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Stereo- and Regioselective Synthesis of Squalene Tetraepoxide

Rongbiao Tong, Matthew A. Boone, and Frank E. McDonald*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

fmcdona@emory.edu

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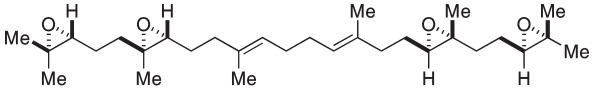

Squalene tetraepoxide, a putative biosynthetic precursor to a variety of oxacyclic triterpenoid natural products, has been efficiently synthesized by anionic coupling of two farnesol-derived diepoxides, which have arisen from electronic control of the regioselectivity in organocatalytic enantioselective epoxidations.

An isomer of squalene tetraepoxide (**1**, Figure 1) has been proposed to be the biogenetic precursor to several oxacyclic triterpenoid natural products, some of which have interesting biological activities.[1] Representative members of this family of natural products, such as abudinols A and B (**2** and **3**), are isomeric to **1** with the formula $C_{30}H_{50}O_4$. Other closely related natural products including raspacionin (**4**) and sodwanone M (**5**) all display highly compact and complex molecular architectures, and may also arise from squalene tetraepoxide (**1**). We have been intrigued by the structural diversity of these compounds, and thus became interested in developing a synthetic route to squalene tetraepoxide as the *all-R*-enantiomer (*ent*-**1**), to test the biomimetic cyclization behavior and potentially gain access to these complex natural products.

A tetraepoxide of squalene has been claimed from the epoxidation of squalene with 4 equiv of perbenzoic acid.[2] The level of characterization available in that era did not conclusively permit positional assignment of the epoxides. Moreover, perbenzoic acid epoxidation would undoubtably have provided a mixture of stereoisomers. However, the recent development of enantio- and regioselective epoxidation methods[3] indicated that the efficient and stereoselective synthesis of squalene tetraepoxide **1** could now be possible.

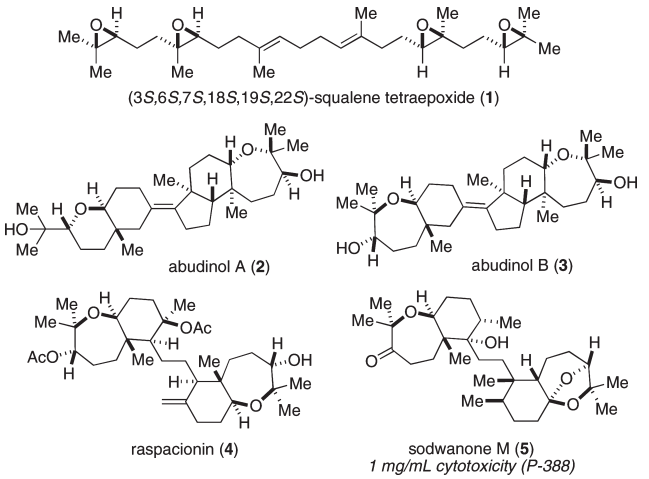

FIGURE 1. Squalene tetraepoxide and representative polycyclic ether natural products.

Our strategy was based on the regio- and enantioselective epoxidation of farnesol derivatives. We anticipated that the Shi enantioselective epoxidation of the alkene nearest to the heteroatom substituent would be disfavored by the presence of an electron-withdrawing allylic substituent.[4,5] Farnesyl acetate **6a** gave reasonable but variable yields of the 6,7:10,11-diepoxide **8a** (Table 1),[6] and this product was always accompanied by substantial quantities of the triepoxide. Farnesyl benzoate **6b** was less reactive (probably due to poor solubility in the polar solvent mixture), but the electron-withdrawing and polar nitrobenzoate ester in **6c** gave superior results (entry 3),[7] providing primarily the diepoxide **8c** along with mixtures of the monoepoxides, which could be converted into additional quantities of **8c** by another cycle of the Shi epoxidation. The toluenesulfonyl substituent[8] in substrate **7** (entry 4) completely suppressed epoxidation at the 2,3-alkene, to afford diepoxide **9** as the major product.[9,10]

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(9) Regioselective (racemic) monoepoxidation of geranyl *p*-tolylsulfone: Eren, D.; Keinan, E. *J. Am. Chem. Soc.* **1988**, *110*, 4356.

(10) Although epoxidations catalyzed by D-epoxone have provided the *all*-(*R*)-epoxides **8** and **9** resulting in *all*-(*R*)-squalene tetraepoxide *ent*-**1**, the (*S*)-antipodes of **8** and/or **9** can be prepared by using L-epoxone arising from L-fructose: Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377.

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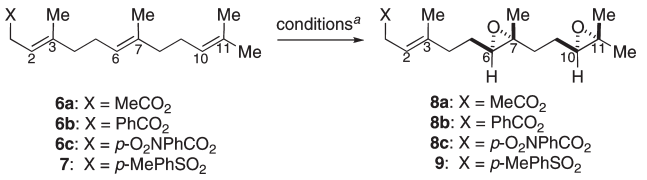
TABLE 1. Regioselectivity of Shi Epoxidations of Farnesyl Esters

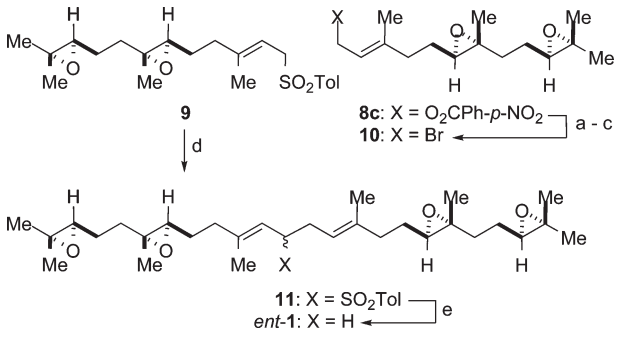


entry	substrate	monoepoxide yield %[b]	diepoxide yield (%)	triepoxide yield (%)
1	**6a**	trace	35−55	40
2	**6b**	61	26	not observed
3	**6c**	28	49−61[c]	trace
4	**7**	trace	71	not observed

[a]Reaction conditions: D-epoxone (0.5 equiv), Oxone (2.8 equiv), K_2CO_3 (8.0 equiv), Bu_4NHSO_4 (0.1 equiv), Na_2EDTA, $Na_2B_4O_7$, DMM:MeCN (2:1), H_2O, 0 °C. [b]Combined yield of 6,7- and 10,11-monoepoxides. [c]Isolated yields of **8c** from one cycle of epoxidation of **6c**.

The diepoxide **8c** was converted into the known diepoxybromide **10**.[6] The 30-carbon chain of squalene tetraepoxide was then constructed by addition of KO-*t*-Bu at low temperature to a THF solution of the two 15-carbon synthons diepoxysulfone **9** and diepoxybromide **10** (1.5 equiv). Palladium-catalyzed reductive desulfonylation[11] of the resulting intermediate **11** provided squalene tetraepoxide *ent*-**1** (Scheme 1).

SCHEME 1. Anionic Coupling of 9 and 10, and Conversion to Squalene Tetraepoxide *ent*-1[a]



[a]Reagents and conditions: (a) K_2CO_3, MeOH, 15 min (88% yield); (b) MsCl, Et_3N, THF, −40 °C, 30 min; then LiBr, THF, 0 °C, 15 min (96% yield); (c) KO-*t*-Bu, THF, −78 °C, 2 h (77% yield); (d) $PdCl_2$(dppp) (20 mol %), $LiBEt_3H$, THF, 0 °C, 40 min (64% yield).

Although preliminary studies on the Lewis acid-promoted cyclizations of *ent*-**1** have not yet proven productive, we believe that our synthesis of tetraepoxide **1** will have value in preparing substrates for biosynthetic feeding experiments. Our synthetic route allows for incorporation of stable isotopes, for instance by double ^{13}C-labeling in farnesol.[12] In addition, the unsymmetrical nature of our synthetic approach provides considerable flexibility in the nature of polyepoxide synthons for preparation of epoxide diastereomers of **1**, and access to several other patterns of squalene polyepoxides.

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Experimental Section

Farnesyl-*p*-tolyl Sulfone 7.[8] To a solution of *trans,trans*-farnesol (10.0 g, 45 mmol) in dry THF (0.22 M, 200 mL) was added triphenylphosphine (PPh_3, 14.7 g, 56 mmol) at 0 °C. *N*-Bromosuccinimide (NBS, 9.23 g, 51.6 mmol) was then slowly added in ten batches over 20 min. The light yellow reaction mixture was stirred for 1.5 h at 0 °C until complete conversion was achieved as monitored by TLC. Then, tetrabutylammonium iodide (Bu_4NI, 1.70 g, 4.5 mmol) and *p*-toluenesulfinic acid sodium salt ($NaSO_2Tol$, 12 g, 68 mmol) were subsequently added. The light yellow suspension was warmed to room temperature and stirred for 16 h. During this time, the reaction became light brown in color. The reaction was quenched with saturated $NaHSO_3$ (200 mL). The layers were separated and the organic layer was collected. The aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic fractions were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), then dried with anhydrous $MgSO_4$. After filtration, the combined solvents were removed under reduced pressure. Chromatography (9:1 hexanes:EtOAc) gave 1-farnesyl *p*-tolyl sulfone **7** (10.8 g, 67%).

***p*-Nitrobenzoyl Diepoxide 8c.** *trans,trans*-Farnesyl *p*-nitrobenzoate **6c** (20 g, 54 mmol)[13] was transferred into a three-necked 3.0 L flask. Then DMM:MeCN (2:1, 0.10 M, 500 mL) and $Na_2B_4O_7$ (0.05 M solution in 4×10^{-4} M Na_2EDTA, 0.15 M, 350 mL) were added, followed by the addition of Bu_4NHSO_4 (1.8 g, 5.4 mmol). D-Epoxone (7.0 g, 27 mmol) was added. The flask was equipped with a mechanical stirrer and two addition funnels. To one addition funnel was added Oxone (140 g, 220 mmol) dissolved in 4×10^{-4} M Na_2EDTA (400 mL). To the other addition funnel was added K_2CO_3 (112 g, 810 mmol) dissolved in distilled H_2O (400 mL). The flask was cooled to 0 °C and the Oxone and K_2CO_3 solutions were added simultaneously dropwise over a 1.25 h period. After the additions were complete, EtOAc (500 mL) was added to the reaction and transferred to a 3.0 L separatory funnel. After the organic layer was collected, the aqueous was extracted with EtOAc (750 mL). The combined organic fractions were dried with $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. Chromatography on silica gel (4:1 → 2:1 hexanes:EtOAc) provided diepoxide **8c** (dr = 4: 1) as a pale yellow oil (10.6 g, 49%), along with the monoepoxide (mixture of the 6,7- and 10,11-epoxides) (5.93 g, 28%). Additional amounts of diepoxide could be obtained by subjecting the monoepoxide to the same reaction conditions, using only 2.0 equiv of Oxone and 8.0 equiv of K_2CO_3. $[\alpha]^{23}_D$ +8.8 (*c* 1.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H), 5.52 (t, J = 7.2 Hz, 1H), 4.90 (d, J = 6.8 Hz, 2H), 2.75 (t, J = 6.0 Hz, 1H), 2.71 (m, 1H), 2.24 (m, 2H), 1.81 (s, 3H), 1.79−1.56 (m, 7H), 1.31 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 150.7, 142.5, 135.9, 130.9 (2×), 123.7 (2×), 118.5, 63.9, 62.8 (2×), 60.5, 58.6, 36.4, 35.4, 27.1, 25.0, 24.7, 18.4, 16.9, 16.8; IR (KBr) 2962, 1724, 1606, 1529, 1456, 1381, 1348, 1271, 1101, 1014, 874, 721 cm^{-1}; HRMS (ESI) [M + H^+] calcd for $C_{22}H_{29}N_1O_6$ 404.20676, found 404.20717.

Sulfonyl Diepoxide 9. 1-Farnesyl-*p*-tolyl sulfone **7** (3.6 g, 10 mmol) was transferred to a three-necked 1.0 L flask, to which was added DMM:MeCN (2:1, 0.067 M, 150 mL), $Na_2B_4O_7$ (0.05 M solution in 4×10^{-4} M Na_2EDTA, 0.091 M, 110 mL), Bu_4NHSO_4 (0.34 g, 1.0 mmol), and D-epoxone (1.3 g, 5.0 mmol) sequentially. The solution was cooled to 0 °C and vigorously stirred. The flask was equipped with two addition funnels. To one addition funnel was added Oxone (17 g, 28 mmol) dissolved in 4×10^{-4} M Na_2EDTA (140 mL). To the other addition funnel was added K_2CO_3 (15 g, 110 mmol) dissolved in distilled H_2O (140 mL). The Oxone and K_2CO_3

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solutions were added dropwise over a 2 h period. Upon completion of the additions, the reaction was allowed to stir for an additional 20 min, at which time H_2O (100 mL) and Et_2O (200 mL) were added. The layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL). The organic extracts were dried with $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. Chromatography on silica gel (2:1 → 1:1 hexanes:EtOAc) gave the diepoxy allylic sulfone **9** (dr = 5: 1) as a yellow oil (2.8 g, 71%). $[\alpha]^{23}_D$ 2.80 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.21 (t, J = 8.0 Hz, 1H), 3.78 (d, J = 8.0 Hz, 2H), 2.69 (m, 2H), 2.43 (s, 3H), 2.14 (m, 2H), 1.78−1.50 (m, 6H), 1.38 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 144.7, 135.9, 129.8 (2×), 128.6 (2×), 111.2, 64.0, 62.7, 60.5, 58.6, 56.2, 36.5, 35.3, 27.1, 25.0, 24.7, 21.8, 18.8, 16.8, 16.4; IR (KBr) cm^{-1} 2962, 2926, 1664, 1597, 1452, 1383, 1313, 1149, 1088, 744; HRMS (ESI) [M + H$^+$] calcd for $C_{22}H_{33}O_4S_1$ 393.20941, found 393.20941.

Diepoxy Allylic Bromide 10. To a solution of *p*-nitrobenzoate diepoxide **8c** (23 g, 57 mmol) dissolved in MeOH (0.50 M, 115 mL) was added K_2CO_3 (3.9 g, 29 mmol) all at once. The reaction was stirred for 15 min. After dilution with Et_2O (100 mL), the reaction was quenched by the addition of a saturated solution of NH_4Cl (250 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (2 × 250 mL). The organic extracts were combined and dried with $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. Prior to chromatography on silica gel, the mixture of diepoxy allylic alcohol product containing the poorly soluble byproduct methyl *p*-nitrobenzoate was dissolved in minimal EtOAc for loading onto the chromatography column. Methyl *p*-nitrobenzoate eluted from the column with 4:1 hexanes:EtOAc, and then flushing with 100% EtOAc provided the polar diepoxy allylic alcohol as an oil (12.8 g, 88%). $[\alpha]^{23}_D$ +11.0 (*c* 0.965, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.46 (m, 1H), 4.16 (d, J = 6.6 Hz, 2H), 2.76−2.71 (m, 2H), 2.21 (m, 1H), 2.16 (m, 1H), 1.79 (m, 1H), 1.70 (s, 3H), 1.68 (m, 3H), 1.60 (m, 3H), 1.60 (m, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 124.3, 64.1, 62.9, 60.5, 59.4, 58.7, 36.4, 35.3, 27.0, 24.9, 24.7, 18.8, 16.9, 16.4; IR (KBr) 3437, 2924, 1666, 1454, 1385, 1250, 1119, 1011, 872 cm^{-1}; HRMS (APCI) [M + H$^+$] calcd for $C_{15}H_{27}O_3$ 255.19547, found 255.19552.

This diepoxy allylic alcohol intermediate (12.8 g, 50 mmol) dissolved in THF (0.30 M, 170 mL) was cooled to −40 °C. Et_3N (10.5 mL, 76 mmol) was then added to the solution all at once, followed by addition of MsCl (4.71 mL, 60 mmol) all at once. The reaction was stirred for 30 min at −40 °C. After warming to 0 °C, flame-dried LiBr (13.1 g, 150 mmol) dissolved in THF (5.0 M, 30 mL) was added all at once. The reaction mixture was stirred for an additional 15 min before being diluted with Et_2O (200 mL) and quenched with H_2O (200 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (100 mL). The organic extracts were combined and dried with $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. To the crude mixture was added hexanes (100 mL), and the solids were filtered. After removal of the volatiles under reduced pressure, the analytically pure allylic bromide **10** (15.3 g, 96%) was obtained.[14] $[\alpha]^{23}_D$ +4.9 (*c* 0.85, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59 (t, J = 8.4 Hz, 1H), 4.02 (d, J = 7.8 Hz, 2H), 2.73 (m, 2H), 2.24 (m, 1H), 2.18 (m, 1H), 1.76 (s, 3H), 1.68 (m, 3H), 1.61 (m, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.6, 121.3, 63.9, 62.7, 60.5, 58.7, 36.4, 35.3, 29.4, 26.9, 25.0, 24.7, 18.8, 16.9, 16.1; IR (KBr) 2962, 1655, 1454, 1381, 1203, 1122, 876 cm^{-1}; HRMS (APCI) [M + H$^+$] calcd for $C_{15}H_{26}O_2Br_1$ 317.11107, found 317.11115.

Tetraepoxy Allylic Sulfone 11. The diepoxy allylic bromide **10** (1.8 g, 5.7 mmol) and diepoxy allylic sulfone **9** (1.6 g, 4.0 mmol) were dissolved in THF (0.05 M, 81 mL) and cooled to −78 °C. Then KO-*t*-Bu (1.0 M solution in THF, 5.3 mL, 5.3 mmol) was added to the solution via syringe pump over a 30 min period. The reaction mixture was stirred for 2 h at −78 °C. Then saturated $NaHCO_3$ (200 mL) was added to quench the reaction. The organic layer was collected and the aqueous layer was extracted with Et_2O (200 mL). The organic extracts were combined and dried with $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. Chromatography on silica gel (9:1 → 1.5:1 hexanes:EtOAc + 0.5% Et_3N) gave the tetraepoxy allylic sulfone **11** as an oil (1.96 g, 77%). $[\alpha]^{23}_D$ +13.8 (*c* 0.745, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 7.3 Hz, 2H), 5.01 (m, 2H), 3.73 (m, 1H), 2.69 (m, 4H), 2.44 (s, 3H), 2.40−2.24 (m, 2H), 2.20−2.00 (m, 4H), 1.80−1.50 (m, 12H), 1.62 (s, 6H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (2×), 137.8, 135.3, 129.6 (2×), 129.3 (2×), 119.5, 117.8, 64.9, 64.2, 64.0 (2×), 62.9, 62.7, 60.5, 58.6, 36.5, 35.8, 35.4, 35.3, 29.9, 27.5, 27.4, 27.0, 25.0 (3×), 24.8 (2×), 21.8, 18.9, 16.8 (2×), 16.6; IR (KBr) 2960, 2926, 2856, 1597, 1456, 1381, 1300, 1144, 1059, 1250, 874 cm^{-1}; HRMS (APCI) [M + H$^+$] calcd for $C_{37}H_{57}O_6S_1$ 629.38704, found 629.38761.

(3*R*,6*R*,7*R*,18*R*,19*R*,22*R*)-Squalene Tetraepoxide (*ent*-1). To a solution of tetraepoxy sulfone **11** (1.96 g, 3.1 mmol) in THF (0.10 M, 31 mL) was added $PdCl_2$(dppp) (370 mg, 0.62 mmol) at 0 °C. Lithium triethylborohydride ($LiBEt_3H$, 1.0 M solution in THF, 6.2 mL, 6.2 mmol) was then added dropwise to the solution over a 15 min period. The reaction mixture was stirred for an additional 40 min at 0 °C and then diluted with Et_2O (40 mL), followed by the addition of saturated NH_4Cl (50 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (50 mL). The combined organic fractions were dried with $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. Chromatography on silica gel (9:1 → 1:1 hexanes:EtOAc + 0.5% Et_3N) gave squalene tetraepoxide (*ent*-**1**) as a clear oil (944 mg, 64%) and recovered **11** (218 mg). $[\alpha]^{23}_D$ +15.1 (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (br s, 2H), 2.72 (m, 4H), 2.16−2.08 (m, 4H), 2.02 (t, J = 2.8 Hz, 4H), 1.78 (m, 2H), 1.70−1.52 (m, 8H), 1.62 (s, 6H), 1.32 (s, 6H), 1.28 (s, 6H), 1.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 125.0, 64.1, 63.2, 60.5, 58.6, 36.5, 35.5, 28.4, 27.5, 25.1, 24.9, 18.9, 16.9, 16.3; IR (KBr) 2960, 2926, 2858, 1452, 1379, 1323, 1250, 1120, 874 cm^{-1}; HRMS (ESI) [M + H$^+$] calcd for $C_{30}H_{51}O_4$ 475.37819, found 475.37829.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) We elected not to subject this sensitive allylic bromide to chromatography, as significant decomposition occurred (even with Et_3N buffering). Once prepared, the allylic bromide **10** was immediately used.