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Synthesis of pseudo-oligosaccharides by a sequence of yne-ene cross metathesis and Diels–Alder reaction

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Various pseudo oligosaccharides were prepared by a combination of selective yne-ene cross metathesis and Diels–Alder reaction from readily available monosaccharide building blocks.

Oligosaccharides have been implicated as key participants in a number of biological processes including signal transduction and a wide range of recognition events.[1] Because of this tremendous biological importance, carbohydrates have aroused much interest in synthetic and medicinal chemistry.[2]

During recent years the number of applications of olefin metathesis as a very mild and competitive synthetic method[3] has been considerably increased, due to the availability of well-defined catalysts, in particular Grubbs' well-established ruthenium initiator $Cl_2(PCy_3)_2Ru{=}CHPh$ (**Ru**, Cy = cyclohexyl).[4] However, olefin metathesis has rarely been used in carbohydrate chemistry. Most applications are ring closing metatheses (RCM) for the synthesis of monosaccharide derivatives[5] and few examples exist for ring opening metathesis polymerisation (ROMP) involving carbohydrates.[6] A very recent publication describes the homodimerisation of a number of olefinated pyranosides.[7] Selective cross metatheses employing monosaccharide building blocks have not been studied, apart from some isolated examples.[8,9] Nonetheless, the selective cross coupling of monosaccharide building blocks is very intriguing since the diversity of accessible carbohydrate derivatives is much higher compared to simple homodimerisation.

A selective cross metathesis between a terminal alkyne and a terminal alkene yielding 1,3-disubstituted butadienes has been found recently in our laboratory.[9] These 1,3-dienes, formed by yne-ene cross metathesis, represent attractive starting materials for subsequent Diels–Alder reactions (Scheme 1).

However, little is known about Diels–Alder transformations of nonactivated acyclic 1,3-dienes,[10] which are regarded as poor substrates for Diels–Alder reactions. As there were no examples of Diels–Alder reactions incorporating carbohydrate-substituted 1,3-butadienes, we started investigations on yne-ene cross metatheses of monosaccharide building blocks and subsequent Diels–Alder transformations, providing an easy and very flexible access towards pseudo-oligosaccharides.

Introducing acetylated 1-*O*-allyl- and 1-*O*-propargyl-glycopyranoside as the alkene and alkyne components to yne-ene cross metathesis followed by $MeAlCl_2$-catalysed Diels–Alder reaction with methyl vinyl ketone yielded compounds **1** and **2**, respectively (Fig. 1).†

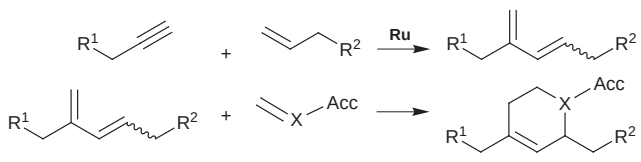
A number of allyl- and propargyl-substituted carbohydrate building blocks was then prepared and introduced to yne-ene cross metathesis followed by Diels–Alder transformation according to Scheme 2. The combination of acetylated 1-*O*-allyl- and 1-*O*-propargyl-glyco- and -galacto-pyranosides afforded pseudo-oligosaccharides **3** and **4** in high yields.‡

A problem of all cross metathesis reactions that has not been solved as yet is the formation of *E*/*Z* mixtures,[3] usually resulting in stereoisomeric mixtures after subsequent transformations. Although the described Diels–Alder reaction proceeds with excellent regioselectivity, diastereomeric mixtures are obtained, due to the incorporation of *E*/*Z* mixtures of the carbohydrate-substituted 1,3-dienes. The diastereomers refer to the relative configuration of the cyclohexene substituents. However, this disadvantage can be overcome by equilibration into the thermodynamically more stable *trans*-configuration using NaOMe in MeOH–THF with simultaneous cleavage of any acetate protective groups (Scheme 2).

This equilibration–deprotection strategy has been successfully applied to the preparation of compounds **8**–**10**, where acetyl- and benzyl-protected β-D-glyco- and β-D-galacto-pyranosides with glycosidic and nonglycosidic linkage of the respective carbohydrate residue have been employed.

In addition to the described Lewis acid catalysed Diels–Alder reactions of 1,3-dienes we focused on aza-Diels–Alder transformations, since these would provide access to biologically interesting pipecolic acid derivatives substituted by two variable carbohydrates (Scheme 3).

As dienophiles we employed *N*-trichloroethylidene toluene-*p*-sulfonamide and ethyl (4-tolylsulfonylimino)acetate. Similar



Scheme 1

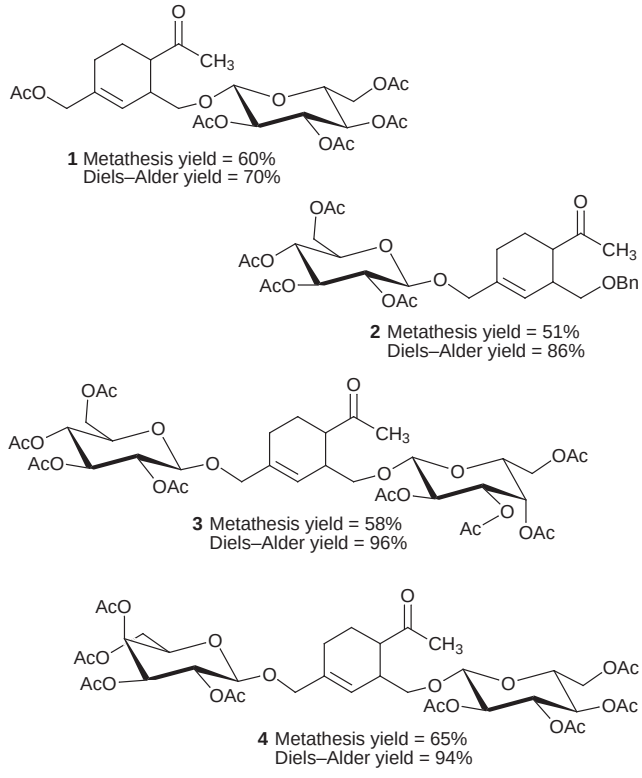
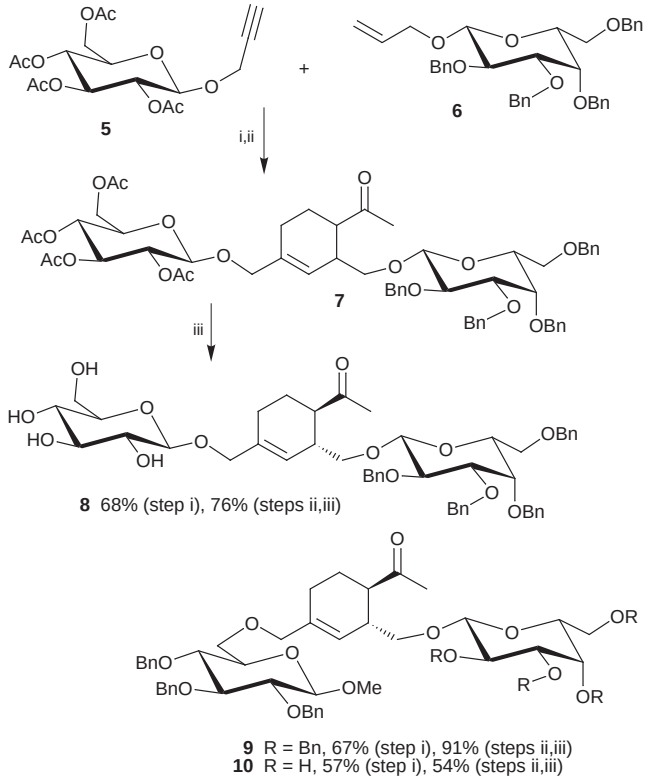
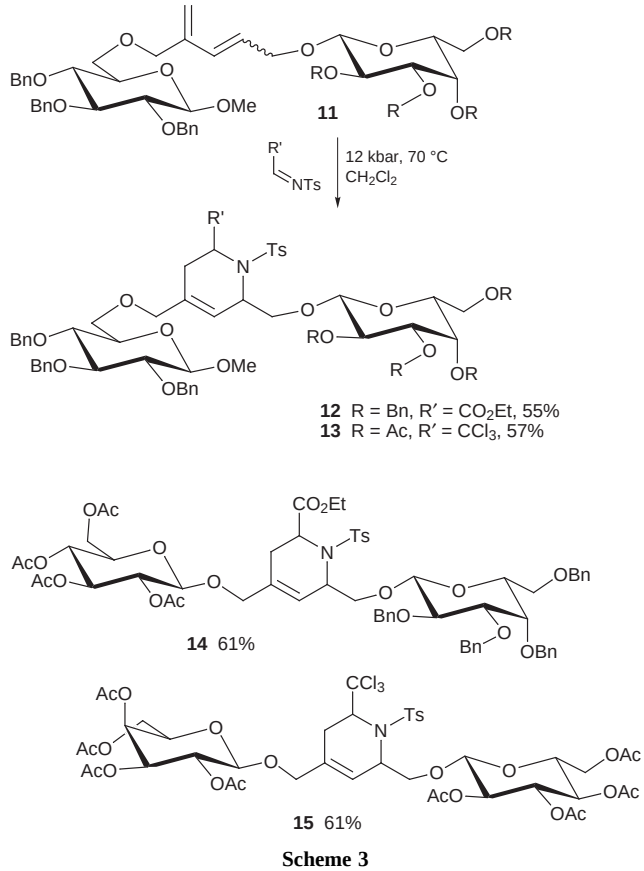


Fig. 1 Yields of **1**–**4**.



Scheme 2 *Reagents and conditions*: i, **Ru** (10%), CH_2Cl_2; ii, methyl vinyl ketone, $MeAlCl_2$, CH_2Cl_2–PhMe, −35 °C; iii, NaOMe, MeOH–THF.



Scheme 3

to the Diels–Alder reactions described above, acetyl- and benzyl-protected β-D-glyco- and β-D-galacto-pyranosides with glycosidic and nonglycosidic linkages have been introduced to aza-Diels–Alder transformations, which were found to proceed with moderate to reasonable yield and excellent regioselectivity under 12 kbar pressure at 70 °C in CH_2Cl_2 to yield pseudo-oligosaccharides **12**–**15**.

In conclusion, we have developed a general sequence of selective yne-ene cross metathesis, Diels–Alder transformation and equilibration–deprotection for the synthesis of various biologically interesting carbohydrate derivatives. The combination of different monosaccharide building blocks and dienophiles has been demonstrated and should potentially give rise to a large number of pseudo-oligosaccharides of the types presented. Further investigations to explore the scope of the described reactions are now in progress.

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Notes and references

† *Yne-ene cross metathesis*: 5 mol% of **Ru** was added to a solution of 0.5 mmol of alkyne and 1.5–2.0 equiv. of alkene in CH_2Cl_2 (0.2 M concentration). After 12 h stirring another 5 mol% of **Ru** was added. After an additional 18 h the product was purified by column chromatography.

$MeAlCl_2$-catalysed Diels–Alder reaction: To a solution of 100 μmol of 1,3-diene and 20 equiv. of methyl vinyl ketone in 3 ml of CH_2Cl_2 and 1 ml of toluene, $MeAlCl_2$ (3 equiv.) was added at −78 °C. The reaction was stirred for 24 h at −35 °C and then quenched at −78 °C by addition of 10 equiv. of Et_3N and 1 ml of MeOH, followed by filtration through silica gel, concentration, and purification by column chromatography.

Equilibration and deprotection: The cycloadducts were stirred with 0.02 M NaOMe in MeOH–THF (1 : 1, v/v) at 0.01 M concentration for 12 h and then neutralised by addition of weakly acidic ion exchange resin, followed by filtration and purification by column chromatography.

High pressure aza-Diels–Alder reaction: A solution of 100 μmol of 1,3-diene and 1.5–2.0 equiv. of dienophile (0.2 M concentration) in CH_2Cl_2 was heated in a Teflon tube to 70–75 °C under 12 kbar pressure for 40 h. The product was purified by column chromatography.

‡ All prepared pseudo-oligosaccharides have been characterised by ^1H NMR, ^{13}C NMR, FAB-MS and IR spectroscopy. Additional 2D NMR spectra (COSY, HMQC, TOCSY, HMBC) have been obtained.

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