Rigid Multivalent Scaffolds Based on Adamantane

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Rigid multivalent scaffolds based on adamantane

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Abstract

We present two new synthetic strategies to rigid multivalent scaffolds of the general structure **1** based on adamantane. Both routes start from arylated adamantane derivatives and give the target compounds **12** and **18** in 5 and 7 steps, respectively. These scaffolds have been designed for the assembly of multivalent binders for cell surface epitopes. The adamantane nucleus exposes three carboxylic acid groups in a well defined tripodal geometry for conjugation of targeting ligands. In addition, an amino group at the fourth bridgehead position provides a flexible linker for attachment of effector molecules such as contrast agents, radiotracers, or cytotoxins without interfering with the cell binding process.

Introduction

Multivalency is a common phenomenon in nature to enhance affinity and specificity of receptor ligand interactions.[1] Chemists have made use of this concept in various contexts.[2-9]

The binding ability of multivalent agents is influenced by the number, size and orientation of the binding sites, as well as the shape, orientation and flexibility of the scaffold to which monomeric ligands are attached. Theoretically, the largest gain of binding affinity for a given ligand-receptor interaction is expected for a perfect fit of the ligands to the binding epitope.[10] A scaffold for the assembly of multivalent ligands must therefore orient the ligands in a defined and proper geometry for binding.[11-13] This geometry, along with other design criteria (such as the number of ligands, solubility, biocompatibility) may vary for different applications and in consequence, a variety of different scaffolds has been used in the past.[14-17]

We have designed adamantyl scaffolds **2** (Figure 1) for multivalent interaction of small molecules with cell surface epitopes[18] and have shown that this adamantane-based strategy can improve binding affinity by over 1.5 logs, taking a prostate-specific membrane antigen (PSMA) small molecule radiotracer from an affinity of 9 nM[19] to 400 pM.[20] A special feature of these conjugates is the geometry of the bridgehead substituted adamantanes, orienting three ligands in a tripodal recognition motif and a fourth functional group for conjugation to contrast agents without interfering with cell surface binding.

Despite our encouraging results, compounds like **2** (n = 3) are not ideal scaffolds, because the propionate linkers between the adamantane nucleus and the ligands are flexible, rather than

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rigid. However, the synthesis of more rigid derivatives **2** (n = 0) proved to be difficult due to the unique reactivity of substituted adamantane derivatives. Other rigid scaffolds with tripodal recognition motifs have been reported and successfully used for applications in material science.[21] However, these systems require rigidifying aromatic spacers and are therefore not optimal for applications in polar media.

Results and discussion

Functionalization of the bridgehead positions in adamantyl scaffolds can be achieved most reliable by radical or cationic chemistry.[22] As a general trend, these substitutions become more difficult with the number of (electron withdrawing) substituents attached to the other bridgehead positions. This is due to statistical and/or electronic factors.[23,24] In particular, electron withdrawing substituents (like carboxy groups) destabilize cationic or radical intermediates leading frequently to drastic reaction conditions for the introduction of additional functionality.

The most obvious retrosynthetic strategies to differentially substituted adamantyl scaffolds **3** are depicted in Figure 2. Route I involves the desymmetrization of a tetrasubstituted adamantane derivative **4** as a key step. In route II, a trisubstituted intermediate **5** is converted to the target structure **3**. Route C is probably the most obvious choice, because a wide range of mono substituted adamantanes **6** is commercially available at low price. However, for the above mentioned reasons, we have not found practical reactions that permit introduction of three appropriate functionalities into various different precursors **6**.[25]

We were therefore focusing on the first two strategies in Figure 2. An essential component of route I is an appropriately (symmetrical) tetrasubstituted adamantane derivative **4** and various derivatives of this general structure are known.[26-38] For our purpose tetracarboxymethyl adamantane **8** seemed to be the most appropriate starting material, because we needed carboxylic acids in the target scaffold **12** (for the conjugation of ligands) and one of the carboxylic acids should be easy to convert to an amine *via* Curtius reaction. However, none of the known syntheses of **8**[26,32,35] is easily scalable, making **8** a precursor of limited value.

We have therefore first tried to develop a more practical synthesis of **8**. In this context tetraphenyladamantane **7**[28] proved to be a good precursor for oxidative degradation.[39] As depicted in Scheme 1, the conversion of **7** to the tetramethylester **8** worked, although the yield is not optimal. We decided to tolerate the low yield of these two early steps, because tetraphenyladamantane **7** can easily be generated in large quantities from 1-bromoadamantane as a cheap precursor. Immediate conversion of the intermediate tetracarboxylic acid to its methyl ester **8** is advantageous for workup and chromatographic purification of the oxidation product. In addition, the following desymmetrization by a partial ester hydrolysis requires the tetramethyl ester **8** as a starting material to give **9** in very good yield.

The resulting monocarboxylic acid **9** is then converted by a Curtius reaction[40] to the corresponding amine, obtained as its Boc-derivative **10** after reflux in *t*-BuOH. The Boc-group is cleaved subsequently with TFA to give the free amine **11** in good yield. This three-step procedure gave much better yields than the direct acidic hydrolysis of the intermediate isocyanate with water (in the latter case partial hydrolysis of the ester groups was observed).

For later conjugation of this sterically hindered amine to bulky effector molecules, we introduced an Ahx-spacer (6-aminohexanoic acid) at this stage with HATU coupling to give the trimethylester **12** as an orthogonally protected scaffold, ready for conjugation of ligands and effector molecules.

An alternative procedure for the synthesis of scaffolds **2** is depicted in Scheme 2. This approach is following the general route II (Figure 2) and does thus require the activation of a relatively unreactive CH-bond in a trisubstituted adamantane for introduction of the last substituent. As mentioned above, the three substituents A in intermediate **5** have to be selected carefully, because any electron withdrawing substituent (like the desired carboxyl group) would deactivate the adamantane nucleus for a fourth bridgehead substitution.

Phenyl rings were again found to be excellent substitutes for the carboxyl groups in the target compound **18** and we started with known triphenyladamantane **13**.[28] Like tetraphenyladamantane **7**, this compound can be easily prepared from cheap 1-bromoadamantane in one step *via* Friedel-Crafts chemistry.

We decided to introduce the fourth substituent to **13** *via* bromination assuming that the resulting bromide **14** would be a reasonable substrate for a radical addition to acrylonitrile. Among many methods known for the bromination of adamantane bridgeheads,[22] only one proved to be compatible with our strategy. The mild phase transfer catalyzed protocol developed by Schreiner and coworker[41] gave bromide **14** in good yield. This reaction is without precedence for highly substituted adamantanes like **13** and provides, for the first time, an easy access to tetrahedrally substituted derivatives like **14**-**18**.

After installation of the bromine in **14**, radical addition to acrylonitrile[42] was achieved in quantitative yield. The resulting cyano compound **15** was then submitted to an oxidative degradation of the phenyl rings with $RuCl_3$ and H_5IO_6 to give the tricarboxylic acid **16**. The cyano group was then reduced with hydrogen and PtO_2 to give the amine **17** which was Boc-protected in a final step to give the target compound **18** with a propionyl-spaced amine function for conjugation of effectors and three carboxylic acids for attachment of ligands. It should be noted that no chromatography is necessary for purification of compounds **13**-**18** because all of them can easily be purified by crystallization.

Summary and Conclusion

In summary, we report efficient syntheses of new adamantane scaffolds. Both routes are short and give the target compounds **12** and **18** in good yields. These scaffolds have been designed to orient three carboxylic acids in a strictly defined tripodal geometry for the conjugation of cell surface binders. In addition, a primary amine allows the conjugation of the scaffold to an effector molecule which is pointing away from the ligands and is therefore unlikely to interfere with the binding process. We are currently evaluating the potential of these scaffolds for various multivalent ligand receptor interactions. It should be noted that our scaffolds are providing a strictly defined tripodal recognition motif (for surfaces) in combination with a fourth binding motif with all four functionalities easily addressable by standard conjugation techniques. Unlike other systems of that sort,[21] no rigidifying (hydrophobic) aromatic spacers are needed, making them a particularly interesting choice for applications in polar media. We suggest that our scaffolds might be of general use as rigid tetravalent building blocks for applications in organic chemistry[43] and material science.[44]

Experimental Section

3,5,7-Tricarboxymethyladamantane-1-carboxylic acid 9

1 N solution of potassium hydroxide (0.01 mL, 0.01 mmol) was added to a solution of 1,3,5,7-tetracarboxymethyladamantane **8** (3.68 mg, 0.01 mmol) in 2 mL of acetonitrile/methanol/water (3:2:5). The reaction mixture was stirred for 3 hours and the completion of the reaction was followed by thin layer chromatography. Solvents were removed *in vacuo* and the aqueous solution was washed with dichloromethane (3 × 5 mL). The aqueous layer was acidified with

1 N HCl and extracted with dichloromethane (3×5 mL). The combined extracts were dried over Na_2SO_4 and solvent was removed *in vacuo* to give 3.1 mg of **9** as white crystals (90%). ^{1}H-NMR (CDCl$_3$, 600 MHz): δ 3.70 (s, 9H), 2.02 (s, *6H*), 2.03 (s, 6H); ^{13}C-NMR (CDCl$_3$, 125 MHz): δ 181.4, 175.6, 52.4, 42.0, 41.8, 38.7, 38.5; MS (ESI) [M-H]$^-$: 353.4; HRMS (EI) calcd for $C_{17}H_{22}O_8$[M]$^+$: 354.1315. Found: 354.1312.

7-Amino-1,3,5-tricarboxymethyladamantane 11

DPPA (0.063 mL, 0.29 mmol) and triethylamine (0.04 mL, 0.29 mmol) were added to a solution of 3,5,7-tricarboxymethyladamantane-1-carboxylic acid **9** (86 mg, 0.24 mmol) dissolved in dichloromethane (2mL). The reaction mixture was stirred for 1 hour and the completion of the reaction was followed by TLC. An additional 10 mL of dichloromethane was added and the reaction mixture was washed with water (3×10 mL), saturated $NaHCO_3$ solution (3×10 mL), saturated NaCl (3×10mL) and dried over Na_2SO_4. Dichloromethane was removed *in vacuo* and *t*-BuOH (50 mL) was added. The reaction mixture was refluxed under nitrogen atmosphere for 5 hours. Excess of *t*-BuOH was removed *in vacuo* and the colorless residue (**10**) was treated with a solution of 50% of TFA in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for one hour. The solvent was removed *in vacuo* and the white residue was purified by column chromatography (silica gel, EtOAc / hexane, 6:4, $R_f = 0.78$) to give 65 mg of **11** as a colorless solid (83%). ^{1}H-NMR (CDCl$_3$, 600 MHz): δ 3.65 (s, 9H), 2.03-1.89 (m, 12H); ^{13}C-NMR (CDCl$_3$, 125 MHz): δ 175.9, 52.4, 52.1 43.2, 42.0, 38.8; HRMS (ESI) calcd. for $C_{16}H_{24}NO_6$ [M+H] : 326.1604. Found: 326.1598.

1-Bromo-3,5,7-triphenyladamantane 14

To a solution of 1,3,5-triphenyladamantane **13** (0.20 g, 0.55 mmol), tetrabrommethane (0.73 g, 2.2 mmol) and tetrabutylammoniumbromide (0.02 g, 0.06 mmol) in 5 mL flourobenzene were added 3 mL NaOH (*wt* 50%) and the resulting reaction mixture was heated to 75 °C for 24 h. The solvent was evaporated *in vacuo*; the crude product was suspended in water and extracted three times with each 20 mL dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo* to give the bromide **14**. After Crystallization from hexane/ethyl acetate (1:1), 0.26 g (0.49 mmol; 89%) of **14** were isolated as a yellow solid. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ 7.23-7.35 (m, 15H), 2.62 (s, 6H), 2.17 (d, 3H, $^2J = 13.4$ Hz), 2.14 (d, 3H, $^2J = 13.4$ Hz); ^{13}C-NMR (CDCl$_3$, 100 MHz): δ 147.8, 128.7, 126.7, 125.0, 65.2, 52.8, 46.7, 42.3; HRMS (EI) calcd. for $C_{28}H_{27}Br$; MS [M]$^+$: 442.1296. Found: 442.1297.

1,3,5-Triphenyl-7-(2-cyanoethyl)-adamantane 15

A solution of 1-bromo-3,5,7-triphenyladamantane **14** (0.50 g, 1.13 mmol), acrylonitrile (0.18 g, 3.39 mmol), tributylstannane (0.65 g, 2.26 mmol) and AIBN (19 mg, 0.113 mmol) in 10 ml toluene was heated to reflux for 6 h. Ethyl acetate und 1 M aqueous NH_3 solution were added and the separated organic phase was washed with 1 M aqueous NH_3 solution and water, dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by filtration over silica (byproducts were eluted with hexane/ethyl acetate 2:1; product with ethyl acetate) to give 0.47 g of **15** (1.13 mmol; quant). ^{1}H-NMR (CDCl$_3$, 400 MHz): 7.21-7.44 (m, 15H), 2.42 (t, 2H, $^3J = 8.1$ Hz), 2.12 (d, 3H, $^2J = 12.3$ Hz), 2.07 (d, 3H, $^2J = 12.3$ Hz), 1.80 (t, 2H, $^3J = 8.1$ Hz), 1.75 (s, 6H); ^{13}C-NMR (CDCl$_3$, 100 MHz): 149.0, 128.6, 126.4, 125.1, 12.5, 47.5, 46.0, 39.1, 39.0, 35.3, 11.5; HRMS (EI) calcd. for $C_{31}H_{31}N$ [M]$^+$: 417.2457. Found: 417.2452.

1,3,5-Tricarboxy-7-(2-cyanoethyl)-adamantane 16

A solution of **15** (550 mg, 1.3 mmol) and H_5IO_6 (12.6 g, 55 mmol) in 50 ml CCl$_4$/MeCN/ H_2O (3:2:3) was cooled to 0 °C and $RuCl_3 \times 3H_2O$ (69 mg, 0.3 mmol) was added. After stirring

for 2 h at 0 °C and 40 h at rt, the resulting reaction mixture was poured on ice and excess oxidant was destroyed by Na_2SO_3 addition. The aqueous layer was washed with ethyl acetate, acidified with 2 N HCl (pH 1) and extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo* to give 360 mg of **16** (1.1 mmol; 85%). ^{1}H-NMR (DMSO-d$_6$, 400 MHz): δ 12.3 (br s, 3H), 2.46 (t, 2H, ^3J = 7.9 Hz), 1.79 (d, 3H, ^2J = 13.7 Hz), 1.72 (d, 3H, ^2J = 13.7 Hz), 1.53 (t, 2H, ^3J = 7.9 Hz), 1.48 (s, 6H); ^{13}C-NMR (DMSO-d$_6$, 100 MHz): δ 177.1, 121.4, 41.1, 40.7, 40.3, 36.8, 33.3, 10.3; $C_{16}H_{19}NO_6$ calcd. C 59.81; H 5.96; N 4.36; found C 59.86; H 6.00; N 4.33; HRMS (EI) calcd. for $C_{16}H_{19}NO_6$ [M]$^+$: 321.1212. Found: 321.1208.

1,3,5-Tricarboxy-7-(3-aminopropyl)-adamantane hydrochloride 17

A solution of nitrile **16** (30 mg, 0.093 mmol) and PtO_2 (4.2 mg, 0.019 mmol) in 10 ml glacial acetic acid/conc. HCl (10:1) was hydrogenated (30 bar, rt) for 48 h. The resulting mixture was filtered and the solvent was evaporated *in vacuo*. The crude product was dissolved in water and washed two times with ethyl acetate. After evaporation of water *in vacuo*, 33 mg (0.091 mmol; 98%) of **17** were isolated as colorless crystals. ^{1}H-NMR (D$_2$O, 400 MHz): δ 2.96 (t, 2H, ^3J = 7.4 Hz), 1.94 (s, 6H), 1.64-1.69 (m, 2H), 1.61 (s, 6H), 1.30-1.34 (m, 2H); ^{13}C-NMR (D$_2$O, 100 MHz): δ 180.8, 41.9, 40.9, 40.0, 38.5, 38.0, 33.0, 20.2; MS (ESI) [M-Cl]$^+$: 326.4; HRMS (EI) calcd. for $C_{16}H_{24}NO_6$ [M-Cl]$^+$: 326.1604. Found: 326.1602.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

(1). Mammen M, Chio S-K, Whitesides GM. Angew. Chem., Int. Ed 1998;37:2755–2794.

(2). Carlson C, Mowery P, Owen R, Dykhuizen E, Kiessling L. ACS Chem. Biol 2007;2:119–127. [PubMed: 17291050]

(3). Wittmann V, Seeberger S. Angew. Chem., Int. Ed. Engl 2004;43:900–903. [PubMed: 14767971]

(4). Griffin JH, Linsell MS, Nodwell MB, Chen Q, Pace JL, Quast KL, Krause KM, Farrington L, Wu TX, Higgins DL, Jenkins TE, Christensen BG, Judice JK. J. Am. Chem. Soc 2003;125:6517–6531. [PubMed: 12785792]

(5). Lundquist JJ, Toone EJ. Chem. Rev 2002;102:555–578. [PubMed: 11841254]

(6). Lindhorst TK. Top. Curr. Chem 2002;218:201–235.

(7). Wright D, Usher L. Curr. Org. Chem 2001;5:1107–1131.

(8). Thumshirn G, Hersel U, Goodman SL, Kessler H. Chem. --Eur. J 2003;9:2717–2725.

(9). Fournel S, Wieckowski S, Sun W, Trouche N, Dumortier H, Bianco A, Chaloin O, Habib M, Peter JC, Schneider P, Vray B, Toes RE, Offringa R, Melief CJ, Hoebeke J, Guichard G. Nat. Chem. Biol 2005;1:377–382. [PubMed: 16370373]

(10). Kitov PI, Bundle DR. J. Am. Chem. Soc 2003;125:16271–16284. [PubMed: 14692768]

(11). Gestwicki JE, Strong LE, Kiessling LL. Chem. Biol 2000;7:583–591. [PubMed: 11048949]

(12). Cairo CW, Gestwicki JE, Kanai M, Kiessling LL. J. Am. Chem. Soc 2002;124:1615–1619. [PubMed: 11853434]

(13). Gestwicki JE, Cairo CW, Strong LE, Oetjen KA, Kiessling LL. J. Am. Chem. Soc 2002;124:14922–14933. [PubMed: 12475334]

(14). Gordon EJ, Gestwicki JE, Strong LE, Kiessling LL. Chem. Biol 2000;7:9–16. [PubMed: 10662681]

(15). Merritt EA, Zhang Z, Pickens JC, Ahn M, Hol WG, Fan E. J. Am. Chem. Soc 2002;124:8818–8824. [PubMed: 12137534]

(16). Roy R, Page D, Perez SF, Bencomo VV. Glycoconjugate J 1998;15:251–263.

(17). Haag R, Kratz F. Angew. Chem., Int. Ed. Engl 2006;45:1198–1215. [PubMed: 16444775]

(18). Maison W, Frangioni JV, Pannier N. Org. Lett 2004;6:4567–4569. [PubMed: 15548077]

(19). Humblet V, Lapidus R, Williams LR, Tsukamoto T, Rojas C, Majer P, Hin B, Ohnishi S, De Grand AM, Zaheer A, Renze JT, Nakayama A, Slusher BS, Frangioni JV. Mol. Imaging 2005;4:448–462. [PubMed: 16285907]

(20). Misra P, Humblet V, Pannier N, Maison W, Frangioni JV. J. Nucl. Med 2007;48:1379–1389. [PubMed: 17631555]

(21)a). Li Q, Rukavishnikov AV, Petukhov PA, Zaikova TO, Jin C, Keana JFW. J. Org. Chem 2003;68:4862–4869. [PubMed: 12790592] b) Li Q, Jin C, Petukhov PA, Rukavishnikov AV, Zaikova TO, Phadke A, LaMunyon DH, Lee MD, Keana JF. J. Org. Chem 2004;69:1010–1019. [PubMed: 14961648]

(22). Moiseev IK, Makarova NV, Zemtsova MN. Russ. Chem. Rev 1999;68:1001–1020.Fokin AA, Shubina TE, Gunchenko PA, Isaev SD, Yurchenko AG, Schreiner PR. J. Am. Chem. Soc 2002;124:10718–10727. [PubMed: 12207527]For a recent mechanistic analysis of these reactions see

(23). Fort RC, Schleyer P. v. R. Chem. Rev 1964;64:277–300.

(24). Saunders M, Jimenez-Vazquez HA. Chem. Rev 1991;91:375–397.

(25). We have tried different reactions for bridgehead functionalization such as arylations, halogenations and Koch-Haaf-type reactions with different substrates **6** (B = NHR, OH, CN, CO_2H, CH_2NH_3, CH_2CN, CH_2CO_2H, $(CH_2)_3NH_2$, $(CH_2)_3CN$, $(CH_2)_3CO_2H$) and achieved only mono- or disubstitution

(26). Landa S, Kamycek Z. Collect. Czech. Chem. Commun 1959;24:4004–4009.

(27). Stetter H, Wulff C. Chem. Ber 1960;93:1366–1371.

(28). Newman H. Synthesis 1972:692–693.

(29). Sollott GP, Gilbert EE. J. Org. Chem 1980;45:5405–5408.

(30). Naemura K, Hokura Y, Nakazaki M. Tetrahedron 1986;42:1763–1768.

(31). Reichert VR, Mathias LJ. Macromolecules 1994;27:7015–7023.

(32). Bashir-Hashemi A, Li J, Gelber N. Tetrahedron Lett 1995;36:1233–1236.

(33). Li Q, Rukavishnikov AV, Petukhov PA, Zaikova TO, Jin C, Keana JFW. J. Org. Chem 2003;68:4862–4869. [PubMed: 12790592]

(34). Dave PR, Duddu R, Yang K, Damavarapu R, Gelber N, Surapaneni R, Gilardi R. Tetrahedron Lett 2004;45:2159–2162.

(35). Lee GS, Bashara JN, Sabih G, Oganesyan A, Godjoian G, Duong HM, Marinez ER, Gutierrez CG. Org. Lett 2004;6:1705–1707. [PubMed: 15151394]

(36). Kozhushkov SI, Yufit DS, Boese R, Blaeser D, Schreiner PR, de Meijere A. Eur. J. Org. Chem 2005:1409–1415.

(37). Menger FM, Migulin VA. J. Org. Chem 1999;64:8916–8921. [PubMed: 11674798]

(38). Martin VV, Alferiev IS, Weis AL. Tetrahedron Lett 1999;40:223–226.

(39). Carlsen PHJ, Katsuki T, Martin VS, Sharpless KB. J. Org. Chem 1981;46:3936–3938.

(40). Smith PAS. Org. React. (N.Y.) 1946;3:337.

(41). Fokin AA, Schreiner PR. Adv. Syn. Cat 2003;345:1035–1052.

(42). Ohno M, Ishizaki K, Eguchi S. J. Org. Chem 1988;53:1285–1288.

(43). Maison W, Frangioni JV. Angew. Chem., Int. Ed. Engl 2003;42:4726–4728. [PubMed: 14562338]

(44). Li Q, Jin C, Petukhov PA, Rukavishnikov AV, Zaikova TO, Phadke A, LaMunyon DH, Lee MD, Keana JF. J. Org. Chem 2004;69:1010–1019. [PubMed: 14961648]
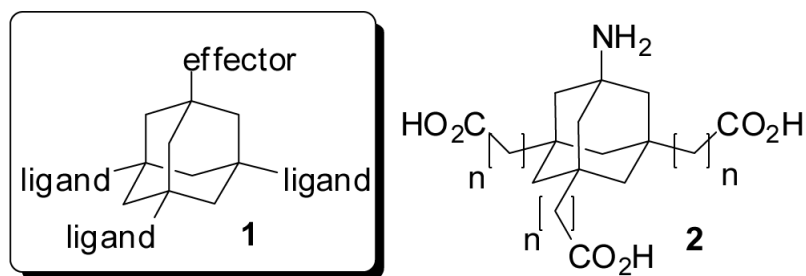
Figure 1.
Schematic drawing of modular multivalent ligands **1** and suitable scaffolds **2**.
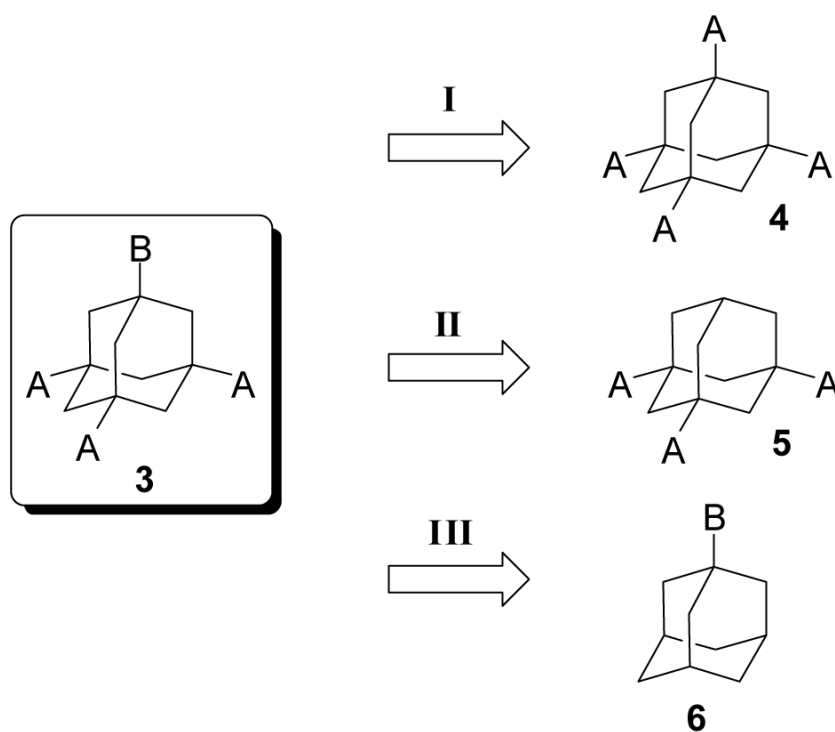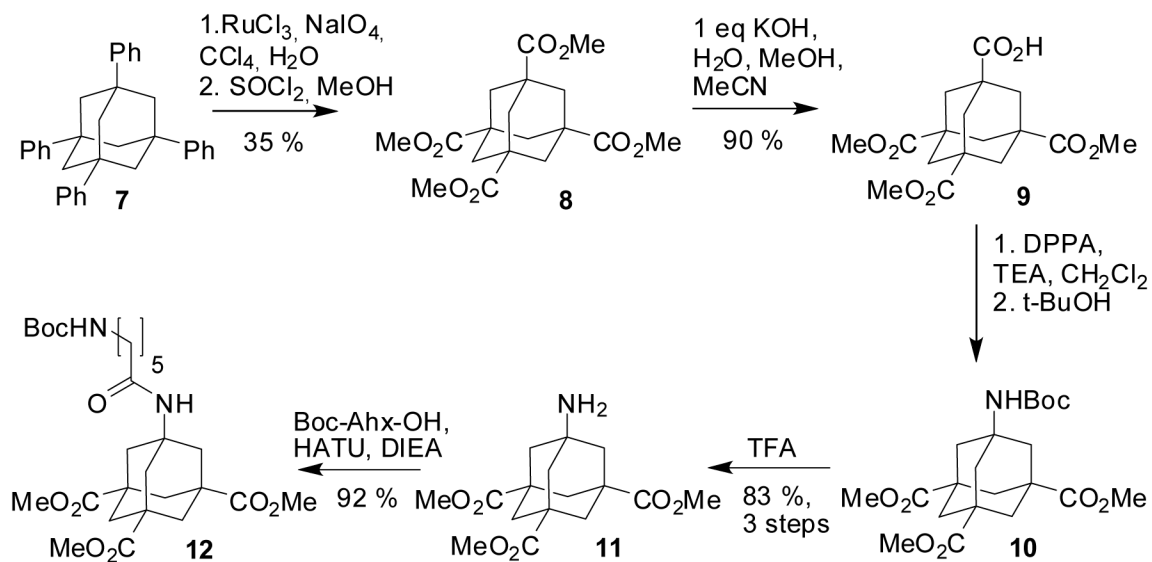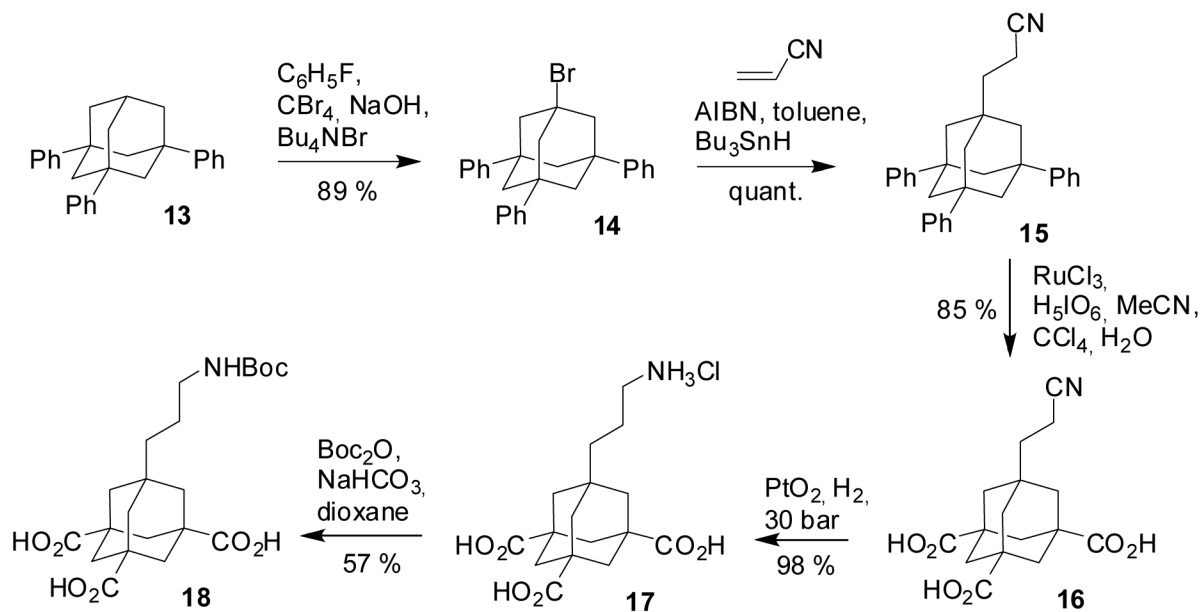
Figure 2.
Retrosynthetic analysis of adamantyl scaffolds **3**.

Scheme 1.
Synthesis of rigid adamantane scaffold **12** following general route **I** (Figure 2).

Scheme 2.
Synthesis of rigid adamantane scaffold **18** following general route **II** (Figure 2).