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TOTAL SYNTHESIS OF (±)-KARATAVIC ACID: STRUCTURE CONFIRMATION OF THE FIRST SECO-DRIMANE TYPE SESQUITERPENOID[1]

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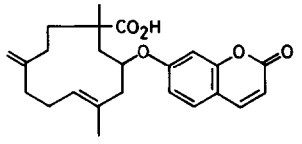
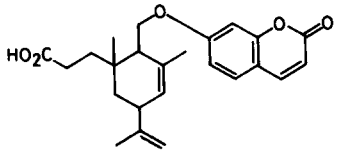
Summary: One of the postulated structures of karatavic acid is confirmed via the total synthesis by means of the mercury(II) triflate/amine complex-induced olefin cyclization and subsequent short step transformations. Stereochemistry of this new class of natural product is also established.

Karatavic acid, $C_{24}H_{28}O_5$, was first isolated by Bercutsky in 1936[2] from the root of Ferula karatavica (Umbelliferae), and three kinds of planer structures I~III have been proposed without any clear experimental evidence.[3] Among these structures, formula III reported by Paknikar[3c] seems most reasonable from its spectral data and the sesquiterpene biogenesis. Although there have been reported many coumarin-containing sesquiterpenoids with drimane skeleton ,[4] the synthesis by the effective cyclization of umbelliprenin (3), a possible biosynthetic precursor, has never been recorded. In 1966, van Tamelen and Coates reported Lewis acid catalyzed cyclization of umbelliprenin terminal epoxide.[5] However, the reaction took place non-selectively to give a variety of products including bicyclic compounds (a mixture of double bond isomers) in only 9% yield. Recently, we have developed a new olefin cyclization agent, mercury(II) triflate/amine complex,[6] which showed a remarkably high selectivity for the cyclization of a series of farnesol derivatives. Thus, we designed the



I



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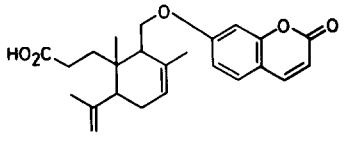

III

synthesis of karatavic acid of the proposed structure III from umbelliprenin by using our synthetic method.

The starting material, umbelliprenin (3),[5] was prepared from E,E-farnesyl bromide and 7-hydroxycoumarin by using sodium hydride and catalytic amount of tetrabutylammonium bromide in DMF. Cyclization of 3 was conducted by the treatment with 1.2 equiv of mercury(II) triflate/N,N-dimethylaniline complex, prepared in situ from equimolar amount of yellow mercuric oxide, trifluoromethanesulfonic anhydride, and N,N-dimethylaniline, in nitromethane at -20 °C for 2 h.[6] The reaction mixture was directly treated with excess of sodium chloride solution at room temperature for 15 h. The cyclization product 4 (mp 221~222 °C) was obtained in 75% yield after silica gel column chromatography. An isomeric product, C-9 epimer 8, was also isolated in 6% yield. The stereochemistry of the major product 4 and the minor product 8 was assigned to be 9β and 9α, respectively, based on the ^{13}C NMR chemical shift value of the C-10 methyl group (δ 14.9 and 23.0, respectively). The corresponding demercuration products 10 and 11 also showed very similar δ-values of the methyl groups (δ 14.9 and 23.3). These data were well consistent with those of drimenol (i), epidrimenol (ii), or their derivatives (iii and iv)[7] with the known stereochemistry.

The major product 4 was subjected to the following transformations. Hydroxylation by Whitesides' procedure ($O_2/NaBH_4$/DMF, room temperature, 1 h)[8] and following Jones oxidation provided a ketone 5 in 80% yield as colorless crystals, mp 146.5~148 °C. The ketone 5 was treated with hydroxylamine hydrochloride in pyridine and ethanol under reflux for 2 h to give an oxime 6 (94% yield, mp 198.5~199 °C) after column chromatography over silica gel. The oxime 6 underwent solvolytic fragmentation upon treatment with p-toluenesulfonyl chloride (3 equiv) in refluxing pyridine[9] to give a seco-nitrile 7 (29% yield, mp 133~135 °C) and a lactam 9 (33% yield, mp 188~190 °C). Alkaline hydrolysis of the seco-nitrile 7 with 20% KOH in ethanol (reflux, 5 h) yielded (±)-karatavic acid (1) in 93% yield as colorless crystals, mp 142~143 °C, after silica gel column chromatography.[10] The synthetic (±)-karatavic acid was converted to its methyl ester 2 with diazomethane, and its ^1H NMR spectrum (100 MHz) was identical with that of the methyl ester of the natural product reported by Bagirov.[3b]

Thus, the structure of karatavic acid was rigidly established to be formulated as 1, which is the first example of 3,4-seco-drimane type sesquiterpenoid.

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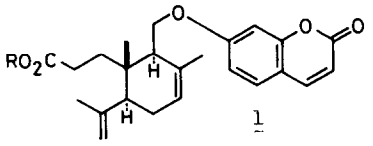
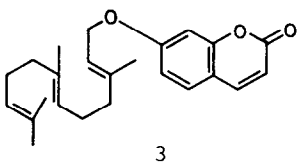


1

1, R = H

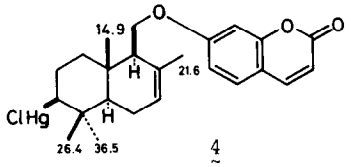
2, R = CH_3



3

a,b

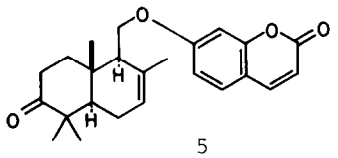
75%



4

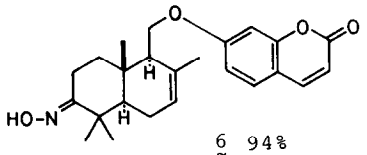
c,d

80%



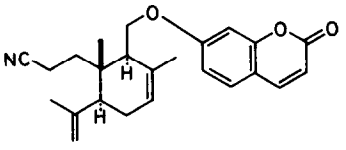
5

e

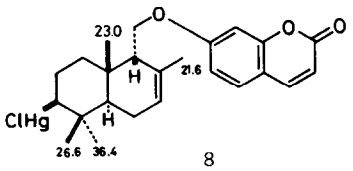


6 94%

f



7 29%



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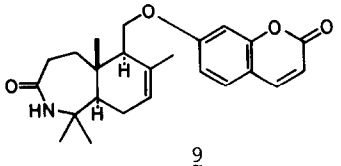
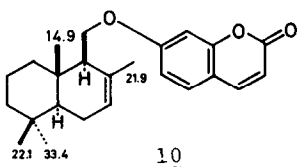
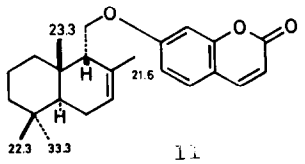


9

a $Hg(OTf)_2$/N,N-dimethylaniline, CH_3NO_2, -20°C, 2h. b aq NaCl. c $O_2/NaBH_4$/DMF. d Jones reagent. e NH_2OH-HCl. f p-TsCl/Py, reflux. g 20% KOH/C_2H_5OH, reflux.



10



11

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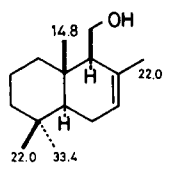
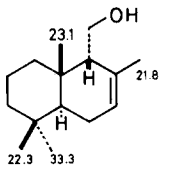
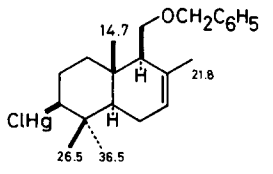
6. M. Nishizawa, H. Takenaka, H. Nishide, and Y. Hayashi, Tetrahedron Lett., 24, 2581 (1983).
7. ^{13}C NMR chemical shifts (δ, in $CDCl_3$).



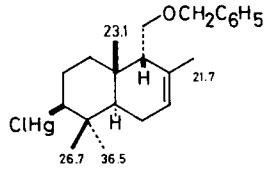
i



ii



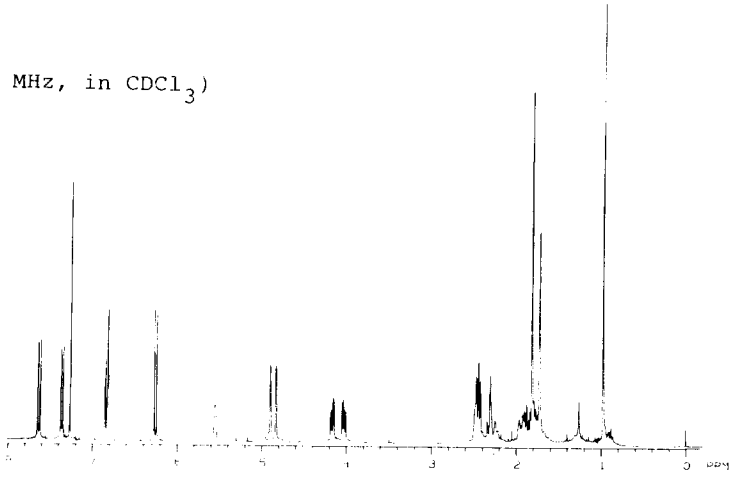
iii



iv

8. C. L. Hill and G. M. Whitesides, J. Am. Chem. Soc., 96, 870 (1974).
9. L. Mangoni and M. Belardini, Tetrahedron Lett., 921 (1963). G. P. Moss and S. A. Nicolaidis, Chem. Commun., 1077 (1969).
10. Spectral data of (±)-karatavic acid (1): IR ($CHCl_3$) 3500~2600, 1720, 1710, 1610, 840 cm^{-1}. ^{13}C NMR (δ, in $CDCl_3$) 17.4q, 22.1q, 22.3q, 28.8t, 29.3t, 32.7t, 38.0s, 46.4d, 48.5d, 67.3t, 101.6d, 112.7s, 113.1dd, 114.6t, 123.8d, 128.8d, 132.7s, 143.5d, 146.9s, 156.0s, 161.4s, 162.0s, 179.7s.

^{1}H NMR (360 MHz, in $CDCl_3$)



Determined by Dr. T. Iwashita of Suntory Institute for Bioorganic Research.

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