COMMUNICATION

Disparity in the tandem epoxide-allylic alcohol-[1,2]/[2,3]-Wittig rearrangement of *cis*- and *trans*-1-benzyloxy-3,4-epoxycyclopentane

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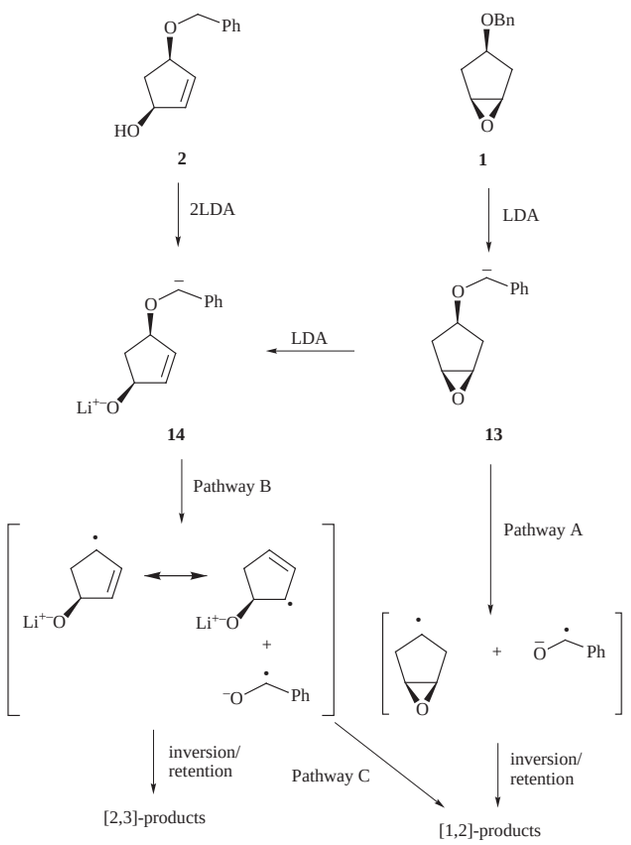
The influence of the relative stereochemistry of the epoxide and benzyloxy functionalities present in *cis*- 1 and *trans*-1-benzyloxy-3,4-epoxycyclopentane 3 on the tandem epoxide–allylic alcohol–[1,2]/[2,3]-Wittig rearrangement has been studied, together with the Wittig rearrangement of the intermediate alcohols 2 and 4.

As part of a project investigating the chiral base induced rearrangement of epoxides to allylic alcohols[1] we have studied the rearrangement of *cis*-1-benzyloxy-3,4-epoxycyclopentane **1** to allylic alcohol **2** with a range of lithium amide bases. In certain cases we began to observe the formation of small amounts of by-products arising from apparent 1,2-Wittig rearrangement of the benzyloxy protecting group, a feature which could be made more prevalent if a stronger base, for example LDA, was employed. We thus decided to perform a systematic investigation of this reaction using the epoxides **1** and **3**, together with the intermediate alcohols **2**† and **4**.‡

Thus, treatment of the above substrates in turn with three equivalents of LDA in THF–hexane at −78 °C to 0 °C over 16 hours led to the formation of several products arising from both the epoxide–allylic alcohol and [1,2]/[2,3]-Wittig rearrangements, results of which are summarised in Tables 1 and 2.

When considering the rearrangement of **1**, which proceeded in reasonable yield, it is interesting to note that the primary products seem to be those of a [1,2]-Wittig rearrangement coupled with the expected epoxide–allylic alcohol rearrangement (*i.e.* **5**, **6**, **9** or **10**). This would seem to suggest that the [1,2]-rearrangement process occurs before the epoxide–allylic alcohol rearrangement. Indeed when the same reaction was performed on the intermediate alcohol **2** a not too dissimilar ratio of products was obtained in a somewhat poorer yield. Further support for this sequence of events is offered by the observation that in all of our reactions a red coloration typical of a benzylic anion intermediate was formed instantaneously on addition of LDA.[2]

It is likely that the formation of the [1,2]-Wittig products **5**, **6**, **9** and **10** in both these reactions is *via* the traditionally invoked radical mechanism[2] (Pathway A); it is also likely that the products **7** and **8** have arisen *via* a sigmatropic rearrangement of anion **14**. However the occurrence of products **11** and **12** which are [2,3]-products of inversion indicates that they must have arisen *via* a radical mechanism (Pathway B). Thus the presence of **7**, **8**, **11** and **12** indicates that some epoxide rearrangement is occurring prior to the Wittig processes and may suggest that Pathway C is also operating for the formation of the 1,2-products (Scheme 1).



Scheme 1

The presence of the alkoxide anion generated from the 1,2-Wittig reaction might also have a beneficial effect on the epoxide–allylic alcohol rearrangement in line with the report of Hodgson.[3] The increased amount of inversion product and poor yield observed in the reaction of the allylic alcohol **2** may also suggest that the alkoxide ion is destabilising the supposed radical pair intermediate, leading to more inversion and possibly lower yields due to increased side reactions.

With these observations in hand we proceeded to investigate the rearrangement of the corresponding *trans*-epoxide **3** and alcohol **4**. It was apparent from the rearrangement of **3** that there was a clear duality of mechanism occurring in this reaction as both products of [1,2]- (Pathway A) and [2,3]-Wittig rearrangement (Pathway B) were present, indicating that the intermediate anion **15** may be relatively long lived and able to undergo the epoxide–allylic alcohol rearrangement to give **16** prior to the [2,3]-process. In contrast, rearrangement of the

† Samples of **2** were prepared using previously developed methodology.[1]

‡ The rearrangement intermediate **4** was prepared by treating the epoxide **3** with four equivalents of (+)- or (−)-ephedrine in a similar manner to that reported previously;[1] details of this work will be published elsewhere.

Table 1 Products from tandem epoxide–allylic alcohol and [1,2]/[2,3]-Wittig rearrangements

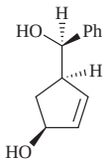
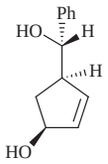
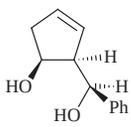
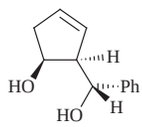
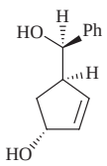
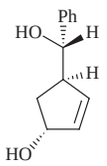
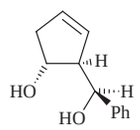
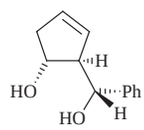
	Products							
								
	5	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Starting materials								
1	37%	17%	1%	1%	3%	1%	0.5%	0.5%
2	21%	7%	2%	1%	5%	1%	1.5%	trace
3	trace	—	—	—	22%	7%	18%	2%
4	—	—	—	—	—	—	74%	8%

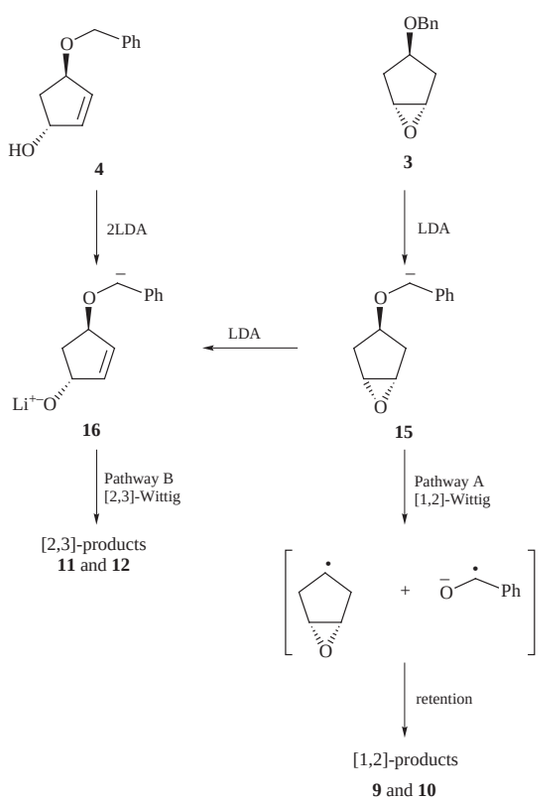
Table 2 Summary of product distribution from epoxide–allylic alcohol and [1,2]/[2,3]-Wittig rearrangements

Entry	Starting material	Overall yield[a]	[1,2]:[2,3]	retention:inversion
1	**1**	61%	95:05	92:08
2	**2**	38.5%	86:14	78:22
3	**3**	50%	60:40	99:01
4	**4**	82%	00:100	100:00

[a] General conditions: 3 equiv., LDA, THF–hexane, −78–0 °C, 16 h.

intermediate alcohol **4** led cleanly and in high yield to solely the [2,3]-products **11** and **12** in a similar ratio (*ca.* 9:1)§ to that observed for those isolated from the epoxide rearrangement. In both cases the lack of any significant quantities of *cis*-product would also seem to suggest that the formation of these products is a high energy process, possibly disfavoured by the oxyanion and epoxide functionalities (Scheme 2).

The relative stereochemistry of **5** (Fig. 1) and **11** (Fig. 2) were determined by X-ray crystallography.¶



Scheme 2

In conclusion, it is apparent that the reaction involving *cis*-epoxybenzyl ether **1** has a strong preference for [1,2]-rearrangement with retention, a factor which might be controlled by some form of internal chelation. In the presence of the anion functionality, as is the case with **2**, the outcome of the rearrangement is complex, leading to some inversion products and a generally lower yield. These observations do not apply to the *trans*-epoxide **3**, in this case the reaction has a complex product outcome with epoxide opening and concomitant [2,3]-rearrangement product competing with [1,2]-rearrangement, with limited inversion. In contrast to all these processes the rearrangement of the intermediate alcohol **4** leads cleanly to a 9:1 mixture of [2,3]-products.

§ The overall stereochemical outcome of this [2,3] rearrangement is consistent with previous reported mechanistic rationale.[4]

¶ X-Ray crystallographic data for **5** and **11**. All crystallographic measurements were made using a FAST area detector diffractometer.[5] *Crystal data for* **5**. $C_{12}H_{14}O_2$, $M_r = 190.23$, orthorhombic, $a = 6.0650(10)$, $b = 7.6740(2)$, $c = 21.728(4)$ Å, $U = 1011.3(3)$ Å^3, space group $P2_12_12_1$, $Z = 4$, μ(Mo-Kα) = 0.084 mm^{-1}, $\lambda = 0.710\,69$ Å, $T = 150$ K, crystal size 0.18 × 0.14 × 0.14 mm. *Crystal data for* **11**. $C_{12}H_{14}O_2$, $M_r = 190.23$, monoclinic, $a = 10.819(2)$, $b = 11.157(5)$, $c = 8.355(2)$ Å, $\beta = 90.210(10)°$, $U = 1008.5(5)$ Å^3, space group $P2_1/c$, $Z = 4$, μ(Mo-Kα) = 0.084 mm^{-1}, $\lambda = 0.710\,69$ Å, $T = 150$ K, crystal size 0.15 × 0.22 × 0.15 mm. Both structures were solved by direct methods (SHELX-S)[6] and refined on F^2 by full-matrix least-squares (SHELXL-93)[7] using all unique data to final wR_2 (on F^2) = 0.0735 (**5**) and 0.0692 (**11**), and R_1 [on F, $F_o > 4\sigma(F_o)$] = 0.0351 (**5**) and 0.0345 (**11**) [non-H atoms anisotropic, H atoms in calculated positions (riding model)]. Further experimental details, atomic coordinates, thermal parameters, and a full list of bond lengths and angles for both compounds have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary material. For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/220.

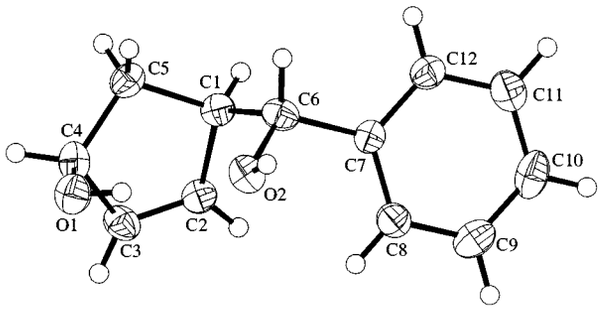


Fig. 1 Molecular structure of **5**

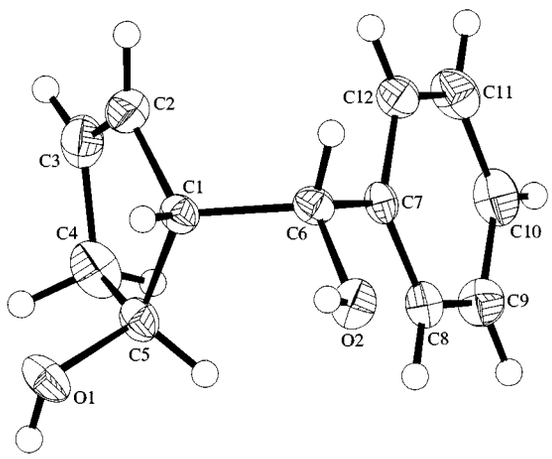


Fig. 2 Molecular structure of **11**

Experimental

General conditions

All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Tetrahydrofuran was freshly distilled from sodium and benzophenone. Diisopropylamine was dried under reflux using calcium hydride and distilled. Column chromatography was carried out on BDH Silica Gel (particle size 40 to 63 μm) and TLCs were conducted on precoated Kieselgel 60 F254 (Art. 5554 Merck). ^{1}H NMR spectra were recorded in deuterochloroform (unless otherwise stated) on a Bruker AC250 spectrometer; signals are quoted as singlet (s), doublet (d), triplet (t) and multiplet (m) with discernable coupling constants, *J*, quoted in Hz.

General conditions for rearrangement reactions

To diisopropylamine (319 mg, 0.44 ml, 3.16 mmol) in freshly distilled THF (5 ml) was added *n*-butyllithium as a solution in hexane (1.35 ml, 2.34 M, 3.16 mmol) at 0 °C under argon; the resulting solution was stirred for 30 min at 0 °C before being cooled to −80 °C. At this point the substrate (**1**–**4**) (1.05 mmol) in dry THF (1.5 ml) was added dropwise *via* syringe. The reaction was stirred to room temperature overnight whereupon water (10 ml) was added and the acidified (1M HCl) mixture extracted with CH_2Cl_2 (3 × 30 ml). The collected organic extracts were then dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product as an oil. Purification was effected using flash column chromatography light petroleum (bp 40–60 °C)–diethyl ether; 100 : 0 to 50 : 50) and recrystallisation (petrol–diethyl ether).

***rac-cis*-4-(α-Hydroxybenzyl)cyclopent-2-en-1-ol 5.** δ_H 1.75 (1H, ddd, *J* 14.2, 2.0, 1.6), 2.34 (1H, *J* 14.2, 8.6, 7.0), 2.56 (2H, br s, 2 × OH), 3.01 (1H, ddddd, *J* 8.6, 3.9, 2.5, 2.0, 1.8), 4.68 (1H, ddd, *J* 7.0, 2.1, 1.6), 4.80 (1H, d, *J* 3.9), 5.70 (1H, dd, *J* 5.6, 2.5), 6.03 (1H, ddd, *J* 5.6, 2.1, 1.8), 7.35 (5H, m, Ph).

***rac-cis*-4-(α-Hydroxybenzyl)cyclopent-2-en-1-ol 6.** δ_H 1.67 (1H, ddd, *J* 14.5, 2.0, 1.6), 2.06 (1H, ddd, *J* 14.5, 8.7, 7.0), 2.72 (2H, br s, 2 × OH), 3.02 (1H, ddddd, *J* 8.7, 3.4, 2.4, 2.0, 1.8), 4.64 (1H, ddd, *J* 7.0, 2.1, 1.6), 4.81 (1H, d, *J* 3.9), 5.91 (1H, dd, *J* 5.6, 2.4), 6.02 (1H, ddd, *J* 5.6, 2.1, 1.8), 7.37 (5H, m, Ph).

***rac-cis*-2-(α-Hydroxybenzyl)cyclopent-3-en-1-ol 7.** δ_H 1.8 (2H, br s, 2 × OH), 2.47 (1H, br d, *J* 17.2), 2.72 (1H, m, *J* 17.2, 6.4), 3.05 (1H, m, *J* 9.6, 6.4), 4.75 (1H, ddd, *J* 6.4, 6.4, 3.1), 4.86 (1H, d, *J* 9.6), 5.16 (1H, m, *J* 6.3), 5.77 (1H, m, *J* 6.0, 2.4), 7.41 (5H, m, Ph).

***rac-cis*-2-(α-Hydroxybenzyl)cyclopent-3-en-1-ol 8.** δ_H 1.7 (2H, br s, 2 × OH), 2.39 (1H, br m, *J* 17.8, 2.9), 2.75 (1H, m, *J* 17.8, 6.6), 3.04 (1H, m, *J* 3.0, 6.6), 4.70 (1H, ddd, *J* 6.6, 6.6, 2.9), 5.25 (1H, d, *J* 3.0), 5.58 (1H, m), 5.91 (1H, m), 7.41 (5H, m, Ph).

***rac-trans*-4-(α-Hydroxybenzyl)cyclopent-2-en-1-ol 9.** δ_H 1.62 (1H, ddd, *J* 14.2, 8.0, 3.1), 1.8 (2H, br s, OH), 1.95 (1H, ddd, *J* 14.2, 7.2, 5.0), 3.28 (1H, m, *J* 6.8, 8.0, 5.0), 4.42 (1H, d, *J* 6.8), 4.78 (1H, m, *J* 7.2, 3.1), 5.91 (1H, ddd, *J* 6.4, 4.0, 2.0), 6.01 (1H, ddd, *J* 6.4, 2.1, 0.8), 7.29 (5H, m, Ph).

***rac-trans*-4-(α-Hydroxybenzyl)cyclopent-2-en-1-ol 10.** δ_H 1.76 (1H, ddd, *J* 14.3, 7.8, 3.2), 1.8 (2H, br s, OH), 2.21 (1H, ddd, *J* 14.3, 7.1, 4.6), 3.29 (1H, m, *J* 6.6, 7.1), 4.51 (1H, d, *J* 6.6), 4.85 (1H, m), 5.66 (1H, ddd, *J* 0.9, 2.1, 5.7), 5.89 (1H, m, *J* 5.7), 7.30 (5H, m, Ph).

***rac-trans*-2-(α-Hydroxybenzyl)cyclopent-3-en-1-ol 11.** δ_H 1.75 (2H, br s, 2 × OH), 2.27 (1H, dddd, *J* 17.2, 3.7, 2.3, 2.2), 2.70 (1H, ddddd, *J* 17.2, 7.0, 2.0, 1.9, 1.8), 3.03 (1H, ddddd, *J* 7.0, 5.9, 2.0, 1.9, 1.8), 4.37 (1H, ddd, *J* 7.0, 7.0, 3.7), 4.77 (1H, d, *J* 5.9), 5.67 (1H, dddd, *J* 6.0, 2.2, 2.1, 2.0), 5.85 (1H, dddd, *J* 6.0, 2.3, 2.0, 1.9), 7.40 (5H, m, Ph).

***rac-trans*-2-(α-Hydroxybenzyl)cyclopent-3-en-1-ol 12.** δ_H 1.9 (2H, br s, 2 × OH), 2.25 (1H, m, *J* 15.0), 2.70 (1H, dddd, *J* 15.0, 7.5, 2.4, 1.9), 2.90 (1H, ddddd, *J* 6.8, 5.0, 2.2, 1.9, 1.8), 4.45 (1H, d, *J* 8.8), 4.50 (1H, m, *J* 7.5, 8.8), 5.20 (1H, dddd, *J* 6.0, 2.1, 1.8, 1.8), 5.70 (1H, dddd, *J* 6.0, 2.9, 2.4, 2.2), 7.40 (5H, m, Ph).

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