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B-2'-ISOPRENYLDIISOPINOCAMPHEYLBORANE: AN EFFICIENT REAGENT FOR THE CHIRAL ISOPRENYLATION OF ALDEHYDES. A CONVENIENT ROUTE TO BOTH ENANTIOMERS OF IPSENOL AND IPSDIENOL

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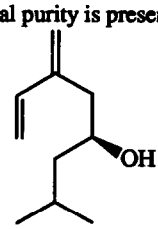
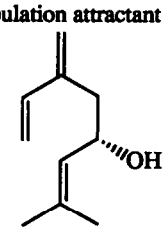
Summary: *B*-2'-Isoprenyldiisopinocampheylborane is prepared by metallation of isoprene with potassium 2,2,5,5-tetramethylpiperidide followed by sequential treatment with *B*-methoxydiisopinocampheylborane and boron trifluoride-etherate. Condensation of this reagent with aldehydes provides isoprenylated chiral alcohols. This methodology is utilized for an efficient one-pot synthesis of both enantiomers of the pheromones of the bark beetle *Ips paraconfusus* Lanier, ipsenol and ipsdienol in 96% ee and 65% isolated yields.

Ipsenol, **1** and ipsdienol, **2** are two of the aggregation pheromones isolated from the bark beetle *Ips paraconfusus* Lanier whose structures have been elucidated by spectral data and confirmed by synthesis.[2] While the natural ipsenol with the *S* configuration is levorotatory,[3] the natural ipsdienol with the *S* configuration is dextrorotatory.[4] Field tests using optically active ipsenol and ipsdienol have been conducted and the pheromonal chirality and integrity of aggregation responses have been reported.[5] Again, it has been demonstrated that the five-spined engraver beetle, *Ips grandicollis*, aggregates only in response to (*S*)-ipsenol.[6] Ipsenol and ipsdienol constitute aggregation pheromones of the spruce-infesting bark beetle, *Ips typographus* [7]and ipsdienol of unknown configuration and optical purity is present in the population attractant of *Ips sexdentatus*.[8]



Ipsenol, **1**



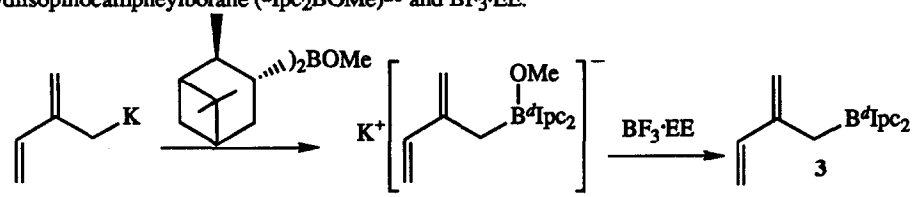
Ipsdienol, **2**

Though many syntheses of racemic ipsenol and ipsdienol are available in the literature,[9] it was Mori who first synthesized both of these pheromones in optically active form and assigned their configurations.[3, 4] Mori's initial synthesis of ipsenol, starting from leucine, was both lengthy and cumbersome. Moreover, the chemical (~5%) and optical yields (80%) were low.[3a] Later, Mori modified his procedure to obtain optically pure **1** (≥99% ee) but the overall yield still remained low.[3b] Ipsdienol was synthesized by Mori in 38% ee using D-mannitol as the starting substrate.[4a] A synthesis of *S*-(+)-ipsdienol starting from (*R*)-malic acid gave 90% ee for the pheromone.[4b] More enantioselective syntheses have been reported since then. Ohloff and Giersch prepared ipsdienol in 91% ee (*R*) and 80% ee (*S*) from the enantiomers of verbenone *via* the corresponding β-pinene-4-ols.[10] Norin prepared racemic ipsdienol *via* sensitized photooxidation of commercially available myrcene followed by acid catalyzed rearrangement.[11] Oxidation of the *tertiary* alcohol obtained from photooxidation to myrcenone, followed by asymmetric reduction of the carbonyl moiety using Noyori's Binal-H[12] provided both enantiomers of ipsdienol in 63% ee. Modified Binal-H provided ipsdienol of even lower optical purity.[11]

Hisashi Yamamoto's condensation of isovaleraldehyde with the tartrate ester of allenyl boronic acid provided the corresponding homopropargylic alcohol which was further elaborated to the 2-brominated alcohol. Protection of the alcohol as the tetrahydropyranyl ether followed by treatment with the vinyl Grignard reagent and deprotection furnished (–)-ipsenol in >99% ee.[13]

We have demonstrated the utility of B-2'-isoprenyl-9-borabicyclo[3.3.1]nonane for the isoprenylation of aldehydes which provided a highly convenient synthesis of racemic ipsenol and ipsdienol in high yields.[14] This coupled with our success in asymmetric synthesis with chiral organoboranes, prompted us to undertake the synthesis of these pheromones in optically active form. As part of our 'Chiral Synthesis *via* Organoboranes' program,[15] we have recently shown that chiral allylboranes[16] and crotylboranes[17] can be condensed with aldehydes to produce optically active homoallyl and β-methyl homoallyl alcohols, respectively. Accordingly, we tested the isoprenylation reaction for the synthesis of chiral isoprenyl alcohols.

Our previous success employing α-pinene as a chiral ligand[18] suggested that the isopinocampheyl (Ipc) moiety might prove useful for the isoprenylation reaction also. The reagent *B*-2'-isoprenyldiisopinocampheylborane, **3** was synthesized by the reaction of 2'-isoprenylpotassium[14,19] with *B*-methoxydiisopinocampheylborane (^{d}Ipc$_2$BOMe)[20] and BF_3·EE.



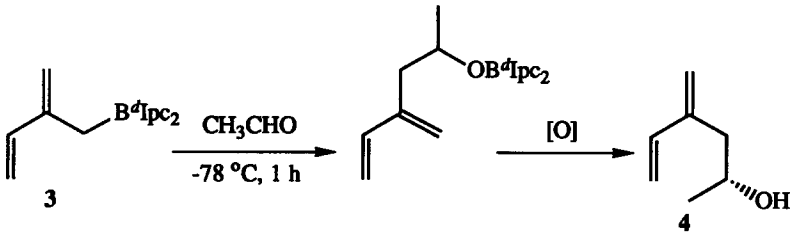
Reagent **3**, upon condensation with several representative aldehydes provided the corresponding chiral homoallylic alcohols. The ee value was established by capillary GC examination of diastereomeric esters. The results are summarized in Table 1.

Table 1. Asymmetric Isoprenylation of Representative Aldehydes With B-2'-^{d}Isoprenyldiisopinocampheylborane

aldehyde	product	yield,[a] %	$[\alpha]_D^{23}$	% ee	confign.
acetaldehyde	(–)-4-methylene-5-hexene-2-ol	65	–19.24° (neat)[b]	90[c]	*R*[d]
2-methyl-propionaldehyde	(–)-2-methyl-5-methylene-6-hepten-3-ol	65	–10.26° (neat)[b]	92[e]	*S*[d]
benzaldehyde	(–)-3-methylene-1-phenyl-4-penten-1-ol	60	–23.56° (*c* 1, MeOH)	93[e]	*S*[d]
isovaleraldehyde	(+)-2-methyl-6-methylene-7-octen-4-ol	60	+17.30° (*c* 1, EtOH)	94[c]	*R*[f]
isovaleraldehyde	(–)-2-methyl-6-methylene-7-octen-4-ol (ipsenol)[g]	65	–17.67° (*c* 1, EtOH)	96[c]	*S*[f]
β,β-dimethylacrolein	(+)-2-methyl-6-methylene-2,7-octadien-4-ol (ipsdienol)	60	+13.18° (*c* 1, MeOH)	96[h]	*S*[i]
β,β-dimethylacrolein	(–)-2-methyl-6-methylene-2,7-octadien-4-ol[g]	60	–13.11° (*c* 1, MeOH)	96[h]	*R*[i]

[a]Isolated yield. [b]Observed rotation. [c]Determined as (–)-menthyl chloroformate (MCF) derivative on a capillary gas chromatograph (GC). [d]Based on analogy with entries 4-7. [e]Determined as (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetates (MTPA) derivative on a capillary GC. [f]From ref. 3. [g]For the reagent **5** prepared from [l]Ipc$_2$BOMe, ref. 20. [h]Determined by comparison with maximum rotation reported: ref. 4b. [i]From ref. 4.

For example, a reaction of **3** with acetaldehyde at –78 °C, for 1 h, provided the borinate which following alkaline hydrogen peroxide oxidation afforded (*R*)-4-methylene-5-hexen-2-ol, **4** in 65% isolated yield and 90% ee: $\alpha_D^{23} = -19.24°$ (neat).

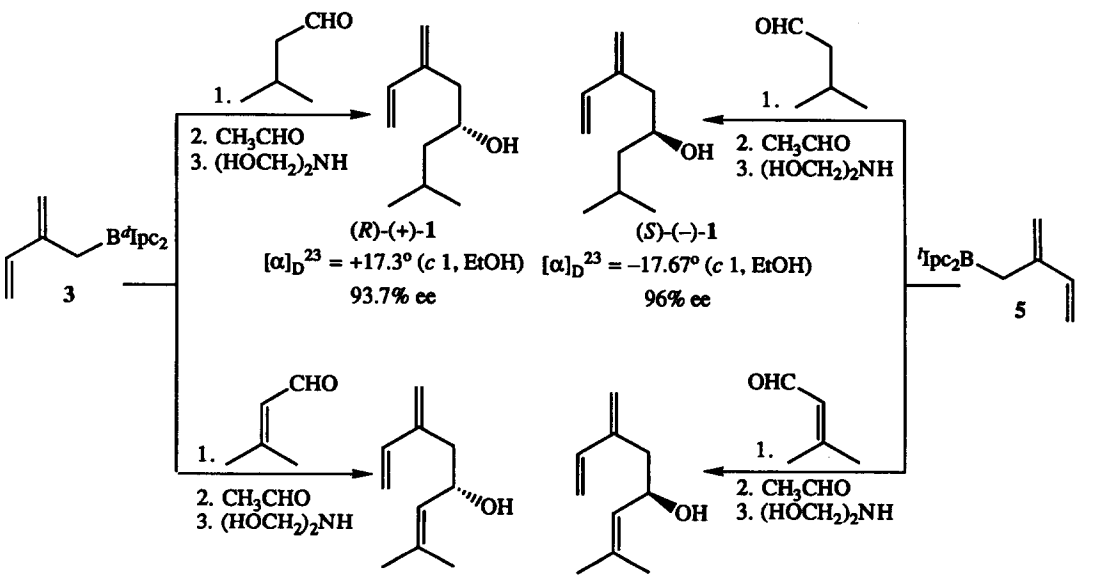


3 **4**

$\alpha_D^{23} = -19.24°$ (neat)

90% ee

This synthetic methodology was then applied to the preparation of both enantiomers of the sex pheromones ipsenol and ipsdienol by reacting the stereoisomers of *B*-2'-isoprenyldiisopinocampheylborane, **3** or **5**, with isovaleraldehyde and β,β-dimethylacrolein, respectively. The product alcohols were isolated by a non-oxidative workup: i.e. addition of acetaldehyde to the reaction mixture converting the borinate intermediate into the corresponding boronate with simultaneous displacement of α-pinene. Addition of diethanolamine precipitated the boron components and the products were isolated from the filtrate by distillation. (*S*)-(-)-Ipsenol was prepared in 96% ee and the enantiomer in 94% ee, while both isomers of ipsdienol were synthesized in 96% ee.



We believe our asymmetric approach to ipsenol and ipsdienol are superior to the procedures described previously for the following reasons: (1) facile preparation of **3** and **5**, (2) ease of subsequent reaction conditions and workup, (3) fewer steps conveniently carried out in a one-pot procedure, (4) high chemical yield and purity

of products , (5) high optical purity of products, (6) amenable to easy scale-up, (7) simple recovery of chiral auxilliary, and most important of all, (8) both enantiomers of α-pinene are readily available.

This asymmetric isoprenylation of aldehydes further indicates the remarkable synthetic utility of chiral organoboranes.[21]

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