Chiral Synthesis via Organoboranes. 10. Preparation of α-Chiral Acyclic Ketones of Exceptionally High Enantiomeric Excess from Optically Pure Borinic Esters

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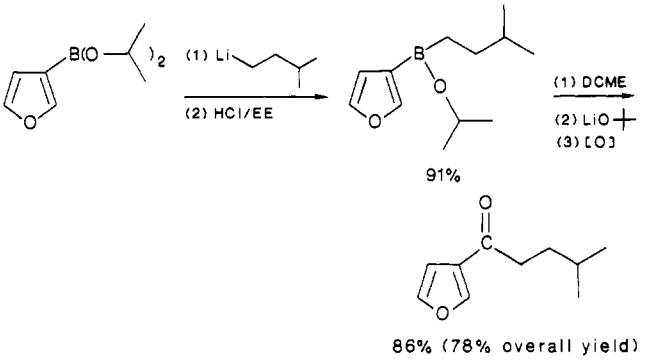
Abstract: Optically pure borinic esters, R*R'BOR'', obtained from optically pure boronic esters, R*B(OR'')$_2$ and organolithium reagents, were treated with dichloromethyl methyl ether (DCME) in the presence of lithium *tert*-butoxide to give, after oxidation with hydrogen peroxide in pH 8 phosphate buffer, α-chiral acyclic ketones of generally high enantiomeric purity (≥99% ee) and of known absolute configuration. For sterically hindered derivatives (R' = *tert*-butyl), oxidation with trimethylamine *N*-oxide gives the ketones smoothly without racemization.

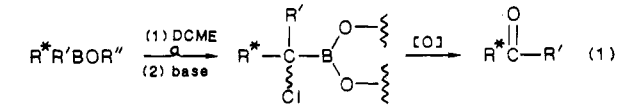
The synthesis of enantiomerically pure compounds has always presented a considerable challenge to the organic chemist. Especially important is the formation of the first asymmetric center in an achiral molecule. These molecules, in turn, can serve as chiral synthons in the elaboration of more complex structures. One important class of such chiral compounds is α-chiral acyclic ketones. These have been prepared in variable enantiometric excess (ee) by asymmetric α-alkylation of carbonyls suitably derivatized with chiral auxiliaries. Achievements in this approach include Meyer's methoximines (18–97% ee)[2] and Ender's hydrazones (10 to ≥99% ee).[3] These two methods, however, in addition to giving variable ee's, are also limited to the alkylation of symmetrical ketones. A similar approach employs α-alkylation of N,N-substituted chiral amides and subsequent reaction with an organolithium reagent (44–77% ee).[4] Other methods include the reaction of chiral secondary-alkyl halides with 2-lithio-1,3-dithianes (58–88% ee)[5] and microbial reductions of α,β-unsaturated ketones (0–90% ee).[6] Of the latter two methods, the first is limited by the ready availability of optically pure secondary-alkyl halides and the other by substrate compatibility.

In 1961 asymmetric hydroboration (AHB) marked a milestone in non-enzymatic chiral synthesis.[7] Since then, we[8] and others[9] have refined AHB to the point where many functional groups of interest to the organic chemist should be accessible in essentially optically pure form. Among the chiral organoboranes attainable via the AHB process, optically pure boronic esters,[10] R*B(OR'')$_2$, have emerged as particularly versatile reagents. They have been converted into optically pure alcohols,[11] aldehydes,[12] acids,[12] and homologated alcohols,[12] as well as borohydrides,[13] diols,[14] and amines.[15] As part of our continuing research efforts to exploit the chiral chemistry of optically pure boronic esters, we have now utilized them in an efficient synthesis of α-chiral acyclic ketones.

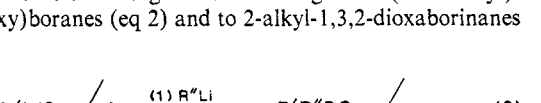
Scheme I



Our approach to the synthesis of this class of ketones is based on the carbon–carbon bond-forming reaction of borinic esters, R*R'BOR'', with dichloromethyl methyl ether (DCME) in the presence of base, referred to as "the DCME reaction" (eq 1).[16]



Borinic esters are attractive organoborane intermediates in carbon–carbon bond-forming reactions. No loss of alkyl groups occurs and such 1,2-migrations are known to proceed with complete retention of stereochemistry and configuration of the migrating carbon nucleus. As part of our efforts to obtain organoboranes not available via hydroboration, we have recently developed a simple methodology for preparing borinic esters by the stepwise addition of an organolithium reagent to (monoalkyl)(diisopropoxy)boranes (eq 2) and to 2-alkyl-1,3,2-dioxaborinanes (eq 3).[17]



(1) (a) Lady Davis Fellow from Hebrew University in Jerusalem. (b) Postdoctoral Research Associate on Grant GM 10937-22 from the National Institutes of Health. (c) Senior Research Associate on funds provided by Purdue University. (d) Presented in part at the 190th ACS Meeting in Chicago, Illinois, September 8–13, 1985.

(2) Meyers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 3088.

(3) Enders, D.; Eichenauer, H.; Baus, U.; Schubart, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345.

(4) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5.

(5) Seebach, D.; Steinmüller, D.; Demuth, F. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 620.

(6) Kergomard, A.; Renard, M. F.; Veschambre, H. *J. Org. Chem.* **1982**, *47*, 792.

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

(8) For a recent review of asymmetric hydroboration, see: Brown, H. C.; Jadhav, P. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, Chapter 1.

(9) Masamune, S.; Kim, B. M.; Petersen, J. S.; Sato, T.; Veenstra, S. J.; Imai, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

(10) Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797.

(11) For leading references, see: Srebnik, M.; Ramachandran, P. V. *Aldrichim. Acta* **1987**, *20*, 9.

(12) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980.

(13) Brown, H. C.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1985**, *107*, 460.

(14) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077.

(15) Brown, H. C.; Kim, K. W.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1986**, *108*, 6761.

(16) For a discussion of the DCME reaction, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.

(17) Brown, H. C.; Cole, T. E.; Srebnik, M. *Organometallics* **1985**, *4*, 1788.

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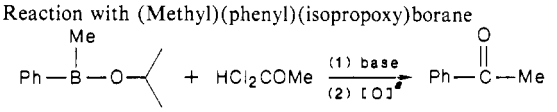
Table I. Influence of Base on the DCME Reaction with (Methyl)(phenyl)(isopropoxy)borane



base	solvent	conditions[b]	yield,[c] %
(1) lithium triethylcarboxide	EE	2 equiv, 0–25 °C/5 min	91
(2) lithium *tert*-butoxide	EE	1 equiv, 0–25 °C/1 h	50
(3) lithium *tert*-butoxide	EE	2 equiv, 0–25 °C/1 h	91
(4) potassium *tert*-butoxide	EE	2 equiv, 0–25 °C/1 h	33
(5) lithium 2,2,6,6-tetramethylpiperidide	EE	2 equiv, 0–25 °C/1 h	32

[a] Hydrogen peroxide, phosphate buffer, pH 8. [b] Reaction run on 5-mmol scale. Initial concentration of borane, 1.0 M. [c] GC yield based on internal standard.

Table II. Achiral Ketones Obtained from Borinates with DCME in the Presence of Lithium *tert*-Butoxide

$RB(O—\langle)_2$	R'Li	R'RBO—⟨	isolated yield, %	physical properties bp [°C] (Torr), $n^{20}D$, ^{11}B NMR (neat) [δ]	ketone	isolated yield, %
(a) phenyl[b]	methyl	(methyl)(phenyl)(isopropoxy)-borane[a]	90	54 (0.1), 1.4838, 47.2	acetophenone	(91)[f]
(b) *trans*-2-methyl-cyclopentyl[b]	phenyl	(*trans*-2-methylcyclopentyl)-(phenyl)(isopropoxy)borane	76	84–86 (0.1), 48.6	*trans*-2-methylcyclopentyl phenyl ketone[g]	81
(c) 2-furyl[c,d]	*n*-butyl	(*n*-butyl)(2-furyl)(isopropoxy)-borane	89	94–96 (15), 1.4516, 41.1	*n*-butyl 2-furyl ketone[h]	65
(d) 3-furyl[c,e]	3-methylbutyl	(3-methylbutyl)(3′-furyl)-isopropoxyborane	91	100–102 (15), 1.4446, 45.4	3-methylbutyl 3-furyl ketone[i]	86
(e) *exo*-2-norbornyl[b]	phenyl	(*exo*-2-norbornyl)(phenyl)-(isopropoxy)borane	81	104–106 (0.1), 1.511, 48.5	*exo*-2-norbornyl phenyl ketone[j]	86

[a] Reference 17. [b] Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311. [c] Prepared according to the procedure of: Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316. [d] For the preparation of 2-lithiofuran, see: Ravianathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216. [e] For preparation of 3-lithiofuran, see: Fukuyama, Y.; Kawashima, Y.; Miwa, T.; Tokoroyama, T. *Synthesis* **1974**, 443. [f] GC yield in the presence of internal standard. [g] Jorgenson, M. J.; Brattesani, A. J.; Thacher, A. F. *J. Org. Chem.* **1969**, *34*, 1103. [h] Gilman, H.; Calloway, N. O. *J. Am. Chem. Soc.* **1933**, *55*, 4197. [i] Reference 20. [j] Lewis, F. D.; Johnson, R. W.; Ruden, R. A. *J. Am. Chem. Soc.* **1972**, *94*, 4292.

Since chiral boronic esters of either the (+)- or (−)-series are readily available in essentially pure optical form,[10] we have now utilized them to prepare a series of optically pure borinic esters (vide infra, Table III) and transformed them via the DCME reaction into synthetically useful α-chiral acyclic ketones of known absolute configuration and of consistently high enantiomeric excess.[1d]

Results and Discussion

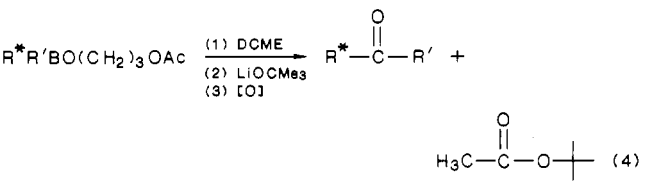
Standardization of the DCME Reaction with Achiral Borinates. In order to establish appropriate conditions for the conversion of optically pure borinates into ketones of high enantiomeric excess and facilitate their isolation, we initially decided to define the experimental protocol on achiral borinates. Previously, we have shown that a hindered base, i.e., lithium triethylcarboxide, is necessary for the success of the DCME reaction with borinates.[18] We therefore investigated several other hindered bases which could be more readily removed during aqueous workup (Table I). While lithium *tert*-butoxide worked extremely well, the more hindered base, lithium 2,2,6,6-tetramethylpiperidide, and commercially available potassium *tert*-butoxide gave poorer yields of ketones, the latter base possibly due to insolubility in the reaction medium (diethyl ether). We thus adopted lithium *tert*-butoxide for all subsequent transformations.

Alkaline hydrogen peroxide has been observed to cause some racemization and epimerization in the conversion of optically active borinates.[19] To optimize optical yields (vide infra), we performed all oxidations with hydrogen peroxide in pH 8 phosphate buffer solution. Under these conditions, no racemization of base-sensitive compounds has been observed.[12]

The conversion of aromatic and heteroaromatic borinates (not readily available heretofore) into ketones considerably broadens the scope of our original DCME reaction. For example, by this present method, we have synthesized the natural product, perilla ketone[20] (Table II, d), in 78% overall yield (Scheme I).

Preparation of Chiral Borinates and Ketones. Having demonstrated the feasibility of effectively using lithium *tert*-butoxide in the DCME reaction, we turned our attention to the synthesis of chiral borinic esters and ketones (Tables III and IV). The chiral borinic esters were prepared in high yield from optically active boronic esters and an organolithium reagent in a manner analogous to the achiral derivatives (eq 2 and 3). The optical purity of the borinates was determined by measuring the rotation of the alcohols obtained following alkaline hydrogen peroxide oxidation or by capillary GC analysis of their MTPA esters.[21]

The α-chiral acyclic ketones (Table IV) were obtained via the DCME reaction of the chiral borinates in the presence of lithium *tert*-butoxide, as described above. With the (dialkyl)(3-acetoxypropoxy)boranes, $R^*R'BO(CH_2)_3OAc$, *tert*-butyl acetate is also formed (eq 4). The carboxylic ester could not be hydrolyzed



(4)

under the conditions of oxidation (H_2O_2/phosphate buffer, pH 8) and codistilled (bulb-to-bulb) during the isolation of volatile ketones, i.e., [*R*]-(−)-3-methylpentan-2-one (Table IV, a). The problem was avoided by using (dialkyl)(3-(trimethylsiloxy)-propoxy)boranes, $R^*R'BO(CH_2)_3OSiMe_3$, easily obtained by quenching the "ate" complexes with chlorotrimethylsilane (eq 5).

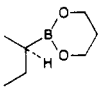
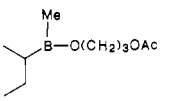
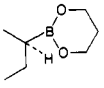
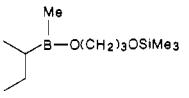
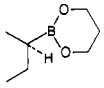
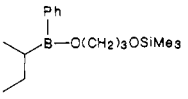
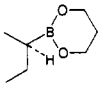
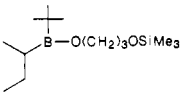
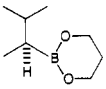
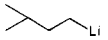
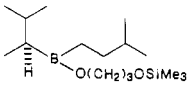
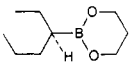
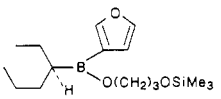
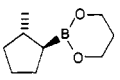
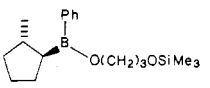
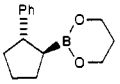
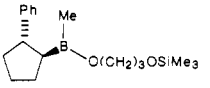
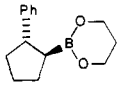
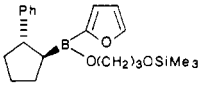
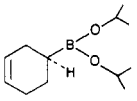
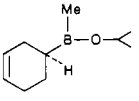
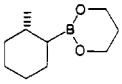
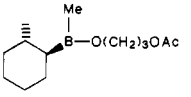
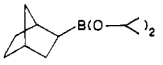
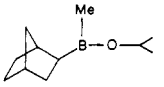
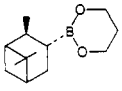
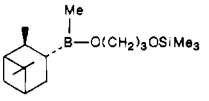
(18) Carlson, B. A.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 6876. Apparently moderate steric congestion is needed to minimize coordination of the base with boron. However, the use of lithium triethylcarboxide (bp 54–56 °C (16 mmHg)) may in certain cases pose specific problems in isolating the ketones, e.g., *trans*-2-methylcyclohexyl methyl ketone (bp 78–80 °C (17 mmHg)).

(19) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *Tetrahedron* **1984**, *40*, 1325.

(20) Isolated from Perilla *frutescens*: Grotto, R. *J. Pharm. Sci. Jpn.* **1937**, *57*, 77. For a recent synthesis, see: Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248.

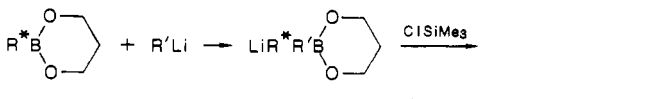
(21) (a) For the preparation of MTPA esters, see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1978**, *43*, 4395. (b) For GC analysis, see: Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.

Table III. Chiral Borinic Esters Obtained from Chiral Boronic Esters and Organolithium Reagents

	boronic ester	R'Li	R'R*BOR''	isolated yield, %	physical properties: bp [°C] (Torr)	physical properties: ^{11}B NMR, δ	physical properties: % ee[c]	config of R*R'BOR''
a		MeLi		85	48–50 (0.2)	54.6	>99	*R*
b		MeLi		*a*		53.8	>99	*R*
c		PhLi		*a*		49.5	>99	*R*
d				*a*		52.3	>99	*R*
e				*b*			>99[e]	*S*
f				*a*		46.4	>99	*R*
g		PhLi		*a*		48.8	>99	1*S*,2*S*
h		MeLi		*a*		52.9	>99	1*S*,2*S*
i				*a*		42.7	>99	1*S*,2*S*
j		MeLi		68	76–78 (15)	52.9	>99	*S*
k		MeLi		72	92–94 (0.2)	54.2	>99	1*S*,2*S*
l		MeLi		86	82–84 (15)	51.9	86[d]	1*S*,2*S*
m		MeLi		*a*		52.6	>99	1*R*,2*R*,3*R*,5*S*

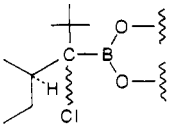
[a] Not distilled. Volatiles removed in vacuo to give essentially quantitative yield of borinate ≥95% purity (^{11}B NMR and ^{1}H NMR). [b] Not isolated. [c] Determined by rotation or by capillary GC analysis of the MTPA ester of the alcohol obtained by alkaline hydrogen peroxide oxidation of the borinate, see ref 21. [d] The starting boronic ester has now been upgraded to >99% ee: Shiner, S. C.; Garner, C. M. 189th ACS National Meeting, Miami Beach, Florida, April 28–May 3, 1985, Abstract 209. Therefore, in principle, the borinate should now be available in >99% ee. [e] Based on the ee of the ketone (Table IV, *d*).

The *O*-trimethylsilyl group is readily hydrolyzed during the aqueous oxidation conditions.



$$R^*R'BO(CH_2)_3OSiMe_3 \quad (5)$$

The α-chloroborinate intermediate, **1**,[22] obtained from ([*R*]-*sec*-butyl)(*tert*-butyl(3-(trimethylsiloxy)propoxy)borane, resisted oxidation under the above conditions.



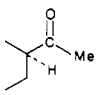
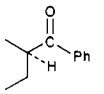
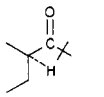
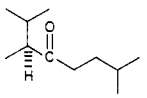
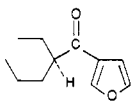
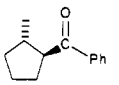
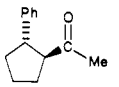
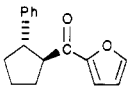
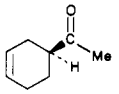
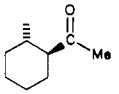
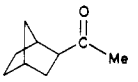
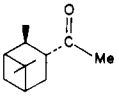
1

Another mild oxidation procedure more applicable to hindered systems was therefore sought.

In addition to hydrogen peroxide (in alkaline or acidic medium),[23] oxidation of the boron–carbon bond has been accomplished

(22) The proposed α-chloro intermediates have not been rigorously proven. For a discussion, see: Carlson, B. A.; Katz, J.-J.; Brown, H. C. *J. Organomet. Chem.* **1974**, *67*, C39.

Table IV. α-Chiral Acyclic Ketones Obtained from Optically Pure Borinic Esters

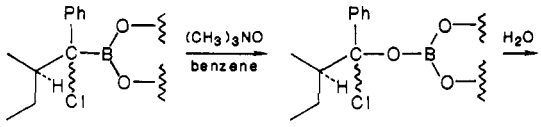
	ketone	isolated yield, %	$[\alpha]^{23}_D$ (c, solvent)	% ee or de	config
a		83	−26.7° (0.77, $CHCl_3$)[b]	≥99	*R*
b		86 73	−36.7° (0.99, EE) −37.2° (1.06, EE)[c,d]	≥97 ≥99	*R*
c		79	−29.6° (1.45, $EtOH_{abs}$)[c,e]	≥99[i]	*R*
d		85	+43.8 (1.36, $EtOH_{abs}$)[e]	≥99[i]	*S*
e		73	+8.8 (1.31, $EtOH_{abs}$)[e]	≥99[i]	*R*
f		81	+85.6 (1.21, $EtOH_{abs}$)[e]	≥99[i,j]	1*S*,2*S*
g		87	+120.8 (5.0, $EtOH_{abs}$)[f]	≥99	1*S*,2*R*
h		67	+111.4 (3.0, $EtOH_{abs}$)[e]	≥99[i,j]	1*S*,2*R*
i		55	−116.3 (1.25, $CHCl_3$)[g]	≥99[i]	*S*
j		90	+17.83 (1.35, $EtOH_{abs}$)[h]	≥99[j]	1*S*,2*S*
k		68	+60.8 (0.99, $EtOH_{abs}$)[e]	86[j,k,l]	1*S*,2*S*
l		92	−31.74 (1.24, $EtOH_{abs}$)[e]	≥99[i,j,m]	1*R*,2*R*,3*R*,5*S*

[a] Bulb-to-bulb distillation. Rotations were taken on compounds purified by preparative GC. [b] $[\alpha]_D$ +24.9° (0.57, $CHCl_3$): Djerassi, C.; Geller, L. E. *J. Am. Chem. Soc.* **1959**, *81*, 2789. [c] Obtained by oxidation with trimethylamine *N*-oxide. [d] $[\alpha]_D$ +36.6° (1.0, EE): Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345. [e] Not previously reported. [f] $[\alpha]_D$ −106.8 (5.0, EtOH), ref 19. [g] $[\alpha]_D$ +100.2 (4.0, $CHCl_3$): Leder, O.; Nilsson, H. G. *Acta Chem. Scand.* **1976**, *B30*, 908. [h] $[\alpha]_D$ +8.7 (1.39, EtOH): Heymes, A.; Dvolaitzky, M.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, 2858. This rotation represents a cis/trans mixture. Calculated maximum rotation by the authors, $[\alpha]_D$ +20.4°. [i] Determined by ^1H NMR in the presence of $Eu(hfc)_3$. [j] Diastereomerically pure by capillary GC (methylsilicone, 50 M). [k] This ketone should now be available in >99% ee: see Table III, footnote *d*. [l] Determined by capillary GC analysis of cyclic ketals obtained with [2*R*,3*R*]-(−)-2,3-butanediol. [m] Bessiere-Chretien, Y.; El Gaied, M. M. *Bull. Soc. Chim. Fr.* **1971**, 2189. The ketone was prepared, but no rotation reported.

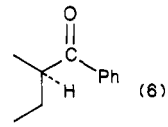
with sodium hypochlorite,[24] various Cr^{VI} species,[25] manganese dioxide[26] or sodium periodate in the presence of RuO_4,[27] anodic oxidations,[28] and amine oxides.[29] Of these methods, oxidation with trimethylamine *N*-oxide is mild and has given consistently high yields.[30] We therefore used this reagent and applied it initially as a test case to the synthesis of [*R*]-(−)-*sec*-butyl phenyl ketone (Table IV, b) which we had already prepared in >97% ee. Thus oxidation of the α-chloro derivative, **2**,[22] with 3 equiv of trimethylamine *N*-oxide in benzene at room temperature for 12 h cleanly gave the borate **3** (^{11}B NMR δ +17), which was readily hydrolyzed to the ketone (eq 6). No racemization of the ketone had occurred, as evidenced by rotation, $[\alpha]^{23}_D$ −37.17° (*c* 1.06, EE), i.e., ≥99% ee.

We then proceeded with the more sterically demanding α-chloroborinate, **1**. In this case, refluxing benzene (12 h) was required to effect complete conversion (eq 7), again without racemization (Table IV, c).

(23) Mikhailov, B. M.; Bubnov, Yu. N. *Organoboron Compounds in Organic Synthesis*; OPA: Amsterdam B.V., 1984; p 228.
(24) Brown, H. C. U.S. Patent 3 439 046, 1969; *Chem. Abstr.* **1969**, *71*, 50273.
(25) Pappo, R. *J. Am. Chem. Soc.* **1959**, *81*, 1010.
(26) Bagli, J. F.; Morano, P. F.; Gaudry, R. *J. Org. Chem.* **1974**, *39*, 2063.
(27) Mueller, R. H.; Di Pardo, R. M. *J. Chem. Soc., Chem. Commun.* **1975**, 565.
(28) Reference 23, p 244.
(29) Köster, R.; Morita, Y. *Angew. Chem.* **1966**, *78*, 589.
(30) Davies, A. G.; Roberts, B. P. *J. Chem. Soc. C* **1968**, 1474.

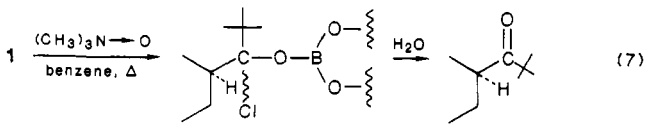


2 3



(6)

>99% ee



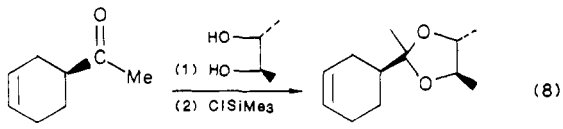
(7)

>99% ee

Thus, the trimethylamine *N*-oxide route should be applicable to sterically hindered derivatives not readily oxidized with hydrogen peroxide in pH 8 phosphate buffer.

The stereochemistry and absolute configuration of the ketones are determined in the asymmetric hydroboration step of the prochiral olefins and reflect the geometries of the boronic and borinic esters[8] (Scheme II).

The percent ee's of ketones a, b, g, i, and j (Table IV) were determined by measuring the rotations and comparing the values with the maximum reported rotations. The percent ee's of ketones c, d, e, f, h, k, and l (Table IV) were determined by ^{1}H NMR analysis in the presence of the chiral shift reagent, Eu(hfc)$_3$.[31] In addition, the cyclic ketones f, g, h, j, k, and l (Table IV), with two adjacent chiral centers, were shown to be diastereomerically pure and therefore enantiomerically pure by capillary GC. In control experiments, the cyclic ketones f, g, h, j, k, and l were equilibrated in 3 N sodium methoxide/methanol for 24 h. Analysis by capillary GC indicated 5–10% epimerization. In addition, we have found that certain optically active acyclic ketones (Table IV, i and k), can be determined via capillary GC analysis of their diastereomeric [2*R*,3*R*]-(−)-2,3-butanediol ketals (eq 8).



(8)

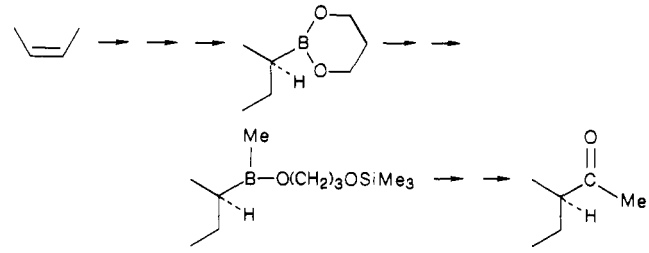
Chlorotrimethylsilane[32] in refluxing benzene had been used previously for effecting this type of condensation with chiral ketones.[2,33] Subsequently, we found that the reaction could also be carried out under much milder conditions (6 equiv of ClSiMe$_3$, 3 equiv of [*R*]-(−)-2,3-butanediol, CH_2Cl_2, −10 °C). Each pair of diastereomers was readily separable by capillary GC. Racemic ketones gave ketals in 1:1 ±3% ratio, thus assuring that no kinetic resolution had taken place.

Isolation of the optically active ketones was done on a 15-mmol scale. After oxidation and aqueous workup, the residual oil was distilled bulb-to-bulb to give ketone of ≥95% purity (GC). To obtain rotations, the samples were further purified by preparatory GC.

Conclusion

The methodology presented here enables the facile preparation and isolation of a wide variety of α-chiral acyclic ketones of uniformly high optical purity (99% ee) from optically pure borinic esters. The latter are obtained from optically pure boronic esters and organolithium reagents. Recently we published a procedure for the synthesis of α-chiral acyclic ketones from optically active borinates obtained by hydroboration.[19] Thus, we now have available a rational approach to the synthesis of α-chiral acyclic ketones, either by hydroboration or by hydroboration/organolithium routes. These two procedures are complementary and make readily available α-chiral acyclic ketones. These can now be transformed by the synthetic chemist into more complex chiral molecules.

Scheme II



Experimental Section

All glassware was dried at 140 °C for at least 3 h, assembled hot, and cooled under a stream of nitrogen. Anhydrous ethyl ether (Mallinckrodt) was stored over 4Å molecular sieves under nitrogen and used without further purification. The commercial organolithium reagents were standardized prior to use. DCME (Aldrich) was distilled from CaH_2 and stored under nitrogen. A stock solution of lithium *tert*-butoxide in hexane was prepared from *n*-butyllithium and *tert*-butyl alcohol and was standardized prior to use. ^{11}B NMR spectra were obtained on a Varian FT-80A spectrometer relative to boron trifluoride etherate.

General Procedure for Isolation of Borinic Esters. All borinic esters (achiral and chiral) were prepared according to the literature procedure.[17]

(*trans*-2-Methylcyclopentyl)(phenyl)(isopropoxy)borane: prepared from (*trans*-2-methylcyclopentylbis(isopropoxy)borane and phenyllithium; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6 Hz, 3 H), 1.25 (d, *J* = 6 Hz, 6 H), 1.50–2.63 (m, 8 H), 4.57 (sept, *J* = 6 Hz, 1 H), 7.23–7.63 (m, 5 H).

(*n*-Butyl)(2-furyl)(isopropoxy)borane: prepared from (2-furyl)bis(isopropoxy)borane and *n*-butyllithium; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, *J* = 7 Hz, 6 H), 4.27 (sept, *J* = 7 Hz, 1 H), 6.43 (m, 1 H), 7.00 (dd, *J* = 2 and 3 Hz, 1 H), 7.63 (m, 1 H).

(3-Furyl)(3-methylbutyl)(isopropoxy)borane: prepared from (3-furyl)bis(isopropoxy)borane and 3-methylbutyllithium;[34] ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6 Hz, 6 H), 1.27 (d, *J* = 6 Hz, 6 H), 4.60 (sept, *J* = 6 Hz, 1 H), 6.53 (d, *J* = 2 Hz, 1 H), 7.37 (t, *J* = 2 Hz, 1 H), 7.67 (m, 1 H).

(*exo*-2-Norbornyl)(phenyl)(isopropoxy)borane: prepared from (*exo*-2-norbornyl)bis(isopropoxy)borane and phenyllithium; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* = 6 Hz, 6 H), 4.47 (sept, *J* = 6 Hz, 1 H), 7.37 (m, 5 H).

(3-Acetoxypropoxy)(methyl)([*R*]-1-methylpropyl)borane: prepared from [*R*]-2-(1-methylpropyl)-1,3,2-dioxaborinane of 99% ee and methyllithium; IR ν_{max} 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 3 H), 0.90 (m, 6 H), 1.70 (s, 3 H), 4.00 (m, 2 H), 4.17 (m, 2 H).

(Methyl)([*R*]-1-methylpropyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [*R*]-2-(1-methylpropyl)-1,3,2-dioxaborinane of 99% ee, methyllithium, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 9 H), 0.37 (s, 3 H), 0.87 (m, 6 H), 1.73 (m, 2 H), 3.67 (t, *J* = 6 Hz, 2 H), 3.93 (t, *J* = 6 Hz, 2 H).

([*R*]-1-Methylpropyl)(phenyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [*R*]-2-(1-methylpropyl)-1,3,2-dioxaborinane of 99% ee and phenyllithium, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 9 H), 1.10 (m, 6 H), 1.87 (quintet, *J* = 6 Hz, 2 H), 3.77 (t, *J* = 6 Hz, 2 H), 4.17 (t, *J* = 6 Hz, 2 H), 7.33 (m, 3 H), 7.53 (m, 2 H).

([*R*]-1-Methylpropyl)(*tert*-butyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [*R*]-2-(1-methylpropyl)-1,3,2-dioxaborinane of 99% ee and *tert*-butyllithium at −100 °C, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 0.90 (s, 9 H), 3.67 (t, *J* = 6

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Hz, 2 H), 4.13 (t, J = 6 Hz, 2 H).

([*R*]-1-Ethylbutyl)(3-furyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [*R*]-2-(1-ethylbutyl)-1,3,2-dioxaborinane of 99% ee and 3-furyllithium, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 3.70 (m, 2 H, 4.23 (m, 2 H), 6.52 (m, 1 H), 7.40 (m, 1 H), 7.70 (m, 1 H).

([1*S*,2*S*]-*trans*-2-Methylcyclopentyl)(phenyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [1*S*,2*S*]-2-(*trans*-2-methylcyclopentyl)-1,3,2-dioxaborinane of 99% ee and phenyllithium, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 1.00 (d, J = 6 Hz, 3 H), 1.77 (m, 8 H), 3.67 (t, J = 6 Hz, 2 H), 4.13 (t, J = 6 Hz, 2 H), 7.23 (m, 3 H), 7.53 (m, 2 H).

(Methyl)([1*S*,2*S*]-*trans*-2-phenylcyclopentyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [1*S*,2*S*]-2-(*trans*-2-phenylcyclopentyl)-1,3,2-dioxaborinane of 99% ee, methyllithium, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 0.30 (s, 3 H), 1.73 (m, 10 H), 3.73 (m, 4 H), 7.17 (br s, 5 H).

(2-Furyl)([1*S*,2*S*]-*trans*-2-phenylcyclopentyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [1*S*,2*S*]-2-(*trans*-2-phenylcyclopentyl)-1,3,2-dioxaborinane of >99% ee and 2-furyllithium, then quenched with chlorotrimethylsilane; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 3.67 (t, J = 6 Hz, 2 H), 4.23 (t, J = 6 Hz, 2 H), 6.33 (m, 1 H), 6.97 (m, 1 H), 7.17 (br s, 5 H), 7.57 (m, 1 H).

([*S*]-Cyclohex-3-enyl)(isopropoxy)(methyl)borane: prepared from [*S*]-(cyclohex-3-enyl)bis(isopropoxy)borane of >99% ee and methyllithium; ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 3 H), 1.10 (d, J = 6 Hz, 6 H), 4.43 (sept, J = 6 Hz, 1 H), 5.73 (m, 2 H).

(3-Acetoxypropoxy)([1*S*,2*S*]-*trans*-2-methylcyclohexyl)(methyl)borane: prepared from [1*S*,2*S*]-2-(*trans*-2-methylcyclohexyl)-1,3,2-dioxaborinane of >99% ee and methyllithium; IR ν_{max} 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.50 (s, 3 H), 0.47 (d, J = 6 Hz, 3 H), 1.57 (s, 3 H), 3.67 (m, 4 H).

(Methyl)([1*S*,2*S*]-*exo*-2-norbornyl)(3-(trimethylsiloxy)propoxy)borane: prepared from ([1*S*,2*S*]-*exo*-norbornyl)bis(isopropoxy)borane of 86% ee and methyllithium; ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 3 H), 1.19 (d, J = 6 Hz, 6 H), 2.23 (m, 2 H), 4.40 (sept, J = 6 Hz, 1 H).

([1*R*,2*R*,3*R*,5*S*]-3-Isopinocampheyl)(methyl)(3-(trimethylsiloxy)propoxy)borane: prepared from [1*R*,2*S*,3*R*,5*R*]-2-(3-isopinocampheyl)-1,3,2-dioxaborinane of 99% ee and methyllithium; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9 H), 0.47 (s, 3 H), 0.87 (d, J = 6 Hz, 3 H), 1.07 (s, 3 H), 1.17 (s, 3 H), 3.67 (m, 2 H), 4.00 (m, 2 H).

General Procedure for the Preparation of Ketones. A 100-mL round-bottom flask containing a magnetic stirring bar was capped with a rubber septum and charged with 15 mmol of borinate. Diethyl ether was added (15 mL) and the reaction cooled to 0 °C. DCME (22.5 mmol, 2.04 mL) was added, followed by lithium *tert*-butoxide (30 mmol, 16.2 mL). The ice bath was removed and the mixture stirred at room temperature for 1 h during which time a slightly exothermic reaction developed and a white precipitate formed. The reaction mixture was cooled to 0 °C and pH 8 phosphate buffer solution (45 mmol, 18 mL) was added, followed by 30% hydrogen peroxide (45 mmol, 5.1 mL). The ice bath was removed and the two-phase system was stirred for 12 h. The phases were separated and the aqueous phase extracted with diethyl ether (2 × 15 mL). The combined extracts were washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, and filtered. The volatiles were removed under reduced pressure, unless otherwise indicated. The residual oil was then distilled bulb-to-bulb. The purity of the ketones, as determined by GC (5% sp 2100 on Chromosorb W, 6 ft × $^1/_8$ in. column), was usually ≥95%. The chiral ketones were further purified by preparative GC (20% sp 2100 on Chromosorb W, 60–80 mesh, 6 ft × 0.5 in.).

***trans*-2-Methylcyclopentyl phenyl ketone**: prepared from (*trans*-2-methylcyclopentyl)(phenyl)(isopropoxy)borane; IR ν_{max} 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6 Hz, 3 H), 1.80 (m, 6 H), 2.43 (m, 1 H), 3.36 (m, 1 H), 7.43 (m, 3 H), 7.90 (m, 2 H); MS, m/e (chemical ionization) 189 (100, M$^+$ + 1); MS, m/e (electron impact) 188 (13, M$^+$).

2-Furyl *n*-butyl ketone: prepared from (*n*-butyl)(2-furyl)(isopropoxy)borane; IR ν_{max} 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.53 (t, J = 6 Hz, 3 H), 1.50 (m, 4 H), 2.86 (t, J = 7 Hz, 2 H), 6.50 (dd, J = 4 Hz, 22 Hz, 1 H), 7.17 (d, J = 4 Hz, 1 H), 7.55 (m, 1 H); MS, m/e (chemical ionization) 153 (100, M$^+$ + 1); MS, m/e (electron impact) 110 (100, M$^+$ - C_3H_6).

3-Furyl 3′-methylbutyl ketone (perilla ketone): prepared from (3-furyl)(3-methylbutyl)(isopropoxy)borane; IR ν_{max} 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6 Hz, 6 H), 1.60 (m, 3 H), 2.77 (t, J = 7 Hz, 2 H), 6.80 (m, 1 H), 7.63 (m, 1 H), 8.03 (br s, 1 H); MS, m/e (chemical ionization) 167 (100, M$^+$ + 1); MS, m/e (electron impact) 166 (2, M$^+$).

(*exo*-2-Norbornyl) phenyl ketone: prepared from (*exo*-2-norbornyl)(phenyl)(isopropyl)borane; IR ν_{max} 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03–2.47 (m, 10 H), 3.20 (m, 1 H), 7.40 (m, 3 H), 7.91 (m, 2 H); MS, m/e (chemical ionization) 201 (100, M$^+$ + 1); MS, m/e (electron impact) 200 (5, M$^+$).

[*R*]-3-Methylpentan-2-one: prepared from (methyl)([*R*]-1-methylpropyl)(3-(trimethylsiloxy)propoxy)borane and the volatiles removed at atmospheric pressure; IR ν_{max} 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H), 1.40 (m, 1 H), 1.61 (m, 1 H), 2.13 (s, 3 H), 2.42 (m, 1 H); MS, m/e % (chemical ionization) 101 (100, M$^+$ + 1); MS, m/e (electron impact) 100 (4, M$^+$).

[*R*]-(−)-1-Methylpropyl phenyl ketone: prepared from ([*R*]-1-methylpropyl)(phenyl)(3-(trimethylsiloxy)propoxy)borane; IR ν_{max} 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3 H), 1.73 (m, 1 H), 3.40 (dd, J = 13 Hz, 1 H), 7.43 (m, 3 H), 7.90 (m, 2 H); MS, m/e (chemical ionization) 163 (100, M$^+$ + 1); MS, m/e (electron impact) 162 (5, M$^+$).

[*S*]-(+)-2,3,7-Trimethyloctan-4-one: prepared from ([*S*]-1,2-dimethylpropyl)(3-methylbutyl)(3-(trimethylsiloxy)propoxy)borane; IR ν_{max} 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 12 H), 1.04 (d, J = 6 Hz, 3 H), 1.47 (m, 2 H), 1.92 (m, 1 H), 1.89–2.45 (m, 3 H); MS, m/e (chemical ionization) 171 (100, M$^+$ + 1); MS, m/e (electron impact) 170 (10, M$^+$); HRMS calcd for $C_{11}H_{22}O$, M = 170.16706, found M = 170.16706.

[*R*]-(+)-1-Ethylbutyl 3-furyl ketone: prepared from ([*R*]-1-ethylbutyl)(3-furyl)(3-(trimethylsiloxy)propoxy)borane: IR ν_{max} 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6 H), 1.23–2.23 (m, 6 H), 2.87 (m, 1 H), 6.73 (m, 1 H), 7.40 (m, 1 H), 8.00 (m, 1 H); MS, m/e (chemical ionization) 181 (100, M$^+$ + 1); MS, m/e (electron impact) 180 (3, M$^+$). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.58; H, 9.03.

[1*S*,2*S*]-(+)-*trans*-2-Methylcyclopentyl phenyl ketone: prepared from ([1*S*,2*S*]-*trans*-2-methylcyclopentyl)(phenyl)(3-(trimethylsiloxy)propoxy)borane; all spectral data are identical with those of the racemic compound (vide supra); mp 48–49 °C (pentane, 0 °C). Anal. Calcd for $C_{13}H_{16}O$: C, 82.84; H, 8.51. Found: C, 83.07; H, 8.62.

[1*S*,2*S*]-(+)-*trans*-2-Phenylcyclopentyl methyl ketone: prepared from (methyl)([1*S*,2*S*]-*trans*-2-phenylcyclopentyl)(3-(trimethylsiloxy)propoxy)borane; IR ν_{max} 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57–2.13 (m, 6 H), 1.97 (s, 3 H), 3.13 (m, 2 H), 7.17 (s, 5 H); MS, m/e (chemical ionization) 189 (100, M$^+$ + 1); MS, m/e (electron impact) 188 (41, M$^+$).

[1*S*,2*S*]-(+)-*trans*-2-Phenylcyclopentyl 2′-furyl ketone: prepared from (2-furyl)([1*S*,2*S*]-*trans*-2-phenylcyclopentyl)(3-(trimethylsiloxy)propoxy)borane; mp 75–76 °C (pentane); IR ν_{max} (Nujol) 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.97 (m, 6 H), 3.57 (m, 2 H), 6.33 (dd, J = 4 and 2 Hz, 1 H), 7.10 (d, J = 4 Hz, 1 H), 7.17 (s, 5 H), 7.40 (m, 1 H); MS, m/e (chemical ionization) 241 (100, M$^+$ + 1); MS, m/e (electron impact) 240 (39, M$^+$). Anal. Calcd for $C_{16}H_{10}O_2$: C, 79.47; H, 6.21. Found: C, 79.67; H, 6.80.

[*S*]-(−)-Cyclohex-3-enyl methyl ketone: prepared from ([*S*]-cyclohex-3-enyl)(methyl)(isopropoxy)borane; IR ν_{max} 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 5.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.54, 24.66, 26.74, 47.23, 125.26, 126.65, 211.53; MS, m/e (chemical ionization) 125 (100, M$^+$ + 1); MS, m/e (electron impact) 124 (18, M$^+$ - CH_3).

[1*S*,2*S*]-(+)-*trans*-2-Methylcyclohexyl methyl ketone: prepared from (methyl)([1*S*,2*S*]-*trans*-2-methylcyclohexyl)(3-(trimethylsiloxy)propoxy)borane; IR ν_{max} 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 6 Hz, 3 H), 2.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.57, 25.64, 25.95, 29.01, 29.55, 33.76, 34.45, 59.24, 213.05; MS, m/e (chemical ionization) 141 (100, M$^+$ + 1); MS, m/e (electron impact) 125 (1, M$^+$ - CH_3).

[1*S*,2*S*]-(+)-*exo*-2-Norbornyl methyl ketone: prepared from (methyl)([1*S*,2*S*]-*exo*-2-norbornyl)(3-(trimethylsiloxy)propoxy)borane; IR ν_{max} 1706 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 28.73, 28.76, 29.64, 32.29, 35.88, 35.98, 39.74, 54.83, 209.76; MS, m/e (chemical ionization) 139 (100, M$^+$ + 1); MS, m/e (electron impact) 138 (1, M$^+$). Anal. Calcd for $C_9H_{18}O$: C, 78.77; H, 10.21. Found: C, 78.44; H, 10.46.

[1*R*,2*R*,3*R*,5*S*]-(−)-3-Isopinocampheyl methyl ketone: prepared from ([1*R*,2*R*,3*R*,5*S*]-3-isopinocampheyl)(methyl)(3-(trimethylsiloxy)propoxy)borane; IR ν_{max} 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz), 1.03 (s, 3 H), 1.23 (s, 3 H), 2.17 (s, 3 H); MS, m/e (chemical ionization) 181 (100, M$^+$ + 1); MS, m/e (electron impact) 180 (2, M$^+$ - CH_3).

Oxidation with Trimethylamine *N*-Oxide. The DCME reaction was carried out as described under the section General Procedure for the Preparation of Ketones. Then, instead of adding phosphate buffer, the volatiles were removed under reduced pressure. Benzene (5 mL) was added, followed by water (15 mL). The flask was vigorously shaken and the organic phase was transferred via a double-ended needle to a 100-mL round-bottom flask charged with dry trimethylamine *N*-oxide (45 mmol, azeotroped in benzene for 6 h), a magnetic stirring bar, and reflux condenser. The reaction was stirred at room temperature under a slow stream of nitrogen, 12 h, diluted with diethyl ether (25 mL), and transferred to a separatory funnel containing phosphate buffer solution (150 mL). The mixture was vigorously shaken for 5 min, the phases separated, and the procedure repeated. The organic phase was washed

with brine (2 × 25 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed under reduced pressure. The residual oil was distilled bulb-to-bulb to give the ketones (≥95% GC). Further purification by preparatory GC gave the analytically pure ketones.

***trans*-Methylpropyl Phenyl Ketone.** For spectral data of this compound, see under the section General Procedure for the Preparation of Ketones.

[*R*]-(−)-2,2,4-Trimethylhexen-3-one: prepared from ([*R*]-1-methylpropyl)(*tert*-butyl)(3-(trimethylsiloxy)propoxy)borane with the reaction mixture heated to reflux 12 h, cooled, and worked up as described above; IR ν_{max} 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H), 1.15 (s, 9 H), 1.33 (m, 1 H), 1.62 (m, 1 H), 2.91 (sext, J = 7 Hz, 1 H); MS, m/e (chemical ionization) 143 (100, M^+ + 1); MS, m/e (electron impact) 142 (1, M^+). Anal. Calcd for $C_9H_{18}O$: C, 76.06; H, 12.68. Found: C, 75.98; H, 12.86.

Epimerization of Cyclic Ketones. The ketone (0.1 mmol) was dissolved in 3 N sodium methoxide in methanol (0.5 mL) and stirred for 24 h at room temperature. The reaction was diluted with water (2 mL) and extracted with ether (1 mL). The organic phase was dried over $MgSO_4$ and filtered. An aliquot was analyzed by capillary GC (methyl silicone, 50 M).

Preparation of Ketals. The ketone (0.1 mmol) was dissolved in dichloromethane (0.5 mL) and cooled to −10 °C. [2*R*,3*R*]-(−)-2,3-butanediol (0.3 mmol) and chlorotrimethylsilane (0.6 mmol) were added sequentially. The reaction was stirred at −10 °C for 30 min, poured into saturated sodium bicarbonate solution, and extracted with ether (1 mL). The ethereal solution was dried over $MgSO_4$ and filtered. An aliquot was injected into capillary GC for analysis.

Further Studies on the Biosynthesis of the Boron-Containing Antibiotic Aplasmomycin

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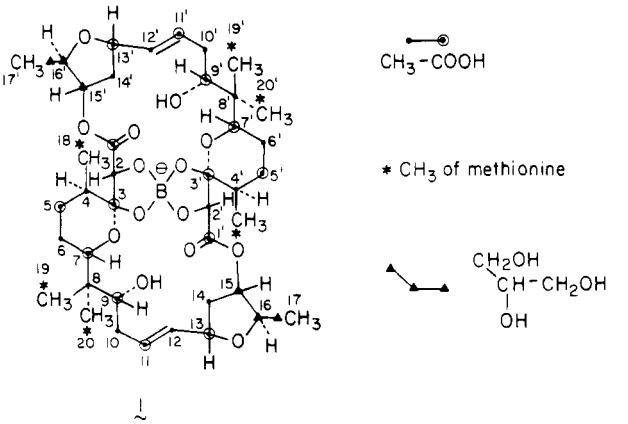
Abstract: In the biosynthesis of aplasmomycin by *Streptomyces griseus*, seven atoms of deuterium from C-2 of acetate are incorporated per chain (one each at C-2, -10, and -12 and two each at C-6 and -14) and 4 atoms of oxygen from C-1 of acetate (one each at C-1, -7, -9, and -13). The two hydrogens of the *pro-R*-hydroxymethyl group of glycerol are incorporated into C-17, giving rise to a chiral methyl group of *S* configuration when (1*R*,2*R*)-[1-$^2H_1$,^3H]glycerol is used as substrate. The three methionine-derived *C*-methyl groups per chain are transferred stereospecifically with inversion of configuration, but racemization is observed during the formation of the methionine methyl group from stereospecifically labeled [3-$^2H_1$,^3H]serine. The stereochemical and precursor feeding experiments point to phosphoglyceric acid or phosphoenolpyruvate as the glycerol-derived polyketide chain starter unit, ruling out serine, methylglyoxal, and pyruvate and compounds derived from these. Mechanistic aspects of the modification of the initial polyketide chain are discussed.

Aplasmomycin (**1**) is a novel ionophoric macrolide antibiotic that was isolated from strain SS-20 of *Streptomyces griseus* obtained from a sample of sea mud.[1] Its structure, as determined by single-crystal X-ray analysis[2] and confirmed by synthesis,[3] is that of a symmetrical dimer built around a boron atom. It is closely related to boromycin, the first boron-containing antibiotic found in nature.[4] The two compounds have very similar conformations and identical configurations at all the asymmetric centers except C-9, but in contrast to boromycin, aplasmomycin does not contain the D-valine moiety. Two minor components of the fermentation, asplasmomycin B and C, have been isolated and identified as the monoacetate at C-9 and the diacetate at C-9 and C-9′.[5]

Studies on the biosynthesis of **1** have established the origin of its carbon skeleton as summarized in Scheme I.[6] Each half of the molecule represents a polyketide chain made up of a starter unit and seven acetate/malonate extension units. The latter are modified by C-methylation through transfer of three methyl groups of methionine. This is in contrast to the biosynthesis of most macrolide antibiotics in which chain branches are formed by

Scheme I. Structure and Biosynthetic Origin of Aplasmomycin



utilization of the appropriate homologues in place of acetate chain extension units, i.e., propionate units, in the form of methylmalonyl

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