(dd, 1, $J_{5,6}$ = 6.9, H6), 4.28 (t, 1, $J_{1,2}$ = 4.0 Hz, H 2), 4.33 (dt, 1, H5), 4.66 and 4.70 (AB q, 2, J_{AB} = 11.5, $PhCH_2$), 4.91 (d, 1, H1), 7.34 (s, 5, aromatic). Anal. Calcd for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.10; H, 7.51; N, 3.80.

For **13b**: syrup $[\alpha]^{23}_D$ +85.1° (c, 0.6 in chloroform); IR ($CHCl_3$) 2240 (CN) cm^{-1}; ^1H NMR δ 1.33, 1.42, 1.47, 1.54 (2 $(CH_3)_2C$), 3.19 (dd, 1, $J_{2,3}$ = 2.8, $J_{3,4}$ = 10.0, H3), 3.39 (s, 3, OCH_3), 3.78 (dd, 1, $J_{4,5}$ = 3.0, H4), 3.82 (dd, 1, $J_{5,6'}$ = 6.8, $J_{6,6'}$ = 8.2 Hz, H6'), 4.03 (dd, 1, $J_{5,6}$ = 6.6 Hz, H6), 4.37 (t, 1, $J_{1,2}$ = 2.5 Hz, H2), 4.40 (dt, 1, H5), 4.64 and 4.72 (AB q, 2, J_{AB} = 11.0 Hz, $PhCH_2$), 5.03 (d, 1, H1), 7.3 (s, 5, aromatic). Anal. Calcd for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.58; H, 7.61; N, 3.73.

Acknowledgment. We are grateful to the University of Maryland for financial assistance.

Registry No. 1a, 24578-12-9; **1b**, 82742-11-8; **1c**, 82742-12-9; **2b**, 82742-13-0; **3b**, 82742-14-1; **4**, 82752-59-8; **5**, 82742-15-2; **6a**, 16939-77-8; **6b**, 33208-46-7; **7a**, 34147-05-2; **7b**, 82742-16-3; **8a**, 82742-17-4; **8b**, 82742-18-5; **9**, 82742-19-6; **10**, 82742-20-9; **11a**, 82742-21-0; **11b**, 82752-60-1; **11c**, 82742-22-1; **12**, 82742-23-2; **13a**, 82742-24-3; **13b**, 82795-70-8.

Regio- and Stereoselective Remote Hydroxylations of the A Ring of Steroids. A Novel Route to 5α Steroids with Cis-Coupled A and B Rings[1]

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Received January 12, 1982

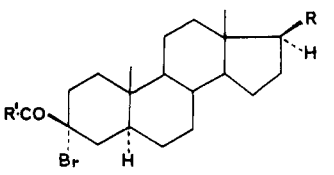
Under nonnucleophilic conditions, the $AgSbF_6$ dehalogenation of steroidal α-bromo ketones derived from cholestan-3-one and (5α)- and (5β)-17-hydroxyandrostan-3-one leads, after hydrolysis, to hydroxylation of the A ring. In compounds with A/B trans ring fusion, hydroxylation takes place at the 10α position (35–45% yield), leading to 5α, A/B cis steroids. In compound with A/B cis ring fusion, hydroxylation takes place at the 5β-position (45% yield). These results are discussed with reference to α-acyl carbenium ions and oxonium salts as intermediates.

The remote functionalization of unactivated ring carbon atoms has generally been achieved by using radical initiators.[2] This paper describes an extension of such strategy to carbocationic initiation[3] by using the now well-established properties of α-acyl carbenium ions.[4-10]

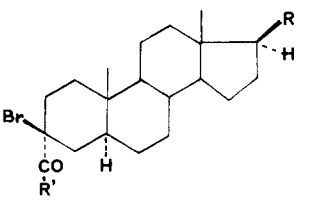
As depicted in Scheme I, these species, generated by dehalogenation of an α-bromo ketone with $AgSbF_6$ in a nonnucleophilic solvent, are converted by a series of hydride shifts to cyclic oxonium salts. Hydrolysis of such salts then leads to an effective remote hydroxylation. The formation of these oxonium salts inhibits skeletal rearrangement, so that selective hydroxylation of a steroidal A ring could be anticipated, following the generation of a C-3 acyl carbenium ion.

Results and Discussion

The bromo ketones **1a** and **2a** were prepared from cholestanone by a classical route. The bromoacetyl compounds **2b** and **3** were obtained from (5α)- and (5β)-17β-hydroxyandrostan-3-one.[8,9]



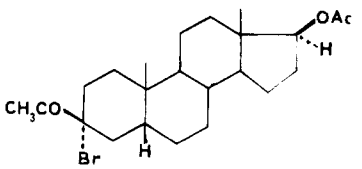
1



2

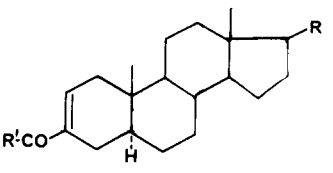
a R = C_8H_{17} R' = C_6H_5

b R = OAc R' = CH_3

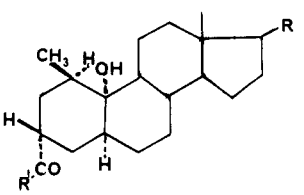


3

Dehalogenation of **1a** or **2a** in CH_2Cl_2 at −20 °C led, after hydrolysis, to the hydroxy ketone **4a** and the unsaturated ketone **5a** (**4a**, 45% yield from **1a**, 33% yield from **2a**; **5a**,



5



4

a R = C_8H_{17} R' = C_6H_5

b R = OAc R' = CH_3

35% yield from **1a**, 25% yield from **2a**). Ketone **4a** is

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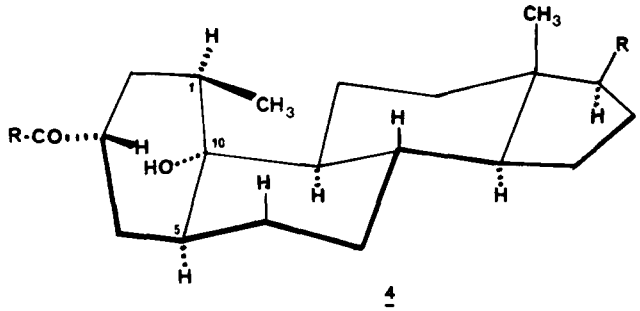

4

stable to sodium methoxide. In addition, the 19-Me group appears as a doublet in the ^1H NMR spectrum, and the hydroxy group is found to be tertiary according to the ^{13}C NMR spectrum. Finally, the A/B cis, 5α-H ring fusion has been confirmed by X-ray diffraction.[10,11]

In the same way, the bromo ketone **2b** led to the hydroxy ketone **4b** (35%), the unsaturated ketone **5b** (6%), 17β-acetoxyandrost-2-ene (20%), and a trace of 3β-acetyl-5β-hydroxy-17β-acetoxyandrostane (**6**) (Chart I).

The bromo ketone **3**, with an A/B cis ring junction, led to 3β-acetyl-5β-hydroxy-17β-acetoxyandrostane (**6**, 45%), together with an olefin (2%), a mixture of olefinic ketones (11%), and a small amount of a hydroxy ketone structure **7** on the basis of its ^1H NMR annd ^{13}C NMR spectra. The structure **6** was determined by correlation with the hydroxy diacetate **8**;[12] thus, epimerization of the acetyl group (methanolic KOH) followed by reacetylation, led to **9**, which was converted to **8** with trifluoroperoxyacetic acid.

As in the earlier studies, the hydroxylation reaction now reported exhibits regio- and stereoselectivity which differ according to the A/B ring fusion.

In the trans series hydroxylation takes place at the 10α-position and in the cis series at the 5β position. The C-17 substituent does not affect the result. The nature of the carbonyl group (acetyl or benzoyl[13,14]) and the configuration of bromo ketone also appear to be unimportant.[15]

Ionization of the C–Br bond by the electrophilic agent $AgSbF_6$ led to a transitory α-acyl carbenium ion. A process of hydrid shifts gave ultimately the more stable oxonium salt, as depicted in Scheme II. The mechanism of these migrations has been thoroughly investigated in the cyclohexane series.[5-7]

The present data raise two questions: (i) about the difference of regioselectivity observed between A/B trans and A/B cis series, or why does, in A/B trans series, the 2-H rather than the 4-H shift, and (ii) about the stereoselectivity of the hydroxylation, or why do we only observe the shift of an axial hydrogen (either 2-Hβ or 4-Hα) which is cis related to Br.

It is well-known that because of conformational preferences,[18] enolization and elimination in the A/B trans series takes place at the 2-position, the opposite being observed in the A/B cis series.[16,17] Identical considerations can likely be applied to the hydride shifts studied here, implying a flattening of the ring.

Regarding the stereoselectivity, the migration of 2-Hβ and 4-Hα, which are axial and cis to Br in **2a,b** and **3**, implies that ionization of the C–Br bond and the hydride shift take place in two sequential steps. In keeping with previous observations,[7] this proves that α-acyl carbenium ions are discrete intermediates. So we have to take into account the structure of the α-acyl carbenium ion, which could have a planar or a bridged structure.[6] If it is planar, the axial hydrogen, which is parallel to the conjugated π system, should migrate more easily than the equatorial one. As for the bridged ion, the 2-Hβ and 4-Hα hydrogens, initially cis to Br (in **2a,b** and **3**) are in a trans antiplanar relationship with the carbon–oxygen bond to be broken. So we except the same result in both cases. But the latter is more likely, considering that intramolecular nucleophilic assistance should favor the formation of the unstable α-acyl carbenium ion.[19] In **1a**, the 2-H is trans and antiperiplanar relative to the leaving group and thus can assist the ionization. But in **2a,b** and **3**, both Br and the trans hydrogen are equatorial. So the molecule has to adopt a high-energy conformation[20,21] to put the trans H and Br in a close diaxial relationship in order for Br to depart. We then assume that the easier 1–3 carbonyl participation takes place, leading to the oxirenium ions **15** and **16** (Scheme III).

The present work shows examples of regio- and stereoselective hydroxylation of the steroidal A ring. Furthermore, the very unusual conversion of an A/B trans 5α to an A/B cis 5α ring fusion has been observed. This procedure, which is new in the steroid field, would be of great utility in achieving generally cumbersome remote hydroxylations.

Experimental Section

$AgSbF_6$ was purchased from Alfa-Ventron Co. and used without purification. Melting points were taken on a Leitz melting point microscope. Solutions were dried over Na_2SO_4 unless otherwise specified. IR spectra were obtained for CCl_4 solutions on a Perkin-Elmer Model 157 spectrometer. NMR spectra were recorded in $CDCl_3$ on Varian T-60 (60 MHz) and Brucker WH-90 (90 MHz) spectrometers. ^{13}C NMR spectra were obtained in $CDCl_3$ on a Varian CFT-20 spectrometer. The internal standard for both ^1H and ^{13}C spectroscopies was Me_4Si. Mass spectra were recorded with a VG 70-70F micromass spectrometer. The optical rotations were measured with a Perkin-Elmer 241MC polarimeter. Column chromatography was carried out by using Kieselgel 60 (0.06–0.2 mm) from Merck Co. Plates of Kieselgel PF 252 (Merck) were used for TLC.

3-Benzoyl-3-bromocholestanes 1a and 2a. To a rapidly stirred suspension of benzyltriphenylphosphonium chloride (11 g) in DME (60 mL) under a nitrogen atmosphere was added dropwise 19 mL of *n*-BuLi 1.5 M in hexane. The red solution was stirred 15 min and then treated with cholestan-3-one (10 g). The reaction mixture was stirred for a further 20 h, poured into water, and extracted (CH_2Cl_2–hexane). After filtration through an alumina column, the crude 3-benzylidenecholestane (6.9 g) was obtained.

To a stirred solution of this crude product in THF (20 mL) under N_2 were added $NaBH_4$ (1.3 g) and, dropwise, BF_3–Et_2O (7 mL). After 16 h, 3 N NaOH was added cautiously, and the THF was evaporated under reduced pressure. The reaction mixture was neutralized to pH 7 with 10% aqueous H_2SO_4. Et_2O (100 mL) was added, and then a solution of $Cr_2O_7K_5$ (5 g) in water (40 mL) and H_2SO_4 (4 mL) was added dropwise. After 2 h of reflux,

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(13) α-Bromoaryl ketones usually lead to many more α–β ethylenic ketones ($\simeq$30%) than α-bromomethyl ketones ($\simeq$5%) in dehalogenation by $AgSbF_6$ in CH_2Cl_2.[5]
(14) The formation of 17-acetoxyandrost-2-ene from **2b** and not cholest-2-ene from **2a** is very surprizing. Several explanations could be proposed, but none is really convincing.
(15) Isomerization of **1** or **2** is not detected in incomplete dehalogenation of **1a** or **2a,b** and **3**.
(16) Fieser, L. F.; Fieser, M."Steroids"; Reinhold: New York, 1959; pp 280.
(17) Kirk, D. N., Hartshorn, M. P. "Steroid Reaction Mechanisms"; Elsevier: Amsterdam, 1969; pp 103–8, 161–2.
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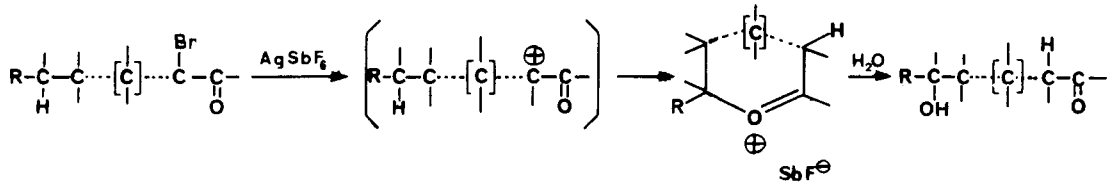
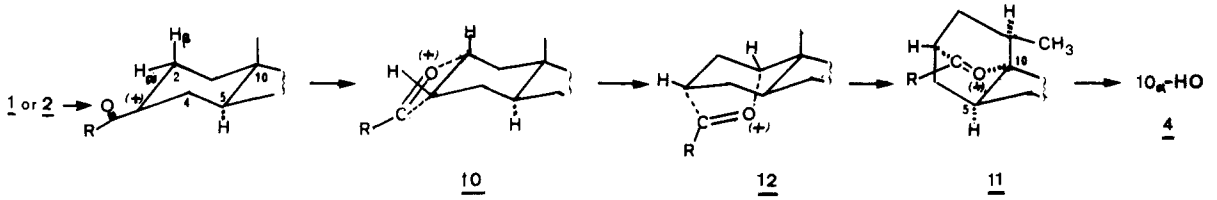
(21) Toromanoff, E. *Tetrahedron* **1980**, *36*, 1971 and references cited therein. Toromanoff, E. *Tetrahedron* **1980**, *36*, 2809.

Scheme I



Scheme II



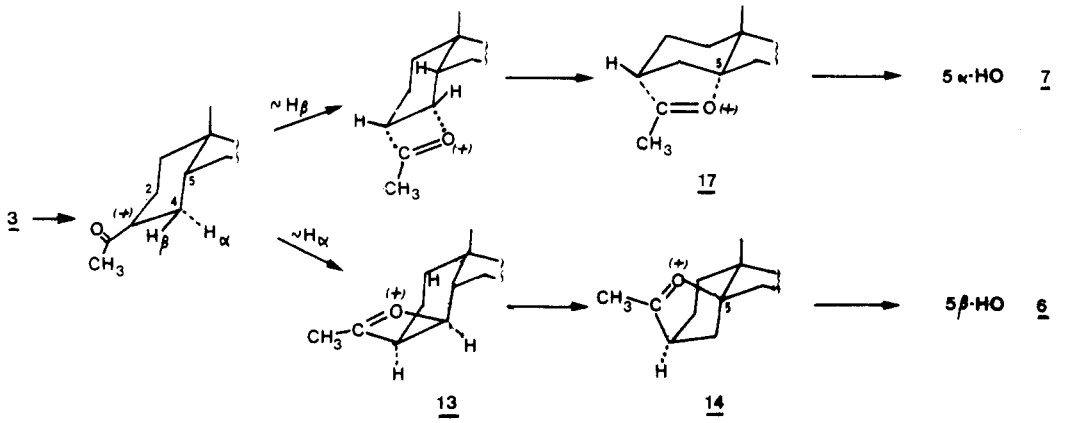
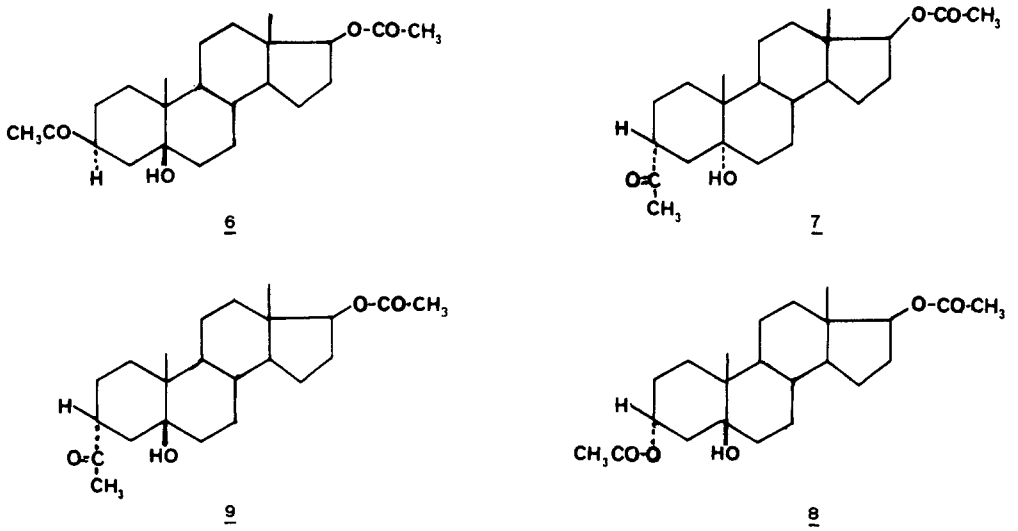


Chart I

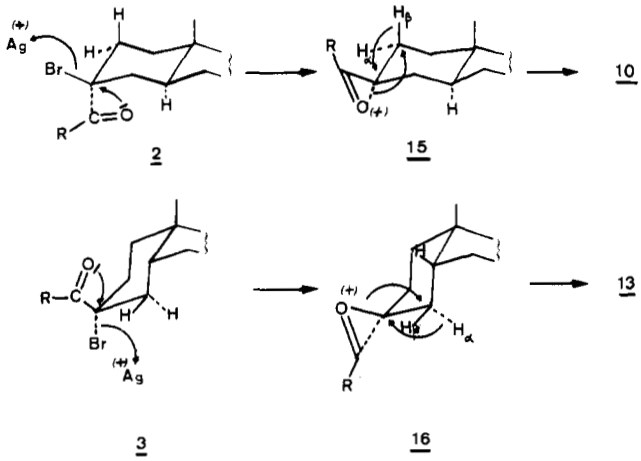


the ethereal layer was separated, washed with water, dried, and concentrated. The residue was refluxed 16 h with 5% methanolic NaOMe solution. After the usual workup and filtration through Florisil (hexane–ether; 80:20), 3β-benzoylcholestane (5.3 g) was obtained: mp 135–140 °C (EtOH); IR (CCl_4) 1685 cm^{-1}; ^1H NMR δ 0.67 (s, 3 H, 18-Me), 0.82 (s, 3 H, 19-Me); $[\alpha]^{29}_{546}$ +42.5° (*c*, 6, CH_2Cl_2).

To a stirred solution of 3β-benzoylcholestane (5.2 g) in CH_2Cl_2 (20 mL) was added dropwise bromine (3.2 mL). After 10 h, the excess of bromine was destroyed by $NaHSO_3$, and the organic layer was washed until neutrality with water, dried, and evaporated. The crude product (**1a**/**2a** ratio of about 70:30) was chromatographied on silica gel (hexane–ether, 99:1) to give **2a** [mp 121.5–123.5 °C (EtOH); IR (CCl_4) 1690 cm^{-1}; ^1H NMR δ 0.63 (s, 3 H, 18-Me), 0.82 (s, 3 H, 19-Me); ^{13}C NMR δ 65.2 (3-C); $[\alpha]^{22}_{546}$ +30.8° (*c* 6.5, CH_2Cl_2)] and **1a** as gummy material: mp 134–137 °C; IR (CCl_4) 1690 cm^{-1}; ^1H NMR δ 0.63 (s, 3 H, 18-Me), 0.75 (s, 3 H, 19-Me); ^{13}C NMR δ 70.6 (3-C); $[\alpha]^{28}_{546}$ +40.1° (*c*, 5, CH_2Cl_2).

Dehalogenation of 1a and 2a. To a solution of **1a** and **2a** (1 g, 70:30 mixture) in CH_2Cl_2 (10 mL) at −20 °C was added $AgSbF_6$ (1 g, 1.6 equiv). The reaction mixture was then stirred for 1 h, poured into an aqueous solution of $NaHCO_3$, extracted (CH_2Cl_2), dried, and concentrated. The crude product (890 mg) was purified by silica gel column chromatography to give 3-benzoylcholest-2-ene (**5a**: 230 mg, 27% yield) and **4a** (380 mg, 43% yield).

Scheme III



5a: mp 96–100 °C (methanol); IR (CCl_4) 1655 cm^{-1}; ^1H NMR δ 0.67 (s, 3 H, 18-Me), 0.79 (s, 3 H, 19-Me), 6.50 (m, half-with = 8.5 Hz, 1 H, 2-H), 7.3–7.8 (m, 5 H, phenyl); ^{13}C NMR δ 141.2 (2-C), 143.5 (3-C), 198.2 (C=O); mass spectrum, *m/e* 474, 459, 105.

4a: mp 155–160 °C (pentane–ether); IR (CCl_4) 3620, 1685 cm^{-1}; ^1H NMR δ 0.75 (s, 3 H, 18-Me), 1.39 (d, 3 H, 19-Me), 3.67 (tt, J = 12, 2.5 Hz, 1 H, 3-H); ^{13}C NMR δ 74.3 (10-C), 203.6 (C=O); mass spectrum, *m/e* 492, 474, 450, 369, 133, 105; $[\alpha]^{22}_{546}$ +22.7 (*c* 6, CH_2Cl_2).

Pure **1a** (400 mg) gave after reaction, workup, and TLC separation **5a** (109 mg, 32% yield) and **4a** (159 mg, 45% yield).

Pure **2a** (294 mg) gave, by the same procedure, **5a** (62 mg, 25% yield) and **4a** (79 mg, 33% yield). Another hydroxy compound, which remains unidentified, was also obtained (16 mg).

Dehalogenation of 2b. To a solution of **2b** (780 mg) in CH_2Cl_2 (10 mL) at −20 °C was added 900 mg of $AgSbF_6$ (1.5 equiv). The reaction mixture was stirred 40 min, poured into aqueous solution of $NaHCO_3$, extracted (CH_2Cl_2), dried, and concentrated. The crude material was purified by silica gel column chromatography (hexane–ether) to give the following compounds successively. 17-Acetoxyandrost-2-ene: 111 mg (20% yield); mp 97–99 °C (pentane) (lit.[22] mp 96 °C); ^1H NMR δ 0.72 (s, 3 H, 18-Me), 0.80 (s, 3 H, 18-Me), 2.05 (s, 3 H, $OCOCH_3$), 4.58 (t, 1 H, C-17 H), 5.60 (m, 2 H, H–C^2=C^3–H). A mixture of olefinic ketones, 68 mg (11% yield). 3-Acetyl-17-acetoxyandrost-2-ene (**5b**): 37 mg (6% yield); mp 135–140 °C; IR (CCl_4) 1735, 1670 cm^{-1}; ^1H NMR δ 0.70 (s, 3 H, 18-Me), 0.78 (s, 3 H, 19-Me), 2.02 (s, 3 H, $OCOCH_3$), 2.26 (s, 3 H, $COCH_3$), 4.57 (m, 1 H, C-17 H), 6.80 (m, 1 H, H_2C=C). **6**, 30 mg (4.5% yield) vide infra. **4b**: 220 mg (35% yield); mp 158–160 °C; IR (CCl_4) 36208 1730, 1710 cm^{-1}; ^1H NMR δ 0.85 (s, 3 H, 18-Me); 1.28 (d, J = 8 Hz, 3 H, 19-Me), 2.05 (s, 3 H, $OCOCH_3$), 2.16 (s, 3 H, $COCH_3$) 2.41 (t, 1 H, C-3 H), 4.61 (t, 1 H, C-17 H); ^{13}C NMR δ 74.0 (s, C-10) 82.6 (d, C-17), 171.1 ($OCOCH_3$), 212.6 ($COCH_3$); $[\alpha]^{20}_{546}$ −5.4° (*c* 4, CH_2Cl_2).

Dehalogenation of 3. To a solution of **3** (1 g) in CH_2Cl_2 (10 mL) at −40 °C was added 1.3 g of $AgSbF_6$ (1.6 equiv). The temperature was raised to 0 °C progressively in 1 h. After the usual workup, silica gel column chromatography (hexane–CH_2Cl_2–Et_2O) gave hydroxy ketone **6**: 383 mg (45% yield); mp 138–142 °C (petroleum ether–Et_2O); IR (CCl_4) 3630, 1730, 1710 cm^{-1}; ^1H NMR δ 0.76 (s, 3 H, 18-C), 0.89 (s, 3 H, 19-C), 2.03 (s, 3 H, $OCCCH_3$), 2.81 (m, half-width = 16 Hz, C-3 H), 4.58 (t, 1 H, C-17 H); ^{13}C NMR δ 12.0 (18-Me), 16.8 (19-Me), 71.7 (s, C-5), 82.8 (d, C-17), 171.1 ($OCOCH_3$), 214.8 ($COCH_3$); $[\alpha]^{23}_{546}$ −2.3° (*c*, 4.5, CH_2Cl_2).

Elution also gives trace of 17-acetoxy-5β-androstene and a mixture of olefinic ketones (95 mg, 11% yield), among which was 3-acetyl-17β-acetoxy-5β-androst-3-ene [^1H NMR δ 0.78 (s, 3 H, 18-Me) 1.3 (s, 3 H, 19-Me), 4.54 (m, 1 H, C-17 H), 6.58 (s, half-width = 3 Hz, HC=)] and another hydroxy ketone, probably **7**: 35 mg (4% yield); IR (CCl_4) 3620, 1735, 1715 cm^{-1}; ^1H NMR δ 0.77 (s, 3 H, 18-Me), 0.92 (s, 3 H, 19-Me), 2.02 (s, 3 H, $OCOCH_3$), 2.23 (s, 3 H, $COCH_3$), 4.58 (m, 1 H, C-17 H).

Equilibration of 6 and 9. A solution of **6** (130 mg) in 1 N methanolic KOH (20 mL) was refluxed for 60 min. The reaction mixture was then diluted with water, extracted (CH_2Cl_2), dried, and concentrated. Treatment with acetic anhydride in pyridine overnight gave **9**: 102 mg; mp 187–190 °C (hexane-CH_2Cl_2); ^1H NMR δ 0.76 (s, 3 H, 18-Me), 0.92 (s, 3 H, 19-Me), 2.03 (s, 3 H, $OCOCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.84 (m, half-width = 31 Hz), 4.55 (t, 1 H, C-17 H); ^{13}C NMR δ 12.0, 16.8, 73.5 (s, C-5), 82.7 (d, C-17), 170.9 and 212.1; $[\alpha]^{23}_{546}$ +31.1° (*c* 5, CH_2Cl_2).

Baeyer–Villiger Oxidation of 9 to 8. To a solution of **9** (100 mg) in CH_2Cl_2 (5 mL) containing Na_2HPO_4 (1.5 g) was added 2 mL of a trifluoroperoxyacetic acid solution (prepared from 2.5 mL of CH_2Cl_2, 3 mL of trifluoro acetic anhydride and 0.4 mL of 90% H_2O_2). After standing at room temperature for 48 h, the mixture was poured into water, extracted (CH_2Cl_2), washed with water, dried and evaporated to yield the diacetate **8**: 70 mg; mp 221–224 °C (lit.[12] mp 217–219 °C); IR (CCl_4) 3620, 1735 cm^{-1}; ^1H NMR δ 0.77 (s, 3 H, 18-Me), 0.91 (s, 3 H, 19-Me), 2.02 (s, 3 H, $OCOCH_3$), 2.04 (s, 3 H, $OCOCH_3$), 4.58 (t, 1 H, C-17 H), 5.11 (m, 1 H, C-3 H); $[\alpha]^{25}_{546}$ +42° (*c* 1.7, CH_2Cl_2) [lit.[12] $[\alpha]_D$ +45° (*c* 0.5, $CHCl_3$)].

Acknowledgment. We are grateful to Professor S. Wolfe, University of Kingston, for critical suggestions during the preparation of the article. We also thank DGRST (Contract No. 787943) for partial financial support of this work and the Roussel-UCLAF Laboratories for a generous supply of starting materials and for biological tests.

Registry No. 1a, 77825-58-2; **2a**, 77825-59-3; **2b**, 82880-41-9; **3**, 82871-81-6; **4a**, 77825-60-6; **4b**, 82871-82-7; **5a**, 77825-61-7; **5b**, 17006-91-6; **6**, 82871-83-8; **7**, 82871-84-9; **8**, 82871-85-0; **9**, 82871-86-1; 5α-cholestan-3-one, 566-88-1; 2-benzylidene-5α-cholestane, 82871-87-2; 3β-benzoyl-5α-cholestane, 82871-88-3; 17β-acetoxy-5α-androst-2-ene, 2324-10-9; 3-acetyl-17β-acetoxy-5β-androst-3-ene, 82871-89-4.

(22) Marker, R. E.; Kamm, D.; Jones, D. M.; Mixon, L. W. *J. Am. Chem. Soc.* **1937**, *59* 1363.

An Approach to the BCDE Ring of Quasimarin

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Received February 17, 1982

A 10-step route to the BCDE ring system of quasimarin (**1**) is described. Key features of the route include the regioselective protection of diketone **7** by use of intramolecular ketal formation, a two-step lactone to ether reduction, and a regioselective lactonization. The tetracyclic system **15** is produced in 29% overall yield.

Quasimarin (**1**) and bruceantin (**2**) are antitumor agents recently isolated from *Quassia amara*[1] and *Brucea antidysenterica*,[2] respectively. Both have shown in vitro activity against human carcinoma of the nasopharynx (KB)

0022-3263/82/1947-4271$01.25/0 © 1982 American Chemical Society