cephem-4-carboxylic acid(6c): 6c was obtained(61%) from 4c by a similar procedure as described for the preparation of 6a, mp 165-168°C(decom). IR(KBr) 1777cm^{-1}(β-lactam); NMR(DMSO-d_6) δ (ppm) 9.59-9.63(1H, d, J=8.0H, amide-H), 7.40-7.79(4H, m, phenyl-H), 7.24(2H, br s, thiazole-NH_2), 6.74(1H, s, thiazole-H), 5.76-5.83(1H, dd, J=4.8H, 8.0H, C_7-H), 5.05-5.11(1H, d, J=4.8H, C_6-H), 4.53-4.60(1H, d, J=13.5H, C_3-CH_2), 4.24-4.31(1H, d, J=13.5H, C_3-CH_2), 3.84 (3H, s, N-OCH_3), 3.64-3.71(2H, d, J=13.5H, C_2-CH_2).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[1-(3′,4′-difluorophenyl)-1H-tetrazol-5-yl] thiomethyl-3-cephem-4-carboxylic acid(6d): 6d was obtained (65%) from 4d by a similar procedure as described for the preparation of 6a, mp 190-195°C(decom). IR(KBr) 1775 cm^{-1} (β-lactam); NMR(DMSO-d_6) δ (ppm) 9.58-9.62(1H, d, J=8.0H, amide-H), 7.59-7.96(4H, m, phenyl-H), 7.25(2H, br s, thiazole-NH_2), 6.78(1H, s, thiazole-H), 5.76-5.83(1H, dd, J=4.8H, 8.0H, C_7-H), 5.01-5.12(1H, d, J=4.8H, C_6-H), 4.49-4.56 (1H, d, J=13.4H, C_3-CH_2), 4.22-4.29 (1H, d, J=13.4H, C_3-CH_2), 3.84(3H, s, N-OCH_3), 3.66-3.72(2H, d, J=12.3H, C_2-CH_2).

7β-[(Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[1-(2′,4′-difluorophenyl)-1H-tetrazol-5-yl] thiomethyl-3-cephem-4-carboxylic acid(6e): 6e was obtained (60%) by a similar procedure as described for the preparation of 6a, mp 194-197°C. IR(KBr) 1775cm^{-1}(β-lactam); NMR (DMSO-d_6) δ (ppm) 9.59-9.63(1H, d, J=7.9H, amide-H), 7.30-7.96(3H, m, phenyl-H), 7.23(2H, br s, thiazole-NH_2), 6.78(1H, s, thiazole-H), 5.74-5.83(1H, dd, J=4.8H, 7.9H, C_7-H), 5.07-5.18(1H, d, J=4.8H, C_6-H), 4.51-4.58(1H, d, J=13.4H, C_3-CH_2), 4.24-4.31(1H, d, C_3-CH_2), 3.84(3H, s, N-OCH_3), 3.64-3.71(2H, d, J=14.5H, C_2-CH_2).

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References

1. J. M. T. Hamilton-Miller, W. Brumfitt, and A. V. Reynolds, *J. Antimicrob. Chemother.*, **4**, 437 (1978).
2. M. Ochiai, A. Morimoto, T. Miyawaki, Y. Matsushita, T. Okada, H. Natsugari, and M. kida, *J. Antibiotics*, **34**, 171 (1981).
3. T. Kamimura, N. O. Matsumoto, M. N. Mine, S. Goto, and S. Kuwahara, *Antimicrob. Agents Chemother.*, **16**, 540 (1979).
4. H. Takasugi, H. Kochi, T. Masugi, H. Nakano, and T. Takaya, *J. Antibiotics*, **36**, 846 (1983).
5. M. Ochiai, O. Aki, A. Morimoto, T. Okada, and Y. Matsushita, *Chem. Pharm. Bull.*, **25**, 3115 (1977).
6. R. Reiner, U. Weiss, U. Brombacher, P. Lanz, M. Montavon, A. Furlenmeier, P. Angehrn, and P. J. Probst, *J. Antibiotics*, **33**, 783 (1980).
7. K. Shannon, A. King, C. Warren, and I. Phillips, *Antimicrob. Agents Chemother.*, **17**, 807 (1980).
8. T. Naito, J. Okumura, H. Kamachi, H. Hoshi, and H. Kawaguchi, *J. Antibiotics*, **30**, 705 (1977).
9. G. S. Lewis and P. N. Nelson, *J. Med. Chem.*, **22(10)**, 1214 (1979).
10. W. Durckheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem. Int. Ed. Engl.*, **24**, 180 (1985).
11. R. B. Morin and M. Gorman: Chemistry and Biology of -Lactam Antibiotics, Vol 1 Penicillins and Cephalosprons, Academic Press, New York 1982.
12. D. Koh, S. Park, and Y. Kim, *Bull. Korean Chem. Soc.*, **8(3)**, 189 (1987).
13. Han-Mi Pharm. Ind.: Preparation of Cefotaxime Derivatives, JP86 118391, March 11, 1984.
14. W. J. Wheeler, D. R. Finley, R. J. Messenger, R. Koehler, and J. T. Ott, *J. Antibiotics*, **39(1)**, 121 (1986).

Enantioselective Reduction of Racemic Three-Membered Heterocyclic Compounds. 3. Reaction of Epoxides with B-Isopinocampheyl-9-borabicyclo[3.3.1]nonane–Potassium Hydride and Potassium B-Isopinocampheyl-9-boratabicyclo[3.3.1]nonane Systems[1]

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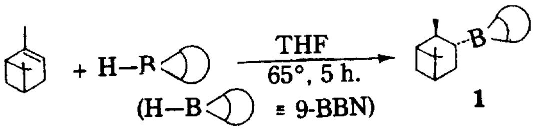
The chiral B-isopinocampheyl-9-borabicyclo[3.3.1]nonane–potassium hydride (IPC-9-BBN–KH) and potassium B-isopinocampheyl-9-boratabicyclo[3.3.1] nonane (K IPC-9-BBNH) systems were applied to the enantioselective reduction of representative racemic epoxides, namely 1,2-epoxybutane, 1,2-epoxyoctane, 3,3-dimethyl-1,2-epoxybutane and styrene oxide. In the case of IPC-9-BBN–KH system, the optical yields are in the range of 8.3-37.4% ee. However, the system of K IPC-9-BBNH provides significantly lower optical yields, showing 7-22.5% ee. These results strongly suggest that the enantioselective coordination of chiral organoborane to the epoxy oxygen of racemic epoxides plays an important role in this resolution.

Introduction

In the previous note[1], we have reported that the optically-active (-)-diisopinocampheylborane-lithium chloride (1:0.1) system reduced enantioselectively various racemic epoxides in the range of 5.5-30.5% ee and racemic episulfide in the range of 6.2-17.7% ee. We have interpreted these results as the chiral organoborane discriminates R- and S-epoxide and episulfide at the step of coordination to the hetero atom of ring. However, the R_2BH-LiCl system can not provide a clear evidence, because the attacking species for reduction has not been defined definately. Therefore, we selected B-isopinocampheyl-9-borabicyclo[3.3.1]nonane—potassium hydride (IPC-9-BBN—KH) and potassium B-isopinocamphey-9-boratabicyclo[3.3.1]nonane (K IPC-9-BBNH) systems, and applied these systems to the enantioselective reduction of various racemic epoxides in the hope to find out the mechanistic importance and to establish the proper system for such resolution.

Results and Discussion

The chiral organoborane, IPC-9-BBN(**1**), can be readily prepared by the reaction of 9-borabicyclo[3.3.1]nonane (9-BBN) and (+)-α-pinene in THF under reflux (eq 1). The chiral trialkylborohydride, K IPC-9-BBNH (**2**), is also readily prepared by the reaction of **1** with excess potassium hydride in THF at room temperature (eq 2).



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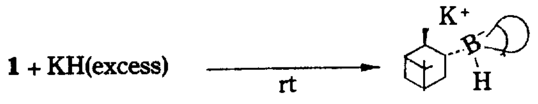
(1)



2

(2)

The chiral organoborane **1** appears to be a promising enantioselective reducing agent for aldehydes[2] and alkynyl ketones[3]. These excellent results seem to come from the initial coordination of the carbonyl oxygen to the boron atom of 9-BBN followed by the enantioselective reduction. We can anticipate that the coordination to oxygen plays an important role for such high enantioselective reduction. Actually, it is of our major interest to see if such role can be extended to the enantioselective coordination of racemic epoxides. In order to define the role of chiral organoborane **1**, we examined the basic borohydride **2** for enantioselective reduction of racemic epoxides and compared each result.

The enantioselective reduction was carried out through either the treatment of 2 equiv of epoxide with 1 equiv of **1** followed by addition of excess KH, or the directive reduction of 2 equiv of epoxide with 1 equiv of **2**, both at 0°C. The reduction went to completion in 7-12 hr and the isolated yields of alcohols are 72-85%.

The optical yields of the alcohols obtained from the reaction of epoxides with the IPC-9-BBN—KH system, as summarized in Table 1, are in the range of 8.3-37.4% ee. The enantiomeric excess values for 1,2-epoxyoctane and 3,3-dimethyl-1,2-epoxybutane appear to be significantly higher than one of 1,2-epoxybutane, which indicates the importance of the structural correlation between the substrate and reagent. However, the ee value for styrene oxide is significantly low. The absolute configuration of alcohols produced is consistently rich in R for aliphatic series and S for the aromatic one with a constant levorotation.

Table 1. Reaction of Racemic Epoxides with B-Isopinocampheyl[a]-9-borabicyclo[3.3.1]nonane (1)—Potassium Hydride System in Tetrahydrofuran at 0°C

Epoxide	Product	Yield (%)	$[\alpha]_D^{22}$ degree	% ee[b]	Absolute confign.
1,2-Epoxybutane	2-Butanol[c]	78	−3.67	27.2	R
	2-Butanol[d]	81	+3.58	26.5	S
1,2-Epoxyoctane	2-Octanol[c]	85	−3.70	37.4	R
	2-Octanol[d]	82	+3.48	35.2	S
3,3-Dimethyl-1,2-Epoxybutane	3,3-Dimethyl-2-butanol[c]	83	−2.40	29.6	R
Styrene oxide	1-Phenylethanol[c]	75	−3.56	8.3	S

[a] Prepared from 92% ee (+)-α-pinene, $[\alpha]_D^{22}$ +47.1[6] Maximum value: (R)-(-)-2-butanol, $[\alpha]_D^{25}$ −13.51[4] (S)-(+)-2-octanol[5], $[\alpha]_D^{20}$ +9.9°; (R)-(-)-3,3-dimethyl-2-butanol[6], $[\alpha]_D^{20}$ −8.1°; (R)-(+)-1-phenylethanol[7], $[\alpha]_D^{20}$ +42.85°. [c] From the reduction of epoxide with the (IPC-9-BBN)-KH system. [d] From the reduction of distillate of the unreacted epoxide with $LiAlH_4$.

Table 2. Reaction of Racemic Epoxides with Potassium B-Isopinocampheyl[a]-9-boratabicyclo[3.3.1]nonane (2) System in Tetrahydrofuran at 0°C

Epoxide	Product	Yield (%)	$[\alpha]_D^{22}$ degree (neat)	% ee[b]	Absolute confign.
1,2-Epoxybutane	2-Butanol[c]	75	−2.51	18.6	R
	2-Butanol[d]	73	+2.42	17.9	S
1,2-Epoxyoctane	2-Octanol[c]	80	−2.23	22.5	R
3,3-Dimethyl-1,2-Epoxybutane	3,3-Dimethyl-2-butanol[c]	80	−1.56	19.3	R
Styrene oxide	1-Phenylethanol[c]	72	−3.00	7.0	S

[a-d] See corresponding footnotes in Table 1.

On the other hand, as shown in Table 2, the results by K IPC-9-BBNH shows similar trend both for the ee value and absolute configuration, only except for the enantioselectivity. The enantioselectivity of the chiral alkylborohydride, which has no vacant orbital for coordination, toward racemic epoxides is significantly lower than that of the IPC-9-BBN—KH system. Thus, the ee values for aliphatic series examined are around 20%, showing no significant structural relationship.

Conclusion

When rearranging the results by these two systems, we can conclude that the enantioselective coordination of chiral organoborane to the epoxy oxygen is more effective for the resolution of racemic epoxides. This also strongly suggests that the enantioselectivity to the coordination between R-and S-epoxides is effected by the structural correlation between the substrate and reagent. Moreover, it should be pointed out that the absolute configuration of alcohols examined by these two systems are exactly same. Thus, all alcohols produced from aliphatic epoxides are rich in R and all alcohols from aromatic epoxide are rich in S. Therefore, it will be interesting to apply the combined system to such enantioselective reduction. This possibility is now under investigation.

Experimental Section

All manipulation were carried out under the positive nitrogen atmosphere, using oven-dried glassware (4 h, at 150°C). The experimental techniques used in handling air-sensitive materials are described elsewhere[8]. The isolated alcohol products obtained from the reduction were further purified through preparative GLC using a 10% Carbowax 20M on Chromosorb p column (6ft × 0.5 inch). Quantitative GLC analysis was performed on a Hewlett-Packard Model 5790A instrument equipped with a flame ionization detector. Optical rotation were measured with a DIP-360 Digital Automatic Polarimeter (Jasco) using micro cells.

9-Borabicyclo[3.3.1]nonane (9-BBN) is prepared by hydroborating 1,5-cyclooctadiene (distilled from $LiAlH_4$) with borane-dimethyl sulfide complex (Aldrich), according to the literature[8]. α-Pinene was treated with $LiAlH_4$ just before use. Epoxides used are either commercial products of the highest quality or products synthesized according to the literature[9].

Preparation of B-Isopinocampheyl-9-borabicyclo [3.3.1]nonane (1). An oven-dried 250-m*l*, round-bottom flask equipped with a septum-capped sidearm, a magnetic stirring bar, a reflux condenser and a stopcock adapter connected to mercury bubbler, was charged with 200 m*l* of 9-BBN in THF solution (0.5M, 100 mmol) and 17.0 m*l* (110 mmol, 10% excess) of (+)-α-pinene ($[\alpha]^{22}_{D}+47.1^0$, 92 % ee). The flask was then heated using an oil bath and the reaction mixture was maintained under reflux with vigorous stirring for 5 h.

The THF solution of **1** was directly used to prepare **2** and the **1**—KH system.

Preparation of Potassium B-Isopinocampheyl-9-boratabicyclo[3.3.1]nonane(2). An oven-dried 500-m*l*, round-bottom flask equipped with a sidearm was attached a mercury bubbler. The flask was charged with *ca.* 15 m*l* of oil suspension of potassium hydride (*ca.* 150 mmol). Then the potassium hydride was washed with pentane (3 × 45 m*l*). To this oil-free potassium hydride (*ca.* 150 mmol), the whole THF solution of **1** prepared above (100 mmol) was transferred *via* a double-ended needle. The reaction was stirred vigorously for 2 h at room temperature. The hydride concentration of the solution was estimated by measuring the number of moles of hydrogen evolved when the aliquot of reagent was hydrolyzed with a hydrolyzing mixture of THF-2 N HCl-glycerine. A 0.71 M concentration of hydride content was observed: IR (THF) 2145 cm^{-1} (B-H); ^{11}B NMR, −16.27 ppm., (d, $J_{B\text{-}H}=69.0$ Hz).

Reaction of Racemic Epoxides with the IPC-9-BBN (1)—KH System. The following procedure for the reduction of racemic 1,2-epoxybutane is representative. A oven-dried 250-m*l* flask, equipped with a septum inlet, a magnetic stirring bar and a mercury bubbler, was charged with 12.9 g (50 mmol) of IPC-9-BBN in 30 m*l* THF and the mixture was cooled to 0°C. To this flask 7.21g (100 mmol) of precooled 1,2-epoxybutane was added quickly with vigorous stirring. The stirring was continued for 12 h at 0°C.[10] The 1,2-epoxybutane—IPC-9-BBN mixture was then transferred to oil-free KH (3g, 75 mmol) *via* a double-ended needle with stirring an the mixture was stirred for 7 h at 0°C. Then, the unreacted epoxide and all other volatile material were distilled and collected using a flask dipped in a ice-water bath. The remaining oily residue was dissolved in THF (30 m*l*) and the excess KH was destroyed carefully by dropwise addition of water. After then, the reaction mixture was oxidized with alkaline hydrogen peroxide in the usual manner[8].
The aqueous layer was saturated with K_2CO_3 and extracted with ether. The combined ethereal extracted was dried over anhydrous $MgSO_4$. The separated organic layer was subjected to fractional distillation, providing, 2.9g of 2-butanol (78% yield). It was further purified through 10% CW 20M column. The optical rotation of 2-butanol was measured by polarimeter; $[\alpha]^{25}_{D}-3.67°$ (neat), 27.2% ee in R[4].

The collected portion of unreacted 1,2-epoxybutane was reduced to 2-butanol with excess lithium aluminum hydride at 0°C. The mixture was oxidized with alkaline hydrogen peroxide. Pure 2-butanol was obtained through purification as described above: $[\alpha]^{25}_{D}+3.58$(neat), 26.5% ee in S[4]. The results are summarized in Table 1.

Reaction of Racemic Epoxides with K IPC-9-BBNH (2) System. The reaction for racemic 1,2-epoxybutane is representative. In the usual set up, the flask was charged with 70.4 m*l* of THF solution of **2** (50 mmol) and then cooled at 0°C. To this was quickly added of precooled 1,2-epoxybutane (7.21g, 100 mmol). The reaction mixture was stirring for 7 h at 0°C. Then, the unreacted epoxide distilled and collected. The residue was dissolved with THF (30 m*l*) and oxidized with alkaline hydrogen peroxide. The alcohol was isolated and purified as described above. The optical rotation of pure 2-butanol was measured by polarimeter; $[\alpha]^{25}_{D}-2.51°$ (neat), 18.6% ee in R[4]. From the reduction of the remained 1,2-epoxybutane with $LiAlH_4$, S-(+)-2-butanol in 17.9% ee was obtained[4]: $[\alpha]^{25}_{D}+2.42°$(neat). The results are summarized in Table 2.

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References and Notes

1. Part 2; J. S. Cha, K. W. Lee, and N. M. Yoon, *Bull. Korean Chem. Soc.*, submitted (1987).
2. M. M. Midland, S. Greer, A. Tramontano, and S. A. Zderic, *J. Am. Chem. Soc.*, **101**, 2352 (1979).
3. M. M. Midland, D. D. McDowell, R. L. Hatch, and A. Tramontano, *J. Am. Chem. Soc.*, **102**, 867 (1980).
4. P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951).
5. (a) S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.*(C)., 2280(1966); (b) S. R. Landor and A. R. Tatchell, *ibid.*, 197 (1967).
6. P. Newman, P. Lutkin, and K. Milsow, *J. Am. Chem. Soc.*, **80**, 465 (1958).
7. R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).
8. H. C. Brown, "Organic Syntheses via Boranes", A Wiley-Interscience Publication, New York, 1975.
9. (a) M. Imuta and H. Ziffer, *J. Org. Chem.*, **44**, 1351 (1979); (b) B. S. Furniss, *et al.* "Vogel's Textbook of Practical Organic Chemistry", 3rd, Longmans, London, 1956.
10. IPC-9-BBN(**1**) does not attack the epoxides examined under these experimental conditions.