9,11-Seco Steroids[1] Derived from Estradiol 3-Methyl Ether[2]

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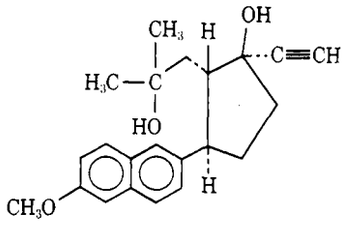
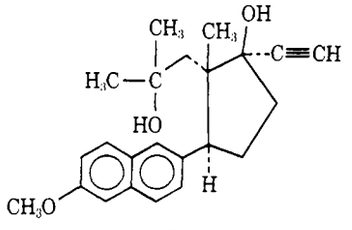
A series of optically active 9,11-seco steroids was prepared starting with estradiol 3-methyl ether (**3**). A key step in one of the reaction sequences involved the stereoselective addition of ethynyl Grignard reagent to the apparently more hindered side of a 2,2-disubstituted cyclopentanone derivative. Another unique feature was the stereospecific addition of ethynyl Grignard reagent to a cyclic hemiketal. Two compounds in the series exhibited biological activity. Compound **9** had weak estrogenic activity while compound **21** exhibited antifertility activity without having estrogenic activity.

Several years ago in our laboratories we[3] prepared compound **1** by total synthesis. The compound ex-



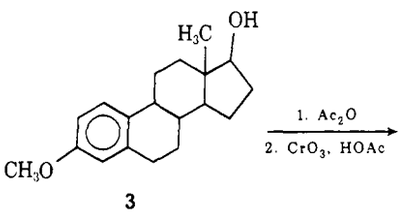
1 (*dl*)

hibited antifertility activity[4] in rats with only minimal estrogenic activity.[5] This desired separation of biological activities led us to speculate that the corresponding analog having an angular methyl group at C-13,[6] compound **2**, might also possess interesting biological properties.



2

We were primarily interested in obtaining the optically active isomer of **2** which we envisioned could be prepared by partial degradation of a steroid of known configuration. Consequently, we chose estradiol 3-methyl ether (**3**) as our starting material. Several workers[7-9] have investigated the reaction of **3** with chromic anhydride under various reaction conditions. Cambie's[8] procedure was used to prepare 17β-hydroxy-3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid 17-acetate (**4**) which was a key intermediate in our synthesis of **2**. Treatment of **4** with sodium borohydride in isopropyl alcohol followed by acidification with acetic acid afforded a mixture of products which was assumed to consist of the two 9-hydroxy derivatives, **5**, along with a small amount of the seven-membered ring lactones, **6**, on the basis of their behavior on thin layer chromatography (tlc). No attempt was made to purify at this stage, however, since treatment of the crude mixture of **5** and **6** with selenous acid in refluxing ethanol afforded a mixture of **7** and **8** which was converted into pure **8** by treatment with sodium hydroxide in aqueous methanol.



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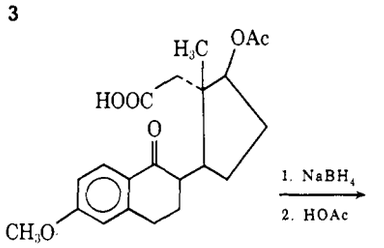

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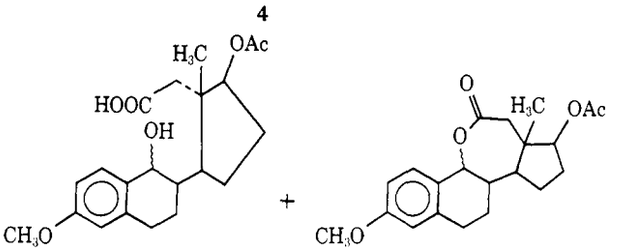
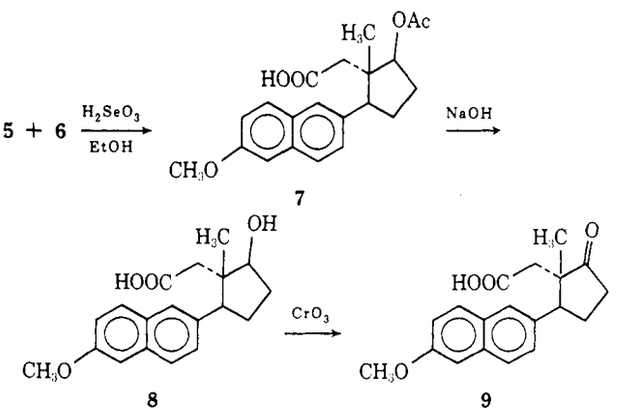


5 **6**



7 **8** **9**

(1) 9,11-Seco steroids have been the subject of two recent reports: (a) N. S. Crossley and R. Dowell, *J. Chem. Soc.*, 2496 (1971); (b) E. G. Brain, F. Cassidy, M. F. Constantine, J. C. Hanson, and D. J. D. Tidy, *ibid.*, 3846 (1971).

(2) Presented in part at the 6th Regional Midwest American Chemical Society Meeting, Houghton, Mich., June 22, 1972.

(3) L. J. Chinn, unpublished results.

(4) The antifertility activity was determined by a standard procedure: R. L. Elton, E. F. Nutting, and F. J. Saunders, *Acta Endocrinol. (Copenhagen)*, **41**, 381 (1962).

(5) The estrogenic activity was determined by standard procedures: (a) B. L. Rubin, A. S. Dorfman, L. Black, and R. I. Dorfman, *Endocrinology*, **49**, 429 (1951); (b) R. A. Edgren, *Proc. Soc. Exp. Biol. Med.*, **92**, 569 (1956).

(6) The steroid numbering system has been used throughout the text of this paper for convenience.

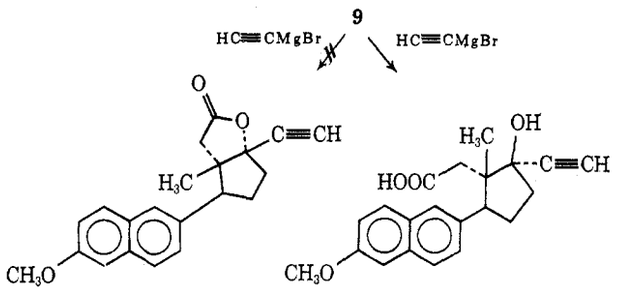
(7) Y. Suzuki, Japan Patent No. 17,831 (1964) [*Chem. Abstr.*, **62**, 5318 (1965)].

(8) R. C. Cambie, V. F. Carlisle, C. J. LeQuesne, and T. D. R. Manning, *J. Chem. Soc.*, 1234 (1969).

(9) P. D. Mainreville and B. Gastambide, *C. R. Acad. Sci., Ser. C*, **273** (7), 507 (1971).

It is not known whether partial hydrolysis of the 17-acetoxy group occurred during the borohydride reduction of **4** or during the aromatization of **5** and **6** with selenous acid. However, this is not important since the 17-hydroxy derivative, **8**, was obtained in 82% yield starting with **4**. Treatment of **8** with Jones'[10] reagent afforded the corresponding ketone, **9**, in high yield.

Based on previous results[11] with the 18-nor analog of **9**, we anticipated that reaction of **9** with a Grignard reagent would lead to a mixture of two products, **10** and **11**. The hydroxy acid, **10**, would arise *via* attack

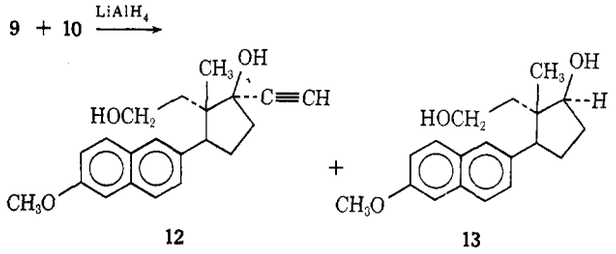


11 10

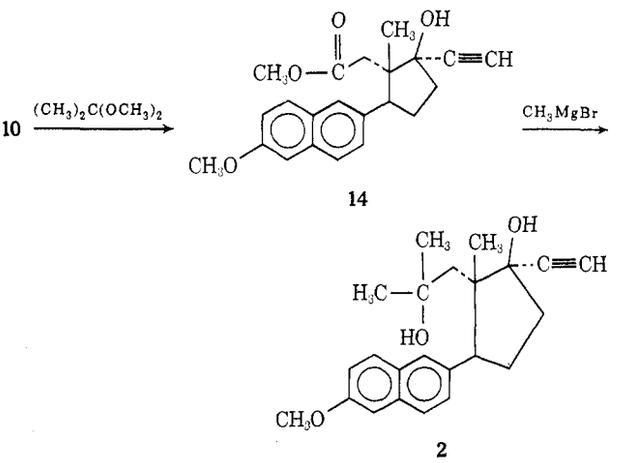
of the Grignard reagent from the α face[12] of the molecule while the lactone, **11**, would arise *via* β-face[12] attack followed by lactonization during the acid work-up.

Addition of Grignard reagents to the 17-keto function of "normal" steroids usually leads to the formation of products derived from α-face attack[13] presumably due to the steric hindrance of the C-18 angular methyl group which inhibits β-face approach of the reagent. The steric environment about the 17-keto function of **9**, however, is markedly different from that in the intact steroid skeleton. Molecular models indicate that approach of a Grignard reagent from either the α or β face of **9** should be severely hindered. *A priori*, we anticipated a sluggish reaction which would give rise to a mixture of **10** and **11**. However, when **9** was treated with ethynylmagnesium bromide in tetrahydrofuran, a single addition product, **10**, was obtained in good yield along with a small amount of starting ketone, **9**, as evidenced by two distinct C-18 methyl resonances in the nmr spectrum of the crude product. No trace of any nonacidic product could be detected by thin layer chromatography.

Although a sample of **10** was obtained pure by column chromatography, a quantitative separation of **9** and **10** could not be effected. Consequently, the crude ethynylation mixture was reduced with lithium aluminum hydride to give a mixture of **12** and **13** which were readily separated by column chromatography to give **12** and **13**[14] in a molar ratio of 7:1. Thus, the ratio of **10** to **9** in the ethynylation mixture must also have been 7:1.



The conversion of **10** into **2** was accomplished in two steps. Esterification of **10** with 2,2-dimethoxypropane afforded **14** which was converted into **2** by treatment with methylmagnesium bromide.



The ethynylation product was initially assigned structure **10** on the basis of its spectral and microanalytical data as well as on its failure to lactonize even when treated with 1.8 *M* sulfuric acid in tetrahydrofuran. Conclusive proof for the assigned structure of **10** was obtained as outlined in Scheme I.

Hydrogenation of **10** over 5% Pd/C afforded the 17α-ethyl derivative **15**. When **15** was treated with 1.8 *M* sulfuric acid in tetrahydrofuran under conditions which left **10** unchanged, there was obtained a lactone whose spectral and microanalytical data were consistent with structure **16**. Treatment of **16** with methylmagnesium bromide afforded the diol **17** in which the hydroxyl group at the 17 position was α. The ethynyl group of **2** was hydrogenated over 5% Pd/C to give compound **18** in which the hydroxyl group at the 17 position was β. Compounds **17** and **18** were shown to be different by comparison of their physical and spectral properties. The fact that **17** and **18** were different indicated that the Grignard reagent added exclusively from the α face of **9** to give **10**.

As indicated earlier, this process would involve severe steric hindrance from the acetic acid side chain adjacent to the carbonyl group in **9**. Secondly, this process would appear to be electronically unfavorable due to the acetic acid anion which is generated on the α face by initial reaction of the acid function with the Grignard reagent. This anion would be expected to repulse severely the approach of a nucleophile such as ethynylmagnesium bromide from the α face of the molecule. One possible explanation of our results is that a second mole of Grignard reagent complexes with the carboxylate anion on the α face and is thus oriented for exclusive attack from the α face to give **10**. Asymmetric syntheses involving complexa-

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

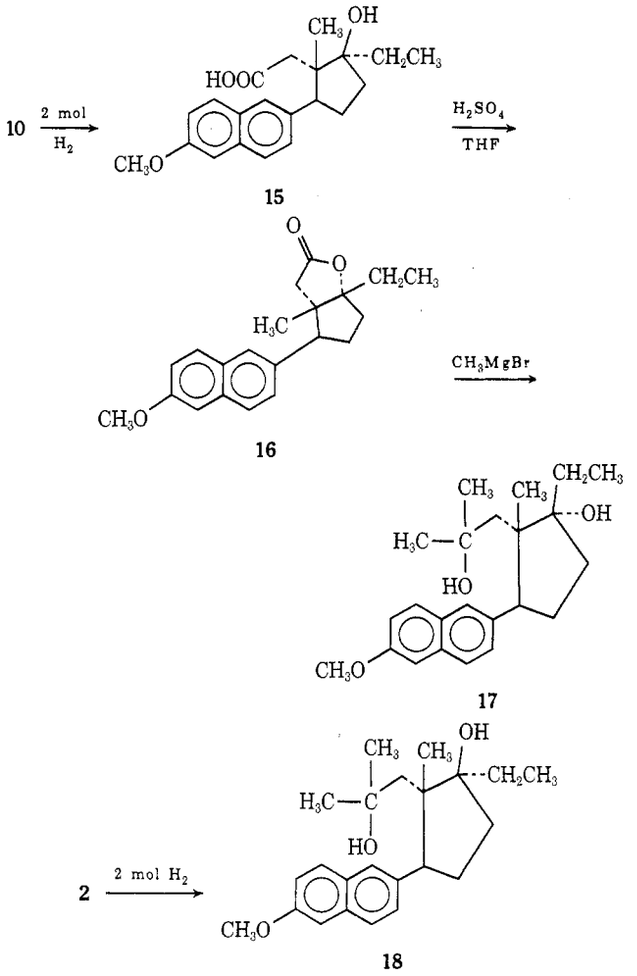
(11) L. J. Chinn, E. A. Brown, R. A. Mikulec, and R. B. Garland, *J. Org. Chem.*, **27**, 1733 (1962).

(12) The terms α and β face are borrowed from steroid nomenclature for convenience. In our case, α face refers to the side of the cyclopentanone ring in **9** on which the acetic acid side chain is located. Similarly, β face refers to the side on which the C-18 methyl group is located.

(13) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(14) An authentic sample of **13** was prepared by lithium aluminum hydride reduction of **7**.

SCHEME I



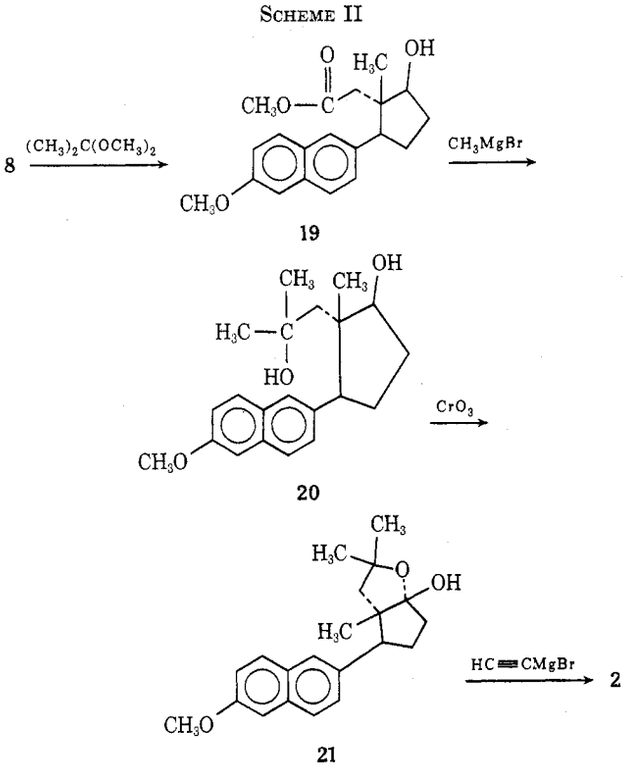
tion of Grignard reagents to groups such as hydroxy, alkoxy, or amino adjacent to a carbonyl group have been reported.[15] Asymmetric induction involving complexation of a Grignard reagent with a group which is three carbons removed from the reaction center appears to be unique.

An alternative explanation for the stereospecificity observed in the ethynylation reaction is suggested by the work of Brain and coworkers.[1b] These authors noted that the reduction of the *dl* form of **9** with sodium borohydride as well as the compound in which the methyl and acetic acid groups were interchanged occurs predominantly from the α face. They proposed that "the direction of borohydride attack must therefore be strongly influenced by the orientation of the 2-methoxynaphthyl group rather than by the two 1 substituents." Molecular models, however, indicate that the 2-methoxynaphthyl group would have to occupy a pseudoaxial rather than a pseudoequitorial configuration in order to sterically hinder the approach of a nucleophile from the β face. Our results unfortunately do not permit a clear-cut distinction between these two possible explanations.

The fact that **15** lactonized to **16** when treated with 1.8 *M* sulfuric acid in tetrahydrofuran while **10** remained unchanged under identical conditions was surprising but not totally unexpected. Although alkynyl carbonium ions have been generated from their corresponding alcohols,[16-18] the process required either very strong acids or the presence of cationic stabilizing groups on the developing carbonium ion. Our results indicate that 1.8 *M* sulfuric acid in tetrahydrofuran is incapable of generating a tertiary carbonium ion adjacent to a carbon–carbon triple bond.

Compound **2** was alternatively prepared by functionalizing the acetic acid side chain before ethynylating the 17-keto function as outlined in Scheme II. Esteri-

SCHEME II



fication of **8** with 2,2-dimethoxypropane gave **19** which was converted into the diol, **20**, with methylmagnesium bromide. Jones'[10] oxidation of **20** did not give the expected 17-keto derivative but instead gave the cyclic hemiketal, **21**, presumably *via* the intermediacy of the 17 ketone. We anticipated that the hemiketal, **21**, might exist in solution in equilibrium with the corresponding 11-hydroxy 17 ketone and that we might be able to trap this uncyclized form with a Grignard reagent and thereby establish a new equilibrium. We envisioned that such a process would eventually consume all of the hemiketal and give a mixture of the two possible Grignard addition products. However, when **21** was treated with ethynylmagnesium bromide in tetrahydrofuran, a single product was obtained which was identical with **2** in all respects. Thus, as in the case with **9**, ethynylation of **21** led exclusively to the product derived from α-face attack of the Grignard reagent.

Compound **2** exhibited no estrogenic or antifertility

(15) (a) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959); (b) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).

(16) H. G. Rickey, Jr., J. C. Philips, and L. E. Rennick, *J. Amer. Chem. Soc.*, **87**, 1381 (1965).

(17) H. G. Richey, Jr., L. E. Rennick, A. S. Kushner, J. M. Richey, and J. C. Philips, *J. Amer. Chem. Soc.*, **87**, 4017 (1965).

(18) C. U. Pittman, Jr., and G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 5632 (1965).

activity in our biology screening assays.[4,5] However, compounds **9** and **20** exhibited weak estrogenic activity and compound **21** exhibited weak antifertility activity while being devoid of estrogenic activity. None of the other compounds described in this paper showed any significant biological activity.

Experimental Section

Melting points were taken on a Fisher-Johns melting block and are uncorrected. Infrared spectra were recorded on a Beckman IR-12 grating spectrophotometer. Nmr spectra were obtained on a Varian A-60 or T-60 spectrometer using tetramethylsilane as internal standard. Specific rotations were obtained in chloroform (*c* 1.0) using a Perkin-Elmer (Model 141) polarimeter. Elemental analyses were performed by the microanalytical group at Searle Laboratories.

Sodium Borohydride Reduction of 4.—Sodium borohydride (6.10 g, 161 mmol) was added portionwise to a stirred suspension of **4** (25.3 g, 67.8 mmol) in 500 ml of isopropyl alcohol at 0°. The solution was warmed to room temperature and stirred an additional 18 hr. The solution was poured on 1.5 l. of water and acidified with hydrochloric acid. The aqueous phase was extracted with methylene chloride and the extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a brown oil which was assumed to be a mixture of **5** and **6** based on its behavior on tlc. The crude product was used without further purification.

Selenous Acid Oxidation of 5 and 6.—The crude mixture of **5** and **6** obtained *via* borohydride reduction of **4** was dissolved in 500 ml of ethanol and treated with selenous acid (35.0 g, 271 mmol). The solution was refluxed for 5 hr, cooled to room temperature, and filtered through Celite. The red-colored filtrate was concentrated *in vacuo* to give a red oil which was dissolved in methylene chloride. The solution was filtered to remove a small amount of red solid, and the filtrate was concentrated *in vacuo* to give a pink oil which was assumed to be a mixture of **7** and **8** based on its behavior on tlc. The crude product was used without further purification.

Saponification of 7.—The crude mixture of **7** and **8** obtained *via* selenous acid oxidation of **5** and **6** was dissolved in 200 ml of methanol and treated with a solution of sodium hydroxide (20.0 g, 0.500 mol) in 100 ml of water. The solution was refluxed for 18 hr, filtered through Celite, and diluted with 1 l. of water. The aqueous phase was acidified with hydrochloric acid, and the solid which formed was collected and thoroughly washed with water. Recrystallization from ethyl acetate afforded **8** (15.4 g, 49.0 mmol): mp 174–175°; $[\alpha]^{27}D$ +67°; nmr (DMSO-d_6) δ 0.67 (s, CH_3), 3.90 (s, OCH_3).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.34; H, 7.10.

An additional 2.10 g (6.70 mmol) of **8** was obtained by chromatographing the mother liquors on 420 g of SilicAR CC-4.

(1*S*,5*S*)-5-(6-Methoxy-2-naphthyl)-1-methyl-2-oxocyclopentaneacetic Acid (9).—Jones'[10] reagent was added dropwise to a stirred solution of **8** (10.0 g, 31.9 mmol) in 300 ml of acetone at room temperature until the orange color persisted for 15 min. The excess reagent was destroyed by the dropwise addition of isopropyl alcohol until the orange color disappeared. The mixture was poured on 1.5 l. of water, and the solid which formed was collected and thoroughly washed with water. The crude product was chromatographed on 800 g of SilicAR CC-4 to give **9** in the 10% ethyl acetate–90% benzene fractions. Recrystallization from benzene–Skellysolve B afforded **9** (7.42 g, 75% yield): mp 143.5–144.5°; $[\alpha]^{27}D$ −3°; ir (KBr) 1755 (C=O), 1730 cm^{-1} (COOH); nmr ($CDCl_3$) δ 0.70 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.27; H, 6.62.

Ethynylation of 9.—Acetylene[19] was bubbled through 100 ml of anhydrous tetrahydrofuran at −78° for 50 min. A 10-ml portion of 3 *M* ethylmagnesium bromide in ether was added and the solution was allowed to warm to room temperature. A solution of **9** (1.33 g, 4.26 mmol) in 25 ml of tetrahydrofuran was added dropwise, and the reaction mixture was stirred at room temperature under nitrogen for 3 days. The reaction mixture was filtered through a glass wool plug onto 1 l. of cold 5% hydrochloric acid. The solution was saturated with sodium chloride and after stirring for 20 min the product was collected, washed with water, and dried in a steam oven to give 1.30 g of a tan solid, mp 168–173°. The crude product was dissolved in 50 ml of anhydrous ether and added dropwise to a stirred suspension of lithium aluminum hydride (1.30 g, 34.3 mmol) in 50 ml of ether. After stirring for 4 hr at room temperature the mixture was hydrolyzed by the dropwise addition of 5.2 ml of 10% sodium hydroxide. The mixture was filtered and the inorganic salts were thoroughly washed with methylene chloride. The combined solvents were removed *in vacuo* to give 1.09 g of a white solid which consisted of two products as evidenced by tlc (40% ethyl acetate–60% benzene). The product was chromatographed on 100 g of SilicAR CC-7 using benzene and ethyl acetate as eluents. Compound **12** (0.804 g, 2.48 mmol) was obtained pure in the first few fractions of 50% ethyl acetate–50% benzene, while compound **13** (0.104 g, 0.347 mmol) was obtained pure in the later fractions of 50% ethyl acetate–50% benzene. Recrystallization from ethyl acetate–Skellysolve B afforded an analytical sample of **12**: mp 199–201°; $[\alpha]^{23}D$ −68°; nmr ($CDCl_3$) at δ 0.88 (s, CH_3), 2.70 (s, C≡CH), 3.90 (s, OCH_3).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.45. Found: C, 78.05; H, 7.55.

Recrystallization from benzene–Skellysolve B afforded an analytical sample of **13**: mp 188–190°, $[\alpha]^{23}D$ +29°. The spectra of this sample were virtually identical with those of an authentic sample of **13**.[14]

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.10; H, 8.10.

In another experiment a pure sample of **10** was obtained by chromatographing the crude ethynylation mixture on SilicAR CC-4 using benzene and ethyl acetate as eluents. Recrystallization from ethyl acetate–Skellysolve B afforded an analytical sample of **10**: mp 204–206°; $[\alpha]^{24}D$ +8°; nmr ($CDCl_3$) δ 0.93 (s, CH_3), 2.67 (s, C≡CH), 3.92 (s, OCH_3); ir (KBr) 1710 (COOH); 3300 cm^{-1} (C≡CH).

Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.40; H, 6.66.

(1*S*,2*S*,5*S*)-2-Hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneethanol (13).—A solution of **7** (1.00 g, 2.71 mmol) in 20 ml of ether–5 ml of tetrahydrofuran was added dropwise to a stirred slurry of lithium aluminum hydride (0.800 g, 21.1 mmol) in 100 ml of anhydrous ether, and the mixture was stirred at room temperature for 18 hr. The mixture was hydrolyzed by the dropwise addition of 3.2 ml of 5% sodium hydroxide solution and filtered. The inorganic salts were washed with methylene chloride and the combined solvents were removed *in vacuo*. The residue was recrystallized from benzene–Skellysolve B to give **13** (0.691 g, 85% yield): mp 192–193°; $[\alpha]^{23}D$ +33°; nmr (DMSO-d_6) δ 0.63 (s, CH_3), 3.89 (s, OCH_3).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.92; H, 8.13.

Attempted Lactonization of 10.—A solution of **10** (0.760 g, 2.25 mmol) in 27 ml of tetrahydofuran with 3 ml of sulfuric acid added was stirred at room temperature for 45 min and was gently heated on a steam bath for 15 min. A tlc on the reaction mixture indicated no change. The mixture was stirred at room temperature for 24 hr at which time tlc indicated a small amount of decomposition but no lactone formation. The mixture was poured on 200 ml of ice–water and the product was collected and air-dried to give 0.707 g of a tan solid. The ir and nmr spectra of the crude product were virtually identical with those of compound **10**. No trace of the corresponding lactone **11** could be detected.

(1*S*,2*S*,5*S*)-2-Ethynyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneacetic Acid Methyl Ester (14).—A solution of **10** (1.00 g, 2.96 mmol), 4 ml of 2,2-dimethoxypropane, and 30 ml of methanol with a trace of *p*-toluenesulfonic acid added was refluxed for 18 hr. The solution was diluted with 150 ml of benzene and washed successively with water, 5% sodium bicarbonate, and saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give **14** (0.889 g, 85% yield): mp 161–163°; $[\alpha]^{24}D$ −22°; ir (KBr) 3430 (OH), 1718 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.93 (s, CH_3), 2.67 (s, C≡CH), 3.64 (s, $COOCH_3$), 3.94 (s, OCH_3).

Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 75.13; H, 6.95.

(19) Acetylene gas was purified by passage through one water trap and two sulfuric acid traps.

(1*S*,2*S*,5*S*)-2-Ethynyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (2).—A 6-ml portion of 3 *M* methylmagnesium bromide in ether was added dropwise to a stirred solution of **14** (0.406 g, 1.15 mmol) in 25 ml of ether, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was quenched by the dropwise addition 5% hydrochloric acid. The mixture was extracted with benzene and the extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give **2** (0.334 g, 82% yield): mp 202–205°; $[\alpha]^{27}D$ −81°; nmr ($CDCl_3$) δ 1.07 (s, CH_3), 1.18 (s, CH_3), 1.32 (s, CH_3), 2.70 (D, C≡CH), 3.92 (s, OCH_3).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.49; H, 8.06.

(1*S*,2*S*,5*S*)-2-Ethyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneacetic Acid (15) —A solution of **10** (1.47 g, 4.35 mmol) in 200 ml of isopropyl alcohol was hydrogenated over 5% Pd/C (0.2 g) in a Paar shaker at room temperature for 24 hr. The solution was filtered and the solvent was removed *in vacuo* to give a white solid. Recrystallization from benzene–Skellysolve B afforded **15** (1.20 g, 81% yield): mp 186–190°; $[\alpha]^{24}D$ +167°; nmr ($CDCl_3$) δ 0.88 (s, CH_3), 1.05 (t, J = 7 Hz, CH_2CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.61; H, 7.50.

***cis*-6a-Ethylhexahydro-4-(6-methoxy-2-naphthyl)-3a-methyl-2*H*-cyclopenta[*b*]furan-2-one (16).**—A solution of **15** (1.20 g, 3.52 mmol) in 41 ml of tetrahydrofuran with 4.5 ml of sulfuric acid added was stirred at room temperature for 45 min and was gently heated on a steam bath for 15 min. The solution was poured onto 300 ml of water, made basic with sodium bicarbonate, and extracted with ether and benzene. The combined extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a tan solid which was recrystallized from ether–Skellysolve B to give **16** (0.838 g, 74% yield): mp 146–148°; $[\alpha]^{27}D$ +11°; ir (KBr) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.80 (s, CH_3), 1.10 (t, J = 7 Hz, CH_2CH_3), 3.94 (s, OCH_3).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.71; H, 7.49.

(1*S*,2*R*,5*S*)-2-Ethyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (17). A solution of **16** (0.224 g, 0.692 mmol) in 5 ml of tetrahydrofuran was added dropwise to a stirred solution of 3 ml of 3 *M* methylmagnesium bromide in 35 ml of ether, and the mixture was stirred at room temperature for 3 hr. The mixture was poured onto 75 ml of a 5% ammonium chloride solution and the layers were separated. The aqueous phase was extracted with benzene and the combined organic phases were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave an oil which solidified upon standing. The crude product was recrystallized twice from benzene–Skellysolve B to give **17** (0.124 g, 50% yield): mp 153–156°; $[\alpha]^{24}D$ −14°; nmr ($CDCl_3$) δ 0.85 (s, CH_3), 1.27 (s, CH_3), 1.32 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.44; H, 9.05.

(1*S*,2*S*,5*R*)-2-Ethyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (18).—A solution of **2** (0.227 g, 0.645 mmol) in 200 ml of isopropyl alcohol was hydrogenated over 5% Pd/C (0.05 g) in a Paar shaker at room temperature for 18 hr. The solution was filtered and the solvent was removed *in vacuo* to give a white solid. Recrystallization from benzene–Skellysolve B afforded **18** (0.183 g, 80% yield): mp 197–198°; $[\alpha]^{27}D$ −8°; nmr ($CDCl_3$) δ 1.08 (s, CH_3), 1.13 (s, CH_3), 1.27 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.88; H, 9.25.

(1*S*,2*S*,5*S*)-2-Hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneacetic Acid Methyl Ester (19).—A solution of **8** (5.00 g, 15.9 mmol), 25 ml of 2,2-dimethoxypropane, 150 ml of methanol, and 0.100 g of *p*-toluenesulfonic acid was refluxed for 16 hr and concentrated *in vacuo*. The residue was dissolved in 250 ml of benzene and washed with 5% sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from acetone–Skellysolve B to give **19** (5.10 g, 98% yield): mp 109–110°; $[\alpha]^{27}D$ +60°; ir (KBr) 3470 (OH), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.80 (s, CH_3), 3.66 (s, $COOCH_3$), 3.96 (s, OCH_3).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.77; H, 7.34.

(1*S*,2*S*,5*S*)-2-Hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (20) —A solution of **19** (5.11 g, 15.6 mmol) in 150 ml of ether was added dropwise to a stirred solution of 100 ml of 3 *M* methylmagnesium bromide in ether and the mixture was stirred at room temperature for 16 hr and refluxed for 6 hr The reaction was quenched by the dropwise addition of 5% hydrochloric acid The mixture was diluted with 100 ml of benzene and the layers were separated The organic phase was dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give **20** (3.84 g, 73% yield): mp 189–190°; $[\alpha]^{25}D$ −10°; nmr ($CDCl_3$) δ 0.97 (s, CH_3), 1.23 (s, CH_3), 1.27 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.76; H, 8.63.

***cis*-Hexahydro-4-(6-methoxy-2-naphthyl)-2,2,3a-trimethyl-2*H*-cyclopenta[*b*]furan-6a-ol (21).**—Jones'[10] reagent was added dropwise to a solution of **20** (3.34 g, 10.2 mmol) in 200 ml of acetone until the orange color persisted for 15 min. The excess reagent was destroyed by adding isopropyl alcohol dropwise until the orange color disappeared The mixture was diluted with 200 ml of water and concentrated *in vacuo*. The aqueous phase was extracted with benzene and the extracts were dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was removed *in vacuo* to give 3.65 g of a red oil which was chromatographed on 300 g of silica gel. The material which was eluted in the 2% ethyl acetate–98% benzene fractions was recrystallized from benzene–Skellysolve B to give **21** (1.25 g, 38% yield): mp 150–151.5°; $[\alpha]^{27}D$ −12°; ir (KBr) 3430 (OH), no absorption between 1650 and 1800 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (s, CH_3), 1.43 (s, CH_3), 1.55 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.45; H, 8.04.

Ethynylation of 21.—Acetylene[19] was bubbled through 50 ml of anhydrous tetrahydrofuran at −78° for 30 min. A 30-ml portion of 3 *M* ethylmagnesium bromide in ether was added, and the solution was slowly allowed to warm to room temperature. A solution of **21** (0.468 g, 1.43 mmol) in 20 ml of tetrahydrofuran was added dropwise, and the reaction mixture was stirred at room temperature under nitrogen for 19 hr. The reaction was quenched by the careful addition of 5% hydrochloric acid and the aqueous phase was extracted with ether. The extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give **2** (0.430 g, 86% yield): mp 200–203°; nmr ($CDCl_3$) δ 1.07 (s, CH_3), 1.18 (s, CH_3), 1.32 (s, CH_3), 2.70 (s, C≡CH), 3.92 (s, OCH_3). Mixture melting point with a sample of **2** prepared by treatment of **14** with methyl Grignard reagent showed no depression, mp 202–205°.

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