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3,3-DIMETHYLALLYLDIISOPINOCAMPHEYLBORANE: A NOVEL REAGENT FOR CHIRAL ISOPRENYLATION OF ALDEHYDES. SYNTHESIS OF (+)- AND (-)-ARTEMISIA ALCOHOL IN EXCEPTIONALLY HIGH ENANTIOMERIC PURITY

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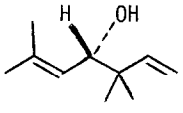
Summary: 3,3-Dimethylallyldiisopinocampheylborane, on condensation with aldehydes, furnishes 3,3-dimethyl-1-alken-4-ols in 89-96% ee, including artemisia alcohol (96% ee) in both natural enantiomeric forms.

Terpenes constitute one of the most fascinating classes of organic compounds in nature. The great majority of terpenes can be represented by the head-to-tail union of isoprene units. However, there are a few less common terpenes that must be represented by non-head-to-tail union of isoprene units. Such "irregular" terpenes are often chemically and biologically interesting. (-)-Artemisia alcohol 1, an acyclic monoterpene containing two isoprene units joined in non-head-to-tail fashion, has been isolated from several plant species.[1] The existence of the relatively rare (+)-enantiomer 2 came to light very recently (1980) when it was isolated from *Artemisia herba-alba*.[2] Herein we report the first asymmetric synthesis[3] of both of these enantiomers of artemisia alcohol, as well as a new general synthesis for 3,3-dimethyl-1-alken-4-ols *via* non-head-to-tail isoprenylation of aldehydes with 3,3-dimethylallyldiisopinocampheylborane, 3.



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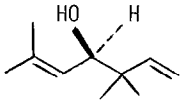

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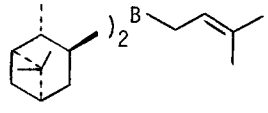
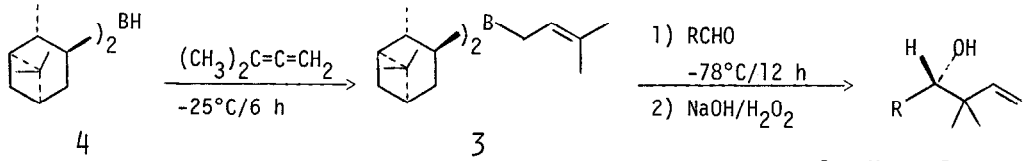


3

Our earlier study with allyldiisopinocampheylborane[4] suggested that boranes containing two isopinocampheyl groups associated with an allylic moiety might provide a general reagent to

achieve chiral allylboration. Hydroboration of 3-methyl-1,2-butadiene gives such a reagent containing the 3,3-dimethylallyl moiety 3. In such structures, boron prefers the less hindered allylic position.[5] The evidence is that in the allylboration of carbonyl groups the reaction takes place exclusively *via* a six-membered transition state.[5] If the same reaction pathway occurs with the diisopinocampheylborane derivative 3, the proper location of the *gem*-dimethyl group would be achieved to provide the desired non-head-to-tail orientation. Both enantiomers of 3 can be readily prepared by selecting the proper isomer of α-pinene to prepare the reagent.

Initial study involved preparation of the reagent and its application to simple model compounds. The preparation of 3,3-dimethylallyldiisopinocampheylborane 3 is extremely simple. Thus, 3-methyl-1,2-butadiene, on hydroboration (-25°C/6 h) with 99% ee (+)-diisopinocampheylborane[6] 4 prepared from (-)-α-pinene[7] of 92% ee, provided 3 in quantitative yield. Condensation of 3 with acetaldehyde (-78°C/12 h), followed by oxidation of the boron intermediate with alkaline hydrogen peroxide, furnished 3,3-dimethyl-4-penten-2-ol in 91% ee (eq 1, R = Me).



4 3 (1)

R = Me, *n*-Pr, *iso*-Pr

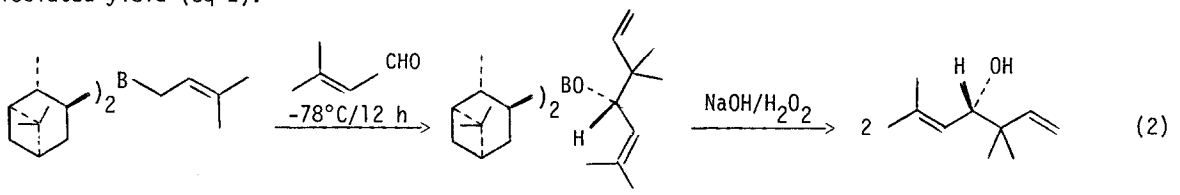
The reagent 3 is generally applicable to a variety of aldehydes, such as *n*-butyraldehyde and isobutyraldehyde (eq 1; R = *n*-Pr, *iso*-Pr).

In this way, 3,3-dimethyl-1-alken-4-ols with enantiomeric purities in the range of 89-96% are readily obtained. Presence of the exposed double bond does not interfere, as shown by the corresponding reaction involving acrolein (Table 1).

It is of special interest to note that the asymmetric synthesis of highly hindered *tert*-butyl alkyl carbinols in excellent ee is difficult. Midland's reagent works well for many carbonyl systems.[8] However, reductions of ketones containing a tertiary alkyl group adjacent to the carbonyl does not give useful asymmetric induction. For example, both *tert*-butyl methyl ketone and 2,2-dimethyl-4-yne-3-one give alcohols of low ee.[8b,c] Hydrogenation[9] of 3,3-dimethyl-1-alken-4-ols obtained by the present method could give a simple route to such highly hindered *tert*-amyl alkyl carbinols in excellent ee.

The new method was immediately applied to the synthesis of artemisia alcohol in both natural enantiomeric forms. Condensation of 3, prepared from (-)-α-pinene,[7] with 3-methyl-2-butenal[10]

(-78°C/12 h), followed by oxidation of the borinate 5 with alkaline hydrogen peroxide, furnished (-)-artemisia alcohol 1, $[\alpha]^{23}D$ -32.12 (neat), 96% ee (natural isomer ref 1a; $[\alpha]^{20}D$ -31.8) in 85% isolated yield (eq 2).



(2)

3 5 1, 96% ee

Similarly, (+)-artemisia alcohol 2, $[\alpha]^{23}D$ +32.10 (neat), was prepared in 96% ee by condensing 3-methyl-2-butenal[10] with 3,3-dimethylallyldiisopinocampheylborane derived from (+)-α-pinene. The results of these reactions are summarized in Table 1.

Table 1. Condensation of Aldehydes with 3,3-Dimethylallyldiisopinocampheylborane[a]

Aldehyde	Alcohol	Yield (isolated)	$[\alpha]^{23}D$ deg C (neat)	% ee[c]	Config.[d]
Acetaldehyde	3,3-dimethyl-4-penten-2-ol	73	-5.95	91	*(S)*
n-Butyraldehyde	3,3-dimethyl-1-hepten-4-ol	79	-38.56	92	*(S)*
2-Methylpropionaldehyde	2,4,4-trimethyl-5-hexen-3-ol	73	-27.95	89	*(S)*
Acrolein	4,4-dimethyl-1,5-hexadien-3-ol	70	-41.53	95	*(S)*
3-Methyl-2-butenal	3,3,6-trimethyl-1,5-heptadien-4-ol	85	-32.12	96	*(S)*
3-Methyl-2-butenal	3,3,6-trimethyl-1,5-heptadien-4-ol[b]	83	+32.10	96	*(R)*

[a](-)-Pinene was used to prepare the reagent. [b](+)-α-Pinene was used to prepare the reagent. [c]As determined by ^1H NMR in the presence of chiral shift-reagent tris[[(heptafluoroprop-1-yl)-hydroxymethylene]-*d*-camphorato]europium (III). [d]Configurations are predicted in analogy to the configurations of the products obtained with allyldiisopinocampheylborane.[4]

The present method reports the first chiral general synthesis for non-head-to-tail isoprenylation of aldehydes. This operationally simple, one-pot procedure makes use of readily available chemicals to provide the product alcohols in high chemical yields and enantiomeric purities. The usefulness of the method is elegantly demonstrated by its application to the synthesis of both

enantiomers of natural artemisia alcohol in 96% ee, as well as in establishing the absolute configuration of the two enantiomers.

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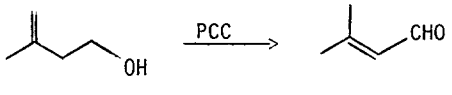

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