Pergamon

Tetrahedron Letters, Vol. 36, No. 47, pp. 8689-8692, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01795-X

1,5-Asymmetric Inductions in the Reactions of 2-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)benzaldehyde with Danishefsky's Diene

Richard P. C. Cousins

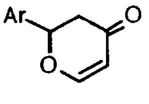
Medicinal Science, Glaxo Wellcome Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, UK

Anthony D. M. Curtis, Woan Chee Ding and Richard J. Stoodley*

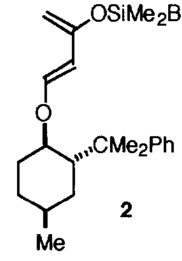
Department of Chemistry, UMIST, PO Box 88, Manchester M60 1QD, UK

Abstract: The title compounds react to give mainly a 9:1 mixture of the aldols **14** and **15** in THF in the presence of $BF_3.OEt_2$, a 6:1 mixture of the cycloadducts **16** and **17** in THF in the presence of $ZnCl_2$, and a 1:3 mixture of the cycloadducts **16** and **17** in toluene in the presence of $Eu(fod)_3$.

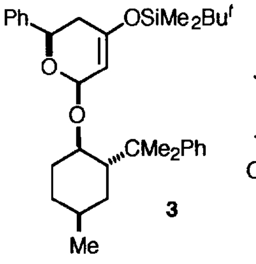
As a consequence of the pioneering studies of Danishefsky and his group,[1] 2-aryl-2,3-dihydropyran-4-ones of type **1** and their relatives have emerged as versatile species in the elaboration of pyranoid systems. To date, two tactics have been developed for the synthesis of enantioenriched versions of such compounds starting from 1-oxy-3-siloxybuta-1,3-dienes and aryl aldehydes. The use of a diene bearing a chiral auxiliary attached to the 1-oxy group has been employed by Danishefsky[2] and by ourselves.[3] Thus, the Yale workers showed that the diene **2** reacted with benzaldehyde in the presence of (+)-$Eu(hfc)_3$[4] to give largely the *cis*-cycloadduct **3**, which was transformed by the action of trifluoroacetic acid into the enantiopure dihydropyranone **1a**. We recently reported that the diene **4** reacted with *p*-nitrobenzaldehyde in the presence of $Eu(fod)_3$[5] to afford mainly the *cis*-cycloadduct **5**, which was converted into the enantiopure dihydropyranone **6**. The use of chiral Lewis acids to promote the cyclocondensation of 1-oxy-3-siloxybuta-1,3-dienes and aromatic aldehydes has been developed by Danishefsky,[2,6] Yamamoto,[7] Corey,[8] Togni[9] and Faller;[10] in the case of the synthesis of compound **1a**, an e.e. of 95% represents the best recorded result.[7]



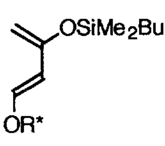
1
a; Ar = Ph



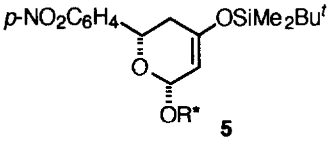
2



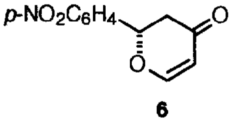
3



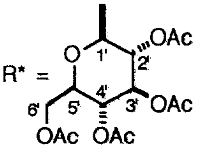
4



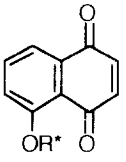
5



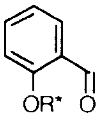
6



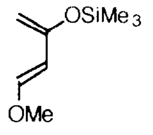
Having shown that the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl auxiliary conferred a high degree of facial reactivity on the olefinic double bond of compound **7** in Diels–Alder reactions,[11] we decided to examine the behaviour of the aromatic aldehyde **8** towards Danishefsky's diene **9**. As well as providing further insights regarding the auxiliary's stereodirecting role with respect to a "remote" reactive site, we hoped that the investigation would lead to new technology for the synthesis of dihydropyranones of type **1** and/or their antipodes. We now report on some of our findings.



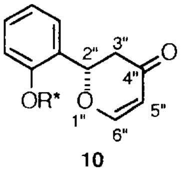
7



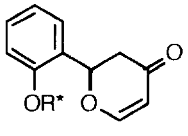
8



9



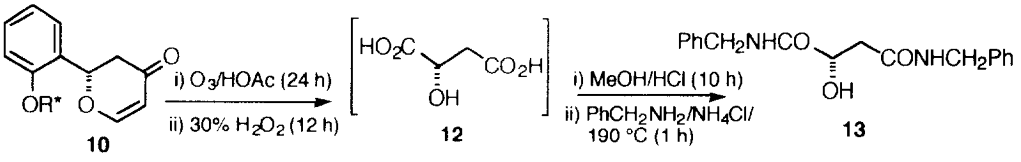
10



11

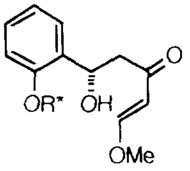
Compound **8**, m.p. 137–138 °C (lit.,[12] 142 °C), $[\alpha]_D$ −36.5 (*c* 2.8, Me_2CO) [lit.,[12] −37.0 (Me_2CO)], prepared (53% yield after chromatography and crystallisation) by a literature procedure,[12] underwent reaction with the diene **9** in THF[13] in the presence of $BF_3.OEt_2$ (1 mol equiv.) over 2 h to give, after a trifluoroacetic acid work-up, a 9:1 mixture of the dihydropyranones **10** and **11**; crystallisation of the mixture (from CH_2Cl_2–Et_2O) provided the major dihydropyranone **10**,[14,15] m.p. 193–194 °C, $[\alpha]_D$ −59 (*c* 0.27, CH_2Cl_2), in 70% yield.

That the major dihydropyranone possessed the stereostructure **10** was established by its degradation to L-malic acid **12**, which was characterised as its dibenzylamide **13**, m.p. 150–151 °C, $[\alpha]_D$ −32.3 (*c* 0.26, MeOH) [an authentic sample, prepared from L-malic acid by a literature method,[16] showed: m.p. 153–154 °C, $[\alpha]_D$ −33.5 (*c* 0.25, MeOH)], as shown in Scheme 1.

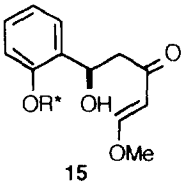


Scheme 1

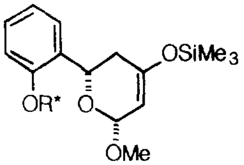
When the reaction of the aldehyde **8** and the diene **9** was repeated without the trifluoroacetic acid work-up, the product comprised mainly a mixture of compounds **10**, **11**, **14** and **15**, which was separated into two fractions by rapid silica-gel chromatography. The minor fraction (21% yield) comprised a 9:1 mixture of the dihydropyranones **10** and **11** whereas the major fraction (48% yield) consisted of a 9:1 mixture of compounds **14** and **15**. After crystallisation, the last-cited material, m.p. 58–60 °C, $[\alpha]_D$ +72 (*c* 0.26, CH_2Cl_2), (which showed no change in its diastereomeric ratio) underwent reaction with trifluoroacetic acid to give a 9:1 mixture of the dihyropyranones **10** and **11** in almost quantitative yield. Evidently, the aldols **14** and **15** are the major products of the reaction of the aldehyde **8** with the diene **9** in THF in the presence of $BF_3.OEt_2$ and these undergo a cyclocondensation to give the dihydropyranones **10** and **11** in the presence of trifluoroacetic acid. Danishefsky has isolated analogous intermediates from related reactions.[17]



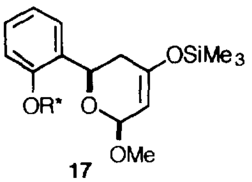
14



15



16



17

The use of other Lewis acids to promote the reaction of the aldehyde **8** with the diene **9** was briefly examined. Whereas $TiCl_4$ and $MgBr_2$ were unsatisfactory, $SnCl_4$ in THF was similar in behaviour to $BF_3.OEt_2$ in THF. Mainly a 6:1 mixture of the cycloadducts **16** and **17**[18] was produced from the reaction involving $ZnCl_2$ (1 mol equiv.) in THF; treatment of the mixture with trifluoroacetic acid resulted in the formation of a corresponding ratio of the dihydropyranones **10** and **11**. In the presence of $Eu(fod)_3$ (5 mol%) in toluene, mainly a 1:3 mixture of the cycloadducts **16** and **17**[18] resulted, which was quantitatively transformed by the action of trifluoroacetic acid into a similar ratio of the dihydropyranones **10** and **11**. After chromatography and crystallisation (from CH_2Cl_2–light petroleum), compound **11**,[14,19] m.p. 172–173 °C, $[\alpha]_D$ +25 (*c* 0.21, CH_2Cl_2), was isolated in 41% overall yield.

The aforecited results are of interest in a number of respects. They show that the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl auxiliary can confer a useful level of diastereofacial reactivity on the formyl group of a 2-oxybenzaldehyde in aldol-like and hetero Diels–Alder reactions, providing notable examples of 1,5-asymmetric inductions. Clearly, the origins of the stereoinductions warrant further investigation. The results also illustrate a new protocol for the assembly of 2-aryl-2,3-dihydropyran-4-ones—a class of compounds of established synthetic versatility. The specific examples reported—compounds **10** and **11**—are novel disaccharide relatives, in which an *O*-glycopyranoside unit and a pyranone unit (which may be regarded as either a 1- or a 5-arylpyranose prototype) are juxtaposed on an aromatic scaffold.

Acknowledgements

We thank the SERC for a research studentship (to A. D. M. C.) and the CVCP for an ORS award (to W. C. D.).

References and Notes

1. Danishefsky, S. J. *Chemtracts: Org. Chem.* **1989**, *2*, 273–289; Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23; Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59–69.
2. Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 7060–7067; *J. Am. Chem. Soc.* **1983**, *105*, 6968–6969.
3. Lowe, R. F.; Stoodley, R. J. *Tetrahedron Lett.* **1994**, *35*, 6351–6354.
4. This is an abbreviation for tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).
5. This is an abbreviation for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III).
6. Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451–3453.

7. Gao, Q.; Ishihara, K.; Maruyama, T.; Moun, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979–988; Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951–1952; Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312.

8. Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907–6910.

9. Togni, A. *Organometallics* **1990**, *9*, 3106–3113.

10. Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1989**, *30*, 1189–1192.

11. Beagley, B.; Curtis, A. D. M.; Pritchard, R. G.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1992,** 1981–1991; *J. Chem. Soc., Chem. Commun.* **1991**, 119–121.

12. Robertson, A.; Waters, R. B. *J. Chem. Soc.* **1930**, 2729–2733.

13. The reaction proceeded very much more slowly when dichloromethane or toluene was employed as the solvent.

14. New compounds gave satisfactory elemental analyses and showed spectral properties consistent with their assigned structures.

15. For compound **10**: δ_H (300 MHz; CDCl$_3$) 2.03, 2.05 and 2.09 (6, 3 and 3 H, each s, 4 x MeCO$_2$), 2.73–2.76 (2 H, m, 3"-H$_2$), 3.84 (1 H, ddd, *J* 10, 5 and 2.5 Hz, 5'-H), 4.16 and 4.27 [each 1 H, dd (*J* 12.5 and 2.5 Hz) and dd (*J* 12.5 and 5 Hz), 6'-H$_2$], 5.10–5.32 (4 H, m, 1'-, 2'-, 3'- and 4'-H), 5.53 (1 H, d, *J* 6 Hz, 5"-H), 5.69 (1 H, br t, separation 9 Hz, 2"-H), 7.06 (1 H, br d, *J* 8 Hz, 3-H), 7.18 (1 H, br t, *J* 7.5 Hz, 5-H), 7.35 (1 H, dt, *J* 7.5, 7.5 and 1.5 Hz, 4-H), 7.45 (1 H, d, *J* 6 Hz, 6"-H) and 7.51 (1 H, dd, *J* 7.5 and 1.5 Hz, 6-H); δ_C (75 MHz; CDCl$_3$) 20.61 and 20.68 (4 xCH$_3$CO$_2$), 42.13 (3"-CH$_2$), 61.74 (6'-CH$_2$), 68.17, 71.14, 72.10 and 72.50 (2'-, 3'-, 4'- and 5'-CH), 75.79 (2"-CH), 99.31 and 107.4 (1'- and 5"-CH), 115.8, 123.9, 127.1 and 130.0 (3-, 4-, 5- and 6-CH), 128.3 (1-C), 153.3 (2-C), 163.1 (6"-CH), 169.1, 169.4, 170.2 and 170.7 (4 x MeCO$_2$), and 192.1 (4"-CO).

16. Hardegger, E.; Braunschweiger, H. *Helv. Chim. Acta* **1961**, *44*, 1413–1417.

17. Danishefsky, S. J.; Larson, E. R.; Askin, D.; Kato, N. *J. Am Chem. Soc.* **1985**, *107*, 1246–1255; Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457–6458.

18. It was not possible to isolate a pure cycloadduct from this mixture, which was very prone to afford a mixture of the corresponding dihydropyranones.

19. For compound **11**: δ_H (300 MHz; CDCl$_3$) 2.04, 2.05 and 2.11 (3, 6 and 3 H, each s, 4 x MeCO$_2$), 2.46 and 2.73 [each 1 H, ddd (*J* 17, 3.5 and 1 Hz) and dd (*J* 17 and 14.5 Hz), 3"-H$_2$], 3.89 (1 H, ddd, *J* 10, 5 and 2.5 Hz, 5'-H), 4.17 and 4.27 [each 1 H, dd (*J* 12.5 and 2.5 Hz) and dd (*J* 12.5 and 5 Hz), 6'-H$_2$], 5.16–5.35 (4 H, m, 1'-, 2'-, 3'- and 4'-H), 5.51 (1 H, dd, *J* 6 and 1 Hz, 5"-H), 5.75 (1 H, dd, *J* 14.5 and 3 Hz, 2"-H), 7.03 (1 H, br d, *J* 8 Hz, 3-H), 7.16 (1 H, br t, *J* 7 Hz, 5-H), 7.34 (1 H, dt, *J* 7.5, 7.5 and 1.5 Hz, 4-H), 7.50 (1 H, d, *J* 6 Hz, 6"-H) and 7.51 (1 H, dd, *J* 7.5 and 1.5 Hz, 6-H); δ_C (75 MHz; CDCl$_3$) 20.51 and 20.54 (4 x CH$_3$CO$_2$), 42.63 (3"-CH$_2$), 61.74 (6'-CH$_2$), 68.17, 70.91, 71.95 and 72.52 (2'-, 3'-, 4'- and 5'-CH), 75.83 (2"-CH), 98.19 and 107.2 (1'- and 5"-CH), 114.6, 123.5, 126.9 and 129.7 (3-, 4-, 5- and 6-CH), 128.0 (1-C), 152.7 (2-C), 163.4 (6"-CH), 169.2, 169.3, 170.1 and 170.4 (4 x MeCO$_2$), and 191.8 (4"-CO).

(Received in UK 5 September 1995; accepted 22 September 1995)