

**(–)-(5*S*,8*S*,9*R*,10*S*,13*R*,14*R*)-
15,16-Dideoxy-16,17-epoxy-
16-oxospongian-15-yl acetate**

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The title compound (aplyroseol-14), C₂₂H₃₄O₄, exhibits a lactone-based structure that is novel for spongian-type diterpenoids. The structure, which features a six-membered lactone ring, was proposed by Arnó, González & Zaragoza [*J. Org. Chem.* (2003), **68**, 1242–1251] on the basis of spectroscopic data and chemical correlations. This assignment has been confirmed, and it is shown that the molecule contains a *trans-anti-trans* 6/6/6 tricyclic hydrocarbon system and that the acetoxymethyl group lies in an equatorial position. Pairs of near-linear C–H...O interactions link molecules into extended chains.

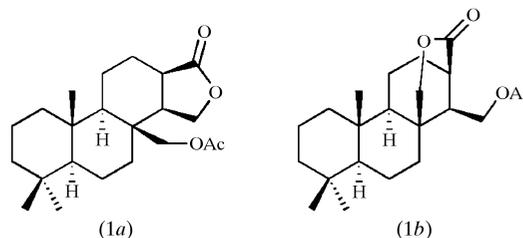
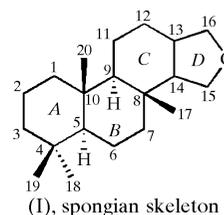
Comment

Spongian diterpenoids are bioactive natural products isolated exclusively from sponges and shell-less molluscs (nudi-branches), which are believed to be capable of sequestering the spongian-derived metabolites from the sponges on which they feed. Most of these compounds play a key role as eco-physiological mediators and are of interest as potential therapeutic agents (Arnó, Betancur-Galvis *et al.*, 2003).

The carbon skeleton (I), named 'spongian' in accordance with IUPAC recommendations (Kazlauskas *et al.*, 1979), was chosen as the fundamental parent structure for this family of natural compounds, with the numbering depicted. Thus, spongians typically exhibit the hydrocarbon ring system (I), consisting of a steroid-like ABCD ring system containing an oxygenated group, such as a tetrahydrofuran ring, and with varying oxidation patterns on rings A–D.

The title compound, (1*b*), was isolated from the sponge *Aplysilla rosea* Barrois by Taylor & Toth (1997), and the structure (1*a*), in which ring D is usually a five-membered lactone typical of other members of the spongian family (Cimino *et al.*, 1974; Karuso & Taylor, 1986; Miyamoto *et al.*, 1996), was assigned from one- and two-dimensional ¹H NMR

data, high-resolution mass spectrometry, and IR spectroscopy. Following our studies directed towards the synthesis of C-17-functionalized spongians (Arnó *et al.*, 2001), we selected (1*a*) as a potential target compound and we readily synthesized



a compound (Arnó, González & Zaragoza, 2003) whose spectroscopic data were in apparently good agreement with those reported for natural aplyroseol-14. However, a careful study of the spectroscopic data, in particular the IR and NMR spectra, indicated that the molecule contained the six-membered lactone (1*b*) instead of the expected five-membered one seen, for example, in (5*R**,7*S**,8*S**,9*S**,10*R**,13*S**,14*S**)-16-oxospongian-7,17-diyl diacetate (Karuso & Taylor, 1986) or 7α-hydroxyspongian-16-one (Miyamoto *et al.*, 1996). We supported our assignment by synthesizing the proposed structure (1*a*) for aplyroseol-14 and making comparisons with the published data. As expected, the synthetic compound (1*a*) gave spectroscopic data that, although generally similar to those reported for natural (1*b*),

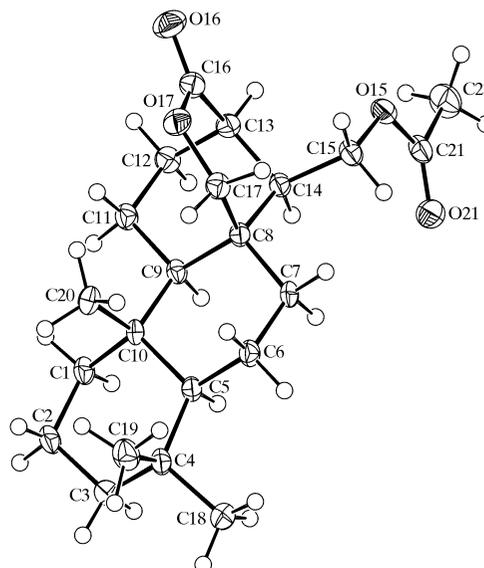


Figure 1

A view of (1*b*), showing the atom-numbering scheme and displacement ellipsoids at the 50% probability level.

were nevertheless clearly different. Owing to the uniqueness of the carbon skeleton of (1*b*), together with apparent disagreement in some reported data (IR bands), a single-crystal X-ray study was carried out on synthetic (1*b*) in order to confirm the structural assignment. The ^1H NMR spectra of synthetic (1*b*) and natural (1*b*) were found to be in excellent agreement.

A perspective view of the molecule is shown in Fig. 1. Both the chemical connectivity and the relative stereochemistry are in full agreement with those proposed by Arnó, González & Zaragoza (2003) for aplyroseol-14 (1*b*). The stereochemistry at atoms C5 (*S*), C9 (*R*) and C10 (*S*) is invariant during the synthesis, but three new asymmetric centres were introduced at C8 (*S*), C13 (*R*) and C14 (*R*). The molecule contains a *trans-anti-trans* 6/6/6 tricyclic hydrocarbon system to which a six-membered lactone ring is attached at atoms C8 and C13. All six-membered rings adopt chair conformations with axially disposed methyl or lactone substituents. However, the lactone ring (C8/C14/C13/C16/O17/C17) is distorted towards a half-chair conformation; while atom C8 lies 0.734 (3) Å below the least-squares mean plane through atoms C14, C13, O17 and C17, atom C16 lies only 0.329 (3) Å above it. The acetoxy-methyl group at atom C14 lies in an equatorial position. Bond lengths and angles are typical for such sterically non-strained molecules.

Molecules are linked by almost linear pairwise C—H...O interactions (Table 1 and Fig. 2). One of these interactions occurs between carbonyl atom O21 of the acetoxy group and atom H15 of the methylene group adjacent to the acetoxy

group in a neighbouring molecule; the other involves methine atom H14 and lactone atom O17 in the same neighbouring molecule. The interactions link the molecules into chains running along the *b* axis. The C—H...O interactions contrast with the situation in analogous compounds containing hydroxy groups (Schmitz *et al.*, 1985; Karuso *et al.*, 1986; Miyamoto *et al.*, 1996), where the presence of the hydroxy groups leads to O—H...O=C hydrogen bonds being the primary intermolecular contacts.

Experimental

Compound (1*b*) was synthesized from the chiral synthon (+)-podocarp-8(14)-en-13-one, readily available from commercial (–)-abietic acid (Abad *et al.*, 1985; see scheme below). The absolute stereochemistry at atoms C5, C9 and C10 was therefore fixed. During the synthesis, the key intermediate methyl 8β,14β-dioxopodocarpan-13β-oate was prepared, in which three new stereocentres, *viz.* C8, C13 and C14, were introduced. This intermediate was transformed into (–)-16-oxospongian-17-al, confirming the absolute stereochemistry of all asymmetric centres. Finally, the latter was converted into (1*b*) by standard reduction followed by acetylation. This two-step process involved a translactonization reaction that occurred during the reduction step. Crystals were grown from a solution of (1*b*) in dichloromethane/hexane (1:4).

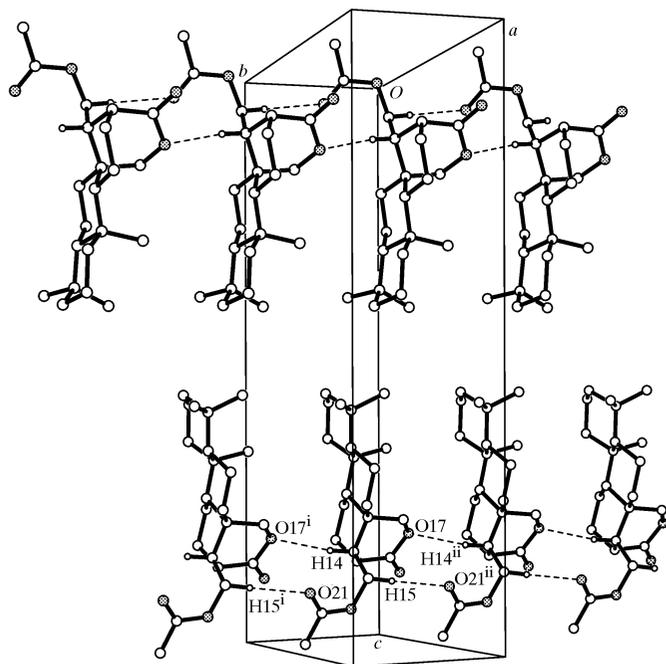
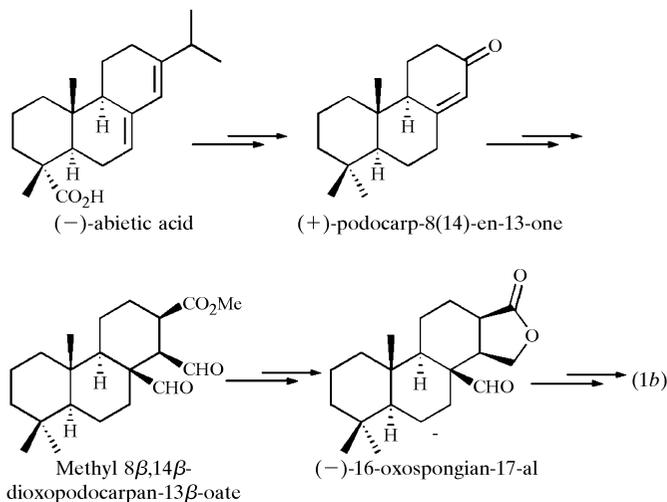


Figure 2

A view of the chains of molecules linked along the *b* axis by pairwise near-linear C—H...O interactions. C atoms are shown as large open circles, O atoms as dotted circles and H atoms as small open circles. [Symmetry codes: (i) $x, y + 1, z$; (ii) $x, y - 1, z$.]

Crystal data

$\text{C}_{22}\text{H}_{34}\text{O}_4$
 $M_r = 362.49$
 Monoclinic, *C*₂
 $a = 13.377$ (2) Å
 $b = 6.0824$ (8) Å
 $c = 23.834$ (3) Å
 $\beta = 94.235$ (2)°
 $V = 1933.9$ (5) Å³
 $Z = 4$

$D_x = 1.245$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 3476 reflections
 $\theta = 2.6$ – 27.5°
 $\mu = 0.08$ mm⁻¹
 $T = 150$ (2) K
 Tablet, colourless
 $1.07 \times 0.50 \times 0.13$ mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
 ω scans
 5352 measured reflections
 2382 independent reflections
 2200 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.133$
 $\theta_{\text{max}} = 27.5^\circ$
 $h = -17 \rightarrow 15$
 $k = -7 \rightarrow 7$
 $l = -30 \rightarrow 22$

Refinement

Refinement on F^2

$$R[F^2 > 2\sigma(F^2)] = 0.049$$

$$wR(F^2) = 0.133$$

$$S = 0.92$$

2382 reflections

239 parameters

H-atom parameters constrained

$$w = 1/[\sigma^2(F_o^2) + (0.106P)^2]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

$$(\Delta/\sigma)_{\max} = 0.001$$

$$\Delta\rho_{\max} = 0.40 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.27 \text{ e } \text{\AA}^{-3}$$

Table 1

Hydrogen-bond geometry (\AA , $^\circ$).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C14—H14 \cdots O17 ⁱ	1.00	2.49	3.486 (3)	171
C15—H15 \cdots O21 ⁱⁱ	0.99	2.52	3.509 (3)	173

Symmetry codes: (i) $x, y + 1, z$; (ii) $x, y - 1, z$.

The absolute configuration of (*1b*) was assigned as for (+)-podocarp-8(14)-en-13-one (Abad *et al.*, 1985), based on the absolute configuration of (−)-abietic acid as determined by optical rotatory dispersion measurements (*e.g.* Bose & Struck, 1959). All H atoms were included at geometrically calculated positions and constrained to ride on their parent C atoms at distances of 0.98, 0.99 or 1.00 \AA for methyl, methylene or methine groups, respectively, and with $U_{\text{iso}}(\text{H})$ values of $1.5U_{\text{eq}}(\text{C})$ for methyl H atoms and $1.2U_{\text{eq}}(\text{C})$ for others. As there are no significant anomalous dispersion effects, Friedel opposites were merged prior to the final cycles of refinement.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT* and *SHELXTL* (Bruker, 2001); program(s) used to solve structure: *SIR2002* (Burla *et al.*, 2003); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003) and *SHELXTL*; software used to prepare material for publication: *enCIFer* (Allen *et al.*, 2004) and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN3004). Services for accessing these data are described at the back of the journal.

References

- Abad, A., Arno, M., Domingo, L. R. & Zaragoza, R. J. (1985). *Tetrahedron*, **41**, 4937–4940.
- Allen, F. H., Johnson, O., Shields, G. P., Smith, B. R. & Towler, M. (2004). *J. Appl. Cryst.* **37**, 335–338.
- Arnó, M., Betancur-Galvis, L., González, M. A., Sierra, J. & Zaragoza, R. J. (2003). *Biorg. Med. Chem.* **11**, 3171–3177.
- Arnó, M., González, M. A., Marín, M. L. & Zaragoza, R. J. (2001). *Tetrahedron Lett.* **42**, 1669–1671.
- Arnó, M., González, M. A. & Zaragoza, R. J. (2003). *J. Org. Chem.* **68**, 1242–1251.
- Bose, A. K. & Struck, W. A. (1959). *Chem. Ind. (London)*, pp. 1628–1630.
- Bruker (2001). *SAINT* (Version 6.36a), *SHELXTL* (Version 6.12) and *SMART* (Version 5.625). Bruker AXS Inc., Madison, Wisconsin, USA.
- Burla, M. C., Camalli, M., Carrozzini, B., Cascarano, G. L., Giacovazzo, C., Polidori, G. & Spagna, R. (2003). *J. Appl. Cryst.* **36**, 1103.
- Cimino, G., De Rosa, D., De Stefano, S. & Minale, L. (1974). *Tetrahedron*, **30**, 645–649.
- Karuso, P., Bergquist, P. R., Cambie, R. C., Buckleton, J. S., Clark, G. R. & Rickard, C. E. F. (1986). *Aust. J. Chem.* **39**, 1643–1653.
- Karuso, P. & Taylor, W. C. (1986). *Aust. J. Chem.* **39**, 1629–1641.
- Kazlauskas, R., Murphy, P. T., Wells, R. J., Noack, K., Oberhänsli, W. E. & Schönholzer, P. (1979). *Aust. J. Chem.* **32**, 867–880.
- Miyamoto, T., Sakamoto, K., Arao, K., Komori, T., Higuchi, R. & Sasaki, T. (1996). *Tetrahedron*, **52**, 8187–8198.
- Schmitz, F. J., Chang, J. S., Hossain, M. B. & van der Helm, D. (1985). *J. Org. Chem.* **50**, 2862–2865.
- Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
- Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
- Taylor, W. C. & Toth, S. (1997). *Aust. J. Chem.* **50**, 895–902.