# Chiral Synthesis via Organoboranes. 2.[1] Rapid Reaction of Boronic Esters of Very High Optical Purity with Lithium Aluminum Hydride. Facile Reaction of Essentially Optically Pure Borinic Esters with Lithium Monoethoxyaluminohydride. A Novel and Quantitative Synthesis of Lithium Monoalkyl- and Dialkylborohydrides of Essentially 100% Optical Purity

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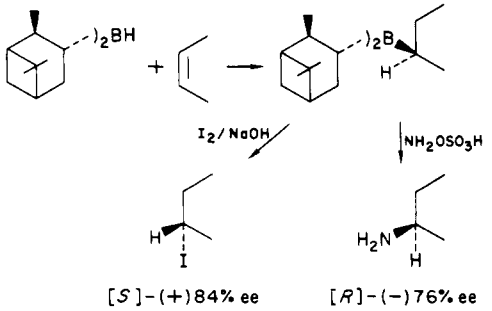
**Abstract:** Boronic esters of very high optical purity readily react with lithium aluminum hydride in diethyl ether–pentane at 0 °C to form the corresponding lithium monoalkylborohydrides of very high optical purity and dialkoxyalane. Under these reaction conditions the dialkoxyalane generally precipitates quantitatively from solution. The reaction is essentially quantitative and is broadly applicable to a representative variety of essentially optically pure boronic esters. Addition of 1 mol equiv of very high optically pure borinic esters to lithium monoethoxyaluminohydride in diethyl ether at 0 °C results in a facile and rapid precipitation of the dialkoxyalane as a solid, producing the corresponding lithium dialkylborohydride of very high optical purity in quantitative yield. The reaction is quite general, proceeds without detectable racemization, and is applicable to essentially optically pure borinic esters of widely varied structural requirements. These lithium monoalkyl- and dialkylborohydrides are very stable and can be stored under nitrogen at 25 °C without hydride loss, redistribution, isomerization, or racemization of the alkyl groups. Methyl iodide or acids readily and quantitatively remove metal hydride from these derivatives, generating the corresponding optically pure monoalkyl- and dialkylboranes for further use. Thus, the present study provides a simple method for preparing essentially 100% optically pure lithium monoalkyl- and dialkylborohydrides under mild conditions, valuable intermediates for storing optically active monoalkyl- and dialkylboranes for extended periods of time, as well as a simple procedure for generating monoalkyl- and dialkylboranes of very high enantiomeric purity, as required for further applications.

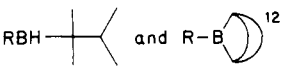
Optically active compounds are of major biological and synthetic importance. Many synthetic procedures have been devised to make optically active compounds more readily accessible through synthesis. Boranes derived from α-pinene exhibit great potential in converting commercially available prochiral olefins into optically active derivatives. Since the original discovery,[3] asymmetric hydroboration–oxidation has become a highly promising synthetic method for the preparation of optically active alcohols.[4]

Furthermore, in the past few years, chiral organoboranes, realized from asymmetric hydroboration, have been utilized to synthesize optically active amines,[5] halides,[6] ketones,[7] and hydrocarbons.[4] However, the optical purities of the compounds thus produced were less satisfactory, only in the range of ee 60–90%.




One reason for this in the past was because chiral organoborane intermediates were difficult to prepare, except in a few cases, in optically pure form. A recent development[8] offers promise of providing both chiral organoborane intermediates and all organic compounds containing a chiral center in essentially ee 100% in both (+) and (-) isomers.

In the recent past, we developed the chemistry of several valuable achiral organoborane intermediates, such as $RB(OR')_2$,[9] $RBH_2$,[10] RBHX,[11] $R_2BH$,[12]




These reagents have been used extensively in organic synthesis involving achiral organoborane intermediates.[13]

By contrast, we did not have available such a broad class of partially substituted chiral organoboranes for chiral organic synthesis. Few optically active mono- and dialkylborane intermediates are known, and the optically active organic moiety in those reagents is essentially restricted to that derived from naturally occurring terpenes, such as α-pinene.[14] In this paper we report a simple and facile synthesis of mono- and dialkylboranes

(1) Addition Compounds of Alkali Metal Hydrides. 27.
(2) Postdoctoral research associate on Grant CHE 79-18881 of the National Science Foundation.
(3) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.
(4) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.
(5) Verbit, L.; Heffron, P. J. *J. Org. Chem.* **1967**, *32*, 3199.
(6) Brown, H. C.; De Lue, N. R.; Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 1290.
(7) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Am. Chem. Soc.* **1982**, *104*, 6844.
(8) Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797.
(9) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.
(10) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1979**, *44*, 465.
(11) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Org. Chem.* **1982**, *47*, 3808.
(12) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975.
(13) Brown, H. C. *Pure Appl. Chem.* **1976**, *47*, 49.
(14) In one case the chiral dialkylborane, bis(2-methylbutyl)borane, was synthesized from optically active 2-methylbutylmagnesium chloride and the reagent utilized for the synthesis of optically active *cis*- and *trans*-3-methyl-5-decene. Giacomelli, G.; Caporusso, A. M.; Lardicci, L. *Gazz. Chem. Ital.* **1974**, *104*, 1311.

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**Table I.** Ethyl Dialkylborinates of High Optical Purity[a]

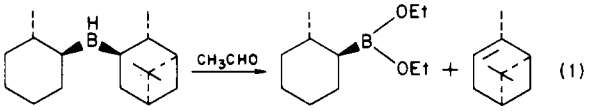
| borinic esters $R^*R_1BOEt$ | yield, % (isolated) | bp, °C (mmHg) | $[\alpha]^{23}_D$, deg (*c*, THF) | % ee[b] | config. of $R^*R_1BOEt$ | $^{11}B$ NMR chem. shift ($\delta$)[g] |
|---|---|---|---|---|---|---|
| ethyl 3-methyl-2-butyl-*n*-pentylborinate | 69 | 50–52 (0.05) | +13.9 (6) | ≥99.6[c] | *S* | +53.6 |
| ethyl *trans*-(2-methylcyclopentyl)-*n*-pentylborinate | 70 | 70 (0.1) | +35.4 (4) | ≥99.7[d] | 1*S*,2*S* | +53.2 |
| ethyl *trans*-(2-methylcyclohexyl)-*n*-pentylborinate | 72 | 72 (0.05) | +29.5 (7) | ≥99.7[e] | 1*S*,2*S* | +53.1 |
| ethyl *erythro*-3-phenyl-2-pentyl-*n*-pentylborinate | 75 | 126–128 (0.01) | −4.1 (7) | 100[f] | 2*S*,3*R* | +54.2 |

[a] $IpcBH_2$, prepared from (+)-$\alpha$-pinene was used for asymmetric hydroboration. [b] Optical purity was determined by measuring the rotation of the alcohols obtained on oxidation and comparing the value with the maximum reported rotations (see fottnotes c–e). [c] Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1966**, *88*, 4185. $\alpha^{27}_D$ +8.12° (neat, *l* 2.0) for 3-methyl-2-butanol. [d] Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797. $[\alpha]^{23}_D$ +46.8° (*c* 1, MeOH) for *trans*-2-methylcyclopentanol. [e] Bäckstrom, R.; Sjöbers, B. *Ark. Kemi* **1967**, *26*, 549. [f] See ref 21. [g] Relative to $EE{\cdot}BF_3$ ($\delta$ 0).

of very high optical purity from readily available, essentially 100% optically pure, monoalkylboronates and dialkylborinates through the intermediate formation of the corresponding lithium mono- and dialkylborohydrides.

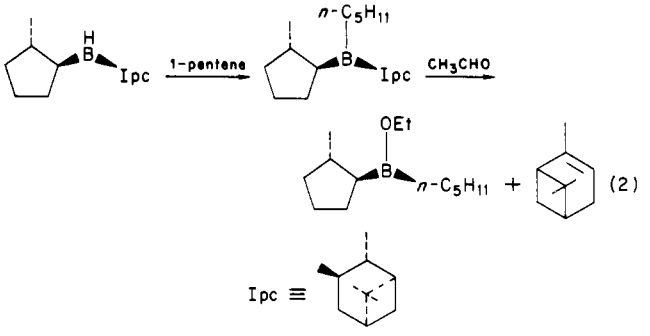
## Results and Discussion

Asymmetric hydroboration of prochiral olefins with monoisopinocampheylborane, $IpcBH_2$, in the molar ratio of 1:1, followed by crystallization, provides the chiral isopinocampheylalkylboranes, IpcRBH, in essentially 100% optical purity. Treatment of these dialkylboranes with acetaldehyde under mild conditions results in the selective, facile elimination of the 3-pinanyl group, providing the corresponding boronic esters in very high optical purity (eq 1). Recently this reaction has been applied for the direct synthesis of various boronic esters in very high optical purity.[8]



(1)

Alternatively, hydroboration of nonprochiral alkenes with the intermediate dialkylboranes, IpcRBH, provides the optically pure mixed trialkylboranes. Reaction of these trialkylboranes with acetaldehyde under very mild conditions results in the selective elimination of the chiral auxiliary, the 3-pinanyl group, to provide the corresponding ethyl dialkylborinate and $\alpha$-pinene. Thus, isopinocampheyl-(1*S*,2*S*)-*trans*-(2-methylcyclopentyl)borane rapidly hydroborates 1-pentene at −25 °C to provide the corresponding chiral mixed trialkylborane. Treatment of the resulting trialkylborane with acetaldehyde at 25 °C liberates $\alpha$-pinene quantitatively and provides ethyl (1*S*,2*S*)-*trans*-(2-methylcyclopentyl)-*n*-pentylborinate in very high optical purity (eq 2). The



(2)

$\alpha$-pinene eliminated is optically pure and is removed by distillation under vacuum. Ethyl (1*S*,2*S*)-(+)-*trans*-(2-methylcyclopentyl)-*n*-pentylborinate, purified by distillation, is obtained in ee >99.5%, as estimated by its oxidation to (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol.[8] Similarly, various other borinic esters have been prepared in very high optical purity (Table I).

Chiral alkylboronic esters and dialkylborinic esters are exceptionally promising intermediates for carbon–carbon bond-forming reactions.[7,15] These reactions are especially promising for chiral synthesis proceeding through boron intermediates. Yet, it is highly desirable to convert the boron–oxygen bonds in these intermediates to boron–hydrogen bonds. Successful achievement of this objective would greatly extend the range of versatility and diversity of chiral organoborane chemistry. We recently reported[16] that lithium aluminum hydride, in a mixture of ethyl ether (EE) and *n*-pentane, reacts rapidly and quantitatively with various achiral boronic esters to give the corresponding achiral lithium monoalkylborohydrides (eq 3). We have also observed[17] that

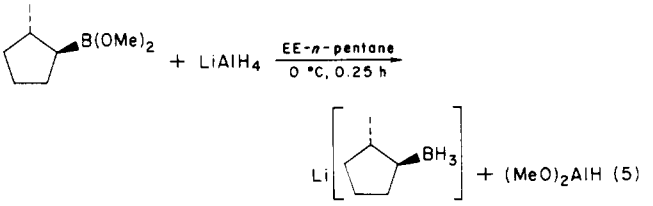
$$RB(OMe)_2 + LiAlH_4 \xrightarrow[0\ °C,\ 0.25\ h]{EE\text{–}n\text{-pentane}} LiRBH_3 + (MeO)_2AlH \quad (3)$$

lithium monoethoxyaluminohydride (LMEA) undergoes facile and quantitative reaction with a wide variety of achiral borinic esters to give the corresponding lithium dialkylborohydrides (eq 4). With the ready availability of boronic and borinic esters of

$$R_2B(OEt) + LiAlH_3(OEt) \xrightarrow[0.25\ h]{EE,\ 0\ °C} LiR_2BH_2 + (EtO)_2AlH \quad (4)$$

very high optical purity, we applied the above reactions to these essentially optically pure boronic and borinic esters with a view to synthesize lithium mono- and dialkylborohydrides containing alkyl groups of very high optical purity.

Addition of an ethereal solution of $LiAlH_4$ (1.0 M) to an equivalent amount of dimethyl (1*S*,2*S*)-(+)-*trans*-(2-methylcyclopentyl)boronate of ee >99.5% in *n*-pentane (0.5 M) at 0 °C resulted in a mildly exothermic reaction with the concurrent formation of a white precipitate. The mixture was centrifuged, and the clear supernatant solution was transferred to another flask. The solid dimethoxyalane was washed with *n*-pentane. The clear centrifuged washings were combined with the supernatant. This solution contained pure lithium (1*S*,2*S*)-*trans*-(2-methylcyclopentyl)borohydride (eq 5). The borohydride was isolated by a




simple evaporation of the solvent, dissolved in a known amount of solvent, and its concentration estimated by hydrolysis.[12] From this value the yield was determined. The purity of the optically active borohydride was examined by $^{11}B$ and $^{27}Al$ NMR and shown to be free of any boron- or aluminum-containing impurities. It is significant that oxidation of the lithium (1*S*,2*S*)-*trans*-(2-methylcyclopentyl)borohydride afforded (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol of ee >99.5%, indicating that the conversion of boronic esters to the borohydride proceeds without any observable racemization. We applied this reaction to various other

(15) (a) Matteson, D. S.; Majumdar, D. S. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (b) Brown, H. C.; Imai, T. *Ibid.* **1983**, *105*, 6285.

(16) Singaram, B.; Cole, T. E.; Brown, H. C. *Organometallics* **1984**, *3*, 774.

(17) Singaram, B.; Cole, T. E.; Brown, H. C. *Organometallics* **1984**, *3*, 1520.

**Table II.** Lithium Monoalkylborohydrides of High Optical Purity

| boronic esters $RB(OMe)_2$ | lithium monoalkylborohydride $LiRBH_3$ R | yield,[b] % | % ee[a] | $^{11}B$ NMR chem. shift, δ (multiplicity) | $^{11}B$ NMR $J_{BH}$, Hz |
|---|---|---|---|---|---|
| methyl (2*S*)-(+)-3-methyl-2-butylboronate | 3-methyl-2-butyl | 92 | ≥99.6 | −26.2 (q) | 74 |
| methyl (1*S*,2*S*)-(+)-*trans*-(2-methylcyclopentyl)boronate | *trans*-2-methylcyclopentyl | 85 | ≥99.8 | −27.4 (q) | 74 |
| methyl (1*S*,2*S*)-(+)-*trans*-(2-methylcyclohexyl)boronate | *trans*-2-methylcyclohexyl | 86 | ≥99.7 | −25.5 (q) | 74 |
| methyl (2*S*,3*R*)-(−)-*erthro*-3-phenyl-2-pentylboronate | 3-phenyl-2-pentyl | 75 | ≥99.8 | −25.1 (q) | 75 |

[a] See footnote b in Table I. [b] Determined by hydride analysis. See Experimental Section.

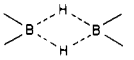
**Table III.** Lithium Dialkylborohydrides of High Optical Purity

| lithium dialkylborohydride $LiR^*R_1BH_2$ | yield,[b] % | % ee[c] | $^{11}B$ NMR chem. shift, δ (multiplicity) | $^{11}B$ NMR $J_{BH}$, Hz | IR $\nu_{BH}$, $cm^{-1}$ |
|---|---|---|---|---|---|
| lithium (2*S*)-3-methyl-2-butyl-*n*-pentylborohydride | 80 | ≥99.6 | −14.5 (t) | 68 | 2093 |
| lithium (1*S*,2*S*)-*trans*-(2-methylcyclopentyl)-*n*-pentylborohydride | 75 | ≥99.8 | −14.8 (t) | 68 | 2089 |
| lithium (1*S*,2*S*)-*trans*-(2-methylcyclohexyl)-*n*-pentylborohydride | 75 | ≥99.7 | −14.5 (t) | 67 | 2105 |
| lithium (2*S*,3*R*)-*erythro*-3-phenyl-2-pentyl-*n*-pentylborohydride | 72 | ≥99.8 | −14.2 (t) | 65 | 2109 |
| lithium diisopinocampheylborohydride[a] | 85 | >99 | −5.5 (t) | 69 | 2100 |

[a] Prepared from (+)-α-pinene. [b] Determined by hydride analysis. See Experimental Section. [c] See footnote b in Table I.

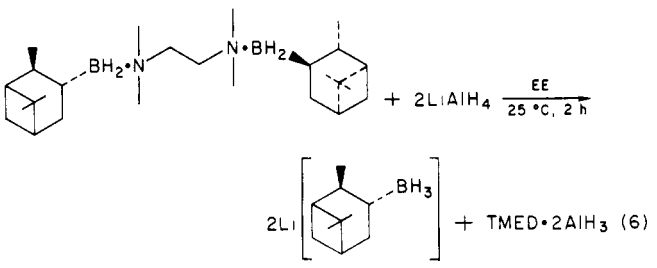
**Table IV.** Monoalkylboranes of High Optical Purity

| monoalkylboranes[a] $RBH_2$ R | yield,[b] % | $^{11}B$ NMR chem. shift, δ (multiplicity) | $^{11}B$ NMR $J_{BH}$, Hz | $TMED{\cdot}2BH_2R$ mp, °C | yield, % (isolated) | $[\alpha]^{23}_D$, deg (*c*, THF) | % ee[c] |
|---|---|---|---|---|---|---|---|
| (2*S*)-3-methyl-2-butyl | 85 | +23.8 (d) | 131 | 46–48 | 94 | +26.8 (4) | ≥99.6 |
| (1*S*,2*S*)-*trans*-2-methylcyclopentyl | 82 | +23.3 (d) | 130 | 88–90 | 95 | +84.1 (3) | ≥99.7 |
| (1*S*,2*S*)-*trans*-2-methylcyclohexyl | 85 | +23.8 (d) | 130 | 68–70 (dec) | 85 | +72.2 (3) | ≥99.7 |
| (2*S*,3*R*)-*erythro*-3-phenyl-2-pentyl | 82 | +23.6 (br s) | | 64–66 (dec) | 82 | +8.2 (4) | ≥99.8 |

[a] These monoalkylboranes actually exist in EE solutions as the dimers, that is, as derivatives of the diborane molecule, as established by the strong absorption at 1565 $cm^{-1}$ for the  bridge. [b] Determined by hydride analysis. [c] See footnote b in Table I.

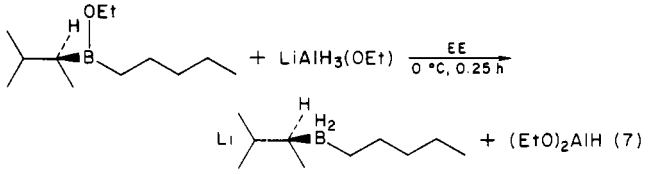
boronic esters of very high optical purity, and the results are summarized in Table II.

Lithium monoisopinocampheylborohydride can be prepared either by the above method or more directly from *N,N,N',N'*-tetramethylethylenediamine–bis(monoisopinocampheylborane) ($TMED{\cdot}2BH_2Ipc$) adduct and $LiAlH_4$ (eq 6). Simple decantation



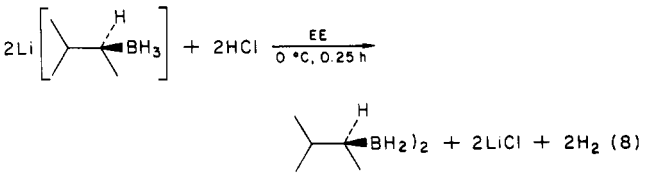

affords optically and chemically pure lithium monoisopinocampheylborohydride free of any aluminum-containing compound.

For preparation of essentially optically pure lithium dialkylborohydrides, the reactions were generally run by adding a solution of optically active borinates in ethyl ether (EE) to lithium monoethoxyaluminohydride (LMEA) in EE. Thus, a 0.5 M EE solution of ethyl (2*S*)-(+)-3-methyl-2-butyl-*n*-pentylborinate was added to LMEA in EE at 0 °C with constant stirring. A voluminous white precipitate of diethoxyaluminohydride formed rapidly (eq 7). The lithium dialkylborohydride was isolated by



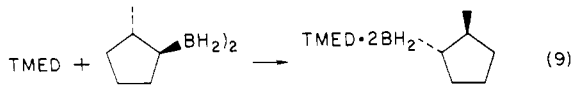

the procedure similar to that described for the isolation of lithium monoalkylborohydride. It was then dissolved in a known amount of solvent and the concentration estimated by hydrolysis. The yield was then calculated from the molarity of the solution. The purity of the dialkylborohydride was determined by its $^{11}B$ NMR, $^{27}Al$ NMR, and IR spectra. The conversion of borinic esters to the corresponding dialkylborohydrides proceeds without any observable racemization, as evidenced by the isolation of (2*S*)-(+)-3-methyl-2-butanol of ee >99.5% from the oxidation product of lithium (2*S*)-3-methyl-2-butyl-*n*-pentylborohydride. Several lithium dialkylborohydrides of very high optical purity were prepared by utilizing the above method, and the results are summarized in Table III.

These lithium monoalkyl- and dialkylborohydrides are very stable and can be stored under nitrogen, even at 25 °C, without any hydride loss, redistribution, isomerization, or racemization of the alkyl groups. Consequently, it is now possible to store these optically active monoalkyl- and dialkylboranes as their lithium borohydrides for extended periods of time, converting them into the corresponding free organoboranes when needed by a convenient simple reaction treatment either with methyl iodide or hydrogen chloride. For example, reaction of lithium (2*S*)-3-methyl-2-butylborohydride with hydrogen chloride in EE cleanly generated bis(monosiamylborane) in ee >99.5% (eq 8). Monosiamylborane



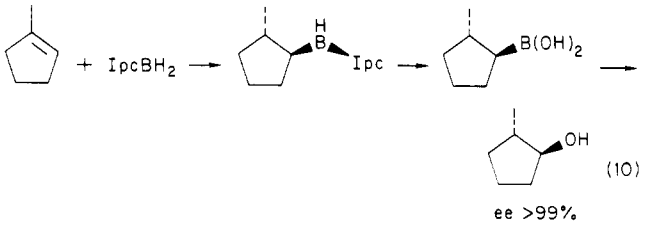

exists as a strong dimer in EE. This is the first time monosiamylborane and the other monoalkylboranes were ever synthesized

and also in an optical purity approaching 100%. Other optically pure monoalkylboranes were generated and characterized as their bis adduct with TMED (Table IV) (eq 9).



(9)

We encountered no difficulty in generating these optically active organoboranes nor in utilizing them for typical organoborane applications. For example, lithium monoisopinocampheylborohydride was utilized for asymmetric hydroboration. This borohydride was treated with HCl in EE at 0 °C to generate free monoisopinocampheylborane ($IpcBH_2$). The $IpcBH_2$ thus prepared was utilized for the synthesis of optically pure (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol (eq 10).[8]



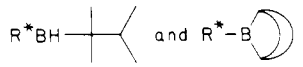
(10)

ee >99%

Similarly, lithium diisopinocampheylborohydride was used in the asymmetric hydroboration of *cis*-2-butene. Thus, lithium diisopinocampheylborohydride in THF was mixed with α-pinene, and a slurry of diisopinocampheylborane ($Ipc_2BH$) was prepared by the addition of methyl iodide. (The α-pinene was added to repress possible dissociation of $Ipc_2BH$.) To this reagent at −25 °C *cis*-2-butene was added, and the reaction was carried out according to the published procedure.[18] The *sec*-butyl alcohol, obtained following oxidation, was isolated in 65% yield and in 97% optical purity.

## Conclusion

The present study provides a convenient and simple procedure for the synthesis of various optically pure lithium mono- and dialkylborohydrides. These are potential asymmetric reducing agents. Furthermore, these borohydrides can be stored for an extended period of time without hydride loss, isomerization, or racemization. The free optically pure mono- and dialkylboranes can be generated as desired, rapidly and quantitatively, simply by reacting these borohydrides with either hydrogen chloride or methyl iodide. For the first time we are in a position to synthesize several chiral organoborane intermediates, such as R*BHX,




in essentially 100% optical purity in both (+) and (−) isomers. These are valuable reagents, especially promising for chiral synthesis proceeding through boron intermediates. We continue to actively explore chiral syntheses via these chiral organoborane intermediates.

## Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[12] The spectra were obtained in an inert atmosphere. The infrared spectra were obtained with a Perkin-Elmer 1420 spectrometer using sealed cells and a two-syringe technique. The $^{11}B$ NMR and $^{27}Al$ NMR spectra were recorded on a Varian FT-80A spectrometer. The $^{11}B$ NMR chemical shifts are in δ relative to $EE{\cdot}BF_3$ with chemical shifts downfield from $EE{\cdot}BF_3$ assigned as positive. Optical rotations were measured on a Rudolph Polarimeter Autopol III. Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 chromatograph with a TC detector.

**Materials.** Tetrahydrofuran (THF) was distilled from $LiAlH_4$ and stored under nitrogen. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and was used directly. *N,N,N′,N′*-Tetramethylethylenediamine (TMED) was distilled from calcium hydride. $LiAlH_4$ (1.0 M) in EE was purchased from Aldrich Chemical Co. Lithium monoethoxyaluminohydride (LMEA) was prepared from $LiAlH_4$ and ethyl acetate in EE following literature procedure.[19] All, optically pure, isopinocampheylalkylboranes were prepared from (+)-α-pinene by a published procedure.[8] Optically pure boronic esters were prepared according to the literature method.[8]

**Preparation of Ethyl Dialkylborinate Esters of High Optical Purity.** The following procedure for the preparation of ethyl (1*S*,2*S*)-(+)-*trans*-(2-methylcyclopentyl)-*n*-pentylborinate is typical. Isopinocampheyl-(1*S*,2*S*)-*trans*-(2-methylcyclopentyl)borane (30 mmol) of ee >99.9% was cooled to −25 °C. Ethyl ether (20 mL) was added, followed by 1-pentene (40 mmol) with constant stirring. The solid dialkylborane gradually (2 h) dissolved to give a clear solution. The reaction mixture was then warmed to 0 °C and stirred at 0 °C for an additional 2 h. The $^{11}B$ NMR of the reaction mixture showed the complete formation of the trialkylborane (δ +83). Acetaldehyde (4 mL, 75 mmol) was added to the trialkylborane at 0 °C, and the reaction mixture was stirred at 25 °C for 4 h. Excess acetaldehyde was evaporated (25 °C, 12 mmHg, 1 h), and the borinic ester residue was purified by distillation (4.5 g, 70% yield): bp 70–72 °C (0.1 mmHg); $[\alpha]^{23}_D$ +35.37 ± 0.02 (*c* 4, THF); $^{11}B$ NMR δ +53.2 (s). Oxidation of the ester with alkaline hydrogen peroxide gave (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol, which exhibited $[\alpha]^{23}_D$ +46.7° (*c* 1, MeOH), suggesting ee ≥99.7% for the ester.

**Reaction of Boronic Esters of High Optical Purity with $LiAlH_4$.** The following procedure for the preparation of lithium (1*S*,2*S*)-*trans*-(2-methylcyclohexyl)borohydride is representative. A 50-mL centrifuge vial fitted with a rubber septum and magnetic stirring bar was charged with 20 mL of a 0.5 M solution of dimethyl (1*S*,2*S*)-(+)-*trans*-(2-methylcyclohexyl)boronate (10 mmol) in *n*-pentane and cooled to 0 °C. A 1.0 M solution of $LiAlH_4$ in EE (10 mL, 10 mmol) was added with vigorous stirring. A voluminous precipitate of $(MeO)_2AlH$ was separated. The reaction mixture was stirred as efficiently as possible for 0.25 h at 0 °C. The reaction mixture was then centrifuged, and the clear supernatant liquid was transferred via a double-ended needle to another vial. The solid $(MeO)_2AlH$ was washed with *n*-pentane (2 × 10 mL), and the washings were combined with the supernatant solution. The solvent was evaporated at 25 °C under reduced pressure (12 mmHg). The residue (1.6 g) was dissolved in EE (18.4 mL) and estimated by hydride analysis:[12] 0.43 M, 8.6 mmol, 86% yield; $^{11}B$ NMR δ −25.5 (q, $J_{BH}$ = 74 Hz); IR ν 2180. No signal attributable to the presence of aluminum compounds in the solution could be detected either in $^{27}Al$ NMR or in the IR spectrum. The borohydride solution was quenched with methanol and then oxidized with alkaline hydrogen peroxide. The product alcohol, (1*S*,2*S*)-(+)-*trans*-2-methylcyclohexanol, exhibited $[\alpha]^{23}_D$ +42.8 ± 0.1° (*c* 1, MeOH), suggesting ee ≥99.7% for the borohydride.

**Preparation of Lithium Monoisopinocampheylborohydride.** Lithium aluminum hydride in EE (30 mL, 30 mmol) was added to crystalline $TMED{\cdot}2BH_2Ipc$ (15 mmol)[20] with stirring at 25 °C. A clear solution was obtained after 4 h, and $TMED{\cdot}2AlH_3$ precipitated from the solution as an oil. The stirring was continued for an additional 2 h, and the oily $TMED{\cdot}2AlH_3$ solidified. Simple decantation afforded lithium monoisopinocampheylborohydride in 92% yield: $^{11}B$ NMR δ −22.6 (q, $J_{BH}$ = 74 Hz); IR ν 2160.

**Reaction of Optically Active Borinic Esters with Lithium Monoethoxyaluminohydride.** The following procedure for the preparation of lithium (2*S*)-3-methyl-2-butyl-*n*-pentylborohydride is typical. A 50-mL centrifuge vial fitted with a rubber septum and a magnetic stirring bar was charged with 10 mL of a 1.0 M EE solution of $LiAlH_4$. To this, a 1.0 M EE solution of ethyl acetate (5 mL, 5 mmol) was added at 25 °C with stirring. The resulting LMEA was cooled to 0 °C, and a 0.5 M EE solution of ethyl (2*S*)-(+)-3-methyl-2-butyl-*n*-pentylborinate of ee ≥99.6% (20 mL, 10 mmol) was added with constant stirring. After the addition, the reaction mixture was mixed well and then centrifuged. The clear supernatant solution was transferred via a double-ended needle to another vial. The solid dialkoxyalane was washed with EE (2 × 5 mL), and the washings were combined with the supernatant solution. The solvent EE was evaporated under reduced pressure (12 mmHg). The residue (2.0 g) was dissolved in THF (18 mL), and the resulting solution was estimated by hydride analysis:[12] 0.4 M, 8.0 mmol, 80% yield; $^{11}B$ NMR δ −14.5 (t, $J_{BH}$ = 68 Hz); IR ν 2093. No signal attributable to the presence of aluminum compounds in the solution could be detected either in $^{27}Al$ NMR or the IR spectrum. The borohydride solution was quenched with methanol and then oxidized with alkaline hydrogen peroxide. The product alcohol, (2*S*)-(+)-3-methyl-2-butanol, exhibited

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$[\alpha]^{23}_D$ +4.94° (neat), suggesting ee ≥99.6% for the borohydride.

**Generation of Optically Active Monoalkylboranes from the Corresponding Borohydrides.** The following procedure for the preparation of essentially optically pure monosiamylborane dimer is representative. A 50-mL centrifuge vial with a rubber septum and a magnetic stirring bar was charged with a 0.5 M EE solution of lithium (2*S*)-3-methyl-2-butylborohydride (20 mL, 10 mmol) and cooled to 0 °C. A 3.0 M solution of HCl in EE (3.3 mL, ~10 mmol) was added slowly with vigorous stirring. Hydrogen gas evolved with the concurrent precipitation of lithium chloride. The reaction mixture was then centrifuged, and the clear supernatant solution (21 mL) containing the free (2*S*)-3-methyl-2-butylborane was transferred to another vial and estimated by hydrolysis: 85% yield; $^{11}$B NMR $\delta$ +23.8 (d, $J_{BH}$ = 131 Hz).

The monosiamylborane (8 mmol) in EE was reacted with 4 mmol of TMED at 0 °C with stirring. The EE was evaporated and the bis-adduct was washed with cold (0 °C) *n*-pentane (2 × 3 mL) and dried at 25 °C under reduced pressure (12 mmHg): 1.07 g (94% yield); mp 46-48 °C; $^{11}$B NMR $\delta$ -0.5 (t, $J_{BH}$ = 90 Hz); $[\alpha]^{23}_D$ +26.87 ± 0.05° (*c* 4, THF). Oxidation of the TMED adduct gave (2*S*)-(+)-3-methyl-2-butanol, which exhibited $[\alpha]^{23}_D$ +4.94° (neat), suggesting ee ≥99.6% for the TMED adduct.

**Application of Lithium Monoisopinocampheylborohydride. Asymmetric Hydroboration of 1-Methylcyclopentene.** Free monoisopinocampheylborane (25 mmol) was generated from lithium monoisopinocampheylborohydride (25 mmol) by treating it with HCl (25 mmol) in EE at 0 °C. Hydroboration of 1-methylcyclopentene (25 mmol) was carried out at -35 °C, using this reagent, as recommended in the literature.[8] Optically pure isopinocampheyl-(1*S*,2*S*)-*trans*-(2-methylcyclopentyl)borane was isolated in 60% yield. This dialkylborane was reacted with acetaldehyde to remove the isopinocampheyl group. The (1*S*,2*S*)-(+)-*trans*-(2-methylcyclopentyl)boronic acid, thus obtained on oxidation, afforded (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol, which exhibited $[\alpha]^{23}_D$ +46.8° (*c* 1, MeOH), ee >99.9%.

**Application of Lithium Diisopinocampheylborohydride. Asymmetric Hydroboration of *cis*-2-Butene.** Lithium diisopinocampheylborohydride (30 mmol) and (+)-$\alpha$-pinene (ee 92%, 9 mmol) in THF was cooled to 0 °C. Free diisopinocampheylborane was generated by adding methyl iodide (40 mmol) with stirring. The resulting slurry was cooled to -25 °C and utilized for the hydroboration of *cis*-2-butene (30 mmol) according to the literature procedure.[18] The reaction mixture was warmed to 25 °C, washed with water (2 × 10 mL) to remove lithium iodide, and then oxidized. Distillation provided (2*R*)-(-)-2-butanol in 65% yield, which exhibited $\alpha^{23}_D$ -10.368° (neat, *l* 1.0), ee ≥97%.

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# Enantiospecific and Stereospecific Synthesis of Lipoxin A. Stereochemical Assignment of the Natural Lipoxin A and Its Possible Biosynthesis

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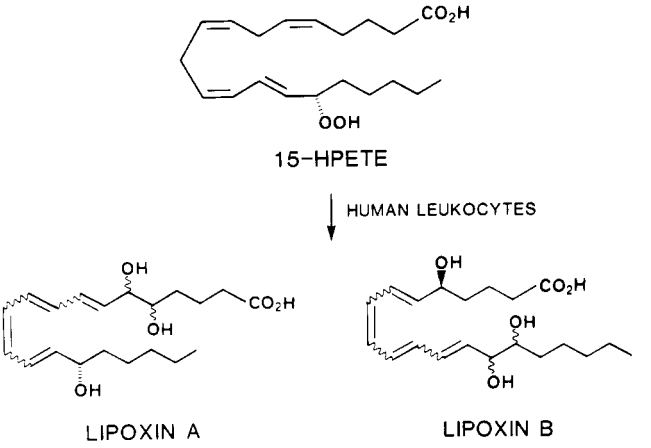
**Abstract:** Both chemical and enzymatic steps were employed to convert leukotriene $A_4$ and its unnatural epoxide isomers into four diastereomeric 5(*S*),6(*S*),15(*S*)-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acids, possible structures for lipoxin A. These compounds were correlated with trihydroxy tetraene eicosatetraenoic acids derived from tetraene epoxide **3**, and the relative stereochemistries of the 5 and 6 positions were assigned. These assignments were confirmed by total synthesis of two diastereomers of lipoxin A. One of these isomers, 5(*S*),6(*S*),15(*S*)-trihydroxy-7-9,13-*trans*-11-*cis*-eicosatetraenoic acid (**1b**), corresponded to lipoxin A derived from natural sources. The structure and possible biosyntheses of lipoxin A are proposed.

In the spring of 1984, Samuelsson announced the isolation of a new class of metabolites of arachidonic acid and coined the names Lipoxin A and Lipoxin B.[1] The lipoxins represent the first natural products containing a fully conjugated tetraene derived from arachidonic acid via 15-HPETE (HP = hydroperoxy) (Scheme I). These novel trihydroxy tetraene eicosanoids possess intriguing biological properties. Samuelsson has proposed a gross chemical structure for the lipoxins, but the relative stereochemistry of the hydroxyl groups and double bond geometry remain unknown.

We have initiated and completed a program to chemically and enzymatically synthesize various lipoxin A isomers with two goals in mind. Firstly, since only minute quantities of lipoxins are available from natural sources, it was our intent to prepare sufficient amounts to allow more extensive evaluation of their biological properties. Secondly, by comparing synthetic samples of unambiguous stereochemical origin to the natural product, we could assign the absolute configurations of the hydroxyl groups and the geometry of the double bonds. With this stereochemical information in hand, we could propose biosynthetic routes which account for the formation of lipoxins.

Scheme I. Formation of Lipoxins A and B




Upon analysis of the reported data and consideration of known polyoxygenated products of arachidonic acid, and in an effort to define the biochemical origins of lipoxins A and B, we considered several biosynthetic routes (Scheme II). Sequence A depicts the

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