Hydroboration. 83. Synthesis and Hydroboration of 2-Ethylapopinene. Comparison of Monoisopinocampheylborane and Its 2-Ethyl Analogue for the Chiral Hydroboration of Representative Alkenes

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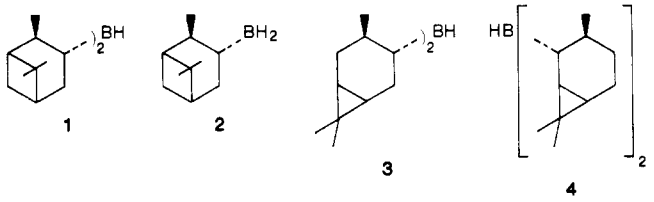
Received May 17, 1988

Reduction of nopol tosylate gives the new chiral ligand (–)-2-ethylapopinene (90.2% ee) with higher steric requirements than those of α-pinene. Reaction of borane with (–)-2-ethylapopinene in THF at 0 °C, in a molar ratio of 1:2, provides an equilibrium mixture of mono- and dialkylboranes $EapBH_2$ and Eap_2BH. With an excess of (–)-2-ethylapopinene (1:10; BMS/2-ethylapopinene), the formation of bis(2-ethylapoisopinocampheyl)borane, Eap_2BH, is essentially quantitative (~98%). Treatment of the equilibrium mixture of boranes (Eap_2BH, $EapBH_2$) with TMED at 34 °C precipitates crystalline $(EapBH_2)_2$·TMED. Treatment of the crystalline product with BF_3·OEt_2 gives $EapBH_2$ (mono(2-ethylapoisopinocampheyl)borane) of essentially 100% ee, enantiomerically purer than the (–)-2-ethylapopinene (~90% ee) utilized for the preparation. Hydroboration of a series of olefins with $EapBH_2$, followed by oxidation of the intermediate organoborane, produces the corresponding alcohols with significantly improved enantiomeric purities over those realized with $IpcBH_2$ under the same conditions. Liberation of the olefin from purified $EapBH_2$ provides (–)-2-ethylapopinene ($[\alpha]^{23}_D$ –46.2° (neat)) in high optical purity (>99% ee). Metalation of (+)-α-pinene ($[\alpha]^{23}_D$ +51.4° (neat)) with the Lochmann reagent, followed by alkylation with methyl iodide, provides in high optical purity (>99% ee) (+)-2-ethylapopinene ($[\alpha]^{23}_D$ +46.4° (neat)), unavailable from commercial (–)-nopol.

The functionalities available through hydroboration of alkenes with subsequent modification of the resulting organoboranes are extensive. Hydroboration of prochiral olefins with chiral hydroborating agents such as Ipc_2BH (**1**), $IpcBH_2$ (**2**), 4-Icr_2BH (**3**), and 2-Icr_2BH (**4**) proceeds



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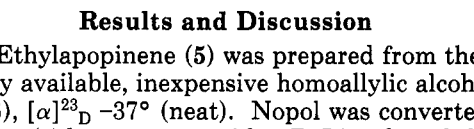
with remarkable asymmetric induction, making this reaction a most valuable one for asymmetric organic synthesis.[2-4]

Ipc_2BH,[5] **1**, hydroborates unhindered cis-olefins in high chemical and optical purities.[6a] Unfortunately, the corresponding reaction with trans and hindered trisubstituted olefins is much more sluggish; moreover, the product alcohols reveal much lower optical purities.[6b] However, these classes of olefins are handled satisfactorily by monoisopinocampheylborane (**2**).[7] Optical purities in the range of 55–75% ee were achieved for most of the aliphatic trisubstituted and trans-disubstituted olefins. Noticeable enhancement in the enantiomeric purity was observed for trisubstituted olefins containing a phenyl group.[7]

These results clearly indicate that the enantiomeric purities of the product alcohols depend upon the steric requirement of the olefins. On this basis, it was thought that it might be possible to match the steric requirements of the chiral hydroborating agent with that of the olefin so as to provide an optimum steric fit and thus optimum asymmetric induction. Consequently, we have undertaken a program to examine the effects of small increases in the steric requirements of the chiral hydroborating reagent itself. We have now prepared such a chiral hydroborating agent by introducing a methyl group at C-10 of α-pinene to study its effect in asymmetric hydroboration. In this paper we discuss our results on the preparation of 2-ethylapopinene of essentially 100% ee and the exploration of mono(2-ethylapoisopinocampheyl)borane as an asymmetric hydroborating reagent for trans-disubstituted and trisubstituted alkenes, with comparison of the results with those previously available for monoisopinocampheylborane itself.[7]

Results and Discussion

(–)-2-Ethylapopinene (**5**) was prepared from the commercially available, inexpensive homoallylic alcohol (–)-nopol (**6**), $[\alpha]^{23}_D$ –37° (neat). Nopol was converted into its tosylate (**7**) by treatment with *n*-BuLi and tosyl chloride in THF at –78 °C. Crystallization of **7** from pentane gave



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colorless white needles of mp 50–51 °C. Treatment of the tosylate with LAH gave (–)-2-ethylapopinene (**5**) in 70% yield (eq 1). It should be noted that an earlier attempt to prepare **5** from nopol via the tosylate had failed.[8] The 2-ethylapopinene obtained by the reduction of the crude tosylate often contained 6–10% of a close boiling impurity, difficult to separate from the desired ethylapopinene. This

(1) (a) Postdoctoral research associate on grant GM 10937-25 from the National Institutes of Health. (b) Visiting Professor on a grant from the Dow Chemical Company. (c) Postdoctoral research associate on grant GM 10937-25 from the National Institutes of Health. (d) Postdoctoral research associate on grant GM 10937-22 from the National Institutes of Health.

(2) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.

(3) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514.

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

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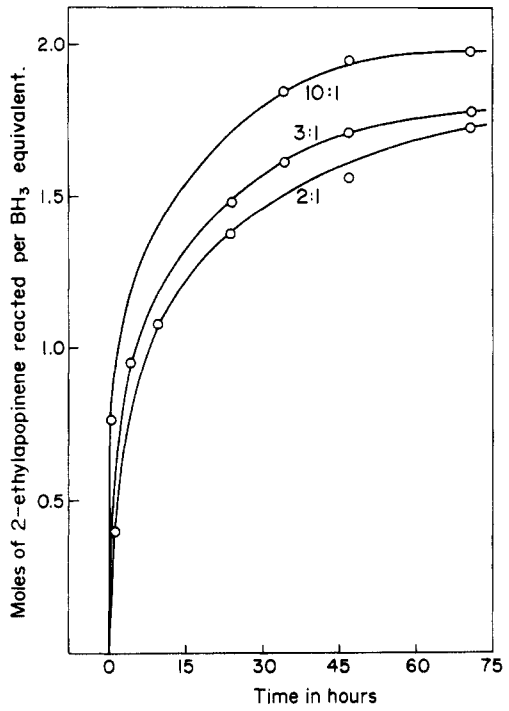
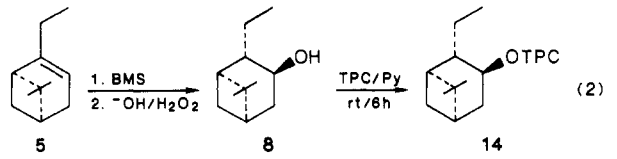


Figure 1. Rate and stoichiometry of the hydroboration of (−)-2-ethylapopinene with BH_3·SMe_2 in THF.

problem was avoided by recrystallizing the tosylate prior to reduction. Alcohol **8** was obtained by hydroboration of **5** with BMS, followed by methanolysis and oxidation with alkaline hydrogen peroxide (eq 2). The enantiomeric



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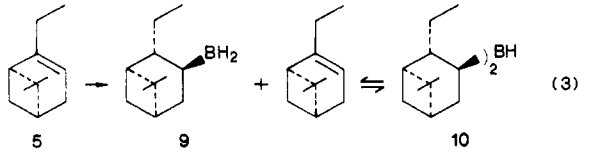
purity of (−)-2-ethylapopinene was then estimated by capillary GC analysis of **8** derivatized with (−)-*N*-(trifluoroacetyl)prolyl chloride.[9] An authenic sample of (−)-2-ethylapoisopinocampheol was prepared by hydroboration–oxidation of (+)-2-ethylapopinene. The *N*-trifluoroacetyl derivatives of (+)- and (−)-2-ethylapoisopinocampheols separated well on a 50-m methylsilicon capillary column. The enantiomeric purity of the (−)-2-ethylapopinene [$[\alpha]^{23}_D$ −42° (neat, d = 0.864)], thus prepared from nopol [$[\alpha]^{23}_D$ −37° (neat, d = 0.973)], was 90.2% ee.

Hydroboration of (−)-2-Ethylapopinene. The preliminary studies on rate and stoichiometry of the reaction of (−)-2-ethylapopinene with BMS in THF at 0 °C was examined at three different molar ratios, namely, 1:2, 1:3, and 1:10 (BMS:olefin). The reaction proceeds with the formation of both monoalkyl- and dialkylborane (eq 3).



(3)

The progress of the reaction was followed by removing aliquots at appropriate intervals of time and analyzing for residual hydride. Aliquots were also oxidized with alkaline hydrogen peroxide and analyzed (GC) for alcohol and residual olefin **5**. All three analytical procedures gave concurring results. The results of the amount of 2-ethylapopinene consumed are summarized in Figure 1.

Table I. Reaction of BMS with (−)-2-Ethylapopinene in THF at 0 °C. Analysis of Reaction Mixtures at 72 h

molar ratio of		% yield of	
BMS	5	$EapBH_2$ (9)	Eap_2BH (10)
1	2	17	73
1	3	12	78
1	10	~2	98

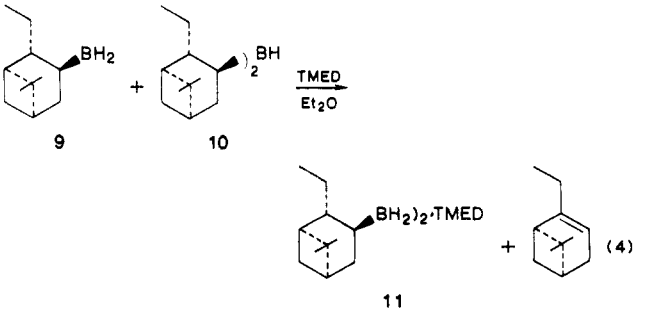
Table II. Preparation and Improvement of the Optical Purity of 11

solvent	molarity of borane solution	% ee[a] of 11	% yield of 11
pentane	1.4	96.0	83
pentane/Et_2O (1:1)	1.4	96.5	81
ether	1.4	97.5	81
ether	1.0	<99	77
ether	0.6	<99	64

[a] % ee was determined by TPC ester analysis of alcohol **8**, obtained by oxidation ($^-OH/H_2O_2$) of TMED adduct **11**.

All three reactions showed acceptable material balance for B–H bonds. It is evident from these observations that the reaction of borane with **5** in THF attains equilibrium in 2–3 days at 0 °C. After the residual hydride in the solution had become constant, an aliquot was methanolyzed and analyzed by ^{11}B NMR. The absence of a peak at δ +18, corresponding to $B(OMe)_3$, revealed the absence of the BH_3 species. The approximate yields of **9** and **10**, after a reaction period of 3 days at 0 °C, are summarized in Table I.

Preparation of Mono(2-ethylapoisopinocampheyl)borane ($EapBH_2$, 9). Hydroboration of olefin **5** with BMS at a 1:1 molar ratio generally led to a mixture of dialkyl- and monoalkylborane. The limiting factor was the inability to stop the hydroboration at the desired monoalkylborane stage under normal conditions. We have previously reported an elegant procedure for the preparation of $IpcBH_2$ with optical upgrading of the α-pinene utilized.[10] We hoped that a similar procedure would make it possible to prepare $EapBH_2$. Indeed, treatment of a mixture of boranes **9** and **10** with TMED gave a crystalline adduct, $(EapBH_2)_2$·TMED (**11**, eq 4), which separated cleanly from the reaction mixtures using either pentane or ethyl ether as the reaction medium.



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From pentane we achieved a synthesis of **11** with an optical purity of 96%, much higher than that of the 2-ethylapopinene (~90% ee) utilized. From ethyl ether we achieved a product with an optical purity approaching 100% ee. Consequently, we favor ethyl ether for the

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

Table III. Asymmetric Hydroboration of Representative Olefins with Mono(2-ethylapoisopinocampheyl)borane ($EapBH_2$, 9)

olefin	alcohol	isolated yield, %	$[\alpha]^{23}_D$, deg	% ee	confign
2-methyl-1-butene	2-methyl-1-butanol	80	+0.123 (neat)	2[a]	*R*
cis-2-butene	2-butanol	73	-4.07 (neat)	30[a]	*R*
trans-2-butene	2-butanol	77	-10.24 (neat)	76[a]	*R*
2-methyl-2-butene	3-methyl-2-butanol	75	-3.27 (neat)	68[b] (65)[a]	*R*
1-methylcyclopentene	*trans*-2-methylcyclopentanol	86	-33.34 (*c* 7.2, MeOH)	68[c] (71)[a]	1*R*,2*R*
1-methylcyclohexene	*trans*-2-methylcyclohexanol	81	-35.02 (*c* 6.4, MeOH)	78[b] (82)[a]	1*R*,2*R*

[a] Values based on the highest reported optical rotation. [b] Determined by using a chiral column [Ni-(*R*)-Cam]. [c] Determined as the acetate on a chiral column [Ni-(*R*)-Cam].

preparation of 11. The results are summarized in Table II.

The generation of $EapBH_2$ (9) from adduct 11 is achieved by treatment with $BF_3{\cdot}OEt_2$ (eq 5). The in-

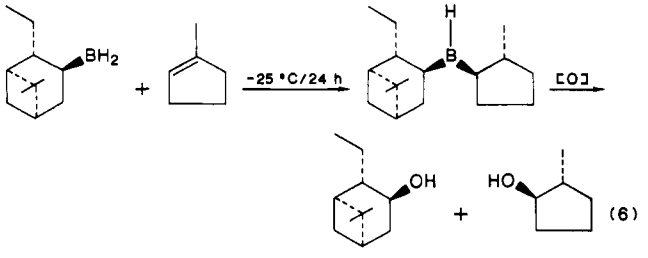
$$(EapBH_2)_2{\cdot}TMED + 2BF_3{\cdot}OEt_2 \rightarrow 2EapBH_2 + (BF_3)_2{\cdot}TMED\downarrow \quad (5)$$

soluble $(BF_3)_2{\cdot}TMED$ is readily separated by filtration through a filter chamber and the molarity of the solution of $EapBH_2$ determined by hydride estimation. This procedure readily provides $EapBH_2$ of optical purity approaching 100% ee from 2-ethylapopinene of significantly lower optical purity (~90%).

Hydroboration of Representative Olefins. For the initial exploration of the hydroboration characteristics of $EapBH_2$, representative terminal, cis,trans-disubstituted, and trisubstituted olefins previously examined with $IpcBH_2$[7] were selected. Each olefin was hydroborated with an equimolar quantity of mono(2-ethylapoisopinocampheyl)borane (9) at -25 °C. The reaction was monitored by quenching the aliquots with methanol, followed by examination of the ^{11}B NMR spectrum of the sample. The resulting boron derivatives were methanolyzed at -25 °C and oxidized with alkaline hydrogen peroxide to yield the desired alcohol and (+)-2-ethylapoisopinocampheol. The product alcohols were separated from the (+)-2-ethylapoisopinocampheol by fractional distillation. Final purification was achieved by preparative GC. The results are summarized in Table III.

Asymmetric induction in the hydroboration of a terminal prochiral alkene, 2-methyl-1-butene, with $EapBH_2$ is poor, providing 2-metyl-1-butanol in only 2% ee. Similar treatment of *cis*-2-butene provided 2-butanol in only 30% ee. The results indicate that $EapBH_2$ resembles $IpcBH_2$ in failing to give good asymmetric induction for 2-methyl-1-butene and *cis*-2-butene.

The hydroboration of *trans*-2-butene with 9 gives (*R*)-(-)-2-butanol of 76% ee. The mono(2-ethylapoisopinocampheyl)borane also reacts smoothly with trisubstituted olefins. The hydroboration of 2-methyl-2-butene, followed by the oxidation of the methanolyzed reaction mixture, provides the corresponding alcohol in 68% ee, as compared to only 53% ee with $IpcBH_2$. Similarly, 1-methylcyclopentene, upon hydroboration with optically pure $EapBH_2$, followed by oxidation, provides (-)-*trans*-2-methylcyclopentanol in 68% ee (eq 6). Similarly, the



(6)

hydroboration of 1-methylcylcohexene gives the corresponding trans alcohol in 78% ee, as compared to only 72% ee by hydroboration with $IpcBH_2$.

Table IV. Comparison of Optical Induction in the Hydroboration-Oxidation of Representative Alkenes with $IpcBH_2$ and $EapBH_2$

alkene	% ee of product: $IpcBH_2$[a]	% ee of product: $EapBH_2$
2-methyl-1-butene	1.5	2[a]
cis-2-butene	24	30[a]
trans-2-butene	73	76[a]
2-methyl-2-butene	53	68[b]
1-methylcyclopentene	66	68[c]
1-methylcyclohexene	72	78[b]

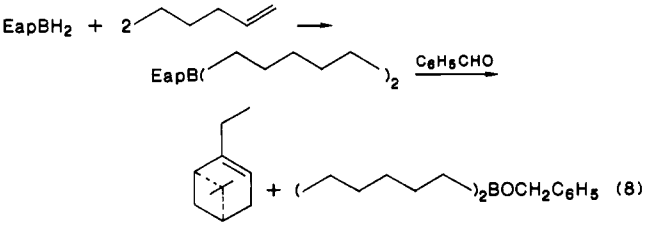
[a] Values based on the highest reported rotations (ref 7). [b] Analyzed as the alcohols on a chiral column [Ni-(*R*)-Cam]. [c] Analyzed as the acetates on a chiral column [Ni-(*R*)-Cam].

A comparison between $EapBH_2$ and $IpcBH_2$[7] (Table IV) reveals that the new reagent provides significantly better optical yields than does $IpcBH_2$. This indicates that further modification in the pinanyl moiety may provide even better chiral auxiliaries for asymmetric hydroboration.

Liberation of (-)-2-Ethylapopinene of High Optical Purity. Elimination of (-)-2-ethylapopinene from $EapBH_2$ (9) of high optical purity would provide a method for upgrading the optical purity of (-)-2-ethylapopinene (5). Direct elimination of (-)-2-ethylapopinene from $EapBH_2$ proved extremely difficult. Treatment of $EapBH_2$ with $(CH_2O)_n/BF_3{\cdot}OEt_2$ or with benzaldehyde at THF reflux temperature afforded only the boronate esters (eq 7).

$$EapB(OCH_2C_6H_5)_2 \xleftarrow{C_6H_5CHO} EapBH_2 \xrightarrow{(CH_2O)_n/BF_3{\cdot}OEt_2} EapB(OCH_3)_2 \quad (7)$$

Fortunately, this difficulty was circumvented by utilizing an alternative procedure.[11] The purified $EapBH_2$ was used to hydroborate 1-hexene at 25 °C in diethyl ether. The trialkylborane thus obtained was freed of the solvent and treated with benzaldehyde at room temperature for 4 h (eq 8), providing (-)-2-ethylapopinene, 80% yield. The



(8)

(-)-2-ethylapopinene thus obtained was further purified by preparative GC, providing material that exhibited $[\alpha]^{23}_D$ -46.2° (neat, d = 0.864) estimated to be 99.1% ee from comparison with the observed rotation for (-)-2-ethylapopinene from nopol of 90% ee. The (-)-2-ethylapopinene thus obtained was hydroborated with BMS. Subsequent methanolysis and oxidation ($^-OH/H_2O_2$) of the

(11) Brown, H. C.; Jadhav, P. K.; Vara Prasad, J. V. N. *J. Org. Chem.* **1985**, *50*, 3203.

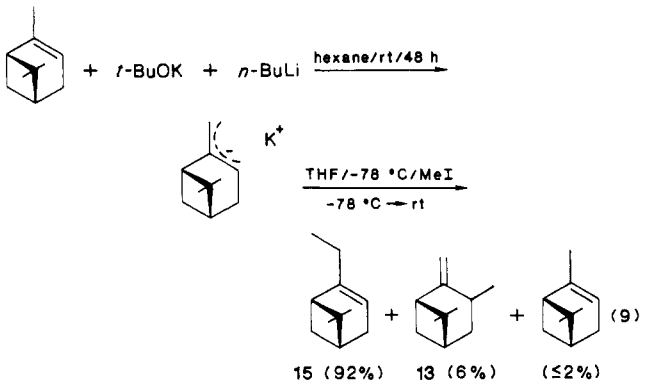
Table V. Metalation of (+)-α-Pinene with *n*-BuLi/*t*-BuOK at Room Temperature

time, h	unreacted α-pinene (%) at various molar ratio of reagents (α-pinene:*t*-BuOK/*n*-BuLi)			
	1:1	1:1.1	1:1.25	1:1.5
12	15	14	7	6.5
24	13	7	3	1.5
36	12	6	2	1
48	12	6	2 (92)[b]	<1 (86)[b]

[a] Aliquots of reaction mixture (potassium salt) were quenched with MeI at −78 °C → rt. The product was analyzed by GC for unreacted α-pinene. [b] Values in parentheses indicate the GC yield of (+)-2-ethylapopinene.

boron intermediate gave (+)-2-ethylapoisopinocampheol, $[\alpha]^{23}_D$ + 24.2° (*c* 3, $CHCl_3$), 99.15% ee, as determined by capillary GC analysis of its *N*-(trifluoroacetyl)prolyl ester. This procedure makes available (−)-2-ethylapopinene of high optical purity.

Preparation of (+)-2-Ethylapopinene. Since (+)-nopol is not commercially available for the synthesis of (+)-2-ethylapopinene, we considered the possibility of a synthesis based on the readily available monoterpene (+)-α-pinene. Various methods for upgrading the optical purity of α-pinene have been described in the literature.[5,12] Metalation of (+)-α-pinene, followed by treatment with methyl iodide, should provide the desired 2-ethylapopinene of high optical purity. However, the choice of metalating agent was crucial. The best results were obtained with *t*-BuOK and *n*-butyllithium as the metalating agents.[13] It was observed that the molar ratio of metalating agent to α-pinene and the duration of metalation was very critical: 12% of unreacted (+)-α-pinene was observed when metalation was carried out with 1:1 *t*-BuOK/*n*-BuLi and α-pinene at room temperature for 48 h. The results are summarized in Table V. The best results were obtained by metalating (+)-α-pinene with 1.25 equiv of *t*-BuOK/*n*-BuLi in hexane at room temperature for 48 h. The potassium salt of α-pinene thus obtained was dissolved in THF, cooled to −78 °C, and treated with excess methyl iodide to give (+)-2-ethylapopinene (**15**) as the major product (eq 9). GC analysis revealed 92% (+)-2-ethylapopinene, 6% isomeric product **13**, and 2% α-pinene. The residual α-pinene was removed by fractionation (1-m packed column, reflux ration 50:1). (+)-2-Ethylapopinene (**15**), free of **13**, was obtained by distillation from 9-BBN (10%) in 65% yield, $[\alpha]^{23}_D$ +46.4 [(neat, *d* = 0.864; prepared from (+)-α-pinene of 99.7% ee $[\alpha]^{23}_D$ +51.45° (neat, *d* = 0.857)]. On the basis of α-pinene used, this method provides both enantiomers of 2-ethylapopinene in very high optical purity. The synthetic procedure outlined above might be extended to the preparation of its analogues by varying the alkylating halides.



Conclusion

Mono(2-ethylapoisopinocampheyl)borane is a superior chiral hydroborating agent for trans and trisubstituted olefins, compared to the other available hydroborating reagents (RBH_2). These results strongly support the speculation that increasing the steric bulk at the 2-position of pinane leads to a favorable increment in the optical induction. We are currently exploring the introduction of a variety of larger substituents into the 2-position of the apopinene system.

The metalation–alkylation route here described for the synthesis of (+)-2-ethylapopinene may be general and extendable to the preparation of the higher analogues of both (+)- and (−)-α-pinene needed for our study.

The present study suggests the possibility of developing a family of asymmetric hydroborating agents of varying steric requirements. It would then be possible to select that hydroborating agent that provides a highly favorable fit with a given olefinic structure to achieve exceptional asymmetric induction.

Experimental Section

All glassware was dried at 140 °C overnight, assembled hot, and cooled to room temperature in a stream of nitrogen.[14] All reactions involving air-sensitive materials were carried out under static pressure of nitrogen. The liquids were transferred with syringes or double-ended needles. ^1H NMR spectra were obtained on a Varian T-60 or a Perkin-Elmer R-32 spectrometer. ^{11}B NMR and ^{13}C NMR spectra were obtained on a Varian FT 80-MHz spectrometer. GC analysis was carried out with a Hewlett-Packard 5740 chromatograph using 9 ft × 0.125 in. columns packed with 10% Carbowax 20M or 10% SE-30 on Chromosorb W (100–120 mesh). Products were purified to 100% GC by preparative GC using either (a) a 6 ft × 0.5 in. column packed with 20% Carbowax (60–80 mesh) or (b) a 6 ft × 0.5 in. column packed with 20% SE-30 on Chromosorb W (60–80 mesh). Optical rotations were measured on a Rudolph Autopol III polarimeter. Capillary GC analysis was carried out on methylsilicon 50 m × 0.25 mm and [Ni-(*R*)-Cam][15] 25 m × 0.25 mm chiral columns.

Materials. Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampule. BMS and (−)-nopol [$[\alpha]^{23}_D$ −37° (neat)] were purchased from Aldrich Chemical Company.

Preparation of (−)-2-Ethylapopinene. A dry, 2-L flask equipped with a septum inlet, magnetic stirring bar, and a reflux condenser leading to a mercury bubbler was flushed with dry nitrogen and maintained under static pressure of nitrogen. The flask was charged with 170 mL (1 mol) of (−)-nopol [$[\alpha]^{23}_D$ −37° (neat)] and 400 mL of THF and cooled to −78 °C. While the solution was stirring at −78 °C, 455 mL (2.2 M, 1 mol) of *n*-BuLi was added slowly and stirred for 1 h at −78 °C; 190 g (1 mol) of *p*-toluenesulfonyl chloride in 200 mL of THF was added slowly and the stirring continued for another hour at −78 °C. It was then warmed to room temperature and stirred for 2 h. The reaction mixture was poured into ice–water and extracted with pentane. Evaporation of the solvent gave a thick semisolid of nopol tosylate in 90% yield (290 g). Nopol tosylate (290 g) was dissolved in hot pentane (800 mL) and stored at 0 °C for 12 h to ensure complete crystallization. Colorless white needles of **7** (mp 50–51 °C) were recovered by fast filtration in 85% yield.

A dry, 3-L flask was charged with 31 g (0.77 mol) of LAH and 1500 mL of anhydrous ether. The tosyl derivative (**7**, 234 g, 0.77

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(13) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257.

(14) For handling of air- and moisture-sensitive compounds, see: Brown, H. C.; Kramer, G.W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.
(15) [Ni-(*R*)-Cam] = nickel(II)bis[1(*R*)-3-(heptafluorobutyryl)camphorate]. This column was supplied by CC & CC, Kirchentellinsfurt, FRG. See: (a) Schurig, V.; Bürkle, W. *J. Am. Chem. Soc.* **1982**, *104*, 7573; (b) *J. Chromatogr.* **1984**, *289*, 321.

Table VI. Reaction of BMS with (-)-2-Ethylapopinene in THF at 0 °C (1:2).[a] Analysis of Reaction Mixtures at Each Period

reactn time, h	residual olefin, 5, mmol	alcohol formed, 8, mmol	residual hydride, mmol
1	26.4	13.3	46.8
2	23.6	16.5	43.6
10	14.6	25.6	34.6
22	11.1	28.6	31.5
46	8.9	31.2	28.9
72	4.4	35.5	24.6
106	4.4	35.5	24.4

[a] 20 mmol BH_3 (BMS) (0.71 M) and 40 mmol (-)-2-ethylapopinene (1.42 M).

mol in ether, 250 mL) was added slowly at 25 °C and refluxed for 5 h. The reaction mixture was poured into ice–water slowly with stirring. The solid $Al(OH)_3$ was filtered off and the filtrate saturated with NaCl and extracted with ether (3 × 150 mL). The combined organic layer was washed with dilute HCl and brine. The crude oil obtained after the evaporation of solvent was distilled from a small excess of LAH to afford pure (-)-2-ethylapopinene (**5**) in 61% overall yield, $[\alpha]^{23}_D$ -42° (neat), bp 88 °C/40 mm.

(+)-2-Ethylapoisopinocampheol (8). In a 100-mL, round-bottom flask equipped with a septum inlet, reflux condenser, stirring bar, and a connecting tube leading to a mercury bubbler was placed 10 mL of a 1-M solution of BH_3 in THF and the solution was cooled to 0 °C. To the reaction flask was added with stirring 3.54 mL (20 mmol) of (-)-2-ethylapopinene (**5**). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The organoboranes were then oxidized by successive addition of 8 mL of 3 N NaOH and 8 mL of 30% H_2O_2. The contents were maintained at 55 °C for 2 h to ensure complete oxidation. The organic layer was separated and the aqueous layer extracted with ether (2 × 10 mL). The combined organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. The concentrated organic layer after distillation gave **8** in 80% yield, bp 80 °C/0.5 mm: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.86 (s, 3 H), 0.96 (br t, 3 H), 1.2 (s, 3 H), and 4.45 (m, 1 H); $[\alpha]^{23}_D$ +21.8° (*c* 3, $CHCl_3$); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.98, 23.84, 27.81, 28.55, 33.92, 38.20, 39.47, 42.15,45.5, 55.71, 70.73.

Rate and Stoichiometry for the Reaction of (-)-2-Ethylapopinene (5) with BMS. The reactions were carried out in THF at 0 °C in three different molar concentrations, namely, BH_3·SMe_2, 20 mmol, (-)-2-ethylapopinene, 40 mmol; BH_3·SMe_2, 20 mmol, **5**, 60 mmol; BH_3·SMe_2, 20 mmol, **5**, 200 mmol. At appropriate periods of time, aliquots of the solution were removed and analyzed for hydrogen by hydrolysis.[13] The hydrolyzed aliquots were next oxidized with alkaline hydrogen peroxide and analyzed for 2-ethylapopinene and 2-ethylapoisopinocampheol by using *n*-nonane as an internal standard. A 10% Carbowax column (6 ft, $^1/_8$ in.) was used and programmed 10°/min from 50 to 170 °C. The reaction of 20 mmol BH_3·SMe_2 with 40 mmol of 2-ethylapopinene is described as representative.

An oven-dried, 100-mL round-bottom flask equipped with a septum inlet and magnetic stirring bar was cooled to 0 °C in an ice bath under slow nitrogen flow. To this flask were added BMS (2 mL, 20 mmol), THF (16 mL), *n*-nonane (3 mL, 17.6 mmol), and (-)-2-ethylapopinene (6.95 mL, 40 mmol) successively. The aliquot samples were oxidized and analyzed for alcohol **8** and unreacted 2-ethylapopinene (**5**) in comparison with *n*-nonane, an internal standard. The results are summarized in Table VI.

At 72 h, GC analysis showed that 35.5 mmol of alcohol **8** and 4.4 mmol of unreacted olefin **5** were present in comparison with the internal standard (*n*-nonane).

From these data, the amounts of $EapBH_2$ and Eap_2BH were calculated. The amount of $EapBH_2$ was assigned equal to the 2-ethylapopinene unreacted, 4.4 mmol, and the amount of Eap_2BH was calculated to be 15.55 mmol: $^1/_2$[35.5 mmol (alcohol **8**) - 4.4 mmol ($EapBH_2$)]. The material balance of the B–H bond was calculated as follows: hydride in solution (24.4 mmol) + alcohol **8** (35.5 mmol) = 59.9 mmol. The expected value was 60 mmol (3 × 20 mmol BH_3). On the basis of these calculations, approximate yields of mono- and dialkylboranes have been calculated. The results are summarized in Table I. The reaction of BMS with 2-ethylapopinene in a 1:10 ratio in THF at 0 °C provided ~98% of Eap_2BH after 72 h.

Preparation of the Bis Adduct of Mono(2-ethylapoisopinocamphenyl)borane with TMED (11). A dry 500-mL round-bottom flask equipped with septum inlet, magnetic stirring bar, and reflux condenser leading to a mercury bubbler was flushed with dry nitrogen and maintained under a static pressure of nitrogen. The flask was charged with 10 mL (10 M, 100 mmol) of neat borane–methyl sulfide complex and 55 mL of anhydrous ether; 36.4 mL (210 mmol) of (-)-2-ethylapopinene [$[\alpha]^{23}_D$ -42° (neat)] was added dropwise with stirring. The reaction mixture was heated under reflux (4 h) until no BH_3 was observed (^{11}B NMR). TMED (7.5 mL, 50 mmol) was added to the refluxing solution and the refluxing was continued for another 0.5 h. Adduct **11** crystallized. Methyl sulfide and 2-ethylapopinene were removed by filtration, and the solid was washed with cold ether (2 × 10 mL) and dried under vacuum: yield 18.0 g (77%). The white solid was recrystallized (2:1 cyclohexane/toluene): mp 138–141 °C; ^{1}H NMR ($CDCl_3$,Me_4Si) δ 0.91 (br t, 6 H),1.06 (s, 6 H), 1.16 (s, 6 H), 2.43 (s, 12 H), and 3.16 (s, 4 H). Oxidation of **11** with alkaline H_2O_2 afforded alcohol **8**, $[\alpha]^{23}_D$ + 24.2° (*c* 3, $CHCl_3$) 99.15% ee (determined by capillary GC analysis of its TPC ester).

Generation of $EapBH_2$ from Bis Adduct 11. To a 250-mL round-bottom flask containing 19.2 g (43.2 mmol) of bis adduct **11** in THF or ethyl ether (80 mL) was added 10.6 mL (86 mmol)of BF_3·OEt_2 dropwise, with stirring, over 10 min, and the reaction mixture was allowed to stir at room temperature for 4 h. Meanwhile, a 250-mL side-arm flask with a magnetic stirring bar and filtration chamber was assembled under dry nitrogen and cooled to 0 °C in an ice bath. The resulting slurry from the reaction flask was transferred with a double-ended needle to the filtration chamber. The solid $(BF_3)_2$·TMED was washed with cold THF (2 × 10 mL). The filtrate was analyzed for $EapBH_2$ by hydrolysis with 1:1:1 glycerol/water/THF as the hydrolyzing mixture and found to be 0.67 M, 110 mL (73.7 mmol), 86% yield. The standard solution of mono(2-ethylapoisopinocampheyl)borane was used immediately for hydroboration.

(*R*)-(+)-2-Methyl-1-butanol from 2-Methyl-1-butene. In a 250-mL flask equipped with a septum inlet, magnetic stirring bar, and a connecting tube leading to a mercury bubbler was placed 46 mL (28.5 mmol of 0.62 M) of mono(2-ethylapoisopinocampheyl)borane in THF and this was cooled to–25 °C; 3 mL (28 mmol) of 2-methyl-1-butene was added slowly to the reaction flask with stirring over a period of 5 min. The reaction mixture was stirred at –25 °C for 24 h, followed by addition of 3 mL (75 mmol) of methanol. The organoboranes were oxidized with alkaline hydrogen peroxide to furnish (*R*)-(+)-2-methyl-1-butanol (2.0 g, 80%), bp 80 °C/100 mm. It was purified on preparative GC to yield GC pure material $[\alpha]^{23}_D$ +0.123° (neat),2% ee.[16a]

(*R*)-(-)-2-Butanol from *cis*-2-Butene. In a 250-mL flask equipped with a septum inlet, magnetic stirring bar, and condenser leading to a mercury bubbler was placed 58 mL (33.4 mmol) of 0.575 M solution of mono(2-ethylapoisopinocampheyl)borane in THF and this was cooled to –25 °C. Meanwhile, 3.05 mL (33.7 mmol) of *cis*-2-butene was condensed in a graduated cylinder cooled in a dry ice–acetone bath and added slowly to the reaction flask with a double-ended needle. The reaction mixture was stirred at –25 °C for 24 h, followed by addition of 3 mL (75 mmol) of methanol. The solvents were removed under vacuum (20 mmHg). The flask was then brought to atmospheric pressure by being flushed with nitrogen gas and charged with 50 mL of ethyl ether. The organoboranes were oxidized and worked up to provide 1.8 g of (*R*)-(-)-2-butanol, bp 94–95 °C/740 mm, 73% yield (>94% GC pure). The alcohol was purified by preparative GC to yield GC pure material, $[\alpha]^{23}_D$ -4.07° (neat), 30% ee.[16b]

(*R*)-(-)-2-Butanol from *trans*-2-Butene. In a 250-mL flask equipped with a septum inlet, magnetic stirring bar, and con-

(16) (a) Whitmore, F. C.; Olewine, J. H. *J. Am. Chem. Soc.* **1938**, *60*, 2569. (b) Leroux, P. J.; Lucas, H. J. *Ibid.* **1951**, *73*, 41. (c) Sanderson, W. A.; Mosher, H. S. *Ibid.* **1966**, *88*, 4185. (d) Brown, H. C.; Singaram, B. *Ibid* **1984**, *106*, 1797. (e) Backström, R.; Sjöbers, B. *Arkiv. Kemi* **1967**, *26*, 549.

necting tube leading to a mercury bubbler was placed 58 mL (33.4 mmol) of a 0.575 M solution of mono(2-ethylapoisopinocampheyl)borane in THF and this was cooled to −25 °C. Meanwhile, 3.15 mL (33.8 mmol) of *trans*-2-butene was condensed in a graduated cylinder, cooled in a dry ice–acetone bath, and added slowly to the reaction flask with a double-ended needle. The reaction mixture was stirred at −25 °C for 24 h and the reaction mixture was methanolyzed. The solvents were removed under vacuum (20 mmHg). The flask was then brought to atmospheric pressure by being flushed with nitrogen gas and charged with 50 mL of ethyl ether. The organoboranes were oxidized and worked up to furnish 1.9 g of (*R*)-(−)-2-butanol, bp 94–95 °C/740 mm, 77% yield (>94% GC pure). It was purified on preparative GC by using column a to yield GC pure material, $[\alpha]^{23}_D$ −10.24° (neat), 76% ee.[16b]

(*R*)-(−)-3-Methyl-2-butanol from 2-Methyl-2-butene. In a 250-mL flask equipped with a septum inlet, magnetic stirring bar, and connecting tube leading to a mercury bubbler was placed 64 mL (35.8 mmol) of a 0.56 M solution of mono(2-ethylapoisopinocampheyl)borane in THF and this was cooled to −25 °C. To the reaction flask was added with stirring 3.8 mL (2.52 g, 36 mmol) of 2-methyl-2-butene over a period of 5 min. The reaction mixture was allowed to stir at −25 °C for 24 h. It was then treated with 3 mL (75 mmol) of methanol dropwise at −25 °C (H_2 elution) and slowly warmed to room temperature. The organoboranes were then oxidized by successive addition of 12 mL (3 M, 36 mmol) of sodium hydroxide and 12 mL of 30% hydrogen peroxide. The usual workup gave 2.4 g of (*R*)-(−)-3-methyl-2-butanol, bp 42 °C/30 mm, 75% yield (>95% GC pure). It was purified by preparative GC, $[\alpha]^{23}_D$ −3.27° (neat), 65% ee.[16c] Analysis of alcohol on a chiral column [Ni-(*R*)-Cam], 25 m, 80 °C, 15 psi, indicated the compound to be 68% ee.

(1*R*,2*R*)-(−)-*trans*-2-Methylcyclopentanol from 1-Methylcyclopentene. With the usual experimental setup, 2.36 mL (22.5 mmol) of 1-methylcyclopentene was added dropwise to 40 mL (22.5 mmol) of a 0.56 M solution of mono(2-ethylapoisopinocampheyl)borane in THF cooled to −25 °C and the reaction mixture was stirred at −25 °C for 24 h. The methanolysis, oxidation, and usual workup gave 1.93 g of (1*R*,2*R*)-(−)-*trans*-2-methylcyclopentanol, bp 98–100 °C/101 mm, 86% yield (>96% GC pure). It was purified by using column a to furnish GC-pure material, $[\alpha]^{23}_D$ −33.34° (*c* 7.2, MeOH), 71% ee.[16d] GC analysis of its acetate (prepared by standard procedure) using a 25-m chiral column at 80 °C and 20 psi indicated the compound to be 68% ee.

(1*R*,2*R*)-(−)-*trans*-2-Methylcyclohexanol from 1-Methylcyclohexene. With the usual experimental setup, 2.36 mL (20 mmol) of 1-methylcyclohexene was added dropwise to 32.5 mL (20.2 mmol) of a 0.62 M solution of mono(2-ethylapoisopinocampheyl)borane in THF cooled to −25 °C and the reaction mixture was stirred at −25 °C for 24 h. The methanolysis, oxidation, and usual workup gave 1.85 g of (1*R*,2*R*)-(−)-*trans*-2-methylcyclohexanol, bp 98–100 °C/65 mm, 81% yield. It was purified by using column a to furnish a GC-pure material, $[\alpha]^{23}_D$ −35.02° (*c* 6.4, MeOH), 82% ee.[14e] Capillary GC analysis of the alcohol on a 25-m chiral column, 80 °C and 20 psi, indicated the compound to be 78% ee.

Neither the enantiomers alcohols nor the acetates of 2-methyl-1-butanol or 2-butanol could be separated by using the chiral column [Ni-(*R*)-Cam].

Liberation of (−)-2-Ethylapopinene of High Optical Purity (~100% ee). A solution of 50 mmol of $EapBH_2$ in 65 mL THF was placed in a dry 250-mL flask equipped with septum inlet, magnetic stirring bar, and adaptor connected to a mercury bubbler for nitrogen, cooled to 0 °C, and treated with 13 mL (105 mmol) of 1-hexene. The reaction flask was allowed to warm to room temperature and the stirring continued for 4 h. ^{11}B NMR indicated an absorption at δ +81, corresponding to the presence of trialkylborane. The resulting trialkylborane was freed from solvent under vacuum (12 mm) and to it was added 3.1 g (30 mmol) of benzaldehyde and the stirring was continued for 4 h at room temperature (^{11}B NMR δ +54). The reaction mixture was fractionated. The constant boiling fraction (90 °C/40 mm) containing 2-ethylapopinene and benzaldehyde was dissolved in 50 mL of ether and the excess benzaldehyde was removed by washing with 10% sodium bisulfite solution (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, the ether evaporated, and the residue distilled over LAH under vacuum (60 °C/12 mm) to give (−)-2-ethylapopinene (6.1 g, 41 mmol) in 81% yield as a liquid; GC purity ≥98%. A small portion of the sample was further purified by preparative GC on column b; $[\alpha]^{23}_D$ −46.2° (neat); 99.1% ee.

Preparation of (+)-2-Ethylapopinene by Metalation and Alkylation (MeI) of (+)-α-Pinene of 99.7% ee. *t*-BuOK (76.3 g, 0.680 mol) was placed in a dry 1-L flask equipped with magnetic stirring bar, septum inlet, and adaptor for nitrogen and cooled to −78 °C. To it was added hexane (250 mL), (+)-α-pinene ($[\alpha]^{23}_D$ +51.45° (neat), 99.7% ee; 68 g, 0.5 mol), followed by *n*-BuLi (2.5 M, 272 mL, 0.680 mol). The reaction mixture was slowly allowed to warm to room temperature and stirring continued for 48 h. The resulting potassium salt was dissolved in THF (200 mL) and cooled to −78 °C. Methyl iodide (142 g, 1 mol) was added slowly to the above solution (30 min). Stirring was continued at −78 °C for 1 h and the mixture was warmed to room temperature and stirred for 1 h. It was then poured onto 1 L of water. The organic layer was separated, and the aqueous layer was saturated with potassium carbonate and extracted with hexane (2 × 50 mL). The combined organic layer was washed with water and brine, dried, and evaporated. Distillation of the residue gave an oil (70 g, 83% yield), consisting mainly of (+)-2-ethylapopinene along with ~2% α-pinene and 6% of **13**, which was fractionated on a packed (Helipack) column (height 1 m, reflux ratio 50:1). The fraction boiling at 70 °C/40 mm (7 mL, consisting mainly of α-pinene) was discarded. The residue (61 g) containing (+)-2-ethylapopinene (90%) and 6% of **13** was stirred over 9-BBN (4.8 g, 10 mol %) at room temperature for 4 h. Distillation afforded (+)-2-ethylapopinene in 65% yield (54 g) GC purity 98%. A small portion of the sample was further purified by preparative GC on column a to obtain 100% GC pure sample, $[\alpha]^{23}_D$ +46.4° (neat, *d* = 0.864), 99.7% ee. Hydroboration–oxidation of (+)-2-ethylapopinene ($^-OH/H_2O_2$) thus obtained gave the (−)-2-ethylapoisopinocampheol; $[\alpha]^{23}_D$ −24.3° (*c* 3, $CHCl_3$); capillary GC analysis of its TPC ester indicated alcohol to be of essentially 100% ee: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.81 (s, 5 H), 0.93 (t, *J* = 7 Hz, 3 H), 1.26 (s, 3 H), 5.1 (m, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 11.73, 21.14, 26.38, 29.68, 31.27, 31.69, 37.2, 41.17, 46.05, 114.51, 150.10.

Acknowledgment. The financial support from the National Institutes of Health and Dow Chemical Company is gratefully acknowledged.