Asymmetric tandem reactions based on nitroalkenes: a one-pot construction of functionalized chiral bicycles by a three-component reaction

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Asymmetric tandem cycloaddition of a chiral carbohydrate nitroalkene with ethyl vinyl ether in the presence of electron-withdrawing alkenes produces a facile assembly of bicyclic systems, which can further be selectively cleaved to give homologated carbohydrates.

The construction of complex organic molecules by sequential transformations is one of the most important and efficient synthetic strategies. The advantages of these so-called tandem or domino reactions are many and have been thoroughly discussed.[1] Sequential [4 + 2]/[3 + 2] cycloadditions relying on nitroalkenes have been developed by Denmark and his group over the last decade, exploiting the use of a homochiral auxiliary on the dienophile and demonstrating the versatility of this methodology in alkaloid synthesis.[2]

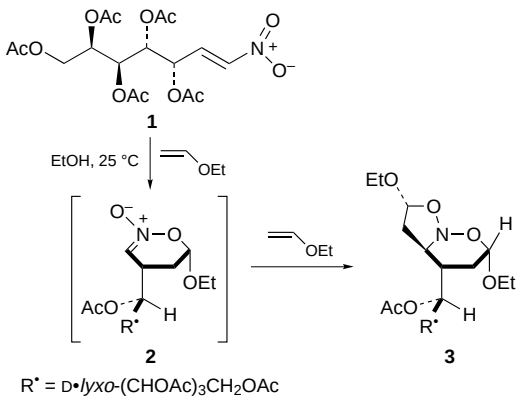
Recently we have also demonstrated the efficiency of the tandem nitroalkene cycloaddition as a viable approach to densely functionalized molecules, but the heterodiene now imparts chirality by using a readily available carbohydrate-appended nitroalkene (Scheme 1).[3] These processes occur through the intermediacy of nitronate species such as **2**.

Given the distinctive electronic character of nitroalkenes and nitronates, it would be possible to perform a multicomponent reaction combining electron-rich and electron-withdrawing alkenes without them interfering with each other. Thus when the heterodiene **1** was reacted with excesses of ethyl vinyl ether (EVE) and an electron-withdrawing alkene such as methyl vinyl ketone (MVK), methyl acrylate (MA), acrylonitrile (AN) and dimethyl maleate (DMM) in ethanolic solution at room temperature for 5–7 days, the corresponding nitrosoacetals **4**–**7** were obtained as crystalline solids (Scheme 2 and Table 1).‡ The initial inverse electronic demand [4 + 2] cycloaddition occurs with ethyl vinyl ether, whereas the resulting nitronate will react exclusively in a [3 + 2] fashion with the electron-deficient alkene.

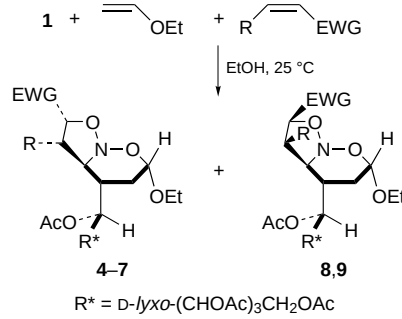
Analyses of crude samples by ^{1}H NMR spectroscopy ($CDCl_3$, 400 MHz) reveal that the reactions are regiospecific and exhibit a pronounced facial diastereoselectivity. Only two diastereoisomers were detected, one of which was always prevalent. Remarkably, the mixtures could be purified by flash chromatography (ethyl acetate–hexane eluent system) and the major isomers were obtained as diastereoisomerically pure samples by crystallization from EtOH. In the cases of the MA and AN reactions, the minor isomers could also be obtained in crystalline form in 4 and 10% yields, respectively.

We have confirmed by X-ray diffractometry that the initial [4 + 2] cycloaddition occurs with a complete *endo* selectivity to the *re* face of the heterodiene, whereas the [3 + 2] cyclization follows in the *exo* sense, which is sterically more favorable than the competitive *endo* approach.[3] This type of *exo–endo* facial selectivity has been observed before with related 5,5-fused systems.[4] Based on such results and with the information provided by proton coupling constants, suggesting that both substituents of five- and six-membered fused rings are located at α-equatorial positions, we have tentatively assigned the absolute stereochemistry of the major isomers **4**–**7**. Because similar coupling constants have also been found for the isolated minor isomers, their formation must have taken place with the opposite *endo* orientation in the [3 + 2] cyclization.

The usefulness of these functionalized polyhydroxyalkyl heterocycles was further illustrated through their selective six-membered ring opening under mild conditions. Cleavage of nitrosoacetals may be induced by acidic treatment with dilute AcOH in ethanolic solution, but reaction mixtures were difficult to purify owing to the presence of unidentified side products. However, when cycloadducts were heated at reflux in a 1 : 1 EtOH–H_2O mixture, homologated sugar aldehydes[5,6] such as **10** and **11** were cleanly obtained in quantitative yield (Scheme 3).‡ These substances were further characterized by preparing their hydrazone derivatives **12** and **13**, respectively. Compounds **10**–**13** also bear an attractive isoxazoline ring that could



Scheme 1

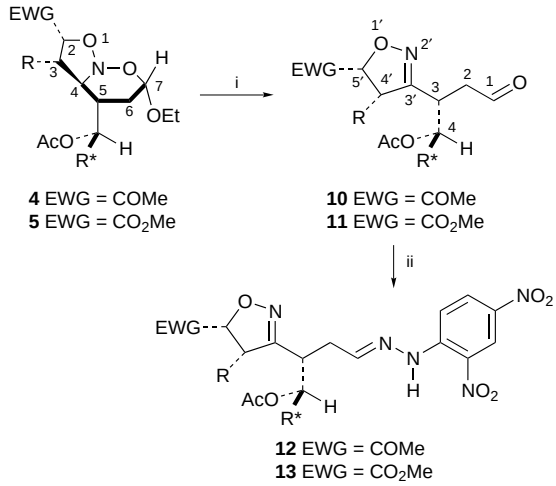


Scheme 2

Table 1 Reaction of **1** with EVE and electron deficient alkenes

		Product (% yield[a])	
R	EWG	Major	Minor
H	COMe	**4** (70)	—[b]
H	CO_2Me	**5** (75)	**8** (4)
H	CN	**6** (60)	**9** (10)
CO_2Me	CO_2Me	**7** (50)	—[b]

[a] Isolated yields after crystallization. [b] Not isolated.



Scheme 3 *Reagents and conditions*: i, EtOH–H_2O, reflux, 12 h, 100%; ii, 2,4-$(O_2N)_2C_6H_3NHNH_2$, MeOH, room temp., 12 h

be further manipulated to afford vicinal amino alcohols and crossed aldol products.[7,8]

In conclusion, we have successfully explored a tandem cycloaddition which involves *in situ* formation of a chiral nitronate having a sugar moiety and its subsequent diastereofacial selective dipolar cycloaddition with a series of electron-deficient alkenes. Variations in the system undergoing cyclization allows subsets of richly functionalized nitrogen-containing polycycles to be produced from an acyclic precursor. The formation of homologated carbohydrates in a few steps is also notable. With the understanding of transition state preferences, this methodology will become a useful element in synthetic design and further investigations are currently under way in our laboratories.

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Notes and References

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‡ Satisfactory spectroscopic (IR, ^{1}H, ^{13}C, ^{1}H-COSY, and ^{1}H-^{13}C-HETCOR NMR) and analytical data were obtained for all new compounds. *Selected data for* **3**: (the numbering system used for NMR assignments is in agreement with the literature data, see ref. 9): mp 188 °C (EtOH); $[\alpha]_D$ +7.5 (*c* 1, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2970, 1730, 1360, 1225, 1100, 1050, 1020; δ_H ($CDCl_3$, 400 MHz) 5.32 (dd, $J_{1',2'}$ 1.2, $J_{2',3'}$ 9.9, 1 H, H-2′), 5.27–5.21 (m, 2 H, H-1′, H-4′), 5.18 (dd, $J_{2',3'}$ = 9.9, $J_{3',4'}$ = 1.8, 1 H, H-3′), 4.90 (dd, $J_{2,3a}$ 9.8, $J_{2,3b}$ = 4.6, 1 H, H-2), 4.75 (t, $J_{6a,7}$ $J_{6b,7}$ 7.0, 1 H, H-7), 4.32 (dd, $J_{4',5a'}$ 4.5, $J_{5a',5b'}$ = 11.8, 1 H, H-5a′), 3.95 (m, 1 H, CH_3CH_2O–C-7), 3.78 (dd, $J_{4',5b'}$ 7.6, $J_{5a',5b'}$ 11.8, 1 H, H-5b′), 3.51 (m, 1 H, CH_3CH_2O–C-7), 3.30 (m, 1 H, H-4), 2.32 (m, 1 H, H-3a), 2.26–2.16 (m, 2 H, H-3b, H-6a), 2.21 (s, 3 H, CH_3CO–C-2), 2.14 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 1.83–1.70 (m, 2 H, H-5, H-6b), 1.27 (t, 3 H, CH_3CH_2O– C-7); δ_C ($CDCl_3$, 100 MHz) 206.2 (CH_3CO), 170.5 (2C, OAc), 170.3 (OAc), 170.1 (OAc), 169.9 (OAc), 99.7 (C-7), 87.9 (C-2), 71.8 (C-4′), 69.7 (C-4), 67.7, 67.6, 67.5 (3C, C-1′, C-2′, C-3′), 63.6 (CH_3CH_2O–C-7), 62.4 (C-5′), 38.7 (C-5), 34.3 (C-3), 28.0 (C-6), 26.7 (CH_3CO), 20.7 (OAc), 20.7 (OAc), 20.6 (3C, OAc), 15.0 (CH_3CH_2O–C-7). Calc. for $C_{25}H_{37}NO_{14}$: C, 52.17; H, 6.48; N, 2.43. Found: C, 52.02; H, 6.51; N, 2.43%). *For* **8** (note that the longest sugar chain is cited first with the lowest number to the aldehyde group; primed numbers are located on the hererocycle): δ_H ($CDCl_3$, 400 MHz) 9.65 (s, 1 H, CHO), 5.37 (dd, $J_{4,5}$ 1.4, $J_{5,6}$ 11.0, 1 H, H-5), 5.25–5.19 (m, 3 H, H-4, H-6, H-7), 4.79 (dd, $J_{5',4a'}$ 5.6, $J_{5',4b'}$ 11.5, 1 H, H-5′), 4.28 (dd, $J_{8a,7}$ 4.7, $J_{8a,8b}$ 11.7, 1 H, H-8a), 3.78 (dd, $J_{8b,7}$ 7.5, $J_{8a,8b}$ 11.7, 1 H, H-8b) 3.29–3.18 (m, 2 H, H-3, H- 4a′), 3.12 (dd, $J_{4b',5'}$ 5.6, $J_{4a',4b'}$ 17.4, 1 H, H-4b′), 2.96 (dd, $J_{2a,3}$ 5.0, $J_{2a,2b}$ 18.3, 1 H, H-2a), 2.82 (dd, $J_{2b,3}$ 2.3, $J_{2a,2b}$ 18.3, 1 H, H-2b), 2.27 (s, 3 H, CH_3CO–C-5′), 2.10 (s, 9 H, 3 OAc), 2.07 (s, 3 H, OAc), 2.02 (s, 3 H, OAc); δ_C($CDCl_3$, 100 MHz) 207.8 (CH_3CO), 198.1 (CHO), 170.5 (OAc), 170.3 (2C, OAc), 170.0 (OAc), 169.8 (OAc), 158.1 (C-3′), 83.5 (C-5′), 69.7 (C-5), 67.9, 67.7, 67.4 (C-4, C-6, C-7), 62.2 (C-8), 43.3 (C-2), 38.4 (C-4′), 33.5 (C-3), 26.4 (CH_3CO), 20.7 (OAc), 20.6 (4C, OAc).

1 For reviews on tandem reactions: T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992; L. F. Tietze, and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; R. A. Bunce, *Tetrahedron*, 1995, **51**, 13 103; J. D. Winkler, *Chem. Rev.*, 1996, **96**, 167.

2 For a review on tandem cycloadditions of nitroalkenes: S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137.

3 M. Avalos, R. Babiano, P. Cintas, F. J. Higes, J. L. Jiménez, J. C. Palacios and M. A. Silva, *J. Org. Chem.*, 1996, **61**, 1880.

4 R. N. Butler, D. Cunningham, E. G. Marren, P. McArdle and D. F. O'Shea, *J. Chem. Res. (S)*, 1992, 256.

5 For reviews on branched and higher carbon sugars: J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, 1984, **42**, 69; A. Zamojski and S. Jarosz, *Pol. J. Chem.*, 1992, **66**, 525.

6 A general route for the homologation-amination of aldehydes by addition of sugar nitrones to metalated thiazoles has been recently devised: A. Dondoni, S. Franco, F. Junquera, F. L. Merchán, P. Merino, T. Tejero and V. Bertolasi, *Chem. Eur. J.*, 1995, **1**, 505 and references cited therein; A. Dondoni, F. Junquera, F. L. Merchán, P. Merino, M.-C. Scherrmann and T. Tejero, *J. Org. Chem.*, 1997, **62**, 5484.

7 For reviews on syntheses of isoxazolines by inter- and intramolecular 1,3-dipolar cycloadditions, see A. Padwa, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and M. F. Semmelhack, Pergamon, Oxford, 1991, vol. 4, pp. 1069–1109; P. A. Wade, *ibid*, vol. 4, pp. 1111–1168; For a review on chiral isoxazolines: B. H. Kim and D. P. Curran, *Tetrahedron*, 1993, **49**, 293; For the formation of aldol-type products by ring-cleavage of isoxazolines: W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, 1990, p. 293.

8 The reduced chiral systems, optically active isoxazolidines, can also be utilized in organic synthesis: M. Frederickson, *Tetrahedron*, 1997, **53**, 403.

9 K. Undheim, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 6, pp. 632–633.

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