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THE SYNTHESIS AND STEREOCHEMISTRY OF CASCARILLIC ACID

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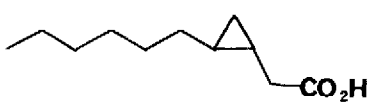
As part of a general research program on the chemistry of the Euphorbiaceae,[1] we have investigated cascarillic acid[2] 1, a C_{11} cyclopropane carboxylic acid which is obtained from the essential oil of Croton eluteria Benett (Euphorbiaceae), a tree-like shrub of the West Indies. Cascarillic acid has the same carbon skeleton as Dictyopterene A (2).[3] Another compound closely related to cascarillic acid, (Z)-3-decenoic acid, has been identified[4] as a sex pheromone of female furniture carpet beetles, Anthrenus flavipes, Leconte. It is possible that the biosynthesis of cascarillic acid involves such an unsaturated acid.[5]



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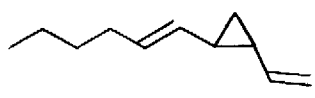

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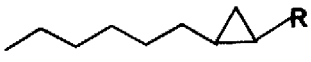
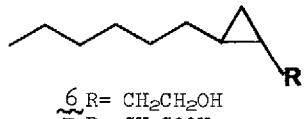
The gross structure of cascarillic acid was determined in 1972[2] and a synthesis of trans-methyl cascarillate reported in 1973.[6] The spectral data for the synthetic ester were "comparable" to those reported for the methyl ester of naturally occurring cascarillic acid and a direct comparison was not cited. There was no evidence presented to rule out the possibility that the cyclopropane ring could not, in fact, be in the cis configuration. We felt that the synthesis of cis- and trans-cascarillic acid would prove conclusively the configuration of the cyclopropane ring.

The methyl esters of cis- and trans-cascarillic acid were prepared by the following series of reactions.[7] Hydrogenation of 3-decyn-1-ol over $Pd/BaSO_4$ poisoned with collidine gave cis-3-decen-1-ol (88%), IR: 3.0 μ; NMR: 0.90 δ(3H-t), 1.1-1.7 δ(8H-m), 1.8-2.5 δ(8H-m), 3.7 δ(2H-t), 5.5 δ(2H-m). Simmons-Smith reaction yields cis-3,4-methylenedecanol 3 (43%); IR: 3.0 μ;

NMR: - 0.25 δ(1H-q), 0.52-0.75 δ(3H-m), 0.84 δ(3H-t), 1.00-1.48 δ(12-m), 2.64 δ(1H-s), 3.75 δ(2H-t); MS[m/e(% base)]: 170(1), 124(31), 110(32), 109(30), 98(32), 96(72), 95(66), 83(41), 82(100), 70(52), 69(56), 68(97), 67(70), 57(36), 56(52), 55(40). The cyclopropyl alcohol 3 was oxidized to cis-cascarillic acid 4 with Jones reagent (71%); IR: 3.2-3.6 μ, 5.85 μ; NMR: -0.11 δ(1H-q), 0.66-0.88 δ(1H-m), 0.89 δ(3H-t), 1.00-1.18 δ(2H-m), 1.18-1.46 δ(10H-m), 2.30 δ(2H-m), 9.05 δ(1H-s). Diazomethane treatment of 4 gave methyl-cis-cascarillate 5 (100%); IR: 5.78 μ; NMR: -0.07 δ(1H-q), 0.72-0.86 δ(1H-m), 0.93 δ(3H-t), 1.07-1.61 δ(12H-m), 2.34 δ(2H-m), 3.72 δ(3H-s); MS[m/e(% base)]: 198(1), 124(20), 101(32), 96(36), 83(43), 82(31), 74(65), 69(71), 68(29), 67(37), 59(100), 56(45), 55(92), 43(73), 41(82). The trans-series was prepared as follows. Reduction of 3-decyn-1-ol with sodium in liquid ammonia gave trans-3-decen-1-ol; IR: 3.0 μ; NMR: 0.90 δ(3H-t), 1.1-1.6 δ(8H-m), 1.7-2.4 δ(4H-m), 2.6 δ(1H-s), 3.6 δ(2H-t), 5.5 δ(2H-m). Simmons-Smith reaction gave trans-3,4-methylenedecanol 6 (45%); IR: 3.0 μ; NMR: 0.22-0.59 δ(4H-m),



3 R= CH_2CH_2OH
4 R= CH_2COOH
5 R= CH_2COOCH_3



6 R= CH_2CH_2OH
7 R= CH_2COOH
8 R= CH_2COOCH_3

0.91 δ(3H-t), 1.11-1.56 δ(12H-m), 2.25 δ(1H-s), 3.68 δ(2H-t); MS[m/e(% base)]: 170(0), 96(31), 95(37), 83(34), 82(61), 81(71), 70(33), 69(66), 68(92), 67(74), 57(36), 56(48), 55(100), 43(55), 41(67). Oxidation of 6 with Jones reagent gave d,l-cascarillic acid 7 (88%); IR: 3.1-3.8 μ, 5.85 μ; NMR: 0.32-0.87 δ(4H-m), 0.94 δ(3H-t), 1.16-1.57 δ(10H-m), 2.27 δ(2H-d), 10.23 δ(1H-s). Methyl cascarillate 8 was obtained in quantitative yield on treatment of 7 with diazomethane; IR: 5.78 μ; NMR: 0.31-0.87 δ(4H-m), 0.94 δ(3H-t), 1.16-1.48 δ (10H-m), 2.25 δ(2H-d), 3.70 δ(3H-s); MS[m/e(% base)]: 198(1), 124(46), 101(47), 96(30), 83(44), 82(34), 74(80), 69(65), 68(29), 67(36), 59(100), 56(38), 55(87), 54(27), 43(60), 41(80). Authentic methyl cascarillate[8] was identical in all respects with ester 8.

The 220 mHz NMR spectra of synthetic cis-5 and trans-8 methyl cascarillate and of the methyl ester of authentic cascarillic acid[8] are shown in the Figure. The spectra for the trans-ester 11 and the authentic cascarillic ester are nearly identical, demonstrating that the cyclopropane ring of cascarillic acid is trans. There are two major differences in the spectra of the cis

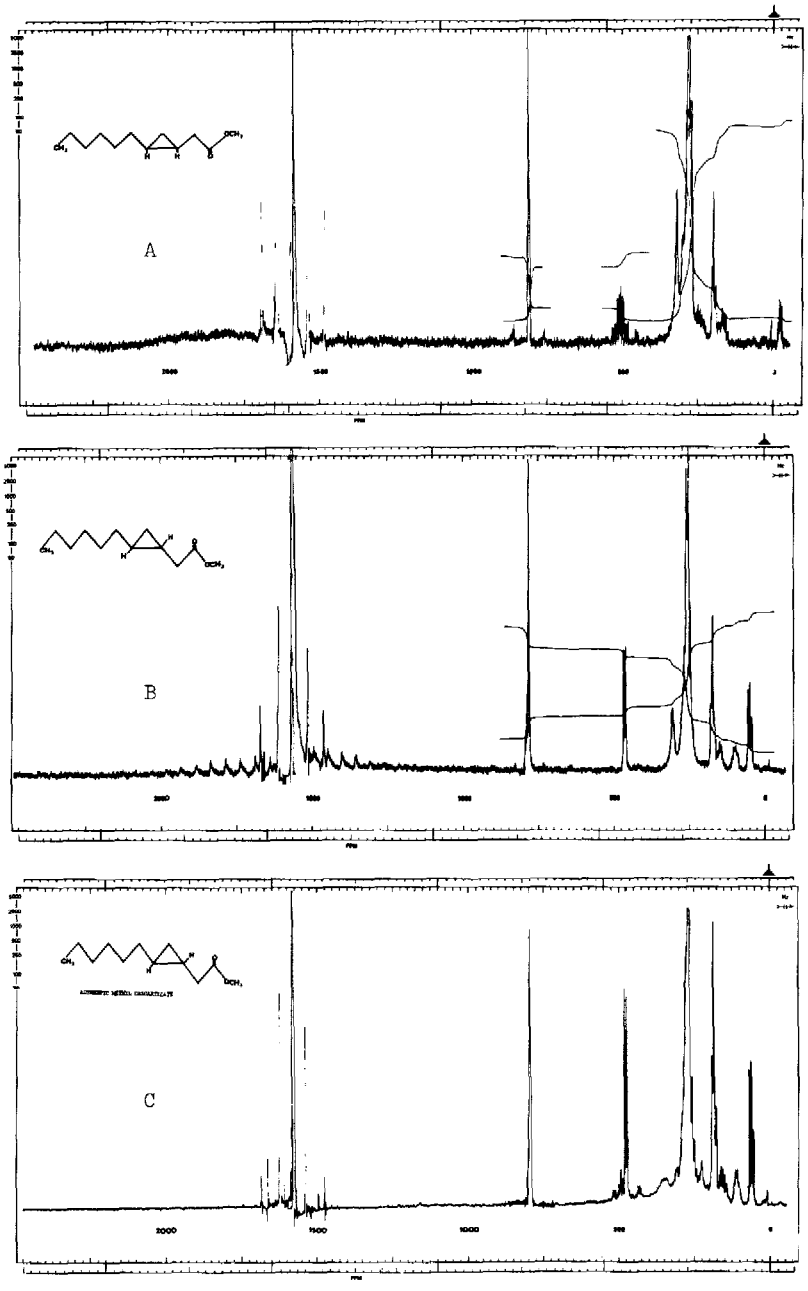


Figure: 220 mHz NMR spectra of A) d,l-cis-methyl cascarillate 5, B) d,l-trans- methyl cascarillate & C) authentic methyl cascarillate.

and trans compounds. In the cyclopropane region the cis-ester 5 shows a signal for one cyclopropyl proton at -0.07 δ due to the cyclopropylmethylene proton cis to the two cyclopropylmethine protons. This proton is heavily shielded by all three of the other cyclopropane protons and is therefore shifted upfield.[9] The other three cyclopropane protons cis-compound give signals between 0.7 and 1.2 δ. Both the trans-ester 8 and the methyl ester of authentic cascarillic acid show no signals above 0 δ; all four of the cyclopropane proton appear between 0.2 and 1.0 δ. The cis and trans esters also differ in the signals for the methylene protons adjacent to the methyl ester group. The signal in the spectra of the tran compound 8 is a sharp doublet, while the cis-ester 5 shows a complex multiplet. In the tran compound the two protons are nearly chemical shift equivalent whereas in the cis-ester the hydrocarbon "tail" is on the same side of the ring as the methylene group, thus affecting th chemical shifts of the two protons and resulting in different chemical shifts for these geminal protons.

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7. All new compounds possessed satisfactory spectral and analytical data.
8. We would like to thank Dr. O. Motl (Czechoslavak Academy of Sciences) for a sample of cascarillic acid.
9. The chemical shifts of the cyclopropane protons are consistent with those reported for other compounds of this type.[10]
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11. The trans-ester 8 and authentic methyl cascarillate also have identical VPC retention times (3.6 minutes at 120°). The retention time of the cis-ester 5 (4.32 minutes at 12 is much longer. (1/4" x 5' SE-30 on Chrom W). In addition glass capillary GC/MS (22M x 0.26 mm ID/SE-30) confirmed the structure assignment.