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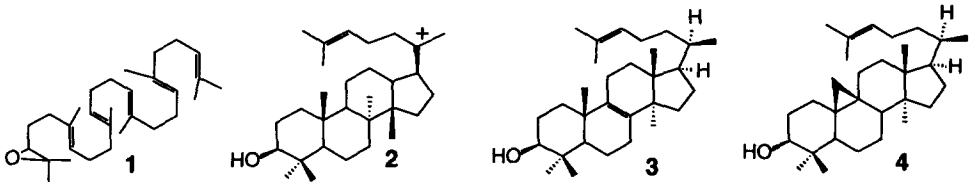
Synthesis of (±)-(15E)&(15Z)-16-Oxa-2,3-oxidosqualenes

Jeongho Park, Changhee Min,[+] Howard Williams, and A.I. Scott*

Center for Biological NMR, Department of Chemistry, Texas A&M University, College Station, TX 77843-3255.
[+]Department of Chemistry, Harvard University, Cambridge, MA 02138.

Abstract: As potential inhibitors of oxidosqualene cyclase (OSC) (±)-(15E)&(15Z)-16-oxa-2,3-oxidosqualenes ((**9**)&(**10**)) were synthesized by the Wittig-Horner reaction from diphenylphosphinoyl-1-ethyl-geranyl ether (**5**) and the epoxy aldehyde (**6**) . An efficient synthetic method for the Wittig-Horner reagent (**5**) was developed.

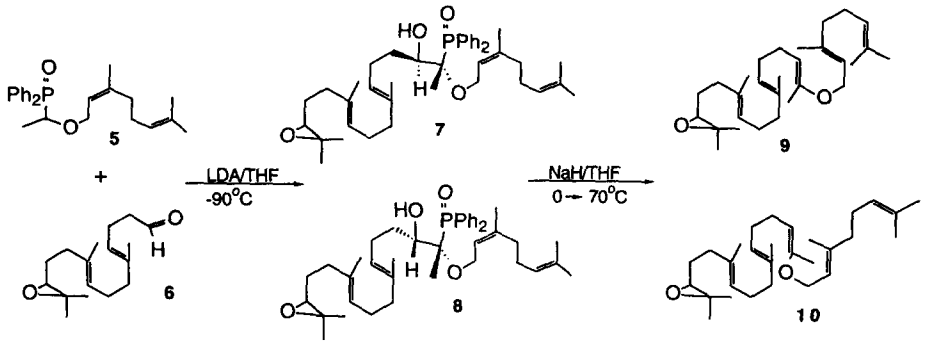
2,3-Oxidosqualene cyclases (OSC) catalyse the cyclization reaction of (3S)-2,3-oxidosqualene (**1**) to lanosterol (**3**) in animals and fungi and to cycloartenol (**4**) in plants via a cationic protosterol intermediate (**2**).



1 **2** **3** **4**

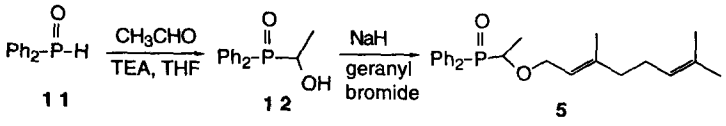
Subsequent enzymatic reactions convert (**3**) and (**4**) to sterols such as ergosterol, cholesterol, and stigmasterol which play an important roles as structural elements of animal cell membranes, regulators, and essential hormones in living organisms. The development of inhibitors of oxidosqualene cyclase[1] in addition to other inhibitors of sterol biosynthesis might produce selective drugs or herbicides. Numerous mechanism-based inhibitors,[2] thio analogue inhibitors,[3] imino or amine analogue inhibitors,[4] and epoxy or ether analogue inhibitors [5] have already been developed. We now describe the synthesis of (±)-(15E)&(15Z)-16-oxa-2,3-oxidosqualenes as potential OSC inhibitors. The enol ethers (**9**) and (**10**) were synthesized by the Wittig-Horner reaction from diphenylphosphinoyl-1-ethyl-geranyl ether (**4**) and the epoxy aldehyde (**5**) (Scheme I).[6]

Scheme I



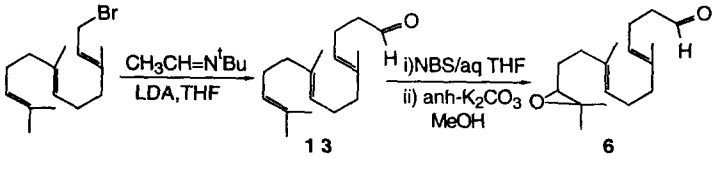
Since general procedures[7] were not applicable to synthesis of the Horner-Wittig reagent (**5**), the latter was synthesized by modification of the synthetic method for diethylphosphorylmethanol.[8] (Scheme II).

Scheme II



Treatment of diphenyl phosphine oxide (**11**) with acetaldehyde in the presence of a catalytic amount of TEA gave diphenyl phosphinoyl-1-ethanol (**12**) (96%). The coupling of geranyl bromide and the phosphinoyl alcohol (**12**) generated phosphinoyl ether (**5**) (50%), which was purified by recrystallization from hexane at -20°C. Aldehyde (**13**) was synthesized by two carbon elongation using the metalloenamine coupling reaction. The imine was generated from acetaldehyde and t-butylamine in the presence of 0.3 equivalent of anhydrous potassium carbonate.[9] Selective epoxidation (via the bromohydrin intermediate) produced the epoxy aldehyde (**6**).[7c] (Scheme III).

Scheme III



Coupling of phosphinoyl ether (**5**) and epoxy aldehyde (**6**) at -90°C generated two stereoisomers (1.1:1 ratio, R_f=0.35 (threo) and 0.5 (erythro) in hexane:ethyl acetate=1:1) of the β-hydroxy phosphine oxides (total 34%) (**7**) and (**8**). Treatment of these isomers with NaH gave rise to the E-enol ether (**9**) from threo (**7**) and the Z-enol ether (**10**) from erythro (**8**).[10] The two enol ethers were identified by ^{13}C-NMR

assignment,[11] the chemical shift (109.84 ppm) of the β-carbon of the Z-enol ether (**10**) appearing at 12.71 ppm downfield from that (97.13 ppm) of the E-enol ether (**9**).[12]

Inhibition studies are now in progress using the E-enol ether (**9**) which has the same geometry as squalene oxide.

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12. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker-WM300MHz spectrometer with TMS as an internal standard, $CDCl_3$ as solvent, chemical shift in ppm, coupling constants J in Hz.

E-enol ether (7);^{1}H NMR ($CDCl_3$): δ 1.23 (s, 3H), 1.27 (s, 3H), 1.58 (s, 9H), 1.64 (s, 3H), 1.65 (s, 3H), 1.76 (s, 3H), 1.97 - 2.07 (m, 16H), 2.68 (t, 1H, J= 6.2 Hz), 4.13 (d, 2H, J=6.4 Hz), 4.37 (t, 1H), 5.07 (br, 1H), 5.14 (br, 2H), 5.38 (t, 1H).^{13}C NMR ($CDCl_3$): δ 15.98, 16.03, 16.36, 16.52, 17.66, 18.72, 24.88, 25.66, 26,35, 26.66, 27.39, 27.45, 29.27, 36.29, 39.55, 39.66, 58.28, 63.43, 64.17, 97.13, 120.08, 123.95, 124.22, 124.88, 131.62, 133.99, 135.12, 139.91, 152.44. MS (+FAB): m/e=429 (M^{+}+1).

Z-enol ether (8); ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 3H), 1.28 (s, 3H), 1.58 (s, 9H), 1.64 (s, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.96 - 2.07 (m, 16H), 2.68 (t, 1H, J=6.3 Hz), 4.23 (d, 2H, J=6.6 Hz), 4.46 (t, 1H, J=6.9 Hz), 5.07 (br, 1H), 5.12 (br, 2H), 5.34 (t, 1H, J=6.5 Hz).^{13}C NMR ($CDCl_3$): δ 15.98, 16.04, 16.46, 17.68, 18.20, 18.73, 24.90, 25.17, 25.69, 26.32, 26.67, 27.42, 28.36, 36.29, 39.52, 39.66, 58.38, 64.23, 64.73, 109.84, 120.88, 123.91, 124.55, 124.95, 131.66, 133.94, 134.92, 139.68, 150.07. MS (+FAB): m/e= 429 (M^{+}+1).

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