Synthesis of Functionalized Adamantane Derivatives: (3 + 1)-Scaffolds for Applications in Medicinal and Material Chemistry

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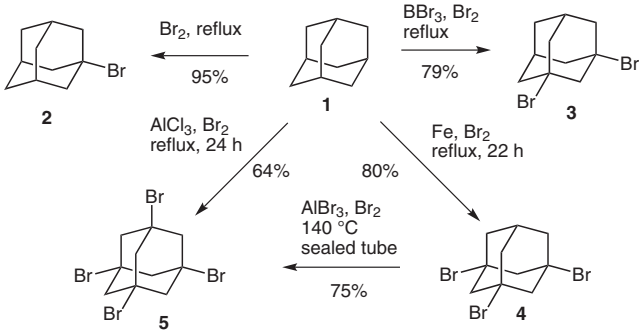
Abstract: Due to its rigid cage structure, adamantane has received considerable interest as a scaffold with a defined tetrahedral geometry. In this paper we describe orthogonally functionalized tetrasubstituted adamantane derivatives. These compounds may be conjugated to other functional molecules by standard techniques such as amide formation or click chemistry and are thus useful (3 + 1) scaffolds for medicinal and material chemistry.

Key words: adamantane, multivalency, dendrimers, C_3 symmetry, diamandoids

Introduction

Adamantane was first isolated from crude oil in Czechoslovakia in 1933.[1] It is the lowest diamandoid followed by diamantane, triamantane etc. and has, like the others, unique chemical properties.[2] The first synthesis of adamantane was achieved by Prelog and Steinwerth in 1941.[3,4] Schleyer published in 1957 a practical method to synthesize adamantane from tetrahydrodicyclopentadiene.[5]

Due to its rigid cage structure, the adamantyl scaffold is an interesting tetrahedral building block in many fields, such as catalysis,[6,7] supramolecular chemistry,[8–10] material science,[11–14] and medicinal chemistry.[15,16] Many bridgehead-substituted adamantane derivatives have been described because they are readily accessible by nucleophilic substitution or radical reactions.[17,18] A number of mono- and disubstituted derivatives are commercially available and have been used frequently in medicinal chemistry as a bulky and lipophilic structural element in drugs. Tri- and tetrabridgehead functionalized derivatives are less common, because they are often more difficult to synthesize. Functionalization of adamantane at the bridgehead positions requires the activation of a tertiary C–H bond and does, therefore, often imply drastic reaction conditions.[19] This is particularly problematic with substituted adamantane derivatives, because the reactivity at each bridgehead position is strongly influenced by the substituents at the other bridgeheads. A good example is the bromination of adamantane **1** (Scheme 1),[20–22] which is often the first step in the synthesis of more complex adamantane derivatives. The introduction of each additional bromine lowers the reactivity of the system for the next bromination significantly.[18] In consequence each bromine derivative **2**–**5** is easy to prepare selectively by a slightly modified protocol. However, the conditions required for the synthesis of tribromoadamantane **4** and tetrabromoadamantane **5** are quite harsh.



Scheme 1 Mono-, di-, tri- and tetrabromoadamantanes **2**–**5** by selectively bromination of adamantane (**1**)

A particularly interesting feature of tetrasubstituted adamantanes is the ability to align rigidly four substituents in a tetrahedral arrangement. The adamantane core may thus be considered a large replacement for a sp^3-carbon.

Tetrasubstituted adamantanes of general type **6** are (3 + 1) scaffolds for applications in medicinal and material chemistry. Known examples of these scaffolds include the amino acids **7**–**9**.

Our group started in 2003 with the design of tetrahedral scaffolds based on the general structure **6** with three functional groups X in a tripodal arrangement and a fourth orthogonal functionality Y pointing in opposite direction (Scheme 2).[13,23–25] These scaffolds offer various fields of applications because threefold rotational symmetry plays a crucial role in various natural molecular recognition systems.[26–28] Among them are important cell surface receptors,[29–33] enzymes,[34] siderophores, and natural adhesives.[35,36] For these applications a number of tripodal scaffolds are known such as 1,3,5-substituted cyclohexanes,[37] 1,3,5-substituted benzenes,[38] or cyclopeptides.[39] However, these scaffolds lack a fourth position for the conjugation of effector molecules, which is an essential component for many fields of application such as surface functionalization and imaging. Like a central sp^3-carbon,[40] adamantane has three bridgehead positions for conjugation of ligands and one additional position for further

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conjugation ('3 + 1 system') of effectors, for example dyes,[41] polymers,[42] or other functional molecules.[15] We have described synthetic routes to three adamantyl-based (3 + 1) scaffolds **7**,[43] **8**,[43] and **9**[23] with orthogonal functionality and have reported their application in tumor imaging,[15,41] targeted tumor therapy,[44] and material chemistry.[42] In this paper we extend this molecular toolbox and describe the synthesis of additional (3 + 1) scaffolds with different functionality and spacing.

Biographical Sketches

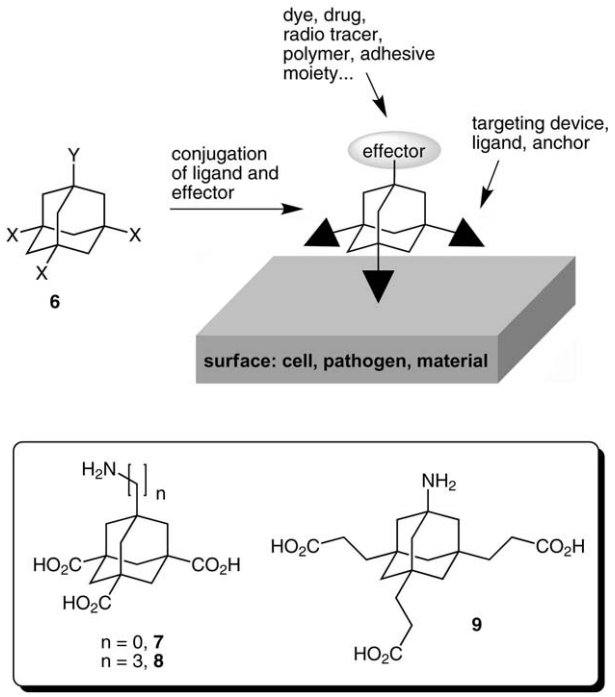
Carsten Fleck studied chemistry at the Justus-Liebig-University Gießen where he obtained his M.Sc. degree in 2010. Subsequently, he moved to the University of Hamburg and joined the research group of Prof. Maison for his Ph.D. studies. He is interested in carbohydrate chemistry and the synthesis of adamantane-based carbohydrate mimics.

Elisa Franzmann studied chemistry at the Justus-Liebig-University Gießen and obtained her Diploma degree in 2009. Currently, she is a Ph.D. candidate supervised by Professor Wolfgang Maison. Her research interests are focused on biomimetic strategies for the functionalization of metal surfaces.

Dorith Claes studied chemistry at the Justus-Liebig-University of Gießen and obtained her M.Sc. degree in 2010 under the guidance of Prof. Maison. She joined his group for her Ph.D. studies and moved from Gießen to the University of Hamburg. Her research interests are multivalent benzoboroxoles for carbohydrate recognition.

Aljona Rickert studied chemistry at the Justus-Liebig-University in Gießen. She obtained her M.Sc. degree in 2010 on a research project about synthetic multivalent ligands for cell recognition. Since 2010 she has worked on her Ph.D. under the guidance of Prof. Wolfgang Maison and Prof. Holger Zorn. Her research focuses on enzymatic allylic oxidations.

Wolfgang Maison studied chemistry at the University of Oldenburg and obtained his Ph.D. degree in 2000 under the guidance of Prof. Jürgen Martens. He joined the group of Prof. Daniel S. Kemp at MIT for a one-year postdoc. From 2001–2006 he was a junior group leader at the University of Hamburg, before he accepted a W2-Professorship at the JLU-Giessen. Since 2011 he has been a full professor at the University of Hamburg. His research interests are linked to natural product syntheses and drug development.



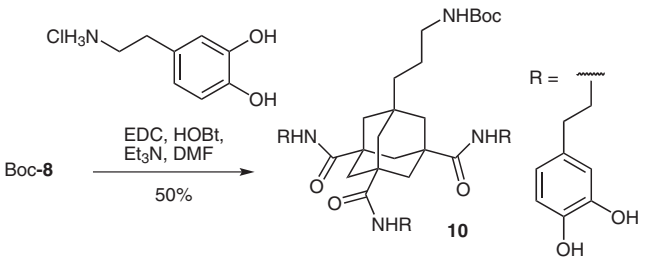
Scheme 2

Results and Discussion

Variations at the Ligand-Conjugation Site

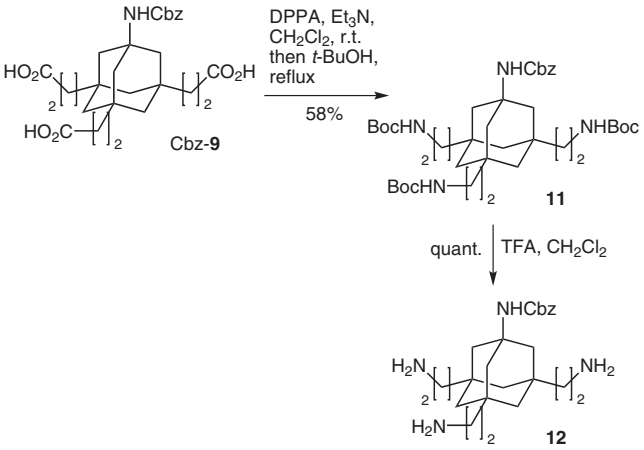
Scaffolds **7**–**9** are restricted to the conjugation of ligands either with a reactive amine functionality via amide formation or with an alcohol moiety via ester formation.

An example is depicted in Scheme 3 with the coupling of dopamine as a ligand to the scaffold Boc-**8**. The resulting triscatecholate **10** is a strong metal binder and may be used for the functionalization of metal surfaces. To increase the range of suitable ligands to be conjugated, we aimed for tetraamines like **12** that would be easily addressed by ligands bearing carboxylic acids or carbonyls.

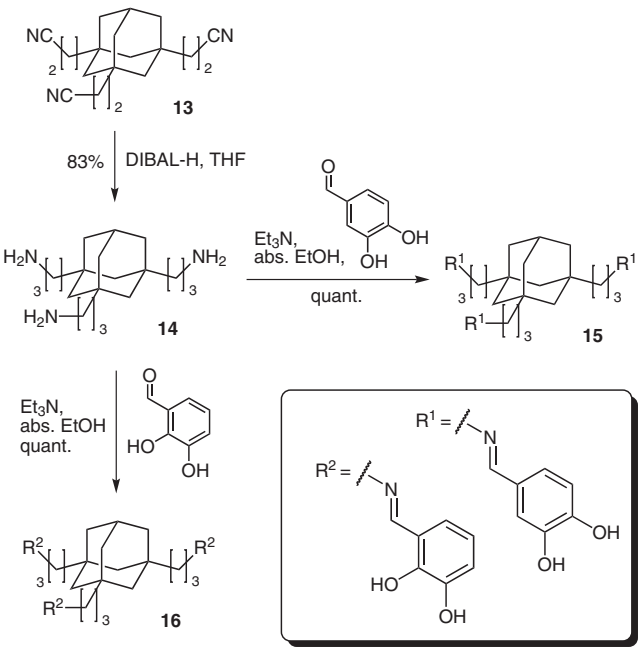


Scheme 3 Synthesis of triscatecholate **10** via EDC/HOBt coupling

A Curtis reaction of the known tricarboxylic acid Cbz-**9**[42] with diphenylphosphoryl azide (DPPA)[45] gave the orthogonally protected tetraamine **11**. Acidic deprotection gave the target amine **12** ready for conjugation of ligands (Scheme 4). A similar trisamine **14** was prepared from tris(cyanoethyl)adamantane **13**,[46] via diisobutylaluminum hydride reduction. The trisamine **14** was conjugated to 2,3-dihydroxybenzaldehyde and 3,4-dihydroxybenzaldehyde via imine formation. The resulting triscatecholates **15** and **16** precipitate from ethanol and are analogues of bacterial siderophores such as enterobactin (Scheme 5).[25]



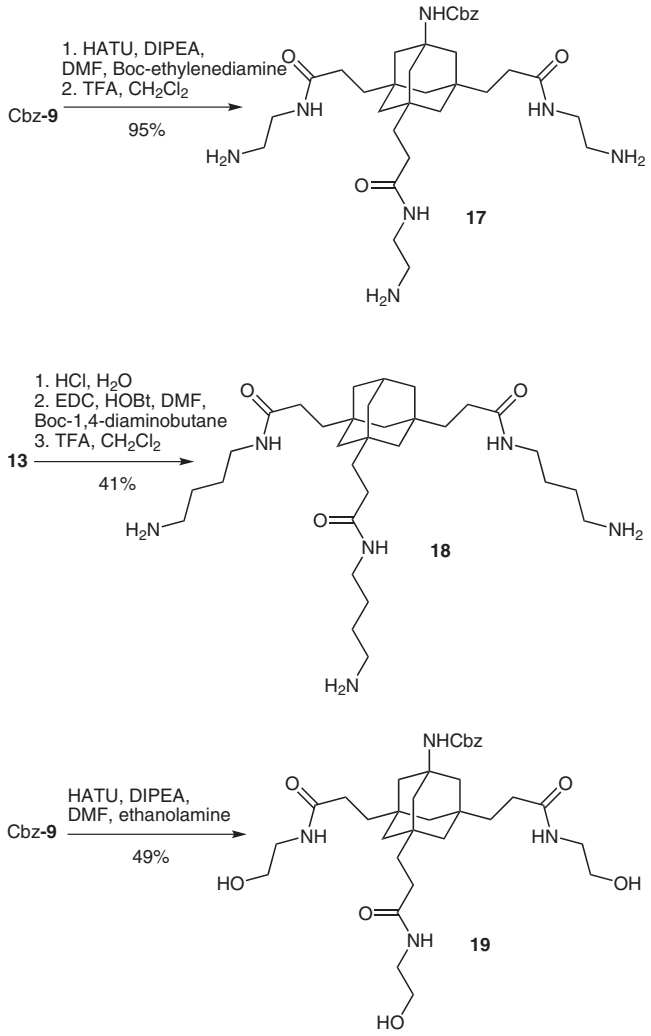
Scheme 4 Synthesis of tetraamine **12** via Curtius degradation of tricarboxylic acid Cbz-**9**



Scheme 5 Synthesis of trisamine **14** and triscatecholates **15** and **16**

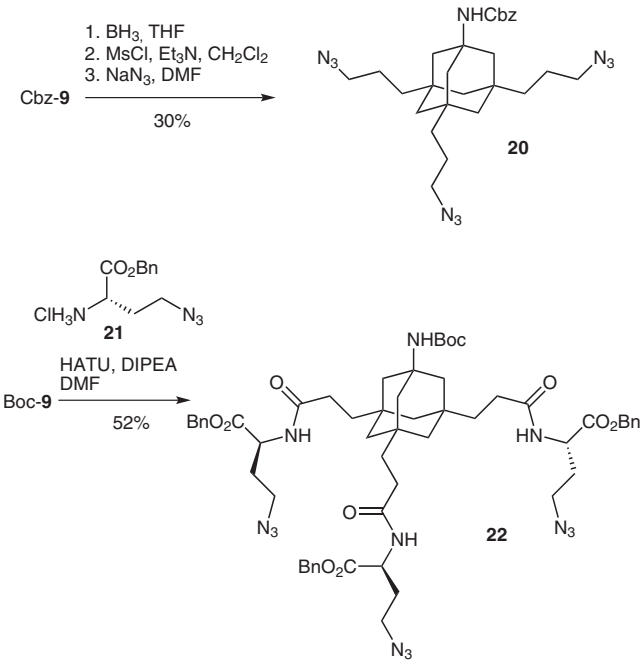
For many applications of our scaffolds it is interesting to vary the spacing of the tripodal conjugation site. Starting from scaffold Cbz-**9**, we have thus coupled mono Boc-protected ethylenediamine (Scheme 6). Trifluoroacetic acid deprotection of the resulting trimeric coupling product gave the free trisamine **17**. In a similar approach, tris(cyanoethyl)adamantane **13** was hydrolyzed to the corresponding tricarboxylic acid, which was then coupled to mono-Boc-protected 1,4-diaminobutane using standard peptide coupling conditions. The resulting product was

deprotected with trifluoroacetic acid to give the trisamine **18**. A similar protocol was used for the synthesis of trisalcohol **19**, which was obtained by peptide coupling of the protected amino acid Cbz-**9** with ethanolamine.



Scheme 6 Preparation of spaced trisamines **17**, **18**, and trisalcohol **19**

For the coupling of densely functionalized and/or polar ligands[47] it is often advantageous to use the Huisgen cycloaddition of alkynes and azides.[48,49] Trisazides like **20** and **22** are thus interesting scaffolds for click conjugations of alkyne functionalized ligands. Trisazide **20** was prepared from the tricarboxylic acid Cbz-**9** via borane reduction, mesylation of the resulting triol, and subsequent nucleophilic displacement with sodium azide (Scheme 7). In addition, the amino acid functionalized derivative **22** was prepared from scaffold Boc-**9** by peptide coupling with azidohomoalanine. Trisazide **22** is particularly interesting for the assembly of complex multivalent structures, because it has three orthogonal functionalities which might be addressed selectively.

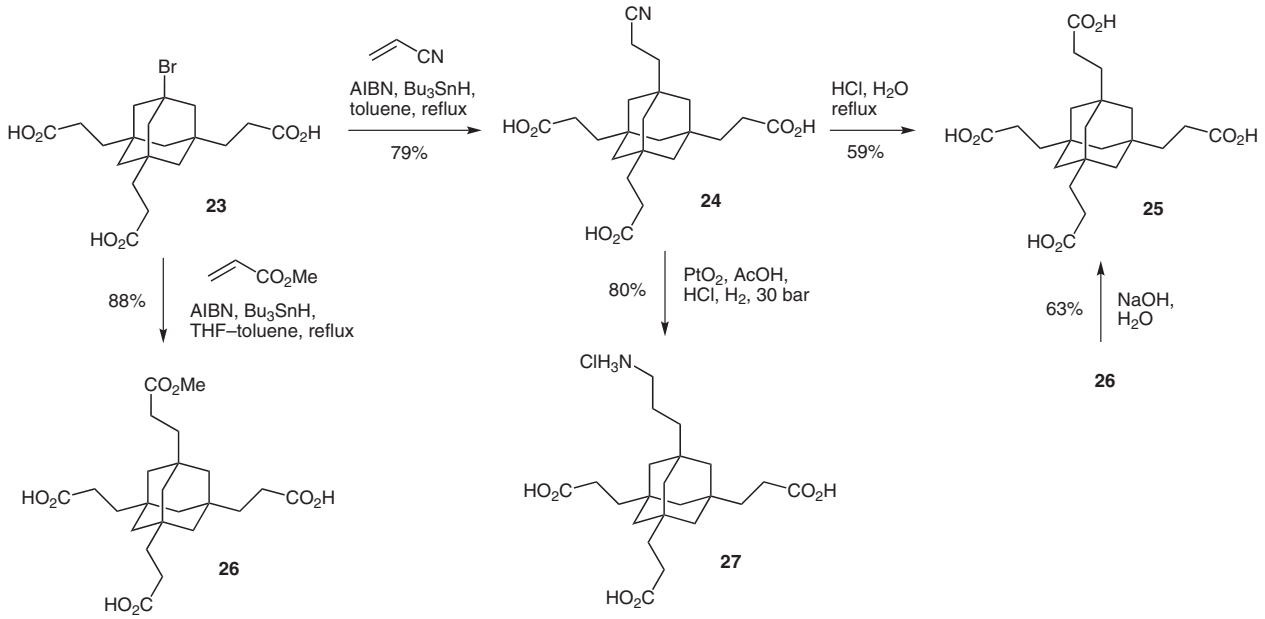


Scheme 7 Synthesis of trisazides **20** and **22**

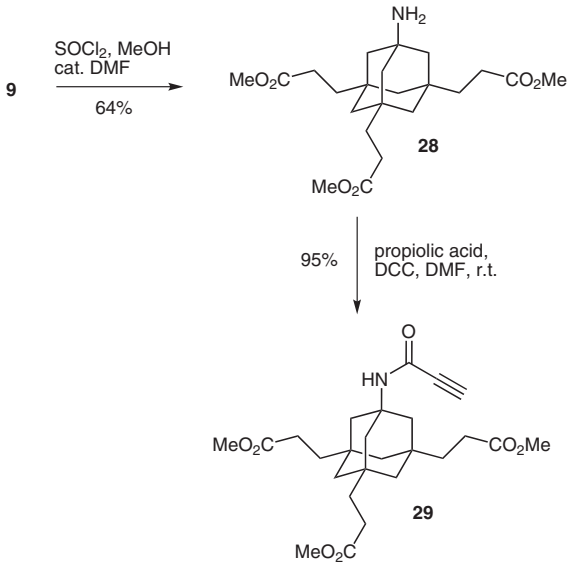
Variations at the Effector-Conjugation Site

Conjugation of effector molecules like dyes to the sterically hindered bridgehead amines of adamantyl scaffolds such as **7** or **9** can be problematic if nonactivated or weakly activated carboxylic acids need to be coupled. Spaced amino groups or alternative functionalities in this position are therefore attractive. The bromo-substituted tricarboxylic acid **23** is an excellent precursor for the introduction of a functional group orthogonal to the three carboxylic acids, because the bridgehead bromine is easily substituted using radical chemistry (Scheme 8). Treatment of **23** with acrylonitrile gave the cyanoethyl derivative **24**, which was reduced to the spaced amine **27**. Alternatively, bromide **23** was treated with methacrylate to give the methyl ester **26**. Both, the methyl ester **26** and the cyanoethyl derivative **24** were also hydrolyzed to tetrakis(carboxyethyl)adamantane **25**, which is an interesting tetrahedral building block for the synthesis of dendritic structures.

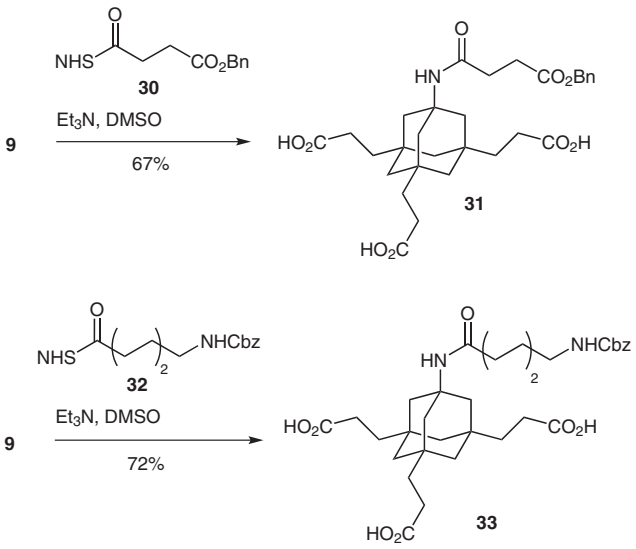
Additional (3 + 1) scaffolds were available starting from amino acid **9** (Scheme 9). Methyl ester **28** was prepared in 80% yield using thionyl chloride in methanol with catalytic amounts of *N*,*N*-dimethylformamide. This triester was coupled to propiolic acid with *N*,*N*′-dicyclohexylcarbodiimide to give the alkyne **29** ready for click conjugation of effector molecules with an azide moiety.



Scheme 8 Bromide **23** as a versatile precursor for the synthesis of (3 + 1) scaffolds **24**, **26**, and **27** and the tetrahedral scaffold **25** via radical chemistry



Scheme 9 Synthesis of the alkyne-functionalized triester **29**



Scheme 10 Elongation of the effector conjugation site via NHS ester coupling to amino acid **33**

Alternatively, the free amino acid **9** may be directly acylated with *N*-hydroxysuccinimide (NHS) benzylglutarate to give benzyl ester **31** (Scheme 10). A spaced amino group in **33** was prepared by NHS ester coupling of Cbz-protected aminohexanoic acid **32**.

Conclusion

We described the synthesis of several new tri- and tetrafunctionalized adamantane derivatives. These compounds belong to a molecular toolbox for applications in medicinal and material chemistry.[50] Most derivatives described are (3 + 1) scaffolds with different orthogonal functionalities such as alcohols, amines, carboxylic acids, azides, or alkynes. They may thus easily be conjugated to other functional molecules by standard coupling techniques such as amide formation or copper catalyzed click reactions.

The following compounds were prepared according to literature protocols: **7**,[43] Boc-**8**,[43] **9**,[23] Boc-**9**,[23] Cbz-**9**,[42] **13**,[46] **14**,[51] **21**,[52] **23**,[23] **30**,[53] and **32**.[54]

TLC was performed on silica gel aluminum sheets. Reagents used for developing plates were cerium-stain [phosphomolybdic acid (5.00 g), $Ce(SO_4)_2 \cdot 4\ H_2O$ (2.50 g), H_2SO_4 (25 mL, and H_2O (225

mL)], $KMnO_4$ soln (0.5% $KMnO_4$–1 M aq NaOH), and detection by UV light was used when applicable. Flash column chromatography was performed on silica gel (60–200 μm). ^1H NMR are referenced to residual non-deuterated solvent ($CDCl_3$, $\delta_H = 7.26$; DMSO-d_6, $\delta_H = 2.50$; CD_3OD, $\delta_H = 3.31$). ^{13}C NMR are referenced to the solvent signal ($CDCl_3$, $\delta_C = 77.16$; DMSO-d_6, $\delta_C = 39.52$; CD_3OD, $\delta_H = 49.0$). NMR spectra were recorded on 200 (50), 400 (100), or 600 (150) MHz instruments. ESI MS were recorded on a TOF instrument operated in positive or negative mode. Samples were dissolved in MeCN–MeOH mixtures and directly injected via syringe. If indicated with as anhyd solvents, these were dried according to standard procedures prior to use.[55,56]

7-[3-(*tert*-Butoxycarbonylamino)propyl]-*N*,*N*′,*N*″-tris[2-(3,4-dihydroxyphenyl)ethyl]adamantane-1,3,5-tricarboxamide (10)

Compound Boc-**8** (0.10 g, 0.24 mmol) was dissolved in DMF (30 mL) and the soln was cooled to 0 °C (ice bath). Et_3N (0.39 mL, 2.82 mmol) was added and the soln was stirred for 5 min. EDC·HCl (0.21 g, 1.06 mmol) and HOBt (0.14 g, 1.06 mmol) were added and the soln was stirred for 5 min. Dopamine hydrochloride (0.20 g, 1.06 mmol) was added and the soln was stirred for 72 h at r.t. The mixture was concentrated and dissolved in a mixture of EtOAc (30 mL) and 1 M HCl (5 mL); the soln was washed with sat. aq $KHSO_4$ soln (3 ×). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Evaporation of the solvent gave a colorless solid that was suspended in Et_2O (100 mL) and stirred for 30 min in a water bath at 30 °C. The resulting slurry was filtered and the procedure was repeated (6 ×) to give **10** (99 mg, 0.12 mmol, 50%) as a colorless sticky solid.

IR (KBr): 3374, 2936, 1633, 1526, 1366, 1285, 1285, 1196–1046 cm^{-1}.

^1H NMR (400 MHz, MeOH-d_4): δ = 7.74–7.42 (m, 3 H), 6.67–6.65 (m, 3 H), 6.61 (s, 3 H), 6.50–6.48(m, 3 H), 3.31–3.29 (m, 6 H), 3.01–2.98 (m, 2 H), 2.64–2.59 (m, 6 H), 1.76–1.69 (m, 6 H), 1.40–1.35 (m, 17 H), 1.14–1.12 (m, 2 H).

^{13}C NMR (100 MHz, MeOH-d_4): δ = 178.9, 146.2, 144.8, 132.0, 121.2, 117.1, 116.3, 80.0, 43.7, 43.4, 42.3, 40.7, 39.4, 35.8, 35.1, 28.8, 24.2, 12.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{45}H_{58}N_4NaO_{11}$: 853.3994; found: 853.3992.

7-(Benzyloxycarbonylamino)-*N*,*N*′,*N*″-tris(*tert*-butoxycarbonyl)adamantane-1,3,5-triethanamine (11)

Compound Cbz-**9** (0.31 g, 0.61 mmol) was dissolved in anhyd CH_2Cl_2 (5 mL). DPPA (0.60 mL, 2.38 mmol) and Et_3N (0.60 mL, 4.32 mmol) were added and the soln was stirred at r.t. for 8 h. The mixture was concentrated; the resulting crude product was dissolved in *t*-BuOH (50 mL) and heated under reflux for 24 h (N_2 atmosphere). The soln was concentrated, the residue was dissolved in CH_2Cl_2 (50 mL), and the soln washed with 2 M NaOH (3 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, EtOAc–MeOH, 10:1; R_f = 0.69) to give **11** (0.25 g, 0.35 mmol, 58%) as a yellow oil.

IR (KBr): 3404, 2898–2841, 1644, 1544–1521, 1463, 1359, 1232, 1025, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, broad signals due to carbamate rotational isomerism): δ = 7.21–7.12 (m, 5 H), 4.90 (s, 2 H), 3.04–2.92 (m, 6 H), 1.57–1.55 (m, 6 H), 1.45 (s, 18 H), 1.35–1.34 (m, 6 H), 1.16–1.14 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$, broad signals due to carbamate rotational isomerism): δ = 155.9, 154.3, 136.5, 129.6, 128.4, 127.9, 78.4, 65.8, 52.3, 45.5, 42.7, 35.6, 35.6, 34.0, 28.4.

MS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{62}N_4NaO_8$: 737.4460; found: 737.4463.

7-(Benzyloxycarbonylamino)adamantane-1,3,5-triethanamine (12)

A soln of **11** (0.25 g, 0.35 mmol) in CH_2Cl_2 (40 mL) and TFA (10 mL) was stirred at r.t. for 24 h. The mixture was concentrated in vacuo and the resulting oil was co-evaporated with CH_2Cl_2 (3 × 20 mL) to give **12** (0.14 g, 0.34 mmol, 99%) as a colorless oil.

IR (film): 2916, 1689, 1520–1365, 1248–1025, 798–720 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.92–7.70 (m, 6 H), 7.35–7.17 (m, 5 H), 4.92 (s, 2 H), 1.52–1.41 (m, 12 H), 1.21–1.13 (m, 6 H), 1.10–0.94 (m, 6 H).

^{13}C-MR (100 MHz, DMSO-d_6): δ 154.1, 137.2, 128.3, 127.7, 64.6, 51.6, 44.7, 44.5, 34.2 34.0, 33.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{39}N_4O_2$: 415.3068; found: 415.3060.

***N*,*N*′,*N*″-Tris(3,4-dihydroxybenzylidene)adamantane-1,3,5-tripropaneamine (15)**

Compound **14** (50 mg, 0.16 mmol) was dissolved in anhyd EtOH (10 mL) and 3,4-dihydroxybenzaldehyde (76 mg, 0.49 mmol) dissolved in a small amount of EtOH was added and the soln was stirred for 24 h under N_2 atmosphere. The precipitate was separated by centrifugation, washed with cold Et_2O and a small amount of EtOH, and dried in vacuo to give **15** (104 mg, 0.16 mmol, 100%) as a sticky solid.

IR (KBr): 3410, 2901–2842, 1583, 1450, 1383, 1285, 1116, 816 cm^{-1}.

^1H NMR (400 MHz, MeOH-d_4): δ = 8.05–8.02 (m, 3 H), 7.16–7.14 (m, 3 H), 6.92.6.89 (m, 3 H), 6.72–6.69 (m, 3 H), 3.40–3.10 (br s, 6 H), 1.90 (s, 1 H), 1.50–1.48 (m, 6 H), 1.29–1.27 (m, 6 H), 1.08–1.05 (m, 12 H).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{40}H_{50}N_3O_6$: 668.3694; found: 668.3691.

***N*,*N*′,*N*″-Tris(2,3-dihydroxybenzylidene)adamantane-1,3,5-tripropaneamine (16)**

Compound **14** (50 mg, 0.16 mmol) was dissolved in anhyd EtOH (10 mL) and 2,3-dihydroxybenzaldehyde (76 mg, 0.49 mmol) dissolved in a small amount of EtOH was added and the soln was stirred for 24 h under N_2 atmosphere. The precipitate was separated by centrifugation and washed with cold Et_2O and a small amount of EtOH. The solid was dried in vacuo to give **16** (103 mg, 0.16 mmol, 100%) as a sticky solid.

^1H NMR (400 MHz, MeOH-d_4): δ = 8.47–8.44 (m, 3 H), 6.80–6.75 (m, 6 H), 6.59–6.50 (m, 3 H), 3.53–3.50 (m, 6 H), 1.91 (br s, 1 H), 1.57–1.50 (m, 6 H), 1.31–1.29 (m, 6 H), 1.13–1.10 (m, 12 H).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{40}H_{50}N_3O_6$: 668.3694; found: 668.3691.

***N*,*N*′,*N*″-tris(2-Aminoethyl)-7-(benzyloxycarbonylamino)adamantane-1,3,5-tripropanamide (17)**

Compound Cbz-**9** (0.21 g, 0.41 mmol) and 0.54 g (1.4 mmol) HATU were dissolved in anhyd DMF (5 mL). DIPEA (0.25 mL, 1.49 mmol) was added and the soln was stirred at 0 °C for 20 min. Boc-protected ethylenediamine (0.21 mL, 1.33 mmol) was added and the soln was stirred for 20 h at r.t. The mixture was concentrated and the residue was dissolved in EtOAc (50 mL). This soln was washed with sat. aq $NaHCO_3$ (3 ×) and sat. aq $KHSO_4$ (3 ×). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the Boc-protected trisamine (345 mg, 0.37 mmol, 91%) as a colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 5 H), 5.00 (s, 2 H), 3.33–3.32 (m, 6 H), 3.23 (s, 6 H), 2.11 (t, ^3J = 7.5 Hz, 6 H), 1.54–1.53 (m, 12 H), 1.43 (s, 27 H), 1.11 (d, ^2J = 12.2 Hz, 3 H), 1.04 (d, ^2J = 12.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 157.0, 136.8, 128.7, 128.2, 128.1, 79.7, 66.1, 52.9, 45.3, 45.0, 40.6, 40.6, 38.2, 35.2, 30.3, 28.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{48}H_{78}N_7O_{11}$: 928.5754; found: 928.5759.

A soln of the Boc-protected trisamine (345 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) and TFA (2.5 mL) was stirred at 0 °C for 2 h and allowed to warm to r.t. The mixture was concentrated in vacuo and the resulting oil was co-evaporated with CH_2Cl_2 (3 ×) and then with 1 M aq HCl to give **17** (0.25 g, 0.34 mmol, 95%) as the hydrochloride salt. Trisamine **17** should be used for functionalization without further purification and is unstable upon storage.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5 H), 5.01 (s, 2 H), 3.45 (t, ^3J = 6.3 Hz, 6 H), 3.08–3.04 (m, 6 H), 2.27–2.23 (m, 6 H), 1.59 (s, 6 H), 1.54–1.50 (m, 6 H), 1.21 (d, ^2J = 12.2 Hz, 3 H), 1.12 (d, ^2J = 12.2 Hz, 3 H).

N,*N*′,*N*″-Tris(4-aminobutyl)adamantane-1,3,5-tripropanamide (18)

A soln of **13** (7.00 g, 23.7 mmol), concd HCl (40 mL), and H_2O (5 mL) was heated to reflux for 20 h. The resulting mixture was poured into ice-H_2O; the product was filtered off, washed with cold H_2O and crystallized (MeCN) to give the tricarboxylic acid (8.00 g, 22.7 mmol, 95%) as a colorless solid.

The tricarboxylic acid (0.30 g, 0.85 mmol) was dissolved in distilled DMF (60 mL). Et_3N (1.52 mL, 11.0 mmol) was added and the soln was stirred at 0 °C for 5 min. EDC·HCl (63 mg, 2.81 mmol) and HOBt (0.38 g, 2.81 mmol) were added to the mixture, which was stirred for 15 min. Mono-Boc-protected 1,4-diaminobutane (0.53 g, 2.81 mmol) was then added and the soln was stirred for 72 h at r.t. The mixture was concentrated and the residue was dissolved in EtOAc. This soln was washed with sat. aq $NaHCO_3$ (3 ×) and sat. aq $NaHSO_4$ (3 ×). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, 10% MeOH–EtOAc) to give the Boc-protected trisamine (0.33 g, 0.39 mmol, 46%) as a colorless solid.

IR (KBr): 3425, 2918–2849, 2416, 1687, 1536, 1450, 1391–1381, 1271–1109 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05–6.94 (m, 3 H), 5.27–5.19 (m, 3 H), 3.31–3.30 (m, 6 H), 3.20–2.17 (m, 6 H), 2.23–2.06 (m, 7 H), 1.64–1.52 (m, 12 H), 1.52–1.40 (m, 33 H), 1.40–1.30 (m, 6 H), 1.21–1.03 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 156.6, 79.3, 46.6, 41.5, 40.5, 39.8, 39.5, 33.7, 30.6, 29.4, 28.2, 27.8, 27.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{46}H_{82}N_6NaO_3$: 885.6035; found: 885.6045.

A soln of the Boc-protected trisamine (0.16 g, 0.19 mmol) in CH_2Cl_2 (40 mL) and TFA (15 mL) was stirred at r.t. for 24 h. The mixture was concentrated in vacuo and the resulting oil was co-evaporated with CH_2Cl_2 (3 ×) to give **18** (0.10 g, 0.18 mmol, 94%) as a colorless oil. Trisamine **18** should be used for functionalization without further purification and is unstable upon storage.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{58}N_6O_3$: 563.4643; found: 563.4641.

7-(Benzyloxycarbonylamino)-*N*,*N*′,*N*″-tris(2-hydroxyethyl)adamantane-1,3,5-tripropanamide (19)

Compound Cbz-**9** (0.10 g, 0.19 mmol) and HATU (0.274 g, 0.72 mmol) were dissolved in anhyd DMF (5 mL). DIPEA (0.1 mL, 0.6 mmol) was added and the soln was stirred at 0 °C for 20 min. Ethanolamine (0.045 mL, 0.72 mmol) was added and the soln was stirred for 20 h at r.t. The mixture was concentrated and the residue was dissolved in H_2O. This soln was washed with CH_2Cl_2 (3 ×) and concentrated to give **19** (0.063 g, 0.10 mmol, 49%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 5 H), 4.96 (s, 2 H), 3.56 (t, ^3J = 5.3 Hz, 6 H), 3.30–3.24 (m, 6 H), 2.12 (m, 6 H), 1.48–1.39 (m, 12 H), 1.06–0.96 (m, 6 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{50}N_4O_8$: 653.3521; found: 653.3520.

3,5,7-Tris(3-azidopropyl)-*N*-(benzyloxycarbonyl)adamantan-1-amine (20)

Compound Cbz-**9** (0.48 g, 0.96 mmol) was dissolved in anhyd THF and 1 M BH_3 in THF (9.57 mL, 9.57 mmol) was slowly added. The soln was stirred at r.t. for 24 h. H_2O (10 mL) and sat. aq $NaHCO_3$ (10 mL) were added to the mixture. The solvent was removed in vacuo and the remaining solid was extracted with hot EtOH (3 × 50 mL). The combined extracts were concentrated to give the intermediate triol (0.50 g), which was used in the next step without further purification.

The crude triol was dissolved in anhyd CH_2Cl_2 (50 mL) and cooled to 0 °C. Freshly distilled Et_3N (0.95 mL, 4.31 mmol) was added and the soln was stirred at r.t. for 15 min. MsCl (0.33 mL, 4.31 mmol) was added and the soln was stirred at r.t. for 20 h. MeOH (20 mL) was added to the mixture and the soln was concentrated. The resulting crude product was dissolved in CH_2Cl_2 (60 mL). The resulting soln was washed with H_2O, sat. aq $NaHCO_3$, and sat. aq $NaHSO_4$, and dried (Na_2SO_4). The reaction soln was concentrated to give the intermediate mesylate, which was again used without further purification in the next step.

The crude mesylate was dissolved in anhyd DMF (40 mL), NaN_3 (0.28 g, 4.31 mmol) was added and the soln was stirred at 60 °C for 26 h. The mixture was concentrated, the resulting crude product was dissolved in EtOAc (30 mL), washed with the same amount of H_2O and sat. aq NaCl soln, dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 10:1) to give **20** (0.15 g, 0.27 mmol, 30% over 3 steps) as a yellowish oil.

IR (film): 3339, 2908–2844, 2096, 1725, 1507, 1453, 1351–1150, 1118, 1025, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.21 (m, 5 H), 4.97 (s, 2 H), 4.62 (s, 1 H), 3.16 (t, ^3J = 8.6 Hz, 6 H), 1.51–1.45 (m, 12 H, 5–H), 1.12–0.95 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 136.4, 128.3, 127.9, 65.9, 52.6, 51.9, 45.5, 45.2, 39.8, 34.9, 22.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{38}N_{10}NaO$: 557.3071; found: 557.3067.

N,*N*′,*N*″-Tris[(*S*)-3-azido-1-(benzyloxycarbonyl)propyl]-7-benzyloxycarbonylaminoadamantane-1,3,5-tripropanamide (22)

Boc-**9** (90 mg, 0.19 mmol), HATU (469 mg, 1.20 mmol), and DIPEA (0.22 mL, 1.20 mmol) were dissolved in anhyd DMF (8 mL) at 0 °C. After 10 min azidoamine **21** (333 mg, 1.20 mmol) and DIPEA (0.22 mL, 1.20 mmol) in anhyd DMF (5 mL) were added. The reaction was warmed to r.t. and stirred for 69 h. The solvent was evaporated in vacuo and the crude product dissolved in EtOAc (20 mL). The organic layer was washed with 1 M aq HCl (3 × 10 mL) and sat. $NaHCO_3$ (3 × 10 mL). The organic layer was separated, dried ($MgSO_4$), and filtered, and the solvent was evaporated. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 1:2; R_f = 0.4) to give **22** (110 mg, 0.10 mmol, 52%) as a colorless oil.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.27–7.42 (m, 15 H), 5.18 (d, ^2J = 12.3 Hz, 3 H), 5.13 (d, ^2J = 12.3 Hz, 3 H), 4.54 (d, ^3J = 5.1 Hz, 1.5 H), 4.52 (d, ^3J = 5.1 Hz, 1.5 H), 3.32–3.45 (m, 6 H), 2.15–2.30 (m, 6 H), 2.02–2.15 (m, 3 H), 1.85–1.97 (m, 3 H), 1.53 (s, 6 H), 1.44–1.51 (m, 6 H), 1.42 (s, 9 H), 1.13 (d, ^2J = 12.1 Hz, 3 H), 1.04 (d, ^2J = 12.1 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 177.0, 172.9, 137.1, 129.6, 129.4, 129.3, 79.3, 68.1, 53.4, 51.5, 49.0, 46.4, 46.0, 39.8, 36.1, 31.6, 30.1, 28.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{57}H_{73}N_{13}NaO_{11}$: 1138.5445; found: 1138.5445.

7-(2-Cyanoethyl)adamantane-1,3,5-tripropanoic Acid (24)
A soln of bromide **23** (0.315 g, 0.73 mmol), acrylonitrile (0.14 mL, 2.12 mmol), Bu_3SnH (0.38 mL, 1.44 mmol), and AIBN (0.012 g, 0.07 mmol) in THF–toluene (1:1, 20 mL) was heated to reflux for 6 h. The resulting mixture was poured into 2 M NaOH (50 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 ×). The aqueous phase was acidified with 4 M HCl and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give **24** (0.262 g, 0.65 mmol, 79%) as a yellowish solid; mp 216 °C.

IR (KBr): 2923, 2261, 1707, 1453, 1411, 1315, 1224, 1153 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.42 (t, ^3J = 7.9 Hz, 2 H), 2.14 (t, ^3J = 7.9 Hz, 6 H), 1.42 (t, ^3J = 7.7 Hz, 2 H), 1.35 (t, ^3J = 8.1 Hz, 6 H), 1.01 (d, ^2J = 9.5 Hz, 12 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 121.7, 44.9, 44.5, 38.0, 37.8, 33.8, 33.5, 27.8, 10.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{30}NO_6$: 405.2151; found: 405.2168.

Adamantane-1,3,5,7-tetrapropanoic Acid (25)
Method A: A soln of **24** (0.073 g, 0.18 mmol), concd HCl (0.5 mL), and H_2O (0.1 mL) was heated to reflux for 48 h. The solvent was evaporated to yield **25** (0.045 g, 0.11 mmol, 59%) as a colorless solid.

Method B: A soln of bromide **23** (0.10 g, 0.23 mmol), methyl acrylate (0.06 mL, 0.68 mmol), Bu_3SnH (0.130 mL, 0.49 mmol), and AIBN (0.004 g, 0.02 mmol) in THF–toluene (1:1, 20 mL) was heated under reflux for 6 h. The resulting mixture was poured into aq 10% NaOH (50 mL) and EtOAc (50 mL). The phases were separated and the organic phase was extracted with 10% aq NaOH (2 ×). The aqueous phase was acidified with HCl and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give **25** (0.068 g, 0.16 mmol, 63%) as a yellowish solid; mp 229 °C.

IR (KBr): 2896, 2843, 1691, 1406, 1310, 1209, 1149 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.05 (s, 4 H), 2.14 (t, ^3J = 7.8 Hz, 8 H), 1.35 (t, ^3J = 7.6 Hz, 8 H), 0.99 (s, 12 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.1, 45.0, 37.8, 33.4, 27.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{32}NNaO_8$: 447.1989; found: 447.1988.

7-[2-(Methoxycarbonyl)ethyl]adamantane-1,3,5-tripropanoic Acid (26)
A soln of bromide **23** (0.10 g, 0.23 mmol), methyl acrylate (0.06 mL, 0.68 mmol), Bu_3SnH (0.130 mL, 0.49 mmol), and AIBN (0.004 g, 0.02 mmol) in THF–toluene (1:1, 20 mL) was heated under reflux for 6 h. The resulting mixture was poured into sat. aq $NaHCO_3$ (50 mL) and EtOAc ((50 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 × 50 mL). The aqueous phase was acidified with HCl and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give **26** (0.099 g, 0.22 mmol, 88%) as a yellowish solid; mp 150 °C.

IR (KBr): 2962, 2846, 1709, 1453, 1261, 1058 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.99 (s, 3 H), 3.57 (s, 3 H), 2.24 (t, ^3J = 8.0 Hz, 2 H), 2.14 (t, ^3J = 7.7 Hz, 6 H), 1.37–1.33 (m, 6 H), 0.99 (s, 12 H), 0.87 (t, ^3J = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 174.0, 51.3, 48.5, 45.0, 44.7, 37.8, 35.4, 33.5, 32.8, 27.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{34}NNaO_8$: 461.2151; found: 461.2153.

7-(3-Aminopropyl)adamantane-1,3,5-tripropanoic Acid Hydrochloride (27)
A soln of nitrile **24** (0.10 mg, 0.25 mmol) and PtO_2 (0.011 mg, 0.05 mmol) in glacial AcOH–concd HCl (1:1, 14 mL) was hydrogenated (30 bar H_2) for 6 d. The resulting mixture was filtered through celite and the solvent was evaporated in vacuo to give **27** (99 mg, 0.22 mmol, 80%) as a colorless oil.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.87 (s, 2 H), 1.87 (s, 2 H), 1.71 (br s, 8 H), 1.59–1.54 (m, 6 H), 1.35 (s, 12 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.2, 68.3, 45.5, 45.1, 37.9, 37.4, 33.7, 33.5, 28.0, 20.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{36}NO_6$: 410.2537; found: 410.2545.

Trimethyl 7-Aminoadamantane-1,3,5-tripropanoate (28)
Compound **9** (0.75 g, 1.85 mmol) was dissolved in anhyd MeOH (75 mL) and cooled to 0 °C. $SOCl_2$ (1.3 mL, 11.1 mmol) was added slowly. Additionally anhyd DMF (5 drops) was added to the mixture. The mixture was stirred for 24 h at r.t. After concentration in vacuo the residue was dissolved in aq $NaHCO_3$ and extracted with EtOAc (3 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to give **28** (0.48 g, 1.17 mmol, 64%) as a colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 9 H), 2.22 (t, ^3J = 8.0 Hz, 6 H), 1.50 (t, ^3J = 8.0 Hz, 6 H), 1.19 (s, 6 H), 1.04 (d, ^2J = 12.0 Hz, 3 H), 1.01 (d, ^2J = 12.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 51.7, 49.6, 49.1, 45.1, 37.5, 35.3, 28.2.

MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{36}NO_6$: 410.2537; found: 410.2538.

Trimethyl 7-(Propynoylamino)adamantane-1,3,5-tripropanoate (29)
Compound **28** (0.69 g, 1.58 mmol) and propiolic acid were dissolved in anhyd CH_2Cl_2 and cooled to 0 °C. After 5 min, DCC (0.42 g, 2.03 mmol) was added and the soln was stirred at r.t. for 24 h. The formed dicyclohexylurea was filtered off and the filtrate was concentrated. The resulting crude product was purified by flash chromatography (silica gel) to give **29** (0.63 g, 1.50 mmol, 95%) as a yellow oil.

IR (film): 3259, 2919–2851, 2104, 1732, 1651, 1535, 1453–1437, 1353–1199, 1087–1018 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.96 (s, 1 H), 3.58 (s, 9 H), 2.69 (s, 1 H), 2.18 (t, ^3J = 8.2 Hz, 6 H), 1.56 (s, 6 H), 1.46 (t, ^3J = 8.2 Hz, 6 H), 1.08 (d, ^2J = 12.0 Hz, 3 H), 0.98 (d, ^2J = 12.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 151.1, 78.1, 71.7, 54.9, 51.6, 44.8, 44.3, 37.3, 34.8, 27.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{35}NNaO_7$: 484.2306; found: 484.2308.

7-{(3-(Benzyloxycarbonyl)propanoyl]amino}adamantane-1,3,5-tripropanoic Acid (31)
Compound **9** (0.314 g, 0.78 mmol) was dissolved in anhyd DMSO (5 mL). Et_3N (0.225 mL, 1.6 mmol) and **30** (0.29 g, 0.95 mmol) were added. The mixture was stirred for 72 h at r.t. The solvent was removed in vacuo and the residue was dissolved in sat. aq $NaHCO_3$ (20 mL) The soln was washed with EtOAc (2 × 20 mL), acidified with HCl, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give **31** (0.29 g, 0.50 mmol, 67%) as a yellowish solid.

^1H NMR (400 MHz, CD_3OD): δ = 7.40–7.32 (m, 5 H), 5.12 (s, 2 H), 2.62 (t, ^3J = 6.5 Hz, 2 H), 2.44 (t, ^3J = 6.6 Hz, 2 H), 2.25 (t, ^3J = 8.0 Hz, 6 H), 1.58 (s, 6 H), 1.52–1.48 (m, 6 H), 1.15 (d, ^2J = 12.1 Hz, 3 H), 1.09 (d, ^2J = 12.1 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 178.2, 174.2, 173.5, 137.6, 129.6, 129.2, 129.1, 67.4, 54.8, 46.2, 45.5, 39.0, 35.8 32.2 30.6, 29.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{40}NO_9$: 558.2698; found: 558.2689.

7-{(6-(Benzyloxycarbonylamino)hexanoyl]amino}adamantane-1,3,5-tripropanoic Acid (33)

Compound **9** (1.26 g, 3.12 mmol) was dissolved in DMSO (20 mL). Et_3N (1.70 mL, 12.5 mmol) and **32** (1.70 g, 4.68 mmol) were added. The mixture was stirred for 12 h at r.t. and concentrated. The residue was dissolved in EtOAc (20 mL) and washed with sat. aq $KHSO_4$. The organic layer was concentrated and the residue dissolved in 1 M NaOH (20 mL). After washing with EtOAc, the alkaline soln was acidified with HCl and extracted with EtOAc (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and filtered and the solvent was removed in vacuo to give **33** (1.37 g, 2.22 mmol, 72%) as a yellowish solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.34–7.29 (m, 5 H), 5.06 (s, 2 H), 3.11 (t, ^3J = 7.0 Hz, 2 H), 2.27 (m, 6 H), 2.10 (t, ^3J = 7.5 Hz, 2 H), 1.66–1.45 (m, 16 H), 1.38–1.28 (m, 2 H), 1.17 (d, ^2J = 12.2 Hz, 3 H), 1.11 (d, ^2J = 12.2 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 178.1, 175.6, 129.5, 128.9, 128.7, 67.3, 54.8, 46.3, 45.6, 41.6, 39.0, 37.8, 35.9, 30.6, 29.0, 27.3, 26.7, 26.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{47}N_2O_9$: 615.3276; found: 615.3273.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Landa, S.; Machacek, V. *Collect. Czech. Chem. Commun.* **1933**, *5*, 1.
(2) Schwertfeger, H.; Fokin, A. A.; Schreiner, P. R. *Angew. Chem.* **2008**, *120*, 1038; *Angew. Chem. Int. Ed.* **2008**, *47*, 1022.
(3) Prelog, V.; Seiwerth, R. *Ber. Dtsch. Chem. Ges. B* **1941**, *74*, 1769.
(4) Prelog, V.; Seiwerth, R. *Ber. Dtsch. Chem. Ges. B* **1941**, *74*, 1644.
(5) Schleyer, P.v. R. *J. Am. Chem. Soc.* **1957**, *79*, 3292.
(6) Müller, C. E.; Hrdina, R.; Wende, R. C.; Schreiner, P. R. *Chem. Eur. J.* **2011**, *17*, 6309.
(7) Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem.* **2008**, *120*, 6275; *Angew. Chem. Int. Ed.* **2008**, *47*, 6180.
(8) Low, N. L.; Dzyuba, E. V.; Brusilowskij, B.; Kaufmann, L.; Franzmann, E.; Maison, W.; Brandt, E.; Aicher, D.; Wiehe, A.; Schalley, C. A. *Beilstein J. Org. Chem.* **2012**, *8*, 234.
(9) Newkome, G. R.; Nayak, A.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem.* **1992**, *57*, 358.
(10) Menger, F. M.; Migulin, V. A. *J. Org. Chem.* **1999**, *64*, 8916.
(11) Kitagawa, T.; Idomoto, Y.; Matsubara, H.; Hobara, D.; Kakiuchi, T.; Okazaki, T.; Komatsu, K. *J. Org. Chem.* **2006**, *71*, 1362.
(12) Li, Q.; Jin, C.; Petukhov, P. A.; Rukavishnikov, A. V.; Zaikova, T. O.; Phadke, A.; LaMunyon, D. H.; Lee, M. D.; Keana, J. F. W. *J. Org. Chem.* **2004**, *69*, 1010.
(13) Li, Q.; Rukavishnikov, A. V.; Petukhov, P. A.; Zaikova, T. O.; Jin, C.; Keana, J. F. W. *J. Org. Chem.* **2003**, *68*, 4862.
(14) Willey, T. M.; Fabbri, J. D.; Lee, J. R. I.; Schreiner, P. R.; Fokin, A. A.; Tkachenko, B. A.; Fokina, N. A.; Dahl, J. E. P.; Carlson, R. M. K.; Vance, A. L.; Yang, W. L.; Terminello, L. J.; van Buuren, T.; Melosh, N. A. *J. Am. Chem. Soc.* **2008**, *130*, 10536.
(15) Misra, P.; Humblet, V.; Pannier, N.; Maison, W.; Frangioni, J. V. *J. Nucl. Med.* **2007**, *48*, 1379.
(16) Lamoureux, G.; Artavia, G. *Curr. Med. Chem.* **2010**, *17*, 2967.
(17) Fort, R. C.; Schleyer, P.v. R. *Chem. Rev.* **1964**, *64*, 277.
(18) Moiseev, I. K.; Makarova, N. V.; Zemtsova, M. N. *Russ. Chem. Rev.* **1999**, *68*, 1001.
(19) Saunders, M.; Jimenezvazquez, H. A. *Chem. Rev.* **1991**, *91*, 375.
(20) Landa, S.; Kriebel, S.; Knobloch, E. *Chem. Listy Vedu Prum.* **1954**, *48*, 61.
(21) Stetter, H.; Wulff, C. *Chem. Ber.* **1960**, *93*, 1366.
(22) Delimarsky, R. E.; Rodionov, V. N.; Yurchenko, A. G. *Ukr. Khim. Zh.* **1988**, *54*, 437.
(23) Maison, W.; Frangioni, J. V.; Pannier, N. *Org. Lett.* **2004**, *6*, 4567.
(24) Lamanna, G.; Russier, J.; Menard-Moyon, C.; Bianco, A. *Chem. Commun.* **2011**, *47*, 8955.
(25) Oganesyan, A.; Cruz, I. A.; Amador, R. B.; Sorto, N. A.; Lozano, J.; Godinez, C. E.; Anguiano, J.; Pace, H.; Sabih, G.; Gutierrez, C. G. *Org. Lett.* **2007**, *9*, 4967.
(26) Gibson, S. E.; Castaldi, M. P. *Angew. Chem.* **2006**, *118*, 4834; *Angew. Chem. Int. Ed.* **2006**, *45*, 4718.
(27) Gibson, S. E.; Castaldi, M. P. *Chem. Commun.* **2006**, 3045.
(28) Mammen, M.; Choi, S. K.; Whitesides, G. M. *Angew. Chem.* **1998**, *110*, 2908; *Angew. Chem. Int. Ed.* **1998**, *37*, 2755.
(29) Rao, J.; Lahiri, J.; Isaacs, L.; Weis, R. M.; Whitesides, G. M. *Science (Washington, D.C.)* **1998**, *280*, 708.
(30) Locksley, R. M.; Killeen, N.; Lenardo, M. J. *Cell* **2001**, *104*, 487.
(31) Banner, D. W.; D'Arcy, A.; Janes, W.; Gentz, R.; Schoenfeld, H.-J.; Broger, C.; Loetscher, H.; Lesslauer, W. *Cell* **1993**, *73*, 431.
(32) Eckert, D. M.; Kim, P. S. *Annu. Rev. Biochem.* **2001**, *70*, 777.
(33) Kwong, P. D.; Wyatt, R.; Robinson, J.; Sweet, R. W.; Sodroski, J.; Hendrickson, W. A. *Nature (London)* **1998**, *393*, 648.
(34) Parkin, G. *Chem. Rev.* **2004**, *104*, 699.
(35) Waite, J. H. *Nat. Mater.* **2008**, *7*, 8.
(36) Keller-Schierlein, W.; Prelog, V.; Zahner, H. *Fortschr. Chem. Org. Naturst.* **1964**, *22*, 279.
(37) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140.
(38) Wiskur, S. L.; Ait-Haddou, H.; Lavigne, J. J.; Anslyn, E. V. *Acc. Chem. Res.* **2001**, *34*, 963.
(39) Bianco, A.; Fournel, S.; Wieckowski, S.; Hoebeke, J.; Guichard, G. *Org. Biomol. Chem.* **2006**, *4*, 1461.
(40) Newkome, G. R.; Kotta, K. K.; Moorefield, C. N. *Chem. Eur. J.* **2006**, *12*, 3726.
(41) Humblet, V.; Misra, P.; Bhushan, K. R.; Nasr, K.; Ko, Y. S.; Tsukamoto, T.; Pannier, N.; Frangioni, J. V.; Maison, W. *J. Med. Chem.* **2009**, *52*, 544.
(42) Franzmann, E.; Khalil, F.; Weidmann, C.; Schröder, M.; Rohnke, M.; Janek, J.; Smarsly, B. M.; Maison, W. *Chem. Eur. J.* **2011**, *17*, 8596.
(43) Nasr, K.; Pannier, N.; Frangioni, J. V.; Maison, W. *J. Org. Chem.* **2008**, *73*, 1056.
(44) Pavet, V.; Beyrath, J.; Pardin, C.; Morizot, A.; Lechner, M. C.; Briand, J. P.; Wendland, M.; Maison, W.; Fournel, S.;

Micheau, O.; Guichard, G.; Gronemeyer, H. *Cancer Res.* **2010**, *70*, 1101.
(45) Shioiri, T.; Yamada, S.; Ninomiya, K. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(46) Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285.
(47) Wienhold, F.; Claes, D.; Graczyk, K.; Maison, W. *Synthesis* **2011**, 4059.
(48) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
(49) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.
(50) Levine, P. M.; Carberry, T. P.; Holub, J. M.; Kirshenbaum, K. *Med. Chem. Commun.* **2013**, *4*, 493.
(51) Pannier, N.; Maison, W. *Eur. J. Org. Chem.* **2008**, 1278.
(52) Roth, S.; Drewe, W. C.; Thomas, N. R. *Nat. Protoc.* **2010**, *5*, 1967.
(53) Sharma, S. K.; Miller, M. J.; Payne, S. M. *J. Med. Chem.* **1989**, *32*, 357.
(54) Leonard, N. M.; Brunckova, J. *J. Org. Chem.* **2011**, *76*, 9169.
(55) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, **1988**.
(56) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Pearson: Harlow, **1989**.