Controlled Payne Rearrangements of 2,3-Epoxy Alcohols in Aprotic Media: an Enantioselective Total Synthesis of (+)-*exo*-Brevicomin

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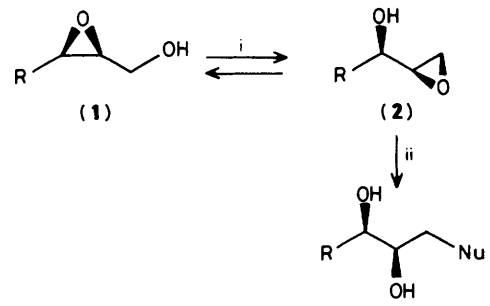
The catalysis of the isomerisation of primary *cis*-2,3-epoxy alcohols to *threo*-1,2-epoxy alcohols by lithium chloride in tetrahydrofuran solution is described; the more reactive terminal epoxides may be selectively trapped *in situ* by reaction with nucleophiles, and this methodology is used in an enantioselective synthesis of (+)-*exo*-brevicomin.

In situ selective nucleophilic cleavage of the more reactive terminal epoxide resulting from the reversible Payne rearrangement[1] of a suitable primary 2,3-epoxy alcohol (Scheme 1) has become a procedure with considerable synthetic potential since the development of the Sharpless asymmetric epoxidation reaction;[2,3] however, it has suffered the great limitation of a protic solvent being necessary for any isomerisation to take place. This requirement clearly places a very severe restriction on the types of nucleophile which may be used in this reaction.

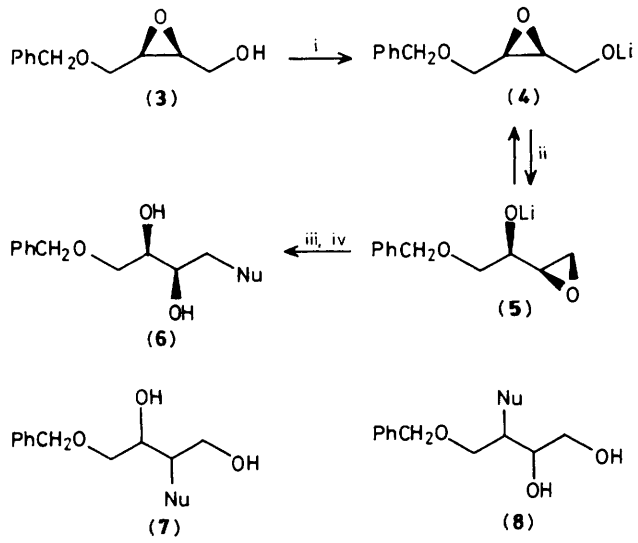
We now report that lithium chloride catalyses the Payne rearrangement in tetrahydrofuran solution thus allowing the use of organometallic reagents as nucleophiles; we assume that the lithium cation is implicated in the reaction mechanism. There is only one report of catalysis by lithium salts of the energetically favourable back reacton, (**2**) → (**1**), in the literature;[4] however, we are aware of no previous examples of such catalysis of the forward reaction, (**1**) → (**2**), or of any selective *in situ* trapping of (**2**) by nucleophilic cleavage.

Treatment of epoxy alcohol (**3**)[5] with n-butyl-lithium (1 equiv.) at −78 °C in a saturated solution of lithium chloride in tetrahydrofuran, followed by warming to room temperature, provides, after 4 h, a 2:1 mixture of the two isomeric epoxy alkoxides (**4**) and (**5**). Addition of organometallic reagents 30 min after alkoxide generation produces a mixture of isomeric diols following protic work-up.

We have carried out a number of such nucleophilic trapping experiments with a range of nucleophiles (Scheme 2, Table 1).



Scheme 1. *Reagents and conditions*: i, HO^-, H_2O, Bu^tOH, heat; ii, Nu^-.



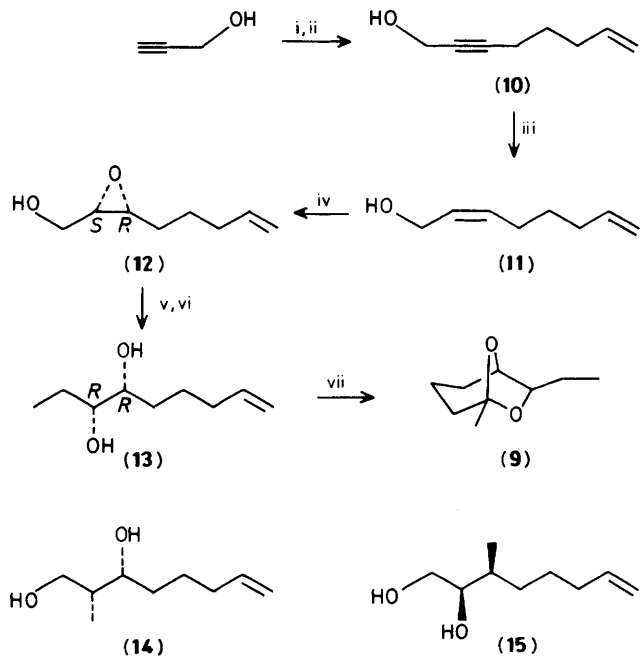
Scheme 2. *Reagents and conditions*: i, Bu^nLi, −78 °C, tetrahydrofuran (thf), LiCl; ii, LiCl, thf, 25 °C; iii, Nu^-, thf, LiCl, 0—25 °C, 16 h; iv, H_3O^+.

Table 1. Trapping of (**4**)/(**5**) with nucleophiles.

Entry	Nucleophilic reagent	Ratio (**6**) : (**7**) : (**8**)	% Yield
1	MeCu	50 : 1 : 1	94
2	MeCuCNLi	50 : 1 : 1	95
3	Me_2CuLi	1 : 3 : 2	95
4	BuCuCNLi	50 : 1 : 1	90
5	Bu_2CuLi	0 : 2 : 1	93
6	$PhCu{\cdot}Me_2S$	50 : 1 : 1	92
7	Ph_2CuLi	2 : 2 : 1	91
8	$(CH_2{=}CMe)_2CuCNLi_2$	20 : 1 : 1	86

We observe a particularly delicate balance between reactivity and selectivity which is crucial to the success of the reaction: if the nucleophile is too reactive then nucleophilic cleavage of the unrearranged epoxide (**4**) predominates (entries 3, 5, and 7); however, if the nucleophile is rather less reactive then it becomes possible to cleave the rearranged and less sterically hindered epoxide (**5**) selectively with little competitive reaction of (**4**) (entries 1, 2, 4, 6, and 8).[6]

We have applied this methodology to a five-step enantioselective total synthesis of (+)-*exo*-brevicomin (**9**) (Scheme 3),[7] an aggregation pheromone of the western pine beetle *Dendroctonus brevicomis*.[8] Alkylation of the lithio dianion of prop-2-ynyl alcohol with 5-bromopent-1-ene in liquid ammonia solution gave the disubstituted acetylene (**10**)† in 80% yield. Catalytic hydrogenation of (**10**) produced the *cis*-allylic alcohol (**11**) (93%, >95% *cis* by capillary g.c.) which was epoxidised using the Sharpless procedure with (+)-diethyl tartrate as the chiral auxiliary resulting in the formation of the (2*S*,3*R*)-epoxy alcohol (**12**) in 78% yield {$[\alpha]_D^{16}$ −3.51°, (*c* 3.45, $CHCl_3$), >94% enantiomeric excess (e.e.)}.‡ Payne rearrangement–nucleophilic trapping with lithium methylcyanocuprate[9] over four days§ gave a mixture of the required diol (**13**), the isomeric ring-cleaved products (**14**) and (**15**), and starting material (**12**) in the ratio 15 : 1 : 4. Cyclisation of the crude product mixture using a Heck reaction[10] followed by column chromatography on silica gel (pentane eluant) gave pure (+)-*exo*-brevicomin (**9**)¶ in 31% overall yield from (**12**).



Scheme 3. *Reagents and conditions*: i, $LiNH_2$, NH_3; ii, $Br[CH_2]_3CH{=}CH_2$, thf; iii, H_2, Lindlar, MeOH; iv, $Ti(OPr^i)_4$ (1.0 equiv.), (+)-diethyl tartrate (1.2 equiv.), Bu^tOOH (2.0 equiv.), 4 Å molecular sieve, −20 °C, 6 days; v, Bu^nLi (1.0 equiv.), thf, LiCl, −78 °C; vi, MeCuCNLi (3.0 equiv.), thf, LiCl, 0—25 °C, 4 days; vii, $PdCl_2$ (cat.), $CuCl_2{\cdot}2H_2O$, thf, 25 °C, 12 h.

† All new compounds gave satisfactory ^1H and ^{13}C n.m.r. and i.r. spectra, and correct mass spectral and/or combustion analysis data.

‡ Determined by ^1H n.m.r. chiral lanthanide shift studies using $Eu(hfc)_3$ measured on the acetate derivative.

§ Prolonged reaction times and larger excesses of organo-copper reagent failed to reduce significantly the amount of starting material present in the crude product mixture.

¶ >98% purity by capillary gas chromatography, spectroscopic data identical to published;[8a] $[\alpha]_D^{18}$ +67.5° (*c* 1.052, ether); +65.1° (*c* 0.756, $CHCl_3$); lit.: $[\alpha]_D^{25}$ +84.1° (*c* 2.2, ether);[8a] $[\alpha]_D^{27}$ +59.0° (*c* 2.5, $CHCl_3$).[8b] The optical purity of this sample was found to be ≥95% e.e. by chiral complexation gas chromatography.[11]

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