ORGANIC LETTERS

2004
Vol. 6, No. 14
2389−2392

Enantioselective Total Synthesis of (+)-Eupenoxide and (+)-Phomoxide: Revision of Structures and Assignment of Absolute Configuration

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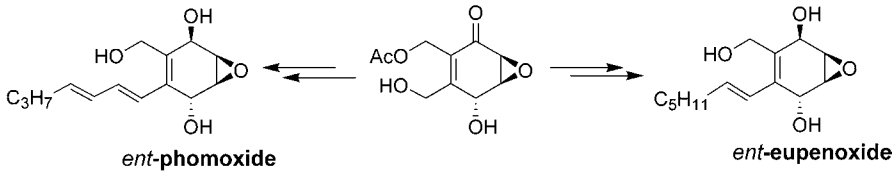
Received April 27, 2004

ABSTRACT



Stereo- and enantioselective total syntheses of the novel, polyketide natural products *ent*-eupenoxide and *ent*-phomoxide have been accomplished from the readily available Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone. These synthetic studies necessitate the revision of the assigned stereostructures of the natural products and reveal their absolute configuration.

In 1984, Duke and Rickards[1] reported a stereospecific synthesis of the polyketide antibiotic eupenoxide **1**, isolated by them from a fungus tentatively identified as belonging to the genus *Eupenicillium*. Curiously enough, neither the structure determination nor the characterization data on **1** ever appeared in the literature, though it was claimed that these details were in press.[2] Almost 20 years later, in 2003, Liu, Jensen, and Fenical reported[3] the isolation of eupenoxide **1** and phomoxide **2** from the fermentation broth of a marine derived fungus of the genus *Phoma* (strain CNC-651). The structure of eupenoxide **1** was determined on the basis of spectral data (mainly two-dimensional NMR) and "...comparison of appropriate ^{1}H NMR data with those reported for a silane-protected intermediate in the synthesis of eupenoxide".[1,3]

This appeared to be somewhat tenuous evidence in the absence of any data on the natural product in the literature.[1,2]

The structure of phomoxide **2** was assigned from its ^{13}C NMR data, ^{1}H NMR COSY experiments, and comparison of its spectral characteristics with eupenoxide. This suggested that it was a vinyl analogue of eupenoxide with a trienone moiety (compound **2** in Figure 1).[3]

Both **1** and **2** belong to a new structural class among the polyoxygenated cyclohexenoid natural products and im-

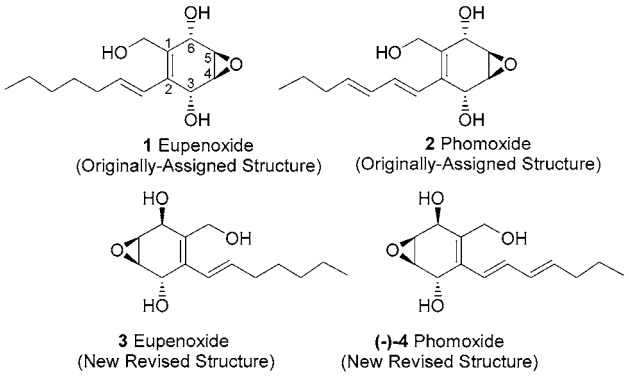
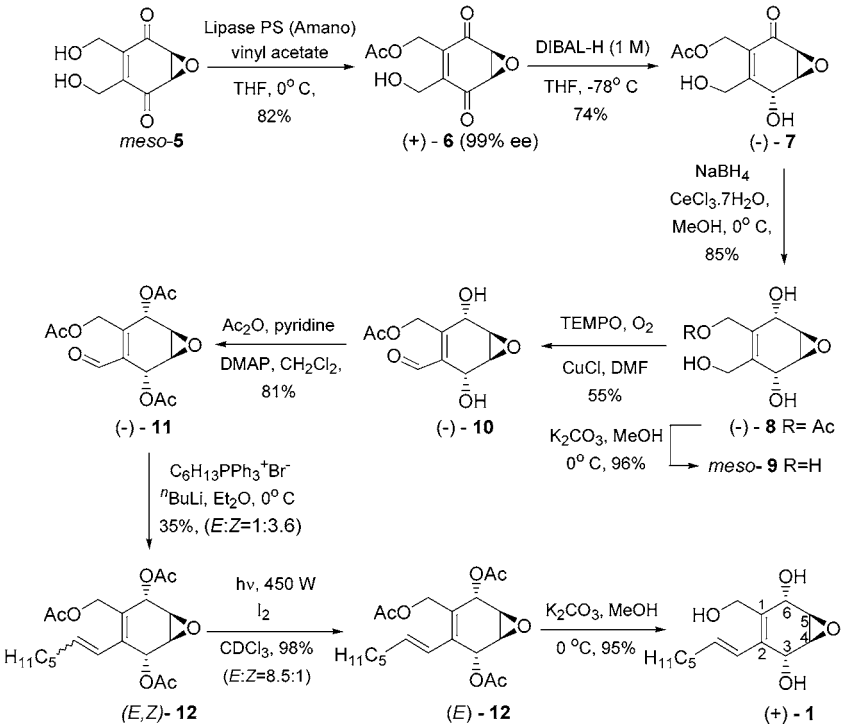


Figure 1.

(1) Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898.
(2) Reference 1 in the Duke and Rickards paper[1] reads "Quinn, R. J.; Rickards, R. W. *Aust. J. Chem.* **1984**, in press."

10.1021/ol0492288 CCC: $27.50
Published on Web 06/17/2004

Scheme 1



mediately caught our attention in view of our ongoing program on the total synthesis of biologically active, naturally occuring epoxyquinones.[4]

Herein, we describe enantioselective total syntheses of the structures assigned to eupenoxide **1** and phomoxide **2** that suggest that these formulations now need to be revised. Moreover, our synthetic endeavors further indicate that these two natural products are more accurately represented by the absolute stereostructures **3** and **4**, respectively.

Recently, we described[4c] an efficient lipase-mediated desymmetrization of the *meso*-epoxyquinone **5**, which delivers the *O*-acetate (+)-6 in 99% ee and 82% yield (Scheme 1). This served as the starting material for our synthetic route to the originally assigned structure **1** for eupenoxide. DIBAL-H reduction of (+)-**6** was directed both by the epoxide oxygen and the primary hydroxyl group to regio- and stereoselectively furnish hydroxy enone (−)-**7**. The Luche reduction[5] of (−)-**7** also showed the directive influence of the epoxide oxygen and furnished the *cis*-1,4-cyclohexenediol (−)-**8** in good yield (85%). At this stage, it was considered essential to unambiguously establish the stereochemistry of the *cis*-1,4-cyclohexenediol moiety in **8**, and this was accomplished through acetate hydrolysis, which furnished the *meso*-tetraol **9** (Scheme 1). After securing the stereochemistry of (−)-**8**, it was subjected to TEMPO-mediated[7] chemoselective oxidation to furnish aldehyde **10**, and the remaining two *cis*-hydroxyl groups at C3 and C6 were then protected to furnish the triacetate **11** (Scheme 1).[6] Wittig olefination of **11** with the ylide derived from *n*-hexyltriphenylphosphonium bromide led to **12** as an *E*:*Z* mixture (1:3.6) in which the unwanted (*Z*)-isomer was the major component. Irradiation of this *E*:*Z* diene mixture **12** in the presence of iodine led to the eventual predominance of the desired, more stable product (*E*)-**12** (*E*:*Z* ratio 8.5:1) (Scheme 1).[6] Purification and base-mediated hydrolysis of (*E*)-**12** led to **1,** whose structure was supposed to correspond to the assigned structure of the natural product eupenoxide.[3,8] However, the spectral data of our synthetic product, though similar, did not completely match the data later reported for this natural product by Fenical, especially the ^{13}C NMR resonances.[3,9] A careful comparison of the ^{13}C NMR data for the natural eupenoxide with our synthetic **1** (Table 1, entries 1 and 2, respectively) indicated that the maximum chemical shift variation between them was in the hydroxymethyl carbon resonance (marked in bold in Table 1). Attributing this difference in ^{13}C NMR values to the stereochemical dissimilarities in the vicinity of the hydroxymethyl carbon, we speculated that the natural product eupenoxide might have an alternate structure with an epimeric hydroxyl group at C6 as in **3**. We therefore ventured to undertake its synthesis.

For the projected synthesis of **3**, enantiomerically pure (−)-**7** was chosen as the starting point. TEMPO-mediated[7] chemoselective oxidation of the primary hydroxyl group and protection of the secondary hydroxyl group led to the aldehyde (−)-**13** (Scheme 2).[6] Wittig olefination with the ylide derived from *n*-hexyltriphenylphosphonium bromide

(3) Liu, Z.; Jensen, P. R.; Fenical, W. *Phytochemistry* **2003**, *64*, 571.
(4)) (a) Mehta, G.; Islam, K. *Tetrahedron Lett*. **2003**, *44*, 3569. (b) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett*. **2004**, *45*, 1985. (c) Mehta, G.; Islam, K. *Tetrahedron Lett*. **2004**, *45*, 3611. (d) Mehta, G.; Islam, K. *Org. Lett*. **2004**, *6*, 807. (e) Mehta, G.; Pan, S. C. *Org. Lett*. **2004**, *6*, 811.
(5) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454.

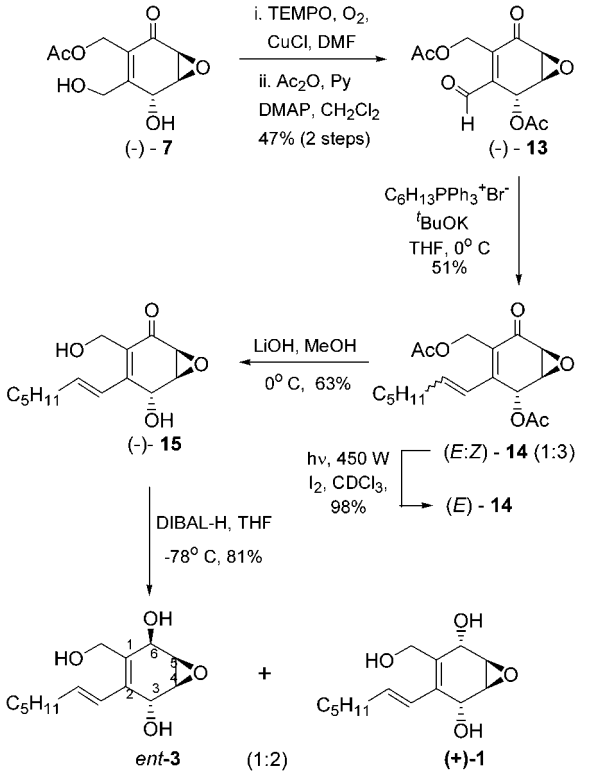
Table 1. ^{13}C NMR Data for Eupenoxide Series[a]

1	δ 134.9, 131.5, 131.3, 124.8, 66.2, 63.1, **58.4**, 54.5, 53.8, 33.5, 31.5, 29.0, 22.5, 14.0
2	δ 135.8, 131.8, 129.9, 124.4, 66.9, 63.1, **62.1**, 52.2, 51.3, 33.5, 31.4, 28.8, 22.5, 14.0
3	δ 135.2, 131.4, 131.3, 124.6, 66.6, 63.2, **58.9**, 54.7, 53.6, 33.5, 31.4, 28.9, 22.5, 14.0

[a] Entry 1: reported data (ref 3) for the natural product. Entry 2: synthetic product **1** corresponding to the "assigned structure" of eupenoxide. Entry 3: synthetic product *ent*-**3**.

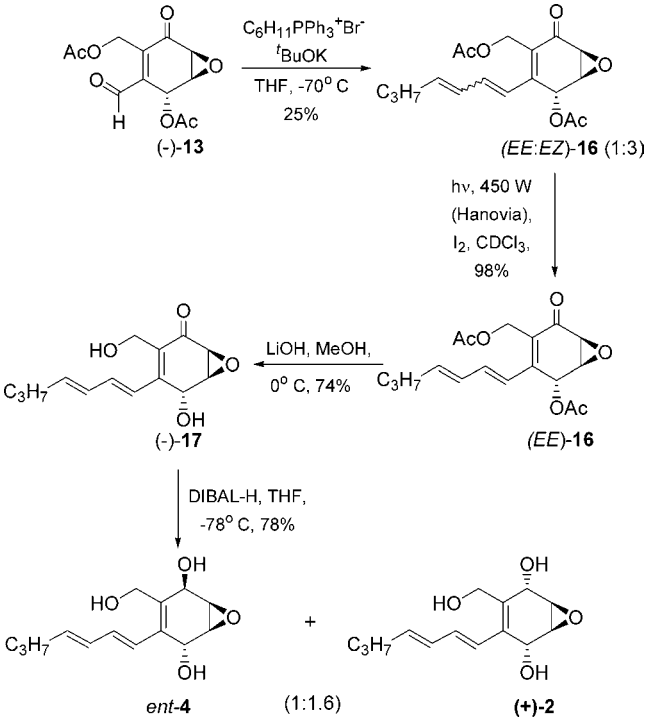
delivered **14** as a mixture of *E*:*Z* isomers (1:3). The dienone moiety in **14** was readily amenable to photoisomerization, and irradiation in the presence of iodine furnished exclusively the required (*E*)-**14** (Scheme 2).[6] Base hydrolysis of **14** led to the keto-diol (−)-**15**.[6] Finally, DIBAL-H reduction of the enone carbonyl in **15** led to a readily separable mixture (1:2) of epimeric alcohols *ent*-**3** and (+)-**1**. The major epimer was identical with the triol (+)-**1** described above.[8] However, the minor epimer (+)-**3**, having β-hydroxyl stereochemistry at C6, had ^{1}H and ^{13}C NMR spectra identical with those reported for natural eupenoxide (Table 1, see entries 1 and 3, respectively).[3] In our view, this result necessitates a revision of the assigned structure for natural eupenoxide from **1** to **3**.[10]

Scheme 2



Next, attention was turned to the closely related natural product phomoxide **2**, and in the light of the results described above and its co-occurrence with eupenoxide, its structural assignment also needed closer scrutiny. The advanced intermediate (−)-**13** described in Scheme 2, in the context of the eupenoxide problem, was recognized as an equally serviceable intermediate for the synthesis of phomoxide. Wittig olefination of (−)-**13** with the ylide derived from (*E*)-2-hexenyltriphenylphosphonium bromide led to the *E*,*E*:*E*,*Z* mixture **16** (1:3) (Scheme 3). Photoirradiation in the presence of iodine isomerized the *E*,*E*:*E*,*Z* mixture of trienones **16** to the required (*E*,*E*)-**16** exclusively.[6] Careful base hydrolysis of **16** delivered the hydroxy-trienone (−)-**17** (Scheme 3). DIBAL-H reduction of (−)-**17** was smooth and led to a readily separable mixture (1:1.6) of triols **2** and **4** in which the former was the major product.[6] On the basis of mechanistic considerations and previous precedence, the major reduction product from (−)-**16** was expected to be **2** with a *cis*-1,4-diol moiety. However, once again the spectral data for our synthetic **2**, particularly the ^{13}C NMR data (Table 2, entries 1 and 2), did not fully match with that quoted for natural phomoxide. As in the case of eupenoxide, the hydroxymethyl carbon resonance (Table 2, entries in bold) of synthetic **2** was distinctly different from that of natural **2**.

Scheme 3



On the other hand, the minor triene triol **4** was found to be spectroscopically identical to phomoxide (Table 2, entries

Table 2. ^{13}C NMR Data for Phomoxide Series[a]

1	δ 137.8, 132.8, 132.8, 131.7, 130.7, 124.7, 66.6, 62.9, **58.8**, 54.7, 53.7, 35.0, 22.3, 13.7
2	δ 138.5, 133.3, 132.1, 130.9, 130.5, 124.5, 66.5, 62.7, **61.7**, 52.4, 51.5, 35.0, 22.3, 13.7
3	δ 137.2, 132.5, 132.4, 131.6, 130.7, 124.9, 66.3, 62.6, **58.3**, 54.4, 53.7, 34.8, 22.3, 13.6

[a] Entry 1: reported data (ref 3) for the natural product. Entry 2: synthetic product **2** corresponding to the "assigned structure" of phomoxide. Entry 3: synthetic product *ent*-**4**.

1 and 3). This led to us reassign the stereostructure of the natural product phomoxide to **4**. While the synthetically prepared **4** had $[\alpha]_D$ +18.3 (*c* 0.71, CH_3OH), the reported optical rotation for the natural product phomoxide was $[\alpha]_D$ −20.0 (*c* 0.050, CH_3OH). Thus, our synthetic product (+)-**4** is *ent*-phomoxide and the natural product has the absolute configuration shown in (−)-**4**. Since, eupenoxide **3** and phomoxide **4** co-occur and are structural siblings, it is reasonable to extrapolate the findings on the latter and assign absolute configuration **3** to eupenoxide.[8,10]

In summary, we have accomplished enantioselective total synthesis of the recently reported epoxycyclohexane natural products eupenoxide and phomoxide, leading to the revision of their stereostructures and the establishment of their absolute configurations.

Acknowledgment. We thank Professor Fenical for the copies of the comparison spectra and prompt, cordial correspondence. This research was supported by the Chemical Biology Unit (CBU) of JNCASR, Bangalore, India.

Supporting Information Available: Spectral data of all the new compounds reported here, along with their spectra (^1H and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0492288

(6) All new compounds were fully characterized on the basis of spectral data (IR, ^1H and ^{13}C NMR, and HRMS). Selected spectral data. (−)-**8**: $[\alpha]^{23}_D$ −13.9 (*c* 2.37, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.83 (d, *J* = 12.6 Hz, 1H), 4.69 (d, *J* = 12.6 Hz, 1H), 4.53 (d, *J* = 1.5 Hz, 1H), 4.40 (d, *J* = 1.5 Hz, 1H), 4.32 (d, *J* = 12.9 Hz, 1H), 4.17 (d, *J* = 12.9 Hz, 1H), 3.32−3.29 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.8, 137.4, 130.1, 64.8, 64.2, 62.2, 59.7, 53.8, 53.8, 20.8; HRMS (ES) *m*/*z* calcd for $C_{10}H_{14}NaO_6$ $[M + Na]^+$ 253.0688, found 253.0691. (−)-**15**: $[\alpha]^{23}_D$ −150.0 (*c* 0.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.65−6.47 (m, 2H), 5.02 (br s, 1H), 4.34 (s, 2H), 3.88−3.86 (m, 1H), 3.49 (d, *J* = 3.6 Hz, 1H), 2.30−2.22 (m, 2H), 1.52−1.28 (m, 6H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 149.1, 143.7, 129.4, 125.0, 63.0, 55.7, 55.5, 52.4, 34.0, 31.4, 28.4, 22.4, 14.0; HRMS (ES) *m*/*z* calcd for $C_{14}H_{20}NaO_4$ $[M + Na]^+$ 275.1259, found 275.1244. (−)-**16**: $[\alpha]^{26}_D$ −167.02 (*c* 0.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.69−6.56 (m, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 6.37 (s, 1H), 6.25−6.17 (m, 1H), 6.10−6.00 (m, 1H), 5.04 (1/2ABq, *J* = 12.3 Hz, 1H), 4.86 (1/2ABq, *J* = 12.3 Hz, 1H), 3.76−3.74 (m, 1H), 3.57 (d, *J* = 3.6 Hz, 1H), 2.19−2.10 (m, 2H), 2.13 (s, 3H), 2.05 (s, 3H), 1.52−1.40 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 170.8, 145.9, 143.6, 139.2, 130.5, 128.4, 124.2, 63.1, 56.4, 52.8, 51.9, 35.1, 22.0, 20.8, 20.8, 13.7; HRMS (ES) *m*/*z* calcd for $C_{18}H_{22}NaO_6$ $[M + Na]^+$ 357.1314, found 357.1295. **1**: $[\alpha]^{25}_D$ +20.0 (*c* 1.95, $CHCl_3$); IR (cm^{-1}) 3372; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, *J* = 15.9 Hz, 1H), 6.15−6.05 (m, 1H), 4.75 (s, 1H), 4.59 (s, 1H), 4.57 (d, *J* = 12.6 Hz, 1H), 4.10 (d, *J* = 12.6 Hz, 1H), 3.46 (br s, 1H), 3.37 (br s, 1H), 2.24−2.07 (m, 2H), 1.44−1.28 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) see Table 1; HRMS (ES) *m*/*z* calcd for $C_{14}H_{22}NaO_4$ $[M + Na]^+$ 277.1416, found 277.1407. **2**: $[\alpha]^{25}_D$ +161.2 (*c* 1.16, CH_3OH); IR (cm^{-1}) 3377; ^1H NMR (300 MHz, $CDCl_3$) δ 6.64−6.55 (m, 1H), 6.35 (d, *J* = 15.3 Hz, 1H), 6.17−6.09 (m, 1H), 5.93−5.83 (m, 1H), 4.77 (br s, 1H), 4.58 (br s, 1H), 4.53 (d, *J* = 12.6 Hz, 1H), 4.09 (d, *J* = 12.6 Hz, 1H), 3.45 (br s, 1H), 3.35 (br s, 1H), 2.15−2.08 (m, 2H), 1.50−1.37 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) see Table 2; HRMS (ES) *m*/*z* calcd for $C_{14}H_{20}NaO_4$ $[M + Na]^+$ 275.1259, found 275.1246. **3**: $[\alpha]^{24}_D$ +1.8 (*c* 1.15, CH_3OH); IR (cm^{-1}): 3387; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, *J* = 15.9 Hz, 1H), 6.08−5.99 (m, 1H), 4.72 (br s, 2H), 4.40 (br s, 2H), 3.48 (s, 2H), 2.16−2.12 (m, 2H), 1.44−1.29 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) see Table 1; HRMS (ES) *m*/*z* calcd for $C_{14}H_{22}NaO_4$ $[M + Na]^+$ 277.1416, found 277.1410. **4**: $[\alpha]^{24}_D$ +18.3 (*c* 0.71, CH_3OH); IR (cm^{-1}) 3392; ^1H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 6.56−6.48 (m, 1H), 6.36 (d, *J* = 15.6 Hz, 1H), 6.14−6.06 (m, 1H), 5.84−5.74 (m, 1H), 4.69 (br s, 1H), 4.66 (br s, 1H), 4.38 (br s, 2H), 3.50 (s, 2H), 2.10−2.03 (m, 2H), 1.45−1.33 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) see Table 2; HRMS (ES) *m*/*z* calcd for $C_{14}H_{20}KO_4$ $[M + K]^+$ 291.0999, found 291.1001.

(7) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374.

(8) Optical rotation of the natural product eupenoxide has not been reported.[3] However, the synthetic material prepared by us in the present study and corresponding to the structure **1** of eupenoxide has $[\alpha]_D$ +20 (*c* 1.95, $CHCl_3$).

(9) We have observed that ^1H and ^{13}C NMR spectra in this series of compounds, particularly of triols **1**−**4**, exhibit small chemical shift and multiplicity variation as a function of concentration and temperature, possibly due to intramolecular hydrogen bonding and aggregation.

(10) While the synthetically prepared sample of eupenoxide had $[\alpha]_D$ +1.8 (*c* 1.15, $CHCl_3$), in the absence of the optical rotation data on the natural product, its absolute configuration has been projected through extrapolation on the basis of the deductions on phomoxide (vide infra). Consequently, (+)-**3** obtained by us is *ent*-eupenoxide and structure **3** represents the absolute configuration of the natural product.