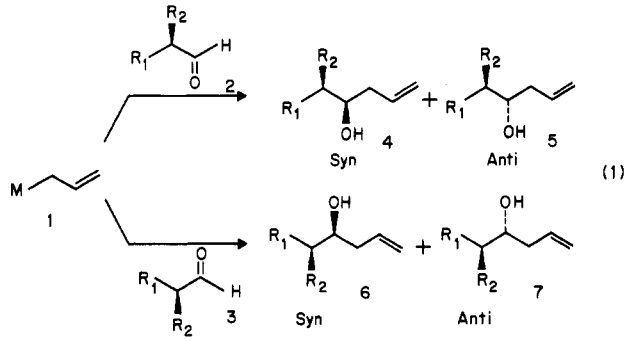
B-Allyldiisopinocampheylborane: A Remarkable Reagent for the Diastereoselective Allylboration of α-Substituted Chiral Aldehydes

Summary: *B*-Allyldiisopinocampheylboranes [**8**, prepared from (+)-α-pinene; **9**, prepared from (−)-α-pinene] were screened for diastereofacial selectivity in their reaction with α-substituted chiral aldehydes. These reagents are the most highly diastereoselective allylboranes reported to date and appear ideally suited for use in synthetic organic chemistry as enolate equivalents.

Sir: The reaction of allylmetal reagents and enolate equivalents with α-substituted chiral carbonyl compounds, the utility of the resulting alcohols in the construction of complex molecules, and their essential feature as biosynthetic intermediates have been amply demonstrated.[2-5] Many allylic organometallic reagents (allyl-M, such as M = Li, B, Si, etc.) react smoothly with carbonyl compounds to yield the corresponding homoallylic alcohols.[6] Reactions of this type have significant advantages over enolate-derived products in that the newly formed alkenes may be readily transformed into aldehydes. In addition, the alkenes may be selectively epoxidized, thus readily introducing a third chiral center.

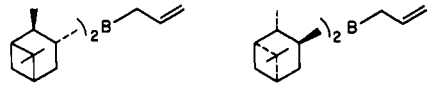
Like enolates, allylic organometallic reagents react with α-substituted chiral aldehydes to furnish diastereomeric mixtures of syn and anti alcohols (eq 1). Enantiomeric



homoallyl alcohol units (eq 1, $R_1 = CH_3$; $R_2 = C_2H_5$, OBz) of both syn and anti configurations constitute a characteristic structural feature of numerous macrolide and polyether antibiotics.[7] The major problem in stereocontrol concerns the selectivity between syn and anti products, which differ in the relative configuration of the newly formed stereocenter at the aldehydic carbonyl position with respect to the existent stereocenter originally present in the aldehyde. Although considerable effort has been devoted to the elucidation of the stereochemistry of the reaction of allylmetal compounds with chiral aldehydes, the stereoselectivity achieved in such synthesis has usually been relatively low. Hence the development of new allyl organometallic reagents possessing high stereoselectivities remains a desirable goal.

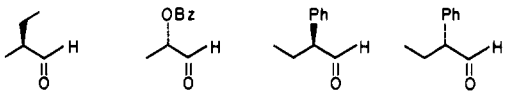
We discovered that readily synthesized simple allylic diisopinocampheylborane derivatives (Ipc_2BR, R = allyl,[8a] 2-methylallyl,[8b] 3,3-dimethylallyl,[8c] 2-cyclohexenyl,[8d] (*Z*)- and (*E*)-crotyl,[8e] Ipc = isopinocampheyl) yield the corresponding homoallylic alcohols on treatment with achiral aldehydes, with excellent enantioselectivities.[8f] There was considerable interest in extending this promising asymmetric synthesis to the stereoselective synthesis of both syn and anti homoallyl alcohols (eq 1) by employing *B*-allyldiisopinocampheylborane with α-substituted chiral aldehydes.

In this communication we wish to report the first example of very high diastereoselective addition of *B*-allyldiisopinocampheylboranes (**8** and **9**) with α-substituted chiral aldehydes to yield the enantiomeric syn and anti homoallylic alcohols in high optical purities.[9]



8 **9**

The reagents, *B*-allyldiisopinocampheylboranes, are readily obtained by hydroboration of α-pinene [**8**, prepared from (+)-α-pinene; **9**, prepared from (−)-α-pinene]. The α-substituted chiral aldehydes, (*S*)-2-methylbutyraldehyde (**10**), (*S*)-2-(benzyloxy)propionaldehyde (**11**), (*S*)-2-phenylbutyraldehyde (**12**), and (*R*)-2-phenylbutyraldehyde (**13**) were selected for initial screening of the reagents **8** and **9**. All allylboration reactions were carried out at −78



10 **11** **12** **13**

°C in ether solvent on a 10-mmol scale. These reactions are extremely rapid and require less than 3 h at −78 °C. The reaction mixture was worked up using alkaline hydrogen peroxide to remove the boron intermediate.[10] The diastereofacial selectivities of the reagents **8** and **9** with chiral aldehydes **10**–**13** are easily assessed by monitoring the overall diastereoselectivities achieved in the reaction.

(1) Postdoctoral research associate on Grant GM 10937-24 from the National Institutes of Health.

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(9) See ref 5a for related studies describing the addition of allylboronate derivatives to α,β-dialkoxy aldehydes utilizing tartaric esters as the chiral auxiliary.

(10) Alternatively, the boron intermediate can be removed by precipitation with ethanolamine.[8d]

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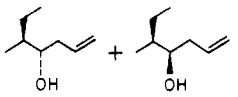
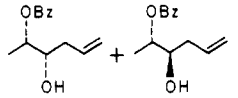
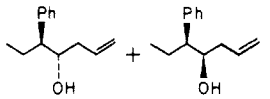
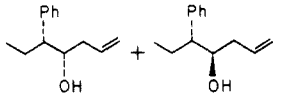
Table I. Reaction of Chiral Aldehydes 10-13 with the Reagents 8 and 9[a,b]

aldehydes[c]	reagents (yield, %)[d]	diastereomeric ratio[e,f]
10	(81) →	
	8	96:4
	9	5:95
11	(80) →	
	8	94:6
	9	4:96
12	(74) →	
	8	97:3
	9	26:74
13	(72) →	
	8	67:33
	9	2:98

[a] All of the reactions were carried out at −78 °C under a nitrogen atmosphere.[11] [b] Reactions were carried out with a 1:1 molar ratio of reagent to chiral aldehyde. [c] Chiral aldehydes (**10**, 95% ee; **11**, 98% ee; **12** and **13**, 80–85% ee) were prepared, stored, and used in solution. The optical purity of all aldehydes were routinely checked by comparing the optical rotations of the corresponding alcohols produced by BMS reduction of the aldehydes. [d] Isolated yield. [e] The ratios of diastereomers were determined by capillary GC analysis of the MTPA esters of the product alcohols using a column, methyl silicone, 50 M × 0.25 mm, except in the reaction of **11** with **8** and **9**. In addition to the presence of the desired two diastereomers, the capillary GC analysis revealed the presence of 2–9% of the other two diastereomers, presumably arising from the presence of small amounts of the other enantiomeric aldehyde. Hence, the diastereomeric ratios were calculated from the two most prominent products postulated to arise from the enantiomerically pure aldehyde present in major amounts. In the reaction of **11** with **8** and **9**, the diastereomeric ratios were obtained by direct capillary GC analysis of the product alcohols using a column, methyl silicone, 50 M × 0.25 mm. [f] Configurations of the newly formed stereocenter at the aldehydic carbonyl position are predicted by analogy to the configuration realized in the products obtained in the reaction of the allyldiisopinocampheylborane derivatives with achiral aldehydes.[8f]

The results are summarized in Table I.

The reagent **8** adds to chiral aldehyde **10** with very high diastereofacial selectivity (96:4). In the reaction of the antipodal reagent **9** with aldehyde **10**, the facial selectivity is completely reversed (5:95). Similar selectivities are exhibited by the reagents **8** and **9** with chiral aldehyde **11** (the reagent **8** furnished 94:6 and **9** furnished 4:96). Even the aldehyde **12** with a more bulky α-substituent exhibited excellent facial selectivity (97:3) with reagent **8** and a moderately lower facial selectivity (26:74) with reagent **9**. Similar selectivities are observed for the antipodal aldehyde **13** with reagents **8** and **9** (the reagent **8** providing 67:33 and **9** providing 2:98).

It is clear from these results that the allyldiisopinocampheylboranes **8** and **9** are highly diastereoselective reagents with α-substituted chiral aldehydes **10–13**. The stereochemistry at the carbonyl carbon of the aldehyde is controlled simply by selecting the appropriate enantiomeric reagent, either **8** or **9**; thus, the chirality of the reagent controls the overall diastereofacial selectivity achieved in the reaction. This synthesis is operationally very simple, providing access to all four possible syn and anti stereoisomers in high optical purity merely by selecting the proper antipode of α-pinene in the preparation of the reagent and either *R* or *S* α-substituted chiral aldehyde. These results further demonstrate the superior chiral-directing properties of the 3-pinanyl group in asymmetric synthesis. Thus the results presently available reveal that the Ipc_2B allyl derivatives, such as **8** and **9**, are not only the most enantioselective[8] but also the most diastereoselective derivatives available for allylborations.

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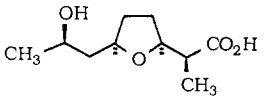
Stereoselective Synthesis of (±)-Methyl Nonactate[1]

Summary: Racemic methyl nonactate has been prepared in 11 steps from 2,2-dimethyl-3(2*H*)-furanone with the diastereoisomeric relationships between C-2 and C-3, C-3 and C-6, and C-6 and C-8 established with stereoselectivities of 32:1, 50:1, and 24:1, respectively.

Sir: Nonactic acid (**1**) is the monomeric subunit of the macrotetrolide nonactin, a meso [(+), (−), (+), (−)] ionophoric antibiotic isolated from a variety of *Streptomyces* cultures.[2] Synthetic effort in this area has been brisk, with eleven reported syntheses of the nonactic acid subunit,[3] four in optically active form[3h,j,k,o] and three of which have also resulted in syntheses of nonactin itself.[3b,e,h] In most cases the levels of relative stereochemical control have not been outstanding at all stages.



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(1) (a) Presented in part at the 189th National Meeting of The American Chemical Society, Miami Beach, FL, April 28–May 5, 1985; paper ORGN 0032. (b) Taken in part from the Ph.D. Dissertation of J.M.M. (Duke University, 1985). (c) All new stable compounds gave satisfactory elemental analyses and spectral data (IR, ^1H NMR, ^{13}C NMR) consistent with the assigned structures.

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