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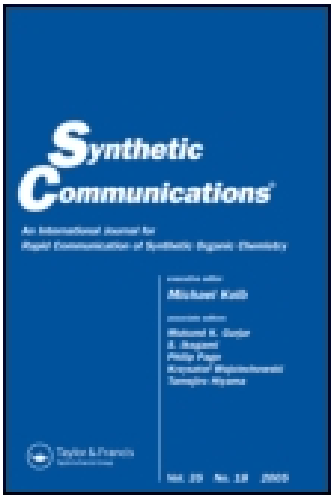

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Enantioselective Synthesis of Ipsenol and Ipsdienol Using a (2-Bromoallyl)borane Derivative

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Published online: 22 Aug 2006.

To cite this article: Yasunori Yamamoto , Shoji Hara & Akira Suzuki (1997) Enantioselective Synthesis of Ipsenol and Ipsdienol Using a (2-Bromoallyl)borane Derivative, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:6, 1029-1036, DOI: 10.1080/00397919708003047

To link to this article: http://dx.doi.org/10.1080/00397919708003047

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SYNTHETIC COMMUNICATIONS, 27(6), 1029-1036 (1997)

ENANTIOSELECTIVE SYNTHESIS OF IPSENOL AND IPSDIENOL USING A (2-BROMOALLYL)BORANE DERIVATIVE

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Abstract: (*S*)-(-)-Ipsenol (**2b**) and (*S*)-(+)-ipsdienol (**4b**), a major component of the sex pheromone of the bark beetle, and their enantiomers (**3b** and **5b**) were prepared enantioselectively using tartrate esters of (2-bromoallyl)boronic acid in the key step.

Recently we have reported the facile synthesis of (2-bromoallyl)dialkoxyborane (**1a**) using the bromoboration reaction of allene and its reaction with carbonyl compounds.[2] We also reported the asymmetric synthesis of 2-bromohomoallylic alcohols by the reaction of the chiral tartrate esters of (2-bromoallyl)boronic acid prepared from **1a** with aldehydes.[3]

We wish to describe here the enantioselective synthesis of (*S*)-(-)-ipsenol (**2b**) and (*S*)-(+)-ipsdienol (**4b**), a major component of the sex pheromone of

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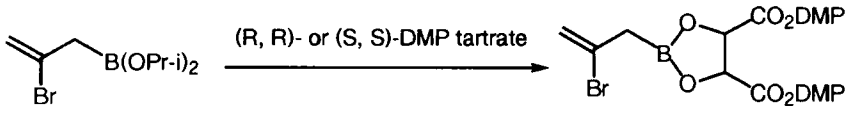
the bark beetle[4,5], and their enantiomers (**3b** and **5b**) using the chiral tartrate esters of (2-bromoallyl)boronic acid.

In a previous study,[3] bis(2,4-dimethyl-3-pentyl) tartrates (DMP tartrates) were found to be the most effective chiral auxiliary for the asymmetric synthesis of 2-bromohomoallylic alcohols. Chiral DMP tartrate esters of (2-bromoallyl)boronic acid (**1b**) were prepared from (*R*, *R*)- or (*S*, *S*)-DMP tartrate[5a] and (2-bromoallyl)diisopropoxyborane (**1a**) by a transesterification method (**Scheme 1**)[3] and used for the reaction with aldehydes without isolation.



1a

(R, R)-**1b**

(S, S)-**1b**

Scheme 1

The reaction of (*S*, *S*)-**1b** with 3-methylbutanal provided (*S*)-2-bromo-6-methyl-1-hepten-4-ol (**2a**) in 83 % yield and 90 %ee which was then converted to (*S*)-(-)-ipsenol (**2b**) in 82 % yield by the palladium-catalyzed cross-coupling reaction with vinyl magnesium bromide.[6] The enantiomeric excess value of **2b** was determined to be 90 %ee by ^{1}H NMR after conversion to (*R*)-(+)-MTPA ester. The absolute configuration of **2b** was shown to be the same as that of the natural product by comparison with the reported optical rotation.[7] (*R*)-(+)-Ipsenol (**3b**) of 91 %ee was prepared from (*R*)-2-bromo-6-methyl-1-hepten-4-ol (**3a**) which was obtained by the reaction of 3-methylbutanal and (*R*, *R*)-**1b** in 90 % yield and 93 %ee (**Scheme 2**).

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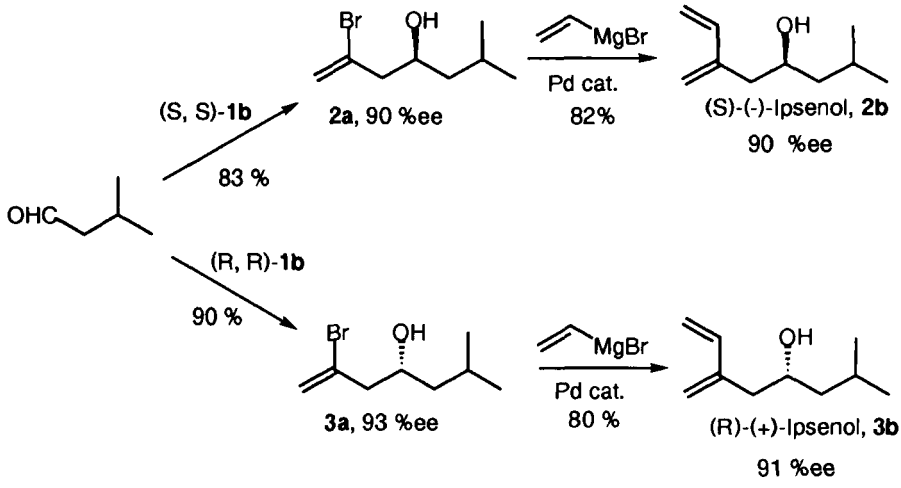

Scheme 2

For the preparation of (*S*)-(+)-ipsdienol (**4b**), 3-methyl-2-butenal was reacted with (*R*, *R*)-**1b** to afford (*S*)-2-bromo-1,5-heptadien-4-ol (**4a**) in 93 % yield and 87 %ee. The palladium-catalyzed cross-coupling reaction of **4a** with vinyl magnesium bromide gave **4b** in 85 % yield. As the MTPA ester of **4b** was unstable, the enantiomeric excess value as well as the absolute configuration was determined by the comparison of the specific rotation with the reported value of the pure compound.[7b] (*R*)-(-)-Ipsdienol (**5b**) was also prepared enantioselectively from 3-methyl-2-butenal in a similar way as **4b** using (*S*, *S*)-**1b** (**Scheme 3**).

Experimental

Materials. (*S*, *S*)- and (*R*, *R*)-Bis(2,4-dimethyl-3-pentyl) tartrates,[5a] (*R*)-(+)-MTPA chloride,[8] $(PPh_3)_4Pd$[9] were prepared according to the literature. Allene in a cylinder was purchased from PCR Inc. BBr_3 of 99.99 % purity was

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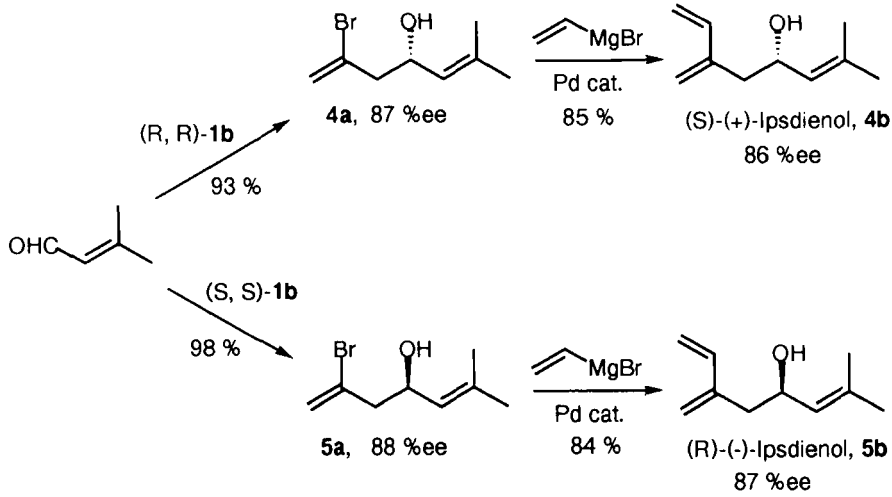

Scheme 3

purchased from Wako Pure Chemical Industries, Ltd., and used without purification. (*S*, *S*)- and (*R*, *R*)-Tartaric acids were purchased from Tokyo Kasei Kogyo Co., Ltd. (*R*)-(+)-MTPA was purchased from Aldrich Chemical Company, Inc.

(2-Bromoallyl)diisopropoxyborane 1a: A 200-mL three-necked flask was equipped with a magnetic stirring bar, a rubber septum, a dropping funnel, and an Allihn type condenser. To the top of the condenser, a 3 l Tedlar® (PVF) bag, a water aspirator through a calcium chloride tube, and an allene gas cylinder were connected with two three-way cocks. For the complete replacement, the flask and the bag were evacuated by the aspirator twice and filled with allene gas each time. The flask was cooled to -20 °C and then 10 ml (0.1058 mol) of tribromoborane was introduced through the rubber septum. When the allene in the bag was consumed completely, the cylinder was replaced by a nitrogen inlet tube and nitrogen was introduced into the flask. The mixture was stirred at -20

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°C for 30 min and then 30 ml of dry dichloromethane and 35 ml (0.25 mol) of diisopropyl ether in 50 ml of dry dichloromethane were added from the dropping funnel successively. The mixture was stirred at -20 °C for 30 min, at room temperature for 2 h, and finally under reflux for 1 h. The mixture was then cooled to room temperature and the volatile part was removed under reduced pressure. After the introduction of nitrogen, the residue was transferred to a distillation flask via a cannula through the septum inlet. The distillation under reduced pressure gave 18.4 g (79 %) of (2-bromoallyl)diisopropoxyborane as a clear moisture-sensitive liquid. B.p. 39-43 °C (0.4 mm); ^{1}H NMR ($CDCl_3$) δ = 5.53 (s, 1H), 5.36 (s, 1H), 4.67-4.16 (m, 2H), 2.26 (s, 2H), 1.20 (d, J = 6.3 Hz, 12H).

(*S*)-2-Bromo-6-methyl-1-hepten-4-ol 2a: To a dry flask connected to the nitrogen inlet and vacuum pump were introduced **1a** (498 mg, 2 mmol) and (*S*, *S*)-bis(2,4-dimethyl-3-pentyl) tartrate (1.038 g, 3 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and at 60 °C for 1 under reduced pressure to remove the liberated isopropyl alcohol. The mixture was then cooled to room temperature and nitrogen was introduced to the flask. After the addition of toluene (10 ml) and powdered molecular sieves 4 A (500 mg), the resulting heterogeneous mixture was cooled to -78 °C and 3-methylbutanal (86 mg, 1 mmol) in 3 ml of toluene was added. The mixture was stirred at -78 °C for 1 h and then 2 ml of water was added. After the extraction with ether, **2a** was isolated by column chromatography (silica gel/dichloromethane) in 83 % yield. The enantiomeric excess value was determined to be 90 %ee by ^{1}H NMR analysis after conversion to the diastereoisomeric mixture of (*R*)-(+)-MTPA esters.[8] The characteristic peaks

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for **2a** appeared at δ = 5.44 (s, 1H) and 5.32 (d, J = 0.2 Hz, 1H), while the minor peak derived from **3a** appeared at 5.62 (s, 1H) and 5.47 (d, J = 0.2 Hz, 1H). IR (neat) 3350 (-OH), 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.69 (s, 1H), 5.55 (s, 1H), 4.19-3.83 (m, 1H), 2.52 (d, J = 6.3 Hz, 2H), 1.97-1.19 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); $[\alpha]_D^{23}$ = -6.71 (c = 1.05, $CHCl_3$); The apparent lability of **2a**, **3a**, **4a** and **5a** allowed neither satisfactory exact mass spectra nor combustion analysis within acceptable ranges.[10]

(*S*)-(-)-Ipsenol 2b: To a toluene solution (8 ml) of **2a** (100 mg, 0.48 mmol) and $Pd(PPh_3)_4$ (30 mg) was added at 0 °C a THF solution of vinyl magnesium bromide (2 ml of 1 M solution, 2 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The consumption of **2a** was confirmed by glpc and then aqueous ammonium chloride was added. The product was extracted with ether three times and the combined organic layers were dried over magnesium sulfate. After the concentration under vacuum, **2b** was isolated by column chromatography (silica gel/hexane : ether = 2 : 1) in 82 % yield. The enantiomeric excess value was determined to be 90 %ee by ^1H NMR analysis of its (*R*)-(+)-MTPA ester. The characteristic peaks for **2b** appeared at δ = 5.01 (s, 1H) and 4.93 (s, 1H), while the minor peak derived from **3b** appeared at 5.11 (s, 1H) and 5.05 (s, 1H). IR 3400 (-OH) 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.33 (dd, J = 12, 17 Hz, 1H), 5.30-4.94 (m, 4H), 3.97-3.61 (m, 1H), 2.6-2.0 (m, 2H) 2.00-1.61 (m, 1H), 1.61-1.19 (m, 3H), 0.92 (d, J = 6 Hz, 3H), 0.88 (d, J = 6 Hz, 3H); $[\alpha]_D^{23}$ = -15.73 (c = 1.00, EtOH); exact mass calcd for $C_{10}H_{18}O$ 154.1412 found 154.1385.

(*R*)-2-Bromo-6-methyl-1-hepten-4-ol 3a: **3a** was prepared by the same procedure as **2a**, using (*R*, *R*)-bis(2,4-dimethyl-3-pentyl) tartrate instead of

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(*S*, *S*)-isomer, in 90 % yield and 93 %ee. All spectra except for optical rotation were the same as those of **2a**. $[\alpha]_D^{23}$ = +6.99 (c = 0.96, $CHCl_3$).

(*R*)-(+)-Ipsenol 3b: **3b** was prepared from **3a** by the same procedure as **2b** in 82 % yield and 90 %ee. All spectra except for optical rotation were the same as those of **2b**. $[\alpha]_D^{23}$ = +15.55 (c =1 .00, EtOH).

(*S*)-(+)-2-Bromo-6-methyl-1,5-heptadien-4-ol 4a: **4a** was synthesized by the same procedure as **2a**, using 3-methyl-2-butenal instead of 3-methylbutanal, in 93 % yield and 87 %ee. The characteristic peaks for MTPA ester of **4a** appeared at 5.02 (d, J = 0.9 Hz, 1H) in ^{1}H NMR analysis, while the minor peak derived from **5a** appeared at δ = 5.18 (d, J = 0.9 Hz, 1H). IR (neat) 3350 (-OH),1630 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 5.68 (s, 1H), 5.52 (s, 1H), 5.14 (d, J = 10 Hz, 1H), 4.81-4.57 (m, 1H), 2.65-2.53(m, 2H), 1.73 (s, 6H), 1.61 (s, 1H); $[\alpha]_D^{23}$ = +3.33 (c = 3.33, $CHCl_3$).

(*S*)-(+)-Ipsdienol 4b: **4b** was synthesized from **4a** by the same procedure as **2b** in 80% yield. The enantiomeric excess value of 86 %ee was determined by comparison with the reported specific rotation value.[7b] IR (neat) 3350 (-OH) 1600 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 6.41 (dd, J = 11.0, 17.6 Hz, 1H), 5.36-5.05 (m, 5H), 4.56-4.39 (m, 1H), 2.39 (d, J = 6.5 Hz, 2H), 1.72 (s, 3H), 1.68 (s, 3H) 1.60 (s, 1H); $[\alpha]_D^{23}$ = +11.87 (c = 1.00, MeOH); exact mass calcd for $C_{10}H_{16}O$ 152.1181 found 152.1191.

(*R*)-(-)-2-Bromo-6-methyl-1,5-heptadien-4-ol 5a: **5a** was synthesized by the same procedure as **3a**, using 3-methyl-2-butenal instead of 3-methylbutanal, in 98 % yield and 88 %ee. All spectra except for optical rotation were the same as those of **4a**. $[\alpha]_D^{23}$ = -3.22 (c = 4.16, $CHCl_3$).

(*R*)-(-)-Ipsdienol 5b: **5b** was prepared from **5a** by the same procedure as

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4b in 84% yield and 87 %ee. All spectra except for optical rotation were the same as those of **4b**. $[\alpha]_D^{23}$ = -11.90 (c = 1.00, MeOH).

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(Received in Japan 22 August 1996)

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