DOI: 10.1002/ejoc.201000570

Metathesis Reactions of Carbohydrates: Recent Highlights in Cross-Metathesis

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Dedicated to Prof. Dr. Antonio García Martínez on the occasion of his retirement

Keywords: Cross metathesis / Carbohydrates / Cyclodextrins / Porphyrins / Glycoconjugates

Metathetical processes play a prominent role in the development of useful transformations because of their mildness, tolerance of functional groups, and synthetic potential. On the other hand, carbohydrates have gained well-deserved relevance in the study of biological processes. This review summarizes a decade of efforts in the application of cross metathesis (CM) reactions to the preparation of some relevant glycoconjugates.

1. Introduction

Metathesis reactions are nowadays well-established as conventional synthetic procedures.[1] Their prominent role as carbon–carbon bond construction methods is evident considering the large number of publications that have appeared within a relatively short time span.[2] Particularly important is the use of this synthetic tool in the field of carbohydrate chemistry[3] regarding two main aspects: *a*) the synthesis of carbohydrate derivatives using metathetical processes, and *b*) the transformation of carbohydrates to new derivatives, with a special mention to the conversion of carbohydrates to carbocycles. Regarding the first issue, several authoritative reviews have been published. Among them, the contributions of Madsen,[4] Roy,[5] Sinou,[6] Postema,[7] and their co-workers, should be emphasized. With respect to the second aspect, two recent reports from Madsen,[8] and Sollogoub and Sinaÿ[9] should also be men-

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Ana Aljarilla was born in 1981 in Madrid (Spain). In 2004 she started Ph. D. research on Organic Chemistry at the Complutense University of Madrid under the supervision of Prof. Joaquin Plumet. In 2006 she spent three months in Berlin (Germany) in Prof. Hans-Ulrich Reissig research group. She completed her PhD in Chemistry on March 2009.

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Joaquín Plumet received his Ph. D. in 1973 from the Complutense University of Madrid (UCM). He continued his scientific education, as an Alexander von Humboldt Postdoctoral Fellow, at the Institute of Organic Chemistry, University in Munich with Prof. Rolf Huisgen. In 1986 he joined the Department of Organic Chemistry in the University of Extremadura in Badajoz (Spain) and in 1988 was promoted to Full Professor at the UCM. He has been Visiting Professor at University Lausanne (Switzerland), Ecole Nationale Superieure de Chimie, Toulouse (France), Chemistry Department University California-Riverside, and Ecole Superieure de Physique et Chemie de la Ville de Paris (France). On January 2010 he was invested Doctor Honoris Causa from the Institut National Polytechnique (INP-ENSIACET, Toulouse). His current research interests focus on the use of bicyclic compounds as chiral building blocks in organic synthesis, metathesis reactions, specially ring-rearrangement metathesis, and on the development of new organocatalysts.

tioned. Additionally, some more specific accounts on this topic have also appeared.[10]

Considering the existence of several metathetical processes: ring-closing metathesis (RCM),[11] cross-metathesis (CM),[12] ring-opening metathesis (ROM), in particular ring-opening metathesis polymerization (ROMP)[13] and tandem metathesis reactions[14] (this last protocol may be categorized within the more general concept of concurrent tandem catalysis[15]) the purpose of this Microreview is to provide a brief survey on the use of CM reactions in the field of carbohydrates since 2000 until January 2010.

2. A Brief Note on the Current Scenario of Metathesis Catalysts[16]

The selection of the catalyst is a key aspect in the Universe of metathetical processes. The carbene-like mechanism, first proposed by Herisson and Chauvin,[17] paved the way for the development of different types of catalysts with well-defined structure.

Although the ROMP (a Ziegler-type process) was in fact the first application of metathesis reactions, "*it was soon emancipated from its polyolefin roots and it evolved into an independent and highly prosperous field of research*" (see Fürstner in ref.[14f]). It has, since, been possible the development of robust, well-defined catalytic agents.[1a] A great number of the advances in transition metal complexes have been incorporated in the design and synthesis of new metathesis catalysts. Following the initial reports on the synthesis and uses of metal alkylidenes such as **1** and **2**, an impressive number of new pre-catalytic agents designated by the name of their promoters (e.g., Grubbs, Schrock, Blechert, Grela, Nolan, Verpoort, Hoveyda), the ligands (actor or ancillary) that they incorporate (NHC, Schiff base, arene, indenylidene, allenylidene etc.), or by the "generation" concept (e.g. Grubbs 1st to 3rd generation) have appeared. In this context, a detailed description of the world of the metathesis catalysts is beyond the scope of this Microreview. However, some specific references on their design, syntheses and uses can be found in the literature (Figure 1).[18]

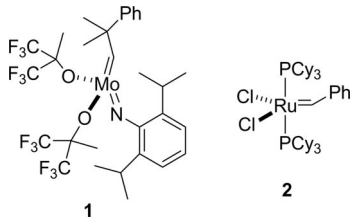


Figure 1. Mo (Schrock), and first-generation Grubbs' ruthenium catalysts.

The Mo catalyst (Schrock's catalyst, **1**) is very active, but it is also highly sensitive to oxygen and humidity (Schlenk techniques are usually required for its manipulation). Conversely, the less reactive Grubbs' Ru catalyst **2** is not affected by air, moisture or reaction impurities. Additionally, catalyst **2** displays a spectacular tolerance against a large array of functional groups, and it has gained enormous popularity within the organic and polymer chemists communities. Different water-soluble[19] and polymer-bound catalysts derived from Grubbs' Ru catalyst have also been prepared.[20] Heterogeneous polymer bound olefin metathesis catalysts have received considerable attention in recent years, the main reason being their easy removal from the crude reaction mixture by simple filtration.

In the second-generation Ru catalysts, one phosphane unit has been replaced by an imidazolidine ring (e.g. **3**, see Figure 2).[21] The activity of these catalysts is significantly higher than the parent Grubbs' carbene, and comes close to, or even surpasses, that of Schrock's Mo catalyst. They also display an exceptional thermal stability and resistance towards oxygen and moisture, showing also good compatibility with many functional groups. The origin of the high activity of these catalysts relies on the strong σ-donor character of the heterocyclic ligand moiety which favours the active conformation of the carbene ligand in the Ru complex.[21d]

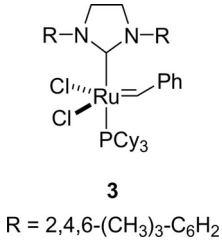


Figure 2. Second generation Grubbs' ruthenium catalyst.

The bis-coordinated carbene Ru complex **4** (Figure 3) constitutes an example of third-generation of Grubbs' Ru catalysts. In this case, the dissociation of the electron-deficient 3-bromopyridine ligand is extremely rapid. In consequence, catalyst **4** is an exceptionally fast initiator for the metathesis of simple olefins. In fact, compound **4** is the *fastest-initiating ruthenium catalysts known*, measured to be more than 4,000 times faster to initiate than the 2nd generation Grubbs catalyst.

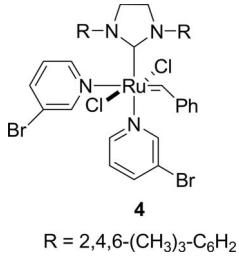


Figure 3. Third generation Grubbs' ruthenium catalyst.

A family of robust Ru catalysts (Hoveyda–Grubbs catalysts, e.g. **5** and **6**, 1st and 2nd generation, respectively, Figure 4) has been developed on the basis of the coordinative effects between an isopropoxy group attached to a benzene ring and the metallic center. These catalysts show an interesting combination between high activity and broad functional group tolerance.

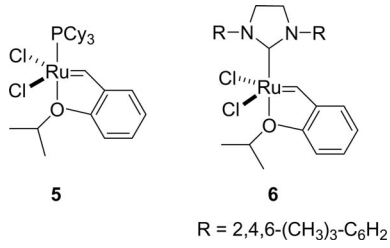


Figure 4. Hoveyda–Grubbs catalysts.

In these cases, although the lateral group on the phenylcarbene units stabilizes the complex, it also opens a coordination site in the presence of the substrate. Moreover, this complex is able to regenerate itself once the substrate is depleted, and it can be recycled by conventional column chromatography.

Piers' derivatives, **7** and **8** (Figure 5)[21e–21l] represent a new addition to the ruthenium olefin-metathesis catalysts' family. Catalyst **7**, a four-coordinate cationic complex with a pseudo-tetrahedral geometry, possesses an open coordination site *trans* to the phosphane (Piers–Grubbs 1st generation catalyst), whereas catalyst **8** possesses a *N*-heterocyclic carbene ligand (Piers–Grubbs 2nd generation catalyst). The open coordination site in these catalysts eliminates the need for any ligand dissociation prior to olefin coordination. As such, olefin binding and activation is anticipated to be more facile with Piers' catalysts.

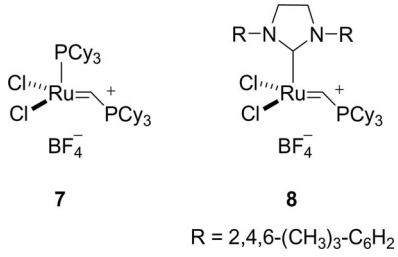


Figure 5. The Piers–Grubbs' catalysts.

Less sterically-demanding *o*-tolyl analogues of compounds **3** and **6** have been described[21m–21o] and are commercially available. The use of these catalysts increases the efficiency in the formation of sterically demanding disubstituted olefins (as consequence of the accessibility of conformations with the *N*-tolyl substituents rotated away from the approaching, coordinated olefins).

Finally, a Mo catalyst for asymmetric ring-opening polymerization (AROMP),[22] and several different chiral Mo[23] and Ru[24] catalysts for enantioselective olefin metathesis have been described.

3. Cross-Metathesis Reactions

Carbohydrate derivatives bearing a terminal double bond are useful precursors for the synthesis of glycoclusters through olefin self-metathesis (SM), and olefin cross-metathesis (CM) reactions (Figure 6).

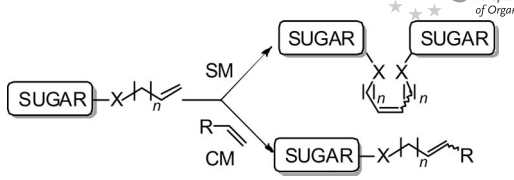


Figure 6. Glycoclusters by SM and CM reactions of carbohydrates.

In a seminal contribution, Grubbs and co-workers developed an empirical model for the prediction of CM selectivity.[12e] The model, which is based in a general ranking of olefin reactivity towards homodimerization, permits the classification of olefins in four general categories according to a reactivity gradient, and gives some rules for CM selectivity based on them. Type I and type II olefins are those that undergo fast and slow homodimerization, respectively, with a given catalyst. Type III olefins undergo no homodimerization, although they can participate in CM reactions, whereas type IV are inert to CM. Apart from these categories are olefins that deactivate the catalyst. According to their model, *a*) reaction between olefins of two different types (reactivities) will give good selectivity in CM, *b*) reaction between two type I olefins will result in statistical CM (controlled by the ratio of reactants), and *c*) reaction between two olefins of the same type (non-type I) will produce a non-selective CM.

Accordingly, the synthesis of complex carbohydrate-based structures using CM reactions is influenced by the reactivity of both partners (glycosyl and aglycon moieties), and a short overview on the scope and limitations of these reactions from the point of view of the structural features of the CM partners seemed pertinent.

3.1. Reactivity Considerations at the Glycosyl Moieties

Regarding unsaturated glycosyl moieties, the structural limitations in both SM and CM are in agreement with those identified by Grubbs and co-workers[12e] when applied to sugar-derived alkenes.[25]

C-Vinyl glycosides of aza sugars **9** and thioglycosides **10** (Figure 7), display poor or no reactivity in CM reactions.

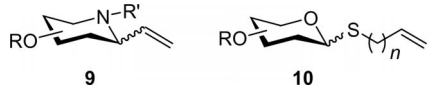
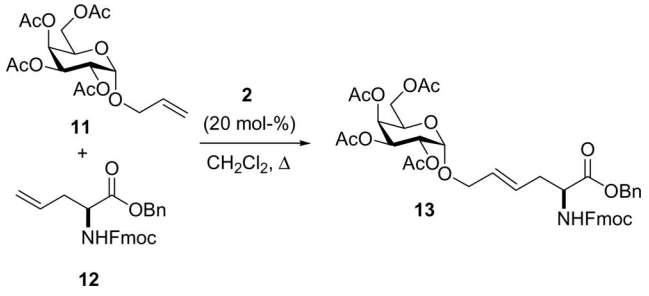


Figure 7. Aza sugar *C*-vinyl glycosides **9** and alkenyl thioglycosides, **10**.

Reports dealing with reactions of allyl and higher homologues (type I olefins) of, *O*- and *C*-glycosides,[26] deoxy sugars,[27] imino *C*-glycosides[28] and amino deoxy sugars,[29] have appeared.

For instance, the CM reaction of allyl galactoside **11** with L-allylglycine derivative **12**[26b] (both type I olefins), in the presence of catalyst **2**, produced a statistical mixture of CM products that required the use of an excess of one CM partner to furnish a good yield of the desired product **13** (Scheme 1, Table 1).

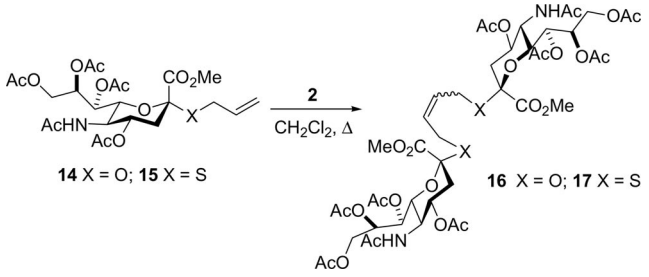


Scheme 1. CM) reaction of allyl galactoside with L-allylglycine derivative **12**, mediated by Grubbs' catalyst, **2**.

Table 1. CM reactions of allyl galactoside **11** and L-allylglycine **12**.

Entry	**2** (mol-%)	Equivalents of **12**	Yield (%)
1	20	2.0	49
2	20	5.0	70

Comparison of allyl sialoside **14**, with its corresponding allyl thioglycoside **15**, in SM reactions[30] (Scheme 2, Table 2) indicated that the sulfur derivative (**15**) was less reactive toward Grubbs' catalyst **2**, than the *O*-allyl derivative (**14**). The homodimer of **15**, compound **17**, was obtained in only 26% yield, whereas SM reaction of **14**, afforded homodimer **16**, in 82%, under less forcing conditions (Table 2). The authors ascribed these results to the poisoning of the transition metal catalyst[31] caused by the strong coordinating properties of the sulfur atom.

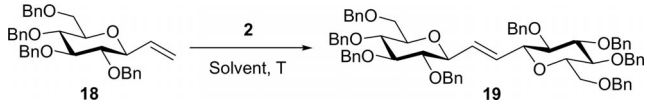


Scheme 2. Self-metathesis (SM) reactions of sialosides **14** and **15** mediated by Grubbs' catalyst, **2**.

Table 2. SM reactions of sialoside **14** and allyl 2-thiosialoside **15**.

	2 (mol-%)	Time	Yield (%)	*E*:*Z* ratio
14 (X = O)	5	6 h	82 (**16**)	7:1
15 (X = S)	10	24 h	26 (**17**)	2.5:1

In general, *C*-vinyl glycosides homodimerize very slowly (type II olefins) and different reasons have been advanced to justify this behavior. For instance, vinyl glycoside **18** homodimerizes to compound **19** in modest yield albeit with excellent diastereoselectivity when treated with catalyst **2** (Scheme 3, Table 3).[26b] In this case, the low reactivity was ascribed to steric effects.



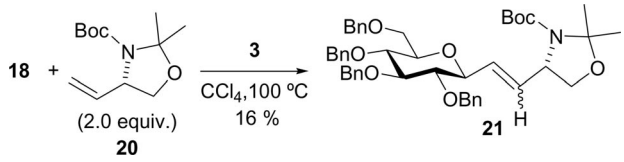
Scheme 3. SM reaction of *C*-vinyl glycoside **18**.

Table 3. Reaction conditions for the SM of vinyl glucoside **18**.

Solvent	*T* [°C]	Reaction time	Isolated yield (%)[a]
CH_2Cl_2	room temp.	24 h	0
CH_2Cl_2	Δ	16 h	8
$ClCH_2CH_2Cl$	70 °C	24 h	24

[a] Only the *E* diastereoisomer was obtained.

According to that, the CM reaction of **18** with 2.0 equiv. of vinyloxazolidine **20** (most likely a type III olefin of low reactivity), in the presence of more active catalyst **3** only afforded a 16% yield of CM product **21** (Scheme 4).[32] In our opinion, a stoichiometric excess of **20** might have been required to produce a higher yield of **21**. According to the authors, the low yield of the reaction was a consequence of the known instability of vinyl *C*-glycosides.[33]



Scheme 4. CM reaction of vinyl glycoside **18** and vinyloxazolidine **20**.

The CM reactions of β-(**22**) and α-(**23**)-*C*-vinyl derivatives of protected 1-deoxynojirimycin (Figure 8) with various alkenes (or their SM reactions) in the presence of catalyst **3** proved to be unsuccessful (type IV olefins).[28a] These results were explained by both, greater Ru–*O* chelation effects, and/or increased steric hindrance owing to close proximity of the reactant alkene and the bulky imino sugar moiety.[34] Along this line, the CM reaction of their corresponding allyl homologues (type I olefin) with type II or type III olefins gave good yield of CM products.[28a]

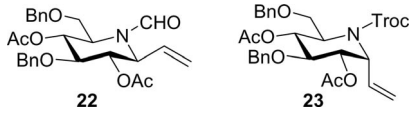


Figure 8. *C*-Vinyl derivatives of protected 1-deoxynojirimycin.

However, *C*-vinyl glycosides can successfully participate in CM reactions.[35] For instance, McGarvey et al.[35b] observed that capped *C*-vinyl glycosides **24**–**26** (Figure 9) reacted with amino acids **27** and **28** (type I olefins) to give the desired CM products, **29** and **30**, in good yields (Table 4).

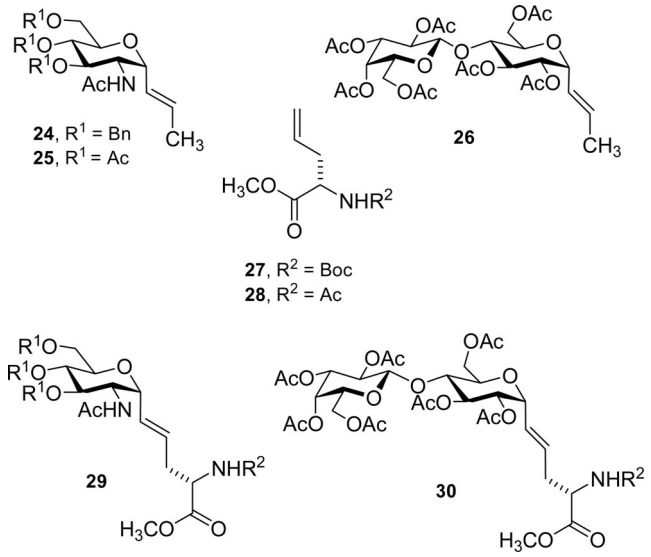


Figure 9. *C*-Glycosides (**24**, **25**, **26**) and amino acids (**27**, **28**) used in CM reactions to give compounds **29** and **30** (see also Table 3).

Table 4. CM reactions between *C*-glycosides **24**–**26**, and amino acids **27** and **28** (2.0 equiv.) using catalyst **3**.[a]

	Sugar	Amino acid	Catalyst (mol-%)	Time [h]	Product (R^1, R^2)	Yield (%)
1	**24**	**28**	10	24	**29** (Bn, Fmoc)	82
2	**24**	**27**	10	48	**29** (Bn, Boc)	77
3	**24**	**28**[b]	10	24	**29** (Bn, Fmoc)	68
4	**25**	**28**	20[c]	48	**29** (Ac, Fmoc)	69
5	**25**	**27**	20[c]	48	**29** (Ac, Boc)	77
6	**25**	**28**	20[c]	48	**30** (–, Fmoc)	60

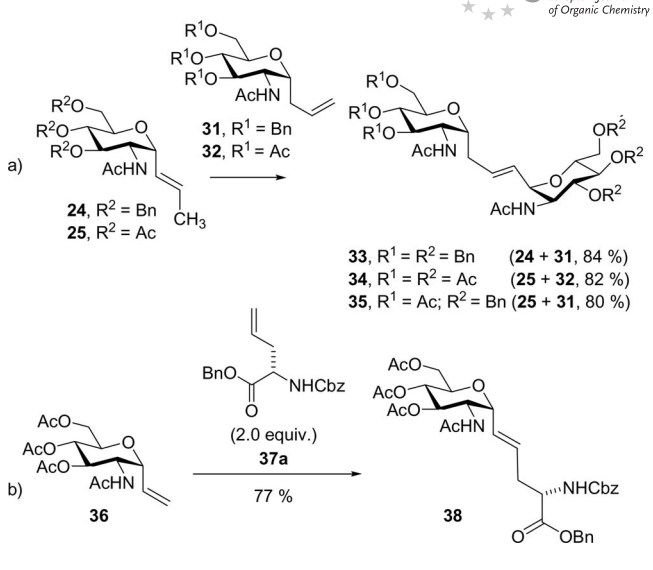
[a] All reactions were carried out using catalyst **3** in CH_2Cl_2, under reflux. [b] One equivalent of amino acid was used.[36] [c] The catalyst was introduced in two equal portions at 24 h intervals.

In a further report,[37] the authors explored the reactivity of *C*-(1-propenyl)- and *C*-vinyl glycosides, both in CM and SM reactions, using catalyst **3**. Their results are quoted in Schemes 5 and 6.

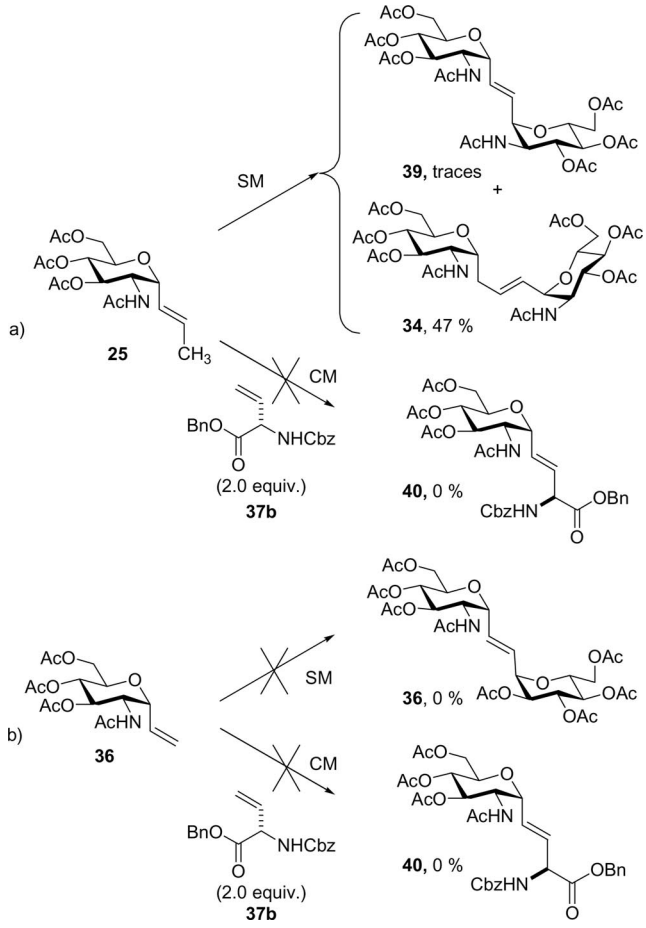
The allylic substrates **31**, **32** and **37a** (type I olefins) reacted well with disubstituted (**24**, **25**) and monosubstituted vinyl glycosides (**36**) (type III olefins, vide infra) in CM reactions (Scheme 5), thus showing that olefin substitution was not the determining principle in these metathesis reactions. *C*-vinyl glycosides **25** and **36** can be categorized as type III olefins of low reactivity with respect to catalyst **3**, since they do not undergo self metathesis (SM), and they do not react with vinyl glycine derivative **37b** (Scheme 6, a and b).

From these data, the authors concluded that the determining structural feature leading these metathesis reactions was the proximity of basic functionality to the olefin, perhaps contributing to the deactivation of the catalyst, rather than the previously mentioned substitution pattern of the olefin.

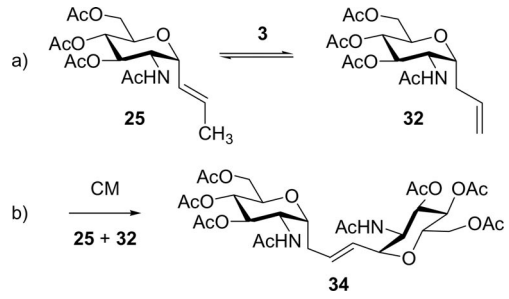
On the other hand, it is noteworthy that SM reaction of *C*-vinyl glycoside **25** did not afford the expected product **39**, but rather its homolog **34**, in 47% yield (Scheme 6, a). In this case, compound **25** had undergone a double-bond isomerization leading to *C*-allyl derivative **32** (Scheme 7, a),[38] thus paving the way for a favored allyl/vinyl metathesis (rather than a disfavored vinyl/vinyl SM) leading to **34** (Scheme 7, b).



Scheme 5. CM reactions of *C*-alkenyl glycosides with catalyst **3**.

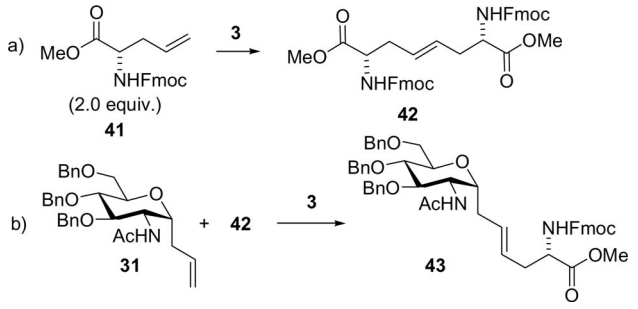


Scheme 6. Metathesis reactions of *C*-alkenyl glycosides **25** and **36**.



Scheme 7. Isomerization and CM reaction of compound **25**.

The course of the reaction between *C*-allyl glycoside **31**, and amino acid derivative **41**, was followed by NMR (Scheme 8). It was then observed that, allylglycine **41** was consumed within the first 2.5 h of reaction (rapid homodimerization, type I olefin), affording the SM product **42**. As the reaction proceeded, it became clear that the disappearance of the *C*-allyl glucosamine **31** (slow dimerization, type II olefin) coincided with the consumption of **42** and the formation of the CM product **43**.

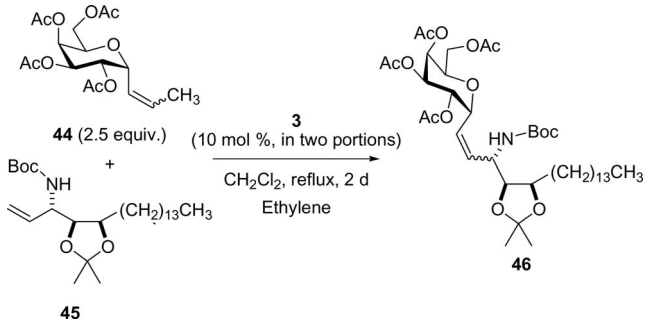


Scheme 8. Proposed reaction pathway for the CM of allyl glycine **41** and *C*-allyl glucosamine **31**.

These results are therefore in agreement with Grubbs' empirical rules. An easily dimerizable type I olefin, **41**, gives consumable homodimer **42** (Scheme 8, a) that undergoes successful CM reaction with, type II olefin **31** to afford *C*-glycoside **43** (Scheme 8, b). Additional support for this proposed reaction pathway was obtained when it was observed that, independently prepared, olefin **42** participated in a CM reaction with *C*-glycoside **31** leading to **43**.

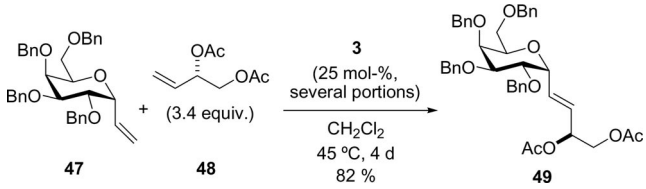
Ethylene has been used as promoter for CM reactions of vinyl glycosides. Thus, the first successful CM reaction of a *C*-vinyl galactoside, **44**, was carried out under an ethylene atmosphere to give *C*-glycoside **46** in 72% yield (Scheme 9). In the absence of ethylene, CM reaction of **44** with **45** produced compound **46** in only 27% yield.[39,40]

On the contrary, CM reaction of *C*-vinyl galactoside **47** and (*S*)-3-butene-1,2-diacetate **48**, in the presence of catalyst **3**, did not take place under an ethylene atmosphere. The authors ascribed this failure to either the dilution required for ethylene bubbling, or to the presence of ethylene itself in the reaction media. The reaction was then successfully carried in concentrated CH_2Cl_2 solution (reflux, 4 d) with periodic addition of fresh catalyst **3** (25% total) to give



Scheme 9. CM Reaction of *C*-glycoside **44** with **45** in the presence of ethylene.

CM product **49**, in 82% yield (Scheme 10).[41] According to the authors, the reaction takes place by dimerization of **48** followed by CM reaction of the ensuing dimer with **47**.



Scheme 10. CM Reaction of vinyl glycoside **47** and diacetate **48**.

3.2. Aglycon Moiety

In general, monosubstituted olefins of general structure **50** (Figure 10) undergo efficient CM reactions with allyl glycosides. In this group should be included amino- and hydroxy derivatives,[42] styrene, and halogen derivatives.[43] Conversely, 1,1-disubstituted olefins, e.g. **51**, display a much smaller reactivity. For instance, dehydroalanine derivatives **52**, were found to be unreactive towards both, allyl- and vinyl *C*-glycosides.[37]

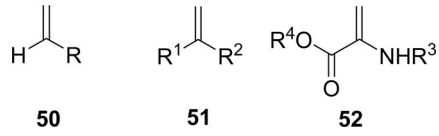


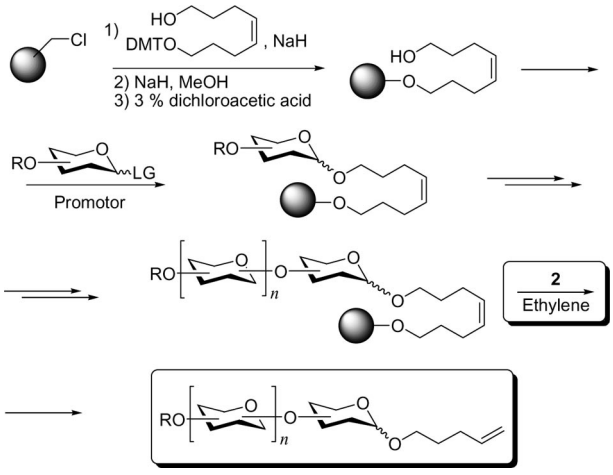
Figure 10. Aglycon partners in CM reactions.

3.3. CM Reactions in Solid-Phase Oligosaccharide Synthesis

The success of the solid-phase synthesis (SPS) of oligosaccharides relies, among other factors, in the design of a stable linker to connect the first sugar to the polymer matrix. On the other hand, the ideal linker should be readily cleaved under mild conditions releasing a functional group able for the synthesis of larger structures.[44,45]

In this context, Seeberger and co-workers[46] developed a new linker based on a 4-octene substructure attached to a Merrifield resin (Scheme 11) that, after the SPOS is completed, can be successfully cleaved using Grubbs' catalyst **2**

under an atmosphere of ethylene. In this way, the newly generated species are *n*-pentenyl glycosides (NPGs), which have proved to be highly valuable glycosyl donors.[47]



Scheme 11. SPS of *n*-pentenyl oligosaccharides. DMT: dimethyltrityl group, LG: leaving group. Phosphates (TMSOTf as promoter, 53%) and trichloroacetimidates (TESOTf, 76%; TMSOTf, 71%) have been used as LGs; see ref.[46]

One selected example on the use of this methodology for the synthesis of complex oligosoccharides will be outlined.[48] To synthesize a vaccine against leishmaniasis,[49] tetrasaccharide **53** was prepared using SPS.[50] The starting materials employed were the mannose-derived trichloroacetimidates **54**,[51] **55**[52] and galactosyl phosphate **56**[53] (Figure 11).

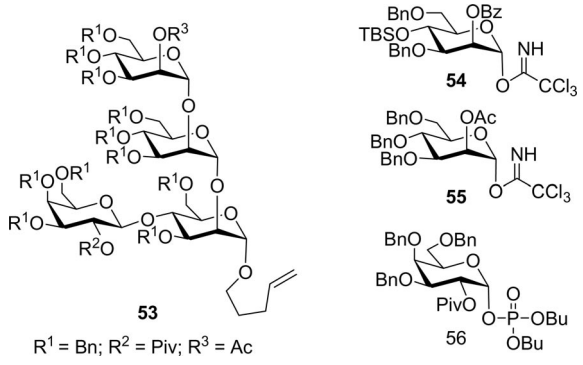
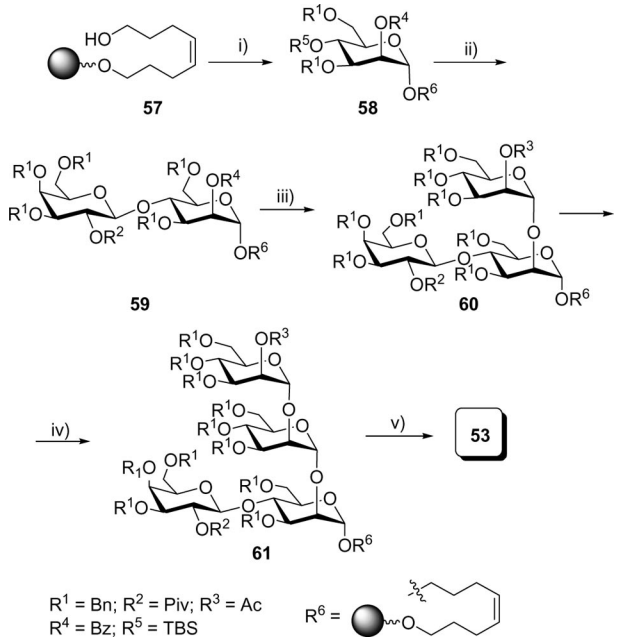


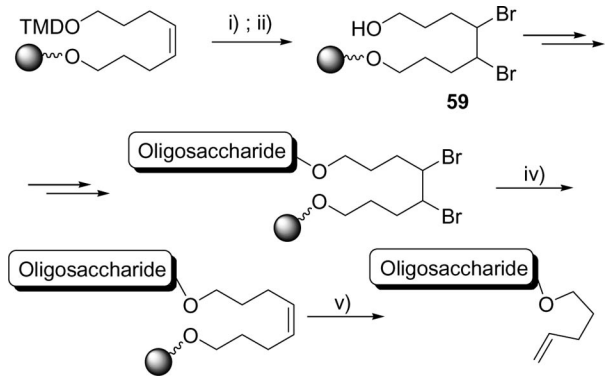
Figure 11. Starting materials **54**–**56** for the SPS of tetrasaccharide **53**.

The synthetic sequence for compound **53** is outlined in Scheme 12. Three comments regarding this protocol should be made: *a*) after every step of the synthesis, a small portion of the resin was set aside and cleaved using a CM reaction with catalyst **2** in the presence of ethylene (see Scheme 12), and the corresponding terminal NPG was then compared with the sample obtained in solution; *b*) the excess of reagent was removed by simple washing of the resin [3 × 5 mL of MeOH, 5 mL of MeOH/THF (1:1), and 3 × 5 mL each, THF and CH_2Cl_2], and after the final CM reaction, the resulting NPG was purified by elution through a plug of Celite followed by flash chromatography; *c*) the desired tetrasaccharide **53** was obtained in 18% overall yield (from **57**) after 4 d. The related solution-phase synthesis required at least two weeks.



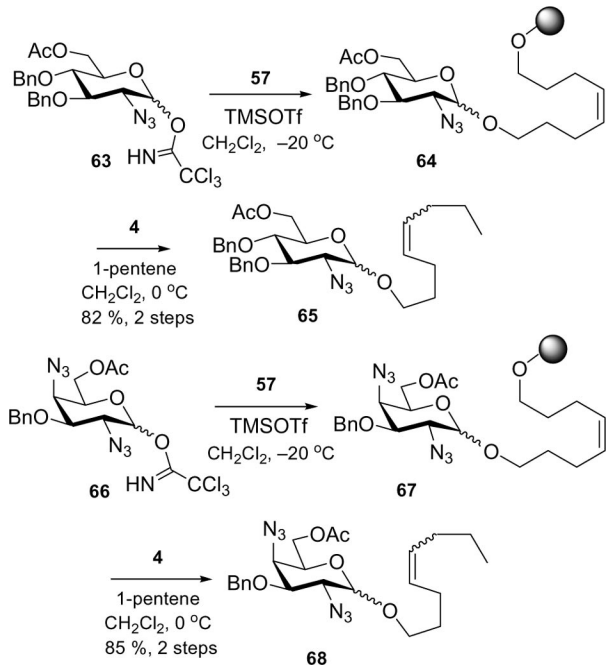
Scheme 12. SPS of tetrasaccharide **53**. Reagents and conditions: i) compound **54**, 0.05 equiv. TBSOTf, room temp.; ii) 1. TBAF, THF; 2. 1.2 equiv. TMSOTf, CH_2Cl_2, –78 °C, compound **55**; iii) 1. MeONa, MeOH; 2. 0.05 equiv. TMSOTf, CH_2Cl_2, compound **56**, room temp.; iv) 1. MeONa, MeOH; 2. 0.05 equiv. TMSOTf, CH_2Cl_2, room temp., compound **55**; v) catalyst **2**, ethylene, CH_2Cl_2, 48 h (yield not mentioned, see ref.[50]).

In order to broaden the scope of this procedure, the linker **57** was converted into 4,5-dibromooctane-1,8-diol linker **62**,[54] compatible with glycosyl donors such as NPGs and thioglycosides.[55] The standard cleavage step from the resin (e.g. v, Scheme 13) has then to be preceded by the reaction of the dibromo derivative with tributylammonium iodide (TBAI) to restore the olefin moiety (Scheme 13).



Scheme 13. Preparation and use of the 4,5-dibromobutane-1,8-diol linker **62** in oligosaccharide synthesis. Reagents and conditions: i) LiBr, $CuBr_2$, MeCN, THF; ii) Cl_2, HCOOH, CH_2Cl_2; iv) TBAI, 4-butanone, 1,4-dioxane, 95 °C, 48 h; v) catalyst **2**, CH_2Cl_2, ethylene, 36 h.

The azido functionality constitutes a common masking group for the amino function in carbohydrate chemistry.[56] For this reason, the issue of its compatibility with metathesis catalysts was addressed.[57] After some experimentation using model compounds,[58] catalyst **4**[59] and 1-pentene were found to be compatible with the azido moiety in CM reactions (Scheme 14).[60]

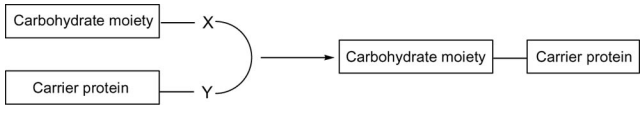


Scheme 14. Cleavage of azide-containing monosaccharides from solid support using CM reactions.

3.4. CM Reactions in the Synthesis of Carbohydrate-Based Vaccines

3.4.1. Carbohydrate-Based Vaccines (CBV). An Overview[61]

Generally speaking, a carbohydrate-based vaccine (CBV) is composed of a carbohydrate antigen conjugated to a carrier protein. In this context, the preparation of CBVs. requires the convergent assembly of carbohydrates and peptides (Scheme 15) and, in this context, CM reactions have become a convenient tool.[61g]



Scheme 15. General strategy for the synthesis of CBVs.

3.4.2. The Use of CM Reactions in the Synthesis of Carbohydrate-Based Vaccines

Many examples of the use of CM reactions for the synthesis of glycopeptides have been published. Two specific, illustrative cases are presented: *i*) the synthesis of an intermediate for the preparation of a CBV against *Burkholderia cepacia*,[62] and *ii*) the total synthesis of a proposed vaccine against ovarian cancer which, in fact, constitutes a new type of antitumor vaccine structure.

3.4.2.1. En Route to a CBV Against Burkholderia Cepacia

Using different analytical techniques, including NMR and fast-atom-bombardment MS experiments, the lipopolysaccharide produced by a clinical isolate *B. cepacia* was shown to be formed by two distinct polymers, both showing a linear trisaccharide repeating unit.[63] The major polymer contains D-rhamnose and D-galactose residues in ratio 2:1, and the minor was constituted by D-rhamnose residues only.[64]

On these basis, Roy and co-workers[65] designed potential vaccines against *B. cepacia* based on the trisaccharide unit of the major polymer isolated from this bacterium. Accordingly, the synthesis of compounds **69** and **70** (Figure 12) was accomplished.

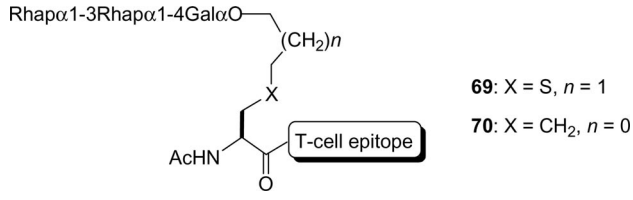
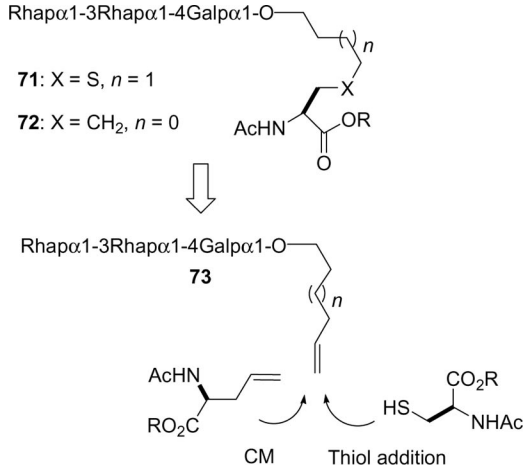


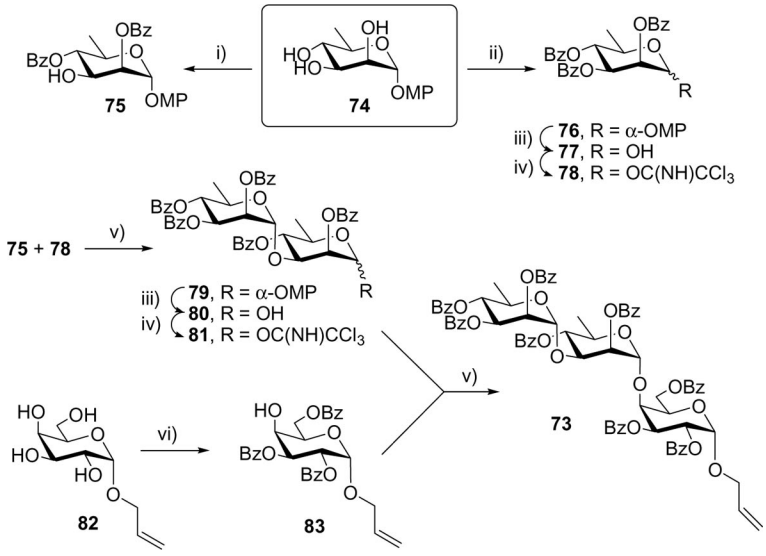
Figure 12. Proposed synthetic CBV against *B. cepacia*.

En route to compounds **69** and **70**, trisaccharide derivatives **71** and **72** were synthesized[65] from a common intermediate, **73**, using the thiol addition of a protected cysteine, or a CM reaction with allyl glycine followed by catalytic hydrogenation, respectively (Scheme 16).



Scheme 16. Synthetic plan for compounds **71** and **72**.

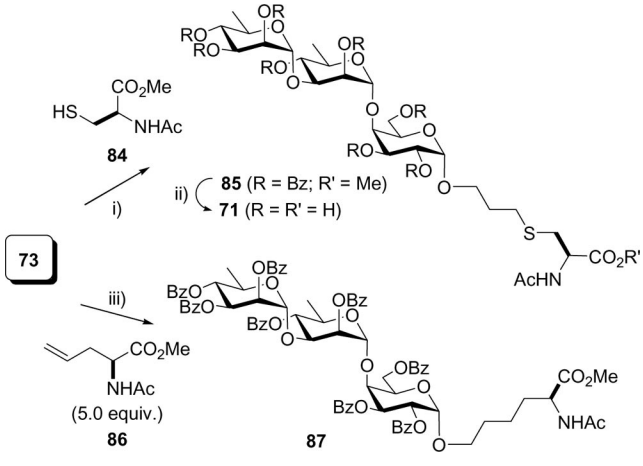
Trisaccharide **73** was synthesized from D-mannose, in a convergent manner, as outlined in Scheme 17.[65] *p*-Methoxy-D-rhamnopyranoside **74**, available from D-mannose in five steps and 87% overall yield,[66] underwent selective benz-



Scheme 17. Synthesis of trisaccharide **73**. Reagents and conditions: i) ref.[66] ii) BzCl, pyridine, room temp., 12 h; iii) CAN, toluene/CH_3CN/H_2O, room temp.; iv) CCl_3CN, DBU, CH_2Cl_2, room temp., 1 h; v) TMSOTf, 4-Å mol. sieves, CH_2Cl_2, –50 °C, 30 min, 66% for **73**; vi) ref.[67]

oylation[66] to give hydroxy derivative **75**. The former, could also be transformed into trichloroacetimidate **78** in three steps. Glycosylation of **75** with **78** as glycosyl donor, afforded disaccharide **79** that was transformed into trichloroacetimidate **81** in two steps. On the other hand, galactosyl acceptor **83** was prepared from commercially available allyl α-D-galactoside **82** by selective benzoylation.[67] Final glycosylation of the former with trichloroacetimidate **81** furnished trisaccharide **73** in 66% yield.

As previously mentioned, compound **73** was then used in the final assembly of compounds **71** and **72** (Scheme 18). Radical addition[68] of *N*-acetyl-L-cysteine methyl ester (**84**) to **73** gave **85** which, after deprotection, afforded **71**. CM Reaction of **73** with *N*-acetyl-L-allylglycine methyl ester (**86**, 5.0 equiv.), followed by catalytic hydrogenation yielded compound **87**, a protected form of **72**.



Scheme 18. Synthesis of **71** and a protected form (**87**) of **72**. Reagents and conditions: i) compound **84**, AIBN, THF, 254 nm, room temp., 24 h; ii) LiOH, THF/H_2O; iii) compound **86** (5.0 equiv.), catalyst **2**, CH_2Cl_2; then H_2, Pd/C (10%), MeOH, 60%, two steps.

3.4.2.2. Synthesis of a Proposed Vaccine Against Ovarian Cancer

In the search for a fully synthetic vaccine against ovarian cancer[69] Danishefsky and co-workers[70] proposed a new type of CBV featuring both a carbohydrate-based antigen and a mucin-derived peptide marker in an alternating pattern (Figure 13). In fact this new model constitutes the fourth generation of CBV's.

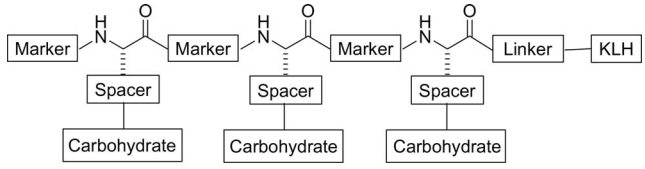


Figure 13. General structure of a CBV against ovarian cancer.

Both the marker and the carbohydrate moieties were selected on the basis of rational criteria. The conjugate Gb_3 **88** [Globotriosyl ceramide, Gal(α1–4)Gal(β1–4)GlcCe, Figure 14][71] and MUC5AC mucin antigen[72] **89** (Figure 14) are overexpressed in ovarian tumor cell surfaces.[73] Considering these observations, globotriaosyl amino acid **90**, showing a non-natural extended hydroxynorleucine linker, was selected as mimic of Gb_3 ceramide, whereas the peptide-basic unit of MUC5AC was designed as marker peptide. A diaminopropyl unit was finally selected as linker to the carrier protein KLH. On the basis of these considerations, the structure of the designed CBV (compound **91**) is depicted in Figure 15.

The synthesis of glycosyl amino acid **92** was envisaged using a CM reaction of trisaccharide **93** and Fmoc-protected allylglycine **12**, followed by catalytic hydrogenation (Scheme 19).

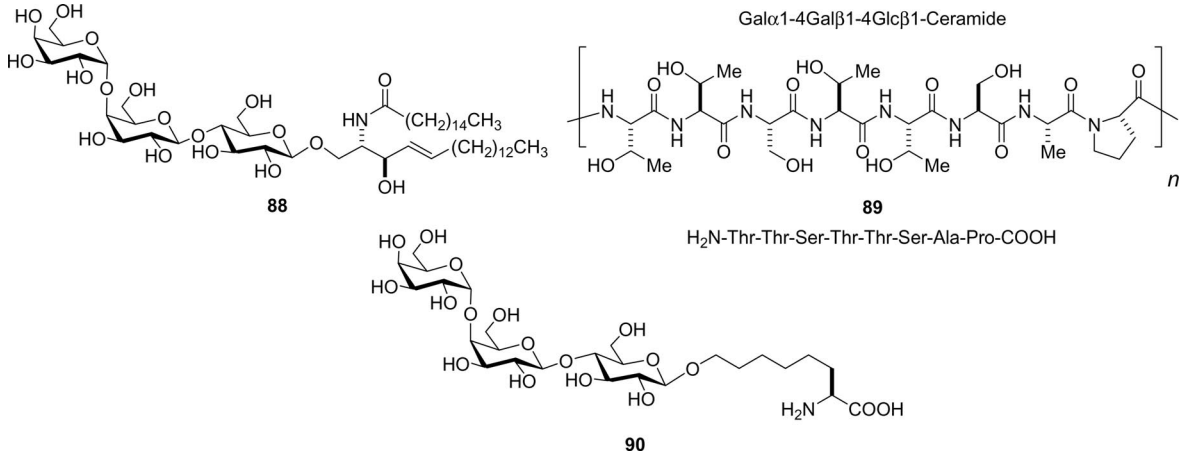


Figure 14. Structures of Gb_3 (**88**), MUC5AC (**89**) and a Gb_3 mimic (**90**).

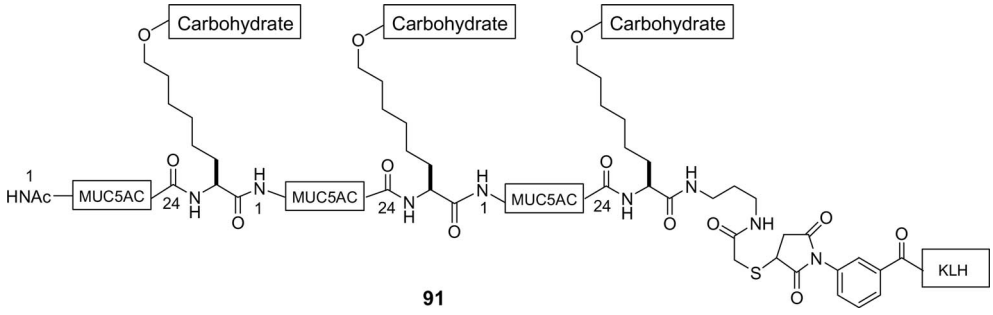
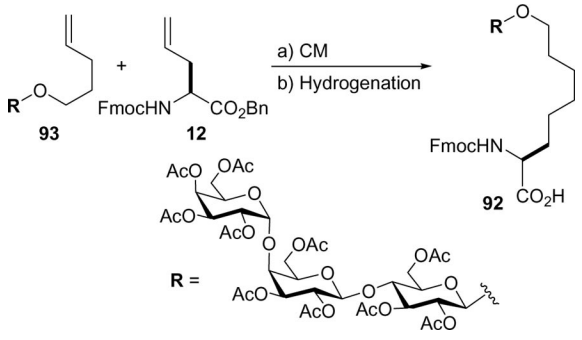


Figure 15. Proposed CBV (**91**) against ovarian cancer.

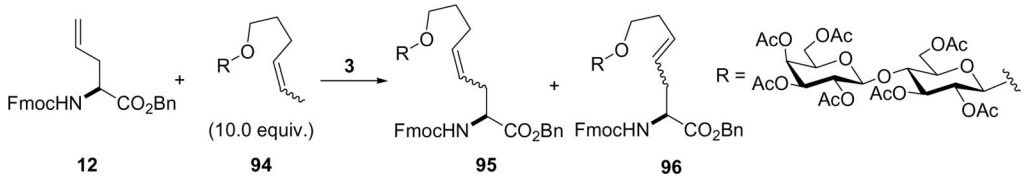


Scheme 19. Proposed synthesis of glycosyl amino acid **92** via CM reaction.

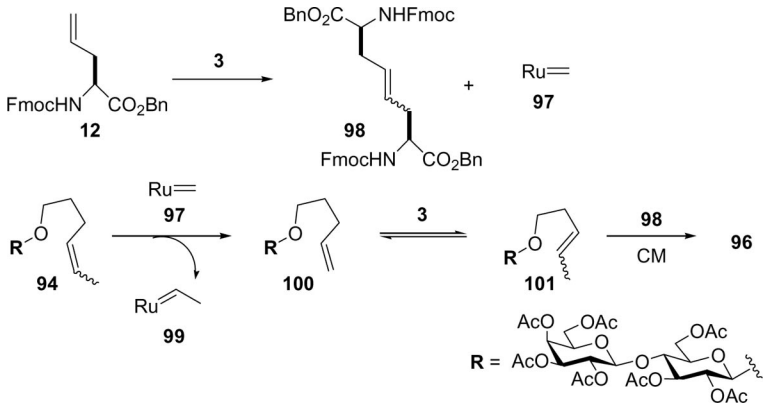
However, it was observed[74] that the CM reaction of β-*O*-*n*-pentenyl-type lactoside **94**[75] with amino acid derivative **12** (10.0 equiv.), in the presence of catalyst **3**, afforded compounds **95** and **96**, as diastereomeric *E*:*Z* mixtures (Scheme 20). Compound **95** is the expected product arising from a "normal" CM reaction, whereas compound **96** will be its lower homolog.

In agreement with previous observations (see Scheme 8) amino-acid-derived (type I) alkene **12** might undergo a SM reaction (homodimerization) to give dimer **98** while liberating the ruthenium carbene **97**. The latter then transforms **94** to **100**,[76] which is susceptible to isomerization to **101**. Finally, CM reaction of **101** with dimer **98** would produce compound **96** (Scheme 21).

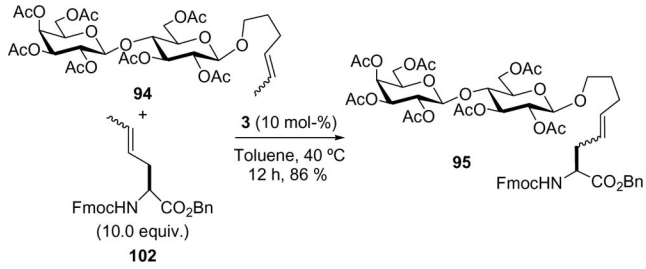
In order to prevent the transformation **12**→**98** (origin of the formation of **96**) amino acid **12** was "capped" with a methyl group (compound **102**[77]). In this way, reaction of **94** with a large excess of **102** (10.0 equiv.) in the presence of catalyst **3** afforded the desired CM product **95** in 86% yield (Scheme 22).



Scheme 20. CM Reaction of lactoside **94** and allyl glycine derivative **12**.



Scheme 21. Proposed reaction pathway for the formation of **96**.



Scheme 22. Synthesis of glycosyl amino acid **95**.

After these observations, glycosylamino acid **91** was synthesized by CM reaction of trisaccharide **103**[78] and an excess of amino acid **102** (8.0 equiv.) followed by catalytic hydrogenation (Scheme 23).[79]

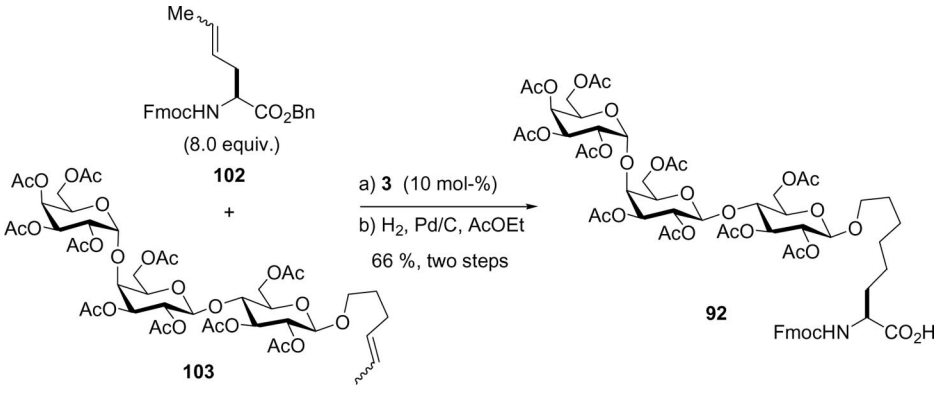
Peptides **104** and **105**, required for the synthesis of **91**, were prepared through Fmoc solid-phase synthesis,[80] and processed subsequently to *C*-terminal thioesters,[81] **106** and **107**, respectively. Coupling of trisaccharide derivative **92** and **107** yielded **108** which was peracetylated to **109** (Scheme 24).

Next, compound **92** was transformed into **110** which incorporates the Boc-protected diaminopropyl unit to be linked to the carrier protein KLH. Thus, the second subunitcarbohydrate-peptide **112** was constructed by Fmoc deprotection[84] of **110** to give **111**, followed by peptide coupling with **109**. Iteration of this last reaction yielded the elongated subunit **113** (Scheme 25).

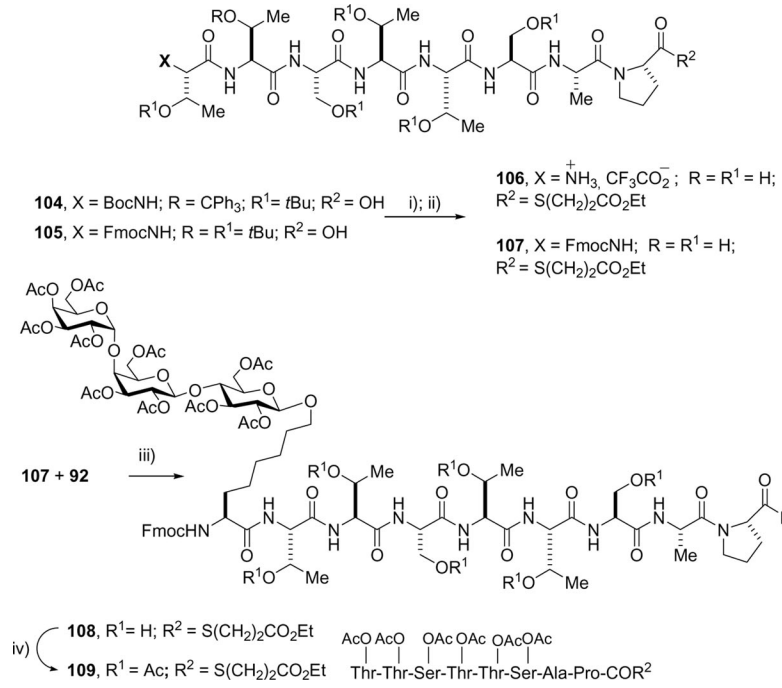
The third peptidyl fragment was installed by reaction of **113** with the MUC5AC in its free hydroxy form, **106**. This was dictated to facilitate a polarity-based separation of the target glycopeptide **114** from other potential side products. In this way, Fmoc cleavage of **113** followed by coupling with **106** afforded **114**. Finally, Fmoc deprotection followed by peracetylation and global deprotection gave the target synthetic clustered Gb3-MUC5Ac **116**[87] (Scheme 26).

Conjugation of **116** to the KLH protein was carried out by reaction with trifluoracetic acid to cleave the Boc functionality. Amidation of the resulting compound with pentafluorophenyl S-acetylglycolate (SAMA-OPfp)[88] **117** provided **118**, which was deprotected to give **119**.[89] Finally the KLH conjugate **91**, was synthesized from **119** by activation of the carrier protein KLH **120** with sulfo-MBS[90] followed by subsequent addition of the terminal thiol functionality to the maleimide olefin center of the activated carrier protein (Scheme 27).

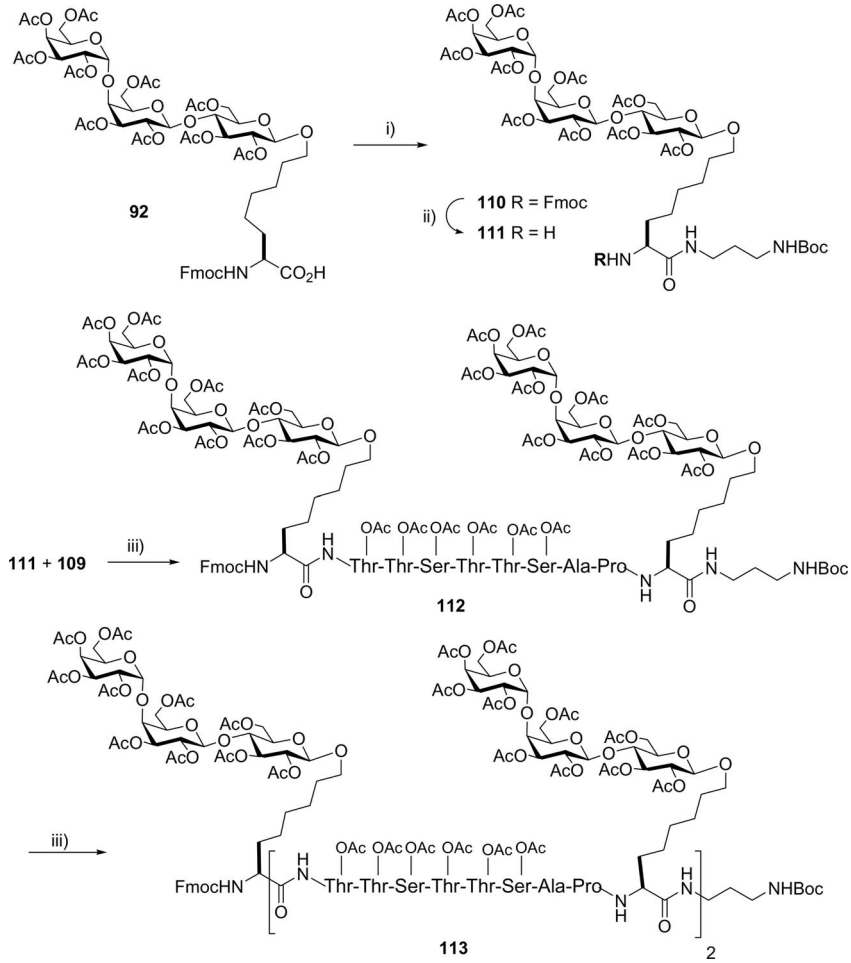
It should be pointed out that compound **91** constitutes the most complex targeted construct to have been assembled by chemical synthesis to the date.



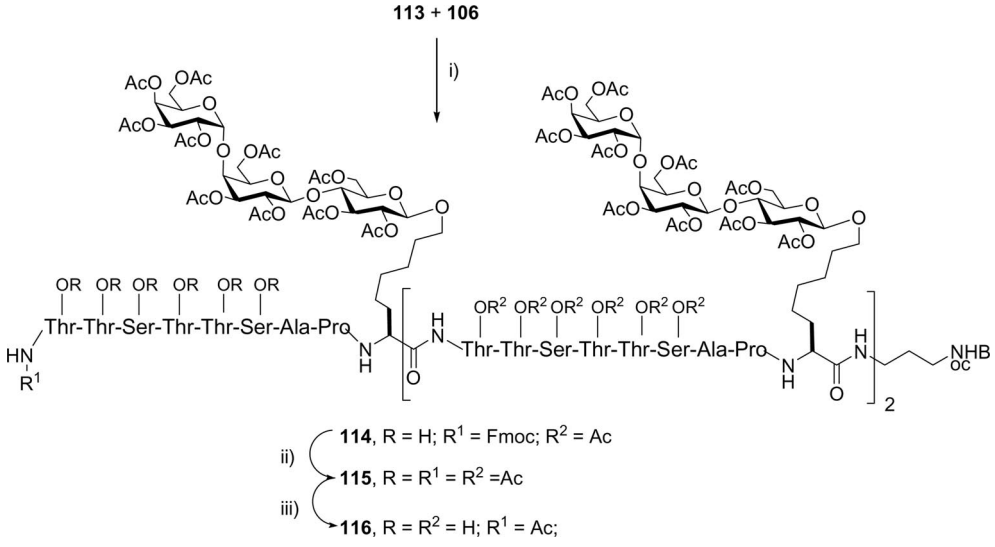
Scheme 23. Synthesis of glycosylamino acid **92**.



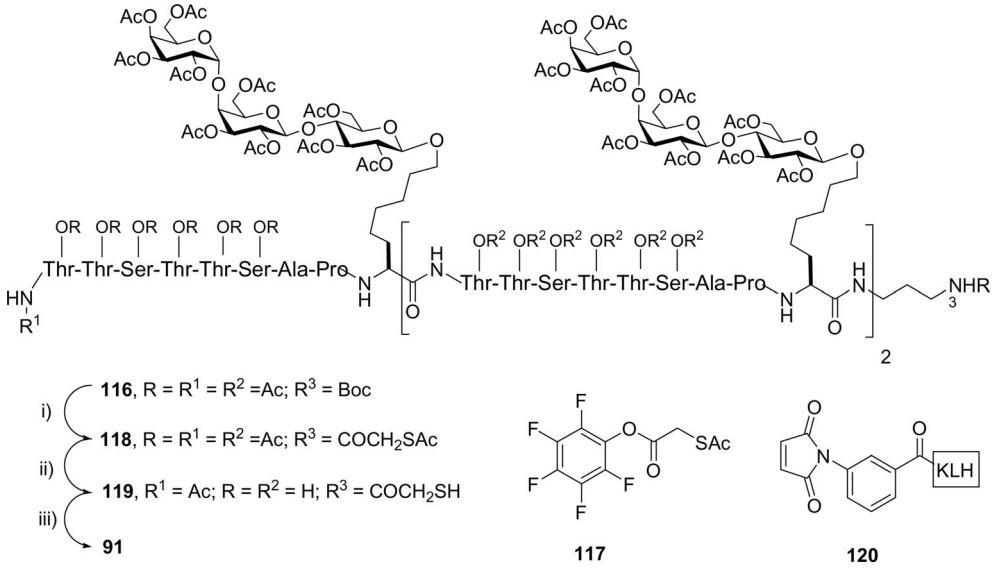
Scheme 24. Insertion of the carbohydrate moiety into the peptidic chain. Reagents and conditions: i) $HS(CH_2)_2CO_2Et$, EDCl,[82] HOBt,[83] DMF, CH_2Cl_2; ii) CF_3COOH, phenol, H_2O, *i*PrSiH; iii) DIEA (diisopropylethylamine), EDCl, HOBt, DMF; iv) Ac_2O, pyridine, DMAP (cat.).



Scheme 25. Synthesis of glycoconjugate **113**. Reagents and conditions: i) $H_2N(CH_2)_3NHBoc$, EDCl, HOOBt;[85] DMF/CH_2Cl_2; ii) 5% Et_2NH in DMF;[86] iii) AgCl, HOOBt, *i*Pr_2NEt, DMSO; iv) **111**, conditions iii).



Scheme 26. Synthesis of the Gb3-MUC5AC glycocluster **116**. Reagents and conditions: i) AgCl, HOOBt, Pri_2NEt, DMSO; ii) Ac_2O, DMAP (cat.), pyridine; iii) MeOH, H_2NNH_2 (4:1).



Scheme 27. Last steps of the synthesis of CBV **91**. Reagents and conditions: i) 1. CF_3CO_2H/CH_2Cl_2 (1:4); 2. Pyridine, **117**); ii) MeOH/NH_2NH_2 (4:1) then TCEP (see ref.[89]); iii) compound **120**.

3.5. CM Reactions in the Synthesis of Glycoporphyrins

3. 5.1. Glycoporphyrins. An Overview

An important application of artificial porphyrins[91] is the called porphyrin-based photodynamic therapeutic (PDT).[92] Porphyrins are non-toxic compounds under dark conditions[93] being efficient photosensitizers to produce singlet oxygen $^1O_2$.[94] However, the use of porphyrins in PDT have two major drawbacks: a) low water solubility, and b) no cell specificity. Regarding the first problem, the introduction of carbohydrate subunits[95] as porphyrin appendages constitutes an appealing solution.[96] Moreover, and considering the importance of the specific carbohydrate–protein interactions on cell surfaces, porphyrin derivatives having multivalent carbohydrates (Figure 16) might acquire convenient cell specificity.

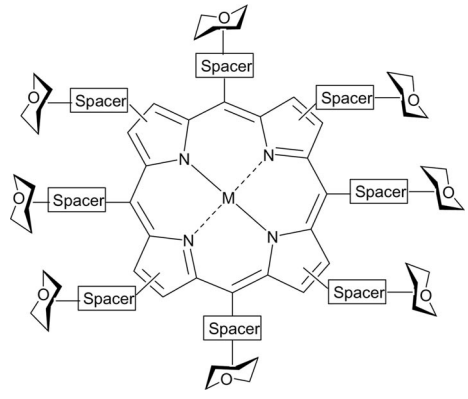
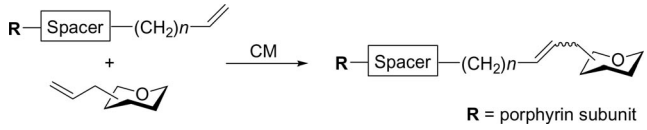


Figure 16. Schematic representation of a multivalent carbohydrate-porphyrin derivative.

3.5.2. CM Reactions in the Assembly of Glycoporphyrins

Inspection of the multivalent carbohydrate-phorpyrin assembly displayed in Figure 16 brings to mind a CM strategy for its preparation. Thus, a conveniently functionalized linker attached to the porphyrin moiety and a sugar derivative, both bearing terminal double bonds could be combined to bring to light such structural design (Scheme 28). However, this approach has only been applied once.[97,98]



Scheme 28. Synthesis of glycoporphyrin-carbohydrate derivatives using CM reactions.

Cavaleiro and co-workers synthesized glycoporphyrin-carbohydrate derivatives **128**–**137** from vinylporphyrins **121** and **122**, and *O*-allyl carbohydrate acetonides **123**–**127** by CM reactions using catalyst **3**. (Scheme 29 and Table 5).

Considering the good results, in terms of yields, depicted in Table 5, this methodology might prove useful in the convergent synthesis of porphyrin glycoconjugates.

Table 5. CM reactions of vinyl porphyrins **121** and **122**, with vinyl acetonides **123**–**127**.[a]

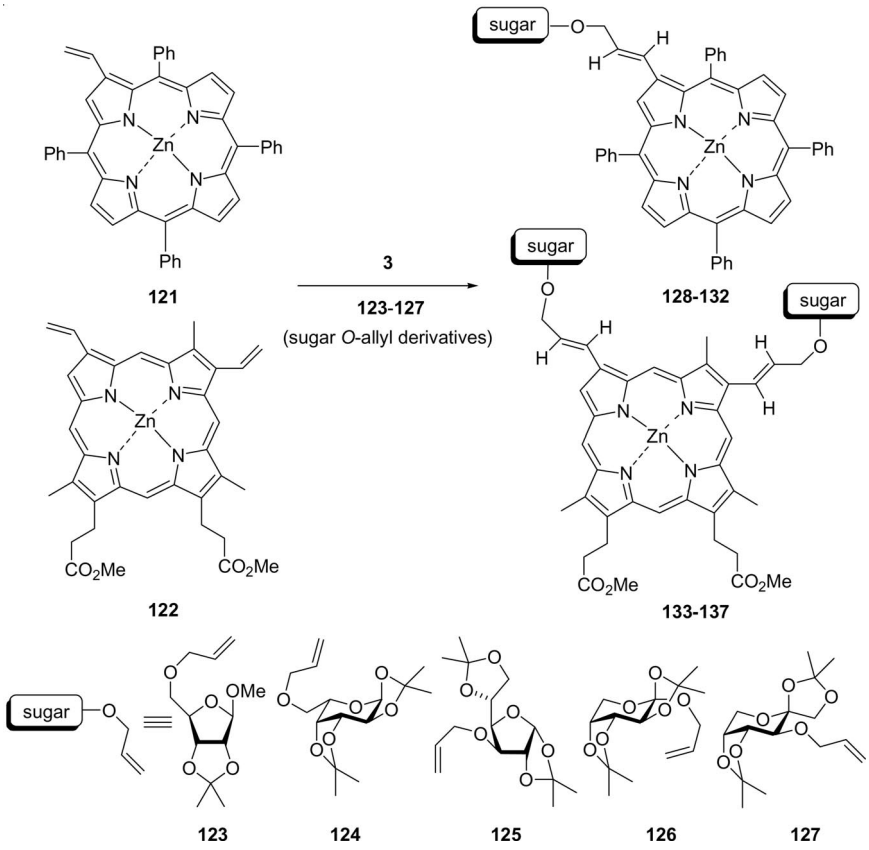
	Vinyl porphyrin	Allyl sugar	Product	Reaction time [h]	Yield (%)
1	**121**	**123**	**128**	4	98
2	**121**	**124**	**129**	4	95
3	**121**	**125**	**130**	4	98
4	**121**	**126**	**131**	4	97
5	**121**	**127**	**132**	4	95
6	**122**	**123**	**133**	8	87
7	**122**	**124**	**134**	8	86
8	**122**	**125**	**135**	8	84
9	**122**	**126**	**136**	8	74
10	**122**	**127**	**137**	8	93

[a] All reactions were carried out under reflux of CH_2Cl_2 using 25% mol of catalyst **3**. For compounds **128**–**132** equimolar amounts of the allyl sugars were used. For compounds **133**–**137**, 2.0 equiv. of carbohydrate were employed.

3.6. CM Reactions in Cyclodextrin (CD) Chemistry

3.6.1. Cyclodextrins – An Overview[99,100]

Cyclodextrins (CDs) are a family of cyclic oligosaccharides composed of α-(1,4)-linked glucopyranose subunits. The three major CDs are crystalline compounds: α-cyclodextrin comprises six glucopyranose units, whereas β- and γ-cyclodextrin consist of seven and eight glucose units,



Scheme 29. Synthesis of glycoporphyrins by cross-metathesis reactions.

respectively (Figure 17). In the CDs, each glucopyranose unit has three free OH groups which differ both in their functions and reactivity. The relative reactivities of the secondary C(2) and C(3), and the C(6) primary hydroxy groups depend on the reaction conditions.

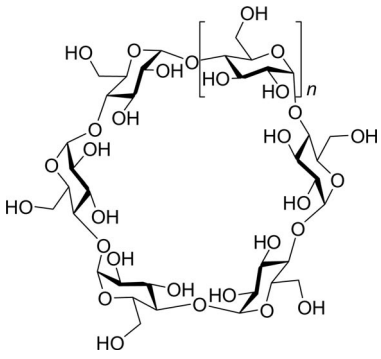
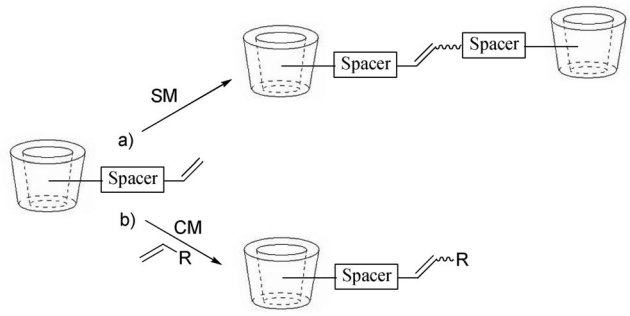


Figure 17. The cyclodextrins: α-cyclodextrin, $n = 1$; β-cyclodextrin, $n = 2$; γ-cyclodextrin, $n = 3$.

3.6.2. The Use of CM Reactions in the Synthesis of Cyclodextrin Derivatives[101]

Cross-metathesis reactions have been applied to cyclodextrins either to produce cyclodextrin dimers (Scheme 30, a), or for the preparation of functionalized derivatives (Scheme 30, b).

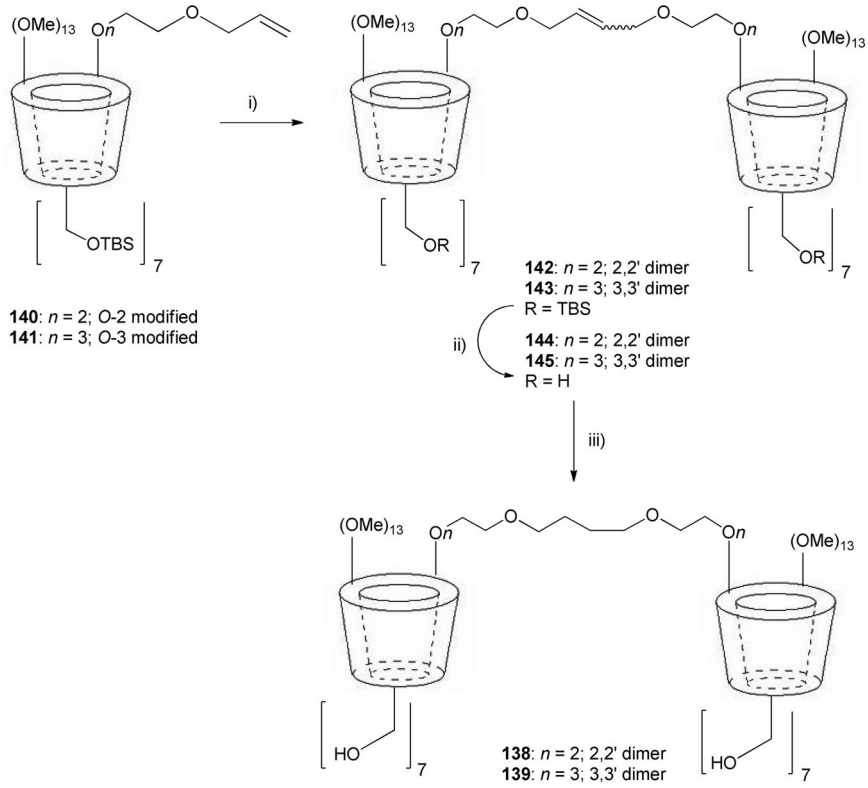


Scheme 30. Functionalization of cyclodextrins using CM reactions.

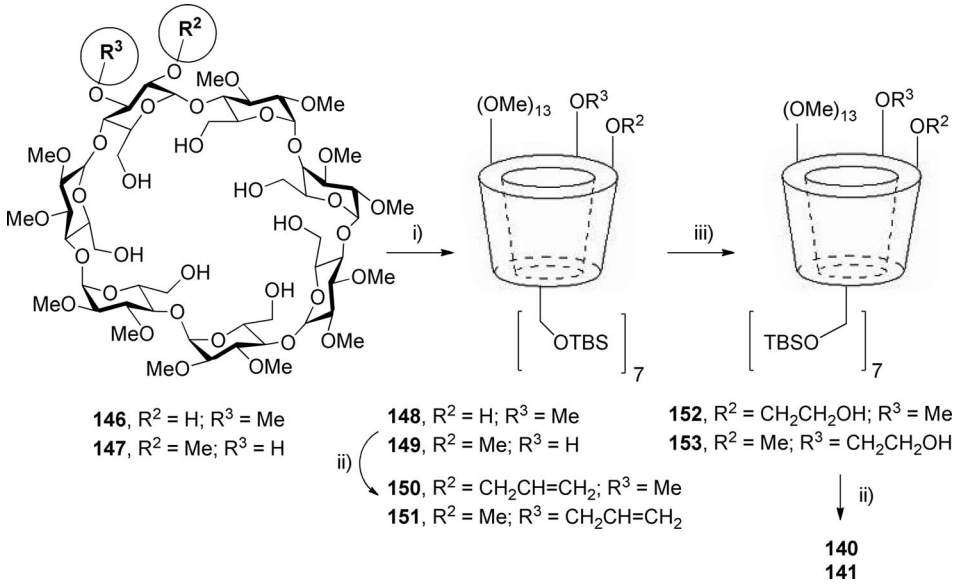
3.6.2.1. CM Reactions (SM) in the Synthesis of Cyclodextrins Dimers

The first report on a SM reaction of a cyclodextrin derivative[102] was published by Stoddart and co-workers,[103] and constitutes a good example of the use of this methodology for the synthesis of cyclodextrin dimers.[104] They reported the preparation of the 2,2′- (**138**) and 3,3′-dimers (**139**) of β-cyclodextrin by CM reaction of allyl derivatives **140** and **141**, respectively (Scheme 31). Deprotection of the primary hydroxy groups followed by reduction of the double bond furnished compounds **138** and **139**.

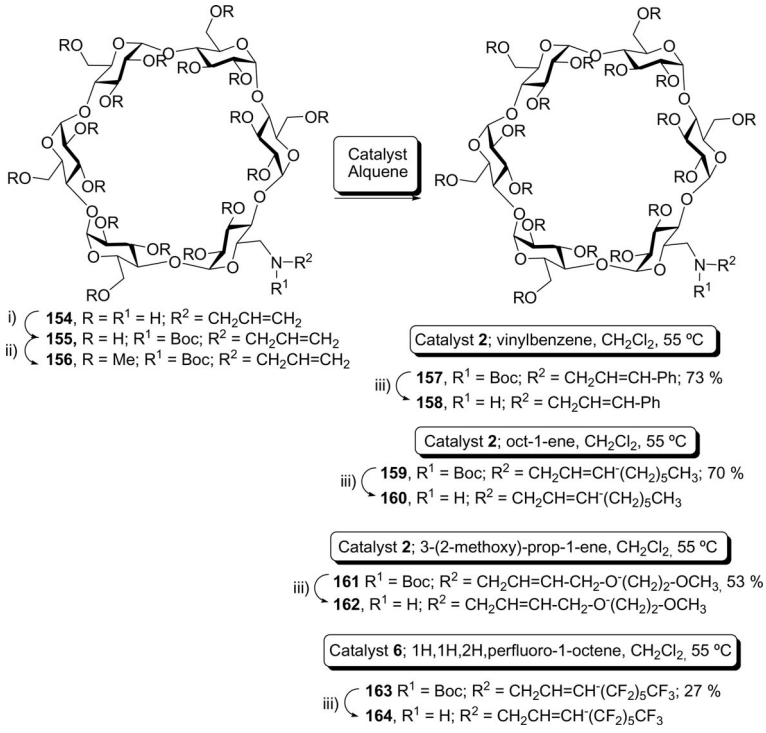
Compounds **140** and **141** were obtained from cyclodextrin derivatives **146**[105] and **147**[105] respectively, according to the sequence of reactions outlined in Scheme 32.



Scheme 31. Synthesis of 2,2′- and 3,3′-β-cyclodextrin dimers, **138** and **139**, respectively. Reagents and conditions: i) catalyst **2**, benzene, 48 h. A large amount of catalyst **2** (0.005 mmol of catalyst for 0.018 mmol of **140** and **141**) was used in both cases; **142** (48% yield), **143** (50% yield); ii) TBAF, THF; iii) $TsNHNH_2$/NaOAc.



Scheme 32. Synthesis of the starting materials **140** and **141**. Reagents and conditions: i) TBSCl/pyridine; ii) allyl iodide, NaH/DMF; iii) a) O_3; b) $NaBH_4$.



Scheme 33. Synthesis of functionalized β-cyclodextrins via CM reactions. Regents and conditions: i) Boc_2O, $NaHCO_3$, ultrasonication; ii) NaH, CH_3I, DMF, 20 °C, 81% two steps; iii) TFA, 20 °C.

3.6.2.2 CM Reactions in the Synthesis of Monofunctionalized Cyclodextrins Derivatives at the Primary Face

New β-cyclodextrin derivatives functionalized at the primary face were synthesized from **156**, via CM reactions (Scheme 33).[106] Compound **156**, which was in turn prepared from mono-6-*O*-allylamino-6-deoxy-β-cyclodextrin **154**. The new double bonds were obtained as *E*-diastereoisomer.

4. Conclusions and Perspectives

Olefin metathesis, one of the most efficient transition-metal-mediated C–C bond forming reactions, asserted itself

during the last decade as a powerful synthetic strategy for obtaining fine chemicals, biologically active compounds, architecturally complex assemblies, new materials, and functionalized polymers tailored for specific utilizations.

In the case of CM reactions applied to carbohydrates, it provides access to diverse types of new complex structures that cannot be readily synthesized using alternative procedures. Ongoing work in the search for more active and tolerant metal complexes promises further useful work ahead.

Acknowledgments

J. C. L. thanks the Spanish Ministerio de Ciencia e Innovación (MICINN) (CTQ2009-10343) and Comunidad de Madrid (S2009/PPQ-1752) for grants. J. P. thanks the Ministerio de Educación y Ciencia (MEC) for a grant (CTQ2006-15279). The authors are also grateful to the reviewers for their useful comments.

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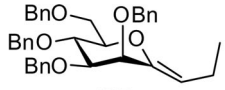

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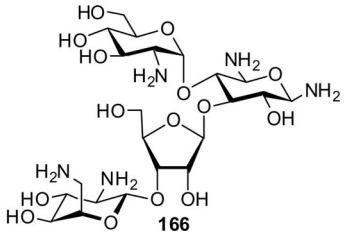

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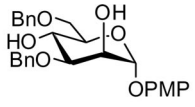

167

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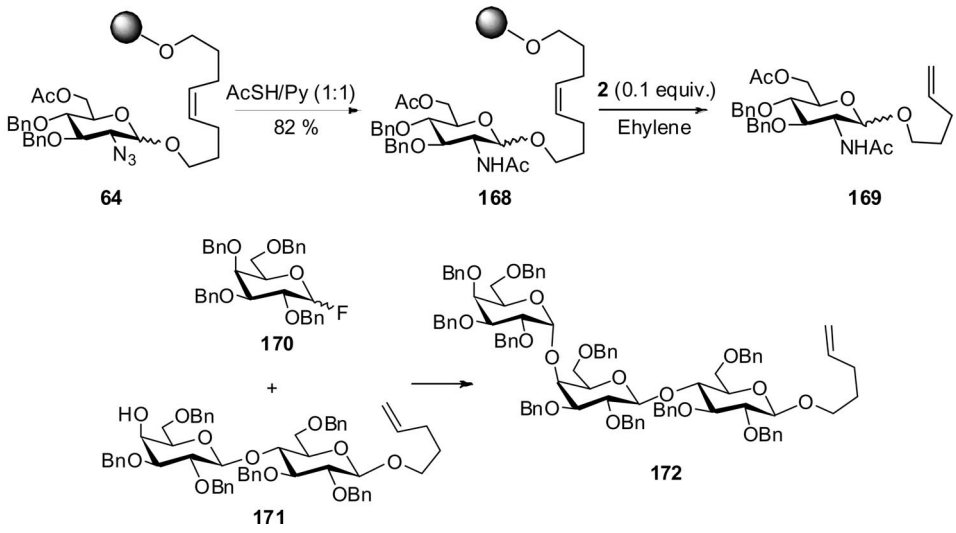
[76] The CM reaction of **99** with **93** in the presence of catalyst **2** (toluene, 40 °C, 12 h) furnished product **94** in 33% yield.

[77] Compound **102** was synthesized by CM reaction of allyl glycine derivative **12** with *trans*-2-butene, in the presence of catalyst **2** (CH_2Cl_2, 40 °C).

[78] Trisaccharide **103** was synthesized from trisaccharide **172** by CM reaction with *trans*-2-butene in the presence of catalyst **2**. On the other hand, trisaccharide **172** was prepared by glycosylation of **170** (J. R. Allen, J. G. Allen, X.-F. Zhang, L. J. Williams, A. Zatorski, G. Ragupathi, P. O. Livingston, S. J. Dani



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[83] 1-Hydroxybenzotriazol is a reagent normally used as a racemization suppressor, and to improve yields in peptide synthesis.

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[88] This reagent provides an effective means for linking synthetic peptide antigens to MAP (Multiple Antigenic Peptides) or carrier proteins for the purpose of raising antibodies.

[89] Some dimers were obtained by disulfide formation. Recuperation of the monomeric compounds was carried out by reduction with tris(2-carboxyethyl)phosphane (TCEP).

[90] *m*-Maleimidobenzoyl-*N*-hydroxysuccinimide (MBS) and its water-soluble analog sulfo-MBS, are heterobifunctional crosslinkers that contain *N*-hydroxysuccinimide (NHS) ester and maleimide groups that allow covalent conjugation of amine- and sulfhydryl-containing molecules.

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Received: April 23, 2010
Published Online: September 17, 2010

