Enantiomeric (*Z*)- and (*E*)-Crotyldiisopinocampheylboranes. Synthesis in High Optical Purity of All Four Possible Stereoisomers of β-Methylhomoallyl Alcohols

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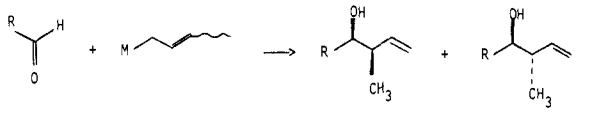
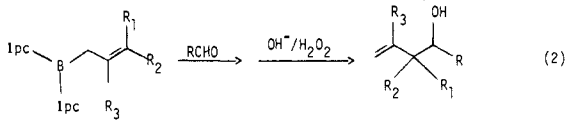
Allylation of aldehydes with allylic organometallic compounds and the utility of the resulting allylic moieties in the construction of complex molecules and their essential feature as biosynthetic intermediates[2] have been amply demonstrated. Many allylic organometallic reagents[3] (allyl-M, such as M = Li, Na, K, Mg, B, etc.) react smoothly with carbonyl compounds to yield the corresponding homoallylic alcohols. Unfortunately, however, the high reactivity of the organometallic reagent frequently causes loss of regio- and stereoselectivity. For example, allylic organometallic reagents, such as the crotyl derivatives, react with aldehydes to give diastereomeric mixtures of the *erythro*- and *threo*-β-methylhomoallyl alcohols;[4] β-methylhomoallyl alcohol



M = Li, Na, K, Mg, B, etc. (1)

units of both the erythro and threo configurations constitute a characteristically structural feature of numerous macrolide[5] and polyether antibiotics. Regretably, the stereoselectivity achieved in such syntheses is usually quite low. Hence, the development of new crotyl organometallic reagents possessing high regio- and stereoselectivities has been a desirable goal in organic synthesis.

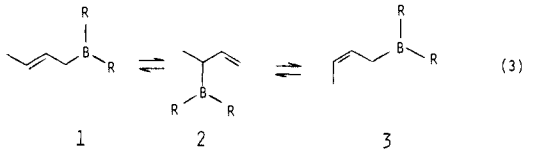
We discovered that simple allylic derivatives (Ipc_2BR, R = allyl,[6] 2-methylallyl,[7] 3,3-dimethylallyl;[8] Ipc = isopinocampheyl) are readily synthesized and yield the homoallylic alcohols on treatment with alldehydes, with high optical purities.



(R_1, R_2, R_3 = H;[6] R_1, R_2 = H, R_3 = Me;[7] R_1, R_2 = Me, R_3 = H[8]) (2)

There was considerable interest in extending such an asymmetric synthesis to the enantioselective synthesis of both the *erythro*- and *threo*-β-methylhomoallyl alcohols. Indeed, a number of experimental approaches have been reported, with only partial success. These include the addition of optically active 2-crotylboron[9] or 2-crotylsilane derivatives to aldehydes[10] and the [2,3]-Wittig sigmatropic rearrangement of chiral 2-crotyl ethers.[11] However, these methods involve difficulties in the preparation of enantiomerically pure starting materials or incomplete chiral selectivity during the carbon–carbon bond-formation process.

The *B*-crotyl derivatives generally exist as an interconvertible mixture of isomers which add to aldehydes to afford a mixture of regioisomers. The reason is the fast equilibration of pure (*E*)- and (*Z*)-crotylboron derivatives, **1** and **3**, via a borotropic rearrangement involving the 1-methylallyl compound **2** as an intermediate.

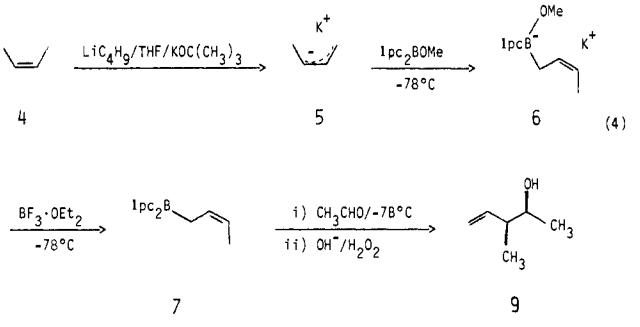


1 2 3 (3)

The rate of isomerization of these intermediate derivatives varies greatly with the nature of the other groups on boron: allyl-BR_2 > allyl-BR(OR') > allyl-$B(OR')_2$.[12] Further, the rate of reaction with aldehydes varies in the same order: allyl-BR_2 reacts readily at −78 °C, the allyl BR(OR') at −15 °C → room temperature,[13] and the allyl $B(OR')_2$ at room temperature.[14] The optical purity achieved is considerably greater the lower the reaction temperature. Thus, the major problem in using our approach, as compared to use of the more stable but less reactive allyl-BR(OR') and allyl-$B(OR')_2$ was the lack of any knowledge about the practical synthesis of isomerically stable (*Z*)- and (*E*)-crotyldiisopinocampheylborane.

In this paper, we wish to report the first example of regio- and stereoselective preparation of optically active (*Z*)- and (*E*)-crotylboranes and their successful reaction with aldehydes to yield the enantiomeric β-methylhomoallylic alcohols in high optical purities.

cis-2-Butene was metalated with potassium *tert*-butoxide and *n*-butyllithium in THF at −45 °C, using a modification of the Schlosser procedure.[15] The resulting organometallic, (*Z*)-crotylpotassium, was treated with methoxydiisopinocampheylborane [derived from (+)-α-pinene] at −78 °C. The ^{11}B NMR spectrum indicates the formation of the "ate" complex **6**. It is known that



4 5 6 (4)

7 9

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

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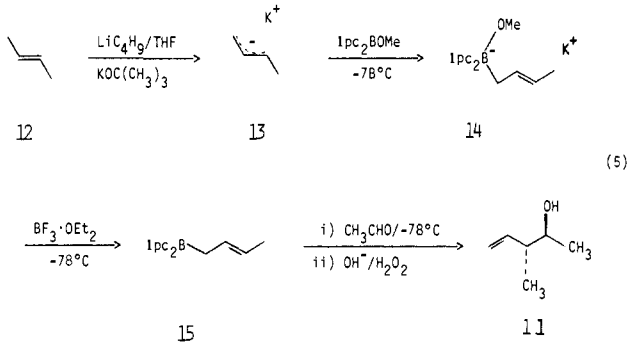
Table I. Synthesis in High Optical Purity via Crotylboration of the Four Stereoisomers of 3-Methyl-4-penten-2-ol

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.

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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.

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

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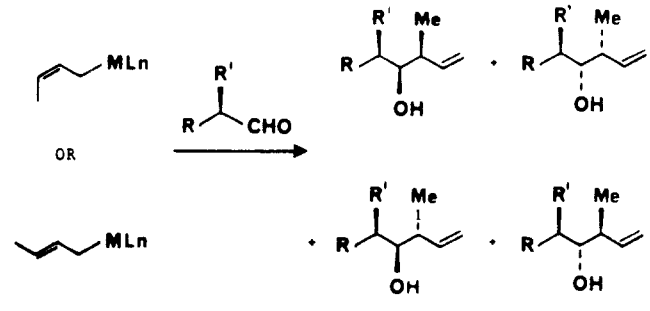
The reactions of crotylmetal reagents and propionate enolate equivalents with chiral carbonyl compounds are of considerable interest in the context of acyclic stereoselective synthesis.[3-6] These transformations generate two new stereochemical relationships and, potentially, four diastereomeric products. 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]



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