A Simple Synthesis of *trans*-Δ^9-Isoambrettolide, Dihydroambrettolide, and Methyl 16-Acetoxy-9-hexadecenoate

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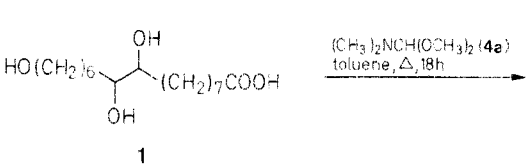
Δ^9-Isoambrettolide (**2**) and methyl 16-acetoxy-9-hexadecenoate (**3**) are prepared from aleuritic acid and dimethylformamide dialkyl acetals by a one-pot reaction. Catalytic hydrogenation of products **2** and **3** affords dihydroambrettolide (**6**) and methyl 16-acetoxyhexadecanoate (**7**), respectively.

Ambrettolide and derivatives (iso and dihydro) are important materials for perfumery with a musk odour. *threo*-Aleuritic acid (**1**), the main constituent of shellac, is readily available and cheaper. Isoambrettolide is formally the dehydration-dehydroxylation product of aleuritic acid. The reported methods for the hemisynthesis of Δ^9-isoambrettolide (**2**) from aleuritic acid are multistep procedures[1] or use expensive reagents such as phosphonium iodide.[2]

We describe herein a one-pot synthesis of trans Δ^9-isoambrettolide (**2**) and methyl 16-acetoxy-9-hexadecenoate (**3**) from aleuritic acid (**1**) in good yield.

Dimethylformamide dialkyl acetals **4** are esterification reagents[3] which react with *vic*-diols to form cyclic formamide acetals having a 1,3-dioxolane structure; these compounds are precursors of olefins.[4]

Dimethylformamide dimethyl acetal (**4a**) reacted with aleuritic acid (**1**) in refluxing toluene to give the formamide acetal **5a**. *In situ* treatment of **5a** with acetic anhydride and pyrolysis gave methyl 16-acetoxy-9-hexadenoate (**3**), a useful synthon for the synthesis of fatty acid derivatives.



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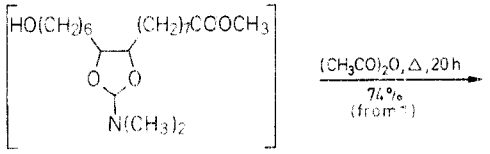
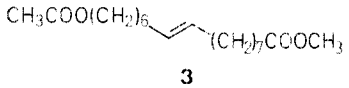


5a



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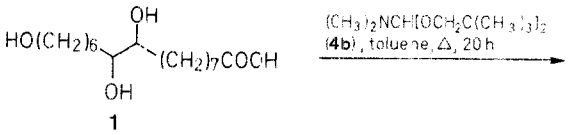
With hindered dimethylformamide acetals such as dimethylformamide bis[2,2-dimethylpropyl] acetal (**4b**), lactone cyclization of acid **1** is preferred over esterification to give lactone **5b** which on treatment with acetic anhydride affords *trans* Δ^9-isoambrettolide (**2**). Catalytic hydrogenation of compounds **2** and **3** easily gives dihydroambrettolide (**4**) and methyl 16-acetoxyhexadecanoate (**7**), respectively.



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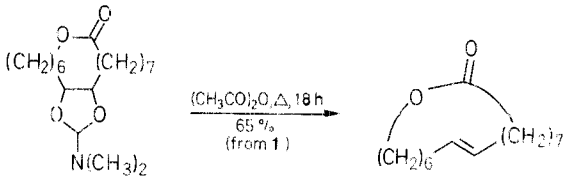
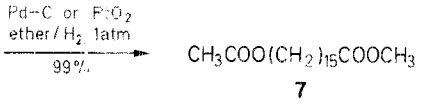


5b 2



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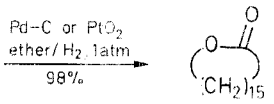

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The efficiency and convenience of the procedure and the relatively low price of the reagents renders the present method competitive with the traditional procedures for the synthesis of the above described perfume derivatives and synthons.

Aleuritic acid (**1**) and the dimethylformamide acetals (**4**) are commercially available from Fluka.

***trans*-Δ^9-Isoambrettolide (2):**

Aleuritic acid (**1**; 3.04 g, 10 mmol) and dimethylformamide bis[2,2-dimethylpropyl] acetal (**4b**; 4.62 g, 20 mmol) in toluene (100 ml) are refluxed under nitrogen for 20 h. The toluene is distilled off under vaccuum, acetic anhydride (100 ml) is added, and the mixture is refluxed for 18 h. It is then filtered and acetic anhydride is distilled off. The resulting oil is distilled in a Kugelrohr apparatus at 110–120°C/0.2 torr to give product **2** as a colorless liquid (yield: 0.9 g), and polymers (1.7 g). Thermal depolymerisation[5] by distillation of the polymer with anhydrous magnesium chloride (0.17 g for 1.7 g polymers) gives an extra amount of **2**; total yield: 1.65 g (65%).

$C_{16}H_{28}O_2$ (252.2) calc. C 76.13 H 11.19 found 75.80 11.00

MS (70 eV): m/e = 252 (M^+), 137, 123.

IR (film): ν = 1730 (CO); 1235, 970 (C=C_{trans}) cm^{-1}.

^{1}H-NMR (CCl_4): δ = 5.4 (m, 2H, CH=CH); 4.1 (t, 2H, CH_2O); 2.4–2.2 (m, 6H, CH_2CO, CH_2–C=); 1.3 ppm (m, 18H, CH_2).

Dihydroambrettolide (6):

Δ^9-Isoambrettolide (**2**; 0.5 g) in ether (30 ml) is hydrogenated in the presence of 5% palladium/charcoal (0.5 g) or platinum oxide (Adam's catalyst; 50 mg) until absorption of hydrogen (1 atm) ceases. After filtering off the catalyst and evaporation of ether, the residue is crystallized from ether; yield: 0.494 g (98%); m.p. 33–34°C (Lit.[1], m.p. 33.5–34°C).

$C_{16}H_{28}O_2$ (254.2) calc. H 72.52 H 11.89 found 72.23 11.72

MS (70 eV): m/e = 254 (M^+), 236, 211.

IR (film): ν = 1730 (CO); 1235 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 4.1 (t, 2H, CH_2O); 2.2 (t, 2H, CH_2CO); 1.3 ppm (m, 26H, CH_2).

Methyl 16-Acetoxy-9-hexadecenoate (3):

Aleuritic acid (**1**; 3.04 g, 10 mmol) and dimethylformamide dimethyl acetal (**4a**; 3.57 g, 30 mmol) in toluene (100 ml) are refluxed under

nitrogen for 18 h. The toluene is distilled off under vacuum and acetic anhydride (100 ml) is added. After a reflux period of 20 h, the solution is filtered and acetic anhydride is distilled off. The resulting product is distilled in a Kugelrohr apparatus to give product **3** as a colorless liquid; yield: 2.45 g (74%); b.p. 150–160°C (bath)/0.1 torr.

$C_{19}H_{34}O_4$ (326.25) calc. C 69.89 H 10.50 found 69.62 10.30

MS (70 eV): *m/e* = 326 (M^+), 295 (M – OCH), 260 (M – AcOH).

IR (film): ν = 1735 (CO); 1720, 1635 (C=C), 1230 (Ac–O); 960 ($CH=CH_{trans}$) cm^{-1}.

^{1}H-NMR (CCl_4): δ = 5.45 (m, 2H, CH=CH); 4.1 (t, 2H, CH_2–O); 3.65 (s, 3H, OCH_3); 2.3 (m, 6H, CH_2–C=, CH_2CO); 2.05 (s, 3H, CH_3CO), 1.4 ppm (m, 18H, CH_2).

Methyl 16-Acetoxyhexadecanoate (7):

Methyl 16-acetoxy-9-hexadecenoate (**3**; 0.65) in ether is hydrogenated in the presence of 5% palladium/charcoal (0.6 g) or platinum oxide (65 mg). The same work-up affords product **7** as colorless plates; yield: 0.6 g (99%); m.p. 30–32°C.

$C_{19}H_{36}O_4$ (328.3) calc. C 65.46 H 11.05 found 65.50 11.08

MS (70 eV): *m/e* = 328 (M^+), 297 (M – OCH_3), 268 (M – AcOH).

IR (film): ν = 1730–1720 (CO); 1450, 1030, 1030, 880, 870 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 4.1 (t, 2H, CH_2O); 3.7 (s, 3H, OCH_3), 2.2 (t, 2H, CH_2CO); 2.05 (s, 3H, CH_3CO); 1.3 ppm (m, 26H, CH_2).

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