Synthesis of Ambrettolide from Phloionolic Acid

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The synthesis of ambrettolide (*cis*-hexadec-7-enolide) and its *trans*-stereoisomer is accomplished from *threo*-9,10,18-trihydroxyoctadecanoic acid (phloionolic acid derived from cork) *via* a high-yielding seven-stage synthesis. Since phloionolic acid has recently been obtained from cork in reasonable yield, the latter may be a commercial starting material for the preparation of ambrettolide.

AMBRETTOLIDE, a naturally occurring compound used to induce musk fragrance in perfumes, is *cis*-hexadec-7-enolide and is found in the vegetable oil of ambrette seeds. It has been made in several ways. Thus, Baudart [2] condensed methyl 9-methoxynonanoate and methyl oct-7-enoate with sodium to give an acyloin that led, *via* an eight-stage sequence, to *trans*-ambrettolide. Sabnis *et al.*[3] started with aleuritic acid (*threo*-9,10,16-trihydroxy-hexadecanoic acid), interchanged its carboxyl and Ω hydroxy groups and, in eight steps, reached *trans*-ambrettolide whilst Mookherjee *et al.*[4] starting from cyclohexadeca-1,9-diene obtained a mixture of ambrettolide and its isomers in several steps. In spite of this work there is still no satisfactory commercial synthesis of ambrettolide. Recently we produced phloionic and phloionolic acids from cork in yields of 5 and 3.5% respectively (based on crude cork), and here we describe the ready conversion of the latter compound into ambrettolide *via* a high-yielding multi-step reaction sequence.

Phloionolic acid (*threo*-9,10,18-trihydroxyoctadecanoic acid) (1) was treated with acetic anhydride–pyridine to give the corresponding 18-triacetoxy-compound (2); its

(1) *threo*-$HOCH_2{\cdot}[CH_2]_7CH(OH){\cdot}CH(OH){\cdot}[CH_2]_7{\cdot}CO_2H$
(2) *threo*-$AcOCH_2{\cdot}[CH_2]_7{\cdot}CH(OAc){\cdot}CH(OAc){\cdot}[CH_2]_7{\cdot}CO_2H$
(3) *threo*-$AcOCH_2{\cdot}[CH_2]_7{\cdot}CH(OAc){\cdot}CH(OAc){\cdot}[CH_2]_5{\cdot}CH{=}CH_2$
(4) $HOCH_2{\cdot}[CH_2]_7{\cdot}CH(OH){\cdot}CH(OH){\cdot}[CH_2]_5{\cdot}CO_2H$ (4a) *threo*, (4b) *erythro*
(5) $BrCH_2{\cdot}[CH_2]_7{\cdot}CH(Br){\cdot}CH(Br){\cdot}[CH_2]_5{\cdot}CO_2H$ (5a) *erythro*, (5b) *threo*
(6) $ICH_2{\cdot}[CH_2]_7{\cdot}CH{=}CH[CH_2]_5{\cdot}CO_2H$ (6a) *trans*, (6b) *cis*
(7) $CH{-}[CH_2]_5{-}C{=}O$ / $CH{-}[CH_2]_8{-}O$ (7a) *trans*, (7b) *cis*

identity was established on the basis of n.m.r. spectral data. On oxidative decarboxylation with lead tetra-acetate, copper acetate, and pyridine in benzene it gave *threo*-8,9,17-triacetoxyheptadec-1-ene (3).[5-7] The latter compound was oxidized by potassium permanganate in benzene–water with methyltrioctylammonium chloride as a phase-transfer agent,[8] and then subjected to alkaline hydrolysis to afford *threo*-7,8,16-trihydroxyhexadecanoic acid (4a) (isoaleuritic acid [9]).

The acid (4a) on treatment with hydrobromic acid in acetic acid was converted into *erythro*-7,8,16-tribromohexadecanoic acid (5a).[10] Bromination of a *threo*-glycol gives an *erythro*-dibromo-derivative, and bromination of an *erythro*-glycol yields a *threo*-dibromo-derivative, the result of three inversions induced by neighbouring-group participation.[11] *erythro*-7,8,16-Tribromohexadecanoic acid was stereospecifically debrominated by sodium iodide in acetone to give 16-iodo-*trans*-hexadec-7-enoic acid (4a) in good yield [12]; the reaction was accompanied by displacement of Br by I. 16-Iodo-*trans*-hexadec-7-enoic acid in dimethyl sulphoxide when treated at 80 °C with cesium carbonate, afforded *trans*-hexadec-7-enolide (7a); potassium carbonate, the more usual reagent for this cyclization [13] gave a lower yield of product.

Since ambrettolide has a *cis* double-bond, it was necessary to convert *threo*-7,8,16-trihydroxyhexadecanoic acid into *erythro*-7,8,16-trihydroxyhexadecanoic acid (4b); this was accomplished by treatment of the *threo*-acid, dissolved in acetic acid, with dry HCl at 110—115 °C.[14] With hydrobromic acid in acetic acid the acid (4b) gave *threo*-7,8,16-tribromohexadecanoic acid (5b), debromination of which with NaI in acetone yielded 16-iodo-*cis*-hexadec-7-enoic acid (6b). Cyclization of this in dimethyl sulphoxide with cesium carbonate led to *cis*-hexadec-7-enolide (7b). Ambrettolide and its *trans*-stereoisomer have many properties closely similar, although they are clearly distinguished by i.r. spectroscopy and gas chromatography; thus *trans*-ambrettolide shows a strong i.r. band at 970 cm^{-1}, which is absent in ambrettolide; ambrettolide shows *cis*-double bond absorption at 694 cm^{-1}. *trans*-Ambrettolide has a higher R_t value than ambrettolide under the same gas chromatography conditions. The physical properties of our ambrettolide are in agreement with literature values.[4,15,16]

EXPERIMENTAL

General Techniques.—The i.r. spectra of oils were recorded as liquid films and of solids as KBr discs; a Perkin-Elmer model 281 spectrotrometry was used. ^1H N.m.r. spectra were determined at 60 MHz on a Perkin-Elmer model R-12B machine with Me_4Si as internal standard. Mass spectra were performed at 70 eV on a Varian 166 machine using a direct-inlet system. Gas chromatography was carried out on a Perkin-Elmer model 3920B, with helium as carrier gas and a Minigrator to integrate the areas. The following conditions were used to distinguish ambrettolide

from its *trans*-stereoisomer: a 2 m × 1/8 in column of 3% SE-30 with $t_{inj.}$ 300 °C, $t_{col.}$ 180 °C, $t_{det.}$ 300 °C at a flow rate of 15 ml/min. Column chromatography was performed on silica-gel Merck (0.063—0.200 mm) and t.l.c. on plates (0.25 mm) of silica gel Merck (G.60 and 60 HF_{254}).

threo-9,10,18-*Trihydroxyoctadecanoic Acid* (1).—This compound may be obtained by the method either of Zetsche-Sonderegger [17] or of Seoane-Ribas.[18] Alternatively one of us has recently patented [19] an improved method of preparation (3.5% of pure phloionolic acid related to the rough cork starting material).

threo-9,10,18-*Triacetoxyoctadecanoic Acid* (2).—*threo*-9,10,18-Trihydroxyoctadecanoic acid (phloionolic acid, m.p. 104 °C) (5 g, 15.06 mmol) dissolved in dry pyridine (50 ml) was treated at room temperature with acetic anhydride (10 ml, 105 mmol) for 4 days; the reaction mixture was poured into water (60 ml), heated at 90 °C for few minutes, and then cooled and extracted with ethyl acetate. Evaporation of solvent from the extract gave *threo*-9,10,18-triacetoxyoctadecanoic acid (2) as an oil (6·508 g, 94.3%), $\nu_{max.}$ 3 200—2 600br (acid), 2 920, 2 860, 1 740 (CO of acetate), 1 710 (CO of acid), 1 380, 1 230, 1 030, 950, and 720 cm^{-1}; δ ($CDCl_3$) 11.0 (s, 1 H, CO_2H), 5.0 (m, 2 H, CHOAc), 4.02 (t, 2 H, *J* 6.6 Hz, CH_2OAc), 2.32 (t, 2 H, *J* 6.6 Hz, CH_2CO_2), 2.02 (s, 6H, CH_3CO), 1.98 (s, 3 H, $CH_3CO_2CH_2$), and 1.31 (m, 26 H).

threo-8,9,17-*Triacetoxyheptadec*-1-*ene* (3).—A mixture of threo-9,10,18-triacetoxyoctadecanoic acid (6.3 g, 13.75 mmol), anhydrous $Cu(OAc)_2$ (1.1 g, 6.06 mmol), and pyridine (1.5 ml) was vigorously stirred with dry benzene (50 ml). The mixture was flushed with nitrogen and then heated to reflux point while lead tetra-acetate (11.8 g, 26.6 mmol) was added slowly (220 mg portions) during 24 h. The excess of lead tetra-acetate was eliminated with ethyleneglycol. The reaction mixture was poured into water and extracted with benzene; the isolated product was chromatographed on a silica-gel column, from which CH_2Cl_2 eluted *threo*-8,9,17-triacetoxyheptadec-1-ene (3) (3.91 g, 69%) as an oil, $\nu_{max.}$ 3 080, 2 930, 2 860, 1 740 (CO ester) 1 640, 1 380, 1 230, 1 030, 990, 910 ($CH{=}CH_2$), and 720 cm^{-1}; δ (CCl_4) 5.85 (m, 1 H, CH=C), 4.97 (m, 4 H, $C{=}CH_2$ and CHOAc), 4.02 (t, 2 H, *J* 6.6 Hz, CH_2OAc), 2.02 (s, 6 H, CH_3CO), 1.98 (s, 3 H, $CH_3CO_2CH_2$), and 1.31 (m, 24 H); *m/e* (rel.int.) (no M^+) 325 (2.94, $M - 60$), 292 (1.34, $M - 2 \times 60$), 232 (0.25, $M - 3 \times 60$), 243 [13.11, $AcO(CH_2)_8\overset{+}{C}HOAc$], 169 [0.51, $ACO\overset{+}{C}H(CH_2)_5CH{=}CH_2$], 201 (41.44, 243 − 42), 109 (7.9, 169 − 60), 125 [2.12, $AcO(CH_2)_8^+$], and 123 (14.68).

threo-7,8,16-*Trihydroxyhexadecanoic Acid* (4a) (*Isoaleuritic Acid*).—*threo*-8,9,17-Triacetoxyheptadec-1-ene (3.9 g, 9.46 mmol) dissolved in benzene (42 ml) was shaken with trioctylmethylammonium chloride (190 mg, 0.47 mmol) and $KMnO_4$ (6.004 g, 38 mmol) in water (28 ml) for 9 h at room temperature. Excess of permanganate was eliminated with sodium sulphite after acidification of the mixture with hydrochloric acid. The reaction product was extracted with 6% aqueous sodium hydroxide and the extract heated to reflux point for 3 h. The solution was cooled and acidified with hydrochloric acid to give a precipitate of *threo*-7,8,16-trihydroxyhexadecanoic acid (4a) (2.362 g, 82%) which, recrystallised from ethyl acetate, had m.p. 94—95 °C; $\nu_{max.}$ 3 300 (OH), 2 920, 2 860, 1 700 (CO acid), 1 465, 1 120, 1 050 and 720 cm^{-1}; δ [$(CD_3)_2SO$] 5.4 (m, 4 H, CO_2H and OH), 3.4 (hidden t, 2 H, CH_2OH) 3.2, (m, 2 H, CHOH), 2.2 (hidden t, 2 H, CH_2COOH), and 1.3 (m, 22 H). This compound has been obtained in a quite different way by Bhattacharyya and his collaborators.[9]

erythro-7,8,16-*Tribromohexadecanoic Acid* (5a).—*threo*-7,8,16-Trihydroxyhexadecanoic acid (0.702 g, 2.3 mmol) was treated with an excess of hydrobromic acid in acetic acid and a little of sulphuric acid, according to the method of Ames and Bowman.[10] The product extracted with ether was erythro-7,8,16-*tribromohexadecanoic acid* (5a) (1.014 g, 89%) as an oil, $\nu_{max.}$ 3 100—2 600 (acid), 2 920, 2 860, 1 700 (CO acid), 1 460, 940, and 720 cm^{-1}; δ ($CDCl_3$) 11.7 (s, 1 H, CO_2H), 4.12 (m, 2 H, CHBr), 3.38 (t, 2 H, *J* 6.6 Hz, CH_2Br), 2.36 (t, 2 H, *J* 6.6 Hz, CH_2CO_2H), 2.0 (m, 6 H, CH_2CHBr and CH_2CH_2Br), and 1.36 (m, 16 H). The mass spectrum gave isotopic peaks for Br_3 at *m/e* (rel. int.) 472 (0.09), 474 (0.34), 476 (0.33), and 478 (0.09), corresponding to $C_{16}H_{27}Br_3O$ (M—H_2O); isotopic peaks for Br_2 at 393 (0.45), 395 (0.86), and 397 (0.54), corresponding to $C_{16}H_{27}Br_2O$ ($M - H_2O - Br$); isotopic peak Br at 313 (13.83) and 315 (13.31) corresponding to $C_{16}H_{26}BrO$ ($M - 2Br - H_3O$).

erythro-7,8,16-*Trihydroxyhexadecanoic Acid* (4b).—*threo*-7,8,16-Trihydroxyhexadecanoic acid (4a) (m.p. 94—95 °C) (1.7 g, 5.59 mmol) dissolved in acetic acid (10 ml) was heated at 110—115 °C and flushed with a stream of anhydrous hydrogen chloride for 3 h. The solvent was removed under reduced pressure and the residue was submitted to saponification by refluxing it with 10% aqueous sodium hydroxide (85 ml) for 3 h. The solution was acidified with hydrochloric acid to give a precipitate which was treated with warmed benzene; the benzene-insoluble portion (1.340 g) was erythro-7,8,16-*trihydroxyhexadecanoic acid* (4b) which, crystallised from ethyl acetate (1.088 g, 64%), had m.p. 121 °C, $\nu_{max.}$ 3 300 (OH), 2 920, 2 860, 1 690 (CO acid), 1 465, 1 100, 1 070, 950, and 720 cm^{-1}; δ [$(CD_3)_2SO$] 5.2 (m, 4 H, CO_2H and OH), 3.4 (t, 2 H, *J* 6.6 Hz, CH_2OH), 3.12 (m, 2 H, CHOH), 2.2 (t, 2 H, *J* 6.6 Hz, CH_2CO_2H) 1.3 (m, 22 H); *m/e* (rel. int.), (no M^+) 305 (0.34, $M + 1$), 159 [36.82, $HO(CH_2)_8\overset{+}{C}HOH$] 145 [28.97, $HO\overset{+}{C}H(CH_2)_5CO_2H$], 269 (0.42, $M + 1 - 2 \times 18$), and 251 (0.60, $M + 1 - 3 \times 18$).

threo-7,8,16-*Tribromohexadecanoic Acid* (5b).—*erythro*-7,8,16-Trihydroxyoctadecanoic acid (0.512 g, 1.68 mmol) treated with hydrobromic acid in acetic acid, according to the method of Ames and Bowman,[10] gave *threo*-7,8,16-tribromohexadecanoic acid (5b) as an oil (0.755 g, 91%), $\nu_{max.}$ 3 100—2 600 (acid), 2 920, 2 860, 1 700 (CO acid), 1 460, 940, and 720 cm^{-1}; δ (CCl_4) 11.7 (s, 1 H, CO_2H), 4.12 (m, 2 H, CHBr), 3.38 (t, 2 H, *J* 6.6 Hz, CH_2Br), 2.36 (def. t, 2 H, *J* 6.6 Hz, CH_2CO_2H), 2.0 (m, 6 H, $BrCCH_2$), and 1.36 (m, 16 H). This tribromo-acid (5b) was treated with diazomethane to give methyl *threo*-7,8,16-tribromohexadecanoate; isotopic peaks for Br_3 at *m/e* (rel. int.) 473 (0.32), 475 (1.06), 477 (1.09), and 479 (0.34) corresponding to $C_{16}H_{28}Br_3O$ ($M - 31$); isotopic peaks for Br_2 at 425 (2.13), 427 (4.15), and 429 (2.02), corresponding $C_{17}H_{31}Br_2O_2$ (M − Br), and 393 (0.71), 395 (1.37), and 397 (1.17), corresponding to $C_{16}H_{27}Br_2O$; isotopic peaks for Br at 313 (14.39) and 315 (14.10) corresponding to $C_{16}H_{26}BrO$ and 345 (23.05) and 347 (22.41) corresponding to $C_{17}H_{30}BrO_2$ and 265 (21.36, $C_{17}H_{29}O_2$).

cis-16-*Iodohexadec*-7-*enoic Acid* (6b).—*threo*-7,8,16-Tribromohexadecanoic acid (0.65 g 1.31 mmol) dissolved in dry acetone was heated to reflux with NaI (1.98 g, 13.2 mmol) for 56 h, under nitrogen and with continuous stirring; a solution of 10% aqueous sodium thiosulphate was then added to eliminate iodine. Ether extracted *cis*-

16-iodohexadec-7-enoic acid (6b) (0.435 g, 87%), $\nu_{max.}$ 3 100—2 500 (acid), 2 920, 2 860, 1 710 (CO acid), 1 460, 940, and 720 cm^{-1}; δ ($CDCl_3$) 10.8 (s, 1 H, CO_2H), 5.35 (m, 2 H, CH=CH), 3.12 (t, 2 H, *J* 6.6 Hz, CH_2I), 2.3 (def. t, 2 H, *J* 6.6 Hz, CH_2CO_2H), 1.98 (m, 6 H, CH_2C and CH_2I), and 1.32 (m, 16 H). Esterification of the iodo-acid (6b) with ethanol and sulphuric acid gave *ethyl* 16-*iodo*-cis-*hexadec-7-enoate*, *m/e* (rel. int.) 408 (0.13, *M*), 379 (0.08, *M* − 29) 362 (1.92, *M* − 46), 281 (6.30, *M* − 127), and 280 (2.08, *M* − IH).

16-Iodo-*trans*-hexadec-7-enoic acid (6a) was obtained in the same way as (6b) from *erythro*-7,8,16-tribromohexadecanoic acid (0.5 g, 1.01 mmol) and NaI (1.515 g, 10.1 mmol). The product (6a) (340 mg, 88%), had $\nu_{max.}$ 3 100—2 600 (acid), 3 000, 2 920, 2 860, 1 710 (CO acid), 970, and 720 cm^{-1}; δ (CCl_4) 10.4 (s, 1 H, CO_2H), 5.35 (m, 2 H, CH=CH), 3.12 (t, 2 H, *J* 6.6 Hz, CH_2I), 2.3 (def. t, 2 H, *J* 6.6 Hz, CH_2CO_2H), and 1.98 (m, 6 H, CH_2C= and CH_2I), 1.32 (m, 16 H). The mass spectrum was similar to that of the *cis*-stereoisomer.

cis-*Hexadec-7-enolide* (7b): *Ambrettolide*.—16-Iodo-*cis*-hexadec-7-enoic acid (0.435 g, 1.14 mmol) dissolved in dimethyl sulphoxide (6 ml) was treated slowly and with continuous stirring with Cs_2CO_3 (1.486 g, 4.56 mmol) in anhydrous dimethyl sulphoxide at 80 °C for 7 h. The solid carbonate was filtered off and the filtrate was poured into water and extracted with ether. The reaction product was purified *via* a column of silica gel; carbon tetrachloride eluted cis-*hexadec-7-enolide* (7b) (0.233 g, 81%), $\nu_{max.}$ 2 930, 2 850, 1 740 (CO lactone), 1 460, 1 382, 1 350, 1 242, 1 180, 1 149, 1 115, 1 065, 1 000, 720, and 694 cm^{-1}; δ (CCl_4) 5.35 (m, 2 H, CH=CH), 4.15 (t, 2 H, *J* 5.3 Hz, CH_2OCO), 2.29 (hidden t, 2 H, CH_2CO_2), 2.0 (m, 4 H, CH_2CH=), and 1.3 (m, 18 H); *m/e* 252 (41.6, M^+), 253 (7.61, *M* + 1), 254 (1.61, *M* + 2), 234 (6.29, *M* − 18), 224 (3.5, *M* − 28), 206 (1.24, *M* − 18 − 28), and 41 (100); R_t 1 339 s.

trans-*Hexadec-7-enolide* (7a): trans-*Ambrettolide*.—This compound was obtained, by the same method as compound (7b), from 16-iodo-*trans*-hexadec-7-enoic acid (0.114 g, 0.30 mmol) with Cs_2CO_3 (0.392 g, 1.20 mmol); the yield of (7b) was 63 mg (83%), $\nu_{max.}$ 2 930, 2 850, 1 740 (CO lactone), 1 460, 1 440, 1 390, 1 250, 1 120, 1 060, 970 (*trans*-CH=CH), and 720 cm^{-1}; δ (CCl_4) 5.3 (m, 2 H, CH=CH), 4.1 (t, 2 H, *J* 5.3 Hz, CH_2OCO), 2.29 (hid. t, 2 H, CH_2CO_2), 2.0 (m, 4 H, CH_2CH=), and 1.3 (m, 18 H). The mass spectrum of (7a) was identical with that of (7b); R_t 1 411 s.

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