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

Karen Fox, Rekha Chadda, Francisco Cardona, Stephen Barron, Patrick McArdle, Paul V. Murphy

PII: S0040-4020(20)30679-7

DOI: https://doi.org/10.1016/j.tet.2020.131495

Reference: TET 131495

To appear in: Tetrahedron

Received Date: 11 June 2020

Revised Date: 31 July 2020

Accepted Date: 10 August 2020

Please cite this article as: Fox K, Chadda R, Cardona F, Barron S, McArdle P, Murphy PV, Building blocks from monosaccharides for synthesis of scaffolds, including macrocycles. Application of allylic azide rearrangement, azide-alkyne cycloaddition and ring closing metathesis, *Tetrahedron* (2020), doi: https://doi.org/10.1016/j.tet.2020.131495.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Ltd.



Building blocks from monosaccharides for synthesis of scaffolds,

including macrocycles. Application of allylic azide rearrangement,

azide-alkyne cycloaddition and ring closing metathesis

Karen Fox,^a Rekha Chadda,^a Francisco Cardona,^a Stephen Barron,^a Patrick McArdle, Paul V. Murphy* School of Chemistry, National University of Ireland Galway, University Road, Galway, Ireland, H91 TK33

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 design² 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 analysis⁶ 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 RCM³⁶ to effect cyclisation (pair). By having allylic azide functionality in both **8** and **10**, the possibility for incorporating Winstein rearrangement³⁷ 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.



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 eunicin⁴² 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-likeness⁴⁷ 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 Me₄Si in CDCl₃ (δ 0.0) or CHCl₃ (δ 7.26) HOD for D₂O (δ 4.84) or CD₂HOD (δ 3.31) for ¹H and CDCl₃ (77.16) or CD₃OD (49.05) for

¹³C NMR spectra were processed and analysed using MestReNova software. ¹H-NMR signals were assigned with the aid of gCOSY. ¹³C-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, H₂O 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 H₂SO₄-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, CH₂Cl₂ 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 data⁴⁹ 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 °C 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 °C, and the resulting mixture was stirred at 25 °C for 16 h under argon. Satd aq NH₄Cl was added and the resulting mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, 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 NaHCO₃ (20 mL) and 1M NaOH (30 mL), and then extracted with CH₂Cl₂ (3 x 20 mL). The organic portions were combined and washed with brine (25 mL), dried over Na₂SO₄ 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 CH₂Cl₂ (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 (Ph₃PCH₃I, 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 Na₂SO₄, 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^{1} H 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 CH(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, CH₃), 1.41 (s, 3H, CH₃); 13 C NMR (126 MHz, chloroform-d) & 159.5 (C), 135.2 (CH, 2C), 129.8 (CH, 2C), 129.7 (C), 119.2 (alkene CH₂), 113.8 (CH), 109.4 (C), 80.7 (CH), 78.3 (CH), 75.6 (CH), 73.0 (CH₂), 55.3 (OCH₃), 51.7 (CH₂), 29.7 (CH₃), 26.9 (CH₃); ESI-HRMS: Calcd for C₁₇H₂₄N₃O₄ [M+H]⁺ 334.1767; found 334.1780.

1-Allyl-1-deoxy-6-O-dimethyl-tert-butylsilyl-2-O-propargyl-3,4-O-isopropylidene-

a-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 H₂O, 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 ¹H 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, CH₂CH=CH₂), 1.50 (3H, s, isopropylidene CH₃), 1.34 (3H, s, isopropylidene CH₃), 0.06 (6H, d, *J* = 1.9 Hz, each SiCH₃); ¹³C-NMR (126 MHz, chloroform-d) δ 134.5 (CH₂CH=CH₂), 117.1 (CH₂CH=CH₂), 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 CH₂), 34.0 (*C*H₂CH=CH₂), 27.1, 25.9, 24.8 (each CH₃), 18.3 (C), -5.4, -5.5 (each SiCH₃); ESI-HRMS: calcd. for C₂₁H₃₇O₅Si, 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 Na₂SO₄ 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); ¹H 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, CH=CH₂), 5.10-4.97 (overlapped signals, 2H, CH=CH₂), 4.86 (d, J = 12.2 Hz, 1H, C(H)HPh), 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, CH₂-CH=CH₂, C≡CH), 1.47 (s, 3H, Me), 1.34 (s, 3H, Me); ¹³C 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 (CH₂), 72.6 (CH), 71.8 (CH), 71.1 (CH), 69.9 (CH₂), 68.4 (C≡CH), 58.6 (CH₂), 34.7 (CH₂), 26.9 (CH₃), 24.8 (CH₃); ESI-HRMS: calcd for $C_{26}H_{34}NO_5$ [M + NH₄]⁺ 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%); ¹H 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, C*H*=CH₂), 5.14 – 5.06 (overlapped signals, 2H, CH=CH₂), 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 CH₂C=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, CH₂CH=CH₂ and CH₂C=C*H*); ¹³C 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 (CH₂), 79.3 (C), 76.7 (CH), 74.8 (CH), 73.5 (CH), 72.9 (CH), 69.6 (CH), 69.4 (2s, 2x CH and CH₂), 58.7 (CH₂), 29.6 (CH₂); 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. Et₂O was added and the mixture was then washed with satd aq NH₄Cl. The organic layer was separated, dried over Na₂SO₄, 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); ¹H 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, CH₃), 1.45 (s, 6H, $C(CH_3)_2$); ¹³C NMR (126 MHz, chloroform-d) δ 138.4 (alkene C), 133.7 (alkene CH), 122.9 (alkene CH), 120.7 (alkene CH₂), 109.6 (*C*(CH₃)₂), 81.7 (CH), 80.7 (CH), 79.6 (alkyne C), 78.1 (CH), 74.5 (alkyne CH), 55.2 (CH₂), 47.7 (CH₂), 27.1 (*C*(*C*H₃)₂), 26.9 (*C*(*C*H₃)₂), 11.8 (CH₃); ESI-HRMS: m/z calc for C₁₅H₂₂N₃O₃: 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 Na₂SO₄, 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 Na₂SO₄, 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 CH₂Cl₂ (30 mL). The solution was cooled to 0 °C and p-TsOH (0.4 g, 2.3 mmol) added. After stirring for 10 mins, 2,2dimethoxypropane (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. NH₄Cl (aq), extracted with EtOAc, dried over Na₂SO₄, 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+CH₃OH]⁺. This alkyne (0.40 g, 1.3 mmol) was dissolved in CH₂Cl₂ (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 H₂O, dried over Na₂SO₄, 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 C₁₅H₂₁O₄: 265.1440, found 265.1436 [M-H]⁻. Finally, this alcohol (0.3 g, 1.1 mmol) was dissolved in anhydrous THF (6 mL) and PPh₃ (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, CH₃), 1.46 (s, 3H, C(CH₃)₂), 1.44 (s, 3H, C(CH₃)₂); 13 C NMR (126 MHz, chloroform-d) δ 137.5 (alkene C), 135.4 (alkene CH), 124.2 (alkene CH), 119.1 (alkene CH₂), 109.6 (C(CH₃)₂), 83.1 (CH), 81.2 (CH), 79.2 (alkyne C), 79.1 (CH), 74.7 (alkyne CH), 55.4 (CH₂), 47.7 (CH₂), 27.0 (*C*(CH₃)₂), 26.8 (*C*(CH₃)₂), 12.8 (CH₃); ESI-HRMS: m/z calc for C₁₅H₂₂O₃N₃: 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%); ¹³C NMR (125 MHz, chloroform-d): δ 137.6 (C), 135.2 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 119.3 (CH₂), 109.4 (C), 80.7 (CH), 78.3 (CH), 76.1 (CH), 73.3 (CH₂), 51.7 (CH₂), 26.9 (CH₃), 26.8 (CH₃). To this azide (54 mg, 0.178 mmol) and 7-O-propargyl-hept-1-ene 12^{29} (54 mg, 0.36 mmol) in THF:H₂O (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 (Na₂SO₄), 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 N2. 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%); ¹H NMR (500 MHz, CDCl₃): 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, OCHHPh), 4.71 (overlapped signals, 2H), 4.67 (d, J = 12.1 Hz, 1H, OCHHPh), 4.62 (d, J = 13.4 Hz, 1H, OCHH-triazole), 4.56 (d, J = 13.4 Hz, 1H, OCHH-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, CH₃), 1.44 (s, 3H, CH₃), 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); ¹³C 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 (CH₂), 69.3 (CH₂), 63.4 (CH₂), 49.7 (CH₂), 31.6 (CH₂), 29.3 (CH₂), 27.3 (CH₂), 27.2 (CH₃), 26.6 (CH₃), 25.3 (CH₂); 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_2O , washed with H₂O, brine, dried over Na₂SO₄, filtered and the solvent removed

under reduced pressure. Flash chromatography (cyclohexane-EtOAc 2:1) gave 15 (125 mg, 43 %) as a colourless oil; ¹H NMR (500 MHz, chloroform-d): δ 7.60 (1H, s, triazole H), 5.75 – 5.63 (2H, overlapped signals, 2 CH₂CH=CH₂), 5.08 – 4.98 (4H, overlapped signals, each CH₂CH=CH₂), 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 = 3.4Hz), 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 CH₃), 1.47 (3H, s, isopropylidene CH₃), 1.35 (3H, s, isopropylidene CH₃), 1.33 (3H, s, isopropylidene CH₃), 0.89 (9H, s, t-Bu), 0.06 (2 x s, 6H, CH₃); ¹³C 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 CH₂), 117.3 (alkene CH₂), 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 (OCH₂), 50.01 (gal C-6), 35.15 (CH₂CH=CH₂), 33.86 (CH₂CH=CH₂), 27.19 (isopropylidene CH₃), 26.73 (isopropylidene CH₃), 25.86 (CH₃), 24.91 (isopropylidene CH₃), 24.54 (isopropylidene CH₃), 18.3 (C), -5.35, -5.47 (each CH₃); 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]pvran-7-ol 16. In a microwave vial in THF-H₂O (1:1, 5 mL), was placed **14** (60 mg, 0.20 mmol), **4** (91 mg, 0.20 mmol), CuSO₄.5H₂O (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 Et₂O, washed with H₂O, brine, dried over Na₂SO₄ 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 CH₃), 1.47 (3H, s, isopropylidene CH₃), 1.35 (3H, s, isopropylidene CH₃), 1.33 (3H, s, isopropylidene CH₃), 0.88 (9H, s, 3 x CH₃), 0.05 (6H, 2 s, each CH₃); ¹³C-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 CH₂), 117.1 (alkene CH₂), 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 (OCH₂), 62.5 (CH₂), 51.9 (CH₂N), 35.2 (allylic CH₂), 34.5 (allylic CH₂), 27.1 (isopropylidene CH₃), 26.6 (isopropylidene CH₃), 25.9 (CH₃), 24.7 (isopropylidene CH₃), 24.5 (isopropylidene CH₃), 18.3 (C) -5.3, -5.5 (each CH₃); 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 17cis: ¹H NMR (500 MHz, chloroform-d) δ 7.62 (1H, s, triazole H), 5.45 (1H, t, J = 11.2Hz, CH=CH), 5.33 (1H, t, J = 10.3 Hz, CH=CH), 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 CH₃), 1.38 (6H, overlapped signals, 2 x isopropylidene CH₃), 0.91 (9H, s, 3 x CH₃), 0.08 (6H, s, 2 x CH₃); 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 (CH₂), 51.2 (CH₂N), 29.4 (CH₂), 28.3 (CH₂), 27.0 (2s, each isopropylidene CH₃), 25.9 (CH₃), 24.7, 24.4 (each isopropylidene CH₃), 18.4 (C), -5.3, -5.4 (each CH₃); ESI-HRMS: calcd. for C₃₁H₅₁O₉N₃SiNa, 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**: ¹H NMR (500 MHz, chloroform-d) δ 7.65 (1H, s, triazole H), 5.36-5.19 (2H, overlapped signals, CH=CH), 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=CHCH₂), 2.24-2.17 (2H, overlapped signals), 1.90 (1H, ddd, J = 13.5, 7.0, 2.9, CH₂=CHCHH), 1.54 (3H, s, isopropylidene CH₃), 1.49 (3H, s, isopropylidene CH₃), 1.38 (3H, s, isopropylidene CH₃), 1.36 (3H, s, isopropylidene CH₃), 0.91 (9H, s, CH₃ x 3), 0.09 (6H, s, CH₃ x 2); ¹³C 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 (CH₂), 62.5 (gal C-6), 50.4 (gal C-6), 34.8 (allyl CH₂), 33.4 (allyl CH₂), 26.9, 26.7 (each isopropylidene CH₃), 25.9 (3 signals, each CH₃), 24.6, 24.4 (each isopropylidene CH₃), 18.4 (C), -5.3, -5.4 (each CH₃); ESI-HRMS: calcd. for $C_{31}H_{52}O_9N_3Si$, 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; ¹H 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=CHCH₂), 2.20 - 2.15 (1H, m, CHHCH=CHCH₂), 2.02 - 1.97 (1H, m, CH₂CH=CHCHH), 1.96 – 1.91 (1H, m, CH₂=CHCHH), 1.55 (3H, s, isopropylidene CH₃), 1.48 (3H, s, isopropylidene CH₃), 1.39 (3H, s, isopropylidene CH₃), 1.37 (3H, s, isopropylidene CH₃), 0.90 (9H, s, CH₃ x 3), 0.07 (3H, s, CH₃), 0.06 (3H, s, CH₃); ¹³C NMR (126 MHz, chloroform-d) & 142.7 (triazole C=C), 128.6 (CH=CH), 125.8 (triazole CH), 125.6 (CH=CH), 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 (CH₂CH=CHCH₂), 28.2 (CH₂CH=CHCH₂), 27.9, 26.9, 26.1 (each isopropylidene CH₃), 25.9 (3 signals, each CH₃), 24.2 (isopropylidene CH₃), 18.3 (C), -5.3, -5.5 (each CH₃); ESI-HRMS: calcd. for $C_{31}H_{51}O_9SiNa$, 660.3266; found m/z660.3292 [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 Na₂SO₄, 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 C₂₅H₃₇O₉N₃Na, 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-H₂O (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 (CH₂Cl₂:MeOH 4:1) gave the title compound (3 mg, ~75%) as a white solid; ¹H NMR (600 MHz, D₂O): 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, D₂O) 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 (CH₂), 59.7 (gal C-6), 47.8 (gal C-6), 32.2 (CH₂), 28.8 (CH₂); ESI-HRMS: calcd. for C₁₉H₂₉O₉N₃Na, 466.1808; found m/z 466.1801 [M+Na]⁺; FT-IR 3360, 1636, 1362, $1077, \text{ cm}^{-1}$.

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 CaCO₃, 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 $C_{25}H_{35}O_9N_3Na$, 546.2401; found m/z546.2403 [M+Na]⁺. This intermediate (8.0 mg, 0.015 mmol) was dissolved in TFA-H₂O (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 (CH₂Cl₂-MeOH 4:1) gave the title compound (4 mg, ~60 %) as a white solid; ¹H NMR (600 MHz, D₂O) 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); ¹³C NMR (126 MHz, D₂O) 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 (CH₂), 60.2 (gal C-6), 51.7 (gal C-6), 26.7 (CH₂), 25.3 (CH₂); 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(PPh₃)₂ (6 mg, 7 μ mol) 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 °C 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; ¹H 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, OCH₃), 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, CH₃), 1.43 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.31 (s, 3H, CH₃); 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 °C. 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 = 10.9 Hz, 1H), 4.49 (dd, J = 14.3, 10.1 Hz, 1H), 4.44 - 4.33 (m, 3H), 4.31 (t, 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 = 10.9 Hz, 1H), 4.31 (t, J =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, CH₃), 1.44 (s, 1H, CH₃), 1.39 (s, 1H, CH₃), 1.27 (s, 1H, CH₃); ¹³C NMR (126 MHz, chloroform-d) § 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 (CH₂), 73.1 (CH), 72.6 (CH₂), 71.9 (CH), 71.0 (CH₂), 69.3 (CH), 68.4 (CH), 60.6 (CH₂), 55.2 (CH₃), 50.6 (CH₂), 34.6 (CH), 27.1 (CH₃), 26.9 (CH₃), 26.8 (CH₃), 24.4 (CH₃); 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), CuSO₄5H₂O (31 mg, 0.128 mmol) and sodium ascorbate (127 mg, 0.64 mmol) in THF:H₂O (1:1, 10 mL) were placed in a microwave vial. The vial containing the mixture was sealed, and then was heated to 60 °C 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; ¹H 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 = 7.3, 2.9 Hz, 1H, gal H-1),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 CH₃); ¹³C 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 (CH₂), 117.2 (CH₂), 113.9 (CH), 109.6 (C), 109.4 (C), 80.6 (CH), 78.0 (CH), 75.6 (CH), 75.3 (CH), 73.5 (CH₂), 72.9 (CH), 72.6 (CH₂), 71.8 (CH), 71.1 (CH), 70.4 (CH₂), 68.4 (CH), 64.9 (CH₂), 55.2 (CH₃), 51.6 (CH₂), 34.7 (CH₂), 27.0 (CH₃), 26.9 (CH₃), 26.7 (CH₃), 24.8 (CH₃); ESI-HRMS: Calcd for C₄₃H₅₄N₃O₉ [M + H] 756.3860; found 756.3827. This triazole (50 mg, 66 µmol) was added to an oven-dried 10 mL roundbottomed 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 °C 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; ¹H NMR (500 MHz, chloroform-d) δ 7.867.78 (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, CH_3), 1.41 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.31 (s, 3H, CH₃); ¹³C NMR (126 MHz, chloroform-d) & 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 (CH₂), 71.6 (CH), 71.4 (CH₂), 71.1 (CH₂), 70.0 (CH), 69.5 (CH), 64.7 (CH₂), 55.3 (CH₃), 48.4 (CH₂), 35.4 (CH₂), 27.1 (CH₃), 26.9 (CH₃), 26.8 (CH₃), 24.4 (CH₃); ESI-HRMS: Calcd for C₄₁H₅₀N₃O₉ [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-5vinyl-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:H₂O (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

33

brine, dried (Na₂SO₄), 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%); ¹H 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 CH=CH₂), 5.25-5.19 (m, 2H, CHCH=CH₂), 5.08 (dq, J =17.1, 1.5 Hz, 1H, CH₂CH=CHH), 5.04 (dd, J = 10.2, 1.6 Hz, 1H, CH₂CH=CHH), 4.78 (s, 2H, CH₂Naph), 4.70 (d, J = 12.7 Hz, 1H, OCHH), 4.62 (d, J = 12.8 Hz, OCHH), 4.58 (dd, J = 14.1, 4.3 Hz, 1H, NCHH), 4.44 (dd, J = 14.0, 8.6 Hz, 1H, NCHH), 4.41-4.36 (overlapping signals, 2H, CHCH=CH₂ and CHHPh), 4.26 (d, J = 11.4 Hz, 1H, CHHPh), 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)9.2, 3.4 Hz, 1H, H-3), 3.80-3.68 (overlapping signals, 4H, H-5, H-6 and CHCHCH=CH₂), 2.45-2.40 (m, 2H, CH₂CH=CH₂), 1.46 (s, 3H, CH₃), 1.43 (s, 3H, CH₃); ¹³C 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 (CH₂), 116.9 (CH₂), 109.7 (C), 80.6 (CH), 78.1 (CH), 76.9 (CH), 75.9 (CH), 73.9 (CH₂), 73.6 (CH), 73.0 (CH₂), 69.9 (CH), 69.6 (CH₂), 69.4 (CH), 69.1 (CH), 64.6 (CH₂), 51.6 (CH₂), 29.7 (CH₂), 27.0 (CH₃), 26.7 (CH₃); 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

34

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%); ¹H 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, CH₂CH=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 = 2.1Hz, 1H, OH), 2.63 (d, J = 5.7 Hz, 1H, gal 3-OH), 2.31-2.11 (overlapped signals, 2H), 1.45 (s, 3H, CH₃), 1.38 (s, 3H, CH₃); ¹³C 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, CH₂ and CH), 72.8 (CH), 72.5 (CH₂), 71.2 (CH), 70.3 (CH), 68.9 (CH), 68.4 (CH₂), 64.5 (CH₂), 48.6 (CH₂), 27.1 (CH₃), 26.7 (CH₂), 26.6 (CH₃); ESI-HRMS: Found 692.2750 required 692.2739 [M+C1]⁻.

(3aS,4R,7R,7aR)-2,2,4,6-tetramethyl-7-(prop-2-ynyloxy)-4-vinyl-3a,4,7,7atetrahydro-[1,3]dioxolo[4,5-c]pyridine 25 & (6R,6aS,9aS,Z)-8,8,10-trimethyl-6vinyl-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 °C 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); ¹H 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 CH-O-propargyl), 3.66 (dd, J = 10.1, 8.8 Hz, 1H, CH-CH-O-propargyl), 2.48 (t, J = 2.4 Hz, 1H, alkyne H), 2.17 (s, 3H, CH₃C=N), 1.46 (s, 3H, CH₃), 1.43 (s, 3H, isopropylidene CH₃), 1.36 (s, 3H, isopropylidene CH₃); ¹³C-NMR (126 MHz, chloroform-d) δ 165.8 (C, imine), 138.9 (alkene CH), 115.6 (alkene CH₂), 110.4 (C(CH₃)₂), 81.2 (CH-Opropargyl), 80.7 (CH), 79.4 (alkyne CH), 76.2 (alkyne C), 74.9 (alkyne CH), 64.0 (C-N), 58.0 (propargyl CH₂), 27.8 (CH₃), 27.0 (isopropylidene CH₃), 26.7 (isopropylidene CH₃), 23.1 (CH₃); ESI-HRMS: m/z calc for C₁₅H₂₂NO₃: 264.1600 found: 264.1611 $[M+H]^+$. Analytical data for 26: $R_f = 0.74$ (EtOAc-hexanes, 1:1); ¹H 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 = 14.2 Hz), 3.62 (dd, J = 8.8, 3.3 Hz, 1H), 3.46 (dd, J = 14.2 Hz), 3.62 (dd, J = 8.8, 3.3 Hz, 1H), 3.46 (dd, J = 14.2 Hz), 3.62 (dd, J = 8.8, 3.3 Hz, 1H), 3.46 (dd, J = 14.2 Hz), 3.62 (dd, J = 8.8, 3.3 Hz, 1H), 3.46 (dd, J = 14.2 Hz), 3.62 (dd, J = 8.8, 3.3 Hz, 1H), 3.46 (dd, J = 14.2 Hz), 3.62 (dd, J = 8.8 (dd, J = 8.8 Hz), 3.62 (dd, J = 14.2 Hz), 3.62 (dd, J =8.3, 3.3 Hz, 1H), 1.78 (t, J = 1.3 Hz, 3H, CH₃), 1.50 (s, 3H, C(CH₃)₂), 1.42 (s, 3H, C(CH₃)₂); ¹³C NMR (126 MHz, chloroform-d): δ 138.2, 133.9, 132.4, 131.6, 123.0, 120.6, 109.4 (C(CH₃)₂), 79.5, 74.1, 73.5, 58.1, 45.5, 27.0 (C(CH₃)₂), 26.7 (C(CH₃)₂), 18.3 (CH₃); 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 (Et₂O-acetone, 1:1) afforded 27 (21 mg, 85%) as a white solid; $R_f = 0.43$ (Et₂O-Acetone, 1:1); ¹H 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), 5.90 (ddd, J = 13.6, 11.7 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, CH₃); ¹³C 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 CH₂), 76.3, 75.1, 71.0 (each CH-O), 58.1 (CH₂O), 46.3 (CH₂N), 18.3 (CH₃); ESI-HRMS: m/z calc for C₁₂H₁₈N₃O₃: 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-6,7dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine 28 and (6S,7R)-6-((4S,5R)-2,2dimethyl-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 °C for 12 h. Water was added, and the product was extracted into EtOAc. The organic portion was dried over Na₂SO₄, 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); ¹H 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 = 15.0Hz, 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-CHO), 3.96 (d, J = 8.4 Hz, 1H, CHO-CHO-CHO), 3.48 (d, J = 3.4 Hz, 1H, OCHC-N), 1.88 (s, 3H, CH₃), 1.44 (overlapped signals, 6H, C(CH₃)₂); ¹³C 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 CH₂), 116.0 (alkene CH₂), 110.3 (C(CH₃)₂), 79.1 (C=C-CHO), 78.5 (OCHC-N), 77.4 (CHO-CHO-CHO), 65.0 (C-N), 62.7 (CH₂O), 27.0 (isopropylidene CH₃), 26.5 (isopropylidene CH₃), 21.9 (CH₃); ESI-HRMS: *m/z* calc for C₁₅H₂₂N₃O₃: 292.1661, found 292.1665 $[M+H]^+$. Analytical data for 29: $R_f = 0.3$ (EtOAc-hexanes, 1:1); ¹H NMR (500 MHz, chloroform-d) δ 7.47 (s, 1H, triazole H), 5.93 (ddd, J = 17.2, 10.8, 2.0Hz, 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, OCH(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-CHO), 3.85 (dd, J = 8.5, 1.9 Hz, 1H, CHO-CHO-CHO), 3.48 (d, J = 1.8 Hz, 1H, CHOCH₂), 1.79 (d, J = 2.1 Hz, 3H, CH₃), 1.44 (s, 3H, ispropylidene CH₃), 1.42 (s, 3H, ispropylidene CH₃); 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 CH₂), 120.1 (alkene CH₂), 110.2 (C(CH₃)₂), 79.4 (CHO), 77.2 (CHO), 76.8 (CHO), 65.1 (C-N), 62.9 (OCH₂C=C), 27.2 $(C(CH_3)_2)$, 26.5 $(C(CH_3)_2)$, 20.8 (CH_3) ; ESI-HRMS: m/z calc for $C_{15}H_{22}N_3O_3$: 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 °C, 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 (CH₂Cl₂-MeOH, 9:1) gave 30 (6 mg, 15 %) as a white solid; ¹H NMR (500 MHz, CD₃OD): 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, OCH(H)), 4.98 (dd, *J* = 15.3, 1.0 Hz, 1H, OCH(H)), 4.18 (ddd, *J* = 6.9, 2.9, 2.1 Hz, 1H, C=C-CH), 3.92 (dd, *J* = 10.9, 6.8 Hz, 1H, CHO-CHO-CHO), 3.70 (d, *J* = 10.9 Hz, 1H, CHO-C-N); 1.55 (s, 3H, CH₃); ¹³C NMR (126 MHz, CD₃OD) δ 132.4 (triazole C), 132.0 (alkene CH), 129.6 (triazole CH), 128.6 (alkene CH), 81.1 (*CH*OCN), 75.2 (C=C-*CH*O), 73.5 (CHO-*CH*O-CHO), 64.1 (OCH₂), 63.2 (*C*-N), 26.0 (CH₃); ESI-HRMS: m/z calc for C₁₀H₁₄N₃O₃: 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

^aThese authors made equal contributions. PMcA solved the X-ray crystal structure. PVM planned the work with the other authors and wrote the paper.

CORRESPONDING AUTHOR

39

* email: paul.v.murphy@nuigalway.ie

ACKNOWLEDGEMENTS

RC and KF thank NUI Galway's College of Science for scholarships. A proportion of the material presented herein was funded by Science Foundation Ireland (13/TIDA/B2651) co-funded by the European Regional Development Fund.

REFERENCES

1. Ganesan, A. Combinatorial Synthetic Design: The Balance of Novelty and Familiarity. In *Exploiting Chemical Diversity for Drug Discovery*; Bartlett, P. A.; Entzeroth, M., Eds.; RSC Biomolecular Sciences, Royal Society of Chemistry: Cambridge, UK, 2006; pp 91–111.

2. Tropsha A. "QSAR in Drug Discovery". *In Drug Design: Structure- and Ligand-Based Approaches*; Reynolds CH, Merz KM, Ringe D (eds.); Cambridge University Press, Cambridge, UK, 2010 pp. 151–164.

3. Rational Methods for the Selection of Diverse Screening Compounds. Huggins, D. J.; Venkitaraman, A. R.; Spring, D. R. *ACS Chem. Biol.* **2011**, *6*, 208–217.

4. Structural Diversity of Organic Chemistry. A Scaffold Analysis of the CAS Registry.

Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, III, W. F.; Schenck, R. J.; Trippe, A. J. J. Org. Chem. 2008, 73, 4443–4451.

5. Chemoinformatic analysis of combinatorial libraries, drugs, natural products, and molecular libraries small molecule repository. Singh, N., Guha, R., Giulianotti, M. A.,

Pinilla, C., Houghten, R. A., and Medina-Franco, J. L. J. Chem. Inf. Model. 2009 49, 1010–1024

6. Natural Products as Sources of New Drugs from 1981 to 2014. Newman, D. J.; Cragg, G. M. J. Nat. Prod. 2016, 79, 629–661.

7 Natural-product-derived fragments for fragment-based ligand discovery. Over, B.; Wetzel, S.; Grütter, C.; Nakai, Y.; Renner, S.; Rauh, D. Waldmann H. *Nat Chem.* **2013** *5*, 21–8.

8. Comprehensive Structure–Activity Relationship Studies of Macrocyclic Natural Products Enabled by Their Total Syntheses. H. Itoh, M. Inoue, *Chem. Rev.* 2019, https://doi.org/10.1021/acs.chemrev.9b00063

9. Can thousands of years of ancient medical knowledge lead us to new and powerful drug combinations in the fight against cancer and dementia? Ji, H.-F.; Li, X.-J.; Zhang, H.-Y. *EMBO Rep.* **2009**, 10: 194–200

10. Enhancements of screening collections to address areas of unmet medical need: an industry perspective. Drewry, D. H.; Macarron. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 289–298.

11. Small Molecule Natural Products in the Discovery of Therapeutic Agents: The Synthesis Connection. Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329–8351.

12. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. Schreiber, S. L. *Science*, **2000**, *287*, 1964–1969.

13 Diversity-oriented synthesis; a spectrum of approaches and results. Spandl, R. J.; Benderb, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149–1158.

14. Biology□Oriented Synthesis. Wetze, S.; Bon, R. S.; Kumar. K.; Waldmann, H. Angew. Chem. Int. Ed. 2011, 50, 10800–10826.

15. Natural product-like synthetic libraries, Thomas, G. L.; Johannes, C. W. *Curr. Opin. Chem. Biol.*, **2011**, *15*, 516–522

16. Following the Lead from Nature: Divergent Pathways in Natural Product Synthesis and Diversity-Oriented Synthesis, Serba, C.; Winssinger, N. *Eur J. Org. Chem*, 2013, 2013, 4195–4214.

17. Carbohydrate-containing natural products in medicinal chemistry, Cao, H.; Hwang, J.; Chen. X. in Opportunity, Challenge and Scope of Natural Products in Medicinal Chemistry. Ed. Vinod K Tiwari; Publisher: Research Signpost. Trivandrum, Kerala, India. (2011), pp 411–431.

18 Approaches to the total synthesis of natural products using "chiral templates" derived from carbohydrates. Hanessian, S. Acc. Chem. Res. **1979**, *12*, 159–165.

19 Total syntheses of bioactive natural products from carbohydrates. Tatsuta K.; Hosokawa, S. *Sci. Technol. Adv. Mater.* **2006**, *7*, 397

20 Nonpeptidal peptidomimetics with beta-D-glucose scaffolding. A partial somatostatin agonist bearing a close structural relationship to a potent, selective substance P antagonist, Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Strader, C. D.; Smith III, A. B. *J. Am. Chem. Soc.* **1992**, *114*, 9217–9218.

21 Carbohydrates in diversity-oriented synthesis: challenges and opportunities. Lenci,E.; Menchia, G.; Trabocchi, A. *Org. Biomol. Chem.* 2016, *14*, 808–825.

22 Dubbu, S. and Vankar, Y. D. Diversity oriented synthesis of carbohydrate scaffolds through the Prins cyclization of differently protected Domannitol derived homoallylic alcohols. *Eur. J. Org. Chem.* **2017**, *2017*, 5986–6002.

23. Versatility of glycals in synthetic organic chemistry: coupling reactions, diversity oriented synthesis and natural product synthesis. Kinfea, H. H. *Org. Biomol. Chem.* **2019**, *17*, 4153–4182.

24. Multi-Targeting Protein-Protein Interaction Inhibitors: Evolution of Macrocyclic Ligands with Embedded Carbohydrates (MECs) to Improve Selectivity. Negi, A.; O'Reilly, C.; Jarikote, D. V.; Zhou, J.; Murphy, P. V. *Eur. J. Med. Chem.* **2019**, *176*, 292–309.

25. Ligand Design for Somatostatin Receptor Isoforms 4 and 5. Negi, A.; Zhou, J.; Sweeney, S.; Murphy, P. V. *Eur. J. Med. Chem.* **2019**, *163*, 148–159.

26. Synthesis of a benzomacrolactone based somatostatin mimetic. Zhou, J.; Matos, M.-

C.; Murphy, P. V. Org. Lett. 2011, 13, 5716–5719.

27. Diversity-Oriented Syntheses Using the Build/Couple/Pair Strategy. Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2007**, *47*, 48–56.

28. New access to 1-deoxynojirimycin derivatives via azide-alkene cycloaddition. Zhou,Y.; Murphy, P. V. *Org. Lett.* 2008, *10*, 3777–3780.

29. Decorated macrocycles via ring closing double reductive amination. Identification of an apoptosis inducer of leukemic cells, which at least partially antagonises a 5-HT2 receptor. Zhou, J.; Reidy, M.; O'Reilly, C.; Jarikote, D. V. Negi, A.; Samali, A. Szegezdi, E. Murphy, P. V. *Org. Lett.* **2015**, *17*, 1672–1675.

30. Rational Design of Benzyl-Type Protecting Groups Allows Sequential Deprotection of Hydroxyl Groups by Catalytic Hydrogenolysis. Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172–4173.

31. Mild Method for 2-Naphthylmethyl Ether Protecting Group Removal Using a Combination of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and β-Pinene.
Lloyd, D. L.; Bylsma, M.; Bright, D. K.; Chen, X.; Bennett, C. S. *J. Org. Chem.* 2017, 82, 3926–3934.

32. Synthesis and Binding Affinities of Novel SRIF-Mimicking β -D-Glucosides Satisfying the Requirement for a π -Cloud at C1. Angeles, A. R.; Neagu, I.; Birzin, E. T.; Thornton, E. R.; Smith, A. B.; Hirschmann, R. *Org. Lett.* **2005**, *7*, 1121–1124.

33. Allylic azide rearrangement in tandem with Huisgen alkene azide cycloaddition for stereoselective synthesis of iminosugars with a quaternary center adjacent to the ring nitrogen. Chadda, R.; Murphy, P. V. *Eur. J. Org. Chem.* **2020**, 10.1002/ejoc.201901875.

34. Ruthenium-Catalyzed Azide–Alkyne Cycloaddition: Scope and Mechanism. Boren,
B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. J.
Am. Chem. Soc. 2008, 130, 8923–8930.

35. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

36. Olefin Metathesis: A Powerful and Versatile Instrument for Organic Synthesis, Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

37. Rearrangement of allylic azides. Gagneux, A.; Winstein, S.; Young, W. G. J. Am. Chem. Soc. **1960**, 82, 5956.

38. Aminopyrimidine–galactose hybrids are highly selective galectin-3 inhibitors.

Dahlqvist, A.; Zetterberg, F. R.; Leffler, H.; Nilsson, U. J. Med. Chem. Commun., 2019, 10, 913–925.

39. Prevention of undesirable isomerization during olefin metathesis. Hong, S. H.; Sanders, D. P.; Lee, C. W. Grubbs, R. H. *J. Am. Chem. Soc.* **2005** *127*, 17160–17161.

40. Allylic azide rearrangement in tandem with intramolecular Huisgen cycloaddition for iminosugar and glycomimetic synthesis. Functionalized piperidine, pyrrolidine and pyrrolotriazoles from D-mannose. Chadda, R.; McArdle, P.; Murphy, P. V. *Synthesis*, **2017**, *49*, 2138–2152

41. Ring closing metathesis (RCM) approach to the synthesis of conduramine B-2, ent-conduramine F-2, aminocyclopentitol and trihydroxyazepane, Harita, V. K.; Ramesh, N. G. *Org. Biomol. Chem.* 2019, *17*, 5951–5961

42. Eunicin, an oxa-bridged cembranolide of marine origin. Weinheimer, A. J.; Middlebrook, R. E.; Bledsoe, J. O.; Marsico, W. O.; Karns, T. K. B. *Chem. Commun.* **1968**, 325–6.

43. Ipomoeassins A–E, Cytotoxic Macrocyclic Glycoresins from the Leaves of Ipomoea squamosa from the Suriname Rainforest. Cao, S.; Guza, R. C.; Wisse, J. H.; Miller, J.

S.; Evans, R.; Kingston, D. G. I. J. Nat. Prod. 2005, 68, 487–492.

44. Computer-based de novo design of drug-like molecules. Schneider, G.; Fechner, U. *Nat. Rev. Drug Discov.*, **2005**, *4*, 649–663.

45. M. Bols, Carbohydrate Building Blocks, Wiley, New York, 1995.

46. Hydroxyl Groups in Synthetic and Natural-Product-Derived Therapeutics: A

Perspective on a Common Functional Group. Cramer, J.; Sager, C. P.; Ernst, B. J. Med.

Chem. 2019, doi:10.1021/acs.jmedchem.9b00179.

47. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25.

48. Developing natural product drugs: Supply problems and how they have been overcome. Newman, D. J. *Pharm. Ther.* **2016**, 132, 1-9.

49. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics,

and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. Fulmer, G.

R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.;

Bercaw, J. E. Goldberg, K. E. Organometallics 2010, 29, 2176-2179.

46

Declaration of interests

 \boxtimes The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: