Naturally Occurring Terpenes. Synthesis of (+)- and (±)-14,15-Bisnor-8α-hydroxylabd-11(E)-en-13-one, (+)-Drimane-8,11-diol, and (−)-Drimenol

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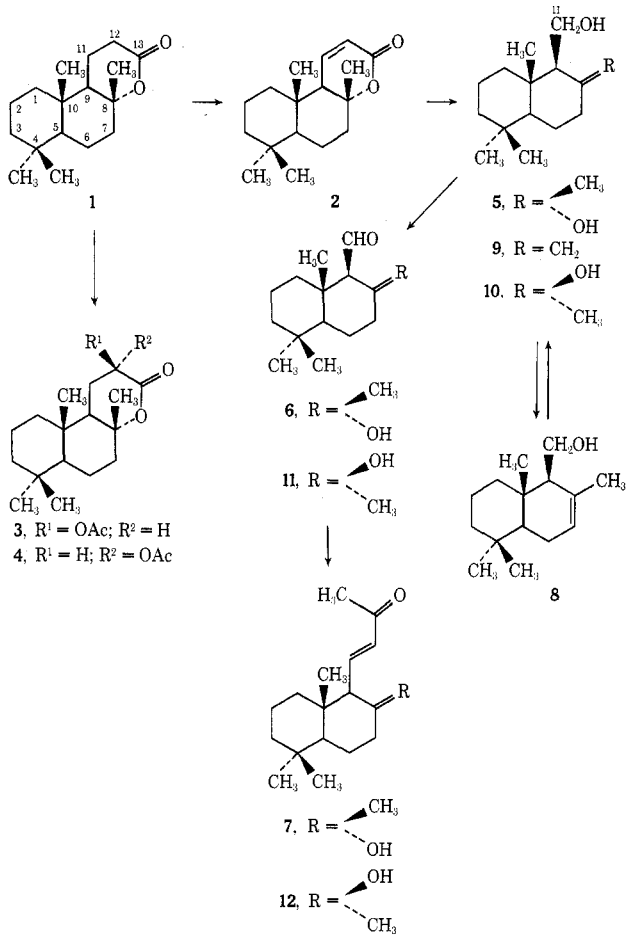
This paper reports a simple method of degradation of the readily available labdane group of diterpenoids to drimanic sesquiterpenes. The synthesis of (+)-drimane-8,11-diol (**5**), the (+) and (±) forms of 14,15-bisnor-8α-hydroxylabd-11(*E*)-en-13-one (**7**), (±)-8-epimeric hydroxy α,β-unsaturated ketone (**12**), and (−)-drimenol (**8**) is described. Treatment of (+)-ambreinolide (**1**) with $Pb(OAc)_4$ in boiling benzene for 120 hr gave compounds **2** (12%), **3** (22%), and **4** 27%). Treatment of **1** with DDQ in boiling *p*-dioxane for 48 hr afforded **2** (40%). Ozonolysis of **2** in methylene chloride at −70°, followed by treatment with Red-Al, gave (+)-**5** (85%). Oxidation of the latter with CrO_3–pyridine gave aldehyde (+)-**6** (50%). Treatment of (+)-**6** with sodium diethyl 2-oxopropylphosphonate in THF gave (+)-**7** (40%). A parallel series of reactions starting with (±)-ambreinolide (**1**) gave (±)-**2**, (±)-**5**, (±)-**6**, and (±)-**7**. Treatment of (+)-**5** with Ac_2O overnight gave a monoacetate which was dehydrated with $POCl_3$–pyridine at 0–5° to give a mixture of isomeric acetates. Basic hydrolysis of the latter gave a mixture of alcohols **8** and **9**. From this mixture (−)-dimenol (**8**) was isolated by preparative TLC. Treatment of (±)-drimenol (**8**) with *m*-chloroperbenzoic acid in methylene chloride at 0–5° gave a mixture of α and β epoxides. Reduction of the β epoxide with $LiAlH_4$ in THF gave diol **10**. Oxidation of **10** with CrO_3–pyridine gave **11**, which on treatment with sodium diethyl 2-oxopropylphosphonate in THF gave ketone **12** (30%).

Chirkova and coworkers have reported the isolation of (±)-14,15-bisnor-8α-hydroxylabd-11(*E*)-en-13-one (**7**) as a new bisnorditerpene hydroxy ketone from *Abies sibirica* Ledb (the oleoresin of the Siberian fir).[1] Recently, Hlubucek et al.[2] reported the isolation of the (+) isomer of this same compound, along with driman-8-ol, and drimane-8,11-diol (**5**) from the medium-volatile, neutral fraction of an extract of sun-cured *Nicotina Tabacum* L. Russian investigators have suggested that (+)-**7** is probably a diterpenoid autooxidation product of Δ^{13}-*cis*- and Δ^{1}-*trans*-neoabienol.[3] We wish to report a simple method of degradation of the readily available labdane group of diterpenoids (e.g., manool and sclareol) to drimanic sesquiterpenes. The synthesis of (+)-drimane-8,11-diol (**5**), and (+) and (±) forms of **7** from (+)- and (±)-ambreinolide, respectively, has been accomplished. Incidental to this work is the synthesis of the (±)-8-epimeric hydroxy α,β-unsaturated ketone **12** and (−)-drimenol (**8**).

The starting material for this synthesis was (+)-ambreinolide (**1**) obtained from manool.[4,5] When (+)-ambreinolide (**1**) was treated with 4 mol of lead tetraacetate[6] in boiling benzene, a very slow reaction occurred, and after 120 hr all starting material was consumed. A careful chromatographic separation of the oily product afforded three components: the unsaturated ambreinolide **2** (12%) and the epimeric acetoxy lactones **3** (22%) and **4** (27%). The structures for the acetoxy lactones were assigned on the basis of a comparison of the ^{13}C NMR shift values with the corresponding values of related steroidal acetoxy lactones.[7] Treatment of (+)-ambreinolide (**1**) with DDQ in boiling *p*-dioxane for 48 hr afforded compound **2** in much higher yield (40%). Exhaustive ozonolysis of the unsaturated (+)-ambreinolide **2** in dry methylene chloride at −70°, after evaporation, afforded an amorphous product which was dissolved in benzene and treated with Red-Al.[8] Work-up in the usual manner gave (+)-drimane-8,11-diol (**5**) in a nearly quantitative yield. The (+)-diol **5** was oxidized with CrO_3–pyridine complex in dry methylene chloride to aldehyde **6** in a yield of 50%. This aldehyde was allowed to react at −20° to room temperature with sodium diethyl 2-oxopropylphosphonate[9] in tetrahydrofuran to give the (+)-hydroxy α,β-unsaturated ketone **7** in a yield of 40%, mp 120–121°, $[\alpha]^{18}D$ +13.2°. The physical properties of the product **7** correspond with the reported data[2] for this compound.

The starting material for the synthesis of racemic hydroxy α,β-unsaturated ketone **7** was (±)-ambreinolide (**1**)



obtained from nerolidol.[10] Treatment of (±)-ambreinolide with DDQ (under conditions similar to those used in the case of (+)-ambreinolide) afforded (±) compound **2**. Ozonolysis of (±) compound **2**, followed by reduction with Red-

Al,[8] yielded (±)-drimane-8,11-diol **5** (87%). (±)-Diol (**5**) was oxidized with CrO_3–pyridine complex to the corresponding hydroxy aldehyde **6** in yields of 40–50%. Treatment of (±) compound **6** with sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran at room temperature overnight and then at 50° for 2 hr gave the (±)-hydroxy α,β-unsaturated ketone **7**, mp 126.5–128° (lit.[1] mp 126°). The ir, NMR, and mass spectra of the product, (±) compound **7**, correspond exactly with reported data for this compound.[1]

(+)-Drimane-8,11-diol (**5**) was used as the starting material for synthesis of (−)-drimenol (**8**).[11] When (+)-diol **5** in pyridine was treated with acetic anhydride at room temperature overnight, the monoacetate was obtained in nearly quantitative yield. The latter was readily dehydrated with phosphorus oxychloride in pyridine at 0–5° to give a mixture of isomeric acetates (endo and exo double bond). Basic hydrolysis of the isomeric acetates yielded a mixture of alcohols **8** and **9**. From this mixture (−)-drimenol (**8**) was isolated by preparative TLC over silica gel in 40% yield, mp 95–96°, $[\alpha]^{19}D$ −20.0° (lit.[12b] mp 96–97°, $[\alpha]^{20}D$ −20°). The ir, NMR, and mass spectra of the product **8** correspond exactly with reported data for this compound.[12]

The starting material for synthesis of (±)-14,15-bisnor-8β-hydroxylabd-11(*E*)-en-13-one (**12**) was (±)-drimenol (**8**) obtained from β-ionone.[13] When 11-acetoxydrim-7-ene (drimenol acetate) was treated with *m*-chloroperbenzoic acid in methylene chloride at −30° for 3 days[2] the α epoxide was obtained in an excellent yield, formed by preferential attack from the sterically less hindered α side. However, treatment of (±)-drimenol (**8**) with the same peracid in methylene chloride at 0–5° (in the refrigerator) overnight afforded two epoxides (α and β) in a ratio of about 1:1, which could be separated by preparative TLC over silica gel. Reduction of the β epoxide (the less polar) with $LiAlH_4$ in boiling tetrahydrofuran gave diol **10**. Treatment of (±)-8β,11-diol **10** with CrO_3–pyridine complex in methylene chloride under the same conditions as used for (±)-8α,11-diol **5** afforded the hydroxy aldehyde **11**. The latter was treated with sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran to give 8β-hydroxy α,β-unsaturated ketone **12** in 30% yield.

Experimental Section

All melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared (ir) spectra were determined in KBr or as film, with Perkin-Elmer Model 137 Infracord and Model 237B spectrometers. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6D2-s spectrometer operating with an ionization energy of 70 eV. The temperature of the ion source was about 200°. NMR spectra were taken in deuteriochloroform, with a Varian A-60 spectrometer. Ozonolysis was carried out using a Welsbach T-408 ozonator.

Oxidation of (+)-Ambreinolide by Means of Lead Tetraacetate (LTA). (+)-Ambreinolide (**1**, 3.0 g) was dissolved in 50 ml of anhydrous benzene and 6.0 g of LTA was added. The reaction mixture was stirred at reflux temperature for 2 days, when 6.0 g more of LTA was added; the heating and stirring were continued until all LTA had reacted (120 hr). The reaction mixture was diluted with ether, lead diacetate was collected, and the solution was washed with water, dried, and evaporated to dryness. The oily residue (4.2 g) was chromatographed on a column of 250 g of silica gel. Elution with hexane–ether (95:5) afforded 430 mg (12%) of unsaturated ambreinolide **2**: mp 193–194°; $[\alpha]^{25}D$ + 5.1° (*c* 2.0, chloroform); ν_{max} (KBr) 1720, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.93 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.46 (3 H, s, C-8 CH_3), 2.56 (1 H, dd, J = 3, 3 Hz, C-9 H), 6.23 (1 H, dd, J = 3, 10 Hz, C-12 H), 7.06 (1 H, dd, J = 3, 10 Hz, C-11 H).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.94; H, 9.99.

Elution with hexane–ether (9:1) afforded 800 mg (22%) of 12β-acetoxyambreinolide (**3**) and 980 mg (27%) of 12α-acetoxyambreinolide (**4**). The characteristics of acetoxy lactones **3** and **4** are as follows.

Acetoxy lactone **3**: mp 157–158°; $[\alpha]^{28}D$ +44.5° (*c* 2.0, chloroform); ν_{max} (KBr) 1760, 1750, 1225 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.88, 0.93 (3 H, s, each, C-4 and C-10 CH_3), 1.53 (3 H, s, C-8 CH_3), 2.21 (3 H, s, C-12β $OCOCH_3$), 5.20–5.55 (1 H, m, C-12α H).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.94; H, 9.43.

Acetoxy lactone **4**: mp 154–155°; $[\alpha]^{25}D$ +74.1° (*c* 2.0, chloroform); ν_{max} (KBr) 1765, 1745, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.93 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.50 (3 H, s, C-8 CH_3), 2.22 (3 H, s, C-12α $OCOCH_3$), 5.68 (1 H, ABX q, $J_1 + J_2$ = 16 Hz, C-12β H).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.76; H, 9.39.

(+)- and (±)-Δ^{11}-Ambreinolide (2). A solution of (+)-ambreinolide (**1**, 2.0 g) and DDQ (3.0 g) in 60 ml of dry *p*-dioxane was refluxed for 48 hr. The reaction mixture was diluted with ether, the precipitated solid was collected, and the solution washed with water, aqueous Na_2CO_3, and water, dried, and evaporated to dryness. The yellow solid residue (3.5 g) was chromatographed on activity III neutral alumina (100 g). Elution with hexane–ether (9:1) afforded 950 mg of material, which on crystallization from EtOAc yielded Δ^{11}-ambreinolide (795 mg, 40%), mp 192–195°, and identical (ir and TLC) with the sample isolated from the (+)-ambreinolide–LTA reaction mixture.

Treatment of (±)-ambreinolide (1.5 g) with DDQ under conditions similar to those used in the case of (+)-ambreinolide afforded (±)-Δ^{11}-ambreinolide (**2**) in a yield of 38% (565 mg), mp 212°.

(+)- and (±)-Drimane-8,11-diol (5). (+)-Δ^{11}-Ambreinolide (**2**, 600 mg) in dry methylene chloride (75 ml) was treated with ozonized oxygen at −70° until the solution was blue (30 min). Evaporation afforded an amorphous product which was dissolved in benzene (50 ml) and treated with Red-Al.[8] The excess hydride was decomposed with dilute HCl (5%) and the mixture was extracted with ether. The combined extracts were washed with water, 5% aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated. The residue (520 mg) was a colorless oil that crystallized from hexane (380 mg). After several recrystallizations the product **5** consisted of colorless prisms, mp 127–128°, $[\alpha]^{26}D$ +4.2° (*c* 1.3, chloroform). The ir, NMR, and mass spectra of the product **5** correspond exactly with data reported for this compound.[2]

The mother liquor was evaporated to dryness and purified by preparative TLC to give 83 mg of a product melting at 85–86°. This product has an identical NMR spectrum and specific rotation with the product melting at 127–128°, and appears to be a different crystalline form. Thus, the total yield of the (+)-drimane-8,11-diol (**5**) is 85%.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.93; H, 11.76.

Exhaustive ozonolysis of (±)-Δ^{11}-ambreinolide (500 mg), followed by reduction with Red-Al,[8] yielded (±)-drimane-8,11-diol (**5**, 87%), mp 100–101.5°.

(+)- and (±)-14,15-Bisnor-8α-hydroxylabd-11(*E*)-en-13-one (7). A solution of (+)-drimane-8,11-diol (**5**, 200 mg) in methylene chloride (4 ml) was treated for 30 min at room temperature with CrO_3–pyridine complex prepared from CrO_3 (750 mg), pyridine (1.28 ml), and methylene chloride (13 ml) at 5°. The reaction mixture was filtered through a short column of silica gel and washed with ether–methylene chloride. Evaporation of the solvent gave an oil, which was purified by preparative TLC on silica gel (50% hexane–ether) to give 100 mg of hydroxy aldehyde **6**: ν_{max} (film) 3500, 3420, 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.90 (3 H, s, each, C-4 CH_3), 1.13 (3 H, s, C-10 CH_3), 1.40 (3 H, s, C-8 CH_3), 2.08 (1 H, d, J = 2.0 Hz, C-9 H), 10.32 (1 H, d, J = 2.0 Hz, C-11 H). The aldehyde was used in the next step without further purification.

A mixture of $NaNH_2$ (140 mg) and diethyl 2-oxopropylphosphonate (170 mg) in tetrahydrofuran (6.0 ml) was stirred at 0° until the evolution of NH_3 has ceased. To the cold mixture (−10°) was added dropwise a solution of the above aldehyde **6** (100 mg) in tetrahydrofuran (6.0 ml). The reaction mixture was stirred at room temperature overnight, poured into ice-water, and extracted with ether. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave an oil, which was chromatographed by preparative TLC on silica gel (50% hexane–ether) to separate a crystalline enone **7** (45 mg). Recrystallization from ether–hexane gave colorless needles: mp 120–121°; $[\alpha]^{18}D$ +13.2° (*c* 0.7, chloroform); ν_{max} (KBr) 3430, 1665, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.82, 0.88 (3 H, s, each, C-4 CH_3), 0.99 (3 H, s, C-10 CH_3), 1.26 (3 H, s,

C-8 CH_3), 2.25 (3 H, s, $COCH_3$), 6.14 (1 H, d, J = 16.0 Hz, C-12 H), 6.81 (1 H, dd, J = 16.0, 10.0 Hz, C-11 H).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.48; H, 10.94.

Treatment of (±)-drimane-8,11-diol (**5**, 174 mg) with CrO_3–pyridine complex under conditions similar to those used in the case of (+)-diol **5** afforded (±)-hydroxy aldehyde **6** (80 mg).

The (±)-hydroxy aldehyde (65 mg) in tetrahydrofuran (4.9 ml) was added dropwise at −5° to the suspension of sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran prepared as described above. The reaction mixture was stirred at room temperature overnight and then at 50° for 2 hr. The mixture was treated as described for the condensation of (+)-hydroxy aldehyde. The crystalline compound (30 mg) obtained was recrystallized from ether–hexane to give colorless needles, mp 126.5–128°, whose physical constants (melting point, ir and NMR spectra, R_f value of TLC) were identical with those of the (+)-hydroxy enone **7**.

(−)-Drimenol (8). A solution of (+)-drimane-8,11-diol (**5**, 200 mg) in pyridine (1 ml) and acetic anhydride (1 ml) was allowed to stand overnight at room temperature, then poured into iced $NaHCO_3$ solution. The solution was extracted with ether and the ether layer was washed with dilute HCl and saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. On removal of the solvent, an oily monoacetate was obtained, ν_{max} (film) 3500, 1750, 1250 cm^{-1}, which without purification was dehydrated.

To a solution of the monoacetate (215 mg) in pyridine (3.0 ml) at 0° was added phosphorus oxychloride (0.5 ml) and the resulting solution was stored overnight at 0–5°. The cold mixture was poured onto about 30 g of crushed ice and the resulting solution was extracted three times with ether. The ethereal solution was washed with water, dilute HCl, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude oil (160 mg) which showed two distinct spots on TLC. The product was dissolved in 2% methanolic potassium hydroxide (20 ml) and stirred overnight at room temperature. The methanolic solution was evaporated to dryness, the residue was dissolved in water, and the aqueous solution was extracted with ether. Evaporation of ether left a gum (120 mg). Separation on a 2-mm thick 200 × 200 mm silica gel plate afforded the less polar compound **8** (52 mg) as an oil that crystallized from hexane: mp 95–96°; $[\alpha]^{19}D$ −20.0° (c 1.3, chloroform); ν_{max} (KBr) 3300 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (9 H, s, C-4 and C-10 CH_3), 1.80 (3 H, s, C-8 CH_3), 3.70–3.86 (2 H, m, C-11 H_2), 5.70 (1 H, m, C-7 H).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.29; H, 11.94.

The more polar compound **9** was isolated as an oil: NMR ($CDCl_3$) δ 0.75, 0.85, 0.90 (3 H, s, each, C-4 and C-10 CH_3), 3.89–4.05 (2 H, m, C-11 H_2), 4.84, 5.16 (1 H, br, each, C-8=CH_2).

Epoxidation of (±)-Dimenol (8). A solution of (±)-drimenol (**8**, 990 mg) and m-chloroperbenzoic acid (800 mg) in methylene chloride (30 ml) was allowed to stand for 17 hr in a refrigerator. The reaction mixture was diluted with ether, washed with saturated aqueous $KHCO_3$ and water, and dried over Na_2SO_4. Evaporation of the solvent gave a colorless oil (1133 mg) which was chromatographed on silica gel (preparative TLC, 80% hexane–ether) to give two epoxides in a ratio of about 1:1. The less polar product (452 mg), the β epoxide, ν_{max} (film) 3430 cm^{-1}, NMR ($CDCl_3$) δ 0.86, 0.91 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.46 (3 H, s, C-8 CH_3), 3.0 (1 H, m, C-7α H), 3.90 (2 H, d, J = 4.5 Hz, C-11 H_2), 2.97 (1 H, br, OH), was used in the next step without further purification. The more polar product (442 mg) crystallized from ether–hexane to give colorless prisms, mp 94–96°, ν_{max} (film) 3420 cm^{-1}, NMR ($CDCl_3$) δ 0.76, 0.86 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.48 (3 H, s, C-8 CH_3), 2.98 (1 H, dd, J = 2, 2 Hz, C-7β H), 3.09 (1 H, br, OH), whose melting point was identical with that of α-epoxydrimenol reported by Appel and coworkers[12a] (mp 96–97°).

(±)-Drimane-8β,11-diol (10). A mixture of 7β,8β-epoxydriman-11-ol (315 mg) and $LiAlH_4$ (160 mg) in tetrahydrofuran (47 ml) was heated under reflux for 16 hr with stirring. The reaction mixture was treated with water to decompose excess $LiAlH_4$, washed with dilute HCl and water, and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline residue (316 mg) which was recrystallized from ether–hexane to afford 268 mg of drimane-8β,11-diol (**10**) as colorless prisms, mp 133.8–134.5°, ν_{max} (KBr) 3280 cm^{-1}, NMR ($CDCl_3$) δ 0.87 (6 H, s, C-4 CH_3), 1.23 (3 H, s, C-10 CH_3), 1.33 (3 H, s, C-8 CH_3), 4.06 (2 H, d, J = 3 Hz, C-11 H_2), ca. 3.00 (1 H, br, OH); whose physical constants (melting point and ir spectra) were identical with those of drimane-8β,11-diol reported by Stadler and coworkers[13c] (mp 133°).

(±)-14,15-Bisnor-8β-hydroxylabd-11(E)-en-13-one (12). A solution of (±)-drimane-8β,11-diol (**10**, 120 mg) in methylene chloride (2.0 ml) was oxidized for 60 min at room temperature with CrO_3–pyridine complex prepared from CrO_3 (500 mg), pyridine (0.85 ml), and methylene chloride (8.5 ml) at 5°. The mixture was treated as described for the oxidation of (+)-drimane-8α,11-diol (**5**) to give hydroxy aldehyde **11** (50 mg) as an oil, ν_{max} (CCl_4) 3540, 1705 cm^{-1}, NMR ($CDCl_3$) δ 0.86, 0.90 (3 H, s, each, C-4 CH_3), 1.17, 1.20 (3 H, s, each, C-8 and C-10 CH_3), 2.12 (1 H, d, J = 2.6 Hz, C-9 H), 10.10 (1 H, d, J = 2.6 Hz, C-11 H), which was used in the next step without further purification.

A solution of hydroxy aldehyde **11** (50 mg) in tetrahydrofuran (3.0 ml) was added dropwise to a cold mixture (−5°) of sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran prepared from 35 mg of $NaNH_2$ and 160 mg of diethyl 2-oxopropylphosphonate in 5 ml of tetrahydrofuran as described above. The mixture was stirred at room temperature overnight and at 40° for 1 hr and then treated as described for the synthesis of (+)-hydroxyenone **7**. The resulting crystalline compound (**12**, 18 mg) was recrystallized from ether–hexane to give colorless prisms: mp 153–153.8°; ν_{max} (KBr) 3420, 1670 (shoulder), 1660, 1635 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (6 H, s, C-4 CH_3), 1.02, 1.10 (3 H, s, each, C-8 and C-10 CH_3), 2.27 (3 H, s, $COCH_3$), 5.98 (1 H, d, J = 16.5 Hz, C-12 H), 6.96 (1 H, dd, J = 16.5, 10.2 Hz, C-11 H).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.71; H, 10.65.

Registry No.—(+)-**1**, 468-84-8; (+)-**2**, 52811-58-2; (±)-**2**, 54656-74-5; **3**, 54632-03-0; **4**, 54656-75-6; (+)-**5**, 52617-99-9; (±)-**5**, 54656-76-7; (+)-**6**, 52618-00-5; (±)-**6**, 54656-77-8; (+)-**7**, 42569-64-2; (−)-**8**, 468-68-8; (±)-**8**, 54750-55-9; **9**, 54632-04-1; (±)-**10**, 54656-78-9; (±)-**11**, 54656-79-0; (±)-**12**, 54656-80-3.

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