Synthesis of Zymosterol: Salient Intermediate of Fungal and Mammalian Sterol Biosynthesis

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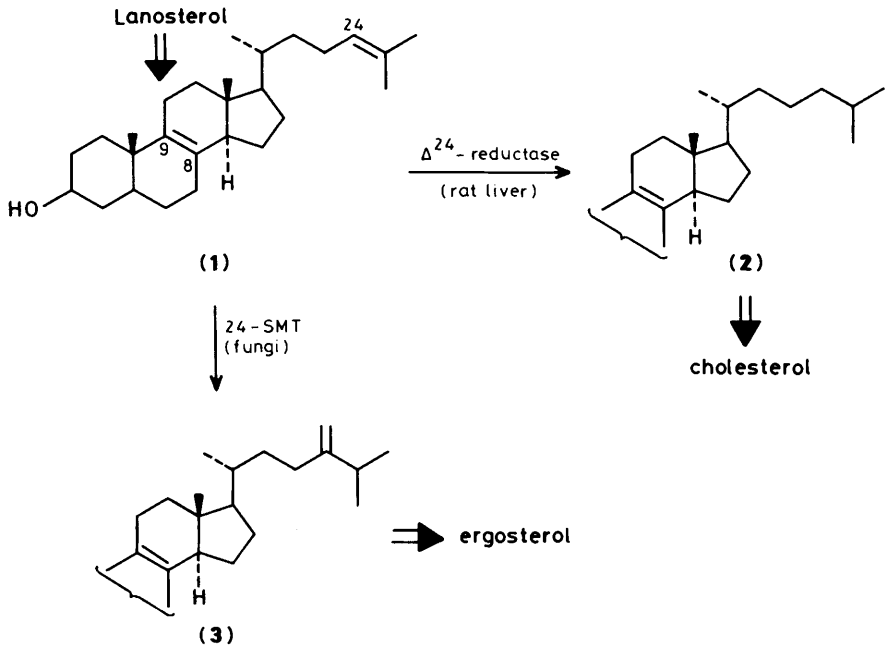
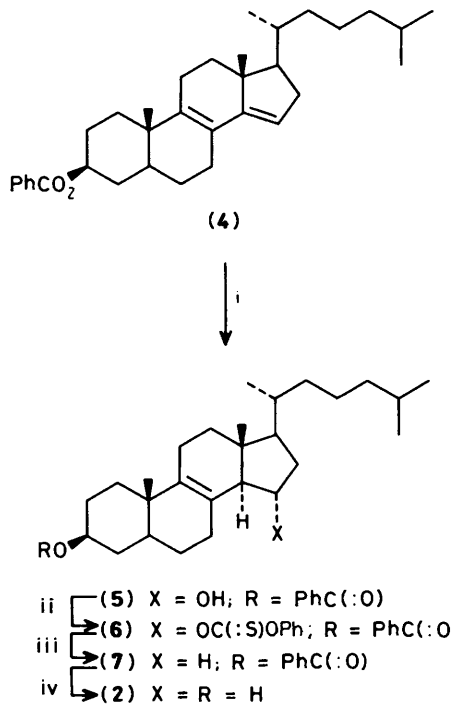
A useful strategy for the construction of sterol biosynthetic intermediates possessing Δ^8-unsaturation is described and exemplified by the synthesis of zymosterol (**1**) and 24,25-dihydrozymosterol (**2**).

Zymosterol (**1**) has been recognised as the common biosynthetic intermediate in both animal tissues and a variety of fungi and yeasts.[1] Sterol (**1**) is transformed to cholest-8-en-3β-ol (**2**) *en route* to cholesterol by Δ^{24}-sterol reductase in mammalian systems.[1b] In fungi and yeasts, (**1**) is initially metabolised to fecosterol (**3**) *via* *S*-adenosylmethionine sterol-C-24-methyltransferase (24-SMT);† further enzymatic transformation produces ergosterol[1c] (Scheme 1). Although iso-

† The mechanism of this biotransformation may be viewed as a formal nucleophilic attack of the Δ^{24}-alkene on the methyl group of *S*-adenosylmethionine (SAM).[1a]



Scheme 1



Scheme 2. *Reagents and conditions:* i, B_2H_6, THF, then ^-OOH (70%); ii, PhOC(S)Cl, pyridine (95%); iii, Bu_3SnH, AIBN, toluene, 80 °C (90%); iv, NaOMe, MeOH (95%).

lated some 50 years ago,[2] the synthesis of (**1**) has not been reported.‡ The key to any approach to the construction of (**1**) is the regio-controlled introduction of C8(9)-unsaturation in the sterol nucleus. Our strategy for Δ^8-incorporation is based on the regioselective hydroboration of the sterol 8,14-diene system[3] followed by Barton-type deoxygenation.[4] This approach, which should find general application for the preparation of other Δ^8-sterol biosynthetic intermediates, is exemplified by the synthesis of (**1**) and (**2**).

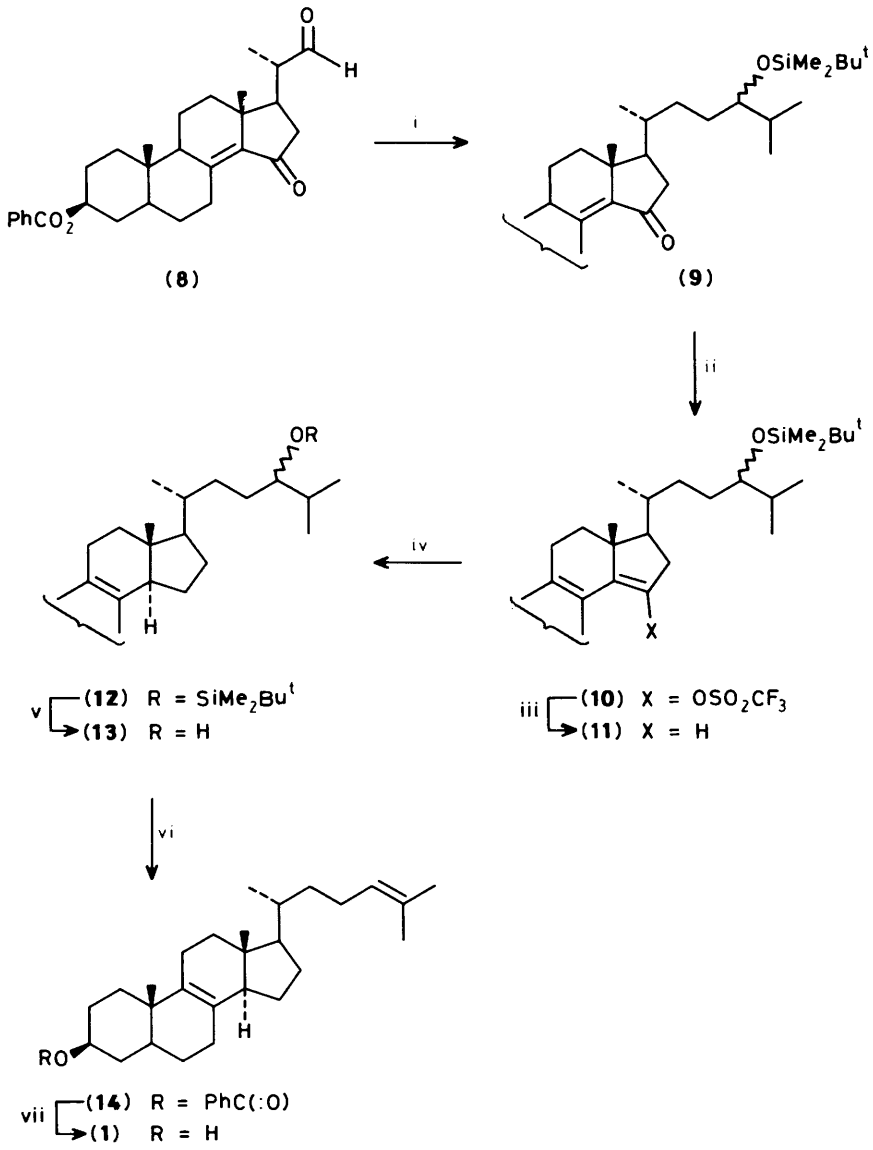
Thus, hydroboration [1.5 equiv. B_2H_6, tetrahydrofuran (THF), 25 °C; then ^-OOH] of the 14,15-double bond in (**4**)[5] afforded 15α-alcohol (**5**)§,¶ (70%, Scheme 2). Thiocarbonate formation [1.5 equiv. PhOC(S)Cl, pyridine] yielded (**6**); deoxygenation [1.3 equiv. Bu_3SnH, azoisobutyronitrile (AIBN), toluene, 80 °C] generated (**7**) which, upon saponification [NaOMe, MeOH/toluene, 25 °C; 85% from (**5**)] furnished crystalline (MeOH) 24,25-dihydrozymosterol (**2**) (m.p. 126—127 °C; lit.[6a] 127—128 °C).

Enone-aldehyde (**8**)[7], a readily available precursor for (**1**), was elaborated to enone (**9**) (Scheme 3) by sequential aldol condensation/dehydration [4 equiv. methyl isopropyl ketone, 4 equiv. lithium di-isopropylamide (LDA), THF, −78 °C; then *p*-$MeC_6H_4SO_3H$, toluene/$CHCl_3$ 3:1, 60 °C], selective hydrogenation (1 atm H_2, Lindlar catalyst) of the 22,23-double bond, chemoselective reduction of the saturated 24-ketone (1.2 equiv. t-butylamine–borane complex, CH_2Cl_2, reflux),[8] and finally silylation [1.1 equiv. $Bu^tMe_2SiOSO_2CF_3$, 1.3 equiv. 2,6-lutidine, CH_2Cl_2, 0 °C; 85% yield from (**8**)]. Transformation of (**9**) into (**11**) required the intermediacy of the dienol trifluoromethanesulphonate (**10**)[9a] [1.2 equiv. $(CF_3SO_2)_2O$, 1.5 equiv. 2,6-di-t-butyl-4-methylpyridine, CH_2Cl_2 25 °C, reflux] and reduction[9b,c] [0.05 equiv. $Pd(OAc)_2(Ph_3P)_2$, 8 equiv. Bu_3N, 4 equiv. HCO_2H, dimethylformamide (DMF), 70 °C]. Application of the hydroboration–deoxygenation sequence (above) to (**11**) provided alkene (**12**). Desilylation (1.4 equiv. Bu_4NF, THF, 25 °C) gave the alcohol

‡ Zymosterol has been isolated from bakers' yeast in 0.025% yield.[11]

§ All new compounds, as well as (**1**) and (**2**), exhibited satisfactory analytical and spectroscopic data.

¶ 5—10% yield of the corresponding diol was also isolated.



Scheme 3. *Reagents and conditions:* i, (a) methyl isopropyl ketone, LDA, −78 °C, (b) *p*-$MeC_6H_4SO_3H$, $CHCl_3$/toluene, 70 °C, (c) H_2/ Lindlar catalyst, (d) $Bu^tNH_2{\cdot}BH_3$, CH_2Cl_2, reflux, (e) $Bu^tMeSiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2 (85% overall); ii, $(CF_3SO_2)_2O$, 2,6-di-t-butyl-4-methylpyridine, CH_2Cl_2 (98%); iii, $Pd(OAc)_2(Ph_3P)_2$ cat., Bu_3N, HCO_2H, DMF (95%); iv, see Scheme 2 i—iii (70%); v, Bu_4NF, THF (100%); vi, $[C_6H_5C(CF_3)_2O]S(C_6H_5)_2$, CH_2Cl_2 (90%); vii, NaOMe, MeOH (95%).

(**13**) quantitatively, which was dehydrated [1.1 equiv. Martin sulfurane (Aldrich), CH_2Cl_2, 0 °C, 1 min] to give (**14**).**

Saponification of the benzoate and recrystallisation (methanol) gave (**1**) (m.p. 110—112 °C, lit.[11] 110.5—112 °C).

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** 5% of the Δ^{23}-isomer was detected. Dehydration of a C-24 alcohol to yield the Δ^{24}-alkene has been previously accomplished using PCl_3/pyridine in low yield.[10]