Anal. Calcd for $C_{39}H_{42}N_6O_6$: C, 67.81; H, 6.13; N, 11.89. Found: C, 67.6; H, 6.4; N, 11.9.

Method B was applied to *cyclo*-(*N*-Me-Ala-D-Phe)$_3$ shown in Table I, with minor modification.

Sequence Dependence of Cyclization Yield. The linear peptides shown in Table II were prepared by solid-phase synthesis and subjected to cyclization, using DPPA (method A). In each case disappearance of starting linear peptide was monitored by TLC, and cyclic monomer was isolated by successive precipitation by using solvents of decreasing polarity (EtOAc → ether → low-boiling petroleum ether) to recover peptidal components. The presence or absence of monomeric peptide in each isolate was determined by TLC. Isolates containing cyclic monomer were subjected to gel filtration on Sephadex G-25 in 50% acetic acid to assess molecular weight homogeneity and to separate and purify monomeric product. The peptide balance reflects the amount of peptidal material recovered, including cyclic monomer (see Table II).

Application of the DPPA Procedure to Coupling of Boc-proline with 2 Equiv of DL-Phenylalanine Methyl Ester. A mixture of 108 mg (0.5 mmol) of Boc-proline and 228 mg (1.0 mmol) of DL-phenylalanine methyl ester HCl salt in 50 mL of DMF was cooled to 0 °C. Triethylamine was added until the pH was 7.5 (as determined by spotting moistened pHydrion paper) followed by 0.11 mL of DPPA. The mixture was stirred for a total of 41 h at 0 °C, the pH being adjusted to 7.5 after 24 h. The reaction mixture was treated with 10 mL of H_2O and then with ca. 20 mL of AG 501-X8 (D) mixed-bed resin, with stirring for 4 h. The resin was removed by filtration, and TLC of the filtrate indicated that >98% of the excess DL-phenylalanine methyl ester had been removed by the resin treatment. The reaction solution was made up to 100 mL with DMF, and aliquots were analyzed, after acid hydrolysis, by the procedure of Manning and Moore.[7] The data showed 50% conversion to the diastereoisomeric dipeptides Boc-Pro-D-Phe-OMe and Boc-Pro-Phe-OMe, with a D-Phe/Phe ratio of 56:44.

A second reaction using 108 mg (0.5 mmol) of Boc-proline and 228 mg (1.0 mmol) of D-phenylalanine methyl ester HCl salt was carried out under exactly the same conditions to be sure that neither the reaction conditions nor the workup procedure was causing racemization. Analysis of aliquots by the procedure of Manning and Moore,[7] after acid hydrolysis, showed 61% conversion to the dipeptide Boc-Pro-D-Phe-OMe, of enantiomeric purity ≥97%.

The results show that coupling of DL-phenylalanine methyl ester is only slightly selective in favor of the D isomer.

Acknowledgment. We thank Mr. Carl Homnick for performing the amino acid analyses and assays by the Manning and Moore method. We also thank Dr. David W. Cochran, Mr. Riley McGaughran, and Ms. Joan Murphy for determining the NMR spectra, and Mr. Robert Rhodes for the mass spectra. We acknowledge the skilled technical assistance of Messrs. E. Whittington and P. Mooney in preparation of the resin-bound peptides. We also thank Dr. Ralph Hirschmann for encouragement and support of this work.

Registry No. 1, 68319-17-5; 2, 69541-41-9; 3, 71048-71-0; **3a**, 71001-82-6; **3b**, 71001-83-7; **3c**, 71001-84-8; 4, 71001-85-9; 5, 71001-86-0; 6, 71001-87-1; (D-Pro-Phe)$_3$, 71048-72-1; (D-Ala-Pro)$_3$, 71001-88-2; (D-Ala-Pro)$_2$(D-Phe-Pro), 71001-89-3; (Sar-Ala)$_3$, 71001-90-6; (Sar-Phe)$_3$, 71001-91-7; (Sar-Leu)$_3$, 71001-92-8; (*N*-Me-Ala-D-Phe)$_3$, 71001-93-9; (D-Ala-Ala)$_3$, 27454-49-5; (D-Phe-Pro)$_2$, 71001-94-0; (D-Ala-Pro)$_2$(β-Ala-Pro), 71001-95-1; (D-Phe-D-Ala-Pro)$_2$, 71048-73-2; H-(D-Phe-Pro)$_3$OH·HBr, 68370-22-9; H-(Azt-D-Phe)$_3$OH·HCl, 69541-40-8; H-(D-Phe-Pro)(Phe-Pro)$_2$OH·HBr, 71001-96-2; H-(D-Pro-Phe)$_3$OH·HBr, 71001-97-3; H-(D-Ala-Pro)$_3$OH·HBr, 71001-98-4; H-(D-Ala-Pro)$_2$(D-Phe-Pro)OH·HBr, 71001-99-5; H-(Sar-Ala)OH·HBr, 71002-00-1; H-(Sar-Phe)$_3$OH·HBr, 71002-01-2; H-(Sar-Leu)$_3$OH·HBr, 71002-02-3; H-(Me-Ala-D-Phe)$_3$OH·HCl, 71002-03-4; H-(D-Ala-Ala)$_3$OH·HBr, 71002-04-5; H-(D-Phe-Pro)$_2$OH·HBr, 71002-05-6; H-(D-Ala-Pro)$_2$(β-Ala-Pro)OH·HBr, 71002-06-7; H-(D-Phe-D-Ala-Pro)$_2$OH·HBr, 71002-07-8; *cyclo*-(D-Phe-Pro)$_4$, 71002-08-9; Boc-azetidine-2-carboxylic acid, 51077-14-6; *tert*-butyl 2,4,5-trichlorophenyl carbonate, 16965-08-5; azetidine-2-carboxylic acid, 2517-04-6.

Norsteroids. 11. Reaction of Various Steroid Bromohydrins with Silver Oxide

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Reaction of 2α-bromo-5α-cholestan-3β-ol with silver oxide gave *A*-nor-5α-cholestane-2-carboxaldehyde (**2a**). Similar treatment of 6α-bromo-5α-cholestane-3β,7β- and -3β,7α-diol, **4** and **6**, gave 3β-hydroxy-*B*-nor-5α-cholestane-6-carboxaldehyde (**5**), but 6β-bromo-5α-cholestane-3β,7β-diol (**7**) gave 3β-hydroxy-5α-cholestan-7-one (**8**) with no rearrangement. 5α-Bromocholestane-3β,6β-diol (**9**) gave mainly 5β,6β-oxidocholestan-3β-ol 3-acetate (**10**) plus a small amount of Westphalen's diol **11**. Finally, 11α,23ζ-dibromo-5α,22a-spirostane-3β,12β-diol 3-acetate (**12**) gave the *C*-noraldehyde **14**. These results show that bromohydrins undergo ring contraction with silver oxide to the noraldehyde if the bromine atom is equatorial but give an oxide or ketone if the bromine atom is axial.

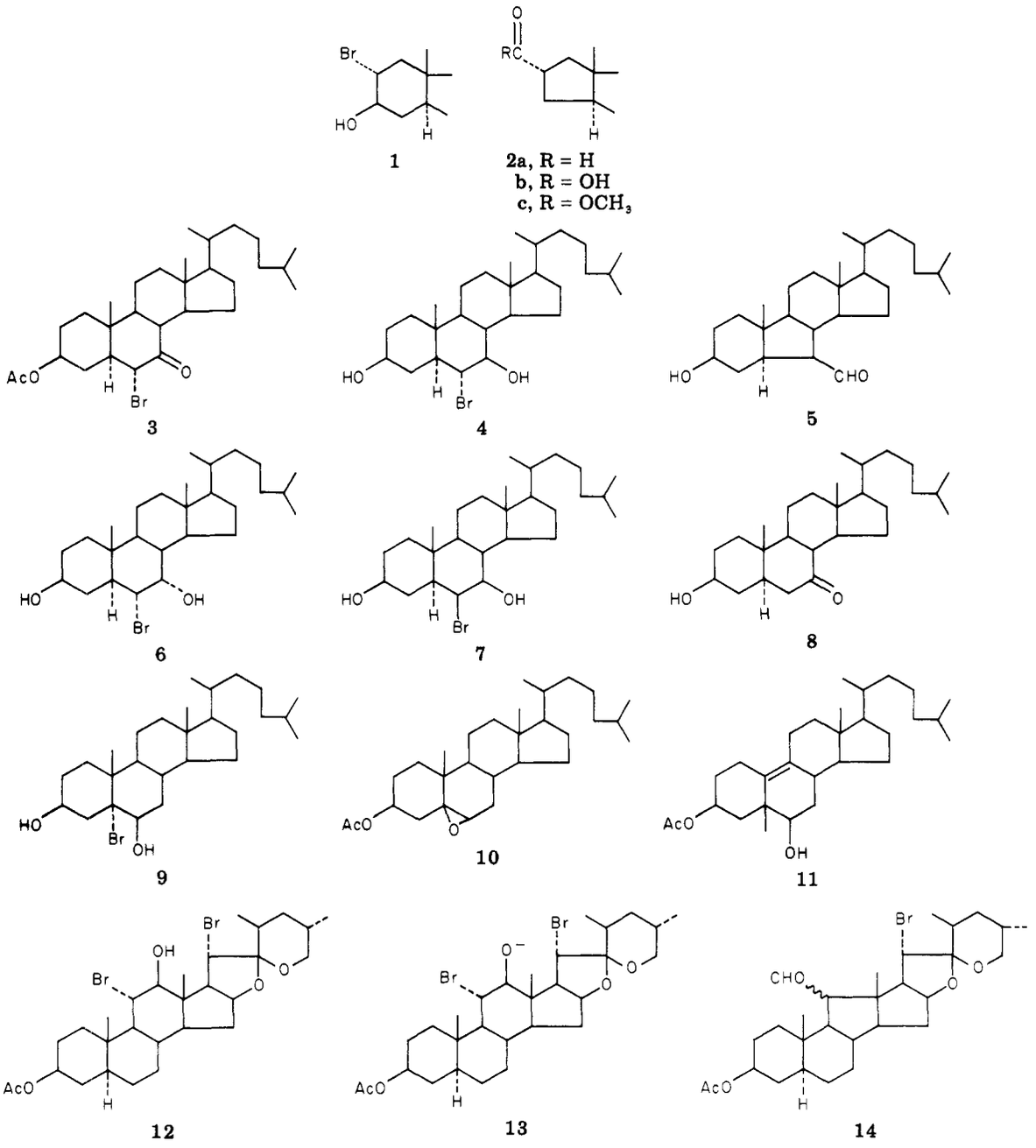
In a previous publication,[1] the reaction of 2α-bromo-5α-cholestan-3β-ol (**1**) with ethanolic silver nitrate was shown to give the diethyl acetal of *A*-nor-5α-cholestane-2-carboxaldehyde (**2a**). This report outlines additional studies which demonstrate that the silver ion induced ring contraction of sterioidal bromohydrins is both stereospecific and highly dependent on the conformation of the bromine atom. Application of the reaction to the synthesis of both B- and C-ring-contracted steroids is also disclosed.

Although the original study of the silver nitrate induced rearrangement of **1** was believed to be stereospecific, firm evidence on this point could not be obtained, due to formation of a 7:3 mixture of the known methyl *A*-nor-5α-cholestane-2α- and 2β-carboxylates from the initial acetal product (Scheme I). In particular, the acid-catalyzed liberation of the intermediate noraldehyde was considered as one cause of the resulting mixture of isomeric esters. Thus a sequence was examined that would avoid isomerization during transformation of the bromohydrin to the *A*-norester. Reaction of 2α-bromo-5α-cholestan-3β-ol (**1**) with silver oxide in hexane resulted in a direct

(1) H. R. Nace and G. A. Crosby, *J. Org. Chem.*, **33**, 834 (1968).

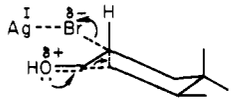
0022-3263/79/1944-3105$01.00/0

Scheme I



and nearly quantitative conversion to *A*-nor-5α-cholestane-2-carboxaldehyde (**2a**). The NMR spectrum of the crude product, mp 65.5–68.5 °C, exhibited only one ^{19}C methyl singlet in both carbon tetrachloride (δ 0.75) and benzene (δ 0.68), suggesting the formation of only one isomer. However, addition of a few drops of carbon tetrachloride saturated with dry hydrogen bromide rapidly led to a decrease in the methyl singlet observed at δ 0.75 (CCl_4), with a concomitant formation of a new singlet at δ 0.58. Integration of the two peaks indicated 72 ± 1.5% of the major isomer (δ 0.75). The *A*-noraldehyde could be obtained as a crystalline product in a yield of 88%.

The formation of a single stereoisomer suggests a transition state resembling the one shown below but does



not necessarily imply a concerted mechanism. The envisioned transition state would lead to an α configuration for the aldehyde group. This was confirmed by conversion of the crude *A*-noraldehyde **2a** to a carboxylic acid **2b** with Sarett's reagent[2] in the presence of added water. The resulting acid was not purified but was treated with 10% dry hydrogen chloride in methanol to produce methyl A-nor-5α-cholestan-2α-carboxylate (**2c**), identical with an authentic sample.[1,3] The esterification conditions were shown not to epimerize an authentic sample[4] of acid **2b**. Further, the methyl ester **2c** produced above via silver oxide exhibited only one ^{19}C methyl singlet at δ 0.66 (benzene) corresponding to the α configuration. Earlier studies have shown that the ^{19}C methyl of the 2β-norester is deshielded in benzene and exhibits a singlet at δ 0.80.[1,3]

Having confirmed the stereospecificity of the silver oxide induced ring contraction of 2α-bromo-5α-cholestan-3β-ol,[5]

(2) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(3) M. P. Cava, P. M. Weintraub, and E. J. Glamkowski, *J. Org. Chem.*, **31**, 2015 (1966).
(4) B. A. Olsen, Ph.D. Thesis, Brown University, 1964.

attention was turned to the application of this reaction to the preparation of both *B*- and *C*-norsteroids.

The first compound studied was 6α-bromo-5α-cholestane-3β,7β-diol (**4**), prepared from 3β-acetoxy-6α-bromo-5α-cholestan-7-one (**3**). Treatment of the bromohydrin with silver oxide in hexane gave *B*-nor-3β-hydroxy-5α-cholestane-6-carboxaldehyde (**5**) in 76% yield. It should be noted that both the bromine atom and the hydroxyl group are equatorial in this bromohydrin.

The ring contraction was then carried out using 6α-bromo-5α-cholestane-3β,7α-diol (**6**) (also prepared from the bromoketone **3**), in which the bromine atom is still equatorial but the hydroxy group is now axial, and the same *B*-noraldehyde **5** was obtained in 75% yield. Only the one isomer could be detected, and there was no evidence for the formation of other compounds, such as 3β-hydroxy-5α-cholestan-7-one.

These two examples reveal several facets of the bromohydrin rearrangement. First, the conformation of the hydroxyl group has no effect on the reaction when the bromine atom is equatorial. Second, production of only one conformational isomer indicates that the B-ring contraction is stereospecific, as was observed in the A-ring rearrangement. Although no evidence was obtained for the actual conformation of the *B*-noraldehyde, the course of the reaction discussed above would again be expected to produce the aldehyde group in the α configuration.

The rearrangement was also carried out using a mixture of the 7α- and 7β-diols, and only the one *B*-noraldehyde **5** was obtained.

Attention was then turned to the rearrangement of 6β-bromo-5α-cholestane-3β,7β-diol (**7**), which on treatment with silver oxide gave a 64% yield of 3β-hydroxy-5α-cholestan-7-one **8**, and no evidence could be obtained for the presence of any *B*-noraldehydes. This example provides further evidence for the mechanism pictured above, with the ketone resulting from a hydride shift of the 7-axial hydrogen to the incipient (or formed) carbonium ion at carbon 6. It also demonstrates further that it is the conformation of the bromine atom, rather than the hydroxyl group, which determines the course of the reaction.

5α-Bromocholestane-3β,6β-diol (**9**) presents an interesting case since the 19-methyl and 6-hydroxyl are both trans to and coplanar with the departing 6-axial bromine atom. Treatment of the 3-acetate of **9** with silver oxide gave an 80% yield of the known 5β,6β-oxidocholestan-3β-ol 3-acetate (**10**) and 8% of the Westphalen's diol[6] **11**. Thus the hydroxyl group, with its nonbonded electrons, appears to assist the departure of the bromide ion much better than the 19-methyl does.

The last compound studied was 11α,23ζ-dibromo-5α,22a-spirostane-3β,12β-diol 3-acetate (**12**). This compound, in which the 11-bromine and 12-hydroxyl group are trans and equatorial, was chosen because very few methods for the synthesis of *C*-norsteroids have been reported. Indeed, it has been reported[7] that treatment of the same compound (minus the 23-bromine) with silver oxide in pyridine gave a nearly quantitative yield of the 11,12-oxide. However, it seemed possible that under these conditions substantial amounts of the anion **13** would be formed, and oxide formation would then take place much more readily than formation of the *C*-noraldehyde, which contains two trans-fused cyclopentane rings. Treatment of **12** with silver oxide in benzene–hexane gave a 50% yield of of the *C*-noraldehyde **14** along with other unidentified products. No evidence could be obtained for the presence of the 11,12-oxide.

These above examples show the utility of the rearrangement of bromohydrins with silver oxide to prepare ring norsteroids. They also establish that ring contraction occurs if the bromine atom is equatorial, and oxide formation or ketone formation (hydride shift) occurs if the bromine atom is axial.

Experimental Section

Melting points are corrected and were determined with a Herschberg apparatus and Anshutz thermometers. Analytical samples were recrystallized to constant melting points, and the analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. The infrared spectra were obtained with a Perkin-Elmer Model 337 spectrometer. NMR spectra were obtained with a Varian HR-60 or HA-60A spectrometer, using 10% solutions in CCl_4 unless stated otherwise. Tetramethylsilane was used as internal standard, and peak positions are reported in parts per million (δ). Thin-layer chromatography (TLC) was done on Eastman chromogram sheets, type K301R (later designated as No. 6061).

Reaction of 2α-Bromo-5α-cholestan-3β-ol (1) with Silver Oxide: Preparation of *A*-Nor-5α-cholestane-2α-carboxaldehyde (2a). A mixture of 500 mg (1.07 mmol) of **1** and 1.05 g of freshly prepared silver oxide[8] was boiled under reflux in 75 mL of dry hexane under nitrogen for 30 min, then cooled to room temperature and filtered to remove silver salts. The salts were washed with several small portions of ether, and the combined filtrate and washings were evaporated to dryness under reduced pressure to yield 444 mg of rosettes: mp 65.5–68.5 °C; IR (CCl_4) 2945, 2715, 1735 cm^{-1}; NMR (25 mg in 0.4 mL of benzene) δ 0.55 (s, C-18 CH_3), 0.68 (s, C-19 CH_3), 0.90 (s), 1.00 (s), and 9.50 (d, CHO, J = 2.0 Hz); NMR (25 mg in 0.4 mL of CCl_4) δ 0.65 (s, C-18 CH_3), 0.75 (s, C-19 CH_3), 0.81 (s), 0.91 (s), and 9.60 (d, CHO, J = 2.0 Hz). Addition of a small amount of CCl_4 saturated with HBr to the CCl_4 NMR sample caused a decrease in the ^{19}C methyl singlet at δ 0.75 and the appearance of a smaller singlet at δ 0.58. The relative peak areas indicated the presence of 72 ± 1.5% of the 2α isomer (δ 0.75).

A 95-mg portion of the crude *A*-noraldehyde was chromatographed on a column of 3.5 g of silica gel prepared with hexane. Elution with 10-mL fractions of 1:1 benzene–hexane gave 83.1 mg (88%) of pure *A*-noraldehyde (**2a**), mp 69–70.5 °C, from fractions 2 and 3.

Oxidation of *A*-Norcholestane-2α-carboxaldehyde (2a) under Nonequilibrating Conditions. To 500 mg (5.0 mmol) of chromic anhydride in 15 mL of pyridine[2] was added a solution of 85 mg (0.22 mmol) of the *A*-noraldehyde **2a** in 2 mL of pyridine containing 2 drops of water. The mixture was stirred at room temperature for 5.5 h, then cooled to 0 °C and acidified with cold 5% HCl. Ether was added, the mixture was filtered to remove chromium salts, the organic layer was evaporated to near-dryness under reduced pressure, benzene was added, and the mixture was distilled to dryness under reduced pressure to give 85.7 mg of semisolid material, which was used as such in the following step.

Esterification of *A*-Nor-5α-cholestane-2α-carboxylic Acid (2b). The crude *A*-noracid from above was mixed with 45 mL of 10% methanolic HCl and heated under reflux for 1.5 h, then cooled overnight to yield 56 mg of needles, mp 94–96.5 °C (lit.[9] mp 97.5–98 °C). The mother liquors yielded an additional 6 mg. The NMR spectrum (benzene) was identical with that of an authentic sample, and there was no evidence of the presence of any 2 β isomer.

A 51.0-mg (0.12 mmol) authentic sample[9] of the *A*-noracid (previously prepared by Dr. B. A. Olsen) in 50 mL of 10% methanolic HCl was warmed to 40 °C and then allowed to stand at room temperature for 43 h. Subsequent cooling gave 42.4 mg (84%) of needles, mp 95–97.5 °C (lit.[9] mp 97.5–98 °C). The NMR

(5) Since completion of this work, somewhat similar results have been reported, using silver carbonate rather than silver oxide, by M. Fetizon, M. Golfier, and J.-M. Louis, *Tetrahedron Lett.*, 1931 (1973).
(6) B. Ellis and V. Petrow, *J. Chem. Soc.*, 2246 (1952).
(7) J. Schmidlin and A. Wettsteim, *Helv. Chim. Acta*, **36**, 1241 (1953).
(8) Prepared by the method of D. Y. Curtin and R. J. Harder, *J. Am. Chem. Soc.*, **82**, 2357 (1960).
(9) H. R. Nace and B. B. Smith, *J. Am. Chem. Soc.*, **76**, 6119 (1954).

spectrum (25 mg in 0.4 mL of benzene) showed only one ^{19}C methyl resonance at δ 0.66, indicating that no isomerization had occurred under these conditions.

3β-Acetoxy-5α-cholestan-7-one. This compound was prepared by the method of Wintersteiner and Moore[10] and had mp 144.5–146 °C (lit.[10] 148–149 °C): IR 2940, 1735, 1715, 1240, and 1030 cm^{-1}; NMR (CCl_4) δ 0.64 (s, C-18 CH_3), 0.82 (s), 0.92 (s), 1.09 (s, C-19CH_3), 1.94 (s, $OCOCH_3$), and 4.60 (br, C-3 H).

3β-Acetoxy-6β-bromo-5α-cholestan-7-one. This compound was prepared as described previously[11] and had mp 176.5–178 °C (lit.[11] mp 173–175 °C); IR (CCl_4) 1738, 1720, 1230, and 1025 cm^{-1}; NMR δ 0.70 (s, C-18 CH_3), 1.31 (s, C-19 CH_3), 1.98 (s, $OCOCH_3$), 4.03 (br, C-6 H).

3β-Acetoxy-6α-bromo-5α-cholestan-7-one 3. To a solution of 3.20 g (20.0 mmol) of bromine in 60 mL of glacial acetic acid was added, in one portion, a solution of 9.00 g (17.1 mmol) of 3β-acetoxy-5α-cholestan-7-one in 165 mL of glacial acetic acid containing 3% by weight of HBr. The solution was kept for 6.75 h at 14–15 °C and then poured into 600 mL of water. The hard orange precipitate was collected and crystallized from methanol to give 7.34 g of crude product, which was taken up in ether. The solution was washed (saturated $NaHCO_3$), the ether was removed at reduced pressure, benzene was added to the wet residue and distilled to remove water, and the residue was recrystallized from methanol to give 3.509 g of white solid. Cooling of the mother liquor for 24 h at 0 °C gave a small amount of the 6β isomer. Then additional cooling of the mother liquors gave 697 mg more of the 6α-bromo isomer: total yield 4.206 g (47%); mp 138–141 °C (lit.[11] mp 142–143 °C); IR (CCl_4) 2955, 1735, 1230, 1026, 680 cm^{-1}; UV (EtOH) max 282 nm (log ϵ 1.64) (lit.[12] 282 (log ϵ 1.16)); NMR δ 0.65 (s, C-18 CH), 0.82 (s), 0.92 (s), 1.15 (s, C-19 CH_3), 1.97 (s, $OCOCH_3$), and 4.47 (d, C-6 H, J = 12 Hz).

Reaction conditions of higher temperatures (25 °C) or longer reaction times (10–12 h) gave a product which was more difficult to purify by recrystallization from ethanol or aqueous acetic acid.

6α-Bromo-5α-cholestane-3β,7α-diol (6) and 6α-Bromo-5α-cholestane-3β,7β-diol (4). These compounds were prepared by the method of Henbest and Wrigley.[13] The 7α-ol had mp 131–132.5 °C (lit.[13] mp 131–132 °C); IR (CCl_4) 3640, 3590, 2950, 1072, and 1037 cm^{-1}. The 7β-ol had mp 209–212 °C (lit.[13] mp 209–212 °C); IR (CCl_4) 3640, 3590, 2955, 1068, 1045, and 1034 cm^{-1}.

Reaction of 6α-Bromo-5α-cholestane-3β,7β-diol (4) with Silver Oxide. 3β-Hydroxy-*B*-nor-5α-cholestane-6-carboxaldehyde (5). A mixture of 91.5 mg (0.19 mmol) of the bromo diol and 300 mg of freshly prepared silver oxide[7] in 20 mL of hexane (distilled from calcium hydride) was boiled under reflux under a nitrogen atmosphere for 30 min, cooled to room temperature, and filtered (medium sintered funnel), the flask and silver salts were washed with ether, and the combined filtrate and washings were evaporated to dryness to give 67 mg of crude aldehyde. The residue was taken up in 6.5 mL of benzene and chromatographed on 2.8 g of silica gel. Elution (5-mL fractions) with 25% ether in benzene and combination of fractions 2–4 gave 58 mg (76%) of crystalline noraldehyde, mp 147–150 °C. (Other physical data and the microanalysis are listed below.)

Preparation of the *B*-Noraldehyde from 6α-Bromo-5α-cholestan-3β,7α-diol (6). A mixture of 100.6 mg (0.208 mmol) of the 3β,7α-diol and 299.3 mg of silver oxide in 20 mL of hexane was treated as above. Chromatography fractions 3 and 4 (5 mL each) and 5 (20 mL) were combined and evaporated to give 61.1 mg (75%) of *B*-noraldehyde, mp 147–150 °C (see below).

Preparation of the *B*-Noraldehyde from the Mixed 6α-Bromo-3β,7α- and -3β,7β-diols. A crude mixture of 245 mg of the isomeric bromohydrins, prepared by lithium aluminum hydride reduction of 278.4 mg of 3β-acetoxy-6α-bromo-5α-cholestan-7-one (3), was treated as above with 750 mg of silver oxide in 30 mL of 1 to 1 benzene–hexane to yield 228.4 mg of the *B*-norcarboxaldehyde: IR (CCl_4) 3640, 2950, 2725, 1720, 1030 cm^{-1}; NMR (benzene) δ 0.57 (s), 0.88 (s), 0.98 (s), and 9.66 (d, –CHO); NMR δ 0.65 (s), 0.82 (s), 0.91 (s), and 9.70 (d, –CHO). The spectra of the two previously described samples were virtually identical.

Satisfactory microanalyses could not be obtained for the aldehyde because of its instability. The 2,4-dinitrophenylhydrazone (from ethanol) had mp 191.5–193.5 °C.

Anal. Calcd for $C_{33}H_{50}O_6N_4$: C, 66.19; H, 8.41; N. 9.36. Found: C, 66.52; H, 8.25; N, 9.48.

Methyl *B*-Nor-3β-hydroxy-5α-cholestane-6-carboxylate. A sample of the *B*-noraldehyde was dissolved in petroleum ether (bp 62.5–65 °C), and the solution was boiled under air for 15–20 min on a steam bath and then refrigerated overnight. The crystalline acid decomposed at 265–275 °C, no melting up to 290 °C; IR (CCl_4) 3640, 3160, (br), 2950, 1730, and 1015 cm^{-1}. A solution of 53.2 mg (0.127 mmol) of the *B*-noracid in 5 mL of 10% methanolic hydrogen chloride was boiled under reflux for 10 h, and then the solvent was evaporated under reduced pressure. The residue was taken up in 8 mL of benzene and chromatographed on 2.5 g of silica gel. Elution with 10-mL fractions of 1:1 benzene–ether gave 19.4 mg of solid material from the second fraction. Recrystallization from benzene–hexane gave mp 204.5–206.5 °C (Kofler Hot Stage); NMR (benzene) δ 0.48 (s), 0.61 (s), 0.88 (s), 3.10 (s, $-COOCH_3$), and 3.47.

Reaction of 6β-Bromo-5α-cholestane-3β,7β-diol (7) with Silver Oxide. A mixture of 204 mg (0.41 mmol) of the bromodiol 7 and 601 mg of silver oxide in 55 mL of hexane was treated in the usual manner and gave 168.6 mg of white solid. A 144-mg sample was taken up in hexane and chromatographed on 3.2 g of silica gel. Elution with 25% ether-in-benzene gave six 5-mL fractions and then one 10-mL fraction. Fractions 5–7 were combined to give 92.2 mg (64%) of crystals of 3β-hydroxy-5α-cholestan-7-one (8) which, after recrystallization from methanol, had mp 170.5–171.5 °C (lit.[10] mp 164–165 °C): IR (CCl_4) 3630, 2950, 1710, 1173, 1072, 1028, and 942 cm^{-1}; NMR (CCl_4) δ 0.64 (s, C-18 CH_3), 0.82 (s), 0.92 (s), 1.07 (s, C-19 CH_3), 1.9–2.5 (br, C-6 and C-8 H's), 3.52. Both spectra were identical with those of an authentic sample.

Reaction of 5α-Bromocholestane-3β,6β-diol 3-Acetate (9) with Silver Oxide. A mixture of 300 mg (0.55 mmol) of the bromodiol 9 and 902 mg of silver oxide in 57 mL of hexane was treated in the usual manner (except 45 min reflux), and 256.4 mg of a waxy solid was obtained. A 210.5-mg sample in 12 mL of benzene was chromatographed on 4.0 g of silica gel (packed in hexane). Eluates of 12 mL (13% ether-in-benzene) were collected. Fraction 2 (67.3 mg) was saved and fraction 3 (120.0 mg) was rechromatographed using 25% ether-in-benzene, and eluate fractions of 7 mL and 1 fraction of 20 mL were combined with fraction 2 above. Evaporation of the solvent gave 165 mg (80%) of 5β,6β-oxidocholestan-3β-ol 3-acetate (10). Three recrystallizations from methanol gave mp 110–112 °C (lit.[14] mp 112–113 °C): IR spectrum identical with that of an authentic sample; NMR δ 0.66 (s, C-18 CH_3), 0.82 (s), 0.92 (s), 0.97 (s, C-19 CH_3), 1.96 (s, $-OCOCH_3$), 2.95 (d, 1, CH, J = 2.5 Hz), and 4.67 (br, 1, C-3 H).

Fractions 9 and 10 (17.7 mg, 8%) were acetylated with pyridine and acetic anhydride, and the NMR spectrum δ 1.20 (C-5 β-CH_3) and 2.0 (3β- and 6β-$OCOCH_3$) was characteristic of that of Westphalen's diol diacetate[15] 11. TLC gave R_f 0.65, also characteristic of Westphalen's diol acetate; however, there was insufficient material for further characterization.

11α,23ζ-Dibromohecogenin Acetate. This compound was prepared by the procedure of Elks et al.[16] and had mp 183–185 °C dec (lit. mp 189–191 °C); IR (CCl_4) 2950, 1735, 1715, 1232, 1130, 1090, 1058, 1030, and 957 cm^{-1}.

11α,23ζ-Dibromo-5α,22a-spirostane-3β,12β-diol 3-Acetate 12. This compound was prepared by the procedure of Cornforth et al.[17] and had mp 192–194 °C dec [lit. mp 197 °C dec]: IR (CCl_4) 3570, 1735, 1230, 1056, 1015 and 942 cm^{-1}; NMR δ 0.83(s, CH_3), 0.89(s, CH_3), 1.00(s, CH_3), 1.93(s, $OCOCH_3$), 3.39 (br), 4.00 (br), and 4.47 (br).

Reaction of the Spirostane Bromohydrin 12 with Silver Oxide. 3β-Acetoxy-23ζ-bromo-5α,22a-C-norspirostan-11-carboxaldehyde (14). A mixture of 130 mg (0.205 mmol) of the

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bromohydrin, 400 mg of silver oxide, 9.5 mL of benzene, and 9.5 mL of hexane was boiled under reflux under nitrogen for 1.25 h. After the usual workup, the residue was recrystallized from hexane (7 mL)–benzene (1.5 mL) to give 36 mg of crystals. Concentration and several days cooling of the mother liquor gave an additional 20 mg (total yield, 50%). Two recrystallizations gave an analytical sample: mp 220.0–220.7 °C dec (placed in bath at 215 °C); NMR δ 0.86 (s), 1.00 (s), 1.13 (s), 1.25 (s), 1.93 (s, $OCOCH_3$), 3.37 (br), 4.50 (br, 3α-**H**), and 9.75 (d, -C**H**O).

Anal. Calcd for $C_{29}H_{43}O_5Br$: C, 63.15; H, 7.86; Br, 14.48. Found: C, 62.73; H, 8.03; Br, 14.16.

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Registry No. 1, 3903-52-4; **2a**, 70896-71-8; **2b**, 2312-00-7; **2c**, 2312-02-9; **3**, 70864-92-5; **4**, 70864-93-6; **5**, 70864-94-7; **5**-2,4-DNP, 70864-95-8; **6**, 70864-96-9; **7**, 70864-97-0; **8**, 7591-17-5; **9**, 1258-35-1; **10**, 1256-31-1; **11**, 2572-56-7; **12**, 70864-98-1; **14**, 70864-99-2; 3β-acetoxy-5α-cholestan-7-one, 6038-71-7; 3β-acetoxy-6β-bromo-5α-cholestan-7-one, 70865-00-8; methyl *B*-nor-3β-hydroxy-5α-cholestane-6-carboxylate, 70865-01-9; *B*-nor-3β-hydroxy-5α-cholestane-6-carboxylic acid, 70865-02-0; 11α,23ζ-dibromohecogenin acetate, 70896-72-9.

Some Aromatic Compounds from the Marine Sponge *Plakortis halichondrioides*

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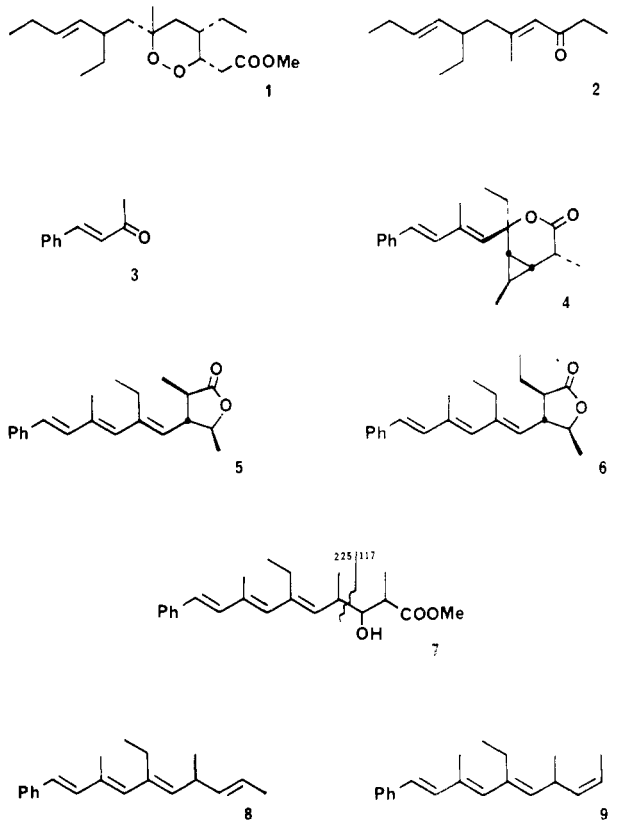
A sample of the marine sponge *Plakortis halichondrioides* was shown to contain *trans*-4-phenyl-3-buten-2-one (**3**), a δ-lactone **4**, two γ-lactones **5** and **6**, a hydroxy ester **7**, and two isomeric hydrocarbons **8** and **9**. The structures of the metabolites were elucidated by detailed analysis of spectral data. The probable biosynthetic correlation between the major metabolites and the relationship between these metabolites and the cyclic peroxides previously isolated from *P. halichondrioides* are discussed.

We have recently described the isolation and identification of a cyclic peroxide, plakortin (**1**), and a related ketone **2** from a sample of *Plakortis halichondrioides* from Panama.[1] During a subsequent research cruise on R/V Alpha Helix to Belize, we collected several sponges which were similar in appearance to the preserved sample of *P. halichondrioides* but which could be distinguished in the field by their patterns of growth or their texture when freshly collected. Some of these samples were indeed *Plakortis halichondrioides* and contained cyclic peroxides which were not always plakortin (**1**), however.[2] One of the samples which has been tentatively identified as *Plakortis halichondrioides* did not contain peroxides. In this paper we wish to describe the isolation and identification of a series of aromatic compounds from this chemically "abnormal" sample of *P. halichondrioides*.

The hexane-soluble material from an ethanol extract of *P. halichondrioides* was chromatographed on Florisil to obtain several fractions which contained aromatic compounds. Rechromatography of these fractions on silica gel gave two major compounds and five minor metabolites, some of which were purified by LC on μ-Porasil. Among the minor metabolites, *trans*-4-phenyl-3-buten-2-one (**3**) (0.006% dry weight) was identified from its spectral data.[3] The major metabolites were a δ-lactone **4** and a γ-lactone **5**. The minor metabolites included a γ-lactone **6**, a hydroxy ester **7**, and two isomeric hydrocarbons **8** and **9**.

The δ-lactone **4** (0.24% dry weight) had the molecular formula $C_{21}H_{26}O_2$. The infrared spectrum contained a band at 1740 cm^{-1} indicating the presence of an ester or δ-lactone functionality. The ^{13}C NMR spectrum confirmed the presence of 21 carbon atoms with a carbonyl carbon signal at δ 171.0, ten olefinic or aromatic carbons between δ 126 and 137, including two signals for two carbons each at δ 128.3 (d, 2C) and 126.2 (d, 2C), suggesting a monosubstituted phenyl ring, and a signal for a carbon atom bearing oxygen at δ 81.8 (s). The UV spectrum showed a strong absorption at 289 nm (ϵ 33 000) which suggested that the phenyl ring and both olefinic bonds were conjugated. The ^1H NMR spectrum contained signals at δ 7.31 (br d, 2 H, J = 7 Hz), 7.24 (br t, 2 H, J = 7 Hz), and 7.15



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