Synthesis of Corticoids from 9α-Hydroxyandrost-4-ene-3,17-dione

Nicholas I. Carruthers*,[1] and Sohaila Garshasb

Chemical Development, Schering-Plough Research, Union, New Jersey 07083

Andrew T. McPhail

Chemistry Department, Duke University, Durham, North Carolina 27706

Received June 20, 1991

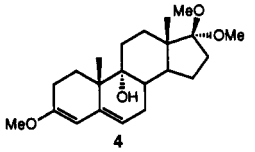
The synthesis of 17α,21-bis(acetyloxy)-16β-methylpregna-4,9(11)-diene-3,20-dione (24) from the sterol-derived 9α-hydroxyandrost-4-ene-3,17-dione (1) has been completed. The key steps in the synthesis are 16β-methylation and conversion of the 17-ketone to 17β-cyanohydrin 11. Elaboration of 11 to 9α-hydroxy-16β-methylpregn-4-ene-3,20-dione (15) followed by 21-acetoxylation and simultaneous introduction of 9,11-unsaturation and 17α-acetoxylation gave 24.

Introduction

The development of efficient fermentation processes that use soy sterols has made 9α-hydroxyandrost-4-ene-3,17-dione (1) readily available for the synthesis of steroidal drugs. The availability of 1, together with the rapid rise in the cost of traditional sapogenin-derived raw materials, has led to intensive efforts to use 1 as a precursor to steroid pharmaceuticals. Although many methods are available for the construction of a dihydroxyacetone function from a 17-keto steroid,[2] not all of these methods are applicable to 16-methylated steroids where the ketone is less susceptible to nucleophilic attack. However, acetylide anion and cyanide anion do add cleanly, and of these we chose to examine cyanohydrin based routes.

Results and Discussion

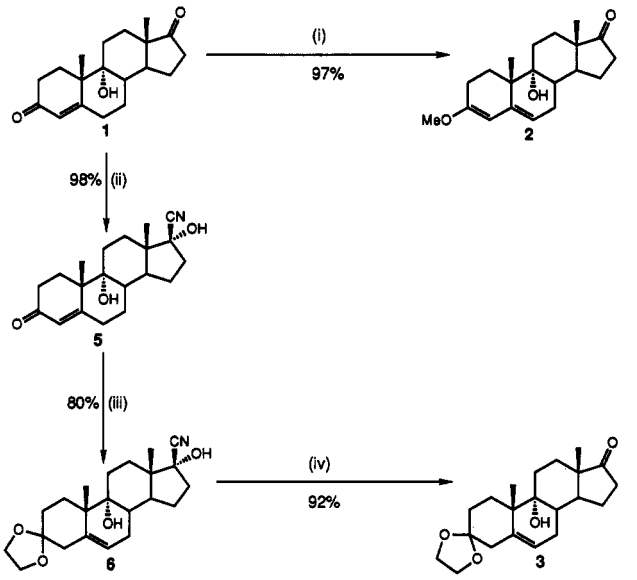
To make 24 from 1 we initially blocked the A-ring enone functionality either as a dienol ether 2 or as a ketal 3 (Scheme I). The ketal was chosen for early investigations due to its stability, although subsequent work was completed with 2. Dienol ether 2 formed in excellent yield, although care had to be taken to prevent further reaction to give the dienol ether–17-ketal 4. Direct conversion of



4

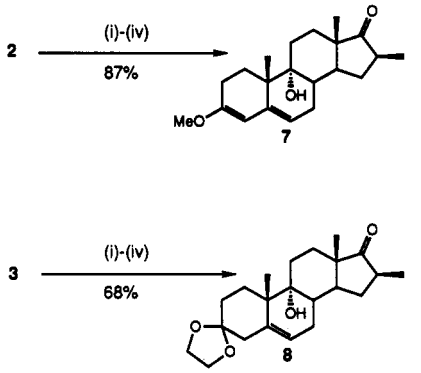
1 to ketal 3 via literature procedures[3] was not successful, and only mixtures of the desired 3-ketal and the 3,17-bis-ketal could be obtained. Although 1 readily formed a bis-ketal, selective removal of the 17-ketal was not possible. However, the dione 1 was cleanly converted to cyanohydrin 5, which was ketalized to 6. Treatment of 6 with aqueous base removed the cyanohydrin blocking group, affording 3. Introduction of the 16β-methyl group was readily accomplished using an oxalate activation/ blocking method[4] to give the 16β-methyl steroids 7 and 8 (Scheme II).

Scheme I[a]



[a] (i) $(MeO)_3CH$, *p*-TSA(cat.), THF; (ii) KCN, AcOH, MeOH; (iii) $HO(CH_2)_2OH$, *p*-TSA(cat.), $PhCH_3$; (iv) KOH, H_2O, MeOH.

Scheme II[a]



[a] (i) NaOMe, $(CO_2Et)_2$, CH_2Cl_2; (ii) MeI, $(CH_3)_2CO$; (iii) NaOMe, MeOH; (iv) AcOH, H_2O.

(1) Present address, Schering-Plough Research, 60 Orange Street, Bloomfield, NJ 07003.

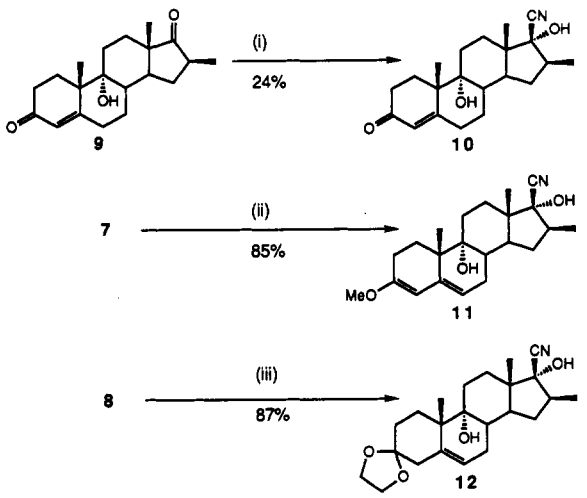
(2) (a) Nitta, I.; Ueno, H. *Yuki Gosei Kagaku* **1987**, *45*, 445. (b) Redpath, J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75. (c) A comprehensive list of references to corticoid construction methods is contained in Livingston, D. A.; Petre, J. E.; Bergh, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 6449.

(3) (a) Herzog, H. L.; Jevnik, M. A.; Tully, M. E.; Hershberg, E. B. *J. Am. Chem. Soc.* **1953**, *75*, 4425. (b) Nitz, T. J.; Paquette, L. A. *Tetrahedron Lett.* **1984**, *25*, 3047.

(4) (a) de Ruggieri, P.; Ferrari, C.; Gandolfi, C. *Gazz. Chim. Ital.* **1961**, *91*, 672. (b) Laurent, H.; Wiechert, R. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reinhold Co.: New York, 1972; Volume 2. Chapter 10. (c) Van Rheenan, V. H.; Timko, J. M. U.S. Patent 4,451,404, 1984.

0022-3263/92/1957-0961$03.00/0

Scheme III[a]



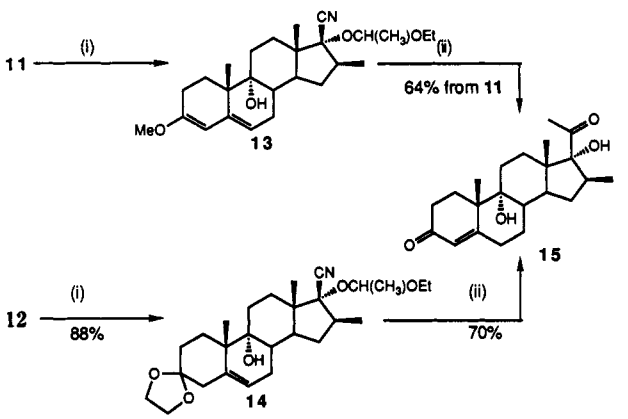
[a] (i) KCN, MeOH, CH_2Cl_2, AcOH; (ii) KCN, MeOH, AcOH; (iii) KCN, MeOH, H_2O, AcOH.

With the 16β-methyl steroids in hand we next examined their conversion to cyanohydrins. The conversion of 16-unsubstituted 17-keto steroids to 17β-cyanohydrins and their further transformation to corticoids is well-known.[5] However the behavior of 16-methylated steroids under cyanohydrin-forming conditions was not known at the outset of this work, and we were uncertain whether the product cyanohydrin, if it formed, would have the α- or β-stereochemistry. Cyanohydrin formation was studied with three substrates: enone **9**, prepared by hydrolysis of **7**, dienol ether **7**, and ketal **8** (Scheme III).

When enone **9** was treated with a large excess of KCN in $MeOH/CH_2Cl_2$ containing HOAc, a single cyanohydrin product was formed, **10** (^1H and ^{13}C NMR). Unambiguous assignment of the 17β-cyanohydrin stereochemistry was achieved by X-ray crystallography. Dienol ether **7** was treated with KCN under similar conditions, and the progress of the reaction was monitored by HPLC. Rapid formation of a single cyanohydrin occurred (60 min), followed by slower equilibration to a second cyanohydrin (2–3 days). Isolation of the second cyanohydrin and acidic hydrolysis of its dienol ether gave **10**, confirming the structure of the second cyanohydrin to be **11**, also having the 17β stereochemistry. Similarly, treatment of the ketal **8** under identical conditions gave β-cyanohydrin **12**. Formation of these products with the 17β-cyanohydrin stereochemistry under heterogeneous equilibrating conditions is consistent with the crystallization of the less soluble cyanohydrin.[5] In addition AM1 calculations suggest that the 17β-cyanohydrin isomer is more stable relative to the 17α-isomer.[6]

Cyanohydrins **11** and **12** were elaborated by first blocking their respective 17-hydroxyls as their ethoxyethyl ethers **13** and **14** (Scheme IV). The 17-hydroxyl could also

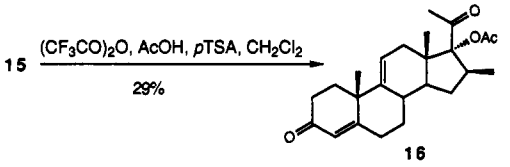
Scheme IV[a]



[a] (i) CH_2=CHOEt, pyridine hydrochloride, CH_2Cl_2; (ii) MeLi, cumene, THF, Et_2O, 40 °C.

be protected satisfactorily as its THP, 1-methoxyethyl, 1-butoxyethyl, or trimethylsilyl ether. Treatment of **13** and **14** with CH_3MgBr gave only unreacted cyanohydrin and CH_3Li in ether gave only low yields of the desired pregnane **15**. The use of CH_3Li in cumene/THF at elevated temperature followed by hydrolysis gave **15** in excellent yield. However, the TMS ether was unstable to the forcing conditions needed to obtain a pregnane.

To convert pregnane **15** to the desired corticoid intermediate a 21-hydroxyl group had to be introduced and the 9α-hydroxyl converted to the 9,11-olefin. Thus **15** was used to investigate methods for 9,11-dehydration. Under a range of acidic and basic conditions ($ClSO_3H$, H_3PO_4, BF_3·OEt_2, $NBA/SO_2/C_5H_5N$, P_2O_5, Vilsmeier reagent), the reaction products were those typical of acid- or base-induced D-homo rearrangement[7] with and without the desired 9,11-unsaturation. In contrast, when **15** was treated with an acylating mixture consisting of TFAA, HOAc, and *p*-TSA, not only did the expected esterification of the 17α-hydroxyl occur but clean dehydration also occurred to afford **16**.



Since **15** could be cleanly dehydrated with simultaneous esterification of the 17-hydroxyl group, the introduction of the 21-hydroxyl was examined next with the option to postpone the dehydration/acylation until the end. Two methods for introducing the 21-hydroxyl were investigated: via iodination[8] and via enamine salt protection, bromination procedure[9] (Scheme V). The iodination procedure proved somewhat capricious under a range of conditions, and the diiodide **17** could only be generated by using a large excess (4.0 equiv) of iodine. In contrast to the behavior of **15**, the conversion of 21-desoxybetamethasone **19** to its diiodide **20** proceeded in excellent yield according to literature procedures.[10] The conversion of 16-unsubstituted pregnanes containing A-ring enones also proceeds well.[5f] We attribute the problems encountered with the

(5) (a) Butenandt, A.; Schmidt-Thome, J. *Chem. Ber.* **1938**, *71*, 1487. (b) Butenandt, A.; Schmidt-Thome, J. *Chem. Ber.* **1939**, *72*, 182. (c) Ercoli, A.; de Ruggieri, P. *J. Am. Chem. Soc.* **1953**, *75*, 650. (d) Gasc, J. C.; Nedelec, L. *Tetrahedron Lett.* **1971**, 2005. (e) Teichmuller, G.; Haessler, G.; Barnikoloc, K.; Grinenko, G.; Dolginowa, E. GDR Patent 147,669, 1981. (f) Nitta, I.; Fujimori, S.; Ueno, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 978. Two recent applications of cyanohydrins in 16-unsubstituted steroids are Reid, J. G.; Debiak-Krook, T. *Tetrahedron Lett.* **1990**, *31*, 3669 and ref 2c.

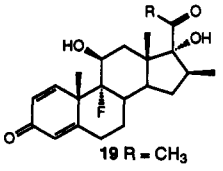
(6) The AM1 calculated value for the gas-phase heat of formation of the 17β-cyanohydrin **10** is H_f = −119.6 kcal/mol and the corresponding value for the 17α-cyanohydrin is H_f = −118.6 kcal/mol. This suggests that the 17β-cyanohydrin **10** is the more stable cyanohydrin diastereomer relative to the 17α-isomer.

(7) (a) Boswell, G. A. In ref 4b, Chapter 14. (b) Draper, R. W.; Puar, M. S. *Steroids.* **1989**, *54*, 1.

(8) (a) Ringold, H.; Stork, G. *J. Am. Chem. Soc.* **1958**, *80*, 250. (b) Mickova, R.; Syhora, K. *Collect. Czech. Chem. Commun.* **1964**, *29*, 1163.

(9) (a) Gadsby, B.; Leeming, M. R. G. *J. Chem. Soc., Chem. Commun.* **1968**, 596. (b) Gadsby, B.; Leeming, M. R. G. U.S. Patent 3,646,012, 1965. (c) Oliveto, E. P. In ref 4b, Chapter 11.

(10) Villax, I. U.S. Patent 3,792,046, 1974.



19 R = CH_3

20 R = CHI_2

iodination of **15** to be due to the presence of both a 16-substituent and a readily enolizable A-ring enone. Thus the 16-substituent reduces the rate of 21-iodination such that iodination at C-6 becomes significant and, in turn, leads to further undesired reactions. Conversion of crude **17** to 21-acetate **18** proceeded readily but in low overall yield from **15**. The enamine salt protection/bromination procedure worked well. Pregnane **15** was converted to its pyrrolidine dienamine **21**, which was protonated and brominated in situ to give the dienamine salt **22**, which in turn gave bromide **23** upon treatment with aqueous bicarbonate solution. Overall yield of **23** from **15** was 51%. Treatment of **23** with KOAc in acetone gave acetate **18**. Finally dehydration/acylation gave **24**, which may be transformed to betamethasone **25** by known procedures.[11]

In summary the synthesis of 17α,21-bis(acetyloxy)-16β-methylpregna-4,9(11)-diene-3,20-dione (**24**), an important intermediate for the preparation of the potent antiinflammatory agent betamethasone (**25**), has been completed from the sterol derived 9α-hydroxyandrost-4-ene-3,17-dione (**1**). The key steps in the synthesis are the introduction of a 16β-methyl group and the selective conversion of the 17-ketone to 17β-cyanohydrin **11**. Elaboration of **11** to 9α-hydroxy-16β-methylpregn-4-ene-3,20-dione (**15**) was followed by 21-acetoxylation, and the synthesis concluded using a novel dehydration that simultaneously acetylated the 17-hydroxyl and introduced 9,11-unsaturation, giving **24**. The synthesis proceeds in 19% overall yield to provide an intermediate that may be converted to 16β-methyl corticoids via existing procedures.

Experimental Section

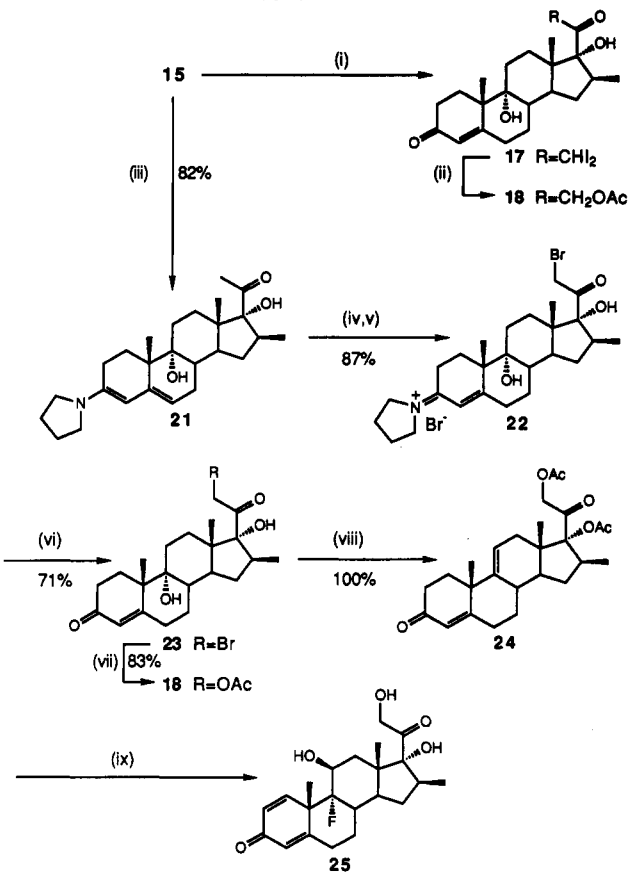
Melting points are uncorrected. Column chromatography was performed on silica gel (60–200 mesh). 9α-Hydroxyandrost-4-ene-3,17-dione and methyllithium in cumene were purchased from Gist-Brocades, Delft, N.V., and Lithco, respectively. All other reagents and solvents were obtained commercially and used without further purification.

9α-Hydroxy-3-methoxyandrosta-3,5-dien-17-one (2). Steroid **1** (100 g, 0.331 mol) in THF (500 mL) was treated with $(CH_3O)_3CH$ (109 mL, 0.993 mol) and *p*-TSA·H_2O (3.14 g, 0.017 mol). The solution was stirred for 90 min and treated with NEt_3 (11.5 mL, 0.83 mol) and then H_2O (40 mL). Evaporation of the solvent gave a wet cake which was stirred with H_2O (1000 mL) and filtered. The solid obtained was washed with H_2O (1000 mL) and dried at 50 °C in vacuo to give **2** (101.1 g, 97%): mp 187–189 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (s, 3 H, 18-CH_3), 1.00 (s, 3 H, 19-CH_3), 3.50 (s, 3 H, CH_3O), 3.62 (s, 1 H, OH), 5.18–5.20 (m, 2 H, H_4 and H_6). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.81; H, 8.72.

9α,17α-Dihydroxy-3-oxoandrost-4-ene-17β-carbonitrile (5). Steroid **1** (50 g, 0.165 mol) in MeOH (250 mL) and H_2O (250 mL) was treated with KCN (50 g, 0.768 mol), and the flask was sealed with a septa. AcOH (25 mL, 0.437 mol) was added via a syringe, and the mixture was stirred for 18 h. The reaction mixture was unsealed and treated with concd HCl (50 mL), stirred for 30 min, poured into H_2O (1500 mL), stirred for a further 60 min, and filtered. The solid was washed with H_2O (3000 mL) and dried at 50 °C in vacuo to give **5** (53.42 g, 98%): mp 214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (s, 3 H, 18-CH_3), 1.25 (s, 3 H, 19-CH_3), 4.16 (s, 1 H, OH), 5.65 (s, 1 H, H_4), 6.22 (s, 1 H, OH); HRMS for $C_{20}H_{27}NO_3$, calcd 329.1991, found 329.1967. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.21; H, 7.95; N, 4.38.

(11) (a) Charney, W.; Herzog, H. L. *Microbial Transformations of Steroids*; Academic Press: New York, 1967. (b) Rausser, R.; Oliveto, E. P. U.S. Patent 3,164,618, 1965.

Scheme V[a]



[a] (i) CaO, I_2, MeOH; (ii) $(CH_3)_2CO$, AcOH, NEt_3; (iii) pyrrolidine, MeOH, 80 °C; (iv) HCl, EtOH; (v) Br_2, EtOH; (vi) $KHCO_3$, EtOH, H_2O; (vii) KOAc, $(CH_3)_2CO$; (viii) $(CF_3CO)_2O$, AcOH, *p*-TSA, CH_2Cl_2; (ix) ref 11.

3,3-(1,2-Ethanediyldioxy)-9α,17α-dihydroxyandrost-5-ene-17β-carbonitrile (6). Nitrile **5** (50.85 g, 0.154 mol) in toluene (500 mL) was treated with $HO(CH_2)_2OH$ (424 mL, 7.7 mol), $(CH_3O)_3CH$ (68 mL, 0.616 mol), and *p*-TSA·H_2O (1.5 g, 7.7 mmol). After 4 h the reaction mixture was treated with H_2O (500 mL), Et_2O (500 mL), and C_5H_5N (10 mL). The solution was stirred for 30 min and filtered. The solid was slurried in H_2O (1000 mL), filtered, and dried in vacuo to give **6** (43.7 g, 80%): mp 205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3 H, 18-CH_3), 1.17 (s, 3 H, 19-CH_3), 3.07 (s, 1 H, OH), 3.97 (s, 4 H, OCH_2CH_2O), 5.367 (br, 1 H, H_6); HRMS for $C_{22}H_{31}NO_4$, calcd 373.2253, found 373.2266.

3,3-(1,2-Ethanediyldioxy)-9α-hydroxyandrost-5-en-17-one (3). Cyanohydrin **6** (43.9 g, 0.117 mol) in 10% aqueous MeOH (300 mL) was treated with 2 M NaOH (129 mL, 0.258 mol) at 0 °C. The reaction mixture was stirred for 3 h, and the MeOH was evaporated under reduced pressure. The wet solid was treated with H_2O (1000 mL) and filtered. The solid was washed with H_2O until the washings were neutral and dried in vacuo to give **3** (37.4 g, 92%): mp 220–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3 H, 18-CH_3), 1.19 (s, 3 H, 19-CH_3), 3.92–3.97 (m, 4 H, OCH_2CH_2O), 5.423 (br, 1 H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 12.74, 21.56, 22.21, 25.45, 26.05, 27.52, 28.13, 30.05, 30.58, 35.90, 41.78, 42.28, 45.21, 47.32, 64.25, 64.34, 74.25, 108.58, 121.44, 138.45, 220.63. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.00; H, 8.33.

9α-Hydroxy-3-methoxy-16β-methylandrosta-3,5-dien-17-one (7). Ketone **2** (28.49 g, 90.0 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C and treated with diethyl oxalate (14.7 mL, 108 mmol) and then NaOMe (7.3 g, 135 mmol). After 90 min a second portion of NaOMe (1.0 g, 18.5 mmol) was added, and after a further 60 min a third portion of NaOMe (1.0 g, 18.5 mmol) and

diethyl oxalate (2.5 mL, 18 mmol) were added (TLC indicated complete consumption of 2). The mixture was stirred for a further 18 h and then evaporated in vacuo. The solid obtained was dissolved in acetone (190 mL) and treated with Na_2CO_3 (2.4 g, 22.5 mmol), and the flask was sealed with a septum. The mixture was treated with MeI (28 mL, 450 mmol) and heated at 55 °C for 18 h. The reaction mixture was cooled, and the solvent was evaporated to give a solid. The solid was slurried in MeOH (180 mL), cooled to 0 °C, and treated with 30% NaOMe in MeOH (18.3 mL, 99 mmol). After 90 min the slurry was poured into ice/H_2O (180 mL) containing AcOH (6.0 mL, 104 mmol). After 15 min the solid product was isolated by filtration, washed with H_2O, and dried in vacuo to afford 7 (24.1 g, 87%): mp 177–180 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (s, 3 H, 18-CH_3), 0.97 (s, 3 H, 19-CH_3), 1.09 (d, 3 H, J = 7.3 Hz, 16-CH_3), 3.47 (s, 3 H, CH_3O), 3.60 (s, 1 H, OH), 5.15–5.17 (m, 2 H, H_4 and H_6). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.54, H, 9.53.

3,3-(1,2-Ethanediyldioxy)-9α-hydroxy-16β-methylandrost-5-en-17-one (8). Ketone 3 (20 g, 57.7 mmol) in CH_2Cl_2 (104 mL) was cooled to 0 °C and treated with diethyl oxalate (9.6 mL, 70.68 mmol) and then NaOMe (5.7 g, 105.5 mmol). After 2 h a second portion of NaOMe (0.4 g, 7.4 mmol) and diethyl oxalate (0.5 mL, 3.68 mmol) were added. After 30 min $NaHCO_3$ (1.8 g, 21.4 mmol) was added, and the solvent was evaporated in vacuo. The residue was dissolved in acetone (152 mL), and the flask was sealed with a septum. The mixture was treated with MeI (20 mL, 321 mmol) and heated at 60 °C for 17 h. The reaction mixture was cooled, and the solvent was evaporated to afford a solid which was dissolved in ice-cold MeOH (160 mL) and treated with 30% NaOMe in MeOH (14 mL, 75.6 mmol). After 2 h the mixture was poured into ice/H_2O (2000 mL) containing AcOH (3.8 mL, 65.9 mmol). After 60 min the solid product was isolated by filtration, washed with H_2O, and dried in vacuo to give 8 (13.98 g, 67%): mp 195 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3 H, 18-CH_3), 1.17 (s, 3 H, 19-CH_3), 1.20 (d, 3 H, J = 7.0 Hz), 3.93 (m, 4 H, OCH_2CH_2O), 5.41 (br, 1 H, H_6); HRMS for $C_{22}H_{32}O_4$, calcd 360.2310, found 360.2296.

9α-Hydroxy-16β-methyl-3-oxoandrost-4-en-17-one (9). Dienol ether 7 (3.93 g, 11.88 mmol) in 10% aqueous MeOH (77.0 mL) was treated with 1 M HCl (12 mL) and stirred for 6 h. The reaction mixture was poured into ice/H_2O (250 mL), stirred for 30 min, and filtered. The solid was washed with H_2O and dried in vacuo to afford 9 (3.19 g, 85%): mp 265–268 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3 H, 18-CH_3), 1.16 (d, J = 6.9 Hz, 3 H, 16-CH_3), 1.29 (s, 3 H, 19-CH_3), 5.84 (d, J = 1.7 Hz, 1 H, H_4); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.05, 16.95, 19.87, 24.34, 26.16, 27.41, 28.46, 30.57, 31.55, 33.95, 36.75, 42.83, 43.69, 44.57, 47.57, 76.78, 127.14, 168.10, 198.98, 222.45; HRMS for $C_{20}H_{28}O_3$ calcd 316.2038, found 316.2044.

9α,17α-Dihydroxy-16β-methyl-3-oxoandrost-4-ene-17β-carbonitrile (10). Ketone 9 (0.5 g, 1.58 mmol) in CH_2Cl_2 (2 mL) and MeOH (2 mL) was treated with KCN (2.5 g, 38.4 mmol) and AcOH (0.85 mL, 14.85 mmol). The reaction mixture was stirred for 18 h, treated with AcOH (1.5 mL, 26.2 mmol), and evaporated. The solid product was stirred in H_2O (100 mL), filtered, washed with H_2O (300 mL), and dried in vacuo. Chromatography on silica gel with 20% acetone–toluene gave 10 (0.13 g, 24%): mp >240 °C dec; ^1H NMR (300 MHz, DMSO-d_6) δ 0.85 (s, 3 H, 18-CH_3), 1.18 (d, J = 7.4 Hz, 3 H, 16-CH_3), 1.23 (s, 3 H, 19-CH_3), 4.16 (s, 1 H, OH), 5.64 (s, 1 H, H_4), 6.20 (s, 1 H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6) δ 15.40, 19.34, 20.15, 24.81, 25.39, 26.16, 27.88, 31.26, 33.66, 37.01, 41.48, 44.10, 45.56, 48.33, 74.87, 81.67, 120.34, 124.94, 170.55, 197.82; HRMS for $C_{21}H_{29}NO_3$, calcd 343.2147, found 343.2166.

9α,17α-Dihydroxy-3-methoxy-16β-methylandrosta-3,5-diene-17β-carbonitrile (11). Ketone 7 (20.1 g, 60.83 mmol), in MeOH (128 mL), was treated with KCN (19.8 g, 304.1 mmol), and the flask was sealed with a septa. AcOH (6.95 mL, 121.7 mmol) was then added via a syringe. The reaction mixture was stirred for 3 days, and a further portion of KCN (4.7 g, 76 mmol) and AcOH (1.8 mL, 30.4 mmol) was added. After 18 h, the reaction mixture was vented and treated with AcOH (13 mL, 228 mmol) and H_2O (918 mL). The mixture was stirred at 0 °C for 45 min and filtered. The solid obtained was washed with H_2O (1800 mL) and dried in vacuo to give 11 (18.59 g, 85%): mp 215–218 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 3 H, 18-CH_3), 0.96 (s, 3 H, 19-CH_3), 1.19 (d, J = 7.3 Hz, 3 H, 16-CH_3), 3.48 (s, 3 H, CH_3O), 5.14 (s, 2 H, H_4 and H_6), 6.18 (s, 1 H, OH); HRMS for $C_{22}H_{31}NO_3$ calcd 357.2304, found 357.2279. Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.43; H, 8.31; N, 3.83.

3,3-(1,2-Ethanediyldioxy)-9α,17α-dihydroxy-16β-methylandrost-5-ene-17β-carbonitrile (12). Ketone 8 (10.8 g, 29.6 mmol) in 20% aqueous MeOH (100 mL) was treated with KCN (10.73 g, 162.8 mmol), and the flask was sealed with a septa. AcOH (4.3 mL, 74 mmol) was then added via a syringe, and the mixture was stirred for 3 days. The mixture was vented and treated with AcOH (6.5 mL, 113.5 mmol) and H_2O (430 mL), stirred for 18 h, and filtered to afford 12 (10.1 g, 87%): mp 231 °C dec; ^1H NMR (300 MHz, DMSO-d_6) δ 0.70 (s, 3 H, 18-CH_3), 0.93 (s, 3 H, 19-CH_3), 1.08 (d, J = 7.4 Hz, 3 H, 16-CH_3), 3.71 (s, 4 H, OCH_2CH_2O), 5.06 (br, 1 H, H_4), 6.09 (s, 1 H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6) δ 15.42, 20.15, 21.74, 25.30, 26.55, 26.80, 27.57, 30.50, 33.72, 34.24, 41.22, 41.43, 42.10, 45.67, 48.38, 63.36, 63.43, 72.35, 81.77, 108.30, 120.37, 120.78, 137.37; HRMS for $C_{24}H_{32}NO_4$ calcd 387.2410, found 387.2409. Anal. Calcd for $C_{24}H_{32}NO_4$: C, 71.29; H, 8.54; N, 3.62. Found: C, 71.24; H, 8.53; N, 3.54.

9α,17α-Dihydroxy-16β-methylpregn-4-ene-3,20-dione (15). Step A. Cyanohydrin 12 (15.16 g, 42.9 mmol) in CH_2Cl_2 (100 mL) was treated with ethyl vinyl ether (50 mL, 523 mmol) and pyridine hydrochloride (0.5 g, 4.33 mmol). The flask was sealed with a septa and heated at 55 °C for 18 h. The reaction mixture was cooled and vented, and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel eluting with 8% acetone in $PhCH_3$ to give **3,3-(1,2-ethanediyldioxy)-17α-(1-ethoxyethoxy)-9α-hydroxy-16β-methylandrost-5-ene-17β-carbonitrile (14)** (17.4 g, 88%): mp 57–61 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.85 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 1.08 (t, J = 6.96 Hz, 3 H, OCH_2CH_3), 1.19 (d, J = 7.38 Hz, 3 H), 2.48 (m, 3 H, $OCH(OEt)CH_3$), 3.79 (s, 4 H, OCH_2CH_2O), 4.96 (m, 1 H, $OCH(OEt)CH_3$), 5.16 (br, 1 H, H_4); HRMS for $C_{27}H_{41}NO_5$ calcd 459.2985, found 459.2985.

Step B. Steroid 14 (17.4 g, 37.86 mmol) in Et_2O (35 mL) was cooled to 0 °C and treated with 1.27 M MeLi in cumene (164 mL, 208.23 mmol). The reaction mixture was heated at 40 °C for 5 h and then cooled to 0 °C, diluted with Et_2O (100 mL), and treated with 2 M HCl (156 mL, 312 mmol). After stirring for 18 h the reaction mixture was diluted with EtOAc (400 mL) and the organic layer was separated. The aqueous portion was extracted with EtOAc (250 mL), and the organic portions were combined, washed with saturated $NaHCO_3$ solution (250 mL), H_2O (250 mL), and brine (250 mL), dried over $MgSO_4$, filtered, and evaporated to give a cumene slurry of 15. Dilution with hexane (500 mL) and filtration gave a solid which was dried in vacuo to give 15 (9.61 g, 70%): mp 202–205 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3 H, 18-CH_3), 1.14 (d, J = 7.4 Hz, 3 H, 16-CH_3), 1.30 (s, 3 H, 19-CH_3), 2.23 (s, 3 H, 21-CH_3), 5.85 (d, J = 1.7 Hz, 1 H, H_4); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.62, 19.88, 20.08, 25.53, 26.07, 27.00, 28.44, 30.07, 31.89, 34.04, 34.85, 36.83, 42.98, 44.39, 46.82, 48.57, 76.49, 90.14, 126.54, 169.45, 199.79, 211.01. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.59; H, 8.62.

Pregnane 15 was also prepared from 11 by the same procedure in 64% overall yield.

17α-(Acetyloxy)-16β-methylpregna-4,9(11)-diene-3,20-dione (16). Steroid 15 (0.541 g, 1.5 mmol) in CH_2Cl_2 (5 mL) was added to an ice-cold solution of p-TSA·H_2O (0.285 g, 1.5 mmol), AcOH (2.92 mL, 51 mmol), and TFAA (2.33 mL, 16.5 mmol) in CH_2Cl_2 (5 mL). After 1 h the reaction mixture was treated with H_2O (10 mL) and then 5 M NaOH until pH 10 was attained. The organic was separated, washed with H_2O (50 mL), dried over $MgSO_4$, filtered, and evaporated to give a solid. Chromatography over silica gel, eluting with 20% EtOAc/hexane gave 16 (0.166 g, 29%): mp 182–185 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3 H, 18-CH_3), 1.33 (s, 3 H, 19-CH_3), 1.38 (d, J = 7.1 Hz, 3 H, 16-CH_3), 1.94 (s, 3 H, OAc), 2.11 (s, 3 H, 21-CH_3), 5.55 (d, J = 5.9 Hz, 1 H, H_{11}), 5.76 (d, J = 1.6 Hz, 1 H, H_4); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 15.02, 19.84, 21.48, 26.07, 28.05, 32.29, 32.81, 33.83, 33.98, 34.25, 36.59, 37.13, 40.97, 46.13, 46.33, 46.45, 95.27, 118.40, 124.09, 143.93, 169.39, 171.09, 199.20, 204.19; HRMS for $C_{24}H_{32}O_4$ calcd 384.2301, found 384.2294.

21-Bromo-9α,17α-dihydroxy-16β-methylpregn-4-ene-3,20-dione (23). Step A. Pregnane 15 (3.04 g, 8.44 mmol) was sus-

pended in MeOH (12 mL), heated to reflux, and treated with pyrrolidine (0.987 mL, 11.82 mmol) whereupon the solution momentarily became homogeneous before precipitation began. The solution was cooled to 0 °C, and the precipitate was isolated by filtration and dried in vacuo to give **9α,17α-dihydroxy-16β-methyl-3-(1-pyrrolidinyl)pregna-3,5-diene (21)** (2.86 g, 82%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 1.10 (d, J = 7 Hz, 3 H, 16-CH_3), 2.21 (s, 3 H, 21-CH_3), 3.89 (br, 4 H, NCH_2), 4.56 (s, 1 H, H_4), 6.50 (d, J = 1.5 Hz, 1 H, H_6). This material was used without further purification.

Step B. Enamine **21** (1.17 g, 2.83 mmol) in EtOH (30 mL) was added to a solution of HCl (0.5 g) in EtOH (20 mL) and cooled to −55 °C. The solution was treated with Br_2 (0.22 mL, 4.25 mmol) in EtOH (10 mL), which was added over 60 min. Once addition was complete the solvent was evaporated in vacuo to give an oil. The oil was crystallized from EtOH/Et_2O to afford **1-(21-bromo-9α,17α-dihydroxy-16β-methyl-20-oxopregn-4-en-3-yl-idene)pyrrolidinium bromide (22)** (1.42 g, 87%): ^{1}H NMR δ (250 MHz, $CDCl_3$) δ 0.77 (s, 3 H, 18-CH_3), 1.06 (d, J = 7 Hz, 3 H, 16-CH_3), 1.25 (s, 3 H, 19-CH_3), 4.48 (AB q, J = 16 Hz, 21-CH_2). This material was used without further purification.

Step C. Enaminium bromide **22** (1.42 g, 2.47 mmol) in EtOH (25 mL) was treated with $KHCO_3$ (1.0 g, 9.88 mmol) in H_2O (25 mL) and stirred for 2 h. Dilution of the reaction mixture with H_2O (75 mL) precipitated a solid which was isolated by filtration and dried in vacuo to give **23** (0.77 g, 71%): mp 210–212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3 H, 18-CH_3), 1.13 (d, J = 7.2 Hz, 3 H, 16-CH_3), 1.34 (s, 3 H, 19-CH_3), 4.25 (AB q, J = 16.2 Hz, 21-CH_2), 5.90 (br, 1 H, H_4). Anal. Calcd for $C_{22}H_{31}O_4Br$: C, 60.14; H, 7.11. Found: C, 60.07; H, 6.89.

21-(Acetyloxy)-9α,17α-dihydroxy-16β-methylpregn-4-ene-3,20-dione (18). Bromide **23** (0.7 g, 1.59 mmol) in acetone (70 mL) was treated with KOAc (3.0 g, 30.46 mmol) and heated at reflux for 5 h. Evaporation of the solvent gave a solid which was recrystallized from acetone/H_2O to give **18** (0.554 g, 83%): mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3 H, 18-CH_3), 1.14 (d, J = 7.3 Hz, 3 H, 16-CH_3), 1.32 (s, 3 H, 19-CH_3), 2.17 (s, 3 H, OAc), 4.96 (s, 2 H, 21-CH_2) 5.87 (s, 1 H, H_4); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 13.91, 19.59, 19.91, 20.66, 25.62, 26.21, 26.83, 28.50, 31.88, 34.09, 34.81, 37.04, 42.95, 44.47, 49.02, 49.53, 69.63, 76.55, 89.80, 126.76, 169.10, 170.71, 199.89, 205.16; HRMS for $C_{24}H_{34}O_6$ calcd 418.2355, found 418.2343.

17α,21α-Bis(acetyloxy)pregna-4,9(11)-diene-3,20-dione (24). Steroid **18** (0.5 g, 1.2 mmol) in CH_2Cl_2 (10 mL) was added to an ice-cold solution of p-TSA·H_2O (0.23 g, 1.2 mmol), AcOH (2.3 mL, 40.8 mmol), and TFAA (1.9 mL, 13.2 mmol) in CH_2Cl_2 (15 mL). After 4 h the mixture was treated with H_2O (10 mL) and 5 M NaOH until pH 10 was attained. The mixture was treated with CH_2Cl_2 (50 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the organic portions were combined, washed with H_2O (20 mL), dried over $MgSO_4$, filtered, and evaporated to afford **24** (0.53 g, 100%): mp 156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (s, 3 H, 18-CH_3), 1.31 (s, 3 H, 19-CH_3), 1.34 (d, J = 7.1 Hz, 3 H, 16-CH_3), 2.11 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 4.59 (AB q, J = 16.5 Hz, 21-CH_2), 5.55 (d, J = 5.9 Hz, 1 H, H_{11}), 5.74 (s, 1 H, H_4); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.08, 19.44, 20.52, 21.62, 26.01, 32.27, 32.82, 33.03, 33.80, 34.24, 36.39, 37.23, 40.97, 46.48, 47.16, 47.29, 67.76, 95.14, 118.55, 124.06, 143.61, 169.50, 170.58, 171.56, 198.93, 199.35; HRMS for $C_{26}H_{34}O_6$ calcd 442.2355, found 442.2349. Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.57; H, 7.74. Found: C, 70.08; H, 7.70.

Acknowledgment. We thank Dr. James J. Kaminski for performing computer calculations and Dr. David R. Andrews for samples of intermediates. The skilled technical assistance of Carmen Alvarez, Shawn Meyer, and Eric Silverberg is gratefully acknowledged. We are also indebted to Dr. George M. Love for helpful discussions throughout the course of this work.

Supplementary Material Available: X-ray crystallographic data for compound **10**, proton NMR spectra for compounds described in the Experimental Section, and computational procedures for AM1 calculations (31 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of the Milbemycin β_3 Spiroketal Subunit

Mark A. Holoboski and Emil Koft*,†

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

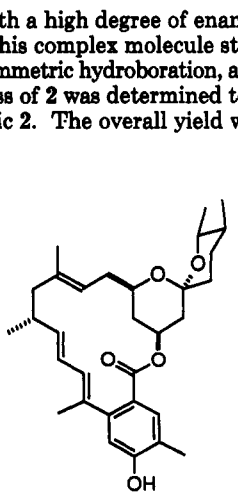
Received May 16, 1991

The milbemycin β_3 spiroketal subunit **2** has been prepared with a high degree of enantiomeric purity. This represents the first reagent-controlled asymmetric synthesis of this complex molecule starting from an achiral starting material. Key reactions include Sharpless epoxidation, asymmetric hydroboration, and the Birch reduction of a meta-substituted cinnamyl epoxide. The enantiomeric excess of **2** was determined to be >95% by a chiral shift ^{1}H NMR experiment with both optically active and racemic **2**. The overall yield was 1.2% from methyl *m*-toluate (**3**).

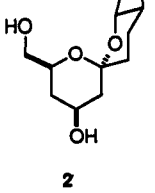
Introduction

Strategies for the construction of spiroketals are well documented, and a substantial amount of work has been reported in the past several years concerning the preparation of the avermectins, milbemycins, and their related key intermediates.[1-3] All of the previous syntheses of the milbemycin β_3 (**1**) spiroketal subunit **2** have utilized asymmetric starting materials from the chiral pool.[4,5]

We now report an enantioselective synthesis of spiroketal **2** according to the strategy outlined in retrosynthetic form in Scheme I. Spiroketal **2** was envisioned to arise from an acid-catalyzed ring closure of structure **B** with the anomeric effect governing the product's relative configu-



1 Milbemycin β_3



2

* Address correspondence concerning this paper to Professor Arthur G. Schultz at RPI.

† Deceased February 17, 1989.

0022-3263/92/1957-0965$03.00/0