Supramolecular activation in triggered cascade inversion†

Hai Dong, Zhichao Pei and Olof Ramström*

Received (in Cambridge, UK) 8th November 2007, Accepted 19th December 2007
First published as an Advance Article on the web 15th January 2008
DOI: 10.1039/b717301f

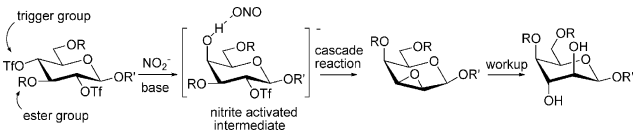
An unexpected activation effect from combinations of anionic reagent and amine base resulted in dramatic rate enhancements in multiple carbohydrate cascade inversion.

Organic synthesis using the principles of supramolecular chemistry is an important advancement in modern synthetic chemistry, for example leading to improved process control and enhanced reaction rates.[1,2] Such supramolecular assistance to synthesis[1] has been extensively applied to template synthesis and reactions in container molecules or nanoreactors,[3] and may also lead to self-replicating systems.[4] Recognition-based proximity and restriction of participating reactants are generally involved in these systems, but supramolecular regulation of auxiliary reagents can also be used to increase the control.

A specific challenge in this respect is constituted by cascade reactions, possessing the advantage of proceeding through several transformations in a single synthetic operation.[5] The synthetic potential of such reactions has been recognized for advanced organic synthesis, often resulting in compounds of highly complex structures. The action of trigger groups can also induce control of the reaction cascade, where the resulting reaction sequence is initiated by an external agent, often a biocatalyst.[6] Control of the trigger mechanism then leads to control of the entire cascade.

In the present study, we report a triggered asymmetric cascade reaction leading to multiple inversions of carbohydrate stereocenters. The reactions are furthermore initiated through supramolecular activation, where a triflate group acts as cascade trigger, released by a nitrite ion in combination with an amine base (Scheme 1).

The cascade reaction is based on a pyranoside scaffold, for which epimerization to the corresponding epi-hydroxy isomers is an important strategy to generate structures that may otherwise be cumbersome to prepare.[7] Recently, the effects of ester activation in the Lattrell–Dax (nitrite-mediated) epimerization,[8] were studied in detail,[9] and from these results, efficient syntheses of β-D-mannosides and β-D-talosides could be developed by employing the reactivity differences between the 2- and 4-positions.[10,11] However, unexpected behavior of the nucleophilic reagent prompted us to study these reactions further, resulting in the discovery of unprecedented carbohydrate cascade reactions involving migration, inversion and epoxidation (Scheme 2).



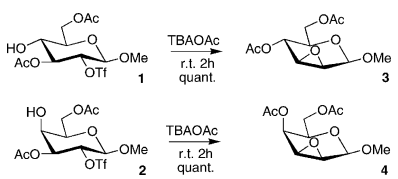
Scheme 1 Multiple inversions through triggered cascade control.

When β-D-glucoside **1** and β-D-galactoside **2** were subjected to tetrabutylammonium acetate (TBAOAc) in order to obtain the corresponding β-D-mannoside- and β-D-taloside inversion products, the 2,3-anhydro structures **3** and **4** were however formed in quantitative yields instead. In contrast, when the same reactions were performed with nitrite alone, the expected inversion products were formed in good yields.[11]

In order to evaluate these results, NMR analyses were carried out (*cf.* Fig. 1 in ESI for **4**†), indicating that only the starting materials and the final products co-exist in the reaction mixture, and no build-up of intermediates could be recorded. These results suggest a base-dependent cascade reaction (Scheme 3), where the acetate anion initially acts as a base in deprotonating the 4-OH group. Dynamic acetyl migration between the 4- and 3-positions subsequently generates the 3-position alkoxide that instantly attacks the 2-position, forming the 2,3-anhydro compounds. Clearly, the stability of the cyclic migration intermediate **M** is low, as expected, since no build-up is visible throughout the process. Because no intermediates were formed, the initial deprotonation step is rate limiting for the entire process.

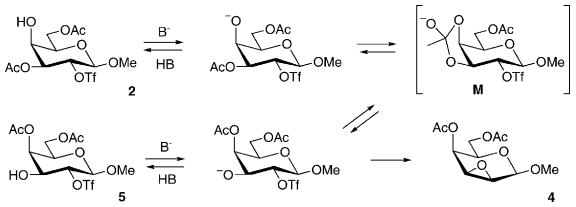
Base-promoted deprotonation being the proposed trigger for the reaction cascade, similar results would also be obtained if the acetate anion is replaced with a different base. With imidazole no reaction occurred, but when acetate was replaced with triethylamine (TEA), or ethylenediamine (EDA), the cascade reaction was also initiated (Table 1). The reaction proceeded however in these cases slowly (Table 1, entries 2–4), and a large amount of migration intermediate **5** accumulated in the reaction mixture (Fig. 1 in ESI†).

However, the combination of anions with amine base resulted in very large rate accelerations (Table 1, entries 7, 9



Scheme 2 Carbohydrate cascade inversion controlled by acetate.

Royal Institute of Technology (KTH), Stockholm, Sweden. E-mail: ramstrom@kth.se; Fax: +46 8 7912333
† Electronic supplementary information (ESI) available: Synthesis of compounds **7**–**8**, general conditions for the triggered cascade reaction and NMR analyses. See DOI: 10.1039/b717301f



Scheme 3 Proposed cascade reaction mechanism for β-D-galactoside **2**.

and 10). For example, the combination of acetate and ethylenediamine yielded full cascade conversion in one hour (Table 1, entry 7). In contrast, acetate or EDA alone resulted in only 50% conversion after 8 and 40 h, respectively (Table 1, entries 5 and 3). For nitrite, the results were even more conspicuous; although nitrite anion alone was unable to induce the cascade reaction (Table 1, entry 8), its combination with EDA resulted in quantitative rapid cascade inversion (Table 1, entries 9 and 10).

Interestingly, the large amount of intermediate **5** that accumulated with amine base alone, rapidly disappeared when adding acetate or nitrite. This suggests that the anions are able to activate the epoxide formation from the 3-OH intermediate. In this case, the acetate anion acts not only as a base, but also as an activator of the whole cascade reaction. The nitrite anion, on the other hand, exclusively acts as a cascade activator.

According to these results, it could also be anticipated that amino acids should display strong activation abilities for the cascade reaction, carrying both an amine and an acetate group. Indeed, this proposition proved to be valid. Starting from compound **2**, and adding only two equivalents of the TBA salt of either α-L-alanine or β-alanine in benzene, the 2,3-anhydro product **4** was obtained in quantitative yield within one hour (Scheme 4).

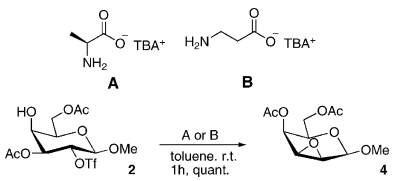
Based on these results, improved triggered cascade reactions starting directly from compounds **6** and **7** could be designed (Scheme 5), where the cascade sequence involved two inversions, migration and epoxidation. By combination of tetrabutylammonium nitrite with ethylenediamine, the cascade reactions proceeded smoothly and compounds **3** and **4** were directly produced in up to 90% yield. Under these conditions, ethylenediamine alone was unable to substitute either triflate group, and only maintained a basic condition. The nitrite ion not only triggered the entire cascade reactions by substitution and inversion of the 4-position, but furthermore activated the epoxidation steps.

Under mild acidic work-up conditions, compounds **3** and **4** could subsequently be transformed to the corresponding β-D-altrosides,[12] and β-D-idosides,[13] respectively, in near quantitative yields (*cf.* Scheme 1). This provides a very efficient route to these unusual carbohydrate structures,[14] accessible in high overall yields (up to 80%) in very few steps from the parent unprotected glucosides/galactosides.[11] The 2,3-anhydro compounds are furthermore potentially useful building blocks for alternative carbohydrate substitution patterns, using a variety of suitable reagents.[15] In addition, the cascade reactions are not confined to carbohydrates, but in principle applicable to any structure carrying the common three-carbon motif as exemplified by positions 2–3–4 in compounds **6** and **7**.

Table 1 Cascade reaction of compound **2** with anionic reagents and/or amine base

Entry	Reagent (eq.)	Base (eq.)	Time/h	Yield (%)
1	—	Imidazole (50)	72	—[b]
2[a]	—	TEA (15)	96	—[b]
3[a]	—	EDA (10)	40	—[b]
4[a]	—	EDA (30)	7	—[b]
5	TBAOAc (1)	—	8	—[b]
6	TBAOAc (5)	—	2	Quant.
7	TBAOAc (1)	EDA (10)	1	Quant.
8	$TBANO_2$ (10)	—	120	—[c]
9	$TBANO_2$ (10)	EDA (30)	0.1	Quant.
10	$TBANO_2$ (1)	EDA (10)	4	Quant.

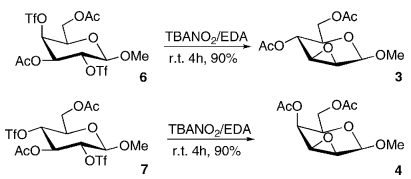
[a] Intermediate **5** formed. [b] 50% conversion. [c] Inversion obtained.



Scheme 4 Carbohydrate cascade epimerization activated by amino acid anions.

To further explore how the anionic reagents activate the cascade reaction, a range of anions was studied. Thus, benzoate, chloride, bromide and thiocyanate were tested in addition to acetate and nitrite. When these anions were tested together with compound **2**, NMR analyses indicated the formation of hydrogen bonds between the anions and the hydroxyl group in the 4-position (*cf.* Fig. 2 in ESI†). The chemical shifts of the 4-OH proton changed from 1.8 for compound **2** alone to up to 9.0 for NO_2^-. With AcO^- and BzO^-, the 4-OH resonances were indiscernible, but the downfield change in chemical shift of the 4-H protons indicates formation of hydrogen bonds. The 4-H resonances thus changed from 3.7 (compound **2** alone) up to 4.8 (NO_2^-, AcO^- and BzO^-).

In analogy with the results for acetate, the benzoate anion alone could also trigger the cascade reaction (Table 2, entry 2). In this case, however, the reaction proceeded at a considerably lower rate. The chloride, bromide, and thiocyanate anions, on the other hand, showed the same behavior as nitrite, and were unable to initiate the reaction by themselves. However, in combination with amine base, all tested anions proved able to activate the cascade reaction (Table 2). This activation ability followed the corresponding H-bond formation tendencies, where anions displaying higher H-bonding also showed stronger activation ability. In combination with EDA the activation follows the order: $AcO^- > BzO^- > NO_2^- > Cl^- > Br^- > SCN^-$ in benzene.



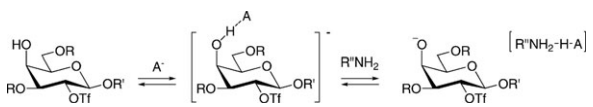
Scheme 5 Carbohydrate cascade epimerization starting from compounds **6** and **7**.

Table 2 Cascade reaction for compound **2** in combinations of anions and 5 eq. of EDA in benzene

Entry	Reagent (eq.)	$\delta_{4\text{-OH}}{}^{a}$/ppm	$\delta_{4\text{-H}}{}^{a}$/ppm	Time/h	Yield (%)
1	TBAOAc (5)	—	4.8	0.5	Quant.
2	TBAOBz (5)	—	4.8	1	Quant.
3	$TBANO_2$ (5)	9.0	4.8	2	Quant.
4	TBACl (5)	7.7	4.7	6	Quant.
5	TBABr (5)	6.7	4.7	7	Quant.
6	TBASCN (5)	6.6	4.4	28	Quant.

[a] The $\delta_{4\text{-OH}}$ and $\delta_{4\text{-H}}$ of **2** are 1.8 and 3.7 ppm, respectively.

These results indicate anion-assisted deprotonation through hydrogen bonding as a rationale for the activation effect.[16] Reactions with amine base alone lead to accumulation of the migration product intermediate (**5**), but when the anionic reagent is present from the start, or added after build-up of the intermediate, this is rapidly consumed and the 2,3-anhydro product formed. With acetate or benzoate alone, hydrogen bond complexes between the carbohydrate and the carboxylate anions can activate the deprotonation process, likely forming a $[RCOO\cdots H\cdots OOR]^{-}$ complex.[17,18] Support for this conclusion was also seen when one equivalent of acetate was used in the reaction, resulting in final 50% conversion. On the other hand, with nitrite and the other anions alone, the hydrogen bond complex is weaker, and the possible $[X\cdots H\cdots X]^{-}$ complex is equally weak.[18] As a result, deprotonation is less efficient. Dramatic rate enhancements were furthermore recorded with combinations of anion and amine base. In analogy with the formation of $[RCOO\cdots H\cdots OOR]^{-}$, this effect suggests possible complex formation between the amine and the anion $[RNH_2\cdots H\cdots X]$, leading to more efficient formation of product **4**, and no accumulation of intermediate **5** (Scheme 6).



Scheme 6 Enhanced deprotonation through anion–amine interaction.

In conclusion, a convenient and highly efficient method for multiple carbohydrate epimerization through triggered cascade reactions is introduced. It was found that reactions that normally involve many steps could be completed in one step in quantitative yields. An intriguing activation effect was furthermore discovered, where combinations of anionic reagent and amine base resulted in dramatic rate enhancements. The mechanism by which anionic reagents activate the cascade reaction was initially explored, suggesting a supramolecular process emanating from the enhanced deprotonation due to plausible amine–anion complexation. This supramolecular effect would not only be specific for pyranoside inversion, but of general use for a wide range of base-dependent reactions. It was also demonstrated that amino acid anions alone show strong activation effects for the triggered cascade reaction.

This work was supported by the Swedish Research Council and the Royal Institute of Technology.

Notes and references

1 (*a*) J.-M. Lehn, *Science*, 2002, **295**, 2400–2403; (*b*) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, Wiley-VCH, Weinheim, 1995.

2 (*a*) L. J. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.*, 2001, **40**, 2383–2426; (*b*) M. C. T. Fyfe and J. F. Stoddart, *Acc. Chem. Res.*, 1997, **30**, 393–401; (*c*) G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen and D. M. Gordon, *Acc. Chem. Res.*, 1995, **28**, 37–44.

3 (*a*) F. Diederich and P. Stang, *Templated Organic Synthesis*, Wiley-VCH, Weinheim, 2000; (*b*) D. M. Vriezema, M. C. Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, *Chem. Rev.*, 2005, **105**, 1445–1489.

4 (*a*) N. Paul and G. F. Joyce, *Curr. Opin. Chem. Biol.*, 2004, **8**, 634–639; (*b*) A. Robertson, A. J. Sinclair and D. Philp, *Chem. Soc. Rev.*, 2000, **29**, 141–152.

5 (*a*) D. Enders, C. Grondal and M. R. M. Huttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*b*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186; (*c*) L. F. Tietze, H. P. Bell and G. Brasche, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; (*d*) H. Pellissier, *Tetrahedron*, 2006, **62**, 1619–1665; (*e*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.

6 (*a*) S. M. Glück, S. F. Mayer, W. Kroutil and K. Faber, *Pure Appl. Chem.*, 2002, **74**, 2253–2257; (*b*) S. F. Mayer, W. Kroutil and K. Faber, *Chem. Soc. Rev.*, 2001, **30**, 332–339.

7 T. K. Lindhorst, *Essentials of Carbohydrate Chemistry and Biochemistry*, Wiley-VCH, Weinheim, 2000.

8 (*a*) R. Lattrell and G. Lohaus, *Justus Liebigs Ann. Chem.*, 1974, 901–920; (*b*) R. Albert, K. Dax, R. W. Link and A. E. Stuetz, *Carbohydr. Res.*, 1983, **118**, C5–C6.

9 H. Dong, Z. Pei and O. Ramström, *J. Org. Chem.*, 2006, **71**, 3306–3309.

10 H. Dong, Z. Pei, S. Byström and O. Ramström, *J. Org. Chem.*, 2007, **72**, 1499–1502.

11 H. Dong, Z. Pei, M. Angelin, S. Byström and O. Ramström, *J. Org. Chem.*, 2007, **72**, 3694–3701.

12 (*a*) K. Fujita, K. Ohta, Y. Ikegami, H. Shimada, T. Tahara, Y. Nogami, T. Koga, K. Saito and T. Nakajima, *Tetrahedron Lett.*, 1994, **35**, 9577–9580; (*b*) N. K. Richtmyer, *Methods Carbohydr. Chem.*, 1962, **1**, 107–113.

13 (*a*) A. S. Perlin, B. Casu, G. R. Sanderson and J. Tse, *Carbohydr. Res.*, 1972, **21**, 123–132; (*b*) E. Sorkin and R. Reichstein, *Helv. Chim.Acta*, 1945, **28**, 1–17.

14 (*a*) R. W. S. Weber, A. Meffert, H. Anke and O. Sterner, *Mycol. Res.*, 2005, **109**, 619–626; (*b*) S. S. Afiyatullov, T. A. Kuznetsova, V. V. Isakov, M. V. Pivkin, N. G. Prokofeva and G. B. Elyakov, *J. Nat. Prod.*, 2000, **63**, 848–850.

15 (*a*) V. L. Maxwell, E. L. Evinson, D. P. G. Emmerson and P. R. Jenkins, *Org. Biomol. Chem.*, 2006, **4**, 2724–2732; (*b*) Y. Wang, Q. Li, S. H. Cheng, Y. F. Wu, D. J. Guo, Q. H. Fan, X. F. Wang, L. H. Zhang and X. S. Ye, *Org. Lett.*, 2005, **7**, 5577–5579; (*c*) A. Procopio, R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi and B. Russo, *Adv. Synth. Catal.*, 2005, **347**, 1447–1450; (*d*) M. A. Probert, J. Zhang and D. R. Bundle, *Carbohydr. Res.*, 1996, **296**, 149–170.

16 V. Amendola, D. Esteban-Gomez, L. Fabbrizzi and M. Licchelli, *Acc. Chem. Res.*, 2006, **39**, 343–353.

17 V. Amendola, M. Boiocchi, L. Fabbrizzi and A. Palchetti, *Chem.–Eur. J.*, 2005, **11**, 5648–5660.

18 M. Boiocchi, L. Del Boca, D. Esteban-Gomez, L. Fabbrizzi, M. Licchelli and E. Monzani, *Chem.–Eur. J.*, 2005, **11**, 3097–3104.