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Synthesis of Adamantane-Based Trimeric Benzoboroxoles

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Benzoboroxoles are known to bind 1,2-diol motifs in carbohydrates in an aqueous environment. Their binding properties have been shown to be dependent on additional recognition sites such as peptides and the number of binding epitopes. In this paper we describe the synthesis of trimeric benzoboroxoles based on a rigid adamantyl core structure. The conjugates are assembled using copper-catalyzed click reactions of azide scaffolds with alkynyl-functionalized benzoboroxoles. The design of our trimeric benzoboroxoles followed a biomimetic principle and imitates the trimeric structure of some natural carbohydrate binding proteins (lectins). With an assortment of appropriately functionalized (3 + 1) adamantane scaffolds, trimeric benzoboroxoles have been generated which were combined with additional functional molecules such as dyes and peptides. In summary, we report a highly effective synthetic approach to modular trimeric boronolectines for the assembly of carbohydrate sensors.

Introduction

Carbohydrates are a complex and fascinating class of biomolecules with various functions in metabolism, as structural substances and for energy storage.[1] In addition, carbohydrates play a key role in cell differentiation, cell–cell and cell–pathogen interactions.[2] In nature, carbohydrates are recognized by carbohydrate binding proteins, the lectins.[3] Water-soluble lectins (e.g. MBP – Mannose binding Protein) are used as a first line of defense by the immune system in recognizing glycotopes on pathogens.[4] Other lectins, such as DC-SIGN, hemagglutinine and CD22 are key players in viral infections and the immune response.[5] Mimicking lectins with small molecules is therefore a highly attractive goal in medicinal chemistry.

Lectins contain one or more carbohydrate recognition domains (CRDs). As most monomeric carbohydrate–lectin interactions are of weak affinity and specificity,[6] nature uses multiple protein–carbohydrate interactions (resulting in the cluster glycoside effect)[7] to strengthen and specify the binding process through establishment of multivalency.[8] Many multimeric lectins have geometrically defined multimeric recognition motifs and important derivatives are trimeric assemblies.[4a,8a] In several pharmaceutically relevant lectins, such as DC-SIGN,[9] the CRDs are assumed to be assembled closely in a tripodal geometry with distances less than 2 nm. It might therefore be possible to mimic these trimeric binding sites with relatively small molecules resembling a tripodal carbohydrate recognition motif.

However, achieving carbohydrate binding with small molecules remains a challenge and only a limited set of structures has been shown to have useful binding affinities in water.[10] Boronic acids bind selectively and with reasonable affinities to different carbohydrates.[11] Particularly, *ortho*-donor substituted arylboronic acids (Wulff-type, **1**) have been used as carbohydrate binders because they bind to diol motifs under aqueous, pH-neutral conditions.[12] Wulff-type boronic acids with a hydroxymethyl group as donor, so called "benzoboroxoles" or "benzoxaboroles" (general structure **2** in Figure 1)[13] have also been studied extensively.[14] They showed reasonable binding affinities and selectivities for non-reducing sugars in aqueous solution.[15] Selectivity and affinity of these boronic acids are influenced by multimerization and additional moieties (e.g. aromatic rings or peptides) that interact with carbohydrates.[16] These conjugates have been termed boronolectins and two examples are depicted in Figure 2.[17] Anslyn reported tripodal boronic acid **3** containing an aromatic core structure. This trimer binds to heparin, a useful property for biomedical applications.[18] Hall reported dimeric benzoboroxole **4** which is able to bind to the TF antigen present on 90% of human cancer cells.[19] As the same structure lacking the boronic acids also showed a small but measurable binding affinity to the TF antigen, it was shown that the boronic acid moieties influence the binding affinity significantly but that the overall binding affinity is due to the additional presence of the peptide.

Herein we describe the synthesis of tripodal boronolectins based on an adamantyl scaffold. The rigid adamantyl

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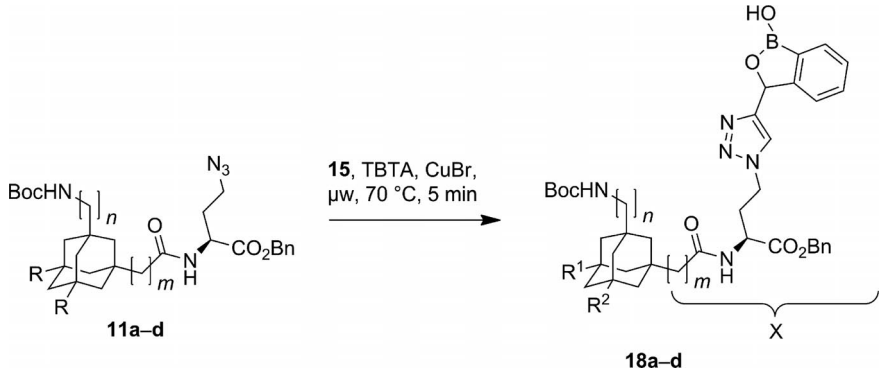


Figure 1. In aqueous solution, boronic acids bind reversibly to diols. Donor-substituted derivatives of arylboronic acids such as the Wulff-type boronic acids **1** or benzoboroxole **2** combine good chemical stability with a relatively high binding affinity to carbohydrates in aqueous solution.

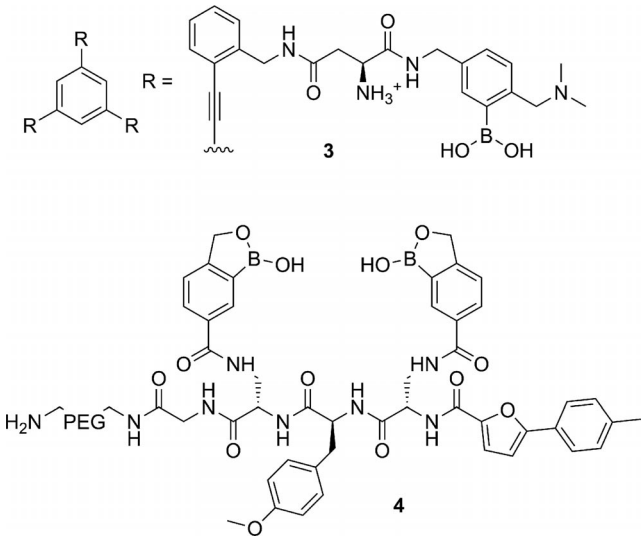


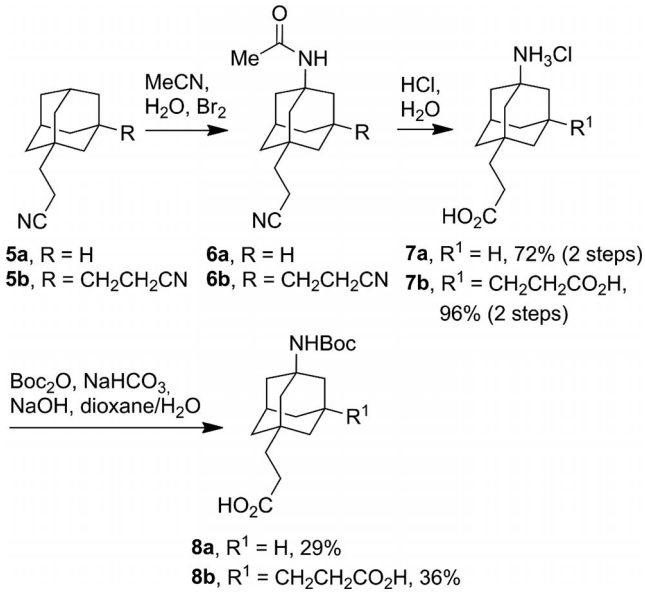
Figure 2. Selected examples for peptide boronolectins: Anslyn's heparin receptor **3** and Hall's dimeric benzoboroxole **4** which is able to recognize the TF-antigen.[17,18]

core structure allows the conjugation of three benzoboroxoles and a reporter moiety such as a fluorescence dye.

Results and Discussion

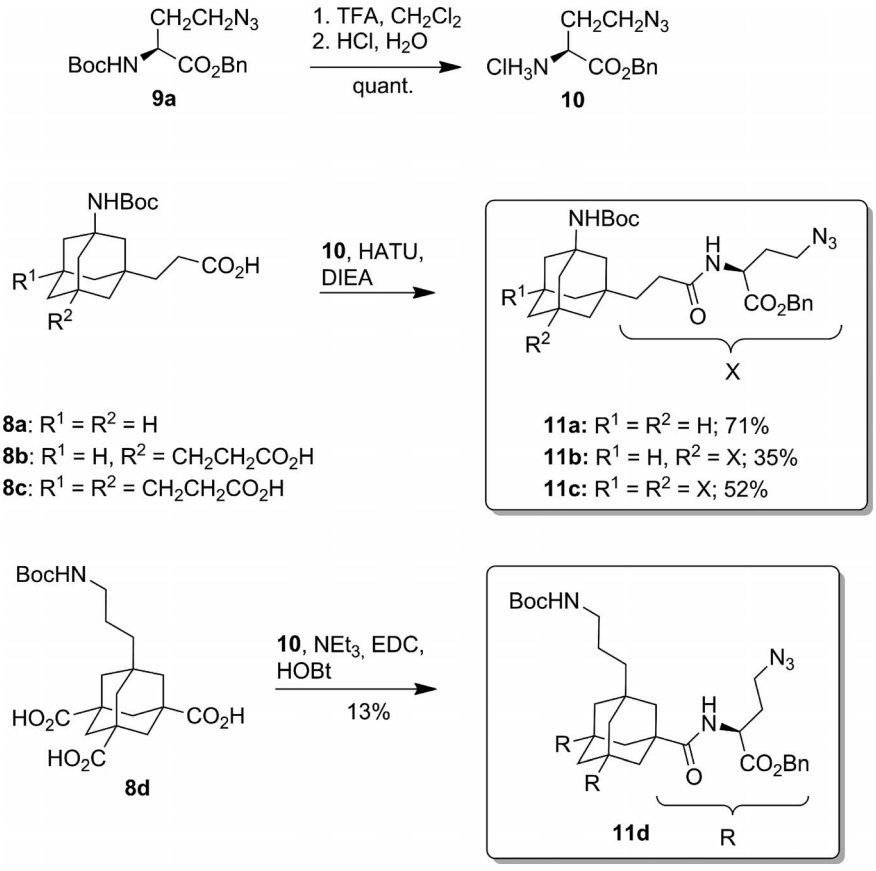
Synthesis of Adamantyl Scaffolds

Adamantyl derivatives are versatile tetrahedral (3 + 1) scaffolds with a range of applications in Medicinal Chemistry,[20] Material Science[21] and Supramolecular Chemistry.[22] A number of appropriately functionalized adamantyl scaffolds such as **8a**–**d** (Scheme 1) are readily available in a few steps from adamantane as a cheap precursor.[23] Scaffolds **8c**–**d** have three carboxylic acid side chains for the conjugation of boronic acids (for the assembly of the tripodal carbohydrate recognition domain) and a fourth position with a primary amine which may be coupled to an additional functional molecule such as a fluorescent dye. For a systematic study of the binding properties of our trimeric boronolectins, we were also interested in scaffolds **8a** and **8b** with one or two carboxylic acids in the side chains, respectively. Both derivatives were synthesized starting from cyanoethyl derivatives **5a** and **5b** (Scheme 1).[24] These starting materials were initially converted into acetamides **6a** and **6b** by a Ritter reaction; hydrolysis of the amide and the cyanide afforded adamantylamino acids **7a** and **7b**, which were then protected with Boc_2O to give Boc-protected scaffolds **8a** and **8b**.



Scheme 1. Synthesis of Boc-protected adamantyl scaffolds **8a** and **8b** with one and two carboxylic acids for the conjugation of benzoboroxoles.

Following a modular design approach of our tripodal boronolectins, we wanted to be able to include additional (peptidic) binding motifs next to the benzoboroxoles. Scaffolds **8a**–**d** were thus coupled to L-azidohomoalanine **10** to give **11a**–**d** (Scheme 2), ideal precursors for the attachment of benzoboroxoles through application of copper-catalyzed cycloaddition of the azide moiety. In addition, the benzyl ester provides an orthogonally protected conjugation site for peptides as an additional element of molecular recognition. With scaffolds **11a**–**d** in hand, a set of modular com-



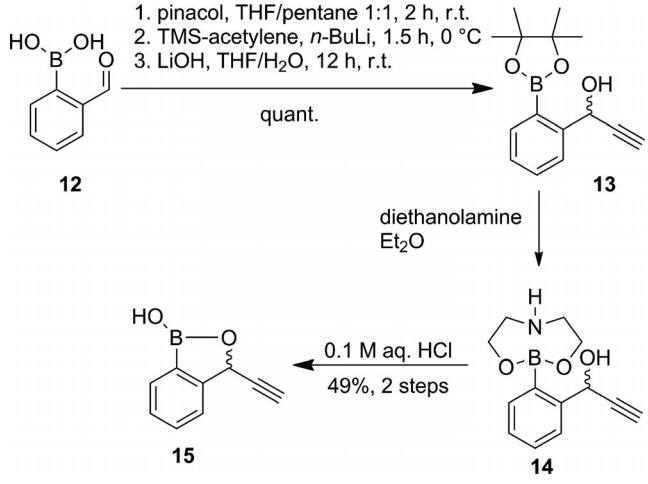
Scheme 2. Deprotection of L-azidohomoalanine **9a** to the corresponding hydrochloride **10** and the preparation of modular scaffolds **11a**–**d**. DIEA: *N*,*N*-diisopropylethylamine, HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOBt: hydroxybenzotriazole, EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

pounds was now available allowing for assembly of boronolectins with different numbers and distances of benzoboroxoles as carbohydrate recognition motifs.

Assembly of Boronolectins

For the attachment of boronic acids to scaffolds **11a**–**d** using copper-mediated cycloaddition,[25] suitable alkyne derivatives are required. We previously reported the synthesis of "clickable" boronic acids and have slightly modified our protocol as depicted in Scheme 3.[26] The preparation of alkynyl benzoboroxole **15** starts from commercial aldehyde **12** which, after protection and addition of an acetylide, gave pinacol ester **13**, following our established protocol. To avoid problems with pinacol deprotection and to simplify the purification of the boronate ester, **13** was then converted to **14** with diethanolamine. Boronate **14** can be easily purified by crystallization.[27] Treatment with HCl ultimately afforded target benzoboroxole **15** in a few steps with good overall yield.

With scaffolds **11a**–**d** and benzoboroxole **15** in hand we sought to conjugate them through application of "click chemistry". Derivatives of arylboronic acids can be problematic substrates for Cu^{I}-catalyzed cycloadditions due to their propensity for deboronation. We had observed this



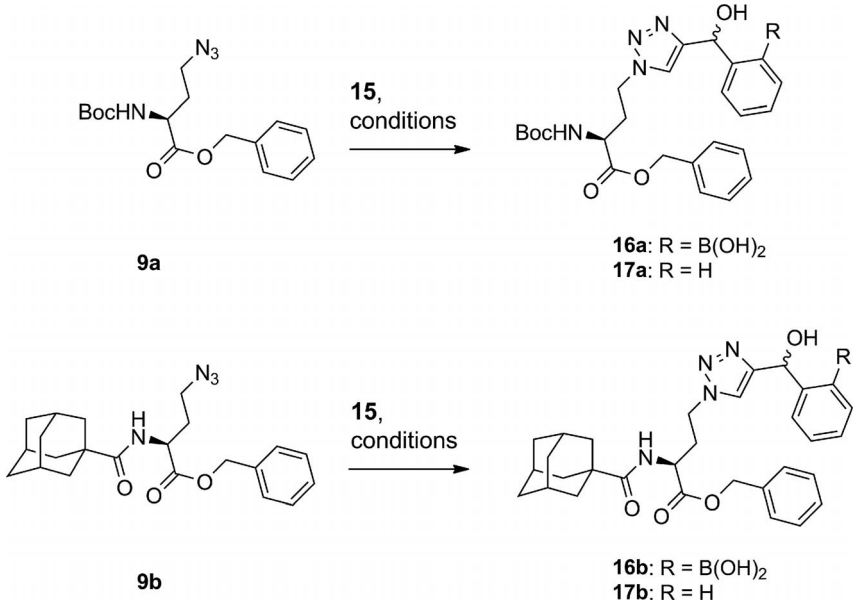
Scheme 3. Improved synthetic protocol for the synthesis of alkynylboronic acid **15**.

side reaction in previous studies and have therefore used CsF as an additive for our cycloadditions. CsF has been reported to suppress deboronation by in situ formation of boronic acid fluorides.[28] However, with benzoboroxole **15** and scaffolds like **11a**–**d**, this protocol (10 mol-% TBTA, 10 mol-%, CuBr, CsF, DMF/*t*BuOH/H_2O, 3:1:1, room

temp., 5 h) gave only low yields of the desired cycloaddition products; deboronation proved to be the major side reaction. In this case, it turned out to be advantageous to run the reaction without CsF and to limit reaction time. As depicted in Table 1, several reaction attempts revealed a suitable microwave-assisted protocol (Table 1, Entries 6 and 7) for conjugation of benzoboroxole **15** to our adamantyl scaffolds.

At low temperature and short reaction time (50 °C, 2 min, Table 1, Entry 1) incomplete conversions were observed with a significant quantity of unreacted starting material left in the crude reaction mixture along with desired cycloaddition product **16a**. At higher temperature and slightly longer reaction time (70 °C, 5 min, Table 1, Entry 2), complete conversion of starting material was achieved and desired product **16a** was formed along with a minor

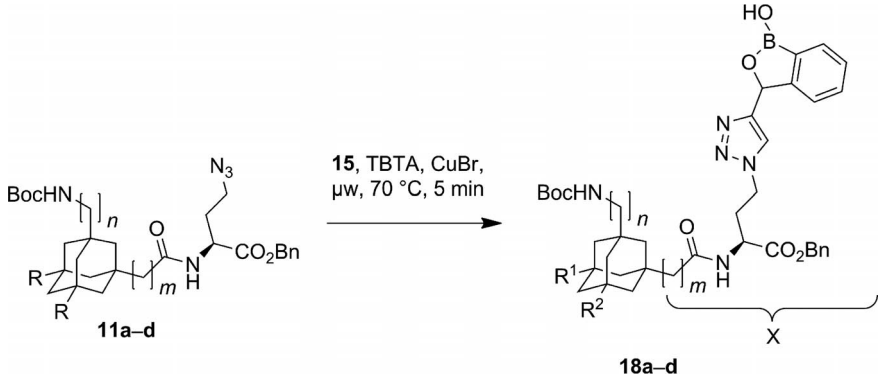
Table 1. Microwave-assisted copper catalyzed cycloadditions of azides **9a** and **9b** with benzoboroxole **15**.



Entry	Azide	Conditions[a]	*t* [min]	*T* [°C]	ratio **9/16/17**[b]
1	**9a**	$Cu^{II}SO_4$/NaAsc	2	50	40:60:0
2	**9a**	$Cu^{II}SO_4$/NaAsc	5	70	0:86:14
3	**9a**	$Cu^{II}SO_4$/NaAsc	10	70	0:50:50
4	**9a**	$Cu^{II}SO_4$/NaAsc/CsF	5	50	2:9:89
5	**9a**	$Cu^{I}Br$/TBTA	5	70	0:92:8
6	**9b**	$Cu^{II}SO_4$/NaAsc	5	70	0:60:40
7	**9b**	TBTA/$Cu^{I}Br$	5	70	0:70:30

[a] NaAsc: sodium ascorbate, TBTA: tris(benzyltriazolylmethyl)amine. [b] The ratio of starting material (**9**), desired cycloaddition product (**16**) and deboronated cycloaddition product (**17**) was measured by ^{1}H NMR analysis of the crude reaction mixture.

Table 2. Copper catalyzed cycloadditions of different adamantane scaffolds **11a**–**d** and alkyne **15**.

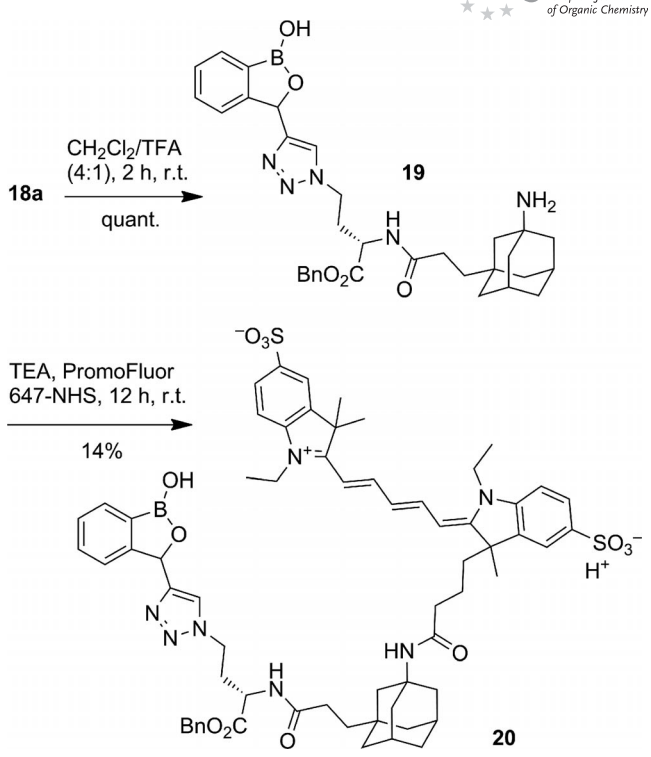


Azide	Triazole	*n*	*m*	R^1	R^2	Yield [%]
11a	**18a**	0	2	H	H	72
11b	**18b**	0	2	H	X	57
11c	**18c**	0	2	X	X	63
11d	**18d**	3	0	X	X	75

amount of deboronated byproduct **17a**. If the reaction time was further increased (Table 1, Entry 3), deboronation was found to become a major side reaction. To our surprise, the addition of CsF also afforded a large amount of deboronated product **17a** in this microwave-assisted protocol (Table 1, Entry 4). The best result for adamantine-based azide **9b** was obtained with CuBr combined with the activating ligand TBTA (Table 1, Entry 7).[29] This protocol was then used for the assembly of boronolectins **18a**–**d** shown in Table 2. All cycloaddition products were formed in good yields after HPLC-purification.

For applications of our boronolectins in binding assays, it would be advantageous to conjugate marker molecules such as fluorescence dyes. A representative example is depicted in Scheme 4. Starting from adamantylboronic acid **18a**, deprotection with TFA gave amine **19**. Labeling was achieved using Promofluor 647, which is commercially available as the activated NHS ester, to give traceable dye-conjugate **20**.

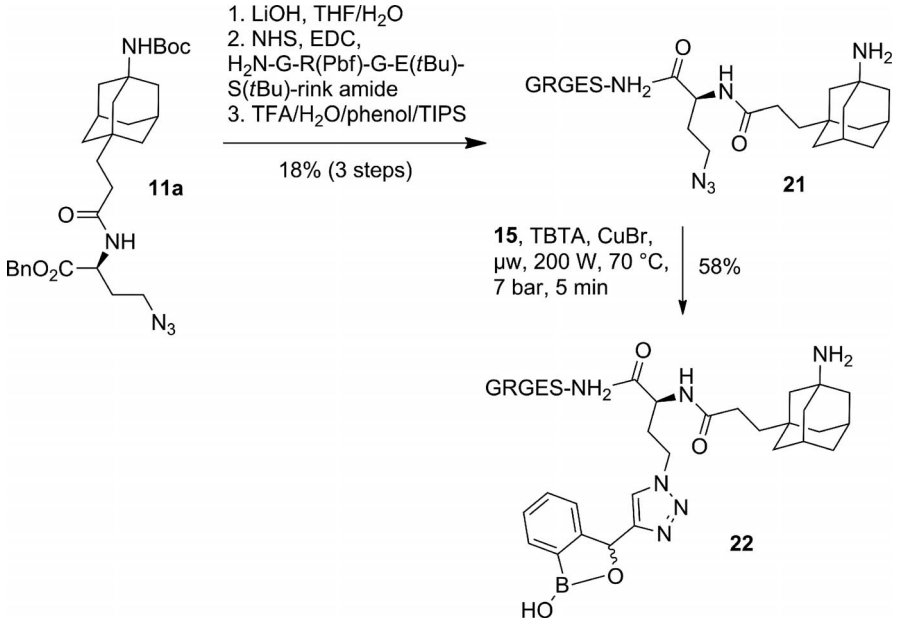
Scaffolds **11a**–**d** allow the conjugation of functional molecules using their protected carboxylic acids. This feature is particularly interesting for the synthesis of boronolectins bearing additional recognition elements such as peptides next to the boronic acid moieties. As a representative example, azide **11a** was deprotected with LiOH to give the corresponding carboxylic acid (Scheme 5). After activation as the NHS ester, a short model peptide sequence [NH_2-G-R(Pbf)-G-E(*t*Bu)-S(*t*Bu)-rink amide] was conjugated through amide formation. This pentapeptide is a known RGD-homologue, relevant to cell adhesion processes.[30] After complete acidic deprotection and HPLC-purification, adamantyl peptide **21** was obtained in reasonable yield over 3 steps. The standard click-protocol was applied to **21** and benzoboroxole **15** to afford desired peptide-boronic acid **22** in good yield.



Scheme 4. Synthesis of fluorescent boronic acid **20**.

Conclusions

Boronic acids of the benzoboroxole type are known to bind to carbohydrates in aqueous solution. However, the binding affinities for monomeric carbohydrate–benzoboroxole interactions are relatively low. Following the tripodal design principle of some lectins as natural (multivalent) carbohydrate binders, we were able to build up a small collection of lectin mimetics with different numbers and spac-



Scheme 5. Conjugation of a pentapeptide to adamantane scaffold **11a** followed by introduction of a boronic acid through the application of click chemistry. NHS: *N*-hydroxysuccinimide, EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, TIPS: triisopropylsilane.

ings of benzoboroxole moieties. Key components of these boronolectins are adamantyl scaffolds **11a–d** bearing azide functionalities and an alkyne functionalized boronic acid **15**. Both components were assembled to mono- di- and trivalent boronolectins using Cu^{I}-catalyzed click chemistry. The resulting conjugates have been labeled with fluorescence dyes and were conjugated to peptides as additional recognition motifs using an L-azidohomoalanine linker. Due to their modular character, adamantane-based benzoboroxoles may be combined with peptide libraries and dyes or a solid phase making the resulting carbohydrate binders eligible for binding assays of high throughput.

Experimental Section

The following compounds were prepared according to literature protocols: **5a** and **5b**,[24] azide **9a**,[31] tricarboxylic acid **8c**,[23a] tricarboxylic acid **8d**,[23c] triazide **11c**,[20e] pinacol ester **13** and boronic acid **15**.[26]

General Methods: TLC was performed on silica gel aluminum sheets (Macherey and Nagel). The reagent used for developing TLC plates was cerium stain (5 g ammonium molybdate, 0.1 g cerium sulfate tetrahydrate, 10 mL sulfuric acid and 90 mL H_2O). Flash column chromatography was performed on silica gel (Macherey and Nagel, 60–200 μm). ^{1}H NMR chemical shifts are referenced to residual non-deuterated solvent ($CDCl_3$, δ_H = 7.26 ppm. CD_3OD, δ_H = 3.31; [D_6]DMSO, δ_H = 2.50 ppm). ^{13}C NMR chemical shifts are referenced to the solvent signal ($CDCl_3$, δ_C = 77.16 ppm. CD_3OD, δ_C = 49.00; [D_6]DMSO, δ_C = 28.06 ppm). NMR spectra were recorded at 400 (100), or 600 (150) MHz with Bruker Avance instruments. Not all ^{13}C signals in the isolated benzoboroxoles were detected due to known carbon–boron couplings and signal broadening.[32] NMR-signals have been assigned on the basis of 2D NMR (HH-COSY, HMBC and HSQC) experiments. The atom numbers do not refer to IUPAC nomenclature and are available from the Supporting Information ESI mass spectra were recorded with a TOF Bruker MicroTOF-Q instrument operating in positive mode. Samples were dissolved in MeCN/H_2O mixtures or pure MeOH and directly injected using a syringe. If indicated with abs., solvents were dried by distillation from sodium under a nitrogen atmosphere prior to use. HPLC was performed with a LaChrom Elite (VWR, pump L-2130) with a UV detector (L-2400) and collected by a fraction collector (Teledyne ISCO Foxy R1). Microwave-assisted reactions were performed in a microwave reactor from CEM. Pentapeptide GRGES was synthesized with standard Fmoc SPPS (using HOBt, DIEA, NMP) on a peptide synthesizer CEM Liberty 12 using a Fmoc-Rink-Amid-2CT resin. As building blocks Fmoc-L-Arg(Pbf)-OH, Fmoc-L-Gly-OH, Fmoc-L-Ser(*t*Bu)-OH, and Fmoc-L-Glu-(*t*Bu)-OH were used. Cleavage of the peptide from the resin was achieved with CH_2Cl_2/TFA (v/v, 99:1) at room temp. for 15 min (four times). The organic phases were combined, concentrated to dryness and freeze dried with 0.1 M aq. HCl to give pentapeptide as a colorless solid that was used without further purification.

General Procedure A (peptide coupling with EDC/HOBt): To a stirred solution of the appropriate carboxylic acid (1.0 mmol) in abs. DMF (8 mL) NEt_3 (4.5 equiv./carboxylic acid) was added and stirred at 0 °C. After 10 min EDC (1.5 equiv./carboxylic acid) was added and after another 5 min HOBT (1.5 equiv./carboxylic acid) was added. The solution was stirred for 10 min before azidohomoalanine **10** (as HCl salt: 1.5 equiv./carboxylic acid) was added. The cooling bath was removed and the reaction was stirred for 3 d at room temp. The solvent was removed in vacuo and the residue was dissolved in EtOAc (10 mL) and 1 M aq. HCl (10 mL). The layers were separated and the organic phase washed with 1 M aq. HCl (2 × 10 mL) and saturated $KHCO_3$ (3 × 10 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The crude product was purified by flash chromatography.

General Procedure B (peptide coupling with HATU): To a stirred solution of the appropriate carboxylic acid (1.0 mmol) in abs. DMF (8 mL), HATU (1.3 equiv./per carboxylic acid) and DIEA (1.3 equiv./carboxylic acid) were added at 0 °C and the resulting solution was stirred for 10 min. L-azidohomoalanine **10** (as HCl salt, 1.3 equiv./carboxylic acid) and DIEA (1.3 equiv./carboxylic acid) were added. The cooling bath was removed and the reaction was stirred for 3 d at room temp. The solvent was removed in vacuo and the residue was dissolved in EtOAc (20 mL) and 0.1 M aq. HCl (10 mL). The layers were separated and the organic phase washed with 0.1 M aq. HCl (2 × 10 mL) and saturated $NaHCO_3$ (3 × 10 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness in vacuo. The crude product was purified by flash chromatography.

General Procedure C (click reaction): To a solution of the appropriate azide (0.1 mmol) in degassed *tert*-BuOH/H_2O/DMF (v/v, 1:1:3), boronic acid (1.3 equiv./azide moiety), CuBr (0.1 equiv./azide moiety) and TBTA (0.1 equiv./azide moiety) were added. The reaction vessel was closed and stirred for 5 min in a microwave reactor at 200 W, 70 °C and 7 bar. The solvent was removed in vacuo and the resulting crude product purified by column chromatography on silica to give desired boronic acids.

1-Amino-3-carboxyethyladamantane 7a: 1-Cyanoethyladamantane **5a** (320 mg, 1.70 mmol) was dissolved in Br_2 (8 mL), MeCN (0.89 mL, 17 mmol) and H_2O (0.15 mL, 8.5 mmol) and heated to reflux for 15 h. The reaction mixture was poured on ice and excess Br_2 was reduced with the addition of aqueous Na_2SO_3 solution (5 mL). The aqueous solution was extracted three times with EtOAc (each 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered and the solvent was removed in vacuo to give acetamide **6a** (420 mg) as a yellow solid, which was used in the next step without further purification. Crude acetamide **6a** was suspended in H_2O (16 mL) and HCl (3.4 mL) and heated to reflux for 40 h. After cooling to room temp., the solution was washed with EtOAc three times (each 20 mL) and the solvent was evaporated in vacuo to give the title compound **7a** (hydrochloride salt, 320 mg, 1.23 mmol, 72%). ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 2.38 [t, ^3J(H,H) = 8.1 Hz, 2 H, 9-H], 2.24–2.22 (m, 2 H, 5-H), 1.84 (br. d, $^2J_{H,H}$ = 12.0 Hz, 2 H, 7a-H), 1.78 (br. d, $^2J_{H,H}$ = 12.0 Hz, 2 H, 7b-H), 1.62 (br. s, 2 H, 6-H), 1.59 (s, 2 H, 2-H), 1.54–1.50 (m, 4 H, 4a-H), 1.44 (br. d, $^2J_{H,H}$ = 11.7 Hz, 2 H, 4b-H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 179.5 (C10), 52.8 (C1), 44.1 (C2), 39.4 (C7), 39.2 (C4), 37.1 (C8), 34.1 (C6), 33.8 (C3), 28.8 (C5), 27.8 (C9) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{21}NO_2$ [M + H]$^+$ = 224.1645, found 224.1649.

Diethyl 1-Aminoadamantane-3,5-dicarboxylate (7b): 1,3-Dicyanoethyladamantane **5b** (0.93 g, 3.80 mmol) was dissolved in Br_2 (10 mL), MeCN (2.02 mL, 38.4 mmol) and H_2O (0.35 mL, 19.0 mmol) and heated to reflux for 14 h. The reaction mixture was poured on ice and excess Br_2 was reduced with the addition of aqueous Na_2SO_3 solution (5 mL). The aqueous solution was extracted three times with EtOAc (each 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered and the solvent was removed in vacuo to give the acetamide **6b** (1.20 g) as

a yellow solid, which was used in the next step without further purification. Crude acetamide **6b** was suspended in H_2O (40 mL) and conc. HCl (8.5 mL) and heated to reflux for 50 h. After cooling to room temp., the solution was washed with EtOAc three times (each 50 mL) and the solvent was evaporated in vacuo to give title compound **7b** (hydrochloride salt, 1.21 g, 3.65 mmol, 96%). ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 2.28 (t, $^3J_{H,H}$ = 8.1 Hz, 4 H, 9-H), 2.19–2.04 (m, 1 H, 6-H), 1.66 (br. s, 2 H, 7-H), 1.50–1.42 (m, 8 H, 2-H, 8-H), 1.32 (br., 4 H, 5-H), 1.18 (d, $^2J_{H,H}$ = 11.8 Hz, 1 H, 4a-H), 1.10 (d, $^2J_{H,H}$ = 11.8 Hz, 1 H, 4b-H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 179.4 (C10), 53.4 (C1), 43.7 (C4), 43.6 (C2), 38.6 (C7), 36.7 (C5), 34.6 (C3), 34.3 (C8), 28.9 (C6), 27.8 (C9) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{25}NO_4$ [M + H]$^+$ = 296.1856, found 296.1859.

Ethyl 1-(3-*tert*-Butoxycarbonylamino)adamantane-3-carboxylate (8a): Amine **7a** (1.26 g, 4.85 mmol) was dissolved in H_2O/dioxane (60 mL v/v, 1:1). Boc_2O (1.23 g, 5.64 mmol) and Na_2CO_3 (1.19 g, 11.2 mmol) were added. The pH was adjusted to 10 with 1 M aqueous NaOH. The reaction was stirred in an ultrasonic bath for 8 h and 12 h at room temp. After a reaction time of 3 h, a second portion of Boc_2O (930 mg, 4.26 mmol) was added. The solvent was evaporated in vacuo and the residue dissolved in EtOAc/H_2O (100 mL v/v, 1:1). The layers were separated and the aqueous phase washed with EtOAc (2× 50 mL). The pH of the aqueous phase was adjusted to ≈ 1 with 1 M aq. HCl and extracted with EtOAc (3× 50 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered and concentrated to dryness in vacuo to give Boc-protected amine **8a** (450 mg, 1.39 mmol, 29%) as a colorless solid. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.96 (br. s, 1 H, 11-H), 6.31 (br. s, 1 H, 12-H), 2.12 (t, $^3J_{H,H}$ = 8.2 Hz, 2 H, 9-H), 2.02 (br. s, 2 H, 5-H), 1.75 (br. s, 4 H, 6-H), 1.55 (s, 2 H, 2-H), 1.53–1.47 (m, 2 H, 7-H), 1.34 (s, 9 H, 15-H), 1.34–1.27 (m, 6 H, 4-H, 8-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 175.0 (C10), 77.0 (C14), 50.3 (C1), 45.4 (C2), 40.7 (C6), 40.4 (C4), 38.0 (C8), 35.5 (C7), 33.5 (C3), 28.9 (C5), 28.3 (C15), 27.7 (C9) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{29}NO_4$ [M + Na]$^+$ = 346.1988, found 346.1989.

1-(3-*tert*-Butoxycarbonylamino)-3,5-bis(2-carboxyethyl)adamantane (8b): Amine **7b** (437 mg, 1.48 mmol) was dissolved in saturated aq. $NaHCO_3$/(30 mL v/v, 1:1). Boc_2O (420 mg, 1.93 mmol) was added and the pH adjusted to 10 with 1 M aq. NaOH. The reaction was stirred at room temp. for 12 h. The solvent was evaporated in vacuo and the residue solved in EtOAc/H_2O (20 mL v/v, 1:1). The layers were separated and the aqueous phase washed with EtOAc (2× 10 mL). With 1 M aq. HCl the pH of the aqueous phase was adjusted to 1 and extracted with EtOAc (3× 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered and concentrated to dryness under reduced pressure to give title compound **8b** (212 mg, 0.54 mmol, 36%) as a pale yellow oil. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 2.27 (t, $^3J_{H,H}$ = 8.4 Hz, 4 H, 9-H), 2.14–2.20 (m, 1 H, 6-H), 1.81 (br. s, 2 H, 7-H), 1.63 (d, $^2J_{H,H}$ = 12.1 Hz, 2 H, 2a-H), 1.57 (d, $^2J_{H,H}$ = 12.4 Hz, 2 H, 2b-H), 1.46–1.54 (m, 4 H, 8-H), 1.31–1.46 (m, 13 H, 5-H, 14-H), 1.18 (s, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 178.2 (C10), 79.5 (C13), 52.8 (C1), 46.8 (C4), 46.5 (C2), 41.5 (C7), 41.3 (C5), 39.3 (C8), 35.5 (C3), 31.1 (C6), 29.0 (C9), 28.9 (C14) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{33}NO_6$ [M + Na]$^+$ = 418.2200, found 418.2210.

Azide 9b: Azide **9b** was synthesized according to general procedure A from adamantane1-carboxylic acid (214 mg, 1.19 mmol) with NEt_3 (0.75 mL, 5.3 mmol), EDC (319 mg, 1.66 mmol), HOBT (254 mg, 1.66 mmol) and azidohomoalanine **10** (as HCl salt: 417 mg, 1.54 mmol). The crude product was purified by flash chromatography (PE/EtOAc v/v, 2:1) and title compound **9b** obtained as a pale yellow solid (277 mg, 0.699 mmol, 59%). R_f = 0.5 (PE/EtOAc, v/v 2:1, cerium stain). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.44–7.30 (m, 5 H, H_{arom}), 6.35 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, 6-H), 5.23 (d, $^2J_{H,H}$ = 12.1 Hz, 1 H, 11a-H), 5.16 (d, $^2J_{H,H}$ = 12.1 Hz, 1 H, 11b-H), 4.73–4.66 (m, 1 H, 7-H), 3.40–3.24 (m, 2 H, 9-H), 2.22–2.10 (m, 1 H, 8a-H), 2.08–2.02 (m, 3 H, 1-H), 2.02–1.91 (m, 1 H, 8b-H), 1.86 (br. d, $^4J_{H,H}$ = 2.5 Hz, 6 H, 2-H), 1.75 (d, $^2J_{H,H}$ = 12.2 Hz, 3 H, 4a-H), 1.69 (d, $^2J_{H,H}$ = 12.2 Hz, 3 H,4b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 178.0 (C5), 171.9 (C10), 135.2 (C12), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.5 (C_{arom}), 67.6 (C11), 50.2 (C7), 47.9 (C9), 39.2 (C2), 36.6 (C4), 31.4 (C8), 28.2 (C1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{22}H_{28}N_4O_3$ [M + Na]$^+$ = 419.2054, found 419.2047.

L-Azidohomoalanine Benzyl Ester (10): Boc-protected **9a** (85 mg, 0.25 mmol) was stirred in CH_2Cl_2/TFA (v/v, 4:1) at room temp. for 1.5 h. The solvent was removed in vacuo to give the title compound as a TFA salt. This TFA salt was dissolved in 0.1 M aq. HCl and MeCN and freeze dried to give title compound **10** as the HCl salt (67 mg, 0.25 mmol, quant.) as a pale yellow oil. **10 as TFA salt** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.58 (br. s, 3 H, 10-H), 7.41–7.28 (m, 5 H, H_{arom}), 5.24 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, 3a-H), 5.16 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, 3b-H), 4.20 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, 1-H), 3.59–3.41 (m, 2 H, 9-H), 2.30–2.09 (m, 2 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.1 (C2), 162.6 (TFA), 162.2 (TFA), 161.8 (TFA), 161.5 (TFA), 134.1 (C4), 129.2 (C_{arom}), 128.9 (C_{arom}), 128.8 (C_{arom}), 69.0 (C3), 51.2 (C1), 47.1 (C9), 29.3 (C8) ppm. **10 as HCl salt** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.86 (br. s, 3 H, 10-H), 7.37–7.27 (m, 5 H, H_{arom}), 5.23 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, 3a-H), 5.15 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, 3b-H), 4.37 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, 1-H), 3.72–3.51 (m, 2 H, 9-H), 2.43–2.22 (m, 2 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.3 (C2), 134.5 (C4), 128.9 (C_{arom}), 128.8 (C_{arom}), 128.6 (C_{arom}), 68.5 (C3), 51.2 (C1), 47.0 (C9), 29.6 (C8) ppm. IR (film): $\tilde{\nu}$ = 3431, 2109, 1635 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{11}H_{14}N_4O_2$ [M + H]$^+$ = 235.1190, found 235.1194.

Azide 11a: This compound was synthesized according to general procedure B from carboxylic acid **8a** (200 mg, 0.618 mmol) with HATU (306 mg, 0.804 mmol), DIEA (0.28 mL, 1.6 mmol), L-azidohomoalanine **10** (as HCl salt: 231 mg, 0.804 mmol). The crude product was purified by flash chromatography (PE/EtOAc v/v, 2:1) and title compound **11a** obtained as colorless oil (236 mg, 0.437 mmol, 71%). R_f = 0.6 (PE/EtOAc, v/v 1:1, cerium stain). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.43–7.31 (m, 5 H, H_{arom}), 6.16 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 11-H), 5.20 (d, $^2J_{H,H}$ = 12.2 Hz, 1 H, 16a-H), 5.17 (d, $^2J_{H,H}$ = 12.2 Hz, 1 H, 16b-H), 4.76–4.66 (m, 1 H, 12-H), 4.41 (br. s, 1 H, 21-H), 3.40–3.26 (m, 2 H, 14-H), 2.24–2.18 (m, 2 H, 9-H), 2.18–2.14 (m, 1 H, 13a-H), 2.14–2.09 (m, 2 H, 5-H), 2.02–1.92 (m, 1 H, 13b-H), 1.90–1.77 (m, 4 H, 6-H), 1.66 (br. s, 2 H, 2-H), 1.64–1.51 (m, 4 H, 4-H), 1.51–1.45 (m, 2 H, 8-H), 1.42 (s, 9 H, 24-H), 1.41–1.35 (m, 2 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.7 (C10), 171.8 (C15), 135.1 (C17), 128.82 (C_{arom}), 128.78 (C_{arom}), 128.6 (C_{arom}), 78.8 (C23), 67.7 (C16), 51.3 (C1), 50.3 (C12), 47.9 (C14), 46.1 (C2), 41.6 (C6), 41.1 (C7), 38.8 (C8), 36.0 (C4), 34.3 (C3), 31.6 (C13), 30.4 (C9), 29.6 (C5), 28.6 (C24) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{29}H_{41}N_5O_5$ [M + Na]$^+$ = 562.3000, found 562.3008.

Azide 11b: This compound was synthesized according to general procedure B from dicarboxylic acid **8b** (0.33 g, 0.94 mmol) with HATU (0.94 g, 2.5 mmol), DIEA (0.86 mL, 5.0 mmol), L-azidohomoalanine **10** (as HCl salt: 0.79 g, 2.9 mmol). The crude product

was purified by flash chromatography (PE/EtOAc v/v, 2:1) and title compound **11b** obtained as a colorless oil (0.27 g, 0.33 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.30 (m, 11 H, NH, H_{arom}), 6.33 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 11-H), 5.23–5.13 (m, 4 H, 16-H), 4.75–4.67 (m, 2 H, 12-H), 3.40–3.27 (m, 4 H, 14-H), 2.25–2.07 (m, 7 H, 6-H, 9-H, 13a-H), 2.01–1.91 (m, 2 H, 13b-H), 1.75 (br. s, 2 H, 7-H), 1.67–1.53 (m, 4 H, 2-H), 1.53–1.47 (m, 4 H, 8-H), 1.42 (s, 9 H, 24-H), 1.38–1.23 (m, 4 H, 5-H), 1.18–1.06 (m, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.7 (C10), 171.9 (C15), 135.1 (C17), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.5 (C_{arom}), 79.2 (C23), 67.7 (C16), 51.9 (C1), 50.3 (C12), 47.9 (C14), 45.6 (C2, C4), 41.0 (C7), 40.7 (C5), 38.4 (C8), 34.7 (C3), 31.5 (C13), 30.3 (C9), 29.7 (C6), 28.6 (C24) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{43}H_{57}N_9O_8$ [M + Na]$^+$ = 828.4403, found 828.4418.

Azide 11d: This compound was synthesized according to general procedure A from tricarboxylic acid **8c** (87 mg, 0.20 mmol) with NEt_3 (0.36 mL, 2.7 mmol), EDC (173 mg, 0.90 mmol), HOBT (138 mg, 0.90 mmol), and L-azidohomoalanine **10** (as HCl salt: 212 mg, 0.90 mmol). The crude product was purified by flash chromatography (PE/EtOAc v/v, 1:3) and title compound **11d** obtained as a colorless oil (28 mg, 26 μmol, 13%). R_f = 0.5 (PE/EtOAc, v/v 1:2, cerium stain). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.48–7.29 (m, 15 H, H_{arom}), 6.43 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, 13-H), 5.21 (d, $^2J_{H,H}$ = 12.1 Hz, 3 H, 18a-H), 5.15 (d, $^2J_{H,H}$ = 12.1 Hz, 3 H, 18b-H), 4.75–4.65 (m, 3 H, 14-H), 4.53 (br. s, 1 H, 8-H), 3.32 (t, $^3J_{H,H}$ = 6.6 Hz, 6 H, 16-H), 3.15–2.99 (m, 2 H, 7-H), 2.19–2.09 (m, 3 H, 15a-H), 2.02–1.89 (m, 9 H, 4-H, 15b-H), 1.54 (s, 6 H, 2-H), 1.51–1.36 (m, 11 H, 6-H, 11-H), 1.26–1.18 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.7 (C12), 171.5 (C17), 155.1 (C9), 135.1 (C19), 128.81 (C_{arom}), 128.77 (C_{arom}), 128.59 (C_{arom}), 79.3 (C10), 67.7 (C18), 50.5 (C14), 47.9 (C16), 42.6 (C2), 42.4 (C7), 40.1 (C5), 39.4 (C4), 34.2 (C1), 31.3 (C15), 28.5 (C11), 23.5 (C6) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{54}H_{67}N_{13}O_{11}$ [M + H]$^+$ = 1074.5156, found 1074.5171.

Boronic Acid 15: Boronate **13** (0.50 g, 1.9 mmol) was dissolved in Et_2O (8 mL) and diethanolamine (0.19 mL, 1.9 mmol) was added. A colorless solid precipitated and was collected by filtration to give intermediate **14**. Boronate **14**: ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.45–7.37 (m, 1 H, H_{arom}), 7.26–7.09 (m, 3 H, H_{arom}), 6.34 (d, $^4J_{H,H}$ = 1.5 Hz, 1 H, 7-H), 3.77 (s, 4 H, 10-H), 3.03 (s, 4 H, 11-H), 2.75 (br. s, 1 H, 9-H) ppm. Boronate **14** was dissolved in 0.1 M aq. HCl (5 mL) and EtOAc (5 mL) and stirred at room temp. for 12 h. The layers were separated and the aqueous phase was washed with EtOAc (3 × 5 mL). The organic layers were combined, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (PE/EtOAc v/v, 2:1) to give title compound **15** as a pale yellow solid (150 g, 0.93 mmol, 49%). The analytical data was identical with the literature data.[26]

Benzoboroxole 16a: This compound was synthesized according to general procedure C from azide **9a** (57 mg, 0.17 mmol) and boronic acid **15** (35 mg, 0.22 mmol), CuBr (2.4 mg, 17 μmol) and TBTA (9.0 mg, 17 μmol). Title compound **16a** (77 mg, 0.16 mmol, 92%) was isolated after purification by HPLC (Nucleodur RP18, 10 × 250 mm ID, 5 μm particle, 65% MeOH in H_2O with 0.1% HCO_2H, 230 nm, t_R = 13.8 min) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = (mixture of diastereomers) = 7.76 (d, $^3J_{H,H}$ = 7.1 Hz, 1 H, 9-H), 7.50–7.42 (m, 2 H, H_{arom}), 7.41–7.27 (m, 7 H, H_{arom}), 6.41 (s, 1 H, 7-H), 5.51–5.29 (m, 1 H, 13-H), 5.11–5.05 (m, 2 H, 18-H), 4.44–4.22 (m, 3 H, 10-H, 12-H), 2.52–2.34 (m, 1 H, 11a-H), 2.29–2.12 (m, 1 H, 11b-H), 1.41 (s, 9 H, 16-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (C17), 155.12 (C8), 155.08 (C8), 148.4 (C_{arom}), 135.1 (C19), 131.5 (C_{arom}), 130.7 (C9), 128.81 (C_{arom}), 128.77 (C_{arom}), 128.6 (C_{arom}), 128.0 (C_{arom}), 122.58 (C_{arom}), 122.56 (C_{arom}), 121.9 (C_{arom}), 80.4 (C15), 76.7 (C7), 67.7 (C18), 51.4 (C12), 46.9 (C10), 33.2 (C11), 28.4 (C16) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{29}BN_4O_6$ [M + Na]$^+$ = 515.2078, found 515.2086. **Deboronated triazole 17a:** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = (mixture of diastereomers) = 7.35 (d, 2 H, H_{arom}), 7.29–7.12 (m, 9 H, H_{arom}), 5.92 (s, 1 H, 5-H), 5.43–5.33 (m, 1 H, 11-H), 5.00 (s, 2 H, 16-H), 4.33–4.14 (m, 3 H, 8-H, 10-H), 4.14–3.79 (m, 1 H, 21-H), 2.41–2.27 (m, 1 H, 9a-H), 2.19–2.05 (m, 1 H, 9b-H), 1.33 (br. s, 9 H, 14-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.4 (C15), 155.6 (C12), 142.2 (C_{arom}), 135.0 (C_{arom}), 129.1 (C_{arom}), 128.71 (C_{arom}), 128.66 (C_{arom}), 128.56 (C_{arom}), 128.48 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 126.5 (C_{arom}), 80.5 (C13), 68.9 (C5), 67.6 (C16), 51.3 (C10), 46.7 (C8), 33.0 (C9), 28.3 (C14) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{25}H_{30}N_4O_5$ [M + Na]$^+$ = 498.0863, found 464.0869.

Benzoboroxole 16b: This compound was synthesized according to general procedure C from azide **9b** (76 mg, 0.19 mmol) and boronic acid **15** (33 mg, 0.19 mmol), CuBr (2.8 mg, 20 μmol) and TBTA (10 mg, 19 μmol). After a reaction time of 5 min a second amount of boronic acid **15** was added (10 mg, 19 μmol). Title compound **16b** (59 mg, 0.11 mmol, 56%) was isolated after purification by HPLC (Nucleodur RP18, 10 × 250 mm ID, 5 μm particle, 70% MeOH in H_2O with 0.1% HCO_2H, 203 nm, t_R = 27.8) as a colorless solid. As a side product, deboronated triazole **17b** was isolated as a colorless solid (14 mg, 26 μmol, 26%, t_R = 15.6). Boronic acid **16b**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = (mixture of diastereomers) = 7.80–7.72 (m, 1 H, 16-H), 7.48–7.26 (m, 9 H, H_{arom}), 6.53–6.46 (m, 1 H, 6-H), 6.38 (s, 1 H, 18-H), 5.13–5.01 (m, 2 H, 11-H), 4.70–4.57 (m, 1 H, 7-H), 4.34–4.23 (m, 2 H, 9-H), 2.52–2.38 (m, 1 H, 8a-H), 2.33–2.20 (m, 1 H, 8b-H), 2.00 (br. s, 3 H, 1-H), 1.82 (br. s, 6 H, 2-H), 1.60–1.57 (m, 6 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (C5), 171.34 (C10), 171.28 (C10), 155.12 (C17), 155.08 (C17), 148.7 (C19), 135.0 (C12), 131.4 (C_{arom}), 130.7 (C16), 128.79 (C_{arom}), 128.78 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 128.0 (C_{arom}), 122.5 (C_{arom}), 121.9 (C_{arom}), 76.11 (C18), 76.09 (C18), 67.9 (C11), 67.8 (C11), 50.02 (C7), 50.01 (C7), 46.9 (C9), 40.9 (C3), 39.1 (C2), 36.5 (C4), 32.84 (C8), 32.78 (C8), 28.1 (C1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{35}BN_4O_5$ [M + Na]$^+$ = 577.2598, found 577.2610. **Deboronated Triazole 17b:** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = (mixture of diastereomers) = 7.47–7.42 (m, 2 H, H_{arom}), 7.38–7.27 (m, 9 H, H_{arom}), 6.37 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 6.02–5.98 (m, 1 H, 18-H), 5.10–5.06 (m, 2 H, 11-H), 4.66–4.59 (m, 1 H, 7-H), 4.29 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, 9-H), 2.54–2.43 (m, 1 H, 8a-H), 2.35–2.24 (m, 1 H, 8b-H), 2.05–2.00 (m, 3 H, 1-H), 1.84–1.80 (br. s, 6 H, 2-H), 1.74 (d, $^4J_{H,H}$ = 12.4 Hz, 3 H, 4a-H), 1.68 (d, $^4J_{H,H}$ = 12.4 Hz, 3 H, 4b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 178.4 (C5), 171. 4 (C10), 151.3 (C_{arom}), 141.9 (C_{arom}), 135.0 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.16 (C_{arom}), 128.15 (C_{arom}), 126.6 (C_{arom}), 126.5 (C_{arom}), 69.4 (C18), 67.8 (C11), 49.9 (C7), 46.9 (C9), 40.9 (C3), 39.2 (C2), 36.5 (C4), 32.9 (C8), 28.2 (C1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{36}N_4O_4$ [M + Na]$^+$ = 551.2629, found 551.2642.

Benzoboroxole 18a: This compound was synthesized according to general procedure C from azide **11a** (50 mg, 0.093 mmol) and boronic acid **15** (20 mg, 0.13 mmol), CuBr (1.3 mg, 0.093 mmol) and TBTA (5.0 mg, 0.093 mmol). Title compound **18a** (47 mg, 0.064 mmol, 72%) was isolated after purification by HPLC (Nucleodur RP18, 10 × 250 mm ID, 5 μm particle, 75% MeOH in H_2O with 0.1% HCO_2H, 5 mL/min, 210 nm, t_R = 23.4 min) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = (mixture of diastereomers) = 7.78 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 15-H), 7.48–7.27 (m,

9 H, H_{arom}), 6.53 (br., 1 H, 11-H), 6.36 (s, 1 H, 17-H), 5.08 (d, $^4J_{H,H}$ = 3.4 Hz, 2 H, 25-H), 4.74–4.60 (m, 1 H, 12-H), 4.40–4.22 (m, 2 H, 14-H), 2.55–2.36 (m, 1 H, 13a-H), 2.36–2.22 (m, 1 H, 13b-H), 2.22–2.11 (m, 2 H, 9-H), 2.08 (br. s, 2 H, 5-H), 1.93–1.70 (m, 4 H, 6-H), 1.68–1.46 (m, 4 H, 2-H, 7-H), 1.43 (s, 9 H, 33-H), 1.41–1.22 (m, 6 H, 4-H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.4 (C10), 171.2 (C24), 155.1 (C16), 148.6 (C_{arom}), 135.0 (C_{arom}), 131.5 (C_{arom}), 130.8 (C15), 128.82 (C_{arom}), 128.78 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 128.04 (C_{arom}), 128.00 (C_{arom}), 122.54 (C_{arom}), 122.46 (C_{arom}), 122.0 (C_{arom}), 79.1 (C32), 76.11 (C17), 76.06 (C17), 67.79 (C25), 67.75 (C25), 51.3 (C1), 50.3 (C12), 47.2 (C14), 47.1 (C14), 45.9 (C2), 41.5 (C6), 41.1 (C4), 38.8 (C8), 35.9 (C7), 34.2 (C3), 32.7 (C13), 32.6 (13), 30.2 (C9), 29.6 (C5), 28.6 (C33) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{38}H_{48}BN_5O$ $[M + Na]^+$ = 720.3546, found 720.3550.

Benzoboroxole 18b: This compound was synthesized according to general procedure C from azide **11b** (76 mg, 0.092 mmol) and boronic acid **15** (39 mg, 0.24 mmol), CuBr (2.6 mg, 0.0184 mmol) and TBTA (9.8 mg, 0.018 mmol). Title compound **18b** (60 mg, 0.053 mmol, 57%) was isolated after purification by HPLC (Nucleodur RP18, 10 × 250 mm ID, 5 µm particle, 80% MeOH in H_2O with 0.1% HCO_2H, 230 nm, t_R = 17.7 min.) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = (mixture of diastereomers) = 7.74 (d, $^4J_{H,H}$ = 3.8 Hz, 2 H, H_{arom}), 7.69 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, H_{arom}), 7.48–7.41 (m, 2 H, H_{arom}), 7.39–7.28 (m, 14 H, H_{arom}), 6.34 (s, 2 H, 23-H), 5.09 (s, 4 H, 16-H), 4.44 (t, $^3J_{H,H}$ = 7.0 Hz, 4 H, 14-H), 4.41–4.36 (m, 2 H, 12-H), 2.53–2.41 (m, 2 H, 13a-H), 2.32–2.21 (m, 2 H, 13b-H), 2.21–2.14 (m, 4 H, 9-H), 2.14–2.09 (m, 1 H, 6-H), 1.77 (s, 2 H, 7-H), 1.62–1.52 (m, 4 H, 2-H), 1.48–1.33 (m, 15 H, 5b-H, 8-H, 33-H), 1.33–1.26 (m, 2 H, 5b-H), 1.05–1.17 (m, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 177.1 (C10), 172.4 (C15), 156.4 (C_{arom})149.3 (C_{arom}), 137.0 (C_{arom}), 132.3 (C_{arom}), 131.4 (C_{arom}), 129.6 (C_{arom}), 129.44 (C_{arom}), 129.36 (C_{arom}), 129.0 (C_{arom}), 124.2 (C_{arom}), 123.4 (C_{arom}), 79.3 (C32), 76.9 (C23), 68.2 (C16), 52.8 (C1), 51.4 (C12), 48.2 (C14), 46.9 (C4), 46.4 (C2), 41.6 (C7), 41.4 (C5), 40.0 (C8), 35.7 (C3), 32.5 (C13), 31.1 (C6), 30.8 (C9), 28.9 (C33) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{61}H_{71}B_2N_9O_{12}$ $[M + H]^+$ = 1144.5487, found 1144.5491.

Benzoboroxole 18c: This compound was synthesized according to general procedure C from azide **11c** (56 mg, 48 µmol) with boronic acid **15** (31 mg, 0.20 mmol), CuBr (2.2 mg, 15 µmol) and TBTA (8.0 mg, 15 µmol). Title compound **18c** (50 mg, 31 µmol, 63%) was isolated after purification by HPLC (Nucleodur RP18, 10 × 250 mm ID, 5 µm particle, 80% MeOH in H_2O with 0.1% HCO_2H, 5 mL/min, 210 m, t_R = 22.9 min.) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = (mixture of diastereomers) = 7.74 (d, $^4J_{H,H}$ = 2.4 Hz, 3 H, H_{arom}), 7.69 (d, $^3J_{H,H}$ = 7.4 Hz, 3 H, H_{arom}), 7.48–7.25 (m, 24 H, H_{arom}), 6.34 (s, 3 H, 14-H), 5.08 (s, 6 H, 22-H), 4.43 (t, $^3J_{H,H}$ = 6.9 Hz, 6 H, 11-H), 4.41–4.35 (m, 3 H, 9-H), 2.53–2.40 (m, 3 H, 10a-H), 2.32–2.21 (m, 3 H, 10b-H), 2.21–2.14 (m, 6 H, 6-H), 1.52 (s, 6 H, 2-H), 1.45 (t, $^3J_{H,H}$ = 7.7 Hz, 6 H, 5-H), 1.40 (s, 9 H, 30-H), 1.11 (d, $^2J_{H,H}$ = 12.0 Hz, 3 H, 4a-H), 1.02 (d, $^2J_{H,H}$ = 12.0 Hz, 3 H, 4b-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 176.7 (C7), 171. 5 (C21), 155.5 (C_{arom}), 149.5 (C_{arom}), 136.9 (C_{arom}), 132.1 (C_{arom}), 131.3 (C_{arom}), 129.4 (C_{arom}), 128.9 (C_{arom}), 123.9 (C_{arom}), 123.1 (C_{arom}), 122.6 (C_{arom}), 79.2 (C29), 76.7 (C14), 68.0 (C22), 53.9 (C1), 51.2 (C9), 47.8 (C11), 46.4 (C4), 45.9 (C2), 39.6 (C5), 35.7 (C3), 32.2 (C10), 30.7 (C6), 28.8 (C30) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{84}H_{94}$ $B_3N_{13}O_{17}$ $[M + H]^+$ = 1590.7243, found 1590.7280.

Benzoboroxole 18d: This compound was synthesized according to general procedure C from azide **11d** (28 mg, 26 µmol) with boronic acid **15** (16.4 mg, 104 µmol), CuBr (1.1 mg, 7.8 µmol) and TBTA (4.1 mg, 7.8 µmol). Title compound **18d** (30 mg, 8.9 µmol, 75%) was isolated after purification by HPLC (Nucleodur RP18, 10 × 250 mm ID, 5 µm particle, 80% MeOH in H_2O with 0.1% HCO_2H, 5 mL/min, 220 nm, t_R = 22.7 min.) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = (mixture of diastereomers) = 7.75–7.71 (m, 3 H, H_{arom}), 7.66 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 17-H), 7.65–7.24 (m, 24 H, H_{arom}), 6.31 (s, 3 H, 19-H), 5.10–5.05 (m, 6 H, 27-H), 4.48–4.33 (m, 9 H, 14-H, 16-H), 3.00 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 7-H), 2.59–2.46 (m, 3 H, 15a-H), 2.40–2.26 (m, 3 H, 15b-H), 1.84 (s, 6 H, 4-H), 1.53–1.44 (m, 6 H, 2-H), 1.44–1.39 (m, 11 H, 6-H, 11-H), 1.21–1.13 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 179.1 (C12), 172.4 (C26), 149.4 (C_{arom}), 137.0 (C_{arom}), 132.2 (C_{arom}), 131.4 (C17), 129.6 (C_{arom}), 129.43 (C_{arom}), 129.36 (C_{arom}), 128.9 (C_{arom}), 123.4 (C_{arom}), 80.0 (C10), 76.9 (C19), 68.2 (C27), 51.5 (C14), 48.1 (C16), 43.7 (C3), 43.1 (C2), 42.0 (C7), 41.4 (C5), 40.3 (C4), 32.0 (C15), 28.8 (C11) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{81}H_{88}N_{13}B_3O_{17}$ $[M + Na]^+$ = 1570.6626, found 1570.6647.

1-(L-triazolbenzoboroxole-homoalanin-Bn)-carboxyethyladamantane 19: The Boc-protected amine **18a** (9.0 mg, 13 µmol) was stirred in CH_2Cl_2/TFA (v/v, 4:1) at room temp. for 1.5 h. The solvent was removed in vacuo, the residue dissolved in 0.1 M aq. HCl and MeCN and freeze dried to give the free amine **19** (8.2 mg, 13 µmol, quant.) as a colorless solid. This amine was used without any further purification in the next step. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = (mixture of diastereomers) = 7.72 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 15-H), 7.53–7.21 (m, 9 H, H_{arom}), 6.41 (d, $^4J_{H,H}$ = 5.2 Hz, 1 H, 17-H), 5.11 (s, 2 H, 25-H), 4.58–4.50 (m, 2 H, 14-H), 4.42–4.33 (m, 1 H, 12-H), 2.58–2.46 (m, 1 H, 13a-H), 2.36–2.28 (m, 1 H, 13b-H), 2.28–2.19 (m, 4 H, 5-H, 9-H), 1.88–1.76 (m, 4 H, 4-H), 1.70–1.64 (m, 2 H, 7-H), 1.62–1.57 (m, 2 H, 2-H), 1.57–1.44 (m, 6 H, 6-H, 8-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 176.2 (C10), 171.6 (C24), 155.2 (C_{arom}), 148.7 (C_{arom}), 137.1 (C_{arom}), 132.4 (C_{arom}), 131.5 (C15), 129.6 (C_{arom}), 129.4 (C_{arom}), 129.3 (C_{arom}), 129.2 (C_{arom}), 125.2 (C_{arom}), 123.5 (C_{arom}), 76.2 (C17), 68.2 (C25), 53.6 (C1), 51.3 (C12), 51.1 (C12), 50.0 (C2), 48.6 (C14), 41.1 (C7), 41.0 (C4), 39.6 (C8), 39.5 (C8), 35.8 (C3), 35.52 (C6), 35.50 (C6), 32.2 (C13), 30.60 (C5), 30.58 (C5), 30.46 (C9), 30.44 (C9) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{33}H_{40}BN_5O_5$ $[M + H]^+$ = 598.3201, found 598.3207.

Fluorescent benzoboroxole 20: Amine **19** (3.8 mg, 5.0 µmol) was stirred in abs. DMF and NEt_3 (15 µL, 0.11 mmol) was added. The reaction solution was cooled to 0 °C and Promofluor 647 (100 µL, *c* = 0.013 M, 1.31 µmol) was added dropwise. The reaction was stirred for 4 h and a second amount of Promofluor 647 (100 µL, *c* = 0.013 M, 1.31 µmol) was added at 0 °C. The reaction was stirred for 12 h and the solvent evaporated in vacuo. The crude product was purified by HPLC (Nucleodur RP8, 10 × 250 mm ID, 5 µm particle, 50% MeCN in H_2O with 0.1% HCO_2H, 3 mL/min, 250 nm, Ex = 657 nm, Em = 672 nm, t_R = 9.0 min) and product **20** (0.442 mg, 0.362 µmol, 14%) isolated as a blue solid. HRMS (ESI): *m*/*z* calcd. for $C_{65}H_{75}BN_7O_{12}S_2^-$ $[M - H]^{2-}$ = 609.7465, found 609.7481.

Azide 21: Bn-protected carboxylic acid **11a** (75 mg, 0.14 mmol) and LiOH (12 mg, 0.50 mmol) were dissolved in THF/H_2O (20 mL v/v, 1:1) and stirred at room temp. for 2 h. The solvent was evaporated and the residue dissolved in Et_2O/H_2O (20 mL, v/v 1:1). The layers were separated and the organic phase was washed with 1 M aq. HCl (2 × 10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers combined, dried with anhydrous $MgSO_4$, filtered and concentrated to dryness in vacuo. The re-

sulting carboxylic acid, EDC (37 mg, 0.23 mmol) and NHS (22 mg, 0.19 mmol) were dissolved in abs. DMF (5 mL) and stirred under N_2 for 16 h. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc/H_2O (20 mL v/v, 1:1). The organic layer was washed with H_2O (2× 10 mL) and the aqueous layer extracted with EtOAc (3× 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered and concentrated to dryness in vacuo. The resulting NHS-ester was used without further purification. H_2N-G-R(Pbf)-G-E(*t*Bu)-S(*t*Bu)-rink amide (126 mg, 0.108 mmol) was dissolved in abs. DMF (5 mL) and the pH adjusted to 8 with NEt_3. The reaction solution was stirred for 15 min at 0 °C and the NHS-ester (47 mg, 0.086 mmol) was added. The reaction was stirred at room temp. for 24 h. The solvent was evaporated under reduced pressure and the crude product dissolved in 4.4 mL TFA, 0.1 mL TIPS, 0.25 mL H_2O and 36 mg phenol. The reaction was stirred for 48 h at room temp. and the solvent removed under reduced pressure. The crude product was purified by HPLC (Nucleodur RP8, 2% MeCN in H_2O with 0.1% HCO_2H than 2%→80% in 20 min MeCN in H_2O with 0.1% HCO_2H, 5 mL/min, 210 nm, t_R = 13.2 min). Title compound **21** (13 mg, 16 µmol, 18%) was obtained as a colorless solid. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{58}N_{14}O_{10}$ $[M + 2H]^{2+}$ = 418.2308, found 418.2316.

Peptide Boronic Acid 22: This compound was synthesized according to general procedure C from azide **21** (13 mg, 16 µmol) with boronic acid **15** (3.2 mg, 20 µmol), CuBr (tip of a spatula) and TBTA (tip of a spatula). Title compound **22** (9 mg, 9 µmol, 58%) was isolated after purification by HPLC (Nucleodur RP8, 10×250 mm ID, 5 µm particle, 2% MeCN in H_2O with 0.1% HCO_2H than 2%→80% MeCN in H_2O with 0.1% HCO_2H in 20 min, 5 mL/min, 250 nm t_R = 16.0 min.) as a colorless solid. HRMS (ESI): *m*/*z* calcd. for $C_{44}H_{65}BN_{14}O_{12}$ $[M - H_2O + 2H]^{2+}$ = 488.2523, found 488.2525.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C-NMR spectra of all new compounds and LC/MS data for compounds **20** and **21**.

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