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TETRAHEDRON: *ASYMMETRY*

A cycloaddition strategy for the synthesis of thiirane-containing glycomimetics

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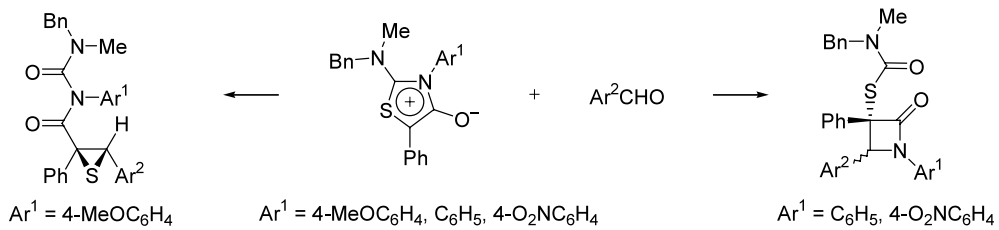
Abstract—This manuscript describes a one-pot, selective synthesis of optically active thiiranes by [3+2] cycloaddition of mesoionic dipoles with sugar aldehydes. Overall, the result is the formation of monosaccharide mimetics that display numerous functional groups for molecular recognition.

There is an ongoing interest in the preparation of structurally modified sugar-containing molecules, collectively denoted 'glycomimetics'.[1] These substances, often inherently chiral, may serve as enzyme inhibitors, drug delivery systems, or as models for receptor binding. Although a strict definition of the term sugar mimetic has not yet been provided, these artificial systems should offer a series of important advantages such as a simplified synthesis, improved stability and selectivity, multivalent functionality and facile access to structurally related libraries.[2]

We have been interested in the synthesis of monosaccharide scaffolds bearing small rings which represent conformationally restricted analogs of their natural counterparts. Our program was triggered by the recent disclosure of a novel dipolar cycloaddition between aromatic aldehydes and mesoionic heterocycles.[3] This strategy leads to either β-lactams or thiiranes depending on the substitution pattern at the heterocyclic ring (Scheme 1).

We envisaged a facile preparation of monosaccharide mimetics by conducting the above-mentioned transformation with sugar aldehydes. Tetra-*O*-acetyl-D-arabinose was chosen for this purpose because we have also observed in previous asymmetric cycloadditions that a *threo* relationship between the first two stereogenic centers of the acyclic carbohydrate chain often results in a greater diastereoselectivity.[4] Accordingly, reactions of **1a**–**1c** with **2** were carried out in refluxing benzene for 1 h. TLC analysis (diethyl ether–*n*-hexane, 5:1) evidenced quantitative conversions of the starting materials and the formation of up to four products, which could be separated by flash chromatography and/or preparative thin-layer chromatography (Scheme 2). The overall yields of isolated, diastereomerically pure products lie in the range 45–50%.[5]



Scheme 1.

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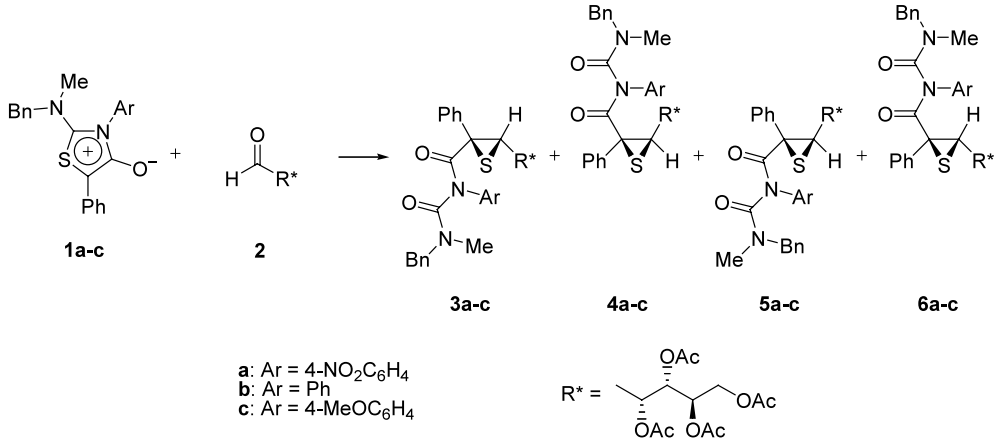
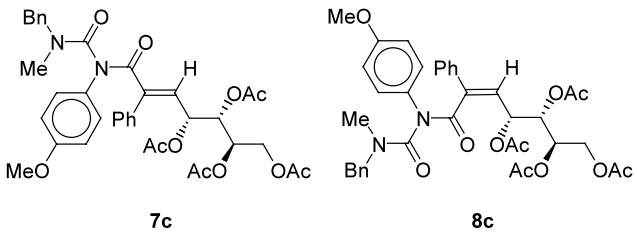


Scheme 2.

At first glance, their spectroscopic data were inconsistent with a structure of β-lactam or that of the intermediate cycloadduct, but they most likely agreed with a thiirane nucleus. Fortunately, suitable crystals for single-crystal X-ray analysis were obtained in the cases of **3b** and **5c**, thereby unequivocally revealing the existence of the three-membered ring (Fig. 1).[6] In the former (monoclinic, space group $P2_1$), the phenyl group adopts a *trans* relationship with respect to the sugar moiety, whereas both groups are *cis* in the latter compound, which belongs to the rather unusual space group $P6_1$ and has a 67 Å axis.[7] Moreover, the four diastereomers in each series exhibit notable chemical shift differences which also enable the assignment of their configuration.

Thiiranes **3**–**6** arise from *exo* and *endo* approaches of the chiral aldehyde to both faces of the mesoionic dipole as depicted in Scheme 3. In all cases, low diastereoselectivity was observed with an almost equal distribution of thiiranes **3**–**6** in the crude mixtures. The structural features of such thiiranes are also supported by the exclusive formation of the alkenes **7c** and **8c** from mixtures of **3c** and **4c**, and **5c** and **6c**, respectively. The alkene **8a** (Ar = 4-$NO_2C_6H_4$) could also be isolated in low yield from the reaction mixture containing **1a** and **2**. It should be pointed out that an (*E*)-configured alkenes adjacent to a stereogenic center is the structural motif encountered in sphingolipids. Sphingosine itself is believed to be the biomimetic precursor of a three-membered marine antibiotic, dysidazirine.[8]



The absence of β-lactam products could be rationalized on the basis of the mechanistic hypothesis outlined in Scheme 4. The reversible cleavage of the initial cycloadduct (i.e. **9**) can lead to the zwitterionic intermediates **10** and **11**. In this case, the presence of the sugar moiety

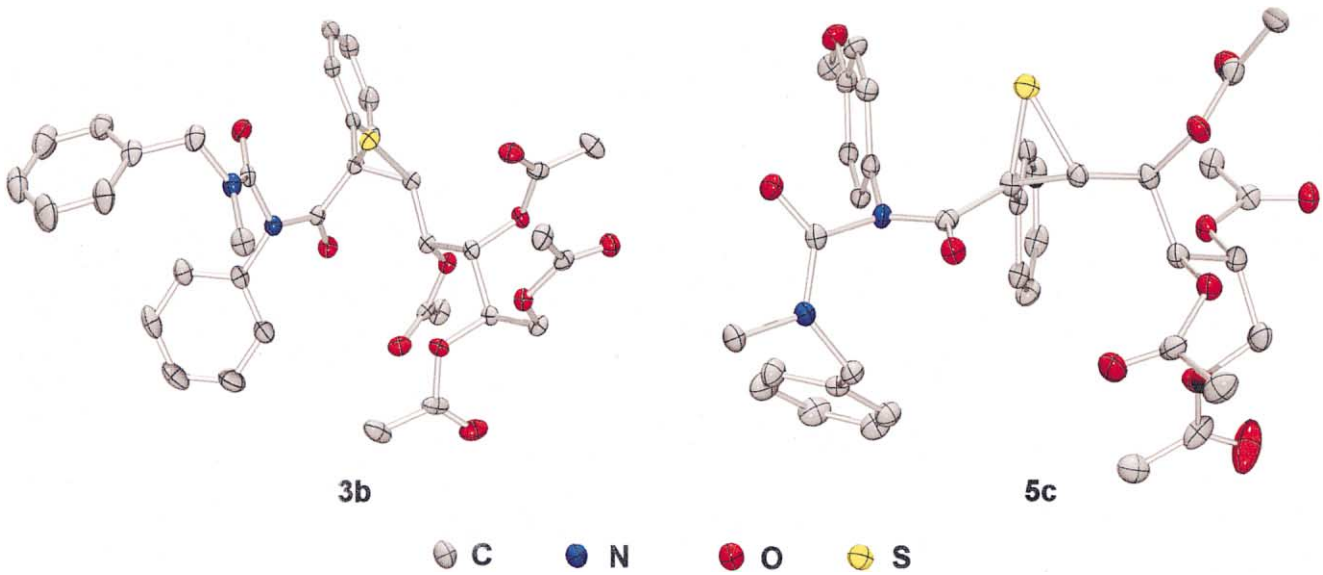
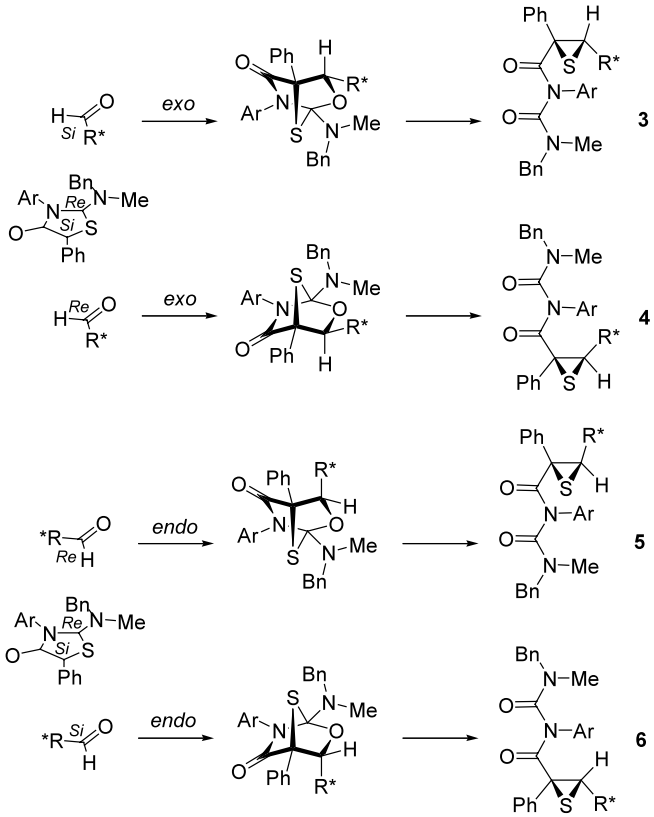


Figure 1. Solid-state, X-ray crystallographic diagrams for compounds **3b** and **5c**.



Scheme 3.

(R*) should make attack of the vicinal thiolate to form the thiirane more feasible (rather than attack of the distant nitrogen atom to form the lactam). From the viewpoint of the facial selection, one would also expect that the sugar moiety had prevented the *endo* attack to any face of the heterocyclic dipole, thus affording selectively thiiranes **3** and **4** (Scheme 3, vide supra), a fact that disagrees with the experimental results encountered so far. The low diastereoselection suggests that steric effects cannot solely be invoked and computational studies currently in progress will be required to account for the nature of the transition structures.

In conclusion, the present paper describes a concise and selective approach to densely functionalized carbohydrate thiiranes. This concept will be extended to oligosaccharide analogs with mixed carbohydrate configurations, including the possibility of combinatorial applications.

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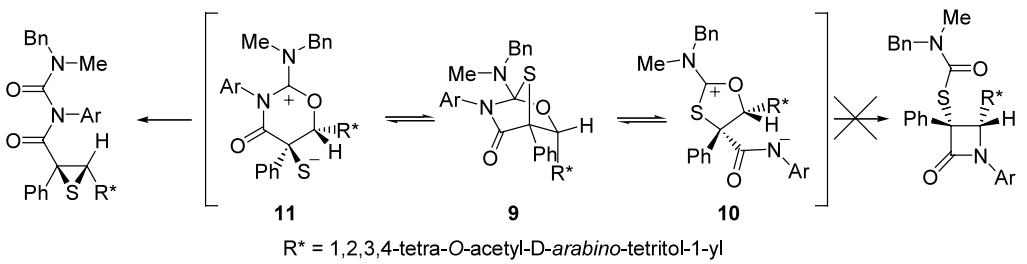
References

1. (a) *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: New York, 1998; (b) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2300–2324.
2. (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2754–2794; (b) Strong, L. E.; Kiessling, L. L. *J. Am. Chem. Soc.* **1999**, *121*, 6193–6196; (c) Turnbull, W. B.; Pease, A. R.; Fraser Stoddart, J. *ChemBioChem* **2000**, *1*, 70–74; (d) Patel, A.; Lindhorst, Th. K. *J. Org. Chem.* **2001**, *66*, 2674–2680.
3. Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Chem. Eur. J.* **2001**, *7*, 3033–3042.
4. (a) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **1996**, *61*, 3738–3748; (b) Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1999**, *64*, 1494–1502; (c) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Jiménez, J. L.; Palacios, J. C.; Sánchez, J. B. *J. Org. Chem.* **1999**, *64*, 6297–6305; (d) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Chem. Eur. J.* **2000**, *6*, 267–277; (e) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C.; Raithby, P. R. *J. Org. Chem.* **2000**, *65*, 5089–5097; (f) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 5139–5145.
5. **Synthesis of 3-(tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-2-(2-aryl-4-benzyl-1,3-dioxo-2,4-diazapentyl)-2-phenylthiirane**. Cycloaddition reaction of **1c** with aldehyde **2**. To a suspension of **1c** (0.51 g, 1.25 mmol) in benzene (20 mL) was added **2** (0.40 g, 1.25 mmol). The reaction mixture was stirred under reflux until the complete disappearance of **1c** (1 h). Compounds **3c**, **4c**, **5c** and **6c** were obtained after separation by preparative TLC (diethyl ether–hexane 5:1) and crystallized from diethyl ether–hexane as colorless



R* = 1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl

Scheme 4.

solids. Diastereomeric mixture of **3c** and **4c** (ratio 1:1.3): ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.81 (d, $J=7.6$ Hz, 2H, Ar **3c**), 7.64 (bs, 2H, Ar **4c**), 7.24 (d, $J=8.8$, 2H, Ar **3c**), 7.10–6.98 (m, 18H, Ar), 6.62 (d, $J=9.0$ Hz, 2H, Ar **3c**), 6.55 (d, $J=8.5$ Hz, 2H, Ar **4c**), 6.42, (dd, $J=8.1$, $J=4$ Hz, 1H, H2′ **4c**), 5.82 (m, 2H, H2′ **3c** and H1′ **4c**), 5.48 (dd, $J=9.5$, $J=2.5$ Hz, 1H, H1′ **3c**), 5.41 (m, 1H, H3′ **4c**), 5.31 (m, 1H, H3′ **3c**), 4.47 (dd, $J=12.4$, $J=2.7$ Hz, 1H, H4′ **3c**), 4,38 (m, 5H, NCH_2 and H4′ **4c**), 4.26 (dd, $J=12.6$, $J=5.2$, 1H, H4″ **3c**), 4.18 (dd, $J=12.3$, $J=5.8$ Hz, 1H, H4″ **4c**), 3.37 (d, $J=9.5$ Hz, 1H, H3 **3c**), 3.30 (bs, 6H, OCH_3), 3.10 (d, $J=8.8$ Hz, 1H, H3 **4c**), 2.78 (bs, 3H, NCH_3 **4c**), 2.64 (s, 3H, NCH_3 **3c**), 2.02 (s, 3H, CH_3CO **3c**), 1.85–1.59 (m, 21H, CH_3CO); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.7, 170.5, 170.4, 170.3, 170.1, 169.9, 169.4 (CH_3CO), 160.6, 160.3 (Ar), 157.9, 157.2 (NCON), 140.0, 138.3, 137.5, 132.1, 131.7, 130.9, 130.6, 130.0, 129.7, 129.5, 129.3, 129.1, 129.0, 128.5, 128.4, 115.4, 115.2 (Ar), 74.1 (C1′ **3c**), 73.3 (C1′ **4c**), 73.0 (C2′ **3c**), 71.2 (C3′ **3c**), 70.7 (C3′ **4c**), 63.4 (C4′ **4c**), 62.8 (C4′ **3c**), 56.6 (C2 **4c**), 56.2 (C2 **3c**), 55.8 (OCH_3), 54.5 (NCH_2), 46.5 (C3 **3c**), 45.5 (C3 **4c**), 35.9 (NCH_3), 21.5, 21.4, 21.3, 21.2, 21.0, 20.9, 20.6 (CH_3CO). Anal. calcd for $C_{37}H_{40}N_2O_{11}S$: C, 61.65; H, 5.59; N, 3.88; S, 4.44. Found: C, 61.44; H, 5.62; N, 3.51; S, 4.01. **Compound 5c**: mp 140°C; $[\alpha]_D=+110.1$ (c 1.2, $CHCl_3$); IR (KBr) ν_{max} 2940, 1740, 1670 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.48 (bs, 2H, Ar), 7.12–6.95 (m, 10H, Ar), 6.44 (d, $J=8.5$ Hz, 2H, Ar), 5.19 (dd, $J=8.9$, $J=1.7$ Hz, 1H, H2′), 5.08 (m, 1H, H3′), 4.69 (dd, $J=9.5$, $J=1.8$ Hz, 1H, H1′), 4.40 (d, $J=9.7$ Hz, 1H, H3), 4.32 (bs, 2H, NCH_2), 4.17 (dd, $J=12.4$, $J=2.3$ Hz, 1H, H4′), 3.93 (dd, $J=12.4$, $J=5.1$ Hz, 1H, H4″), 3.32 (s, 3H, OCH_3), 2.63 (bs, 3H, NCH_3), 2.05 (s, 3H, CH_3CO), 1.79 (s, 3H, CH_3CO), 1.75 (s, 3H, CH_3CO), 1.61 (s, 3H, CH_3CO); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.2, 169.8, 169.6 CH_3CO), 160.4 (Ar), 156.7 (NCON), 137.7, 134.0, 131.5, 130.7, 129.9, 129.5, 129.2, 129.1, 129.0, 128.4, 115.0 (Ar), 72.2 (C1′), 70.6 (C2′), 69.5 (C3′), 62.9 (C4′), 55.8 (OCH_3), 54.2 (NCH_2), 54.0 (C2), 44.8 (C3), 35.4 (NCH_3), 21.0, 20.9 (CH_3CO). Anal. calcd for $C_{37}H_{40}N_2O_{11}S$: C, 61.65; H, 5.59; N, 3.88; S, 4.44. Found: C, 61.79; H, 5.34; N, 3.66; S, 4.19%. **Compound 6c**: mp 69.2°C; $[\alpha]_D=-88.3$ (c 0.4, $CHCl_3$); IR (KBr) ν_{max} 1740, 1680 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.20–6.93 (m, 12H, Ar), 6.46 (d, 2H, $J=8.6$ Hz, 2H, Ar), 5.59 (dd, $J=8.1$, $J=2.6$ Hz, 1H, H2′), 5.07 (m, 1H, H3′), 4.47 (dd, $J=9.5$, $J=2.4$ Hz, 1H, H1′), 4.32 (m, 4H, NCH_2, H3 and H4′), 4.13 (dd, $J=12.4$, $J=5.0$ Hz, 1H, H4″), 3.35 (s, 3H, OCH_3), 2.62 (s, 3H, NCH_3), 1.78 (s, 3H, CH_3CO), 1.74 (s, 3H, CH_3CO), 1.68 (s, 3H, CH_3CO), 1.64 (s, 3H, CH_3CO); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.2, 170.0, 168.3 (CH_3CO), 160.5 (Ar), 155.2 (NCON), 137.7, 133.8, 131.5, 130.1, 129.6, 129.3, 129.1, 128.9, 128.4, 115.1 (Ar), 72.9 (C2′), 72.1 (C1′), 70.4 (C3′), 62.7 (C4′), 55.9 (OCH_3), 54.3 (C2), 54.1 (NCH_2), 43.4 (C3), 35.3 (NCH_3), 21.1, 20.8, 20.7 (CH_3CO). Anal. calcd for $C_{37}H_{40}N_2O_{11}S$: C, 61.65; H, 5.59; N, 3.88; S, 4.44. Found: C, 61.14; H, 5.35; N, 3.25; S, 4.30%.

6. ORTEP-3 was used to generate Fig. 1: Farrugia, L. J. *J. Appl. Cryst*. **1997**, *30*, 565.
7. Crystallographic data for compounds **3b** and **5c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications with registry numbers CCDC 162508 and CCDC 143673, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
8. Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc*. **1995**, *117*, 3651–3652.