# A New Approach to Cyclopropene Fatty Acids involving 1,2-Deiodination

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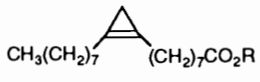
Methyl sterculate and methyl α-hydroxysterculate have been prepared by deiodination of 1,2-diiodocyclopropanes with butyllithium at low temperature.

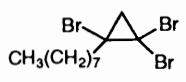
Sterculic acid **1a** is a potent inhibitor of the enzyme $\Delta^9$-desaturase which converts stearic acid into oleic acid and is important in relation to the diet and to a number of medical conditions.[1] Similar compounds have recently been implicated in the inhibition of a number of related enzymes, such as $\Delta^{12}$-, $\Delta^{11}$- and $\Delta^5$-desaturases.[2-4] Although several syntheses of sterculic acid and the lower homologue, malvalic acid, based on the formal addition of a methylene unit to an alkyne were reported some years ago,[5,6] and a route based on alkylation of a lithiocyclopropene was reported recently,[7] many of these rely on the introduction of the acid group by hydrolysis of the corresponding cyanide. This must be carried out under relatively basic rather than acidic conditions because of the known reactivity of cyclopropenes towards acids.[8] In approaching the synthesis of cyclopropene fatty acids which are more sensitive to base, we have developed a method in which the acid functionality is present before the introduction of the cyclopropene double bond. This utilises the observation that addition of iodine to sterculic acid leads to an (unseparated) mixture of diidocyclopropanes, which regenerates the cyclopropene on treatment with potassium hydroxide in ethanol, albeit only in a rather low yield.[9] In a model experiment, 1,2-dibutylcyclopropene was treated with iodine in diethyl ether at −80 °C and then warmed to 20 °C for 1 h; chromatography gave *trans*-1,2-diiodo-1,2-dibutylcyclopropane (44%), the *cis*-isomer (22%) and a small amount (*ca.* 6%) of a ring-opened alkene, 5-iodo-6-(iodomethyl)dec-5-ene, of unknown stereochemistry. Treatment of the crude mixture, or of either of the cyclopropanes, with butyllithium at −80 °C regenerated the cyclopropene as the only product observed by $^1$H NMR spectroscopy on the crude reaction product.



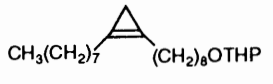

**1a** R = H
**b** R = Me

Treatment of the tribromide **2**[7] with 2.1 mol equiv. of butyllithium in diethyl ether at −40 °C followed by warming to 20 °C for 30 min, cooling again to −40 °C and then addition of hexamethylphosphoramide (HMPA) and the tetrahydropyranyl (THP) ether of 8-iodooctanol led to the cyclopropene **3** in reasonable yield (59%). Treatment of **3** with iodine in diethyl ether led to a mixture of *cis*- and *trans*-1,2-diiodocyclopropanes **4** (79%). Deprotection of the acetal **4**, followed by oxidation of the derived alcohol in benzene with aq. potassium permanganate under phase-transfer conditions, catalysed by tetrabutylammonium bromide, and then treatment with diazomethane in diethyl ether gave the diiodo esters **5**; treatment of these esters with 1.1 mol equiv. of butyllithium at −80 °C and quenching with water at that temperature gave methyl sterculate **1b** (76%) which was identical by NMR spectroscopy to an authentic sample.

Sterculic acid is thought to be metabolised by oxidation α- to the acid group, leading first to the hydroxy acid **6a** and then to malvalic acid. The hydroxy acid was isolated some years ago,[10] and has been shown recently to have the *R*-configuration[11] but no synthesis, even of the racemic acid, has been reported. Preparation of the iodide **7** by the method previously described,[7] followed by oxidation with trimethylamine *N*-oxide led to the aldehyde **8**; treatment of this with HCN and oxynitrilase gave the corresponding cyanohydrin **9** (75%)† which was protected as its *tert*-butyldimethylsilyl (TBDMS) ether (93%). Addition of iodine in diethyl ether at −78 °C followed by warming to 20 °C gave the diiodocyclopropane **10** as a mixture of isomers (89%). Because the cyclopropene was protected as the diiodide, this could be hydrolysed under acidic conditions to give, after esterification, compound **11**; had the cyclopropene been unprotected it would have been destroyed under these conditions.[8] Treatment of **11** with 1.1 mol equiv. of butyllithium at −90 °C gave the hydroxy ester **6b** (85%). The $^1$H and $^{13}$C NMR spectra of this are essentially identical with those reported recently,[12] except that in our case the proton α- to the hydroxy group was resolved into a double doublet as anticipated.




**2**

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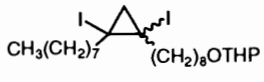
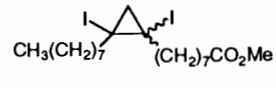



**4**

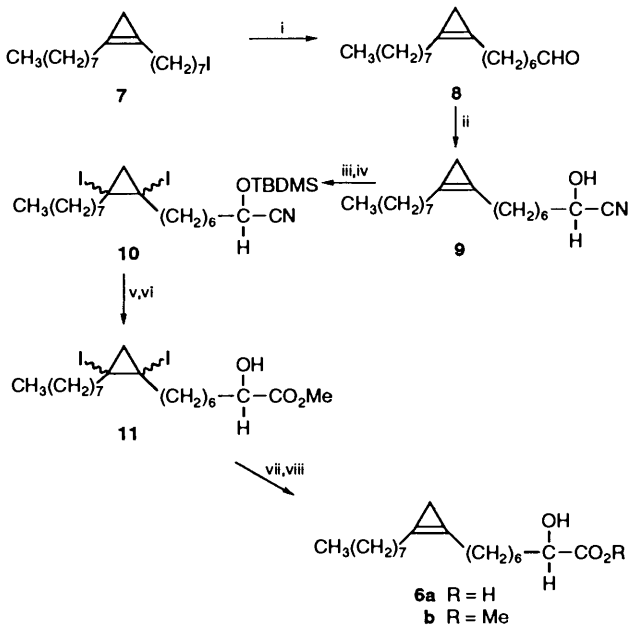



**5**

## Experimental

*Deprotection of Diiodide* **11** *to Methyl 2-Hydroxysterculate* **6b**.—Butyllithium (1.3 mol dm$^{-3}$; 2.4 equiv., 1.6 cm$^3$, 2.08 mmol) was added dropwise to a solution of 2-hydroxy-8-(1,2-diiodo-2-octylcyclopropyl)octanoate (0.5 g, 0.87 mmol) in diethyl ether (10 cm$^3$) at −80 °C. Stirring was continued for 5 min before the reaction was quenched with water (5 cm$^3$) at −80 °C. The aqueous layer was extracted with the diethyl ether (5 × 20 cm$^3$) and these extracts were dried and evaporated to give a pale-yellow oil. Purification by column chromatography, using light petroleum and diethyl ether (1:1) as eluent, gave methyl 2-hydroxysterculate as a colourless oil (0.24 g, 85.1%) which showed $\nu_{max}$(film)/cm$^{-1}$ 3462br s, 2927s, 2856s, 1870w, 1738s, 1464m, 1217m, 1116w and 1008w; $\delta_H$ 0.77 (2 H, s), 0.88 (3 H, t, *J*

† This system is known to convert aldehydes up to hexanal into the corresponding cyanohydrins with good enantiomeric excesses of the *R*-form (see *e.g.*, J. Brussee, W. T. Lors, C. G. Kruse and A. Van Der Gen, *Tetrahedron Lett.*, 1990, 979). In the present case, the reaction was rather slow (40 h, 20 °C) and addition of a chiral lanthanide shift reagent to the product indicated either no, or a very low, enantiomeric excess.




*Reagents and conditions:* i, $Me_3NO$, $CHCl_3$, 55 °C, 13 h; ii, KCN, water, citric acid, oxynitrilase, $Me_3COMe$, 20 °C, 40 h; iii, TBDMSCl, imidazole, dimethyl formamide (DMF), 35 °C, 18 h; iv, $I_2$, diethyl ether, −80 ⟶ 20 °C, 2 h; v, −10 °C, HCl, MeOH, diethyl ether, then 20 °C, 16 h; vi, water; vii, BuLi, diethyl ether, −80 °C, 5 min; viii, water, −80 °C

7.0 Hz), 1.22–1.45 (16 H, br m), 1.48–1.60 (4 H, m), 1.76 (2 H, m), 2.37 (4 H, t, *J* 7.1 Hz), 2.83 (1 H, br, s), 3.78 (3 H, s) and 4.16 (1 H, dd, *J* 7.2 and 4.2 Hz); $\delta_C$ 7.3 (t), 14.1 (q), 22.7 (t), 24.7 (t), 25.9 (t), 26.0 (t), 27.3 (t), 27.4 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 31.9 (t), 34.4 (t), 52.4 (q), 70.4 (d), 109.4 (s) and 175.8 (s) (Found: $M^+$, 324.2664: $C_{20}H_{36}O_3$ requires, $M^+$, 324.2664).

## Acknowledgements

We thank the SERC and Medeva Plc for the award of a studentship to B. G.

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*Paper* 3/02620E
*Received* 7*th May* 1993
*Accepted* 25*th May* 1993