Synthesis of Digitoxigenin from 3β-Acetoxyandrost-5-en-17-one. Construction of a Suitably Functionalized Pregnane Side Chain via Presumed Allene Oxide Intermediate

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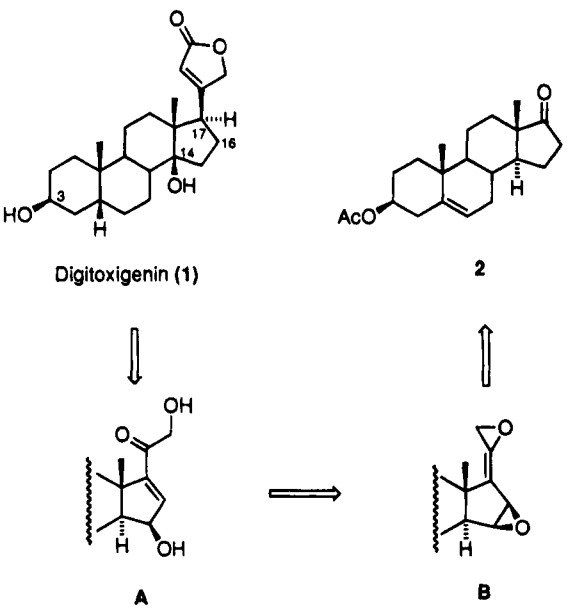
The synthesis of digitoxigenin (**1**) from 3β-acetoxyandrost-5-en-17-one (**2**) involves construction of the 21-hydroxy-20-keto pregnane side chain from 1-bromo-1-(trimethylsilyl)ethylene via presumed intermediate allene oxide **11**. The key intermediate alcohol **10** is obtained by addition of 1-lithio-1-(trimethylsilyl)ethylene to the carbonyl group of **4** followed by selective epoxidations of the double bonds in **5**. Reaction of trifluoroacetate **8** with aqueous tetra-*n*-butylammonium fluoride affords 15β,21-dihydroxypregn-16-en-20-one **12**. After hydrogenation of the C-16,17 double bond, the butenolide ring is formed using (triphenylphosphoranylidene)ketene to give 15β-hydroxycardenolide **14**, which has previously been converted to digitoxigenin (**1**).

The cardiac glycosides (*digitalis*) are steroids found in a widely distributed variety of plants. Characteristically containing a lactone ring at the 17β position and a sugar moiety at the 3β position, these natural products are considered unique in being the only inotropic drugs suitable for the chronic treatment of congestive heart failure.[1] The genins of naturally-occurring glycosides are distinguished from other steroids by three unusual features: a *cis* C/D ring junction, a 14β-hydroxyl group, and a 17β-unsaturated lactone. In addition, most genins have a *cis* A/B ring junction. A representative cardenolide, produced by *Digitalis purpurea* and *Digitalis lanata*, is digitoxigenin (**1**).

For the synthesis of cardenolides, pregnane derivatives have been most frequently employed as the starting materials.[2] Recently, 17-oxoandrostanes, which are readily available by total synthesis[3] as well as by microbiological[4] and chemical degradation of sitosterols have become particularly advantageous steroidal substrates.[5] The synthesis of cardenolides from 17-oxoandrostanes involves stereochemical problems concerned with the introduction of 17β substituents and the 14β hydroxyl group. The steric requirements of the C and D rings of 17-oxoandrostanes dictate that the butenolide ring should be introduced *prior* to hydroxylation at C-14. Applying that constraint to a retrosynthetic plan, precursors having a β-hydroxyl group at C-15, a suitable substituent at C-17, a double bond at C-16,17, and a *trans* C/D ring junction would have to be properly functionalized to allow further transformations into the desired cardenolides. The following points are of critical concern: (a) hydrogenation of the C-16,17 double bond proceeds from the less hindered α-face furnishing a product with a 17β substituent, (b) elimination of the C-15β hydroxyl group generates a C-14,15 double bond,[5d] (c) introduction of the 14β hydroxyl group can be accomplished from C-14,15 unsaturated derivatives.[6] We report the synthesis of digitoxigenin (**1**) from 3β-acetoxyandrost-5-en-17-one (**2**) (Scheme 1) in which a suitably functionalized 21-hydroxy-20-keto pregnane side chain (**A**) needed for the butenolide

Scheme 1



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(1) For a recent review, see: Thomas, R.; Gray, P.; Andrew, J. *Adv. Drug Res.* **1990**, *19*, 312.

(2) (a) Kocovsky, P.; Stieborowa, I. *Tetrahedron Lett.* **1989**, *30*, 4295. (b) Welzel, P.; Stein, H.; Milkova, T. *Liebigs Ann. Chem.* **1982**, 2119. (c) Kocovsky, P. *Collect Czech. Chem. Commun.* **1980**, *45*, 2998. (d) Nickisch, K.; Kose, W.; Bohlmann, F. *Chem. Ber.* **1980**, *113*, 2038. (e) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, 3287. (f) Lenz, G. R.; Schulz, J. A. *J. Org. Chem.* **1978**, *43*, 2334. (g) Fritsch, W.; Haede, W.; Radscheit, K.; Stache, U.; Ruschig, H. *Liebigs Ann. Chem.* **1974**, 621.

(3) For example: (a) Daniewski, A. R.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 1397. (b) Daniewski, A. R.; Valenta, Z.; White, P. *Bull. Pol. Acad. Sci. Chem.* **1984**, *32*, 29.

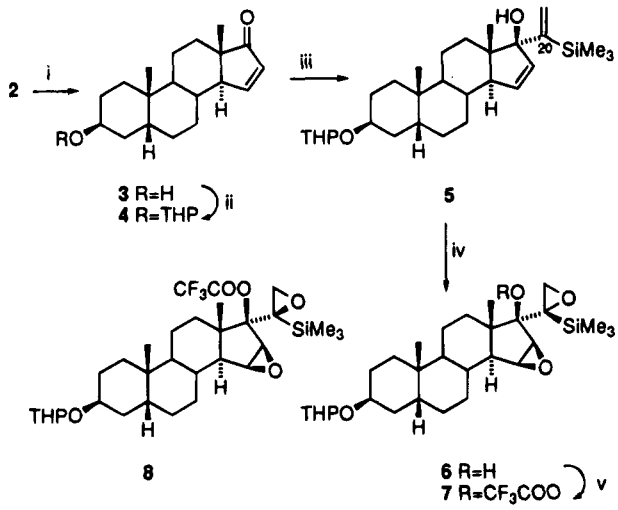
(4) (a) Wovcha, M. G.; Antosz, F. J.; Knight, J. C.; Kominek, L. A.; Pyke, T. R. *Biochim. Biophys. Acta* **1978**, *531*, 308. (b) Eder, U.; Sauer, G.; Haffer, G.; Neef, G.; Wiechert, R.; Weber, A.; Poper, A.; Kenneckie, M.; Mueller, R. *Ger. Offen.* 2 534 911, 1977; *Chem. Abstr.* **1977**, *86*, 187659n.

(5) (a) Daniewski, A. R.; Kabat, M. M.; Masnyk, M.; Wojciechowska, W.; Wicha, J. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1064. (b) Groszek, G.; Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron* **1989**, *45*, 2223. (c) Daniewski, A. R.; Kabat, M. M.; Masnyk, M.; Wicha, J.; Wojciechowska, W.; Dudeck, H. *J. Org. Chem.* **1988**, *53*, 4888. (d) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1601. (e) Harnish, W.; Morera, E.; Ortar, G. *J. Org. Chem.* **1985**, *50*, 1990. (f) Wicha, J.; Kabat, M. M. *J. Chem. Soc., Chem. Commun.* **1983**, 985. (g) Kabat, M. M.; Kurek, A.; Wicha, J. *J. Org. Chem.* **1983**, *48*, 4248. (h) Kurek, A.; Kabat, M. M.; Gumulka, M.; Wicha, J. *Pol. J. Chem.* **1981**, *55*, 1369. (i) Tsai, T. Y. R.; Minta, A.; Wiesner, K. *Heterocycles* **1979**, *12*, 1397.

(6) (a) Heller, M.; McEvoy, F. J.; Bernstein, S. *Steroids* **1964**, *3*, 193. (b) Engel, Ch. R.; Bach, G. *Steroids* **1964**, *3*, 593.

0022-3263/95/1960-1823$09.00/0

Scheme 2



[a] (i) References 5g and 8 (40%); (ii) DHP/H^+ (88%); (iii) CH_2=C(Br)$SiMe_3$, *n*-BuLi, BF_3·Et_2O (93%); (iv) *m*-CPBA (89%); (v) $(CF_3CO)_2O$/Py (91%).

ring formation, via an intermediate allene oxide (**B**), has been constructed.[7]

As previously described[5g,8] (Scheme 2), 3β-acetoxyandrost-5-en-17-one (**2**) was transformed into the α,β-unsaturated ketone **3** (40% overall yield) possessing the required *cis* A/B ring junction and 3β-hydroxyl group, which was then protected as its THP ether **4**. For the introduction of the pregnane side chain, it was necessary to introduce a two-carbon-atom substituent at C-17. For this purpose we employed 1-bromo-1-(trimethylsilyl)-ethylene. Thus, treatment of compound **4** with CH_2=C(SiMe_3)Br/*n*-BuLi in the presence of BF_3·Et_2O in THF solution afforded[9] exclusively **5** (93% yield) (^{1}H NMR: olefinic protons δ 5.37, 5.43, 5.49, and 5.99). The configuration at C-17, *i.e.*, α for the vinylsilane and β for the hydroxyl group, was ascribed on the basis of the well-documented approach of reagents at C-17 from the less hindered α-face when the C/D ring fusion is *trans*. This configuration at C-17 in compound **5**, however, is opposite in respect to configuration of the side chain in the target product. Therefore, a major problem of the synthesis was to invert the configuration at C-17 in order to obtain an intermediate with the necessary β side chain. With this in mind, our plan was to transform double bonds of **5** into a diepoxide which, after fluoride-promoted formation of an allene oxide[10] and subsequent opening with a nucleophile, would provide the desired unsaturated dihydroxy 20-keto pregnane derivative **12**. To this end, diene **5** was treated with 2 equiv of *m*-CPBA in dichloromethane to give a diepoxide that, according to ^{1}H NMR (500 MHz), was shown to be a single diastereomer (**6**) (epoxide protons at δ 2.84, 2.88, 3.38 and 3.46). The β configuration of the C-15,16 epoxide was assigned according to a general rule of peracid addition to carbocyclic systems directed by a hydroxyl group. The *R* configuration of the epoxide function at C-20 was tentatively assigned by examination of Dreiding molecular models; the conformation of the vinylsilane substituent in **5** with the least steric interaction of the trimethylsilyl group with the steroid skeleton was chosen. Utilization of compound **6** in the crucial step of the synthesis, *i.e.*, formation of the pregane side chain, required transformation of the C-17 hydroxyl into a good leaving group. Several attempts to prepare a leaving group such as methanesulfonyloxy, *p*-toluenesulfonyloxy, trifluoromethanesulfonyloxy, or acetoxy were unsuccessful, apparently due to severe steric congestion around C-17; however, trifluoroacetic anhydride in pyridine provided the trifluoroacetate **7** in good yield (89%). Ester **7** was expected to undergo the crucial transformation in the synthesis—fluoride-promoted formation of the allene oxide. However, contrary to expectations, nucleophilic attack of fluoride occurred on the carbonyl group of the ester function instead on the silicon atom. Treatment of trifluoroacetate **7** with 1 equiv of tetra-*n*-butylammonium fluoride trihydrate (TBAF·3H_2O) in THF solution in the presence of an additional 10 equiv of water regenerated alcohol **6**. This result led to the assumption that, because of steric effects, the antiperiplanar conformation of substituents (Me_3SiC and $COCOCF_3$) required for the desired elimination to occur could not be attained. These findings prompted us to investigate the desirability of synthesizing compound **8**, epimeric to **7** at C-20.

Computer modeling (SYBYL) suggested that diepoxide **8** and not **7** would populate a conformation that would favor elimination to give the allene oxide. Because of the above findings, we decided to prepare compound **8** and study its reaction with fluoride.

Oxidation of allylic alcohol **5** (Scheme 3) with *t*-BuOOH/$VO(acac)_2$[11] in toluene solution afforded the monoepoxide **9** [δ 2.27 and 2.88 (epoxide 21-H), 5.40 and 5.96 (15-H and 16-H)]. The C-15,16 double bond was inert to epoxidation with an excess of reagent but was successfully oxidized with *m*-CPBA, giving the diepoxide **10** (epoxide protons at δ 2.60, 3.03, 3.32, and 3.49).[12]

Esterification of **10** with trifluoroacetic anhydride in pyridine provided trifluoroacetate **8** in 91% yield. The ^{1}H NMR spectrum of **8** displayed expected sharp signals [δ 0.99 (s, 18-Me), 1.10 (s, 19-Me), 2.63 (d, J = 4.2 Hz, epoxide-H) and 3.55 (s, epoxide-H)], as well as two very broad signals, corresponding to the second pair of epoxide protons (at δ 3.05 and 4.25, $\nu_{1/2}$ = 65 Hz), indicating that the rotation of the silyl epoxide substituent had been decisively slowed down by the introduction of the trifluoroacetate group. Since the range of epoxide proton signals overlapped those of the THP protons and also because the THP protective group created diasteromers,

(7) This work was inspired by Prof. Wicha's idea to synthesize pregnenolone from **2** via an allene oxide: (a) Wicha, J.; Kabat, M. M. Patent PL 154 774, 1991. (b) Wicha, J.; Kabat, M. M. Patent PL 154 094, 1991. (c) Kabat, M. M.; Wicha, J. *Book of Abstracts*, XIIIth Conference on Isoprenoids, September 24–29, 1989, Poznan, Poland; 78.

(8) (a) Groszek, G.; Kabat, M. M.; Kurek, A.; Masnyk, M.; Wicha, J. *Bull. Pol. Acad. Sci., Chem.* **1986**, *34*, 305. (b) Kelly, R. W.; Sykes, P. *J. Chem. Soc. C.* **1968**, 416.

(9) The addition of 1-lithio-1-(trimethylsilyl)ethylene to the corresponding C-15,16 saturated ketone, 3β-[(tetrahydro-2*H*-pyran-2′-yl)-oxy]-androst-5-en-17-one, was sluggish[7a] and of lower yield (ca. 35–60%, depending on the presence of BF_3·Et_2O) probably due to enolization of the carbonyl group.

(10) For a review article on the chemistry of the allene oxides, see: Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2289.

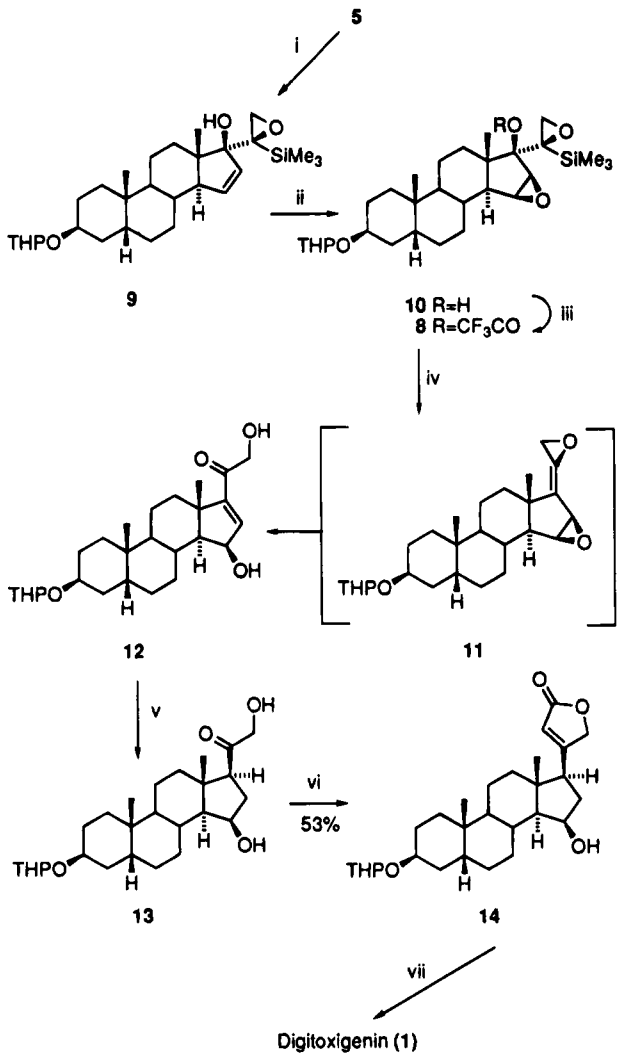
(11) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(12) Reaction of the known 15β,16β-epoxy-3β-((tetrahydro-2*H*-pyran-2′-yl)oxy)-5β-androstan-17-one[8a] with CH_2=C(SiMe_3)Br/*n*-BuLi afforded the product of addition to the C-17 carbonyl group in 42% yield (and 36% yield of the product of epoxide opening) which by treatment with (a) *m*-CPBA gave compound **6** or (b) *t*-BuOOH/$VO(acac)_2$ gave **10**.

(13) Main, P.; Fiske, S.; Hull, S.; Lessinger, L.; Germain, G.; Declerq, J. P.; Woolfson, M. MULTAN 11/82, University of York, England and University of Louvain, Belgium, 1982.

(14) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.

Scheme 3



[a] (i) *t*-BuOOH/VO(acac)$_2$ (86%); (ii) *m*-CPBA (87%); (iii) $(CF_3CO)_2O$, Py (87%); (iv) TBAF, H_2O, THF, rt; (v) H_2, Pd/C (97%); (vi) $Ph_3P{=}C{=}C{=}O$, Et_3N (53%); (vii) refs 5d and 6b.

the THP ether group of **8** was removed and the resulting 3β hydroxyl group was acetylated. X-ray crystallography of acetate **15** verified the *S* configuration at C-20 and the β configuration of the 15,16 epoxide function (Figure 1).

Treatment of compound **8** with 1 equiv of TBAF·3H_2O and an additional 10 equiv of water in THF solution at ambient temperature afforded two products which were separated by column chromatography. The less polar compound was the hydrolysis product **10**. The second product, obtained in 53% yield,[15] was the desired 15β,21-dihydroxypregn-16-en-20-one (**12**) (IR: 3540, 1680, 1600 cm^{-1}). Formation of **12** from **8** can be explained as a sequence of reactions initiated by fluoride attack on silicon with formation of an allene oxide (**11**), followed by opening of the C-20,21 oxide by water, to give the 21-hydroxy intermediate, which rearranged in a concerted process (or possibly via the β,γ-epoxy ketone) to the γ-hydroxy-α,β-unsaturated product.

The one-pot transformation of compound **8** into pregnane **12**, bearing a hydroxyl group at C-15 and a C-16,17 double bond, proved to be a practical solution to the stereochemical and chemical problems in the synthesis of digitoxigenin (**1**) from ketone **3** (*vide supra*).[17] Catalytic addition of hydrogen to the C-16,17 double bond of **12** using 10% Pd/C occurred from the α-face, furnishing pregnane **13**. The latter was transformed into the butenolide using the method of Nickisch *et al.*[2d] in which **13** was reacted with (triphenylphosphoranylidene) ketene[16] ($Ph_3P{=}C{=}C{=}O$) to afford the 15β-hydroxycardenolide **14**, mp 144–148 °C IR: 3620 (OH), 1790, 1750, and 1630 (butenolide) cm^{-1} (lit.[5d] mp 145–147 °C) whose analytical and spectral properties were in full agreement to those previously reported by Wicha and Kabat.[5d] The conversion of compound **14** into **1** had already been reported,[5d,6b] and consequently, the present study constitutes a complete synthesis of digitoxigenin (**1**).

Experimental Section

Melting points were recorded on Koefler hot-stage apparatus and are uncorrected. The spectra were recorded using the following instruments: IR spectra, Beckman 4240 or Unicam SP 200; ^1H NMR spectra, Bruker AM 500 (500 MHz) in $CDCl_3$ solution with Me_4Si as the internal standard; mass spectra, Finnigan MAT 8200. Column chromatography was performed on Kieselgel 60 (70–230 mesh), Merck, and TLC on aluminum sheets–Kieselgel 60, Merck. *J* values are in hertz. Organic solvents were dried over anhydrous $MgSO_4$ and filtered, and the solvents were evaporated under reduced pressure on a rotary evaporator. Yields refer to homogeneous products (TLC). Elemental analyses were performed in the Analytical Laboratory of our Institute, headed by Mrs. K. Branicka.

3β-[(Tetrahydro-2*H*-pyran-2′-yl)oxy]-5β-androst-15-en-17-one (4). A solution of alcohol **3** (2.0 g, 6.9 mmol), dihydropyran (750 mg, 8.97 mmol), and *p*-TsOH (10 mg) in dichloromethane (30 mL) was stirred at rt for 3 h. The solution was then washed with saturated $NaHCO_3$ solution and dried. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (80 g) with hexane–Et_2O (92:8) to give THP ether **4** (2.28 g, 88%), mp 109–114 °C (from pentane): UV (EtOH) λ = 233 nm (ε = 6000); IR (film) 1710 (C=O) and 1580 (C=C) cm^{-1}; ^1H NMR δ 1.016 and 1.018 (3 H, 2s, 18-Me), 1.06 (3 H, s, 19-Me), 3.48 (1 H, m, -OC*H*), 3.90 (1 H, m, -OC*H*), 3.97 (1 H, m, 3 H), 4.62 and 4.65 (1 H, 2m, -OC*H*O-), 6.02 (1 H, dd, *J* = 3.2 and 6.0, 15-H), 7.52 (1 H, d, *J* 5.9, 16-H); MS *m*/*z* (rel intensity) 372 (M^+, 15), 271 (100), 253 (25), 85 (68), 57 (69), 43 (73); HRMS for $C_{24}H_{36}O_3$ calcd 372.2665, found 372.2664. Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.52; H, 9.86.

3β-[(Tetrahydro-2*H*-pyran-2′-yl)oxy]-20-(trimethylsilyl)-5β,17α-pregna-15,20-dien-17-ol (5). To a solution of 1-lithio-1-(trimethylsilyl)ethylene in THF (25 mL), which had been prepared under argon from 1-bromo-1-(trimethylsilyl)ethylene (866 mg, 4.84 mmol) and *n*-BuLi (3.03 mL of 1.6 M solution in hexane, 4.84 mmol) at −25 °C, was added a solution of enone **4** (1.5 g, 4.03 mmol) and BF_3·Et_2O (572 mg, 4.03 mmol) in THF (10 mL). The reaction mixture was stirred at −25 °C for 1 h; then the temperature was raised to rt during 1 h. Et_2O (100 mL) was added, and the solution was washed successively with saturated $NaHCO_3$ and water and then dried. Evaporation of solvent and chromatography of the crude product on silica gel (150 g) with hexane–Et_2O (97:3) afforded allylic alcohol **5** (1.73 g, 91%) as a colorless oil: IR ($CHCl_3$) 3620 (OH) and 1250 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.15 (9 H, s, $SiMe_3$), 0.96 (3 H, s, 19-Me), 0.971 and 0.972 (3 H, 2s, 18-H), 3.49 (1 H, m, -OC*H*), 3.90 (1 H, m, -OC*H*), 3.94 (1 H, m, 3-H), 4.61 and 4.64 (1 H, 2m, -OC*H*O-), 5.37 (1 H, dd, *J* = 2.5 and 1.0, 21-H), 5.43 (1 H, ddd, *J* = 5.8, 3.2 and 0.7, 15-H), 5.48 (1 H, d, *J* 2.5, 21-H), 5.99 (1 H, d, *J* 5.7 16-H); MS *m*/*z* (rel intensity) 472 (M^+, 13),

(15) Taking into account recovered alcohol **10**. The yield of **12** can be improved by repeating the sequence of reactions **10** → **8** → **12**.

(16) Bestman, H. J.; Sandmeier, D. *Chem. Ber.* **1980**, *113*, 274.

(17) Steroids having a substructure of 15β,21-dihydroxypregn-16-en-20-one may be useful intermediates for the general synthesis of 15β-hydroxy-16α-alkyl pregnanes that are currently of interest as antiinflamatory agents.

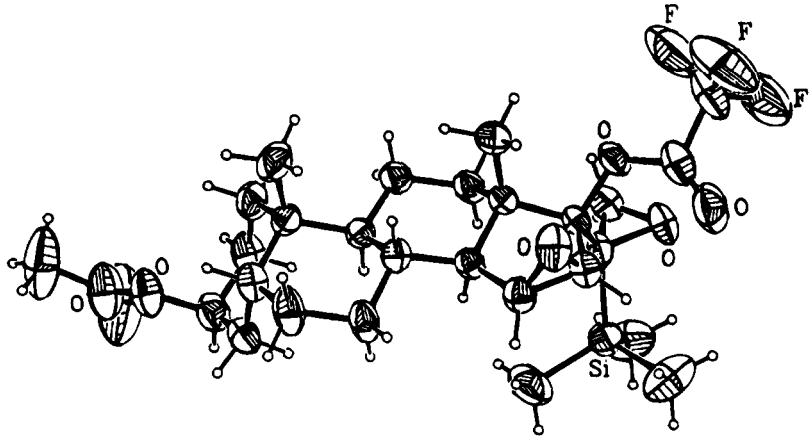


Figure 1. X-ray structure of compound **15**.

457 (M − 15, 3), 388 (M − 84, 100), 370 (M − 84 − 18, 32), 355, (25), 85 (34); HRMS for $C_{29}H_{48}O_3Si$ calcd 472.3373, found 472.3373. Anal. Calcd for $C_{29}H_{48}O_3Si$: C, 73.67; H, 10.23. Found: C, 73.89, H, 10.43.

(20*R*)-15β,16β:20,21-Diepoxy-3-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-20-(trimethylsilyl)-5β,17α-pregnan-17-ol (6). A solution of **5** (150 mg, 0.32 mmol) and *m*-CPBA (161 mg of 85% peracid, 0.8 mmol) in dichloromethane (3 mL) was stirred at rt for 8 h. After standard workup, the crude product was chromatographed on silica gel (15 g) with hexane−Et_2O (92:8) to give the epoxide **6** (142 mg, 89%), as a colorless oil: IR ($CHCl_3$) 3620 (OH) cm^{-1}; ^1H NMR δ 0.13 (9 H, s, $SiMe_3$), 1.00 (3 H, s, 18-Me), 1.04 (3 H, s, 19-Me), 2.84 (1 H, dd, J = 4.3 and 0.8, 21 H), 2.88 (1 H, dd, J = 4.3 and 1.1, 21-H), 3.38 (1 H, d, J = 2.9, 16-H), 3.46 (1 H, d, J = 2.8, 15-H), 3.49 (1 H, m, -OC*H*), 3.91 (1 H, m, -OC*H*), 3.98 (1 H, m, 3-H), 4.64 and 4.67 (1 H, 2m, -OC*H*O-); MS m/z (rel intensity) 504 (M^+, 0.4%), 402 (M − 84 − 18, 9), 229 (28), 85 (100); HRMS for $C_{29}H_{48}O_5Si$ calcd 504.3271, found 504.3271. Anal. Calcd for $C_{29}H_{48}O_5Si$: C, 69.00; H, 9.58. Found: C, 69.17; H, 9.76.

(20R)-15β,16β:20,21-Diepoxy-3-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-20-(trimethylsilyl)-5β,17α-pregnan-17-ol Trifluoroacetate (7). Alcohol **6** (120 mg, 0.24 mmol) in pyridine (3 mL) was treated at 0 °C with trifluoroacetic anhydride (250 mg, 0.96 mmol) for 30 min and then at rt for 5 h. Water (15 mL) was added, and the solution was extracted with Et_2O (2 × 30 mL). The ether extracts were combined and washed successively with water, 5% HCl, and saturated $NaHCO_3$. The solution was dried, and the solvent was evaporated *in vacuo*. The crude product was chromatographed on silica gel (15 g) with hexane−Et_2O (9:1) to give ester **7** (131 mg, 91%), mp 197−201 °C (from hexane−Et_2O): IR (Nujol) 1790 (C=O) cm^{-1}; ^1H NMR δ 0.12 and 0.13 (9 H, 2s, $SiMe_3$), 1.00 (3 H, s, 18-Me), 1.09 (3 H, s, 19-Me), 2.92 (2 H, s, 21-H), 3.42 (1 H, d, J 2.6, 15-H), 3.48 (1 H, m, -OC*H*), 3.91 (1 H, m, -OC*H*), 3.97 (1 H, m, 3-H), 4.27 (1 H, dd, J = 3.1 and 0.6, 15-H), 4.64 (1 H, m, -OC*H*O-); MS m/z (rel intensity) 600 (M^+, 6), 585 (M − 15, 11), 515 (M − 85, 15), 499 (M − 101, 13), 471 (25), 85 (100); HRMS for $C_{31}H_{47}O_6SiF_3$ calcd 600.3093, found 600.3094. Anal. Calcd for $C_{31}H_{47}O_6SiF_3$: C, 61.98; H, 7.89. Found: C, 62.09; H, 8.12.

(20*S*)-20,21-Epoxy-3-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-20-(trimethylsilyl)-5β,17α-pregn-15-en-17-ol (9). A solution of alcohol **5** (1.6 g, 3.39 mmol) in toluene (10 mL) containing vanadyl acetylacetonate (10 mg) was treated with *t*-BuOOH (2.26 mL of 3.3 M solution in hexane, 7.46 mmol) and then was stirred at rt for 5 h. Then solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (100 g) with hexane−Et_2O (97:3) to give epoxide **9** (1.42 g, 86%), as a colorless oil: IR ($CHCl_3$) 3620 (OH) and 1250 (SiMe) cm^{-1}; ^1H NMR δ 0.07 (9 H, s, $SiMe_3$), 0.91 (3 H, s, 18-Me), 0.971 and 0.973 (3 H, 2s, 19-Me), 2.57 (1 H, dd, J = 5.1 and 1.8, 21-H), 2.83 (1 H, d, J = 5.1, 21-H) 3.47 (1 H, m, -OC*H*), 3.90 (1 H, m, -OC*H*), 3.96 (1 H, m, 3-H), 4.62 and 4.64 (1 H, 2m, -OC*H*O-), 5.40 (1 H, ddd, J = 5.7, 3.2 and 2.3, 15-H), 5.96 (1 H, dt, J = 5.8 and 1.5, 16-H); MS m/z (rel intensity) 488 (M^+, 0.1), 470 (M − 18, 10), 455 (M − 18 − 15, 17), 404 (M − 84, 56), 271 (100), 85 (69); HRMS for $C_{29}H_{48}O_4Si$ calcd 488.3322, found 488.3322. Anal. Calcd for $C_{29}H_{48}O_4Si$: C, 71.26; H, 9.90. Found: C, 71.13; H, 9.81.

(20*S*)-15β,16β:20,21-Diepoxy-3-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-20-(trimethylsilyl)-5β,17α-pregnan-17-ol (10). A solution of compound **9** (650 mg, 1.33 mmol) and *m*-CPBA (350 mg of 85% peracid, 1.73 mmol) in dichloromethane (10 mL) was stirred at rt for 5 h. After standard work up, the crude product was obtained which was chromatographed on silica gel (60 g) with hexane−Et_2O (98:2) to afford epoxide **10** (584 mg, 87%), as a colorless oil: IR ($CHCl_3$) 3620 (OH) cm^{-1}; ^1H NMR δ 0.16 (9 H, s, $SiMe_3$), 0.985 and 0.986 (3 H, 2s, 18-Me), 1.10 (3 H, s, 19-Me), 2.60 (1 H, dd, J = 1.3 and 4.6, 21-H), 3.03 (1 H, d, J = 4.6, 21-H), 3.22 (1 H, dd, J = 3.0 and 0.8, 15-H), 3.49 (1 H, d, J = 3.0, 16-H, overlapped with 1 H, m, -OC*H*), 3.90 (1 H, m, -OC*H*), 3.97 (1 H, m, 3-H), 4.63 and 4.66 (1 H, 2m, -OC*H*O-); MS m/z (rel intensity) 504 (M^+, 0.6), 486 (M − 18, 0.3), 402 (M − 18 − 84, 11), 259 (20), 229 (32), 85 (100); HRMS for $C_{29}H_{48}O_5Si$ calcd 504.3271, found 504.3271. Anal. Calcd for $C_{29}H_{48}O_5Si$: C, 69.00; H, 9.58. Found: C, 69.23; H, 9.80.

(20*S*)-15β,16β:20,21-Diepoxy-3-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-20-(trimethylsilyl)-5β,17α-pregnan-17-ol Trifluoroacetate (8). A solution of alcohol **10** (500 mg, 0.99 mmol) and trifluoroacetic anhydride (830 mg, 3.96 mmol) in pyridine (5 mL) was stirred at 0 °C for 15 min and then at rt for 5 h. Water (15 mL) was added, and the solution was extracted with Et_2O (3 × 20 mL). Extracts were combined and washed successively with water, 5% HCl, and $NaHCO_3$ and then dried. After evaporation of solvent, the crude product was chromatographed on silica gel (50 g) with hexane−Et_2O (95:5) to give ester **8** (548 mg, 92%), mp 178.5−180 °C (from hexane−Et_2O): IR ($CHCl_3$) 1790 (C=O) cm^{-1}; ^1H NMR δ (23 °C) 0.17 (9 H, brs, $SiMe_3$), 0.933 and 0.994 (3 H, 2s, 18-Me), 1.10 (3 H, s, 19-Me), 2.63 (1 H, d, J = 4.4, epoxide-H), 3.05 (1 H, brs, $\nu_{1/2}$ = 65 Hz, epoxide-H), 3.48 (1 H, m, -OC*H*), 3.55 (1 H, s, epoxide-H), 3.91 (1 H, m, -OC*H*), 4.25 (1 H, brs, $\nu_{1/2}$ = 65 Hz, epoxide-H), 4.63 and 4.65 (1 H, 2m, -OC*H*O-); ^1H NMR δ (−40 °C) 0.10 and 0.23 (9 H, 2s, $SiMe_3$), 0.98 and 1.00 (3 H, 2s, 18-Me), 1.08 and 1.12 (3 H, 2s, 19-Me), 2.68 (d, J = 3.4, epoxide-H), 2.72 (t, J = 3.7, epoxide-H), 2.83 (d, J = 4.5, epoxide-H), 3.46 (d, J = 3.3, epoxide-H), 3.49 (1 H, m, -OC*H*), 3.69 (d, J = 2.8, epoxide-H), 3.90 (1 H, m, -OC*H*), 3.98 (1 H, m, 3-H), 4.06 (d, J = 2.5, epoxide-H), 4.48 (t, J = 2.4, epoxide-H), 4.61 (1 H, m, -OC*H*O-); HRMS for $C_{31}H_{47}O_6SiF_3$ calcd 600.3093, found 600.3094. Anal. Calcd for $C_{31}H_{47}O_6SiF_3$: C, 61.98; H, 7.89. Found: C, 62.22; H, 8.03.

(20*S*)-3-(Acetoxy)-15β,16β:20,21-diepoxy-20-(trimethylsilyl)-5β,17α-pregnan-17-ol trifluoroacetate (15). A solution of compound **8** (80 mg, 0.13 mmol) and *p*-TsOH (5 mg) in MeOH (5 mL) was stirred at rt for 3 h. Then solvent was evaporated *in vacuo*, and the residue was dissolved in pyridine (3 mL) and acetic anhydride (2 mL) and stirred at rt for 18 h.

Table 1

temp, °C	$SiMe_3$	18-Me	19-Me	AcO	3-H	epoxide protons (δ, ppm; J or $\nu_{1/2}$, Hz)			
50	0.16	1.02	1.11	2.03	5.08	2.61	3.06	3.52	4.22
	s	s	s	s	m	d, $J = 4.4$	brs	d, $J = 2.8$	brs
35	0.16	1.02	1.11	2.05	5.08	2.62	3.06	3.56	4.22
	s	s	s	s	m	d, $J = 4.4$	$\nu_{1/2} = 46$	s	$\nu_{1/2} = 23$
24	0.16	1.02	1.11	2.06	5.08	2.63	3.05	3.55	4.25
	brs	s	s	s	m	d, $J = 4.3$	$\nu_{1/2} = 65$	brs	$\nu_{1/2} = 65$
0	0.19	1.02	1.10	2.08	6.08	2.65	3.40	3.55	4.04
	$\nu_{1/2} = 58$	brs	brs	s	m	brs	$\nu_{1/2} = 71$	$\nu_{1/2} = 52$	$\nu_{1/2} = 48$
−20	0.10	1.02	1.09	2.10	5.08	2.64	3.43	3.52	4.05
	brs	brs	brs	s	m	s	s	s	s
	0.23	1.03	1.12			2.69	2.81	3.66	4.47
	brs	brs	brs			d, $J = 3.9$	d, $J = 3.1$	s	s
−40	0.10	1.02	1.09	2.11	5.09	2.67	3.46	3.54	4.07
	s	s	s	s	m	d, $J = 3.7$	d, $J = 3.6$	d, $J = 2.8$	d, $J = 2.8$
	0.23	1.03	1.12	2.12		2.71	2.83	3.69	4.49
	s	s	s	s		d, $J = 4.6$	d, $J = 4.5$	d, $J = 2.7$	d, $J = 2.8$

After standard workup and chromatography on silica gel (10 g) with hexane−Et_2O (95:5), the acetate **15** was obtained (61 mg, 82%), mp 174−179 °C (from hexane−Et_2O): IR ($CHCl_3$) 1790 and 1730 (C=O) cm^{-1}; ^1H NMR see Table 1; MS *m/z* (rel intensity) 558 (M^+, 0.1), 543 (M − CH_3, 0.1), 449 (M − AcOH, 1), 429 (1), 356 (3), 147 (49), 105 (40), 91 (48), 73 (85), 43 (100). Anal. Calcd for $C_{28}H_{41}O_6SiF_3$: C, 60.19; H, 7.40. Found: C, 60.23; H, 7.51. Crystal data. Formula: $C_{28}H_{41}F_3O_6Si$; M_r =558.72. Crystal system: orthorombic; space group $P2_12_12_1$, a = 10.911 (3), b = 12.251 (1), and c = 22.139 (1) Å, Z = 4, d_{calc} = 1.254 g cm^{-1}, μ(Cu Kα) = 11.8 cm^{-1}. The structure and absolute configuration of **15** have been determined by a single-crystal X-ray analysis.[18] A perspective drawing of molecule is shown in the Figure 1. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω−2θ scans). The size of the crystal used for data collection was approximately 0.17 × 0.25 × 0.80 mm. The data were corrected for absorption. Of the 3433 independent reflections for θ <75°, 2533 were considered observed [$I > 3.0\sigma(I)$]. The structure was solved by a multiple-solution procedure[13] and was refined by full-matrix least squares. Three reflections, which were strongly affected by extinction, were excluded from the final refinement and difference map. In the final refinement, the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.052 and R_w = 0.062 for the 2530 observed reflections. The major peaks (<0.4 e $Å^{-3}$) of the final difference map are near the fluorine atoms.

The absolute configuration of **15** is based on the anomalous scattering of the silicon atom and was established by refining both enantiomers. The final weighted R values were 0.0624 for the configuration shown above and 0.0661 for its antipode. Thus, by Hamilton test,[14] the configuration shown is absolute.

15β,21-Dihydroxy-3β-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-5β-pregn-16-en-20-one (12). A solution of compound **8** (550 mg, 0.92 mmol), TBAF·$3H_2O$ (290 mg, 0.92 mmol), and H_2O (166 mg, 9.2 mmol) was stirred in THF (2 mL) at 0 °C for 5 h. Then Et_2O (20 mL) was added, and the solution was washed with water and dried. After evaporation of solvent, the residue was chromatographed on silica gel (30 g) using the following solvent systems: (a) hexane−Et_2O (95:5) gave alcohol **10** (200 mg, 43%) and then (b) hexane−Et_2O−CH_2Cl_2 (5:4:1) gave pregnane **12** (120 mg, 30%), mp 172−178 °C (from hexane−Et_2O): UV (EtOH) λ = 233 nm (ϵ = 6200); IR (KBr) 3540 (OH), 1680 (C=O) and 1600 (C=C) cm^{-1}; ^1H NMR δ 1.031 and 1.032 (3 H, 2s, 18-Me), 1.26 (3 H, s, 19-Me), 3.48 (1 H, m, -OC*H*), 3.91 (1 H, m, -OC*H*), 3.96 (1 H, m, 3-H), 4.42 and 4.57 (2 H, J_{AB} = 18.3, 21-H), 4.62 and 4.65 (1 H, 2m, -OC*H*O-), 4.67 (1 H, dd, J = 5.3 and 3.6, 15-H), 6.68 (1 H, dd, J = 2.9 and 0.8, 16-H); MS *m/z* (rel intensity) 432 (M^+, 4), 331 (58), 313 (26), 299 (11), 255 (7), 85 (100); HRMS for $C_{26}H_{40}O_5$ calcd 432.2875, found 432.2876. Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.03; H, 9.36.

15β,21-Dihydroxy-3β-[(tetrahydro-2H-pyran-2′-yl)oxy]-5β-pregnan-20-one (13). Compound **12** (105 mg, 0.24 mmol) was stirred under a hydrogen atmosphere in ethyl acetate (3 mL) with 10% Pd/C (10 mg) at rt for 30 min. Then the catalyst was removed by filtration and the solvent by evaporation *in vacuo* to afford pregnane **13** (101 mg, 97%), mp 170−174 °C (from pentane−Et_2O): IR (KBr) 3440 (OH) and 1700 (C=O) cm^{-1}; ^1H NMR δ 0.89 (3 H, s, 18-Me), 0.984 and 0.985 (3 H, 2s, 19-Me), 2.41 (1 H, t, J = 9.4, 17-H), 3.48 (1 H, m, -OC*H*), 3.90 (1 H, m, -OC*H*), 3.97 (1 H, m, 3-H), 4.16 and 4.22 (2 H, J_{AB} = 18.9, 21-H), 4.34 (1 H, m, 15-H), 4.63 (1 H, m, -OC*H*O-); MS *m/z* (rel intensity) 434 (M^+, 2), 416 (M − 18, 4), 332 (M − 84, 14), 315 (42), 85 (100); HRMS for $C_{26}H_{42}O_5$ calcd 434.3032, found 434.3030. Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.08; H, 9.92.

15β-Hydroxy-3β-[(tetrahydro-2*H*-pyran-2′-yl)oxy]-5β,14α-card-20(22)-enolide (14). A solution of pregnane **13** (75 mg, 0.17 mmol), triethylamine (24 μL, 0.17 mmol), and (triphenylphosphoranylidene)ketene (62 mg, 0.20 mmol) in benzene (20 mL) was stirred at rt for 20 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (10 g) with hexane−Et_2O (3:2) to give cardenolide **14** (43 mg, 53%), mp 144−148 °C (from Et_2O−hexane) (lit.[5d] mp 145−147 °C): UV (EtOH) λ = 217 nm (ϵ = 12 900); IR ($CHCl_3$) 3620 (OH), 1790, 1750 and 1630 (butenolide) cm^{-1}; ^1H NMR δ 0.88 (3 H, s, 18-Me) 0.993 and 0.995 (3 H, 2s, 19-Me), 2.30 (1 H, t, J = 9.8, 17-H), 3.49 (1 H, m, -OC*H*), 3.91 (1 H, m, 3-H), 4.39 (1 H, m, 15-H), 4.63 and 4.65 (1 H, 2m, -OC*H*O-), 4.70 and 4.82 (2 H, ABX, J = 17.3 and 1.6, 21-H), 5.88 (1 H, d, J = 1.6, 22-H). Anal. Calcd for $C_{28}H_{42}O_5$: C, 73.33; H, 9.23. Found: C, 73.39; H, 9.19.

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(18) The author has deposited atomic coordinates for compound **15** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.