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A Very Efficient Synthesis of a Mannosyl Orthoester [2]Rotaxane and Mannosidic [2]Rotaxanes

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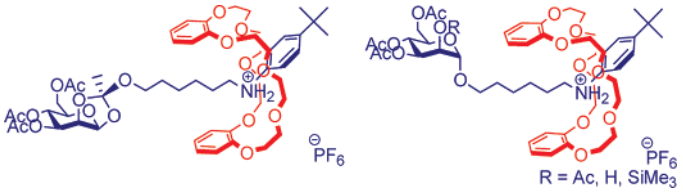
ABSTRACT



The direct preparation of mannosyl[2]rotaxane derivatives by *O*-glycosylation from tetra-*O*-acetyl-α-D-mannosyltrichloroacetimidate and a *tert*-butylanilinium alcohol in the presence of dibenzo-24-crown-8 is described. The method appears to be very efficient and allows for the preparation of either orthoester or mannosyl rotaxane derivatives, depending on reaction conditions.

As part of our ongoing studies concerning the preparation of glycoconjugated molecular machines, we focused on a quick access to glycosidic rotaxanes using the Schmidt glycosylation method.[1] Interlocked molecular architectures such as rotaxanes and catenanes have attracted much attention during the past decade, especially in the domain of nanotechnology and materials.[2] However, very few papers have been devoted to the synthesis of molecular machines and interlocked molecules which are designed to possess interesting properties in physiological media.[3] In this area, glycosylrotaxanes constitute a class of molecules of great interest, especially for recognition studies between lectin receptors and glycosidic ligands. Indeed, localization of a macrocycle along a glycosidic thread could dramatically influence recognition between receptors and glycosylrotaxanes. Some preparations of glycosidic rotaxanes, where glycosides are located on the macrocycle or directly linked to the thread, have been investigated and described,[4] but none of them concern the end-capping of semirotaxanes via Schmidt glycosylation.

A wide variety of [2]rotaxanes incorporating the dibenzo-24-crown-8 (DB24C8) as the macrocycle and a linear cationic species as the templating thread has already been reported. Early studies found that the ammonium cation interacts strongly with DB24C8 and resides within the

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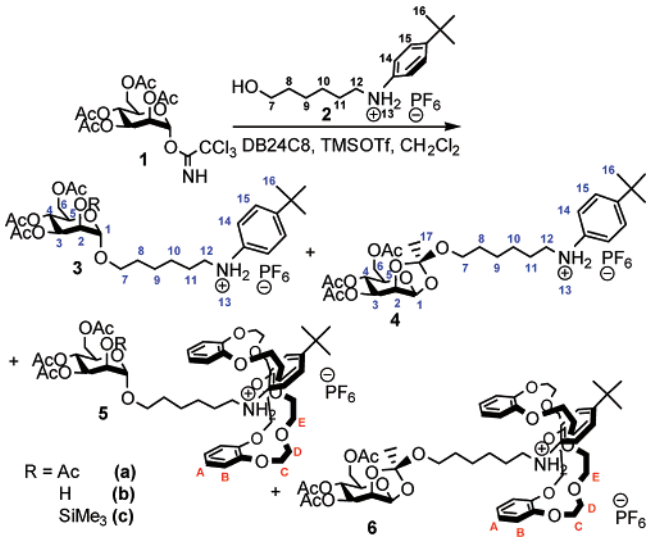
macrocycle cavity, thus acting as a good template for the formation of rotaxanes.[5] Template moieties such as benzylic ammonium,[6] *N*,*N*′-dialkyl-4,4′-bipyridinium,[7] and 1,2-bis-(pyridinium)ethane cations[8] have been investigated and used to prepare rotaxanes in various yields. The type of interaction between macrocycle and thread varies depending on the nature of the functional groups involved. Whereas the benzylammonium cation binds with the crown ether macrocycle via hydrogen bond and ion−dipole interactions, the *N*,*N*′-dialkyl-4,4′-bipyridinium interacts via $\pi-\pi$ stacking between the electron-rich catechol ring and electron-poor pyridinium rings. To our knowledge, with the exception of the *N*-benzylic anilinium,[9] no other secondary anilinium moiety has been used with a crown ether for rotaxane formation thus far.

The *N*-alkyl secondary anilinium moiety contained in compound **2** (Scheme 1) proved to have a good affinity for

Scheme 1. Synthesis of Rotaxanes **5** and **6**



the crown ether macrocycle. This affinity was measured by ^{1}H NMR spectroscopy of **2** in $CDCl_3$ at room temperature at a concentration of 10 mM with addition of increasing amounts of DB24C8 (Figure 1). On addition of DB24C8 (0.5 equiv), the C_6-alkyl chain of **2** was found to be of sufficient length to slow down the rate of the ring slipping off the tether, thus allowing to distinguish two sets of resonance for both unbound and bound tether on one hand and complexed and uncomplexed crown-ether on the other hand (Figure 1). A higher proportion of the semirotaxane

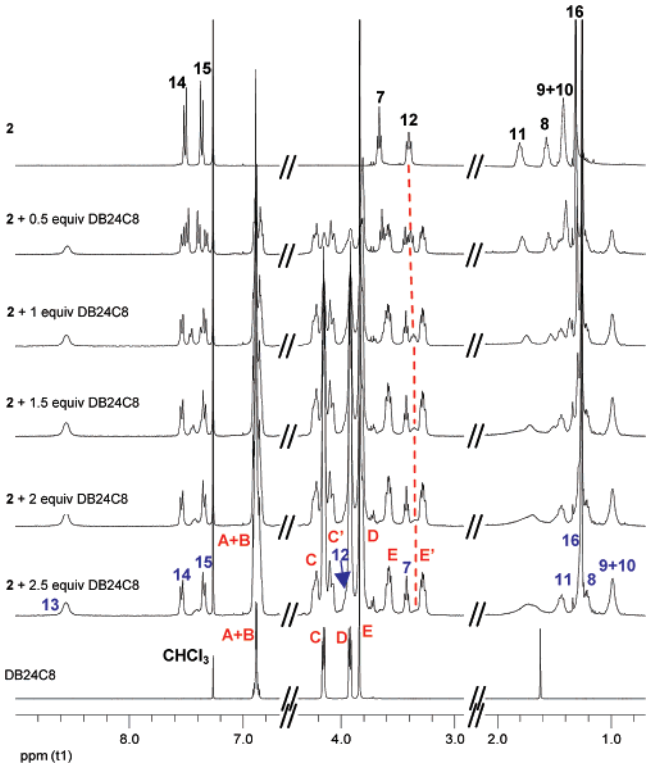


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) showing formation of the semirotaxane. The concentration of **2** in $CDCl_3$ was maintained at 10 mM, and the concentration of DB24C8 was varied from 0 to 25 mM. The lettering and numbering correspond to the proton assignments indicated in Scheme 1. The red dotted line indicates the disappearance of signal for H_{12}. Blue lettering corresponds to compound **2** complexed with DB24C8.

was obtained upon addition of more DB24C8. A reasonable ratio of semirotaxane to thread **2** (78:22) was obtained when 2 equiv of the DB24C8 were added. In comparison with the spectrum of the uncomplexed compound **2**, the thread methylene reasonances H_{12} of the semirotaxane are shifted downfield ($\Delta\delta$ = 0.55 ppm) in the complexed structure, which can be explained by hydrogen bonding with the oxygens of the crown ether. Methylene groups H_8, H_9, H_{10}, and in a lesser proportion H_7 and H_{11} are all shifted upfield ($\Delta\delta$ = −0.59 to −0.24 ppm), due to the shielding effect of the aromatic rings of the crown ether. Very small variations in chemical shift are observed for the aromatic hydrogen H_{14} and H_{15} between uncomplexed **2** and the semirotaxane. This observation can be explained by an absence of $\pi-\pi$ stacking between the electron-rich aromatic rings of DB24C8 and the sterically hindered electron-poor aromatic moiety of compound **2**.[10] For the DB24C8 adduct, ^{1}H NMR signals for H_C and H_E in the semirotaxane are split, due to their different orientations toward the two nonsymmetrical ends of the axle. Hydrogens H_E, and in a lesser proportion H_D are shifted upfield in the semirotaxane spectrum, indicating interactions between oxygen of the macrocycle and the hydrogens of the thread.

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Mannosyl rotaxane derivatives were synthesized from protected mannosyl trichloroacetimidate[11] **1** and *tert*-butylanilinium alcohol cationic aglycon chain **2** in the presence of DB24C8 using a catalytic amount of TMSOTf (Scheme 1). To our knowledge, glycosylation with a naked protonated amine group-containing acceptor like anilinium has not been described thus far. Strategies usually consist of a two-step sequence utilizing azido alcohols or *N*-protected amino alcohol as glycosyl acceptors, which can be respectively hydrogenated or deprotected in the ultimate step. A preliminary study of the reaction without the crown ether macrocycle led us to define the experimental conditions for this glycosylation (Scheme 1 and Table 1, entries 1 and 2). This latter

Table 1. Synthesis of Threads **3** and **4** and [2]Rotaxanes **5** and **6**[a]

entry	DB24C8/TMSOTf (equiv)	time (min)	*T* (°C)	**3a** (%)	**4** (%)	**5a** (%)	**6** (%)	Σ_1[b] (%)	Σ_2[c] (%)
1	0/0.2	5	−15	40	30			70	
2	0/0.2	5	0	31	13			60	
3	2.2/0.2	1	0			11		11	40
4	2.2/0.2	1	−30			17	74		91
5[d]	1.1/0.2	1	−30	4	12	12	20	16	32
6	1.1/0.2	5	−30	5	10	17	42	15	59
7[e]	1.1/0.2	5	−15			12		14	47
8	1.1/0.2	1	0	7		15		18	45
9	1.1/0.5	1	−30	4		15		13	44

[a] Reaction conditions: **1** (1 equiv), **2** (1.1 equiv), DB24C8 (0−2.2 equiv), TMSOTf (0.2−0.5 equiv), CH_2Cl_2. Reported yields correspond to conversion and are measured by ^{1}H NMR of the crude at 400 MHz. [b] Σ_1 corresponds to the sum of threads (**3a**−**c** and **4**). [c] Σ_2 corresponds to the sum of rotaxanes (**5a**−**c** and **6**). [d] 42% of trichloroacetamidate **1** did not react. [e] The deacetylated rotaxane **5b** was obtained in a 26% conversion yield and the silylated rotaxane **5c** in 9% yield.

was carried out in dichloromethane, which is a solvent known to optimize interactions between the crown ether and ammonium species,[6] in the presence of 4 Å molecular sieves at various temperatures. In a typical procedure, 0.2 equiv of TMSOTf was added to a cooled mixture of the glycoside donor and acceptor. The reaction was then quenched by addition of 0.2 equiv of triethylamine at the same temperature, and the crude material was evaporated and directly purified by chromatography.

Total conversion was observed after only 5 min of reaction at −15 °C and afforded a mixture of thread **3a** and orthoester **4** in 40% and 30% yields, respectively, from **1** (entry 1, Table 1). If the reaction was performed at higher temperature (0 °C) or with an increased amount of lewis acid catalyst, the orthoester ratio decreased, but lower yields of the desired compound **3a** were observed. In addition, two side products were also observed, resulting from acetylation of compound **2** by the tetraacetylated glycoside to give the acetylated glycoside acceptor and the deacetylated[12] thread **3b** (16%) (entry 2, Table 1).

As expected, when applying Schmidt's glycosylation conditions to a mixture of **1**, **2** and DB24C8 in the presence of Lewis acid catalyst (entries 3−9, Table 1), a high ratio of rotaxane/thread was observed, which confirmed the effectiveness of the chelation between the anilinium templating thread and the crown ether. When the reaction was carried out at a temperature of 0 °C, degradation, side deacetylation, and silylation were detected (entry 3, Table 1). At low temperatures (−75 °C), no reaction occurred. Complete conversion to rotaxanes was observed at low temperature (−30 °C) upon addition of 2.2 equiv of crown ether, and no thread was isolated in this case (entry 4, Table 1). At this temperature, glycosylation appeared to proceed very differently in the presence of the crown ether macrocycle. Even though complete reaction was achieved after 1 min (no starting glycoside donor **1** was detected by ^{1}H NMR spectroscopy of the crude), the major product obtained (74%) was not the expected *O*-glycoside rotaxane **5a**. It was instead found to be the mannoside orthoester rotaxane derivative **6** resulting from nucleophilic attack of the cyclic dioxacarbenium ion by **2**.[13] If reaction is carried out for a longer period of time, no significant variation in the ratio of the orthoester **6** and *O*-mannoside rotaxanes **5a** was observed, which indicates that the well-known isomerization[14] of the orthoester to the *O*-glycoside product did not occur under these experimental conditions. Since affinity of compound **2** for DB24C8 proved to be even better at −30 °C in dichloromethane than at room temperature in $CDCl_3$ (no thread was observed at this temperature in this solvent after glycosylation), it was expected that only a small concentration of the free DB24C8 would be present if only a stoichiometric amount of crown ether was used. Thus, experiments with only 1.1 equiv of DB24C8 (entries 5−9, Table 1) and 1.1 equiv of compound **2** were carried out to verify the role of the crown ether macrocycle in the selectivity of the reaction. Obviously, the ratio between rotaxanes and threads synthesized decreased since the concentration of DB24C8 was lower. More interestingly, the presence of free DB24C8 dramatically influenced the reaction duration and the ratio between the orthoester rotaxane derivative **6** and *O*-glycoside rotaxane derivative **5a**. We surmise that the free crown ether may be involved in the stabilization of the cyclic dioxacarbenium carbocation rather than the oxacarbenium, thus allowing for the selective formation of the mannosylorthoester rotaxane derivative **6**.[15] Indeed, contrary to the experiment with 2.2 equiv of crown ether, the reaction was not complete after 1 min at a temperature of −30 °C (compare entries 4 and 5, Table 1). Moreover, every experiment involving a stoichiometric amount of DB24C8 afforded a mixture of both the *O*-glycoside **5a** and orthoester **6** rotaxanes but with poorer selectivity. In order to improve the yield of the desired product **5a**, variations in the temperature and in the amount

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(15) Supplementary experiments to understand the role of crown ether in other glycosylations are in progress and will be reported later.

of Lewis catalyst were investigated (entries 7−9, Table 1). Even though the quantity of the orthoester rotaxane decreased, degradation occurred and isomerization was followed by the appearance of side-products such as deacetylated and silylated rotaxanes **5b** and **5c** in almost 35% yield. Thus, one-pot isomerization of orthoester rotaxane **6** to rotaxanes **5a**−**c** could be realized under harsher experimental conditions with yields ranging from 44% to 47% (entries 7−9, Table 1).

Isomerization of the isolated orthoester **6** was investigated (Table 2). It appeared that whatever experimental conditions

Table 2. Isomerization of the Isolated Orthoester Rotaxane **6**[a]

entry	time (min)	T (°C)	**6** (%)	**5a** (%)	**5b** (%)	**5c** (%)	Σ_1[b] (%)	Σ_2[c] (%)
1	5	−15		28	21		19	49
2	10	−30		26	20		22	46

[a] Reaction conditions: **6** (1 equiv), TMSOTf (0.2 equiv), CH_2Cl_2. Reported conversion yields are measured by ^{1}H NMR of the crude at 400 MHz. [b,c] Σ_1 and Σ_2 are defined in Table 1.

are used, when reaction was carried out to completion (entries 1−2, Table 2), no more than 49% of the rotaxanes **5a**−**c** were obtained, which is consistent with the direct one pot isomerization. Moreover, apart from degradation side products, the appearance of the threads **3a**−**c** was observed in a similar proportion to when glycosylation was carried out with 1 equiv of DB24C8 with respect to compound **2**. In order to decrease side reactions the temperature was lowered to −45 °C but isomerization proved to be very slow.

The ^{1}H NMR spectra (Figure 2) of both rotaxanes **5a** and **6** (shown with DB24C8) confirmed the interlocked architectures. For both rotaxanes, chemical shifts of the complexed crown ether hydrogens H_C and H_E are split, indicating that they are facing the two non-symmetrical ends of the threaded mannoside. Methylene hydrogens H_D are shifted slightly upfield; the upfield shift of hydrogen H_E is more pronounced.

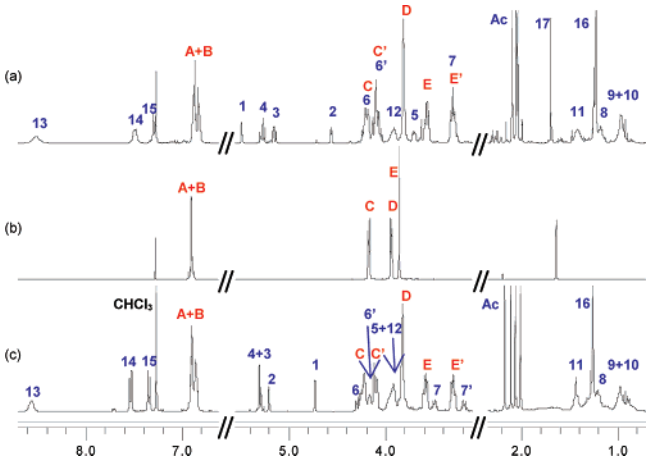

Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) orthoester rotaxane **6**, (b) DB24C8, and (c) *O*-mannoside rotaxane derivative **5a**. Lettering and numbering correspond to the proton assignments indicated in Scheme 1.

In conclusion, we have described a new and easy end-capping method to yield glyco[2]rotaxanes via Schmidt glycosylation of an anilinium alcohol. Our non-benzylic anilinium derivative appeared to be a good template for [2]rotaxane synthesis. Orthoester [2]rotaxanes could be obtained this way in as fast as 1 min with very good conversion of up to 74% (Table 1) and in 60% isolated yield. Isomerization led to yields of up to 49%, although some side deacetylation and degradation were also observed. Further investigations toward the synthesis of glyco[2]rotaxanes with other glycosides are in progress.

Supporting Information Available: Complexation study between compound **2** and DB24C8, characterization data, and full experimental procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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