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Stereoselective synthesis and properties of glycoazobenzene macrocycles through intramolecular glycosylation

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Intramolecular glycosylation strategy was used to synthesize a series of new glycoazobenzene macrocycles with high α-selectivity and interesting chiroptical property. The photoisomerization of azobenzene template influences mainly the efficiency of the glycosylation.

Macrocycles represent an interesting class of molecules because of their unique structural, physicochemical and biological properties as well as their potential applications in nanotechnology, biology and medicine.[1] Natural and synthetic glycomacrocycles have attracted increasing interest in chemistry and biology.[2] Development of switchable glycomacrocycles is appealing for controlling conformation, function and properties of macrocycles by applying external stimuli. Light is an extremely attractive orthogonal stimulus for controlling chemical and biological systems thanks to its non-invasibility and excellent spatial and temporal precision.[3-4] Photochromic molecules have shown increasing applications not only for reversibly photomodulating properties of molecules, but also for remote-controlling chemical reactivity or catalytic activities as photoswitchable catalysts.[5,6] Several photoswitchable glycomacrocycles have been reported since 2017.[7-10] These 'smart' glycomacrocycles displayed very interesting properties like chirality transfer and supramolecular chirality, photocontrolled molecular shape or solubility, as well as multistimuli-responsive gelation ability in organic solvents.

Macrocycle synthesis remains a challenging task because of competition between inter- and intra-molecular reactions, and conformational restriction imposed by the cyclization. The efficiency of the macrocyclization could be highly influenced by the conformation of the substrate.[11] For the synthesis of azobenzene glycomacrocycles through thiourea formation[7] or Glaser coupling,[9] G. Despras and coll. reported that only *Z*-azobenzene-lined substrates underwent the macrocyclization. To investigate the influence of the photoisomerization on the efficiency of the macrocyclization and enlarge the library of photoswitchable glycomacrocycles, we decided to employ the intramolecular glycosylation approach,[12] by linking glycosyl donor and acceptor together via non-reacting centre to a photochromic template (Fig. 1). As molecular photoswitch, azobenzene has been chosen because of its small size, its excellent photostability and the large changes in molecular size and shape induced by the photoisomerization between the thermodynamically favoured *E*-isomer and the energetically higher *Z*-isomer.[13] The *Z*-isomer can thermally return to the more stable *E* isomer. It's expected that photoisomerization of the photochromic template would induce large concomitant geometrical change and the disposition between the glycosyl donor and glycosyl acceptor, and consequently influence the efficiency and the stereoselectivity of the macrocyclization by stereoelectronic and conformational effects.

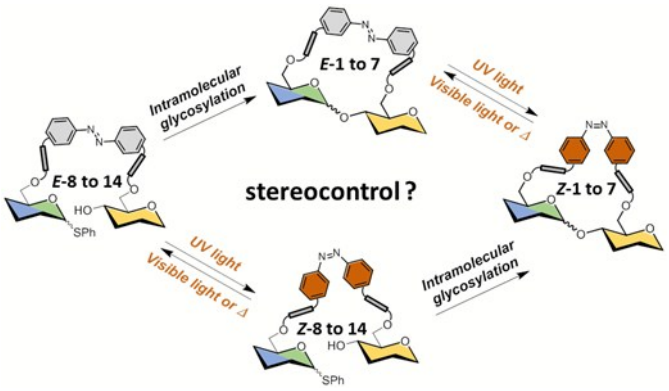
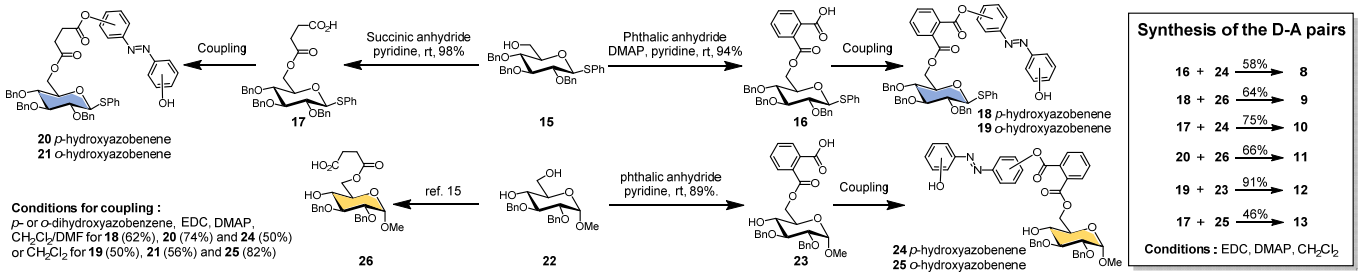


Fig. 1. Photoswitchable glycomacrocycles through intramolecular glycosylation approach.

We decided to use commercially available *p*- and *o*-dihydroxy azobenzenes as photochromic templates for the flowing reasons. First, the hydroxyl group allowed gathering together the glycosyl donor and acceptor through cleavable

ester function. Second, the *Z*-isomers of *O*-substituted dihydroxy azobenzenes are stable at room temperature, permitting to realize the glycosylation without *in situ* thermal isomerization to the more stable *E*-isomers.[8] Phthaloyl (Phth) and/or succinoyl (Suc) linkers were chosen to investigate the influence of relative rigidity/flexibility of the linkers on the intramolecular glycosylation reaction, while maintaining the chain length. We have firstly prepared photochromic glycosyl donor-acceptor compounds **8**-**13** (Table 1) based on *p*- and *o*-dihydroxy azobenzenes through a convergent strategy: coupling of azobenzene-functionalized glucosyl acceptors **24** or **25** with the thioglucoside donors **16** or **17** (for **8**, **10** and **13**) or azobenzene-functionalized thioglucosides **18**-**20** with the glycosyl acceptors **23**[12] or **26**[12] (for **9**, **11** and **12**) according to Scheme 1. The Phth and Suc linkers can be readily introduced into phenyl β-D-thioglucoside **15** and methyl α-D-glucoside **22** by using phthalic or succinic anhydride; while the azobenzene-functionalized glycosides were prepared by esterification with *p*- or *o*-dihydroxy azobenzenes.

We have firstly investigated the *p*-dihydroxy azobenzene



Scheme 1 Synthesis of azobenzene-linked glycosyl donor-acceptor pairs **8**-**13**.

functionalized substrates **8** to **11** in *E*-form (Table 1). The intramolecular glycosylation was activated by NIS/TfOH. Compound **8** with two Phth linkers led to the best yield of the macrocyclization (entry 1). Interestingly, the macrocycle **1** was isolated in 60% yield with very good α-selectivity (α/β: 9/1). The intramolecular glycosylation yield dropped to 20% with the substrate **9** bearing a Phth linker on the glycosyl donor and a Suc linker on the acceptor side, with excellent α-selectivity (entry 2). Inversion of the Phth/Suc linkers in **10** furnished however the macrocycle **3** as a mixture of α/β isomers (~1:1) in 12% yield (entry 3). Glycosylation of the substrate **11** with two flexible Suc linkers gave the corresponding macrocycle **4** in 15% yield with complete α-selectivity (entry 4). The α-configuration was confirmed by the coupling constant $J_{1',2'}$ = 3.6 Hz for the macrocycles **1**,**2** and **4**. We have also observed the formation of several intermolecular glycosylation products which remain difficult for separation and characterization. For *o*-dihydroxy azobenzene-linked substrates, intramolecular glycosylation of **12** containing two Phth linkers led to 45% of the macrocycle **5** with complete α-selectivity (entry 5), while **13** with Suc and Phth linkers furnished the macrocycle **6**-α in 30% yield (entry 6). The α-configuration was confirmed by the coupling constant ($J_{C1',H1'}$ = 167 Hz for **5**-α).[14]

In order to study the influence of photoisomerization on the glycosylation, photochromic properties were firstly investigated. Compounds **8**-**13** can be readily converted into the corresponding *Z*-isomers under illumination at 370 nm in CH_2Cl_2. For example, compound **13** showed a relatively strong π→π* transition (λmax = 328 nm) and a weaker forbidden n→π* transition (λmax = 454 nm) (Fig. 2b, black line). Irradiation at 370 nm resulted in the decrease of the bands at 328, 454 nm and appearance of a new band at 440 nm, revealing the *E* to *Z* isomerization of **13** (Fig. 2b, orange line). Two isobestic points can be observed at 282 and 386 nm. The *Z*:*E* ratio at the photostationary state (PSS) can be determined by the integration of the ^{1}H NMR signals after irradiation at 370 nm (Fig. S10). At PSS_{370}, 84% of *E*-**13** has been converted to the corresponding *Z*-isomer. The *E*→*Z* conversion varied from 78 to 89% for compounds **8**-**13** (Table 1). The thermal stability of *Z*-**13** has been followed by monitoring the absorption increase at room temperature in CH_2Cl_2, with the half-life ($t_{1/2}$) estimated to be 114.2 h (Fig. S1,7). The $t_{1/2}$ values for compounds *Z*-**8** to **13** are between 27.7 h (for *Z*-**11**) to 127.7 h (for *Z*-**12**) (Fig. S2-6, Table S1). Consequently, all the *Z*-isomers should be stable during the glycosylation reaction (2-3 h at -78°C).

We then studied the photoisomerization effect on the intramolecular glycosylation. Substrates **8** to **11** were irradiated at 370 nm in CH_2Cl_2 until the PSS to mostly convert into the corresponding *Z*-isomers. Intramolecular glycosylation of *Z*-**8** with two Phth linkers appeared to be much less efficient than the *E*-**8**: many spots have been observed on TLC. After purification, 12% *Z*-**1**-α, 5% of *E*-**1**-α and 16% *E*-**8** have been isolated, along with several unidentified oligomers. Consequently, the photoisomerization of the azobenzene template did not influence the stereoselectivity of the glycosylation, since mainly α-isomers have been obtained. For compounds *Z*-**9** and *Z*-**10** with one Phth and one Suc linkers in inverted positions, the glycomacrocycle *Z*-**2** with complete α-selectivity has been isolated in 15% yield from *Z*-**9**, along with 8% of recovered *E*-**9** (entry 2); while reaction of *Z*-**10** led to a complex mixture of compounds from which we have only isolated 8% of the starting material *E*-**10** without any desired macrocycle *Z*-**3** (entry 3).[15] Interestingly, the substrate *Z*-**11** with two flexible Suc linkers furnished the desired macrocycle *Z*-**4** in 13% yield with complete α-selectivity (entry 4). For *o*-substituted azobenzenes **12** and **13**, the *Z*-**12** gave an inseparable mixture of *Z*- and *E*-**5**-α (ratio *Z*/*E* ~3/1) in 30% yield, while the *Z*-**13** led only to 6% of *E*-**6**-α (entry 6). The *Z*-azobenzene substrates seem to favour

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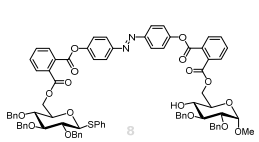
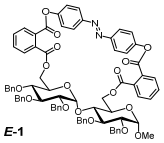
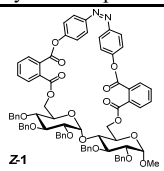
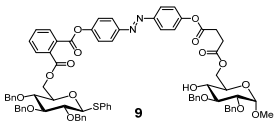
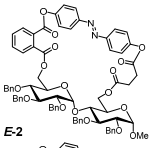
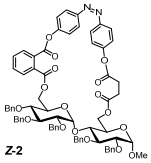
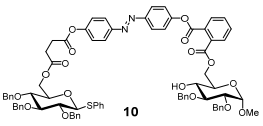
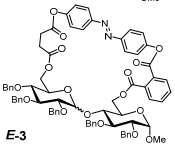
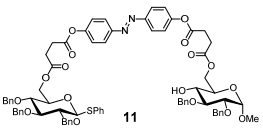
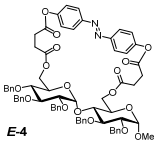
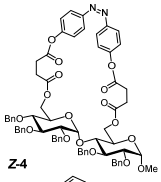
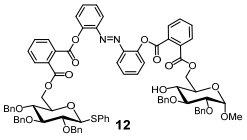
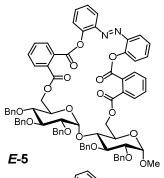
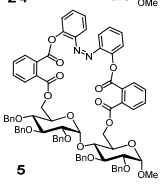
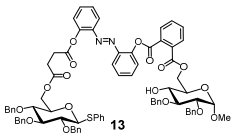
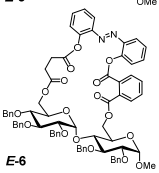
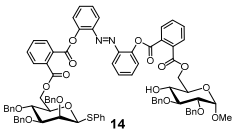
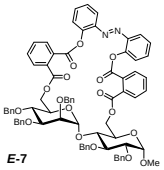
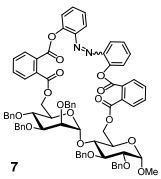
Table 1 Intramolecular glycosylation outcome with azobenzene linked glycosyl donor-acceptor pairs

	Glycosylation from *E*-isomer[a]			Glycosylation from PSS_{370}[b]		
Entry	*E*-Azobenzene-linked substrates	Cyclization product	yield, α/β ratio	Substrate at PSS_{370}	Cyclization product	yield, α/β ratio
1			60% α/β: 9/1	*Z*/*E* ≅ 80/20		12% ***Z*-1** only α + 5% ***E*-1**, only α + 16% ***E*-8**
2			20% only α	*Z*/*E* ≅ 86/14		15% ***Z*-2** only α + 8% ***E*-9**
3			12% α/β: ~1:1	*Z*/*E* ≅ 78/22	-	8% ***E*-10**
4			15% only α	*Z*/*E* ≅ 89/11		13% ***Z*-4** only α
5			45% only α	*Z*/*E* ≅ 84/16		30% ***Z*-5**/***E*-5** : 3/1 only α
6			30% only α	*Z*/*E* ≅ 84/16	***E*-6**	6% ***E*-6** only α
7			54% only α	*Z*/*E* ≅ 85/15		30% ***E*-7**/***Z*-7** only α

[a] 1) CH_2Cl_2, 4Å, Ar, 5h; 2) NIS (2 equiv.), TfOH (0.4 equiv.), -78 ℃, 2-3h. [b] 1) CH_2Cl_2, 4Å, Ar, 5h; 2) irradiation at 370 nm until PSS; 3) NIS (2 equiv.), TfOH (0.4 equiv.), -78 ℃, 2-3h.

intermolecular glycosylation, leading to complex reaction products. The above studies demonstrate that the intramolecular glycosylation outcome is influenced not only by the structure (*p*- or *o*-substituted) and configuration of the photochromic template (*E* or *Z*-azobenzene), but also by the nature and relative position of the used linkers (Phth or Suc). Substrates **8** and **12** with two Phth linkers gave better yields of cyclization products. The photoisomerization influences mainly the efficiency of the macrocyclization reaction, without significant impact on the stereoselectivity with the tested substrates. Having established that stereoselective α-glucosylation can be achieved with azobenzene template bearing two Phth linkers, we have

then used the Phth linker for the mannosylation with the substrate **14** (Table 1, entry 7). Reaction of *E*-**14** led to the corresponding macrocycle **7** with excellent α-selectivity ($J_{C1',H1'}$ = 167 Hz) in 54% yield. *E*→*Z* photoisomerization at 370 nm gave 85% of *Z*-**14** which, after glycosylation, furnished in 30% yield a mixture of *E*,*Z*-**7**-α. After thermal return, the mixture is totally converted to *E*-**7**-α, confirming the α-stereoselectivity for the *Z*-isomer. This result suggest that the change from the *gluco* to *manno* glycosyl donor maintained the similar conformation favouring the α-glycosylation. Finally, the photochromic template can be readily cleaved under Zemplen conditions and acetylated to the corresponding α-disaccharide in 83% yield from the macrocycle **5** (Scheme S2).

The obtained excellent α-stereoselectivity with both *E* and *Z*-substrates might be explained by a relatively favouring conformation for the 4-OH attack from the α-face of the intermediate oxocarbenium ion, or by the steric hindrance on the β-face. DFT calculations showed that all the *E*-α macrocycles are more stable than the *Z*-α isomers, with the macrocycles bearing two Phth linkers more stable (**1**, **5**, **7** vs **2**-**4**, **6**) (Fig. S15-21, Table S2). The *E*-**1**,**7**-α are also more stable than the corresponding *E*-**1**,**7**-β macrocycles (Fig. S22-23).

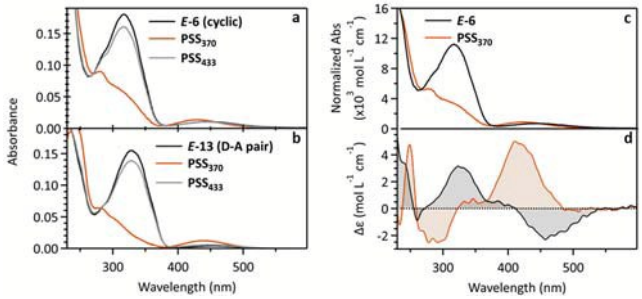


Fig. 2. Absorption spectra of **6** (a) and **13** (b) in CH_2Cl_2 before (black line) and after irradiation at 370 (orange line) and 433 nm (grey line). Normalized absorption (c) and circular dichroism spectra (d) of **6** (C = 11.4 μM) in *E*-isomer (black line) or at PSS_{370} (orange line) in MeCN.

With the synthesized new glycomacrocycles, we have investigated their photochromic properties. All macrocycles can be reversibly photoswitched between *E*- and Z-isomers under UV and visible illumination (see Fig. 2c for the macrocycle *E*-**6**), and high fatigue resistance (Fig. S11-14). Furthermore, we have found that among the compounds **1**-**14**, only the *o*-substituted cycloazobenzenes **6** and **7** showed chiroptical properties as previously reported glycomacrocycles.[7-10] On the CD spectra, a negative band at 457 nm ($\Delta\varepsilon$ = -2.6 M^{-1} cm^{-1}) and a positive band at 323 nm corresponding respectively to n→π* and π→π* transitions of *E*-azobenzene in acetonitrile have been observed for **6** (Fig. 2d, black line). The macrocycle **7** showed also a negative band at 416 nm ($\Delta\varepsilon$ = -1.7 M^{-1} cm^{-1}) (Fig. S24). Consequently, there are chirality transfers from the disaccharide to the azobenzene moiety. Irradiation at 370 nm led to *Z*-**6** and *Z*-**7** which induced the inversion of the Cotton effect in the case of *Z*-**6**: from negative to positive at 410 nm ($\Delta\varepsilon$ = +5.6 M^{-1} cm^{-1}), indicating an inversion of helical chirality between *E*- and Z-macrocycles **6**. A blue shift of CD bands has been observed for *Z*-**7**, with slightly increased intensity ($\Delta\varepsilon$ = -2.0 M^{-1} cm^{-1} at 403 nm), without inversion of helical chirality (Fig. S24). It's also interesting to notice that the corresponding maltose-constituted macrocycle did not show chiroptical properties (**5**-α vs **7**-α).

In conclusion, we have synthesized seven new photoswitchable glycomacrocycles through intramolecular glycosylation, which enlarges the chiral cycloazobenzene library. Excellent α-stereoselectivity can be achieved by using *p*- and *o*-dihydroxy azobenzenes templates, demonstrating the proof-of-concept of using photoswitchable template to achieve the challenging 1,2-*cis* glycosylation.[16] The *E*→*Z* photoisomerization influenced mainly the efficiency of the intramolecular glycosylation. Chiroptical property has been observed for two of the *o*-substituted azobenzene macrocycles with inversion of helical chirality upon *E*→*Z* photoisomerization for one of them. These newly synthesized photoswitchable glycomacrocycles with chiroptical property should find interesting applications in light-driven materials.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental section, additional figures and original spectral copies]. See DOI: 10.1039/c000000x/

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