The Determination by N.M.R. Methods of the Structure and Stereochemistry of Astellatol, a New and Unusual Sesterterpene

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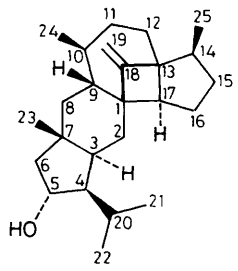
The full structure of astellatol, a new complex sesterterpene isolated from *Aspergillus variecolor*, has been determined solely by the use of one- and two-dimensional n.m.r. techniques.

During the course of structural and biosynthetic studies on a series of xanthone pigments[1] of *Aspergillus variecolor* (*syn. A. stellatus*), a colourless crystalline compound with molecular formula $C_{25}H_{40}O$, m.p. 120—122 °C, was isolated. Preliminary chemical and n.m.r. spectroscopic studies indicated the presence of a secondary alcohol, an exocyclic double bond, and one tertiary and four secondary methyl groups, indicating that the compound was pentacyclic. Although crystals of the alcohol were unsuitable for *X*-ray crystallographic examination, the derived ketone crystallised as prisms which allowed diffraction patterns to be obtained. Repeated attempts to solve the *X*-ray crystallographic data failed. However, application of a variety of one- and two-dimensional (2D) n.m.r. techniques to the alcohol in deuteriochloroform solution have shown that this compound, for which we propose the trivial name astellatol, is a new and unusual sesterterpene with the unique structure (**1**).

The connectivity of the carbon skeleton was deduced from a 2D ^{13}C–^{13}C INADEQUATE experiment[2] carried out at natural abundance and optimised to give responses from single bonded pairs of carbon atoms. All such pairs were observed and, as expected, no correlation was observed between the double bonded pair of carbon atoms. Interpretation was aided by prior classification of the ^{13}C resonances as methyl methylene, methine, or quaternary *via* spectra obtained by the DEPT technique,[3] and by the symmetrical disposition of related pairs of ^{13}C doublets about the diagonal of the 2D n.m.r. spectrum (Figure 1). The skeleton is most easily visualised as being derived from a tricycloundecane ring system (C-1 and C-9 to C-18) to which is fused a six-membered ring further fused to a five-membered ring. Examination of



(**1**)

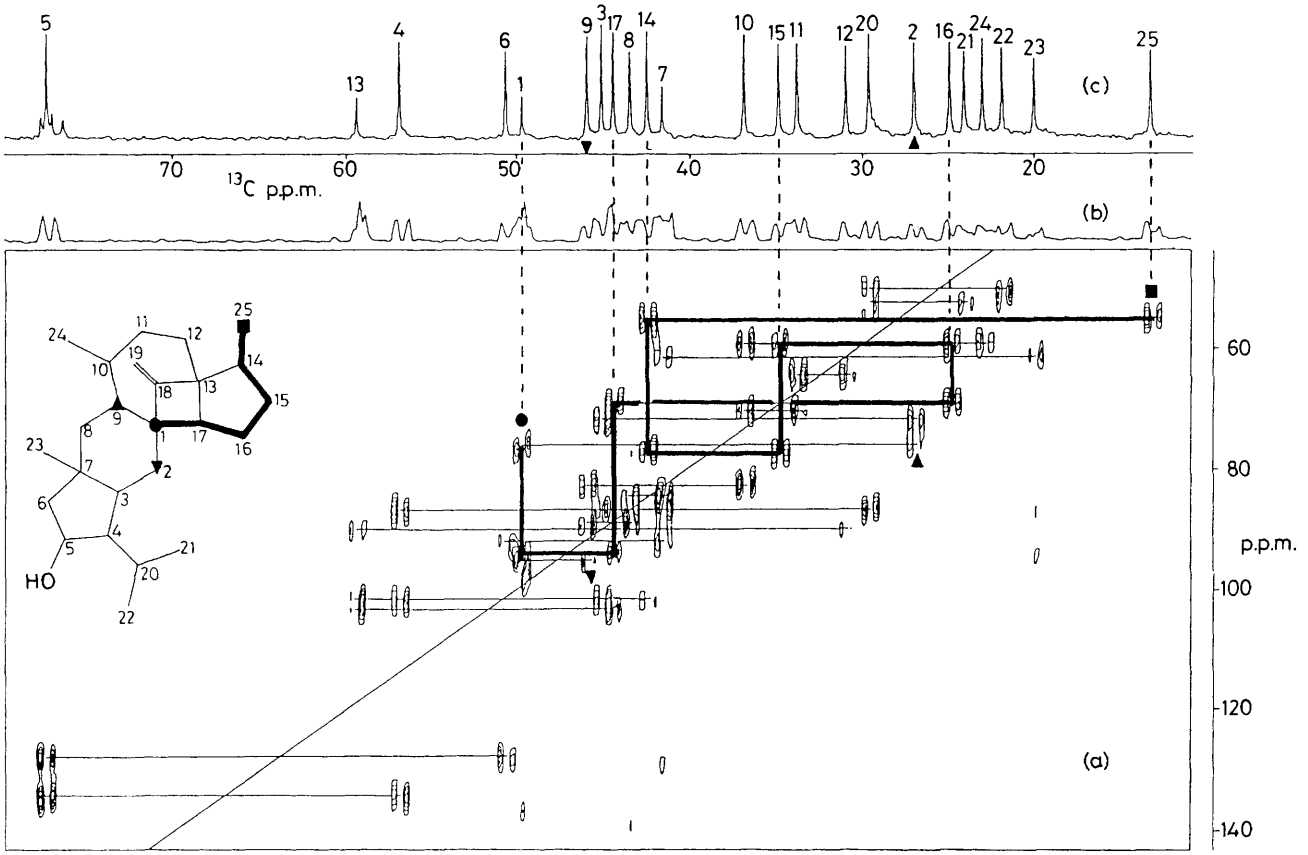


Figure 1. (a) Contour plot of low frequency region of the 50 MHz 2D INADEQUATE ^{13}C–^{13}C n.m.r. spectrum of astellatol. The full plot also shows correlation of C-18 with C-1 and C-13. Single and double quantum frequencies are referenced to tetramethylsilane (TMS). A portion of the skeleton is traced out on the plot to illustrate the interpretation. (b) 'Skyline' projection on to the single quantum axis. (c) Natural abundance broad-band proton decoupled ^{13}C n.m.r. spectrum.

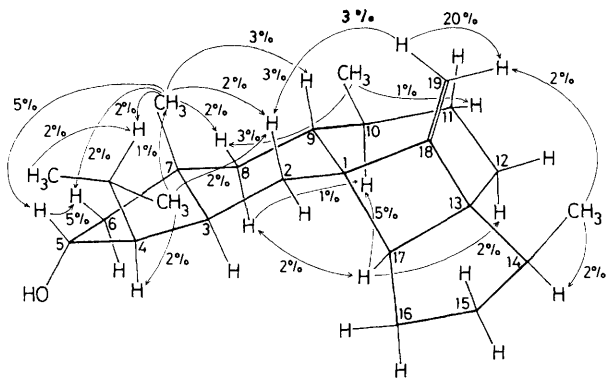


Figure 2. A 3D view of the astellatol molecule with observed homonuclear n.O.e. results. Enhancements (%) are obtained for those nuclei at the arrow heads on irradiating those at the arrow tails.

Dreiding stereomodels shows that the basic tricyclic system is relatively rigid and adopts either of two approximately equal low energy conformations. From either of these conformations, two modes of fusion are possible for the six-membered ring, which may itself be *cis* or *trans* fused to the five-membered ring. To distinguish between the numerous possible ring fusions and conformations, and also to determine the spatial positions of the methyl, hydroxy, and isopropyl groups, extensive analysis of the proton spectrum was necessary.

The chemical shifts of the protons were individually obtained from a 2D ^{1}H –^{13}C one-bond heteronuclear correlation experiment set up so that proton–carbon and all proton–proton couplings were absent.[4] Except for C-16 where the bonded protons exhibited the same chemical shift, each of the methylene carbons correlated with two well separated proton shifts. It was then possible to extract from a resolution enhanced one-dimensional 360 MHz proton spectrum the coupling constants for the protons bonded to C-5, C-6, C-9, C-17, and C-19, for one of the protons bonded to each of C-8 and C-12, and for the protons of the methyl groups. Further analysis was hampered by extensive overlap of the multiplets from the remaining fifteen protons in the region 1.3—1.8 p.p.m. By careful examination and analysis of spin decoupling difference spectra and 2D proton COSY and *J*-resolved spectra it was possible to obtain the coupling constants for all these remaining protons except for those between the protons bonded to C-15 and C-16. Particularly significant were the 12—14 Hz three-bond couplings between one H-2 and H-3, one H-8 and H-9, H-9 and H-10, H-10 and one H-11, and the same H-11 and one H-12, with which only six fused pentacyclic ring systems were consistent. It was possible to show which of these was adopted by astellatol and also deduce the spatial positions of the substituents from a series of nuclear Overhauser enhancement (n.O.e.) difference spectra obtained by the selective multi-line irradiation technique.[5] The principal n.O.e.s. obtained are summarised on the 3D structure shown in Figure 2.

Astellatol therefore represents a hitherto unobserved sesterterpene skeleton. Biogenetic considerations suggest that it is formed *via* a folding and initial cyclisation of geranylfarnesyl pyrophosphate, similar to that involved in its conversion to the lichen product retigeranic acid[6] followed by further cyclisation and rearrangement. It is noteworthy that another sesterterpene, stellatic acid,[7] previously isolated from *A. stellatus* appears to be formed *via* a different initial folding of geranylfarnesyl pyrophosphate.

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