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ASYMMETRIC METHALLYLBORATION OF PROCHIRAL ALDEHYDES WITH METHALLYLDIISOPINOCAMPHEYLBORANE·SYNTHESIS OF 2-METHYL-1-ALKEN-4-OLS IN $\geq$ 90% ENANTIOMERIC PURITIES

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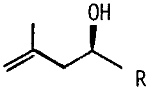
Summary: Methallyldiisopinocampheylborane, on condensation with aldehydes, provides 2-methyl-1-alken-4-ols in $\geq$ 90% enantiomeric purities.

In recent years synthetic chemists have directed their efforts toward the synthesis of biologically active macrolide and ionophore antibiotics. These natural products are structurally acyclic in nature. Consequently, there has been heavy emphasis on the development of synthetic methods for control of absolute and relative stereochemistry in acyclic systems.[1]

Homoallylic alcohols of the general structural type 1 are valuable intermediates for elaboration



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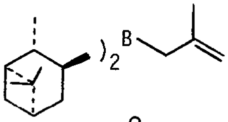

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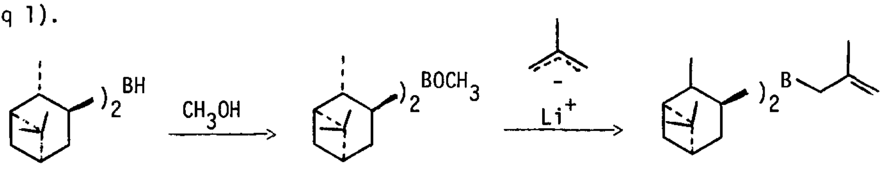
into more complex acyclic compounds. For example, epoxidation[2] or iodocyclization[3] of homoallylic alcohols proceed with excellent diastereoselectivity. Despite many advances in the rapidly growing area of asymmetric synthesis, there is no practical method available for the synthesis of these useful intermediates in excellent ee.[4] We now report a simple and convenient synthesis of 2-methyl-1-alken-4-ols with > 90% enantiomeric purities.

Allyldiisopinocampheylborane[5] and 3,3-dimethylallyldiisopinocampheylborane[6] are excellent reagents for asymmetric allylboration of prochiral aldehydes. Consequently it appeared that methallyldiisopinocampheylborane, 2, might provide a direct route to 2-methyl-1-alken-4-ols in excellent ee.

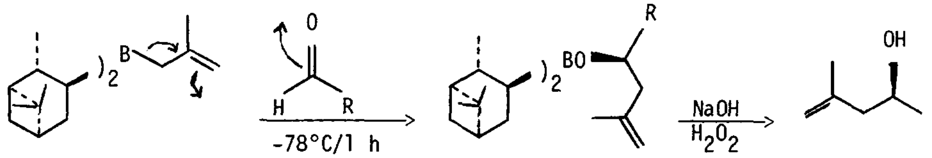
Methallyldiisopinocampheylborane, 2, was readily prepared by methanolysis of diisopinocamphe borane,[7] 3, followed by treatment of the resulting organoboron intermediate, 4, with methallyllithium[8] (eq 1).



(1

3, 99% ee 4 2, 99% ee

The reagent, 2, is extremely reactive. It undergoes condensation with acetaldehyde within 1 at -78°C. The condensation product 5 (R = CH_3) on oxidative workup provides 4-methyl-4-penten-2-o in 90% enantiomeric purity (eq 2).



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5 ≥ 90% ee

The reagent, 2, is generally applicable to a variety of aldehydes such as *n*-propionaldehyde, *n*-butyraldehyde, isobutyraldehyde and pivaldehyde, providing the corresponding 2-methyl-1-alkene-4 ols in 90-96% ee (Table). It is also applicable to a representative α,β-unsaturated aldehyde (eq 2; R = $-CH_2=CH_2$).

A typical experimental procedure follows. All operations were carried out under N_2 atmosphere.[9] Methallyllithium[8] (50 mmol) was added dropwise to the stirred solution of *B*-methoxydiisopinocampheylborane[5,7] (99% ee; 50 mmol) in 50 ml anhydrous ethyl ether at -78°C. The reaction mixture was stirred at -78°C for 1 h, the cooling bath was removed and the reaction mixture was allow to warm up to 25°C (∿ 1 h). The formation of $Ipc_2BCH_2C(CH_3)=CH_2$ is indicated by ^{11}B NMR (δ +84). The reaction mixture was cooled to -78°C and treated with 2.8 ml (50 mmol) of acetaldehyde. The contents were stirred for 1 h at -78°C and then allowed to warm up to 25°C. The completion of the reaction was evident from ^{11}B NMR (δ +54). The organoboron intermediate was treated with 18 ml (5 mmol) of 3 *M* NaOH, followed by 18 ml of 30% H_2O_2 and the contents were stirred at 30°C for 3 h. Th residue, after the usual workup was distilled, bath 80-100°/40-60 mm, and the distillate was passe through a small silica gel column. Elution with pentane removed α-pinene and hexanes and elution with ethyl ether provided 2.8 g (56% yield) of 4-methyl-4-penten-2-ol, bp 72-74°/76 mm, $[\alpha]^{23}D$ +4.94° (neat), 90% ee.

Condensation of Aldehydes with Methallyldiisopinocampheylborane[a]

	Alcohol				
Aldehyde	Alcohol	Yield[b] (isolated)	$[\alpha]^{23}D$ deg C (neat)	% ee[c]	Config.[d]
Acetaldehyde	4-methyl-4-penten-2-ol	56	+ 4.94	90	*S*
n-Propionaldehyde	5-methyl-5-hexen-3-ol	54	- 3.07	90	*S*
n-Butyraldehyde	2-methyl-1-hepten-4-ol	56	- 9.53	91	*S*
2-Methylpropionaldehyde	2,5-dimethyl-5-hexen-3-ol	57	+ 2.84	96	*R*
2,2-Dimethylpropionaldehyde	2,2,5-trimethyl-5-hexen-3-ol	55	- 0.65	90	*R*
Acrolein	5-methyl-1,5-hexadien-3-ol	57	-20.62	92	*R*

[a] (-)-α-Pinene was used to prepare the reagent. [b] We believe that the chemical yields approach 90% with losses primarily involved in isolation (silica gel chromatography) of the highly volatile alcohols. We made no attempts to maximize chemical yields. [c] As determined by ^1H NMR in the presence of the chiral shift reagent $Eu(hfc)_3$. [d] Configurations are predicted in analogy to the configurations of the products obtained with allyldiisopinocampheylborane; see also ref. 4(a).

We are currently exploring the chiral allyldialkylboranes containing a variety of representative substituents in the allylic moiety. If these prove as promising as the four derivatives (6,[5] 7,[6] 8 and 9[10]) already examined, this new asymmetric synthesis should possess considerable generality

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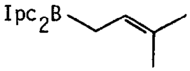

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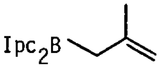

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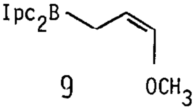

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and make possible the synthesis of a wide variety of structures.

Present results suggest that these chiral allyldiisopinocampheylboranes are superior to the chiral allylboronates utilized by Hoffmann and his coworkers. Thus the allyldialkylboranes are much more reactive toward aldehydes, permitting a lower reaction temperature and improved chirality. The condensation products are obtained in $\geq$ 90% ee versus the 45-70% ee realized with the boronates. The preparation of the allyldiisopinocampheylboranes is considerably simpler than that of the

Hoffmann chiral auxiliary. The products of both absolute configurations can be readily achieved with the diisopinocampheylborane derivatives. On the other hand, it is possible that future research will reveal significant advantages in certain cases for the more stable borinates.

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REFERENCES AND NOTES

1. (a) D. A. Evans, J. V. Nelson and T. R. Taber, "Topics in Stereochemistry," Wiley-Interscience, New York, 1982; Vol. 13, p 1. (b) T. Mukaiyama, "Organic Reactions," Wiley-Interscience, New York, 1982; Vol. 28; p 203. (c) S. Masamune and W. Choy, *Aldrichimica Acta*, 15, 47 (1982). (d) P. A. Bartlett, *Tetrahedron*, 35, 3 (1979).
2. E. D. Mihelich, K. Daniels and D. Eickhoff, *J. Am. Chem. Soc.*, 103, 7690 (1981).
3. (a) P. A. Bartlett and K. K. Jernstedt, *J. Am. Chem. Soc.*, 99, 4829 (1977). (b) P. A. Bartlett and K. K. Jernstedt, *Tetrahedron Lett.*, 1607 (1980). (c) G. Cardillo, M. Orena, G. Porzi and S. Sandri, *J. Chem. Soc. Chem. Commun.*, 465 (1981). (d) M. F. Haslanger and S. Ahmed, *J. Org. Chem.*, 46, 4808 (1981).
4. For somewhat less effective enantioselective allylboration, see: (a) T. Herold and R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, 17, 768 (1978). (b) T. Herold, U. Schrott and R. W. Hoffmann *Chem. Ber.*, 114, 359 (1981). (c) R. W. Hoffmann and T. Herold, *Ibid.*, 375.
5. H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.*, 105, 2092 (1983).
6. H. C. Brown and P. K. Jadhav, *Tetrahedron Lett.*, 1215 (1984).
7. H. C. Brown, M. C. Desai and P. K. Jadhav, *J. Org. Chem.*, 47, 5065 (1982).
8. S. Akiyama and J. Hooz, *Tetrahedron Lett.*, 4115 (1973).
9. For handling air- and moisture-sensitive compounds, see: H. C. Brown, G. W. Kramer, A. B. Levy and M. M. Midland, "Organic Syntheses via Boranes," Wiley-Interscience, New York, 1975, p 191.
10. [*Z*]-3-Methoxydiisopinocampheylborane, **9**, on condensation with aldehydes provides *threo*-1,2-diol derivatives in $\geq$ 98.5% *threo* selectivity and $\sim$ 90% ee. The work was presented at the ACS National Meeting, Spring 1984, St. Louis, Missouri, U.S.A.

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