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Stereoselective Syntheses of 1,24-Dihydroxy Squalene 2,3;22,23-dioxides by Double Sharpless Epoxidation

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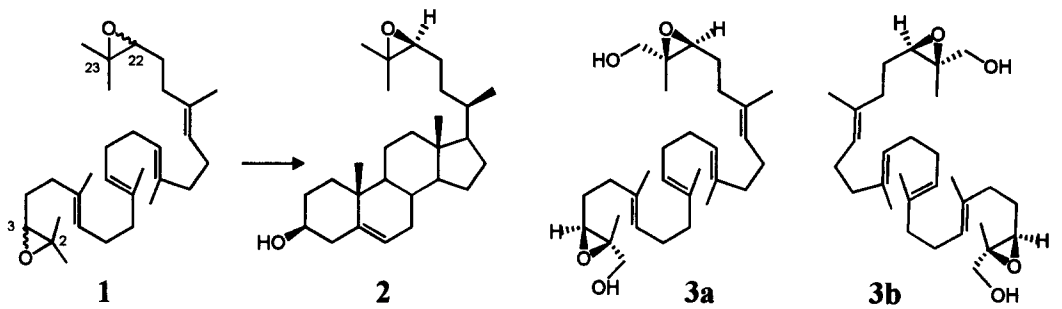
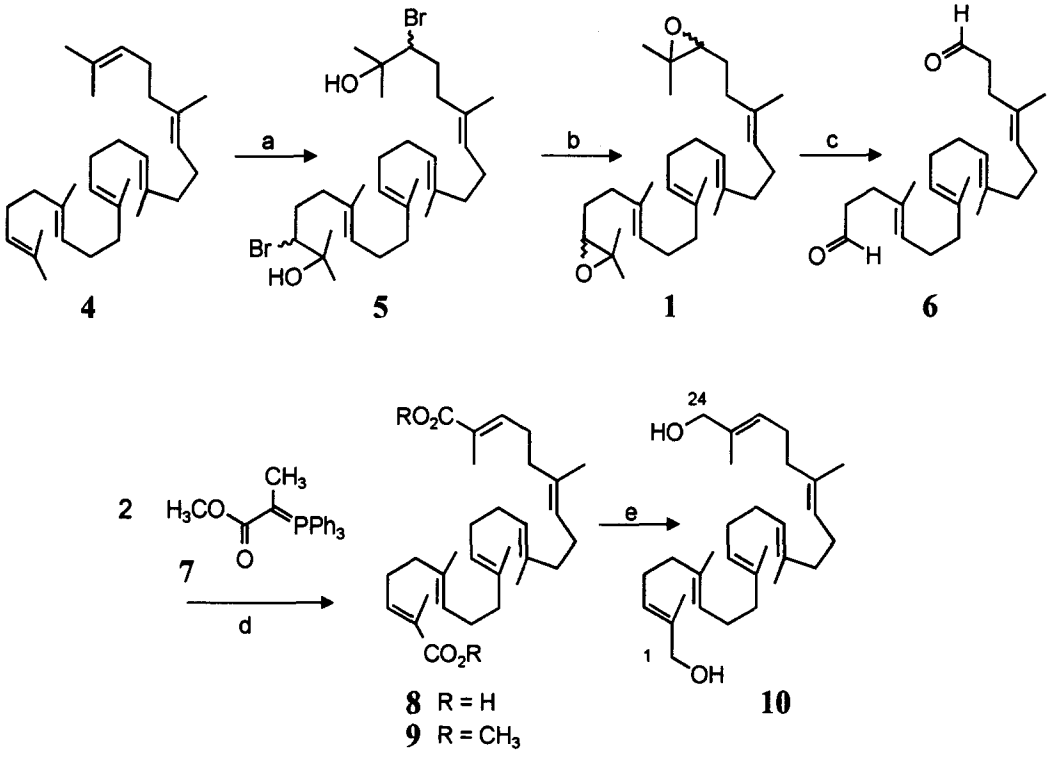
Abstract: A few step synthesis of the (all-E) squalene diol **10** from squalene **4**, its double Sharpless epoxidation to the (-)-dihydroxy squalene 2,3;22,23-dioxide **3a**, its enantiomer **3b**, and the formation of a tetradeutero derivative **12** is described. Copyright © 1996 Elsevier Science Ltd

Squalene 2,3:22,23-dioxides **1** have been transformed under enzymatic conditions into the tetracyclic triterpenes epoxycholesterol **2**[1] and α-onocerin[2] Thus its derivatives deserve attention as possible sterol biosynthesis inhibitors. Taking also into account that some squalene derivatives with polar end groups revealed properties as inhibitors of post-squalene biosynthesis[3], we were interested in the synthesis of the hitherto unknown dihydroxy squalene 2,3;22,23-dioxides **3a, 3b.**[4]



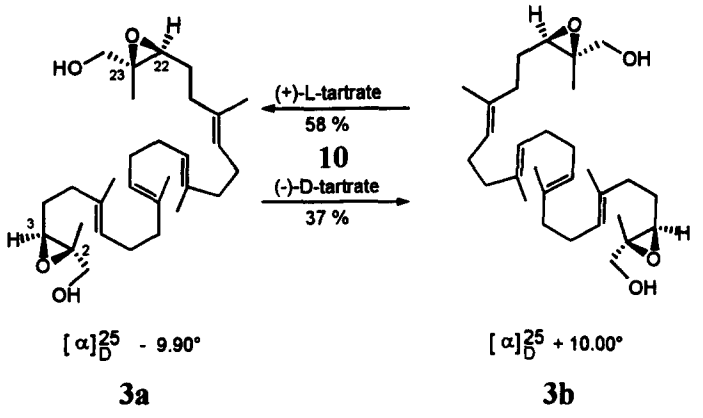
Double Sharpless epoxidation[6] of the 1,24-dihydroxy-squalene **10** was the method of choice for stereoselective syntheses of the desired dihydroxy squalene 2,3;22,23-dioxides. Yamada et al.[7] had prepared **10** from the readily available[8] squalene **4** by microbiological transformation to its 1,24-dicarboxylic acid **8** and subsequent $LiAlH_4$ reduction. We obtained 1,24-dihydroxy-squalene **10** from squalene **4** by a five step chemical procedure (Scheme 1), starting with van Tamelen's[9] elegant regioselective bromohydrine reaction. The bisbromohydrine **5** was separated from the monoproduct and then treated with K_2CO_3 in methanol at 20°C to give the stereoisomers of squalene dioxide **1** in high yield. Periodate degradation led to the dialdehyde **6.**

After its subjection to a twofold Wittig reaction with α-carbomethoxyethylidene triphenylphosphorane **7**, followed by repeated chromatography (silicagel, cyclohexane/ethylacetate 7:1), the (all-E)-dimethylester **9** was obtained.[10] Final reduction of **9** with $LiAlH_4$ led to the 1,24-dihydroxy-squalene **10**.[11]



Scheme 1.[4] Synthesis of 1,24-dihydroxy-squalene **10**
a: NBS/THF, 0°C, 27 %; b: K_2CO_3/MeOH, 2 h, 20°C, 87 %; c: H_5IO_6/Et_2O, 2 h, 20°C, 90 %; d: **7**/CH_2Cl_2, 6 h, reflux under argon, 62 %; e: $LiAlH_4/Et_2O$, 6 h, 0°→20°C, 77 %.

The double Sharpless epoxidation of the 1,24-dihydroxy squalene **10** (Scheme 2) revealed an interesting parallel to a recent analogous enantioselective synthesis of a 1,5-bisepoxide.[12] Thus, the double enantioselective bisepoxidation of **10** could only be achieved with the catalytic variant of the Sharpless reaction[13] and not under stoichiometric conditions. With (+)-L-tartrate the levorotatory bisepoxide **3a** was obtained with 58% yield after chromatography.[14a] According to the mechanism of the Sharpless epoxidation[6] it has to be the (2S,3S,22S,23S)-2,3:22,23-diepoxysqualene-1,24-diol **3a**. Its ^1H NMR spectrum (Figure 1) reveals a triplet at 3.02 ppm for the epoxy protons and two doublets at 3.55, 3.67 ppm (J = 12.1 Hz) for the diastereotopic protons of the E-configurated CH_2OH groups. Epoxidation of 1,24-dihydroxy squalene **10** (Scheme 2) with the (-)-L-tartrate reaction variant led to the enantiomeric 2R,3R,22R,23R bisepoxide **3b**.[14b]



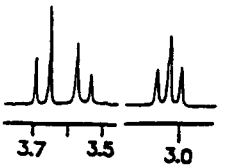
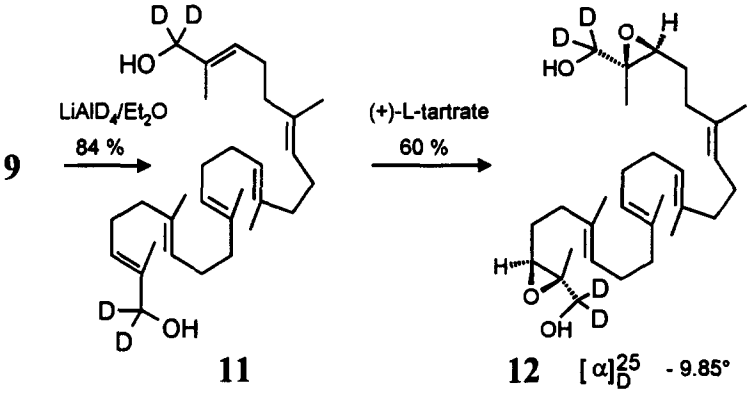


Figure 1. Part of the ^{1}H NMR spectrum of **3a** (300 MHz, $CDCl_3$, ppm)

Scheme 2. Sharpless epoxidations of 1,24-dihydroxysqualene **10**

With respect to intended incorporation experiments with enzyme preparations the tetradeuterated dihydroxy squalene dioxide **12** was also synthesized by analogous procedures (Scheme 3). The good yields, spectroscopic data, and the $[\alpha]_D$ value, corresponded exactly to **3a**. In its proton decoupled ^{2}H NMR spectrum the tetradeutero compound **12** revealed only two singlets at $\delta = 3.51$ and 3.62 ppm for the diastereotopic deuterons of the CD_2OH groups.[15]



Scheme 3.[4] Synthesis of (-)-(2S,3S,22S,23S)-[1,1,24,24-D_4]-2,3;22,23-diepoxysqualene-1,24-diol **12**

Due to the excellent availability of the steroid precursor squalene **4**, its easy chemical transformation into the 1,24-dihydroxy compound **10** together with the highly selective Sharpless epoxidations a new group of polar, optically active squalenoid dioxides **3a**, **3b**, **12** is now ready for use. This may concern investigations on postsqualene steroid biosynthesis for scientific and medicinal purposes as well as for applications in plant protection. Some preliminary results will be published separately.

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10. Before the synthesis of **9** as described in Scheme 1 we carried out a twofold Wittig-Horner reaction of the dialdehyde **6** with $(EtO)_2PO\text{-}CH(CH_3)\text{-}CO_2Et$, to give the corresponding bis-ethylester of **9**. It resulted in a 1:7 mixture of the two E,Z isomers and the E,E isomer, which was difficult to separate. Better results were then achieved by the twofold Wittig reaction (Scheme 1), after which the pure (E,E)dimethylester **9** could be obtained with 62% yield by repeated chromatography (cyclohexane/ethylacetate 7:1 on silicagel 60, Merck). Data for **9**: Colorless oil, TLC (cyclohexane/ethylacetate, 7:1): R_f = 0.37. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (m, 12H, CH_3), 1.83 (s, 6H, 2-CH_3, 23-CH_3), 1.90-2.32 (2m, 2O*H*, CH_2), 3.73 (s, 6H, CO_2CH_3), 5.07-5.20 (m, 4H, C*H*), 6.74 (t, *J* = 7.2 Hz, 2H, 3-*H*, 22-*H*). MS (70 eV): m/z (%) = 498 (8) [M^+], 467 (8) [M^+ - OCH_3], 439 (8) [M^+ - CO_2CH_3], 149 (66), 93 (100).
11. Data for **10**: m.p. 47-48°C (Lit.[7]: 48°C). TLC (cyclohexane/EtOAc, 1:1): R_f = 0.40; (CH_2Cl_2/Et_2O/Et_3N, 49:49:2): R_f = 0.56. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 69.0 (t, C-1, C-24). MS (70 eV) : *m/z* (%) = 442 (3) [M^+], 426 (1) [M^+ - H_2O], 289 (6) [M^+ - $C_{10}H_{17}O$], 95 (64), 81 (80), 55 (100).
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14. a) Data for **3a**: $[\alpha]_D^{25}$ = -9.90 (c = 3.00, $CHCl_3$). TLC (silica gel, CH_2Cl_2/ether/Et_3N 49:49:2): R_f = 0.31. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.27 (s, 6H, 2-CH_3, 23-CH_3), 1.60 (s, 6H, 2 CH_3), 1.62 (s, 6H, 2 CH_3), 1.57-2.25 (2m, 22H, CH_2, O*H*), 3.02 (t, *J* = 6.3 Hz, 2H, 3-*H*, 22-*H*), 3.55 and 3.67 (2d, *J* = 12.1 Hz, 4H, 1-*H*, 24-*H*), 5.09-5.21 (m, 4H, C*H*).MS (70 eV): (*m/z*) (%) = 456 (1) [M^+ - H_2O], 111 (60), 93 (98), 81 (100), 55 (88). b) Data for **3b**: $[\alpha]_D^{25}$ = +10.00 (c = 0.70 in CH_2Cl_2). Properties identical with **3a**.
15. Data for **12**: $[\alpha]_D^{25}$ = -9.85 (c = 1.00 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 6H, 2-CH_3, 23-CH_3), 1.60 (s, 6H, CH_3), 1.62 (s, 6H, CH_3), 1.57-2.25 (2m, 22H, CH_2, O*H*), 3.02 (t, *J* = 6.3 Hz, 2H, 3-*H*, 22-*H*), 5.09-5.21 (m, 4H, C*H*). ^2H NMR (55.28 MHz, $CHCl_3$, ^1H decoupled): δ = 3.51 and 3.62 (CD_2OH).

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