COMMUNICATIONS

LETTERS

Asymmetric Reduction of Ketones with Chiral Limonylborane

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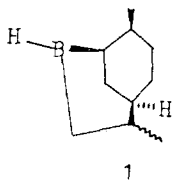
The asymmetric reduction of ketones has beed carried out with a number of chiral metal hydride complexes[1]. In particular, lithium aluminum hydride complexes with chiral alkaloids (ephedrine, quinine, cinchonine, *etc*), chiral aminoalcohols, and monosaccharides have been explored in detail. Unfortunately, such reagents appear not reliable for stereochemical correlations. However, the first chiral trialkylborohydride, lithium B-isopinocampheyl-9-borabicyclo[3.3.1] nonyl hydride, synthesized from (+)-α-pinene and 9-BBN, has been appeared as a new reagent for the asymmetric reduction of ketones with remarkable consistency in the stereochemical results[2].

Recently, (−)-diisopinocampheylborane in high optical purity has been synthesized by the hydroboration with (+)-α-pinene[3]. The hydroboration of *cis*-2-butene with this reagent of high purity followed by alkaline oxidation provided (R)-(−)-2-butanol in 98.4 %. e.e., indicating essentially complete asymmetric induction. It has also been examined for the asymmetric reduction of representative ketones, showing the optical purity of alcohols in the range of 9-37 %[4]. Unfortunately, the rate of reduction with hindered ketones is quite sluggish and the displacement of α-pinene occurs with possible changes in the stereochemical results. Later, the developments of new reagents and procedures enabled the preparation of the first chiral monoalkylborane, monoisopinocampheylborane[5]. More recently, dilongifolylborane, prepared from (+)-longifolene, has been successfully applied for asymmetric hydroboration of *cis*-and trisubstituted olefins[6].

We now wish to report the asymmetric reducing characteristics of the bicyclic chiral reducing agent, 2-bora-4,8-dimethylbicyclo[3.3.1]nonane (limonylborane, 1 and 2), from one of the most abundant monoterpenes, (+)-limonene.



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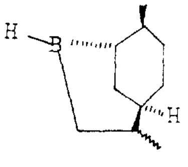

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Cyclic hydroboration of dienes is a versatile tool for the synthesis of boraheterocycles.[7,8] The reaction of (+)-limonene with borane in tetrahydrofuran (THF) proceeds in the *cis*-to-*trans* ratio (the ratio of 1 to 2) of 7:3 in almost quantitative yield.[9]

This chiral reducing agent was applied for the asymmetric reduction of representative ketones. The reagent was generated *in situ* by the hydroboration of (+)-limonene with BH_3-THF solution. The reactions of ketones with limonylborane in THF solution were complete within 4 days at 0 °C. The resulting organoborinic acid intermediates were hydrolyzed and followed by oxidation with alkaline hydrogen peroxide to provide the corresponding alcohols.

The results of asymmetric reduction of prochiral ketones of structural features are summarized in Table 1. Thus, 2-butanone is reduced to (S)-(+)-2-butanol in 3.3 % e.e. Increasing the chain length has a little effect [(S)-(+)-2-heptanol obtained in 7.8 % e.e]. The introduction of alkyl substituents in the α-position decreases the asymmetric induction [(S)-(+)-3,3-dimethyl-2-butanol, 2.8 % e.e.]. However, the introduction of alkyl substituent in the β-position increases the asymmetric induction significantly [(S)-(+)-4-methyl-2-pentanol, 8.6 % e.e]. Methyl phenyl ketone also yields alcohols enriched in the S enantiomer.

It is clearly evident that from the above discussion that all of the alcohols obtained from the reduction of five different ketones with this reagent [from(+)-limonene] are consistently enriched in the enantiomer with the S configuration.

The following procedure for the asymmetric reduction of 2-butanone is representative. All operations were carried out under nitrogen[10]. To a solution of BH_3-THF(150 mmol, 1.0 *M* solution) taken in a 500 m*l* flask was slowly added limonene $[\alpha]^{20}_{D}+120.4°$(neat) (157.5 mmol, 25.3 m*l*) at 0 °C with stirring. In 3 h at 0 °C, hydroboration was complete. To this solution at 0 °C was added slowly with stirring the solution of 2-butanone in THF (4 *M*, 25 m*l*, 100 mmol). The reduction was complete after 24 h at 0 °C. The solvent was removed under reduced pressure and then 100 m*l* of anhydrous ether was added. Then 20 m*l* of water was added

TABLE 1: Asymmetric Reduction of Ketones by Limonylborane in Tetrahydrofuran at 0 °C[a,b]

Ketone	Alcohol (*lit.*[c] 100 %e.e.)	Yield[d] (%)	$[\alpha]_D^{20}$ deg(neat)	Enantiomeric excess, %	Confign
2-Butanone	2-Butanol(13.5)	86	+0.45	3.3	S
4-Methyl-2-pentanone	4-Methyl-2-pentanol(20.5)	72	+1.76	8.6	S
3,3-Dimethyl-2-butanone	3,3-Dimethyl-2-butanol(7.8)	75	+0.22	2.8	S
2-Heptanone	2-Heptanol(10.5)	53	+0.82	7.8	S
Acetophenone	1-Phenylethanol(42.9)	72	−1.18	2.8	S

[a] The ratio of reagent and ketone is 1.5:1; concentrations of ketones were 0.5 *M*. [b] Reactions were essentially over in 4 days. [c] W. Klyne and J. Buckingham, "Atlas of Stereochemistry," Oxford University Press, New York, N. Y., 1974. The values listed are the maximum values for $[\alpha]_D$, degree, reported, presumably 100 % e.e. or close to that quality. [d] Isolated yields of 95 % pure (gc) alcohols and purified by preparative gc.

to destroy residual hydride. The organoborinic acid was oxidized at 40 °C by the successive addition of a 3 *M* NaOH (60 m*l*) and 30 % H_2O_2 (40 m*l*). The reaction mixture was refluxed for 1 hr, cooled and saturated with sodium chloride. The ether layer was separated and dried (K_2CO_3 and $MgSO_4$). The residue after removal of solvent was fractionally distilled to provide 6.4 g (86 % yield) of 2-butanol (>95 % gc purity): bp 97°/762 mm. It was further purified by preparative gas chromatography using 5 % carbowax 20 *M* column: n_D^{20} 1.3969. The optical rotation of 2-butanol product was measured by an auto-digital polarimeter: $[\alpha]_D^{20}$+0.45°(neat), 3.3 % e.e. in *S*.

In conclusion, this bicyclic reducing agent is consistent and promising for configurational assignments and stereochemical correlations. Further, the ready availability of both enantiomers of limonene provides a convenient route to chiral centers of opposite configuration.

References

(1) (a) For a detailed review, see J. D. Morrison and H. R. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J. 1971, pp 202–218 and the references cited therein; (b) S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973); (c) O. Cervinka and O. Belovskt, *Collect. Czech. Chem. Commun.*, **32**, 3897 (1968); (d) S. R Landor, B. J. Millers, and A. R. Tatchell, *J. Chem. Soc.*, C, 2280 (1966), 197(1967).

(2) S. Krishnamurthy, F. Vogel, and H. C. Brown, *J. Org. Chem.*, **42**, 2534 (1977).

(3) H. C. Brown and N. M Yoon, *Israel J. Chem.*, **15**, 12 (1977).

(4) H. C. Brown and A. K. Mandal, *J. Org. Chem.*, **42**, 2996 (1977).

(5) (a) H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **99**, 5514 (1977); (b) A. K. Mandal, P. K. Jadhav and H. C. Brown, *J. Org. Chem.*, **45**, 3543 (1980).

(6) P. K. Jadhav and H. C. Brown, *J. Org. Chem.*, **46**, 2988 (1981).

(7) F. Negishi, S. U. Kulkarni, and H. C. Brown, *Heterocycles*, **5**, 883 (1976).

(8) H. C. Brown and E. Negishi, *Tetrahedron*, **33**, 2331 (1977).

(9) H. C. Brown and C. D. Pfaffenberger, *Tetrahedron*, **31**, 925 (1975).

(10) For handling of air and moisture sensitive compounds, see "Organic Syntheses *via* Boranes," p. 191, H. C. Brown, Wiley–Interscience, New York, 1975.