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Building blocks from monosaccharides for synthesis of scaffolds, including macrocycles. Application of allylic azide rearrangement, azide-alkyne cycloaddition and ring closing metathesis

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ABSTRACT
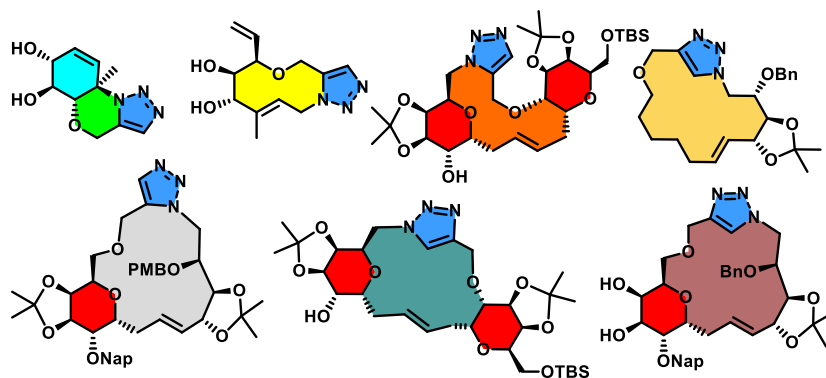
Synthesis of compounds with characteristics of natural products are required to increase the diversity and biological relevance of compounds for screening. These include new frameworks/scaffolds, with multiple stereogenic centres and various functional groups. Carbohydrates are renewable and are readily available with stereochemical diversity and functionality. Herein, building blocks derived from monosaccharides with alkene, alkyne and organic azide functional groups are used. The build-couple-pair strategy of diversity oriented synthesis was employed taking advantage of RuAAC, CuAAC and thermally promoted azide-alkyne cycloadditions, allylic azide (Winstein) rearrangement and ring closing metathesis, leading to polyhydroxylated small, medium and macrocyclic ring containing scaffolds. There is potential to graft appendages (e.g. pharmacophoric groups) to further increase diversity of compounds available for screening, or to consider the scaffolds in ligand design.

1. INTRODUCTION

Drug discovery and chemical biology rely on the identification of at least one hit compound for a target at an early stage.[1] Strategies for hit identification include structure based design, ligand design[2] or screening of chemical libraries,[3] with both synthetic and natural product research being sources of compounds, including providing inspiration for scaffold selection. In an analysis of over 24 million known compounds, Lipkus and co-workers showed that, as of 2008, as few as 143 scaffolds or frameworks accounted for ~50% of all known compounds, with frameworks tending to occur more frequently once reliable and relatively inexpensive synthesis had been established.[4]

As well, many synthetic compounds reported have different properties to those of drugs or natural products and may not be as biologically relevant.[5] The most recent Newman and Cragg analysis[6] has shown that in the area of anti-cancer drug discovery from 1981-2014 that 49% of the approved drugs are natural products or directly derived from them. Natural products are believed to be more successful in drug discovery, partly because they have 'privileged scaffolds'.[7] Many natural products are structurally complex (poly)cyclic rigid molecules, including macrocycles,[8] containing a variety of functional groups and multiple stereogenic centres as well as heteroatoms, such as oxygen or nitrogen that have evolved to have the capability to interact with protein targets.[9] As a consequence of such observations, there have been proposals, including from industry, for chemists to produce synthetically tractable 'natural product like compounds' as a basis to increase the diversity and biological relevance of chemical libraries.[10] These observations have inspired areas such as 'diverted total synthesis',[11] 'diversity oriented synthesis' and 'biology oriented synthesis',[12,13,14] all with a goal to improve the quality and quantity of hits for chemical biology and drug discovery.[15,16]

Carbohydrates are chiral, renewable, readily available precursors for synthesis, which are rich in stereogenic centres, with various functional groups and they are components of natural products of medicinal relevance.[17] They have been used as precursors in both natural product [18, 19] and scaffold [20] syntheses as well as in diversity oriented synthesis.[21,22,23] In earlier work we have used carbohydrate building blocks for synthesis of scaffolds that are appended with pharmacophoric groups, giving rise, for example, to multitargeting ligands for G-protein coupled receptors and the sodium channel (see chart 1).[24,25,26] In this paper, building blocks derived from carbohydrates, already available from other projects, were instead used to generate new appendable scaffolds. The 'build-couple-pair' strategy of diversity oriented synthesis was applied.[27] The building blocks had alkenes, alkynes and azides and the synthesis strategy included various types of azide alkyne cycloaddition, including the incorporation of allylic azide rearrangement and ring closing metathesis.
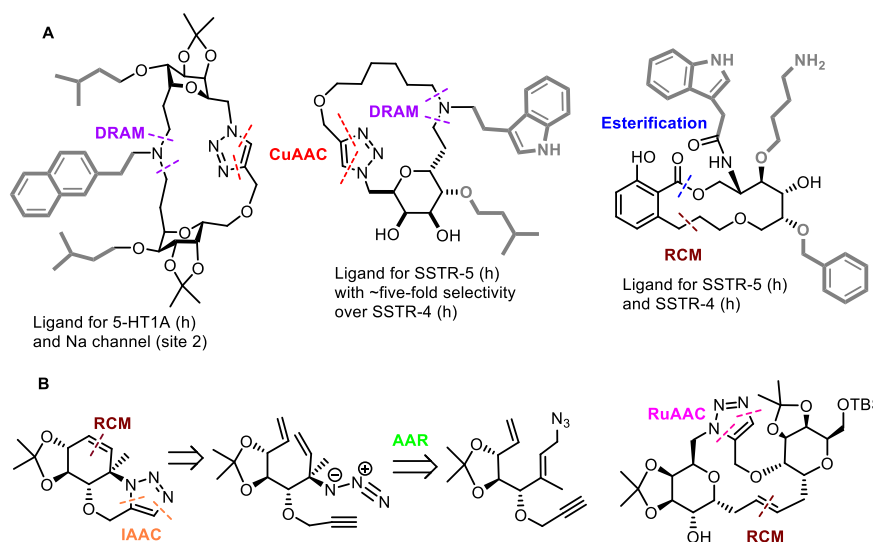

Chart 1: A. Previous work: Bioactive compounds with pharmacophoric groups (grey) appended to macrocyclic scaffold. Disconnections and key reactions used to generate the frameworks are indicated (DRAM = double reductive amination macrocyclization; CuAAC = copper catalysed azide-alkyne cycloaddition; RCM = ring closure metathesis). **B. Examples from this work:** Scaffolds prepared using RuAAC (ruthenium catalysed azide-alkene cycloaddition); IAAC (intramolecular azide alkyne cycloaddition) combined with AAR (allylic azide rearrangement) and RCM.

2.   RESULTS AND DISCUSSION

2.1   *Synthesis of building blocks (build)*

The use of building blocks containing at least two functional groups, drawn from that of alkene, alkyne and organic azide, was envisaged for the generation of frameworks. Compound **1**, derived from D-glucuronolactone,[28] was converted to **2**, containing the alkene and azide groups in addition to protected hydroxyl groups. Thus, reaction of **1** with *p*-methoxybenzyl chloride under basic conditions, then regioselective acetonide hydrolysis followed by oxidative cleavage of the resulting diol to an aldehyde and subsequent Wittig reaction gave **2** (Scheme 1). Intermediate **3** has been used in the synthesis of peptidomimetics based on macrocycles with embedded carbohydrates (MECs).[29] Here, propargylation of the free hydroxyl group of **3** gave building block **4** with alkene and alkyne groups. Also **3** was used to give **5** and **6** (Scheme 1), with these similarly containing alkene and alkyne groups. Aside from the napththylmethyl ether being a protecting group,[30,31] which can be removed in the presence of other benzyl like protecting groups, it is also pharmacophoric.[32]
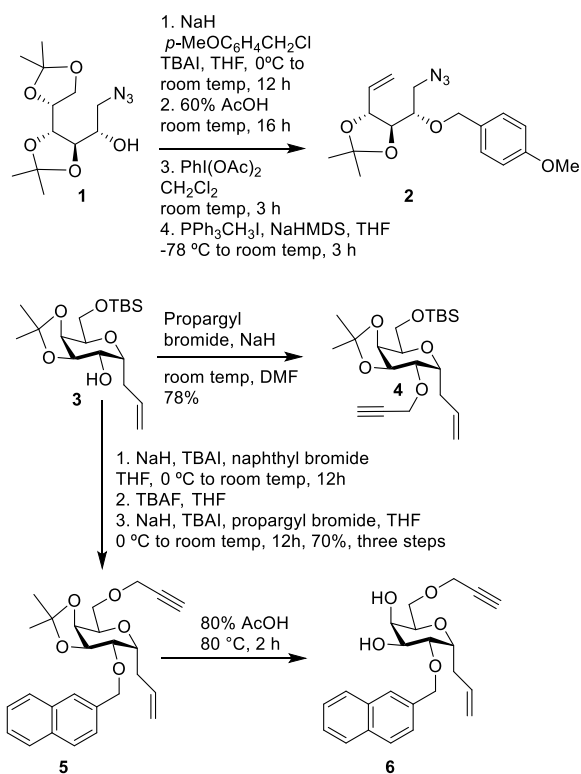
Scheme 1: Synthesis of building blocks **2**, **4** and **6**

Intermediate **7**, derived from methyl α-D-mannopyranoside was used previously in the synthesis of iminosugars with quaternary centres.[33] Here, a propargyl group was grafted to the 2-oxygen atom of **7** giving **8**, a building block with allylic azide, alkene and alkyne groups. A regioisomer of **8** was also generated from **9**, an intermediate used for the synthesis of **8**.[33] Thus, the TES and acetonide groups were first removed from **9** using TBAF-THF in aqueous acetic acid to give a triol. Then reaction of this triol with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid followed by propargylation, reduction of the ester and finally azidation gave **10** (Scheme 2).
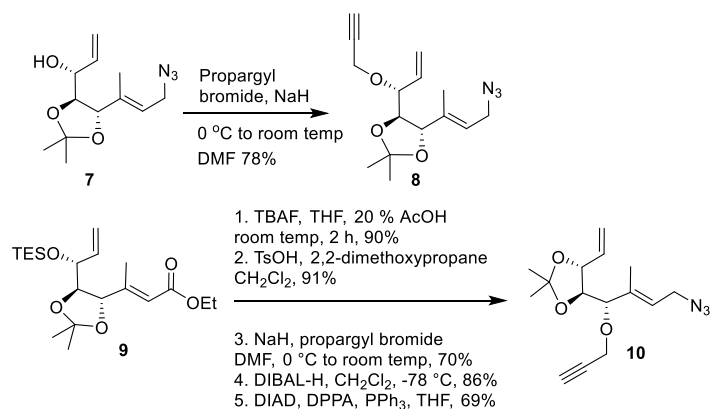
Scheme 2: Synthesis of **8** and **10**

2.2. Use of the saccharide building blocks in scaffold synthesis (couple and pair)

The joining together of two building blocks (couple) with azide and alkyne groups was envisaged by using either the ruthenium catalysed azide-alkyne cycloaddition (RuAAC)[34] or copper catalysed azide-alkyne cycloaddition (CuAAC)[35] to produce triazoles, to be followed by RCM[36] to effect cyclisation (pair). By having allylic azide functionality in both **8** and **10**, the possibility for incorporating Winstein rearrangement[37] in tandem with Huisgen cycloaddition for the new scaffold synthesis was included.

Reaction of intermediate **11**, (see experimental section for synthesis), with alkyne **12**,[29] in the presence of copper sulfate and sodium ascorbate gave a 1,5-triazole intermediate (67%) that after ring closing metathesis gave macrocycle **13** (64%) with *trans* alkene (Scheme 3).
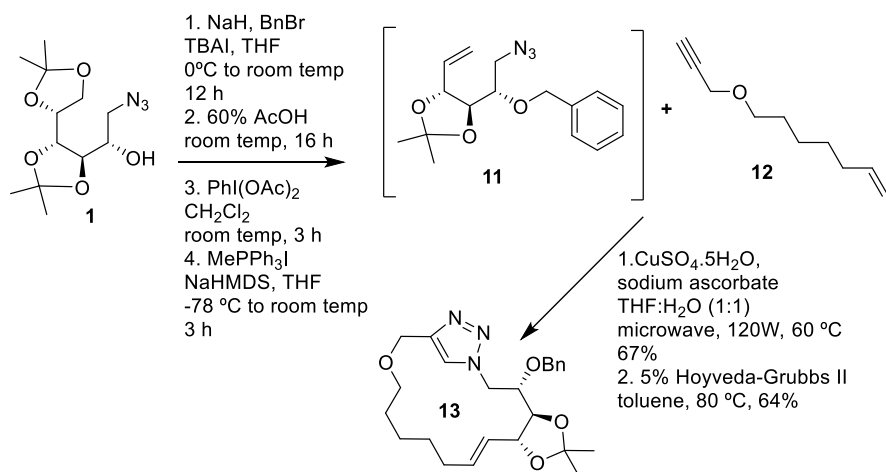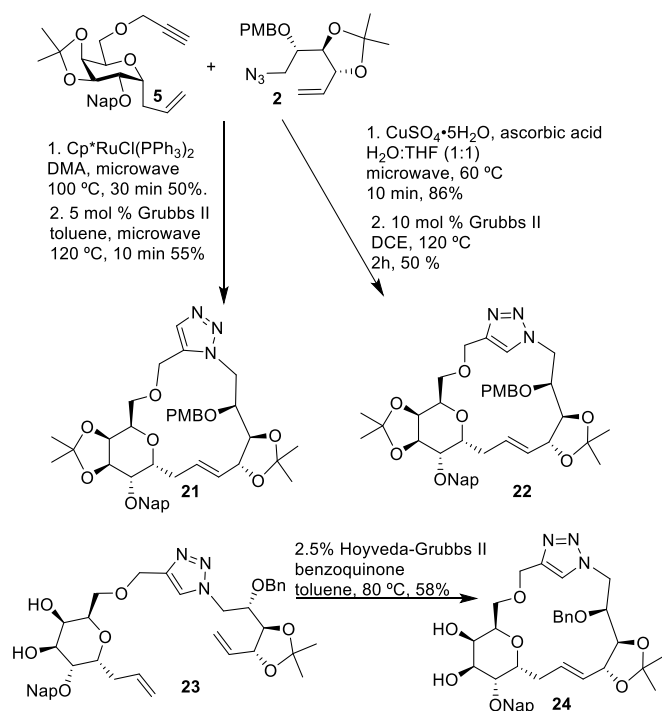
Scheme 3. Synthesis of **13**

Reaction of **4** with **14**,[29] previously used for the synthesis of macrocyclic peptidomimetics, either gave **15** or **16**, depending on whether RuAAC or CuAAC was used (Scheme 4). Ring closure metathesis using the Hoyveda-Grubbs II catalyst gave in the case of **15** a mixture of alkene stereoisomers **17** (**17-cis**:**17-trans** = 2:3). In contrast, the reaction from **16** gave the trans isomer **18** isolated as the major product. The protecting groups were removed from **17-trans** and **18** to give the new polyhydroxylated macrocycles **19** and **20**. The yield for removal of the TBS groups was low from **17**; this reaction has not been optimised. These MECs (macrocycles with embedded carbohydrates). They are digalactosyl derivatives and both α- and β-D-galactopyranose derivatives have been of interest, for example, as galectin inhibitors,[38] and could be screened against such lectin targets.

Pairing **2** and **5**, using either RuAAC or CuAAC (Scheme 5) and subsequent ring closure metathesis using the Grubbs II catalyst gave **21** and **22**. Precursor **23** was prepared from **11** and diol **6** using CuAAC. Subsequent RCM from **23** proceeded to give **26**, this time with the Hoveyda-Grubbs II catalyst in the presence of benzoquinone, the latter used to prevent or reduce alkene isomerisation during metathesis.[39]
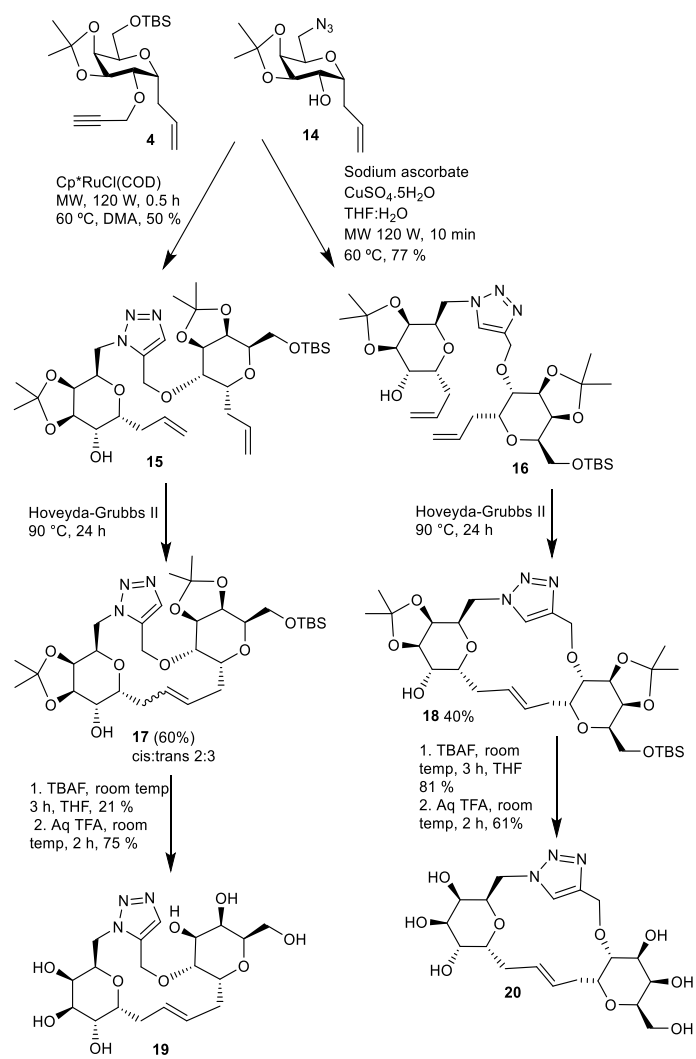
Scheme 4. Synthesis of MECs with two embedded galactopyranose residues.

Scheme 5 Synthesis of MECs with one embedded pyranose residue

Next, allylic azide rearrangement and intramolecular cycloaddition were combined for the generation of new scaffolds (Scheme 6 & 7). In this regard the thermally promoted reactions of regioisomers **8** and **10** were investigated. Reaction of **8** gave two isolated products, **25** and **26**. The imine **25** resulted from allylic azide rearrangement of primary azide **8** to tertiary azide **8a**, which then underwent thermally promoted azide-alkene cycloaddition to give triazoline intermediate **8b** and the latter's subsequent decomposition to the imine **25**. Formation of an imine is known to occur from triazolines, or alternatively, an aziridine intermediate is formed that can be trapped with nucleophiles.[40] The medium ten membered ring product **26** was formed directly from primary azide **8** by competitive intramolecular azide-alkyne cycloaddition. Determination of the crystal structure of **26** confirmed its structure. Removal of the acetonide under acidic conditions gave the diol **27**.

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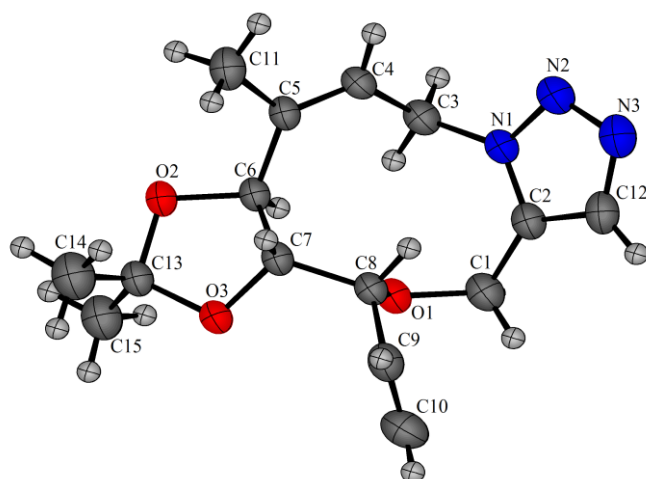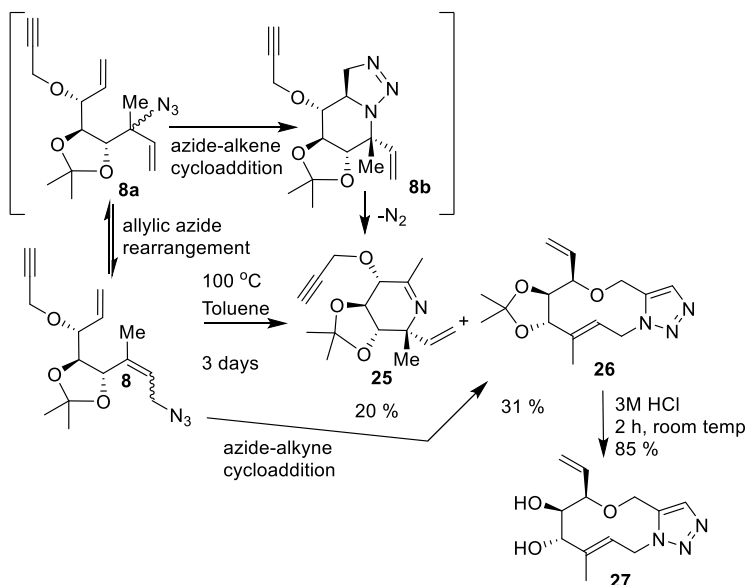
Scheme 6 Synthesis of medium ring **26** and **27**. Crystal structure of **26**

The thermally promoted reaction of **10** gave a mixture of dienes **28** and **29**, which have quaternary centers adjacent to a triazole nitrogen atom. Either intramolecular azide-alkene or azide-alkyne cycloaddition were possible from reaction of **10a**, formed via allylic azide rearrangement. However, triazole formation via alkyne-azide cycloaddition were clearly preferred. Ring closing metathesis from the major product **29** was investigated, and while occurring in low yield (not optimised), it did give rise to a product

with similarity to naturally occurring conduramine-A.[41] It is likely that the yield is low

due to steric hindrance caused by the quaternary centre adjacent to the alkene.
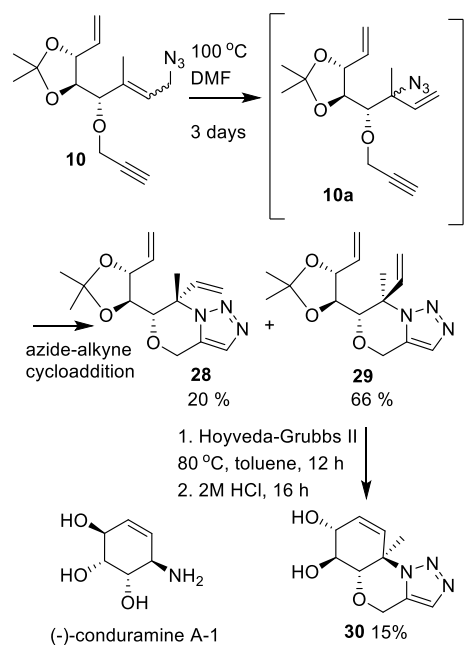
Scheme 7 Synthesis of **30** and structure of (-)-conduramine A-1

Other scaffolds generated herein can also be considered 'natural product like', if one

considers structures of frameworks found in eunicin[42] and ipomoeassin A (Chart 2), for

example. The latter, known as a resin glycoside, is a macrolactone with embedded

discaccharides, where the hydroxyl groups have appendages and it belongs to a family of
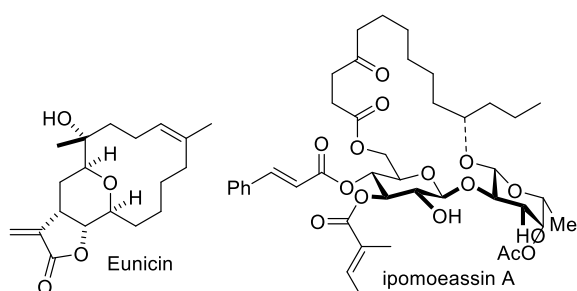
compounds with interesting cytotoxic properties.[43]

Chart 2. Structures of selected natural products

3. SUMMARY

Expanding the number and diversity of scaffolds or frameworks is desired in order to provide a basis for synthesis of new compounds for chemical biology and drug discovery.[44] We have demonstrated herein, the synthesis of a set of (poly)cyclic functionalised scaffolds via intermediates derived from carbohydrates.[45] The reactions chosen to generate the scaffolds, such as allylic azide rearrangement used in tandem with various types of cycloaddition, or CuAAC/RuAAC followed by metathesis, have led to small to medium to macrocyclic ring containing products. The frameworks generated incorporate features of natural products (rigidity, complexity, chirality, scaffold diversity, increased aliphatic content, stereogenic centres, increased oxygen content). They are appendable, meaning pharmacophoric groups can be attached via the hydroxyl groups.[46] This is facilitated by regioselectively protected carbohydrate precursors, which will allow further chemical modification of the framework in due course. Although macrocycles, like many natural products, do not often fit within the Lipinski 'rule of 5' for drug-likeness[47] they are still finding application as drugs or as tools for research. Macrocycles with embedded carbohydrates with pharmacophoric appendages were reported recently and were used to develop multitargeting ligands for protein receptors.[29] To conclude, carbohydrate derived intermediates can be used to generate new frameworks, providing a strategy that can be considered in medicinal chemistry projects and topics such as structure and ligand based design.[48]

4. EXPERIMENTAL SECTION

General: NMR spectra were recorded with 500 MHz Varian spectrometers. Chemical shifts are reported relative to internal Me$_4$Si in CDCl$_3$ (δ 0.0) or CHCl$_3$ (δ 7.26) HOD for D$_2$O (δ 4.84) or CD$_2$HOD (δ 3.31) for ^{1}H and CDCl$_3$ (77.16) or CD$_3$OD (49.05) for ^{13}C

NMR spectra were processed and analysed using MestReNova software. ^{1}H-NMR signals were assigned with the aid of gCOSY. ^{13}C-NMR signals were assigned with the aid of APT, gHSQCAD and/or gHMBCAD. Coupling constants are reported in Hertz, with all J values reported uncorrected. Low- and high-resolution mass spectra were measured on a Waters LCT Premier XE Spectrometer, measuring in both positive and/or negative mode as, using MeCN, H_2O and/or MeOH as solvent. Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel 60 (HF254, E. Merck) and spots visualized by UV and charring with H_2SO_4-EtOH (1:20), cerium molybdate or phosphomolybdic acid staining agents. Flash chromatography was carried out with silica gel 60 (0.040-0.630 mm, E. Merck or Aldrich) and using a stepwise solvent polarity gradient (starting with the conditions indicated in each case and increasing the polarity as required), correlated with TLC mobility. Chromatography solvents, cyclohexane, EtOAc, CH_2Cl_2 and MeOH were used as obtained from suppliers (Fisher Scientific and Sigma-Aldrich). Anhydrous pyridine and DMF were purchased from Sigma Aldrich with other dried solvents (methanol, THF, dicholoromethane, toluene, diethyl ether) being used as obtained after treating with Pure Solv™ Solvent Purification System. Purity of compounds synthesised may be qualitatively assessed by examination of NMR spectra provided in the supporting information. Well known impurities in NMR spectra were identified on the basis of previously reported NMR data[49] and where possible these are labelled on the spectra in supporting information. Unidentified components are also indicated. The yields calculated are maximum yields based on the weight of the final substance reported and may contain impurities as can be evaluated by examination of the spectra.

(4S,5R)-4-((S)-2-Azido-1-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane 2   To a stirred solution of **1** (9.52 g, 33.1 mmol) in anhydrous THF (66 mL, 0.5 M) at 0 ºC was added NaH (60 % in mineral oil, 1.19 g, 49.7 mmol) portion wise, and the suspension was stirred at this temperature for 30 min. Then PMBCl (46 mmol, 6.3 mL) and TBAI (1.1 g, 3.3 mmol) were added sequentially at 0 ºC, and the resulting mixture was stirred at 25 ºC for 16 h under argon. Satd aq NH_4Cl was added and the resulting mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc) of the residue gave the PMB derivative, which was used in the next step without further purification; ESI-HRMS: calcd for $C_{16}H_{23}N_3O_5Na$ $[M + MeCN + Na]^+$ 471.2220; found 471.2228. The PMB derviative (5.36 g, 13.2 mmol) was then dissolved in 60% AcOH (50 mL) and the mixture was stirred at room temp for 15 h. The mixture was neutralized with satd aq $NaHCO_3$ (20 mL) and 1M NaOH (30 mL), and then extracted with CH_2Cl_2 (3 x 20 mL). The organic portions were combined and washed with brine (25 mL), dried over Na_2SO_4 and the solvent was removed under reduce pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 1:1) gave the desired diol intermediate (2.44 g, 50 %) as a green pale oil. To this diol (1.9 g, 5.2 mmol) in CH_2Cl_2 (52 mL) was added $PhI(OAc)_2$ (2.0 g, 6.2 mmol). The mixture was stirred at room temperature for 3 h and then the solvent was removed at reduced pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 1:1) gave the intermediate aldehyde (1.6 g, 91 %) as a yellow oil. To a cooled solution of methyltriphenylphosphonium iodide (Ph_3PCH_3I, 2.5 g, 6.2 mmol) in anhydrous THF (69 mL) at -78 °C was added 1.0 M NaHMDS solution (5.8 mL, 5.8 mmol) dropwise and stirring was continued at -78 °C for 25 min followed by 15 min at 0 °C and a further 30 min at room temperature under argon

atmosphere. The mixture was cooled again to -78 °C and the intermediate aldehyde (1.5 g, 4.4 mmol) in anhydrous THF (40 mL) was then added dropwise via syringe. The mixture was then stirred at -78 °C for 10 min and stirring was continued at room temp for a further 2 h under argon atmosphere. The mixture was quenched by the addition of water (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layer dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 9:1) gave **2** (810 mg, 55%) as a green pale oil; δ ^1H NMR (500 MHz, chloroform-d) δ 7.49 – 7.06 (overlapped signals, 2H, aromatic H), 6.96 – 6.77 (overlapped signals, 2H, aromatic H), 5.77 (ddd, J = 16.5, 10.8, 7.4 Hz, 1H, alkene H), 5.20-5.23 (2H, overlapped signals, alkene H), 4.69 (d, J = 11.5 Hz, 1H, benzyl C*H*(H)), 4.59 (d, J = 11.4 Hz, 1H, benzyl CH(*H*)), 4.29 (t, J = 7.8 Hz, 1H), 3.84 – 3.76 (overlapped signals, 5H), 3.57 (ddd, J = 6.3, 5.3, 4.0 Hz, 1H), 3.42 (dd, J = 5.9, 3.5 Hz, 2H), 1.42 (s, 3H, C*H₃*), 1.41 (s, 3H, C*H₃*); ^{13}C NMR (126 MHz, chloroform-*d*) δ 159.5 (C), 135.2 (CH, 2C), 129.8 (CH, 2C), 129.7 (C), 119.2 (alkene CH_2), 113.8 (CH), 109.4 (C), 80.7 (CH), 78.3 (CH), 75.6 (CH), 73.0 (CH_2), 55.3 (OCH_3), 51.7 (CH_2), 29.7 (CH_3), 26.9 (CH_3); ESI-HRMS: Calcd for $C_{17}H_{24}N_3O_4$ $[M+H]^+$ 334.1767; found 334.1780.

1-Allyl-1-deoxy-6-*O*-dimethyl-tert-butylsilyl-2-*O*-propargyl-3,4-O-isopropylidene-α-D-galactopyranose 4. To **3** (0.35 g, 0.96 mmol) in dry DMF (10 mL) was added NaH (60% dispersion on mineral oil, 153 mg, 3.84 mmol) and the mixture was stirred at room temp for 0.5 h. To this was added propargyl bromide (0.33 mL, 3.84 mmol) and the mixture stirred for a further 1 h. Then MeOH (5 mL) was added and stirring was continued for 5 min and EtOAc was added. The mixture was washed with H_2O, brine, filtered and the solvent was removed under reduced pressure. Flash chromatography (cyclohexane-EtOAc 9:1) gave the title compound **4** (363 mg, 95 %) as a yellow oil; δ

^{1}H NMR (500 MHz, chloroform-d) δ 5.82 (ddt, J = 17.1, 10.3, 6.9 Hz, 1H), 5.13 (dd, J = 17.1, 1.9 Hz, 1H), 5.06 (dd, J = 10.3, 1.8 Hz, 1H), 4.37 (dd, J = 7.0, 1.8 Hz, 1H), 4.33 (dd, J = 7.0, 3.7 Hz, 1H), 4.28 (d, J = 2.4 Hz, 2H), 4.05 (ddd, J = 7.8, 6.5, 3.0 Hz, 1H), 3.92 (ddd, J = 7.8, 5.8, 1.8 Hz, 1H), 3.76 (dd, J = 9.7, 7.9 Hz, 1H), 3.71 (dd, J = 9.6, 5.7 Hz, 1H), 3.64 (t, J = 3.4 Hz, 1H). 2.43 (1H, t, J =2.3 Hz, alkyne CH), 2.38 – 2.33 (2H, overlapped signals, CH$_2$CH=CH_2), 1.50 (3H, s, isopropylidene CH$_3$), 1.34 (3H, s, isopropylidene CH$_3$), 0.06 (6H, d, J = 1.9 Hz, each SiCH$_3$); ^{13}C-NMR (126 MHz, chloroform-d) δ 134.5 (CH$_2$$C$H=CH$_2$), 117.1 (CH$_2$CH=$CH_2$), 109.1 (isopropylidene C), 79.7 (alkyne CH), 75.9 (C-2), 74.7 (alkyne C), 72.2 (C-4), 72.1 (C-3), 70.9 (C-1), 69.5 (C-5), 62.4 (C-6), 57.7 (alkyne CH$_2$), 34.0 (CH$_2$CH=CH$_2$), 27.1, 25.9, 24.8 (each CH$_3$), 18.3 (C), -5.4, -5.5 (each SiCH$_3$); ESI-HRMS: calcd. for C$_{21}$H$_{37}$O$_5$Si, 397.2369; found m/z 397.2386 [M+H]$^+$; FT-IR 3307, 2930, 1472, 1257, 1085, 834, 737 cm^{-1}.

3-[2-O-(2-Naphthylmethyl)-3,4-O-isopropylidene-6-O-propargyl-α-D-galactopyranosyl]-1-propene 5 The reaction of **3** (5.22 g, 14.6 mmol), NaH (60 % in mineral oil, 520 mg, 21.8 mmol), 2-(bromomethyl)naphthalene (4.50 g, 20.4 mmol), TBAI (470 mg, 1.45 mmol) in anhydrous THF (29 mL), as described earlier for the preparation of **2**, gave, after flash column chromatography (silica gel, petroleum ether-EtOAc, 19:1), the title compound **5** (5.80 g, 80%) as a yellow oil. Flash column chromatography (silica gel, petroleum ether:EtOAc) gave the corresponding alcohol and to this intermediate (5.78 g, 11.6 mmol) in anhydrous THF (116 mL) TBAF (1.0 M in THF, 23.2 mmol, 23.2 mL) was added and the mixture stirred for 16 h under argon. Water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 6:4) gave

the desired alcohol intermediate (4.0 g, ~95 %) as a colorless oil. Reaction of this intermediate (3.96 g, 11.4 mmol), NaH (60 % in mineral oil, 409 mg, 17.0 mmol), propargyl bromide (16 mmol, 1.4 mL) and TBAI (37 mg, 0.11 mmol) in anhydrous THF (22.7 mL) as described in the methoxybenzylation of **1** gave the title compound (4.1 g, 92 %) as a yellow oil after flash column chromatography (silica gel, petroleum ether-EtOAc, 8.5:1.5); ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.86-7.81 (overlapped signals, 3H, aromatic H), 7.77 (br s, 1H, aromatic H), 7.51-7.43 (overlapped signals, 3H, aromatic H), 5.74 (dddd, *J* = 16.9, 10.2, 7.5, 6.4 Hz, 1H, C*H*=CH$_2$), 5.10-4.97 (overlapped signals, 2H, CH=C*H*$_2$), 4.86 (d, *J* = 12.2 Hz, 1H, C(H)*H*Ph), 4.70 (d, *J* = 12.2 Hz, 1H, C(H)*H*Ph), 4.42 (dd, *J* = 7.3, 3.3 Hz, 1H, H-3), 4.33 (dd, *J* = 7.3, 1.8 Hz, 1H, H-4), 4.27-4.16 (overlapped signals, 3H), 4.06 (td, *J* = 7.3, 3.3 Hz, 1H, H-1), 3.73 (dd, *J* = 9.8, 5.9 Hz, 1H, H-6a), 3.67 (dd, *J* = 9.8, 6.6 Hz, 1H, H-6b), 3.58 (t, *J* = 3.3 Hz, 1H, 2-H), 2.48-2.35 (overlapped signals, 3H, C*H*$_2$-CH=CH$_2$, C≡C*H*), 1.47 (s, 3H, Me), 1.34 (s, 3H, Me); ^{13}C NMR (126 MHz, chloroform-*d*) δ 135.3 (C), 134.5 (CH), 133.2 (C), 133.0 (C), 128.2, 127.9 (CH), 127.7 (CH), 126.5 (CH), 126.1 (CH), 125.9 (CH), 125.7 (CH), 117.2 (C), 109.5 (CH), 79.8 (C), 75.6 (CH), 74.4 (C), 72.9 (CH$_2$), 72.6 (CH), 71.8 (CH), 71.1 (CH), 69.9 (CH$_2$), 68.4 (*C*≡CH), 58.6 (CH$_2$), 34.7 (CH$_2$), 26.9 (CH$_3$), 24.8 (CH$_3$); ESI-HRMS: calcd for C$_{26}$H$_{34}$NO$_5$ [M + NH$_4$]$^+$ 440.2437; found 440.2426.

3-[2-O-(2-Naphthylmethyl)-6-O-propargyl-α-D-galactopyranosyl]-1-propene 6

Propene **5** (201 mg, 0.475 mmol) was dissolved in 80% AcOH and the solution was stirred at 80°C for 2 h. The solvent was removed under reduced pressure and flash chromatography of the residue (petroleum ether-EtOAc, 1:1) gave the title compound **6** as a white solid (145 mg, 0.38 mmol, 80%); ^{1}H NMR (500 MHz, chloroform-d): δ 7.86 – 7.81 (overlapped signals, 3H, aromatic H), 7.77 (s, 1H, aromatic H), 7.51 – 7.44

(overlapped signals, 3H, aromatic H), 5.81 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H, CH=CH$_2$),

5.14 – 5.06 (overlapped signals, 2H, CH=CH_2), 4.79 (d, J = 11.7 Hz, 1H, OCHHAr), 4.74

(d, J = 11.8 Hz, 1H, OCHHAr), 4.24 – 4.14 (overlapped signals, 3H, H-1 and CH_2C≡CH),

4.07 – 4.05 (br signal, 1H, H-4), 3.92 (dd, J = 9.3, 5.6 Hz, 1H, H-2), 3.85 – 3.75

(overlapped signals, 3H, H-3, H-5 and H-6a), 3.71 (dd, J = 9.4, 5.2 Hz, 1H, H-6b), 2.73

(d, J = 4.1 Hz, 1H, 4-OH), 2.68 (d, J = 3.0 Hz, 1H, 3-OH), 2.50 – 2.38 (overlapped signals,

3H, CH_2CH=CH$_2$ and CH$_2$C≡CH); ^{13}C NMR (125 MHz, chloroform-d): δ 135.2 (C),

134.6 (CH), 133.2 (C), 133.1 (C), 128.4 (CH), 127.9 (CH), 127.7 (CH), 126.8 (CH), 126.3

(CH), 126.1 (CH), 125.7 (CH), 117.1 (CH$_2$), 79.3 (C), 76.7 (CH), 74.8 (CH), 73.5 (CH),

72.9 (CH), 69.6 (CH), 69.4 (2s, 2x CH and CH$_2$), 58.7 (CH$_2$), 29.6 (CH$_2$); ESI-HRMS:

Found 405.1686 required 405.1678 [M+Na]$^+$.

(4S,5S)-4-((E)-4-azidobut-2-en-2-yl)-2,2-dimethyl-5-((R)-1-(prop-2-ynyloxy)allyl)-

1,3-dioxolane 8   Alcohol **7** (1.0 g, 4.0 mmol) in anhydrous DMF was cooled to 0 °C

and NaH (0.2 g, 60% in mineral oil, 5.1 mmol) charged portion wise and the mixture was

stirred for 30 min and propargyl bromide (0.8 mL, 80 wt. % in toluene, 7.10 mmol) then

added. The reaction mixture was allowed attain room temp and stirred for 16 h. Et$_2$O was

added and the mixture was then washed with satd aq NH$_4$Cl. The organic layer was

separated, dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced

pressure. Flash chromatography (hexane-EtOAc, 4:1) afforded alkyne **8** (0.92 g, 80 %)

as a clear oil; R$_f$ = 0.51 (hexane-EtOAc, 4:1); ^{1}H NMR (500 MHz, chloroform-d) δ 5.77-

5.68 (overlapped signals, 2H), 5.40 – 5.34 (overlapped signals, 2H), 4.48 (d, J = 8.2 Hz,

1H), 4.29 (dd, J = 16.0, 2.5 Hz, 1H), 4.09 (dd, J = 16.2, 2.2 Hz, 1H), 4.05 (dd, J = 8.4, 4.3

Hz, 1H), 3.89 (dd, J = 14.0, 7.7 Hz, 1H), 3.83 (ddd, J = 8.2, 4.2 Hz, 1H), 3.77 (dd, J =

14.0, 6.7 Hz, 1H); 2.42 (t, 2.4 Hz, 1H), 1.74 (s, 3H, CH$_3$), 1.45 (s, 6H, C(CH$_3$)$_2$); ^{13}C

NMR (126 MHz, chloroform-d) δ 138.4 (alkene C), 133.7 (alkene CH), 122.9 (alkene

CH), 120.7 (alkene CH$_2$), 109.6 (*C*(CH$_3$)$_2$), 81.7 (CH), 80.7 (CH), 79.6 (alkyne C), 78.1 (CH), 74.5 (alkyne CH), 55.2 (CH$_2$), 47.7 (CH$_2$), 27.1 (C(*C*H$_3$)$_2$), 26.9 (C(*C*H$_3$)$_2$), 11.8 (CH$_3$); ESI-HRMS: m/z calc for C$_{15}$H$_{22}$N$_3$O$_3$: 292.1661 found: 292.1665 [M+H]$^+$.

(4S,5R)-4-((S,E)-4-Azido-2-methyl-1-(prop-2-ynyloxy)but-2-enyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane 10   To compound **9** (2.12 g, 5.51 mmol) in anhydrous THF (40 mL), TBAF (11.0 mL, 1 M in THF buffered with 20 % AcOH) was charged slowly and the mixture was stirred at room temp for 2 h, followed by the addition of pH 7 buffer (30 mL). The aqueous layer was then extracted with EtOAc and the combined organic layers were then dried over Na$_2$SO$_4$, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexane, 3:7) afforded alcohol intermediate (1.3 g, 90 %) as a clear oil (R$_f$ = 0.63, EtOAc-hexane, 3:7). This alcohol (1.25 g, 4.62 mmol) was dissolved in 2M HCl (10 mL) and the mixture stirred at room temp for 1 h. The solution was extracted with EtOAc, dried over Na$_2$SO$_4$, filtered and solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded the required triol (0.88 g, 82 %) as a clear oil (R$_f$ = 0.53 (hexanes-EtOAc, 7:3)). The triol (2.67 g, 11.6 mmol) was dissolved in CH$_2$Cl$_2$ (30 mL). The solution was cooled to 0 ˚C and *p*-TsOH (0.4 g, 2.3 mmol) added. After stirring for 10 mins, 2,2-dimethoxypropane (2.85 mL, 23.2 mmol) was added. The reaction mixture was subsequently stirred at room temp for 15 mins and triethylamine (1.60 mL, 11.6 mmol) charged. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 7:3) afforded the needed isopropylidene intermediate (2.85 g, 91 %) as a clear oil. This oil (0.93 g, 3.4 mmol) was dissolved in anhydrous DMF (30 mL). The solution was cooled to 0 °C and NaH (190 mg, 60% in mineral oil, 4.8 mmol) charged portionwise. The reaction mixture was stirred for a further 30 min and propargyl bromide (0.7 mL, 80 wt. % in toluene, 6.2 mmol)

added, reaction mixture warmed to rt and stirred for 4 h. The solution was quenched with satd. NH_4Cl (aq), extracted with EtOAc, dried over Na_2SO_4, filtered & solvent removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 4:1) gave the desired alkyne (0.74 g, 70 %) as a clear oil; R_f 0.4 (hexanes-EtOAc, 4:1); ESI-HRMS: m/z calc for $C_{18}H_{29}O_6$: 341.1964, found 341.1971 $[M+H+CH_3OH]^+$. This alkyne (0.40 g, 1.3 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to -78 °C and DIBAL-H (3.9 mL, 1M in THF, 3.9 mmol) was charged slowly. The solution was then stirred at -78 °C for 4 h and the mixture was subsequently quenched with the slow addition of MeOH. The solution was warmed to room temp and stirred with potassium tartrate (aq) until clear. The organic layer was separated and subsequently washed with H_2O, dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the desired primary alcohol (0.3 g, 86 %) as a clear oil; ESI-HRMS: m/z calc for $C_{15}H_{21}O_4$: 265.1440, found 265.1436 $[M-H]^-$. Finally, this alcohol (0.3 g, 1.1 mmol) was dissolved in anhydrous THF (6 mL) and PPh_3 (0.53 g, 1.92 mmol) charged. The solution was cooled to 0 °C, followed by the addition of DIAD (0.38 mL, 1.92 mmol) and DPPA (0.4 mL, 1.9 mmol). The reaction mixture was adjusted to room temp and stirred for a further 12 h. The solvent was then removed under reduced pressure. Flash chromatography (hexanes-EtOAc, 10:1) gave the azide **10** (220 mg, 69 %) as a clear oil; R_f = 0.75 (EtOAc-hexanes, 1:4); FTIR 3414, 2983, 1712, 1654, 1372, 1214, 1151, 1097, 1040, 994, 928, 873, 764 cm^{-1}; ^1H NMR (500 MHz, chloroform-d): δ 5.77 (ddd, J = 17.4, 10.3, 7.4 Hz, 1H, alkene H), 5.69 (t, J = 7.1 Hz, 1H, alkene H), 5.34 (d, J = 17.1 Hz, 1H, alkene H), 5.25 (d, J = 10.3 Hz, 1H, alkene H), 4.31 − 4.24 (overlapped signals, 2H), 4.07 − 3.98 (overlapped signals, 2H), 3.92 (dd, *J* = 14.1, 7.2 Hz, 1H), 3.85 (dd, J = 8.1, 6.2 Hz, 1H), 3.79 (dd, J = 14.1, 6.9 Hz, 1H), 2.42 (t, J = 2.4 Hz, 1H), 1.66 (s, 3H, CH_3), 1.46 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (126 MHz, chloroform-d) δ 137.5 (alkene C), 135.4 (alkene

CH), 124.2 (alkene CH), 119.1 (alkene CH_2), 109.6 ($C(CH_3)_2$), 83.1 (CH), 81.2 (CH), 79.2 (alkyne C), 79.1 (CH), 74.7 (alkyne CH), 55.4 (CH_2), 47.7 (CH_2), 27.0 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 12.8 (CH_3); ESI-HRMS: m/z calc for $C_{15}H_{22}O_3N_3$: 292.1661, found 292.1650 $[M+H]^+$.

(3S,4S,5R,E)-3-(Benzyloxy)-4,5-O-isopropylidene-13-oxa-1,16,17-triazabicyclo[13.2.1]octadeca-6,15(18),16-triene-4,5-diol 13   The benzylation of **1** using benzyl bromide, and subsequent reactions as described for the preparation of **2** gave (4S,5R)-4-((S)-2-azido-1-(benzyloxy)ethyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane as a clear oil (140 mg, 0.46 mmol, 46%); ^{13}C NMR (125 MHz, chloroform-d): δ 137.6 (C), 135.2 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 119.3 (CH_2), 109.4 (C), 80.7 (CH), 78.3 (CH), 76.1 (CH), 73.3 (CH_2), 51.7 (CH_2), 26.9 (CH_3), 26.8 (CH_3). To this azide (54 mg, 0.178 mmol) and 7-O-propargyl-hept-1-ene **12**[29] (54 mg, 0.36 mmol) in THF:H_2O (1:1, 3mL), in a microwave vial was added copper sulphate pentahydrate (18 µL of a 0.2 M solution, 0.0036 mmol) and sodium ascorbate (4 mg, 0.02 mmol). The mixture was stirred in a microwave (120 W, 60 °C) for 15 mins and then diluted with EtOAc. The layers were separated and the organic layer washed with brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether-EtOAc, 3:1 to 1:1) of the residue gave 1,4-triazole as a clear oil (53 mg, 0.12 mmol, 67%). A solution of this intermediate (10 mg, 0.022 mmol) in dry, degassed toluene (10 mL) in an oven dried, two necked round bottomed flask, equipped with a reflux condenser, was stirred under N_2. The solution was heated to 80 °C and the 2nd generation Hoveyda-Grubbs II catalyst (3 mg, 0.005 mmol) in dry, degassed toluene (0.3 mL) was added via cannula. The solution was stirred for 6 h after which the solvent was removed under reduced pressure. Flash chromatography (cyclohexane-EtOAc, 3:1 to 1:1) gave **13**

as a clear oil (6 mg, 64%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.45 (s, 1H, triazole H), 7.40-7.33 (overlapped signals, 5H, phenyl H), 5.07-5.04 (overlapped signals, 2H, alkene H), 4.90 (d, J = 12.1 Hz, 1H, OC*H*HPh), 4.71 (overlapped signals, 2H), 4.67 (d, J = 12.1 Hz, 1H, OCH*H*Ph), 4.62 (d, J = 13.4 Hz, 1H, OC*H*H-triazole), 4.56 (d, J = 13.4 Hz, 1H, OCH*H*-triazole), 4.14-4.10 (m, 1H), 3.47-3.39 (overlapped signals, 2H), 3.37 (td, J = 6.1, 1.3 Hz, 1H), 3.33 (dd, J = 8.4, 1.3 Hz, 1H), 1.95-1.83 (overlapped signals, 2H), 1.47 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$), 1.41-1.34 (overlapped signals, 2H), 1.28-1.19 (m, 1H), 1.16 – 1.07 (m, 1H), 0.91 – 0.74 (overlapped signals, 2H); ^{13}C NMR (125 MHz, chloroform-d): δ 146.8 (C), 136.6 (C), 134.3 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 127.4 (CH), 122.7 (CH), 109.8 (C), 80.7 (CH), 76.6 (CH), 73.1 (CH), 72.2 (CH$_2$), 69.3 (CH$_2$), 63.4 (CH$_2$), 49.7 (CH$_2$), 31.6 (CH$_2$), 29.3 (CH$_2$), 27.3 (CH$_2$), 27.2 (CH$_3$), 26.6 (CH$_3$), 25.3 (CH$_2$); ESI-HRMS: Found 462.2150 required 462.2160 [M+Cl]$^-$.

(3aS,4R,6R,7S,7aR)-6-Allyl-4-((5-(((3aS,4R,6R,7S,7aR)-6-allyl-4-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol 15. To compounds **4** (170 mg, 0.44 mmol) and **14** (130 mg, 0.44 mmol) in DMA (2 mL) was added Cp*RuCl(COD) (33 mg, 0.088 mol). The mixture was transferred to a microwave via, which was sealed and placed in a microwave reactor for 30 min at 60 °C and 120 W. The mixture was then diluted with Et$_2$O, washed with H$_2$O, brine, dried over Na$_2$SO$_4$, filtered and the solvent removed under reduced pressure. Flash chromatography (cyclohexane-EtOAc 2:1) gave **15** (125 mg, 43 %) as a colourless oil; ^{1}H NMR (500 MHz, chloroform-d): δ 7.60 (1H, s, triazole H), 5.75 – 5.63 (2H, overlapped signals, 2 CH$_2$C*H*=CH$_2$), 5.08 – 4.98 (4H, overlapped signals, each CH$_2$CH=C*H$_2$*), 4.92 (1H, d, J = 12.6), 4.61 (2H, overlapped signals), 4.52-4.45 (2H, overlapped signals), 4.37 (1H, dd, J = 6.9, 1.8 Hz, galactose H-4), 4.28-4.33 (2H,

overlapped signals, galactose H-3 signals), 4.26 (1H, dd, J = 7.4, 1.7, galactose H-4), 4.04 (1H, td, J = 7.8, 7.4, 2.8 Hz, anomeric H), 4.00 (td, J = 7.5, 7.0, 3.0 Hz, anomeric H), 3.90 (1H, ddd, J = 7.7, 5.8, 1.8 Hz, galactose H-5), 3.82 (1H, q, J = 3.4 Hz), 3.76 (1H, dd, J = 9.6, 7.9 Hz, galactose H-6), 3.70 (1H, dd, J = 9.6, 5.8 Hz, galactose H-6), 3.46 (1H, t, J = 3.6 Hz, galactose H-2), 2.33 (1H, ddd, J = 14.4, 8.2, 6.4 Hz, allylic H), 2.28 – 2.16 (3H, overlapped signals), 2.08 (1H, d, J = 4.3 Hz, OH), 1.53 (3H, s, isopropylidene CH$_3$), 1.47 (3H, s, isopropylidene CH$_3$), 1.35 (3H, s, isopropylidene CH$_3$), 1.33 (3H, s, isopropylidene CH$_3$), 0.89 (9H, s, t-Bu), 0.06 (2 x s, 6H, CH$_3$); ^{13}C NMR (126 MHz, chloroform-d) δ 134.3 (triazole C=C), 134.1 (CH=CH), 134.0 (CH=CH), 133.6 (triazole CH), 117.6 (alkene CH$_2$), 117.3 (alkene CH$_2$), 109.9 (isopropylidene C), 109.3 (isopropylidene C), 76.73 (galactose (gal) C-2), 74.35 (gal C-3), 72.54 (gal C-4), 72.27 (gal C-4'), 72.15 (gal C-3), 70.94 (gal C-1), 70.90 (gal C-1), 69.50 (gal C-5), 69.47 (gal C-5), 68.44 (gal C-2), 62.48 (gal C-6), 60.61 (OCH$_2$), 50.01 (gal C-6), 35.15 (CH$_2$CH=CH$_2$), 33.86 (CH$_2$CH=CH$_2$), 27.19 (isopropylidene CH$_3$), 26.73 (isopropylidene CH$_3$), 25.86 (CH$_3$), 24.91 (isopropylidene CH$_3$), 24.54 (isopropylidene CH$_3$), 18.3 (C), -5.35, -5.47 (each CH$_3$); ESI-HRMS: calcd. for C$_{33}$H$_{55}$N$_3$O$_9$SiNa, 688.3626; found m/z 688.3629 [M+Na]$^+$; FT-IR 3374, 2929, 1724, 1461, 1380, 1210, 1061, 835, 777 cm^{-1}.

(3aS,4R,6R,7S,7aR)-6-Allyl-4-((4-(((3aS,4R,6R,7S,7aR)-6-allyl-4-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol 16. In a microwave vial in THF-H$_2$O (1:1, 5 mL), was placed **14** (60 mg, 0.20 mmol), **4** (91 mg, 0.20 mmol), CuSO$_4$.5H$_2$O (50 mg, 0.20 mmol) and sodium-L-ascorbate (20 mg, 0.10 mmol). The vial was sealed, and the mixture

was heated to 60 °C for 10 min at 120 W in a microwave reactor. The mixture was diluted with Et_2O, washed with H_2O, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (cyclohexane-EtOAc, 1:1) gave **16** (97 mg, 73 %) as a colourless oil; ^1H NMR (500 MHz, chloroform-d): δ 7.70 (1H, s, triazole H), 5.75 (2H, overlapped signals, alkene H), 5.14 – 4.99 (4H, overlapped signals, alkene H), 4.83 (1H, d, J = 12.1 Hz), 4.66 (1H, d, J = 12.2 Hz), 4.62 (1H, dd, J = 13.9, 4.1 Hz, gal H-6), 4.44 (1H, dd, J = 13.9, 8.5 Hz, gal H-6b), 4.38-4.31 (3H, overlapped signals), 4.23 (1H, dd, J = 7.5, 1.9 Hz, gal H-5), 4.08 (1H, td, J = 7.2, 2.0 Hz, gal H-1), 4.00 (1H, td, J = 7.3, 2.9 Hz, gal H-1), 3.93 (1H, ddd, J = 7.5, 5.5, 1.5 Hz, gal H-5), 3.85 (1H, q, J = 3.2 Hz, gal H-2), 3.74 (1H, dd, J = 9.6, 8.0 Hz, gal H-6), 3.68 (1H, dd, J = 9.6, 5.7 Hz, gal H-6), 3.54 (1H, t, J = 3.1, gal H-2), 2.37 – 2.24 (4H, overlapped signals), 1.92 (d, J = 4.1 Hz, 1H, OH), 1.53 (3H, s, isopropylidene CH_3), 1.47 (3H, s, isopropylidene CH_3), 1.35 (3H, s, isopropylidene CH_3), 1.33 (3H, s, isopropylidene CH_3), 0.88 (9H, s, 3 x CH_3), 0.05 (6H, 2 s, each CH_3); ^{13}C-NMR (126 MHz, chloroform-d): δ 144.9 (triazole C) 134.5 (alkene CH), 134.1 (alkene CH), 124.1 (triazole CH) 117.7 (alkene CH$_2$), 117.1 (alkene CH$_2$), 110.0 (isopropylidene C), 109.1 (isopropylidene C), 76.3 (gal C-2), 74.3 (CH), 72.5 (gal C-5), 72.0 (CH), 70.9 (gal C-1), 70.7 (gal C-1'), 69.5 (gal H-5), 68.9 (CH), 68.4 (gal C-2), 64.1 (OCH_2), 62.5 (CH_2), 51.9 (CH_2N), 35.2 (allylic CH_2), 34.5 (allylic CH_2), 27.1 (isopropylidene CH_3), 26.6 (isopropylidene CH_3), 25.9 (CH_3), 24.7 (isopropylidene CH_3), 24.5 (isopropylidene CH_3), 18.3 (C) -5.3, -5.5 (each CH_3); ESI-HRMS: calcd. for $C_{33}H_{55}N_3O_9SiNa$, 688.3584; found m/z 688.3605 [M+Na]$^+$; FT-IR 3384, 2929, 2100, 1373, 1210, 1058, 910, 835, 777, 732 cm^{-1}.

Macrocycles 17-cis and 17-trans To diene **15** (65 mg, 0.1 mmol) in toluene (150 mL), was added the first generation Hoveyda-Grubbs II catalyst (12 mg, 0.02 mmol) and the

mixture stirred at 90 °C for 24 h. The solvent was then removed under reduced pressure

and flash chromatography (cyclohexane-EtOAc, 7:3) of the residue gave **17-cis** (15 mg)

and **17-trans** (23 mg) both as white solids (overall yield, 60 %). Analytical data for **17-cis**: ^{1}H NMR (500 MHz, chloroform-d) δ 7.62 (1H, s, triazole H), 5.45 (1H, t, J = 11.2

Hz, C*H*=CH), 5.33 (1H, t, J = 10.3 Hz, CH=C*H*), 4.96 (1H, d, J = 12.2 Hz), 4.77 (1H,

dd, J = 14.4, 3.2 Hz, gal H-6), 4.71 (1H, d, J = 12.1 Hz), 4.48 (1H, dd, J = 7.3, 1.6 Hz,

H-4), 4.41 (2H, overlapped signals), 4.31 (1H, dd, J = 14.5, 7.0 Hz, gal H-6), 4.26 (1H,

dd, J = 7.1, 4.0 Hz, gal H-3), 4.22 – 4.16 (1H, m, gal H-5), 4.12 (1H, ddd, J = 10.1, 6.0,

2.1 Hz, gal H-1), 4.05 (1H, dt, J = 10.9, 2.1 Hz, gal H-1), 4.00 (1H, ddd, J = 8.0, 5.9, 1.5

Hz, gal H-5), 3.81 (q, J = 3.4 Hz, 1H, gal H-2), 3.78 – 3.70 (2H, overlapped signals, H-6a & H-6b), 3.52 (1H, t, J = 2.5 Hz, H-2), 2.59 (2H, overlapped signals), 2.22 (2H,

overlapped signals), 1.95 (1H, d, J = 14.9 Hz), 1.52 (6H, overlapped signals, 2 x

isopropylidene CH$_3$), 1.38 (6H, overlapped signals, 2 x isopropylidene CH$_3$), 0.91 (9H, s,

3 x CH$_3$), 0.08 (6H, s, 2 x CH$_3$); ^{13}C NMR (126 MHz, chloroform-d) δ 134.4 (triazole

C), 133.6 (triazole CH), 128.8 (alkene CH), 126.1 (alkene CH), 109.9 (isopropylidene C),

109.3 (isopropylidene C), 75.6 (gal C-2), 75.0 (gal C-3), 73.2 (CH), 71.8 (CH), 71.4

(CH), 70.6 (gal C-1), 70.3 (gal C-4), 70.2 (gal C-5), 69.9 (gal C-5), 62.4 (gal C-6), 61.9

(CH$_2$), 51.2 (CH$_2$N), 29.4 (*C*H$_2$), 28.3 (*C*H$_2$), 27.0 (2s, each isopropylidene CH$_3$), 25.9

(CH$_3$), 24.7, 24.4 (each isopropylidene CH$_3$), 18.4 (C), -5.3, -5.4 (each CH$_3$); ESI-HRMS:

calcd. for C$_{31}$H$_{51}$O$_9$N$_3$SiNa, 660.3250; found m/z 660.3249 [M+Na]$^+$; FT-IR 2931, 2298,

1462, 1379, 1248, 1210, 1060, 834, 777, 660 cm^{-1}. Analytical data for **17-trans**: ^{1}H NMR

(500 MHz, chloroform-d) δ 7.65 (1H, s, triazole H), 5.36-5.19 (2H, overlapped signals,

C*H*=C*H*), 4.92 (1H, d, J = 12.2 Hz), 4.73 (1H, d, J = 12.2 Hz), 4.56 (1H, dd, J = 14.4,

2.1 Hz, H-6'a), 4.45 – 4.31 (5H, overlapped signals), 4.19 – 4.10 (2H, overlapped signals),

3.98 (1H, t, J = 6.8 Hz, gal H-5), 3.92 (1H, dt, J = 11.2, 2.7, gal H-1), 3.83 – 3.70 (3H,

overlapped signals), 3.61 – 3.52 (1H, m, gal H-2), 2.48 (1H, ddd, J = 13.6, 10.4, 7.6, CHHCH=CHCH$_2$), 2.24-2.17 (2H, overlapped signals), 1.90 (1H, ddd, J = 13.5, 7.0, 2.9, CH$_2$=CHCHH), 1.54 (3H, s, isopropylidene CH$_3$), 1.49 (3H, s, isopropylidene CH$_3$), 1.38 (3H, s, isopropylidene CH$_3$), 1.36 (3H, s, isopropylidene CH$_3$), 0.91 (9H, s, CH$_3$ x 3), 0.09 (6H, s, CH$_3$ x 2); ^{13}C NMR (126 MHz, chloroform-d) δ 136.8 (triazole C=C), 131.9 (triazole CH), 129.7 (alkene CH), 127.4 (alkene CH), 109.9 (isopropylidene C), 109.3 (isopropylidene C), 78.3 (gal C-2), 74.5, 72.6, 72.0, 71.6 (each CH), 71.2 (gal C-1), 71.1 (gal C-1), 70.4 (gal C-5), 69.8 (CH), 68.7 (gal C-2), 64.1 (CH$_2$), 62.5 (gal C-6), 50.4 (gal C-6), 34.8 (allyl CH$_2$), 33.4 (allyl CH$_2$), 26.9, 26.7 (each isopropylidene CH$_3$), 25.9 (3 signals, each CH$_3$), 24.6, 24.4 (each isopropylidene CH$_3$), 18.4 (C), -5.3, -5.4 (each CH$_3$); ESI-HRMS: calcd. for C$_{31}$H$_{52}$O$_9$N$_3$Si, 638.3416; found m/z 638.3405 [M+H]$^+$; FT-IR 3386, 2928, 1462, 1379, 1249, 1209, 1057, 982, 835 cm^{-1}.

Macrocycle 18. The diene **16** (532 mg, 0.835 mmol) in degassed toluene (200 mL) was preheated and the second generation Grubbs catalyst (75 mg, 0.12 mmol) was then added. The mixture was stirred at 120 °C for 10 min and the solvent was then removed under reduced pressure. Flash chromatography (cyclohexane-EtOAc 1:3) of the residue gave trans isomer **18** (253 mg, 40 %) as a white solid; ^{1}H NMR (500 MHz, chloroform-d): δ 7.68 (1H, s, triazole H), 5.03 (1H, dt, J = 15.9, 6.0, CH=CH), 4.95 (1H, d, J = 13.4 Hz), 4.82 (1H, dt, J = 14.7, 7.0, CH=CH), 4.75 (1H, dd, J = 14.2, 2.0, gal H-6), 4.50 (1H, dd, J = 7.6, 1.5, gal H-4), 4.47 (1H, d, J = 13.4), 4.45 – 4.42 (1H, m, gal H-6'), 4.41 – 4.39 (1H, m, H-3), 4.28 (1H, dd, J = 5.9, 2.2, H-3'), 4.16 (1H, t, J = 6.3, H-2'), 4.04 – 3.99 (2H, overlapped signals, H-5 & H-5'), 3.99 – 3.96 (1H, m, H-1), 3.96 – 3.92 (2H, overlapped signals, H-1' & H-4'), 3.75 – 3.68 (2H, overlapped signals, H-6a & H-6b), 3.33 (1H, t, J = 1.8, H-2), 2.23 (1H, d, J = 3.5, CHHCH=CHCH$_2$), 2.20 – 2.15 (1H, m,

CH*H*CH=CHCH$_2$), 2.02 – 1.97 (1H, m, CH$_2$CH=CHC*H*H), 1.96 – 1.91 (1H, m, CH$_2$=CHCH*H*), 1.55 (3H, s, isopropylidene CH$_3$), 1.48 (3H, s, isopropylidene CH$_3$), 1.39 (3H, s, isopropylidene CH$_3$), 1.37 (3H, s, isopropylidene CH$_3$), 0.90 (9H, s, CH$_3$ x 3), 0.07 (3H, s, CH$_3$), 0.06 (3H, s, CH$_3$); ^{13}C NMR (126 MHz, chloroform-d) δ 142.7 (triazole C=C), 128.6 (*C*H=CH), 125.8 (triazole CH), 125.6 (CH=*C*H), 110.3 (isopropylidene C), 109.0 (isopropylidene C), 76.7 (C-2'), 74.2 (C-1), 73.5 (H-3'), 72.1 (C-2), 71.8 (C-4), 70.7 (C-1' or C-4'), 70.0 (C-3), 69.7 (C-5 or C-5'), 68.6 (C-1'), 67.9 C-5 or C-5'), 62.4 (C-6), 60.8 (C-7), 51.4 (C-6'), 32.6 (*C*H$_2$CH=CHCH$_2$), 28.2 (CH$_2$CH=CHC*H*$_2$), 27.9, 26.9, 26.1 (each isopropylidene CH$_3$), 25.9 (3 signals, each CH$_3$), 24.2 (isopropylidene CH$_3$), 18.3 (C), -5.3, -5.5 (each CH$_3$); ESI-HRMS: calcd. for C$_{31}$H$_{51}$O$_9$SiNa, 660.3266; found *m/z* 660.3292 [M+Na]$^+$

Macrocycle 19 Macrocycle **17-trans** (23 mg, 0.036 mmol) was first dissolved in THF (2 mL) and TBAF (1 M in THF, 0.11 mL, 0.36 mmol) was added dropwise. The resulting solution was stirred at room temperature for 3 h. Then EtOAc was added, and the mixture was washed with 1 M HCl, water, brine, dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. Flash chromatography (EtOAc) gave desilylated intermediate (4.0 mg, 21 %) as a white solid; ESI-HRMS: calcd. for C$_{25}$H$_{37}$O$_9$N$_3$Na, 546.2402; found *m/z* 546.2427 [M+Na]$^+$; FT-IR 3383, 2921, 1617, 1458, 1375, 1210, 1057, 790 cm^{-1}. This intermediate (4 mg, 0.008 mmol) was dissolved in TFA-H$_2$O (4:1, 0.25 mL) and the mixture was stirred at room temperature for 2 h. Toluene was added and the volatile materials were removed under reduced pressure. The resulting residue was taken up in MeOH and Dowex M-43 ion exchange resin was added, adjusting the pH to 8, and the mixture was then filtered and the solvent was removed under reduced pressure. Flash chromatography (CH$_2$Cl$_2$:MeOH 4:1) gave the title compound (3 mg, ~75%) as a white solid; ^{1}H NMR (600 MHz, D$_2$O): δ 7.74 (1H, s, triazole H), 5.41 (1H,

dt, J = 15.1, 7.4 Hz, alkene H), 5.19 (1H, dt, J = 15.6, 7.4 Hz, alkene H), 4.78 (d, J = 12.8 Hz, 1H), 4.73 (d, J = 12.8 Hz, 1H), 4.59 (1H, dd, J = 15.3, 3.3 Hz, gal H-6), 4.33 (1H, dd, J = 15.1, 7.2 Hz, gal H-6), 4.15 – 4.06 (2H, overlapped signals), 4.00-3.70 (8H, overlapped signals), 3.58 (1H, q, J = 8.5 Hz, gal H-6), 2.41 (1H, m), 2.22 – 2.02 (3H, overlapped signals); ^{13}C NMR (151 MHz, D$_2$O) δ 136.3 (triazole C), 133.2 (triazole CH), 129.2 (alkene CH), 129.0 (alkene CH), 79.3, 74.2 (each CH), 71.6 (CH), 69.7 (CH), 69.1 (gal C-5), 68.3, 68.1, 68.0 (each CH), 68.0 (CH), 62.8 (CH$_2$), 59.7 (gal C-6), 47.8 (gal C-6), 32.2 (CH$_2$), 28.8 (CH$_2$); ESI-HRMS: calcd. for C$_{19}$H$_{29}$O$_9$N$_3$Na, 466.1808; found m/z 466.1801 [M+Na]$^+$; FT-IR 3360, 1636, 1362, 1077, cm^{-1}.

Macrocycle 20 Macrocycle **18** (15 mg, 0.02 mmol) was dissolved in THF (6 mL) and TBAF (1 M in THF, 0.06 mL, 0.2 mmol) was added dropwise. The resulting solution was stirred at room temperature for 3 h. Then CaCO$_3$, Dowex-50X8 and MeOH were added and stirring was continued for a further 1 h. The slurry was filtered through Celite®, washed thoroughly with MeOH and the solvent was removed under reduced pressure. Flash chromatography (EtOAc only) gave the desilylated intermediate (9 mg, 81 %) as a white solid; ESI-HRMS: calcd. for C$_{25}$H$_{35}$O$_9$N$_3$Na, 546.2401; found m/z 546.2403 [M+Na]$^+$. This intermediate (8.0 mg, 0.015 mmol) was dissolved in TFA-H$_2$O (4:1, 0.25 mL) and the mixture was stirred at room temp for 2 h. Toluene was added and the volatile materials were removed under reduced pressure. The residue was taken up in MeOH and Dowex M-43 ion exchange resin was added until the pH reached 8. The mixture was then filtered and the solvent removed under reduced pressure. Flash chromatography (CH$_2$Cl$_2$-MeOH 4:1) gave the title compound (4 mg, ~60 %) as a white solid; ^{1}H NMR (600 MHz, D$_2$O) δ 8.02 (1H, s, triazole H), 5.31 (1H, dt, J = 17.0, 5.1 Hz, alkene H), 5.03 (1H, d, J = 14.2 Hz), 4.86 (1H, m, alkene H), 4.66 (1H, dd, J = 14.6, 2.1 Hz, gal H-6),

4.58 (1H, d, J = 14.2 Hz), 4.54 (1H, dd, J = 14.6, 10.5 Hz, gal H-6), 4.13 (1H, d, J = 3.5 Hz, gal H-4), 4.09 – 3.75 (8H, overlapped signals), 3.69 (1H, dd, J = 11.6, 3.9, gal H-6b), 2.33 – 2.12 (3H, overlapped signals), 1.90 (1H, m); ^{13}C NMR (126 MHz, D_2O) δ 144.4 (triazole C), 128.8 (alkene CH), 126.3 (triazole CH), 126.2 (alkene CH), 75.6 (gal C-1'), 72.4 (gal C-5), 70.2 (CH), 69.7 (gal C-4), 69.4 (CH), 68.4 (2 signals, each CH), 68.1 (gal C-1), 67.9 (2 signals, each CH), 63.3 (CH_2), 60.2 (gal C-6), 51.7 (gal C-6), 26.7 (CH_2), 25.3 (CH_2); ESI-HRMS: calcd. for $C_{19}H_{29}O_9N_3Na$, 466.1794; found m/z 466.1794 [M+Na]$^+$; FT-IR 3386, 2446, 1717, 1448, 1062, 710 cm^{-1}.

Macrocycle 21   Compounds **5** (50 mg, 0.12 mmol) and **2** (80 mg, 0.24 mmol) and Cp*RuCl(PPh$_3$)$_2$ (6 mg, 7 μmol) in DMA (1.8 mL) were placed in a microwave vial, which was flushed with argon for 12 min and sealed. The sealed vial containing the mixture was then heated to 100 ℃ for 30 min in a microwave reactor. To the resulting mixture was added water (15 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 7:3) gave the triazole intermediate (45 mg, 50 %) as a brown pale oil; ^{1}H NMR (500 MHz, chloroform-d) δ 7.85 – 7.79 (overlapped signals, 3H, aromatic H), 7.76 (s, 1H, aromatic H), 7.61 (s, 1H, aromatic H), 7.51 – 7.43 (overlapped signals, 3H, aromatic H), 7.04 (overlapped signals, 2H, aromatic H), 6.80 (overlapped signals, 2H, aromatic H), 5.77 – 5.65 (overlapped signals, 2H, alkene H), 5.21– 5.17 (overlapped signals, 2H, alkene H), 5.07 – 4.95 (overlapped signals, 2H, alkene H), 4.84 (d, J = 11.9 Hz, 1H), 4.69 (d, J = 11.9 Hz, 1H), 4.63 – 4.45 (overlapped signals, 4H), 4.41-4.35 (overlapped signals, 2H), 4.28 (d, J = 11.2 Hz, 1H), 4.22 (dd, J = 7.3, 1.8 Hz, 1H, gal H-4), 4.15 (d, J = 11.2 Hz, 1H), 4.11 (td, J = 6.3, 1.6 Hz, 1H, 5-H), 4.05 – 3.98 (overlapped signals, 2H), 3.77 (s, 3H,

OC*H*₃), 3.66 (dd, *J* = 8.3, 3.4 Hz, 1H), 3.61 – 3.50 (overlapped signals, 3H), 2.47 – 2.29 (overlapped signals, 2H, 1′-H), 1.44 (s, 3H, C*H*₃), 1.43 (s, 3H, C*H*₃), 1.40 (s, 3H, C*H*₃), 1.31 (s, 3H, C*H*₃); ¹³C NMR (126 MHz, chloroform-*d*): δ 159.4 (C), 135.2 (C), 134.9 (CH), 134.8 (C), 133.7 (CH), 133.1 (C), 133.0 (C), 129.7 (CH), 129.3 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 126.6 (CH), 126.2 (CH), 126.0 (CH), 125.8 (CH), 119.5 (CH₂), 117.2 (CH₂), 113.8 (CH), 109.5 (C), 80.6 (CH), 78.1 (CH), 75.8 (CH), 75.4 (CH), 73.4 (CH₂), 72.8 (CH), 72.7 (CH₂), 71.7 (CH), 71.0 (CH), 70.4 (CH₂), 68.4 (CH), 61.3 (CH₂), 55.2 (CH₃), 49.2 (CH₂), 34.8 (CH₂), 27.0 (CH₃), 26.8 (CH₃), 26.7 (CH₃), 24.7 (CH₃). To this triazole intermediate (46 mg, 0.06 mmol), in anhydrous degassed toluene (1.8 mL) in a 10 mL glass vial, was added Grubbs II catalyst (3 mg, 3 μmol, 5 mol%). The vial was sealed, and the mixture was irradiated in a microwave at a maximum power level of 150 W, for 10 min at 120 ºC. The mixture was then diluted with CH₂Cl₂ (20 mL) and washed with brine (5 mL) and saturated NaHCO₃ (5 mL) and H₂O (5 mL), dried over Na₂SO₄ filtered and the solvent was removed under reduce pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 6:4) gave **21** (24 mg, 55 %) as a brown pale oil; ¹H NMR (500 MHz, chloroform-*d*): δ 7.86-7.78 (overlapped signals, 3H, aromatic H), 7.75 (s, 1H), 7.58 (s, 1H), 7.52 – 7.42 (overlapped signals, 3H aromatic H), 7.02 (overlapped signals, 2H, aromatic H), 6.78 (overlapped signals, 2H, aromatic H), 5.68 (ddd, *J* = 14.7, 9.6, 3.0 Hz, 1H, alkene H), 5.52 (dd, *J* = 14.7, 9.4 Hz, 1H, alkene H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.70 (overlapped signals, 2H), 4.57 (d, *J* = 10.9 Hz, 1H), 4.49 (dd, *J* = 14.3, 10.1 Hz, 1H), 4.44 – 4.33 (m, 3H), 4.31 (t, *J* = 9.6 Hz, 1H), 4.25 (d, *J* = 10.9 Hz, 1H), 4.12 (overlapped signals, 3H), 3.97 (dt, *J* = 11.9, 2.7 Hz, 1H), 3.76 (s, 3H), 3.68 (dd, *J* = 8.8, 5.5 Hz, 1H), 3.44 (t, *J* = 3.0 Hz, 1H), 3.41 – 3.32 (overlapped signals, 2H), 2.66 – 1.50 (overlapped signals, 4H), 1.46 (s, 1H, C*H*₃), 1.44 (s, 1H, C*H*₃), 1.39 (s, 1H, C*H*₃), 1.27 (s, 1H, C*H*₃); ¹³C NMR (126 MHz, chloroform-*d*) δ 159.1 (C), 135.5

(CH), 134.9 (CH), 133.1 (C), 133.1 (C), 130.4 (C), 129.6 (CH), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.3 (CH), 126.1 (CH), 126.0 (CH), 113.6 (CH), 109.7 (C), 109.4 (C), 82.6 (CH), 78.7 (CH), 77.2 (CH), 75.7 (CH), 73.8 (CH_2), 73.1 (CH), 72.6 (CH_2), 71.9 (CH), 71.0 (CH_2), 69.3 (CH), 68.4 (CH), 60.6 (CH_2), 55.2 (CH_3), 50.6 (CH_2), 34.6 (CH), 27.1 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 24.4 (CH_3); ESI-HRMS: Calcd for $C_{41}H_{50}N_3O_9$ [M + H] 728.3547; found 728.3544.

Macrocycle 22 Compounds **5** (543 mg, 1.28 mmol) and **2** (600 mg, 1.80 mmol), $CuSO_45H_2O$ (31 mg, 0.128 mmol) and sodium ascorbate (127 mg, 0.64 mmol) in $THF:H_2O$ (1:1, 10 mL) were placed in a microwave vial. The vial containing the mixture was sealed, and then was heated to 60 ℃ for 10 min in a microwave reactor. Then EtOAc (20 mL) was added and the mixture washed with brine (2 x 10 mL). The organic layer was dried, and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, petroleum ether-EtOAc, 1:1) of the residue gave the intermediate triazole (834 mg, 86 %) as a colorless oil; ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.82 (overlapped signals, 3H aromatic H), 7.76 (s, 1H), 7.60 (s, 1H), 7.50 – 7.42 (overlapped signals, 3H, aromatic H), 7.10 (overlapped signals, 2H, aromatic H), 6.83 (overlapped signals, 2H, aromatic H), 5.78 – 5.66 (overlapped signals, 2H, alkene H), 5.25 – 5.16 (overlapped signals, 2H), 5.06 – 4.94 (overlapped signals, 2H), 4.85 (d, *J* = 11.9 Hz, 1H), 4.76 – 4.64 (m, 3H), 4.56 (dd, *J* = 13.9, 4.4 Hz, 1H), 4.47 – 4.34 (overlapped signals, 3H), 4.30 (dd, *J* = 7.3, 1.8 Hz, 1H, gal H-4), 4.18 (td, *J* = 6.3, 1.7 Hz, 1H, gal H-5), 4.04 (td, *J* = 7.3, 2.9 Hz, 1H, gal H-1), 3.94 (dt, *J* = 8.2, 3.7 Hz, 1H), 3.76 (s, 3H, OMe), 3.73 – 3.64 (overlapped signals, 3H), 3.56 (t, *J* = 3.3 Hz, 1H), 2.49 – 2.29 (overlapped signals, 2H), 1.45 (2s) 1.42, 1.32 (each 3H, each C*H₃*); ^{13}C NMR (126 MHz, chloroform-*d*) δ 159.5 (C), 145.1 (C), 135.3 (C), 134.8 (CH), 134.5 (CH), 133.2 (C),

133.0 (C), 130.0 (CH), 129.1 (C), 128.2 (CH), 127.9 (CH), 127.7 (CH), 126.5 (CH), 126.1 (CH), 126.0 (CH), 125.8 (CH), 124.3 (CH), 119.6 (CH_2), 117.2 (CH_2), 113.9 (CH), 109.6 (C), 109.4 (C), 80.6 (CH), 78.0 (CH), 75.6 (CH), 75.3 (CH), 73.5 (CH_2), 72.9 (CH), 72.6 (CH_2), 71.8 (CH), 71.1 (CH), 70.4 (CH_2), 68.4 (CH), 64.9 (CH_2), 55.2 (CH_3), 51.6 (CH_2), 34.7 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 26.7 (CH_3), 24.8 (CH_3); ESI-HRMS: Calcd for $C_{43}H_{54}N_3O_9$ [M + H] 756.3860; found 756.3827. This triazole (50 mg, 66 μmol) was added to an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar, and placed under argon. Then Grubbs 2nd generation metathesis catalyst (2.8 mg, 6.6 μmol, 10 mol %) and anhydrous 1,2-dichloroethane (3.3 mL) were added. The mixture was stirred for 2 h at 120 ºC while maintaining the argon atmosphere. The solvent was then removed under reduced pressure and then flash column chromatography (silica gel, petroleum ether-EtOAc, 1:1) gave **22** (24 mg, 50 %) as a brown pale oil; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.86-7.78 (overlapped signals, 4H, aromatic H), 7.74 (s, 1H), 7.53-7.41 (overlapped signals, 3H, aromatic H), 7.35 (overlapped signals, 2H), 6.89 (overlapped signals, 2H, aromatic H), 5.62 (dd, *J* = 15.5, 8.4 Hz, 1H, alkene H), 5.47 (ddd, *J* = 15.0, 9.8, 4.4 Hz, 1H, alkene H), 4.91 (d, *J* = 14.4 Hz, 1H), 4.89 – 4.77 (overlapped signals, 3H), 4.68 (overlapped signals, 2H), 4.54 (d, *J* = 14.4 Hz, 1H), 4.40 (dd, *J* = 7.5, 3.1 Hz, 1H, gal H-3), 4.33 (d, J = 14.4 Hz, 1H), 4.19 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.08-4.15 (overlapped signals, 3H), 3.94 (dt, J = 11.3, 2.1 Hz, 1H), 3.78 (overlapped signals, 4H), 3.69 (dd, *J* = 10.1, 2.1 Hz, 1H, gal H-6), 3.61 (t, J = 6.0 Hz, 1H), 3.50 – 3.39 (overlapped signals, 2H), 2.62 (dt, J = 14.8, 10.4 Hz, 1H), 1.97 (br d, 1H, J = 15.0 Hz), 1.42 (s, 3H, C*H$_3$*), 1.41 (s, 3H, C*H$_3$*), 1.39 (s, 3H, C*H$_3$*), 1.31 (s, 3H, C*H$_3$*); ^{13}C NMR (126 MHz, chloroform-*d*) δ 159.5 (C), 146.6 (C), 134.9 (C), 133.9 (CH), 133.0 (C), 130.7 (CH), 130.1 (CH), 129.3 (CH), 128.4 (C), 127.9 (CH), 127.7 (CH), 126.9 (CH), 126.2 (CH), 126.1 (CH), 125.9 (CH), 123.2 (CH), 113.9 (CH), 109.8 (C), 109.7 (C), 79.7 (CH),

78.9 (CH), 76.2 (CH), 74.8 (CH), 73.3 (CH), 72.6 (CH$_2$), 71.6 (CH), 71.4 (CH$_2$), 71.1 (CH$_2$), 70.0 (CH), 69.5 (CH), 64.7 (CH$_2$), 55.3 (CH$_3$), 48.4 (CH$_2$), 35.4 (CH$_2$), 27.1 (CH$_3$), 26.9 (CH$_3$), 26.8 (CH$_3$), 24.4 (CH$_3$); ESI-HRMS: Calcd for C$_{41}$H$_{50}$N$_3$O$_9$ [M+H]$^+$ 728.3547; found 728.3552.

(2R,3R,4S,5R,6R)-6-Allyl-2-(((1-((S)-2-(benzyloxy)-2-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)-5-(naphthalen-2-ylmethoxy)tetrahydro-2H-pyran-3,4-diol 23 To alkyne **6** (35 mg, 0.092 mmol) and intermediate **11** (28 mg, 0.092 mmol, generated from **1** as described above) in THF:H$_2$O (1:1, 1 mL) in a microwave vial, was added copper sulphate pentahydrate (2 mg, 0.009 mmol) and sodium ascorbate (9 mg, 0.05 mmol). The vial was sealed and the mixture was stirred while irradiating in a microwave (120 W, 60 °C) for 15 min, then diluted with EtOAc. The organic layer was washed with brine, dried (Na$_2$SO$_4$), filtered and the solvent was removed under reduced pressure. Flash chromatography (petroleum ether-EtOAc, 1:2 to 0:1) of the residue gave the diene **23** as a clear oil (40 mg, 0.058 mmol, 63%); ^{1}H NMR (500 MHz, chloroform-d): δ 7.84-7.80 (overlapped signals, 3H, aromatic H), 7.77 (s, 1H, aromatic H), 7.55 (s, 1H, triazole H), 7.50-7.43 (overlapped signals, 3H, aromatic H), 7.33-7.27 (overlapped signals, 3H, aromatic H), 7.19-7.16 (overlapped signals, 2H, aromatic H), 5.83-5.70 (overlapping signals, 2H, 2x C*H*=CH$_2$), 5.25-5.19 (m, 2H, CHCH=C*H$_2$*), 5.08 (dq, *J* = 17.1, 1.5 Hz, 1H, CH$_2$CH=C*H*H), 5.04 (dd, *J* = 10.2, 1.6 Hz, 1H, CH$_2$CH=CH*H*), 4.78 (s, 2H, CH$_2$Naph), 4.70 (d, *J* = 12.7 Hz, 1H, OC*H*H), 4.62 (d, *J* = 12.8 Hz, OCH*H*), 4.58 (dd, *J* = 14.1, 4.3 Hz, 1H, NC*H*H), 4.44 (dd, *J* = 14.0, 8.6 Hz, 1H, NCH*H*), 4.41-4.36 (overlapping signals, 2H, C*H*CH=CH$_2$ and C*H*HPh), 4.26 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 4.17 (dt, *J* = 9.3, 5.6 Hz, 1H, H-1), 4.06 (dd, *J* = 3.2, 1.2 Hz, 1H, H-4), 3.96 (dt, *J* = 8.0, 4.0 Hz, 1H, CH(OBn)), 3.89 (dd, *J* = 9.2, 5.5 Hz, 1H, H-2), 3.82 (dd, *J* = 9.2, 3.4 Hz, 1H,

H-3), 3.80-3.68 (overlapping signals, 4H, H-5, H-6 and CHCHCH=CH$_2$), 2.45-2.40 (m, 2H, CH_2CH=CH$_2$), 1.46 (s, 3H, CH$_3$), 1.43 (s, 3H, CH$_3$); ^{13}C NMR (125 MHz, chloroform-d): δ 144.6 (C), 137.0 (C), 135.4 (C), 134.8 (CH), 134.7 (CH), 133.2 (C), 133.0 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 126.7 (CH), 126.2 (CH), 126.0 (CH), 125.7 (CH), 124.1 (CH), 119.8 (CH$_2$), 116.9 (CH$_2$), 109.7 (C), 80.6 (CH), 78.1 (CH), 76.9 (CH), 75.9 (CH), 73.9 (CH$_2$), 73.6 (CH), 73.0 (CH$_2$), 69.9 (CH), 69.6 (CH$_2$), 69.4 (CH), 69.1 (CH), 64.6 (CH$_2$), 51.6 (CH$_2$), 29.7 (CH$_2$), 27.0 (CH$_3$), 26.7 (CH$_3$); ESI-HRMS: Found 686.3433 required 686.3441 [M+H]$^+$.

Macrocycle 24 To diene **23** (13 mg, 0.019 mmol) and benzoquinone (0.8 mg, 0.008 mmol) in dry, degassed toluene (20 mL) in an oven dried, two necked round bottomed flask, equipped with a reflux condenser, was stirred under a N$_2$ atmosphere. The solution was heated to 80 °C and a solution of Hoveyda-Grubbs II catalyst (1 mg, 0.007 mmol) in dry, degassed toluene (0.5 mL) was added via cannula. The solution was stirred for 16 h after which time, the solvent was removed under reduced pressure. Flash chromatography (EtOAc) of the residue gave **24** as a pale brown oil (7 mg, 58%); ^{1}H NMR (500 MHz, chloroform-d): δ 7.87 (d, J = 8.4 Hz, 1H), 7.84 (overlapped signals, 2H, aromatic H), 7.79 (s, 1H, aromatic H), 7.55 (s, 1H, triazole H), 7.51-7.45 (overlapped signals, 3H, aromatic H), 7.42-7.35 (overlapped signals, 4H, aromatic H), 7.31 (m, 1H, aromatic H), 5.06 (dd, J = 15.6, 7.9 Hz, 1H, CH$_2$CH=CH), 4.89-4.76 (overlapped signals, 6H), 4.67 (d, J = 13.4 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H, benzyl H), 4.53 (dd, J = 13.7, 3.1 Hz, 1H), 4.10 (q, J = 2.0 Hz, 1H, gal H-4), 4.01-3.94 (overlapped signals, 2H), 3.80 (ddd, J = 11.8, 6.0, 2.2 Hz, 1H, gal H-1), 3.67 (ddd, J = 9.0, 5.0, 3.1 Hz, 1H, gal H-3), 3.52-3.46 (overlapped signals, 2H)), 3.42 (broad signal, 1H, gal H-5), 3.36 (dd, J = 10.3, 4.0 Hz, 1H, gal H-6), 3.01 (dd, J = 8.7, 1.6 Hz, 1H), 2.99 (d, J = 2.1 Hz, 1H, OH), 2.63 (d, J = 5.7 Hz, 1H, gal 3-OH), 2.31-2.11 (overlapped signals, 2H), 1.45 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$); ^{13}C

NMR (125 MHz, chloroform-d): δ 145.7 (C), 136.8 (C), 135.3 (C), 133.2 (C), 133.1 (C), 132.0 (CH), 129.8 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 126.9 (CH), 126.4 (CH), 126.2 (CH), 125.7 (CH), 122.9 (CH), 109.8 (C), 78.4 (CH), 77.2 (CH), 76.4 (CH), 73.3 (2s, CH_2 and CH), 72.8 (CH), 72.5 (CH_2), 71.2 (CH), 70.3 (CH), 68.9 (CH), 68.4 (CH_2), 64.5 (CH_2), 48.6 (CH_2), 27.1 (CH_3), 26.7 (CH_2), 26.6 (CH_3); ESI-HRMS: Found 692.2750 required 692.2739 $[M+Cl]^-$.

(3aS,4R,7R,7aR)-2,2,4,6-tetramethyl-7-(prop-2-ynyloxy)-4-vinyl-3a,4,7,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridine 25 & (6R,6aS,9aS,Z)-8,8,10-trimethyl-6-vinyl-6,6a,9a,12-tetrahydro-4H-[1,3]dioxolo[4,5-h][1,2,3]triazolo[5,1-c][1,4]oxazecine 26 Compound **8** (100 mg, 0.343 mmol) in toluene (20 mL) was heated at 100 ºC for 12 h. The solvent was then removed under reduced pressure and flash column chromatography (hexane-EtOAc, 1:1) gave **25** (18 mg, 20 %, clear oil) as well as **26** (31 mg, 31 %) as a crystalline solid as well as unreacted **8** (6 mg, 6%). Analytical data for **25:** R_f = 0.67 (EtOAc-hexanes, 1:1); ^{1}H NMR (500 MHz, , chloroform-d) δ 5.95 (dd, J = 17.5, 10.8 Hz, 1H, alkene H), 5.15 (dd, J = 10.8, 1.5 Hz, 1H, alkene H), 4.95 (dd, J = 17.5, 1.5 Hz, 1H, alkene H), 4.43 (dd, J = 15.7, 2.4 Hz, 1H, propargyl H), 4.34 (dd, J = 15.7, 2.3 Hz, 1H, propargyl H), 4.13 (d, J = 8.8 Hz, 1H C*H*-O-propargyl), 3.66 (dd, J = 10.1, 8.8 Hz, 1H, C*H*-CH-O-propargyl), 2.48 (t, J = 2.4 Hz, 1H, alkyne H), 2.17 (s, 3H, C*H₃*C=N), 1.46 (s, 3H, CH_3), 1.43 (s, 3H, isopropylidene CH_3), 1.36 (s, 3H, isopropylidene CH_3); ^{13}C-NMR (126 MHz, chloroform-d) δ 165.8 (C, imine), 138.9 (alkene CH), 115.6 (alkene CH_2), 110.4 ($C(CH_3)_2$), 81.2 (CH-O-propargyl), 80.7 (CH), 79.4 (alkyne CH), 76.2 (alkyne C), 74.9 (alkyne CH), 64.0 (C-N), 58.0 (propargyl CH_2), 27.8 (CH_3), 27.0 (isopropylidene CH_3), 26.7 (isopropylidene CH_3), 23.1 (CH_3); ESI-HRMS: m/z calc for $C_{15}H_{22}NO_3$: 264.1600 found: 264.1611 $[M+H]^+$. Analytical data for **26**: R_f = 0.74 (EtOAc-hexanes, 1:1); ^{1}H NMR (500 MHz, chloroform-d) δ 7.49 (s, 1H,

triazole H), 5.94 – 5.84 (overlapped signals, 2H), 5.39 (ddd, J = 10.3, 1.5, 0.7 Hz, 1H), 5.35 – 5.29 (overlapped signals, 2H), 5.39 (dd, J = 9.8, 1.3 Hz, 1H), 5.15 (ddd, J = 17.3, 1.5, 0.9 Hz, 1H), 4.91 (ddd, J = 14.2, 5.7 Hz, 1H), 4.86 (J = 14.4 Hz, 1H), 4.76 (d, J = 14.2 Hz), 3.62 (dd, J = 8.8, 3.3 Hz, 1H), 3.46 (dd, J = 8.3, 3.3 Hz, 1H), 1.78 (t, J = 1.3 Hz, 3H, CH_3), 1.50 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (126 MHz, chloroform-d): δ 138.2, 133.9, 132.4, 131.6, 123.0, 120.6, 109.4 ($C(CH_3)_2$), 79.5, 74.1, 73.5, 58.1, 45.5, 27.0 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 18.3 (CH_3); ESI-HRMS: m/z calc for $C_{15}H_{22}N_3O_3$: 292.1661 found: 292.1669 [M+H]$^+$. A pure crystal of **26** was obtained and the X-ray crystal structure was determined and is shown in Scheme 6.

(6R,7R,8S,Z)-9-Methyl-6-vinyl-6,7,8,11-tetrahydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazecine-7,8-diol 27 Compound **26** (30 mg, 0.10 mmol) was stirred in 3M HCl (5 mL) for 2 h. The volatiles were removed under reduced pressure and flash chromatography (Et$_2$O-acetone, 1:1) afforded **27** (21 mg, 85%) as a white solid; R$_f$ = 0.43 (Et$_2$O-Acetone, 1:1); ^{1}H NMR (500 MHz, chloroform-d) δ 7.45 (s, 1H, triazole H), 5.90 (ddd, J = 17.3, 10.3, 8.1 Hz, 1H, alkene H), 5.74 (ddt, J = 11.4, 5.0, 1.5, 1.0 Hz, 1H, alkene H), 5.44 (dd, J = 10.3, 1.4 Hz, 1H, alkene H); 5.32 (dd, J = 13.6, 11.7 Hz, 1H, CH(H)-N), 5.18 (dd, J = 17.4, 1.5 Hz, 1H, alkene H), 5.01 (d, J = 9.1 Hz, 1H, C=CCH-OH), 4.97 (dd, J = 14.2, 5.0 Hz, 1H, CH(H)-N), 4.75 (d, J = 14.8 Hz, 1H, CH(H)O), 3.51 (overlapped signals, 2H), 2.66 (s, 1H, OH), 2.49 (s, 1H, OH), 1.75 (t, J = 1.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, chloroform-d) δ 139.6 (C), 133.2 (triazole CH), 132.5 (alkene CH), 131.7 (C), 123.4 (alkene CH), 121.5 (alkene CH$_2$), 76.3, 75.1, 71.0 (each CH-O), 58.1 (CH$_2$O), 46.3 (CH$_2$N), 18.3 (CH$_3$); ESI-HRMS: m/z calc for $C_{12}H_{18}N_3O_3$: 252.1348 found: 252.1359 [M+H]$^+$.

(6S,7S)-6-((4S,5R)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methyl-7-vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine 28 and (6S,7R)-6-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-7-methyl-7-vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine 29

Compound **10** (140 mg, 0.41 mmol) in DMF (5 mL) was heated at 100 ºC for 12 h. Water was added, and the product was extracted into EtOAc. The organic portion was dried over Na$_2$SO$_4$, filtered and solvent removed under reduced pressure. Flash chromatography (EtOAc-hexanes, 1:1) of the residue gave **29** (93 mg, 66 %) as a white solid and **28** (28 mg, 20 %) as a clear oil. Analytical data for **28:** R$_f$ = 0.35 (EtOAc-hexanes, 1:1); ^{1}H NMR (600 MHz, chloroform-d) δ 7.50 (s, 1H, triazole H), 6.28 (dd, J = 17.1, 10.6 Hz, 1H, alkene H), 5.85 (ddd, J = 17.6, 10.2, 7.5 Hz, 1H, alkene H), 5.41 (d, J = 16.9 Hz, 1H, alkene H), 5.33 (d, J = 10.2 Hz, 1H, alkene H), 5.24 (d, J = 15.0 Hz, 1H, CH(H)O), 5.20 (d, J = 10.7 Hz, 1H, alkene H), 4.87 (d, J = 15.1 Hz, 1H, CH(*H*)O), 4.61 (d, J = 17.0 Hz, 1H, alkene H), 4.53 (t, J = 8.1 Hz, 1H, C=C-C*H*O), 3.96 (d, J = 8.4 Hz, 1H, CHO-C*H*O-CHO), 3.48 (d, J = 3.4 Hz, 1H, OC*H*C-N), 1.88 (s, 3H, CH$_3$), 1.44 (overlapped signals, 6H, C(C*H*$_3$)$_2$); ^{13}C NMR (151 MHz, chloroform-d): δ 137.3 (alkene CH), 134.7 (alkene CH), 130.2 (triazole C), 127.8 (triazole CH), 120.3 (alkene CH$_2$), 116.0 (alkene CH$_2$), 110.3 (*C*(CH$_3$)$_2$), 79.1 (C=C-*CH*O), 78.5 (O*CH*C-N), 77.4 (CHO-*CH*O-CHO), 65.0 (C-N), 62.7 (CH$_2$O), 27.0 (isopropylidene *C*H$_3$), 26.5 (isopropylidene *C*H$_3$), 21.9 (CH$_3$); ESI-HRMS: *m/z* calc for C$_{15}$H$_{22}$N$_3$O$_3$: 292.1661, found 292.1665 [M+H]$^+$. Analytical data for **29**: R$_f$ = 0.3 (EtOAc-hexanes, 1:1); ^{1}H NMR (500 MHz, chloroform-d) δ 7.47 (s, 1H, triazole H), 5.93 (ddd, J = 17.2, 10.8, 2.0 Hz, 1H, alkene H), 5.80 (dddd, J = 17.7, 9.9, 7.8, 2.0 Hz, 1H, alkene H), 5.61 – 5.49 (overlapped signals, 2H, alkene H), 5.39 (d, J = 17.1 Hz, 1H, alkene H), 5.31 (d, J = 10.3 Hz, 1H, alkene H), 5.23 (dd, J = 14.8, 2.0 Hz, 1H, OC*H*(H)C-N), 4.84 (dd, J = 14.7, 1.9 Hz, 1H, OCH(*H*)C-N), 4.49 (td, J = 8.2, 2.0

Hz, 1H, C=C-C*H*O), 3.85 (dd, J = 8.5, 1.9 Hz, 1H, CHO-C*H*O-CHO), 3.48 (d, J = 1.8

Hz, 1H, C*H*OCH$_2$), 1.79 (d, J = 2.1 Hz, 3H, CH$_3$), 1.44 (s, 3H, ispropylidene CH$_3$), 1.42

(s, 3H, ispropylidene CH$_3$); ^{13}C NMR (101 MHz, chloroform-d): δ 137.0 (alkene CH),

134.8 (alkene CH), 129.7 (triazole C), 127.8 (triazole CH), 120.4 (alkene CH$_2$), 120.1

(alkene CH$_2$), 110.2 (*C*(CH$_3$)$_2$), 79.4 (CHO), 77.2 (CHO), 76.8 (CHO), 65.1 (C-N), 62.9

(O*C*H$_2$C=C), 27.2 (C(*C*H$_3$)$_2$), 26.5 (C(*C*H$_3$)$_2$), 20.8 (CH$_3$); ESI-HRMS: m/z calc for

C$_{15}$H$_{22}$N$_3$O$_3$: 292.1661, found 292.1649 [M+H]$^+$.

(5aS,6S,7R,9aR)-9a-Methyl-5a,6,7,9a-tetrahydro-4H-benzo[b][1,2,3]triazolo[1,5-d][1,4]oxazine-6,7-diol 30   Compound **29** (50 mg, 0.17 mmol) in anhydrous degassed

toluene (150 mL) was heated to 80 ºC, and then 2,6-dichloro-1,4-benzoquinone (12 mg,

0.069 mmol) and Hoyveda-Grubbs II catalyst (11 mg, 0.017 mmol) were added and the

mixture stirred at 80 °C for 5 h. The solvent was removed under reduced pressure and 2M

HCl was added to the residue and the mixture left for 12 h. The volatiles were removed

under reduced pressure and then flash column chromatography (CH$_2$Cl$_2$-MeOH, 9:1)

gave **30** (6 mg, 15 %) as a white solid; ^{1}H NMR (500 MHz, CD$_3$OD): δ 7.54 (d, J = 0.9

Hz, 1H, triazole H), 6.66 (dd, J = 10.2, 2.1 Hz, 1H, alkene H), 5.79 (dd, J = 10.2, 2.9 Hz,

1H, alkene H), 5.23 (dd, J = 15.4, 0.7 Hz, 1H, OC*H*(H)), 4.98 (dd, J = 15.3, 1.0 Hz, 1H,

OC*H*(H)), 4.18 (ddd, J = 6.9, 2.9, 2.1 Hz, 1H, C=C-C*H*), 3.92 (dd, J = 10.9, 6.8 Hz, 1H,

CHO-C*H*O-CHO), 3.70 (d, J = 10.9 Hz, 1H, C*H*O-C-N); 1.55 (s, 3H, CH$_3$); ^{13}C NMR

(126 MHz, CD$_3$OD) δ 132.4 (triazole C), 132.0 (alkene CH), 129.6 (triazole CH), 128.6

(alkene CH), 81.1 (*C*HOCN), 75.2 (C=C-*C*HO), 73.5 (CHO-*C*HO-CHO), 64.1 (OCH$_2$),

63.2 (*C*-N), 26.0 (CH$_3$); ESI-HRMS: m/z calc for C$_{10}$H$_{14}$N$_3$O$_3$: 224.1035, found 224.1028

[M+H]$^+$.

SUPPORTING INFORMATION

NMR Spectra (word document)

X-ray crystal structure (ORTEP, CIF) files for compound **26**.

AUTHOR CONTRIBUTIONS

[a]These authors made equal contributions. PMcA solved the X-ray crystal structure. PVM planned the work with the other authors and wrote the paper.

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