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TETRAHEDRON: *ASYMMETRY*

Carbohydrates as chiral controllers: synthesis of dihydrothieno[2,3-*c*]furanones

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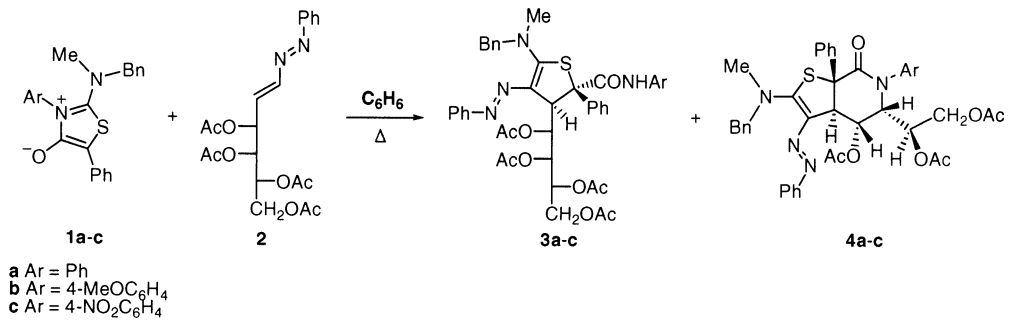
Abstract—Chiral dihydrothiophenes derived from carbohydrates can be transformed into a novel class of bicyclic and highly functionalized chirons by treatment with NaH. A mechanistic rationale is proposed which is consistent with experimental observations and demonstrates the stereodiscriminating properties exerted by carbohydrate chains with different configurations.

Diastereoselective reactions based on carbohydrates constitute a convenient and versatile approach to optically active substances. Because of the abundance and varied functionality of the carbohydrate chiral pool, carbohydrates are increasingly being exploited as a highly diverse source of chirons for asymmetric synthesis.[1] A common way of integrating chirality into molecular targets is by carrying out transformations on a chiral core. However, acyclic sugar templates are sterically unbiased systems due to their greater conformational flexibility, a fact that often hampers highly stereoselective transformations. In a series of recent papers we have investigated in detail the stereochemical issues of cycloaddition reactions involving dipolar heterocycles (**1a**–**1c**) with unsaturated carbohydrates, generated in a few steps from commercially available precursors.[2,3] When mesoionic compounds **1** were combined with the chiral 1,2-diaza-1-3-butadiene **2**, we were able to isolate not only the expected 1,2-dihydrothiophenes **3a**–**3c** as major isomers, but also dihydrothieno[2,3-*c*]piperidines **4a**–**4c**.[3b] The latter substances are especially interesting as they constitute *trans*-fused bicyclic ring systems with several reactive functional groups (Scheme 1).



Scheme 1.

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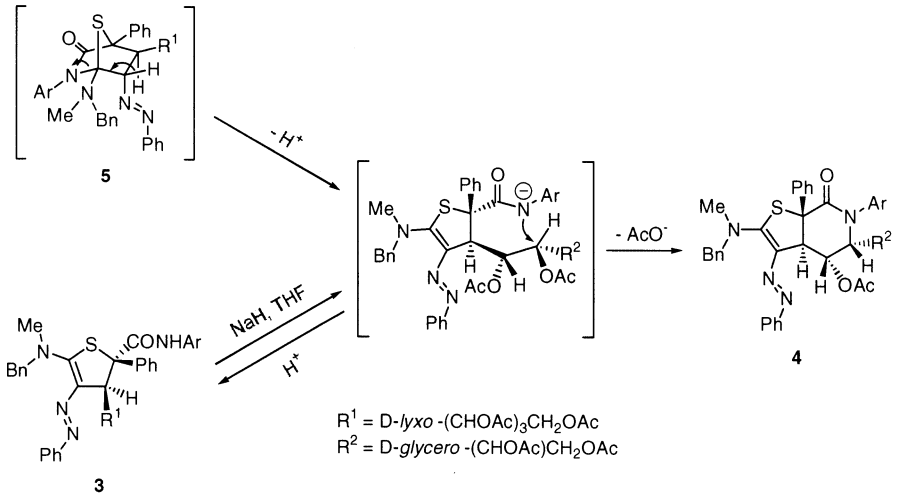
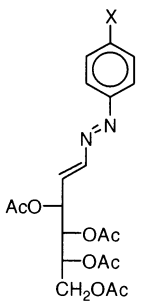


Scheme 2.

Like **3a**–**3c**, compounds **4a**–**4c** arise from the same intermediate cycloadducts **5** as depicted in Scheme 2. Moreover, compound **4a** was also obtained by treatment of **3a** with NaH in dry THF. This represents a novel access to these complex structures, which have also been obtained by alternative photochemical protocols.[4]



Assuming that the carbohydrate moiety with D-*lyxo* configuration should have a stereodifferentiating influence, next we decided to investigate the role exerted by an acyclic chain of D-*arabino* configuration. With this aim, the [3+2] cycloaddition reaction of heterocycles **1** with 1,2-diaza-1,3-butadienes **6** afforded the corresponding dihydrothiophenes **7a**–**7g**,[3a] which were then reacted with NaH in THF. In general, these transformations yielded complex reaction mixtures although a series of substances exhibiting a chromatographic behavior equivalent to that of **4a**–**4c** could be separated and isolated as crystalline materials. To our surprise, the spectroscopic and analytical data of these products did not match with those expected for dihydrothieno[2,3-*c*]piperidines. Fortunately, the structure of compound **8a** could be solved by X-ray crystallographic analysis (Fig. 1),[5] thereby unequivocally revealing that the structure possessed a *cis*-fused dihydrothieno[2,3-*c*]furanone skeleton.[6]

An electron-withdrawing group located at the amide group ($Ar^1 = 4\text{-}NO_2C_6H_4$) led to faster reactions and higher yields. This is consistent with the mechanistic pathway outlined in Scheme 3 in which the initial proton abstraction affords an anionic intermediate, which is stabilized by an electron-deficient substituent. In the reaction with **7a**, amide **9a** could also be isolated, an argument that validates the rationale for Scheme 3. The stereochemical switching observed in the case of dihydrothiophenes **7**, with respect to compounds **3**, is attributed to a different configurational disposition of the acyclic sugar chains. A D-*lyxo* configuration enables attack of the anionic center to the second stereogenic carbon atom with concomitant displacement of an acetate group, thereby leading to a six-membered ring, while for compounds **7** only the carbonyl group attached to the first stereocenter is sterically accessible.

In conclusion, we have described the preparation of a series of novel chirons **8**, which are susceptible to further functionalization and which should also be suited to asymmetric transformations. Further optimization of the reaction conditions and studies on the applications of compounds **8** are currently under way in our laboratories.

Acknowledgements

Financial support from the *Dirección de Investigación Científica y Técnica* (Projects No. PB98-0997 and BQU2000-0248) and the *Junta de Extremadura–Fondo Social Europeo* (Projects IPR98-A064 and IPR98-A065) is gratefully acknowledged. R.G. thanks the *Junta de Extremadura-Fondo Social Europeo* for a predoctoral fellowship.

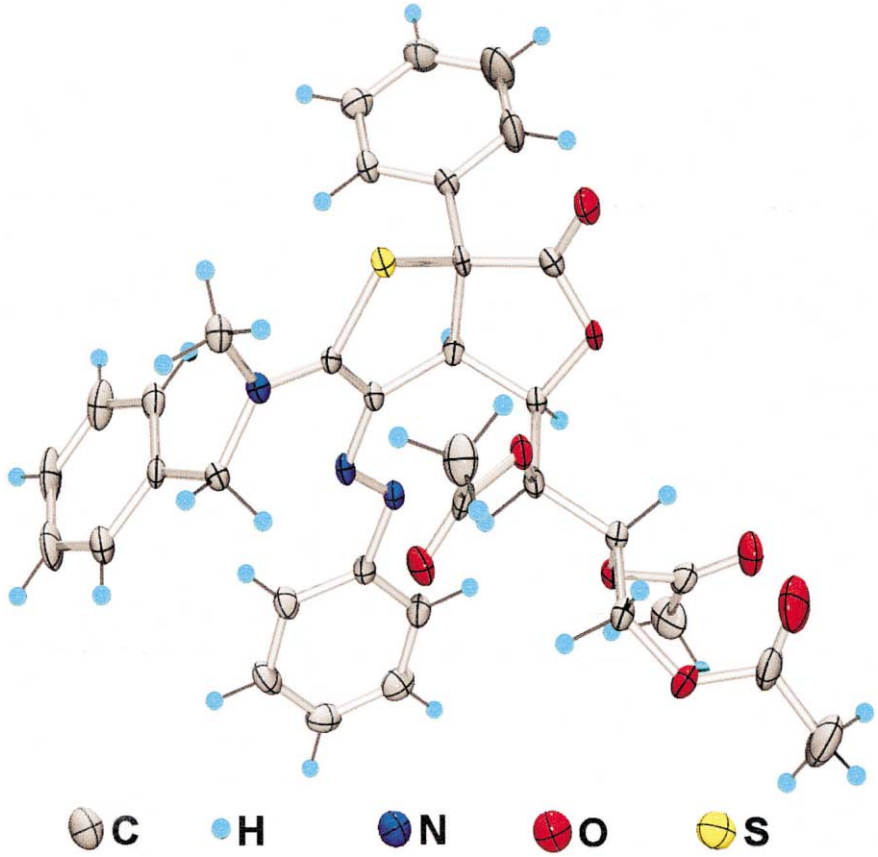
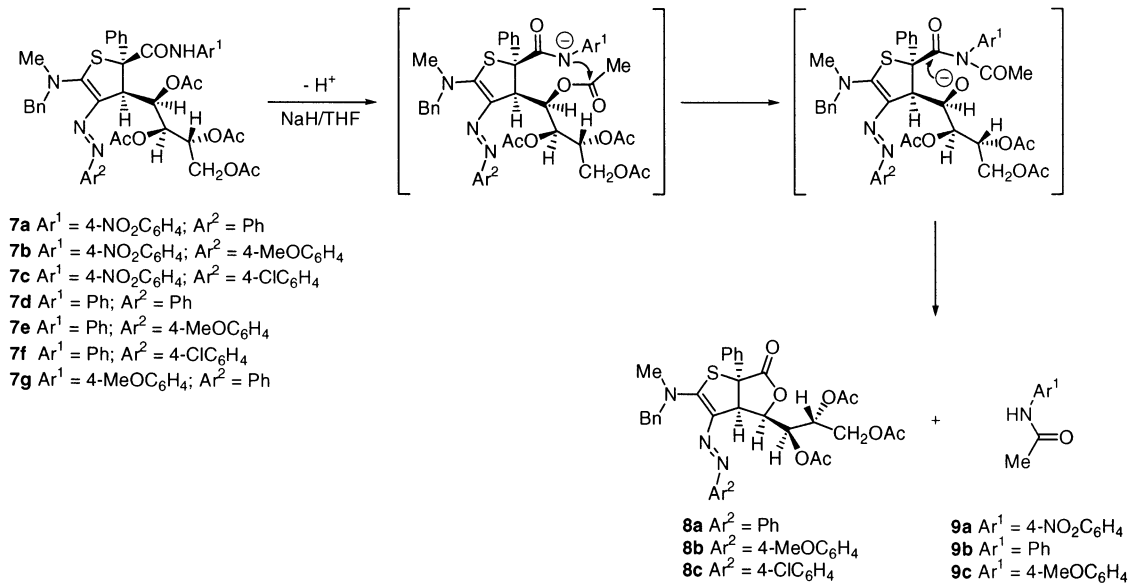


Figure 1. X-Ray molecular structure of **8a**.



Scheme 3.

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5. Crystallographic data for compound **8a**: orthorhombic, space group $P2_12_12_1$, $a=10.43450(10)$, $b=12.6233(2)$, $c=24.7141(4)$ Å, $V=3255.29(8)$ Å^3, $Z=4$, $\rho_{calc}=1.342$ Mg/m^3, θ range for data collection $=2.95$–$25.03°$, index ranges $=-11\leq h\leq 12$, $-15\leq k\leq 14$, $-28\leq l\leq 29$, μ(Mo Kα)$=0.157$ mm^{-1}. From a total of 18597 collected reflections, 5725 were independent reflections [$R_{int}=0.0959$]. The final R indices were $R_1=0.0514$, $wR_2=0.1281$ [$F^2>2\sigma(F^2)$], $R_1=0.0671$, $wR_2=0.1366$ (all data). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC–149094. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
6. Synthetic procedure for (3a*R*,4*R*,6a*S*)-4-(1′,2′,3′-tri-*O*-acetyl-D-*erythro*–tritol-1-yl)-3-[(1*E*)-(4-chlorophenyl)azo]-2-(*N*-methyl)benzylamino-6a-phenyl-3a*H*,4*H*,6a*H*-thieno[2,3-*c*]furan-6-one **8c**: To a suspension of NaH (5.4 mmol) in dry THF (8.0 mL) was added **7c**[3a] (0.787 g, 0.9 mmol) and the reaction mixture was stirred during 40 min. TLC analysis (diethyl ether) revealed the appearance of compound **8c** (R_f 0.7) and other unidentified side compounds. Compound **8c** was purified by preparative TLC (diethyl ether) and crystallized from diethyl ether–hexane as an orange solid (0.203 g, 32.5%). Mp 135°C; $[\alpha]_{578}=-1365.4$ (*c* 1.1 $CHCl_3$); IR (KBr) 3477, 3364, 3063, 1770, 1560 cm^{-1}, ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, $J=1.5$ Hz, Ar-H), 7.42–7.14 (m, 12H, Ar-H), 5.29 (dd, $J=9.4$ Hz, $J=0.8$ Hz, 1H, H4), 5.23 (m, 2H, H2′ and N-CHa), 4.99 (d, $J=9.2$ Hz, 1H, H3a), 4.91 (d, $J=5.3$ Hz, 1H, H1′), 4.57 (d, $J=15.7$ Hz, 1H, N-CHb), 4.27 (dd, $J=12.2$, $J=3.7$ Hz, 1H, H3′), 4.08 (dd, $J=12.1$, $J=6.8$ Hz, 1H, H3″), 3.36 (s, 3H, N-CH_3), 2.12 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.86 (s, 3H, OAc); ^{13}CNMR (100 MHz, $CDCl_3$): δ 174.1 (C6), 170.4, 169.7, 169.1, (*C*OCH_3), 158.7 (C2), 152.2 (C3), 139.9, 135.9, 132.0, 129.1, 128.8, 128.6, 127.9, 127.1, 125.7, 125.1, 122.2 (Ar), 78.9 (C4), 70.6 (C2′), 70.1 (C1′), 61.6 (C3′), 61.0 (N-CH_2), 60.1 (C6a), 56.8 (C3a), 43.1 (N-CH_3), 20.8, 20.7, 20.4 (CO*C*H_3). Anal. calcd for $C_{35}H_{34}ClN_3O_8S$: C, 60.73; H, 4.95; N, 6.07; S, 4.63. Found: C, 61.12; H, 4.99; N, 6.29; S, 4.85%.