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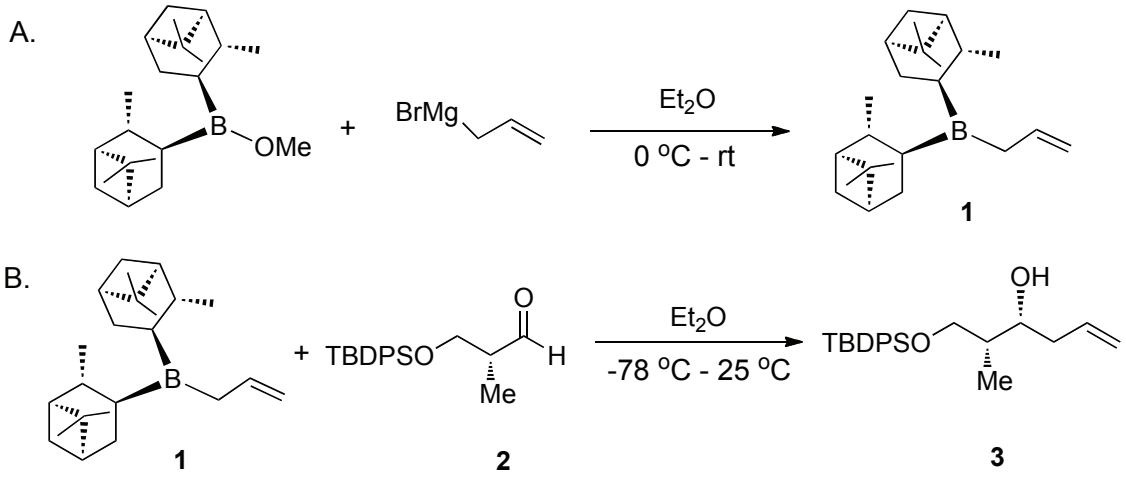
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

SYNTHESIS OF (+)-B-ALLYLDIISOPINOCAMPHEYLBORANE AND ITS REACTION WITH ALDEHYDES



Submitted by Huikai Sun and William R. Roush.[1]
Checked by David Hughes.[2]

1. Procedure

A. *(+)-B-allyldiisopinocampheylborane ((+)-(Ipc)$_2$B(allyl) or (^{d}Ipc)$_2$B(allyl)) (**1**)*. A 500-mL, 3-necked oven-dried round-bottomed flask equipped with a 3-cm oval Teflon-coated magnetic stir bar is fitted with a gas inlet adapter connected to a nitrogen line and a gas bubbler. The other two necks are capped with rubber septa; a thermocouple probe is inserted through one of the septa. (Note 1) The flask is charged with (+)-B-methoxydiisopinocampheylborane ((+)-(Ipc)$_2$BOMe) (13.3 g, 42.1 mmol, 1.25 equiv) (Note 2) and diethyl ether (45 mL), which results in a clear and colorless solution. The solution is cooled to 3 °C in an ice/water bath and vigorously stirred. Allylmagnesium bromide solution (1.0 M in diethyl ether, 40 mL, 40 mmol, 1.20 equiv) (Notes 2 and 3) is then added dropwise over 20 min via a 60 mL disposable syringe with 18-gauge needle, maintaining the temperature below 6 °C. A large amount of white solids (presumably MgBr(OMe)) precipitate during the addition. After the addition is complete, the ice/water bath is removed, then the reaction mixture is vigorously stirred (Note 4) for 1 h at room temperature. The resulting (^{d}Ipc)$_2$B(allyl) mixture in ether is used immediately in the next step without further purification (Note 5).

B. *(2R,3R)-1-(tert-Butyldiphenylsilyloxy)-2-methylhex-5-en-3-ol (**3**)*. The heterogeneous mixture of (^{t}Ipc)$_2$B(allyl) generated in Step A is cooled to –75 °C with a dry ice/acetone bath under vigorous stirring, then a solution of (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal (**2**) (10.9 g, 33.4 mmol, 1.00 equiv) (Note 6) in diethyl ether (25 mL) is added dropwise over 20 min via syringe (Note 7), maintaining the temperature below –70 °C. The resulting mixture is vigorously stirred at –70 to –75 °C for 1.5 h (Note 8), then the dry ice/acetone bath is removed, and the reaction mixture is allowed to warm to room temperature (22 °C) over 1 h. The reaction mixture is cooled to 3 °C with an ice/water bath. A 125-mL gas equilibrating dropping funnel is attached to the flask, moving the gas adapter from one neck of the flask to the top of the dropping funnel. A premixed solution of 3M NaOH (64 mL) and 30 % H_2O_2 (26 mL) (Note 9) is carefully added via the dropping funnel over 10 min (exothermic), keeping the temperature below 15 °C, followed by addition of saturated aqueous $NaHCO_3$ (80 mL) over 3 min via the dropping funnel (Note 10). The resulting biphasic mixture is vigorously stirred for 10 h at room temperature (Note 11) to completely hydrolyze borinate ester products, then the organic phase is separated, and the aqueous phase is extracted with diethyl ether (2 x 80 mL). After the combined organic layers are washed with brine (2 x 50 mL), the ether solution is transferred to a 1-L round-bottomed flask, equipped with a 3-cm, egg-shaped Teflon-coated stir bar, then THF (150 mL), water (80 mL) and iron (II) sulfate heptahydrate salt (15.0 g) are added (Note 12). The flask is fitted with a gas inlet adapter connected to a nitrogen line and a gas bubbler. The resulting mixture is vigorously stirred for 14 h, then the organic phase is separated and the aqueous phase is extracted with diethyl ether (2 x 50 mL). The combined organic layers are washed with brine (2 x 50 mL), dried over 100 g of anhydrous Na_2SO_4 and vacuum filtered through a medium porosity sintered-glass funnel. The filtrate is concentrated (40 °C bath temperature, 100 mmHg initial to 20 mmHg) by rotary evaporation to give a light yellow residue (32 g), containing a 93 : 7 mixture of **3** and its anti diastereomer (**5**) (Note 13). This mixture is purified by column chromatography (Note 14) to provide 9.1 – 9.4 g (74 – 77%) of >98% pure (2*R*,3*R*)-1-(*tert*-butyldiphenylsilyloxy)-2-methylhex-5-en-3-ol **3** (Note 15) as a colorless oil.

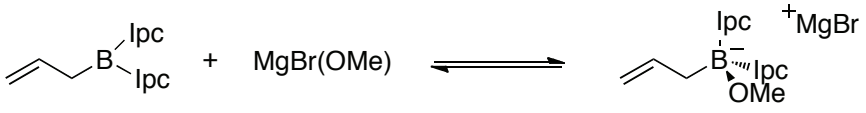
2. Notes

1. The internal temperature was monitored using a J-Kem Gemini digital thermometer with a Teflon-coated T-Type thermocouple probe (12-inch length, 1/8 inch outer diameter, temperature range –200 to +250 °C).

2. (+)-B-Methoxydiisopinocampheylborane was purchased from Sigma-Aldrich and used as received. The submitters stored and transferred this material in the glove box. The checker stored it in the freezer and weighed and transferred (rapidly) in open air. Diethyl ether (anhydrous, ACS reagent) and allylmagnesium bromide (1.0 M in diethyl ether, stored in refrigerator) were purchased from Sigma-Aldrich and used as received.

3. The specified amounts of (+)-$(Ipc)_2$BOMe (1.25 equiv) and allylmagnesium bromide (1.20 equiv) are used in order to generate a sufficient amount of allylborane **1** to completely consume 1.0 equiv of aldehyde **2** in the allylboration step. Unreacted aldehyde (8-10%) remains at the end of the allylboration reaction when 1.0 equiv of both (+)-$(Ipc)_2$BOMe and allylmagnesium bromide are used. A slight excess of (+)-$(Ipc)_2$BOMe is used over allylmagnesium bromide in order to ensure complete consumption of the latter before addition of the aldehyde; the submitters observed that the allylboration diastereoselectivity decreased by 1-2% if a slight excess of (+)-$(Ipc)_2$BOMe is not used.

4. The stirring of the thick mixture should be vigorous but balanced. Solids that stick on the walls above the mixture may contain entrapped reagent, perhaps in the form of the ate complex indicated in equation 1,[3] and cannot be washed back into the reaction mixture. In such cases, unreacted aldehyde is often observed after conclusion of the allylboration reaction.



equation 1

5. (-)-B-allyldiisopinocampheylborane ((-)-$(Ipc)_2$B(allyl) or (^{d}Ipc)$_2$B(allyl)), can be prepared using the same procedure starting from (-)-B-methoxydiisopinocampheylborane ((-)-$(Ipc)_2$BOMe). The $(Ipc)_2$B(allyl) reagents are sensitive to air and moisture.

6. (*R*)-3-(t-Butyldiphenylsilyloxy)-2-methylpropanal **2** was prepared (10.0 - 12.0 g scale) according to the procedure of Marshall et al.[4] and obtained in 75–80% yield as a white solid following column chromatography with 3% EtOAc/hexanes with $[\alpha]_D^{20}$ –26.4 ($CHCl_3$, c = 1.8).

Aldehyde **2** was stored at –20 °C for up to 2 weeks prior to use without racemization (as determined by measuring its optical rotation and ee determination of the allylation product **3**).

7. An oven-dried, 100-mL, single-necked, round-bottomed flask was charged with (*R*)-3-(*t*-butyldiphenylsilyloxy)-2-methylpropanal **2** (10.9 g), then 25 mL of diethyl ether was added, and the mixture was swirled to completely dissolve the aldehyde. The resulting solution was transferred to the reaction mixture via a 40 mL disposable syringe with a 15 cm needle (18 gauge) over 20 min. Additional diethyl ether (2 x 5 mL) was used to rinse the flask and then was added to the reaction mixture over 1 min. For the addition of the aldehyde solution to the cold reaction mixture, the tip of the syringe needle should be kept >5 cm above the surface and added at a steady rate to prevent crystallization of the aldehyde in the syringe. The submitters used a syringe pump for this addition.

8. The progress of the reaction was monitored by ^{1}H NMR spectroscopy monitoring the aldehyde proton at δ 9.8. (Typical procedure for ^{1}H NMR analysis: an aliquot of the reaction mixture was quickly transferred via a syringe to a small vial containing methanol (0.5 mL) at rt. The solvent was evaporated and the residue was dissolved in $CDCl_3$.)

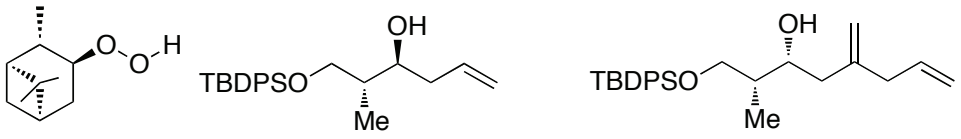
9. 30% H_2O_2 was purchased from Fisher Chemical Company, stored at 5 °C and used as received.

10. The oxidative hydrolysis was not complete in 16 h at ambient temperature or under reflux without addition of the saturated $NaHCO_3$ solution. The pH of the hydrolysis reaction mixture after bicarbonate addition was 11.

11. The progress of the oxidative hydrolysis was monitored by ^{1}H NMR spectroscopy using $CDCl_3$ as solvent (An aliquot of the organic layer was evaporated to dryness and the residue dissolved in $CDCl_3$.) Completion of the oxidative hydrolysis was indicated by disappearance of the mutiplet resonances of the internal olefin hydrogen (δ 5.78 – 5.68) and terminal olefin hydrogens (δ 5.05 – 4.95) in the intermediate borinate ester (e.g., $ROBIpc_2$). In comparison, the chemical shift range of the multiplet of the corresponding olefinic hydrogens in the major product **3** are from δ 5.92 – 5.81 and 5.16 – 5.09. The hydrolysis was complete within 1.5 h in the hands of the submitters but typically required 8-10 h for the checkers. Agitation efficiency of the 3-phase mixture (aqueous, organic, solids) may affect the reaction rate.

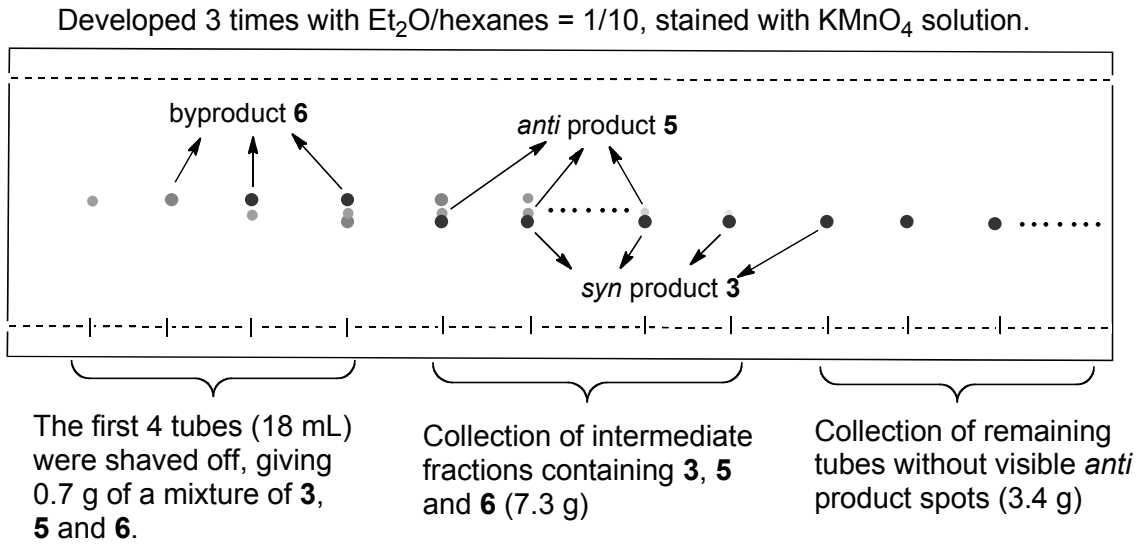
12. Isopinocampheyl hydroperoxide **4** is produced in the reaction. This compound migrates with the *syn* product **3** on the TLC plate (EMD, silica gel, grade 60, F254) in this exemplified allylboration reaction, so the iron (II) sulfate reduction step is included to ensure that hydroperoxide **4** is completely consumed prior to product isolation. A reference sample of **4** was prepared by stirring a solution of Ipc_2BOMe (1.0 g) in THF under air for 1 h. This solution was cooled to 0 °C and a premixed solution of 3 N NaOH (2.3 mL) and 30% H_2O_2 (0.9 mL) was added followed by sat. $NaHCO_3$ (3.0 mL) solution. The resulting mixture was vigorously stirred for 1.5 h. The organic phase was separated and hydroperoxide **4** was separated from isopinocampheol (1 : 4 mixture, respectively) by column chromatography using 1:10 Et_2O-hexanes as eluent (R_f=0.5, 1:5 Et_2O-hexanes, staining with PMA).

13. The reaction diastereoselectivity was determined as follows. A small sample of the crude reaction product (80 mg) was purified (collecting all fractions containing product with R_f = 0.4 to 0.5) by flash column chromatography (8 g silica gel) using ether/hexanes = 1/8 as the eluent to provide a mixture of three products. This mixture was analyzed by the submitters using normal phase HPLC (5% EtOAc in hexanes, 1.0 mL/min, 4.6 X 250 mm Varian column, UV detection at 254 nm; t_R(**3**) = 16.2 min; t_R(**5**) = 13.9 min; t_R(**6**) = 13.0 min). The checkers used a reverse phase assay to analyze diastereomeric ratios using an Agilent 1100 HPLC system; Ascentis Express C-18 fused-core column, 4.6 x 100 mm, 2.7 um particle size; 1.8 mL/min flow; temperature 40 °C; detection at 210 nm; gradient elution from 50/50 MeCN/water containing 0.1% H_3PO_4 to 95% MeCN/5% aq. over 14 min; t_R (**3)** 9.6 min, t_R (**5)** 9.8 min, t_R **(6)** 11.6 min). The crude reaction product was determined to contain (2*R*,3*R*)-1-(*t*-butyldiphenylsilyloxy-2-methylhex-5-en-3-ol (**3**) (90%), (2*R*,3*S*)-1-(*t*-butyldiphenylsilyloxy)-2-methylhex-5-en-3-ol (**5**) (7%), and (2*R*, 3*R*)-1-(*t*-butyldiphenylsilyloxy)-2-methyl-5-methyleneoct-7-en-3-ol (**6**) (3%). The stereochemistry of the hydroxyl group of **6** is assumed, by analogy to the stereochemistry of the major product of the reaction (**3**). A use test (by direct reaction with aldehyde **2**) indicated that the solutions of allylmagnesium bromide in diethyl ether contain ca. 3% of 2-((bromomagnesium)methyl)-1,4-pentadiene.



4 **5** **6**

14. The crude product was purified by three flash column chromatography steps owing to the difficulty of separating the syn diastereomer **3** from the anti diastereomer **5** and the byproduct **6**. The first chromatography was performed using 300 g of silica gel (Fisher, 230-400 mesh, 60 Å) in a 5 cm diameter column using 10:1 hexanes-diethyl ether as the eluent (18-mL fractions). All fractions were analyzed by TLC (1:10 Et_2O-hexanes, 3 developments, staining with $KMnO_4$ solution), as depicted



graphically below. Early fractions contained 0.7 g of a mixture of **5** and predominantly by-product **6**. Late eluting fractions without detectable *anti* diastereomer **5** were pooled, giving 3.7 g of *syn* diastereomer **3**. The intermediate fractions, containing 8.1 g of a mixture of **3**, **5** and **6** were pooled and subjected to a second chromatography as described above (250 g silica gel, 5 cm diameter column). Early eluting fractions containing predominantly **5**, **6** and a small amount of **3** were discarded. Late eluting fractions, without detectable *anti* diastereomer **5** according to TLC analysis, were combined to give an additional 3.4 g of *syn* diastereomer **3**. The intermediate, mixed fractions, consisting of 4.5 g of a mixture of **3**, **5** and **6** were subjected to a third column chromatography (200 g of silica gel in a

5 cm diameter column). This provided an additional 2.3 g of essentially pure *syn* diastereomer **3**, along with 1.5 g (12% yield) of mixed fractions that consisted of mixture **3** (ca. 80%), **4** (ca. 20%) and **6** (ca. 1 %). The latter fraction could be subjected to additional purification if desired. The three main fractions of *syn* diastereomer **3** were combined, giving 9.4 g (77% yield) which contained 1.3% of *anti* diastereomer **5** and 0.2% of by-product **6** according to HPLC analysis as described in note 13.

15. The submitters obtained pure samples of **3**, **5** and **6** by preparative HPLC for spectroscopic analysis (5% EtOAc in hexanes, 18.0 mL/min, 21.4 x 250 mm Varian Dynamax column, Microsorb 60-8; t_R(**3**) = 9.8 min; t_R(**5**) = 9.1 min; t_R(**6**) = 8.3 min). The enantiomers of both **3** and **5** have been synthesized and characterized previously.[5] The checker prepared a mixture of the (2*S*, 3*S*) and (2*S*, 3*R*) diastereomers by the same protocol starting with (*S*)-3-(*t*-butyldiphenylsilyloxy)-2-methylpropanal and (+)-B-methoxydiisopinocampheylborane, which produced a 78:22 mixture of (2*S*, 3*R*):(2*S*, 3*S*) diastereomers.

The *syn* product **3** exhibits the following physical and spectroscopic properties: colorless oil; $[\alpha]_D^{21}$ = +3.7 (c = 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (d, *J* = 7.1 Hz, 3 H), 1.08 (s, 9 H), 1.77–1.82 (m, 1 H), 2.20–2.33 (m, 2 H), 2.73 (d, *J* = 3.4 Hz, 1 H), 3.70 and 3.77 (ABX, *J* = 10.1, 4.3 Hz, 2 H), 3.92–3.97 (m, 1 H), 5.09–5.16 (m, 2 H), 5.81–5.92 (m, 1 H), 7.30–7.48 (m, 6 H), 7.67–7.71 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.5, 19.4, 27.1, 39.1, 39.3, 68.7, 73.5, 117.3, 128.0, 130.00, 130.04, 133.2, 133.4, 135.79, 135.81, 135.9; IR (KBr) 3468, 2955, 2858, 1606, 1515, 1471, 1427, 1112, 701 cm^{-1}; LC-MS calcd for $[M+Na]^+$ ($C_{23}H_{32}NaO_2Si$) 391.6, found, 391.7 m/z. Purity by reverse phase HPLC was >98% (see note 13 for method), t_R **(3)** 9.6 min (98.3%); t_R **(5)** 9.8 min (1.3%); t_R **(6)** 11.6 min (0.2%); $\mathbf{t_R}$ 9.1 min (unknown, 0.2%). A reverse phase chiral HPLC assay was developed to separate the (2*S*, 3*S*) and (2*R*, 3*R*) enantiomers: OJ-RH (150 x 4.6mm, 5um) isocratic 60% MeCN (pH 3.5, 2mM ammonium formate), 40% aqueous (pH 3.5, 2mM ammonium formate), 0.75mL/min, ambient temp, 215 nm, 20 min method time; t_R(**3**) (2*R*, 3*R*) 11.5 min; t_R (2*S*, 3*S*) 13.2 min; t_R (**5**) (2*R*, 3*S*) and (2*S*, 3*R*) co-elute 12.5 min. The enantiomeric purity of **3** was 99.0% indicating that aldehyde **2** did not racemize during its preparation and application in the exemplified procedure. An analytical sample of **3** was prepared by dissolving ~100 mg of the product from the pooled chromatographies in 5 mL of diethyl ether, filtering through a 0.45 micron PTFE syringe filter, and concentrating to

dryness under vacuum for 16 h. Anal. calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75; found: C, 74.85; H, 8.78.

The *anti* product **5** exhibits the following physical and spectroscopic properties: colorless oil; $[\alpha]_D^{21}$ = –2.6 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (d, *J* = 6.8 Hz, 3 H), 1.06 (s, 9 H), 1.80–1.84 (m, 1 H), 2.17–2.23 (m, 1 H), 2.34–2.39 (m, 1 H), 3.49 (d, *J* = 3.2 Hz, 1 H), 3.65 and 3.77 (ABX, *J* = 10.0, 4.4 Hz, 2 H), 3.65–3.73 (m, 1 H), 5.10–5.15 (m, 2 H), 5.88–5.98 (m, 1 H), 7.38–7.45 (m, 6 H), 7.67–7.69 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.4, 19.1, 26.8, 39.4, 39.5, 68.6, 75.1, 117.2, 127.8, 129.8, 132.9, 135.3, 135.6, 135.7; IR (KBr) 3496, 2959, 2930, 2858, 1589, 1472, 1427, 1390, 1112, 701 cm^{-1}; LC-MS calcd for $[M+Na]^+$ ($C_{23}H_{32}NaO_2Si$) 391.6, found, 391.7 m/z.

The side product **6** exhibits the following physical and spectroscopic properties: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, *J* = 6.8 Hz, 3 H), 1.07 (s, 9 H), 1.76–1.80 (m, 1 H), 2.20–2.28 (m, 2 H), 2.49 (d, *J* = 3.6 Hz, 1 H), 2.82 (d, *J* = 6.8 Hz, 2 H), 3.68 and 3.73 (ABX, *J* = 10.4, 4.8 Hz, 2 H), 4.04–4.07 (m, 1 H), 4.90 (d, *J* = 0.8 Hz, 2 H), 5.05–5.10 (m, 2 H), 5.78-5.88 (m, 1 H), 7.38–7.46 (m, 6 H), 7.66–7.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.4, 19.2, 26.9, 39.3, 40.6, 41.1, 68.0, 70.8, 112.9, 116.5, 127.7, 129.7, 129.8, 133.1, 133.3, 135.6, 135.7, 136.1, 145.3; IR (KBr) 3400, 2928, 2859, 1607, 1515, 1470, 1463, 1455, 1112, 822, 702, 505 cm^{-1}; LC-MS calcd for $[M+Na]^+$ ($C_{26}H_{36}NaO_2Si$) 431.6, found, 431.6 m/z.

Isopinocampheyl hydroperoxide **4** exhibits the following physical and spectroscopic properties: colorless oil; $[\alpha]_D^{21}$ = + 33.2 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (s, 3 H), 1.01 (d, *J* = 9.6 Hz, 1 H), 1.17 (d, *J* = 7.2 Hz, 3 H), 1.22 (s, 3 H), 1.79–1.86 (m, 2 H), 1.90–1.95 (m, 1 H), 2.00–2.03 (m, 1 H), 2.30–2.42 (m, 2 H), 4.27 (ddd, *J* = 3.6, 4.4 and 8.8 Hz, 1 H), 7.73 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 1.41, 23.61, 27.30, 32.48, 33.56, 38.40, 40.87, 42.14, 47.24, 84.99; IR (KBr) 3391, 2908, 1453, 1367, 1158, 1035 cm^{-1}; LC-MS calcd for $[M-H_2O]^+$ ($C_{10}H_{18}O_2$) 152.1, found, 152 m/z. This compound is readily reduced by Fe_2SO_4 to give isopinocampheol.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Chiral allylmetal reagents are valuable intermediates in organic synthesis, and are especially useful for the synthesis of enantioenriched homoallylic alcohols.[6] Since the first chiral allylborane reagent was reported by Hoffman in 1978,[7] many more efficient and practical chiral allylmetal reagents or allylmetallation procedures have been reported,[6] including those by Brown,[8] Roush,[5,9] Corey,[10] Leighton,[11] Denmark,[12] Soderquist,[13] Hall[14] and Krische.[15] The present enantioselective aldehyde allylation procedure developed by Brown and his coworkers is one of the most widely adopted methods as it employs commercially available (+)-$(Ipc)_2$BOMe and commercially available allylmagnesium bromide for synthesis of the (^{l}Ipc)$_2$B(allyl) reagent;[8b] the enantiomeric (^{d}Ipc)$_2$B(allyl) species can be accessed from commercially available (-)-$(Ipc)_2$BOMe by using the same protocol.

The $(Ipc)_2$B(allyl) reagents were prepared in Brown's original procedure[8b] by treating $(Ipc)_2$BOMe with allylmagnesium bromide at –78 ^{o}C and then allowing the reaction mixture to warm to rt over 1 h. The procedure described herein follows an alternative protocol subsequently published by Brown, in which allylmagnesium bromide is added to a solution of $(Ipc)_2$BOMe in diethyl ether at 0 ^{o}C and then stirring the reaction mixture at rt for 1 h.[3] The allylboration of aldehydes can be performed after removal of the magnesium salts by filtration under an inert atmosphere (salt free procedure), which is reported to provide much improved enantioselectivites.[3] However, the procedure described here, by performing the allylboration in the presence of the magnesium salts, is more convenient as it avoids filtration and extra manipulations of the moisture and air sensitive allylborane species.

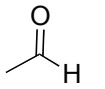
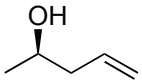
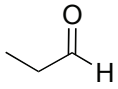
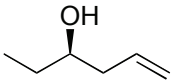
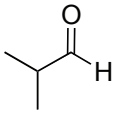
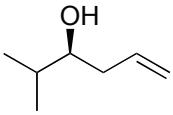
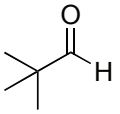
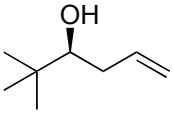
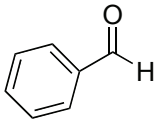
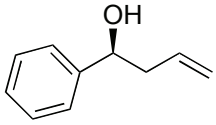
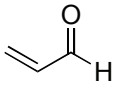
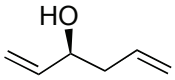
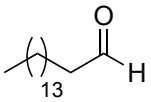
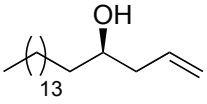
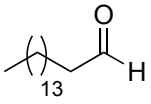
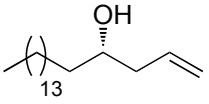
We found that use of slight excesses of both $(Ipc)_2$BOMe (1.25 equiv) and allylmagnesium bromide (1.2 equiv) were needed in order to achieve complete allylboration of aldehyde **2**. Generally, the secondary alcohol products can be isolated following oxidative hydrolytic workup by treating the intermediate borinate esters with a solution of 3 N sodium hydroxide and 30% hydrogen peroxide under reflux for several hours or at rt for 16 h. However, we found that the hydrolysis did not proceed to completion in the allylboration reaction reported here unless a solution of sat. sodium bicarbonate was also added. These optimized workup conditions not only

resulted in complete oxidative hydrolysis in 10 h at room temperature, but also led to formation of two clear phases that facilitated the separation process. The submitters also found that isopinocampheyl hydroperoxide **4** is produced in 4-6% yield. While the origin of **4** has not been rigorously established, it seems likely that it arises via a radical process when the borinate ester intermediates are exposed to O_2 during reaction workup.[16] Hydroperoxide **4** is difficult to separate from *syn* product **3** in this exemplified reaction, so the submitters further modified the reaction workup by addition of an aqueous solution of iron (II) sulfate to reduce hydroperoxide **4** before product purification via column chromatography.[17]

The submitters also identified (2R, 3R)-1-(*tert*-butyldiphenylsilyloxy)-2-methyl-5-methyleneoct-7-en-3-ol (**6**, 3% according to HPLC analysis) as a by-product of this procedure. A use test (by direct reaction with aldehyde **2**) indicated that the solutions of allylmagnesium bromide in diethyl ether contains ca. 3% of 2-((bromomagnesium)methyl)-1,4-pentadiene. Production of analogous products deriving from 2-((bromomagnesium)methyl)-1,4-pentadiene as a contaminant of allylmagnesium bromide have not been described in the literature, to the best of the knowledge of the submitters. Whether the formation of this by-product can be avoided by using freshly prepared allylmagnesium bromide has not been determined.

Reactions of $(Ipc)_2B(allyl)$ reagents with achiral aldehydes are reported to furnish the corresponding secondary homoallylic alcohols with 80 to 95% enantiomeric excess, as shown in Table 1. The substrate scope has been extended in the literature to a large number of aliphatic aldehydes, aromatic aldehydes and α, β-unsaturated aldehydes.[6f]

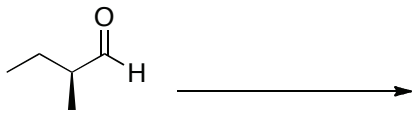
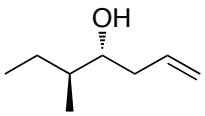
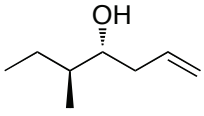
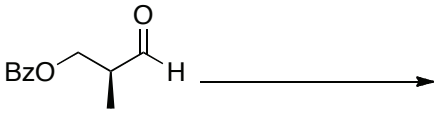
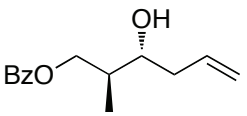
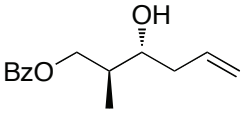
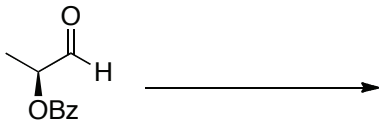
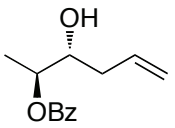
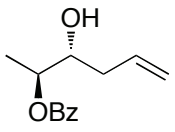
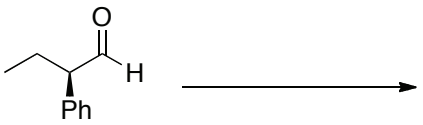
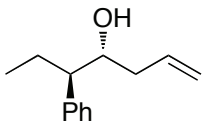
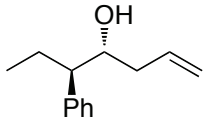
Table 1. Allylboration of achiral aldehydes with (^{d}Ipc)$_2$B(allyl) or (^{l}Ipc)$_2$B(allyl)

Entry	aldehydes	(Ipc)$_2$B(allyl)	product	ee (%)	yield (%)[a]
1		(^{d}Ipc)$_2$B(allyl)		93	74
2		(^{d}Ipc)$_2$B(allyl)		86	71
3		(^{d}Ipc)$_2$B(allyl)		90	86
4		(^{d}Ipc)$_2$B(allyl)		83	88
5		(^{d}Ipc)$_2$B(allyl)		96	81
6		(^{d}Ipc)$_2$B(allyl)		92	no reported yield
8[b]		(^{d}Ipc)$_2$B(allyl)[c]		80	78
9[b]		(^{l}Ipc)$_2$B(allyl)[c]		84	80

[a] Isolated yields; [b] see reference 18; [c] (Ipc)$_2$B(allyl) was prepared from the corresponding (Ipc)$_2$BCl

Allylboration of α-chiral aldehydes with (Ipc)$_2$B(allyl) reagents are also reported to produce secondary homoallylic alcohols in excellent diastereoselectivity and in good to excellent yields as shown in Table 2.[8c,19] In most cases (entries 1-3), with aldehyde substrates with very modest diastereofacial biases, the facial selectivity of the reaction is completely reversed upon switching the chirality of the chiral allylborane reagents. Numerous other applications of the use of the (Ipc)$_2$B(allyl) reagents in matched and mismatched double asymmetric reactions with chiral aldehydes are summarized in the cited review literature.[6a,6f]

Table 2. Allylboration of α-chiral aldehydes with (^{d}Ipc)$_2$B(allyl) or (^{l}Ipc)$_2$B(allyl)

Entry	aldehyde	conditions	diastereomeric products/ratio		yield
1					
		(^{d}Ipc)$_2$B(allyl)	96	4	81%
		(^{l}Ipc)$_2$B(allyl)	5	95	83%
2					
		(^{d}Ipc)$_2$B(allyl)	96	4	80%
		(^{l}Ipc)$_2$B(allyl)	2	98	78%
3					
		(^{d}Ipc)$_2$B(allyl)	94	6	80%
		(^{l}Ipc)$_2$B(allyl)	4	96	75%
4					
		(^{d}Ipc)$_2$B(allyl)	67	33	68%
		(^{l}Ipc)$_2$B(allyl)	2	98	70%

1. Department of Chemistry, The Scripps Research Institute, Scripps Florida, 130 Scripps Way #3A2, Jupiter, FL 33458. E-mail: roush@scripps.edu. This research was supported by a grant from the National Institutes of Health (GM038436).

2. Checker is indebted for the analytical support from Kevin Maloney for the reverse-phase HPLC assay of diastereomers and Zainab Pirzada for the chiral HPLC assay.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(+)-B-Allyldiisopinocampheylborane ((+)-$(Ipc)_2B(allyl)$ or $(^{l}Ipc)_2B(allyl)$); (106356-53-0)

(+)-B-Methoxydiisopinocampheylborane (+)-$(Ipc)_2BOMe$); (99438-28-5)

Allylmagnesium bromide; (1730-25-2)

(*R*)-3-(*t*-Butyldiphenylsilyloxy)-2-methylpropanal: Propanal, 3-[[(1,1-dimethylethyl)diphenylsilyl] oxy]-2-methyl-, (2*R*)-; (112897-04-8)

Hydrogen peroxide; (7722-84-1)

(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ol; (+)-isopinocampheol; (24041-60-9)

(2*R*,3*R*)-1-(*t*-Butyldiphenylsilyloxy)-2-methylhex-5-en-3-ol

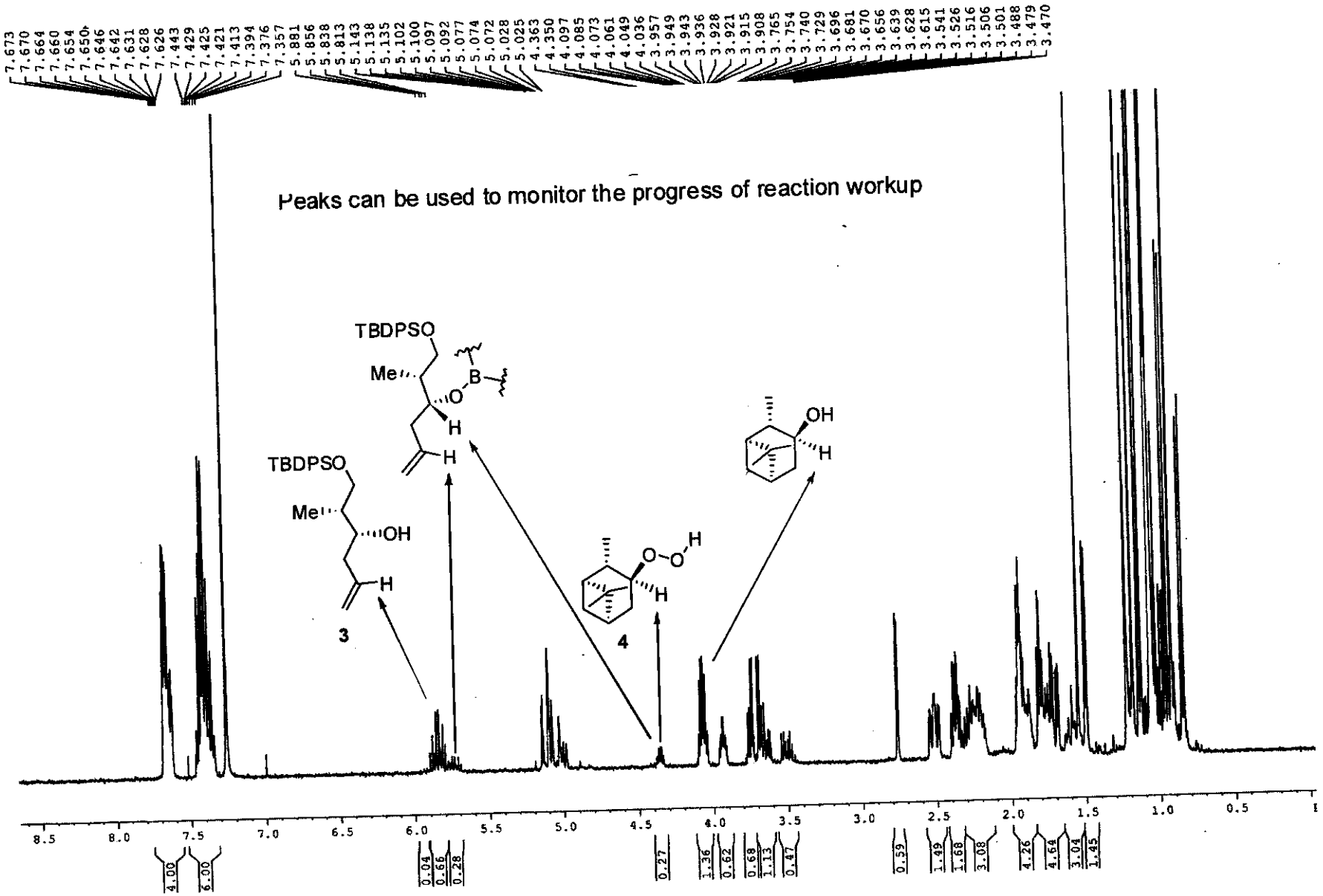
(2*R*,3*S*)-1-(*t*-Butyldiphenylsilyloxy)-2-methylhex-5-en-3-ol

(2*R*,3*R*)-1-(*t*-Butyldiphenylsilyloxy)-2-methyl-5-methyleneoct-7-en-3-ol

(1*S*,2*S*,3*S*,5*R*)-3-hydroperoxy-2,6,6-trimethylbicyclo[3.1.1]heptane; (+)-isopinocampheylperoxide

William R. Roush is Professor of Chemistry, Executive Director of Medicinal Chemistry and Associate Dean of the Kellogg School of Science and Technology at The Scripps Research Institute, Florida. His research interests focus on the total synthesis of natural products and the development of new synthetic methodology. Since moving to Scripps Florida in 2005, his research program has expanded into new areas of chemical biology and medicinal chemistry. Dr. Roush was a member of the *Organic Syntheses* Board of Editors from 1993-2002 and was Editor of Volume 78. He currently serves on the *Organic Syntheses* Board of Directors (2003-present).

Huikai Sun received both his BS and MS degrees in Organic Chemistry from Nankai University in China. He joined the Department of Chemistry at Case Western Reserve University for his Ph. D. degree, which was completed in 2007 under the supervision of Professor Anthony J. Pearson. He is currently a postdoctoral research associate in the laboratory of Professor William R. Roush at Scripps Florida. His research interests focus on the total synthesis of natural products and the development of cysteine protease inhibitors.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3.628
3.615
3.541
3.526
3.516
3.506
3.501
3.488
3.479
3.470
Peaks can be used to monitor the progress of reaction workup
TBDPSO
Me
B
O
H
H
TBDPSO
Me
OH
H
3
O
O
H
H
4
OH
H
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
4.00
6.00
0.04
0.66
0.28
0.27
1.36
0.62
0.68
1.13
0.47
0.59
1.49
1.68
3.08
4.26
4.64
3.04
1.45

32077-131D
3 chromatographies combined
nmr400b h-1

Current Data Parameters

NAME	32077-131
EXPNO	16
PROCNO	1

F2 - Acquisition Parameters

Date_	20100918
Time	12.07
INSTRUM	spect
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TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	6578.947 Hz
FIDRES	0.200774 Hz
AQ	2.4904180 sec
RG	228.1
DW	76.000 usec
DE	7.00 usec
TE	300.1 K
D1	0.10000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	11.20 usec
PL1	6.00 dB
SFO1	399.8724694 MHz

F2 - Processing parameters

SI	16384
SF	399.8700087 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	7.7085	3082.3980	0.15
2	7.7039	3080.5586	0.89
3	7.7000	3078.9991	1.33
4	7.6961	3077.4396	0.65
5	7.6938	3076.5199	0.94
6	7.6899	3074.9604	1.53
7	7.6842	3072.6811	1.47
8	7.6800	3071.0017	1.64
9	7.6770	3069.8021	0.48
10	7.6741	3068.6424	1.28
11	7.6700	3067.0030	1.31
12	7.4790	2990.6278	0.16
13	7.4751	2989.0683	0.36
14	7.4712	2987.5088	0.24
15	7.4660	2985.4295	0.22
16	7.4566	2981.6707	1.21
17	7.4495	2978.8316	0.39
18	7.4433	2976.3524	0.83
19	7.4392	2974.7130	1.55
20	7.4349	2972.9935	0.88
21	7.4282	2970.3144	1.56
22	7.4234	2968.3950	0.69
23	7.4107	2963.3167	1.62
24	7.4091	2962.6769	1.61
25	7.3978	2958.1584	0.22
26	7.3948	2956.9587	0.57
27	7.3920	2955.8391	0.50
28	7.3901	2955.0794	0.41
29	7.3870	2953.8398	0.33
30	7.2706	2907.2949	0.47
31	5.9171	2366.0708	0.13
32	5.8995	2359.0331	0.29
33	5.8916	2355.8741	0.15
34	5.8817	2351.9154	0.14
35	5.8742	2348.9164	0.45
36	5.8565	2341.8387	0.48
37	5.8489	2338.7997	0.16
38	5.8391	2334.8810	0.16
39	5.8313	2331.7620	0.35
40	5.8135	2324.6443	0.16
41	5.1634	2064.6888	0.20
42	5.1593	2063.0493	0.42
43	5.1546	2061.1699	0.55
44	5.1510	2059.7304	0.22
45	5.1192	2047.0145	0.59
46	5.1164	2045.8949	0.75
47	5.1132	2044.6153	0.61
48	5.1117	2044.0155	0.63
49	5.1083	2042.6560	0.27
50	5.0961	2037.7776	0.25
51	5.0934	2036.6979	0.46
52	5.0911	2035.7782	0.39
53	5.0883	2034.6586	0.37
54	3.9710	1587.8838	0.12
55	3.9631	1584.7248	0.20
56	3.9573	1582.4056	0.19
57	3.9558	1581.8058	0.18
58	3.9503	1579.6065	0.33
59	3.9424	1576.4475	0.33
60	3.9371	1574.3282	0.18
61	3.9356	1573.7284	0.18
62	3.9296	1571.3292	0.20
63	3.9217	1568.1702	0.13
64	3.7804	1511.6686	0.37
65	3.7696	1507.3500	0.43
66	3.7552	1501.5919	0.81
67	3.7444	1497.2733	0.84
68	3.7183	1486.8367	0.82
69	3.7041	1481.1585	0.79
70	3.6931	1476.7599	0.38
71	3.6788	1471.0418	0.37
72	2.7320	1092.4449	0.67
73	2.7234	1089.0060	0.66
74	2.3272	930.5775	0.15
75	2.3241	929.3379	0.14
76	2.3126	924.7394	0.14
77	2.3097	923.5798	0.28
78	2.3067	922.3801	0.23
79	2.2922	916.5820	0.34
80	2.2893	915.4224	0.33
81	2.2744	909.4643	0.14
82	2.2715	908.3047	0.23
83	2.2685	907.1051	0.15
84	2.2611	904.1461	0.14
85	2.2580	902.9065	0.21
86	2.2548	901.6269	0.14
87	2.2443	897.4283	0.30
88	2.2410	896.1087	0.29
89	2.2375	894.7091	0.15
90	2.2302	891.7901	0.15
91	2.2270	890.5105	0.25
92	2.2238	889.2309	0.20
93	2.2092	883.3928	0.13
94	2.2059	882.0733	0.13
95	1.8195	727.5635	0.14
96	1.8124	724.7244	0.15
97	1.8085	723.1649	0.14
98	1.8053	721.8853	0.18
99	1.8017	720.4458	0.23
100	1.7984	719.1262	0.16
101	1.7946	717.6067	0.22
102	1.7911	716.2072	0.15
103	1.7875	714.7676	0.24
104	1.7842	713.4481	0.17
105	1.7806	712.0085	0.15
106	1.7770	710.5690	0.14
107	1.7700	707.7699	0.14
108	1.5967	638.4724	0.70
109	1.0874	434.8186	1.11
110	1.0801	431.8996	20.00
111	1.0727	428.9406	1.23
112	0.9790	391.4727	4.22
113	0.9613	384.3950	3.55