

A short route for the synthesis of “sweet” macrocycles *via* a click-dimerization–ring-closing metathesis approach†

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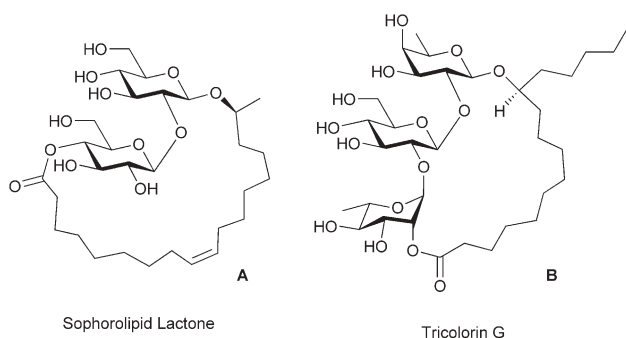
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A facile and flexible approach for the preparation of macrocyclic molecules containing different carbohydrate moieties is presented, employing the reaction cascade: click-dimerization and ring-closing metathesis.

Carbohydrate containing macrocycles such as cyclic glycolipids sophorolipid lactone (**A**) and tricolorin G (**B**) constitute a class of molecules with diverse structural characteristics and interesting biological profiles.¹ They contain a variable number of linked carbohydrate units tied up by a lipophilic aglycon. In an elegant approach Fürstner and co-workers reported the synthesis of several cyclic glycolipids and analogues using ring-closing metathesis (RCM).² This methodology was also used to synthesize structurally related cyclic neoglycoconjugates combining structural preorganized carbohydrate moieties and lipophilic subunits. Kirschning *et al.* synthesized spacer-linked aminoglycoside mimics to target polynucleotides³ while Murphy *et al.* fashioned cyclic multivalent carbohydrate scaffolds.⁴ All these examples among others constitute elegant applications of ring-closing metathesis in macrocycle synthesis.⁵

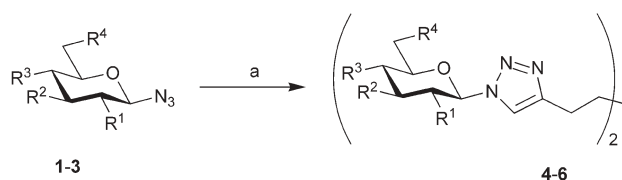


In order to develop a short entry to new sugar-containing macrocyclic compounds we sought to combine the highly reliable RCM with another reaction which allows for a facile linkage of carbohydrate monomers. In this context the Cu-catalyzed modification of the classic Huisgen-reaction (“click-reaction”),⁶ which was successfully employed for the synthesis of glycoconjugates recently,⁷ seemed to be promising. Therefore, we settled on the following reaction sequence: i) dimerization of carbohydrate

azides by 1,3-dipolar cycloadditions with a dialkyne, ii) ring-closing metathesis. We reasoned that synthetic operations would be minimal by starting with a precursor molecule that incorporates both the azide and the alkene functionality so that the 1,3-dipolar cycloaddition and the RCM could be carried out in a consecutive manner without necessity for functionalization after each step. Additionally, potential problems of stereocontrol are ruled out while starting from bifunctional carbohydrate units. With this in mind we examined first the dimerization of anomeric carbohydrate azides with a dialkyne (Scheme 1).

The azides **1** and **2** were prepared starting from glucose and glucosamine according to literature procedures. Azide **3** was readily prepared from the commercially available neomycin B by degradation to the corresponding anomeric bromide⁸ and subsequent replacement of bromine with an azide residue under phase transfer conditions.⁹ We found that after addition of an aqueous copper(II)acetate–sodium ascorbate solution to the mixture of the corresponding carbohydrate azide and 1,7-octadiyne in *tert*-butanol, the carbohydrate dimers **4–6** could be isolated in good yields.

Encouraged by these results, we turned our attention to the synthesis of suitable bifunctional building blocks containing olefinic and azide groups. For the ring-closing metathesis the prerequisite olefinic functions are introduced at the anomeric centre as an *O*-allyl side chain *via* a classic Königs–Knorr-reaction furnishing **7**, or Keck-allylation leading to the *C*-glycosidic compound **8**.¹⁰ In contrast to the initial dimerization reactions outlined in Scheme 1 we decided to incorporate the azide

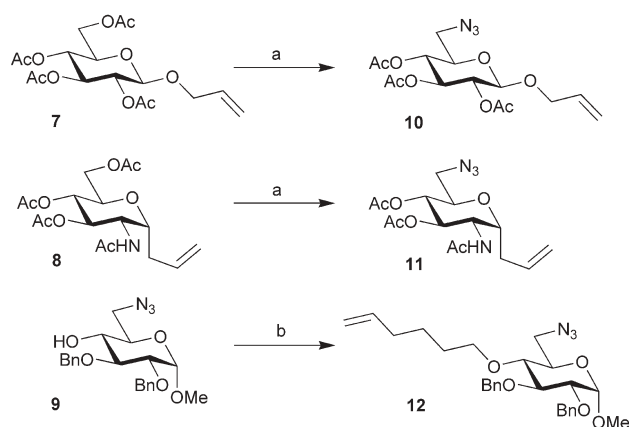


	R ¹	R ²	R ³	R ⁴	Yield (%)
1 → 4	OBn	OBn	OBn	OBn	77
2 → 5	NHAc	OAc	OAc	OAc	76
3 → 6	NHTfa	OAc	OAc	NHTfa	54

Scheme 1 Carbohydrate dimerization. *Reagents and conditions:* (a) **1–3** (1 eq.) 0.1 M solution in *t*-BuOH, 1,7-octadiyne (0.5 eq.), sodium ascorbate (0.4 eq., 0.08 M solution in H₂O), Cu(OAc)₂ (0.2 eq., 0.04 M solution in H₂O), 12 h, rt.

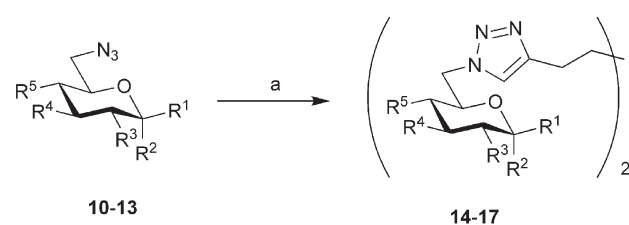
† Electronic supplementary information (ESI) available: nmr data and copies of nmr-spectra of all compounds. See <http://www.rsc.org/suppdata/cc/b5/b502682b/>

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Scheme 2 Synthesis of bifunctional building blocks. *Reagents and conditions:* (a) i. NaOMe, MeOH, rt; ii. TsCl, pyridine, 0 °C → rt then Ac₂O; iii. NaN₃, DMF, 90 °C, 70% (**10**), 64% (**11**); (b) 6-bromo-1-hexene, NaH, THF, rt → reflux, 43%.

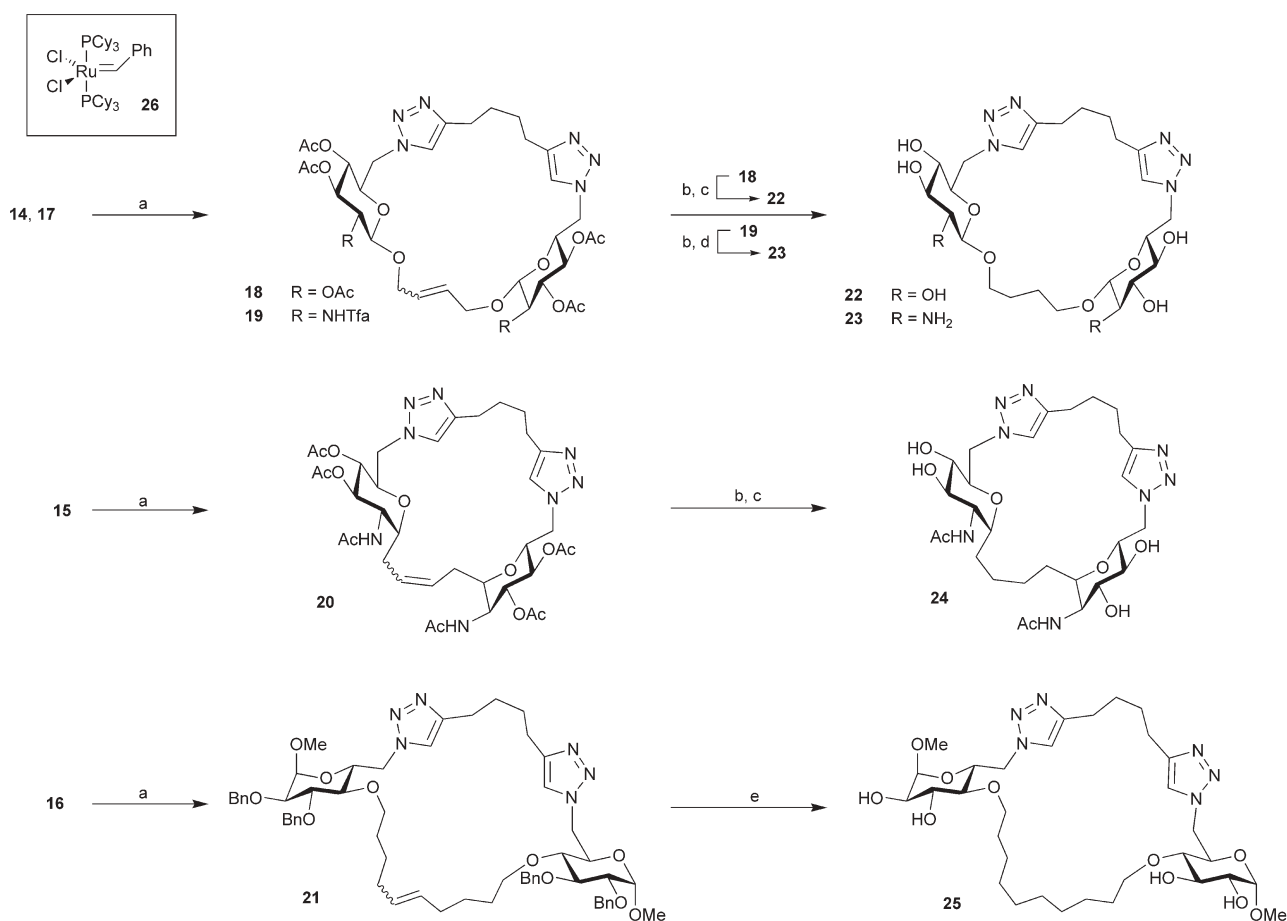
functionality at C-6 of the sugar core rather than the anomeric centre to allow more flexibility for the heterocycle formation. Therefore, after deacetylation of **7** and **8**, the azide residue was introduced by tosylation of the primary hydroxy group followed



	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)
10 → 14	OAll	H	OAc	OAc	OAc	98
11 → 15	H	All	NHAc	OAc	OAc	99
12 → 16	H	OMe	OBn	OBn	OHexenyl	99
13 → 17	OAll	H	NHTfa	OAc	OAc	79

Scheme 3 Dimerization of bifunctional carbohydrate building blocks. For conditions (a) see Scheme 1.

by substitution with sodium azide. Starting with the literature-known molecule **9**¹¹ a hexenyl residue was attached by alkylation at C-4 of the sugar moiety (Scheme 2).



Scheme 4 Preparation of macrocycles. *Reagents and conditions:* (a) **14–17** (2 mmolar solution in DCM), Grubbs I catalyst **26** (5 mol%), reflux, 12–24 h, 73–95%; (b) **18–20**, MeOH, Pd(OH)₂/C/H₂, 87–99%; (c) acetyl protected compounds (solution in MeOH), NaOMe, 2 h, 79–99%; (d) NaOH (0.1 M), THF, 12 h, 40%; (e) MeOH, Pd(OH)₂/C/H₂, 88%.

With these molecules in hand the stage was set for the click-dimerization. Except for azide **13**¹² that provided the dimerized product in only 79% yield, it was found that by employing the same reaction conditions as described for **1–3**, the reaction of **10**, **11** and **12**, having primary azide groups at C-6, went to completion (Scheme 3). This might indicate that steric and electronic effects are less favorable for the reaction of azides at the anomeric center.

Having successfully finished the assembly of dimeric precursors **14–17**, only a few steps had to be effected to finish the synthesis of the desired macrocyclic compounds. To accomplish the ring-closing metathesis, the diolefinic molecules were reacted for 12–24 hours with a 5 mol% loading of Grubbs' ruthenium catalyst **26**. The ring formation reactions were carried out in a 2 mmolar dichloromethane solution at 40 °C to facilitate the macrocyclization and to prevent a competitive homodimerization. These reactions proceeded smoothly to yield **18–21** (Scheme 4). As expected, no *E/Z*-selectivity was observed during the metathesis leading to a non-separable mixture of both isomers in 73–95% yield. In order to obtain single compounds for clear characterization the double bonds of the products **18–21** were reduced hydrogenolytically. This task was easily accomplished using palladium hydroxide on charcoal as a catalyst under a hydrogen atmosphere. While in the case of molecules **18–20** the reduced macrocycles had to be deprotected by saponification to provide **22–24**, the hydroxyl groups of **21** were unveiled during double bond reduction in a single operation affording **25** in good yield. By variation of the length of the olefinic side chain, macrocycles of different ring sizes and hence lipophilicity were obtained.

In summary, we presented a short route for the synthesis of sugar-containing macrocycles by an amalgamation of click-reactions and RCM. Employing different precursors, this cascade transformation constitutes a powerful approach to generate molecular complexity. A large number of potential sugar precursors for the assembly of compound libraries following this strategy can be found in literature. While azide groups are found in large number in sugar chemistry as surrogates for amine functions, olefins occur as part of protecting or activating groups.

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