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Studies on the Synthesis of Cardiotonic Steroids. 4.[1] Synthesis of Strophanthidin

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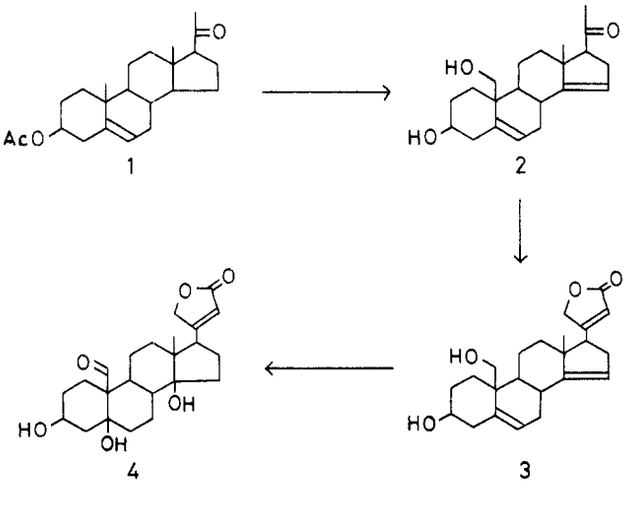
The synthesis of strophanthidin (4) starting with pregnenolone acetate (1) is described. 19-Hydroxylation and introduction of a 14 double bond afforded 9, which was then transformed into the cardatrienolide 13. By stepwise introduction of 5β- and 14β-hydroxy groups, strophanthidol (22) was obtained. Conversion of strophanthidol to strophanthidin was successfully carried out by the oxidation with chromic trioxide in hexamethylphosphoric triamide.

Since Sondheimer's first synthesis of digitoxigenin in 1962,[2] there have been recorded the syntheses of several other natural cardenolides—periplogenin,[3a,4] xysmalogenin,[3b] uzarigenin,[3c,4] and canarigenin.[3d,4] However, the synthesis of more complex 19-oxygenated cardenolides represented by strophanthidin (4)[5] has not been accomplished, seemingly due to the difficulty in assembling unstable functionalities on the steroid nucleus.[6] We now describe the synthesis of strophanthidin, starting with readily available pregnenolone acetate (1).

Our synthetic approach to strophanthidin involved the following principal phases of conversion (Scheme I): (1) derivation of a 19-hydroxy group and a 14 double bond from 1 leading to the dihydroxydienone 2, (2) transformation of 2 to the cardatrienolide 3 without affecting functional groups in the steroid skeleton, (3) formation of two tertiary β-hydroxy groups at the 5 and 14 positions, followed by selective oxidation of the 19-hydroxymethyl moiety to an aldehyde group.

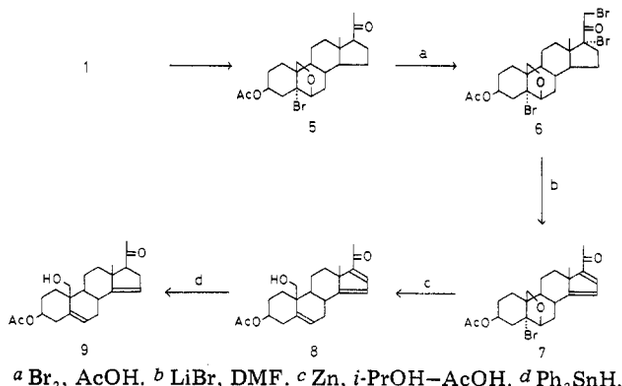
Scheme I



Preparation of the 3-acetate of the dihydroxy ketone 2 is outlined in Chart I. 5-Bromo-6,19-oxidopregnenolone acetate (5) prepared from pregnenolone acetate (1) by an established method[7] was brominated with 2 equiv of bromine to give the 17,21-dibromo compound 6 in 63% yield. It was then subjected to lithium bromide catalyzed dehydrobromination in *N*,*N*-dimethylformamide[8] to furnish the conjugated dienone 7 in 70% yield. Treatment of 7 with zinc dust in weakly acidic 2-propanol at reflux temperature generated the 5 double bond,[7a] yielding the trienone 8 in 89% yield. Selective hydrogenation of the 16 double bond of 8 leading to the dienone 9 was accomplished in 82% yield by heating with triphenylstannane in toluene, a convenient method for the partial reduction of conjugated dienones developed in our laboratory.[9]

The next task—construction of the cardatrienolide structure 13—was then performed by the reaction sequence (Chart II) which had been developed during our digitoxigenin synthesis.[9] First, the 21-methylthio derivative 10 was obtained in 44% yield by the base-catalyzed reaction of 9 with diethyl oxalate followed by the reaction of the resulting 21-oxalyl derivative with methyl thiotosylate in the presence of excess

Chart I



[a] Br_2, AcOH. [b] LiBr, DMF. [c] Zn, *i*-PrOH–AcOH. [d] Ph_3SnH, PhMe.

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Chart II

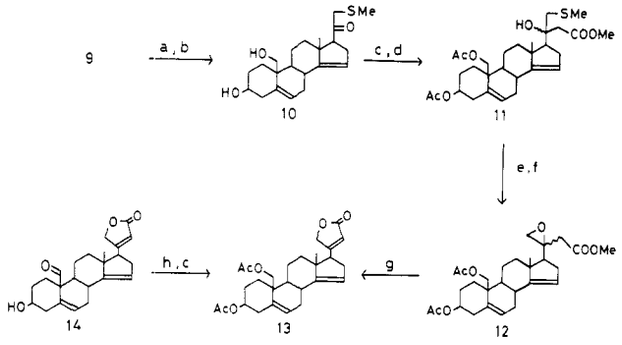
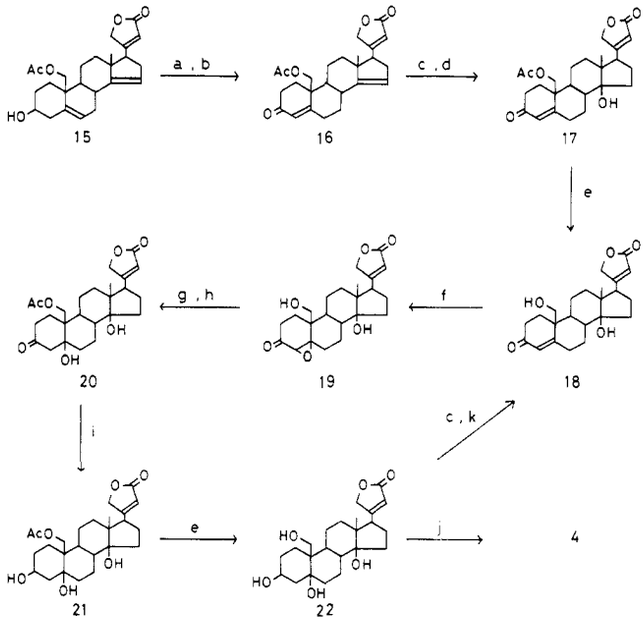


Chart III



[a] $(COOEt)_2$, MeOK. [b] TsSMe, AcOK. [c] Ac_2O, pyr. [d] $BrCH_2COOMe$, Zn. [e] $Me_3{}^+OBF_4{}^-$. [f] 0.5 N NaOH, CH_2Cl_2. [g] Alumina. [h] $NaBH_4$.

[a] Cr(VI). [b] $(COOH)_2$. [c] AcNHBr, H_2O. [d] Raney Ni. [e] $KHCO_3$. [f] H_2O_2, NaOH. [g] Ac_2O, pyr. [h] $Cr(OAc)_2$. [i] Urushibara Ni A. [j] CrO_3, $(Me_2N)_3PO$. [k] AcOH, Δ.

potassium acetate in ethanol.[8a] Reaction of the diacetate of ketone **10** with methyl bromoacetate and zinc dust in boiling benzene for a short period gave the Reformatsky product (**11**) as a mixture of 20-epimers. Treatment of **11** with an equivalent amount of trimethyloxonium tetrafluoroborate in nitromethane at room temperature gave the corresponding methylsulfonium salt, which was stirred in dichloromethane with dilute sodium hydroxide to produce the β,γ-epoxy ester **12**. The latter compound was then absorbed on an alumina column, and after 1 to 5 h the column was eluted to furnish anhydropachygenol diacetate (**13**).[10] The steps from **11** to **13** were carried out without purification of the intermediates in an overall yield of 61%. The structure of **13** was confirmed by comparisons of the spectral data and TLC with those of an authentic sample prepared from dianhydrostrophanthidin (**14**)[11] by sodium borohydride reduction followed by acetylation.

With the synthesis of the cardatrienolide **13** in hand, effort was directed to the introduction of two tertiary and β-oriented hydroxyl groups at the 5 and 14 positions (Chart III). Selective hydrolysis of **13** under weakly basic condition produced the 19-monoacetate **15**, which, on chromic acid oxidation and subsequent treatment of the product with oxalic acid, afforded the conjugated ketone **16** in 60% yield.

Now, according to an established procedure[12] for the introduction of the 14β-hydroxy group, **16** was subjected to the addition of hypobromous acid with aqueous *N*-bromoacetamide followed by hydrogenolysis of the intermediate bromohydrin with Raney Ni to give a bromine-free product. Although TLC of the product showed a single spot under a variety of solvent systems, MS clearly indicated that it was a mixture of two components showing two molecular ion peaks—*m/e* 428 ($C_{25}H_{32}O_6$) ascribable to the desired product **17** and *m/e* 426 ($C_{25}H_{30}O_6$). The byproduct having two hydrogen atoms less than the 14β-hydroxy cardenolide **17** could not be the 14,15-epoxide, since in the NMR spectrum no peak due to 15-hydrogen was observed; nor could it be the 15-ketone,[13] since the intense peak observed in the MS at *m/e* 408 ($M^+ - H_2O$) was not compatible with that structure. Based on these facts, the structure of an 8(14)-en-15-ol was tentatively assigned to the $C_{25}H_{30}O_6$ product.[14] Although the mixture was resolved by high-pressure liquid chromatography, revealing an ca. 75% content of **17**, isolation of **17** was successfully carried out by oxidative destruction of the by product with Jones reagent followed by preparative TLC. The 14β-hydroxy compound **17** thus obtained in 72% yield was identical with an authentic sample[15] prepared from strophanthidol (**22**) (comparisons of spectral data and TLC). Hydrolysis of the 19-acetate group by potassium bicarbonate afforded the 19-hydroxy compound **18** in almost quantitative yield.

The reaction of **18** with cold alkaline hydrogen peroxide proceeded smoothly to give the 4β,5β-epoxide **19** in 87% yield. The β orientation of the epoxy group expected from the literature precedents[16] was firmly supported by the circular dichroism which showed a positive Cotton effect.[17] Reductive cleavage of the epoxide ring was then carried out on the 19-acetate of **19** by treatment with chromium(II) acetate in ethanol. The product consisted of an easily separable mixture of the β-hydroxy ketone **20**[15a] and of the conjugated ketone **17** (ca. 1:1). Treatment of **20** with Urushibara nickel A[18] in refluxing ethanol provided strophanthidol 19-acetate (**21**). Strophanthidol (**22**) was obtained by saponification of **21** with potassium bicarbonate at room temperature. The identity of the synthetic and natural specimens was proved by comparisons of spectral data and TLC.

The final step in our strophanthidin synthesis consisted in the selective oxidation of the 19-hydroxy group of strophanthidol. Literature precedents concerned with the oxidation of strophanthidol and related systems indicate that chromic acid,[19a] *N*-haloamide[19a,b] and PtO_2[15b,19c] all favor the oxidation of the secondary 3-hydroxy group in preference to the 19-primary alcohol. In our hands also, oxidation with both pyridinium chlorochromate[20] and sulfur trioxide–pyridine–dimethyl sulfoxide[21] proceeded in the same fashion, and therefore the protection of the 3-hydroxy group seemed to be essential.[19a] Fortunately, we found, however, that chromic trioxide in hexamethylphosphoric triamide[22] was an excellent reagent for this particular oxidation. Although the rate of the oxidation was very slow, strophanthidin was obtained in good yield, no ketonic product being noticed. The synthetic and natural specimens of strophanthidin were completely identical in IR, NMR, MS, and TLC behavior.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Jeol PMX-60 or a Varian EM-390 instrument. Chemical shifts are reported in units δ (ppm) from internal tetramethylsilane. Infrared spectra were taken on a Jasco IRA-1 spectrometer and ultraviolet spectra on a Hitachi 124 instrument. Mass spectral data were obtained on a Jeol JMS-01SG-2 instrument at an ionization potential of 75 eV. Optical rotations were measured on a Jasco DIP-4 automatic polarimeter, and circular dichroism spectra were recorded on a Jasco J-20 spectrometer. Combustion analyses were carried out at the Microanalytical Laboratory of this

university. Dry argon was used in reactions requiring an inert atmosphere. Most reactions were followed by thin-layer chromatography over Merck precoated silica gel plates. Preparative TLC was carried out on Merck silica gel (0.06–0.20 mm). High-pressure liquid chromatography was performed on a Toyo Soda HLC-803 instrument.

3β-Acetoxy-6β,19-oxido-5α,17α,21-tribromopregnan-20-one (6). A solution of 5.43 g of bromine in 200 mL of acetic acid was added slowly to a stirred solution of 7.44 g of **5**[7a] in 75 mL of acetic acid at 40–45 °C over a period of 1 h. After consumption of bromine was complete, the pale yellow solution was poured into ice–water. The white precipitate was filtered, washed well with water, and dried. The crude product (8.95 g) was crystallized from acetone–methanol to give 6.31 g of **6**, mp 172.5–175.5 °C, which was contaminated with a trace amount of impurities as evidenced by TLC (probably 5,17-dibromide and 5,17,21,21-tetrabromide) and was used for the next step without further purification. An analytical sample was obtained by chromatography over silica gel (elutions with benzene–ether) followed by recrystallization from acetone as colorless needles: mp 178–179 °C; $[\alpha]^{27}_D$ −8.0° (*c* 0.68, $CHCl_3$); IR (KBr) 1730, 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (s, 18-H), 2.07 (s, OAc), 3.86 (AB q, *J* = 10, 32 Hz, 19-H), 4.34 (AB q, *J* = 14, 32 Hz, 21-H), 5.20 (m, 3-H).

Anal. Calcd for $C_{23}H_{31}O_4Br_3$: C, 45.20; H, 5.11. Found: C, 45.43; H, 5.28.

3β-Acetoxy-5α-bromo-6β,19-oxidopregna-14,16-dien-20-one (7). To a solution of 6.95 g of **6** in 55 mL of dry *N*,*N*-dimethylformamide was added 2.72 g of anhydrous lithium bromide, and the mixture was stirred and heated at 90–95 °C under an Ar atmosphere. After 4 h the dark brown reaction mixture was poured into water. The precipitate was filtered, washed with water, and dried. The crude product (4.55 g) was dissolved in 150 mL of hot ether, decolorized with active charcoal, and concentrated to a small volume. The pale yellow crystals of the dienone **7** which had separated were collected, mp 169–171 °C (3.53 g). An analytical sample was obtained by chromatography over silica gel (elutions with benzene–ether) and crystallization from ether as prisms: mp 174–175 °C; $[\alpha]^{27}_D$ +297.6° (*c* 0.39, $CHCl_3$); IR (KBr) 1735, 1640, 1520 cm^{-1}; UV λ_{max} (MeOH) 206 (ε 6430) and 306 nm (12 800); NMR (CCl_4) δ 1.20 (s, 18-H), 1.98 (s, OAc), 2.25 (s, 21-H), 3.89 (AB q, *J* = 9, 12 Hz, 19-H), 4.09 (d, *J* = 5 Hz, 6-H), 5.07 (m, 3-H), 5.95 (br d, *J* = 3 Hz, 15-H), 7.08 (d, *J* = 3 Hz, 16-H); MS *m/E* (rel abundance) 448, 450 (M^+, 8), 369 (19), 309 (100).

Anal. Calcd for $C_{23}H_{29}O_4Br$: C, 61.47; H, 6.50. Found: C, 61.45; H, 6.30.

3β-Acetoxy-19-hydroxypregna-5,14,16-trien-20-one (8). To a solution of 3.36 g of **7** in 200 mL of 2-propanol was added 1.84 g of zinc dust and 1 mL of acetic acid. The mixture was stirred and heated under reflux for 5.5 h. After cooling to room temperature, it was filtered and evaporated in vacuo. The residue was dissolved in dichloromethane, washed with water, dried ($MgSO_4$), and evaporated. The residual crystalline mass was recrystallized from methanol–dichloromethane to give 2.47 g of **8**: mp 236–237.5 °C; $[\alpha]^{27}_D$ +305.3° (*c* 0.38, $CHCl_3$); IR (KBr) 3490, 1730, 1710, 1640, 1520 cm^{-1}; UV λ_{max} (MeOH) 206.5 (ε 6950), 310 nm (11 150); NMR ($CDCl_3$) δ 1.23 (s, 18-H), 2.02 (s, OAc), 2.32 (s, 21-H), 3.87 (AB q, *J* = 10, 21 Hz, 19-H), 4.60 (m, 3-H), 5.87 (br s, 6-H), 5.97 (t, *J* = 3 Hz, 15-H), 7.20 (d, *J* = 3 Hz, 16-H).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.34; H, 8.31.

3β-Acetoxy-19-hydroxypregna-5,14-dien-20-one (9). To a solution of 3.7 g of triphenylstannane in 40 mL of toluene was added 2.18 g of **8** and few milligrams of azobis(isobutyronitrile) and the mixture was heated under reflux with occasional additions of the radical initiator (1–2-h interval). After 10 h (disappearance of **8** on TLC, chloroform–ethyl acetate, 10:3), the solution was allowed to cool and the precipitate of white crystals of hexaphenylditin was removed by filtration. The filtrate was evaporated in vacuo and the residual viscous oil was subjected to silica gel chromatography (elutions with benzene–chloroform). Crystalline fractions showing a single spot on TLC were collected (1.79 g, mp 148–152 °C) and recrystallized from isopropyl ether to give 1.45 g of **9**: mp 154–155 °C; $[\alpha]^{27}_D$ −9.5° (*c* 0.53, $CHCl_3$); IR (KBr) 3410, 1730, 1695 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 18-H), 2.07 (s, OAc), 2.20 (s, 21-H), 4.60 (m, 3-H), 5.15 (m, 15-H), 5.80 (m, 6-H); MS *m/e* (rel abundance) 372 (M^+, 14), 312 (82), 294 (30), 281 (100).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.19; H, 8.80.

3β,19-Dihydroxy-21-methylthiopregna-5,14-dien-20-one (10). Potassium methoxide was prepared in 30 mL of dry benzene by the reaction of 0.90 mL of dry methanol with 4.0 g of 22.7% KH (mineral oil was removed by washing with benzene) under an Ar atmosphere. To the resulting suspension were added 1.56 g of diethyl oxalate and 2.02 g of **9** in 20 mL of benzene, and the mixture was stirred overnight at room temperature. After the addition of 2 M NaH_2PO_4, the organic product was isolated by extraction with a mixture of ether–methanol and dried in vacuo over P_2O_5. The crude 21-oxalyl derivative obtained was dissolved in 40 mL of dry ethanol followed by the addition of 1.32 g of methyl thiotosylate and 3.20 g of anhydrous potassium acetate. The solution was then heated at 60 °C for 8 h, cooled, mixed with 10 mL of 10% KOH, and stirred for 1.5 h at room temperature. The mixture was diluted with ether, and the organic solution was washed with water, dried ($MgSO_4$), and evaporated to give 885 mg of **10** as a pale yellow solid (mp 154–158 °C; essentially one spot on TLC, ethyl acetate–chloroform, 1:1) which without further purification was employed for the next step. An analytical sample was obtained by silica gel chromatography (elutions with chloroform–ethyl acetate, 3:7) followed by crystallization from isopropyl ether–methanol: mp 159–160 °C; IR (KBr) 3400, 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 18-H), 2.08 (s, SMe), 3.20 (br s, 21-H), 3.70 (AB q, *J* = 12, 18 Hz, 19-H), 5.12 (m, 15-H), 5.75 (m, 6-H); MS *m/e* (rel abundance) 376 (M^+, 68), 358 (32), 346 (36), 239 (100).

Anal. Calcd for $C_{22}H_{32}O_3S$: C, 70.18; H, 8.57. Found: C, 70.02; H, 8.74.

The diacetate of **10** (not crystallizable) was obtained by the usual procedure employing acetic anhydride and pyridine: IR (film) 1735, 1700 cm^{-1}; NMR (CCl_4) δ 0.87 (s, 18-H), 1.93 (s, OAc), 2.00 (s, SMe), 3.01 (br s, 21-H), 4.15 (AB q, *J* = 12, 36 Hz, 19-H), 5.10 (m, 15-H), 5.60 (m, 6-H); MS *m/e* 460 (M^+), 400, 340, 251.

Methyl 3β,19-Diacetoxy-20-hydroxy-21-methylthio-24-norchola-5,14-dienoate (11). To a solution of 730 mg of the diacetate of compound **10** in 25 mL of dry benzene was added 0.5 mL of methyl bromoacetate and 124 mg of freshly activated zinc dust. The mixture was heated with stirring and the solvent was slowly distilled. When ca. 15 mL of benzene was removed, vigorous reaction occurred. After continued heating and stirring for 10 min, the homogeneous reaction mixture was cooled, washed with dilute HCl and water, dried ($MgSO_4$), and evaporated. The residual viscous oil was chromatographed over silica gel (30 g), eluting with mixtures of chloroform–benzene to give 280 mg of **11** as a pale yellow gum which could not be induced to crystallize and was shown by spectral data to be a mixture of 21-epimers: NMR (CCl_4) δ 1.13 (s, 18-H), 2.00 (br s, OAc), 2.08, 2.12 (s, SMe), 2.60, 2.72 (br s, 21-H), 3.67 (br s, COOMe), 4.18 (AB q, *J* = 12, 34 Hz, 19-H), 4.47 (br m, 3-H), 5.12 (m, 15-H), 5.63 (m, 6-H); MS *m/e* 534 (M^+), 516, 503, 473, 460, 413, 400, 353, 340, 251.

3β,19-Diacetoxycarda-5,14,20(22)-trienolide (13). (A) From 11. A solution of 207 mg of **11** in 2 mL of nitromethane was treated with 64 mg of trimethyloxonium tetrafluoroborate at room temperature. After 40 min the solvent was evaporated in vacuo at 20–25 °C. The residual *S*-methyl compound was dissolved in 7 mL of dichloromethane and the solution was vigorously stirred with 7 mL of 0.5 N NaOH at room temperature for 1 h. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The gummy β,γ-epoxy ester (**12**) which on TLC (benzene–ethyl acetate, 10:1) showed two partially overlapping spots originating from 20-epimers was dissolved in a small volume of benzene and charged on an alumina column (basic, activity II, 27 g). After 5 h the column was eluted with benzene–ether (5:1) to give 108 mg of crystalline product (**13**), which showed a single spot on TLC. Recrystallization from methanol produced white needles: mp 193–194.5 °C; $[\alpha]^{22}_D$ −92.9° (*c* 1.32, $CHCl_3$); IR (KBr) 1785 (sh), 1740, 1625 cm^{-1}; UV λ_{max} (MeOH) 217 nm (ε 12 700); NMR ($CDCl_3$) δ 0.86 (s, 18-H), 2.05 (s, OAc), 4.28 (AB q, *J* = 12, 54 Hz, 19-H), 4.78 (br s, 21-H), 5.30 (m, 15-H), 5.72 (m, 6-H), 5.92 (br s, 22-H); MS *m/e* 454 (M^+), 394, 334, 321, 319. The spectral data were completely identical with those of an authentic sample (below).

Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.61; H, 7.73.

(B) From Dianhydrostrophanthidin (14). To a solution of 90 mg of **14**[11] in 4.5 mL of 80% dioxane was added 32 mg of sodium borohydride in 3 mL of 80% dioxane. After 2 h at room temperature, the mixture was acidified by the addition of 4 N H_2SO_4 and diluted with water. The white precipitate was collected and crystallized from acetone to give a quantitative yield of the 3,19-diol (anhydropachygenol),[10] mp 240–243 °C.

The diacetate **13** was obtained by the usual manner as white needles: mp 194.5–196 °C; $[\alpha]^{22}_D$ −99.2° (*c* 1.32, $CHCl_3$).

Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.38; H, 7.32.

19-Acetoxy-3β-hydroxycarda-5,14,20(22)-trienolide (15). To a solution of 86 mg of the diacetate **13** in 8.6 mL of methanol was added 0.2 mL of 2 M $KHCO_3$ and the mixture was stirred for 14 h at

room temperature. Extraction with chloroform and crystallization of the product from methanol afforded 44 mg of **15** as white needles: mp 212–215 °C; IR (KBr) 3460, 1778, 1745, 1695, 1623 cm^{-1}; NMR ($CDCl_3$) δ 0.84 (s, 18-H), 2.03 (s, OAc), 3.5 (br m, 3-H), 4.20 (AB q, J = 12, 34 Hz, 19-H), 4.71 (br s, 21-H), 5.20 (m, 15-H), 5.60 (m, 6-H), 5.85 (br s, 22-H).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.80; H, 8.05.

19-Acetoxy-3-oxocarda-4,14,20(22)-trienolide (16). To a stirred suspension of 62 mg of pyridinium chlorochromate in 0.5 mL of dichloromethane was added 78 mg of **15** in 2 mL of dichloromethane. Usual workup of the reaction mixture afforded a resinous material, which was then treated with 1 mL of 1% ethanolic oxalic acid at 70 °C for 2 h. The mixture was extracted with chloroform, washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residual pale yellow gum was subjected to preparative TLC (chloroform–methanol, 100:3), affording 47 mg of crystals which on recrystallization from acetone gave 45 mg of **16** as prisms: mp 181.5–183 °C; IR (KBr) 1780, 1750, 1735, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (s, 18-H), 2.02 (s, OAc), 4.40 (AB q, J = 11, 33 Hz, 19-H), 4.75 (br s, 21-H), 5.29 (m, 15-H), 5.91 (br s, 4-H and 22-H); MS m/e 410 (M^+), 350.

Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.15; H, 7.31.

19-Acetoxy-14β-hydroxy-3-oxocarda-4,20(22)-dienolide (17). To a stirred solution of 90 mg of **16** in 3.6 mL of acetone was added 0.3 mL of water, 37 mg of N-bromoacetamide, and 90 μL of 70% $HClO_4$ at 0 °C. After continued stirring and cooling for 20 min, the reaction mixture was treated with 5% $Na_2S_2O_3$ and extracted with dichloromethane. The organic solution was washed with cold brine, dried ($MgSO_4$), and evaporated in vacuo at room temperature. The pale yellow resinous residue (essentially homogeneous to TLC, chloroform–methanol, 25:1) was then dissolved in a mixture of 7 mL of methanol and 7 mL of dichloromethane, and the solution was added to a suspension of ca. 3 g of Raney Ni (W-4, H_2 saturated at 2 atm) in 20 mL of methanol containing an acetate buffer for controlling pH at 6.7. The suspension was stirred for 2 h at 20 °C, filtered, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated to give 90 mg of a semicrystalline residue. Although TLC showed the product to be essentially homogeneous (chloroform–methanol, 20:1), MS and high-pressure liquid chromatography (4 mm × 30 cm, Toyo Soda LS-410 ODS packing, MeOH) indicated that it was a mixture of two products (ca. 3:1), **17** (major product) and presumably the compound having the 8(14)-en-15-ol structure: MS (obtained by subtraction of the peaks due to **17** from those of the mixture) m/e (rel abundance) 426 (M^+, 11), 408 (100), 366 (17), 348 (38). A 20-mg portion of the mixture was titrated with Jones reagent in acetone at 0 °C. The product isolated by chloroform extraction was then subjected to preparative TLC (chloroform–methanol, 20:1) to give **17** (15 mg) which was crystallized from ethanol as prisms: mp 189–190 °C (lit.[15a] mp 185–187 °C, lit.[15b] mp 186–187 °C); $[\alpha]^{27}_D$ +118.2° (c 0.18, MeOH) (lit.[15b] +101°); UV λ_{max} (MeOH) 227 nm (ϵ 24 200);[15a] IR (KBr) 3500, 1780, 1755 (sh), 1740, 1660, 1615 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (s, 18-H), 2.01 (s, OAc), 4.37 (AB q, J = 12, 32 Hz, 19-H), 4.87 (br s, 21-H), 5.89 (br s, 4-H and 22-H); MS m/e (rel abundance) 428 (M^+, 96), 410 (12), 408 (24), 368 (61), 356 (65), 350 (37), 245 (35), 215 (100).

Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.81; H, 7.55.

14β,19-Dihydroxy-3-oxocarda-4,20(22)-dienolide (18). (A) From 17. To a solution of 10 mg of **17** in 1 mL of methanol was added 30 μL of 2 M $KHCO_3$, and the solution was stirred at room temperature for 48 hr. Extraction of the mixture with chloroform followed by drying ($MgSO_4$) and evaporation of the solvent afforded 9.2 mg of **18**, mp 248–251 °C, from acetone–ether (lit.[15b] mp 247–251 °C, lit.[19c] mp 232–240 °C): NMR ($CDCl_3$) δ 0.93 (s, 18-H), 3.98 (br s, 19-H), 4.90 (br s, 21-H), 5.90 (br s, 4-H and 22-H); MS m/e (rel abundance) 386 (M^+, 5), 368 (40), 356 (30), 350 (18), 338 (100).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.24; H, 7.59.

(B) From Strophanthidol (22). To a solution of 500 mg of **22**[23,24] in 12.5 mL of *tert*-butyl alcohol was added 2.5 mL of water and 207 mg of N-bromoacetamide. The mixture was kept in the dark and at 20 °C overnight. After decolorization by the addition of 10% $Na_2S_2O_3$ and dilution with 15 mL of water, the solution was extracted thoroughly with chloroform. The organic layers were washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in 10 mL of acetic acid, and the solution was refluxed for 18 min. After dilution with 5 mL of water, the solution was concentrated in vacuo and extracted with chloroform. The chloroform solution was washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. On trituration of the residue with acetone, 494 mg of a pale yellow solid was obtained and recrystallized from acetone–ether: mp 251–252 °C; $[\alpha]^{27}_D$ +83.6° (c 0.79, MeOH) (lit.[15b] +91°); UV λ_{max} (MeOH) 222 nm (ϵ 22 700);[15b] IR (KBr) 3500, 3430, 1780, 1740, 1650–1630 cm^{-1}.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.58; H, 7.79.

14β,19-Dihydroxy-4β,5β-epoxy-3-oxocard-20(22)-enolide (19). To a solution of 203 mg of **18** in 20 mL of methanol was added 0.30 mL of 2 N NaOH and 0.75 mL of 30% H_2O_2 at 0 °C, and the homogeneous mixture was stirred at 0 °C for 1 h. Another 0.10 mL of 2 N NaOH and 0.25 mL of 30% H_2O_2 were added, and the solution was stirred for 45 min at 0 °C. The solution was neutralized by the addition of acetic acid, diluted with 10 mL of water, and extracted thoroughly with chloroform. The extracts were washed with aqueous $FeSO_4$, 5% $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. The residual gum (178 mg) which was essentially homogeneous to TLC was crystallized from methanol to give 142 mg of **19** as white needles; mp 198–200 °C; IR (KBr) 3560, 3410, 3320, 1735, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (s, 18-H), 2.93 (s, 4-H), 3.93 (AB q, J = 11, 23 Hz, 19-H), 4.90 (br s, 21-H), 5.90 (br s, 22-H); CD (c 0.006, MeOH) $[\theta]_{345}$ 0, $[\theta]_{302}$ +13 020, $[\theta]_{263}$ +2000, $[\theta]_{236}$ +11 340, $[\theta]_{225}$ +6040.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.90; H, 7.44.

The acetate of **19** was obtained by the usual procedure employing acetic anhydride and pyridine as an amorphous solid: NMR ($CDCl_3$) δ 0.91 (s, 18-H), 2.13 (s, OAc), 2.91 (s, 4-H), 4.37 (AB q, J = 11, 24 Hz, 19-H), 4.87 (br s, 21-H), 5.85 (br s, 22-H).

19-Acetoxy-5β,14β-dihydroxy-3-oxocard-20(22)-enolide (20). To a stirred suspension of freshly prepared chromous acetate (from 0.3 g of $CrCl_3 \cdot 6H_2O$)[25] in 1 mL of ethanol was added 70 mg of the 19-acetate of **19** in 7.5 mL of ethanol under an Ar atmosphere. After 30 min, the mixture was filtered, and the filtrate was evaporated in vacuo and extracted with chloroform. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 69 mg of a mixture of the enone **17** and the desired product **20** (ca. 1:1 by NMR). Preparative TLC (chloroform–methanol, 8:1) afforded 32 mg of **20** (not crystallizable):[15a] IR (film) 3480, 1740, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (s, 18-H), 2.07 (s, OAc), 4.40 (s, 19-H), 4.85 (br s, 21-H), 5.84 (br s, 22-H).

Strophanthidol 19-Acetate (21). To a solution of 15 mg of **20** in 1 mL of ethanol was added an excess amount of freshly prepared Urushibara nickel A,[18] and the mixture was refluxed gently with stirring. After 1.5 h the mixture was filtered and evaporated. Preparative TLC (ethyl acetate) of the residue afforded 0.5 mg of **17** and 7.5 mg of strophanthidol 19-acetate (**21**). The latter product was crystallized from aqueous acetone as prisms: mp 136–139 °C (lit.[15a] mp 136–139 °C, lit.[23] mp 134–136 °C); $[\alpha]^{27}_D$ +35.7° (c 0.75, EtOH) (lit.[15a] +34.8°); IR (KBr) 3380, 1780, 1750, 1710, 1615 cm^{-1}; NMR ($CDCl_3$) δ 0.84 (s, 18-H), 2.08 (s, OAc), 4.15 (m, 3-H), 4.39 (br s, 19-H), 4.86 (br s, 21-H), 5.84 (br s, 22-H). The spectral data and TLC were identical with those of an authentic sample prepared by monoacetylation of strophanthidol (**22**) according to literature.[15a,23]

Strophanthidol (22). To a solution of 10 mg of strophanthidol 19-acetate (**21**) in 1 mL of methanol was added 20 μL of 2 M $KHCO_3$, and the homogeneous mixture was stirred at room temperature for 20 h. The mixture was diluted with 50 mL of chloroform, and the organic layer was washed with a small amount of water and brine, dried ($MgSO_4$), and evaporated. The residue (one spot on TLC, chloroform–methanol, 10:1) was recrystallized three times from acetone–ether to give 4.5 mg of **22** as granules: mp 138–140 °C (lit.[19c] mp 138–142/152/222 °C, lit.[24] mp 136–140 °C); $[\alpha]^{27}_D$ +38.4° (c 0.26, MeOH) (lit.[24] +36.9°); IR (KBr) 3400, 1780, 1750–1740, 1620 cm^{-1}; MS m/e (rel abundance) 402 (M^+, 100), 384 (14), 372 (17), 368 (22), 354 (17). IR, MS and TLC were completely identical with those of an authentic sample prepared by sodium borohydride reduction of strophanthidin.[23,24]

Strophanthidin (4). To 0.2 mL of hexamethylphosphoric triamide was added 60 mg of chromic trioxide, and the mixture was stirred for 1 h at room temperature to give a homogeneous solution. A solution of 40.6 mg of strophanthidol (**22**) in 0.4 mL of hexamethylphosphoric triamide was then added and the stirring was continued for 24 h. The reaction mixture was extracted with ethyl acetate, and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was subjected to preparative TLC (chloroform–methanol, 9:1) to give 13 mg of strophanthidin (**4**) and 1 mg of unreacted **22**. Strophanthidin was recrystallized from aqueous methanol as white needles: mp 221.5–223.5 °C, mmp 215–217 °C with Merck strophanthidin (mp 208–212 °C, $[\alpha]_D$ +45.4°); $[\alpha]^{27}_D$ + 42.2° (c 0.15, MeOH); UV λ_{max} (MeOH) 217 nm (ϵ 15 500); NMR ($CDCl_3$) δ 0.86 (s, 18-H), 4.16 (m,

3-H), 4.85 (br s, 21-H), 5.84 (br s, 22-H), 9.93 (s, CHO); MS *m/e* (rel abundance) 404 (M^+, 1), 386 (3), 358 (23), 340 (100), 322 (63).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.21; H, 7.71.

Registry No.—**4,** 66-28-4; **5,** 41767-48-0; **6,** 67270-86-4; **7,** 67270-87-5; **8,** 67270-88-6; **9,** 67270-89-7; **9** 21-oxalyl derivative, 67270-90-0; **10,** 67270-91-1; **10** diacetate, 67270-92-2; **11** isomer 1, 67270-93-3; **11** isomer 2, 67335-50-6; **12** isomer 1, 67270-94-4; **12** isomer 2, 67335-51-7; **13,** 67270-95-5; **14,** 6785-67-7; **15,** 67270-96-6; **16,** 67270-97-7; **17,** 19667-18-6; **18,** 3566-40-3; **19,** 67270-98-8; **19** 19-acetate derivative, 67270-99-9; **20,** 67335-52-8; **21,** 17162-14-0; **22,** 560-54-3; methyl thiotosylate, 4973-66-4; methyl bromoacetate, 96-32-2; diethyl oxalate, 95-92-1.

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Dibenzocyclooctadiene Antileukemic Lignan Synthesis. (±)-Steganone[1]

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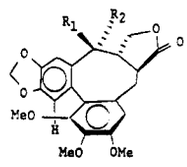
A new route to the unsaturated oxo ester **16**, an intermediate in the Raphael synthesis of steganone (**4**) and its companion antileukemic lignans steganacin (**1**) and steganangin (**2**), is described. Key reactions utilized in the synthetic sequence were photochemical ring closure of a stilbenecarboxylic acid to a phenanthrene, the trimethylsilyl azide modification of the Curtius rearrangement of carboxylic acids, and a two-carbon ring expansion of a 9-phenanthrylamine with dimethyl acetylenedicarboxylate.

Kupchan[2] has reported the isolation and structural determination of the dibenzocyclooctadiene lignan lactones[3] **1–4** from an alcoholic extract of *Steganotaenia araliacea* Hochst. Because of the significant[2] antileukemic activity reported for steganacin **1** and steganangin **2** (the *O*-acetyl and *O*-angelyl



1 R_1 = OAc, R_2 = H
2 R_1 = OOC(angelyl), R_2 = H
3 R_1 = OH, R_2 = H
4 R_1, R_2 = O

derivatives of the β-alcohol steganol **3**), there has been considerable interest in the synthesis of this class of dibenzo[*a*,*c*]cyclooctadiene.[3,4] In light of recent publications on the total syntheses of steganone **4** and its companion lignans **1–3**,[4] we wish to report our independent synthetic efforts similar to those of Raphael[4a] in this area.

The general approach which was conceived for the synthesis of the lignans **1–4** is outlined in Scheme I. The critical feature of our plan was to find a method for the formation of the dibenzocyclooctadiene skeletal system of these lignans. The precedent for our synthetic approach was the synthesis of dibenzocyclooctatetraene **5** by a 2 + 2 cycloaddition utilizing the 9,10 bond of phenanthrene, followed by electrocyclic ring opening of an intermediate cyclobutene **6**.[5] We envisioned the 2 + 2 cycloaddition of an acetylenedicarboxylic acid ester or masked acetylene equivalent to an appropriately substituted phenanthrene **7**, followed by concomitant thermal ring opening of an initially formed cyclobutene, would lead to a dienamine or dienol ether **8**. Hydrolysis might afford **9**, a template for elaboration of the lactone ring of steganone **4**. The ketone steganone **4** has been converted by Kupchan[2] to steganol **3**, the parent alcohol from which steganacin **1** and steganangin **2** are derivable.[2,4a,b]

Oxidative photochemical ring closure of stilbene α-carboxylic acids is a straightforward entry to phenanthrene-9-carboxylic acids,[6] and 3,4-methylenedioxy-3′,4′,5′-trime-

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