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Synthesis of Some *B*-Nor-6,8-secoestranes and *B*,19-Dinor-6,8-secopregnanes

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Dehydrogenation of dehydroepiandrosterone (**1a**) and pregnenolone (**1b**) with DDQ, followed by dienone–phenol rearrangement and then hydrolysis and methylation, gave 3-methoxy-1-methylestra-1,3,5(10),6-tetraen-17-one (**3e**) and 3-methoxy-1-methyl-19-norpregna-1,3,5(10),6-tetraen-20-one (**3f**). The 6,7-olefinic moiety of **3e** and **3f** was cleaved with osmium tetroxide–sodium periodate to yield dialdehyde products **4a** and **4b**. Individual rotational isomers of the dialdehydes were seen in their ^{1}H NMR spectra. Decarbonylation of dialdehydes **4a** and **4b** to *B*-nor-6,8-secoestratriene **5a** and *B*,19-dinorpregnatriene **5b**, respectively, was accomplished with tris(triphenylphosphine)chlororhodium. The *B*-nor-6,8-secosteroids **5a** and **5b** were used as intermediates to prepare variously 17-substituted compounds **5c–e** and 4-en-3-one compounds **6a** and **6b**.

Since there are no reports in the literature of the preparation of either *B*-nor-6,8-secoestranes or *B*,19-dinor-6,8-secopregnanes, we undertook the synthesis of steroids with this feature. A brief degradative route (Scheme I) from naturally occurring steroids was chosen for investigation since this would provide final products with the natural stereochemical configuration.

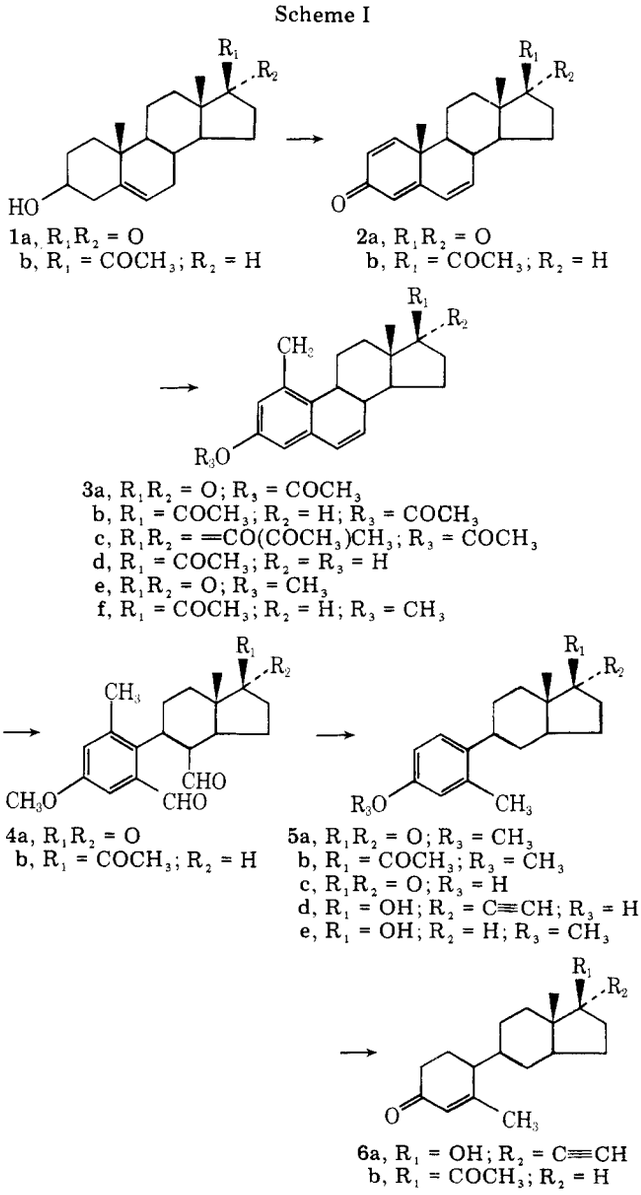
Dehydroepiandrosterone (**1a**) and pregnenolone (**1b**) were dehydrogenated with dichlorodicyanoquinone (DDQ) in refluxing dioxane to the corresponding trienes **2a** and **2b**.[1] On dienone–phenol rearrangement in acetic anhydride with toluenesulfonic acid catalyst, triene **2a** was converted to tetraene **3a**,[2] while triene **2b** was converted to a mixture of tetraene **3b** and diacetate **3c** with **3c** the major product.

The need for additional quantities of **3b** prompted a study of the hydrolysis of diacetate **3c** to determine if the 17-acetyl functionality with the normal β configuration and free of any 17α isomer contamination could be regenerated from the $\Delta^{17,20}$ enol acetate. Precedent existed for the conversion since Rubin and Blossey[3] have shown that pregnanes with the abnormal 17α configuration can be equilibrated to a mixture (85:15) of 17β and 17α isomers. The ^{1}H NMR spectrum of the crude phenol **3d**, obtained from basic hydrolysis of diacetate **3c**, had C-18 methyl absorptions at δ 0.52 and 0.87 ppm, clearly indicating the presence of both 17β- and 17α-acetyl moieties. Phenol **3d** was chromatographed and both early and late fractions gave identical ^{1}H NMR spectra; none of the 17α isomer could be found. Hydrolysis of monoacetate **3b** gave phenol **3d** whose melting point and ^{1}H NMR spectrum were identical with those of the phenol obtained from diacetate **3c**.

Hydrolysis of diacetate **3c** with methanolic sodium hydroxide followed by methylation with dimethyl sulfate also gave only the 17β isomer of *O*-methyl ether **3f**. This was confirmed by hydrolysis and methylation of monoacetate **3b**. In subsequent preparations, the mixture of acetates **3b** and **3c**, after filtration through a short column of alumina to remove polar impurities, was hydrolyzed, methylated, and purified. None of the 17α isomer could be detected in the *O*-methyl ether product **3f**.

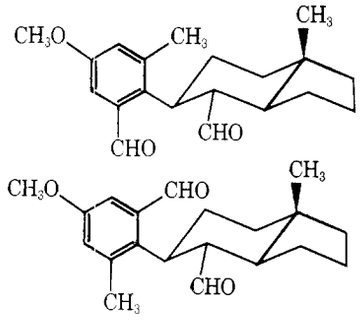
Attempts to transform the 6,7-olefinic moieties of compounds **3e** and **3f** into dialdehyde functionalities employing sodium periodate and a catalytic amount of osmium tetroxide

Scheme I



0022-3263/78/1943-0113$01.00/0

Chart I



produced vastly different results depending upon the reaction medium. In tetrahydrofuran–water, no hydroxylation or cleavage products were detectable even after heating, and a quantitative yield of starting material was reclaimed. However, in acetic acid–water medium,[4,5] new products were apparent by both GLC and TLC analysis within a few hours. After 3 days at room temperature, all the starting material was consumed and there was no further change in the reaction composition. After chromatography, aldehydes **4a** and **4b** were isolated in 47 and 49% yield, respectively.

Strikingly, the ^{1}H NMR spectrum of aldehydes **4a** and **4b** each clearly showed the presence of two rotational isomers. Both the C-18 and C-6 methyl resonances consisted of double absorptions, while the 3-*O*-methyl signal was a singlet because of its symmetric position (Chart I). The aromatic hydrogens were also configurationally split, but the presence of two isomers was most clearly shown by the aldehyde absorptions, which were well separated in their chemical shifts and each distinctly split into two bands. The ratios of isomers for the individual aldehydes **4a** and **4b** were quite different. For estrone dialdehyde **4a** the ratio was 4:1, while the ratio was 2:1 for pregnane compound **4b.** Chart I emphasizes the point that all the functionalities described, except the 3-*O*-methyl group, should have different structural environments and therefore different chemical shifts. Attempts to separate the isomers by chromatography were unsuccessful.

The reaction medium was also found to affect the outcome of bisdecarbonylation of dialdehydes **4a** and **4b** to *B*-nor-6,8-secosteroids **5a** and **5b.** In refluxing benzene containing two molar equivalents of tris(triphenylphosphine)chlororhodium, the starting aldehyde rapidly disappeared, but the absence of gas evolution and the failure to detect new products indicated a stable complex was being formed. However, when the reaction was conducted in refluxing benzonitrile, gas evolution was readily apparent, and after workup, products **5a** and **5b** were isolated in 70 and 67% yield, respectively.

The transformation of *B*-nor-6,8-secosteroid **5b** to progesterone analogue **6b** was accomplished by initially reducing the 20-ketone moiety to a mixture of epimeric alcohols followed by Birch reduction of the A ring. Acid hydrolysis of the dihydro product to an α,β-unsaturated ketone followed by Jones oxidation of the 20-alcohol to a ketone completed the preparation of *B*,19-dinor-6,8-secoprogesterone (**6b**).

Estrone 3-methyl ether analogue **5a** was likewise used as an intermediate to prepare various 17-substituted products. Thiophenoxide demethylation[8] of **5a** gave a poor yield of difficultly purifiable phenol **5c.** An improved yield of **5c** was achieved by pyridine hydrochloride fusion[9] of **5a.** Treatment of **5c** with lithium acetylide–ethylenediamine complex gave the *B*-nor-6,8-seco analogue of mestranol (**5d**).

The *B*-nor-6,8-seco analogue of norethindrone (**6a**) was also prepared from **5a.** Sodium borohydride reduction of **5a** in ethanol gave alcohol **5e** which was then reduced with sodium in liquid ammonia to the dihydro intermediate.[10] Attempted steam distillation of the solvent to isolate the dihydro intermediate resulted in extensive oxidation and hydrolysis of the product. In subsequent preparations, the isolation step was omitted and the 17-hydroxyl of the crude product was directly oxidized to the corresponding ketone under Oppenhauer conditions with cyclohexanone.[11] This intermediate also proved to be labile and after vacuum removal of most of the cyclohexanone, the product was ethynylated with a large excess of lithium acetylide. After workup, pure **6a** was isolated in 46% overall yield for the three step sequence (**4a–6a**).

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 337 spectrophotometer. Ultraviolet spectra were run on a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model HA-100, using tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts are expressed in δ units. Coupling constants (J) are expressed in hertz (Hz).

3-Acetoxy-1-methylestra-1,3,5(10),6-tetraen-17-one (3a). A modification of the procedure described by Djerassi et al.[2] was employed. Androstratriene **3a**[1] (5.8 g, 206 mmol) and *p*-toluenesulfonic acid (1.46 g) in acetic anhydride (225 mL) were heated on the steam bath for 5 h, then cooled and evaporated under reduced pressure to remove excess acetic anhydride. Residual acetic anhydride was removed by stirring with saturated sodium bicarbonate, then extracting with methylene chloride (2 × 100 mL). The residue remaining after vacuum removal of the solvent was chromatographed on alumina (activity III, 180 g, benzene) to give 3.8 g (57%) of pure **3a:** mp 152–153 °C; (lit.[1] mp 152–153 °C).

Dienone–Phenol Rearrangement of Pregna-1,4,6-tetraene-3,20-dione (2b). The reaction was performed as described above. From trienone **3b**[1] (2.0 g, 6.45 mmol), toluenesulfonic acid (458 mg), and acetic anhydride, there was isolated 2.7 g of crude product containing **3b** and **3c.** The mixture was separated by chromatography (silica gel, 100 g). Elution with 10% methylene chloride–benzene gave 1.35 g (38%) of compound **3c** as a foam: NMR ($CDCl_3$) δ 0.93 (s, 3, 18-CH_3), 1.81 (s, 3, 21-CH_3), 2.10 (s, 3, O_2CCH_3), 2.23 (s, 3, O_2CCH_3), 2.47 (s, 3, $ArCH_3$), 5.96 (dd, J = 8 Hz, 1, =CH), 6.37 (dd, J = 8, 3 Hz, 1, =CH), 6.6 ppm (s, 2, Ar-H), m/e = 394.

Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.67. Found: C, 75.97; H, 7.70.

Elution with 50% methylene chloride gave 1.15 g (51%) of **3b** as an oil: NMR (CCl_4) δ 0.86 (s, 3, 18-CH_3), 1.75 (s, 3, 21-CH_3), 2.04 (s, 3, 20-OAc), 2.16 (s, 3, 3-OAc), 2.49 (s, 3, $ArCH_3$), 5.9 (d, 1, J = 10 Hz, =CH), 6.32 (dd, 1, J = 10, 3 Hz, =CH), and 6.56 ppm (s, 2, ArH).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.25; H, 7.95.

In subsequent preparations the yield and ratio of products **3b** and **3c** were found to be variable. Prolonged heating gave increased amounts of **3c.**

3-Hydroxy-1-methyl-19-norpregna-1,3,5(10),6-tetraen-20-one (3d). Hydrolysis of **3c** and **3b** was performed with 10% methanolic sodium hydroxide. The ^{1}H NMR spectrum of the crude phenol product from hydrolysis of **3c** had absorptions at δ 0.52 and 0.87 ppm (17α- and 17β-acetyl configuration, respectively) for the C-18 methyl group. Both products gave, after chromatography (silica gel; 10% EtOAc–CH_2Cl_2), pure phenol **3d:** mp 227–230 °C (methanol); NMR (acetone-d_6) δ 0.64 (s, 3, 18-CH_3), 2.08 (s, 3, $COCH_3$), 2.44 (s, 3, $ArCH_3$), 5.87 (d, 1, J = 10 Hz, =CH), 6.27 (s, 0.5, =CH), 6.4 ppm (s, 2.5, ArH, =CH).

3-Methoxy-1-methylestra-1,3,5(10),6-tetraen-17-one (3e) and 3-Methoxy-1-methyl-19-norpregna-1,3,5(10),6-tetraen-20-one (3f). Either **3a** or **3b** (2 g) in methanol (60 mL) was refluxed with 10% methanolic sodium hydroxide until TLC analysis (silica gel; 5% ethyl acetate–chloroform) indicated that the acetate was converted to the phenol. Dimethyl sulfate (4 mL) was added, and the course of the reaction was followed by TLC analysis and monitoring the pH. When the solution became acidic, additional quantities of sodium hydroxide and dimethyl sulfate were added. The methanol was evaporated and water (100 mL) was added to precipitate the product which was collected and recrystallized from methanol–water. The yield of **3e** was 1.55 g (85%); mp 151–152 °C (lit.[2] mp 151.5–152 °C). The yield of **3f,** an oil, was 1.45 g (79%): NMR (CCl_4) δ 0.71 (s, 3, 18-CH_3), 2.01 (s, 3, $COCH_3$), 2.46 (s, 3, $ArCH_3$), 3.68 (s, 3, OCH_3), 5.83 (dd, J = 9 Hz, 1, =CH), 6.24 (d, J = 3 Hz, 0.5, =CH), 6.35 ppm (s, 1.5, ArH and =CH).

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.42; H, 8.70. Found: C, 81.30; H, 8.59.

3-Methoxy-1-methyl-17-oxo-6,7-secoestra-1,3,5(10)-triene-6,7-dial (4a). A mixture of sodium metaperiodate (4.35 g, 20.3 mmol), steroid **3e** (2.00 g, 6.76 mmol), water (34 mL), and acetic acid (150 mL) was heated on a steam bath until the solids dissolved. When the solution cooled to room temperature, osmium tetroxide (20 mg in 2 mL of CCl_4) was added, and the reaction was stoppered and stirred. After 18–24 h, TLC (silica gel; 5% EtOAc/$CHCl_3$) and GLC analysis (1% OV-17) indicated that steroid **3e** was completely consumed. An additional 24-h period was required for GLC analysis to show no further change in the product ratios. The acetic acid was removed under vacuum, water (50 mL) was added, and the product was extracted with chloroform (3 × 10 mL). The chloroform extracts were washed with saturated sodium bicarbonate and then with water and dried ($MgSO_4$). After vacuum removal of the solvent, the residue was chromatographed (30 g; silica gel; CH_2Cl_2–4% EtOAc/CH_2Cl_2) to give 1.05 g (47% yield) of pure dialdehyde **4a** as a gum. The presence of two rotational isomers in an approximate ratio of 4:1 was apparent in the NMR spectrum. The minor rotamer product is marked with an s: NMR ($CDCl_3$) δ 1.00 (s), 1.20 (s, 3, 18-CH_3), 2.36, 2.53 (s) (s, 3, 1-CH_3), 3.80 (s, 3, OCH_3), 6.84 (s), 6.87, 7.00 (s), 7.14 (d, J = 3 Hz, Ar-H), 9.25 (s), 9.8 (d, J = 4 (s), J = 3 Hz, CHO), 10.02 (s), 10.07 ppm (s, 1, ArCHO).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.39; H, 7.45.

3-Methoxy-1-methyl-20-oxo-19-nor-6,7-secopregna-1,3,5(10)-triene-6,7-dial (4b). The experimental conditions and workup for this preparation were identical with the procedure used to prepare dialdehyde **4a.** From tetraene **3f** (3.65 g, 11.25 mmol), sodium periodate (7.27 g, 34 mmol), and osmium tetroxide (60 mg) in acetic acid (240 mL)–water (60 mL), there was obtained 1.95 g (49% yield) of pure dialdehyde **4b** as a gum. The ^1H NMR spectrum of aldehyde **4b** showed the presence of two isomers in an approximate ratio of 2:1. The smaller absorption is marked with an s: NMR ($CDCl_3$) δ 0.82 (s), 0.94 (s, 3, 18-CH_3), 2.15 (s, 3, $COCH_3$), 2.41, 2.54 (s) (s, 3, $ArCH_3$), 6.88 (s), 6.95, 7.10 (s), 7.24 (d, J = 3 Hz, 2, Ar-H), 9.33 (s), 9.40 (d, J = 4 (s), J = 0.5 Hz, 1, RCHO), 10.17 (s), 10.37 ppm (s, 1, ArCHO).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.96; H, 8.10.

3-Methoxy-*B*-nor-6,8-secoestra-1,3,5(10)-trien-17-one (5a). A mixture of dialdehyde **4a** (0.285 g, 0.87 mmol) and tris(triphenylphosphine)chlororhodium[6] (1.44 g, 1.57 mmol) in benzonitrile (1 mL) was heated under nitrogen at 180–190 °C for 1.5 h. After the reaction cooled, ethanol (50 mL, 95%) was added and the yellow solid which precipitated was removed by filtration. The filtrate was evaporated under vacuum and the residue was chromatographed on alumina (III; 50 g; 10% CH_2Cl_2–C_6H_6). The solvent was evaporated and the residue was sublimed to give 166 mg (70% yield) of pure nor-seco steroid **5a:** mp 110–112 °C; NMR ($CDCl_3$) δ 1.01 (s, 3, 18-CH_3), 3.31 (s, 3, 6-CH_3), 3.77 (s, 3, OCH_3), 6.74 (s, d, 2, Ar-H), 7.17 ppm (d, J = 8 Hz, Ar-H); IR (CH_2Cl_2) 1745 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.24; H, 8.96.

3-Methoxy-*B*,19-dinor-6,8-secopregna-1,3,5(10)-trien-20-one (5b). The reaction conditions for this decarbonylation were described for the preparation of compound **5a.** Dialdehyde **4b** (2.29 g, 6.42 mmol) and tris(triphenylphosphine)chlororhodium (11.125 g) in benzonitrile (3 mL) were reacted. The catalyst was precipitated with methanol and filtered. After evaporation of the solvent, the residue was chromatographed on alumina (50 g, activity III, CH_2Cl_2) to give a yellow oil. A TLC analysis of this product showed the presence of remaining polar impurities, while analysis of the ^1H NMR spectrum showed that both triphenylphosphine and benzonitrile were present. Rechromatography of the product on alumina (activity II, 100 g, benzene) effected complete purification of this product. There was obtained 1.3 g (66% yield) of steroid **5b** as an oil: NMR ($CDCl_3$) δ 0.71 (s, 3, CH_3), 2.10 (s, 3, $COCH_3$), 2.25 (s, 3, $ArCH_3$), 3.70 (s, 3, OCH_3), 6.70 (m, 2, ArH), 7.14 ppm (m, 1, ArH).

Anal. Required for $C_{20}H_{28}O_2$: m/e 300.2089. Found: m/e 300.2085.

***B*,19-Dinor-6,8-secopregn-4-ene-3,20-dione (6b).** To a stirred solution of steroid **5b** (1.287 g, 3.9 mmol) in ethanol (50 mL, 95%) was added sodium borohydride (3.04 g) in small portions. TLC analysis of the reaction after 30 min of stirring indicated that no starting material remained. Acetone (10 mL) was added dropwise to destroy excess sodium borohydride and the solution was evaporated to dryness at reduced pressure. The residue was taken up in water (50 mL) and extracted with methylene chloride (3 × 50 mL). The solution was dried ($MgSO_4$) and the solvent evaporated to give 0.91 g (76.9% yield) of an epimeric alcohol mixture which was used without purification in the next step.

The alcohol mixture (634 mg, 2.08 mmol), dissolved in tetrahydrofuran (30 mL) and *tert*-butyl alcohol (30 mL), was added dropwise to freshly distilled refluxing liquid ammonia. Sodium (200 mg) was added and the solution was vigorously magnetically stirred until the blue color disappeared (1.5–2 h). Ammonium chloride (2 g) was cautiously added, followed by dropwise addition of methanol (10 mL). The ammonia was allowed to evaporate before the remaining solution and solids were transferred with methanol wash to a flask and evaporated to dryness at reduced pressure. Water (75 mL) was added to dissolve solids and the resulting solution was extracted with methylene chloride (3 × 75 mL) and then dried (Na_2SO_4). The solvent was removed at reduced pressure to give 631 mg of crude dihydro steroid. A ^1H NMR spectrum of the product showed that the reduction was complete: NMR (CCl_4) δ 0.77 (s, 3, CH_3), 1.66 (s, 3, $=CCH_3$) and 3.52 ppm (s, 3, OCH_3).

The dihydro product in methanol (25 mL) and hydrochloric acid (15 mL, 3 N) was heated at reflux for 10 min on the steam bath, then cooled and neutralized with sodium bicarbonate. Methanol was removed at reduced pressure and additional water (50 mL) was added. The solution was extracted with methylene chloride (3 × 75 mL), dried ($MgSO_4$) and evaporated to give 726 mg of crude product.

The hydrolysis product from above (726 mg) was dissolved in acetone (85 mL) and stirred while Jones reagent was added dropwise until the orange color persisted. Stirring was continued under nitrogen for 10 min further while the completeness of the reaction was established by TLC analysis. Isopropyl alcohol was added to destroy excess oxidizing agent; then the solvent was removed at reduced pressure.

The residue was diluted with water (50 mL), extracted with methylene chloride (3 × 75 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue was chromatographed to give 448 mg (65% yield) of pure steroid **6b** as a viscous oil: IR (CH_2Cl_2) 1713 and 1695 cm^{-1}; NMR ($CDCl_3$) δ 0.60 (s, 3, CH_3), 0.60 (s, 3, CH_3), 1.98 (s, 3, $=CCH_3$), 2.12 (s, 3, $COCH_3$), 5.91 ppm (br s, 1 H, =CH).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.97; H, 9.84.

***B*-Nor-6,8-secoestra-1,3,5(10)-trien-17α-yne-3,17β-diol (5d).** Steroid **5a** (241 mg, 0.886 mmol) was fused at 210–220 °C for 1 h with pyridine hydrochloride (9.5 g). The reaction mixture was cooled, diluted with water (50 mL), extracted with methylene chloride, and dried. The residue remaining after removal of the solvent was chromatographed (silica gel, 30 g, CH_2Cl_2–10% EtOAc/CH_2Cl_2) to yield 77 mg (34% yield) of phenol **5c** which was used without further purification: NMR ($CDCl_3$) δ 1.02 (s, 3, 18-CH_3), 2.28 (s, 3, Ar-CH_3), 4.95 (br, 1, OH), 6.58 (m, 2, Ar-H), 7.05 ppm (d, J = 10 Hz, 1 H, Ar-H).

Lithium acetylide–ethylenediamine complex (292.9 mg, 3.18 mmol) was added to a solution of phenol **5c** (77 mg, 0.298 mmol) in toluene (7 mL) and dimethyl sulfoxide (7 mL), then stirred at room temperature under nitrogen for 20 h. Ammonium chloride (2 g) and water were added, and the solution was extracted with methylene chloride. The solvent was dried (Na_2SO_4) and then evaporated at reduced pressure, and the residue was chromatographed (silica gel, 30 g, CH_2Cl_2–10% EtOAc/CH_2Cl_2) to give 41 mg (49% yield) of **5d:** mp 110–112 °C; IR (KBr) 3260 cm^{-1} (C≡CH); NMR ($CDCl_3$) δ 0.99 (s, 3, 18-CH_3), 2.27 (s, 3, Ar-CH_3), 2.98 (s, 1, ≡CH), 4.90 (br, 1, OH), 6.65 (m, 2, Ar-H), 7.10 ppm (d, J = 8 Hz, 1, Ar-H).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.06; H, 8.60.

17-Hydroxy-*B*,19-dinor-6,8-seco-17α-pregn-4-ene-20-yn-3-one (6a). A solution of sodium borohydride (2.05 g, 54 mmol) in ethanol (30 mL, 95%) was added to a stirred solution of keto-steroid **5a** (0.977 g, 3.6 mmol) in ethanol (20 mL) at room temperature. After the reaction was stirred overnight, it was diluted with water (50 mL) and extracted with methylene chloride (3 × 75 mL). The extracts were dried ($MgSO_4$) and the solvent was evaporated to give 0.880 g (90%) of **5e** which was used without further purification.

The above steroid (0.443 g, 1.62 mmol), dissolved in tetrahydrofuran (30 mL) and *tert*-butyl alcohol (30 mL), was added dropwide to liquid ammonia (60 mL) being stirred at reflux under nitrogen. Sodium (0.109 g) was added and the resulting dark blue solution faded to become colorless within 2 h. Ammonium chloride (3 g) and methanol (30 mL) were carefully added. The solution remaining after evaporation of the ammonia was evaporated at reduced pressure, diluted with water (60 mL), extracted with methylene chloride, and dried (Na_2SO_4). The solvent was evaporated at reduced pressure, and a ^1H NMR spectrum of the residue indicated that less than 10% starting material remained: NMR (CCl_4) δ 0.73 (s, 3, 18-CH_3), 1.62 (s, 3, $=CCH_3$), 3.47 (s, 4, $(=C)_2CH_2$), 4.50 (m, 1, CHOH), 5.26 ppm (s, 1, =CH).

To the above product dissolved in freshly distilled toluene (15 mL)

was added cyclohexanone (3.8 mL, 3.6 g, 36.7 mmol) and aluminum isopropanoxide (0.432 g, 2.12 mmol). The reaction was distilled slowly for 1 h (5 mL distillate was collected which was replaced with toluene) and then refluxed for 3 h. The cooled solution was diluted with potassium–sodium tartrate solution (25 mL) and water (25 mL) and then extracted with toluene (3 × 50 mL). After drying (Na_2SO_4), the solvent was evaporated under vacuum to give an oil which was chromatographed (alumina, III, 30 g, toluene). The collected product showed no 4.50 ppm (CHOH) absorption in the ^1H NMR spectrum but did contain cyclohexanone as an impurity.[12] This product was dissolved in toluene (3 mL) and dimethyl sulfoxide (2.7 mL) before lithium acetylide–ethylenediamine complex (2.3 g, 2.5 mmol) was added. After the solution was stirred at room temperature under nitrogen for 20 h, ammonium chloride (3 g) was cautiously added, followed by dropwise addition of water (10 mL). Additional water (50 mL) was added and the solution was extracted with methylene chloride. The residue remaining after drying (Na_2SO_4) and evaporating the solvent was chromatographed (alumina, III, 50 g, toluene–5% EtOAc/toluene): NMR (CCl_4) δ 0.82 (s, 3, CH_3), 1.65 (s, 3, $=CCH_3$), 2.44 (s, 1, $\equiv CH$), 3.56 (s, 3, OCH_3), 7.1 ppm (s, 1, $=CH$).

To the above product in methanol (25 mL) was added 3 N hydrochloric acid (15 mL) and the resulting solution was heated for 15 min on the steam bath. Solid sodium bicarbonate was added to neutralize the hydrochloric acid. The solution was evaporated, diluted with water (50 mL), extracted with methylene chloride, and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was chromatographed (alumina, III, 50 g) to give 212 mg (46% yield) of pure steroid **6a**: mp 122–124 °C; IR (CH_2Cl_2) 3260 ($C\equiv CH$) and 1685 cm^{-1} ($=CC=C$); NMR (CCl_4) δ 0.79 (s, 3, CH_3), 1.95 (s, 3, $=CCH_3$), 2.42 (s, 1, $\equiv CH$), 5.80 ppm (s, 1, $=CH$).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.75; H, 9.12.

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Registry No.—**2b,** 4192-93-2; **3b,** 63976-96-5; **3c,** 63976-97-6; **3d,** 63976-98-7; **3f,** 63976-99-8; **4a,** 63977-00-4; **4b,** 63977-01-5; **5a,** 63977-02-6; **5b,** 63977-03-7; **5b** epimeric alcohol derivative, 63977-04-8; **5b** epimeric alcohol derivative 2, 63977-05-9; **5b** dihydro alcohol derivative, 63977-06-0; **5c,** 63977-07-1; **5d,** 63977-08-2; **5e,** 63977-09-3; **5e** dihydro derivative, 63977-10-6; **5e** dihydro ketone derivative, 63988-55-6; **5e** dihydro ethynylated derivative, 639777-11-7; **6a,** 63977-12-8; **6b,** 63977-13-9; **6b** 20 alcohol derivative, 63977-14-0.

References and Notes

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Halogenated Alicyclic Monoterpenes from the Red Algae *Placamium*

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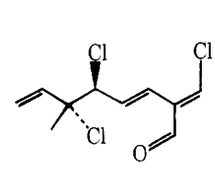
The red algae *Placamium violaceum* (Farlow) and *P. cartilagineum* (Dixon), collected from the vicinity of Monterey Bay, Calif., yield a number of halogenated alicyclic terpenes. The structures of placamene D (**4**), placamene D′ (**5**), and placamene E (**8**) have been elucidated by a combination of spectroscopic and chemical experiments. Additional structural details and chemical properties are discussed for other *Placamium* alicycles including placamene B (**2**), violacene (**3**), and placamene C (**9**). Their composite structures suggest several biosynthetic generalizations about these and other halogenated monoterpenes known from *Placamium*.

The red alga *Placamium* has been under study in our lab because it is a source of unique monterpenes.[1,2] Recent work by ourselves and others has shown that both acyclic and cyclic halogenated monoterpenes are elaborated by *Placamium* (order Gigartinales),[3–5] and as well by other red algae including *Microcladia* (order Ceramiales)[6] and *Chondrococcus* (order Cryptonemiales).[7,8]

Our investigation of the natural products chemistry of *Placamium* was first prompted by an observation that extracts of *Placamium cartilagineum* (Dixon) and *Placamium violaceum* (Farlow) collected from Four-Mile Beach (Santa Cruz County, Calif.) showed toxicity in two bioassays. A nonpolar chromatographic fraction from either of these *Placamium* species was highly toxic to goldfish,[9] and these extracts exhibited LC_{50} growth inhibition against mosquito larvae at 0.03 and 0.09 ppm dilutions, respectively.[10] Subsequent isolation work yielded cartilagineal (**1**) as a major component from *P. cartilagineum*[1] and placamene B (**2**) as a major component from *P. violaceum*.[2] In both *Placamium* species we observed another major haloterpene component,[2] violacene (**3**),[11] whose structure has been recently revised after



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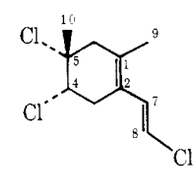

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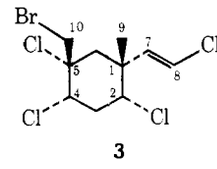

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x-ray study.[12] Interestingly, both placamene B (**2**) and violacene (**3**) are highly toxic to goldfish, and they display significant growth inhibition against mosquito larvae. In order to further explore the toxic metabolites from *Placamium*, we extended out study of *P. violaceum* to several other collection sites in the Monterey Bay area. This yielded new halogenated

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