Synthesis of Δ^9-Isoambrettolide and Its Isomers from 1,9-Cyclohexadecadiene

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Monoepoxycyclohexadecene **2** was reduced with lithium aluminum hydride to cyclohexadecenol **3** and then oxidized to the cyclohexadecenone **4**. This was hydroxylated by Brown's oxymercuration–demercuration process to the hydroxy ketones **5a** and **5b** and then acetylated to the corresponding acetoxy lactones **7a–c** which were pyrolyzed to produce Δ^9-isoambrettolide (**8d**) together with small amounts of the mixture of ambrettolide **8a** and its isomers **8b** and **8c**.

Ambrettolide **8a** (lactone of 16-hydroxy-Δ^7-hexadecenoic acid) is the principal odorous constituent of ambrette seed,[1] *Hibiscus Abelmochus.* Δ^9-Isomabrettolide (**8d**), though not a natural product, possesses the characteristic musk note of oil of ambrette seed.[2] Owing to their importance in the perfume industry, several methods[3a–e] have been developed for the synthesis of **8a** and **8d**. In this paper we report a synthesis of Δ^9-isoambrettolide (**8d**) together with small amounts of the mixture of ambrettolide **8a** and its isomers **8b** and **8c** from now available 1,9-cyclohexadecadiene (**1**).[4]

Unsaturated monoepoxide **2**[5] (69%) obtained from **1** was reduced with lithium aluminum hydride to cyclohexadecenol **3** (80%) and then oxidized with Jones reagent to the corresponding ketone **4**[6,7] (80%). Hydration of the isolated carbon–carbon double bond of **4** was achieved by Brown's oxymercuration–demercuration method[8] to produce a mixture of two hydroxy ketones **5a** and **5b** (56%). Though we could not separate **5a** from **5b** by glc methods, the position of the hydroxyl group was determined by the oxidation of the mixture of **5a** and **5b** into the diketones **11a** and **11b**, which were then separated using an analytical glc column (silicone SE-30). The mass spectral fragmentation patterns were used to distinguish between **11a** and **11b**.[7] The mixture of hydroxy ketones **5a** and **5b** thus obtained was then acetylated to the corresponding acetoxy ketones **6a** and **6b** (Scheme I).

Recently we found that macrocyclic ketones could be easily converted to the corresponding lactones in superior yield by treatment with peracetic acid in the presence of boron trifluoride etherate.[9,10] Thus, when cyclododecanone **9a** was treated with 3 mol of peracetic acid at 50° in the presence of boron trifluoride etherate, it was oxidized to cyclododecanolide **10a** in 55% yield. Under similar conditions, cyclohexadecanone **9b** was converted to cyclohexadecanolide **10b** in 46% yield. When the reaction was carried out at 25° for 2 weeks, the yield of **10a** and **10b** was increased to 77 and 54%, respectively. It should be noted that, when boron trifluoride etherate was replaced by either sulfuric acid[10a] or Caro's acid,[10b] the yield of **10b** was 32% (Scheme II).

Therefore, the boron trifluoride etherate method was applied to the acetoxy ketones **6a** and **6b**. Treatment of the mixture of **6a** and **6b** with 4 mol of peracetic acid at 50° in the presence of boron trifluoride etherate afforded acetoxy lactones (42%). This treatment should produce three lactones, *viz.* **7a**, **7b**, and **7c**. All our attempts to separate the individual acetoxy lactones by column chromatography, tlc, and capillary glc methods were unsuccessful. Therefore, the acetoxy lactones mixture was pyrolyzed at 325° under an atmosphere of nitrogen. This produced Δ^9-isombrettolide (**8d**) (80%) together with small amounts (20%) of the mixture of **8a**, **8b**, and **8c**.

Experimental Section

Melting points were uncorrected. Glc analyses were performed on an F & M 810 instrument using a 5% Carbowax 20M and 5% silicone SE-30 column (0.25 in. × 25 ft). The following spectrometers were used: ir, Beckman IR-5A; nmr, Varian HA-100 (CCl_4, TMS as internal standard); mass spectra, CEC Model 21-110 and AEI-MS9 for high resolution spectra. Mass spectral major fragmentation peaks were recorded in decreasing order of intensity except for the molecular ion. Deactivated silicic acid (5%) made by adding 5 ml of water to 95 g of silicic acid (Grace, 100–200 mesh) was used for column chromatography. Sodium sulfate was used for drying purposes.

8-Cyclohexadecen-1-ol (3).—To a stirred suspension of lithium aluminum hydride (3.8 g, 0.093 mol) in ether (120 ml) was added slowly a solution of **2**[5] (11.1 g, 0.046 mol) in ether (100 ml) and the mixture was refluxed for 3 hr. The reaction mixture was cooled to 0°, and the excess lithium aluminum hydride was decomposed by the addition of ice–water (100 ml). The ether layer was separated, and the white precipitate was extracted with ether. The combined ether extracts were dried and concentrated to obtain 9.8 g of crude material, which was chromatographed on deactivated silicic acid (100 g); 10–50% ether in hexane eluted **3** (8.75 g, 80%). Glc (Carbowax 20M) showed two peaks due to cis and trans isomers which were isolated by preparative glc: ir (neat, 8-*trans*-cyclohexadecen-1-ol) 3.05, 3.32, 3.42, 3.5, 6.85, 6.95, 7.15, 7.35, 7.43, 7.72, 8.5, 9.1, 9.7, 9.85, 10.0, 10.4, 11.1, 14.0 μ; nmr δ 1.1–1.7 (m, 22 H, s at 1.3, internal CH_2), 2.0 (b, 4 H, $CH_2C{=}CCH_2$), 3.7 (m, 1 H, CHOH), 5.3 (m, 2 H, $CH{=}CH$); mass spectrum m/e 238 (molecular ion), 80, 41, 55, 67, 81, 220; ir (neat, 8-*cis*-cyclohexadecen-1-ol) 3.05, 3.32, 3.42, 3.50, 6.85, 6.95, 7.15, 7.43, 7.73, 9.10, 9.45, 9.90, 14.0 μ; nmr δ 1.1–1.7 (m, 22 H, s at 1.32, internal CH_2), 2.0 (b, 4 H, $CH_2C{=}CCH_2$), 3.7 (m, 1 H, CHOH), 5.34 (t, 2 H, $CH{=}CH$); mass spectrum m/e 238 (molecular ion), 80, 55, 41, 220, 67, 81.

Anal. Calcd for $C_{16}H_{30}O$: m/e 238.2296. Found: m/e 238.2290.

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(1) M. Kerschbaum, *Ber.*, **60**, 908 (1927).

(2) "The Givaudan Index," Givaudan-Delawana, Inc., New York, N. Y., 1961, p 46.

(3) (a) Haarman and Reimer and M. Kerschbaum, German Patent 449,217, (1926); (b) M. Stoll and R. E. Gardner, *Helv. Chim. Acta*, **17**, 1609 (1934); (c) Baudard, *C. R. Acad. Sci.*, **221**, 205 (1945); (d) S. D. Sabnis, H. H. Mathur, and S. C. Bhattacharyya, *J. Chem. Soc.*, 2477 (1963); (e) H. H. Mathus and S. C. Bhattacharyya, *ibid.*, 3505 (1963).

(4) N. Calderon, E. A. Ofstead, and W. A. Indy, *J. Polym. Sci.*, **5**, 2209 (1967).

(5) B. D. Mookherjee, R. Trenkle, and R. R. Patel, *J. Org. Chem.*, **36**, 3266 (1971).

(6) Ketone **4** could also be made (~50%) either by the direct treatment of epoxide **2** with butyllithium[5] or by the hydroboration–oxidation[7] of **1**.

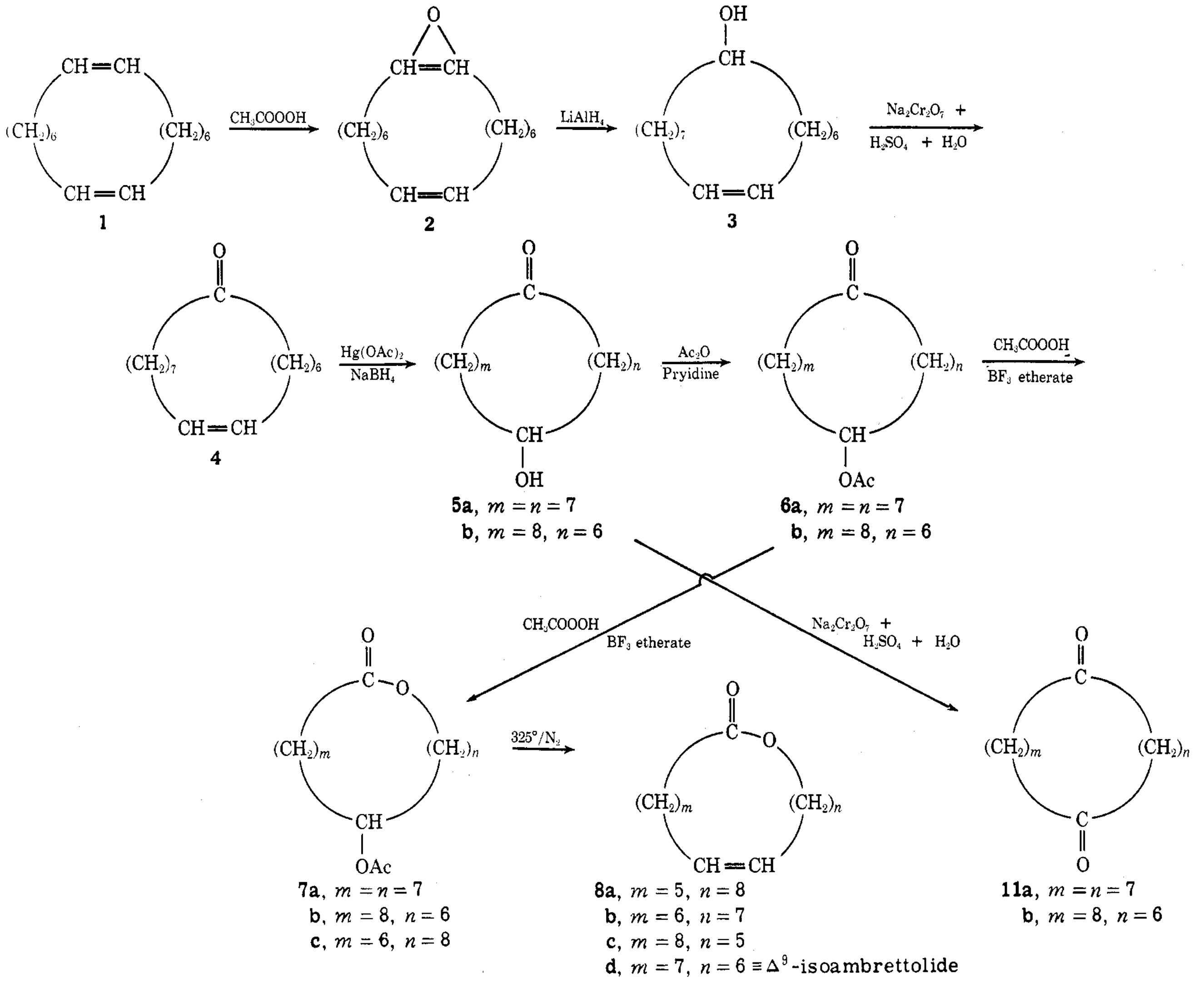
(7) L. Q. Wideman, *J. Org. Chem.*, **33**, 4541 (1968).

(8) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

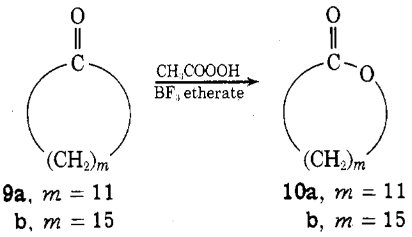
(9) Despite the wide use of boron trifluoride etherate in organic chemistry, its applicability in the Baeyer–Villiger oxidation of macrocyclic ketones to the corresponding lactones with peracetic acid was never explored.

(10) For other known procedures for the conversion of macrocyclic ketones to corresponding lactones, see (a) K. Kosswig, W. Stumf, and Kirchhof, *Justus Liebigs Ann. Chem.*, **681**, 28 (1965); (b) L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

SCHEME I



SCHEME II



8-Cyclohexadecen-1-one (4).—A solution of sodium dichromate (6 g) in concentrated sulfuric acid (4.9 ml) and water (25 ml) was added to a stirred solution of **3** (8.7 g, 0.037 mol) in ether (60 ml) over a 0.5-hr period at room temperature, and the mixture was stirred for an additional 3 hr at that temperature. Water (25 ml) was added, and the resulting green mixture was extracted with ether. The ether extract was washed with aqueous sodium bicarbonate solution (5%) and saturated sodium chloride solution, dried, and on evaporation of solvent yielded 8.6 g of crude material which was chromatographed on deactivated silicic acid (90 g); 5–50% ether in hexane (500 ml/fraction) eluted **4**[5,6] (6.9 g, 80%). Glc (Carbowax 20M) showed two peaks due to cis and trans isomers: ir (neat, 8-*trans*-cyclohexadecen-1-one) 3.41, 3.5, 5.82 (C=O), 6.82, 6.92, 7.02, 7.09, 7.2, 7.29, 9.0, 9.55, 9.7, 10.3 μ (trans CH=CH); mass spectrum *m/e* 236 (molecular ion), 41, 55, 67, 81; ir (neat, 8-*cis*-cyclohexadecen-1-one) 3.33, 3.41, 3.5, 5.82, 6.81, 6.9, 7.02, 7.09, 7.3, 9.0, 9.8, 10.3 (very weak), 13.95 μ (broad, cis CH=CH–); mass spectrum *m/e* 236 (molecular ion), 41, 55, 67, 81, 29.

Anal. Calcd for $C_{16}H_{28}O$: *m/e* 236.2140. Found: *m/e* 236.2148.

9-Hydroxycyclohexadecan-1-one (5a) and 8-Hydroxycyclohexadecan-1-one (5b).—In a 500-ml flask, fitted with a magnetic stirrer, was placed mercuric acetate (40 g, 0.128 mol). To this was added water (60 ml), followed by tetrahydrofuran (30 ml). An intense yellow color was formed. Then a solution of **4** (16.6 g, 0.065 mol) in tetrahydrofuran (30 ml) was slowly added. The reaction mixture was stirred for 20 hr at room temperature. Then 3 *N* sodium hydroxide (60 ml) was added, followed by a solution of 0.5 *M* sodium borohydride (120 ml) in 3 *N* sodium hydroxide, maintaining the temperature of the reaction mixture at 20° by external cooling. The color of the mixture was changed from yellow to olive. The mercury was allowed to settle. Sodium chloride was added to saturate the water layer and then extracted with ether. The combined ether extracts were washed with sodium chloride solution until neutral, dried, and on removal of solvent yielded 18.8 g of crude material which was chromatographed on deactivated silicic acid (200 g); 10–20% ether in hexane (500 ml/fraction) eluted unreacted **4** (6.5 g) and 50–80% ether in hexane eluted the mixture of **5a** and **5b** (10 g, 56%). Glc (both Carbowax 20M and silicone SE-30) of the mixture of **5a** and **5b** showed one peak: ir (neat) 2.92, 3.4, 3.48, 5.81, 5.88 (weak shoulder), 6.8, 6.84, 6.89, 7.05, 7.25, 7.8, 8.45, 8.6, 8.95, 9.1, 9.75, and 14.0 μ (broad); nmr δ 1.1–1.9 (m, 24 H, with strong s at 1.33, internal CH_2), 2.35 (m, 4 H, CH_2COCH_2), 3.58 (b, 1 H, CHOH); mass spectrum *m/e* 254 (molecular ion), 55, 41, 43, 57, 69.

Anal. Calcd for $C_{16}H_{30}O_2$: *m/e* 254.2245. Found: *m/e* 254.2234.

9-Acetoxycyclohexadecan-1-one (6a) and 8-Acetoxycyclohexadecan-1-one (6b).—A solution of the mixture of **5a** and **5b** (4

g) in pyridine (12.6 g) and acetic anhydride (6.5 g) was stirred at room temperature for 20 hr. Water (20 ml) was added and extracted with ether. The combined ether extracts were washed successively with dilute (5%) hydrochloric acid, saturated sodium bicarbonate solution, and sodium chloride solution and dried, and on evaporation of solvent yielded the mixture of **6a** and **6b** (4.5 g, 97%). Glc (silicone SE-30) showed two unresolved peaks; ir (neat, mixture of **6a** and **6b**) 3.45, 3.55, 5.79, 5.84, 6.9, 7.1, 6.3, 8.04, 8.95, 9.74, 10.4 μ; nmr δ 1.1–1.9 (m, 24 H, with strong s at 1.32, internal CH_2), 2.0 (s, 3 H, CH_3COO–), 2.4 (m, 4 H, CH_2COCH_2–), 4.85 (m, 1 H, CHOAc); mass spectrum *m/e* 296 (molecular ion), 43, 55, 41, 236 (M − 60).

Anal. Calcd for $C_{18}H_{32}O_3$: *m/e* 296.2351. Found: *m/e* 296.2345.

Acetoxy Lactones 7 (Probably the Mixture of 7a, 7b, and 7c).—To a stirred solution of **6a** and **6b** (4.3 g, 0.015 mol) in chloroform (100 ml) was slowly added freshly distilled 98% boron trifluoride etherate (2.1 g, 0.015 mol). Peracetic acid (40%, 12 g, 0.06 mol) was added over a period of 15 min and the reaction mixture was stirred for 12 hr at 50°. The mixture was cooled and water was added. The organic layer was separated, washed with water, dried, and concentrated to obtain 4.2 g of crude material which was chromatographed on deactivated silicic acid (100 g); 10% ether in hexane (500 ml) eluted the mixture of acetoxy lactones **7a–c** (2 g, 44%). Glc (silicone SE-30) showed two unresolved peaks: ir (neat mixture) 3.41, 3.5, 5.75, 6.82, 7.28, 8.02, 8.48, 8.65, 9.0, 9.05, 9.3, 9.5, 9.75, 10.4 μ; nmr δ 1.1–1.9 (m, 24 H, s at 1.35, internal CH_2), 2.0 (s, 3 H, CH_3COO), 2.3 (t, 2 H, CH_2CO), 4.1 (t, 2 H, $COOCH_2$), 4.85 (m, 1 H, CHOAc); mass spectrum *m/e* 312 (molecular ion), 43, 55, 255, 252, 82.

Anal. Calcd for $C_{18}H_{32}O_4$: *m/e* 312.2300. Found: *m/e* 312.2309.

Δ^9-Isoambrettolide (8d).—A glass tube (12 × 0.25 in.) filled with nickel turnings was heated to 325° with electrical heating wire. A slow stream of nitrogen (15 ml/min) was passed through the tube, and simultaneously a solution of acetoxy lactones **7** (0.29 g from the previous experiment) in ether (3 ml) was introduced into the tube at a rate of 1 ml/min by means of a 5-ml syringe, followed by 2 ml of ether. The pyrolyzate was collected in two cold traps cooled by a Dry Ice bath. The crude product thus obtained was chromatographed on deactivated silicic acid (10 g); 5–10% ether in hexane (50 ml/fraction) eluted a mixture of products (0.144 g, 62%) whose glc (silicone SE-30) showed one major peak (80%) due to Δ^9-isoambrettolide (**8d**) having a minor shoulder peak (20%) due to the mixture of **8a**, **8b**, and **8c**.

Ir (neat) of Δ^9-isoambrettolide (**8d**): 3.43, 3.51, 5.77, 6.83, 6.93, 7.05, 7.2, 7.4, 8.05, 8.48, 8.74, 8.98, 9.3, 9.45, 9.75, 10.3, 13.85 μ; mass spectrum *m/e* 252 (molecular ion), 82, 41, 67, 96, 55, 81 (all these spectral data are similar to those of authentic *trans*-Δ^9-isoambrettolide from aleuritic acid[8e]).

Anal. Calcd for $C_{16}H_{28}O_2$ (**8d**): *m/e* 252.2089. Found: *m/e* 252.2081.

Ir (neat) of the minor peak (mixture of **8a**,[11] **8b**, and **8c**): 3.41, 3.51, 5.75, 6.85, 6.93, 7.05, 7.2, 7.95, 8.49, 9.0, 9.3, 10.10, 10.32, 11.0 μ; mass spectrum *m/e* 252 (molecular ion), 82, 41, 67, 55, 81.

Anal. Calcd for $C_{16}H_{28}O_2$: *m/e* 252.2089. Found: *m/e* 252.2094.

Cyclododecanolide 10a. A. With Boron Trifluoride Etherate at 50°.—A solution of cyclododecanone **9a** (182.3 g, 1 mol) in chloroform (1 l.) was treated with freshly distilled boron trifluoride etherate (145 g, 1 mol) and 40% peracetic acid (570 g, 3 mol) as in the case of **7**. The usual work-up and distillation gave 108.6 g (54.8%) of **10a**: bp 82–87° (0.5–0.7 mm); ir (neat) 3.45, 3.52, 5.78, 6.9, 7.25, 7.45, 8.0, 8.5, 8.7, 9.1, 9.5, 10.05 μ; nmr δ 1.1–2.0 (m, 18 H, s at 1.35, internal CH_2), 2.35 (diffused t, 2 H, CH_2COO), 4.15 (t, 2 H, $COOCH_2$); mass spectrum *m/e* 198 (molecular ion), 41, 55, 29, 27, 42.

Anal. Calcd for $C_{12}H_{22}O_2$: *m/e* 198.1619. Found: *m/e* 198.162.

B. With Boron Trifluoride Etherate at 25°.—A solution of **9a** (18.2 g, 0.1 mol) in chloroform (100 ml), 40% peracetic acid (57 g, 0.3 mol), and freshly distilled boron trifluoride etherate (2 g) was allowed to react at 25° in the dark for 2 weeks with occasional shaking. The usual work-up and distillation gave 15.8 g (yield 77.2%) of **10a** containing 3% unreacted **9a** (by glc).

Cyclohexadecanolide 10b. A. With Boron Trifluoride Etherate at 50°.—A solution of cyclohexadecanone **9b** (2.15 g, 0.009 mol) in chloroform (18 ml) was treated with boron trifluoride etherate (1.3 g, 0.009 mol) and 40% peracetic acid (5.13, 0.027 mol) as in the case of **7**. After usual work-up and chromatography on deactivated silicic acid (75 g) was obtained 1 g (46%) of **10b**: mp 35° (lit.[10b] mp 33–34°); ir (neat) 3.45, 3.51, 5.78, 6.82, 7.2, 7.4, 8.0, 8.5, 8.75, 9.0, 9.35, 9.45, 10.0, 13.9 μ; nmr δ 1.2–1.8 (broad m, 26 H, s at 1.32, internal CH_2), 2.31 (t, 2 H, CH_2COO), 4.12 (t, 2 H, $COOCH_2$); mass spectrum *m/e* 254 (molecular ion), 55, 41, 69, 43, 29, 83.

Anal. Calcd for $C_{16}H_{30}O_2$: *m/e* 254.2245. Found: *m/e* 254.2250.

B. With Boron Trifluoride Etherate at 25°.—A solution of **9b** (1.67 g, 0.007 mol) in chloroform (14 ml), freshly distilled boron trifluoride etherate (0.35 ml), and 40% peracetic acid (5.32 g, 0.028 mol) was kept at 25° in the dark for 2 weeks with occasional shaking. After usual work-up, the crude material was chromatographed on deactivated silicic acid (50 g); 5% ether in hexane (200 ml) eluted 0.96 g (54%) of **10b**.

C. With Sulfuric Acid and Acetone.[10a]—To a solution of **9b** (1 g) in glacial acetic acid (7 ml), concentrated sulfuric acid (4 ml) was slowly added at 8–10°. Then a solution of 40% peracetic acid (4.5 g) in acetone (2 ml) was added dropwise, keeping the temperature at 30 ± 2°. The reaction mixture was stirred for 1 hr and worked up to give 0.47 g of material. Glc analysis indicated the presence of 70% of **10b** (yield 30.8%) and 30% of **9b**.

D. With Caro's Acid.[10b]—To a stirred solution of **9b** (1 g) in petroleum ether (bp 30–60°) (5 ml) was added dropwise Caro's acid, prepared from concentrated sulfuric acid (40 g), water (7.7 ml), and potassium persulfate (16 g). The resulting dark reaction mixture was stirred for 15 min at 30–40° and then worked up to give 0.35 g (32.8%) of pale yellow oil **10b** which solidified on standing.

Oxidation of Hydroxy Ketones 5a and 5b.—A solution of **5a** and **5b** (9.4 g, 0.037 mol) in ether (100 ml) was treated with a solution of sodium dichromater (6.5 g) in concentrated sulfuric acid (6 ml) and water (30 ml) as in the case of **4**. After usual work-up and chromatography on deactivated silicic acid (100 g) was obtained 7.5 g (80%) of diketones **11a** and **11b**.

Registry No.—*cis*-**3**, 36504-16-2; *trans*-**3**, 36504-17-3; *cis*-**4**, 5120-20-7; *trans*-**4**, 5365-06-0; **5a**, 34778-01-3; **5b**, 34801-49-5; **6a**, 36547-05-4; **6b**, 36508-26-6; **7a**, 36508-27-7; **7b**, 36508-28-8; **7c**, 36508-29-9; **8a**, 17598-28-6; **8b**, 36508-30-2; **8c**, 36508-31-3; **8d**, 28645-51-4; **10a**, 947-05-7; **10b**, 109-29-5.

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[11] Natural ambrettolide **8a** has the following spectral properties: ir (neat) 3.4, 3.5, 5.72, 6.81, 6.9, 7.2, 7.35, 7.74, 7.95, 8.1, 8.4, 8.7, 8.92, 9.2, 9.32, 9.85, 9.95, 10.55, 11.8, 13.4, 13.9 and 14.4 μ (broad); mass spectrum *m/e* 252 (molecular ion), 82, 41, 55, 67, 96.