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Sapidolide A: An Unprecedented Spherical Carbocyclic Lactone from *Baccaurea sapida* Seed Kernels : Is It a Meroisoprenoid ?

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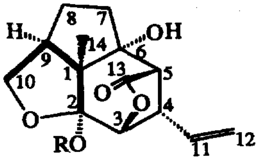
Abstract: A novel tetrahydrofurano-lactone meroisoprenoid (sapidolide A) 1 has been isolated from a tropical plant *Baccaurea sapida*, and its structure has been determined on the basis of DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, (+)-FABMS, low energy EIMS, and ion desorption chemical ionization mass spectrometry, and was confirmed by X-ray crystallography of its single crystal. Copyright © 1996 Elsevier Science Ltd

In continuation of our interest on the search for bioactive molecules from the plants of the Sub-Himalayan region of North East India,[1] we undertook the chemical investigation of a plant of the Euphorbiaceae family — *Baccaurea sapida*,[2] growing widely in the Brahmaputra valley, India. The medium polar fraction of the crude extract of seed kernels of this plant gave a major compound, sapidolide A, the structure of which has been assigned as **1**.[3] Sapidolide A has exhibitted strong inhibitory activity against pathogenic fungi such as *Helminthosporium oryzae*, *Phytophthera oryzae, Alternaria solani, Curvularia eragrostidis, Collectotrichum gleosporioides*.[4]

Sapidolide A, **1**, mp 147° C, $[\alpha]^{31}_{D}$ = +23.2 (c,0.4 $CHCl_3$), $C_{14}H_{18}O_5$ by low energy EIMS, (+)-FABMS and Ion Desorption Chemical Ionization Mass spectrometry, was isolated from the cold chloroform extracts of previously defatted, dried seed kernels of *Baccaurea sapida*, collected from the Lakhimpur district of Assam, India (August 1993). The $CHCl_3$ extracts were concentrated under reduced pressure to give a thick liquid from which sapidolide A 1 (6.3 g from 400 g of dry seed kernels) crystallized out. IR (KBr) 1770 (δ-lactone), 3490 and 3390 cm.$^{-1}$

The ^{1}H NMR data (400 MHz) revealed that **1** contained one exo-methylene group (two dd at δ 5.12 & 5.25 with J= 2,17 & 2,10 Hz respectively), one olefinic proton (δ 6.2 ddd with J=10,10,17 Hz), one allylic proton (δ3.28, ddd, J=4,4,10 Hz), two D_2O exchangeable hydroxyl functionalities (δ 3.02 br and 4.32 br), one tertiary methyl group (δ 1.24 s), one proton under lactone (δ 4.47, d, J= 4 Hz) and eight methylene and methine protons. The ^{1}H and ^{13}C NMR signals were assigned by combined use of DEPT and an ^{1}H-^{13}C COSY NMR experiments. All the proton-proton connectivities were determined by a COSY45 experiment which characterized all the five methine and four methylene protons. Based on the above evidences, the structure of the compound sapidolide A was settled as depicted in structure **1**. This structure was further supported by the fact that acetylation of sapidolide A, **1** with acetic anhydride and pyridine at room temperature (48 hours) gave a mono acetate, **2** whose ^{1}H NMR spectrum revealed a three proton sharp singlet at δ 2.00, but devoid of a signal for proton under acetate. The structure of sapidolide A, **1** , was finally confirmed by X-ray crystallography of its single crystal.



1 R = H
2 R = Ac

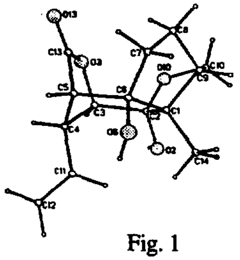


Fig. 1

X-ray crystallographic[5] view of sapidolide A[6] is presented in Fig. 1. The nearly spherical molecule consists of three five-membered and one six-membered rings. Three of these rings (cyclopentane, oxacyclopentane and cyclohexane) are fused in such a way that they share a common vertex at C(1). The forth one, the γ-lactone ring, is bridged with the cyclohexane ring at C(3) and C(5). Methyl substituent at C(1) and its two neighbouring hydroxyl groups at C(2) and

C(6) are mutually cis so that the configuration at the ring junctions at C(1)-C(2) and C(1)-C(6) cis and the configuration at C(1), C(2) and C(6) is S,S,R. The axial substituents at C(3) and C(5), forming the lactone bridge, are mutually cis, and are oriented trans with respect to the axial vinyl substituent at C(4) so that the configuration at the remaining chiral centers C(3), C(4), C(5) and C(9) is R,S,S,R. The cyclohexane ring displays a sofa conformation, with an approximate Cs symmetry, the approximate mirror plane passing through C(1) and C(4). The average magnitude of the six endocyclic torsion angles is 38.2(28.0)°, and the asymmetry parameter ΔC_s^1=0.6°.[7] At the "flat" end there is a severe eclipsing around the C(1)-C(2) and C(1)-C(6) bonds. The significant flattening of the ring in the region C(1), C(2) and C(6) is accompanied by the simultaneous puckering at the other end. This is manifested in the torsion angles as well as in the valence angle deformation. Within the cyclohexane ring the valence angles at C(1) and C(2) are 115.6(1) and 116.1(1)°, respectively, while the valence angle at C(4) amounts to 97.1(1)°. Moreover, bond distances involving C(1) are among the longest in the structure, e.g. 1.580(2)A and 1.59(2)A for C(1)-C(2) and C(1)-C(6) bonds, respectively. Of the five C_{sp^3}-O distances in the range 1.397(2) to 1.460(2)A the C(2)-(O2) bond is the shortest, significantly shorter than the analogous bond C(6)-O(6) of 1.434(2)A, and shorter than the expected value of 1.431A.[8] Worth to mention is a close contact between 1,4 alkyl substituents, the H(142)...H(11) distance being only 2.09A.

Three five-membered rings i.e. cyclopentane, tetrahydrofuran and lactone have envelope conformations with, respectively, C(8), C(10) and C(4) constituting the flaps. The corresponding values of the asymmetry parameters and the average torsion angle moduli for the three rings are : ΔC_s^8= 7.7° and $|w|$=26.1(12.6)°; ΔC_s^{10}=1.8° and $|w|$=23.3(13.3)°; ΔC_s^4=1.3° and $|w|$=30.2(16.0)°.

The structure **1** represents an unprecedented natural product carbocyclic arrangement. The unusualness of this nearly spherical molecule was also evident in the coupling patterns of the molecule, e.g. the ^1H-^1H coupling constants of H-3, H-4 and H-5 ($J_{3,4} = J_{4,5} = 4$ Hz) of the central cyclohexane ring are very low. The ^1H-^1H geminal coupling constants of the cyclopentane ring attached protons (H-7 and H-8) and those of oxacyclopentane ring are also too low ($J_{7\alpha,7\beta}=J_{8\alpha,8\beta}=12$ Hz and $J_{10\alpha,10\beta} = 8$ Hz respectively).[9] There is no coupling between H-9 and H-10β. The ^{13}C NMR shifts for C-1, C-2, C-6, C-8, C-9 & C-10 are also down shifted. Biogenesis of this highly oxygenated compound **1**, is baffling, formed probably from the fusion of one isoprenoid moiety (bold part) with fatty acid moiety. Meroisoprenoids are reported from lower organisms such as algae.[10] But this is the first report of a meroisoprenoid from a higher plants (Gymnosperm).[11]

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