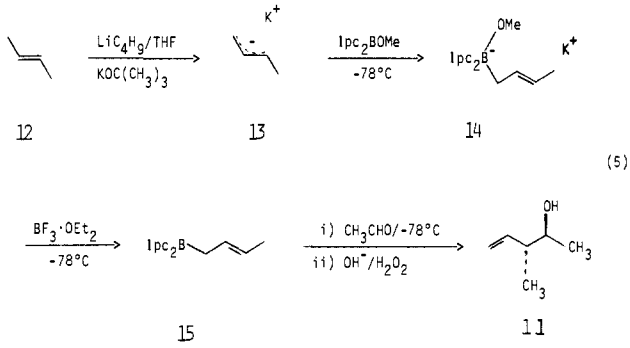
Table I. Synthesis in High Optical Purity via Crotylboration of the Four Stereoisomers of 3-Methyl-4-penten-2-ol

crotylboration reagent Ipc_2BOMe^a + $KCH_2CH{=}CHCH_3$		3-methyl-4-penten-2-ol					
Ipc_2BOMe from	potassium salt from	yield %	configuration[b]	$[\alpha]^{23}_D$, deg (neat, l = 0.5)	diastereoselectivity,[c] %	enantioselectivity,[d] %	no.
(+)-α-pinene	*cis*-2-butene	75	2*R*,3*R*	+19.30	99	95	**8**
(+)-α-pinene	*trans*-2-butene	78	2*R*,3*S*	-9.04	99	95	**10**
(-)-α-pinene	*cis*-2-butene	72	2*S*,3*S*	-19.56	99	96	**9**
(-)-α-pinene	*trans*-2-butene	76	2*S*,3*R*	+9.14	99	96	**11**

[a] Ipc_2BOMe of 99% ee was prepared according to the literature procedure.[6] [b] Configurations are predicted in analogy to the configurations of the products obtained with allyldiisopinocampheylborane[6] and are supported by the literature.[9b] [c] Diastereomeric ratios were determined by capillary GC analysis using a column, Supelcowax 10, 15 m × 0.25 mm. [d] Enantiomeric ratios were determined by GC analysis of the MTPA esters of the alcohols, using a column, methylsilicon, 50 m × 0.25 mm.

such "ate" complexes react with 1.33 equiv. of boron trifluoride etherate and generate trialkylborane.[16] Hence, the "ate" complex **6** was treated with boron trifluoride etherate and the resulting crotyldialkylborane, **7**, was immediately treated with acetaldehyde at -78 °C. The reaction mixture, on the usual alkaline hydrogen peroxide workup, furnished *erythro*-(+)-3-methyl-4-penten-2-ol (**8**) with ≥99% diastereoselectivity and 95% enantioselectivity (Table I).

The same modified Schlosser procedure[15] successfully metalated *trans*-2-butene, forming (*E*)-crotylpotassium. The synthesis then provided *threo*-(-)-3-methyl-4-penten-2-ol (**10**) with ≥99% diastereoselectivity and 95% enantioselectivity (Table I).



Ipc = Isopinocampheyl derived from (-)-α-pinene

Use of *B*-methoxydiisopinocampheylborane derived from (-)-α-pinene provided the enantiomeric threo and erythro isomers (Table I).

The following experimental procedure is representative:

***erythro*-(-)-3-Methyl-4-penten-2-ol (9).** To a stirred mixture of potassium *tert*-butoxide (2.8 g, 25 mmol, dried at 0.5 mm/80 °C/8 h), THF (7 mL), and *cis*-2-butene (4.5 mL, 50 mmol), *n*-butyllithium in THF (2.3 M, 25 mmol) was added at -78 °C. After complete addition of *n*-butyllithium, the mixture was stirred at -45 °C for 10 min. The resulting orange solution was recooled to -78 °C and to it was added dropwise methoxydiisopinocampheylborane in ether [1 M, 30 mmol, derived from (-)-α-pinene]. After stirring the reaction mixture at -78 °C for 30 min, boron trifluoride etherate (4 mL, 33.5 mmol) was added dropwise. Then acetaldehyde (2 mL, 35 mmol) was added dropwise at -78 °C. The mixture was now stirred at -78 °C for 3 h and then treated with 18.3 mL (55 mmol) of 3 N NaOH and 7.5 mL of 30% H_2O_2 and the contents were refluxed for 1 h. The organic layer was separated, washed with water (30 mL) and brine (30 mL), and dried over anhydrous $MgSO_4$. The residue, after removal of the solvent, was carefully fractionated to furnish **9**: yield 72%; erythro selectivity, ≥99%. 100% pure erythro material was obtained by preparative GC, using a column, 20% Carbowax on Chromosorb W (60-80 mesh), 6 ft × 0.5 in.: enantioselectivity, 96%; $[\alpha]^{23}_D$ -19.56° (neat, l = 0.5).

This one-pot synthesis of enantiomeric β-methylhomoallylic alcohols is operationally very simple, making use of readily available chemicals and providing access to all four possible stereoisomers by selecting either *cis*- or *trans*-2-butene and the proper antipode of α-pinene for preparation of the reagent. Further, it demonstrates the superior chiral-directing property of the 3-pinanyl group in asymmetric synthesis. Earlier studies have demonstrated the insensitivity of this synthetic method for broad variations in the structure of the aldehyde.[6-8] Consequently, this development promises to make readily available a large variety of such diastereomeric compounds in high optical purity.

Acknowledgment. The financial support from the National Institutes of Health is gratefully acknowledged (Grant GM 10937-22).

Registry No. 4, 590-18-1; **5**, 59304-72-2; (+)-**6**, 99397-93-0; (-)-**6**, 99438-34-3; (+)-**7**, 99397-92-9; (-)-**7**, 99438-30-9; **8**, 74080-50-5; **9**, 99438-31-0; **10**, 74080-51-6; **11**, 99438-32-1; **12**, 624-64-6; **13**, 60647-48-5; (+)-**14**, 99438-33-2; (-)-**14**, 99438-35-4; (+)-**15**, 99438-29-6; (-)-**15**, 99493-12-6; (+)-Ipc_2BOMe, 85134-98-1; (-)-Ipc_2BOMe, 99438-28-5; acetaldehyde, 75-07-0.

(16) Brown, H. C.; Sinclair, J. A. *J. Organomet. Chem.* **1977**, *131*, 163.

Diisopropyl Tartrate Modified (*E*)-Crotylboronates: Highly Enantioselective Propionate (*E*)-Enolate Equivalents

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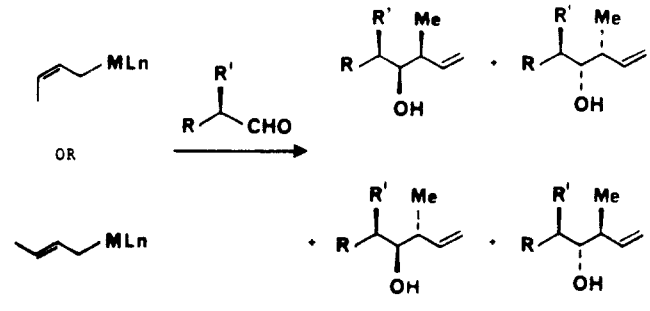
The reactions of crotylmetal reagents and propionate enolate equivalents with chiral carbonyl compounds are of considerable interest in the context of acyclic stereoselective synthesis.[3-6] These transformations generate two new stereochemical relationships and, potentially, four diastereomeric products. One objective of research in this area is the development of methodology and/or reagents suitable for synthesis of each diastereomeric relationship with exceptional selectivity and control.[6]



(1) Fellow of the Alfred P. Sloan Foundation, 1982-1986.
(2) NIH Postdoctoral Fellow, 1985-1987 (GM 10753).
(3) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357.
(4) (a) Barlett, P. A. *Tetrahedron* **1980**, *36*, 3. (b) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
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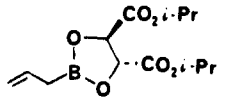
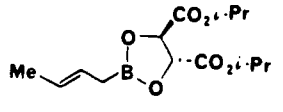
A major step toward the accomplishment of this goal has been realized in the aldol arena where it is now possible to synthesize the 2,3-syn-3,4-syn and 2,3-syn-3,4-anti β-hydroxycarbonyl diastereomers with excellent selectivity by using one of several highly efficient chiral [*Z*(O)]-enolate equivalents.[5,6] Unfortunately, comparably efficient chiral [*E*(O)]-enolates required for synthesis of the two 2,3-anti diastereomers have not until now been available.[7,8] Our observation that tartrate ester modified allylboronate **1** undergoes highly enantioselective additions to both



(-)-**1**



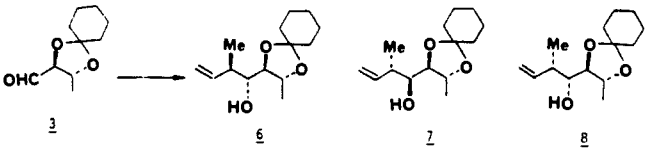
(-)-**2**

chiral and achiral aldehydes[9] prompted us to extend this auxiliary system to the (E)-crotylboron family.[10] We are pleased therefore to report our preliminary findings that reagent **2** is the most highly enantioselective (*E*)-crotylboronate reported to date, is very easily prepared in either enantiomeric series from readily available starting materials, and consequently is well suited for use in organic synthesis as an (*E*)-propionate enolate equivalent.[11,12]

Reagent **2** is easily prepared by using modifications of Schlosser's crotylboronate synthesis.[13] Thus, treatment of (*E*)-crotylpotassium (generated from (*E*)-2-butene (2 equiv), *n*-BuLi (1.0 equiv), and KO-*t*-Bu (1.0 equiv) in THF at −78 °C, 12 h, or −50 °C, 15 min)[12b] with $FB(OMe)_2$ (1.0 equiv) at −78 °C for 1 h followed by hydrolysis with saturated aqueous NaCl containing 1 equiv of HCl gives crude crotylboronic acid that is extracted into ether, concentrated, and then esterified with 0.4 or 1.0 equiv of DIPT (THF, $MgSO_4$, 2 h, 23 °C). Distillation (Kugelrohr, 70–75 °C, 0.1 mmHg) of the product obtained in the former case gives >96% isomerically pure **2** in 88% yield based on DIPT. Since the purity of **2**, however, does not appear to influence the diastereofacial selectivity, we routinely use crude **2** (containing ≥0.3 equiv of excess DIPT) prepared via the second procedure in aldehyde addition reactions.[14]

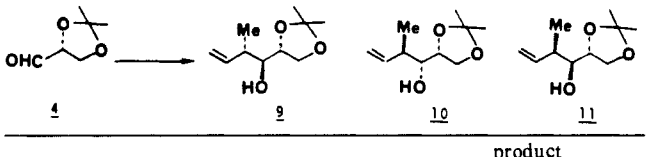
Results of reactions of **2** with chiral aldehydes **3** and **4** are summarized in Table I. These aldehydes were selected for initial screening of **2** since they do not display any appreciable facial preference in reactions with achiral pinacol (*E*)-crotylboronate

Table I. Reactions of Chiral Crotylboronate **2** with Chiral Aldehydes **3** and **4**[a]



3 **6** **7** **8**

entry	reagent[b,c]	conditions	product ratios[d] (yield)[e] 6	7	8	
1[f]	(+)-**2**	toluene, −78 °C, 4-Å sieves	88	4	8	(80%)
2	(+)-**2**	CH_2Cl_2, −78 °C 4-Å sieves	77	15	8	
3	(+)-**2**	Et_2O, −78 °C, 4-Å sieves	87	5	8	
4	(+)-**2**	THF, −78 °C, 4-Å sieves	84	8	8	
5	**5**	toluene, 23 °C, 4-Å sieves	66	28	6	
6[g]	**5**	CH_2Cl_2, 23 °C	51	47	2	
7	(−)-**2**	toluene, −78 °C, 4-Å sieves	4	93	3	(88%)
8	(−)-**2**	toluene, −78 °C	6	89	5	
9	(−)-**2**	toluene, 23 °C, 4-Å sieves	19	77	4	
10	(−)-**2**	toluene, 23 °C	33	62	5	



4 **9** **10** **11**

entry	reagent[b,c]	conditions	product ratios[d] (yield)[e] 9	10	11	
11[f]	(−)-**2**	toluene, −78 °C, sieves	87	9	4	(87%)
12	**5**	toluene, 23 °C	53	38	9	
13	(+)-**2**	toluene, −78 °C, sieves	2	96	2	(85%)

[a] Analytical scale reactions were performed by addition of 1.3–1.5 equiv of aldehyde to a 0.1 M solution of **2** and powdered 4-Å molecular sieves (50 mg/mL) at the indicated tempertures. Reactions at 23 °C were complete within 30 min, whereas reactions at −78 °C required less than 5 h to reach completion. Reactions were worked up as described in ref 9. [b] See ref 17. [c] Isomeric purity of **2** was >96% as determined by capillary GC analysis (12-m dimethylsilicone on fused silica column). [d] Diastereomer ratios determined as described in ref 15. [e] Yields are for preparative-scale experiments and are based on aldehyde as limiting reagent. [f] The ratio of **6**:**7** or **9**:**10** was not affected by the chemical purity of **2** (e.g., use of distilled or crude reagent) or by the reaction stoichiometry (either reagent used in excess). The isomeric purity of **2**, however, does influence the amount of **8** and **11** produced in these experiments. [g] See ref 15.

5 (entries 5, 6, 12).[15] Consequently, the enantioselectivity of **2** is easily assessed by monitoring the overall reaction diastereoselectivity. Best results in all cases were obtained in reactions performed at −78 °C in toluene in the presence of powdered 4-Å molecular sieves (50 mg/mL).[16] These reactions are extremely rapid and require less than 5 h to reach completion at −78 °C. Under these conditions the reaction of L-deoxythreose ketal **3** with (−)-DIPT derived (+)-**2**[17] is highly selective for **6** (22:1 diastereofacial selectivity, entry 1) whereas with the antipodal (−)-**2** prepared from (+)-DIPT the facial selectivity is reversed and favors **7** over **6** by a factor of 23:1 (entry 7). Similarly, the reaction of D-glyceraldehyde acetonide **4** with (+)-**2** is 96% selective for **10** (48:1 diastereofacial selectivity, entry 13). The least selective example of the four cases reported here is the reaction of **4** with (−)-**2** which resulted in a "disappointing" facial selectivity of only ca. 10:1 (entry 11).[18] These reactions also produce small amounts

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(8) For enolate systems that show considerable promise, see: (a) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125. (b) Liebeskind, L. S.; Welker, M. E. *Ibid.* **1984**, *25*, 4341. (c) Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4278.

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(10) For previous studies in this area, see: (a) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375. (b) Hoffmann, R. W.; Helbig, W. *Ibid.* **1981**, *114*, 2802. (c) Hoffmann, R. W.; Zeiss, H.-J.; Ladner, W.; Tabche, S. *Ibid.* **1982**, *115*, 2357. (d) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320. (e) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330.

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(12) (a) We thank Prof. H. C. Brown for informing us prior to publication of his exciting recent results of enantioselective aldehyde additions obtained using (*Z*)- and (*E*)-crotyldiisopinocamphenylboranes (Brown, H. C.; Bhat, K. S., unpublished results). (b) We also thank Prof Brown for bringing to our attention his procedure for preparation of (*E*)-crotylpotassium (metalation of (*E*)-2-butene at −50 °C for 15 min).

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(14) (a) Reagent **2** prepared on a 0.1-mol scale has been stored at 0 °C under an inert atmosphere for several weeks without apparent decomposition. This compound, however, is very sensitive to moisture and readily hydrolyzes upon exposure to wet solvents or moist air or upon TLC analysis. (b) If desired, this material can be enriched (≤0.2 equiv of excess DIPT) by distillation (60% yield based on DIPT).

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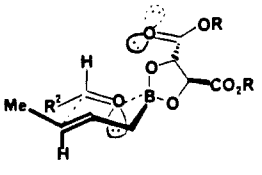
(16) The sieves presumably function by maintaining a rigorously anhydrous reaction medium, thereby preventing adventitious hydrolysis of **2** in situ to achiral crotylboronic acid (compare entries 7–10). The temperature and solvent dependencies indicated in entries 1–4 and 7–10 were observed for each combination of reagent and aldehyde reported herein.

(17) The optical rotation of (+)-**2** prepared from (−)-DIPT is $[\alpha]^{22}_D$ +40.2° (*c* 20.0, CH_2Cl_2).

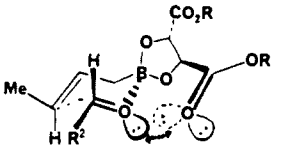
(18) It is interesting to note that the reaction of **4** with Hoffmann's chiral (*E*)-crotylreagent gave a 72:28 mixture of **9** and **10** (see ref 10c).

of 3,4-syn-4,5-anti diastereomers **8** and **11** that may derive from the *Z* olefin contaminant (2–4%) present in **2**. Only in the case of (+)-**2** and **3** does the amount of **8** (8%) exceed the level expected on the basis of the isomeric purity of the reagent.

It is clear from these results that reagent **2** is highly enantioselective since the stereochemistry at C(3) and C(4) of **6**, **7**, **9**, and **10** is controlled simply by selecting the appropriate enantiomer of **2**. The origin of asymmetry in these reactions is consistent with the stereoelectronic model proposed previously,[9] namely, that transition state A is favored as a consequence of n/n electronic repulsive interactions involving the indicated aldehydic oxygen atom and the β-face ester carbonyl that destabilizes B relative to A. Further studies and applications of these reagents in organic synthesis will be reported shortly.



A (favored)



B (disfavored)

Acknowledgment. This research was generously supported by grants from the National Institutes of Health (GM 26782 and AI 20779).

Electrophilic and Nucleophilic Character of the Carbon 10 Methylene Group in Mitosenes Revealed

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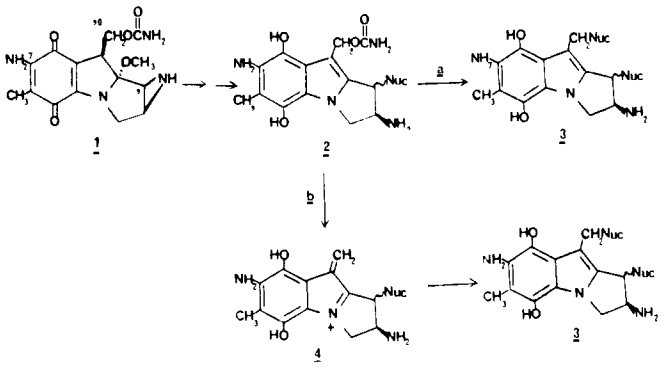
Mitomycin C (**1**) belongs to a class of antibiotics that exhibit potent, specific antitumor activity.[1] Recent studies[2-12] have supported the contention that the drug functions as a bioreductive alkylating agent.[13] Both carbons 1 and 10 in **1** have been invoked as the likely centers for nucleophilic attack by DNA.[1] Considerable evidence has been amassed indicating that carbon 1 is more reactive than carbon 10 toward nucleophiles at neutral pH in the presence of a reducing agent[2-12] and in dilute acid.[14-18] Moreover, isolation of both carbon 1 diastereomeric products in many of these reactions has suggested that ring opening of the aziridine moiety precedes attack by the nucleophile. In contrast to our considerable understanding of the mode of reaction at carbon 1, little is known about the corresponding mechanism for carbon 10 alkylation, a situation partly due to diminished reactivity and achirality of this site. Several possibilities can be envisioned for carbon 10 alkylation. Two of the more attractive routes are (1) S_N2 substitution of the carbamate group in **2** by the genetic material to yield **3** (Scheme I, path a) and (2) initial loss of the carbamate moiety in **2** to yield iminium ion **4**, followed by nucleophilic attack by DNA to produce the disubstituted adduct **3** (Scheme I, path b). In the second mechanism, ionization should be facilitated by delocalization of the electron pair on the indole nitrogen atom. Herein, we present evidence favoring the second pathway (route b) and demonstrate for the first time the potential nucleophilic character of carbon 10.

Scheme I



Scheme II

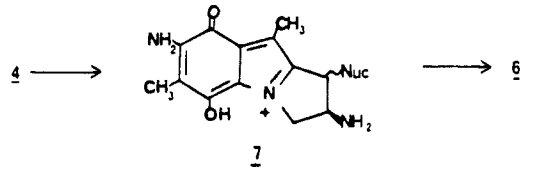


Table I. Percent Deuterium Incorporation Observed in the Conversion of **5** to **6**

entry	substrate	gas utilized	solvent utilized	% D incorporation at C-10 in **6**[a]
1	**5a**	D_2	CH_3OH	0
2	**5a**	H_2	CH_3OD	91
3	**5b**	D_2	C_2H_5OH	0
4	**5b**	H_2	C_2H_5OD	86

[a] Percent deuterium incorporation was determined by ^1H NMR. Accuracy of the measurement is ±5%.

Treatment of an 0.2 mM methanol solution of 1,2-*trans*-1-hydroxy-2,7-diaminomitosene[8,19] (**5a**) with PtO_2 and H_2 (27 °C, 7 min) led to the isolation of the carbon 10 methyl adduct **6a**[20] in approximately 80% yield after oxidative workup. No other significant products were detected by HPLC analyses.[21] A comparable result was obtained for the reduction of **5b** in etha-

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(20) Compound **6a**: HPLC retention time 14.6 min; IR (KBr) 1607, 1385 cm^{-1}; ^1H NMR (300.1 MHz, CD_3OD) δ 1.70 (s, 3 H, C_6CH_3), 2.22 (s, 3 H, $C_{10}CH_3$), 3.78–3.81 (m, 1 H, C_2H), 3.87 (dd, 1 H, J = 3.8, 13.0 Hz, C_3H_β), 4.45 (dd, 1 H, J = 6.1, 13.0 Hz, C_3H_α), 4.69 (d, 1 H, J = 2.8 Hz, C_1H); ^{13}C NMR (75.5 MHz, Me_2SO-d_6) 8.47, 9.88, 53.19, 63.79, 73.26, 104.46, 113.22, 123.32, 127.11, 140.63, 147.22, 178.91 ppm (only one carbonyl carbon resonance was observed); UV (MeOH) λ_{max} 248, 309, 525 nm; field-desorption mass spectrum, m/z calcd for $C_{13}H_{15}N_3O_3$ 261.111, found 261.113.

(21) HPLC conditions: C_{18} μBondapak (ss) 3.9 mm × 15 cm; flow rate 1 mL/min at room temperature; gradient linear from 0% B to 50% B in 20 min; buffer A, aqueous 3 mM TEAP (pH 4.5); buffer B, 3 mM TEA in acetonitrile; wavelength of detection 254–312 nm.

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