Synthesis of Antifungal Antibiotic A25822 Factor A

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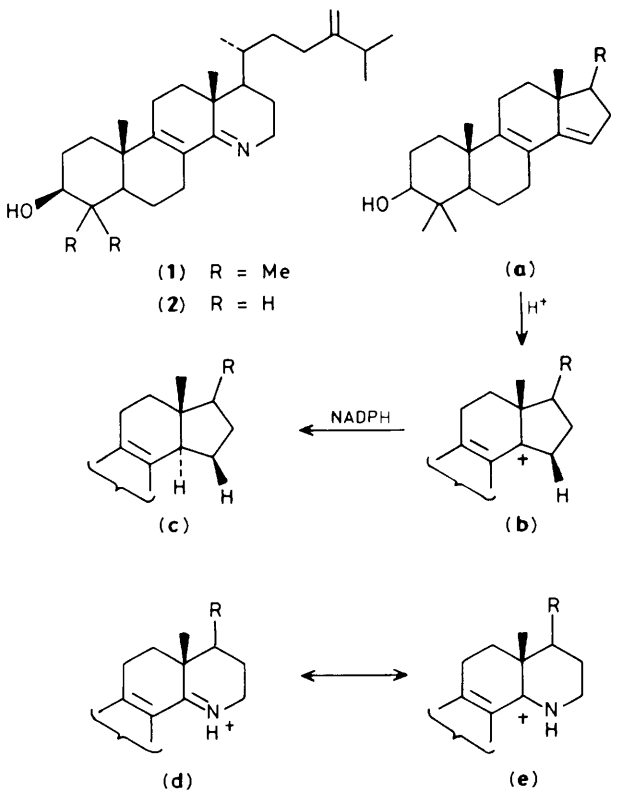
An intramolecular aza-Wittig cyclization reaction has been employed as a key step in the preparation of the antifungal antibiotic A25822 factor A from ergosterol.

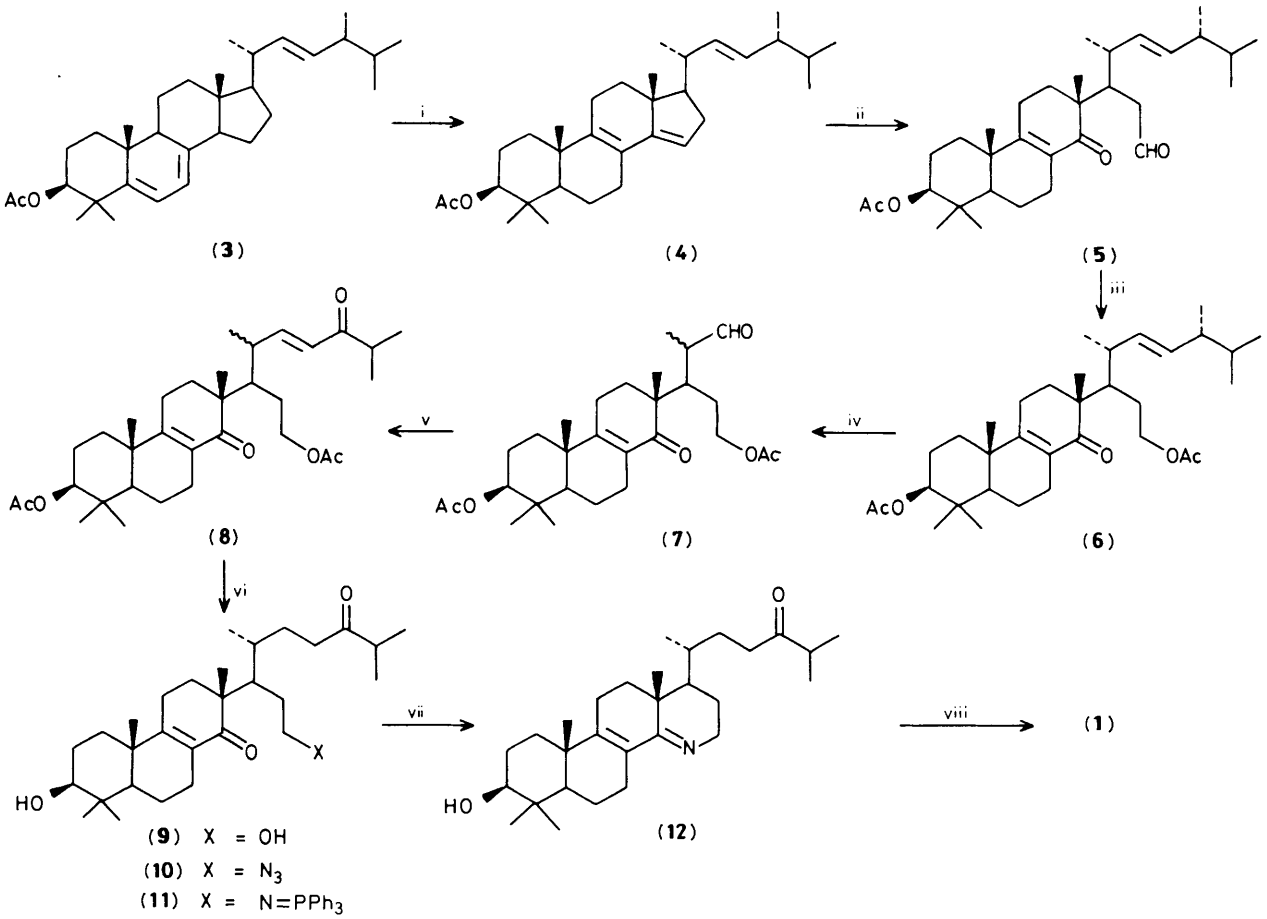
The 15-azahomosterol antibiotics A25822 factors A (**1**) and B (**2**) possess impressive *in vitro* and *in vivo* antifungal activity against a variety of fungi and yeasts including pathogenic *Candica albicans*.[1] This activity of (**1**) and (**2**) is attributed to a potent inhibition (K_i = 2 nM) of Δ^{14}-sterol reductase,[1c] an NADPH dependent enzyme which catalyses the formal *trans*-addition of hydrogen across the 14,15-π bond in 8,14-sterol dienes (**a**) → (**c**), Scheme 1.[2a,b] Enzyme-mediated reduction of (**a**) is believed to occur *via* a two step protonation –hydride capture event (**a**) → (**b**) → (**c**). The high affinity of inhibitors (**1**) and (**2**) for the enzyme is thought to derive from the structural similarity of protonated azasterols, (**d**) ⟷ (**e**), and the intermediate (**b**) which is tightly bound to the enzyme during catalysis.[1c] Fungal Δ^{14}-sterol reductase is a salient member of a multi-enzyme cascade which transforms lanosterol into ergosterol, the later sterol being a key membrane component of fungi and yeast cell walls.[2c,d] As part of a programme directed toward the design of steroid-based ergosterol biosynthesis inhibitors, we have explored the chemistry of these azasterols and report here the first synthesis of (**1**).[3]

(3β,22*E*)-4,4-Dimethylergosta-5,7,22-trien-3-ol acetate (**3**)[4a] was recognised as an ideal precursor for the synthesis of (**1**), Scheme 2. Thus, thermodynamically controlled homonuclear 5,7-diene isomerization of acetate (**3**) afforded (3β,5α,22*E*)-4,4-dimethylergosta-8,14,22-trien-3-ol acetate (**4**) (m.p. 201—202 °C; 65%).[4b†] Selective ozonolysis of the



Scheme 1

† All new compounds exhibited satisfactory spectroscopic and analytical data.



Scheme 2. *Reagents and conditions*: i, HCl gas, $CHCl_3$, reflux, 15 min; ii, 1.1 equiv. O_3, CH_2Cl_2, −78 °C then Zn/HOAc, −78 °C to 25 °C; iii, 1.1 equiv. $But_3N \cdot BH_3$, CH_2Cl_2, 0 °C, 2 min, then 1 M aq. HCl followed by 2.5 equiv. Ac_2O, 3 equiv. 4-*N*,*N*-dimethylaminopyridine, 0 °C; iv, 1.1 equiv. O_3, CH_2Cl_2, −78 °C, then Me_2S; v, isopropyl methyl ketone, lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C, then *p*-$MeC_6H_4SO_3H$, toluene/$CHCl_3$ (1:1), 70 °C; vi, 1 atm H_2, Lindlar catalyst, then K_2CO_3, MeOH; vii, DPPA, DEAD, TPP, THF, 25 °C, 12 h then excess TPP, 70 °C, 12 h; viii, 4 equiv. Ph_3PMeBr, 4 equiv., potassium t-pentoxide, toluene, 60 °C.

14,15-double bond‡ in the acetate (**4**) generated the intermediate keto-aldehyde (**5**) (oil, 23%). Sequential chemoselective reduction of the formyl moiety in (**5**) with the t-butylamine–borane complex,[5] and then acetylation led to the diacetate (**6**) in quantitative yield. Oxidative cleavage of the Δ^{22}-side chain double bond in (**6**) was readily accomplished to generate the aldehyde (**7**) (76%); however, ^{13}C n.m.r. studies of this material revealed complete racemization of the α-formyl methyl group at C-20. Although partial epimerization at C-20 had been observed previously during ozonolysis of a Δ^{22}-steroidal alkene,[6] we suspect the particularly facile C-20 racemization in this instance may be a result of the enone oxygen functioning as an internal base.§ Bis-enone (**8**) was prepared *via* a standard aldol condensation/dehydration sequence (65%).¶ Subsequent reduction of the exocyclic enone double bond in (**8**) then deacetylation afforded keto-diol (**9**) (95%). Several recrystallizations (Et_2O/hexane) of (**9**) removed most of the unwanted C-20 epimer.

Regiospecific dienimine formation was accomplished by treating diol (**9**) with 1.1 equiv. each of diphenylphosphoryl azide (DPPA), diethylazodicarboxylate (DEAD), and triphenylphosphine (TPP) in tetrahydrofuran followed by excess of TPP. In this fashion, (**9**) was converted *in situ* to azide (**10**), then to aza-ylide (**11**) (with excess TPP), a reactive intermediate which underwent smooth intramolecular aza-Wittig cyclisation[7] to yield dienimine (**12**) (70%).‖ Final alkenation

‡ Regioselective electrophilic additions to the 14, 15-π bond in 7, 14- and 8, 14-dienes are known. See ref. 4a and ref. therein.

§ Conditions for the oxidative cleavage of the Δ^{22}-alkene (O_3 or $OsO_4/NaIO_4$) without C-20 racemization could not be found.

¶ Other attempts to introduce a side chain equivalent, such as the addition of 2-(isopropyl)propenylmagnesium chloride to aldehyde (**7**) occurred in poor yield (<15%).

‖ Complete removal of the undesired C-20 epimer was accomplished by converting (**12**) to the 3β-benzoate ester (benzoyl chloride, pyridine) and recrystallizing (ether/hexane) to a constant m.p. (m.p. benzoate (**12**): 157—158 °C).

and recrystallization (acetone) completed the synthesis of (**1**) (80%) (m.p. 145—147 °C; lit.[1a] 147 °C; undepressed mixed m.p.) which was spectroscopically identical with the authentic natural product.

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