Synthesis of (+)-Ambreinolide from Abietic Acid

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An efficient transformation of the diene **1**, obtained in three steps from commercial colophony or abietic acid, into (+)-ambreinolide (**10**) was developed. The sequence was carried out in 47–57% overall yield and involves as the key step the rearrangement of the epoxy lactone **6** to produce the intermediate dial **7**.

Ambergris[1] is a metabolic product of the sperm whale that accumulates as a concretion in the gut of the animal. In the form of an ethanolic tincture, it has been widely used in perfumery as a highly valuable perfume base. Its fixative properties, which surpass that of the civet and musk, are primarily due to ambreinolide (**10**), an odorless component formed by autoxidative degradation of the diterpene ambrein during the aging of the ambergris. In recent times, the decreasing availability of ambergris has prompted chemists to develop synthetic approaches to ambreinolide[2] and other related ambergris fragrance chemicals.[3] In line with our interest in the use of resin acids as starting materials for the synthesis of biologically active natural compounds, we describe in this paper a short route for the transformation of *l*-abietic acid into (+)-ambreinolide (**10**, Scheme I).

Diene **1** was obtained in three steps from commercial colophony or abietic acid by the procedure previously described.[4] Reduction of the C_{18} methoxycarbonyl group of **1** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) in toluene at 0 °C gave the alcohol **2** in almost quantitative yield. The use of other reducing reagents (e.g., $LiAlH_4$) resulted in partial isomerization of double bonds, which lowered the yield of the ketone **3** in the subsequent step (vide infra). Chemoselective ozonolysis of the 13(15) double bond of **2** in ethyl acetate–dichloromethane (1:1) at −78 °C afforded the enone **3** in 84% yield. Isomerization of the enone **3** by refluxing with HCl in methanol gave the α,β-unsaturated ketone **4** in 90% yield, which on oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the epoxy lactone **5**. The conditions of this reaction were somewhat critical to ensure a good yield of the desired epoxy lactone, and although analogous oxidations reported by earlier workers[2d,5,6] are conducted in refluxing dichloromethane, in our case the best result was obtained when **4** was treated with a large excess of *m*-CPBA in dichloromethane at room temperature for 6 h. Under these conditions the epoxy lactone **5** (>95% purity by ^1H NMR) was obtained in almost quantitative yield. On account of its chromatographic instability, **5** was not purified but oxidized directly with pyridinium chlorochromate (PCC)[7] to the corresponding aldehyde. In this manner we were able to realize a 95% overall yield of the crystalline aldehyde epoxy–lactone **6** after rapid column chromatography of the oxidation mixture.

Treatment of the epoxy lactone **6** with aqueous methanolic sodium hydroxide at 0 °C for 20 min resulted in rearrangement to the formyl lactone **7** in essentially quantitative yield. Although apparently obtained in a pure form (^1H NMR), **7** was isolated in only 40% yield after silica gel column chromatography of the crude reaction mixture. Although this purified material was not homogeneous (TLC), its proton and ^{13}C NMR spectra are consistent with the structure **7**. It seems that opening of the lactone moiety occurred on silica gel. Therefore, the crude dial lactone **7** was used for the next step without further purification.[8]

The final step in the synthesis required the reduction of both aldehyde functions of **7** to methyl groups. The Huang–Minlon modification of the Wolff–Kishner reduction was selected.[9] Treatment of the crude dial **7** with hydrazide hydrate and potassium hydroxide in diethyl glycol under standard conditions afforded a mixture of ambreinolide (**10**) and the known unsaturated acid **9**. The mixture was treated with diazomethane to give, after column chromatography, the methyl ester **8** (75% from **6**) and ambreinolide (**10**, 9% from **6**). The formation of the acid **9** in the above reaction was not particularly surprising since it is well documented[10] that with many α-substituted carbonyl compounds elimination of the substituent (carboxylate or hydroxy group in this case) accompanies reduction.[11] The methyl ester **8** was hydrolyzed to give again the acid **9**, which in turn was readily converted to ambreinolide (**10**) in high yield through an acid-mediated intramolecular cyclization by using a procedure slightly modified from that already described.[12] Once the individual steps had been established, the sequence of steps

(1) For a general discussion of the ambergris chemistry see: Ohloff, G. The Fragrance of Ambergris. In *Fragrance Chemistry. The Science of the Sense and Smell*; Theimer, T., Ed.; Academic Press: New York, 1982; p 535.

(2) (a) Christenson, P. A. *Tetrahedron* **1988**, *44*, 1925. (b) Daniewski, W. M.; Kubak, E.; Jurczak, J. *J. Org. Chem.* **1985**, *50*, 3963. (c) Semenovskii, A. V.; Emel'yanov, M. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, *6*, 1359. (d) Cambie, R. C.; Palmer, B. D. *Aust. J. Chem.* **1981**, *34*, 1265. (e) Semenovskii, A. V.; Smit, V. A.; Kucherov, V. F. *Dolk. Akad. Nauk SSSR* **1966**, *168*, 606. Dominguez, G.; Marco, J. L.; Hueso-Rodriguez, J. A.; Rodriguez, B. *An. Quim.* **1988**, *84C*, 211. For earlier syntheses of ambreinolide see ref 2b.

(3) (a) Koyama, H.; Kaku, Y.; Ohno, M. *Tetrahedron Lett.* **1987**, *28*, 2863. (b) Decorzant, R.; Vial, C.; Näf, F. *Tetrahedron* **1987**, *43*, 1871. (c) Ohloff, G.; G. Vial, C.; Demde, E.; Enggist, P.; Giersch, W.; Jégou, E.; Caruso, J. A.; Polonsky, J.; Lederer, E. *Helv. Chim. Acta* **1986**, *69*, 163. (d) Buchbauer, H. *Monatsh. Chem.* **1985**, *116*, 1345. Also see ref 1.

(4) Abad, A.; Arnó, M.; Domingo, L. R.; Zaragozá, R. J. *Tetrahedron* **1985**, *41*, 4937.

(5) Pelletier, S. W.; Chang, C. W. J.; Iyer, K. N. *J. Org. Chem.* **1969**, *34*, 3477.

(6) Grant, P. K.; Liau, H. T. L.; Temple, W. A. *Aust. J. Chem.* **1979**, *32*, 1353.

(7) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

(8) When the order of the oxidation–rearrangement steps was reversed (i.e., rearrangement of **5** to the corresponding formyl lactone first, followed by oxidation with PCC), the overall yield of the dial **7** was lower (76%).

(9) This method has previously been used for the reduction of the C-18 aldehyde group of related systems, e.g.: Tahara, A.; Shimagaki, M.; Ohara, S.; Tanaka, T.; Nakata, T. *Chem. Pharm. Bull.* **1975**, *23*, 2329.

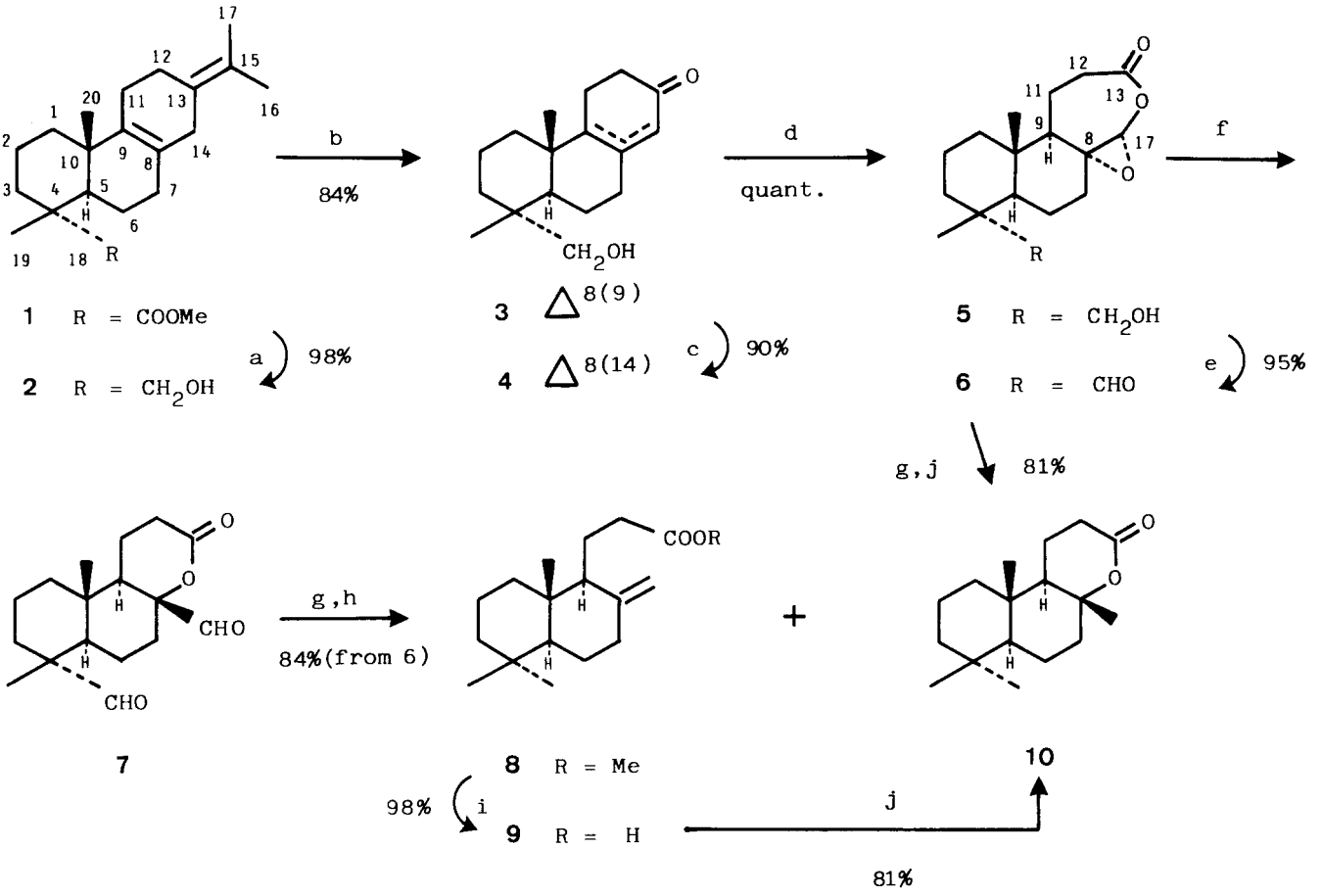
(10) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: Menlo Park, CA, 1972; p 228.

(11) It is worth noting that only the acid **9** was isolated from the Wolff–Kishner reduction of the dial **7** if this was dissolved in diethylene glycol, treated with hydrazine, and heated to 115 °C previous to the addition of potassium hydroxide.

(12) (a) Schenk, H. R.; Gutmann, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta.* **1952**, *35*, 817. (b) Schenk, H. R.; Gutmann, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* **1954**, *37*, 543. (c) Scheidegger, U.; Schnaffner, K.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 400. (d) Cambie, R. C.; Joblin, K. N.; Preston, A. F. *Aust. J. Chem.* **1971**, *24*, 2365.

0022-3263/89/1954-5123$01.50/0

Scheme I[a]



[a] (a) SMEAH, toluene, 0 °C; (b) O_3, Cl_2CH_2–EtOAc, −78 °C, then CH_3SCH_3; (c) HCl, CH_3OH, reflux; (d) m-CPBA, Cl_2CH_2, room temperature; (e) PCC, Cl_2CH_2; (f) NaOH, CH_3OH, 0 °C; (g) NH_2NH_2, NaOH, diethylene glycol, 115°, 2 h, then 210 °C, 2 h; (h) CH_2N_2; (i) NaOH, CH_3OH; (j) H_2SO_4-HOAc, −10 °C.

from **7** to ambreinolide (**10**) was carried forward without previous separation of **9** and **10**, and it proved possible to abbreviate the overall sequence such that only two steps were needed to transform the epoxy lactone **6** into the target ambreinolide (**10**). Instead of proceeding as before, the epoxy lactone **6** was directly subjected to the Wolff–Kishner reaction. Under these conditions rearrangement of the epoxy lactone to the formyl lactone moiety followed by Wolff–Kishner reduction took place, to give a mixture of the acid **9** and ambreinolide (**10**, similar by ^1H NMR to that obtained when both steps were carried out separately), which on subsequent exposure to the above-mentioned acid-catalyzed cyclization afforded ambreinolide (**10**) in a yield comparable to that previously obtained (see Experimental Section).

Experimental Section

All melting points are uncorrected. ^1H NMR spectra were measured at 200.13 MHz in $CDCl_3$ solution. Analytical TLC was carried out on Merck precoated 0.25-mm-thick plates of silica gel 60 HF_{254}. Chromatography refers to flash chromatography and was performed on Merck silica gel 60 (230–400 mesh). All reactions were conducted under an argon atmosphere. Commercially available chemicals were used as obtained without further purification, except for solvents, which were purified and dried before use by standard methods. Anhydrous sodium sulfate was used for drying organic solvent extracts, and removal of the solvent was performed with a rotary evaporator and finally under high vacuum.

(+)-Abieta-8,13(15)-dien-18-ol (2). A stirred solution of **1** (5 g, 15.8 mmol) in dry toluene (50 mL) was cooled to 0 °C, and sodium bis(2-methoxyethoxy)aluminum hydride (6.7 mL of a 3.5 M solution in toluene, 23.5 mmol) was added over 10 min. After stirring at the same temperature for 1 h, the reaction mixture was quenched by the addition of water. The reaction mixture was diluted with saturated sodium potassium tartrate solution and extracted with methylene chloride. The combined organic extracts were washed with brine, dried, and concentrated in vacuo. The residue was subjected to chromatography over silica gel with hexane–ether (3:2) as eluent to give **2** (4.45 g, 98%) as a semisolid; $[\alpha]_D$ +145° (*c* 0.63, $CHCl_3$); IR (KBr) 3370, 1380, and 1050 cm^{-1}; ^1H NMR δ 3.45 and 3.19 (each d, 1 H each, J = 10.8 Hz, H-18), 1.70 and 1.68 (each br s, 3 H each, both CH_3 at C-15), 1.05 (s, 3 H, 10-CH_3), and 0.84 (s, 3 H, 4-CH_3); MS, *m/e* (rel intensity) 289 (M^+ + 1, 10), 288 (M^+, 44), 287 (11), 273 (22), 270 (1.6), 269 (5), 271 (4), 257 (7), 148 (34), and 135 (100). Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.32; H, 11.05.

(+)-18-Hydroxypodocarp-8-en-13-one (3). Diene **2** (4.08 g, 14.0 mmol) was dissolved in methylene chloride–ethyl acetate (1:1, 100 mL) and cooled to −78 °C. The solution was magnetically stirred, and ozone (O_2 flow 12 L/h, 7 mmol of O_3/h) was bubbled through until TLC analysis showed the presence of only traces of starting material (ca. 2 h, 14.0 mmol of O_3). Nitrogen was bubbled through the mixture, which was then treated with dimethyl sulfide (30 mL). The mixture was allowed to warm to room temperature and stirred for 48 h. The solvent was removed in vacuo, and the residue dissolved in ether. The ether phase was washed with brine, dried, and concentrated in vacuo to afford a solid, which was purified by chromatography on silica gel with hexane–ether (1:1) as eluent to give **3** (3.12 g, 84%) as a solid: mp 83–83.5 °C (from hexane–ether); $[\alpha]_D$ +176° (*c* 0.34, $CHCl_3$); IR (KBr) 3440, 1710, 1385, and 1030 cm^{-1}; ^1H NMR δ 3.42 and 3.13 (each d, 1 H each, J = 10.8 Hz, H-18), 2.67 (br s, 2 H, H-14), 2.35 (m, 4 H, H-11 and H-12), 1.03 (s, 3 H, 10-CH_3), 0.78 (s, 3 H, 4-CH_3); MS, *m/e* (rel intensity) 263 (M^+ + 1, 14), 262 (M^+, 83), 248 (11), 247 (73), 233 (13), 232 (80), 231 (70), 229 (51), and 41

(100). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.53; H, 10.28.

(+)-18-Hydroxypodocarp-8(14)-en-13-one (4). A solution of **3** (3.02 g, 11.5 mmol) and concentrated HCl (36 mL) in methanol (90 mL) was heated at reflux for 40 min. The mixture was cooled, diluted with water, and extracted with ether. The combined extracts were washed successively with water, saturated $NaHCO_3$ solution, and brine, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with hexane–ethyl acetate (1:1) as eluent to give **4** (2.72 g, 90%) as colorless needles: mp 114–114.5 °C (from hexane–ether); $[\alpha]_D$ +48° (*c* 0.22, $CHCl_3$); IR (KBr) 3380, 1645, 1610, and 1050 cm^{-1}; ^1H NMR δ 5.83 (br s, 1 H, H-14), 3.43 and 3.05 (each d, 1 H each, J = 10.9 Hz, H-18), 0.79 and 0.77 (each s, 3 H each, 10-CH_3 and 4-CH_3); MS, *m/e* (rel intensity) 263 (M^+ + 1, 1.5), 262 (M^+, 8), 247 (1), 233 (3), 232 (13), 231 (14), and 110 (100). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.55; H, 9.78.

(−)-8α,17-Epoxy-18-hydroxy-14,15,16-trinorlabdan-13,17-olide (5). To a stirred solution of the enone **4** (2.28 g, 8.7 mmol) in dry methylene chloride (60 mL) was added a solution of 85% *m*-chloroperbenzoic acid (7.14 g, 34.8 mmol) in dry methylene chloride (60 mL) at room temperature over a period of 15 min. The reaction mixture was stirred at the same temperature for 6 h, diluted with ether, and washed successively with an aqueous solution of sodium thiosulfate, $NaHCO_3$, and brine. The organic layer was dried and concentrated to give **5** (2.50 g, 98%) as a solid, which was used in the next step without further purification. An analytical sample was obtained by column chromatography with hexane–ethyl acetate (1:1) as eluent: mp 144–146 °C (dec, from hexane–dichloromethane); $[\alpha]_D$ −80° (*c* 0.50, $CHCl_3$); IR (KBr) 3350, 1745, and 1060 cm^{-1}; ^1H NMR δ 4.79 (d, 1 H, J = 1 Hz, H-14β), 3.33 and 3.02 (each d, 1 H each, J = 10.9 Hz, H-18), 3.0 (ddd, 1 H, J = 14.3, 10.4, and 3.9 Hz, H-12α), 2.41 (ddd, 1 H, J = 14.3, 7.6, and 3.9 Hz, H-12β), 1.96 (td, 1 H, J = 9.2 and 1 Hz, H-9α), 1.93–1.55 (m, 2 H, H-11), 0.91 (s, 3 H, 10-CH_3), and 0.74 (s, 3 H, 4-CH_3); MS, *m/e* (rel intensity) 295 (M^+ + 1, 0.5), 294 (M^+, 0.5), 276 (1.3), 265 (12), 251 (23), 247 (45), 235 (27), 217 (36), and 41 (100). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.11; H, 9.20.

(−)-8α,17-Epoxy-18-oxo-14,15,16-trinorlabdan-13,17-olide (6). To a stirred solution of pyridinium chlorochromate (0.74 g, 3.4 mmol) in dry methylene chloride (4 mL) was added a solution of **5** (0.5 g, 1.7 mmol) in methylene chloride (3 mL). The mixture was stirred for 2 h at room temperature, during which time the solution became dark brown and a dark polymer separated. The solution was decanted from the black polymer and was adsorbed on a short silica gel column, which was eluted with methylene chloride to afford **6** (0.47 g, 95%) as a solid: mp 140–143 °C (dec, from hexane–dichloromethane); $[\alpha]_D$ −118° (*c* 0.7, $CHCl_3$); IR (KBr) 2700, 1760, and 1735 cm^{-1}; ^1H NMR δ 9.23 (s, 1 H, H-18), 4.84 (d, J = 0.8 Hz, 1 H, H-14β), 3.13 (ddd, 1 H, J = 14.8, 11.4, and 3.5 Hz, H-12α), 2.50 (ddd, 1 H, J = 14.8, 7.3, and 3.4 Hz, H-12β), 2.10 (ddd, 1 H, J = 9.4, 9.2, and 0.8 Hz, H-9α), 1.10 (s, 3 H, 4-CH_3), and 0.99 (s, 3 H, 10-CH_3); MS, *m/e* (rel intensity) 292 (M^+, 0.6), 277 (0.6), 274 (2.3), 264 (6), 263 (27), 249 (30), 245 (15), 235 (9), 217 (54), and 41 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.56; H, 8.35.

(−)-17,18-Dioxo-14,15,16-trinorlabdan-13,8-olide (7). To a well-stirred suspension of **6** (0.45 g, 1.54 mmol) in methanol (18 mL) was added dropwise at 0 °C aqueous sodium hydroxide (2 M, 3.7 mL). After continued stirring at the same temperature for 20 min, the reaction mixture was carefully acidified by addition of hydrochloric acid and poured into ether. The organic layer was washed with water and brine, dried, and concentrated to give **7** (0.45 g, 100%) as a solid, which although apparently pure by ^1H NMR showed two spots on TLC. Since attempted purification of **7** by chromatography caused substantial material loss to occur, it was used for the next step without further purification; mp 133–135 °C (from hexane–ethyl acetate); $[\alpha]_D$ −94° (*c* 0.5, $CHCl_3$); IR (KBr) 2700, 1735, and 1720 cm^{-1}; ^1H NMR δ 9.74 (s, 1 H, H-17), 9.22 (s, 1 H, H-18), 2.75 (dd, 1 H, J = 17.5 and 7.7 Hz, H-12), 2.50 (dt, 1 H, J = 17.7 and 8.5 Hz, H-12), 1.05 (s, 3 H, 4-CH_3), and 0.78 (s, 3 H, 10-CH_3); MS, *m/e* (rel intensity) 292 (M^+, 0.4), 264 (6), 263 (35), 245 (23), 235 (7), 227 (5), 217 (4), and 55 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.71; H, 8.29.

(+)-14,15,16-Trinorlabd-8(17)-en-13-oic Acid (9). Crude dialdehyde **7** (340 mg, 1.16 mmol) was dissolved in diethylene glycol (17 mL). 80% Hydrazine hydrate (1.3 mL) and powdered potassium hydroxide (1.6 g) were added, and the mixture was heated at 115 °C during 2 h. The temperature was raised to 210 °C while water and excess hydrazine were distilled off. After 2 h the reaction mixture was cooled, poured into water, and acidified with dilute hydrochloric acid. The mixture was extracted with ether, and the combined extracts were washed with water and brine, dried, and concentrated. The yellowish residue (307 mg), which showed a major spot on TLC, was esterified with diazomethane. Chromatography on a silica gel column with hexane–ether (95:5) as the eluent gave the methyl ester **8** (243 mg, 75%) as an oil: IR (film) 3040, 1730, 1630, and 880 cm^{-1}; ^1H NMR δ 4.81 and 4.46 (each s, 1 H each, H-17), 3.63 (s, 3 H, CO_2CH_3), 0.84 and 0.77 (each s, 3 H each, 4-CH_3), and 0.66 (s, 3 H, 10-CH_3). Further elution with hexane–ether (1:1) gave ambreinolide (**10**, 28 mg, 9%) as colorless needles whose spectra were identical with those of natural ambreinolide (see below). To a mixture of the methyl ester **8** (240 mg, 0.86 mmol) and ethanol (5 mL) was added 2% alcoholic NaOH (26 mL, 13.0 mmol), and the mixture stirred overnight at room temperature. The reaction mixture was diluted with water, acidified with hydrochloric acid, and extracted with ether. The extracts were washed with brine and dried. Evaporation of the solvent gave pure acid **9** (223 mg, 98%) as a solid: mp 110–112 °C (from hexane) (lit.[12a] mp 108.5–109 °C); $[\alpha]_D$ +37° (*c* 0.42, $CHCl_3$); IR (KBr) 3600–2400, 1700, 1635, and 890 cm^{-1}; ^1H NMR δ 4.82 and 4.46 (each br s, 1 H each, H-17), 0.84 and 0.78 (each s, 3 H each, 4-CH_3), and 0.66 (s, 3 H, 10-CH_3).

(+)-14,15,16-Trinorlabdan-13,8-olide (Ambreinolide, 10).

(a) From Acid 9. To a vigorously stirred mixture of glacial acetic acid (8 mL) and sulfuric acid (4 mL) at −10 °C was added, dropwise via syringe, a solution of the acid **9** (200 mg, 0.76 mmol) in glacial acetic acid (2 mL). The resulting suspension was allowed to warm to 0 °C until a clear solution was obtained (a few minutes), and the mixture was cooled again to −10 °C and then stirred at this temperature during 1 h. The colorless reaction mixture was quickly poured into cold water–ether. The organic phase was washed with water and brine, dried, and concentrated to give ambreinolide (**10**, 196 mg, 98%). TLC (hexane–ethyl acetate 7:3), GLC ($^1/_8$-in. diameter, 2-m column packed with 3% SE-30 on Chromosorb W HP; 300 °C injector and detector temperature, 230 °C column temperature), and ^1H NMR analysis indicated a purity greater than 95% for the crude ambreinolide. Recrystallization from hexane provided pure ambreinolide (**10**, 159 mg, after three crops, 81%): mp 140–141 °C (lit.[2d] mp 140–142 °C); $[\alpha]_D$ +32° (*c* 0.2, $CHCl_3$); IR (KBr) 1720, 1300, 1285, 1270, 1120, and 970 cm^{-1}; ^1H NMR δ 2.75–2.40 (m, 2 H, H-12), 1.35 (s, 3 H, 8-CH_3), 0.86 (s, 3 H, 10-CH_3), 0.81 (s, 3 H, 4α-CH_3), and 0.78 (s, 3 H, 4β-CH_3).

(b) From Epoxy Lactone 6. A mixture of **6** (257 mg, 0.88 mmol), diethylene glycol (13 mL), 80% hydrazine hydrate (1 mL), and powdered potassium hydroxide (1.17 g) was stirred at room temperature for 30 min. The mixture was heated at 115 °C for 2 h and then at 210 °C for 2 h. Workup as described for **7** afforded an oil (232 mg), which was chromatographed through a short silica gel column with hexane–ethyl acetate (7:3) as eluent to give 190 mg (82%) of a mixture of acid **9** (87%) and ambreinolide (**10**, 13%), which on treatment with acetic acid and sulfuric acid in the same way as described above for pure **9** afforded ambreinolide (**10**, 188 mg, 81% from **6**).

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Supplementary Material Available: Table of ^{13}C NMR spectral data for compounds **1–10** (1 page). Ordering information is given on any current masthead page.