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Semipinacol and protoadamantane-adamantane rearrangements of 5,6-dibromoadamantan-2-one and -2-ol

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ABSTRACT

A number of new polybrominated adamantanes were formed by rearrangements and bromination of 2,2,6,6-tetrabromoadamantane under Friedel-Crafts conditions. Protoadamantane-4,10-dione, 10-acetoxyprotoadamantan-4-one, 1,2,6-triacetoxyadamantane and 5,6-diacetoxyadamantan-2-one were formed by successive semipinacol and protoadamantane-adamantane rearrangements of 5,6-dibromoadamantan-2-one and 5,6-dibromoadamantan-2-ol. This work may open up new pathways for the synthesis of 1,2,6-trisubstituted adamantanes.

1. Introduction

Substituted adamantanes have long been important tools in mechanistic organic chemistry.[1,2] Compounds with adamantane substructures also play important roles in medicinal chemistry and material science.[3,4] Most mono- and disubstituted adamantane derivatives are readily accessible, but tri- and tetrasubstituted adamantanes are less common,[5] and most of these are 1,3,5- and 1,3,5,7-bridgehead substituted adamantanes. For the synthesis of the latter, successive bridgehead substitutions under Friedel-Crafts conditions become more difficult due to destabilization of cationic intermediates by electron withdrawing substituents.[6] This is well illustrated in the bromination of adamantane where, by using increasingly more reactive Lewis acid catalysts and vigorous reaction conditions, adamantane may be selectively mono-, di-, tri-, and tetrabrominated at the bridgehead positions.[7]

We were interested in 1,2,6-trihydroxyadamantane (**1**) and its corresponding ketone, 5,6-dihydroxyadamantan-2-one (**2**), as synthetic precursors to oxidative metabolites[8] of the antimalarial ozonide OZ439 (**3**)[9] (Fig. 1). However, 1,2,6-substituted adamantanes are uncommon, and they are only described in theoretical studies.[10,11] Our initial attempts to synthesize **1** and **2** involved oxidation reactions of adamantane-2,6-dione (**4**)[12] and its corresponding diol esters. However, we found that **4** resisted oxidation by chromium, oxone, periodate, and ruthenium reagents, due presumably to bridgehead deactivation[13] by the twin ketone functional groups. This outcome parallels previous observations that adamantanes with even one ketone functional group are relatively resistant not only to oxidation,[14,15] but also to Friedel-Crafts bromination.[16,17]

2. Results and discussion

Based on aluminum halide-induced halogen migrations in 2,2-dihaloadamantanes,[18,19] and the aluminum bromide/bromine-induced rearrangement/bromination of 2,2-dichoroadamantane (**5**) to 1,3,6-tribromoadamantane (**6**)[20] (Scheme 1), we reasoned that a similar rearrangement of 2,2,6,6-tetrabromoadamantane (**9**) under Friedel-Crafts conditions might provide an avenue to 1,2,6-trisubstituted adamantanes (Scheme 2). As a prelude, we confirmed that exposure of 2,2-dibromoadamantane (**7**)[21] to either iron powder in refluxing bromine[22] or aluminum bromide in

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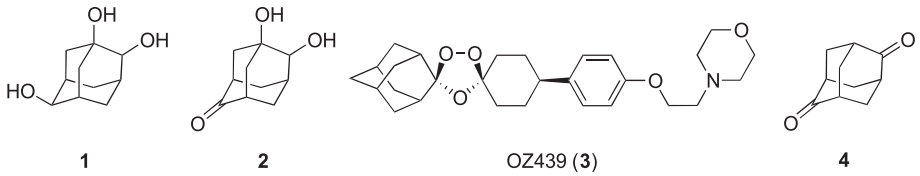
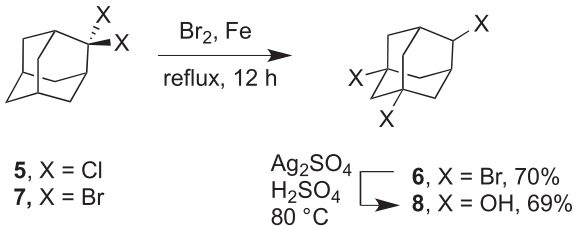


Fig. 1. Structures of **1**–**4**.



Scheme 1. Model rearrangement/bromination reactions of adamantane geminal dihalides **5** and **7**.

bromine at rt readily formed the desired **6** in 70% yield after a single crystallization from EtOH (Scheme 1). 1,3,6-Tribromoadamantane (**6**) was then hydrolyzed to 1,3,6-trihydroxyadamantane (**8**) with Ag_2SO_4 in concentrated H_2SO_4 in 69% yield according to a modified[23] procedure of Song and le Noble.[17] We thus had confidence to move forward with a parallel reaction sequence for **9** (Scheme 2).

Exposure of **4** to hot thionyl bromide afforded 2,2,6,6-tetrabromoadamantane (**9**) in 72% yield. Subjecting the latter to various Friedel-Crafts reaction conditions led to the formation of various proportions of 2,2,5,6-tetrabromoadamantane (**10**), 2,2,5,6,6-pentabromoadamantane (**11**), and 1,2,5,6-tetrabromoadamantane (**12**) (Scheme 2). For example, treatment of **9** with aluminum bromide (3.6 mol equiv) in bromine[24] at 40–50 °C for 48 h gave a mixture of **10** (31%) and **11** (25%), isolated by chromatography and crystallization, respectively. We were pleased to discover that using less aluminum bromide (1.8 mol equiv) and a slightly higher temperature (50–60 °C) for 24 h led to the formation of a 79:17 ratio (GC-MS data) of **10**:**12** as the major products. From the crude reaction product, **10** was isolated in 54% yield after a single crystallization from ethanol and **12** was isolated in 10% yield after chromatographic purification. Unlike the racemic pair **10**, we anticipated that **12** would be a pair of diastereomers, but the NMR data for **12** indicated that it was a single diastereomer. X-ray crystallographic data[25] for **12** revealed that the pairs of bromine atoms on C-1 and C-6 and on C-2 and C-5 were in a cis configuration (Fig. 2). As was the case for the parallel rearrangement of **7** to **6**, we surmise that the reaction sequence to form **10**, **11**, and **12** from **9** proceeded by disproportionation-comproportionation pathways involving intermolecular hydride shifts.[7,18,26,27] For both reactions, we also observed small quantities of unidentified isomeric tetrabromo and pentabromoadamantanes (GC-MS data).

All attempts to directly convert **10** to 5,6-dihydroxyadamantan-2-one (**2**) using Ag_2SO_4 in concentrated H_2SO_4 failed. Further attempts to hydrolyze **10** or **11** with 1 M HCl in THF/EtOH at 50–60 °C

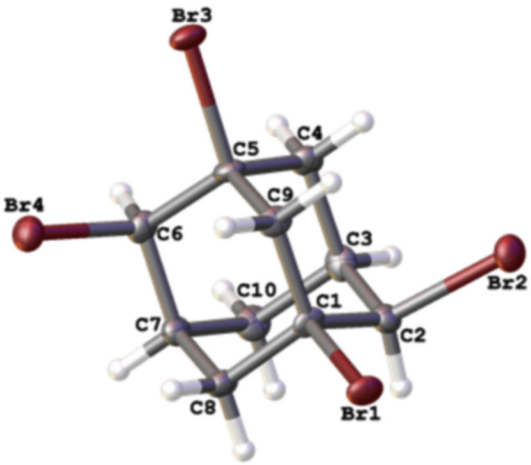
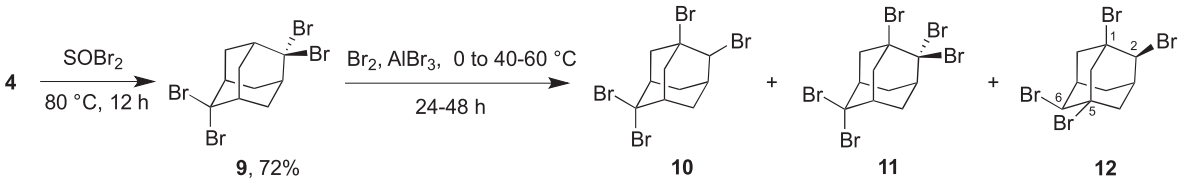


Fig. 2. Thermal ellipsoid plot of 1,2,5,6-tetrabromoadamantane (**12**).

also gave complex mixtures which we attribute in part to disproportionation reactions of the geminal dibromide substructure in the acidic media. However, we found that treatment of **10** with Ag_2O in AcOH at 120 °C afforded **13** in 56% yield (Scheme 3); unexpectedly, the bridgehead bromine atom was completely stable under these more weakly acidic conditions.[28] As these reactions reveal, with the strongly deactivating ketone functional group, bromine atoms become more difficult to remove just as they were more difficult to introduce with a carbonyl group in the substrate.

Since we had previously succeeded in converting **6** to **8** with Ag_2SO_4 in concentrated H_2SO_4 at 80 °C (Scheme 1), we used these same conditions in an attempt to hydrolyze **13** to **2**. However, this reaction led to skeletal rearrangement to produce protoadamantane-4,10-dione (**14**)[29] instead of the desired product (Scheme 3). One plausible mechanism to account for the formation of **14** is by a semipinacol-type rearrangement[30] of an intermediate 6-adamantyl carbocation. The structure of diketone **14** was strongly suggested by ten signals in the $^{13}C\{^1H\}$ NMR spectrum including two downfield signals at 212.1 and 212.8 ppm and a molecular formula of $C_{10}H_{12}O_2$ determined by HRMS. This structural assignment was confirmed by key COSY correlations between the 3-H methine hydrogen and its vicinal hydrogen partners on C-2 and C-8 and HMBC correlations between 3-H and C-4, 1-H and C-3, H-6 and C-4, and one of the C-5 methylene hydrogens and C-10.

We then postulated that reducing the ketone functional group of **13** to an alcohol (**15**) (or alcohol derivative) could improve the



Scheme 2. Rearrangement/bromination of **9** to form **10**–**12**.

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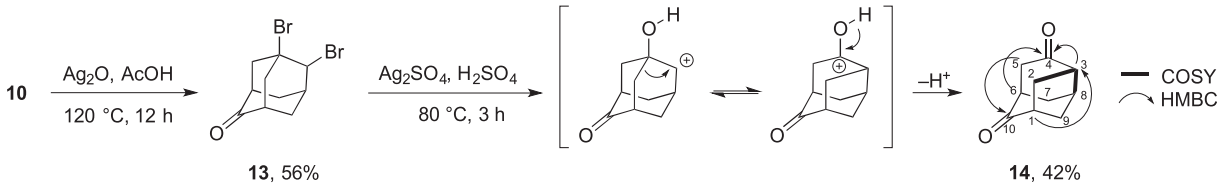
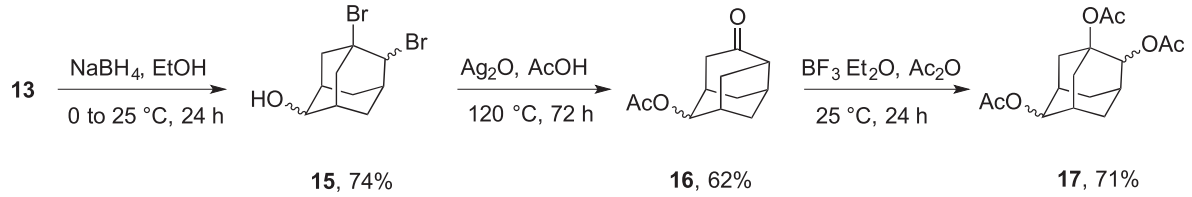


Scheme 3. Selective solvolysis of **10** to **13** and semipinacol rearrangement of **13** to **14**.



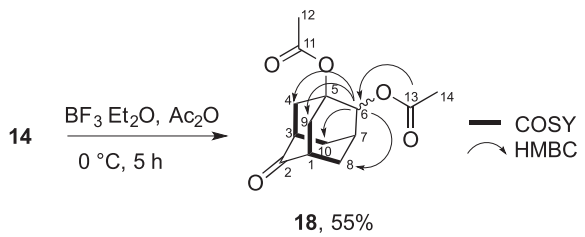
Scheme 4. Reduction of **13** to **15**, semipinacol rearrangement of **15** to **16**, and protoadamantane-adamantane rearrangement of **16** to **17.**

reactivity of the C-6 C-Br bond for substitution reactions. When **15** (mixture of diasteromers) was treated with Ag_2O in AcOH at 110–120 °C (conditions under which **13** was stable), the semipinacol rearrangement product 10-acetoxyprotoadamantan-4-one (**16**) was formed (Scheme 4). Although this was not the desired 1,2,6-triacetoxyadamantane (**17**), the formation of **16** implied that the proposed strategy was working – that is, the C-Br bonds of **15** were sufficiently reactive for substitution reactions using Ag_2O in AcOH. Since protoadamantan-4-one rearranges to 1,2-diacetoxyadamantane with BF_3 Et_2O in acetic anhydride at rt,[31] we were pleased that exposure of **16** to these same conditions afforded **17** (mixture of diastereomers) as the only product in 71% yield.

Heartened by the successful conversion of **16** to **17**, we revisited our earlier but unsuccessful attempts to coax dione **14** to undergo a parallel protoadamantane-adamantane rearrangement. The key was to lower the reaction temperature; exposure of **14** to BF_3 Et_2O in acetic anhydride at 0 °C for 5 h with quenching at 0 °C formed the desired rearrangement product **18** in 55% yield (Scheme 5). The structure of the racemic 5,6-diacetoxyadamantan-2-one **18** was suggested by fourteen signals in the $^{13}C\{^1H\}$ NMR including three downfield signals at 170.13, 170.15, and 214.1 ppm and a molecular formula of $C_{14}H_{18}O_5$ determined by HRMS. This structural assignment was consistent with COSY correlations between 1-H and and its vicinal hydrogen partners on C-8 and C-9, and between 3-H and its vicinal hydrogen partners on C-4 and C-10. HMBC correlations between 6-H and C-13, and between methylene carbon C-4, C-8, C-9, and C-10 hydrogen atoms and C-6 added further evidence for the structural assignment of **18**.[32]

3. Conclusion

In summary, we synthesized a number of new polybrominated adamantanes by rearrangements/bromination of 2,2,6,6-tetrabromoadamantane (**9**) under Friedel-Crafts conditions. We also isolated protoadamantane-4,10-dione (**14**), 10-acetoxyprotoadamantan-4-one (**16**), 1,2,6-triacetoxyadamantane (**17**) and 5,6-diacetoxyadamantan-2-one (**18**) by semipinacol and protoadamantane-adamantane rearrangements. This work may open up new pathways for the synthesis of 1,2,6-trisubstituted adamantanes.



Scheme 5. Protoadamantane-adamantane rearrangement of **14** to **18.**

4. Experimental

4.1. General experimental details

Melting points are uncorrected. 1D ^1H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer using $CDCl_3$ (**6**, **7**, **9**–**18**) D_2O (**8**), or DMSO-d_6 (**8**) as solvents. 2D NMR spectra for **14** and **18** were obtained on a 400 MHz spectrometer using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^1H and $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.7 ppm) for ^{13}C NMR. Peak multiplicites are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). EI GC-MS data were obtained using a quadrapole mass spectrometer with 30 m DB-5 type columns and a He flow rate of 1 mL/min. Silica gel (sg) particle size 40–63 μm was used for all flash column chromatography. Reported reaction temperatures are those of the oil bath.

4.2. 1,3,6-Tribromoadamantane (*6*)

Iron powder (5.0 g, 89.3 mmol) was added at 0 °C to bromine (25 mL, 78.0 g, 490 mmol) and the resulting mixture was stirred for 30 min at 0 °C. Then **7** (8.0 g, 27.2 mmol) was added in portions and the reaction mixture was refluxed overnight before pouring on a mixture of 1 M HCl and ice. The resulting suspension was treated with Na_2SO_3 and filtered to give the crude product as a yellow solid. Purification by crystallization from EtOH afforded **6** (7.1 g, 70%) as a colorless solid. mp 169–170 °C, lit.[1] mp 169–170 °C; ^1H NMR ($CDCl_3$) δ 2.16 (d, J = 12.5 Hz, 2H), 2.34–2.48 (m, 6H), 2.88 (s, 2H), 2.92 (d, J = 13.0 Hz, 2H), 4.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 41.0, 42.2, 47.3, 55.1, 58.2, 59.0, 59.4.

4.3. 2,2-Dibromoadamantane (*7*)

A mixture of 2-adamantanone (5.0 g, 30 mmol) and thionyl

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bromide (10 mL, 26.8 g, 129 mmol) was stirred at rt for 12 h. The excess thionyl bromide was removed in vacuo and the residue was diluted with ice water. The solid was collected by filtration to afford **7** as pale yellow solid (9.7 g, 99%). mp 163–164 °C, lit.[2] mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 1.74–1.84 (m, 6H), 1.87–1.95 (m, 2H), 2.50–2.63 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 26.5, 35.4, 38.9, 46.8, 85.9.

4.4. 1,3,6-Trihydroxyadamantane (*8*).[1]

To a mixture of **6** (5.0 g, 13.4 mmol) and silver sulfate (5.0 g, 16.0 mmol) at rt was added concentrated sulfuric acid (10 mL). The reaction mixture was heated at 80 °C for 3 h, cooled to rt, filtered and the solid was washed with water. The filtrate was neutralized with solid KOH and filtered, and the solid was washed with EtOH. The filtrate was concentrated in vacuo and then purified by silica gel chromatography with an EtOAc eluant to provide the **8** as a white solid (1.7 g, 69%). mp 272–273 °C dec.; ^{1}H NMR (D_2O) δ 1.40 (d, J = 12.5 Hz, 2H), 1.56–1.70 (m, 4H), 1.66 (s, 2H), 1.88 (d, J = 12.0 Hz, 2H), 2.13 (s, 2H), 3.73 (s, 1H); ^{1}H NMR (DMSO-d_6) δ 1.15 (d, J = 11.0 Hz, 2H), 1.36–1.52 (m, 4H), 1.48 (s, 2H), 1.86 (d, J = 11.0 Hz, 2H), 1.90 (s, 2H), 3.46 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.9, 38.2, 42.6, 53.8, 68.3, 68.4, 70.5.

4.5. 2,2,6,6-Tetrabromoadamantane (*9*)

A mixture of adamantane-2,6-dione (**4**) (1.0 g, 6.10 mmol) and thionyl bromide (2 mL, 1.12 g, 54 mmol) was refluxed at 80 °C for 12 h. The excess thionyl bromide was removed in vacuo and the residue was diluted with ice water and then filtered to afford **9** as pale yellow solid (1.98 g, 72%). mp 134–135 °C. ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 4H), 2.59 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 32.5, 44.7, 82.6. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{12}^{79}Br_4$ 447.7672; Found 447.7678.

4.6. 1,2,6,6-Tetrabromoadamantane (*10*) and 1,2,2,6,6-pentabromoadamantane (*11*)

Tetrabromoadamantane **9** (2.0 g, 2.12 mmol) was added to a mixture of $AlBr_3$ (2.0 g, 7.5 mmol) and bromine (10 mL, 31.2 g, 195 mmol) at 0 °C. The resulting reaction mixture was heated at 40–50 °C for 48 h (monitored by GC-MS until starting material disappeared) and then cooled to rt. The reaction mixture was quenched with ice water, treated with saturated aq. Na_2SO_3, and then filtered to give a mixture of **10** and **11**. Crystallization of the crude product from EtOH afforded pure **11** (0.60 g, 26%). mp 139–140 °C. ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 2H), 2.61 (d, J = 14.5 Hz, 2H), 2.67 (d, J = 14.5 Hz, 2H), 2.85 (s, 1H), 2.96 (d, J = 13.5 Hz, 2H), 3.19 (d, J = 13.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.48, 42.3, 47.01, 48.7, 66.9, 78.7, 84.7. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{11}^{79}Br_4^{81}Br$ 527.6757; Found 527.6756. The residue from the mother liquor was purified by sg chromatography (EtOAc-hexanes) to afford **10** as white solid (0.63 g, 31.5%). mp 137–138 °C. ^{1}H NMR ($CDCl_3$) δ 1.93 (dd, J = 14.0, 2.5 Hz, 1H), 2.34–2.53 (m, 4H), 2.55 (s, 1H), 2.63 (s, 1H), 2.70–2.82 (m, 2H), 2.97 (dd, J = 13.0, 1.5 Hz, 1H), 3.47 (dt, J = 13.5, 3.0 Hz, 1H), 4.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 35.0, 37.3, 39.8, 46.3, 48.9, 49.2, 61.0, 67.1, 78.5. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{12}^{79}Br_4$ 447.7672; Found 447.7684.

4.7. 1,2,6,6-Tetrabromoadamantane (*10*) and 1,2,5,6-tetrabromoadamantane (*12*)

Tetrabromoadamantane **9** (2.0 g, 2.12 mmol) was added to a mixture of $AlBr_3$ (1.0 g, 3.75 mmol) and bromine (10 mL, 31.2 g, 195 mmol) at 0 °C. The reaction mixture was heated at 50–60 °C for 24 h (monitored by GC-MS until starting material disappeared) and then cooled to rt. At this time, GC-MS data indicated a 79:17:4 ratio of **10**:**12**:unidentified tetrabromoadamantane isomers. The reaction mixture was quenched with ice water, treated with saturated aq. Na_2SO_3, and filtered to give 1.5 g of a crude product. Crystallization of the latter from EtOH afforded **10** (1.08 g, 54%). The residue from the mother liquor was purified by sg chromatography (EtOAc-hexanes) to afford **12** (0.20 g, 10%) as a pale yellow solid. mp 184–185 °C. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 2H), 2.29 (d, J = 14.0 Hz, 2H), 2.56 (d, J = 2.5 Hz, 2H), 3.11 (s, 2H), 3.26 (d, J = 13.5 Hz, 2H), 4.58 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 36.6, 41.3, 42.1, 46.6, 61.5, 63.8. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{12}^{79}Br_4$ 447.7672; Found 447.7687.

4.8. 5,6-Dibromo-2-adamantanone (*13*)

A mixture of **10** (2.63 g, 2.21 mmol), silver oxide (2.20 g, 9.50 mmol) and acetic acid (30 mL) was heated at 120 °C for 12 h. The reaction mixture was cooled to rt, filtered and the resulting solid was washed with CH_2Cl_2 (20 mL). The filtrate was concentrated in vacuo to afford **13** as white solid (1.01 g, 56%). mp 183–184 °C. ^{1}H NMR ($CDCl_3$) δ 1.93 (d, J = 12.5 Hz, 1H), 2.16–2.28 (m, 2H), 2.41 (d, J = 13.0 Hz, 1H), 2.54–2.72 (m, 4H), 2.78 (dd, J = 13.5, 3.0 Hz, 1H), 2.94 (d, J = 11.0 Hz, 1H), 3.05 (dt, J = 13.5, 3.0 Hz, 1H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.7, 38.5, 38.6, 42.8, 47.9, 48.1, 49.5, 61.1, 65.2, 212.8. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{12}^{79}Br_2O$ 305.9255; Found 305.9265.

4.9. Protoadamantane-4,10-dione (*14*)

A mixture of **13** (1.00 g, 3.25 mmol), silver sulfate (2.20 g, 7.06 mmol) and concentrated sulfuric acid (6 mL) was heated at 0 °C for 3 h and then cooled to rt. The reaction mixture was diluted with THF (30 mL) and neutralized with solid potassium carbonate. The solid was removed by filtration and rinsed with THF. The filtrate was then concentrated in vacuo. Purification of the residue by sg chromatography (EtOAc) afforded **14** (0.22 g, 42%) as a white solid. mp 222–223 °C. ^{1}H NMR ($CDCl_3$) δ 1.75–1.83 (m, 1H), 1.88–2.25 (m, 5H), 2.38–2.48 (m, 1H), 2.58–2.66 (m, 1H), 2.80 (s, 1H), 2.89 (s, 1H), 3.00 (s, 1H), 3.06 (t, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.1, 35.2, 35.9, 40.9, 41.1, 45.1, 49.6, 52.4, 212.0, 212.7. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{12}O_2$ 164.0837; Found 164.0840.

4.10. 2-Hydroxy-5,6-dibromoadamane (*15*)

$NaBH_4$ (0.20 g, 5.26 mmol) was added slowly to a solution of **13** (0.8 g, 2.60 mmol) in EtOH (20 mL) at 0 °C. The resulting mixture was stirred at rt for 24 h and then quenched with water (10 mL) and 1 M aq. NaOH (5 mL). The mixture was concentrated under reduced pressure to about 15 mL and then filtered to afford **15** (mixture of diastereomers) as a white solid (0.60 g, 74%). mp 147–149 °C. ^{1}H NMR ($CDCl_3$) δ 1.55–2.55 (m, 10H), 2.59 (d, J = 13.0 Hz, 0.3H), 2.69 (d, J = 13.5 Hz, 0.7H), 2.86 (dt, J = 13.5, 3.5 Hz, 0.7H), 3.05 (dt, J = 13.0, 3.5 Hz, 0.3H), 3.87 (s, 0.3H), 3.97 (s, 0.7H), 4.65 (s, 0.3H), 4.68 (s, 0.7H); ^{13}C NMR ($CDCl_3$) δ 23.6, 28.8, 31.1, 35.7, 36.5, 37.2, 37.6, 37.8, 38.1, 38.3, 39.1, 41.6, 43.4, 48.1, 64.0, 65.0, 67.6, 67.7, 71.7, 72.3. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{14}^{79}Br_2O$ 307.9411; Found 307.9423.

4.11. 10-Acetoxyprotoadamantan-4-one (*16*)

A mixture of **15** (0.50 g, 1.61 mmol), silver oxide (1.00 g, 4.32 mmol) and AcOH (10 mL) was heated at 120 °C for 36 h, cooled to rt, filtered and the resulting solid was washed with CH_2Cl_2. The filtrate was then concentrated in vacuo to afford a residue that was purified by sg chromatography (EtOAc-hexanes) to afford **16**

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(mixture of diastereomers) as a white solid (0.21 g, 62%). mp 85–87 °C. 1H NMR ($CDCl_3$) δ 1.42–1.49 (m, 0.4H), 1.56–1.66 (m, 1H), 1.68–1.74 (m, 1.2H), 1.76–2.12 (m, 4H), 2.10 (s, 3H), 1.15–2.21 (m, 0.4H), 2.26–2.34 (m, 0.4H), 2.44–2.52 (m, 1H), 2.53–2.58 (m, 0.4H), 2.60–2.68 (m, 1.6H), 2.71–2.80 (m, 1H), 2.86–2.94 (m, 0.6H), 4.91 (s, 0.4H), 5.09 (t, J = 2.5 Hz, 0.6H); ^{13}C NMR ($CDCl_3$) δ 21.26, 21.34, 31.1, 32.4, 32.9, 33.0, 33.5, 34.2, 35.97, 36.02, 36.4, 37.7, 39.5, 40.6, 41.4, 41.6, 49.6, 50.2, 74.6, 170.1, 170.2, 214.5, 215.0. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{16}O_3$ 208.1099; Found 208.1105.

4.12. 1,2,6-Triacetoxyadamantane (**17**)

To a stirred mixture of **16** (0.21 g, 1.01 mmol) and acetic anhydride (5 mL, 5.4 g, 53 mmol) was added boron trifluoride etherate (0.15 mL, 1.20 mmol). The resulting mixture was stirred at rt for 24 h and then quenched with ice water (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford **17** (mixture of diastereomers) as a pale yellow oil (0.22 g, 71%). ^{1}H NMR ($CDCl_3$) δ 1.50 (d, J = 13.5 Hz, 0.6H), 1.64 (d, J = 13.0 Hz, 0.4H), 1.78 (m, 1.4H), 1.948 (s, 1.2H), 1.953 (s, 1.2H), 2.09 (s, 1.8H), 2.10 (s, 3H), 2.23 (s, 1.8H), 1.88–2.46 (m, 8.0H), 2.50 (d, J = 13.0 Hz, 0.6H), 4.78 (s, 0.6H), 4.92 (s, 0.4H), 5.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.1, 22.05, 22.10, 24.7, 29.0, 29.3, 30.8, 32.5, 32.6, 32.8, 33.1, 33.4, 33.5, 33.68, 33.72, 34.5, 37.2, 74.1, 74.5, 74.8, 75.2, 78.1, 78.5, 169.69, 169.71, 169.77, 169.80, 170.13, 170.15. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{22}O_6Na$ 333.1314; Found 333.1321.

4.13. 5,6-Diacetoxyadamantan-2-one (**18**)

To a stirred mixture of **14** (0.18 g, 1.10 mmol) and acetic anhydride (5 mL, 5.4 g, 53 mmol) at 0 °C was added boron trifluoride etherate (0.15 mL, 1.20 mmol). The resulting mixture was stirred at 0 °C for 5 h and then quenched with ice water (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by sg chromatography (EtOAc-hexanes) to afford **18** as a colorless oil (0.16 g, 55%). ^{1}H NMR ($CDCl_3$) δ 1.73–1.80 (m, 1H), 1.97 (s, 3H), 1.99–2.06 (m, 1H), 2.08–2.20 (m, 1H), 2.15 (s, 3H), 2.26–2.33 (m, 1H), 2.34–2.48 (m, 3H), 2.50–2.57 (m, 1H), 2.57–2.70 (m, 3H), 5.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.05, 22.07, 32.40, 33.50, 36.45, 36.65, 38.91, 45.81, 45.96, 74.01, 77.52, 169.79, 169.81, 214.14. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{18}O_5Na$ 289.1052; Found 289.1052.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.04.006.

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24. Similar reactions with aluminum bromide in other solvents such as dibromomethane and acetonitrile led to conversion of the geminal dibromide substructures of 9 to the corresponding ketones without the desired bromine atom migrations.
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