subjected to amino acid analysis. About 5% less glutamic acid than glycine was found, and there was thus an indication of slight reaction of the N-terminal amino group with Br-butanone-P_2. The hydrolysate contained about 0.05 molar equiv of cystine, but did not contain significant quantities of other ninhydrin-positive compounds. Since the derivatives arising from the cysteinyl residue were apparently converted to ninhydrin-negative compounds during the hydrolysis procedure, some of the reaction mixture (1.0 ml) was treated with [^{3}H]$NaBH_4$ (0.1 M at pH 8.0 for 30 min) so as to reduce the carbonyl group of the glutathione derivative and thus provide a radioactive marker. The major glutathione derivative (4.0 μmol, 40%) was separated from the excess reagent on a 1.2 × 25 cm column of Dowex 50 (H^+) that was equilibrated and eluted with 0.05 N HCl. A hydrolysate of the derivative was chromatographed on the amino acid analyzer, and the effluent was monitored for radioactivity (Figure 2).

Reaction of Br-Butanone P_2 with N-α-Acetyl-L-Lysine. A solution of N-α-acetyl-L-lysine (40 μmol) and Br-butanone-P_2 (50 μmol) in 2 ml of 0.2 M $NaHCO_3$ (pH 8.0) was incubated in the dark at room temperature. Periodically, 0.05-ml aliquots were withdrawn and added to 0.95 ml of 0.1 N HCl. One-half of these diluted aliquots was analyzed on the long column of the amino acid analyzer by elution with the second buffer (pH 4.25) only (acetyllysine eluted at 64 min). The percentages of acetyllysine remaining at 0.5, 1, 2, 4, 24, and 48 hr were 94, 87, 77, 63, 51, and 49, respectively. After 48 hr a sample (1.0 ml) of the incubation mixture was reduced with [^{3}H]$NaBH_4$ as described for the glutathione derivative. A portion (0.1 ml) of the reduced reaction mixture was hydrolyzed and then inspected on the amino acid analyzer. The hydrolysate contained ninhydrin-positive components that eluted from the short column at 11 min (0.19 μmol based on the constant for leucine) and 18 min (0.26 μmol based on the constant for leucine) in addition to lysine (0.8 μmol) (Figure 3A). Much of the radioactivity coincident with the ninhydrin-positive peak at 11 min was assumed to be from unreacted reagent. The remainder of the reduced mixture was fractionated on a 1.2 × 25 cm column of Dowex 1 (Cl^-) using a linear gradient of LiCl (0–0.5 M) in 0.001 N HCl. The major radioactive lysyl derivative eluted at about 0.2 M LiCl and was obtained in a 39% yield. Hydrolysates of this material contained both of the ninhydrin-positive peaks found in the hydrolysate of the unfractionated reaction mixture (Figure 3A), and both were radioactive (Figure 3B). Both derivatives were converted to lysine upon treating the hydrolysate with sodium metaperiodate (Figure 3C).

Registry No.—1, 6117-80-2; 2, 55759-07-4; 3, 55759-08-5; 4, 55759-09-6; 5 triscyclohexylamine, 55759-10-9; 5 tetralithium, 55759-11-0; 6, 52084-24-9; *cis*-1,4-di-*O*-benzoyl-2-butene-1,4-diol, 55759-12-1; benzoyl chloride, 98-88-4; N-bromosuccinimide, 128-08-5; triethyl orthoformate, 122-51-0; diphenyl chlorophosphate, 2524-64-3; glutathione, 70-18-8; N-α-acetyl-L-lysine, 1946-82-3; ribuluse 1,5-P_2, 2002-28-0.

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(3) Abbreviations used are: Br-butanone-P_2, 3-bromo-1,4-dihydroxy-2-butanone 1,4-bisphosphate; DTNB, 5,5′-dithiobis(2-nitrobenzoic acid); Pipes, piperazine-N,N'-bis(2-ethanesulfonic acid); Bicine, N,N-bis(2-hydroxyethyl)glycine.
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Synthesis of the 2,5-Protoadamantanediols[1]

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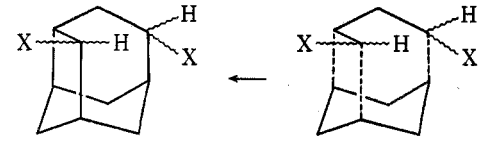
Acid-catalyzed conjugate additions to 8,9-dehydro-2-adamantanone provide a general route to 2-exo-substituted 5-protoadamantanones. 2-*exo*-Acetoxy-5-protoadamantanone, thus generated, is shown to be a useful precursor for the synthesis of 2-*exo*-5-*exo*-, 2-*exo*-5-*endo*-, and 2-*endo*-5-*endo*-protoadamantanediol. 2-*endo*-5-*exo*-Protoadamantanediol has been prepared by a reaction sequence which features the Lewis acid catalyzed regioselective ring cleavage of 3-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecane. Thus, the four possible 2,5-protoadamantanediols have been synthesized.

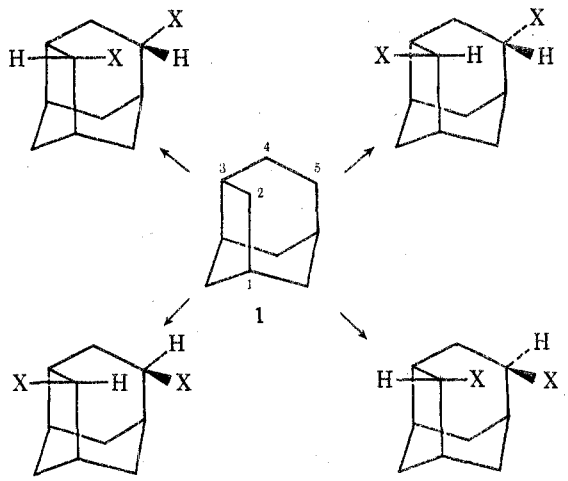
The chemistry of protoadamantane (1) and its derivatives has attracted significant attention.[3-5] However, although both 2-substituted[4] and 5-substituted[4a,5] protoadamantanes have been known for some time, no 2,5-disubstituted protoadamantanes have been reported. In principle, substitution of 1 at C-2 and C-5 with different substituent groups such that C-2 and C-5 remain sp^3 hybridized may lead to eight isomeric 2,5-disubstituted protoadamantanes. Of course, if the substituents are identical, only four isomeric 2,5-disubstituted protoadamantanes can be realized (Scheme I). We now wish to report the synthesis of the four 2,5-protoadamantanediols.

Results and Discussion

In terms of molecular architecture, a 2,5-disubstituted protoadamantane may be viewed as a 1,4-disubstituted butane that has been attached to the C-1, C-3, and C-5 axial positions of cyclohexane. Since it is well known that 1,4-disubstituted butanes may be prepared by acid-catalyzed



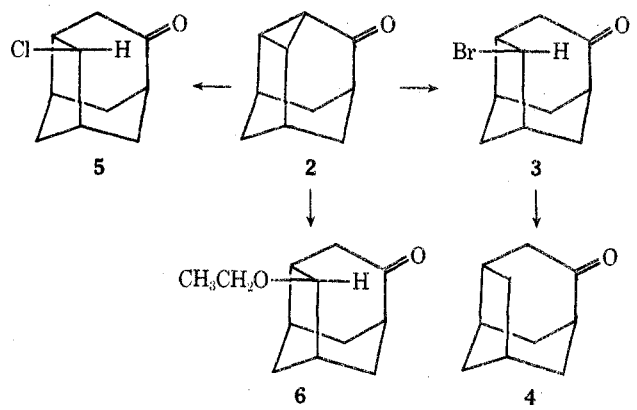
Scheme I



conjugate additions to cyclopropyl ketones,[6] we anticipated that 8,9-dehydro-2-adamantanone (**2**) might prove to be a useful precursor for the synthesis of 2,5-disubstituted protoadamantanes.

Treatment of **2**[7] with hydrobromic acid in glacial acetic acid provides 2-*exo*-bromo-5-protoadamantanone (**3**) in ca. 95% yield (Scheme II). The skeletal framework of **3** and the

Scheme II

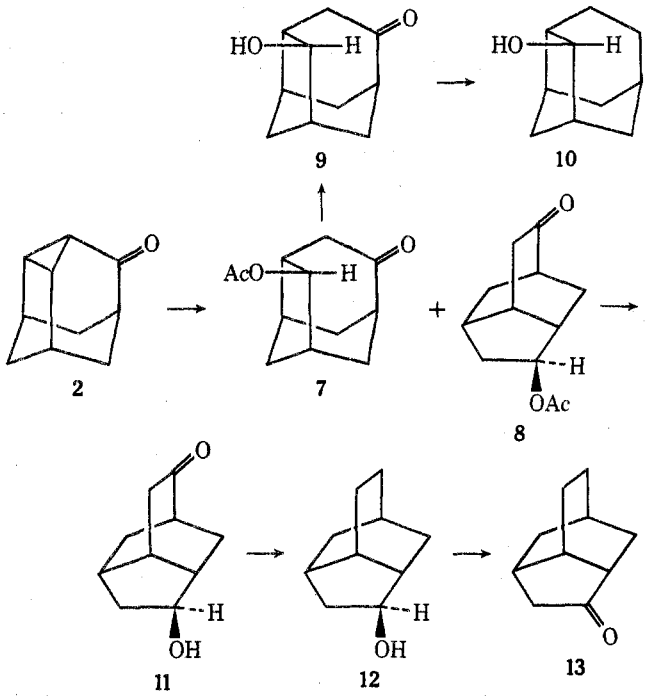


skeletal position of the carbonyl substituent in **3** were established by hydrogenolysis of **3** with palladium on calcium carbonate to give the known ketone, 5-protoadamantanone (**4**).[4a,5b,d] The assigned skeletal position and stereochemistry of the bromo substituent in **3** are consistent with the observation that treatment of **3** with alkali regenerates **2**.

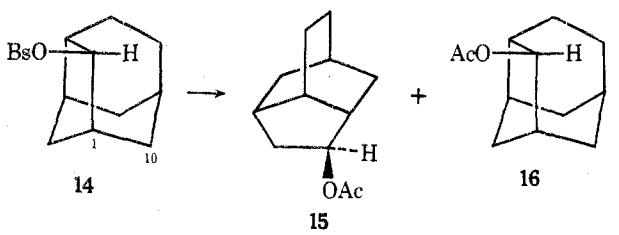
Other 2,5-disubstituted protoadamantanes can be prepared from **2** in good yield through analogous reactions. Thus, treatment of **2** with acetic acid which has been saturated with dry hydrogen chloride gas gives 2-*exo*-chloro-5-protoadamantanone (**5**) in ca. 85% yield. Refluxing an ethanolic solution of **2** in the presence of *p*-toluenesulfonic acid, followed by aqueous work-up, affords 2-*exo*-ethoxy-5-protoadamantanone (**6**) in ca. 80% yield.[8,9]

Perchloric acid catalyzed acetolysis of **2** gives not only 2-*exo*-acetoxy-5-protoadamantanone (**7**) in ca. 80% yield, but also 2-*exo*-acetoxy-7-isotwistanone (**8**)[12] in ca. 10% yield (Scheme III). The skeletal framework of **7** and the skeletal position and stereochemistry of the acetoxy substituent in **7** follow from the conversion of **7** to the known alcohol, 2-*exo*-protoadamantanol (**10**).[4d,13] Hydrolysis of **7** gives 2-*exo*-hydroxy-5-protoadamantanone (**9**) and Wolff–Kishner reduction of **9** provides **10**. The skeletal framework of **8** and the skeletal position of the acetoxy substituent in **8** were established by the conversion of **8** to the known ketone, 2-

Scheme III



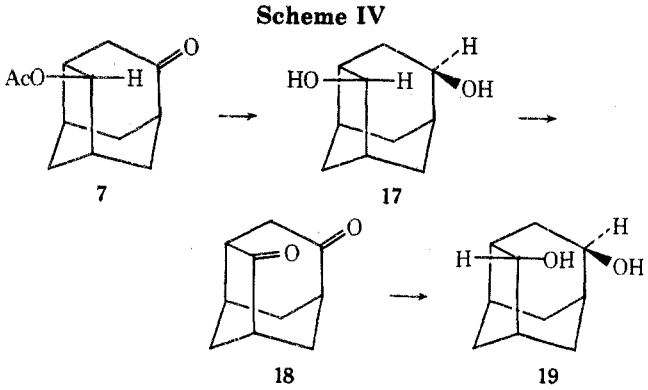
isotwistanone (**13**).[4d] Hydrolysis of **8** affords 2-*exo*-hydroxy-7-isotwistanone (**11**) and Wolff–Kishner reduction of **11** provides 2-*exo*-isotwistanol (**12**). Jones oxidation of **12** gives **13**. The formation of **8** is not unexpected. Spurlock and Clark have reported that the major products resulting from the acetolysis of 2-*exo*-protoadamantyl brosylate (**14**) are 2-*exo*-isotwistyl acetate (**15**) and 2-*exo*-protoadamantyl acetate (**16**).[4d] The formation of **15** was accounted for by



anchimeric assistance of the C-1 to C-10 σ bond of **14** in the ionization process, accompanied by nucleophilic attack at C-1 of **14**. The stereochemistry of the acetoxy substituent and the position of the keto substituent in **8** follow from a similar mechanism rationalizing the formation of **8**.

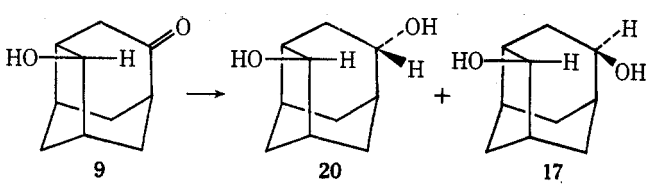
The synthesis of acetoxy ketone **7** permits the facile preparation of three of the 2,5-protoadamantanediols. Treatment of **7** with lithium aluminum hydride affords a single product to which we have assigned the structure of 2-*exo*-5-*endo*-protoadamantanediol (**17**) (Scheme IV). An

Scheme IV



examination of molecular models clearly shows that whereas there is no apparent steric hindrance to attack at the exo face of the C-5 carbonyl carbon in **7**, attack at the endo face of the C-5 carbonyl carbon should be significantly impeded by the endo hydrogen at C-2. Consistent with the structure assignment, Jones oxidation of **17** affords 2,5-protoadamantanedione (**18**), which shows carbonyl absorptions in the infrared at 1743 and 1721 cm^{-1}.[14] Sodium borohydride reduction of **18** provides 2-*endo*-5-*endo*-protoadamantanediol (**19**). Jones oxidation of **19** regenerates **18**.

Since 2-*exo*-5-*exo*-protoadamantanediol (**20**) is undoubtedly thermodynamically more stable than diol **17**, it was anticipated that **20** might be obtained from **17** via equilibration. However, treatment of **17** with aluminum isopropoxide in isopropyl alcohol[15] gave only recovered starting material. Boyd and Overton were similarly unsuccessful in equilibrating 5-*endo*-protoadamantanol.[5b] However, they did find that 5-*exo*-protoadamantanol could be obtained in ca. 70% yield by reduction of 5-protoadamantanone with lithium in ammonia.[5b] Diol **20** may be synthesized by means of an analogous reaction. Thus, treatment of **9** with a large excess of lithium in ammonia provides a 2:1 mixture of **20** and **17** in an overall yield of ca. 50%. The diols can be

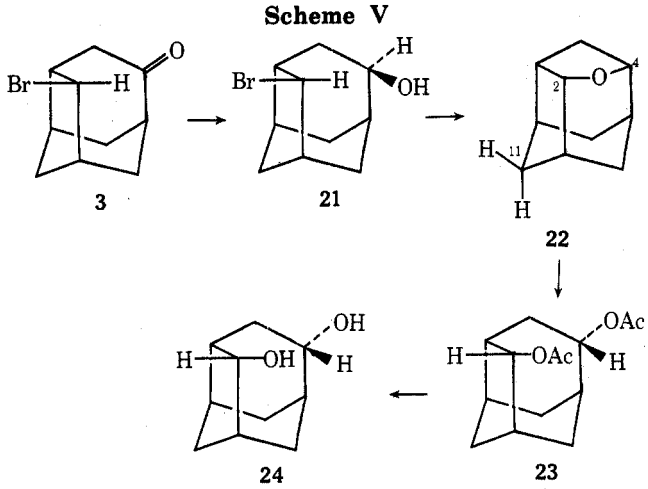


9 20 17

readily separated by GLC. As expected, Jones oxidation of **20** gives **18**.

In view of the conversion of **9** to **20**, it appears that 2-*endo*-5-*exo*-protoadamantanediol (**24**) might also be prepared from **9**.[16] However, we have developed an alternative

Scheme V



3 21 22 23 24

and less obvious synthesis of **24** (Scheme V). The key intermediate in this reaction sequence is cage ether **22**. 3-Oxatetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecane (**22**) was prepared via an internal Williamson ether synthesis from 2-*exo*-bromo-5-*endo*-protoadamantanol (**21**) which, in turn, was obtained by sodium borohydride reduction of bromo ketone **3**. Refluxing **22** with a mixture of zinc chloride and acetic anhydride provides 2-*endo*-5-*exo*-diacetoxy protoadamantane (**23**) in ca. 85% yield.[17,18] Since treatment of **22** under these reaction conditions might well lead to both 2-endo-5-exo- and 2-exo-5-endo-disubstituted protoadamantanes, it is apparent that **22** → **23** is a strikingly regioselective reaction which proceeds by preferential attack at C-4 rather than at C-2 of **22**. From an examination of molecular models, it is tempting to suggest that this is the case because the equatorial hydrogen at C-11 of **22** sterically hinders attack at C-2. There is no apparent steric hindrance to attack at C-4 of **22**. Hydrolysis of **23** gives diol **24** in nearly quantitative yield. The skeletal framework of **24** and the skeletal positions of the substituent groups in **24** were confirmed by Jones oxidation of **24** to give dione **18**.

Aspects of the chemical and physical properties of the 2,5-protoadamantanediols are currently under active investigation.

Experimental Section

All melting points were obtained in sealed capillary tubes using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers and proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers. Apparent splittings are given in all cases. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^1H NMR spectrum of the product(s) vs. the signal of a predetermined amount of added standard (generally trichloroethylene) and are regarded as being accurate to ca. ±10%. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

2-*exo*-Bromo-5-protoadamantanone (3). To a solution of 227 mg (1.53 mmol) of 8,9-dehydro-2-adamantanone (**2**)[7] in 20 ml of acetic acid was added 1 ml of a 30–32% solution of hydrobromic acid in acetic acid and the resulting solution was stirred for 1 hr at 80–100°. The reaction mixture was then quenched in aqueous sodium bicarbonate (250 ml) and extracted with ether (4 × 100 ml). The combined ether extracts were washed with water (2 × 50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 327 mg of a tan solid which by ^1H NMR analysis contained a ca. 95% yield of **3**. Recrystallization of this material from heptane gave pure **3**: mp 127–127.5°; δ_{Me_4Si} ($CDCl_3$) 3.79 (d, J = 3.5 Hz, 1 H, CHBr), 3.3–1.5 (br m, 12 H); ν (CCl_4) 2960, 2885, 1725, 1455, 1425, 1400, 1310, 1250, 1240, 1145, 1065, and 1045 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}OBr$: C, 52.42; H, 5.72; Br, 34.87. Found C, 52.52; H, 5.70; Br, 34.96.

5-Protoadamantanone (4). A solution of 69 mg (0.3 mmol) of **3** in 25 ml of methanol was stirred with 250 mg of 5% palladium on calcium carbonate under an atmosphere of hydrogen for 21 hr. The reaction mixture was filtered to remove the catalyst and the methanol was then evaporated at reduced pressure to afford 37 mg (ca. 80% yield) of an off-white solid which GLC analysis (5 ft × 0.25 in. FFAP column, 160°) showed contained a single component. Purification of this compound by GLC (above conditions) gave pure **4**, whose physical and spectral properties were identical with those previously reported.[4a,5b]

Dehydrobromination of 3. A solution of 105 mg (1.85 mmol) of potassium hydroxide in 3 ml of methanol was added to a solution of 22 mg (0.1 mmol) of **3** in 2 ml of methanol and the resulting solution was refluxed for 0.5 hr. The reaction mixture was then quenched in water (100 ml) and extracted with ether (4 × 25 ml). The combined ether extracts were washed with water (3 × 10 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 21 mg of a yellow oil which GLC analysis (5 ft × 0.25 in. FFAP column, 190°) showed contained a single component. Isolation of this compound by GLC (above conditions) provided pure **2**, which was identified by comparison of its ir spectrum with that of an authentic sample.[7]

2-*exo*-Chloro-5-protoadamantanone (5). To 102 mg of **2** was added 4 ml of acetic acid which had been saturated with dry hydrogen chloride gas. The reaction mixture was refluxed for 1 hr and then quenched in water (50 ml). The resulting mixture was neutralized with solid sodium bicarbonate and extracted with ether (4 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to afford 139 mg of an off-white solid which by ^1H NMR analysis contained a ca. 85% yield of **5**. Recrystallization of this material from chloroform–heptane gave pure **5**: mp 170–171°; δ_{Me_4Si} ($CDCl_3$) 3.68 (d, J = 1.5 Hz, 1 H, CHCl), 3.1–1.3 (br m, 12 H); ν ($CHCl_3$) 2950, 2865, 1710, 1475, 1460, 1450, 1420, 1345, 1270, 1240, 1150, 1120, 1070, 1045, and 1015 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.04; H, 7.10; Cl, 19.20. Found: C, 65.31; H, 7.15; Cl, 19.46.

2-*exo*-Ethoxy-5-protoadamantanone (6). A solution of 193

mg of *p*-toluenesulfonic acid monohydrate in 10 ml of benzene was refluxed for 20 min and the water was removed azeotropically. The remaining benzene was evaporated at reduced pressure and 93 mg of **2** and 10 ml of ethanol were added to the residue. The solution was refluxed for 10 hr, after which the mixture was poured onto 20 ml of 10% aqueous sodium bicarbonate. An additional 30 ml of water was added, and the solution was saturated with sodium chloride and then extracted with ether (5 × 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to give 131 mg of a brown oil which by ^{1}H NMR analysis contained a ca. 80% yield of **6**. Isolation by GLC (5 ft × 0.25 in. FFAP column, 160°) gave pure **6**: δ_{Me_4Si} ($CDCl_3$) 3.36 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 3.08 (d, J = 1.5 Hz, 1 H, $CHOCH_2CH_3$), 2.9–1.3 (br m, 12 H), and 1.14 (t, J = 7 Hz, 3 H, $-OCH_2CH_3$); ν ($CHCl_3$) 2925, 2870, 1715, 1470, 1445, 1375, 1360, 1340, 1150, 1120, 1085, and 1015 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.31; H, 9.53.

Perchloric Acid Catalyzed Addition of Acetic Acid to 2. A solution containing 100 mg (0.7 mmol) of **2** and 50 μl of 70% perchloric acid in 4 ml of acetic acid was stirred for 4 hr at 80–100°, then quenched in water and neutralized with solid sodium bicarbonate. The resulting mixture was extracted with ether (5 × 75 ml) and the combined ether extracts were washed with water (2 × 50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 134 mg of yellow oil which GLC analysis (5 ft × 0.25 in. FFAP column, 190°) showed contained a major and a minor component. ^{1}H NMR and GLC analysis indicated that the products were obtained in ca. 80 and 10% yields, respectively. The reaction products were separated and purified by GLC (above conditions) to give, as the major product, **2-*exo*-acetoxy-5-protoadamantanone (7)**: mp 66–68°; δ_{Me_4Si} (CCl_4) 4.26 (d, J = 1.5 Hz, 1 H, $CHOCOCH_3$) and 2.6–1.2 (br m, 15 H, containing $CHOCOCH_3$ singlet at δ 1.93); ν (CCl_4) 2950, 2875, 1739, 1726, 1360, 1250, 1235, 1165, 1075, 1055, and 1030 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.18; H, 7.48.

2-*exo*-Acetoxyisotwistan-7-one (8) was obtained as the minor product: mp 79.5–80.5°; δ_{Me_4Si} (CCl_4) 4.87 (m, 1 H, $CHOCOCH_3$, an apparent ABX multiplet where J_{AX} = 6 and J_{BX} = 3.3 Hz) and 2.5–1.2 (br m, 15 H, containing $CHOCOCH_3$ singlet at δ 1.92); ν (CCl_4) 2945, 2870, 1738, 1728, 1395, 1375, 1355, 1240, 1170, 1140, 1080, 1045, and 1030 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.07; H, 7.92.

2-*exo*-Hydroxy-5-protoadamantanone (9). A reaction mixture containing 422 mg of **7**, 113 mg of sodium hydroxide, 6 ml of methanol, and 8 ml of water was refluxed for 2 hr and then quenched in water (100 ml). The resulting solution was saturated with sodium chloride and extracted with ether (4 × 100 ml). The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 389 mg of material which by ^{1}H NMR analysis contained a ca. 100% yield of **9**. Isolation of the product by GLC (5 ft × 0.25 in. FFAP column, 220°) afforded pure **9**: mp 244–246°; δ_{Me_4Si} ($CDCl_3$) 3.54 (d, J = 1 Hz, 1 H, CHOH) and 2.6–1.2 (br m, 13 H); ν (CCl_4) 3625, 3440, 2935, 2875, 1715, 1470, 1440, 1410, 1290, 1235, 1165, 1150, 1050, 1030, and 1000 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.21; H, 8.43.

2-*exo*-Protoadamantanol (10). A stirred solution containing 34 mg (0.2 mmol) of **9**, 130 μl (3.9 mmol) of 95% hydrazine, and 32 μl (0.5 mmol) of acetic acid in 2 ml of diethylene glycol was heated at 90° under a nitrogen atmosphere for 24 hr. At this point 275 mg (4.8 mmol) of potassium hydroxide was added and the reaction mixture was heated at 190° for an additional 5 hr. During this time, a white solid appeared on the condenser. The system was cooled and the material on the condenser was dissolved in pentane. The pot residue was quenched in water (50 ml) and extracted with pentane (4 × 25 ml). The pentane extracts from condenser and pot were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 21 mg of material which GLC analysis (5 ft × 0.25 in. FFAP column, 175°) showed contained a single component. Isolation of this compound by GLC (above conditions) gave pure **10**, mp 218–220°, which was identified by comparison of its ir spectrum with that of an authentic sample.[4d,13]

2-*exo*-Hydroxy-7-isotwistanone (11). A reaction mixture containing 55 mg of **8**, 13 mg of sodium hydroxide, 3 ml of methanol, and 4 ml of water was refluxed for 2 hr and then quenched in water (100 ml). The resulting solution was extracted with ether (5 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 44 mg of material which by ^{1}H NMR analysis contained a ca. 40% yield of **11**. Purification of the product by GLC (5 ft × 1.25 in. FFAP column, 215°) provided pure **11**: mp 61–62°; δ_{Me_4Si} ($CDCl_3$) 4.18 (m, 1 H, CHOH, an apparent ABX multiplet where J_{AX} = 5.5 and J_{BX} = 2.7 Hz) and 2.7–1.1 (br m, 13 H); ν ($CHCl_3$) 3610, 3450, 3005, 2940, 2865, 1715, 1400, 1350, 1325, 1235, 1130, 1125, 1045, and 1030 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.30.

2-*exo*-Isotwistanol (12). By a procedure analogous to that employed for **9** → **10**, Wolff–Kishner reduction of **11** provided **12** in yields of 50–60%. Purification by GLC (5 ft × 0.25 in. FFAP column, 165°) gave pure **12**: mp 57.5–58.5°; δ_{Me_4Si} (CCl_4) 4.04–3.76 (br m, 1 H, CHOH), 2.80 (br s, 1 H), and 2.5–0.8 (br m, 14 H); ν (CCl_4) 3625, 3345, 2935, 2860, 1445, 1280, 1215, 1165, 1080, 1040, and 1025 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.10; H, 10.52.

2-Isotwistanone (13). To a stirred solution of 9 mg of **12** in 5 ml of acetone at 0° was added 40 μl of a freshly prepared solution of Jones reagent (2.8 g of chromic anhydride, 4.5 ml of sulfuric acid, and 12 ml of water). The reaction mixture was stirred for 4 hr and allowed to gradually warm to room temperature. The reaction was then quenched with 4 ml of 25% aqueous sodium bisulfite and the volume of the mixture was increased to 20 ml by the addition of water. The resulting solution was extracted with ether (4 × 25 ml) and the combined ether extracts were then washed successively with saturated aqueous sodium bicarbonate (2 × 10 ml) and saturated aqueous sodium chloride (2 × 10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated at reduced pressure and the residue was purified by GLC (5 ft × 0.25 in. FFAP column, 175°) to give pure **13** whose physical (mp 112–114°) and spectral properties were identical with those previously reported.[4d]

2-*exo*-5-*endo*-Protoadamantanediol (17). To a solution of 187 mg (0.9 mmol) of **7** in 20 ml of freshly distilled dry ether at 0–5° was added 333 mg (8.8 mmol) of lithium aluminum hydride and the resulting reaction mixture was stirred at 0–5° for 1 hr and then at 25° for 12 hr. The reaction mixture was cautiously quenched with 10 ml of saturated aqueous ammonium chloride and the resulting precipitate was filtered. The filtrate was saturated with sodium chloride and extracted with ether (4 × 50 ml). The precipitate from the reaction was washed with several portions of ether and the ether extracts and washings were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 181 mg of material which by ^{1}H NMR analysis contained a ca. 70% yield of **17**. Isolation by GLC (5 ft × 0.25 in. FFAP column, 205°) provided pure **17**: mp 271–272°; δ_{Me_4Si} (CD_3OD) 4.13–3.84 (br m, 2 H, CHOH) and 2.5–1.0 (br m, 12 H); ν ($CHCl_3$) 3630, 3440, 3000, 2940, 2835, 1090, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.56.

2,5-Protoadamantanedione (18). Oxidation of 56 mg of **17** with Jones reagent by the procedure described for **12** → **13** provided 59 mg of material which was purified by GLC (5 ft × 0.25 in. FFAP column, 200°) to give pure **18**: mp 264–267°; δ_{Me_4Si} ($CDCl_3$) 2.9–1.5 (br m); ν ($CHCl_3$) 3020, 2940, 2875, 1743, 1721, 1465, 1450, 1440, 1400, 1180, 1175, 1140, 1070, 1040, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.90; H, 7.08.

2-*endo*-5-*endo*-Protoadamantanediol (19). Sodium borohydride (670 mg, 17.6 mmol) was added to a stirred solution of 145 mg (0.9 mmol) of **18** in 20 ml of methanol at 0–5°. The solution was stirred for 12 hr while it gradually warmed to room temperature. At this point 50 ml of saturated aqueous ammonium chloride was added and the solution was saturated with sodium chloride. The reaction mixture was extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 173 mg of crude diol which was purified by GLC (5 ft × 0.25 in. FFAP column, 200°) to give **19**: mp >290°; δ_{Me_4Si} (CD_3OD) 4.5–3.8 (br m, 2 H, CHOH) and 3.0–1.1 (br m, 12 H); ν (CCl_4) 3610, 3270, 2930, 2860, 1450, 1170, 1085, 1055, and 1015 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.30.

Oxidation of **19** with Jones reagent by the procedure described for **12** → **13** gave **18**.

2-*exo*-5-*exo*-Protoadamantanediol (20). To a stirred slurry of 381 mg (54.5 mmol) of lithium metal in ca. 100 ml of liquid ammonia was added 326 mg (2.0 mmol) of **9**. The stirred solution was refluxed for 1.5 hr, at which point ca. 8 g of ammonium chloride was carefully added and the ammonia was allowed to evaporate. Water (100 ml) was added to the reaction mixture and the resulting solution was saturated with sodium chloride and extracted with ether (4 × 100 ml). The combined ether extracts were washed successively with 5% hydrochloric acid (2 × 50 ml) and water (50 ml) and then dried over anhydrous magnesium sulfate. GLC analysis (5 ft × 0.25 in. QF-1 column, 200°) of the crude reaction mixture indicated the presence of two components: a minor product (which proved to be **17**) and a major product **20** (longer retention time). Evaporation of the solvent at reduced pressure gave 295 mg of material which by ^{1}H NMR analysis contained a ca. 50% yield of the two diols. The diols were separated by GLC (5 ft × 0.25 in. QF-1 column, 165°) to provide pure **20**: mp 235–236°; δ_{Me_4Si} (CD_3OD) 3.96–3.50 (br m, 2 H, CHOH) and 2.5–0.6 (br m, 12 H); ν ($CHCl_3$) 3625, 3300, 2925, 2860, 1155, 1030, 1010, and 995 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.48.

Oxidation of **20** with Jones reagent by the procedure described for **12** → **13** gave **18**.

2-*exo*-Bromo-5-*endo*-Protoadamantanol (21). To a stirred solution of 361 mg (1.73 mmol) of **3** in 25 ml of methanol at 0–5° was added 610 mg (16.0 mmol) of sodium borohydride. Over a period of 2 hr the reaction mixture was allowed to warm to room temperature and it was then quenched with water (50 ml). The resulting solution was saturated with sodium chloride and extracted with ether (4 × 25 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 306 mg of material which by ^{1}H NMR analysis contained a ca. 75% yield of **21**. Recrystallization of this material from chloroform–heptane gave pure **21**: mp 113.5–114.5°; δ_{Me_4Si} ($CDCl_3$) 4.51 (d, J = 1.6 Hz, 1 H, CHBr), 4.34–3.94 (br m, 1 H, CHOH), and 3.0–1.2 (br m, 14 H); ν ($CHCl_3$) 3615, 3450, 2950, 2870, 1465, 1450, 1435, 1085, 1040, and 1030 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.96; H, 6.54; Br, 34.57. Found: C, 52.06; H, 6.35; Br, 34.79.

3-Oxatetracyclo[5.3.1.0^{2,6}.0^{4,9}]undecane (22). A solution of 209 mg of **21** and 108 μl of water in 10 ml of methanol was added to a stirred solution of 293 mg of sodium in 20 ml of methanol and the reaction mixture was refluxed for 12 hr. At this point the solution was concentrated by evaporation of most of the methanol at reduced pressure and 50 ml of water was added. The solution was extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 168 mg of material which by ^{1}H NMR analysis contained a ca. 60% yield of **22**. Purification by GLC (10 ft × 0.25 in. Carbowax column, 150°) provided pure **22**: mp 238–239°; δ_{Me_4Si} ($CDCl_3$) 4.60–4.15 (br m, 2 H, CHOCH, containing an apparent triplet centered at δ 4.43) and 2.8–0.8 (br m, 12 H); ν ($CHCl_3$) 2985, 2860, 1470, 1450, 1340, 1315, 1180, 1145, 1125, 1100, 1030, 1000, 985, and 930 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.81; H, 9.22.

2-*endo*-5-*exo*-Diacetoxyprotoadamantane (23). To a stirred solution of 82 mg (0.55 mmol) of **22** in 7 ml of acetic anhydride was added 66 mg (0.49 mmol) of zinc chloride and the reaction mixture was refluxed for 10 hr and then quenched in 100 ml of ice–water. The resulting solution was neutralized with solid sodium bicarbonate and extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 194 mg of a brown oil which by ^{1}H NMR analysis contained a ca. 85% yield of **23**. GLC analysis (5 ft × 0.25 in. Carbowax column, 210°) indicated a single major reaction product and several minor products. Isolation of the major product by GLC (above conditions) gave pure **23** as an oil: δ_{Me_4Si} ($CDCl_3$) 5.11–4.75 (br m, 2 H, $CHOCOCH_3$) and 2.8–1.1 (br m, 18 H, containing $OCOCH_3$ singlets at δ 2.12 and 1.98); ν ($CHCl_3$) 2940, 2875, 1720, 1460, 1250, 1070, and 1025 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.52; H, 7.86.

2-*endo*-5-*exo*-Protoadamantanediol (24). Hydrolysis of 117 mg of **23** by the procedure described for **7** → **9** provided 127 mg of material which by ^{1}H NMR analysis contained a ca. 100% yield of **24**. The reaction product was sublimed and finally purified by GLC (5 ft × 0.25 in. Carbowax column, 235°) to give pure **24**: mp 286–288°; δ_{Me_4Si} (CD_3OD) 4.34–3.60 (br m, 2 H, CHOH) and 2.6–0.9 (br m, 12 H); ν ($CHCl_3$) 3610, 3360, 2925, 2865, 1455, 1260, 1095, and 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.31.

Oxidation of **24** with Jones reagent by the procedure described for **12** → **13** gave **18**.

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References and Notes

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(16) Such a synthesis of **24** might involve the following sequence of reactions.

$$9 \xrightarrow[H^+]{HOCH_2CH_2OH} \xrightarrow[Py]{CrO_3} \xrightarrow[CH_3OH]{NaBH_4} \xrightarrow[H_2O]{H^+} \xrightarrow[NH_3]{Li} 24 + 19$$

(17) A number of minor products were also detected in the reaction mixture, but they were not identified.
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