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Novel 1,4-Disubstituted Adamantane Stereoisomers: Synthesis and Spectroscopic Characterization

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A series of new 1,4-disubstituted adamantane derivatives [*e.g.,* 1-chloro-4-(carbethoxymethylene)adamantane (**3**), 1-chloro-4-(carbethoxymethyl)adamantane (**4**), 1-chloro-4-(2-hydroxyethyl)adamantane (**5**), 1-chloro-4-(2-bromoethyl)adamantane (**6**), 1-bromo-4-(2-bromoethyl)-adamantane (**7**), 1-hydroxy-4-(carbethoxymethylene)adamantane (**8**), 1-hydroxy-4-(carbethoxymethyl)adamantane (**9**), 1-acetoxy-4-(carbethoxymethyl)adamantane (**10**), 1-hydroxy-4-(2-hydroxyethyl)adamantane (**11**), 1-hydroxy-4-cyanoadamantane (**12**), 1-hydroxy-4-carboxyadamantane (**13**), and 1-hydroxy-4-carbmethoxyadamantane (**14**)] have been synthesized, and their respective *syn*- and *anti*-isomers have been separated and identified.

INTRODUCTION

Progress in adamantane chemistry has been accompanied by the development of effective methods for functionalization of the adamantane skeleton.[1] 1,4-Disubstituted adamantanes possess a unique and very useful, rigid and symmetrical carbon skeleton that provides a crucial model for a variety of mechanistic[2] and stereochemical[3] studies and also offers a useful starting material for the preparation of more complex polycyclic systems.[4]

As a part of our continuing program concerned with the synthesis and chemistry of novel polycyclic molecules,[5] we sought for new synthetic entries into stereospecific, polyfunctionalized adamantane derivatives. We now report the synthesis of a variety of new 1,4-disubstituted adamantane derivatives and separation of their corresponding *syn*- and *anti*-stereoisomers.

RESULTS AND DISCUSSION

A series of new 1,4-disubstituted adamantane derivatives **3**–**14** were prepared as shown in Scheme 1. We approached the syntheses of dihaloadamantanes **6** and **7** *via* two routes by starting with 1-hydroxyadamantan-4-one (**1**),[6] for which several methods of preparation are known in the literature.[7] 1-Chloroadamantan-4-one (**2**)[6] was readily prepared from **1** *via* its reaction with thionyl chloride.[7b] Reaction of **1** and **2** with ethyl (diethoxyphosphinyl)acetate[8] afforded the corresponding 4-carbethoxymethylene derivatives **3** and **8** in 83 % and 88 % yields, respectively. A mixture of *syn*- and *anti*-4-carbethoxymethyl derivatives **4** was prepared in quantitative yield by catalytic hydrogenation of **3**. GLC-analysis (DB-210, 180 °C) revealed that these two isomers were present in a 1.6:1 ratio.[9] However, catalytic hydrogenation of **8** afforded a

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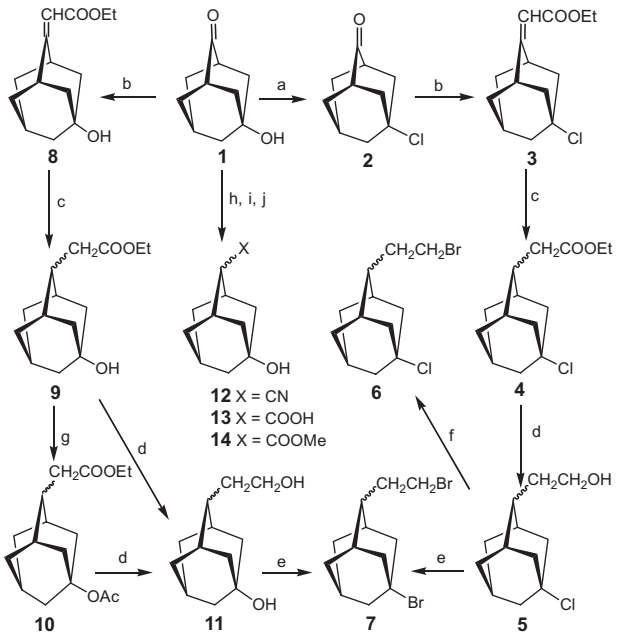

Scheme 1. Reagents and solvents: a) $SOCl_2$; b) $(Et_2O)_2POCH_2COOEt$, NaH, dimethylglycole; c) H_2, Pd/C, EtOH; d) $LiAlH_4$, Et_2O; e) 62 % HBr, H_2SO_4; f) Ph_3P, CBr_4; g) Ac_2O, AcOH; h) TosMIC, EtOH, *t*-KOBu; i) 50 % H_2SO_4; j) MeOH, H_2SO_4.

1:1 mixture of s*yn*- and *anti*-1-hydroxy-4-(carbethoxymethyl)adamantane isomers, **9**.

Reduction of **4** with $LiAlH_4$ afforded a mixture of chloroalcohols **5**, which were converted to chlorobromides **6** (in 80 % yield) and to dibromides **7** (in 93 % yield) by treatment with CBr_4/Ph_3P[5h] and 62 % HBr/H_2SO_4, respectively.

Alternatively, *syn*- and *anti*-dibromides **7** were obtained in 73 % yield *via* bromination of diols **11**. *syn*- and *anti*-Diols **11** were obtained as the product of $LiAlH_4$ reduction of either compound **9** or **10**, in 84 % and 94 % yields, respectively. Compound **10** was prepared *via O*-acetylation of the OH group in **9** in 62 % yield using a standard procedure.

Nitrile **12** was prepared in 98 % yield *via* direct conversion of hydroxyketone **1** by using tosylmethylisocyanide (TosMIC)[10] and *t*-KOBu. Subsequent hydrolysis of **12** with 50 % sulfuric acid at 100 °C afforded the corresponding carboxylic acid **13** in 62 % yield. Since the hydrolysis of both isomers, *syn*-**12** and *anti*-**12**, gave a mixture of *syn*- and *anti*-**13**,[11] the mixture of acids **13** was converted to the corresponding methyl esters **14**, which were then separated by column chromatography.

Structures of adamantane derivatives **3–14** were established on the basis of their spectral data. The ^{13}C NMR signals of all *syn*- and *anti*-1,4-disubstituted adamantane isomers are given in Table I. *syn*- and *anti*-Isomers were assigned by a combination of 2D NMR techniques (COSY and HETCOR) by invoking the fact that an electron-withdrawing group at C–1 (Chart 1) is expected to shift the resonance signals of the neighboring carbons to lower field.[12] As a result of the combined influence of 1,4-substituents, the *syn*-isomers have the signals of flank-

TABLE I. ^{13}C chemical shifts (δ /ppm) of 1,4-disubstituted adamantanes

Isomer	C–1	C–2,9	C–3,5	C–4	C–7	C–6,10	C–8	Other C
syn-**4**	68.03	41.67	35.24	39.03	30.97	36.53	47.99	14.04; 37.44; 60.18; 172.98
anti-**4**	67.61	48.37	34.66	39.24	30.98	29.43	47.99	14.02; 36.89; 60.18; 173.01
syn-**5**	68.60	41.73	35.24	38.50	31.23	36.64	48.02	35.04; 60.77
anti-**5**	68.29	48.65	34.78	38.87	31.15	29.52	48.10	34.55; 61.20
syn-**6**	68.15	41.86	34.76	40.74	31.27	36.61	48.01	31.85; 35.05
anti-**6**	67.91	48.45	34.21	41.08	31.05	29.64	48.01	31.95; 34.60
syn-**7**	65.65	43.44	35.61	40.77	32.17	36.61	49.63	31.78; 35.10
anti-**7**	65.28	50.07	35.18	41.08	31.95	29.68	49.61	31.83; 34.72
syn-**9**	67.89	39.27	34.35	39.44	29.97	37.00	45.62	14.00; 37.60; 60.08; 173.26
anti-**9**	67.70	45.93	33.67	39.72	30.01	29.84	45.53	14.02; 37.01; 60.09; 173.33
syn-**10**	79.69	37.15	34.47	39.63	30.10	35.23	41.67	14.13; 22.52; 37.66; 60.05; 170.12; 173.01
anti-**10**	79.47	42.05	33.79	39.80	30.15	30.03	41.50	14.14; 22.57; 37.03; 60.16; 170.19; 173.03
syn-**11**	68.01	39.46	34.47	39.07	30.39	37.29	45.79	35.40; 61.10
anti-**11**	68.17	46.13	33.76	39.23	30.80	29.98	45.63	34.71; 61.30
syn-**12**	66.61	40.72	32.84	35.29	28.84	34.81	43.91	121.36
anti-**12**	66.43	43.76	32.60	35.56	29.12	31.43	44.30	121.53
syn-**14**	67.46	41.33	31.98	47.88	29.71	36.24	44.68	51.36; 174.35
anti-**14**	67.58	45.18	31.64	48.22	29.58	31.90	44.90	51.36; 174.30

ing carbons (C–2,9 and C–6,10) fairly close together, whereas those of the *anti*-isomers are relatively far apart.

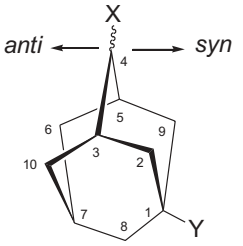

Chart 1.

In conclusion, we have synthesized a series of new stereospecific polyfunctionalized adamantane derivatives **3**–**14**, and their structures were established on the basis of their spectroscopic data.

EXPERIMENTAL

General

IR spectra were recorded on a Perkin Elmer 297 instrument and FT spectrometer Bomem MB200. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ on a Varian Gemini 300 MHz spectrometer. Chemical shifts are given as δ values (ppm). APT, COSY and HETCOR sequences were used for assignments of multiplicity in ^{1}H and ^{13}C NMR spectra. GC analyses were conducted on Varian 3300 and Varian CP-3380 instruments using DB-210 or DB-1701 capillary columns. A Lobar B 310-25 LiChroprep Si_{60}, 40–63 μm column was used for MPLC separations. High-resolution mass spectra were recorded on an Extrel FTMS 2001 spectrometer.[13] Melting points were determined on a Koffler hot stage melting point apparatus and are uncorrected.

*1-Chloro-4-(carboxymethylene)adamantane (**3**)*

Ethyl (diethoxyphosphinyl)acetate (0.707 g, 3.16 mmol) was added dropwise to a well stirred suspension of sodium hydride (0.151 g, 3.16 mmol) in dry 1,2-dimethoxyethane (DME, 2.1 mL), under a nitrogen atmosphere, at 20 °C. The resulting mixture was stirred at room temperature for an additional 2 h, at which time a solution of 1-chloroadamantan-4-one (**2**, 0.388 g, 2.10 mmol) in dry DME (3.15 mL) was added rapidly. Stirring was continued overnight at 45–50 °C, and the reaction mixture was then concentrated under reduced pressure. Water (15 mL) was added to the residue, and the resulting aqueous suspension was extracted with ether (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. Pure **3** (0.460 g, 86 %) was thereby obtained as a dense yellow oil.

An analytical sample of **3** was obtained as a colorless oil by vacuum distillation: b. p. 118–119 °C at 2 × 10^{-2} Torr. IR (KBr-film) ν_{max}/cm^{-1}: 2980 (m), 2930 (s), 2860 (m), 1710 (s), 1650 (m), 1450 (m), 1230 (s), 1215 (s) 1155 (s), 1035 (s), 830 (m). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.28 (t, $J_{H–H}$ = 7.2 Hz, 3H), 1.74–1.95 (m, 4H), 2.22–2.32 (m, 7H) 2.61 (br s, 1H), 4.15 (q, $J_{H–H}$ = 7.2 Hz, 2H), 4.25 (br. s, 1H), 5.62 (s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 13.91 (q, 1C), 30.89 (d, 1C), 34.58 (d, 1C), 36.90 (t, 1C), 37.86 (t, 1C), 43.04 (d, 1C), 46.53 (t, 1C), 47.56 (t, 1C), 48.37 (t, 1C), 59.32 (t, 1C), 66.06 (s, 1C), 110.33 (d, 1C), 166.29 (s, 1C), 166.46 (s, 1C).

Anal. Calcd. for $C_{14}H_{19}O_2Cl$ (M_r = 254.75): C 66.00, H 7.52 %; found: C 66.12, H 7.43 %.

*1-Chloro-4-(carbethoxymethyl)adamantane (**4**)*

5% Palladized charcoal (150 mg) was added to a solution of 1-chloro-4-(carbethoxymethylene)adamantane (**3**, 1.77 g, 6.94 mmol), in EtOH (40 mL), and the resulting mixture was hydrogenated (H_2, 55 psi) on a Parr-shaker apparatus for 12 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*, thereby affording product **4** (1.73 g, 97 %) as a colorless viscous oil. According to GC (DB-210, 180 °C), product **4** was a mixture of *syn*- and *anti*-isomers (ratio 1.6:1). The isomers were separated either by column chromatography on Al_2O_3 (activity II/III) using CCl_4 as eluent, or on MPLC by eluting with 1 % EtOAc–hexane.

syn-**4**: IR (KBr-film) ν_{max}/cm^{-1}: 2980 (w), 2920 (s), 2860 (m), 1735 (s), 1455 (m), 1160 (s), 1030 (m), 825 (m). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.26 (t, $J_{H–H}$ = 7.2 Hz, 3H), 1.65–1.72 (br. s, 4H), 1.86–1.94 (m, 4H), 2.05–2.20 (m, 6H), 2.43 (d, $J_{H–H}$ = 7.7 Hz, 2H), 4.13 (q, $J_{H–H}$ = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.04 (q, –CH_3), 30.97 (d, 1C), 35.24 (d, 2C), 36.53 (t, 2C), 37.44 (t, 1C), 39.03 (d, 1C), 41.67 (t, 2C), 47.99 (t, 1C), 60.18 (t, 1C), 68.03 (s, 1C), 172.98 (s, 1C).

anti-**4**: IR (KBr-film) ν_{max}/cm^{-1}: 2980 (w), 2920 (s), 2860 (m), 1740 (s), 1460 (m), 1305 (m), 1160 (m), 1030 (m), 830 (m). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.25 (t, $J_{H–H}$ = 7.2 Hz, 3H), 1.49 (d, $J_{H–H}$ =13.2 Hz, 2H), 1.80 (d, $J_{H–H}$ = 13.2 Hz, 2H), 1.94 (br. s, 4H), 2.08–2.30 (m, 6H), 2.42 (d, $J_{H–H}$ = 7.4 Hz, 2H), 4.13 (q, $J_{H–H}$ = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.02 (q, –CH_3), 29.43 (t, 2C), 30.98 (d, 1C), 34.66 (d, 2C), 36.89 (t, 1C), 39.24 (d, 1C), 47.99 (t, 1C), 48.37 (t, 2C), 60.18 (t, 1C), 67.61 (s, 1C), 173.01 (s, 1C).

Anal. Calcd. for $C_{14}H_{21}ClO_2$ (M_r = 256.76): C 63.27, H 8.24 %; found: C 63.25, H 8.36 %.

*1-Chloro-4-(2-hydroxyethyl)adamantane (**5**)*

A 1.6:1 mixture of *syn*- and *anti*-1-chloro-4-(carbethoxymethy)adamantane **4** (0.371 g, 1.45 mmol) in freshly distilled dry ether (10 mL) was added dropwise under stirring to a suspension of $LiAlH_4$ (0.122 g, 3.21 mmol) in dry ether (21 mL). The reaction mixture was refluxed overnight and then allowed to cool gradually to room temperature. Excess $LiAlH_4$ was destroyed by careful, dropwise addition of water (*ca.* 1 mL). The ether layer was decanted, and water (20 mL) was added to the residue. The resulting aqueous suspension was extracted with ether (3 × 20 mL). The combined ethereal extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. A colorless oily product **5** (0.296 g, 95 % yield) was thereby obtained as a

mixture of *syn*- and *anti*-1-chloro-4-(2-hydroxyethyl)adamantane.

IR (KBr-film) ν_{max}/cm^{-1}: 3330 (s), 2910 (s), 2860 (m), 1450 (m), 1350 (w), 1290 (w), 1105 (m), 1070 (m), 1040 (s), 1010 (s), 825 (s).

Anal. Calcd. for $C_{12}H_{19}ClO$ (M_r = 214.729): C 67.12, H 8.92 %; found: C 67.17, H 8.90 %.

Isomeric alcohols were separated *via* MPLC by elution with 1→20 % EtOAc-hexane.

syn-**5**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.62–1.72 (m, 8H), 1.90–2.00 (m, 4H), 2.00–2.19 (m, 3H), 2.26 (d, $J_{H–H}$ = 10.5 Hz, 2H), 3.68 (t, $J_{H–H}$ = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 31.23 (d, 1C), 35.04 (t, 1C), 35.24 (d, 2C), 36.64 (t, 2C), 38.50 (d, 1C), 41.73 (t, 2C), 48.02 (t, 1C), 60.77 (t, 1C), 68.60 (s, 1C).

anti-**5**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.47 (d, $J_{H–H}$ = 12.8 Hz, 2H), 1.64–1.96 (m, 8H), 2.06–2.22 (m, 7H), 3.68 (t, $J_{H–H}$ = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.52 (t, 2C), 31.15 (d, 1C), 34.55 (t, 1C), 34.78 (d, 2C), 38.87 (d, 1C), 48.10 (t, 1C), 48.65 (t, 2C), 61.20 (t, 1C), 68.29 (s, 1C).

*1-Chloro-4-(2-bromoethyl)adamantane (**6**)*

A solution of Ph_3P (0.333 g, 1.27 mmol) in CH_2Cl_2 (3.5 mL) was added dropwise to a stirred mixture of *syn*- and *anti*-chloroalcohols **5** (0.173 g, 0.807 mmol) and CBr_4 (0.378 g, 1.14 mmol) in CH_2Cl_2 (6.5 mL) at room temperature during 20 min. After the addition of reagents was completed, the resulting mixture was stirred at room temperature during an additional 20 h, at which time the reaction mixture was concentrated to a volume of 5 mL. Byproduct triphenylphosphonium oxide was partially precipitated by addition of ether (15 mL). The precipitate was removed by filtration, and the mother liquor was concentrated to a volume of *ca*. 3 mL. A yellow oil was separated from the remaining PH_3P=O *via* column chromatography on silica gel by elution with pentane. The isomers were not separated. The volatile oily product **6** (178 mg, 80 %) was further purified by vacuum-transfer at 40–50 °C and 6 Torr.

HRMS for $C_{12}H_{18}BrCl$: calculated [M$^+$] 276.02804; found 276.035034.

IR (KBr-film) ν_{max}/cm^{-1}: 2914 (s), 2859 (m), 1456 (m), 1255 (m), 1030 (m), 828 (s). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.50 (d, $J_{H–H}$ = 13.2 Hz, 2H), 1.70–2.25 (m, 30H), 3.38–3.45 (m, 4H).

syn-**6**: ^{13}C NMR ($CDCl_3$) δ/ppm: 31.27 (d, 1C), 31.85 (t, 1C), 34.76 (d, 2C), 35.05 (t, 1C), 36.61 (t, 2C), 40.74 (d, 1C), 41.86 (t, 2C), 48.01 (t, 1C), 68.15 (s, 1C).

anti-**6**: ^{13}C NMR ($CDCl_3$) δ/ppm: 29.64 (t, 2C), 31.05 (d, 1C), 31.95 (t, 1C), 34.21 (d, 2C), 34.60 (t, 1C), 41.08 (d, 1C), 48.01 (t, 1C), 48.45 (t, 2C), 67.91 (s, 1C).

*1-Bromo-4-(2-bromoethyl)adamantane (**7**)*

Conc. H_2SO_4 (1.2 mL) and 62 % HBr (2.4 mL) were added dropwise to a solution of 1-chloro-4-(2-hydroxyethyl)adamantane (**5**, 0.200 g, 0.93 mmol) at room temperature during 20 min. The reaction mixture was stirred overnight at 85–90 °C, and then it was allowed to cool gradually to room temperature. Ether (30 mL) was added, and the ether layer was separated; the aqueous layer was extracted with ether (4 × 20 mL). The combined etheral extracts were washed with saturated $NaHCO_3$ solution (2 × 40 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. Pure 1-bromo-4-(2-bromoethyl)adamantane (**7**, 0.277 g, 73 %) was thereby obtained as a colorless oil.

An alternative synthesis of **7** was achieved from the mixture of diols **11**. Thus, diols **11** (1.38 g, 6.3 mmol) were dissolved in 62 % hydrobromic acid (21 mL), and conc. H_2SO_4 (4 mL) was added dropwise under stirring at room temperature. The resulting mixture was stirred overnight at 80–90 °C. After cooling to room temperature, ether (250 mL) was added, and the ether layer was separated. The water layer was extracted with ether (3 × 150 mL), and the combined etheral extracts were washed with saturated $NaHCO_3$ solution (3 × 50 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. Crude **7** (1.89 g, 93 %) was thereby obtained as a colorless oil. The corresponding *syn*- and *anti*-isomers of **7** were separated by column chromatography on silica gel by elution with pentane (compound:SiO_2 ratio was 1:380).

HRMS for $C_{12}H_{18}Br_2$: calculated [M$^+$] 319.976697; found 319.976973.

IR (KBr-film) ν_{max}/cm^{-1}: 2912 (s), 2857 (m), 1455 (m), 1289 (m), 1104 (m), 1026 (m), 813 (s).

syn-**7**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.72–2.06 (m, 9H), 2.08–2.24 (m, 3H), 2.32–2.48 (m, 4H), 3.43 (t, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 31.78 (t, 1C), 32.17 (d, 1C), 35.10 (t, 1C, –CH_2Br), 35.61 (d, 2C), 36.61 (t, 2C), 40.77 (d, 1C), 43.44 (t, 2C), 49.63 (t, 1C), 65.65 (s, 1C).

anti-**7**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.56 (d, $J_{H–H}$ = 13.0 Hz, 2H), 1.84 (d, $J_{H–H}$ = 13.0 Hz, 2H), 1.91–2.10 (m, 6H), 2.32–2.46 (m, 6H), 3.42 (t, $J_{H–H}$ = 6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.68 (t, 2C), 31.83 (t, 1C), 31.95 (d, 1C), 34.72 (t, 1C), 35.18 (d, 2C), 41.08 (d, 1C), 49.61 (t, 1C), 50.07 (t, 2C), 65.28 (s, 1C).

*1-Hydroxy-4-(carbethoxymethylene)adamantane (**8**)*

Ethyl (diethoxyphosphinyl)acetate (5.00 g, 22.3 mmol) was added dropwise to a well-stirred suspension of 50 % NaH (1.24 g, 51.8 mmol) and ethylene glycol dimethyl ether (DME, 19 mL), under a nitrogen atmosphere. The resulting suspension was stirred at room temperature for an additional 2 h, and then 1-hydroxyadamantan-4-one (**1**, 2.37 g, 14.3 mmol) in dry DME (25 mL) was added rapidly. The resulting mixture was heated overnight at 43–53 °C under stirring and then concentrated *in vacuo*. Water (60 mL) was added to the residue, and the resulting aqueous suspension was extracted with ether (3 × 50 mL). The combined etheral extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. A dense, colorless oil was thereby obtained, which was subsequently identified as 1-hydroxy-4-(carbethoxymethylene)adamantane (**8**, 3 g, 88 % yield).

IR (KBr-film) ν_{max}/cm^{-1}: 3320 (s), 2980 (m), 2920 (s), 2860 (m), 1710 (s), 1650 (m), 1450 (m), 1160 (s), 1090 (s), 1035 (s), 925 (w), 875 (w). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.28 (t, J = 7.2 Hz, 3H), 1.74–1.89 (m, 10H), 2.24 (br. s, 1H), 2.27 (s, 1H), 2.6 (s, 1H), 4.14 (q, J_{H-H} = 7.2 Hz, 2H), 4.22 (br. s, 1H), 5.60 (s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.03 (q, 1C), 30.12 (d, 1C), 33.67 (d, 1C), 37.61 (t, 1C), 38.55 (t, 1C), 42.39 (d, 1C), 44.10 (t, 1C), 45.23 (t, 1C), 45.92 (t, 1C), 59.38 (t, 1C), 67.18 (s, 1C), 109.58 (d, 1C), 166.49 (s, 1C), 168.44 (s, 1C).

Anal. Calcd. for $C_{14}H_{20}O_3$ (M_r = 236.30): C 71.16, H 8.53 %; found: C 71.20, H 8.49 %.

*1-Hydroxy-4-(carbethoxymethyl)adamantane (**9**)*

5% Palladized charcoal (400 mg) was added to a solution of 1-hydroxy-4-(carbethoxymethylene)adamantane (**8**, 2.96 g, 12.5 mmol), in EtOH (100 mL) and the resulting mixture was hydrogenated (H_2, 55 psi) on a Parr-shaker apparatus for 12 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*, thereby affording product **9** (2.84 g, 83 %) as a colorless, viscous oil. GC analysis of the product (DB-210, 180 °C) revealed that it consisted of a 1:1 mixture of *syn*- and *anti*-1-hydroxy-4(carbethoxymethyl)adamantane (**9**).

IR (KBr-film) ν_{max}/cm^{-1}: 3397 (s), 2980 (m), 2915 (s), 2856 (m), 1734 (s), 1457 (m), 1158 (m), 1027 (m), 915 (m) cm^{-1}.

Anal. Calcd. for $C_{14}H_{22}O_3$ (M_r = 238.316): C 70.55, H 9.31 %; found: C 70.54, H 9.04 %.

syn-**9**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.25 (t, J_{H-H} = 7.2 Hz, 3H), 1.53 (d, J_{H-H} = 12.3 Hz, 2H), 1.68–1.76 (m, 7H), 1.82 (d, J_{H-H} = 12.3 Hz, 2H), 1.96 (br. s, 2H), 2.07–2.19 (m, 2H), 2.38 (d, J_{H-H} = 7.4 Hz, 2H), 4.10 (q, J_{H-H} = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.00 (q, 1C), 29.97 (d, 1C), 34.35 (d, 2C), 37.00 (t, 2C), 37,60 (t, 1C), 39.27 (t, 2C), 39.44 (d, 1C), 45.62 (t, 1C), 60.08 (t, 1C), 67.89 (s, 1C), 173.26 (s, 1C).

anti-**9**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.26 (t, J_{H-H} = 7.1 Hz, 3H), 1.41 (d, J_{H-H} = 12.8 Hz, 2H), 1.67–1.81 (m, 9H), 1.93 (br. s, 2H), 2.08–2.21 (m, 2H), 2.43 (d, J_{H-H} = 7.7 Hz, 2H), 4.13 (q, J_{H-H} = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.02 (q, 1C), 29.84 (t, 2C), 30.01 (d, 1C), 33.67 (d, 2C), 37.01 (t, 1C), 39.72 (d, 1C), 45.53 (t, 1C), 45.93 (t, 2C), 60.09 (t, 1C), 67.70 (s, 1C), 173.33 (s, 1C).

*1-Acetoxy-4-(carbethoxymethyl)adamantane (**10**)*

A mixture of *syn*- and *anti*-alcohol **9** (0.531 g, 2.23 mmol), acetic acid anhydride (3 mL), and 99 % acetic acid (7 mL), was stirred overnight at 110–115 °C. The reaction mixture was cooled to room temperature. Water (20 mL) was added, and the resulting aqueous suspension was extracted with ether (4 × 20 mL). The combined etheral extracts were washed sequentially with water (3 × 30 mL), 5 % aqueous NaOH (3 × 20 mL), and saturated aqueous NaCl (3 × 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. Isomers **9**, *syn*- and *anti*-1-acetoxy-4-(carbethoxymethyl)adamantane (0.6 g, 62 % yield), were thereby obtained as a colorless oil. This mixture (0.220 g) was submitted to column chromatography on silica gel by elution with 10 % ether–pentane. After chromatography, *syn*-isomer (37 mg), *anti*-isomer (30 mg) and a mixture of *syn*- and *anti*-isomers (150 mg) were obtained.

Anal. Calcd. for $C_{16}H_{24}O_4$ (M_r = 280.35): C 68.54, H 8.62 %; found: C 68.44, H 8.62 %.

IR (KBr-film) ν_{max}/cm^{-1}: 2980 (m), 2915 (s), 2860 (m), 1735 (s), 1460 (m), 1370 (s), 1245 (s), 1160 (s), 1045 (s), 1035 (s), 955 (w), 865 (w).

syn-**10**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.25 (t, J_{H-H} = 7.1 Hz, 3H), 1.55–1.83 (m, 5H), 1.85–2.28 (m, 12 H), 2.44 (d, J_{H-H} = 7.7 Hz, 2H), 4.12 (q, J_{H-H} = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.13 (q, 1C), 22.52 (q, 1C), 30.10 (d, 1C), 34.47 (d, 2C), 35.23 (t, 2C), 37.15 (t, 2C), 37.66 (t, 1C), 39.63 (d, 1C), 41.67 (t, 1C), 60.05 (d, 1C), 79.69 (s, 1C), 170.12 (s, 1C), 173.01 (s, 1C).

anti-**10**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.26 (t, J_{H-H} = 7.1 Hz, 3H), 1.49 (d, J_{H-H} = 13.2 Hz, 2H), 1.78 (d, J_{H-H} = 13.2 Hz, 2H), 1.93–2.06 (m, 5H), 2.11–2.30 (m, 8H), 2.43 (d, J_{H-H} = 7.7 Hz, 2H), 4.13 (q, J_{H-H} = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 14.14 (q, 1C), 22.57 (q, 1C), 30.03 (t, 2C), 30.15 (d, 1C), 33.79 (d, 2C), 37.03 (t, 1C), 39.80 (d, 1C) 41.50 (t, 1C), 42.05 (t, 2C), 60.16 (t, 1C), 79.47 (s, 1C), 170.19 (s, 1C), 173.03 (s, 1C).

*1-Hydroxy-4-(2-hydroxyethyl)adamantane (**11**)*

A solution of *syn*- and *anti*-1-acetoxy-4-(carbethoxymethyl)adamantane (**10**, 0.293 g, 1.045 mmol) in dry ether (25 mL) was added dropwise to a suspension of $LiAlH_4$ (0.292 g, 7.68 mmol) in dry ether (20 mL) for 30 min. The reaction mixture was refluxed for 24 h and was then allowed to cool gradually to room temperature. Excess $LiAlH_4$ was destroyed gradually by careful dropwise addition of H_2O (0.7 mL) followed by a few drops of 10 % aqueous NaOH. The ether layer was separated; the white granular precipitate was dissolved in water (75 mL), and the resulting aqueous solution was extracted with ether (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The colorless solid, 1-hydroxy-4-(2-hydroxyethyl)adamantane **11** (193 mg, 94 % yield), thus obtained consisted of a mixture of *syn*- and *anti*- isomers. This mixture was further purified by vacuum-sublimation at 65–80 °C, 1–5 Torr, and the isomers were then separated by column chromatography on silica gel by elution with ether. Starting with 193 mg of **11**, 27 mg of *syn*-**11**, 22 mg of *anti*-**11**, and 125 mg of the mixture of isomers were obtained.

HRMS for $C_{12}H_{20}O_2$: calculated [M$^+$] 196.145781, found 196.145848.

IR (KBr) ν_{max}/cm^{-1}: 3305 (s), 2920 (s) 2850 (m), 1460 (m), 1260 (s), 1100 (s), 1020 (s), 805 (s).

syn-**11**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.50 (d, J_{H-H} = 11.8 Hz, 2 H), 1.55–1.95 (m, 13 H), 2.11 (br. s, 2H), 2.37 (s, OH), 3.60–3.67 (m, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 30.39 (d, 1C),

34.47 (d, 2C), 35.40 (t, 1C), 37.29 (t, 2C), 39.07 (d, 1C), 39.46 (t, 2C), 45.79 (t, 1C), 61.10 (t, 1C), 68.01 (s, 1C).

anti-**11**: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.38 (d, J_{H-H} = 12.6 Hz, 2H), 1.73–1.97 (m, 15 H), 2.07–2.16 (br. s, 1H), 3.67 (t, J_{H-H} = 6.46 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.98 (t, 2C), 30.80 (d, 1C), 33,76 (d, 2C), 34.71 (t, 1C), 39.23 (d, 1C), 45.63 (t, 1C), 46.13 (t, 2C), 61.30 (t, 1C), 68.17 (s, 1C).

*1-Hydroxy-4-cyanoadamantane (**12**)*

Potassium *t*-butoxide (2.16 g, 19.28 mmol) was added in small portions to a well stirred, moisture-protected suspension of hydroxyketone **1** (1.00 g, 6.02 mmol), tosylmethylisocyanide (TosMIC, 1.45 g, 7.4 mmol) and EtOH (0.6 mL) in dimethoxyethane (35 mL). The reaction mixture was maintained at 5–10 °C through the application of an external ice-water bath. After the addition of reagents was completed, the mixture was heated under stirring for 1 h at 35–40 °C and was then allowed to cool gradually to room temperature. The reaction mixture was then filtered *in vacuo* through a sintered glass funnel, and the residue was washed with ether (30 mL). The filtrate was concentrated to a small volume (2–3 mL), which resulted in formation of a precipitate. The precipitate was isolated by filtration and was dried *in vacuo*. GC analysis (DB-210, 150 °C/6'→220 °C) of the product thus obtained (**12**, 1.05 g, 98 %) indicated that it consisted of a 1.1:1 mixture of the corresponding *syn*- and *anti*-isomers. The mixture of *syn*- and *anti*-**12** (0.71 g) was separated by column chromatography on silica gel by elution with ether. This procedure afforded 143 mg of *syn*-**12**, 250 mg of a mixture of isomers **12**, and 110 mg of *anti*-**12**.

Anal. Calcd. for $C_{11}H_{15}NO$ (M_r = 177.24): C 74.54, H 8.53, N 7.90 %; found: C 74.48, H 8.55, N 8.00 %.

syn-**12**: m.p. 116–120 °C. IR (KBr) ν_{max}/cm^{-1}: 3270 (s), 2920 (s), 2850 (m), 2230 (m), 1450 (m), 1355 (m), 1120 (m), 1110 (s), 1080 (m), 1010 (m), 920 (m). ^{1}H NMR ($CDCl_3$) δ/pmm: 1.58–2.00 (m, 9H), 2.05–2.25 (m, 3H), 2.43 (br. s 2H), 2.78 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 28.84 (d, 1C), 32.84 (d, 2C), 34.81 (t, 2C), 35.29 (d, 1C), 40.72 (t, 2C) 43.91 (t, 1C), 66.61 (s, 1C), 121.36 (s, 1C).

anti-**12**: m.p. 113–117 °C. IR (KBr) ν_{max}/cm^{-1}: 3280 (s), 2920 (s), 2850 (m), 2230 (m), 1450 (m), 1355 (m), 1120 (s), 1100 (s), 1075 (s), 975 (m), 925 (m). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.55–2.15 (m, 11H), 2.22 (br. s, 1H), 2.40 (br. s, 2H), 2.81 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.12 (d, 1C), 31.43 (t, 2C), 32.60 (d, 2C), 35.56 (d, 1C), 43.76 (t, 2C), 44.30 (t, 1C), 66.43 (s, 1C), 121.53 (s, 1C).

*1-Hydroxy-4-carboxyadamantane (**13**)*

A mixture of hydroxynitrile **12** (245 mg, 1.38 mmol) and 50 % aqueous H_2SO_4 (5 mL) was stirred overnight under heating at 90–100 °C. After cooling, water (10 mL) was added, and the resulting aqueous suspension was extracted with ether (4 x 15 mL). The combined etheral extracts were washed with brine (10 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. Pure acid **13** (167 mg, 62 %) was thereby obtained as a colorless solid. This material consisted of two isomers, which could be separated by fractional crystallization from 10 % ether/CH_2Cl_2.

13: IR (KBr) ν_{max}/cm^{-1}: 3350 (s), 2920 (s), 2850 (m), 1700 (s), 1450 (m), 1100 (m), 1070 (m), 925 (m). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.49–2.00 (m, 24 H), 2.05–2.20 (m, 2H), 2.45–2.65 (m, 4H), 6.68 (br. s, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.52 (d), 29.60 (d), 31.51 (d), 31.68 (t), 31.86 (d), 36.20 (t), 41.13 (t), 44.41 (t), 44.64 (t), 44.98 (t), 47.70 (d), 48.07 (d), 67.72 (s), 67.84 (s), 178.22 (s), 178.55 (s).

*1-Hydroxy-4-(carbmethoxy)adamantane (**14**)*

Conc. H_2SO_4 (0.1 mL) was added to a solution of acid **13** (220 mg, 1.13 mmol) in MeOH (15 mL), and the resulting mixture was refluxed under stirring overnight. After cooling, the reaction mixture was evaporated to dryness to afford a crude mixture of *syn*- and *anti*-esters **14** (155 mg, 67 %) as a dense oil. Separation by column chromatography on silica gel using 0→100 % CH_2Cl_2–EtOAc gradient elution scheme afforded 35 mg of *anti*-**14** and 105 mg of the mixture of isomers enriched on *syn*-**14**.

HRMS for $C_{12}H_{18}O_3$: calculated [M$^+$] 210.125594, found 210.125485.

syn-isomer: ^{1}H NMR ($CDCl_3$) δ/ppm: 1.57–2.20 (m, 13H), 2.58 (br. s, 2H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.71 (d, 1C), 31.98 (d, 2C), 36.24 (t, 2C), 41.33 (t, 2C), 44.68 (t, 1C), 47.88 (d, 1C), 51.36 (q, 1C), 67.46 (s, 1C), 174.35 (s, 1C).

anti-isomer: m.p. 105–107 °C. IR (KBr) ν_{max}/cm^{-1}: 3270 (s), 2920 (s), 2850 (m), 1735 (s), 1330 (m), 1210 (s), 1110 (m), 1100 (s), 1080 (m). ^{1}H NMR ($CDCl_3$) δ/ppm: 1.40–1.90 (m, 11H), 2.12 (br. s, 1H), 2.55 (br. s, 3H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 29.58 (d, 1C), 31.64 (d, 2C), 31.91 (t, 2C), 44.90 (t, 1C), 45.18 (t, 2C), 48.22 (d, 1C), 51.36 (q, 1C), 67.58 (s, 1C), 174.30 (s, 1C).

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SAŽETAK

Novi adamantanski 1,4-disupstituirani stereoizomeri: priprava i spektroskopska karakterizacija

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Pripravljen je niz novih 1,4-disupstituiranih derivata adamantana [npr. 1-klor-4-(karbetoksimetilen)adamantan (**3**), 1-klor-4-(karbetoksimetil)adamantan (**4**), 1-klor-4-(2-hidroksietil)adamantan (**5**), 1-klor-4-(2-brometil)adamantan (**6**), 1-brom-4-(2-brometil)adamantan (**7**), 1-hidroksi-4-(karbetoksimetilen)adamantan (**8**), 1-hidroksi-4-(karbetoksimetil)adamantan (**9**), 1-acetoksi-4-(karbetoksimetil)adamantan (**10**), 1-hidroksi-4-(2-hidroksietil)-adamantan (**11**), 1-hidroksi-4-cijanoadamantan (**12**), 1-hidroksi-4-karboksiadamantan (**13**) i 1-hidroksi-4-karbmetoksiadamantan (**14**)], odvojeni su *syn*- i *anti*-izomeri, a njihove strukture su potvrđene spektroskopskim metodama.