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Rigid C_3-Symmetric Scaffolds Based on Adamantane

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Efficient syntheses of rigid C_3-symmetric scaffolds based on adamantane are described. The scaffolds are available in multigram quantities and have been designed for conjugation to various natural products such as carbohydrates and peptides. They are thus valuable for the construction of strictly defined molecular architectures with threefold geometry for applications in bioorganic chemistry, catalysis or material science.

Introduction

Threefold rotational symmetry plays an important role in various artificial and natural molecular recognition systems.[1] In consequence, a number of applications of C_3-symmetric molecules to diverse areas such as catalysis, supramolecular chemistry, material science and receptor-ligand interactions are known and have been highlighted recently.[2] Examples include catalysts of C_3-symmetry, which have been shown to be efficient for stereoselective synthesis,[3] artificial C_3-symmetric receptors for specific binding to small molecules or ions,[4] scaffolds for the assembly of materials with liquid crystalline properties,[5] scaffolds for the assembly of nanostructures[6] and trivalent interactions of ligands with natural receptors.[7]

The relevance of C_3-symmetry in biological systems is obvious in several cases were either binding sides of enzymes have a pseudo C_3-symmetric geometry like the (tris)-histidine motifs in certain zinc-dependent transesterases[8] or in many cases where binding of a given receptor to its natural substrate occurs with trimerisation leading to a receptor–ligand complex with threefold geometry.[9] In some cases these oligomerisation processes are important for proper signaling of transmembrane receptors and interaction with trivalent C_3-symmetric ligands can be used to modulate these natural properties.[7] In addition, a tripodal geometry can be extremely powerful for the recognition of binding motifs on cell surfaces as Whitesides' work on trimeric derivatives of Vancomycin[10] and our own work on cancer cell targeting revealed.[11]

Designed for numerous applications, many different C_3-symmetric scaffolds have been reported so far and a small collection is depicted in Figure 1. The shape of the scaffolds varies significantly from flexible tripodal molecules like **5**[12] to relatively rigid cyclohexane derivatives **1**[13] (derived from Kemps' triacid) or **2**[14,5] and absolutely rigid and planar aromatic structures like **4**.[15] Cyclic α- and β-peptides like **6**[16] have been used for biochemical applications.

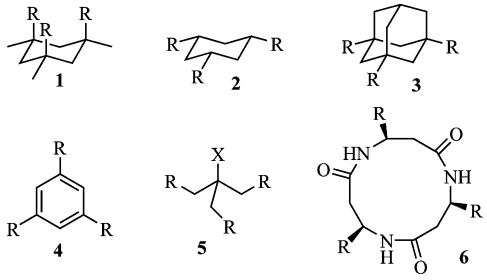

Figure 1. A selection of common C_3-symmetric scaffolds **1**–**6** and adamantane-based system **3**.

Adamantane-based scaffolds **3** share the tripodal arrangement of R groups with cyclohexane cores like **2**, but are more rigid and most importantly permit introduction of additional functionality into the fourth bridgehead position without disturbing the geometry of the molecule or interfere with binding processes at the R groups.[17] Although some adamantane-based C_3-symmetric scaffolds **3** are known, they have rarely been used as scaffolds for the assembly of functional molecules with threefold geometry.[18] This is probably due to a lack of proper functional groups in known scaffolds **3** or their difficult chemical synthesis. In this paper we summarize scalable and short syntheses to scaffolds **3** with suitable anchor groups for the conjugation of functional molecules, in particular biomolecules.

Results and Discussion

The conjugation of biomolecules like amino acids, peptides or sugars to adamantane scaffolds requires suitable functional groups attached to three bridgehead positions

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of the adamantane core. These functional groups include amines, carboxylic acids and alcohols. Furthermore, alkynes and azides are useful for conjugation via click-chemistry.[19] These functional groups can be attached directly to the adamantane core or spaced with rigid or flexible linkers to achieve the optimal geometry and spacing for a particular application (Figure 2).

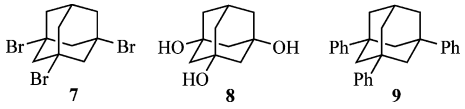
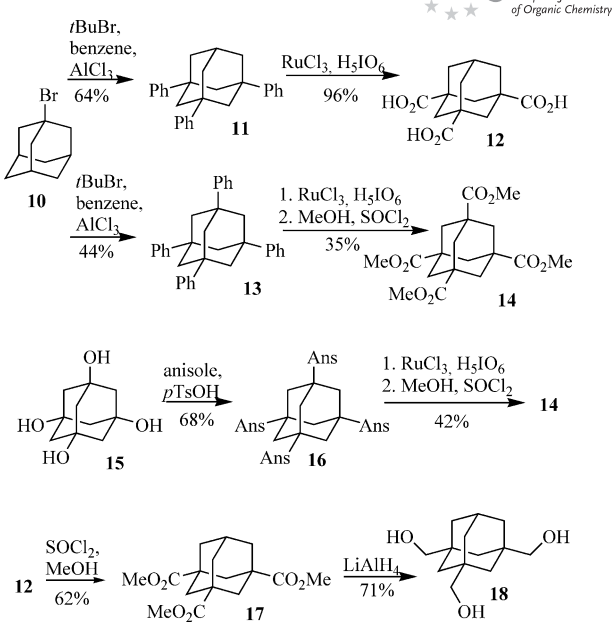


Figure 2. Readily available trisubstituted adamantane derivatives **7**–**9**.

Introduction of functionality at the adamantane bridgehead positions requires C–H bond activation. Different procedures are known to perform these transformations the most popular of which are halogenation, hydroxylation, carboxylation, radical alkylation and arylations with Friedel–Crafts-type chemistry.[20] The unique structure of adamantane leads to a significant degree of selectivity in these reactions for radical *and* cationic intermediates. Selectivity is therefore often not a problem and protocols, for example, for the selective introduction of one, two, three or four bromine atoms at the adamantane bridgeheads are well known and give all four different adamantyl bromides in good yields.[21] However, as a general trend, substitutions get more difficult with the number of electron-withdrawing substituents attached to the bridgehead positions due to statistical and electronic effects.[22] Consequently, methods for the generation of tri- or tetrasubstituted adamantanes are often not compatible with functional groups, such as amines, alcohols, carboxylic acids or alkynes.[23]

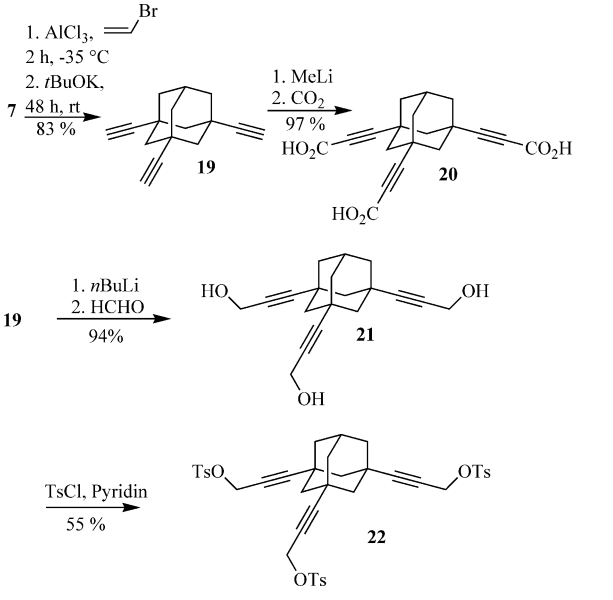


Scheme 1. Oxidative degradation of aryladamantanes to the corresponding carboxylic acids. Ans: 2- or 4-anisyl. Compound **16** was obtained as a mixture of 2- and 4-anisyl derivatives.

Rigid Trifunctional Adamantane Derivatives

The direct attachment of three hydroxy or amino groups to the bridgehead positions of adamantane leads to known compounds and especially 1,3,5-trihydroxyadamantane (**8**) is readily available by Stetter's[24] practical synthesis. In contrast, adamantane-1,3,5-tricarboxylic acid (**12**) is only known from the patent literature and no practical synthesis has been described so far.[25] We found triphenyladamantane (**11**) to be a suitable precursor for **12**. Arylation of commercially available bromoadamantane (**10**) is a known procedure leading to phenyladamantanes **11** and **13** (Scheme 1).[26] Depending on the reaction conditions either tetra-, tri- or diphenyladamantane can be obtained selectively. The following oxidation[27] proceeds smoothly with **11** to give triacid **12** in excellent yield as depicted in Scheme 1. This triacid can be converted into the corresponding triol **18** by reduction of the intermediate ester **17**.

Given the easy synthesis of tricarboxylic acid **12**, oxidation with $RuCl_3$ might also be a good alternative for large-scale synthesis of adamantane-tetracarboxylic acid, a well known and valuable tetrahedral building block.[28] However, the oxidation of tetraphenyladamantane **13** was slow (most likely due to its low solubility) and gave only low yields of the adamantane-tetracarboxylate **14** after oxidation and following esterification. An exchange of phenyl groups for more electron-rich anisyl groups brought better results in this series. The 1,3,5,7-tetraanisyladamantane (**16**) can be synthesized from 1,3,5,7-tetrahydroxyadamantane (**15**) according to a protocol of Stetter[29] and is a reasonable substrate for oxidative degradation with $RuCl_3$ as indicated in Scheme 1.

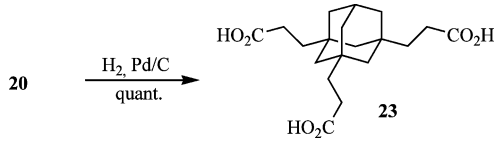


Scheme 2. Synthesis of expanded rigid adamantane scaffolds **20**, **21** and **22**.

An interesting scaffold for chemoselective conjugation of unprotected biomolecules via click-chemistry is 1,3,5-triethynyladamantane (**19**). This compound has not yet found applications in biological studies, but has been used to construct rigid tripodal molecules in material science.[30] Trialkyne **19** is readily available from tribromoadamantane[31] following a protocol from Malik.[32] Trialkyne **19** is also an excellent precursor for rigid expanded analogs of tricarboxylic acid **12**. Deprotonation of **19** with MeLi and subsequent quenching with CO_2 gives the tricarboxylic acid **20** in very good yields. Again, various functional groups can be introduced into these types of scaffolds as depicted in Scheme 2. The trimeric propargyl alcohol **21**, for example, was synthesized from trialkyne **19** via deprotonation and subsequent addition to formaldehyde in high yield. Using the trialcohol **21** as a starting material, tosylate **22** can be generated, which might be substituted with a range of different nucleophiles to give other valuable scaffolds for conjugation of functional molecules.

Semi-rigid Trifunctional Adamantane Derivatives

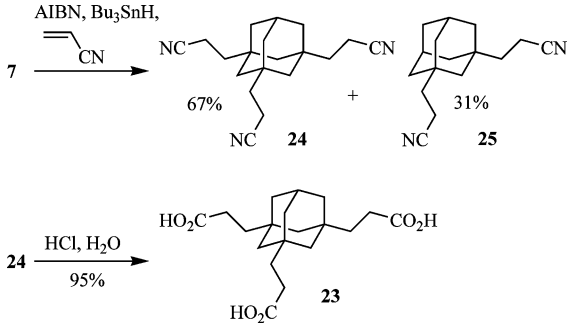
To optimize the rigidity and spacing of a given scaffold for a particular application it is necessary to introduce different spacers between the adamantane core and the anchor groups. The rigid alkyne linkage in tricarboxylic acid **20**, for example, can be converted quantitatively by hydrogenation into a more flexible alkyl spacer in **23**[17] (Scheme 3).



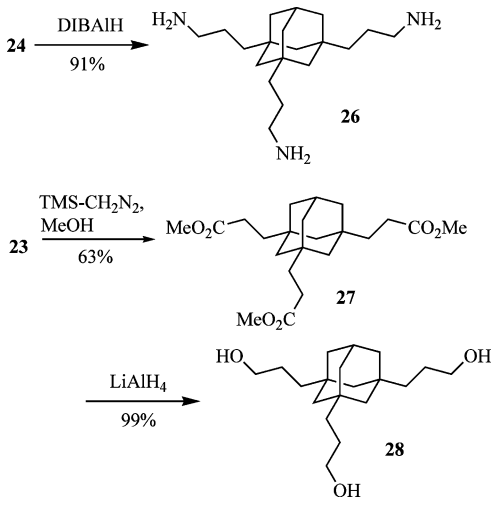
Scheme 3. Synthesis of semi-rigid adamantane-tricarboxylic acid.

A shorter and more practical approach to semi-rigid scaffolds like **23** again starts from tribromoadamantane. However, it relies not on the cationic Friedel–Crafts-type chemistry depicted in Scheme 2 but uses radical chemistry to introduce the spacer and a functional group (in this case a cyano group) in one step.[23b] This reaction was reported to give trisubstituted adamantane **24** in low yield (20%) along with a large portion of the disubstituted analog **25**. However, with a slight change in reaction and workup conditions we managed to prepare **24** in good yield (67%) along with some disubstituted byproduct **25** (31%). Compound **24** crystallizes from hexane and can therefore be prepared in large quantities. Hydrolysis of the cyanide **24** gives the tricarboxylic acid **23** in excellent yield.

The radical approach outlined in Scheme 4 opens an access to different functionalized adamantanes. The cyanide **24** can, for example, be reduced to give triamine **26** and the carboxylic acid **23** is a suitable starting material for the alcohol **28**, which is synthesized by esterification of carboxylic acid **23** to the corresponding methyl ester **27** and its subsequent reduction with $LiAlH_4$ as depicted in Scheme 5.



Scheme 4. Optimized synthesis of semi-rigid adamantane-tricarboxylic acid.



Scheme 5. Syntheses of the semi-rigid adamantane-triamine **26** and -triol **28**.

Geometry of the Scaffolds

A MM2-minimized structure of triamine **26** is shown in Figure 3 in top view, highlighting the threefold geometry of the system in an extended conformation. The figure includes the distance ***a*** between the anchor groups (identical with the distances of hypothetical ligands conjugated to **26**) and the radius r_u of the outer circle of the molecule, charac-

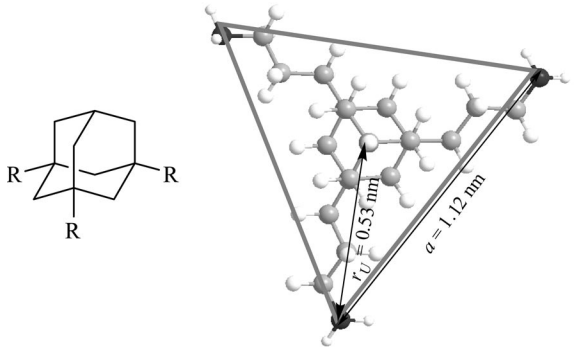


Figure 3. The general scaffold of adamantane derivatives **12**–**28** with different substituents R is shown next to the structure of triamine **26**. The distance ***a*** between two anchor groups (amines for **26**) and the radius r_U for the outer circle is given.

terizing the distance of any (hypothetical) conjugated ligand to the middle of the system. Table 1 summarizes these geometric data for all of the scaffolds reported in this paper.

Table 1. Distances ***a*** between anchor groups and radius r_U for the outer circle of each scaffold **12**–**28** (see Figure 3).

Compound	R	*a* [nm][a]	r_U [nm][a]
19	C≡CH	0.69	0.4
20	C≡CCO_2H	0.97	0.56
21	C≡CCH_2OH	1.06	0.61
8	OH	0.48	0.28
12	CO_2H	0.50	0.29
18	CH_2OH	0.66	0.38
23	$(CH_2)_2CO_2H$	0.92	0.53
26	$(CH_2)_3NH_2$	1.13	0.65
28	$(CH_2)_3$OH	1.12	0.65
ada	H	0.25	0.14

[a] The distances are given for energy-minimized (MM2) structures. They were measured from the last atom of a given anchor group, that remains an integral part of the structure after conjugation to other molecules. Note that in carboxylic acids like **23**, this atom is the carboxy carbon atom.

From the data in Table 1 it is clear that adamantane-based scaffolds can be used as an architectural element to define distances between almost any conjugated ligand in the range of ca. 0.5 to 1.1 nm in a defined threefold geometry. Distances of this order are useful to probe binding properties of ligands to multimeric receptors in bioorganic chemistry.[7] In this context, it is interesting to note that several pharmaceutically important receptors resemble a threefold geometry.[33]

Conclusions

In this paper we provide suitable synthetic strategies to rigid and semi-rigid scaffolds based on adamantane. Appropriate functionalities have been introduced as anchor groups for conjugation of the scaffolds to a wide range of different functional molecules. Compounds of type **3** can thus be used as C_3-symmetric scaffolds for the assembly of more complex molecular architectures and the rigidity of the systems can be tuned with the choice of the scaffold. Rigid derivatives like **20** provide a strictly defined threefold geometry of anchor groups and are thus valuable as molecular rulers in three dimensions. The spacing of anchor groups between 0.5 and 1.1 nm is in a useful range for bioorganic or biomedical applications and might also be useful for applications in catalysis and material science. It should be noted, that the remaining bridgehead position in adamantyl scaffolds of type **3** allows further derivatisation without disturbing the threefold geometry of the scaffold.

Experimental Section

General: NMR spectra were recorded on a Bruker AMX 400 spectrometer (400 MHz/100.6 MHz). Chemical shifts, δ values, are represented in parts per million (ppm) and coupling constants, *J*, in Hertz (Hz) from tetramethylsilane (TMS, 0 ppm) as the internal standard for $CDCl_3$ and residual solvent peaks for [D_6]DMSO and D_2O. Mass spectra were obtained with a Varian MS MAT 311A in EI mode. The following starting materials were synthesized according to literature procedures: 1,3,5-triphenyladamantane (**11**),[25] tetraphenyladamantane (**13**),[25] tribromoadamantane (**7**),[29] tetrahydroxy-adamantane (**15**).[34]

Adamantane-1,3,5-tricarboxylic Acid (12):[25] 1.00 g of **11** (2.74 mmol) and 26.26 g of H_5IO_6 (115.2 mmol) were dissolved in 70 mL of $CCl_4/CH_3CN/H_2O$ (2:2:3) and the reaction mixture was cooled to 0 °C. 140 mg of $RuCl_3 \cdot 3H_2O$ (0.5 mmol) were added and the mixture was stirred for 2 h at 0 °C and 12 h at room temperature. The resulting suspension was poured on a mixture of ice/aqueous HCl and excess oxidant was destroyed by addition of Na_2SO_3. The aqueous phase was extracted three times with ethyl acetate, the combined organic phases were dried with Na_2SO_4, filtered and the solvent was evaporated to give 0.71 g (2.65 mmol, 96%) of the triacid **12** as a colorless solid, m.p. 205 °C. IR (KBr): $\tilde{\nu}$ = 3496, 2945, 2867, 1708, 1456, 1412, 1310, 1278, 1227, 692 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 12.26 (s, 3 H), 2.15–2.18 (m, 1 H), 1.86 (d, ^2J = 12.3 Hz, 3 H), 1.76 (d, ^2J = 12.3 Hz, 3 H), 1.70 (d, ^3J = 2.0 Hz, 6 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 172.3, 39.8, 35.6, 34.0, 28.1 ppm. HR-MS (EI): calcd. ($C_{13}H_{16}O_6$) 268.0947, found 268.0948. $C_{13}H_{16}O_6$ (268.27): calcd. C 58.20, H 6.01; found C 57.99, H 6.09.

Tetramethyl Adamantane-1,3,5,7-tetracarboxylate (14) from 13:[28] To a mixture of 1.00 g (2.26 mmol) 1,3,5,7-tetraphenyladamantane (**13**) and 70 mL of $CH_3CN/CCl_4/H_2O$ (2:2:3), 28.14 g (124.2 mmol) H_5IO_6 und 60 mg of $RuCl_3 \cdot 3\ H_2O$ were added. The reaction mixture was vigorously stirred at room temperature for 7 d. In the meantime, two portions of 30 mg of $RuCl_3 \cdot 3H_2O$ were added. The solvent was evaporated in vacuo and the crude product was dissolved in hot CH_3CN and filtered while hot (to separate most of inorganic salts) and the residue was washed with hot CH_3CN again. After evaporation, the resulting product was used in the next step without further purification.

To a suspension of the resulting crude carboxylic acid in 40 mL of dry MeOH was added 5 mL of freshly distilled $SOCl_2$ at 0 °C. After 24 h at reflux temperature, the solvent was evaporated in vacuo. The crude product was dissolved in 100 mL ethyl acetate, washed three times with saturated aqueous Na_2SO_3 solution and three times with water, dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo. The resulting product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 4:1). 292 mg (0.79 mmol; 35%) of colorless crystals was isolated; R_f = 0.45 (petroleum ether/ethyl acetate, 4:1), m.p. 168 °C. IR (KBr): $\tilde{\nu}$ = 3437, 2955, 2915, 2866, 1722, 1430, 1307, 1255, 1205, 1123, 1042, 971, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.69 (s, 12 H), 1.99 (s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 52.3, 42.0, 38.7 ppm. HR-MS (EI): calcd. for $C_{18}H_{24}O_8$ 368.1471, found 368.1470.

1,3,5,7-Tetrakis(4-methoxyphenyl)adamantane (16):[29] A mixture of 1,3,5,7-tetrahydroxyadamantane (4.51 g, 22.5 mmol), *p*-toluenesulfonic acid monohydrate (2.14 g, 11.3 mmol) and anisole (100 mL) was heated for 40 h with a Dean–Stark apparatus. Then the solvent was evaporated in vacuo and the crude product was dissolved in CH_2Cl_2. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$, 2 N HCl and water, dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo. The resulting product was filtered through silica (3 cm) and the filter cake was rinsed with CH_2Cl_2. Evaporation of the solvent in vacuo gave 8.55 g of **16** as a mixture of *o*-/*p*-substituted derivatives (15.2 mmol; 68%) and used without further purification in the next step; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.27 (m, 8 H), 6.80–6.87 (m, 7 H), 3.65, 3.72, 3.73 (3 s, 12 H), 2.01–2.48 (m, 12 H) ppm.

Tetramethyl Adamantane-1,3,5,7-tetracarboxylate (14) from 16: A solution of **16** (4.49 g, 8.0 mmol) and H_5IO_6 (102.2 g, 448.4 mmol) in 350 mL $CH_3CN/CCl_4/H_2O$ (2:2:3) was cooled to 0 °C and 419 mg of $RuCl_3 \cdot 3H_2O$ were added. The resulting mixture was stirred for 2 h at 0 °C and 16 h at room temperature. The layers were separated and the solvent of the aqueous solution was evaporated in vacuo. The crude product was dissolved in hot CH_3CN and filtered while hot (to separate most of inorganic salts) and the residue was washed with hot CH_3CN again. After evaporation of the solvent in vacuo, the resulting product was used in the next step without further purification.

To a suspension of the resulting crude carboxylic acid in 100 mL dry MeOH was added 7 mL of freshly distilled $SOCl_2$ at 0 °C. After 24 h at reflux temperature, the solvent was removed in vacuo. The crude product was dissolved in ethyl acetate, washed three times with saturated aqueous Na_2SO_3 solution and three times with water, dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo. The resulting product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 4:1). 1.24 g (3.4 mmol; 42%) of colorless crystals was isolated.

Trimethyl Adamantane-1,3,5-tricarboxylate (17): 2.31 g of **12** (8.6 mmol) were dissolved in 6 mL thionyl chloride and heated to reflux for 4 h. The solvent was evaporated and the residue was suspended in 30 mL dry methanol. The resulting mixture was heated to reflux for 3 h and the solvent was evaporated in vacuo. The crude product was dissolved in 0.5 M NaOH and extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo to give 1.65 g (5.3 mmol; 62%) of the methyl ester **17** as a colorless oil. IR (film): $\tilde{\nu}$ = 2957, 2916, 2863, 1729, 1454, 1434, 1258, 1218, 1109, 1040, 803 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 9 H), 2.29 (sept, ^3J = 3.0 Hz, 1 H), 2.03 (d, ^2J = 12.6 Hz, 3 H), 1.98 (d, ^2J = 12.6 Hz, 3 H), 1.84 (d, ^3J = 3.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 52.1, 41.5, 39.3, 37.2, 28.1 ppm. HR-MS (EI): calcd. for $C_{16}H_{22}O_6$ 310.1416, found 310.1414.

1,3,5-Tris(hydroxymethyl)adamantane (18): A solution of **17** (1.63 g, 5.3 mmol) in 50 mL dry THF was cooled to 0 °C and $LiAlH_4$ (0.70 g, 18.4 mmol) was added. The reaction mixture was heated to reflux for 2 h and the resulting solution was poured on ice/HCl. The aqueous phase was extracted three times with ethyl acetate, the combined organic phases were washed with 1 M NaOH and water, dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo to give 0.84 g (3.7 mmol; 71%) of pure **18** as a colorless oil. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 4.30 (br. s, 3 H), 3.01 (s, 6 H), 2.05 (sept, ^3J = 2.9 Hz, 1 H), 1.29 (d, ^3J = 2.9 Hz, 6 H), 1.13 (d, ^3J = 11.7 Hz, 3 H), 1.04 (d, ^3J = 11.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 71.6, 40.8, 38.6, 35.2, 28.1 ppm. HR-MS (EI): calcd. for $C_{13}H_{22}O_3$ 226.1569, found 226.1570.

1,3,5-Tris(3-hydroxy-1-propynyl)adamantane (21): A solution of 1,3,5-triethynyladamantane (**19**) (1.00 g, 4.8 mmol) in 15 mL dry THF were cooled to 0 °C and 5.8 mL 2.5 M *n*BuLi solution (in hexane) was added dropwise. Paraformaldehyde (0.43 g, 14.4 mmol) was added in portions (over 30 min) at 0 °C. The resulting reaction mixture was heated at reflux for 4 h. The mixture was poured on ice and the aqueous phase was extracted three times with ethyl acetate. The resulting organic phases were washed with saturated aqueous NH_4Cl solution and water, dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo to give the crude product which was crystallized from petroleum ether/ethyl acetate to give 1.34 g (4.5 mmol; 94%) of the alcohol **21** as a colorless solid, m.p. 163 °C. IR (KBr): $\tilde{\nu}$ = 3289, 2928, 2905, 2859, 2236, 1451, 1357, 1229, 1156, 1021, 960, 645 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 5.06 (t, ^3J = 5.8 Hz, 3 H), 4.02 (d, ^3J = 5.8 Hz, 6 H), 2.03 (br. s, 1 H), 1.78 (br. s, 6 H), 1.68 (br. s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 89.8, 80.1, 49.0, 46.3, 40.0, 29.6, 27.5 ppm. $C_{19}H_{22}O_3$ (298.38): calcd. C 76.48, H 7.43; found C 76.39, H 7.40.

1,3,5-Tris(3-tosyloxy-1-propynyl)adamantane (22): A solution of alcohol **21** (100 mg, 0.34 mmol) and tosyl chloride (230 mg, 1.2 mmol) in 20 mL dry THF was cooled to 0 °C and KOH powder (282 mg, 5.03 mmol) was added in portions. The reaction mixture was stirred at 0 °C for 6 h and additional 6 h at room temp. The resulting mixture was poured on ice and the aqueous layer was extracted three times with dichloromethane. The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 7:3) to give 140 mg of **22** (0.18 mmol; 55%) as a colorless sticky foam. IR (film): $\tilde{\nu}$ = 2934, 2859, 2244, 1598, 1451, 1368, 1176, 940, 816, 761, 665, 584, 555 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, ^3J = 8.2 Hz, 6 H), 7.35 (d, ^3J = 8.2 Hz, 6 H), 4.70 (s, 6 H), 2.45 (s, 9 H), 1.97 (sept, ^3J = 2.9 Hz, 1 H), 1.42–1.49 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 133.6, 130.0, 128.3, 94.8, 72.5, 58.5, 45.2, 39.9, 29.8, 27.6, 21.8 ppm. HR-MS (EI): calcd. ($C_{40}H_{40}O_9S_3$) 760.1834, found 760.1832.

1,3,5-Tris(2-cyanoethyl)adamantane (24):[23b] A solution of 1,3,5-tribromoadamantane (30.00 g, 80.5 mmol), acrylonitrile (42.4 mL, 644 mmol), tributylstannane (86.6 mL, 322 mmol) and AIBN (2.6 g, 16 mmol) in 200 mL toluene was heated to reflux in a 2-L flask for 3 h. The resulting reaction mixture was washed with 0.5 M ammonia and water. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo. The crude product was filtered through silica gel. Byproducts were eluted with 5% ethyl acetate in petroleum ether, the disubstituted product **25** (6.10 g, 25.2 mmol; 31%) was eluted with 10% ethyl acetate in petroleum ether and the trisubstituted product **24** (15.91 g, 58.8 mmol; 67%) was eluted with 50% ethyl acetate in petroleum ether. **24**: m.p. 118 °C. IR (KBr): $\tilde{\nu}$ = 3439, 2916, 2850, 2245, 1453, 1367 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (t, ^3J = 7.9 Hz, 6 H), 2.21 (sept, ^3J = 3.1 Hz, 1 H), 1.56 (t, ^3J = 7.9 Hz, 6 H), 1.39 (d, ^3J = 3.0 Hz, 6 H), 1.23 (d, ^2J = 11.9 Hz, 3 H), 1.13 (d, ^2J = 11.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.4, 45.5, 42.0, 40.1, 33.7, 28.7, 11.3 ppm. HR-MS (EI): calcd. ($C_{19}H_{25}N_3$) 295.2048, found 295.2087. $C_{19}H_{25}N_3$ (295.43): calcd. C 77.25, H 8.53; found C 77.08, H 8.55.

1,3,5-Tris(2-carboxyethyl)adamantane (23): A solution of **24** (7.0 g, 24 mmol), 40 mL concentrated HCl and 5 mL water was heated to reflux for 20 h. The resulting mixture was poured on ice water; the product was filtered off, washed with cold water and crystallized from MeCN. 8.0 g (23 mmol; 95%) of the title compound was isolated as a colorless solid, m.p. 108 °C, ^1H NMR (400 MHz, D_2O): δ = 1.93–1.97 (m, 6 H), 1.68–1.71 (m, 1 H), 1.18–1.22 (m, 6 H), 1.14 (d, ^3J = 2.1 Hz, 6 H), 0.98 (d, ^2J = 11.8 Hz, 3 H) 0.90 (d, ^2J = 11.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 185.4, 46.1, 40.9, 40.3, 33.4, 32.0, 29.5 ppm. MS (EI): calcd. for $C_{19}H_{28}O_6$ [MH$^+$] = 353.19, found 353.20. $C_{19}H_{28}O_6$ (352.43): calcd. C 64.75, H 8.01; found C 64.63, H 7.97.

1,3,5-Tris(3-aminopropyl)adamantane (26): 3.34 g of **24** was dissolved in 400 mL dry THF and the resulting solution was cooled to 0 °C. 226 mL of a 1 M DIBAlH solution in hexane was added dropwise to the reaction mixture at 0 °C. After heating to reflux for 22 h, 90 mL methanol were added dropwise. The resulting solids were filtered and the solvent was evaporated to give 3.16 g

(10.3 mmol; 91%) of the amine **26** as a colorless oil. IR (film): $\tilde{\nu}$ = 3283, 2923, 2844, 1579, 1451, 1386, 1317, 818 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 2.35 (t, ^3J = 7.0 Hz, 6 H), 1.91 (br. s, 1 H), 1.13–1.23 (m, 12 H), 0.92–1.02 (m, 12 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 46.8, 42.9, 41.4, 41.0, 33.0, 29.0, 26.8 ppm. HR-MS (ESI): calcd. (MH^+: $C_{19}H_{38}N_3$) 308.3057, found 308.3060.

1,3,5-Tris[2-(methoxycarbonyl)ethyl]adamantane (27): 6.5 mL (13.0 mmol) of a 2 M solution of (trimethylsilyl)diazomethane in diethyl ether was added dropwise, at room temperature, to a solution of 1.00 g (2.8 mmol) of **23** in 20 mL of toluene/methanol (1:3). The resulting suspension was stirred for 40 h at room temperature and 0.5 mL acetic acid was added. The solvent was evaporated in vacuo and the residue was dissolved in 100 mL of 1 M aqueous NaOH. The resulting suspension was extracted three times with 100 mL of dichloromethane. The combined extracts were dried with Na_2SO_4, filtered and the solvent was removed in vacuo to give 0.70 g (1.8 mmol; 63%) of pure triester **27** as an oil. IR (film): $\tilde{\nu}$ = 2911, 2845, 1739, 1452, 1436, 1310, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 9 H), 2.24 (t, ^3J = 8.3 Hz, 6 H), 2.09 (sept, ^3J = 2.9 Hz, 1 H), 1.13 (d, ^2J = 11.9 Hz, 3 H), 1.04 (d, ^2J = 11.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 51.7, 46.2, 40.9, 38.4, 33.4, 29.2, 28.2 ppm. HR-MS (EI): calcd. ($C_{22}H_{34}O_6$) 394.2355, found 394.2356.

1,3,5-Tris(3-hydroxypropyl)adamantane (28): A solution of **27** (0.67 g, 1.70 mmol) in 15 mL dry THF was cooled to 0 °C and $LiAlH_4$ (0.58 g, 15.3 mmol) were added. The reaction mixture was heated to reflux for 4 h and the resulting solution was poured on ice/HCl. The aqueous phase was extracted three times with ethyl acetate, the combined organic phases was washed with 1 M NaOH and water, dried with Na_2SO_4, filtered and the solvent was evaporated in vacuo to give 0.52 g (1.67 mmol; 99%) of pure **28** as a colorless oil. IR (film): $\tilde{\nu}$ = 3289, 2920, 2840, 1449, 1055, 1011 cm^{-1}. ^1H NMR (400 MHz, [D$_4$]MeOH): δ = 3.35 (t, ^3J = 6.8 Hz, 6 H), 2.07 (sept, ^3J = 2.8 Hz, 1 H), 1.45–1.53 (m, 6 H), 1.38 (d, ^3J = 2.8 Hz, 6 H), 1.11–1.22 (m, 12 H) ppm. ^{13}C NMR (100 MHz, [D$_4$]-MeOH): δ = 64.0, 48.3, 42.7, 41.2, 34.4, 31.1, 26.9 ppm. HR-MS (EI): calcd. ($C_{19}H_{34}O_3$) 310.2508, found 310.2505.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C-NMR spectra of all new compounds.

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[1] a) S. E. Gibson, M. P. Castaldi, *Chem. Commun.* **2006**, 3045–3062; b) C. Moberg, *Angew. Chem.* **1998**, *110*, 260–281; *Angew. Chem. Int. Ed.* **1998**, *37*, 228–268.

[2] a) S. E. Gibson, M. P. Castaldi, *Angew. Chem.* **2006**, *118*, 4834–4837; *Angew. Chem. Int. Ed.* **2006**, *45*, 4718–4720.

[3] a) S. Bellemin-Laponnaz, L. H. Gade, *Actualite Chimique* **2007**, *307*, 16–20; b) G. Bringmann, R.-M. Pfeifer, C. Rummey, K. Hartner, M. Breuning, *J. Org. Chem.* **2003**, *68*, 6859–6863; c) T. Fang, J. Xu, D.-M. Du, *Synlett* **2006**, *10*, 1559–1563.

[4] a) F. Fabris, L. Pellizzaro, C. Zonta, O. De Lucchi, *Eur. J. Org. Chem.* **2007**, 283–291; b) G. Haberhauer, T. Oeser, F. Rominger, *Chem. Eur. J.* **2005**, *11*, 6718–6726; c) M. C. Schopohl, C. Siering, O. Kataeva, S. R. Waldvogel, *Angew. Chem.* **2003**, *115*, 2724–2727; *Angew. Chem. Int. Ed.* **2003**, *42*, 2620–2623; d) D. Q. McDonald, W. C. Still, *J. Am. Chem. Soc.* **1996**, *118*, 2073–2077; e) S.-G. Kim, K.-H. Kim, J. Jung, S. K. Shin, K. H. Ahn, *J. Am. Chem. Soc.* **2002**, *124*, 591–596.

[5] M. de Loos, J. H. van Esch, R. M. Kellogg, B. L. Feringa, *Tetrahedron* **2007**, *63*, 7285–7301.

[6] a) J. Van Gestel, A. R. A. Palmans, B. Titulaer, J. A. J. M. Vekemans, E. W. Meijer, *J. Am. Chem. Soc.* **2005**, *127*, 5490–5494; b) M. L. Bushey, T.-Q. Nguyen, W. Zhang, D. Horoszewski, C. Nuckolls, *Angew. Chem.* **2004**, *116*, 5562–5570; *Angew. Chem. Int. Ed.* **2004**, *43*, 5446–5453.

[7] a) S. Fournel, S. Wieckowski, W. Sun, N. Trouche, H. Dumortier, A. Bianco, O. Chaloin, M. Habib, J. C. Peter, P. Schneider, B. Vray, R. E. Toes, R. Offringa, C. J. Melief, J. Hoebeke, G. Guichard, *Nat. Chem. Biol.* **2005**, *1*, 377–382; b) H. Li, Y. Guan, A. Szczepanska, A. J. Moreno-Vargas, A. T. Carmona, I. Robina, G. K. Lewis, L. X. Wang, *Bioorg. Med. Chem.* **2007**, *15*, 4220–4228.

[8] G. Parkin, *Chem. Rev.* **2004**, *104*, 699–767.

[9] a) R. Wyatt, J. Sodroski, *Science* **1998**, *280*, 1884–1888; b) D. M. Eckert, P. S. Kim, *Annu. Rev. Biochem.* **2001**, *70*, 777–810; c) D. W. Banner, A. D'Arcy, W. Janes, R. Gentz, H. J. Schoenfeld, C. Broger, H. Loetscher, W. Lesslauer, *Cell* **1993**, *73*, 431–445.

[10] J. Rao, J. Lahiri, L. Isaacs, R. M. Weis, G. M. Whitesides, *Science* **1998**, *280*, 708–711.

[11] P. Misra, V. Humblet, N. Pannier, W. Maison, J. V. Frangioni, *J. Nucl. Med.* **2007**, *48*, 1379–1389.

[12] a) N. Weibel, L. Charbonniere, R. Ziessel, *Tetrahedron Lett.* **2006**, *47*, 1793–1796; b) P. R. Ashton, S. E. Boyd, C. L. Brown, N. Jayaraman, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.* **1996**, *2*, 1115–1128; c) G. R. Newkome, R. K. Behera, C. N. Moorefield, G. R. Baker, *J. Org. Chem.* **1991**, *56*, 7162–7167.

[13] a) D. S. Kemp, K. S. Petrakis, *J. Org. Chem.* **1981**, *46*, 5140–5143; b) E. A. Jefferson, E. Locardi, M. Goodman, *J. Am. Chem. Soc.* **1998**, *120*, 7420–7428.

[14] J. B. Bialecki, L.-H. Yuan, B. Gong, *Tetrahedron* **2007**, *63*, 5460–5469.

[15] a) R. Welti, F. Diederich, *Helv. Chim. Acta* **2003**, *86*, 494–503; b) K. H. Lee, J.-I. Hong, *Tetrahedron Lett.* **2000**, *41*, 6083–6087; c) A. Vacca, C. Nativi, M. Cacciarini, R. Pergoli, S. Roelens, *J. Am. Chem. Soc.* **2004**, *126*, 16456–16465; d) W. C. Still, R. Liu, *Philos. Trans. R. Soc. London, Ser. A* **1993**, *345*, 97–104.

[16] a) A. Bianco, S. Fournel, S. Wieckowski, J. Hoebeke, G. Guichard, *Org. Biomol. Chem.* **2006**, *4*, 1461–1463; b) J. Bitta, S. Kubik, *Org. Lett.* **2001**, *3*, 2637–2640.

[17] W. Maison, J. V. Frangioni, N. Pannier, *Org. Lett.* **2004**, *6*, 4567–4569.

[18] Q. Li, C. Jin, P. A. Petukhov, A. V. Rukavishnikov, T. O. Zaikova, A. Phadke, D. H. LaMunyon, M. D. Lee, J. F. W. Keana, *J. Org. Chem.* **2004**, *69*, 1010–1019.

[19] a) M. V. Gil, M. J. Arevalo, O. Lopez, *Synthesis* **2007**, 1589–1620; b) D. Fournier, R. Hoogenboom, U. S. Schubert, *Chem. Soc. Rev.* **2007**, *36*, 1369–1380; c) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249–1262; d) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51–68; e) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

[20] Review: I. K. Moiseev, N. V. Makarova, M. N. Zemtsova, *Russ. Chem. Rev.* **1999**, *68*, 1001–1020.

[21] H. Stetter, C. Wulff, *Chem. Ber.* **1960**, *93*, 1366–1371.

[22] R. C. Fort, P. v. R. Schleyer, *Chem. Rev.* **1964**, *64*, 277–300.

[23] Notable exceptions are: a) A. A. Fokin, P. R. Schreiner, *Adv. Synth. Catal.* **2003**, *345*, 1035–1052; b) M. Ohno, K. Ishizaki, S. Eguchi, *J. Org. Chem.* **1988**, *53*, 1285–1288.

[24] H. Stetter, C. Wulff, *Chem. Ber.* **1960**, *93*, 1366–1371. For an alternative oxidation procedure see: R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, R. Curci, *Tetrahedron Lett.* **1990**, *31*, 3067–3070.

[25] Y. Ishii, T. Nakano, N. Hirai, PCT Int. Appl. (**1998**), WO 9840337.

[26] H. Newman, *Synthesis* **1972**, 692–693.

[27] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.
[28] a) S. Landa, Z. Kamvcek, *Collect. Czech. Chem. Commun.* **1959**, *24*, 4004–4009; b) S. I. Kozhushkov, D. S. Yufit, R. Boese, D. Blaeser, P. R. Schreiner, A. de Meijere, *Eur. J. Org. Chem.* **2005**, 1409–1415; c) G. S. Lee, J. N. Bashara, G. Sabih, A. Oganesyan, G. Godjoian, H. M. Duong, E. R. Marinez, C. G. Gutierrez, *Org. Lett.* **2004**, *6*, 1705–1707.
[29] H. Stetter, J. Gaertner, P. Tacke, *Chem. Ber.* **1965**, *98*, 3888–3891.
[30] A. V. Rukavishnikov, A. Phadke, M. D. Lee, D. H. LaMunyon, P. A. Petukhov, J. F. W. Keana, *Tetrahedron Lett.* **1999**, *40*, 6353–6356.
[31] R. E. Delimarskii, V. N. Rodionov, A. G. Yurchenko, *Ukr. Khim. Zh. (Russ. Ed.)* **1988**, *54*, 437–438.
[32] A. A. Malik, T. G. Archibald, K. Baum, M. R. Unroe, *J. Polym. Sci., Part A Polym. Chem.* **1992**, *30*, 1747–1754.
[33] Examples: gp120: R. Wyatt, P. D. Kwong, E. Desjardins, R. G. Sweet, J. Robinson, W. A. Hendrickson, J. G. Sodroski, *Nature* **1998**, *393*, 705–711; TNFR; R. M. Locksley, N. Killeen, M. J. Lenardo, *Cell* **2001**, *104*, 487–501.
[34] F. M. Menger, V. A. Migulin, *J. Org. Chem.* **1999**, *64*, 8916–8921.

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