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On the stereostructures of (+)-eupenoxide and (–)-3′,4′-dihydrophomoxide: a caveat on the spectral comparisons of oxygenated cyclohexenoids

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ABSTRACT

The structural ambiguity surrounding the structure of eupenoxide has been clarified and the absolute configuration of this natural product has been assigned. It is firmly established that 'eupenoxide' recently reported by Liu et al. is in fact a new natural product, (–)-3′,4′-dihydrophomoxide. The NMR spectra of these polyoxygenated cyclohexenoids exhibit subtle solvent, concentration, and temperature dependent variations, and due caution should be exercised when making spectral comparisons for structural assignments.

Polyoxygenated cyclohexenoid natural products, particularly those based on an epoxyquinone motif, are being encountered in Nature with regular frequency and hold special appeal on account of the extensive oxygenation pattern and stereochemical variations they embody.[1] Many of the polyoxygenated cyclohexenoids and epoxyquinone natural products also exhibit diverse and impressive bioactivity profiles. It is hardly surprising that in recent years they have emerged as widely pursued targets of total synthesis and have also been engaging our attention.[2,3]

In 1984, Quinn and Rickards isolated the oxygenated cyclohexenoid metabolite eupenoxide from the genus *Eupenicillium* sp.[4,5] Subsequently, Duke and Rickards reported its stereospecific synthesis in racemic form and named this antifungal agent eupenoxide (Fig. 1).[4] Quite unusually, neither the structure determination details nor the characterization data on the natural or synthetic eupenoxide were reported by these authors. However, the identity of natural and synthetic eupenoxide was claimed on the basis of spectral comparison, and it was indicated that the details concerning eupenoxide were in press.[4,5] Unfortunately, the full spectroscopic data for eupenoxide were never published.

In 2003, Liu et al. reported the isolation of 'eupenoxide' and the new fungal metabolite, phomoxide (Fig. 1), from the fermentation

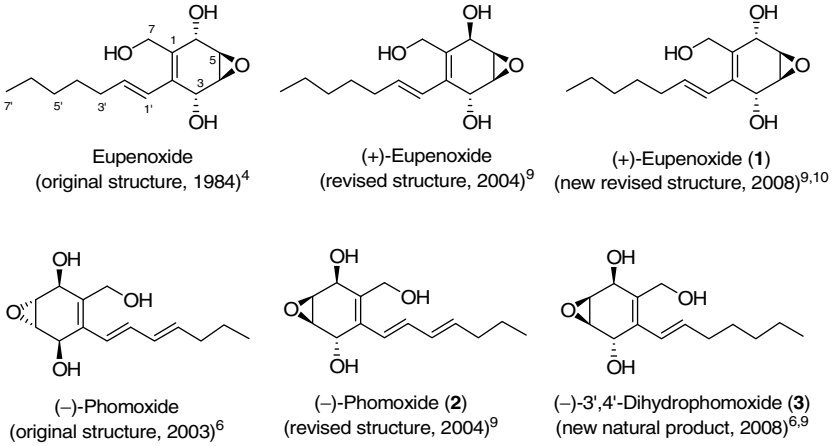

Figure 1.

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broth of a marine-derived fungus of the genus *Phoma* sp. (strain CNC-651).[6] The structure of this 'eupenoxide' was determined through incisive analysis of high-field NMR spectral data and confirmed through spectral comparison with the *bis*-TBDMS derivative of eupenxoide as reported by Duke and Rickards.[4] The structure of phomoxide was assigned on the basis of its NMR data, and by comparison of its spectral characteristics with those of its sibling natural product 'eupenoxide'. Phomoxide was therefore recognized as a vinylogue of eupenoxide containing a conjugated trienol moiety.[6] However, the specific rotation for only phomoxide was reported; no such data for 'eupenoxide' were available.

Eupenoxide and phomoxide appeared as members of a new structural type among the epoxyquinone natural products, and captured our attention in view of our ongoing interest in the total synthesis of biologically active epoxyquinol natural products.[7] Consequently, we undertook enantioselective total syntheses of the structures assigned to eupenoxide and phomoxide from a chiral building block of secured absolute configuration,[8] obtained from the readily accessible Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone. As part of these endeavors, we also synthesized epimeric compounds of eupenoxide and phomoxide following stereoselective protocols.[9]

We found that the spectral data (^{1}H and ^{13}C NMR) for our synthetic eupenoxide (+)-**1** did not match with the values reported by Liu et al.[6] for their 'eupenoxide'.[9] Such comparison was not possible with the eupenoxide originally isolated by Quinn and Rickards[4,5] as no literature data were available, and we did not receive any response to our requests for spectral data. However, we observed that the spectral data (^{1}H and ^{13}C NMR) of our synthetic product (+)-**3** (now named as 3′,4′-dihydrophomoxide) matched fully with the Liu et al. 'eupenoxide' (Table 1). Similarly, the spectral data (^{1}H and ^{13}C NMR) of our synthetic product (+)-**2** was identical with that reported for the natural product 'phomoxide' (Table 1). In 2004, this led us to propose that the structures assigned by Liu et al. to 'eupenoxide' and 'phomoxide', be revised to those shown in Figure 1.[9]

In 2005, Davis and coworkers again reported the isolation of eupenoxide from an endophytic fungus *Eupenicillium* sp. along with other related compounds.[10] Davis et al. elucidated the structure of eupenoxide following analysis of 1D and 2D NMR data of **1** in DMSO-d_6.[11,12] ^{13}C NMR spectral comparison with the $CDCl_3$ data reported for 'eupenoxide' by Liu et al. showed only small differences, which were attributed to solvent effects. This paper drew our immediate attention as we had already proposed revision of the 'eupenoxide' of Liu et al. based on a mismatch with our synthetic **1**.[9]

After some constructive correspondence, a search for the original Quinn and Rickards spectra and incisive spectral comparisons (see Table 1),[12] we are now able to present the following points clearly:

(i) Eupenoxide **1** originally reported by Rickards et al.[4] and more recently isolated by Davis et al.[10] indeed has stereostructure **1**, as originally proposed. Their spectral data (available now)[11,12] are identical with those of our synthetic compound **1**.

(ii) The 'eupenoxide' of Liu et al. corresponds neither to the originally reported eupenoxide **1** of Rickards and Quinn[4] nor to that reported recently by Davis et al., but is in fact a new natural product, now identified as (−)-3′,4′-dihydrophomoxide **3** and is spectroscopically identical with our synthetic compound (+)-**3**.

(iii) Comparison of the NMR data of Liu et al.[6] for their 'eupenoxide' with the *bis*-TBDMS eupenoxide derivative reported by Duke and Rickards[3] was incorrect and led to structural mis-assignment, which in turn led Mehta et al. to propose[9] a revision of the original eupenoxide structure in 2004.

(iv) NMR spectral comparison between the eupenoxide **1** isolated by Davis et al.[10] and the 'eupenoxide' reported by Liu et al.[6] (now formulated as (−)-3′,4′-dihydrophomoxide), established that the identity was incorrect.[11]

v) Conclusions[9] on the revision of the structure of (−)-phomoxide to **2** in 2004 remain valid.

Davis et al.[10,12] recorded a specific rotation of $[\alpha]_D^{25}$ +21.8 (*c* 0.80, $CHCl_3$) for their isolated eupenoxide.[11] The specific rotation of our synthetic eupenoxide was measured to be $[\alpha]_D^{25}$ +20.0 (*c* 1.95, $CHCl_3$).[9] This leads to the absolute configuration of eupenoxide as (+)-**1**. No specific rotation data were available for the original eupenoxide isolated by Quinn et al.,[11] however, based on source organism taxonomy (both *Eupenicillium* species) and biosynthetic grounds, we assume that the enantiomer, (+)-**1**, isolated by Davis et al.[10] was most likely also isolated by Quinn et al.[5] Since this Letter clarifies the stereostructure of **1** for the first time, we feel that it is appropriate to report the full spectroscopic data of (+)-eupenoxide as recorded and assigned by Davis et al.[10,12]

Further, while the specific rotation recorded for our synthetic (+)-phomoxide was $[\alpha]_D^{24}$ +18.3 (*c* 0.71, CH_3OH), the reported value for the natural product was $[\alpha]_D$ −20.0 (*c* 0.05, CH_3OH).[9] This indicated that the natural product was enantiomeric with respect to our synthetic compound of known absolute configuration. Therefore, natural phomoxide is represented by absolute configuration (−)-**2**. The specific rotation of our synthetic 3′,4′-dihydrophomoxide was $[\alpha]_D^{24}$ +1.8 (*c* 1.15, CH_3OH). The specific rotation for the new natural product 3′,4′-dihydrophomoxide[6] has not been reported, but in view of its co-occurrence with (−)-phomoxide, with which it shares the same chiral centers, the absolute configuration of (−)-**3** has been assigned as drawn in Figure 1.[9]

While the prevailing confusion in the literature[4,6,9,10] regarding the structures of (+)-eupenoxide, (−)-3′,4′-dihydrophomoxide and (−)-phomoxide stands clarified, it is recognized that the problem primarily arose due to errors in the comparison of NMR spectral data which might have appeared similar but were not identical. During our extensive studies on the synthesis of polyoxygenated cyclohexenoids,[3,7,9] we have frequently encountered solvent, con-

Table 1
^{13}C NMR data for compounds **1**–**3**

Eupenoxide (**1**)	Quinn[a]	δ 135.7, 131.8, 130.0, 124.7, 65.7, 63.1, 61.1, 52.6, 51.7, 33.6, 31.6, 29.0, 22.5, 14.0
	(+)-Synthetic[b]	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
	(+)-Davis[c]	δ 135.8, 132.0, 130.1, 124.5, 66.9, 63.3, 62.2, 52.1, 51.3, 33.5, 31.4, 28.8, 22.5, 14.0
3′,4′-Dihydrophomoxide (**3**)	(+)-Synthetic[b]	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
	Fenical[d]	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
Phomoxide (**2**)	(+)-Synthetic[b]	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
	(−)-Fenical[d]	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

[a] Recorded in $CDCl_3$ at 25 °C at 25 MHz.
[b] Recorded in $CDCl_3$ at 25 °C at 75 MHz.[9]
[c] Recorded in $CDCl_3$ at 30 °C at 125 MHz.
[d] Recorded in $CDCl_3$ at 100 MHz (temperature not noted in the Letter).

centration and temperature dependent variations in chemical shifts and multiplicities, which make NMR spectral comparisons somewhat tenuous. Great care should therefore be exercised in making deductions about identities of compounds in this class of natural products.

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Supplementary data

^{1}H and ^{13}C NMR spectra for (+)-eupenoxide in $CDCl_3$ and DMSO-d_6. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.076.

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11. Private communication with Professor Ronald J. Quinn.
12. *Data for (+)-eupenoxide* **1** *as recorded by Davis et al.*:[10] Stable clear gum; $[\alpha]_D^{25}$ +82.8 (*c* 0.8, MeOH); $[\alpha]_D^{25}$ +21.8 (*c* 0.8, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 206 (3.72), 244 nm (4.01); IR ν_{max} (film) 3500–3100, 2956, 2926, 2856, 1646, 1456, 1283, 1244, 1019, 846 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.86 (3H, t, J = 6.6 Hz, H-7′), 1.27 (2H, m, H-6′), 1.27 (2H, m, H-5′), 1.37 (2H, tt, J = 7.2, 7.2 Hz, H-4′), 2.10 (1H, dt, J = 7.2, 7.2 Hz, H-3′), 3.21 (1H, m, H-5), 3.23 (1H, m, H-4), 3.93 (1H, dd, J = 12.6, 6.0 Hz, H-7b), 4.20 (1H, dd, J = 12.6, 4.8 Hz, H-7a), 4.37 (1H, d, J = 8.4 Hz, H-6), 4.41 (1H, d, J = 9.0 Hz, H-3), 4.65 (1H, dd, J = 6.0, 4.8 Hz, 7-OH), 4.71 (1H, d, J = 8.4 Hz, 6-OH), 4.78 (1H, d, J = 9.0 Hz, 3-OH), 5.98 (1H, dt, J = 15.6, 7.2 Hz, H-2′), 6.35 (1H, d, J = 15.6 Hz, H-1′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.9 (C-7′), 22.0 (C-6′), 28.6 (C-4′), 30.8 (C-5′), 32.8 (C-3′), 52.0 (C-5), 52.8 (C-4), 57.6 (C-7), 62.2 (C-3), 62.8 (C-6), 126.3 (C-1′), 129.5 (C-2), 132.4 (C-2′), 132.4 (C-1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz, H-7′), 1.31 (2H, m, H-6′), 1.31 (2H, m, H-5′), 1.42 (2H, tt, J = 6.6, 6.6 Hz, H-4′), 2.13 (1H, m, H-3a′), 2.20 (1H, m, H-3b′), 3.01[a] (1H, br s, 7-OH), 3.38 (1H, s, H-5), 3.47 (1H, s, H-4), 3.78[a] (1H, br s, 3-OH), 4.05[a] (1H, br s, 6-OH), 4.13 (1H, d, J = 12.6 Hz, H-7b), 4.61 (1H, d, J = 12.6 Hz, H-7a), 4.64 (1H, br s, H-6), 4.77 (1H, s, H-3), 6.10 (1H, ddd, J = 15.6, 6.6, 6.6 Hz, H-2′), 6.29 (1H, d, J = 15.6 Hz, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (C-7′), 22.5 (C-6′), 28.8 (C-4′), 31.4 (C-5′), 33.5 (C-3′), 51.3 (C-5), 52.1 (C-4), 62.2 (C-7), 63.3 (C-3), 66.9 (C-6), 124.5 (C-1′), 130.1 (C-1), 132.0 (C-2), 135.8 (C-2′); (+)-LRESIMS *m/z* (rel. int.) 277 (100) $[M+Na]^+$. (+)-HRESIMS *m/z* 277.14051 ($C_{14}H_{22}O_4Na$ $[M+Na]^+$ requires 277.14103).[a] Interchangeable signals.