Hydroboration of Terpenes. 11. Convenient Method for Upgrading 2-Organylapopinenes to High Optical Purity by Reaction of 2-Organylapoisopinocampheylboranes with Suitable Dienes Followed by Displacement with Acetaldehyde

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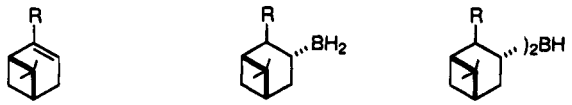
Received May 3, 1994

Organoborane chemistry is now widely used as one of the important tools to bring about numerous nonenzymatic asymmetric transformations.[2] The 2-organylapopinenes (2-R-apopinenes) such as α-pinene (**1a**), 2-ethylapopinene (**1b**), and 2-*n*-propylapopinene (**1c**) are versatile chiral auxiliaries for asymmetric synthesis *via* organoborane chemistry.[2c-e] The efficacy of borane reagents derived from these 2-R-apopinenes is noteworthy. For example, *B*-chlorodiisopinocampheylborane (Ipc_2BCl) prepared from (+)-α-pinene has been effectively used for the asymmetric reduction of many prochiral ketones.[3]



1a R = Me **1d** R = *i*-Bu
1b R = Et **1e** R = Ph
1c R = Pr **1f** R = *i*-Pr

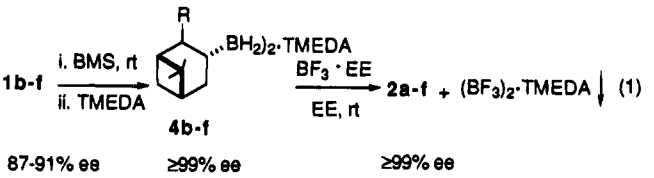
2a-f **3a-f**

Although borane reagents based on α-pinene have been remarkably useful for asymmetric allylboration[4] and reduction,[2c] other borane reagents such as *B*-2-ethylapoisopinocampheyl-9-boracyclo[3.3.1]nonane (Eapine-borane) and *B*-2-*n*-propylapoisopinocampheyl-9-boracyclo-[3.3.1]nonane (Prapine-borane), derived from 2-ethylapopinene (**1b**)[5] and 2-*n*-propylapopinene (**1c**),[6] respectively, have proved to be effective chiral reducing agents.[6] We have recently reported the synthesis of 2-R-apopinenes **1c-f** which are promising for these applications of organoborane chemistry.[7,8] The utility of 2-phenylapopinene (**1e**)[8] for such organoborane reactions is yet to be explored. However, the direct method of preparation of 2-R-apopinenes **1b-f** does not provide material of the desired ≥99% optical purity to permit the enantioselective synthesis of desired chiral borane reagents. We have demonstrated that α-pinene can be obtained in ≥99% optical yield by the convenient displacement of α-pinene from the optically pure Ipc_2BH (**3a**), obtained from the (+)-α-pinene of 91% ee, upon treatment with benzaldehyde.[9] However, this methodology was unsatisfactory for the synthesis of the optically pure 2-R-apopinenes **1b-f**, since the sterically bulkier 2-R-apopinenes fail to undergo dihydroboration to yield a crystalline, optically pure bis(2-R-apoisopinyl)borane (Rap_2BH, **3b-f**).[7] Thus, the inapplicability of this method, so valuable for the preparation of optically pure α-pinene, initiated a search for another suitable, elegant, and convenient procedure for the preparation of optically pure (≥99% ee) 2-R-apopinenes **1b-f**.

The present study describes a general procedure to obtain 2-R-apopinenes **1b-f** of high optical purity from chiral 2-organylapoisopinocampheylboranes (2-R-apoisopinylboranes, **2b-f**) of essentially ≥99% ee.

Results and Discussion

Reaction of 2-R-apoisopinylboranes ($RapBH_2$, 2a-f) with 1,5-Cyclooctadiene (1,5-COD) and 1,5-Hexadiene. Recently, we have reported a general, convenient procedure for the synthesis of optically pure (≥99%) tetramethylethylenediamine (TMEDA) adducts [$(RapBH_2)_2$·TMEDA, **4b-f**], obtained by the hydroboration of 2-R-apopinenes **1b-f** with BH_3·SMe_2 (BMS). These adducts **4b-f** selectively crystallize in ≥99% ee upon treatment of the reaction mixture (containing $RapBH_2$ (**2b-f**) as major and Rap_2BH (**3b-f**) as minor components) with TMEDA.[10] Treatment of these adducts **4b-f** with BF_3·EE readily provides $RapBH_2$ (**2b-f**) of ≥99% optical purity (eq 1).[10]



We have demonstrated that the ^{i}PraBH$_2$ (**2f**) hydroborates prochiral *trans*-disubstituted and trisubstituted alkenes to achieve significantly better optical induction than those realized by **2a,b,e**.[11,12]

A number of publications have described the cyclic hydroboration of dienes and polyenes,[13] but less effort has been devoted to exploring the asymmetric cyclic hydroboration of dienes. It has been demonstrated in previous work from this laboratory that the cyclic hydroboration

(1) Postdoctoral Research Associate on a Grant from the National Institutes of Health.
(2) (a) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287. (b) Matteson, D. S. *Synthesis* **1986**, 973. (c) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991**, *63*, 307. (d) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201. (e) Brown, H. C.; Ramachandran, P. V. *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, Vol. 1, in press.
(3) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
(4) (a) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
(5) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Weissman, S. A.; Jadhav, P. K.; Perumal, P. T. *J. Org. Chem.* **1988**, *53*, 5513.
(6) Brown, H. C.; Ramachandran, P. V.; Weissman, S. A.; Swaminathan, S. *J. Org. Chem.* **1990**, *55*, 6328.
(7) Brown, H. C.; Dhokte, U. P. *J. Org. Chem.* **1994**, *59*, 2025.
(8) Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217.
(9) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059.
(10) Brown, H. C.; Dhokte, U. P. *J. Org. Chem.* **1994**, *59*, 2365.
(11) Dhokte, U. P.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 4715.
(12) The synthesis of (+)- and (−)-[2-(1,3-dithianyl)]myrtenylborane has been described as an alternative means of achieving an improvement in the asymmetric hydroboration characteristics of $IpcBH_2$ (**2a**) (Richter, R. K.; Bonato, M.; Follet, M.; Kamenka, J.-M. *J. Org. Chem.* **1990**, *55*, 2855).
(13) (a) Brown, H. C.; Negishi, E.; Burke, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 3561. (b) Brown, H. C.; Negishi, E.; Kulkarni, S. U. *Heterocycles* **1976**, *5*, 883. (c) Brown, H. C.; Negishi, E. *Tetrahedron* **1977**, *33*, 2331.

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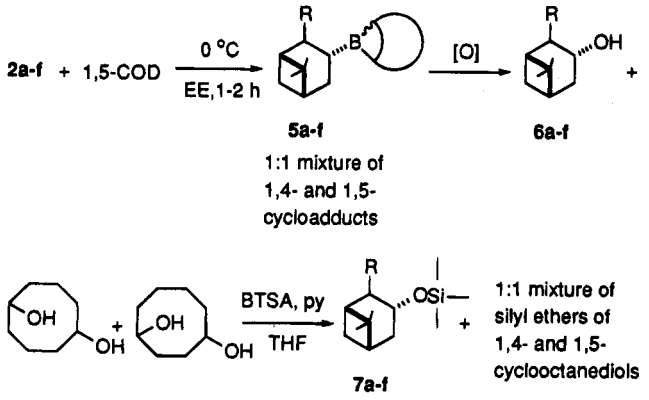
Scheme 1



of 1,5-COD with thexylborane ($ThxBH_2$) gives two regioisomeric products, arising from the 1,4- and 1,5-cycloaddition in a 4:1 ratio, respectively.[14] It has also been reported that the chiral monoalkylboranes (R^*BH_2) react with 1,5-COD to give a 70:30 mixture of the 1,4- and 1,5-cyclic adducts.[15] The less stable 1,4-regioisomer is readily isomerized to the 1,5-isomer at 65 °C.[15]

As a part of our research program to explore asymmetric syntheses using dienes *via* chiral organoboranes, the hydroboration of inexpensive and easily accessible 1,5-COD with $RapBH_2$ **2a–f** was investigated.[16]

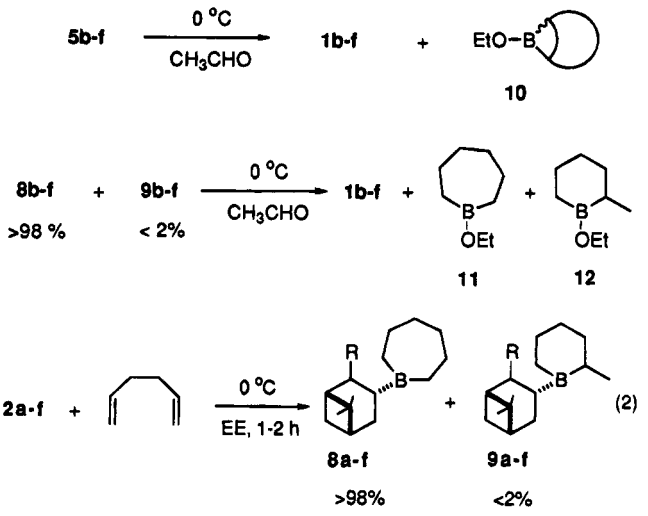
Thus, the hydroboration of 1,5-COD with an ethereal solution of 2-R-apoisopinylboranes **2a–f** at 0 °C for 1–2 h achieved the quantitative formation of mixed trialkylboranes **5a–f** as determined by ^{11}B NMR (δ 82–87). Interestingly, the alkaline peroxide oxidation of an aliquot of the solution and subsequent analysis of their silyl ethers on capillary GC established the reaction product to be a 50/50 mixture of 1,4- and 1,5-cyclooctanediols. The silyl ethers were prepared from the reaction of alcohols with bis(trimethylsilyl)acetamide (BTSA)[17] (Scheme 1).

Since the mixture of trialkylboranes **5b–f** on treatment with acetaldehyde would furnish the same product, *i.e.*, optically pure 2-R-apopinenes **1b–f**, no attempt was made to isomerize this mixture to the presumably more thermodynamically stable 1,5-regioisomer.

The cyclic hydroboration of 1,5-hexadiene with borane reagents, such as BH_3·THF, BH_2Cl·EE, thexylborane, and disiamylborane (Sia_2BH), has been extensively studied.[13c] It has been observed that the regioselectivity in the hydroboration of 1,5-hexadiene with thexylborane to give *B*-thexylborepane was 90%, while the other borane reagents furnished a 70:30 mixture of 1,4- and 1,5-cyclic adducts.[13c] It was, therefore, interesting to investigate the hydroboration of 1,5-hexadiene with 2-R-apoisopinylboranes **2a–f**. Unlike the hydroboration of 1,5-COD, hydroboration of 1,5-hexadiene with 2-R-apoisopinylboranes **2a–f** under similar conditions furnished a 49:1 mixture of *B*-(2-R-apoisopinyl)borepane (**8**) and *B*-(2-R-apoisopinyl)-2-methylborinane (**9**) (eq 2).

The percentage formation of trialkylboranes was determined as described in Scheme 1. Capillary GC analysis indicated the formation of 98% of 1,6-hexanediol and ~2% of 1,5-hexanediol, which in turn confirmed the

Scheme 2



49:1 formation of **8a–f** and **9a–f**, respectively, in the hydroboration.

An expected by-product of this investigation is the discovery of a valuable new route to the essentially pure (98%) *B*-alkoxyborepane (**11**) system and to the many derivatives to which this can be readily converted, such as cycloheptanone.

Liberation of Optically Pure 2-R-apopinenes 1b–f from the Trialkylboranes by Reaction with Acetaldehyde. The displacement of one or two Ipc groups from boron by treating Ipc_2BR or $IpcB(R)_2$ with aldehydes is well documented in literature.[18] However, the displacement of the third alkyl group is very difficult even under drastic conditions.[18b] This chemistry was successfully applied in displacing the optically pure 2-R-apopinenes **1b–f** from the corresponding mixture of trialkylboranes **5** or **8** and **9** (Scheme 2).

Thus, the trialkylboranes **5** or **8** and **9** instantaneously underwent reaction with ~1.1 equiv of acetaldehyde at 0 °C resulting in the quantitative liberation of optically pure 2-R-apopinenes **1b–f** along with the formation of mixed borinates **10** or **11** and **12**. It was interesting to note that the displacement of 2-R-apopinenes **1b–f** from the boron atom of trialkylboranes **5** or **8** and **9** was the predominant reaction with complete retention of configuration. As a result, racemization of the product 2-R-apopinenes **1b–f** was not observed.

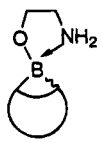
Purification of the Liberated 2-R-apopinenes 1b–f from the Reaction Mixture Containing Mixed Borinates 10 or 11 and 12. Two methods were suc-

(14) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1972**, *94*, 3567.
(15) Brown, H. C.; Joshi, N. N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 1754.

(16) The hydroboration of α-pinene with 9-BBN proceeds smoothly to provide Ipc-9-BBN (Alpine–Borane) [(a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352. (b) Reference 19b]. However, we have observed that as the R group in the 2-R-apopinenes become bulkier, the rate of hydroboration become so slow to be impractical (ref 8 and Dhokte, U. P.; Brown, H. C. unpublished results). Thus, the reaction of $RapBH_2$ with 1,5-COD provides an independent route to 2-R-apopinene-9-BBN compounds, potentially useful in the selective asymmetric reduction of acetylenic ketones and α-keto esters. Also, the corresponding lithium trialkylborohydride would produce a sterically bulkier analogue of lithium *B*-isopinocampheyl-9-boracyclo[3.3.1]nonyl hydride (Alpine–Hydride), perhaps more valuable for the asymmetric reduction of prochiral ketones (Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534).
(17) Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*; Wiley-Interscience: New York, 1972; Vol. 3, p 23.
(18) (a) Brown, H. C.; Jadhav, P. K.; Desai, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 4303. (b) Brown, H. C.; Jadhav, P. K.; Desai, M. J. *J. Org. Chem.* **1985**, *47*, 4583.

cessfully employed for the removal of borinates: (A) by treatment with ethanolamine and (B) by alkaline peroxide oxidation.

Method A. The numerous borinic acid derivatives, such as 9-borabicyclo[3.3.1]borinates,[19] dicyclohexylborinates,[20] and diisopinocampheylborinates,[21] have been shown to precipitate quantitatively as crystalline solids from their solution in pentane upon treatment with ethanolamine.[22] Therefore, this reaction was successfully applied. Thus, the addition of acetaldehyde to the reaction mixture at 0 °C liberated 2-R-apopinenes **1b–f** along with the formation of borinates **10** or **11** and **12** in pentane[23] as determined by ^{11}B NMR (δ 55–58). The instantaneous reaction of ethanolamine with the mixed borinates **10** or **11** and **12** provided a quantitative separation of the borinates as a mixture of crystalline ethanolamine adducts **13** or **14** and **15**, leaving behind the optically pure 2-R-apopinenes **1b–f** in the solution along with ethanol as a water-miscible side product. The ethanolamine adduct **14** was further crystallized from THF/pentane (1:2) and compared with the authentic sample reported in the literature.[24]



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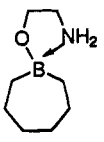

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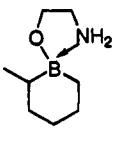

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The enantiomeric purity of the 2-R-apopinenes **1b–f** was conveniently determined as described in the Experimental Section.

Method B. The reaction mixtures containing optically pure 2-R-apopinenes **1b–f** and mixed borinates **10** or **11** and **12** in diethyl ether (EE) were oxidized with alkaline hydrogen peroxide at 0 °C. The products of the reaction, *i.e.*, 1,4- and 1,5-cyclooctanediols or 1,6- and 1,5-hexanediols, were easily separated from the ethereal solution of optically pure 2-R-apopinenes **1b–f** by washing with water. Thus, the 2-R-apopinenes **1b–f** of essentially ≥99% chemically and optically pure material were obtained conveniently in 85–90% isolated yields by this one-pot procedure.

Conclusions

This procedure describes a simple, convenient, one-pot means of preparing 2-R-apopinenes of general interest in essentially ≥99% optical and high chemical yields from their corresponding 2-R-apoisopinylboranes, derived from 2-R-apopinenes of only 87–91% ee, under mild reaction conditions. The 2-R-apopinenes are obtained in 85–90% isolated yields. Therefore, this procedure provides a practical means for preparing 2-R-apopinenes which can be readily used to make enantiomerically pure organoborane reagents with controlled changes in the steric requirements of the organyl group in the 2-position of apopinene.

Experimental Section

All glassware were dried overnight at 140 °C, assembled hot, and cooled to ambient temperature in a stream of nitrogen.[25] All reactions were performed under static pressure of dry nitrogen. The reported boiling points are uncorrected. The ^{11}B NMR were recorded at 96 MHz and were referenced to BF_3·EE. The ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. Samples were purified by preparative GC (20% SE-30 column), and optical rotations were measured on a digital polarimeter.

Materials. Anhydrous EE, acetaldehyde, and borane–dimethyl sulfide complex were used as obtained. The 2-R-apopinenes **1b–f** were prepared as described elsewhere.[5–8] The $(RapBH_2)_2$·TMEDA adducts, **4a**[26] and **4b–f**,[10] were prepared using previously described procedures. The 2-R-apoisopinylboranes ($RapBH_2$, **2a–f**) were prepared by the reaction of BF_3·EE with bis-adducts **4a–f** according to the literature procedure.[10, 26] 1,5-Hexadiene and 1,5-COD were distilled over LAH prior to use.

General Procedure for Liberation of 2-R-apopinenes 1b–f of ≥99% ee from the Corresponding 2-R-apoisopinylboranes ($RapBH_2$, 2b–f). Method A. An ethereal solution of $RapBH_2$ **2b–f** (0.60–0.80 M, 30 mmol) was cooled to 0 °C, and 1,5-cyclooctadiene (31 mmol) or 1,5-hexadiene (31 mmol) was then added over a period of 5 min. The mixture was warmed to 25 °C and stirred for 1–2 h. The ^{11}B NMR indicated quantitative formation of a mixture of trialkylboranes **5** or **8** and **9** (δ 82–87). The volatiles of the reaction mixture were removed (12 mmHg, 40 °C, 1 h). Dry pentane[23] (30 mL) was placed in the flask, and acetaldehyde (40 mmol) was slowly added at 0 °C. The mixture was further stirred for 1–2 h (^{11}B NMR δ 55–58). The ethanolamine (31 mmol) was added to the mixture at 25 °C, which readily precipitated ethanolamine derivative of borinates. The clean pentane layer was removed. The precipitate was washed with cold pentane (2 × 10 mL) and centrifuged. The combined solvent was distilled off, and the residual oil on distillation under reduced pressure over LAH furnished 2-R-apopinenes **1b–f** (85–90% yields). A small amount of 2-R-apopinene was further purified to give material of ≥99% GC purity and ≥99% ee by rotation. Small amounts of 2-R-apopinenes **1b–f** were subjected to the hydroboration–oxidation to obtain the corresponding alcohols **6b–f**, derivatized[10] as the menthyl carbonate[27] (of **6b–d,f**) or MTPA[28] (**6e**). These derivatives were analyzed on a SPB-5 capillary GC column, revealing optical purities of ≥99% ee, in comparison with the equal diastereomeric mixture of derivatives of the alcohols **6b–f** obtained from hydroboration–oxidation of the corresponding racemic 2-R-apopinenes **1b–f**.[10] The ^1H and ^{13}C NMR spectral data obtained for purified 2-R-apopinenes were identical with the reported values.[5–8,10] (−)-2-Ethylapopinene (**1b**): bp 88–90 °C/40 mmHg; $[\alpha]^{24}_D$ −45.7° (neat) [lit.[5] $[\alpha]^{23}_D$ −46.2° (neat), 99% ee]. (+)-2-*n*-Propylapopinene (**1c**): bp 100–102 °C/30 mmHg; $[\alpha]^{20}_D$ +43.68° (*c* 1.0, MeOH) [$[\alpha]^{21}_D$ +39.29° (*c* 1.0, MeOH), 90% ee]. (+)-2-Isobutylapopinene (**1d**): bp 53–54 °C/0.9 mmHg; $[\alpha]^{20}_D$ +15.29° (neat) [$[\alpha]^{20}_D$ +13.67° (neat), 90% ee]. (−)-2-Phenylapopinene (**1e**): bp 80–82 °C/0.1 mmHg; $[\alpha]^{23}_D$ −19.89 (neat) [$[\alpha]^{21}_D$ −17.28 (neat), 87% ee]. (+)-2-Isopropylapopinene (**1f**): bp 70–72 °C/12 mmHg; $[\alpha]^{20}_D$ +39.00° (*c* 1.0, MeOH) [$[\alpha]^{20}_D$ +35.31° (*c* 1.0, MeOH), 91% ee].

(19) (a) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954. (b) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384. (c) Brown, H. C.; Molander, G. A.; Singh, S. M.; Racherla, U. S. *J. Org. Chem.* **1985**, *50*, 1577 and references cited therein.

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(21) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564.

(22) (a) Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem.* **1976**, *41*, 1778. (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *42*, 1197.

(23) During this study we confirmed that the pentane was a better solvent than EE for the quantitative precipitation of the solid ethanolamine adduct of these borinates **10** or **11** and **12**.

(24) Brown, H. C.; Phadke, A. S.; Rangaishenvi, M. V. *Heteroatom. Chem.* **1990**, *1*, 83.

(25) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

(26) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.

(27) Westley, J. W.; Halpern, B. J. *J. Org. Chem.* **1968**, *33*, 3978.

(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Method B. The ethereal solution of trialkyboranes **5** or **8** and **9** was treated with acetaldehyde (40 mmol) at 0 °C. After 1–2 h, the borinic acid derivatives **10** or **11** and **12** were oxidized by the successive addition of 3 N aqueous NaOH (10.5 mL) and 30% H_2O_2 (7.1 mL). The organic phase was separated and the aqueous phase extracted with ether (2 × 30 mL). The combined organic extract was stirred with water (60 mL) for 1 h. The organic layer was treated with brine and Na_2SO_4. Removal of solvent, and vacuum distillation of residual liquid over LAH, gave the 2-R-apopinenes (85–90% yields). The optical rotation of purified material (preparative GC) showed ≥99% ee of 2-R-apopinenes **1b–f**.

Acknowledgment. We gratefully acknowledge the financial support of this research by the National Institutes of Health, GM 10937.

Supplementary Material Available: Copies of the ^1H and ^{13}C NMR spectra for **1b–f** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.