Pergamon

Tetrahedron Letters 40 (1999) 8637–8640

TETRAHEDRON LETTERS

On the mechanism of base-induced rearrangements of epoxides to ketones: a formal synthesis of (*S*)-physoperuvine

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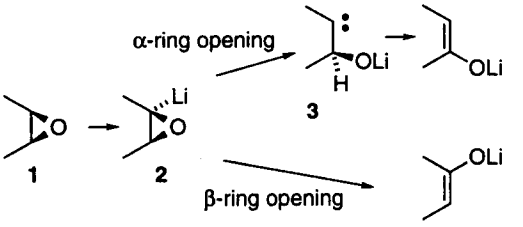
Received 31 August 1999; accepted 22 September 1999

Abstract

The enantioselective α-deprotonation–rearrangement of *trans*- and *cis*-5-silyloxycycloheptene oxides (*trans*-**8** and *cis*-**8**) using organolithiums in the presence of (−)-sparteine **16** or (−)-α-isosparteine **17** to give predominantly 4-silyloxycycloheptanone [(*R*)-**9** (up to 87% *ee*), a known intermediate in the synthesis of (*S*)-physoperuvine (**10**), and (*S*)-**9** (up to 71% *ee*), respectively] is described; the results indicate an α-ring opening mechanism.

Keywords: epoxide; epoxidation; ketone; organolithium.

Base-induced rearrangements of epoxides,[1] particularly enantioselective rearrangements of achiral epoxides,[2] are attracting increasing interest. The isomerisation of epoxides to carbonyl compounds under basic conditions is generally considered to occur by α-deprotonation of the epoxide (**1**→**2**, Eq. 1), followed by rearrangement to enolate.



(1)

Formation of the enolate from the deprotonated (usually lithiated) epoxide **1** could occur by two mechanisms: α-ring opening and insertion of the carbene **3** into the LiOC–H bond or electrocyclic β-ring opening. There is experimental evidence in support of both mechanisms. For example, epoxide **4** gives ketone **5** (Eq. 2[3]), suggesting α-ring opening if the reasonable assumption is made that initial deprotonation occurs at the benzylic position.[3] In contrast, aldehyde **7** was obtained from epoxide **6**

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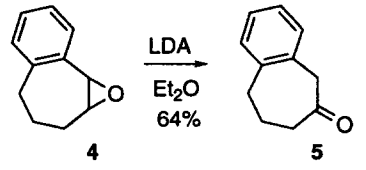
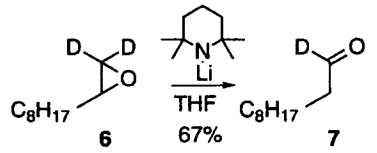
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01810-9

(Eq. 3[4]), which is indicative of electrocyclic β-ring opening.[4] However, in these systems the epoxide substitution pattern is likely to be biasing not only the site of deprotonation but also the rearrangement mode (favouring benzylic carbene formation from epoxide **4** and disfavouring carbene formation at the terminal carbon with epoxide **6**). Examination of the rearrangement mechanism in an unbiased system becomes possible using enantioselective α-deprotonation of an achiral epoxide,[5] where there is a strong preference for deprotonation at the *R*- or *S*-epoxide stereocentre and this preference is known or can be predicted with confidence. Here we report our preliminary studies with such a system, which also leads to a formal synthesis of the alkaloid (*S*)-physoperuvine.

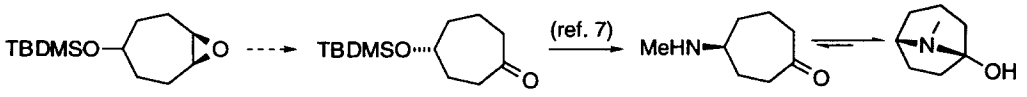


4 **5** (2)



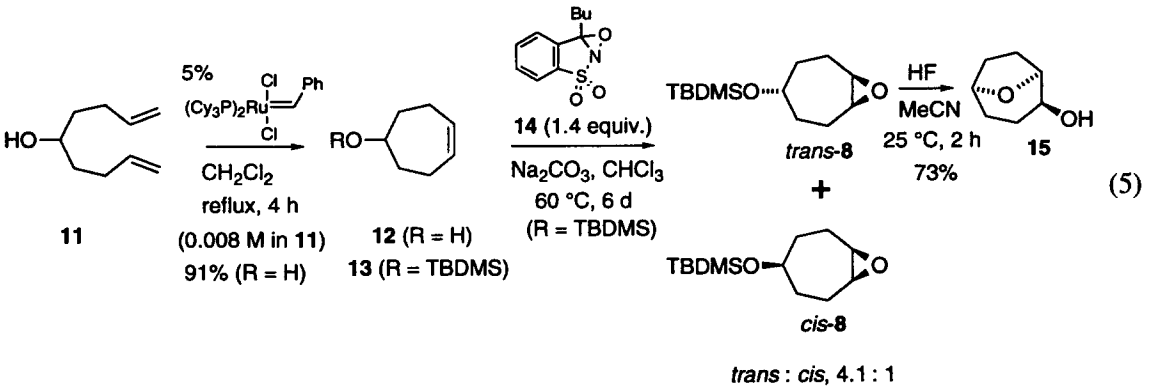
6 **7** (3)

As cycloheptene oxide has been reported to rearrange predominantly to cycloheptanone (cycloheptanone:bicyclo[4.1.0]hexan-2-ol 6.5:1) using Bu^{n}Li (3 equiv.) in Et_2O–hexane (at −78°C for 3 h followed by warming to room temperature),[6] we examined the enantioselective α-deprotonation of 5-substituted cycloheptene oxides where the pseudoasymmetric C-5 carbon atom would lead to chirality in the rearranged ketone. We selected 5-silyloxycycloheptene oxides **8** (Eq. 4), since correlation of sign of specific rotation with absolute configuration of the corresponding ketone **9** is known: the (*R*)-ketone (+)-**9** (70% *ee*) has been converted by desilylation, mesylation and treatment with $MeNH_2$ into (*S*)-physoperuvine (**10**).[7]



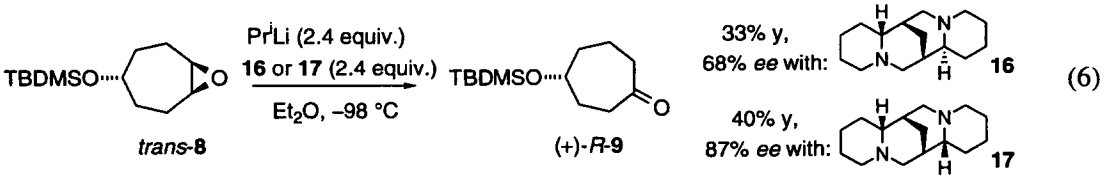
8 (+)-*R*-**9** (−)-(*S*)-pysoperuvine (**10**) (4)

The 5-silyloxycycloheptene oxides **8** were readily prepared from 1,8-nonadien-5-ol **11**[8] (Eq. 5) by catalytic RCM,[9] silylation (TBDMSCl, imidazole, CH_2Cl_2, 25°C, 94%) and epoxidation. Epoxidation of silyl ether **13** using various peracids under a variety of conditions gave moderate selectivity in favour of *trans*-**8** (*trans*-**8**:*cis*-**8**, 1.5–1.9:1), whereas methyl(trifluoromethyl)dioxirane[10] showed no selectivity. The best selectivity for *trans*-**8** found in the present study (*trans*-**8**:*cis*-**8**, 4.1:1) used saccharin-based oxaziridine **14**,[11] which gave pure *trans*-**8** (64%) and *cis*-**8** (15%) following separation by column chromatography. *cis*-**8** Could be selectively prepared (*trans*-**8**:*cis*-**8**, 1:3.3) from silyl ether **13** using 1,3-dibromo-5,5-dimethylhydantoin (0.5 equiv., H_2O–acetone, −5°C) followed by reaction of the bromohydrin with NaH (THF, 25°C),[12] which gave *trans*-**8** (15%) and *cis*-**8** (51%). The relative configuration of the 5-silyloxycycloheptene oxides **8** was determined by desilylation of *trans*-**8** to give the known *endo*-alcohol **15**.[13]



(5)

Subjection of the individual epoxides *trans*-**8** and *cis*-**8** to typical asymmetric rearrangement conditions[5] [Bu^{s}Li (2.4 equiv.) and (–)-sparteine **16** (2.5 equiv.) in Et_2O at –78°C for 5 h, followed by warming to 25°C over 15 h] gave (*R*)-ketone (+)-**9** [30% yield, 68% *ee*,[14] $[\alpha]_D^{33}$ +7.3 (*c* 1.2 in $CHCl_3$)] (cf. Eq. 6) and (*S*)-ketone (–)-**9** [31% yield, 71% *ee*, $[\alpha]_D^{32}$ –8.9 (*c* 1.2 in $CHCl_3$)], respectively. These results indicate an α-ring opening mechanism if one assumes selective removal of the hydrogen at the *R*-configured carbon of the epoxide ring; this assumption is based on all our related observations to date on enantioselective α-deprotonation rearrangement of epoxides [medium-sized (eight-, nine- and ten-membered) cycloalkene oxides,[5] silyloxysubstituted cyclooctene oxides,[15] and (aza)norbornene oxides[16]] using (–)-sparteine **16** where proton removal at the *R*-epoxide stereocentre is consistently observed.



(6)

As in our earlier work,[5] moving to Pr^{i}Li and (–)-α-isosparteine **17** and initiating the reaction at –98°C was found to be the reaction conditions which delivered the best *ee* of (*R*)-ketone (+)-**9** (40% yield, 87% *ee*) from *trans*-**8** (Eq. 6). In the asymmetric desymmetrisations of *trans*-**8** and *cis*-**8**, 5-silyloxybicyclo[4.1.0]hexan-2-ols **18** and **19** were formed respectively in ~10% yields, paralleling the original observations with cycloheptene oxide.[6] Reductive alkylation[5,17] to give the alkenes **20** and **21** was also found to be a competing reaction [~20% with (–)-sparteine **16**, ~10% with (–)-α-isosparteine **17**].

18 (X = H, Y = OTBDMS)
19 (X = OTBDMS, Y = H)

20 (R = Bu^i)
21 (R = Pr^i)

In conclusion, we have developed a new enantioselective route to the alkaloid (*S*)-physoperuvine (up to 87% *ee*) based on α-deprotonation–rearrangement of an achiral epoxide to a chiral ketone; comparison with the sense (and similar magnitude) of asymmetric induction in related α-deprotonation–transannular reactions of medium-sized cycloalkene oxides[5] indicates the epoxide–ketone transformation proceeds solely by α-ring opening.

Acknowledgements

We thank the EPSRC for a research grant (GR/L39940: postdoctoral support to L.A.R.) and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

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