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Synthesis of Antibiotic A25822 B

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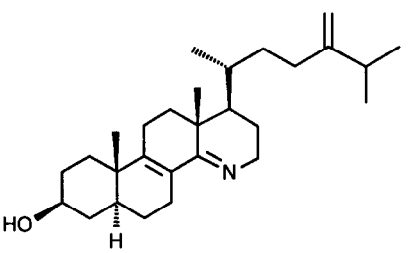
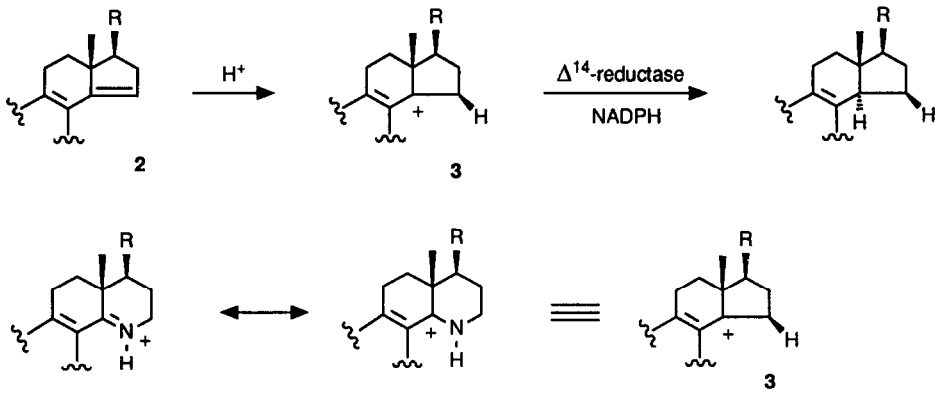
Abstract: The first synthesis of antibiotic A25822 B, a 15-aza-D-homosterol that displays powerful antifungal activity, was achieved from epiandrosterone.

The mold *Geotrichum flavo-brunneum* produces a group of 15-aza-D-homosterols that possess powerful antimycotic activity, as reported in 1974 by workers at the Eli Lilly laboratories.[1] The most potent member of this class is antibiotic A25822 B (**1**).[2]



Antibiotic A25822 B (**1**)

15-Aza-D-homosterols such as **1** block the biosynthesis of ergosterol, an essential component of the cell membranes of yeasts and fungi, by inhibiting the enzyme Δ^{14}-sterol reductase.[3] The latter is required in the NADPH-mediated reduction of the $\Delta^{14(15)}$ double bond of the ergosterol precursor **2**, via the carbocation intermediate **3**, as shown in Scheme 1. Presumably, the relatively stable conjugate acid of **1** resembles the structure of carbocation **3** and binds competitively to the active site of the enzyme.[3a] The activity of antibiotic A25822 B against pathogens such as *Candida albicans* makes it and related compounds of interest as therapeutically useful antimycotic agents.[4] To date, the preparations of several congeners of **1** have appeared,[3a,5] and we now report the first synthesis of antibiotic A25822 B itself.



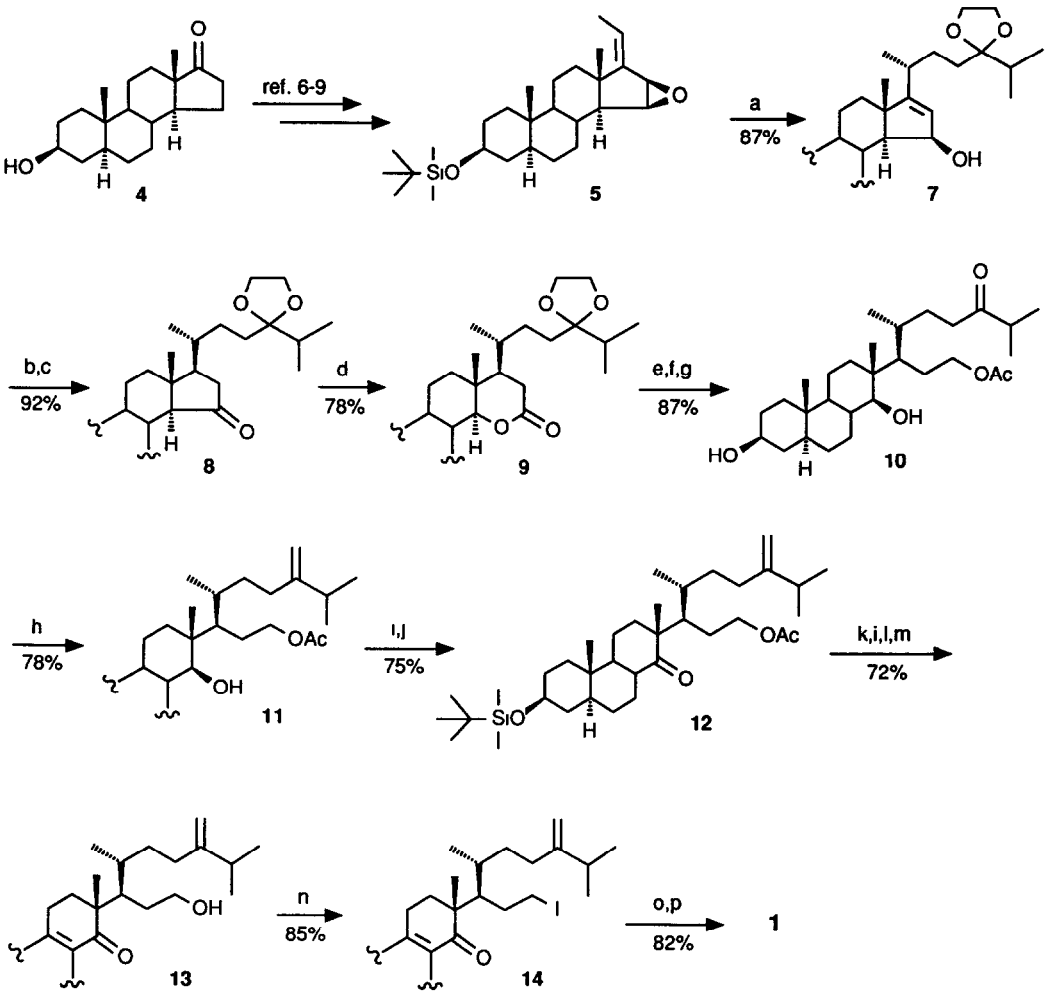
Scheme 1

RESULTS AND DISCUSSION

Our approach is shown in Scheme 2. Epiandrosterone (**4**) was first converted into the epoxy olefin **5** by literature methods.[6-9] Marino and Abe[9] had previously demonstrated that the 1,4-addition of organocuprates to such systems occurs with high stereoselectivity, thereby producing the desired configuration at C-20. Thus, the reaction of **5** with the organocuprate reagent obtained from the lithiated derivative of iodide **6** and 1 equivalent of cuprous cyanide afforded **7**. Iodide **6** was in turn prepared as shown in Scheme 3. Regulation of the stereocenter at C-17 was achieved by oxidation of **7** to the corresponding enone with pyridinium dichromate (PDC),[10] followed by stereoselective hydrogenation of the α-face[11] of the enone to give **8**. The same product was obtained, albeit in lower yield, when the hydrogenation step preceded the PDC oxidation in the transformation of **7** to **8**. This shows that epimerization of C-14 does not occur in the enone intermediate in the original sequence of steps, since Δ^{16}-15-keto steroids with the 14-β configuration undergo preferential hydrogenation from the β-face.[11] Baeyer-Villiger oxidation of ketone **8** then provided the key intermediate lactone **9** without any substantial accompanying formation of the undesired 15-keto-16-oxa regioisomer.[12]

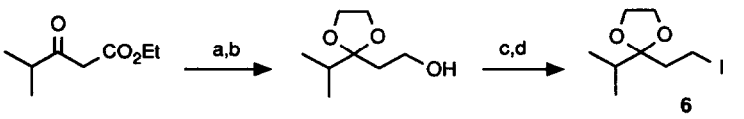
At this point, attempts to introduce the 24-methylene group by deprotection of the 24-ketone, followed by a Wittig reaction with the ylide $Ph_3P{=}CH_2$, resulted chiefly in the formation of the corresponding aldol condensation product **15**, as shown in Scheme 4. Lactone **9** was therefore reduced, monoacetylated and deprotected to afford **10**, and the required 24-methylene group was introduced by means of zinc-mediated methylenation with dibromomethane in the presence of titanium tetrachloride[13] to afford **11**. Selective resilylation of the 3-hydroxyl group,[8] followed by oxidation with pyridinium chlorochromate (PCC)[14] afforded **12**. Surprisingly, when the latter was subjected to α-bromination and dehydrobromination,[15-16] it produced only the $\Delta^{8(9)}$ enone with no significant amount of the undesired $\Delta^{7(8)}$ regioisomer. Saponification of the acetate moiety then provided the hydroxy enone **13**. Finally, conversion of the primary hydroxyl

group of **13** into the corresponding iodide **14**,[17] followed by ammonolysis in methanol[18] and acid-catalyzed cyclization afforded antibiotic A25822 B (**1**), with properties in close agreement with those reported in the literature.[1,2b]



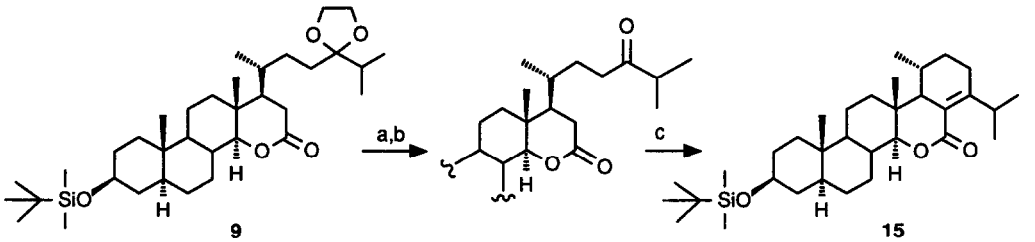
Scheme 2

Reagents for Scheme 2: a) **6**, t-BuLi, Et_2O, -78°; then CuCN, Et_2O, -78°; then **5**. b) PDC, CH_2Cl_2, RT. c) H_2, Pd-C, EtOAc, 1 atm, RT. d) MCPBA, $CHCl_3$, RT. e) $LiBH_4$, DME, Δ. f) Ac_2O, Py, 0°. g) H_3O^+, acetone, RT. h) Zn, CH_2Br_2, $TiCl_4$, CH_2Cl_2, RT. i) t-$BuMe_2SiCl$, imidazole, DMF, RT. j) PCC, CH_2Cl_2, RT. k) $Me_3PhN^+Br_3^-$, THF, 0°. l) Zn, $TiCl_4$, THF, RT. m) KOH, MeOH, RT. n) I_2, Ph_3P, imidazole, MeCN-Et_2O, RT. o) NH_3, MeOH, NH_4Cl, RT. p) H_3O^+, THF.



Scheme 3

Reagents for Scheme 3: a) $HOCH_2CH_2OH$, p-TsOH, C_6H_6, Δ. b) $LiAlH_4$, THF, RT. c) p-TsCl, Py, RT. d) NaI, acetone, Δ.



Scheme 4

Reagents for Scheme 4: a) H_3O^+, acetone, RT. b) t-$BuMe_2SiCl$, imidazole, DMF, RT. c) $Ph_3P{=}CH_2$, THF, RT.

The above method therefore provides convenient access to the 15-aza-D-homosterol nucleus and permits the installation of the side chain of antibiotic A25822 B with excellent stereoselectivity at C-17a and C-20.

EXPERIMENTAL SECTION

Melting points were obtained on an A.H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Mattson 4030 spectrometer and NMR spectra were obtained on either a Bruker AC-E 200 or AM 400 instrument, using deuteriochloroform as the solvent and residual chloroform as the internal standard. ^{1}H-NMR spectra were recorded at 200 MHz unless otherwise indicated. Mass spectra were obtained on either a Kratos MS80 or a VG 7070 instrument with the assistance of Dr. R. Yamdagni, Dr. Q. Wu and Ms. D. Fox, and elemental analyses were performed by Ms. D. Fox. Chromatography was carried out with silica gel as the adsorbent. Epiandrosterone (**4**) was purchased from the Sigma Chemical Co. and was converted into the corresponding 15β,16β-epoxy-17(*E*)-ethylidene derivative **5** by literature methods.[6-9]

1-Iodo-4-methyl-3-pentanone Ethylene Ketal (6). A mixture of ethyl isobutyrylacetate (10 g, 0.063 mol), ethylene glycol (40 mL), and p-toluenesulfonic acid monohydrate (1.2 g, 6.3 mmol) in 300 mL of benzene was refluxed for 4 hours using a Dean-Stark trap to remove water. The mixture was then poured into saturated $NaHCO_3$ solution and the organic layer was separated. The water layer was extracted with benzene and the combined extracts were washed with brine, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the corresponding ketal in quantitative yield.

The latter compound in 20 ml of anhydrous THF was added dropwise over 20 min to a suspension of lithium aluminum hydride (2.40 g, 0.063 mol) in 30 mL of anhydrous THF at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then quenched with ethyl acetate at 0 °C, followed by the addition of saturated NH_4Cl solution. The mixture was filtered, concentrated, diluted with ether, washed with saturated NH_4Cl solution, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave 9.72 g (96%) of the corresponding crude alcohol as a colorless oil.

The crude alcohol (9.72 g, 0.0607 mol) and p-toluenesulfonyl chloride (14.0 g, 0.0734 mol) were stirred in 80 mL of dry pyridine at room temperature overnight. The resulting mixture was filtered, concentrated under reduced pressure and treated with saturated $NaHCO_3$ overnight. It was then extracted with ether, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded 18.6 g of the oily tosylate, which was used in the next reaction without further purification.

The latter product (18.6 g, 0.0592 mol) and sodium iodide (20.0 g, 0.133 mol) were refluxed for 6 h in 200 mL of acetone. The mixture was filtered, concentrated under reduced pressure, poured into water, and extracted with ether. The combined extracts were washed with $NaHSO_3$ solution and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded an oil which was chromatographed (elution with benzene) to give 11.89 g (75%) of the iodide **6** as a colorless oil, IR (film): 1213, 1182, 1167, 1113, 1086, 1026, 999, 951, 866 cm^{-1}; ^{1}H-NMR δ 3.96 (s, 4 H), 3.16 (m, 2 H), 2.28 (m, 2 H), 1.89 (septet, J = 6.8 Hz, 1 H), 0.93 (d, J = 6.8 Hz, 6 H). Anal. Calcd. for $C_8H_{15}IO_2$: C, 35.57; H, 5.61. Found: C, 35.68; H, 5.70.

3β-t-Butyldimethylsilyloxy-15β-hydroxycholest-16-en-24-one Ethylene Ketal (7) A 1.7 M solution of t-butyllithium in pentane (10.5 mL, 17.85 mmol) was added dropwise to a solution of the iodide **6** (2.41 g, 8.92 mmol) in anhydrous ether (15 mL) at -78°C under argon and stirring was continued for 2 h at this temperature. This solution was then added dropwise to a cooled suspension of copper (I) cyanide (0.80 g, 8.94 mmol) in 20 mL of anhydrous ether at -78°C. The reaction mixture was stirred at this temperature for 10 min, then at -30°C for 1 h and at -20°C for 1 h. The resulting gray suspension was then recooled to -78°C and the epoxide **5** (0.792 g, 1.84 mmol) in 5 mL of anhydrous ether was added dropwise. After stirring at -78°C for 1 h, the reaction was quenched with saturated NH_4Cl solution, and the whole mixture was filtered through Celite. The filtrate was washed with saturated NH_4Cl solution and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure left a residue which was chromatographed (elution with 25% ethyl acetate-hexane) to afford 0.915 g (87%) of the allylic alcohol **7**, mp 145-146°C (from hexane); IR (KBr) 3476 (br), 1622, 1094, 1076, 870, 855, 835, 775 cm^{-1}; ^{1}H-NMR δ 5.53 (d, J = 2.6 Hz, 1 H, H-16), 4.45 (br s, 1 H, H-15), 3.95 (s, 4 H, ketal), 3.56 (m, 1 H, H-3), 1.10 (s, 3 H, H-18), 1.00 (d, J = 6.8 Hz, 3 H, H-21), 0.93 and 0.92 (two overlapping d, J = 6.9 and 7.0 Hz, total 6 H, H-26 and H-27), 0.89 (s, 9 H, t-Bu), 0.88 (s, 3 H. H-19), 0.06 (s, 6 H, Me_2Si); ^{13}C-NMR δ 166.6, 123.2, 113.9, 73.7, 72.1, 65.4, 59.7, 55.7, 47.5, 45.5, 38.7,

37.0, 35.9, 35.4, 34.5, 32.5, 32.4, 32.0, 31.5, 31.3, 30.0, 28.7, 26.0, 23.4, 21.9, 20.9, 18.3, 17.1, 12.4, -4.5; mass spectrum, *m/z* (relative intensity, %) 574 (M^+, 0.2), 556 (6), 517 (67), 513 (38), 499 (11), 426 (71), 115 (79), 75 (100). Anal. Calcd. for $C_{35}H_{62}O_4Si$: C, 73.12; H, 10.87. Found: C, 73.22; H, 11.09.

3β-(t-Butyldimethylsilyloxy)cholestane-15,24-dione 24-Ethylene Ketal (8). A mixture of allylic alcohol **7** (0.886 g, 1.55 mmol) and PDC (0.874 g, 2.32 mmol) in 20 mL of dichloromethane was stirred at room temperature for 15 h. The mixture was concentrated to half of its volume, diluted with ether, and filtered through Celite. After removal of the solvent under reduced pressure, the residue was chromatographed (elution with 30% ethyl acetate-hexane) to give 0.830 g (94%) of the corresponding enone, mp 177-178°C (from hexane); IR (film) 1703, 1591, 1252, 1092, 1071, 874, 837, 774 cm^{-1}; ^{1}H-NMR δ 5.65 (s, 1 H, H-16), 3.93 (s, 4 H, ketal), 3.55 (m, 1 H, H-3), 2.71 (m, 1 H, H-14), 1.12 (d, J = 6.8 Hz, 3 H, H-21), 1.00 (s, 3 H, H-18), 0.92 and 0.91 (two overlapping d, J = 6.9 and 6.6 Hz, total 6 H, H-26 and H-27), 0.89 (s, 9 H, t-Bu), 0.87 (s, 3 H, H-19), 0.06 (s, 6 H, Me_2Si); ^{13}C-NMR δ 207.7, 188.1, 124.5, 113.5, 71.9, 65.3, 63.9, 55.1, 47.0, 45.1, 38.5, 37.0, 35.8, 34.5, 33.4, 32.6, 32.4, 31.8, 30.4, 29.3, 28.3, 25.9, 23.6, 21.3, 20.5, 18.1, 17.1, 17.0, 12.3, -4.6; mass spectrum, *m/z* (relative intensity, %) 572 (M^+, 2), 557 (3), 529 (26), 515 (100), 471 (6), 385 (12), 236 (7), 115 (32), 99 (41), 75 (39). Anal. Calcd. for $C_{35}H_{60}O_4Si$: C, 73.37; H, 10.55. Found: C, 73.16; H, 10.55.

The above enone (0.827 g, 1.45 mmol) and 0.3 g of 10%-Pd/C were stirred in 25 mL of ethyl acetate at room temperature for 2 h under positive pressure of hydrogen maintained with a balloon. The mixture was then filtered through Celite. After removal of the solvent under reduced pressure, the residue crystallized from hexane to give 0.814 g (98%) of ketone **8**, mp 171.5-172.5°C (from methanol); IR (film) 1738, 1254, 1088, 1068, 870, 837, 775 cm^{-1}; ^{1}H-NMR δ 3.93 (s, 4 H, ketal), 3.55 (m, 1 H, H-3), 2.65 (m, 1 H, H-14), 2.45 (m, 1 H, H-16), 2.10 (m, 1 H, H-16), 0.99 (d, J = 6.0 Hz, 3 H, H-21), 0.92 (d, J = 6.9 Hz, 6 H, H-26 and H-27), 0.89 (s, 9 H, t-Bu), 0.81 (s, 3 H, H-18), 0.74 (s, 3 H, H-19), 0.05 (s, 6 H, Me_2Si); ^{13}C-NMR δ 215.9, 113.8, 72.0, 65.9, 65.3, 54.1, 51.3, 45.0, 42.4, 41.9, 39.9, 38.5, 37.2, 35.6, 35.4, 34.4, 31.9, 30.7, 30.5, 29.1, 28.3, 25.9, 20.8, 19.0, 18.2, 17.2, 17.0, 13.0, 12.2, -4.6; mass spectrum, *m/z* (relative intensity, %) 574 (M^+, 0.3), 559 (2), 531 (46), 517 (100), 473 (13), 115 (45), 75 (50). Anal. Calcd. for $C_{35}H_{62}O_4Si$: C, 73.12; H, 10.87. Found: C, 73.43; H, 10.96.

3β-t-Butyldimethylsilyloxy-15-oxa-D-homo-cholestane-16,24-dione 24-Ethylene Ketal (9). A mixture of ketone **8** (0.814 g, 1.42 mmol) and m-chloroperbenzoic acid (80%) (0.921 g, 4.26 mmol) in 20 mL of chloroform was allowed to stand at room temperature for 14 days. The mixture was treated with saturated sodium bisulfite solution at room temperature for 15 min, concentrated under reduced pressure, extracted with ether, washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Evaporation of the solvent under vacuum produced a crude residue, which was chromatographed (elution with 30% ethyl acetate-hexane) to afford 0 656 g (78%) of the lactone **9** and 0.120 g (15%) of recovered starting material **8** Compound **9** had: mp 136-137°C (from MeOH); IR (film) 1736, 1248, 1096, 1053, 870, 835, 775 cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.94 (s, 4 H, ketal), 3.53 (m, 1 H, H-3), 3.51 (d, J = 10.3 Hz, 1 H, H-14), 2.62 (dd, J = 18.8, 8.2 Hz, 1 H, H-17), 2.50 (dd, J = 18 8, 10.7 Hz, 1 H, H-17), 0.93-0.92 (three overlapping d, J = 6.9, 6.8, 6.7 Hz, total 9 H, H-21, H-26 and H-27), 0.918 (s, 3 H, H-18), 0.89 (s, 9 H, t-Bu), 0.82 (s, 3 H, H-19), 0.06 (s, 6 H, Me_2Si); ^{13}C-NMR δ 172.3, 113.7, 91.3, 71.9, 65.42, 65.40, 51.9, 50.0, 44.6, 38.4, 37.2, 37.0,

35.8, 35.6, 35.5, 34.6, 32.7, 31.8, 30.0, 29.3, 27.8, 25.9, 20.8, 19.7, 18.2, 17.2, 17.1, 12.5, 12.2, -4.6; mass spectrum, *m/z* (relative intensity, %) 590 (M^+, 0.3), 575 (2), 547 (28), 533 (100), 518 (10), 505 (9), 489 (44), 426 (15), 115 (46), 75 (54). Anal. Calcd. for $C_{35}H_{62}O_5Si$: C, 71.14; H, 10.57. Found: C, 70.98; H, 10.48.

15-Acetoxy-3β,14β-dihydroxy-14,15-seco-cholestan-24-one (10). A mixture of lactone **9** (0.251 g, 0.427 mmol) and lithium borohydride (18.6 mg, 0.854 mmol) in 3 mL of anhydrous DME was refluxed for 20 h under argon. After cooling to room temperature, the mixture was quenched with saturated NH_4Cl solution, extrated with ether and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed (elution with 60% ethyl acetate-hexane) to give 0.230 g (91%) of the corresponding 14,15-seco-14,15-diol, mp 106-106.5°C (from pentane); IR (film) 3408 (br), 1252, 1096, 1078, 868, 835, 773 cm^{-1}; ^{1}H-NMR δ 3.95 (s, 4 H, ketal), 3.80-3.45 (m, 3 H, H-3 and H-15), 3.20 (d, J = 9.7 Hz, 1 H, H-14), 0.93 (d, J = 7.0 Hz, 6 H, H-26 and H-27), 0.90 (s, 3 H, H-18), 0.89 (s, 9 H, t-Bu), 0.79 (s, 3 H, H-19), 0.06 (s, 6 H, Me_2Si); ^{13}C-NMR δ 113.9, 80.2, 72.1, 65.3, 64.6, 52.1, 47.6, 44.5, 41.8, 39.0, 38.4, 37.0, 35.5, 34.4, 33.3, 32.6, 32.4, 31.8, 30.9, 28.7, 28.4, 26.4, 25.9, 21.6, 20.2, 18.2, 17.2, 17.1, 17.0, 12.2, -4.6; mass spectrum, *m/z* (relative intensity, %): 594 (M^+, 4), 551 (8), 537 (57), 533 (61), 519 (100), 475 (15), 115 (99), 75 (71). Anal. Calcd. for $C_{35}H_{66}O_5Si$: C, 70.65; H, 11.18. Found: C, 70.92, H, 11.43.

The above 14,15-diol (0.203 g, 0.343 mmol) was stirred in 1 mL of acetic anhydride and 2 mL of anhydrous pyridine at 0 °C for 3 h. Evaporation of volatile material under reduced pressure gave a quantitative amount of the corresponding 15-monoacetate, which was used directly in the next step without further purification. The monoacetate had IR (film) 3520 (br), 1740, 1250, 1094, 1080, 870, 835, 775 cm^{-1}; ^{1}H-NMR δ 4.08 (t, J = 7.7 Hz, 2 H, H-15), 3.94 (s, 4 H, ketal), 3.55 (m, 1 H, H-3), 3.22 (d, J = 9.5 Hz, 1 H, H-14), 2.05 (s, 3 H, OAc), 0.93 (d, J = 6.8 Hz, 6 H, H-26 and H-27), 0.89 (s, 12 H, H-18 and t-Bu), 0.79 (s, 3 H, H-19), 0.05 (s, 6 H, Me_2Si); mass spectrum, *m/z* (relative intensity, %) 636 (M^+, 3), 593 (13), 579 (7), 533 (23), 519 (55), 115 (100), 75 (45). High resolution mass spectrum, calcd. for $C_{37}H_{68}O_6Si$: 636.4785; found: 636.4728.

The preceding crude monoacetate (0.218 g, 0.342 mmol) was stirred with p-toluenesulfonic acid (6.6 mg, 0.034 mmol) in 5 mL of acetone containing 0 1 mL of water at room temperature for 15 h. After removal of the acetone under reduced pressure, the mixture was treated with saturated $NaHCO_3$ solution, then extracted with ether, washed with brine and dried over $MgSO_4$. Evaporation of the solvent under vacuum and chromatography of the residue (elution with 60% ethyl acetate-hexane) afforded 0.158 g (96%) of ketone **10** as a solid foam, IR (film): 3462 (br), 1732, 1710, 1246, 1041, 957, 918, 733 cm^{-1}; ^{1}H-NMR δ 4.07 (m, 2 H, H-15), 3.59 (m, 1 H, H-3), 3.21 (d, J = 9.5 Hz, 1 H, H-14), 2.68-2.25 (m, 3 H, H-23 and H-25), 2.04 (s, 3 H, OAc), 1.10 (d, J = 6.9 Hz, 6 H, H-26 and H-27), 0.94 (d, J = 7.0 Hz, 3 H, H-21), 0.90 (s, 3 H, H-18), 0.79 (s, 3 H, H-19); ^{13}C-NMR δ 214.9, 171.0, 78.6, 71.2, 66.1, 51.9, 47.4, 44.4, 42.1, 40.9, 39.2, 39.1, 38.0, 36.8, 35.5, 31.7, 31.4, 31.2, 30.8, 28.3, 27.1, 24.5, 21.6, 21.0, 20.2, 18.31, 18.26, 17.7, 12.2; mass spectrum, *m/z* (relative intensity, %): 478 (M^+, 2), 460 (0.9), 418 (10), 400 (6), 291 (54), 71 (90), 43 (100). High resolution mass spectrum, calcd. for $C_{29}H_{50}O_5$: 478.3658; found: 478.3636.

15-Acetoxy-3β,14β-dihydroxy-14,15-seco-ergost-24(28)-ene (11). Ketone **10** (51.9 mg, 0.108 mmol) and an excess of the reagent prepared from zinc, dibromomethane and $TiCl_4$ according to the literature[13] were stirred in 5 mL of dichloromethane at room temperature for 10 min. The reaction was quenched with

saturated $NaHCO_3$, the mixture was filtered through Celite, washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed (elution with 50% ethyl acetate-hexane) to give 40.3 mg (78%) of the olefin **11** as a solid foam, IR (film) 3487 (br), 1742, 1642, 1250. 1096, 1078, 1047, 868, 835, 774 cm^{-1}; ^{1}H-NMR δ 4.75 (s, 1 H, H-28), 4.68 (s, 1 H, H-28), 4.10 (t, J = 7.8 Hz, 2 H, H-15), 3.60 (m, 1 H, H-3), 3.24 (m, 1 H, H-14), 2.05 (s, 3 H, OAc), 1.04 and 1.03 (two overlapping d, J = 6.7 and 6.8 Hz, total 6 H, H-26 and H-27), 0.98 (d, J = 6.9 Hz, 3 H, H-21), 0.90 (s, 3 H, H-18), 0.80 (s, 3 H, H-19); mass spectrum, *m/z* (relative intensity, %): 476 (M^+, 0.2), 458 (0.8), 414 (9), 332 (57), 291 (41), 82 (100). High resolution mass spectrum, calcd. for $C_{30}H_{52}O_4$: 476.3866; found: 476.3860.

15-Acetoxy-3β-t-butyldimethylsilyloxy-14,15-seco-ergost-24(28)-en-14-one (12). The 3β-hydroxyl group of diol **11** was selectively silylated[8] in 86% yield with excess t-butyldimethylsilyl chloride and imidazole in anhydrous DMF at room temperature for 1 hour. The silyl ether (85.4 mg, 0.144 mmol) and PCC (46.7 mg, 0.217 mmol) were stirred in 5 mL of dichloromethane at room temperature for 5 h. After the dichloromethane was removed under reduced pressure, the mixture was dissolved in ether and filtered through Celite. Evaporation of the solvent provided a yellow oil which was chromatographed (elution with 15% ethyl acetate-hexane) to give 74.0 mg (87%) of ketone **12** a solid foam with IR (film) 1742, 1701, 1643, 1246, 1096, 1080, 870, 835, 775 cm^{-1}; ^{1}H-NMR δ 4.74 (s, 1 H, H-28), 4.66 (s, 1 H, H-28), 4.10 (m, 2 H, H-15), 3.54 (m, 1 H, H-3), 2.05 (s, 3 H, OAc), 1.12 (s, 3 H, H-18), 1.02 (d, J = 6.8 Hz, 6 H, H-26 and H-27), 0.96 (d, J = 6.6 Hz, 3 H, H-21), 0.89 (s, 9 H, t-Bu), 0.85 (s, 3 H, H-19), 0.05 (s, 6 H, Me_2Si); ^{13}C-NMR δ 216.3, 171.0, 156.2, 106.5, 71.8, 65.5, 53.8, 52.7, 45.4, 44.8, 43.9, 38.4, 37.0, 36.2, 35.3, 33.7, 33.1, 32.8, 32.5, 31.8, 27.9, 26.7, 25.9, 23.5, 22.0, 21.7, 21.4, 21.0, 20.3, 18.2, 11.8, -4.6; mass spectrum, *m/z* (relative intensity, %) 588 (M^+, 1), 573 (2), 531 (34), 528 (23), 473 (14), 364 (56), 307 (57), 75 (100). High resolution mass spectrum, calcd. for $C_{36}H_{64}O_4Si$: 588.4574; found: 588.4533.

3β-t-Butyldimethylsilyloxy-15-hydroxy-14,15-seco-ergosta-8(9),24(28)-dien-14-one (13). Ketone **12** (74.0 mg, 0.126 mmol) and phenyltrimethylammonium perbromide (70.9 mg, 0.189 mmol) were stirred in 3 mL of THF at 0 °C for 3 h. An additional portion of the perbromide (23.6 mg, 0.063 mmol) was added during this time and the reaction mixture was maintained at 0 °C overnight. The mixture was then concentrated under reduced pressure, dissolved in ether, washed with $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Removal of the solvent under vacuum produced an oil that was silylated[8] with t-butyldimethylsilyl chloride (47.2 mg, 0.314 mmol) and imidazole (42.7 mg, 0.628 mmol) in 3 mL of anhydrous DMF at room temperature for 1 h, resulting in simultaneous dehydrobromination. The reaction mixture was poured into water, extracted with ether and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a mixture of the desired enone and its 24,28-dibromo derivative The entire mixture was then debrominated as follows.[16]

One drop of $TiCl_4$ was added to a suspension of zinc dust (41.1 mg, 0.629 mmol) in 3 mL of anhydrous THF at 0 °C, and the reaction mixture was stirred at this temperature for 20 min. The crude enone product obtained above was then dissolved in 2 mL of THF and added to the suspension. The reaction mixture was stirred at 0 °C for 3 h, and quenched with saturated $NaHCO_3$. The mixture was filtered through Celite and the filtrate was extracted with ether, washed with brine, and dried over $MgSO_4$. Evaporation of

the solvent and chromatography (elution with 15% ethyl acetate-hexane afforded 56.0 mg (76%) of the 15-acetate derivative of **13** as a solid foam, IR (film) 1740, 1661, 1622, 1248, 1105, 1072, 1034, 872, 837, 775 cm^{-1}.

The above acetate (50.0 mg, 0.0860 mmol) was saponified with 0.3 mL of 2 N KOH solution in 5 mL of methanol at room temperature for 1 h. After evaporation of the methanol under reduced pressure, the mixture was treated with saturated NH_4Cl solution, extracted with ether, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and chromatogaraphy of the crude product (elution with 25% ethyl acetate-hexane) afforded 44.5 mg (95%) of the alcohol **13** as a solid foam, IR (film): 3474 (br), 1659, 1622, 1252, 1134, 1105, 1070, 872, 837, 775 cm^{-1}; ^{1}H-NMR δ 4.75 (s, 1 H, H-28), 4.67 (s, 1 H, H-28), 3.60 (m, 1 H, H-3), 3.36 (m, 2 H, H-15), 1.04 and 1.03 (two overlapping d, J = 6.8 and 6.9 Hz, total 6 H, H-26 and H-27), 1.02 (s, 3 H, H-18 or H-19), 1.00 (s overlapping with d, J = 6.8 Hz, total 6 H, H-18 or H-19 and H-21), 0.90 (s, 9 H, t-Bu), 0.07 (s, 6 H, Me_2Si); ^{13}C-NMR δ 205.3, 161.6, 156.1, 129.0, 106.6, 71.4, 63.5, 47.5, 41.6, 40.3, 38.3, 37.7, 34.0, 33.7, 33.3, 33.2, 32.6, 32.0, 31.5, 28.7, 25.9, 24.5, 23.5, 22.0, 21.9, 21.8, 21.7, 19.7, 17.4, -4.6; mass spectrum, *m/z* (relative intensity, %) 544 (M^+, 3), 526 (65), 487 (35), 469 (12), 411 (11), 362 (100). High resolution mass spectrum, calcd. for $C_{34}H_{60}O_3Si$: 544.4312; found: 544.4303.

3β-t-Butyldimethylsilyloxy-15-iodo-14,15-seco-ergosta-8(9),24(28)-dien-14-one (14) A solution of imidazole (5.7 mg, 0.084 mmol) and iodine (19.3 mg, 0.0760 mmol) in 2 mL of a 38% acetonitrile-ether mixture was added dropwise over 5 min to a mixture of the alcohol **13** (32.5 mg, 0.0596 mmol) and triphenylphosphine (18.9 mg, 0.0721 mmol) in 3 mL of the same solvent. The reaction was stirred at room temperature for 20 min, then poured into saturated $NaHCO_3$, extracted with ether, washed with $NaHSO_3$ solution and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue which was chromatographed (elution with 10% ethyl acetate-hexane) to give 33.2 mg (85%) of the iodide **14** as a solid foam with IR (film) 1659, 1622, 1250, 1132, 1105, 1074, 870, 835 cm^{-1}; ^{1}H-NMR δ 4.75 (s, 1 H, H-28), 4.66 (s, 1 H, H-28), 3.60 (m, 1 H, H-3), 3.12 (m, 1 H, H-15), 2.93 (m, 1 H, H-15), 1.03 (d, J = 6.8 Hz, 6 H, H-26 and H-27), 1.025 (s, 3 H, H-18 or H-19), 0.98 (s, 3 H, H-18 or H-19), 0.90 (s, 9 H, t-Bu), 0.07 (s, 6 H, Me_2Si). This product was used directly in the next step without further characterization.

Antibiotic A25822 B (1). Ammonia gas was bubbled through a solution containing iodide **14** (33.2 mg, 0.0507 mmol) and ammonium chloride (5.0 mg, 0 093 mmol) in 2 mL of dry methanol in a glass tube at -10 °C until the solution was saturated. The tube was sealed and the reaction mixture was stirred at room temperature for 2 days. The glass tube was opened, the mixture was concentrated under reduced pressure and the residue was treated with 0.3 mL of 0 2 N aqueous sulfuric acid in 5 mL of THF at room temperature overnight. The reaction mixture was then basified with 5% NaOH solution, concentrated under vacuum, extracted with ether, and dried over K_2CO_3. Evaporation of the solvent produced an oily residue which was chromatographed (elution with hexane-ethyl acetate-triethylamine; V/V/V: 2:3.1) to afford 17.2 mg (82%) of **1** as white crystals, mp 111-113 °C (from acetone) (lit.[1,2b]: mp 115-118 °C); $[\alpha]_D^{22}$ -16° [c 0.77, MeOH] (lit.[1] $[\alpha]_D^{25}$ -20° [c 0.775, MeOH]; lit.[2b] $[\alpha]_D^{25}$ -16° [c 0.775, MeOH]; IR (film) 3400 (br), 1643, 1620, 1373, 1090, 1055, 1038, 1022, 887, 754 cm^{-1}; ^{1}H-NMR (400 MHz) δ 4.74 (s, 1 H, H-28), 4.67 (s, 1 H, H-28), 4.00 (m, 1 H, H-16), 3.64 (m, 1 H, H-3), 3.52 (m, 1 H, H-16), 1 04 (s, 3 H, H-18), 1.032 and 1.029

(two overlapping d, J = 6.2 and 7.2 Hz, total 6 H, H-26 and H-27), 0.97 (d, J = 6.8 Hz, 3 H, H-21), 0.96 (s, 3 H, H-19); ^{13}C-NMR δ 172.9, 156.4, 148.1, 127.3, 106.4, 70.8, 51.0, 48.2, 40.6, 38.2, 37.7, 37.3, 34.8, 33.8, 33.4, 33.3, 31.6, 31.5, 30.7, 27.1, 25.4, 22.0, 21.8, 21.4, 20.7, 19.2, 18.5, 16.9; mass spectrum, *m/z* (relative intensity, %) 411 (M^+, 100), 396 (45), 394 (10), 393(6). High resolution mass spectrum, calcd. for $C_{28}H_{45}NO$: 411.3501; found: 411.3490.

Formation of 15 by Intramolecular Aldol Condensation. Lactone **9** (0.170 g, 0.289 mmol) and p-toluenesulfonic acid monohydrate (5.5 mg, 0.029 mmol) in 10 mL of acetone containing 0.1 mL of water were stirred at room temperature for 4 h. The mixture was concentrated under vacuum, diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a solid foam which was silylated[8] with t-butyldimethysilyl chloride (0.216 g, 1.45 mmol) and imidazole (0.250 g, 3.68 mmol) in 2 mL of anhydrous DMF at room temperature for 1 h. The normal workup afforded 0.125 g (79%) of the silyl ether after chromatography (elution with 25% ethyl acetate-hexane).

A solution of LDA (0.214 mmol) in 2 mL of THF was added to a suspension of methyltriphenylphosphonium iodide (86.3 mg, 0.213 mmol) in 3 mL of THF at 0 °C. After 15 min, the reaction was cooled to -78 °C and a solution of the above silyl ether (77.4 mg, 0.142 mmol) in 2 mL of anhydrous THF was added. The reaction mixture was allowed to warm slowly to room temperature overnight and was then quenched with saturated NH_4Cl solution and concentrated under reduced pressure. The mixture was diluted with ether, washed with saturated NH_4Cl solution, and dried over $MgSO_4$. After removal of the solvent under vacuum, the residue was chromatographed (elution with 15% ethyl acetate-hexane) to afford 49.5 mg (66%) of **15** as white crystals, mp 199.5-201 °C (from hexane); λ_{max} 236 nm (ε 9800, MeOH); IR (film) 1711, 1609, 1208, 1171, 1152, 1098, 1069, 870, 835, 775 cm^{-1}; ^{1}H-NMR δ 3.84 (septet, J = 6.8 Hz, 1 H, i-Pr CH), 3.56 (d, J = 10.4 Hz, 1 H, H-14) overlapping with 3.54 (m, 1 H, H-3), 1.05, 1.02 and 1.01 (three overlapping d, J = 6.5, 6.8 and 6.8 Hz, total 9 H, H-21, H-26 and H-27), 0.89 (s, 9 H, t-Bu), 0.83 (s, 3 H, H-18), 0.81 (s, 3 H, H-19), 0.06 (s, 6 H, Me_2Si); ^{13}C-NMR δ 165.7, 164.7, 121.9, 89.7, 71.9, 53.8, 51.7, 44.6, 38.4, 37.7, 37.0, 36.3, 35.9, 35.5, 31.8, 31.0, 30.0, 27.9, 27.4, 25.9, 23.6, 23.4, 20.3, 20.2, 20.1, 18.2, 12.3, 12.2, -4.6; mass spectrum, *m/z* (relative intensity, %) 528 (M^+, 77), 471 (100), 180 (49), 75 (45). High resolution mass spectrum, calcd. for $C_{33}H_{56}O_3Si$: 528.3998; found: 528.3970. Anal. Calcd. for $C_{33}H_{56}O_3Si$: C, 74.92; H, 10.67. Found: C, 74.55; H, 10.51.

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16. The $\Delta^{24(28)}$ olefin was regenerated by debromination of the crude product prior to isolation of the enone **13**, using the method of Sato, F.; Akiyama, T.; Iida, K.; Sato, M. *Synthesis* **1982**, 1025.

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18. The amination of **13** was also achieved in lower yield by conversion of the alcohol moiety into the corresponding azide, followed by reduction with a phosphite. The azide route has been previously employed in the preparation of other 15-aza-D-homosterols (see references 5a and 5c).