Aleuritic Acid in Perfumery and Pheromones

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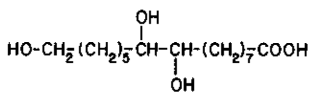
The lac insect *Laccifer Lacca Kerr*, native to India and Thailand, secretes a resin whose processed form known as shellac[1] has been marketed commercially for a long time. An alkaline hydrolysis of the resin yields aleuritic acid [**1**], also sold on commercial scale in recent years. It was first isolated several decades ago by Tschirch and Farner[2] and its structure was shown subsequently to be 9,10,16-trihydroxyhexadecanoic acid by Nagel and coworkers.[3,4] The natural acid is of threo configuration, conclusively shown by later work.[5] The natural acid is racemic in nature and has been resolved into the enantiomers through the brucine[6] as well as the ephedrine salts.[7] The racemic isomer of erythro configuration has also been reported[5] through a configurational inversion in several steps. Different methods of synthesis[8-10] of aleuritic acid have also been reported.

threo



$HO{-}CH_2{-}(CH_2)_5{-}\overset{OH}{\overset{|}{C}H}{-}\underset{OH}{\underset{|}{C}H}{-}(CH_2)_7{-}COOH$

I

Reactions of Aleuritic Acid

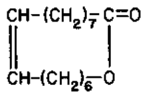
Aleuritic acid has been olefinated[10-15] at the 9,10-position by several procedures, most of them stereospecific. The terminal alcohol function has been converted into aldehyde[16,17] with CrO_3-pyridine in good yield. The aldehyde has been masked as the corresponding dithiane derivative,[18] obtainable as a stable crystalline solid. Synthesis of the terminal bromo,[19] as well as iodo, derivatives by simple classical procedures have also been reported.[16]

The structural features of aleuritic acid are quite amenable to a variety of modifications as shown above. With the availability of terminal functionalities at both ends, cyclizations and chain elongations by well-known procedures are feasible. Further, with numerous procedures available for stereospecific olefinations, the configurationally pure erythro and threo 1,2-glycols provide a Z or E double bond, respectively, of high purity at the appropriate position and at an appropriate stage where feasible. An added advantage is that most of the glycols are crystalline solids, especially those of erythro configuration. Moreover, chain shortening is also feasible, leading to a variety of uses for aleuritic acid in organic synthesis. These objectives have been pursued extensively by us for some time, and some of the results are described in this article.

Cyclization

A large number of macrocyclic lactones and ketones possessing musk odor have been synthesized starting from aleuritic acid. The early work of Hunsdiecker on the use of aleuritic acid in the synthesis of 9-hexadecen-1,16-olide[19] [**2**] and civetone[11,20] [**3**] stands out prominently. His key compound was 16-bromo(E/Z)-9-hexadecenoic acid [**4**] for cyclization using K_2CO_3 under conditions of high dilution to get the lactone. For the synthesis of civetone [**3**], the required increase in chain length was affected by an acetoacetic ester condensation on the acid chloride of [**4**] at the carbonyl end before the cyclization reaction.

E/Z



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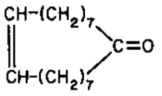
E/Z



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$Br{-}CH_2{-}(CH_2)_5{-}CH{=}CH{-}(CH_2)_7{-}COOH$ 4

E/Z

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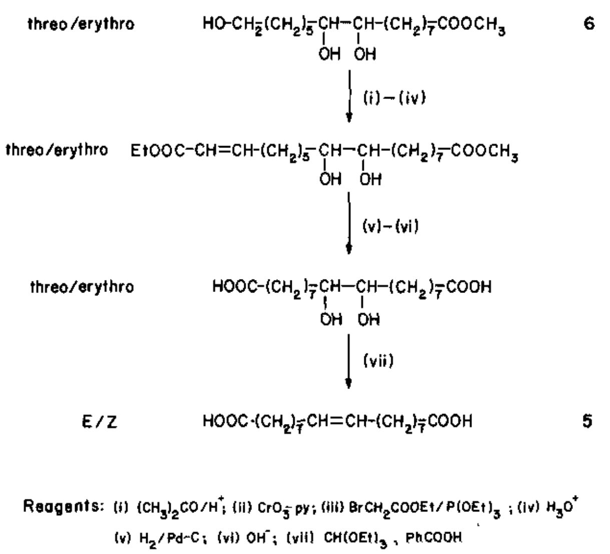
Later, Blomquist and his group[21] utilized 9-octadecene-1,18-dioic acid [**5**], obtained by chain elongation of [4] by alkylation of the ω-bromo end, using the reaction with malonic ester. The cyclization of the dioic acid [**5**] was accomplished using the corresponding diacid chloride through the formation of the bifunctional ketene under high dilution in the presence of Et_3N, leading to the synthesis of civetone [**3**].

$HOOC-(CH_2)_7-CH=CH-(CH_2)_7-COOH$ 5

E/Z

We have prepared[22] the dioic acid [**5**] (both pure E and Z isomers) from methyl threo/erythro aleuritate [**6**] (Scheme 1) giving good yields at all stages.

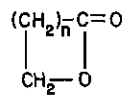


Reagents: (i) $(CH_3)_2CO/H^+$; (ii) CrO_3-py; (iii) $BrCH_2COOEt/P(OEt)_3$; (iv) H_3O^+ (v) H_2/Pd-C; (vi) OH^-; (vii) $CH(OEt)_3$, PhCOOH

Scheme 1. Synthesis of 9-octadecene-1,18-dioic acid from methyl aleuritate for cyclization to civetone

Subsequent to these syntheses, in a series of publications[23,24] Bhattacharyya reported starting with threo aleuritic acid and synthesizing the following:

pentadecan-1,15-olide [7] (n=13) (Exaltolide)
hexadecan-1,16-olide [7] (n=14)
9-hexadecen-1,16-olide [**2**]
cyclopentadecanone [8] (n=12) (Exaltone)
civetone [**3**]
dihydrocivetone [8] (n=14)



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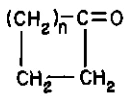

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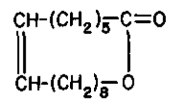
For cyclization to lactones, p-TsOH was employed on the corresponding ω-hydroxy acids. For the formation of cyclic ketones, intramolecular acyloin condensation was utilized. Using different procedures and retaining the same thematic approach, Majee et al.[25] reported the synthesis of 9-hexadecen-1,16-olide [**2**] and its dihydro derivative [**7**] (n=14).

Bhattacharyya et al.[26] also reported the synthesis of the E-isomer of natural ambrettolide [**9**], a highly valuable perfumery material, starting from threo aleuritic acid by interchanging the terminal functionalities in several steps and finally affecting the cyclization using p-TsOH. A cyclization of 16-hydroxy(E)-9-hexadecenoic acid (threo aleuritic acid's acetonide) and 16-hydroxy pentadecanoic acid with cyanuric chloride in Et_3N has also been reported.[27] A single-pot reaction yielding (E)-9-hexadecen-1,16-olide [**2**] (trans- Δ^9-iso-ambrettolide) by heating threo aleuritic acid with dimethylformamide dialkyl acetal is also known.[14] Phloionolic acid (threo-9,10,18 trihydroxy-octadecanoic acid, obtained from cork) was also used in the synthesis of (E and Z)-7-hexadecen-1,16-olide [**9**] (ambrettolides) after cutting off two carbon atoms from the carboxyl end.[28]



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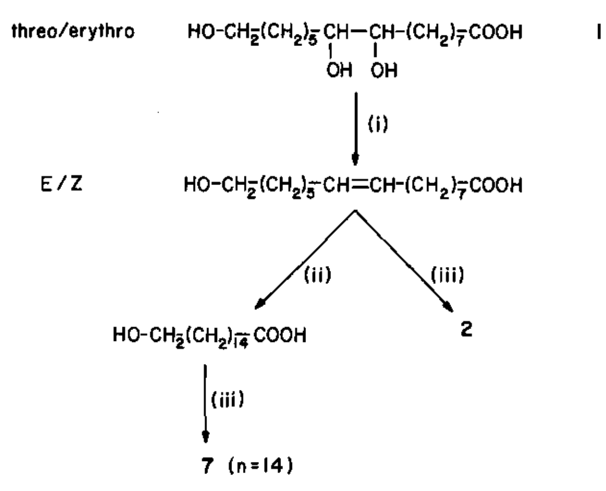
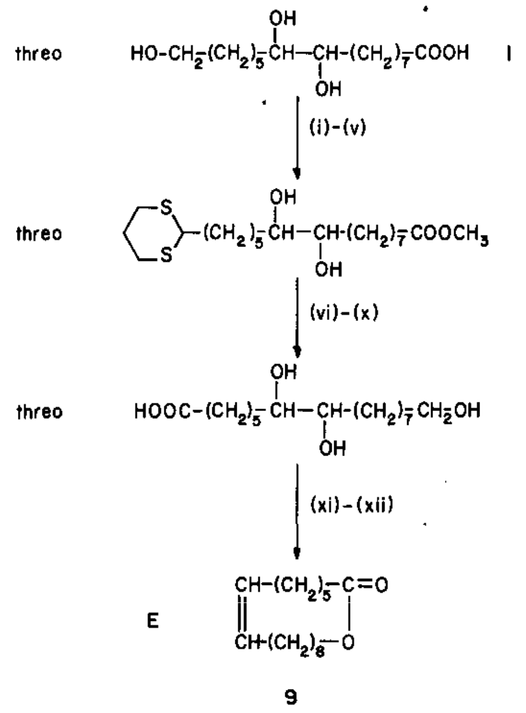
During the course of our work on aleuritic acid and its derivatives, we utilized the cesium carbonate procedure for the preparation of pentadecan-1,15-olide [**7**] (n=13), 9,10-dihydroxyhexadecan-1,16-olide, and (E and Z) 9-hexadecen-1,16-olide [**2**] (iso-ambrettolides) from the corresponding ω-iodo acids.[29] The cesium was recovered as cesium iodide. The above lactones are commercial compounds, obtained from various sources and procedures.

The cyclization is also successful using di-n-butyltin oxide[30] (Bu_2SnO) with several aleuritic acid derivatives.[18,31] This is illustrated by the example of hexadecan-1,16-olide [**7**] (n=14), (E and Z)-9-hexadecen-1,16-olide [**2**] (iso-ambrettolides) and (E and Z)-7-hexadecen-1,16-olide[18] [**9**] (ambrettolides), all highly valued perfumery compounds with musk odors. During the cyclization process, approximately 5% of the dimer (confirmed by isolation and MS) and some polymeric products were also formed, but these were readily separated by column chromatography. The yields were typically 50% based on the parent ω-hydroxy acids. The cyclization step can, of course, be carried out by any of the other available procedures.[32] The reaction sequences from threo/erythro aleuritic acids are given in Schemes 2-4.



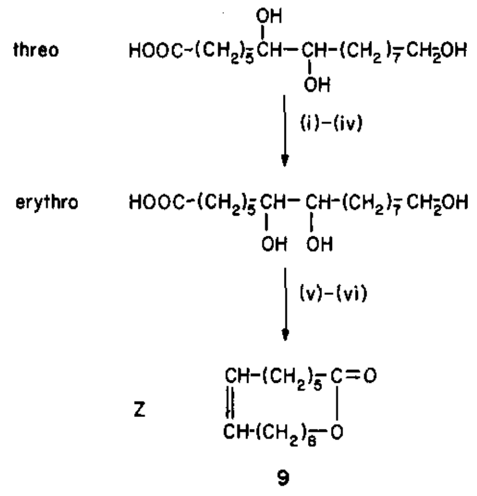
Reagents: (i) $CH(OEt)_3$, PhCOOH; (ii) H_2/Pd-C; (iii) Bu_2SnO-mesitylene

Scheme 2. Synthesis of 9-hexadecen-1,16-olide [2] and hexadecan-1,16-olide [7] from aleuritic acid



Reagents: (i) MeOH/H^+; (ii) $(CH_3)_2CO/H^+$; (iii) CrO_3-py; (iv) HS-$(CH_2)_3$-SH, $BF_3 \cdot Et_2O$; (v) H^+; (vi) LAH; (vii) Ac_2O/py; (viii) $HgCl_2$-HgO; (ix) $KMnO_4$; (x) OH^-; (xi) $CH(OEt)_3$, PhCOOH; (xii) Bu_2SnO-mesitylene

Scheme 3. Synthesis of E-ambrettolide [9] from aleuritic acid

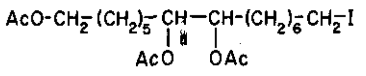


Reagents: (i) AcOH-HCl (dry); (ii) OH^-; (iii) AcOH; (iv) OH^-; (v) $CH(OEt)_3$, PhCOOH; (vi) Bu_2SnO-mesitylene

Scheme 4. Synthesis of Z-ambrettolide [9] from aleuritic acid

Chain Shortening or Elongation

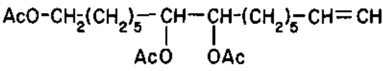
Aleuritic acid is amenable to chain shortening by one carbon atom. The triacetate of aleuritic acid, upon reaction with lead tetraacetate and iodine in presence of light, according to the procedure of Barton and Serebryakov,[33] undergoes oxidative decarboxylation-iodination to yield a C-15 iodo derivative [**10**].[34]



$AcO\text{-}CH_2\text{-}(CH_2)_5\text{-}CH(OAc)\text{-}CH(OAc)\text{-}(CH_2)_6\text{-}CH_2\text{-}I$

10

This reaction was utilized in the synthesis of pentadeca-1,15-olide.[29] Similarly triacetoxy threo aleuritic acid underwent decarboxylation-olefination upon reaction with cupric acetate and lead tetraacetate to yield [**11**] with one carbon less.[35] A second carbon was removable by a simple permanganate oxidation in the presence of a phase transfer catalyst giving a C-14 chain, the glycol system remaining intact and retaining the optical purity. Employing this procedure, the insect pheromone (Z)-7-tetradecenyl acetate[35] was made from erythro aleuritic acid. A pheromone may be regarded as a specific scent substance, usually for insects. However, mammalian pheromones also are known.

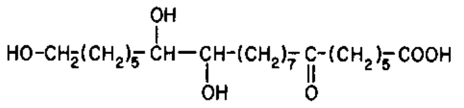


$AcO\text{-}CH_2(CH_2)_5\text{-}CH(OAc)\text{-}CH(OAc)\text{-}(CH_2)_5\text{-}CH{=}CH_2$

11

The ω-aldehydes derivable from aleuritic acid and derivates are amenable to chain elongation by several procedures. We carried out both a Grignard reaction and a Wittig reaction on them, leading to the synthesis of several pheromones (such as muscalure[36] and hexalure[37]) and a plant growth regulator (1-triacontanol[38]).

The acid chloride of aleuritic acid is amenable to base catalyzed enamine reaction. For example, triacetyl aleuritoyl chloride and cyclohexanone enamine react well. Appropriate hydrolysis[17] yields [**12**].



$$HO{-}CH_2(CH_2)_5{-}\overset{OH}{CH}{-}\underset{OH}{CH}{-}(CH_2)_7{-}\underset{\underset{O}{\|}}{C}{-}(CH_2)_5{-}COOH$$

12

It is worthwhile mentioning in passing that several pheromones have also been synthesized from the glycol fission products of aleuritic acid.[39,40]

The brief account given above indicates the vast potential which aleuritic acid holds in the synthesis of numerous useful organic compounds possessing olfactory properties. With a steady and substantial availability of threo aleuritic acid, its utility is expected to increase enormously.

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