EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202301294

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

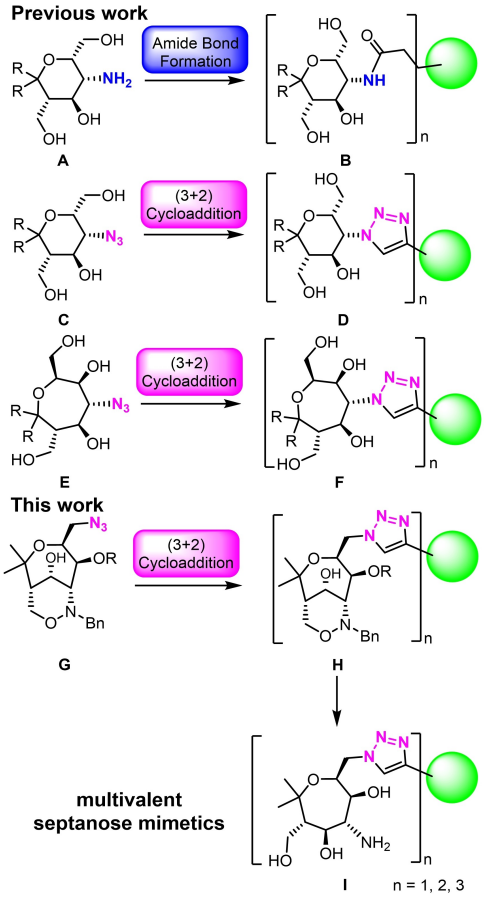
Multivalent Aminoseptanose Mimetics by Copper-Catalyzed (3 + 2) Cycloadditions of Azidomethyl-Substituted Bicyclic 1,2-Oxazines

Léa Bouché,[a] Reinhold Zimmer,[a] and Hans-Ulrich Reissig*[a]

Starting from readily available enantiopure azidomethyl-substituted bicyclic 1,2-oxazine derivatives and mono-, di- or trialkynes, their copper-catalyzed (3 + 2) cycloadditions furnished a series of 1,2,3-triazolyl-linked compounds in good yields. These click reactions proceeded smoothly at room temperature when copper iodide as catalyst was used in the presence of triethylamine and tris[(1-gbenzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine as ligand. Generally, the unprotected bicyclic 1,2-oxazine derivatives seemed to show slightly higher reactivity and provided better yields compared with their silyl-protected counterparts. Exhaustive hydrogenolysis with cleavage of the 1,2-oxazine N–O bonds in the presence of palladium on charcoal as promotor is feasible but was found to be capricious. Reasonable results were obtained when acetic acid was employed as cosolvent. By applying these conditions, several of the bicyclic 1,2-oxazine derivatives were successfully converted into the expected mono- or divalent aminooxepine derivatives which can be regarded as aminoseptanose mimetics.

Introduction

In previous reports, we enclosed the preparation of multivalent aminopyran and aminooxepane derivatives which were designed to imitate multivalent carbohydrate conjugates (Scheme 1).[1,2] Easily available aminopyran derivatives **A** were connected by amide bonds to give different multivalent carbohydrate mimetics **B**.[3,4] Furthermore, the related azidopyran **C** and suitable alkynes could be converted into di- and trivalent systems **D**[5–7] by applying the well-established copper-catalyzed (3 + 2) cycloaddition (CuAAC) approach.[8–10] As alternative, we also studied the Sakai-Westermann reaction[11,12] which directly converted aminopyrans **A** into triazoles **D**.[6] Moreover, the azidooxepanes **E** were transferred by the CuAAC method into multivalent triazole derivatives **F**.[13] The multivalent compounds **B**, **D** and **F** bear the connecting functional groups directly at the heterocyclic core, which results in restricted conformational flexibility of the synthesized systems. With the intention to study the biological activity of more flexible compounds we also prepared pyran[14,15] and oxepane derivatives[16] which contain a terminal azidomethyl group.



Scheme 1. Previously prepared multivalent pyran and oxepane systems **B**, **D**, and **F** and aim of the current work converting azidomethyl-substituted bicyclic 1,2-oxazine **G** into intermediates **H** and finally into aminoseptanose mimetics **I**.

[a] *Dr. L. Bouché, Dr. R. Zimmer, Prof. Dr. H.-U. Reissig*
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustr. 3, D-14195 Berlin, Germany
E-mail: hans.reissig@chemie.fu-berlin.de

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202301294

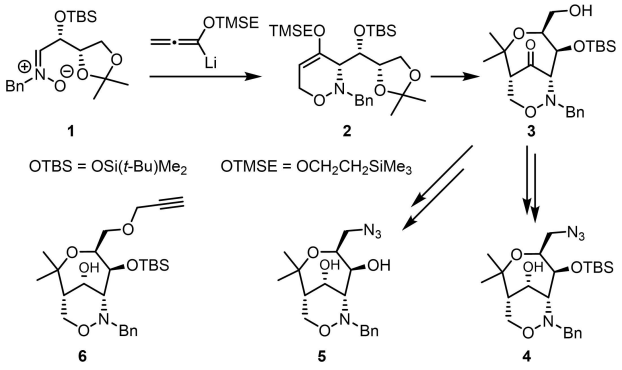
Research Article
doi.org/10.1002/ejoc.202301294

In the current report we describe the employment of the bicyclic 1,2-oxazine derivative **G** (Scheme 1) which can be regarded as a protected precursor of an aminoseptanose mimetic.[17] The conversion of **G** into triazole derivatives **H** and finally the cleavage of the N–O bonds should lead to a series of the mono-, di- and trivalent aminoseptanose mimetics **I**. All final multivalent compounds of these studies were prepared in order to assess their potential to act as inhibitors of P- and L-selectin binding. These glycoproteins[18] are crucial in the inflammation cascade[19] and several of our earlier prepared compounds displayed IC_{50} values in the nanomolar to picomolar range, however, generally only after O-sulfation of the hydroxyl groups.[3–7]

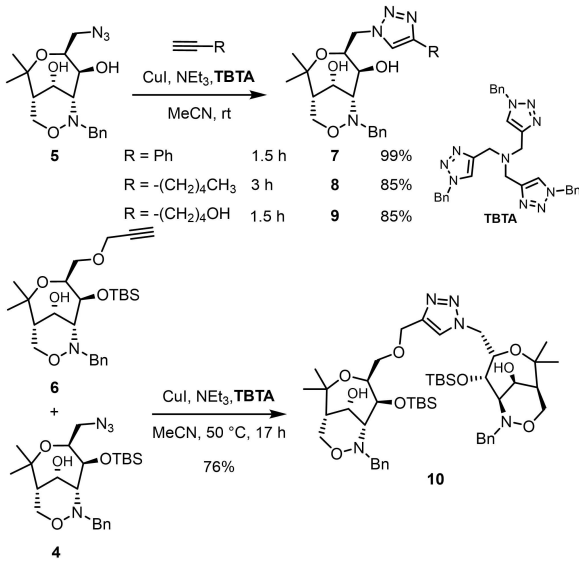
Results and Discussion

The key precursor compound **3** of our study is easily available by a (3 + 3)-cyclization process from enantiopure L-threose-derived nitrone **1** and lithiated 2-(trimethylsilyl)ethoxyallene, which furnished the 1,2-oxazine derivative **2** with excellent diastereoselectivity.[20] Its Lewis acid-promoted rearrangement[21] incorporates the 1,3-dioxolane side chain and provided the bicyclic compound **3** in good overall yield. Standard synthetic operations introduced the azido group delivering the protected and unprotected azidomethyl-substituted building blocks **4** and **5**. The propargyl ether **6** was also efficiently prepared from precursor **3** by straightforward reactions (Scheme 2).[20]

We first examined the reactivity of protected and unprotected azides **4** and **5** with simple alkynes. It was found in earlier studies[13–15] that the copper-catalyzed Huisgen-Meldal-Sharpless (3 + 2) cycloaddition (CuAAC) of equimolar amounts of organic azides and alkynes proceeded efficiently at room temperature in acetonitrile as solvent when copper iodide, triethylamine, and **TBTA** (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine)[22] were employed as catalyst and additives (0.2 equivalents each). Under these approved conditions the CuAAC of unprotected bicyclic azidomethyl-substituted compound **5** with phenylacetylene, 1-heptyne, and 5-hexyn-1-ol, respectively, furnished the expected triazole derivatives **7**–**9** in 85–95% yield (Scheme 3). The protected azide **4** similarly reacts



Scheme 2. Origin of key compounds **3**–**6** which are easily available from enantiopure nitrone **1** via 1,2-oxazine derivative **2**.[20]

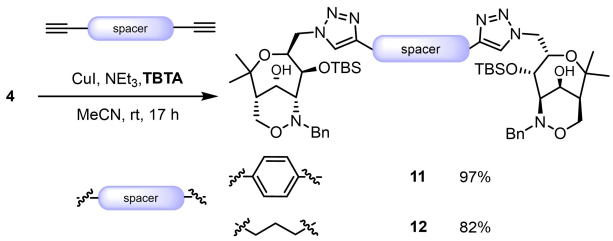


Scheme 3. CuAACs of azide **5** with simple monoalkynes and of protected azide **4** with propargyl ether **6** furnishing triazole derivatives **7**–**10**.

with the propargylic ether **6** to give the unsymmetric divalent compound **10** in 76% yield. It is noteworthy that for this cycloaddition a slightly higher temperature (50 °C) is required to achieve good conversion. The lower reactivity may be caused by the bulky *tert*-butyl(dimethyl)siloxy groups at both components. Nevertheless, the model reactions illustrated in Scheme 3 demonstrate that the standard reaction conditions of the CuAAC reactions work well with the azidomethyl-substituted bicyclic 1,2-oxazines **4** and **5**.

Next, we examined the capability of protected azidomethyl-substituted compound **4** to undergo CuAACs with dialkynes (Scheme 4). The reactions of **4** with 1,4-diethynylbenzene and with 1,6-heptadiyne proceeded well under standard conditions and the two divalent aminoseptanose mimetic precursors **11** and **12** were isolated in 97% and 82% yield, respectively. Both transformations occur at room temperature which indicates that steric hindrance by the *tert*-butyl(dimethyl)siloxy group of **4** is not decisive in this case. The two examples of Scheme 4 reveal that rigid and flexible spacer elements between the two end groups can be introduced.

The examples shown in Scheme 3 had clearly proven that the CuAACs of the unprotected azidomethyl-substituted com-

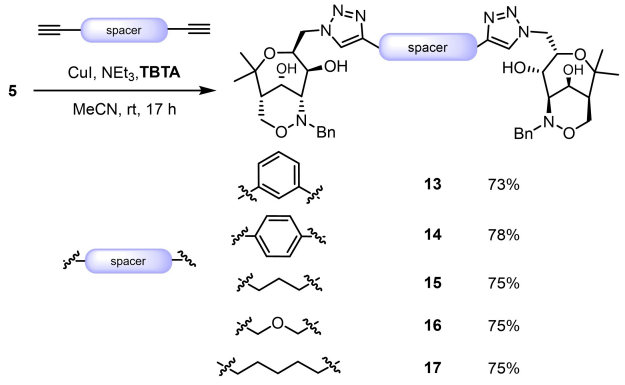


Scheme 4. CuAACs of protected azidomethyl-substituted compound **4** with dialkynes furnishing divalent systems **11** and **12** with rigid or flexible spacer units.

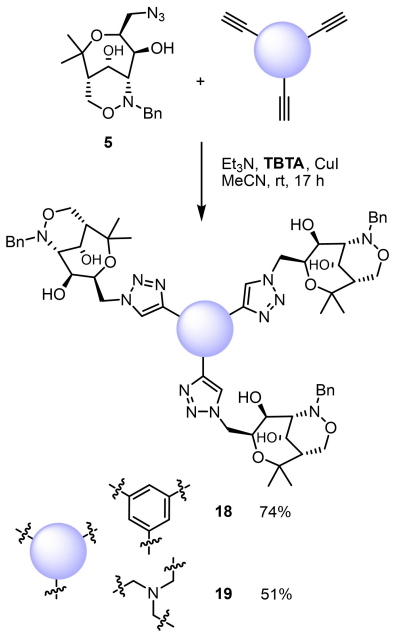
Research Article
doi.org/10.1002/ejoc.202301294

pound **5** proceed efficiently and, if the bulkiness of the protective group of **4** is returning to mind, the use of **5** may even have advantages. We therefore employed precursor **5** for the synthesis of a series of divalent and trivalent compounds. In Scheme 5 the CuAACs with five dialkynes are presented, demonstrating that the approved standard conditions provide the expected divalent systems in satisfying yields in the range of 75%. Again, rigid spacer elements (compounds **13** and **14**) as well as flexible units (compounds **15**–**17**) can be incorporated into the products.

Furthermore, compound **5** and two trialkynes furnished the expected trivalent systems **18** and **19** as illustrated in Scheme 6. The standard conditions worked reasonably well in the CuAAC of **5** with 1,3,5-triethynylbenzene whereas the reaction with tri(prop-2-ynyl)amine gave only a moderate yield of 51%. This observation was unexpected, since at first glance the flexible



Scheme 5. CuAACs of unprotected azidomethyl-substituted compound **5** with dialkynes giving divalent systems **13**–**17** containing rigid or flexible spacer units.



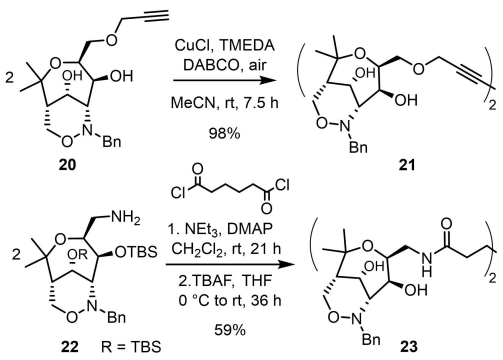
Scheme 6. CuAACs of unprotected azidomethyl-substituted compound **5** with trialkynes giving trivalent systems **18** and **19** with rigid or flexible spacer units.

trialkyne should be a better cycloaddition partner than the rigid compound (electronic effects being neglected). It was also observed that tri(prop-2-ynyl)amine and the protected precursor **4** reacted quite sluggishly and needed higher amounts of catalyst and longer reaction times for full consumption of the starting material.[16] In cases where we could compare the CuAACs with unprotected azidomethyl-substituted precursor **4** with those of its *tert*-butyl(dimethyl)siloxy-protected counterpart **5** we generally observed higher reactivity (shorter reaction times, higher yields) employing the unprotected compound.[16] It should be noted that the protected divalent compounds **11** and **12** can easily be converted into the unprotected compounds **14** or **15** by standard application of tetra-*n*-butylammonium fluoride in tetrahydrofuran, however, this "detour" did not have any advantage in comparison to the direct route.

During the preparation of compounds **3**–**6** (Scheme 2) we also synthesized intermediates **20** and **22**.[20] Therefore, the potential of these compounds was briefly examined in order to prepare divalent septanose mimetics by alternative methods (Scheme 7). Progargylic ether **20** (the deprotected form of compound **6**) was oxidatively dimerized applying the method of Eglington et al.[23] by cuprous chloride, TMEDA (tetramethylethylenediamine) and DABCO (1,4-diazabicyclo[2.2.2]octane) in acetonitrile under air atmosphere at room temperature. The desired dialkyne **21** was isolated in almost quantitative yield. We also applied the method of Hay[24] employing copper(II) acetate as oxidation promotor, however, this alternative was less efficient.[16]

On the route to azide **5** we also prepared the primary amine **22** which was treated with adipoyl chloride by a Schotten-Baumann protocol to give the expected bisamide. This intermediate was deprotected with tetra-*n*-butylammonium fluoride in tetrahydrofuran to furnish the final product **23** of the two-step sequence in 59% overall yield.

In earlier studies we had already recognized difficulties during the hydrogenolysis of bicyclic 1,2-oxazine derivatives which are connected with 1,2,3-triazole moieties.[14,15,25] The intended reductive removal of the N-benzyl group as a first step[26] followed by the cleavage of the N–O bonds is apparently complicated or even retarded by the presence of the triazolyl unit. Probably, partial cleavage of the benzyl type bond



Scheme 7. Syntheses of dialkyne **21** by oxidative dimerization of propargylic ether **20** and of bisamide **23** by coupling of amine **22** with adipoyl chloride and subsequent desilylation.

Research Article
doi.org/10.1002/ejoc.202301294

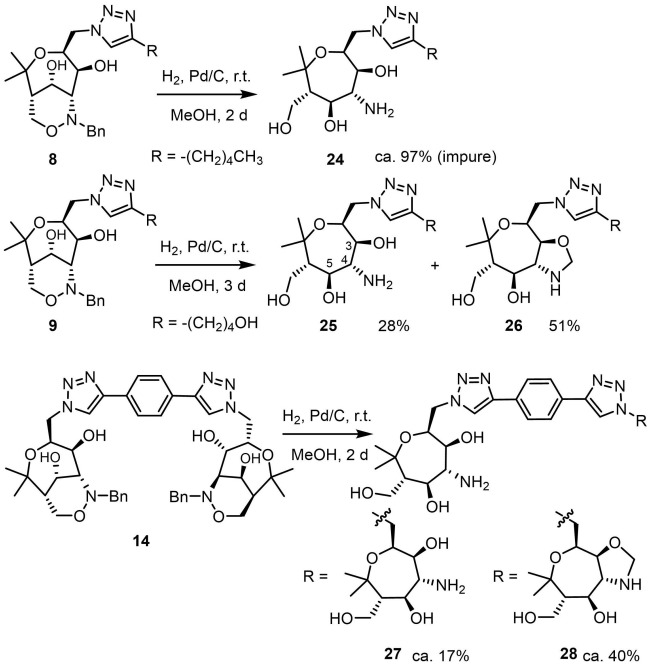
connecting the triazolyl group with the bicyclic 1,2-oxazine moiety can occur under the applied hydrogenolysis conditions. As an alternative approach for the construction of multivalent systems we changed the sequence and thus performed first the hydrogenolysis and only subsequently introduced the azido group and performed the (3 + 2) cycloadditions.[6,7,13]

The difficulties to obtain clean products with compounds containing 1,2,3-triazole moieties were confirmed when model compounds **8** and **9** were subjected to hydrogenolysis reactions and treated with hydrogen at atmospheric pressure in the presence of palladium on charcoal in methanol as solvent (Scheme 8). Relatively high amounts of the catalyst (ca. 0.4 equivalents) were required to achieve reasonable conversion of the precursor compounds. The bicyclic 1,2-oxazine **8** was consumed after two days at room temperature and converted into the expected oxepine derivative **24** in high yield, however, the obtained sample contained considerable amounts of unknown impurities.

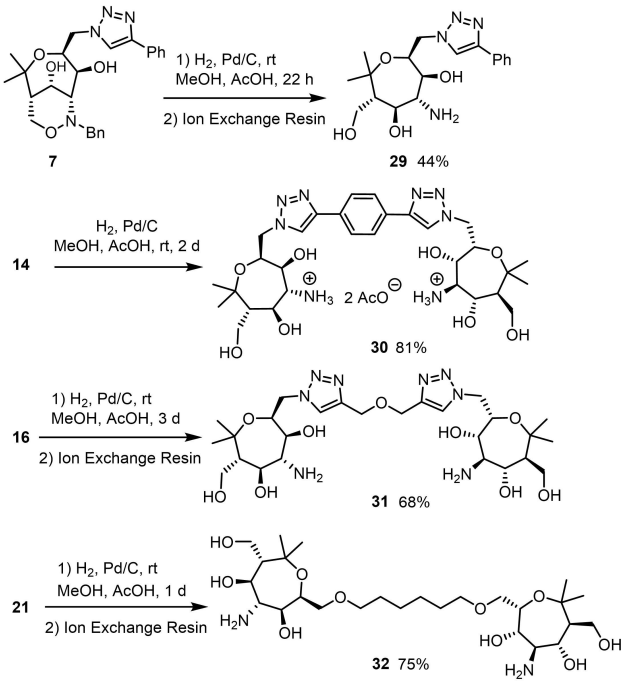
The second model compound **9** was similarly transferred into the expected product **25**, but in this case, the bicyclic oxazolidine derivative **26** was isolated and identified as major component (Scheme 8). This compound was obviously formed by the reaction of a hydroxyl group and the amino group of compound **25** with in situ generated formaldehyde. For compound **26** we propose involvement of the 3-OH group, however, reaction of the 5-OH group providing a constitutional isomer of the drawn product cannot be excluded. The generation of formaldehyde from methanol in the presence of palladium catalysts is a process well known in the literature[27] and has also been observed in earlier studies of our group.[20,27d] A similar result was obtained with the divalent compound **14** which provided **27** and **28** as products (ratio ca. 30:70). Again, the compound **28** with the proposed oxazolidine structure is the major component.

Gratifyingly, we found that the reaction leading to oxazolidines can be largely suppressed if the hydrogenolysis was performed in the presence of acetic acid as co-solvent (ca. 30 vol-%).[20] The protonation of the amino group[28] apparently prevents the subsequent condensation reaction with formaldehyde. The hydrogenolysis of phenyl-substituted model compound **7** hence furnished the anticipated oxepane derivative with an ammonium group, which was subsequently converted into the free amine by neutralization employing an ion exchange resin (Scheme 9). Thus, the simple amino-substituted oxepine derivative **29** was isolated in moderate yield over two steps. The related divalent precursor compound **14** was converted under similar conditions into the bisammonium salt **30** in 81% yield, but in this case the neutralization employing the ion exchange method failed for unknown reason. It should be noted that the resulting amino polyols are generally quite sensitive compounds showing considerably tendency to decompose. On the other hand, the divalent compound **16** with a flexible spacer moiety could be converted into the expected bisammonium salt and subsequently into the deprotonated product **31** with reasonable efficacy (68% overall yield).[29] The divalent compound **21** without triazole moiety could smoothly be transferred into the expected divalent products **32**. In this example, the required reduction of the two central triple bonds of precursor **21** proceeded very well together with the N-debenzylation and the N–O bond cleavage as probable final step.[30]

The examples collected in Schemes 8 and 9 revealed that hydrogenolysis reactions of the studied bicyclic 1,2-oxazine



Scheme 8. Palladium-catalyzed hydrogenolyses reactions of compounds **8**, **9**, and **14** leading to amino-substituted oxepane derivatives **24**–**28**.



Scheme 9. Hydrogenolyses reactions in the presence of acetic acid as co-solvent transferring compound **7** and divalent precursor compounds **14**, **16**, and **21** into compounds **29**–**32**.

derivatives and the purification of the resulting products is challenging. In several cases, the expected mono- and divalent aminooxepane derivatives were obtained in reasonable purity, but there is certainly room for further optimization and generalization. However, we discontinued the efforts to improve the hydrogenolysis reactions at this point since none of the obtained mono- or divalent aminooxepane derivatives could be satisfactorily sulfated employing the standard methods. Neither the SO_3-pyridine complex[31] nor the SO_3-DMF complex[32] generated clean samples of fully sulfated aminooxepane derivatives and all attempts to purify the obtained mixtures failed completely due to the extreme polarity of the samples. It was found only later that very careful NMR control of the sulfation process employing the SO_3-DMF complex in DMF-d_7 as solvent and a subsequent dialysis afforded reasonably pure samples in several cases,[4–7,27d] although even this method was not generally successful. As a consequence of this failure other divalent or trivalent aminooxepane precursors were not studied in hydrogenolysis reactions. Furthermore, the intended biological evaluation of the compounds had to be discarded.

Conclusions

The copper-catalyzed (3 + 2) cycloadditions of enantiopure azidomethyl-substituted 1,2-oxazine derivatives **4** and **5** with a series of alkynes, dialkynes and trialkynes proceeded smoothly with copper iodide as catalyst in the presence of triethylamine and **TBTA** as ligand. The expected simple 1,2,3-triazole derivatives **7**–**9**, the divalent systems **10**–**17** and the trivalent compounds **18** and **19** were isolated in good to excellent yields. These examples prove again the practicality of the azide-alkyne cycloaddition[33] as prime example of the click approach[34] to higher order structures and multivalent systems.

The products obtained during this study can be regarded as protected precursors of aminoseptanose mimetics. However, the essential reductive transformation of the bicyclic 1,2-oxazine moieties into aminooxepanes units turned out to be quite capricious, which is probably caused by the presence of the 1,2,3-triazole moieties. Although satisfying conditions were found for a few examples, the applied hydrogenolysis method is apparently not general. An alternative method to connect two bicyclic 1,2-oxazine moieties was established by the efficient oxidative dimerization of propargyl ether **20** which resulted in diyne **21**. This compound lacks the 1,2,3-triazole unit and it was cleanly reduced to give the divalent aminooxepane derivative **32**. This alternative approach to (multivalent) aminoseptanose mimetics employing bicyclic 1,2-oxazine derivatives as crucial building block certainly deserves further exploration.[35]

Experimental Section

For general information, all experimental and analytical details see Supporting Information.

General procedure 1 (GP1), copper-catalyzed (3 + 2)-cycloaddition in the presence of TBTA as ligand

The corresponding bicyclic azide (1.00–3.05 equiv), the mono-, di-, or trialkyne (1.00 equiv.), triethylamine, **TBTA** and CuI (each 0.22 equiv. with respect to azide) were dissolved in acetonitrile (ca. 35 mL/mmol with respect to azide). The slightly yellow reaction mixture was stirred at room temperature for the time indicate in the individual experiments. For removal of the copper catalyst, the work up was carried either by method A or method B.

Method A: An aqueous ammonia solution was added and the mixture was stirred until the color of the reaction mixture turned to green or blue. After stirring for 0.5 to 2 h, dichloromethane or ethyl acetate was added and the aqueous phase was three times extracted with the corresponding solvent. The collected organic phases were dried (Na_2SO_4) filtrated through a pad of cotton and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by chromatography.

Method B: A solution of dichloromethane/7 N ammonia in methanol (30 : 1) was added and the mixture was stirred until the color of the reaction mixture turned to green or blue. After 0.5 to 2 h, the mixture was filtrated through a short silica gel column (elution with dichloromethane/7 N ammonia in methanol, 10 : 1). The filtrate was concentrated in vacuo and the resulting crude product was then purified by column chromatography (silica gel) and if required subsequently by HPLC (reversed phase, Gemini-NX-column, methanol/aqueous ammonia 85 : 15).

(1*S*,4*S*,5*S*,6*R*,10*S*)-7-Benzyl-2,2-dimethyl-4-[(4'-phenyl-1*H*-1',2',3'-triazol-1'-yl)methyl]-3,8-dioxa-7-azabicyclo[4.3.1]decan-5,10-diol (7)

Following **GP1**, phenylacetylene (35 mg, 0.34 mmol), azide **5** (80 mg, 0.23 mmol), NEt_3 (7.3 mg, 0.072 mmol), **TBTA** (51 mg, 0.095 mmol), and CuI (18 mg, 0.095 mmol) were stirred in acetonitrile (8 mL) for 1.5 h. During work-up, the copper catalyst was removed using method A (extraction with dichloromethane). The obtained crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3 : 1 to 1 : 1) furnishing triazole **7** (103 mg, 99 %) as a colorless solid.

Melting range: 196–200 °C; $[\alpha]^{22}_D = +17.8$ ($c = 0.35$, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): $\delta = 0.73$, 1.45 (2 s, 3 H each, Me), 2.09 (m_c, 1 H, 1-H), 3.47 (m_c, 1 H, 6-H), 3.69, 3.81 (AB part of ABX system, $J_{AB} = 12.5$ Hz, $J_{AX} = 2.5$ Hz, 1 H each, 9-H), 3.86, 4.11 (2 d, $J = 14.2$ Hz, 1 H each, NCH_2), 4.30 (s_b, 2 H, OH), 4.43 (m_c, 1 H, 5-H), 4.53 (m_c, 1 H, 10-H), 4.63, 4.70, 4.79 (ABX system, $J_{AB} = 13.8$ Hz, $J_{AX} = 9.8$ Hz, $J_{BX} = 3.9$ Hz, 1 H each, 4-CH_2, 4-H), 7.26, 7.32, 7.37 (3 m_c, 1 H, 4 H, 1 H, Ph), 7.46 (t, $J = 7.7$ Hz, 2 H, Ph), 7.84* (d, $J = 7.7$ Hz, 2 H, Ph), 7.85* (s, 1 H, Tr#) ppm; * overlapping signals, # Tr = triazole; ^{13}C NMR (175 MHz, $CDCl_3$): $\delta = 23.4$, 34.2 (2 q, Me), 47.1 (d, C-1), 52.7 (t, 4-CH_2), 58.4 (t, NCH_2), 65.3 (d, C-6), 69.0 (t, C-9), 69.6 (d, C-5), 73.7 (d, C-10), 74.4 (d, C-4), 78.4 (s, C-2), 122.0 (d, Tr#), 125.8, 127.4, 128.2, 128.3, 128.5, 129.0, 130.6, 137.4 (6 d, 2 s, Ph), 147.2 (s, Tr) ppm; # Tr = triazole; IR (ATR): $\nu = 3045$ (O–H), 3140–3025 (=C–H), 2995–2865 (C–H), 1730–1545, 1495 (C=C, N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{30}N_4NaO_4$: 473.2159; found: 473.2180.

Divalent compound 13

Following **GP1**, 1,3-diethynylbenzene (17.7 mg, 0.140 mmol), azide **5** (100 mg, 0.29 mmol), NEt_3 (6.2 mg, 0.062 mmol), **TBTA** (33 mg, 0.062 mmol), and CuI (12 mg, 0.062 mmol) were stirred in acetonitrile (10 mL) for 17 h. During work-up, the copper catalyst was removed using method A (extraction with ethyl acetate). The

obtained crude product was semi-purified by column chromatography (silica gel, dichloromethane/methanol, 50:1) furnishing triazole **13** (92 mg) as yellow solid. This sample was further purified by HPLC (reversed phase, Gemini-NX-column, methanol/aqueous ammonia, 85:15) providing 84 mg (73%) of **13** as a slightly yellow solid.

Melting range: 158–162 °C; $[\alpha]^{22}_D = +43.3$ ($c = 0.57$, MeOH); ^{1}H NMR (700 MHz, $CDCl_3$): $\delta = 0.73$, 1.40 (2 s, 6 H each, Me), 2.09 (m_c, 2 H, 1-H), 3.50 (m_c, 2 H, 6-H), 3.68 (m_c, 2 H, 9-H), 3.79 (B part of ABX system, $J_{AB} = 12.5$ Hz, 2 H, 9-H), 3.86, 4.09 (2 d, $J = 14.3$ Hz, 2 H each, NCH_2), 4.41 (m_c, 2 H, OH), 4.45 (m_c, 2 H, 5-H), 4.54 (m_c, 2 H, 10-H), 4.65, 4.72, 4.81 (ABX system, $J_{AB} = 13.4$ Hz, $J_{AX} = 9.8$ Hz, $J_{BX} = 3.6$ Hz, 2 H each, 4-CH_2, 4-H), 7.22–7.24, 7.28–7.32 (2 m, 2 H, 8 H, Ph), 7.52 (t, $J = 7.7$ Hz, 1 H, Ar), 7.83 (dd, $J = 7.7$, 0.4 Hz, 2 H, Ar), 8.02 (s, 2 H, Tr), 8.36 (s, 1 H, Ar) ppm; two OH signals could not be detected; ^{13}C NMR (175 MHz, $CDCl_3$): $\delta = 23.4$, 34.3 (2 q, Me), 47.0 (d, C-1), 52.8 (t, 4-CH_2), 58.5 (t, NCH_2), 65.4 (d, C-6), 69.1 (t, C-9), 69.5 (d, C-5), 73.7 (d, C-10), 74.4 (d, C-4), 78.5 (s, C-2), 122.5 (d, Tr), 122.9, 125.5 (2 d, Ar), 127.4, 128.2, 128.5 (3 d, Ph), 129.8, 131.3 (d, s, Ar), 137.5 (s, Ph), 146.8 (s, Tr) ppm; IR (ATR): $\nu = 3350$ (O–H), 3140–3030 (=C–H), 2975–2860 (C–H), 1620–1455 (C=C, N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{44}H_{55}N_8O_8$: 823.4137; found: 823.4143; $C_{44}H_{54}N_8O_8$ (823.0): calcd C 64.22, H 6.61, N 13.62; found: C 64.19, H 6.66, N 13.66.

Divalent compound 16

Following **GP1**, 3-(prop-2-yn-1yl-oxy)prop-1-yne (20 mg, 0.21 mmol), azide **5** (150 mg, 0.431 mmol), NEt_3 (9.2 mg, 0.092 mmol), **TBTA** (49 mg, 0.092 mmol), and CuI (17.6 mg, 0.092 mmol) were stirred in acetonitrile (15 mL) for 17 h. During work-up, the copper catalyst was removed using method B. The obtained crude product was semi-purified by column chromatography (silica gel, dichloromethane/ammonia in methanol, 30:1 to 10:1) furnishing triazole **16** (147 mg) as colorless solid. This sample was further purified by HPLC providing 124 mg (75%) of **16** as colorless solid.

M. p. 128–130 °C; $[\alpha]^{22}_D = -11.9$ ($c = 0.63$, MeOH); ^{1}H NMR (700 MHz, $CDCl_3/CD_3OD = 2:1$): $\delta = 0.65$, 1.38 (2 s, 6 H each, Me), 2.02 (m_c, 2 H, 1-H), 3.36 (dd, $J = 4.9$, 2.8 Hz, 2 H, 6-H), 3.67, 3.79 (AB part of ABX system, $J_{AB} = 12.9$ Hz, $J_{AX} = 2.9$ Hz, 2 H each, 9-H), 3.84, 4.07 (2 d, $J = 14.1$ Hz, 2 H each, NCH_2), 4.28 (m_c, 2 H, 5-H), 4.44 (m_c, 2 H, 10-H), 4.53, 4.58 (AB part of ABX system, $J_{AB} = 13.8$ Hz, $J_{AX} = 9.7$ Hz, $J_{BX} = 3.6$ Hz, 2 H each, 4-CH_2), 4.67 (s, 4 H, OCH_2), 4.70 (dd, $J = 9.7$, 3.6 Hz, 2 H, 4-H), 7.21, 7.28, 7.30 (3 m_c, 2 H, 4 H, 4 H, Ph), 7.78 (s, 2 H, Tr) ppm; ^{13}C NMR (175 MHz, $CDCl_3/CD_3OD = 2:1$): $\delta = 23.5$, 34.2 (2 q, Me), 47.7 (d, C-1), 53.1 (t, 4-CH_2), 58.8 (t, NCH_2), 63.6 (t, OCH_2), 65.2 (d, C-6), 69.2 (t, C-9), 70.0 (d, C-5), 73.6 (d, C-10), 74.7 (d, C-4), 78.5 (s, C-2), 125.8 (d, Tr), 127.7, 128.6, 128.8, 137.9 (3 d, s, Ph), 144.4 (s, Tr) ppm; IR (ATR): $\nu = 3395$ (O–H), 3060–3025 (=C–H), 2970–2860 (C–H), 1740, 1630–1605, 1495–1455, 1375, 1350 (C=C, N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{54}N_8NaO_9$: 813.3906; found: 813.3930; $C_{40}H_{54}N_8O_9$ (790.9): C 60.74, H 6.88, N 14.17; found: C 60.22, H 6.87, N 14.09.

Trivalent compound 19

Following **GP1**, tri(prop-2-ynyl)amine (18.4 mg, 0.141 mmol), azide **5** (150 mg, 0.431 mmol), NEt_3 (9.3 mg, 0.093 mmol), **TBTA** (49 mg, 0.093 mmol), and CuI (18 mg, 0.093 mmol) were stirred in acetonitrile (10 mL) for 17 h. During work-up, the copper catalyst was removed using method B. The obtained crude product was semi-purified by column chromatography (silica gel, dichloromethane/ammonia in methanol, 20:1) furnishing triazole **19** (135 mg) as yellow solid. This sample was further purified by HPLC providing 84 mg (51%) of **19** as colorless solid.

M. p. 158–160 °C; $[\alpha]^{22}_D = +2.36$ ($c = 0.69$, MeOH); ^{1}H NMR (700 MHz, $CDCl_3/CD_3OD = 2:1$): $\delta = 0.44$, 1.14 (2 s, 9 H each, Me), 1.79 (m_c, 3 H, 1-H), 3.15 (m_c, 3 H, 6-H), 3.44 (AB part of ABX system, $J_{AB} = 12.8$ Hz, $J_{AX} = 2.7$ Hz, 3 H, 9-H), 3.52–3.58 (m, 9 H, CH_2, 9-H), 3.62, 3.85 (2 d, $J = 14.2$ Hz, 3 H each, NCH_2), 4.08 (m_c, 3 H, 5-H), 4.22–4.24 (m, 3 H, 10-H), 4.32–4.38 (m, 6 H, 4-CH_2), 4.51 (dd, $J = 9.3$, 4.0 Hz, 3 H, 4-H), 6.99–7.01, 7.05–7.09 (2 m, 3 H, 12 H, Ph), 7.68 (s, 3 H, Tr) ppm; ^{13}C NMR (175 MHz, $CDCl_3/CD_3OD = 2:1$): $\delta = 22.9$, 33.4 (2 q, Me), 46.8 (d, C-1), 47.1 (t, CH_2), 52.3 (t, 4-CH_2), 58.0 (t, NCH_2), 64.6 (d, C-6), 68.5 (t, C-9), 69.1 (d, C-5), 72.8 (d, C-10), 73.9 (d, C-4), 77.7 (s, C-2), 125.4 (d, Tr), 126.9, 127.8, 128.0, 137.1 (3 d, s, Ph), 143.2 (s, Tr) ppm; IR (ATR): $\nu = 3355$ (O–H), 3085–3025 (=C–H), 2975–2850 (C–H), 1495–1395 (C=C, N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{60}H_{82}N_{13}O_{12}$: 1176.6200; found: 1176.6240; $C_{60}H_{81}N_{13}O_{12}$ (1176.4): calcd C 61.26, H 6.94, N 15.48; found: C 61.26; H 6.98; N 15.42.

(1*S*,1'*S*,4*S*,4'*S*,5*S*,5'*S*,6*R*,6'*R*,10*S*,10'*S*)-4,4-{[Hexa-2,4-diyne-1,6-diylbis(oxy)]bis(methylene)}bis(7-benzyl-2,2-dimethyl-3,8-dioxa-7-azabicyclo[4.3.1]decane-5,10-diol) (21)

In a 10 mL flask (open to air), alkyne **20** (54 mg, 0.15 mmol) was dissolved in acetonitrile (0.8 mL) and 1,4-diazabicyclo[2.2.2]octane (17 mg, 0.15 mmol), tetramethylethylenediamine (30 mg, 0.26 mmol) and cuprous chloride (3 mg, 0.03 mmol) were added. The resulting green reaction mixture was stirred under air atmosphere for 3.5 h at room temperature. Since the conversion was not complete (TLC control) further CuCl (3 mg, 0.03 mmol) was added. After 4 h, dichloromethane/ammonia in methanol (10:1) was added dropwise until the solution became blue. The mixture was filtrated through a short column (silica gel, dichloromethane/ammonia in methanol, 10:1) and the solvents were removed in vacuo. Purification of the crude product by column chromatography (silica gel, hexanes/ethyl acetate, 2:1 to 1:2) furnished 53 mg (98%) of **21** a colorless solid.

M. p. 67–70 °C; $[\alpha]^{22}_D = -26.6$ ($c = 0.14$, MeOH); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.30$, 1.47 (2 s, 6 H each, Me), 2.10 (dd, $J = 5.5$, 1.9 Hz, 2 H, 1-H), 3.33 (dd, $J = 5.0$, 2.5 Hz, 2 H, 6-H), 3.55, 3.70 (AB part of ABX system, $J_{AB} = 9.7$ Hz, $J_{AX} = 6.7$ Hz, $J_{BX} = 6.6$ Hz, 2 H each, 4-CH_2), 3.72, 3.93 (ABX system, $J_{AB} = 12.8$ Hz, $J_{AX} = 3.1$ Hz, 2 H each, 9-H), 3.88, 4.09 (AB system, $J_{AB} = 14.1$ Hz, 2 H each, NCH_2), 4.28, 4.32 (AB system, $J_{AB} = 17.0$ Hz, 2 H each, CH_2), 4.36 (d, $J = 2.5$ Hz, 2 H, 5-H), 4.44 (t, $J \approx 5.5$ Hz, 2 H, 10-H), 4.56 (t, $J \approx 6.7$ Hz, 2 H, 4-H), 7.22, 7.29, 7.35 (3 m_c, 2 H, 4 H, 4 H, Ph) ppm; ^{13}C NMR (125 MHz, CD_3OD): $\delta = 24.7$, 34.6 (2 q, Me), 48.7 (d, C-1), 59.4 (t, NCH_2), 59.9 (t, O-CH_2), 65.9 (d, C-6), 69.9 (d, C-5), 70.0 (t, C-9), 71.0 (s, C-2), 71.8 (t, 4-CH_2), 74.4 (d, C-4), 74.8 (d, C-10), 76.9, 79.0 (2 s, C≡C), 128.1, 129.2, 129.5, 139.2 (3 d, s, Ph) ppm; IR (ATR): $\nu = 3405$ (O–H), 3085–3000 (=C–H), 2975–2860 (C–H), 1640–1605, 1490–1450 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{52}N_2NaO_{10}$: 743.3509; found: 743.3506.

(2*S*,3*S*,4*R*,5*S*,6*S*)-4-Amino-2-{[4'-(4''-hydroxybutyl)-1*H*-1',2',3'-triazol-1'-yl]methyl}-6-(hydroxymethyl)-7,7-dimethyloxepan-3,5-diol (25) and (2*S*,2a*S*,5a*S*,6*S*,7*S*)-2-{[4'-(4''-Hydroxybutyl)-1*H*-1',2',3'-triazol-1'-yl]methyl}-7-(hydroxymethyl)-8,8-dimethyloctahydrooxepino[4,5-*d*]oxazol-6-ol (26)

In a two-neck flask, palladium (10%) on charcoal (100 mg, 0.094 mmol Pd) was suspended in dry methanol (34 mL) and the mixture was saturated with hydrogen at room temperature for 30 min. Then, compound **9** (99 mg, 0.22 mmol, dissolved in 9 mL of ethyl acetate) was added and the mixture was stirred under

hydrogen pressure (balloon) at room temperature for three days. The mixture was filtered through Celite, washed with ethanol and the solvents were removed in vacuo. The resulting mixture was separated by column chromatography (silica gel, dichloromethane to dichloromethane/ammonia in methanol, 10:1) providing starting material **9** (24 mg, 24%), product **25** (17 mg) and side-product **26** (32 mg) as colorless oils. Calculated yields with respect to consumed starting material: **25** (28%), **26** (51%).

Data of compound **25**: $[\alpha]^{22}_{D} = +1.3$ ($c = 0.32$, MeOH); ^{1}H NMR (700 MHz, CD_3OD): $\delta = 0.46$, 1.20 (2 s, 3 H each, Me), 1.56–1.61, 1.70–1.75 (2 m, 2 H each, CH_2), 1.80 (ddd, $J = 10.2$, 7.0, 3.4 Hz, 1 H, 6-H), 2.73 (m_c, 2 H, CH_2), 3.29 (t, $J \approx 8.3$ Hz, 1 H, 4-H), 3.58 (m_c, 3 H, CH_2, 6-CH_2), 3.65 (m_c, 1 H, 6-CH_2), 3.92 (dd, $J = 8.3$, 3.6 Hz, 1 H, 3-H), 3.95 (t, $J \approx 9.8$ Hz, 1 H, 5-H), 4.12 (m_c, 1 H, 2-H), 4.38, 4.54 (AB part of ABX system, $J_{AB} = 14.2$ Hz, $J_{AX} = 9.8$ Hz, $J_{BX} = 2.6$ Hz, 1 H each, 2-CH_2), 7.76 (s, 1 H, Tr) ppm; ^{13}C NMR (175 MHz, CD_3OD): $\delta = 20.1$ (q, Me), 26.0, 27.1 (2 t, CH_2), 31.2 (q, Me), 33.0 (t, CH_2), 52.8 (t, 2-CH_2), 59.7 (d, C-6), 62.5 (t, CH_2), 63.3 (d, C-4), 63.4 (t, 6-CH_2), 68.1 (d, C-5), 72.7 (d, C-3), 73.0 (d, C-2), 77.8 (s, C-7), 125.1, 148.8 (d, s, Tr) ppm; IR (ATR): $\nu = 3260$ (O–H, N–H), 2980–2915 (C–H), 1600 (C=C), 1360 (N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{16}H_{31}N_4O_5$ 359.2289; found: 359.2295.

Data of compound **26**: $[\alpha]^{22}_{D} = -6.7$ ($c = 0.15$, MeOH); ^{1}H NMR (700 MHz, CD_3OD): $\delta = 0.45$, 1.21 (2 s, 3 H each, Me), 1.59, 1.73 (2 m_c, 2 H each, CH_2), 1.78 (dt, $J \approx 10.6$, 5.1 Hz, 1 H, 7-H), 2.73 (m_c, 2 H, CH_2), 3.13 (dd, $J = 8.8$, 8.0 Hz, 1 H, 5a-H), 3.50 (dd, $J = 11.6$, 5.3 Hz, 1 H, 7-CH_2), 3.55 (dd, $J = 10.6$, 9.2 Hz, 1 H, 6-H), 3.58 (m_c, 2 H, CH_2), 3.67 (dd, $J = 11.6$, 5.5 Hz, 1 H, 7-CH_2), 3.83 (dd, $J = 7.7$, 3.8 Hz, 1 H, 2a-H), 4.06 (m_c, 1 H, 2-H), 4.38, 4.51* (AB part of ABX system, $J_{AB} = 14.3$ Hz, $J_{AX} = 9.7$ Hz, $J_{BX} = 2.8$ Hz,, 1 H each, 2-CH_2), 4.44 (d, $J = 5.8$ Hz, 1 H, 4-H), 4.52* (d, $J = 5.8$ Hz, 1 H, 4-H), 7.72 (s, 1 H, 5′-H) ppm; * overlapping signals; ^{13}C NMR (175 MHz, CD_3OD): $\delta = 19.8$ (q, Me), 26.0, 27.1 (2 t, CH_2), 31.5 (q, Me), 33.0 (t, CH_2), 53.1 (t, 2-CH_2), 57.8 (d, C-7), 62.5 (t, CH_2), 63.2 (t, 7-CH_2), 71.2 (d, C-5a), 73.6 (d, C-2a), 75.0 (d, C-2), 77.7 (s, C-8), 78.9 (d, C-6), 81.8 (t, C-4), 125.1, 148.6 (d, s, Tr) ppm; IR (ATR): $\nu = 3290$ (O–H, N–H), 3145 (=C–H), 2970–2865 (C–H), 1570, 1550, 1460, 1380 (C=C, N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{31}N_4O_5$: 371.2289; found: 371.2296; *m/z* $[M+Na]^+$ calcd for $C_{17}H_{30}N_4NaO_5$: 393.2108; found: 393.2120.

General procedure 2 (GP2), hydrogenolysis in the presence of palladium on charcoal in methanol/acetic acid

In a two-neck flask, palladium (10%) on charcoal was suspended in dry methanol and acetic acid and the mixture was saturated with hydrogen at room temperature for 30 min. After addition of the corresponding substrate, the mixture was saturated with hydrogen for another 30 min and then stirred under hydrogen pressure (balloon). After reaction completion (see time indicated in the individual experiments), the mixture was filtered through Celite, washed with ethanol and the solvents were removed in vacuo.

In selected experiments, the isolated ammonium salt was dissolved in water and filtered through a Dowex® column (H_2O) which was washed with water until the complete acid was removed (pH control). The column was subsequently washed with aqueous ammonia solution (2 to 5%) to furnish the free amine.

(2*S*,3*S*,4*R*,5*S*,6*S*)-3,5-Dihydroxy-6-(hydroxymethyl)-7,7-dimethyl-2-[(4'-phenyl-1*H*-1',2',3'-triazol-1'-yl)methyl]oxepan-4-aminium acetate

Following **GP2**, compound **7** (91 mg, 0.20 mmol) was stirred with Pd/C (95 mg, 0.09 mmol Pd), methanol (9.1 mL) and acetic acid (3.7 mL). After 22 h stirring and filtration through Celite the expected ammonium salt (≈91 mg) was isolated as a colorless solid which was only analyzed by ^{1}H NMR spectroscopy and HRMS.

^{1}H NMR (700 MHz, CD_3OD): $\delta = 0.48$, 1.21 (2 s, 3 H each, Me), 1.82 (m_c, 1 H, 6-H), 1.96 (s, 3 H, OAc), 3.31 (m_c, 1 H, 4-H), 3.55–3.63 (m, 2 H, 6-CH_2), 3.93–3.97 (m, 2 H, 3-H, 5-H), 4.18 (d, $J \approx 9.2$ Hz, 1 H, 2-H), 4.48 (dd, $J = 14.2$, 9.7 Hz, 1 H, 2-CH_2), 4.63 (dd, $J = 14.2$, 2.0 Hz, 1 H, 2-CH_2), 7.35, 7.44, 7.82 (3 m_c, 1 H, 2 H, 2 H, Ph), 8.31 (s, 1 H, Tr) ppm; HRMS (ESI-TOF): *m/z* $[M-AcO]^+$ calcd for $C_{18}H_{28}N_4O_4$: 363.2027; found: 363.2021.

(2*S*,3*S*,4*R*,5*S*,6*S*)-4-Amino-6-(hydroxymethyl)-7,7-dimethyl-2-[(4'-phenyl-1*H*-1',2',3'-triazol-1'-yl)methyl]oxepane-3,5-diol (29)

The ammonium salt (91 mg) was filtered through a Dowex® column following **GP2** to afford the desired amine **29** (32 mg, 44%) as colorless solid.

M. p. 173–175 °C; $[\alpha]^{24}_{D} = +51.3$ ($c = 0.32$, H_2O); ^{1}H NMR (700 MHz, CD_3OD): $\delta = 0.46$, 1.21 (2 s, 3 H each, Me), 1.78 (dt, $J \approx 10.0$, 5.5 Hz, 1 H, 6-H), 3.40 (dd, $J = 9.1$, 7.6 Hz, 1 H, 4-H), 3.45 (dd, $J = 11.5$, 4.8 Hz, 1 H, 6-CH_2), 3.63 (dd, $J = 11.5$, 6.0 Hz, 1 H, 6-CH_2), 3.75 (t, $J \approx 10.0$ Hz, 1 H, 5-H), 3.89 (dd, $J = 7.4$, 3.6 Hz, 1 H, 3-H), 4.11 (dt, $J = 9.6$, 3.6 Hz, 1 H, 2-H), 4.47 (dd, $J = 14.2$, 9.6 Hz, 1 H, 2-CH_2), 4.59 (dd, $J = 14.2$, 2.9 Hz, 1 H, 2-CH_2), 7.35, 7.44, 7.82 (3 m_c, 1 H, 2 H, 2 H, Ph), 8.30 (s, 1 H, Tr) ppm; ^{13}C NMR (175 MHz, CD_3OD): $\delta = 19.7$, 31.4 (2 q, Me), 53.3 (t, 2-CH_2), 59.3 (d, C-6), 63.6 (t, 6-CH_2), 70.9 (d, C-4), 73.8 (d, C-3), 75.0 (d, C-2), 78.8, 79.0 (d, s, C-5, C-7), 124.2 (d, Tr), 126.6, 129.4, 130.0, 131.7 (3 d, s, Ph), 148.4 (s, Tr) ppm; IR (ATR): $\nu = 3350$ (O–H, N–H), 2985–2845 (C–H), 1595, 1440–1325 (C=C, N=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{28}N_4O_4$: 363.2027; found: 363.2051.

(2*S*,2'*S*,3*S*,3'*S*,4*R*,4'*R*,5*S*,5'*S*,6*S*,6'*S*)-2,2′-{[(Oxybis(methylene))-bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis[4-amino-6-(hydroxymethyl)-7,7-dimethyloxepane-3,5-diol] (31)

Following **GP2**, divalent compound **16** (38 mg, 0.048 mmol) was stirred with Pd/C (90 mg, 0.085 mmol Pd), in methanol (6 mL) and acetic acid (7 mL). After three days, the mixture was filtrated through Celite to provide the expected divalent bisammonium salt (≈35 mg, 99%) as a yellow solid.

M. p. 102–105 °C; $[\alpha]^{24}_{D} = +156.9$ ($c = 0.55$, MeOH); ^{1}H NMR (700 MHz, D_2O): $\delta = 0.36$, 1.20 (2 s, 6 H each, Me), 1.90 (m_c, 2 H, 6-H), 2.03 (s, 6 H, OAc), 3.42 (t, $J \approx 8.7$ Hz, 2 H, 4-H), 3.61 (m_c, 2 H, 6-CH_2), 4.02 (t, $J \approx 9.9$ Hz, 2 H, 5-H), 4.11 (m_c, 2 H, 3-H), 4.18 (d, $J \approx 9.4$ Hz, 2 H, 2-H), 4.49 (dd, $J = 14.1$, 9.4 Hz, 2 H, 2-CH_2), 4.64 (d, $J \approx 14.1$ Hz, 2 H, 2-CH_2), 4.75 (s, 4 H, OCH_2), 8.08 (s, 2 H, Tr) ppm; ^{13}C NMR (175 MHz, D_2O): $\delta = 18.7$ (q, Me), 21.8 (q, OAc), 29.7 (q, Me), 51.5 (t, 2-CH_2), 58.2 (d, C-6), 61.4 (t, 6-CH_2), 61.7 (d, C-4), 62.2 (t, OCH_2), 65.8 (d, C-5), 71.0 (d, C-3), 71.5 (d, C-2), 77.4 (s, C-7), 126.6, 143.6 (d, s, Tr), 178.9 (C=O) ppm; HRMS (ESI-TOF): *m/z* $[(M-2(AcOH)+Na]^+$ calcd for $C_{26}H_{46}N_8NaO_9$: 637.3280; found: 637.3318.

The bisammonium salt (35 mg) was filtered through a Dowex® column according to **GP2** to afford diamine **31** (20 mg, 68% for two steps) as a yellow solid.

M. p. 130–133 °C; $[\alpha]^{24}_{D} = -3.4$ ($c = 0.2$, MeOH); ^{1}H NMR (700 MHz, CD_3OD): $\delta = 0.43$, 1.19 (2 s, 6 H each, Me), 1.76 (m_c, 2 H, 6-H), 3.38 (t, $J \approx 8.3$ Hz, 2 H, 4-H), 3.45 (dd, $J = 11.5$, 4.8 Hz, 2 H, 6-CH_2), 3.63 (dd, $J = 11.5$, 5.9 Hz, 2 H, 6-CH_2), 3.74 (t, $J \approx 9.8$ Hz, 2 H, 5-H), 3.86 (dd, $J =$ 7.3, 3.5 Hz, 2 H, 3-H), 4.07 (m_c, 2 H, 2-H), 4.42 (dd, $J = 14.2$, 9.7 Hz, 2 H, 2-CH_2), 4.55 (dd, $J = 14.2$, 2.5 Hz, 2 H, 2-CH_2), 4.66 (s, 4 H, OCH_2), 7.95 (s, 2 H, Tr) ppm; ^{13}C NMR (175 MHz, CD_3OD): $\delta = 19.8$, 31.4 (2 q, Me), 53.2 (t, 2-CH_2), 59.3 (d, C-6), 63.5 (t, 6-CH_2), 64.0 (t, OCH_2), 70.8 (d, C-4), 73.8 (d, C-3), 74.9 (d, C-2), 78.8, 78.9 (d, s, C-5, C-1), 127.1, 145.3 (d, s, Tr) ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{26}H_{47}N_8O_9$: 615.3461; found: 615.3557.

(2*S*,2'*S*,3*S*,3'*S*,4*R*,4'*R*,5*S*,5'*S*,6*S*,6'*S*)-2,2'-((Hexane-1,6-diylbis(oxy))bis(methylene))bis(4-amino-6-(hydroxymethyl)-7,7-dimethyloxepane-3,5-diol) (32)

Following **GP2**, divalent compound **21** (42 mg, 0.058 mmol) was stirred with Pd/C (89 mg, 0.084 mmol Pd), in methanol (5.1 mL) and acetic acid (3.4 mL). After 24 h the mixture was filtrated through Celite to provide the expected bisammonium salt. Filtration through a Dowex column furnished 24 mg (75%) of diamine **32** as yellow solid.

M. p. 82–85 °C; $[\alpha]^{22}_{D} = +45.2$ ($c = 0.12$, MeOH); ^{1}H NMR (700 MHz, CD_3OD): $\delta = 1.19$, 1.32 (2 s, 6 H each, Me), 1.39, 1.56 (2 m_c, 4 H each, CH_2), 1.77 (m_c, 2 H, 6-H), 2.97 (m_c, 2 H, 4-H), 3.40, 3.52 (AB part of ABX system, $J_{AB} = 10.3$ Hz, $J_{AX} = 7.4$ Hz, $J_{BX} = 4.3$ Hz, 2 H each, 2-CH_2), 3.46 (m_c, 4 H, CH_2), 3.56 (m_c, 2 H, 3-H), 3.67 (m_c, 4 H, 6-CH_2), 3.77 (t, $J = 9.6$ Hz, 2 H, 5-H), 3.84 (m_c, 2 H, 2-H) ppm; ^{13}C NMR (175 MHz, CD_3OD): $\delta = 21.1$ (q, Me), 27.1, 30.8 (2 t, CH_2), 31.6 (q, Me), 60.1 (d, C-6), 64.0 (d, C-4), 64.1 (t, 6-CH_2), 70.6 (d, C-5), 72.2 (d, C-2), 72.4 (t, 2-CH_2), 72.5 (t, CH_2), 76.0 (d, C-3), 77.3 (s, C-7) ppm; IR (ATR): $\nu =$ 3355 (O–H, N–H), 2975–2865 (C–H) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$: $C_{26}H_{52}N_2NaO_{10}$: 575.3514; found: 575.3534.

Supporting Information

All experimental procedures, analytical details and copies of the NMR spectra are given in the Supporting information.

Acknowledgements

This work was supported by Bayer HealthCare and the Deutsche Forschungsgemeinschaft (SFB 765). Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: alkynes · azides · carbohydrate mimetics · click chemistry · reductions

[1] Selected reviews on carbohydrate mimetics: a) P. Sears, C.-H. Wong, *Angew. Chem. Int. Ed.* **1999**, *38*, 2300–2324; *Angew. Chem.* **1999**, *111*, 2446–2471; b) D. C. Koester, A. Holkenbrink, D. B. Werz, *Synthesis* **2010**, 3217–3242; c) F. Pfrengle, H.-U. Reissig, *Chem. Soc. Rev.* **2010**, *39*, 549–557; d) L. Bouché, H.-U. Reissig, *Pure Appl. Chem.* **2012**, *84*, 23–36; e) Y. Yang, B. Yu, *Chem. Rev.* **2017**, *117*, 12281–12356; f) D. Hazelard, P. Compain, *Org. Biomol. Chem.* **2017**, *15*, 3806–3827; g) S. Leusmann, P. Ménova, E. Shanin, A. Titz, C. Rademacher, *Chem. Soc. Rev.* **2023**, *52*, 3663–3740; h) P. Compain, *Synlett* **2023**, *34*, 1866–1892.
[2] Review on multivalent effects: C. Fasting, C. A. Schalley, M. Weber, O. Seitz, S. Hecht, B. Koksch, J. Dernedde, C. Graf, E.-W. Knapp, R. Haag, *Angew. Chem. Int. Ed.* **2012**, *51*, 10472–10498; *Angew. Chem.* **2012**, *124*, 10622–10650.
[3] a) J. Dernedde, S. Enders, H.-U. Reissig, M. Roskamp, S. Schlecht, S. Yekta, *Chem. Commun.* **2009**, 932–934; b) M. Roskamp, S. Enders, F. Pfrengle, S. Yekta, V. Dekaris, J. Dernedde, H.-U. Reissig, S. Schlecht, *Org. Biomol. Chem.* **2011**, *9*, 7448–7456.
[4] J. Salta, J. Dernedde, H.-U. Reissig, *Beilstein J. Org. Chem.* **2015**, *11*, 638–646.
[5] J. Salta, H.-U. Reissig, *Synthesis* **2015**, *47*, 1893–1898.
[6] J. Salta, H.-U. Reissig, *Eur. J. Org. Chem.* **2020**, 4361–4370.
[7] J. Salta, F. F. Arp, C. Kühne, H.-U. Reissig, *Eur. J. Org. Chem.* **2020**, 7333–7342.
[8] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.
[9] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711.
[10] Selected reviews: a) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015; b) D. S. Pederson, A. Abell, *Eur. J. Org. Chem.* **2011**, 2399–2411; c) K. Kacprzak, I. Skiera, M. Piasecka, Z. Paryzek, *Chem. Rev.* **2016**, *116*, 5689–5743; d) V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh, X. Chen, *Chem. Rev.* **2016**, *116*, 3086–3240; e) C. Silva Santos, R. J. de Oliveira, R. N. de Oliveira, J. C. R. Freitas, *Arkivoc* **2020**, *part I*, 219–271.
[11] K. Sakai, N. Hida, K. Kondo, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179–183.
[12] a) S. S. van Berkel, S. Brauch, L. Gabriel, M. Henze, S. Stark, D. Vasilev, L. A. Wessjohann, M. Abbas, B. Westermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 5343–5346; *Angew. Chem.* **2012**, *124*, 5437– 5441; b) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann, M. W. Paixao, *Chem. Commun.* **2015**, *51*, 10784–10796.
[13] L. Bouché, H.-U. Reissig, *Eur. J. Org. Chem.* **2014**, 3697–3703.
[14] P. Kóóš, H.-U. Reissig, *Synthesis* **2024**, *56*, in press; DOI: 10.1055/s-0043-1763619.
[15] As an alternative, we also prepared conformationally flexible divalent pyran derivates by double click reactions of in situ generated benzylic biazides with pyran derivatives bearing propargylic ethers moieties: F. Yu, H.-U. Reissig, *Beilstein J. Org. Chem.* **2023**, *19*, 1399–1407.
[16] L. Bouché, Dissertation, Freie Universität Berlin (Germany), **2013**.
[17] Reviews on septanose derivatives: a) Z. Pakulski, *Pol. J. Chem.* **1996**, *70*, 667–707; b) Z. Pakulski, *Pol. J. Chem.* **2006**, *80*, 1293–1326; c) J. Saha, M. W. Peczuh, *Adv. Carbohydr. Chem. Biochem.* **2011**, *66*, 121–186; d) R. Vannam, M. W. Peczuh, *Eur. J. Org. Chem.* **2016**, 1800–1812; e) N. Jayaraman, *Chem. Rec.* **2021**, *21*, 3049–3062; f) S. Manta, N. Kollatos, *Nucleosides Nucleotides Nucleic Acids* **2023**, *42*, 407–4025.
[18] Selected references: a) R. McEver, K. Moore, R. Cummings, *J. Biol. Chem.* **1995**, *270*, 11025–11028; b) E. E. Simanek, G. J. McGarvey, J. A. Jablonski, C.-H. Wong, *Chem. Rev.* **1998**, *98*, 833–862; c) V. Wittmann, in *Highlights in Bioorganic Chemistry: Methods and Applications* (Eds.: C. Schmuck, H. Wennemers); Wiley-VCH, Weinheim, **2004**, pp. 203–213; d) B. Ernst, J. L. Magnani, *Nat. Rev. Drug Discovery* **2009**, *8*, 661–677; e) B. A. H. Smith, C. R. Bertozzi, *Nat. Rev. Drug Discovery* **2021**, *20*, 217–243.
[19] C. M. Serhan, P. A. Ward, D. W. Gilroy, *Fundamentals of Inflammation*, Cambridge University Press, **2014**.
[20] L. Bouché, M. Kandziora, H.-U. Reissig, *Beilstein J. Org. Chem.* **2014**, *10*, 213–223.
[21] a) A. Al-Harrasi, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2005**, *44*, 6227–6231; *Angew. Chem.* **2005**, *117*, 6383–6387; b) F. Pfrengle, D. Lentz, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2009**, *48*, 3165–3169; *Angew. Chem.* **2009**, *121*, 3211–3215; c) A. Al-Harrasi, F. Pfrengle, V. Prisyazhnyuk, S. Yekta, P. Kóóš, H.-U. Reissig, *Chem. Eur. J.* **2009**, *15*, 11632–11641.

[22] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853–2855.
[23] G. Elington, A. R. Galbraith, *J. Chem. Soc.* **1959**, 889–896.
[24] A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320–3321.
[25] S. Yekta, F. Yu, P. Koóš, H.-U. Reissig, unpublished results; also see ref. 20.
[26] a) M. Helms, Dissertation, Freie Universität Berlin (Germany), **2005**; b) N. Moinizadeh, R. Klemme, M. Kansy, R. Zimmer, H.-U. Reissig, *Synthesis* **2013**, *45*, 2752–2762.
[27] a) G. V. Smith, F. Notheisz, Hydrogenolysis of Benzyl-Nitrogen Bonds. In *Heterogeneous Catalysis in Organic Chemistry*, Academic Press, **1999**, pp 171–172; b) X. Fu, J. M. Cook, *J. Am. Chem. Soc.* **1992**, *114*, 6910–6912; c) X. Fu, J. M. Cook, *J. Org. Chem.* **1993**, *58*, 661–672; d) J. Salta, Dissertation, Freie Universität Berlin (Germany), **2014**.
[28] The protonation may also occur already at the stages with intact 1,2-oxazine moieties.
[29] In this case, an ion exchange resin with smaller mesh size was employed.
[30] Bisamide **23** was also successfully converted into the expected bisammonium salt in high yield, however, the neutralization and purification of the compound failed.
[31] O. P. Dhamale, C. Zhong, K. Al-Mafraji, G. J. Boons, *Org. Biomol. Chem.* **2014**, *12*, 2087–2098.
[32] R. G. Schweiger, *Carbohydr. Res.* **1972**, *21*, 219–228.
[33] a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–599; *Angew. Chem.* **1963**, *75*, 604–632; b) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633–645; *Angew. Chem.* **1963**, *75*, 742–754; c) R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry, Vol. 1* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 1–176; d) M. Breugst, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2020**, *59*, 12293–12307; *Angew. Chem.* **2020**, *132*, 12389–12404.
[34] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; b) F. P. J. T. Rutjes, *Science of Synthesis: Click Chemistry*; Thieme Verlag: Stuttgart, Germany, **2022**.
[35] For an alternative approach to aminoseptanose derivatives based on alkoxyallenes and nitrones, see: M. Jasiński, G. Utecht, A. Fruziński, H.-U. Reissig, *Synthesis* **2016**, *48*, 893–905.

Manuscript received: December 19, 2023
Revised manuscript received: January 19, 2024
Accepted manuscript online: January 24, 2024
Version of record online: February 12, 2024