Norsesterterpene Peroxides from the Sponge *Latrunculia* sp.

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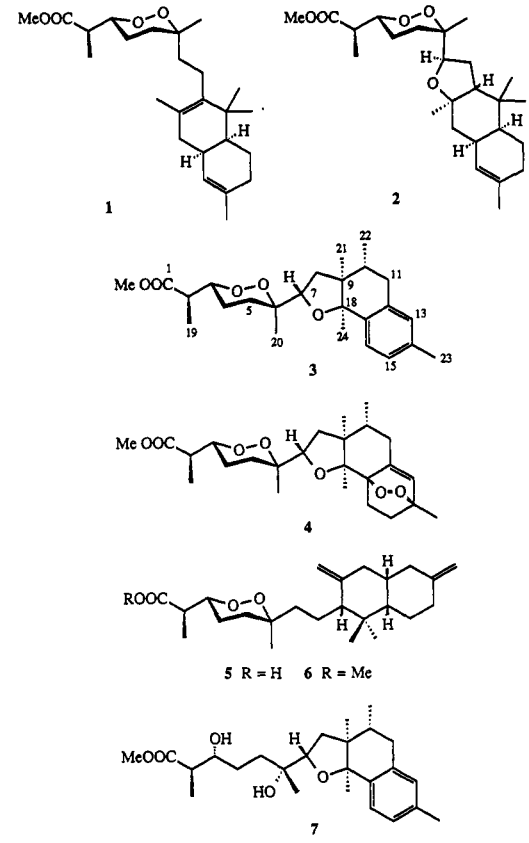
A specimen of the sponge *Latrunculia* sp. from Jervis Bay, Australia, contained three new norsesterterpene peroxides, trunculin C methyl ester (3), trunculin D methyl ester (4), and trunculin E (5). The structure of trunculin C methyl ester (3) was determined by X-ray analysis, and the absolute configuration was established by application of the Horeau method to the diol 7. The structures of trunculin D methyl ester (4) and trunculin E (5) were elucidated by interpretation of spectral data, by chemical interconversion, and by using a biosynthetic hypothesis. Trunculin C methyl ester (3) and trunculin D methyl ester (4) have a novel carbon skeleton.

Compounds of the norsesterterpene peroxide class were first reported in 1979 by Albericci et al., who isolated sigmosceptrellins-A, -B, and -C and the corresponding methyl esters from the Papua New Guinea sponge *Sigmosceptrella laevis*,[1,2] and by Kashman and Rotem, who reported the isolation of muqubilin from a Red Sea species of *Prianos*.[3] Muqubilin and sigmosceptrellin-B were subsequently reported under the redundant names prianicin A and prianicin B, respectively.[4] Muqubilin was also isolated from a Tongan species of *Prianos*.[5] The difficulties inherent in assigning the structures of the norsesterterpene peroxides by using spectroscopic methods were discussed by Capon and MacLeod, who proposed empirical rules for assigning the stereochemistry about the peroxide ring in five new sesterterpenes from a species of *Latrunculia* and *Mycale* (*aegogrophila*) cf. *ancorina*.[6,7] Most pertinent to this study was the isolation and structural elucidation of trunculin A methyl ester (1) and trunculin B methyl ester (2) from the Australian sponge *Latrunculia brevis*.[8] Elucidation of the stereochemistry of many of the norsesterterpene peroxides is complicated because the molecules consist of two isolated ring systems, each of known relative stereochemistry, that are joined by a flexible unit that prevents determination of the relative stereochemistry of the entire molecule by spectroscopic methods. Thus, many of the structures were determined by X-ray crystallographic studies[1,8] or by chemical correlation with those X-ray determined structures.[2,6,7]

In this paper we report the structural elucidation of three new norsesterterpene peroxides, trunculin C methyl ester (3), trunculin D methyl ester (4), and trunculin E (5), by using X-ray crystallographic and spectroscopic methods.

Trunculin C methyl ester (3) was isolated as colorless crystals, mp 138 °C. The molecular formula, $C_{25}H_{36}O_5$, was determined by high-resolution chemical ionization mass spectrometry (CIMS). The infrared band at 1730 cm^{-1}, the ^{13}C NMR signals at δ 174.3 and 51.8, and the ^1H NMR signal at δ 3.70 (s, 3 H) were all assigned to a methyl ester. The presence of six additional methyl signals in both the ^1H and ^{13}C NMR spectra was suggestive of a terpenoid structure, and we were therefore guided toward the norsesterterpene peroxide class of compounds. The ^1H NMR spectrum contained a methine signal at δ 2.59 (dq, 1 H, J = 7.6, 7.2 Hz) coupled to both a methyl signal at 1.15 (d, 3 H, J = 7.2 Hz) and a methine signal at 4.24 (ddd, 1 H, J = 8.8, 7.2, 4.1 Hz). These data, together with selected signals in the ^{13}C NMR spectrum, are typical of the ester terminus of the sesterterpene peroxides.[1-8] Applying the empirical rules established by Capon and MacLeod,[6] the chemical shift of the methyl signal at δ 1.15 indicated a 2,3-*erythro* geometry, and the coupling constants of the H-3 signal required an equatorial side chain. Comparison of the ^{13}C NMR chemical shift of the Me-20 signal in peroxide 3 at δ 17.5 with that of the same signal in trun-



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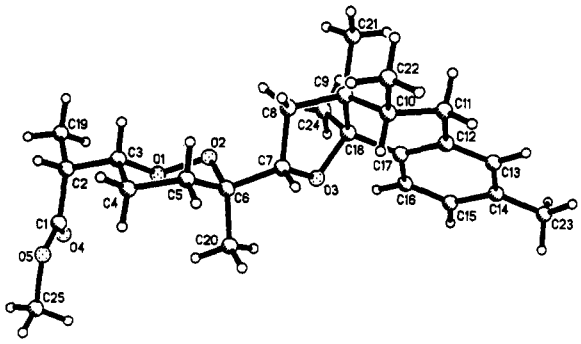

Figure 1. A computer-generated perspective drawing of the final X-ray model of trunculin C methyl ester (**3**). Only one of the two independent but essentially identical molecules in the asymmetric unit is shown.

culin B methyl ester (**2**) at 20.6 suggested that the methyl group at C-6 in peroxide **3** was axial with respect to the peroxide ring. The same 3 ppm difference between axial and equatorial methyl signals was observed by Capon and MacLeod.[6]

The presence of six signals in the ^{13}C NMR spectrum at δ 137.7 (s), 136.3 (s), 135.8 (s), 128.4 (d), 127.8 (d), and 127.4 (d) and of ^1H NMR signals at δ 7.41 (d, 1 H, J = 7.9 Hz), 7.02 (br d, 1 H, J = 7.9 Hz), 6.86 (br s, 1 H), and 2.28 (br s, 3 H) indicated that trunculin C methyl ester (**3**) contained a 1,2,4-trisubstituted aromatic ring with one methyl substituent. Two benzylic proton signals centered at δ 2.54 (m, 2 H) were coupled to a signal at 1.92 (m, 1 H), which was in turn coupled to a methyl signal at 1.04 (d, 3 H, J = 6.8 Hz). Irradiation of the signals at δ 2.54 caused a strong nuclear Overhauser enhancement (NOE) of the aromatic signal at 6.84.

Another isolated spin system consisted of ^1H NMR signals at δ 3.76 (dd, 1 H, J = 10.8, 6.2 Hz), 2.01 (dd, 1 H, J = 12.6, 6.2 Hz), and 1.82 (dd, 1 H, J = 12.6, 10.8 Hz) that could be assigned to an isolated $-CH(OR)CH_2-$ group. The remaining ^1H NMR signals could be assigned to the methyl and methylene protons associated with the peroxide ring and to methyl signals at δ 0.97 (s, 3 H) and 1.41 (s, 3 H). The methyl groups must be attached to fully substituted carbon atoms that are situated at a carbocyclic ring junction and an ether ring junction, respectively, as depicted in the tricyclic ring system of peroxide **3**. The location of the ether bridge at C-18 was established from the COLOC experiment (J = 8 Hz) that showed correlations between the C-17 signal at δ 137.7 and both the H-13 signal at 6.86 and the methyl signal at 1.41 that is at the correct chemical shift for a methyl group on a carbon bearing oxygen. The stereochemistry about the tricyclic ring system was defined by the observation of nuclear Overhauser enhancements between the methyl signals at δ 1.41 and 0.97 and between the signals at 3.76 (H-7) and 1.93 (H-10).

Although we had elucidated the relative stereochemistry about the peroxide ring and the relative stereochemistry about the tricyclic ring system, it was not possible to employ spectroscopic methods to define the stereochemistry about the carbon–carbon bond that joins the two systems. The complete relative stereochemistry of trunculin C methyl ester (**3**) was therefore determined by a single-crystal X-ray crystallographic experiment.

A computer-generated perspective drawing of the final X-ray model of trunculin C methyl ester (**3**) is given in Figure 1. The two independent molecules in the asymmetric unit had essentially the same molecular conformation and standard molecular parameters. The peroxide ring has a chair conformation, while the other six-membered ring has a half-chain conformation. The tetrahydrofuran ring is in an envelope (C_m) conformation with C(12) serving as the flap. Following the procedures of Capon and MacLeod,[6,8] the 3*R* absolute configuration of trunculin C methyl ester (**3**) was determined by application of the Horeau method to the diol **7** that was obtained by hydrogenation of **3** over 5% palladium on carbon catalyst in methanol solution.

Trunculin D methyl ester (**4**) was isolated as a colorless oil. The molecular formula, $C_{25}H_{38}O_7$, was determined by high-resolution chemical ionization mass spectroscopy: the electron impact mass spectrum failed to produce a molecular ion. A preliminary comparison of the spectral data of trunculin D methyl ester (**4**) with those of trunculin C methyl ester (**3**) revealed that the two compounds were closely related except that the bis-peroxide **4** contained two olefinic, two methylene and two "ether" carbons in place of the aromatic ring of **3**. A detailed analysis of the spectral data revealed that the substitution patterns and geometries about the common peroxide ring and the tetrahydrofuran ring were identical for both compounds. The COSY experiment revealed that the C-10 methyl signal at δ 0.95 (d, 3 H, J = 6.4 Hz) was coupled to a signal at 1.88 (m, 1 H) that was in turn coupled to two methylene proton signals at 2.63 (br dd, 1 H, J = 14.4, 4.5 Hz) and 2.11 (dd, 1 H, J = 14.4, 4.3 Hz). The signal at δ 2.63 showed additional allylic coupling to an olefinic proton signal at 6.00 (br s, 1 H). The chemical shift of the olefinic signal strongly implied that one of the two unassigned carbon atoms bearing oxygen (^{13}C NMR δ 79.7 and 75.4) be placed adjacent to the olefinic bond. The ^1H NMR spectrum contained four mutually coupled signals at δ 2.26 (ddd, 1 H, J = 13.3, 9.3, 3.6 Hz), 1.98 (m, 1 H), 1.57 (m, 1 H), and 1.52 (dt, 1 H, J = 9.3, 3.6 Hz), indicating that the last two methylene groups were adjacent to one another. These data were compatible with the bis-peroxide structure **4**.

The majority of the stereochemistry of trunculin D methyl ester (**4**) was defined as a result of its facile conversion into trunculin C methyl ester (**3**) on treatment with *p*-toluenesulfonic acid in benzene. The stereochemistry of the new peroxide bridge was defined by a single nuclear Overhauser enhancement experiment in which irradiation of the C-18 methyl signal at δ 1.17 caused strong enhancements of the C-16 methylene signals at 2.26 (14%) and 1.98 (8%).

Trunculin E (**5**), which has a molecular formula of $C_{24}H_{38}O_4$, was isolated as an acid but was converted into the more stable methyl ester **6**, $C_{25}H_{40}O_4$, for structural studies. The presence of only four oxygen atoms, two associated with the ester and two with the cyclic peroxide, indicated that trunculin E methyl ester (**6**) was most likely related to trunculin A methyl ester (**1**). Analysis of the ^1H and ^{13}C NMR spectra [δ 4.25 (td, 1 H, J = 7.6, 5.4 Hz, H-3), 1.14 (d, 3 H, J = 7.2 Hz, H-19), 20.3 (q, C-20)] according to the empirical rules of Capon and MacLeod[6] required the 2,3-erythro/3-axial hydrogen/6-axial methyl stereochemistry about the peroxide ring.

The remaining hydrocarbon portion of the molecule contained two olefinic bonds and was therefore bicyclic, like trunculin A methyl ester (**1**). Although the two olefinic bonds were obviously exocyclic, a detailed analysis of the ^1H and ^{13}C NMR spectra revealed that the carbon skeleton of peroxide **6** was the same as that of trunculin A methyl ester (**1**). The COSY, XHCORR, and COLOC (J = 8 Hz) experiments performed on a solution of **6** in benzene-d_6 allowed all of the ^1H NMR signals associated with the bicyclic ring system to be assigned and the relative stereochemistry at C-9, C-12, and C-17 was then determined

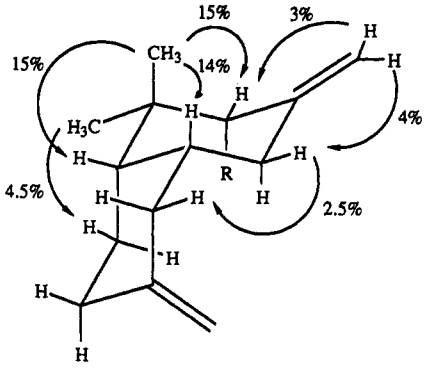

Figure 2. Selected nuclear Overhauser enhancements for trunculin E methyl ester (6).

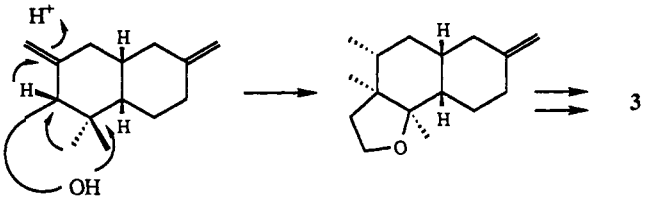

Figure 3. A proposed biosynthetic pathway that accounts for the stereochemistry of trunculin E (5).

by interpretation of NOEDS experiments (Figure 2).

Once again it was not possible to determine the stereochemical relationship between the two remote portions of the molecule by using spectroscopic methods. There is, however, strong circumstantial evidence, based on the probability that all metabolites from this sponge have a common biosynthetic origin, to support the stereochemistry proposed. The stereochemistry of trunculin C methyl ester (3) can be derived from the proposed stereochemistry of trunculin E (5) by a series of concerted 1,2-migrations as shown in Figure 3.

Antimicrobial assays performed on this series of peroxides showed that the antimicrobial activity of the crude extracts of *Latrunculia* sp. is associated with the free acids but not with the corresponding methyl esters. Of the four compounds reported in this paper, only trunculin E (5) inhibits the growth of *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans* when tested at 100 μg/disk in the standard disk assay.[9]

Experimental Section

Collection, Extraction, and Isolation. A frozen specimen of *Latrunculia* sp. (5.2 g dry wt) from Jervis Bay, Australia was chopped and extracted with methanol (3 × 200 mL). The combined extracts were filtered, and the methanol was removed under reduced pressure to obtain an aqueous suspension that was extracted with hexane (2 × 100 mL). The hexane extract was dried over anhydrous sodium sulfate, and the solvent was evaporated to yield an oil (360 mg). The oil was chromatographed on silica gel using eluants of increasing polarity from hexane to ethyl acetate. The fraction eluting with 2% ethyl acetate in hexane consisted of a mixture of methyl esters that were separated by LC on Porasil using 3:1 hexane/ethyl acetate to obtain trunculin C methyl ester (3, 22 mg, 0.42% dry wt) and trunculin D methyl ester (4, 17 mg, 0.33% dry wt). The fractions eluting with 5–10% ethyl acetate in hexane were combined to obtain, after final purification by LC on Porasil, using 4:1 hexane/ethyl acetate containing 0.2% acetic acid as eluant, trunculin E (5, 34 mg, 0.66%). A portion of the acid 5 (20 mg) in dry ether (5 mL) was treated with excess ethereal diazomethane solution to obtain a pale yellow solution. Evaporation of the solvent gave an oil that was purified by LC on Porasil to obtain trunculin E methyl ester (6) in nearly quantitative yield.

(9) A second specimen of *Latrunculia* sp. has recently been examined. This specimen contained trunculins A (1) and B (2), together with five minor metabolites that are either stereoisomers or oxidation products of the trunculins.

Table I. ^{13}C NMR Data [δ (mult)] for Trunculin C Methyl Ester (3), Trunculin D Methyl Ester (4), and Trunculin E Methyl Ester (6)

C no.	3	4	6
1	174.3 (s)	174.3 (s)	174.0 (s)
2	42.8 (d)	42.8 (d)	43.1 (d)
3	81.6 (d)	81.7 (d)	81.9 (d)
4	22.3 (t)	22.4 (t)	23.0 (t)
5	29.4 (t)	28.7 (t)	33.2 (t)
6	81.2 (s)	81.3 (s)	79.7 (s)
7	79.5 (d)	81.0 (d)	26.5 (t)
8	37.7 (t)	34.9 (t)	23.0 (t)
9	46.4 (s)	46.5 (s)	55.1 (d)
10	33.6 (d)	37.0 (d)	149.9 (s)
11	34.4 (t)	44.7 (t)	32.6 (t)
12	135.8 (s)	142.7 (s)	35.8 (d)
13	128.4 (d)	129.2 (d)	41.2 (t)
14	136.3 (s)	75.4 (s)	146.7 (s)
15	127.4 (d)	30.1 (t)	36.0 (t)
16	127.8 (d)	23.7 (t)	41.0 (t)
17	137.7 (s)	79.7 (s)	46.4 (d)
18	84.2 (s)	85.3 (s)	37.8 (s)
19	12.7 (q)	12.7 (q)	12.9 (q)
20	17.5 (q)	17.9 (q)	20.3 (q)
21	16.5 (q)	20.3 (q)	25.5 (q)
22	15.9 (q)	18.5 (q)	32.0 (q)
23	20.9 (q)	21.5 (q)	108.4 (t)
24	27.1 (q)	20.2 (q)	110.6 (t)
25	51.8 (q)	51.9 (q)	51.3 (q)

Trunculin C methyl ester (3): mp 138 °C; $[\alpha]_D$ −46° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 1730, 1610, 1500 cm^{-1}; UV (MeOH) 274 nm (ε 234), 266 (ε 229), 214 (ε 8710); ^1H NMR ($CDCl_3$) δ 7.41 (d, 1 H, *J* = 7.9 Hz, H-16), 7.02 (br d, 1 H, *J* = 7.9 Hz, H-15), 6.86 (br s, 1 H, H-13), 4.24 (td, 1 H, *J* = 8.2, 4.1 Hz, H-3), 3.76 (dd, 1 H, *J* = 10.8, 6.2 Hz, H-7), 3.70 (s, 3 H, OMe), 2.59 (dq, 1 H, *J* = 7.6, 7.2 Hz, H-2), 2.54 (m, 2 H, H-11,11′), 2.28 (br s, 3 H, Me-23), 2.01 (dd, 1 H, *J* = 12.6, 6.2 Hz, H-8), 1.93 (m, 1 H, H-10), 1.82 (dd, 1 H, *J* = 12.6, 10.8 Hz, H-8′), 1.41 (s, 3 H, Me-24), 1.34 (s, 3 H, Me-20), 1.15 (d, 3 H, *J* = 7.2 Hz, Me-19), 1.04 (d, 3 H, *J* = 6.8 Hz, Me-22), 0.97 (s, 3 H, Me-21); ^{13}C NMR ($CDCl_3$) see Table I; HRCIMS obsd *m/z* 417.2639, $C_{25}H_{37}O_5$ (M + 1) requires 417.2640.

Trunculin D methyl ester (4): oil; $[\alpha]_D$ −24° (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^{H} NMR ($CDCl_3$) δ 6.00 (br s, 1 H, H-13), 4.23 (ddd, 1 H, *J* = 9.3, 7.6, 3.6 Hz, H-3), 3.90 (dd, 1 H, *J* = 10.6, 6.4 Hz, H-7), 3.70 (s, 3 H), 2.63 (br dd, 1 H, *J* = 14.4, 4.5 Hz, H-11), 2.57 (dq, 1 H, *J* = 7.6, 7.6 Hz, H-2), 2.26 (ddd, 1 H, *J* = 13.3, 9.3, 3.6 Hz, H-16), 2.11 (dd, 1 H, *J* = 14.4, 4.3 Hz, H-11′), 2.03 (dd, 1 H, *J* = 12.2, 10.6 Hz, H-8), 1.98 (m, 1 H, H-16′), 1.88 (m, 1 H, H-10), 1.76 (dd, 1 H, *J* = 12.2, 6.4 Hz, H-8′), 1.57 (m, 1 H, H-15), 1.52 (dt, 1 H, *J* = 9.3, 3.6 Hz, H-15′), 1.34 (s, 3 H, Me-23), 1.28 (s, 3 H, Me-20), 1.17 (s, 3 H, Me-24), 1.15 (d, 3 H, *J* = 7.6 Hz, Me-19), 0.97 (s, 3 H, Me-21), 0.95 (d, 3 H, *J* = 6.4 Hz, Me-22); ^{13}C NMR ($CDCl_3$) see Table I; HRCIMS obsd *m/z* 451.2718, $C_{25}H_{39}O_7$ (M + 1) requires 451.2696.

Trunculin E (5): mp 103 °C; $[\alpha]_D$ −69° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (br d, 1 H, *J* = 2.3 Hz), 4.66 (br s, 1 H), 4.57 (br s, 1 H), 4.52 (br d, 1 H, *J* = 2.3 Hz), 4.21 (td, 1 H, *J* = 8.3, 4.7 Hz), 2.59 (dq, 1 H, *J* = 8.3, 7.2 Hz), 1.27 (s, 3 H), 1.19 (d, 3 H, *J* = 7.2 Hz), 0.98 (s, 3 H), 0.97 (s, 3 H); HREIMS obsd *m/z* 390.2796, $C_{24}H_{38}O_4$ requires 390.2770.

Trunculin E methyl ester (6): oil; $[\alpha]_D$ −64° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (br d, 1 H, *J* = 2.2 Hz), 4.65 (br s, 1 H), 4.57 (br s, 1 H), 4.52 (br d, 1 H, *J* = 2.2 Hz), 4.21 (td, 1 H, *J* = 7.6, 5.4 Hz), 3.70 (s, 3 H), 2.56 (dq, 1 H, *J* = 7.6, 7.2 Hz), 1.27 (s, 3 H), 1.14 (d, 3 H, *J* = 7.2 Hz), 0.98 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) see Table I; HREIMS obsd *m/z* 404.2909, $C_{25}H_{40}O_4$ requires 404.2927.

Single-Crystal X-ray Diffraction Analysis of Trunculin C Methyl Ester (3). Trunculin C methyl ester (3) crystallized in the orthorhombic space group $P2_12_12_1$ as slightly elongated rectangular solids. Lattice constants of *a* = 10.621 (3), *b* = 14.603 (4), and *c* = 29.985 (7) Å were determined by diffractometer

measured 2θ values for 30 moderate angle reflections. A crystal density of approximately 1.2 g/cm^3 indicated that two molecules of composition $C_{25}H_{38}O_5$ formed the asymmetric unit ($Z = 8$). All diffraction maxima with $2\theta \leq 112°$ were collected on a computer controlled four-circle diffractometer using graphite monochromated Cu Kα X-rays (1.541 78 Å) and 2θ-θ scans. A total of 3792 reflections were measured in this manner, and 2467 of the 3539 unique reflections were judged observed ($|F_o| \geq 4.0\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. No corrections were deemed necessary for absorption or decomposition. The structure was solved routinely using the SHELXTL system of programs. Full-matrix least-squares refinements with anisotropic heavy atoms and fixed, isotropic and riding hydrogens have converged to a standard crystallographic residual of 5.54%. Additional crystallographic information is available and is described in the paragraph at the end of this paper.

Absolute Configuration of Trunculin C Methyl Ester (3). A solution of trunculin C methyl ester (4.2 mg) in methanol (0.5 mL) containing 5% palladium on carbon catalyst (2 mg) was stirred under an atmosphere of hydrogen at room temperature for 1.5 h. The catalyst was removed by filtration, and the solvent was evaporated to obtain the 3,6-diol 7 (3.7 mg): ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1 H, J = 7.9 Hz, H-16), 7.05 (br d, 1 H, J = 7.9 Hz, H-15, 6.88 (br s, 1 H, H-13), 3.73 (dd, 1 H, J = 10.4, 6.1 Hz, H-7), 3.71 (s, 3 H, OMe), 3.66 (m, 1 H, H-3), 2.57 (m, 2 H, H-11), 2.56 (dq, 1 H, J = 7.2, 7.2 Hz, H-2), 2.30 (s, 3 H, Me-23), 1.78-2.00 (m, 3 H), 1.58-1.65 (m, 4 H), 1.45 (s, 3 H, Me-24), 1.21 (d, 3 H, J = 7.2 Hz, Me-19), 1.20 (s, 3 H, Me-20), 1.06 (d, 3 H, J = 6.8 Hz, Me-22), 0.99 (s, 3 H, Me-21); CIMS m/z 419 (MH^+, 10), 401 ($MH^+ - H_2O$, 100).

A solution of 14% 2-phenylbutyric acid in pyridine (60.7 mg) was added to the 3,6-diol 7 (3.7 mg), and the solution was stirred at 25 °C for 24 h. The excess anhydride was destroyed by addition of water (2.5 mL), and the resulting suspension was titrated against 0.005 N sodium hydroxide solution using phenolphthalein as indicator. The volume of base consumed was 9.3 mL and the percentage of esterification was 94%. The ester was removed by extraction with ethyl acetate, the aqueous phase was acidified with dilute hydrochloric acid and the partially resolved 2-phenylbutyric acid was extracted with benzene. The optical rotation, measured in methanol solution, indicated an excess of (+)-2-phenylbutyric acid with an optical yield of 12%. This result requires a 3R absolute configuration for trunculin C methyl ester (3).

Conversion of Trunculin D Methyl Ester (4) into Trunculin C Methyl Ester (3). A small crystal of p-toluenesulfonic acid was added to a solution of trunculin D methyl ester (4, 5 mg) in dry benzene (0.2 mL), and the solution was warmed to 55 °C for 40 min. The cooled solution was passed through a short column of silica gel, and the solvent was evaporated to obtain trunculin C methyl ester (3, 2.8 mg), which was identified by comparison of the TLC behavior and NMR spectrum with those of authentic material.

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Supplementary Material Available: Tables of crystal data, fractional coordinates, interatomic distances, interatomic angles, and thermal parameters (11 pages). Ordering information is given on any current masthead page.

Synthesis and Preliminary Evaluation of the Fredericamycin A ABCDE Ring System

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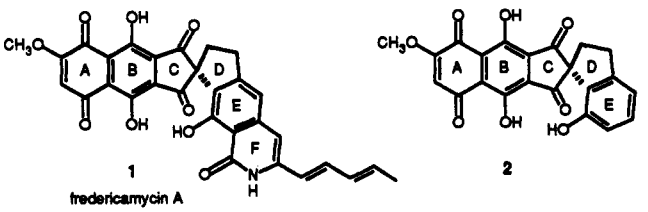
A concise preparation of **2** constituting the fully functionalized fredericamycin A ABCDE ring system is detailed and is based on the implementation of a regiospecific, intermolecular alkyne-chromium carbene complex benzannulation reaction for introduction of the AB ring system and a facile aldol closure for introduction of the spirocyclic CD ring system. Chemical and preliminary biological comparisons of **2** with fredericamycin are described.

Fredericamycin A (1, NSC-305263), a quinone antitumor antibiotic[1] isolated from *Streptomyces griseus*[2] bearing a unique spiro[4.4]nonene central to its structure, has been shown to possess potent in vitro cytotoxic activity and confirmed in vivo antitumor activity. The biological properties of fredericamycin A have been suggested to be derived from inhibition of RNA and protein synthesis through the nondiscriminant oxidative damage of DNA and/or through effective inhibition of DNA processing



enzymes including topoisomerase I and II.[1,3-5] Thus, since the establishment of the fredericamycin A structure that required a single-crystal X-ray structure determination[6] after extensive spectroscopic studies failed to resolve tautomeric structures,[3] it has remained the subject of continued biological[5] and extensive synthetic efforts[6] al-

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