

CYCLOFUNCTIONALISATION OF EPOXYALCOHOL DERIVATIVES.<sup>1</sup> 2. STEREO-  
 AND REGIOSPECIFIC CONVERSION TO 1,3-DIOXOLANES

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**Abstract:** 2,3-Epoxyalcohols react with paraformaldehyde and either cesium carbonate or potassium carbonate/phase-transfer catalyst in polar, aprotic solvents to give excellent yields of 4-(1-hydroxyalkyl)-1,3-dioxolanes, with inversion at C-2.

Carbonates and carbamates of 2,3-epoxyalcohols undergo cyclisation induced by protic or Lewis acids, delivery of oxygen to C-2 being the dominant result<sup>2</sup>. A thorough study by Roush, et al<sup>3</sup> has established that product distribution (reflecting competition between C-2/C-3 attack, capture of external nucleophile and equilibration of cyclic carbonate isomers) is markedly dependent on both substrate and conditions but that in general, the BF<sub>3</sub>-induced cyclisation of *N*-phenylcarbamates (1) is a satisfactory route to the cyclic carbonates (2). In this paper, we report a new method for oxygen delivery to C-2 under basic conditions, which is insensitive to electron-releasing oxirane ring substituents<sup>4</sup> and which produces a 1,2-blocked triol devoid of isomeric contaminants.

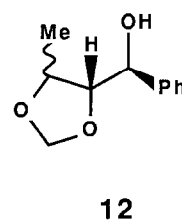
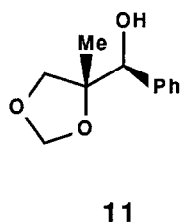
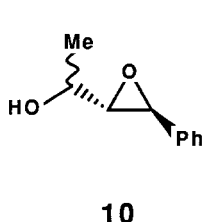
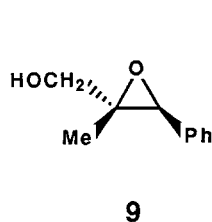
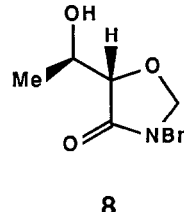
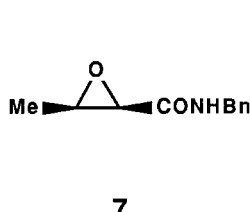
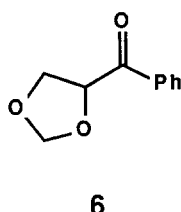
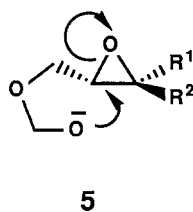
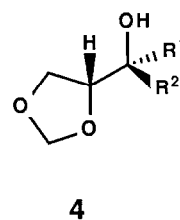
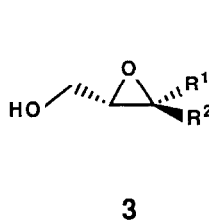
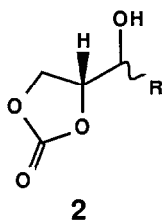
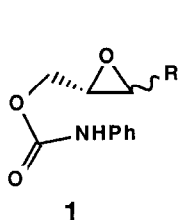
Reaction of several 2,3-epoxyalcohols (3) with paraformaldehyde (2 eq) and Cs<sub>2</sub>CO<sub>3</sub> (0.5 eq) in dry MeCN for 20 h. at room temperature proceeded very cleanly (See Table) to yield in each case a single 1,3-dioxolane (4). After conventional workup, the crude products were usually pure enough for further reactions; traces of polar impurities could be removed by short-path, silica gel chromatography.

Table

	Epoxyalcohol <sup>a</sup>		1,3-Dioxolane (% yield) <sup>b,c</sup>
	R <sup>1</sup>	R <sup>2</sup>	
3a	H	Ph	4a (95) <sup>d</sup>
3b	Ph	H	4b (92)
3c	H	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	4c (91)
3d	BnOCH <sub>2</sub>	H	4d (88)
3e	-(CH <sub>2</sub> ) <sub>5</sub> -		4e (60) <sup>e</sup>

## Notes

- Racemic substance prepared by oxidation of the corresponding allylic alcohol by mCPBA or  $t\text{-BuO}_2\text{H-V}(\text{AcAc})_2$ .
- Conditions as noted in the text with 10 mmol (3) in 20 mL of MeCN. After  $\text{H}_2\text{O-Et}_2\text{O}$  workup the product was purified on silica gel, eluting with  $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$  mixtures.
- Isolated yields refer to chromatographically homogeneous, solvent-free oils which gave IR, PMR and mass spectra consonant with the assigned structures. PMR spectra were also recorded for the O-(N-trichloroacetyl)-carbamates, prepared in situ by adding excess  $\text{CCl}_3\text{CO.NCO}$  to the  $\text{CDCl}_3$  solution of (4). For selected data, see Reference 6.
- This yield was obtained on both 0.05 mol and 0.1 mol scales.
- Material balance was starting epoxyalcohol.



That the reaction involves clean  $S_N2$  attack at C-2 by the (presumed) intermediate hemiacetal anion (5) was indicated by the production of distinct, pure isomers (4a, 4b) from trans and cis starting materials (3a, 3b). Both dioxolanes gave the same ketone (6) on oxidation with  $\text{pyHClCrO}_3$ <sup>7</sup>, and reduction ( $\text{NaBH}_4$ , EtOH) of (6) regenerated a mixture of the alcohols (ratio of 4a:4b was approximately 3:2, by PMR analysis). Hydrolysis ( $\text{HCl-H}_2\text{O-MeOH}$ ,  $65^\circ$ , 6 h.) of (4a) gave a high yield of ( $\pm$ )-erythro-1-phenylpropane-1,2,3-triol (mp  $90-93^\circ$ , crude) which gave a tri-O-benzoate of mp  $149-151^\circ$  (lit<sup>8</sup>, purified triol, mp  $98.5^\circ$ ; tri-O-benzoate, mp  $151-152^\circ$ ).

Replacing  $\text{Cs}_2\text{CO}_3$  with the inexpensive  $\text{K}_2\text{CO}_3$  gave incomplete reaction even after 72 h., but the combination of powdered  $\text{K}_2\text{CO}_3$  with either 18-crown-6 or methyl-tri-n-octyl-ammonium chloride<sup>9</sup> (5-10 mol % of either catalyst) led to complete conversion of substrate (3c) after 6-12 h.

The reaction appears to be quite general for oxirane derivatives: under standard conditions the epoxyamide (7) gave 72% of (8)<sup>6</sup> and in slower, incomplete reactions<sup>10</sup> the methyl substituted epoxyalcohols (9) and (10) gave the dioxolanes (11) and (12). Attempts with other, non-enolisable aldehydes (chloral, p-nitrobenzaldehyde) did not give useful amounts of dioxolane products from (3a).

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#### References and Notes:

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4.  $\text{BF}_3\cdot\text{Et}_2\text{O}$  treatment (in  $\text{Et}_2\text{O}$  at  $-20^\circ$ ) of the N-methyl and N-phenyl carbamates of trans-cinnamyl alcohol epoxide led to complex product mixtures.
5. Equally satisfactory results were obtained in DMF, but THF gave poor rates. The use of  $\text{Cs}_2\text{CO}_3$ -paraformaldehyde for N-hydroxymethylation of an amide has been reported: R. A. Gobao, M. L. Bremmer and S. M. Weinreb, J. Am. Chem. Soc., 1982, 104, 7065.
6. Selected physical data: (4a), PMR ( $\text{CDCl}_3$ ):  $\delta$  2.6 (br, s, 1, exch. by  $\text{D}_2\text{O}$ ); 3.75 (dd, 1, J = 10 and 8); 3.98 (dd, 1, J = 10 and 7); 4.87 and 5.12 (both s, 1); 4.95 (d, 1, J = 5) and 7.3-7.5 (m, 5). p-Nitrobenzoate ester of (4a), mp  $83.5-85^\circ$  ( $\text{CH}_2\text{Cl}_2$ -hexanes). (4b), PMR ( $\text{CDCl}_3$ ):  $\delta$  2.79 (d, 1, J = 3, exch. by  $\text{D}_2\text{O}$ ); 3.72 (m, 2); 4.22 (m, 1); 4.61 (dd, 1, J = 7.5 and 3; collapses to d, J = 7.5 after  $\text{D}_2\text{O}$

exch.); 4.97 and 5.14 (both s, 1) and 7.3-7.5 (m, 5). (4a +  $\text{CCl}_3\text{CONCO}$ ), PMR ( $\text{CDCl}_3$ ):  $\delta$  3.9-4.1 (m, 2); 4.43 (m, 1); 4.90 and 5.01 (both s, 1), 5.97 (d, 1,  $J = 6$ ); 7.3-7.5 (m, 5) and 8.63 (br. s, 1, exch. by  $\text{D}_2\text{O}$ ). (4b +  $\text{CCl}_3\text{CONCO}$ ), PMR ( $\text{CDCl}_3$ ):  $\delta$  3.61 (dd, 1,  $J = 9.5$  and  $5.5$ ); 3.75 (dd, 1,  $J = 9.5$  and  $7$ ); 4.4-4.6 (m, 2); 5.01 and 5.12 (both s, 1), 7.3-7.5 (m, 5) and 8.54 (br. s, 1, exch. by  $\text{D}_2\text{O}$ ). (6), IR (film):  $\nu(\text{C=O})$   $1715\text{ cm}^{-1}$ . (8), mp  $86-88^\circ$  ( $\text{Et}_2\text{O}$ ), PMR ( $\text{CDCl}_3$ ):  $\delta$  1.34 (d, 3,  $J = 7$ ); 2.20 (br. s, 1, exch. by  $\text{D}_2\text{O}$ ); 4.1-4.3 (m, 2); 4.53 (AB, 2,  $J = 15$ ); 4.96 (s, 2) and 7.2-7.5 (m, 5).

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8. M. Tiffeneau, I. Neuberg-Rabinovitch and H. Cahnmann, Bull. Soc. Chim. France, 1935, 2, 1866. K. H. Kruger, Chem. Berichte, 1956, 89, 1016.
9. Aliquat 336, as supplied by the Aldrich Chemical Company. This is the preferred catalyst for reactions using  $\text{K}_2\text{CO}_3$ , based on ease of separation from the product.
10. Heating under reflux results in loss of formaldehyde; a sealed tube would presumably accelerate reaction rates for difficult substrates.

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