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TETRAHEDRON: *ASYMMETRY*

A simple synthesis of (−)-(*R*)-ipsdienol and (−)-(*S*)-ipsenol

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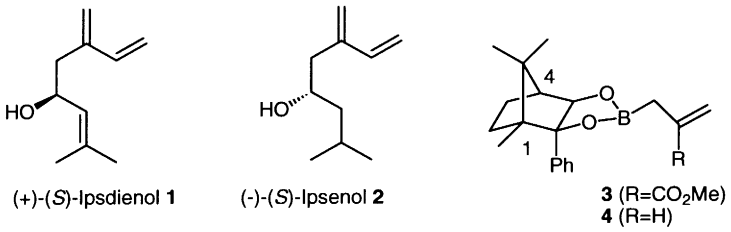
Abstract

A short and efficient synthesis of the unnatural enantiomer of (+)-(*S*)-ipsdienol **1** and (−)-(*S*)-ipsenol **2** is presented via an asymmetric allylboration. The synthesis was achieved by using a one-pot reduction–methylenation of an *exo*-methylene lactone intermediate. © 1999 Elsevier Science Ltd. All rights reserved.

The synthesis of isoprenylated naturally occurring materials, especially the synthesis (+)-(*S*)-ipsdienol **1** and (−)-(*S*)-ipsenol **2**, principal components of the aggregation pheromones of *Ips paraconfusus*,[1] a bark beetle of California ponderosa pine, has been the subject of numerous synthetic approaches.[2] In connection with our synthetic studies on the application of the allylation of aldehydes with chiral allylic boron reagents,[3] we found that (+)-(1*R*,2*R*,3*R*,4*S*)-2-*endo*-phenyl-2,3-*exo*-bornanediol β-functionalized allylboronate **3**[4] provides one of the most convenient and simple routes to this series of natural compounds and we describe herein the synthesis of the unnatural enantiomer of (+)-(*S*)-ipsdienol **1** and of (−)-(*S*)-ipsenol **2** (Scheme 1).



(+)-(*S*)-Ipsdienol **1** (-)-(*S*)-Ipsenol **2** **3** (R=CO_2Me) **4** (R=H)

Scheme 1.

Condensation of the chiral allylic β-functionalized allylboronate **3** with β,β-dimethylacrolein **5** in toluene at room temperature gave, after 8 days, the homoallylic alcohol **6** in 82% yield after purification (Scheme 2). Analysis of the proton NMR spectrum of the (*R*)-*O*-acetylmandelic ester derivative from alcohol **6** indicated an enantiomeric excess of 88%, as well as unambiguous proof of the (*R*)-absolute configuration.[5,6] This absolute configuration is in agreement with the proposed transition state of this

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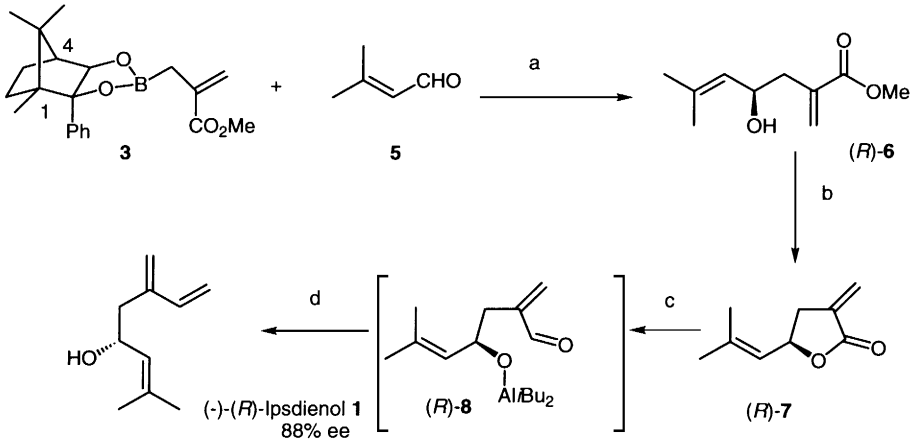
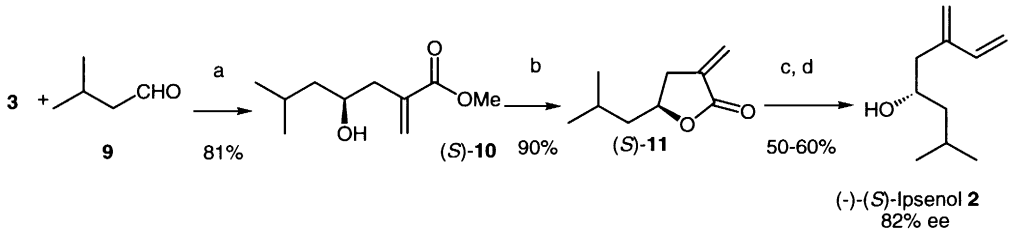
allylation.[3,7] The homoallylic alcohol **6** was carefully[8] treated with sodium hydride to afford the corresponding lactone **7** in high yield. We next examined the one-pot two-step reactions: reduction/Wittig methylenation of lactone **7**. Thus, reduction of this chiral material **7** with diisobutylaluminium hydride (DIBAL-H) in toluene at low temperature,[9,10] followed by in situ condensation of the corresponding *exo*-methylene aldehyde intermediate **8** with triphenyl(methylidene)phosphorane (formed from the phosphonium bromide using *n*-BuLi as a base), afforded the (−)-(*R*)-ipsdienol **1** in an acceptable yield (50–60%)[10] and in 88% ee, as determined by (*R*)-*O*-acetylmandelic ester analysis. Attempts to improve the yield of this one-pot procedure by changing either the nature of the base used to form the ylide [*tert*-BuOK, sodium bis(trimethylsilyl)amide (NaHMDS)] and/or the solvent used in the reduction step (THF instead of toluene) were unsuccessful. Nevertheless, close analysis of the proton NMR spectrum of the crude product showed that no by-product was formed in this step. Thus, it seems reasonable to consider that the modest yield is essentially due to the high volatility of the (−)-(*R*)-ipsdienol **1**. To underline the efficiency of this transformation, it should be pointed out that under our conditions no migration and/or over-reduction of the *exo*-methylene occurred.



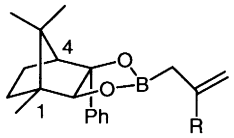
Scheme 2. *Reagents and conditions*: (a) toluene, 8 days, rt, 82%; (b) 1.0 equiv. NaH, THF, 1 min, 0°C, 93%; (c) 1.3 equiv. DIBAL-H, toluene, 1 h, −78°C; (d) 2.3 equiv. $Ph_3P{=}CH_2$, THF, rt, 50–60%

The (−)-(*S*)-ipsenol **2** (40% overall yield, 82% ee) was synthesized using the same sequence starting from 3-methylbutyraldehyde **9** as described in Scheme 3.



Scheme 3. *Reagents and conditions*: see Scheme 2

To complete this work, the synthesis of (+)-(*S*)-ipsdienol **1** and the unnatural enantiomer of (−)-(*S*)-ipsenol **2** was attempted using the (1*R*,2*S*,3*S*,4*S*)-3-*endo*-phenyl-2,3-*exo*-bornanediol allylboronate **12** (R=CO_2Me), an isomer of **3**. The chiral intermediate diol of **12** was prepared from natural (−)-camphor following Hoffmann's procedure.[4]



12 (R=CO_2Me)
13 (R=H)

As reported in the literature,[4,11] the condensation of **13** (R=H) with acetaldehyde afforded the corresponding (*R*)-(−)-pent-4-en-2-ol **14** in 86% yield with 86% ee. On the other hand, with the allylboronate **4** (R=H) the (*S*)-(+)-pent-4-en-2-ol **15** is obtained in 92% yield with only 38% ee. From **12** (R=CO_2Me) the sequence described in Schemes 2 and 3 was applied from β,β-dimethylacrolein **5** and 3-methylbutyraldehyde **9** to give the corresponding (+)-(*S*)-ipsdienol **1** and the unnatural enantiomer of (−)-(*S*)-ipsenol **2**, respectively, with 25 and 20% ee.

Obviously, if the absolute configurations observed in all the cases summarized in Table 1 are in accord with the proposed transition state,[3,7] the disappointing values of the ees in our cases with the chiral reagent **12** are difficult to explain. The β-functionalized allylboronates are less reactive compared to simple allylboronates. However, the position of the methyl group on C-1 in these chiral auxiliaries seems to be crucial for the enantioselectivity. It is noteworthy that moving the methyl group in the allylboronate **3** from C-1 to C-4 should give the enantiomer of **12**, in which the ee is lower. The same observation may be done between **4** and **13**, but in this case the ee with the late allylboronate is higher.

Table 1
Enantiomeric excesses and absolute configuration of homoallylic alcohols from condensation of aldehydes with chiral allylic boron reagents (**3**, **4**, **12** and **13**)

	CH_3CHO [4,11]	5 CHO	9 CHO
3 (R=CO_2Me)		(*R*)-**6** 88% ee	(*S*)-**10** 82% ee
4 (R=H)	(*S*)-**15** 38% ee		
12 (R=CO_2Me)		(*S*)-**6** 20% ee	(*R*)-**10** 25% ee
13 (R=H)	(*R*)-**14** 86% ee		

Our synthetic samples of ipsdienol **1** and ipsenol **2** exhibit spectral data in agreement with those reported.[2]

Compared to the reported methods, our synthesis constitutes a straightforward route to these natural products. If desired, this synthesis could also be applied for the preparation of either natural antipode of **1** starting from commercially available unnatural (−)-camphor to prepare the (−)-(1*S*,2*S*,3*S*,4*R*)-2-*endo*-phenyl-2,3-*exo*-bornanediol β-functionalized allylboronate **3**.

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6. Characterization data of the (*R*)-*O*-acetylmandelic ester derivative of (*R*)-**6**: Major diastereoisomer (*R*,*R*): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (br s, 3H, CH_3), 1.61 (br s, 3H, CH_3), 2.17 (s, 3H, CH_3-CO), 2.58 (d, 2H, CH_2, J=7.3 Hz), 3.74 (s, 3H, CH_3O), 4.88 (d, 1H, -HC=, J=9.0 Hz), 5.56 (s, 1H, CH-OCH_3), 5.67 (m, 1H, CH-O), 5.88 (s, 1H, =CH), 6.17 (br s, 1H, =CH), 7.33–7.45 (m, 5H, H aromatic). Minor diastereoisomer (*R*,*S*): 1.71 (br s, 6H, CH_3), 2.16 (s, 3H, CH_3-CO), 2.40 (d, 2H, CH_2, J=7.3 Hz), 3.70 (s, 3H, CH_3O), 5.00 (s, 1H, CH-O), 5.14 (d, 1H, -HC=, J=9.0 Hz), 5.71 (m, 1H, CH-O), 5.78 (br s, 1H, =CH), 5.87 (s, 1H, =CH), 7.33–7.45 (m, 5H, H aromatic).
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