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# Complete assignment of the stereostructure of a new squalene-derived epoxy tri-THF diol from *Spathelia glabrescens* by total synthesis

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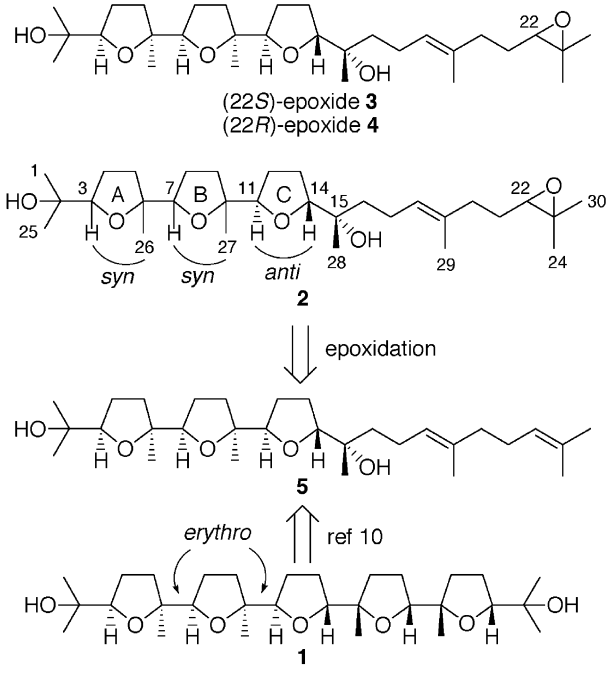
**Abstract**—The total assignment of the incomplete stereostructure of a new squalene-derived epoxy tri-tetrahydrofuran (THF) diol (**2**) to the structural formula **3** has been achieved through the first asymmetric syntheses of (22*S*)-**3** and its epimer (22*R*)-**4**. 

Recently, biologically active and structurally unique triterpene polyethers, which are thought to be biogenetically squalene-derived natural products (oxasqualenoids), have been isolated from both marine and terrestrial plants.[1,2] Among them are glabrescol (**1**)[3] and an epoxy tri-THF diol (**2**)[4] biogenetically related to each other, isolated from the endemic Jamaican plant *Spathelia glabrescens* (Rutaceae) by Jacobs et al., one of the authors in this paper (Scheme 1). Although there is no report on the biological activities of both compounds, these polyethers containing five or three THF rings may be expected to exhibit ionophoric functions[5,6] as well as cytotoxicities,[1,2] because of the recent active research studies on remarkable interactions (membrane transport and ion channel) of neutral oligotetrahydrofuranyl derivatives with metal cations in natural products[7] and artificial systems.[8,9] Many types of oxasqualenoids have been isolated; however, it is often difficult to determine their stereostructures only by spectroscopic analysis, especially in systems including acyclic quaternary carbon centers. In such cases, it is effective to predict and synthesize the possible stereoisomers.[10–12] Although the planar structure and partial relative configuration of **2** were also elucidated by NMR methods as shown in **2**,[4] determination of the entire stereochemistry of compound **2** has not been reached. In this paper, we report that the stereostructure of the new squalene-derived epoxy tri-THF diol (**2**) is completely assigned to **3** by its total synthesis.

There are four possible *syn*, *syn*, *anti* stereoisomers of the C1–C15 fragment and attached methyl groups with the relative stereochemistry as shown at C11, C14, and C15, and eight for the entire molecule **2**. We have previously accomplished the total synthesis of (–)-




**Scheme 1.** Possible stereostructure for the natural product **2**.

*Keywords*: asymmetric synthesis; epoxides; polyethers; squalene; stereochemistry.

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glabrescol (**1**) by way of the tri-THF intermediate **5**, and revised the originally proposed *meso* structure[3] to the $C_2$ symmetric **1**.[10] Considering the relative stereochemistry between each A, B, and C THF ring in **2**, it is likely that **2** also possesses the same *erythro* configuration of **1** on biogenetic grounds, because both **1** and **2** were isolated from *S. glabrescens*. In practice, chemical shifts observed for C1–C17 and C25–C28 in the $^{13}C$ NMR spectrum of **2** are almost identical with those of **5** (Table 1), strongly suggesting that the relative configuration of **2** and **5** is the same. Therefore, we decided to synthesize the two remaining possible stereoisomers **3** and **4** by epoxidation of our synthetic intermediate **5** to compare their spectroscopic data with those of the natural product **2**.

We adopted Shi's asymmetric epoxidation[13] as a reliable method to be able to predict the stereochemical outcome of the reaction, because many examples for trisubstituted alkene substrates similar to **5** have been reported without exception.[11,14–16] Reagent-controlled epoxidation of the optically active diene **5**, $[\alpha]_D^{24}$ −12.5 (*c* 1.32, $CHCl_3$),[10] with Shi's chiral dioxirane in situ generated from ketone **6**[13] afforded monoepoxides *endo* **7** and *exo* **4** as an inseparable 1:1.3 mixture, respectively, in 43% yield along with 52% recovery of the starting material **5** (Scheme 2). For the purpose of separating the two products, the mixture was treated with camphorsulfonic acid (CSA) to give the diastereomerically homogeneous (22*R*)-epoxide **4**,[†] $[\alpha]_D^{22}$ −13.1 (*c* 0.14, $CHCl_3$), and tetra-THF **8** in 37% and

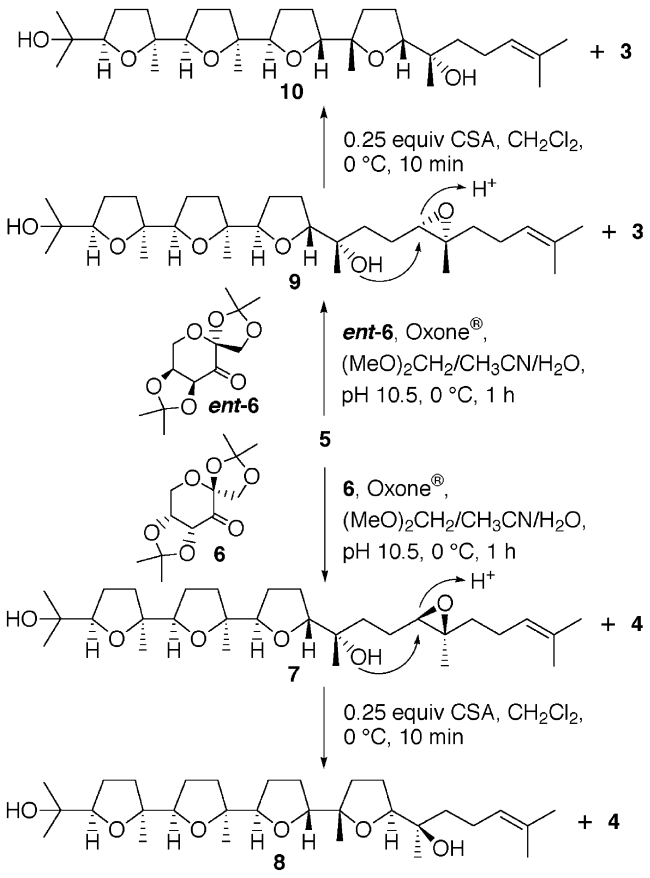
**Table 1.** $^{13}C$ NMR data for compounds **2**–**5**

| Position | **2**[a] | **5**[a] | **2** (2.6 mM)[b] | **3** (16 mM)[b] | **4** (8.7 mM)[b] | $\Delta\delta=\delta_3-\delta_2$ | $\Delta\delta=\delta_4-\delta_2$ |
|---|---|---|---|---|---|---|---|
| 1 | 25.2 | 25.2 | 25.392 | 25.370 | 25.386 | −0.022 | −0.006 |
| 2 | 72.3 | 72.3 | 72.462 | 72.458 | 72.446 | −0.004 | −0.016 |
| 3 | 85.9 | 85.9 | 86.012 | 85.993 | 86.004 | −0.019 | −0.008 |
| 4 | 26.0 | 26.1 | 26.199 | 26.188 | 26.192 | −0.011 | −0.007 |
| 5 | 29.8 | 30.0 | 30.072 | 30.052 | 30.060 | −0.020 | −0.012 |
| 6 | 86.1 | 86.1 | 86.169 | 86.162 | 86.166 | −0.007 | −0.003 |
| 7 | 82.7 | 82.9 | 82.828 | 82.836 | 82.819 | +0.008 | −0.009 |
| 8 | 28.9 | 28.9 | 28.773 | 28.787 | 28.768 | −0.014 | −0.005 |
| 9 | 30.8 | 31.0 | 30.706 | 30.732 | 30.706 | +0.026 | 0.000 |
| 10 | 85.9 | 85.9 | 85.866 | 85.880 | 85.862 | +0.014 | −0.004 |
| 11 | 84.2 | 84.3 | 84.303 | 84.301 | 84.297 | −0.002 | −0.006 |
| 12 | 29.5 | 29.5 | 29.648 | 29.642 | 29.641 | −0.006 | −0.007 |
| 13 | 26.4 | 26.5 | 26.657 | 26.636 | 26.648 | −0.021 | −0.009 |
| 14 | 85.8 | 85.8 | 85.977 | 85.993 | 85.979 | +0.016 | +0.002 |
| 15 | 72.9 | 73.0 | 73.076 | 73.058 | 73.077 | −0.018 | +0.001 |
| 16 | 36.6 | 36.8 | 36.957 | 36.954 | 36.915 | −0.003 | **−0.042** |
| 17 | 22.1 | 22.1 | 22.375 | 22.354 | 22.354 | −0.021 | −0.021 |
| 18 | 125.3 | 124.7 | 125.678 | 125.650 | 125.711 | −0.028 | **+0.033** |
| 19 | 133.9 | 134.9 | 134.020 | 134.010 | 133.981 | −0.010 | **−0.039** |
| 20 | 36.2 | 39.7 | 36.512 | 36.489 | 36.531 | −0.023 | +0.019 |
| 21 | 27.3 | 26.7 | 27.645 | 27.621 | 27.598 | −0.024 | **−0.047** |
| 22 | 64.1 | 124.3 | 64.039 | 64.056 | 64.056 | +0.017 | +0.017 |
| 23 | 58.4 | 131.3 | 58.022 | 58.051 | 58.041 | +0.029 | +0.019 |
| 24 | 18.7 | 17.6 | 18.775 | 18.766 | 18.773 | −0.009 | −0.002 |
| 25 | 27.8 | 27.8 | 28.003 | 27.981 | 27.990 | −0.022 | −0.013 |
| 26 | 25.2 | 25.2 | 25.203 | 25.197 | 25.198 | −0.006 | −0.005 |
| 27 | 23.4 | 23.3 | 23.304 | 23.314 | 23.302 | +0.010 | −0.002 |
| 28 | 24.0 | 24.1 | 24.272 | 24.252 | 24.229 | −0.020 | **−0.043** |
| 29 | 15.9 | 16.0 | 16.025 | 16.018 | 15.980 | −0.007 | **−0.045** |
| 30 | 24.8 | 25.7 | 24.888 | 24.882 | 24.890 | −0.006 | +0.002 |

[a] The data for **2** and **5** were cited from Refs. 4 and 10, respectively.

[b] The spectra were recorded at 300 K and the indicated concentrations in 60%$CDCl_3$/40%$C_6D_6$ on a Bruker AVANCE 600 (150 MHz) spectrometer. Chemical shifts are in ppm down field from the peak of TMS as an internal standard.

[†] Compound **4**: $^1H$ NMR (600 MHz, 60%$CDCl_3$/40%$C_6D_6$) $\delta$ 5.21 (1H, t, $J=6.7$ Hz), 4.43 (1H, br s), 4.04 (1H, t, $J=7.7$ Hz), 3.88 (1H, dd, $J=10.9$, 4.9 Hz), 3.79 (1H, dd, $J=8.4$, 3.5 Hz), 3.71 (1H, dd, $J=9.6$, 6.2 Hz), 3.42 (1H, br), 2.61 (1H, t, $J=6.2$ Hz), 2.47 (1H, dt, $J=11.7$, 9.6 Hz), 2.27–1.96 (6H, m), 1.88–1.67 (5H, m), 1.64–1.47 (4H, m), 1.61 (3H, s), 1.37–1.26 (4H, m), 1.29 (3H, s), 1.24 (3H, s), 1.20 (3H, s), 1.16 (3H, s), 1.07 (3H, s), 1.04 (3H, s), 1.00 (3H, s); IR (neat) 3422, 1650, 1067 $cm^{-1}$; FAB-HRMS calcd for $C_{30}H_{53}O_6$ [$(M+H)^+$] 509.3842, found 509.3860. Compound **3**: $^1H$ NMR (600 MHz, 60%$CDCl_3$/40%$C_6D_6$) $\delta$ 5.21 (1H, t, $J=6.6$ Hz), 4.45 (1H, br s), 4.04 (1H, t, $J=7.7$ Hz), 3.88 (1H, dd, $J=10.9$, 4.9 Hz), 3.79 (1H, dd, $J=8.4$, 3.5 Hz), 3.71 (1H, dd, $J=9.7$, 6.1 Hz), 2.61 (1H, t, $J=6.2$ Hz), 2.47 (1H, dt, $J=11.6$, 9.6 Hz), 2.27–1.96 (6H, m), 1.88–1.67 (5H, m), 1.64–1.47 (4H, m), 1.61 (3H, s), 1.37–1.26 (4H, m), 1.29 (3H, s), 1.24 (3H, s), 1.20 (3H, s), 1.16 (3H, s), 1.07 (3H, s), 1.04 (3H, s), 1.00 (3H, s); IR (neat) 3420, 1650, 1067 $cm^{-1}$; FAB-HRMS calcd for $C_{30}H_{53}O_6$ [$(M+H)^+$] 509.3842, found 509.3826.




**Scheme 2.** Synthesis of the two possible stereoisomers **3** and **4**.

43% isolated yields, respectively, after column chromatography on silica gel. On the other hand, the same procedure for the diene **5** using ketone ***ent*-6**[13] enantiomeric to **6** furnished monoepoxides *endo* **9** and *exo* **3** as a mixture (**9**:**3** = 1:1.4 in 47% yield and recovered **5** in 39% yield), acid treatment of which provided (22*S*)-epoxide **3**,† $[\alpha]_D^{22}$ −12.3 (*c* 0.235, $CHCl_3$), in 53% yield and tetra-THF **10** (38%).

It appears that the synthetic compounds **3** and **4** and the natural product **2** are indistinguishable from one another by the 600 MHz $^1$H NMR spectra,† even in a $CDCl_3/C_6D_6$ mixed solvent system with comparatively good proton resolution. Therefore, the stereostructure of **2** must be either **3** or **4**; however, it seems difficult to distinguish **3** from **4**. In that case, we focused on the critical stereochemical discussions utilizing carbon chemical shift differences ($\Delta\delta$) below the 0.1 ppm level reported by Kishi et al.[17] 150 MHz $^{13}$C NMR data of **2**–**4** measured by the same spectrometer are summarized in Table 1. Comparing the chemical shifts, $|\Delta\delta = \delta_3 - \delta_2|$ of all the carbons in **3** is less than 0.03 ppm, while there are six carbons (C16, C18, C19, C21, C28, and C29) of $|\Delta\delta = \delta_4 - \delta_2| > 0.03$ ppm in the region linking between C15 and C22 chiral carbons of **4** (Fig. 1). An optical rotation of the authentic sample **2**, $[\alpha]_D^{25}$ −11.5 (*c* 0.03, $CHCl_3$), remeasured by us[4] is also nearer to that of (22*S*)-**3** than that of (22*R*)-**4**. Furthermore, to rule out the possibility that the chemical shift differences

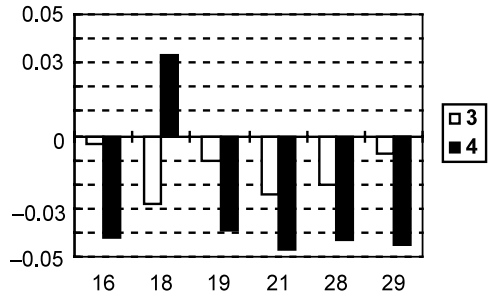



**Figure 1.** Chemical shift differences ($\Delta\delta$) observed for the carbons of $|\Delta\delta = \delta_4 - \delta_2| > 0.03$ ppm in **3** and **4**. The *x* and *y* axes represent carbon number and $\Delta\delta$ in ppm, respectively.

$|\Delta\delta = \delta_4 - \delta_2| > 0.03$ ppm are an experimental error and unambiguously differentiate the synthetic **4** from the natural **2**, 150 MHz $^{13}$C NMR spectrum of a 1.3:1 mixture of **4** and **2**, respectively, was measured at 300 K and 6.1 mM in 60%$CDCl_3$/40%$C_6D_6$. Seven distinguishable peaks with $\Delta\delta = \delta_4 - \delta_2$ indicated in parentheses were observed for the carbons C16 (−0.025), C18 (+0.052), C19 (−0.029), C20 (+0.037), C21 (−0.030), C28 (−0.027), and C29 (−0.042), still in the region linking between C15 and C22 chiral carbons and with the same signs as those of $\Delta\delta$ independently measured (Table 1). From these facts, we judged that the spectral characteristics including the optical rotation of the synthetic (22*S*)-**3** are identical to those of the natural product **2**. Thus, it has been found that the hitherto unknown relative and absolute configuration of the epoxy tri-THF diol (**2**) is as indicated in the structural formula **3**, which possesses the same absolute stereochemistry as glabrescol (**1**).

In conclusion, we have accomplished complete assignment of the stereostructure of the new squalene-derived epoxy tri-THF diol (**2**), which is difficult to determine the stereochemistry only by spectroscopic methods, through its first asymmetric total synthesis. This will be useful to deduce the biogenetic relationships not only between epoxy tri-THF diol (**2**) and glabrescol (**1**) but also among the relevant oxasqualenoids, and evaluate biological activities of **2**.

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