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PII: S0040-4020(15)00087-3
DOI: 10.1016/j.tet.2015.01.044
Reference: TET 26367

To appear in: *Tetrahedron*

Received Date: 9 October 2014
Revised Date: 7 January 2015
Accepted Date: 19 January 2015

Please cite this article as: Kolocouris A, Koch A, Kleinpeter E, Stylianakis I, 2-Substituted and 2,2-Disubstituted Adamantane Derivatives as models for Studying Substituent Chemical Shifts and C-H_{ax}•••Y_{ax} Cyclohexane Contacts - Results from experimental and theoretical NMR spectroscopic chemical shifts and DFT structures, *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.01.044.

2-Substituted and 2,2-Disubstituted Adamantane Derivatives as models for Studying Substituent Chemical Shifts and C-H_{ax}···Y_{ax} Cyclohexane Contacts - Results from experimental and theoretical NMR spectroscopic chemical shifts and DFT structures

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Abtract: The complete ^{1}H and ^{13}C NMR chemical shifts assignment for various 2-substituted and 2,2-disubstituted adamantane derivatives **1−38** in CDCl$_3$ solution was realized on the basis of NMR experiments combined with chemical structure information and DFT-GIAO (B3LYP/6-31+G(d,p)-GIAO) calculations of chemical shifts in solution. Substituent-induced ^{13}C NMR chemical shifts (SCS) are discussed. C-H$_{ax}$···Y$_{ax}$ contacts are a textbook prototype of steric hindrance in organic chemistry. The nature of these contacts will be further investigated in this work on basis of new adamantane derivatives which are substituted at C-2 to provide models for 1,4-C-H$_{ax}$···Y$_{ax}$ and 1,5-C-H$_{ax}$···Y$_{ax}$ contacts. The B3LYP/6-31+G(d,p) calculations predicted the presence of NBO hyperconjugative attractive interactions between C-H$_{ax}$ and Y$_{ax}$ groups along C-H$_{ax}$···Y$_{ax}$ contacts. The ^{1}H NMR signal separation, Δδ(γ-CH$_2$), reflects the strength of the H-bonded C-H$_{ax}$···Y$_{ax}$ contact.

Keywords: 2-substituted adamantane derivatives; 2,2-disubstituted adamantane derivatives; ^{1}H NMR; ^{13}C NMR; B3LYP/6-31G**+ calculations; GIAO calculations; substituent chemical shifts

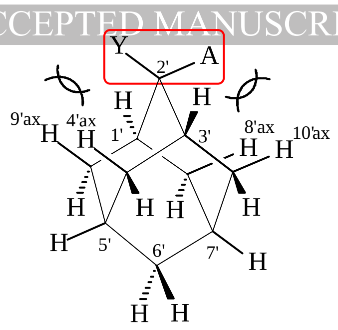
1. Introduction

Cyclohexane derivatives are popular model compounds in organic chemistry and are particularly useful, both experimentally and theoretically for studying the shielding tensors contributing to proton and carbon chemical shifts; these shielding tensors are strongly linked with the position of the atoms and their interactions in a molecule. Concerning ^{1}H NMR spectroscopy, rather than discern and analyze the axial or equatorial proton resonances, the difference in chemical shift [Δδ(γ-CH$_2$)] and one-bond $^{1}J_{C\text{-}H}$ coupling constants between the axial and equatorial protons within one methylene group in the cyclohexane chair are used as experimental probes.[1] Regarding the carbon nuclei, the substituent effects upon carbon atoms especially in the γ position (γ SCS, γ

Substituent Chemical Shifts) are of considerable interest because their magnitude and sign depend strongly on the stereochemistry of the attached substituent. Steric and electronic substituent phenomena are responsible for stabilizing a particular cyclohexane conformer and for the differentiation of the values of certain NMR parameters like ^{1}J coupling constants.[2] In addition, the interpretation of the chemical $\Delta\delta$(γ-CH_2) in terms of the magnetic contributions and the underlying intramolecular bonding interactions are currently being studied.[1a,3,4] Similarly the origin of the substituent effects on the carbon resonances shifts is not fully understood, even for the familiar γ-gauche effect.[5]

Adamantane derivatives are rigid and include fixed cyclohexane rings providing useful models employing NMR parameters to study of intramolecular interactions.[6] In the general formula of a 2,2-disubstituted adamantane shown in Scheme 1, each of the substituents Y and A is axial in the different adamantane cyclohexane ring 1′-2′-3′-4′-5′-9′ and 1′-2′-3′-10′-7′-8′, respectively (Scheme 1).

Scheme 1. In 2,2-disubstituted adamantanes each of the two geminal substituents adopts an axial orientation in a different cyclohexane ring sub-unit of adamantane. Scheme 1 also depicts the 2-substituted and 2,2-disubstituted adamantane derivatives **1−38** that were studied for this report.



1 (Y = H, A = H)[c]
2 (Y = CH_3, A = H)[c]
3 (Y = $C(CH_3)_3$, A = H)[c]
4 (Y = C≡N, A = H)[c]
5 (Y = OH, A = H)[c]
6 (Y = OMe, A = H)[c]
7 (Y = NH_2, A = H)[c]
8 (Y = NMe_2, A = H)[c]
9 (Y = NH-CO-Me, A = H)
10(Y = NO_2, A = H)
11 (Y = F, A = H)[c]
12 (Y = Cl, A = H)[c]

13 (Y = SH, A = H)[c]
14 (Y = OH, A = CH_3)
15 (Y = OH, A = $C(CH_3)_3$)
16 (Y = OH, A = Ph)
17 (Y = OH, A = C≡CH)
18 (Y = OH, A = C≡N)
19 (Y = $OSiMe_3$, A = C≡N)
20 (Y = O-COMe, A = CH_3)
21 (Y = O-CO*t*Bu, A = CH_3)
22 (Y = NH_2, A = CH_3)
23 (Y = NMe_2, A = CH_3)
24 (Y = $NHMe_2^+$, A = CH_3)

25 (Y, A = $NH(CH_2)_4$)
26 (Y, A = $NMe(CH_2)_4$)[d]
27 (Y = NHCOMe, A = CH_3)
28 (Y = NHCO*t*Bu, A = CH_3)
29 (Y = N-N≡N, A = CH_3)
30 (Y = F, A = CH_3)
31 (Y = Cl, A = CH_3)
32 (Y = CMe_2OH, A = H)
33 (Y = CMe_2F, A = H)
34 (Y = COMe, A = H)
35 (Y = CO_2H, A = H)
36 (Y, A= $CO(CH_2)_2$
37 (Y, A= $CO(CH_2)_3$
38 (Y, A= $CO(CH_2)_4$

When an axial substituent is attached to the cyclohexane ring, the major effect of the C-$H_{ax}\cdots Y_{ax}$ contact in the ^{1}H NMR spectrum increases $\Delta\delta$(γ-CH_2 values and causes an upfield shift on the resonance of γ-carbons. From a single NMR spectrum of a disubstituted adamantane *at ambient temperature*, the corresponding spectroscopic characteristics on the relative effect of two axial substituents Y_{ax} and A_{ax} can be investigated.[6] To observe such effects in the flexible cyclohexane derivatives, the NMR spectra of axial conformers are accessible only at low temperatures when ring inversion is slow on the NMR time scale.[7]

The studied compounds **1−38** are 2-substituted or 2,2-disubstituted adamantane derivatives bearing alkyl groups of various sizes (A = H, Me, HC≡C, Ph, *t*-Bu) and some common second row polar groups (Y = OH, OCOR, NR_2, NHCOR, NO_2, $NHMe_2^+$, N_3, CN, F, Cl, SH, CMe_2OH, CMe_2F, $CO(CH_2)n$, n=2-4) (Scheme 1).

In a preceding paper, DFT calculations at the B3LYP/6-31+G(d,p) level predicted an improper H-bonding character of C-$H_{ax}\cdots Y_{ax}$ contacts in common cyclohexane derivatives, due to the presence of $n(Y) \rightarrow \sigma^*$(C-H or σ(C-H) $\rightarrow \sigma^*$(C-H) hyperconjugative interactions, and the variation of its strength according to the nature of contact atom in group Y_{ax}.[8] By increasing the strength of the contact the electronic redistribution inside the γ-methylene is affected consistently, raising the relevant chemical shift separation between axial and equatorial protons inside a γ-CH_2, $\Delta\delta$(γ-CH_2).[9] The present research work is a continuation of our previous studies.[9] A large set of 2-substituted and 2,2-disubstituted adamantane derivatives **1−38** have been synthesized and both ^1H and ^{13}C NMR spectra assigned to analyze conformational effects due to present $C\text{-}H_{ax}\cdots Y_{ax}$ interactions.

2. Results and Discussion

2.1 ^1H and ^{13}C NMR spectra assignment

2.1.1 ^1H NMR spectroscopy

The most characteristic feature in the ^1H NMR spectrum of a 2-substituted adamantane, is the appearance of a downfield and an upfield doublet (J_{gem}= 11-12 Hz), assigned to 4′ax,9′ax-H and 4′eq,9′eq-H, respectively.[10] In these molecules the equivalent axial protons of γ-syn carbons 4′ or 9′ interact with substituent Y, which is axial with respect to the 1′-2′-3′-4′-5′-9′ cyclohexane ring sub-unit (Scheme 1), and their resonances are shifted downfield from the geminal 4′eq, 9′eq protons. In contrast, the separation of the signals due to the protons attached to the γ-anti carbons 8′ and 10′, that is, the chemical shift difference between 8′ax,10′ax-H and 8′eq,10′eq-H, is small because of the equatorial position of substituent Y in the 1′-2′-3′-10′-7′-8′ cyclohexane ring (Scheme 1). When a second substituent A is attached at the 2-adamantane position, the resonances of 8′ax,10′ax-H and 8′eq,10′eq-H should be affected mainly by their interaction with A which is axial in the 1′-2′-3′-10′-7′-8′ cyclohexane ring. In a 2,2-disubstituted adamantane derivative, 4′,9′-H resonances are affected by the Y_{ax}, A_{eq} substitution, with Y having an axial orientation in the 1′-2′-3′-4′-5′-9′ cyclohexane ring, and the 8′,10′-H doublets are affected by A_{ax}, Y_{eq} substitution, with substituent A being axial in the 1′-2′-3′-10′-7′-8′ cyclohexane ring (Scheme 1).

In order to: a) differentiate the doublets between $4'_{ax},9'_{ax}$-H and $8'_{ax},10'_{ax}$-H protons and between $4'_{eq},9'_{eq}$-H and $8'_{eq},10'_{eq}$-H protons and also to compare the proton chemical shift separation effect within the cyclohexane ring γ-CH_2 for the two orientations Y_{ax}, A_{eq} and Y_{eq}, A_{ax} (correspoinding to fixed 1Y,1A-cyclohexane conformational isomers included inside the adamantane framework), b) to study the effect of the different orientations Y_{ax}, A_{eq} and Y_{eq}, A_{ax} on the resonances of γ-carbons 4′,9′-C and δ-carbons 5′,7′-C, and c) to study the substituent effects on the carbons chemical shifts, the full assignment of the ^{1}H and ^{13}C NMR spectra of compounds **1−38** is a precondition. Although the ^{13}C spectra of some substituted adamantanes at C-2 have been investigated,[11] there is no detailed report on their ^{1}H NMR spectra.[12,7a]

The geometry of each compound was optimized at B3LYP/6-31+G(d,p) level.[13a] This level of theory is adequate with reproducing accurately geometries; nevertheless we are more interested in relative geometrical changes and not absolute values.[13b] The gauge-invariant atomic orbital (GIAO)[14] for calculation of the magnetic shielding tensors of nuclei was applied for compounds **1−38** after optimizing their geometry using the IEF-PCM solvent model[15] (solvent $CHCl_3$) for consistency with the experimental conditions. For GIAO calculations we used the global minimum which is more than 2.7 kcal/mol lower in potential energy for all molecules, that is, every other conformer is less than 1% populated. It has been recently published that B3LYP/6-31G(d,p) gave a deviation within 0.2 ppm for ^{1}H chemical shifts and B3LYP/6-31G(d) gave a deviation of 5 ppm for ^{13}C chemical shifts;[16a] also that a DZ basis set is a fair choise. [16b] For the calculation of proton chemical shifts it was recommended that the modeling of solvent through SCRF-type calculation may improve predictions significantly in certain cases; TMS was found to be an acceptable reference since the deviation from experimental values was found to be inside acceptable limits.[16] We applied here GIAO calculations in order to check their ability to reproduce experimentally determined assignments for example the relative location of 8′,10′-H and 4′,9′-H proton doublets in the studied adamantane derivatives. The calculated chemical shifts follow the same order compared to the experimental chemical shifts; we checked if the GIAO calculated chemicals shifts predict the same relative chemical shift positions with experimental results and we did not attempt to predict absolute calculated values. It is known that this can be accomplished for example for ^{13}C only with demanded computational methods, possibly with CCSD(T).[16c] We used GIAO results for assignment purposes when differentiation was difficult like for 5′, 7′ protons and carbons. In most of the cases the deviation of the calculated chemical shift is similar for the same carbon or proton inside series **1−38**. In all cases we used the results from the GIAO calculations to compare relative chemical shifts positions, for example the position of 8′,10′ carbons compared to 4′,9′ carbons or the position of 5′ proton or carbon compared to 7′ proton or carbon, and not absolute values. Since the chemical shifts difference for 5′ and 7′ carbons and protons is small (see discussion followed) even the more accurate MP2 level can not give accurate chemical shifts for these carbons and protons having an error of ~ 2 ppm and 0.1 ppm for carbons and proton chemical shifts respectively;[16b] this last level is also computationally expensive for this large set of compounds.

The ^{1}H chemical shifts of compounds **1−38** (experimental and calculated values) are depicted in Table 1.

Table 1. ^{1}H chemical shifts (400 MHz, $CDCl_3$)[a] and signal separation of the γ-CH_2 pairs[b] of adamantane cyclohexane ring sub-units for 2,2-disubstituted adamantanes **1−38**.

Compound		1′, 3′	2′	5′	7′	6′	4′ax, 9′ax	8′ax, 10′ax	4′eq, 9′eq	8′eq, 10′eq	Δ$\delta_{4′,9′\text{-H}}$	Δ$\delta_{8′,10′\text{-H}}$
1 (Y = **H**, A = H)[c]	Exp.	1.87	1.75	1.87	1.87	1.75	1.75	1.75	1.75	1.75	0.0	0.0
	Calc.	1.78, 1.80	1.84	1.78	1.78	1.84	1.82, 1.84	1.82, 1.84	1.82, 1.84	1.82, 1.84	0	0
		(Δδ=-0.08)	(Δδ=0.09)	(Δδ=-0.09)	(Δδ=-0.09)	(Δδ=0.09)	(Δδ=0.08)	(Δδ=0.08)	(Δδ=0.08)	(Δδ=0.08)	(Δδ=0)	(Δδ=0)
2 (Y = **C**H$_3$, A = H)[c]	Exp.	1.57	1.75	1.84	1.75	1.69	1.91	1.81	1.46	1.72	0.45	-0.09
	Calc.	1.58, 1.58	1.86	1.73	1.71	1.77, 1.76	2.09, 2.08	1.92, 1.92	1.55, 1.56	1.79, 1.79	0.53	0.13
		(Δδ=0.01)	(Δδ=0.11)	(Δδ=-0.13)	(Δδ=-0.02)	(Δδ=0.08)	(Δδ=0.18)	(Δδ=0.11)	(Δδ=0.09)	(Δδ=-0.02)	(ΔΔδ=0.08)	(ΔΔδ=0.22)
3 (Y = C(**C**H$_3$)$_3$, A = H)[c]	Exp.	2.05	1.86	1.86	1.79	1.70	2.03	1.81	1.53	1.71	0.50	0.10
	Calc.	1.92, 1.91	1.21	1.54	1.56	1.45, 1.43	1.88, 1.98	1.57, 1.61	1.33, 1.28	1.43, 1.48	0.62	0.13
		(Δδ=-0.14)	(Δδ=-0.65)	(Δδ=-0.32)	(Δδ=-0.43)	(Δδ=-0.26)	(Δδ=-0.10)	(Δδ=-0.22)	(Δδ=-0.23)	(Δδ=-0.25)	(ΔΔδ=0.12)	(ΔΔδ=0.03)
4 (Y = **C≡N**, A = H)[c]	Exp.	2.16	2.89	1.90	1.83	1.68	2.14	1.88	1.73	1.72	0.41	0.16
	Calc.	1.98, 1.98	2.71	1.79	1.70	1.81, 1.81	2.33, 2.33	1.70, 1.70	1.66, 1.66	1.90, 1.90	0.67	-0.20
		(Δδ=-0.18)	(Δδ=-0.18)	(Δδ=-0.11)	(Δδ=-0.13)	(Δδ=0.13)	(Δδ=0.19)	(Δδ=-0.18)	(Δδ=-0.07)	(Δδ=0.18)	(ΔΔδ=0.26)	(ΔΔδ=-0.36)
5 (Y = **O**H, A = H)[c]	Exp.	1.88	3.86	1.79	1.81	1.71	2.06	1.84	1.52	1.68	0.54	0.16
	Calc.	1.49, 1.96	3.91	1.67	1.67	1.77, 1.76	2.43, 2.48	1.90, 1.89	1.47, 1.45	1.68, 1.70	1.00	-0.02
		(Δδ=-0.16)	(Δδ=0.05)	(Δδ=-0.12)	(Δδ=-0.14)	(Δδ=0.06)	(Δδ=0.40)	(Δδ=0.06)	(Δδ=-0.06)	(Δδ=0.01)	(ΔΔδ=0.46)	(ΔΔδ=-0.18)
6 (Y = **O**Me, A = H)[c]	Exp.	2.02	3.34	1.77	1.83	1.70	2.01	1.65	1.47	1.84	0.54	0.19
	Calc.	1.88, 2.05	3.27	1.36	1.68	1.77, 1.72	2.26, 2.38	1.90, 1.89	1.43, 1.46	1.62, 1.74	0.87	-0.07
		(Δδ=-0.06)	(Δδ=-0.07)	(Δδ=-0.41)	(Δδ=-0.15)	(Δδ=0.05)	(Δδ=0.31)	(Δδ=0.25)	(Δδ=-0.03)	(Δδ=-0.16)	(ΔΔδ=0.33)	(ΔΔδ=-0.26)
7 (Y = **N**H$_2$, A = H)[c]	Exp.	1.75	2.99	1.78	1.81	1.70	1.97	1.84	1.52	1.72	0.45	0.12
	Calc.	1.50, 1.50	3.33	1.67	1.70	1.78, 1.78	2.73, 2.73	1.90, 1.90	1.40, 1.40	1.72, 1.72	1.33	0.18
		(Δδ=-0.25)	(Δδ=0.34)	(Δδ=-0.11)	(Δδ=-0.11)	(Δδ=0.08)	(Δδ=0.76)	(Δδ=0.06)	(Δδ=-0.12)	(Δδ=0)	(ΔΔδ=0.88)	(ΔΔδ=0.06)
8 (Y = **N**Me$_2$, A = H)[c]	Exp.	1.96	2.10	1.78	1.82	1.71	2.28	1.80	1.41	1.63	0.87	0.17
	Calc.	1.94, 1.94	1.84	1.66	1.72	1.72, 1.72	2.42, 2.42	1.91, 1.91	1.44, 1.44	1.72, 1.72	0.98	-0.19
		(Δδ=-0.02)	(Δδ=-0.26)	(Δδ=-0.12)	(Δδ=-0.10)	(Δδ=0.01)	(Δδ=0.14)	(Δδ=0.11)	(Δδ=0.03)	(Δδ=0.09)	(ΔΔδ=0.11)	(ΔΔδ=-0.36)
9 (Y = **N**H-CO-Me, A = H)	Exp.	1.93	4.03	1.82	1.83	1.78	1.90	1.82	1.63	1.67	0.27	0.15
	Calc.	2.06, 2.47	4.13	1.70	1.68	1.79, 1.77	1.62, 1.90	1.91, 1.83	1.73, 1.61	1.89, 1.90	0.16	-0.05
		(Δδ=0.33)	(Δδ=0.10)	(Δδ=-0.12)	(Δδ=-0.15)	(Δδ=0.0)	(Δδ=-0.14)	(Δδ=0.04)	(Δδ=0.04)	(Δδ=0.23)	(ΔΔδ=-0.11)	(ΔΔδ=-0.20)
10(Y = **N**O$_2$, A = H)	Exp.	2.75	4.38	1.97	1.97	1.70	2.05	1.95	1.52	1.83	0.53	0.12
	Calc.	2.98, 2.95	4.11	1.71	1.71	1.78, 1.78	1.81, 1.84	2.00, 2.00	1.64, 1.63	1.72, 171	0.19	0.28
		(Δδ= 0.22)	(Δδ=-0.27)	(Δδ=-0.26)	(Δδ=-0.26)	(Δδ=0.08)	(Δδ=-0.22)	(Δδ=0.05)	(Δδ=0.12)	(Δδ=-0.11)	(ΔΔδ=-0.34)	(ΔΔδ= 0.14)
11 (Y = **F**, A = H)[c]	Exp.	2.09	4.65	1.81	1.81	1.73	2.08	1.86	1.55	1.67	0.53	-0.19
	Calc.	2.05, 2.05	4.84	1.65	1.73	1.75, 1.76	2.34, 2.34	1.90, 1.89	1.53, 1.53	1.67, 1.67	0.81	-0.05
		(Δδ=-0.04)	(Δδ=0.19)	(Δδ=-0.16)	(Δδ=-0.08)	(Δδ=0.03)	(Δδ=0.26)	(Δδ=0.04)	(Δδ=0.02)	(Δδ=0)	(ΔΔδ=0.28)	(ΔΔδ=0.14)
12 (Y = **Cl**, A = H)[c]	Exp.	2.06	4.38	1.84	1.84	1.73	2.25	1.93	1.55	1.78	0.70	-0.15
	Calc.	1.94, 1.94	4.44	1.62	1.72	1.75, 1.75	2.44, 2.44	1.94, 1.94	1.51, 1.51	1.75, 1.75	0.93	-0.19
		(Δδ=-0.12)	(Δδ=0.06)	(Δδ=-0.22)	(Δδ=-0.12)	(Δδ=0.02)	(Δδ=0.19)	(Δδ=0.01)	(Δδ=-0.04)	(Δδ=-0.03)	(ΔΔδ=0.23)	(ΔΔδ=-0.04)
13 (Y = **SH**, A = H)[c]	Exp.	1.82	3.34	1.79	1.80	1.69	2.15	1.86	1.50	1.76	0.68	-0.10
	Calc.	1.53, 1.99	3.68	1.72	1.78	1.79, 1.80	2.31, 2.87	1.98, 1.94	1.58, 1.49	1.77, 1.82	1.05	-0.17
		(Δδ=-0.06)	(Δδ=0.34)	(Δδ=-0.07)	(Δδ=-0.02)	(Δδ=0.11)	(Δδ=0.44)	(Δδ=0.10)	(Δδ=0.04)	(Δδ=0.04)	(ΔΔδ=0.37)	(ΔΔδ=-0.07)

14 (Y = **O**H, A = **C**H$_3$)	Exp.	1.65	-	1.76	1.76	1.64	2.15	1.83	1.52	1.70	0.63	0.13
	Calc.	1.33, 1.71		1.66	1.66	1.71, 1.70	2.64, 2.69	1.92, 1.94	1.45, 1.45	1.78, 1.75	1.22	0.16
		(Δδ=-0.13)		(Δδ=-0.10)	(Δδ=-0.10)	(Δδ=0.07)	(Δδ=0.52)	(Δδ=0.10)	(Δδ=-0.07)	(Δδ=0.07)	(ΔΔδ=0.59)	(ΔΔδ=0.03)
15 (Y = **O**H, A = C(**C**H$_3$)$_3$	Exp.	2.02	-	1.73	1.59	1.66	2.26	2.17	1.47	1.68	0.79	0.49
	Calc.	1.85, 2.07		1.71	1.64	1.70, 1.68	2.53, 2.86	2.32, 2.32	1.45, 1.38	1.69, 1.78	1.44	0.59
		(Δδ=-0.06)		(Δδ=-0.02)	(Δδ=0.05)	(Δδ=0.03)	(Δδ=0.44)	(Δδ=0.15)	(Δδ=-0.06)	(Δδ=0.06)	(ΔΔδ=0.65)	(ΔΔδ=0.10)
16 (Y = **O**H, A = **Ph**)	Exp.	2.60	-	1.94	1.74	1.73	2.45	1.76	1.77	1.74	0.68	0.02
	Calc.	1.96, 1.96		1.55	1.42	1.43, 1.44	2.58, 2.48	1.25, 1.57	1.36, 1.38	1.39, 1.83	1.16	0.24
		(Δδ=0.64)		(Δδ=-0.39)	(Δδ=-0.32)	(Δδ=-0.29)	(Δδ=0.08)	(Δδ=-0.35)	(Δδ=-0.40)	(Δδ=-0.13)	(ΔΔδ=0.48)	(ΔΔδ=0.22)
17 (Y = **O**H, A = **C**≡**C**H)	Exp.	1.93	-	1.79	1.66	1.66	2.14	2.11	1.52	1.75	0.62	0.36
	Calc.	1.81, 2.10		1.55	1.39	1.46, 1.47	1.61, 1.70	1.72, 1.75	0.98, 1.01	1.67, 1.65	0.67	0.08
		(Δδ=0.03)		(Δδ=-0.24)	(Δδ=-0.27)	(Δδ=-0.20)	(Δδ=-0.48)	(Δδ=-0.37)	(Δδ=-0.52)	(Δδ=-0.09)	(ΔΔδ=0.05)	(ΔΔδ=0.28)
18 (Y = **O**H, A = **C**≡**N**)	Exp.	1.73	-	1.80	1.92	1.73	2.13	2.10	1.62	1.91	0.51	0.19
	Calc.	1.31, 1.70		1.73	1.61	1.72, 1.71	2.37, 2.47	2.22, 2.22	1.53, 1.53	1.85, 1.84	0.89	0.38
		(Δδ=-0.22)		(Δδ=-0.07)	(Δδ=-0.31)	(Δδ=-0.01)	(Δδ=0.29)	(Δδ=0.12)	(Δδ=-0.09)	(Δδ=-0.06)	(ΔΔδ=0.38)	(ΔΔδ=0.19)
19 (Y = **O**SiMe$_3$, A = **C**≡**N**)	Exp.	2.05	-	1.76	1.84	1.71	2.10	2.07	1.55	1.86	0.55	0.21
	Calc.	1.77, 1.79		1.51	1.39	1.53, 1.51	2.10, 2.26	1.95, 1.96	1.22, 1.25	1.52, 1.52	0.94	0.43
		(Δδ=-0.27)		(Δδ=-0.25)	(Δδ=-0.45)	(Δδ=-0.19)	(Δδ=0.08)	(Δδ=-0.12)	(Δδ=-0.31)	(Δδ=-0.34)	(ΔΔδ=0.39)	(ΔΔδ=0.22)
20 (Y = **O**-COMe, A = **C**H$_3$)	Exp.	2.20	-	1.73	1.73	1.63	1.95	1.80	1.49	1.65	0.46	0.15
	Calc.	3.03, 1.67		1.65	1.67	1.73, 1.78	2.47, 1.94	2.01, 1.92	1.56, 1.56	1.74, 1.71	0.64	0.24
		(Δδ=0.15)		(Δδ=-0.07)	(Δδ=-0.06)	(Δδ=0.12)	(Δδ=0.25)	(Δδ=0.16)	(Δδ=0.07)	(Δδ=0.07)	(ΔΔδ=0.24)	(ΔΔδ=0.09)
21 (Y = **O**-CO*t*Bu, A = **C**H$_3$)	Exp.	2.24	-	1.73	1.73	1.64	1.95	1.80	1.49	1.65	0.46	0.15
	Calc.	2.97, 1.51		1.48	1.49	1.49, 1.52	2.24, 1.69	1.79, 1.64	1.30, 1.19	1.48, 1.44	0.71	0.25
		(Δδ=0.0)		(Δδ=-0.25)	(Δδ=-0.24)	(Δδ=-0.13)	(Δδ=0.01)	(Δδ=-0.08)	(Δδ=-0.24)	(Δδ=-0.19)	(ΔΔδ=0.25)	(ΔΔδ=0.11)
22 (Y = **N**H$_2$, A = **C**H$_3$)	Exp.	1.55	-	1.81	1.78	1.65	2.07	1.93	1.59	1.62	0.48	0.31
	Calc.	1.33, 1.33		2.02	1.68	1.73, 1.73	2.87, 2.87	2.02, 2.02	1.38, 1.38	1.73, 1.73	1.44	0.29
		(Δδ=-0.22)		(Δδ=0.21)	(Δδ=-0.10)	(Δδ=0.08)	(Δδ=0.82)	(Δδ=0.09)	(Δδ=-0.21)	(Δδ=0.11)	(ΔΔδ=0.96)	(ΔΔδ=0.02)
23 (Y = **N**Me$_2$, A = **C**H$_3$)	Exp.	1.75	-	1.75	1.75	1.63	2.22	1.85	1.34	1.64	0.88	0.21
	Calc.	1.81, 1.81		1.69	1.66	1.70, 1.70	2.57, 2.57	1.99, 1.99	1.33, 1.33	1.70, 1.70	1.24	0.29
		(Δδ=0.06)		(Δδ=-0.06)	(Δδ=-0.09)	(Δδ=0.07)	(Δδ=0.35)	(Δδ=0.14)	(Δδ=-0.01)	(Δδ=0.06)	(ΔΔδ=0.36)	(ΔΔδ=0.08)
24 (Y = **N**HMe$_2^+$, A = **C**H$_3$)	Exp.	2.03	-	1.93	2.00	1.73	2.18	1.97	1.72	1.87	0.46	0.10
	Calc.	2.02, 2.02		1.97	2.04	1.92, 1.92	1.45, 1.46	2.11, 2.13	2.21, 2.21	2.17, 2.17	0.76	0.05
		(Δδ=-0.01)		(Δδ=0.04)	(Δδ=0.04)	(Δδ=0.19)	(Δδ=-0.72)	(Δδ=0.15)	(Δδ=0.49)	(Δδ=0.30)	(ΔΔδ=0.30)	(ΔΔδ=0.05)
25 (Y, A = **N**H(**C**H$_2$)$_4$)	Exp.	1.78	-	1.74	1.74	1.60	1.93	1.87	1.45	1.53	0.48	0.34
	Calc.	1.00, 2.24		1.68	1.65	1.70, 1.70	2.67, 2.74	1.91, 2.01	1.40, 1.34	1.71, 1.65	1.33	0.28
		(Δδ=-0.16)		(Δδ=-0.06)	(Δδ=-0.09)	(Δδ=0.10)	(Δδ=0.77)	(Δδ=0.09)	(Δδ=-0.08)	(Δδ=0.15)	(ΔΔδ=0.85)	(ΔΔδ=0.06)
26 (Y, A = **N**Me(**C**H$_2$)$_4$)[d]	Exp.	1.60, 2.43	-	1.80	1.80	1.65	2.24, 2.10	1.60, 1.82	1.43, 1.39	1.47, 1.60	0.81, 0.71	0.13, 0.22
	Calc.	1.36, 2.24		1.44	1.42	1.34, 1.35	2.53, 2.21	1.62, 1.63	1.08, 1.10	1.41, 1.32	1.43, 1,13	0.30, 0.22
		(Δδ=-0.24, -0.19)		(Δδ=-0.36)	(Δδ=-0.38)	(Δδ=-0.30)	(Δδ=0.20)	(Δδ=-0.10)	(Δδ=-0.32)	(Δδ=-0.17)	(ΔΔδ=0.52)	(ΔΔδ=0.08)
27 (Y = **N**HCOMe, A = **C**H$_3$)	Exp.	2.15	-	1.81	1.81	1.70	1.97	1.95	1.61	1.66	0.36	0.29
	Calc.	3.16, 1.28		1.67	1.67	1.75, 1.74	2.03, 2.15	1.67, 1.66	1.62, 1.53	2.15, 2.01	0.51	0.40
		(Δδ=0.07)		(Δδ=-0.14)	(Δδ=-0.14)	(Δδ=0.04)	(Δδ=0.12)	(Δδ=-0.29)	(Δδ=-0.03)	(Δδ=0.42)	(ΔΔδ=0.15)	(ΔΔδ=0.11)

28 (Y = **N**HCO*t*Bu, A = **C**H$_3$)	Exp.	2.13	-	1.77	1.77	1.65	1.94	1.86	1.62	1.57	0.32	0.29
	Calc.	3.18, 0.98		1.49	1.47	1.47, 1.46	2.18, 2.12	1.42, 1.42	1.25, 1.23	1.81, 1.75	0.91	0.36
		(Δδ=-0.05)		(Δδ=-0.28)	(Δδ=-0.30)	(Δδ=-0.18)	(Δδ=0.11)	(Δδ=-0.44)	(Δδ=-0.38)	(Δδ=0.31)	(ΔΔδ=0.59)	(ΔΔδ=0.07)
29 (Y = **N**-N≡N, A = **C**H$_3$)	Exp.	1.72	-	1.80	1.81	1.67	2.11	1.87	1.56	1.68	0.55	0.19
	Calc.	1.46, 1.94		1.66	1.73	1.74, 1.74	2.48, 2.29	1.71, 1.82	1.51, 1.62	1.97, 1.94	0.82	0.18
		(Δδ=-0.02)		(Δδ=-0.14)	(Δδ=-0.07)	(Δδ=0.07)	(Δδ=0.27)	(Δδ=-0.10)	(Δδ=0.00)	(Δδ=0.27)	(ΔΔδ=0.27)	(ΔΔδ=0.01)
30 (Y = **F**, A = **C**H$_3$)	Exp.	1.90	-	1.78	1.82	1.69	2.17	1.80	1.56	1.67	0.61	0.13
	Calc.	1.83, 1.83		1.65	1.68	1.73, 1.73	2.48, 2.48	1.81, 1.81	1.53, 1.53	1.84, 1.84	0.95	0.03
		(Δδ=-0.07)		(Δδ=-0.10)	(Δδ=-0.17)	(Δδ=0.04)	(Δδ=0.31)	(Δδ=0.01)	(Δδ=-0.03)	(Δδ=0.17)	(ΔΔδ=0.34)	(ΔΔδ=0.10)
31 (Y = **Cl**, A = **C**H$_3$)	Exp.	1.67	-	1.79	1.80	1.67	2.18	1.86	1.55	1.73	0.63	0.13
	Calc.	1.91, 1.91		1.65	1.69	1.71, 1.71	2.66, 2.66	2.06, 2.06	1.59, 1.59	1.76, 1.76	1.07	0.30
		(Δδ=0.24)		(Δδ=-0.14)	(Δδ=-0.11)	(Δδ=0.04)	(Δδ=0.48)	(Δδ=0.20)	(Δδ=0.04)	(Δδ=0.03)	(ΔΔδ=0.44)	(ΔΔδ=0.17)
32 (Y = CMe$_2$**O**H, A = H)	Exp.	2.18	1.54	1.86	1.85	1.73	2.18	1.82	1.53	1.70	0.65	0.13
	Calc.	2.16, 2.16	1.38	1.75	1.71	1.75, 1.75	2.92, 2.93	1.94, 1.94	1.51, 1.51	1.70, 1.70	1.41	0.24
		(Δδ=-0.02)	(Δδ=1.16)	(Δδ=-0.11)	(Δδ=-0.14)	(Δδ=0.02)	(Δδ=0.74)	(Δδ=0.12)	(Δδ=-0.02)	(Δδ=0.00)	(ΔΔδ=0.76)	(ΔΔδ=0.11)
33 (Y = CMe$_2$**F**, A = H)	Exp.	2.15	2.87	1.82	1.60	1.65	2.12	1.82	1.48	1.69	0.64	0.13
	Calc.	2.20, 2.21		1.77	1.77	1.76, 1.77	2.59, 2.61	1.69, 1.70	1.57, 1.56	1.96, 1.96	1.04	0.27
		(Δδ=0.05)	(Δδ=0.24)	(Δδ=-0.05)	(Δδ=0.17)	(Δδ=0.11)	(Δδ=0.48)	(Δδ=-0.13)	(Δδ=0.08)	(Δδ=0.27)	(ΔΔδ=0.40)	(ΔΔδ=0.14)
34 (Y = C**O**Me, A = H)	Exp.	2.36	2.47	1.79	1.70	1.71	1.88	1.77	1.59	1.75	0.29	0.13
	Calc.	1.95, 2.02	2.63	1.56	1.47	1.47, 1.45	1.33, 2.32	1.65, 1.59	1.32, 1.21	1.55, 1.33	0.56	0.18
		(Δδ=-0.37)	(Δδ=0.16)	(Δδ=-0.23)	(Δδ=-0.23)	(Δδ=-0.25)	(Δδ=-0.06)	(Δδ=-0.26)	(Δδ=-0.32)	(Δδ=-0.31)	(ΔΔδ=0.27)	(ΔΔδ=0.05)
35 (Y = C**O**$_2$H, A = H)	Exp.	2.35	2.66	1.90	1.85	1.74	1.91	1.87	1.64	1.75	0.27	0.12
	Calc.	2.35, 2.52	2.53	1.70	1.76	1.78, 1.81	1.62, 1.69	1.94, 1.91	1.62, 1.69	1.72, 1.82	0.00	0.15
		(Δδ=0.08)	(Δδ=-0.13)	(Δδ=-0.20)	(Δδ=-0.09)	(Δδ=0.05)	(Δδ=-0.25)	(Δδ=0.05)	(Δδ=0.01)	(Δδ=0.02)	(ΔΔδ=0.27)	(ΔΔδ=0.03)
36 (Y, A= C**O**(CH$_2$)$_2$	Exp.	1.90	-	1.79	1.77	1.70	2.18	1.74	1.62	1.62	0.56	0.12
	Calc.	1.73, 1.73		1.75	1.67	1.75, 1.75	2.53, 2.53	1.63, 1.63	1.56, 1.56	1.82, 1.82	0.97	0.19
		(Δδ=-0.17)		(Δδ=-0.04)	(Δδ=-0.10)	(Δδ=0.05)	(Δδ=0.35)	(Δδ=-0.11)	(Δδ=-0.06)	(Δδ=0.20)	(ΔΔδ=0.41)	(ΔΔδ=0.07)
37 (Y, A= C**O**(CH$_2$)$_3$	Exp.	1.84	-	1.78	1.78	1.69	2.42	1.95	1.38	1.62	1.04	0.33
	Calc.	1.45, 1.62		1.75	1.68	1.77, 1.75	2.40, 3.47	1.62, 1.57	1.45, 1.36	2.14, 1.81	1.53	0.37
		(Δδ=-0.31)		(Δδ=-0.03)	(Δδ=-0.10)	(Δδ=0.07)	(Δδ=0.51)	(Δδ=-0.35)	(Δδ=0.02)	(Δδ=0.35)	(ΔΔδ=0.49)	(ΔΔδ=0.04)
38 (Y, A= C**O**(CH$_2$)$_4$	Exp.	2.16	-	1.80	1.67	1.65	2.01	1.88	1.57	1.63	0.44	0.25
	Calc.	1.64, 1.71		1.69	1.67	1.70, 1.73	2.77, 1.57	1.51, 1.62	1.44, 1.66	1.95, 2.24	0.62	0.48
		(Δδ=-0.49)		(Δδ=-0.11)	(Δδ=0)	(Δδ=0.06)	(Δδ=0.16)	(Δδ=-0.31)	(Δδ=-0.02)	(Δδ=0.41)	(ΔΔδ=0.18)	(ΔΔδ=0.23)

[a] spectra were recorded at 298 K (unless otherwise stated) and the signal of CHCl$_3$ residue was calibrated at 7.26 ppm.

[b] Signals for 4′,9′-H and 8′,10′-H pairs of compounds **1−38** appear in general as broad doublets with J_{gem} ~ 12 Hz.

[b] Signal for the 5′,7′-H of compounds **1−38** appeared either as a broad singlet or as a narrow broad multiplet.

[b] Signal for the 1′,3′-H and 6′-H of compounds **1−38** is broad singlet.

[c] Data taken from the literature.[17]

[d] Spectra recorded at 273 K.[18]

As a representative example, the assignment of the 4′,9′-H and 8′,10′-H doublets is described for the conformationally homogeneous *N*,*N*-dimethyl-2-methyl-2-adamantanamine **23** (see Figure 1 and Scheme 2).

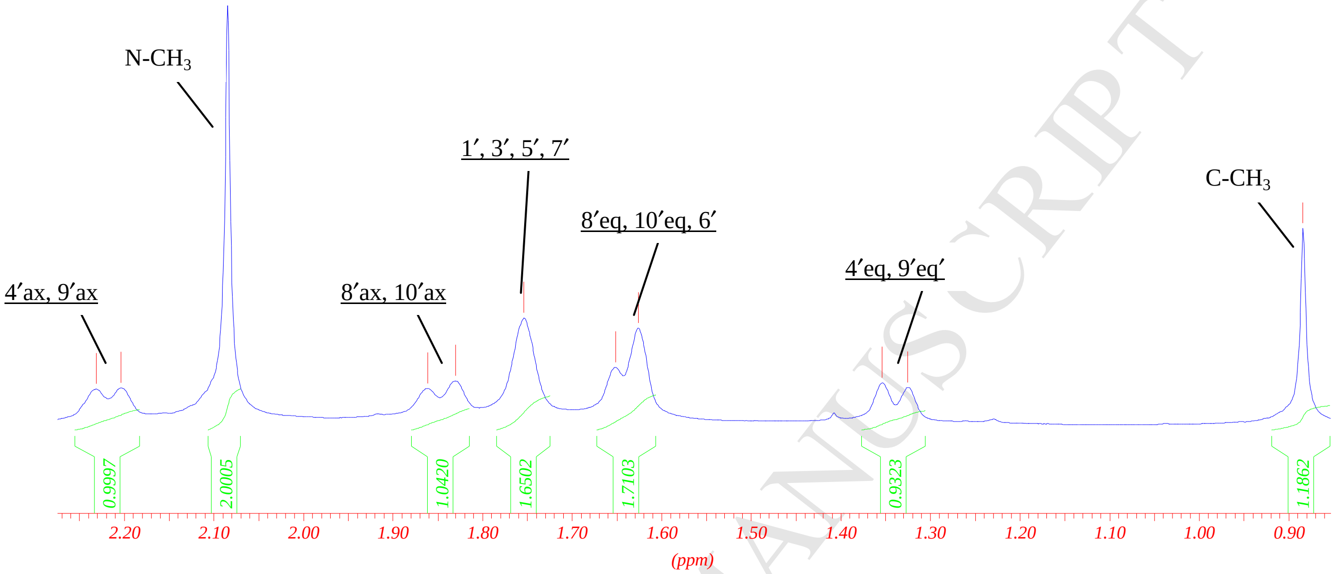
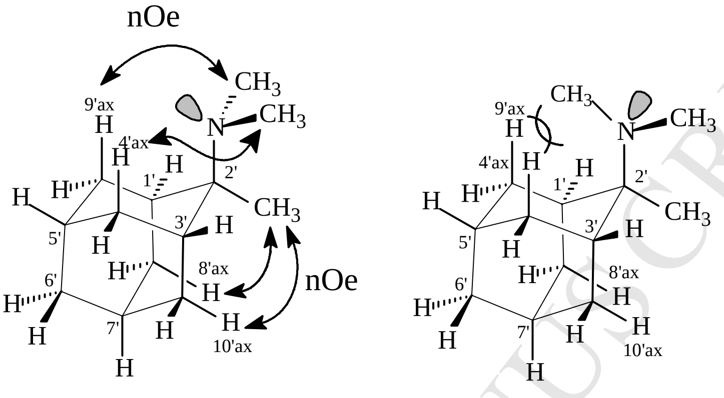


Figure 1. ^{1}H NMR spectrum of the *N*,*N*-dimethyl-2-methyl-2-adamantanamine **23** in CDCl$_3$ solution (400 MHz) at 298 K (Nitrogen quadruple moment broadening effect combined with a defined orientation of lone pair effects a broadening of the proton spectrum).

Molecular mechanics calculations using MM3 or MMFF94 force fields[19] predicted that conformer **23a**, having an anti arrangement with respect to the CH$_3$-C2′-N-lp dihedral angle, is the only populated conformer for **23** since the next different conformer **23g** is more than 10 kcal mol^{-1} higher in energy (Scheme 2). Conformer **23g** results from **23a**, either by rotation around the C2′-N bond or nitrogen inversion; in **23g** the N-Me group lies above the 1′-2′-3′-4′-5′-9′ cyclohexane ring where 1,5-steric interactions with the 4′ax and 9′ax methine groups are severe (Scheme 2).

Scheme 2. Scheme depicts nOe connectivities obtained for compound **23** being consistent with conformer **23a**; 1,5-interactions strongly destabilize conformer **23g** and thus conformer **23a** is the only populated conformer**.**



The doublet resonance at 1.85 ppm was assigned to the protons 8′ax, 10′ax (*J* ~ 12 Hz) because of its dipolar nOe correlation with C-Me at 0.88 ppm, and differentiated from the 4′ax,9′ax-H doublet (*J* ~ 12 Hz) at 2.22 ppm which showed an nOe correlation with *N*-Me at 2.08 ppm (Scheme 2, Figure 1). Using the scalar connectivities in the ^{1}H-^{1}H COSY spectrum, the corresponding pairs of equatorial protons were identified at lower frequencies, the signal of 4′eq,9′eq-H appeared at 1.34 ppm and that of 8′eq,10′eq-H occurred at 1.64 ppm. In general, for the assignment of the different doublets $4'_{ax}$,$9'_{ax}$-H and $8'_{ax}$,$10'_{ax}$-H, $4'_{eq}$,$10'_{eq}$-H and $8'_{eq}$,$10'_{eq}$-H in 2,2-disubstituted adamantanes **14**–**31, 36**–**38** a similar procedure was used; in 2-substituted adamantanes **1**–**13, 32**–**35** the assignment of the relevant protons was straightforward as described into the first paragraph of Results and Discussion section.

In all cases, the $\Delta\delta$(γ-CH$_2$) value is higher for the C-$H_{4'ax}\cdots Y_{ax}$ or C-$H_{9'ax}\cdots Y_{ax}$ contacts (Y_{ax} = NR$_2$, OR, F, CN, CMe$_2$-OH or C = O) than for the C-$H_{8'ax}\cdots A_{ax}$ or C-$H_{10'ax}\cdots A_{ax}$ contacts (A_{ax} = H, CH$_3$, t-Bu, C≡CH, C≡N); chemical shift difference ranges of $\Delta\delta_{4',9'\text{-H}}$ = 0.30 - 1.05 ppm for the 4′,9′-

H pairs (higher separation is observed in compound **37**) and $\Delta\delta_{8',10'\text{-H}}$ = 0.1 - 0.5 ppm for the 8′,10′-H pairs (Table 1) were obtained. Protons 4′ax, 9′ax-H are more deshielded than the 8′ax,10′ax-H protons. For example, in the spectrum of compound **23** (Figure 1) the $\Delta\delta$(γ-CH_2) value is 0.88 ppm for the 4′,9′-H pairs compared to 0.21 ppm for the 8′,10′-H pairs; this in turn implies that redistribution of electronic shielding over the γ-cyclohexane CH_2 group is affected more from C-$H_{ax}\cdots NMe_2$ contact rather than the C-$H_{ax}\cdots$H-C contact (Y = NMe_2, A = CH_3). The GIAO calculations predicted correctly the relative chemical shifts positions.

The positions of the other resonances in the ^{1}H NMR spectrum were identified as follows. The broad signal of the equivalent protons 1′,3′-H was easily assigned using the corresponding carbon resonances 1′,3′-C via $^1J_{CH}$ correlations in the HMQC 2D spectra. The resonances of the chemically non equivalent protons 5′,7′-H were coincident for compounds **11, 12, 14, 20, 21, 23, 25**–**28** and **37**; in all the other cases the broad signals of the 5′-H and 7′-H protons, differing a little in the chemical shift, can be differentiated through their ^3J scalar correlations with 4′,9′-H or 8′,10′-H doublets, respectively, in the 2D COSY spectra. A discussion about the relative position of 5′-H and 7′-H resonances can be found in the Supporting Information. The GIAO calculations predicted correctly the relative chemical shifts position of 5′- and 7′-H proton resonances in the above cases. The deviation of GIAO calculated values from experimental values for most ^{1}H NMR chemical shifts is <0.7 ppm; this deviation is similar to the values previously observed**.**[16,21]

2.1.2 ^{13}C NMR Spectroscopy

The ^{13}C chemical shifts of the adamantane derivatives **1**–**38** are given in Table 2. The differentiation between γ-, and δ-carbons, that is, between 4′,9′-C and 8′,10′-C and between 5′-C and 7′-C was the main task of the ^{13}C NMR spectra assignment.

The first reported assignment of carbons 4′,9′ and 8′,10′ of a 2,2-disubstituted adamantane was made for 2-methyl-2-adamantanol **14** on the basis of lanthanide-induced shift experiments.[11e]

In another previous work, the signals of 4′,9′-C and 8′,10′ carbon pairs were assigned systematically by measuring the ^{13}C-^{13}C coupling constants using the 2D INADEQUATE experiment.[11c,20] This experiment was first applied to 2-substituted adamantanes for the differentiation of 5′,7′-C signals; however the assignment of these carbon signals in 2,2-disubstituted adamantanes was not unambiguous. Rather than performing time consuming and sample demanded experiments, we identified the location of 4′,9′-C and 8′,10′-C peaks (see Table 2) using the unequivocal assignment of 4′,9′-H and 8′,10′-H proton signals and their $^1J_{\text{C-H}}$ correlations with the studied carbons (2D HSQC or HMQC experiment). The resonances of 5′,7′-carbon resonances were differentiated using the $^1J_{\text{C-H}}$ correlations and the assigned 5′,7′-proton resonances. When 5′,7′-H signals were almost overlapped (see for example compounds **17**, **26** etc), the $^2J_{\text{C-H}}$ correlations between 4′,9′-H and 5′-C carbon or between 8′,10′-H and 7′ were employed as obtained from 2D HMBC spectra, but also the GIAO calculations results were used to assign 5′,7′-C signals and to confirm other carbon resonance assignments.[21]

Table 2. ^{13}C Chemical shifts of adamantane carbons for the adamantanes derivatives **1**–**38**.

Compound[a]		*α*-C C(2′)	*β*-C C(1′,3′)	*γ*-syn C(4′,9′)	*γ*-anti C(8′,10′)	*δ*-syn C(5′)	*δ*-anti C(7′)	*ε*-C C(6′)
1 (Y = **H**, A = H)	Exp.	37.90	28.60	37.90	37.90	28.60	28.60	38.90
	Calc.	41.78	35.02	41.66	41.79	34.90	34.90	41.63
		(Δδ=3.88)	(Δδ=6.42)	(Δδ=3.76)	(Δδ=3.89)	(Δδ=6.30)	(Δδ=6.30)	(Δδ=2.73)
2 (Y = **C**H$_3$, A = H)	Exp.	39.10	33.80	31.20	39.50	28.50	28.20	38.60
	Calc.	45.14	40.10	35.73	43.40	35.10	34.56	42.66
		(Δδ=6.04)	(Δδ=6.30)	(Δδ=4.53)	(Δδ=3.90)	(Δδ=6.60)	(Δδ=6.36)	(Δδ=4.06)
3 (Y = C(**C**H$_3$)$_3$, A = H)	Exp.	54.10	29.50	33.10	41.90	28.80	27.80	38.70
	Calc.	57.63	35.64	35.05	43.94	34.53	33.39	40.89
		(Δδ=3.53)	(Δδ=6.14)	(Δδ=1.95)	(Δδ=2.04)	(Δδ=5.73)	(Δδ=5.59)	(Δδ=2.19)
4 (Y = **C**≡**N** , A = H)	Exp.	37.16	30.54	33.24	36.77	27.05	26.89	36.86
	Calc.	40.93	38.05	36.48	41.04	33.60	33.57	40.90
		(Δδ=3.77)	(Δδ=7.51)	(Δδ=3.24)	(Δδ=4.27)	(Δδ=6.55)	(Δδ=6.68)	(Δδ=4.04)
5 (Y = **O**H, A = H)	Exp.	74.66	34.64	31.12	36.62	27.62	27.17	37.69
	Calc.	79.37	41.45	35.09	40.59	34.28	33.94	41.49
		(Δδ=4.64)	(Δδ=6.81)	(Δδ=3.97)	(Δδ=3.97)	(Δδ=6.66)	(Δδ=6.77)	(Δδ=3.80)
6 (Y = **O**Me, A = H)	Exp.	83.41	31.47	31.58	36.65	27.61	27.57	37.75
	Calc.	87.37	37.53	35.48	40.56	34.33	34.12	41.76
		(Δδ=3.96)	(Δδ=6.06)	(Δδ=3.90)	(Δδ=3.91)	(Δδ=6.72)	(Δδ=6.62)	(Δδ=4.01)
7 (Y = **N**H$_2$, A = H)	Exp.	55.62	35.08	30.86	37.82	27.84	27.40	38.06
	Calc.	60.59	40.82	34.63	41.19	35.00	34.34	42.14
		(Δδ=4.97)	(Δδ=5.74)	(Δδ=3.77)	(Δδ=3.37)	(Δδ=7.16)	(Δδ=6.94)	(Δδ=4.08)
8 (Y = **N**Me$_2$, A = H)	Exp.	70.20	31.64	30.20	37.54	28.05	27.67	38.19
	Calc.	74.55	36.90	35.37	41.21	34.19	33.75	42.32

		(Δδ=4.35)	(Δδ=5.26)	(Δδ=5.17)	(Δδ=3.67)	(Δδ=6.14)	(Δδ=6.08)	(Δδ=4.13)
9 (Y = NHCOMe, A = H)	Exp.	53.42	30.45	32.03	37.24	27.34	27.23	37.65
	Calc.	57.65	38.03	36.45	41.52	34.01	33.99	41.37
		(Δδ=4.23)	(Δδ=7.58)	(Δδ=4.42)	(Δδ=4.28)	(Δδ=6.65)	(Δδ=6.78)	(Δδ=3.72)
10 (Y = NO_2, A = H)	Exp.	89.13	31.54	32.50	37.44	27.10	27.10	37.44
	Calc.	92.75	36.53	36.71	40.98	33.28	33.01	41.26
		(Δδ=3.62)	(Δδ= 4.99)	(Δδ=4.21)	(Δδ=3.54)	(Δδ=6.18)	(Δδ=5.91)	(Δδ=3.82)
11 (Y = F, A = H)	Exp.	95.60	32.90	31.50	35.80	27.70	27.30	37.30
	Calc.	99.61	39.22	35.90	39.72	33.90	33.39	41.45
		(Δδ=4.01)	(Δδ=6.32)	(Δδ=4.40)	(Δδ=3.92)	(Δδ=6.20)	(Δδ=6.09)	(Δδ=4.15)
12 (Y = Cl, A = H)	Exp.	68.10	36.00	35.00	38.30	27.60	27.00	37.90
	Calc.	78.56	42.25	34.95	42.31	33.89	33.34	41.78
		(Δδ=10.46)	(Δδ=6.25)	(Δδ=0.05)	(Δδ=4.01)	(Δδ=6.29)	(Δδ=6.34)	(Δδ=3.88)
13 (Y = SH, A=H)	Exp.	46.50	35.70	31.0	38.90	27.90	27.10	37.90
	Calc.	57.29	41.32	34.99	43.51	34.92	34.11	42.02
		(Δδ=10.46)	(Δδ=5.62)	(Δδ=3.99)	(Δδ=4.61)	(Δδ=7.02)	(Δδ=7.01)	(Δδ=4.12)
14 (Y = OH, A = CH_3)	Exp.	73.97	39.19	33.06	35.22	27.61	27.11	38.39
	Calc.	77.25	45.27	38.93	37.31	34.37	33.80	41.92
		(Δδ=3.28)	(Δδ=6.08)	(Δδ=5.87)	(Δδ=2.09)	(Δδ=6.76)	(Δδ=6.69)	(Δδ=3.53)
15 (Y = OH, A = $C(CH_3)_3$)	Exp.	77.40	34.60	35.60	35.00	27.10	27.00	39.50
	Calc.	82.68	41.35	38.50	39.50	33.84	33.78	43.36
		(Δδ=5.28)	(Δδ=6.75)	(Δδ=3.50)	(Δδ=4.90)	(Δδ=6.68)	(Δδ=6.84)	(Δδ=3.86)
16 (Y = OH, A = Ph)	Exp.	75.71	35.69	33.05	34.97	27.02	27.53	37.77
	Calc.	81.12	42.34	36.12	37.14	33.27	34.13	40.07
		(Δδ=5.41)	(Δδ=6.65)	(Δδ=3.07)	(Δδ=2.17)	(Δδ=6.25)	(Δδ=6.60)	(Δδ=2.30)
17 (Y = OH, A = C≡CH)	Exp.	72.76	38.64	31.51	35.33	26.84	26.63	37.60
	Calc.	74.50	48.30	39.76	33.67	33.73	32.72	41.35
		(Δδ=1.74)	(Δδ=9.66)	(Δδ=8.25)	(Δδ=1.66)	(Δδ=6.89)	(Δδ=6.09)	(Δδ=3.75)
18 (Y = OH, A = C≡N)	Exp.	74.01	37.17	30.84	35.00	26.47	26.36	37.16
	Calc.	76.63	44.03	38.53	35.31	32.80	33.04	41.40
		(Δδ=2.62)	(Δδ=6.86)	(Δδ=7.69)	(Δδ=0.31)	(Δδ=6.33)	(Δδ=6.68)	(Δδ=4.24)
19 (Y = $OSiMe_3$, A = C≡N)	Exp.	74.89	37.39	31.13	34.91	26.54	26.37	38.28
	Calc.	81.31	44.87	36.71	36.57	32.18	32.27	39.55
		(Δδ=6.42)	(Δδ=7.48)	(Δδ=5.58)	(Δδ=1.66)	(Δδ=6.26)	(Δδ=5.90)	(Δδ=1.27)
20 (Y = O-COMe, A = CH_3)	Exp.	86.69	36.09	33.10	34.42	27.35	26.71	38.15
	Calc.	90.84	41.50	38.86	37.57	34.23	33.54	41.86
		(Δδ=4.15)	(Δδ=5.41)	(Δδ=5.76)	(Δδ=3.15)	(Δδ=6.88)	(Δδ=6.83)	(Δδ=3.71)
21 (Y = O-CO*t*Bu, A = CH_3)	Exp.	86.08	36.32	33.12	34.57	26.82	26.56	38.27
	Calc.	86.49	41.02	37.21	35.32	26.52	33.40	40.79
		(Δδ=0.41)	(Δδ=4.70)	(Δδ=4.09)	(Δδ=0.75)	(Δδ=0.30)	(Δδ=6.84)	(Δδ=2.52)
22 (Y = NH_2, A = CH_3)	Exp.	52.85	38.89	33.10	34.66	27.88	27.57	39.53
	Calc.	57.91	44.58	37.12	38.19	34.51	34.82	42.75
		(Δδ=5.06)	(Δδ=5.69)	(Δδ=4.02)	(Δδ=3.53)	(Δδ=6.63)	(Δδ=7.25)	(Δδ=3.22)
23 (Y = NMe_2, A = CH_3)	Exp.	58.77	34.48	32.15	34.18	27.44	27.44	37.43
	Calc.	64.06	40.42	36.37	38.18	33.58	34.34	42.58
		(Δδ=5.29)	(Δδ=5.94)	(Δδ=4.22)	(Δδ=4.00)	(Δδ=6.14)	(Δδ=6.90)	(Δδ=5.15)
24 (Y = $NHMe_2^+$, A = CH_3)	Exp.	~77.0	33.23	30.61	34.29	26.03	25.55	37.71
	Calc.	83.24	39.94	36.47	37.66	31.57	31.45	40.07
		(Δδ=6.24)	(Δδ=6.71)	(Δδ=5.86)	(Δδ=3.37)	(Δδ=5.54)	(Δδ=5.90)	(Δδ=2.36)
25 (Y, A = $NH(CH_2)_4$)	Exp.	54.40	34.06	32.19	33.47	28.00	27.50	39.10
	Calc.	58.98	42.17	36.68	37.26	35.12	35.44	42.80
		(Δδ=4.58)	(Δδ=8.11)	(Δδ=4.49)	(Δδ=3.79)	(Δδ=7.12)	(Δδ=7.94)	(Δδ=3.70)
26 (Y, A = $NMe(CH_2)_4$)[b]	Exp.	57.90	34.50	31.40	33.00	27.20	27.00	38.60
	Calc.	64.74	38.57	34.65	35.78	33.92	33.83	40.52
		(Δδ=6.84)	(Δδ=4.07)	(Δδ=3.25)	(Δδ=2.78)	(Δδ=6.72)	(Δδ=6.83)	(Δδ=1.98)
27 (Y = NHCOMe, A = CH_3)	Exp.	58.52	35.36	33.22	33.32	27.55	26.91	38.54
	Calc.	63.98	40.84	37.63	37.70	33.83	34.33	42.15
		(Δδ=5.46)	(Δδ=5.48)	(Δδ=4.41)	(Δδ=4.38)	(Δδ=6.28)	(Δδ=7.42)	(Δδ=3.61)
28 (Y = NHCO*t*Bu, A = CH_3)	Exp.	57.75	35.49	33.34	33.37	27.56	26.96	38.54
	Calc.	65.61	41.32	35.93	36.48	33.17	34.16	40.48
		(Δδ=7.86)	(Δδ=5.83)	(Δδ=2.59)	(Δδ=3.11)	(Δδ=5.61)	(Δδ=7.20)	(Δδ=1.94)
29 (Y = N-N≡N, A = CH_3)	Exp.	67.31	36.38	33.54	34.04	26.97	27.42	38.35
	Calc.	72.59	42.33	37.90	37.98	34.42	33.72	42.25

		(Δδ=5.28)	(Δδ=5.95)	(Δδ=4.36)	(Δδ=3.94)	(Δδ=7.45)	(Δδ=6.30)	(Δδ=3.90)
30 (Y = **F** , A = **C**H$_3$)	Exp.	98.88[c]	37.96[d]	33.14	35.55	25.53	26.80	37.93
	Calc.	102.30	43.88	37.51	39.21	33.24	34.06	41.47
		(Δδ=3.42)	(Δδ=5.92)	(Δδ=4.37)	(Δδ=3.66)	(Δδ=7.71)	(Δδ=7.26)	(Δδ=3.54)
31 (Y = **Cl**, A = **C**H$_3$)	Exp.	73.78	39.26	33.10	35.27	27.68	27.17	38.45
	Calc.	93.92	46.92	39.52	38.16	33.99	33.50	43.04
		(Δδ=20.14)	(Δδ=7.66)	(Δδ=6.42)	(Δδ=2.89)	(Δδ=6.31)	(Δδ=6.33)	(Δδ=4.59)
32 (Y = CMe$_2$**O**H, A = H)	Exp.	53.78	29.25	33.12	38.55	27.73	27.14	41.23
	Calc.	57.12	37.07	36.25	44.98	34.26	35.19	42.59
		(Δδ=3.34)	(Δδ=7.82)	(Δδ=3.13)	(Δδ=6.43)	(Δδ=6.53)	(Δδ=8.05)	(Δδ=1.36)
33 (Y = CMe$_2$**F**, A = H)	Exp.	-[e]	29.0	32.60	38.50	27.60	26.30	-[e]
	Calc.	56.16	36.82	36.20	44.62	34.26	35.01	42.44
			(Δδ=7.82)	(Δδ=3.60)	(Δδ=6.12)	(Δδ=6.66)	(Δδ=8.71)	
34 (Y= C**O**Me, A = H)	Exp.	57.86	29.39	33.45	38.49	27.67	27.67	37.40
	Calc.	62.48	35.71	35.13	40.85	33.72	33.50	39.88
		(Δδ=4.62)	(Δδ=6.32)	(Δδ=1.68)	(Δδ=2.36)	(Δδ=6.05)	(Δδ=5.83)	(Δδ=2.48)
35 (Y= C**O**$_2$H, A = H)	Exp.	49.60	29.50	37.45	33.68	27.51	27.53	38.20
	Calc.	53.59	35.67	37.40	42.33	33.88	34.04	41.38
		(Δδ=3.99)	(Δδ=6.17)	(Δδ=0.05)	(Δδ=8.65)	(Δδ=6.35)	(Δδ=6.53)	(Δδ=3.18)
36 (Y, A= C**O**(CH$_2$)$_2$	Exp.	71.57	33.44	33.72	33.84	27.14	26.88	37.34
	Calc.	76.55	40.48	38.13	36.98	33.05	34.00	41.29
		(Δδ=4.98)	(Δδ=7.04)	(Δδ=4.41)	(Δδ=3.14)	(Δδ=5.91)	(Δδ=7.12)	(Δδ=3.95)
37 (Y, A= C**O**(CH$_2$)$_3$	Exp.	53.09	32.17	32.03	33.97	27.58	27.25	38.17
	Calc.	59.01	39.90	35.12	38.80	33.95	34.54	42.78
		(Δδ=5.92)	(Δδ=7.73)	(Δδ=3.09)	(Δδ=4.83)	(Δδ=6.37)	(Δδ=7.29)	(Δδ=4.61)
38 (Y, A= C**O**(CH$_2$)$_4$	Exp.	55.38	32.54	32.10	34.51	28.26	27.61	38.55
	Calc.	61.33	38.99	38.39	35.94	34.93	34.34	42.46
		(Δδ=5.95)	(Δδ=6.45)	(Δδ=6.29)	(Δδ=1.43)	(Δδ=6.67)	(Δδ=6.73)	(Δδ=3.91)

[a]spectra recorded at 298 K or otherwise stated; [b]recorded at 273 K; [c]doublet $^1J_{C-F}$=171.8, [d]doublet $^2J_{C-F}$=19.2,3 [e]not clearly resolved.

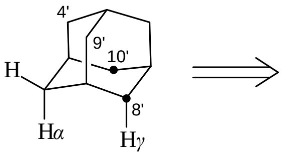
The spectra of compounds **1**–**38** showed that 4′,9′-C or 8′,10′-C resonances are shifted upfield relative to the carbon resonances of the parent adamantane molecule. For the monosubstituted adamantane derivatives **1**–**13** and **32**–**35**, these are the resonances of the 4′,9′-C carbons which are shifted upfield with respect to 8′,10′-C signals because of the γ-gauche effect exerted from substituent Y_{ax} on the resonances of 4′,9′-C carbons.[3,11] In the 2,2-disubstituted adamantanes **14**–**17** and **20**–**31** and **36**–**38**, 4′,9′-C resonances are generally shifted upfield with respect to 8′,10′-C signals, that is, a stronger upfield γ-effect of (Y_{ax}, A_{eq}) compared to that of (A_{ax}, Y_{eq}) was observed. In the above cases, carbons 4′,9′-C are in a syn-orientation with Y_{ax} group, which is, in general, a second or third row heteroatom or C=O group, and 8′,10′-C are in a γ-syn-orientation with A_{ax} group, which can be considered in general as an alkyl group. Compound **15** (Y = OH, A = tBu) represents the only exception, having a Δδ($\gamma_{a,s}$) = - 0.60 ppm; in this last compound 8′,10′-C resonances are shifted upfield with respect to 4′,9′-C signals (Table 2). The spectra of the adamantane derivatives showed that 5′-C resonance lies slightly downfield relative to 7′-C in most cases and the relevant discussion is provided in the Supporting information. The deviation of GIAO calculated values from experimental values for ^{13}C NMR chemical shifts is < 7ppm; this deviation is similar to the values previously observed.[16,21] In some cases GIAO failed to predict correctly the relative position of carbon signals (see Supporting Information).

2.2 ^{13}C Substituent Chemical Shifts

The upfield shift of 4′,9′-C with respect to 8′,10′-C carbons in the disubstituted adamantane derivatives **15**–**31** and **36**–**38** results from the effect of (Y_{ax}, A_{eq}) and (A_{ax}, Y_{eq}) fragments on the resonances of γ-carbons 4′,9′-C and 8′,10′-C, respectively. We will try next to comprehend the relative position of carbon resonances through considering the γ-effect (γ_g and γ_a) contributions from each of the two substituents Y, A on the resonances of these carbons. In the next paragraphs, we shall discuss first the γ_g and the γ_a effect contributions on the resonances of 4′,9′-C and then on the resonances of the 8′,10′-C carbons. Useful schemes first published by Duddeck's group are depicted also in the present study and the results for common substituents are similar (see Schemes 3-10).[11]

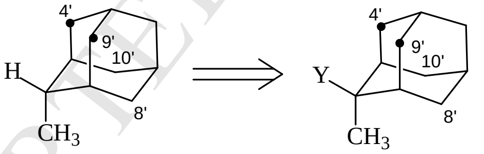
4′,9′-C resonances: The existence of a γ-gauche shielding effect on the resonances of 4′,9′-C, which can be attributed to the interaction between the polar substituent Y_{ax} (NR_2, OH, F, Cl, SH, N_3, CN, OCOR, NHCOR etc) and these carbons, is legitimate. In the related 2-substituted adamantanes **1-13**, the γ_g SCS value on the 4′,9′-C resonances exerted by the group Y, where Y = NR_2, OH, F, CN, OCOR, NHCOR, NO_2, COMe, CO_2H, OCOR, NHCOR, alkyl, CMe_2OH, CMe_2F, ranges from -2.9 to -7.3 ppm (Scheme 3).[11h] From Scheme 4 it becomes obvious that the presence of an alkyl substituent (A = Me, C_2H, Ph, *t*-Bu) at the same carbon doesn’t substantially influence the γ_g SCS of these substituents Y. And also from Scheme 5 is obvious that the addition of an alkyl group at the C-2 carbon of a monosubstituted adamantane derivative although it causes a downfield shift (an exception is present in the case of the 2-chloro group), will not change the upfield effect on the 4′,9′-C carbon resonances. Overall, it seems that a net upfield shift of the 4′,9′-C resonances relative to the corresponding carbon resonances of parent adamantane molecules is legitimate based on the γ_g effect of the substituent Y_{ax} (NR_2, OH, F, Cl, etc).

Scheme 3

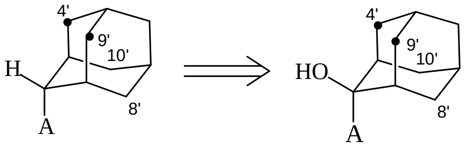


Y	Me	tBu	CN	NH_2	NMe_2	NH-COMe	OH	O-Me	O-COMe	NO_2	F	Cl	SH	COMe	CO_2H	CMe_2OH	CMe_2F
γ_gSCS	-6.6	-4.9	-4.8	-7.3	-6.3	-5.8	-6.5	-6.3	-5.9	-5.4	-6.4	-2.9	-6.9	-4.5	-4.2	-4.8	-4.9

Scheme 4

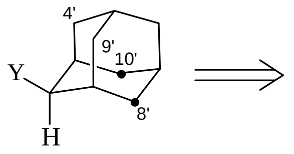


Y	Me	CN	N_3	NH_2	NMe_2	NHAc	OH	OMe	OAc	F	Cl
γ_gSCS	-6.3	-8.8	-6.0	-6.4	-7.4	-6.3	-6.4	-6.9	-6.4	-6.4	-6.4



A	Me	Ph	t-Bu
γ_gSCS	-6.5	-6.4	-6.9

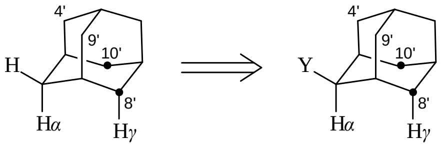
Scheme 5



Y	Me	CN	NH_2	NMe_2	NH-CO-Me	OH	O-Me	O-CO-Me	F	Cl
γ_aSCS	+2.0	-2.4	+1.9	+0.5	+0.6	+1.6	+1.1	+1.2	+1.6	-1.9

8′,10′-C resonances: In the 2-monosubstituted adamantanes **1**–**13, 32**–**35**, carbons 8′,10′-C experience the γ-anti effect (γ_a SCS) of the Y_{eq} group (Y = NR_2, OH, F, N_3, CN, OCOR, NHCOR, Cl etc). A polar group Y causes a small negative γ_a SCS (upfield shift) to the carbon atom situated in the γ-anti position, when 1,3-diaxial positions are free,[11h,k] and this structural issue is present in the 2-substituted adamantanes (Scheme 6); the γ_a SCS magnitude raises as electronegativity increases and the values for Y = NH_2, OH, F are ~ - 0.4, -1, and -2 ppm and respectively. An alkyl substituent causes a downfield effect. A second row heteroatom like Cl or SH exerted a small positive γ_a SCS (downfield shift).

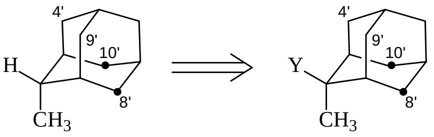
Scheme 6



Y	Me	CN	NH_2	NMe_2	NH-CO-Me	NO_2	OH	O-Me	O-CO-Me	F	Cl	SH
γ_aSCS	+1.6	-0.7	-0.3	-0.4	-0.5	-0.5	-1.1	-1.2	-1.3	-2.1	+0.4	+1.0

The γSCS values depend on conformation, branching and substituent pattern.[3b] It has been reported that the γ-anti effect of a second row polar group changes sign in systems having the heteroatom attached to a bridghead atom.[11k] Thus, when the α-hydrogen in the 2-monosubstituted adamantane is replaced by the axial alkyl substituent, γ_aSCS increases by 3-6 ppm, so the shielding contribution from substituent Y_{eq} on the γ-anti carbon signals disappear and 8′,10′-C carbons experience a downfield (positive) γ_aSCS in compounds **14**–**31**, **36**–**38** (Scheme 7). The magnitude of this downfield effect is smaller for the related 1-substituted adamantanes, being ~ +2.2 ppm for 1-adamantanol and +0.8 ppm for 1-adamantanamine. It is obvious from Scheme 10 that the magnitude of the downfield γ_a SCS increases with the electronegativity of the substituent, and the values for the amino, hydroxy and fluoro groups are ~ + 3.5, + 4.0 and + 4.4 ppm respectively.[11k]

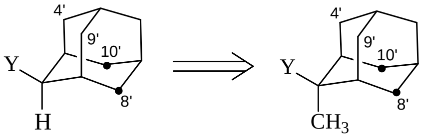
Scheme 7



Y	Me	CN	N_3	NH_2	NMe_2	NH-CO-Me	OH	O-Me	O-CO-Me	F	Cl
γ_aSCS	+2.0	+4.1	+2.8	+3.5	+3.0	+2.1	+4.0	+3.5	+3.2	+4.4	+4.4

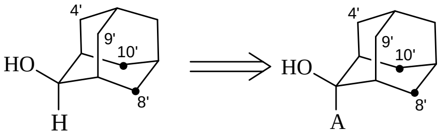
The resonances of 8′,10′-C should be affected from the upfield γ-gauche effect of the alkyl A_{ax} substituent, but its magnitude is expected to be seriously diminished when a first row atom substituent is already present at the same carbon, as it is shown for some examples in Schemes 8 and 9.

Scheme 8



Y	NH_2	NMe_2	NH-CO-Me	OH	O-Me	O-CO-Me	F	Cl
γ_gSCS	-2.9	-3.4	-4.0	-1.6	-1.9	-2.1	-0.3	-3.0

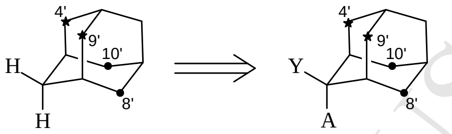
Scheme 9



A	Me	C_2H	Ph	t-Bu
γ_gSCS	-1.7	+0.1	-1.9	-1.9

Finally, the SCS effected from a pair of substituents Y,A attached at 2-position on the resonances of *γ*-carbons were compared; two pairs of *γ*-carbons exist, that is, the carbons 4′,9′-C and 8′,10′-C (Scheme 10). Carbons 4′,9′-C experienced the effect of the Y_{ax},A_{eq} arrangement in cyclohexane ring sub-unit 1′-2′-3′-4′-5′-9′ and 8′,10′-C experienced the effect of the A_{ax},Y_{eq} arrangement in cyclohexane ring sub-unit 1′-2′-3′-10′-7′-8 (see Scheme 1). Data for 2,2-disubstituted adamantane derivatives **14**–**31** and **36**–**38** were analyzed.

Scheme 10



Y	Me	CN	N_3	$NHMe_2^+$	NH_2	NMe_2	NH-Ac	OH	$OSiMe_3$	O-Ac	OCOtBu	OH	OH	OH	F
A	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Me	Ph	C_2H	*t*-Bu	Me
$\gamma_{(4',9')}$SCS	-4.5	-7.2	-4.4	-7.3	-4.8	-5.8	-4.7	-4.8	-6.8	-4.8	-4.8	-4.9	-4.8	-2.3	-4.8
$\gamma_{(8',10')}$SCS	-4.5	-2.6	-3.9	-3.6	-3.2	-3.7	-4.6	-2.7	-2.9	-3.5	-3.3	-2.9	-0.9	-2.9	-2.3

Y	Cl	C=O	C=O	C=O
A	Me	$(CH_2)_2$	$(CH_2)_3$	$(CH_2)_4$
$\gamma_{(4',9')}$SCS	-4.8	-4.2	-5.6	-5.8
$\gamma_{(8',10')}$SCS	-2.6	-4.1	-3.9	-3.4

It becomes clear from the above discussion that both pairs of *γ*-carbons experience a total upfield shift effect compared to the carbons of the parent adamantane. The upfield shift is larger in magnitude for 4′,9′-C, effected from heteroatom substituents Y, resulting in the downfield shift of 8′,10′-C relative to 4′,9′-C resonances. The downfield shift of the γ-carbons in the (Y_{eq}, Me_{ax}) conformer relative to (Y_{ax}, Me_{eq}) has been observed in 1-Y-1-methylcyclohexanes and 4-tert-butyl-1-Y-1-methylcyclohexanes using DNMR spectroscopy.[11a,22]

2.3 C-H_{ax}···Y_{ax} contacts

It has been suggested that the identification of a delocalization interaction $n(Y) \rightarrow \sigma^*(C\text{-}H$ or $\sigma(C\text{-}H) \rightarrow \sigma^*(C\text{-}H)$ assures the presence of a hydrogen bonded contact.[23-26] In a preceding paper, the calculations predicted the improper H-bonding character of $C\text{-}H_{ax}\cdots Y_{ax}$ contacts in common cyclohexane derivatives, due to the presence of $n(Y) \rightarrow \sigma^*(C\text{-}H$ or $\sigma(C\text{-}H) \rightarrow \sigma^*(C\text{-}H)$ hyperconjugative interactions, and the variation of its strength according to the nature of contact atom in group Y_{ax}.[6] By increasing the strength of the contact the electronic redistribution inside the γ-methylene is affected consistently raising the relevant chemical shift separation between the γ-methylene protons, $\Delta\delta(\gamma\text{-}CH_2)$.[7] It is noted that changes of 0.1–1 ppm in the C–H proton chemical shift have been observed in a limited number of cases and are taken as evidence for the existence of $C\text{–}H\cdots O$ hydrogen bonds in solution.[27]

An attempt was sought to analyze the interactions between axial substituents and C-Hax groups using natural bond orbital (NBO) analysis[24a] - which analyzes the molecular wave function to a set of localized bond and lone pair orbitals – applied in the B3LYP/6-31+G**geometry optimized structures of the global minima at the same level of theory. Selected calculated parameters are included in Table 3. The NBO analysis revealed that in all molecules the $C\text{-}H_{ax}\cdots Y$ contacts cause an increase in % s-character and a contraction of the $C\text{-}H_{ax}$ bonds relative to the equatorial bonds, and an increase in proton positive charge of axial relative to equatorial hydrogens in the cyclohexane-subunit of the adamantane ring (the corresponding values of Δ% s-char. = (% s-char. $C_{4'}\text{-}H_{ax}$ − % s-char $C_{4'}\text{-}H_{eq}$), $\Delta r_{4'} = r(C_{4'}\text{-}H_{ax}) - r(C_{4'}\text{-}H_{eq})$, $\Delta r_{9'} = r(C_{9'}\text{-}H_{ax}) - r(C_{9'}\text{-}H_{eq})$ and $\Delta q = q(H_{4'ax}) - q(H_{4'eq})$ or $q(H_{9'ax}) - q(H_{9'eq})$ respectively are included in Table 3). In compounds **2**–**38**, the $C\text{-}H_{ax}\cdots Y$ contact distances were smaller than the sum of the van der Waals radii.[28] The existence of hyperconjugative interactions $n(Y) \rightarrow \sigma^*(C\text{-}H_{ax})$ in molecules **2**–**38** was examined by the NBO method at the B3LYP/6-31+G**; second order perturbative energies are shown in Table 3 and the energy difference between the interacting orbitals and the matrix elements are included in Table S2 in the Supporting Information. The calculations located overlap interactions in most of compounds **2–38** (see Table 3). Although the first effects, i.e., the inequality $r_{H\cdots Y} < r_{vdw,H} + r_{vdw,Y}$, the increase in the % s-character and the contraction of the C-H bond, are common in improper H-bonded contacts,[29] the identification of a covalent component in a C-H···Y contact, i.e., the calculation of a hyperconjugative interaction n(Y) → σ*(C-H) is diagnostic for the presence of improper hydrogen bonding.[24] The resonance structures, $C^{\delta-}$-$H^{\delta+}$ + :Y ↔ C^{-} + H-Y^{+} for a neutral H-bonded complex describe qualitatively this electron transfer. However, the degree of hyperconjugative electron transfer is only one of the effects contributing to improper hydrogen bonding, the strength of which is also reflected by the increase in the % s-character and the contraction of the C-H_{ax} bond length.

Table 3. Structural parameters[a-c] calculated and hyperconjugative energies for the C-H$_{ax}\cdots$Y$_{ax}$ contacts included in the adamantane derivatives **1**–**38** calculated at the B3LYP/6-31G+** level of theory; in addition ^{1}H chemical shift separation of the γ-CH$_2$ pairs[d] of adamantane cyclohexane ring subunits for molecules **1**–**38**.

System	C4-H$_{ax}$, C9-H$_{ax}$ C4-H$_{eq}$, C9-H$_{eq}$ Å	C8-H$_{ax}$, C10-H$_{ax}$ C8-H$_{eq}$, C10-H$_{eq}$ Å	$r_{C4'Hax\cdots Y}$, $r_{C9'Hax\cdots Y}$ $r_{C8'Hax\cdots Y}$, $r_{C10'Hax\cdots Y}$ Å	$\theta_{C4'Hax\cdots Y}$, $\theta_{C9'Hax\cdots Y}$ $\theta_{C8'Hax\cdots Y}$, $\theta_{C10'Hax\cdots Y}$ deg	$\Delta r_{4'},\Delta r_{9'}$[a] $\Delta r_{8'},\Delta r_{10'}$[b] *m*Å	$\Delta q_{4'},\Delta q_{9'}$[c] $\Delta q_{8'},\Delta q_{10'}$[d] *m*e	Δ% s-char $_{4',9'}$[e] Δ% s-char $_{8',10'}$.[f]	hyperconjugative interaction kcal mol^{-1} $E[n_a \text{ or } \sigma(Y) \rightarrow \sigma^*(C4'\text{-}H_{ax})]$ $E[n_a \text{ or } \sigma(Y) \rightarrow \sigma^*(C9'\text{-}H_{ax})]$	$\Delta\delta_{4',9'\text{-H}}$	$\Delta\delta_{8',10'\text{-H}}$
1 (Y = **H**, A = H)[c]	1.0986, 1.0986	1.0986, 1.0986	2.56, 2.56	89, 89	0, 0	0, 0	0	-	0.0	0.0
	1.0986, 1.0986	1.0986, 1.0986	2.56, 2.56	88.8, 88.8	0, 0	0, 0	0			
2 (Y = C**H**$_3$, A = H)	1.0972, 1.0972	1.0986, 1.0986	2.29, 2.29	95.8, 95.8	-1.4, -1.4	-2, 0	0.31, 0.31	$E[\sigma(C\text{-}H) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.21$	0.45	-0.09
	1.0986,1.0986	1.0987, 1.0987	2.44, 2.44	113.4, 113.4	0, 0	0, 0	-0.01, 0.01	$E[\sigma(C\text{-}H) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.21$		
3 (Y = C(**CH**$_3$)$_3$, A = H)	1.0931, 1.0956	1.0983, 1.0988	2.10, 2.10	117.1, 120.2	-5.9, -3.4	2, -3	0.97, 0.61	$E[\sigma(C\text{-}H)^g \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.63$	0.50	0.10
	1.0990, 1.0990	1.0988, 1.0987	2.30, 2.32	89.6, 89.4	-0.5, 0.1	-2, 0	0.13, 0.13	$E[\sigma(C\text{-}H)^g \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.60$		
4 (Y = **CN**, A = H)	1.0968, 1.0968	1.0985, 1.0985	2.93, 2.93	107.0, 107.0	-0.8, -0.8	9, 9	0.37, 0.37	$E[\pi(C\equiv N) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.13$	0.41	0.16
	1.0976, 1.0976	1.0976, 1.0976	2.48, 2.48	89.3, 89.4	0.9, 0.9	-6, -6	-0.02, -0.02	$E[\pi(C\equiv N) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.11$		
5 (Y = **O**H, A = H)	1.0954, 1.0959	1.0988, 1.0986	2.62, 2.68	96.0, 96.0	-3.0, -2.6	16, 16	0.59, 0.37	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.21, \alpha = sp^{1.1}$	0.54	0.16
	1.0984, 1.0985	1.0980, 1.0978	2.46, 2.47	89.8, 89.3	0.8, 0.8	-4, -4	-0.24, -0.09	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.25, \beta = p$		
6 (Y = **O**Me, A = H)	1.0954, 1.0960	1.0989, 1.0987	2.60, 2.68	96.1, 95.9	-3.1, -2.5	20, 14	0.65, 0.46	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.25, \alpha = sp^{1.4}$	0.54	0.19
	1.0985, 1.0985	1.0982, 1.0979	2.50, 2.49	91.3, 91.4	-0.7, -0.8	-3, -4	-0.06, -0.02	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.18, \beta = p$		
7 (Y = **N**H$_2$, A = H)	1.0949, 1.0949	1.0987, 1.0987	2.67, 2.67	96.7, 96.7	-3.8, -3.8	22, 22	0.71, 0.71	$E[n_a(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.40, \alpha = sp^{4.3}$	0.45	0.12
	1.0987, 1.0987	1.0981, 1.0981	2.43, 2.43	89.4, 89.4	0.6, 0.6	-3, -3	-0.03, -0.03	$E[n_a(N) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.40$		
8 (Y = **N**Me$_2$, A = H)	1.0958, 1.0958	1.0985, 1.0985	2.71, 2.71	97.2, 97.2	-2.9, -2.9	14, 14	0.64, 0.64	$E[n_a(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.23, \alpha = sp^{6.2}$	0.87	0.17
	1.0987, 1.0987	1.0983, 1.0983	2.48, 2.48	89.6, 89.6	0.2, 0.2	-2, -2	0, 0	$E[n_a(N) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.23$		
9 (Y = **NH**Ac, A = H)	1.0981, 1.0997	1.0979, 1.0979	2.16, 2.67	93.8, 95.3	0.2, 1.7	-5, -26	-0.01, -0.30	$E[n_\alpha(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})]=0.21, \alpha = p$	0.27	0.15
	1.0979, 1.0980	1.0981, 1.0980	2.47, 2.46	89.5, 89.5	-0.2, -0.1	3, 4	0.11, 0.09	$E[n_a(N\text{-}H) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.15$		
10(Y = **N**O$_2$, A = H)	1.0973, 1.0974	1.0986, 1.0986	2.81, 2.81	95.67, 95.78	-0.3, -0.2	6, 6	1.06, 0.38	$E[n_\alpha(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})]=0.21$	0.49	0.15
	1.0976, 1.0976	1.0974, 1.0974			1.2, 1.2	-8, -8	0.02, 0.03	$\alpha = p$		
11 (Y = **F**, A = H)	1.0957, 1.0957	1.0987, 1.0987	2.61, 2.61	95.3, 95.3	-2.3, -2.3	16, 16	0.44, 0.44	-	0.53	-0.19
	1.0980, 1.0980	1.0976, 1.0975	2.54, 2.54	88.9, 88.9	1.1, 1.2	-5, -5	-0.03, -0.03			
12 (Y = **Cl**, A = H)	1.0956, 1.0956	1.0984, 1.0984	2.88, 2.88	102.2, 102.2	-2.2, -2.2	14, 14	0.55, 0.55	$E[n_a(Cl) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.37$	0.70	-0.15
	1.0978, 1.0978	1.0977, 1.0977	2.48, 2.48	89.3, 89.3	0.7, 0.7	-5, -5	0.11, 0.11	$E[n_a(Cl) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.37, \alpha = p$		
								$E[n_\beta(Cl) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.15$		
								$E[n_\beta(Cl) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.15, \beta = p$		
13 (Y = **S**H, A = H)	1.0970, 1.0962	1.0984, 1.0987	2.88. 2.93	102.3, 102.7	-1.3, -2.2	16, 14	0.46, 0.99	$E[n_a(S) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.30$	0.68	-0.10
	1.0983, 1.0984	1.0983, 1.0984	2.46, 2.46	89.3, 89.5	0.1, 0.3	-5, -3	0.12, 0.05	$E[n_\alpha(S) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.10, \alpha = sp^{0.5}$		
								$E[n_a(S) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.11$		
								$E[n_\alpha(S) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.73, \alpha = p$		
14 (Y = **O**H, A = C**H**$_3$)	1.0939, 1.0945	1.0965, 1.0966	2.46, 2.53	97.2, 96.9	-4.5, -3.9	26, 19	0.94, 0.70	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.40, \alpha = sp^{1.1}$	0.63	0.13
	1.0984, 1.0984	1.0981, 1.0979	2.21, 2.22	113.3, 113.2	-1.6, -3.3	-3, -5	0.36, 0.40	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.37, \beta = p$		
15 (Y = **O**H, A = C(**CH**$_3$)$_3$)	1.0919, 1.0935	1.0902, 1.0941	2.34, 2.44	97.3, 96.5	-6.9, -5.0	30, 14	1.42, 0.91	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.54, \alpha = sp^{1.1}$	0.79	0.49
	1.0988, 1.0985	1.0985, 1.0984	1.96, 2.04	117.7, 121.6	-8.3, -4.3	3, -8	1.37, 0.87	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.38, \beta = p$		
16 (Y = **O**H, A = **Ph**)	1.0942, 1.0945	1.0962, 1.0965	2.47, 2.53	97.4, 97.2	-4.0, -3.8	25, 21	0.96, 0.79	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.39, \alpha = sp^{1.1}$	0.68	0.02
	1.0984, 1.0983	1.0983, 1.0980	3.55, 3.56	119.4, 119.5	-2.1, -1.5	5, 4	0.45, 0.54	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.42, \beta = p$		
17 (Y = **O**H, A = **C$_2$**H)	1.0943, 1.0946	1.0963, 1.0965	2.49, 2.53	97.1, 97.0	-3.9, -3.5	22, 17	0.90, 0.82	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.33, \alpha = sp^{1.2}$	0.62	0.36
	1.0982, 1.0981	1.0979, 1.0978	2.91, 2.89	108.0, 108.1	-1.6, -1.3	8, 7	0.53, 0.53	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.41, \beta = p$		
18 (Y = **O**H, A = C**N**)	1.0942, 1.0946	1.0966, 1.0967	2.52, 2.60	96.7, 96.4	-3.5, -3.2	17, 10	0.84, 0.60	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.33, \alpha = sp^{1.2}$	0.51	0.19
	1.0977, 1.0978	1.0974, 1.0973	2.85,2.83	107.9, 108.1	-0.8, -0.6	6, 6	0.50, 0.51	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.41, \beta = p$		

19(Y = **O**TMS, A = C**N**)	1.0944, 1.0958	1.0962, 1.0960	2.56, 2.52	96.6, 96.9	-3.5, -3.2	16, 12	0.79, 0.66	$E[n_a$(O) → σ^*(C4′-H$_{ax}$)] = 0.24, α = sp$^{1.2}$	0.55	0.21
	1.0981, 1.0979	1.0978, 1.0978	2.81, 2.81	108.2, 108.1	-1.6, -1.8	6, 6	0.51, 0.51	$E[n_\beta$(O) → σ^*(C9′-H$_{ax}$)] = 0.33, β = p		
20 (Y= **O**Ac, A = C**H**$_3$)	1.0944, 1.0958	1.0962, 1.0960	2.45, 2.58	97.3, 96.3	-3.7, -2.1	3, 15	0.40, 0.71	$E[n_a$(O)→σ^*(C4′-H$_{ax}$)] =0.49	0.46	0.15
	1.0981, 1.0979	1.0978, 1.0978	2.17, 2.23	113.2, 112.7	-1.6, -1.8	-5, -3	0.50, 0.50	$E[n_\beta$(O)→σ^*(C4′-H$_{ax}$)] =1.09		
								α = sp$^{0.7}$, β = p		
21 (Y = **O**COtBu, A= C**H**$_3$)	1.0941, 1.0955	1.0959, 1.0962	2.47, 2.59	97.1, 96.2	-4.1, -2.4	12, 7	0.48, 0.32	$E[n_a$(O) → σ^*(C4′-H$_{ax}$)] = 0.27,α=sp$^{1.83}$	0.46	0.15
	1.0982, 1.0979	1.0978, 1.0978	2.16, 2.23	113.1, 112.6	-1.9, -1.6	1, -1	0.12, 0.09			
22 (Y = **N**H$_2$, A = C**H**$_3$)	1.0935, 1.0935	1.0959, 1.0959	2.54, 2.54	97.6, 97.6	-5.2, -5.2	26, 26	1.0, 1.0	$E[n_a$(N) → σ^*(C4′-H$_{ax}$)] = 0.63, α = sp$^{4.2}$	0.48	0.31
	1.0987, 1.0987	1.0982, 1.0982	2.17, 2.17	113.4, 113.4	-2.3, -2.3	-3, -3	0.52, 0.52	$E[n_a$(N) → σ^*(C9′-H$_{ax}$)] = 0.63		
23 (Y = **N**Me$_2$, A = C**H**$_3$)	1.0939, 1.0939	1.0960, 1.0960	2.55, 2.55	98.2, 98.2	-4.9, -4.9	17, 17	0.97, 0.97	$E[n_a$(N) → σ^*(C4′-H$_{ax}$)] = 0.28, α = sp$^{7.4}$	0.88	0.21
	1.0988, 1.0988	1.0983, 1.0983	2.15, 2.15	113.0, 113.0	-2.3, -2.3	-3, -3	0.53, 0.53	$E[n_a$(N) → σ^*(C9′-H$_{ax}$)] = 0.28		
24 (Y = N**H**Me$_2^+$, A = C**H**$_3$)	1.1016, 1.1015	1.0946, 1.0947	1.96, 1.97	105.6, 105.4	6.1, 6.0	-55, -55	-0.85, -0.80	$E[\sigma$(C4′-H$_{ax}$) → σ^*(N-H)]=2.06	0.46	0.10
	1.0955, 1.0955	1.0960, 1.0960	2.16, 2.14	112.1, 112.4	-1.4, -1.3	-14, -14	0.44, 0.44	$E[\sigma$(C9′-H$_{ax}$) → σ^*(N-H)]=1.92		
25 (Y,A = **N**H(CH$_2$)$_4$)	1.0937, 1.0938	1.0961, 1.0959	2.55, 2.54	98.2, 97.4	-5.1, -5.0	20, 24	0.96, 0.97	$E[n_\alpha$(N)→σ^*(C4′-H$_{ax}$)]=0.50, α=sp$^{3.33}$	0.48	0.34
	1.0988, 1.0988	1.0983, 1.0982	2.12, 2.18	113.2, 112.5	-2.2, -2.3	-4, -3	0.53, 0.54			
26 (Y,A = **N**Me(CH$_2$)$_4$)^d	1.0939, 1.0943	1.0961, 1.0961	2.56, 2.60	98.9, 96.7	-4.9, -4.5	19, 20	-0.96, -0.97	-	0.81;0.71	0.13;0.22
	1.0988, 1.0988	1.0984, 1.0984	2.14, 2.14	112.9, 112.9	-2.3, -2.3	-5, -3	0.53, 0.54			
27 (Y = **N**HAc, A = C**H**$_3$)	1.0956, 1.0969	1.0954, 1.0956	2.18, 3.07	108.8, 96.9	-2.2, -1.3	4, -9	0.50, 0.23	$E[n_\alpha$(N) → σ^*(C4′-H$_{ax}$)]=0.21	0.36	0.29
	1.0978, 1.0982	1.0980, 1.0980	2.18, 2.14	113.2, 113.3	-2.6, -2.4	1, -2	0.60, 0.58	α = p		
28 (Y = **N**HCOtBu, A = C**H**$_3$)	1.0968, 1.0956	1.0956, 1.0952	2.16, 3.05		-1.4, -2.3	-9, 4	0.26, 0.49	$E[n_\alpha$(N)→σ^*(C4′-H$_{ax}$)]=0.11, α = sp$^{1.83}$	0.32	0.29
	1.0982, 1.0979	1.0979, 1.0980		113.3, 113.2	-2.3, -2.8	-2, 1	0.56, 0.58	$E[\sigma$(N-H) → σ^*(C4′-H$_{ax}$)] =0.11		
								$E[n_\beta$(N) → σ^*(C9′-H$_{ax}$)]=0.15, β =p		
29 (Y = **N**$_3$, A = C**H**$_3$)	1.0946, 1.0952	1.0959, 1.0961	2.49, 2.60	98.3, 97.0	-3.4, -2.6	8, 18	0.51, 0.76	$E[n_\alpha$(N)→σ^*(C4′-H$_{ax}$)]=0.57, α =sp$^{1.2}$	0.55	0.19
	1.0980, 1.0978	1.0978, 1.0976	2.19, 2.19	113.0, 113.2	-1.9, -1.5	-6, -5	0.45, 0.43			
30 (Y = **F**, A = C**H**$_3$)	1.0945, 1.0946	1.0967, 1.0967	2.48, 2.48	96.4, 96.4	-3.6, -3.4	20, 20	0.73, 0.73	-	0.61	0.13
	1.0981, 1.0980	1.0977, 1.0977	2.28, 2.28	113.2, 113.2	-1.0, -1.0	-5, -5	0, 0			
31 (Y = **Cl**, A = C**H**$_3$)	1.0940, 1.0940	1.0956, 1.0956	2.73, 2.73	104.0, 104.1	-4.0, -3.9	18, 18	0.90, 0.91	$E[n_\beta$(Cl) → σ^*(C4′-H$_{ax}$)]=0.64, β =p	0.63	0.13
	1.0980, 1.0979	1.0977, 1.0977			-2.1, -2.1	-6, -6	0.63, 0.63	$E[n_\beta$(Cl) → σ^*(C9′-H$_{ax}$)]=0.63		
32 (Y = CMe$_2$**O**H, A = H)	1.0933, 1.0933	1.0989, 1.0989	2.41, 2.41	118.9, 118.9	-6.0, -6.0	31, 31	1.39, 1.38	$E[n_a$(O) → σ^*(C4′-H$_{ax}$)] = 1.34	0.65	0.13
	1.0993, 1.0993	1.0986, 1.0986			0.3, 0.3	-4, -4	0.03, 0.03	$E[n_a$(O) → σ^*(C9′-H$_{ax}$)] = 0.98, α = sp$^{1.2}$		
								$E[n_\beta$(O) → σ^*(C4′-H$_{ax}$)] = 0.66		
								$E[n_\beta$(O) → σ^*(C9′-H$_{ax}$)] = 0.98, β = p		
33 (Y = CMe$_2$**F**, A = H)	1.0939, 1.0939	1.0989, 1.0989	2.39, 2.39	118.78,117.88	-5.1, -5.1	33, 33	1.18, 1.17	$E[n_a$(F) → σ^*(C4′-H$_{ax}$)] = 0.43	0.54	0.13
	1.0990, 1.0990	1.0984, 1.0984			0.5, 0.5	-5, -5	0, 0	$E[n_a$(F) → σ^*(C9′-H$_{ax}$)] = 0.30, α = sp$^{0.5}$		
								$E[n_\beta$(F) → σ^*(C4′-H$_{ax}$)] = 0.32		
								$E[n_\beta$(F) → σ^*(C9′-H$_{ax}$)] = 0.29, β = p		
								$E[n_\gamma$(F) → σ^*(C4′-H$_{ax}$)] = 0.41		
								$E[n_\gamma$(F) → σ^*(C9′-H$_{ax}$)] = 0.27, γ = p		
34 (Y = C**O**Me, A = H)	1.0924, 1.0963	1.0984, 1.0989	2.40, 2.77	$\underline{119.0}$, 115.0	-6.4, -2.2	34, 13	1.5, 0.64	$E[n_a$(O) → σ^*(C4′-H$_{ax}$)] = 0.49, α = sp$^{0.7}$		0.13
	1.0988, 1.0985	1.0983, 1.0980			0.1, 0.9	-5, -7	0.03, -0.04			
35 (Y = C**O**$_2$H, A = H)	1.0981, 1.0958	1.0988, 1.0986	2.82, 2.84	96.11, 96.22	0.1, -2.3	11, -1	0.65, 0.12		0.27	0.12
	1.0980, 1.0981	1.0978, 1.0980			1.0, 0.6	-5, -4	-0.08, -0.01			

36 (Y, A = C**O**(CH_2)$_2$	1.0952, 1.0952 1.0985, 1.0985	1.0978, 1.0978 1.0982, 1.0982	2.63, 2.63 2.42, 2.42	121.1, 121.2 97.7, 97.7	-3.3, -3.3 -0.4, -0.4	22, 22 -5, -4	0.88, 0.87 -0.08, -0.01	$E[n_\alpha(O)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.10$ $E[n_\alpha(O)\rightarrow\sigma^*(C9'\text{-}H_{ax})]=0.11$ $E[n_\beta(O)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.38$ $E[n_\beta(O)\rightarrow\sigma^*(C9'\text{-}H_{ax})]=0.39$ $\alpha = sp^{0.8}$, $\beta = p$ $E[\pi(C{=}O\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.13$ $E[\pi(C{=}O\rightarrow\sigma^*(C9'\text{-}H_{ax})]=0.13$	0.56	0.12
37 (Y, A = C**O**(C**H**$_2$)$_3$	1.0918, 1.0939 1.0988, 1.0985	1.0956, 1.0968 1.0983, 1.0981	2.33, 2.46 2.03, 2.64	120.7, 119.2 98.4, 96.5	-7.0, -4.6 -2.7, -1.3	20, 22 -8, -5	1.59, 1.10 0.55, 0.37	$E[n_\alpha(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.10$ $E[n_\alpha(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.11$, $\alpha = sp^{0.8}$ $E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.38$ $E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.39$, $\beta = p$ $E[n_\alpha(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.20$ $E[n_\alpha(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.60$, $\alpha = sp^{0.8}$ $E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.26$ $E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 1.17$, $\beta = p$ $E[\pi(C{=}O\rightarrow\sigma^*(C9'\text{-}H_{ax})] = 0.43$	1.04	0.33
38 (Y, A = C**O**(C**H**$_2$)$_4$	1.0920, 1.0983 1.0985, 1.0983	1.0964, 1.0959 1.0985, 1.0985	2.35, 3.17 2.11, 2.14	117.6, 109.9 96.7, 97.0	-6.5, 0.0 -2.1, -2.6	26, -1 -5, -6	1.46, 0.18 0.48, 0.47	$E[n_\alpha(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.42$, $\alpha = sp^{0.8}$ $E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.58$, $\beta = p$ $E[\pi(C{=}O\rightarrow\sigma^*(C9'\text{-}H_{ax})] = 0.37$	0.44	0.25

[a] $\Delta r_{4'} = r(C_{4'}\text{-}H_{ax}) - r(C_{4'}\text{-}H_{eq})]$, $\Delta r_{9'} = r(C_{9'}\text{-}H_{ax}) - r(C_{9'}\text{-}H_{eq})]$, [b] $\Delta r_{8'} = r(C_{8'}\text{-}H_{ax}) - r(C_{8'}\text{-}H_{eq})]$, [b] $\Delta r_{10'} = r(C_{10'}\text{-}H_{ax}) - r(C_{10'}\text{-}H_{eq})]$, [c] $\Delta q_{4'} = (qH_{4'ax} - qH_{4'eq})$, [c] $\Delta q_{9'} = (qH_{9'ax} - qH_{9'eq})$, [d] $\Delta q_{8'} = (qH_{8'ax} - qH_{8'eq})$, [d] $\Delta q_{4'} = (qH_{10'ax} - qH_{10'eq})$, [e] Δ% s-char.$_{4'}$ = (% s-char. $C_{4'}$-H_{ax} − % s-char. $C_{4'}$-H_{eq}), [e] Δ% s-char.$_{9'}$ = (% s-char. $C_{9'}$-H_{ax} − % s-char. $C_{9'}$-H_{eq}), [f] Δ% s-char.$_{8'}$ = (% s-char. $C_{8'}$-H_{ax} − % s-char. $C_{8'}$-H_{eq}); [f] Δ% s-char.$_{10'}$ = (% s-char. $C_{10'}$-H_{ax} − % s-char. $C_{10'}$-H_{eq}); [g] ^{1}H NMR chemical shift separation within γ-CH_2, $[\Delta\delta(\gamma\text{-}CH_2)_{4',9'} = \Delta\delta_{4',9'} = \delta(H_{4',9'ax}) - \delta(H_{4',9'eq})]$, $[\Delta\delta(\gamma\text{-}CH_2)_{8',10'} = \Delta\delta_{8',10'} = \delta(H_{8',10'ax}) - \delta(H_{8',10'eq})]$; [g] correspond to different C-H bonds included by the same methyl or by different methyl groups inside a t-Bu group.

When an axial substituent is attached to a cyclohexane ring sub-unit of adamantane **1** in derivatives **2**–**38**, the calculations locate hyperconjugative interactions in all compounds **2**–**38**, suggesting the presence of improper hydrogen bonding in C-H_{ax}···Y contacts, for example n(N or O or F or Cl) → σ^*(C-H) in **5**–**23**, **25**–**38** or/and σ(C-H) → σ^*(C-H) in **2**, **3**, **20**–**31**, **36**–**38**, π(C≡N or C≡C) → σ^*(C-H) in **4, 17-19**. In an improper H-bonded contact, the major C-H bond shortening contributors are steric compression between C-H_{ax} and Y_{ax} together with electrostatic attraction between positive H and negative C; these prevail the major lengthening contributors of the weak H-bonded C-H_{ax}···Y_{ax} contact which are the electrostatic attraction (or dispersion) between the positive H of C-H dipole, and the Lewis base Y and the hyperconjugative electron donation n(Y) → σ^*(C-H).[25,26] The relative strength of the improper H-bonded contacts included by compounds **2**–**38** in Table 3, is reflected by the changes on the contraction of the C-H_{ax} bonds, the increase in the % s-character of the C-H_{ax} bonds relative to the equatorial bonds of the cyclohexane-subunit of adamantane ring, and the relevant energy values of hyperconjugative interactions. The effect of a stronger contact is to increase the contraction and the % s-character of C-H_{ax} bonds, and the postive charge of H_{ax} protons compared to adamantane **1**; the observed increased difference between the ^1H chemical shifts of the axial and equatorial protons within the γ-methylene group, $\Delta\delta(\gamma\text{-}CH_2)$, can likely represent an experimental parameter reflecting the strength of the contact.[27]

When the acceptor group is Y = OR, NR_2 and the second row lone-pair bearing heteroatom is directly connected to the cyclohexane ring-subunit, the weak interaction [$n(Y_{ax}) \rightarrow \sigma^*(C\text{-}H_{ax})$, $E \leq 0.63$ kcal mol^{-1}] is located; the hyperconjugative interaction efficiency was increased on going from Y = F and OH or OMe to NH_2 or NMe_2, which is consistent with the basicity order of these groups. The contact angle for the 1,4-C-H_{ax}···Y_{ax} contacts in compounds **2, 4-23, 25-31** is larger than 90° permitting weak overlap interactions for these contacts.[30]

When the interacting atom of the Y group in C-H_{ax}···Y contacts changes from a second row to a third row lone-pair bearing heteroatom[31] (Y = SR, Cl in compounds **12, 13**), a substantial elongation of contact distances by 0.2-0.5 Å and an increase in contact angles by 5-6° is calculated (for example θ(C-H_{ax}···Y_{ax}) is 95° in compounds **11** and **5** and changes to 102-103° in **12**, **13**). The interaction energy $E[n(Y_{ax}) \rightarrow \sigma^*(C\text{-}H_{ax})]$ increases by 0.2 – 0.7 kcal mol^{-1} because of a more effective orbital overlap. The

% s-character and the contraction of the C-H$_{ax}$ bonds relative to the equatorial bonds is also increased. Recent comparative studies of the hydrogen bonded dimers Me$_2$O···HOMe, Me$_2$S···HOMe and S···HN showed that sulfur can be an almost equally good hydrogen bond acceptor as oxygen.[32] In agreement with these observations, the calculations predicted the stronger hyperconjugative interactions for the C-H···S contact in compound **13**, where the contact atom of the axial substituent is tetrahedral sulfur, compared to its oxygen analog **5,** and for the C-H···Cl contact in compounds **12**, **31** compared to **11**, **30**. The examined experimental value of $\Delta\delta(\gamma\text{-CH}_2)$ increases consistently from 0.53, 0.54, 0.54 ppm in **11** (Y = F), **5**, **6** (Y = OH, OMe respectively), to 0.70 in **12** (Y = Cl) and 0.68 ppm in **13** (Y = SH).

The geminal *equatorial* alkyl group, methyl and *tert*-butyl, in compounds **14** and **15** respectively forces the corresponding *axial group* to approach C-H$_{ax}$ bonds and reduces the contact distance C-H$_{ax}$···Y$_{ax}$, resulting in the enhancement of the hyperconjugative energy and the other characteristic improper hydrogen bonding interaction parameters (Δ% s char., Δr). Thus, the interaction energy $E[n(\text{Y}_{ax}) \rightarrow \sigma^*(\text{C-H}_{ax})]$ and the value of $\Delta\delta(\gamma\text{-CH}_2)$ increases consistently from 0.24 kcal mol^{-1} and 0.54 ppm in **7** (Y = OH, A = H) to 0.24 kcal mol^{-1} and 0.63 in **14** (Y = OH, A = Me) and 0.54 kcal mol^{-1} and 0.79 ppm in **15** (Y = OH, A = *t*-Bu) respectively; in the last compound t-Bu reduced the C-H$_{ax}$···Y contact distance by ~ 0.3 Å, increases the contact angle by 6° and raised the value by 0.25 ppm. Upon capping heteroatom lone pair in the acetylated derivatives **9, 20, 21, 27, 28** (Y = OAc or NHAc) the strength of the contact is seriously reduced and the relevant values of $\Delta\delta(\gamma\text{-CH}_2)$ are 0.27, 0.46, 0.46, 0.36, 0.32 ppm, respectively, compared to the parent lone pair bearing compounds having values 0.54, 0.63 in **5**, **14** (Y = OH) and 0.45 or 0.48, 0.87 or 0.88 in **7, 8, 22, 23** (Y = NH$_2$, NMe$_2$).

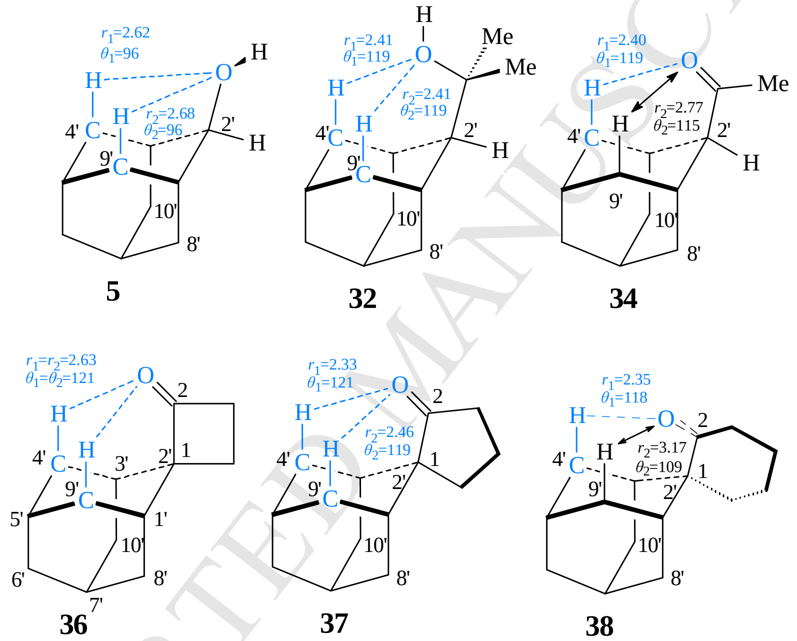
The relative strength of the effect from different substituents on the C-H$_{ax}$···Y$_{ax}$ contact and the $\Delta\delta(\gamma\text{-CH}_2)$ values can be obtained from the data of the monosubstituted compounds **2**–**13**. The disubstituted derivatives, including those mentioned in the previous paragraph, can be also used to compare the relative strength of the effect from different substituents on the C-H$_{ax}$···Y contact and the $\Delta\delta(\gamma\text{-CH}_2)$ values. For example in disubstituted derivatives **14**–**19** and **20**–**31**, Y is an heteroatom (N, O, F or Cl) and is axial in the cyclohexane ring sub-unit 1′-2′-3′-4′-5′-9′. Also A is an alkyl group in compounds **14**, **15** and **20**–**31** or Ph or C≡CH or C≡N groups in compounds **16**, **17**, **18**, **19**, respectively, and is axial in the cyclohexane ring sub-unit 1′-2′-3′-10′-7′-8. For example, the stronger effect of Y_{ax} compared to that of A_{ax} in the chemical shift separation within the γ-cyclohexane CH_2 was observed in the case of compound **15** (Y = OH, A = *t*-Bu) where OH group antagonizes the large t-Bu group. Thus, in compound **15**, 8′ax,10′ax-H are sterically compressed by the syn axial *t*-butyl group and the observed separation for the 8′,10′-H pairs was 0.49 ppm and the 8′ax,10′ax-H doublet resonance appeared at 2.17 ppm, whereas the values for the γ-CH_2 of 4′ax,9′ax-H indicated a more significant interaction; the electronic distribution within the 4′,9′ γ-CH_2 was affected to a greater effect by the hydroxyl group in the axial position and the 4′ax,9′ax-H signal appeared more downfield at 2.26 ppm, that is, 0.79 ppm from the 4′eq,9′eq-H signal.

It is interesting to note that when the NMe_2 group of compound **23** was protonated, upon addition of a drop of TFA inside the NMR tube resulting in **24**, $\Delta\delta_{4',9'\text{-H}}$ was reduced from 0.88 to 0.46 ppm. The calculations suggested that the N^+-H proton strongly repels the 4′ax proton, since the distance between these protons was calculated to be ~ 1.99 Å. This can explain why protonation was so slow, the time required in order to obtain sharp signals in the ^{1}H NMR spectrum being several weeks!

Of considerable interest are the structures **32**–**38** and **3** and **24** with contacts in which the improper hydrogen bonding character can be enhanced because of a linker group between adamantane C-2 and Y group; in these compounds X_{ax}-Y bond vector bisects the cyclohexane ring sub-unit (allowing the formation of a six-membered ring) and interacts more effectively with both the C-H_{ax} bonds of cyclohexane ring 1′-2′-3′-4′-5′-9′; 1,5-C-$H_{ax}\cdots Y_{ax}$ contacts are formed between atoms H_{ax} and O for **32**–**38** and H_{ax} and C-$H_{t\text{-Bu}}$ for **3**. The transition from compound **5** to compound **32** results in increased contact C-$H_{ax}\cdots O_{ax}$-C angles ($\theta_{\text{C-Hax}\cdots\text{O}}$ = 96° in **5** to $\theta_{\text{C-Hax}\cdots\text{O}}$ = 119° in **32**) and reduced contact distances (by ~ 0.2-0.3 Å, Scheme 6) giving rise to increased hyperconjugative energies by ~ 1 kcal mol^{-1} when the stronger orbital interactions $n(O) \rightarrow \sigma^*(C\text{-}H_{ax})$ for each compound are compared. The improper H-bonding interactions strengthen considerably, since the CMe_2-OH group is conformationally homogenous and the C-OH bond bisects cyclohexane ring, resulting in a significant contraction and increase of the % s-character of the C-H_{ax} bonds relative to the equatorial bonds; the axial proton positive charge changes also increase (the values of the Δ% s-char. and Δ*q* and of the C-H_{ax} bond contraction changes from C-H_{ax}

bond contraction changes from ~0.5, 16 *me* and -3 *m*Å in **5** to ~1.39, 31 *me* and -6 *m*Å in **32**) (Scheme 11). The signal separation Δδ(γ-CH$_2$) was 0.54 ppm in **5** whereas in compound **32** was 0.63 ppm. Interestingly in **33**, which is the fluorine analog of **32**, C-H$_{ax}$ bond contraction was calculated to be ~ -5 *m*Å and signal separation was 0.54 ppm.

Scheme 11. Improper hydrogen bonded C-H$_{ax}$···O=C$_{ax}$ contacts (coloured in blue) in some axial cyclohexane moieties [B3LYP/6-31+G(d,p) calculations].



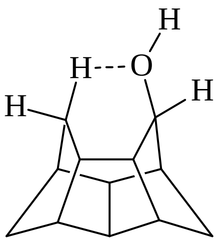
In the acetyl derivative **34** and the cyclohexanone **38** the C=O bond eclipses the cyclohexyl C2′-C3′ bond favoring improper H-bonding interactions with only one C-H$_{ax}$ bond, compared to compound **37** in which the C=O bond bisects cyclohexane ring allowing the oxygen lone pair(s) electrons and the π-bond of the carbonyl group to donate electron charge to both C-H$_{ax}$ anti-bonding orbitals, according to the calculated hyperconjugative energies (Scheme 12, Table 3). In cyclobutanone derivative **36** the C=O bond vector also bisects the relevant cyclohexane moiety, but the contact distances are ~ 0.2 – 0.3 Å longer resulting in weaker improper H-bonded C-H$_{ax}$···O contacts with respect to the cyclopentanone analogue **37** (Table 2). In the cyclopentanone derivative **37** the improper H-bonding interaction C-H$_{ax}$···O is considerably stronger than that of compounds **34**, **36, 38**; thus (i) the % s-character, the contraction of bond length and the proton charges for C-H_{ax} bonds relative to the equatorial bonds C-H_{eq} and (ii) the overlap interactions n(O) → σ*(C-H_{ax}) have increased values for compound **37** compared to **34**, **36, 38** (Table 3). The stronger H-bonded contacts cause a more pronounced redistribution of electronic shielding within the cyclohexane ring γ-CH_2s effecting higher values of proton chemical shift separation within the cyclohexane ring γ-CH_2 group. Indeed, in compounds **34, 36, 38** the signal separation Δδ(γ-CH_2) was 0.18, 0.56, 0.44 ppm whereas in compound **37** was 1.04 ppm respectively (Table 1). It is interesting that an enhancement of the hydrogen bonded C-H_{ax}···O contact formed between carbonyl oxygen and 2-adamantyl C-H group and has been noted in (1-adamantyl)alkylketones on the basis of 0.1-0.3 downfield shift of 2-adamantyl protons when the alkyl group changes from a smaller to a bulkier one.[33]

The strength of the dihydrogen-bonded interaction C-H_{ax}···H–C increases from the primary methyl (compound **2**) to the tertiary t-Bu group (compound **3**). This is indicated from the shorter C-H_{ax}···H–C(tBu) distance, the increase in the % s-character for C-H_{ax} bonds relative to the equatorial bonds C-H_{eq}, and the higher values of second order perturbative energies of σ(C-H_{ax}) → σ*(C-Hax) hyperconjugative interactions inside C-H_{ax}···H–C contacts (Table 2).

The contacts between the axial substituents Y and the axial C-H bonds in cyclohexane derivatives were traditionally considered to include only van der Waals spheres crowding (which is usually attributed to Pauli repulsions[4a]) and similarly the observed boost in chemical shift differences, Δδ(γ-CH_2), was attributed to steric compression. In the past, before the observation of the existence of improper hydrogen bonding contacts, the C-H bond shortening in the relevant contacts was attributed only to steric compression.[34] It is generally believed that the interaction of groups that are close in space normally results in shielding of the carbon and deshielding of the protons involved. It was proposed that a remarkable demonstration of a steric compression effect was the δ- or ε-effect on the proton chemical shifts in some norbornyl systems (see ocompound **39** in Scheme 12). In these systems the repulsion between groups separated by four or five bonds was so severe that the compressed proton appears uncommonly downfield by 3.1-3.5 ppm, but also, the uncompressed proton moves upfield by 0.8-0.9 ppm.[35,36] We performed an NBO calculation on the B3LYP/6-31+G(d,p) geometry optimized structure, which located for the contact between hydroxyl oxygen and the facing δ-C-H bond (contact distance $r_{\text{C-H--}}$

$_{\text{-O}}$ = 1.99 Å) the hyperconugative interaction, *E*[*n*(O) → *σ**(δ-C-H)] of 4.41 kcal mol^{-1}, suggesting a significant covalent character for this contact. Other cage compounds have been reported recently to include an intrabridge C-H---F with an intrabridgehead H---F distance of 1.94 Å; this contact has a significant covalent character leading to a resonance of 3.16 for the *in* proton and 1.30 ppm for the *out* geminal proton.[37]

Scheme 12. Structure of pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{4,10}]dodecanol **39** with strong C-H···O contacts.



39

Compounds **1-31** contain 1,4-C-H$_{ax}$···Y$_{ax}$ contacts and compounds **32-38** include 1,5-C-H$_{ax}$···Y$_{ax}$ contacts. The existence of weak 1,5-CH$_3$/O hydrogen bonding interaction between the 2-oxygen and the terminal 6-methyl in 1,2-dimethoxyethane (1,2-DME) was verified to be the reason for the experimentally observed and theoretically calculated stability of GG′ conformer around O2-C-C-O-C fragment of 1,2-DME and poly(propylene oxide), which leads to the stabilization of TGG′ rotamer relative to TTT rotamer. The stabilization energy associated with a pair of these attractive nonbonding H-bonding C-H···O interactions was calculated as 1.2-1.4 kcal mol^{-1}.[38] Similarly the gauche stability of the C-C bond conformer in the O-C-C-O sequence appears to arise from the 1,4-C-H···O attraction. It was proposed that this weak interaction should be considered in a relevant force field construction in order to predict correctly the energy changes associated with rotation around the dihedrals included by a C-O-C-C-O-C motif.[39] The presence of attractive 1,4-CH$_3$···O contacts was revealed by the electron diffraction data of dimethoxymethane and 2,2-dimethoxypropane.[40]

In addition crystal structures were reported where *trans*-cyclohexane-1,4-diol is observed in the unexpected biaxial conformation due to intramolecular attractive C-H$_{ax}$···O$_{ax}$. The contact angle for the 1,4-C-H$_{ax}$···O$_{ax}$ contacts in the crystal structure is larger than 90° (~ 96°) permitting weak overlap interactions for these contacts. These cyclohexanes with axial O-substituents are almost unstrained although steric conflict between the substituent and the axial H-atoms of the cyclohexane moiety exists. In a database analysis of *trans*- and *cis*-1,4-disubstituted cyclohexanes, it was found that the steric distortions caused by axial substituents, X, depend strongly on the chemical nature of X. These distortions are surprisingly small for X = O and N, larger for X = S, and more pronounced for X = C.[41]

It is striking to compare compounds **3** and **32**, **33, 37** bearing significant improper hydrogen bonding contacts, according to the results included in Table 3. In compound **3**, the bulky t-Bu substituent, effects the largest van der Waals spheres crowding in γ-axial hydrogens and the resulting $\Delta\delta$(γ-CH_2) was 0.50 ppm with the 4′ax, 9′ax protons resonance at 2.03 ppm, compared to the chemical shift separation of 0.45 ppm and the 4′ax, 9′ax protons resonance at 1.91 ppm of the methyl analogue **2**. In the compounds **32**, **37** the C-H_{ax}···O contacts, which are included in the six-membered ring $H_{4'ax}$-$C_{4'}$-$C_{3'}$-$C_{2'}$-C_{ax}-O (or the ring which contains 9′$_{ax}$-CH groups instead of the 4′$_{ax}$-CH groups), should be more relaxed from van der Waals spheres repulsion compared to C-H_{ax}···$(CH_3)_2$-CMe contacts in compound **3**. The relevant $\Delta\delta$(γ-CH_2) was 0.54 and 1.04 ppm with the 4′ax, 9′ax protons resonance at 2.18 and 2.42 ppm. In compounds **3, 32, 37** the C-H_{ax}···Y contact distances were smaller than the sum of the van der Waals radii of the interacting atoms by about the same value, that is, 0.3 Å. It seems that steric crowding is not the main reason for the deshielding of 4′ax, 9′ax protons in compounds **32, 33, 37.** The significant electropositive character of H in the cases of compounds **32**, **33**, **37**, that is, the enhanced electrostatic character of these C-H_{ax}···O contacts, is also consistent with the largest calculated positive charges of γ-axial protons between the compounds in the series **1-38** (see Δq charge values in Table 3).[4e] The significant electropositive character of H in the cases of compounds **18**, **21**, **23**, i.e., the electrostatic character of these C-H_{ax}···O contacts, is consistent with the highest calculated Δq charge values (Table 3).

The data suggest that the t-Bu group in the C-H_{ax}···t-Bu contact (compound 3) effects a compression in proton H_{ax} electron cloud, which can be attributed mainly to van der Waals spheres repulsion, whereas in C-H_{ax}···O contacts of compounds **32, 33, 37** electrostatic attractive forces are also likely to effect the compression of H_{ax} electron cloud; these forces can be exerted by a) the electron-rich acceptor group C-O or C=O and b) from the negative charged carbon of C-H_{ax} bond. An excess of a negative charge can be produced on C-H_{ax} carbon when a stronger hydrogen bonding contact is formed because of a suitably modified substituent from one compound to another. This charge should be detected in NBO calculations results and experimentally through a shielding of carbons C-4′ and C-9′ chemical shifts when the NMR data of the two compounds are compared. Neither an excess of negative charge excess nor a ^{13}C NMR chemical shift upfield shift was observed (Table S1 and Table 2). A negative charge excess can be dispersed through the adamantane carbon framework. One clear case can be the comparison of the data on going from **36** or **38** to **37** where the hydrogen bonding strength was predicted through calculations to be increased. In that case the chemical shift of carbons C-4′ and C-9′ was indeed shifted upfield from 33.72 or 32.10 to 32.03 respectively.

Overall, it was shown from the discussion in Section 2.3 that electron transfer hypercongjugative interactions (attractive forces) co-exist with Pauli repulsions (repulsive forces) in $\text{C-H}_{ax}\cdots \text{Y}_{ax}$ according to DFT claculations and NMR chemical shifts changes. The study of a large and rationally selected series was necessary.

The existence of attractive and repulsive forces is a general phenomenon. For example, the common C=O···H-N hydrogen bonds within various protein structures maybe viewed as favored by the delocalization of the carbonyl oxygen lone pair n_O into the antibonding orbital σ^* of the N-H bond, but disfavored by Pauli repulsion between oxygen lone pairs and the N-H bonding orbital. It has been proposed that inside C=O···C=O contacts, attractive $n_O \rightarrow \sigma^*_{C=O}$ interactions and repulsive n_O)($\sigma_{C=O}$ Pauli forces antagonize each other and contribute to the stabilization of protein structures (helices, β-sheets etc). A recent elegant study of N-Ac proline esters and analogues showed how by selected structural modifications the attractive $n_O \rightarrow \sigma^*_{C=O}$ interaction can predominate over the repulsive n)($\sigma_{C=O}$ and vice-versa.[42] It has recently proposed that in alkane dimers stabilizing dispersive interactions between C-H···H-C fragments can be explained by means of resonance structures $C^+H^-\cdots C^-H^+ \leftrightarrow C^-H^+\cdots C^+H^-$ (oscillating dipoles) for small alkanes or reorganization of the four bonding electrons of the two interacting CH bonds via recoupling of these electrons to atoms H···H, C···C included by interactions fragments. Charge transfer interactions $\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}H}$ were also located which are consistent with the formation of long-range C···H bonds.[43] A series of papers indicate that contact atoms separated by distances where steric crowding is increased also attractive dispersion forces are present arised from the correlated motion of electrons. This kind of interactions stabilize branched over straight chain alkanes,[44] diadamantanes with very long C-C bonds,[45] hexaphenylethane[46] etc.

3. Conclusions

In this work a complete assignement of the ^1H and ^{13}C NMR spectra of 38 adamantane derivatives (**1−38**) was realized; GIAO calculations help towards that aim, especially in confirming differentiation of 4′, 9′ from 8′, 10′ protons and carbons, and helping on the assignment of 5′ and 7′ protons and carbons. The deviation of GIAO B3LYP/DZ calculated values from experimental values for most ^1H NMR chemical shifts was <0.7 ppm and for ^{13}C NMR chemical shifts was < 7ppm; these deviations were similar to the values previously observed.[16,21] The effects on ^{13}C resonances of γ-carbons in the adamantane series **1-38** were analyzed based on the γ_g and γ_a SCS.

Compounds **1-31** contain 1,4-C-H_{ax}···Y_{ax} contacts and compounds **32-38** include 1,5-C-H_{ax}···Y_{ax} contacts. The existence of weak 1,5-CH_3/O improper hydrogen bonding interaction and 1,4-C-H···O attraction were proposed on the basis of experimental and theoretical work to be really important for stabilizing gauche conformer in 1,2-dimethoxyethane fragments while the presence of attractive 1,4-CH_3···O contacts was proposed to be present in dimethoxymethane and 2,2-dimethoxypropane;[38-40] *trans*-cyclohexane-1,4-diol adopts a diaxial conformer in the crystal structures.[41] Interestingly, when an alkyl group is attached at the geminal cyclohexane C-1 position it pushes the axial group towards C-H_{ax} bond reducing the contact distance C-H_{ax}···Y, increasing the contact angle; this effect results in the enhancement of the hyperconjugative energy and chemical shift separation, $\Delta\delta$(γ-CH_2). Thus, the value of $\Delta\delta$(γ-CH_2) increases consistently by 0.25 ppm from **7** (Y = OH, A = H) to 0.79 ppm to **15** (Y = OH, A = *t*-Bu). In general the proton signal separation within the cyclohexane ring γ-CH_2s raises when the strength of the C-H_{ax}···Y_{ax} contact is increased. It was observed that when the calculated parameters, reflecting the strength of the H-bonding interaction, are increased (i.e., % s-character, contraction of C-H_{ax} bonds and energy values of hyperconjugative interactions) the difference between the ^{1}H chemical shifts of the axial and equatorial protons within the γ-methylene group, $\Delta\delta$(γ-CH$_2$), is raised.

The addition of an appropriate fragment X_{ax} resulting in a X_{ax}-Y bond vector bisecting cyclohexane ring, increases the interaction between $n(Y_{ax})$ and $\sigma^*(C\text{-}H_{ax})$ orbitals. It is striking that in compound 3, with the bulky t-Bu effecting the largest van der Waals repulsion to γ-axial hydrogens the $\Delta\delta$(γ-CH$_2$) value was 0.50 ppm. In compounds **32, 33, 37** which bear important improper H-bonded contacts the $\Delta\delta$(γ-CH$_2$) values were 0.65 ppm, 0.64 ppm and 1.04 ppm respectively. In the later molecules, C-H$_{ax}$···O contacts include clearly not only van der Waals spheres crowding. The electron cloud compression of the γ-axial hydrogens and the large chemical shift separations should be resulted from the electron cloud withdraw of H$_{ax}$ from the negative C of the C-H$_{ax}$ bond or more likely from electrostatic attraction (dispersion forces) from the acceptor group O-C or O=C bond.

It has been suggested that in the contacts C-H$_{ax}$···Y$_{ax}$ with distances ranging from 2.1 to 2.7 Å dispersion attraction can result in significant thermodynamic stability of molecules.[44-46] It is expected that in all molecules **2-38** bearing different substituents Y, a balance between van der Waals spheres repulsion and electrostatic/dispersion attractive forces should work.

4. Experimental Part

4.1 Chemistry

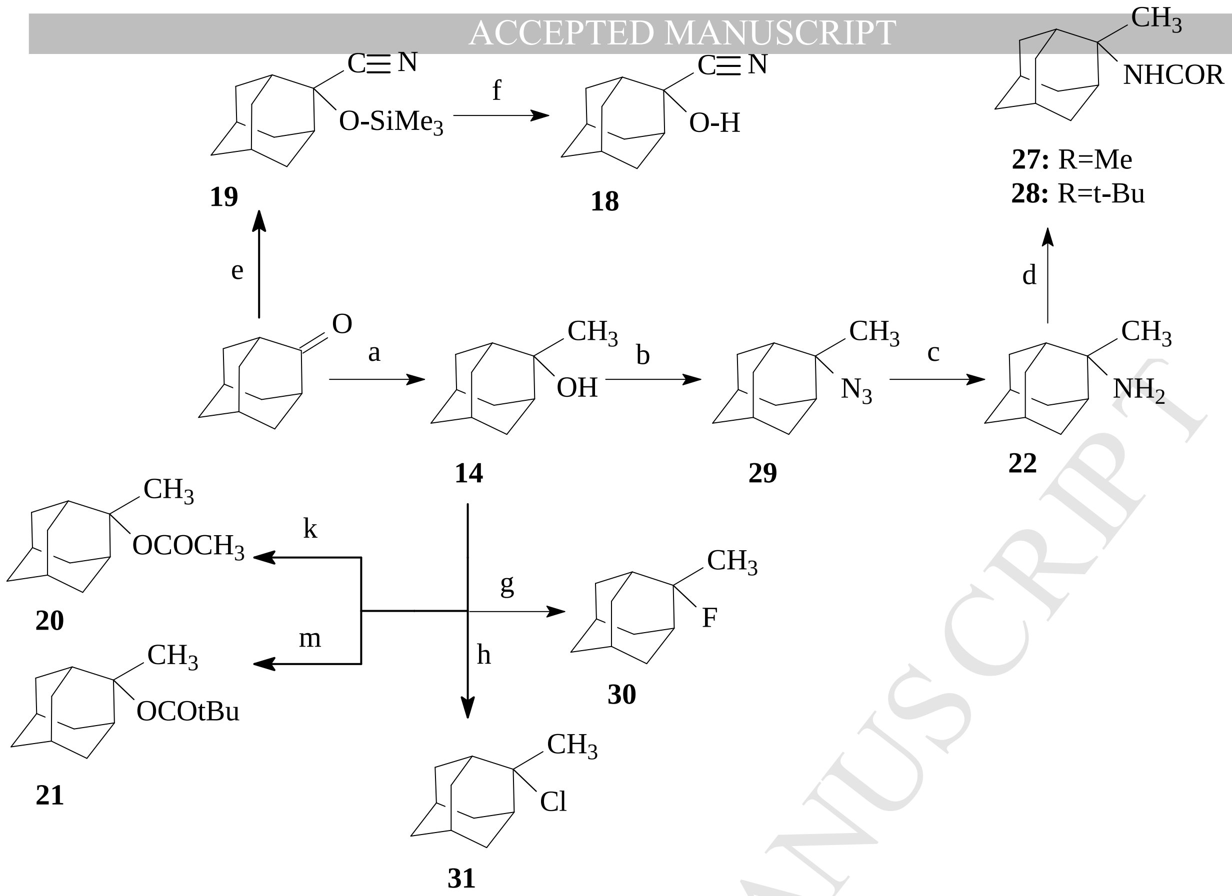
The synthetic pathways of most of the compounds included in this work has been published already in older work by us or by other research groups. Many of the compounds can be synthesized according to these previously published procedures (see Supporting Information). In synthetic schemes 13 and 14 new synthetic procedures or revised procedures of new or already published compounds are presented. The description of the synthesis of known compounds and the experimental procedures for new compounds in Schemes 13 and 14 are given in the Supporting Information.

Reaction of 2-methyl-2-adamantanol **14** with $NaN_3/H_2SO_4/CHCl_3$ at room temperature afforded the azide **29** using a concentration of 78% w/w rather than the 57% w/w reported in the literature,[49] which failed to yield **29**, quantitatively. Azide **29** was converted to the 2-methyl-2-adamantanamine **22** through reduction with $LiAlH_4$ (Scheme 13); the $CDCl_3$ solution of the TFA salt of **6** was obtained by treating the $CDCl_3$ solution of amine **5** (50 mg) with TFA (2 drops) inside the NMR tube.

Treatment of amine **22** with acetyl chloride/Et_3N or pivaloyl chloride/Et_3N gave the N-acetyl derivative **27** or the *N*-pivaloyl derivative **28**. While O-acetylation of 2-adamantanol **5** can be easily realized upon treatment with acetyl chloride/Et_3N these conditions are not useful for 2-methyl-2-adamantanol **14** since the product was in 2-methyl-2-chloroadamantane **31** resulted through the attack of a chloride ion to 2-methyl-2-adamantyl cation (Scheme 13).[50]

Successful *O*-acetylation conditions for 2-methyl-2-adamantanol **14** included the combination of acetic anhydride, triethylamine and 4-pyrrolidinopyridine as the acylation catalyst acting through activation of acetic anhydride.[51] Since the hindered pivalic anhydride can not be activated by a 4-dialkylaminopyridine, the activation using $MgBr_2$ was found to be efficient for the synthesis of the *O*-pivaloyl anhydride **21** (Scheme 13).[52]

Scheme 13. Synthesis of some selected adamantane derivatives substituted at C-2.



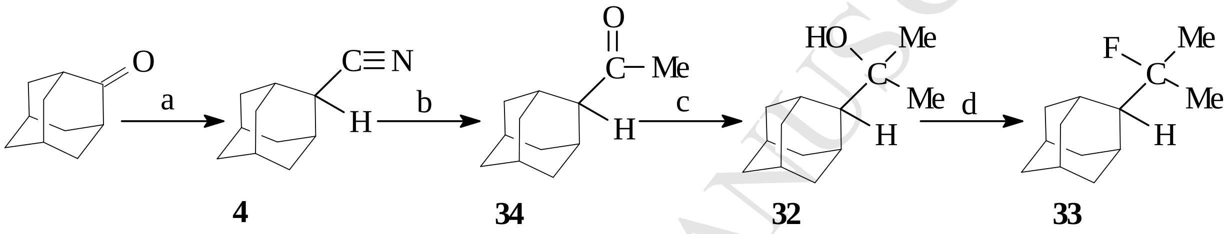
Reagents and Conditions: (a) CH_3MgI, ether, THF, r.t., 2 h then NH_4Cl/H_2O (quant.); (b) NaN_3, H_2SO_4 78 % w/w, $CHCl_3$, 0 °C, then r.t., 48 h (66 %); (c) $LiAlH_4$, ether, r.t., 24 h (83 %); (d) RCOCl, Et_3N, ether, 0 °C, then r.t. 12 h or 48 h for **27** and **28** respectively (91% for **27** or 50% for **28**); (e) Et_3N, Me_3SiCN, 20 h (81 %); (f) KF, MeOH, r.t., 5½ h (g) DAST, CH_2Cl_2, Ar, -78 ^{0}C, then r.t. 1 h; (h) $SOCl_2$, K_2CO_3, CH_2Cl_2, reflux, 8 h (54 %); (k) $(CH_3CO)_2O$, Et_3N, DMAP, 72 h (60 %); (m) (i) $MgBr_2$, THF, Ar; (ii) $(t\text{-}BuCO)_2O$, Et_3N, CH_2Cl_2, 48 h then DMAP-MeOH.

Reaction of 2-adamantanone with Me_3SiCN/Et_3N with no solvent in the reaction mixture afforded the O-$SiMe_3$ derivative **19** of adamantanone cyanydrin **18**. This was converted to the corresponding alcohol **18** through treatment with KF in MeOH; partial deprotection of trimethylsilyl group was observed when the O-$SiMe_3$ was treated with HCl 3N (Scheme 13).[53]

The synthesis of alkyl chlorides **12** and **31** was accomplished through the reaction of alcohols **5** and **14** with $SOCl_2/K_2CO_3$ in boiling CH_2Cl_2; the use of refluxing benzene instead of led to a decomposition mixture. The synthesis of fluorides **11**, **30** and **33** was realized upon treatment of the corresponding alcohols with DAST in CH_2Cl_2 at -78 ºC (see Scheme 14).[54]

For the synthesis of the ketone **34**, the 2-cyanoadamantane **4** was used as a starting material; 2-cyanoadamantane **4** can be prepared through reaction of 2-adamantanone with tosyl methyl isocyanate in the presence of sodium ethoxide or potassium tert-butoxide (Scheme 14).[47c,55] Nitrile **4** was afforded through acidic hydrolysis carboxylic acid **35**. Reaction of 2-cyanoadamantane **4** with methyl lithium afforded the 2-acetyl adamantane **34**. Further reaction of **34** with methyl lithium afforded the tertiary alcohol **32**.[9c]

Scheme 14. Synthetic pathway leading to the fluoride 33.



Reagents and Conditions: (a) EtONa, TOSMIC, EtOH, THF, r.t., 2 h (quant.); (b) (i) MeLi, ether, Ar, 0 °C, then r.t. 90 min (ii) acetone, HCl 6N, reflux 2 h (78 %); (c) (i) MeLi, ether, Ar, 0 °C, then r.t. 12 h (ii) NH_4Cl(aq), 0 °C (78 %); (d) DAST, CH_2Cl_2, Ar, -78 ^{0}C, then r.t. 1 h (50 %).

4.2 NMR Spectroscopy

NMR experiments were conducted i. on a 400 MHz Bruker DRX-Avance operating at 400.13 for obtaining the ^{1}H NMR spectra and ii. on a 200 MHz Bruker Avance operating at 50.32 MHz for the ^{13}C NMR spectra at 298 K. The ^{1}H NMR experiments were run at 298 K (400 MHz) by dissolving 5 mg of compound in 0.5 mL of $CDCl_3$; the protonated sample **24** was prepared by addition of a drop of trifluoroacetic acid to the $CDCl_3$ solution inside the NMR tube of compound **23**. The ^{13}C NMR experiments were run at 298 K (at 50 MHz) by dissolving 20-30 mg of the compound in 0.5 mL of $CDCl_3$. ^{1}H chemical shifts (δ) are reported in ppm relative to the residual $CHCl_3$ signal at 7.26 ppm (s); ^{13}C chemical shifts (δ) are reported in ppm relative to the $CDCl_3$ signal at 77.0 ppm (t).

The ^{1}H spectra (at 400 MHz) were acquired using a spectral width of 12 ppm, 2 s relaxation delay between cycles, 16 transients, 32K data points zero-filled to 64K data points before Fourier transformation (FT) and baseline correction. The ^{13}C spectra (at 50 MHz) were recorded using 3 s relaxation delay, 512 transients, 64K data points and 3 Hz line broadening prior to FT. DEPT-135 spectrum was recorded using 2 s relaxation delay, 800 transients 32K data points and 3 Hz line broadening prior to FT. The assignments of ^{1}H and ^{13}C signals were achieved by the combined use of DEPT, 2D COSY and HMQC experiments; for the latter 2D NMR experiments the 400 MHz Bruker DRX-Avance machine was used. The 2D NOESY were run in $CDCl_3$ solutions (400 MHz) at a concentration of 0.02 M using a mixing time of 1.2 – 1.5 s. All data were collected using pulse sequence and routines provided in the Bruker library of pulse programs. Data processing was performed using the XWIN-NMR Bruker program.

4.3 Details of the Computations and Methods

4.3.1 Structures and NBO analysis

All structures were fully optimized at the B3LYP/6-31+G**[16] level using the GAUSSIAN 03 package (see Supporting Information); frequency calculations were also performed to locate minima. The NBO 4.0 program[56-58] was used as implemented in the GAUSSIAN 03 package. NBO analysis was realized at the B3LYP/6-31+G** level. The NBO analysis transforms the canonical delocalized Hartree-Fock (HF) MOs into localized orbitals that "are closely tied to chemical bonding concepts". This process involves sequential transformation of nonorthogonal atomic orbitals (AOs) to the sets of "natural" atomic orbitals (NAOs), hybrid orbitals (NHOs) and bond orbital (NBOs). Each of these localized basis sets is complete and orthonormal. Importantly, these sets also describe the wave function in the most "economic" way since electron density and other properties are described by the minimal amount of filled orbitals in the most rapidly convergent fashion. Filled NBOs describe the hypothetical, strictly localized Lewis structure.

The interactions between filled and antibonding (or Rydberg) orbitals represent the deviation of the molecule from the Lewis structure and can be used as a measure of delocalizations. This method can give energies of hyperconjugative interactions from the standard second-order perturbation approach

$$E(2) = -p_n \frac{\langle n|F|\sigma^*\rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_n} = -p_n \frac{F_{ij}^2}{\Delta\varepsilon} \qquad (1)$$

where $F_{n\sigma^*}$ is the Fock matrix element between the i and j NBO orbitals, ε_n and ε_{σ^*} are the energies of n and σ^* NBO's, and p_n is the population of the donor n orbital. A threshold of 0.10 kcal mol^{-1} for printing second order perturbation energies was used (the default value is 0.50 kcal mol^{-1}). Detailed descriptions of the NBO calculations are available.[56-58]

It should be empasized that MP2 level is more appropriate for describing the geometries of these molecules and the relevant contacts. We made in previous publications this comparison and the calculations suggesting more compact structure for adamantane predicting for example shorter C-H bond lengths.[7] However, the distances C-H$_{ax}$···Y$_{ax}$ were just a little bit shorter and the hyperconjugative energies a liitle bit higher. However, although the electron correlated method MP2 method is indeed better to describe structure, the purpose of this work including the minimization of a large set of adamantane derivatives, the location of hyperconjugative energies and the description of C-H$_{ax}$···Y$_{ax}$ contacts geometry can be better served by the computationally cheaper B3LYP method.

4.3.2 GIAO calculations

The geometries of all compounds were reoptimized at the B3LYP/6-31+G(d,p) level including the SCRF IEF-PCM solvent model (solvent CHCl$_3$). Using these geometries, NMR chemical shifts were computed at the B3LYP/6-31+G(d,p) level using the GIAO method and are given relative to that of TMS calculated at the same level of theory.[21]

ACKNOWLEDGMENT. A.K. thanks Professor H. Duddeck from the University of Hannover for providing chemical shift values for some adamantane derivatives in the early steps of this research. This research activity was partly supported through a research grant from Chiesi Hellas.

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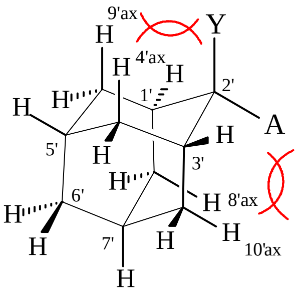
GRAPHICAL ABSTRACT



2-Substituted and 2,2-Disubstituted Adamantane Derivatives as models for Studying Substituent Chemical Shifts and C-$H_{ax}\cdots Y_{ax}$ Cyclohexane Contacts - Results from experimental and theoretical NMR spectroscopic chemical shifts and DFT structures

Supporting Information

A. Details about the relative chemical shift information of 5′, 7′ protons and 4′, 9′ and 5′, 7′ carbons

A.1 Protons 5′, 7′-H

A.2 Carbons 4′, 9′-C and 5′, 7′-C

B. Tables including calculated parameters

Table S1, including geometrical parameters of the C-$H_{ax}\cdots Y_{ax}$ contacts and charges of 4'ax,9'ax-H, 8'ax,10'ax-H protons, and charges of 4',9'-C, 8',10'-C carbons calculated through NBO analysis at the B3LYP/6-31G+(d,p) level for molecules **1**–**38**.

Table S2, including geometrical parameters of the C-$H_{ax}\cdots Y_{ax}$ contacts and complete second order perturbation NBO analysis at the B3LYP/6-31G+(d,p) level for **1**–**38**.

C. Cartesian coordinates of the optimized compounds 1–38 at the B3LYP/6-31+G level**.

D. Chemistry

D.1 Synthesis of known monosubstituted derivatives

D.2 Synthesis of known disubstituted derivatives.

D.3 Experimental details for the synthesis of 2,2-disubstitued derivatives (including raw spectra for compounds **18, 19, 20, 21, 22, 27, 28, 29, 30, 31, 32, 33**).

A. Details about the relative chemical shift information of 5′, 7′ protons and 4′, 9′ and 5′, 7′ carbons

A.1 Protons 5′, 7′-H

For 2-substituted adamantanes, where the substituent is a second row or third row heteroatom bearing a lone pair (compounds **5**–**8, 11**–**13**), the 7′-H proton resonance is generally slightly shifted downfield by 0.02–0.06 ppm compared to the 5′-H resonance; the effect was almost neglected upon capping heteroatom with an acyl group (compound **9**). For a third row bearing heteroatom substitution the experimental values were almost coincident (compounds **12, 13**). When the substituent is an alkyl (Me, t-Bu) or a substituted alkyl group (CMe_2OH, CMe_2F) the relative position of 5′- and 7′-H proton resonances was reversed, that is, 5′-H proton was more deshielded by 0.05-0.09 ppm. For compounds **4** (Y = CN), **34** (Y = COMe) and **35** (Y = CO_2H) 5′-H resonance is also downfield relative to the 7′-H proton signal. The GIAO calculations predicted correctly the relative chemical shifts position of 5′- and 7′-H proton resonances in the above cases.

In the 2-alkyl-2-Y disubstituted adamantanes **14**–**19, 22**, **23**, **25**, **26**, **29**–**38** the difference in chemical shift between 5′-H and 7′-H protons was again small (0 - 0.13 ppm). Only in the case of compounds **16** (Y = OH, A = Ph) and **15** (Y = OH, A = t-Bu) the difference in resonance position becomes slighty larger, that is, 5′-H was 0.20 and 0.14 ppm downfield from 7′-H. The 5′-H resonance was more generally downfield in compounds **14**–**17** and **22, 23** where Y substituent is a second row lone pair bearing heteroatom and A is an alkyl group (Y = OH, NH_2, A = alkyl). GIAO calculations supported the same relative signal position. In cyanohydrines **18** and **19**, 7′-H resonance was more downfield than that of 5′-H resonance; in that case calculations failed to support the experimental result. In compounds **20, 21, 27, 28**, where second row heteroatom lone pair was capped with a small or a large acyl group, the difference in chemical shifts was diminished. In compound **24** (Y = $NHMe_2^+$, A = Me), where the second row heteroatom lone pair was protonated, and in compounds **29** (Y = N_3, A = Me), and **30**, **31** (Y = F or Cl, A = Me) the 7′-H proton resonance was marginally downfield relative to 5′-H and this assignment was also supported by the GIAO calculations; in these cases it was found that 7′-H was shifted downfield from 5′-H by 0.01 - 0.07 ppm. The deviation of GIAO calculated values from experimental values for most ^1H NMR chemical shifts is <0.7 ppm; this deviation is similar to the values previously observed (see references 16, 21 of the draft).

A.2 Carbons 4′, 9′-C and 5′, 7′-C

The spectra of compounds **1**–**38** showed that 4′,9′-C or 8′,10′-C resonances are shifted upfield relative to the carbon resonances of the parent adamantane molecule. For the monosubstituted adamantane derivatives **1**–**13** and **32**–**35**, these are the resonances of the 4′,9′-C carbons which are shifted upfield with respect to 8′,10′-C signals because of the γ-gauche effect exerted from substituent Y_{ax} on the resonances of 4′,9′-C carbons (references 3, 11 of the draft). The chemical shift difference $\Delta\delta(\gamma_{a,s}) = \delta_{8',10'\text{-C}} - \delta_{4',9'\text{-C}}$ for the monosubstituted adamantane derivatives **1**–**13**, **32**–**35** ranges from 3.30 to 8.80 ppm; representative values are 8.30 and 8.80 ppm for CH_3 and t-Bu group respectively, 3.53 ppm for CN group, 5.50 ppm for OH group, 5.43 for CMe_2OH group, 6.96 ppm for NH_2 group, 4.30 and 3.30 ppm for Cl and F substituents. In the 2,2-disubstituted adamantanes **14**–**17** and **20**–**31** and **36**–**38** (where Y = OR, NR_2, NR_2H+, OCOR, NHCOR, C=O, N_3, X (F, Cl) etc, and A = carbon chain), 4′,9′-C resonances are generally shifted upfield with respect to 8′,10′-C signals, that is, a stronger upfield γ-effect of (Y_{ax}, A_{eq}) compared to that of (A_{ax}, Y_{eq}) was observed. In the above cases, carbons 4′,9′-C are in a syn-orientation with Y_{ax} group, which is, in general, a second or third row heteroatom or C=O group, and 8′,10′-C are in a γ-syn-orientation with A_{ax} group, which can be considered in general as an alkyl group. In the cyanohydrin **18** and its trimethylsilyl derivative **19**, where Y = OH or $OSiMe_3$ and A = CN, 4′,9′-C signals are still shifted upfield with respect to 8′,10′-C signals. The chemical shift difference $\Delta\delta(\gamma_{a,s}) = \delta_{8',10'\text{-C}} - \delta_{4',9'\text{-C}}$ for the disubstituted adamantane derivatives **14**–**31, 36**–**38** ranges from 0.03 (Y = NHCOtBu, A = Me) to 4.16 ppm (Y = OH, A = CN) with compound **15** (Y = OH, A = tBu) being the only exception, having a $\Delta\delta(\gamma_{a,s})$ = - 0.60 ppm; in this last compound 8′,10′-C resonances are shifted upfield with respect to 4′,9′-C signals (Table 2). Other representative values are 2.16, 1.92 for compounds **14** (Y = OH, A = Me) and **16** (Y = OH, A = Ph) respectively, 1.56 for compound **22** (Y = NH_2, A = Me), 2.41 and 2.17 for compounds **30** (Y = F, A = Me) and **31** (Y = Cl, A = Me) respectively, 0.50 ppm for compound **29** (Y = N_3, A = Me) etc. GIAO calculations predicted correctly the downfield position of 8′,10′-C signals relative to the 4′,9′-C resonances for all the monosubstituted adamantanes. When di-substituted molecules are considered, GIAO calculations failed to predict the correct relative postion of the carbon signals in molecules **14, 15, 17**–**21**; in these cases Y = OR, OCOR and A = alkyl or CN. In contrast in compounds **22**–**31** and **36**–**38** where Y = NR_2, NHCOR,

N_3, NMe_2H^+, F, Cl, C=O and A = alkyl, GIAO calculations predicted correctly the relative position of 4′,9′-C signals relative to 8′,10′-C signals.

The spectra of the monosubstituted adamantane derivatives **1**–**13** showed that 5′-C resonance lies slightly downfield relative to 7′-C resonance by 0.04 ppm (Y = OMe) – 1.0 ppm (Y = tBu); GIAO calculations predicted correctly the relative position of 5′-C and 7′-C signals in monosubstitured adamantane derivatives. The spectra of the di-substituted adamantane derivatives **14**–**15**, **17**–**21**, **22**–**28**, **36**–**38** reveal the same signal sequence for these carbons and the GIAO calculations supported this observation. GIAO calculations did not predict correctly for compounds **19** and **20** but the chemical shift difference in these cases was marginal only. In 2-phenyl-2-adamantanol **16**, 7′-C resonance was downfield relative to 5′-C resonance and the calculations predicted well. For molecules **30** and **31** both experimental and DFT GIAO calculations predicted that 7′-C resonance was also downfield to 5′-C resonance. The deviation of GIAO calculated values from experimental values for ^{13}C NMR chemical shifts is < 7ppm; this deviation is similar to the values previously observed (see references 16, 21 of the draft).

B. Tables

Table S1. Selected structural parameters calculated at the B3LYP/6-31G+** level of theory, charges of 4'ax,9'ax-H, 8'ax,10'ax-H protons, and charges of 4',9'-C, 8',10'-C carbons, for the 2-substituted and 2,2-disubstituted adamantanes **1**–**38**

System	C_4-H_{ax}, C_9-H_{ax} C_4-H_{eq}, C_9-H_{eq}	C_8-H_{ax}, C_{10}-H_{ax} C_8-H_{eq}, C_{10}-H_{eq}	$q_{4'ax}$, $q_{9'ax}$ $q_{4'eq}$, $q_{9'eq}$	$q_{8'ax}$, $q_{10'ax}$ $q_{8'eq}$, $q_{10'eq}$	$q_{4'C}$, $q_{9'C}$	$q_{8'C}$, $q_{10'C}$	% s-char. C_4-H_{ax}, C_9-H_{ax} C_4-H_{eq}, C_9-H_{eq}	% s-char. C_8-H_{ax}, C_{10}-H_{ax} C_8-H_{eq}, C_{10}-H_{eq}
1 (Y=H, A=H)^c	1.0986, 1.0986	1.0986, 1.0986	0.242, 0.242	0.242, 0.242	-0.462, -0.462	-0.462, -0.462	23.69, 23.69	23.69, 23.69
	1.0986, 1.0986	1.0986, 1.0986	0.242, 0.242	0.242, 0.242			23.69, 23.69	23.69, 23.69
2 (Y=Me, A=H)^c	1.0972, 1.0972	1.0986, 1.0986	0.242, 0.242	0.241, 0.241	-0.464, -0.464	-0.460, -0.460	23.90, 23.90	23.64, 23.64
	1.0986,1.0986	1.0987, 1.0987	0.242, 0.242	0.241, 0.241			23.59, 23.59	23.63, 23.63
3 (Y=*t*-Bu, A=H)^c	1.0931, 1.0956	1.0983, 1.0988	0.243, 0.238	0.240, 0.241	-0.460, -0.459	-0.467, -0.457	24.27, 24.02	23.73, 23.75
	1.0990, 1.0990	1.0988, 1.0987	0.241, 0.241	0.242, 0.241			23.30, 23.41	23.60, 23.62
4 (Y=CN, A=H)^c	1.0968, 1.0968	1.0985, 1.0985	0.257, 0.257	0.244, 0.244	-0.463, -0.463	-0.469, -0.469	24.14, 24.14	23.78, 23.78
	1.0976, 1.0976	1.0976, 1.0976	0.248, 0.248	0.250, 0.250			23.77, 23.77	23.80, 23.80
5 (Y=OH, A=H)^c	1.0954, 1.0959	1.0988, 1.0986	0.256, 0.256	0.242, 0.242	-0.468, -0.468	-0.464, -0.464	24.25, 24.07	23.59, 23.67
	1.0984, 1.0985	1.0980, 1.0978	0.240, 0.240	0.246, 0.246			23.66, 23.70	23.83, 23.76
6 (Y=OMe, A=H)^c	1.0954, 1.0960	1.0989, 1.0987	0.260, 0.254	0.242, 0.242	-0.466, -0.467	-0.463, -0.463	24.30, 24.12	23.67, 23.70
	1.0985, 1.0985	1.0982, 1.0979	0.240, 0.240	0.245, 0.246			23.65, 23.66	23.73, 23.72
7 (Y=NH_2, A=H)^c	1.0949, 1.0949	1.0987, 1.0987	0.260, 0.260	0.241, 0.241	-0.467, -0.467	-0.462, -0.462	24.28, 24.28	23.65, 23.65
	1.0987, 1.0987	1.0981, 1.0981	0.238, 0.238	0.244, 0.244			23.57, 23.57	23.68, 23.68
8 (Y=NMe_2, A=H)^c	1.0958, 1.0958	1.0985, 1.0985	0.253, 0.253	0.242, 0.242	-0.464, -0.464	-0.458, -0.458	24.23, 24.23	23.67, 23.60
	1.0987, 1.0987	1.0983, 1.0983	0.239, 0.239	0.244, 0.244			23.59, 23.59	23.67, 23.60
9 (Y=NHAc, A=H)	1.0981, 1.0997	1.0979, 1.0979	0.242, 0.223	0.248, 0.249	-0.467, -0.464	-0.462, -0.464	23.79, 23.52	23.80, 23.84
	1.0979, 1.0980	1.0981, 1.0980	0.247, 0.249	0.245, 0.245			23.80, 23.82	23.69, 23.75
10(Y=NO_2, A=H)	1.0973, 1.0974	1.0986, 1.0986	0.256, 0.256	0.245, 0.245	-0.470, -0.470	-0.462, -0.462	24.82, 24.15	23.83, 23.84
	1.0976, 1.0976	1.0974, 1.0974	0.250, 0.250	0.253, 0.253			23.76, 23.77	23.81, 23.81
11 (Y=F, A=H)^c	1.0957, 1.0957	1.0987, 1.0987	0.259, 0.259	0.244, 0.244	-0.469, -0.468	-0.465, -0.465	24.20, 24.20	23.78, 23.78
	1.0980, 1.0980	1.0976, 1.0975	0.243, 0.243	0.249, 0.249			23.76, 23.76	23.81, 23.81
12 (Y=Cl, A=H)^c	1.0956, 1.0956	1.0984, 1.0984	0.259, 0.259	0.245, 0.245	-0.469, -0.469	-0.462, -0.462	24.23, 24.23	23.83, 23.83
	1.0978, 1.0978	1.0977, 1.0977	0.245, 0.245	0.250, 0.250			23.68, 23.68	23.72, 23.72
13 (Y=SH, A=H)	1.0970, 1.0962	1.0984, 1.0987	0.258, 0,254	0.242, 0.244	-0.467, -0.469	-0.459, -0.462	24.12, 24.23	23.82, 23.77
	1.0983, 1.0984	1.0983, 1.0984	0.242, 0.244	0.247, 0.247			23.66, 23.24	23.70, 23.72
14 (Y=OH, A=Me)	1.0939, 1.0945	1.0965, 1.0966	0.265, 0.258	0.242, 0.241	-0.465, -0.465	-0.463, -0.464	24.47, 24.26	23.92, 23.92
	1.0984, 1.0984	1.0981, 1.0979	0.239, 0.239	0.245, 0.246			23.53, 23.56	23.56, 23.52
15 (Y=OH, A=tBu)	1.0919, 1.0935	1.0902, 1.0941	0.267, 0.253	0.245, 0.237	-0.461, -0.460	-0.461, -0.459	24.77, 24.37	24.54, 24.16
	1.0988, 1.0985	1.0985, 1.0984	0.237, 0.239	0.242, 0.245			23.35, 23.46	23.17, 23.29
16 (Y=OH, A=Ph)	1.0942, 1.0945	1.0962, 1.0965	0.265, 0.261	0.249, 0.249	-0.463, -0.462	-0.466, -0.466	24.43, 24.30	24.02, 24.05
	1.0984, 1.0983	1.0983, 1.0980	0.240, 0.240	0.244, 0.245			23.47, 23.51	23.57, 23.51

17 (Y=OH, A=C_2H)	1.0943, 1.0946	1.0963, 1.0965	0.265, 0.260	0.254, 0.253	-0.467, -0.466	-0.467, -0.467	24.46, 24.41	24.15, 24.13
	1.0982, 1.0981	1.0979, 1.0978	0.243, 0.243	0.246, 0.246			23.56, 23.59	23.62, 23.60
18 (Y=OH, A=CN)	1.0942, 1.0950	1.0966, 1.0967	0.265, 0.258	0.258, 0.257	-0.468, -0.467	-0.470, -0.470	24.50, 24.29	24.23, 24.21
	1.0976, 1.0976	1.0973, 1.0971	0.248, 0.248	0.251, 0.251			23.66, 23.69	23.73, 23.70
19 (Y=$OSiMe_3$, A=CN)	1.0942, 1.0946	1.0966, 1.0967	0.263, 0.259	0.256, 0.256	-0.466, -0.465	-0.470, -0.470	24.46, 24.35	24.23, 24.21
	1.0977, 1.0978	1.0974, 1.0973	0.247, 0.247	0.250, 0.250			23.67, 23.69	23.72, 23.70
20 (Y=OAc, A=Me)	1.0944, 1.0958	1.0962, 1.0960	0.248, 0.257	0.243, 0.245	-0.461, -0.463	-0.462, -0.461	24.05, 24.31	24.05, 24.06
	1.0981, 1.0979	1.0978, 1.0978	0.245, 0.242	0.248, 0.248			23.65, 23.60	23.55, 23.56
21 (Y=OCOtBu, A=Me)	1.0958, 1.0962	1.0981, 1.0983	0.255, 0.251	0.248, 0.246	-0.467, -0.465	-0.462, -0.463	24.18, 24.08	23.90, 23.83
	1.0981, 1.0980	1.0977, 1.0977	0.243, 0.244	0.247, 0.247			23.70, 23.76	23.78, 23.74
22 (Y=NH_2, A=Me)	1.0935, 1.0935	1.0959, 1.0959	0.263, 0.263	0.241, 0.241	-0.465, -0.465	-0.462, -0.462	24.45, 24.45	23.97, 23.97
	1.0987, 1.0987	1.0982, 1.0982	0.237, 0.237	0.244, 0.244			23.45, 23.45	23.45, 23.45
23 (Y=NMe_2, A=Me)	1.0939, 1.0939	1.0960, 1.0960	0.255, 0.255	0.241, 0.241	-0.462, -0.462	-0.459, -0.459	24.40, 24.40	23.94, 23.94
	1.0988, 1.0988	1.0983, 1.0983	0.238, 0.238	0.244, 0.244			23.43, 23.43	23.41, 23.41
24 (Y=$NHMe_2^+$, A=Me)	1.1016, 1.1015	1.0946, 1.0947	0.*224*, 0.224	0.254, 0.254	-0.474, -0.474	-0.462, -0.462	23.40, 23.43	24.32, 24.32
	1.0955, 1.0955	1.0960, 1.0960	0.279, 0.279	0.268, 0.268			24.25, 24.23	23.88, 23.88
25 (Y,A=$NH(CH_2)_4$)	1.0937, 1.0938	1.0961, 1.0959	0.258, 0.261	0.240, 0.242	-0.463, -0.463	-0.461, -0.461	24.41, 24.41	23.94, 24.00
	1.0988, 1.0988	1.0983, 1.0982	0.238, 0.237	0.244, 0.245			23.45, 23.44	23.41, 23.46
26 (Y,A=$NMe(CH_2)_4$)[d]	1.0939, 1.0943	1.0961, 1.0961	0.258, 0.258	0.240, 0.242	-0.461, -0.462	-0.460, -0.458	24.34, 24.39	23.93, 23.98
	1.0988, 1.0988	1.0984, 1.0984	0.239, 0.238	0.245, 0.245			23.40, 23.45	23.40, 23.39
27 (Y=NHAc, A=Me)	1.0956, 1.0969	1.0954, 1.0956	0.250, 0.237	0.247, 0.245	-0.463, -0.462	-0.460, -0.462	24.12, 23.83	24.10, 24.09
	1.0978, 1.0982	1.0980, 1.0980	0.246, 0.246	0.246, 0.247			23.62, 23.60	23.50, 23.51
28 (Y=NHCOtBu, A=Me)	1.0968, 1.0956	1.0956, 1.0952	0.237, 0.249	0.245, 0.247	-0.462, -0.462	-0.462, -0.460	23.85, 24.12	24.08, 24.09
	1.0982, 1.0979	1.0979, 1.0980	0.246, 0.245	0.247, 0.246			23.59, 23.63	23.52, 23.51
29 (Y=N_3, A=Me)	1.0946, 1.0952	1.0959, 1.0961	0.253, 0.262	0.243, 0.244	-0.466, -0.464	-0.461, -0.463	24.17, 24.37	24.02, 24.04
	1.0980, 1.0978	1.0978, 1.0976	0.245, 0.244	0.249, 0.249			23.66, 23.61	23.57, 23.61
30 (Y=F, A=Me)	1.0945, 1.0946	1.0967, 1.0967	0.262, 0.262	0.243, 0.243	-0.466, -0.466	-0.464, -0.464	24.35, 24.35	23.97, 23.63
	1.0981, 1.0980	1.0977, 1.0977	0.242, 0.242	0.248, 0.248			23.63, 23.63	23.97, 23.63
31 (Y=Cl, A=Me)	1.0940, 1.0940	1.0956, 1.0956	0.262, 0.262	0.244, 0.244	-0.467, -0.467	-0.462, -0.462	24.43, 24.43	24.15, 24.15
	1.0980, 1.0979	1.0977, 1.0977	0.244, 0.244	0.250, 0.250			23.53, 23.52	23.52, 23.52
32 (Y=CMe_2OH, A=H)	1.0933, 1.0933	1.0989, 1.0989	0.266, 0.266	0.238, 0.238	-0.467, -0.467	-0.457, -0.457	24.70, 24.69	23.64, 23.64
	1.0993, 1.0993	1.0986, 1.0986	0.235, 0.235	0.242, 0.242			23.31, 23.31	23.61, 23.61
33 (Y=CMe_2F, A=H)	1.0939, 1.0939	1.0989, 1.0989	0.261, 0.261	0.239, 0.239	-0.467, -0.467	-0.457, -0.457	24.55, 24.54	23.64, 23.64
	1.0990, 1.0990	1.0984, 1.0984	0.238, 0.238	0.244, 0.244			23.37, 23.37	23.64, 23.64
34 (Y=COMe, A=H)[c]	1.0924, 1.0963	1.0984, 1.0989	0.273, 0.256	0.241, 0.240	-0.470, -0.469	-0.459, -0.461	24.89, 24.18	23.71, 23.67
	1.0988, 1.0985	1.0983, 1.0980	0.239, 0.243	0.246, 0.247			23.39, 23.54	23.68, 23.71
35 (Y=COOH, A=H)[c]	1.0981, 1.0958	1.0988, 1.0986	0.256, 0.245	0.242, 0.243	-0.468, -0.466	-0.461, -0.462	24.26, 23.83	23.67, 23.69
	1.0980, 1.0981	1.0978, 1.0980	0.245, 0.246	0.247, 0.247			23.61, 23.71	23.75, 23.70
36 (Y,A=$CO(CH_2)_2$)	1.0952, 1.0952	1.0978, 1.0978	0.264, 0.264	0.242, 0.242	-0.468, -0.468	-0.461, -0.461	24.39, 24.38	23.83, 23.83
	1.0985, 1.0985	1.0982, 1.0982	0.242, 0.242	0.247, 0.247			23.51, 23.51	23.66, 23.66
37 (Y,A=$CO(CH_2)_3$)	1.0918, 1.0939	1.0956, 1.0968	0.273, 0.263	0.239, 0.241	-0.469, -0.468	-0.460, -0.462	24.92, 24.52	24.05, 23.95
	1.0988, 1.0985	1.0983, 1.0981	0.253, 0.241	0.247, 0.246			23.33, 23.42	23.50, 23.58
38 (Y,A=$CO(CH_2)_4$)	1.0920, 1.0983	1.0964, 1.0959	0.267, 0.244	0.241, 0.240	-0.466, -0.463	-0.461, -0.461	24.82, 23.77	23.96, 24.00
	1.0985, 1.0983	1.0985, 1.0985	0.241, 0.245	0.246, 0.246			23.36, 23.59	23.48, 23.53

Table S2. Geometrical parameters of the C-H$_{ax}$···Y$_{ax}$ contacts and complete second order perturbation NBO analysis at the B3LYP/6-31G+(d,p) level for **1**–**38**.

System	Hyperconjugative interaction (kcal mol^{-1})[1]	r(C-H$_{ax}$··· O): r_1, r_2 Å	θ(C-H$_{ax}$···O); θ_1, θ_2 deg	($\varepsilon_{\sigma*}$-ε_n) a.u.	$F_{n\sigma*}$ a.u.
1 (Y=H, A=H)[c]	---	2.56, 2.56	89, 89	0.95	0.013
		2.56, 2.56	88.8, 88.8	0.95	0.013
2 (Y=Me, A=H)[c]	$E[\sigma(\text{C-H})_{\text{Me}} \rightarrow \sigma^*(\text{ C4}'\text{-H}_{\text{ax}})\ ] = 0.21$	2.29, 2.29	95.8, 95.8	0.95	0.013
	$E[\sigma(\text{C-H})_{\text{Me}} \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})\ ] = 0.21$	2.44, 2.44	113.4, 113.4	0.95	0.013
3 (Y=*t*-Bu, A=H)[c]	$E[\sigma(\text{C2}'\text{-H})_{t\text{-Bu}} \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})] = 0.63$	2.10, 2.10	117.1, 120.2	0.96	0.022
	$E[\sigma(\text{C2}'\text{-H})_{t\text{-Bu}} \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})] = 0.11$	2.30, 2.32	89.6, 89.4	0.96	0.009
	$E[\sigma(\text{C2}'\text{-H})_{t\text{-Bu}} \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})] = 0.60$			0.97	0.022
4 (Y=CN, A=H)[c]	$E[\pi(\text{C}\equiv\text{N}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})] = 0.11$	2.93, 2.93	107.0, 107.0	0.79	0.008
	$E[\pi(\text{C}\equiv\text{N}) \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})] = 0.13$	2.48, 2.48	89.3, 89.4	0.79	0.009
5 (Y=OH, A=H)[c]	$E[n_a(\text{O}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})] = 0.21,\ \alpha = \text{sp}^{1.1}$	2.62, 2.68	96.0, 96.0	1.07	0.013
	$E[n_\beta(\text{O}) \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})] = 0.25,\ \beta = \text{p}$	2.46, 2.47	89.8, 89.3	0.76	0.012
6 (Y=OMe, A=H)[c]	$E[n_a(\text{O}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})] = 0.25,\ \alpha = \text{sp}^{1.36}$	2.60, 2.68	96.1, 95.9	1.02	0.014
	$E[n_\beta(\text{O}) \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})] = 0.18,\ \beta = \text{p}$	2.50, 2.49	91.3, 91.4	0.75	0.010
7 (Y=NH_2, A=H)[c]	$E[n_a(\text{N}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})]=0.40$	2.67, 2.67	96.7, 96.7	0.78	0.016
	$E[n_\alpha(\text{N}) \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})]=0.40,\ \alpha = \text{sp}^{4.3}$	2.43, 2.43	89.4, 89.4	0.78	0.016
8 (Y=NMe_2, A=H)[c]	$E[n_a(\text{N}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})]=0.23$	2.71, 2.71	97.2, 97.2	0.74	0.012
	$E[n_\alpha(\text{N}) \rightarrow \sigma^*(\text{C9}'\text{-H}_{\text{ax}})]=0.23,\ \alpha = \text{sp}^{6.18}$	2.48, 2.48	89.6, 89.6	0.74	0.012
9 (Y=NHAc, A=H)	$E[n_\alpha(\text{N}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})]=0.21,\ \alpha = \text{p}$	2.16, 2.67	93.8, 95.3	0.70	0.012
	$E[n_a(\text{N-H}) \rightarrow \sigma^*(\text{C4}'\text{-H}_{\text{ax}})] = 0.15$	2.47, 2.46	89.5, 89.5	1.10	0.012
10(Y=NO_2, A=H)	-	2.81, 2.81	95.67, 95.78	-	-
11 (Y=F, A=H)[c]	not located using a threshold of 0.1 kcal mol^{-1}	2.61, 2.61	95.3, 95.3	---	---
		2.54, 2.54	88.9, 88.9		

12 (Y=Cl, A=H)^c	$E[n_a(Cl)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.37, \alpha = p$	2.88, 2.88	102.2, 102.2	0.76	0.015
	$E[n_a(Cl)\rightarrow\sigma^*(C9'\text{-}H_{ax})]=0.37$	2.48, 2.48	89.3, 89.3	0.76	0.015
	$E[n_\beta(Cl) \rightarrow \sigma^*(C4'\text{-}H_{ax})]=0.15, \beta = p$			0.76	0.010
	$E[n_\beta(Cl) \rightarrow \sigma^*(C9'\text{-}H_{ax})]=0.15$			0.76	0.010
13 (Y=SH, A=H)	$E[n_a(S)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.30, \alpha = sp^{0.45}$	2.88. 2.93	102.3, 102.7	1.09	0.016
	$E[n_a(S)\rightarrow\sigma^*(C9'\text{-}H_{ax})]=0.10$	2.46, 2.46	89.3, 89.5	1.09	0.010
	$E[n_a(S)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.11, \beta = p$			0.70	0.008
	$E[n_\beta(S) \rightarrow \sigma^*(C9'\text{-}H_{ax})]=0.73$			0.71	0.020
14 (Y=OH, A=Me)	$E[n_a(O)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.40, \alpha = sp^{1.1}$	2.46, 2.53	97.2, 96.9	1.07	0.019
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})]=0.37, \beta = p$	2.21, 2.22	113.3, 113.2	0.76	0.015
15 (Y=OH, A=tBu)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.54, \alpha = sp^{1.12}$	2.34, 2.44	97.3, 96.5	1.07	0.022
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.38, \beta = p$	1.96, 2.04	117.7, 121.6	0.76	0.015
16 (Y=OH, A=Ph)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.39, \alpha = sp^{1.1}$	2.47, 2.53	97.4, 97.2	1.07	0.018
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.42, \beta = p$	3.55, 3.56	119.4, 119.5	0.77	0.016
17 (Y=OH, A=C_2H)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.33, \alpha = sp^{1.2}$	2.49, 2.53	97.1, 97.0	1.07	0.017
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.41, \beta = p$	2.91, 2.89	108.0, 108.1	0.78	0.016
18 (Y=OH, A=CN)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.33, \alpha = sp^{1.2}$	2.52, 2.60	96.7, 96.4	1.07	0.015
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.41, \beta = p$	2.85,2.83	107.9, 108.1	0.79	0.014
19 (Y=OSiMe$_3$, A=CN)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.24, \alpha = sp^{1.2}$	2.56, 2.52	96.6, 96.9	0.78	0.011
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.33, \beta = p$	2.81, 2.81	108.2, 108.1	0.92	0.016
	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.13, \alpha = sp^{1.2}$				
20 (Y=OAc, A=Me)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.21, \alpha = sp^{0.69}$	2.45, 2.58	97.3, 96.3	1.02	0.013
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.11, \beta = p$	2.17, 2.23	113.2, 112.7	0.78	0.009
21 (Y=OCOtBu, A=Me)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.27, \alpha=sp^{1.83}$	2.47, 2.59	97.1, 96.2	1.01	0.015
		2.16, 2.23	113.1, 112.6		
22 (Y=NH$_2$, A=Me)	$E[n_a(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.63, \alpha = sp^{4.2}$	2.54, 2.54	97.6, 97.6	0.78	0.020
	$E[n_a(N) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.63$	2.17, 2.17	113.4, 113.4	0.78	0.020
23 (Y=NMe$_2$, A=Me)	$E[n_a(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.28, \alpha = sp^{7.4}$	2.55, 2.55	98.2, 98.2	0.73	0.013
	$E[n_a(N) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.28$	2.15, 2.15	113.0, 113.0	0.73	0.013
24 (Y=NHMe$_2^+$, A=Me)	$E[\sigma(C4'\text{-}H_{ax}) \rightarrow \sigma^*(N\text{-}H)]=2.06$	1.96, 1.97	105.6, 105.4	0.83	0.037
	$E[\sigma(C9'\text{-}H_{ax}) \rightarrow \sigma^*(N\text{-}H)]=1.92$	2.16, 2.14	112.1, 112.4	0.83	0.036
25 (Y,A=NH(CH$_2$)$_4$)	$E[n_\alpha(N)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.50, \alpha = sp^{5.33}$	2.55, 2.54	98.2, 97.4	0.75	0.018
		2.12, 2.18	113.2, 112.5		
26 (Y,A=NMe(CH$_2$)$_4$)^d	N/A	2.56, 2.60	98.9, 96.7	N/A	N/A
		2.14, 2.14	112.9, 112.9		
27 (Y=NHAc, A=Me)	$E[n_\alpha(N) \rightarrow \sigma^*(C4'\text{-}H_{ax})]=0.21, \alpha = p$	2.18, 3.07	108.8, 96.9	0.70	0.012
		2.18, 2.14	113.2, 113.3		
28 (Y=NHCOtBu, A=Me)	$E[n_\alpha(N)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.11, \alpha = sp^{1.83}$	2.16, 3.05		0.70	0.008
	$E[\sigma(N\text{-}H)\rightarrow \sigma^*(C4'\text{-}H_{ax})] =0.11$		113.3, 113.2	1.11	0.010
	$E[n_a(N) \rightarrow \sigma^*(C9'\text{-}H_{ax})]=0.15, \beta =p$			0.72	0.010
29(Y=N$_3$, A=Me)	$E[n_\alpha(N)\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.57, \alpha =sp^{1.2}$	2.49, 2.60	98.3, 97.0	0.89	0.021
		2.19, 2.19	113.0, 113.2		
30 (Y=F, A=Me)	-	2.48, 2.48	96.4, 96.4	-	-
		2.28, 2.28	113.2, 113.2		
31 (Y=Cl, A=Me)	$E[n_\beta(Cl) \rightarrow \sigma^*(C4'\text{-}H_{ax})]=0.64, \beta =p$	2.73, 2.73	104.0, 104.1	0.76	0.020
	$E[n_\beta(Cl) \rightarrow \sigma^*(C9'\text{-}H_{ax})]=0.63$			0.76	0.020
32 (Y=CMe$_2$OH, A=H)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 1.34$	2.41, 2.41	118.9, 118.9	1.08	0.034
	$E[n_a(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.98, \alpha = sp^{1.2}$			1.08	0.029
	$E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.66$			0.80	0.021
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.98, \beta = p$			0.80	0.019
33 (Y=CMe$_2$F, A=H)	$E[n_a(F) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.43$	2.39, 2.39	118.78,117.88	1.50	0.023
	$E[n_a(F) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.30, \alpha = sp^{0.5}$			1.50	0.019
	$E[n_\beta(F) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.32$			0.89	0.015
	$E[n_\beta(F) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.29, \beta = p$			0.89	0.015
	$E[n_\gamma(F) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.41$			089	0.017
	$E[n_\gamma(F) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.27, \gamma = p$			0.89	0.014
34 (Y=COMe, A=H)^c	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.49, \alpha = sp^{0.74}$	2.40, 2.77	119.0, 115.0	1.18	0.021
	$E[n_\beta(O)\rightarrow\sigma^*(C4'\text{-}H_{ax})] =1.09, \beta = p$			0.75	0.026
	$E[\pi(C=O\rightarrow\sigma^*(C4'\text{-}H_{ax})]=0.19$			0.84	0.011
35 (Y=COOH, A=H)^c	-	2.82, 2.84	96.11, 96.22	-	-
36 (Y,A=CO(CH$_2$)$_2$)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.10$	2.63, 2.63	121.1, 121.2	1.16	0.010
	$E[n_a(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.11, \alpha = sp^{0.8}$		97.7, 97.7	1.16	0.010
	$E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.38$			0.74	0.016
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.39, \beta = p$			0.74	0.016
	$E[\pi(C=O\rightarrow\sigma^*(C4'\text{-}H_{ax})] = 0.13$			0.86	0.009
	$E[\pi(C=O\rightarrow\sigma^*(C4'\text{-}H_{ax})] = 0.13$			0.86	0.009
37 (Y,A=CO(CH$_2$)$_3$)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.20$	2.33, 2.46	120.7, 119.2	1.16	0.014
	$E[n_a(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 0.60, \alpha = sp^{0.8}$		98.4, 96.5	1.18	0.024
	$E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.26$			0.74	0.013
	$E[n_\beta(O) \rightarrow \sigma^*(C9'\text{-}H_{ax})] = 1.17, \beta = p$			0.76	0.027
	$E[\pi(C=O\rightarrow\sigma^*(C9'\text{-}H_{ax})] = 0.43$			0.86	0.017
38(Y,A=CO(CH$_2$)$_4$)	$E[n_a(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.42, \alpha = sp^{0.8}$	2.35, 3.17	117.6, 109.9	1.17	0.020
	$E[n_\beta(O) \rightarrow \sigma^*(C4'\text{-}H_{ax})] = 0.58, \beta = p$		96.7, 97.0	0.75	0.019
	$E[\pi(C=O\rightarrow\sigma^*(C9'\text{-}H_{ax})] = 0.37$			0.87	0.016

C. Cartesian coordinates of the optimized compounds 1–38 at the B3LYP/6-31+G** level

Compound 1

Ad

0 1

C	0.00000000	0.00000000	0.00000000
C	1.54396725	0.00000000	0.00000000
H	1.91250271	1.03436755	0.00000000
C	-0.52153267	-1.45349760	-0.00238611
H	-1.61957017	-1.45054009	-0.00373694
C	-0.00372859	-2.18256263	-1.26215672
H	-0.37864696	-1.68452968	-2.16687375
H	-0.38356183	-3.21316831	-1.28462248
C	2.05679598	-0.73308138	-1.25957003
H	3.15514257	-0.72407496	-1.27978172
H	1.71648470	-0.21080494	-2.16425305
C	1.54034988	-2.18839546	-1.26310047
H	1.90628960	-2.70713549	-2.15904967
C	2.05012615	-2.91489631	0.00079198
H	1.70428254	-3.95774382	0.00137787
H	3.14841273	-2.94345457	0.00232100
C	2.05435871	-0.73176816	1.26103398
H	1.71232442	-0.20843626	2.16450597
H	3.15269022	-0.72242698	1.28335150
C	-0.00654895	-2.18209623	1.25887488
H	-0.38509779	-1.68394917	2.16196389
H	-0.38679034	-3.21256847	1.27963946
C	1.53758898	-2.18710030	1.26312692
H	1.90118171	-2.70541594	2.16037956
H	-0.37719822	0.53494973	0.88290834
H	-0.37662535	0.53726725	-0.88193446

Compound 2

2-MeAd

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.55227104
H	1.03822074	0.00000000	1.91242816
C	-1.47310614	-0.02940405	-0.48783042
H	-1.48827903	-0.05023732	-1.58640343
C	-2.21221763	-1.27058583	0.06205950
H	-1.74965615	-2.19527543	-0.30500248
H	-3.24770530	-1.27307560	-0.30479557
C	-0.73762435	-1.24129178	2.10381545
H	-0.71478027	-1.22345161	3.20198713
H	-0.23147821	-2.16496137	1.79654103
C	-2.19949758	-1.24326110	1.60620116
H	-2.71945310	-2.12917487	1.99437514
C	-2.91139442	0.03342875	2.10212282
H	-3.95857389	0.03441045	1.76986307
H	-2.92430766	0.05469097	3.20048129
C	-0.71895910	1.27161104	2.05518517
H	-0.19299500	2.16767616	1.69826136
H	-0.69693175	1.30586841	3.15307607
C	-2.19394656	1.24210223	0.01207874
H	-1.70140481	2.13755032	-0.39113379
H	-3.22950211	1.25621894	-0.35461581
C	-2.18011758	1.27905016	1.55594615
H	-2.68496504	2.18854235	1.90760520
C	0.87548445	-1.09992570	-0.61786380
H	0.87513765	-1.02533838	-1.71194406

H	1.91408829	-1.00432594	-0.27938828
H	0.53775147	-2.10804065	-0.35847929
H	0.42936404	0.96026011	-0.32388709

Compound 3

2-t-Bu-Ad

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.55985231
H	1.02860537	0.00000000	1.93464005
C	-1.48906866	0.07059574	-0.45953160
H	-1.54195505	0.13531914	-1.55292468
C	-2.18745553	-1.23419708	-0.00245171
H	-1.69225814	-2.10494678	-0.45259000
H	-3.22902776	-1.24258610	-0.35199662
C	-0.68834142	-1.30592127	2.02797591
H	-0.66118014	-1.36856887	3.12461992
H	-0.13970549	-2.17698742	1.64524658
C	-2.15187122	-1.33782547	1.53867910
H	-2.62780443	-2.27526162	1.85565435
C	-2.90757770	-0.13830202	2.14792828
H	-3.95862187	-0.15042750	1.82857668
H	-2.90459942	-0.20811884	3.24431411
C	-0.76666903	1.19521940	2.16953940
H	-0.29539959	2.14652761	1.89901037
H	-0.72528610	1.12836805	3.26567907
C	-2.26370394	1.26109379	0.15761371
H	-1.85292607	2.22008009	-0.16881806
H	-3.30309771	1.22999105	-0.19809630
C	-2.23498846	1.17462391	1.69647588
H	-2.77320354	2.03088567	2.12404686
C	1.04101726	0.91171707	-0.75907190
C	2.42691833	0.77952070	-0.08814152
H	3.19595539	1.24523011	-0.71542921
H	2.46120270	1.27212929	0.88893038
H	2.70593256	-0.27173120	0.05345137
C	1.17611129	0.37497805	-2.20503836
H	1.91214540	0.96309219	-2.76530687
H	1.51017542	-0.66929170	-2.21125457
H	0.23008838	0.42786832	-2.75347722
C	0.69437781	2.41306806	-0.85351760
H	-0.21750695	2.58544662	-1.43249637
H	0.57064196	2.87904725	0.12797819
H	1.50674844	2.94357185	-1.36511620
H	0.34151246	-1.01030788	-0.27332062

Compound 4

2-CN-Ad

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.55965043
H	1.03665266	0.00000000	1.91600440
C	-1.47186900	0.02775435	-0.51520615
H	-1.46546082	0.04723987	-1.61120350
C	-2.17896456	-1.24957931	-0.01380629
H	-1.67774417	-2.14242280	-0.41162573
H	-3.20856314	-1.26751662	-0.39363182
C	-0.72311381	-1.27698680	2.03860951
H	-0.70535826	-1.31449074	3.13539525
H	-0.19325640	-2.17046496	1.68138403
C	-2.17981447	-1.27866399	1.52914288
H	-2.68821033	-2.18655291	1.87768315
C	-2.91402921	-0.03108958	2.06661110
H	-3.95795699	-0.03364727	1.72550162
H	-2.93737037	-0.05286259	3.16439757

C	-0.74049567	1.24689970	2.08627878
H	-0.22442182	2.15976758	1.76478343
H	-0.72323171	1.24157261	3.18374294
C	-2.19793071	1.27437327	0.03177751
H	-1.71249849	2.18780397	-0.33292087
H	-3.22798812	1.28870240	-0.34709898
C	-2.19763603	1.24603685	1.57554282
H	-2.71875520	2.13284198	1.95714785
C	0.79427105	1.10689437	-0.54900257
N	1.42413056	1.98103565	-0.98556178
H	0.47875142	-0.92422859	-0.35196551

Compound 5

2AdOH

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.53861968
H	1.04046388	0.00000000	1.88564382
C	-1.45509490	-0.03889077	-0.51710311
H	-1.44518066	-0.06003093	-1.61713887
C	-2.17932153	-1.29029635	0.02289585
H	-1.67206503	-2.19639598	-0.32725063
H	-3.20613224	-1.31990831	-0.36617842
C	-0.73205043	-1.25011292	2.07341549
H	-0.71264056	-1.24383558	3.17161281
H	-0.21189413	-2.15584533	1.74329754
C	-2.18950342	-1.25546047	1.56569247
H	-2.70964513	-2.14282596	1.94941593
C	-2.91399846	0.01873932	2.04923934
H	-3.95631947	0.01522946	1.70174922
H	-2.94386179	0.04193093	3.14717749
C	-0.72702091	1.27365947	2.02566465
H	-0.20484977	2.17092249	1.66618962
H	-0.70858474	1.31307921	3.12260313
C	-2.17548984	1.23857481	-0.02942255
H	-1.66692974	2.13142174	-0.41883434
H	-3.20134665	1.26233727	-0.42003989
C	-2.18411649	1.26993279	1.51441224
H	-2.69916371	2.17548274	1.86056253
O	0.77756167	-1.12071521	-0.44511311
H	0.86005280	-1.07813575	-1.40664909
H	0.47742823	0.92932399	-0.35153902

Compound 6

2AdOMe

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.54030905
H	1.04175329	0.00000000	1.88359366
C	-1.45900989	-0.02447390	-0.51514335
H	-1.46285240	-0.03036301	-1.61258642
C	-2.18291789	-1.27868776	0.01836155
H	-1.68264561	-2.18367182	-0.34493968
H	-3.21260954	-1.29996367	-0.36375808
C	-0.72919474	-1.25358272	2.06995676
H	-0.71009894	-1.25109141	3.16831156
H	-0.20649119	-2.15675360	1.73699228
C	-2.18681881	-1.25793844	1.56238112
H	-2.70583770	-2.14846970	1.94029634
C	-2.91081726	0.01273793	2.05787747
H	-3.95460787	0.01102423	1.71478201
H	-2.93630680	0.02748224	3.15618804
C	-0.72561625	1.26919958	2.03799412
H	-0.20381568	2.16996100	1.68659438
H	-0.70538829	1.29729030	3.13538433

C	-2.17726554	1.24799682	-0.01276586
H	-1.67647531	2.14594054	-0.40056968
H	-3.20561820	1.26749826	-0.39753579
C	-2.18320937	1.26865399	1.53051826
H	-2.69784874	2.17145558	1.88471575
O	0.77200499	-1.12239802	-0.43642114
H	0.49408572	0.91945905	-0.36141836
C	1.17554740	-1.07737858	-1.79275951
H	1.84384611	-1.92707296	-1.95280866
H	0.32783004	-1.16219927	-2.48743030
H	1.72129914	-0.14734022	-2.01663913

Compound 7

2AdNH$_2$

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.54758049
H	1.04049919	0.00000000	1.90445151
C	-1.46489999	-0.02978607	-0.49818288
H	-1.46746543	-0.05099489	-1.59797336
C	-2.19873911	-1.27435602	0.04719688
H	-1.70798701	-2.18585720	-0.30947999
H	-3.23086909	-1.28498778	-0.32930329
C	-0.73552620	-1.24460426	2.09060420
H	-0.71153730	-1.23376177	3.18899606
H	-0.22722678	-2.15574864	1.75843253
C	-2.19596721	-1.24151875	1.59053211
H	-2.71883021	-2.12585346	1.97781192
C	-2.90758197	0.03702954	2.08147918
H	-3.95351364	0.04070960	1.74481868
H	-2.92594830	0.06160326	3.17983509
C	-0.71365709	1.27717925	2.04105546
H	-0.18649917	2.17128331	1.68085839
H	-0.69247056	1.31400013	3.13829836
C	-2.17954675	1.24737306	-0.00609000
H	-1.68107044	2.14089392	-0.40634154
H	-3.21185009	1.26277314	-0.38006766
C	-2.17356113	1.28252074	1.53773818
H	-2.67925114	2.19256345	1.88659509
N	0.75036671	-1.15274257	-0.52052771
H	0.76608637	-1.14027212	-1.53786030
H	1.71824051	-1.12091180	-0.20815720
H	0.44471099	0.95599849	-0.33236129

Compound 8

2-AdNMe$_2$

0 1

C	0.00000000	0.00000000	0.00000000
H	0.00000000	0.00000000	1.09465954
C	1.39612617	0.00000000	-2.08302901
H	2.40864757	0.00000000	-2.49905775
C	0.61542700	-1.22396896	-2.60905846
H	1.11151222	-2.15014270	-2.29764824
H	0.60566516	-1.20848075	-3.70760029
C	-0.78326579	-1.22396896	-0.52220003
H	-1.80308820	-1.20848075	-0.11372517
H	-0.30668362	-2.15014270	-0.18169114
C	-0.82859617	-1.18849811	-2.06474026
H	-1.38351113	-2.05981431	-2.43666561
C	-1.52587501	0.10725927	-2.53208336
H	-1.57760334	0.13230800	-3.62927323
H	-2.56039638	0.13230800	-2.16293984
C	-0.69523695	1.29506805	-0.47232598
H	-0.15965984	2.17436823	-0.08920785
H	-1.71001680	1.33399061	-0.05401524

C	0.69501437	1.29506805	-2.54658967
H	1.25293285	2.17436823	-2.19680500
H	0.69626680	1.33399061	-3.64420548
C	-0.74866361	1.33568591	-2.01116639
H	-1.24448263	2.25727952	-2.34348337
N	2.22512234	-1.18740650	-0.01802065
C	2.26189133	-1.23970445	1.44276885
H	2.88834238	-2.08007134	1.75539195
H	2.67787689	-0.31710691	1.89597078
H	1.26639986	-1.40447718	1.85925080
C	3.59027518	-1.23970445	-0.53918820
H	4.16756756	-0.31710691	-0.32665705
H	4.11752517	-2.08007134	-0.07855649
H	3.59716666	-1.40447718	-1.61826789
C	1.46174189	-0.02874940	-0.52966759
H	1.96346594	0.90528848	-0.19339283

Compound 9

2AdNHCOMe

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.54399694
C	1.45937640	0.00000000	2.04909583
C	0.73479428	1.25624005	-0.52285456
C	2.19343498	1.29559873	-0.01033679
C	2.19057444	1.26025276	1.54035933
C	-0.72294423	1.26402418	2.05624615
C	0.00368944	2.52472290	1.53965194
C	1.46022225	2.52117913	2.05106487
C	0.00583952	2.51592337	-0.00410033
N	2.99904569	0.22962852	-0.60711061
H	-1.02924526	-0.00606948	-0.38228120
H	0.46643185	-0.92278243	-0.37459080
H	-0.51856811	-0.89543697	1.91042644
H	1.97883923	-0.90663279	1.71147451
H	1.47874541	-0.02020489	3.14666153
H	0.74206177	1.25939884	-1.62074321
H	3.22950887	1.26378632	1.88812340
H	-0.74332403	1.26490278	3.15433216
H	-1.76797246	1.26437927	1.71735516
H	-0.51283985	3.42352215	1.90013918
H	1.47560276	2.54017845	3.14876823
H	1.98528080	3.42301880	1.71001006
H	-1.02411411	2.52883246	-0.38457616
H	0.49941868	3.41854389	-0.38743115
C	4.33889941	0.36034429	-0.84056574
O	4.96783732	1.37437189	-0.54216326
C	5.01692655	-0.82723475	-1.50680494
H	2.54806145	-0.63130231	-0.87772673
H	5.84594586	-1.15803515	-0.87515283
H	5.44180931	-0.49738941	-2.45931338
H	4.34746606	-1.67317757	-1.68994138
H	2.66422950	2.23124734	-0.32971547

Compound 10

2Ad-NO$_2$

0 1

C	0.05208200	-1.26278700	-0.36272100
C	-0.27995200	-1.27742500	1.14607700
C	-1.10340200	-0.02535100	1.51546800
C	-0.27525300	1.23579700	1.18951000
C	0.05525300	1.27299500	-0.31917400
C	0.83425900	0.01072000	-0.73048400
C	-2.41370500	-0.00916500	0.69843700

C	-2.08733200	0.01633500	-0.81073100
C	-1.25981300	1.27710000	-1.13550200
C	-1.26299200	-1.23442200	-1.17923100
N	2.25508200	0.00093600	-0.14479300
O	2.79768700	-1.08637200	0.04898900
O	2.80930700	1.08197200	0.05196500
H	0.63821900	-2.14600100	-0.63477900
H	0.64012400	-1.31929300	1.74244900
H	-0.84660000	-2.18865900	1.37694500
H	-1.33604800	-0.04355500	2.58857300
H	0.64595800	1.25274000	1.78557200
H	-0.83762600	2.14065200	1.45349300
H	0.64383100	2.16336200	-0.56069800
H	1.04784300	0.02934800	-1.80951800
H	-3.01460400	0.87012600	0.96746900
H	-3.01666000	-0.89578500	0.93712400
H	-3.01814900	0.02743300	-1.39342300
H	-1.82884200	2.18226000	-0.88803300
H	-1.03819000	1.32202600	-2.21054700
H	-1.83432900	-2.14618700	-0.96342500
H	-1.04132600	-1.24259000	-2.25517900

Compound 11

2AdF

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.53214328
H	1.03840094	0.00000000	1.88561539
C	-1.43170135	-0.03172722	-0.54505646
H	-1.39229295	-0.05393856	-1.64104577
C	-2.17089804	-1.27783375	-0.01120968
H	-1.67359833	-2.18819240	-0.36403519
H	-3.19423747	-1.29336938	-0.40883138
C	-0.74403800	-1.24628692	2.05896931
H	-0.73673580	-1.23870360	3.15691417
H	-0.22438479	-2.15626623	1.73892658
C	-2.19535115	-1.24455735	1.53217033
H	-2.72394296	-2.12913304	1.90991778
C	-2.91676315	0.03428640	2.01038438
H	-3.95648308	0.03635824	1.65596042
H	-2.95372822	0.05869210	3.10796001
C	-0.72505078	1.28111669	2.00703686
H	-0.19343006	2.17537950	1.65382815
H	-0.71658408	1.32047235	3.10384617
C	-2.15180774	1.24941369	-0.06296523
H	-1.64481993	2.14287637	-0.45252922
H	-3.17406284	1.26631065	-0.46207345
C	-2.17642138	1.28202347	1.48040581
H	-2.68956594	2.19082747	1.82005369
F	0.71185767	-1.13433621	-0.47328534
H	0.54666643	0.86783721	-0.38992760

Compound 12

2AdCl

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.53818132
H	1.03464872	0.00000000	1.89937869
C	-1.44000458	-0.05622861	-0.53775174
H	-1.41540961	-0.09564419	-1.63264908
C	-2.19140357	-1.28148706	0.02395133
H	-1.71202745	-2.20639116	-0.31535669
H	-3.21653007	-1.28787593	-0.36882510
C	-0.75826160	-1.22550453	2.09002026

H	-0.74979216	-1.19152576	3.18727540
H	-0.24909361	-2.14925696	1.79367967
C	-2.21044617	-1.22020012	1.56634823
H	-2.74512927	-2.09357038	1.96090969
C	-2.91996301	0.07274227	2.02341643
H	-3.96014850	0.07816879	1.67063562
H	-2.95471123	0.11740373	3.12034850
C	-0.71676081	1.29633090	1.99235272
H	-0.17578076	2.17911984	1.62566919
H	-0.70572901	1.35013405	3.08868404
C	-2.14932528	1.24042168	-0.07293550
H	-1.63870395	2.12201684	-0.48341066
H	-3.17317694	1.25387851	-0.46854909
C	-2.16848681	1.30268182	1.46891702
H	-2.67135281	2.22287469	1.79284793
H	0.50759102	0.89172996	-0.37626568
Cl	1.02497764	-1.37747425	-0.67372452

Compound 13

Ad-2-SH

0 1

C	1.06571600	-0.19625800	-1.70121100
C	1.89767600	0.53939500	-0.62928300
C	-0.24201300	-0.73574400	-1.07534700
C	-1.04663600	0.47275900	-0.53979500
C	-0.23465200	1.17873800	0.57142900
C	1.07154900	1.71409700	-0.06379200
C	2.24364000	-0.44131600	0.51195200
C	0.94229100	-0.98007700	1.14342300
C	0.11663800	0.19611400	1.70794600
C	0.11169600	-1.71317500	0.06793800
S	-2.74413400	-0.08334600	-0.01325000
H	1.64225100	-1.03214500	-2.11906900
H	0.83569100	0.48090400	-2.53466100
H	2.82117900	0.92421400	-1.08106600
H	-0.83039700	-1.25216600	-1.84334700
H	-0.81737400	2.01831300	0.97193900
H	0.83769900	2.43202300	-0.86186300
H	1.65154500	2.25776000	0.69369000
H	2.85084500	0.06592900	1.27404400
H	2.84796100	-1.27216000	0.12302400
H	1.18727900	-1.67802800	1.95433800
H	0.68976100	0.72405000	2.48175400
H	-0.79873200	-0.17610600	2.18101300
H	0.68343300	-2.55660300	-0.34145900
H	-0.79774400	-2.13337900	0.51370400
H	-1.21185300	1.17281900	-1.36613800
H	-3.24083600	1.15091700	0.20653600

Compound 14

2-Me-2AdOH

0 1

C	0.00000000	0.00000000	0.00000000
C	1.55072064	0.00000000	0.00000000
H	1.89190066	1.04318875	0.00000000
C	-0.48077786	-1.48026979	0.00547417
H	-1.58135997	-1.49015659	0.01385608
C	0.03732283	-2.20176866	-1.25979568
H	-0.35194266	-1.71444969	-2.15918718
H	-0.32819640	-3.23757591	-1.26256491
C	2.07252546	-0.71950781	-1.26535971
H	3.17059566	-0.69184906	-1.26911422
H	1.72823886	-0.19672540	-2.16243802
C	1.58102226	-2.18306099	-1.27251306
H	1.94536573	-2.68806442	-2.17669833

C	2.11315538	-2.91159737	-0.02081676
H	1.78483944	-3.96023319	-0.02397241
H	3.21180801	-2.92109867	-0.02688269
C	2.09016196	-0.73652326	1.24786917
H	1.78414340	-0.23056495	2.17134782
H	3.18766247	-0.71156360	1.22980542
C	0.05395548	-2.22122276	1.25376195
H	-0.33105362	-1.77192421	2.17688340
H	-0.30647039	-3.25841244	1.23898104
C	1.59789623	-2.20000389	1.24813303
H	1.97508631	-2.71485696	2.14148900
C	-0.59428411	0.82394227	1.15158505
H	-0.25044088	1.86057853	1.07628934
H	-1.69076721	0.82302025	1.09105432
H	-0.32519371	0.44429828	2.13936383
O	-0.38956543	0.64430521	-1.23408932
H	-1.35143153	0.74305440	-1.23682170

Compound 15

2-tBu-2AdOH

0 1

C	0.00000000	0.00000000	0.00000000
C	1.56361675	0.00000000	0.00000000
H	1.91972417	1.03418777	0.00000000
C	-0.43789855	-1.50507993	0.03724669
H	-1.53422733	-1.56507077	0.08496384
C	0.05350612	-2.20665582	-1.25635694
H	-0.37750297	-1.73726629	-2.14500536
H	-0.28737116	-3.25087391	-1.24313479
C	2.07159908	-0.69150982	-1.29150745
H	3.16988404	-0.65882294	-1.29648717
H	1.72339344	-0.15003087	-2.17337292
C	1.59621185	-2.15871221	-1.32917178
H	1.93176303	-2.63189425	-2.26136745
C	2.19132004	-2.90868459	-0.12081636
H	1.88295436	-3.96314186	-0.13402056
H	3.28869377	-2.89363290	-0.16957963
C	2.16364443	-0.76242547	1.20336647
H	1.89735698	-0.29360803	2.15536108
H	3.25869070	-0.71224602	1.13451251
C	0.16683029	-2.28853067	1.23152165
H	-0.18875296	-1.91510486	2.19209302
H	-0.17049257	-3.33187827	1.16333524
C	1.70660321	-2.23650034	1.17899295
H	2.12032406	-2.76472181	2.04812567
C	-0.71742928	0.97222267	1.05463763
O	-0.32699027	0.55143991	-1.30077328
H	-1.27506689	0.45199349	-1.45193353
C	-0.01515125	2.34904387	1.04326284
H	-0.62517518	3.08016613	1.58620922
H	0.96238797	2.31367682	1.53547471
H	0.12390939	2.71329045	0.02165074
C	-2.19316628	1.19876565	0.62620228
H	-2.71931521	1.75306117	1.41061139
H	-2.27668491	1.79474109	-0.28784509
H	-2.73544367	0.25616007	0.48594150
C	-0.78436016	0.48847187	2.52279871
H	-1.44250388	-0.37679949	2.64358685
H	0.19065559	0.24203128	2.94592002
H	-1.20393762	1.29587712	3.13447820

Compound 16

2-Ph-2AdOH

0 1

C	0.00000000	0.00000000	0.00000000

C	1.54093566	0.00000000	0.00000000
C	2.03021792	1.46086193	0.00000000
C	-0.52809826	0.73022473	1.25593064
C	-0.05585380	2.21086216	1.25162146
C	1.50469575	2.19240426	1.25587507
C	2.06018829	-0.71822430	1.26235901
C	1.53792548	0.00737007	2.52025716
C	2.03025349	1.46922497	2.51754997
C	-0.00519719	0.00479618	2.51619825
C	-0.67158891	3.06230888	2.38211594
O	-0.53773348	2.77187789	0.00312480
H	-0.37894283	-1.03095163	0.00597869
H	-0.38303300	0.48325805	-0.90389086
H	1.91017421	-0.51344082	-0.89736595
H	1.68878439	1.97463018	-0.90406121
H	3.12802008	1.49468438	0.00335182
H	-1.62205515	0.70505409	1.23141000
H	1.88110098	3.22202207	1.23197371
H	3.15888992	-0.73212363	1.26527421
H	1.72714179	-1.76514161	1.26670750
H	1.90431553	-0.50178508	3.42114967
H	3.12810104	1.50158558	2.52327905
H	1.69184536	1.97868092	3.42727942
H	-0.38125792	-1.02683713	2.51689523
H	-0.38503065	0.48279022	3.42695244
H	-0.50115918	3.73546150	0.07080798
C	-1.98804777	2.83845752	2.82029380
C	0.00806813	4.16702250	2.92350810
C	-2.59410717	3.66991395	3.76327358
C	-0.59457636	5.00553251	3.86679112
C	-1.89988273	4.76014977	4.29396037
H	-2.56005180	2.01058340	2.41685362
H	1.02605076	4.38528529	2.61978643
H	-3.61334420	3.46618715	4.07983805
H	-0.03752657	5.84792570	4.26753910
H	-2.37065771	5.40873588	5.02706192

Compound 17

2-C$_2$H-2AdOH

0 1

C	0.00000000	0.00000000	0.00000000
C	1.55626898	0.00000000	0.00000000
H	1.89033649	1.04356749	0.00000000
C	-0.48956547	-1.48354862	0.00589197
H	-1.58768813	-1.48254247	0.01362136
C	0.03003220	-2.19426572	-1.26133972
H	-0.35877717	-1.70045789	-2.15753962
H	-0.34281160	-3.22715237	-1.26789422
C	2.06510820	-0.72027897	-1.26719810
H	3.16281096	-0.68943845	-1.27337170
H	1.71935527	-0.19621033	-2.16341618
C	1.57359661	-2.18344478	-1.27244956
H	1.93711925	-2.68972605	-2.17596178
C	2.10308599	-2.91109875	-0.01845366
H	1.77212088	-3.95867028	-0.02052525
H	3.20154296	-2.92281693	-0.02370141
C	2.08073650	-0.73402303	1.25302748
H	1.74972604	-0.22239192	2.16456794
H	3.17807505	-0.70382300	1.24963641
C	0.04550940	-2.21033519	1.25973525
H	-0.33437718	-1.73389800	2.17113374
H	-0.32483586	-3.24387725	1.26028984
C	1.58914687	-2.19733939	1.24941027
H	1.96438144	-2.71143336	2.14370130
O	-0.41016277	0.67005848	-1.21028539
H	-1.34346184	0.90820232	-1.12552267
C	-0.54779316	0.74656906	1.14664850
C	-1.04563255	1.38360696	2.04813588

H	-1.47168240	1.94675917	2.84723537

Compound 18

2-CN-2AdOH

0 1

C	1.08563500	0.46584400	-0.01432900
C	0.21433400	0.18852100	-1.27131500
H	0.82796100	0.38784700	-2.15674700
C	0.23364300	0.18146400	1.26035400
H	0.85799400	0.36898600	2.14460500
C	-0.98965400	1.12247200	1.26372200
H	-0.66732900	2.16861600	1.28826700
H	-1.57110900	0.93946000	2.17645300
C	-1.00931700	1.12919900	-1.24883500
H	-1.60575900	0.94744500	-2.15211700
H	-0.68396200	2.17349100	-1.27814000
C	-1.85580700	0.85928100	0.01333300
H	-2.72413700	1.52992600	0.02292000
C	-2.33037900	-0.60941700	0.01446000
H	-2.94755400	-0.80711200	0.90117200
H	-2.96113400	-0.80290400	-0.86341000
C	-0.26081900	-1.28089900	-1.26063500
H	0.59492800	-1.96558900	-1.30171800
H	-0.85695300	-1.46479400	-2.16311800
C	-0.24196400	-1.28878900	1.25417200
H	0.61474200	-1.97287400	1.27795700
H	-0.82368100	-1.47716200	2.16525600
C	-1.10697100	-1.54978400	0.00235600
H	-1.43983600	-2.59511500	0.00248100
O	1.50966200	1.83091500	-0.08760500
H	2.08844200	2.02609500	0.66332400
C	2.30357500	-0.38562200	-0.01985800
N	3.28091800	-1.01389300	0.00187000

Compound 19

2-CN-2AdOTMS

0 1

C	0.00000000	0.00000000	0.00000000
C	1.56065776	0.00000000	0.00000000
H	1.89536103	1.04355709	0.00000000
C	-0.49203361	-1.48282179	0.01716728
H	-1.58780529	-1.48179876	0.03365336
C	0.01970330	-2.18855509	-1.25683794
H	-0.37662920	-1.69304194	-2.14875992
H	-0.35450048	-3.22054520	-1.26248597
C	2.05516949	-0.71616304	-1.27475266
H	3.15229751	-0.68460310	-1.29300552
H	1.69810323	-0.18782266	-2.16394156
C	1.56258724	-2.17838940	-1.27957321
H	1.91769348	-2.68144341	-2.18789454
C	2.10204936	-2.91088699	-0.03269905
H	1.76967241	-3.95781109	-0.03592630
H	3.20022911	-2.92429695	-0.04796859
C	2.09432927	-0.73838650	1.24716392
H	1.77603184	-0.23063487	2.16560353
H	3.19116269	-0.70836103	1.23360722
C	0.05709093	-2.21057425	1.26535372
H	-0.31424480	-1.74001560	2.18365243
H	-0.31663697	-3.24238073	1.26578603
C	1.59989490	-2.20026937	1.24202384
H	1.98100008	-2.71747311	2.13142357
O	-0.44657650	0.67118184	-1.16645356
C	-0.49826418	0.70982429	1.20798232
N	-0.90297805	1.27496427	2.13935045
Si	-1.79873504	1.61622726	-1.55689960

C	-3.39078555	0.83361121	-0.91574998
H	-4.25281896	1.43733281	-1.22568418
H	-3.53380512	-0.17573556	-1.31773959
H	-3.40951514	0.77492200	0.17771563
C	-1.59500857	3.35958687	-0.87507152
H	-2.42102035	3.99878019	-1.21070378
H	-1.58491614	3.37096947	0.21921842
H	-0.66060995	3.81017141	-1.22858266
C	-1.77156582	1.63614990	-3.43762510
H	-2.58144036	2.26088291	-3.83268254
H	-0.82423315	2.04066869	-3.81069780
H	-1.89254807	0.62837849	-3.84972555

Compound 20

2-Me-2AdOAc

0 1

C	2.70746500	-0.11532700	0.16164300
O	2.85632300	0.58404200	1.14540600
C	3.77183300	-1.03348100	-0.39910100
H	4.66384400	-0.97593900	0.22455500
H	4.01522800	-0.74095500	-1.42526400
H	3.40487000	-2.06387900	-0.43213400
O	1.58513800	-0.18770300	-0.58204800
C	-0.88750000	-1.36815400	-1.21051800
C	-1.45763000	-1.65982700	0.19339500
C	-0.44833700	-1.17936700	1.25756400
C	-0.63471100	0.14934800	-1.36870900
C	0.38702600	0.64159200	-0.30801100
C	-0.19347400	0.33726900	1.10052200
C	-2.79227100	-0.90598600	0.37321200
C	-2.55366200	0.60972900	0.21107400
C	-1.54091100	1.08192500	1.27418900
C	-1.98105800	0.89045800	-1.19447700
C	0.79532900	2.10412200	-0.51541100
H	-1.59680900	-1.69500900	-1.98250300
H	0.04104200	-1.92520100	-1.36926600
H	-1.62487300	-2.73900600	0.30515700
H	0.48916000	-1.73998700	1.17074000
H	-0.83881400	-1.37333500	2.26513600
H	-0.22065000	0.35372300	-2.36443800
H	0.51695900	0.67810800	1.85773700
H	-3.21464700	-1.11611100	1.36526100
H	-3.52546000	-1.25394400	-0.36713500
H	-3.50074600	1.15019500	0.33722700
H	-1.92748800	0.87317200	2.28022800
H	-1.40088800	2.16761200	1.21710800
H	-2.68079300	0.53800000	-1.96346500
H	-1.86567000	1.96879900	-1.35296600
H	1.52050200	2.41293300	0.23960000
H	1.24498900	2.22248800	-1.50716400
H	-0.06403400	2.77381900	-0.45750400

Compound 21

2AdMeOCOtBu

0 1

C	-1.37482700	1.45031000	1.09035000
C	-1.98875900	1.72235700	-0.29891500
C	-1.13225200	1.02453000	-1.37666500
C	-1.32934200	-0.07258800	1.35502100
C	-0.46266100	-0.78429300	0.28056200
C	-1.08611100	-0.49788700	-1.11309600
C	-3.42673400	1.16460900	-0.34252700
C	-3.39631300	-0.35444900	-0.07339900
C	-2.53532100	-1.04433900	-1.15157000

C	-2.77717100	-0.61605400	1.31589600
H	-1.97963000	1.93093100	1.87091600
H	-0.36976900	1.87803800	1.15321100
H	-2.00601500	2.80387900	-0.48636700
H	-0.12146800	1.44664200	-1.38915300
H	-1.56006600	1.20129500	-2.37224100
H	-0.88321300	-0.26572100	2.33910100
H	-0.48421700	-0.99290300	-1.87886200
H	-3.88087200	1.36422100	-1.32259100
H	-4.05031300	1.66867800	0.40840300
H	-4.41707300	-0.75722900	-0.10230500
H	-2.95487700	-0.85111200	-2.14743600
H	-2.54951200	-2.13218200	-1.01728300
H	-3.36568800	-0.10939600	2.09185900
H	-2.80786600	-1.68543600	1.55352900
C	1.91109900	-0.43243200	-0.36926000
O	1.86698900	-1.20313000	-1.31018600
C	3.18357200	0.31204600	0.07848200
C	4.32902600	-0.03319800	-0.88732800
H	5.24143800	0.48637300	-0.57499900
H	4.52843300	-1.10817800	-0.90009700
H	4.09162600	0.26914800	-1.91125000
C	2.92777300	1.83565700	0.06778600
H	2.65076600	2.18575900	-0.93287100
H	2.13127800	2.11259600	0.76296700
H	3.84136000	2.36270100	0.36476700
C	3.54813400	-0.14354500	1.51061000
H	3.71923900	-1.22503500	1.55084500
H	4.47074000	0.35366100	1.83025000
H	2.75690200	0.10759200	2.22177400
O	0.86126000	-0.12873600	0.42078300
C	-0.25894000	-2.27308200	0.58204800
H	0.35985700	-2.74122300	-0.18544400
H	0.23495300	-2.38674800	1.55303300
H	-1.20903600	-2.80727200	0.62750400

Compound 22

2-Me-2AdNH$_2$

0 1

C	1.08208300	0.77101100	0.00000000
C	0.32880800	0.23193800	1.25534700
H	0.84163200	0.60315000	2.15571100
C	0.32880800	0.23193800	-1.25534700
H	0.84163200	0.60315000	-2.15571100
C	0.32880800	-1.31449400	-1.25919600
H	1.35407400	-1.69357700	-1.28682900
H	-0.18383100	-1.67301100	-2.16244500
C	0.32880800	-1.31449400	1.25919600
H	-0.18383100	-1.67301100	2.16244500
H	1.35407400	-1.69357700	1.28682900
C	-0.39602700	-1.83725200	0.00000000
H	-0.38315800	-2.93516400	0.00000000
C	-1.85537000	-1.33522000	0.00000000
H	-2.38728000	-1.71598400	-0.88285300
H	-2.38728000	-1.71598400	0.88285300
C	-1.13875500	0.71966100	1.26228000
H	-1.19627400	1.81245800	1.32129000
H	-1.63951400	0.33412300	2.16039500
C	-1.13875500	0.71966100	-1.26228000
H	-1.19627400	1.81245800	-1.32129000
H	-1.63951400	0.33412300	-2.16039500
C	-1.86625000	0.20742400	0.00000000
H	-2.90216200	0.57154900	0.00000000
N	2.45107800	0.20652800	0.00000000
C	1.16453500	2.31477200	0.00000000
H	1.71362700	2.65779400	0.88583500
H	1.71362700	2.65779400	-0.88583500
H	0.19492000	2.81840900	0.00000000

H	2.96390800	0.53996400	-0.81537000
H	2.96390800	0.53996400	0.81537000

Compound 23

2-Me-2AdNMe$_2$

0 1

C	0.30464000	0.87418900	0.00000000
C	0.24007900	-0.06988100	-1.25055400
H	0.32379600	0.53025500	-2.16399600
C	0.24007900	-0.06988100	1.25055400
H	0.32379600	0.53025500	2.16399600
C	-1.09125100	-0.85612900	1.25970500
H	-1.94318100	-0.17081700	1.29287400
H	-1.13492900	-1.48249700	2.16142900
C	-1.09125100	-0.85612900	-1.25970500
H	-1.13492900	-1.48249700	-2.16142900
H	-1.94318100	-0.17081700	-1.29287400
C	-1.17996200	-1.74398600	0.00000000
H	-2.13536300	-2.28513000	0.00000000
C	-0.01247200	-2.75333600	0.00000000
H	-0.07358800	-3.40447500	0.88294800
H	-0.07358800	-3.40447500	-0.88294800
C	1.40316000	-1.09123700	-1.25114000
H	2.37477600	-0.58662100	-1.30136900
H	1.32778700	-1.70599200	-2.15818400
C	1.40316000	-1.09123700	1.25114000
H	2.37477600	-0.58662100	1.30136900
H	1.32778700	-1.70599200	2.15818400
C	1.32574400	-1.98599100	0.00000000
H	2.16254500	-2.69705900	0.00000000
N	-0.90197500	1.76667600	0.00000000
C	-1.09125100	2.58795000	-1.19217100
H	-2.06825200	3.07870500	-1.12462500
H	-0.33358700	3.38408700	-1.31916000
H	-1.09821600	1.98059800	-2.09880400
C	-1.09125100	2.58795000	1.19217100
H	-0.33358700	3.38408700	1.31916000
H	-2.06825200	3.07870500	1.12462500
H	-1.09821600	1.98059800	2.09880400
C	1.59855100	1.72146800	0.00000000
H	1.64194300	2.36541300	-0.88503300
H	1.64194300	2.36541300	0.88503300
H	2.50569400	1.11564300	0.00000000

Compound 24

2-Me-2AdNMe2H+

1 1

C	1.41319000	1.07368900	-1.28918200
C	2.26438300	0.83266300	-0.02794600
C	1.41580400	1.15474500	1.21657400
C	0.14876100	0.17578300	-1.26296800
C	-0.71868400	0.53161600	-0.01509300
C	0.15124600	0.25636900	1.25162700
C	2.70736800	-0.64377200	0.01949500
C	1.46069200	-1.55195000	0.05064100
C	0.62024600	-1.21984100	1.30330500
C	0.61761700	-1.30109800	-1.21937500
N	-1.96036100	-0.46346000	0.01680100
C	-2.82122700	-0.45980700	-1.21742200
C	-2.83980600	-0.35543300	1.23318500
H	1.98584200	0.82325900	-2.18945300
H	1.14471500	2.13063600	-1.38401400
H	3.14408900	1.48510000	-0.04984900
H	1.14684000	2.21553300	1.24360300
H	1.98992500	0.96292000	2.13018600

H	-0.41460100	0.51081400	2.15454600
H	3.32667100	-0.82686600	0.90569500
H	3.32438300	-0.88398100	-0.85458000
H	1.76584700	-2.60368300	0.08403000
H	1.21947200	-1.36334200	2.20912300
H	-0.21781100	-1.92717200	1.40782300
H	1.21593600	-1.50252600	-2.11471000
H	-0.22029500	-2.01378800	-1.27691300
C	-1.28810800	1.95224300	-0.05784400
H	-1.53067800	-1.39036400	0.05941200
H	-0.41846900	0.37129200	-2.17960000
H	-3.55346900	-1.26294500	-1.12297300
H	-3.33877100	0.49484700	-1.29400500
H	-2.21002900	-0.62894100	-2.10002900
H	-3.56006500	-1.17424700	1.20511500
H	-2.23977100	-0.43114800	2.13638400
H	-3.37053000	0.59482800	1.21115100
H	-1.90643900	2.12450200	-0.94304500
H	-1.87127400	2.19053700	0.83584300
H	-0.47788400	2.67770200	-0.10132500

Compound 25

spiropiperidine NH

0 1

C	0.00000000	0.00000000	0.00000000
C	1.54333596	0.00000000	0.00000000
C	2.04878570	1.45778071	0.00000000
C	-0.52555693	0.73563299	1.25452740
C	-0.04719289	2.22671325	1.24521883
C	1.51273137	2.19342782	1.25077289
C	2.06063613	-0.72280626	1.26125688
C	1.54277713	0.00699973	2.51850951
C	2.04637276	1.46625911	2.50648731
C	-0.00013411	-0.00180681	2.50862556
N	-0.47579118	2.87849593	-0.01920352
C	-0.59094353	3.04290367	2.45350035
C	-2.10277220	3.31656362	2.37352261
C	-2.47371404	3.98737992	1.04493083
C	-1.90840027	3.17680200	-0.13120345
H	-0.37587535	0.48520456	-0.90541695
H	-0.37427978	-1.03306284	0.00473540
H	1.91006386	-0.51546004	-0.89747837
H	3.14734928	1.47509702	0.01606548
H	1.72527129	1.96588141	-0.91293228
H	-1.62126859	0.69782182	1.25804545
H	1.87784401	3.23208439	1.25071601
H	3.15915307	-0.74341004	1.26217931
H	1.72003522	-1.76739952	1.26596040
H	1.90903440	-0.50121802	3.42035425
H	3.14435709	1.48175302	2.48846695
H	1.74490684	1.98297032	3.42474859
H	-0.39171165	0.44542216	3.42954063
H	-0.36489220	-1.03764221	2.49056022
H	0.05172044	3.74328973	-0.13067730
H	-0.05838174	4.00638122	2.46212355
H	-0.36126362	2.56066750	3.40731878
H	-2.40751264	3.94383714	3.22021208
H	-2.65872355	2.37438440	2.47506692
H	-2.05171160	5.00306924	1.01830905
H	-3.56240638	4.09220855	0.94783221
H	-2.06344069	3.70579890	-1.07880988
H	-2.45286014	2.22718324	-0.21667398

Compound 26

spiropiperidine NMe

0 1

C	-1.06668700	0.47732800	1.72433400
C	-2.13280100	1.08119000	0.78713500
C	-1.43173000	1.65924200	-0.45917000
C	-0.29425200	-0.63944800	0.98731200
C	0.46335100	-0.04876900	-0.25687500
C	-0.64735200	0.54111500	-1.18665800
C	-3.12805900	-0.01567700	0.35497800
C	-2.36577600	-1.13647400	-0.38140400
C	-1.65819700	-0.54890500	-1.61746800
C	-1.30416300	-1.73268700	0.56279900
N	1.37883700	1.05039100	0.19993400
C	1.30930200	-1.12628200	-0.99641700
C	2.48608900	-1.65659000	-0.15476400
C	3.35573300	-0.50972400	0.38168800
C	2.47349700	0.55968400	1.05064100
H	-0.37519100	1.25749900	2.05684000
H	-1.54734500	0.05522800	2.61774600
H	-2.67115400	1.88311500	1.30948600
H	-2.17662900	2.08156700	-1.14780900
H	-0.76509400	2.47311200	-0.15943600
H	0.42052300	-1.09305100	1.68076900
H	-0.17977800	0.94418200	-2.09274900
H	-3.89927900	0.41014200	-0.30181000
H	-3.64623000	-0.42592700	1.23277100
H	-3.06782900	-1.92105600	-0.69354600
H	-2.39699300	-0.09456600	-2.29150100
H	-1.16594900	-1.34326800	-2.19022000
H	-0.79721000	-2.57862700	0.08438600
H	-1.78738800	-2.13314500	1.46427200
H	1.70339400	-0.67489700	-1.91761200
H	0.69219100	-1.96774400	-1.32101400
H	3.08926300	-2.34473000	-0.75987600
H	2.10253700	-2.24846300	0.68746000
H	3.92077100	-0.05833800	-0.44489700
H	4.09697700	-0.88440400	1.09942800
H	3.07775200	1.42410700	1.34986600
H	2.04626200	0.15300400	1.97460300
C	1.87825100	1.94528600	-0.84523100
H	1.06306100	2.51419000	-1.29781700
H	2.55490000	2.67015300	-0.38102600
H	2.43334400	1.45344800	-1.66325600

Compound 27

2-Me-2AdNHAc

0 1

C	-0.96730000	-1.37333500	-1.21754000
C	-1.51748000	-1.65597000	0.19603000
C	-0.48190600	-1.19685200	1.24473600
C	-0.67254200	0.13917900	-1.37327300
C	0.38493100	0.61530600	-0.32836800
C	-0.20158900	0.31482200	1.09014900
C	-2.83445400	-0.87626100	0.39204400
C	-2.56496400	0.63422600	0.23113600
C	-1.53283600	1.07857500	1.28781300
C	-2.00147300	0.90572100	-1.18062000
C	0.75350300	2.10171200	-0.51438900
N	1.62047400	-0.17166600	-0.57179500
H	-1.70117300	-1.67294900	-1.97758900
H	-0.07204200	-1.98114300	-1.39710500
H	-1.70456400	-2.73205000	0.30661600
H	0.44502100	-1.77175000	1.14192300
H	-0.86265900	-1.38958900	2.25617000
H	-0.28177500	0.34096600	-2.38226900

H	0.52761800	0.63436600	1.83888700
H	-3.24834100	-1.08024500	1.38870700
H	-3.58335000	-1.20835300	-0.34009900
H	-3.49954000	1.19411700	0.36572600
H	-1.91463500	0.86358200	2.29453600
H	-1.37948500	2.16251000	1.24440000
H	-2.71816600	0.56957800	-1.94151400
H	-1.86307600	1.98069900	-1.33914700
H	1.54388800	2.37488800	0.18883000
H	1.12193000	2.26711000	-1.53345300
H	-0.09221700	2.77121000	-0.35178400
C	2.77073000	-0.12369400	0.16191400
O	2.88771700	0.51523100	1.20743600
C	3.93676000	-0.93149200	-0.39502700
H	1.66878400	-0.67134900	-1.44791200
H	4.31620200	-1.58485900	0.39490000
H	4.74189400	-0.24103500	-0.66454900
H	3.68234300	-1.53751900	-1.26982700

Compound 28

2-Me-2AdNHCOtBu

0 1

C	1.51635700	-1.46797100	1.10407700
C	2.09235900	-1.71926200	-0.30518300
C	1.18169100	-1.04579900	-1.35410700
C	1.42045600	0.05531900	1.36773400
C	0.49001400	0.74793000	0.32243400
C	1.10075700	0.47473400	-1.09097300
C	3.51097900	-1.11899600	-0.38663200
C	3.44034400	0.39852400	-0.11732600
C	2.53163600	1.05742500	-1.17579300
C	2.84867700	0.64194500	1.28800700
N	-0.85200300	0.12256500	0.45647000
H	2.16534400	-1.92123900	1.86522900
H	0.54044100	-1.95906100	1.20038500
H	2.13713100	-2.79998500	-0.49317600
H	0.18193400	-1.49351500	-1.33362500
H	1.58257200	-1.21520200	-2.36202900
H	1.01071400	0.23537700	2.37315700
H	0.45937500	0.94646500	-1.83949600
H	3.94311700	-1.30536500	-1.37895800
H	4.16967900	-1.60455800	0.34655000
H	4.44737700	0.83235300	-0.16977900
H	2.93023800	0.86477200	-2.18050300
H	2.52506000	2.14607800	-1.05302200
H	3.47466000	0.15598300	2.04796100
H	2.84811400	1.71149500	1.52381500
C	-1.94476800	0.38468400	-0.31331500
O	-1.90509700	1.12270900	-1.30057800
C	-3.28356700	-0.29695500	0.08362900
H	-0.99707200	-0.44232600	1.27886800
C	-3.74027400	-1.13623800	-1.13023900
H	-4.72872300	-1.56880400	-0.93807600
H	-3.79660700	-0.51329700	-2.02590700
H	-3.04368200	-1.95902000	-1.32861100
C	-3.20170600	-1.20358600	1.32678400
H	-2.50446400	-2.03825800	1.18681900
H	-2.91529900	-0.64844200	2.22846300
H	-4.18606400	-1.64119300	1.52492900
C	-4.30422000	0.83383000	0.34213400
H	-4.37525300	1.49022100	-0.52832900
H	-5.29349100	0.40807500	0.54520300
H	-4.01424200	1.44248700	1.20664200
C	0.31755000	2.25314300	0.61273900
H	-0.39394200	2.68423800	-0.09533600
H	-0.07313500	2.39209100	1.62749800

H	1.25330700	2.80865000	0.53683200

Compound 29

2-Me-2AdN$_3$

0 1

C	-0.75438800	0.57348000	0.20361700
C	0.37740300	0.56552800	1.26686200
H	-0.00648900	1.03222000	2.18288400
C	-0.20636700	-0.10230600	-1.08859300
H	-0.99650900	-0.10275500	-1.85200000
C	1.01730900	0.68535500	-1.61686700
H	0.73999300	1.70859500	-1.89446400
H	1.37975400	0.20286100	-2.53391500
C	1.60164200	1.35266800	0.74219500
H	2.38264900	1.34584100	1.51329400
H	1.35174400	2.40505000	0.56482800
C	2.13316000	0.69718800	-0.55040400
H	2.99166000	1.26911600	-0.92529300
C	2.56399400	-0.75304100	-0.24702100
H	2.96387900	-1.22508900	-1.15473800
H	3.37068000	-0.75769100	0.49841100
C	0.81701800	-0.88593500	1.56572500
H	-0.02409800	-1.45845500	1.96940700
H	1.60013500	-0.87248500	2.33518600
C	0.23738300	-1.55327000	-0.79067200
H	-0.61110100	-2.15585300	-0.44942800
H	0.60413000	-2.01313100	-1.71761700
C	1.35065000	-1.54914900	0.27856200
H	1.65156900	-2.58193500	0.49602600
N	-1.87039100	-0.25322200	0.80365000
N	-3.82058600	-0.70308700	-0.47060000
C	-1.32594500	1.97886800	-0.04659900
H	-2.14488800	1.93943700	-0.77389200
H	-1.71814100	2.39271100	0.88779000
H	-0.57660700	2.66979700	-0.43612400
N	-2.85609800	-0.45148400	0.09392400

Compound 30

2-Me-2AdF

0 1

C	1.30670800	-0.03270200	0.00007300
C	0.41353000	-0.00559700	1.25847000
H	1.06037100	-0.02747600	2.14481400
C	0.41342100	-0.00565800	-1.25843400
H	1.06043000	-0.02784600	-2.14465300
C	-0.52345800	-1.23552700	-1.25815700
H	0.06600000	-2.15730000	-1.28808200
H	-1.14388000	-1.21592200	-2.16393800
C	-0.52332900	-1.23543200	1.25830400
H	-1.14368100	-1.21580400	2.16410000
H	0.06606000	-2.15727200	1.28817300
C	-1.41722500	-1.20920600	0.00008500
H	-2.07549600	-2.08753700	0.00015200
C	-2.26809300	0.07811600	0.00006500
H	-2.92223200	0.09941200	-0.88231000
H	-2.92208800	0.09963100	0.88253200
C	-0.44701000	1.28097800	1.25893300
H	0.18298700	2.17763300	1.30202000
H	-1.06927500	1.29343000	2.16311800
C	-0.44706300	1.28077700	-1.25913300
H	0.18285900	2.17747600	-1.30239900
H	-1.06935100	1.29302400	-2.16328800
C	-1.34022300	1.31169800	-0.00007100
H	-1.94255200	2.22934700	-0.00008500

C	2.42523100	1.00384800	-0.00003300
H	3.05178100	0.87143500	0.88750900
H	3.05208300	0.87075400	-0.88722100
H	2.04415000	2.02735100	-0.00041100
F	1.99632200	-1.29312300	-0.00007400

Compound 31

2-Me-2AdCl

0 1

C	-1.02289400	0.44416000	0.00005100
C	-0.15935500	0.17742700	-1.25827900
H	-0.77591600	0.34002300	-2.15046100
C	-0.15917800	0.17689300	1.25845800
H	-0.77579300	0.33900500	2.15066700
C	0.40354600	-1.26270000	1.25868900
H	-0.41222800	-1.99042000	1.30116600
H	1.01060100	-1.40600400	2.16229400
C	0.40284300	-1.26233000	-1.25889000
H	1.00931200	-1.40576400	-2.16281800
H	-0.41314100	-1.98986700	-1.30093600
C	1.26710100	-1.49028800	-0.00032400
H	1.64789300	-2.51958200	-0.00056400
C	2.44776700	-0.49768700	-0.00045900
H	3.08045300	-0.66204000	0.88217800
H	3.07991500	-0.66151900	-0.88357800
C	1.03906600	1.16364500	-1.26074100
H	0.69934800	2.20342200	-1.32169700
H	1.63840300	0.98068400	-2.16197600
C	1.03905400	1.16311900	1.26126000
H	0.69899300	2.20277500	1.32268500
H	1.63838600	0.97984500	2.16240700
C	1.90324500	0.94594900	0.00015700
H	2.73821500	1.65840000	0.00025100
C	-1.69851900	1.81857600	0.00009500
H	-2.32896600	1.93319600	-0.88610000
H	-2.32918800	1.93312300	0.88605500
H	-0.96403400	2.62715100	0.00012100
Cl	-2.47166500	-0.75429500	0.00001200

Compound 32

2-CMe2OH-Ad

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.57826659
H	1.03508769	0.00000000	1.94230267
C	-1.51985807	-0.01997037	-0.41013306
H	-1.59916957	-0.03424047	-1.50365146
C	-2.28852822	-1.23097536	0.18024590
H	-1.88534983	-2.17748044	-0.18149843
H	-3.33482099	-1.16773647	-0.15027766
C	-0.76003226	-1.20612424	2.18821290
H	-0.71777697	-1.12461580	3.28420948
H	-0.29731501	-2.15028991	1.90837771
C	-2.23183759	-1.19207081	1.72420156
H	-2.74901055	-2.07154579	2.13020501
C	-2.91681591	0.09276532	2.22984504
H	-3.97198099	0.10853467	1.92302237
H	-2.89966576	0.12469818	3.32792779
C	-0.70350938	1.27306215	2.12332230
H	-0.17630253	2.18845351	1.83696193
H	-0.67687150	1.24162986	3.22130702
C	-2.24203801	1.25299609	0.10934153
H	-1.83384930	2.16635446	-0.33463374

H	-3.29415684	1.20937282	-0.20470223
C	-2.17487050	1.31372504	1.65137601
H	-2.64836284	2.24065122	2.00238822
C	0.86765963	-1.19137502	-0.66842736
C	2.34880947	-1.13007264	-0.21329869
H	2.90559537	-1.93240609	-0.70976076
H	2.84150587	-0.18964967	-0.46647969
H	2.44337627	-1.27801493	0.86864825
C	0.84806743	-1.07429796	-2.21400903
H	1.26325209	-0.13069906	-2.57685958
H	1.45188438	-1.88273535	-2.64081233
H	-0.16793395	-1.16973041	-2.61275004
H	0.43641180	0.91217611	-0.34982779
O	0.37810713	-2.49168120	-0.33013431
H	0.92065541	-3.15923442	-0.75629634

Compound 33

2-CMe2F-Ad

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.57826659
H	1.03508769	0.00000000	1.94230267
C	-1.51985807	-0.01997037	-0.41013306
H	-1.59916957	-0.03424047	-1.50365146
C	-2.28852822	-1.23097536	0.18024590
H	-1.88534983	-2.17748044	-0.18149843
H	-3.33482099	-1.16773647	-0.15027766
C	-0.76003226	-1.20612424	2.18821290
H	-0.71777697	-1.12461580	3.28420948
H	-0.29731501	-2.15028991	1.90837771
C	-2.23183759	-1.19207081	1.72420156
H	-2.74901055	-2.07154579	2.13020501
C	-2.91681591	0.09276532	2.22984504
H	-3.97198099	0.10853467	1.92302237
H	-2.89966576	0.12469818	3.32792779
C	-0.70350938	1.27306215	2.12332230
H	-0.17630253	2.18845351	1.83696193
H	-0.67687150	1.24162986	3.22130702
C	-2.24203801	1.25299609	0.10934153
H	-1.83384930	2.16635446	-0.33463374
H	-3.29415684	1.20937282	-0.20470223
C	-2.17487050	1.31372504	1.65137601
H	-2.64836284	2.24065122	2.00238822
C	0.86765963	-1.19137502	-0.66842736
C	2.34880947	-1.13007264	-0.21329869
H	2.90559537	-1.93240609	-0.70976076
H	2.84150587	-0.18964967	-0.46647969
H	2.44337627	-1.27801493	0.86864825
C	0.84806743	-1.07429796	-2.21400903
H	1.26325209	-0.13069906	-2.57685958
H	1.45188438	-1.88273535	-2.64081233
H	-0.16793395	-1.16973041	-2.61275004
H	0.43641180	0.91217611	-0.34982779
F	0.40549468	-2.41893680	-0.34905980

Compound 34

2-Ad-COMe

0 1

C	0.00000000	0.00000000	0.00000000
C	0.00000000	0.00000000	1.54394522
C	1.45163313	0.00000000	-0.52647608
C	2.22033431	-1.26810817	-0.02702930
C	2.16283153	-1.30227574	1.52375825

C	0.70941514	-1.27339643	2.04816982
C	0.74575836	1.24734313	2.06319737
C	2.20192938	1.22884812	1.54980254
C	2.90760163	-0.05266912	2.04805531
C	2.19258320	1.24610257	0.00652931
C	1.74196301	-2.53084104	-0.73925464
O	0.86474317	-3.25916960	-0.30133579
H	-0.51903690	0.89066333	-0.37936689
H	-0.54704216	-0.87304124	-0.37469222
H	-1.03565822	0.01173858	1.90710839
H	1.44811748	0.02074307	-1.62433421
H	2.66306334	-2.21089316	1.88197163
H	0.17327239	-2.16666635	1.71966767
H	0.72668478	-1.28138459	3.14676024
H	0.73303080	1.26292445	3.16129186
H	0.24045019	2.16220505	1.72414299
H	2.73861373	2.11109147	1.92239554
H	2.92419948	-0.06782943	3.14586685
H	3.95423670	-0.06249866	1.71324929
H	1.69304139	2.15451771	-0.35615234
H	3.21986023	1.26942280	-0.38150051
H	3.27083573	-1.13505469	-0.32563049
C	2.42496951	-2.85079866	-2.05991983
H	3.46725600	-3.13720440	-1.87082639
H	1.90979902	-3.67431940	-2.55705648
H	2.45138730	-1.97363430	-2.71655908

Compound 35

2-Ad-CO$_2$H

0 1

C	-1.23906100	1.49482100	-0.86933400
C	-2.11121100	0.22436000	-0.79019700
C	-1.33139800	-0.96706000	-1.38769500
C	0.07108500	1.28804100	-0.07791300
C	0.83762000	0.09113400	-0.70593000
C	-0.02399600	-1.19073500	-0.59714800
C	-2.44644100	-0.07081700	0.68806500
C	-1.14115300	-0.28933800	1.48305000
C	-0.36596900	-1.48062500	0.88116800
C	-0.26640300	0.98007600	1.39744400
C	2.24495000	-0.10833700	-0.16856400
O	2.90776000	1.06671200	0.00996600
H	3.80616100	0.83725600	0.30279800
H	-1.78414800	2.35341900	-0.45534400
H	-1.01288300	1.73637400	-1.91687800
H	-3.03854400	0.37948400	-1.35662100
H	-1.10760400	-0.77942900	-2.44695200
H	-1.94452700	-1.87688300	-1.34879900
H	0.68805600	2.18973800	-0.14002900
H	0.99561100	0.31764100	-1.77305600
H	0.53247800	-2.03427400	-1.01828600
H	-3.08395300	-0.96235100	0.75907400
H	-3.01614000	0.76415100	1.11833900
H	-1.38001400	-0.49919800	2.53363700
H	0.54991600	-1.67269900	1.45125900
H	-0.97279700	-2.39392600	0.94080400
H	-0.79553600	1.83615500	1.83655500
H	0.65419000	0.84639600	1.98094400
O	2.78494000	-1.17558400	0.04189400

Compound 36

adamantane-spirocyclobutanone

0 1

C	0.00000000	0.00000000	0.00000000
C	1.54306034	0.00000000	0.00000000

C	-0.52166029	1.45362845	0.00000000
C	-0.02249124	2.19858774	-1.27042858
C	1.53235338	2.18143433	-1.27170462
C	2.04535251	0.72473301	-1.26628110
C	2.06100640	0.73282839	1.25599942
C	1.54484664	2.18761426	1.25492657
C	2.04763570	2.91187180	-0.01162657
C	0.00164314	2.18681119	1.25517308
C	-0.68582166	3.59786502	-1.54026164
C	-0.67031691	1.72168991	-2.58851018
C	-1.32346194	3.07731648	-2.86227418
O	-0.66972304	0.67213925	-3.19149538
H	-0.37868957	-0.52003634	0.89042829
H	-0.37636800	-0.53791334	-0.87658830
H	1.90840783	-1.03482683	-0.00211218
H	-1.62045234	1.45165331	0.00659394
H	1.89629571	2.69775733	-2.17077895
H	1.70116701	0.19824278	-2.16279559
H	3.14359010	0.72805744	-1.29017807
H	3.15933276	0.72372276	1.27346121
H	1.72211283	0.21447740	2.16329005
H	1.91106421	2.71240571	2.14679034
H	3.14559663	2.93109234	-0.02660343
H	1.71289816	3.95735794	-0.00743875
H	-0.37698967	1.68267558	2.15439391
H	-0.37705090	3.21670721	1.28669913
H	0.03048956	4.41163757	-1.68103920
H	-1.41346333	3.90113498	-0.78285376
H	-2.41791536	3.03752062	-2.88901154
H	-0.97689222	3.55120189	-3.78715351

Compound 37

adamantane-spirocyclopentanone

0 1

C	0.00000000	0.00000000	0.00000000
C	1.54391490	0.00000000	0.00000000
C	-0.53165698	1.45296491	0.00000000
C	-0.04454223	2.22374501	-1.28672646
C	1.51508624	2.17644776	-1.28257809
C	2.05146040	0.72673431	-1.26235153
C	2.06587654	0.73035912	1.25431637
C	1.54488308	2.18254276	1.25034589
C	2.03993527	2.90599781	-0.02211275
C	0.00212328	2.16089582	1.26871466
C	-0.60716483	3.67282848	-1.36035752
C	-0.69061891	1.58799983	-2.54470086
C	-1.82126919	2.47766429	-3.06530398
C	-2.00678182	3.55766495	-1.99469847
O	-0.37183529	0.53925463	-3.07499689
H	-0.37614741	-0.51218262	0.89599853
H	-0.37263776	-0.55139574	-0.86813561
H	1.90608675	-1.03613350	-0.00329819
H	-1.62956235	1.43982384	0.02647552
H	1.88239369	2.68999335	-2.18172793
H	1.73829635	0.19063621	-2.16044396
H	3.14984619	0.75692614	-1.25897577
H	3.16431045	0.72163679	1.26724092
H	1.73079668	0.21439711	2.16476064
H	1.91286337	2.71188542	2.13910077
H	3.13783701	2.91177801	-0.04265329
H	1.72185456	3.95556675	-0.01250782
H	-0.35260829	1.61376503	2.15250878
H	-0.39494874	3.17805020	1.35838333
H	0.04197862	4.26734287	-2.01905828
H	-0.63179981	4.18635095	-0.39822286
H	-2.70577101	1.87604604	-3.29477919

```
 H                 -1.47616848    2.91009862   -4.01498168
 H                 -2.36079902    4.51069309   -2.39889401
 H                 -2.73874614    3.23214109   -1.24617095
```

Compound 38

```
adamantane-spirocyclohexanone

0 1
 C                  0.00000000    0.00000000    0.00000000
 C                  1.54168845    0.00000000    0.00000000
 C                 -0.52876232    1.45584710    0.00000000
 C                 -0.03670781    2.23246422   -1.26136512
 C                  1.53152807    2.21777047   -1.22343680
 C                  2.04473322    0.75818419   -1.24647894
 C                  2.05639474    0.70208686    1.27352464
 C                  1.52801020    2.15146223    1.30702809
 C                  2.04856145    2.90097695    0.06346554
 C                 -0.01669533    2.13840056    1.29155493
 C                 -0.62031086    3.68816083   -1.30164018
 C                 -0.58221424    1.61216966   -2.56687985
 C                 -0.17733793    2.30343617   -3.86253593
 C                 -0.69162110    3.76136298   -3.84297519
 O                 -1.40000856    0.70515763   -2.58060630
 H                 -0.37225528   -0.51201151    0.89776771
 H                 -0.38724372   -0.54634318   -0.86249643
 H                  1.91071564   -1.03346363   -0.02830057
 H                 -1.62493535    1.43891737   -0.00497671
 H                  1.93624814    2.75201665   -2.08947583
 H                  1.71161747    0.24416751   -2.15812966
 H                  3.14278265    0.76164932   -1.27061002
 H                  3.15502880    0.70150106    1.29326677
 H                  1.71956877    0.15590181    2.16480376
 H                  1.88372702    2.65515874    2.21532596
 H                  1.75304486    3.95623338    0.09707205
 H                  3.14691114    2.88946906    0.05345609
 H                 -0.39181788    1.57960476    2.15913174
 H                 -0.40747965    3.15725495    1.39240442
 H                 -1.71498680    3.60792366   -1.23566476
 H                 -0.30475127    4.24568984   -0.41702114
 H                 -0.60484980    1.73930488   -4.69545892
 H                 -0.34156986    4.29308175   -4.73537254
 H                 -1.78849529    3.74540240   -3.89354822
 C                 -0.25100355    4.48429791   -2.56392347
 H                  0.91428357    2.30204683   -3.96927109
 H                  0.83182239    4.66193835   -2.59239364
 H                 -0.72097419    5.47420001   -2.51454120
```

rb3lyp/6-31+g(d,p) pop=(savenbo,nboread) scf=tight

pentacyclo[6.2.1.1^{3,6}.0^{2,7}.0^{4,10}]dodecanol

```
0 1
 C
 C        1   1.57013005
 C        2   2.25569152   1   74.02847020
 C        3   1.53184933   2   76.22637866   1  -19.71654077   0
 H        1   1.08302395   4  111.83482113   3 -149.14896843   0
 H        4   1.08685886   3  108.60650910   2  -95.32534651   0
 H        4   1.06964425   3  115.63155511   2  143.75943906   0
 C        2   1.53758438   1  106.50605714   4   -9.17665407   0
 H        8   1.08669473   2  111.47623353   1  160.67218630   0
 H        8   1.08469634   2  115.43990068   1  -75.27060816   0
 H        3   1.08398553   2  158.91296359   1 -143.58122190   0
 H        2   1.08385758   1  115.40119694   4 -140.96038310   0
 C        3   1.56527693   2   75.59107809   1   97.34985596   0
```

H	13	1.08505043	3	108.46241399	2	123.20455793	0
C	2	1.51419754	1	99.70876007	4	94.70963407	0
H	15	1.08512268	2	114.59074673	1	172.11042066	0
C	15	1.51463292	2	109.76120859	1	41.93415830	0
H	17	1.08327912	15	115.65024788	2	83.11461150	0
C	13	1.57180000	3	124.03850223	2	-109.56073824	0
H	19	1.08513790	13	113.88156914	3	-89.01038890	0
C	19	1.54582622	13	114.80095701	3	45.15929743	0
H	21	1.08622924	19	105.99559528	13	152.96994597	0
C	21	1.54110881	19	100.47422567	13	42.50892746	0
H	23	1.08331824	21	110.91419972	19	152.84574641	0
O	21	1.40222734	19	120.14588741	13	-87.19421732	0
H	25	0.94668002	21	108.37069151	19	-71.76757765	0
C	19	1.54264324	13	99.99148623	3	146.13771487	0
H	27	1.08427222	19	113.69880797	13	-176.78669913	0
H	27	1.08520604	19	113.86405521	13	59.03895539	0

D. Chemistry

D.1 Synthesis of monosubstituted derivatives

Compounds **2-12** can be synthesized according to conventional methods described several times in the literature (see for example ref. 46 in the draft). Thus, compound **5** can be prepared through the $NaBH_4$ reduction of 2-adamantanone in ethanol; methylation of 2-adamantanol **6** with CH_3I/NaH in DMF afforded the methyl ether **6**; compound **7** was prepared through the Raney-Ni catalytic hydrogenation of 2-adamantanone oxime in ethanol; Borch-Hassid reductive methylation ($NaCNBH_3$/CH_2=O) of 2-adamantanamine **7** afforded the N,N-dimethyl derivative **8**; the treatment of 2-adamantanamine **7** with CH_3COCl/Et_3N in ether afforded the acetylated derivatives **9**; the treatment of 2-adamantanol with $SOCl_2$ afforded the 2-chloroadamantane **12**; 2-Nitroadamantane **10** was prepared from 2-adamantanone oxime; 2-Floroadamantane can be prepared from 2-adamantanol and DAST (see experimental part for compound **30**); for the preparation of 2-cyanoadanantane **4** see preparation of compound **32**. Hydrocarbons **2** and **3** were prepared from the corresponding alcohols **14** and **15** through TFA/ Et_3SiH treatment (see reference 47a of the draft). Compound **13** was prepared from 2-adamantanone (Greidanus, J. W. *Can. J. Chem.* **1970**, *48*, 3593).

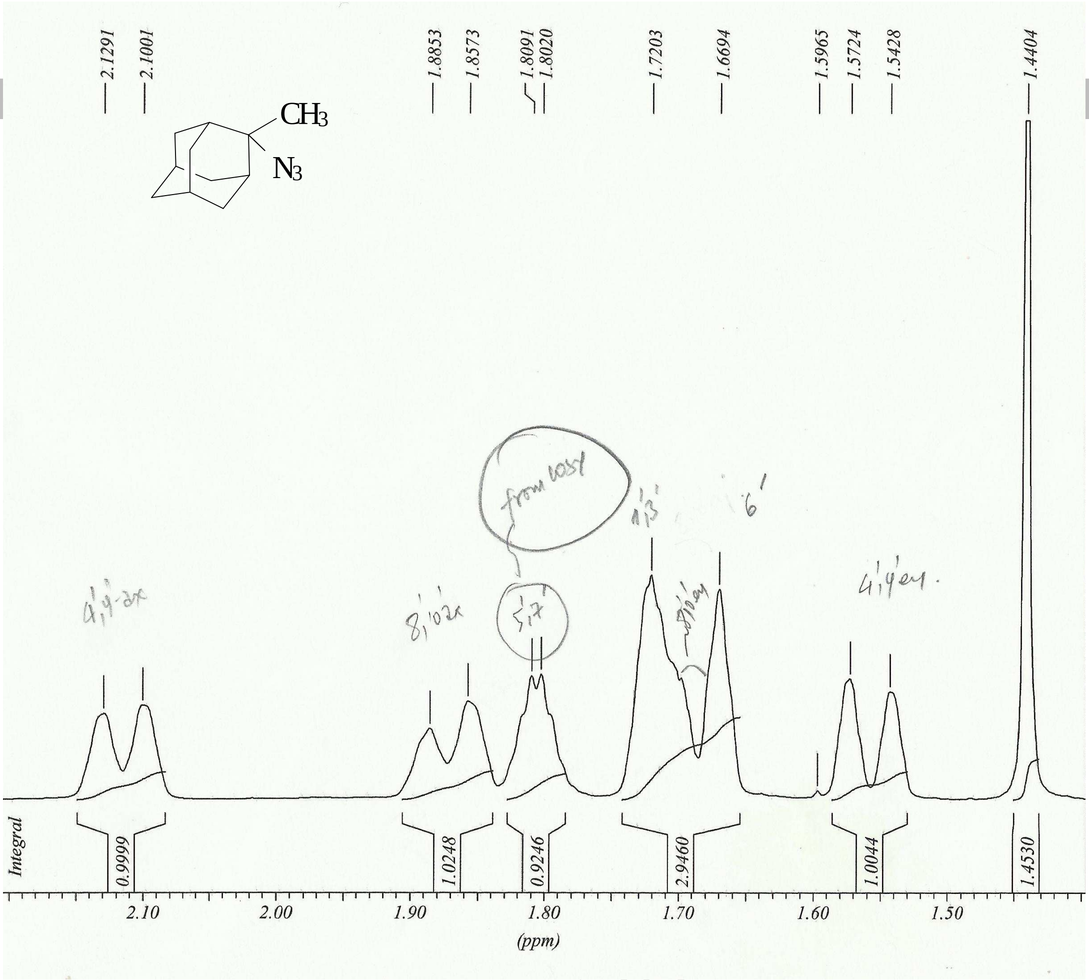
D.2 Synthesis of known disubstituted derivatives

Compounds **14-17** were prepared from 2-adamantanone and the suitable organometallic reagent; compound **14** was prepared from 2-adamantanone/MeMgI according to the procedure described below for compound **29**; a similar procedure afforded *tert*-alcohol **16** (2-adamantanone/PhMgBr)**;** *tert*-alcohol **17** was prepared using 2-adamantanone/HC≡CNa; for the preparation of compound **15** see reference 47a in the draft (2-adamantanone/*tert*-BuLi). Details for the synthesis of compounds **23-26** and **36-38** can be found in ref. 46 of the draft. The preparation of compounds **25** and **26** has been reported.[46b] Compounds **34–35** were synthesized according to known procedures.[10c]

D.3 Experimental details for the synthesis of 2,2-disubstitued derivatives (including raw spectra for compounds **18, 19, 20, 21, 22, 27, 28, 29, 30, 31, 32, 33**).

2-azido-2-methyladamantane, 29. The dropwise addition of a solution of 2-adamantanone (1.50 g, 10.0 mmol) in dry THF to a mixture of methylmagnesium iodide in dry ether [obtained from addition of a solution of CH_3I (2.84 g, 20.0 mmol) in dry ether (20 mL) in magnesium turnings (530 mg, 22.0 gr-at)] afforded quantitatively, after saturated NH_4Cl treatment of the reaction mixture, extraction with ether and standard work-up, 2-methyl-2-adamantanol **14**.

The solid alcohol **14** (700 mg, 4.22 mmol) was added to a vigorously stirred mixture of H_2SO_4 70% (10 mL) and chloroform (25 mL) at 0 ºC. Then, sodium azide (1.65 g, 25.4 mmol) was added portionwise and stirring was maintained for 48 h at room temperature (TLC monitoring). A mixture of ice-water was added and the mixture was extracted with dichloromethane. The combined organic phase was washed with water, saturated $NaHCO_3$, water, brine and dried (Na_2SO_4). After solvent evaporation the solid mixture was chromatographed on silica gel column using hexane:AcOEt as an eluent to afford pure azide **29**. Yield: 530 mg, 66 %.


2.1291
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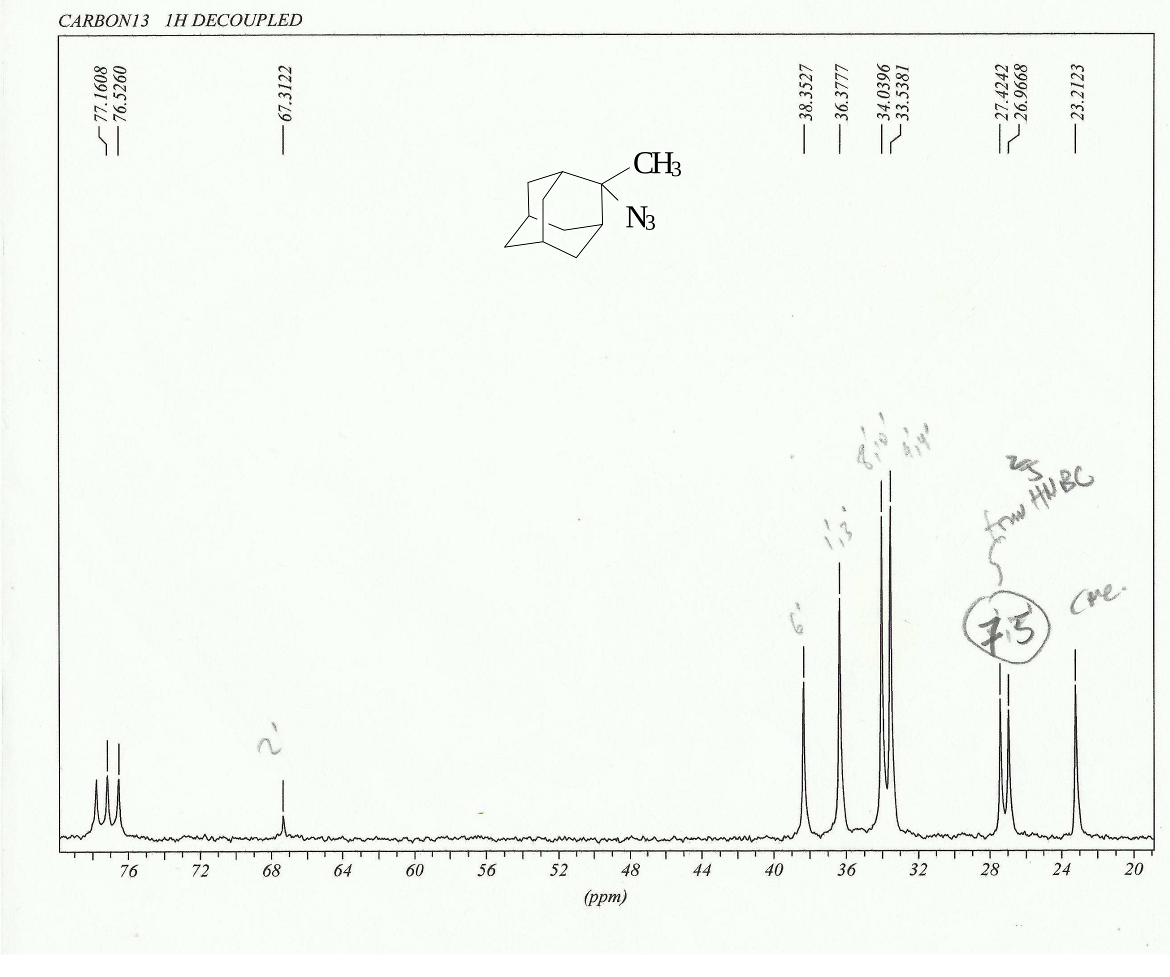
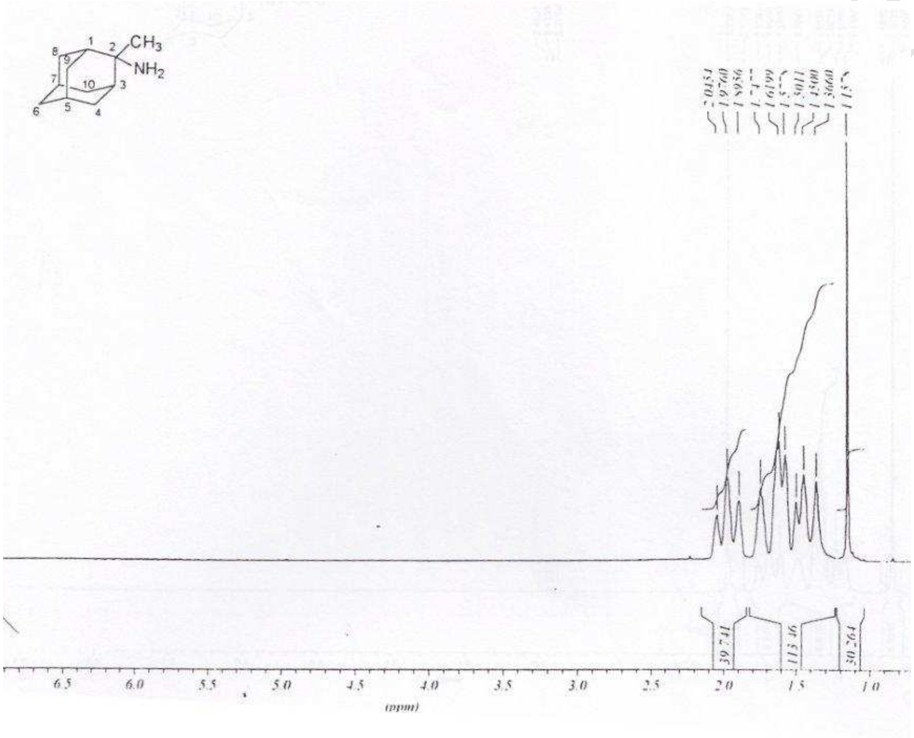
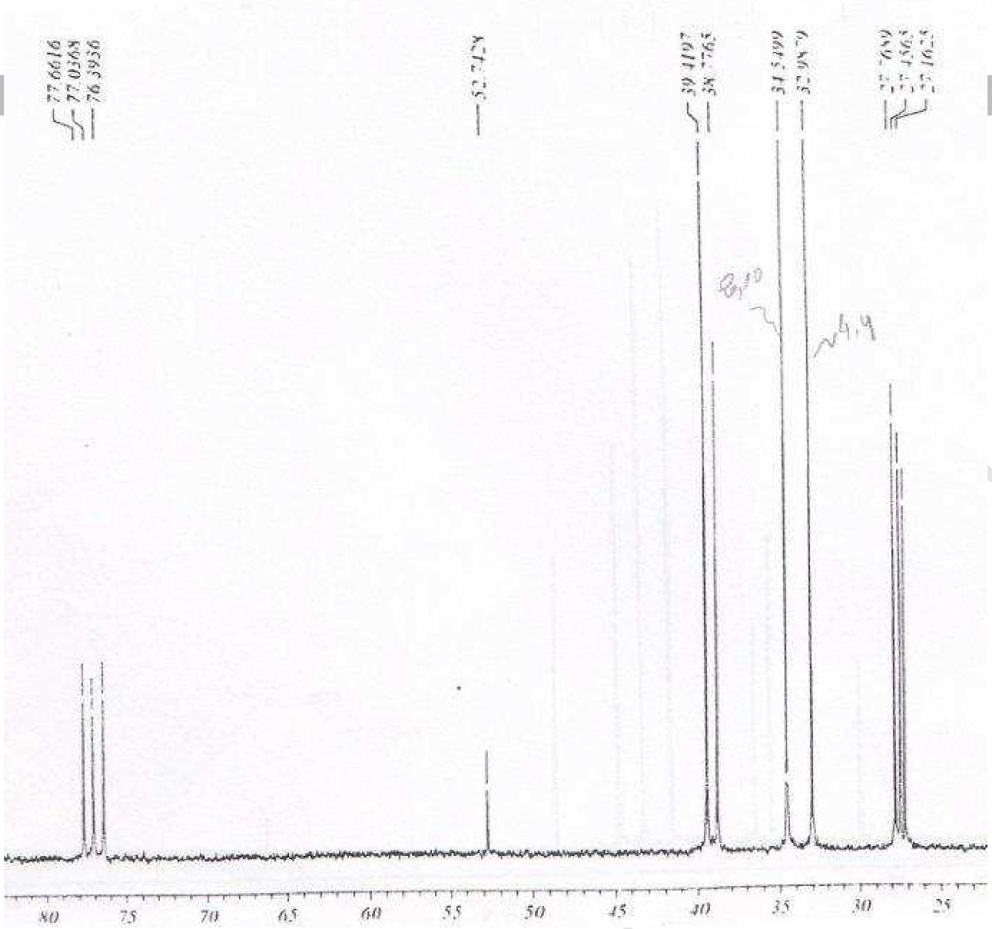
1.8853
1.8573
1.8091
1.8020
1.7203
1.6694
1.5965
1.5724
1.5428
1.4404
CH3
N3
4',9'-ax
8',10'ax
from COSY
5',7'
1',3'
8',10'eq
6'
4',9'eq.
Integral
0.9999
1.0248
0.9246
2.9460
1.0044
1.4530
2.10
2.00
1.90
1.80
1.70
1.60
1.50
(ppm)

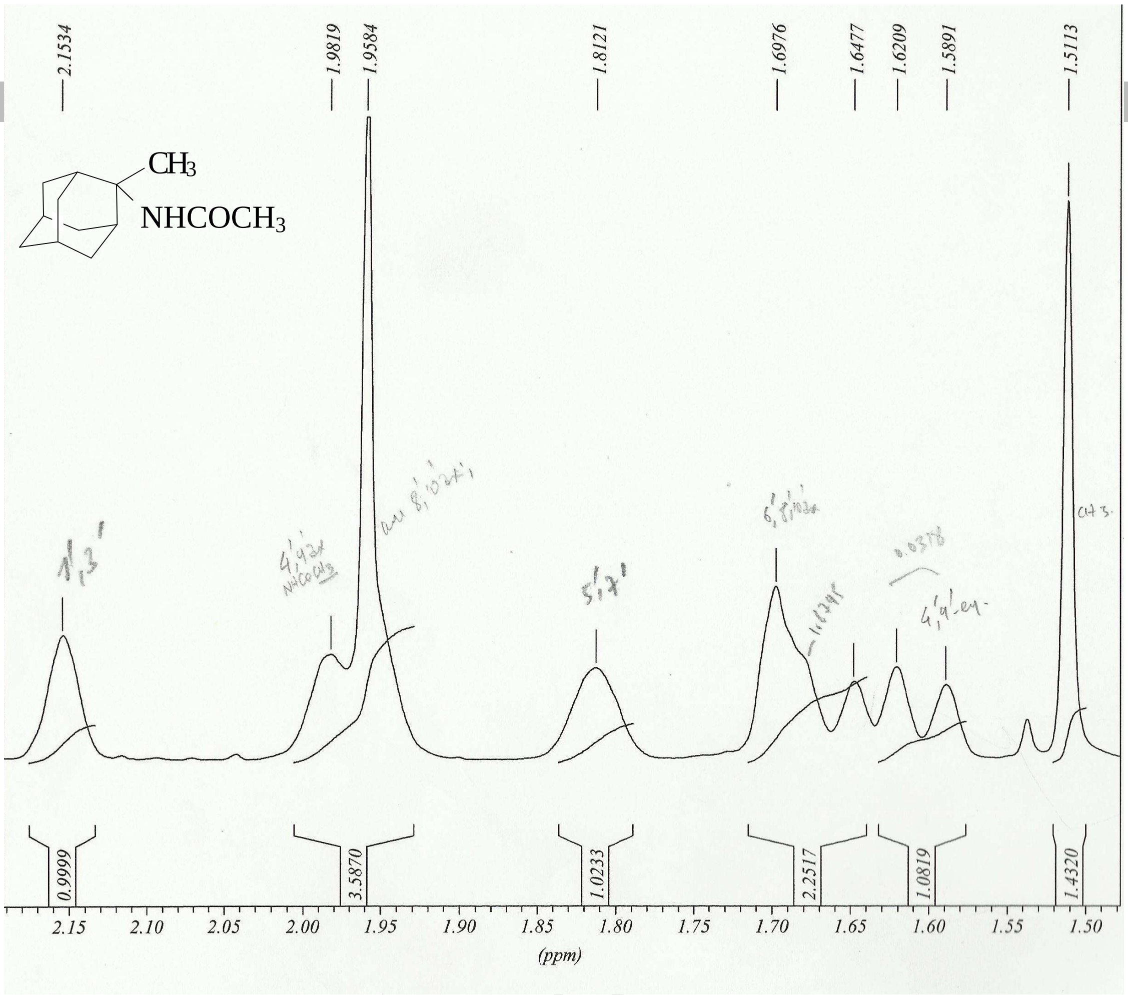

CARBON13 1H DECOUPLED
77.1608
76.5260
67.3122
38.3527
36.3777
34.0396
33.5381
27.4242
26.9668
23.2123
CH3
N3
2'
6'
1',3'
8',10'
4',9'
7',5'
from HMBC
25
Cme.
76
72
68
64
60
56
52
48
44
40
36
32
28
24
20
(ppm)

2-Methyl-2-adamantanamine, 22. To a stirring suspension of $LiAlH_4$ (390 mg, 10.3 mmol) in dry ether (20 mL), a solution of azide **29** (490 mg, 2.57 mmol) in dry ether (10 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 24 h (TLC monitoring, ether) and then water, NaOH 15 % w/v and water was added under ice cooling. The inorganic precipitate was filtered off, washed with ether and the organic solution was extracted with HCl 6%. The aqueous solution was made alkaline with solid Na_2CO_3 and the mixture was extracted with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and evaporated to afford the pure oily amine **22**. Yield: 350 mg, 83%.





N-Acetyl 2-methyl-2-adamantanamine, 27. To a stirred solution of amine **22** (70.0 mg, 0.42 mmol) and triethylamine (150 mg, 1.48 mmol) in dry ether (5 mL) was added dropwise at 0 ºC a solution of acetyl chloride (67 mg, 0.84 mmol) in dry ether (5 mL) and the mixture was then stirred at ambient temperature overnight. The precipitated thiethylamine hydrochloride was filtered off and washed with ether. The filtrate was washed with cold water, HCl 3%, brine, dried (Na_2SO_4) and evaporated. The residue was filtrated over alkaline aluminium oxide column using hexane and then AcOEt as eluent to afford pure actamide **27**. Yield: 80 mg, 91 %;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1.8121
1.6976
1.6477
1.6209
1.5891
1.5113
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NHCOCH3
1',3'
4',9'ax
NHCOCH3
ax 8',10'ax'
5',7'
6',8',10'ax
1.6295
0.0378
4',9'-eq.
CH3.
0.9999
3.5870
1.0233
2.2517
1.0819
1.4320
2.15
2.10
2.05
2.00
1.95
1.90
1.85
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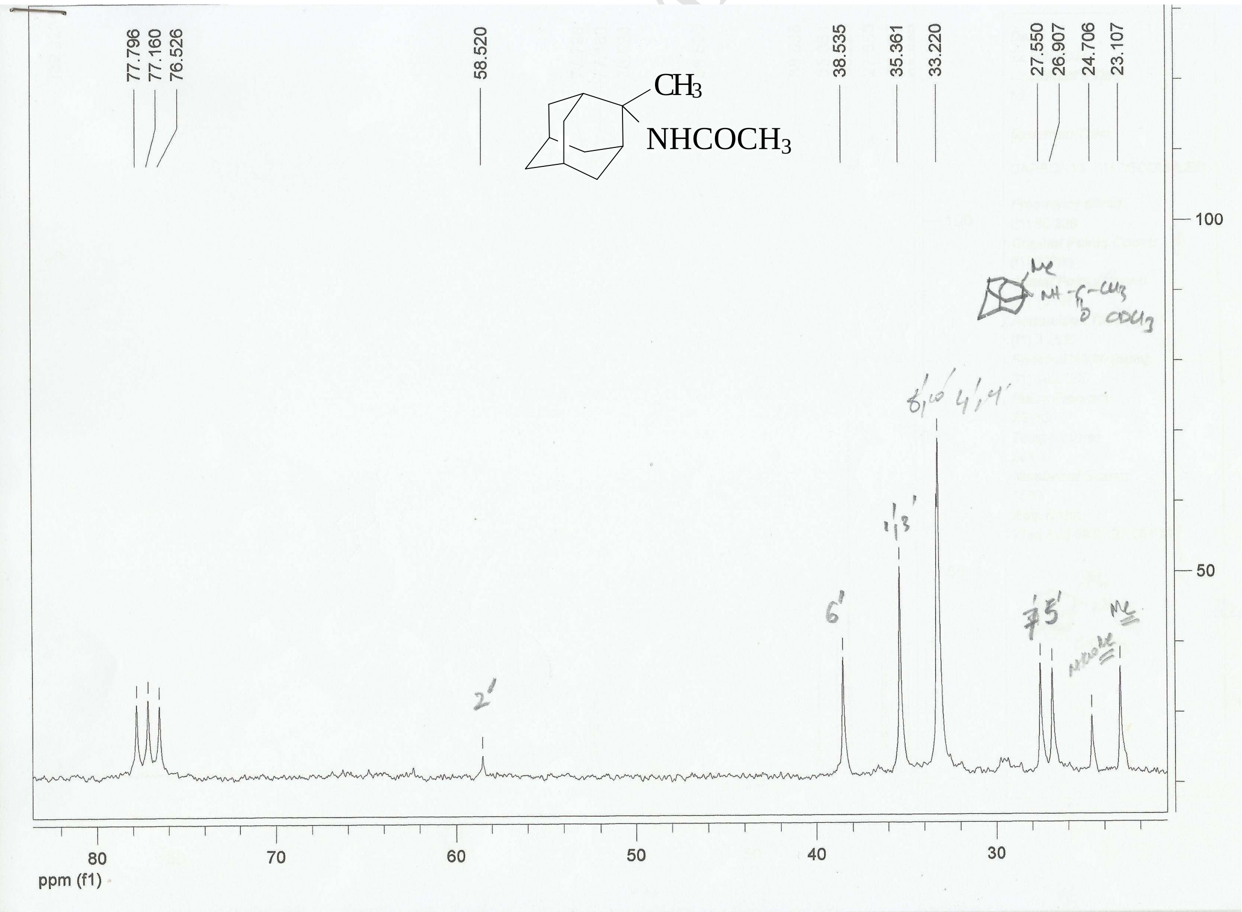
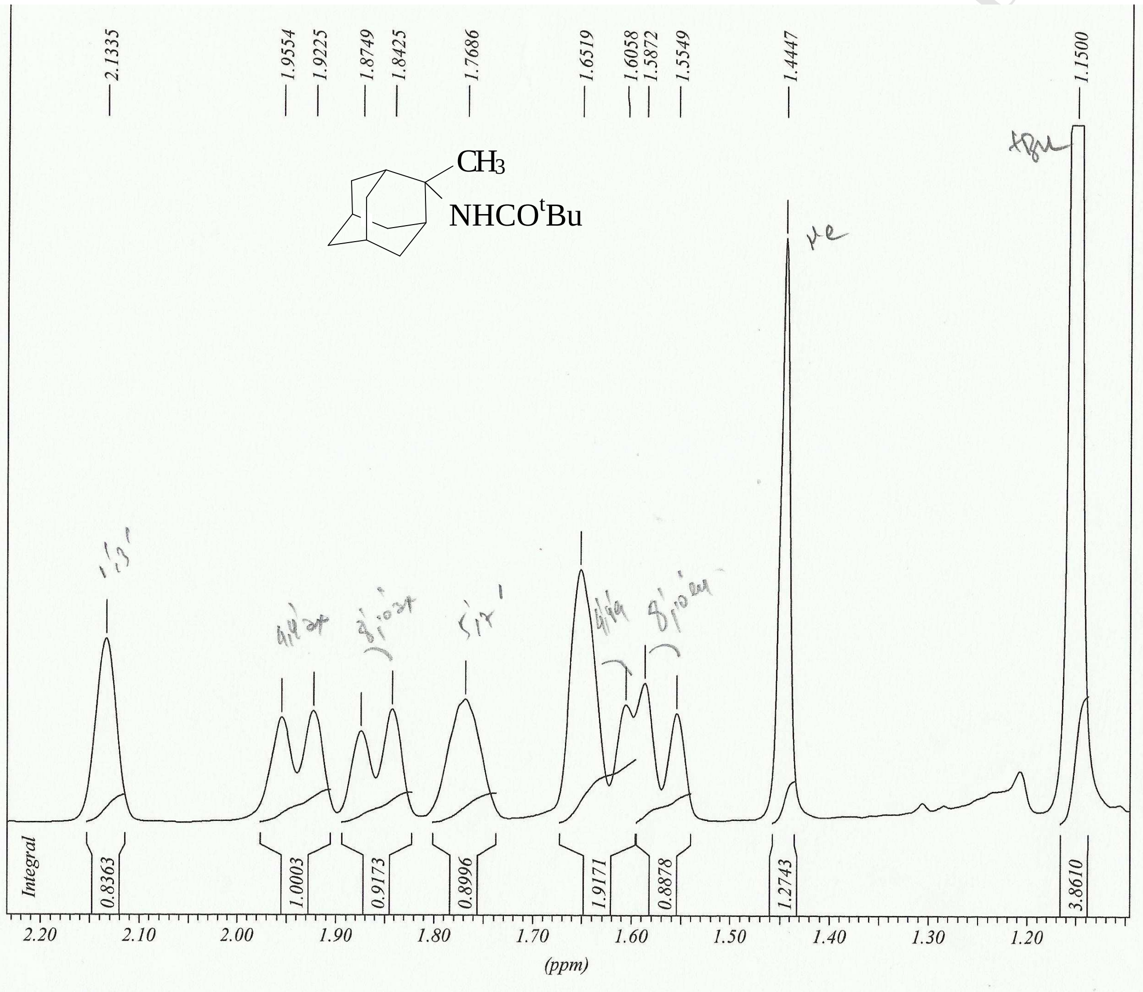
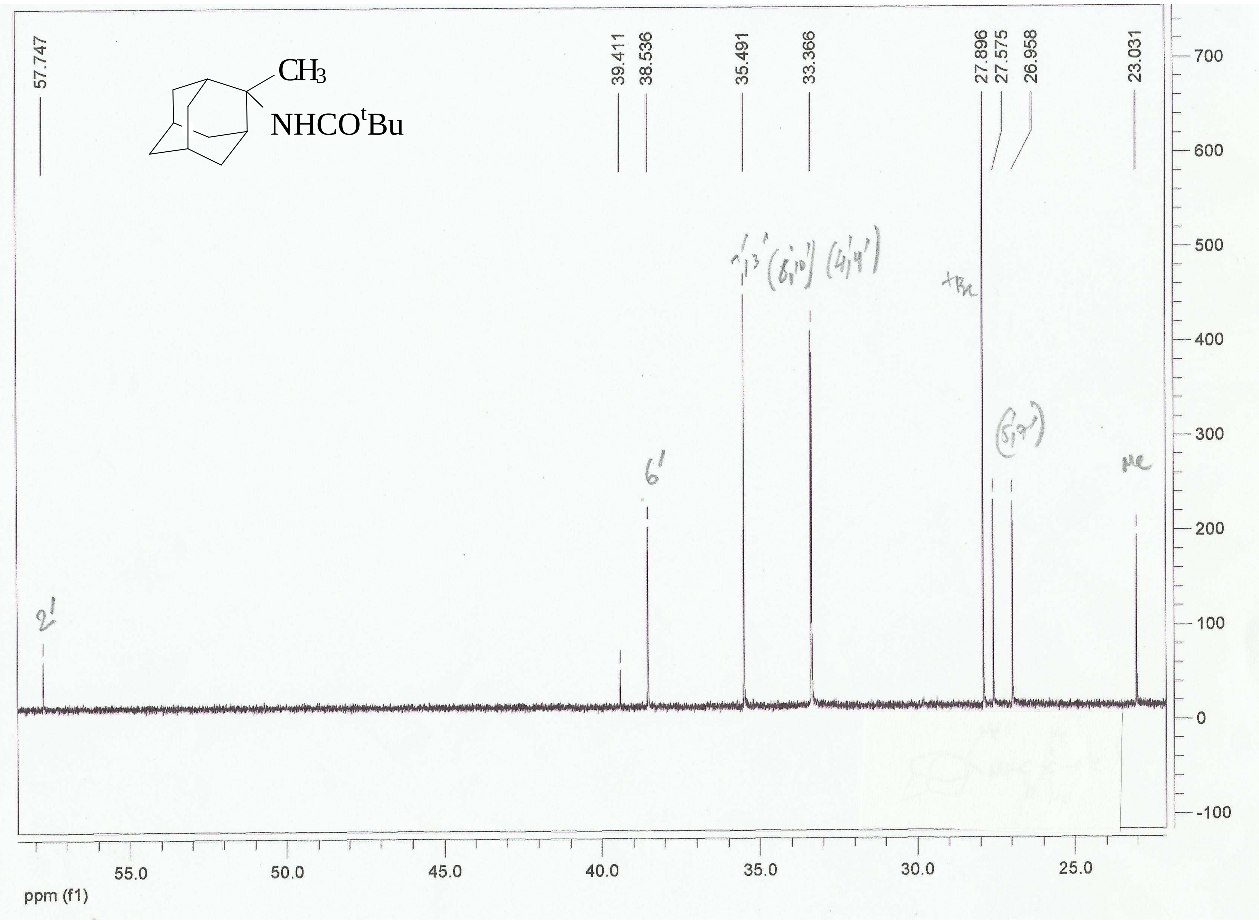
1.60
1.55
1.50
(ppm)

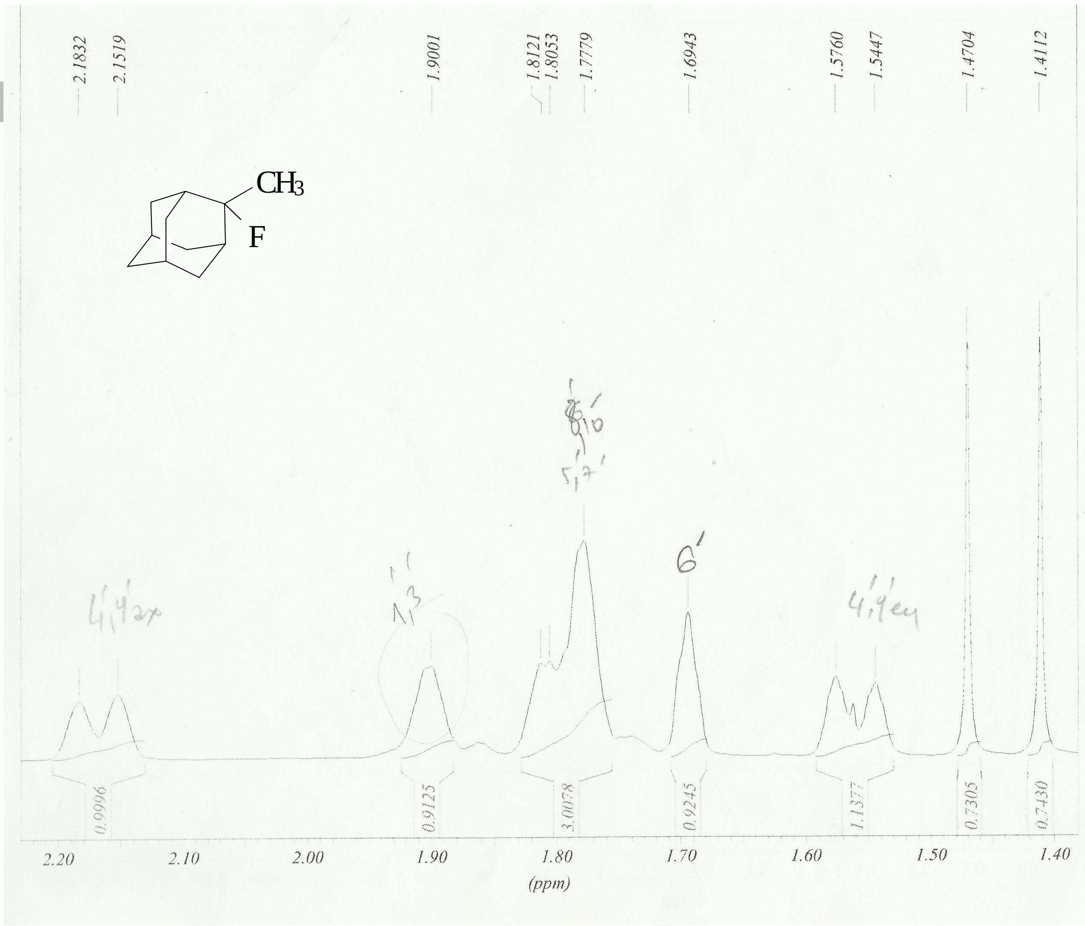

77.796
77.160
76.526
58.520
38.535
35.361
33.220
27.550
26.907
24.706
23.107
CH3
NHCOCH3
Me
NH-C-CH3
O
CDCl3
8',10' 4',9'
1',3'
6'
7' 5'
Me
NHCOMe
2'
100
50
80
70
60
50
40
30
ppm (f1)

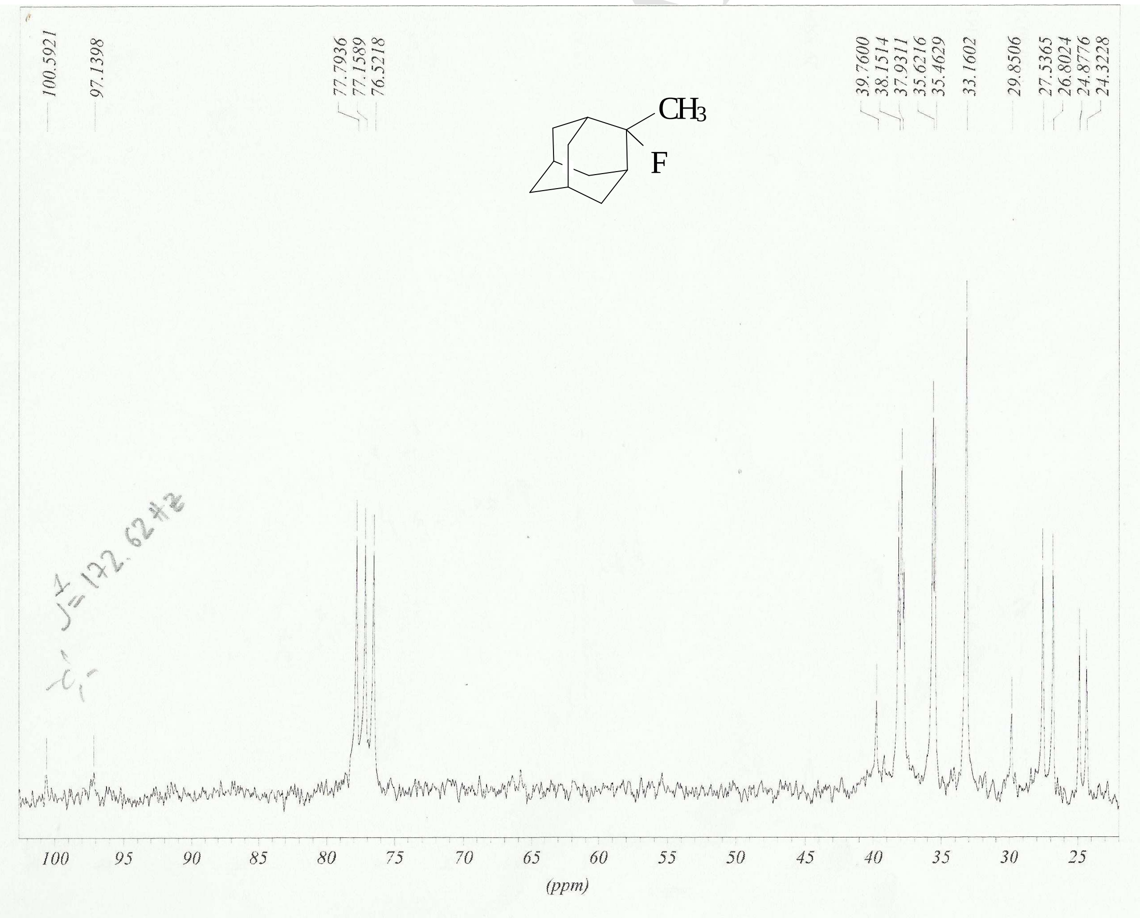
N-Pivaloyl 2-methyl-2-adamantanamine, 28. To a stirred solution of amine **22** (70.0 mg, 0.42 mmol) and triethylamine (150 mg, 1.48 mmol) in dry ether (10 mL) was added dropwise at 0 ºC a solution of pivaloyl chloride (102 mg, 0.84 mmol) in dry ether (10 mL) and the mixture was then stirred at ambient temperature for 24 h. The precipitated thiethylamine hydrochloride was filtered off and washed with ether. The filtrate was washed with cold water, HCl 3%, brine, dried (Na_2SO_4) and evaporated. The residue was filtrated over alkaline aluminium oxide column using ether as eluent to afford pure pivalamide **28**. Yield: 50 mg, 50 %.





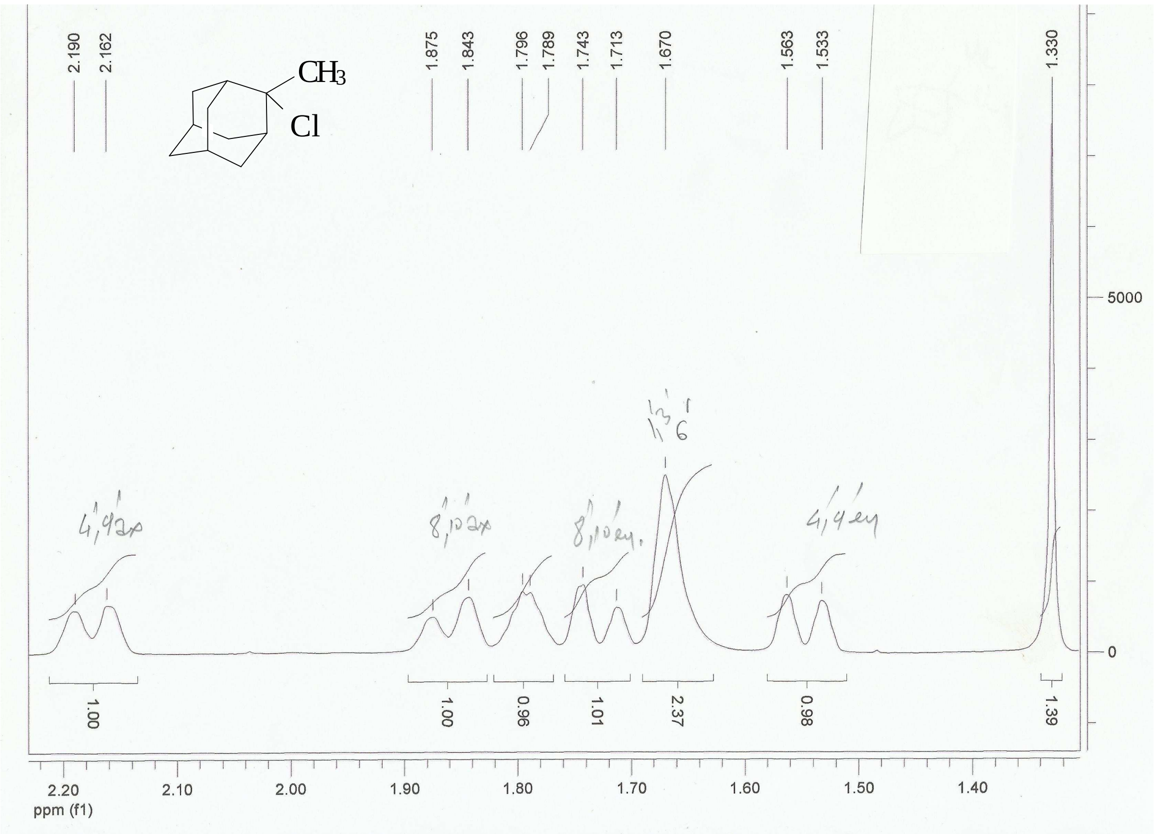
2-Fluoro-2-methyladamantane, 30. To a stirred solution of alcohol **14** (100 mg, 0.60 mmol) in anhydrous dichloromentane (2 mL) was added dropwise, under an argon atmosphere, a solution of diethylaminosulfur trifluoride (DAST) (97 mg, 0.60 mmol) in anhydrous dichloromethane (2 mL) at -78 ºC. The mixture was allowed to warm slowly at 0 ºC under stirring and then was stirred overnight at ambient temperature for 1 h. Water was added and the mixture was extracted with dichloromethane. The organic phase was washed with water, brine and dried over Na_2SO_4. After solvent evaporation the solid mixture was chromatographed on silica gel column using cyclohexane as eluent to afford the pure solide fluoride **30**. Yield: 70 mg, 69 %.

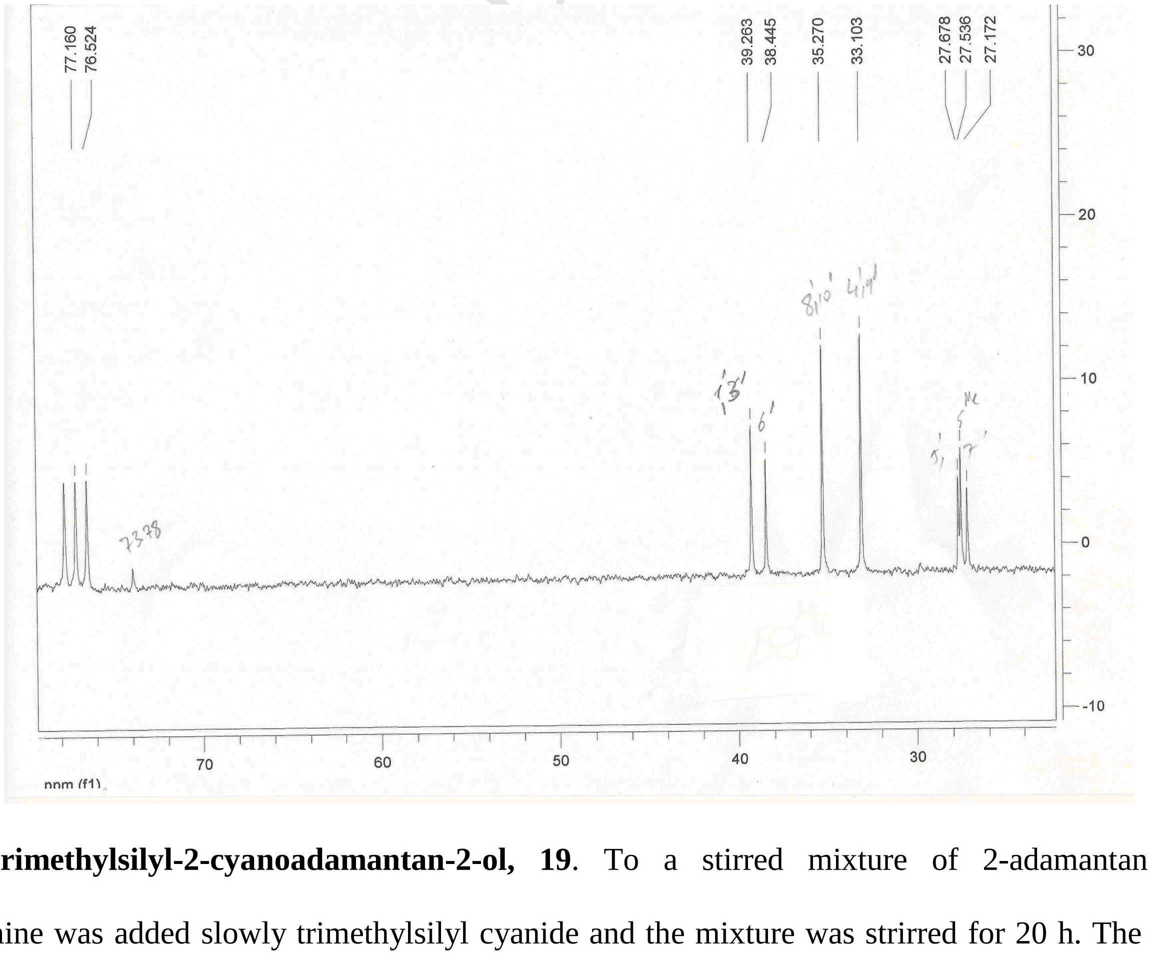




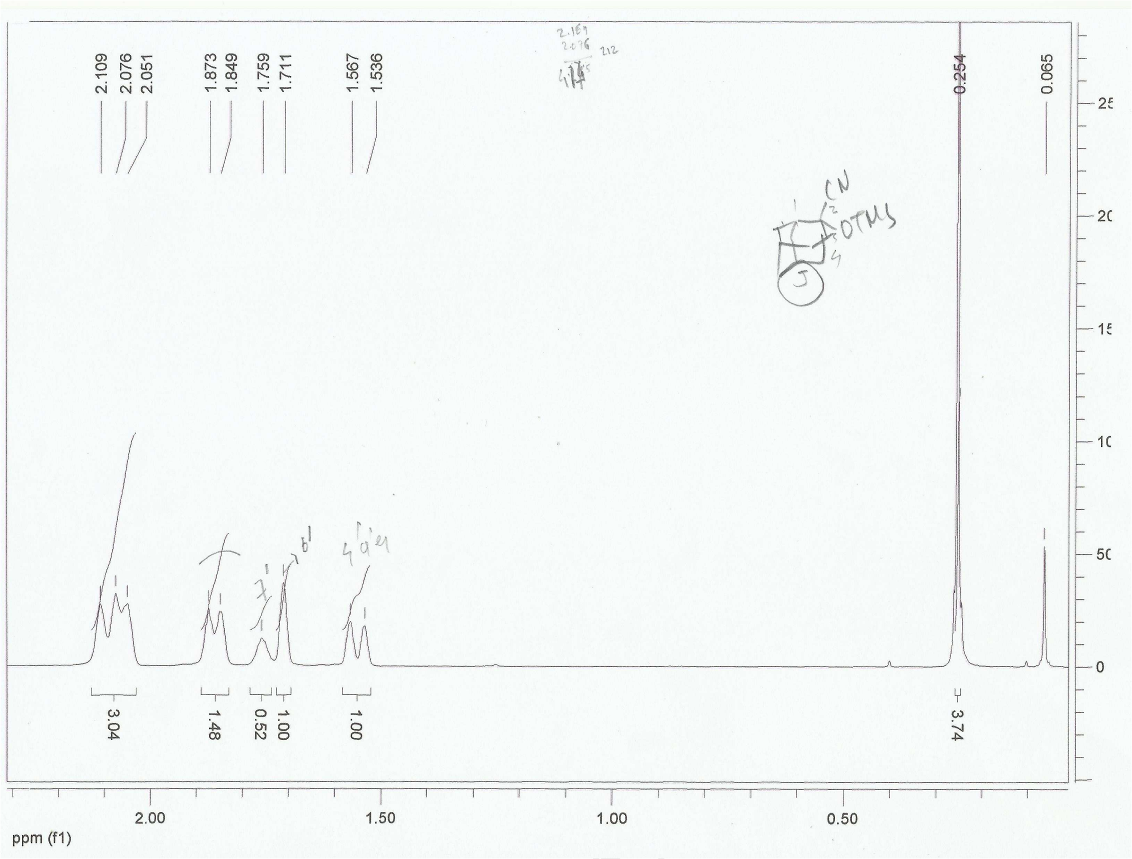
2-Chloro-2-methyladamantane, 31. A mixture of alcohol **14** (150 mg, 0.90 mmol), thionyl chloride (430 mg, 3.61 mmol) and potassium carbonate (200 mg) in dry dichloromentane (5 mL) was refluxed for 8

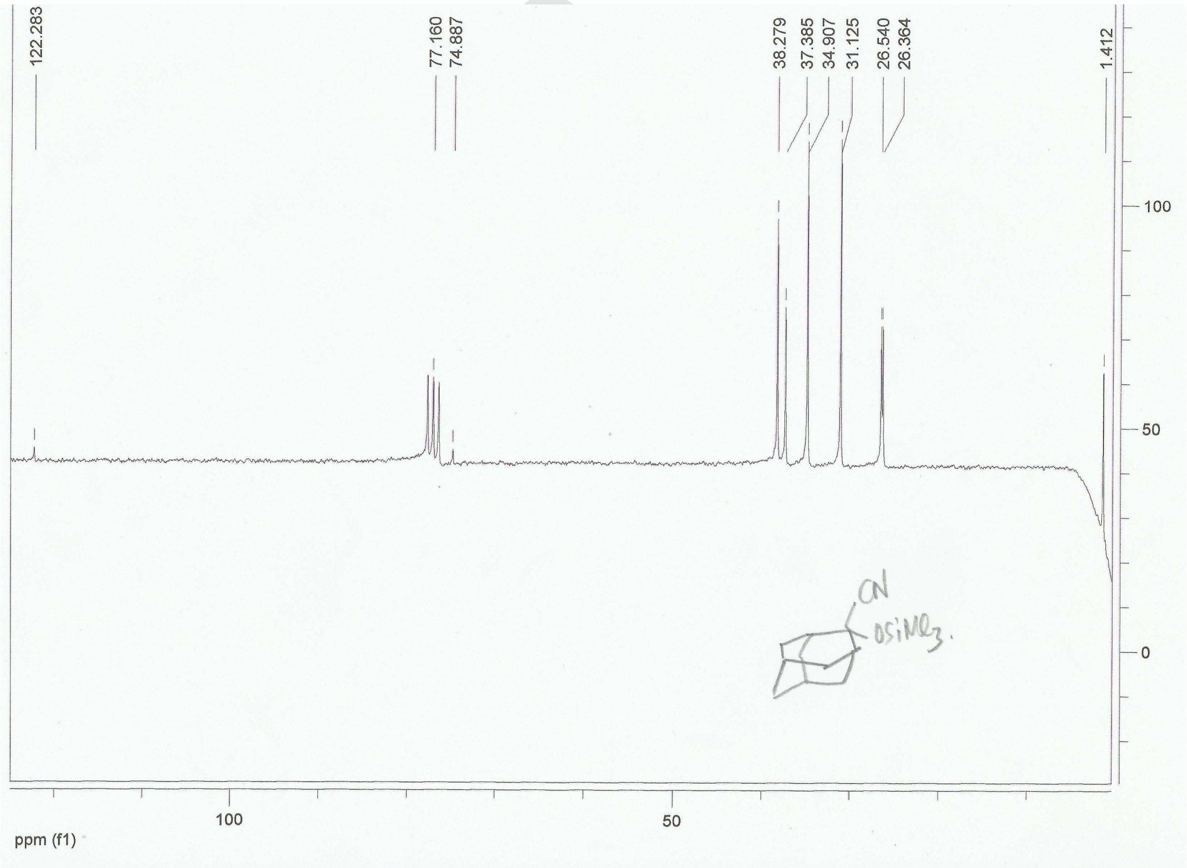
h. Dichloromethane was added the inorganic solid was filtered off. After solvent evaporation the solid mixture was chromatographed on silica gel column using hexane as eluent to afford the pure solide chloride **31**. Yield: 90 mg, 54 %.



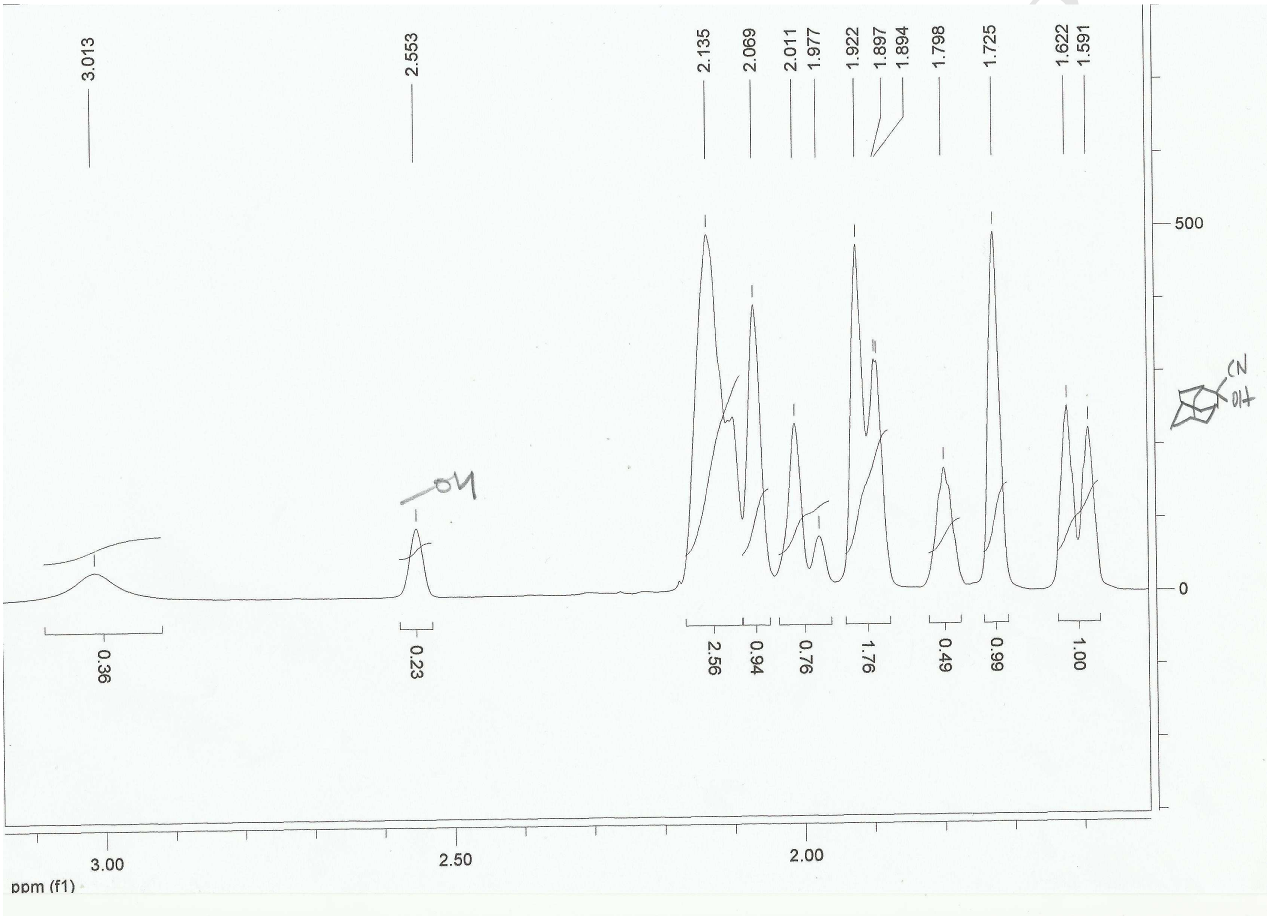


***O*-Trimethylsilyl-2-cyanoadamantan-2-ol, 19**. To a stirred mixture of 2-adamantanone and triethylamine was added slowly trimethylsilyl cyanide and the mixture was strirred for 20 h. The resulting mixture was dissolved with petroleum ether and cooled at -5 ºC to crystallize. After suction filtration the *O*-trimethylsilyl adamantanone cyanohydrin **19** was obtained. Yield: 670 mg, 81 %.

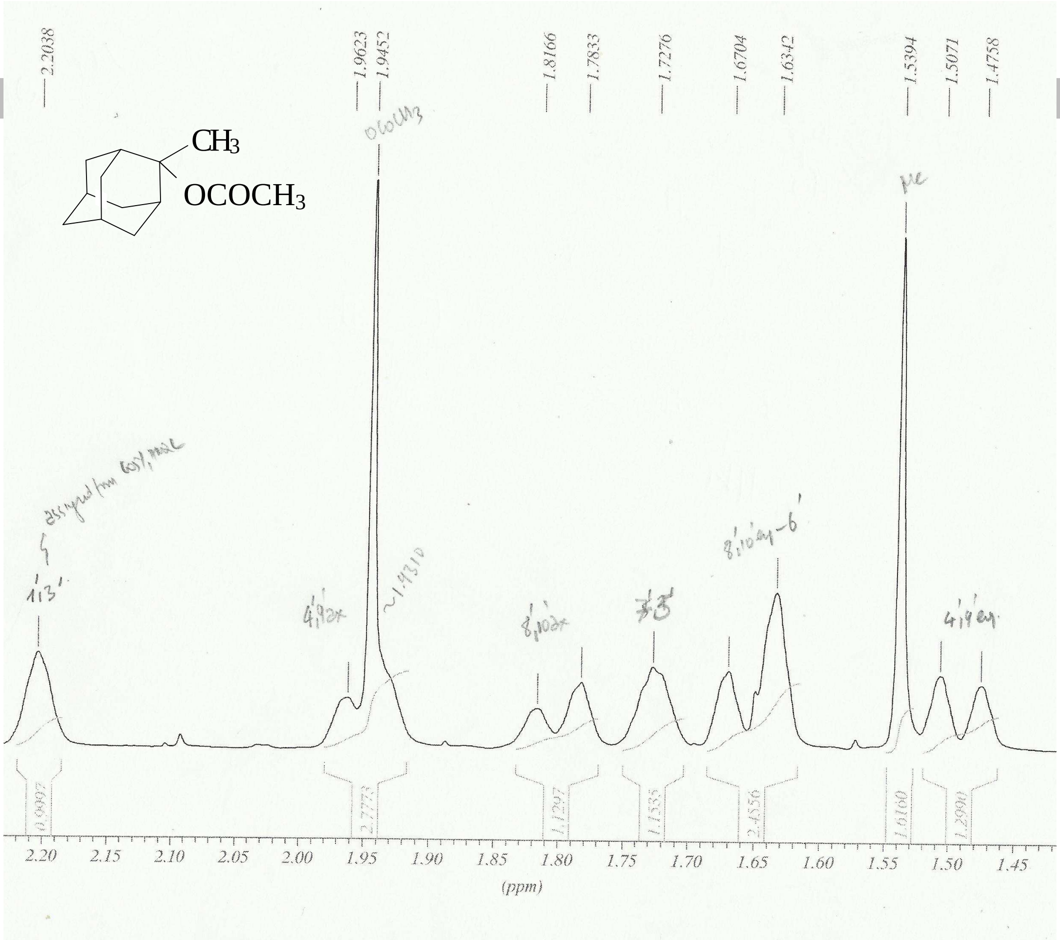


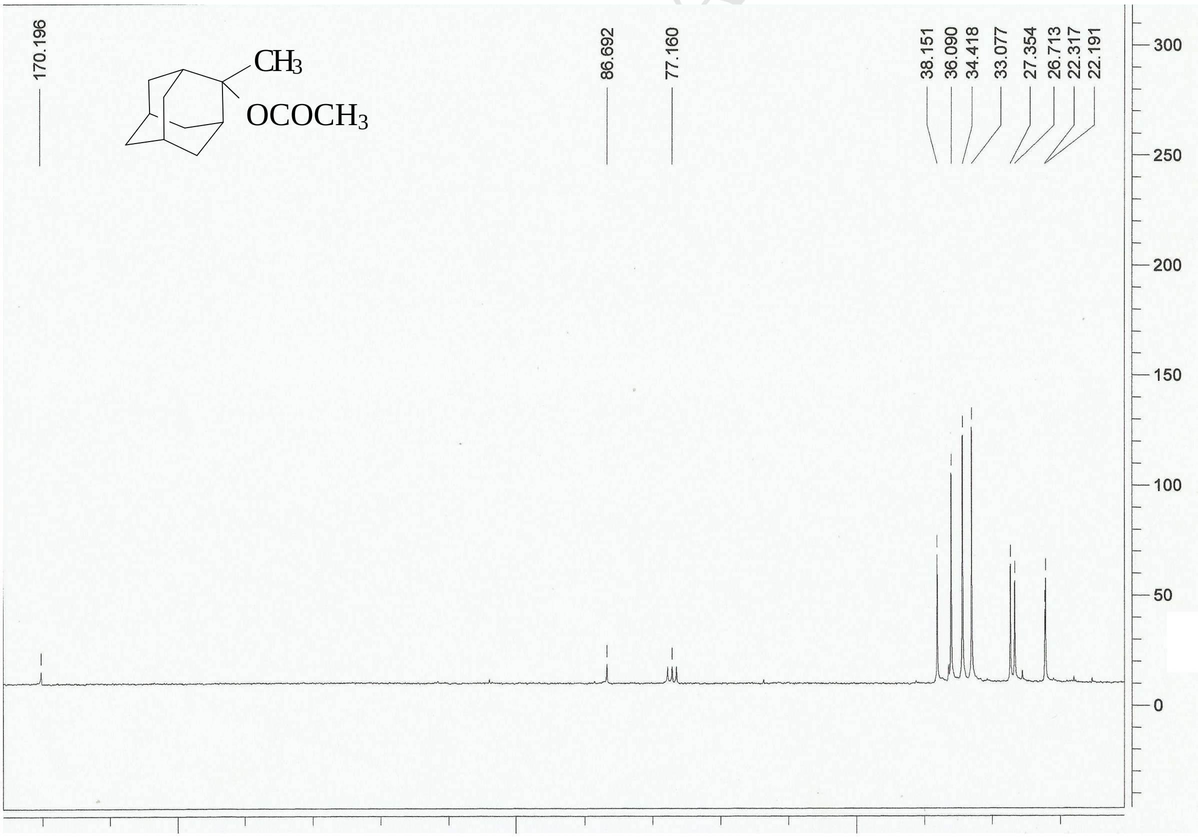


2-Cyanoadamantan-2-ol, 18. To a stirred solution of *O*-trimethylsilyl adamantanone cyanohydrin **19** (230 mg, 1.28 mmol) in methanol (10 mL) potassium fluoride (298 mg, 5.14 mmol) was added at room temperature and stirring was maintained for 5½ h (TLC monitoring). Solvent was evaporated in vacuo and water was added to the solid residue. The mixture was extracted with ether and the organic phase was washed with water and brine, dried over Na_2SO_4. After solvent removal 210 mg (93 %) of adamantanone cyanohydrin **18** was obtained.



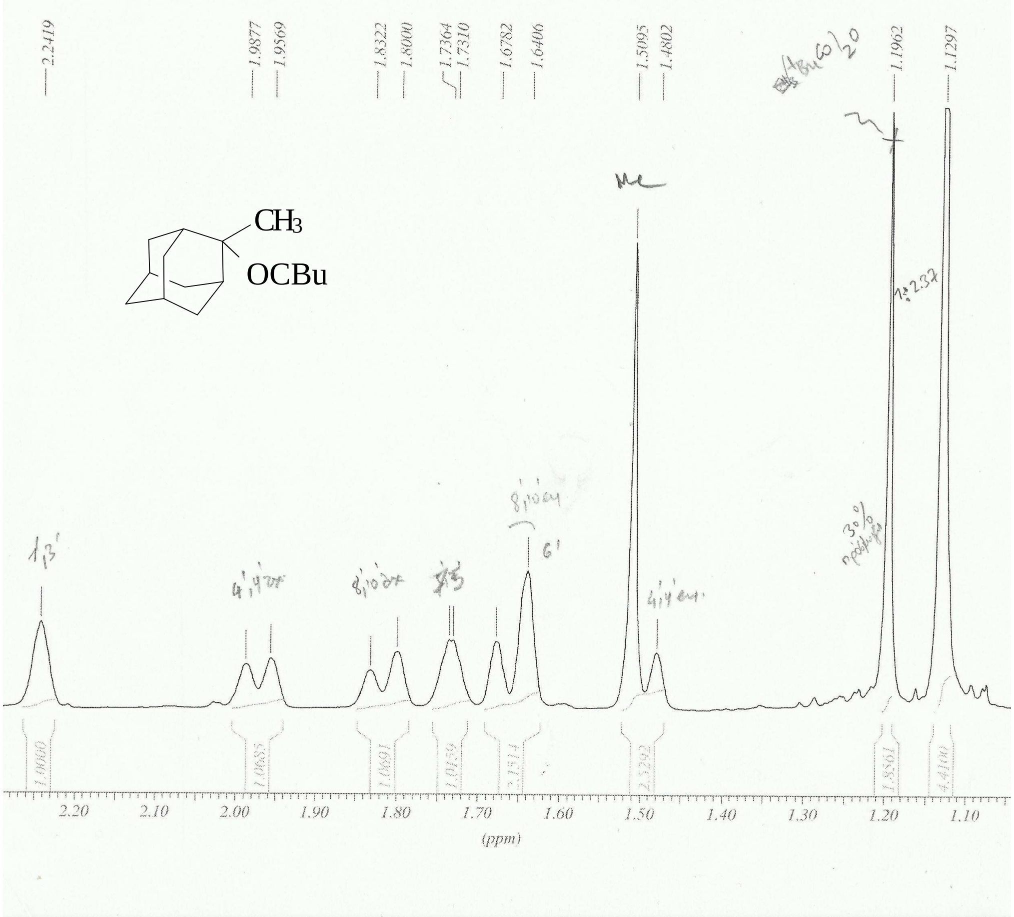
***O*-Acetyl-2-methyladamantan-2-ol, 20**. To a stirred mixture of 2-methyl-2-adamantanol **14** (200 mg, 1.21 mmol), triethylamine (243 mg, 2.41 mmol) and acetic anhydride (246 mg, 2.41 mmol), 4-dimethylaminopyridine (DMAP) (18 mg, 0.12 mmol) was added as the acetylation catalyst. The mixture was stirred at room temperature for 72 h (TLC minitoring, hexane/ether 3:1). Petroleum ether was added and the mixture was washed with HCl 5%, saturated $NaHCO_3$, brine and dried (Na_2SO_4). After solvent evaporation the residue was chromatographed on silica gel column using hexane-ether 4:1 as eluent to afford 150 mg (60 %) of pure acetyl derivative **20** (a second fraction including 2-methylene adamantane was obtained).

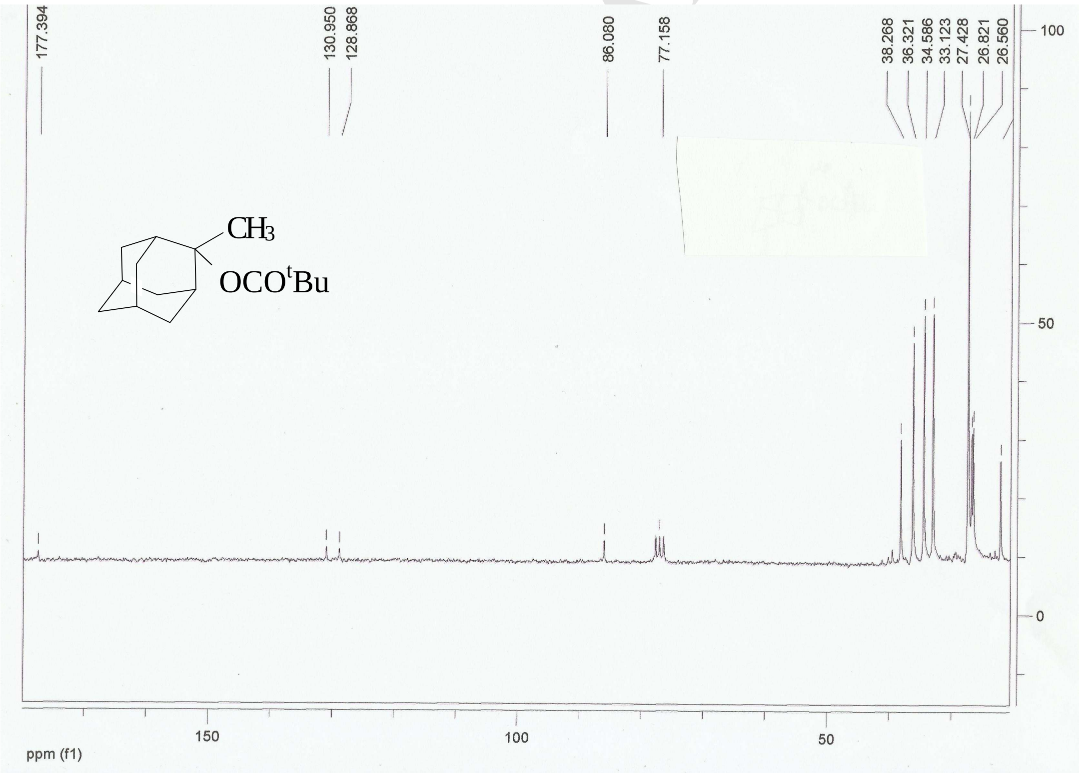


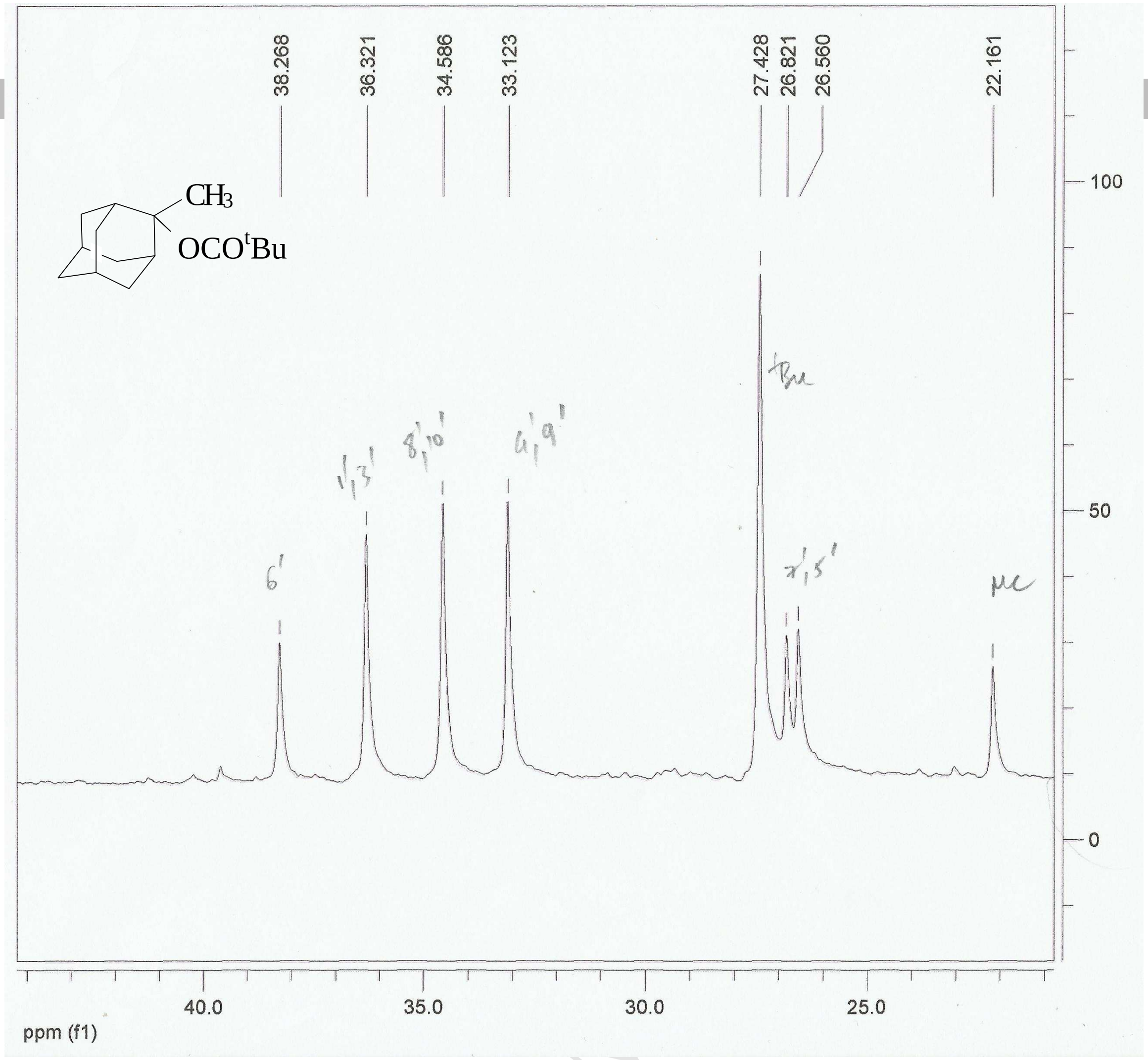


***O*-Pivaloyl-2-methyladamantan-2-ol, 21**. A solution of $MgBr_2$ (555 mg, 3.01 mmol) in anhydrous THF (15 mL) was evaporated by allowing an argon flow to pass through the flask. To the solid material dichloromethane (15 mL) was added and the suspension was poured to a flask containing pivalic anhydride

(561 mg, 3.01 mmol). Triethylamine (456 mg, 4.52 mmol) and 2-methyl-2-adamantanol **14** (250 mg, 1.51 mmol) was added and the resulting mixture was stirred for 48 h. Then water (30 mL) was added and the mixture was stirred vigorously for 5 min. The organic phase was separated and kept and the aqueous was extracted with dichloromethane (30 mL). To the combined organic solution 4 mL of methanol and 80 mg DMAP was added and the mixture was stirred for 1 h. After solvent evaporation the residue was chromatographed on silica gel column using hexane and then hexane-AcOEt 3:1 as eluent to afford 260 mg of a mixture including the product **21** and 30% of pivalic anhydride (detected through NMR).



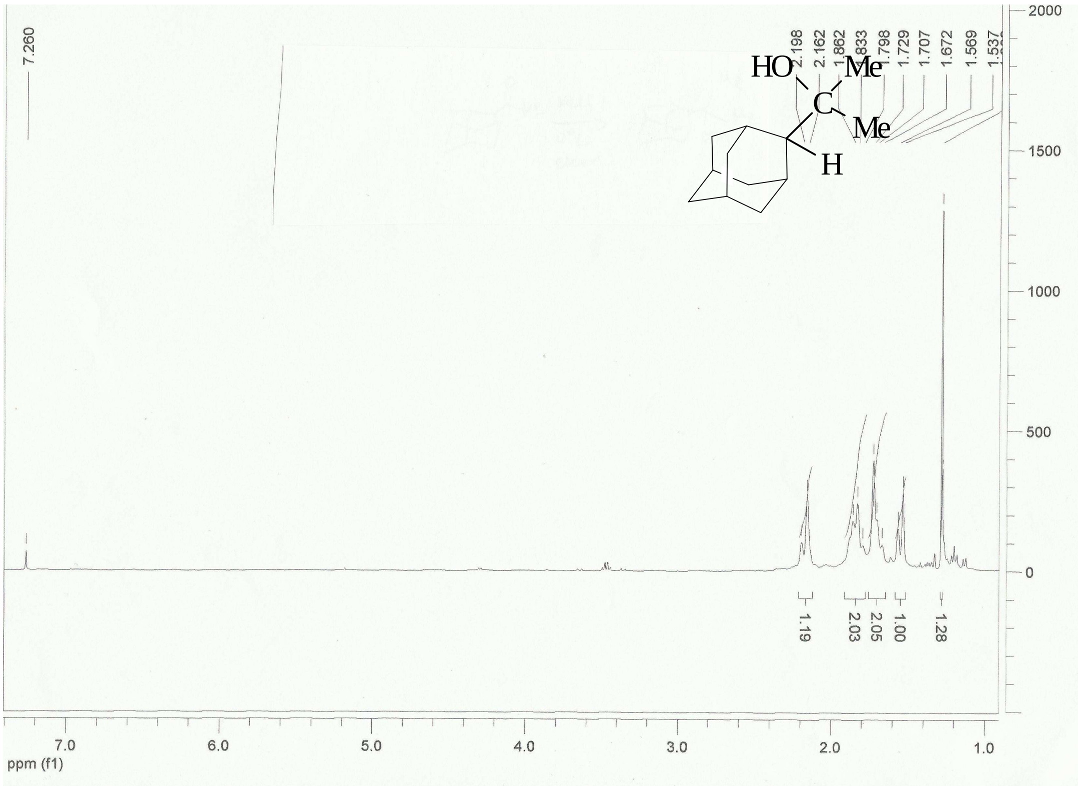

177.394
130.950
128.868
86.080
77.158
38.268
36.321
34.586
33.123
27.428
26.821
26.560
CH_3
OCO^tBu
100
50
0
150
100
50
ppm (f1)

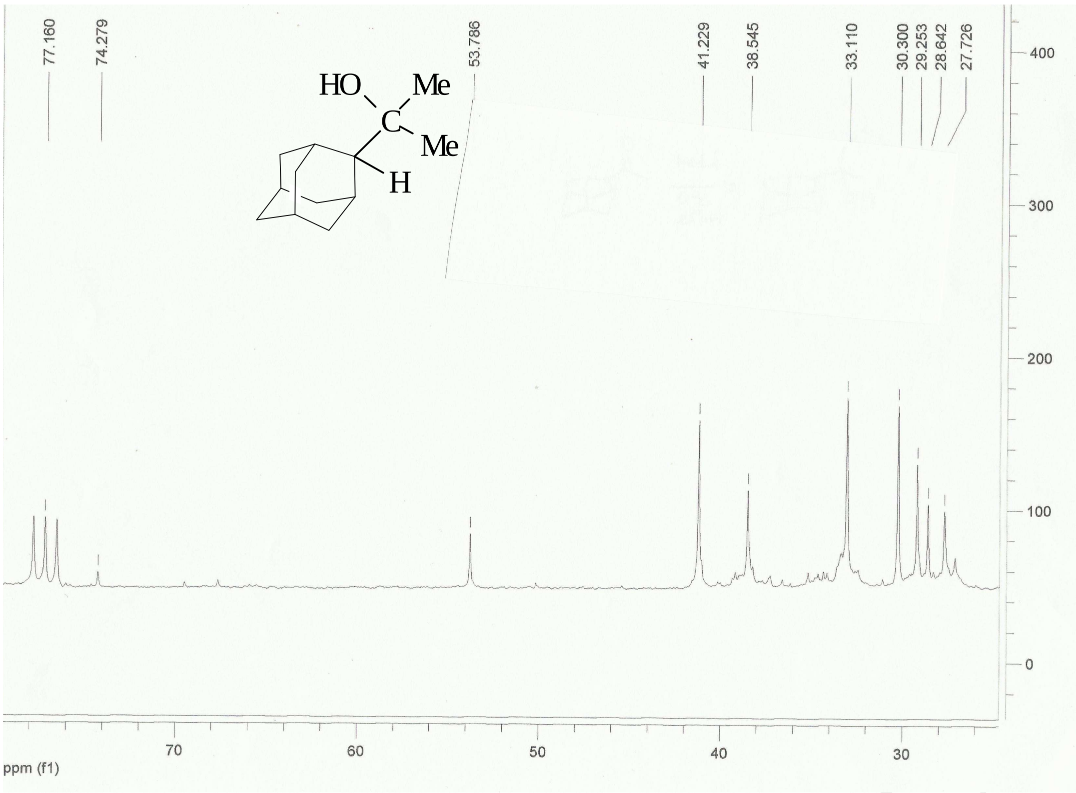


2-(2-Adamantyl-2-propanol, 32. To a stirred solution of sodium ethoxide (220 mg, 9.60 mmol) in absolute ethanol (5 mL) and anhydrous THF (11 mL), a solution of 2-adamantanone (960 mg, 6.40 mmol) and toluenesulfonylmethyl isocyanide (TOSMIC) (1.49 g, 7.68 mmol) in anhydrous THF (25 mL) at room temperature. The mixture was stirred at room temperature for 2 h, then solvent was evaporated in vacuo and water (15 mL) was added. The mixture was extracted with ether and the organic solution was dried (Na_2SO_4). Solvent was removed to afford quantitatively 2-cyanoadamantane **4** (ethanol – water).

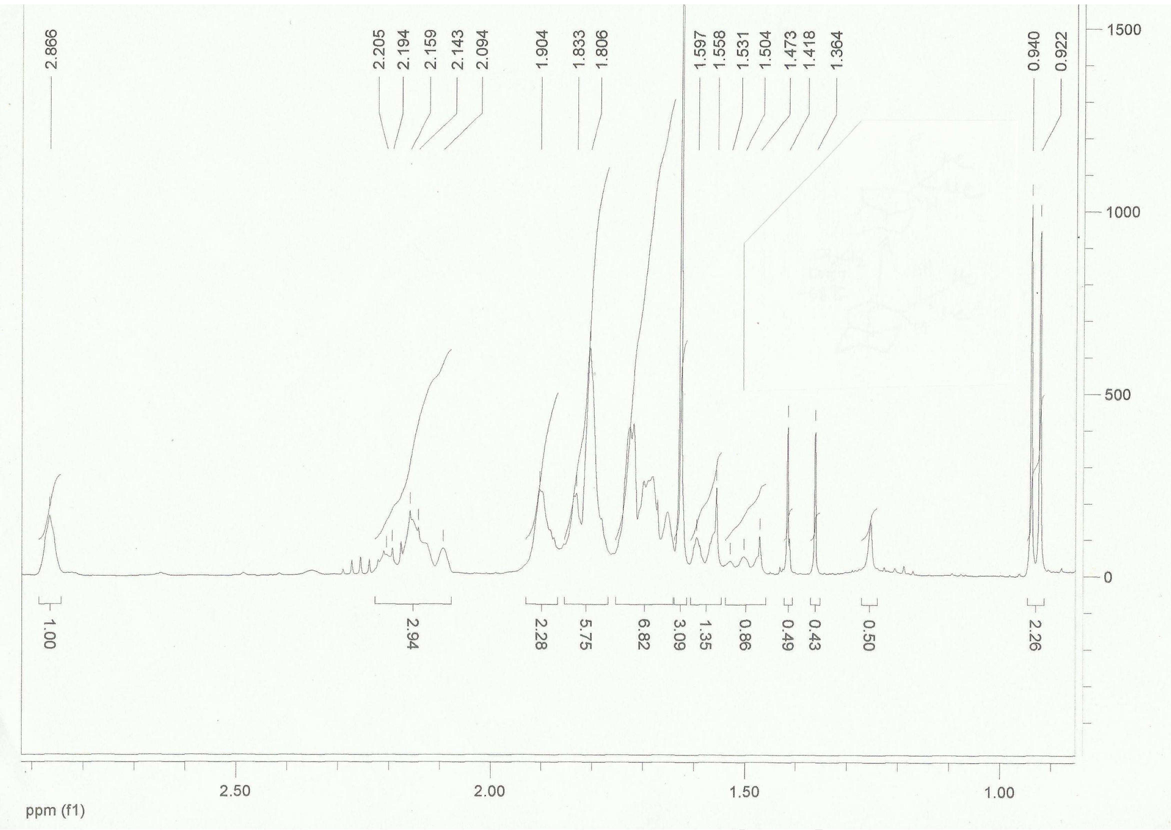
To a stirred solution of 2-cyanoadamantane **4** (350 mg, 2.17 mmol) in anhydrous ether was added during a 2 min period, under an argon atmosphere, a solution of MeLi 1.6 M in ether (4.1 mL, 6.56 mmol) at 0 ºC. The yellow complex formed was stirred for 90 min at ambient temperature and hydrolyzed with water (8 mL) at 0 ºC. The residue was treated with a mixture of acetone (5 mL) and HCl 6N (5 mL) and the mixture was refluxed for 2 h. Acetone was removed in vacuo and the resulting mixture was extracted with ether. The organic solution was washed with water and brine, was dried (Na_2SO_4) and evaporated in vacuo to afford 2-acetyladamantane **34** (302 mg, 78 %).

To a stirred solution of 2-acetyladamantane **34** (590 mg, 3.31 mmol) in anhydrous ether (40 mL) was added dropwise, under an argon atmosphere, a solution of MeLi 5 % in ether (4.4 mL, 10.0 mmol) at 0 ºC. The mixture was stirred overnight at ambient temperature, then a saturated solution of NH_4Cl (50 mL) was added at 0 ºC. The organic phase was separated, washed with water, brine and dried over Na_2SO_4. After solvent evaporation the liquid alcohol **32** (502 mg, 78 %).





2-(2-Adamantyl)-2-fluoropropane, 33. To a stirred solution of alcohol **32** (100 mg, 0.51 mmol) in anhydrous dichloromentane (2 mL) was added dropwise, under an argon atmosphere, a solution of diethylaminosulfur trifluoride (DAST) (90 mg, 0.56 mmol) in anhydrous dichloromethane (2 mL) at -78 ºC. The mixture was allowed to warm slowly at 0 ºC under stirring and then was stirred overnight at ambient temperature for 1 h. Water was added and the mixture was extracted with dichloromethane. The organic phase was washed with water, brine and dried over Na_2SO_4. After solvent evaporation the solid mixture was chromatographed on silica gel column using cyclohexane as eluent to afford pure fluoride **33**. Yield: 50.0 mg, 50 %.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2.194
2.159
2.143
2.094
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1.833
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1.597
1.558
1.531
1.504
1.473
1.418
1.364
0.940
0.922
1500
1000
500
0
1.00
2.94
2.28
5.75
6.82
3.09
1.35
0.86
0.49
0.43
0.50
2.26
2.50
2.00
1.50
1.00
ppm (f1)