Organic Syntheses

Preparation of Crystalline (Diisopinocampheyl)borane

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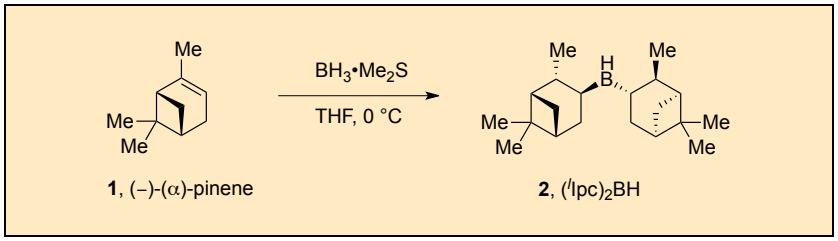

Procedure

A. *(+)-(Diisopinocampheyl)borane ((+)-(Ipc)$_2$BH) or ((^{l}Ipc)$_2$BH) (**2**).* A flame-dried 250-mL, two-necked, round-bottomed flask is equipped with a 4-cm Teflon-coated egg-shaped magnetic stir bar, a rubber septum, a thermometer (Note 1), and an argon line. The flask is charged with tetrahydrofuran (THF) (80 mL) and borane-methyl sulfide complex (Note 2) (8.2 mL, 6.47 g, 80.1 mmol, 1.00 equiv) is added via syringe. The mixture is cooled to 0 °C (Note 3) with an ice/water bath and (–)-(α)-pinene (**1**) (25.5 mL, 22.3 g, 160.2 mmol, 2.00 equiv) (Note 4) is added over 30 min using a syringe pump. Upon complete addition, the stirring is terminated, the thermometer replaced with a rubber septum, the argon line removed, and the septa are wrapped thoroughly with Parafilm®. The reaction flask is then placed in a 0 °C ice/water bath in a 4 °C cold room for 46 h (Note 5). After this time, the flask is allowed to warm to room temperature, the Parafilm® is discarded, and the supernatant is removed via cannula. Trituration of the residual chunks of (^{l}Ipc)$_2$BH is performed by introduction of diethyl ether (50 mL) via syringe and subsequent removal of the

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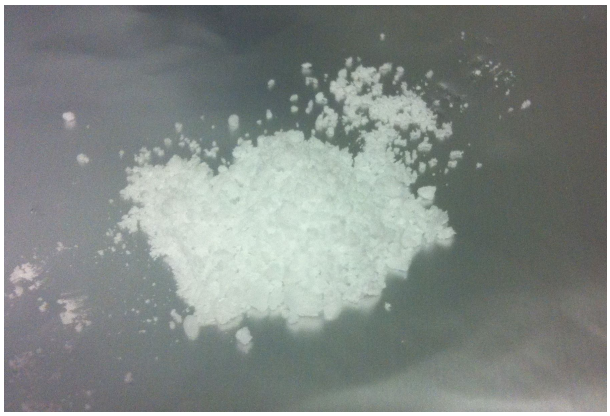
supernatant by cannula. The trituration process is repeated two additional times before the cannula is removed and replaced with a needle attached to a vacuum line. The white crystals of $(^{l}Ipc)_2BH$ are allowed to dry at <5 mmHg for 2 h. After this time, the flask is back-filled with argon, the septa are wrapped thoroughly with Parafilm®, and the flask is moved into a glovebox. Once inside, the chunks of $(^{l}Ipc)_2BH$ are pulverized using a spatula and stored at –20 °C (Note 6). This procedure



provides 10.2–12.1 g (45–52%) of 97% pure (+)-(diisopinocampheyl)borane ($(^{l}Ipc)_2BH$) (**2**) (Notes 7 and 8) as a fine white powder (Note 9). The enantiomeric purity of the crystalline (+)-(diisopinocampheyl)borane ($(^{l}Ipc)_2BH$) (**2**) was determined to be 97% ee by Mosher ester analysis of the (+)-isopinocampheol produced by oxidation of **2** with sodium perborate (Note 10).

Notes

1. The submitters used a single-necked flask and monitored the internal temperature of the reaction mixture using an Oakton Instruments Temp JKT temperature meter with a Teflon-coated thermocouple probe (30.5 cm length, 3.2 mm outer diameter, temperature range –250 to 400 °C).
2. THF (HPLC Grade) and diethyl ether (Certified ACS, stabilized with BHT) were obtained from Fisher Scientific and purified by passage through activated alumina using a GlassContour solvent purification system.[2] Borane-methyl sulfide complex (94%) was obtained from Acros Organics and used as received. (–)-(α)-Pinene (**1**) (98%, ≥81% ee) and (+)-(α)-pinene (98%, ≥91% ee) were obtained from Aldrich Chemical Co., Inc. and used as received.
3. The internal temperature of the reaction mixture remained between 0.3 and 1.1 °C throughout the course of the reaction.
4. Due to the viscosity of (–)-(α)-pinene, it is recommended that a large-gauge (16-18) needle be used.
5. As reported by Brown and Singaram,[3] it is imperative that the crystallization be carried out at 0 °C. The submitters observed a significant decrease in yield (from 64–66% at 0 °C to 31% at –18.5 °C) with no discernable increase in reagent purity when the crystallization was carried out at –18.5 °C for 46 h. As shown in the companion article, the checkers found that the yield can vary between batches of borane-methylsulfide even from the same supplier (57-60% instead of 45-52%).
6. (+)-(Diisopinocampheyl)borane ($(^{l}Ipc)_2BH$) stored in this way remains stable for periods of >1 year.
7. The sample for analysis was prepared as a solution in anhydrous, degassed d^8–THF in a J. Young NMR tube in a nitrogen-filled glovebox. It is important to use anhydrous NMR solvent as the presence of adventitious water will lead to hydrolysis of the borane. ^{1}H, ^{13}C and ^{11}B NMR spectra of the hydrolysis product, resulting from addition of water to a solution of **2** in anhydrous d^8-THF, are provided for the benefit of the user. The detailed appearance of the spectra of the hydrolysis product depends on the quantity of water added; representative spectra are included. Compound **2** exists as a mixture of species in anhydrous solution, and the utility of NMR spectroscopy in establishing the identity and purity of **2** is, therefore, limited.

Additional information on NMR spectroscopy of **2** can be found in the text of a report by Fürstner.[4] The signals corresponding to methyl groups in the ^{1}H NMR spectrum of **2** are tabulated as single peaks in the range of 0.85–1.27 ppm without assignment of their multiplicity: Crystalline (^{l}Ipc)$_2$BH (**2**) exhibits the following properties: mp 95–98 °C; ^{1}H NMR (500 MHz, d^8–THF) δ: 0.85, 0.87, 0.89, 0.91, 0.92, 0.93, 0.94, 0.96, 0.97, 0.99, 1.00, 1.02, 1.04, 1.05, 1.06, 1.07, 1.09, 1.12, 1.13, 1.14, 1.15, 1.17 (2), 1.19, 1.21, 1.23, 1.24, 1.27, 1.64 (m), 1.65–2.45 (m), 5.18 (m); ^{13}C NMR (125 MHz, d^8–THF) δ: 21.3, 22.6, 22.9, 23.1, 23.2, 23.3 (2), 23.4 (2), 23.7, 25.5, 26.8, 26.9, 27.6, 29.0, 29.2, 29.4, 30.1, 31.9, 32.2, 32.3, 32.6, 34.0, 34.7, 35.1, 35.6, 37.0, 38.9, 39.7, 39.8, 40.2, 40.3, 40.9, 41.6, 41.9, 42.6, 43.1 (2), 43.2, 43.3, 48.1, 49.6, 49.7, 49.9, 50.2, 117.0, 145.4. The sample for melting point determination was sealed in a capillary tube under argon.

8. The submitters were unsuccessful in repeated attempts to obtain acceptable mass spectral data and combustion analytical data for crystalline (Ipc)$_2$BH (**2**). Under GCMS (EI) conditions, the only observable peak was due to α-pinene (presumably from retro-hydroboration in the GC). Attempted HRMS analyses (performed at the University of Illinois Mass Spectroscopy Center) under a range of conditions (ESI+, ESI-, CI, MALDI) did not provide any mass fragments that could be attributed to (Ipc)$_2$BH. Finally, attempted combustion analysis (also performed at the University of Illinois; samples sealed under argon) gave acceptable values for hydrogen and boron, but consistently gave low carbon analyses. Calcd for $C_{20}H_{35}B$ (or $C_{40}H_{35}B_2$ for the dimer): C, 83.90%; H, 12.32%; B, 3.78%. Found, C, 80.97%; H, 12.19%; B, 3.70%. The checkers obtained the following results: C, 83.40%; H, 12.28%.
9. (–)-(Diisopinocampheyl)borane ((^{d}Ipc)$_2$BH) has also been synthesized by the submitters using the same procedure starting from (+)-(α)-pinene (98%, ≥91% ee) (Note 2) affording 17.46 g (76%) of white crystals. The enantiomeric purity of the crystalline (–)-(diisopinocampheyl)borane ((^{d}Ipc)$_2$BH) was determined by Mosher ester analysis[5] of (–)-isopinocampheol produced by oxidation with sodium perborate.[6] The ee of the (–)-isopinocampheol thus obtained was >97%.
10. Perborate oxidation of crystalline (+)-(diisopinocampheyl)borane ((^{l}Ipc)$_2$BH) (**2**) was performed as described by Kalbaka.[6] The enantiomeric purity the (+)-isopinocampheol so obtained was determined to be 97% ee by Mosher ester analysis.[5] Thus, a mixture of (+)-isopinocampheol (0.018 g, 0.117 mmol, 1.0 equiv) in

dichloromethane (0.80 mL, obtained from Fisher Scientific and dried by passage through activated alumina using a GlassContour solvent purification system (see Note 2)), pyridine (0.038 mL, 0.037 g, 0.47 mmol, 4 equiv; obtained from EMD and distilled from CaH_2 under Ar) and a catalytic amount of dimethylaminopyridine (DMAP; one small crystal; obtained from Sigma-Aldrich and used as obtained) was stirred under Ar at ambient temperature. (*R*)-(–)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.044 mL, 0.059 g, 0.233 mmol, 2 equiv; obtained from Matrix Scientific, used as obtained) was added via syringe. The mixture was stirred at ambient temperature for 18 h, at which point TLC analysis ((9:1 CH_2Cl_2-EtOAc); R_f isopinocampheol = 0.43; R_f for Mosher ester product = 0.98) indicated that the reaction was complete. The mixture was diluted with hexanes (1 mL), filtered to remove the white precipitate, then directly filtered through a short, Pasteur pipette column of silica gel using 30 mL of 9:1 hexanes-EtOAc. The filtrate was collected as a single fraction and concentrated on a rotary evaporator to give the (*S*)-MTPA ester as an oil. By using the same procedure, the (*R*)-MPTA ester was prepared (using (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, obtained from Alfa Aesar). Key resonances in the ^{19}F and ^{1}H NMR spectra of the diastereomeric MTPA esters that may be used in making enantiomeric purity determinations are as follows. Partial data for the (*S*)-MTPA ester of (+)-isopinocampheol: ^{19}F ($CDCl_3$, 376 MHz) δ: –71.46; ^{1}H (400 MHz, $CDCl_3$) δ: 5.31 (m, 1 H), 2.66 (m, 1 H), 2.35 (m, 1 H), 2.24 (m, 1 H), 1.94 (m, 1 H), 1.85 (m, 1 H), 1.69 (m, 1 H). Partial data for the (*R*)-MTPA ester of (+)-isopinocampheol: ^{19}F ($CDCl_3$, 376 MHz) δ: –71.56; ^{1}H (400 MHz, $CDCl_3$) δ: 5.31 (m, 1 H), 2.68 (m, 1 H), 2.37 (m, 1 H), 2.12 (m, 1 H), 1.97 (m, 1 H), 1.82 (m, 2 H).

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at

http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

(Diisopinocampheyl)borane ($(Ipc)_2BH$) is a useful chiral organoborane reagent for asymmetric synthesis. $(Ipc)_2BH$ can serve as a precursor of a range of reagents, such as $(Ipc)_2BCl$ and $(Ipc)_2BOTf$, that have been employed in asymmetric aldol reactions by Paterson.[7] Methanolysis of $(Ipc)_2BH$ leads to $(Ipc)_2BOMe$, which is a starting material used for the synthesis of Brown's chiral allylborane[8] and crotylborane[8c,9] reagents. These reagents react with aldehydes to provide homoallylic alcohols with high enantioselectivity.[10] $(Ipc)_2BH$ has been widely used in hydroboration reactions with alkenes leading, after oxidation of the resulting B–C, bond to enantioenriched secondary alcohols.[11] Hydroboration reactions of alkynes[12] and allenes[13] with $(Ipc)_2BH$ have also been reported. The reaction of $(Ipc)_2BH$ with α,β-unsaturated carbonyl derivatives is known to give enolborinates that can be used in aldol reactions.[14] The reductive aldol reaction[15] of 4-acryloylmorpholine with ($^{l}Ipc)_2BH$ (**2**), as illustrated in the

accompanying procedure,[16] leads exclusively to the *Z*(O)-enolborinate which reacts with a range of aldehydes to give *syn*-aldol adducts with excellent diastereoselectivity and with very high levels of enantioselectivity.[17]

Organic Syntheses has published several procedures in which (diisopinocampheyl)borane ($(Ipc)_2BH$) is generated in situ and used immediately in subsequent transformations.[6,18] Several of these procedures specify the use of >98% ee pinene, which while commercially available is very expensive. A procedure for the synthesis of crystalline $(Ipc)_2BH$, which can be prepared with high enantiomeric purity starting from either (–)-(α)-pinene (**1**) (≥81% ee) or (+)-(α)-pinene (≥91% ee) by using the protocol originally developed by Brown,[3] has not been published in *Organic Syntheses*. This procedure, described in detail above, is the preferred method for making this reagent owing to the bulk availability and very low cost of the two (α)-pinene enantiomers.

Implicit in this procedure is the significant enhancement of enantiomeric purity of $(Ipc)_2BH$, to 97% ee, in comparison to the considerably lower enantiomeric purity of the commercially available, inexpensive (α)-pinene starting materials [(–)-(α)-pinene (**1**) (≥81% ee) and (+)-(α)-pinene (≥91% ee), respectively]. The enhancement of enantiomeric purity is a consequence of the fact that a mixture of *d,d*-, *l,l*-, and *d,l*- isomers of $(Ipc)_2BH$ are generated in the hydroboration reaction, and that the major *l,l*- isomer (or *d,d*- isomer, depending on the major (α)-pinene enantiomer in the commercially available starting material) is highly crystalline, whereas the meso (*d,l*-) isomer remains in solution during the crystallization process. It is also instructive to note that as long as the hydroboration reaction gives the statistical mixture of *l,l*-, *d,d*-, and *d,l*-$(Ipc)_2BH$ isomers, the minor enantiomer present in the commercial (α)-pinene starting material will be selectively converted into the *d,l*- (meso) isomer of $(Ipc)_2BH$.[19]

By following the procedure described herein, crystalline $(^{l}Ipc)_2BH$ (**2**) was obtained in 45-52% yield starting from (–)-(α)-pinene (**1**) (98%, ≥81% ee) with an enantiomeric purity of 97% ee as determined by Mosher ester analysis[5] of the (+)-isopinocampheol produced by oxidation of **2** with sodium perborate.[6] The yield of crystalline $(^{d}Ipc)_2BH$ (76%, >97% ee; Note 8) starting from (+)-(α)-pinene (98%, ≥91% ee) is typically higher than the yield of $(^{l}Ipc)_2BH$, owing to the greater enantiomeric purity of the starting material. The colorless crystals of **2,** or its enantiomer, obtained by this procedure can be stored for months at –20 °C in a glovebox, and then weighed out in the exact amount needed for use in any reaction involving

$(Ipc)_2BH$. Alternatively, crystalline $(Ipc)_2BH$ (97% ee) can be generated in a pre-tared flask and then used directly in a subsequent reaction without transfer to another reaction vessel, thereby avoiding use of a glovebox. The latter procedure is illustrated in the reductive aldol reaction described in the accompanying procedure.[16]

References

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

(+)-(Diisopinocampheyl)borane ((+)-$(Ipc)_2BH$) or ($(^{l}Ipc)_2BH$: borane, bis[(1*S*,2*R*,3*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]; (21947-87-5)
(–)-(Diisopinocampheyl)borane ((–)-$(Ipc)_2BH$) or ($(^{d}Ipc)_2BH$: borane, bis[(1*R*,2*S*,3*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]; (21932-54-7)
Borane-methyl sulfide complex: boron, trihydro[thiobis[methane]]-(T-4)-; (13292-87-0)
(–)-(α)-Pinene: (1*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene; (7785-26-4)
(+)-(α)-Pinene: (1*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene; (7785-70-8)
diethyl ether; (60-29-7)

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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).

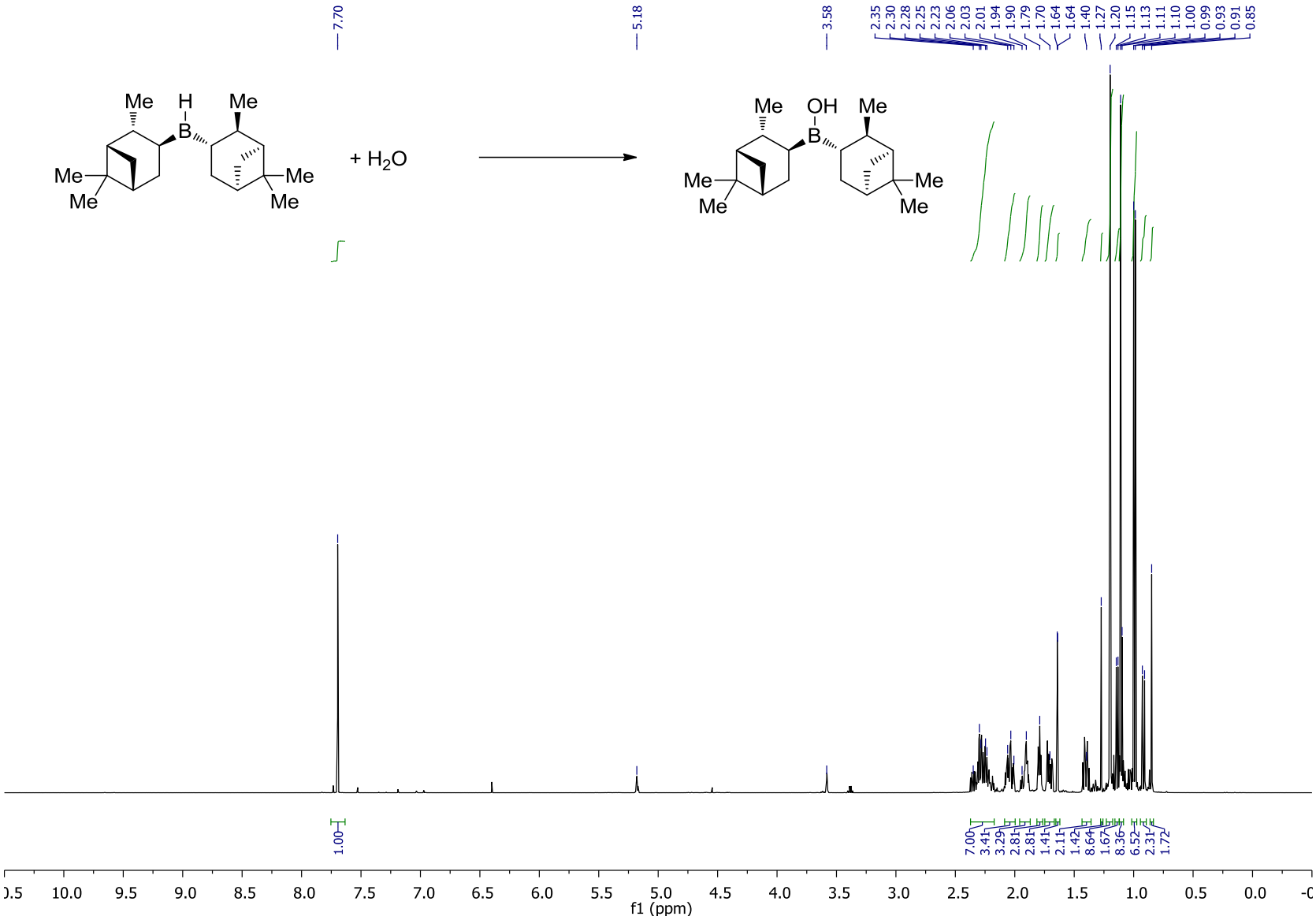
Jason R. Abbott received his B.S. in Chemistry from Northeastern University in Boston, MA. In 2008, Mr. Abbott enrolled in the Kellogg School of Science and Technology at the Scripps Research Institute–Florida to pursue his Ph. D. in Organic Chemistry. He joined the Roush Group shortly thereafter and defended his Ph. D. in early 2014.

Christophe Allais obtained his Ph. D. in 2010 from Université Paul Cézanne (Marseille, France), under the supervision of Prof. Constantieux and Prof. Rodriguez where he focused on the development of convergent and selective methods to access various heterocycles. In 2011, he joined Prof. Roush's Group as a research associate, expanding his research into the areas of medicinal chemistry, natural product synthesis, and the development of boron-mediated asymmetric methodologies. In March 2014, he joined Pfizer (Groton, CT) as a Senior Scientist.

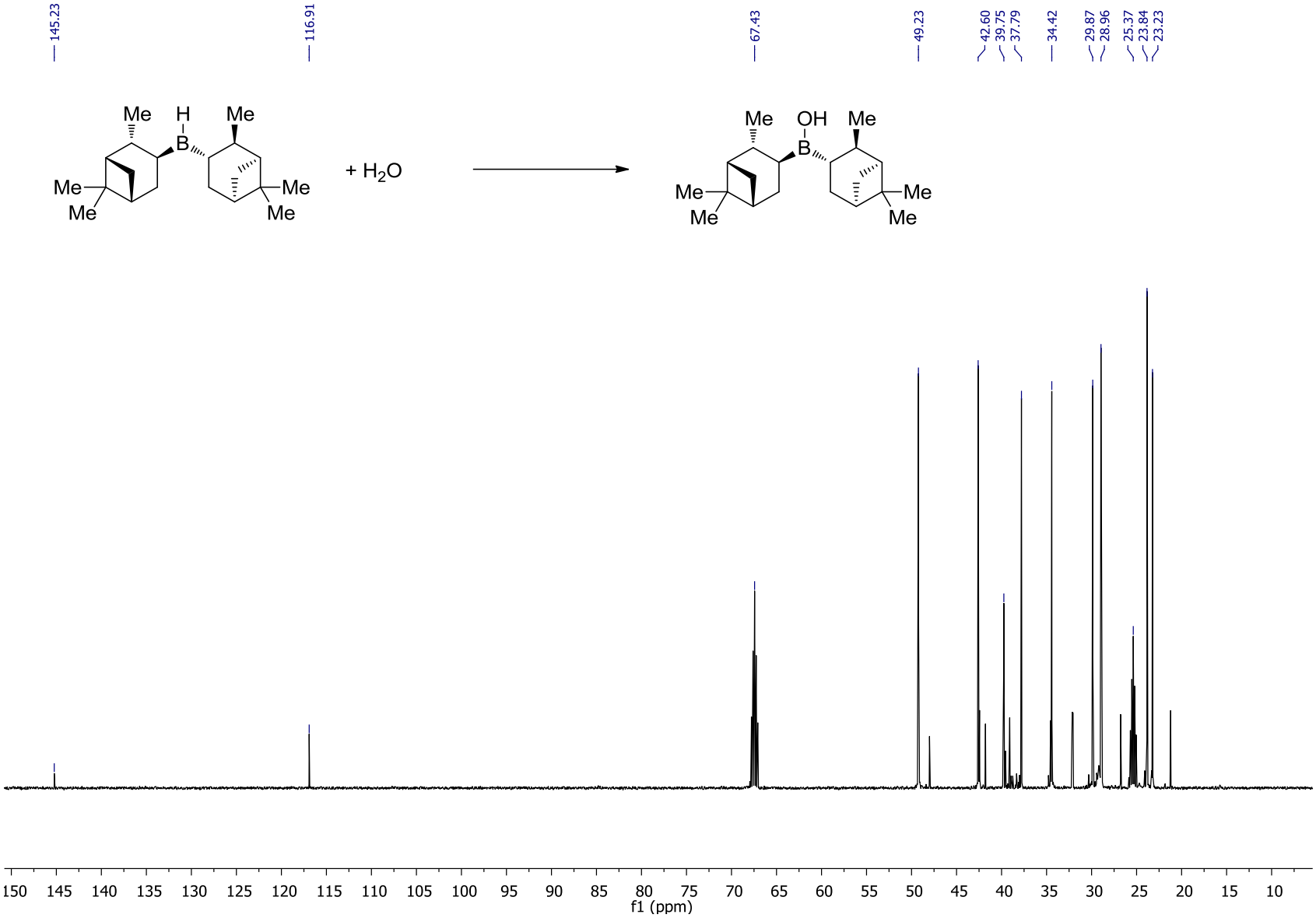
Simon Breitler, born in Basadingen, Switzerland, studied chemistry at ETH Zurich, which he concluded with a M. Sc. degree in 2011. During his undergraduate education, he carried out research projects in the laboratories of Prof. Erick M. Carreira and Prof. Antonio Togni. After an internship as a research trainee at Syngenta Crop Protection, Stein, Switzerland, he completed his studies with a Master's thesis in the laboratories of Prof. Stephen L. Buchwald at Massachusetts Institute of Technology, Cambridge MA, USA. Currently pursuing a Ph. D. in synthetic organic chemistry with Prof. Erick M. Carreira, his research focuses on natural product synthesis and asymmetric catalysis.

Simon Krautwald was born in Aachen, Germany, in 1986. He received a M. Sci. degree in Chemistry from Imperial College London in 2010. Simon is currently a Ph. D. candidate in Professor Erick M. Carreira's research laboratory at ETH Zurich, where he is studying iridium-catalyzed enantioselective allylic substitution reactions.

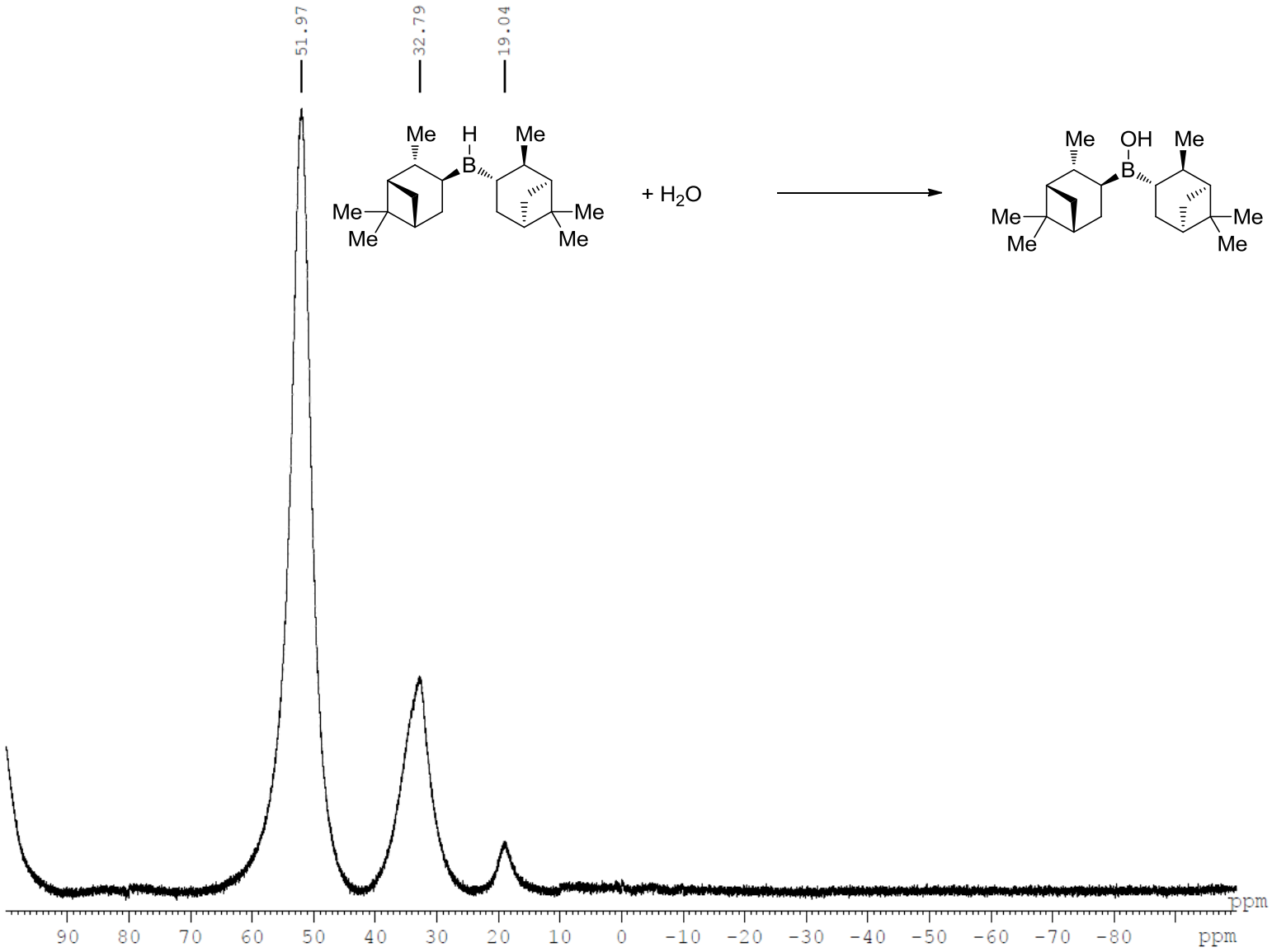
^{1}H NMR spectrum (500 MHz) of the compound formed by addition of water to **2** in d8-THF



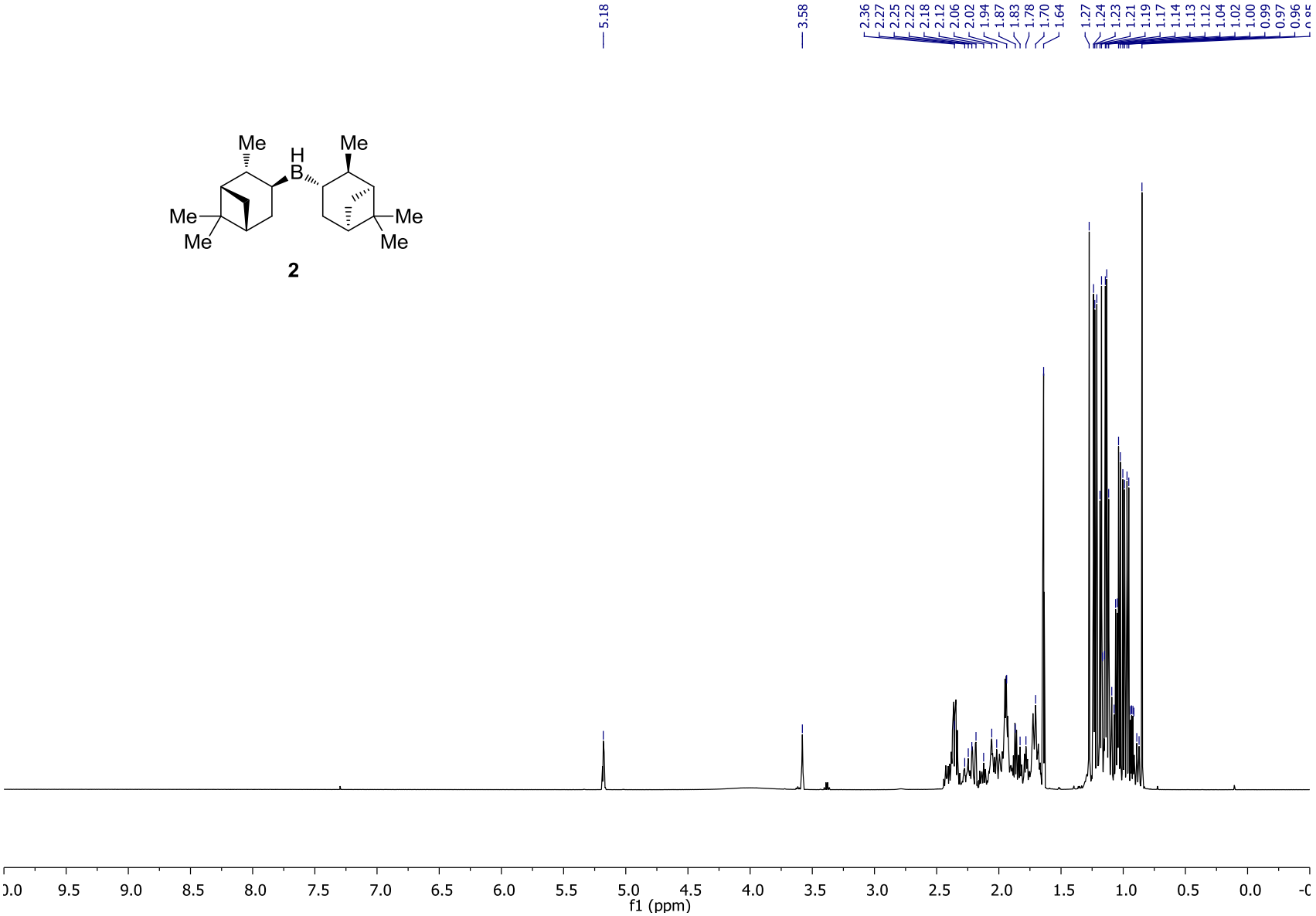
^{13}C NMR spectrum (125 MHz) of the compound formed by addition of water to **2** in d8-THF



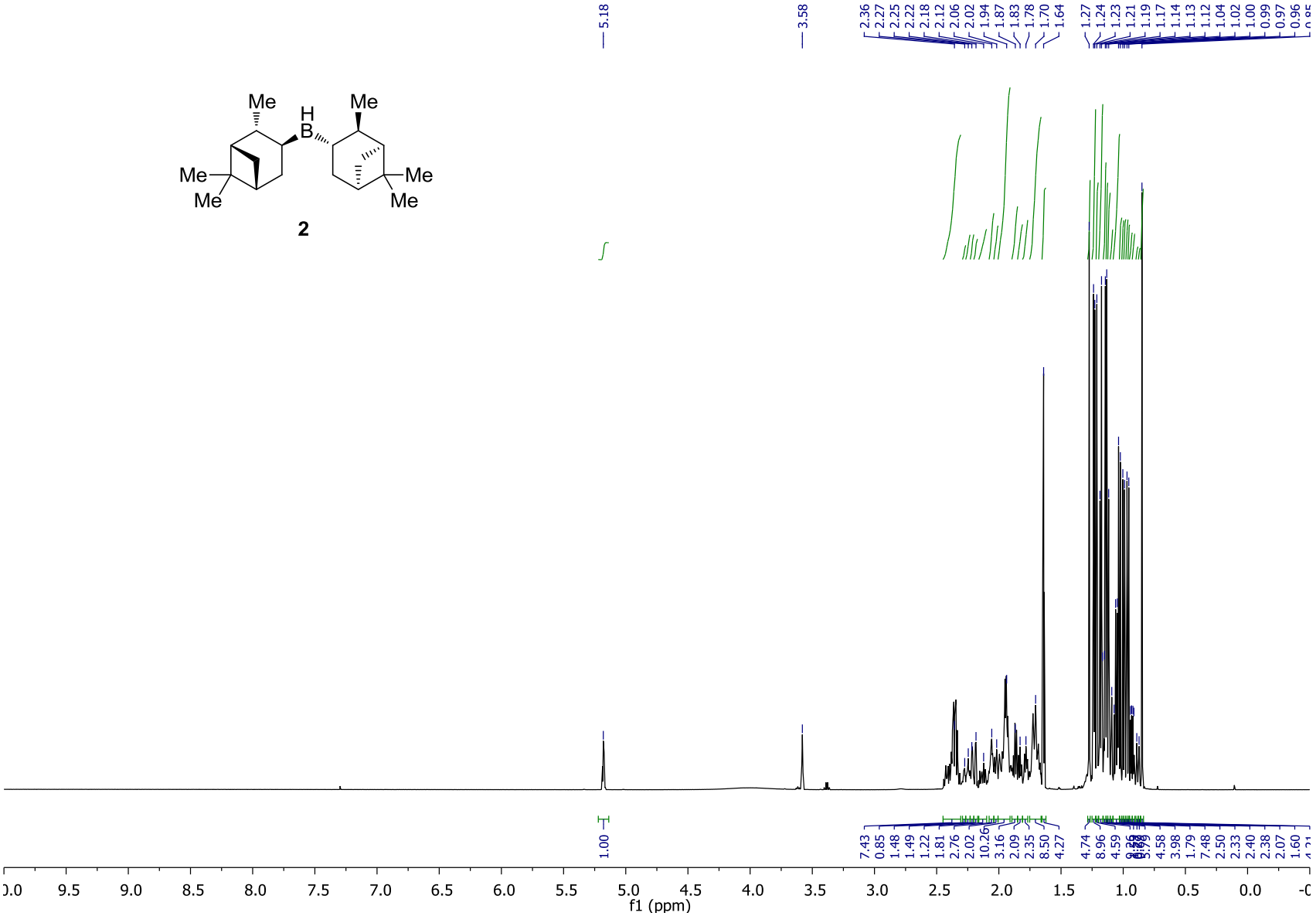
^{11}B NMR spectrum of the compound formed by addition of water to **2** in d8-THF



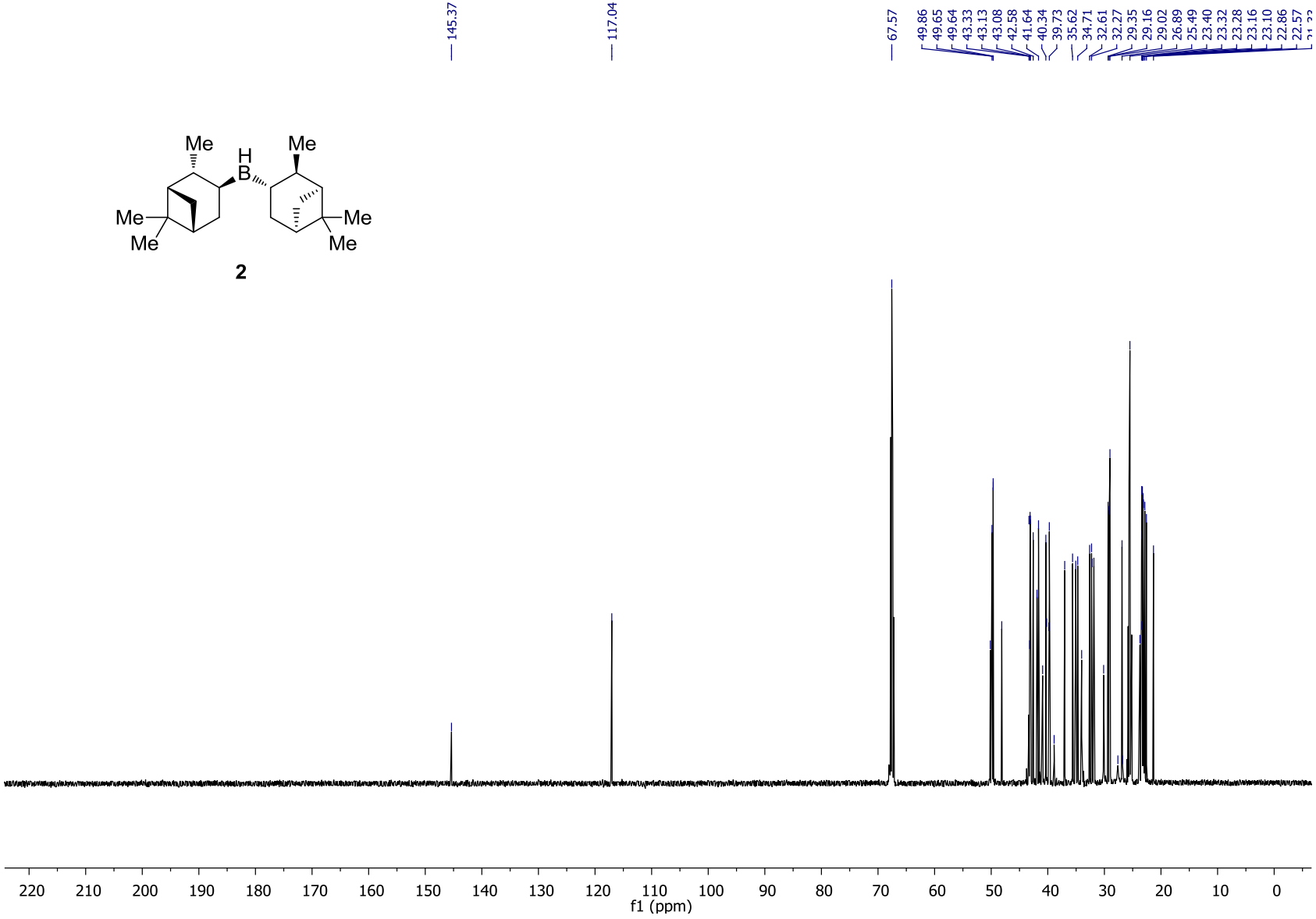
^{1}H NMR spectrum (500 MHz, anhydrous d8-THF) of compound **2**



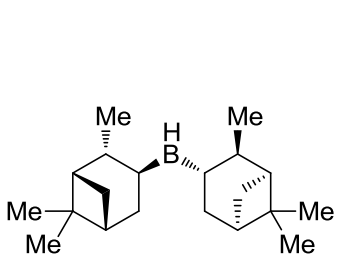
^{1}H NMR spectrum (500 MHz, anhydrous d8-THF) of compound **2**



^{13}C NMR spectrum (125 MHz, anhydrous d8-THF) of compound **2**



^{11}B NMR (anhydrous d8-THF) of compound **2**



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