volatile components were then removed by distillation. *N,O*-Dimethylhydroxylamine hydrochloride (0.62 g, 6.4 mmol) was added, and the resulting mixture was dissolved in 40 mL of CH_2Cl_2. The purple solution was cooled to 0 °C and pyridine (1.04 mL, 12.9 mmol) was added, upon which the mixture changed to a light orange color. The mixture was stirred overnight and evaporated in vacuo. The residue was partitioned between brine and a 1:1 mixture of Et_2O and CH_2Cl_2, washed with 5% HCl, dried over Na_2SO_4, and evaporated. The crude amide was dissolved in 30 mL of dry THF, 0.7 g of $LiAlD_4$ was added, and the solution was refluxed for 3 h. After stirring overnight, the mixture was quenched at 0 °C with 5% HCl and was extracted with a 1:1 mixture of Et_2O and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to afford *α-deuterio*-**3a** (0.46 g, 51%). The ^1H NMR spectrum of the acylal prepared from this material was identical with that of **3b** except for the absence of the singlet at δ 8.23.

Acknowledgment. Financial support by the National Science Foundation (grant 85-02078) and from the State of Connecticut High Technology Collaborative Program is gratefully acknowledged.

Chiral Synthesis via Organoboranes. 30. Facile Synthesis, by the Matteson Asymmetric Homologation Procedure, of α-Methyl Boronic Acids Not Available from Asymmetric Hydroboration and Their Conversion into the Corresponding Aldehydes, Ketones, Carboxylic Acids, and Amines of High Enantiomeric Purity

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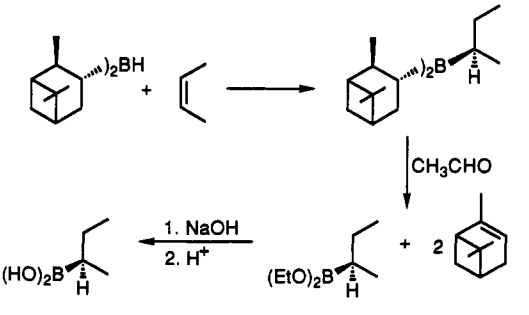
2-(α-Methylalkyl)- or 2-(α-arylethyl)-1,3,2-dioxaborinanes, $RMeHC^*BO_2(CH_2)_3$ (R = alkyl or aryl), of very high enantiomeric purity, not available from asymmetric hydroboration, can be prepared by the Matteson asymmetric homologation procedure of optically pure pinanediol or 2,3-butanediol boronate esters with (dichloromethyl)lithium, $LiCHCl_2$, conveniently generated in situ in THF at −78 °C, followed by reaction with either a Grignard reagent or an alkyllithium, with subsequent removal of the chiral auxiliaries. α-Methyl boronic esters thus obtained are readily converted into the corresponding aldehydes by the reaction with [methoxy(phenylthio)methyl]lithium [LiCH(OMe)SPh] (MPML) and mercuric chloride, followed by oxidation with hydrogen peroxide in a pH 8 buffer medium. The two-phase aqueous chromic acid procedure can be used to oxidize these aldehydes to the corresponding α-methyl carboxylic acids of very high enantiomeric purity without significant racemization. Additionally, pinanediol or 2,3-butanediol α-methylorganylboronate esters can be conveniently converted into borinic ester derivatives, RMeHC*BMe(OMe), of very high enantiomeric purity by reaction with methyllithium, followed by treatment with methanolic hydrogen chloride and subsequent recovery of the valuable chiral auxiliaries. These borinic ester derivatives are converted into α-methyl ketones and α-methyl primary amines of known absolute configuration by the α,α-dichloromethyl methyl ether (DCME) reaction and the reaction with hydroxylamine-*O*-sulfonic acid, respectively. The present synthesis of chiral 2-organyl-1,3,2-dioxaborinanes by the Matteson route, together with our direct asymmetric hydroboration procedure, makes it possible to synthesize many chiral boronic acid derivatives in very high enantiomeric purities. These complementary procedures greatly expand the scope of asymmetric synthesis via chiral organoboranes.

The synthesis of enantiomerically pure compounds has always presented a considerable challenge to organic chemists. Recently intense interest has been aroused in the development of efficient methods for asymmetric synthesis.[1] Of these procedures, asymmetric hydroboration is especially promising for providing a general synthesis of pure enantiomers.[2] For example, diisopinocampheylborane (Ipc_2BH) hydroborates *cis*-alkenes, resulting in asymmetric induction in the range of 80–99% ee.[3] Similarly, monoisopinocampheylborane ($IpcBH_2$) hydroborates *trans*-alkenes and trisubstituted alkenes with optical inductions ranging from 53% to 98% ee.[4] It was later established in our laboratory[5] that the treatment with acetaldehyde of the trialkylborane derived via the asymmetric hydroboration of prochiral olefin with Ipc_2BH resulted in the selective, facile elimination of the pinanyl groups, providing the corresponding boronic ester in very high enantiomeric purity (Scheme I). Such chiral boronic esters and acids are exceptionally promising intermediates

Scheme I



† Present address: Department of Chemistry, University of California, Santa Cruz, California 95064.

(1) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2.
(2) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.

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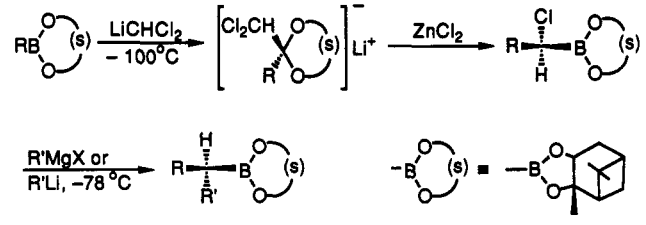
Scheme II



for asymmetric carbon–carbon bond forming reactions proceeding through organoborane intermediates.[6,7]

However, except in some cases, such as 1-phenylethylboronic acid, it is difficult to synthesize α-methyl boronic esters of very high enantiomeric purity by the direct asymmetric hydroboration procedure due to the controlling directive effects of the hydroboration reaction.[8]

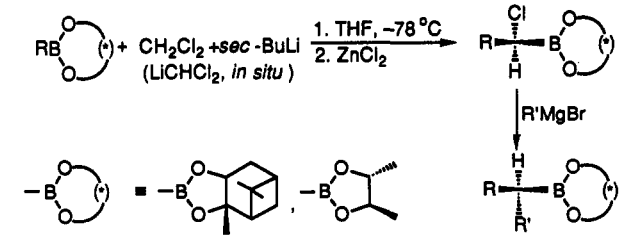
Matteson and co-workers have described[9] a highly promising alternative route to such optically active boronate ester derivatives via the one-carbon homologation of pinanediol boronate esters with preformed (dichloromethyl)lithium, $LiCHCl_2$, at −100 °C (Scheme II).

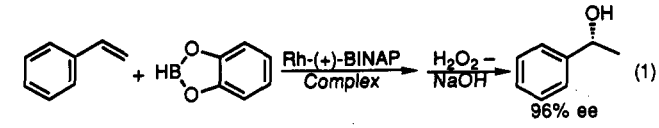
However, apart from the many elegant features of this asymmetric synthesis, such as the prediction of chirality at each chiral center and the possibility of an immediate repetition of the cycle to form additional chiral centers, the above synthesis suffers from certain serious difficulties, such as the requirement of inconvenient reaction temperatures, −100 °C, and the difficulties encountered in the recovery of the pinanediol chiral auxiliary. These optically active pinanediol boronate esters are unusually stable toward hydrolysis, transesterification, or ligand exchange, making the isolation of the corresponding chiral boronic acid exceptionally difficult without destruction of the valuable chiral auxiliary.[10a]

Pinanediol boronate esters have been utilized previously[9] for the synthesis of optically active *vic*-diols, amino alcohols, amino acids, and pheromones but have not been fully explored in other useful carbon–carbon bond forming reactions,[7] possibly because of the lack of a satisfactory procedure for the generation of the chiral boronic acids from these chiral pinanediol boronate esters. A systematic study in our laboratories has now made available convenient procedures for the recovery of the valuable pinanediol auxiliary with satisfactory isolation of the corresponding boronic acids.[10b]

Recently the catalytic asymmetric hydroboration of styrene derivatives has been reported.[11] Although excellent enantioselectivity to the extent of 96% ee (eq 1) has been achieved by this procedure for the synthesis of 1-arylethanol derivatives, these workers have not attempted to isolate the intermediate chiral boronate esters, which we have developed as important building blocks in asymmetric synthesis. Indeed, oxidation with alkaline hydrogen peroxide to produce the 1-arylethanol derivative appears to have been the only synthetically important reaction to which these chiral boronate esters have been subjected.

Scheme III





(1)

96% ee

It should be emphasized that the discovery of the asymmetric hydroboration procedure for the synthesis of optically active boronic acids/esters has proven to be an exceptionally promising route for the synthesis of pure enantiomers via boron-mediated carbon–carbon bond forming reactions.[7] We have recently reported an effective way of converting chiral boronate esters into enantiomerically pure aldehydes,[12] ketones,[13] and primary amines.[14] However, these procedures are limited since we could use only those boronic acids that are readily available by the direct asymmetric hydroboration procedure. Now that we have a convenient procedure for the isolation of boronic acid derivatives from pinanediol boronate esters of very high enantiomeric purity,[10] we undertook to explore the possibility of synthesizing α-methylorganylboronic acid derivatives not available by the direct asymmetric hydroboration route and then utilizing them for the synthesis of chiral α-methyl aldehydes, carboxylic acids, ketones, and amines of very high enantiomeric purity.

Results and Discussion

During the course of our investigation of the one-carbon homologation of cyclic boronate esters, we established the utility of (dichloromethyl)lithium, $LiCHCl_2$, generated in situ by reaction of CH_2Cl_2 and *sec*-BuLi in THF at −78 °C in the presence of the boronate ester. We thought it worthwhile to apply this in situ procedure for the generation of $LiCHCl_2$ in the Matteson asymmetric homologation procedure, thereby avoiding the requirement for temperatures of −100 °C for the generation of preformed $LiCHCl_2$. Indeed, this in situ procedure proved to be very effective[10] for the insertion of a chloromethyl group with excellent diastereoselectivity, providing boronate esters of high optical purities (Scheme III).

By following this simple and convenient in situ procedure for the generation of $LiCHCl_2$, we have prepared the following representative boronate esters derived either

(3) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065.
(4) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074.
(5) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *Tetrahedron* **1984**, *40*, 1325.
(6) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287.
(7) Brown, H. C.; Jadhav, P. K.; Singaram, B. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, Heidelberg, 1986; Vol. 4, pp 307–356.
(8) Brown, H. C.; Singaram, B. *Proc. Indian Acad. Sci.* **1988**, *100*, 119.
(9) (a) Matteson, D. S.; Sadhu, K. M.; Ray, R.; Peterson, M. L.; Majumdar, D.; Hurst, G. D.; Jesthi, P. K.; Tsai, D. J. S.; Erdik, B. *Pure Appl. Chem.* **1985**, *57*, 1741. (b) Matteson, D. S. *Synthesis* **1986**, 973; (c) *Acc. Chem. Res.* **1988**, *21*, 294; (d) *Tetrahedron* **1989**, *45*, 1859; (e) *Chem. Rev.* **1989**, *89*, 1535.
(10) (a) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536. (b) Brown, H. C.; Rangaishenvi, M. V. *J. Organomet. Chem.* **1988**, *358*, 15.
(11) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 2280.
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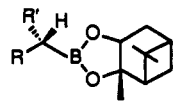
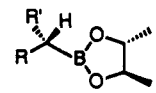
(13) Brown, H. C.; Srebnik, M.; Bakshi, R. K.; Cole, T. E. *J. Am. Chem. Soc.* **1987**, *109*, 5420.
(14) Brown, H. C.; Kim, K.-W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761.
(15) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150.

from (*s*)-pinanediol or (2*R*,3*R*)-butanediol, as outlined in Scheme III (see Experimental Section).

2-Alkyl- or 2-Aryl-Substituted Boronate Esters of High Optical Purity Derived from Either (*s*)-Pinanediol or (*R*,*R*)-2,3-Butanediol. It should be mentioned that for the preparation of the boronate esters **2** and **4**, the reaction mixture, after the generation of $LiCHCl_2$ in situ at −78 °C, was warmed to 0 °C instead of 25 °C (as utilized by Matteson). Moreover, the transfer reaction



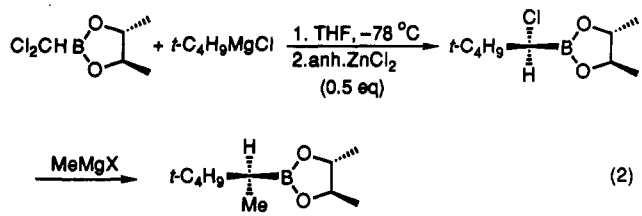
1 R=Chx, R'=Me: 98% ee
2 R=Ph-, R'=Me: 88% ee
3 R=$PhCH_2$-, R'=Me: 99% ee
4 R=6-Methoxynaphthyl-, R'=Me: 86% ee



5 R=Chx, R'=Me: 92% ee
6 R=$PhCH_2$-, R'=Me: 90% ee
7 R=*t*-C_4H_9-, R'=Me:94% ee

was essentially complete in 1 h at 0 °C as evidenced by the ^{11}B NMR spectrum. Such α-chloro boronate esters in which the chloride is situated on a benzylic carbon are especially susceptible to epimerization. A fast workup is essential for such cases. After repeated modification of the experimental conditions, the best ee we could achieve was only 88%. We did not attempt to recrystallize the intermediate α-chloro boronate ester derivative, as reported by Matteson et al.[16] In other cases the asymmetric syntheses yielded much better optical yields.

Our repeated efforts to induce transfer reaction in (*s*)-pinanediol *tert*-butylboronate with $LiCHCl_2$ generated in situ failed, presumably due to the combined steric hindrance exerted by the *tert*-butyl and pinanediol moieties. In all attempts we recovered the starting pinanediol *tert*-butylboronate ester unchanged. Consequently, we tested the transfer reaction of $LiCHCl_2$, generated in situ, with (*R*,*R*)-2,3-butanediol *tert*-butylboronate ester (Scheme III). This homologation sequence proceeded smoothly to provide the desired optically active boronate ester **7** in 94% ee. Alternately, we have prepared the boronate ester **7** by reacting (*R*,*R*)-2,3-butanediol dichloromethylboronate[17] with *tert*-butylmagnesium halide at −78 °C, followed by treatment with anhydrous $ZnCl_2$ (0.5 equiv) and methyl Grignard reagent (eq 2).

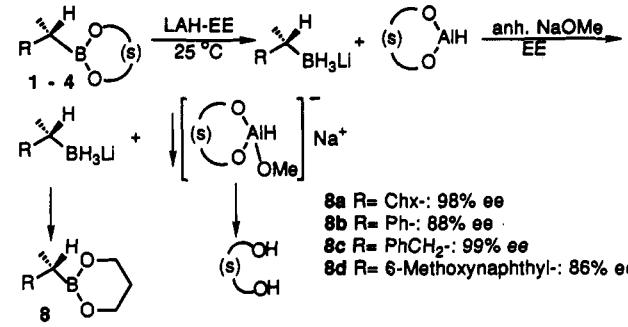


(2)

The enantiomeric purity of all boronate esters was determined by capillary GC analyses of the oxidation product alcohols as their MTPA ester derivatives.[18]

Synthesis of α-Chiral Aldehydes and Carboxylic Acids. With the availability of optically active boronate esters **1**–**7** established, we undertook the synthesis of α-chiral aldehydes. Rathke et al. have reported[19] the synthesis of aldehydes from α-chloro boronate esters via oxidation with H_2O_2 in a pH 8 phosphate buffer medium. Accordingly, we prepared the corresponding α-chloro boronate ester of **1** by treatment with $LiCHCl_2$ generated in situ in THF at −78 °C. Unfortunately, attempts to oxidize such α-chloro boronate esters to aldehydes under the conditions reported by Rathke repeatedly failed and we obtained only a complex mixture of products. Aldehydes are known to produce aldehyde–peroxide complexes, and these are known to be explosive.[20] Hence, we did not pursue this reaction further.

Scheme IV



8a R= Chx-: 98% ee
8b R= Ph-: 88% ee
8c R= $PhCH_2$-: 99% ee
8d R= 6-Methoxynaphthyl-: 86% ee

On the basis of our success in converting boronate esters to aldehydes through the α-methoxy derivatives,[12] we attempted the synthesis of α-chiral aldehydes from optically active pinanediol boronate esters using MPML. The reaction of the boronate ester **1** with [methoxy(phenylthio)methyl]lithium (MPML) followed by the transfer reaction induced by the addition of mercury(II) chloride furnished the desired α-methoxy derivative. However, the oxidation of this pinanediol α-methoxy boronic ester with H_2O_2 in a pH 8 phosphate buffer medium was sluggish and took ~24 h for completion, presumably because of the bulky pinanediol chiral auxiliary. The desired aldehyde, obtained via steam distillation of the oxidation product, had undergone significant racemization, either during oxidative workup or during steam distillation. On the other hand, the optically active butanediol α-methoxy boronate esters underwent complete oxidation with H_2O_2 in a pH 8 phosphate buffer medium in 1.5–2 h at 25 °C to provide the desired α-chiral aldehydes in high optical purity.

Matteson and Beedle have recently reported[21] an elegant procedure for the oxidation of pinanediol 1-chloro-2-azidoalkylboronates to the corresponding α-azido carboxylic acids using sodium chlorite in the presence of a large excess of alkene (to suppress radical side reactions). We applied this oxidation procedure to the α-chloro boronate esters derived from the optically active pinanediol boronate esters **1**–**4**. Unfortunately, the yields of the derived α-chiral carboxylic acids were poor. More importantly, undesired destruction of the valuable pinanediol chiral auxiliary to pinonic acid was observed. These results clearly revealed that the pinanediol boronate esters are not suitable for some of the valuable carbon–carbon bond forming reactions previously achieved with the 2-alkyl-1,3,2-dioxaborinanes.

Consequently, we applied our recent procedure[9] to convert the pinanediol boronate esters **1**–**4** into the corresponding optically active 2-alkyl-1,3,2-dioxaborinanes (Scheme IV). This enabled us not only to isolate the desired optically active boronic esters and pinanediol but also to overcome the steric hindrance posed by the bulkier and expensive pinanediol chiral auxiliary.

The enantiomeric purity of the chiral 2-organyl-1,3,2-dioxaborinanes **8a**–**d** was determined by capillary GC

(16) Matteson, D. S.; Erdik, E. *Organometallics* **1983**, *2*, 1083.
(17) Sadhu, K. M.; Matteson, D. S.; Hurst, G. D.; Kurosky, J. M. *Organometallics* **1984**, *3*, 804.
(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(19) Rathke, M. W.; Chao, E.; Wu, G. *J. Organomet. Chem.* **1976**, *122*, 145.
(20) Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091.
(21) Matteson, D. S.; Beedle, E. C. *Tetrahedron Lett.* **1987**, *28*, 4499.

Table I. α-Chiral Aldehydes of Very High Optical Purity

R*CHO	yield, % (isolated)	bp, °C (mmHg)	$[\alpha]^{23}_D$, deg	% ee[a]	confign of R*CHO
2-cyclohexyl-1-propanal	75	76–78 (20)	+4.57 ● 0.02 (c 4, MeOH)	95	S
2-methyl-3-phenyl-1-propanal	72	112–114 (20)	−4.42 ± 0.02 (c 4, MeOH)	94	S
2,3,3-trimethylbutanal	60	88–90 (100)	+17.82 ● 0.02 (c 2, EtOH)	94	S

[a] Enantiomeric purity was determined by capillary GC analysis of the α-chiral acid obtained via chromic acid oxidation of these chiral aldehydes. See Table II.

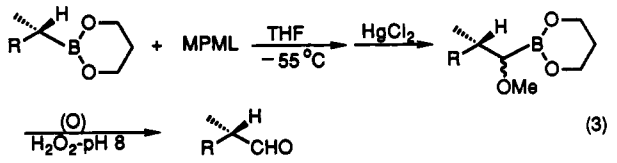
Table II. α-Chiral Carboxylic Acids of High Optical Purity

R*COOH	yield, % (isolated)	bp, °C (mmHg)	$[\alpha]^{23}_D$, deg	% ee[a]	confign of R*COOH
2-cyclohexylpropanoic acid	70	94–96 (1)	+18.32 ± 0.02 (c 4, MeOH)[b]	95	S
2-methyl-3-phenylpropanoic acid	90	96–98 (1)	+21.54 ± 0.02 (c 4, EtOH)[c]	94	S
2,3,3-trimethylbutyric acid	82	85–86 (4)	+39.7 ± 0.02 (c 1, EtOH)[d]	94	S

[a] Enantiomeric purity was determined by capillary GC analysis of the corresponding (R)-α-methylbenzylamides (ref 23). [b] Maximum reported rotation for (S)-2-cyclohexylpropanoic acid is +18.9° (c 4, MeOH) (see ref 29). [c] Maximum reported rotation for 2-methyl-3-phenylpropanoic acid is +22.2° (EtOH) (see ref 34). [d] Reported rotation for the R enantiomer of 80.5% optical purity is $[\alpha]_D$ −33.0° (c 1, EtOH) (see ref 32).

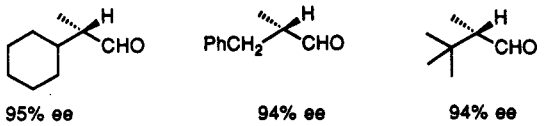
analyses of the oxidation product alcohols derivatized as MTPA esters. Evidently, there was no noticeable racemization during the synthetic transformation, as depicted in Scheme IV.

These 2-substituted 1,3,2-dioxaborinanes **8a–d** were smoothly converted into the corresponding optically active aldehydes via our published procedure (eq 3).[12]



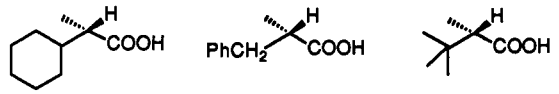
(3)

Unlike oxidation of the pinanediol boronate esters, oxidation of the 1,3-propanediol boronate esters proceeded smoothly and was essentially complete in 1.5 h at 25 °C (Table I). A similar procedure was adopted for the synthesis of α-chiral aldehydes from the respective 2,3-butanediol boronate esters. The intermediates derived from (2*R*,3*R*)-butanediol also underwent oxidation with H_2O_2 in a buffered medium with ease (25 °C, 1.5–2 h) without any significant racemization. It is pertinent to mention that the 2-phenylpropionaldehyde and 2-(6-methoxy-1-naphthyl)propionaldehyde prepared by following the above procedure undergo fast racemization under the reaction conditions and were obtained with little optical activity, presumably because of the activating effect of the α-aryl substituent in facilitating racemization.



95% ee 94% ee 94% ee

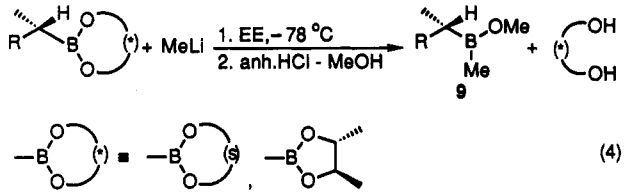
Previously we have shown[12] that *trans*-2-methylcyclopentanecarboxaldehyde of 99% ee can be readily converted into *trans*-2-methylcyclopentanecarboxylic acid of 99% ee by using the two-phase chromic acid oxidation procedure.[22] However, we did not check the generality of this simple procedure. Consequently, we undertook the oxidation of (*R*)-2-phenylbutyraldehyde of 88% ee to the corresponding acid. We were gratified to find that the oxidation proceeded smoothly under the two-phase conditions to provide (*R*)-2-phenylbutyric acid of 88% ee. Evidently, there is no significant racemization during this two-phase chromic acid oxidation. We then converted the above α-methyl aldehydes to the corresponding carboxylic acids without any significant racemization, thereby establishing the generality of this reaction (Table II).



95% ee 94% ee 94% ee

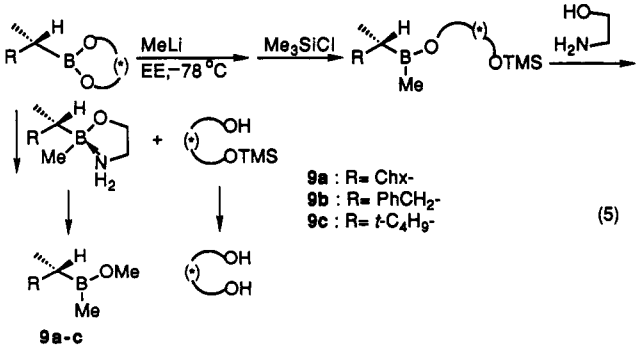
The optical purity of these α-chiral carboxylic acids was determined by the capillary GC analysis of the diastereomeric amides prepared by using (*R*)-α-methylbenzylamine and 1,1′-carbonyldiimidazole.[23]

Synthesis of α-Chiral Ketones. We then studied the conversion of optically active pinanediol and 2,3-butanediol boronate esters to the corresponding *B*-methylorganylborinate esters (eq 4). We also successfully recovered the



(4)

valuable pinanediol chiral auxiliary from these reactions. We also tested the utility of Me_3SiCl for the opening of the "ate" complex and purification of the resulting borinate ester via chelation with ethanolamine (eq 5).



(5)

(22) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387.

(23) Cuppa, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.

(24) Brown, H. C.; Kim, K.-W.; Srebnik, M.; Singaram, B. *Tetrahedron* **1987**, *43*, 4071.

(25) Amphetamines. In *The Merck Index*, 10th ed.; Windholz, M., Ed.; Merck & Company: New Jersey, 1983; p 601.

Table III. α-Chiral Acyclic Ketones of High Optical Purity

R*COMe	yield, % (isolated)	bp, °C (mmHg)	$[\alpha]^{23}_D$, deg	% ee[a]	confign of R*COMe
3-cyclohexyl-2-butanone	81	100–102 (20)	+42.0 ± 0.02 (c 1, $CHCl_3$)	98	S
4-phenyl-3-methyl-2-butanone	83	74–75 (1)	+45.52 ● 0.02 (c 2, EtOH)[b]	99	S
3,4,4-trimethyl-2-pentanone	72	85–86 (60)	+107.8 ● 0.02 (c 1, $CHCl_3$)	94	S

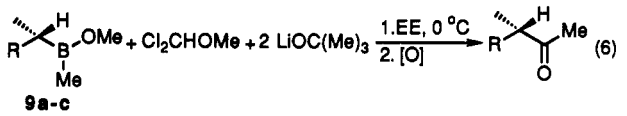
[a] Enantiomeric purity was determined on a capillary GC column using a chiral column or by derivatizing as the diastereomeric (2R,3R)-butanediol ketals. [b] Reported optical rotation $[\alpha]_D$ = +36.8° (c 3, EtOH) for 4-phenyl-3-methyl-2-butanone of 81% optical purity (see ref 33).

Table IV. α-Chiral Primary Amines/Hydrochlorides of High Optical Purity

R^*NH_2/R^*NH_2·HCl	yield, % (isolated)	mp, °C/bp, °C (mmHg)	$[\alpha]^{23}_D$, deg	% ee[a]	confign of R^*NH_2/ R^*NH_2·HCl
1-cyclohexylethylamine	69	72–74 (20)	−11.68 ● 0.02 (neat, l 0.5)[b]	96	S
1-phenylethylamine hydrochloride	70	148–150	−4.6 ± 0.02 (c 4, MeOH)	99	S
1-methyl-2-phenylethylamine hydrochloride	75	150–152	+8.44 ● 0.02 (c 4, MeOH)	99	S
3,3-dimethyl-2-butylamine hydrochloride	65	>250	+2.80 ● 0.02 (c 4, MeOH)	96	S

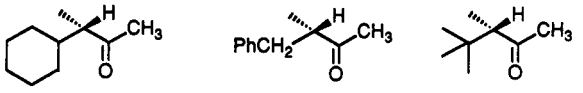
[a] Enantiomeric purity was determined by capillary GC analyses of the MTPA amides. [b] Observed rotation.

However, we then adopted the method depicted in eq 5 for the preparation of optically pure B-methylorganylborinate esters **9a–c** for conversion to the optically active ketones. These optically active borinate esters were treated with 1 equiv of α,α-dichloromethyl methyl ether (DCME) in diethyl ether (EE) at 0 °C in the presence of 2 equiv of lithium *tert*-butoxide.[13] Oxidation with H_2O_2 in a pH 8 buffer medium afforded the desired α-chiral acyclic ketones in high optical purity (Table III) (eq 6).[13] The

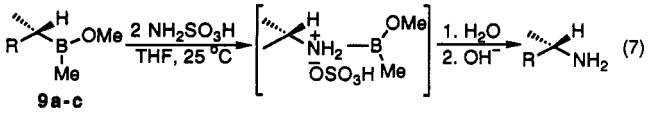


(6)

optical purity of these ketones was determined by measuring the optical rotations and comparing the values with the maximum reported data. This was further confirmed by using capillary GC analyses, either directly on a 25 m × 0.25 mm Ni(HFB-IR-Cam)$_2$ chiral column or by analysis of the diastereomeric (2R,3R)-(−)-butanediol ketals produced from the ketones.[13]



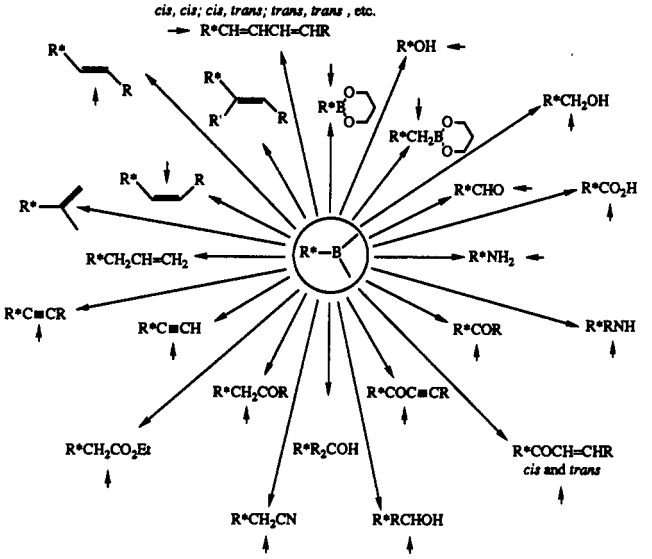
Synthesis of α-Chiral Primary Amines. As we had successfully developed simple and convenient procedures for the syntheses of optically active borinate esters **9a–c** through the pinanediol and butanediol boronate esters, we thought it desirable to extend the amination reaction[15] to these substrates. Success would provide a synthesis of chiral α-methylorganyl primary amines difficult to prepare via direct asymmetric hydroboration. The borinate ester **9a–c** was treated with 2 equiv of hydroxylamine-O-sulfonic acid (HSA) at 25 °C in THF and stirred at 25 °C for 12 h to ensure the completion of the reaction. Water was



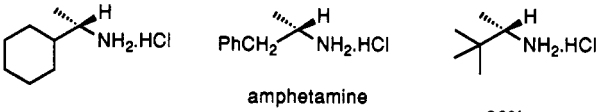
(7)

added to the reaction mixture, and the acidic aqueous portion was separated from the organic phase containing the boronic acid derivative. The acidic aqueous layer was made strongly alkaline, and the desired α-chiral amines were isolated by extraction with ether and converted to

Chart I. General Synthesis of Enantiomers via Asymmetric Hydroboration



the corresponding amine hydrochlorides by treatment with anhydrous HCl–ether. By following this general procedure (eq 7), we prepared the following primary amine hydrochlorides in high optical purities (Table IV).



96% ee — amphetamine 99% ee — 96% ee

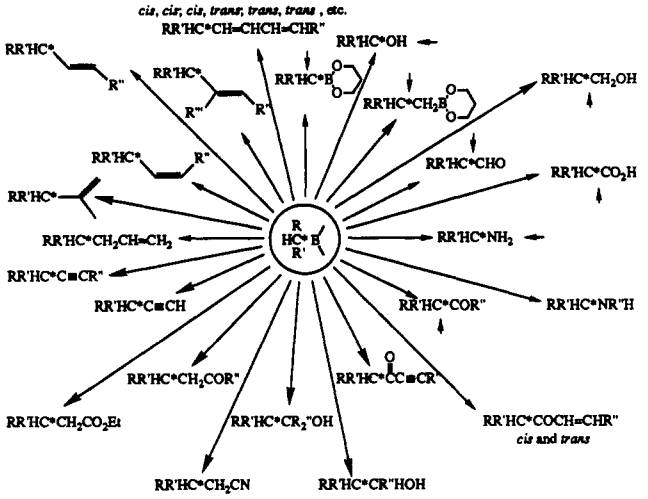
The enantiomeric excess of these chiral amines was determined by converting them to the corresponding MTPA amides and analyzing these amides on a capillary GC column.[14]

Conclusion

It has been demonstrated beyond doubt that the great majority of the transfer reactions of organoboranes proceed with complete retention of configuration. Consequently, it has been possible to achieve a general synthesis of pure enantiomers starting from chiral organoborane intermediates (Chart I).

However, the generality of this procedure is restricted to the availability of the chiral organoborane intermediates via asymmetric hydroboration. For instance, it is not possible to achieve the synthesis of chiral α-methyl-

Chart II. General Synthesis of Enantiomers via Asymmetric Homologation



organoborane intermediates with high optical purity using the asymmetric hydroboration procedure due to the controlling directive effects of the hydroboration reaction.

Fortunately, the synthesis of such chiral α-methylorganoborane intermediates can be achieved by using the Matteson asymmetric synthesis involving a one-carbon homologation of boronate esters.[9] Again, this procedure was handicapped by the requirement for inconvenient temperatures, −100 °C, for the generation of $LiCHCl_2$ and by the absence of a suitable procedure for the recovery of the valuable pinanediol chiral auxiliary.

Gratifyingly, in the present study we have circumvented the requirement for inconvenient temperatures by the development of an in situ procedure for the generation of $LiCHCl_2$. We have also developed simple procedures for the recovery of the pinanediol chiral auxiliary. These developments make the Matteson asymmetric synthesis both simpler and more practical for larger scale operations. Consequently, the present study provides preferable procedures for the preparation of optically active α-methylorganylboronate esters, $RMeHC^*B(OR')_2$, difficult to prepare via direct asymmetric hydroboration, and also provides convenient methods for the conversion of optically active pinanediol boronate esters into the corresponding optically active boronic acid/1,3-propanediol ester derivatives with recovery of the pinanediol chiral auxiliary for recycling. The α-substituted chiral 1,3,2-dioxaborinanes whose syntheses are reported in this paper and those available by direct asymmetric hydroboration are complementary. Together they make it possible to synthesize a much wider variety of chiral boronic acid derivatives in very high enantiomeric purities. We have successfully demonstrated the synthetic utility of such α-chiral boronate esters for the preparation of representative α-methyl aldehydes, α-methyl carboxylic acids, α-methyl acyclic ketones, and α-methyl amines in high enantiomeric purities. Together with the work of Matteson and his coworkers, seven such transformations have now been successfully demonstrated (indicated by a small arrow (→) pointing toward the pure enantiomer), nearly one-third of the total transformations indicated in Chart II. Consequently, a truly general asymmetric synthesis of pure enantiomers via chiral organoboranes is now available (Charts I and II).

Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[26] The spectra were obtained from the samples in an inert atmosphere.[26] The ^{11}B NMR chemical shifts are in δ ppm relative to $BF_3{\cdot}OEt_2$ with chemical shifts downfield from $BF_3{\cdot}OEt_2$ as positive. The chemical shifts are in δ relative to Me_4Si for ^1H and ^{13}C NMR spectra. Gas chromatographic analyses were carried out with a gas chromatograph equipped with a FI detector. Capillary GC analyses were performed by using either (a) a 50 m × 0.25 mm column packed with methyl silicone, (b) a 30 m × 0.25 mm column packed with SPB-5, (c) a 15 m × 0.25 mm column packed with Supelcowax, or (d) a 25 m × 0.25 mm column packed with $Ni(HFB\text{-}1R\text{-}Cam)_2$ with helium as a carrier gas.

Materials. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and was used directly. Dichloromethane and chloroiodomethane were purchased from Aldrich Chemical Company, distilled over P_2O_5, and stored over 4-Å molecular sieves under N_2. (*s*)- and (*r*)-pinanediol of ≥99% ee were purchased from Aldrich. *n*-Butyllithium (Alfa) in hexane was estimated to be 2.2 M. *sec*-Butyllithium in cyclohexane and *tert*-butyllithium in pentane were purchased from Aldrich and were estimated to be 1.2 and 1.5 M, respectively. Methylmagnesium chloride (Aldrich) in THF was estimated to be 3.0 M. 2-Bromo-6-methoxynaphthalene, α,α-dichloromethyl methyl ether, and hydroxylamine-*O*-sulfonic acid (HSA) were purchased from Aldrich. Methoxymethyl phenyl sulfide was prepared in accordance with the reported procedure.[12]

Preparation of Boronic Acids and Boronic Esters. Phenylboronic acid was purchased from Aldrich. Cyclohexylboronic acid was prepared via hydroborations of cyclohexene with $HBBr_2$ following the reported procedure.[27] Benzyl- and *tert*-butylboronic acids were prepared via the reaction of the corresponding Grignard reagent with trimethyl borate.[28] (6-Methoxy-1-naphthyl)boronic acid was prepared by reacting the lithio derivative (prepared via metalation of 2-bromo-6-methoxynaphthalene with 2 equiv of *t*-BuLi in THF at −78 °C) with triisopropyl borate.

The esterification of the above-mentioned boronic acids was performed with either pinanediol or (2*R*,3*R*)-butanediol in *n*-pentane according to the reported procedure[27] and purified by distillation under reduced pressure. Alternately, pinanediol boronate esters have been purified by chromatography over a small column of silica gel in pentane–ether eluate. Pinanediol benzylboronate was also prepared[10] via one-carbon homologation of pinanediol phenylboronate with $LiCH_2Cl$ generated in situ at −78 °C.

Homologation of 2-Alkyl- and/or 2-Arylboronate Esters Derived from (*s*)-Pinanediol or (2*R*,3*R*)-Butanediol. General Procedure. The procedure for the one-carbon homologation of (*s*)-pinanediol cyclohexylboronate to (*s*)-pinanediol 1-chloro-1-cyclohexylmethylboronate[10a] using $LiCHCl_2$ generated in situ in THF at −78 °C is representative. A solution of (*s*)-pinanediol cyclohexylboronate (5.24 g, 20 mmol) and dichloromethane (1.42 mL, 22 mmol) in freshly distilled THF (40 mL) was cooled to −78 °C by using a dry ice–acetone bath. To this was added *sec*-BuLi (18.4 mL, 22 mmol, 1.2 M in cyclohexane) dropwise over a period of 0.5 h by means of a cannula, the temperature being maintained at −78 °C. The reaction mixture was stirred at −78 °C for an additional 0.25 h, and to the reaction mixture was added freshly fused and finely powdered anhydrous $ZnCl_2$ (1.94 g, 11 mmol) under N_2. The reaction mixture was allowed to warm to 25 °C over a period of 18 h. The ^{11}B NMR spectrum of the reaction

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mixture displayed a peak at δ 32 ppm, indicating the transfer reaction to be complete. Solvent THF and the volatiles were pumped off in vacuo, to the resulting gummy mass was added *n*-pentane (50 mL), and the mixture was stirred at 25 °C for 0.25 h. The metal salts were allowed to settle, and the supernatant pentane layer was transferred into another flask by means of a cannula. The residue was triturated with *n*-pentane (2 × 15 mL), and the pentane portion was transferred. *n*-Pentane was removed from the combined portion to obtain the crude (*s*)-pinanediol 1-chloro-1-cyclohexylmethylboronate[10a] (2.65 g, 85%), which was further purified by fractional distillation under reduced pressure: bp 134–135 °C (0.5 mm); 2.49 g, 80% yield.

(*s*)-Pinanediol (*S*)-1-chloro-1-cyclohexylmethylboronate:[10a] yield, 80%; bp 140–142 °C (0.2 mm) ^{11}B NMR δ 32 (s); ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.30 (s, 3 H), 1.40 (s, 3 H), 1.2–2.43 (m, 18 H), 3.23 (m, 1 H, CHCl), 4.3 (dd, *J* = 8, 2 Hz, 1 H, BOCH).

(*s*)-Pinanediol (*S*)-1-chloro-1-phenylmethylboronate:[16,10a,35] yield, 83%; bp 141–142 °C (0.5 mm); ^{11}B NMR δ 31 (s); ^{1}H NMR ($CDCl_3$) δ 0.9 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.8–2.59 (m, 6 H), 4.4 (dd, *J* = 8, 2 Hz, 1 H, BOCH), 4.53 (s, 1 H, CHCl), 7.23–7.9 (m, 5 H, Ar H).

(*s*)-Pinanediol (*S*)-1-chloro-2-phenylethylboronate:[21,35,37] yield, 78%; bp 144–145 °C (0.5 mm) (a low-melting solid); ^{11}B NMR ($CDCl_3$) δ 32 (s); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.80–2.13 (m, 6 H), 3.15 (m, 2 H, CH_2Ph), 3.66 (m, *J* ~ 8 Hz, CHCl), 4.34 (dd, *J* = 8, 2 Hz, 1 H, CHOB), 7.05–7.26 (m, 5 H, C_6H_5).

(*s*)-Pinanediol (*S*)-1-chloro-1-(6-methoxy-1-naphthyl)methylboronate: yield, 72%; ^{11}B NMR ($CDCl_3$) δ 32 (s); ^{1}H NMR ($CDCl_3$) δ 0.9 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.7–2.36 (m, 6 H), 3.73 (m, 1 H, CHCl), 3.9 (s, 3 H, OCH_3), 4.46 (dd, *J* = 8, 2 Hz, 1 H, CHOB), 7.1–7.7 (m, 6 H, aromatic).

(*R*,*R*)-2,3-Butanediol (*S*)-1-chloro-1-cyclohexylmethylboronate: yield, 75%; bp 98–100 °C (2 mm); ^{11}B NMR ($CDCl_3$) δ 32; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 6 H, CH_3), 1.4–1.90 (m, 11 H), 3.4 (m, 1 H, CHCl), 4.10 (m, 2 H, BOCH).

(*R*,*R*)-2,3-Butanediol (*S*)-1-chloro-2-phenylethylboronate:[38] yield, 76%; bp 106–108 °C (4 mm); ^{11}B NMR ($CDCl_3$) δ 32; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 6 H, CH_3), 3.1–3.26 (m, 2 H, CH_2Ph), 3.66 (m, 1 H, CHCl), 4.1 (m, 2 H, BOCH), 7.05–7.26 (m, 5 H, C_6H_5).

(*R*,*R*)-2,3-Butanediol (*S*)-1-chloro-1-*tert*-butylmethylboronate:[38] yield, 78%; bp 80–82 °C (14 mm); ^{11}B NMR ($CDCl_3$) δ 31; ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 9 H, CH_3), 1.33 [d, *J* = 6 Hz, 6 H, $CH(CH_3)_2$], 3.23 (s, 1 H, CHCl), 4.1 (m, 2 H, BOCH).

General Procedure for the Conversion of α-Chloro Boronate Esters into α-Methyl Boronate Esters via Reaction with Methylmagnesium Halide. The procedure for the conversion of (*s*)-pinanediol (*S*)-1-chloro-1-cyclohexylmethylboronate to (*s*)-pinanediol (*S*)-1-cyclohexylethylboronate (1) is representative. A solution of (*s*)-pinanediol (*S*)-1-chloro-1-cyclohexylmethylboronate (4.67 g, 15 mmol) in freshly distilled THF (30 mL) was cooled to −78 °C by using a dry ice–acetone bath. To this mixture was added methylmagnesium chloride (5 mL, 15 mmol, 3.0 M solution in THF) dropwise at −78 °C by means of a syringe over a period of 0.1 h. The reaction mixture was gradually allowed to warm to 25 °C overnight. The ^{11}B NMR spectrum of the reaction mixture showed a peak at δ 34 ppm, indicating the transfer reaction to be complete. The solvent THF was pumped off in vacuo (20 mm) and the residue extracted with *n*-pentane (2 × 30 mL). Removal of pentane in vacuo (20 mm) at 25 °C afforded the desired (*s*)-pinanediol (*S*)-1-cyclohexylethylboronate (1), which was further purified by distillation under reduced pressure, bp 130–132 °C (0.1 mm): yield, 3.90 g, 85%.

(*s*)-Pinanediol (*S*)-1-cyclohexylethylboronate (1):[10a] yield, 85%; bp 110–112 °C (0.1 mm); ^{11}B NMR ($CDCl_3$) δ 34 (s); ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3 H, CH_3), 0.91 (d, *J* = 6 Hz, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.5–2.3 (m, 18 H), 4.23 (dd, *J* = 8, 2 Hz, 1 H, BOCH). The optical purity was checked by oxidation with alkaline hydrogen peroxide to (*S*)-1-cyclohexylethanol, bp 89–90 °C (20 mm). This alcohol was then derivatized as the MTPA ester and analyzed by capillary GC on a 50 m × 0.25 mm methyl silicone capillary column at 180 °C, ee 98%.

(*s*)-Pinanediol (*S*)-1-phenylethylboronate (2):[21,10a,35] yield, 80%; bp 131–133 °C (0.5 mm); ^{11}B NMR ($CDCl_3$) δ 34 (s); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.37 (s, 3 H), 1.4 (d, *J* = 7 Hz, 3 H, CH_3), 1.80–2.50 (m, 6 H), 4.26 (dd, *J* = 8, 2 Hz, 1 H, BOCH), 7.26 (m, 5 H, Ar H). The optical purity was determined to be 88% ee by the capillary GC analyses of the oxidation product, i.e., (*S*)-1-phenylethanol; bp 109–111 °C (30 mm) derivatized as MTPA ester on a 50 m × 0.25 mm methyl silicone capillary column at 175 °C.

(*s*)-Pinanediol (*S*)-1-methyl-2-phenylethylboronate (3): yield, 78%; bp 140–141 °C (0.6 mm); ^{11}B NMR ($CDCl_3$) δ 34 (s); ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.78–2.4 (m, 7 H), 2.73 (m, 2 H, CH_2Ph), 4.26 (dd, *J* = 8, 2 Hz, 1 H, CHOB), 7.05–7.21 (m, 5 H, C_6H_5). Our attempts to determine the optical purity of **3** via oxidation to (*S*)-1-phenyl-2-propanol, followed by derivatization as MTPA, MCF, or TPC esters and capillary GC analyses, failed. However, the enantiomeric purity of **3** was successfully determined as 99% ee by conversion of **3** to β-methylphenethylamine derivatized as the MTPA amide and then analysis by capillary GC (vide supra).

(*s*)-Pinanediol (*S*)-1-(6-methoxy-1-naphthyl)ethylboronate (4): yield, 78%; ^{11}B NMR ($CDCl_3$) δ 35 (s); ^{1}H NMR ($CDCl_3$) δ 0.9 (s, 3 H, CH_3), 1.20–1.42 (m, 6 H, CH_3), 1.6 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.7–2.36 (m, 7 H), 3.9 (s, 3 H, OMe), 4.4 (dd, *J* = 8, 2 Hz, 1 H, CHOB), 7.1–7.7 (m, 6 H, aromatic). The optical purity of **4** was found to be 86% ee by capillary GC analysis of the oxidation product on a 50 m × 0.25 mm methyl silicone column at 190 °C.

(*R*,*R*)-2,3-Butanediol (*S*)-1-cyclohexylethylboronate (5): yield, 85%; bp 94–96 °C (2 mm); ^{11}B NMR ($CDCl_3$) δ 35 (s); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 6 H, CH_3), 1.40–2.1 (m, 12 H), 4.0 (m, 2 H, BOCH). The optical purity was determined to be 92% ee by oxidation to (*S*)-1-cyclohexylethanol and by capillary GC analyses of the derivatized MTPA ester derivative.

(*R*,*R*)-2,3-Butanediol (*S*)-1-methyl-2-phenylethylboronate (6): yield, 80%; bp 101–102 °C (4 mm); ^{11}B NMR ($CDCl_3$) δ 35 (s); ^{1}H NMR ($CDCl_3$) δ 1.0–1.33 (m, 9 H, CH_3), 1.86–3.03 (m, 3 H), 3.93 (m, 2 H, BOCH), 7.1–7.3 (m, 5 H, C_6H_5). The optical purity of **6** was found to be 90% ee by conversion to β-methylphenethylamine derivatized as the MTPA ester and analysis by capillary GC.

(*R*,*R*)-2,3-Butanediol (*S*)-1-*tert*-butylethylboronate (7): yield, 83%; bp 71–73 °C (12 mm); ^{11}B NMR ($CDCl_3$) δ 35 (s); ^{1}H NMR ($CDCl_3$) δ 0.96 [s, 9 H, $C(CH_3)_3$], 1.1 (d, *J* = 9 Hz, 3 H, $CHCH_3$), 1.33 (d, *J* = 6 Hz, 6 H, CH_3), 3.93 (m, 2 H, BOCH). The optical purity of **7** was ascertained to be 94% ee by capillary GC analysis of the oxidation product (*S*)-3,3-dimethyl-2-butanol derivatized as the MTPA ester.

Conversion of Pinanediol Boronate Esters into the Corresponding Optically Active 2-Substituted 1,3,2-Dioxaborinanes. The optically active pinanediol boronate esters **1–4** have been converted to the corresponding optically active 2-substituted 1,3,2-dioxaborinanes by following the reported procedure[10b] using lithium aluminum hydride (LAH) in EE, followed by treatment with anhydrous NaOMe. The optical purities of such 1,3,2-dioxaborinanes were ascertained by the capillary GC analyses of the oxidation product alcohols or amination product α-chiral amines derivatized as MTPA esters and MTPA amides, respectively. The spectral properties are as follows.

(*S*)-2-(1-Cyclohexylethyl)-1,3,2-dioxaborinane (8a): bp 90–93 °C (1 mm); ^{11}B NMR ($CDCl_3$) δ 31 (s); ^{1}H NMR ($CDCl_3$) δ 0.92–2.03 (m, 17 H), 3.93 (t, *J* = 7 Hz, 4 H, $BOCH_2$); optical purity, 98% ee, determined by capillary GC analysis of the oxidation product alcohol derivatized as the MTPA ester.

(*S*)-2-(1-Phenylethyl)-1,3,2-dioxaborinane (8b): bp 100–101 °C (1 mm); ^{11}B NMR ($CDCl_3$) δ 29 (s); ^{1}H NMR ($CDCl_3$) δ 1.0 (d, *J* = 6 Hz, 3 H, CH_3), 1.93 (m, 2 H), 3.96 (t, *J* = 7 Hz, 4 H, $BOCH_2$), 7.0–7.2 (m, 5 H, aromatic H).

(*S*)-2-(1-Methyl-2-phenylethyl)-1,3,2-dioxaborinane (8c): bp 96–98 °C (1 mm); ^{11}B NMR ($CDCl_3$) δ 31 (s); ^{1}H NMR ($CDCl_3$)

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δ 1.01 (d, J = 6 Hz, 3 H, CH_3), 1.93–2.3 (m, 4 H), 3.96 (t, J = 7 Hz, 4 H, $BOCH_2$), 7.01–7.3 (m, 5 H, C_6H_5).

Preparation of α-Chiral Aldehydes. General Procedure. [Methoxy(phenylthio)methyl]lithium (MPML) was prepared in a 250-mL round-bottom flask by addition of 15 mmol of *sec*-BuLi in cyclohexane to a stirred solution of 15 mmol of methoxymethyl phenyl sulfide in 25 mL of freshly distilled THF at −55 °C. After the mixture was stirred for about an hour, the optically active 2-alkyl- or -aryl-1,3,2-dioxaborinane (15 mmol) was added dropwise, but rapidly. The bath was allowed to warm to −5 °C over a period of 1.5–2 h. To this mixture was added finely powdered $HgCl_2$ (18 mmol) under nitrogen with vigorous stirring. The reaction mixture was allowed to warm to 25 °C and stirred for an additional 2 h at 25 °C. The reaction mixture was transferred to another flask containing 150 mL of anhydrous *n*-pentane by cannula, and the mixture was stirred at 25 °C overnight to precipitate the metal salts. The *n*-pentane layer was decanted, and removal of pentane in vacuo furnished the crude 2-(1-methoxyalkyl)-1,3,2-dioxaborinane in quantitative yield. This was then dissolved in diethyl ether (30 mL), and oxidation was performed by the successive addition of pH 8 phosphate buffer (15 mL) and hydrogen peroxide (30 mmol). After 1.5–2 h of stirring, the organic phase was separated and subjected to steam distillation. The aqueous phase of the distillate was saturated with NaCl and extracted with EE (2 × 20 mL). The ether extract was dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under N_2 at atmospheric pressure by using a small Vigreux column, followed by distillation, afforded the desired α-chiral aldehyde. In the case of 2-(6-methoxy-1-naphthyl)propionaldehyde, the product was extracted from the non-steam-volatile fraction by using EE.

(2*S*)-(+)-2-Cyclohexyl-1-propanal: bp 76–78 °C (20 mm); ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, 3 H, CH_3), 1.26–1.80 (m, 11 H), 2.25 (m, 1 H), 9.62 (m, J = 3 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 10.2, 25.3, 26.2, 26.6, 26.7, 38.8, 50.2, 205.7; $[\alpha]^{23}_D$ = +4.51° ± 0.02° (*c* 4, MeOH).

(2*S*)-(−)-2-Benzyl-1-propanal: bp 112–114 °C (20 mm); ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, CH_3), 1.21 (m, 1 H), 3.37 (dd, J = 12, 5 Hz, 2 H, CH_2Ph), 7.14–7.35 (m, 5 H, C_6H_5), 9.6 (m, J = 3 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 13.3, 36.8, 48.2, 126.8, 128.9, 129.5, 129.9, 139.3, 205; $[\alpha]^{23}_D$ = −4.42° ± 0.01° (*c* 4, MeOH).

(2*S*)-2,3,3-Trimethylbutanal: ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9 H, CH_3), 1.1 (d, J = 8 Hz, 3 H, CH_3), 2.3 (m, 1 H), 9.5 (m, J = 3 Hz, 1 H, CHO); $[\alpha]^{23}_D$ = +17.82° ± 0.02° (*c* 2, EtOH).

Chromic Acid Oxidation of α-Chiral Aldehydes to α-Chiral Carboxylic Acids. General Procedure. The chromic acid solution used for the oxidation was prepared from the appropriate amount of sodium dichromate and aqueous H_2SO_4 as described previously.[22] To a solution of (2*S*)-(+)-2-cyclohexyl-1-propanal (5 mmol) in diethyl ether (4 mL) was added chromic acid solution (4 mL) with stirring over 10 min. The temperature was maintained below 25 °C by using a water bath and the reaction mixture stirred for an additional 2 h. The reaction mixture was extracted with diethyl ether (2 × 20 mL), and the organic layer was washed with 3 M NaOH (2 × 2 mL). The aqueous alkaline layer was made acidic with 3 N HCl and saturated with NaCl, extracted with EE, and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the desired (*S*)-2-cyclohexylpropanoic acid (yield, 88%).

(2*S*)-(+)-2-Cyclohexylpropanoic acid: bp 94–96 °C (1 mm); ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 8 Hz, CH_3), 1.17–1.96 (m, 11 H), 2.26 (m, 1 H, $CHCH_3$), 11.96 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 14.1, 25.9, 26.3, 26.7, 26.8, 26.9, 29.3, 43.6, 184; $[\alpha]^{23}_D$ = +18.32° ■ 0.02° (*c* 4, MeOH) [lit.[29] [α] +18.9° (*c*, 2.1, EtOH)]. Anal. Calcd for $C_9H_{16}O_2$: C, 68.75; H, 10.53. Found: C, 68.47; H, 10.53. The optical purity was found to be 95% ee by conversion to the corresponding (*R*)-α-methylbenzylamide[23] and analysis by capillary GC on a 30 m × 0.25 mm SPB-5 column at 180 °C (isothermal). The conditions for the capillary GC analyses were standardized with the α-methylbenzylamide prepared from racemic 2-cyclohexylpropanoic acid. This racemic acid was prepared by reacting a dilithio derivative of cyclohexaneacetic acid (prepared by using 2 equiv of LDA)[30] with excess methyl iodide, followed by hydrolysis.

(2*S*)-2-Methyl-3-phenylpropanoic acid: bp 96–98 °C (1 mm); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 8 Hz, 3 H, CH_3), 2.75 (m, 1 H), 3.10 (dd, J = 12, 5 Hz, 2 H, CH_2Ph), 7.16–7.32 (m, 5 H, C_6H_5), 11.5 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 16.8, 39.7, 41.7, 127.1, 129.1, 130.1, 139.7, 184; $[\alpha]^{23}_D$ = +21.54° ± 0.02° (*c* 4, EtOH). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.0; H, 7.17. The enantiomeric purity was 94% ee by capillary GC analyses of the α-methylbenzylamide prepared from the α-chiral carboxylic acid and (*R*)-α-methylbenzylamine (conditions 30 m × 0.25 mm SPB-5 column at 180 °C). The racemic 2-methyl-3-phenyl-1-propanoic acid was prepared by reacting the sodio derivative of ethyl α-methylacetoacetate[31] with benzyl bromide, followed by saponification.

(2*S*)-(+)-2,3,3-Trimethylbutyric acid: bp 85–86 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9 H, CH_3), 1.1 (d, J = 8 Hz, 3 H, CH_3), 2.7 (m, 1 H), 11.9 (br s, 1 H, COOH); $[\alpha]^{23}_D$ = +39.7° ± 0.02° (*c*, 1, EtOH) [lit.[32] [α] −33.0° (*c*, 1, EtOH) for the *R* enantiomer of 80.5% optical purity]. The enantiomeric purity was found to be 94% ee by capillary GC analysis of the corresponding α-methylbenzylamide.

Conversion of Optically Active 2-Substituted Pinanediol Boronate Esters into Borinate Esters. The optically active pinanediol boronate esters 1–4 were converted to the corresponding B-substituted (methyl) (methoxy) boranes via reaction with methyllithium.[10] The same procedure was followed to convert the optically active butanediol boronate esters to the corresponding *B*-methyl(alkyl)borinate esters.

[(1*S*)-1-Cyclohexylethyl]methoxymethylborane (9a): prepared from (*s*)-pinanediol (*S*)-1-cyclohexylethylboronate (1) and MeLi; yield, 85%; bp 76–78 °C (15 mm); ^{11}B NMR ($CDCl_3$) δ 54 (s); ^{1}H NMR ($CDCl_3$) δ 0.53 (br s, 3 H, BCH_3), 0.9–2.02 (m, 15 H), 3.52 (s, 3 H, OCH_3).

[(1*S*)-1-Phenylethyl]methoxymethylborane: prepared from (*s*)-pinanediol (*S*)-1-phenylethylboronate (2) and MeLi; yield, 88%; bp 56–57 °C (0.1 mm); ^{11}B NMR ($CDCl_3$) δ 54 (s); ^{1}H NMR ($CDCl_3$) δ 0.73 (br s, 3 H, BCH_3), 1.30 (d, J = 6 Hz, 3 H, CH_3), 2.52 (m, 1 H, CH_3), 3.66 (s, 3 H, $BOCH_3$), 7.3–7.8 (m, 5 H, C_6H_5).

[(1*S*)-1-Methyl-2-phenylethyl]methoxymethylborane (9b): prepared from (*s*)-pinanediol (*S*)-1-methyl-2-phenylethylboronate (3) and MeLi; yield, 83%; bp 64–65 °C (0.1 mm); ^{11}B NMR ($CDCl_3$) δ 55 (s); ^{1}H NMR ($CDCl_3$) δ 0.5, (s, 3 H, BMe), 1.06 (m, 3 H, CH_3), 2.66 (m, 2 H, CH_2Ph), 3.6 (s, 3 H, BOMe), 7.06–7.2 (m, 5 H, Ph).

[(1*S*)-1,2,2-Trimethylpropyl]methoxymethylborane (9c): prepared from (*R*,*R*)-2,3-butanediol (*S*)-1-*tert*-butylethylboronate (7) and MeLi; yield, 88%; bp 92–93 °C (741 mm); ^{11}B NMR ($CDCl_3$) δ 55 (s).

Preparation of α-Chiral Ketones from Borinic Esters. General Procedure. A solution of the borinate ester **9a–c** (10 mmol) in anhydrous ether (10 mL) was cooled to 0 °C by using an ice bath. To this was added DCME (15 mmol) followed by lithium *tert*-butoxide (20 mmol in hexane) at 0 °C, and the reaction mixture was gradually allowed to warm to 25 °C, whereupon a white precipitate was formed. The reaction mixture was cooled to 0 °C, and to this was added a pH 8 phosphate buffer solution (30 mmol), followed by H_2O_2 (30 mmol, 30% solution). The ice bath was removed, and the reaction mixture was stirred for 12–24 h at 25 °C. The organic phase was separated, and the aqueous layer was saturated with NaCl and extracted with ether (2 × 20 mL). The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. Removal of the volatiles, followed by distillation, afforded the desired α-chiral ketone (yield 68–75%).

(*S*)-3-Cyclohexyl-2-butanone: bp 100–102 °C (20 mm); IR ν_{max} (neat) 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J = 7 Hz, 3 H, CH_3), 1.23–1.93 (m, 12 H), 2.16 (s, 3 H, $COCH_3$); $[\alpha]^{23}_D$ = +42.0° ± 0.02° (*c* 1, $CHCl_3$). The enantiomeric purity of this ketone was found to be 98% ee by capillary GC analysis on a 50 m × 0.25 mm methyl silicone column at 100 °C.

(*S*)-(+)-4-Phenyl-3-methyl-2-butanone: bp 75–76 °C (1 mm); IR ν_{max} (neat) 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 7 Hz, 3 H, CH_3), 2.26 (s, 3 H, $COCH_3$), 2.83 (m, 2 H, CH_2Ph), 7.1–7.3 (m, 5 H, C_6H_5); $[\alpha]^{23}_D$ = +45.52° ± 0.02° (*c* 2, EtOH) [lit.[33] [α] +36.8° (*c* 3, EtOH), 81% optical purity. Anal. Calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.42; H, 8.62. The optical purity of this ketone was found to be 99% ee by capillary GC analysis

on a 25 m × 0.25 mm Ni(HFB-1R-Cam)$_2$ column and also by the analysis of diastereomeric (2*R*,3*R*)-butanediol ketals on a 50 m × 0.25 mm methyl silicone column at 145 °C.

(*S*)-(+)-3,4,4-Trimethyl-2-pentanone: bp 85–86 °C (60 mm); IR ν_{max} (neat) 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9 H, $C(CH_3)_3$), 1.1 (d, J = 7 Hz, 3 H, CH_3), 2.2 (s, 3 H, $COCH_3$), 2.46 (m, 1 H); $[\alpha]^{23}_D$ = +107.8° ± 0.02° (*c* 1, $CHCl_3$). The enantiomeric purity of this ketone was found to be 94% ee by capillary GC analysis of the diastereomeric (2*R*,3*R*)-butanediol ketals on a 30 m × 0.26 mm methyl silicone column.

Preparation of Achiral Ketones. Racemic 3-cyclohexyl-2-butanone and 4-phenyl-3-methyl-2-butanone were prepared[31] via alkylation of the sodio derivative of ethyl α-methylacetoacetate with cyclohexyl bromide and benzyl bromide, respectively, followed by base-catalyzed hydrolysis. Racemic 3,4,4-trimethyl-2-pentanone was prepared via the DCME reaction of racemic (1,2,2-trimethylpropyl)methoxymethylborane derived from 2-(1-*tert*-butylethyl)-1,3,2-dioxaborinane.

Determination of the Enantiomeric Purity of α-Chiral Ketones. The enantiomeric purity of these α-chiral ketones was determined by capillary GC analysis on a 25 m × 0.25 mm Ni-(HFB-1R Cam)$_2$ column or on a 50 m × 0.25 mm methyl silicone column. Further evidence for the minor enantiomer is provided by equilibration of these chiral ketones with 3 N NaOMe–MeOH and the capillary GC analysis of the equilibration product mixture.[13] Diastereomeric ketals derived from (2*R*,3*R*)-butanediol and α-chiral ketone were prepared by following the reported[13] literature procedure and analyzed on a 50 m × 0.25 mm methyl silicone column or a 30 m × 0.25 mm SPB-5 column.

Synthesis of Optically Active Amines from Borinate Esters 9a–c. The conversion of optically active borinate esters **9a–c** into the corresponding α-chiral amines has been achieved by following the reported procedure.[14] These chiral amines were further converted into the amine hydrochlorides by reaction with anhydrous HCl in EE. The spectral properties of these α-chiral amine hydrochlorides are as follows.

(*S*)-1-Cyclohexylethylamine: bp 72–74 °C (20 mm); ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 14 H), 2.2 (br m, 2 H, NH_2), 3.43 (m, 1 H, $CHNH_2$); $[\alpha]^{23}_D$ = −11.68° (neat, *l* 0.5); converted to the corresponding amine HCl by reacting with anhydrous HCl in EE, mp >250 °C. The optical purity was found to be 96% ee by the capillary GC analysis of the MTPA amide[14] on a 50 m × 0.25 mm methyl silicone column at 200 °C.

(*S*)-(−)-1-Phenylethylamine hydrochloride: mp 148–150 °C; ^{1}H NMR (D_2O) δ 1.6 (d, J = 8 Hz, 3 H, CH_3) 4.52 [m, 1 H, $CHCH_3(NH_2)$], 4.70 (s, 3 H), 7.43 (m, 5 H, C_5H_5); $[\alpha]^{23}_D$ = −4.6° ± 0.02° (*c* 4, MeOH). The optical purity was found to be 99% ee by capillary GC analysis of the MTPA amide on a 50 m × 0.25 mm methyl silicone column at 200 °C. Presumably, 1-phenylethylamine might have upgraded from 88% ee to 99% ee during the preparation of the amine hydrochloride.

(*S*)-(+)-1-Methyl-2-phenylethylamine hydrochloride or (*S*)-amphetamine hydrochloride: mp 150–152 °C; ^{1}H NMR (D_2O) δ 1.30 (d, J = 8 Hz, 3 H, CH_3), 2.93 (m, 2 H, $PhCH_2$), 3.63 (m, 1 H), 4.70 (m, 3 H), 7.16–7.50 (m, 5 H, C_6H_5); $[\alpha]^{23}_D$ = +8.44° ± 0.02° (*c* 4, MeOH). The optical purity was found to be ≥99% ee by capillary GC analysis of the MTPA amide on a 50 m × 0.25 mm methyl silicone column at 210 °C.

(*S*)-(+)-3,3-Dimethyl-2-butylamine hydrochloride: mp >250 °C; ^{1}H NMR (D_2O) δ 1.0 (s, 9 H, CMe_3), 1.26 (d, J = 7 Hz, CH_3), 3.2 (m, 1 H, $CHNH_2$), 4.70 (s, 3 H); $[\alpha]^{23}_D$ = +2.80 ± 0.02° (*c* 4, MeOH). The optical purity was determined to be 96% ee by capillary GC analysis of the corresponding MTPA amide on a 50 m × 0.25 mm methyl silicone column at 180 °C.

Preparation of Racemic Primary Amines. The racemic primary amines required for the capillary GC analyses were prepared via $LiAlH_4$ reduction of the corresponding ketoximes.

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Supplementary Material Available: ^{11}B NMR, ^{1}H NMR, ^{13}C NMR, and IR spectra for the compounds reported (55 pages). Ordering information is given on any current masthead page.

Angular Hydroxymethylation of Functionalized Decalin Systems

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Functionalized β-dicarbonyl bicyclic compounds **5** and **17** were hydroxymethylated at the angular position as the (benzyloxy)methoxy derivatives with diisopropylethylamine (DIPEA) and benzyl chloromethyl ether in the presence of paraformaldehyde. The stereochemistry of *cis*-8a-[[(benzyloxy)methoxy]methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4*H*,7*H*)-dione (**12**) was confirmed by X-ray analysis of the ethylene ketal **16**.

Introduction

A number of natural products have a hydroxymethyl function at the angular position of a decalin system. Azadirachtin (**1**),[1] clerodin (**2**),[2] and sicannin (**3**)[3] are some of the examples in the terpenoid area. In steroids, it is known that biological hydroxylation of the angular methyl group to give the hydroxymethyl compound is the intermediate step in biological demethylation.

Because of our interest in the chemistry of insect antifeedants,[4] we became interested in the synthesis of analogues of azadirachtin (**1**) and clerodin (**2**). Both compounds are known to possess potent insect antifeeding activities. Furthermore, we have recently developed an annelation reaction based on tandem Michael–Claisen condensation of the siloxy diene **4** with α,β-unsaturated ketones.[5] The reaction has been used to construct the

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