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A FACILE SYNTHESIS OF 7-METHYLENEBICYCLO-[3.3.1]NONAN-3-ONE AND ITS TRANSFORMATION LEADING TO THE NOVEL TRICYCLIC SYSTEM, PROTOADAMANTANE

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ABSTRACT: A practical synthesis of 7-methylenebicyclo[3.3.1]nonan-3-one **2** by the fragmentation of 1,3-adamantanediol **8**, which was prepared effectively by the ruthenium-catalized oxyfunctionalization of 1-adamantanol **7**, is described. Characteristic transannular cyclization of **2** leading to a novel tricyclic system, 1-hydroxy-4-protoadamantanone **9**, *via* the corresponding *exo*-epoxide **10** is also presented.

The selective oxyfunctionalization of "unactivated" C-H bonds of saturated hydrocarbons continues to be a subject of great topical concern.[1] In particular, methods making it possible to achieve the functionalization of adamantane **1** are relevant, since its derivatives are of interest as energetic materials and

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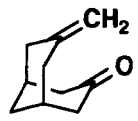
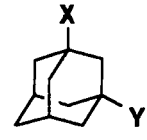
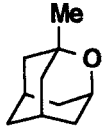
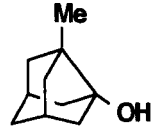
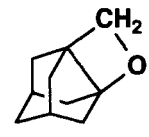
pharmaceuticals.[2] A variety of methods either directly with oxygen or with other oxidizing reagents has been developed.[3]











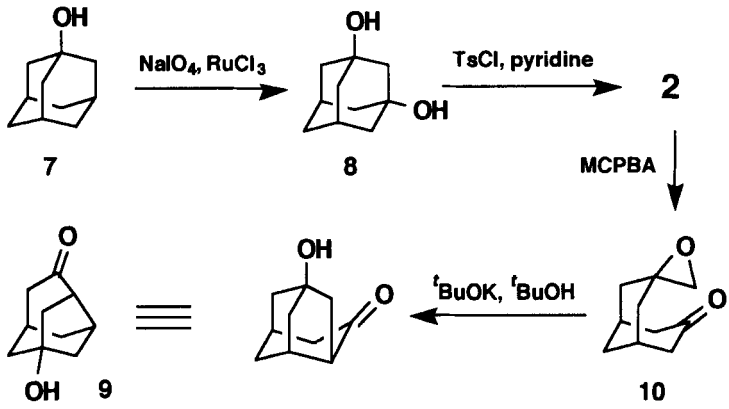
On the other hand, 7-methylenebicyclo[3.3.1]nonan-3-one **2**[4] is known as a versatile intermediate for the synthesis of a variety of functionalized adamantanes **3**,[5] and also to display characteristic reactivities based on its two faced sp^2-type functional groups, *i.e.*, *exo*-methylene and carbonyl moieties, and much have been known about its transannular reactions; hydride attacks the carbonyl group to give oxaadamantane **4**:[6] reaction under radical conditions yields noradamantane **5**:[7] photolysis of **2** results in the formation of an oxetane **6**[8] in good yield. The intensive exploratory studies on the intramolecular orbital interaction between these two π-orbitals,[9] and derivatization to other useful substances of the system have also been reported.[10]

We describe here an application of ruthenium-catalized oxyfunctionalization developed by Tenaglia[1c] to the selective transformation of 1-adamantanol **7** to 1,3-adamantanediol **8**, the Grob fragmentation of which afforded effectively the enone **2** in good yield. Additional characteristic transannular cyclization of **2** leading to a compound of the novel tricyclic skeleton, 1-hydroxyprotoadamantan-4-one **9**, is also presented.

According to the protocol described by Tenaglia,[1c] adamantanol **7** was treated with sodium metaperiodate in the presence of ruthenium trichloride to afford diol **8** in 92% yield. Attempts to convert **1** directly to the diol **8** were found less effective;[11] affording the mixture with monool **7**, diol **8** and triol.

Diol **8** was then treated with *p*-toluenesulfonyl chloride in pyridine to give the desired enone **2** in 88% yield, the physical and spectral properties of which were completely in accord with those of the authentic specimen obtained *via* the alternative route.[4] Thus, concise synthetic method of enone **2** was established.

The conversion of **2** to tricyclic ketol **9** has been achieved in the following manner. Epoxidation of **2** with *m*-chloroperbenzoic acid (MCPBA) afforded an *exo*-epoxide **10**[8b,12] quantitatively, which was then treated with potassium *t*-butoxide to give ketol **9** in 90% yield. The MS spectrum showed the molecular-ion peak at *m/z* 166 (23%) and absorptions due to the hydroxy and carbonyl groups were observed at 3423 and



1706 cm^{-1}, respectively, in its IR spectrum. The ^{13}C-NMR spectrum showed ten signals involving those at δ 216.1 and δ 77.8, due to carbonyl and *tert*-alcoholic carbons, respectively, supporting the asymmetric structure.

We previously developed a facile synthetic route to 4-protoadamantane[13] starting from 2-adamantanone.[14] This is a practical alternative for the construction of the

protoadamantane skeleton, and would provide with a new route to hardly obtainable trisubstituted adamantanes.

EXPERIMENTAL

Melting points were taken on a Yanagimoto MP-3S micromelting point apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-435 grating infrared spectrophotometer. NMR spectra were recorded on either a JEOL JNM-GSX 270 (270 MHz ^{1}H, 67.5 MHz ^{13}C) or a JEOL JNM-GSX 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer. All the NMR spectra were taken for $CDCl_3$ solutions with tetramethylsilane as internal standard, and coupling constants (J) are given in hertz (Hz). Low-resolution and high-resolution mass spectra (electron impact) were recorded on either a Shimadzu QP 1000EX or a JEOL JMS-HX 100 spectrometer. All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

1,3-Adamantanediol 8. A mixture of 1-adamantanol **7** (5.9 g, 33 mmol), sodium metaperiodate (16.0 g, 74.8 mmol), ruthenium chloride hydrate (160 mg, 0.66 mmol), carbon tetrachloride (20 ml), acetonitrile (30 ml) and water (30 ml) was stirred vigorously at 60 °C for 8 h After being cooled, the reaction mixture was poured into aq. sodium thiosulfate–sodium hydrogen carbonate, and extracted with chloroform. The extract was washed with brine, and evaporated to give 5.28 g of a colorless solid, which, on recrystallization from a mixture of methanol and hexane, gave 5.1 g (92%) of **8** as colorless prisms, mp 255—256 °C (lit.[15] 256—258 °C). The spectral data were in accord with those reported. Formation of a small amount of triol was detected by GC-MS analysis.

Dihydroxylation of Adamantane 1. Adamantane **1** (500 mg, 3.7 mmol) was treated with a mixture of sodium metaperiodate (2.3 g, 11.0 mmol) and ruthenium

chloride hydrate (18 mg, 0.07 mmol) in the same manner as described for the oxidation of 1-adamantanol **7**. The progress of the reaction was followed by GC analysis. This analysis indicated conversion of **1** to **7** (3%), diol **8** (51%) and triol (15%) in 6 h. The formation of a small amount of other oxidized compounds was also detected.

7-Methylenebicyclo[3.3.1]nonan-3-one 4. A mixture of diol **8** (1.5 g, 8.9 mmol), *p*-toluenesulfonyl chloride (2.2 g, 11.6 mmol), benzene (30 ml) and pyridine (10 ml) was stirred at 70 °C for 12 h. The reaction mixture was poured into 10% hydrochloric acid, and extracted with diethyl ether. The extract was washed successively with aq. sodium hydrogen carbonate and brine, and evaporated to give 1.8 g of a colorless solid, which, on recrystallization from a mixture of ethanol and *n*-hexane, gave 1.18 (88%) g of enone **2** as colorless needles, mp 160—162 °C (lit.[4] 160—164 °C, lit.[10], 157—158 °C). The spectral data were in accord with those reported.

7-Methylenebicyclo[3.3.1]nonan-3-one 7-*exo* Epoxide 10. A mixture of enone **2** (300 mg, 2.0 mmol), MCPBA (800 mg, 4.6 mmol) and dichloromethane (20 ml) was stirred at room temperature for 4 h. The reaction mixture was washed successively with aq. sodium thiosulfate–sodium hydrogen carbonate and brine, and evaporated to give 331 mg of a colorless solid, which was used in the next step without purification. Analytical sample of **10** was obtained as colorless needles by recrystallization from benzene, mp 257—259 °C (lit.,[8b] 258—260 °C). The spectral data were in accord with those reported.

1-Hydroxy-4-protoadamantanone 9. A mixture of epoxide **10** (90 mg, 0.54 mmol), potassium *t*-butoxide (73 mg, 0.65 mmol) and *t*-butanol (10 ml) was stirred at 55 °C for 4 h. The reaction mixture was poured into ice-cooled water (10 ml), and neutralized with 10% hydrochloric acid, and extracted with diethyl ether. The extract was washed successively with aq. sodium hydrogen carbonate and brine, and

evaporated to give 86 mg of a colorless waxy solid, which, on recrystallization from *n*-hexane, gave 81 mg (90%) of **9** as colorless needles, mp 224—226 °C. IR ($CHCl_3$): 3581, 3423, 1706 cm^{-1}. ^1H NMR: δ 1.51 (1H, dm, *J* = 14.0), 1.57 (1H, dd, *J* = 11.0, 2.5), 1.61 (1H, dddd, *J* = 13.5, 4.5, 3.0, 1.5), 1.66 (1H, br s, exchangeable with D_2O), 1.82 (1H, ddd,*J* = 13.0, 2.5, 1.5), 1.96 (1H, dddd, *J* = 13.0, 3.5, 2.0, 2.0), 2.03 (1H, ddd, *J* = 13.0, 11.5, 3.0), 2.03—2.08 (1H, m), 2.14 (1H, dddd, *J* = 13.0, 5.5, 3.0, 1.5), 2.36 (1H, dddd, *J* = 18.5, 7.5, 1.5, 1.5), 2.43—2.48 (1H, m), 2.62 (1H, dd, *J* = 18.5, 3.0), 2.62—2.68 (1H, m) 2.81 (1H, dddd, *J* = 11.5, 8.0, 1.5, 1.5). ^{13}C NMR: δ 29.5 (d), 33.8 (t), 36.2 (d), 42.0 (t), 44.8 (t), 45.3 (t), 46.8 (t), 48.8 (d), 77.8 (s), 216.1 (S). MS *m/z* (%): 166 (M^+, 23), 124 (26), 95 (100), 82 (26). HRMS *m/z*: 166.0993 ($C_{10}H_{14}O_2$ requires 166.0994).

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