

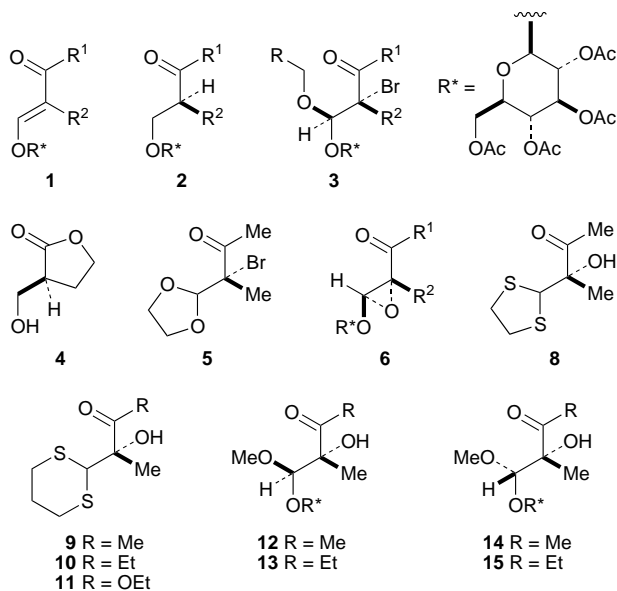
# Stereoselective epoxidations of vinylogous esters/carbonates directed by the 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl auxiliary: a route to near stereopure tertiary alcohols bearing functional arms

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The 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl auxiliary is effective in directing the epoxidation of vinylogous esters/carbonates with dimethyldioxirane; the derived epoxides are convertible into a versatile class of 1,2,3-trifunctional chirons.

As part of a programme to develop the 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl unit as an auxiliary in asymmetric synthesis, we have embarked on a study of vinylogous esters/carbonates of type **1**.<sup>1,2</sup> To date, we have established that such systems undergo stereoselective catalytic hydrogenations (to give mainly dihydro derivatives of type **2**) and regio- and stereoselective bromoalkoxylations (to furnish bromoalkoxy adducts of type **3** preferentially). Whilst the diastereomeric ratios were not high (generally, around 85:15), it was possible to isolate many of the major adducts in stereopure states and in acceptable yields simply by fractional crystallisation. Moreover, in selected cases, it was possible to remove the auxiliary under mildly acidic conditions to give chirons featuring tertiary stereogenic centres, *e.g.* **4** and **5**. Recognising the potential synthetic versatility of epoxides of type **6**, we have sought to prepare such compounds and to study their reactivity. Our findings are the subject of this communication.



After screening a variety of epoxidising agents, dimethyldioxirane (DMDO)<sup>3,4</sup> was found to be extremely effective in promoting the oxidation of vinylogous esters/carbonates<sup>†</sup> of type **1**. Table 1 summarises the outcome of the reactions. From the results, it is clear that better stereoselectivities are observed with the reactants **1a**,<sup>1,5</sup> **1b**,<sup>2,6</sup> **1c**,<sup>1</sup> **1e**<sup>1</sup> and **1f**<sup>1</sup> (*i.e.* R<sup>2</sup> = alkyl group) than with the reactants **1d**<sup>7</sup> and **1g**<sup>††</sup> (*i.e.* R<sup>2</sup> = H). Moreover, in the former examples, the major epoxides **6a**§ {mp

126–127 °C, [ $\alpha$ ]<sub>D</sub> –8.3 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>)}, **6b**§¶ {mp 106–107 °C}, **6c**§ {mp 93–94 °C, [ $\alpha$ ]<sub>D</sub> –40 (*c* 0.3, CH<sub>2</sub>Cl<sub>2</sub>)}, **6e**§ {mp 108 °C, [ $\alpha$ ]<sub>D</sub> –33 (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>)} and **6f**§ {mp 171–172 °C, [ $\alpha$ ]<sub>D</sub> –46 (*c* 0.7, CH<sub>2</sub>Cl<sub>2</sub>)} could be isolated in stereopure states and in reasonable yields simply by fractional crystallisation.

That the major epoxide arising from the reaction of the vinylogous ester **1a** with DMDO possessed the stereostructure **6a** was established by X-ray crystallography\*\* (Fig. 1).

Seeking to detach the auxiliary and generate the dithiolane **8**, the epoxide **6a** was treated with ethane-1,2-dithiol under a range of acidic conditions. The best yield of the desired product (56% after chromatography) was achieved by heating the epoxide **6a** with the dithiol (120 mol%) and toluene-*p*-sulfonic acid monohydrate (*p*-TsOH·H<sub>2</sub>O) (100 mol%) in toluene (*ca.* 72 °C, 3 h); however, the dithiolane **8**,§ [ $\alpha$ ]<sub>D</sub> +35 (*c* 0.6, MeOH), was found to possess an ee of only 66% by HPLC analysis.†† Under similar conditions (1.5 h), the epoxide **6a** reacted with propane-1,3-dithiol to give the dithiane **9**§¶ (54% yield after chromatography), mp 80 °C, with an ee of 82%.†† Clearly, the dithioacetalisation reactions were accompanied by partial racemisation.

When subjected to methanolysis conditions [MeOH–CH<sub>2</sub>Cl<sub>2</sub> (4:1), *p*-TsOH·H<sub>2</sub>O (cat.), 19 h], the epoxide **6a** was converted essentially quantitatively into a 90:10 mixture of the alcohols **12** and **14** (tentative stereostructures); crystallisation of the mixture provided the major diastereomer **12**,§ mp 112 °C, [ $\alpha$ ]<sub>D</sub> –46 (*c* 0.3, CH<sub>2</sub>Cl<sub>2</sub>), in 58% yield. The mixture of the alcohols **12** and **14** reacted with propane-1,3-dithiol [CHCl<sub>3</sub>, *p*-TsOH·H<sub>2</sub>O (100 mol%), CF<sub>3</sub>SO<sub>3</sub>H (cat.), 21 h] to give the dithiane **9**¶ (55% yield based on **6a**), mp 102–103 °C, with an ee of 98%. Under the acidic conditions mentioned earlier

**Table 1** Epoxidation of vinylogous esters/carbonates of type **1** with DMDO<sup>a</sup>

Reactant <b>1</b>	R <sup>1</sup>	R <sup>2</sup>	Products	Ratio <sup>b</sup>	Yield (%) <sup>c</sup>
<b>a</b>	Me	Me	<b>6a,7a</b>	90:10	73
<b>b</b>	Et	Me	<b>6b,7b</b>	90:10	52
<b>c</b>	–CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> –	H	<b>6c,7c</b>	91:9	64
<b>d</b>	Me	H	<b>6d,7d</b>	69:31	—
<b>e</b>	OEt	Me	<b>6e,7e</b>	91:9	74
<b>f</b>	–OCH <sub>2</sub> CH <sub>2</sub> –	H	<b>6f,7f</b>	86:14	70
<b>g</b>	OEt	H	<b>6g,7g</b>	67:33	—

<sup>a</sup> The oxidations were carried out using a distilled solution of DMDO in acetone (*ca.* 0.08 mol dm<sup>–3</sup>). <sup>b</sup> The product ratio was determined by NMR spectroscopic and/or HPLC analysis. <sup>c</sup> The yield refers to the major epoxide isolated in a stereopure state after crystallisation.

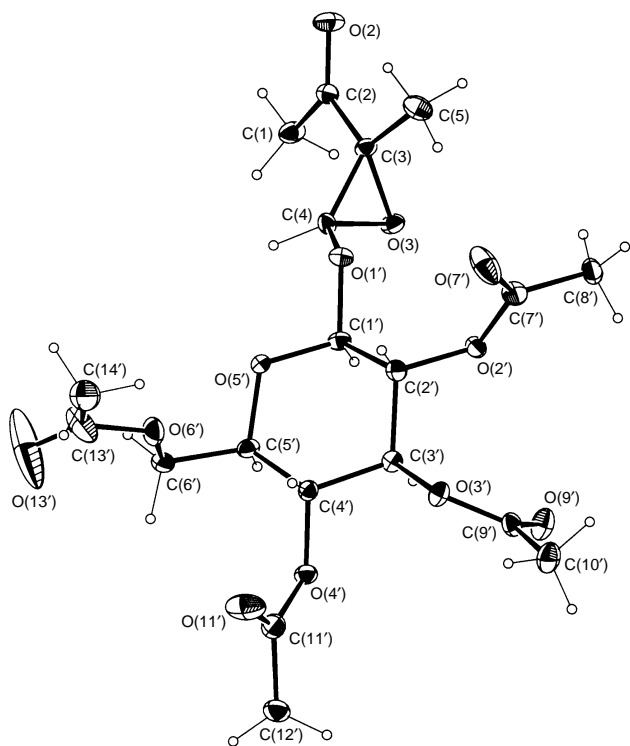


Fig. 1 Molecular structure of compound **6a**

[PhMe, *p*-TsOH·H<sub>2</sub>O (100 mol%), *ca.* 72 °C, 4 h], the dithiane **9** underwent significant racemisation (98% → 29% ee). Presumably, the partial racemisations noted in the **6a** → **8** and **6a** → **9** transformations were the results of acid-induced  $\alpha$ -ketol rearrangements<sup>8</sup> of the products **8** and **9**.

Conversion of the epoxide **6b**, by way of a 89:11 mixture of the alcohols **13** and **15**, into the dithiane **10**§ (48% yield), [ $\alpha$ ]<sub>D</sub> +2.2 (*c* 0.5, MeOH), with an ee of 93%,<sup>††</sup> was similarly effected.

Under the conditions used to effect the direct **6a** → **9** transformation, the epoxide **6e** was converted into the dithiane **11**§¶ (83% yield), mp 61–62 °C, with an ee of 98%.<sup>††</sup> The lack of any significant racemisation in this process supports the notion that  $\alpha$ -ketol rearrangements are implicated in the partial racemisation of compounds **8** and **9**.

The afore-cited findings are of note in several respects. They extend further the role of the 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl unit as an auxiliary in asymmetric synthesis. They reveal that the model used to explain the diastereofacial reactivity of vinylogous esters/carbonates of type **1** in catalytic hydrogenations<sup>1</sup> and bromoalkoxylations<sup>2</sup> is also applicable to epoxidation reactions. They illuminate a reactivity feature of vinylogous esters/carbonates that hitherto has not been exploited. Finally, compounds **6a–c**, **6e–f**, **8–11** and **12** are

representatives of new classes of trifunctional chirons with notable synthetic potential.

We thank the EPSRC for a research grant (GR/J/65464), the Isle of Man Government for a research studentship (to R. F. L.), Dr C. M. Raynor for performing the HPLC analyses and Dr J. A. Whatley (Roche Products Ltd.) for help in devising the conditions used for the HPLC analyses.

## Footnotes and References

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† There appear to be relatively few studies of epoxidations of vinylogous esters/carbonates using DMDO (see ref. 9).

‡ The vinylogous carbonate **1g**, mp 116–118 °C, [ $\alpha$ ]<sub>D</sub> –13 (*c* 1.1, CHCl<sub>3</sub>), was prepared (53% yield after crystallisation) by the Wittig condensation of ethoxycarbonylmethylenetriphenylphosphorane with 1-*O*-formyl-2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranose (see ref. 6).

§ This compound displayed analytical and spectral properties that supported its assigned structure.

¶ This compound possessed no significant optical rotation in a range of solvents.

|| The thermal stability of epoxides of type **6** is striking. In general, epoxides derived from vinylogous esters/carbonates tend to decompose at ambient temperature (see ref. 9).

\*\* Crystal data for **6a**: C<sub>19</sub>H<sub>26</sub>O<sub>12</sub>, *M* = 446.4, monoclinic, space group *P*2<sub>1</sub> (no. 4), *a* = 11.621(3), *b* = 7.500(2), *c* = 12.855(3) Å,  $\beta$  = 98.53(2)°, *Z* = 2, *D*<sub>c</sub> = 1.338 g cm<sup>–3</sup>, *F*(000) = 472,  $\mu$ (Mo-K $\alpha$ ) = 1.05 cm<sup>–1</sup>, crystal size 0.40 × 0.25 × 0.25 mm. A total of 2022 reflections were measured, 1893 unique (*R*<sub>int</sub> = 0.0336), on a Siemens R3m/V diffractometer using the  $\omega/2\theta$  scan method ( $\lambda$  = 0.71069 Å) at 23 °C. The structure was solved by direct methods and refined by full-matrix least-squares based on *F*<sup>2</sup>, with all non-hydrogen atoms anisotropic and hydrogen atoms constrained in calculated positions. The final cycle converged to *R* = 0.053 and *wR*<sup>2</sup> = 0.115. CCDC 182/589.

†† The enantiomers were separated on a Chiralpak AD column, using hexanes–propan-2-ol (9:1) as eluent (flow rate: 1 cm<sup>3</sup> min<sup>–1</sup>) in the cases of **8/ent-8** and **9/ent-9** and hexanes–ethanol (9:1) as eluent (flow rate: 1 cm<sup>3</sup> min<sup>–1</sup>) in the case of **10/ent-10**.

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Received in Liverpool, UK, 29th July 1997; 7/05498J