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Three-Step Synthesis of Methyl Sterculate[1a]

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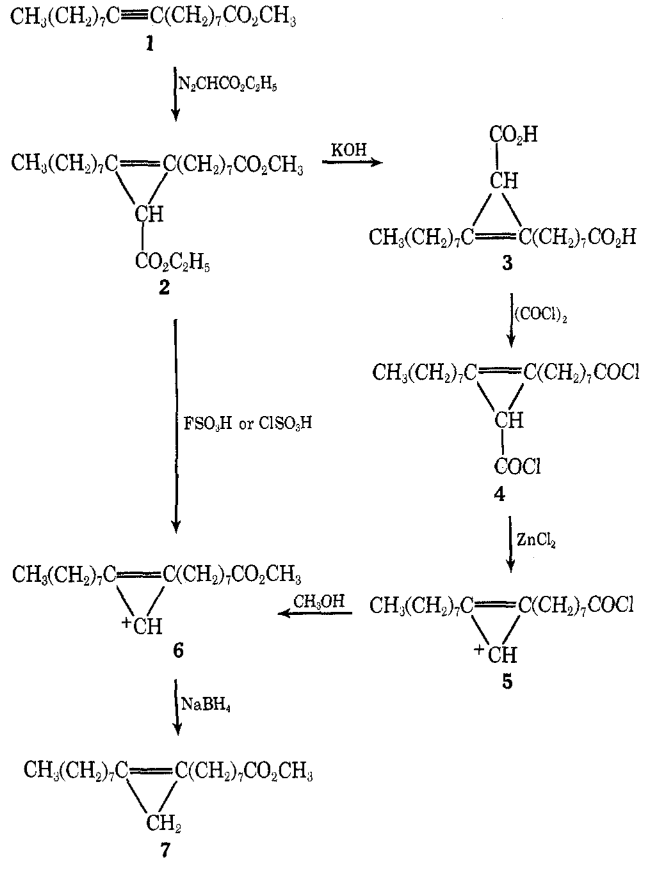
Studies to elucidate details of the metabolism[2,3] of the physiologically important cyclopropenoic acids have made the availability of these acids highly desirable. Several devised syntheses have provided possible routes but the low overall yield realized in these procedures offered no satisfactory solution to the problem.[4–7] Recently, however, Gensler and his associates[7,8] published a method for the synthesis of methyl sterculate with an overall yield in the order of 30%. A vital sequence in their synthesis was the decarbonylation of 2 to 7 *via* the corresponding biacid chloride 4.



We have now developed an alternate method (reaction 2 → 7) for a direct decarbonylation of 2 by employing either fluorosulfonic or chlorosulfonic acids[9] and we have arrived at the final methyl sterculate 7 in a three-step synthesis (60–65% yield). Fluorosulfonic acid in methylene chloride reacted upon 9,10-(carbethoxymethano)-9-octadecenoate and the reaction proceeded with gas evolution and formation of cyclopropenium cation ester 6. The obtained yield as a function of the amount and the concentration of the reagent are given in Table I.

TABLE I

DETERMINATION OF THE PER CENT DECARBONYLATION OF THE CYCLOPROPENIUM CARBONYL BY FLUOROSULFONIC ACID AT ROOM TEMPERATURE[a]

Amount of FSO_3H, mmol	FSO_3H in CH_2Cl_2, *M*	Cyclopropeniod diester, mmol	Decarbonylation,[b] %
5.25	0.28	5.25	
5.25	0.53	5.25	
5.25	1.72	5.25	10
34.58	1.72	5.25	25
43.74	4.37	5.25	20
43.74	17.50	5.25	100

[a] The extent of decarbonylation was followed by monitoring the disappearance of the cyclopropenium carbonyl absorption at 1730 cm^{-1} after complete work-up of the solution. [b] Reaction time 1 hr.

The analogous reaction with a solution of chlorosulfonic acid in methylene chloride was difficult to predict. In that respect, the difference in performance between chlorosulfonic and fluorosulfonic acids may be due to the high ionizing power and low nucleophilicity of the latter.[10] However, when chlorosulfonic acid was added without any previous dilution it performed better than fluorosulfonic acid and the reaction proceeded and afforded cyclopropenium cation ester. We elected to use fluorosulfonic acid in methylene chloride as our standard decarbonylation reagent.

Experimental Section

Melting points and boiling points are uncorrected. Elementary analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. Infrared analyses were made in CCl_4 solution on a Beckman IR-7 spectrophotometer. All nmr spectra were taken on a Varian A-60A instrument as saturated solutions in chloroform-*d*, using tetramethylsilane as the internal standard. Chemical shifts are reported in τ units (τ 10.00 for tetramethylsilane). Glpc analyses were carried out on a Barber-Coleman Model 5000 equipped with a flame ionization detector. The column (6 ft × $^1/_8$ in. glass) was packed with 10% EGS on Chromosorb W 60–80 mesh. The temperature was 175° and the helium flow was 45 ml/min.

Methyl Stearolate (1).—Stearolic acid, mp 45.5–46.0°, was synthesized according to the method of Butterfield and Dutton.[11] Methyl stearolate prepared with diazomethane gave a single peak on glpc with a relative retention time of 1.90 (methyl stearate 1.00).

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(1) (a) Abstracted in part from a thesis submitted by J. L. Williams to the University of Illinois, Aug 1970, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) Tuskegee Institute, School of Veterinary Medicine, Tuskegee Institute, Ala. 36088.

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Preparation of 9,10-(Carbethoxymethano)-9-octadecenoate (2).—Ethyl diazoacetate (3.4 g, 29.3 mmol) in the presence of 0.2 g of powdered copper bronze[12] was allowed to react with 5.9 g (20 mmol) of methyl stearolate to form the corresponding cyclopropenoid diester **2** as previously described.[8] Subsequently it was cooled to room temperature, filtered to remove the catalyst, and distilled *in vacuo*, bp[4] 174–176° (0.05 mm). The desired diester **2** was obtained in this way as a yellowish oil (3.9 g, 15.4 mmol, 77% yield).

Preparation of the Fluorosulfonic Acid Decarbonylation Reagent.—This reagent was prepared by mixing 2.5 ml of fluorosulfonic acid in 2.5 ml of methylene chloride at room temperature. The resulting 50% (v/v) solution contained 43.7 mmol of fluorosulfonic acid (17.5 *M*).

Decarbonylation of 9,10-(Carbethoxymethano)-9-octadecenoate (2).—Throughout the experiment a current of argon blanketed the reaction mixture. Decarbonylation was accomplished by slowly dropping 5 ml of the 17.5 *M* fluorosulfonic acid solution on 5.25 mmol of cyclopropenoid ester over a 0.5-hr interval at room temperature. After the solution had stood for an additional 0.5 hr, 20 ml of cold (−78°) methylene chloride was added and 5 g of type 4A or 5A molecular sieves.[13] The cold solution with the molecular sieves was allowed to stand for 1 hr under argon.

Preparation of the Sodium Borohydride Reducing Solution.—A three-necked round-bottomed flask equipped with a magnetic bar stirrer was placed in a Dry Ice–trichloroethylene bath maintained at −50°. Sodium borohydride (1 g) was charged in the flask followed by 25 ml of a stock solution of methanol saturated with sodium hydroxide. The reaction was blanketed by argon all the time and the solution was stirred and allowed to stand at −50°. This solution was designated as a 1.05 *M* sodium borohydride reducing reagent.

Methyl Sterculate (7).—Under a blanket of argon, the cyclopropenium cation solution was slowly dropped into the 1.05 *M* sodium borohydride reducing reagent. The mixture was stirred for 20 min at −50°. After stirring for an additional 10 min, the reaction mixture was allowed to warm to room temperature. During the reduction of the brown cyclopropenium cation solution, gas evolved and the solution was placed in a separatory funnel containing 10 ml of cold (−78°) petroleum ether (bp 55–60°) and 50 ml of saturated sodium bicarbonate. The ethereal layer was removed and further extraction was accomplished with two 50-ml portions of petroleum ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate at room temperature for 2 hr. The dry petroleum ether solution was filtered and the solvent was evaporated under reduced pressure. The residual yellow oil in a small volume of petroleum ether was placed on top of a 1.2 × 100 cm column of 200–325 mesh silicic acid (Unisil)[14] prepared as a slurry in petroleum ether under a blanket of argon and water jet pump vacuum. A total of 750 ml of petroleum ether was passed through the column. Fractions of 50 ml were collected and the elutions were monitored by using silica gel G tlc and a solvent system consisting of petroleum ether–diethyl ether (95:5, v/v). All eluates which furnished a compound with the same R_f value as a reference methyl sterculate were combined. Evaporation of the solvent under vacuum at room temperature yielded a colorless oil (1.03 g, 65%).

The synthetic methyl sterculate (*Anal.* Calcd for $C_{20}H_{36}O_2$: C, 77.82; H, 11.76. Found: C, 77.72; H, 11.61) gave a positive Halphen test. In infrared absorption spectra it showed peaks at 1750 (carbonyl), 1880 (cyclopropene), and 1020 cm^{-1} (cyclopropene). In the last case, the vibration given by cyclopropenes normally at 1010 was shifted to 1020 cm^{-1} due to the way the spectra were taken. Masson[15] also reported a value of 1020 cm^{-1} for methyl sterculate when its infrared spectrum was taken in carbon tetrachloride. A check using pure methyl sterculate prepared from natural sources[16] verified this observation.

In nmr is showed signals at 9.23 (s, 2 H, cyclopropenyl CH_2), 9.10 (m, 3 H, distal terminal CH_3), 8.63–8.71 (m, 22 H, internal CH_2), 7.61–7.78 (diffuse m, 6 H, α to cyclopropenyl and $-CO_2-CH_3$), and 6.32 ppm (s, 3 H, methyl ester CH_3). Generally, the spectra were identical with those obtained with pure methyl sterculate obtained from *sterculia foetida*. Furthermore, the synthetic and natural materials gave single spots with the same R_f value on thin layer plates and identical gas chromatographic curves.[17]

Registry No.—**2**, 30689-71-5; **7**, 3220-60-8.

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(12) Purchased from The British Drug House, Poole, England.

(13) Linde Division of Union Carbide Corp., Chicago, Ill.

(14) Clarkson Chemical Co., Inc., Williamsport, Pa.

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Absolute Configuration of the Phenyl-2-piperidylcarbinols

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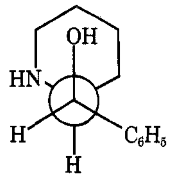
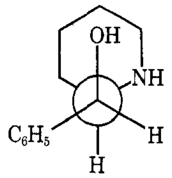
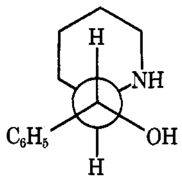
The Cotton effect associated with the $^1L_b\ \pi \rightarrow \pi^*$ transition[2] has been reported to be a reliable guide to the absolute configuration of both the ephedrine and the chloramphenicol stereoisomers.[3] This ^1L_b absorption band, as measured *via* circular dichroism (CD), is now used to assign the absolute configuration of the phenyl-2-piperidylcarbinols (**1** and **2**).



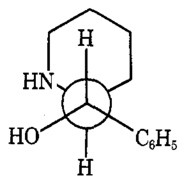
1a



1b



2a



2b

The diastereomeric carbinols (**1** and **2**) were prepared *via* the reduction of phenyl 2-pyridyl ketone with Brown catalyst,[4] which is a modification of the method of Crook and McElvain,[5] and separated *via* fractional crystallization. Diastereomers **1** and **2** were demonstrated to be erythro and threo, respectively, by acyl migration studies.[6] This conclusion is confirmed by

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