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Synthesis of Di- and Trivalent Carbohydrate Mimetics with Oxepane Substructure by Employing Copper-Catalyzed [3+2] Cycloadditions of Alkynes with Azidooxepanes

Léa Bouché[a] and Hans-Ulrich Reissig*[a]

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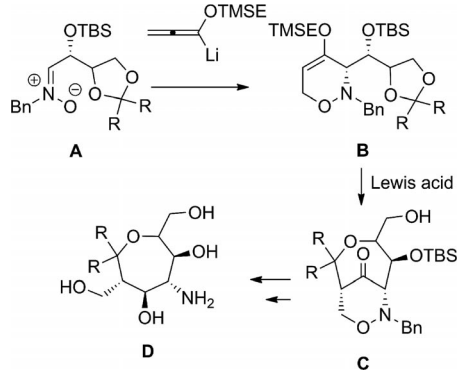
A series of enantiopure poly(hydroxy)aminooxepanes was converted into the corresponding azidooxepanes by a safe and efficient copper(II)-catalyzed diazo transfer reaction employing nonafluorobutanesulfonyl azide as nitrogen donor. These azidooxepanes underwent smooth copper(I)-catalyzed [3+2] cycloadditions with alkynes (click reaction) to provide a series of simple triazoles. With dialkynes and a tri-alkyne, bis- and tristriazoles containing oxepane substructures were prepared. Due to the polyhydroxylated end groups, these compounds are regarded as carbohydrate mimetics with potential biological activities, for example, as selectin inhibitors. In addition, unsymmetrical systems and macrocyclic compounds were prepared, again by employing [3+2] cycloadditions as key steps.

Introduction

As reported in previous studies, enantiopure 3,6-dihydro-2*H*-1,2-oxazines are versatile building blocks for the synthesis of highly functionalized compounds,[1] in particular of natural products[2] and of compounds to be considered as carbohydrate mimetics.[3] The key heterocycles are easily obtained in a stereocontrolled fashion by [3+3] cyclizations of nitrones derived from chiral pool compounds and lithiated alkoxyallenes.[4] In Scheme 1 we illustrate the synthesis of poly(hydroxy)aminooxepanes **D** and their precursors **C**, which were smoothly prepared with varying configurations and functional groups starting from nitrones **A** and lithiated (2-trimethylsilyl)ethoxyallene via 1,2-oxazines **B** with a Lewis-acid-mediated rearrangement as the crucial step.[5]

The similarity of compounds such as **D** to carbohydrates prompted us to regard them as carbohydrate mimetics[6] and to study their influence on biological processes. Very promising results have already been obtained with related aminopyrans that were connected by amide bonds to gold nanoparticles and subsequently O-sulfated. The achieved multivalent presentation (ca. 1000–1200 ligands on one nanoparticle) of the sulfated pyrans resulted in extremely high binding affinities in sub-nanomolar concentrations towards L- and P-selectins.[7] Sialyl Lewis X (sLe^x) analogues of this type have the potential to be used for treatment of diseases such as chronic inflammations.[8] The presentation of multivalent structures is a strategy frequently



Scheme 1. General approach to enantiopure poly(hydroxy)aminooxepanes **D** by [3+3] cyclization of nitrones **A** and lithiated TMSEO-allene followed by Lewis-acid-induced rearrangement of 3,6-dihydro-2*H*-1,2-oxazines **B**; TBS = *tert*-butyldimethylsilyl, TMSE = 2-(trimethylsilyl)ethyl.

realized by nature.[9] In the context of our aminopyran and aminooxepane compounds, we were interested in finding smaller inhibitors to study the influence of their multivalent presentation more systematically.[10] We therefore wanted to prepare carbohydrate mimetics derived from compounds **D** (Scheme 1) in mono-, di- and trivalent fashion. For this purpose, an efficient and flexible method was required that would allow the use of easily accessible spacer molecules with varying length and flexibility. An obvious choice to achieve this goal was the use of the well-developed copper-catalyzed [3+2] cycloaddition of alkynes and azides (Huisgen–Sharpless–Meldal reaction also known as the click reaction).[11] We also present a simple, safe, and reliable method to prepare azidooxepanes from the corresponding amines **D**, which should have general importance.

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
E-mail: hans.reissig@chemie.fu-berlin.de
http://www.bcp.fu-berlin.de/en/chemie/chemie/forschung/OrgChem/reissig/index.html

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Results and Discussion

Starting from poly(hydroxy)aminooxepanes **D**, we first developed a safe and efficient method to prepare the corresponding azidooxepanes. The azido group is a versatile functional moiety that allows many chemical transformations.[12] For the amino to azido conversion, the copper(II)-catalyzed diazo transfer reaction was selected. This process has been known for a long time[13] and was further developed by Wong through the use of metal catalysis.[14] The reaction has frequently been used in carbohydrate chemistry and, in 2007, our group successfully applied it to generate azidopyrans.[3b,15] The crucial feature of our new protocol is the use of freshly prepared nonafluorobutanesulfonyl azide (NfN_3),[16] which is less explosive and probably less toxic than the conventionally applied trifluoromethanesulfonyl azide (TfN_3). A systematic evaluation of NfN_3 in the copper(II)-catalyzed diazo transfer reactions and other processes were later reported by the group of Chiara.[17] The very mild conditions of the diazo transfer reaction allowed the preparation of azides with complete retention of configuration. A practical advantage of this protocol is that the completion of the reaction can be followed by the color change of the reaction mixture.

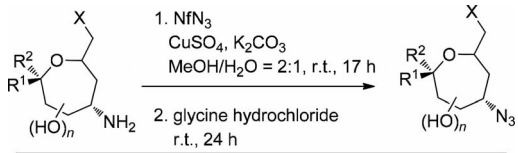
By using our method with NfN_3, poly(hydroxy)aminooxepanes[5] **1**, **3**, **5**, **7**, **9**, and **11**, containing an amino group at C-4, were smoothly converted into the new azidooxepanes **2**, **4**, **6**, **8**, **10**, and **12**, respectively, in yields ranging from 59 to 90% (Table 1, entries 1–6). Due to the diversity of the precursor amines, azides bearing variable substituents at C-2, C-5, and C-7 were accessible. Of particular interest is bis(azido)oxepane **10** (entry 5), which was obtained through a twofold diazo transfer reaction in very good yield. The recorded yields do not strongly depend on the structure or configuration of the starting materials, and there was no indication of chemical instability of the resulting azidooxepanes or of an erosion of their configurational homogeneity.

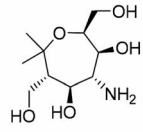
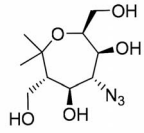
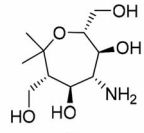
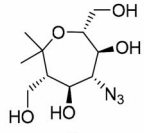
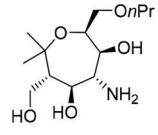
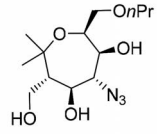
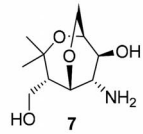
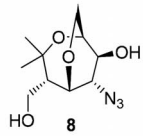
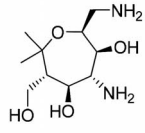
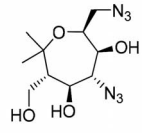
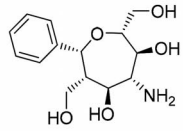
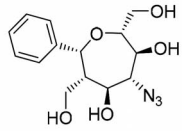
Having the highly substituted enantiopure azidooxepanes **2**, **4**, **6**, **8**, **10** and **12** in hand, we first studied the [3+2] cycloaddition of model compounds **2** and **4** with several simple terminal alkynes (Table 2). The conditions introduced by Sharpless et al. employing copper(I) iodide and the ligand tris(benzyltriazolylmethyl)amine (TBTA)[18,19] were carefully screened in our laboratory and have been frequently used.[20] The copper(I)-catalyzed cycloadditions were efficient at room temperature and no sideproducts could be detected. For the synthesis of the simple triazoles, 1.5–3.0 equiv. of the alkynes were used. Because we wanted to examine the biological activity of our products, the copper catalyst needed to be removed as completely as possible. Addition of ammonia solution to the crude product mixtures before filtration and chromatography was a simple procedure that reliably achieved this goal.

Addition of phenylacetylene (Table 2, entry 1) led to the smooth conversion of azidooxepane **2** into the corresponding 1,2,3-triazole derivative **13** in excellent yield (96%). Three other alkynes with functional groups were also examined (entries 2–4). Azidooxepane **4** furnished cycloadduct **14** in nearly quantitative yield (entry 2). Similarly, the reaction of **2** with an alkyne bearing a methoxycarbonyl group[21] gave the expected triazolinyl-substituted oxepane **15** in reasonable efficiency (entry 3). In addition, the click protocol reported by Lipshutz[22] was examined with **2** and cyclopropylethyne, but, in our case, the reaction required longer and the yield of **16** was significantly lower (entry 4); however, we did not perform this reaction under the standard conditions. All presented transformations show the usefulness of the applied conditions for the copper(I)-catalyzed [3+2] cycloaddition and we were thus encouraged to apply these conditions to the preparation of di- and trivalent structures.

For the synthesis of divalent compounds, the required dialkynes were combined with a slight excess of the corre-

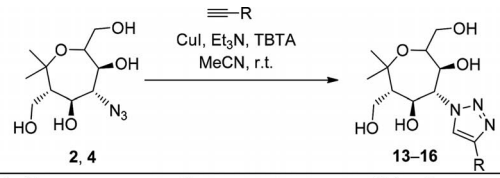
Table 1. Synthesis of enantiopure azidooxepanes **2**, **4**, **6**, **8**, **10**, and **12** by copper(II)-catalyzed diazo transfer employing nonafluorobutanesulfonyl azide; Nf = nonafluorobutylsulfonyl.

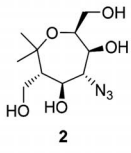
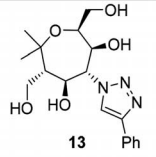
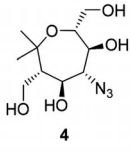
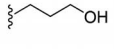
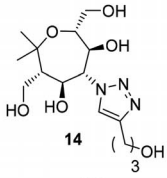
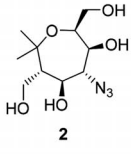
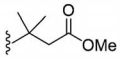
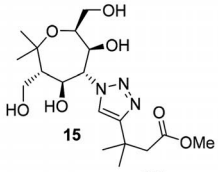
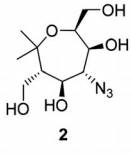
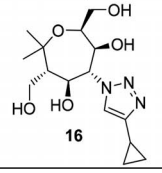


Entry	Aminooxepane	Azidooxepane	Yield [%][a]
1	 **1**	 **2**	87
2	 **3**	 **4**	90
3	 **5**	 **6**	59
4	 **7**	 **8**	69
5	 **9**	 **10**	77
6	 **11**	 **12**	72

[a] Yield of purified compound.

Table 2. Copper(I)-catalyzed [3+2] cycloadditions of azidooxepanes **2** and **4** with terminal alkynes to give the corresponding triazoles **13**–**16**; TBTA = tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methylamine.



Entry	Azidooxepane	R	*t* [h]	Triazole	Yield [%][a]
1	 **2**		13	 **13**	96
2	 **4**		5	 **14**	99
3	 **2**		72	 **15**	78
4[b]	 **2**		18	 **16**	66

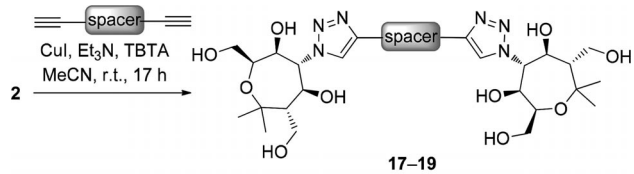
[a] Yield of purified compound. [b] *Reaction conditions:* Cu/C, Et_3N, dioxane, 60 °C.[22]

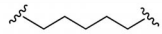
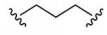
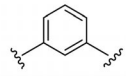
sponding azidooxepane (ca. 2.1 equiv.) to avoid formation of the mono-cycloaddition products. We used dialkynes with aliphatic or aromatic central units to obtain divalent oxepane derivatives either with flexible (Table 3, entries 1 and 2) or with rigid (entry 3) spacer units. Gratifyingly, the desired bistriazoles **17**–**19** were isolated in good yields.

This established method was also applied to phenyl-substituted azidooxepane **12** and nona-1,8-diyne, which provided the divalent oxepane **20** in comparable efficiency (Scheme 2). This latter compound, bearing hydrophilic and hydrophobic groups, was more difficult to purify due to its lower solubility. The divalent structure, the long flexible spacer, and the terminal aryl groups of product **20** show, in part, resemblance to the known selectin inhibitor Bimosiamose. This compound is a carbohydrate mimetic that was developed in industry and has already been investigated in clinical studies.[23]

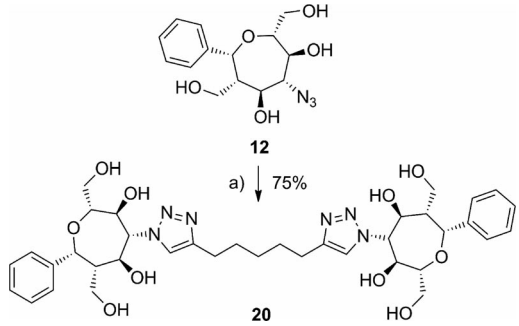
The preparation of trivalent compound **21** from azidooxepane **2** and 1,3,5-tri(ethynyl)benzene was found to be challenging (Scheme 3). Difficulties were encountered in the separation of TBTA from the final product, showing the limitation of the applied protocol. Gratifyingly, Wang recently reported an alternative method,[24] using acid/base

Table 3. Copper(I)-catalyzed [3+2] cycloadditions of azidooxepane **2** with three different dialkynes to give the corresponding bistriazoles **17**–**19** with flexible and rigid spacer moieties.



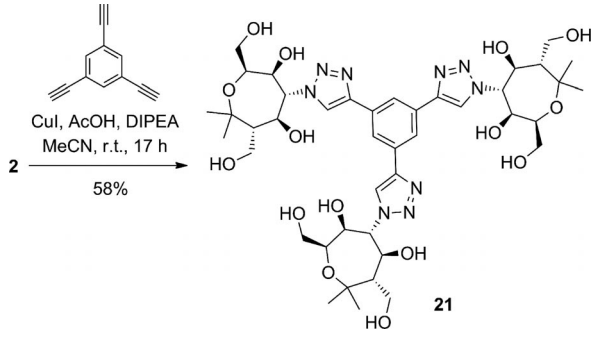
Entry	Spacer	Bistriazole	Yield [%][a]
1		**17**	80
2		**18**	63
3		**19**	75

[a] Yield of purified compound.



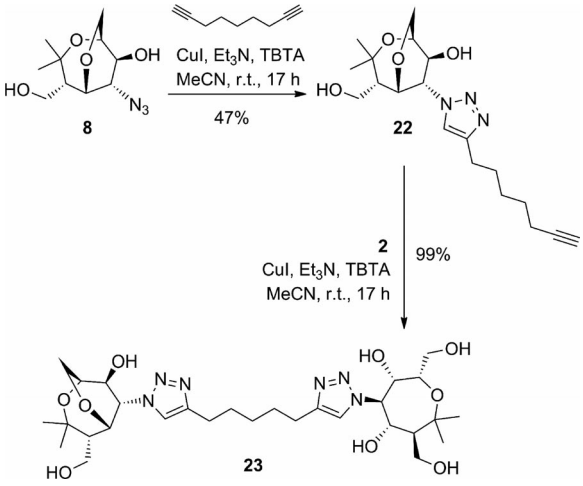
Scheme 2. Synthesis of divalent compound **20** from azidooxepane **12** and nona-1,8-diyne. *Reagents and conditions:* (a) CuI, Et_3N, TBTA, nona-1,8-diyne, MeCN, r.t., 17 h.

catalysis, which could be successfully applied to our problematic transformation. After addition of copper(I) iodide and equimolar amounts of acetic acid and of Hünig base, we isolated the tristriazole derivative **21** in pure form and in an acceptable yield of 58%. It should be mentioned that the obtained carbohydrate mimetic **21** bears twelve hydroxy groups and therefore intense purification by column chromatography was required. To the best of our knowledge, this example represents the first trivalent carbohydrate mimetic bearing an oxepane moiety.[25]



Scheme 3. Synthesis of the tristriazole derivative **21** from azidooxepane **2** and 1,3,5-tri(ethynyl)benzene by employing Wang's acid/base protocol.[24]

Taking into account that simple triazoles are very easily formed, we also planned to prepare unsymmetrically substituted divalent compounds. Bicyclic azidooxepane **8** was therefore treated with an excess of nona-1,8-diyne (2.4 equiv.) under standard conditions (Scheme 4). After stirring overnight, the desired alkynyl-substituted oxepane **22** was isolated in moderate yield; the corresponding bistriazole could not be detected in the crude reaction mixture. A second copper(I)-catalyzed cycloaddition of alkyne **22** with azidooxepane **2** (1.2 equiv.) under the same conditions provided the unsymmetrical divalent bistriazole **23** in excellent yield. This example demonstrates that our concept also allows the synthesis of unsymmetrically substituted divalent carbohydrate mimetics with reasonable overall efficacy.

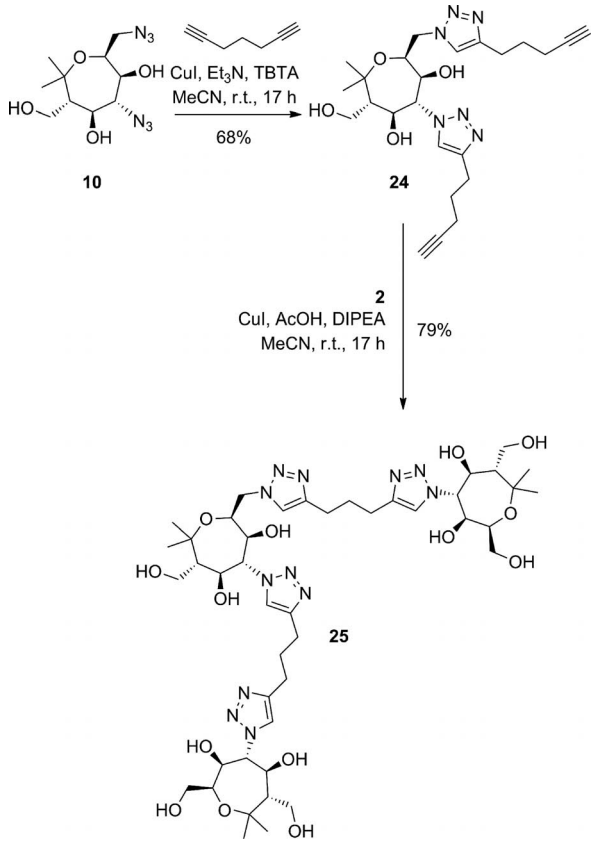


Scheme 4. Synthesis of unsymmetrical divalent oxepane derivative **23** by two sequential [3+2] cycloadditions starting from nona-1,8-diyne and two different azidooxepanes.

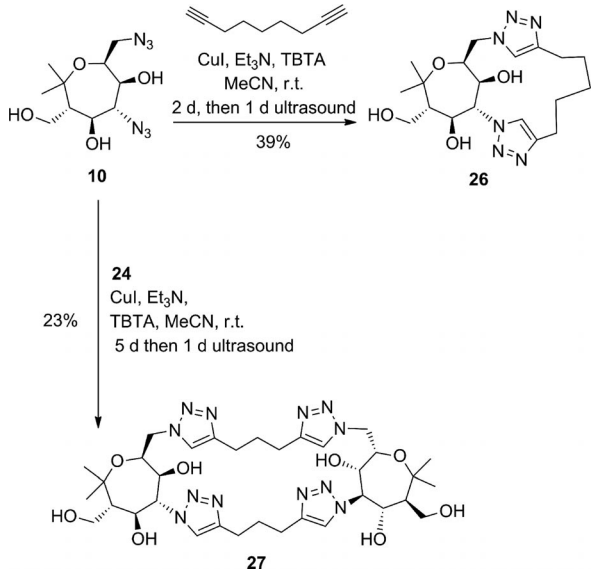
The procedure described above was also applied to the construction of more complex architectures. Cycloaddition of bis(azido)oxepane **10** with an excess of hepta-1,6-diyne (7.4 equiv.) furnished dialkynyl-substituted triazole **24** in 68% yield (Scheme 5). Two subsequent [3+2] cycloadditions of **24** with azidooxepane **2** allowed successful isolation of the unsymmetrical trivalent tristriazole derivative **25**, which contains eleven hydroxy groups. This example shows the potential of our approach for the preparation of new oligomeric oxepane derivatives connected by triazole units.

A final challenging goal was the use of azidooxepane/alkyne cycloadditions for the construction of novel macrocycles. Fascinating examples of macrocycles containing carbohydrate substructures are known.[26] Gratifyingly, macrocycle **26** was obtained from bis(azido)oxepane **10** and nona-1,8-diyne in 39% yield after two days stirring at room temperature under high dilution conditions and final ultrasonication (0.007 mmol/mL) (Scheme 6). Hence, both the intermolecular and subsequent intramolecular [3+2] cycloaddition proceed with reasonable efficacy.

In a second example, precursor **10** was combined with unsymmetrical bisalkyne **24** containing an oxepane core. In this case, high dilution (0.0043 mmol/mL) and the use of



Scheme 5. Two-step synthesis of unsymmetrical trivalent tristriazole derivative **25** with dialkynyl-substituted triazole **24** and azidooxepane **2** as building blocks.



Scheme 6. Syntheses of two macrocyclic carbohydrate mimetics **26** and **27** (proposed constitution) bearing oxepane units prepared from bis(azido)oxepane **10**.

ultrasound were advantageous to promote the conversion of the precursors.[27] Due to the asymmetry of **24** the formation of two regioisomeric macrocycles is possible. The pri-

mary azide moiety of **10** will certainly undergo the first cycloaddition, however the two alkyne units of **24** should have very similar reactivity. Therefore, it was hard to predict which isomer would be favored. One compound was isolated after chromatography in pure form in 23% yield, whereas a minor fraction consisting of an inseparable mixture of this compound, a second isomer, and unknown impurities (possibly oligomers) was also obtained. Currently it is not clear which product was actually isolated as the major product. The drawn structure of **27** is C_2-symmetric whereas the alternative regioisomer (not shown) has an inversion center. This does not allow a distinction to be made based on the existing NMR spectroscopic data.

Conclusions

By using a safe and efficient diazo transfer method, poly(hydroxy)aminooxepanes were converted into azidooxepanes, including one bisazide. Subsequent copper(I)-catalyzed cycloaddition (click reaction) of these azides with mono-, bis-, and trisalkynes allowed the flexible synthesis of triazole derivatives with oxepane end groups that can be regarded as new multivalent carbohydrate mimetics. Both symmetrically and unsymmetrically substituted systems were prepared. Other architectures were also constructed by this method, for example, macrocycles with oxepane subunits. No protective groups were required to achieve the transformations. Together, these experiments demonstrate the versatility and efficacy of the cycloaddition approach to new multivalent carbohydrate mimetics with poly(hydroxy)oxepane end groups. In a future publication we shall report on the sulfation of the reported multivalent polyols and of related compounds prepared in our group and on an evaluation of their biological activity.

Experimental Section

General Methods: See the Supporting Information.

Typical Procedure for the Copper(II)-Catalyzed Diazo Transfer (Procedure 1); (2*S*,3*S*,4*R*,5*S*,6*S*)-4-Azido-2,6-bis(hydroxylmethyl)-7,7-dimethyloxepan-3,5-diol (2): Aminooxepane **1** (55 mg, 0.23 mmol) dissolved in MeOH (1 mL) was stirred with $CuSO_4 \cdot H_2O$ (7.0 mg, 0.028 mmol) dissolved in H_2O (0.5 mL), K_2CO_3 (65 mg, 0.47 mmol), and freshly synthesized NfN_3 (220 mg, 0.677 mmol) at room temp. for 17 h. Upon completion of the reaction the blue solution became green, then glycine hydrochloride (180 mg, 1.61 mmol) was added and the mixture was stirred for a further 24 h. A solution of CH_2Cl_2/7 N NH_3 in MeOH (30:1) was added and the mixture was stirred for 10 min. The mixture was filtered through a short column (silica gel) and the solvents were removed in vacuo. The crude material (55 mg, colorless solid) was then purified by column chromatography (silica gel; CH_2Cl_2 to CH_2Cl_2/MeOH, 20:1) to give azidooxepane **2** (53 mg, 87%) as a colorless solid; m.p. 146 °C; $[\alpha]_D^{22}$ = –34.2 (c = 0.04, MeOH); R_f = 0.07 (silica gel; CH_2Cl_2/7 N NH_3 in MeOH, 20:1). ^{1}H NMR (700 MHz, CD_3OD): δ = 1.17, 1.35 (2s, 3 H each, Me), 1.88 (ddd, J = 3.5, 6.1, 9.8 Hz, 1 H, 6-H), 3.50–3.57 (m, 4 H, 2-CH_2, 3-H, 4-H), 3.64–3.67 (m, 3 H, 2-H, 6-CH_2), 3.89 (t, $J \approx$ 9.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (175 MHz, CD_3OD): δ = 21.0, 31.5 (2q, Me), 59.9 (d, C-6), 63.4 (t, 2-CH_2), 64.2 (t, 6-CH_2), 72.3 (d, C-5), 73.6 (d, C-2), 74.8, 76.8 (2d, C-3, C-4), 77.0 (s, C-7) ppm. IR (ATR): $\tilde{\nu}$ = 3355 (OH), 2990–2835 (C–H), 2120 (N_3), 1645 (C=C), 1265 (C–O), 1015 (C–O–C) cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{10}H_{19}N_3O_5Na$ $[M + Na]^+$ 284.1217; found 284.1225. $C_{10}H_{19}N_3O_5$ (261.3): calcd. C 45.97, H 7.33, N 16.08; found C 46.03, H 7.15, N 15.99.

Typical Procedure for Copper(I)-Catalyzed [3+2] Cycloaddition with TBTA as Ligand (Procedure 2); Bistriazole 20: Azide **12** (66 mg, 0.21 mmol), nona-1,8-diyne (15.7 μL, 0.104 mmol), Et_3N (6.3 μL, 0.046 mmol), TBTA (24.3 mg, 0.046 mmol), and CuI (8.7 mg, 0.046 mmol) were dissolved in MeCN (6 mL). The yellow mixture was stirred at room temp. for 17 h and, upon completion of the reaction, a solution of 7 N NH_3 in MeOH (10:1) was added. The mixture was stirred for a further 10 min, filtered through a small column (silica gel), and the solvents were removed in vacuo. The crude product (yellow solid, 117 mg) was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 25:1 to 10:1) to give bistriazole **20** (58 mg, 75%) as a yellow solid; melting range 185–192 °C; $[\alpha]_D^{22}$ = +20.8 (c = 0.27, DMF); R_f = 0.14 (silica gel; CH_2Cl_2/MeOH, 7:1). ^{1}H NMR (700 MHz, [D$_7$]DMF): δ = 1.47, 1.70 (2m$_c$, 2 H, 4 H, CH_2), 2.65 (m$_c$, 2 H, 6-H), 2.66 (t, J = 7.6 Hz, 4 H, CH_2), 3.35, 3.49 (AB part of ABX system, J_{AX} = 5.3, J_{BX} = 7.7, J_{AB} = 10.7 Hz, 2 H each, 6-CH_2), 3.70 (dd, J = 6.0, 11.4 Hz, 2 H, 2-CH_2), 3.77 (m$_c$, 2 H, 2-H), 3.92 (dd, J = 2.2, 11.4 Hz, 2 H, 2-CH_2), 4.21 (t, $J \approx$ 9.5 Hz, 2 H, 3-H), 4.51 (br. s, 2 H each, OH), 4.54 (dd, J = 7.7, 9.3 Hz, 2 H, 5-H), 4.78 (t, J = 9.5 Hz, 2 H, 4-H), 4.76 (br. s, 2 H, OH), 5.05 (br. s, 2 H, OH), 5.18 (d, J = 7.6 Hz, 1 H, 7-H), 5.40 (br. s, 2 H, OH), 7.29, 7.37, 7.55 (2t, d, $J \approx$ 7.5 Hz, 2 H, 4 H, 4 H, ArH), 7.88 (s, 2 H, 5′-H) ppm. ^{13}C NMR (175 MHz, [D$_7$]DMF): δ = 25.2 (d, C-6), 28.9, 29.4, 50.4 (3t, CH_2), 61.2 (t, 6-CH_2), 63.7 (t, 2-CH_2), 69.7 (d, C-5), 72.0 (d, C-3), 73.7 (d, C-4), 79.4 (d, C-7), 82.0 (d, C-2), 123.3 (d, C-5′), 127.2, 127.3, 128.0, 141.2 (3d, s, Ar), 146.2 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3350 (OH), 3080–3000 (=C–H), 2930–2770 (C–H), 1600 (C=C, C=N), 1090, 1060 (C–O–C) cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{37}H_{50}N_6O_{10}Na$ $[M + Na]^+$ 761.3486; found 761.3481.

Typical Procedure for Copper(I)-Catalyzed [3+2] Cycloaddition Employing DIPEA and AcOH (Procedure 3); Tristriazole 21: Azide **2** (70 mg, 0.27 mmol), DIPEA (62.5 μL, 0.351 mmol), AcOH (20.1 μL, 0.351 mmol), 1,3,5-tri(ethynyl)benzene (11.7 mg, 0.078 mmol), and CuI (11.0 mg, 0.058 mmol) were dissolved in MeCN (1 mL). The yellow solution was stirred at room temp. for 17 h. Upon completion of the reaction, a mixture of CH_2Cl_2/7 N NH_3 in MeOH (20:1) was added, the reaction mixture was filtered through a small column (silica gel) and the solvents were removed in vacuo. The crude product (94 mg, yellow solid) was then purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 10:1 to 4:1) and filtered twice through a syringe filter to give tristriazole **21** (42 mg, 58%) as a colorless solid; melting range 205–210 °C; $[\alpha]_D^{22}$ = –55.1 (c = 0.56, MeOH); R_f = 0.21 (silica gel; CH_2Cl_2/MeOH, 4:1). ^{1}H NMR (700 MHz, [D$_5$]py/CD_3OD, 2:1): δ = 1.33, 1.39 (2s, 9 H each, Me), 2.23 (ddd, J = 3.4, 6.1, 9.7 Hz, 3 H, 6-H), 3.82, 3.87 (AB part of ABX system, J_{AX} = 3.4, J_{BX} = 6.1, J_{AB} = 11.5 Hz, 3 H each, 6-CH_2), 3.92, 3.97 (AB part of ABX system, J_{AX} = 5.4, J_{BX} = 7.1, J_{AB} = 11.4 Hz, 3 H each, 2-CH_2), 4.22 (m$_c$, 3 H, 2-H), 4.67 (t, $J \approx$ 9.5 Hz, 3 H, 5-H), 4.82 (dd, J = 2.8, 7.2 Hz, 3 H, 3-H), 5.06 (dd, J = 7.2, 9.5 Hz, 3 H, 4-H), 8.35 (s, 3 H, ArH), 8.49 (s, 3 H, 5′-H) ppm. ^{13}C NMR (175 MHz, [D$_5$]py/CD_3OD, 2:1): δ = 21.5, 32.0 (2q, Me), 60.5 (d, C-6), 63.6 (t, 2-CH_2), 63.9 (t, 6-CH_2), 70.3

(d, C-5), 74.06 (d, C-2), 74.12 (d, C-3), 76.0 (d, C-4), 77.1 (s, C-7), 122.7 (d, Ar), 124.7 (d, C-5′), 133.5, 147.1 (2s, Ar, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3375 (OH), 2980–2845 (C–H), 1545–1490 (C=C, C=N), 1220 (C–O), 1065, 1020 (C–O–C) cm^{-1}. HRMS (ESI-TOF): *m/z* calcd. for $C_{42}H_{63}N_9O_{15}Na$ $[M + Na]^+$ 956.4436; found 956.4314.

Supporting Information (see footnote on the first page of this article): Experimental procedures, analytical data and copies of the NMR spectra.

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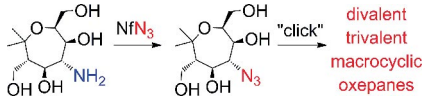
A safe and reliable copper(II)-catalyzed diazo transfer method leads to azidooxepanes that smoothly undergo copper(I)-catalyzed [3+2] cycloadditions with alkynes to provide triazole derivatives. This sequence allows the preparation of di- and trivalent carbohydrate mimetics including novel macrocyclic compounds.



Carbohydrate Mimetics

Keywords: Cycloaddition / Click chemistry / Macrocycles / Alkynes / Azides / Carbohydrate mimetics

