A Stereoselective Hetero-Diels–Alder Approach to Carbon–Carbon Linked Disaccharides

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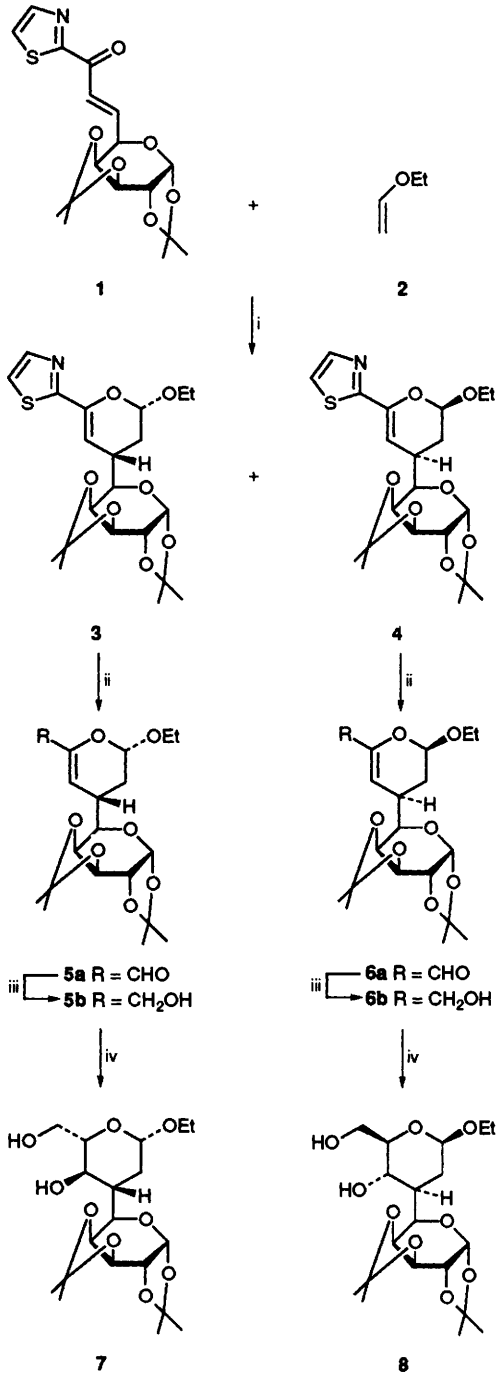
The chiral 1-oxabuta-1,3-diene **1** bearing the thiazol-2-yl ring at C-2 and the D-*galacto*-pentopyranosid-5-yl ring at C-4 reacts with ethyl vinyl ether **2** in an endo-specific hetero-Diels–Alder process to give a mixture of diastereoisomeric 3,4-dihydro-2*H*-pyran derivatives **3** and **4** in 4 : 1 ratio and 97% overall yield; these compounds are transformed by thiazole-to-formyl unmasking and hydroxylation into stereoisomeric C-3–C-5 linked dipyranosides **7** and **8**.

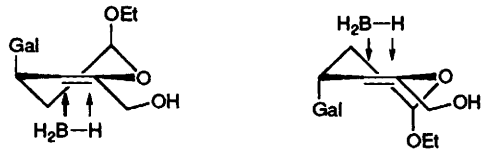
Because of the potential inhibitory activity of various carbohydrate-based biological processes,[1] pseudodisaccharides are the targets of considerable synthetic efforts. In addition to genuine *C*-disaccharides[2] in which the interglycosidic oxygen atom that is present in natural products has been replaced by a methylene group, other types of carbon-linked disaccharides having different spacers between the two aldose rings have been described.[3] Attention has been given in two instances only,[4] to the best of our knowledge, to the synthesis of disaccharides containing no spacer, *i.e.* compounds wherein the two aldose rings are directly joined by a carbon–carbon bond. We report here our approach to this class of compounds employing an asymmetric hetero-Diels–Alder reaction (HDA)[5] of a vinyl ether with a pyranosidyl substituted oxadiene.[6]

To approach rapid construction of a newly emerging pyranose from C-5 of an existing pyranose we considered the readily available[7] chiral 1-oxabuta-1,3-diene **1** bearing the thiazol-2-yl ring at C-2 and the D-*galacto*-pentopyranosid-5-yl moiety at C-4. Successful asymmetric cycloaddition reaction of this heterodiene with an alkoxylated alkene would produce a functionalized dihydropyran suitable for elaboration into the second aldose. The thiazole ring ensured a conveniently masked formyl group[8] that could be eventually employed for further elaboration of the final product. Hence, reaction of oxabutadiene **1** (17 mmol) with neat ethyl vinyl ether **2** (35 ml) in sealed tube at 80 °C afforded, after 5 days, a mixture of diastereoisomeric 3,4-dihydro-2*H*-pyran derivatives **3** and **4** in 4 : 1 ratio and 97% overall yield (Scheme 1). In the presence of lithium perchlorate[9] (1 equiv.) the reaction was completed after 18 h at room temp. to give, however, cycloadducts **3** and **4** in 1 : 1 ratio, although in almost quantitative overall yield. Flash column chromatography [SiO_2, light petrol (40–60)–diethyl ether 4 : 1] of the reaction mixture afforded the individual products† **3** and **4**. The structure and stereochemistry of the cycloadduct **4** were directly defined by X-ray crystallographic analysis.[10] On the other hand, the *cis*-stereochemical relationship between the ethoxy and the D-*galacto*-pentopyranosid-5-yl and the absolute configurations at the newly formed stereocentres in the isomer **3** were deduced from the structure (confirmed later on by X-ray crystallographic analysis[10]) of a compound derived from it.‡ It is thus seen that the topology of the cycloaddition reaction is endo specific and that, in the absence of lithium perchlorate, its diastereofacial selectivity leading to **3** as major product indicates attack by the vinyl ether **2** to the oxabutadiene **1** face opposite to the plane of the pyranose ring. The preference of **1** for the reactive conformation shown in Scheme 1 has been already noticed in conjugate addition reaction.[7]

Hydroxylation of 3,4-dihydro-2*H*-pyran derivatives **3** and **4** by either hydroboration of the double bond with $BH_3{\cdot}SMe_2$ or $BH_3{\cdot}THF$ complexes or addition of benzyl oxide anion was unsuccessful. Hence elaboration of these compounds by conversion of the thiazole ring into the formyl group was considered. The combination of the original[8] and improved[11] one-pot deblocking protocol afforded the corresponding formyl substituted dihydropyrans **5a** (92%) and **6a** (90%), thus showing that the cleavage of the thiazole ring of compounds **3** and **4** occurs without concomitant reduction of the adjacent carbon–carbon double bond. In a similar way, treatment of both **5a** and **6a** with $NaBH_4$ led to the exclusive



Scheme 1 *Reagents and conditions*: i, neat reagents in sealed tube, 80 °C, 5 days; ii, $CF_3SO_3CH_3$, CH_3CN, room temp. 10 min, then $NaBH_4$, MeOH, 0 °C, 30 min, then $HgCl_2$, CH_3CN–H_2O, room temp, 15 min; iii, $NaBH_4$, MeOH, room temp. 15 min; iv, BH_3THF, THF, room temp. 18 h then H_2O_2 and NaOH, 60 °C, 1 h



5b **6b**

Fig. 1 (Gal = D-*galacto*-pentopyranosid-5-yl)

reduction of the formyl group giving rise to C-6 hydroxymethyl substituted dihydropyrans **5b** (89%) and **6b** (91%). Thus, the remaining carbon–carbon double bond of these compounds was available for *cis*-specific borane addition using the BH_3·THF complex and subsequent hydroxy group introduction with hydrogen peroxide, providing dipyranosides **7** and **8**, wherein L- and D-antipode 2,3-dideoxy-*ribo*-hexopyranosid-3-yl rings are diastereospecifically installed at C-5 of a D-*galacto*-pentopyranosidyl moiety. As shown in Fig. 1, due to anomeric effect and allylic strain, one conformer is preferred in both compounds **5b** and **6b**, which is diastereospecifically attacked by the borane reagent from the less hindered side.

In summary we have developed a stereoselective inverse-type hetero-Diels–Alder approach to a class of unnatural disaccharides. This synthetic strategy suggests extensions to other 1-oxabuta-1,3-dienes bearing different pyranosidyl or furanosidyl moieties as well as other electron-rich dienophiles.

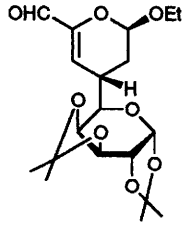
We thank the Commission of European Economic Communities, Bruxelles, for a fellowship to L. K. (COST program). Financial support from the CNR, Rome, Progetto Finalizzato 'Chimica Fine II' and Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Italy, is gratefully acknowledged.

Received, 20th May 1994; Com. 4/03015J

Footnotes

† All new compounds exhibited consistent spectral (^1H and ^{13}C NMR, IR) and analytical data. Optical rotations were measured at *ca.* 20 °C in $CHCl_3$ and are given in units of 10^{-1} deg cm^2 g^{-1}; ^1H NMR spectra were measured at 300 MHz in $CDCl_3$ at 25 °C; *J* values given in Hz. *Selected data*: **3**: oil, $[\alpha]_D$ = −82.0 (*c* 2.72). **4**: mp 158–160 °C (diethyl ether), $[\alpha]_D$ = −77.4 (*c* 0.52). **5a**: oil, $[\alpha]_D$ = −64.4 (*c* 0.63). **6a**: oil, $[\alpha]_D$ = −39.0 (*c* 1.1). **7**: 70%, oil, $[\alpha]_D$ = −29.1 (*c* 0.7), selected ^1H NMR (pyran numbering) δ 1.21 (t, 3H, *J* 7.0), 1.39–1.45 (m, 1H, H_{3ax}), 1.99 (dddd, 1H, *J* 12.4, 10.5, 6.6, 4.1, H_4), 2.26 (ddd, 1H, *J* 13.2, 4.4, 2.0, H_{3eq}), 2.42 (bt, 1H, *J* 5.5 O*H*), 3.26 (d, 1H, *J* 4.4, O*H*), 3.31 (ddd, 1H, *J* 9.2, 4.9, 4.0, H_6), 3.34 (dq, 1H, *J* 9.3, 7.0), 3.56 (ddd, 1H, *J* 10.5, 9.2, 4.4, H_5), 3.78 (m, 1H), 3.90 (m, 1H), 3.91 (dq, 1H, *J* 9.3, 7.0), 4.56 (dd, 1H, *J* 9.0 2.0, H_2). **8**: 64%, mp 114–116 °C, $[\alpha]_D$ = −82.8 (*c* 0.62), selected ^1H NMR (pyran numbering) δ 1.23 (t, 3H, *J* 7.1), 1.23–1.30 (m, 1H, H_{3ax}), 2.02 (ddd, 1H, *J* 12.7, 4.5, 2.1, H_{3eq}), 2.14 (dddd, 1H, *J* 12.7, 9.2, 9.1, 4.5, H_4), 2.32 (dd, 1H, *J* 6.9, 6.2, O*H*), 3.38 (ddd, 1H, *J* 9.4, 5.4, 4.2, H_6), 3.50 (dd, 1H, *J* 9.4, 9.1, H_5), 3.56 (dq, 1H, *J* 9.4 7.1), 3.77 (ddd, 1H, *J* 11.5, 6.9, 5.4), 3.93 (ddd, 1H, *J* 11.5, 6.2, 4.2), 3.96 (dq, 1H, *J* 9.4, 7.1), 4.15 (s, 1H, O*H*), 4.63 (dd, 1H, *J* 9.7, 2.1, H_2).

‡ As shown below, this compound **9**, mp 163–164 °C (diethyl ether), $[\alpha]_D$ = −253.5 (*c* 0.51) is the epimer at C-2 of the aldehyde **5a**; it formed from **3** as a side product of **5a** when the formyl group unmasking was carried out by the original protocol (ref. 8) employing MeI in refluxing MeCN (12 h) for the methylation of the thiazole ring. This anomerization is very likely due to traces of acetic acid present in the solvent.



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References

1 J. F. Kennedy and C. A. White, *Bioactive Carbohydrates in Chemistry, Biochemistry and Biology*, Wiley, New York, 1983; I. Tvaroska and T. Bleha, *Adv. Carbohydr. Chem. Biochem.*, 1989, **47**, 45.
2 D. Rouzaud and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1983, 1353; Y. C. Xin, J.-M. Mallet and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1993, 864; L. Lay, F. Nicotra, C. Pangrazio, L. Panza and G. Russo, *J. Chem. Soc., Perkin Trans. 1*, 1994, 333.
3 O. R. Martin and W. Lai, *J. Org. Chem.*, 1993, **58**, 176 and refs. therein.
4 S. J. Danishefsky, C. J. Maring, M. R. Barbachyn and B. E. Segmuller, *J. Org. Chem.*, 1984, **49**, 4564; R. W. Armstrong and B. R. Teegarden, *J. Org. Chem.*, 1992, **57**, 915.
5 Reviews: G. Helmchen, R. Karge and J. Weetman, in *Modern Synthetic Methods*, ed. R. Scheffold, Springer, Berlin, 1986, vol. 4, pp. 261–306; D. L. Boger and S. N. Weinreb, *Hetero-Diels–Alder Methodology in Organic Synthesis*, Academic, London, 1987.
6 For oxadiene-based HDA approaches to monosaccharides, see: R. R. Schmidt, *Acc. Chem. Res.*, 1986, **19**, 250; D. L. Boger and K. D. Robarge, *J. Org. Chem.*, 1988, **53**, 5793; L. F. Tietze, *J. Heterocyclic Chem.*, 1990, **27**, 47.
7 A. Dondoni, S. Ianelli, L. Kniezo, P. Merino and M. Nardelli, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1231.
8 A. Dondoni, in *Modern Synthetic Methods*; ed. R. Scheffold, Verlag Helvetica Chimica Acta, Basel, 1992, vol. 6, pp. 377–437.
9 H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1306.
10 M. Nardelli, Università di Parma, personal communication.
11 A. Dondoni, A. Marra and D. Perrone, *J. Org. Chem.*, 1993, **58**, 275.