Tetrahedron Letters,Vol.29,No.34,pp 4241-4244,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

MALABAROLIDE, A NOVEL FURANOID BISNORDITERPENOID FROM *TINOSPORA MALABARICA*

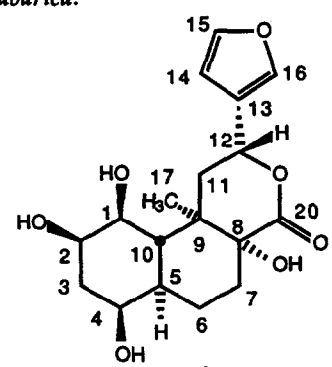
Atta-ur-Rahman* and Sultan Ahmad
H.E.J Research Institute of Chemistry
University of Karachi, Karachi-32, Pakistan

David S. Rycroft
Department of Chemistry, University of Glasgow
Glasgow, G12 8QQ, Scotland, U. K

László Párkányi[1], M. Iqbal Choudhary, Jon Clardy*
Department of Chemistry - Baker Laboratory
Cornell University, Ithaca, New York 14853-1301, U.S.A.

Summary: A novel furanoid bisnorditerpene has been isolated from the fresh stems of *Tinospora malabarica* Miers (Menispermaceae) and structurally characterized using X-ray crystallographic and spectroscopic techniques.

Aqueous extracts of *Tinospora malabarica* (Miers), cultivated throughout Pakistan, are used in the indigenous system of medicine for the treatment of various diseases.[2] Previously, diterpenes and alkaloids have been reported from this plant.[3-5] In the present communication we report the isolation[6] and structure determination of a novel furanoid bisnorditerpene, malabarolide (**1**), from the stems of *Tinospora malabarica*.



1

Malabarolide (1) was isolated by open column chromatography on silica gel using petroleum ether(40-60°)-acetone (7:3) as the eluting solvent. It was crystallized from EtOH to afford light-yellow crystals, m.p. 199-200° C. The UV spectrum (CH_3OH) showed an absorption at 210 nm which indicated the presence of a furan ring.[7-10] The IR spectrum ($CHCl_3$) showed absorptions at 3480, 3440, 3380 (OH), 1685 (lactone) and 1505, 880 cm^{-1} (furan ring). The presence of a furan ring was also indicated by a positive Ehrlich color test.[11]

Malabarolide (1) had the formula $C_{18}H_{24}O_7$ on the basis of a molecular ion at m/z 352.1523 (calc. 352.1522). Fragments at m/z 81 resulted from the cleavage of C11-C12 bond. Ions at m/z 94 and 95 were due to the cleavage of the γ-lactone ring along the C11-C12 and C12-O bonds. These observations clearly indicated that the furan occupied the C12 position, as in other furanoid diterpenoids.[7-10,12]

Because of the unusual formula, an X-ray crystal structure determination was undertaken. Crystals formed in the orthorhombic space group $P2_12_12_1$ with a=9.616(2), b=11.938(2), and c=14.789(4) Å. All unique diffraction maxima were collected ($2\theta \leq 114°$) using ω-scans with graphite monochromated Cu-Kα radiation (1.54178 Å). Of the 1416 unique reflections, 1296 (92%) had $|F_o| \geq 3\sigma(F_o)$ and were judged observed. The structure was solved by direct methods and refined by block-diagonal least-squares techniques to a final discrepancy index of 0.051 for the observed data. A computer generated drawing of the final X-ray model is given in Figure 1.

The NMR spectroscopic measurements were completely consistent with formulation 1. The ^{1}H-NMR spectrum[13a] (d_6-DMSO) showed a multiplet at δ 1.40 which was assigned to H5. The C6 methylene protons appeared as multiplets at δ 1.30 and 1.50, while C7 methylene protons resonated at δ 1.51 and 2.17. The signals for H1 and H4 in the d_6-DMSO spectrum overlapped at δ 3.51, but were resolved in CD_3OD with H1 at δ 3.70 (dd, J=10.4 and 3.0 Hz) and H4 at δ 3.68 (br.s.). A multiplet at δ 3.79 was assigned to H2. The configurational assignment of the signals of the C3 protons was determined from the 2D long-range C/H chemical shift correlation spectrum optimized for J=10.0 Hz. The resonance of C5 was correlated with the proton at δ 1.93 but not with the one at δ 1.57. Hence δ 1.93 was assigned to the equatorial proton H3β which had an antiperiplanar relationship to H5. The ^{13}C-NMR[13b] spectrum was assigned on the basis of DEPT spectra[14] and 2D direct C/H chemical shift correlation spectra. A 2D long-range C/H chemical shift correlation experiment, modified for repression of one-bond couplings both by incorporation of the BIRD[15] sequence and by use of a TANGO[16] sequence for the initial 90° pulse to select protons not directly bound to ^{13}C, was also consistent with structure 1.

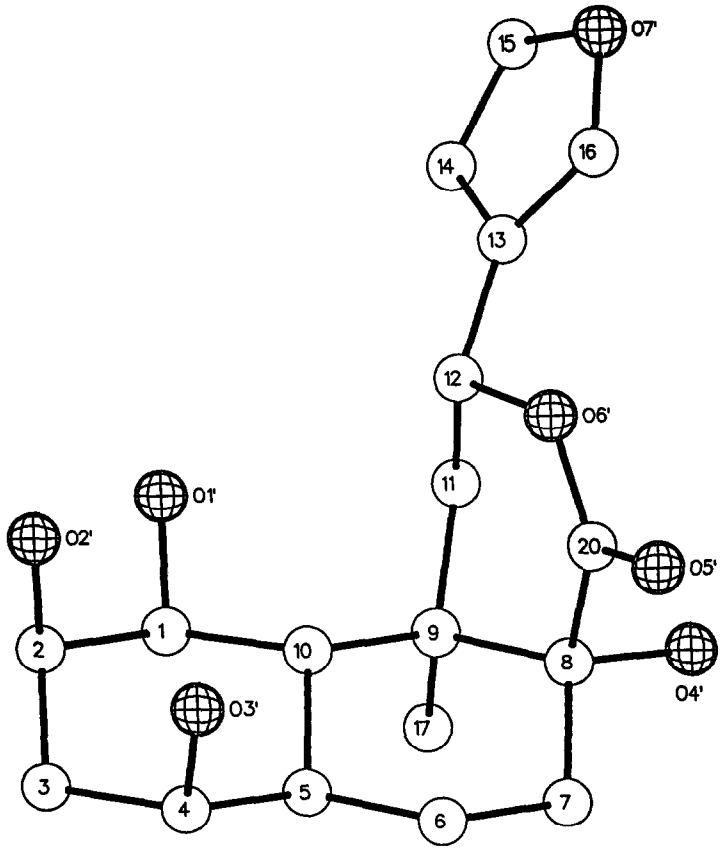


Figure 1 : A computer generated perspective drawing of the final X-ray model. Hydrogens are omitted for clarity and the absolute configuration is assumed.

A number of 19-norclerodanes[17] have been reported previously, but malabarolide (1) represents the first example of an 18,19-bisnorclerodane and thus provides a biogenetic curiosity. A plausible biogenesis of malabarolide (1) would involve oxidative removal of the 18-methyl group from a 19-norclerodanes or decarboxylation of a tinophyllol type compound.[18]

Acknowledgments. The work at Cornell was partially supported by NIH CA24487.

References and Notes

1. On leave from Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest, Hungary.

2. L. M. Perry, *Medicinal Plants of East and Southeast Asia*, MIT Press, Cambridge, Massachusetts, 1980, p.268.
3. R. Mehta, O. P. Arora, and M. Mehta, *Ind. J. Chem.*, Sect. B20, 834 (1981).
4. I. H. Bowen, and H. M. Motawe, *Planta Medica*, No. 6, 529.(1985).
5. Atta-ur-Rahman, S. Ahmad, *Fitoterapia*, V.LVIII. N. 4, 266, (1987).
6. Fresh stems of *T. malabarica* (120 kg) were crushed, extracted with EtOH (120 L), and the extract was concentrated to a crude gum (300 g). The gum was acidified with 10% CH_3COOH and extracted with $CHCl_3$. The chloroform soluble fraction was subjected to column chromatography on silica gel (900 g). Increasing polarities of mixtures of petroleum ether and acetone were used as eluants. The fraction obtained on elution with petroleum ether:acetone (7:3) was evaporated to dryness. This fraction was crystallized from acetone-MeOH (1:1) to give tinosporricide (structure under investigation). Multiple TLC of the mother liquors gave a band which crystallized from acetone. Recrystallization from EtOH gave malabarolide as light yellow crystals, m.p. 199-200° C, $[\alpha]_D$ = -4.48° (*c* 1.97, MeOH). TLC of a fresh extract indicated that malabarolide was not an artifact of the acid treatment.
7. T. Hori, A. K. Kiang, K. Nakanishi, S. Sasaki, and M. C. Woods, *Tetrahedron*, **23**, 2649 (1967).
8. M. Yonemitsu, N. Fukuda, T. Kimura, and T. Komori, *Liebigs Ann. Chem.*, No. 8, 1327 (1986).
9. N. Fukuda, M. Yonemitsu, and T. Kimura, *Chem. Pharm. Bull.*, **34**, 2868 (1986).
10. H. Wagner, R. Seitz, H. Lotter and W. Herz, *J. Org. Chem.*, **43**, No. 17. 3339 (1978).
11. T. Reichstein, *Helv. Chim. Acta*, **15**, 1110 (1932).
12. H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry*, Holden-Day Inc, San Francisco. Vol. II, 1964, p. 156.
13. (a) ^{1}H-NMR (400 Hz, d_6-DMSO): δ 7.65 (m, H16), 7.63 (t, J=1.7 Hz, H15), 6.47 (dd, J=1.7 Hz, and 0.8 Hz, H14), 5.72 (s, 8-OH), 5.69 (dd, J=12.4 and 4.0 Hz, H12), 4.97 (d, J=5.2 Hz, 2-OH), 4.65 (d, J=7.4 Hz, OH), 4.53 (d, J=6.8 Hz, OH), 3.79 (m, H2), 3.51 (m, H1), 3.51 (m, H4), 2.65 (dd, J=13.4 and 4.0 Hz, H11), 2.33 (t, J=13.0 Hz, H11α), 2.17 (m, H7β),1.93 (dt, J=14.4 and 3.1 Hz, H3β), 1.91 (t, J=10.2 Hz, H10), 1.57 (dt, J=14.4 and 3.0 Hz, H3α), 1.50 (m, H7α), 1.50 (m, H6β),1.40 (m, H5), 1.30 (m, H6α), 1.03 (s, H9).
(b) ^{13}C-NMR (100 MHz, d_6-DMSO, carbon assignment in parenthesis): δ 15.10 (17), 25.60(6), 29.40 (7), 35.00 (11), 35.50 (3), 35.80 (10), 39.00 (5), 39.20 (9), 67.30 (4), 71.10 (12), 72.00 (2), 72.5 (1), 74.70 (8), 108.90 (14), 126.00 (13), 139.70 (16), 143.40 (15), 171.80 (20).
14. Atta-ur-Rahman, *Nuclear Magnetic Resonance*, Springer-Verlag, New York. 1984, p.202.
15. A. Bax, *J. Mag. Reson.*, **53**, 517 (1984).
16. S. Wimperis and R. Freeman, *J. Mag. Reson.*, **58**, 348 (1984).
17. H. M. G. Al-Hamzi and G. A. Miana, *J. Chem. Soc. Pakistan*, **9**, 125 (1987).
18. T. Kuni, K. Kagei, Y. Kawakami, Y. Nagei, Y. Nezu and T. Sato, *Chem. and Pharm. Bull.* (Japan), **33**, 479 (1985).

(Received in USA 25 May 1988)