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# Intramolecular Diels-Alder Reactions on Pyranose Trienes. Stereoselective Access to bis-Annulated Pyranosides.

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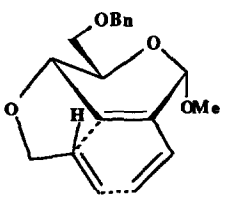
*Intramolecular Diels-Alder reactions on pyranose trienes furnished stereoselectively bis-annulated pyranosides with good yields.*

Since the pioneering report by David et al[1] on the diastereoselectivity in the intermolecular Diels-Alder reaction of carbohydrate derived dienes, considerable attention to sugar-based Diels-Alder reactions has been devoted[2]. As a result of this effort, a great deal of predictability on the stereoselection in intermolecular cycloaddition reactions in carbohydrate substrates has been achieved. Surprisingly, the intramolecular variation of the Diels Alder reaction (IMDA)[3] in these substrates has remained virtually inexplored. To the best of our knowledge, only one report by Fraser-Reid's group[4] on IMDA of furanose trienes and a more recent one by Herczegh, Bognar et al.[5] on acyclic trienes are known in this area. The promising results obtained (complete stereoselectivity in both cases) appeared to indicate that further research in this area should be of value. In this context and as part of a program[2g,6] aimed at extending the scope of carbohydrates as chirons[7] for the synthesis of natural products via annulated pyranosides, we report in this communication our preliminary results concerning the scope and limitations of IMDA from readily available pyranose-trienes. Another approach has recently been used for the synthesis of bis-annulated pyranosides[8].

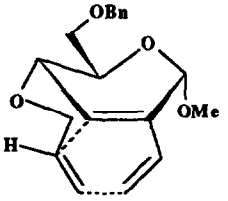
Compounds **1b** and **2b** were chosen for our studies, the dienophilic unit was then tethered to the sugar by utilising an adjacent hydroxyl group. Acid-catalysed opening of the 4,6-O-benzylidene acetal group of 2,3-unsaturated carbohydrates has been shown to afford furan derivatives[9]. Therefore, cleavage of the 4,6-O-benzylidene acetal of **1a**[10] was accomplished according to the procedure of Horne and Jordan[11] using sodium cyanoborohydride (9 eq.) and HCl (gas) in ether at 0°C in an argon atmosphere and in the presence of molecular sieves. Under these conditions, the 6-O-benzyl ether **1b** [syrup, $[\alpha]_D^{22}$ + 85° (c=2.6, $CHCl_3$), $MH^+$-MeOH 245, yield 90%, $^{13}C$ NMR δ ($CDCl_3$): 66.4 (C-4), 70.8 (C-6)] was obtained. Spectral comparison of **1b** with **1c** [syrup, $(\alpha)_D^{22}$ +25° (c=0.1, $CHCl_3$), $MH^+$-MeOH 245, yield 98%, $^{13}C$ NMR δ ($CDCl_3$): 68.9 (C-4), 62.4 (C-6)], prepared by the Liptak procedure[12] from **1a**, unambiguously established the structure of both of these derivatives. Standard allylation at the C-4 hydroxy group of **1b** gave quantitatively **1d**. When heated in refluxing toluene for 24 h in an argon atmosphere, triene **1d** cyclised to afford a mixture of **3a** and **3b** (80%) in a 3:1 ratio, respectively. Geometrical restrictions impose an α-side attack at C-3, thus assuring complete π-facial stereoselection. The stereochemistry at C-11 in both of these bis-annulated pyranosides **3a** [syrup, $[\alpha]_D^{22}$ +100° (c=0.4, $CHCl_3$), $MH^+$-MeOH 285, $^{13}C$ NMR δ ($CDCl_3$): 98.8 (C-1), 135.1 (C-2), 44.8-43.9 (C-3, C-11), 73.5-72.3 (C-4, C-5), 70.1-72.0-73.7 (C-6, C-7, C-12), 127.6 (C-8), 26.2 (C-9), 21.0 (C-10), 55.0 (OMe), + aromatic carbon signals] and **3b** [syrup, $[\alpha]_D^{22}$ + 97° (c=0.2, $CHCl_3$), $MH^+$-MeOH 285, $^{13}C$ NMR δ ($CDCl_3$): 99.9 (C-1), 135.7 (C-2), 38.5-37.0 (C-3,C-11), 78.4-71.7

(C-4, C-5), 71.0-70.7 (C-6, C-7), 127.6 (C-8), 23.3 (C-9), 20.9 (C-10), 55.2 (OMe), + aromatic carbon signals]was assigned on the basis of high field $^1$H NMR spectroscopy and spectral comparison with related compounds **4a** and **4b** of well established structures[13]. Coupling constants between hydrogens H-11, H-12 and H-12' appeared especially of diagnostic value: $^1$H NMR δ ($CDCl_3$) **3a**: 4.00 (t, 1H, $J_{3,4}=J_{4,5}=10$Hz, H-4), 3.85 (dd, 1H, $J_{11,12}=5$Hz, $J_{12,12'}=8$Hz, H-12), 3.30 (dd, 1H, $J_{11,12'}=11$Hz, $J_{12,12'}=8$Hz, H-12') and **3b**: 4.03 (t, 1H, $J_{3,4}=J_{4,5}=7.5$Hz, H-4), 3.80 (t, 1H, $J_{11,12}=J_{12,12'}=7.5$Hz, H-12), 3.55 (t, 1H, $J_{11,12'}=J_{12,12'}=7.5$Hz, H-12'). Similar coupling constants were reported for related structures: **4a**: 3.80 (dd, 1H, $J_{11,12}=6.2$Hz, $J_{12,12'}=7.5$Hz, H-12), 3.48 (dd, 1H, $J_{11,12'}=11.7$Hz, $J_{12,12'}=7.5$Hz, H-12') and **4b**: 3.70 (dd, 1H, $J_{11,12'}=8.2$Hz, $J_{12,12'}=8.7$Hz, H-12'), 3.57 (t, 1H, $J_{11,12}=J_{12,12'}=8.7$Hz, H-12).

The trans relationship between H-3 and H-11 in the major isomer **3a** is the result of a preferential anti transition state (see figure) and is in agreement with literature precedents[13,14].




ANTI

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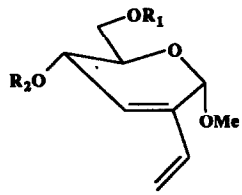
Compounds **2c** and **2d**, prepared by Wittig reaction of previously described α,β-unsaturated aldehyde **2a**[10] followed, respectively, by etherification and esterification at the C-6 hydroxy group, were next studied.

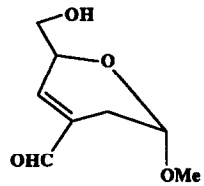
In refluxing cyclohexane, trienic structure **2c** cyclised with a complete stereoselectivity to afford the bis-annulated pyranoside **5** (69%), [mp 45-47°C, $[\alpha]_D^{22}$ + 91° (c=0.13, $CHCl_3$), $^{13}$C NMR δ ($CDCl_3$): 101.5 (C-1), 35.9 (C-2), 133.4 (C-3), 41.9 (C-4), 64.8 (C-5), 69.9-71.7 (C-6, C-7), 34.5 (C-8), 24.5-24.1 (C-9, C-10), 123.2 (C-11), 54.9 (OMe), $^1$H NMR ($CDCl_3$): 3.97 (ls, 1H, H-5) and 1.78 (q, 1H, $J_{4,8}=J_{7a,8}=J_{8,9a}=11$Hz, H-8)]as the only reaction product as judged from the $^{13}$C NMR spectrum of the crude reaction mixture. The stereochemistry at the two new asymmetric centers of **5** was established on the basis of the singlet type H-5 signal and the large doublet of doublets type H-8 resonance. Complete π-facial selectivity and anti mode[15] of attack are responsible for the observed result.

When an ester group was the link between the diene and the dienophile, as in **2d**, cyclisation in refluxing toluene afforded two isomeric products **6** [$[\alpha]_D^{22}$ + 24° (c=0.82, $CHCl_3$), $MH^+$ 297, $^{13}$C NMR δ ($CDCl_3$): 100.0 (C-1), 36.8 (C-2), 129.6 (C-3), 38.3 (C-4), 62.2 (C-5), 67.7 (C-6), 61.0 (C-7), 38.5 (C-8), 39.9 (C-9), 28.9 (C-10), 122.2 (C-11), 55.3 (OMe)] and **7** [$[\alpha]_D^{22}$ + 37° (c=0.32, $CHCl_3$), $MH^+$ 297, $^{13}$C NMR δ ($CDCl_3$): 99.9 (C-1), 37.8 (C-2), 127.9 (C-3), 35.0 (C-4), 64.0 (C-5), 68.5 (C-6), 61.0 (C-7), 37.2 (C-8), 36.7 (C-9), 22.6 (C-10), 122.2 (C-11), 55.2 (OMe)] in a 75% yield and in a ratio of 1/3: 2/3, respectively.

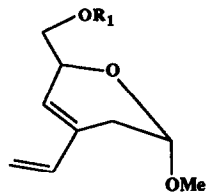
The stereochemistry at the three new asymmetric centers of **6** and **7** was determined on the basis of proton decoupling experiments as well as NOE difference spectroscopy. In the $^1$H NMR spectrum of **6**, H-8 [2.97 (t, 1H, $J_{4,8}=J_{8,9}=12$Hz)] exhibited a large triplet indicating a trans relationship of this hydrogen with both H-4 and H-9. At the same time, evidence was obtained by NOE about the cis relationship between H-4 and H-5. In the $^1$H NMR spectrum of **7**, H-8 [3.69 (dd, 1H, $J_{4,8}=9$Hz, $J_{8,9}=2$Hz)] revealed a doublet of



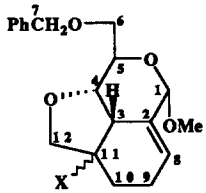
1a $R_1$ , $R_2$ = CHPh
1b $R_1$ = $CH_2Ph$ , $R_2$ = H
1c $R_1$ = H , $R_2$ = $CH_2Ph$
1d $R_1$ = $CH_2Ph$ , $R_2$ = $CH_2CH{=}CH_2$



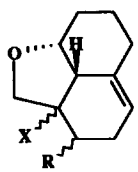
2a



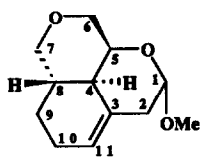
2b $R_1$ = H
2c $R_1$ = $CH_2CH{=}CH_2$
2d $R_1$ = $COCH{=}CHCO_2Et$ (E)



3a X = Hα
3b X = Hβ



4a R = Meβ, X = Hα
4b R = Meα, X = Hβ



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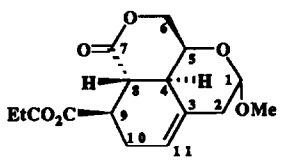
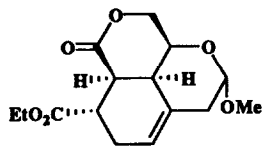


6



7

doublets. Final proof for the stereostructure of **7** was obtained by the large NOE effects observed between both H-4 and H-8 and H-4 and H-5.

As a consequence, IMDA reaction with **2d**, while maintaining complete π-facial selectivity, results in an attack in both the anti[15] and syn[15] mode, to afford the homologated bis-annulated pyranosides **6** and **7** [16,17]. The loss of total anti selectivity in this case is due to the C-7 carbonyl and the absence of interaction in the transition state between H-4 and hydrogen atoms at C-7.

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**BIBLIOGRAPHY**

1) S. David, J. Eustache, A. Lubineau, *J. Chem. Soc. Perkin Trans. I* ., 1974, 2274; S. David, A. Lubineau, J. M. Vatele, *ibid* , 1976, 1831.

2) a) J. L. Primeau, R. C. Anderson, B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1980, 6; b) idem, *J. Am. Chem. Soc* , 1983, **105**, 5874; c) D. Horton and T. Machinami, *J. Chem. Soc., Chem.Commun.*, 1981, 88; d) R. W. Franck, T. V. John, and K. Olejniczak, *J. Am. Chem. Soc* ., 1982, **104**,1106; e) R. M. Giuliano and J. H. Buzby, *Carbohydr. Res* ., 1986, **158**, C1; f) M. Isobe, T.Nishikawa, S. Pikul, and T. Goto, *Tetrahedron Lett* ., 1987, **28**, 6485; g) J. C.Lopez, E. Lameignère, and G. Lukacs, *J. Chem. Soc., Chem. Commun* ., 1988, 706.

3) For recent reviews: a) E. Ciganek, *Organic Reactions*, 1984, **32**, p. 1; b) D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187.

4) K. M. Sun, R. M. Giuliano, and B. Fraser-Reid, *J. Org. Chem.*, 1985, **50**, 4774; B. Fraser-Reid, Z. Benko, R. Giuliano, K. M. Sun, N. Taylor. *J. Chem. Soc., Chem. Commun.*, 1984, 1029.

5) P. Herczegh, M. Zsely, L. Szilagyi, G. Batta, I. Bajza, R. Bognar, *Tetrahedron.*, 1989, **45**, 2793; P. Herczegh, M. Zsely, L. Szilagyi, R. Bognar, *Tetrahedron Lett.*, 1988, **29**, 481.

6) C. Burnouf, J. C. Lopez, M. Laborde, A. Olesker, and G. Lukacs, *J.Chem. Soc., Chem. Commun.*, accepted for publication.

7) S. Hanessian, "Total Synthesis of Natural Products. The Chiron Approach", Pergamon Press, Oxford,U.K., 1983.

8) a) J. K. Dickson Jr, R. Tsang, J. M. Llera, and B. Fraser-Reid, *J. Org. Chem.*, 1989, **54**, 5350; b) H. Pak, J. K. Dickson Jr., and B. Fraser-Reid, *ibid*, 1989, **54**, 5357.

9) D. Horton, and T. Tsuchiya, *Carbohydr. Res.*, 1966, **3**, 257.

10) a) J. C. Lopez, E. Lameignère, and G. Lukacs, *J. Chem. Soc., Chem. Commun* ., 1988, 514; b) J. C. Lopez, E. Lameignère, C. Burnouf, M. Laborde, A. Olesker, G. Lukacs, *J. Org. Chem.*, submitted to publication.

11) a) D. A. Horne, and A. Jordan, *Tetrahedron Lett.*, 1978, 1357; b) P. J. Garegg, and H. Hultberg, *Carbohydr. Res.*, 1981, **93**, C10.

12) A. Liptak, J. Imre, J. Harangi, P. Nanasi, and A. Neszmelyi, *Tetrahedron* , 1982, **38**, 3721.

13) R. L. Funk, C. J. Mossman, and W. E. Zeller, *Tetrahedron Lett.*, 1984, 25, 1655.

14) a) S. J. Hecker and C. H. Heathcock, *J. Org. Chem.*, 1985, **50**, 5159. b) S. D. Burke, S. M. Smith Strickland, T. H. Powner, *J. Org. Chem.*, 1983, **48**, 454.

15) We use the terms syn and anti according to Ciganek in ref. 3a to denote the orientation of the dienophile, as defined by its attachment to the chain, relative to the diene.

16) B. J. Fitzsimmons, and B. Fraser Reid, *J. Am. Chem. Soc* ., 1979, **101**, 6123; see also ref 2a.

17) B. Fraser Reid, L. Magdzinski, and B. Molino, *J. Am. Chem. Soc* ., 1984, **106**, 731

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