Cardiotonic Steroids. 5. A Synthesis of Bufadienolides and Cardenolides from 3β-Acetoxy-5-androsten-17-one via Common Intermediates[1]

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The starting ketone **3** was transformed to the protected aldehyde **8** via its 5β-H derivative **5**, Knoevenagel adduct **6**, and hydroxy nitrile **7**. The intermediate **8** was acetylated and treated with an ylide derived from triethyl phosphonoacetate to give compound **9**. Removal of the tetrahydropyranyl group in **9** followed by oxidation afforded aldehyde **10** which was cyclized to the bufadienolide **2b**. Alternatively, compound **8** was treated with sodium cyanide and hydrochloric acid to give hydroxy lactone **12**. Eventually, the hydroxy group in the side chain was dehydrated to give the cardenolide **1b**.

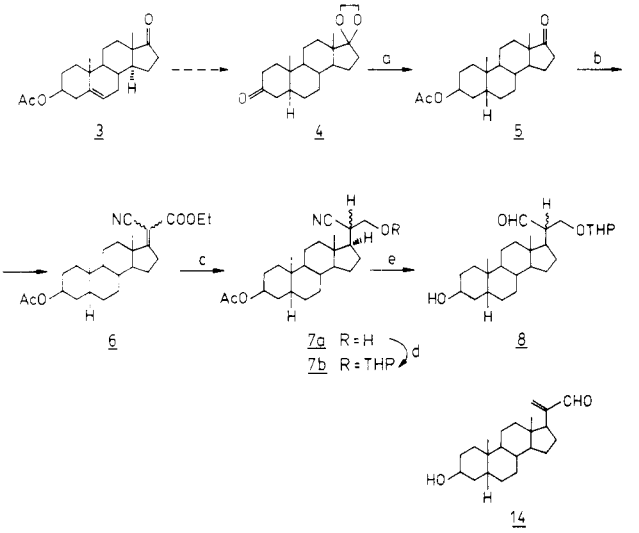
Synthesis of cardenolides and bufadienolides (exemplified here by digitoxigenin (**1a**) and bufalin (**2a**), respectively) has received considerable attention[2] due to their utility in the treatment of heart diseases. However, only in a few cases[2c,2d,3] were androstane derivatives chosen as a starting point for the construction of the heterocyclic 17β-substitutent. Recent availability of 17-oxoandrostane derivatives by microbiological degradation of abundant sitosterols,[4] as well as progress in total synthesis,[5] has placed these intermediates in a central position in the synthesis of pharmacologically important steroids. In the present publication we wish to report a simple synthesis of cardenolide **1b** and bufadienolide **2b** (see Figure 1) from 3β-hydroxy-5-androsten-17-one acetate (**3**) via the common intermediate **8**. The transformation of compound **1b** into digitoxigenin (**1a**) has recently been described.[6]

The starting material of our synthesis, acetoxy ketone **3**, was transformed in four steps, in accordance with described methods,[13] into the protected diketone **4** in an 86% overall yield (see Scheme I). The carbonyl group in compound **4** was reduced with lithium tri-*sec*-butylborohydride (L-Selectride; Aldrich) in hexane–tetrahydrofuran (THF) solution to the axial hydroxyl group, then the ketal group was hydrolyzed with *p*-toluenesulfonic acid (*p*-TSA) in acetone, and the crude hydroxy ketone was acetylated to afford compound **5** in 76% yield.

Condensation of ketone **5** with ethyl cyanoacetate in boiling toluene, in the presence of ammonium acetate, gave rise to the cyano ester **6**, presumably as a mixture of *E* and *Z* isomers (89% yield). The condensation product was reduced with an excess of sodium borohydride in methanol to the saturated alcohol **7a** (97% yield), present as a mixture of stereoisomers. The denoted configuration on C-17 in compound **7a** was expected on the basis of model experiments[7] and was later confirmed by the structure of the final products of the syntheses. The stereochemistry at C-20 in compound **7a** is of no consequence since this chiral center was to be destroyed at one of the last steps of the synthesis.

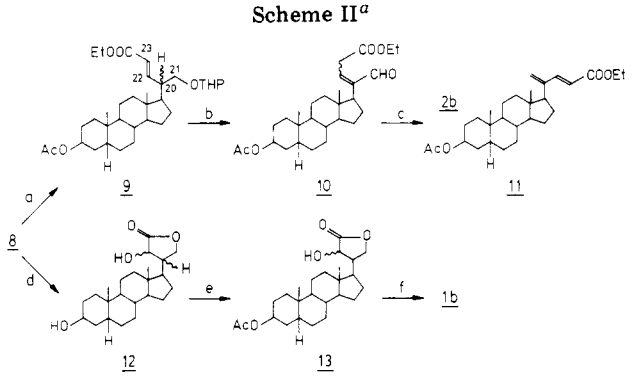
The hydroxy group in compound **7a** was then protected as its tetrahydropyranyl (THP) ether and the derivative **7b** was subjected to reduction with an excess of diisobutylaluminum hydride (DIBAL) in toluene at −78 °C.

Scheme I[a]



[a] a, Selectride-L/THF, *p*-TSA/acetone, Ac_2O/pyridine (75% yield); b, $NCCH_2COOEt$, $AcONH_4$, AcOH/toluene (89%); c, $NaBH_4$/MeOH (97%); d, dihydropyran/*p*-TSA/CH_2Cl_2 (99%); e, DIBAL/toluene/−78 °C (80%).

Scheme II[a]



[a] a, Ac_2O/pyridine, $(EtO)_2POCHCOOEt$/THF/−20 °C, room temperature (79%); b, *p*-TSA/MeOH, PCC/CH_2Cl_2 (84%); c, *p*-TSA/benzene; d, NaCN/MeOH/aqueous HCl, room temperature then reflux (99%); e, $NaHCO_3$/MeOH–$CHCl_3$ (92%); f, $SOCl_2$/DMF/room temperature, Li_2CO_3/LiCl, reflux (84%).

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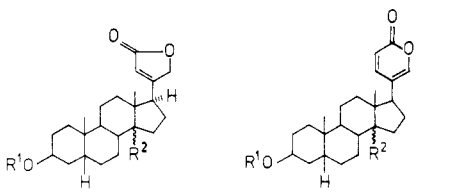

1a R^1=H, R^2=βOH 2a R^1=H, R^2=βOH
1b R^1=Ac, R^2=αH 2b R^1=Ac, R^2=αH

Figure 1.

The obtained aldehyde **8** (80% yield) was contaminated with small amounts of (ca. 3%) the unsaturated derivative **14**, which was removed by chromatography.

For the synthesis of the bufadienolide **2b**, the key intermediate **8** was first acetylated and then treated in THF solution with an ylide prepared from triethyl phosphonoacetate and sodium hydride in THF (see Scheme II). Chromatography yielded a minor amount of the dienoic ester **11** and the required condensation product **9** (79% yield). The *E* configuration of the double bond in compound **9** was evident[8] from its ^{1}H NMR spectrum in which the coupling constant for the vinylic protons was 15 Hz. The protective THP group in compound **9** was removed and the alcohol was oxidized with pyridinium chlorochromate[9] (PCC) to give the α,β-unsaturated aldehyde **10** in 75% yield. The structure of compound **10** was supported by an IR spectrum in which bands at 1730, 1700, and 1630 cm^{-1} had appeared for the ester carbonyl, aldehyde carbonyl, and conjugated double bond, respectively, and by its ^{1}H NMR spectrum in which sharp singlets for the aldehydic protons in two isomers occurred at 9.50 and 10.0 ppm and for the C-22 vinylic proton at 6.78 ppm (1 H, t, J = 7 Hz). It is of interest that the oxidation with PCC in the presence of sodium acetate buffer proceeds sluggishly and gives distinctly lower yields of the product.

The final step in the bufadienolide synthesis was performed according to described methods[10] as follows: Compound **10** was heated in benzene solution in the presence of a catalytic amount of *p*-TSA. The crude product was filtered through silica gel and crystallized to afford pentadienolide **2b**, having physical and spectroscopic properties (mp, IR, UV, and ^{1}H NMR) in agreement with those already reported.[11]

For the cardenolide synthesis, the key intermediate **8** was treated at room temperature with hydrogen cyanide generated in situ from sodium cyanide and hydrochloric acid, and then the acidic reaction mixture was heated under reflux. Under these conditions, the dihydroxycardanolide **12** was formed in nearly quantitative yield. The structure of product **12** follows from an IR spectrum (in KBr) in which a carbonyl absorption appears at 1775 cm^{-1} and from a mass spectrum containing the appropriate peak corresponding to the molecular ion. In a ^{1}H NMR spectrum of product **12**, three singlets for angular methyl group protons were observed at 1.05, 0.85, and 0.74 ppm and integrated for 6 H. This result correlates with a mixture of diastereomers.

Diol **12** was acetylated and, without purification, the resulting diacetate was partially hydrolyzed with sodium hydrogen carbonate. The monoacetate **13** was thus obtained in 90% yield. Examination of the hydrolysis sequence on TLC plates revealed the presence of a polar constituent of the reaction mixture prior to acidification, indicating that opening of the lactone ring occurs concomitantly with hydrolysis of the C-22 acetoxy group.

Compound **13** was dehydrated by treating it first with thionyl chloride (3 equiv) in dimethylformamide (DMF) at room temperature and subsequently with an excess of lithium carbonate and lithium chloride. The butenolide **1b** was obtained in 84% yield; it showed spectroscopic properties with the structure and a melting point in agreement with that reported in the literature.[12]

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus. The spectra were recorded with the following instruments: IR, Beckman 4240 or Unicam SP200; UV, Beckman MIV; NMR, Jeol JNM-4H-100 (in $CDCl_3$ solutions unless otherwise stated); mass spectra, LKB2091 (at 15 eV ionization potential). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Column chromatography was performed on kieselgel 60, and TLC on silica gel G, Merck. Organic solutions were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo on a rotary evaporator. Yields refer to products homogenous on TLC which were used further, without any purification. Microanalyses were performed in our analytical laboratory.

3β-Hydroxy-5β-androstan-17-one Acetate (5). To a stirred solution of 17,17-(ethylenedioxy)-5β-androstan-3-one[13] (3.3 g, 10 mmol) in THF (30 mL) at 0 °C under argon, Selectride-L (1 M in hexane, 13 mL) was added during 30 min. The reaction mixture was stirred for 2 h and then sequentially treated with 3 N aqueous NaOH (5 mL), 30% hydrogen peroxide (5 mL), and H_2O (50 mL). Isolation of the product with ether and crystallization from MeOH gave 17,17-(ethylenedioxy)-5β-androstan-3β-ol (3.0 g, 91%), mp 123–125 °C.

The product (4.15 g) was dissolved in acetone (200 mL) containing *p*-TSA (100 mg). After 6 h, 3β-hydroxy-5β-androstan-17-one was isolated in the usual way (3.28 g, 91%), mp 154–155 °C (from acetone–hexane).

The latter product (3.1 g) was acetylated with Ac_2O (20 mL) and pyridine (40 mL) at room temperature for 18 h. The usual workup gave compound **5** (3.27 g, 92%), mp 158–159 °C.

Ethyl 3β-Acetoxy-20ξ-cyano-5β-pregn-17(20)-en-21-oate (6). A mixture of compound **5** (7.31 g), ethyl cyanoacetate (5.4 mL), HOAc (23 mL), NH_4OAc (3.3 g), and toluene (250 mL) was heated under reflux for 10 h under a Dean–Stark water separator. Additional NH_4OAc (3 g) was added and heating continued for 14 h, and then the solution was cooled and washed with saturated aqueous $NaHCO_3$ and with H_2O. The crude product was filtered through a SiO_2 column (hexane–ethyl acetate, 9:1) to give **6** (8.7 g, 89%). An analytical sample was secured from MeOH: mp 143–146 °C; λ_{max} (EtOH) 240 nm (ε = 13 500), ν_{max} ($CHCl_3$) 2220 (C≡N), 1730 (C=O), and 1605 (C=C) cm^{-1}; ^{1}H NMR 1.00 (s, 6 H, angular CH_3), 1.33 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 2.04 (s, 3 H, $OCOCH_3$), 4.26 (q, 2 H, J = 7.5 Hz, OCH_2CH_3), 5.07 (m, 1 H, 3-H).

Anal. Calcd for $C_{26}H_{37}O_4N$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.17; H, 8.92; N, 3.22.

3β-Acetoxy-20ξ-cyano-5β-pregnan-21-ol (7a). $NaBH_4$ (3 g) was added to an ice cooled solution of compound **6** (3.74 g) in MeOH (100 mL) and the resulting mixture was stirred for 3 h. The excess reagent was destroyed with acetone, the mixture was acidified with 10% HCl, and the product was isolated with ethyl

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(13) This compound was prepared from 3β-hydroxy-5-androsten-17-one acetate by (a) ketalization with ethylene glycol (92% yield), (b) hydrolysis (96.5%) and Oppenauer oxidation (93%), and (c) catalytic hydrogenation over 10% palladium on charcoal in ethanol in the presence of potassium hydroxide[14] (97%).
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acetate. The crude material (2.85 g, 97%) was homogeneous according to TLC; recrystallization of a sample gave **7a**, mp 213–217 °C (ethyl acetate); ν_{max} ($CHCl_3$) 3620 (OH), 2240 (C≡N), 1730 (C=O) cm^{-1}; ^1H NMR 0.75 and 0.98 (2 s, angular CH_3), 2.04 (s, 3 H, $OCOCH_3$), 2.84 (m, 1 H, 20-H), 3.74 (d, 2 H, J = 6.5 Hz, 21-H), 5.06 (m, 1 H, 3-H).

Anal. Calcd for $C_{24}H_{37}O_3N$: C, 74.38; H, 9.62; N, 3.61. Found: C, 74.33; H, 9.82; N, 3.57.

3β-Acetoxy-20ξ-cyano-21-hydroxy-5β-pregnane 21-Tetrahydropyranyl Ether (7b). Crude **7a** (2.25 g, 5.8 mM) was dissolved in CH_2Cl_2 (30 mL) and treated with dihydropyran (0.64 mL, 7 mM) and *p*-TSA (20 mg). The resulting mixture was stirred for 2 h at ambient temperature. Workup and filtration of the crude product through a SiO_2 column gave **7b** (2.72 g, 99%), mp 144–148 °C (MeOH); ν_{max} ($CHCl_3$) 2240 (C≡N), 1730 (C=O) cm^{-1}; ^1H NMR 0.74 and 0.99 (2 s, angular CH_3), 2.03 (s, 3 H, $OCOCH_3$), 2.9 (m, 1 H, 20-H), 3.6 (m, 2 H, –OCH), 3.8 (m, 2 H, –OCH), 4.66 (s, 1 H, –OCHO–), 5.06 (m, 1 H, 3-H).

Anal. Calcd for $C_{29}H_{45}O_4N$: C, 73.85; H, 9.62; N, 2.97. Found: C, 73.56; H, 9.73; N, 2.57.

3β,21-Dihydroxy-20ξ-formyl-5β-pregnane 21-Tetrahydropyranyl Ether (8) and 3β-Hydroxy-5β-pregn-20-ene-20-carboxaldehyde (14). To a stirred solution of compound **7b** (447 mg, 0.95 mM) in dry toluene (25 mL) at –78 °C under argon DIBAL (1 M in hexane, 4 mL) was added dropwise. After 20 min, MeOH (2 mL) was added carefully and the mixture was allowed to warm up to ambient temperature. The solution was filtered through Celite, the solvent removed, and the oily residue (456 mg) was chromatographed on a SiO_2 column (15 g, hexane–acetone) to give compound **14** (11 mg, 3.5%): mp 170 °C (hexane); λ_{max} (EtOH) 223 nm (ϵ = 7040); ν_{max} (KBr) 3600 (OH), 1680 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR 0.56 and 0.99 (2 s, angular CH_3), 2.80 (t, 1 H, J = 10 Hz, 17-H), 4.17 (m, 1 H, 3-H), 6.17 and 6.34 (2 s, 2 H, $C=CH_2$), 9.57 (s, 1 H, –CHO).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.82, H, 10.53.

Compound **8** (328 mg, 80%): as an oil; ν_{max} (film) 3500 (OH), 2700 (–CHO) cm^{-1}; ^1H NMR 0.78 and 1.05 (2 s, angular CH_3), 3.42–4.32 (m, 5 H, –CHO–), 4.69 (br s, 1 H, –OCHO–), 9.80 (m, 1 H, –CHO).

Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.82; H, 10.47.

(*E*)-Ethyl 3β-Acetoxy-21-(tetrahydropyranyloxy)-5β,20ξ-chol-22-en-24-oate (9) and Ethyl 3β-Acetoxy-5β-chola-20,22-dien-24-oate (11). The alcohol **8** (0.77 g) was acetylated with acetic anydride (5 mL) and pyridine (10 mL) to give 3β-acetoxy-21-(tetrahydropyranyloxy)-5β-pregnane-20-carboxaldehyde (0.79 g, 94%): as an oil; ν_{max} (film) 2720 (CHO), 1730 (C=O) cm^{-1}; ^1H NMR 0.70 and 0.96 (2 s, angular CH_3), 2.05 (s, 3 H, $OCOCH_3$), 2.6 (m, 1 H, 20-H), 3.4–4.2 (m, 4 H, –OCH–), 4.57 (1 H, –OCHO–), 5.06 (m, 1 H, 3-H); MS 474 (23%, M^+), 414 (4%, M^+ – 60), 344 (13%), 85 (100%).

A solution of the above acetate (1.23 g) in THF (5 mL) was added, at –20 °C under argon, to a stirred solution of the ylide [prepared from triethylphosphonoacetate (1.01 mL) and NaH (50% in mineral oil, 250 mg) in THF (20 mL)]. The resulting mixture was allowed to warm to room temperature in ca. 1 h. Chromatography of the crude material on a SiO_2 column (5 g, hexane–ether, 95:5) afforded compounds **11** and **9**.

Compound 11 (20 mg): oil; ν_{max} (EtOH) 216 nm (ϵ = 9000); ν_{max} (film) 1725 and 1715 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR 0.52 and 0.98 (2 s, angular CH_3), 1.31 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 4.21 (q, 2 H, J = 7 Hz, OCH_2CH_3), 5.08 (m, 1 H, 3-H), 5.29 (s, 1 H, 21-H), 5.99 (d, 1 H, J = 16 Hz, C_{22}-H), 7.36 (d, 1 H, J = 16 Hz, 23-H); high-resolution MS calcd for $C_{28}H_{42}O_4$, 442.3083; found, 442.3082.

Compound 9 (1.11 g, 79%): oil; λ_{max} (EtOH) 212 nm (ϵ = 12500); ν_{max} (film) 1735 (C=O), 1720 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR 0.64, 0.70, 0.95, and 0.96 (4 s, angular CH_3), 1.27 (t, 3 H, J = 7 Hz), 2.01 (s, 3 H), 2.40 (m, 1 H, 20-H), 3.2–4.0 (m, 4 H, –CHO–), 4.18 (q, 2 H, J = 7 Hz), 4.55 (br s, 1 H, –OCHO–), 5.06 (m, 1 H, 3-H), 5.83 (d, 1 H, J = 15 Hz, 23-H), 6.88 (2 d, 1 H, $J_{22,23}$ = 15 Hz, $J_{22,20}$ = 10 Hz, 22-H); MS 430 (M^+ – 84 – 30, 41%), 370 (14%), 92 (30%), 85 (53%), 56 (100%).

Ethyl 3β-Acetoxy-21-oxo-5β-chol-20(22)-en-24-oate (10). A solution of **9** (953 mg) in MeOH (10 mL) containing *p*-TSA (15 mg) was stirred for 4 h at room temperature. Workup in the usual manner gave ethyl (*E*)-3β-acetoxy-21-hydroxy-5β,20ξ-chol-22-en-24-oate (765 mg, 95%): as an oil; ν_{max} (EtOH) 216 nm (ϵ = 12100); ν_{max} (film) 3620 (OH), 1720 (C=O), 1650 (C=C) cm^{-1}; ^1H NMR 0.71 and 0.98 (2 s, angular CH_3), 1.29 (t, 3 H, J = 7 Hz), 2.03 (s, 3 H), 3.4–4.0 (m, 3 H, 20-H and 21-H), 4.18 (q, 2 H, J = 7 Hz), 5.06 (m, 1 H, 3-H), 5.87 (d, 1 H, J = 15 Hz, 23-H), 6.91 (2 d, 1 H, $J_{22,23}$ = 15 Hz, $J_{22,20}$ = 10 Hz, 22-H); MS 430 (73%; M^+ – 30), 400 (100%; M^+ – 60), 370 (77%), 257 (95%), 215 (43%), 144 (51%).

After a mixture of the above alcohol (100 mg, 0.22 mM) and pyridinium chlorochromate (190 mg, 0.88 mM) in CH_2Cl_2 (10 mL) was stirred for 6 h, it was diluted with ether (10 mL) and stirring was continued for 30 min. The solution was decanted, the inorganic material was washed with ether, and the combined ether solutions were evaporated. The residue was taken in CH_2Cl_2 and filtered through a SiO_2 column (0.5 g, hexane–ether, 10:1). Compound **10** was obtained as an oil (88 mg, 88%): λ_{max} (EtOH) 233 nm (ϵ = 6700) and 300 nm (ϵ = 1000), ν_{max} (film) 2720 (CHO), 1730 (C=O), 1700 (C=O), 1630 (C=C) cm^{-1}; ^1H NMR 0.58, 0.61, and 0.97 (3 s, angular CH_3), 1.28 (t, 3 H, J = 7 Hz, OCH_2CH_3), 2.04 (s, 3 H), 3.40 (d, 1 H, J = 7.5 Hz, 23-H), 4.16 (q, 2 H, J = 7 Hz, OCH_2CH_3), 5.03 (m, 1 H, 3-H), 6.78 (t, 1 H, J = 7 Hz, 22-H), 9.50 and 10.0 (2 s, 1 H, –CHO); MS 458 (1.4%, M^+), 302 (26%), 272 (100%); high-resolution MS calcd for $C_{28}H_{42}O_5$, 458.3032; found, 458.3029.

3β-Hydroxy-5β,14α-bufadienolide Acetate (2b). A solution of compound **10** (161 mg) in benzene (5 mL) containing *p*-TSA (5 mg) was heated under reflux in an argon atmosphere for 2 h. Workup and filtration of the crude product through a SiO_2 column (1 g, hexane–ether, 85:15) gave compound **2b** (59 mg, 41%): mp 161–164 °C (diisopropyl ether) (reported[11] mp 160–164 °C); λ_{max} (EtOH) 223 nm (ϵ = 5160) and 298 nm (ϵ = 3700); IR (KBr) 1755 (lactone C=O), 1740 (acetate C=O), 1645 and 1545 (diene), 1240 (C–O–C) cm^{-1}; ^1H NMR (CCl_4) 0.53 (3 H, s, 18-CH_3), 0.98 (s, 3 H, 19-CH_3), 1.98 (s, 3 H, $OCOCH_3$), 5.00 (m, 1 H, 3-H), 6.12 (d, 1 H, J = 15 Hz, 23-H), 7.15–7.30 (m, 2 H, 21-H and 22-H) [reported[11] ^1H NMR (CCl_4) 0.53 (18-CH_3), 0.97 (19-CH_3)].

Anal. Calcd for $C_{25}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.63; H, 8.67.

3β,22ξ-Dihydroxy-5β,14α,20ξ-cardanolide (12). Concentrated HCl (4 mL) was added dropwise during 15 min to a stirred mixture of compound **8** (236 mg, 0.55 mM), sodium cyanide (80%, 274 mg, 4.5 mM), and MeOH (13 mL). It was stirred for 30 min at room temperature and then heated under reflux for 20 min. The hot solution was diluted with H_2O (15 mL) and left for crystallization. Crude **12** thus obtained (203 mg, 99%) was used for the next step without purification. A sample recrystallized from hexane–acetone showed mp 228–235 °C; ν_{max} (KBr) 3450 (OH), 1775 (C=O) cm^{-1}; ^1H NMR 0.74 and 1.05 (2 s, 6 H, angular CH_3), 3.4–4.6 (m, 6 H, CHO– and –OH); MS 376 (22%, M^+), 361 (18%), 358 (100%), 343 (65%), 215 (72%).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.27; H, 9.58.

3β,20ξ-Dihydroxy-5β,14α,20ξ-cardanolide 3-Acetate (13). Diol **12** (203 mg) was acetylated with acetic anhydride (2 mL) and pyridine (1.5 mL) to give diacetate (241 mg, 97%): as an oil; ν_{max} (film) 1795 (lactone C=O), 1750 and 1730 (acetates C=O), 1240 (C–O–C) cm^{-1}; ^1H NMR 0.72, 0.74, and 1.04 (3 s, 6 H, angular CH_3), 2.10, 2.18, and 2.22 (3 s, 6 H, $OCOCH_3$), 5.12 (m, 1 H, 3-H), 5.22–5.6 (m, 1 H, 22-H).

The diacetate (121 mg) was dissolved in $CHCl_3$ (3.5 mL) and MeOH (4.5 mL), $NaHCO_3$ (323 mg) was added, and the mixture was heated under reflux for 4 h. The solution was cooled and acidified with diluted HCl, and the product was isolated with $CHCl_3$ and chromatographed on a SiO_2 column (5 g, hexane–acetone, 93:7) to afford monoacetate **13** as an oil (101 mg, 92%): ν_{max} (film) 3400 (OH), 1790 (lactone C=O), 1740 (acetate C=O) cm^{-1}; ^1H NMR 0.72, 0.78, and 1.02 (3 s, 6 H, angular CH_3), 2.12 (s, 3 H, $OCOCH_3$), 3.7–4.6 (3 H, m, 21-H and 22-H), 5.12 (m, 1 H, 3-H); MS (70 eV) 358 (100%, M^+ – AcOH), 343 (39%), 215 (23%).

3β-Hydroxy-5β,14α-card-20(22)-enolide Acetate (1b). Thionyl chloride (0.06 mL, 0.82 mM) was added to a stirred solution of compound **13** (101 mg, 0.24 mM) in DMF (4 mL). After 1 h at room temperature Li_2CO_3 (314 mg) and LiCl (92 mg) were

added. The resulting suspension was heated under reflux for 15 min, and then it was cooled and poured into 3% aqueous HCl. The product was isolated with $CHCl_3$ and the crude material (90 mg) was chromatographed on a SiO_2 column (5 g, hexane–acetone, 93:7) to give compound **1b** (81 mg, 84%), mp 194–197 °C. A sample recrystallized from acetone–hexane had: mp 196.5–197.5 °C (reported[12] mp 195–197 °C); ν_{max} (KBr) 1790, 1750, and 1630 (lactone moiety), 1750 and 1240 (acetate) cm^{-1}; ^1H NMR 0.66 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 2.1 (s, 3 H, $OCOCH_3$), 4.75 and 4.83 (2 d, 2 H, J = 18 Hz, 21-H), 5.13 (m, 1 H, 3-H), 5.89 (br s, 1 H, 22-H).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.87; H, 9.13.

Acknowledgment. We thank Dr. David M. Piatak and Dr. Marcel Gut for helpful discussions and for their assistance in the preparation of the manuscript.

Registry No. **1b**, 6564-57-4; **2b**, 14414-50-7; **3**, 853-23-6; **3** ethylene ketal, 17921-59-4; **4**, 5615-32-7; **4** (4-ene), 1044-89-9; **4**-ol, 5717-77-1; **5**, 4820-41-1; **5**-ol, 571-31-3; (*E*)-**6**, 87393-39-3; (*Z*)-**6**, 87372-91-6; **7a** (isomer 1), 87372-92-7; **7a** (isomer 2), 87393-40-6; **7b**, 87372-93-8; **8**, 87372-94-9; **8** acetate, 87372-95-0; **9**, 87372-96-1; **9** (deTHP), 87372-97-2; **10**, 87420-82-4; **11**, 87372-98-3; **12**, 87372-99-4; **12** diacetate, 87373-00-0; **13**, 87373-01-1; **14**, 87393-41-7; ethyl cyanoacetate, 105-56-6; dihydropyran, 110-87-2; triethyl phosphonoacetate, 867-13-0.

Acid Cyclization and Other Products of the Germacranolide Epoxide Lipiferolide[1]

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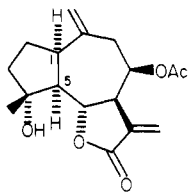
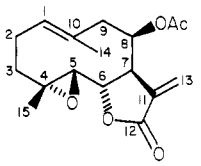
A comparison was made of the products generated from lipiferolide (**2**) upon treatment with $SOCl_2$, HCl, and BF_3·Et_2O. $SOCl_2$ formed three epoxide-opened compounds, chlorohydrin **3** and two allylic alcohols, **4** and **5**, three cyclization products of the guaianolide type, chloro compound **9** and olefins **1** and **10**, as well as three novel bicyclo[6.2.0]decanes, **6**, **7**, and **8**. HCl generated the epoxide-opened substances **3**, **4**, and **5** and guaianolides **1**, **9**, and **10**, but no cyclobutane products. BF_3·Et_2O gave the fluorohydrin **11** as the major component and ketone **12**, xanthanolide **13**, and epitulipinolide (4,5-deoxylipiferolide) as compounds not observed from the other reagents, along with small yields of allylic alcohol **4** and guaianolides **1** and **10**.

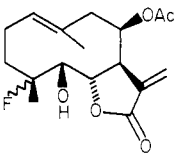
Cyclizations of germacranolides and their derivatives have been of significant value in structure elucidation studies,[2] because the bicyclic products are more rigid and overcome the flexibility and conformational uncertainty of the ten-membered ring. As a result, application of spectral methods to these derivatives, particularly ^1H NMR, can provide useful stereochemical information. From spectral data, the structure of β-cyclolipiferolide[3] (**1**)



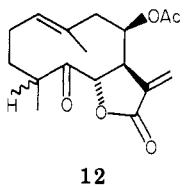
1



2

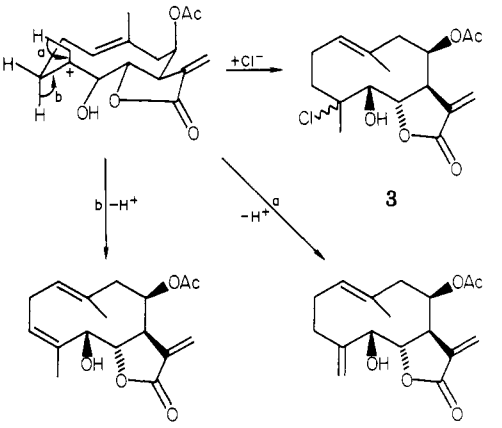


11



12

Scheme I



5 **4**

appeared to be a cyclized product of lipiferolide[4] (**2**), and treatment of lipiferolide (**2**) with $SOCl_2$ as a cyclizing reagent[5] gave, indeed, the natural product **1**. However, the yield was only 9% and TLC analyses showed the reaction mixture to contain many more substances than would be expected from a single epoxide ring opening followed by a cyclization between C(1) and C(5). This report is on the nature of those compounds, their yields, and a comparison study of the products formed by two other cyclization reagents, HCl and BF_3·Et_2O.

Nine pure products were obtained from the $SOCl_2$ cyclization after careful chromatography and accounted for

(1) Taken in part from the Ph.D. Dissertation of J.H.W. that was accepted in Aug. 1982 by the Graduate School, The Ohio State University.

(2) A summary and list of references to studies with a variety of acidic reagents and sesquiterpenes are given by Fischer, N. H.; Olivier, E. J.; Fischer, H. D. "The Biogenesis and Chemistry of Sesquiterpene Lactones" in "Progress in the Chemistry of Organic Natural Products"; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, pp 105–110.

(3) Doskotch, R. W., Wilton, J. H.; Harraz, F. M.; Fairchild, E. H.; Huang, C.-T.; El-Feraly, F. S. *J. Nat. Prod.*, in press.

(4) Doskotch, R. W.; Keely, Jr., S. L.; Hufford, C. D.; El-Feraly, F. S. *Phytochemistry* **1975**, *14*, 769.

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