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# CARBOXYMETHYL TRI-*O*-ACETYL- $\alpha$ -D-GLUCOPYRANOSIDE 2-*O*-LACTONE: A SYNTHON FOR THE PREPARATION OF NEOGLUCOCONJUGATES

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**Abstract.** *Carboxymethyl tri-*O*-acetyl- $\alpha$ -D-glucopyranoside 2-*O*-lactone (CMGL), the bicyclic lactone obtained in two steps from isomaltulose by an oxidation-acetylation sequence, is a convenient synthon for connecting a glucosyl moiety with other constructs. Its synthesis and its reactivity with regards to various nucleophilic species are described and the different types of glucoconjugates which have been prepared by this method, as well as other sources of carboxymethyl glycosides, are reviewed.*

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## 1. Introduction

Being involved in the use of carbohydrates as organic raw materials,<sup>1</sup> we have studied the reactivity of isomaltulose (6- $\alpha$ -D-glucopyranosyl-D-fructofuranose, **1**) and found that its oxidation conveniently provided

carboxymethyl tri-O-acetyl- $\alpha$ -D-glucopyranoside (CMG, **2**).<sup>2</sup> Also, its 2-O-lactone (CMGL, **3**) proved to easily open by reaction with nucleophilic species leading to neoglucoconjugates as depicted in Figure 1. Such molecular constructs involving a carbohydrate moiety are interesting chemical systems, most often because of their biological significance. Indeed, various types of glycoconjugates appear to be essential species in many biological phenomena and have attracted considerable attention in terms of drug-discovery.<sup>3</sup> Other applications lie in the high polarity of a glucidic moiety which brings improved water solubility to the whole molecule with eventual self association properties.

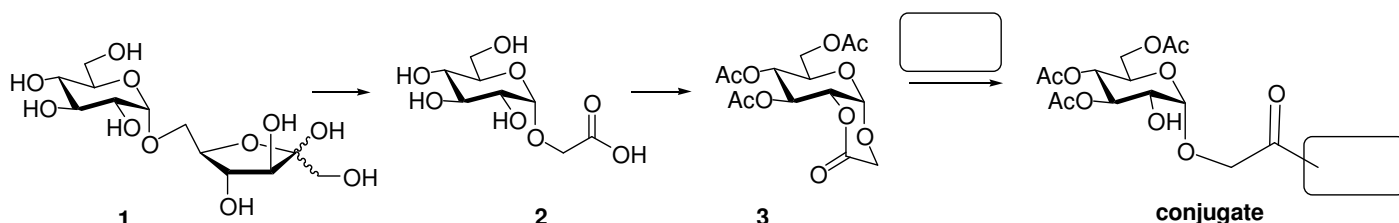


Figure 1

Among synthons designed for glycoconjugate synthesis, carboxymethyl glycosides have been used efficiently either as carbohydrate provider in the preparation of glycoconjugates analogues or as carbohydrates scaffolds able to serve as a polyfunctional and structurally constrained backbone. In the same idea, we have demonstrated that carboxymethyl glycoside lactones could be used as an activated analogues of carboxymethyl glycoside able to deliver a carbohydrate moiety under extremely mild conditions. In this first section, we will detail the synthesis and the uses of carboxymethyl glycoside lactones from isomaltulose and review some other studies of the literature in which carboxymethyl glycosides have been used as synthons as well as the main methods for their preparation.

### 1.1. Synthesis of carboxymethyl glucoside and its lactone from isomaltulose

Isomaltulose (**1**) and trehalulose (**5**), 6- $\alpha$ -D-glucopyranosyl-D-fructofuranose and 1- $\alpha$ -D-glucopyranosyl-D-fructopyranose respectively, are obtained in one step from sucrose (**4**) by bioconversion (Figure 2).<sup>4</sup> The chemistry of these available carbohydrates has been recently reviewed.<sup>5</sup>

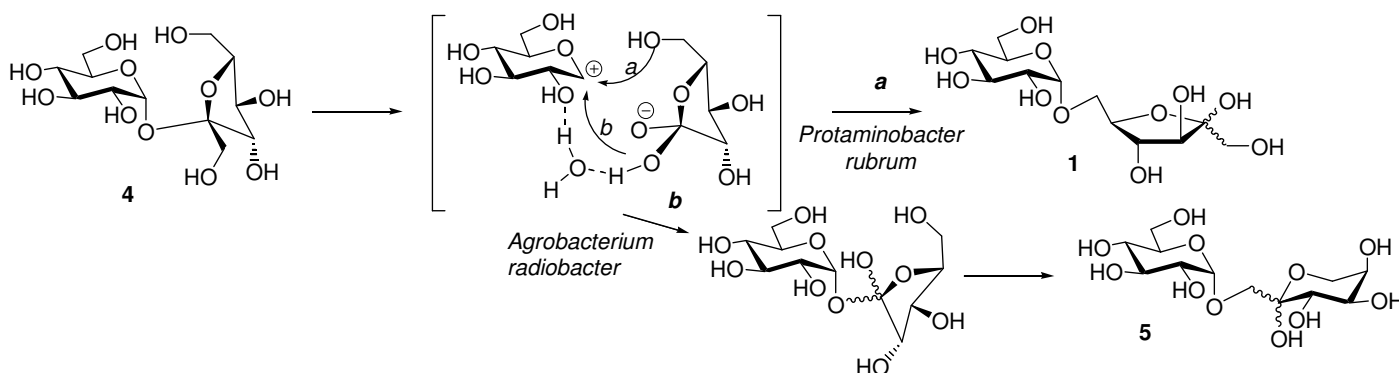
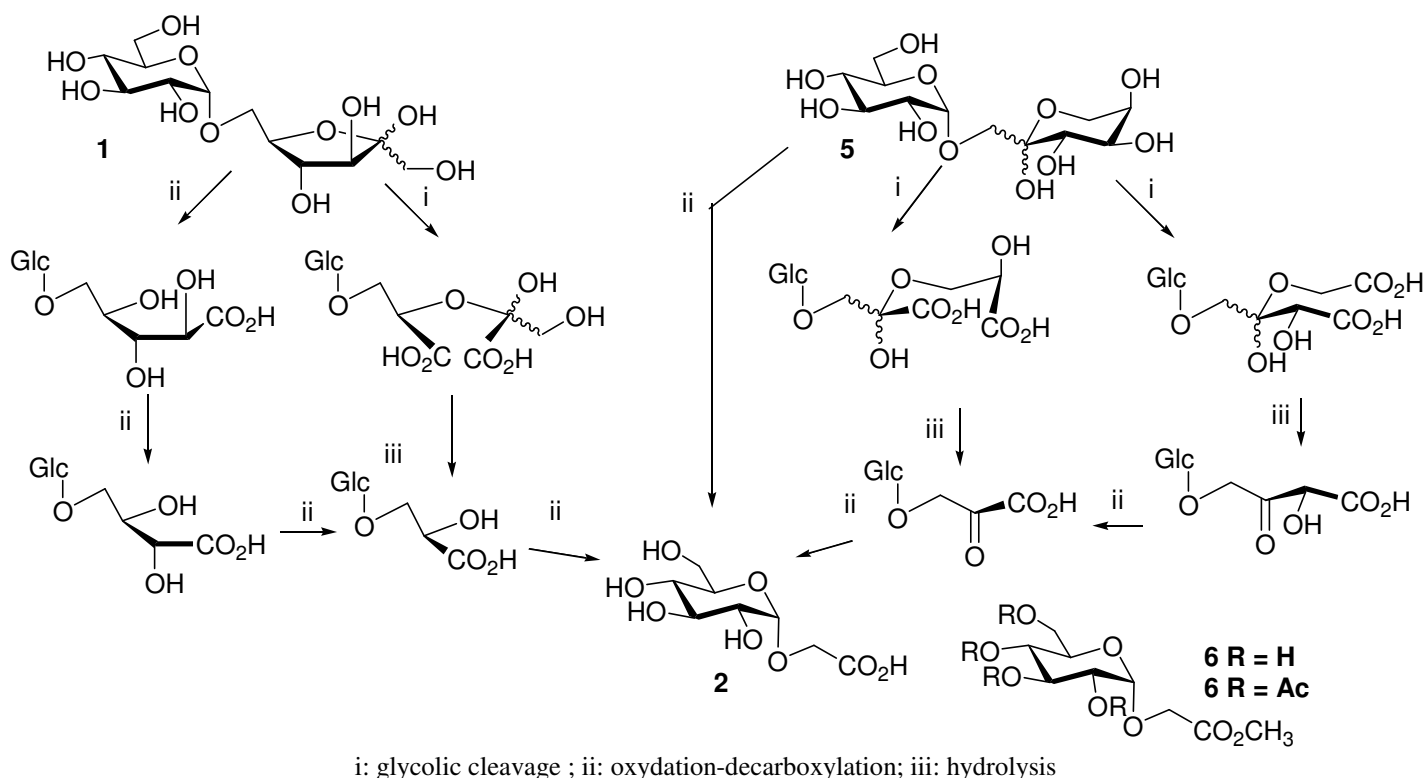


Figure 2

Upon oxidation by air under basic conditions, isomaltulose is known to provide glucosyl- $\alpha$ -D-arabinonates or more carboxylated derivatives under platinum-catalysed oxidation conditions.<sup>6</sup> Such compounds might be interesting as potential cation sequestering agents.<sup>7</sup>

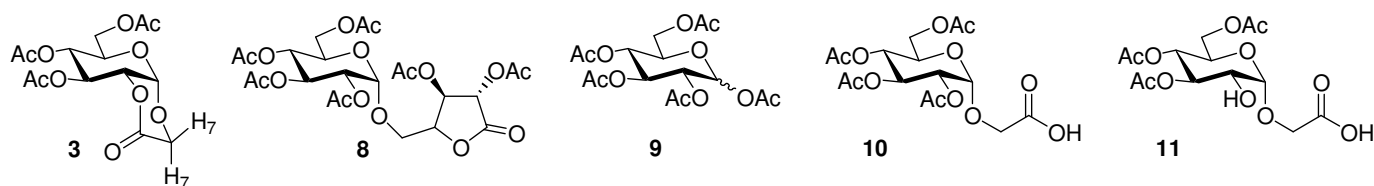
We focused our efforts on the use of aqueous hydrogen peroxide, because it is easy to handle, easily available and generates no by-products. The efficiency and the outcome of the oxidation of carbohydrates by hydrogen peroxide depends on the occurrence of hemiacetalic centres, the basic or acidic conditions and the presence of additives such as metal salts.<sup>8</sup> Some of these reactions are degradative oxidation-decarboxylation sequences since the first oxidation products are themselves oxidisable, and so on, leading to short acids as final products. What we found is that under acidic conditions, the hydrogen peroxide oxidation of isomaltulose led to  $\alpha$ -CMG (**2**). The reaction was also studied in the presence of sodium tungstate, known to promote the oxidative cleavage of glycols *via* peroxotungstate species when used in combination with hydrogen peroxide.<sup>9</sup> Applied to starch and maltodextrins, erythronic acid-terminated oligoglucosides were obtained.<sup>10</sup>  $\alpha$ -CMG can also be obtained from isomalt, the hydrogenation product of isomaltulose, and in this case, the presence of tungstate salts proved to be indispensable.<sup>11</sup> A typical procedure is to treat isomaltulose with excess hydrogen peroxide in acidic conditions (pH 2) at 90 °C. The reaction can also be performed under basic conditions, but the formation of  $\alpha$ -CMG is much slower. The possible routes towards CMG from these disaccharidic substrates are depicted in Figure 3. It is related to the work by Isbel and Frush who studied the base catalysed oxidation of other disaccharides with hydrogen peroxide leading to mixtures of oxidised products, among which carboxymethyl  $\beta$ -D-glucopyranoside was identified when cellobiose was used as starting material.<sup>12</sup> The product **2**, which can be obtained at the 5-10 g scale in *ca.* 35% yield, was identified and characterised as its methyl ester **6** and the corresponding tetraacetyl derivative **7**.



**Figure 3**

We also found that the direct treatment of  $\alpha$ -CMG under acetylation conditions led to a new product which was identified as the triacetyl lactone **3** ( $\alpha$ -CMGL, Figure 4). <sup>1</sup>H and <sup>13</sup>C one- and two-dimensional NMR spectroscopic analyses were consistent with the presence of the  $\alpha$ -carboxymethyl linkage, and HMBC C-H correlations were observed between H-7ab and C-1 and between H-7ab and C=O. The most likely hypothesis for the formation of this lactone is an intermediate mixed anhydride formed first, followed by the

cyclisation by reaction with OH-2. The formation of such a glucoside lactone had never been described, although it was suggested as an intermediate in the case of a  $\beta$ -lactoside.<sup>13</sup> A comparable structure has been described among intermediates towards the synthesis of a lipid-A analog in a recent patent.<sup>14</sup> Likewise, a phostone was observed during the acetylation step of a phosphono-C-glycoside.<sup>15</sup> The diverse side products observed after acetylation are also a way to have a clearer view of the outcome of the oxidation step. Notably, another lactone (**8**) arising from incomplete oxidation was formed when the reaction is not carefully maintained at 90 °C and glucose pentaacetate (**9**) can be present when the pH is not well controlled. Also, acetylated carboxymethyl glucosides arising from the opening of the lactone were observed, either with four acetyl groups (**10**) formed during the acetylation step or with OH-2 still unprotected (**11**), thus formed during the purification procedure.



**Figure 4**

The ability of lactone **3** to open up in the presence of a nucleophilic species was first observed when traces of ethyl ester **31** (*vide infra*, Figure 11) were identified during a recrystallization in ethanol. This led us to investigate in a more general way whether lactone **3** could be used as a synthon for connecting a carbohydrate moiety to other systems, as detailed in the following sections. Indeed, opening of carbohydrate lactones is a popular way for such connective strategies, which can be considered as an alternative to glycosylation. It has been used for the synthesis of a variety of conjugates such as amphiphilic derivatives,<sup>16</sup> carbohydrate terminated dendrimers<sup>17</sup> and hybrid polymers.<sup>18</sup> Only uronic acid lactones or more complex bicyclic structures based on carbohydrates have been used in similar strategies, with the purpose of preparing either surfactants or glycopeptide analogs.<sup>19,20</sup>

## 1.2. Alternative accesses to carboxymethyl glucosides

Carboxymethyl glycosides can be prepared by different routes. The most simple one is the direct Fischer glycosylation of glycolic acid by glucose in the presence of hydrochloric acid, described by Petersson *et al.*, leading to an 70:30  $\alpha/\beta$  mixture of the glycosides in a 6 % yield (Figure 5, path a).<sup>21</sup> The method described in section 1.1., which leads exclusively to the  $\alpha$  anomer, constitutes path b.<sup>2</sup>

A major alternative involves intermediate allyl glycosides, obtained either *via* Fischer or Koenigs-Knorr type glycosylations, which can be oxidized either by the  $\text{RuCl}_3\text{-NaIO}_4$  method,<sup>22-26</sup> developed by Sharpless and co-workers,<sup>27</sup> by bishydroxylation followed by glycolic cleavage,<sup>28-30</sup> or by ozonolysis (path c).<sup>31,32</sup> Following Fischer and Helferich early report who described ethoxycarbonylmethyl  $\beta$ -D-glucopyranoside and its subsequent saponification to the carboxylic function in 1911,<sup>33</sup> glycolic acid esters were directly used (path d) in glycosylations involving activated glycosyl donor instead of allyl alcohol (glycosyl bromide,<sup>34-37</sup> fluoride,<sup>38</sup> trichloroacetimidate<sup>13,31,39</sup>). The anomeric configuration of the carboxymethyl glycoside relies therefore on the classical parameters which control the selectivity of the glycosylation step. The more stable tetrabenzylated carboxymethyl glycoside can be obtained by acid catalysed reaction with glycolic acid ethyl ester.<sup>29</sup> An example using the silver (I) salt of glycolic acid has

been described.<sup>40</sup> Also, the bisdimethylacetal of glycolylaldehyde has been used, with a subsequent oxidation step by NaClO<sub>2</sub>.<sup>41</sup> Finally, let us mention that the carboxymethylation of alcohols or amines using  $\alpha$ -halogenoacetic acid derivatives is a very common reaction, widely used in polysaccharide chemistry for example. Typical conditions are sodium chloroacetate in basic solution, or bromoacetonitrile in acetonitrile in the presence of NaH, followed by transformation of the nitrile group to a carboxylic acid.<sup>42</sup> Some esters (*t*-butyl, benzyl) of bromoacetic acid are also often used, but there has been only rare mention of their use for anomeric alkylation (path a).<sup>43</sup>

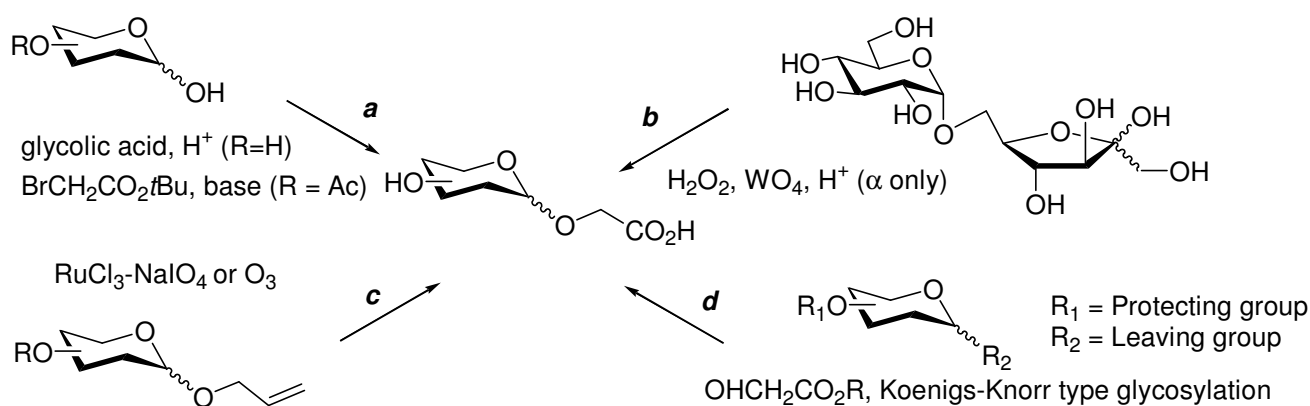


Figure 5

### 1.3. Uses of carboxymethyl glycosides

Carboxymethyl glycosides have been used in different syntheses of peptidomimetics constructed on carbohydrate scaffolds (Figure 6). For example, Nicolaou and co-workers designed non-peptide mimetics **12** of cRGDFV pentapeptide, a potent angiogenesis inhibitor.<sup>38</sup> In the field of cell adhesion inhibition, related with inflammatory processes, Kessler and co-workers have prepared a series of peptidomimetic integrin antagonists constructed on a carboxymethyl mannoside backbone **13**.<sup>41</sup> A multifunctionalised scaffold (**14**) was prepared by Ghosh and co-workers for the construction of broad screening libraries, based on a *N*-acetyl glucosamine carboxymethyl glycoside, also bearing an azido residue at C-6.<sup>22</sup>

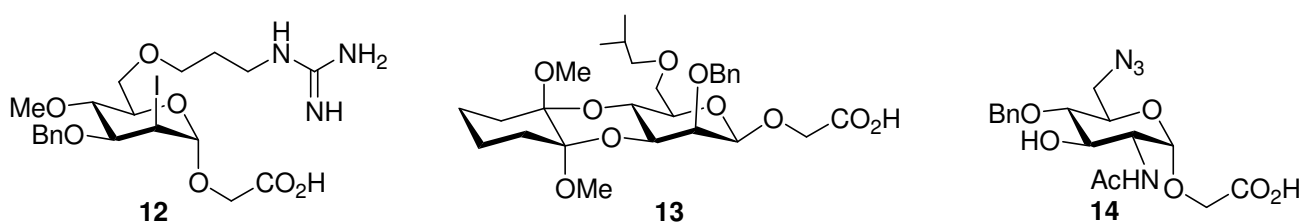
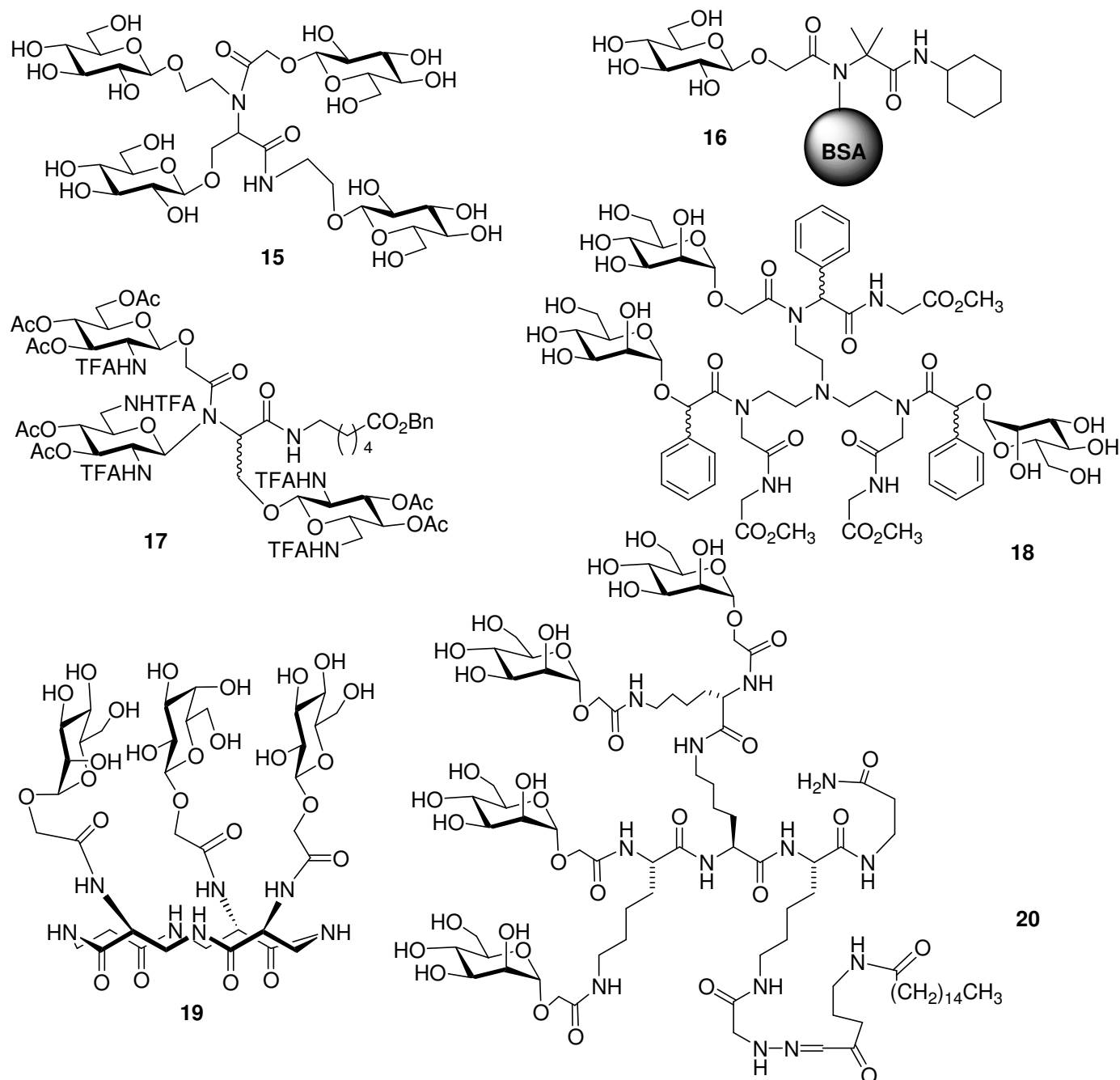


Figure 6

Glycodendrimers have stimulated considerable interest in the recent years.<sup>44</sup> Glycoconjugate libraries (including compound **15**) were prepared by Lockhoff with carboxymethyl glycosides serving as the carboxylic acid partner in four components Ugi reactions (Figure 7).<sup>31</sup> This reaction was also used by Ziegler and co-workers for the preparation of neoglycoproteins (**16**),<sup>34</sup> and by Westermann and Dörner, and Li and co-workers for the synthesis of glycoclusters **17** and **18**, designed for RNA and lectin binding properties.<sup>23,24</sup> Virta and co-workers have connected carboxymethyl glycosides to cyclopeptidic scaffolds, leading thus to diverse di and trivalent glycoclusters (including compound **19**) using a solid support methodology.<sup>25</sup> Other types of amphiphilic glycopeptidic clusters (**20**) were prepared by Grandjean and co-workers.<sup>45</sup>



**Figure 7**

A tetrameric glucose based cluster (**21**) was prepared by Binder and Schmid on pentaerythritol as central polyol (Figure 8).<sup>28</sup> Using a carboxymethyl lactoside, Toyokuni *et al.* synthesized multivalent lactosyl clusters (**22**) designed as potential tumour metastasis inhibitors.<sup>13</sup> Here again, carboxymethyl glycosides are useful synthons for the connection of the external carbohydrate function to the internal multivalent core. For example, Kitaoka and co-workers prepared PAMAM dendrimers decorated with cellobiose (**23**), designed for studying the accessibility of cyclodextrin phosphorylase.<sup>35</sup> Multivalent systems such as **24**, involving specific disaccharides were prepared by Khan, Pieters and co-workers for the study of their properties as E-Coli antiadhesion agents.<sup>39</sup>

The carboxymethyl residue at the anomeric position has been also used in other types of conjugates. In a solid-phase approach to galactose based trisaccharide epitopes involved in hyperacute rejection in xenotransplantation, Elofsson, Kihlberg and co-workers used a carboxymethyl linkage for the connection of the first carbohydrate with the resin (**25**) (Figure 9).<sup>26</sup>

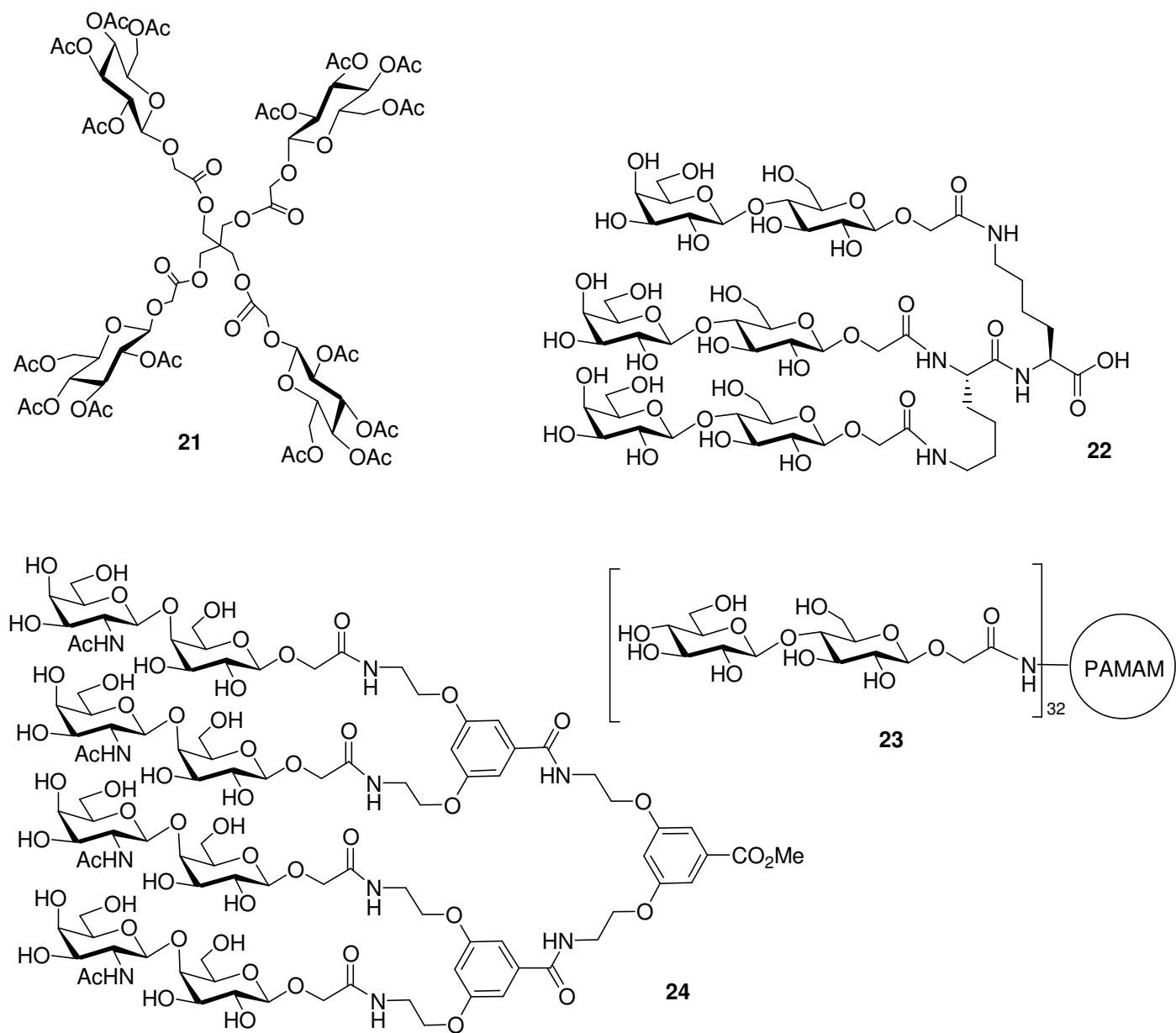


Figure 8

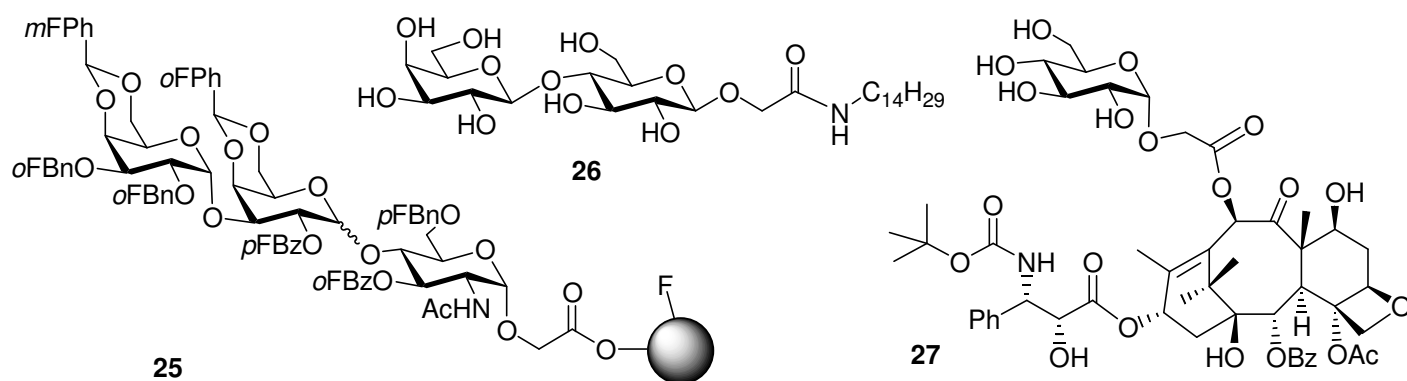
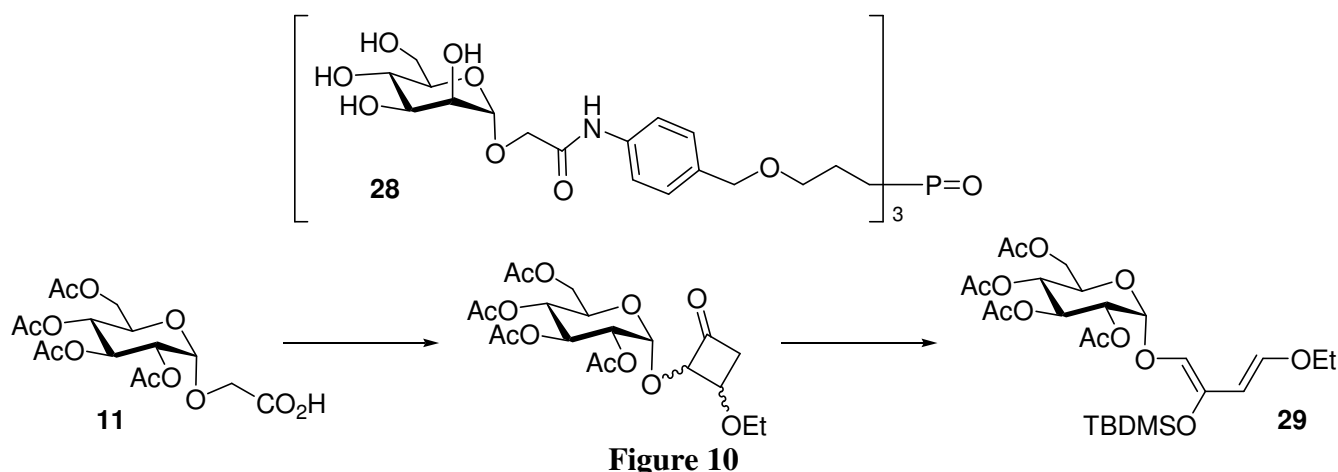


Figure 9

Basu and Santacrose prepared disaccharidic fatty amides (including compound **26**) linked at the anomeric position *via* amide formation from the corresponding carboxymethyl glycosides. The carbohydrate-carbohydrate interactions of these synthetic glycolipids with natural gangliosides and sphingolipids were investigated in the context of a study of the activity of cell surface glycolipids as mediators in cell adhesion.<sup>32</sup> A carboxymethyl glycoside moiety was used by Mandai and co-workers as a water-solubility

promoter for anticancer taxoids, *i.e.* CMG-docetaxel (**27**).<sup>29</sup> This approach was also shown to provide prolonged duration of action of some peptide drugs.<sup>46</sup>

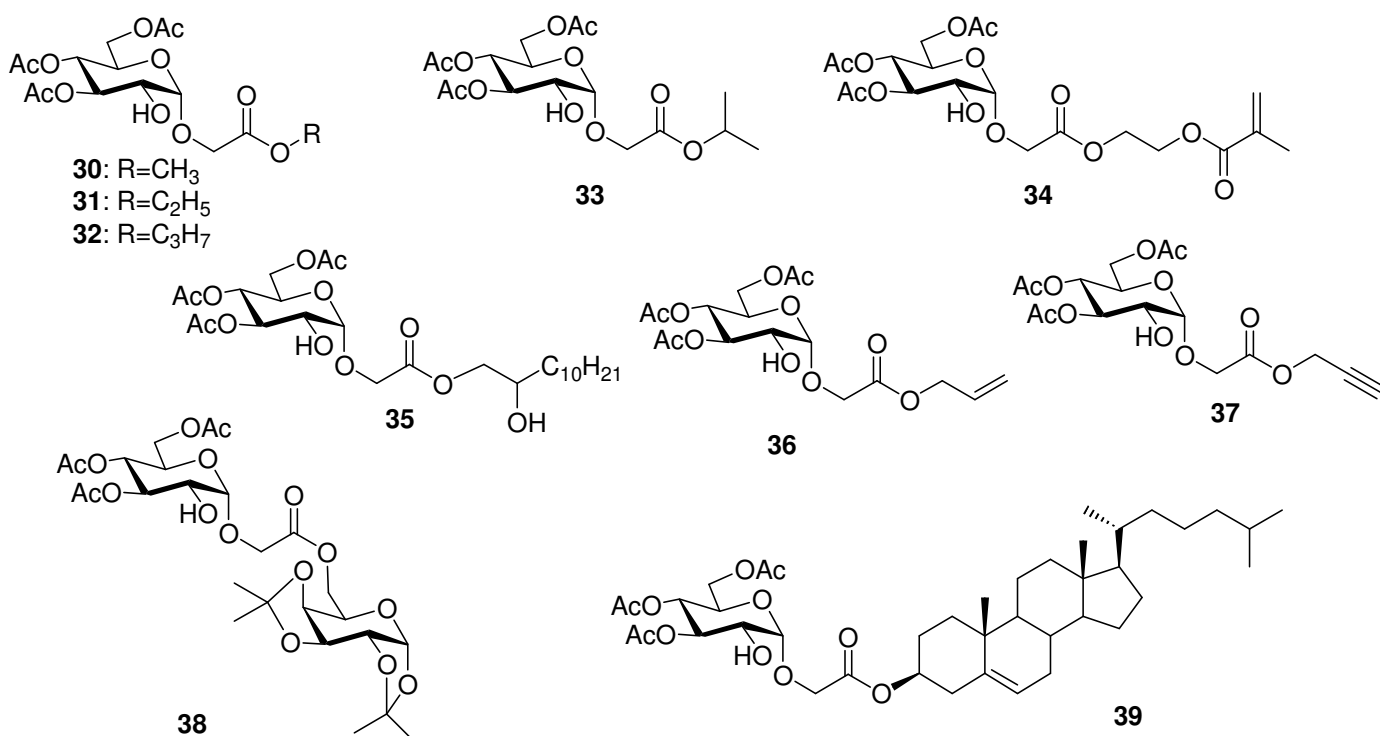
Let us mention two last examples of the use of carboxymethyl residues. The strategy was mentioned for the preparation of complex phosphine oxides (**28**) designed for metal coordination properties as well as water solubility<sup>47</sup> and carboxymethyl glycosides were used by Stoodley and co-workers as starting material towards highly oxygenated dienes (**29**) used in asymmetric hetero-Diels-Alder reactions (Figure 10).<sup>48</sup>



Finally, the properties of carboxymethyl glycoside itself were investigated among other glycosides, in the context of cation complexation studies by Van Bekkum and co-workers,<sup>36</sup> and for the rate of the glycosidic bond hydrolysis by Timell.<sup>37</sup>

## 2. Reactions of carboxymethyl glucoside lactone with alcohols

Alcohols react with  $\alpha$ -CMGL (**3**) to provide the corresponding glycosyloxyacetylated compounds which have unsubstituted OH-2<sup>49</sup> (Figure 11, Table 1).

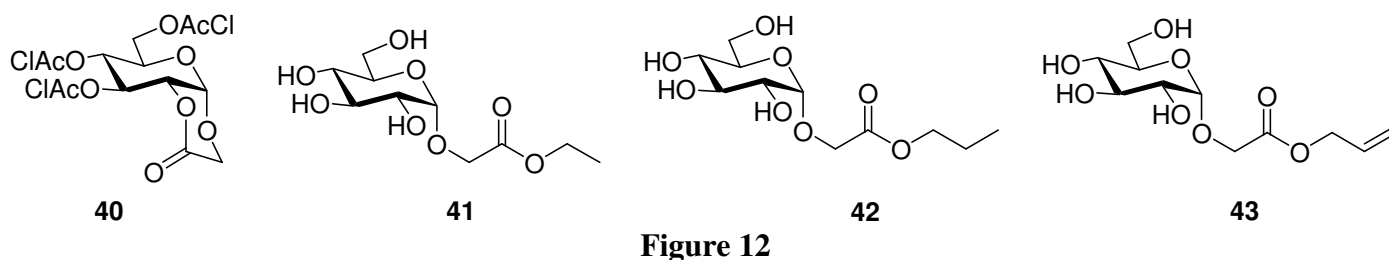


**Table 1.** Reaction of CMGL **3** with alcohols.

Alcohol	Catalyst	Equivalents	Reaction time (h)	Temperature	Obtained adducts	Yields (%)
EtOH	no	/	168	RT	<b>31</b>	26
EtOH	DMAP	0.1	38	RT	<b>31</b>	50
EtOH	DMAP	2.0	48	RT	<b>31</b>	50
EtOH	NEt <sub>3</sub>	1.0	34	RT	<b>31</b>	45
EtOH	AlCl <sub>3</sub>	0.1	36	RT	<b>31</b>	42
EtOH	AlCl <sub>3</sub>	1.0	7	RT	<b>31</b>	34
EtOH	Sc(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub>	0.1	26	RT	<b>31</b>	48
EtOH	Yb(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub>	0.1	27	RT	<b>31</b>	51
EtOH	La(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub>	0.1	30	RT	<b>31</b>	52
EtOH	APTS	0.1	24	RT	<b>31</b>	50
MeOH	DMAP	2.0	2	RT	<b>30</b>	68
MeOH	Yb(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub>	0.1	288	RT	<b>30</b>	52
iPrOH	DMAP	0.5	12	RT	<b>33</b>	55
Propan-1-ol	La(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub>	0.1	168	40	<b>32</b>	57
Allyl alcohol	DMAP	0.5	120	RT	<b>36</b>	88
Dodecane-1,2-diol	DMAP	0.5	120	RT	<b>35</b>	46
1,2:3,4-di-O-isopropylidene-D-galactopyranose	DMAP	1.0	48	40	<b>38</b>	45
Cholesterol	La(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub>	1.0	120	RT	<b>39</b>	42

The reaction proceeds with either base, acid or lanthanide salts catalysis, using either alcohol as solvent (or mixed with CH<sub>2</sub>Cl<sub>2</sub>) or with stoichiometric amount in CH<sub>2</sub>Cl<sub>2</sub>. A series of alcohols were used, including simple aliphatic alcohols, glycol, cholesterol, and a protected carbohydrate having only one OH available, 1,2,3,4-di-*O*-isopropylidene- $\alpha$ -D-galactopyranose. Methanol led to the fully deacetylated product.

When the chloroacetyl analog **40** of the lactone is used, concomitant ester deprotection is observed. Therefore, the chloroacetyl lactone is a more convenient starting material for providing the deprotected conjugates (Figure 12, Table 2).

**Table 2.** Reaction of chloroacetyl lactone **40** with alcohols.

Alcohol	Catalyst	Equivalents	Reaction time (h)	Temperature	Obtained adducts	Yields (%)
EtOH	DMAP	2	5	RT	<b>41</b>	60
Propan-1-ol	DMAP	5	5	RT	<b>42</b>	40
Allyl alcohol	DMAP	5	3	RT	<b>43</b>	57

### 3. Reactions of carboxymethyl glucoside lactone with amines

The main applications of CMGL as a carbohydrate connecting synthon were obtained when amines were used as the nucleophilic species for opening the lactone. Enhanced nucleophilicity of amines compared to alcohols makes the reaction general and easy to perform, even under very mild conditions. The high stability of the amide function which is thus created permits easy further elaboration of the adducts (functionalisation, deprotection). The reaction was applied to the synthesis of various types of conjugates such as glycoaminoacid hybrids,<sup>49</sup> pseudo disaccharides,<sup>50</sup> glycosylated porphyrins<sup>51</sup> and glycosteroids.<sup>52</sup>

#### 3.1. Glycoaminoacid hybrids

Glycopeptides are an important class of biomolecules, involved in many physiological and pathological processes. Therefore various strategies have been established for the synthesis of their analogs and mimetics.<sup>22,38,41,53,54</sup> We thus investigated the potential of CMGL in similar strategies and examined its opening by variously protected aminoacids (Figure 13).<sup>49</sup> Glycine methyl ester was first used as a simple model to give the amide **44**.

The case of aspartic acid dimethyl ester permitted to verify that no loss of configurational integrity at the amino acid chiral center occurred during the reaction (**45**). Indeed, from either L- or the D- amino acids, two diastereoisomers are formed and NMR spectroscopy clearly shows that both compounds are different and pure. Lysine methyl ester, which possesses an amino group on the side chain, gave the *N,N'*-bis(glycosyl) diacetamide **50**, with small amounts of the monoamide **49**. This latter compound has still the side chain amino group available for incorporation into a peptide sequence. The alternative lysine monoamide could be prepared from benzyloxycarbonyl *N*-protected lysine methyl ester.

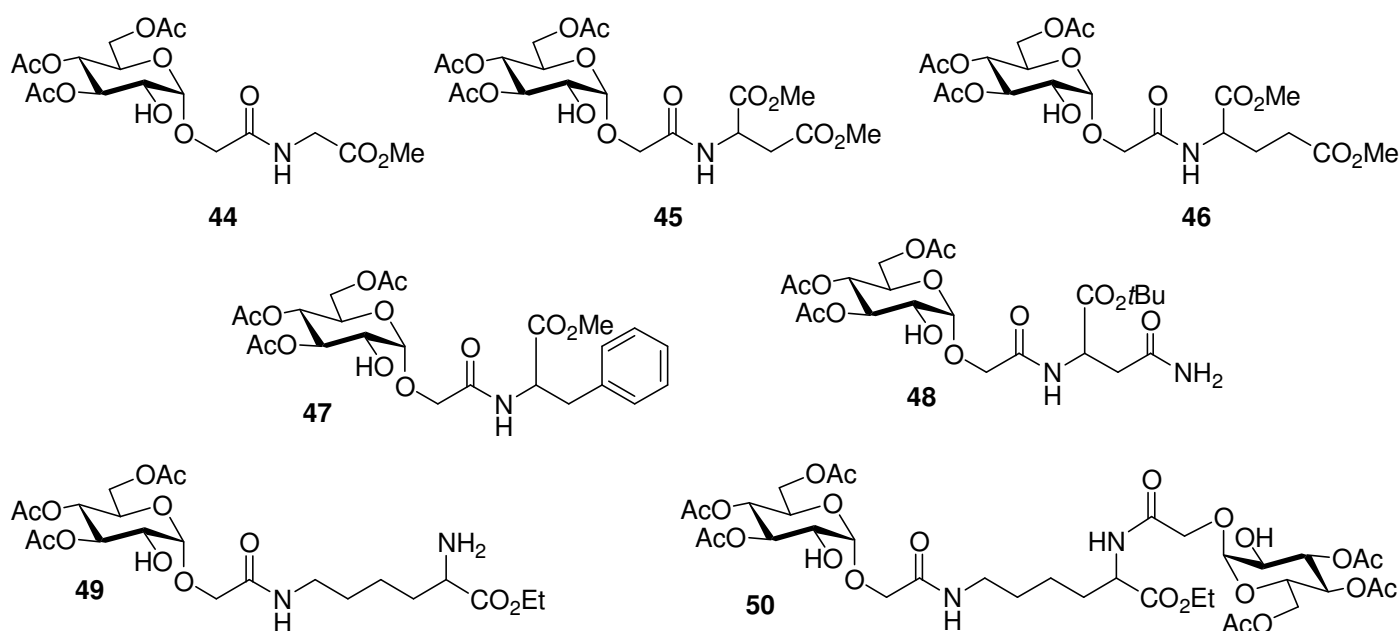
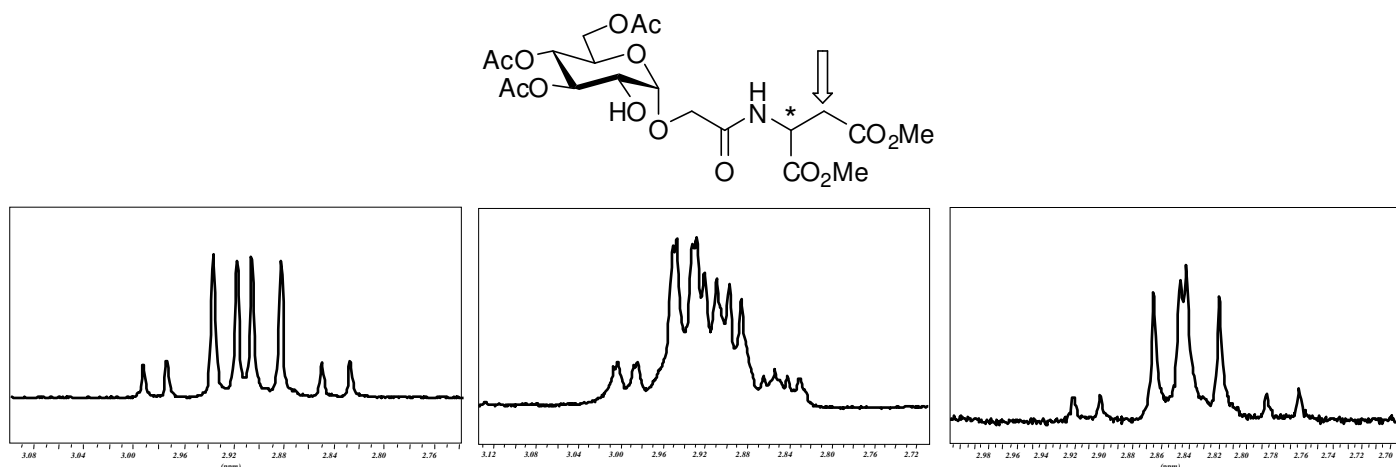


Figure 13

Removal of acetyl groups proceeded without loss of chirality at the  $\alpha$ -amino acid centres using hydrazine in either methanol or methanol-dichloromethane, known to respect amino acid chirality<sup>55</sup> or acetyl chloride in methanol. This method proved to be more general because methyl ester protecting groups are not compatible with the hydrazine/methanol method. Again in this case, NMR spectroscopy clearly indicated that the chirality at the AA-center was not affected (Figure 14), unlike in the case of the NaOMe-MeOH

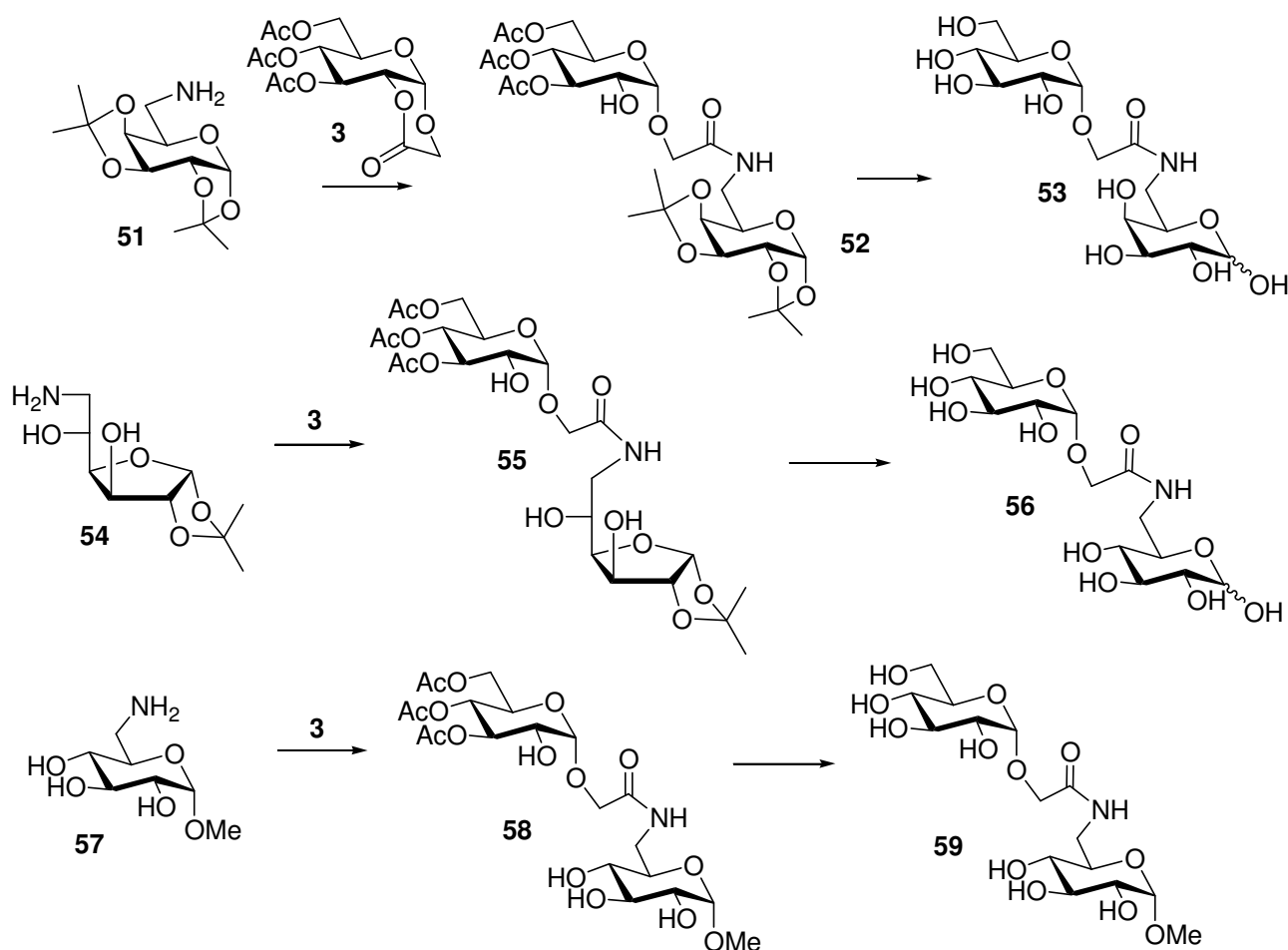
reaction which led to 1:1 mixtures of epimers, although this latter method was reported to allow *O*-acyl group deprotection of a disaccharidic hexapeptide.<sup>56</sup>



**Figure 14.** NMR evidence for the configurational integrity at the AA centre as observed at the CH<sub>2</sub>-AB system of CMG-(L or D)-ASP: (left) deprotection with AcCl-MeOH of **45** and of its (D)-ASP-analog (right); mixture obtained by deprotection of **45** with MeONa-MeOH.

### 3.2. Pseudodisaccharides

Oligosaccharides play key roles in many biological processes. Among analogues, amide-linked saccharidic structures have attracted some interest.<sup>54,57</sup>



**Figure 15**

Sugar amino acids (SAAs) chemistry has provided compounds such as antiviral activity against HIV and inhibitors of sialyl Lewis x-dependant cell adhesion and other peptidomimetics which are interesting because of restricted conformational behavior.<sup>58</sup>

New amide-linked pseudodisaccharides (**53**, **56**, **59**) have been synthesised by reaction of aminodeoxy sugars with  $\alpha$ -CMGL (Figure 15).<sup>50</sup> Taking into account the length (four-atom) of the inter-glycosidic linkage, these compounds are equivalent to trisaccharide mimetics. Similar examples have been described in the literature, such as linear or cyclic oligosaccharides with a four-carbon rigid connection, and a competitive inhibitor of the hydrolysis of *p*-nitrophenyl  $\alpha$ -maltotriose by porcine alpha-amylase having a six-atom acyclic spacer between two glucose residues.<sup>59</sup>

Unlike the case of alcohols, the reaction with aminodeoxy sugars does not require the presence of base. This has also the advantage of limiting the formation of the undesired *N*-acetylation of the starting aminosugar arising from competitive intermolecular O-to-*N* acetyl exchange. Best conditions proved to be THF with a slight excess of CMGL or DMF for some aminosugars with unprotected OH groups. Deprotection of the obtained amide-linked pseudodisaccharide **58** was performed using Zemplén conditions or, in the case of compounds **52** and **55** having isopropylidene and acetyl groups, using a 0.5 M HCl solution at 50 °C (proving the satisfactory stability of the  $\alpha$ -carboxymethyl linkage under acidic conditions).

The amide-linked sugar/nucleoside adduct **61** which could mimic the glucosyltransferases substrate (UDP-Glc) was obtained by the same strategy (Figure 16) from 5'-deoxy-5'-azidouridine (**60**).<sup>60</sup>

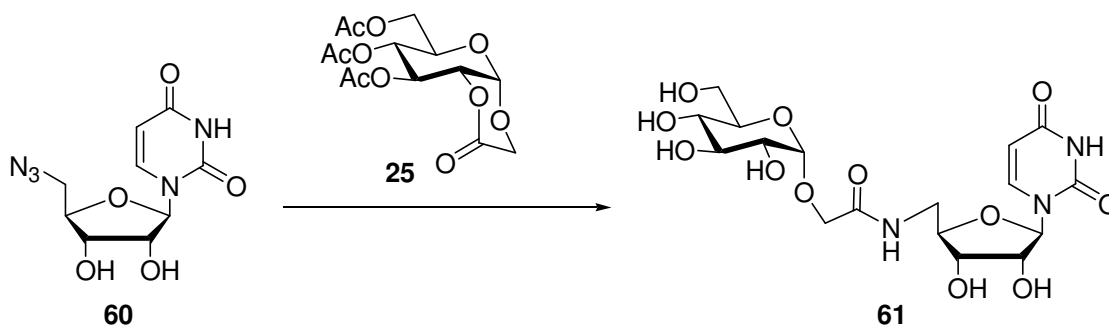


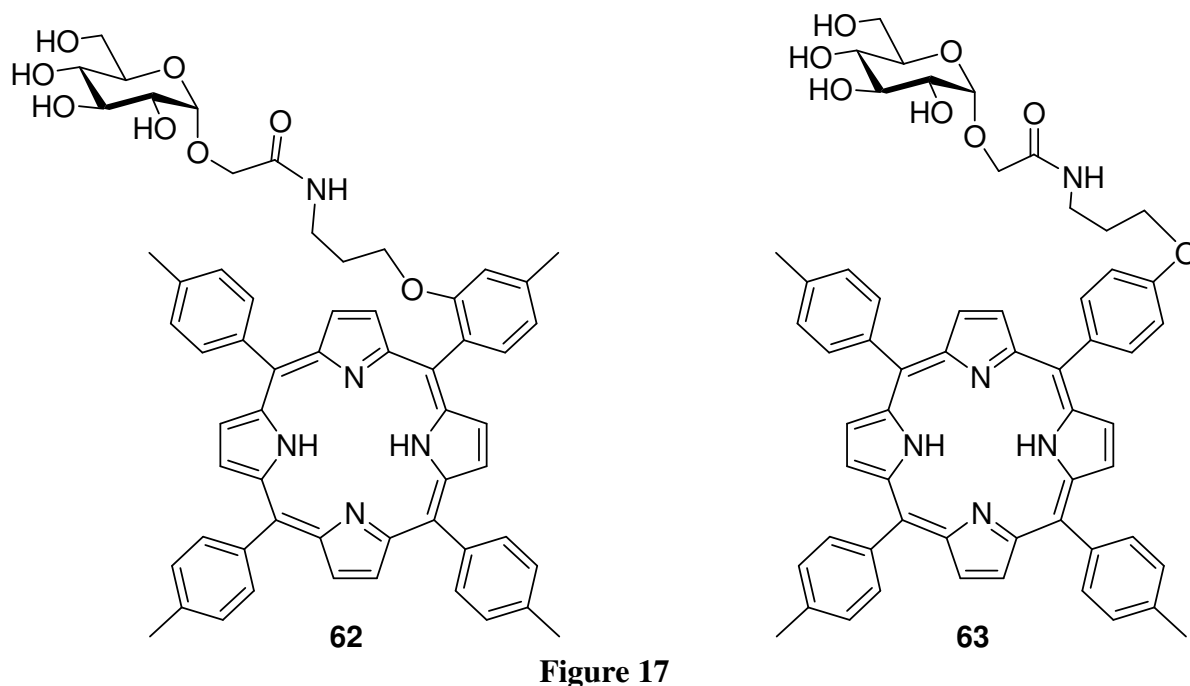
Figure 16

### 3.3. Glycosylated porphyrins

Porphyrins bearing glycosylated groups have potential interest as photosensitizers for cancer photochemotherapy.<sup>61</sup> The sugar moieties have been shown to modulate the amphiphilicity of the photosensitizers and specific membrane interactions,<sup>62</sup> and in some cases to increase their plasmatic life time.<sup>63</sup> The presence of carbohydrates on porphyrins is also known to allow cancer cell surface targeting through specific binding to membrane receptors.<sup>64</sup> Use of synthetic carbohydrates as carriers in directed drug delivery could thus be an interesting approach in cancer cell targeting.

New glucosylated porphyrins **62** and **63**, having an  $\alpha$ -D linkage, have thus been prepared by reaction of CMGL (Figure 17) with aminopropylated monohydroxyphenyltritylporphyrins.<sup>51,65</sup> The decay of fluorescence observed for these porphyrins in H<sub>2</sub>O/THF (8/2) compared to THF suggests the formation of aggregates.<sup>66</sup> The *in vitro* photocytotoxicity of the new porphyrins was evaluated using a K562 chronic leukaemia cell line and compared to that of Photofrin<sup>®</sup>. The *ortho* porphyrin **62** is much more active than *para* porphyrin **63**, although less active than Photofrin<sup>®</sup> at the same ponderal concentration. It induces probably early necrotic death more than secondary necrosis that could be attributed to the induction of

apoptosis. However, the photoactivity of the glycosylated porphyrin was clearly improved compared to the non glycosylated one.

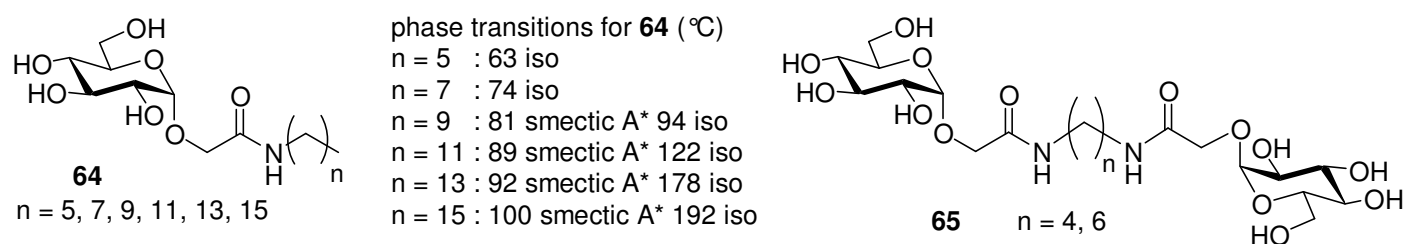


### 3.4. Neoglycolipids

Glycolipids have important properties in terms of biological or physicochemical viewpoints, these two aspects being sometimes correlated. For example, glycolipids are involved in complex mechanisms that are thought to involve membrane sub-domains, containing liquid-ordered phases, termed lipid rafts.<sup>67</sup>

Being interested in the synthesis and study of the surface activity and thermotropic liquid-crystalline behaviour of a variety of synthetic glycolipids, notably arising from simple and available sugars,<sup>1a,68</sup> we also developed the CMGL strategy towards such materials.<sup>49,52</sup>

A series of aliphatic amines ( $C_6$ ,  $C_8$ ,  $C_{10}$ ,  $C_{12}$ ,  $C_{14}$ ,  $C_{16}$ ) were condensed with CMGL in THF. The resulting amides **64** were deacetylated in methanol using catalytic amounts of sodium methanolate in good yields (Figure 18). Some symmetrical diamines were also prepared and new bolaform carbohydrate based amides **65** were thus obtained. In terms of thermotropic properties, it was shown that the minimum chain length is of 10 carbon atoms, the  $C_{10}$ ,  $C_{12}$ ,  $C_{14}$ , and  $C_{16}$  exhibiting all lamellar phases. The stability of the amide linkage, as well as that of the  $\alpha$ -glucosidic bond, allowed full cycles of heating up and down for the DSC analysis experiments, unlike other glycolipids such as sucrose esters or hydroxyalkylethers we had previously studied.



**Figure 18**

Four different amino steroids were also coupled onto CMGL. The 3-aminocholesterols ( $\alpha$  and  $\beta$ ) were obtained by reduction of 3-azido-5-cholestene prepared itself by reaction of  $\text{HN}_3$  with cholesterol or epicholesterol under Mitsunobu conditions. The saturated equivalent systems were prepared from cholestanol and involving the same Mitsunobu reaction conditions to establish the stereochemistry at C-3 of the steroid followed by reduction of the azido group (Figure 19).<sup>69</sup> Reaction with CMGL was performed in anhydrous THF leading to the steroidal amides in very good yields. The typical proton NMR patterns for the CMG conjugates were observed, notably H-2, H-3 and H-4 at 3.82, 5.28 and 5.04 ppm respectively. Final amphiphilic glyco steroids **66-69** were obtained by deprotection of acetyl groups performed under Zemplén conditions.

Only the saturated steroid amides **66** and **67** exhibited some liquid crystalline behaviour, in a very limited temperature range (181-230 dec and 202-230dec). This is often the case for steroidal glycolipids having direct connection or short spacer (1-4 atoms) between the carbohydrate moiety and the steroid backbone.<sup>70</sup> Furthermore, the relatively high melting points of these compounds increase their tendency to decompose at elevated temperatures through caramelization. The 3- $\beta$ -cholestane amide **67** exhibits a wider temperature range of the liquid crystal phase with a lower melting point compared to the  $\alpha$  one. The unsaturated analogues **68** and **69**, less flexible, did not exhibit any liquid crystalline phase as they decompose at lower temperatures.

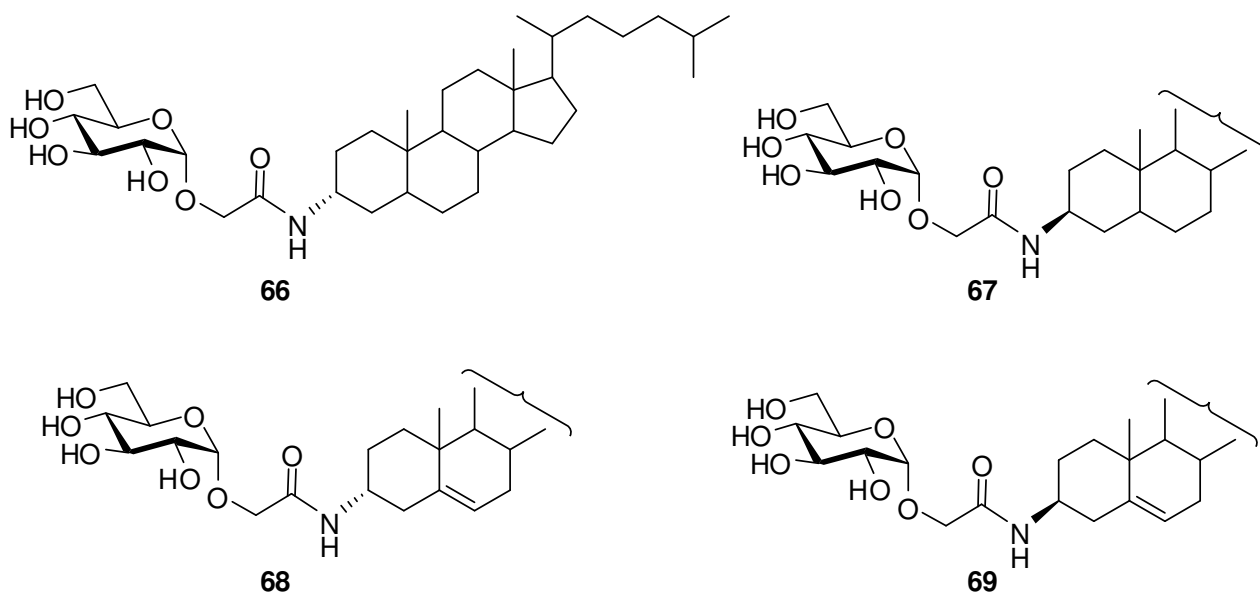


Figure 19

### 3.5. Miscellaneous

Other various other amines were used in the CMGL opening reaction. Notably, some amines with polymerisable residues provide amides such as the methacrylate **70** or allyl and propargyl amides **71** and **72** (Figure 20).<sup>49</sup> Also, some multivalent species were obtained such as the triamide **73**<sup>71</sup> and an octa amide on a PAMAM backbone (**74**) was identified by mass spectrometry. Likewise, a resin bearing free amino functions was shown to react with CMGL and could be used for example to eliminate excess CMGL from the reaction mixture providing **75** which could be easily removed by filtration. Finally the reaction with monoamino- $\beta$ -cyclodextrin led to the corresponding amide **76**.<sup>72</sup>

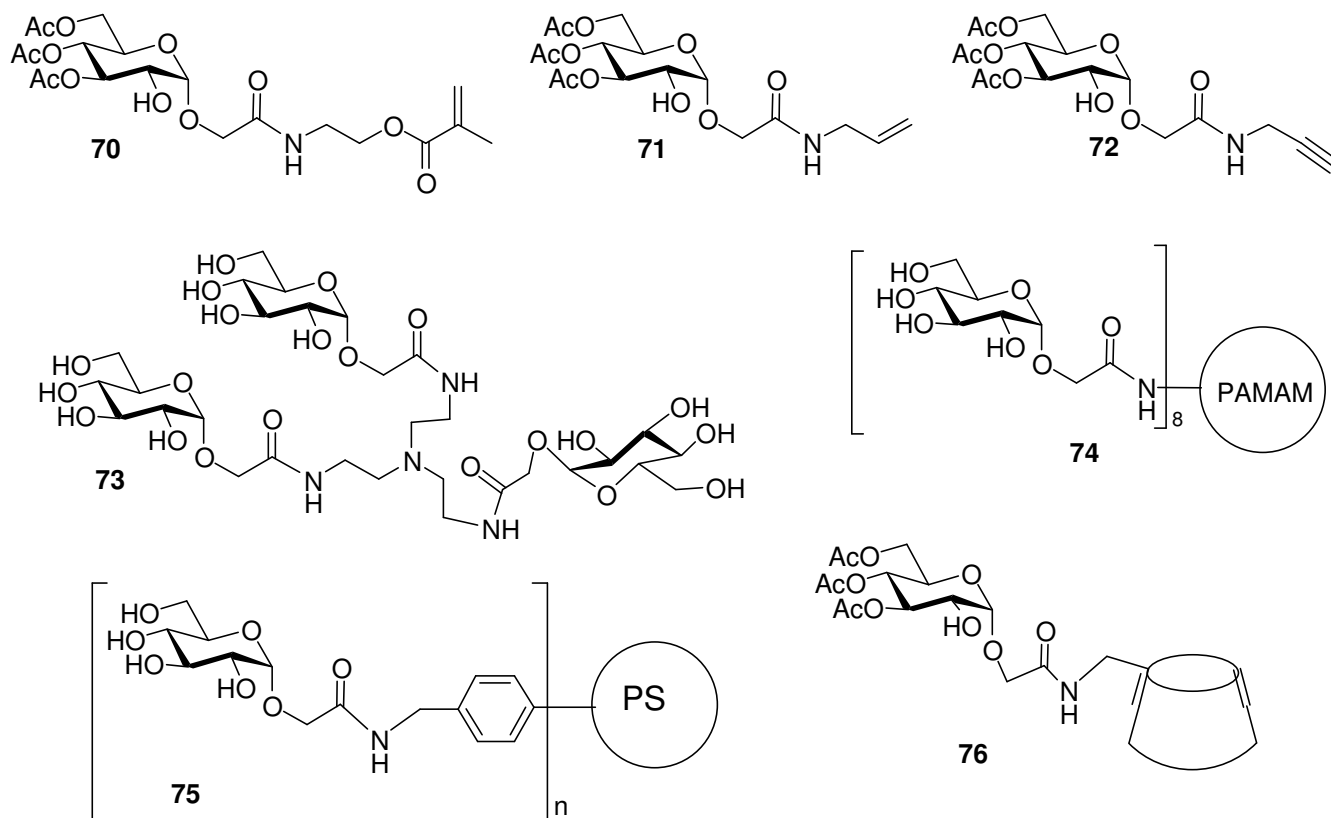


Figure 20

#### 4. Reactions of carboxymethyl glucoside lactone with vinyl magnesium bromide

A short exploration of the reaction with vinyl magnesium bromide proved that CMGL can also be used for carbon-carbon bond connections with the carbohydrate moiety. However, yields remained rather low because of the lack of stability of the ester groups, even when the more stable tripivaloylated lactone was used. Actually, the best was to directly remove all esters in order to simplify the mixture of products, allowing the identification of the bis-vinyl alcohol **77** (Figure 21).<sup>73</sup>

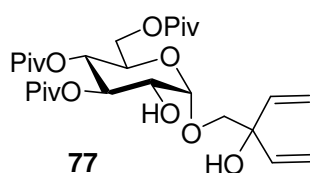


Figure 21

#### 5. Structural variations on CMG-adducts

A major interest of the CMGL approach is to provide an isolated OH group at position 2 after the opening step (Figure 22). The selective further transformation of this function can therefore provide 1,2-disubstituted compounds in a very straightforward manner. An example is the reaction of amide **78** with dihydropyran under acidic catalysis which yield the acetal **79**, from which the acetyl groups could be exchanged to benzyl ethers to yield **80**.<sup>74</sup> Another example is the oxidation of the ester **32** under Swern conditions which give the non-isolable corresponding 2-keto derivative, which undergo immediate elimination of one acetic acid molecule leading to the enone **81**.<sup>75</sup> Further studies taking advantage of this selective functionalisation are currently ongoing in our laboratory.

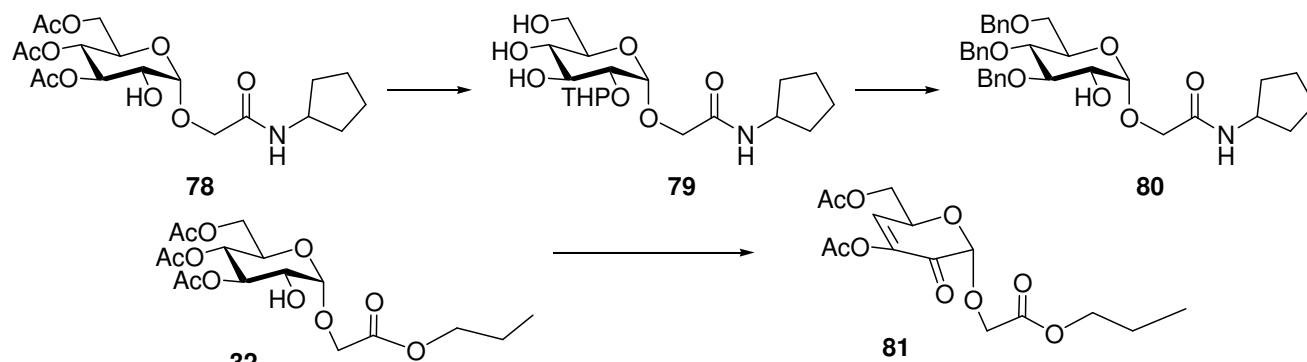


Figure 22

## 6. Conclusions and perspectives

Carboxymethyl  $\alpha$ -D-glucopyranoside and its acetylated 2-*O*-lactone (CMGL) are easily prepared from the very available isomaltulose. The opening of CMGL by nucleophilic species, which occurs under very mild conditions, provides glucosyloxyacetylated compounds which can be seen as analogs of glucoconjugates. In particular, a wide variety of amides have been obtained with examples among pseudo disaccharides, gluco-aminoacids and neoglucolipids. More work is currently in progress in our laboratory to extend the scope of this strategy toward conjugates constructed on other carbohydrates, mono- or oligosaccharides. With this aim, new ways to prepare similar lactones are studied and the results will be reported soon.

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