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A new squalene-derived epoxy tri-THF diol from *Spathelia glabrescens*

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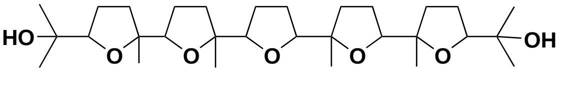
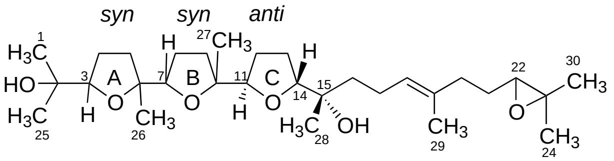
Abstract—A new triterpenoid polyether containing three THF rings and an epoxide has been isolated from *Spathelia glabrescens* and the structure determined by NMR methods. © 2001 Elsevier Science Ltd. All rights reserved.

Six years ago we reported the structure of the first penta-THF squalene derivative glabrescol (**1**) from the endemic Jamaican plant *Spathelia glabrescens* (Rutaceae).[1] This remarkable natural product attracted some synthetic interest[2] and at least three total syntheses of the diastereomer with the originally assigned *meso* stereochemistry have been published.[3–5] Differences between the natural and synthetic compounds in chromatographic behaviour and spectroscopic properties[3–5] have led to the conclusion that the *meso* stereochemistry assigned to the natural product was wrong and that the observed symmetrization of the NMR spectra is likely due to C_2 symmetry. It became necessary to re-isolate glabrescol (**1**) for the purpose of preparing a crystalline derivative. For this a new batch of plant material was collected and in the process of re-isolation of **1** the new compound (**2**) was obtained.



1



2

Compound **2** was isolated in low yield (0.003% of dried heartwood) as a colorless non UV-absorbing oil with the following physicochemical and spectral characteristics: $[\alpha]_D$ −32.0° (*c* 0.13, $CHCl_3$); IR (film) 3381, 1626, 1071 cm^{-1}; HRMS 508.375368, calcd for $C_{30}H_{52}O_6$ 508.376390; ^1H and ^{13}C NMR (Table 1).

Inspection of the initially obtained ^1H and DEPT-edited ^{13}C NMR spectra suggested that **2** contained three THF rings, one of which was in the center of the oxasqualenoid[1] structure, two tertiary hydroxyl groups, one internal trisubstituted double bond and a trisubstituted epoxide. From the HMBC spectra it was established that the three THF rings are contiguous, and flanked by a hydroxy isopropyl residue and the quaternary carbon bearing the second tertiary hydroxyl group. The remaining two functionalities were placed in the portion of the molecule numbered C-16 to C-24 on the basis of COSY and HMBC associations.

In 60% $CDCl_3$–40% C_6D_6 the ^1H signals for the C-26, C-27 and C-28 methyl groups were well separated, and clear T-ROESY correlations between H-3 and the C-26 methyl and between H-7 and the C-27 methyl indicated that these groups in the α-THF positions of rings A and B are *syn*. Absence of correlation between H-11 and H-14 suggested *anti* stereochemistry for these α-THF protons of ring C. This was borne out by T-ROESY cross peaks from H-14 (δ 3.70) to one hydrogen of each of the ring C THF methylene groups, i.e. H-13β (δ 1.71) and H-12β (δ 1.28) and from H-11 (δ 3.88) to H-12α (δ 1.76). Additionally, by analogy with eurylene and related compounds,[6] a strong cross peak between H-14 and the C-28 methyl group suggests that the relative stereochemistry at C-15 is as shown in **2**.

Keywords: epoxide; natural product; NMR; polyether; squalene.

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Table 1. NMR data for compound **2**[a]

Pos	$CDCl_3$			60% $CDCl_3$–40% C_6D_6		
	δC	δH[b]	HMBC[c]	δC	δH[b]	T-ROESY[d]
1	25.2	1.04	25	25.4	1.04	3, 4β, 5α
2	72.3		1, 3, 25	72.5		
3	85.9	3.85 (dd, 8.3, 3.7)	25	86.0	3.79 (dd, 8.4, 3.4)	4α, 25
4	26.0	α 1.95	5β	26.1	α 1.84	
		β 2.10			β 2.08	
5	29.8	α 1.42	3, 7, 26	30.0	α 1.31	
		β 2.47 (ddd, 9.5, 9.5, 11.7)			β 2.47 (ddd, 9.4, 9.4, 11.6)	
6	86.1		3, 5β, 7, 26	86.1		
7	82.7	4.09 (dd, 7.7, 7.7)	5β, 26	82.7	4.04 (dd, 7.6, 7.6)	8α, 26, 27
8	28.9	α 1.98		28.8	α 1.79	
		β 1.64			β 1.49	9β
9	30.8	α 1.53	11, 27	30.6	α 1.33	27
		β 2.08			β 1.98	
10	85.9			85.9		
11	84.2	3.92 (dd, 10.9, 4.9)	13, 27	84.2	3.88 (dd, 11.0, 4.8)	12α, 27
12	29.5	α 1.94	13	29.7	α 1.76	
		β 1.47			β 1.28	
13	26.4	α, β 1.86		26.6	α 1.83	
					β 1.71	
14	85.8	3.78 (dd, 8.9, 7.0)		85.9	3.70 (dd, 9.6, 6.1)	12β, 13β, 28
15	72.9		28	73.0		
16	36.6	1.48, 1.30	28	36.9	1.54, 1.30	
17	22.1	2.13, 2.00	18	22.3	2.21, 2.03	
18	125.3	5.18 (dt, 7.1, 1.2)	20 (2.14), 29	125.6	5.21 (br. t, 7.0)	20
19	133.9		20 (2.14), 29	133.9		
20	36.2	2.14, 2.08	18, 22	36.5	2.12, 2.05	
21	27.3	1.62	20 (2.14), 22	27.6	1.61, 1.55	
22	64.1	2.70 (t, 6.3)	20 (2.14), 24, 30	64.0	2.61 (t, 6.3)	21 (1.61), 30
23	58.4		22, 24, 30	58.1		
24	18.7	1.26	30	18.3	1.16	21
25	27.8	1.22	1	28.0	1.29	1, 3, 5β
26	25.2	1.14	7, 5β	25.2	1.07	3, 5α, 7, 8α, 8β
27	23.4	1.13	11	23.3	1.00	7, 8α, 9α, 11
28	24.0	1.21	14	24.2	1.24	12α, 14, 17
29	15.9	1.63	18, 20 (2.14)	16.0	1.61	
30	24.8	1.30	22, 24	24.9	1.20	22

[a] Recorded on a Varian UNITY-500 NMR spectrometer, chemical shifts in ppm from TMS.

[b] Multiplicity, J_{HH} in brackets.

[c] Proton correlating with carbon resonance.

[d] Irradiated shift in proton (H) column.

There are four possible *syn*, *syn*, *anti* stereoisomers of the C-1 to C-15 fragment and attached methyl groups with the relative stereochemistry as shown at C-11, C-14 and C-15, and eight for the entire molecule **2**. One might think that it should be possible to predict the stereochemistry of **2** on biogenetic grounds, assuming C_2 symmetry of its congener **1**. However, the occurrence in *Eurycoma longifolia* of four THF-containing oxasqualenoids evidently derived from three different stereoisomers of a squalene tetraepoxide[6] demonstrates the unpredictability of the stereochemical outcome of multiple epoxidation of squalene and subsequent processes. Determination of the stereochemistry of compound **2** in its entirety will require X-ray crystal structure analysis of a derivative.

Compound **2** is the latest addition to the relatively small number of natural acyclic triterpenoids and triterpenoid polyethers containing oxygen heterocycles. The diverse sources from which these compounds and related structures derived from methyl squalene and tetraterpenoids[7] have been isolated include marine microorganisms[8] and animals[9] and higher plants of the closely related sapindalean families Rutaceae,[1] Meliaceae[10] and Simaroubaceae.[6,11]

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