved by using (±)-**4** that aphidicolan-16β-ol synthase catalyzed the cyclization of (+)-**4** to aphidicolan-16β-ol (**6**). We describe here the total synthesis of (±)-*syn*-copalol [(±)-**5**] from a known racemic lactone in 8 steps.

We chose a known lactone (**8**)[6)] as the most appropriate substrate for the synthesis of (±)-**5**, because **8** has the three required stereogenic centers of (±)-**5**, C-5, C-9 and C-10. Reduction of **8** with sodium borohydride in an alkaline medium gave a lactone (**9**) in a 92% yield (Scheme). Reduction of **9** with DIBAH in THF gave a lactol, which was treated with the Wittig reagent ($Ph_3P=CH_2$) in DMSO to give a C_1-elongated olefin (**10**) in an 82% yield (2 steps). To introduce the *exo*-methylene of **12a**, regioselective elimination was achieved *via* acetate (**11**).[7)] The tertiary hydroxyl group of **10** was acetylated with acetic anhydride, triethylamine and 4-dimethylaminopyridine in toluene at 70°C to give **11** in a 91% yield. Treatment of **11** in 2,4,6-collidine at refluxing temperature[8)] regioselectively gave a 4.7:1 mixture of diene **12a** and its *endo*-isomer (C-7-ene, **12b**) in a 93% yield. The ^{1}H- and ^{13}C-NMR spectra of the mixture of **12a** and **12b** respectively showed the *exo*-olefin signals (^{1}H: 4.52 and 4.69 ppm; ^{13}C: 109.3 and 149.1 ppm) and *endo*-olefin signals (^{1}H: 5.25 ppm; ^{13}C: 119.7 and 136.6 ppm). Therefore, the ratio of **12a** and **12b** could be readily determined from the integral values of the respective olefin signals in the ^{1}H-NMR spectrum.

Since resulting **12a** corresponds to the C-9 epimer of the synthetic intermediate of **3** previously reported,[1)] the same protocol (Wacker oxidation, Horner-Emmons olefination and DIBAH reduction) as that

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Abbreviations: DIBAH, diisobutylaluminumhydride; DMSO, dimethylsulfoxide; THF, tetrahydrofuran; PTLC, preparative thin-layer chromatography; HSQC, heteronuclear single-quantum coherence; HMBC, heteronuclear multiple-bond coherence; DQFCOSY, double-quantum filtered correlation spectroscopy; NOESY, nuclear Overhauser enhancement and exchange spectroscopy

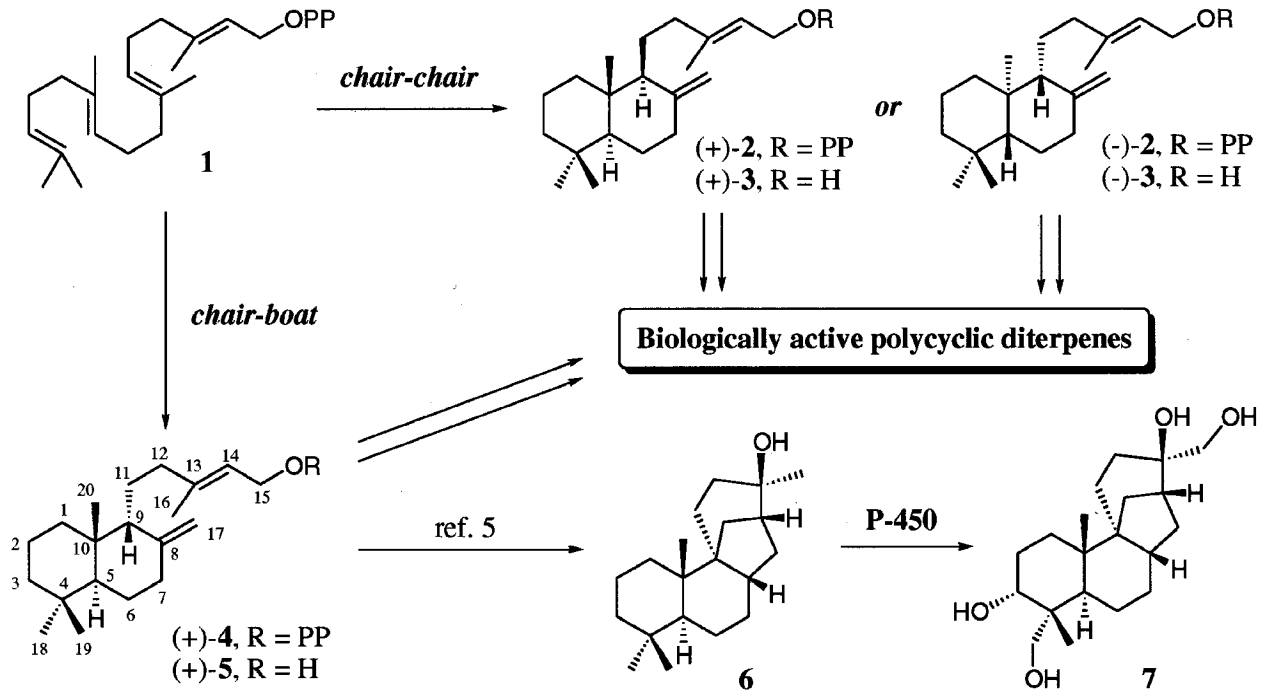
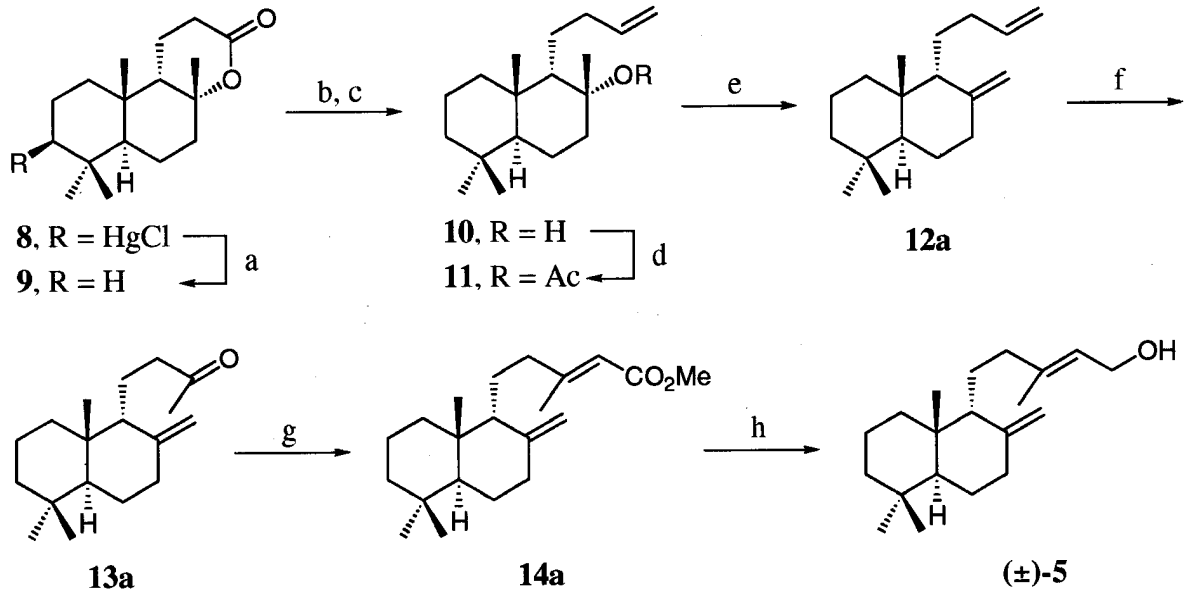


Fig. 1. Biosynthetic Pathway to Polycyclic Diterpenes.



Scheme. Reagents and Conditions: (a) $NaBH_4$/3 M NaOH, EtOH–$CHCl_3$, 4°C-r.t., 30 min, 92%; (b) DIBAH/THF, −78°C, 30 min; (c) Ph_3PCH_3Br, NaH/DMSO, r.t.-70°C, 2 h, 82%, 2 steps; (d) Ac_2O, Et_3N, DMAP/toluene, 70°C, 2 d, 91%; (e) 2,4,6-collidine, reflux, 8 h, 93%, **12a** (*exo*):**12b** (*endo*) = 4.7:1; (f) O_2, $PdCl_2$, CuCl/DMF-H_2O, r.t., 5 h, 82%, **13a** (*exo*):**13b** (*endo*) = 4.3:1; (g) $(EtO)_2P(O)CH_2CO_2Me$, NaH/THF, −78°C-r.t., overnight, 83%, **14a** (*exo*):**14b** (*endo*) = 4.2:1; (h) DIBAH/Et_2O, 4°C, 1 h, 99%, (±)-**5** (*exo*):*endo*-isomer = 4.2:1.

used for **3** would be applicable to the synthesis of (±)-**5**. The mixture of **12a** and **12b** could not be separated by silica gel column chromatography, and was used as such in the three subsequent steps. Wacker oxidation of **12a**/**12b** gave a 4.3:1 mixture of methylketone **13a** and its *endo*-isomer (**13b**) in an 82% yield. The ratio of the *exo*- and *endo*-isomers from the Wacker oxidation and the subsequent reactions could be also determined from the integral values of the respective olefin signals in the ^{1}H-NMR spectra.

Another characteristic of the reactivity of **13a** was found while keeping **13a** in a $CHCl_3$ solution. A more polar spot apart for **13a** appeared by TLC within several hours, and the product could be separated by PTLC. Its structure was determined to be that of **15**

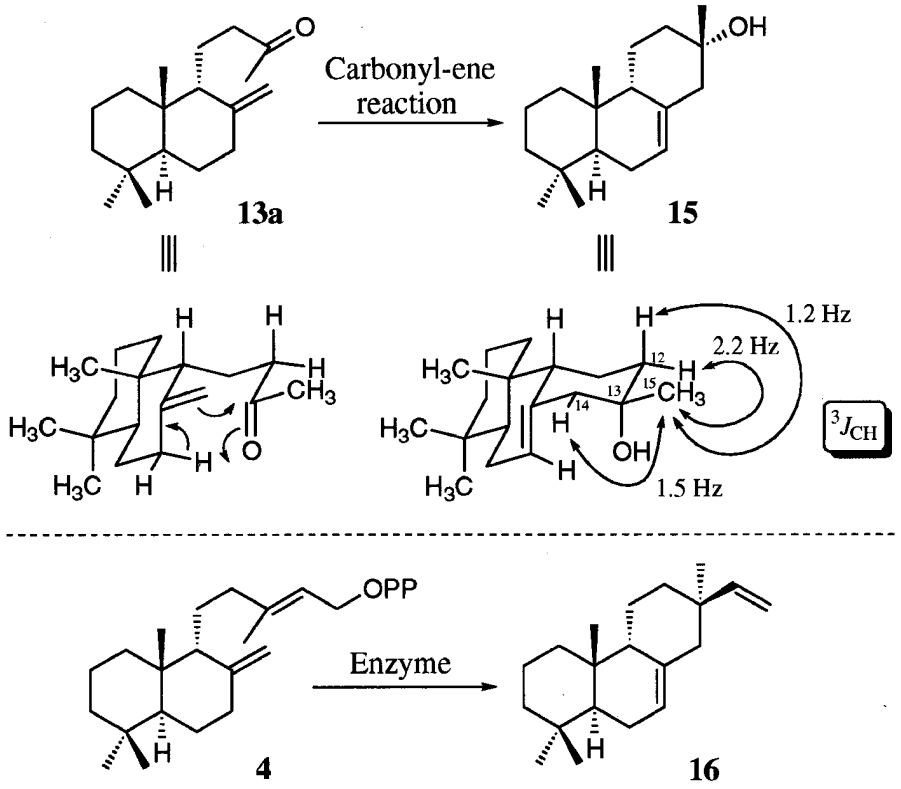


Fig. 2. Structure of the Carbonyl-ene Reaction Product (**15**) and Similarity between Chemical and Enzymatic Cyclization.

as the sole isomer with respect to the position of the double bond by NMR experiments (500 MHz and 800 MHz), including HSQC, HMBC, DQFCOSY, and phase-sensitive NOESY. The gradient-selected *J*-HMBC experiment[9] in particular gave structurally informative values for $^3J_{CH}$ (C-15/H-12eq. = 2.2 Hz; C-15/H-12ax. = 1.2 Hz; and C-15/H-14eq. = 1.5 Hz) which revealed a C-13 stereogenic center as shown in Fig. 2. The typical values for diaxial $^3J_{CH}$ have been reported to be in the range between 5–9 Hz.[10] The carbonyl-ene reaction[11] would be promoted to give **15** in the presence of a trace amount of HCl generated from $CHCl_3$. The corresponding C-9 epimer of **13a** did not provide any cyclization products, suggesting that the conformation of the transition state of **13a** was significantly more stable than that of the C-9 epimer. It is noteworthy that this cyclization resembles the enzymatic cyclization of (+)-**4** to 9β-pimara-7,15-diene (**16**).[4] The resulted tricyclic system of **15** might be useful as a synthetic intermediate and analog of more complex diterpenes.

Horner-Emmons olefination of **13a**/**13b** with diethyl methoxycarbonylmethyl phosphonate and sodium hydride in THF gave a 4.2:1 mixture of (*E*)-α,β-unsaturated ester **14a** and its *endo*-isomer (**14b**) in an 83% yield after chromatographic separation of the corresponding *exo*- and *endo*-isomers of the (*Z*)-α,β-unsaturated ester (13% yield). Reduction of **14a**/**14b** with DIBAH in ether gave (±)-**5** containing the *endo*-isomer in a 99% yield. The ratio of *endo*/*exo* was scarcely affected in the last three steps. At this stage, the *endo*-isomer derived from **12b** could be separated by HPLC. The spectral data (^{1}H-NMR, ^{13}C-NMR, and IR) are identical with those of **5**.[4]

In conclusion, we developed a practical new synthetic route to (±)-*syn*-copalol [(±)-**5**] *via* diene **12a** corresponding to the C-9 epimer of the synthetic intermediate of **3**. The same protocol (Wacker oxidation, Horner-Emmons olefination and DIBAH reduction) as that used for the synthesis of **3** was applicable to the synthesis of (±)-**5**. In addition to both enantiomers of copalol (**3** and *ent*-**3**), (±)-**5** could be obtained by this synthesis. These compounds are essential for the biosynthetic study of polycyclic diterpenes. The optical resolution of (±)-**5** is in progress.

Experimental

General methods. ^{1}H- and ^{13}C-NMR spectra were recorded with Jeol JNM-EX-270 (^{1}H at 270 MHz; ^{13}C at 67.8 MHz), Bruker AMX 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz) and Bruker AVANCE 800 (^{1}H at 800 MHz) spectrometers. Chemical shifts in the ^{1}H-NMR spectra are reported as δ (ppm) values relative to the residual proton [δ 7.26 ppm ($CDCl_3$) or δ 7.15 ppm (C_6D_6)], and in the ^{13}C-NMR spectra as δ (ppm) values relative to the ^{13}C signal of the solvent [δ 77.0 ppm ($CDCl_3$) or 128.0 ppm (C_6D_6)]. IR spectra were measured with a Perkin Elmer 2000 FT-IR spectrometer, and mass spectra were recorded with a

Jeol JMS-AX500 or Jeol JMS-SX102A spectrometer. Melting point (mp) values were obtained with Yanaco micro-melting point apparatus and are uncorrected. Analytical and preparative TLC were respectively performed on precoated silica gel 60 F_{254} plates of Merck Art. 5715 and Art. 5744. Column chromatography was carried out with 60 N silica gel (spherical, neutral, 100–210 μm) from Kanto Chemical Co.

(4aR,6aS*,10aS*,10bS*)-4a,7,7,10a-Tetramethyldodecahydrobenzo[f]chromen-3-one (9).* To a stirred solution of **8**[6] (715 mg, 1.43 mmol) in 3 M NaOH (1.0 ml), EtOH (7.0 ml) and $CHCl_3$ (7.0 ml) was added $NaBH_4$ (108 mg, 2.86 mmol) at 4°C. After being stirred for 30 min at room temperature, the mixture was acidified with 3 M HCl and extracted with $CHCl_3$ (3 × 10 ml). The combined extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crystalline residue was recrystallized from EtOAc/hexane to give **9** (347 mg, 92%) as colorless needles. Mp 125–127°C; EIMS *m/z*: 265 (9.9, MH^+), 264 (31.9, M^+), 249 (50.3, $M^+ - CH_3$), 221 (6.0), 192 (50.0), 177 (54.8), 137 (90.6), 136 (100), 123 (67.7), 109 (64.9), 95 (59.9), 81 (68.7), 69 (53.0), 55 (43.7), 43 (52.9), 41 (59.2); HRMS *m/z* (M^+): calcd. for $C_{17}H_{28}O_2$, 264.2090; found, 264.2064; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.82 (6H, s), 0.88 (3H, s), 1.16 (3H, s), 1.63 (3H, s), 1.07–2.10 (14H, m), 2.26 (1H, ddd, J = 17.5, 13.4, 6.1 Hz), 2.61 (1H, ddd, J = 17.5, 4.5, 2.5 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 18.8, 19.5, 20.8, 21.8, 24.5, 30.8, 31.4, 33.3, 33.4, 36.9, 37.6, 38.1, 42.2, 47.2, 54.1, 88.0, 171.0; IR ν_{max} (film) cm^{-1}: 2947, 2870, 1731, 1466, 1421, 1388, 1352, 1337, 1324, 1292, 1269, 1242, 1217, 1195, 1160, 1141, 1117, 1096, 1080, 1040, 1024, 1002, 975, 955, 896, 802, 753.

(1S,2R*,4aS*,8aS*)-1-(But-3-enyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (10).* To a stirred solution of **9** (340 mg, 1.29 mmol) in dry THF (7.0 ml) at −78°C under an argon atmosphere was added dropwise DIBAH (a 0.93 M hexane solution, 1.52 ml, 1.41 mmol). The mixture was stirred for 30 min at the same temperature. After successively adding sat. aq. Rochelle salt (3.0 ml), H_2O (3.0 ml), and EtOAc (5.0 ml) at −78°C, the resulting mixture was stirred for 1 h at room temperature and then filtered through a Celite pad. The resulting filtrate was separated, and the aqueous layer was extracted with EtOAc (2 × 10 ml). The combined organic layers were washed with brine (10 ml) and concentrated under reduced pressure to give a crude lactol, which was used for the next Wittig reaction without purification. A suspension of NaH (*ca.* 60% in an oil, 155 mg, 3.87 mmol) in dry DMSO (8.0 ml) was stirred at 70°C for 30 min under an argon atmosphere. To the resulting solution of dimsyl sodium in DMSO was added methyltriphenylphosphonium bromide (1.38 g, 3.87 mmol), and the mixture was stirred at 70°C for 30 min. To the resulting ylide solution was added a solution of the crude lactol in dry THF (4.0 ml) at room temperature. After being stirred for 2 h, the reaction mixture was partitioned between EtOAc (20 ml) and H_2O (20 ml). The organic layer was successively washed with H_2O (20 ml) and brine (10 ml), and concentrated under reduced pressure. The residue was purified by column chromatography (50 g of silica gel, hexane:EtOAc = 10:1) to give **10** (280 mg, 82%) as a colorless oil. EIMS *m/z*: 265 (1.0, MH^+), 264 (5.0, M^+), 249 (5.0, $M^+ - CH_3$), 246 (6.2, $M^+ - H_2O$), 231 (11.7), 221 (4.2), 206 (3.6), 195 (51.3), 192 (21.9), 177 (69.3), 137 (39.4), 136 (13.5), 123 (41.8), 109 (52.9), 95 (64.4), 81 (80.0), 69 (100), 55 (69.6), 43 (55.5), 41 (54.2); HRMS *m/z* (M^+): calcd. for $C_{18}H_{32}O$, 264.2453; found, 264.2429; ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.74 (3H, s), 0.81 (3H, s), 0.96 (3H, s), 1.27 (3H, s), 0.90–1.74 (14H, m), 1.94–2.26 (3H, m), 5.01 (1H, dq, J = 10.2, 1.3 Hz), 5.12 (1H, dq, J = 17.1, 1.3 Hz), 5.93 (1H, ddt, J = 17.1, 10.2, 6.7 Hz); ^{13}C-NMR (67.8 MHz, C_6D_6) δ: 19.2, 21.2, 21.7, 25.1, 27.0, 32.5, 33.2, 33.5, 37.0, 38.1, 38.2, 39.0, 42.6, 46.9, 61.0, 72.9, 114.4, 139.8; IR ν_{max} (film) cm^{-1}: 3457, 3074, 2998, 2947, 2868, 1640, 1461, 1462, 1414, 1384, 1365, 1332, 1295, 1268, 1240, 1207, 1183, 1159, 1110, 1089, 1068, 1053, 1012, 999, 973, 936, 906, 889, 869, 853, 821, 779.

(1R,2R*,4aS*,8aS*)-2-Acetoxy-1-(but-3-enyl)-2,5,5,8a-tetramethyldecahydronaphthalene (11).* A mixture of **10** (190 mg, 0.72 mmol), Et_3N (1.0 ml, 7.18 mmol), DMAP (261 mg, 2.15 mmol), and Ac_2O (0.34 ml, 3.59 mmol) in dry toluene (7.0 ml) was stirred for 2 days at 70°C. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (40 g of silica gel, hexane:EtOAc = 10:1) to give **11** (200 mg, 91%) as a colorless oil. EIMS *m/z*: 307 (0.3, MH^+), 306 (1.2, M^+), 291 (0.4, $M^+ - CH_3$), 264 (6.0, $M^+ - C_2H_2O$), 246 (18.0, $M^+ - C_2H_4O_2$), 231 (39.1), 205 (14.9), 192 (28.9), 177 (40.4), 149 (25.0), 137 (60.5), 136 (31.9), 123 (63.2), 109 (87.7), 95 (76.0), 81 (100), 69 (77.7), 55 (60.2), 43 (82.9), 41 (56.4); HRMS *m/z* (M^+): calcd. for $C_{20}H_{34}O_2$, 306.2559; found, 306.2588; ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.71 (3H, s), 0.78 (3H, s), 0.95 (3H, s), 1.75 (3H, s), 1.76 (3H, s), 1.00–1.74 (13H, m), 2.04–2.35 (3H, m), 4.98 (1H, dq, J = 10.2, 1.3 Hz), 5.09 (1H, dq, J = 17.1, 1.3 Hz), 5.87 (1H, ddt, J = 17.1, 10.2, 6.7 Hz); ^{13}C-NMR (67.8 MHz, C_6D_6) δ: 19.0, 20.2, 21.6, 22.3, 24.6, 27.6, 28.2, 33.1, 33.4, 36.4, 37.0, 37.2, 39.2, 42.5, 46.7, 57.3, 85.5, 114.1, 139.6, 169.4; IR ν_{max} (film) cm^{-1}: 3075, 2991, 2946, 2901, 2869, 1732, 1640, 1460, 1449, 1385, 1366, 1320, 1277, 1251, 1206,

1181, 1158, 1115, 1086, 1051, 1016, 974, 940, 908, 841, 820, 784.

(1R,4aS*,8aS*)-1-(But-3-enyl)-2-methylene-5,5,8a-trimethyldecahydronaphthalene (**12a**).* A solution of **11** (152 mg, 0.50 mmol) in 2,4,6-collidine (4.0 ml) was refluxed for 8 h. After being cooled, the reaction mixture was diluted with Et_2O (20 ml), and successively washed with 0.5 M HCl (2 × 10 ml), sat. aq. $NaHCO_3$ (10 ml) and brine (10 ml). The organic layer was concentrated under reduced pressure. The residue was purified by column chromatography (30 g of silica gel, hexane:EtOAc = 50:1) to give a 4.7:1 mixture of **12a** and **12b** (114 mg, 93%) as a colorless oil. Data are given for **12a** containing **12b**. EIMS *m/z*: 247 (2.2, MH^+), 246 (11.1, M^+), 231 (74.3, $M^+ - CH_3$), 217 (4.1), 205 (13.5), 192 (22.3), 177 (31.8), 149 (34.6), 137 (89.3), 123 (45.9), 109 (83.4), 95 (76.6), 81 (100), 69 (62.4), 55 (52.0), 43 (15.9), 41 (61.5); HRMS *m/z* (M^+): calcd. for $C_{18}H_{30}$, 246.2347; found, 246.2382; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.81 (3H, s), 0.87 (3H, s), 0.92 (3H, s), 1.00–2.26 (16H, m), 4.52 (1H, dd, J = 2.5, 1.5 Hz), 4.69 (1H, br. t, J = 2.5 Hz), 4.94 (1H, dq, J = 10.2, 1.3 Hz), 4.99 (1H, dq, J = 17.1, 1.3 Hz), 5.82 (1H, ddt, J = 17.1, 10.2, 6.7 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 19.3, 22.3, 22.4, 23.7, 25.8, 31.7, 32.5, 33.3, 33.6, 36.8, 42.8, 45.8, 57.7, 109.3, 114.0, 139.4, 149.1 (one ^{13}C signal overlaps); IR ν_{max} (film) cm^{-1}: 3068, 2939, 2868, 1642, 1460, 1443, 1415, 1389, 1380, 1366, 1340, 1279, 1260, 1225, 1209, 1169, 1143, 1101, 1043, 991, 978, 936, 909, 888, 852, 832, 808, 755. Partial NMR data were assigned for **12b**. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.86 (3H, s), 0.90 (3H, s), 0.92 (3H, s), 5.25 (1H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 18.9, 22.08, 22.12, 23.6, 24.3, 31.0, 32.9, 33.2, 35.9, 36.4, 38.0, 42.2, 42.9, 53.9, 114.1, 119.7, 136.6, 139.2.

(1R,4aS*,8aS*)-2-Methylene-1-(3-oxobutyl)-5,5,8a-trimethyldecahydronaphthalene (**13a**).* A mixture of **12a**/**12b** (112 mg, 0.45 mmol), $PdCl_2$ (8.1 mg, 0.05 mmol), and CuCl (45.1 mg, 0.05 mmol) in DMF (3.5 ml) and H_2O (0.5 ml) was stirred at room temperature for 5 h under an oxygen atmosphere. The reaction mixture was acidified with 0.5 M HCl (10 ml) and extracted with EtOAc (2 × 10 ml). The combined organic layers were successively washed with water (10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PTLC (hexane:EtOAc = 15:1) to give a 4.3:1 mixture of **13a** and **13b** (97.3 mg, 82%) as a colorless oil. Data are given for **13a** containing **13b**. EIMS *m/z*: 263 (10.8, MH^+), 262 (54.5, M^+), 247 (14.2, $M^+ - CH_3$), 244 (41.0), 229 (32.3), 204 (100), 189 (19.1), 177 (20.1), 137 (43.9), 123 (21.4), 109 (49.9), 95 (53.1), 81 (35.5), 69 (29.6), 55 (26.5), 43 (54.1), 41 (33.9); HRMS *m/z* (M^+): calcd. for $C_{18}H_{30}O$, 262.2297; found, 262.2314; ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.79 (3H, s), 0.84 (3H, s), 0.95 (3H, s), 1.69 (3H, s), 0.98–2.19 (16H, m), 4.51 (1H, dd, J = 2.5, 1.5 Hz), 4.73 (1H, br. t, J = 2.5 Hz); ^{13}C-NMR (67.8 MHz, C_6D_6) δ: 19.7, 20.4, 22.6, 22.8, 24.1, 29.8, 31.9, 33.4, 33.8, 37.1, 38.4, 42.1, 42.9, 46.0, 57.7, 110.1, 149.4, 206.2; IR ν_{max} (film) cm^{-1}: 3065, 2939, 2868, 2845, 1718, 1645, 1459, 1409, 1389, 1379, 1365, 1253, 1226, 1159, 1115, 1044, 976, 888. Partial NMR data were assigned for **13b**. ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.82 (3H, s), 0.87 (3H, s), 0.93 (3H, s), 1.67 (3H, s), 5.30 (1H, m); ^{13}C-NMR (67.8 MHz, C_6D_6) δ: 19.3, 22.4, 24.0, 24.7, 25.4, 29.6, 33.1, 33.5, 36.9, 37.2, 42.5, 43.1, 45.1, 54.2, 120.9, 136.0, 205.7 (one ^{13}C signal overlaps).

*Methyl (9βH)-labda-8(17),13(E)-dien-15-oate [methyl syn-copalate (**14a**)].* To a solution of $(EtO)_2P(O)CH_2CO_2Me$ (291 mg, 1.38 mmol) in dry THF (4.0 ml) was added NaH (60% in an oil, 56.0 mg, 1.38 mmol) at 4°C. The mixture was stirred at room temperature for 30 min under an argon atmosphere. To the resulting solution at −78°C was added a mixture of **13a**/**13b** (90.2 mg, 0.34 mmol) in dry THF (2.0 ml). The mixture was gradually allowed to warm to room temperature and then stirred overnight. After being diluted with sat. aq. NH_4Cl (5 ml) and water (10 ml), the reaction mixture was extracted with EtOAc (2 × 10 ml). The combined organic layers were washed with brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PTLC (hexane:EtOAc = 30:1) to give a mixture of (*Z*)-isomers (R_f = 0.63, 14.1 mg, 13%) and a 4.2:1 mixture of **14a** and **14b** (R_f = 0.58, 90.7 mg, 83%) as colorless oils. Data are given for **14a** containing **14b**. EIMS *m/z*: 319 (5.4, MH^+), 318 (20.1, M^+), 287 (6.8, $M^+ - CH_3O$), 271 (11.6), 244 (16.6), 229 (9.7), 205 (36.7), 177 (40.8), 163 (11.9), 149 (30.3), 137 (64.3), 109 (90.9), 95 (77.5), 81 (100), 69 (69.9), 55 (57.8), 43 (21.1), 41 (66.4); HRMS *m/z* (M^+): calcd. for $C_{21}H_{34}O_2$, 318.2559; found, 318.2548; ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.79 (3H, s), 0.85 (3H, s), 0.93 (3H, s), 0.95–2.12 (16H, m), 2.22 (3H, br. s), 3.44, (3H, s), 4.55 (1H, dd, J = 2.5, 1.5 Hz), 4.75 (1H, br. t, J = 2.5 Hz), 5.87 (1H, br. s); ^{13}C-NMR (67.8 MHz, C_6D_6) δ: 19.2, 19.7, 22.5, 22.7, 24.1, 24.6, 31.9, 33.5, 33.8, 37.1, 38.4, 39.9, 43.0, 46.2, 50.5, 58.0, 110.3, 115.8, 148.8, 160.6, 166.8; IR ν_{max} (film) cm^{-1}: 3067, 2945, 2869, 2845, 1723, 1651, 1457, 1435, 1388, 1381, 1359, 1323, 1279, 1224, 1204, 1188, 1148, 1115, 1060, 1034, 978, 922, 946, 888, 864, 809, 738. Partial NMR data were assigned for **14b**. ^{1}H-NMR (270 MHz, C_6D_6) δ: 0.83 (3H, s), 0.86 (3H, s), 0.92 (3H, s), 1.61 (3H, br. s), 2.22 (3H, br. s), 3.43 (3H, s), 5.26 (1H, m); ^{13}C-NMR (67.8 MHz, C_6D_6) δ: 19.24, 22.5, 22.4, 23.8, 24.1, 24.7, 29.9, 33.1, 33.4, 36.8, 37.2, 43.1, 43.2, 54.4, 115.8, 120.7, 136.0,

160.2, 166.7 (two ^{13}C signals overlap).

(±)-(9βH)-Labda-8(17),13(E)-dien-15-ol [(±)-syn-copalol, (±)-(5)]. To a solution of a mixture of **14a**/**14b** (85.3 mg, 0.27 mmol) in dry Et_2O (3.0 ml) was added DIBAH (a 0.93 M hexane solution, 0.86 ml, 0.80 mmol) at 4°C under an argon atmosphere. The mixture was stirred at the same temperature for 1 h. After successively adding sat. aq. Rochelle salt (3.0 ml), H_2O (3.0 ml), and EtOAc (5.0 ml) at 4°C, the reaction mixture was stirred for 1 h at room temperature and then extracted with EtOAc (2×10 ml). 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 column chromatography (10 g of silica gel, hexane:EtOAc=4:1) to give (±)-(**5**) containing the *endo*-isomer (77.0 mg, 99%, *exo*:*endo*=4.2:1) as a colorless oil. The desired *exo*-isomer was obtained as the sole isomer by HPLC separation under the following conditions: column, Wakosil-5C18 (ϕ5×250 mm, Wako); UV, 210 nm; solvent, 100% CH_3CN; flow rate, 1.5 ml/min; t_R: *endo*-isomer, 10.30 min; *exo*-isomer [(±)-(**5**)], 10.42 min. Repeated separation gave (±)-(**5**) (44.6 mg) and a mixture of both iomers (28.0 mg) as colorless oils. Data are given for (±)-(**5**). EIMS *m/z*: 291 (3.8, MH^+), 290 (14.1, M^+), 275 (37.0, M^+-CH_3), 272 (60.5, M^+-H_2O), 257 (89.0), 229 (10.6), 205 (13.6), 204 (35.9), 192 (49.6), 191 (53.6), 177 (65.4), 163 (15.7), 149 (39.6), 137 (55.7), 123 (46.5), 109 (100), 95 (81.6), 81 (86.1), 69 (63.1), 55 (47.4), 43 (17.9), 41 (54.3); HRMS *m/z* (M^+): calcd. for $C_{20}H_{34}O$, 290.2610; found, 290.2606; ^1H-NMR (270 MHz, $CDCl_3$) δ: 0.81 (3H, s), 0.88 (3H, s), 0.92 (3H, s), 1.67 (3H, br. s), 0.98–2.23 (17H, m), 4.16 (2H, d, J=6.9 Hz), 4.51 (1H, dd, J=2.5, 1.5 Hz), 4.69 (1H, br. t, J=2.5 Hz), 5.41 (1H, br. t, J=6.9 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 16.6, 19.2, 22.2, 22.4, 23.7, 24.5, 31.6, 33.3, 33.6, 36.8, 38.1, 38.2, 42.7, 45.8, 57.9, 59.5, 109.4, 122.8, 140.5, 149.1; IR ν_{max} (film) cm^{-1}: 3318, 3066, 2938, 2868, 1646, 1459, 1444, 1388, 1379, 1366, 1225, 1097, 1001, 887, 853, 810, 735. The spectral data for (±)-(**5**) were identical with those for **5**.[4] Partial NMR data were assigned for the *endo*-isomer of (±)-(**5**). ^1H-NMR (270 MHz, $CDCl_3$) δ: 0.87 (3H, s), 0.90 (6H, s), 1.67 (3H, br. s), 5.25 (1H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 16.5, 18.8, 22.1, 23.5, 24.2, 30.1, 32.9, 33.2, 36.4, 36.9, 41.7, 42.3, 42.8, 54.2, 119.4, 123.0, 136.5, 140.3 (two ^{13}C signals overlap).

Data for (4aS,4bS*,8aS*)-2,4b,8,8-Tetramethyl-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodeca-hydrophenanthren-2-ol (15).* EIMS *m/z*: 263 (7.5, MH^+), 262 (37.6, M^+), 245 (5.5, M^+-OH), 244 (22.3, M^+-H_2O), 229 (24.1), 204 (100), 189 (12.8), 175 (5.0), 161 (16.3), 123 (8.7), 109 (43.7), 95 (30.5), 81 (13.9), 69 (13.9), 55 (13.5), 43 (19.1), 41 (15.4); HRMS *m/z* (M^+): calcd. for $C_{18}H_{30}O$, 262.2296; found, 262.2261; ^1H-NMR (800 MHz, $CDCl_3$) δ: 0.89 (3H, s), 0.91 (3H, s), 0.95 (3H, s), 1.16 (1H, m), 1.19 (1H, m), 1.22 (3H, s), 1.24 (1H, m), 1.25 (1H, m), 1.34 (1H, br. dd, J=12.6, 2.7 Hz), 1.42 (2H, m), 1.44 (2H, m), 1.57 (1H, m), 1.74 (1H, m), 1.75 (1H, m), 1.88 (1H, m), 2.02 (1H, m), 2.02 (OH), 2.03 (1H, m), 2.13 (1H, dt, J=12.6, 1.6 Hz), 5.47 (1H, d, J=5.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 18.7, 22.0, 22.6, 23.8, 25.4, 28.9, 32.8, 33.4, 35.1, 36.6, 39.3, 42.9, 43.2, 50.4, 52.6, 70.4, 122.1, 137.2; IR ν_{max} (film) cm^{-1}: 3482, 2930, 2867, 1456, 1378, 1365, 1317, 1296, 1238, 1186, 1159, 1124, 1106, 1085, 1033, 1018, 978, 922, 882, 870, 810, 796, 740.

Acknowledgments

We are grateful to Mr. K. Watanabe and Dr. E. Fukushi (Faculty of Agriculture at Hokkaido University) for measuring the MS and NMR (500 MHz) data. Financial support by grant-aid for scientific research (No. 11460053) from the Ministry of Education, Science, Sports and Culture of Japan is gratefully acknowledged.

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