KINETIC RESOLUTION OF *CIS*-3-ALKYLCYCLOHEXENE OXIDE BY A CHIRAL LITHIUM AMIDE – AN APPLICATION TO A SYNTHESIS OF BOTH ENANTIOMERS OF ISOMENTHONE –†

Masatoshi Asami,* Shinsuke Sato, Kiyoshi Honda, and Seiichi Inoue

Department of Chemistry and Biotechnology, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan

Abstract- Kinetic resolution of *cis*-3-alkylcyclohexene oxide (**1**) was examined using chiral lithium amide, lithium (*S*)-2-(pyrrolidin-1-yl)methylpyrrolidide (**2**). High ee (84–>98% ee) of **1** was obtained by using 1.1–1.2 equiv of **2**, while 6-alkyl-2-cyclohexenol (**3**) was obtained in moderate ee (60–68% ee) by using 0.5–0.75 equiv of **2**. Both enantiomers of *cis*-2-isopropyl-5-methylcyclohexanone (isomenthone) were derived from (1*S*,2*R*,3*R*)-(+)-3-isopropylcyclohexene oxide (**1b**) or (1*R*,6*R*)-(–)-6-isopropyl-2-cyclohexenol (**3b**) in a few steps, respectively.

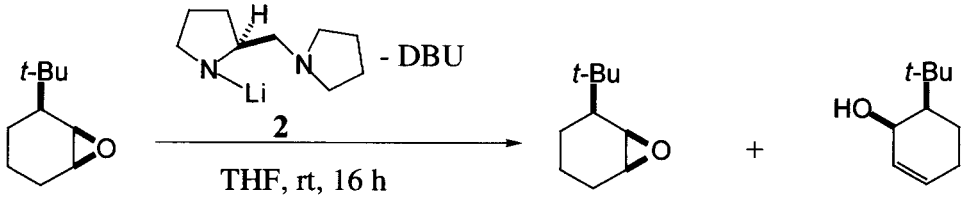
Chiral epoxides are valuable intermediates in the synthesis of more complex natural products. Therefore, considerable efforts have been made to develop efficient methods for the synthesis of enantiomeric epoxides, and various methods have been reported.[1~3] Most successful results were obtained by the enantioselective epoxidation of prochiral olefins using artificial chemical reagents[1,3] or by the enzymatic kinetic resolution of racemic epoxides.[2,3b] There are only a limited number of reports on the kinetic resolution of racemic epoxides employing artificial reagents.[3a,4]

As a part of our investigation on asymmetric reactions using chiral lithium amides,[5] we reported the kinetic resolution of racemic epoxides derived from acyclic olefins.[4b] Good selectivity was obtained in the reaction of *cis*-disubstituted epoxides and lithium (*S*)-2-(pyrrolidin-1-yl)methylpyrrolidide (**2**). Then we examined the kinetic resolution of racemic *cis*-3-alkylcyclohexene oxide (**1**) with **2**, because **1** has three consecutive asymmetric centers on cyclohexane ring and is expected to be a useful chiral intermediate in the synthesis of various substituted cyclohexane natural products.

In 1982 Bellucci *et al.* reported the kinetic resolution of racemic *cis*-3-*tert*-butylcyclohexene oxide (**1a**) by rabbit liver microsomal epoxide hydrase (EC 3.3.2.3), and partially resolved (1*R*,2*S*,3*R*)-**1a** was obtained in 40% ($[\alpha]_D^{20}$ –16.2° (ethyl acetate)) or 25% ($[\alpha]_D^{20}$ –20.6° (ethyl acetate)) after 4 h or 11 h of incubation, respectively.[6] Thus, we firstly examined the kinetic resolution of **1a** using 0.50 equiv of chiral lithium amide (**2**) in the presence of DBU in THF at room temperature for 16 h. (–)-*cis*-6-*tert*-Butyl-2-cyclo-

† Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 73th birthday.

hexenol (**3a**) ($[\alpha]_D^{20}$ −158.4° (*c* 1.04, $CHCl_3$))[7,8] was obtained in 25% and unreacted (+)-**1a** ($[\alpha]_D^{20}$ +8.0° (*c* 2.02, ethyl acetate)) was recovered in 61%. The absolute configuration of the resulting alcohol (**3a**) was (1*R*,6*R*) as (1*S*,2*R*,3*S*)-**1a** was recovered. The ee of **3a** was estimated to be 68% by ^{1}H-NMR after the conversion to the corresponding (*S*)-α–methoxy–α-trifluoromethylphenylacetic acid (MTPA) ester.[9] The ee of **1a** was determined in a similar manner after **1a** was converted to (1*S*,6*S*)-**3a** by excess lithium diethylamide. Then the reaction was carried out under various molar ratios of the substrate and reagents, and high ee (92%) of (1*S*,2*R*,3*S*)-**1a** was obtained in 21% ($[\alpha]_D^{20}$ +30.1° (*c* 1.69, ethyl acetate)) using 1.20 equiv of **2**. (Scheme 1) It is of interest that the selectivity of **2** to **1a** is higher than that obtained by the enzymatic reaction.

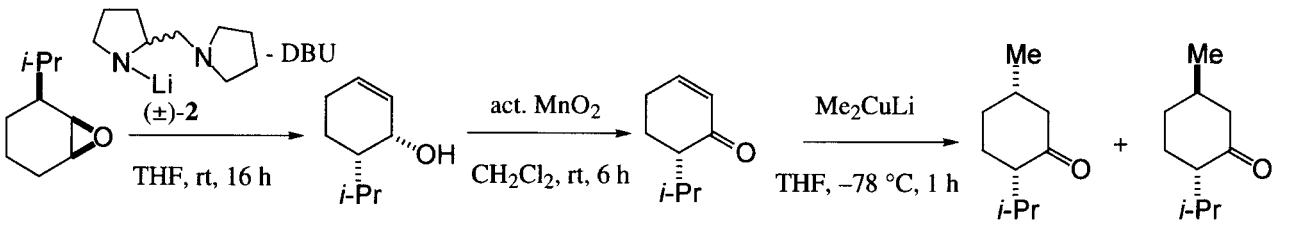


(±)-**1a** : **2** : DBU	(+)-**1a**	(−)-**3a**
1.00 : 0.50 : 0.55	61%, 24% ee	25%, 68% ee
1.00 : 0.75 : 0.82	49%, 49% ee	44%, 58% ee
1.00 : 1.00 : 1.10	39%, 63% ee	55%, 52% ee
1.00 : 1.20 : 1.32	21%, 92% ee	73%, 29% ee

Scheme 1

Next, kinetic resolution of racemic *cis*-3-isopropylcyclohexene oxide (**1b**)[7,10] and *cis*-3-hexylcyclohexene oxide (**1c**)[7,10] was examined. High ee (>98%, 84%) of (1*S*,2*R*,3*S*)-**1b**[11,12] (15%, $[\alpha]_D^{20}$ +40.3° (*c* 1.02, $CHCl_3$)) and (1*S*,2*R*,3*R*)-**1c**[11,13] (30%, $[\alpha]_D^{20}$ +35.6° (*c* 0.86, $CHCl_3$)) were obtained using 1.20 or 1.10 equiv of **2** in the presence of DBU under the same reaction conditions described for **1a**. (Table 1, Entries 4,6) The corresponding alcohols (**3b**)[14] (28%, $[\alpha]_D^{20}$ −174.0° (*c* 0.99, $CHCl_3$)) and (**3c**)[7,15] (42%, $[\alpha]_D^{20}$ −110.9° (*c* 0.99, $CHCl_3$)) were also obtained in moderate ee (66%, 60%)[16] using 0.60 or 0.75 equiv of **2**. (Table 1, Entries 1,5)

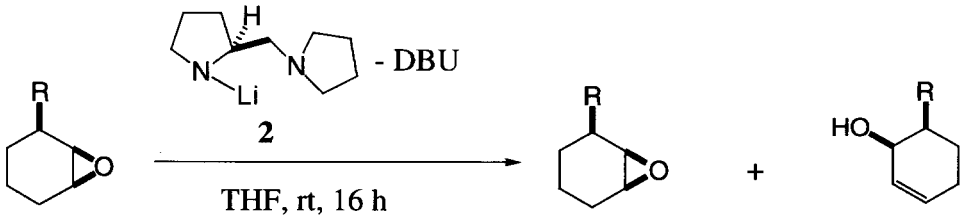
(−)-Isomenthone, a component of geranium oils, was synthesized starting from (+)-**1b**. Allyl alcohol ((+)-**3b**) (91% (by GC), $[\alpha]_D^{20}$ +256.8° (*c* 0.99, $CHCl_3$)) was obtained in high ee (>98% ee by GC (Chiraldex B-DM)) by the reaction of (+)-**1b** (>98% ee) and 3.0 equiv of lithium (±)-2-(pyrrolidin-1-yl)methylpyrrolidide in the presence of DBU in THF (room temperature, 16 h). Interestingly, the use of



(+)-**1b** (+)-**3b** (91%) (−)-**4** (88%) (−)-Isomenthone (79%) (−)-Menthone (7%)

Scheme 2

Table 1



(±)-**1** (+)-**1** (–)-**3**

Entry	(±)-**1**	R	(±)-**1** : **2** : DBU	(+)-**1**[a]	(–)-**3**[a]
1	**b**	*i*-Pr	1.00 : 0.60 : 0.66	71%, 26% ee	28%, 66% ee
2	**b**	*i*-Pr	1.00 : 0.75 : 0.82	62%, 35% ee	37%, 61% ee
3	**b**	*i*-Pr	1.00 : 1.10 : 1.21	27%, 95% ee	72%, 35% ee
4	**b**	*i*-Pr	1.00 : 1.20 : 1.32	15%, >98% ee	84%, 21% ee
5	**c**	C_6H_{13}	1.00 : 0.75 : 0.82	57%, 40% ee	42%, 60% ee
6	**c**	C_6H_{13}	1.00 : 1.10 : 1.21	30%, 84% ee	65%, 42% ee

[a] The yields were based on (±)–**1**, and determined by GC.

lithium diisopropylamide, lithium diethylamide, or lithium pyrrolidide in place of lithium (±)-2-(pyrrolidin-1-yl)methylpyrrolidide gave poor results. The alcohol ((+)-**3b**) was then oxidized with excess activated MnO_2 in dichloromethane at room temperature for 6 h to give (–)-6-isopropyl-2-cyclohexenone (**4**)[17] ($[\alpha]_D^{20}$ –6.4° (*c* 0.83, $CHCl_3$)) in 88% (by GC). Conjugated addition of lithium dimethylcuprate (3.0 equiv) to (–)-**4** in THF at –78℃ for 1 h afforded (–)-isomenthone (>98% ee by GC (Chiraldex B-DM), $[\alpha]_D^{16}$ –114.8° (*c* 0.89, $CHCl_3$) (lit.,[18] $[\alpha]_D^{16}$ +114° (*c* 5.09, $CHCl_3$) for (+)-isomenthone)) in 79% (by GC) along with (–)-menthone as a minor product (7% by GC). (Scheme 2)

(+)-Isomenthone, a component of penny royal oils, was also obtained by similar reactions starting from (–)-**3b**. Treatment of (–)-**3b** ($[\alpha]_D^{20}$ –174.0° (*c* 0.99, $CHCl_3$)), 66% ee) with excess activated MnO_2 (92%) followed by the reaction with lithium dimethylcuprate (3.0 equiv) gave (+)-isomenthone (70% ee by GC (Chiraldex B-DM), $[\alpha]_D^{20}$ +80.6° (*c* 0.58, $CHCl_3$)) with a small amount of (+)-menthone.

It is known that the deprotonation of cyclohexene oxide is selective for the *syn* hydrogen that occupies quasiaxial orientation.[19] Assuming the six-membered cyclic transition state,[19] the reaction of (1*R*,2*S*,3*R*)-**1** with **2** proceeds through the transition state (A) without steric interaction between the substrate and **2**. However, the steric repulsion between cyclohexane ring and **2** arises in the transition state (B) for the reaction of (1*S*,2*R*,3*S*)-**1** with **2**. Thus, (1*R*,2*S*,3*R*)-**1** reacted with **2** predominantly. (Figure 1)

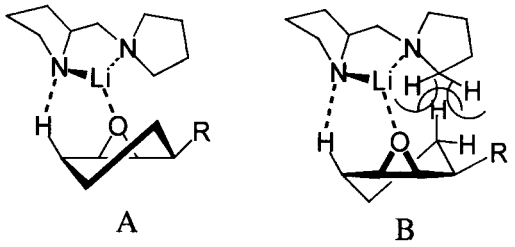


Figure 1

In conclusion, we have demonstrated a convenient method for the preparation of optically active *cis*-3-alkylcyclohexene oxide (**1**) in high ee by the kinetic resolution of racemic **1** with chiral lithium amide (**2**). This method serves for the synthesis of chiral multi-substituted cyclohexane derivatives by subsequent stereoselective reactions as shown in the syntheses of both enantiomers of isomenthone.

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REFERENCES AND NOTES

1. R. A. Johnson and K. B. Sharpless, 'Catalytic Asymmetric Synthesis', ed. by I. Ojima, Wiley-VCH, Inc., 1993, pp.103-158; E. N. Jacobsen, 'Catalytic Asymmetric Synthesis', ed. by I. Ojima, Wiley-VCH, Inc., 1993, pp.159-202; R. Noyori, 'Asymmetric Catalysis in Organic Synthesis', John Wiley & Sons, Inc., 1994.
2. P. L. Barili, G. Berti, E. Mastrorilli, *Tetrahedron*, 1993, **49**, 6263; C. A. G. M. Weijers, *Tetrahedron: Asymmetry*, 1997, **8**, 639, and references cited therein.
3. a) V. Schurig and F. Betschinger, *Chem. Rev.*, 1992, **92**, 873; b) P. Besse and H. Veschambre, *Tetrahedron*, 1994, **50**, 8885.
4. a) Y. Naruse, T. Esaki, and H. Yamamoto, *Tetrahedron Lett.*, 1988, **29**, 1417; b) M. Asami and N. Kanemaki, *Tetrahedron Lett.*, 1989, **30**, 2125; c) J. F. Larrow, S. E. Schaus, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 7420; d) M. Tokunaga, J. F. Larrow, F. Kakiuchi, and E. N. Jacobsen, *Science*, 1997, **277**, 936; e) A. Bigi, A. Mordini, A. Thurner, F. Faigl, G. Poli, and L. Tõke, *Tetrahedron: Asymmetry*, 1998, **9**, 2293.
5. M. Asami, *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 188, and references cited therein.
6. G. Belluchi, G. Berti, R. Bianchini, P. Cetera, and E. Mastrorilli, *J. Org. Chem.*, 1982, **47**, 3105.
7. All new compounds gave satisfactory IR, 270 MHz ^{1}H-NMR, and MS spectra.
8. *cis*-2-*tert*-Butylcyclohexanol[20] was obtained by the catalytic hydrogenation of **3a**.
9. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
10. Epoxides (**1b**) and (**1c**) were prepared by a similar method as reported for **1a**; G. Bellucci, G. Berti, M. Ferretti, G. Ingrosso, and E. Mastrorilli, *J. Org. Chem.*, 1978, **43**, 422.
11. The ee was determined by ^{1}H-NMR using Eu(hfc)$_3$ as a chiral shift reagent.
12. The absolute configuration was determined by the conversion of **1b** to (–)-isomenthone.
13. The absolute configuration was determined tentatively in analogy with both **1a** and **1b**.
14. Racemic **3b** was reported; G. Stork and A. F. Kraft, III, *J. Am. Chem. Soc.*, 1977, **99**, 3850.
15. *cis*-1-Hexyl-2-methoxycyclohexane[21] was obtained by the catalytic hydrogenation of **3c** followed by its methylation.
16. The ee's were determined by GC after the conversion of **3b** or **3c** to the corresponding (*S*)-MTPA esters.[8]
17. Racemic **4** was reported; L. A. Paquette and R. F. Doehner, *J. Org. Chem.*, 1980, **45**, 5105.
18. L. Lombardo, *Org. Synth.*, 1987, **65**, 81.
19. R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, 1970, **92**, 2064.
20. J. Iwamura, *Nippon Kagaku Kaishi*, 1977, 1003.
21. H. Oda, K. Oshima, and H. Nozaki, *Chem. Lett.*, 1985, 53.

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