culations carried out on the 3-21G optimized geometries using a 6-31G* basis and many-body perturbation theory to second order to calculate the electron correlation energy (Table II). However, the agreement between theory and experiment is not as good at the 3-21G level[5] (Table II) with the relative energy of tautomer **3** predicted to be so high that it would be unobservable in the gas phase.

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Registry No. C1, 71-30-7; **C2**, 66398-98-9; **C3**, 66460-21-7.

Supplementary Material Available: Three tables of observed and calculated transition frequencies used to derive the data in Table I (10 pages). Ordering information is given on any current masthead page.

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Vinyl Group Rearrangement in the Enzymatic Cyclization of Squalenoids: Synthesis of 30-Oxysterols

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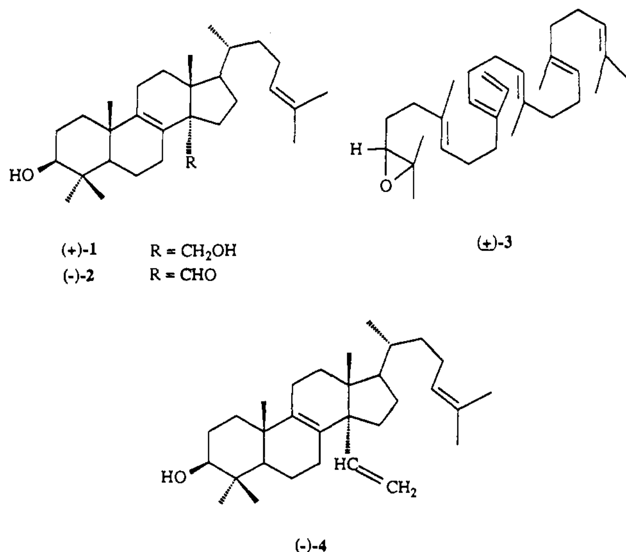
There is currently an intense search for agents which inhibit HMG-CoA reductase due to their potential use as hypocholesteremic drugs.[1] The tentative identification of 30-hydroxylanosterol (**1**) and its corresponding aldehyde **2** in mevalonate-treated cell cultures suggested that they may be natural receptor-mediated feedback inhibitors of HMG-CoA reductase.[2] This view is supported by studies which have shown that the 24,25-dihydro derivatives of **1** and **2** strongly suppress HMG-CoA reductase activity[3] presumably at the level of transcription that involves binding of the sterol to a specific, intracellular receptor.[3b,4]

We wish to report the first synthesis of the putative natural oxysterols (+)-**1** and (−)-**2** where the key step involves the enantioselective enzymatic cyclization of the internally functionalized substrate **3** using bakers' yeast to obtain the lanostatriene (−)-**4**. Moreover, the enzymatic conversion of the C-10 vinylic substrate **3** to **4** is the first demonstration of *the remarkable ability of the oxidosqualene-lanosterol cyclase to rearrange a substituent other than a hydrogen or methyl group* along with the normal sequence of migrations which generates the natural lanosterol skeleton.

The substrate for the enzymatic reaction was constructed by the convergent sequence shown in Scheme I.[5] The anion from methyl 2-[(bis(trifluoroethyl)phosphono]acetate[6] was alkylated with homogeranyl iodide[7] to afford ester **5** which was converted,



via the standard terminal epoxidation procedure,[8] to the epoxy ester **6**. Oxidation of the farnesylic alcohol **7**[9] to the corresponding aldehyde **8** followed by the stereoselective coupling[6] of **8** to the anion from ester **6** and $KN(TMS)_2$/18-crown-6 gave a 58% yield of the α,β-unsaturated ester **9** after chromatographic separation of a 6.5:1 mixture of Z/E-isomers. Reduction of **9** using AlH_3[10] in THF afforded the epoxy allylic alcohol **10**[11] which was transformed to the aldehyde **11** by PDC[12] in DMF. Lastly, condensation of aldehyde **11** with 1.5 equiv of $Ph_3P{=}CH_2$ produced the desired vinylic substrate **3**.

The enzymatic cyclization of the substrate to the desired lanostane intermediate involved the anaerobic incubation of 1.00 g of (±)-**3** and 14 g of Triton X-100 with 1.5 L of ultrasonicated bakers' yeast homogenate (150 g of yeast in 0.10 M phosphate buffer prepared as previously described[13,14]) at 23 °C for 48 h to give, after extractive workup with ether and silica gel chromatography, 0.310 g of (−)-**4** ($[\alpha]_D^{23} = -47.3°$,[15] 62% conversion based on one enantiomer of (±)-**3**) as the only new sterol product. Control incubations using a boiled enzyme homogenate failed to produce any new sterol products. Since the ^1H NMR spectrum[16] of **4** displayed chemical shift values for the C-18,19,21,28, and 29 methyls and the C-20 proton (1.44 ppm) consistent with those in lanostane sterols[17] but not the unrearranged dammarane skeleton (C-20-H, 2.42 ppm),[17,18] we inferred that **4** also possessed the Δ^8-olefinic bond. This assignment was ultimately confirmed by converting **4** to the known 24,25-dihydro analogues of (+)-**1** and (−)-**2**.

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(16) 400 MHz ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.81 (s, 3 H), 0.88 (d, J = 7 Hz, 3 H), 0.99 (s, 3 H), 1.01 (s, 3 H), 1.59 (s, 3 H), 1.69 (s, 3 H), 3.23 (dd, J = 10.8, 4 Hz, 1 H), 4.88 (d, J = 16.5 Hz, 1 H), 4.93 (d, J = 10.5 Hz, 1 H), 5.08 (t, J = 7 Hz, 1 H), 5.76 (dd, J = 16.5, 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 15.3, 16.5, 17.4, 18.4, 18.6, 19.2, 21.4, 24.8, 25.6, 26.7, 27.5, 27.8, 28.3, 29.4, 31.1, 35.6, 36.0, 36.1, 37.2, 38.8, 43.0, 50.2, 50.4, 56.7, 78.8, 111.8, 125.1, 129.8, 130.9, 137.0, 143.2.

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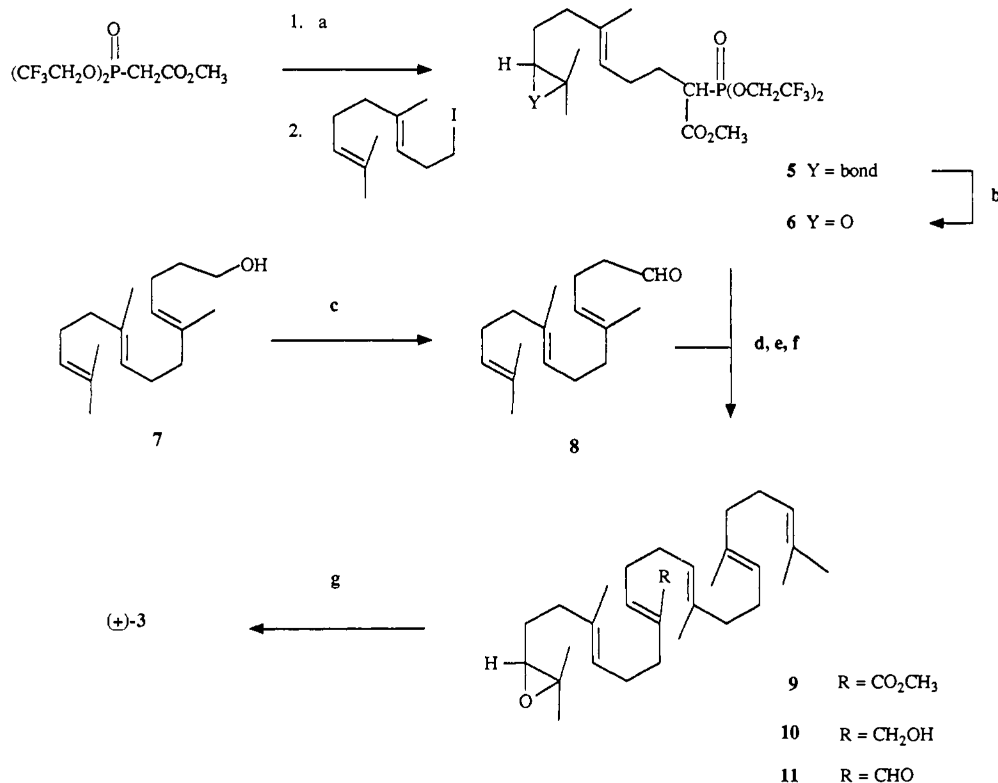
Scheme I[a]



[a] (a) 1.1 equiv of KH, 1 equiv of 18-crown-6, 10% HMPA-THF, -40 °C, 1 h. (b) 1. 1.2 equiv of NBS, 30% aqueous THF, 0 °C, 1 h; 2. K_2CO_3, CF_3CH_2OH (74% yield). (c) 6 equiv of CrO_3, 12 equiv of C_5H_5N, CH_2Cl_2, 0 °C, 6 h (93%). (d) 1.1 equiv of $KN(TMS)_2$, 5 equiv of 18-crown-6, THF, -50 °C, 1.5 h (58% *Z*-isomer). (e) 1 equiv of AlH_3, THF, -78 °C, 6 h (68%). (f) 1.5 equiv of pyridinium dichromate, DMF, -15 °C, 2 h, (89%). (g) 1.5 equiv of $Ph_3P{=}CH_2$, 10% HMPA-THF, -15 °C, 30 min (90%).

The completion of the synthesis of the putative natural sterols was accomplished as follows: **4** was converted to the 3β-acetate and then treated with 1.2 equiv of *m*-CPBA in CH_2Cl_2 at 23 °C to afford the 24,25-epoxide (93%). Oxidative cleavage of the C-14 vinyl appendage and sequential deoxygenation of the 24,25-oxido group was performed in one-pot by ozonolysis of the 24,25-epoxy 3β-acetate in 1:4 CH_2Cl_2–methanol[19] at -78 °C and treatment of the crude ozonolysis mixture with an excess of Zn/AcOH/NaI[20] (-78 °C for 1 h then 40 °C for 6 h) to produce 30-oxolanosteryl acetate. Cleavage of the 3β-acetoxy group by K_2CO_3/MeOH gave 30-oxolanosterol, (-)-**2**, $[\alpha]_D^{23} = -322°$, in 43% overall yield from the lanostatriene (-)-**4**. Lastly, reduction of (-)-**2** with $NaBH_4$ in methanol at 0 °C gave (+)-30-hydroxylanosterol **1** (98%) $[\alpha]_D^{23} = +57°$. Support for the identity of the synthetic sterols (+)-**1** and (-)-**2** was obtained by hydrogenating (1 atm H_2, PtO_2, 23 °C) each sterol to afford the corresponding 24,25-dihydrosterols whose melting points, IR, NMR, mass spectroscopic, and optical rotation data were in agreement with those previously reported.[3a,21]

The synthesis described herein illustrates a new approach to the asymmetric preparation of C-30 functionalized lanosterols where the key transformation invokes oxidosqualene cyclase in bakers' yeast for the construction of the steroid nucleus from a completely acyclic progenitor. However, an attempt to apply this enzymic cyclization method to an isomeric substrate possessing a vinyl appendage at C-15 in the squalene backbone was not successful. This latter result supports our recent hypothesis that structural features perturbing the β-face region, but not the α-face, of the substrate's chair–boat–chair conformation interfere with the enzyme's normal cyclizing operation.[14]

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The Furan Approach to Higher Monosaccharides. A Concise Total Synthesis of (+)-KDO

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The higher monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid, (+)-KDO (**1**), is the essential ketosidic component that links the carbohydrate and lipid subunits of lipopolysaccharides (LPS) of Gram negative bacteria;[2] incorporation of KDO appears to be vital for the growth and proliferation of these bacteria. Significant interest in the design and synthesis of KDO analogues as potential antibiotics[3] has been aroused consequent to recent discoveries that derivatives of 2-deoxy-KDO are effective inhibitors of LPS biosynthesis.[4] Although several syntheses of KDO and its analogues have been reported,[5] with one exception,[5c] carbohydrate precursors

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