Generation and fate of a novel homochiral mesoionic dipole: synthesis of *C*-nucleoside analogs

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Abstract—A mesoionic acyclic *C*-nucleoside **4**, generated readily from δ-gluconolactone in a few synthetic steps, serves as the chiral core to construct a series of functionalized nucleosides bearing 2-aza-7-thiabicycle[2.2.1]heptane or 2-(1*H*)-pyridone moieties as the aglycon. The key step involves a [3+2] cycloaddition of **4** with several olefinic dipolarophiles followed by hydrogen sulfide elimination with mercury(II) acetate. © 2002 Elsevier Science Ltd. All rights reserved.

Carbohydrates are used extensively as starting materials in chiral-pool synthesis of natural products, including bioactive carbohydrates (e.g. glycosides and nucleosides) and their surrogates.[1] Acyclic nucleosides constitute an important family of chemotherapeutic agents, effective against herpes and cytomegalovirus infections, as well as antineoplasic drugs.[2] As part of our ongoing research focused on mesoionic heterocycles,[3,4] we report herein the synthesis and reactivity of a novel mesoionic dipole directly linked to a flexible carbohydrate chain, an uncommon structural feature in this type of homochiral derivative.[5,6] In this study, compound **4**, which is itself a *C*-nucleoside, could be prepared from δ-gluconolactone **1**.[7] The key step was the cyclization of *N*-methyl-D-thiogluconamide **3** with α-chlorophenylacetyl chloride in dry chloroform followed by addition of triethylamine. The reaction mixture was heated under reflux for 30 min and conventional workup gave rise to the expected mesoionic system **4** (Scheme 1).

The structure of **4** was established on the basis of its spectroscopic data:[8] [13]C resonances at 159.8, 143.6 and 99.9 ppm could easily be attributed to carbon atoms of the heterocyclic fragment: C(4), C(2), and C(5), respectively. In the ^{1}H NMR spectra the C(1′) proton was observed as a doublet at δ 6.30 ppm and the *N*-CH₃ protons resonated at 3.81 ppm. These protons are

shifted downfield in comparison with analogous protons in thioamide **3** (δ 5.71 and 3.15 ppm, respectively).

Although **4** could be precipitated as a yellowish solid (chloroform/diethyl ether/petroleum ether), because of its air sensitivity and gradual decomposition at room temperature, we were unable to obtain satisfactory combustion analysis for this product. However, **4** could be utilized to perform subsequent 1,3-dipolar cycloadditions with a series of electron-deficient dipolarophiles such as *N*-phenylmaleimide, methyl vinyl ketone, methyl acrylate, and acrylonitrile in dichloromethane or toluene at reflux.[9] All of these reactions were highly regiospecific processes but none of them showed appre-
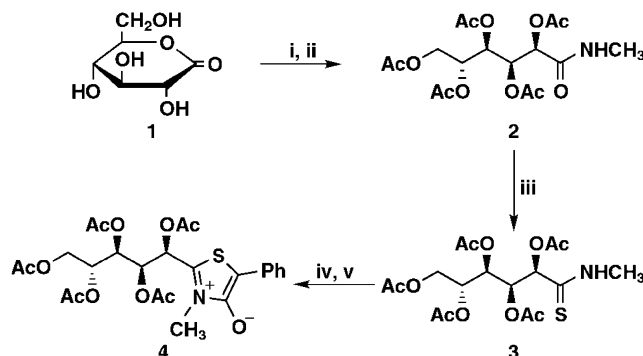

Scheme 1. (i) MeNH₂, H₂O; (ii) Ac₂O, py; (iii) Lawesson's reagent, PhH; (iv) PhCH(Cl)COCl, CHCl₃; (v) Et₃N, CHCl₃.

ciable facial diastereoselectivity.[10] Diastereomeric mixtures (ca. 1:1 ratio) of *exo* cycloadducts **5–8**, which were further separated by column chromatography on silica gel using diethyl ether as eluent, arose from the approach of the dipolarophile to both faces of the dipole. Isolated yields of each diastereomer lie in the range 10–30% (Scheme 2).

The structure of **8a** could unequivocally be determined by single-crystal X-ray analysis (Fig. 1).[11]

In the ^{1}H NMR spectrum of **8a**, the resonances of protons $C(5)H_{endo}$, $C(6)H_{endo}$, and $C(6)H_{exo}$ appeared as double doublets. The signal centered at δ 3.56 ppm contains a *trans* coupling ($J = 3.6$ Hz) and a *cis* coupling
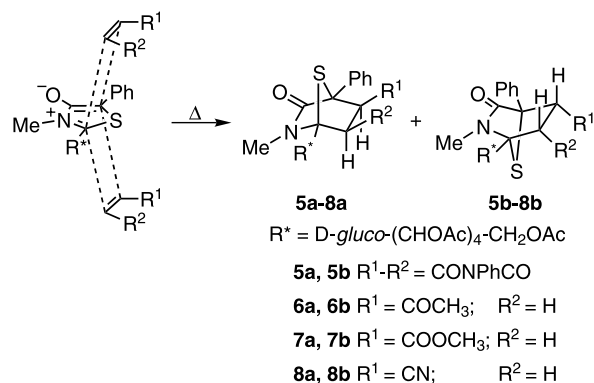
($J = 8.0$ Hz) and it is therefore assigned to the $C(5)H_{endo}$ proton. The signal at δ 2.85 ppm showed a *trans* coupling as above along with a geminal coupling ($J = 12.7$ Hz), consistent with the $C(6)H_{exo}$ proton. Finally, the resonance at δ 2.74 ppm exhibited both *cis* and geminal couplings and it was attributed to the $C(6)$ *endo* proton. The other cycloadduct isolated from the reaction using acrylonitrile as dipolarophile, **8b**, showed a similar coupling pattern for the above-mentioned protons, although resonating at different chemical shifts: δ 3.51 ppm ($C(5)H_{endo}$), and 2.80 ppm ($C(6)H_{exo}$ and $C(6)H_{endo}$). These assignments are consistent with previous spectroscopic data reported in the literature.[12] The stereochemistry of the remaining cycloadducts **5–7** was assigned by comparison with the NMR data of **8a** and **8b** as listed in Table 1.

Moreover, NOE experiments measured on compounds **6a** and **6b** allowed us to confirm the stereochemistry of the newly formed stereogenic centers. The existence of an NOE between the $C(6)H_{endo}$ and *N*-CH$_3$ protons and the absence of such an effect between $C(6)H_{exo}$ and *N*-CH$_3$ protons suggested that the C(5) proton is in an *endo* disposition (Fig. 2).

The transformation of the bicyclic moiety of such nucleosides into the corresponding modified nitrogenated base required the elimination of hydrogen sulfide. Mercury(II) acetate in acetic acid–acetone at room temperature, followed by purification using silica gel chromatography, proved to be the most appropriate
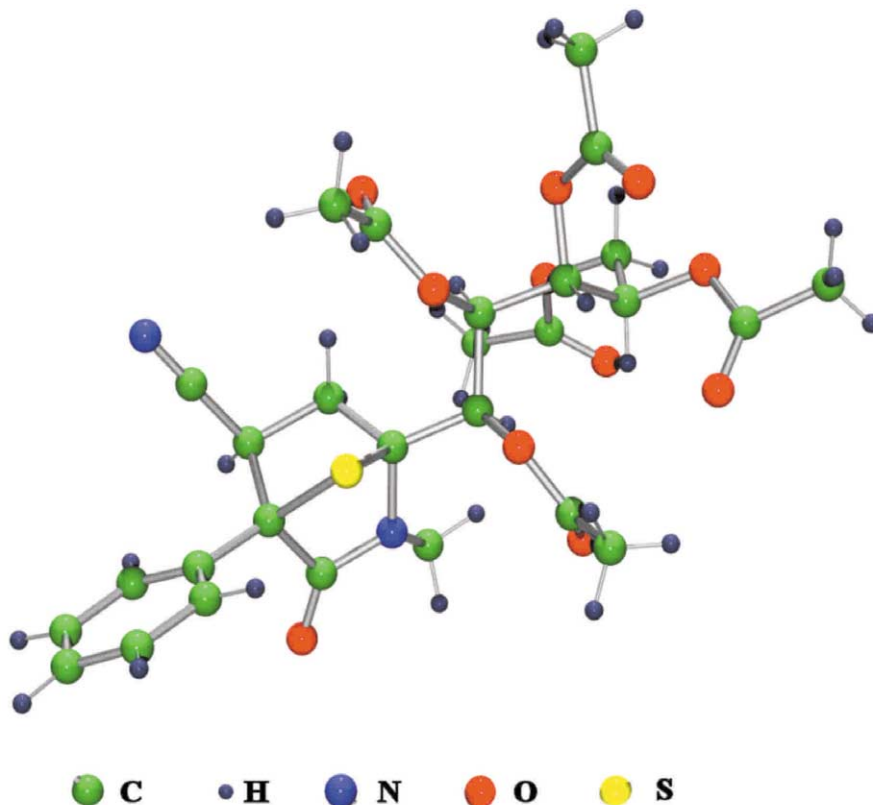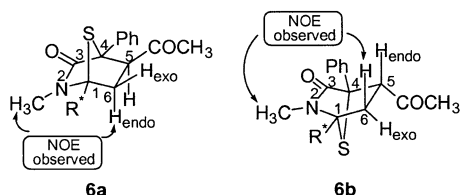

Scheme 2.

R* = D-*gluco*-(CHOAc)$_4$-CH$_2$OAc

5a, 5b R^1-R^2 = CONPhCO
6a, 6b R^1 = COCH$_3$; R^2 = H
7a, 7b R^1 = COOCH$_3$; R^2 = H
8a, 8b R^1 = CN;   R^2 = H


Figure 1. ORTEP view of **8a**.

Table 1. ^{1}H NMR chemical shift (ppm) and coupling constant (Hz) data of diastereomers **5–8** (CDCl$_3$)

Diastereomer	C(5)H$_{endo}$	C(6)H$_{exo}$ ($J_{5,6}$)	C(6)H$_{endo}$ ($J_{5,6}$)
5a	4.03		3.79
			(6.8)
5b	3.92		3.77
			(6.7)
6a	3.44	2.70	2.50
		(4.2)	(8.1)
6b	3.39	2.76	2.44
		(4.3)	(8.1)
7a	3.26	2.78	2.56
		(4.4)	(8.2)
7b	3.30	2.70	2.60
		(4.4)	(8.0)
8a	3.56	2.85	2.74
		(3.6)	(8.0)
8b	3.51	2.80	2.80
		(3.9)	(8.1)

Figure 2.

choice of reagent to accomplish such a goal (Scheme 3).[13] The proposed structures for 2(1*H*)-pyridone were supported by analytical and spectroscopic data. In particular, the signals for the C(5) and C(6) protons in the starting cycloadducts were now missing, and ^{13}C resonances at $\delta \sim 145$, ~ 138, ~ 132, and ~ 105 ppm can be attributed to C(4), C(6), C(3), and C(5), respectively.[6g]

In conclusion, our preliminary experiments have shown that it is possible to prepare a new family of acyclic, yet homochiral, nucleoside analogs via [3+2] cycloaddition of a five-membered mesoionic nucleoside. Although overall yields are modest due to the inherent instability of the cyclic mesoionic template, its cycloadducts are
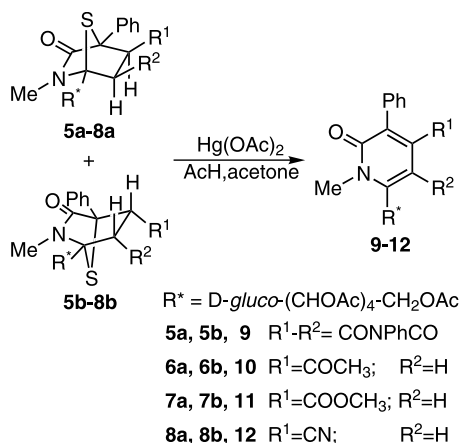
Scheme 3.

obtained as stable and crystalline substances in a few steps. Furthermore, the synthetic utility of this protocol should stimulate numerous ways of further derivatization, including a tunable stereoselectivity.

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8. Compound **4**: yield 63%; mp 65–70°C; $[\alpha]_D$ +128, $[\alpha]_{578}$ +140, $[\alpha]_{546}$ +167 (*c* 0.5, chloroform); ^{1}H NMR (CDCl$_3$) δ 7.90–7.16 (m, 5H, phenyl), 6.30 (d, 1H, *J* = 6.3 Hz, H-1′), 5.69 (dd, 1H, *J* = 4.3, 6.3 Hz, H-2′), 5.34 (dd, 1H, *J* = 4.3, 6.6 Hz, H-3′), 5.02 (m, 1H, H-4′), 4.38 (dd, 1H, *J* = 2.5, 12.7 Hz, H-5′), 4.09 (dd, 1H, *J* = 5.6, 12.7 Hz, H-5″), 3.81 (*N*-CH$_3$), 2.18 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc); ^{13}C NMR (CDCl$_3$) δ 170.7, 169.7, 169.5, 169.3, 169.0, 159.8, 143.6, 132.6, 128.6, 125.7, 124.1, 99.9, 68.9, 68.5, 68.2, 67.1, 61.4, 33.1, 20.6, 20.5, 20.3, 20.2.

9. Typical [3+2] cycloaddition procedure. A solution of **4** (1.0 g, 1.81 mmol) and acrylonitrile (0.14 mL, 2.17 mmol) in dry dichloromethane (15 mL) was heated under reflux for 5 h. The solvent was then evaporated under reduced pressure and the residue subjected to flash chromatography (silica gel, diethyl ether). The resulting oil was further purified by preparative chromatography on silica gel (diethyl ether) to give **8a** and **8b**.
Compound **8a**: mp 95–98°C (dec.); $[\alpha]_D$ +6, $[\alpha]_{578}$ +6, $[\alpha]_{546}$ +6.5 (*c* 0.5, chloroform); ^{1}H NMR (CDCl$_3$) δ 7.47–7.43 (m, 5H, phenyl), 5.77 (d, 1H, *J* = 5.4 Hz, H-1′), 5.60 (t, 1H, *J* = 4.7 Hz, H-2′), 5.44 (dd, 1H, *J* = 4.6, 6.5 Hz, H-3′), 5.13 (m, 1H, H-4′), 4.39 (dd, 1H, *J* = 3.0, 12.6 Hz, H-5′), 4.17 (dd, 1H, *J* = 5.1, 12.6 Hz, H-5″), 3.56 (dd, 1H, *J* = 3.6, 8.0 Hz, H-5), 2.85 (m, 2H, H-6$_{exo}$ and *N*-CH$_3$), 2.74 (dd, 1H, *J* = 3.6, 12.7 H-6$_{endo}$), 2.22 (s, 3H, OAc), 2.18 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.09 (s, 3H, OAc); ^{13}C NMR (CDCl$_3$) δ 173.1, 171.1, 170.7, 170.5, 169.8, 169.3, 130.7, 129.4, 128.8, 128.3, 118.3, 80.1, 69.9, 69.4, 69.1, 67.9, 66.8, 61.7, 42.4, 39.1, 28.5, 20.7, 20.6, 20.5, 20.5. Anal. calcd for C$_{28}$H$_{32}$N$_2$O$_{11}$S: C, 55.62; H, 5.33; N, 4.63; S, 5.30. Found: C, 55.31; H, 5.28; N, 4.64; S, 5.48%.
Compound **8b**: mp 90–95°C (dec.); $[\alpha]_D$ +67.5, $[\alpha]_{578}$ +71.5, $[\alpha]_{546}$ +82 (*c* 0.5, chloroform); ^{1}H NMR (CDCl$_3$) δ 7.48–7.43 (m, 5H, phenyl), 5.82 (d, 1H, *J* = 4.1 Hz, H-1′), 5.46 (t, 1H, *J* = 4.1 Hz, H-2′), 5.41 (dd, 1H, *J* = 4.1, 6.3 Hz, H-3′), 5.14 (m, 1H, H-4′), 4.38 (dd, 1H, *J* = 2.9, 12.5 Hz, H-5′), 4.19 (dd, 1H, *J* = 5.6, 12.5 Hz, H-5″), 3.51 (dd, 1H, *J* = 3.9, 8.1 Hz, H-5), 2.85 (*N*-CH$_3$), 2.80 (m, 2H, H-6$_{exo}$ and H-6$_{endo}$), 2.25 (s, 3H, OAc), 2.18 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.09 (s, 3H, OAc); ^{13}C NMR (CDCl$_3$) δ 172.7, 170.6, 169.8, 169.7, 169.6, 130.8, 129.4, 128.8, 128.2, 118.2, 78.8, 70.2, 69.2, 67.4, 67.0, 61.4, 42.4, 37.9, 28.0, 21.0, 20.8, 20.7, 20.2. Anal. calcd for C$_{28}$H$_{32}$N$_2$O$_{11}$S: C, 55.62; H, 5.33; N, 4.63; S, 5.30. Found: C, 55.33; H, 5.43; N, 4.77; S, 5.22%.

10. This fact was somewhat surprising because previous results have revealed that [3+2] cycloadditions based on mesoionics proceed with a high level of facial diastereoselectivity (see Refs. 4b–d and 4g–i). An explanation of this abnormal behavior will be the subject of a further theoretical analysis.

11. Compound **8a**: orthorhombic, space group $P2_12_12_1$, $a =$ 10.9877(7), $b = 11.9703(8)$, $c = 22.4663(18)$ Å, $V =$ 2954.9(4) Å^3, $Z = 2$, $d_{calcd} = 1.359$ Mg/m^3, θ range for data collection = 3.10–25.02°, index ranges = $-12 \leq h \leq 11$, $-14 \leq k \leq 11$, $-26 \leq l \leq 26$, (Mo K) = 0.172 mm^{-1}. For a total of 13093 collected reflections, 5105 were independent reflections [$R_{int} = 0.2525$]. The final R indices were $R_1 = 0.0848$, $wR_2 = 0.1318$ [$F^2 > 2\sigma(F^2)$], $R_1 = 0.3088$, $wR_2 = 0.1930$ (all data). A final difference map displayed the highest electron density of -0.366 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-14652. Copies of the data can be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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13. Hydrogen sulfide elimination procedure. The latter cycloadducts, either **8a** (0.16 mmol, 0.1 g) or **8b** (0.16 mmol, 0.1 g) were poured into a stirred solution of mercury(II) acetate (0.32 mmol, 0.10 g) in acetic acid (6 mL) and the mixture was stirred at room temperature. Acetone (6 mL) was added to the resulting suspension and stirring was continued for 3 h. The reaction mixture was filtered and diluted with water (6 mL). After adjusting the pH to ∼5 with sodium hydrogen carbonate, the mother liquors were extracted with chloroform (3×6 mL). The organic layers were washed with a 1 M solution of sodium hydrogen carbonate followed by distilled water, then dried over anhydrous magnesium sulfate and concentrated. The residue was purified by preparative chromatography on silica gel (diethyl ether) to give **12** as a white amorphous solid: 40% yield; mp 85–87°C; $[\alpha]_D$ +114, $[\alpha]_{578}$ +123, $[\alpha]_{546}$ +147 (*c* 0.5, chloroform); ^{1}H NMR (CDCl$_3$) δ 7.55–7.44 (m, 5H, phenyl), 6.34 (s, 1H, H-5), 6.06 (d, 1H, *J* = 4.0 Hz, H-1′), 5.57 (t, 1H, *J* = 5.0 Hz, H-2′), 5.45 (t, 1H, *J* = 5.0 Hz, H-3′), 5.06 (m, 1H, H-4′), 4.38 (dd, 1H, *J* = 2.8, 12.5 Hz, H-5′), 4.11 (dd, 1H, *J* = 5.9, 12.5 Hz, H-5″), 3.76 (*N*-CH$_3$), 2.23 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc); ^{13}C NMR (CDCl$_3$) δ 170.7, 169.8, 169.5, 160.9, 144.3, 137.3, 132.6, 129.6, 128.3, 119.2, 116.1, 105.7, 69.6, 69.2, 69.0, 68.2, 61.5, 32.1, 20.6, 20.2. Anal. calcd for C$_{28}$H$_{30}$N$_2$O$_{11}$: C, 58.94; H, 5.30; N, 4.91. Found: C, 58.93; H, 5.27; N, 5.0%.