Synthesis of Functionalized Benzoboroxoles for the Construction of Boronolectins

Falk Wienhold, Dorith Claes, Karolina Graczyk, Wolfgang Maison*

Department of Chemistry, University of Hamburg, Bundesstraße 45, 20146 Hamburg, Germany
Fax +49(40)428386519; E-mail: maison@chemie.uni-hamburg.de

Received 24 August 2011; revised 29 September 2011

Abstract: Adducts of peptides and arylboronic acids are attractive tools for the selective recognition of carbohydrates. These structures resemble at least some of the properties of natural carbohydrate binders and have therefore been termed lectin mimetics or boronolectins. In this report, we describe the synthesis of appropriately functionalized benzoboroxoles as modular components for the assembly of boronolectins. These benzoboroxoles have been prepared in a few steps from readily available starting materials. In conclusion, versatile functionalized benzoboroxoles are reported that can be used for the construction of larger conjugates by peptide coupling or copper-mediated cycloadditions (click reactions) with azides.

Key words: carbohydrate recognition, boronic acids, click reactions, boronolectins, benzoboroxoles

The boronic acid moiety is a promising structural motif for pharmaceuticals.[1] In addition, it is a highly versatile motif in synthetic organic chemistry including applications in catalysis, Pd-catalyzed cross-coupling reactions and hydroborations. Boronic acids are therefore extremely useful synthetic building blocks. In particular, functionalized derivatives of phenylboronic acids have received considerable attention as catalysts and intermediates of complex natural products such as Vancomycin.[2] In addition to their applications in organic synthesis, phenylboronic acids are of interest as carbohydrate sensors. This function is due to their ability to reversibly bind to 1,2-diols (Figure 1, A).[3] Carbohydrates are essential elements of molecular recognition on cell surfaces[4] and are involved in many pharmaceutically relevant processes such as immune responses to pathogens,[5] cancer development,[6] and infective diseases.[7] The molecular recognition of carbohydrates with small molecules is therefore a highly attractive area of research.[8] Among the many different approaches,[9] boronic acids are a promising class of molecules for carbohydrate recognition and many derivatives have been demonstrated to bind sugars with reasonable affinities and specificities.[10] Derivatives of phenylboronic acids have been particularly successful examples, and a number of good carbohydrate binders are based on this structural motif.[3,11] However, the field remains challenging and most carbohydrate binders suffer from relatively low affinities and specificities in water, particularly for non-reducing sugars and pyranoses.[12] Reasonable binding affinities to non-reducing sugars were achieved with phenylboronic acids of the Wulff type **1** (Figure 1, B) with donor substituents *ortho* to the boronic acid moiety.[13] In this context, Hall and co-workers have reported several benzoboroxole derivatives of type **2** that were found to bind to non-reducing sugars with moderate affinities in water.[14]

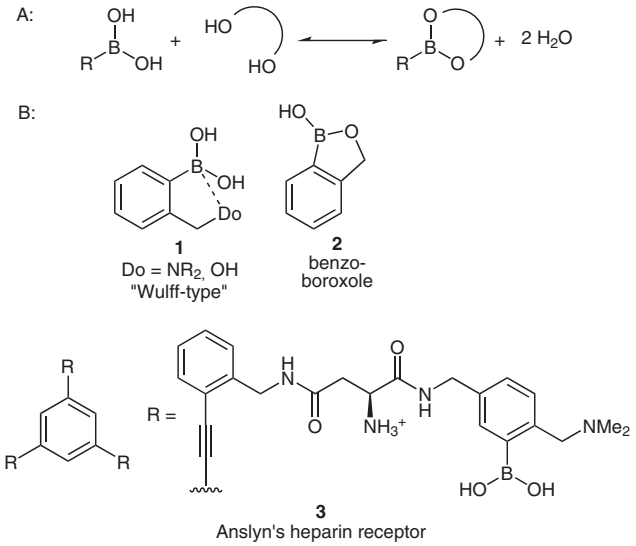


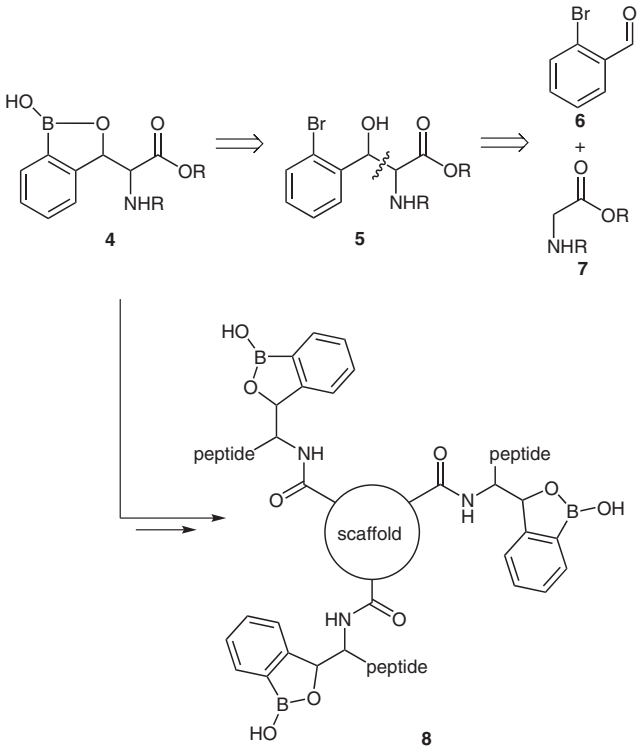
Figure 1 (A) Reversible formation of boronic esters. (B) Selected examples of known carbohydrate binders: Wulff type benzoboroxole **1** with a donor substituent in the *ortho* position, benzoboroxole scaffold **2**, and Anslyn's trimeric heparin receptor **3**.

Another attractive strategy to increase binding affinities and specificities to sugars is the construction of mostly peptidic hybrids of phenylboronic acids.[15] These conjugates resemble the characteristics of natural carbohydrate binding proteins, such as lectins, and were therefore termed boronolectins. Anslyn has reported particularly attractive multivalent combinations of peptides with boronic acids that imitate the defined tripodal geometry of natural lectins. One example is receptor **3**, which is able to bind the anticoagulant heparin and is thus used as a heparin sensor for biomedical applications.[16]

We report here new derivatives of benzoboroxoles that are appropriately functionalized for easy conjugation to peptides and other biomolecules by bioorthogonal coupling techniques. These boronic acids are attractive building blocks for the assembly of boronolectins.

SYNTHESIS 2011, No. 24, pp 4059–4067
Advanced online publication: 27.10.2011
DOI: 10.1055/s-0031-1289577; Art ID: T83611SS

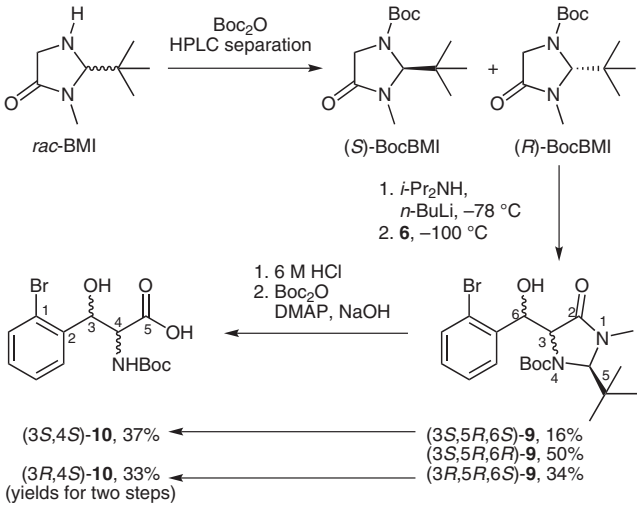
Our first target compounds were benzoboroxole–amino acid conjugates of type **4** (Scheme 1). Boronic acids of type **4** combine several useful features; namely, a benzoboroxole of the Hall type for sugar binding, an amino group for the conjugation to multimeric scaffolds, and a carboxylic acid for the introduction of biomolecules such as peptides in close vicinity to the boronic acid moiety. Compounds **4** would therefore be valuable for the construction of boronolectins such as **8**, with three-fold geometry, by conjugation to known tripodal scaffolds.[17]



Scheme 1 Retrosynthesis of benzoboroxole-amino acid **4** and assembly of tripodal boronolectins **8**

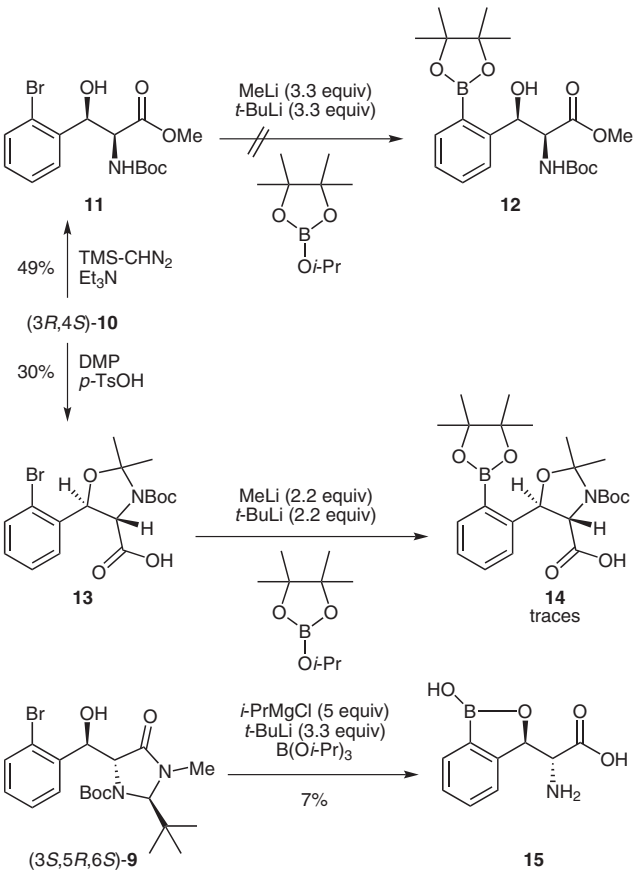
We planned to use 2-bromobenzaldehyde (**6**) as a precursor of benzoboroxole **4**, which would be treated with a chiral glycine equivalent **7** to give the threonine derivative **5** as an intermediate. In a last step, the boronic acid moiety would be introduced by lithiation and subsequent transmetalation to give benzoboroxole **4**.

In a first attempt, we used Seebach's chiral glycine derivative (BocBMI), which is readily available from glycine and pivalaldehyde.[18] Racemic BMI may be separated into both optical isomers by fractionated crystallization with mandelic acid. Alternatively, we used preparative HPLC separation on a chiral stationary phase (see the Supporting Information) to gain access to sufficient quantities of enantiomerically pure (*R*)- and (*S*)-BocBMI. The following addition of the enolate derived from BocBMI to 2-bromobenzaldehyde (**6**) was performed according to Scheme 2, following the original Seebach protocol. The reaction proceeded with low diastereoselectivity to give a mixture of three diastereomers **9**, which were separable by chromatography. Hydrolysis and subsequent Boc-protection of the two diastereomers (3*S*,5*R*,6*S*)-**9** and (3*R*,5*R*,6*S*)-**9** gave the protected β-hydroxy amino acids (3*S*,4*S*)-**10** and (3*R*,4*S*)-**10**.

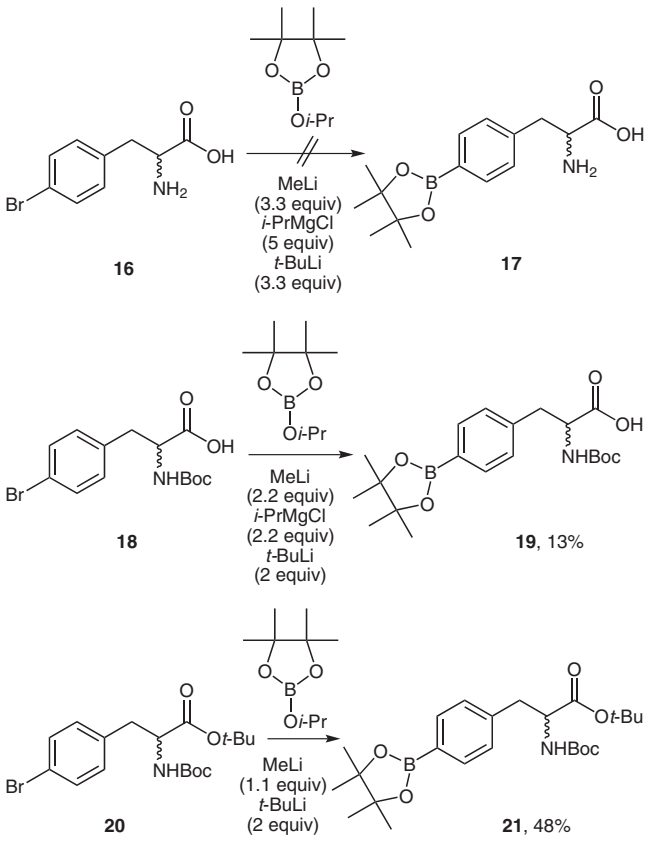


Scheme 2 Synthesis of β-hydroxy amino acids (3*S*,4*S*)-**10** and (3*R*,4*S*)-**10** using Seebach's chiral glycine equivalent BocBMI

Unfortunately, the attempted lithiation and transmetallation of densely functionalized amino acids **10** failed, and the introduction of various protecting groups in derivatives **11** and **13** (Scheme 3) did not improve the situation;



Scheme 3 Synthesis of protected amino acids and their conversion into boronic acids



Scheme 4 Halogen–metal exchange with protected derivatives of *p*-bromophenylalanine

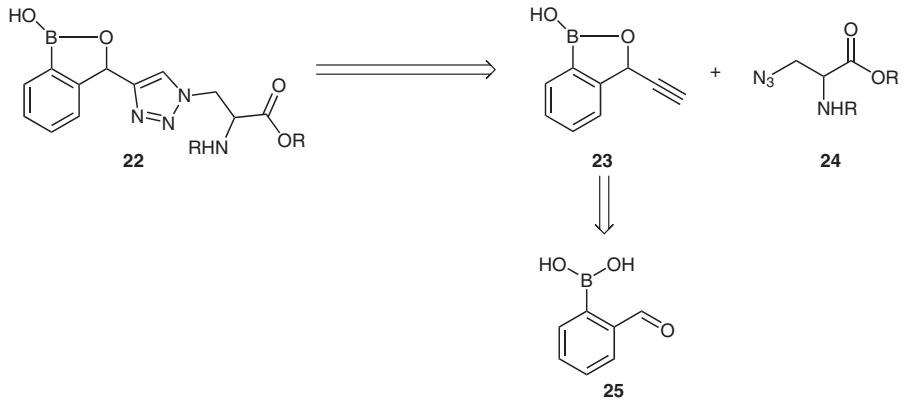
none of the desired compounds **12** or **14** were obtained. In most cases, dehalogenated species were the major side-products formed in these reactions. Boronic ester **14** was identified in trace amounts by MS analysis, and only for the conversion of (3*S*,5*R*,6*S*)-**9** was a small quantity of the deprotected boronic acid **15** isolated (Scheme 3).

A few attempts with less functionalized model compounds confirmed our assumption that the high density of functional groups in the β-hydroxy amino acids was the reason for the failure of the borylations. Only in the conversion of fully protected *p*-bromophenylalanine (**20**) was the corresponding boronic ester **21** obtained in acceptable yield (Scheme 4). Similar observations have been reported by Morin.[19]

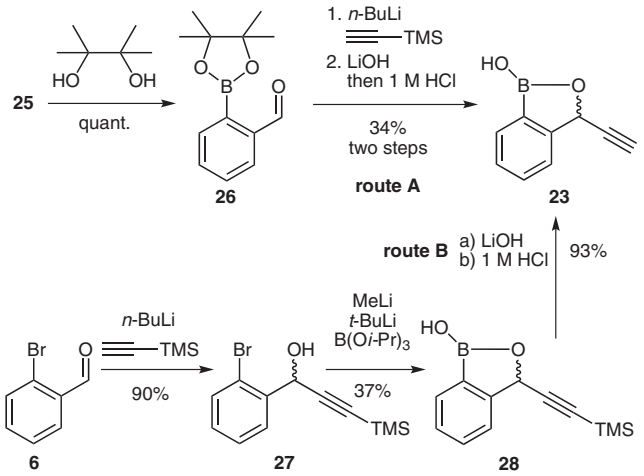
To avoid complex protecting group manipulations in the amino acids of type **10**, we decided to introduce the amino acid part after installing the boronic acid moiety, and focused on triazole derivative **22** as a target structure (Scheme 5). The triazole linkage would be generated in a [3+2] cycloaddition of azide **24** and alkyne **23**,[20] which, in turn, would be prepared from aldehyde **25**. A nice feature of this approach is that alkyne **23** is not only a precursor for the amino acid conjugate **22**, but can also be used for the conjugation of benzoboroxoles to various other biomolecules through copper-catalyzed cycloaddition protocols.

A key intermediate in our sequence was alkyne **23**, and we evaluated two different routes to this compound (Scheme 6). A first attempt started from the commercially available aldehyde **25**, which was protected with pinacol to give the corresponding pinacolate **26** in quantitative yield.[21] This pinacolate was treated with TMS-acetylide to give the corresponding addition product, which, upon treatment with LiOH, gave the target compound **23**. Alternatively, the nucleophilic addition of TMS-acetylide to 2-bromobenzaldehyde **6** proceeded smoothly and gave the propargylic alcohol **27** in excellent yield. Introduction of the boronic acid was performed by halogen–metal exchange and subsequent treatment with $B(O\textit{i}\text{-}Pr)_3$ to give **28** in moderate yield. The TMS group in **28** was removed by treatment with LiOH to provide alkyne **23** in excellent yield (Scheme 6).

With alkyne **23** in hand, we attempted the copper-catalyzed cycloaddition with the known azido alanine **29** (Table 1).[22] However, standard protocols for click-reactions gave only disappointing results. It has previously been reported that boronic acids are often problematic substrates for copper-catalyzed click-reactions, with deboronation being the major side reaction.[23] A common workaround is the addition of fluoride, which has been used to suppress deboronation in these conversions before.[24] However, the use of sodium ascorbate and $CuSO_4$ with CsF or CuBr and tetrabutylammonium fluoride (TBAF) (Table 1, entries 1 and 2) gave none of the desired cycloaddition product **30**. A slight improvement was realized when the reaction was performed under microwave conditions (Table 1, entry 3), and a mixture of boronic



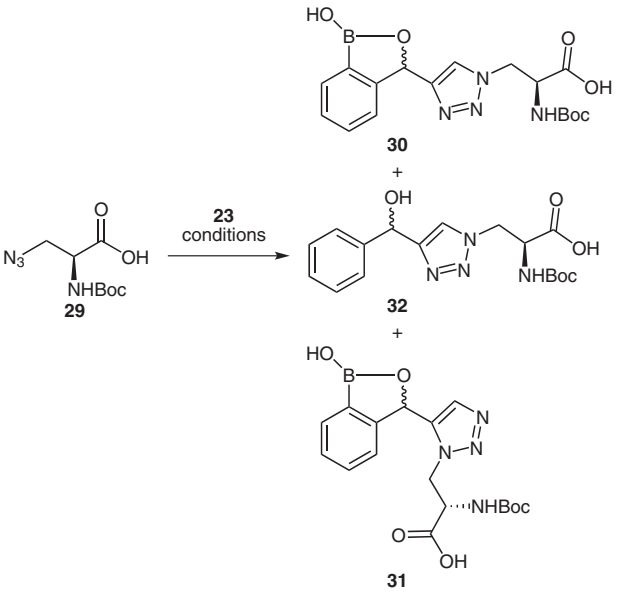
Scheme 5 Retrosynthesis of triazole derivative **22**



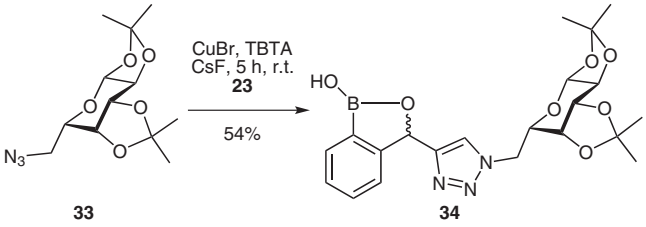
Scheme 6 Two different approaches to alkyne **23**

acid **30** and the corresponding deboronated derivative **32** was obtained in moderate yield.

Fokin and Sharpless have shown that the addition of tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) can improve the yields of click conversions.[25] By using $CuSO_4$ in the presence of TBTA, sodium ascorbate, and CsF, we were thus able to obtain the desired product along with a significant amount of the 1,5-regioisomer **31** (Table 1, entry 4). Finally, a mixture of CuBr, TBTA, and CsF[24] was used, and the reaction gave 1,4-regioisomer **30** in quantitative yield (Table 1, entry 5). Using these conditions, different biomolecules may be conjugated to boronic acid **23** as demonstrated with the sugar azide **33**.[26] The cycloaddition again provided the desired triazole derivative **34** in good yield (Scheme 8).



Scheme 7 Cycloadditions of alkyne-substituted benzoboroxole **23** and azido alanine **29**



Scheme 8 Copper-catalyzed cycloaddition of alkyne **23** and azide **33**

In conclusion, we have developed an efficient synthetic approach to a new benzoboroxole–amino acid conjugate **30**, which was obtained in a few steps from readily available starting materials. Conjugate **30** combines three useful functionalities: (1) a benzoboroxole moiety for carbohydrate binding; (2) an amine group for attachment to multimeric scaffolds, and (3) a carboxylic acid for the conjugation of biomolecules such as peptides or sugars. We have designed boronic acid **30** as modular components for the assembly of tripodal boronolectins. Alternatively, the intermediate alkyne **23** may be used for the conjugation of various biomolecules to the benzoboroxole core for a specific tailoring of their sugar-binding properties.

The following compounds were prepared according to literature protocols: *rac*-BMI,[18] (*R*)- and (*S*)-BocBMI[27] (*rac*-BocBMI was separated by HPLC on a chiral stationary phase. For details see the Supporting Information), pinacolate **26**,[21] azidoalanine **29**,[22] and 6-azido-D-galactose **33**.[26]

TLC was performed on silica gel aluminum sheets. Reagents used for developing plates were cerium reagent (5 g molybdatophosphoric acid, 2.5 g cerium sulfate tetrahydrate, 25 mL sulfuric acid and 225 mL H_2O), $KMnO_4$ (0.5% in 1N NaOH w/v), and detection by UV light was used when applicable. Flash column chromatography was performed on silica gel (60–200 μm). ^1H NMR chemical shifts are referenced to residual non-deuterated solvent ($CDCl_3$, δ_H = 7.26 ppm; DMSO-d_6, δ_H = 2.50 ppm). ^{13}C NMR chemical shifts are referenced to the solvent signal ($CDCl_3$, δ_C = 77.16 ppm;

Table 1 Conditions and Product Distribution for Cycloadditions According to Scheme 7

Entry	Conditions	**30** (%)	**31** (%)	**32** (%)
1	sodium ascorbate, $CuSO_4$, CsF, r.t.	0	0	0
2	CuBr, TBAF, r.t.	0	0	0
3	sodium ascorbate, $CuSO_4$, CsF, 100 °C, MW, 30 min	13	0	24
4	sodium ascorbate, $CuSO_4$, CsF, TBTA, r.t., 5 h	15	30	0
5	CuBr, CsF, TBTA, r.t., 5 h	quant.	0	0

DMSO-d_6, δ_C = 28.06 ppm). NMR spectra were recorded at 200 (50), 400 (100), or 600 (150) MHz on Bruker Avance instruments. ESI mass spectra were recorded with a TOF Bruker MicroTOF instrument operated either in positive or negative mode. Samples were dissolved in MeCN–MeOH mixtures and directly injected by using a syringe. If indicated with abs., solvents were dried by distillation from sodium under a nitrogen atmosphere prior to use.

Imidazolidinones (3*S*,5*R*,6*S*)-9, (3*S*,5*R*,6*R*)-9, and (3*R*,5*R*,6*S*)-9

Diisopropylamine (1.55 mL, 11 mmol) was dissolved in abs. THF (35 mL) and cooled to –78 °C under an N_2 atmosphere. *n*-BuLi (2.22 M in hexane, 5.85 mL, 13 mmol) was added and the solution was stirred for 10 min. A solution of (*R*)-BocBMI (2.56 g, 10 mmol) in abs. THF (3 mL) was added (the reaction mixture became yellow). After 30 min, the mixture was cooled to –100 °C and benzaldehyde (1.5 mL, 11 mmol) was added. The reaction was quenched with sat. aq ammonium chloride solution (30 mL) and the aqueous layer was extracted with Et_2O (2 × 75 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography (silica; PE–EtOAc, 2:1) to give three diastereomers (3*S*,5*R*,6*S*)-**9**, (3*S*,5*R*,6*R*)-**9**, and (3*R*,5*R*,6*S*)-**9** in a ratio of 16:50:34 (total 3.84 g, 8.7 mmol, 87%).

Imidazolidinone (3*S*,5*R*,6*S*)-9

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.90 [s, 9 H, $C(CH_3)_3$], 1.24 [s, 9 H, $OC(CH_3)_3$], 2.93 (s, 3 H, NCH_3), 4.56–4.53 (m, 1 H, CHN), 5.00 [s, 1 H, C*H*C$(CH_3)_3$], 5.46 (dd, *J* = 2.6, 6.7 Hz, 1 H, C*H*OH), 5.80 (d, *J* = 6.7 Hz, 1 H, OH), 7.15 (dt, *J* = 7.9, 1.5 Hz, 1 H, ArH), 7.29 (t, *J* = 7.3 Hz, 1 H, ArH), 7.36 (d, *J* = 7.5 Hz, 1 H, ArH), 7.52 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.2, 27.6, 31.8, 40.5, 61.3, 71.1, 80.1, 80.1, 122.0, 126.8, 128.7, 129.2, 132.3, 141.6, 152.2, 170.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{29}BrN_2O_4$: 463.1203; found: 463.1199.

Imidazolidinone (3*S*,5*R*,6*R*)-9

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.07 [s, 9 H, $C(CH_3)_3$], 1.38 [s, 9 H, $OC(CH_3)_3$], 2.84 (s, 3 H, NCH_3), 4.32 (d, *J* = 3.3 Hz, 1 H, CHN), 4.89 [s, 1 H, C*H*C$(CH_3)_3$], 5.26 (dd, *J* = 3.9, 4.7 Hz, 1 H, C*H*OH), 5.81 (d, *J* = 5.1 Hz, 1 H, OH), 7.18 (dt, *J* = 7.8, 1.7 Hz, 1 H, ArH), 7.35 (t, *J* = 7.1 Hz, 1 H, ArH), 7.52 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 7.74 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.0, 28.0, 30.5, 36.8, 62.9, 72.3, 80.5, 80.8, 121.4, 127.1, 129.0, 131.0, 131.7, 141.7, 155.3, 167.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{29}BrN_2O_4$: 463.1203; found: 463.1206.

Imidazolidinone (3*R*,5*R*,6*S*)-9

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.87 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $OC(CH_3)_3$], 2.85 (s, 3 H, NCH_3), 4.21 (s, 1 H, CHCON), 5.09–4.99 [m, 1 H, C*H*C$(CH_3)_3$], 5.69 (s, 1 H, C*H*OH), 6.22–5.93 (m, 1 H, OH), 7.16 (d, *J* = 7.3 Hz, 1 H, ArH), 7.31 (t, *J* = 7.4 Hz, 1 H, ArH), 7.50 (d, *J* = 8.1 Hz, 1 H, ArH), 7.52 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.0, 28.2, 31.1, 40.2, 60.6, 68.4, 79.3, 80.4, 120.4, 126.2, 128.7, 131.4, 131.5, 140.7, 167.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{29}BrN_2O_4$: 463.1203; found: 463.1205.

Hydrolysis and Boc-Protection; General Procedure

Imidazolidinone **9** (1.0 mmol) was dissolved in 6 M HCl and stirred for 12 h at reflux. The solvent was removed in vacuo and the resulting crude product was used without any further purification in the next step. H_2O–THF (20 mL, 1:1 v/v), NaOH (0.12 g, 3.1 mmol), and DMAP (0.01 g, 0.1 mmol) were added to the product and the reaction mixture was cooled to 0 °C. Boc_2O (0.62, 2.8 mmol) was added and the solution was allowed to warm to r.t. and stirred for 12 h. The solvent was removed in vacuo and the remaining solid was extracted with EtOH (3 × 30 mL). The crude product was purified by HPLC.

β-Hydroxyamino Acid (3*S*,4*S*)-10

The title compound was synthesized following the general procedure for hydrolysis and Boc-protection from (3*S*,5*R*,6*S*)-**9** (416 mg, 0.94 mmol). Compound (3*S*,4*S*)-**10** (126 mg, 0.35 mmol, 37%) was isolated after purification by HPLC (RP 18; MeCN–H_2O, 35%; 230 nm; 3 mL/min) as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.20 [s, 9 H, $C(CH_3)_3$], 4.41 (dd, *J* = 10.0, 2.3 Hz, 1 H, C*H*NH), 5.40 (d, *J* = 1.8 Hz, 1 H, C*H*OH), 5.86 (d, *J* = 10.1 Hz, 1 H, OH), 6.29 (d, *J* = 10.0 Hz, 1 H, NH), 7.18 (dt, *J* = 7.7, 1.6 Hz, 1 H, ArH), 7.36 (t, *J* = 7.0 Hz, 1 H, ArH), 7.59–7.52 (m, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.9, 56.7, 71.6, 78.1, 120.9, 127.1, 129.0, 129.0, 131.9, 140.5, 155.2, 171.7.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{18}BrNO_5$: 358.0296; found: 358.0295.

β-Hydroxyamino Acid (3*R*,4*S*)-10

The title compound was synthesized following the general procedure for hydrolysis and Boc-protection from (3*R*,5*R*,6*S*)-**9** (1.56 g, 3.5 mmol). Compound (3*R*,4*S*)-**10** (352 mg, 0.98 mmol, 28%) was isolated after purification by HPLC (RP 18; MeCN–H_2O, 10→40%; 230 nm; 3 mL/min).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.33 [s, 9 H, $C(CH_3)_3$], 4.33 (dd, *J* = 5.3, 9.2 Hz, 1 H, C*H*NH), 5.02 (d, *J* = 5.2 Hz, 1 H, C*H*OH), 5.84 (br s, 1 H, OH), 6.70 (d, *J* = 9.2 Hz, 1 H, NH), 7.20 (dt, *J* = 7.6, 1.4 Hz, 1 H, ArH), 7.35 (t, *J* = 7.4 Hz, 1 H, ArH), 7.49 (dd, *J* = 7.7, 1.0 Hz, 1 H, ArH), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 12.40 (br s, 1 H, COOH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.9, 57.9, 72.0, 78.3, 121.9, 127.0, 129.0, 129.1, 131.9, 140.2, 154.7, 171.1.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{18}BrNO_5$: 358.0296; found: 358.0292.

β-Hydroxyamino Acid (11)

β-Hydroxyamino acid (3*R*,4*S*)-**10** (47 mg, 0.13 mmol) was dissolved in MeOH (5 mL) and trimethylsilyl diazomethane (2.0 M in hexane, 0.07 mL, 0.14 mmol) was added. The resulting solution was stirred for 1 h at r.t. before adding a second portion of trimethylsilyl diazomethane (2.0 M in hexane, 0.07 mL, 0.14 mmol). The solution was stirred for 12 h and heated to 40 °C for 2 h. After an additional amount of trimethylsilyl diazomethane (2.0 M in hexane, 0.21 mL, 0.42 mmol) and a few drops of Et_3N were added, the solution was stirred for 7 h at r.t. The solvent was removed in vacuo and the crude product was purified by HPLC (RP 18; MeCN–H_2O, 5→95% in 10 min; 3 mL/min; 230 nm). The desired product **11** (24 mg, 0.06 mmol, 49%) was obtained as an oil.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 3.55 (s, 3 H, CO_2CH_3), 4.59 (d, *J* = 5.4 Hz, 1 H, C*H*NH), 5.24 (d, *J* = 5.4 Hz, 1 H, C*H*OH), 7.2 (t, *J* = 7.5 Hz, 1 H, ArH), 7.36 (t, *J* = 7.5 Hz, 1 H, ArH), 7.53 (dd, *J* = 7.9, 1.59 Hz, 1 H, ArH), 7.55 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (150 MHz, CD_3OD): δ = 28.6, 52.2, 59.4, 73.9, 80.9, 123.4, 128.4, 129.7, 130.5, 133.6, 141.3, 157.3, 172.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}BrNO_5$: 396.0417; found: 396.0420.

β-Hydroxyamino Acid (13)

β-Hydroxyamino acid (3*R*,4*S*)-**10** (50 mg, 0.14 mmol), dimethoxypropane (0.25 mL, 2.00 mmol) and a small quantity of *p*-toluenesulfonic acid were dissolved in acetone (10 mL) and stirred at 70 °C for 2.5 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. The crude product was purified by HPLC (RP 18; MeCN–H_2O, 5→95% in 15 min; 3 mL/min; 230 nm). The product **13** (17 mg, 0.04 mmol, 30%) was obtained as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 1.51–1.41 [m, 9 H, $C(CH_3)_3$], 1.80–1.70 [m, 6 H, $C(CH_3)_2$], 4.13 (d, *J* = 8.2 Hz, C*H*NH), 4.24 (d, *J* = 8.0 Hz, C*H*NH), 5.60 (d, *J* = 8.2 Hz, C*H*OH), 5.64 (d, *J* = 8.0 Hz, C*H*OH), 7.21 (dt, *J* = 7.9, 1.6 Hz, 1 H, ArH), 7.38 (t, *J* = 7.5 Hz, 1 H, ArH), 7.55 (dd, *J* = 8.1, 1.0 Hz, 1 H, ArH), 7.59 (d, *J* = 7.2 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.0, 26.3, 27.5, 28.2, 28.3, 66.1, 66.3, 77.9, 81.3, 81.6, 95.1, 95.8, 123.1, 128.1, 128.5, 130.3, 133.0, 136.3, 150.7, 151.9, 175.0, 176.5.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{22}BrNO_5$: 398.0609; found: 398.0607.

β-Hydroxyamino Acid (15)

Imidazolidinone (3*S*,5*R*,6*S*)-**9** (31 mg, 0.07 mmol) was dissolved in abs. toluene (10 mL) and cooled to 0 °C under an N_2 atmosphere. *i*-PrMgCl (14% in THF, LiCl complex, 0.35 mL, 0.35 mmol) was added dropwise and the solution was stirred for 15 min at 0 °C. After cooling to –78 °C, *t*-BuLi (1.6 M in hexane, 0.23 mL, 0.35 mmol) was added. After stirring for 10 min, triisopropyl borate (0.08 mL, 0.35 mmol) was added. The reaction mixture was allowed to warm to r.t. slowly and stirred for 12 h. H_2O (10 mL) was added and the pH was adjusted to 1–2 by adding 50% H_2SO_4. The aqueous phase was extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (silica; *n*-hexane–EtOAc, 1:1) and the product **15** (1 mg, 0.005 mmol, 7%) was obtained as a colorless oil.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.49 (d, *J* = 7.2 Hz, 1 H, CHN), 6.07 (d, *J* = 7.2 Hz, 1 H, CHO), 7.71–7.67 (m, 1 H, ArH), 7.90–7.84 (m, 3 H, ArH).

^{13}C NMR (100 MHz, CD_3OD): δ = 59.9, 77.6, 125.7, 128.8, 132.5, 136.3, 137.8, 151.3, 160.5, 201.0.

^{11}B NMR (128 MHz, CD_3OD): δ = 18.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_9H_{10}BNO_4$: 206.0630; found: 206.0634.

Boronic Ester (19)

Arylbromide **18** (34 mg, 0.10 mmol) was dissolved in abs. THF (5 mL) and cooled to –78 °C under an N_2 atmosphere. With 15 min intervals MeLi (5% in Et_2O, 0.14 mL, 0.22 mmol), *i*-PrMgCl (14% in THF, LiCl complex, 0.22 mL, 0.22 mmol), *t*-BuLi (1.6 M in hexane, 0.12 mL, 0.20 mmol), and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.08 mL, 0.40 mmol) were added dropwise. The reaction mixture was allowed to warm to r.t. slowly and stirred for 2 h. HCl (aq, 0.5 M, 20 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layers were combined, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by HPLC (RP 18; MeCN–H_2O, 10→90% in 15 min; 2 mL/min; 230 nm) to give the desired product **19** (5 mg, 0.01 mmol, 13%) as a colorless solid.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.34–1.37 (m, 21 H, CH_3), 2.94–2.85 (m, 1 H, CH_2), 3.12–3.19 (m, 1 H, CH_2), 4.37–4.32 (m, 1 H, C*H*NH), 7.24 (d, *J* = 7.7 Hz, 2 H, ArH), 7.66 (d, *J* = 7.8 Hz, 2 H, ArH).

^{13}C NMR (150 MHz, CD_3OD): δ = 25.1, 25.2, 28.5, 28.7, 38.2, 38.8, 38.9, 56.1, 56.2, 56.2, 80.6, 85.1, 129.8, 135.8, 142.2, 157.8, 157.9, 175.1, 175.3, 175.4

^{11}B NMR (128 MHz, $CDCl_3$): δ = 27.6.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{20}H_{30}BNO_6$: 390.2093; found: 390.2092.

β-Hydroxyamino Acid (20)

Arylbromide **16** (240 mg, 1 mmol) and Boc_2O (1.09 g, 5 mmol) were dissolved in *t*-BuOH (15 mL) and a small amount of DMAP was added. The reaction mixture was stirred at 30 °C for 60 h. The solvent was removed in vacuo and the crude product was purified by flash chromatography (silica; *n*-hexane–EtOAc, 19:1). The product **20** (94 mg, 0.2 mmol, 23%) was obtained as a colorless oil.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 1.41 [s, 9 H, $C(CH_3)_3$], 2.85 (dd, *J* = 13.8, 8.8 Hz, 1 H, CH_2), 3.02 (dd, *J* = 13.8, 6.0 Hz, 1 H, CH_2), 4.21 (dd, *J* = 6.0, 8.8 Hz, 1 H, C*H*NH), 7.15 (d, *J* = 8.3 Hz, 2 H, ArH), 7.43 (d, *J* = 8.3 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, CD_3OD): δ = 28.2, 28.7, 38.2, 57.0, 80.6, 82.9, 121.5, 132.4, 138.0, 157.8, 172.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}BrNO_4$: 422.0943; found: 422.0946.

Boronic Ester (21)

Arylbromide **20** (28 mg, 0.07 mmol) was dissolved in abs. toluene (10 mL) and cooled to –78 °C under an N_2 atmosphere. With 10 min intervals MeLi (5% in Et_2O, 0.08 mL, 0.08 mmol), *t*-BuLi (1.5 M in hexane, 0.1 mL, 0.14 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.06 mL, 0.28 mmol) were added. The reaction mixture was allowed to warm to r.t. slowly and H_2O (10 mL) was added. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4. The crude product was purified by flash chromatography (silica; *n*-hexane–EtOAc, 9:1) and the product **21** (15 mg, 0.03 mmol, 48%) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two diastereomers) = 1.34 [s, 12 H, $C(CH_3)_2$], 1.41 [s, 18 H, $C(CH_3)_3$], 3.09–3.07 (m, 2 H, CH_2), 4.45 (dd, *J* = 6.0, 8.0 Hz, 1 H, C*H*NH), 4.95 (d, *J* = 8.1 Hz, 1 H, CHN*H*), 7.17 (d, *J* = 7.9 Hz, 2 H, ArH), 7.73 (d, *J* = 7.9 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 28.1, 28.5, 29.8, 38.6, 54.8, 79.8, 82.1, 83.9, 129.1, 134.9, 139.8, 155.2, 170.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 31.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{38}BNO_6$: 470.2684; found: 470.2685.

Benzoboroxole (23; Route A)

n-BuLi (1.4 M in hexane, 1.6 mL, 2.2 mmol) was added under an N_2 atmosphere to a stirred solution of (trimethylsilyl)acetylene (0.34 mL, 2.4 mmol) in anhydrous Et_2O (7 mL) at 0 °C. After 15 min, aldehyde **26** (0.50 g, 2.2 mmol) was added and the reaction mixture was stirred for 2.5 h at 0 °C. The reaction was quenched with aq $NaHCO_3$ (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and washed with brine (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude product was dissolved in THF–H_2O (10 mL, 1:1 v/v), treated with LiOH (105 mg, 4.4 mmol) and stirred for 12 h at r.t. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with aq 1 M HCl (5 mL) and the organic layer was separated, washed with brine (5 mL) and dried

over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica; CH_2Cl_2 to CH_2Cl_2–MeOH, 50:1) to give the desired boronic acid **23** (115 mg, 0.7 mmol, 34%) as a colorless solid.

Benzoboroxole (23; Route B)

To a solution of **28** (0.21 g, 0.9 mmol) in H_2O–THF (15 mL, 1:2 v/v), LiOH (0.03 g, 1.4 mmol) was added and the resulting mixture was stirred for 12 h at r.t. The reaction mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (50 mL). The solution was washed with aq 1 M HCl (2 × 10 mL). The organic layer was separated, washed with brine (5 mL), and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica; CH_2Cl_2–MeOH, 100:1) to afford the alkyne **23** as a colorless oil (0.13 g, 0.8 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (d, *J* = 2.2 Hz, 1 H), 5.88 (s, 1 H), 7.61–7.39 (m, 3 H), 7.81–7.74 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.8, 74.6, 80.8, 121.8, 128.3, 130.6, 131.8, 153.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_7BO_2$: 159.0612; found: 159.0612.

Propargylic Alcohol (27)

n-BuLi (1.4 M in hexane, 3.9 mL, 5.4 mmol) was added to a stirred solution of (trimethylsilyl)acetylene (0.85 mL, 5.9 mmol) in anhydrous Et_2O (7 mL) at 0 °C under an N_2 atmosphere. After 15 min, 2-bromobenzaldehyde **6** (0.63 mL, 5.4 mmol) was added and the reaction mixture was stirred for 2.5 h at 0 °C. The reaction was quenched with aq $NaHCO_3$ (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and washed with brine (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude product was purified by flash chromatography to give the title compound **27** as a colorless oil (1.37 g, 4.8 mmol, 90%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.21 (s, 9 H), 3.22–3.05 (m, 1 H), 5.76 (s, 1 H), 7.21–7.09 (m, 1 H), 7.39–7.27 (m, 1 H), 7.57–7.48 (m, 1 H), 7.80–7.71 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.1, 64.7, 92.1, 103.8, 123.2, 128.0, 128.8, 130.1, 133.1, 139.4.

Benzoboroxole (28)

Propargylic alcohol **27** (0.57 g, 2.0 mmol) was dissolved in abs. toluene (10 mL) and cooled to –40 °C under an N_2 atmosphere. With 1 h intervals, MeLi (5% in Et_2O, 2.5 mL, 4.0 mmol), *t*-BuLi (1.7 M in pentane, 2.4 mL, 4.0 mmol) and triisopropyl borate (2.3 mL, 10.0 mmol) were added. The mixture was allowed to warm to r.t. slowly and stirred for 12 h. After dilution with EtOAc (20 mL), the organic layer was washed with aq 1 M HCl (2 × 10 mL), dried over Na_2SO_4, and the solvent was removed in vacuo to give a brown oil (0.50 g), which was purified by flash chromatography (silica; *n*-hexane–EtOAc, 4:1). The desired alkyne **28** (0.17 g, 0.7 mmol, 37%) was isolated as a colorless solid as well as starting material (0.14 g, 0.5 mmol, 25%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.19 (s, 9 H), 5.90 (s, 1 H), 7.58–7.38 (m, 3 H), 7.80–7.74 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.1, 71.7, 91.6, 102.1, 122.1, 128.2, 130.5, 131.9, 154.3.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.1.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{12}H_{15}BO_2Si$: 229.0862; found: 229.0859.

Click Reactions; General Procedure A

Alkyne (0.34 mmol), azide (0.34 mmol), sodium ascorbate (7 mg, 0.03 mmol), $CuSO_4$ (6 mg, 0.04 mmol), and CsF (260 mg, 1.71 mmol) were dissolved in dist. DMF (5 mL) and heated in a microwave for 30 min at 100 °C (P_{max} 200 W). The reaction mixture was concentrated to dryness in vacuo and the crude residue was dissolved in CH_2Cl_2 (10 mL), washed with H_2O (10 mL), EDTA (1 M), and dried over Na_2SO_4. The crude product was purified by flash chromatography (silica; CH_2Cl_2–MeOH, 20:3).

General Procedure B

Alkyne (0.2 mmol), azide (0.2 mmol), TBTA (10 mg, 0.02 mmol), $CuSO_4$ (3 mg, 0.02 mmol), sodium ascorbate (3 mg, 0.02 mmol), and CsF (90 mg, 0.6 mmol) were dissolved in DMF (5 mL) and stirred for 5 h at r.t. The reaction mixture was concentrated to dryness in vacuo and the crude residue was purified twice by flash chromatography (silica; CH_2Cl_2–MeOH, 10:3).

General Procedure C

Alkyne (0.2 mmol) and azide (0.2 mmol), TBTA (10 mg, 0.02 mmol), CuBr (3 mg, 0.02 mmol), and CsF (90 mg, 0.6 mmol) were dissolved in H_2O–DMF–*t*-BuOH (1:3:1 v/v, 5 mL) and stirred for 5 h at r.t. The reaction mixture was concentrated to dryness in vacuo and the crude residue was purified twice by flash chromatography (silica; CH_2Cl_2–MeOH, 10:3).

Benzoboroxole Amino Acid (30)

Starting from alkyne **23** (30 mg, 0.2 mmol) and azidoalanine **29** (43 mg, 0.2 mmol), TBTA (10 mg, 0.02 mmol), CuBr (3 mg, 0.02 mmol), and CsF (90 mg, 0.6 mmol), the title compound **30** (86 mg, 0.2 mmol, 99%) was obtained as a colorless solid following General Procedure C.

^{1}H NMR (400 MHz, CD_3OD): δ (mixture of two diastereomers) = 1.36 (s, 4 H), 1.39 (s, 5 H), 4.31–4.24 (m, 1 H), 4.72–4.62 (m, 1 H), 4.84–4.76 (m, 1 H), 6.08 (s, 1 H), 7.12–7.02 (m, 3 H), 7.49–7.43 (m, 1 H), 7.64–7.57 (m, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 28.7, 28.7, 53.0, 74.8, 80.5, 122.6, 122.6, 124.2, 124.3, 127.2, 127.3, 130.2, 151.3, 151.4, 154.4, 157.3, 175.0.

^{11}B NMR (128 MHz, CD_3OD): δ = 10.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}BN_4O_6$: 411.1446; found: 411.1447.

Benzoboroxole Amino Acid (31)

Starting from alkyne **23** (30 mg, 0.2 mmol), azidoalanine **29** (43 mg, 0.2 mmol), TBTA (10 mg, 0.02 mmol), $CuSO_4$ (3 mg, 0.02 mmol), sodium ascorbate (3 mg, 0.02 mmol), and CsF (90 mg, 0.6 mmol), the title compound **31** (22 mg, 0.06 mmol, 30%) was obtained as a colorless solid by following General Procedure B.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.33 (s, 9 H), 4.29 (t, *J* = 6.23, 4.19 Hz, 1 H), 4.63–4.57 (m, 1 H), 4.81 (br s, 1 H), 5.84 (br s, 1 H), 7.21 (t, *J* = 7.07 Hz, 1 H), 7.28 (t, *J* = 7.29 Hz), 7.38 (d, *J* = 7.82 Hz, 1 H), 7.64 (br s, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 28.7, 53.3, 57.2, 70.1, 80.5, 124.1, 127.8, 128.7, 129.3, 129.4, 144.1, 157.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}BN_4O_6$: 411.1446; found: 411.1442.

Amino Acid (32)

Starting from alkyne **23** (53 mg, 0.34 mmol), azidoalanine **29** (77 mg, 0.34 mmol), sodium ascorbate (7 mg, 0.03 mmol), $CuSO_4$ (6 mg, 0.04 mmol), and CsF (260 mg, 1.71 mmol), the title compound **32** (31 mg, 0.08 mmol, 24%) was obtained as a colorless solid by following General Procedure A.

^{1}H NMR (600 MHz, CD_3OD): δ = 1.36 (s, 9 H), 4.36–4.33 (m, 1 H), 4.68–4.60 (m, 1 H), 4.86 (br s, 1 H), 5.89 (s, 1 H), 7.44–7.26 (m, 5 H), 7.69 (s, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 28.9, 52.9, 57.1, 70.3, 80.6, 124.2, 127.8, 128.7, 129.5, 144.2, 152.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{22}N_4O_5$: 363.1663; found: 363.1668.

Benzoboroxole (34)

Starting from alkyne **23** (20 mg, 0.13 mmol) and 6-azido-D-galactose **33** (36 mg, 0.13 mmol), TBTA (4 mg, 0.008 mmol), CuBr (2 mg, 0.01 mmol), and CsF (57 mg, 0.38 mmol), the title compound **34** (30 mg, 0.07 mmol, 54%) was obtained as a colorless solid by following General Procedure C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two diastereomers) = 1.40–1.22 (m, 9 H), 1.41–1.48 (s, 3 H), 3.91 (d, *J* = 2.5 Hz, 1 H), 4.20–4.12 (m, 2 H), 4.32–4.27 (m, 1 H), 4.44–4.35 (m, 1 H), 4.64–4.52 (m, 2 H), 5.53–5.43 (m, 1 H), 6.44–6.40 (m, 1 H), 7.55–7.30 (m, 4 H), 7.89–7.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 24.5, 25.0, 26.0, 26.0, 50.6, 67.2, 67.2, 70.5, 70.8, 71.2, 76.3, 76.5, 96.3, 109.2, 110.0, 110.0, 121.9, 122.6, 122.7, 122.7, 127.9, 128.2, 128.9, 129.2, 130.4, 130.6, 131.3, 131.4, 148.0, 148.1, 148.2, 155.3, 155.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 32.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}BN_3O_7$: 444.1937; found: 444.1940.

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

Acknowledgment

Support by the DFG is gratefully acknowledged.

References

(1) (a) Trippier, P. C.; McGuigan, C. *Med. Chem. Commun.* **2010**, *1*, 183. (b) Touchet, S.; Carreaux, F.; Carboni, B.; Bouillon, A.; Boucher, J.-L. *Chem. Soc. Rev.* **2011**, *40*, 3895.
(2) (a) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584. (b) Nicolaou, K. C.; Boddy, C. N. C.; Li, H.; Koumbis, A. E.; Hughes, R.; Natarajan, S.; Jain, N. F.; Ramanjulu, J. M.; Bräse, S.; Solomon, M. E. *Chem. Eur. J.* **1999**, *5*, 2602. (c) Nicolaou, K. C.; Koumbis, A. E.; Takayanagi, M.; Natarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chem. Eur. J.* **1999**, *5*, 2622. (d) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem. Eur. J.* **1999**, *5*, 2648. (e) Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724.
(3) Lorand, J. P.; Edwards, J. O. *J. Org. Chem.* **1959**, *24*, 769.
(4) Roseman, S. *J. Biol. Chem.* **2001**, *276*, 41527.
(5) (a) Drickamer, K.; Taylor, M. E. *Annu. Rev. Cell Biol.* **1993**, *9*, 237. (b) Wallis, R. *Immunobiology* **2002**, *205*, 433.
(6) Dube, D. H.; Bertozzi, C. R. *Nat. Rev. Drug Discovery* **2005**, *4*, 477.
(7) (a) Pieters, R. J. *Med. Res. Rev.* **2007**, *27*, 796. (b) Astronomo, R. D.; Burton, D. R. *Nat. Rev. Drug Discovery* **2010**, *9*, 308.
(8) (a) Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Discovery* **2009**, *8*, 661. (b) Yan, J.; Fang, H.; Wang, B. *Med. Res. Rev.* **2005**, *25*, 490.
(9) (a) Mazik, M.; König, A. *J. Org. Chem.* **2006**, *71*, 7854. (b) Mazik, M. *ChemBioChem* **2008**, *9*, 1015. (c) Mazik, M. *Chem. Soc. Rev.* **2009**, *38*, 935. (d) Davis, A. P.; Wareham, R. S. *Angew. Chem. Int. Ed.* **1999**, *38*, 2978. (e) Ferrand, Y.; Crump, M. P.; Davis, A. P. *Science* **2007**, *318*, 619. (f) Nativi, C.; Cacciarini, M.; Francesconi, O.; Vacca, A.; Moneti, G.; Ienco, A.; Roelens, A. *J. Am. Chem. Soc.* **2007**, *129*, 4377.
(10) James, T. D.; Phillips, M. D.; Shinkai, S. *Boronic Acids in Saccharide Recognition*; The Royal Society of Chemistry: Cambridge, **2006**.
(11) (a) Kuivila, H. G.; Keough, A. H.; Soboczenski, E. J. *J. Org. Chem.* **1954**, *19*, 780. (b) Yoon, J.; Czarnik, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 5874. (c) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1910.
(12) (a) Norrild, J. C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479. (b) Bielecki, M.; Eggert, H.; Norrild, J. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 449.
(13) (a) Lauer, M.; Böhnke, H.; Grotstollen, R.; Salehnia, M.; Wulff, G. *Chem. Ber.* **1985**, *118*, 246. (b) Collins, B. E.; Sorey, S.; Hargrove, A. E.; Shabbir, S. H.; Lynch, V. M.; Anslyn, E. V. *J. Org. Chem.* **2009**, *74*, 4055.
(14) (a) Dowlut, M.; Hall, D. G. *J. Am. Chem. Soc.* **2006**, *128*, 4226. (b) Berube, M.; Dowlut, M.; Hall, D. G. *J. Org. Chem.* **2008**, *73*, 6471. (c) Pal, A.; Berube, M.; Hall, D. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 1492.
(15) (a) Edwards, N. Y.; Sager, T. W.; McDevitt, J. T.; Anslyn, E. V. *J. Am. Chem. Soc.* **2007**, *129*, 13575. (b) Pal, A.; Bérubé, M.; Hall, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 1492. (c) Duggan, P. J.; Offermann, D. A. *Tetrahedron* **2009**, *65*, 109. (d) Zou, Y.; Broughton, D. L.; Bicker, K. L.; Thompson, P. R.; Lavigne, J. J. *ChemBioChem* **2007**, *8*, 2048. (e) Levonis, S. M.; Kiefel, M. J.; Houston, T. A. *Chem. Commun.* **2009**, 2278.
(16) Wright, A. T.; Zhong, Z.; Anslyn, E. V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5679.
(17) (a) Pannier, N.; Maison, W. *Eur. J. Org. Chem.* **2008**, *2008*, 1278. (b) 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. (c) Nasr, K.; Pannier, N.; Frangioni, J. V.; Maison, W. *J. Org. Chem.* **2008**, *73*, 1056. (d) Maison, W.; Frangioni, J. V.; Pannier, N. *Org. Lett.* **2004**, *6*, 4567.
(18) Fitzi, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 345.
(19) Malan, C.; Morin, C. *J. Org. Chem.* **1998**, *63*, 8019.
(20) (a) Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967**, *100*, 2494. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (d) Huisgen, R.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 1153. (e) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613. (f) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
(21) Schnurch, M.; Holzweber, M.; Mihovilovic, M. D.; Stanetty, P. *Green Chem.* **2007**, *9*, 139.
(22) Panda, G.; Rao, N. V. *Synlett* **2004**, 714.
(23) (a) Dai, C.; Cheng, Y.; Cui, J.; Wang, B. *Molecules* **2010**, *15*, 5768. (b) Scrafton, D. K.; Taylor, J. E.; Mahon, M. F.; Fossey, J. S.; James, T. D. *J. Org. Chem.* **2008**, *73*, 2871.
(24) Jin, S.; Choudhary, G.; Cheng, Y.; Dai, C.; Li, M.; Wang, B. *Chem. Commun.* **2009**, 5251.
(25) (a) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (b) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.

(26) Yang, J.; Fu, X.; Jia, Q.; Shen, J.; Biggins, J. B.; Jiang, J.; Zhao, J.; Schmidt, J. J.; Wang, P. G.; Thorson, J. S. *Org. Lett.* **2003**, *5*, 2223.

(27) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.