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Synthesis and Biomimetic Rearrangement of a Chiral Diterpene Dioxide

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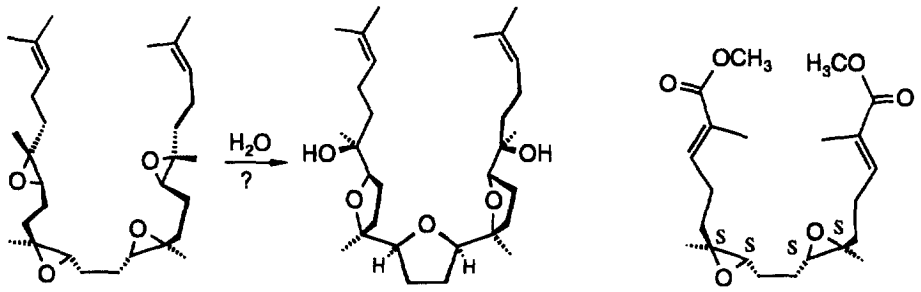
Abstract: As part of a biomimetic approach towards the marine triterpene teurilene (**2**), the synthesis of the chiral diepoxide **3** is described. Aiming at the synthesis of the squalene tetraepoxide **1**, double Sharpless epoxidation led to the intermediate bisglycidic alcohol **7** being subject to a stereochemical analysis.

The discovery of the steroid biosynthesis from squalene oxide[1] has found exciting continuation as an expanding principle in recent years. For numerous terpenoids, 1,5-oligoepoxides are discussed as biogenetic precursors.[2] Typical examples are biologically active polycyclic triterpenes like magireol[3a] and teurilene **2**[3b] from the red alga *Laurencia obtusa* whose structures suggest formation by rearrangement of the hitherto unknown squalene tetraepoxide **1**. In this respect, the diterpene dioxide **3** deserves special attention as a model compound for biomimetic rearrangements and as a synthon for terpenoid cyclic ethers. In the following we shall describe the synthesis of the chiral diterpene **3** applying a double Sharpless epoxidation[4a] as the key step. The teurilene related *meso*-compound **12** was formed from **3** in a biomimetic, acid catalyzed epoxide cascade.

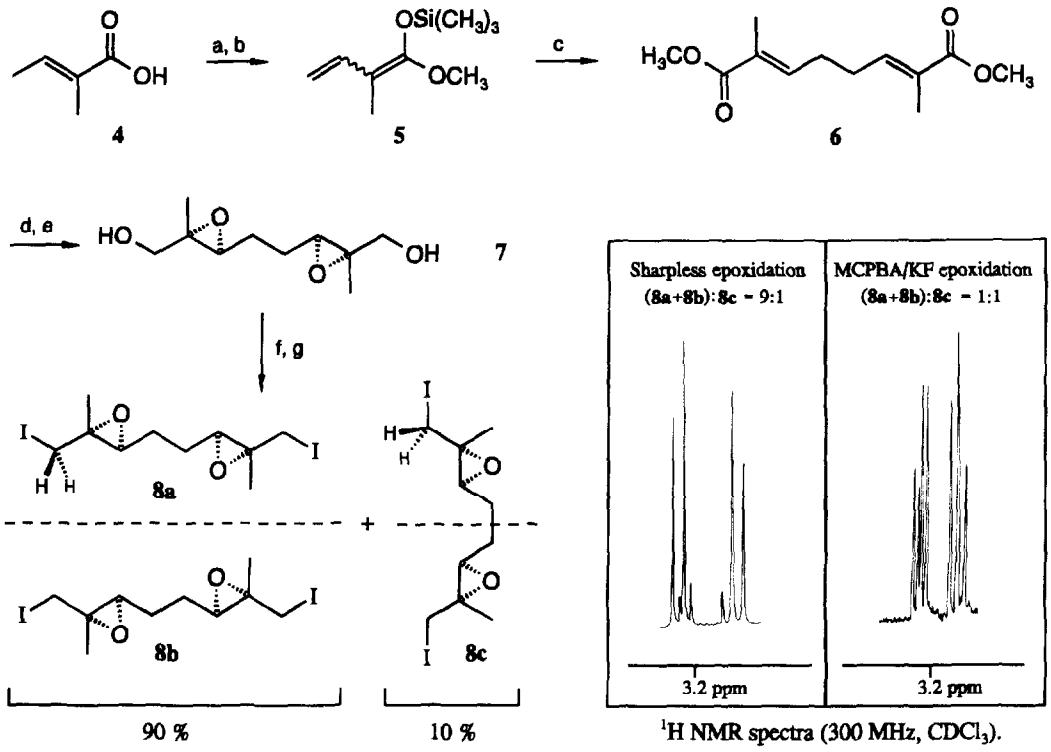


1 **2** **3**

The titanium mediated γ-dimerization of the silylvinylketene acetal **5** obtained from tiglic acid (**4**) proved to be an efficient way to prepare stereochemically pure, crystalline bisallylic ester **6** in a yield of 90 % (scheme 1).[5] The alternative double Wittig reaction starting from succinic aldehyde yielded an undesired 9:1 mixture (GC analysis) of **6** and its (*E,Z*)-isomer. After reduction of **6** with $LiAlH_4$, the resulting (*E,E*)-bisallylic alcohol was subject to a double Sharpless epoxidation giving rise to the bisglycidic alcohol **7**[6]. Probably due to the close neighbourhood of the two epoxide rings, **7** could only be obtained under catalytic[4b] but not under stoichiometric reaction conditions.

We were able to separate the chiral diepoxy diiodides **8a** and **8b** from the *meso*-form **8c** on an analytical scale determining the overall diastereomeric excess after the two epoxidation steps to be 80% (GC analysis). Scheme 1

shows the ^{1}H NMR signals of the diastereotopic iodomethyl protons for the product of the double asymmetric epoxidation and for the 1:1-diastereomeric mixture obtained using *m*-chloroperbenzoic acid (MCPBA)/KF as epoxidizing agent[7]. The average stereoselectivity of each catalytic Sharpless epoxidation can be calculated to 89% which is slightly lower than the *ee* values described for trisubstituted allylic alcohols. Assuming that the first epoxidation proceeded with an *ee* of 92 %, the presence of the first chiral oxirane would have diminished the diastereoselectivity of the second epoxidation.

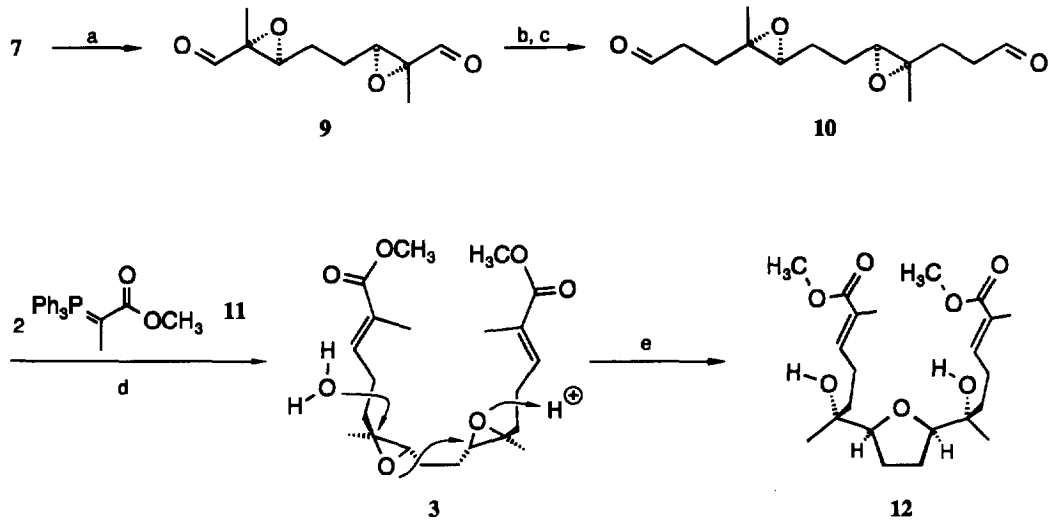


Scheme 1. Synthesis and stereochemical analysis of the central diepoxy unit. a: $CH_3OH/BF_3{\cdot}Et_2O$, reflux, 24 h, 70 %; b: LDA, THF, -65 °C, 2 h; TMSCl, -65 °C to 15 °C, 2h, 61 %; c: $TiCl_4$, CH_2Cl_2, 0 °C, 90 %; d: $LiAlH_4$, Et_2O, 80 %; e: TBHP, 5 mol% $Ti(O^iPr)_4$, 7 mol% L(+)-DET, CH_2Cl_2, 4 Å sieves, -25 °C, 6 h; $^nBu_3P$, citric acid, 85 %; f: *p*-TosCl, pyridine, CH_2Cl_2, 0 °C, 4 h, 50 %; g: NaI, acetone, reflux, 12 h, quant. conversion, 52 % isolated product.

Oxidation of **7** to its corresponding bisaldehyde **9** with Collins' reagent[8] proceeded smoothly (scheme 2). After an *in situ* double Wittig reaction with two equiv. of the phosphorane Ph_3P=CH-CHO and subsequent bis-hydrogenation of the resulting bisvinylogous aldehyde employing Rh/Al_2O_3 as a catalyst, the saturated aldehyde **10** was obtained in a satisfying yield. Reaction of **10** with two equiv. of the phosphorane **11** led us to the diester **3**[9].

3 was exposed to *p*-TosOH in THF/water (9:1) for 2 d, yielding a compound the spectroscopical data of which were in complete accordance with the dihydoxy tetrahydrofuran **12**[10]. Its FDMS spectrum clearly indicated the uptake of one molecule of water and the symmetry of **12** caused eleven signals in the ^{13}C NMR spectrum. Instead of the two

peaks of **3** corresponding to the four oxirane carbon atoms (at δ = 60.3 ppm and at δ = 62.7 ppm in $CDCl_3$), resonances at δ = 73.4 ppm (quaternary carbon atoms) and at δ = 85.2 ppm (α-THF carbon atoms) were observed.



Scheme 2. Synthesis and rearrangement of the diterpenoid diepoxide **3**. a: CrO_3·2Py, CH_2Cl_2, 4 Å sieves, 0 °C, 1 h, quant. conversion; *in situ* b: Ph_3P=CHCHO, CH_2Cl_2, diethyl amino polystyrene, reflux, 4 h, 63 %; c: H_2, Rh/Al_2O_3, 1 atm, 24 h, 71 %; d: **11**, CH_2Cl_2, 24 h, 30 %; e: H_2O, *p*-TosOH, THF, 2 d, 36 %.

The formation of **12** is one of the few synthetic examples of an epoxide cascade involving an acid catalyzed, intermolecular attack of a water molecule.[11] The bidirectional synthetic strategy leading to the diepoxy diester **3** in nine steps with an overall yield of 4.2 % appears to provide an efficient access to terpenoid oligoepoxides being of interest as precursors of biologically active, natural tetrahydrofuran systems.

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6. Hoye et al.[2c] had described an interesting alternative synthesis of **7** starting from 1,5-cyclooctadiene with convincing but not complete characterization of the end product. Due to the water solubility of **7**, our work-up was as follows. After quenching, the suspension was stirred at 0 °C for 30 min and then filtered through a Kieselguhr pad. The evaporation residue was partitioned between H_2O/$^iPr_2O$ followed by exhaustive extraction of the aqueous phase with $^iPr_2O$ and Et_2O. Chromatography on silica gel (EtOAc/acetone, 4:1) yielded **7** as a colourless oil solidifying at -30 °C; m. p. 28-32°C, $[\alpha]_D^{20}$ = -20.0 (*c* = 2.54, methanol). - TLC (ethyl acetate/acetone, 4:1): R_f = 0.38. - IR (neat, NaCl): $\tilde{\nu}$ = 3300 cm^{-1} (br., OH), 2860 (CH), 1620, 1380, 1025. - ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 6H, 2 CCH_3), 1.76 (m, 4H, -CH_2CH_2-), 2.19 (br, 2H, 2 CH_2OH), 3.09 (dd, *J* = 5.5, 7.7 Hz, 2H, epoxide-*H*), 3.58, 3.65 (2d, *J* = 12.2 Hz, 4H, 2 CH_2OH). - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.2 (q, 2 CCH_3), 25.4 (t, -CH_2CH_2-), 59.8 (d, 2 *C*H, epoxide), 61.5 (s, 2 *C*, epoxide), 64.4 (t, CH_2OH). - MS (NH_3-CI, compound was silylated using MSTFA): *m/z* (%) = 364 (100) [$(M + NH_4)^+$], 347 (37) [$(M + 1)^+$], 329 (16), 274 (27) [347 - $Si(CH_3)_3$], 257 (61), 239 (20), 234 (51), 217 (81). - $C_{10}H_{18}O_4$ (202.3): calcd. C 59.39, H 8.97; found C 59.16, H 8.74.
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9. **3**: $[\alpha]_D^{20}$ = -20.9 (*c* = 6.30, THF). - TLC (CH_2Cl_2/ethyl acetate, 5:1): R_f = 0.40. - IR (neat, NaCl): $\tilde{\nu}$ = 2930 cm^{-1} (CH), 1705 (C=O), 1430, 1240, 1185. - UV (CH_2Cl_2): λ_{max} (lg ε) = 230 nm (4.072). - ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 6H, 2 oxirane-CH_3), 1.5-1.7 (m, 8H, -CH_2CH_2- and 2 =$CHCH_2CH_2$), 1.84 (d, *J* = 1.1 Hz, 6H, 2 =$CHCH_3$), 2.28 (ddd, *J* = 7.4 Hz, 4H, =$CHCH_2CH_2$), 2.79 (dd, *J* = 7.7, 5.5 Hz, 2H, 2 oxirane-*H*), 3.73 (s, 6H, 2 OCH_3), 6.72 (tq, *J* = 1.4, 7.4 Hz, 2H, 2 =CH). - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.3 (q, 2 oxirane-CH_3), 16.5 (q, 2 H_3CC=), 24.3 (t, 2 CH_2), 25.7 (t, -CH_2CH_2-), 37.3 (t, 2 CH_2), 51.7 (q, 2 OCH_3), 60.3 (s, 2 *C*, oxirane), 62.7 (d, 2 *C*H, oxirane), 126.4 (s, 2 H_3CC=CH), 141.1 (d, 2 H_3CC=*C*H), 168.3 (s, 2 *C*=O). - MS (NH_3-DCI): *m/z* (%) = 412 (100) [$(M + NH_4)^+$], 395 (34) [$(M + 1)^+$], 377 (22), 363 (14). - $C_{22}H_{34}O_6$ (394.5): calcd. C 66.98, H 8.69; found C 66.60, H 8.90.
10. **12**: TLC (cyclohexane/EtOAc, 2:1): R_f = 0.13. - IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 2968, 2951, 2931, 1714 (C=O), 1649, 1460, 1437, 1283, 1257, 1082. - ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 6H, 2 C(OH)CH_3), 1.4-1.7 (2m, 4H, 2 CH_2), 1.84 (s, 6H, 2 CH=CCH_3), 1.88 (m, 4H, 2 β-THF-*H*), 2.25 (br. m, 6H, 2 CH_2 and 2 O*H*), 3.73 (s, 6H, 2 OCH_3), 3.77 (m, 2H, 2 α-THF-*H*), 6.75 (td, *J* = 1.3, 6.1 Hz, 2H, 2 *C*H=CCH_3). - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.3 (q, 2 CH=*C*CH_3), 22.9 (t, 2 CH_2), 23.9 (q, C(OH)CH_3), 25.8 (t, 2 CH_2), 36.9 (t, 2 β-THF-CH_2), 51.6 (q, 2 OCH_3), 73.4 (s, 2 *C*(OH)CH_3), 85.2 (d, 2 α-THF-*C*), 127.8 (s, 2 CH=*C*CH_3), 142.1 (d, 2 *C*H=CCH_3), 166.6 (s, 2 *C*=O). - MS (NH_3-DCI): *m/z* (%) = 430 (38) [$(M + NH_4)^+$], 412 (9) [M^+], 395 (100), 377 (8), 297 (27), 171 (15). - MS (FD): *m/z* (%) = 413 (42) [$(M + H)^+$], 241 (100), 171 (37) [M - 241], 127 (30).
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