

Asymmetric induction using novel chiral auxiliaries derived from D-glucose

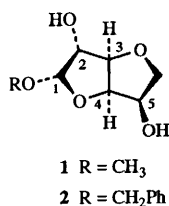
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Asymmetric synthesis of lactones **15a–16b**, using the novel auxiliaries **1** and **2** readily available from D-glucose, is described.

Asymmetric synthesis using chiral auxiliaries has continued to be an area of topical interest.^{1–3} The auxiliaries that have attracted the most attention are those derived from natural amino acids⁴ and monoterpenes.⁵ Carbohydrates, although abundant and inexpensive, have found relatively less use as chiral auxiliaries⁶ and it was of interest to undertake some investigations in this area.

The anhydrosugars **1** and **2**, readily available from D-glucose,⁷ appeared particularly attractive for chiral induction since the two *cis* fused five membered rings form a wedge and there are two hydroxy groups which can be differentiated in their reactivity. This difference in reactivity is due to the fact that the 5-OH group is pointing towards the wedge and is hydrogen bonded with the ring oxygen atom, whereas the 2-OH is projecting away from the wedge and is accessible for attaching prochiral groups. We have undertaken some investigations using **1** and **2** as auxiliaries for the reduction of

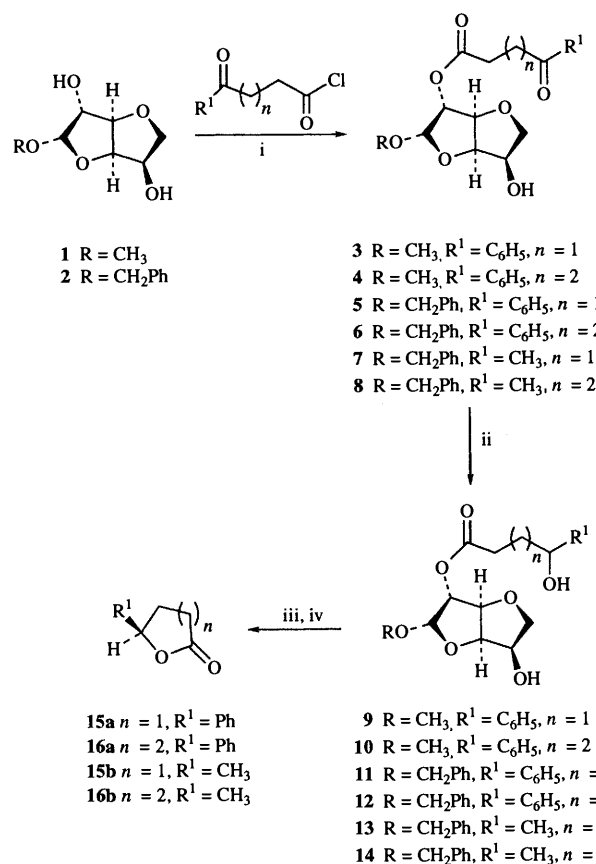


prochiral ketones (Scheme 1) and our preliminary results, which show a high level of enantioselectivity, are reported here.

The keto esters **3–8** were synthesized by routine procedure and were reduced under different conditions to afford the hydroxy esters **9–14**. These hydroxy esters were hydrolysed using LiOH (1 mol dm⁻³) and on acidification using aq. HCl (1 mol dm⁻³) afforded the lactones **15a–16b**^{8–10} in optically active form. The structures of all the compounds were established by spectral and analytical data. Experimental conditions and the ee values obtained are given in Table 1.

As shown in Table 1 high ee values are obtained when the reduction is carried out in the presence of ZnCl₂ especially when using the auxiliary **2**. Both a chelating and steric effect can be attributed to the observed stereodifferentiation.† Presumably the observed configuration of the product resulting from hydride addition from the α -face of the prochiral ketone is predicated by the wedge shaped geometry of the ring system, α -orientation of the OR group and the chelation of Zn²⁺ with the 5-OH and the keto group.

In conclusion, we have achieved the highly enantioselective reduction of prochiral ketones using the auxiliaries **1** and **2**. It is noteworthy that the ee values obtained for **15a** compare favourably with those obtained in the alternative chemical and enzymatic procedures.^{9,10} It is anticipated that the ready



Scheme 1 Reagents and conditions: i, pyridine, CHCl₃, RT; ii, for reduction conditions, see Table 1; iii, LiOH (1 mol dm⁻³); iv, HCl (1 mol dm⁻³)

availability of **2** coupled with the experimental simplicity will make the present procedure useful in organic synthesis. Further work is in progress to evaluate the use of **2** and related auxiliaries in other asymmetric transformations.

Experimental

Typical experimental procedure for the keto esters **3–8**

Benzyl 2-O-(4-oxo-4-phenylbutanoyl)-3,6-dihydro- α -D-glucopyranoside **5.** A solution of **2** (1.26 g, 5 mmol) in CHCl₃ (15 cm³) containing pyridine (0.81 cm³, 10 mmol) was treated with 4-oxo-4-phenylbutanoyl chloride (1.17 g, 6 mmol) in dry CHCl₃ (10 cm³) at room temperature. After 3.5 h the reaction mixture was diluted with CHCl₃ (25 cm³) and successively washed with saturated aq. CuSO₄, aq. NaHCO₃, water and then brine. The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure. Chromatography of the product on silica gel, eluting with EtOAc–light petroleum (15:85) afforded **5** (1.79 g, 87%) as a colourless solid; mp 105–106 °C (EtOAc–light petroleum); ν_{\max} (CH₂Cl₂)/cm⁻¹ 3515, 2990, 1740, 1735 and 1428; δ_{H} (270 MHz, CDCl₃) 7.75 (2 H, m, Ar-H), 7.5 (8 H, m, Ar-H), 4.86 (1 H, d, *J* 6.8 Hz), 3.65 (2 H, br s), 3.3–3.2 (6 H, m, OCH), 2.9 (4 H, m, COCH) and 2.1 (1 H, br s, OH); δ_{C} (22.4

† Experiments with NaBH₄ afforded the lactones with very low ee values; this indirectly supports the probable chelating effect of Zn²⁺

Table 1

Entry	Ketoester	Reduction conditions	Lactone	ee (%)	Yield (%)
1	3	ZnCl ₂ , NaBH ₄ , -5 °C	R-15a	72	83
2	4	ZnCl ₂ , NaBH ₄ , -5 °C	R-16a	31	79
3	3	ZnCl ₂ , NaBH ₄ , -78 °C	R-15a	73	80
4	4	ZnCl ₂ , NaBH ₄ , -78 °C	R-16a	30	76
5	5	ZnCl ₂ , NaBH ₄ , -5 °C	R-15a	91	82
6	6	ZnCl ₂ , NaBH ₄ , -5 °C	R-16a	56	76
7	5	ZnCl ₂ , NaBH ₄ , -78 °C	R-15a	93	82
8	6	ZnCl ₂ , NaBH ₄ , -78 °C	R-16a	53	76
9	7	ZnCl ₂ , NaBH ₄ , -5 °C	S-15b	82	80
10	8	ZnCl ₂ , NaBH ₄ , -5 °C	S-16b	48	75

MHz, CDCl₃) 192.0, 135.1, 127.0, 88.2, 82.2, 75.9, 76.3, 71.9, 43.5 and 42.5 (Found: C, 66.9; H, 5.8. Calc. for C₂₃H₂₄O₇: C, 66.97; H, 5.87%).

Typical experimental procedure for carbinol 9–14

Benzyl 2-O-(4-hydroxy-4-phenylbutanoyl)-3,6-anhydro- α -D-glucopyranoside 11. To a stirred solution of compound **5** (1.65 g, 4 mmol) in THF (20 cm³), ZnCl₂ (0.33 g, 2.4 mmol) was added at -5 °C. After 15 min NaBH₄ (0.34 g, 6 mmol) was added and the mixture was stirred for 10 min. The excess of NaBH₄ was quenched with dilute HCl, the reaction mixture was diluted with water (15 cm³) and the product extracted into ethyl acetate (4 × 15 cm³). The combined organic extracts were dried (Na₂SO₄) and the product was purified by silica gel column chromatography. Elution with ethyl acetate–light petroleum (20:80) afforded **11** as a colourless solid (1.529 g, 92%); ν_{\max} (KBr)/cm⁻¹ 3465, 1735 and 1425; δ_{H} (90 MHz, CDCl₃) 7.4 (10 H, br s, Ar-H), 4.8 (1 H, d, *J* 6.7 Hz), 3.8–3.6 (9 H, m, OCH), 2.8 (2 H, m, COCH), 2.0 (2 H, br s, OH) and 1.85–1.70 (4 H, m); δ_{C} (22.4 MHz, CDCl₃) 179.5, 135.6, 129.2, 127.0, 126.5, 87.5, 86.0, 82.4, 75.6, 44.6, 44.0, 25.7 and 25.0; $[\alpha]_{\text{D}}^{26}$ +81 (*c* 1, CHCl₃); Diastereoisomeric ratio ‡ 96:4.

Typical experimental procedure for lactones 15a–16b

5-Phenyltetrahydrofuran-2-one 15a. Compound **11** (0.83 g, 2 mmol) in THF (25 cm³) was saponified using LiOH (1 mol dm⁻³; 10 cm³). The reaction mixture was acidified with HCl (1 mol dm⁻³) and the products were extracted into ethyl acetate (4 × 15 cm³). The combined extracts were dried (Na₂SO₄) and the product was purified by column chromatography on silica gel. Elution with ethyl acetate–light petroleum (10:90) afforded **15a** as a viscous liquid (0.26 g, 79%); $[\alpha]_{\text{D}}^{26}$ +31 (*c* 1.0, CHCl₃), [lit.^{9b} +32.5 (*c* 4.3, CHCl₃)].

‡ Determined by HPLC analysis: 254 nm, ODS column.

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