Substrate-Controlled Stereodifferentiation of Tandem [4 + 2]/[3 + 2] Cycloadditions by a Vicinal Carbohydrate-Based Template

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Tandem pericyclic reactions are among the most versatile strategies for the stereocontrolled preparation of complex, polycyclic structures from relatively simple starting materials.[1] In particular the tandem nitroalkene [4 + 2]/[3 + 2] cycloaddition, mainly developed by Denmark and his associates, represents a powerful and elegant protocol en route to functionalized pyrrolidine-based alkaloids.[2] Alkenes and vinyl ethers can be utilized as appropriate dienophiles, which react with selective *exo* and *endo* orientations, respectively. Furthermore, asymmetric modifications have also been described by the use of chiral vinyl ethers.[2e,g−m] Remarkably, a reversal of selectivity has been observed as a function of the transition metal catalyst utilized.[2g,k] Though nitronates are often stable compounds and can be isolated as intermediates of the tandem reaction, in some instances the domino Diels−Alder/cyclopentannulation sequence can be easily performed in a one-step procedure.

In no previous studies on this tandem cycloaddition has the heterodiene been amenable to asymmetric derivatization, with the exception of only one example by Chattopadhyaya *et al.* who utilized a rather complex thymidine nucleoside-derived nitroalkene.[3] Although a carbohydrate-based strategy is certainly attractive for tandem cyclizations, the preparation of nitroalkenyl sugars often involves a lengthy multistep sequence from unprotected materials,[4] thus hampering the potential applicability of this extremely useful reaction.

As a part of our ongoing program on asymmetric transformations, we wish to report a highly stereoselective variation of the tandem [4 + 2]/[3 + 2]-fused mode Denmark-type reaction,[5] in which the auxiliary is a D-galactose-based template. For clarity we selected the heterodiene **1**, readily available from commercial D-galactose in a three-step protocol,[6] and ethyl vinyl ether as the test dienophile/dipolarophile. We were pleased to find that the double cycloadduct **2** *was cleanly obtained in ethanolic solution at room temperature without any catalyst* (Scheme 1).[7] Attempts to isolate the transient nitronate under these conditions, even at lower temperatures, were unsuccessful, thus indicating the extreme lability of this particular intermediate, in clear contrast with previous findings. Compound **2** was obtained in 89% yield as a single diastereomer. Five- and six-membered fused rings showed pseudoanomeric protons at 5.60 ppm (J = 10.2 Hz) and 4.68 ppm (J = 12.8 Hz), respectively, both of them consistent with an antiperiplanar arrangement of vicinal protons and placing alkoxy groups at α equatorial positions. The full stereostructure of **2** was unequivocally established by X-ray crystallographic analysis which, in turn, confirmed the original assignments of the cycloadduct as having arisen from an exclusive *endo* [4 + 2] cycloaddition to the *re* face of the heterodiene (respect to the nitroalkene β carbon atom). The solid state structure also reveals the *cis* disposition between both alkoxy groups and the chiral side chain, as well as a twist boat conformation of the six-membered oxazine ring.[8]

Taking into account that the conformational barrier between *s-cis* and *s-trans* conformers of ethyl vinyl ether is very low,[9] a percentage of both conformers should contribute to the *endo* approach. This stereochemical outcome is not fully understood, albeit secondary orbital interactions have been proposed.[2,10] Semiempirical PM3 and AM1 calculations do indeed indicate the existence of such orbital interactions as well as Coulombic ones between the electron rich-vinyl ether oxygen with the positively charged nitrogen atom of the nitroalkene, which would be otherwise absent in an *exo* orientation.[11] These electrostatic interactions have also been suggested by Houk[12] and Hehre[13] in other cycloaddition processes. Regarding the [3 + 2] cycloaddition, which has not been previously rationalized, the absolute configurations of cycloadduct **2** could be interpreted by assuming either an *endo si*-face or *exo re*-face attack. Even if the latter is not favored by Coulombic interactions, the *endo*

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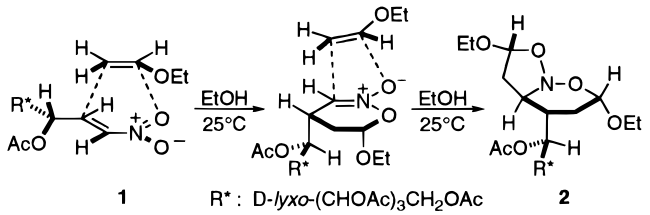
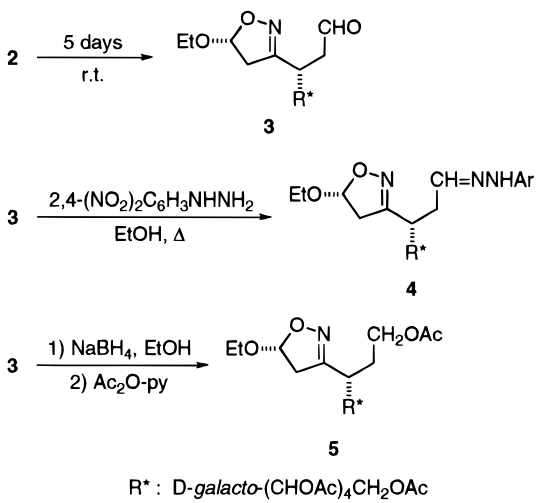
Scheme 1



Scheme 2



approach would afford a very constrained transition state owing to steric hindrance between the two ethoxy groups as revealed by simple inspection of CPK models. Moreover, the bulky polyhydroxyl side chain must also play a crucial role as a vicinal controller in discriminating π enantiotopic faces of ethyl vinyl ether in both cycloadditions.[14] It should be noted that this useful principle of substrate-controlled stereodifferentiation has been recently exploited by Saito *et al.* in nitrone−olefin dipolar cycloadditions.[15]

Although compound **2** is relatively stable and could be thoroughly characterized, we have observed that it slowly decomposes on standing (even under vacuum) at room temperature after several days. This enables the isolation of fragmentation product **3** selectively as an amorphous powder that could not be crystallized and gave no satisfactory elemental analysis.[16] The unequivocal characterization of this *elongated eight carbon aldehyde* was carried out *via* its hydrazone derivative **4**. Alternatively, **3** was subjected to reduction with $NaBH_4$ followed by acetylation to afford crystalline **5** as the sole product (Scheme 2). It is noteworthy that **3**−**5** are examples of homologated sugars bearing an attractive isoxazoline ring for further synthetic manipulations.[17,18]

In summary, we have achieved a short, straightforward, and highly stereoselective synthesis of **2**, which is amenable and adaptable for the synthesis of other nitrosoacetals from chiral heterodienes. The lability of such a cycloadduct, in this particular case, offers an exciting derivatization to higher−carbon and branched−chain carbohydrates. Such studies are in progress.

Experimental Section

General Methods. Melting points were determined with a capillary apparatus and are uncorrected. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ and referenced to internal TMS. FT-IR spectra were performed using KBr pellets. Optical rotations were measured at 20 °C in $CHCl_3$ solution. TLC analysis was conducted on Merck precoated silica plates (0.25 mm layer thickness), and flash chromatography was carried out on Merck silica gel (230−400 mesh). All materials were commercially available and used as received. All glassware was oven-dried. Combustion analyses were performed by the Servei de Microanàlisis del CSIC, Barcelona.

(2*R*,4*R*,5*S*,7*S*)-2,7-Diethoxy-5-(1′,2′,3′,4′,5′-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)perhydroisoxazolo[2,3-*b*][1,2]-oxazine (2). To a suspension of **1** (2.00 g, 4.61 mmol) in anhydrous ethanol (40 mL) was added ethyl vinyl ether (40 mL). The reaction mixture was stirred at 25 °C until complete disappearance of compound **1** (7 days, TLC: AcOEt−hexane 1:1). The resulting clear solution was concentrated to a third of the volume and kept at 0 °C, to give compound **2** as white crystals (2.37 g, 89%): mp 116 °C; $[\alpha]_D$ +30.0° (*c* 1, $CHCl_3$); IR (KBr) 2970, 1730, 1370, 1225, 1110, 1055, 1020 cm^{-1}; ^1H NMR δ 5.60 (d, $J_{2,3}$ = 10.2 Hz, 1H, H-2), 5.32 (dd, $J_{1',2'}$ = 1.0 Hz, $J_{2',3'}$ = 10.0 Hz, 1H, H-2′), 5.26−5.24 (m, 2H, H-1′, H-4′), 5.16 (dd, $J_{3',4'}$ = 1.0 Hz, 1H, H-3′), 4.68 (t, $J_{6a,7} = J_{6b,7}$ = 12.8 Hz, 1H, H-7), 4.33 (dd, $J_{4',5a'}$ = 4.2, $J_{5a',5b'}$ = 11.8 Hz, 1H, H-5a′), 3.91 (m, 1H, CH_3CH_2O−C-2), 3.80−3.68 (m, 2H, H-5b′, CH_3CH_2O−C-7), 3.52−3.43 (m, 3H, H-4, CH_3CH_2O−C-2, CH_3CH_2O−C-7), 2.80−1.97 (m, 3H, H-3a, H-3b, H-6a), 2.12 (s, 9H, 3 OAc), 2.08 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.76 (m, 2H, H-5, H-6b), 1.25 (t, 3H, CH_3CH_2O−C-2), 1.14 (t, 3H, CH_3CH_2O−C-7); ^{13}C NMR δ 170.34, 170.23, 170.15, 169.95, 169.90 (5 OAc), 107.79 (C-2), 99.48 (C-7), 71.77 (C-4), 67.77, 67.64 (C-1′, C-2′, C-3′, C-4′), 64.04 (CH_3CH_2O−C-7), 63.33 (CH_3CH_2O−C-2), 62.45 (C-5′), 38.43 (C-3), 38.01 (C-5), 28.17 (C-6), 20.61, 20.53 (5 OAc), 14.96, 14.91 (2 CH_3CH_2O). Anal. Calcd for $C_{25}H_{39}NO_{14}$: C, 51.99; H, 6.81; N, 2.43. Found: C, 51.85; H, 6.83; N, 2.44.

(5′*R*)-3-(5′-Ethoxy-2′-isoxazolin-3′-yl)-2,3-dideoxy-4,5,6,7,8-penta-*O*-acetyl-D-*glycero*-L-*gluco*-octose (3). Compound **2** decomposes at 25 °C within 5 days to afford **3** quantitatively as an amorphous powder. Diagnostic ^1H and ^{13}C NMR δ 9.63 (m, 1H, H-1); 198.33 (C-1), 157.39 (C-3′), 102.76 (C-5′).

(5′*R*)-3-(5′-Ethoxy-2′-isoxazolin-3′-yl)-2,3-dideoxy-4,5,6,7,8-penta-*O*-acetyl-D-*glycero*-L-*gluco*-octose 2,4-Dinitrophenylhydrazone (4). Compound **3** (0.69 g, 1.30 mmol) was dissolved in ethanol (15 mL), and acetic acid (0.5 mL) and 2,4-dinitrophenylhydrazine (0.31 g, 1.56 mmol) were added. The reaction mixture was heated until dissolution and filtered off. The clear solution was kept at 0 °C, and the resulting crystalline product (0.44 g) was purified by flash chromatography (AcOEt−hexane, 1:8) in order to eliminate the starting hydrazine, to give pure **4** (0.32 g, 35%): mp 172−173 °C (ethanol); $[\alpha]_D$ +166.6° (*c* 1, $CHCl_3$); IR (KBr) 3290, 3070, 2950, 1745, 1615, 1590, 1510, 1370, 1330, 1220, 1085, 1035 cm^{-1}; ^1H NMR δ 11.01 (s, 1H, NH), 9.08 (d, *J* = 2.6 Hz, 1H, phenyl), 8.30 (dd, *J* = 9.6 Hz, 1H, phenyl), 7.85 (d, 1H, phenyl), 7.40 (dd, $J_{1,2a}$ = 5.9 Hz, $J_{1,2b}$ = 4.0 Hz, 1H, H-1), 5.52−5.47 (m, 2 H, H-5, H-5′), 5.37 (dd, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 1.4 Hz, 1H, H-4), 5.31−5.26 (m, 2 H, H-6, H-7), 4.32 (dd, $J_{7,8a}$ = 4.3 Hz, $J_{8a,8b}$ = 11.9 Hz, 1H, H-8a), 3.85−3.78 (m, 2H, H-8b, CH_3CH_2O), 3.54 (m, 1H, CH_3CH_2O), 3.32 (m, 1H, H-3), 2.97−2.89 (m, 3H, H-2a, H-4a′, H-4b′), 2.56 (m, 1H, H-2b), 2.15 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc),

(14) The inherent asymmetric environment provided by the carbohydrate chiron must affect the overlap with the approaching dienophile. Semiempirical calculations and an *ab-initio* study on a reduced model are in progress in search of transition states.

(15) Japanese authors have shown the efficiency of the substrate stereocontrol exerted by a bis-silylated *threo*-diol structure onto the π-faces of the alkene: (a) Saito, S.; Ishikawa, T.; Moriwake, T. *Synlett* **1994**, 279. (b) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282.

(16) In some cases, plates of **3** were grown under vacuum, but any attempt to solve the structure failed because of the absence of reflections at room temperature, thus confirming its amorphous character.

(17) Chiral isoxazolines have been previously obtained through asymmetric thermal cycloadditions with nitrile oxides: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293.

(18) For reviews on branched and higher carbon sugars: (a) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69. (b) Zamojski, A.; Jarosz, S. *Pol. J. Chem.* **1992**, *66*, 525 and references therein.

2.02 (s, 3H, OAc), 1.20 (t, 3H, C*H*$_3$CH$_2$O); ^{13}C NMR δ 170.62, 170.48, 170.37, 170.26, 169.86 (5 OAc), 157.46 (C-3′), 147.16 (C-1), 144.85, 138.24, 130.07, 129.20, 123.38, 116.41 (phenyl), 102.66 (C-5′), 69.10, 68.05, 67.81 (C-4, C-5, C-6, C-7), 64.07 (CH$_3$*C*H$_2$O), 62.43 (C-8), 41.16 (C-4′), 37.57 (C-3), 32.22 (C-2), 20.79, 20.70 (5 OAc), 15.04 (*C*H$_3$CH$_2$O). Anal. Calcd for $C_{29}H_{37}N_5O_{16}$: C, 48.95; H, 5.24; N, 9.84. Found: C, 48.93; H, 5.25; N, 9.86.

(5′*R*)-3-(5′-Ethoxy-2′-isoxazolin-3′-yl)-2,3-dideoxy-1,4,5,6,7,8-hexa-*O*-acetyl-D-*glycero*-L-*gluco*-octitol (5). Compound **3** (1.00 g, 1.88 mmol) was dissolved in anhydrous ethanol (40 mL) and was treated with sodium borohydride (0.92 g, 24.2 mmol) at 0 °C for 1 h. Then acetic acid (10 mL) was added, the reaction mixture was filtered off, and the solution was evaporated to dryness. The residue was dissolved in a mixture of pyridine (15 mL) and acetic anhydride (15 mL), and the reaction mixture was left at 0 °C for 5 h. Then, it was poured into ice−water, extracted with dichloromethane, washed with sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from diethyl ether−hexane (0.62 g, 55%): mp 159−161 °C; $[\alpha]_D$ +98.8° (*c* 1, $CHCl_3$); IR (KBr) 2980, 2960, 1750, 1375, 1230, 1100, 1040, 960 cm^{-1}; ^{1}H NMR δ 5.49 (d, $J_{4a',5'}$ = 6.5 Hz, 1H, H-5′), 5.46 (dd, $J_{4,5}$ = 1.7 Hz, $J_{5,6}$ = 10.0 Hz, 1H, H-5), 5.29−5.20 (m, 3H, H-4, H-6, H-7), 4.31 (dd, $J_{7,8a}$ = 4.6 Hz, $J_{8a,8b}$ = 11.8 Hz, 1H, H-8a), 4.07 (m, 1H, H-1a), 3.86−3.76 (m, 3H, H-1b, H-8b, CH$_3$C*H*$_2$O), 3.55 (m, 1H, CH$_3$C*H*$_2$O), 3.00 (m, 1H, H-3), 2.96 (dd, $J_{4a',4b'}$ = 17.6 Hz, 1H, H-4a′), 2.84 (d, 1H, H-4b′), 2.16−1.90 (m, 1H, H-2a), 2.12 (s, 6H, 2 OAc), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.02 (s, 6H, 2 OAc), 1.70 (m, 1H, H-2b), 1.19 (t, 3H, C*H*$_3$CH$_2$O); ^{13}C NMR δ 170.42, 170.14, 170.09, 170.01, 169.87, 169.68 (6 OAc), 157.52 (C-3′), 102.33 (C-5′), 69.12 (C-4), 67.67, 67.59, 67.50 (C-5, C-6, C-7), 63.63 (CH$_3$*C*H$_2$O), 62.16 (C-8), 61.17 (C-1), 40.55 (C-4′), 37.07 (C-3), 27.70 (C-2), 20.52, 20.36, 20.31 (6 OAc), 14.79 (*C*H$_3$CH$_2$O). Anal. Calcd for $C_{25}H_{37}NO_{14}\cdot H_2O$: C, 50.58; H, 6.62; N, 2.36. Found: C, 50.88; H, 6.44; N, 2.38.

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Supporting Information Available: Crystal structure and X-ray crystallographic information for compound **2** and copies of NMR spectra for compounds **2**, **4**, and **5** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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