Chiral Synthesis via Organoboranes. 13. A Highly Diastereoselective and Enantioselective Addition of [(Z)-γ-Alkoxyallyl]diisopinocampheylboranes to Aldehydes

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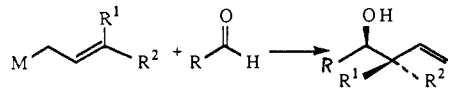
Abstract: Isomerically pure [(Z)-γ-methoxyallyl]diisopinocampheylboranes [**1**, prepared from (+)-α-pinene; **2**, prepared from (−)-α-pinene] have been prepared from *B*-methoxydiisopinocampheylborane and lithiated allyl methyl ether. These enantiomeric [(Z)-γ-methoxyallyl]diisopinocampheylboranes, the first such derivatives to be synthesized, retain their stereochemical identity under the reaction conditions. They have been successfully condensed with various aldehydes, such as acetaldehyde, propionaldehyde, 2-methylpropionaldehyde, and benzaldehyde in a regioselective and stereoselective manner to yield the corresponding *threo*-β-methoxyhomoallyl alcohols in ≥99% diastereoselectivities and ≥95% enantioselectivities. Similarly, [(Z)-γ-(methoxymethoxy)allyl]diisopinocampheylborane (**3**) was prepared and was utilized for the preparation of *threo*-1,2-diol.

The stereocontrolled construction of acyclic compounds with one or more asymmetric centers is currently a topic of intensive study. In recent years many different approaches to achieve a broad solution of this major problem have been explored. At the present time the use of allylic organometallic compounds appears to be an especially promising route to achieve the desired goal.[2]

Many allylic organometallic reagents (M-allylic, M = Li, Na, K, Mg, B, etc.) undergo smooth reaction with carbonyl compounds to yield the corresponding homoallylic alcohols with considerable stereocontrol[3] (eq 1). The addition of γ-alkoxyallyl organometallic

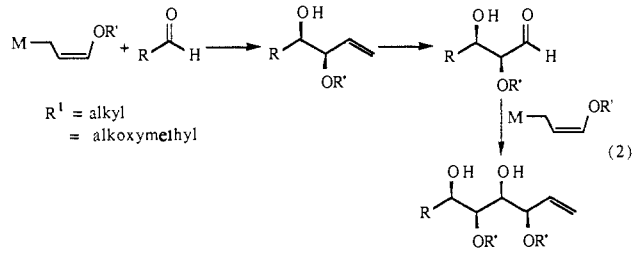


(1)

M = Li, Na, K, Mg, B, etc.

$R^1 = R^2 = H$
$R^1 = H; R^2 = CH_3$
$R^1 = CH_3; R^2 = H$

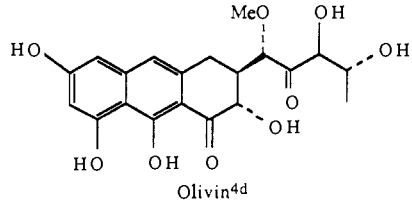
reagents to aldehydes forming alkoxyhomoallyl alcohols (eq 2)



R^1 = alkyl
= alkoxymethyl

(2)

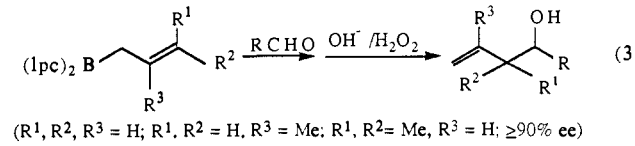
could be very valuable for the synthesis of highly oxygenated natural products, such as carbohydrates or antibiotics.[4] This



Olivin[4d]

method is quite attractive, since it has been possible to achieve carbon–carbon bond formation with simultaneous generation of two asymmetric centers (eq 2).[5] This procedure supplements existing synthetic routes to *vic*-diol derivatives by the (1) polar addition of α-oxygenated carbanions or enolates to aldehydes,[6] (2) alkylation of α-hydroxy carbonyl compounds,[7] and (3) dihydroxylation of stereodefined olefins.[8]

We have observed that many allylic derivatives Ipc_2BR (R = allyl, 2-methallyl, 3,3-dimethylallyl; Ipc = isopinocampheyl) are readily synthesized and yield the homoallylic alcohols on treatment with aldehydes, with high optical purities (eq 3).[9] Further, use



(3)

(R^1, R^2, R^3 = H; R^1, R^2 = H, R^3 = Me; R^1, R^2 = Me, R^3 = H; ≥90% ee)

of isomerically pure (Z)- or (E)-crotyldiisopinocampheylborane reagent makes possible the stereocontrolled formation of two asymmetric centers at one time (eq 4).[9d] Indeed, by judicious use of (E)- and (Z)-crotylborane reagents with Ipc groups from (+)- or (−)-α-pinene, it is possible to synthesize all four possible isomers of 3-methyl-4-penten-2-ol.

(1) Postdoctoral Research Associates on Grants GM 10937-25 from the National Institutes of Health.

(2) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243 and references cited therein.

(3) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(4) (a) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, *23*, 4991. (b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (c) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109. (d) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227.

(5) (a) Metternich, R.; Hoffmann, R. W. *Tetrahedron Lett.* **1984**, *25*, 4095 and references cited therein. (b) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353 and references cited therein. (c) Wuts, P. G. M.; Bigelow, S. S. *J. Chem. Soc., Chem. Commun.* **1984**, 736. (d) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (e) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143. (f) Koreeda, M.; Tanaka, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 845. (g) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, 292. (h) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1981**, 1005. (i) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982**, *47*, 2498.

(6) (a) Bernardi, A.; Cardani, S.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron. Lett.* **1985**, *26*, 6509. (b) Paulsen, H.; Sumfleth, E.; Sinnwell, V.; Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 2055. (c) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900. (d) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 1279. (e) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242. (f) Beak, P.; Baillargeon, M.; Carter, L. G. *J. Org. Chem.* **1978**, *43*, 4255. (g) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620. (h) Ciochetto, L. J.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1977**, *42*, 2948. (i) Touzin, A. M. *Tetrahedron Lett.* **1975**, 1477. (j) Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1987**, *52*, 3176.

(7) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447. (c) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 125–155. (d) Sato, F.; Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 558.

(8) Schroder, M. *Chem. Rev.* **1980**, *80*, 187.

(9) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Jadhav, P. K.; Bhat, K. S.; Perumal, P. T. *J. Org. Chem.* **1986**, *51*, 432 and references cited therein. (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564. (d) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

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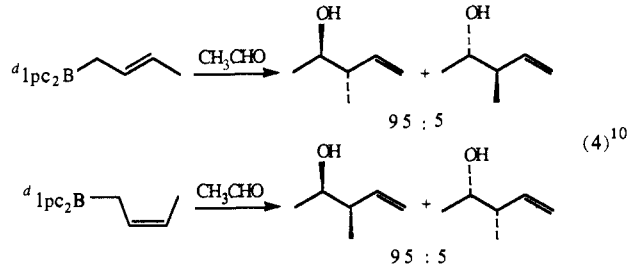
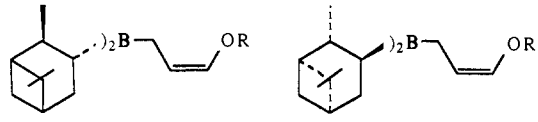


The evidence is that boron is especially valuable in providing stereocontrolled addition of allylic groups to the aldehydes. Moreover, the isopinocampheyl group readily obtained by the hydroboration of α-pinene appears to possess significant advantages as a chiral auxillary. A major advantage of this approach is that it does not require the use of prior synthesized optically active aldehydes or other intermediates to achieve the synthesis of products of high optical purities.

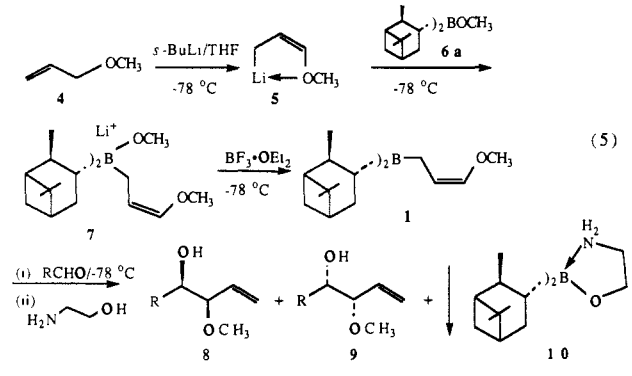
An interest in extending our method to make possible the synthesis of highly oxygenated natural products led us to examine the corresponding reactions of (γ-alkoxyallyl)diisopinocampheylboranes. We discovered that [(Z)-γ-alkoxyallyl]diisopinocampheylboranes [^{d}Ipc$_2$BCH$_2$CH=CHOCH$_3$ (**1**), ^{l}Ipc$_2$BCH$_2$CH=CHOCH$_3$ (**2**), ^{d}Ipc$_2$BCH$_2$CH=CHOCH$_2$OCH$_3$ (**3**)][10] add to aldehydes with excellent threo selectivities[11] and enantioselectivities. We describe herein the results of this study.



1. R = ·CH$_3$ 2. R = ·CH$_3$
3. R = ·CH$_2$OCH$_3$

Results and Discussion

[(*Z*)-γ-Methoxyallyl]diisopinocampheylboranes (1, 2) and Their Reaction with Aldehydes. Preparation of *threo*-1,2-Diol Derivatives. Synthetic access to the [(*Z*)-γ-methoxyallyl]diisopinocampheylborane [**1**, derived from (+)-α-pinene] was made possible by the reaction of the lithium salt **5** of allyl methyl ether (**4**)[12] and *B*-methoxydiisopinocampheylborane [**6a**, derived from (+)-α-pinene]. **4** was metalated with *sec*-butyllithium in THF at −78 °C.[13] The resulting organolithium compound **5** was treated with **6a** at −78 °C (eq 5). The ^{11}B NMR spectrum indicated



(5)

R, A=-CH$_3$, B=-C$_2$H$_5$; C=-CH(CH$_3$)$_2$; D=-C$_6$H$_5$.

the formation of "ate" complex **7** (δ +4). It is known that such ate complexes react with 1.33 equiv of boron trifluoride ethereate and generate the corresponding trialkylborane.[14] Hence, the ate complex was treated with boron trifluoride etherate, and the resulting [(*Z*)-γ-methoxyallyl]borane **1** was immediately treated with acetaldehyde at −78 °C. The reaction mixture upon workup with monoethanolamine furnished *threo*-3-methoxy-4-penten-2-ol (**8A**) with ≥99% diastereoselectivity and 95% enantioselectivity. Similarly, enantiomeric [(*Z*)-γ-methoxyallyl]borane (**2**) was prepared, employing the *B*-methoxydiisopinocampheylborane (**6b**) derived from (−)-α-pinene. **2** on further reaction with acetaldehyde provided the anantiomeric *threo*-3-methoxy-4-penten-2-ol (**9A**) in ≥99% diastereoselectivity and 96% enantioselectivity.

The two diastereomeric MTPA esters were well resolved on a methyl silicone capillary column, 12.5 m × 0.25 mm, at 130 °C, exhibiting retention time of 15.40 min for the isomer **8** and 15.95 min for the isomer **9**.

It was necessary to carry out the synthesis of the reagent **1** at lower temperature. It was observed that bringing the reagent **1** to room temperature for 2 h prior to reaction with acetaldehyde at −78 °C provides a mixture of diastereomers (87:13; analyzed on a Carbowax column), with the desired diastereomer as the major isomer. If the reagent **1** was synthesized and maintained at −78 °C, we experienced no difficulty in achieving diastereoselectivity of ≥99%.

In their related study, P. G. M. Wuts and S. S. Bigelow[5i] reported that the reaction of (RO)$_2$BX (X = Cl, F) with the related anion **5** resulted in some attachment of the boron to the position α to the methoxy substituent. This side reaction was not detected in the present study. Presumably, the large bulk of the Ipc$_2$B moiety results in a marked preference for the less hindered position of the allylic system.

Further, no difficulty was observed in extending this synthesis to other representative aldehydes, such as propionaldehyde, 2-methylpropionaldehyde, and benzaldehyde; thus, the carbon chain is extended providing hydroxy and methoxy groups as new appendages. In all cases comparable optical purities and threo selectivities were realized (Table I).

We have now examined the reaction of a large number of allylic derivatives (allyl, methallyl, 3,3-dimethylallyl, (*E*)-crotyl, (*Z*)-crotyl[9]) of diisopinocampheylborane with aldehydes. In all cases consistent results have been realized, so we have no qualms in using the prior experience as a means of assigning absolute configurations to the products. However, the present case is unusual in having a methoxy rather than a methyl substituent. Consequently, we decided it would be desirable to confirm our assignment in the present case by synthesizing symmetrical derivatives. In such symmetrical derivatives, the product assigned the threo structure should be optically active, whereas the erythro derivative would not.

Accordingly, we applied the reagent **2** to acrolein; assuming that the reaction proceeds in the same manner previously estab-

Table I. Preparation of *threo*-1,2-Diol Derivatives

aldehyde (RCHO)	reagents	threo alcohols[a] yield,[b] %	R[c]	8:9	12:13
CH_3CHO	**1**	57	A	95:5	
	2	59	A	4:96	
C_2H_5CHO	**1**	65	B	94:6	
	2	68	B	5:95	
$(CH_3)_2CHCHO$	**1**	57	C	94:6	
	2	62	C	6:94	
C_6H_5CHO	**1**	72	D	95:5	
	2	75	D	5:95	
CH_2=CHCHO	**1**	63			6:94
	2	69			95:5

[a] Enantiomeric ratios were determined by GC analysis of the α-methoxy-α-(trifluoromethyl)phenylacetic acid esters of the alcohols by using either a methyl silicone, 12.5 m × 0.25 mm, or Supelcowax 10, 50 m × 0.25 mm, column. In the benzaldehyde condensation product, the anantiomeric ratios were determined by ^{19}F NMR analysis of the α-methoxy-α-(trifluoromethyl)phenylacetic acid esters of the alcohols with a Varian XL-200 spectrometer. [b] Isolated yield. [c] See eq 1.

(10) ^{d}Ipc$_2$B from (+)-α-pinene; ^{l}Ipc$_2$B from (−)-α-pinene.

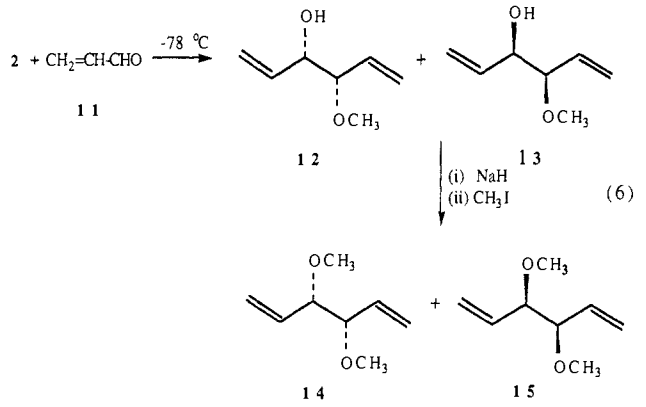
(11) The threo assignment was made here by reference to threose, following the sugar conversion; but for simplicity, the structures are drawn on the basis of a staggered carbon-chain backbone.

(12) (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. (b) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620.

(13) Alternatively, the metalation can be carried out with *n*-BuLi-TMEDA: Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1981**, *22*, 5263.

(14) Brown, H. C.; Sinclair, J. A. *J. Organomet. Chem.* **1977**, *131*, 163.

lished for the saturated derivatives, the structure of the product should be 4-methoxy-1,5-hexadien-3-ol (**12**). Indeed, that product was obtained in ≥99% diostereoselectivity and 95% enantioselectivity (eq 6). Similarly, the reagent **1** with acrolein furnished the enantiomeric 4-methoxy-1,5-hexadien-3-ol (**13**) in comparable diastereoselectivities and enantioselectivities.



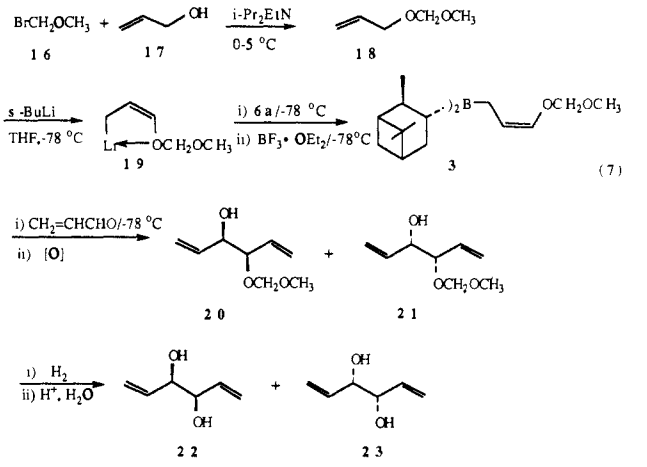
(6)

The diol derivatives **12** and **13** [95:5; $[\alpha]^{23}_D$ −26.81° (neat)], obtained from the reaction of acrolein with the reagent **2**, were methylated by using sodium hydride and methyl iodide.[15] The reaction mixture, after the usual workup, provided optically active symmetrical 3,4-dimethoxy-1,5-hexadiene (**14**, **15**), which exhibited a rotation of $[\alpha]^{23}_D$ +1.78° (neat). Consequently, it cannot be the erythro isomer, which has a plane of symmetry, but must be the threo isomer.

[(*Z*)-γ-(Methoxymethoxy)allyl]diisopinocampheylborane (3) and Its Condensation with Acrolein. Preparation of *threo*-1,2-diol. Free hydroxy functions are useful in many natural product syntheses, especially in carbohydrate chemistry. We also wanted to synthesize the known 3,4-hexanediol as a further proof of our configurational assignments. But both of these objectives required the presence of an easily removable ether grouping. We therefore turned to the allylborane [(*Z*)-γ-(methoxymethoxy)allyl]diisopinocampheylborane (**3**), carrying a protected hydroxy group, which can be deprotected easily under mild conditions. **3** was easily prepared following the route described for the preparation of **1** and **2**. The starting material methoxymethyl allyl ether (**18**) was prepared from methoxymethyl bromide and allyl alcohol in the presence of diisopropylethylamine.[16] **18** was then metalated with *sec*-butyllithium in THF at −78 °C. The resulting organolithium compound **19** was treated with *B*-methoxydiisopinocampheylborane (**6a**) at −78 °C; ^{11}B NMR indicated the formation of ate complex, which was then treated with boron trifluoride etherate. The resulting allylborane **3** was immediately condensed with acrolein at −78 °C. The usual workup with alkaline hydrogen peroxide provided the *threo*-4-[(methoxymethyl)oxy]-1,5-hexadien-3-ol (**20**) in ≥99% diastereoselectivity and 95% enantioselectivity (eq 7).

To establish the absolute configuration of the products the mixture of diol derivatives **20** and **21** [95:5; $[\alpha]^{23}_D$ −52.07° (neat)] upon catalytic hydrogenation (5% Pt on C) and deprotection of the methoxymethyl group in the presence of aqueous methanolic HCl[17] furnished the (3*R*,4*R*)-*threo*-3,4-hexanediol, exhibiting a rotation of $[\alpha]^{23}_D$ +20.9° (*c* 1.0, H_2O) in satisfactory agreement with that reported by A. C. Cope et al.[18] [$[\alpha]^{23}_D$ +22.7° (*c* 2.5, H_2O)]. Consequently, here also the product is unambiguously the threo isomer.

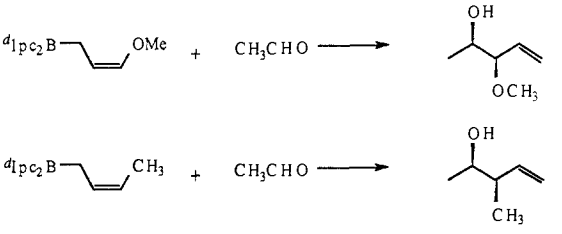
The consistency observed for these allylboration reactions that utilize diisopinocampheyl as the chiral auxilliary suggests that this reaction may prove valuable in providing reliable evidence



(7)

for the absolute configuration of the allylboration products.

It is interesting to compare the products from [(*Z*)-γ-methoxyallyl]- and (*Z*)-crotyldiisopinocampheylborane[19] in their reaction with acetaldehyde (eq 8).



(8)

It is evident that there is no detectable difference in the course of the reaction resulting from the difference in the nature of the substituents, methyl versus methoxy.

In conclusion, this one-pot synthesis of enantiomeric *threo*-1,2-diol derivatives is operationally very simple, making use of readily available chemicals and providing access to both the enantiomers by simply selecting the proper antipode of α-pinene for the preparation of the reagents. Further, it demonstrates the superior chiral-directing property of the 3-pinanyl group in asymmetric synthesis. The reagents **1**–**3** are the most highly enantioselective and diastereoselective [(*Z*)-γ-alkoxyallyl]dialkylborane reagents with achiral aldehydes reported to date.

Experimental Section

General Methods. All operations were carried out under a nitrogen atmosphere with oven-dried glassware. Special experimental techniques used in handling air-sensitive materials are described in detail elsewhere.[20] The spectra were obtained in inert atmospheres. Spectroscopic measurements (NMR, ^{1}H, ^{11}B, ^{13}C, ^{19}F; IR; polarimetric) were made with standard instruments. GC analysis was carried out with a Hewlett-Packard 5740 chromatograph using (a) a 9 ft × 0.125 in. column packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh) or (b) a 9 ft × 0.125 in. column packed with 10% SE-30 on Chromosorb W (100–120 mesh). All alcohols were purified to 100% GC pure by preparative GC with either (a) a 6 ft × 0.5 in. column packed with 20% Carbowax W (60–80 mesh) or (b) a 6 ft × 0.5 in. column packed with 20% SP-2100 on Chromosorb W (60–80 mesh).

Determination of Optical Activity. Diastereomeric ratios were determined by capillary GC analysis with (a) Supelcowax 10, 50 m × 0.25 mm, or (b) methyl silicone, 12.5 m × 0.25 mm, columns. Enantiomeric ratios were determined by GC analysis of the MTPA esters of the alcohols with (a) Supelcowax 10, 50 m × 0.25 mm, or (b) methyl silicone, 12.5 m × 0.25 mm, columns. Configurations are predicted in analogy with the configurations of the products obtained with allyldiisopinocampheylborane[9a] and are supported by the literature.[18]

Preparation of [(*Z*)-γ-Methoxyallyl]diisopinocampheylborane (1) and Its Reaction with Aldehydes. Typical Procedure. To a stirred solution of allyl methyl ether **4** (5.85 mL, 62.5 mmol) in THF (25 mL) was added

(15) Brown, C. A.; Barton, D.; Sivaram, S. *Synthesis* **1974**, 434.
(16) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
(17) Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.
(18) (a) Cope, A. C.; Shen, T. Y. *J. Am. Chem. Soc.* **1956**, *78*, 5916. (b) Buckingham, J. Ed. *Dictionary of Organic Compounds*, 5th ed.; Academic: New York, 1982; Vol. 3, p 2928.
(19) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
(20) For handling air- and moisture-sensitive compounds, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; p 191.

sec-butyllithium in cyclohexane (43.1 mL, 1.16 M, 50 mmol) at −78 °C, over the period of 20–25 min. The mixture was stirred at −78 °C for an additional 10 min and to it was added dropwise *B*-methoxydiisopinocampheylborane[21] (**6a**) in THF (1 M, 50 mL, 50 mmol). After the reaction mixture was stirred at −78 °C for 1 h (^{11}B NMR spectra showed δ +4), boron trifluoride etherate (8.17 mL, 66.5 mmol) was added dropwise at −78 °C. Immediately, acetaldehyde (2.80 mL, 50 mmol) was added, and the mixture was stirred at −78 °C for 3 h and then slowly warmed to room temperature. All volatile compounds were removed at 25 °C (18 mm/1 h, 0.05 mm/12 h). The residue was dissolved in pentane and the pentane layer decanted. The residue was washed with pentane. The combined pentane layers were cooled to 0 °C and treated with monoethanolmine (3.0 mL, 50 mmol). After the reaction mixture was stirred (2 h/0 °C), the white turbid solution was seeded with a crystal of diisopinocampheylborane–ethanolamine complex. At this point the highly crystalline enthanolamine complex **8** separated out. The crystals were filtered and washed with cold pentane. The combined extracts were carefully fractionated to furnish (2*R*,3*R*)-3-methoxy-4-penten-2-ol (**8A**): yield, 57%; bp 119–120 °C (745 mm); threo selectivity, ≥99% (100% pure threo material was obtained by preparative GC); enantioselectivity, 95%; $[\alpha]^{23}_D$ −12.47° (neat); ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 7 Hz), 3.30 (s, 3 H), 3.25–3.90 (m, 3 H), 5.00–5.95 (m, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 18.13, 56.15, 69.21, 88.31, 119.20, 135.25.

Similarly, condensation of ragent **2** [obtained from *B*-methoxydiisopinocampheylborane[21] (**6b**)] with acetaldehyde furnished (2*S*,3*S*)-3-methoxy-4-penten-2-ol (**9A**): yield, 59%; bp 120 °C (745 mm); threo selectivity ≥99%; enantioselectivity, 96%; $[\alpha]^{23}_D$ +12.58° (neat).

(3*R*,4*R*)-4-Methoxy-5-hexen-3-ol (**8B**): yield, 65%; bp 92 °C (40 mm); $[\alpha]^{23}_D$ +0.69° (neat); ^{1}H NMR ($CDCl_3$) δ 0.8–1.75 (m, 5 H), 3.30 (s, 3 H), 3.18–3.70 (m, 3 H), 4.95–6.00 (m, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 9.70, 25.33, 56.27, 74.58, 86.72, 119.44, 135.25.

(3*R*,4*R*)-2-Methyl-4-methoxy-5-hexen-3-ol (**8C**): yield, 57%; bp 88 °C (20 mm); $[\alpha]^{23}_D$ −3.30° (neat); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 6 H, J = 7 Hz), 1.50–2.15 (m, 1 H), 2.60–2.95 (br s, 1 H), 3.30 (s, 3 H), 3.15–3.55 (m, 2 H), 5.10–6.05 (m, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 15.69, 20.02, 29.26, 55.97, 77.66, 85.02, 118.84, 135.38.

(1*R*,2*R*)-1-Phenyl-2-methoxy-3-buten-1-ol (**8D**): yield, 72%; bp 90 °C (0.5 mm); $[\alpha]^{23}_D$ −17.65° (neat); ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 3 H), 3.40–4.00 (m, 2 H), 4.48 (d, 1 H, J = 9 Hz), 4.80–5.88 (m, 3 H), 7.33 (s, 5 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 56.79, 76.85, 87.58, 119.50, 127.42, 127.87, 128.10, 134.21, 139.90.

(3*R*,4*R*)-4-Methoxy-1,5-hexadien-3-ol (**12**): yield, 69%; bp 90 °C (40 mm); $[\alpha]^{23}_D$ +26.81° (neat); ^{1}H NMR ($CDCl_3$) δ 3.00–3.20 (br s, 1 H), 3.35 (s, 3 H), 3.35–3.60 (m, 1 H), 4.00–4.38 (m, 1 H), 5.15–6.30 (m, 6 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 56.27, 74.22, 86.30, 115.97, 119.14, 134.76, 136.71.

(3*S*,4*S*)-3,4-Dimethoxy-1,5-hexadiene: To a stirred suspension of dry sodium hydride (25 mmol), THF (20 mL), and methyl iodide (4.25 g, 30 mmol) was added the alcohol **12** [95% enantiomerically pure; 2.6 g, 20 mmol; $[\alpha]^{23}_D$ −26.82° (neat)] in 5 mL of THF dropwise at 45–50 °C. During the addition of alcohol, evolution of hydrogen was noticed. Following complete addition of alcohol, the reaction mixture was stirred for 30 min and then cooled to 0 °C. The excess of sodium hydride was destroyed by the slow addition of water (5 mL). The aqueous layer was separated and extracted with ether (2 × 20 mL). The combined organic solutions were washed with brine and dried over anhydrous $MgSO_4$. Careful fractionation furnished 3,4-dimethoxy-1,5-hexadiene: bp 91 °C (35 mm); $[\alpha]^{23}_D$ +1.78° (neat); ^{1}H NMR ($CDCl_3$) δ 3.30 (s, 6 H), 3.40–3.72 (m, 2 H), 5.00–6.10 (m, 6 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 56.77, 84.84, 118.59, 135.01.

Preparation of [(*Z*)-γ-(Methoxymethoxy)allyl]diisopinocampheylborane and Its Condensation with Aldehyde. (3*R*,4*R*)-4-[(Methoxymethyl)oxy]-1,5-hexadien-3-ol (20). Step 1. Preparation of methoxymethyl allyl ether (**18**): To a stirred solution of allyl alcohol (**17**, 6.8 mL, 100 mmol) and diisopropylethylamine (19 mL, 110 mmol) was added bromomethyl methyl ether (**16**) dropwise at 0–5 °C. After 15 min, the reaction mixture was slowly warmed to room temperature and stirred for 2 h. It was then diluted with water and extracted with ether (3 × 50 mL). The combined ether extract was washed with brine and dried over anhydrous magnesium sulfate. Careful fractionation furnished methoxymethyl allyl ether (**18**): yield 7.3 g (72%); bp 81 °C.

Step 2. To a stirred solution of **18** (6.12 g, 60 mmol) in THF (25 mL) was added *sec*-butyllithium in cyclohexane (43.1 mL, 1.16 M, 50 mmol) at −78 °C over the period of 20–25 min. The mixture was stirred at −78 °C for an additional 30 min, and *B*-methoxydiisopinocampheylborane (**6a**) in THF (1 M, 50 mL, 50 mmol) was added dropwise. After the reaction mixture was stirred at −78 °C for 1 h, boron trifluoride etherate (8.17 mL, 66.5 mmol) was added dropwise. Immediately afterwards, acrolein (3.34 mL, 50 mmol) was added dropwise and the mixture stirred at −78 °C for 3 h and then slowly warmed to room temperature. All volatile compounds were removed at 25 °C, (18 mm/1 h, 0.05 mm/12 h). The residue was dissolved in ether and oxidized with alkaline hydrogen peroxide. The workup and fractional distillation provided **20**: yield, 62%; bp 102 °C (20 mm); threo selectivity ≥99% (100% pure threo material was obtained by preparation GC); enantioselectivity, 95%; $[\alpha]^{23}_D$ −52.07° (neat); ^{1}H NMR ($CDCl_3$) δ 2.60–2.90 (br s, 1 H), 3.40 (s, 3 H), 3.70–4.38 (m, 2 H), 4.50–4.90 (m, 2 H), 5.05–6.20 (m, 6 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 55.60, 74.52, 80.99, 94.24, 116.57, 119.50, 134.46, 136.65.

Acknowledgment. Financial support from the National Institutes of Health (Grant GM 10937-25) is acknowledged. We also acknowledge the assistance of one of the reviewers in pointing out some pertinent references we had missed.

(21) *B*-Methoxydiisopinocampheylborane of 99% ee was prepared from diisopinocampheylborane of 99% ee[22] according to the procedure reported earlier.[9b]

(22) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.