

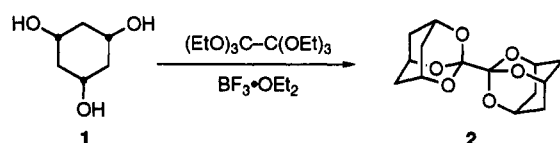
Synthesis of 5,5'-Bi-2-oxadamantane

David S. Teager and Roger K. Murray, Jr.*

Department of Chemistry and Biochemistry,
University of Delaware, Newark, Delaware 19716

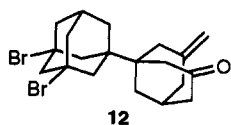
Received April 23, 1993

Although the synthesis and chemistry of heteroadamantanes have received considerable attention,¹ 3,3'-bi(2,4,10-trioxadamantane) (2) is the only known 1,1'-biadamantane that contains one or more non-carbon skeletal atoms. Stetter and Hunds obtained 2 in 58% yield by treating *cis,cis*-1,3,5-cyclohexanetriol (1) with hexaethoxyethane in the presence of boron trifluoride



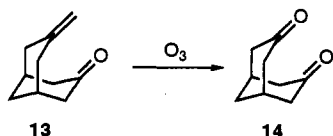
etherate.² We now report the synthesis of 5,5'-bi-2-oxadamantane (11) in five steps from 1,1'-biadamantane³ (3).

Treatment of **3** with bromine containing a catalytic amount of aluminum bromide for 3 h at room temperature gives 3,3',5,5'-tetrabromo-1,1'-biadamantane (**4**) in 87% yield (Scheme I). Consistent with the presence of a center of symmetry in **4**, its ¹³C NMR spectrum consists of only seven resonances. Heating a solution of **4** in dioxane with 1 N aqueous sodium hydroxide at 180–185 °C for 24 h proceeds with 95% conversion of **4** to give a 50:50 mixture of *dl*- and *meso*-1,1'-bi(7-methylenebicyclo[3.3.1]nonan-3-one) (**5** and **6**, respectively) in 75% yield and 1-(3',5'-dibromo-1'-adamantyl)-7-methylenebicyclo[3.3.1]nonan-3-one (**12**) in 8% yield. Enone **12** was separated from the



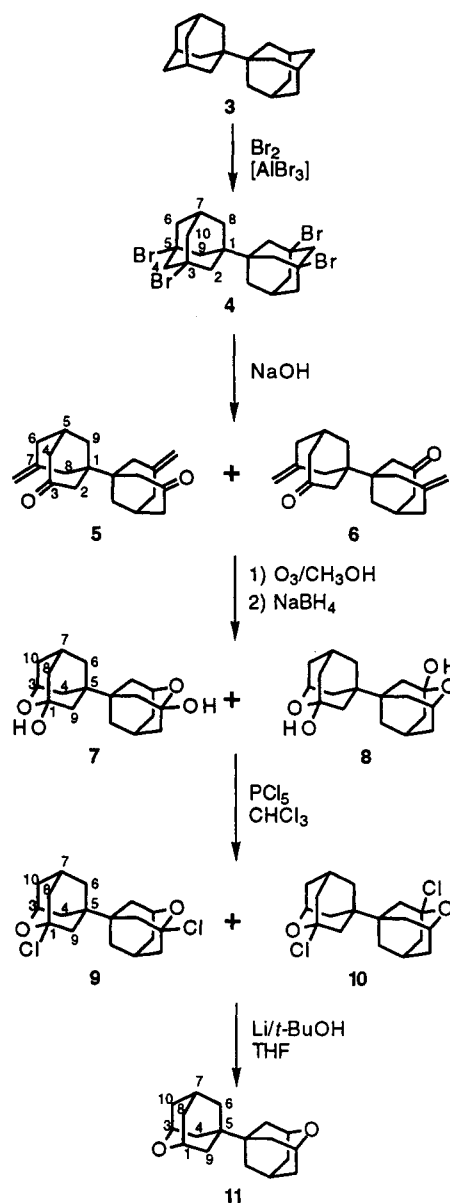
mixture of **5** and **6** by column chromatography on silica gel with dichloromethane/ethyl acetate as the eluent. Although the ¹³C NMR resonances for C-1 and C-1', C-3 and C-3', and C-9 and C-9' are each accidentally coincident in **5** and **6**, distinct ¹³C NMR resonances are apparent for all of the other carbons in these compounds.

Ozonolysis of the 50:50 mixture of **5** and **6**, followed by reductive workup with dimethyl sulfide, gives only polymeric material. This is a surprising result since ozonolysis of **13** provides **14** in 82% yield⁴ and **14** polymerizes only when it is subjected to strongly acidic conditions.⁵ How-



ever, if the solution obtained from the reaction of **5/6** with ozone is treated immediately with sodium borohydride,⁶ then a mixture of *dl*- and *meso*-5,5'-bi(1-hydroxy-2-oxadamantane) (**7** and **8**, respectively) is obtained in 54% yield. In CD_3OD , the ¹³C NMR resonances for the

Scheme I



corresponding carbons in **7** and **8** are each accidentally coincident. In CDCl_3 , a slight resolution of the signals for C-6 and C-6', C-8 and C-8', and C-9 and C-9' in **7** and **8** can be observed. The mixture of **7** and **8** was converted to **11** by a sequence of reactions analogous to that employed by Stetter and his co-workers for the synthesis of oxaadamantane from 1-hydroxy-2-oxadamantane.⁷ Treatment of this mixture of **7** and **8** with phosphorus pentachloride gives a mixture of *dl*- and *meso*-5,5'-bi(1-chloro-2-oxadamantane) (**9** and **10**, respectively). Some resolution of the resonances for C-4 and C-4' and for C-6 and C-6' in **9** and **10** can be seen in the ¹³C NMR spectrum. Since column chromatography on silica gel of the crude product

(1) For reviews see: (a) Fort, R. C., Jr. *Adamantane: The Chemistry of Diamond Molecules*; Marcel Dekker: New York, 1976; Chapter 6. (b) Ganter, C. *Fortschr. Chem. Forsch.* 1976, 67, 15.

(2) Stetter, H.; Hunds, A. *Liebigs Ann. Chem.* 1984, 1577.

(3) (a) Landa, S.; Hála, S.; *Chem. Listy* 1957, 51, 2325. (b) Reinhardt, H. F. *J. Org. Chem.* 1962, 27, 3258.

(4) Stetter, H.; Tacke, P. *Chem. Ber.* 1963, 96, 694.

(5) Stetter, H.; Tacke, P.; Gärtner, J. *Chem. Ber.* 1965, 98, 3888.

(6) Diaper, D. G. M.; Mitchell, D. L. *Can. J. Chem.* 1960, 38, 1976.

(7) Stetter, H.; Tacke, P.; Gärtner, J. *Chem. Ber.* 1964, 97, 3480.

from this reaction results in a significant loss of material, it is best to prepare 11 by reducing the crude mixture of 9 and 10 with lithium/*tert*-butyl alcohol in tetrahydrofuran.⁸ Consistent with the presence of a center of symmetry in 11, its ¹³C NMR spectrum consists of only six resonances. This sequence of reactions provides 11 in an overall yield of 10% from 3.

Experimental Section

3,3',5,5'-Tetrabromo-1,1'-biadamantane (4). A mixture of 3³ (405 mg, 1.5 mmol) and AlBr₃ (ca. 100 mg) was stirred with Br₂ (15 mL) for 3 h at rt. The catalyst was destroyed by the addition of ice, and the reaction mixture was poured into a well-stirred mixture of CCl₄ (50 mL) and ice (100 mL). The excess bromine present was destroyed by the addition with stirring of solid NaHSO₃. The phases were separated, and the aqueous phase was extracted with additional CCl₄ (50 mL). The extract was combined with the organic phase and dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave 1.09 g of crude 4. Crystallization of 4 from CHCl₃/acetone gave 761 mg (87% yield) of 4 as an off-white solid: mp 270–271 °C; ¹³C NMR δ 61.9 (C-3, C-3', C-5, and C-5'), 58.5 (C-4 and C-4'), 46.5 (C-6, C-6', C-10, and C-10'), 46.1 (C-1 and C-1'), 45.8 (C-2, C-2', C-9, and C-9'), 34.3 (C-7 and C-7'), 32.3 (C-8 and C-8'); ¹H NMR δ 2.80 (AB multiplet, 4 H), 2.33 (m, 1 H), 2.22 (m, 4 H), 2.14 (bs, 4 H), 1.59 (bd, *J* = 2.9 Hz, 2 H); HRMS calcd for C₂₀H₂₆Br₄ (M⁺ - Br) 502.9579, found 502.9547. Anal. Calcd for C₂₀H₂₆Br₄: C, 40.99; H, 4.47. Found: C, 40.84; H, 4.49.

1,1'-Bi(7-methylenebicyclo[3.3.1]nonan-3-one) (5/6). A stirred mixture of 4 (586 mg, 1.0 mmol), dioxane (15 mL; Note: poor results were obtained when the dioxane was not of the highest purity), and 1 N aqueous NaOH (15 mL) was heated at 180–185 °C for 24 h in a stainless steel reactor bomb. During this time, the initially cloudy mixture became a pale yellow solution. The reaction mixture was cooled and then diluted with CH₂Cl₂ (60 mL) and H₂O (40 mL). The layers were separated, and the aqueous portion was extracted with CH₂Cl₂ (2 × 30 mL). The extracts were combined with the organic layer, washed with H₂O (50 mL), and dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave 346 mg of a near-white solid. Column chromatography of this material on TLC mesh silica gel with 98:2 CH₂Cl₂/ethyl acetate gave 27 mg (5% recovery) of 4, followed by 35 mg (8% yield) of 12: mp 166–168 °C (crystallized from hexanes/CHCl₃); ¹³C NMR δ 209.8 (C-3), 141.3 (C-7), 115.8 (C=CH₂), 62.1 (C-3' and C-5'), 58.6 (C-4'), 46.9 and 46.6 (C-2 and C-4), 46.7 (C-2' and C-9'), 46.4 (C-1'), 46.1 (C-6' and C-10'), 42.3 (C-1), 41.0 and 40.7 (C-6 and C-8), 34.4 (C-7'), 32.5 (C-8'), 31.0 (C-9), 30.0 (C-5); ¹H NMR δ 4.82 (bs, 2 H), 2.81 (AB multiplet, 2 H), 2.52 (m, 1 H), 2.4–2.1 (m, 17 H), 1.80 (m, 2 H), 1.62 (bd, *J* = 3 Hz, 2 H); HRMS calcd for C₂₀H₂₆Br₂O 440.0350, found 440.0311. Anal. Calcd for C₂₀H₂₆Br₂O: C, 54.32; H, 5.93. Found: C, 54.12; H, 5.91.

Further elution with 75:25 CH₂Cl₂/ethyl acetate gave 223 mg (75% yield) of a 50:50 mixture (no separation seen on column or TLC) of 5 and 6: ¹³C NMR δ 210.6 (C-3 and C-3'), 141.6 and 141.5 (C-7 and C-7' in 5 and 6), 115.9 and 115.7 (C=CH₂ in 5 and 6), 47.1, 47.0, 46.6 and 46.5 (C-2 and C-2' or C-4 and C-4' in 5 and 6), 42.4 (C-1 and C-1'), 41.0, 40.9, 40.80 and 40.78 (C-6 and C-6' or C-8 and C-8' in 5 and 6), 31.0 (C-9 and C-9'), 29.99 and 29.95 (C-5 and C-5' in 5 and 6); ¹H NMR δ 4.83 (bs, 4 H), 2.53 (m, 2 H), 2.45–2.20 (complex m, 16 H), 1.85 (m, 4 H); HRMS calcd for C₂₀H₂₆O₂ 298.1927, found 298.1916. Anal. Calcd for C₂₀H₂₆O₂: C, 80.50; H, 8.78. Found: C, 80.77; H, 8.74.

5,5'-Bi(1-hydroxy-2-oxadamantane) (7/8). A stirred solution of 5/6 (290 mg, 1.0 mmol) and Sudan III indicator (ca. 0.5 mg) in absolute ethanol (6 mL) and CHCl₃ (4 mL) was cooled to 0 °C. Ozone was bubbled through the solution until the pink color of the indicator faded (about 12 min at 1 L/min). The solution was then purged with N₂, and a suspension of NaBH₄ (120 mg, 3.2 mmol) in absolute ethanol (3 mL) was added. The mixture was stirred overnight as the reaction warmed slowly to

rt. The thick reaction mixture was diluted with H₂O (5 mL), and the resulting solution was transferred to a separatory funnel. The reaction vessel was rinsed with brine (20 mL) and ether (20 mL), and these solutions also were transferred to the separatory funnel. The layers were separated, and the aqueous portion was extracted with ether (2 × 20 mL). The ether extracts were combined with the organic layer, washed with brine, and dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave 209 mg of an off-white solid. Column chromatography of this material on TLC mesh silica gel with 90:10 CH₂Cl₂/CH₃OH as eluent gave 166 mg (54% yield) of a mixture of 7 and 8 as a near-white solid: ¹³C NMR (in CD₃OD) δ 95.5 (C-1 and C-1'), 73.0 (C-3 and C-3'), 42.4 (C-8 and C-8'), 41.1 (C-9 and C-9'), 40.6 (C-5 and C-5'), 35.4 (C-10 and C-10'), 34.0 and 33.8 (C-4 and C-4' or C-6 and C-6'), 30.5 (C-7 and C-7'); ¹H NMR (in CD₃OD) δ 4.84 (bs, 2 H), 4.28 (bs, 2 H), 2.33 (bs, 2 H), 1.9–1.4 (m, 20 H, including 1.56, bs, 4 H); HRMS calcd for C₁₈H₂₆O₄ 306.1831, found 306.1846. Anal. Calcd for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C, 70.81; H, 8.51.

5,5'-Bi(1-chloro-2-oxadamantane) (9/10). PCl₅ (470 mg, 2.3 mmol) was added under N₂ to a stirred mixture of 7/8 (138 mg, 0.45 mmol) in CHCl₃ (9 mL; washed with H₂O to remove the ethanol stabilizer, and distilled from anhydrous CaCl₂). As the mixture was heated to reflux, the solids dissolved rapidly. The stirred reaction mixture was heated at reflux for 30 min. The resulting solution was cooled in an ice bath, and a few pieces of ice were added to the reaction mixture. Stirring was continued for an additional 45 min, and then the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 15 mL). The extracts were combined with the organic phase, washed with 10% aqueous NaHCO₃, and dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave 165 mg of a white solid. Analysis of this material by ¹³C NMR spectroscopy showed that it was a fairly pure mixture of 9 and 10. Column chromatography of this material on TLC mesh silica gel with CH₂Cl₂ as eluent provided 40 mg (26% yield) of a mixture of 9 and 10: ¹³C NMR δ 98.4 (C-1 and C-1'), 73.7 (C-3 and C-3'), 45.4 (C-8 and C-8'), 44.2 (C-9 and C-9'), 40.7 (C-5 and C-5'), 33.8 (C-10 and C-10'), 32.39 and 32.36 (C-4 and C-4' or C-6 and C-6' in 9 and 10), 32.09 and 32.06 (C-4 and C-4' or C-6 and C-6' in 9 and 10), 29.9 (C-7 and C-7'); ¹H NMR δ 4.45 (bs, 2 H), 2.40 (m, 2 H), 2.31 (dm, *J* = 12.3 Hz, 2 H), 2.2–1.8 (m, 10 H), 1.66 (bs, 4 H), 1.55–1.4 (m, 4 H); HRMS calcd for C₁₈H₂₄Cl₂O₂ 342.1153, found 342.1164. Further elution with CH₂Cl₂ afforded 19 mg of a mixture of 9/10 and an unidentified impurity. Since column chromatography of the crude product of this reaction resulted in a significant loss of 9/10, it is best to use the crude mixture of 9/10 directly for the preparation of 11.

5,5'-Bi-2-oxadamantane (11). Freshly cut pieces of Li (220 mg) were added under N₂ to a solution of 9/10 (124 mg, ca. 0.33 mmol) in anhydrous *tert*-butyl alcohol (5 mL) and anhydrous THF (20 mL). Several pieces of crushed glass were added to help clean the metal surface, and the reaction mixture was stirred vigorously for 18 h at rt. At this point, H₂O (15 mL) was added and stirring was continued for 15 min. The phases were separated, and the aqueous portion was extracted with ether (2 × 15 mL). The ether extracts were combined with the organic phase, washed sequentially with H₂O (10 mL) and saturated aqueous KCl (10 mL), and dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave 81 mg of a thick oil. Column chromatography of this material on TLC mesh silica gel with CH₂Cl₂ gave 13 mg (11% recovery) of 9/10. Further elution with 95:5 CH₂Cl₂/CH₃OH gave 26 mg (32% yield based on 89% conversion of 9/10) of 11 as a white solid: mp 184–186 °C (sealed tube); ¹³C NMR δ 68.6 (C-1, C-1', C-3, and C-3'), 36.0 (C-8, C-8', C-10, and C-10'), 35.8 (C-5 and C-5'), 33.8 (C-4, C-4', C-9, and C-9'), 33.5 (C-6 and C-6'), 27.0 (C-7 and C-7'); ¹H NMR δ 4.13 (bs, 4 H), 2.19 (m, 2 H), 2.01 (bd, *J* = 12.5 Hz, 4 H), 1.87 (dm, *J* = 12.3 Hz, 4 H), 1.70 (bs, 4 H), 1.6–1.4 (m, 8 H); HRMS calcd for C₁₈H₂₆O₂ 274.1933, found 274.1913. Anal. Calcd for C₁₈H₂₆O₂: C, 78.79; H, 9.55. Found C, 78.85; H, 9.53.

(8) Bruck, P.; Thompson, D.; Winstein, S. *Chem. Ind. (London)* 1960, 405.