Trunculins A and B, Norsesterterpene Cyclic Peroxides from a Marine Sponge, *Latrunculia brevis*

Robert J. Capon,* John K. MacLeod, and Anthony C. Willis

Research School of Chemistry, Australian National University, GPO Box 4, Canberra, ACT 2601, Australia

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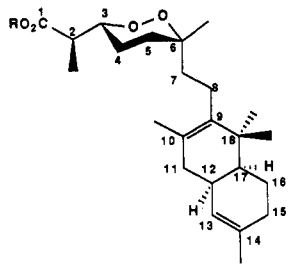
Two norsesterterpene cyclic peroxides possessing a new carbon skeleton, trunculins A (1) and B (2), together with their methyl esters 3 and 4 have been isolated from a marine sponge, *Latrunculia brevis*. The esters 3 and 4 have been characterized and their relative stereostructures secured by detailed spectroscopic and X-ray analysis. Absolute stereochemistries are proposed on the basis of Horeau determinations carried out on the diol derivatives 11 and 12. The acids 1 and 2 exhibit antimicrobial activity.

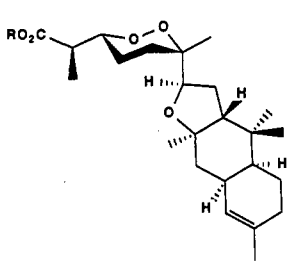
In a recent report,[1] we described the isolation and structure elucidation of a number of antimicrobially active norterpene cyclic peroxides from two Australian sponges, a *Latrunculia* sps. and *Mycale* (*aegogrophila*) cf. *ancorina*. Another specimen from the same location, *Latrunculia brevis*,[2] has yielded two further examples of this class of marine natural product.

Discussion

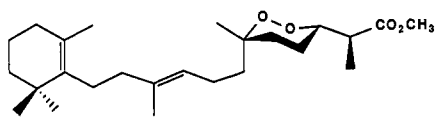
As with earlier studies, an ethanol extract of *L. brevis* was found to show significant growth-inhibitory activity against the Gram-positive bacteria *Bacillus subtilis* and the "yeast" *Saccharomyces cerevisae*. Trituration of the concentrated extract with dichloromethane gave an antimicrobially active lipid-soluble material that on fractionation by rapid elution through silica yielded an active two-component mixture, trunculin A[3] (1) and trunculin B (2), together with an inactive mixture of the corresponding methyl esters 3 and 4. Although these could be resolved by reverse-phase HPLC, a more convenient separation was achieved by first methylating the crude extract with diazomethane followed by MPLC on silica, to yield[4] the monomethyl esters 3 and 4.



1. R = H
3. R = CH_3



2. R = H
4. R = CH_3



5.

Table I. ^{13}C NMR ($CDCl_3$, 50 MHz) Assignments for 3 and 4 and Selected Shifts for Model Compounds 5 and 10.

carbon	3	4	5[a]	10[a,c]
1	174.1 (s)	174.1 (s)	174.4 (s)	
2	42.6 (d)	42.6 (d)	42.6 (d)	
3	81.1 (d)	81.4 (d)	81.3 (d)	
4	22.5 (t)	22.4 (t)	22.6 (t)	
5	32.6 (t)	30.1 (t)	32.4 (t)	
6	79.9 (s)	80.7 (s)	79.9 (s)	
2-CH_3	12.5 (q)	12.8 (q)	12.8 (q)	
6-CH_3	23.6 (q)	20.6 (q)	23.9 (q)	
O-CH_3	51.7 (q)	51.7 (q)	51.8 (q)	
7	34.9 (t)	73.1 (d)		
8	23.6 (t)	23.8 (t)		
9	137.6 (s)	50.9 (d)		
10	126.7 (s)	81.4 (s)		
11	40.1 (t)	41.7 (t)		
12	32.8 (d)	33.0 (d)		31.8 (d)
13	126.1 (d)	125.6 (d)		126.3 (d)
14	133.2 (s)	133.1 (s)		133.2 (s)
15	31.4 (t)	31.7 (t)		27.5 (t)
16	22.4 (t)	18.8 (t)		19.4 (t)
17	47.0 (d)	45.0 (d)		45.2 (d)
18	38.6 (s)	34.6 (s)		
10-CH_3	19.9 (q)	28.6[b] (q)		
14-CH_3	23.3 (q)	23.1 (q)		23.5 (q)
18-CH_3	21.6 (q)	19.0 (q)		
18-CH_3	25.8 (q)	23.0[b] (q)		

[a] Numbering assigned to model compounds 5 and 10 is as for 3 and 4. [b] May be interchanged. [c] Assignments made by current authors.

Table II. ^1H NMR ($CDCl_3$, 200 MHz) Assignments for 3 and 4

proton	3	4
2-H	2.56 (dq, 1 H, J = 8.0, 8.0 Hz)	2.51 (dq, 1 H, J = 8.0, 8.0 Hz)
3-H	4.24 (bddd, 1 H, J = 4.0, 8.0, 8.0 Hz)	4.25 (ddd, 1 H, J = 4.0, 8.0, 8.0 Hz)
2-CH_3	1.14 (d, 3 H, J = 8.0 Hz)	1.14 (d, 3 H, J = 8.0 Hz)
6-CH_3	1.16 (s, 3 H)	1.19 (s, 3 H)
O-CH_3	3.69 (s, 3 H)	3.69 (s, 3 H)
7-H		4.54 (t, 1 H, J = 6.0, 6.0 Hz)
12-H		2.38 (br d, 1 H, J = 10.0 Hz)
13-H	5.20 (br s, 1 H)	5.34 (d, 1 H, J = 4.0 Hz)
15-H_2		1.95 (br m, 2 H)
10-CH_3	1.64 (s, 3 H)	0.90 (s, 3 H)
14-CH_3	1.64 (s, 3 H)	1.63 (s, 3 H)
18-CH_3	1.03 (s, 3 H)	0.90 (s, 3 H)
18-CH_3	0.84 (s, 3 H)	0.99 (s, 3 H)

Comparison of the spectral data for 3 and 4 with that of known[1] norsesterterpene cyclic peroxides, e.g. 5, confirmed the presence of the peroxide moiety (C1 to C6, Tables I and II). The equatorial nature of a carbon chain at C3 was apparent from the magnitude of the ^1H NMR

(1) Capon, R. J.; MacLeod, J. K. *Tetrahedron* **1985**, *41*, 3391.
(2) A specimen is lodged at the Northern Territory Museum of Arts and Sciences, Darwin, Australia, under the registry number Z4968.
(3) Assignment of the trivial name latrunculin to a series of unrelated marine natural products from *Latrunculia magnifica*[13] precludes its use here. Instead, the name trunculin has been coined to describe the natural products described herein.
(4) Both trunculin A (1) and its methyl ester 3 show characteristic bright green coloration on silica TLC when visualized with 5% vanillin in 3 M H_2SO_4. Trunculin B (2) and its methyl ester 4 exhibit an intense blue color under the same conditions.

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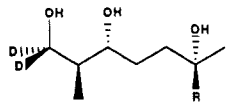
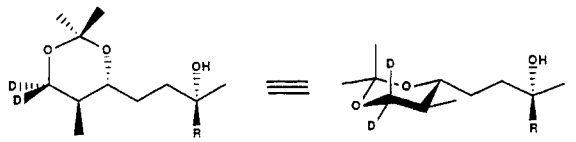
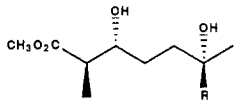
couplings to the C3 peroxymethine (J = 4, 8, and 8 Hz) while the equatorial orientation of the C6-methyl could be ascertained from both ^1H and ^{13}C NMR shift data for **3**, although a definitive assignment could not be made for **4**.[5] It had previously been proposed[1] that the relative configuration between C2 and C3 in cyclic peroxy systems such as these could be assigned on the basis of the ^1H NMR shift for the C2 secondary methyl (erythro ~ δ 1.14 and threo ~ δ 1.25). Thus it seemed likely that both trunculin A (δ 1.14) and trunculin B (δ 1.14) possessed an erythro configuration between C2 and C3. To confirm this, the cyclic peroxides **3** and **4** were converted via the triols **6** and **7** to the dioxans **8** and **9**. Both the ^1H NMR shifts of the C2 secondary methyls (δ 0.76, d, J = 7.0 Hz) and couplings to the C3 oxymethines (ddd, J = 2.0, 9.0, and 9.0 Hz) in **8** and **9** were consistent[1] with an erythro configuration.



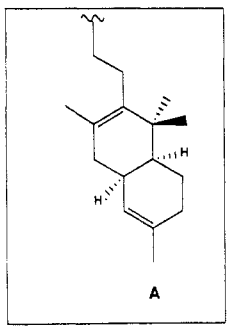
6. R = A
7. R = B



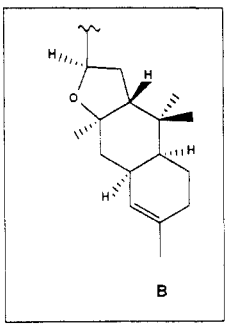
8. R = A
9. R = B



11. R = A (tetrahydro-)
12. R = B (dihydro-)



A



B

Also apparent from the ^1H and ^{13}C NMR analysis of **3** was the presence of a tri- and a tetrasubstituted double bond, two olefinic methyls, and a *gem*-dimethyl moiety. In the absence of other unsaturated functionalities, the unassigned portion of **3** was therefore bicyclic. Similarly, the unassigned portion of **4** possessed a trisubstituted double bond and a *gem*-dimethyl system. The presence of an additional oxygen atom and absence of a tetrasubstituted double bond in **4** relative to **3**, together with lack of an exchangeable proton or a ketone ^{13}C NMR resonance, suggested the incorporation of a cyclic ether. Comparison

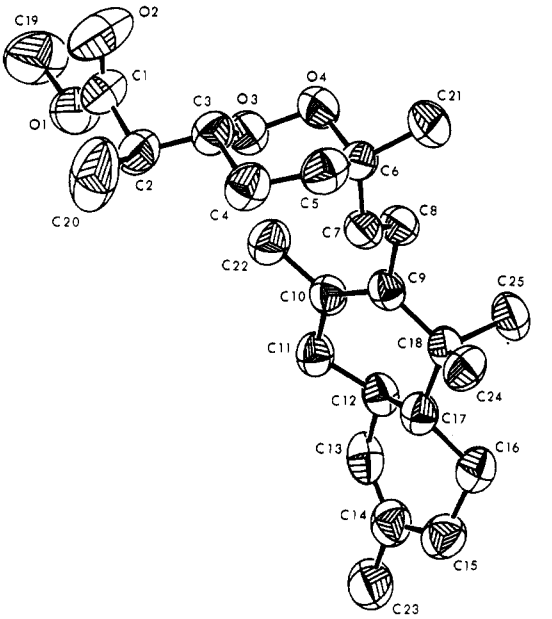


Figure 1. A view of molecule 1 of **3**, $C_{25}H_{40}O_4$. Thermal ellipsoids enclose 50% probability levels, and hydrogen atoms have been deleted for clarity, here and in Figure 2.

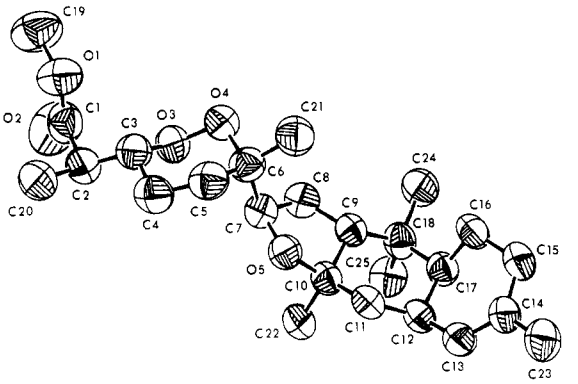
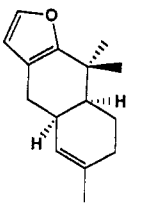


Figure 2. Thermal ellipsoid diagram of **4**, $C_{25}H_{40}O_5$.

of selected ^{13}C NMR resonances in both **3** and **4** with those assigned to the carbocyclic system in furodysinin[6] (**10**)



10.

(Table I), together with one- and two-dimensional homo- and heteronuclear decoupling experiments, supported assignment of the gross structures as indicated. To confirm these assignments and to ascertain relative stereostructures for **3** and **4**, an X-ray analysis was undertaken.

Crystals of **3** and **4** suitable for X-ray analysis were obtained with difficulty from methanol/water. X-ray analysis of these crystals provided complete relative stereostructures for **3** and **4** (Figures 1 and 2),[7] which were fully consistent with the partial stereostructures proposed on the basis of spectroscopic evidence.

(5) In the case of **4**, the ^{13}C NMR resonance attributed to the C6-CH_3 is at higher field than might otherwise be expected for an equatorial methyl in these systems, due to the influence of an adjacent five-membered ether moiety.

(6) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J.; Schonholzer, P. *Tetrahedron Lett.* **1978**, 4951.

(7) Johnson, C. K. "ORTEP-II: A FORTRAN Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations"; Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN.

Absolute stereochemistries for trunculins A and B were determined by asymmetric esterification (Horeau analysis) of the saturated diol esters **11** and **12**. In this manner the absolute stereochemistry about C3 was established as R, since both **11** and **12** returned a preponderance of (+)-α-phenylbutyric acid with optical yields of 9.3% and 4.8%, respectively. This procedure has previously been used[1] to assign absolute stereochemistries to marine norterpene cyclic peroxides of this class.

Experimental Section

General Experimental. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on either a JEOL JNM-FX-200 or a Varian XL-200-E spectrometer. EIMS (70 eV) and CIMS (NH_3) were obtained on a VG Micromass 7070F instrument. High-resolution accurate mass measurements were determined on an AEI MS 902 mass spectrometer. Optical rotations were recorded on a Perkin-Elmer 121 polarimeter. Antimicrobial activity was determined from a standard disc assay, with zones of inhibition being used as a measure of activity. For a description of the Horeau procedure, see ref 1.

L. brevis (Z4968) was collected by hand (SCUBA) at a depth of 20–25 m off South Durras, N.S.W., Australia. The fresh specimen was immersed in ethanol, packed in dry ice, transported to the laboratory, and stored at −20 °C. A portion of the EtOH extract was then examined by TLC, ^{1}H NMR spectroscopy, and antimicrobial assay.

The EtOH extract of Z4968 (50 g dry wt) after concentration to a brown gum (24 g) was triturated with CH_2Cl_2 to give an antimicrobially active lipid-soluble fraction (3 g). Rapid silica filtration with stepwise gradient elution from hexane to EtOAc of a portion of this material (1 g) yielded an inactive fraction (20% EtOAc/hexane, 70 mg, **3** and **4**) and an antimicrobially active fraction (EtOAc, 550 mg, **1** and **2**). The latter material could be resolved by reverse-phase high-performance liquid chromatography (10-μm C8 radial pak column eluted with 10% H_2O/MeOH) into the crystalline solids trunculin A (**1**, mp 157–158 °C) and trunculin B (**2**, mp 96–98 °C). Methylation of **1** and **2** with diazomethane yielded monomethyl esters identical with those present (**3** and **4**) in the earlier inactive fractions. Thus a more convenient approach to purification involved methylation with diazomethane prior to rapid silica filtration, followed by elution through silica with 20% EtOAc/hexane to give a single inactive mixture of **3** and **4**. This material was readily resolved by medium-pressure liquid chromatography (Lichroprep S_1 60 (40–63 μm) eluted with 20% Et_2O/hexane) into the methyl esters of trunculins A (**3**) and B (**4**). Thus *L. brevis* (Z4968) contained four norsesterterpene cyclic peroxides, **1** (400 mg, 0.8%), **2** (1.22 g, 2.4%), **3** (100 mg, 0.2%), and **4** (110 mg, 0.22%), of which only the acids **1** and **2** exhibited antimicrobial activity.

Trunculin A, methyl ester (3): crystals from MeOH/H_2O, mp 66.5–67.5 °C; $[\alpha]_D$ +158.3° (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) (see Table II); ^{13}C NMR ($CDCl_3$, 50 MHz) (see Table I); EIMS, *m/z* 404.2915 (8%, M^+ requires $C_{25}H_{40}O_4$, 404.2926), 389 (7), 386 (13), 373 (5), 335 (7), 317 (11), 299 (10), 203 (55), 202 (72), 201 (60), 187 (100), 81 (92).

Trunculin B, methyl ester (4): crystals from MeOH/H_2O, mp 91–93 °C; $[\alpha]_D$ +13.1° (*c* 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) (see Table II); ^{13}C NMR ($CDCl_3$, 50 MHz) (see Table I); EIMS, *m/z* 420 (~1%, M^+), 405 (3), 402 (4), 389.2679 (5, $M^+ - OCH_3$ requires $C_{24}H_{37}O_4$, 389.2692), 316.2399 (5, $C_{21}H_{33}O_2$ requires 316.2402), 233.1899 (100, $C_{16}H_{25}O$ requires 233.1905).

$LiAlD_4$ Reduction of 3. To a solution of the cyclic peroxide **3** (26 mg, 0.06 mmol) in dry ether (3 mL) was added excess $LiAlD_4$ (10 mg, 0.24 mmol), and the resulting mixture was stirred under reflux for 2 h. The reaction was quenched by addition of 10% aqueous HCl (2 mL) and extracted with EtOAc. The EtOAc extract was then washed with H_2O, dried with anhydrous $MgSO_4$, and evaporated to yield the deuteriated triol **6** (21 mg, 86%) as a stable colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3 H), 0.86 (d, 3 H, J = 7.0 Hz), 1.02 (s, 3 H), 1.24 (s, 3 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 3.58 (m, 1 H), 5.19 (br s, 1 H); EIMS, *m/z* 362.3146 (1%, $M^+ - H_2O$ requires $C_{24}H_{38}O_2D_2$, 362.3154).

$LiAlD_4$ Reduction of 4. Reduction of **4** (17 mg) as described above for **3** yielded the deuteriated triol **7** (14 mg, 87%) as a stable colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (d, 3 H, J = 7.0 Hz), 0.90 (s, 3 H), 0.91 (s, 3 H), 1.16 (s, 3 H), 1.18 (s, 3 H), 1.63 (s, 3 H), 3.62 (br t, 1 H, J = 8.0 Hz), 3.85 (t, 1 H, J = 6.0 Hz), 5.34 (br d, 1 H, J = 4.0 Hz); EIMS, *m/z* 378.3110 (1%, $M^+ - H_2O$ requires $C_{24}H_{38}O_3D_2$, 378.3103), 363 (2), 317 (6), 145 (100).

Isopropylidene Derivative 8. The deuteriated triol **6** (20 mg) in DMF (1 mL) was treated with 2,2-dimethoxypropane (0.2 mL) and *p*-toluenesulfonic acid (2 mg) and the resulting mixture stirred at room temperature overnight. The H_2O-quenched reaction was then extracted with EtOAc to yield the isopropylidene derivative **8** (19 mg, 86%) as a stable colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.76 (d, 3 H, J = 7.0 Hz), 0.84 (s, 3 H), 1.03 (s, 3 H), 1.20 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.63 (s, 3 H), 1.66 (s, 3 H), 3.47 (ddd, 1 H, J = 2.0, 2.0, and 9.0 Hz), 5.19 (br s, 1 H); EIMS *m/z* 405.3338 (13%, $M^+ - CH_3$ requires $C_{26}H_{41}O_3D_2$, 405.3338), 402 (16), 344 (12), 329 (10), 202 (80), 187 (65), 145 (71), 43 (100).

Isopropylidene Derivative 9. Treatment of the deuteriated triol **7** (12 mg) as described above for **6** yielded the isopropylidene derivative **9** (11 mg, 83%) as a stable colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.76 (d, 3 H, J = 7.0 Hz), 0.90 (s, 3 H), 0.91 (s, 3 H), 1.12 (s, 3 H), 1.18 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.63 (s, 3 H), 3.46 (br t, 1 H, J = 9.0 Hz), 3.87 (t, 1 H, J = 6.0 Hz), 5.35 (br d, 1 H, J = 3.0 Hz); EIMS, *m/z* 421.3298 (5%, $M^+ - CH_3$ requires $C_{26}H_{41}O_4D_2$, 421.3287), 233 (11), 203 (27), 145 (100); CIMS (NH_3), 437 (M + H, 50), 419, (55), 379 (80), 361 (100), 355 (66), 337 (61).

Hydrogenation of 3. A sample of the cyclic peroxide **3** (12 mg) in Et_2O with 10% Pd/C catalyst (10 mg) was stirred under an atmosphere of H_2 for 4 h. The catalyst was removed by filtration through Celite and the product purified by stepwise elution (hexane to Et_2O) through a silica sep-pak to give the saturated diol ester **11** (8 mg, 67%) as a stable colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.68 (d, 3 H, J = 8.0 Hz), 0.72 (d, 3 H, J = 8.0 Hz), 0.88 (s, 3 H), 0.97 (d, 3 H, J = 8.0 Hz), 1.20 (s, 3 H), 1.23 (s, 3 H), 2.56 (dq, 1 H, J = 8.0 and 8.0 Hz), 3.71 (s, 3 H), 3.70 (br m, 1 H); EIMS, *m/z* 392.3291 (2%, $M^+ - H_2O$ requires $C_{25}H_{44}O_3$, 392.3290), 377 (5), 374 (4), 359 (4), 305 (4), 261 (2), 191 (24), 171 (100).

Hydrogenation of 4. Treatment of **4** (19 mg) as described above for **3** yielded the saturated diol ester **12** (15 mg, 79%) as a stable colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3 H), 0.85 (s, 3 H), 1.02 (d, 3 H, J = 6.0 Hz), 1.13 (s, 3 H), 1.16 (s, 3 H), 1.22 (d, 3 H, J = 6.0 Hz), 2.55 (dq, 1 H, J = 6.0 and 6.0 Hz), 3.71 (s, 3 H), 3.70 (br m, 1 H), 3.85 (br t, 1 H, J = 6.0 Hz); EIMS, *m/z* 406.3081 (1%, $M^+ - H_2O$ requires $C_{25}H_{42}O_4$, 406.3083), 368 (4), 319 (3), 191 (5), 171 (100).

Crystallography. X-ray diffraction data were collected for compounds **3** and **4** on a Picker FACS-I diffractometer using graphite-monochromated Cu Kα radiation. In each case, unit cell parameters were determined by least-squares analysis of the setting angles of 12 accurately centered reflections (80.6° < 2θ < 85.7° for **3** and 86.4° < 2θ < 96.1° for **4**). λ(Cu Kα_1) = 1.5405 Å. Reflections with $I > 3\sigma(I)$ were regarded as "observed" and were used in the structure solution and refinement. Data were corrected for anisotropic decay[8] and for absorption.[9] Both structures were solved by MULTAN[10] and the remaining non-hydrogen atoms located in difference electron-density maps. The chirality of the molecules was adjusted to give *S* configurations at C3 to be consistent with the Horeau determinations. Hydrogen atoms were positioned geometrically (r_{C-H} = 0.95 Å, methyl groups derived from peaks in difference maps), $B_{iso}(H) = 1.2 \times B_{eq}$(adjacent C). Carbon and oxygen atoms were refined with anisotropic temperature factors, but hydrogen parameters were not varied. Block-diagonal least-squares analysis was used throughout for **3** in view of the large number of parameters, but full-matrix analysis was used in the final stages of refinement of **4**. The function minimized in the least-squares analysis was $\sum w(|F_o| -$

(8) Churchill, M. R.; Kalra, K. L. *Inorg. Chem.* **1974**, *13*, 1427.
(9) Sheldrick, G. M. SHELX-76, *Program for Crystal Structure Determination*; University of Cambridge, England.
(10) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; Universities of York, England, and Louvain-la-Neuve, Belgium.

$|F_c|)^2$ where $w = 1/[(\sigma(F))^2 + 0.25(0.05F)^2]$. Neutral-atom scattering factors with anomalous dispersion corrections for oxygen and carbon were used throughout.[11] Computing[12] was carried out on a UNIVAC-1100/82 computer.

Crystal Data. Compound 3: $2(C_{25}H_{40}O_4)\cdot 2.67H_2O$, M_r 857.27, orthorhombic, space group $P2_12_12_1$, a = 10.325 (1) Å, b = 14.856 (1) Å, c = 34.476 (3) Å, V = 5288.2 Å^3, D_{calcd} = 1.079 g cm^{-3}, Z = 4, μ(Cu Kα) = 5.58 cm^{-1}. The crystal was colorless and of dimensions 0.27 × 0.32 × 0.14 mm. θ–2θ scans were used to collect intensity data on 3753 unique reflections to $2\theta_{max}$ 110°, 3168 being "observed". The final R factor was R = 0.046, R_w = 0.064. The maximum shift/error ratio was <0.4 for "solvent molecules" and >0.2 for other atoms. All features in a final difference map were <0.16 e Å^{-3}.

Compound 4: $C_{25}H_{40}O_5$, M_r 420.59, monoclinic, space group $P2_1$, a = 11.553 (1) Å, b = 9.759 (1) Å, c = 11.900 (2) Å, β = 114.56 (1)°, V = 1220.3 Å^3, D_{calcd} = 1.144 g cm^{-3}, Z = 2, μ(Cu Kα) = 5.89 cm^{-1}. The crystal was colorless, 0.18 × 0.39 × 0.17 mm. Intensity data were collected by ω scans to $2\lambda_{max}$ 125°, yielding 2091 unique reflections, 1856 "observed". Six reflections suffering from extinction were removed from the data set. The final R factor was R = 0.059, R_w = 0.077. The maximum shift/error ratio was >0.1. All features in a final difference map were <0.19 e Å^{-3}.

Crystals of compound **3** were found to contain two independent molecules of $C_{25}H_{40}O_4$, showing essentially the same lengths and angles for equivalent bonds and very similar conformations, whithin the lattice. In addition, there were columns of electron density ($\rho_{max} \sim 1.2$ e Å^{-3}) running in the a direction through the crystal lattice, which would appear to correspond to disordered molecules of solvate, either H_2O or CH_3OH. Four oxygen atoms of occupancy 0.67 were introduced to model this region, though its exact nature was not determined.

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Registry No. 1, 105969-64-0; **2**, 105969-65-1; **3**, 105969-66-2; **4**, 105969-67-3; **6**, 105969-68-4; **7**, 105969-69-5; **8**, 105969-70-8; **9**, 105969-71-9; **11**, 105969-72-0; **12**, 105969-73-1; 2,2-dimethoxypropane, 77-76-9.

Supplementary Material Available: Figure 3 (showing molecule 2 of **3**) and Tables III–IX (atomic parameters and selected bond lengths and angles for **3** and **4**) (20 pages). Ordering information is given on any current masthead page. Structure factor listings for **3** and **4** are available on request.

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O^5-Methyl-(±)-(2′*R*,3′*S*)-psorospermin

David K. Ho, Ann T. McKenzie, Stephen R. Byrn, and John M. Cassady*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

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Psorospermin (**1**), a novel xanthone isolated from the ethanolic extract of the root of the woody African plant *Psorospermum febrifugum* Spach. (Guttiferae), has shown biological activity in the 9KB cell culture and in vivo P388 mouse leukemia systems, leading to further investigation of **1** as a potential antineoplastic agent. Following the reisolation, studies were initiated to determine the absolute stereochemistry and to complete the total synthesis of **1**. O^5-Methyl-(±)-(2′*R*,3′*S*)-psorospermin (**2**) was chosen as our initial target to test the feasibility of the formation of the dihydrofuran and epoxide moieties in a stereoselective manner. The 4-allyl group of **7**, which was formed by an ortho-Claisen rearrangement, was oxidized to aldehyde **9**. A Wittig reaction gave the *E* allylic ester **10** as the predominant product. Reduction of **10** to **11**, epoxidation, mesylation, and deblocking gave the free phenol **14**. Compound **14** was cyclized with potassium *tert*-butoxide in one step to give (±)-**2**, an epimer of **1**, demonstrating that the epoxydihydrofuran system could be constructed in a concerted and stereoselective manner and providing indirect proof of the absolute stereochemistry of **1**.

Psorospermin (**1**) (NSC-266491) is an antitumor xanthone originally isolated by Kupchan and co-workers[1] as a result of an activity-directed fractionation of the ethanolic extract of the root of the African woody plant *Psorospermum febrifugum* Spach. (Guttiferae). The cytotoxicity of **1** in the in vitro 9KB cell culture system, and the significant activity in the in vivo P388 mouse leukemia system suggested further investigation of **1** as a potential antineoplastic agent. Research efforts in our laboratories have resulted in the reisolation[2] of **1** from *P. febrifugum* and the recent assignment of the absolute stereochemistry[3] to be 2′*R*,3′*R* as shown in Figure 1. We report here the total synthesis of (±)-**2**, an epimer of **1**, which serves both as a confirmation of the assignment of configuration of **1** and as a demonstration that the dihydrofuran and the epoxide moieties can be constructed in a concerted and stereoselective manner.[4]

Based on the retrosynthetic analysis in Figure 1, it is proposed that an intramolecular attack of an appropriate epoxide by a phenoxide ion would result in formation of

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