Conversion of Cholic Acids into Aza Steroids

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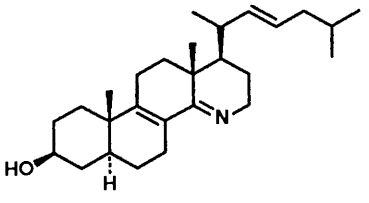
Cholic and chenodeoxycholic acids have been transformed into analogues of the anti-fungal aza steroid A25822A *via* the 8(14)-ene and 8,14-diene derivatives.

The A25822 group of fungal metabolites isolated and characterised by the Lilly group[1] have been shown to exhibit anti-fungal activity under certain circumstances.[2] This activity has been traced to their inhibition of the 14-ene hydrogenation step of sterol biosynthesis.[3] At the inception of our work the only synthetic studies published were those of the Barton group[4] who prepared the aza steroid **1** from ergosterol. Since then Dolle and Kruse have described a synthesis of the 4,4-dimethyl compound.[5]



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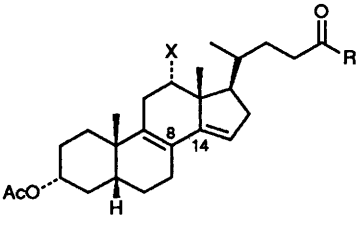
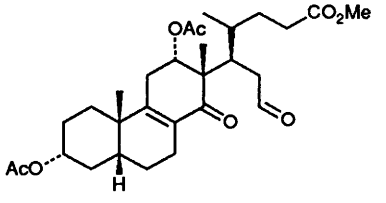


2 X = OAc, R = OMe
3 X = H, R = Pr^{i}
4 X = H, R = OMe
5 X = H, R = OH
6 X = H, R = OAc

We wished to investigate whether cholic† acid could be used as a source of aza steroids of this type. The Fetizon group[6] has described the conversion of methyl 3α,12α-diacetoxychol-8(14)-en-24-oate into the 8,14-diene **2** by reaction with Bu^{t}OOH–SeO_2 and its further transformation into the 14-hydroxy-15-oxo compound. Since the preparation of this ketone proved to be capricious‡ and cleavage of ring *D* difficult we turned to reaction of the diene **2** with OsO_4–Me_3NO which gave a 1:1 mixture of 14,15-diols (80%). Oxidation with $NaIO_4$ gave the ketoaldehyde **7** (90%).

Reaction of the aldehyde **7** with NH_3–MeOH gave a variety of products from which the carbinolamine **8** (30%) could be isolated. The presence of the unsaturated imine was confirmed by the shift of λ_{max} from 242 nm (ε 10 300) to 282 nm (ε 10 100) on acidification. Attempts to reduce the carbinolamine **8** to the



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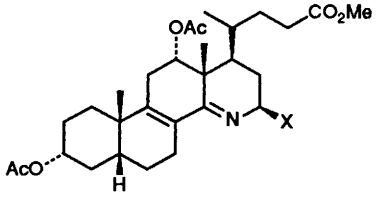
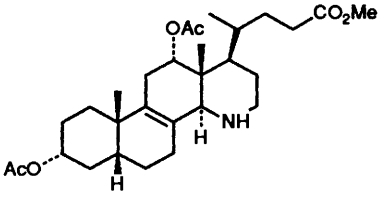


8 X = OH
9 X = H

azasteroid **9** with $NaBH_3CN$ were unsuccessful, the allylamine **10** being obtained (92%). Direct oxidation of the amine **10** with $Hg(OAc)_2$ or $Pb(OAc)_4$ failed to form the azomethine, but the two step process[7] of *N*-chlorination with Bu^{t}OCl followed by dehydrochlorination with DBU§ formed compound **9** (84%).[8]



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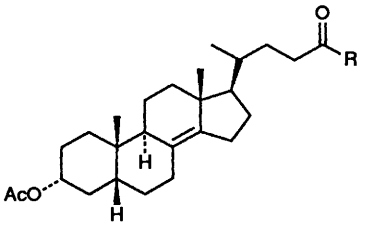
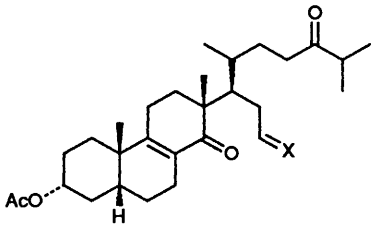
Now that we had developed a method for the construction of the aza compound we endeavoured to apply it to a target more closely related to the natural products. The starting material was chenodeoxycholic acid¶ which was converted to the 8(14)-ene apo compound using the conditions previously described; however in this case the 8(14)-ene isomer was contaminated with the 7-ene compound.‖ After acetylation exposure of the mixture to Pt–H_2 converted it to pure 8(14)-ene material **11**. Reaction of the acid with $(COCl)_2$ formed the acid chloride which was treated with Pr^{i}MgCl–CuCN to give ketone **12**. Attempts to transform the enone into the 8,14-diene **3** using

† 3α,7α,12α-Trihydroxy-5β-cholan-24-oic acid.
‡ The hydroxy ketone was accompanied by varying amounts of 8-en-15-one and 8(14)-en-15-one according to the base used.

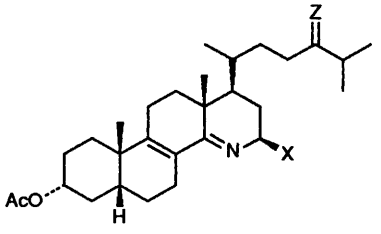
§ 1,8-Diazabicyclo[5.4.0]undec-7-ene.
¶ 3α,7α-Dihydroxy-5β-cholan-24-oic acid.
‖ MM2 calculations confirm that removal of the 12-acetate reduces the energy differences between the 7-ene and Δ8(14)-ene isomers from 2.2 to 0.9 kcal (1 cal = 4.18 J).



11 R = OH
12 R = Pr^i



13 X = O
14 X = H, OH
15 X = H, Br
16 X = H, N_3



17 X = OH, Z = O
18 X = H, Z = O
19 X = H, Z = CH_2

Bu^tOOH–SeO_2 gave intractable materials, presumably due to interference by the side-chain ketone. Thus it was decided to introduce the diene first and then complete the side-chain. The known diene ester **4** was hydrolysed to the acid and acetylated with Ac_2O–pyridine. On aqueous work-up the acid **5** was obtained, but the bulk of the material from the reaction was present as the mixed anhydride **6**. It was possible to hydrolyse the anhydride selectively, but in poor yield; however the anhydride could be converted into the acid chloride using $(COCl)_2$. Reaction of the acid chloride with Pr^iMgCl–CuCN gave the ketone **3**.

The results of OsO_4–Me_3NO oxidation of the diene **3** were disappointing since the 14,15-diol was obtained in poor yield, the major product being an unidentified ether. Stoichiometric OsO_4 oxidation gave the 14,15-diol (28%) which proved to be unstable.* We next turned to selective ozonolysis which had been used by Dolle and Kruse[5] in a similar situation. Reaction of the diene with O_3 in CH_2Cl_2 at −78 °C followed by reduction of the reaction mixture with Zn–AcOH gave the ketoaldehyde **13** (23%) which was treated with NH_3 to form the carbinolamine **17** (25%). Reduction of the carbinolamine **17** as before gave the allylamine (29%). This succession of poor yields caused us to examine other routes from the ketoaldehyde to the imine. Dolle and Kruse[5] had converted their ketoaldehyde to primary alcohol and thence to the unsaturated imine using $(PhO)_2PON_3$–$(Pr^iOCON)_2$–Ph_3P in an aza-Wittig reaction. The ketoaldehyde was reduced with Bu^tNH_2–BH_3 in CH_2Cl_2 to the alcohol **14** (54%) but all attempts to form the imine **18** in one step failed so a well established route was adopted. Reaction of the alcohol with Ph_3P–*N*-bromosuccinimide gave the bromide **15** (90%) which with NaN_3–Me_2NCHO formed the azide **16** (100%); reduction of **16** with H_2–Lindlar catalyst gave the imine **18** (64%). The synthesis was completely by Wittig reaction of **18** with CH_2PPh_3 to give the analogue **19**.

* The diol dehydrated readily to a triene tentatively identified as the 8(14),9,15-compound.

Experimental

NMR spectra were measured in $CDCl_3$ at 300 MHz (*J* values in Hz), IR spectra as thin films, and UV spectra in EtOH. 'Usual work-up' implies extractions with an organic solvent, washing the combined extracts with brine, drying the organic solvent over Na_2SO_4, and concentration of the extract under reduced pressure.

Oxidation of Methyl 3α,12α-Diacetoxy-5β-chola-18,14-dien-24-oate **2**.—OsO_4 (50 mg) in Bu^tOH (1 cm^3) was added dropwise to a solution of the diene **2** (383 mg) and Me_3NO (103 mg) in Bu^tOH (20 cm^3), water (5 cm^3) and pyridine (1.2 cm^3) at ambient temperature under N_2. After 1 h aqueous $Na_2S_2O_5$ (20%) was added to the dark red solution. Extraction with Et_2O (3 × 50 cm^3) followed by work-up in the usual way gave a green oil which was chromatographed on SiO_2; elution with light petroleum (b.p. 60–80 °C)–EtOAc (1:1) gave the 14,15-diols (340 mg) as a glass.

The diols (310 mg) and $NaIO_4$ (400 mg) were dissolved in MeOH (20 cm^3) and water (10 cm^3) and the solution left at ambient temperature for 3 h. A white precipitate formed which dissolved on the addition of water (50 cm^3) and the resulting mixture was extracted with Et_2O (3 × 40 cm^3). Work-up in the usual way gave an oil which solidified on trituration with light petroleum. Recrystallisation from MeOH–H_2O gave the *ketoaldehyde* **7** (298 mg, 90%), m.p. 137–141 °C; δ_H 9.66 (1 H, s), 5.16 (1 H, q), 4.78 (1 H, m), 3.66 (3 H, s), 2.10 (3 H, s), 1.99 (3 H, s), 1.14 (3 H, s), 1.08 (3 H, s) and 0.84 (3 H, d); ν_{max}/cm^{-1} 1735, 1666 and 1624; λ_{max}/nm 248 (ε 8500) (Found: C, 66.9; H, 8.1. $C_{29}H_{42}O_8$ requires C, 67.2; H, 8.1%).

Reaction of Methyl 3α,12α-Diacetoxy-14,15-dioxo-14,15-seco-5β-chola-8,14-dien-24-oate **7** *with* NH_3.—Aqueous ammonia (*d* 0.880; 0.1 cm^3) was added to the aldehyde **7** (55 mg) in MeOH (1.5 cm^3). After 8 h water (20 cm^3) was added and the mixture extracted with Et_2O (3 × 10 cm^3). Concentration of the dried extract gave an oil which was chromatographed on SiO_2; elution with light petroleum (b.p. 60–80 °C)–EtOAc (1:1) gave the *carbinolamine* **8** (16 mg, 30%); δ_H 5.32 (1 H, m), 5.10 (1 H, q), 4.80 (1 H, m), 2.02 (3 H, s), 2.00 (3 H, s), 1.14 (3 H, s), 1.10 (3 H, s) and 0.86 (3 H, d) (Found: M^+, 517.3041. $C_{29}H_{43}O_7$ requires *M*, 517.3036).

Reduction of Methyl 3α,12α-Diacetoxy-16-hydroxy-15-aza-17a-homo-5β-chola-8,14-dien-24-oate **8**.—$NaBH_3CN$ (10 mg) was added to the carbinolamine **8** (16 mg) in MeOH (1 cm^3). After 1 h the mixture was diluted with water (10 cm^3) and extracted with Et_2O (2 × 10 cm^3). The extract was washed with aqueous $NaHCO_3$, dried and concentrated to give the *amine* **10** as an oil (15 mg); δ_H 0.81 (3 H, d), 0.86 (3 H, s), 1.00 (3 H, s), 2.00 (3 H, s), 2.06 (3 H, s), 3.25 (2 H, m), 3.66 (3 H, s), 3.80 (1 H, m), 4.76 (1 H, m) and 5.22 (1 H, d) (Found: M^+, 503.3245. $C_{29}H_{45}NO_6$ requires *M*, 503.3243).

Methyl 3α,12α-Diacetoxy-5-aza-17a-homo-5β-chola-8,14-dien-24-oate **9**.—Bu^tOCl in Et_2O (10 cm^3, 1 mol dm^{-3}) was added to the amine **10** (5 mg) in Et_2O (1 cm^3). After 1 h in Et_2O (10

cm^3) was added and after washing with aqueous $NaHCO_3$ the dried solution was concentrated to give the *N*-chloro compound (5 mg). This was dissolved in CH_2Cl_2 (1 cm^3) and DBU (50 cm^3) added. After 30 min CH_2Cl_2 (10 cm^3) was added and the solution worked up in the usual way to give an oil which was chromatographed on SiO_2; elution with light petroleum (b.p. 60–80 °C)–EtOAc (1:1) gave the *imine* **9** (4 mg) as an oil; λ_{max}/nm 242 (ε 10 300); λ_{max} + H^+/nm 282 (ε 10 100) (Found: M^+, 501.3091. $C_{29}H_{43}NO_6$ requires *M*, 501.3088).

3α-*Acetoxy*-5β-*chol*-8(14)-*en*-24-*oic Acid* **11**.—Apochenodeoxycholic acid (9.36 g) in AcOH (150 cm^3) containing H_2SO_4 (0.5 cm^3, conc.) and Ac_2O (5 cm^3) was stirred at room temp. for 4 h. The reaction mixture was then poured into EtOAc (200 cm^3) and worked up in the usual way, to give an orange solid (11.03 g). SiO_2 column chromatography (35% EtOAc–hexane; 7:13) gave the acetates as pale yellow crystals. The acetates in AcOH (50 cm^3) containing PtO_2 were shaken under an H_2 atmosphere for 24 h. The Pt was filtered off and the filtrate evaporated to give the pure (14)-*ene acid* **11** (7.21 g), m.p. 120–124 °C (Et_2O); $[\alpha]_D$ +57 (*c* 1.0); ν_{max}/cm^{-1} 2940, 2870, 1740 and 1710; δ_H 4.75 (1 H, m), 2.0 (3 H, s), 1.0 (3 H, d), 0.85 (3 H, s), 0.8 (3 H, s) (Found: C, 75.3; H, 10.0 $C_{26}H_{40}O_4$ requires C, 75.0; H, 9.6%).

3α-*Acetoxy*-5β-*cholest*-8(14)-*en*-24-*one* **12**.—$(COCl)_2$ (168 mm^3) was added to a stirred solution of the acid **11** (410 mg) in PhMe (20 cm^3) at room temp. Once effervescence had stopped the orange solution was evaporated to give the acid chloride (405 mg) as an orange solid, ν_{max}/cm^{-1} 1740.

Pr^iMgCl in Et_2O (2 mol dm^{-3}; 9.2 cm^3) was added to a stirred suspension of CuCN (817 mg) in tetrahydrofuran (THF) (40 cm^3) under N_2 at −78 °C. The solution was then warmed to 0 °C. When clear, the solution was recooled to −78 °C and the acid chloride (2.055 g) in THF (10 cm^3) was added. The mixture was stirred for 15 min and then MeOH (20 cm^3) added at −78 °C. After the mixture had warmed to room temp. Et_2O (150 cm^3) and water (100 cm^3) were added and the resulting suspension was filtered through Celite. Work-up in the usual way followed by SiO_2 column chromatography (hexane–EtOAc; 9:1) furnished the *ketone* **12** (1.449 g); m.p. 95–97 °C (hexane); $[\alpha]_D$ +72 (*c* 1.2); ν_{max}/cm^{-1} 1740 and 1715; δ_H 4.7 (1 H, m), 2.0 (3 H, s), 1.05 (6 H, d), 0.9 (3 H) and 0.8 (3 H); *m/z* 442 (Found: C, 79.1; H, 10.7. $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.4%).

3α-*Hydroxy*-5β-*chola*-8,14-*dien*-24-*oic Acid*.—LiOH (1 g) was added to a stirred solution of the diene **4** (2.03 g) in AnalaR MeOH (90 cm^3) and water (30 cm^3) at room temp. After 48 h a white precipitate had formed and the suspension was acidified with HCl (3 mol dm^{-3}) to pH 2. The precipitate was then filtered off, washed with water (4 × 50 cm^3) amd dried to give the acid (1.625 g); m.p. 149–151 °C (Me_2CO–H_2O); $[\alpha]_D$ −20 (*c* 2.0); λ_{max}/nm 247 (ε 17 125); ν_{max}/cm^{-1} 3600–2450 and 1710; δ_H 5.3 (1 H, br s), 3.65 (3 H, s), 1.05 (3 H, s), 0.95 (3 H, d) and 0.8 (3 H, s); *m/z* 372.

3α-*Acetoxy*-5β-*chola*-8,14-*dien*-24-*oic Acid* **5**.—Ac_2O (60 cm^3) was added dropwise to a stirred solution of 3α-hydroxy-5β-chol-8,14-dienoic acid (202 mg), pyridine (0.5 cm^3) and DMAP* (20 mg) in CH_2Cl_2 (10 cm^3). After 3 h the reaction mixture was diluted further with CH_2Cl_2 (30 cm^3) and washed with water (3 × 30 cm^3). Work-up in the usual way gave a pale yellow oil, purified by SiO_2 column chromatography (EtOAc–hexane 3:7) to give the acid **5** (52 mg) as a colourless oil; λ_{max}/nm 246 (ε 17 100); ν_{max}/cm^{-1} 3400–2600; δ_H 5.3 (1 H, s), 4.7 (1 H, m), 2.0 (3 H, s), 1.1 (3 H, s), 1.0 (3 H, d) and 0.85 (3 H, s); *m/z* 414.

3α-*Acetoxy*-5β-*cholesta*-8,14-*dien*-24-*one* **3**.—Pyridine (6 cm^3) was added dropwise to a stirred suspension of 3α-hydroxy-5β-chola-8,14-dienoic acid (1.6 g) in CH_2Cl_2 (50 cm^3) at room temp. Ac_2O (5 cm^3) was then added once the suspension had dissolved. After 1.5 h the solution was washed with saturated aqueous $NaHCO_3$ and worked up in the usual way to give a colourless oil. This material was then dissolved in PhMe (30 cm^3) and $(COCl)_2$ (3 cm^3) was added. Once effervescence had stopped, evaporation yielded the crude acid chloride (1.792 g) as orange crystals.

Pr^iMgCl (2 mol dm^{-3} in Et_2O; 8 cm^3) was added to a stirred suspension of CuCN (716 mg) in THF (40 cm^3) at −78 °C under N_2. The mixture was warmed to 0 °C and upon dissolution of all the material was cooled to −78 °C; a solution of the acid chloride (1.792 g) in THF (10 cm^3) was then added. After 15 min MeOH (20 cm^3) was added at −78 °C and the mixture warmed to ambient temperature. Et_2O (150 cm^3) and water (100 cm^3) were added and the mixture filtered through Celite. Work-up in the usual way gave an oil, purified by SiO_2 chromatography (EtOAc–hexane 1:10) to give the *ketone* **3** (1.515 g) m.p. 66–67 °C (hexane); λ_{max}/nm 247 (ε 17 300); ν_{max}/cm^{-1} 1735 and 1715; δ_H 5.3 (1 H, s), 4.7 (1 H, m), 2.0 (3 H, s), 1.1 (3 H, s), 1.05 (6 H, d), 0.9 (3 H, d) and 0.8 (3 H, s) (Found: C, 79.5; H, 10.4. $C_{29}H_{44}O_3$ requires C, 79.1; H, 10.0%).

Ozonolysis of the Diene **3**.—The ketone **3** (1.4 g) dissolved in CH_2Cl_2 (350 cm^3) containing Sudan III (5 mg) was cooled to −78 °C and O_3 passed until the solution was colourless. Zn dust (10 g) and AcOH (30 cm^3) were then added and the mixture warmed to ambient temp. After 2 h the mixture was filtered and the filtrate concentrated to give an oil, which was chromatographed (SiO_2, 1:3 EtOAc–light petroleum) to give the ketoaldehyde **13** (368 mg), λ_{max}/nm 250 (ε 10 200); ν_{max}/cm^{-1} 1730, 1655 and 1620; δ_H 9.6 (1 H, s), 4.75 (1 H, m), 2.00 (3 H, s), 1.10 (6 H, s), 1.08 (3 H, s) and 0.90 (3 H, d); *m/z* 490 and 472.

Reduction of 3α-*Acetoxy*-14,15-*seco*-5β-*cholest*-8-*ene*-14,15,-24-*trione* **13**.—To a stirred solution of trione **13** (475 mg) in CH_2Cl_2 (20 cm^3) at 0 °C Bu^tNH_2–BH_3 was added. After 1 h HCl (1 mol dm^{-3}; 1 cm^3) was added followed by work-up in the usual way to give an oil which on SiO_2 column chromatography (EtOAc–light petroleum, 1:1) furnished the alcohol **14** (275 mg) as a colourless oil, λ_{max}/nm 250; ν_{max}/cm^{-1} 3480, 1735 and 1710; δ_H 4.7 (1 H, m) and 3.35 (2 H, m).

3α-*Acetoxy*-16-*hydroxy*-15-*aza*-17a-*homo*-5β-*cholesta*-8,14-*diene*-24-*one* **17**.—To a stirred room temp. solution of the trione **13** (71 mg) in AnalaR MeOH (10 cm^3) NH_3 (*d* 0.88) was added dropwise until no starting material remained. The solution was then poured into water (100 cm^3) and worked up in the usual way to give a pale yellow brown oil (60 mg), which on SiO_3 column chromatography (EtOAc–hexane, 4:6) furnished the carbinolamine **17** (16 mg) as a colourless oil, λ_{max}/nm 243 (ε 14 600), λ_{max} + H^+/nm 280 (ε 14 800); ν_{max}/cm^{-1} 1615; δ_H 5.1 (1 H, q) and 4.75 (1 H, m); *m/z* 470.

3α-*Acetoxy*-15-*aza*-17a-*homo*-5β-*cholest*-8-*en*-24-*one*.—$NaBH_2CN$ (3.8 mg) was added to a stirred room temp. solution of the carbinolimine **17** (14 mg) in AnalaR MeOH (2 cm^3) with 2 drops of AcOH. After 30 min the solution was poured into Et_2O (50 cm^3) and worked-up in the usual way to give an oil which on SiO_2 chromatography (CH_2Cl_2–MeOH; 9:1) produced the *allylamine* (4 mg) as a colourless oil, ν_{max}/cm^{-1} 3400;

* 4-Dimethylaminopyridine.

δ_H 4.7 (1 H, m), 3.5 (1 H, m), 3.2 (1 H, m) and 2.8 (1 H, m) (Found; M^+, 457.3556. $C_{29}H_{47}NO_3$ requires *M*, 457.3553).

Conversion of 3α-*Acetoxy*-15-*hydroxy*-14,15-*seco*-5β-*cholest*-8-*ene*-14,24-*dione* **14** *to* 3α-*Acetoxy*-15-*bromo*-14,15-*seco*-5β-*cholest*-8-*ene*-14,24-*dione* **15**.—A solution of Ph_3P (284 mg) in THF (5 cm^3) was added dropwise to a stirred solution of *N*-bromosuccinimide* (194 mg) in THF (10 cm^3) at room temp. After 10 min a white precipitate had formed and a solution of the alcohol **14** (257 mg) in THF (5 cm^3) was added. Et_2O (100 cm^3) was added after a further 2 h and the mixture washed (water, 3 × 80 cm^3 and brine 50 cm^3). Work-up in the usual way followed by SiO_2 column chromatography (EtOAc–light petroleum; 1:5) gave the bromide **15** (263 mg); m.p. 135–137 °C; λ_{max}/nm 249 (ε 12 400); ν_{max}/cm^{-1} 1735, 1710 and 1660; δ_H 4.7 (1 H, m) and 3.25 (2 H, m); *m*/*z* 457 (M^+ − Br).

Conversion of Bromide **15** *into* 3α-*Acetoxy*-15-*azido*-14,15-*seco*-5β-*cholest*-8-*ene*-14,24-*dione* **16**.—NaN_3 (1 g) was added to a stirred solution of the bromide **15** (263 mg) in Me_2NCHO (10 cm^3) and water (1 cm^3) at room temp. The solution was stirred for 2 d and then poured into Et_2O (50 cm^3) and worked up in the usual way to give the azide **16** (247 mg) as a pale yellow oil, λ_{max}/nm 249 (ε 10 100); ν_{max}/cm^{-1} 2100, 1735, 1710 and 1660; δ_H 4.7 (1 H, m), 3.20 (1 H, q, *J* 6.3) and 3.00 (1 H, m); *m*/*z* 500.

3α-*Acetoxy*-15-*aza*-17a-*homo*-5β-*cholesta*-8,14-*dien*-24-*one* **18**.—Lindlar catalyst (100 mg) was added to a stirred solution of the azide **16** (247 mg) in AnalaR MeOH (15 cm^3) at room temp. and the mixture agitated under H_2 (1 atm) for 3 h. The catalyst was then filtered off and the solution evaporated. SiO_2 column chromatography (MeOH–$CHCl_3$, 1:19) gave the *imine* **18** (145 mg), m.p. 138–142 °C; λ_{max}/nm 241 and 276 (ε 4400 and 1900); $\lambda_{max}+H^+$/nm 273 (ε 5600); ν_{max}/cm^{-1} 1735, 1715 and 1620; δ_H 4.75 (1 H, m), 4.0 (1 H, m) and 3.50 (1 H, q) (Found: M^+, 455.3399. $C_{29}H_{45}NO_3$ requires *M*, 455.3397).

3α-*Acetoxy*-15-*aza*-17a-*homo*-5β-*ergost*-8,14,24(24^1)-*triene* **19**.—BuLi (1.6 mol dm^{-3}; 0.5 cm^3) was added dropwise to a stirred suspension of methyl(triphenyl)phosphonium iodide (286 mg) in THF (10 cm^3) at −78 °C under N_2. The solution was left to warm to room temp. and after 1 h the solution had become clear yellow. This solution was then added dropwise to a stirred solution of the imine **18** (91 mg) in THF (10 cm^3) under N_2 at room temp. After 1 h the reaction was quenched with water (10 cm^3) and worked up in the usual way to give a colourless oil, which on SiO_2 column chromatography (CH_2Cl_2–MeOH; 49:1) yielded the *imine* **19** (40 mg) as a white solid, $[\alpha]_D$ −24 (*c* 0.8); λ_{max}/nm 238 (ε 10 650); $\lambda_{max}+H^+$/nm 277 (ε 9000); ν_{max}/cm^{-1} 1715 and 1620; δ_H 4.75 (2 H, m), 4.65 (1 H, m), 4.00 (1 H, m), 3.5 (1 H, m), 2.00 (3 H, s), 1.10 (3 H, s), 1.00 (6 H, d) and 0.95 (6 H, d) (Found: M^+, 453.3607. $C_{30}H_{47}NO_2$ requires *M*, 453.3604).

* 1-Bromopyrrolidine-2,5-dione.

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References

1 J. W. Chamberlin, M. D. Chaney, S. Chen, P. V. Demarco, N. D. Jones and J. L. Occolowitz, *J. Antibiot.*, 1974, **27**, 992; L. D. Boeck, M. M. Hoehn, J. E. Westhead, R. K. Wolter and D. N. Thomas, *J. Antibiot.*, 1975, **28**, 95; K. H. Michel, R. L. Hamill, S. H. Larsen and R. H. Williams, *J. Antibiot.*, 1975, **28**, 102; R. S. Gordee and T. F. Butler, *J. Antibiot.*, 1975, **28**, 112.
2 J. D. Bu'Llock, K. Demnerova, W. J. Kilgour, F. Knauseder and A. Steinbuchel, *Biotechnol. Lett.*, 1980, **2**, 285.
3 P. R. Hays, W. D. Neal and L. W. Parks, *Antimicrob. Agents Chemother.*, 1977, **12**, 185; C. K. Bottema and L. W. Parks, *Biochim. and Biophys. Acta*, 1978, **531**, 301.
4 D. H. R. Barton, X. Lusinichi, A. M. Mendez and P. Milliet, *Tetrahedron*, 1983, **39**, 2201.
5 R. E. Dolle and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 1988, 133.
6 G. Aranda, M. Fetizon and N. Tayeb, *Tetrahedron*, 1985, **41**, 5661.
7 R. Ray and D. S. Matteson, *Tetrahedron Lett.*, 1980, **21**, 449.
8 A. Brossi, F. Schenker and W. Leimgruber, *Helv. Chim. Acta*, 1964, **47**, 2089.

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