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THE STEREOCHEMISTRY OF GUGGULSTEROL-1

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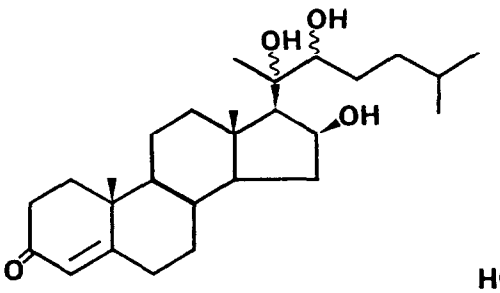
Summary: The steroechemistry of guggulsterol-1, a component of the exudate of Commiphora mukul, is shown to be 20(R), 22(R)(3).

Guggulu, the exudate of Commiphora mukul (Hook, ex Stocks) Engl., is mentioned in classical Ayurvedic literature as an efficacious treatment of rheumatoid arthritis, obesity and allied disorders.[1,2] One of the compounds isolated from this source, guggulsterol-1, was assigned structure 1 on spectral grounds.[2] The stereochemistry at C(20) and C(22) was not assigned. A later investigation, employing the induced circular dichroism method,[3] indicated 20(S) and 22(S) as the correct absolute configurations for these centers. However, if one makes the reasonable assumption that cholesterol (2) would be the precursor of 1 in the plant, one would expect 20(R) chirality. 20, 22-dihydroxycholesterol, which lies on the pathway from cholesterol to progesterone, is known to have the 20(R), 22(R) configuration and this result might be expected to hold for guggulsterol-1.[4] In view of these conflicting indications we elected to establish the configuration of guggulsterol-1 by a single crystal x-ray diffraction analysis.



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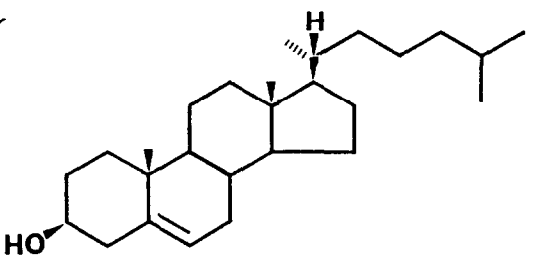

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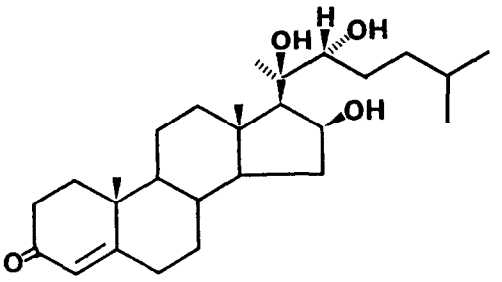

3

A single crystal of guggulsterol-1 (MeOH, .4x.25x.25mm) displayed orthorhombic symmetry. Accurate lattice constants were $\underset{\sim}{a}$ = 16.049(4), $\underset{\sim}{b}$ = 25.640(5) and $\underset{\sim}{c}$ = 12.434(3)Å and the crystal density, systematic extinctions and the presence of chirality were uniquely accommodated by space group $P2_12_12_1$ with two molecules of $C_{27}H_{44}O_4$ forming the asymmetric unit. All diffraction maxima with $2\theta \leq 114.1°$ were surveyed on a four-circle diffractometer using graphite monochromated CuK$\bar{\alpha}$ (1.54178Å) radiation and a variable speed, 1° ω-scan technique. Of the 3873 reflections surveyed in this fashion, 3567 (92%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization and background effects. Obtaining a phasing model for guggulsterol-1 was complicated by the presence of two molecules in the asymmetric unit. Several initial attempts using multisolution techniques failed. The approach that finally succeeded began by modifying the normalized structure factors with a spherically averaged

fragment representing the B and C rings and two angular methyl groups.[5] A multisolution tangent formula approach using 175 E's yielded an E-synthesis for the best solution which contained two major fragments which appeared to be steroid nuclei. Using twenty atoms from both fragments in a Karle tangent formula recycling procedure[6] and 300 E's gave an E-synthesis which displayed most of the two steroid molecules. A fifty-one atom fragment was recycled with 445 E's and 59 of the 62 nonhydrogen atoms in the asymmetric unit were identified. The nonhydrogen framework was completed by an F-synthesis following partial least squares refinement and most hydrogen atoms were found in a ΔF-synthesis. Block-diagonal least squares refinements with anisotropic carbons and oxygens and isotropic (fixed) hydrogens have converged to a standard crystallographic residual of 0.05 for the observed data.[7] Both independent molecules have the same stereostructure. A computer generated perspective drawing of the final x-ray model is shown in Figure 1. The absolute configuration shown is assumed. The most significant aspects are the configurations at C(20) and C(22) which are both R as suggested by the biogenetic considerations.

It is conceivable that the induced CD method failed because of possible interference from the C(16) hydroxyl group. In this regard it is interesting to note that all of the hydroxyl groups are intramolecularly hydrogen bonded to each other. The hydrogen bonding network is: O(22)H $\xrightarrow{2.62}$ O(20) $\xrightarrow{2.61}$ O(16) $\xrightarrow{2.73}$ O(16') $\xrightarrow{2.62}$ O(20') $\xrightarrow{2.60}$ O(22') $\xrightarrow{2.79}$ O(22) ($\frac{1}{2}$+x, $\frac{1}{2}$-y, -z). The network begins with the donor hydroxyl O(22)H and continues in an intramolecular fashion to O(20) and O(16); O(16) then makes an intermolecular contact with the other independent molecule via O(16') which then forms the same intramolecular hydrogen bonds in the opposite sense. There is finally an intermolecular contact along the two-fold screw along x. Bond distances and angles agree well with generally accepted values.

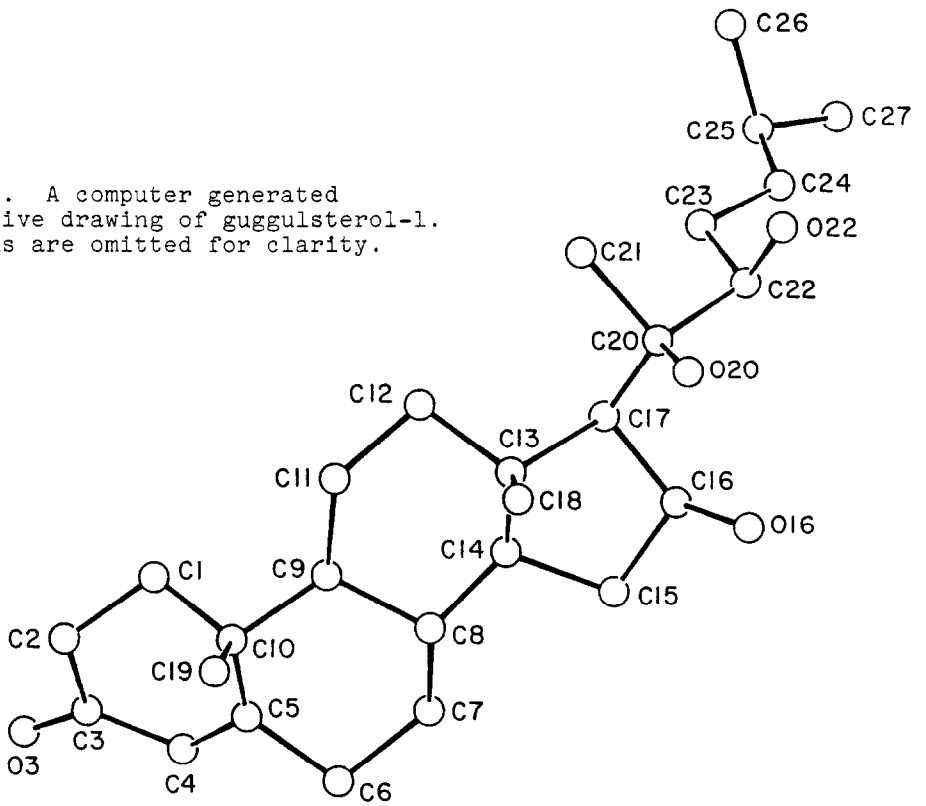

Figure 1. A computer generated perspective drawing of guggulsterol-1. Hydrogens are omitted for clarity.

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Notes and References

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4. See e.g.: C. Duque, M. Morisaki, N. Ikekawa and M. Shikita, Tetrahedron Letters 4479 (1979).
5. Programs used are described in J. Am. Chem. Soc. 103, 1243 (1981).
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7. X-ray data have been deposited with the Cambridge Crystallographic Data Centre.

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