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A SHORT AND CONVERGENT ENANTIOSELECTIVE SYNTHESIS OF (3*S*)-2,3-OXIDOSQUALENE

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Summary: *A very useful synthesis of (3S)-2,3-oxidosqualene from geraniol, farnesol and E-1-bromo-4-chloro-3-methyl-2-butene is described which makes use of enantioselective and catalytic dihydroxylation of geranyl acetate and two E-stereospecific allylic coupling reactions mediated by E-prenylbarium reagents.*

(3*S*)-2,3-Oxidosqualene (**1**) is an important biogenetic precursor of steroids and polycyclic terpenoids.[1] It is a valuable intermediate for the study of sterol biosynthesis[2] and a useful substrate for enzymatic and chemical syntheses of polycyclic terpenoid natural products.[3] (3*S*)-2,3-Oxidosqualene and similar epoxides have been prepared utilizing chiral precursors,[4] asymmetric[5] or enzymatic[6] reactions, and resolution of enantiomers.[7] This study details a new approach to the convergent synthesis of (3*S*)-2,3-oxidosqualene employing asymmetric dihydroxylation and organobarium-mediated prenyl coupling reactions as key steps. This methodology is readily extendable to the general preparation of enantiomerically pure oxidosqualene analogs and should greatly simplify their synthesis.

The synthesis of **1** began with the preparation of chloro alcohol **2** from the corresponding acetate[8] (excess K_2CO_3, MeOH, 25 °C, 2 h, 80%), conversion to the corresponding mesylate (MsCl, Et_3N, CH_2Cl_2, -40 °C, 30 min), and *in situ* selective displacement (LiBr, THF) gave chloro bromide **3** in 60% yield. Organobarium coupling of **3** with two oligoprenoid fragments was chosen as the key C–C bond forming reaction for the synthesis due to high levels of regio and stereospecificity observed in similar prenyl coupling reactions.[9] The first coupling involved formation of organobarium reagent **4** from farnesyl chloride and Rieke barium in THF at -78 °C and subsequent reaction with **3** to give tetraprenoid **5** in 55% yield.[9]

Although the asymmetric dihydroxylation of squalene[10a] and farnesol[10b] are not sufficiently position-selective to be useful, the asymmetric dihydroxylation of geranyl acetate (1 mol % PYDZ ligand,[10c] 0.01 mol % K_2OsO_4, 4 equiv K_2CO_3, 4 equiv $K_3Fe(CN)_6$, 1 : 1 *t*-BuOH/H_2O, 4 °C, 12 h) gave diol **7** in 76% yield and >95% ee (determined by ^1H NMR integration of the mono MTPA ester derivative) with none of the other position isomer observed. The resulting diol acetate **7** was cleanly converted to (3*S*)-2,3-oxidogeraniol **8** by mesylation of the secondary alcohol (MsCl, pyridine, -40 °C, 30 min) followed by ring closure and hydrolysis of the acetate with K_2CO_3 in methanol (91% yield over two steps). This sequence is a considerable improvement over earlier methods for preparation of **8** requiring several more steps.[4c,6b,7b,11] The resulting allylic alcohol **8** was

transformed into the mesylate (1.3 eq MsCl, 1.5 eq Et_3N) and thence by *in situ* displacement into bromide **9** (LiBr, THF, 98% yield over two steps) for use in the barium mediated allylic coupling reaction. Formation of the organobarium reagent **10** from chloride **5** and Rieke barium in THF at -78 °C, followed by coupling with bromide **9**, provided (3*S*)-2,3-oxidosqualene (**1**) of 92% ee in 66% yield.

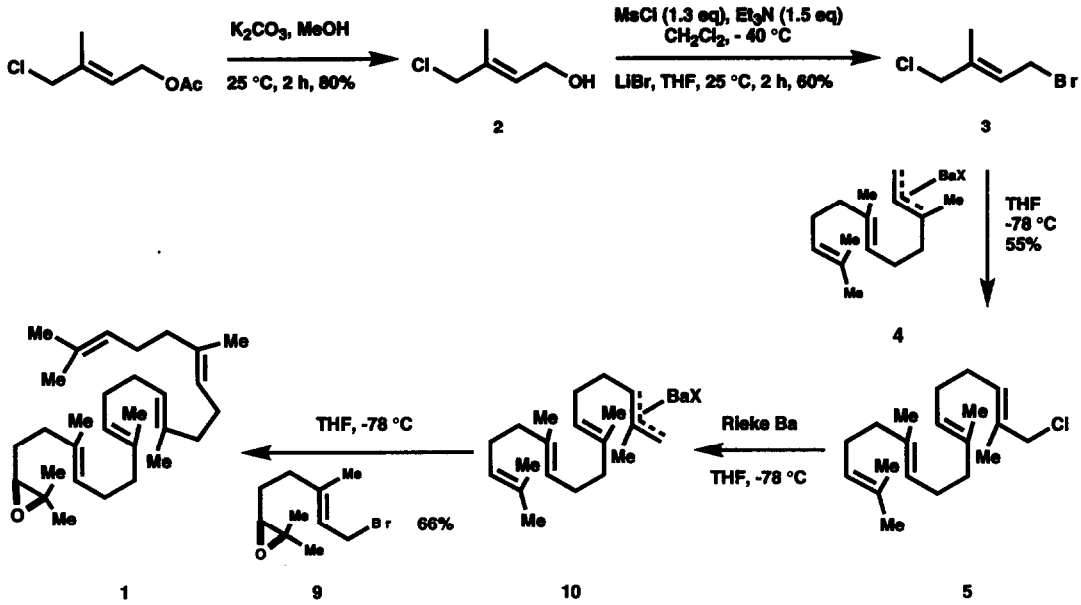
The synthesis of **1** which is outlined herein possesses a number of interesting and practical characteristics including: (1) the first simple and effective synthesis of 2,3-(*S*)-oxidogeraniol (**8**) and the use of this chiral substance in a three-component assembly of the C_{30}-skeleton of squalene, (2) the use of the *E* chloro bromide **3** as a linker which allows selective and direct attachment of the other two components for the assembly of the triterpenoid system, (3) an unusual flexibility and versatility which offers considerable advantage for the synthesis of numerous (3*S*)-2,3-oxidosqualene analogs.

This work also provides another demonstration of the utility of the asymmetric dihydroxylation reaction which works extremely well for *E*-1,2 disubstituted and trisubstituted olefins.[12] Use of the organobarium allylic coupling reaction with the chiral epoxide **9** allows modification of any site beyond the first C_{10} unit and provides ready access to analogs of **1** for the study of sterol biosynthesis and to intermediates for the synthesis of polycyclic oligoterpenoids using stereoselective cation-π cyclization reactions. Within this context, chiral fragment **9** emerges as a valuable reagent for the preparation of many chiral polyterpenoids.

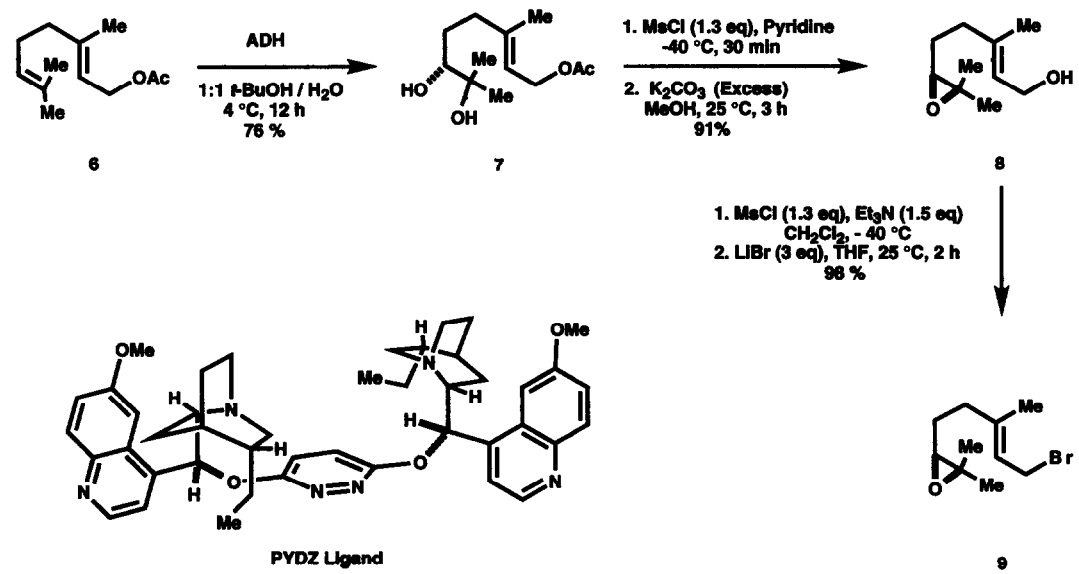
Tetraprenyl Chloride (5). Farnesyl chloride (0.845 g, 3.5 mmol in 4 mL of THF) was added to a -78 °C suspension of Rieke barium (prepared by reaction of 7.8 mmol of lithium biphenylide with 3.9 mmol of BaI_2 in 20 mL of THF), giving red prenyl barium complex **4**. *Caution:* under Ar with rigorous exclusion of air. After stirring for 20 min at -78 °C, the mixture was transferred via insulated cannula to a -78 °C solution of **3** (0.495 g, 2.7 mmol) in 4 mL of THF. After stirring 1 h at -78 °C, the mixture was partitioned between 100 mL of saturated aqueous NH_4Cl and 100 mL of ether. The ether extract was washed with 10 mL of brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by C_{18} chromatography (1% CH_2Cl_2/CH_3CN), giving farnesyl prenyl chloride (**5**) (0.455 g, 55%) as a colorless oil. IR (NaCl film): 2967, 2919, 2858, 1441, 1383, 1263, 686 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.52 (t, 1H, J = 7.1 Hz), 5.12 (m, 3H), 4.03 (s, 2H), 2.08 (m, 12H), 1.75 (s, 3H), 1.68 (s, 3H), 1.63 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.8, 134.9, 131.7, 131.2, 130.7, 124.3, 124.1, 123.5, 52.5, 39.7, 28.3, 27.5, 26.7, 26.5, 25.7, 17.6, 16.0, 15.9, 14.1 ppm. MS (EI): 308. Calculated for $C_{20}H_{33}Cl$: 308.2271; Observed: 308.2285.

(3*R*)-2,3Dihydroxygeranyl acetate (7). A mixture of DHQD–PYDZ ligand[10c] (0.19 g, 0.26 mmol), K_2OsO_4 (0.02 g, 0.05 mmol), $K_3Fe(CN)_6$ (25 g, 76.5 mmol), K_2CO_3 (10.6 g, 76.5 mmol), methanesulfonamide (2.42 g, 25.5 mmol), geranyl acetate (5 g, 25.5 mmol) and 300 mL of 1 : 1 *t*-butyl alcohol–water was stirred 12 h at 4 °C. Sodium sulfite (30 g) was added, and the mixture was concentrated under reduced pressure. The residue was taken up in 200 mL of CH_2Cl_2, washed with 100 mL of 2M KOH, dried over Na_2SO_4, filtered and concentrated. The residue was filtered through silica (2 : 1 ethyl acetate–hexane), giving (3*R*)-2,3-dihydroxygeranyl acetate (**7**) (4.3 g, 75%) as a colorless oil. The enantiomeric purity of **7** was determined to be >95% by ^1H NMR integration of the mono-MTPA ester. $[\alpha]_D^{23}$ +24.6° (c=1.75, EtOH) (lit. +25.1°).[11] IR (NaCl film): 3451, 2974, 1738, 1719, 1445, 1383, 1234, 1160, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.40 (dt, 1H, J = 1.2, 7.1 Hz), 4.59 (dd, 2H, J = 1.2, 7.1 Hz), 3.35 (dd, 1H, J = 1.9, 10.5 Hz), 2.43 (m, 1H), 2.1 (m, 1H), 2.08 (s, 3H), 1.63 (s, 3H), 1.58 (m, 1H), 1.48 (m, 1H), 1.21 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 142.0, 118.7, 78.0, 73.0, 61.3, 36.5, 29.4, 26.4, 23.2, 21.0, 16.4 ppm. MS (CI, NH_3): 248 (M+NH_4). Calculated for $C_{12}H_{22}O_4$+NH_4: 248.1862; Observed: 248.1853. Determination of enantiomeric purity: ^1H NMR integration of mono-MTPA Ester: ($CDCl_3$, 500 MHz): δ 5.30 ppm (t, 1H, (*S*)), 5.23 ppm (t, 1H, (*R*)).

Scheme 1



Scheme 2



PYDZ Ligand

(3*S*)-2,3-Oxidogeraniol (8). A 0 °C solution of (3*R*-2,3-dihydroxygeranyl acetate (**7**) (0.5 g, 2.17 mmol) and pyridine (0.35 mL, 4.34 mmol) in 5 mL of CH_2Cl_2 was treated with methanesulfonyl chloride (0.32 g, 2.82 mmol). After 30 min, the mixture was warmed to 25 °C and stirred for 3 h. An additional 1 mL pyridine was added, and the mixture was stirred for 8 h. The mixture was poured into a suspension of 5 g of K_2CO_3 in 20 mL of methanol and stirred for 6 h at 25 °C. The mixture was concentrated, diluted with 5 mL of water, extracted with ethyl acetate, washed with 10% aqueous $CuSO_4$, brine, dried over $MgSO_4$, filtered and concentrated, affording (3*S*)-2,3-oxidogeraniol (**8**) (0.34 g, 91%) as a light yellow oil. $[\alpha]_D^{23}$ -8.4° (c=1.38, MeOH) (lit. -7.9°).[11] IR (NaCl film): 3417, 2982, 2926, 1448, 1380, 1249, 1178, 1118, 1002 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.46 (dt, 1H, J = 1.2, 7.1 Hz), 4.16 (t, 2H, J = 6.0 Hz), 2.72 (t, 1H, J = 6.3 Hz), 2.18 (m, 2H), 1.69 (s, 3H), 1.65 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 124.0, 64.0, 59.1, 58.3, 36.2, 27.1, 24.8, 18.7, 16.2 ppm. MS (CI, NH_3): 188 (M+NH_4). Calculated for $C_{10}H_{18}O_2$+NH_4: 188.1650; Observed: 188.1649.

(3*S*)-2,3-Oxidosqualene (1). Tetraprenyl chloride **5** (0.285 g, 0.93 mmol in 2 mL THF) was added to a -78 °C suspension of Rieke barium (prepared by reaction of 2.06 mmol of lithium biphenylide with 1.03 mmol of BaI_2 in 7 mL THF), giving red prenyl barium complex **10** (under Ar). After stirring for 20 min at -78 °C, the mixture was transferred via insulated cannula to a -78 °C solution of **9** (0.166 g, 0.71 mmol) in 5 mL THF. After stirring for 1 h at -78 °C, the mixture was partitioned between 20 mL of saturated aqueous NH_4Cl and 200 mL of ether. The ether extract was washed with 50 mL water, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (5% ether–hexane), giving (3*S*)-2,3-oxidosqualene (**1**) (0.200 g, 66%) as a colorless oil. $[\alpha]_D^{23}$ -1.3° (c=0.85, MeOH) (lit. -1.8°).[5b] IR (NaCl film): 2962, 2923, 2855, 1447, 1377 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.11 (m, 5H), 2.70 (t, 1H, J = 6.1 Hz), 2.08 (m, 20H), 1.68 (s, 3H), 1.62 (s, 15H), 1.30 (s, 3H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.1, 134.9, 133.9, 131.3, 124.9, 124.4, 124.2, 64.2, 58.2, 39.7, 39.6, 36.3, 28.3, 27.5, 26.8, 26.7, 25.7, 24.9, 18.7, 17.7, 16.0, 15.9 ppm. MS (EI): 426. Calculated for $C_{30}H_{50}O$: 426.3861; Observed: 426.3841. Enantiomeric purity of 92% was determined by chiral HPLC (Chiralpak AS column, .05% *i*-propyl alcohol–hexane, 210 nm, (*R*) 6.2 min, (*S*) 8.9 min).[13]

References and Notes

1. Harrison, D. M. *Nat. Prod. Rep.* **1985**, *2*, 525-560; *Ibid.* **1988**, *5*, 387-415.
2. (a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429-6431. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025-4026. (c) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171-8172.
3. (a) Bujons, J.; Guajardo, R.; Kyler, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 604-606. (b) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005-7008.
4. (a) Mori, K.; Mori, H. *Tetrahedron* **1987**, *43*, 4097-4106. (b) Abdallah, M. A.; Shah, J. N. *J. Chem. Soc. Perkin Trans. I* **1975**, 888-894. (c) Yamada, S.; Oh-hashi, N.; Achiwa, K. *Tetrahedron Lett.* **1976**, 2557-2560. (d) Yamada, S.; Oh-hashi, N.; Achiwa, K. *Tetrahedron Lett.* **1976**, 2561-2564.
5. (a) Tani, K.; Hanafusa, M.; Otsuka, S. *Tetrahedron Lett.* **1979**, 3017-3020. (b) Corey, E. J.; Yi, K.-Y.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, 2319-2322.
6. (a) Fourneron, J. D.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1989**, *54*, 4686-4689. (b) Kodama, M.; Minami, H.; Mima, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1990**, *31*, 4025-4026.
7. (a) Boar, R. B., Damps, K. *Tetrahedron Lett.* **1974**, 3731-3732. (b) Boar, R. B.; Damps, K. *J. Chem. Soc. Perkin Trans. I* **1977**, 709-712. (c) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747-4756. (d) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1417-1420.
8. Oroshnik, W.; Mallory, R. *J. Am. Chem. Soc.* **1950**, *72*, 4608-4613.
9. Corey, E. J.; Shieh, W.-C. *Tetrahedron Lett.* **1992**, *33*, 6435-6438. See also Yanagisawa, A.; Halboue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5893-5895; **1991**, *113*, 8955-8956.
10. (a) Crispino, G. A.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 4273-4274. (b) this work. (c) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828-3829.
11. Eschenmoser, W.; Uebelhardt, P.; Eugster, C. H. *Helv. Chim. Acta.* **1983**, *66*, 82-91.
12. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771.

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