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Metathesis and Macrocycles with Embedded Carbohydrates

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Macrocycles containing embedded carbohydrates are found in nature. Tricholorin A and G, woodrosin, sophorolipid lactone, cycloviracin B1, glucolipsin A and ipomoeassins A–F are natural products with interesting biological properties. They have inspired synthesis of non-natural macrocyclic structures which contain embedded carbohydrates. Glycophanes (hybrids of carbohydrates and cyclophanes) were prepared which show potential in host-guest chemistry and which have been applied as rigid scaffolds for the synthesis of bivalent inhibitors of lectin binding to tumour cells. Macrocyclic neoglycoconjugates have also been prepared. These include macrocyclic neooligoaminodeoxysaccharides which bind to RNA regions containing either asymmetric internal loop or hairpin loop-stem junctions, and vaccine candidates. Non-natural macrolides having antibacterial and antifungal activity have been synthesised. Metathesis using Grubbs and Hoyveda-Grubbs catalysts has been key to the successful generation of these compounds. Herein we review the recent application of metathesis to the synthesis of ipomoeassins A, B and F, glycophanes, neooligoaminodeoxysaccharides, macrolides and other macrocycles with embedded carbohydrates.

1. Introduction

Macrocyclic structures that contain embedded carbohydrate residues can be defined as those where at least two bonds from a monosaccharide residue form part of the macrocycle.[1] Such structures occur in nature as resin glycosides or as other kinds of macrocyclic glycolipids. These include tricolorin A and G, woodrosin, sophorolipid lactone, cycloviracin B1, glucolipsin A and ipomoeassins (Figure 1) which have interesting biological properties.[1]

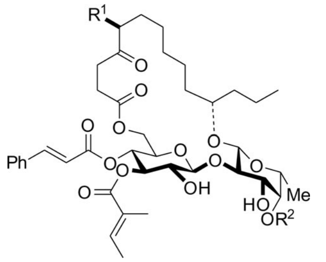

Figure 1. Core structure of Ipomoeassins.

The synthesis of such compounds has generated samples of the natural products and their analogues for biological testing. Macrocyclic structures which contain embedded

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Paul Murphy received his BSc in Chemistry (1990) and his PhD in Organic Chemistry (1994) from the National University of Ireland, Galway. He then worked at the University of York as a Chiroscience Postdoctoral Fellow under the guidance of Professor Richard J. K. Taylor for two years. He was appointed in 1996 as a lecturer in Organic Chemistry at University College Dublin and was subsequently promoted to the post of Associate Professor of Bioorganic Chemistry in 2006. In 2008 he was appointed to the Established Chair of Chemistry at the National University of Ireland, Galway. He has been a research visitor at the University of Pennsylvania and the University of Mainz. He is a member of the Scientific Advisory Board of ERA Chemistry and of the Editorial Board of Carbohydrate Research. Prof. Murphy was awarded an Astellas USA Foundation Award in 2005 and is a Science Foundation Ireland Principal Investigator since 2004. His group is active in the synthesis of antitumour and antiinfective agents. Molecules of interest include natural products, macrocyclic structures, peptidomimetics, carbohydrates, glycomimetics, glycoclusters and glycolipids.

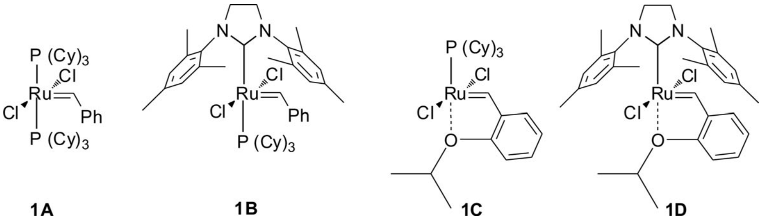


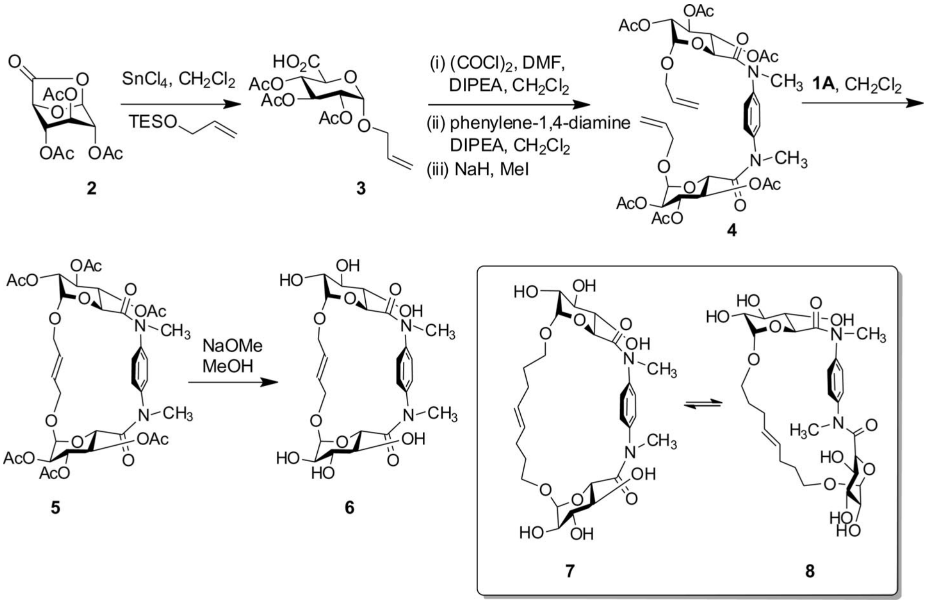
Figure 2. Commonly used metathesis catalysts; **1A** = Grubbs I, **1B** = Grubbs II, **1C** = Hoveyda–Grubbs I and **1D** = Hoveyda–Grubbs II.

carbohydrates that do not occur naturally, but which still have interesting properties have emerged.[2] Inevitably the synthetic routes to such compounds involves a macrocyclization step, which can prove challenging. The intramolecular Diels–Alder reaction,[3] aldol reactions,[4] copper catalysed azide-alkyne cycloaddition[5] and various lactonizations[6] have been used for formation of macrocycles. In recent years, metathesis[7] has become very popular. It has been possible to use both ring closing alkene metathesis (RCM) and ring closing alkyne metathesis (RCAM)[8] to construct large rings, including those of the resin glycosides and other macrocyclic glycolipids.[1] Catalysts required for RCM are readily available and are easy to handle and stable at room temperature. The homogeneous transition metal catalysts that have been developed display high functional group tolerance, selectivity and have proven useful under mild reaction conditions. Several different catalysts used for RCM are shown in Figure 2. This microreview focuses on work published since 2004 where metathesis has been used to generate members of the ipomoeassin family of natural products as well as a range of non-natural products, all of which contain carbohydrate residues inherent in the macrocyclic ring. The non-natural structures prepared include macrocyclic neoglycoconjugates, macrolides and glycophanes. Previous reviews on applications of metathesis to glycobiology and carbohydrate containing macrocycles include relevant examples prior to 2004.[1,7c,9]

2. Glycophanes and Application as Scaffolds in Glycobiology

Cyclophanes have found wide interest in bioactive molecule development and in biomimetic, supramolecular and materials chemistry.[10] Polyfunctional compounds, such as saccharides and their derivatives have been applied as scaffolds for synthesis of new bioactive molecules, including peptidomimetics. More highly functionalized cyclophane[11] derivatives have potential as scaffolds. Murphy and coworkers[12] developed the syntheses of hybrids of cyclophanes and carbohydrates (glycophanes)[11d] with a view to providing constrained functionalised macrocyclic scaffolds[13] displaying specific recognition groups with well defined structure to address questions of relevance to biology. A potential advantage of such scaffolds are that its hydroxyl groups can be modified. Aside from being scaffolds the glycophanes could have potential in host-guest chemistry. The synthesis of such these glycophanes used RCM in the macrocyclisation step.

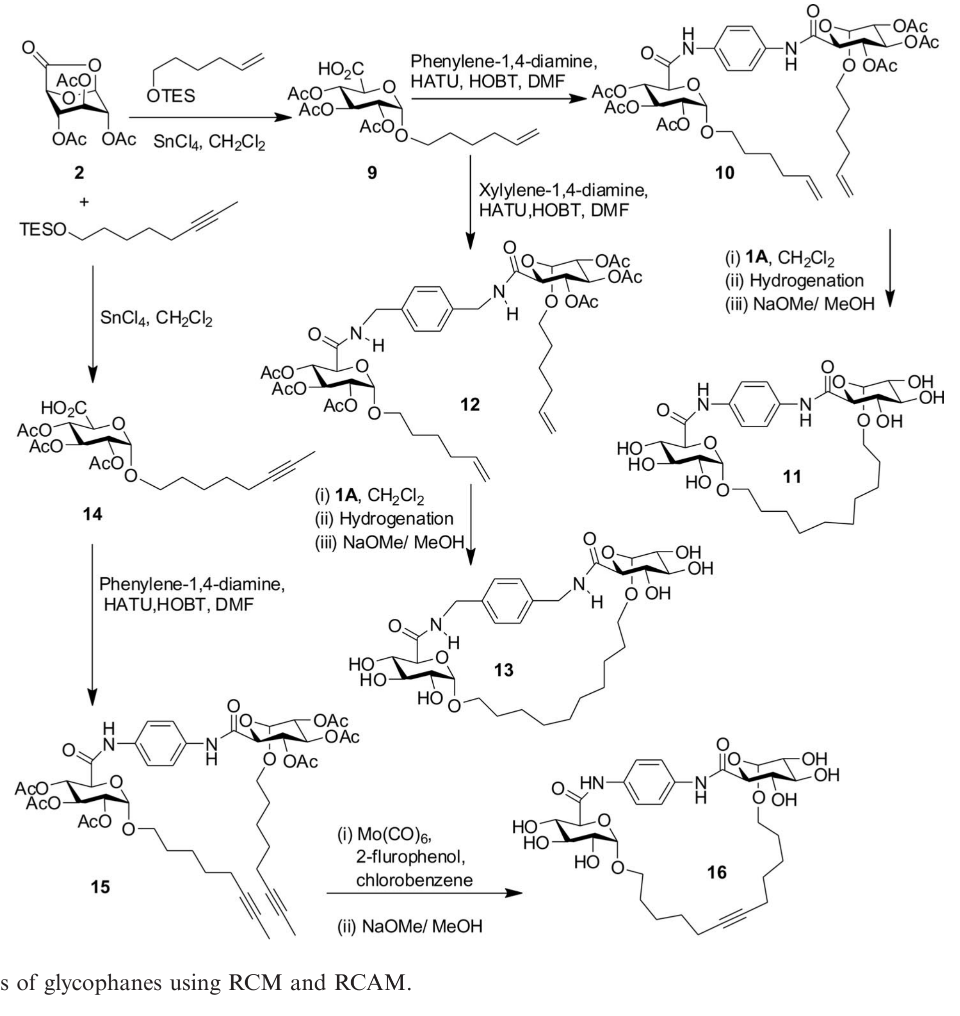
A water soluble structure **6** which had two carbohydrate residues embedded was first synthesized (Scheme 1) using



Scheme 1. Synthesis of a glycophane.

RCM. The glycoside **3** was first prepared from the D-glucuronic acid 6,1-anydro derivative **2**.[14] The free acid in **3** was then converted to its acid chloride, which was then reacted with phenylene-1,4-diamine to yield the diamide. This intermediate was di-N-methylated using methyl iodide in the presence of sodium hydride in DMF to give **4**. Ring closing metathesis using the catalyst **1A** gave a 4:1 mixture of *E*/*Z* isomers (96%) with the *E*-isomer **5** shown in Scheme 1. Subsequent deacetylation gave **6**. The alkylation of the secondary amides was essential to achieving macrocyclisation as shown; efforts to carry out RCM with secondary amides derived from **3** proceeded to give products of cross-metathesis rather than RCM. This is due to a more folded structure being adopted by the tertiary amide which facilitated ring closure. The more lipophilic structure **7** which was prepared by RCM from closely related substrates and which was in equilibrium with amide isomer **8** displayed properties similar to β-cyclodextrin in host-guest chemistry. With a view to further study the host-guest chemistry, glycophanes with secondary amides were subsequently prepared (Scheme 2).[15] Here the researchers utilised the coupling of alkenyl and alkynyl glucopyranosiduronic acids with phenylene-1,4-diamine and xylylene-1,4-diamine to obtain dialkenes and dialkynes. The glycosidation using donor **2** with an appropriate silyl ether derivative in the presence of tin(IV) chloride gave the α-glycosides **9** and **14**, respectively. The reaction of **9** with phenylene-1,4-diamine and xylylene-1,4-diamine promoted by HATU and HOBt gave **10** and **12**, respectively. Similar conditions were used for the synthesis of **15** from **14**. The RCM of **10** and **12** using catalyst **1A** in dichloromethane followed by catalytic hydrogenation and deacetylation gave access to **11** (48% for RCM) and **13** (80% for RCM), respectively. Alkyne metathesis with **15** was carried out using $Mo(CO)_6$ and 2-fluorophenol in chlorobenzene at reflux.[8b,16] The acetate protecting groups were removed using sodium methoxide in methanol to give **16** (27% for RCAM). These macrocyclic compounds were found to have low solubility in water and host-guest chemistry was hence not investigated at this time.

Having established that RCM was useful for the synthesis of glycophanes the preparation of glycophanes presenting carbohydrate recognition motifs was next investigated (see Schemes 3 and 4).[17] In this case the glycophane is a scaffold and the recognition groups are appended to its entrenched hydroxyl groups. The researchers prepared bivalent mannoside ligands (**18**, **20**) where the mannose units were displayed on a glycophane scaffold. They also prepared flexible analogues (**17**, **19**). The selection of compounds for synthesis was based on exploring how changing both rigidity (cf. **18**, **20** with **17**, **19**) and the spatial presen-



Scheme 2. Synthesis of glycophanes using RCM and RCAM.

tation of the ligands (cf. **18** with **20**) would alter inhibition of lectin binding. Compounds **18** and **20** (Figure 3) are derived from allyl glucopyranosiduronic acids. Both **18** and **20** are constrained and molecular modelling has shown that the spatial or geometric relationship between the two mannose ligands in the two molecules is significantly different. These two compounds are also significantly more flexible than **17** and **19**. These (and other) bivalent mannosides, which were less rigid than **18** and **20**, were studied in a series of cell-based assays, that involved evaluation of the inhibition of lectin binding to various tumour cell surfaces. They observed a clear trend of enhanced inhibitory properties for macrocyclic compounds compared to non-macrocyclic derivatives and the glycocyclophane **20** was generally more active than **18**. Thus the use of the glycophane scaffolds showed that both constraint and geometrical presentation of recognition groups can be important to consider when designing glycoclusters as inhibitors of biological events.

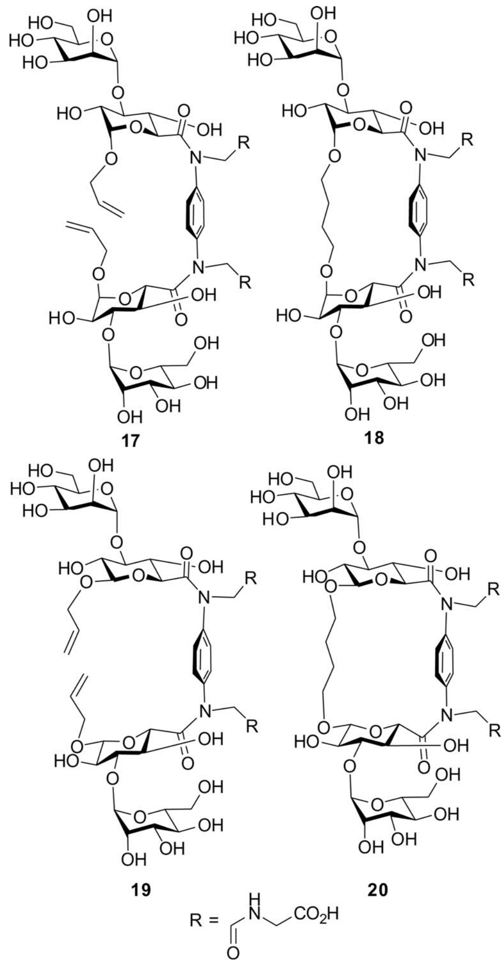
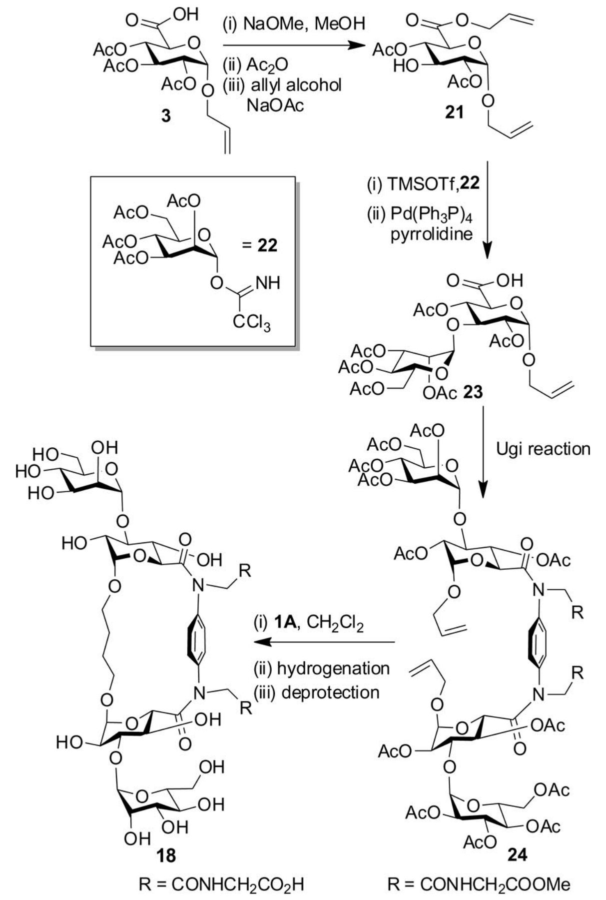


Figure 3. Structures of glycophane-based bivalent mannosides and flexible analogues.

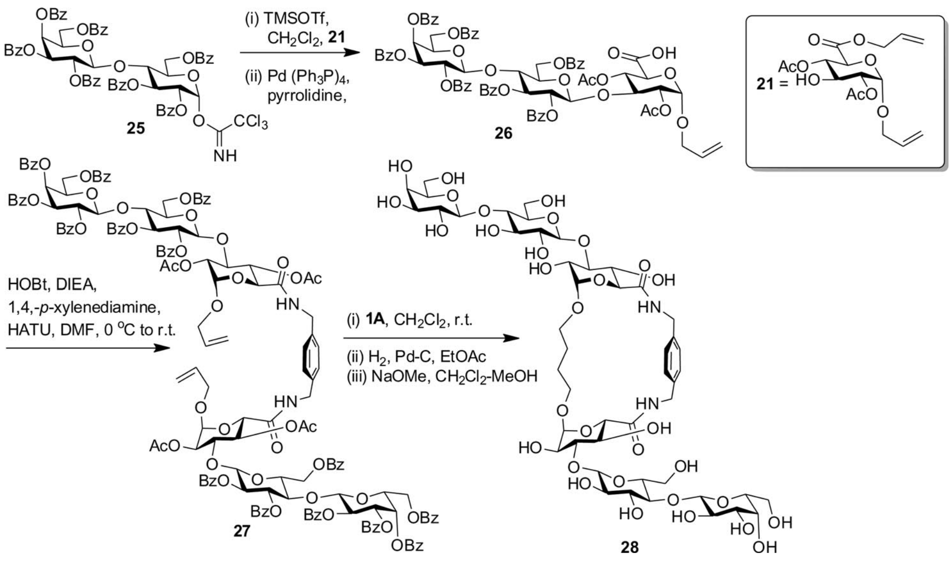
Both of the macrocyclic derivatives **18** and **20** were prepared via RCM. The synthesis of **18** is shown in Scheme 3. The α-glycoside **3**[14] was treated with sodium methoxide in methanol and subsequent acetylation produced a 6,3-lactone intermediate. This lactone was immediately reacted with allyl alcohol in the presence of molecular sieves and sodium acetate to give **21**. Glycosidation using the trichloroacetamide donor **22** promoted by TMSOTf in presence of acceptor **21** and the subsequent removal of the allyl ester from the product gave **23**.[18] The presence of the free carboxyl group on **23** facilitated the generation of a divalent compound using the Ugi reaction:[19] thus reaction of **23** with formaldehyde, phenylene-1,4-diamine and methyl isocyanoacetate gave **24**. The dialkene **24** was subjected to RCM using **1A** in dichloromethane to give macrocycle (71 %); subsequent reduction and removal of acetate groups gave **18**. The compound **20** was synthesized starting from an allyl β-D-glucuronide using a similar strategy.



Scheme 3. Synthesis of a rigid macrocyclic glycocluster.

With a view to inhibiting lectin binding to tumour cells and to plant toxins, Murphy and co-workers also prepared a variety of rigid (Scheme 4) and flexible bivalent lactosides that included a compound based on a glycophane scaffold.[20] The synthesis of the rigid macrocyclic compound **28** was achieved via RCM.

Glycosidation of **25** with **21** and subsequent palladium catalyzed cleavage of the allyl ester gave **26**. Reaction of **26** with *p*-xylylenediamine in presence of HOBt, HATU and DIPEA generated the protected divalent lactoside **27**. The subsequent RCM of **27** using the catalyst **1A** in dichloromethane gave a mixture of macrocyclic isomers containing

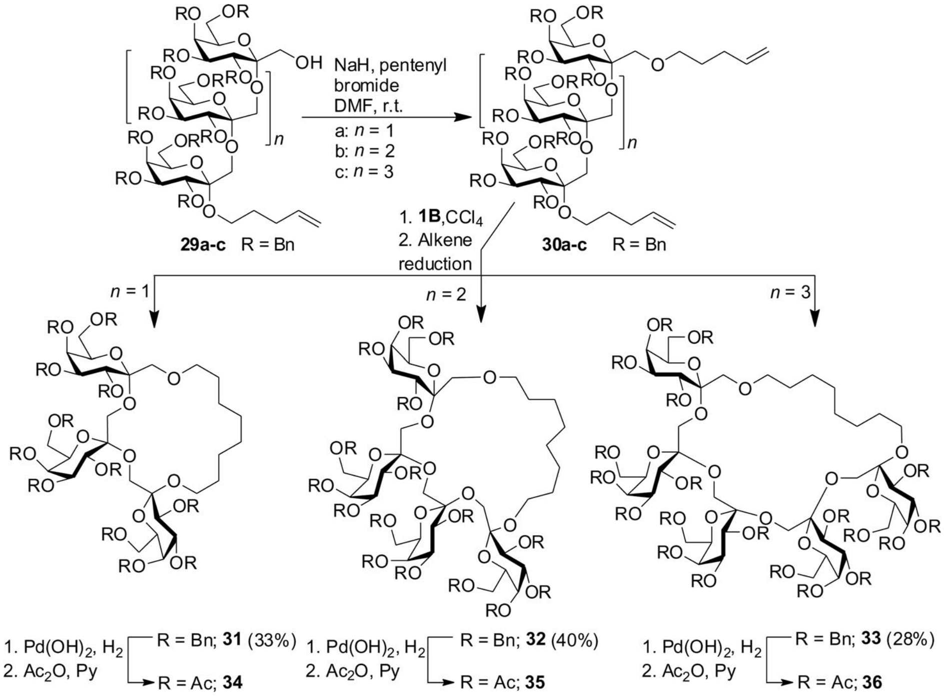


Scheme 4. Synthesis of a bivalent lactoside based on a glycophane scaffold.

E and *Z* alkene groups. The unreacted dialkene was also recovered in this particular reaction. Hydrogenation of the alkene mixture (32% over two steps) followed by removal of acetyl groups proceeded to give the desired constrained macrocyclic bivalent lactoside **28**. Compound **28** was found to be active as an inhibitor of lectin binding in a solid phase assay and also inhibited binding of lectins to cell surfaces.

3. Macrocyclic Neoglycoconjugates

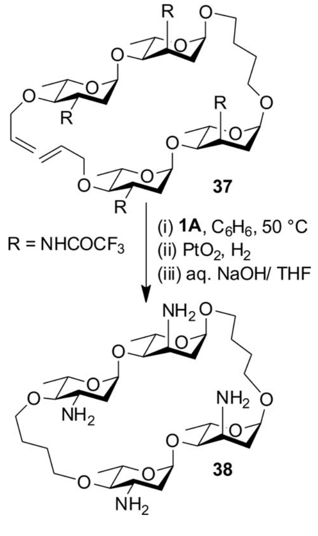
Macrocyclic neoglyconjugate synthesis (Scheme 5) has been reported by Dondoni and Marra[21] using RCM of D-*galacto*-2-heptulopyranose derivatives. Interest in carbohydrate-based moieties which have lipophilic subunits as chiral amphiphilic receptors stimulated the synthesis of these compounds. The oligosaccharides **29a–c** on reaction with pentenyl bromide using NaH in DMF gave compounds **30a–c**, respectively. The dialkenes **30a–c** were treated with catalyst **1B** in carbon tetrachloride at 100 °C to give the macrocyclic products **31–33**, respectively, after reduction of the olefins. The alkene double bond was reduced using diimide, generated from tosylhydrazide and sodium acetate to give corresponding cyclic neoglycoconjugates.[22]



Scheme 5. Linear D-*galacto*-2-heptulopyranose derivatives.

Compound **31** has an 18-membered macrocyclic ring whereas **32** and **33** have 21- and 24-membered rings, respectively. The yield of macrocyclic products from RCM was reported to decrease on increasing the number of carbohydrate units in the linear ketoside. The preparation of **33**, which contains a pentaketoside segment was still achieved in a satisafactory yield (43%). The cleavage of the benzyl groups of **31**–**33** was effected using palladium hydroxide and hydrogen. Subsequent acetate protection using acetic anhydride and pyridine gave **34**–**36**, respectively with very good yield. Thus RCM offered a facile route to macrocycles containing various ketosides.

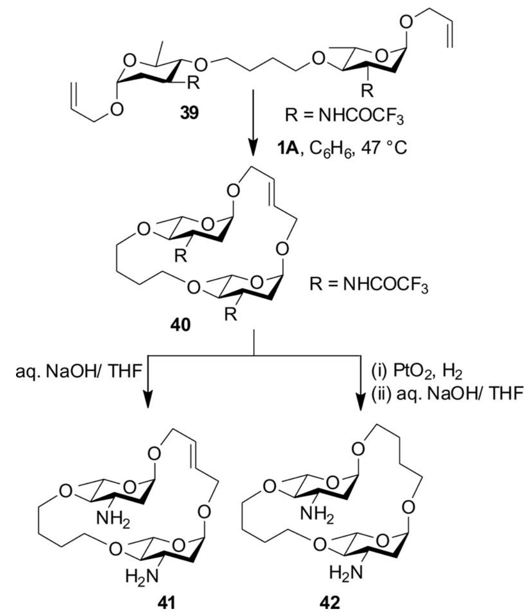
Macrocyclic neooligoaminodeoxysaccharides have potential to bind to polynucleotides and several such derivatives been synthesized (see Schemes 6, 7, and 8) by Kirschning and co-workers.[23] The protonatable polyamines of oligocationic compounds play a key role in biological processes such as specific binding to a polynucleotide leading to the inhibition of DNA duplication. It is also possible to use such compounds to inhibit an RNA target or to force RNA to adopt alternative conformations. In these contexts there was the need to prepare a variety of macrocyclic aminoglycosides. Lewis acid promoted glycosidation of a disaccharide acceptor with butane-1,4-diol was used to prepare compound **37**. The RCM of the neotetrasaccharide **37** using catalyst **1A** in benzene at 50 °C was slow and a mixture of different products resulted. The researchers isolated the desired compound (22%), after hydrogenation of the product mixture. The final target **38** was then obtained after the removal of trifluoroacetyl group.



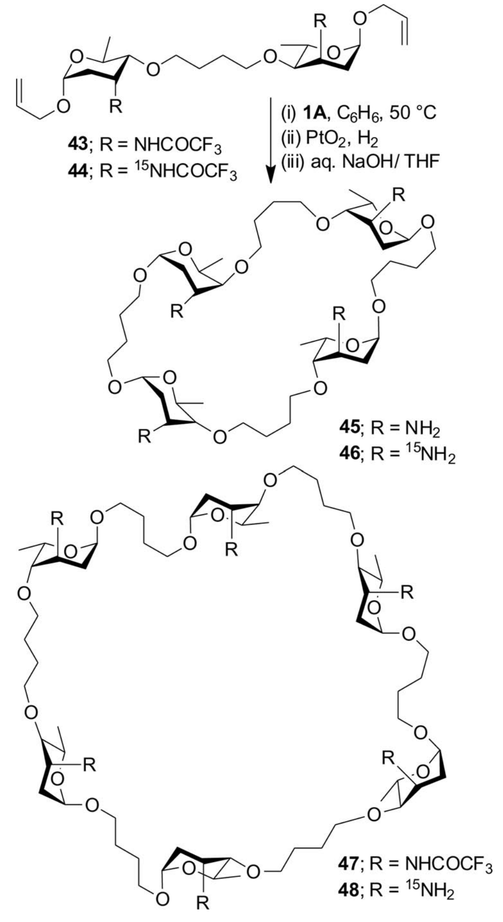
Scheme 6. Cyclic neooligoaminodeoxysaccharide **38**.

Kirschning and his co-workers also reported that the outcome from metathesis applied to the preparation of the macrocyclic neooligoaminodeoxysaccharides was highly dependent on the configuration of the saccharide. This conclusion was based on observations of the outcome of RCM of dialkenes derived from arabinose and ribose configured saccharide derivatives.

The *arabino*-configured homodimer **39** gave the desired intramolecular metathesis product **40** in 67% yield. The removal of protecting groups from **40** using basic conditions gave **41**. Macrocycle **42** was obtained by catalytic hydrogenation and removal of protecting groups.



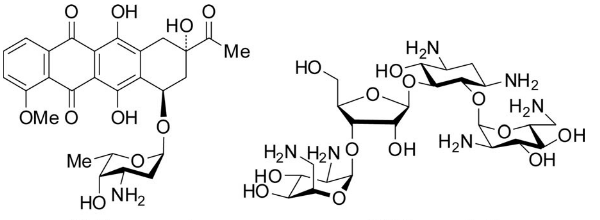
Scheme 7. Cyclic neooligoaminodeoxysaccharides **41** and **42**.



Scheme 8. L-Ristosamine derivatives and ^{15}N-labelled variants.

Under similar reactions conditions to that used to prepare **41** and **42** the ribo-configured starting homodimer **43** afforded the cyclic neotetra- (**45**–**46**; 64%) and neohexasaccharides (**47**–**48**; 16%), respectively (Scheme 8). The authors suggested that the formation of these mixtures of macrocycles rather than a single neodisaccharide product could be because of the axial amino substituent at *C*-3 that may be preventing direct intramolecular macrocyclization of linear diene **43**. Dimerization or trimerization of neodisaccharides **43** and **44** by cross-metathesis occurred followed by RCM.[23] The macrocyclic neotetrasaccharide gave **45** after catalytic hydrogenation and cleavage of protection group. Macrocycle **47** was obtained by catalytic hydrogenolysis of the formed macrocyclic neohexasaccharide.

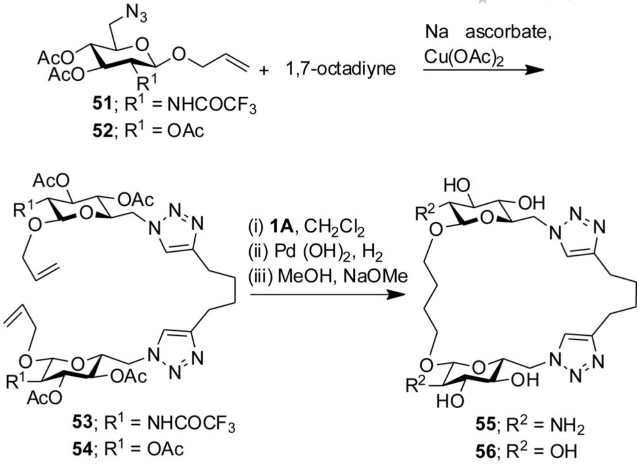
The preparation of ^{15}N-labelled derivatives, such as those shown in Scheme 8, facilitated the NMR study of the mode of interaction of the macrocyclic derivatives with regulatory RNA structures.[23b] The interaction of these neooligoaminodeoxysaccharides derivatives with various RNA targets was studied[23b] and the results suggested that they preferably bind to RNA regions containing either an asymmetric internal loop or hairpin loop-stem junctions. Nature has utilized the anthracycline antibiotic daunomycin **49** as well as amino glycoside antibiotic neomycin B **50** to target such polynucleotides. The macrocyclic neooligoaminodeoxysaccharides, which contain the embedded amino sugars provide a new class of compound to target these interactions (Figure 4).



49; Daunomycin **50;** Neomycin B

Figure 4. Structure of daunomycin and neomycin B.

Synthesis of macrocycles containing triazole moieties (Scheme 9) via copper catalysed azide-alkyne cycloaddition and subsequent RCM reaction has been carried out by Westermann and co-workers.[24] The syntheses of these compounds was inspired by cyclic glycolipids like sophorolipid lactone and tricolorin-G, which exhibited diverse structural and biological characteristics.[25] Such compounds are made up of lipophilic aglycons linked to the variable number of carbohydrate units. While using RCM as the key macrocyclisation step Westermann and coworkers synthesized four macrocycles (Scheme 9 and Figure 5) starting from glucose and glucosamine. For example, compound **51** was synthesized starting from commercially available 2-amino-2-deoxy-D-glucose.[26]



Scheme 9. Macrocycles containing triazoles.

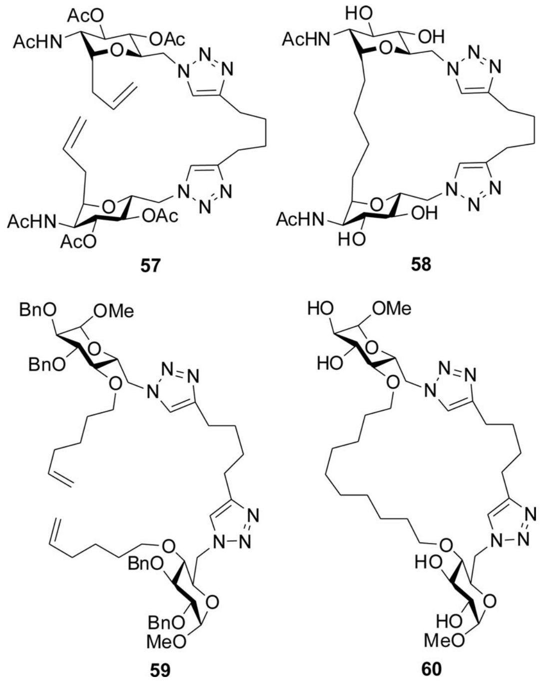
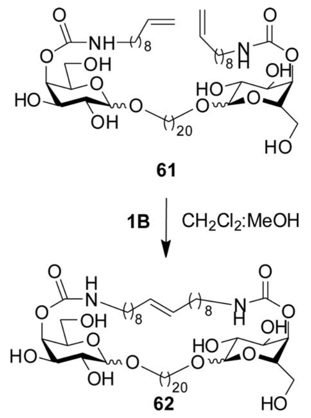


Figure 5. Diolefinic and macrocyclic compounds containing triazoles.

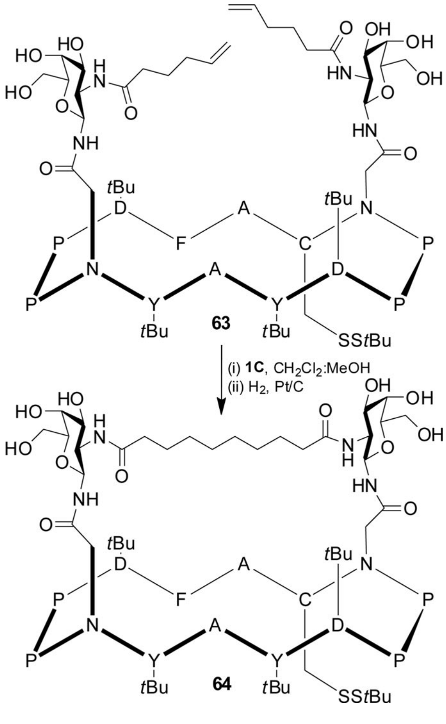
The introduction of olefinic functions to anomeric centres in the synthesis of **51** or **52** was carried out by using Köenigs–Knorr reaction or Keck allylation, respectively.[27] Compounds **51** and **52** on copper catalysed azide–alkyne cycloaddition[28] with commericially available 1,7-octadiyne gave **53** and **54**, respectively. The diolefinic molecules **53**, **54** were then subjected to RCM using catalyst **1A** to obtain the respective macrocyclic non-separable mixture of both isomers. Reduction of the alkenes and subsequent debenzylation and removal of acetate and TFA protecting groups gave **55** and **56**, respectively.[29] A similar strategy was used to prepare **58** and **60** from **57** and **59** respectively, which were derived from C-glycosides. The RCM reaction proceeded in 73–95% yields.

Galactose-based macrocyclic surfactants were synthesised by Krausz and co-workers (Scheme 10).[30] The reaction of **61** with catalyst **1B** gave **62** in 33% yield.



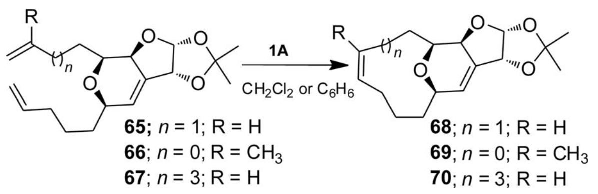
Scheme 10. Surfactant **62**.

The synthesis of antitumour vaccines in highly clustered modes by RCM is reported by Danishefsky and co-workers (Scheme 11).[31] They have designed and synthesised the RCM precursor **63** and other clustered glycopeptides. Compound **63** gave a macrocyclic product **64** using catalyst **1C** (65%), and subsequent metal-catalysed hydrogenation. Danishefsky and colleagues indicated that the protected macrocycle **64** may further be modified to give synthetic vaccines candidates by the attachment of multiple different antigens, to reflect heterogeneity of target cancers. The authors expect that these highly clustered compounds may help in gaining insights into the way that carbohydrate clusters are recognized by the immune system.



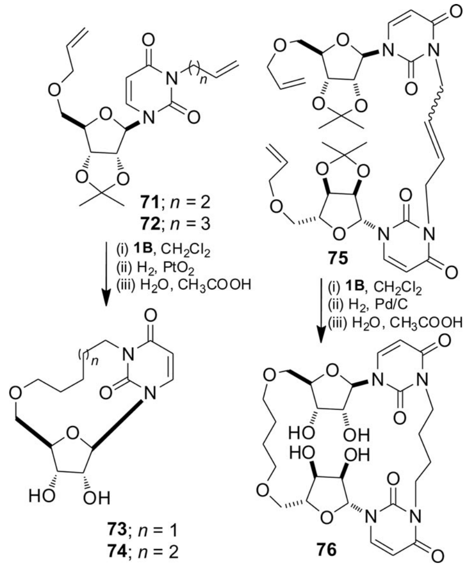
Scheme 11. A cross-linked glycopeptide.

Gurjar and co-workers[32] reported the synthesis of tricyclic framework of the natural compound eunicin by RCM (Scheme 12). The RCM precursors **65**–**67** were synthesised in several steps starting from D-glucose and their reaction with catalyst **1A** gave **68**–**70** (46–48%) yields.



Scheme 12. Eunicin-related frameworks.

Cyclonucleoside analogues of uridine has been synthesized by Len and his co-workers (Scheme 13).[33] Reaction of **71**, **72** and **75** with catalyst **1B** gave the macrocyclic products **73**, **74** and **76** (50–74%) after hydrogenation and subsequent deprotection.

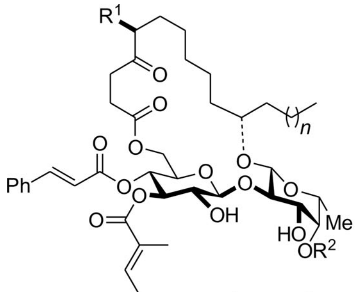


Scheme 13. Constrained uridine derivatives.

4. Natural Products: Ipomoeassins A–F

Cytotoxic resin glycosides have been known to exhibit various biological activities such as laxative, purgative, haemolytic, antibacterial, antifungal properties; they also can inhibit plant growth inhibition as well as have notable cytotoxicity.[25,34] However, their mode of action is still not well understood.[35] It is also reported that variations in the peripheral oxygenation and acylation pattern alter the cytotoxicity of the compounds.[36] Structures of ipomoeassin A–F (**77**–**82**) are shown in Figure 6. Ipomoeassin F differs from its close analogue ipomoeassin A only by the presence of two additional methylene units at the fucose anomeric centre. Differences between other ipomoeassin derivatives include the presence/absence of free OH or acetate groups at C-5 within the fatty acid tether and at the C-4 of the sugar moiety.[37] Fuerstner reported the syntheses of ipomoeassin E and B in 2007.[38] In 2009 Postema[39] and co-workers reported the synthesis of Ipomoeassin F whereas

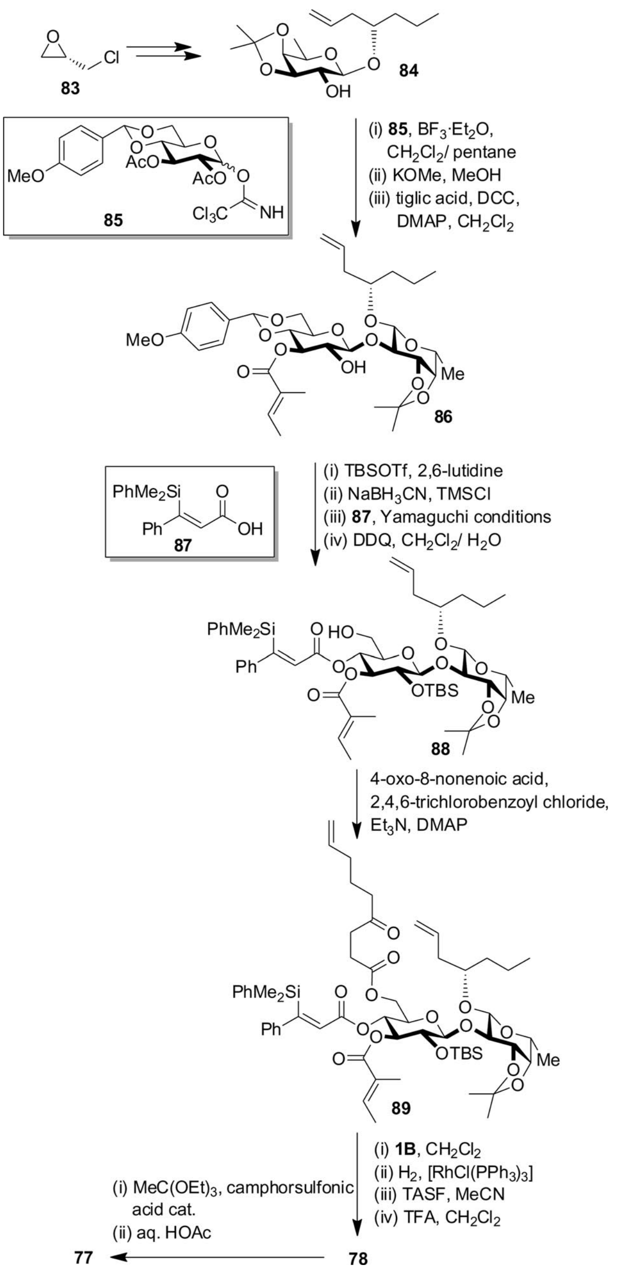
Fuerstner[37a] and co-workers reported syntheses of Ipomoeassin A, C, D and F. Both groups used RCM for the key macrocyclization steps for all compounds.



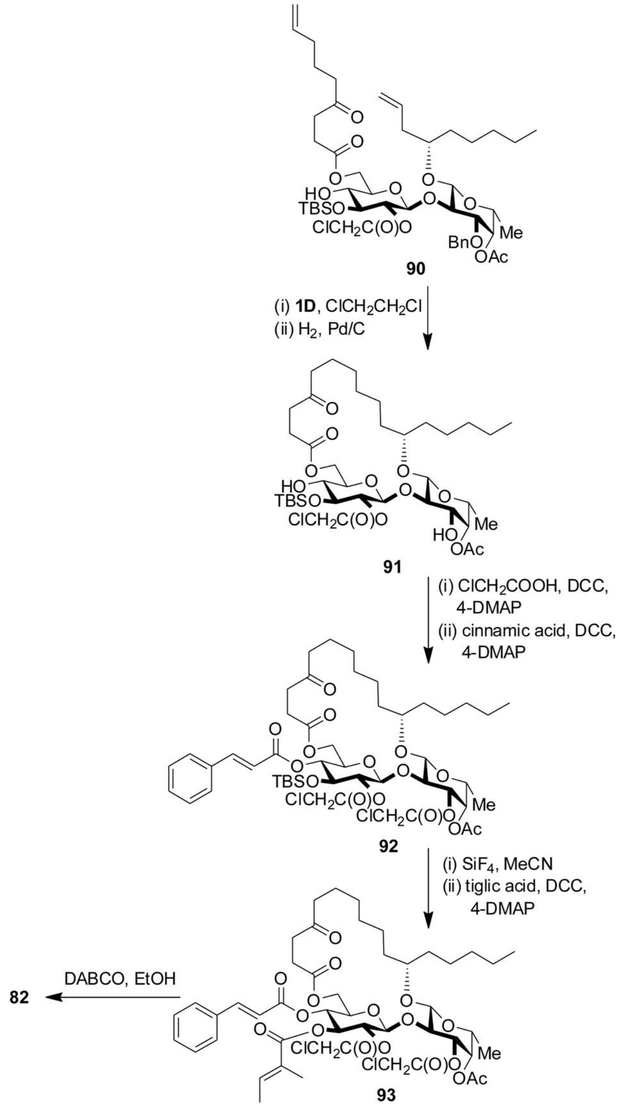
	R^1	R^2	n
77; Ipomoeassin A	H	Ac	1
78; Ipomoeassin B	H	H	1
79; Ipomoeassin C	OH	Ac	1
80; Ipomoeassin D	OAc	Ac	1
81; Ipomoeassin E	OAc	H	1
82; Ipomoeassin F	H	Ac	3

Figure 6. Ipomoeassins A–F.

The synthesis of **77** and **78** by Fuerstner and co-workers is illustrated in Scheme 14. Closely related routes were employed to prepare **79**–**82**. Alkene **84** was synthesized by several steps starting from *S*-epichlorohydrin **83**.[38–40] The glucosyl donor **85** was synthesized starting from a hemiketal precursor.[41] The reaction of **84** with **85** in the presence of $BF_3{\cdot}Et_2O$ furnished the corresponding disaccharide. Subsequent cleavage of the acetate groups and then a regioselective esterification with tiglic acid was carried out at the more nucleophilic *O*-3′′ site of the β-glucoside to give **86**. The free OH group was then protected as a TBS ether using TBSOTf and 2,6-lutidine in dichloromethane. The reductive opening of the benzylidene acetal was achieved using a combination of $NaBH_3CN$ with TMSCl and gave a 4:1 mixture of PMB ether derivatives in good yield, the desired 6-*O*-PMB ether being the major product. The 6-*O*-PMB derivative was subjected to the Yamaguchi esterification with **87** and this reaction was followed by the oxidative removal of the PMB group using DDQ to give **88**. Next the attachment of 4-oxo-8-nonenoic acid ester on **88** was carried out also using Yamaguchi conditions to give **89**. The resulting diene precursor **89** on RCM reaction in dichloromethane gave the desired macrocycle in 81% yield. The alkene reduction was carried out using hydrogen with $[RhCl(PPh_3)_3]$ and the *C*-silyl group and *O*-TBS ether were removed at the same time using tris(dimethylamino) sulfonium difluoro trimethyl silicate in acetonitrile. The isopropylidene acetal was cleaved off with the help of dilute trifluoroacetic acid. This gave **78** (Ipomoeassin B) which was then elaborated to **77** (Ipomoeassin A) by treatment with $MeC(OEt)_3$ in the presence of camphorsulfonic acid, followed by an HOAc-induced orthoester rearrangement to provide its required axial acetate. The synthesis of **82** by Postema and co-workers[39] was achieved from dialkene **90** (Scheme 15). The RCM of **90** using catalyst **1D** in 1,2-dichloroethane gave the desired macrocyclic compound in 84% yield as a mixture of isomers. Catalytic hydrogenation of the mixture gave **91**. Compound **91** was then subjected to selective chloroacetylation using chloroacetic acid, DCC and 4-DMAP. Subsequent coupling with cinnamic acid promoted by DCC in 1,2-dichloroethane gave **92**. The TBS group of **92** was removed using SiF_4.[42] Then tigloylation at *O*-3′′ gave the fully protected precursor **93**. The α-chloroacetates of **93** were cleaved by employing an excess of DABCO[43] in hot ethanol to finally give **82** (Ipomoeassin F).



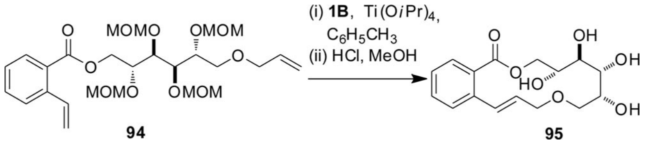
Scheme 14. Synthesis of Ipomoeassin A and B.



Scheme 15. Synthesis of Ipomoeassin F.

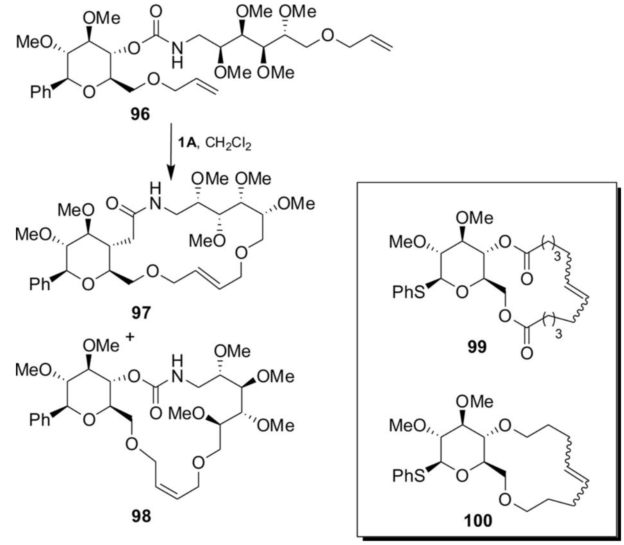
5. Non-Natural Macrolides

Benzomacrolactones have been reported that possess diverse biological and medicinal properties and these are often natural products found in plants, fungi and insects.[44] The synthesis of non-natural analogues of the benzomacrolactones offers the opportunity to generate new compounds for screening. The synthesis of **95** (Scheme 16) and other macrolides was reported by Matos and Murphy using RCM.[45] The polyhydroxylated fragment in **94** was generated from D-mannitol.



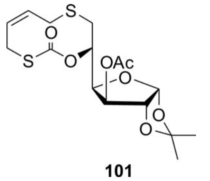
Scheme 16. Synthesis of polyhydroxylated oxamacrolide.

Eycken and his group have also prepared carbohydrate-based macrolides (Scheme 17).[46,47] The diene **96** was synthesised in several steps from penta-*O*-acetyl-β-D-glucopyranose. The reaction of **96** with catalyst **1A**, gave a mixture of **97/98** (3.7:1) in 94% yield. A similar synthetic route was applied for the synthesis of other related macrolides. The yields for the RCM reactions (precursors not shown) that gave **99** and **100** was 34% and 86%, respectively. Some of the macrolides were found to be active against gram-positive and gram-negative bacteria as well as fungi. Moderate antibacterial activity of macrolide **97** and **98** against *C. neoforman* was observed. Macrolide **99** was found active against *M. gypseum* and **100** showed good activity against gram-positive bacteria, including resistant strains such as MRSA (Methicillin-resistant *Staphylococcus aureus*).



Scheme 17. Carbohydrate-based macrolides.

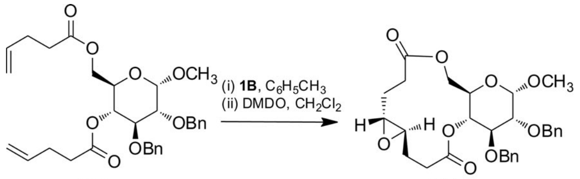
Benazza and co-workers[48] have recently used RCM for the short and stereoselective synthesis of sulphur containing macrocyclic compounds (Figure 7). Thioallyl ether extracts from Liliaceae plants has been reported showing potential antioxidant properties.[49] The authors suggested that 10-membered macrocyclic thiocarbonates[50] could have biological applications. They prepared **101** using RCM promoted by catalyst **1B** in dichloromethane (75%).



101

Figure 7. Structure of **101**.

Peczuh and co-workers have reported the synthesis of 13-membered macro-dilactones by use of RCM (Scheme 18).[51] Starting from methyl α-D-glucopyranoside the precursor **102** was synthesised. When **102** was treated with catalyst **1B** it gave the ring-closed product in 78% yield. The DMDO-mediated epoxidation of the *trans*-alkene product gave **103** (62%). These researchers reported other two macro-dilactones using a similar synthetic strategy from a septanoside derivative.



102 **103**

Scheme 18. Carbohydrate-based macrodilactones.

Conclusions

Macrocyclic compounds with embedded carbohydrates were recently synthesised. Metathesis chemistry has been very important in enabling the synthesis of these biologically important natural products such as the ipomoeassin natural products. Researchers have also been stimulated to construct non-natural macrocyclic compounds based on carbohydrates for application in bioorganic, medicinal and supramolecular chemistry. This has led to the generation of new inhibitors of carbohydrate–protein and nucleic acid–protein interactions, molecules with potential as vaccines and compounds for investigation in supramolecular chemistry. New antiinfective compounds which are carbohydrate-based analogues of macrolides have also been synthesised.

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