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Diastereoselective Hydrogenations of α-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyloxymethylene) Carboxylic Esters: A Route to Stereopure Aldol Derivatives

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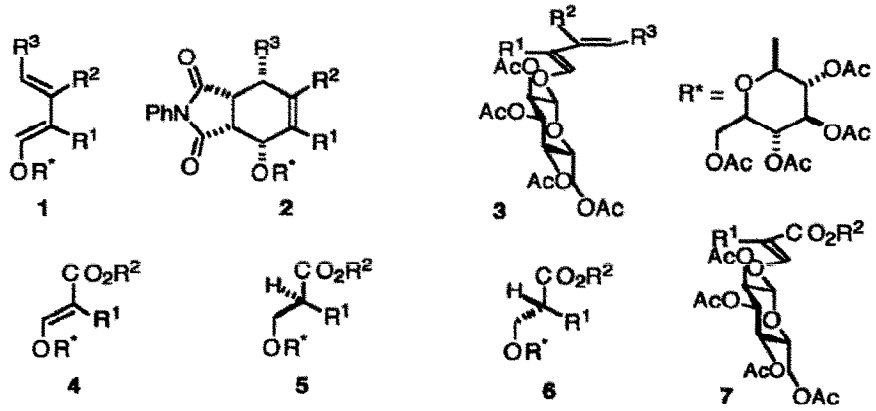
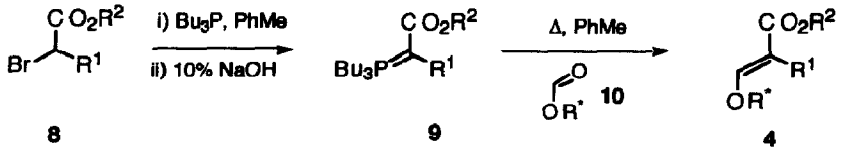
Abstract: New methodology for the stereoselective α-oxymethylation of esters/lactones is described.

Processes in which stereogenic centres are introduced into prochiral substrates in a defined manner, through the influence of a temporarily attached stereodirector, are of continuing interest to the synthetic chemist. Moreover, models that facilitate the interpretation, and thence prediction, of such asymmetric inductions are of both mechanistic and theoretical relevance.

Over the past few years, we have shown that the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl auxiliary confers a notable diastereofacial reactivity on dienes of type **1** in their reactions with dienophiles (under thermal conditions)[1-3] and heterodienophiles (under thermal conditions and in the presence of Lewis acids).[4] Significant features of the technology are its predictable stereochemical outcome (*e.g.* with *N*-phenylmaleimide cycloadducts of type **2** predominate) and its practicality (in almost all cases, the major cycloadducts can be isolated in a pure state simply by crystallisation). We have postulated[2-4] that the major cycloadducts arise by *endo*-addition of the dienophiles/heterodienophiles to the less-hindered "top" faces of conformers of type **3** of the dienes, which are favoured by a combination of *exo*-anomeric and steric effects. Based upon the aforecited model, we reasoned that vinylogous carbonates of type **4** would undergo catalytic hydrogenations[5] to give adducts of type **5** in preference to adducts of type **6**. This reasoning was based upon the assumption that systems of type **4** would react by way of conformers of type **7** and that hydrogen would be delivered by the catalyst (in a *syn*-selective manner) to the less-hindered "top" faces of the olefinic bonds. We now report results that are consistent with these expectations.



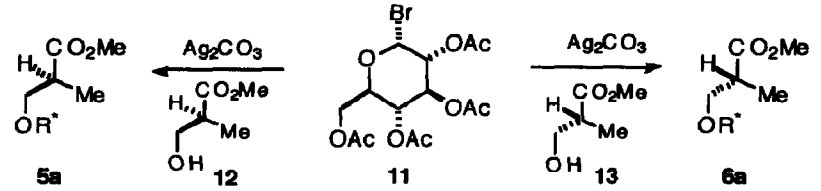
Compound **4a** was selected for the initial hydrogenation studies. Its synthesis is outlined in Scheme 1. Thus, the phosphorane **9a** (prepared in 79% yield by sequential treatment of the bromo ester **8a** with Bu_3P and NaOH) underwent reaction with the formate **10**[3,6] in boiling toluene to give the propenoate **4a**[7,8] (79% yield after crystallisation), m.p. 161–163 °C, $[\alpha]_D$ –19 (*c* 0.8, CH_2Cl_2). A brief survey of catalysts and solvents revealed that the hydrogenation of compound **4a** was rapidly effected in ethyl acetate using hydrogen (ambient pressure) in the presence of 10% palladium on activated carbon (0.5 mass equiv.); an 85:15 mixture of the dihydro derivatives **5a** and **6a** was produced in high yield. After three crystallisations (from MeOH), the major dihydro derivative **5a**,[7,9] m.p. 62–64 °C, $[\alpha]_D$ –15 (*c* 0.54, CH_2Cl_2), was obtained in poor yield (*ca.* 15%).



a; R^1 = Me, R^2 = Me **b**; R^1 = Me, R^2 = Et

Scheme 1

The stereostructures of the dihydro derivatives **5a** and **6a** were established by synthesis (Scheme 2). Thus, in the presence of silver(I) carbonate, the acetobromoglucose **11**[10] underwent condensation with methyl (*S*)-3-hydroxy-2-methylpropanoate **12** to give the glucoside **5a**[9] (40% yield after chromatography and crystallisation), m.p. 67–69 °C, $[\alpha]_D$ –14 (*c* 0.3, CH_2Cl_2), and with methyl (*R*)-3-hydroxy-2-methylpropanoate **13** to afford the glucoside **6a**[7,11] (25% yield after chromatography and crystallisation), m.p. 92–94 °C, $[\alpha]_D$ –24 (*c* 0.3, CH_2Cl_2).

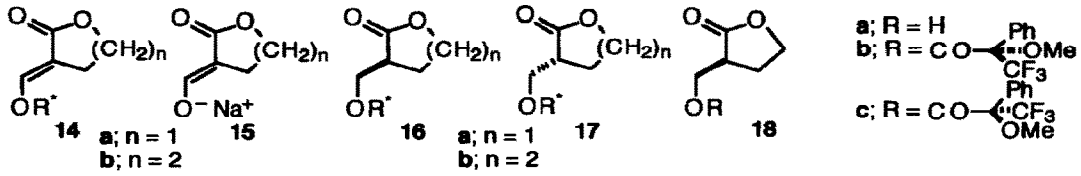


Scheme 2

In the hope that the separation of the dihydro derivative **5b** from its diastereomer **6b** would prove to be more efficient, the hydrogenation of the propenoate **4b** was examined. Compound **4b**[7] (prepared in 68% yield after crystallisation from the reaction of the phosphorane **9b** with the formate **10** as outlined in Scheme 1), m.p. 139–142 °C, $[\alpha]_D$ –11 (*c* 1.5, CH_2Cl_2), underwent hydrogenation (H_2, 10% Pd–C, EtOAc) to give an 84:16 mixture of the dihydro derivatives **5b** and **6b** in high yield. After one crystallisation (from EtOAc–light petroleum), the major dihydro derivative **5b**,[7,12] m.p. 79–81 °C, $[\alpha]_D$ –13 (*c* 0.9, CH_2Cl_2) was obtained in 68% yield.

To further define the scope of the reaction, the synthesis of the lactones **14a** and **14b** was undertaken. Treatment of the salt **15a** (obtained in 69% yield by addition of a mixture of γ-butyrolactone and HCO_2Et to a slurry of NaOMe in Et_2O)[13] with the acetobromoglucose **11** in aqueous acetone provided compound **14a**[7,8] (39% yield after crystallisation), m.p. 167–169 °C, $[\alpha]_D$ –12 (*c* 0.5, CH_2Cl_2). In a similar manner, the salt **15b** (prepared in 77% yield from δ-valerolactone, HCO_2Et and Et_2O)[14] was transformed into compound **14b**[7,8] (44% yield after crystallisation), m.p. 122–123 °C, $[\alpha]_D$ –2.5 (*c* 0.88, CH_2Cl_2). Subjection of the lactone **14a** in a 1:1 mixture of ethanol and ethyl acetate to the action of hydrogen over 1% palladium on activated carbon (0.1 mass equiv.) gave an 83:17 mixture of the dihydro derivatives **16a** and **17a** in high yield. After one crystallisation (from CH_2Cl_2–Et_2O), the major dihydro derivative **16a**,[7,15] m.p. 150–152 °C, $[\alpha]_D$ –9 (*c* 1.6,

CH_2Cl_2), was isolated in 71% yield. In a similar manner (except for the use of 3% Pd–C), the lactone **14b** was transformed into a 75:25 mixture of the dihydro derivatives **16b** and **17b**. After two crystallisations (from CH_2Cl_2–Et_2O), the major dihydro derivative **16b**,[7,16] m.p. 114 °C, $[\alpha]_D$ –29 (*c* 0.84, CH_2Cl_2), was obtained in 49% yield.



To determine whether it was possible to remove the sugar auxiliary from the hydrogenation products without damage to the new stereogenic centre, efforts were made to convert the dihydro derivative **16a** into (*S*)-α-hydroxymethyl-γ-butyrolactone **18a**.[17] Thus, compound **16a** was heated under reflux for 2.5 h with a 1:1 mixture of methanol and 5M hydrochloric acid and the hydrolysate (after partial concentration to remove MeOH) was subjected to continuous extraction with chloroform for 48 h. Evaporation of the extract gave compound **18a**, $[\alpha]_D$ +20.3 (*c* 1.9, $CHCl_3$), as an essentially pure oil in 90% yield. On the basis of its optical rotation {*enant*-**18a**[17] is reported to show $[\alpha]_D$ –21.1 (*c* 4.2, $CHCl_3$)}, the material was considered to possess the (*S*)-configuration and to be of high enantiomeric purity. In accord with the latter notion, the alcohol was converted into the Mosher esters[18] **18b** and **18c** which were essentially diastereomerically pure according to 300 MHz ^1H and 188 MHz ^{19}F NMR spectroscopy.

The foregoing results are of note in four respects. First, they reveal that the model developed to account for the diastereofacial reactivity of dienes of type **1** in Diels–Alder reactions can be extended to accommodate the diastereofacial reactivity of esters of type **4** and lactones of type **14** in catalytic hydrogenation reactions. Secondly, they expand the role of the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl unit as a cheap and practical auxiliary in stereoselective synthesis. Thirdly, compounds **5b**,[19] **16a**,[20] **16b**[21] and **18a**[20] are of interest as building blocks in organic synthesis and the present technology makes them available in multigram quantities. Finally, the results exemplify new methodology for the stereoselective α-oxymethylation[22,23] of esters and lactones.

Acknowledgements

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5. Surprisingly, the hydrogenation of vinylogous carbonates does not appear to have been widely studied. We are aware of only one asymmetric version of the reaction that is directed by a detachable stereodirector (Sato, M.; Takayama, K.; Furuya, T.; Inukai, N.; Kaneko, C. *Chem. Pharm. Bull.* **1987**, *35*, 3971–3974).

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7. All new compounds gave satisfactory elemental analyses.

8. The (*E*)-configuration of this compound was inferred on the basis of NOED spectroscopic experiments.

9. For compound **5a**: δ (300 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 7 Hz, 2-Me), 2.00, 2.02, 2.04 and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.72–2.79 (1 H, m, 2-H), 3.66–3.72 (2 H, m, 3- and 5'-H), 3.68 (3 H, s, MeO_2C), 3.87 (1 H, dd, *J* 9.5 and 5.5 Hz, 3-H), 4.13 and 4.26 [each 1 H, dd (*J* 12.5 and 2.5 Hz) and dd (*J* 12.5 and 4.5 Hz), 6'-H_2], 4.49 (1 H, dd, *J* 8 Hz, 1'-H), 4.96 (1 H, dd, *J* 9.5 and 8 Hz, 2'-H), 5.07 (1 H, t, *J* 9.5 Hz, 4'-H) and 5.19 (1 H, t, *J* 9.5 Hz, 3'-H).

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11. For compound **6a**: δ (300 MHz; $CDCl_3$) 1.17 (3 H, d, *J* 7 Hz, 2-Me), 2.00, 2.02, 2.04 and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.68–2.79 (1 H, m, 2-H), 3.58 and 4.06 [each 1 H, dd (*J* 10 and 7 Hz) and dd (*J* 10 and 6 Hz), 3-H_2], 3.67 (3 H, s, MeO_2C), 3.69 (1 H, ddd, *J* 10, 5 and 2.5 Hz, 5'-H), 4.12 and 4.26 [each 1 H, dd (*J* 12.5 and 2.5 Hz) and dd (*J* 12.5 and 5 Hz), 6'-H_2], 4.50 (1 H, d, *J* 8 Hz, 1'-H), 4.97 (1 H, dd, *J* 9.5 and 8 Hz, 2'-H), 5.07 (1 H, t, *J* 10 Hz, 4'-H) and 5.19 (1 H, t, *J* 9.5 Hz, 3'-H).

12. The stereostructure of compound **5b** was deduced from a comparison of its 300 MHz ^1H NMR spectrum with those of compounds **5a** and **6a**. In particular, the 2-methyl group appeared as a d (*J* 7 Hz) at δ 1.13 and the 3-methylene group as a dd (*J* 9.5 and 8.5 Hz) at δ 3.70 and a dd (*J* 9.5 and 5.5 Hz) at δ 3.86.

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15. For compound **16a**: δ (300 MHz; $CDCl_3$) 2.00, 2.01, 2.05 and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.28–2.37 (2 H, m, β–H_2), 2.71–2.76 (1 H, m, α-H), 3.66 (1 H, ddd, *J* 10, 4 and 2.5 Hz, 5'-H), 3.94 and 4.07 [each 1 H, dd (*J* 11 and 4.5 Hz) and dd (*J* 11 and 5 Hz), α-CH_2], 4.17 (1 H, dd, *J* 12 and 2.5 Hz, 6'-H), 4.21–4.28 (2 H, m, 6'- and γ-H), 4.37 (1 H, ddd, *J* 12, 7.5 and 4.5 Hz, γ-H), 4.52 (1 H, d, *J* 8 Hz, 1'-H), 4.99 (1 H, dd, *J* 9.5 and 8 Hz, 2'-H), 5.08 (1 H, t, *J* 9.5 Hz, 4'-H) and 5.18 (1 H, t, *J* 9.5 Hz, 3'-H).

16. For compound **16b**: δ (300 MHz; $CDCl_3$) 1.74–1.96 (4 H, m, β– and γ-H_2), 2.00, 2.02, 2.05 and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.61–2.71 (1 H, m, α-H), 3.66 (1 H, ddd, *J* 10, 4 and 2.5 Hz, 5'-H), 3.90 and 4.12 [each 1 H, dd, (*J* 10.5 and 5 Hz) and dd (*J* 10.5 and 5.5 Hz), α–CH_2], 4.15 (1 H, dd, *J* 12.5 and 2 Hz, 6'-H), 4.25–4.36 (3 H, m, 6'-H and δ-H_2), 4.56 (1 H, d, *J* 8 Hz, 1'-H), 4.99 (1 H, dd, *J* 9.5 and 8 Hz, 2'-H), 5.08 (1 H, t, *J* 9.5 Hz, 4'-H) and 5.19 (1 H, t, *J* 9.5 Hz, 3'-H).

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