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(−)-Fern-7-en-3α-ol from *Sebastiania brasiliensis*

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Key indicators

Single-crystal X-ray study
T = 170 K
Mean σ(C–C) = 0.003 Å
R factor = 0.044
wR factor = 0.103
Data-to-parameter ratio = 7.7

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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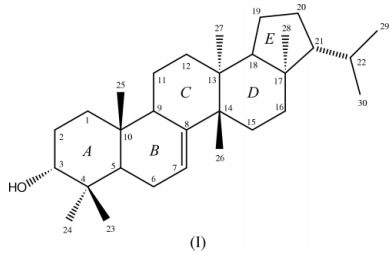
The structure of a fernane isolated from *S. brasiliensis* was established as fern-7en-3α-ol, $C_{30}H_{50}O$. Rings *A* and *D* assume a chair conformation, while rings *B* and *C* adopt a twist-boat conformation. Rings *A*/*B*, *C*/*D*, and *D*/*E* are *trans* fused. The relative orientation of the hydroxy group and that of the isopropyl group is α.

Comment

The growing number of deaths due to tuberculosis (TB) and the existence of strains of TB resistant to existing drugs has created an urgent need for the identification of leads for new antimycobacterial drugs. There are 8 million new cases of tuberculosis each year (Dye *et al.*, 1999) and it is estimated that this number will increase to 10 million cases per year. There are an estimated 3 million deaths due to TB every year. Strains of TB resistant to existing drugs are found in nearly every country (Cohn *et al.*, 1997), and a percentage of these are resistant to multiple drugs making effective treatment extremely expensive and in many cases impossible. Most patients in developing countries, where TB is an even bigger problem than elsewhere in the world, can not afford expensive drug treatments. There have been no new drugs developed for TB in over 30 years. Current activity in new drug development has centered around the rifamycins, rifabutin, rifapentine and KRM-1648, some of which exhibit cross-resistance with rifampin. It is in this regard that the bioassay guided fractionation of the antitubercular methanol extract of *S. brasiliensis* Spreng. (Euphorbiaceae), found active against the $H_{37}Rv$ strain (ATCC 27294) of *Mycobacterium tuberculosis*, was initiated, leading to the isolation of the title compound, (I).



(I)

X-ray crystallographic analysis of (I) was undertaken to unequivocally establish the structure and to assign the relative stereochemistry at C3. Although (I) has previously been reported in the literature (Nakane *et al.*, 1999), this is the first report of its isolation from *S. brasiliensis* and of its crystal structure. The X-ray structure of (I) can now serve as a standard for comparison of related fernanes. With reference to the *Scheme*, the absolute configuration at all chiral centers is 3*R*, 5*S*, 9*R*, 10*S*, 13*S*, 14*S*, 17*R*, 18*R*, 21*R*.

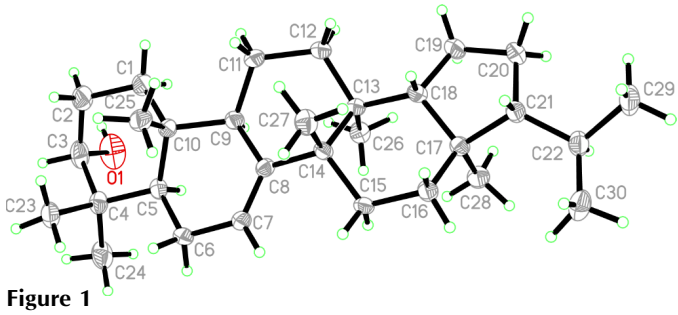


Figure 1
A displacement ellipsoid plot (50% probability level) of (I).

As shown in Fig. 1, rings *A* and *D* assume a chair conformation, while rings *B* and *C* adopt a twist-boat conformation. The *A*/*B*, *C*/*D*, and *D*/*E* ring junctions are *trans* fused about the C5—C10, C13—C14 and C17—C18 bonds, respectively. The relative orientation of the hydroxyl group at C3, and that of the isopropyl group at C21 is α. No hydrogen bonds were detected between the hydroxyl groups of screw-related molecules; however, the molecules pack such that the hydroxyls of adjacent molecules are as close to each other as possible [5.075 (2) Å]. The distance between hydroxyls related by unit translation along the *b* axis is 7.5526 (11) Å. Hydrogen bonding was observed between the C24 methyl H and the hydroxyl oxygen of screw-related molecule with a bond length 2.72 (3) Å and a bond angle of 162 (2)°. [Note: the standard numbering convention for the methyl groups in ring *A* is C23 for the α-methyl and C24 for the β-methyl.]

Experimental

The antitubercular CH_2Cl_2–MeOH extract of *S. brasiliensis* was chromatographed on a silica gel column with increasing concentrations of EtOAc in *n*-hexane. The fraction eluting with 10% EtOAc in *n*-hexane was found to inhibit the growth of *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) by 90% at 50 µg ml^{-1} concentration. This fraction, when treated with ether, gave a crystalline substance which on thin-layer chronatography (TLC) showed essentially one major spot. Preparative silica gel TLC of this fraction followed by crystallization led to the isolation of fern-7-en-3α-ol, (I). Crystals were obtained by slow evaporation of *n*-hexane/acetone. Colorless shining transparent rectangular rods were formed after 3 d.

Crystal data

$C_{30}H_{50}O$
M_r = 426.70
Monoclinic, $P2_1$
a = 12.4234 (18) Å
b = 7.5526 (11) Å
c = 13.628 (2) Å
β = 101.320 (3)°
V = 1253.8 (3) Å^3
Z = 2
D_x = 1.130 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4025 reflections
θ = 2.5–23.4°
μ = 0.07 mm^{-1}
T = 170 (2) K
Parallelepiped, colorless
0.35 × 0.27 × 0.19 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.978, T_{max} = 0.988
15 904 measured reflections
3278 independent reflections
2947 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 28.3°
$h = -16 \rightarrow 16$
$k = -10 \rightarrow 10$
$l = -18 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.103
S = 1.06
3278 reflections
427 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0564P)^2 + 0.2128P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C24—H24C···O1^{i}	0.99 (3)	2.72 (3)	3.677 (3)	162 (3)

Symmetry code: (i) $3-x, \frac{1}{2}+y, 2-z$.

H-atom positions were easily visible in difference Fourier maps and all H atoms were allowed to refine freely, except for the hydroxyl H atom, which was constrained to an O—H distance of 0.84 Å and a C—O—H angle of 109.47°, with U_{iso}(H) = 1.5U_{eq}(O). Owing to the absence of any heavy atoms, anomalous dispersion could not be used to define absolute configuration. In the final cycles of refinement, all Friedel pairs were merged. The enantiomer was selected based on the observed negative optical rotation of the compound in solution and the fact that this is the most common enantiomer observed in nature (Ahmad & Atta-ur-Rahman, 1994).

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Bruker, 1997); program(s) used to refine structure: *SHELXL*97 (Bruker, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

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