Stereocontrolled Synthesis of (+)-Nootkatone from (-)-β-Pinene

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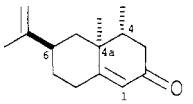
A stereocontrolled synthesis of (+)-nootkatone (1) starting from (-)-β-pinene is described. Methyl (1*R*,3*R*,5*R*)-3,6,6-trimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (**3**) prepared from nopinone (**2a**) was converted into (1*R*,2*S*,5*S*,8*S*,10*R*)-5,8,11,11-tetramethyl-7-methylene-3-oxatricyclo[8.1.1.0^{2,8}]dodecan-4-one (**8a**), a key intermediate for the introduction of the vicinal *cis*-dimethyl group by the following procedures: (1) borohydride reduction of **3** followed by methylation to give the corresponding 3-(1-hydroxy-1-methylethyl) 2-ol compound **6a**, (2) propionylation of **6a** followed by dehydration to give (1*R*,2*S*,3*S*,5*R*)-3,6,6-trimethyl-3-isopropenylbicyclo[3.1.1]hept-2-yl propionate (**7a**), and (3) allylic bromination of **7a** with NBS followed by intramolecular alkylation. Lithium–ethylamine reduction of enol ether **14** prepared from **8a** afforded (1*R*,2*S*,7*R*,8*S*,10*R*)-5,7,8,11,11-pentamethyl-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.0^{2,8}]dodec-4-ene (**15a**), bearing the desired vicinal *cis*-dimethyl group. In contrast, catalytic hydrogenation of **8a** yielded the trans isomer **9**. The conversion of **15a** into (+)-**1** in ca. 16% overall yield (from **2a**) was achieved by ozonolysis of **15a**, leading to (1*R*,2*S*,5*R*)-3-[(1*R*)-1-methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (**17b**), and subsequent intramolecular aldol cyclization of **17b** followed by dehydrochlorination.

There is a continuing interest in the development of efficient methods for the synthesis of (+)-nootkatone (**1**),[1]



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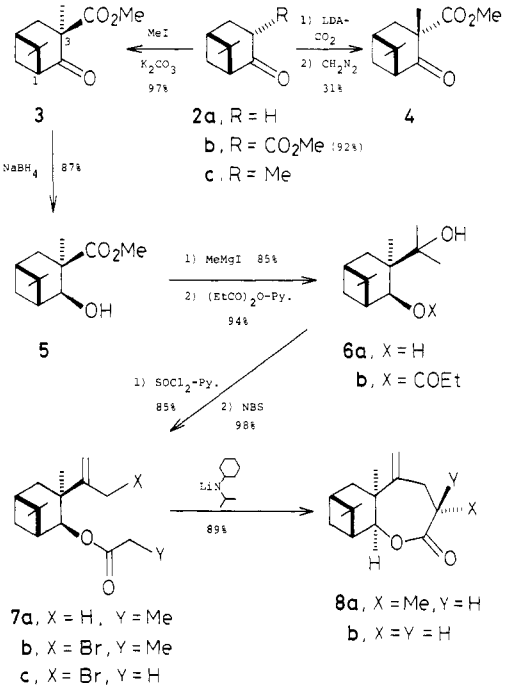
an eremophilane-type sesquiterpene, since it has been established that only the (+) enantiomer of **1** bears the characteristic flavor of grapefruit.[2] Most of the efforts for the synthesis[3] of the (+) isomer **1** by Robinson annulation of derivatives of (+)-nopinone[4,5a] and (-)-sabina ketone[5b] have been faced with difficulties in control of the configuration of the vicinal *cis*-dimethyl and the isopropenyl groups on the valencane skeleton. Yoshikoshi and his co-workers reported an example of the synthesis of (+)-**1** by employing the conjugate addition of allylsilanes to ethylidenenopinone to give a 4:1 ratio of the *cis*- and *trans*-methyl groups at C-4 and C-4a of (+)-**1**.[6] We now describe a complete stereoselective synthesis of (+)-**1** starting from (-)-β-pinene by reduction of an *exo*-methylene group attached to a seven-membered enol ether ring system as in the intermediate **14**. Thus, the major strategy for the synthesis of compound (+)-**1** involves conversion of keto ester **3** into cis-fused lactone **8a**, bearing an *exo*-methylene group, and the stereocontrolled reduction of the *exo*-methylene group to afford the vicinal *cis*-dimethyl group.

The starting compound **3** was prepared from nopinone (**2a**)[5a,7] by the usual methoxycarbonylation and subsequent

Scheme I



methylation of the β-keto ester **2b** with methyl iodide (89% yield from **2a**). The stereochemistry of the methyl group at C-3 of **3**[8] was corroborated by the comparison with stereoisomer **4** obtained by carbomethoxylation of 3-methylnopinone (**2c**)[9] on treatment with carbon dioxide–lithium diisopropylamide followed by diazomethane. Reduction of **3** with sodium borohydride gave only the 2β-alcohol **5** by the attack of hydride ion from less hindered α face.[9a] Methylation of the ester group of **5** with methylmagnesium iodide provided diol **6a** (74% yield from **5**), and subsequent propionylation of the secondary hydroxyl group of **6a** followed by dehydration gave **7a** (75%

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(2) (a) Berry, R. E.; Wagner, C. J., Jr.; Moshonas, M. G. *J. Food Sci.* **1967**, *32*, 75. (b) Haring, H. G.; Rijkens, F.; Boelens, H.; van der Gen, A. *J. Agric. Food Chem.* **1972**, *20*, 1018. (c) Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 477–8.

(3) For a synthesis of racemic **1**, see: Torii, S.; Inokuchi, T.; Handa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 887 and references cited therein.

(4) (a) Bessière, Y.; Barthélémy, M.; Thomas, A. F.; Pickenhagen, W.; Starkemann, C. *Nouv. J. Chim.* **1978**, *2*, 365. (b) Takagi, Y.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 517.

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(6) Yanami, T.; Miyashita, M.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 607.

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(8) Nopinone derivatives have been converted into 4-isopropenylcyclohexanones by the action of strong acids; see: Lewis, K. G.; Williams, G. J. *Aust. J. Chem.* **1968**, *21*, 2467.

(9) (a) Bessière-Chrétien, Y.; Meklati, B. *Bull. Chim. Soc. Fr.* **1971**, 2591. (b) McMurry, J. E.; Musser, J. H.; Ahmad, M. S.; Blaszczak, L. C. *J. Org. Chem.* **1975**, *40*, 1829.

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Scheme II

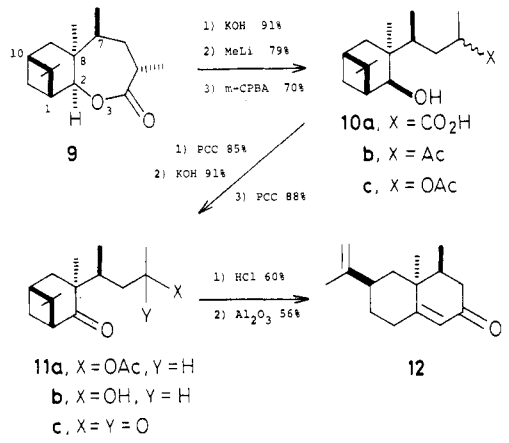
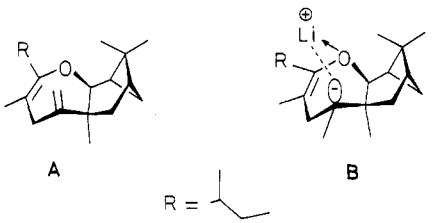


Chart I

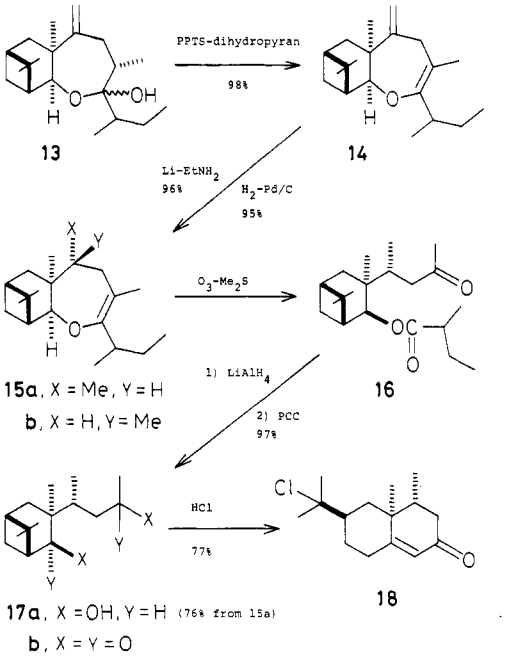


yield from **6a**). Allylic bromination of **7a** with *N*-bromosuccinimide gave **7b** (98% yield), and the intramolecular alkylation of **7b** on treatment with lithium *N*-cyclohexylisopropylamide afforded the desired **8a** in 89% yield. However, the treatment of **7c** under the same conditions resulted in **8b** in poor yield (10–15%; Scheme I).

Initially, we anticipated that a steric effect caused by the C-8 angular methyl of **8a** could be observed in the catalytic hydrogenation of the *exo*-methylene group to provide the vicinal *cis*-dimethyl group.[10] Hydrogenation of **8a** over platinum dioxide, however, afforded only lactone **9** bearing the trans-disposed dimethyl group in 97% yield. The configuration of the C-7 methyl of **9** was confirmed by the following transformation into the known 1,5-diketone **11c**.[6] Hydrolysis of **9** with aqueous potassium hydroxide, giving the carboxylic acid **10a**, and subsequent treatment with methyllithium afforded methyl ketone **10b** (71% yield from **9**). Baeyer–Villiger oxidation of ketone **10b** with *m*-chloroperbenzoic acid followed by treatment of **10c** with pyridinium chlorochromate (PCC)[11] afforded **11a** smoothly (60% yield from **10b**). Oxidation of **11b** obtained by hydrolysis of **11a** with PCC gave **11c** in 80% yield. (+)-4-Epinootkatone (**12**) was obtained in 35% yield by cyclization of **11c** with hydrogen chloride in acetic acid followed by dehydrochlorination on activated alumina at 60 °C[6] (Scheme II).

These results may be consistent with the influence of the geminal methyl groups on the cyclobutane ring in the stereochemical control of the catalytic hydrogenation. Lactone **9** may be produced by the attack of a hydrogen atom from the side opposite the geminal dimethyl group of **8a**. On the other hand, lithium metal reduction of the *exo*-methylene group of **14**, as a model compound prepared from **8a**, showed promise for the formation of the *cis*-dimethyl group. The preferred conformation of enol ether

Scheme III



14 is as shown in A, and thermodynamic control of the reduction will lead to a quasi-equatorial 7-methyl group.[12] The intermediate lithiated carbanion may be stabilized by chelation with oxygen as noted in B,[13] which may affect the stereochemical control in the protonation process (Chart I).[14] This hypothesis requires enol ether **14** which can be prepared from the lactone **8a**. The reaction of **8a** with *sec*-butyllithium at −78 °C provided lactol **13** in 96% yield. Dehydration of **13** was carried out by treatment with pyridinium *p*-toluenesulfonate (PPTS)[15] in dichloromethane in the presence of dihydropyran to give enol ether **14** in 98% yield. In this reaction it is essential to remove the liberated water with dipyranyl ether because of the tendency of **14** to revert to the lactol **13** in the acidic media.

Reduction of the *exo*-methylene group of **14** with an excess of lithium metal in liquid ethylamine at 0–5 °C gave successfully the desired **15a**, bearing the *cis*-dimethyl group, in 96% yield. In contrast, the catalytic hydrogenation of **14** over 10% palladium on carbon afforded exclusively the *trans*-dimethyl isomer **15b** in 95% yield.[16] Ozonolysis of **15a** and subsequent workup with dimethyl sulfide smoothly afforded keto ester **16**. Reduction of **16** with lithium aluminum hydride gave diol **17a** (76% yield from **15a**). Oxidation of **17a** with PCC provided the 1,5-diketone **17b** (97% yield) whose IR and ^{1}H NMR spectra were identical with those of an authentic specimen.[17] The cyclization was attended by the cleavage of the cyclobutane ring of **17b** and afforded (+)-nootkatone hydrochloride (**18**) in 77% yield. The usual dehydrochlorination of **18** with activated alumina in hexane[6,18] furnished (+)-**1** in 54%

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(16) **15b** was also converted into **11c** in the same manner as in the case of conversion of **15a** into **17b**.

(17) We are grateful to Professor A. Yoshikoshi, Tohoku University, for providing the ^{1}H NMR and IR spectra of **17b** and **11c**.

yield (from **17b**; Scheme III).

Experimental Section

Melting points are uncorrected, and boiling points are indicated without correction by the air-bath temperature. IR spectra were determined on a JASCO IRA-1 grating spectrometer. ^1H NMR spectra were obtained on a Hitachi R-24 (60 MHz) or a JEOL FX-100 (100 MHz) and ^{13}C NMR spectra on a JEOL FX-100 (25.05 MHz). Samples were dissolved in $CDCl_3$, and the chemical shift values are expressed in δ values relative to Me_4Si as an internal standard. Optical rotations were taken on a JASCO DIP-140 digital polarimeter in $CHCl_3$. Elemental analyses were performed in our laboratory.

Methyl (1*R*,3*S*,5*R*)-6,6-Dimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (2b). A suspension of nopinone **2a**[9] ($[\alpha]_D^{17}$ +17.4° (neat); 600 mg, 4.34 mmol) and NaH (209 mg, 8.7 mmol) in dimethyl carbonate (2 mL) was heated at 80–90 °C for 5 h. The mixture was quenched with cold aqueous 10% HCl and extracted with benzene–AcOEt (1:1). The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (SiO_2; hexane–AcOEt, 7:1) to give 720 mg (92%) of **2b**: bp 117 °C (12.5 mm); $[\alpha]_D^{20}$ +24.4° (*c* 1.9); IR (neat) 1745 (ester C=O), 1713 (C=O), 1650, 1615 cm^{-1}; ^1H NMR (60 MHz) δ 0.89, 0.96 (s, 3, CH_3), 1.05–2.75 (m, 6, CH_2, CH), 1.35 (s, 3, CH_3), 3.35–4.25 (m, COCHCOO), 3.77, 3.79 (s, 3, OCH_3), 11.90 (br s, C=COH). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.26.

Methyl (1*R*,3*R*,5*R*)-3,6,6-Trimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (3). To a suspension of **2b** (2.0 g, 10.2 mmol) and K_2CO_3 (7.4 g, 53.5 mmol) in acetone (70 mL) was added MeI (1.74 g, 12.3 mmol).[19] The mixture was stirred at room temperature for 1 h and at reflux for 24 h, and the solids were filtered off. The filtrate was concentrated, and the residue was chromatographed (SiO_2; hexane–AcOEt, 5:1) to give 2.07 g (97%) of **3**: mp 41–42 °C; $[\alpha]_D^{19}$ +31.8° (*c* 1.4); IR (Nujol) 1728 (ester C=O), 1704 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 0.97, 1.35, 1.68 (s, 9, CH_3), 1.78 (d, J = 11 Hz, 1, CH_2), 1.96 (dd, J = 15, 4 Hz, 1, CH_2), 2.16–2.86 (m, 4, CH_2, CH), 3.76 (s, 3, OCH_3); ^{13}C NMR δ 21.7 (q, C-9), 26.5 (t, C-7), 26.7 (q, C-8), 29.9 (q, C-10), 34.2 (t, C-4), 41.1 (d, C-5), 42.7 (s, C-6), 52.7 (q, OCH_3), 52.9 (s, C-3), 58.7 (d, C-1), 173.8 (s, COO), 211.1 (s, C-2). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.39; H, 8.54.

Methyl (1*R*,3*S*,5*R*)-3,6,6-Trimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (4). To a solution of $(i\text{-}Pr)_2NLi$ prepared from a hexane solution of 1.5 M BuLi (0.8 mL, 1.2 mmol) and $(i\text{-}Pr)_2NH$ (133.5 mg, 1.32 mmol) in THF (3 mL) was added a solution of **2c** (100 mg, 0.66 mmol) in THF (2 mL) at −70 °C. After being stirred at −70 °C for 1 h and at −10 °C for 1 h, the solution was treated with excess gaseous CO_2 for 1 h. The mixture was quenched with ice–water, acidified with cold aqueous 10% HCl, and extracted with benzene–AcOEt (1:1). The usual workup and esterification of the crude product with CH_2N_2 gave 62 mg (62%) of (1*R*,3*R*,5*R*)-3-methylnopinone[5a] (R_f 0.7; hexane–AcOEt, 7:1) and 43 mg (31%) of **4** (R_f 0.48) after chromatography (SiO_2; hexane–AcOEt, 7:1). **4**: bp 92–93 °C (3 mm); $[\alpha]_D^{20}$ +152.5° (*c* 1.5); IR (neat) 1738 (ester C=O), 1715 (C=O); ^1H NMR (100 MHz) δ 0.77, 1.35, 1.44 (s, 9, CH_3), 1.47 (dt, J = 15, 1.5 Hz, 1, CH_2), 2.10–2.60 (m, 2, CH_2), 2.71 (t, J = 5 Hz, 1, CH), 2.98 (dd, J = 14, 5 Hz, 1, CHCO), 3.71 (s, 3, OCH_3); ^{13}C NMR δ 22.4 (q, C-9, C-10), 25.0 (t, C-7), 26.4 (q, C-8), 34.7 (t, C-4), 41.2 (d, C-5), 45.6 (s, C-6), 52.4 (s, C-3), 53.0 (q, OCH_3), 58.5 (d, C-1), 175.0 (s, COO), 209.9 (s, C-2). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.50; H, 8.55.

Methyl (1*R*,2*S*,3*R*,5*R*)-2-Hydroxy-3,6,6-trimethylbicyclo[3.1.1]heptane-3-carboxylate (5). To a solution of **3** (210 mg, 1.0 mmol) in MeOH (2 mL) was added a solution of $NaBH_4$ (73 mg, 1.9 mmol) in H_2O (0.5 mL) at 5 °C. The mixture was stirred at room temperature for 12 h, quenched with aqueous 10% AcOH, and extracted with benzene–AcOEt (1:1). The usual workup and chromatography (SiO_2; hexane–AcOEt, 5:1) gave 185 mg (87%) of **5**: bp 72–73 °C (0.015 mm); $[\alpha]_D^{25}$ +27.5° (*c* 2.1); IR (neat) 3520 (OH), 1725, 1700 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.99, 1.23, 1.54 (s, 9, CH_3), 1.20–2.32 (m, 5, CH_2, CH), 2.98 (d, J = 14 Hz, 1, CH), 3.10 (br, 1, OH), 3.76 (s, 3, OCH_3), 4.10 (d, J = 4 Hz, 1, CH—O). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.92; H, 9.42.

(1*R*,2*S*,3*R*,5*R*)-3-(1-Hydroxy-1-methylethyl)-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (6a). To a solution of methylmagnesium iodide prepared from MeI (6.5 g, 45.8 mmol) and Mg (1.0 g, 41.2 mmol) in ether (45 mL) was added a solution of **5** (1.95 g, 9.19 mmol) in ether (10 mL) at 0–5 °C. After the mixture was stirred at reflux for 12 h, most of the solvent was removed by distillation, and the residue was heated at 75–80 °C for 24 h, quenched with cold aqueous 10% NH_4Cl, and extracted with benzene–AcOEt (1:1). The usual workup and chromatography (SiO_2; hexane–AcOEt, 3:1) gave 1.66 g (85%) of **6a**: mp 98–99 °C (from hexane); $[\alpha]_D^{26}$ +25.9° (*c* 1.64); IR (Nujol) 3230 cm^{-1} (OH); ^1H NMR (60 MHz) δ 1.21 (s, 3, CH_3), 1.25 (s, 9, CH_3), 1.30–2.27 (m, 5, CH_2, CH), 1.46 (s, 3, CH_3), 2.54 (d, J = 14 Hz, 1, CH), 3.57 (br, 1, OH), 4.27 (d, J = 4 Hz, 1, CH–O), 4.70 (br, 1, OH). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.75; H, 11.33.

(1*R*,2*S*,3*R*,5*R*)-3-(1-Hydroxy-1-methylethyl)-3,6,6-trimethylbicyclo[3.1.1]hept-2-yl Propionate (6b). A solution of **6a** (6.2 g, 29.2 mmol) and propionic anhydride (11.4 g, 87.6 mmol) in pyridine (24 mL) was heated at 100 °C for 8 h. The mixture was poured into cold aqueous 5% $NaHCO_3$ and extracted with benzene–AcOEt (1:1). The usual workup gave 7.4 g (94%) of **6b**: bp 85 °C (0.0075 mm); $[\alpha]_D^{26}$ +49.5° (*c* 1.7); IR (neat) 3560 (OH), 1735 cm^{-1} (ester C=O); ^1H NMR (60 MHz) δ 0.90–2.45 (m, 10, CH_3, CH_2, CH), 1.17 (s, 3, CH_3), 1.21 (s, 6, CH_3), 1.24 (s, 3, CH_3), 1.34 (s, 3, CH_3), 2.67 (d, J = 14 Hz, 1, CH), 3.45 (br s, 1, OH), 5.42 (d, J = 4 Hz, 1, CH—O). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.70; H, 10.57.

(1*R*,2*S*,3*S*,5*R*)-3,6,6-Trimethyl-3-(1-methylvinyl)bicyclo[3.1.1]hept-2-yl Propionate (7a). To a solution of **6b** (6.2 g, 23.1 mmol) in pyridine (20 mL) was added $SOCl_2$ (4.9 g, 41.3 mmol) at −10 °C. After being stirred at −10 °C for 3 h and at room temperature for 5 h, the mixture was poured into cold water and extracted with benzene–AcOEt (1:1). The usual workup and chromatography (SiO_2; hexane–AcOEt, 10:1) gave 4.9 g (85%) of **7a**: bp 76–77 °C (0.015 mm); $[\alpha]_D^{25}$ +5.8° (*c* 1.66); IR (neat) 3070, 1725 (ester C=O), 1635 (C=C), 882 cm^{-1}; ^1H NMR (60 MHz) δ 0.93, 1.19, 1.41, 1.67 (s, 12, CH_3), 0.90–2.45 (m, 7, CH_2, CH), 1.08 (t, J = 8 Hz, 3, CH_3), 2.65 (d, J = 14 Hz, 1, CH), 4.87, 5.00 (br s, 2, H_2C=C), 5.26, (d, J = 4 Hz, 1, CH—O); ^{13}C NMR δ 9.0 (q), 21.0 (q), 23.4 (q), 24.6 (t), 27.0 (q), 28.4 (t), 34.4 (t), 36.3 (q), 38.4 (s), 40.3 (s), 41.3 (d), 45.9 (d), 81.1 (d), 109.5 (t), 148.9 (s), 173.0 (s). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.91; H, 10.40.

(1*R*,2*S*,3*S*,5*R*)-3-[1-(Bromomethyl)vinyl]-3,6,6-trimethylbicyclo[3.1.1]hept-2-yl Propionate (7b). A suspension of **7a** (1.03 g, 4.11 mmol) and *N*-bromosuccinimide (808 mg, 4.54 mmol) in CCl_4 (15 mL) was gently refluxed for 15 h. The mixture was concentrated, and the residue was passed through a short silica gel column. Elution with hexane–AcOEt (5:1) gave 1.32 g (98%) of **7b**: bp 102 °C (0.015 mm); $[\alpha]_D^{17}$ −60.1° (*c* 1.9); IR (neat) 3080, 1726 (ester C=O), 1630 cm^{-1} (C=C); ^1H NMR (60 MHz) δ 0.89, 1.19, 1.56 (s, 9, CH_3), 1.07 (t, J = 7.5 Hz, 3, CH_3), 1.10–2.75 (m, 8, CH_2, CH), 3.71, 4.01 (d, J = 11 Hz, 2, CH_2Br), 5.35 (d, J = 4 Hz, 1, CH—O), 5.48, 5.56 (br s, 2, H_2C=C); ^{13}C NMR δ 8.9 (q), 23.3 (q), 24.5 (t), 26.8 (q), 28.2 (t), 33.2 (t), 34.5 (t), 36.5 (d), 38.0 (s), 41.1 (d), 41.1 (s), 45.6 (d), 81.2 (d), 117.0 (t), 150.0 (s), 173.1 (s). Anal. Calcd for $C_{16}H_{25}BrO_2$: C, 58.36; H, 7.65. Found: C, 58.24; H, 7.68.

(1*R*,2*S*,5*S*,8*S*,10*R*)-5,8,11,11-Tetramethyl-7-methylene-3-oxatricyclo[8.1.1.0^{2,8}]dodecan-4-one (8a). To a solution of lithium *N*-isopropylcyclohexylamide prepared from a hexane solution of 1.6 M BuLi (3.0 mL, 4.8 mmol) and *N*-isopropylcyclohexylamine (690 mg, 4.86 mmol) in THF (30 mL) was added a solution of **7b** (692 mg, 2.1 mmol) in THF (5 mL) at −70 °C. After the mixture was stirred at −50 °C for 30 min, HMPA (2.5 mL) was added, and the mixture was warmed gradually to room temperature over about 2 h, quenched with cold aqueous 10% NH_4Cl, and extracted with benzene–AcOEt (1:1). The usual workup and chromatography (SiO_2; hexane–AcOEt, 5:1) gave 470 mg (89%) of **8a**: mp 114–115 °C (from hexane); $[\alpha]_D^{22}$ −29° (*c*

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0.9); IR (Nujol) 3080, 1730 (ester C=O), 1635 (C=C), 905 cm^{-1}; ^1H NMR (100 MHz) δ 0.96, 1.24, 1.51 (s, 9, CH_3), 1.10–3.16 (m, 9, CH_2, CH), 1.20 (d, J = 6 Hz, 3, CH_3), 4.63 (d, J = 4 Hz, 1, CH—O), 5.07, 5.15 (br s, 2, H_2C=C); ^{13}C NMR δ 16.4 (q), 23.1 (q), 24.5 (t), 26.6 (q), 34.3 (q), 34.6 (d), 34.7 (t), 38.1 (s), 39.9 (s), 40.5 (t), 41.2 (d), 46.5 (d), 87.1 (d), 113.4 (t), 147.3 (s), 176.2 (s). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.23; H, 9.92.

(1*R*,2*S*,5*S*,7*S*,8*S*,10*R*)-5,7,8,11,11-Pentamethyl-3-oxatricyclo[8.1.1.0^{2,8}]dodecan-4-one (9). A suspension of **8a** (130 mg, 0.52 mmol) and PtO_2 (30 mg) in AcOEt (5 mL) was treated with excess H_2 at room temperature for 15 h. The catalyst was filtered off, and the filtrate was concentrated to give 127 mg (97%) of **9**: mp 113–114 °C (from hexane); $[\alpha]^{24}_D$ +4.1° (*c* 1.08); IR (Nujol) 1720 cm^{-1} (ester C=O); ^1H NMR (100 MHz) δ 1.13, 1.27, 1.48 (s, 9, CH_3), 1.19, 1.32 (d, J = 6 Hz, 6, CH_3), 1.10–3.08 (m, 10, CH_2, CH), 4.74 (d, J = 4 Hz, 1, CH—O); ^{13}C NMR δ 17.6 (q), 20.7 (q), 21.9 (q), 25.2 (t), 28.0 (q), 32.8 (d), 35.0 (t), 36.5 (t), 36.9 (s), 37.4 (q), 37.9 (s), 42.1 (d), 42.1 (d), 46.6 (d), 87.6 (d), 177.3 (s). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.65; H, 10.66.

(4*S*)-4-[(1*R*,2*S*,3*S*,5*R*)-2-Hydroxy-3,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-2-methylpentanoic Acid (10a). Hydrolysis of **9** (127 mg, 0.5 mmol) in an MeOH (5 mL)–KOH (360 mg, 6.4 mmol)–H_2O (0.5 mL) system was carried out at 65–70 °C for 14 h. The mixture was acidified with aqueous 5% HCl and extracted with benzene–AcOEt (1:1). The usual workup gave 124 mg (91%) of **10a**: $[\alpha]^{24}_D$ −14.5° (*c* 1.2); IR (neat) 3600–2500 (COOH), 3420 (OH), 1705 cm^{-1} (COO); ^1H NMR (60 MHz) δ 0.97, 1.08, 1.20 (s, 9, CH_3), 1.07, 1.21 (d, J = 6 Hz, 6, CH_3), 1.00–2.85 (m, 10, CH_2, CH), 3.83 (m, 1, CH–O), 6.44 (br, 2, OH, COOH). Attempts at further purification for a satisfactory elemental analysis were unsuccessful.

(1*R*,2*S*,3*S*,5*R*)-3-[(1*S*)-1,3-Dimethyl-4-oxopentyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (10b). To a solution of **10a** (70 mg, 0.26 mmol) in ether (3 mL) was added an ethereal 1.05 M MeLi solution (1.25 mL, 1.3 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, quenched with cold aqueous 10% NH_4Cl, and extracted with ether. The usual workup and chromatography (SiO_2; hexane–AcOEt, 7:1) gave 55 mg (79%) of **10b**: bp 95–96 °C (0.03 mm); $[\alpha]^{29}_D$ +11.4° (*c* 1.6); IR (neat) 3460 (OH), 1704 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.97–1.21 (m, 15, CH_3), 1.10–2.90 (m, 11, CH_2, CH, OH), 2.13, 2.14 (s, 3, $COCH_3$), 3.92 (m, 1, CH—O). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.67; H, 11.36.

(1*R*,2*S*,3*S*,5*R*)-3-[(1*S*)-3-Acetoxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (10c). A solution of **10b** (55 mg, 0.21 mmol) and MCPBA (108 mg, 0.63 mmol) in $CDCl_3$ (3 mL) was stirred at 5–10 °C for 36 h. The mixture was diluted with $CHCl_3$, washed with cold aqueous 5% NaOH, dried (Na_2SO_4), and concentrated. The residue was chromatographed (SiO_2; hexane–AcOEt, 5:1) to give 41 mg (70%) of **10c**: bp 102–103 °C (0.03 mm); $[\alpha]^{30}_D$ −14.1° (*c* 1.13); IR (neat) 3470, 3370 (OH), 1735, 1708 cm^{-1} (ester C=O); ^1H NMR (100 MHz) δ 0.91–1.31 (m, 15, CH_3), 1.10–2.45 (m, 9, CH_2, CH), 2.03 (s, 3, $COCH_3$), 3.69 (br s, 1, OH), 3.98 (d, J = 4 Hz, 1, CH—O), 4.77–5.31 (m, 1, CH–O). Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.58; H, 10.63.

(1*R*,3*S*,5*R*)-3-[(1*S*)-3-Acetoxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (11a). To a suspension of PCC (200 mg, 0.93 mmol) and AcONa (82 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added a solution of **11c** (44 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at 0–5 °C. The mixture was stirred at 5 °C for 30 min and at room temperature for 2 h. The usual workup and chromatography (SiO_2; hexane–AcOEt, 4:1) gave 38 mg (85%) of **11a**: bp 85–86 °C (0.01 mm); $[\alpha]^{29}_D$ −15.6° (*c* 1.05); IR (neat) 1735 (ester C=O), 1700 cm^{-1} (C=O); ^1H NMR (100 MHz) δ 0.89 (s, 3, CH_3), 1.15–2.66 (m, 12, CH_2, CH), 1.19–1.34 (m, 9, CH_3), 2.02, 2.04 (s, 3, $COCH_3$), 4.82–5.18 (m, 1, CH—O). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.63; H, 10.11.

(1*R*,3*S*,5*R*)-3-[(1*S*)-3-Hydroxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (11b). Similar hydrolysis of **11a** (36 mg, 0.13 mmol) as described above gave 30 mg (91%) of **11b**: bp 85–86 °C (0.05 mm); $[\alpha]^{18}_D$ −31.5° (*c* 0.7); IR (neat) 3395 (OH), 1695 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.90 (s, 3, CH_3), 1.07–1.35 (m, 6, CH_3), 1.28, 1.32 (s, 6, CH_3), 1.40–2.72 (m, 10, CH_2, CH, OH), 3.66–4.10 (m, 1, CH—O). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.56; H, 10.96.

(1*R*,3*S*,5*R*)-3-[(1*S*)-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (11c). Similar oxidation of **11b** (30 mg, 0.13 mmol) with PCC as described above gave 27 mg (88%) of **11c**: mp 106–107 °C (lit.[6] mp 106–107 °C); $[\alpha]^{30}_D$ +22° (*c* 1.1); ^{13}C NMR δ 16.5 (q), 22.6 (q), 26.2 (t), 26.6 (q), 27.0 (q), 30.4 (q), 36.2 (t), 37.0 (d), 41.9 (d), 42.9 (s), 45.6 (s), 47.7 (t), 60.0 (d), 208.3 (s), 218.2 (s). IR and ^1H NMR spectral data were identical with those of an authentic specimen.[17]

(4*S*,4a*S*,6*R*)-4,4a,5,6,7,8-Hexahydro-6-isopropenyl-4,4a-dimethyl-2(3*H*)-naphthalenone (4-Epinootkatone, 12). The diketone **11c** was converted to 4-epinootkatone hydrochloride by the literature method[6] in 60% yield: bp 98–101 °C (0.025 mm) [lit.[6] bp 135–145 °C (0.2 mm)]; $[\alpha]^{17}_D$ +82.2° (*c* 0.68); ^{13}C NMR δ 15.8 (q), 24.6 (q), 29.0 (t), 30.3 (q), 30.7 (q), 32.5 (t), 36.2 (t), 39.2 (d), 39.4 (s), 42.4 (t), 45.2 (d), 73.8 (s), 123.4 (d), 167.1 (s), 199.2 (s). The following treatment of 4-epinootkatone hydrochloride with activated alumina in hexane at 60 °C for 24 h gave **12**: 56%;[6] bp 111–113 °C (1.5 mm); $[\alpha]^{16}_D$ +83° (*c* 0.28) (lit.[6] +85°); ^{13}C NMR δ 15.8 (q), 21.0 (q), 24.5 (q), 32.7 (t), 33.0 (t), 39.1 (d), 39.6 (s), 39.7 (s), 40.0 (d), 42.4 (t), 109.3 (t), 123.5 (d), 148.9 (s), 168.2 (s), 199.4 (s).

(1*R*,2*S*,5*S*,8*S*,10*R*)-5,8,11,11-Tetramethyl-7-methylene-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.0^{2,8}]dodecan-4-ol (13). To a solution of **8a** (186 mg, 0.75 mmol) in THF (7 mL) was added a hexane solution of 1.0 M *sec*-BuLi (0.78 mL, 0.78 mmol) at −78 °C. The mixture was stirred at −78 °C for 45 min, quenched with cold aqueous 10% NH_4Cl, and extracted with benzene–AcOEt (1:1). The usual workup and chromatography (SiO_2; hexane–AcOEt, 7:1) gave 219 mg (96%) of **13**: bp 145–146 °C (0.025 mm); $[\alpha]^{17}_D$ +12.4° (*c* 1.4); IR (neat) 3480 (OH), 3080, 1669 (C=O), 1624 (C=C), 1020, 988, 885 cm^{-1}; ^1H NMR (60 MHz) δ 0.76–1.29 (m, 9, CH_3), 0.98, 1.21, 1.39 (s, 9, CH_3), 1.30–3.18 (m, 13, CH_2, CH, OH), 4.05 (m, 1, CH—O), 4.97, 5.19 (br s, 2, H_2C=C). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.48; H, 11.17.

(1*R*,2*S*,8*S*,10*R*)-5,8,11,11-Tetramethyl-7-methylene-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.0^{2,8}]dodec-4-ene (14). A solution of **13** (108 mg, 0.35 mmol) and dihydropyran (460 mg, 5.5 mmol) in CH_2Cl_2 (7 mL) containing pyridinium *p*-toluenesulfonate (5 mg) was stirred at room temperature for 5 h. The mixture was poured into cold aqueous 5% $NaHCO_3$ and worked up in the usual manner to give 99.5 mg (98%) of **14** after chromatography (SiO_2, hexane): bp 81–82 °C (0.02 mm); $[\alpha]^{18}_D$ −37.5° (*c* 0.94); IR (neat) 3080, 1680 (C=C), 1628 (C=C), 1228, 1180, 1131, 900 cm^{-1}; ^1H NMR (60 MHz) δ 0.83 (t, 3, CH_3), 0.88 (d, J = 6 Hz, 3, CH_3), 0.94, 1.24, 1.42 (s, 9, CH_3), 1.10–3.38 (m, 11, CH_2, CH), 1.58 (s, 3, CH_3C=C), 3.88 (d, J = 4.5 Hz, 1, CH—O), 4.89, 4.99 (br s, 2, H_2C=C). Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.35; H, 11.26.

(1*R*,2*S*,7*R*,8*S*,10*R*)-5,7,8,11,11-Pentamethyl-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.0^{2,8}]dodec-4-ene (15a). To a blue solution of Li (80 mg, 11.4 mmol) in $EtNH_2$ (ca. 12 mL) was added a solution of **14** (156 mg, 0.54 mmol) and *t*-BuOH (400 mg, 5.41 mmol) at −30 °C. After the mixture was stirred at −30 °C for 30 min, additional Li (120 mg, 17.1 mmol) was added. The mixture was stirred at −20 to −10 °C for 2 h, was allowed to stand at room temperature until most of the $EtNH_2$ had evaporated, and was poured into ice–water. The usual workup and chromatography (SiO_2, hexane) gave 151 mg (96%) of **15a**: bp 95–96 °C (0.03 mm); $[\alpha]^{18}_D$ −37.5° (*c* 0.94); IR (neat) 1682 (C=C), 1457, 1386, 1229, 1080, 1010 cm^{-1}; ^1H NMR (60 MHz) δ 0.86, (d, J = 6 Hz, 3, CH_3), 0.89 (d, J = 6 Hz, 3, CH_3), 0.99 (t, 3, CH_3), 0.99, 1.09, 1.23 (s, 9, CH_3), 1.10–2.95 (m, 12, CH_2, CH), 1.50 (s, 3, CH_3C=C), 3.72 (d, J = 4 Hz, 1, CH—O). Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.89; H, 11.90.

(1*R*,2*S*,7*S*,8*S*,10*R*)-5,7,8,11,11-Pentamethyl-4-(1-methylpropyl)-3-oxatricyclo[8.1.1.0^{2,8}]dodec-4-ene (15b). Hydrogenation of **14** (50 mg, 0.17 mmol) over 10% Pd/C (30 mg) with excess H_2 was carried out in AcOEt (5 mL) at room temperature for 12 h to give 48 mg (95%) of **15b**: bp 84–86 °C (0.02 mm); $[\alpha]^{15}_D$ −17.0° (*c* 0.83); IR (neat) 1672 (C=C), 1455, 1225, 1135, 1076, 1015 cm^{-1}; ^1H NMR (60 MHz) δ 0.80 (t, 3, CH_3), 0.87 (d, J = 6.5 Hz, 3, CH_3), 0.91 (d, J = 6.5 Hz, 3, CH_3), 1.10, 1.21, 1.34 (s, 9, CH_3), 1.15–3.03 (m, 12, CH_2, CH), 1.52 (s, 3, CH_3C=C), 3.93 (m, 1, CH—O). Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.80; H, 11.91.

(1*R*,2*S*,3*S*,5*R*)-3-[(1*R*)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]hept-2-yl 2-Methylbutyrate (16). Into a solution of **15a** (131 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) and MeOH (4 mL) was passed excess ozone at -78 °C for 1 h. After the excess ozone was removed by bubbling through with nitrogen gas for 30 min, dimethyl sulfide (280 mg, 4.5 mmol) was added. The mixture was stirred at -70 °C for 1 h and at room temperature for 12 h and concentrated. The residue was chromatographed (SiO_2; hexane-AcOEt, 7:1) to give 109 mg (75%) of **16** (R_f 0.51, Merck F 254; hexane-AcOEt, 5:1) and 31 mg of unidentified compound (R_f 0.34). **16**: bp 82-83 °C (0.02 mm); $[\alpha]^{26}_D$ +34.0° (*c* 1.5); IR (neat) 1720 (ester C=O), 1705 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.82 (t, 3, CH_3), 0.87 (d, J = 6 Hz, 3, CH_3), 1.03 (s, 3, CH_3), 1.06 (d, J = 6 Hz, 3, CH_3), 1.18 (s, 6, CH_3), 1.20-3.00 (m, 12, CH_2, CH), 2.06 (s, 3, $COCH_3$), 3.14 (d, J = 4 Hz, 1, CH—O). Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.22; H, 10.68.

(1*R*,2*S*,3*S*,5*R*)-3-[(1*R*)-3-Hydroxy-1-methylbutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (17a). To a suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in ether (2 mL) was added a mixture of **16** (109 mg, 0.34 mmol) and 31 mg of unidentified compound obtained above in ether (5 mL) at 0 °C. The mixture was stirred at 2-5 °C for 1 h and at room temperature for 2 h, quenched with AcOEt (0.5 mL) and aqueous 5% $NaHCO_3$, and worked up in the usual manner to give 82 mg (76% yield from **15a**) of **17a**: mp 96-97 °C; $[\alpha]^{19}_D$ +27.0° (*c* 1.1); IR (Nujol) 3350 (OH), 3280 (OH), 1458, 1136, 1031 cm^{-1}; ^1H NMR (60 MHz) δ 0.94 (d, J = 7 Hz, 3, CH_3), 1.04, 1.11 (s, 6, CH_3), 1.17 (d, J = 7 Hz, 3, CH_3), 1.21 (s, 3, CH_3), 1.20-2.40 (m, 9, CH_2, CH), 2.87 (br s, 2, OH), 3.66-3.98 (m, 1, CH-O), 4.08 (d, J = 4 Hz, 1, CH-O). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.75; H, 11.55.

(1*R*,3*S*,5*R*)-3-[(1*R*)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (17b). To a suspension of PCC (410 mg, 1.9 mmol) and AcONa (312 mg, 3.5 mmol) in CH_2Cl_2 (7 mL) was added a solution of **17a** (65 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) at 0-5 °C. After being stirred at 0-5 °C for 1 h and at room temperature for 3 h, the mixture was worked up as described in the preparation of **11a** to give 62 mg (97%) of **17b**: bp 74-75 °C (0.025 mm) [lit.[6] mp 100 °C (0.1 mm)]; $[\alpha]^{15}_D$ +94.0° (*c* 0.5) (lit.[6] +120°); ^{13}C NMR δ 16.4 (q), 22.7 (q), 24.9 (q), 25.9 (t), 26.4 (q), 30.4 (q), 35.3 (d), 37.0 (t), 41.8 (d), 42.8 (s), 44.8 (s), 47.4 (t), 59.6 (d), 208.3 (s), 219.9 (s). IR and ^1H NMR spectral data were identical with those of an authentic specimen.[17]

(4*R*,4a*S*,6*R*)-4,4a,5,6,7,8-Hexahydro-6-(1-chloro-1-methylethyl)-4,4a-dimethyl-2(3*H*)-naphthalenone (Nootkatone Hydrochloride, 18). The diketone **17b** was converted to **18** by the literature method[6] in 77% yield: mp 84-85 °C (lit.[6] mp 84-85.5 °C); $[\alpha]^{16}_D$ +159.5° (*c* 0.43) (lit. +146°,[5b] +160°[6]); ^{13}C NMR δ 15.0 (q), 16.9 (q), 28.1 (t), 30.1 (q), 30.5 (q), 32.6 (t), 39.1 (s), 40.0 (t), 40.4 (d), 42.0 (t), 45.3 (d), 73.7 (s), 124.5 (s), 170.0 (d), 199.0 (s).

(4*R*,4a*S*,6*R*)-4,4a,5,6,7,8-Hexahydro-6-isopropenyl-4,4a-dimethyl-2(3*H*)-naphthalenone ((+)-Nootkatone, 1). The treatment of **18** with activated alumina in hexane at 60 °C for 24 h afforded a mixture of (+)-**1** and isonootkatone (91:1) in 76% yield by HPLC analysis (Waters Associates Model 6000A; μ-Porasil, 7.8 × 30 cm column; 10:1 hexane-AcOEt at 1.5 mL/min at room temperature): mp 29-30 °C (lit. mp 36-37,[1a] 28-30 °C[4b]); $[\alpha]^{15}_D$ +184° (*c* 0.94) (lit. +195.5°,[1a] +188°[6]). IR, ^1H NMR, ^{13}C NMR[20] spectral data were identical with those of the authentic sample of (+)-**1**.[21]

Registry No. **1**, 4674-50-4; **2a**, 38651-65-9; **2b**, 83198-84-9; **2c**, 29362-79-6; **3**, 73675-69-1; **4**, 83198-85-0; **5**, 83152-42-5; **6a**, 81550-51-8; **6b**, 83152-43-6; **7a**, 81550-52-9; **7b**, 81550-53-0; **7c**, 83152-44-7; **8a**, 81550-54-1; **8b**, 83152-45-8; **9**, 81550-55-2; **10a**, 81550-56-3; **10b**, 81550-57-4; **10c**, 83152-46-9; **11a**, 81550-58-5; **11b**, 83152-47-0; **11c**, 72521-65-4; **12**, 27621-99-4; **13**, 83152-48-1; **14**, 83152-49-2; **15**, 83152-50-5; **16**, 83152-51-6; **17a**, 81550-62-1; **17b**, 72453-41-9; **18**, 72453-44-2; dimethyl carbonate, 616-38-6.

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Regio- and Stereocontrolled Synthesis of Epoxy Alcohols and Triols from Allylic and Homoallylic Alcohols via Iodo Carbonates

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The regio- and stereoselective synthesis of cyclic iodo carbonates **1-10**, resulting from allylic and homoallylic alcohols, was investigated. These useful intermediates were easily hydrolyzed to epoxy alcohols **11-20** or triols **21-30**, depending on the polymeric reagent employed (Amberlyst A 26 in the OH^- or CO_3^{2-} form, respectively). Stereochemical assignments were carried out by ^{13}C NMR or ^1H NMR correlations and by conversion of the compounds to products of known stereostructures.

In connection with the total synthesis of macrolide antibiotics and polyether ionophores, there is increasing interest in methods for stereocontrolled double bond functionalization.[1] Recently Bartlett[2] achieved 1,3-asymmetric induction through the phosphate chain-extended epoxidation, Kishi[3] reported 1,4-asymmetric induction in the preparation of bis-homoallylic epoxy alcohols, and Still[4] showed that boranes may be used to hydroborate dienes to give diols with high 1,2, 1,3, and 1,4 remote asymmetric induction.

In recent papers we have described a novel functionalization of double bonds of allylic and homoallylic alcohols.[5-7]

We report here further developments of our process, concerning the regio- and stereoselective synthesis of epoxy

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