

# Furanosides to functionalized 9-membered ethers: ring expansion *via* the oxy-Cope rearrangement

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## The oxy-Cope rearrangement is utilized for ring expansion of furanosides to chiral hexahydrooxoninones.

The synthesis of medium and large ring ethers has received an impetus in recent years due to their presence in marine natural products such as brevetoxin A,<sup>1</sup> ciguatoxin,<sup>2</sup> gambieric acids<sup>3</sup> and obtusenyne.<sup>4</sup> Construction of 9-membered ring ethers and lactones has been performed by several groups, the prominent contributions coming from Trost,<sup>5</sup> Overman,<sup>6</sup> Nicolaou,<sup>7</sup> Holmes<sup>8</sup> and Taylor.<sup>9</sup> However, few general methods are available for their preparation, especially in chiral form.

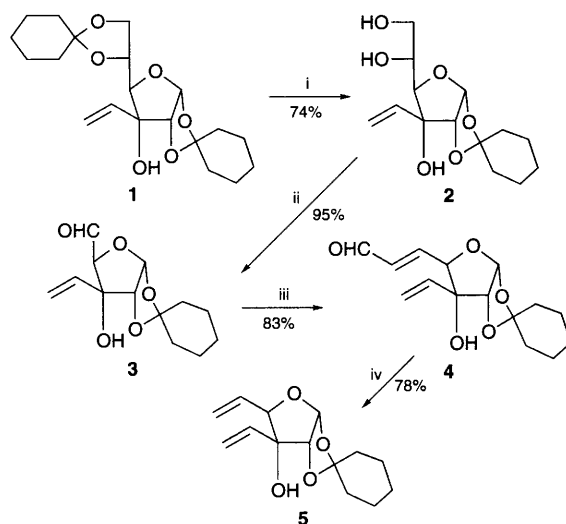
We report here a rapid, flexible and convenient conversion of D-glucose into highly functionalized 9-membered ring ethers which can be further manipulated to functionalized 9-membered lactones. This transformation has been achieved by applying the oxy-Cope rearrangement for the first time to a carbohydrate substrate.

As reported by Tatchell, D-glucose was converted to 1,2:5,6-di-O-cyclohexylidene-3-C-vinyl- $\alpha$ -D-allofuranose **1**.<sup>10</sup> Under acidic conditions, the 5,6-O-cyclohexylidene group in **1** was selectively deprotected to give **2**. The resulting triol, upon oxidative cleavage using NaIO<sub>4</sub>, furnished **3** in quantitative yield. Attempts to methylenate **3** using methylene-(triphenyl)phosphorane or CH<sub>2</sub>I<sub>2</sub>-Zn-Ti(OPr)<sub>4</sub><sup>11</sup> were unsuccessful. Finally, treatment of **3** with formylmethylene-(triphenyl)phosphorane in toluene at 80 °C afforded **4**, which in turn was decarbonylated by Wilkinson's catalyst to give **5**† (Scheme 1).

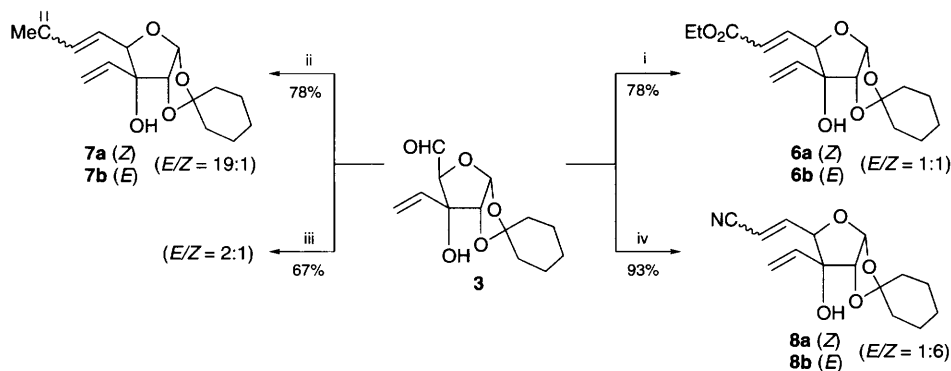
With compound **5** in hand, conditions for its conversion to the ring expanded hexahydrooxoninone were investigated. The standard oxy-Cope rearrangement protocol (KH, THF, reflux) resulted in recovery of starting material. Use of higher temperatures (KH, 1,4-dioxane, reflux or KH, diglyme, reflux) were of no avail, as were the modifications involving the use of 18-crown-6 and I<sub>2</sub>.<sup>12</sup> In all cases, no rearrangement occurred. The reason for this is not clear.

Having failed to achieve the anionic oxy-Cope rearrangement on **5**, the thermal counterpart was attempted. Heating **5** in a sealed tube in *o*-dichlorobenzene at 220 °C afforded the rearranged hexahydrooxoninone **9**‡ in 40% yield, based on

recovered starting material. The product **9** was chromatographically purified. Its IR spectrum showed absence of the hydroxyl band at 3470 cm<sup>-1</sup> and presence of a carbonyl absorption at 1738 cm<sup>-1</sup>, which indicated the formation of the rearranged hexahydrooxoninone. The structure was further confirmed from the <sup>1</sup>H NMR spectrum of **9**.§ While the <sup>1</sup>H NMR spectrum of **5** showed the presence of six dienylic protons, which appear as multiplets from  $\delta$  5.24–5.84, the rearranged hexahydrooxoninone **9** displayed only two protons which correspond to the enol ether double bond at  $\delta$  6.15 and 4.77–4.86. The <sup>13</sup>C NMR spectrum revealed a carbonyl signal at  $\delta$  206, the  $\alpha$ -carbon of the enol ether double bond at  $\delta$  142.7 and the  $\beta$ -carbon at  $\delta$  113.9. These structural assignments were further confirmed by <sup>1</sup>H-<sup>1</sup>H COSY. Finally, elemental analyses showed that **5** and **9** were isomeric.



**Scheme 1** Reagents and conditions: i, 75% AcOH, reflux, 2 h; ii, NaIO<sub>4</sub>, H<sub>2</sub>O, room temp., 1 h; iii, Ph<sub>3</sub>P=CHCHO, toluene, 80 °C, 4.5 h; iv, (PPh<sub>3</sub>)<sub>3</sub>RhCl, benzene, reflux, 2 h.



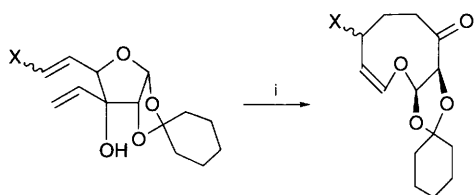
**Scheme 2** Reagents and conditions: i, Ph<sub>3</sub>P=CHCO<sub>2</sub>Et, benzene, reflux, 4.5 h; ii, Ph<sub>3</sub>P=CHCOCH<sub>3</sub>, benzene, reflux, 4.5 h; iii, Ph<sub>3</sub>P=CHCOCH<sub>3</sub>, MeOH, -78 °C, 2 h; iv, Ph<sub>3</sub>P=CHCN, benzene, reflux, 4.5 h

Encouraged by this result, we sought to extend the scope of this rearrangement to substituted analogues of **5**. These were obtained from **3** under neutral conditions using stable ylides, as outlined in Scheme 2. In each case, both the *E*- and *Z*-isomers were isolated.

With X = CN, the *E*-isomer **8b** was directly formed only in low yields. It was readily obtained by photolytic isomerisation of the *Z*-isomer **8a** in the presence of diphenyl disulfide. All the geometric isomers were easily separable by column chromatography and the stereochemistry of the double bond was assigned on the basis of the coupling constants of the alkenic protons (*E*-isomer, *J* 15–16 Hz, *Z*-isomer, *J* 12 Hz).

The thermal oxy-Cope rearrangement on all the above substrates was performed under similar conditions as used for parent substrate **5** and the results are summarized in Table 1. The structures of all new compounds were unambiguously established from their analytical and spectral (IR, <sup>1</sup>H and <sup>13</sup>C NMR) data.

All the hexahydrooxoninone derivatives have the *Z*-stereochemistry at the double bond as evidenced by the coupling constant between the alkenic protons (*J* 5.0–5.5 Hz). The stereochemistry of the newly formed chiral centre in **9**, **10**, **11** and **12** is yet to be determined.



**Scheme 3** Reagents and conditions: i, *o*-dichlorobenzene, 200–220 °C (sealed tube), 12 h.

**Table 1** Thermal oxy-Cope rearrangement of compounds **5–8**

Substrate (X)	Product	Yield (%) <sup>a</sup>
<b>5</b> (H)	<b>9</b>	40
<b>6a</b> ( <i>Z</i> -CO <sub>2</sub> Et)	<b>10</b>	40
<b>6b</b> ( <i>E</i> -CO <sub>2</sub> Et)	—	—
<b>7a</b> ( <i>Z</i> -COCH <sub>3</sub> )	<b>11</b>	<5
<b>7b</b> ( <i>E</i> -COCH <sub>3</sub> )	<b>11</b>	20
<b>8a</b> ( <i>Z</i> -CN)	<b>12</b>	60
<b>8b</b> ( <i>E</i> -CN)	<b>12</b>	~5

<sup>a</sup> Yields are based on recovered starting material.

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### Footnotes

† *Physical data* for **5**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.35–1.90 (m, 10 H), 4.26 (d, 1 H, H-2, *J* = 3.8 Hz), 4.31 (br, 1 H, H-4), 5.24–5.33 (m, 2 H), 5.41–5.43 (t, 1 H), 5.50 (d, 1 H), 5.69–5.84 (m, 2 H), 5.86 (d, 1 H, H-1, *J* = 3.8 Hz); <sup>13</sup>C NMR: δ 23.63, 24.03, 24.97, 36.24, 80.75, 82.99, 83.31, 103.23, 113.53, 116.07, 118.50, 132.04, 134.84.

‡ *Typical experimental procedure*: A solution of **5** (200 mg, 0.8 mmol) in 1,2-dichlorobenzene (3 ml) was heated at 200 °C in a sealed tube for 12 h. After removal of solvent, the crude mixture was chromatographed on silica gel (hexane–ethyl acetate eluent) to give the product **9** (37 mg) and unreacted **5** (108 mg). No other tractable material could be isolated. Based on recovered **5**, **9** was obtained in 40% yield.

§ *Physical data* for **9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.38–2.13 (m, 12 H), 2.23–2.36 (m, 2 H, H-6), 2.67–2.81 (m, 2 H, H-5), 4.58 (d, 1 H, H-2, *J* 4.7 Hz), 4.77–4.86 (m, 1 H, H-7), 5.58 (d, 1 H, H-1, *J* 4.7 Hz), 6.15 (d, 1 H, H-8, *J* 5.3 Hz); <sup>13</sup>C NMR: δ 22.63, 23.37, 23.76, 23.93, 24.92, 35.87, 36.18, 37.02, 37.23, 84.57, 101.29, 113.98, 114.39, 142.7, 206.56.

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