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Functionalized Bicyclo[3.3.0]octanes by Enantioselective Transannular Desymmetrization

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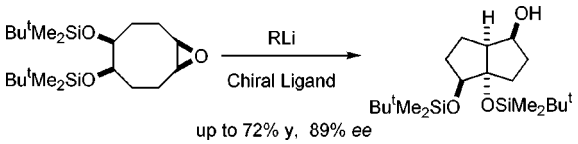
ABSTRACT

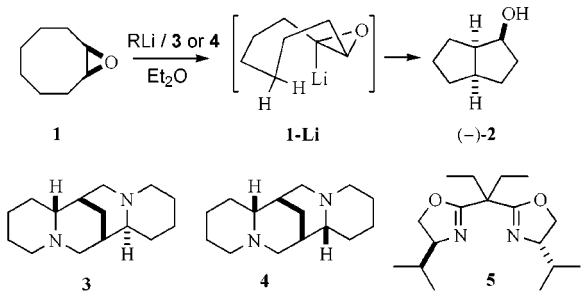


Enantioselective α-deprotonation–rearrangement of achiral substituted cyclooctene oxides 7, 17, and 18 using organolithiums in the presence of (–)-sparteine (3) or (–)-α-isosparteine (4) gives the functionalized bicyclo[3.3.0]octan-2-ols 8, 19, and 20 in 56–72% yields and 83–89% ee's.

Enantioselective desymmetrization of achiral materials is an attractive and powerful concept in asymmetric synthesis.[1] Achiral epoxides represent an important class of substrates for new desymmetrization methodologies,[1,2] and base-induced enantioselective rearrangements of such epoxides are a focus of current interest.[3] The α-deprotonation transannular C−H insertion chemistry of cyclooctene oxide (**1**) was originally investigated by Cope and subsequently studied further by Whitesell and by Boeckman.[4] We recently reported an asymmetric variant of this process for the synthesis of fused ring systems by enantioselective α-deprotonation of achiral medium-sized cycloalkene oxides.[5]

This method uses a secondary organolithium in combination with a chiral ligand such as (−)-sparteine (**3**)[6] to give bicyclic alcohols such as **2** in good yields and ee's (77−84% ee, Scheme 1).

Scheme 1



So far this method has only been studied with unsubstituted cycloalkene oxides which generate a single functional group in the bicyclic products.[5,7] Bicyclo[3.3.0]octanes with func-

(1) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784.
(2) (a) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769−3826. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.
(3) (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361−14384. (b) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439−1457.
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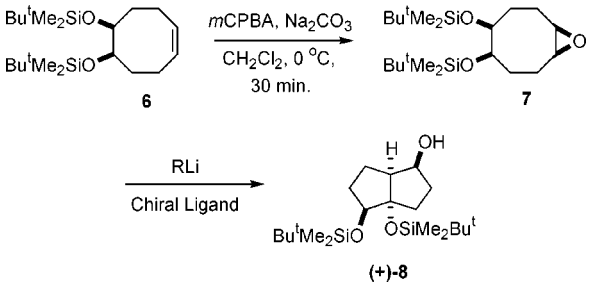
tionality in each ring suitable for the stereocontrolled assembly of more complex structures are versatile intermediates, particularly in polycyclopentanoid synthesis.[8] Here we communicate our preliminary results concerning the viability of synthesizing such systems in an enantioenriched manner by elaboration of readily available 1,5-cyclooctadiene.

Epoxidation of the known alkene **6**, available in two steps from 1,5-cyclooctadiene,[9] resulted in exclusive formation of epoxide **7** (97%), assigned as the all-*cis* compound (vide infra, Scheme 2). The same single isomer of epoxide **7** was

Scheme 2



obtained, although less efficiently, if monoepoxidation was carried out first on 1,5-cyclooctadiene followed by dihydroxylation[10] and protection. Pleasingly, the presence of the additional substituents did not impede base-induced transannular desymmetrization of epoxide **7** to give the desired bicyclic alcohol **8**.

Several reaction conditions were examined with epoxide **7** (Table 1), and it was found that, as in our earlier studies,[5]

Table 1. Effect of Experimental Conditions on the Rearrangement of Epoxide **7**

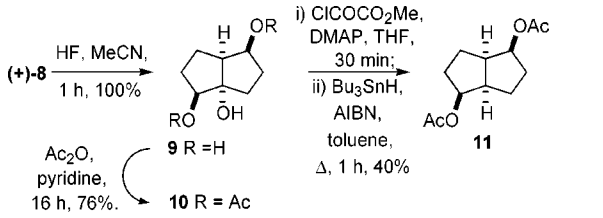
entry	RLi	ligand	*T* (°C)	yield (%)	ee (%)[a]
1	*s*-BuLi	none	−78	18[b]	
2	*s*-BuLi	TMEDA	−78	43	
3	*n*-BuLi	**3**	−78	47	39
4	*s*-BuLi	**3**	−78	51	73
5	*i*-PrLi	**3**	−78	52	76
6	PhLi	**3**	−78	12[c]	32
7	*s*-BuLi	**3**	−90	59	73
8	*i*-PrLi	**3**	−90	57	80
9	*s*-BuLi	**4**	−90	71	84
10	*i*-PrLi	**4**	−90	72	89
11	*s*-BuLi	**5**	−78	15[d]	−52[e]
12	PhLi	**5**	−78	0	
13	*t*-BuLi	**5**	−78	49[f]	−52[e]

[a] Ee's were determined on the 2,6-dibenzoylated derivative of the corresponding triol **9** by HPLC [Daicel Chiralpak AD column, 10:90 EtOH/hexane as eluent]. [b] 27% based on recovered starting material **7** (brsm). [c] 20% brsm. [d] 48% brsm. [e] Enriched in (−)-**8**. [f] 66% brsm.

moving to *i*-PrLi and (−)-α-isosparteine (**4**) and initiating the reaction at −90 °C gave the best results: providing alcohol (+)-**8** in 72% yield and 89% ee (Table 1, entry 10). The enantiomeric alcohol (−)-**8** could also be obtained, albeit in modest yield and ee, by using bisoxazoline **5**[5] as ligand (Table 1, entry 13).

Proof that the stereochemical course of events from alkene **6** to alcohol (+)-**8** is as discussed above was provided by the following transformations. Desilylation of alcohol (+)-**8** (of 73% ee) gave triol **9**, which was selectively diacetylated at the secondary hydroxyl groups followed by deoxygenation[11] of the tertiary alcohol **10** to give the diacetate **11** (Scheme 3), which has been used in prostaglandin syntheses.[12]

Scheme 3



The ^{13}C spectral data of diacetate **11** indicated a symmetric compound (six signals) and were in agreement with the data previously reported for the *endo,endo,cis*-fused system[13] and differed significantly from the ^{13}C data of the *exo,exo,cis*-fused diacetate.[12] The absolute stereochemistry of the major enantiomer of the alcohol (+)-**8** obtained with the sparteines is as shown in Scheme 2 and was established by polarimetric comparison for diacetate **11** ($[\alpha]^{22}_D$ −78.7 (*c* 1.0 in $CHCl_3$), lit.[12] $[\alpha]^{20}_D$ +104.3 (*c* 1.0 in $CHCl_3$) for 1*S*,2*R*,5*S*,6*R* isomer). The sense of asymmetric induction observed with epoxide **7** using RLi/**3** (or **4**) parallels all our previous observations on enantioselective α-deprotonation rearrangement of epoxides using the sparteines, where proton removal at the *R*-epoxide stereocenter is consistently seen.[5,14]

The effect of varying the position and relative stereochemistry of substituents on the desymmetrization process was next examined. The known hemiacetal **13** was first prepared by base-induced rearrangement[15] of readily available *cis,cis*-1,5-cyclooctadiene dioxide **12**[16] (Scheme 4).

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(12) Lemke, K.; Ballschuh, S.; Kunath, A.; Theil, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2051−2055.

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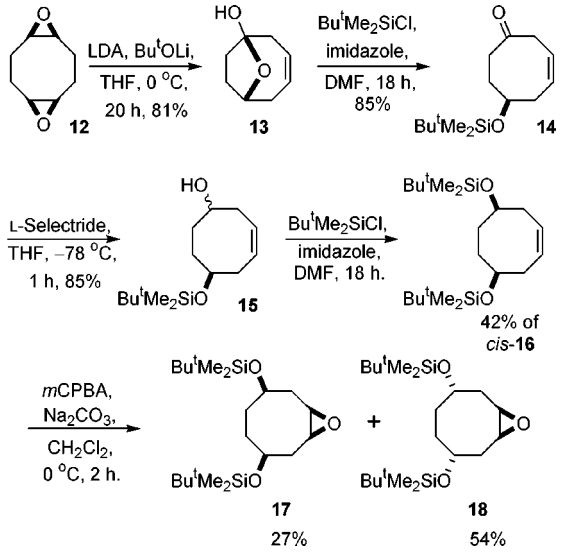
Scheme 4



Reduction of hemiacetal **13** with either $LiAlH_4$ or L-Selectride was unselective, generating a chromatographically inseparable 1:1 mixture of *cis*- and (undesired) *trans*-cyclooct-6-ene-1,4-diol. Silylation of hemiacetal **13** gave enone **14**, which underwent reduction using L-Selectride with modest selectivity (1.7:1) in favor of the alcohol *cis*-**15**. The relative stereochemistry was determined by silylation to the easily separable bis ethers **16** followed by epoxidation with *m*CPBA of the individual isomers. The *trans*-bis ether gave a single epoxide, which was not symmetrical (four methine and four methylene signals in the ^{13}C NMR spectrum), whereas the *cis*-bis ether (*cis*-**16**) gave two epoxides **17** and **18** (2:1), which when separated were both symmetrical (two methine and two methylene signals in each ^{13}C NMR spectrum). Selectivity for the formation of **17** or **18** was not probed further, as the rearrangement chemistry of both *meso*-epoxides **17** and **18** was of interest.

The rearrangement of epoxide **17** proceeded smoothly to afford the bicyclic alcohol **19** in up to 70% yield and 84% ee (Scheme 5, Table 2). Desilylation (HF, MeCN, 25 °C, 1 h) of bicyclic alcohol **19** afforded the *meso*-triol **20** quantitatively, which establishes the relative stereochemistry of the precursor epoxide **17**.

Scheme 5

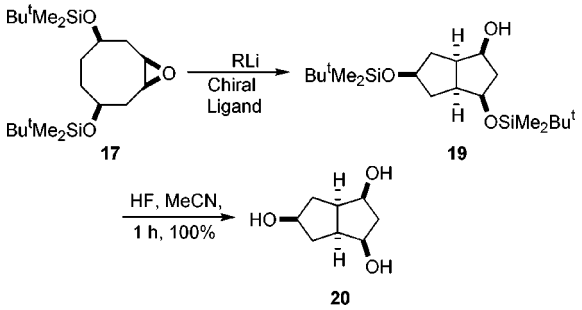


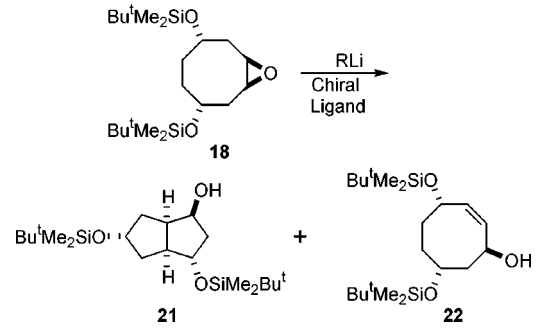
Table 2. Effect of Experimental Conditions on the Rearrangement of Epoxide **17**

entry	RLi	ligand	*T* (°C)	yield (%)	ee[a]
1	*s*-BuLi	none	−78	31[b]	
2	*s*-BuLi	**3**	−90	58	76
3	*s*-BuLi	**4**	−90	52	78
4	*i*-PrLi	**3**	−90	70	84
5	*i*-PrLi	**4**	−90	48	82

[a] Ee's were determined by HPLC [Daicel Chiralpak AD column, 60:40 EtOH/hexane as eluent] on the diol derived from 2,4-dinitrobenzoylation followed by desilylation using $BF_3{\cdot}Et_2O$. [b] 47% brsm.

Most interestingly, the rearrangement of epoxide **18** resulted in two principal products, the ratio between them being found to be strongly influenced by the ligand present (Scheme 6, Table 3). In the absence of a ligand, bicyclic

Scheme 6



alcohol **21** was observed as the minor product, with allylic alcohol **22** as the major product (**21**:**22**, 16:84). When TMEDA was used as ligand, *only* allylic alcohol **22** was detected. The proportion of bicyclic alcohol **21** increased when (−)-sparteine (**3**) was used, although the reaction still favored allylic alcohol **22** (**21**:**22**, 45:55).[17] However, the use of (−)-α-isosparteine (**4**) resulted in a ratio of up to 87:13 in favor of the bicyclic alcohol **21**.

Bicyclic alcohol **21** and allylic alcohol **22** arising from the rearrangement of epoxide **18** are inseparable by flash chromatography. However, allylic alcohol **21** is easily removed by palladium-catalyzed isomerization (Pd/C, H_2 (1 atm), EtOAc, 25 °C, 1 h),[18] to *cis*-3,6-di(*tert*-butyldimethylsilyloxy)cyclooctanone, allowing isolation of the bicyclic alcohol **21** in 83% ee and 56% yield from epoxide **18** when using *s*-BuLi/**4**.

Allylic alcohols were not observed as byproducts in the rearrangements of epoxides **1**, **7**, and **17**, either in the absence of ligands or in the presence of TMEDA or sparteine. The observation of allylic alcohol **22** in the desymmetrization of

(17) For other observations of changes in product profile when using an organolithium with sparteine compared with TMEDA, see: (a) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *64*, 22996-2997. (b) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537−10538.

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Table 3. Effect of Experimental Conditions on the Rearrangement of Epoxide **18**

entry	RLi	ligand	yield (%) of **21** + **22**	**21**:**22**	ee of **21** (%)[a]	ee of **22** (%)[a]
1	*s*-BuLi	none	43	16:84		
2	*s*-BuLi	TMEDA	70	0:100		
3	*s*-BuLi	**3**	60	45:55	71	62
4	*i*-PrLi	**3**	44	45:55	73	70
5	*s*-BuLi	**4**	75	87:13	83	61
6	*i*-PrLi	**4**	44	72:28	85	60

[a] Ee's were determined by HPLC [Daicel Chiralpak AD column, 60:40 EtOH/hexane as eluent] on the diol derived from 2,4-dinitrobenzoylation followed by desilylation using $BF_3{\cdot}Et_2O$.

epoxide **18** indicates that appropriate positioning of ring substituents can significantly alter the reaction course in these rearrangements. Our results with epoxide **18** using TMEDA and the sparteines show that different diamines can be used to direct the reaction to different products.[17] Although allylic alcohol **22** may be (partly) formed by a β-deprotonation/elimination process, the fact that the ee's are similar for bicyclic alcohol **21** and allylic alcohol **22** (at least when using **3**) suggest that they may both be derived from α-lithiation of epoxide **18** (compare **1**-**Li**, Scheme 1) followed by transannular or adjacent[19] C−H insertion, respectively.

In summary, we report the first examples of α-deprotonation transannular C−H insertion of substituted cyclooctene oxides, which provide enantioselective access to functionalized bicyclo[3.3.0]octan-2-ols in good yields and ee's (84−89%). In particular, the ready availability of bicyclic alcohol **8** (four steps from 1,5-cyclooctadiene) suggests it can be considered as an attractive new precursor in asymmetric synthesis, especially in polycyclopentanoid construction.

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Supporting Information Available: ^{13}C NMR spectra for compounds **7**, **8**, and **17**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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