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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.

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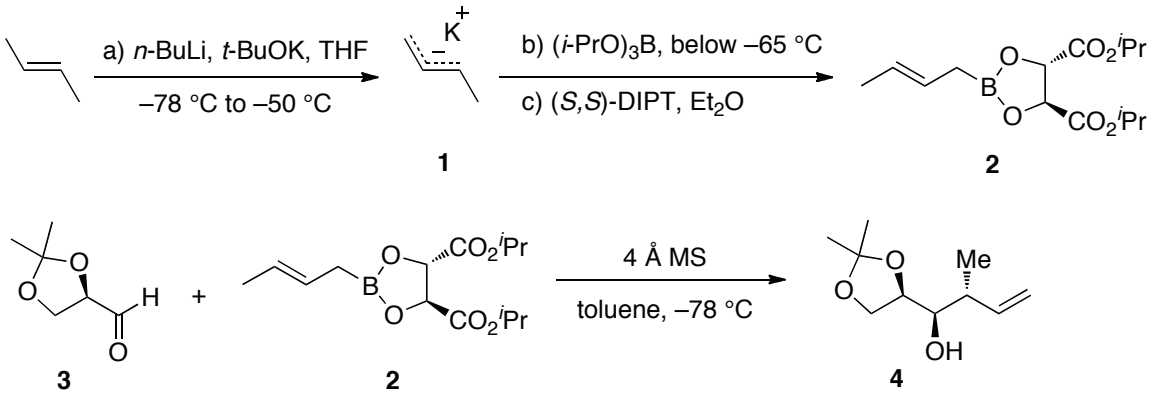
SYNTHESIS OF (*S*,*S*)-DIISOPROPYL TARTRATE (*E*)-CROTYLBORONATE AND ITS REACTION WITH ALDEHYDES: (2R,3R,4R)-1,2-DIDEOXY-2-ETHENYL-4,5-O-(1-METHYLETHYLIDENE)-XYLITOL



Submitted by Huikai Sun and William R. Roush.[1]
Checked by David A. Candito, Mathieu Blanchot, and Mark Lautens.

1. Procedure

A. (S,S)-Diisopropyl tartrate (E)-crotylboronate ***2***. An oven-dried 500-mL, three-necked, round-bottomed flask equipped with a 5-cm, egg-shaped stir bar, a rubber septum, and a digital and traceable thermocouple (Note 1) is connected to an argon line and is charged with *t*-BuOK (20.0 g, 95% purity, 170 mmol, 1.0 equiv) (Note 2) and anhydrous THF (85 mL) (Note 3) added by a syringe. This mixture is cooled to –78 °C with a dry ice/acetone bath, and then *trans*-2-butene (19.2 mL, 204 mmol, 1.2 equiv) (Note 4), condensed from a gas lecture cylinder into a 25-mL graduated cylinder immersed in a dry ice/acetone bath, is added via cannula. *n*-BuLi (2.5 M in hexane, 68.0 mL, 170.0 mmol) (Note 5) is added dropwise over 50 min using a syringe pump to make sure that the internal temperature does not rise above –65 °C. After the addition is complete, the cooling bath is removed, and the resultant yellow mixture is allowed to warm until the internal temperature reaches –50 °C (about 5 min). Then the reaction flask is quickly moved to an acetone bath precooled with dry ice to –50 °C. The internal temperature of the reaction solution is maintained between –50.0 °C to –50.5 °C for 25 min (Note 6) and then immediately recooled to –78 °C by moving the reaction flask to a dry ice/acetone bath.

Triisopropylborate (39.9 mL, 98% purity, 170 mmol) (Note 7) is added dropwise over 50 min via a syringe pump to the above orange solution of (*E*)-crotylpotassium **1** to make sure that the internal temperature does not rise above –65 °C. After completion of the addition, the reaction mixture is allowed to cool until the internal temperature remains constant around –72.5 °C, maintained at this temperature for 10 min, and then rapidly poured into a 1-L separatory funnel containing 1N HCl solution (320 mL) saturated with NaCl and shaken vigorously. The aqueous layer is adjusted to pH 1 by adding 1N HCl solution (110 mL), and then a solution of (*S*,*S*)-diisopropyl tartrate ((*S*,*S*)-DIPT) (40.6 g, 98% purity, 170 mmol) (Note 8) in Et_2O (60 mL) is added and the mixture is shaken vigorously. The organic phase is separated, and the aqueous layer is extracted with Et_2O (4 x 80 mL). The combined organic layers are dried with $MgSO_4$ (120 g) over 2.5 h and then vacuum filtered through a fritted glass funnel under an argon blanket (Note 9) into a 1-L, oven-dried and pre-tared round-bottomed flask. The filter cake is washed with anhydrous Et_2O (2 x 70 mL) (Note 10), and then the combined filtrate is concentrated on the rotary evaporator (from 40 mmHg to 10 mmHg at rt) to a colorless thick liquid, which is further concentrated on a vacuum line (0.5–1 mmHg) with stirring by a 5-cm, egg-shaped and pre-tared stir bar to constant weight (57 g). The crude product is dissolved in anhydrous toluene (120 mL) (Note 11) to form a clear solution (173 mL) of (*S*,*S*)-diisopropyl tartrate (*E*)-crotylboronate 2 (Note 12). The material so obtained has ≥98% isomeric purity (Note 13), the resulting toluene solution has a reagent concentration of 0.65 mol/L, and the yield of reagent is 66% according to titration analysis (Note 14).

*B. (2R,3R,4R)-1,2-Dideoxy-2-ethenyl-4,5-O-(1-methylethylidene)-xylitol **4***. An oven-dried, 500-mL, single-necked, round-bottomed flask equipped with a 5-cm, egg-shaped stir bar, a rubber septum, and an argon balloon, is charged with powdered 4 Å molecular sieves (12.0 g) (Note 15) and anhydrous toluene (160 mL) added by syringe. After a solution of (*E*)-crotylboronate **2** in toluene (72.0 mL, 0.69 mol/L, 49.7 mmol, 1.2 equiv) is added by syringe, the resulting mixture is stirred at rt for 30 min and then cooled to –78 °C with a dry ice/acetone bath. A solution of D-(*R*)-glyceraldehyde acetonide **3** (6.0 g, 90% purity, 41.5 mmol) (Note 16) in anhydrous toluene (15.0 mL) is added dropwise over 50 min (Note 17) via a syringe pump, and after completion of the addition, the reaction mixture is stirred at this temperature for 2.0 h (Note 18). The reaction is quenched by slowly adding aqueous 2 N NaOH (130 mL) over 5 min by syringe, then the

cooling bath is removed. After ambient temperature is reached (about 1.5 h), the mixture is vigorously stirred for an additional 20 min. The toluene layer is separated, and then the reaction flask containing some solid residue is rinsed with Et_2O (120 mL), which is then used to extract the aqueous solution. The same rinse and extraction operation is repeated two more times with Et_2O (2 x 120 mL). The combined organic layers are washed with sat. $NaHCO_3$ (100 mL), brine (2 x 100 mL), dried with Na_2SO_4 (120 g) and vacuum filtered through a Büchner funnel. The filtrate is concentrated (from 35 to 8 mmHg) by rotary evaporation at ambient temperature to give a colorless liquid, containing a >98% of **4** (Note 19). Purification of the product by flash column chromatography (Note 20) using ether/hexanes (1/4 to 1/3) as the eluent provides 5.1 g (66% yield) of (2*R*,3*R*,4*R*)-1,2-dideoxy-2-ethenyl-4,5-*O*-(1-methylethylidene)-xylitol **4** as a colorless oil (Note 21).

2. Notes

1. The digital and traceable thermocouple (Fisherbrand, –200 °C ~ +1370 °C) was purchased from Fisher Scientific Company.

2. Potassium *tert*-butoxide (95% purity) was purchased from Sigma-Aldrich chemical Company, Inc., and stored and transferred in a glove box.

3. Tetrahydrofuran was purchased from Fisher Chemical Company and dried by fresh distillation from sodium/benzophenone ketyl under an atmosphere of dry argon.

4. The checkers purchased *trans*-2-butene from TCI (min. 99.0%, GC). The submitters purchased *trans*-2-butene (99+% purity) from Aldrich Chemical Company, Inc. and used as stored. It is necessary to use 1.1–1.2 equiv of *trans*-2-butene in order to compensate for the loss of the material during transfer.

5. *n*-Butyllithium (2.5 M in hexane) was purchased from Aldrich Chemical Company, Inc., stored at 5 °C and used as received.

6. The temperature of the central part of the reaction solution was monitored. Placing the probe of the thermocouple against reaction flask wall resulted in the isomeric purity of the crotylboronate reagent being reduced by 1-2%. The internal temperature of the solution was maintained between –55 °C and –50 °C by removing the flask from the cooling bath (dry ice/acetone) and allowing it to approach –50 °C, at which time the flask was resubmerged to lower the temperature. No deterioration of selectivity was observed.

7. Triisopropylborate (≥98% purity) was purchased from Sigma-Aldrich Chemical Company, Inc. and used as stored.

8. (*S*,*S*)-Diisopropyl tartrate ((*S*,*S*)-DIPT) (98% purity) was purchased from Sigma-Aldrich Chemical Company, Inc. and used as received.

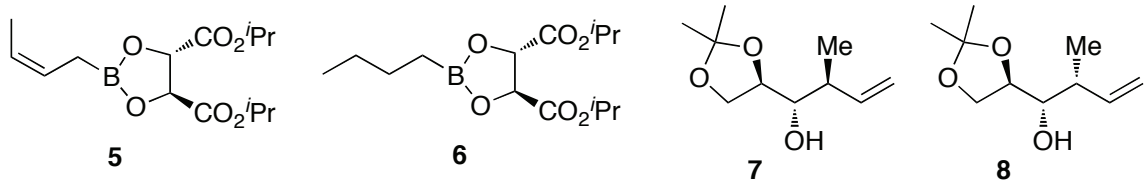
9. The fritted glass funnel was covered with a Fisherbrand long-stem analytical funnel, to which an argon flow was applied through the long-stem end in order to prevent the solution from being exposed to moisture in air.

10. Anhydrous diethyl ether was purchased from Fisher Chemical Company and purified by passage through activated alumina using a GlassContour solvent purification system under argon.

11. Toluene was purchased from Fisher Chemical Company and purified by passage through activated alumina using a GlassContour solvent purification system under argon.

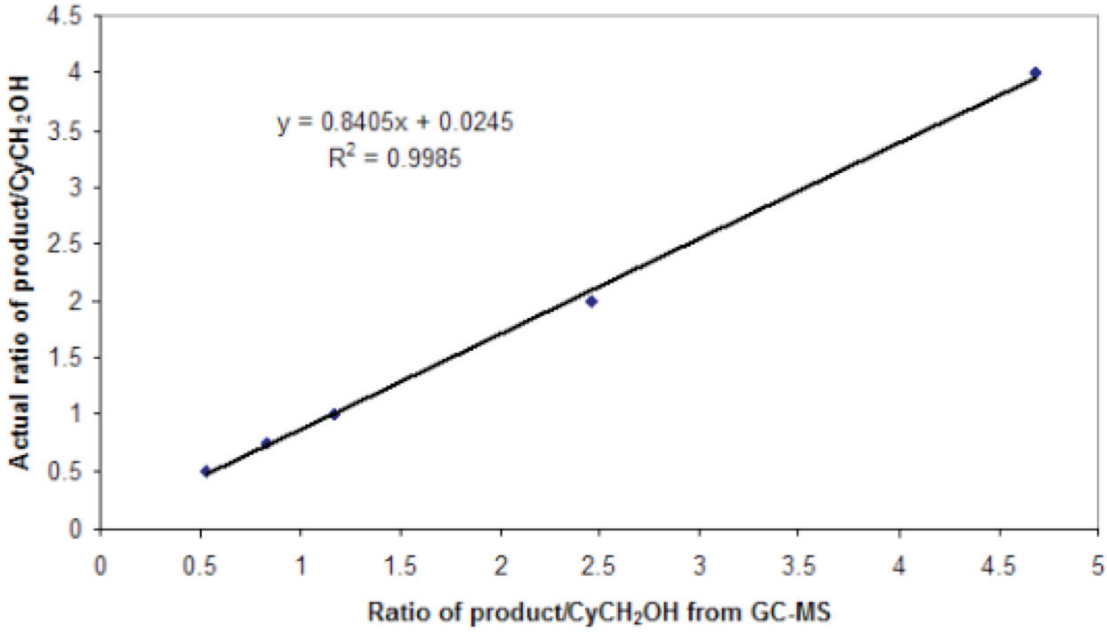
12. (*S*,*S*)-DIPT (*E*)-crotylboronate **2** is moisture sensitive, so it is handled as a solution in toluene. The total volume was measured when the toluene solution was transferred to an oven-dried, 250-mL, single-necked, round bottom flask by a syringe. No apparent decomposition was observed after this solution was stored at –20 °C under Ar for several months. It was previously reported that the reagent could be purified by distillation,[2] but the submitters found the procedure not to be reproducible owing to ease of decomposition. Therefore, for the past two decades the reagent has been consistently used in the submitter's laboratory as a solution in toluene without further purification.

13. The checkers determined isomeric purity by GC/MS (Elmer Autosystem XL GC coupled to Perkin Elmer turbomass MS; Column: 0.25 mm x 30 m, 0.25 μm film thickness, ZB5 (5% diphenyl/95%dimethyl-polysiloxane); Temperature program 70 °C to 170 °C over 10 min, then hold at 170 °C for 10 min; t_R for **2** is 11.85 min). The submitters determined isomeric purity of the product by GC analysis (30 m x 0.32 mm Agilent capillary metal column packed with silicon polymers; temperature program: 70 °C to 170 °C over 10 min, then hold at 170 °C for 10 min; t_R for **2** is 11.9 min; t_R for (*Z*)-crotylboronate **5** is 12.0 min). 11% of tartrate *n*-butylboronate **6** (t_R is 11.6 min) was present, reflecting incomplete metallation of *trans*-2-butene in this experiment, along with 8% of DIPT (t_R is 8.2 min) according to GC analysis.



5 **6** **7** **8**

14. The checkers determined the yield and concentration of tartrate (*E*)-crotylboronate **2** by NMR. A 1-mL aliquot of the solution of (*E*)-crotylboronate **2** was withdrawn and transferred to a 25-mL round-bottomed flask and the solvent was removed under high vacuum. Then 30 μL of mesitylene (Aldrich, >99% purity) was measured accurately and added using a syringe. Then $CDCl_3$ was added (approximately 5 mL) and the flask was swirled a few times to ensure a homogenous concentration. Some of the solution was transferred to an NMR tube and the spectra was recorded using a 10 second relaxation delay. The concentration was then determine by the relative integration of the internal standard peak at 6.78 ppm (s, 3 H) and the signal of **2** centered on 5.47 ppm (m, 2 H). The submitters determined the yield and concentration of the solution of tartrate (*E*)-crotylboronate **2** by a titration procedure as described below. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a stir bar, a rubber septum, and an argon balloon, is charged with cyclohexanecarboxaldehyde (112 mg, 1.0 mmol) and toluene (1.5 mL). A toluene solution (1.0 mL) of reagent **2** was added and stirred at rt for 1.0 h. The reaction solution was cooled to 0 °C by an ice bath, and methanol (1.0 mL) was added followed by $NaBH_4$ (113 mg, 3.0 mmol, 3.0 equiv). The resulting reaction mixture was vigorously stirred at rt for 1.5 h, and then 2 N NaOH (2 mL) was added carefully and the mixture vigorously stirred at rt for 30 min to hydrolyze the tartrate ester. The organic phase was separated and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were dried over K_2CO_3 and concentrated in vacuo (> 25 mmHg) to remove Et_2O, and then more toluene was added to make a 10 mL solution for GC analysis (the same temperature program was used as described in Note 13). Under these conditions cyclohexylmethanol (from reduction of unconsumed aldehyde) elutes at 3.0 min and homoallylic alcohol products (anti and syn) elute at 6.2 min. From the measured ratio of homoallylic alcohols over cyclohexylmethanol, the submitters calculate the concentration of reagent **2** solution and its yield accordingly. A standard curve was made by using cyclohexylmethanol (4.0 mg/mL) as internal standard and samples with ratios of homoallylic alcohols/cyclohexylmethanol of 0.5, 0.75, 1.0, 2.0 and 4.0.



15. Powdered 4 Å molecular sieves (activated, 2.5 μm) were purchased from Sigma-Aldrich Chemical Company, Inc., further activated by flame heating under vacuum (0.5–1 mmHg) for 15 min and used a hour after cooling to rt under dry Ar atmosphere.

16. D-(*R*)-glyceraldehyde acetonide **3** was prepared according to the procedure of Schmid and Bryant.[3] The product (roughly 90% purity by ^{1}H NMR analysis) was obtained as a colorless liquid by distillation under vacuum (19–20 mmHg); fractions distilling at 46–48 °C were collected with an oven-dried flask immersed in an ice/water bath. The aldehyde **3** so obtained was used in the crotylboration reaction 30–45 min after distillation.

17. Aldehyde **3** (6.0 g) was dissolved in anhydrous toluene (12 mL) in an oven-dried, 50-mL, single-necked, round-bottomed flask. Then the resultant solution was added to the reaction mixture via a syringe pump over 45 min. An additional 3 mL of anhydrous toluene was used to rinse the flask and then was added to the reaction mixture via a syringe pump over 5 min.

18. The progress of the reaction cannot be monitored by TLC analysis because aldehyde **3** overlaps with impurities on the TLC plate. Submitters performed a small-scale reaction under the same conditions for 3.0 h and observed no increase in yield after product purification. Therefore, it was concluded that the reaction is complete after 2.0 h.

19. The checkers determined the isomeric purity of the crude reaction mixture to be >98% by GC/MS (Elmer Autosystem XL GC coupled to

Perkin Elmer turbomass MS; Column: 0.25 mm x 30 m, 0.25 μm film thickness, ZB5 (5% diphenyl/95%dimethylpolysiloxane); Temperature program 60 °C for 40 min, then increased to 170 °C over 5.5 min and hold at 170 °C for 10 min; t_R for **4** is 32.19 min. The submitters report that the crude product contains >98.0% of **4**, <1.5% of the (2*R*,3*S*,4*S*)-isomer **7** and <0.5% of the (2*R*,3*S*,4*R*)-diastereomer **8** (which derives from the minor (Z)-crotylboronate present in the reagent). Accordingly, the diastereoselectivity of this reaction was determined to be > 98.5:1.5. These data were obtained from GC-MS analysis (temperature program: 60 °C for 40 min, then increased to 170 °C over 5.5 min and hold at 170 °C for 10 min; t_R for **4** is 25.9 min; t_R for **7** is 27.6 min; t_R for **8** is 26.1 min).

20. Flash column chromatography was performed on a silica gel (EMD, grade 60, 40-63 μm) column. 10% Et_2O in hexanes (10 mL) was used to load the crude product onto a glass column (6.5 cm diameter) packed with 410 g of silica gel. The column was eluted with Et_2O/hexanes = 1/4 (1000 mL) followed by Et_2O/hexanes = 1/3 (ca 2000 mL) at 40 mL/min flow rate. Individual fractions (ca. 25 mL) were analyzed by TLC, and fractions were combined based on their composition as determined by TLC analysis. The first set of pooled fractions (1-2% yield, R_f = 0.57, Et_2O/hexanes = 1/3, 3 developments, UV and $KMnO_4$ active) contains a mixture of several unidentified compounds. The second set of pooled fractions (ca 15 to 20 test tubes) contain the desired product **4** (R_f = 0.52, Et_2O/hexanes = 1/3, 3 developments, UV and $KMnO_4$ active). The purity of **4** obtained in this way was determined to be 99+% by both ^{1}H NMR and GC-MS (Note 19). Mixed, trailing fractions containing ca. 80 mg of **4** (85-90% purity by ^{1}H NMR) mixed together with **8** (R_f = 0.42, Et_2O/hexanes = 1/3, 3 developments, UV and $KMnO_4$ active) and some unidentified compounds (R_f = 0.40, Et_2O/hexanes = 1/3, 3 developments, UV and $KMnO_4$ active) were recovered. A small sample of adduct **8** (from a separate run) was purified by a second column purification with Et_2O/hexanes = 1/3, which gave **8** with 92% purity according to GC-MS analysis. Finally, a small sample of diastereomer **7** (R_f = 0.34, Et_2O/hexanes = 1/3, 3 developments, UV and $KMnO_4$ active) was obtained in 96% purity from the first column as determined by GC-MS analysis. Diastereomers **4**, **7** and **8** displayed physical properties in agreement with data previously reported.[4]

21. Product **4** exhibits the following properties: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (d, *J* = 6.9 Hz, 3 H), 1.36 (s, 3 H), 1.42 (s, 3 H), 2.20 – 2.30 (m, 2 H), 3.39 (dd, *J* = 10.6, 5.0 Hz, 1 H), 3.73 (dd, *J* = 8.0, 7.0

Hz, 1 H), 4.00 (dd, J = 8.0, 6.5 Hz, 1 H), 4.10 (dd, J = 12.9, 6.5 Hz, 1 H), 5.00–5.11 (m, 2 H), 5.87 (ddd, J = 17.2, 10.4, 8.1 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 16.90, 25.64, 26.77, 41.51, 66.34, 75.44, 77.22, 109.41, 115.72, 139.71. $[\alpha]^{D}_{26}$ 15.7 (*c* 0.93, CH_2Cl_2). IR (film): 3476 (br), 2985, 2877, 1458, 1373, 1215, 1157, 1072, 1045, 914, 860 cm^{-1}. The material so obtained was identical in all respects with the compound described in the literature.[4]

Safety and Waste Disposal Information

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

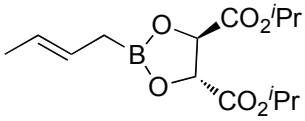
3. Discussion

Chiral crotylmetal reagents are important and useful reagents that react with aldehydes to give α-methyl-homoallylic alcohols with excellent stereoselectivity.[5] The reactions of (E)-crotylboron reagents with aldehydes is particularly useful, in that these reagents provide 2,3-*anti* diastereomers typically with greater selectivity than can be obtained by using propionate enolates via aldol reactions. To date, many efficient and practical chiral crotylmetal reagents or crotylmetallation procedures have been reported,[5] including those by Roush,[2,6] Brown,[7] Corey,[8] Leighton,[9] Denmark,[10] Soderquist,[11] Hall[12] and Krische,[13] among others. The DIPT modified (E)-crotylboronate reagent developed by Roush and his coworkers, and which is illustrated in the present procedure, is one of the most widely adopted reagents due to the ease of preparation, storage and handling, and the high selectivity obtained in crotylboration reactions of chiral aldehydes—especially in the matched double asymmetric mode.[2,6c-f]

The current procedure for preparation of (*S*,*S*)-diisopropyl tartrate (*E*)-crotylboronate (**2**) follows the protocol previously reported by the Roush group.[2] This procedure involves the metallation of *trans*-2-butene with *n*-BuLi and *t*-BuOK in THF at –50 °C for 25 min to generate (*E*)-crotylpotassium **1** with high isomeric purity (>98%). Treatment of **1** with $(i\text{-PrO})_3B$ followed by aqueous hydrolysis and esterification with (*S*,*S*)-diisopropyl tartrate (DIPT) furnished the (*S*,*S*)-DIPT (*E*)-crotylboronate reagent, **2**. Care must be taken in this procedure to minimize isomerization

of (*E*)-crotylpotassium **1** to the thermodynamically more stable (*Z*)-isomer. The conditions for metallation of *trans*-2-butene reported here are those that maximize conversion while minimizing production of the (Z)-crotylpotassium (and subsequently the (Z)-crotylboronate) isomer. Thus, the reagent obtained as described here has >98% isomeric purity, but contains 10–12% of butylboronate **6** from borylation of residual BuLi that remains owing to incomplete metallation of 2-butene under these conditions. Previous studies in the submitter's laboratory indicate that amount of **6** can be suppressed by increasing reaction temperature to –45 °C for 15 min, or by increasing the reaction time at –50 °C to up to 45 min, but with some erosion of isomeric purity. With these modifications, the isomeric purity of **2** is reduced by 1–2% (e.g., 96–97% isomeric purity for **2**).[2]

(*R*,*R*)-DIPT (*E*)-crotylboronate **9** can be prepared from *trans*-2-butene and (*R*,*R*)-DIPT according to the same procedure as described here.[2] The preparation of (*Z*)-crotylboronates **5** and **10** by using *cis*-2-butene and the appropriate enantiomer of DIPT is analogous to the procedure described for (*E*)-crotylboronates with the exception that the metallation of (Z)-2-butene is performed at –20 to –25 °C for 30–45 min, which ensures high conversion in the metallation step to form (*Z*)-crotylpotassium. In comparison to preparation of (*E*)-crotylpotassium, the temperature control is less critical since (*Z*)-crotylpotassium is highly favored at equilibrium (>99:1). The remaining procedure is the same as that described for the synthesis of (*E*)-crotylboronate **2**.



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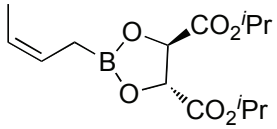

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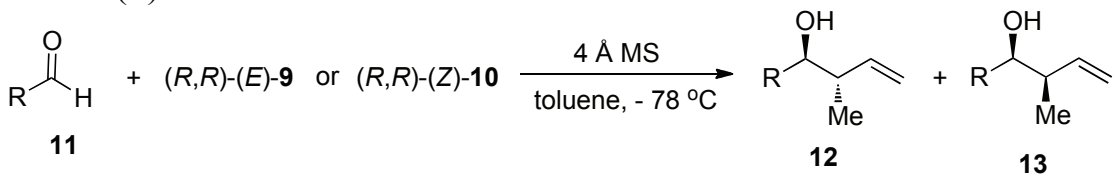
The crotylboration reactions of aldehydes are performed in toluene solution at –78 °C for aliphatic aldehydes and in THF for aromatic aldehydes.[2, 6c, 6h] Best results are obtained by performing the reactions in the presence of powdered 4 Å molecular sieves to maintain an anhydrous reaction environment. Otherwise, crotylboronic acid resulting from hydrolysis of the moisture-sensitive chiral crotylboronate can function as a competitive, but achiral crotyl transfer reagent.

Reactions of crotylboronate reagents (*R,R*)-(*E*)-**9** and (*R,R*)-(*Z*)-**10** with achiral aliphatic aldehydes are reported to furnish the corresponding secondary homoallylic alcohols with 70 to 88% enantiomeric excess, as

summarized in Table 1.[2] In some cases, the enantioselectivity can be increased to 91% ee when crotylboration is performed at –95 °C (entry 4). The reactions with pivalaldehyde, α,β-unsaturated aldehydes and aromatic aldehydes are less enantioselective (entries 8-13). *Anti* products **12** are usually obtained with >99% diastereoselectivity when 98% isomeric pure (*E*)-crotylboronate reagents are used. However, the reactions with 99% isomeric pure (*Z*)-crotylboronates afford *syn* products **13** with 97–98% diastereoselectivity. In addition, *anti* products **12** also exhibit higher enantiomeric purity than *syn* products **13**. These different results between **12** and **13** indicate that (*E*)-crotylboronates are more reactive and more enantioselective than their *Z*-crotyl counterparts

Double asymmetric reactions of the tartrate ester modified crotylboronates with chiral, non-racemic α-branched aldehydes also provide high diastereoselectivity in matched and in many mismatched double asymmetric reactions, as shown in Table 2.[6c-g] The facial selectivity of the crotylboration reaction is reversed upon switching the chirality of the chiral crotylboronate reagents, especially in reactions with chiral aldehydes with very modest intrinsic diastereofacial preferences. Numerous applications of these tartrate ester modified crotylboronate reagents have been reported in the total syntheses of natural products in the past two decades.[5a, 5f, 15]

Table 1. Crotylboration of Achiral Aldehydes with (*R*,*R*)-(*E*)-**9** and (*R*,*R*)-(*Z*)-**10**.



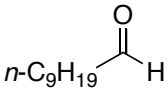
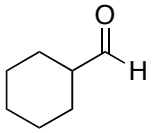
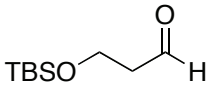
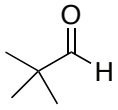
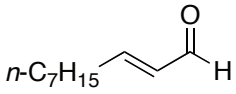
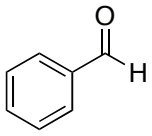
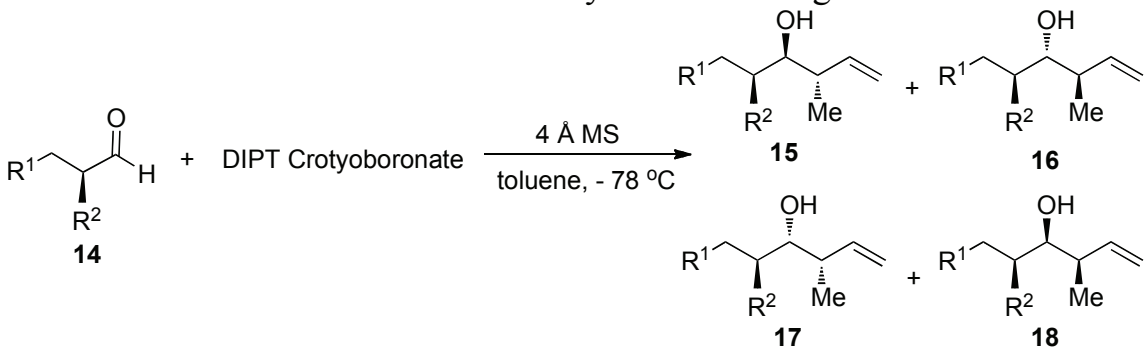
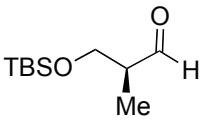
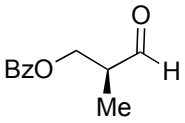
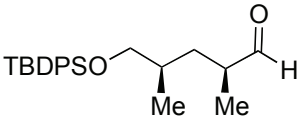
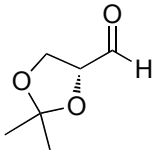
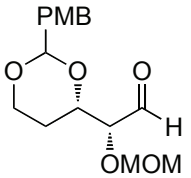
Entry	aldehydes (**11**)	reagent	isomeric purity	reaction time (yield)	anti:syn (**12** : **13**)	ee of major isomer
1		(*R*,*R*)-*E*-**9**	99.4	3 h (87%)	>99 : 1	88%
2		(*R*,*R*)-*Z*-**10**	98	6 h (80%)	3 : 99	82%
3		(*R*,*R*)-*E*-**9**	99.3	3 h (94%)	>99 : 1	85%
4		(*R*,*R*)-*E*-**9**	98	4 h (100%) (–95 °C)	>99 : 1	91%
5		(*R*,*R*)-*Z*-**10**	99	6 h (90%)	2 : 98	83%
6		(*R*,*R*)-*E*-**9**	98	4 h (71%)	>98 : 2	85%
7		(*R*,*R*)-*Z*-**10**	98	4 h (68%)	2 : >98	72%
8		(*R*,*R*)-*E*-**9**	99	6 d (41%)	95 : 5	73%
9		(*R*,*R*)-*Z*-**10**	99.5	6 d (66%)	1 : >99	70%
10		(*R*,*R*)-*E*-**9**	99	4 h (91%)	>99 : 1	74%
11		(*R*,*R*)-*Z*-**10**	98	6 h (83%)	3 : 97	62%
12		(*R*,*R*)-*E*-**9**	99.3	3 h (91%)	>99 : 1	66%
13		(*R*,*R*)-*Z*-**10**	99	6 h (94%)	2 : 98	55%

Table 2. Double Asymmetric Crotylboration of Chiral Aldehydes with Tartrate Ester Modified Crotylboronate Reagents



Entry	aldehydes (**14**)	reagent[a]	yield[b]	**15** (%)	**16** (%)	**17** (%)	**18** (%)
1	 **14a**	(*R*,*R*)-(*E*)-**9**	80%	[97]	3	—	—
2		(*S*,*S*)-(*E*)-**2**	--	16	[81]	3	—
3		(*S*,*S*)-(*Z*)-**5**	71%	—	4	[95]	1
4[c]		(*R*,*R*)-(*Z*)-**10**	--	12	2	45	41
5	 **14b**	(*R*,*R*)-(*E*)-**9**	--	[93]	5	1	1
6		(*S*,*S*)-(*E*)-**2**	--	15	[85]	—	—
7		(*S*,*S*)-(*Z*)-**5**	--	—	3	[88]	9
8		(*R*,*R*)-(*Z*)-**10**	--	2	—	46	[52]
9	 **14c**	(*R*,*R*)-(*E*)-**9**	56%	[98]	2	1	1
10		(*S*,*S*)-(*E*)-**2**	55%	16	[84]	—	—
11		(*S*,*S*)-(*Z*)-**5**	51%	—	—	[94]	6
12		(*R*,*R*)-(*Z*)-**10**	52%	6	—	16	[78]
13[d]		(*R*,*R*)-(*E*)-**9**	87%	[87]	9	—	4
14[e]		(*S*,*S*)-(*E*)-**2**	70%	2	[97]	1	—
15		(*S*,*S*)-(*Z*)-**5**	--	—	—	16	84
16		(*R*,*R*)-(*Z*)-**10**	80%	—	—	1	[99]
17[f]		(*S*,*S*)-(*E*)-**2**	86%	6	[94]	—	—

[a] 98-99% isomeric pure reagents were used. [b] Yields are for two steps including preparation of aldehydes. [c] In retrospect, the crotylboronate had pure isomeric purity. [d] 1.3-1.5 equiv. of aldehyde was used. [e] The reaction was performed under the conditions as described in the present procedure. [f] See reference 14.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

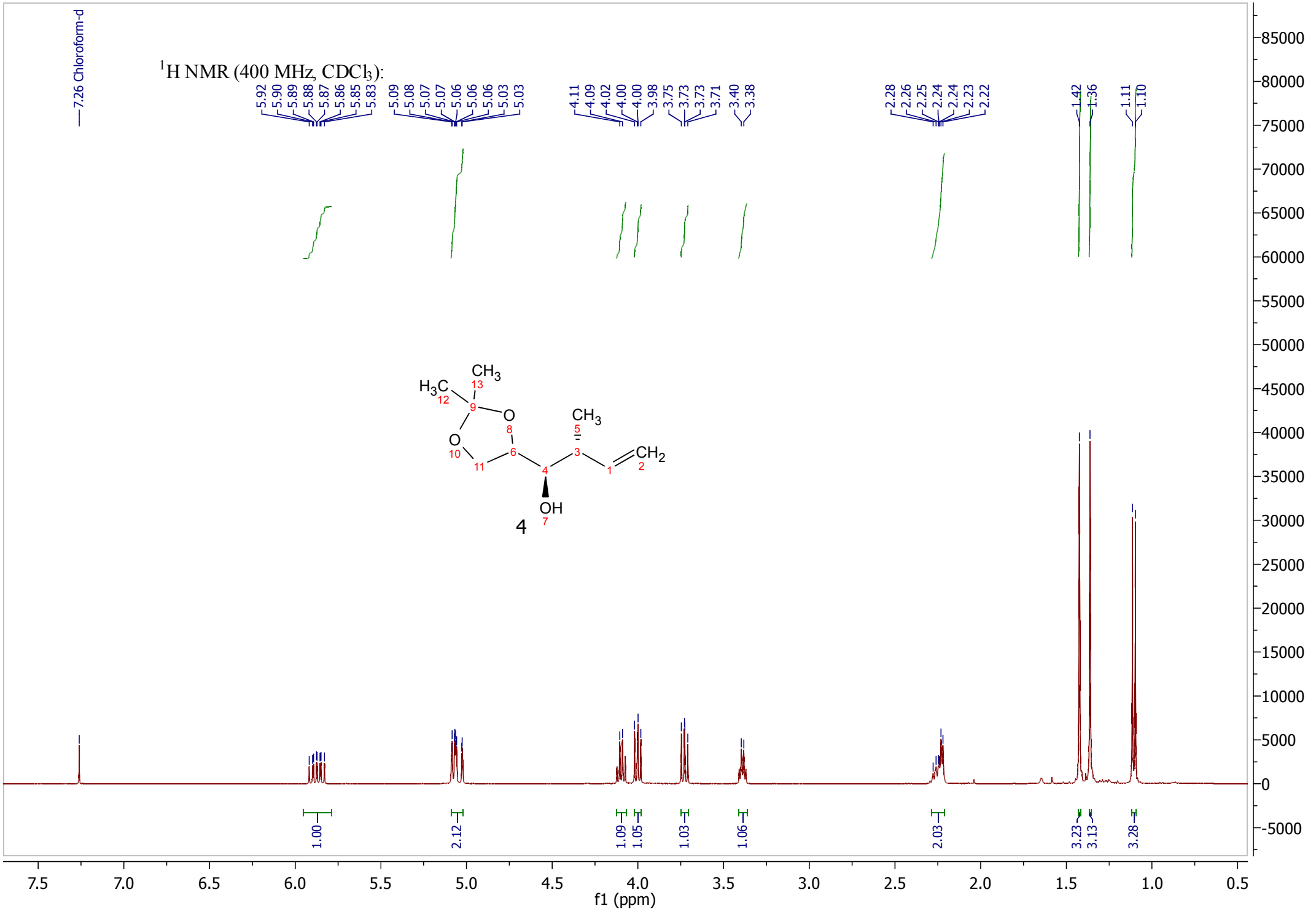
Potassium *tert*-butoxide; (865-47-4)
Trans-butene; (624-64-6)
Triisopropylborane; (5419-55-6)
(*S*,*S*)-Diisopropyl tartrate ((*S*,*S*)-DIPT); Diisopropyl *D*-tartrate (*D*-DIPT); (62961-64-2)
(*S*,*S*)-Diisopropyl tartrate (*E*)-crotylboronate; (99687-40-8)
(*R*,*R*)-Diisopropyl tartrate (*E*)-crotylboronate; (99745-86-5)
(*S*,*S*)-Diisopropyl tartrate (*Z*)-crotylboronate; (106357-33-9)
(*R*,*R*)-Diisopropyl tartrate (*Z*)-crotylboronate; (106357-20-4)
D-(*R*)-glyceraldehyde acetonide; (15186-48-8)
(*3R*,*4R*,*5R*)-3-Methyl-5,6-O-isopropylidene-hex-1-ene-4-ol ((2R,3R,4R)-1,2-dideoxy-2-ethenyl-4,5-O-(1-methylethylidene)-xylitol); (88424-94-6)
(*3S*,*4S*,*5R*)-3-Methyl-5,6-O-isopropylidene-hex-1-ene-4-ol; (88424-95-7)
(*3S*,*4R*,*5R*)-3-Methyl-5,6-O-isopropylidene-hex-1-ene-4-ol; (96094-43-8)

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. Then he moved to his current position as a postdoctoral research associate in Professor William R. Roush's group. His current research interests focus on the total synthesis of natural products and the development of cysteine protease inhibitors.

David A. Candito completed his undergraduate degree at York University in 2007 where he had the opportunity to work with Professor Michael Organ on palladium-catalyzed cross-coupling reactions employing the Pd-PEPPSI-IPr catalyst system. He then joined the group of Professor Mark Lautens at the University of Toronto where he is currently pursuing a Ph.D. His doctoral research has focused upon palladium-catalyzed domino reactions involving the use of norbornene to functionalize aryl C–H bonds and he is also engaged in exploring the use of aryne intermediates in transition metal catalyzed processes.

Mathieu Blanchot was born in Autun (France) in 1982 and studied chemistry in Dijon and Lyon (France). After completing his Diploma-Thesis under the direction of Prof. Genevieve Balme, he joined the group of Prof. Lukas Gooßen in Kaiserslautern (Germany) where he received his Ph.D. for his work on the Hydroamidation of Alkynes. He is currently working as a Postdoctoral researcher with Prof. Mark Lautens in Toronto, ON (Canada) where his research is focused upon palladium-catalyzed domino direct arylation/N-arylation.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4.11 4.09 4.02 4.00 4.00 3.98 3.75 3.73 3.73 3.71 3.40 3.38
2.28 2.26 2.25 2.24 2.24 2.23 2.22
1.42 1.36
1.11 1.10
CH3
H3C
O
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CH2
OH
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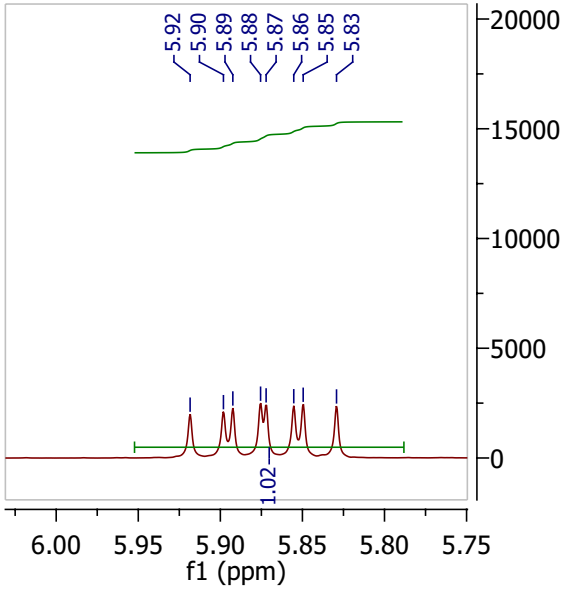
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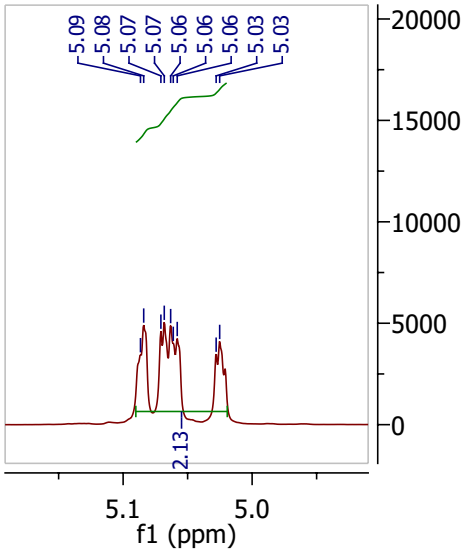
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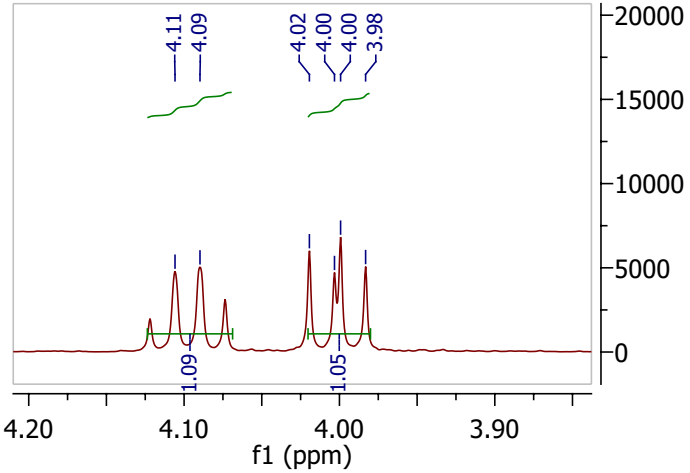
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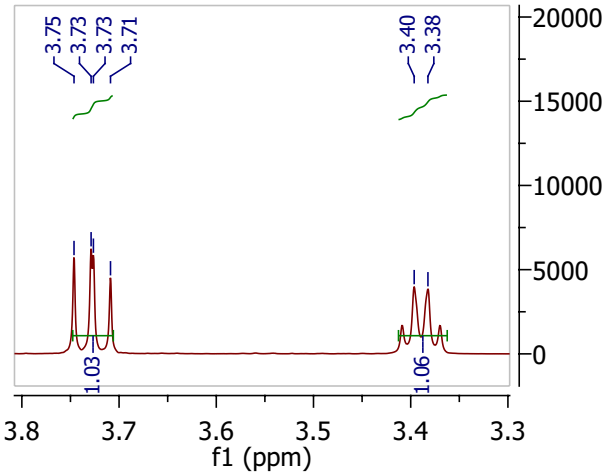
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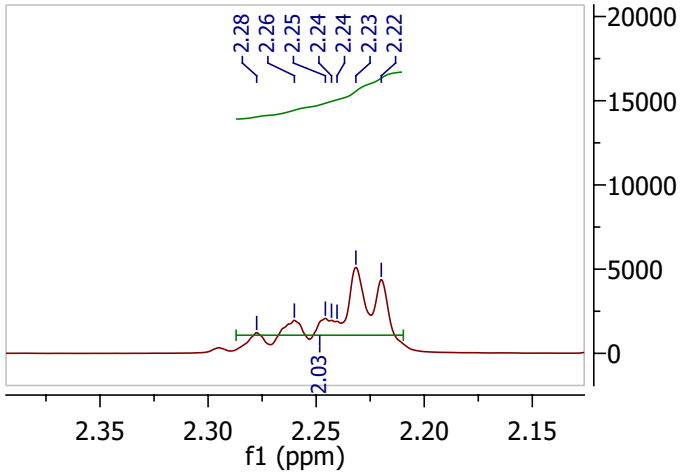
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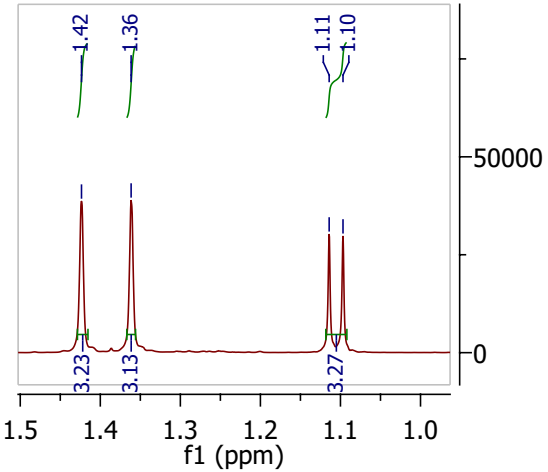
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