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Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonanes

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Supporting Information

ABSTRACT: Trifluoromethanesulfonic acid and other electrophiles promote formation of the adamantanone core from the readily accessible 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one **2**. Because adamantyl cation **3** can be trapped by a range of nucleophiles, including aromatic and heteroaromatic rings, alcohol, nitriles, and halides, access to a wide variety of functionality at the newly formed tertiary position is provided.

The diamond-like structure of adamantane has fascinated chemists since its discovery in petroleum in 1933.[1] Studies have shown that adamantane is the most stable of the $C_{10}H_{16}$ isomers and can be easily prepared by the Lewis acid promoted rearrangement of other $C_{10}H_{16}$ species, e.g., tetrahydrodicyclopentadiene.[2] The first instance of the adamantane structure in drugs involved 1-aminoadamantane, amantadine, a selective antiviral agent, which was used against influenza upon its approval in 1966.[3] Since then, a number of 1-aminoadamantanes have been synthesized, and one, 3,5-dimethyl-1-amino-adamantane, memantine, has been approved for the treatment of Alzheimer's disease.[4] However, the biological mechanism of action of the adamantane derivatives is still unclear.

For a project aimed at the total synthesis of rugulosone, **1**[5] (Figure 1), we prepared 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one **2** by the very efficient quadruple alkylation of 3-pentanone with 1,1-bis(chloromethyl)ethylene, a reaction that proceeded in 90% yield.[6] We were interested to see if this bis(methylene) system could be used to efficiently construct various substituted adamantanones, which might serve as precursors to the corresponding adamantanes. The ability to construct a large variety of substituted adamantanones in a highly efficient and simple manner could allow for more rapid testing of derivatives to study both the biological activity and the mechanism of action of this class of compounds.

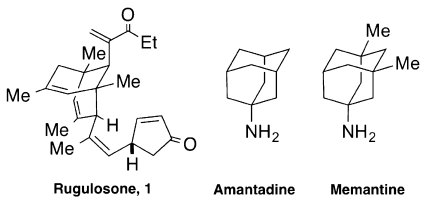

Figure 1. Rugulosone, amantadine, and memantine structures.

The Friedel–Crafts alkylation of benzenoid aromatic rings with the adamantane core has been reported occasionally, but harsh conditions, including high temperature, long reaction times, and high pressure mercury lamps, were often employed.[7] In many cases, a multistep procedure is involved in which a 1-haloadamantane is first formed and then used to generate a carbocation at the tertiary position, which is subsequently trapped by a nucleophile. Although there is one example of the cyclization of the simple unsubstituted 3,7-dimethylenebicyclo[3.3.1]nonane in anisole as solvent giving the aryl adamantane,[8] to our knowledge, no systematic study of the Friedel–Crafts alkylation of adamantyl cations generated by this type of cyclization has been carried out. This limited reaction scope therefore prompted us to investigate a more efficient way of rapidly constructing substituted adamantanones.

Synthesis of Adamantanones from 2. We now present a new and efficient method for the construction of adamantan-2-ones substituted at the 7-position with aryl, heteroaryl, alkoxy, amido, and alkynyl groups, starting from the 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one core **2**. We envisioned forming the adamantyl cation with acid, followed by trapping with a nucleophile to obtain the tetrasubstituted adamantanone core. Consequently, we screened various acidic conditions for the formation of the desired product, 1,3,5-trimethyl-7-phenyladamantan-2-one **4a**, from **2** (Table 1).

Without the presence of an added nucleophile, the cation can be quenched by the benzene solvent. Thus, treatment of the diene **2** with trimethylsilyl triflate in benzene afforded the 7-phenyl-substituted adamantanone **4a** in 65% yield. Other protic and Lewis acids produced the same product **4a** in moderate to good yields, with trifluoromethanesulfonic acid, triflic acid, being the best of those tested, giving the desired product in

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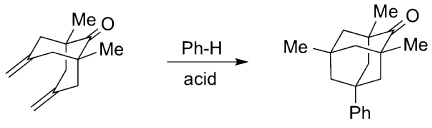
Table 1. Conversion of Diene 2 to Trimethylphenyladamantanone 4a[a]



2 4a

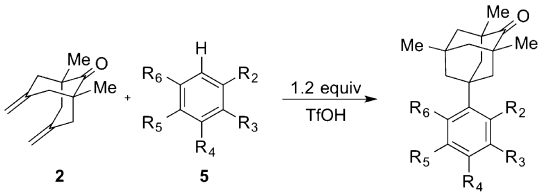
entry	acid	yield (%)
1	TMSOTf	65
2	$BF_3{\cdot}OEt_2$	78
3	$AlCl_3$	47
4	H_2SO_4	21
5	TFA	59
6	TfOH	90
7	$Cu(OTf)_2$	0
8	None	0

[a]Reaction conditions: **2** (1.05 mmol), acid (1.2 equiv), benzene (5 mL), Ar, 3 h.

90% yield. Some Lewis acid catalysts, e.g., cupric triflate, did not provide any product but only returned starting material.

Substrate Scope. Next, we investigated the substrate scope of our reaction using the same mild conditions and short reaction times (Table 2). Various aromatic rings with electron-

Table 2. Reaction of 2 with Aromatic Rings 5 To Give 4[a]



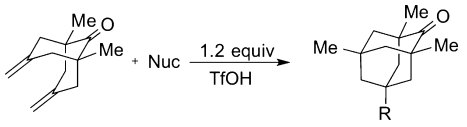
2 5 4

entry	Nu	R_2	R_3	R_4	R_5	R_6	yield (%)
1[b]	**5a**	H	H	H	H	H	**4a**, 90
2[b]	**5b**	H	H	Me	H	H	**4b**, 57
		Me	H	H	H	H	**4b′**, 19
3[b]	**5c**	Me	H	H	Me	H	**4c**, 47
4	**5d**	OMe	H	OMe	H	H	**4d**, 47
5	**5e**	OMe	H	OMe	H	OMe	**4e**, 36

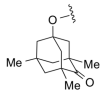
[a]Reaction conditions: **2** (1.05 mmol), TfOH (1.2 equiv), nucleophile (5.0 equiv), CH_2Cl_2 (5 mL), Ar, 3 h, unless otherwise specified. [b]Reactions are performed with nucleophile as solvent.

donating groups **5a−e** reacted as good nucleophiles to produce the substituted adamantanones **4a−e** in moderate yields. Thus, toluene **5b** gave a 76% combined yield of a 3:1 mixture of the 4-methyl and 2-methyl products **4b** and **4b′**. *p*-Xylene **5c** gave the expected product **4c** in 47% isolated yield; similarly, *m*-dimethoxybenzene **5d** afforded the expected product **4d** in 47% yield. The more hindered 1,3,5-trimethoxybenzene **5e** gave the expected product **4e** in only 36% yield, perhaps due to the steric hindrance of the only available aromatic position. Again, there have been scattered reports of the trapping of adamantyl cations with benzenoid nucleophiles, but no systematic study has been reported.[9] As far as we can tell, no heterocycles have ever been used to trap an adamantyl cation under these conditions. Therefore, we studied the use of several five-membered heterocyclics in this regard (Table 3). Furan and *N*-methylindole gave very poor results, with a multitude of

Table 3. Reactions of 2 with Nucleophiles To Give 4[a]



2 4

entry	nuc	R	yield (%)
1			**4f**, 33
			**4f′**, 17
2			**4g**, 26
			**4g′**, 21
3[b]	HOMe	OMe	**4h**, 52
4[b]	HOAc	OAc	**4i**, 88
5[c]	H_2O	OH	**4j**, 74
6	$HOCH_2CCH$	$OCH_2C{\equiv}CH$	**4k**, 35
7	HOPh	OPh	**4l**, 36
8	HOTf	OSO_2CF_3	**4m**, trace
			**4n**, trace
9[b]	CH_3CN	NHCOMe	**4o**, 88
10	TMS-C≡C-H	C≡CH	**4p**, 44

[a]Reaction conditions: **2** (1.05 mmol), TfOH (1.2 equiv), nucleophile (5.0 equiv), CH_2Cl_2 (5 mL), unless otherwise specified. [b]Reactions performed with nucleophile as solvent. [c]Conc. H_2SO_4 as solvent.

unidentified products being formed. However, the reaction of **2** in the presence of triflic acid with *N*-methylpyrrole **5f** gave a mixture of the 2- and 3-substituted pyrrole products, **4f** and **4f′**, in yields of 33 and 17%, respectively. The assignment of the structures was based on the pattern of the absorptions in the proton NMR spectrum and matched literature data.[10] In this case, the ratio of the trapping at C2 vs C3 (1.9:1) is somewhat surprising given that the reported ratio of trapping of a *tert*-butyl cation with *N*-methylpyrrole is 1:1.4 (C2/C3).[11] Likewise, reaction of **2** with thiophene **5g** in the presence of triflic acid afforded the 2- and 3-substituted products, **4g** and **4g′**, in a 1.2:1 ratio in yields of 26 and 21%, respectively. The assignment was made by comparing the coupling constants for the three aromatic protons and by analogy to literature data.[12]

In addition to trapping the adamantyl cation, generated from **2** by protonation with triflic acid, with aromatic nucleophiles, we also investigated trapping with other simple nucleophiles. Again, there are reports of such nucleophilic trapping in the literature,[8,13] but no systematic study has been carried out. Thus, we treated the diene **2** with triflic acid in the presence of various nucleophiles, with the results shown in Table 3. Methanol and acetic acid as nucleophilic solvents gave good yields of the expected trapping of the oxygen atom to produce **4h** and **4i** in 52 and 88% yields, respectively. The tertiary alcohol **4j** could also be prepared by treating **2** with conc. sulfuric acid in 74% yield. Propargyl alcohol also trapped on oxygen to give the propargyl ether **4k** in 35% yield. Somewhat surprisingly, phenol gave trapping only on the oxygen atom to give **4l** in 36% yield, with no evidence for trapping on carbon, either C4 or C2, being observed. In the absence of any external

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trapping agent, one obtains trace amounts of the triflate **4m** and the symmetrical ether **4n**. One can also carry out a Ritter reaction, namely, treatment of **2** with triflic acid in acetonitrile as solvent to generate the acetamide **4o** in 88% yield.[14] This trapping would be useful for preparing analogues of memantine. Finally, we could also effect C−C bond formation of a nonaromatic substrate, namely, trimethylsilyl acetylene, to give the acetylene product **4p** in 44% yield.

We also examined the addition of electrophiles other than proton to one of the exocyclic methylenes of **2** with the idea of triggering the cyclization to produce the adamantyl cation, which could then be trapped with simple nucleophiles (Table 4). Reports of such dual addition of electrophiles and

Table 4. Reactions of 2 with Both Electrophiles and Nucleophiles To Give 4

2 **4**

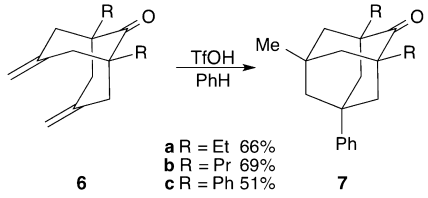
entry	conditions	R_1	R_2	yield (%)
1	NBS, aq. DMSO	Br	OH	**4q**, 66
2	NBS, MeOH	Br	OMe	**4r**, 89
3	Br_2, CH_2Cl_2	Br	Br	**4s**, 88
4	I_2, CH_2Cl_2	I	I	**4t**, 77
5	$Hg(OAc)_2$, MeOH, aq. NaCl	HgCl	OMe	**4u**, 26

nucleophiles to similar dienes have appeared in the literature,[15] but here again no systematic study has been carried out. Thus, treatment of the diene **2** with *N*-bromosuccinimide (NBS) in aqueous DMSO or in methanol gave the bromomethyl alcohol and methyl ether, **4q** and **4r**, in 66 and 89% yields, respectively. Addition of either bromine or iodine to **2** in dichloromethane gave the dihalo products, **4s** and **4t**, in yields of 88 and 77%, respectively.[8,16] Nonhalogenated electrophiles could also be used. Thus, addition of mercuric acetate to **2** in methanol provided the acetoxymercurio ether, which, for ease of isolation, was converted into the chloromercurio ether by addition of NaCl to give **4u** in 26% yield.

We tested the generality of this process by examining the cyclization of other substrates, namely, the three analogues of the dimethyl compound **2** with ethyl, propyl, and phenyl groups adjacent to the ketone. The additional di(exo)-methylene compounds, **6a−c**, were prepared from the corresponding substituted ketones and the bis(chloromethyl)-ethylene.[6] Treatment of all of these three analogues **6a−c** with triflic acid in benzene afforded the expected adamantanone products **7a−c** in good yields (Scheme 1). No attempts at optimization of these yields have been made. Thus, simple alkyl and aryl substituents are well-tolerated.

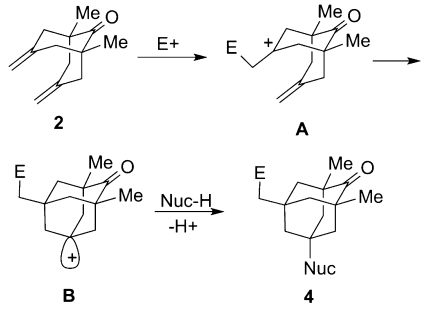
The mechanism of this process (Scheme 2) would involve the addition of an electrophile, E+ (H+, X+), to one of the two identical alkenes of **2** from the exo face to generate the tertiary carbocation **A**. Cyclization of the other alkene on to this carbocation would then generate the adamantyl cation **B**, despite the instability inherent in a nonplanar cation. Attack of the nucleophile on **B**, with loss of a proton, would afford the observed products **4**. Although the formation of adamantyl cations is well-known,[7c,17] they are often formed from adamantyl halides and not from bicyclo[3.3.1]diene systems.

Scheme 1. Cyclization of Analogues 6 To Give Adamantanones 7



6 **7**

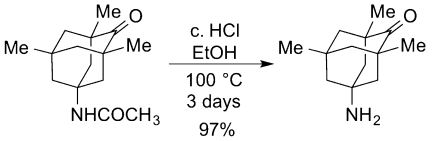
Scheme 2. Mechanism of 2 Forming Adamantane Core 4



2 **A** **B** **4**

We have shown that the acetamide **4o**, obtained from **2** by the Ritter reaction, can be hydrolyzed to the amine **8**, an analogue of memantine, in 97% yield under strongly acidic conditions (Scheme 3), i.e., conc. HCl in ethanol in a sealed tube at 100 °C for 3 days.

Scheme 3. Hydrolysis of 4o To Give Memantine Analogue 8



4o **8**

In summary, we have shown that the readily available 1,5-dimethyl-3,7-dimethylene-bicyclo[3.3.1]nonan-9-one **2** can be easily converted into a wide variety of adamantanone derivatives by treatment with various electrophiles, especially proton, in the presence of a nucleophilic trapping agent. Other analogues, e.g., **6a−c**, also give the corresponding adamantanones **7a−c**.

EXPERIMENTAL SECTION

General. All reactions were carried out under an argon atmosphere unless otherwise specified. Dichloromethane was distilled from calcium hydride under an argon atmosphere. Trifluoromethanesulfonic acid of 99% purity was used. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR spectra were recorded on a high-field NMR spectrometer (at 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad. ^{13}C NMR spectra were recorded on a high-field NMR spectrometer (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift and are reported in parts per million (ppm, δ). Thin-layer chromatography (TLC) was carried out using precoated silica gel sheets (Merck 60 F254). Visual detection was performed using phosphomolybdic acid or iodine. Flash chromatography was performed using SilicaFlash P60 (60 A, 40−63 μm) silica gel with compressed air. High-resolution mass spectrometry

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was taken on a quadrupole mass spectrometer equipped with a DART ion source.

General Procedure for Acid-Promoted Cyclization in Benzene. To a solution of diene **2** (0.200 g, 1.05 mmol) in benzene (5 mL) was added trifluoromethanesulfonic acid (0.111 mL, 1.26 mmol) at 0 °C. The reaction was warmed to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with hexanes (3 × 20 mL), and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the trimethylphenyladamantanone **4a** (0.253 g, 0.94 mmol, 90%) as a light yellow oil.

General Procedure for the Triflic Acid-Promoted Cyclization and Trapping of Nucleophiles. To a solution of diene **2** (0.200 g, 1.05 mmol) in dichloromethane (5 mL) was added *m*-dimethoxybenzene **5d** (0.030 mL, 5.25 mmol) followed by trifluoromethanesulfonic acid (0.111 mL, 1.26 mmol) at 0 °C. The reaction was warmed to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to give a crude light yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the 2,4-dimethoxyphenyladamantanone **4d** (0.162 g, 0.49 mmol, 47%) as a light yellow oil.

General Procedure for the Addition of Various Electrophiles and Subsequent Trapping of Nucleophiles. To a solution of diene **2** (0.100 g, 0.525 mmol) in 1:1 methanol/dichloromethane (6 mL) was added NBS (0.121 g, 0.068 mmol) at 0 °C. The reaction was warmed to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL). The mixture was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to give crude bromomethyl methoxyadamantanone **4r** (0.140 g, 89%) as a light yellow oil.

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-2-one, 2. To a suspension of 60% NaH in mineral oil (0.176 g, 4.40 mmol) (washed three times with hexanes) in toluene (5 mL) was added 3-pentanone (0.086 g, 1.00 mmol) in toluene (2 mL) dropwise. A solution of 1-chloro-2-(chloromethyl)-2-propene (0.254 g, 2.20 mmol) in toluene (2 mL) was added dropwise, and the reaction was refluxed overnight. The solution was then cooled to room temperature and quenched with a saturated solution of NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and washed with brine (20 mL), and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the bicyclononanone **2** (0.171 g, 0.90 mmol, 90%) as a light yellow oil.

5-Hydroxy-1,3,7-trimethyladamantan-2-one, 4j. To a solution of the diene **2** (0.050 g, 0.26 mmol) in DMSO (1 mL) were added conc. H_2SO_4 (1 mL) and water (0.1 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. The solution was quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give hydroxyadamantanone **4j** (0.041 g, 0.20 mmol, 74%) as a light yellow oil.

5-Amino-1,3,7-trimethyladamantan-2-one, 8. To a solution of the acetamide **4o** (0.087 g, 0.35 mmol) and ethanol (2 mL) were added conc. HCl (0.5 mL) and water (0.1 mL) in a sealed tube. The vessel was heated at 100 °C for 3 days. The solution was then cooled to 0 °C and quenched with a saturated solution of $NaHCO_3$ (20 mL). The mixture was extracted with dichloromethane (3 × 20 mL) and washed with brine (20 mL), and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude 5-aminoadamantanone **8** (0.070 g, 0.34 mmol, 97%) as a yellow oil.

1,3,5-Trimethyl-7-phenyladamantan-2-one, 4a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.31 (m, 4H), 7.23 (bt, J = 7.0 Hz, 1H), 1.98 (bd, J = 12 Hz, 2H), 1.88−1.85 (m, 4H), 1.64 (bd, J = 12.5 Hz, 2H), 1.57−1.54 (m, 4H), 1.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5, 147.7, 128.3, 126.2, 124.9, 52.5, 51.5, 48.1, 45.9, 38.4, 32.1, 28.8, 22.6. HRMS (ESI, m/z): 269.1895; calcd for $C_{19}H_{24}OH$ $(M + H)^+$, 269.1905.

1,3,5-Trimethyl-7-(4-methylphenyl)adamantan-2-one, 4b, and 1,3,5-Trimethyl-7-(2-methylphenyl)adamantan-2-one, 4b′. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H), 1.96 (m, 2H), 1.85 (m, 4H), 1.65 (bd, J = 12.5 Hz, 2H), 1.54 (m, 2H), 1.00 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6, 144.7, 135.7, 129.1, 124.8, 52.5, 51.5, 48.1, 45.9, 38.5, 32.1, 28.8, 22.8, 20.9. HRMS (ESI, m/z): 283.2051; calcd for $C_{20}H_{26}OH$ $(M + H)^+$, 283.2062.

5-(2,5-Dimethylphenyl)-1,3,7-trimethyladamantan-2-one, 4c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 2.55 (s, 3H), 2.32 (s, 3H), 2.07 (m, 4H), 1.99 (s, 2H), 1.64 (d, J = 12.0 Hz, 2H), 1.56 (d, J = 12.0 Hz, 2H), 1.03 (s, 6H), 1.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6, 144.1, 135.4, 133.4, 132.7, 127.0, 126.9, 52.4, 49.8, 46.2, 45.9, 39.9, 32.2, 29.0, 23.2, 22.8, 21.2. HRMS (ESI, m/z): 297.2197; calcd for $C_{21}H_{28}OH$ $(M + H)^+$, 297.2218.

1,3,5-Trimethyl-7-(2,4-dimethoxyphenyl)adamantan-2-one, 4d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.44 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.15 (d, J = 11.5 Hz, 2H), 1.97 (d, J = 9 Hz, 2H), 1.55 (m, 6H), 0.98 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 159.4, 159.2, 127.5, 126.9, 103.6, 99.7, 55.2, 54.9, 52.7, 49.2, 45.9, 45.8, 38.4, 32.0, 29.0, 22.8. HRMS (ESI, m/z): 329.2100; calcd for $C_{21}H_{28}O_3H$ $(M + H)^+$, 329.2117.

1,3,5-Trimethyl-7-(2,4,6-trimethoxyphenyl)adamantan-2-one, 4e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (s, 2H), 3.78 (s, 3H), 3.74 (s, 6H), 2.36 (bd, J = 12.5 Hz, 2H), 2.25 (bd, J = 12 Hz, 2H), 2.16 (s, 2H), 1.53 (s, 4H), 0.95 (s, 6H), 0.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.9, 160.5, 158.9, 115.4, 93.1, 55.8, 55.1, 52.5, 50.4, 46.1, 45.8, 41.1, 31.9, 29.3, 23.0. HRMS (ESI, m/z): 359.2210; calcd for $C_{22}H_{30}O_4H$ $(M + H)^+$, 359.2222.

1,3,5-Trimethyl-7-(1-methyl-1*H*-pyrrol-2-yl)adamantan-2-one, 4f, and 1,3,5-Trimethyl-7-(1-methyl-1*H*-pyrrol-3-yl)-adamantan-2-one, 4f′. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (t, J = 2.5 Hz, 1H), 6.48 (t, J = 2.5 Hz, 1.9H) 6.40 (t, J = 2.0 Hz, 1H), 6.04 (t, J = 2.0 Hz, 1H), 6.01 (t, J = 2.5 Hz, 1.9H), 5.94 (t, J = 2 Hz, 1.9H), 3.76 (s, 5.7H), 3.60 (s, 3H), 2.05 (d, J = 12.0 Hz, 4H), 1.95−1.87 (m, 10H), 1.77 (m, 4H), 1.62 (d, J = 12.5 Hz, 4H), 1.60−1.50 (m, 8H), 0.99 (s, 18H), 0.96 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.1, 218.2, 138.0, 132.6, 124.4, 121.6, 116.8, 106.1, 105.9, 105.1, 52.7, 52.4, 49.8, 49.1, 46.5, 45.9, 45.6, 37.2, 36.4, 36.1, 34.6, 32.0, 31.8, 28.8, 28.7, 22.65, 22.60. HRMS (ESI, m/z): 272.2005; calcd for $C_{18}H_{25}NOH$ $(M + H)^+$, 272.2014.

1,3,5-Trimethyl-7-(thiophen-2-yl)adamantan-2-one, 4g, and 1,3,5-Trimethyl-7-(thiophen-3-yl)adaman-tan-2-one, 4g′. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, J = 5.0, 3.0 Hz, 1H), 7.16 (dd, J = 5.0, 1.0 Hz, 1H), 7.07 (dd, J = 5.0, 1.5 Hz, 1H), 6.98 (dd, J = 3.0, 1.5 Hz, 1H), 6.94 (m, 1H), 6.84 (dd, J = 3.5, 1.5 Hz, 1H), 2.02 (d, J = 12.0 Hz, 2H), 1.97 (d, J = 12.0 Hz, 2H), 1.90 (m, 4H), 1.83 (m, 4H), 1.62 (d, J = 12 Hz, 4H), 1.56 (m, 4H), 1.00 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 217.8, 153.8, 149.8, 126.5, 125.6, 125.3, 122.6, 121.2, 118.2, 52.7, 52.5, 52.4, 51.6, 49.7, 48.4, 46.0, 45.9, 38.1, 37.3, 32.3, 32.0, 28.7, 28.5, 22.5, 22.4. HRMS (ESI, m/z): 275.1460; calcd for $C_{17}H_{22}OSH$ $(M + H)^+$, 275.1470.

5-Methoxy-1,3,7-trimethyladamantan-2-one, 4h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 (s, 3H), 1.77 (bd, J = 15 Hz, 2H), 1.68−1.65 (m, 4H), 1.53 (bd, J = 15 Hz, 2H), 1.47−1.43 (m, 2H) 0.98 (s, 3H), 0.97 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 72.5, 52.5, 48.8, 47.7, 46.1, 45.4, 33.5, 28.2, 22.2. HRMS (ESI, m/z): 223.1689; calcd for $C_{14}H_{22}O_2H$ $(M + H)^+$, 223.1698.

3,5,7-Trimethyl-4-oxoadamantan-1-yl Acetate, 4i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13−2.02 (m, 6H), 1.97 (s, 3H), 1.52 (s, 4H), 0.96 (bs, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216 4, 170.1, 79.2, 52.1, 47.7, 46.3, 45.2, 33.8, 28.0, 22.0, 21.9. HRMS (ESI, m/z): 251.1638; calcd for $C_{15}H_{22}O_3H$ $(M + H)^+$, 251.1647.

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5-Hydroxy-1,3,7-trimethyladamantan-2-one, 4j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 (m, 2H), 1.65 (m, 4H), 1.49 (m, 4H), 1.23 (s, 1H), 0.97 (s, 3H), 0.95 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 69.0, 52.3, 51.8, 49.8, 46.4, 33.9, 28.1, 22.1. HRMS (ESI, m/z): 209.1538; calcd for $C_{13}H_{20}O_2H$ $(M + H)^+$, 209.1542.

1,3,5-Trimethyl-7-(prop-2-yn-1-yloxy)adamantan-2-one, 4k. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (d, J = 2.5 Hz, 2H), 2.39 (t, J = 2 Hz, 1H), 1.83 (bd, J = 11 Hz, 2H), 1.73 (s, 2H), 1.75−1.72 (m, 2H), 1.52 (bd, J = 12.5 Hz, 2H), 1.46 (bd, J = 10 Hz, 2H) 0.98 (s, 3H), 0.97 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0, 81.2, 74.4, 73.6, 52.2, 49.8, 48.1, 46.3, 45.9, 33.7, 28.2, 22.2. HRMS (ESI, m/z): 247.1686; calcd for $C_{16}H_{22}O_2H$ $(M + H)^+$, 247.1698.

1,3,5-Trimethyl-7-phenoxyadamantan-2-one, 4l. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (bt, J = 8.5 Hz, 2H), 7.13 (bt, J = 7.5 Hz, 1H), 6.98 (bd, J = 8.5 Hz, 2H), 1.91 (bd, J = 10.5 Hz, 2H), 1.81 (s, 2H), 1.79−1.78 (m, 2H), 1.52 (bd, J = 12.5 Hz, 2H), 1.47−1.44 (m, 2H), 0.98 (s, 3H), 0.97 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0, 153.8, 129.0, 124.7, 124.2, 77.5, 52.3, 49.3, 47.2, 46.4, 33.9, 28.2, 22.2. HRMS (ESI, m/z): 285.1849; calcd for $C_{19}H_{24}O_2H$ $(M + H)^+$, 285.1855.

3,5,7-Trimethyl-4-oxoadamantan-1-yl Trifluoromethanesulfonate, 4m. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (m, 2H), 1.70 (bs, 2H), 1.77 (bd, J = 13.0 Hz, 2H), 1.52 (bd, J = 15.0 Hz, 2H), 1.47 (m, 2H), 0.99 (s, 3H), 0.96 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 69.3, 52.2, 51.5, 49.6, 46.3, 33.9, 27.9, 21.8. GC-MS (EI+): found, 340.1; calcd for $C_{14}H_{19}F_3O_4S$, 340.0.

7,7′-Oxybis(1,3,5-trimethyladamantan-2-one), 4n. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (d, J = 11.5 Hz, 4H), 1.78 (m, 4H), 1.56 (s, 4H), 1.48 (m, 8H), 0.97 (s, 6H), 0.96 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 75.2, 52.3, 52.2, 50.1, 46.6, 33.9, 28.5, 22.4. GC-MS (EI+): found, 398.4; calcd for $C_{26}H_{38}O_3$, 398.3.

***N*-(3,5,7-Trimethyl-4-oxoadamantan-1-yl)acetamide, 4o.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (bs, 1H), 1.97 (s, 4H), 1.94 (s, 2H), 1.90 (s, 3H), 1.51 (s, 4H), 0.94 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.2, 169.8, 52.9, 52.3, 48.5, 45.9, 45.8, 32.7, 28.2, 24.5, 22.2. HRMS (ESI, m/z): 250.1799; calcd for $C_{15}H_{23}NO_2H$ $(M + H)^+$, 250.1807.

5-Ethynyl-1,3,7-trimethyladamantan-2-one, 4p. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 1H), 1.91 (bd, J = 12.5 Hz, 2H), 1.83−1.80 (m, 4H), 1.52−1.47 (m, 4H), 0.95 (s, 6H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1, 89.4, 68.0, 52.2, 50.5, 47.5, 45.5, 31.5, 31.3, 28.5, 22.3. HRMS (ESI, m/z): 217.1581; calcd for $C_{15}H_{21}OH$ $(M + H)^+$, 217.1592.

5-(Bromomethyl)-7-hydroxy-1,3-dimethyladamantan-2-one, 4q. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 (s, 2H), 2.60 (s, 1H), 1.79 (m, 4H), 1.69 (m, 2H), 1.59 (s, 4H), 0.99 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1, 68.8, 51.7, 48.3, 46.1, 45.9, 43.5, 37.7, 22.0. HRMS (ESI, m/z): 287.0628; calcd for $C_{13}H_{19}BrO_2H$ $(M + H)^+$, 287.0647.

5-(Bromomethyl)-7-methoxy-1,3-dimethyladamantan-2-one, 4r. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 (s, 2H), 3.25 (s, 3H), 1.78−1.70 (m, 6H), 1.62−1.56 (m, 4H), 1.00 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 72.5, 49.1, 48.5, 47.7, 45.7, 43.7, 41.9, 37.3, 22.2. HRMS (ESI, m/z): 301.0785; calcd for $C_{14}H_{21}BrO_2H$ $(M + H)^+$, 301.0803.

5-Bromo-7-(bromomethyl)-1,3-dimethyladamantan-2-one, 4s. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 2H), 2.33 (m, 2H), 2.21 (m, 2H), 1.67 (s, 4H), 0.99 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 59.1, 55.5, 49.5, 48.0, 47.6, 42.9, 38.7, 21.8. HRMS (ESI, m/z): 348.9797; calcd for $C_{13}H_{18}Br_2OH$ $(M + H)^+$, 348.9803.

5-Iodo-7-(iodomethyl)-1,3-dimethyladamantan-2-one, 4t. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (s, 2H), 2.52 (s, 2H), 2.51 (d, J = 11.0 Hz, 2H), 2.41 (d, J = 12.5 Hz, 2H), 1.75 (d, J = 12.0 Hz, 2H), 1.68 (d, J = 11.5 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 58.8, 53.7, 49.0, 48.6, 39.9, 37.5, 21.6, 19.1. HRMS (ESI, m/z): 444.9519; calcd for $C_{13}H_{18}I_2OH$ $(M + H)^+$, 444.9525.

7-Methoxy-3,5-dimethyl-4-oxoadamantan-1-yl)methyl)-mercury(II) chloride, 4u. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 3H), 2.05 (s, 2H), 1.67 (m, 4H), 1.55 (m, 4H), 1.44 (m, 4H), 0.89 (s, 6H).

1,3-Diethyl-5-methyl-7-phenyladamantan-2-one, 7a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (bd, J = 8.4 Hz, 2H), 7.34 (bt, J = 7.6 Hz, 2H), 7.22 (bt, J = 6.8 Hz, 1H), 1.94 (bd, J = 12 Hz, 2H), 1.87 (s, 2H), 1.84 (bd, J = 12.4 Hz, 2H), 1.56 (m, 4H), 1.47 (qd, J = 7.2, 2.4 Hz, 4H), 1.04 (s, 3H), 0.85 (t, J = 7.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0, 147.9, 128.2, 126.1, 124.8, 49.3, 48.6, 48.55, 48.50, 37.9, 31.6, 29.1, 28.3, 7.8. HRMS (ESI, m/z): 297.2209; calcd for $C_{21}H_{28}OH$ $(M + H)^+$, 297.2218.

5-Methyl-7-phenyl-1,3-dipropyladamantan-2-one, 7b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (bd, J = 8.0 Hz, 2H), 7.34 (bt, J = 7.5 Hz, 2H), 7.23 (bt, J = 7.0 Hz, 1H), 1.95 (bd, J = 12.5 Hz, 2H), 1.86 (s, 2H), 1.85 (d, J = 12 Hz, 2H), 1.60 (d, J = 12.5 Hz, 2H), 1.55 (d, J = 12.5 Hz, 2H), 1.38 (m, 4H), 1.28 (m, 4H), 1.02 (s, 3H), 0.92 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.1, 148.0, 128.4, 126.2, 124.9, 50.0, 49.1, 48.8, 48.6, 38.4, 38.0, 31.8, 29.3, 16.7, 15.0. HRMS (ESI, m/z): 325.2522; calcd for $C_{23}H_{32}OH$ $(M + H)^+$, 325.2531.

5-Methyl-1,3,7-triphenyladamantan-2-one, 7c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.0 Hz, 2H), 7.42−7.20 (m, 13H), 2.81 (d, J = 12.0 Hz, 2H), 2.45 (d, J = 12.5 Hz, 2H), 2.38 (d, J = 12.5 Hz, 2H), 2.09 (d, J = 12.5 Hz, 2H), 2.05 (s, 2H), 1.28 (s, 6H), 1.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 147.4, 142.8, 128.9, 128.8, 128.6, 128.1, 127.1, 126.6, 54.0, 50.7, 49.8, 48.2, 38.6, 32.4, 29.7. HRMS (ESI, m/z): 393.2204; calcd for $C_{29}H_{28}OH$ $(M + H)^+$, 393.2218.

5-Amino-1,3,7-trimethyladamantan-2-one, 8. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (d, J = 11.5 Hz, 2H), 1.53 (m, 4H), 1.43 (d, J = 11.5 Hz, 2H), 1.24 (s, 2H), 0.96 (s, 3H), 0.94 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0, 53.3, 52.4, 50.8, 46.0, 33.1, 28.2, 22.2. HRMS (ESI, m/z): 208.1691; calcd for $C_{13}H_{21}NOH$ $(M + H)^+$, 208.1701.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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