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1,3-Dipolar Cycloadditions as a Tool for the Preparation of Multivalent Structures

Francisco G. Calvo-Flores, Joaquín Isac-García, Fernando Hernández-Mateo, Francisco Pérez-Balderas, Jose A. Calvo-Asín, Eduardo Sanchéz-Vaquero, and Francisco Santoyo-González*

Instituto de Biotecnología, Departamento de Química Orgánica, Facultad de Ciencias, Campus Fuentenueva s/n, Universidad de Granada, Granada E−18071,Spain

fsantoyo@ugr.es

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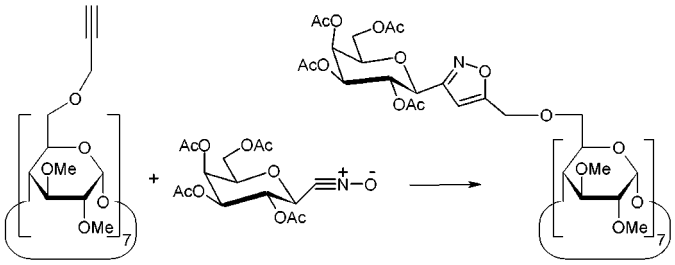
ABSTRACT



The construction of multivalent structures such as sugar heterodimers, glycoclusters, calix sugars, multicalixarenes, and glycocyclodextrins is designed by using 1,3-dipolar cycloaddition as a versatile and efficient tool which allows the creation of heterocyclic bridges between the different units that are coupled.

The rational design of supramolecular structures with a well-defined architecture has attracted much attention during the past few decades.[1] Work on these molecular assemblies ranges from the attempt to understand the molecular recognition phenomena to the capacity to mimic the catalytic capacity of enzymes. As a consequence, new terms and structures such as crown ethers, dendrimers, calixarenes, clusters, cyclophanes, etc. have emerged in organic chemistry and the preparation of such entities has contributed to the development of suitable synthetic protocols.

In the field of molecular recognition and following the observation of the so-called "cluster" or "multivalent effect"[2] high-affinity lectin ligands have been developed by coupling saccharides in a multiple fashion to a variety of different carriers, giving rise to chemically well-defined homogeneous neoglycoconjugates (glycopolymers—linear polymers, glycoclusters, oligomers, and polyamino acids—and glycodendrimers) with systematic varied shapes and carbohydrate densities.[3] Among these neoglycoconjugates, glycoclusters or nonlinear medium-sized glycoconjugates have usually been constructed using aza macrocycles,[4] polyamines,[5] pentaerythritol-based cores,[6] cyclodextrins,[7] and calixarenes.[8] Formation of the link glycan scaffold for the synthesis of

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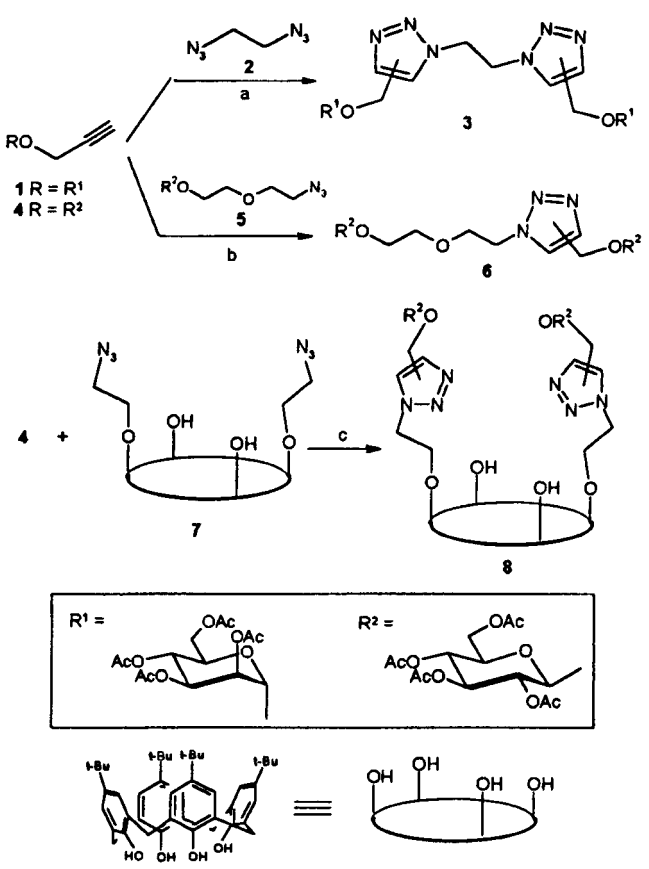
such multivalent structures is usually performed in the later steps of the synthesis and have been carried out using a variety of strategies such as formation of thiourea[5a−c,7a,b,8i] or amide bridges[5b,9] by reaction of amines with isothiocyanates or carboxylic acids, respectively, by use of glycosylation[5b,6,9e] or by nucleophilic substitution.[7b,c,9c,10]

On the other hand, the versatility of calix[4]arenes as host molecules has been widely exploited for designing a large variety of synthetic receptor molecules for the binding of relatively small guest species (cations, anions) and small neutral molecules.[11] Most synthetic-based calixarene receptors have been prepared using the methodologies of classical organic synthesis and, recently, by combination of different or similar molecular building blocks in the so-called modular approach.[11c]

In the search for new strategies for the covalent assembly of the different components of such multivalent or supramolecular structures, we thought that 1,3-dipolar cycloaddition reactions could be used as an efficient tool allowing for the simultaneous building up of aromatic systems that could positively contribute to the hydrophobicity and rigidity. 1,3-Dipolar cycloaddition to alkenes and alkynes is a well-established and general method for the synthesis of both nonaromatic and aromatic five-membered-ring heterocycles.[12] In the carbohydrate field inter- as well as intramolecular 1,3-dipolar cycloaddition has found application in the synthesis of a variety of compounds such as higher sugars,[13] C-disaccharides,[14] and aminocyclitols.[15] On the basis of the easy introduction of alkynes in a substrate, we designed two approaches that use such a function as the dipolarophile in the cycloaddition reaction: synthesis of 1,2,3-triazole and synthesis of isoxazoles (1,2-oxazoles) by reaction, respectively, with azides and nitrile oxides as the 1,3-dipolar functions.

Following the first approach, our first goal was the construction of sugar-containing molecules using *O*-propargyl glycosides that are easily obtainable. Thus, we achieved the assembly of two sugar units by reaction of compound **1**[16] with 1,2-ethanediazide **2**[17a] as the connecting spacer, leading to a mixture of the bis(triazole) sugar dimer **3** (Scheme 1). In a slight variation, the construction of sugar dimers was also shown to be possible when the 1,3-dipole function was incorporated into a monosaccharide unit. The

Scheme 1[a]



[a] Legend: (a) 0.61 mmol of **1**, 0.27 mmol of **2**, toluene, reflux, 72 h, 70%; (b) 1.1 mmol of **4**, 1.0 mmol of **5**, toluene, reflux, 30 h, 70%; (c) 0.7 mmol of **4**, 0.2 mmol of **7**, toluene, reflux, 6 days, 80%.

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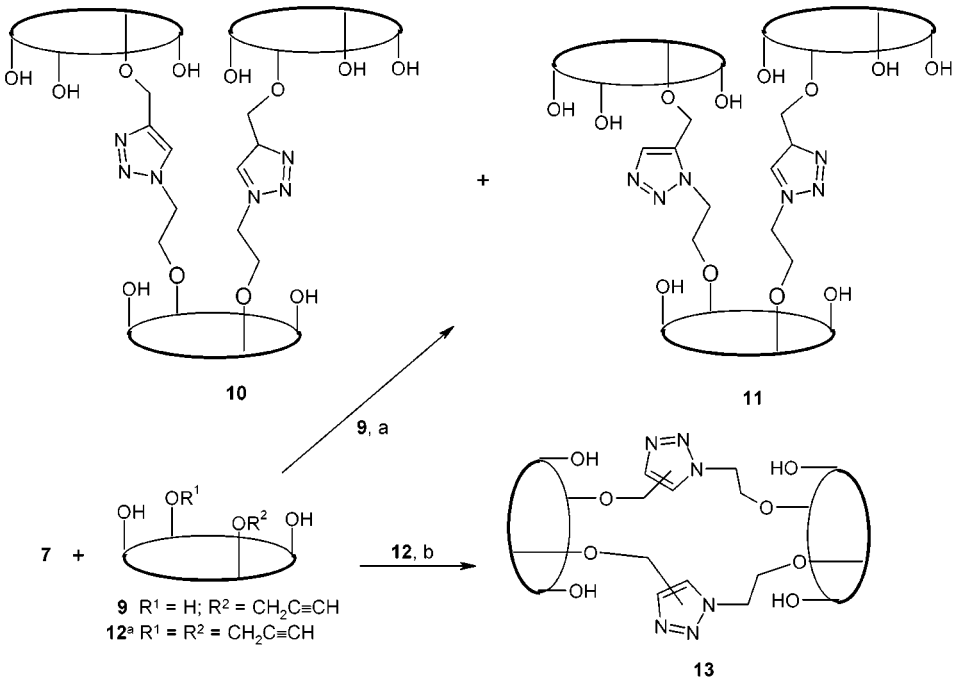
Scheme 2[b]



[a] Obtained from *p-tert*-butylcalix[4]arene and propargyl bromide with 84% yield. [b] Legend: (a) 0.1 mmol of **7**, 0.24 mmol of 9, toluene, reflux, 6 days, 57% overall yield for **10** + **11**; (b) 0.14 mmol of **7**, 0.14 mmol of 12, toluene, reflux, 5 days, 90% overall yield.

intermolecular cycloaddition reaction of compounds **4**[18] and **5**[17b] afforded in this case the triazole sugar dimer **6** as a mixture of the two possible regioisomers. These cycloaddition reactions also were shown to be adequate for the construction of calix sugars. Starting from 25,27-bis(bromoethoxy)-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butylcalix[4]arene,[19] we prepared in a straightforward fashion the diazide calixarene derivative **7**, which was then reacted with the propargyl glycoside **4**, giving a regioisomeric mixture of calix sugar **8**. All the aforementioned reactions of propargyl glycosides with azides allowed the assembly in good to high yields, but in all cases no regioselectivity was observed and a mixture of regioisomers was obtained.

We also performed the preparation of multicalix[4]arenes by following the same last principle: i.e., incorporation of the 1,3-dipole function and the dipolarophile in different calixarene units. Reaction of the mono(propargyloxy)calix[4]arene derivative **9**[20] with the diazide calixarene derivative **7** yielded the tris(calix[4]arene) derivatives **10** and **11**, which could be isolated as pure compounds from the crude reaction mixture (Scheme 2). When we applied the cycloaddition strategy in the difunctional bis(propargyloxy)calix[4]arene **12** instead of the mono(propargyloxy) derivative **9**, the reaction with the diazide **7** led to the three possible regioisomers of the corresponding double-bridged bis(calix[4]arene) derivative **13**.

Next, we investigated the utility of the nitrile oxide based approach. Two general methods are in common usage for the generation of such a function. The first one is the thermal or base-mediated dehydrochlorination of a hydroximoyl chloride.[21] The second method for the in situ production of nitrile oxides uses the dehydration of nitromethyl compounds under widely used Mukaiyama conditions (use of phenyl isocyanate).[22] On the basis of this last procedure, we efficiently prepared the dimer glycosides **17**−**19** by reaction of the galactopyranosyl nitrile oxide derivative **14b** (obtained in situ from 2,6-anhydro-1-deoxy-1-nitro-D-glycero-D-mannoheptitol[23] (**14a**)) with the propargyl glycosides **7**, **15**, and **16** derived from D-glucose, D-galactose, and lactose, respectively (Scheme 3). We also synthesized the trivalent and tetravalent galactose clusters **22** and **23** by reaction of the same nitrile oxide derivative **14b** with the tri- and tetrapropargyl pentaerythritol derivatives **20b** and **21**.

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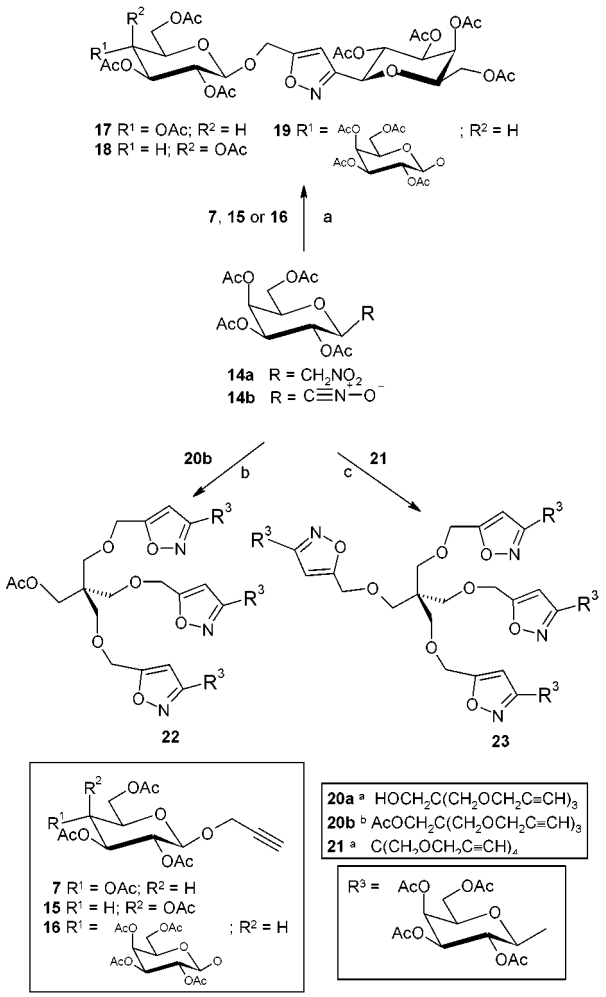
(25) Selected physical properties of compound **26** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41(s, 7 H), 5.52 (d, J = 3.0 Hz, 7 H), 5.35 (t, J = 10.2 Hz, 7 H), 5.19 (dd, J = 10.2, 3.4 Hz, 7 H), 5.12 (br s, 7 H), 4.65−4.50 (m, 21 H), 3.65, 3.53 (2 s, 42 H), 3.20 (br d, J = 9.5 Hz, 7 H), 2.18, 2.03, 1.99, 1.92 (4 s, 84 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.3, 169.7, 169.4, 160.9, 114.1, 101.6, 99.2, 81.7, 74.8, 73.1, 71.7, 71.2, 70.2, 67.6, 67.5, 61.2, 61.6, 61.5, 58.7, 20.7, 20.6. HR-MS (FAB+): calcd for $C_{182}H_{245}N_7O_{105}Na$ $[M+Na]^+$, 4231.394; found, 4231.394.

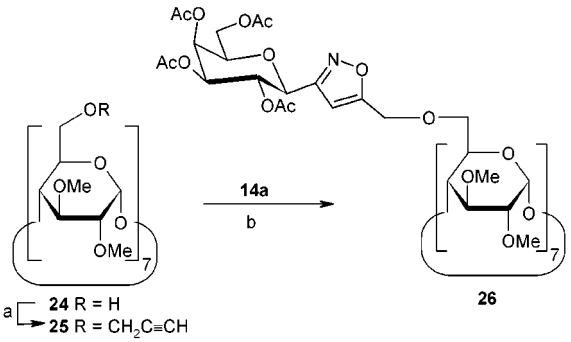
Scheme 3[a]



[a] Obtained from pentaerythritol: 14.7 mmol of pentaerythritol, in 15 mL of DMSO, 50 mmol of NaOH in 5 mL of H_2O, 8.8 mmol of $BrCH_2C{\equiv}CH$, room temperature, 24 h, 71% of **20a** and 18% of **21**. [b] Conventional acetylation of **20a** yields **20b**, 92%. [c] Legend: (a) 1 mmol of **14a**, 1 mmol of C_6H_5NCO, 0.1 mL of Et_3N, 1 mmol of **7**, **15**, or **16**, toluene, reflux, 16 h for **7**, 36 h for **15** and 18 h for **16**, 93% for **17**, 92% for **18** and 90% for **19**; (b) 1.23 mmol of **14**, 0.34 mmol of **20b**, toluene, reflux, 2 days, 57%; (c) 0.77 mmol of **14a**, 0.8 mmol of C_6H_5NCO, 0.1 mL of Et_3N, 0.18 mmol of **23**, toluene, reflux, 2 days, 64%.

In a final experiment, the reaction of heptakis(2,3-di-*O*-methyl-6-*O*-propargyl)cyclomaltoheptaose (**25**), obtained from heptakis(2,3-di-*O*-methyl)cyclomaltoheptaose (**24**),[24] with **14b** gave rise to the glycocyclodextrin **26**[25] in high yields (Scheme 4). It should be noted that the utilization of

Scheme 4[a]



[a] Legend: (a) 1 mmol of **24**, 14 mmol of $BrCH_2C{\equiv}CH$, $Br(Bu)_4N$, 50% NaOH aqueous solution, CH_2Cl_2, 48 h, 70%; (b) 0.52 mmol of **14a**, 0.063 mmol of **25**, 0.52 mmol of C_6H_5NCO, 0.1 mL of Et_3N, toluene, reflux, 24 h, 78%.

nitrile oxides as the dipolar function allowed the regioselective formation of the isoxazole ring and the isolation of pure isomers in the assembled structures.

In conclusion, the results described herein demonstrate that 1,3-dipolar cycloadditions are an efficient and highly versatile tool for the construction of multivalent structures, creating aromatic heterocyclic bridges between the different units that are coupled. To date the application by us of this strategy has allowed the preparation of a wide variety of these structures, such as sugar heterodimers, glycoclusters, calix sugars, multicalixarenes, and glycocyclodextrins. The wide variety of 1,3-dipolar cycloadditions using different 1,3-dipolar functions and different dipolarophiles opens a new gateway for the construction of tailored multivalent structures.

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