Organic & Biomolecular Chemistry

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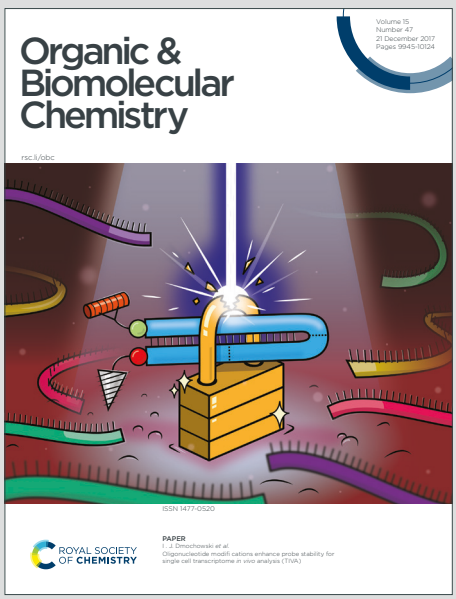

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View Article Online
DOI: 10.1039/D0OB00228C

ARTICLE

Synthesis of β-lactams *via* diastereoselective, intramolecular Kinugasa reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Intramolecular Kinugasa reactions on *in situ* generated carbohydrate-derived alkynylnitrones are described. The effects of chains length, their mutual configuration, and influence of experimental conditions on products distribution and feasibility of the β-lactam ring construction were studied. Intramolecular reactions proceeds with high stereoselectivity to provide in each case one product only. The cycloadducts from tartaric acid were converted into corresponding non-racemic 4-acetoxy azetidinones in a good yield.

Introduction

Intramolecular reactions usually offer distinct advantages over their intermolecular counterparts by providing a tethering unit which connects reacting functionalities. The proximity of the reacting functionalities, combined with some reduction of degrees of freedom of the system, render the intramolecular transformation more entropically and kinetically favourable. These factors lead to a more stereo-, regio- and chemoselective process which is often reflected in an increased yield of the desired product.

Over the past few years it has been demonstrated that the reaction between nitrones and the *in situ* generated Cu(I)–acetylide species, known as the Kinugasa reaction, has been a robust and versatile route for the synthesis of non-racemic β-lactam derivatives.[1-10] However, probably due to the simultaneous presence of a nitrone and a terminal acetylide group on a chiral scaffold and the high probability of a spontaneous reaction between those reactive groups, the Kinugasa reaction has been realized predominately as an intermolecular process and only a few communications on the catalytic enantioselective intramolecular version of that reaction have been reported.[11-13]

The 1,3-dipolar cycloaddition between a nitrone and acetylide (the first step of the β-lactam ring formation) with the dipole and dipolarophile linked by several atoms, should induce a highly ordered transition state providing the configuration control at C-4 of the azetidinone ring,[14-16] which is crucial for biological activity of the target compound. Recently, Hein and co-workers[17] proposed a new mechanism of Kinugasa reaction which postulated a cascade involving (3+2) cycloaddition, (3+2) cycloreversion to ketene and imine and, finally, [2+2] cycloaddition. If this mechanism is correct, then the configuration of the stereogenic center at C-4 of the four membered β-lactam ring should depend on the Staudinger [2+2] cycloaddition, and not on the 1,3-dipolar cycloaddition of a nitrone and terminal Cu(I) acetylide.

Results and discussion

Due to their easy transformation into many different structural forms, monosaccharides offer scaffolds that allow to place both reacting functions in a variety of spatial arrangements. In the present paper we selected diacetone-D-glucose and diethyl L-tartrate for that purpose. The starting substrates, enantiopure alkynylaldehydes **1**–**4** and **5**–**6** were conveniently synthesised following standard transformations that allow to arrange nitrone and terminal acetylene groups at varying distances from one another (Figure 1). Compounds **1**, **2**, **5**, and **6** were obtained from their alcoholic precursors *via* standard Dess-Martin periodinane oxidation.[18] It should be emphasized that the presence in the same molecule of nitrone and a triple bond might lead to the intramolecular 1,3-dipolar cycloaddition and formation an isoxazoline ring without participation of Cu(I) ion. Therefore, the proper selection of reaction conditions was essential for the successful formation of β-lactam fragment.

Initially, we investigated reactions of alkynylaldehyde **1** with *N*-benzylhydroxylamine (1.5 equiv.) (Scheme 1). After several attempts, we found out that regardless of chosen reaction conditions, the isoxazoline **8** was the only isolated product, although the expected nitrone **7** was observed in the crude reaction mixture. The product **8** was unambiguously characterized with the help of IR, NMR (1D, 2D, NOE) spectroscopy, and ESI-HRMS analysis.

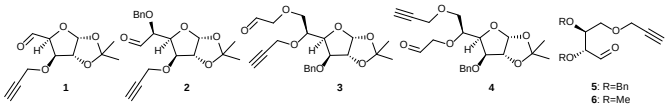

Fig. 1 Substrates for the Kinugasa reaction used in this work.

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Electronic Supplementary Information (ESI) available: CCDC 1975296. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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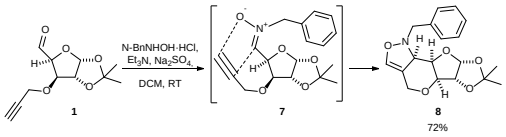
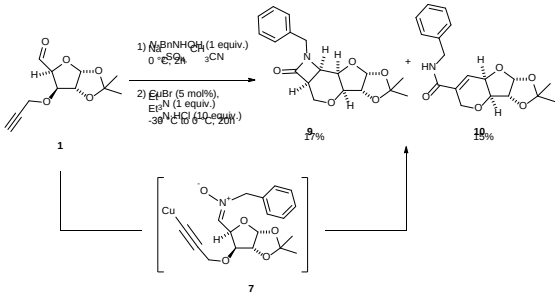
DOI: 10.1039/D0OB00228C



Scheme 1 Synthesis of isoxazoline **8**.

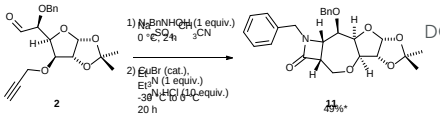


Scheme 2 An attempt to the synthesis of β-lactam **9**.

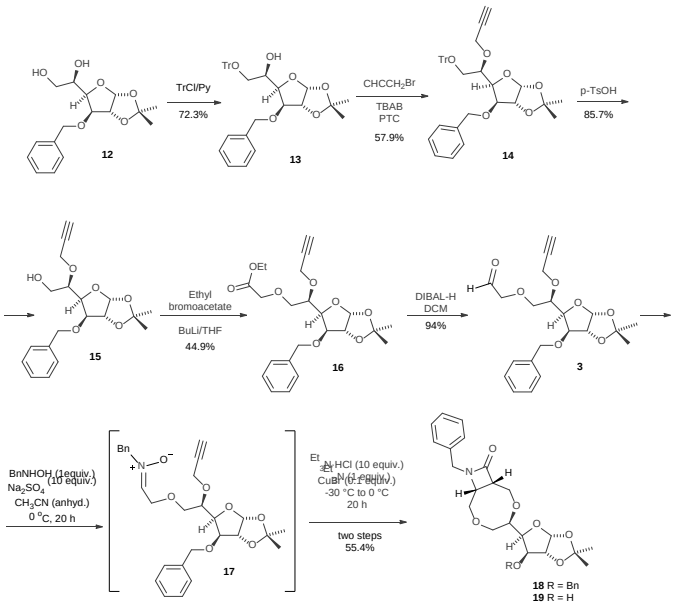
Following the observation of unwanted side reactions, we decided to perform the intramolecular reaction as a one-pot process with the *in situ* generated nitrone. We found that the most effective conditions for the nitrone **7** formation consisted of treatment of substrate **1** at 0 °C with *N*-benzylhydroxylamine in the presence of anhydrous Na_2SO_4 as a water scavenging agent. After 2 h, the temperature was lowered to -30 °C and triethylamine hydrochloride, triethylamine and CuBr were added. The addition of triethylamine hydrochloride as a proton donor to the reaction mixture was found to be essential for the β-lactam ring formation. The mixture was then stirred for 20 h, while the temperature was slowly increased to 0 °C to complete the intramolecular Kinugasa reaction. After purification by chromatography, the expected β-lactam **9** was obtained in 17% yield (Scheme 2). The compound **9** was accompanied by the product of the four-membered ring opening **10**.

Introduction of the nitrone function to the end of the sugar chain (**2**) increased the distance between reacting groups to allow for their more convenient mutual approach (Scheme 3). Under reaction conditions applied previously for **9**, β-lactam **11** was obtained as a single diastereomer in 49% yield. The presence of the stereogenic center at C-5 of the sugar chain and a rigid transition state of the intramolecular reaction, controlled configuration of the final product **11**. The structures and configurations of β-lactams **9** and **11** were fully corroborated by their respective IR and NMR (NOEs) data.

Extension of the distance between nitrone and alkyne groups could be easily achieved by placement of both substituents in the side chain of 1,2-isopropylidene-gluco-furanose *via* introduction of *O*-propargyl and *O*-carbonylmethyl substituents in two variants (Scheme 4). The first one located the *O*-propargyl residue at C-5 of the sugar chain (**15**), whereas the nitrone was formed by a three step procedure: (i) alkylation of the terminal hydroxyl with ethyl bromoacetate (**16**), (ii) reduction of ethoxycarbonyl to the aldehyde group (**3**) and (iii) formation of the nitrone (**17**) which *in situ* reacted with the alkyne under conditions used for **9** and **11** formation to afford β-lactam **18** in 55.4% yield as a single isomer.



Scheme 3 Synthesis of β-lactam **11**.

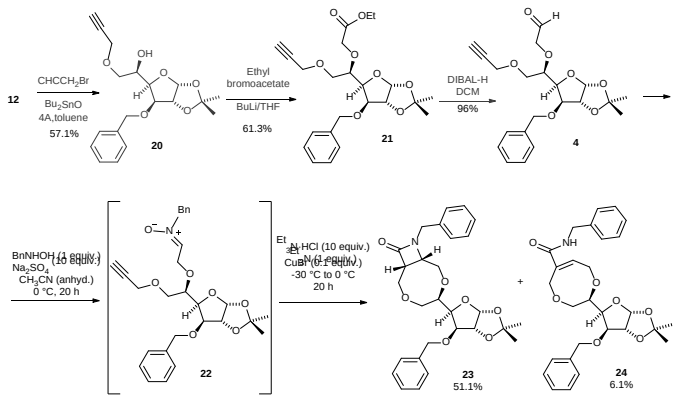


Scheme 4 Synthesis of β-lactam **18**.

The alternative option located both substituents in opposite places; propargyl at C-6 of the sugar chain and the nitrone at C-5 carbon atoms. The alkyne-ester **21** was obtained in two steps from **12**. Reduction of **21** with DIBAL to the aldehyde **4** and the Kinugasa reaction in **22**, performed under the general procedure provided β-lactam **23** in 51.1 % yield. The product **23** was accompanied by a minute amount of the α,β-unsaturated amide **24** (6.1%) (Scheme 5).

Structure and configuration of compound **18** was proven easily by the ^{1}H NMR (NOEs and coupling constant between four-membered ring protons) of 3-*O*-debenzylated compound **19** and CD spectroscopy (absolute configuration of the β-lactam fragment).[19-26] Compound **18** exhibited a positive sign of the Cotton effect (CE) signal of the $n\rightarrow\pi^*$ β-lactam amide transition (*R* configuration at C-4 of the azetidinone ring). Due to the overlapping of protons in ^{1}H NMR spectrum of compound **23**, the absolute configuration of the β-lactam fragment could not be verified unambiguously by NOEs. On the other hand, the absolute configuration of **23** was established by the CD spectroscopy showing the ECD signal negative (*S* configuration at C-4).[19,25]

DOI: 10.1039/D0OB00328C



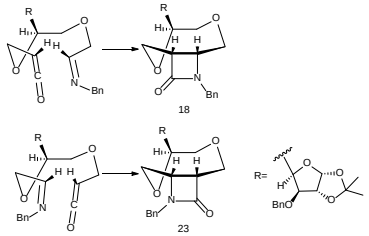
Scheme 5 Synthesis of β-lactam **23**.

In accordance with the alternative regiochemistry, the inductive stereogenic center (C-5 of the sugar chain) was closer to the triple bond (Scheme 4), or to the nitrone (Scheme 5). In both cases the cis substituted β-lactam ring was fused to the 1,4-dioxa-cyclooctane ring and located *anti* to the carbohydrate substituent. Consequently, the opposite absolute configuration of the four membered ring carbon atoms were induced.

In the case of β-lactams **9** and **11** the influence of geometry of the sugar skeleton upon configuration of new stereogenic centers of the four-membered ring is rather obvious. On the other hand, the effect of the sugar chain stereogenic center (C-5) configuration upon intramolecular 1,3-dipolar cycloaddition of the nitrones **17** and **22** to the terminal copper acetylide and formation of the eight-membered ring fused to the metalated isoxazolidine ring (suggested the first step of the Kinugasa reaction) is not straightforward. It looks that a rigid transition state of the cycloaddition and formation of the eight-membered ring placed the five-membered ring *anti* to the sugar substituent in both cases. Subsequent rearrangement and exclusive formation of only *cis*-substituted β-lactam rings are obvious. Consequently, in both cases [propargyl at C-5 (**17**), or propargyl at C-6 (**22**) of the sugar chain] the terminal sugar stereogenic center affects the configuration of the β-lactam ring in the same direction to provide in the case of **18** - (*R*) configuration at the carbon atom next to the nitrogen atom (C-4 of the azetidinone ring), whereas in the case of **23** - (*S*) configuration.[25]

Formation of *cis* substituted β-lactam can be explain by the generally accepted mechanism of Kinugasa reaction involving formation of isoxazoline, rearrangement to the enol form of azetidinone, and the final protonation. The mechanism proposed by Hein and co-workers[17] involving Staudinger's [2+2] cycloaddition could also explain the stereochemical pathway of the intramolecular Kinugasa reaction (Scheme 6). That mechanism, however, does not provide an universal explanation for the observed general stereochemical outcome of Kinugasa reactions.[3] The plausible formation of β-lactam enolate as a secondary process[27] does not explain well the ratio of *cis–trans* isomeric products (kinetic versus thermodynamic product) usually observed in the intermolecular Kinugasa reactions.[3]

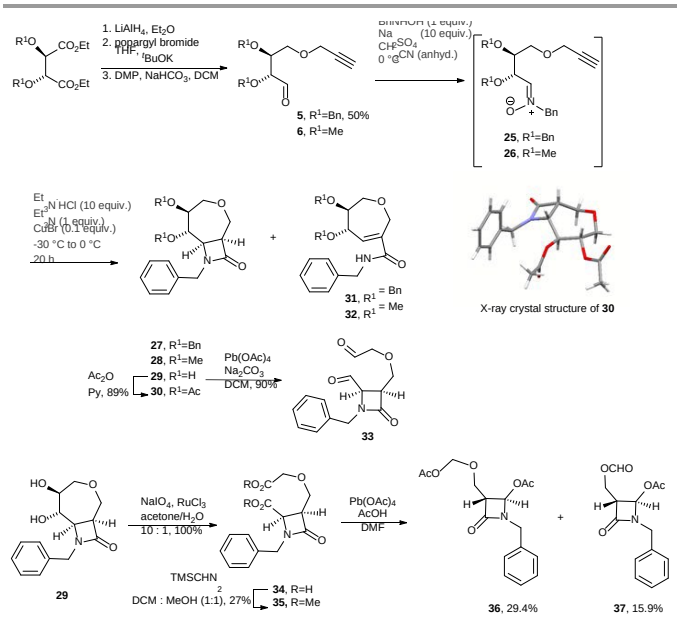
Tartaric acid derivatives **5** and **6** provided a simplified model for the intramolecular Kinugasa reaction (Scheme 7). Dibenzyl ether of diethyl tartrate was easily transformed into the propargyl aldehyde **5** by the standard reaction sequence. Intramolecular Kinugasa reaction *via* the *in situ* formation of the nitrone group (**25**) led to the bicyclic product **27** with the β-lactam fragment fused to the seven-membered ring in 54% yield (Scheme 7).



Scheme 6 Stereochemical pathway of the [2+2]cycloaddition step of the intramolecular Kinugasa reaction in compounds **18** and **23** following Hein *et al.*[17] mechanistic proposition.

The presence of other stereoisomers was not observed. The only isolated side product **31** was likely formed by opening of β-lactam ring. Formation of the seven-membered ring in 1,3-dipolar cycloaddition in the first step of the Kinugasa reaction caused location of the five-membered ring *anti* to the next stereogenic center. The alternatively proposed mechanism involving intramolecular Staudinger [2+2] cycloaddition of the ketene to imine located both substituents of the β-lactam ring *cis*, *anti* to the next benzyloxy group. The same reaction sequence was performed for dimethyl ether **6** to afford β-lactam **28**. The side product **32** was not isolated. Structures and configurations of β-lactams **27** and **28** were established easily by the ^{1}H NMR spectroscopy (NOEs).

Benzyl groups in **27** were removed by hydrogenation to give the diol **29**. The X-ray of the acetate **30** fully corroborated the NMR spectral assignments. Glycolic cleavage in **29** opened the seven membered ring to afford unstable dialdehyde **33** (Scheme 7). Reduction of the crude dialdehyde **33** leads to the mixture of products of β-lactam ring openings. Oxidative opening of the diol **29** with $NaJO_4$ and $RuCl_3$ provided a dicarboxylic acid **34** which was esterified with trimethylsilyl diazomethane to afford dimethyl ester **35**. The acid **34** treated with lead tetraacetate afforded an exchange of both carboxylic groups into acetoxy substituents **36**. The product **36** was accompanied by a minute amount of the formyloxy derivative **37** which probably originated from participation of the solvent (DMF). The acetoxy group at C-4 of the azetidinone ring in **36** could offer a possible pathway to introduction of a variety of substituents located *anti* to the substituent at C-3, thus providing the absolute configuration at C-4 carbon atom representative for biologically active β-lactams.



Scheme 7 Synthesis and transformations of β-lactams **27** and **28**.

Conclusion

As was anticipated, the facility of intramolecular Kinugasa reaction depends mainly on the size of the ring which is fused to the four-membered one. In the case of a six-membered ring (Scheme 2), under typical Kinugasa reaction condition, the 1,3-dipolar cycloaddition occurred. Addition of a proton donor allowed to obtain β-lactam product, albeit in a low yield. Transformation of the intermediary form **7** into products **8** and **9** depends on the relatively inflexible bicyclic sugar skeleton. An approach of reacting groups (a nitrone and a triple bond) is easy if a seven (Schemes 3 and 7), or eight membered ring (Schemes 4 and 5) is formed. The experiments showed that even a three bond distance between the cycloaddition place and the stereogenic center located in the ring fused to the four-membered one decides on configuration of the β-lactam stereogenic centers, causing *anti* location of the β-lactam ring to the R sugar substituent. No formation of a *trans* substituted four-membered ring was observed, although the α,β-unsaturated amide **24** as the by-product might suggests primary formation of the *trans* substituted β-lactam followed by the opening of the ring.

Experimental

General remarks:

All reagents were purchased from Sigma Aldrich, Alfa Aesar, or TCI Chemicals and used without further purification. All reactions involving air- and moisture-sensitive materials were carried out under argon atmosphere in oven-dried glassware with magnetic stirring. THF was distilled from Na and benzophenone. CH_2Cl_2 was distilled from CaH_2. Column chromatography was performed with silica gel 60 (240–400 mesh). Analytical TLC was performed with Silica gel 60 F254 aluminum plates (Merck) with visualization by UV light and charring with Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O). NMR spectra were recorded using Varian VNMRS 500 MHz and 600 MHz and Bruker 400 MHz spectrometers. Chemical shifts are calibrated using residual solvent signals ($CDCl_3$: δ (^{1}H)= 7.26, δ (^{13}C)= 77), or TMS and are reported in ppm using 1D, 2D, NOE measurements. Infrared spectra (IR) were recorded on FT-IR-1600-Perkin Elmer spectrophotometer and are reported in frequency of absorption (cm^{-1}). HRMS spectra were recorded on ESI-TOF Mariner spectrometer (Perspective Biosystem) and are given in m/z. ECD spectra were recorded using Jasco J-815 spectropolarimeter. Optical rotation measurements were carried out using Jasco P-2000 polarimeter. Melting points were measured on Melting Point Meter MPMH2 apparatus and are uncorrected.

Enantiopure alkynylaldehydes **1**–**4** and **5**–**6** were synthesised following standard carbohydrate transformations.

1,2-*O*-Isopropylidene-3-*O*-propargyl-1,5-dialdo-α-D-xylo-pentofuranose (1)

(79%), colorless oil; $[\alpha]_D$ = - 89.9 (*c* 1.44, C_6H_6); IR (film, DCM) ν_{max}: 3461, 3280, 2987, 2938, 2865, 1738, 1453, 1378 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 9.61 (d, *J* = 1.6 Hz, 1H), 5.85 (d, *J* = 3.6 Hz, 1H), 4.42 (dd, *J* = 3.8, 1.6 Hz, 1H), 4.23 (d, *J* = 3.6 Hz, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 3.60 (dd, *J* = 16.0, 2.4 Hz, 1H), 3.55 (dd, *J* = 16.0, 2.4 Hz, 1H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.28 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 198.9, 112.4, 106.6, 84.8, 83.9, 82.6, 78.8, 75.6, 57.7, 27.1, 26.4; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}O_5Na$ 249.0739; found 249.0732;

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-propargyl-1,5-dialdo-α-D-gluco-hexofuranose (2)

(80%), colorless oil; $[\alpha]_D$ = – 3.9 (*c* 1.8, C_6H_6); IR (film, DCM) ν_{max}: 3280, 2987, 2930, 2856, 1736, 1454, 1377 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ: 9.76 (d, *J* = 1.8 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.16 – 7.10 (m, 2H), 7.10 – 7.06 (m, 1H), 5.76 (d, *J* = 3.7 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.52 (dd, *J* = 8.4, 3.4 Hz, 1H), 4.29 – 4.24 (m, 2H), 4.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.07 (d, *J* = 3.4 Hz, 1H), 3.71 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.65 (dd, *J* = 15.8, 2.4 Hz, 1H), 1.92 (t, *J* = 2.4 Hz, 1H), 1.28 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ: 199.7, 138.1, 128.6, 128.4, 128.3, 112.1, 106.0, 81.9, 81.9, 80.3, 79.7, 79.2, 75.4, 72.9, 57.5, 27.0, 26.4; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{22}O_6Na$ 369.1314, found 369.1309;

(2*R*,3*S*)-2,3-Dibenzyloxy-4-propargyloxybutanal (5)

(81.7%), colorless oil; $[\alpha]_D$ = + 37.9 (*c* 1.13, DCM); IR (film, DCM) ν_{max}: 3444, 3286, 2925, 2871, 2116, 1730, 1454, 1096, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 7.34 -7.24 (m, 10H), 4.76 (d, *J* = 11.9 Hz 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.07 (d, *J* = 2.3 Hz, 2H), 3.97 - 3.93 (m, 2H), 3.75 - 3.71 (m, 1H), 3.69 - 3.65 (m, 1H), 2.41 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 202.4, 137.5, 137.1, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 82.6, 79.2, 77.6, 74.8, 73.4, 73.0, 67.7, 58.5; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{22}O_4Na$ 361.1416; found 361.1413;

(2*R*,3*S*)-2,3-Dimethoxy-4-propargyloxybutanal (6)

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DOI: 10.1039/D0OB00338C

(59%), colorless oil; $[\alpha]_D$ = + 59.8 (c 1.4, DCM); IR (film, DCM) ν_{max}: 3447, 3279, 2935, 2833, 2116, 1732, 1462, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.78 (d, *J* = 1.1 Hz, 1H), 4.16 (dd, *J* = 2.4, 1.8 Hz, 2H), 3.77 – 3.72 (m, 3H), 3.70 – 3.66 (m, 1H), 3.52 (s, 3H), 3.42 (s, 3H), 2.44 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 85.2, 80.1, 79.3, 75.0, 67.3, 59.7, 59.1, 58.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_9H_{14}O_4Na$ 209.0790; found 209.0780;

3-*O*-Benzyl-6-*O*-ethoxycarbonylmethyl-5-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose (16)

To a solution of **15** (0.180 g, 0.517 mmol) in anhydrous THF (11 mL) cooled to -78 °C the BuLi (0.246 ml 2.2 M solution) was added dropwise and the reaction was stirred for 2 h. Ethyl bromoacetate (0.177 g, 1.034 mmol) was added to the mixture. The reaction was allowed to warm to RT and was monitored by TLC. After the reaction was completed, the mixture was quenched with sat. NH_4Cl (2 mL) and diluted with Et_2O. Organic phase was separated, dried and concentrated to dryness. The residue (0.271 g) was purified by chromatography with hexane-AcOEt (4 : 1) to yield **16** (0.101 g 44.9%) as colorless oil; $[\alpha]_D$ = -37.0 (*c* 1.1, DCM); IR (film, DCM) ν_{max}: 3276, 2985, 2936, 2117, 1752, 1374, 1211 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ*: 7.36 – 7.26 (m, 5H), 5.87 (d, *J* = 3.7 Hz, 1H), 4.67, 4.63 (ABq, *J* = 11.5 Hz, 2H), 4.57 (d, 3.7 Hz, 1H), 4.45 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.29 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.22 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.19 (ddd, *J* = 14.2, 7.1, 1.0 Hz, 2H), 4.15 (d, *J* = 16.5 Hz, 1H), 4.08 (d, *J* = 16.5 Hz, 1H), 4.09 (d, *J* = 3.1 Hz, 1H), 4.06 – 4.00 (m, 2H), 3.67 (dd, *J* = 10.1, 5.5 Hz, 1H), 2.32 (t, *J* = 2.4 Hz, 1H), 1.46 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.29 (s, 3H); ^{13}C NMR, (150 MHz, $CDCl_3$) *δ*: 170.4, 137.6, 128.4, 127.8, 127.7, 111.8, 105.1, 82.1, 81.6, 80.0, 78.6, 74.5, 74.3, 72.3, 72.0, 68.9, 60.8, 57.5, 26.8, 26.3, 14.2; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}O_8Na$ 457.1838; found 457.1829.

3-*O*-Benzyl-5-*O*-ethoxycarbonylmethyl-6-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose (21)

Compound **21** was obtained following procedure described for **16** (61.3%); $[\alpha]_D$ = - 31.2 (*c* 1.1, DCM); IR (film, DCM) ν_{max}: 3276, 2985, 2936, 2116, 1754, 1375, 1210, 1144, 1075, 1029 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ*: 7.36 – 7.26 (m, 5H), 5.88 (d, *J* = 3.8 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 3.8 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 16.1 Hz, 1H), 4.21 (dd, J = 9.2, 3.1 Hz, 1H), 4.18 – 4.09 (m, 5H), 4.06 (d, *J* = 16.2 Hz, 1H), 3.97 – 3.92 (m, 2H), 3.68 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.38 (t, *J* = 2.3 Hz, 1H), 1.48 (s, 3H), 1.30 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 170.3, 137.6, 128.4, 127.8, 127.6, 111.8, 105.2, 81.8, 81.7, 79.6, 78.9, 77.0, 74.4, 72.1, 72.07, 69.0, 60.6, 58.6, 26.8, 26.3, 14.1; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}O_8Na$ 457.1838; found 457.1820.

3-*O*-Benzyl-6-*O*-carbonylmethyl-5-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose (3)

To a solution of compound **16** (76 mg, 0.175 mmol) in anhydrous DCM (7 mL) the DIBAL (0.210 ml, 1 M solution in hexane) was added at -78 °C. After 1 h sat. Na_2SO_4 (2 mL) was added and the mixture was allowed to warm to RT. The mixture was diluted with Et_2O, filtered through Celite and concentrated to dryness. The crude aldehyde **3** (64 mg 94%) was used in the next step without purification; $[\alpha]_D$ = - 37.2 (*c* 0.8, DCM); IR (film, DCM) ν_{max}: 3279, 2985, 2931, 2118, 1736, 1377, 1216, 1077, 1027 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ*: 9.75 (t, *J* = 0.8 Hz, 1H), 7.37 – 7.28 (m, 5H), 5.89 (d, *J* = 3.9 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 3.7 Hz, 1H), 4.36 (dd, *J* = 15.6, 2.4 Hz, 1H), 4.26 (dd, *J* = 9.0, 3.2 Hz, 1H), 4.25 (dd, *J* = 15.6, 2.4 Hz, 1H), 4.12 (bs, 2H), 4.11 (d, *J* = 3.2 Hz, 1H), 4.07 – 4.0 (m, 2H), 3.72 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.36 (t, *J* = 2.4 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 201.1, 137.5, 128.5, 127.9, 127.7, 111.9, 105.1, 81.9, 81.5, 79.9, 78.4, 76.9, 74.8, 74.5, 72.2, 72.2, 57.8, 26.8, 26.3; HRMS (ESI) *m/z*: $[M + Na]^+$calcd for $C_{21}H_{26}O_7Na$ 413.1576; found 413.1573.

3-*O*-Benzyl-5-*O*-carbonylmethyl-6-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose (4)

Aldehyde **4** was obtained following the procedure described above for **3** (96%); $[\alpha]_D$ = – 30.5 (*c* 1.08, DCM); IR (film, DCM) ν_{max}: 3279, 2934, 2116, 1735, 1377, 1076, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 9.54 (s, 1H), 7.36 – 7.27 (m, 5H), 5.90 (d, *J* = 3.6 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 3.7 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.28 (dd, *J* = 17.9, 1.0 Hz, 1H), 4.21 – 4.09 (m, 4H), 3.98 (dd, *J* = 17.9, 1.0 Hz, 1H), 3.95 – 3.91 (m, 2H), 3.68 (dd, *J* = 10.4, 7.2 Hz, 1H), 2.41 (t, *J* = 2.4 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 200.9, 137.3, 128.6, 128.1, 127.8, 111.9, 105.2, 81.7, 81.5, 79.4, 78.8, 76.9, 76.8, 74.7, 72.0, 71.7, 58.6, 26.8, 26.3; HRMS (ESI) *m/z*: $[M + MeOH + Na]^+$ calcd for $C_{22}H_{30}O_8Na$ 455.1838; found 455.1841.

(5aS,5bR,8aR,9aR,9bR)-1-Benzyl-7,7-dimethyl-1,5a,5b,8a,9a,9b-hexahydro-4H-[1,3]dioxolo[4'',5'':4',5']furo[3',2':2,3]pyrano[4,5-c][1,2]oxazole (8)

Reaction was performed under argon atmosphere. A mixture of *N*-benzylhydroxylamine hydrochloride (0.120 g, 0.75 mmol, 1.5 equiv.) and trimethylamine (0.139 mL, 1 mmol, 2 equiv.) in anhydrous DCM (3.5 mL) was stirred at RT for 1 h. Next, the anhydrous sodium sulfate (0.710 g, 5 mmol, 10 equiv.) was added to the mixture followed by the solution of aldehyde **1** (0.113 g, 0.5 mmol) in anhydrous DCM (1.5 mL). The resulted mixture was vigorously stirred at RT for 2 h and monitored by TLC. When the starting aldehyde was no longer present, the mixture was filtered, and the filtrate evaporated under reduced pressure. The residue was adsorbed on silica gel and purified by flash column chromatography (hexane/ethyl acetate, 9:1) to give compound **8** (0.119 g, 72%) as a white foam; $[\alpha]_D$ = - 269.2 (*c* 1.19, DCM); IR (film, DCM) ν_{max}: 3097, 3028, 2989, 2927, 2900, 2868, 1678, 1495, 1454, 1377 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.44 – 7.39 (m, 2H), 7.37 – 7.31 (m, 2H), 7.32 – 7.26 (m, 1H), 6.25 (dd, *J* = 2.3, 1.2 Hz, 1H), 5.94 (d, *J* = 3.8 Hz, 1H), 4.61 (t, *J* = 3.4 Hz, 1H), 4.56 – 4.52 (m, 2H), 4.50 – 4.44 (m, 1H), 4.17 (d, *J* = 13.8 Hz, 1H), 4.14 (d, *J* = 13.8 Hz, 1H), 4.12 – 4.10 (m, 1H), 3.99 (d, *J* = 3.4 Hz, 1H), 1.49 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.5, 135.9, 129.2, 128.5, 127.7, 112.0, 105.8, 105.1, 86.2, 83.4, 80.4, 71.6, 64.7, 62.5, 27.1, 26.6; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{21}NO_5Na$ 354.1317; found 354.1310.

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DOI: 10.1039/D0OB00228C

General procedure for the intramolecular Kinugasa reaction (GP):

Reaction was performed under argon atmosphere. In a flame-dried Schlenk flask aldehyde (0.5 mmol, 1 equiv.) was dissolved in anhydrous acetonitrile (10 mL) and the mixture was cooled to 0 °C. Next, anh. sodium sulfate (5 mmol, 10 equiv.) and *N*-benzylhydroxylamine (0.5 mmol, 1 equiv.) were added. The mixture was stirred at 0 °C and was monitored by TLC. After full consumption of the starting aldehyde, the mixture was cooled to -30 °C and triethylamine hydrochloride (5 mmol, 10 equiv.), triethylamine (0.5 mmol, 1 equiv.) and copper(I) bromide (0.05 mmol, 10 mol%) were added. Reaction was continued at 0 °C and was monitored by TLC. Upon completion, the reaction mixture was filtered through a pad of Florisil, pad was thoroughly washed with ethyl acetate and combined filtrates were concentrated *in vacuo*. The residue was submitted for purification by flash column chromatography.

(2aS,4aS,4bR,7aR,8aR,8bR)-1-Benzyl-6,6-dimethyloctahydro-2H-[1,3]dioxolo [4'',5'':4',5']furo[3',2':2,3]pyrano[4,5-b]azetidin-2-one (9) and (3aR,3bS,7aR,8aR)-N-Benzyl-2,2-dimethyl-3a,5,7a,8a-tetrahydro-3bH-[1,3]dioxolo[4',5':4,5]furo[3,2-b]pyran-6-carboxamide (10)

Products **9** and **10** were obtained according to GP starting from aldehyde **1** (0.170 g, 0.75 mmol) and *N*-benzylhydroxylamine (0.092 g, 0.75 mmol) in the presence of sodium sulfate (1.065 g, 7.50 mmol, 10 equiv.), triethylamine hydrochloride (1.032 g, 7.50 mmol, 10 equiv.), triethylamine (0.105 mL, 0.75 mmol, 1 equiv.) and copper(I) bromide (11 mg, 0.075 mmol, 10 mol%) in anhydrous acetonitrile (15 mL). The mixture was stirred for 2 h during the *in situ* formation of the nitrone, and for the intramolecular Kinugasa reaction the process was continued for 20 h. Crude product was adsorbed on silica gel and purified by flash column chromatography (hexane/ethyl acetate from 4:1 to 2:3) to give compound **9** (42 mg, 17%) as a slightly yellow foam and compound **10** (37 mg, 15%) as a colorless oil:

Compound **9**; $[\alpha]_D$ = + 3.5 (*c* 2.56, DCM); IR (film, DCM) ν_{max}: 2985, 2930, 2876, 1755, 1455, 1402, 1378 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.38 – 7.33 (m, 2H), 7.34 – 7.28 (m, 3H), 5.81 (d, *J* = 3.9 Hz, 1H), 4.52 (d, *J* = 15.0 Hz, 1H), 4.48 (d, *J* = 3.9 Hz, 1H), 4.32 (d, *J* = 15.0 Hz, 1H), 4.07 (dd, *J* = 4.1, 2.3 Hz, 1H), 3.93 (dd, *J* = 12.2, 3.1 Hz, 1H), 3.88 (dd, *J* = 5.5, 2.3 Hz, 1H), 3.82 (d, *J* = 4.1 Hz, 1H), 3.75 (dd, *J* = 12.2, 4.1 Hz, 1H), 3.28 (ddd, *J* = 5.5, 4.1, 3.1 Hz, 1H), 1.33 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.7, 135.8, 129.1, 128.6, 128.3, 111.8, 104.7, 86.1, 77.4, 72.4, 60.1, 48.4, 47.4, 45.8, 26.9, 26.3; HRMS (ESI) *m/z*: calcd for $C_{18}H_{21}NO_5Na$ $[M + Na]^+$ 354.1317; found 354.1310;

Compound **10**; $[\alpha]_D$ = - 27.2 (*c* 1.38, $CHCl_3$); IR (film, DCM) ν_{max}: 3333, 3062, 3031, 2986, 2934, 2847, 1735, 1670, 1631, 1536, 1453, 1378 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.38 – 7.30 (m, 2H), 7.32 – 7.24 (m, 3H), 6.50 – 6.46 (m, 1H), 6.21 (t, *J* = 5.8 Hz, 1H), 5.91 (d, *J* = 3.8 Hz, 1H), 4.61 (d, *J* = 3.8 Hz, 1H), 4.56 (dd, *J* = 16.8, 1.4 Hz, 1H), 4.51 – 4.42 (m, 3H), 4.25 (dt, *J* = 16.8, 2.2 Hz, 1H), 3.94 (d, *J* = 2.7 Hz, 1H), 1.50 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.6, 139.1, 137.8, 128.9, 128.0, 127.9, 123.4, 111.9, 105.3, 84.2, 79.0, 70.8, 64.6, 43.7, 27.0, 26.3; HRMS (ESI) *m/z*: calcd for $C_{18}H_{21}NO_5Na$ $[M + Na]^+$ 354.1317; found 354.1305.

(3a*R*,4a*R*,5*R*,5a*S*,7a*R*,9a*S*,9b*R*)-6-Benzyl-5-(benzyloxy)-2,2-dimethyloctahydro[1,3] dioxolo[4'',5'':4',5']furo[2',3':6,7] oxepino[4,3-*b*]azet-7-(3a*H*)-one (11)

Product **11** was obtained according to GP starting from the aldehyde **2** (83 mg, 0.24 mmol) and *N*-benzylhydroxylamine (30 mg, 0.24 mmol) in the presence of sodium sulfate (0.341 g, 2.40 mmol, 10 equiv.), triethylamine hydrochloride (0.330 g, 2.40 mmol, 10 equiv.), triethylamine (0.033 mL, 0.24 mmol, 1 equiv.) and copper(I) bromide (3 mg, 0.024 mmol, 10 mol%) in anhydrous acetonitrile (4.8 mL). The mixture was stirred for 2 h during *in situ* formation of the nitrone, and for the intramolecular Kinugasa reaction the process was continued for 20 h. Crude product was adsorbed on silica gel and purified by flash column chromatography (hexane/ethyl acetate 4:1) to give compound **11** (56 mg, 49%) as a slightly yellow oil; $[\alpha]_D$ = + 30.2 (c 1.4, DCM); IR (film, DCM) ν_{max}: 3062, 3031, 2985, 2935, 2882, 1750, 1496, 1454, 1404, 1383, 1351 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.38 – 7.33 (m, 2H), 7.32 – 7.28 (m, 3H), 7.27 – 7.22 (m, 3H), 7.15 (dd, *J* = 7.5, 2.0 Hz, 2H), 5.83 (d, *J* = 3.6 Hz, 1H), 4.60 – 4.54 (m, 2H), 4.42 – 4.38 (m, 2H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.22 (d, *J* = 14.9 Hz, 1H), 4.14 (dd, *J* = 12.5, 5.2 Hz, 1H), 4.05 – 3.98 (m, 2H), 3.95 (d, *J* = 2.0 Hz, 1H), 3.56 (t, *J* = 12.5 Hz, 1H), 3.48 (dt, *J* = 12.5, 5.2 Hz, 1H), 1.39 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.1, 137.5, 136.5, 128.7, 128.6, 128.3, 128.1, 127.9, 127.5, 111.9, 104.8, 83.1, 82.6, 79.8, 77.6, 71.3, 64.6, 53.7, 51.2, 45.4, 26.8, 26.2; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{29}NO_6Na$ 474.1893; found 474.1882.

3(*S*), 6(*R*), 10(*R*)-3,10-*cis*-6-(1',2'-Isopropylidene-3'-*O*-benzyl- α-*D*-xylo-pentofuranos-4'-yl)-1-benzylamino-5,8-dioxa-2-one-bicyclo[2.0.6]decane (18)

Product **18** was obtained according to GP starting from aldehyde **3** (51 mg, 0.131 mmol) and *N*-benzylhydroxylamine (16 mg, 0.131 mmol) in the presence of sodium sulfate (0.186 g, 1.31 mmol, 10 equiv.), triethylamine hydrochloride (0.180 g, 1.31 mmol, 10 equiv.), triethylamine (0.018 mL, 0.131 mmol, 1 equiv.) and copper(I) bromide (2 mg, 0.013 mmol, 10 mol%) in anhydrous acetonitrile (3 mL). The mixture was stirred for 20 h during *in situ* formation of the nitrone, and for the intramolecular Kinugasa reaction the process was continued for 20 h. Crude product was purified by flash column chromatography (hexane/ethyl acetate 3 : 2) to give compound **18** (36 mg, 55.4%) as a colorless oil.

$[\alpha]_D$ = – 18.3 (*c* 1.14, DCM); Mol. CD (MeCN): + 2.29 (228 nm); IR (film, DCM) ν_{max}: 2930, 1750, 1376, 1075, 1024, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.40 - 7.20 (m, 10H), 5.85 (d, *J* = 3.8 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 15.4 Hz, 1H), 4.56 (d, *J* = 3.8, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.18 - 4.15 (m, 2H), 4.11 (d, *J* = 15.4 Hz, 1H), 4.00 (d, *J* = 3.1 Hz, 1H), 3.99 – 3.91 (m, 4H), 3.69 (dd, *J* = 13.3, 2.8 Hz, 1H), 3.64 (ddd, *J* = 7.4, 4.9, 2.8 Hz, 1H), 3.55 – 3.50 (m, 2H), 1.44 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.4, 137.3, 135.5, 128.9, 128.6, 128.2, 128.1, 127.9, 127.8, 111.7, 105.1, 82.0, 81.2, 80.2, 76.8, 74.2, 72.3, 66.8, 66.5,

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53.7, 53.4, 44.5, 26.7, 26.2; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{28}H_{33}NO_7Na$ 518.2155; found 518.2144.

3(*S*), 6(*R*), 10(*R*)-3,10-*cis*-6-(1',2'-Isopropylidene-3'-*O*-hydroxyl-α-*D*-xylo-pentofuranos-4'-yl)-1-benzylamino-5,8-dioxa-2-one-bicyclo[2.0.6]decane (19)

Compound **18** (33 mg; 0.066 mmol) in AcOEt (2 mL) and Pd (50 mg, 10% on activated carbon) was stirred under hydrogen for 18 h. Subsequently the mixture was filtered through Celite and evaporated to afford **19** (18 mg, 66.6%) as a colorless oil; $[\alpha]_D$ = + 4.08 (*c* 1.4, DCM); IR (film) ν_{max}: 3409, 2925, 1732, 1375, 1073, 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35 – 7.21 (m, 5H), 5.89 (d, *J* = 3.7 Hz, 1H), 4.60 (d, *J* = 15.2 Hz, 1H), 4.48 (d, *J* = 3.7 Hz, 1H), 4.27 (dd, *J* = 13.2, 5.5 Hz, 1H), 4.22 (d, *J* = 2.6 Hz, 1H), 4.11 (d, *J* = 15.2 Hz, 1H), 4.07 (dd, *J* = 13.4, 2.6 Hz, 1H), 4.05 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.00 (dd, *J* = 7.6, 2.7 Hz, 1H), 3.96 (dd, *J* = 13.4, 6.5 Hz, 1H), 3.89 (dd, *J* = 7.3, 2.6 Hz, 1H), 3.77 (dd, *J* = 13.4, 2.6 Hz, 1H), 3.68 (ddd, *J* = 6.7, 5.1, 2.6 Hz, 1H), 3.58 (dd, *J* = 13.2, 7.7 Hz, 1H), 3.51 (dt, *J* = 9.5, 5.3 Hz, 1H), 1.44 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.7, 135.4, 128.9, 128.2, 127.9, 111.6, 104.8, 85.0, 79.5, 78.2, 74.8, 73.3, 67.2, 66.0, 54.0, 52.9, 44.7, 26.7, 26.1; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{21}H_{27}O_7Na$ 428.1685; found 428.1682.

3(*R*), 7(*R*), 10(*S*)-3,10-*cis*-7-(1',2'-Isopropylidene-3'-*O*-benzyl-α-*D*-xylo-pentofuranos-4'-yl)-1-N-benzyl-5,8-dioxa-2-one-bicyclo[2.0.6]decane (23) and 3-(1',2'-Isopropylidene-3'-*O*-benzyl-α-*D*-xylo-pentofuranos-4'-yl)-7-N-benzyl carboxamino-1,4-dioxa-cyclooctan-6-ene (24)

Products **23** and **24** were obtained according to GP from aldehyde **4** (79 mg, 0.202 mmol) and *N*-benzylhydroxylamine (25 mg, 0.202 mmol) in the presence of sodium sulfate (0.287 g, 2.02 mmol, 10 equiv.), triethylamine hydrochloride (0.277g, 2.02 mmol, 10 equiv.), triethylamine (0.028 mL, 0.202 mmol, 1 equiv.) and copper(I) bromide (3 mg, 0.020 mmol, 10 mol%) in anhydrous acetonitrile (5 mL). The mixture was stirred for 20 h during *in situ* formation of the nitrone, and for the intramolecular Kinugasa reaction the process was continued for 20 h. Crude product was purified by flash column chromatography (hexane/ethyl acetate 1:2) to give compounds **23** (51 mg, 51.1%) and **24** (6.1 mg, 6.1%) as a colorless oils;

Compound **23**

$[\alpha]_D$ = – 48.5 (*c* 1.1, DCM); Mol. CD (MeCN): – 3.59 (220 nm); IR (film, DCM) ν_{max}: 2931, 1751, 1374, 1116, 1075, 1023 cm^{-1} ; ^{1}H NMR (600 MHz, $CDCl_3$ + C_6D_6) δ: 7.17 – 7.00 (m, 10H), 5.72 (d, *J* = 3.7 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 3.8 Hz, 1H), 4.26 (d, *J* = 11.8 Hz, 1H), 4.23 (d, *J* = 15.1 Hz, 1H), 4.08 (dd, *J* = 13.4, 1.8 Hz, 1H), 3.98 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.92 - 3.87 (m, 1H), 3.89 (d, *J* = 15.1 Hz, 1H), 3.84 – 3.77 (m, 3H), 3.60 (dd, *J* = 4.0, 3.6 Hz, 1H), 3.46 (ddd, *J* = 10.0, 4.9, 4.0 Hz, 1H), 3.35 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.31 (dd, *J* = 12.7, 10.1 Hz, 1H), 3.24 (ddd, *J* = 9.5, 4.9, 3.8 Hz, 1H), 1.31 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$ + C_6D_6) δ: 166.7, 137.4, 135.6, 128.7, 128.3, 128.2, 128.0, 127.9, 127.6, 111.5, 105.0, 81.9, 81.1, 79.7, 77.0, 72.5, 71.9, 67.3, 63.1, 54.0, 52.9, 44.7, 26.0, 25.6; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{28}H_{33}NO_7Na$ 518.2155; found 518.2147.

Compound **24**

$[\alpha]_D$ = – 20.0 (*c* 1.47, DCM); IR (film) ν_{max}: 3340, 2931, 1752, 1666, 1631, 1527, 1454, 1376, 1075, 1024 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 7.11 – 7.04 (m, 10H), 6.13 (dd, *J* = 3.7, 3.7 Hz, 1H), 5.75 (d, *J* = 3.6 Hz, 1H), 5.64 (bt, *J* = 3.6 Hz, 1H), 4.63 (d, *J* = 13.9 Hz, 1H), 4.46 (d, *J* = 13.9 Hz, 1H), 4.29 – 4.02 (m, 9H), 4.01 (d, *J* = 2.9 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.56 -3.50 (m, 1H), 1.39 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 167.7, 139.1, 137.8, 135.2, 135.0, 128.4 (2C), 127.2, 127.0, 111.3, 105.4, 81.9, 81.6, 79.7, 79.3, 77.7, 71.3, 70.8, 67.9, 66.2, 43.3, 29.7, 26.6, 26.0; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{28}H_{33}NO_7Na$ 518.2155; found 518.2157.

3(*S*), 7(*S*), 8(*S*), 9(*S*)-3,9-*cis*-7,8-Dibenzyloxy-1-N-benzyl-5-oxa-2-one-bicyclo[2.0.5]nonane (27) and 5(*S*), 6(*S*)-7,8-dibenzyloxy-3-benzyloxycarbonylo-1-oxa-cyclohept-3-ene (31)

Products **27** and **31** were obtained according to GP from aldehyde **5** (0.261 g, 0.772 mmol) and *N*-benzylhydroxylamine (0.095 g, 0.772 mmol) in the presence of sodium sulfate (1.097 g, 7.72 mmol, 10 equiv.), triethylamine hydrochloride (1.062 g, mmol, 10 equiv.), triethylamine (0.107 mL, 0.772 mmol, 1 equiv.) and copper(I) bromide (11 mg, 0.077 mmol, 10 mol%) in anhydrous acetonitrile (15 mL). The mixture was stirred for 20 h during *in situ* formation of the nitrone, and for the intramolecular Kinugasa reaction the process was continued for 20 h. Crude product was purified by flash column chromatography (hexane/ethyl acetate 7:3) to give compounds **27** (0.184 g, 54%) and **31** (0.028 g, 8%) as a colorless oils;

Compound **27**:

$[\alpha]_D$ = – 5.7 (*c* 1.1, DCM); IR (film, DCM) ν_{max}: 2866, 1751, 1112, 1074, 699 cm^{-1}; ^{1}H NMR (600 MHz, toluene 80 °C) δ: 7.15 - 6.94 (m, 15H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 15.1 Hz, 1H), 4.33, 4.29 (ABq, *J* = 11.6 Hz, 2H), 4.15 (d, *J* = 11.5 Hz, 1H), 3.88 (d, *J* = 15.1 Hz, 1H), 3.82 (dd, *J* = 12.8, 4.9 Hz 1H), 3.67 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.59 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.52 (dd, *J* = 12.5, 9.9 Hz, 1H), 3.39 (dd, *J* = 7.4, 5.6 Hz, 1H), 3.34 (dd, *J* = 12.8, 7.4 Hz, 1H), 3.20 (ddd, *J* = 7.7, 7.7, 2.8 Hz, 1H), 3.02 (ddd, *J* = 9.9, 5.4, 4.9 Hz, 1H); ^{13}C NMR, (150 MHz, toluene 80 °C) δ: 165.1, 138.6, 138.2, 128.6, 128.2, 128.1, 128.0 (2C), 127.7, 127.5, 127.3, 126.9, 124.9, 82.9, 80.4, 73.6, 72.6, 70.7, 67.4, 55.5, 53.3, 44.9; HRMS (ESI) *m/z*: [M + Na] $^+$ calcd for $C_{28}H_{29}NO_4Na$ 466.1994; found. 466.1998.

Compound **31**

$[\alpha]_D$ = + 35.9 (*c* 0.9, DCM); IR (film, DCM) ν_{max}: 3322, 3030, 2866, 1739, 1662, 1624, 1533, 1453 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 – 7.22 (m, 15H), 6.21 - 6.18 (m, 1H), 5.87 – 5.80 (m, 1H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.74 (d, *J* = 11.8 Hz, 1H), 4.71 – 4.61 (m, 3H), 4.58 – 4.51 (m, 1H), 4.46 - 4.38 (m, 3H), 3.93 (dd, *J* = 13.1, 4.1 Hz 1H), 3.83 (dd, *J* = 13.1, 4.8 Hz, 1H), 3.75 (ddd, *J* = 8.7, 8.7, 4.4 Hz 1H); ^{13}C NMR, (125 MHz, $CDCl_3$) δ: 166.7, 138.3, 138.1, 137.8, 136.5, 134.8, 128.8, 128.4 (2C), 128.0 (2C), 127.8, 127.7 (3C), 81.2, 78.8, 73.6, 72.9, 72.2, 70.71, 43.75; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{28}H_{29}NO_4Na$ 466.1994; found. 466.1991.

(5S,6S)-8-Benzyl-5,6-dimethoxy-3-oxa-8-azabicyclo[5.2.0]nonan-9-one (28)

DOI: 10.1039/D0OB00228C

Product **28** was obtained according to GP from aldehyde **6** (0.112 g, 0.60 mmol) and *N*-benzylhydroxylamine (0.074 g, 0.60 mmol) in the presence of sodium sulfate (0.852 g, 6.00 mmol, 10 equiv.), triethylamine hydrochloride (0.826 g, 6.00 mmol, 10 equiv.), triethylamine (0.084 mL, 0.60 mmol, 1 equiv.) and copper(I) bromide (3 mg, 0.024 mmol, 10 mol%) in anhydrous acetonitrile (12 mL). The mixture was stirred for 2 h during *in situ* formation of the nitrone, and for the intramolecular Kinugasa reaction the process was continued for 20 h. Crude product was adsorbed on silica gel and purified by flash column chromatography (hexane/ethyl acetate for 9:1 to 2:3) to give compound **27** (0.075 g, 43%) as a colorless oil; $[\alpha]_D$ = - 14.9 (*c* 1.62, DCM); IR (film, DCM) ν_{max}: 3489, 3030, 2930, 2827, 1751, 1665, 1496, 1455, 1406, 1356 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6 at 85 °C) δ: 7.38 – 7.34 (m, 2H), 7.30 – 7.26 (m, 3H), 4.54 (d, *J* = 15.4 Hz, 1H), 4.15 (d, *J* = 15.4 Hz, 1H), 3.80 – 3.72 (m, 2H), 3.69 – 3.63 (m, 3H), 3.55 (dd, *J* = 12.9, 6.5 Hz, 1H), 3.43 (dt, *J* = 8.4, 5.0 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 3.26 (td, *J* = 6.8, 2.9 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6 at 85 °C) δ: 165.6, 136.4, 128.0, 127.3, 126.7, 82.4, 81.3, 68.9, 66.2, 58.2, 57.5, 54.9, 52.2, 44.1; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{16}H_{21}NO_4Na$ 314.1368, found 314.1358;

3(*S*), 7(*S*), 8(*S*), 9(*S*)-3,9-*cis*-7,8-Dihydroxy-1-*N*-benzyl-5-oxa-2-one-bicyclo[2.0.5]nonane (29)

Compound **27** (0.170 g; 0.383 mmol) in ethyl alcohol (15 mL) and Pd (0.200 g, 10% on activated carbon) was stirred under hydrogen for 18 h. Subsequently the mixture was filtered through Celite and evaporated to afford colorless oil. Crude product was adsorbed on silica gel and purified by flash column chromatography (DCM / methanol 95 : 5) to give diol **29** (72 mg, 71.3%) as a colorless syrup; $[\alpha]_D$ = – 52.1 (*c* 1.0, MeOH); IR (film, DCM) ν_{max}: 3402, 2924, 1727, 1414, 1030, 701 cm^{-1}; ^1H NMR (600 MHz, toluene 80 °C) δ: 7.27 - 6.96 (m, 5H), 4.46 (d, *J* = 14.8 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.86 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.66 (dd, *J* = 12.1, 3.9 Hz, 1H), 3.30 (dd, *J* = 8.7, 8.7 Hz, 1H), 3.12 - 2.99 (m, 3H), 2.91 (ddd, *J* = 9.3, 9.3, 3.8 Hz, 1H), 2.82 (dd, *J* = 11.8, 9.8 Hz, 1H), 2.12 (bs, 1H, OH), 1.63 (bs, 1H, OH); ^{13}C NMR (150 MHz, toluene 80 °C) δ: 164.9, 137.2, 128.6, 127.7, 127.2, 76.1, 74.3, 70.5, 67.6, 56.8, 52.8, 45.2; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{14}H_{17}NO_4Na$ 286.1055; found 286.1072.

3(*S*), 7(*S*), 8(*S*), 9(*S*)-3,9-*cis*-7,8-Diacetoxy-1-*N*-benzyl-5-oxa-2-one-bicyclo[2.0.5]nonane (30)

Acetylation of **29** under standard condition gave **30** (89%) as white crystals m.p. 99 -101 °C; $[\alpha]_D$ = – 4.14 (*c* 1.0, DCM); IR (film, DCM) ν_{max}: 2930, 1749, 1370, 1238, 1037 cm^{-1}; ^1H NMR (600 MHz, toluene 80 °C) δ: 7.13 - 7.02 (m, 5H), 5.31 (dd, *J* = 9.0, 7.8, 1H), 4.75 (ddd, *J* = 9.1, 8.1, 3.5 Hz 1H), 4.58 (d, *J* = 15.4 Hz, 1H), 3.75 (d, *J* = 15.4 Hz, 1H), 3.72 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.60 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.37 - 3.30 (m, 2H), 3.23 (dd, *J* = 8.1, 2.5 Hz, 1H), 3.01 (ddd, *J* = 10.0, 5.3, 5.3 Hz, 1H), 1.60 (s, 3H), 1.57 (s, 3H); ^{13}C NMR, (150 MHz, toluene 80 °C) δ: 167.9, 167.8, 164.6, 136.2, 128.6, 128.5, 127.7, 73.7, 70.8, 70.6, 67.5, 54.3, 53.7, 44.6, 19.7, 19.5; HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{18}H_{21}NO_6Na$ 370.1267; found 370.1248.

3(S), 4(R)-*N*-Benzyl-3-carbonylmethoxymethyl-4-carbonyl-azetidin-2-one (33)

To compound **29** (50 mg, 0.190 mmol) in dry DCM (3 mL) Na_2CO_3 (24 mg, 0.228 mmol) was added. Subsequently the mixture was cooled to 0 °C and $Pb(OAc)_4$ (93 mg, 0.209 mmol) was added. The mixture was stirred for 1.5 h at 0 °C and 20 min at RT Subsequently AcOEt (1.5 mL) was added and the mixture was filtered through a pad of silica gel, washed with ethyl acetate and concentrated *in vacuo* to give the crude dialdehyde **33** (45 mg, 90%) as a colorless oil. $[\alpha]_D$ = + 2.66 (*c* 0.5, MeOH); IR (film, DCM) ν_{max}: 3372, 1735, 1571, 1415, 1285, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.62 (d, *J* = 1.7 Hz, 1H), 9.60 (bs, 1H), 7.38 - 7.23 (m, 5H), 4.66 (d, *J* = 14.9 Hz, 1H), 4.44 (d, *J* = 14.9 Hz, 1H), 4.09, 4.01 (ABq, *J* = 17.9 Hz, 2H), 4.02 (dd, *J* = 5.8, 1.7 Hz, 1H), 3.87 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.79 - 3.75 (m, 1H), 3.70 (dd, *J* = 10.3, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.7, 198.6, 165.7, 134.8, 129.1, 128.6, 128.3, 76.2, 65.3, 59.5, 55.6, 46.2; HRMS (ESI) *m/z*: [M + 2MeOH + Na]$^+$ calcd for $C_{16}H_{23}NO_6Na$ 348.1423; found 348.1427.

3(S),4(*R*)-*N*-Benzyl-3-methoxycarbonylmethoxymethyl-4-methoxycarbonlmetyl-azetidin-2-one (35)

$NaJO_4$ (52 mg, 0.242 mmol) was added to a solution of **29** (29 mg, 0.11 mmol) in a mixture of acetone/H_2O (10 : 1 v/v, 3 mL) $RuCl_3$ x H_2O (1.5 mg) was added to the resulting suspension, and the obtained brown mixture was stirred for 3 h. Next, the reaction mixture was diluted with acetone, filtered through Celite and evaporated to afford the crude diacid **34** as a colorless oil (32 mg).

To stirred solution of crude carboxylic diacid **34** (32 mg, 0.11 mmol) in a mixture of dichloromethane : methanol (1 : 1, v/v, 1 mL) and 2M hexane solution of $TMSCHN_2$ (0.165 ml, 0.331 mmol) was added dropwise until the yellow color persisted. The mixture was stirred for 30 min at RT and one drop of CH_3COOH was added. After 10 min the mixture was concentrated. The residue was purified on a silica gel column using hexane/ethyl acetate 4 : 1- 1: 2 v/v as eluent to afford **35** (9.4 mg 27%) as a colorless oil; $[\alpha]_D$ = - 48.3 (*c* 0.7, DCM); IR (film, DCM) ν_{max}: 2953, 1758, 1438, 1218, 1143, 703 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37 - 7.26 (m, 3H), 7.25 - 7.20 (m, 2H), 4.87 (d, *J* = 14.9 Hz, 1H), 4.18 (d, *J* = 14.9 Hz, 1H), 4.09 – 4.00 (m, 3H), 3.92 - 3.84 (m, 2H) 3.76 (s, 3H), 3.73 (s, 3H), 3.68 (ddd, *J* = 5.8, 5.8, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1, 169.7, 165.9, 134.8, 128.9, 128.5, 127.9, 68.5, 65.9, 54.4, 52.7, 52.3, 51.8, 45.3. HRMS (ESI) *m/z*: [M + Na] $^+$ calcd for $C_{16}H_{19}NO_6Na$ 344.1110; found 344.1104.

3(S), 4(R)-*N*-Benzyl-3-acetoxycarbonylmethoxymethyl-4-acetoxy-azetidin-2-one (36) and 3(S), 4(R)-*N*-Benzyl-3-formyloxymethyl-4-acetoxy-azetidin-2-one (37)

The crude diacid **34** (32 mg, 0.11 mmol) in dry DMF (0.480 mL) was treated with $Pb(OAc)_4$ (0.193 g, 0.436 mmol) and acetic acid (0.207 ml, 3.597 mmol). The mixture was stirred for 3 h and then the solvents were evaporated. The residue was treated with DCM (5 mL), filtered and evaporated. The crude product was purified by chromatography using hexane-AcOEt (first only

hexane and then 6:4 v/v as an eluent) to afford **36** (9.4 mg, 29.4%) and **37** (5.1 mg; 15.9 %), both as a colorless oils.

Compound **36**

$[\alpha]_D$ = + 31.1 (*c* 0.36, DCM); IR (film, DCM) ν_{max}: 3501, 2925, 1754, 1365, 1228, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.34 - 7.26 (m, 5H), 5.83 (d, *J* = 1.0 Hz, 1H), 5.22 (ABq, *J* = 6.3 Hz, 2H), 4.53 (d, *J* = 15.4 Hz, 1H), 4.27 (d, *J* = 15.4 Hz, 1H), 3.99 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.94 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.33 - 3.30 (m, 1H), 2.07 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 170.4, 165.6, 135.4, 128.7, 128.3, 127.7, 88.6, 78.8, 64.4, 58.0, 45.0, 29.7, 20.6; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{19}NO_6Na$ 344.1110; found 344.1114.

Compound **37**

$[\alpha]_D$ = + 29.3 (*c* 0.6, DCM); IR (film, DCM) ν_{max}: 3531, 2925, 1773, 1729, 1228, 1170 cm^{-1} ^1H NMR (600 MHz, $CDCl_3$) δ: 7.94 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.35-7.27 (m, 5H), 5.78 (d, *J* = 1.1 Hz, 1H), 4.54 (d, *J* = 15.0 Hz, 1H), 4.47 – 4.45 (m, 2H), 4.27 (d, *J* = 15.0 Hz, 1H), 3.45 -3.43 (m, 1H) 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5, 164.5, 160.1, 135.4, 128.7, 128.3, 127.9, 78.6, 58.4, 56.7, 45.1, 20.6; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{15}O_5Na$ 300.0848; found 300.0846.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

Financial support of this research by the National Science Centre (Poland), Grant OPUS 2015/17/B/ST5/01011 is gratefully acknowledged.

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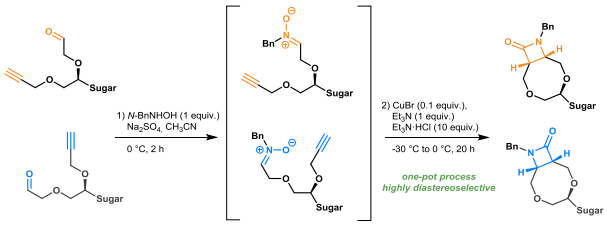
DOI: 10.1039/D0OB00228C



Intramolecular Kinugasa reactions on *in situ* generated carbohydrate-derived alkynylnitrones are described. Subsequent transformations of cycloadducts from alkynylnitrones followed by epimerization at the C-4 carbon atom led to the trans-substituted azetidinones with high stereoselectivity, mimicking variety of important β-lactam structures.