

Aspterric Acid, a New Sesquiterpenoid of the Carotane Group, a Metabolite from *Aspergillus terreus* IFO-6123. X-Ray Crystal and Molecular Structure of its *p*-Bromobenzoate

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Summary The structure and the absolute configuration of the sesquiterpenoid metabolite aspterric acid, from *Aspergillus terreus* IFO-6123 were established as (1) by chemical means and confirmed by X-ray analysis of its *p*-bromobenzoate.

The fungus *Aspergillus terreus* IFO-6123 produces a variety of compounds: terrein, 2,5-dihydroxy-6-methyl-*p*-benzoquinone, terremutin hydrate, 3-methylorsellinic acid, 4-*O*-demethylbarbatic acid, and asterriquinone,¹ together with aspulvinones-D, -F, and -G.² In addition to these known compounds we have isolated a new sesquiterpenoid, aspterric acid, from the acidic fraction of the culture broth of the fungus.

Aspterric acid (1), C₁₅H₂₂O₄, formed colourless needles from *n*-hexane, m.p. 158–159 °C, [α]_D¹⁵ -33°, † p*K*_a' 4.4, ν_{max} 3400 and 1720 cm⁻¹. It afforded the methyl ester (2), oil, on methylation with diazomethane and the monoacetate (3), m.p. 100–104 °C, [α]_D¹⁵ -112°, on acetylation with acetic anhydride and sodium acetate. It was hydrogenated over PtO₂ to the dihydro-compound (7), m.p. 186–187 °C, [α]_D¹⁷ -58°.

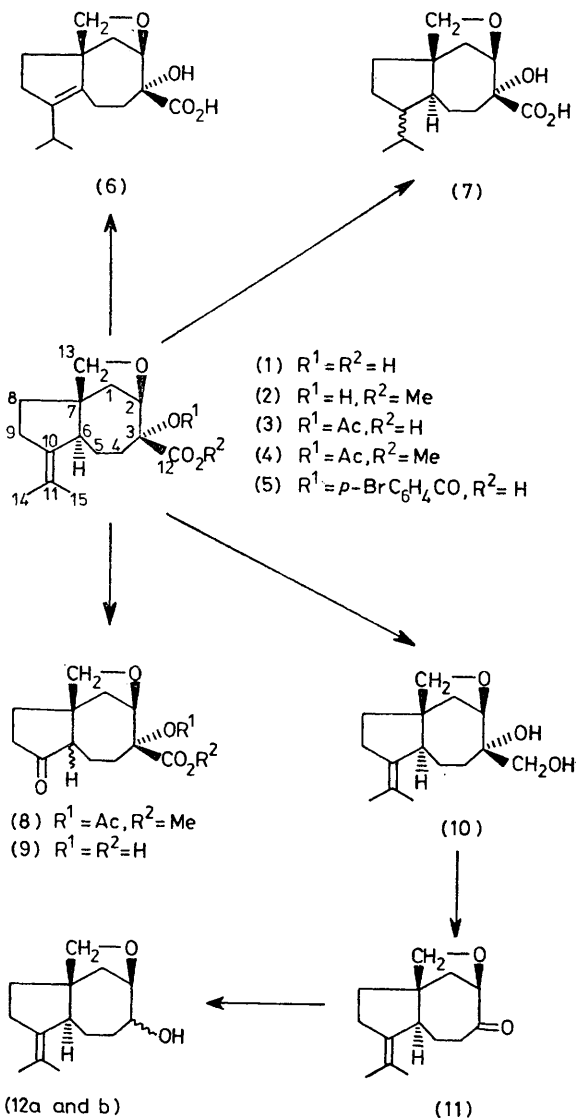
Spectral data (¹H and ¹³C n.m.r.) of (1) and its derivatives indicated the presence of the following groupings: >C-CH₂-O-CH< [δ 3.70 (2H, ABq, δ_{AB} 0.46 p.p.m., *J* 8.0 Hz) and 4.97 (1H, q, *J*₁ 6.5, *J*₂ 1.5 Hz)] and >C=CMe₂ (δ 1.57 and 1.72), together with CO₂H, >C-OH, an additional 5 >CH₂, and 1 >CH, in the original compound.

The isopropylidene unit in (1) was converted on treatment with mineral acids or Pd-C into the isopropyl unit yielding the isomer (6), m.p. 165–166 °C, [α]_D¹⁷ -17°. Ozonolysis of the methyl ester acetate (4) gave acetone and the trisnor-ketone (8), m.p. 126–127 °C, [α]_D¹⁵ -221°, the ketone group of which was shown to be part of the five-membered ring from the i.r. absorption (1758 cm⁻¹) of the corresponding acid (9), m.p. 189–190 °C.

Reduction of (1) with LiAlH₄ gave the diol (10), m.p. 98–99 °C, [α]_D¹⁷ -32°, which exhibited an additional AB quartet at δ 3.67 (δ_{AB} 0.54 p.p.m., *J* 11 Hz) and was cleaved with NaIO₄ into formaldehyde and the nor-ketone (11), oil, ν_{max} 1705 cm⁻¹. On LiAlH₄ reduction, (11) afforded a pair of epimeric alcohols (12a), oil, [α]_D¹⁵ -41°, and (12b), m.p. 115–116 °C, [α]_D¹⁷ ca. 0°, whose ¹H n.m.r. spectra showed the presence of the partial structure -(HO)CH-CH(-O)-. The above reactions, which establish structure (1) for aspterric acid, are summarized in the Scheme.

This assignment was confirmed and the absolute stereochemistry was determined by X-ray analysis of the *p*-bromobenzoate (5), colourless prisms from CCl₄, m.p. 156–157 °C, [α]_D¹⁵ -25°.

† All [α]_D values were measured in EtOH solution. Satisfactory elemental analyses were obtained for all crystalline compounds; all compounds reported had spectroscopic properties in accord with their assigned structures.



SCHEME

The crystals are monoclinic, space group *P*2₁, *a* = 17.906, *b* = 6.853, *c* = 10.942 Å, β = 90.26°, *Z* = 2. 1336 intensity data including 102 Friedel pairs were collected on a Philips PW-1100 diffractometer using monochromated Cu-K_α radiation, and 1121 of these above background were

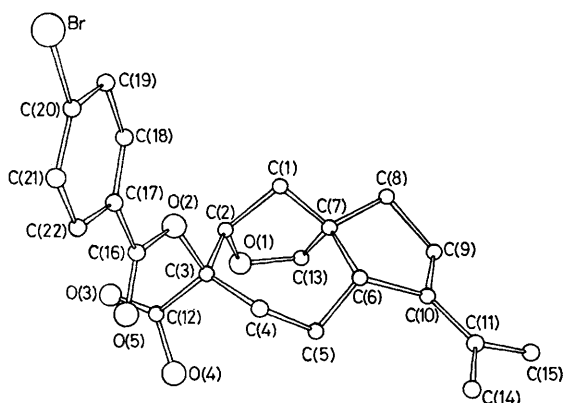


FIGURE. Perspective drawing of the *p*-bromobenzoate (5) showing the absolute configuration.

used for the structure determination. Corrections for a decrease in intensities during data collection because of crystal decomposition[§] were applied using standard reflections. The structure was solved by the heavy atom method. Block-diagonal least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms

reduced *R* to 0.12. The absolute configuration was determined using the anomalous dispersion effect of the bromine atom by comparing the observed and the calculated ratios of $|F(hkl)|^2/|F(\bar{h}\bar{k}\bar{l})|^2$ for 57 Friedel pairs.[¶] The structure is shown in the Figure.[¶]

Aspterric acid is the first example of a carotane sesquiterpenoid isolated from a fungal origin; all carotanes so far known are from the plant Umbelliferae⁴ and have the same absolute stereochemistry at C-7^{4c,5} as that in aspterric acid.

Using aspterric acid, the biosynthesis of the carotane skeleton was examined by feeding ¹³CH₃CO₂Na and ¹⁴CH₃CO₂Na simultaneously to the fungus. The incorporation of the ¹³C-labelled acetate into (1) calculated from the ¹⁴C content was 1.32%. Aspterric acid (1) thus isolated showed ¹³C enrichment in its ¹³C n.m.r. spectra at C-2, -4, -6, -8, -10, -12, -14, and -15 as expected. Moreover, ¹³C-¹³C coupling (42.7 Hz) was observed between C-6 and C-10, hence confirming the concerted cyclization of *trans-cis*-farnesyl pyrophosphate in formation of the carotane skeleton.

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[§] This is probably due to slow evaporation of the solvent of crystallization (CCl₄) during the data collection. Refinement showed a high thermal vibration of CCl₄; the position and dimensions obtained for CCl₄ are thus not reliable and not given in the text.

[¶] The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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