

Factors Affecting Migration of Tertiary Alkyl Groups in Reactions of Alkylboronic Esters with Bromomethylithium

Mark C. Elliott,* Keith Smith,* D. Heulyn Jones, Ajaz Hussain and Basil A. Saleh

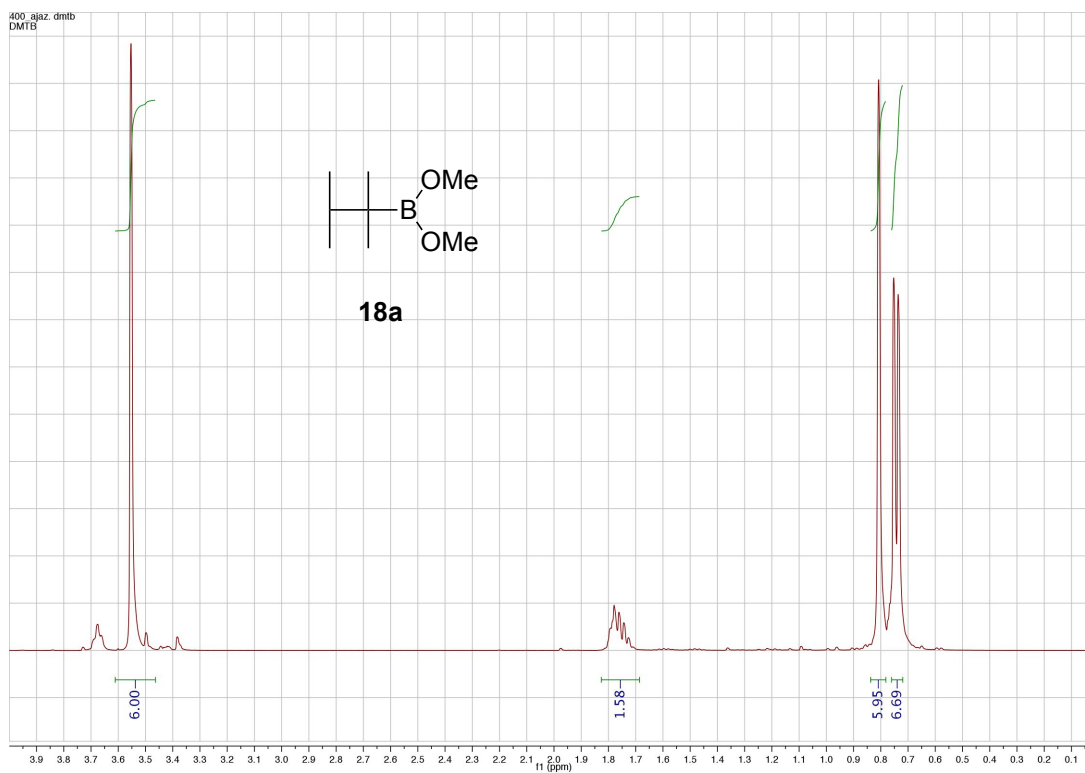
School of Chemistry, Cardiff University, Main College Building, Park Place, Cardiff, CF10 3AT, UK

Supporting Information – Synthetic Study

Copies of ^1H , ^{13}C and ^{11}B NMR Spectra	3
Dimethyl thexylboronate (18a)	3
2-Thexyl-1,3,2-dioxaborolane (18b)	4
2-Thexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18c)	6
2-Thexyl-1,3,2-dioxaborinane (18d)	8
2-Thexyl-5,5-dimethyl-1,3,2-dioxaborinane (18e)	10
Bis(2,2,2-trichloroethyl) 2-thexylboronate (18f)	12
2-Thexyl-1,3,2-oxathiaborolane (19)	14
2-Thexyl-1,3,2-dithiaborolane (20)	16
2,2,3-Trimethyl-1-butanol (thexylmethanol) (purified)	18
Thexylmethanol crude reaction mixtures after oxidation	19
5,5-Dimethyl-2-(3-ethylpent-2-yl)-1,3,2-dioxaborinane (28)	22
Homologation of compound 28 using Methods A and B	24
2,2-Diethyl-1-butanol	25
2-(9-Octylheptadecan-9-yl)-1,3,2-dioxaborolane (29)	26
Homologation of compound 29 using Method A	28
Homologation of compound 29 using Method B	28
5,5-Dimethyl-2-(9-octylheptadecan-9-yl)-1,3,2-dioxaborinane (30)	29
Homologation of compound 30 using Method B	31
2-(Tricyclopentylmethyl)-1,3,2-dioxaborolane (31)	32

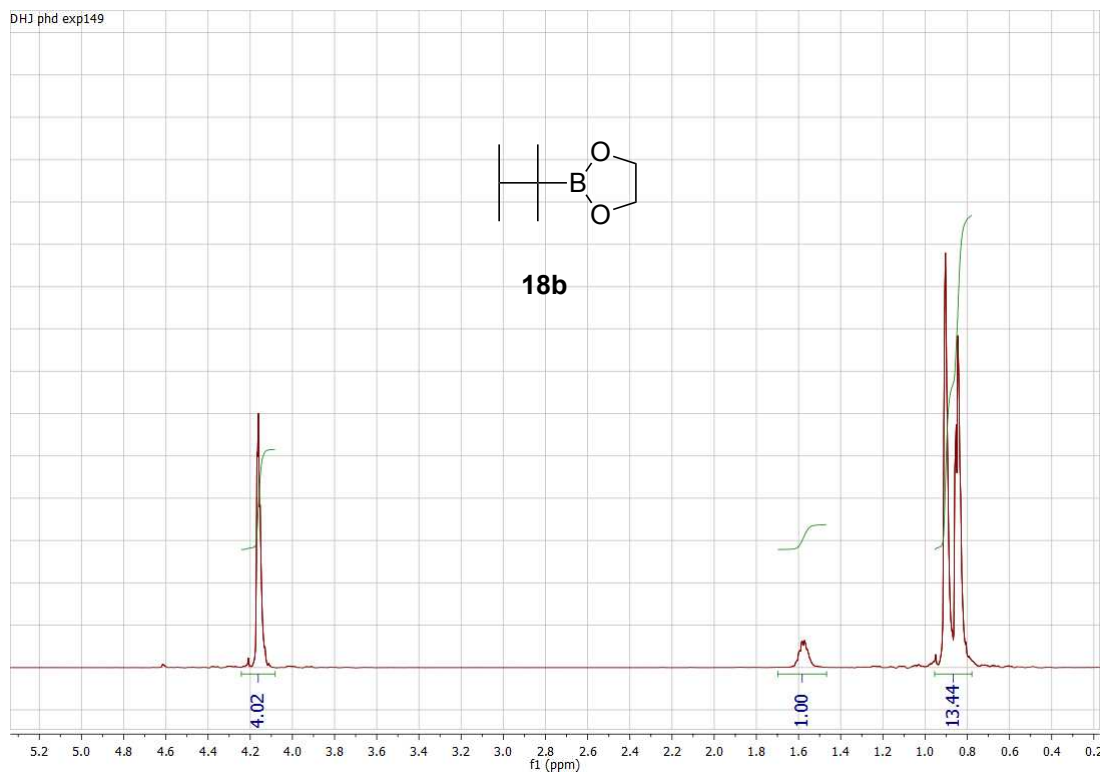
2-(Tricyclopentylmethyl)-1,3,2-dioxaborinane (32)	34
Tricyclopentylmethanol	36
Synthesis of compounds 35 and 36 – Reaction Schemes	37
(±)-1-Phenylethyl <i>N,N</i> -diisopropylcarbamate	38
2-Isopropyl-1,3,2-dioxaborinane	39
2-Isopropyl-5,5-dimethyl-1,3,2-dioxaborinane	41
(±)-5,5-Dimethyl-2-(3-methyl-2-phenylbutan-2-yl)-1,3,2-dioxaborinane (35)	43
(±)-2-(3-Methyl-2-phenylbutan-2-yl)-1,3,2-dioxaborinane (36)	45
2,3-Dimethyl-2-phenyl-1-butanol (34)	47
3-Methyl-2-phenyl-2-butanol (37)	48
Spectroscopic Study	49

Copies of ^1H , ^{13}C and ^{11}B NMR Spectra
Dimethyl thexylboronate (18a)



2-*Thexyl*-1,3,2-dioxaborolane (18b)

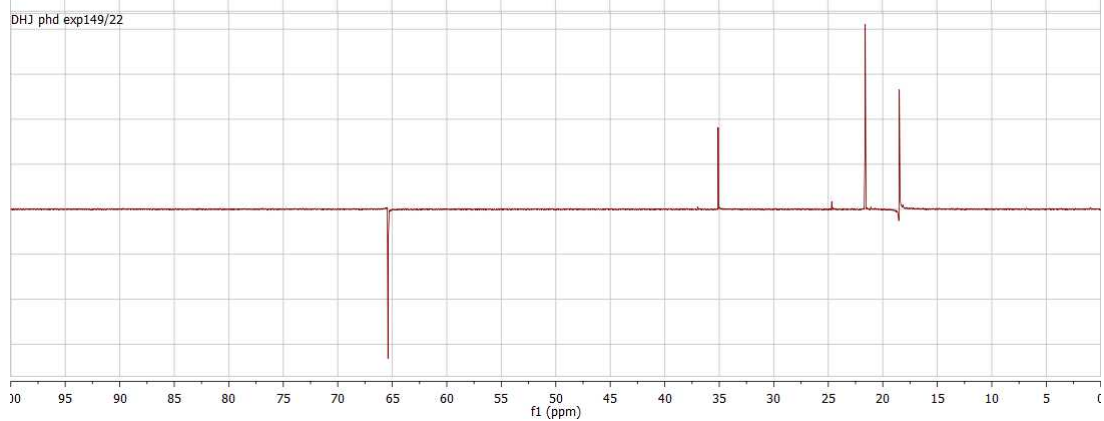
DHJ phd exp149



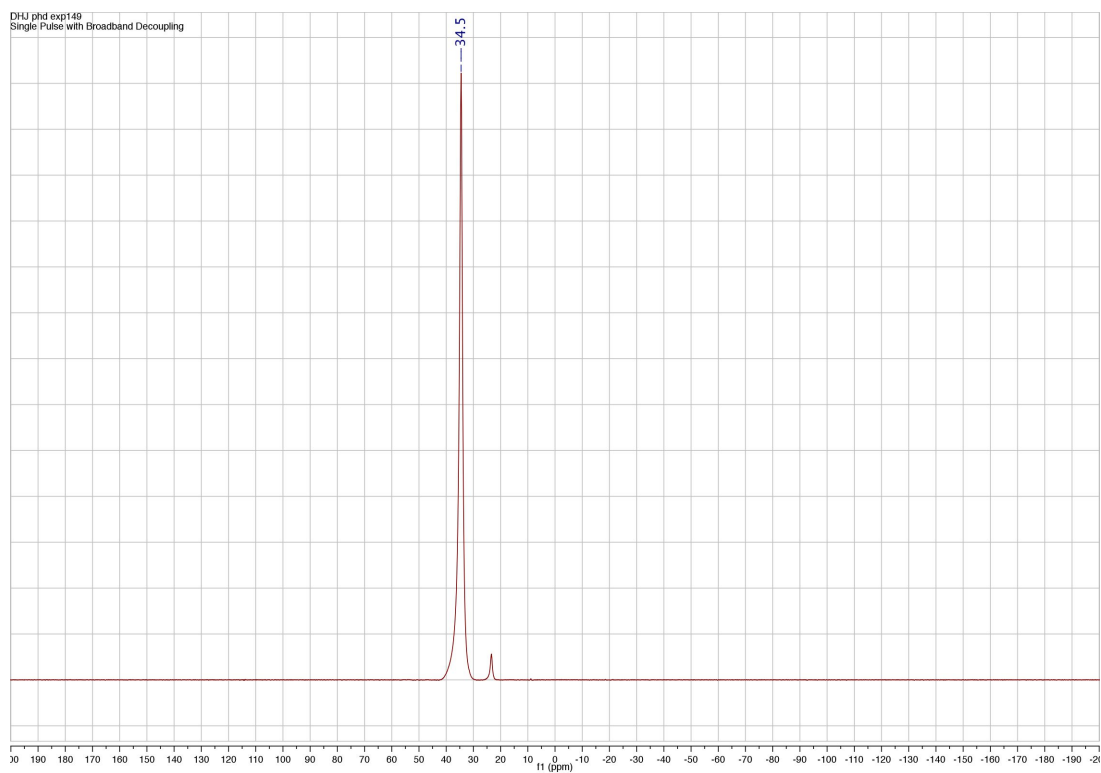
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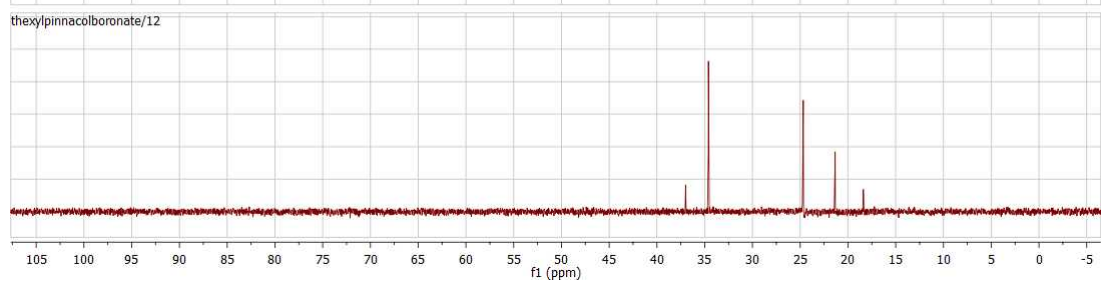
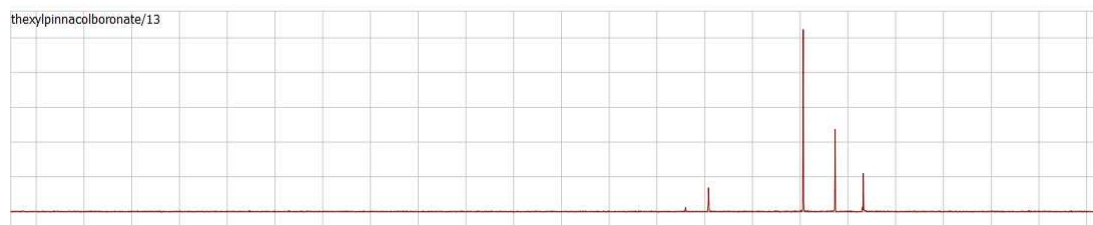
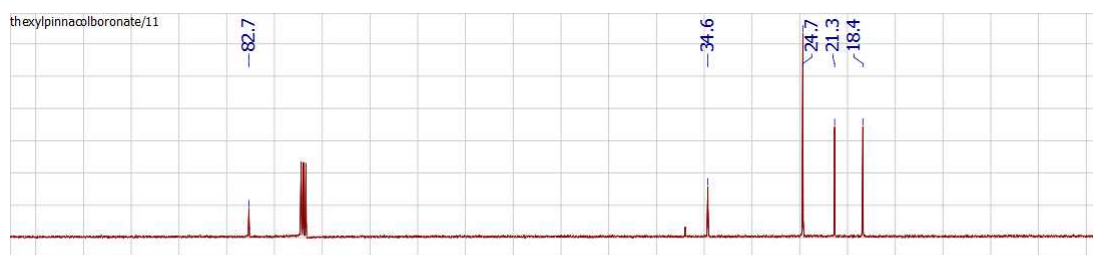
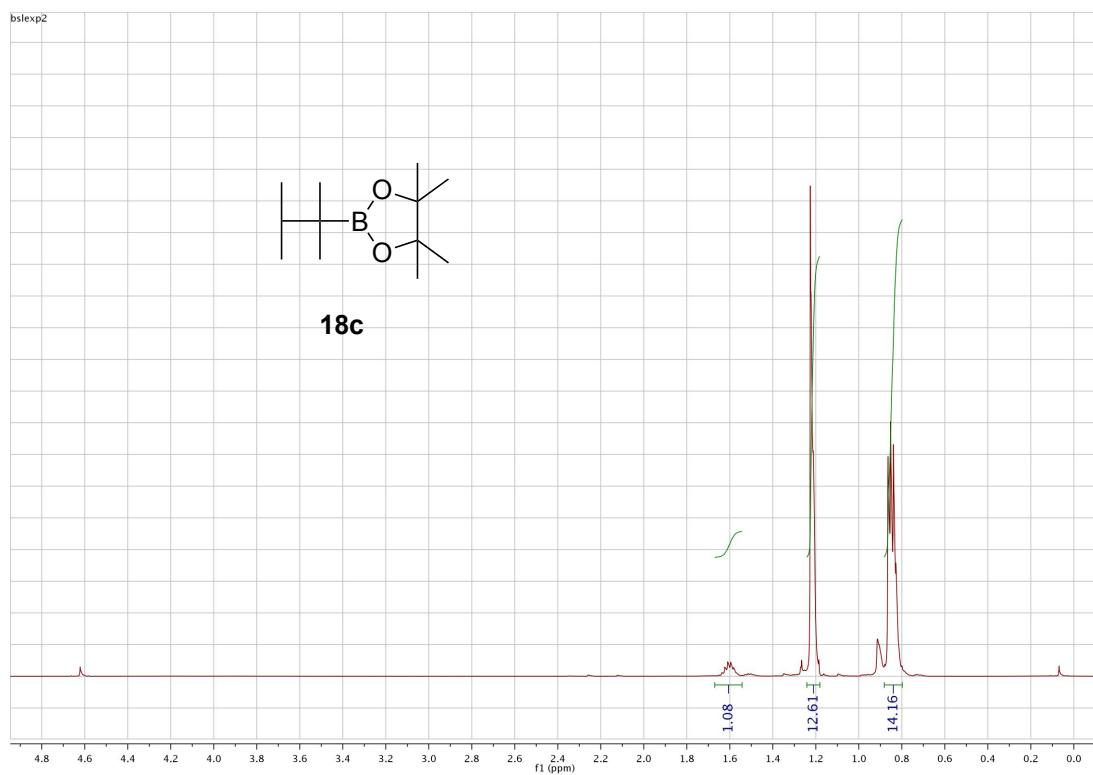
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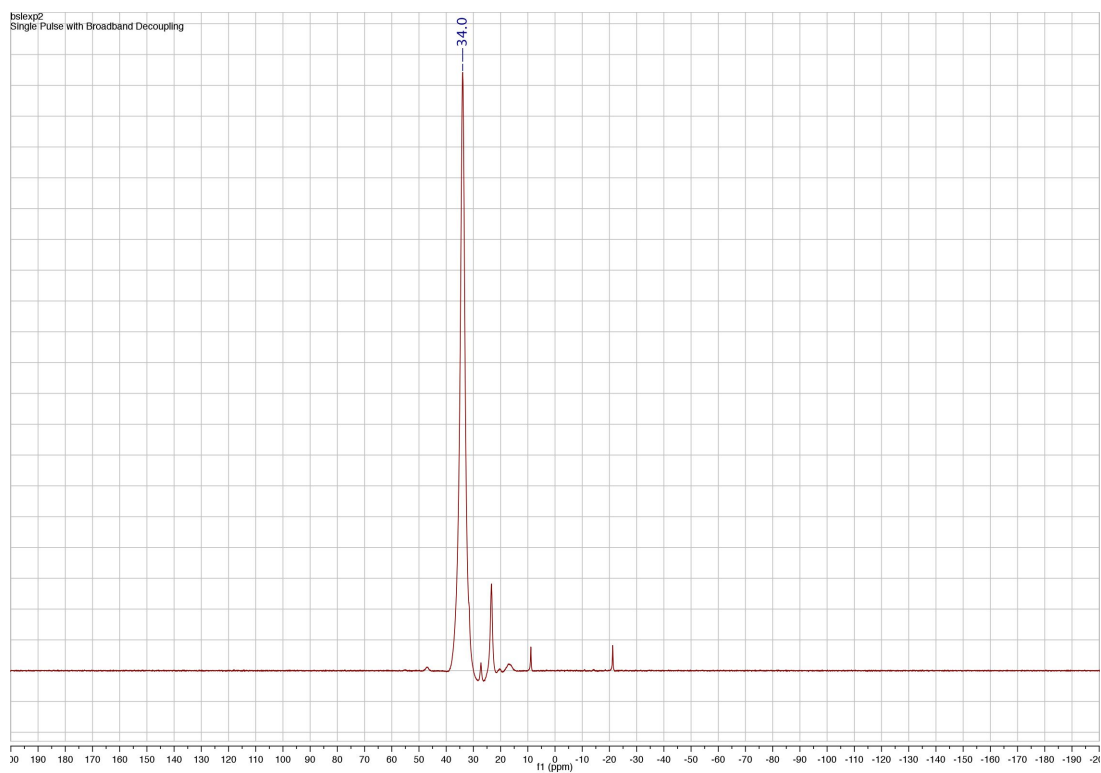


DFJ phd exp149
Single Pulse with Broadband Decoupling

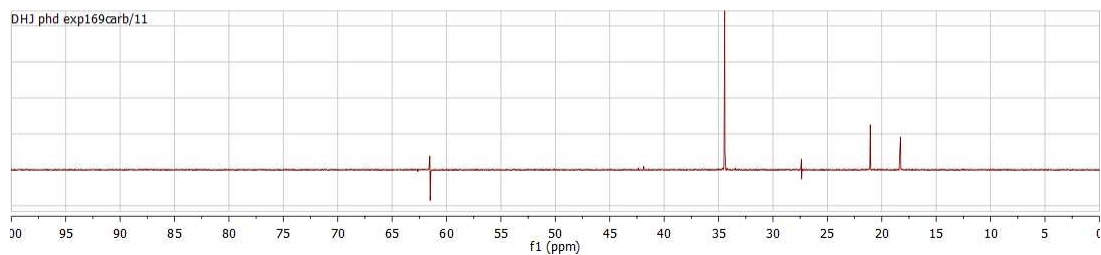
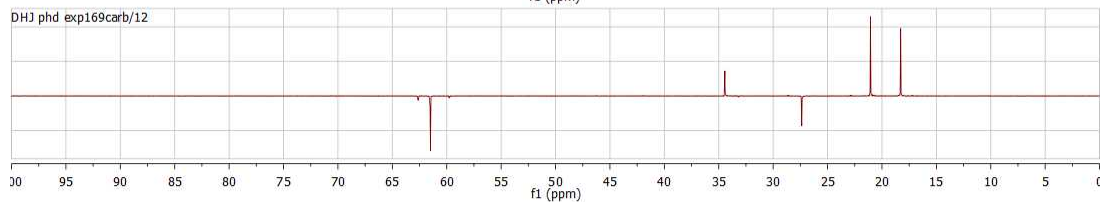
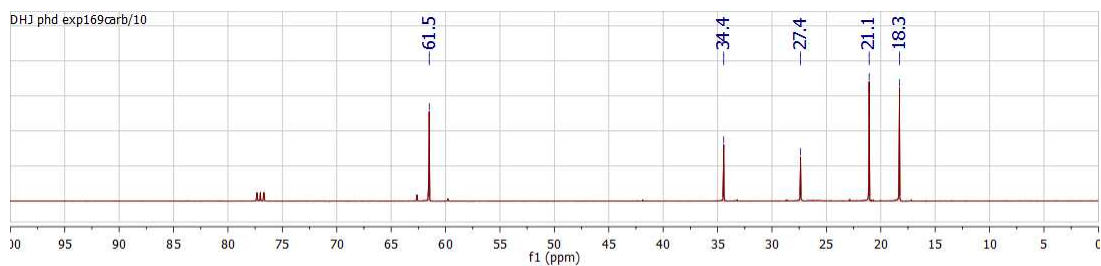
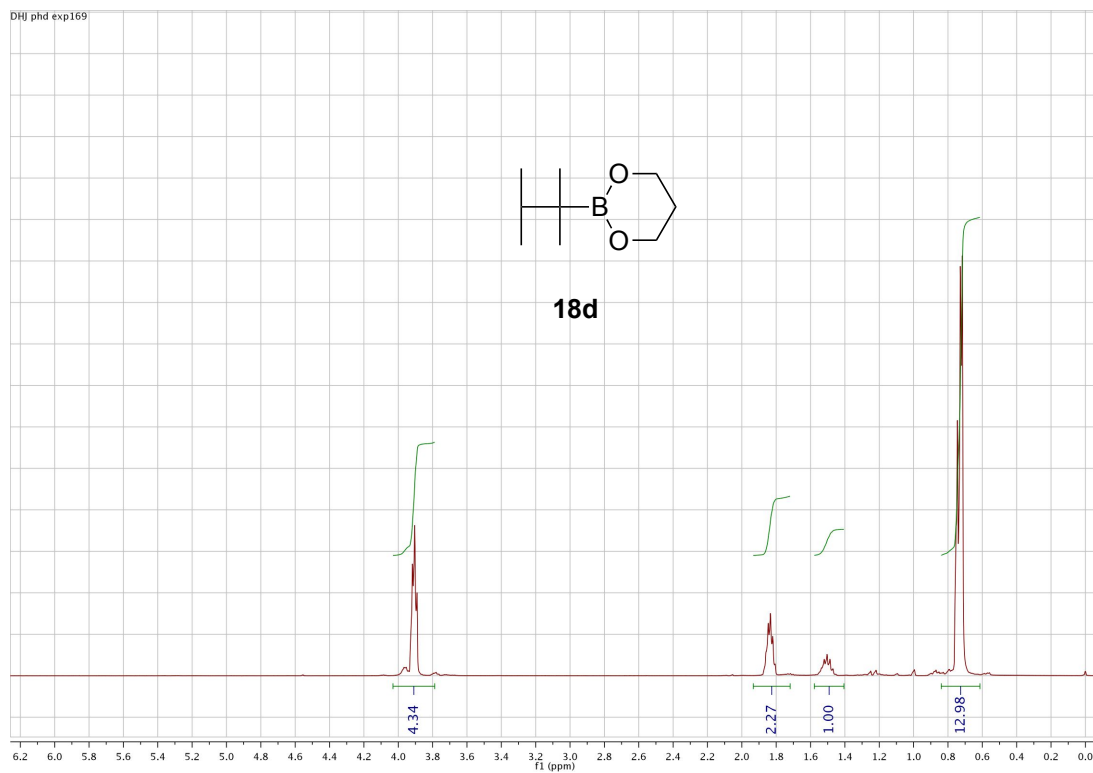


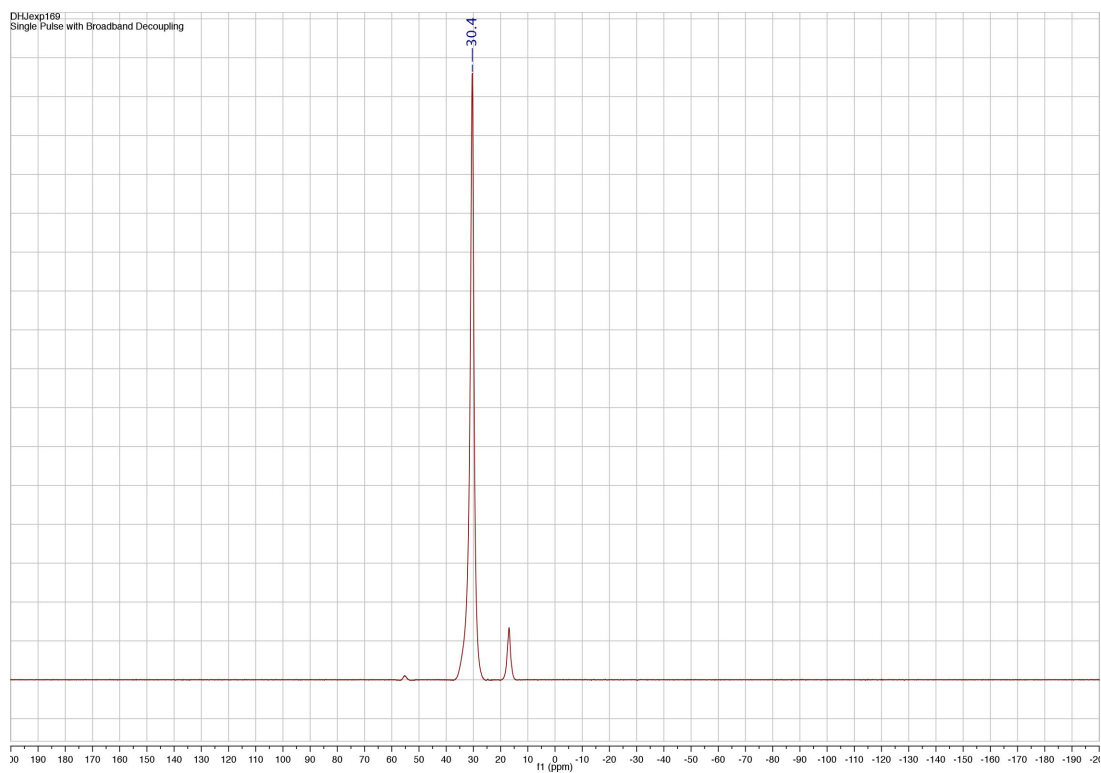
2-Thexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18c)



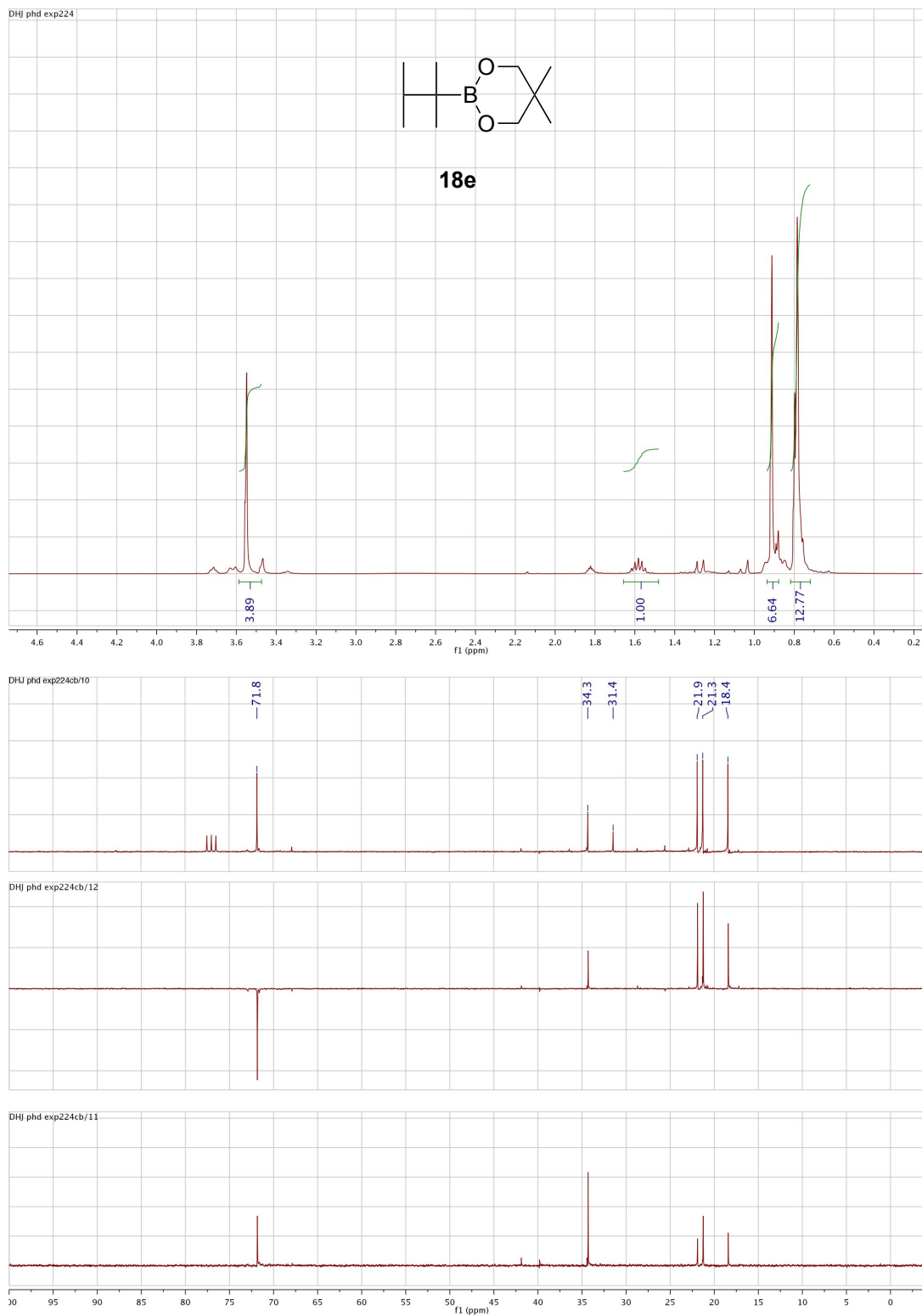


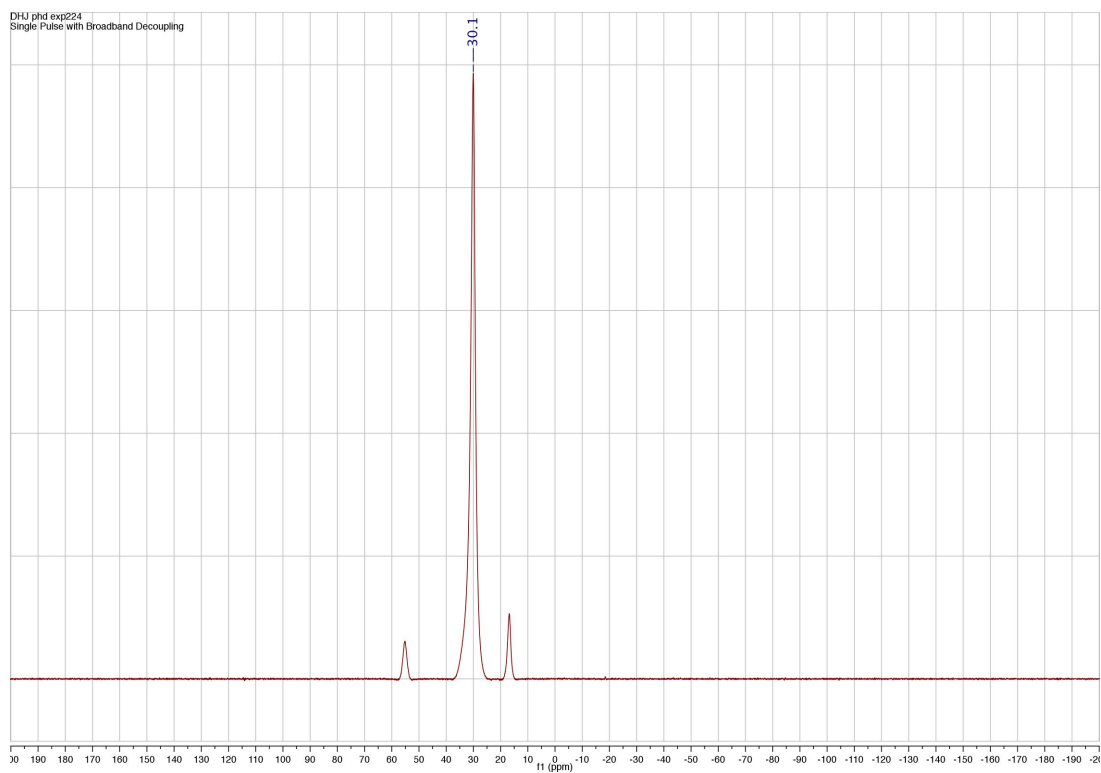
2-*Thexyl*-1,3,2-dioxaborinane (18d)



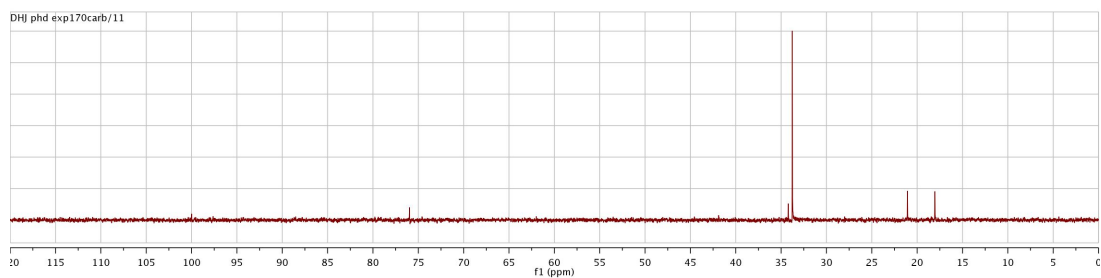
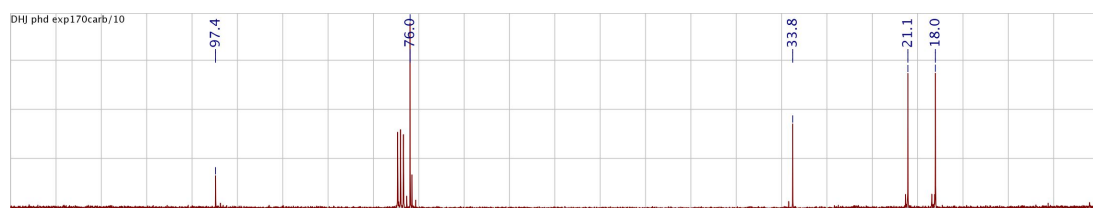
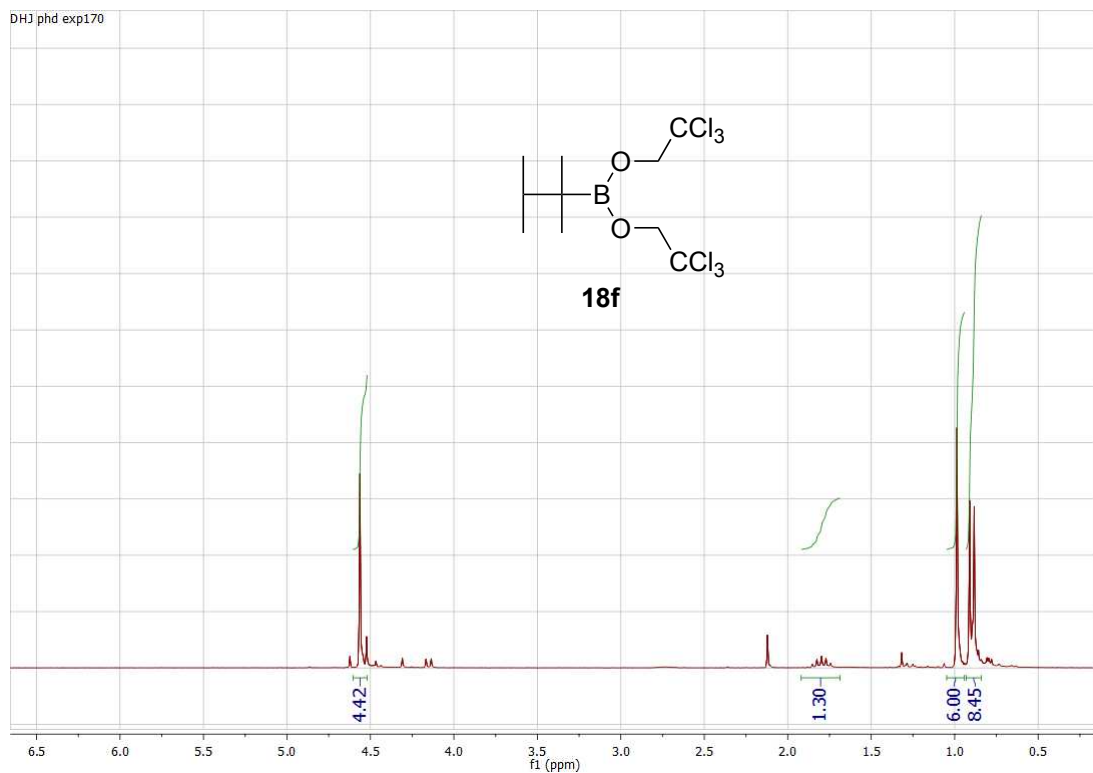


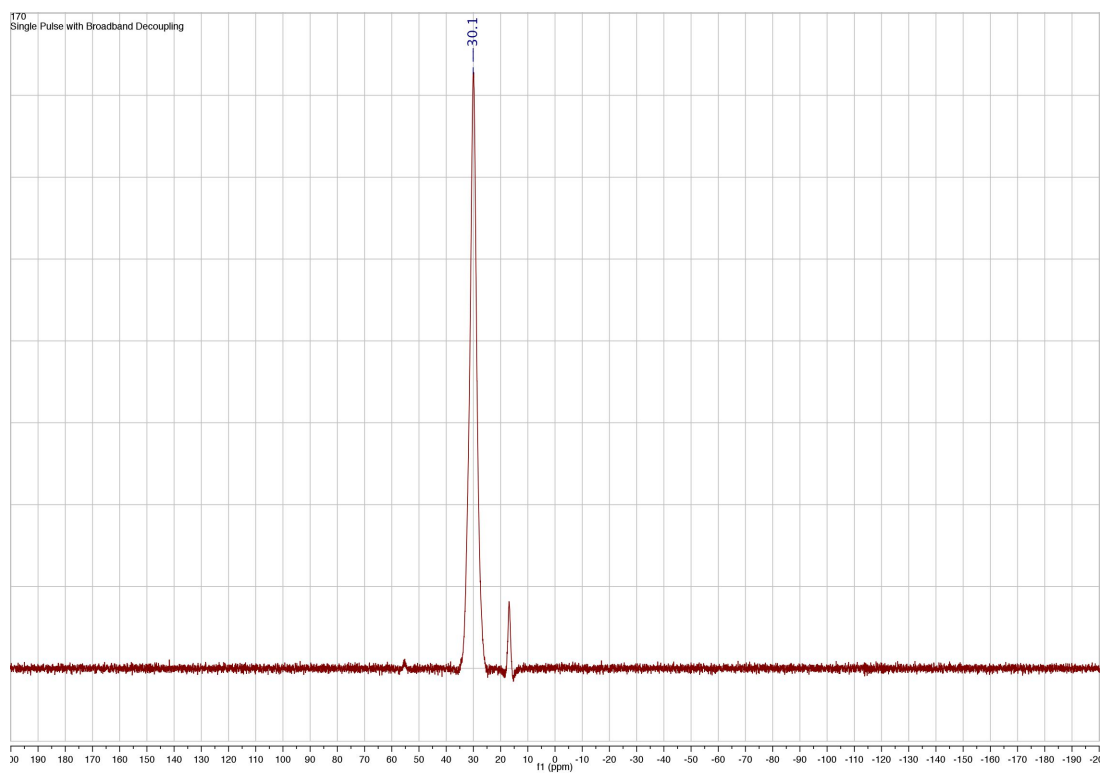
2-*Thexyl*-5,5-dimethyl-1,3,2-dioxaborinane (**18e**)





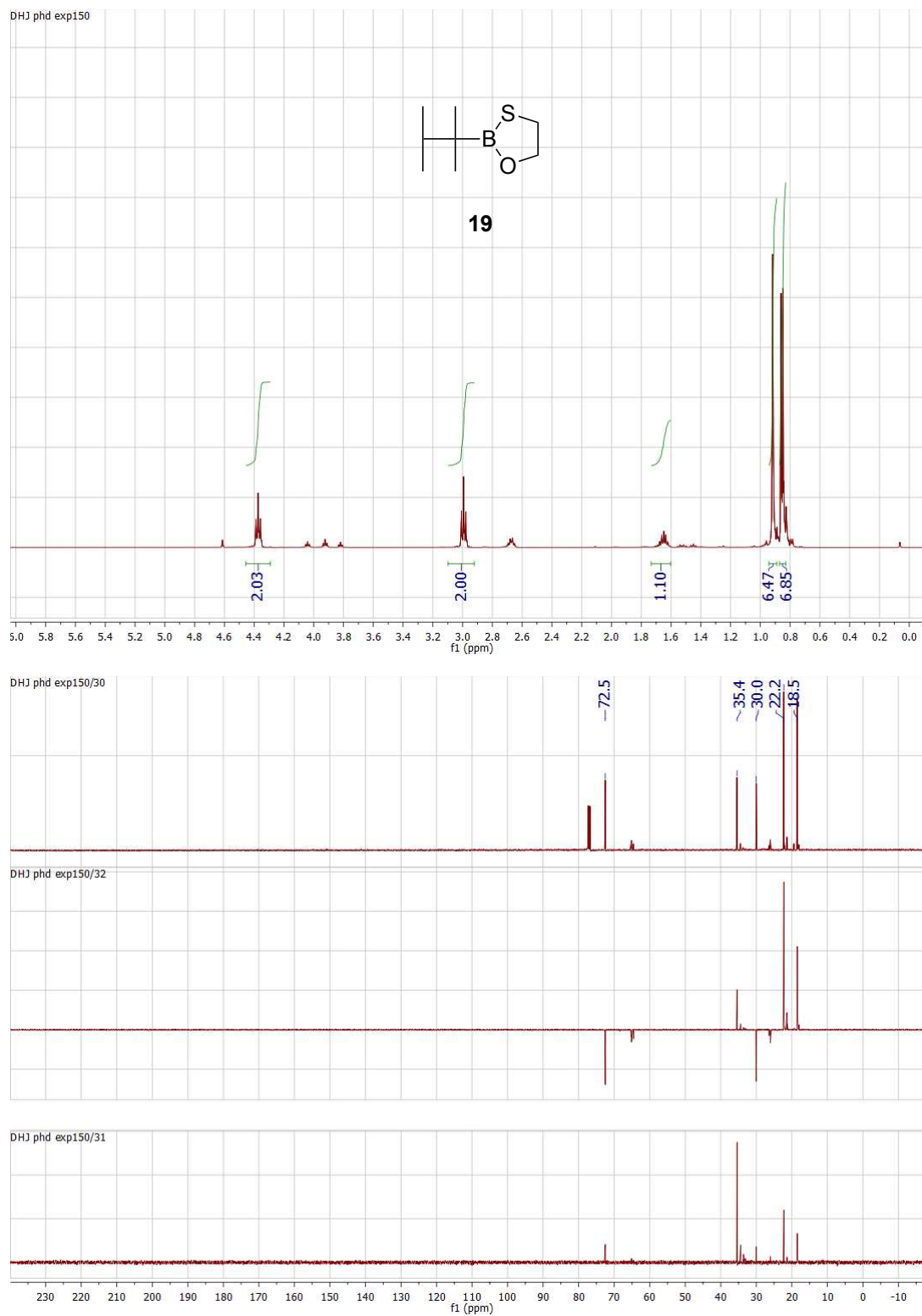
Bis(2,2,2-trichloroethyl) 2-thexylboronate (18f)

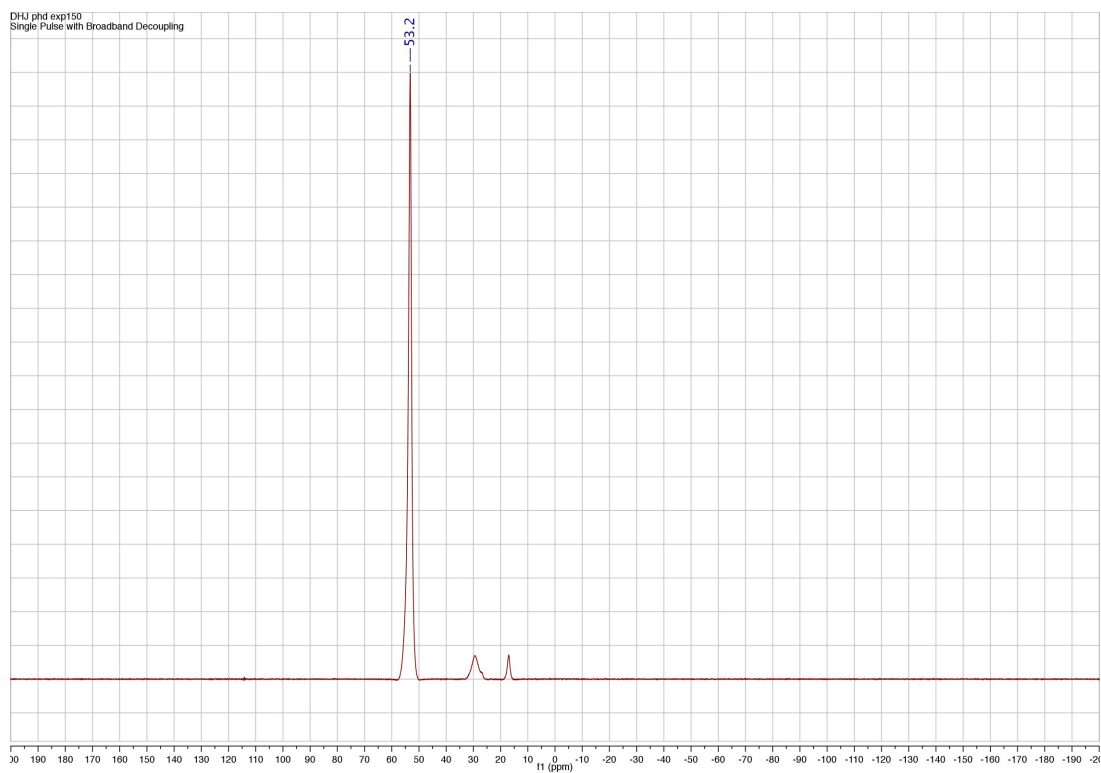




2-Thexyl-1,3,2-oxathiaborolane (19)

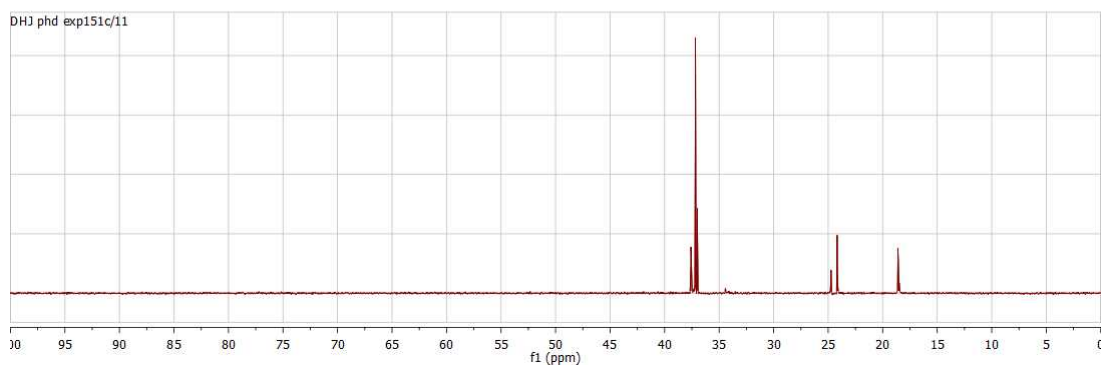
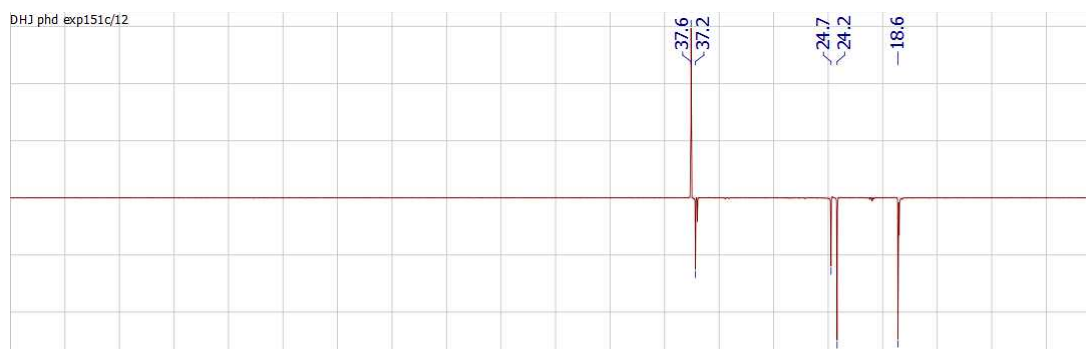
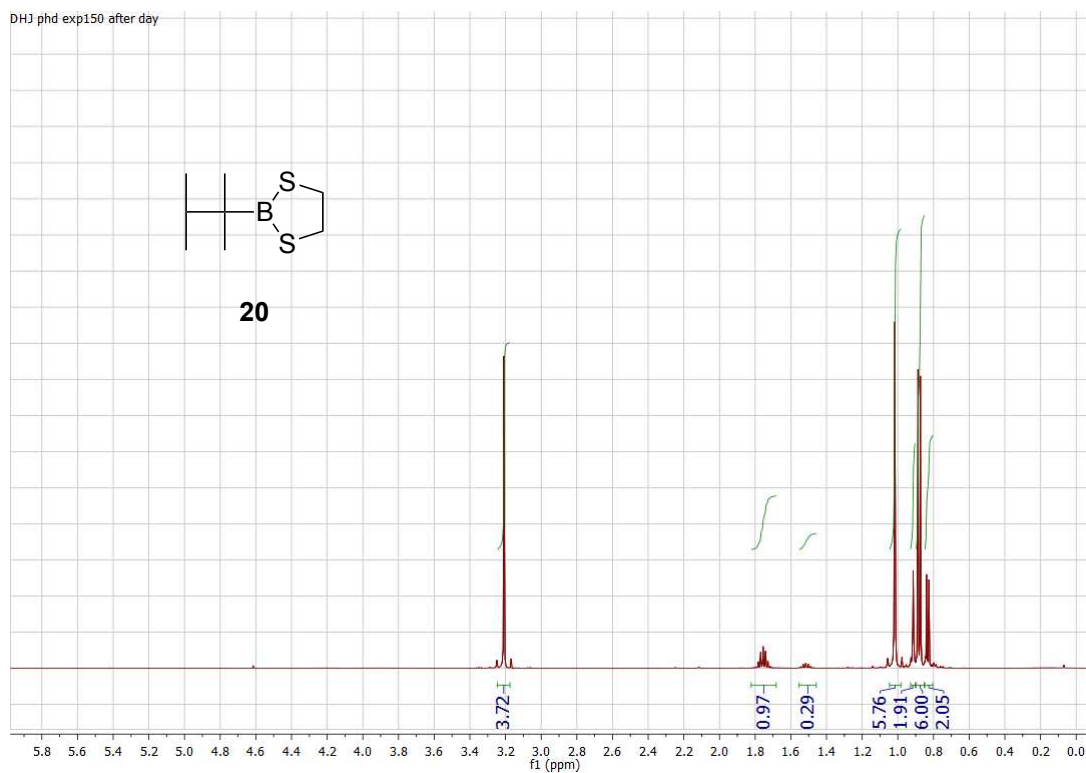
Note that this compound was not obtained in analytically pure form.

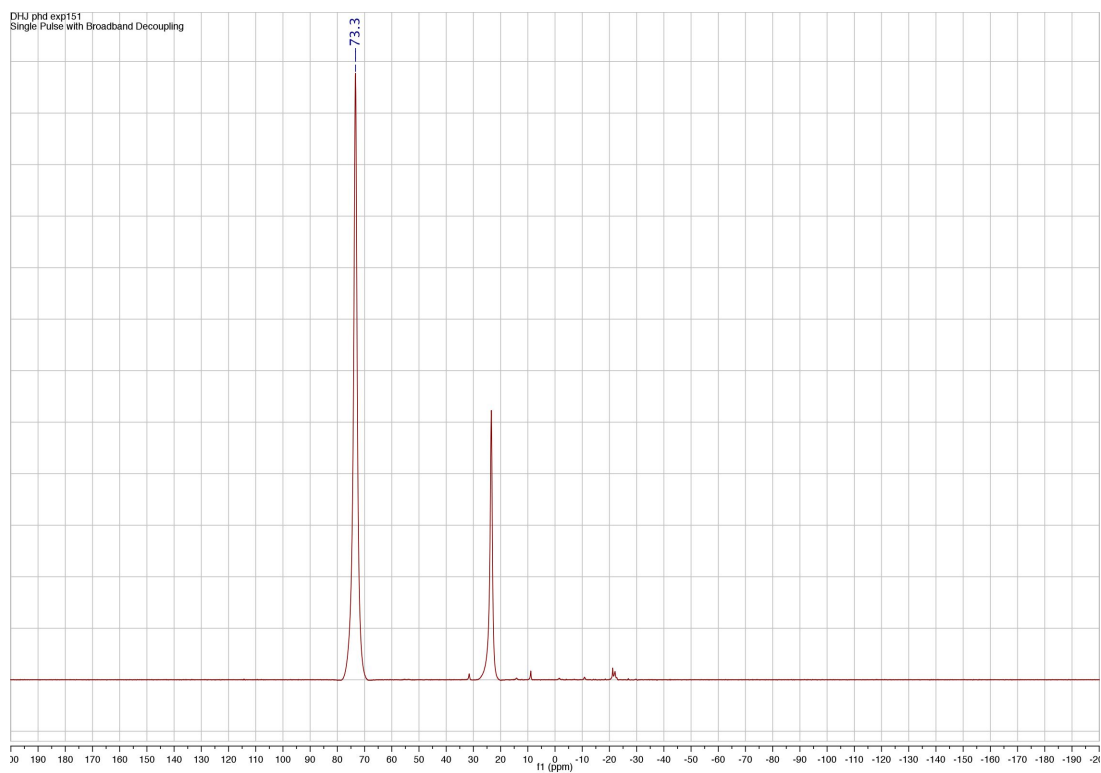




2-*Thexyl*-1,3,2-dithiaborolane (20)

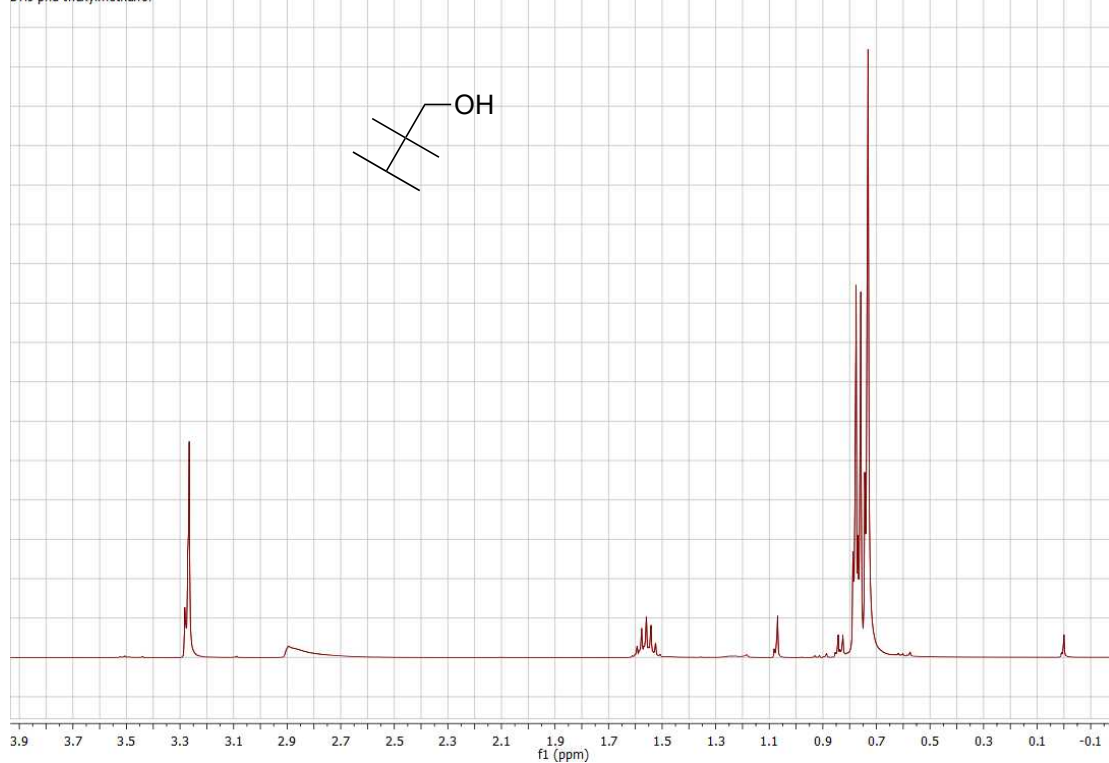
Note that this compound was not obtained in analytically pure form.





2,2,3-Trimethyl-1-butanol (thexylmethanol) (purified)

DHJ phd thexylmethanol



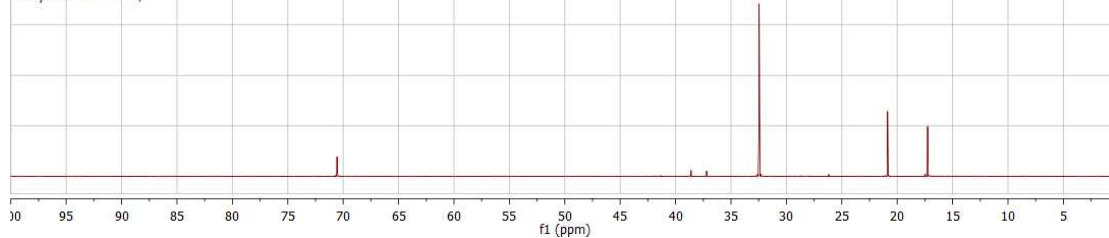
Thexyl methanol clean/10



Thexyl methanol clean/12



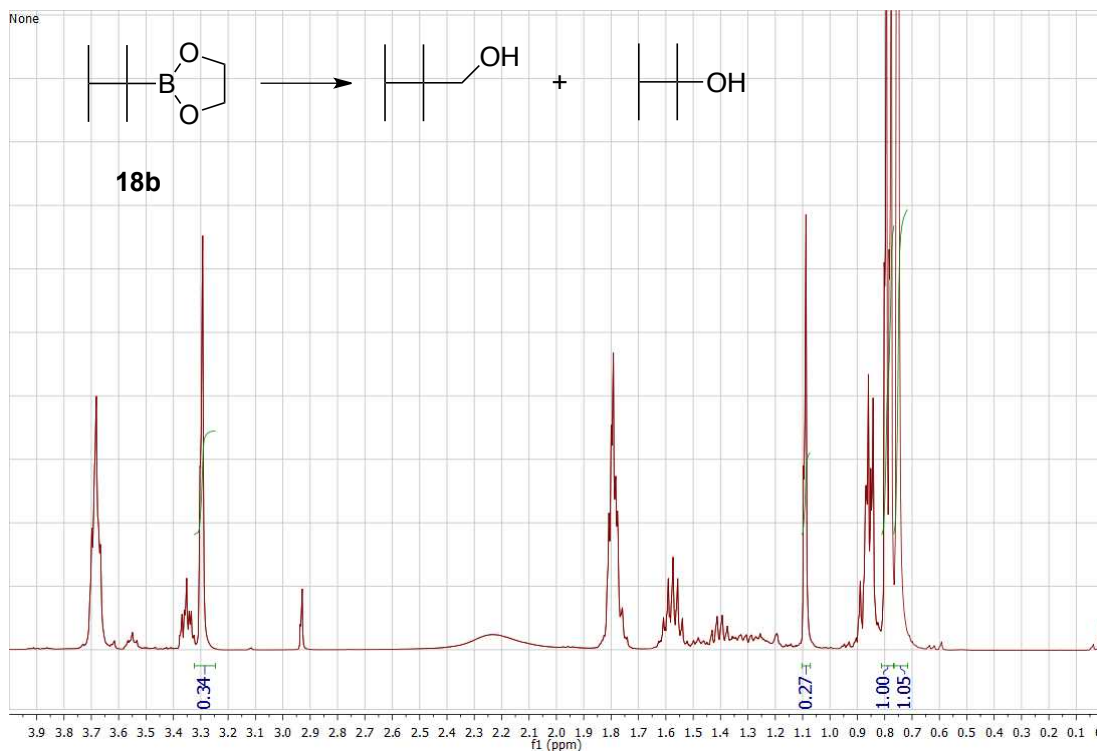
Thexyl methanol clean/11



Thexylmethanol crude reaction mixtures after oxidation

In all cases, evaporation of solvent was deliberately incomplete so that no loss of the homologated products took place.

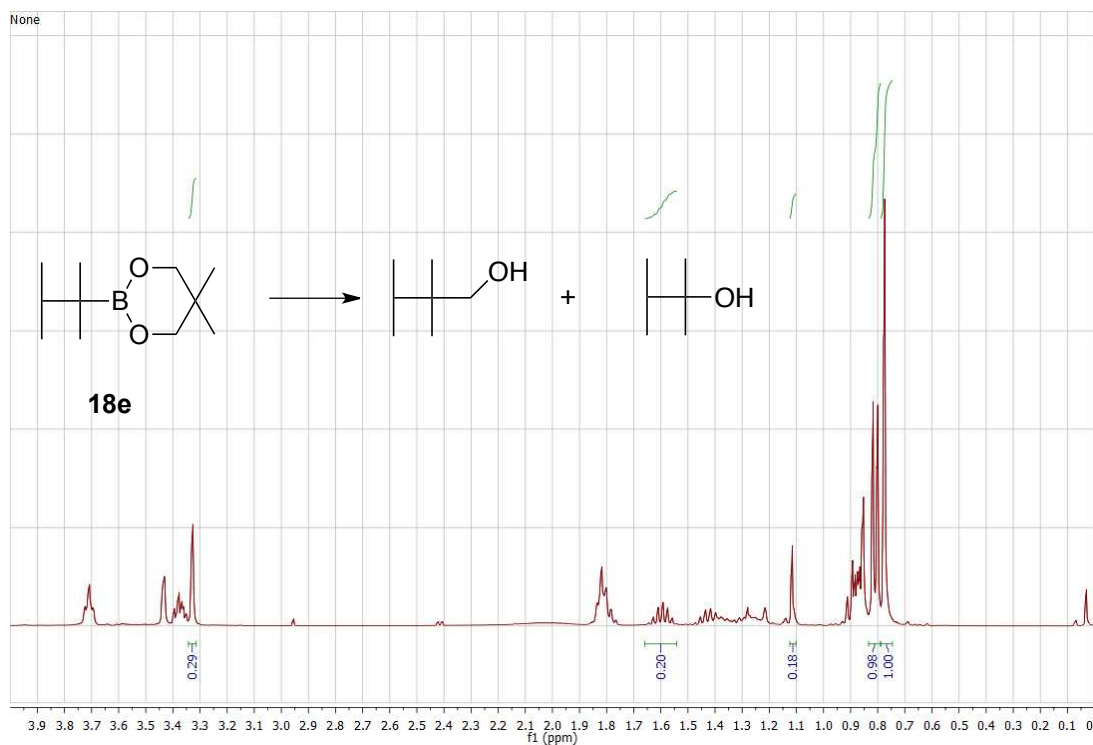
Homologation of 18b using Method A



An 80:20 mixture of thexylmethanol:thexanol according to integration of the thexylmethanol Me_2C peak (1.05; 0.75 ppm) and the thexanol $\text{Me}_2\text{C}(\text{OH})$ peak (0.27; 1.1 ppm).

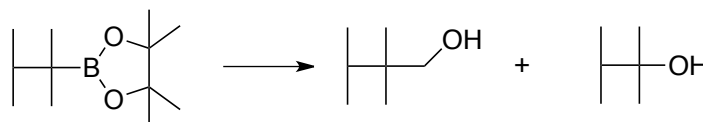
There is clearly a small margin for error in these values, so that all spectra were directly compared to ensure that (for example) a ratio reported as 84:16 does correspond to a better result than a ratio of 80:20.

Homologation of 18e using Method B

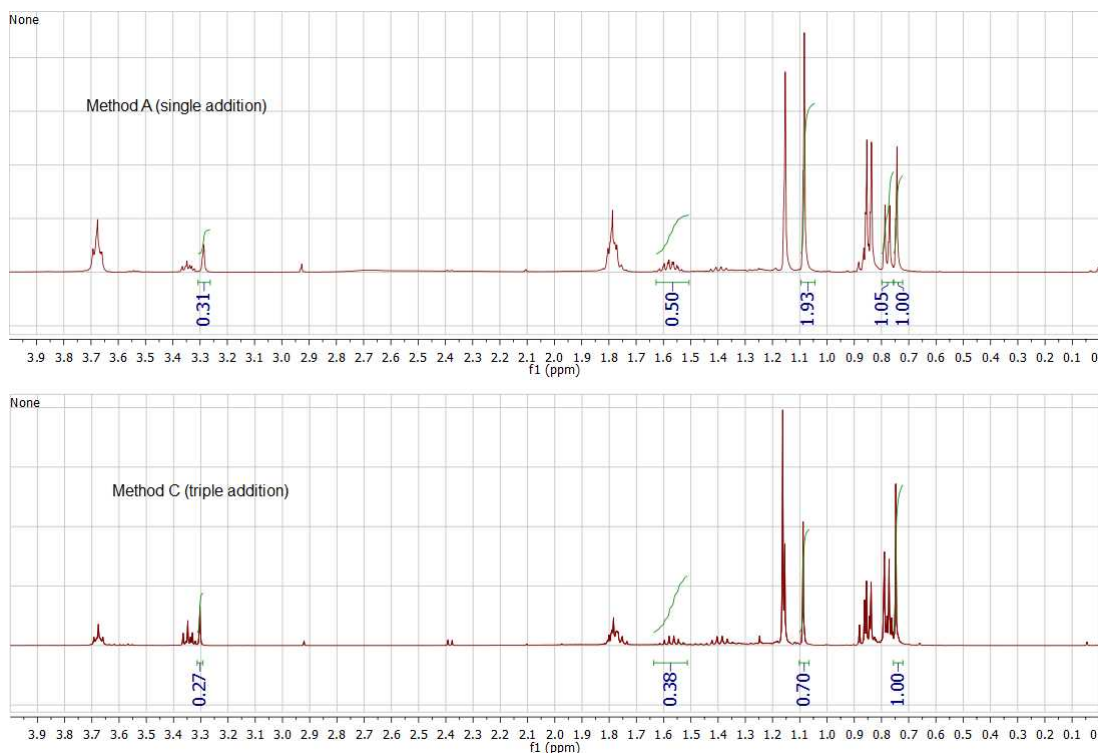


A similar analysis to that described above showed that an 85:15 mixture of hexylmethanol:hexanol was obtained.

Comparison of Method A and Method B for the homologation of 18c

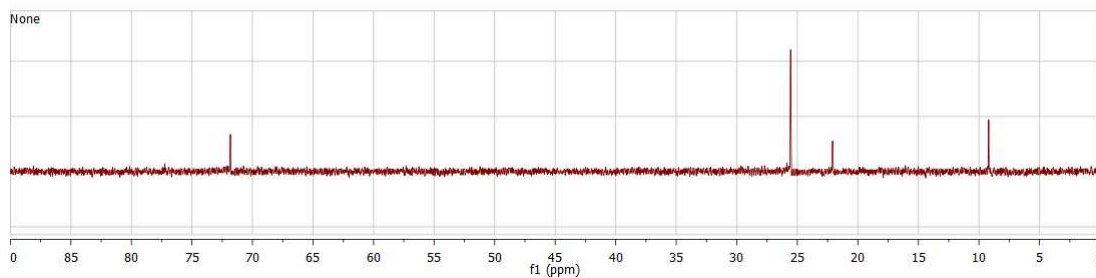
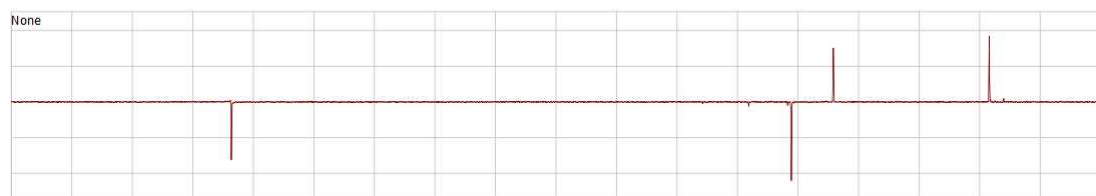
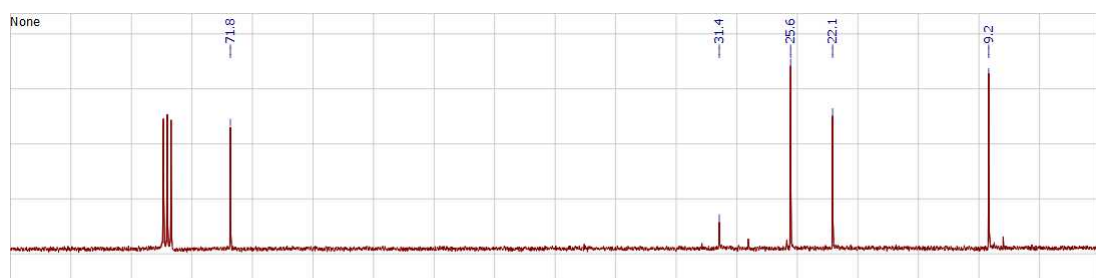
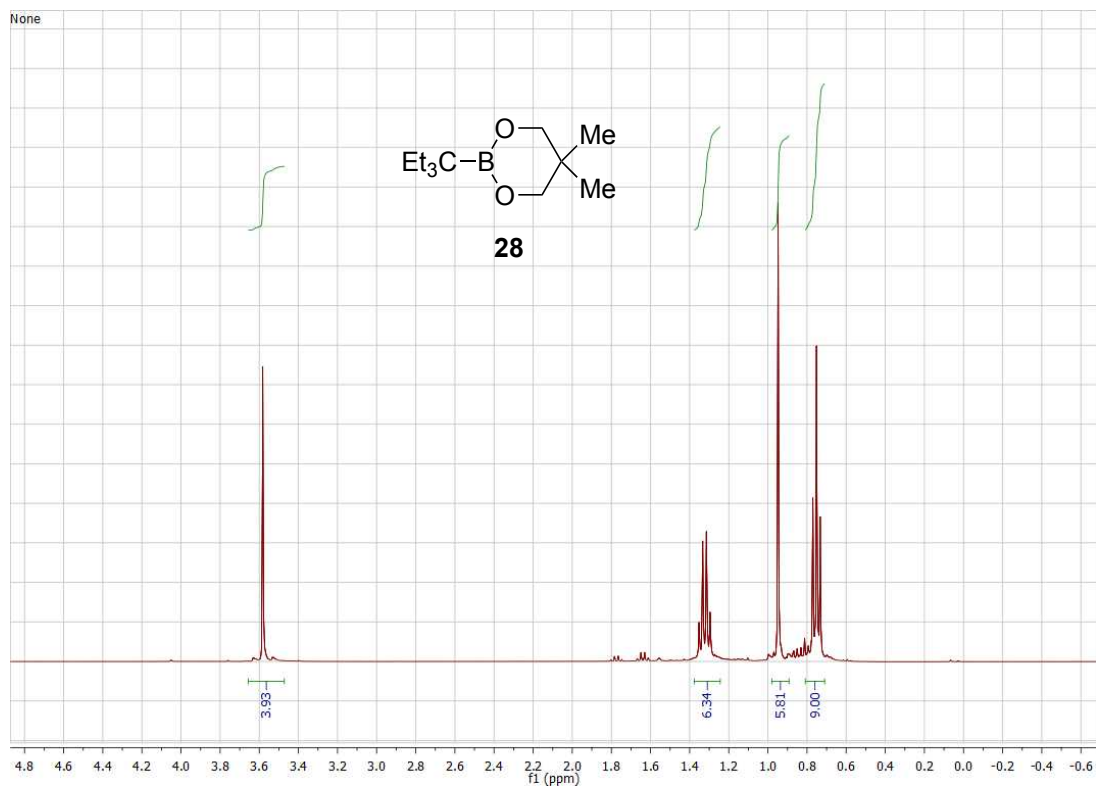


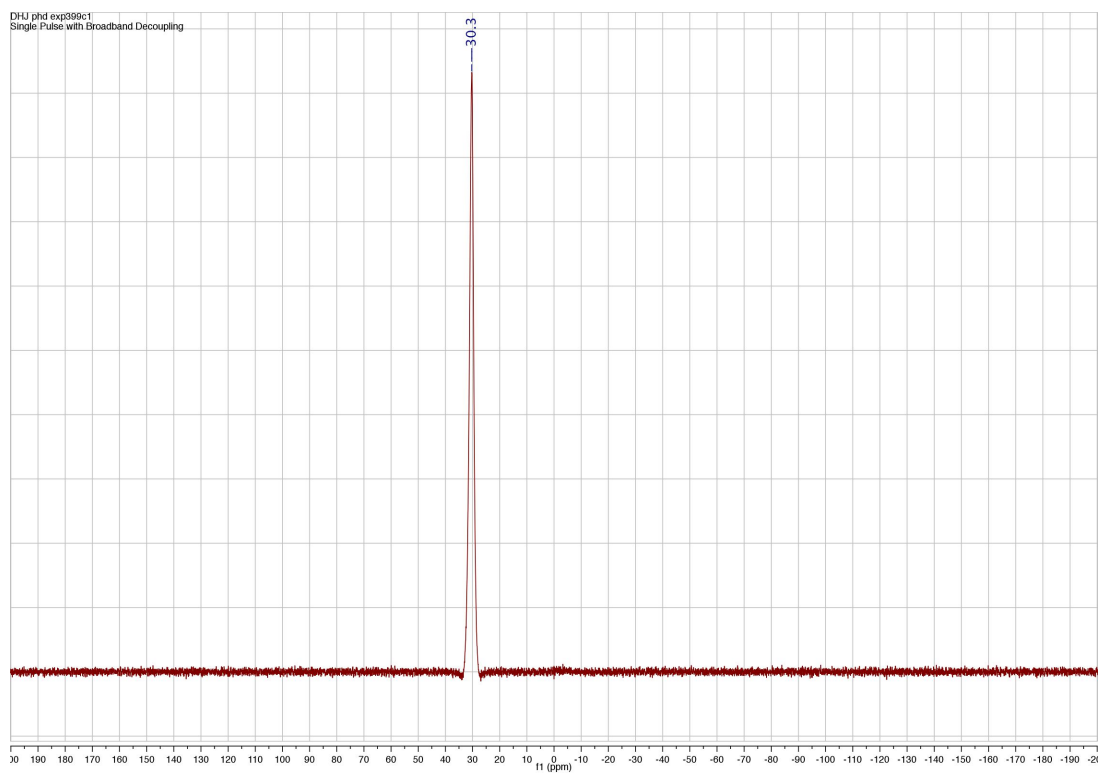
18c



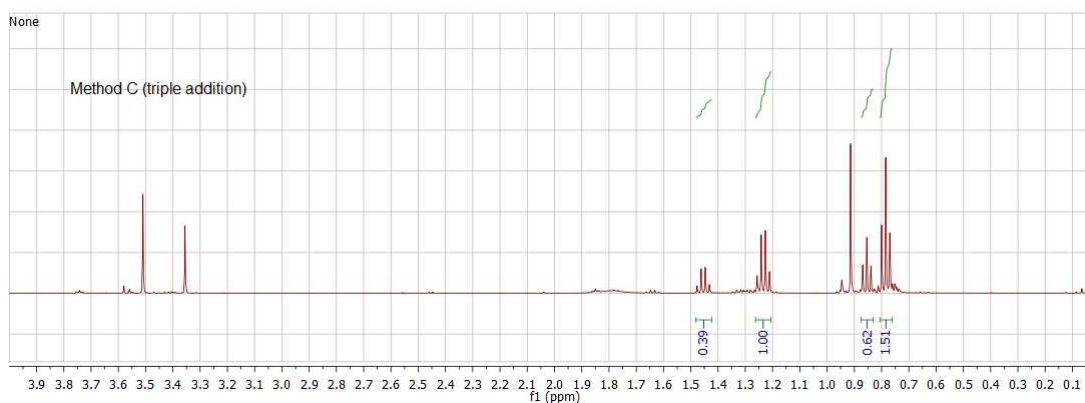
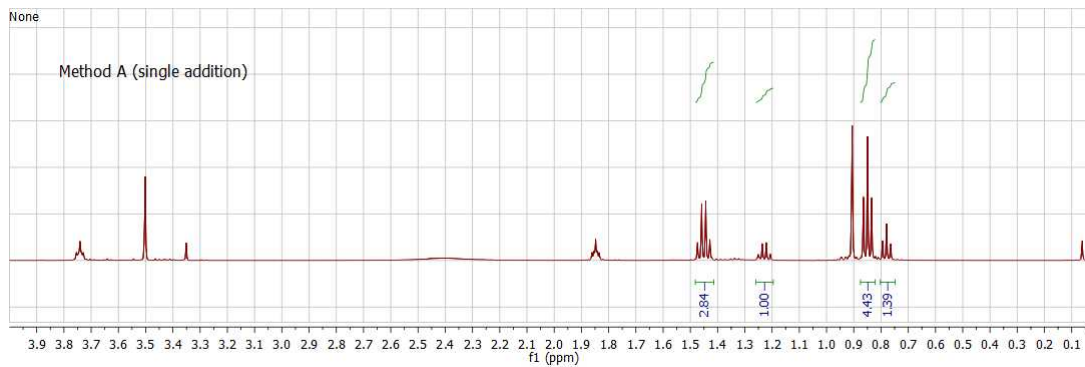
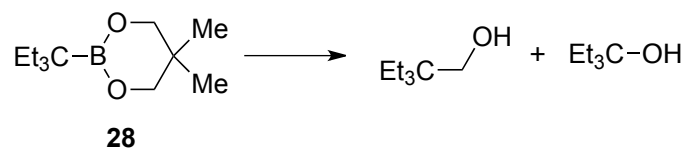
The upper spectrum (**Method A**) shows a 34:66 mixture of hexylmethanol:hexanol, whereas the lower spectrum (**Method B**) shows a greatly improved 59:41 mixture of hexylmethanol:hexanol. In these cases, the methyl singlet peaks are distinct for both reactions, so that these were considered to give a more accurate representation.

5,5-Dimethyl-2-(3-ethylpent-2-yl)-1,3,2-dioxaborinane (28)



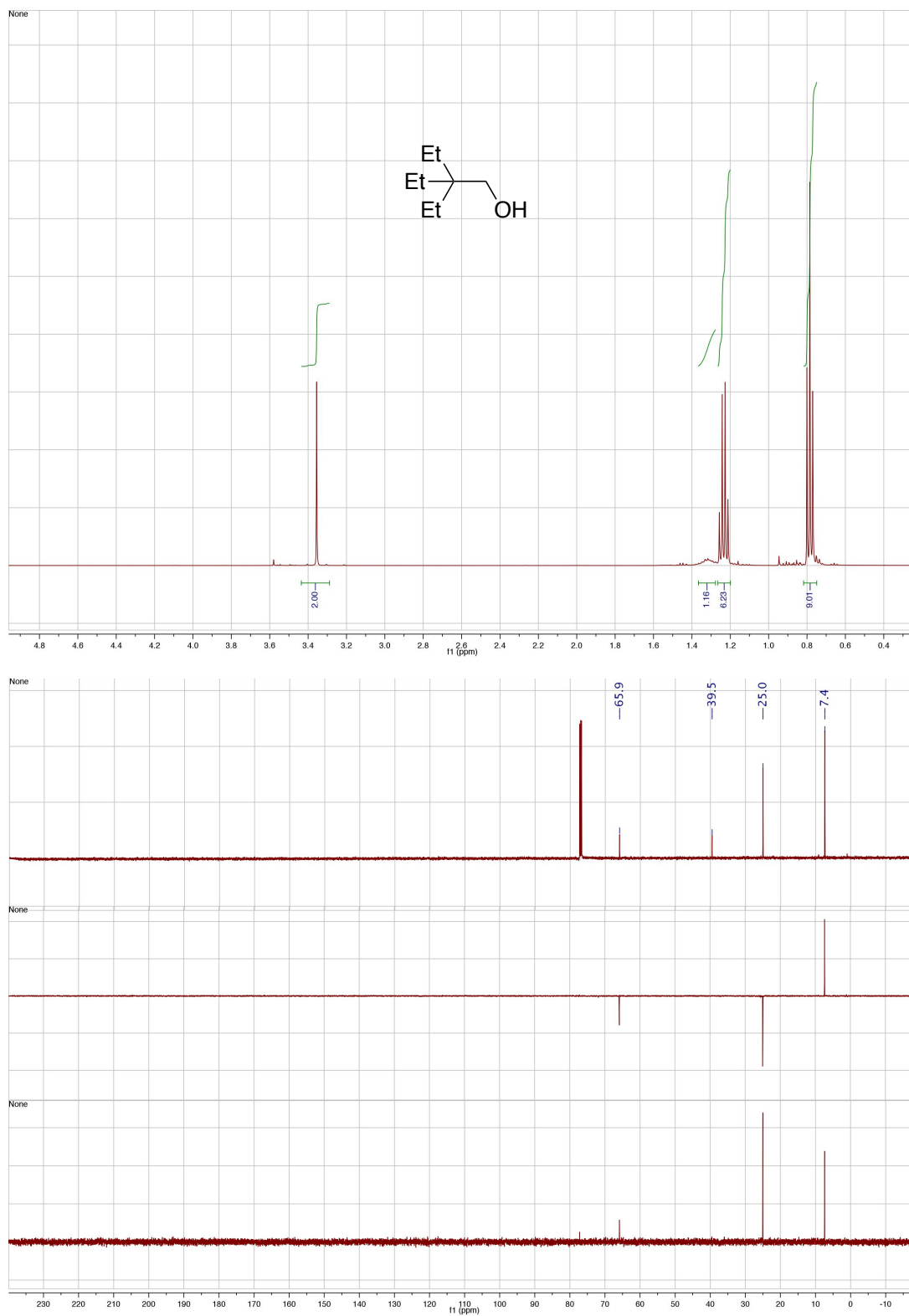


Homologation of compound 28 using Methods A and B

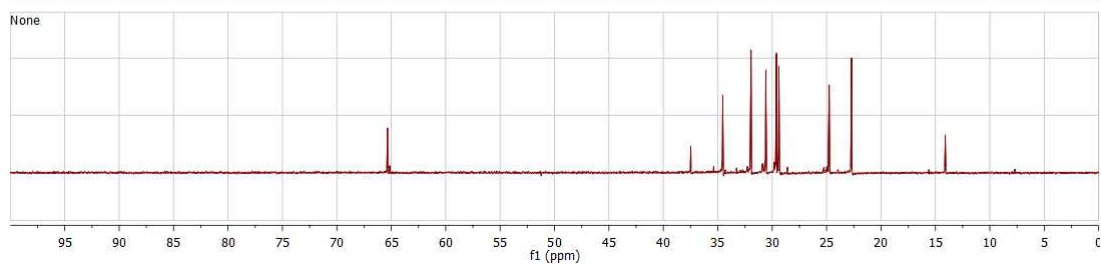
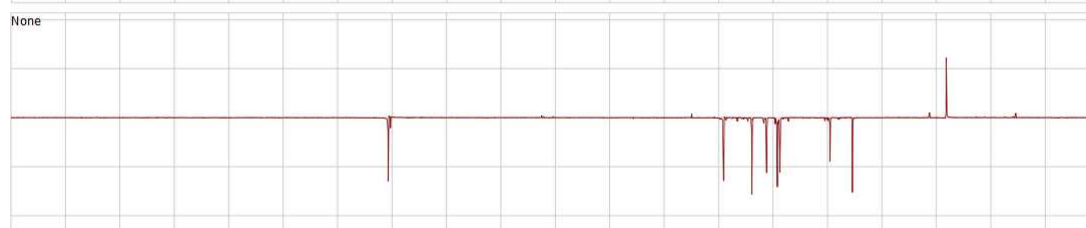
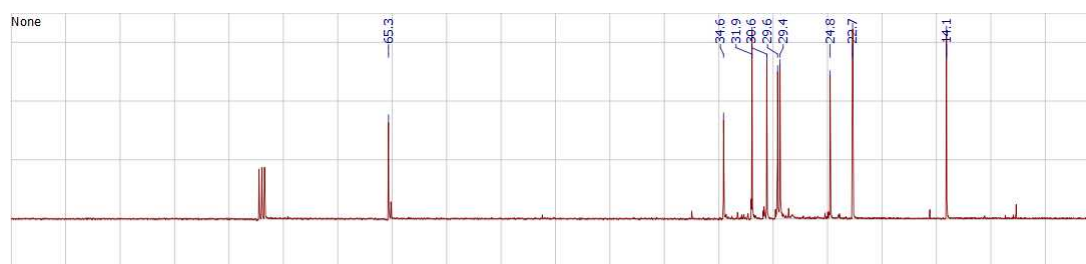
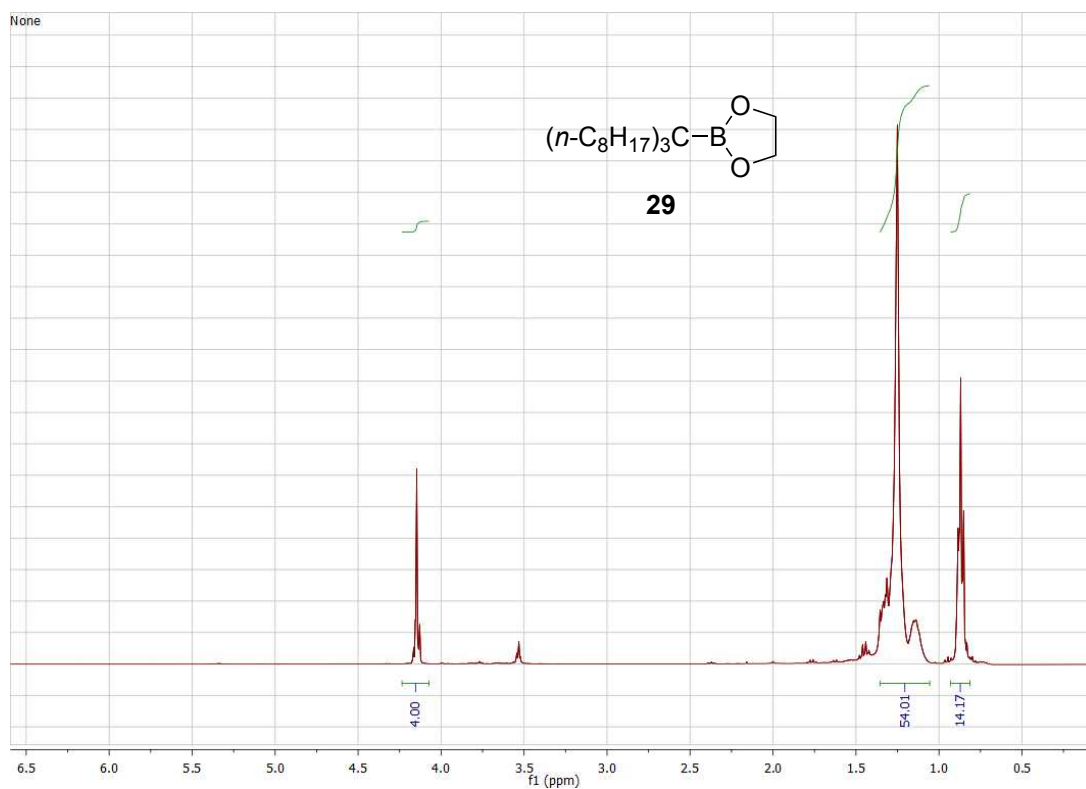


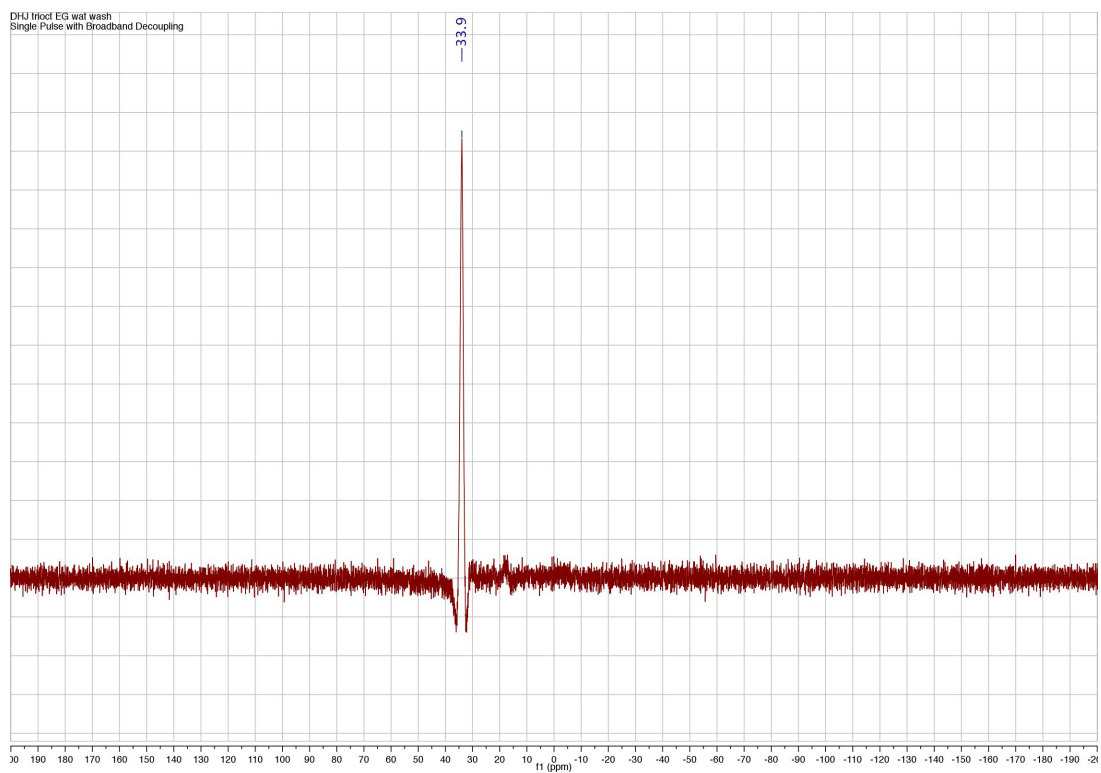
Ratio using **Method A** 26:74 non-homologated:homologated by taking an average of the integrations of the ethyl peaks. Ratio using **Method B** 72:28 homologated:non-homologated.

2,2-Diethyl-1-butanol (from the homologation of compound 28)

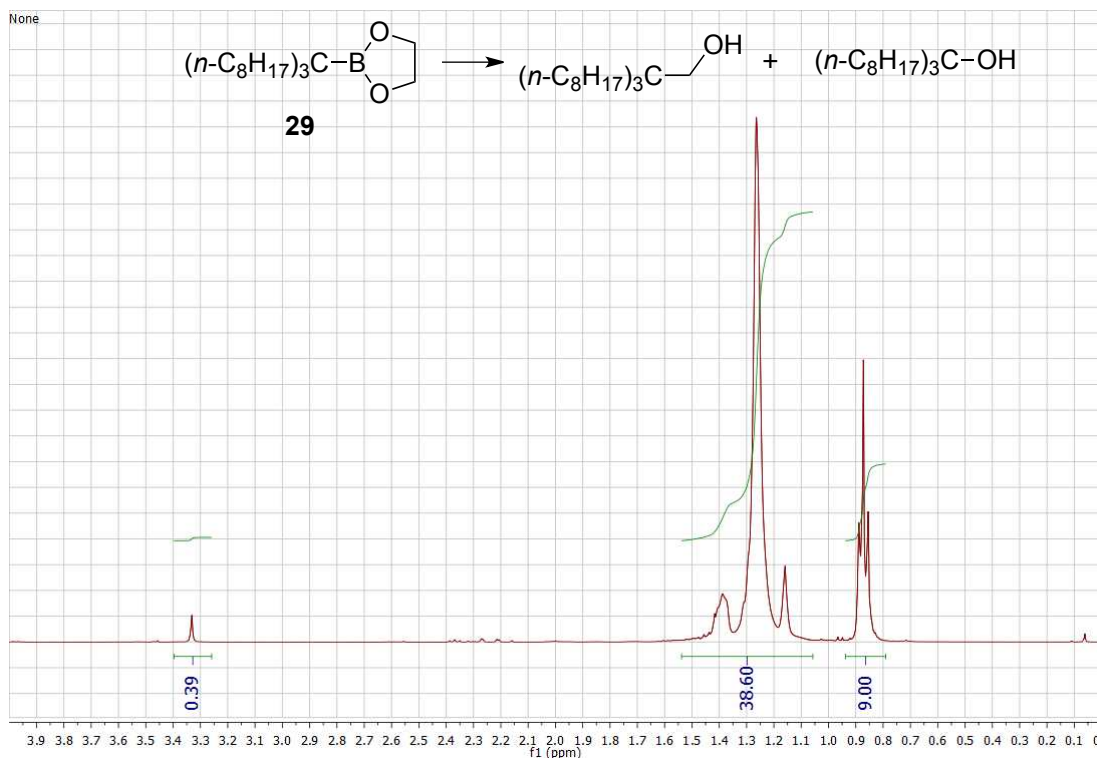


2-(9-Octylheptadecan-9-yl)-1,3,2-dioxaborolane (29)



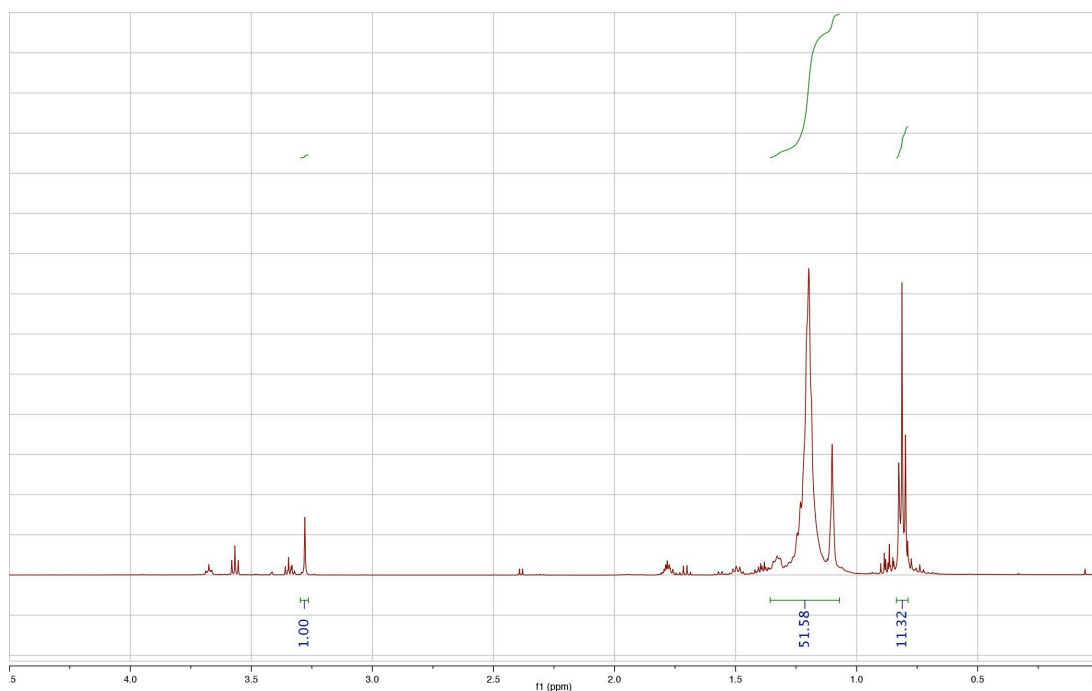


Homologation of compound 29 using Method A



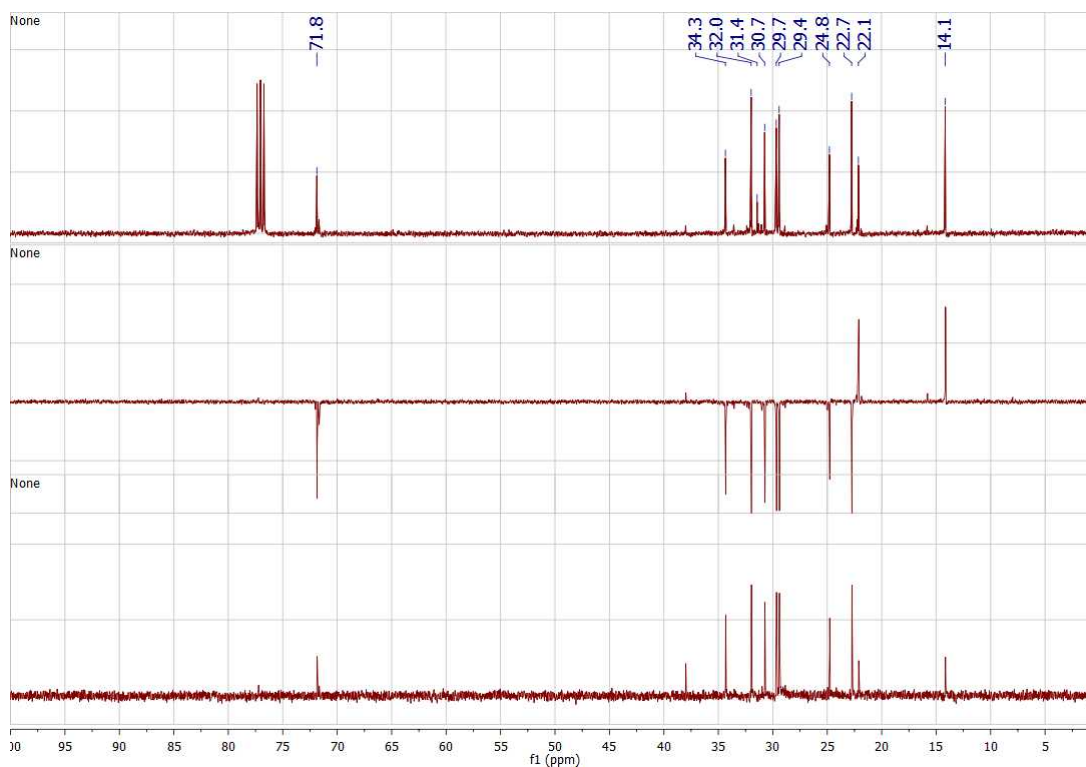
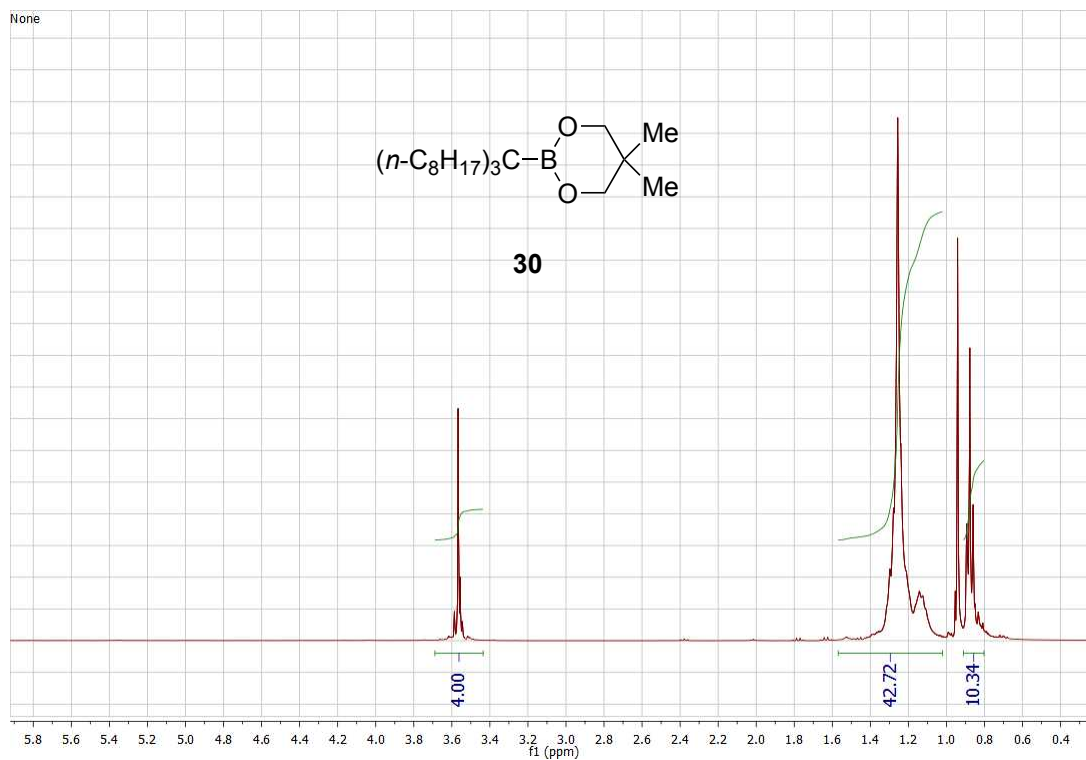
The ratio was determined by assuming that the triplet at 0.9 ppm corresponds to the methyl groups in both compounds (homologated and non-homologated). Since the peak at 3.3 ppm corresponds to the CH₂ group in the homologated product, this leads to a calculated ratio of 20:80 homologated:non-homologated. Any impurities, which are more likely to affect the triplet peak at 0.9 ppm, will render this ratio somewhat conservative.

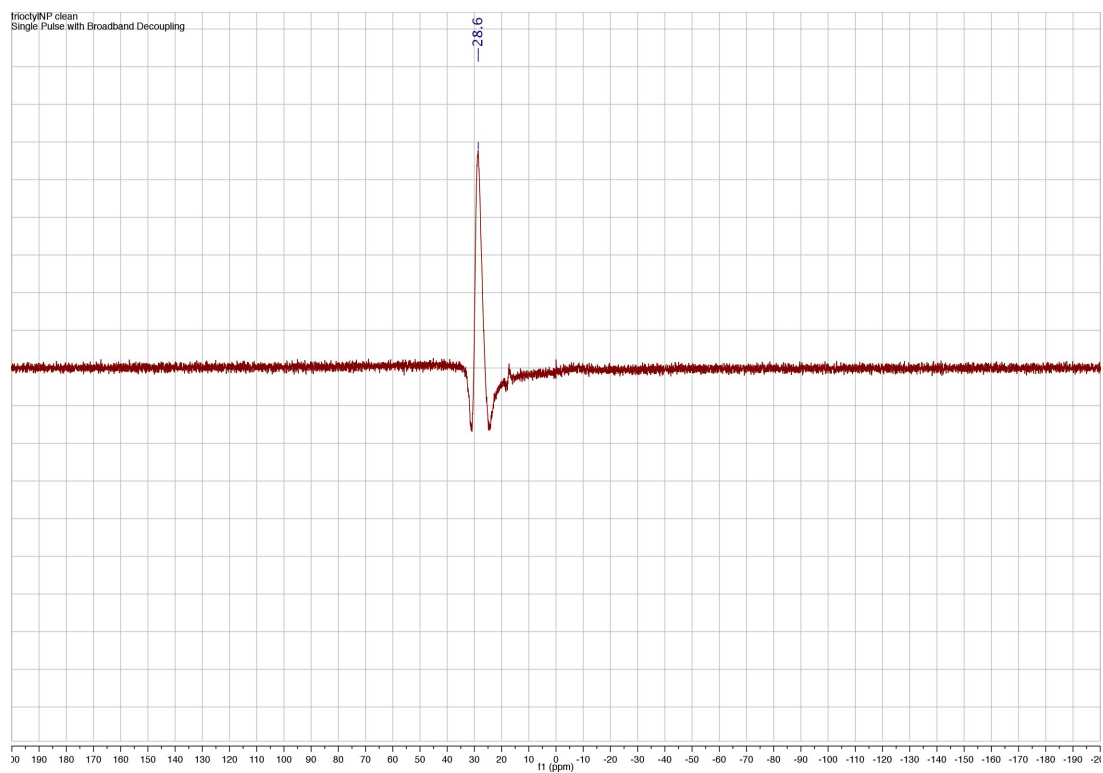
Homologation of compound 29 using Method B



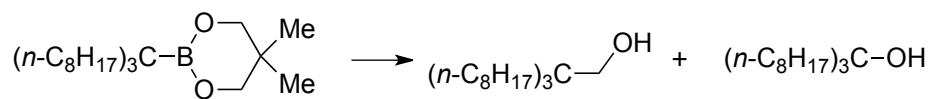
The ratio of homologated:non-homologated products was determined by the method described above to be 40:60. Once again, this will be a conservative estimate.

5,5-Dimethyl-2-(9-octylheptadecan-9-yl)-1,3,2-dioxaborinane (30)

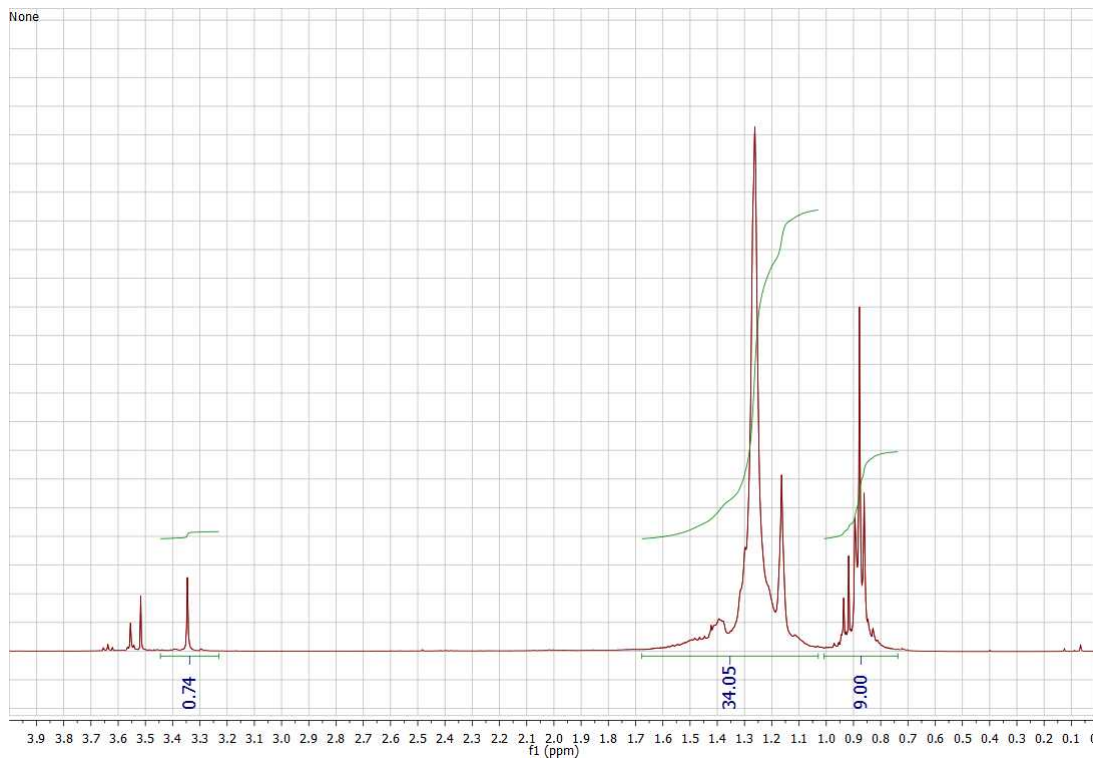




Homologation of compound 30 using Method B



30



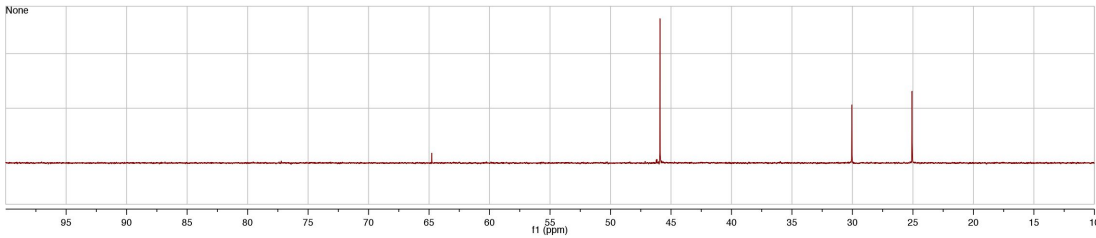
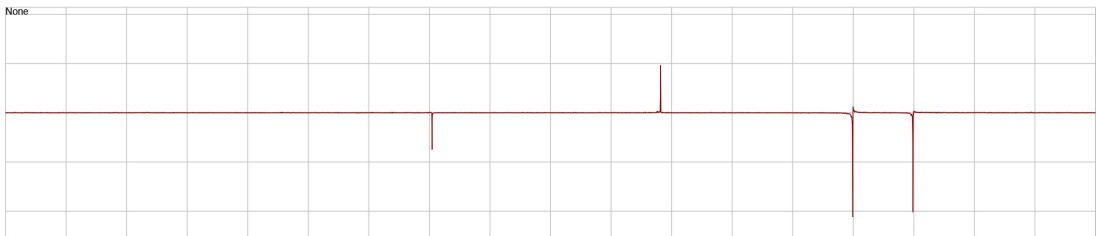
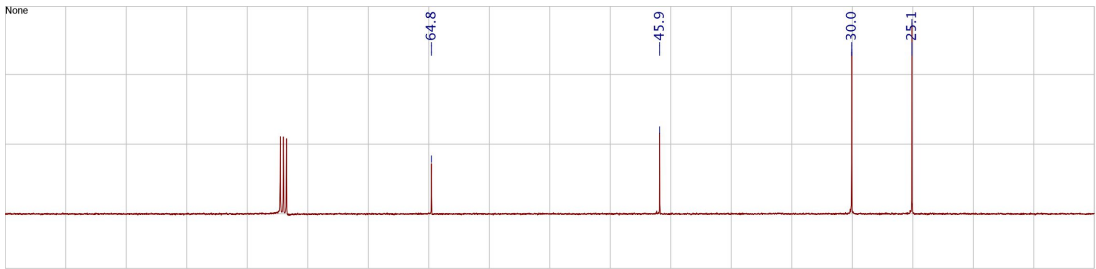
The ratio of homologated:non-homologated products was determined to be 37:63 by the method described above. However, in this case the triplet peak is becoming resolved into two distinct triplets. While we assume that these correspond to the two products, it is possible that one of them is an impurity, which would place the ratio very much on the conservative side.

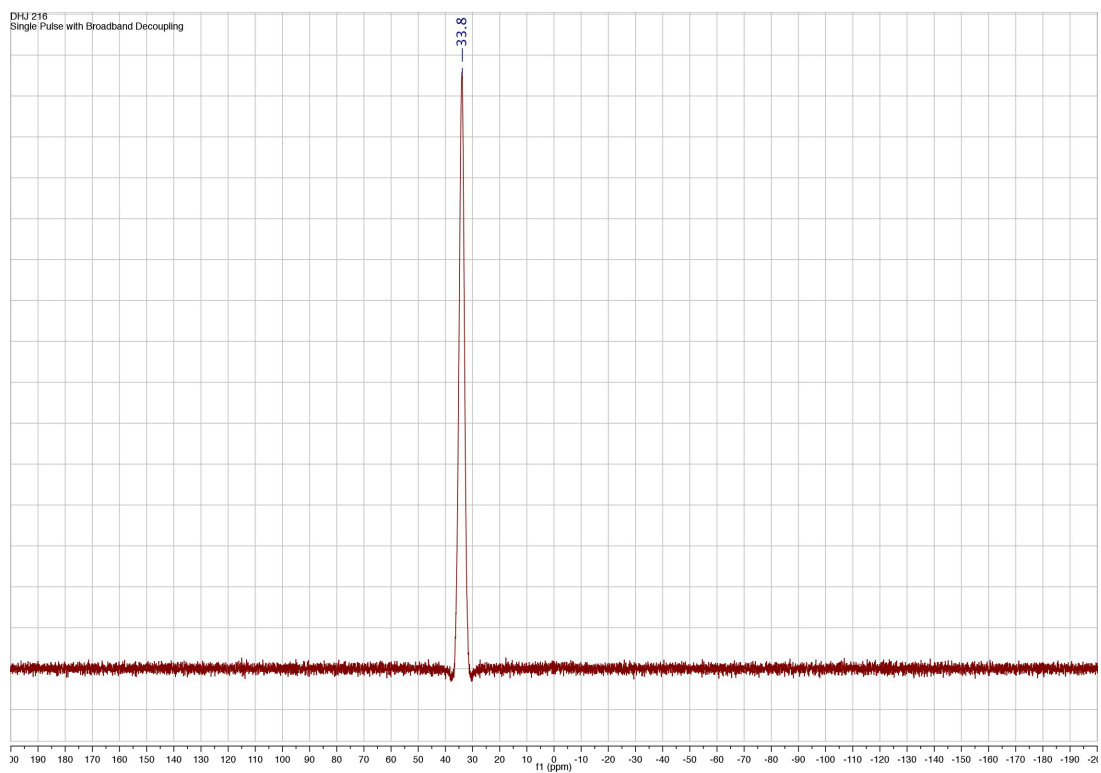
None

31

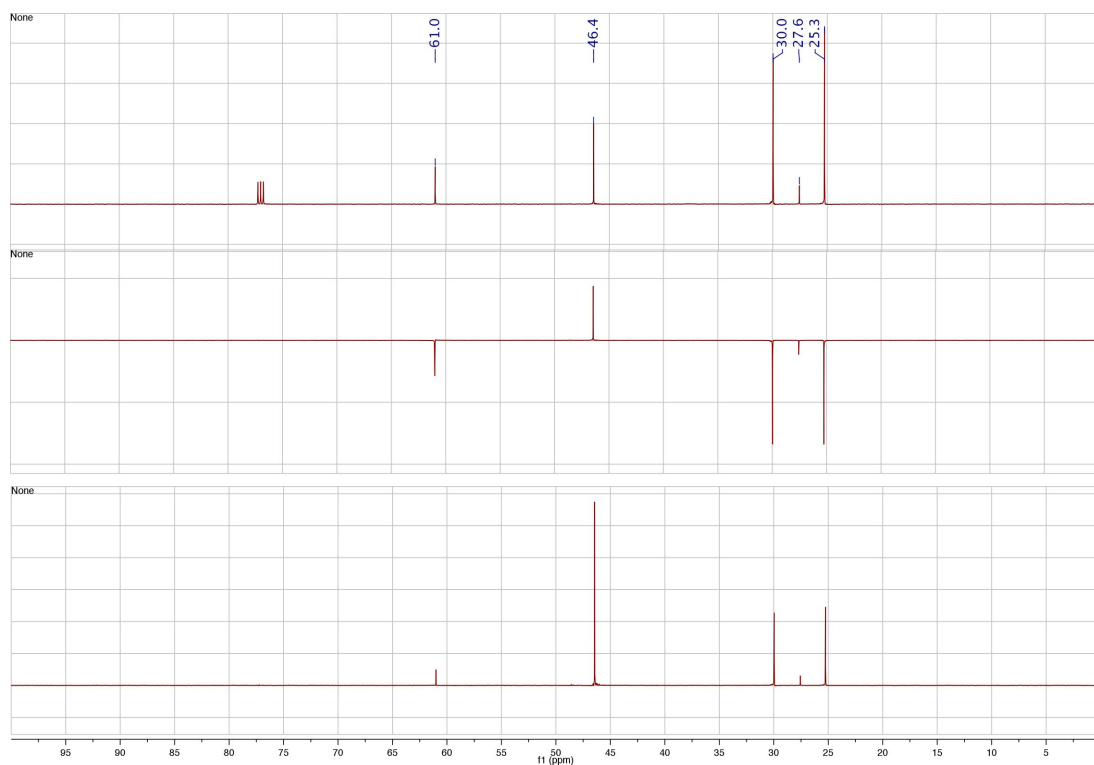
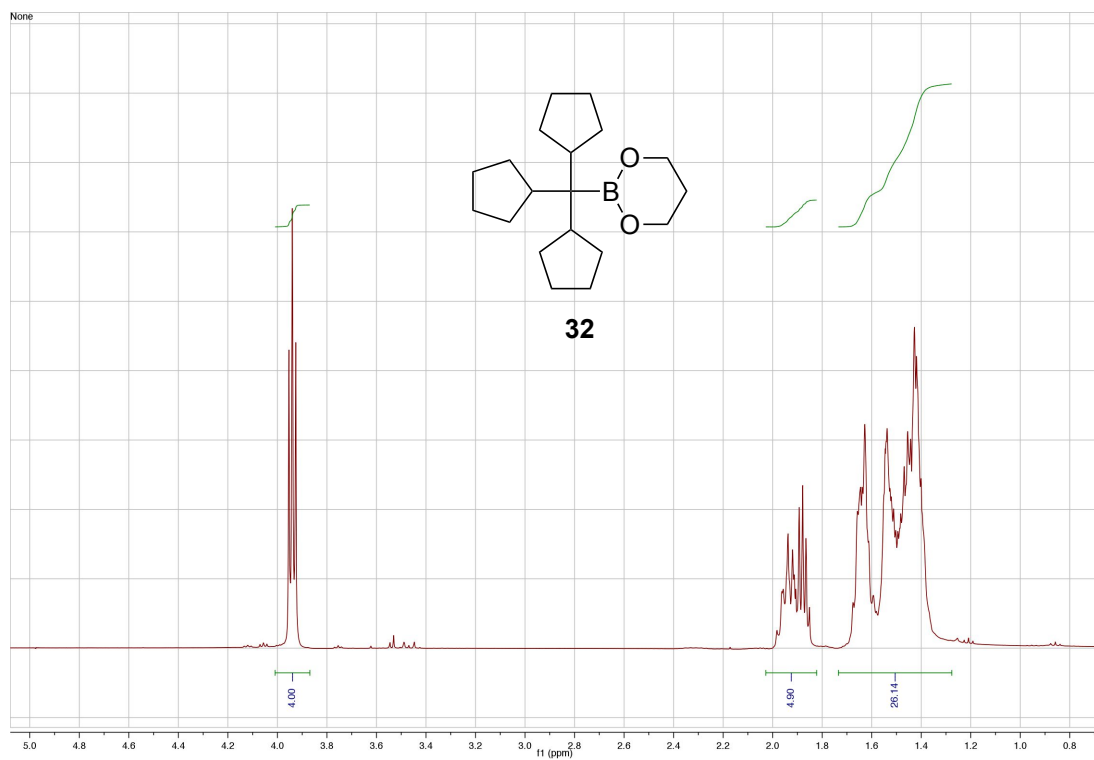
Chemical structure of **31** is shown above the spectrum. It is 1,1,1,3,3,3-hexaphenyl-1,3,2-oxodiphosphorinane, a bicyclic boronate ester with six phenyl groups and a 1,3,2-oxodiphosphorinane ring.

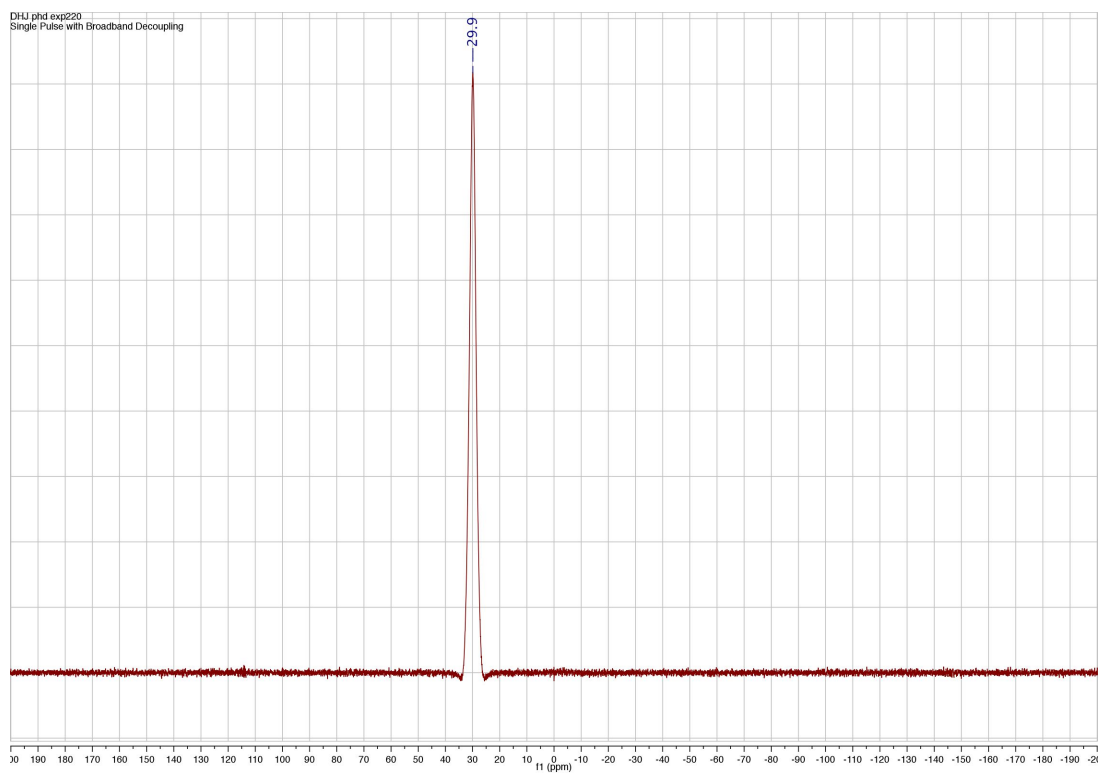
¹H NMR spectrum (CDCl₃) of compound **31**. The x-axis represents the chemical shift in ppm, ranging from 0.0 to 1.8. The spectrum shows a sharp singlet at approximately 4.1 ppm (integration 4.00), a small multiplet at approximately 3.4 ppm (integration 2.92), and a complex multiplet between 1.2 and 1.6 ppm (integration 24.72).



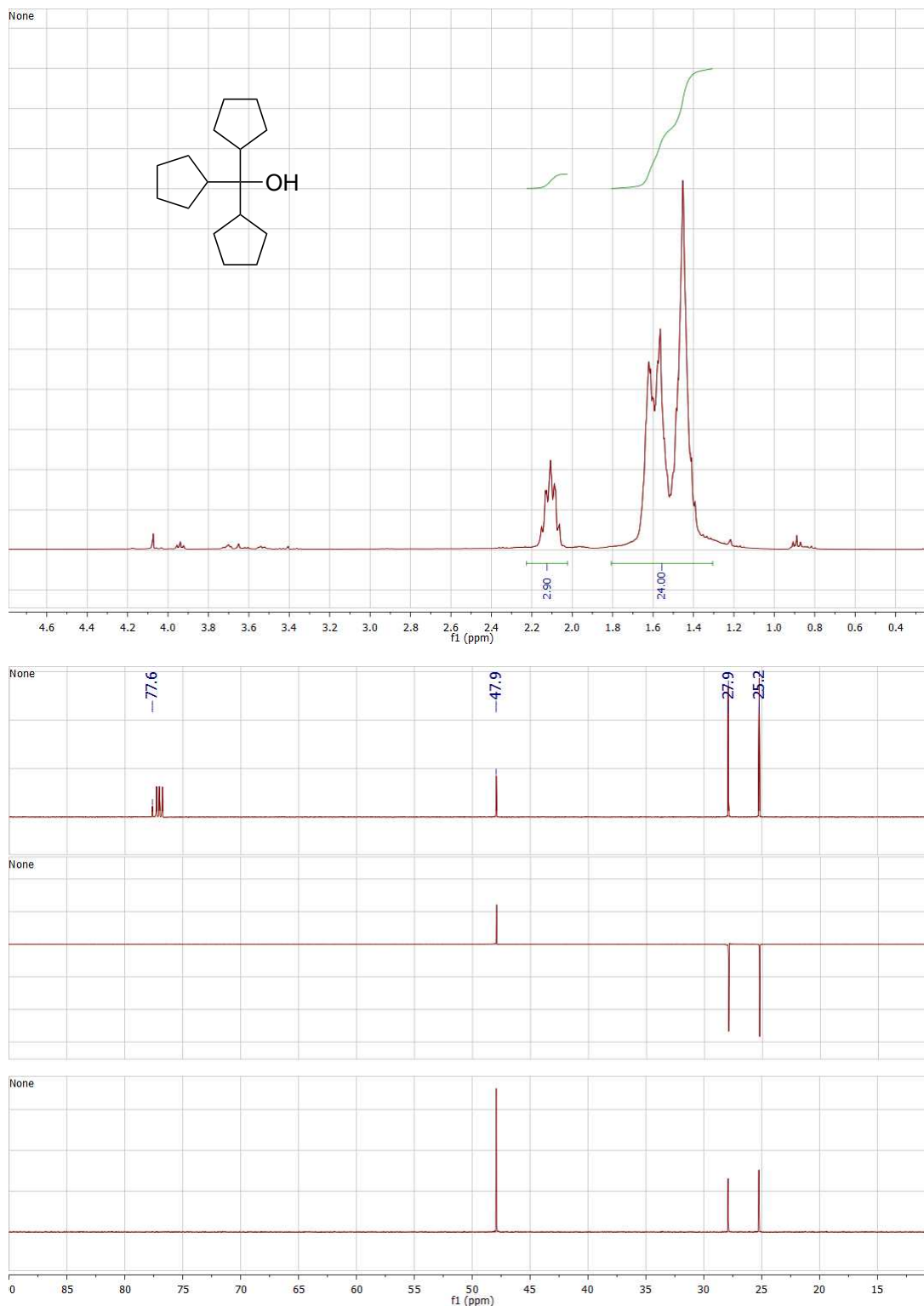


2-(Tricyclopentylmethyl)-1,3,2-dioxaborinane (32)





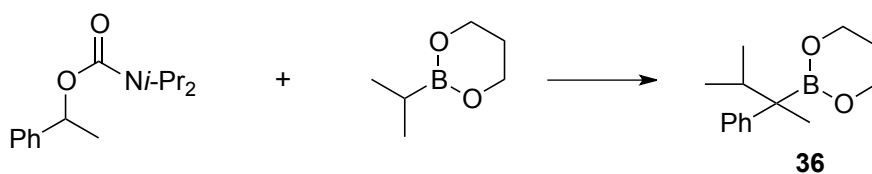
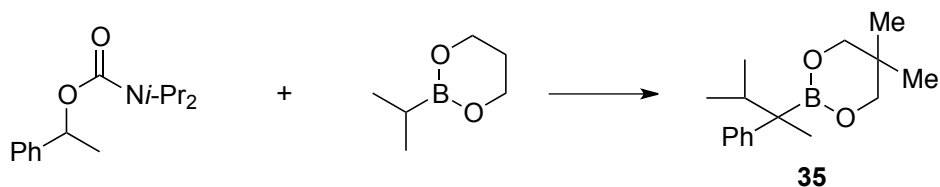
Tricyclopentylmethanol



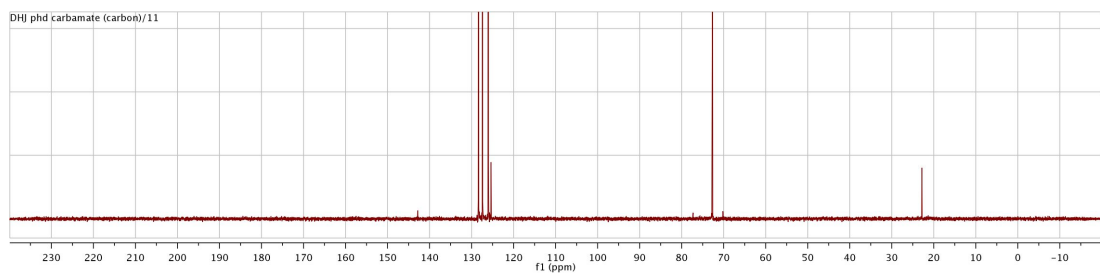
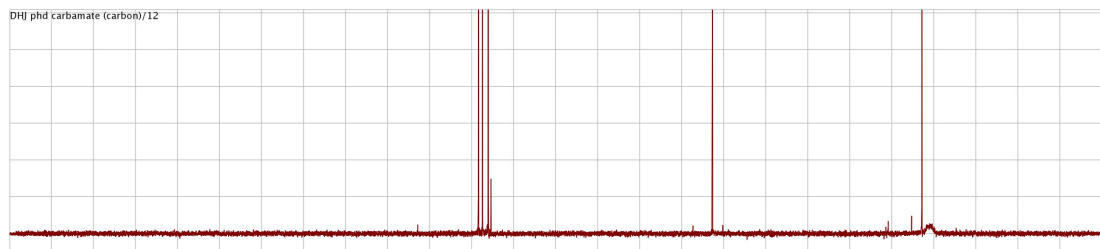
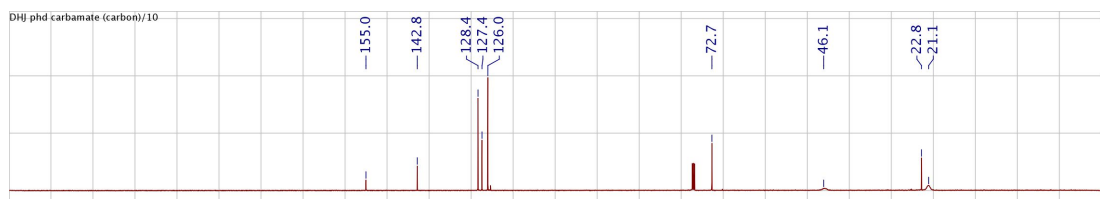
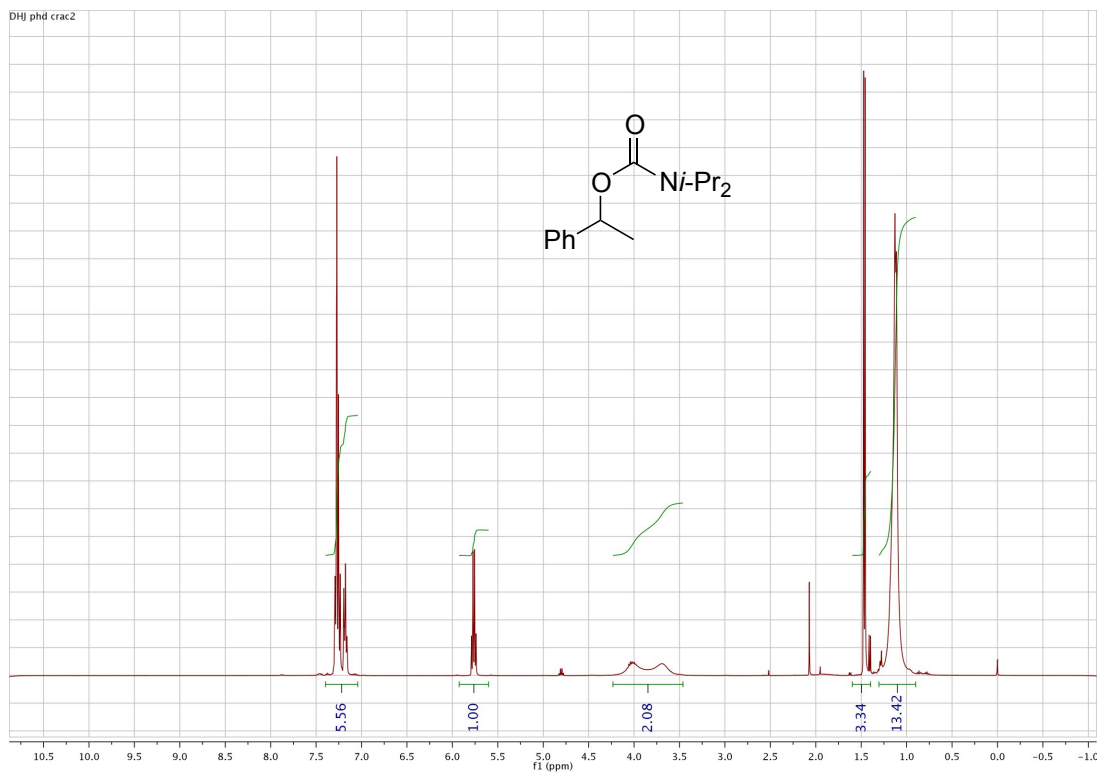
This sample was the crude reaction mixture from the attempted homologation of compound **32** using **Method B**. It is clear that no homologation has taken place, and the sample is extremely clean.

Synthesis of compounds **35** and **36** – Reaction Schemes

Boronic esters **35** and **36** were prepared according to the method of Aggarwal and co-workers (Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760-3763) according to the following reaction schemes.

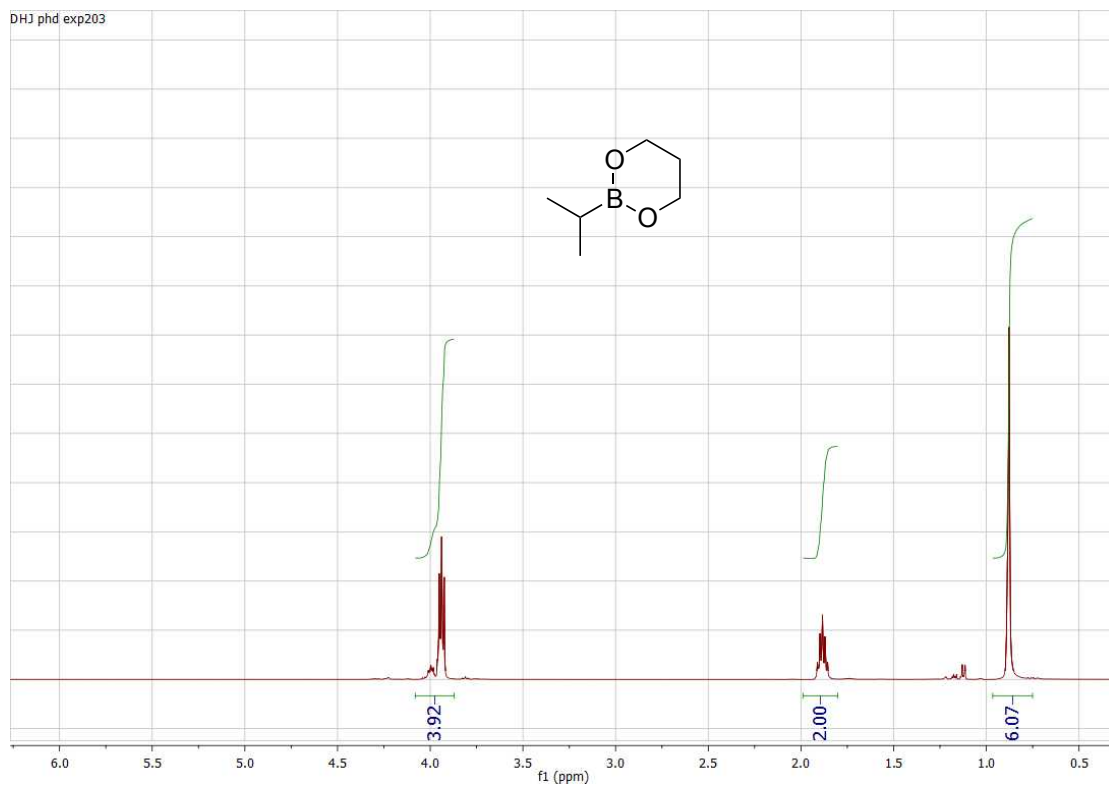


(±)-1-Phenylethyl *N,N*-diisopropylcarbamate

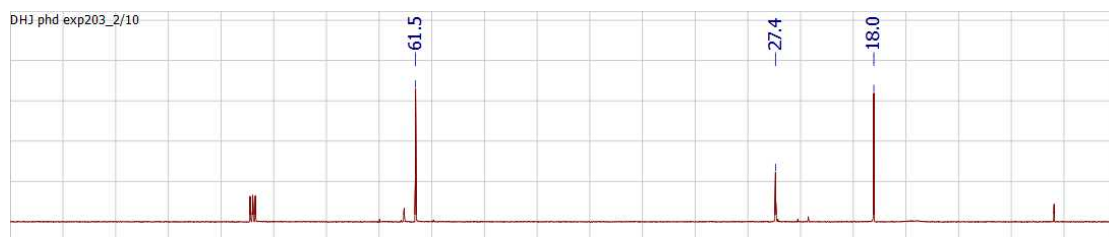


2-Isopropyl-1,3,2-dioxaborinane

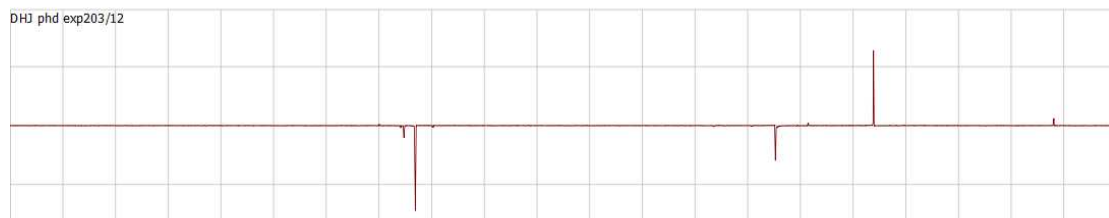
DHJ phd exp203



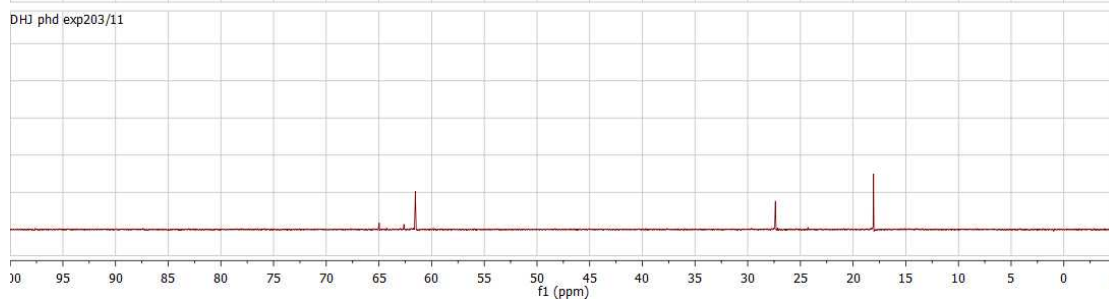
DHJ phd exp203_2/10

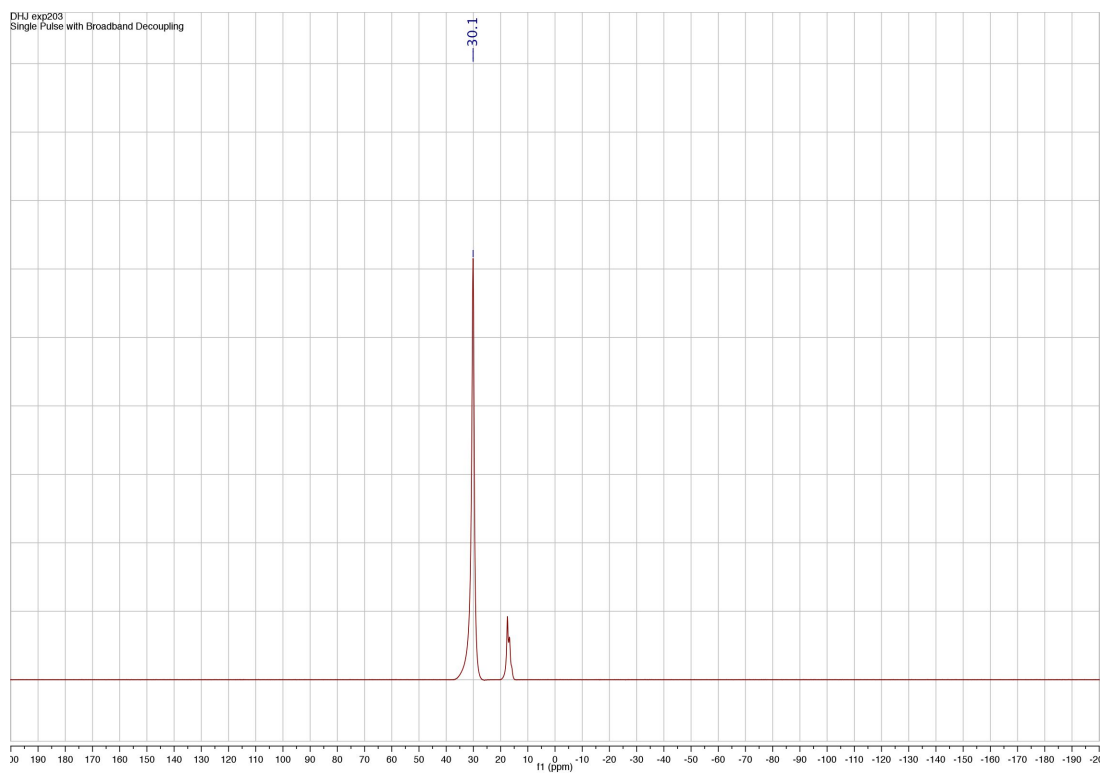


DHJ phd exp203/12



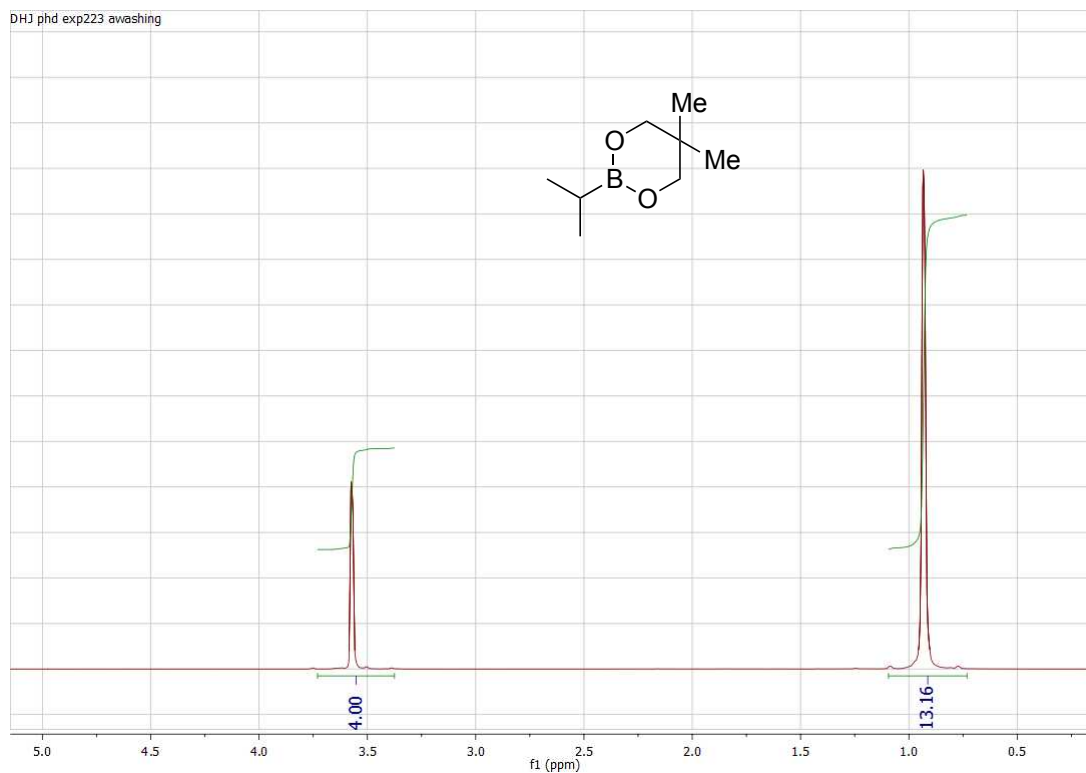
DHJ phd exp203/11



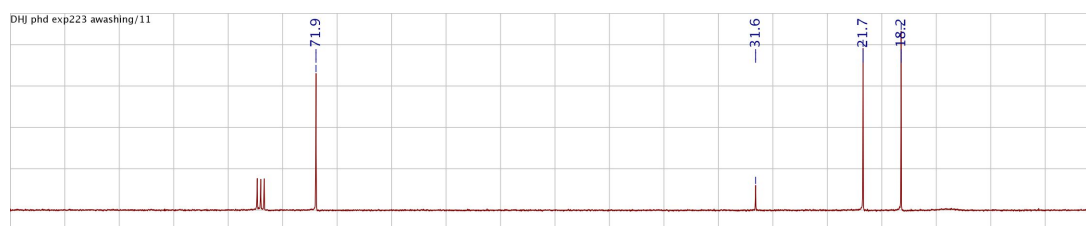


2-Isopropyl-5,5-dimethyl-1,3,2-dioxaborinane

DHJ phd exp223 awashing



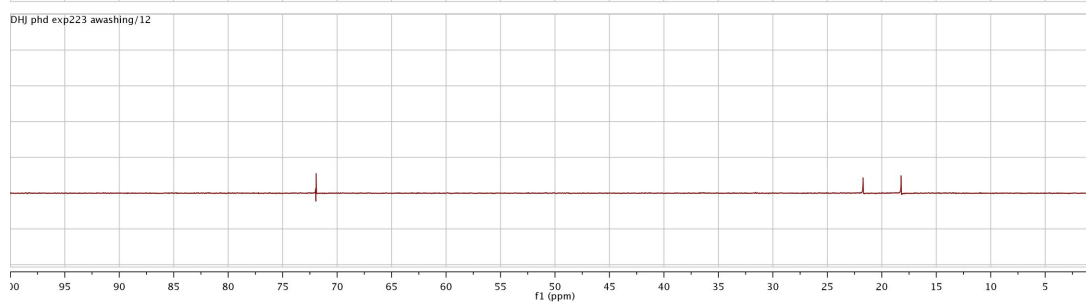
DHJ phd exp223 awashing/11

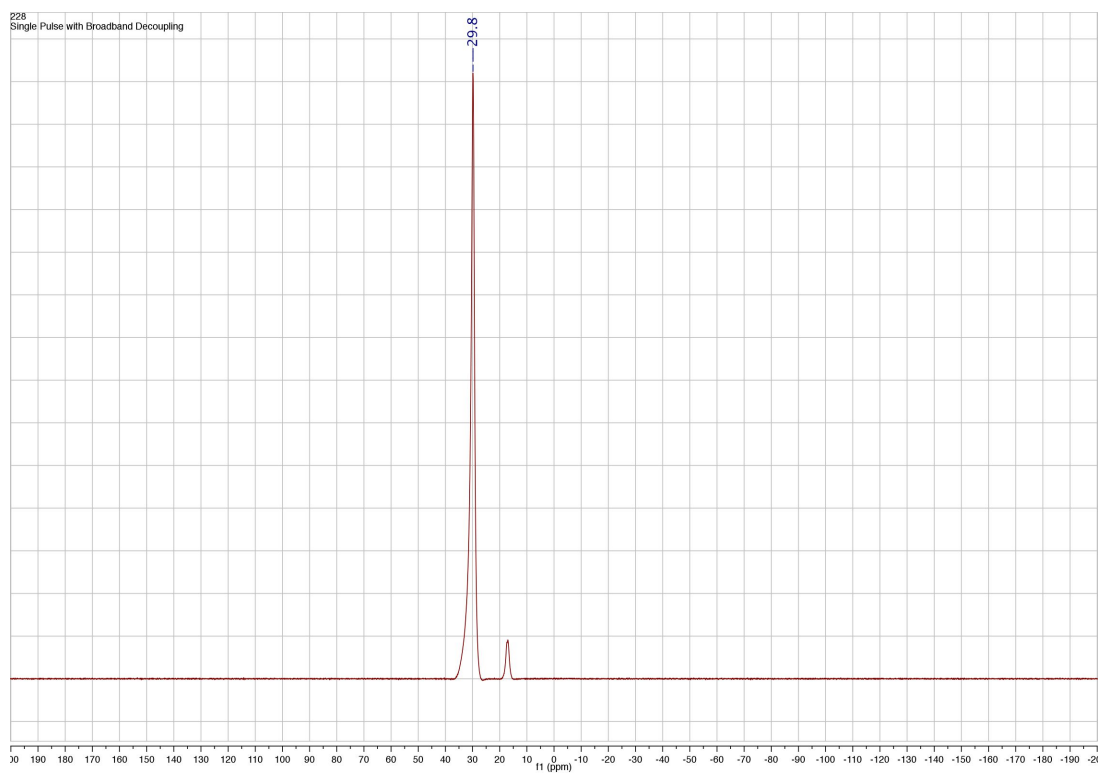


DHJ phd exp223 awashing/13



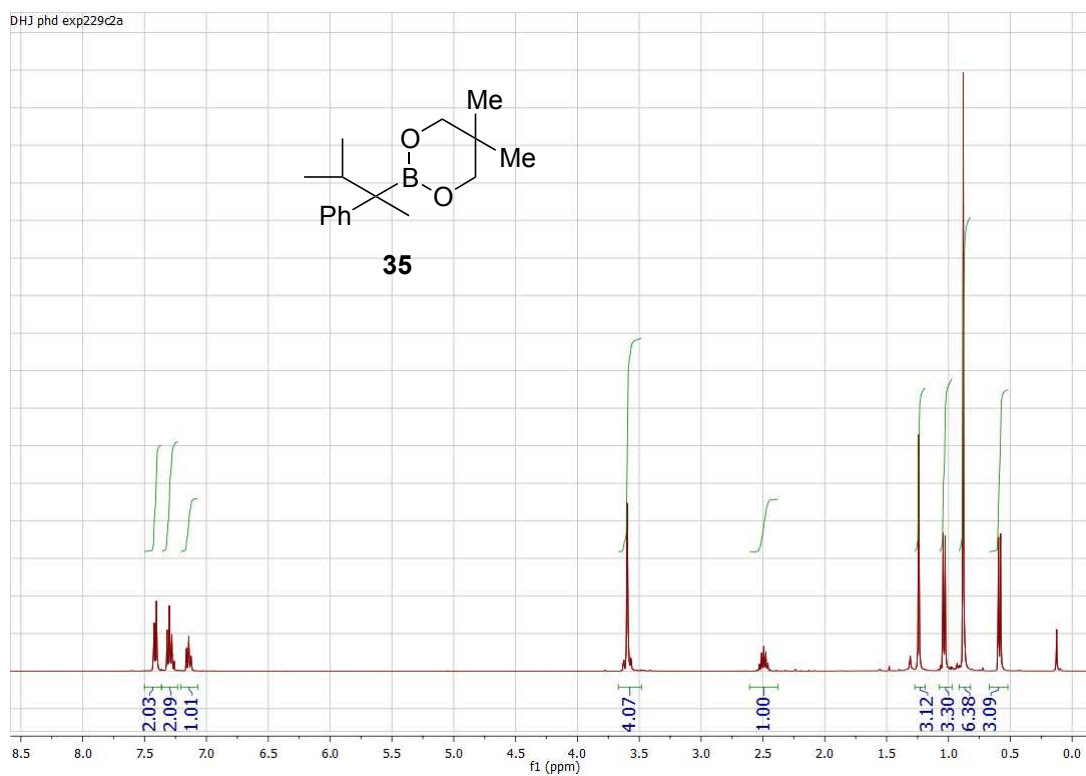
DHJ phd exp223 awashing/12





(±)-5,5-Dimethyl-2-(3-methyl-2-phenylbutan-2-yl)-1,3,2-dioxaborinane (35)

DHJ phd exp229c2a



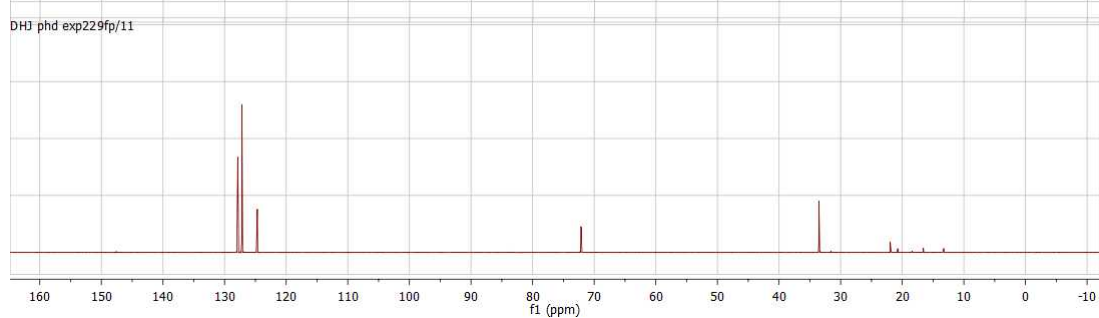
DHJ phd exp229fp/10



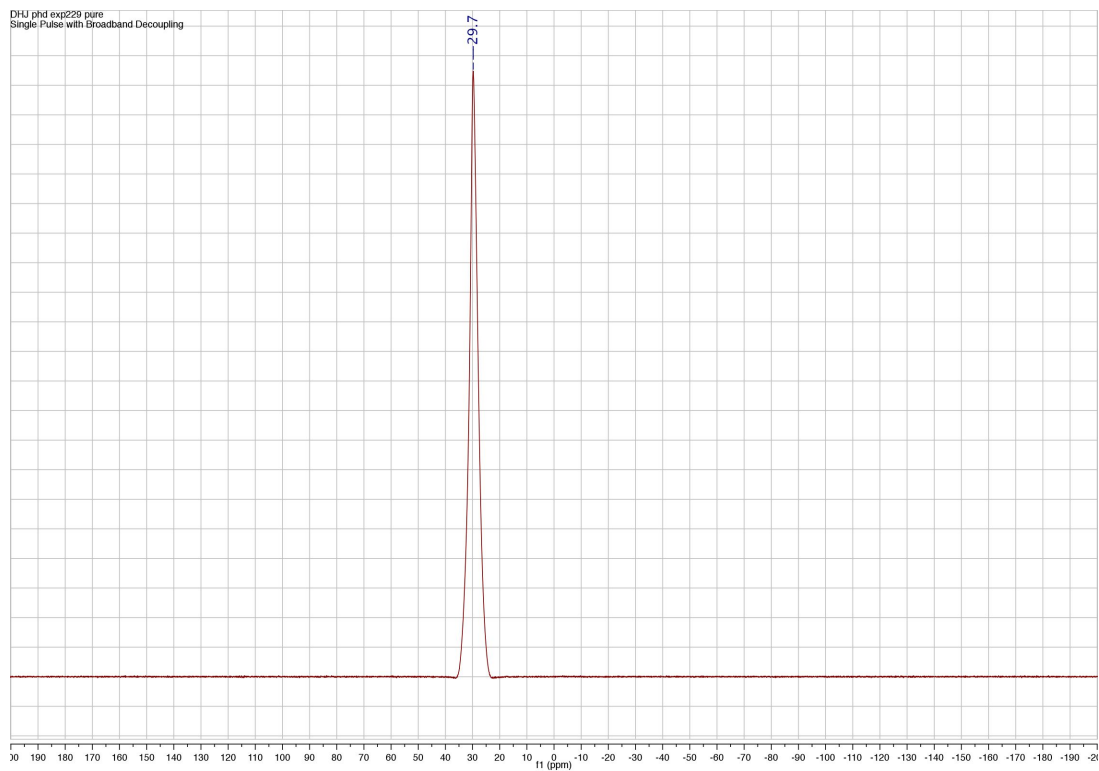
DHJ phd exp229fp/12



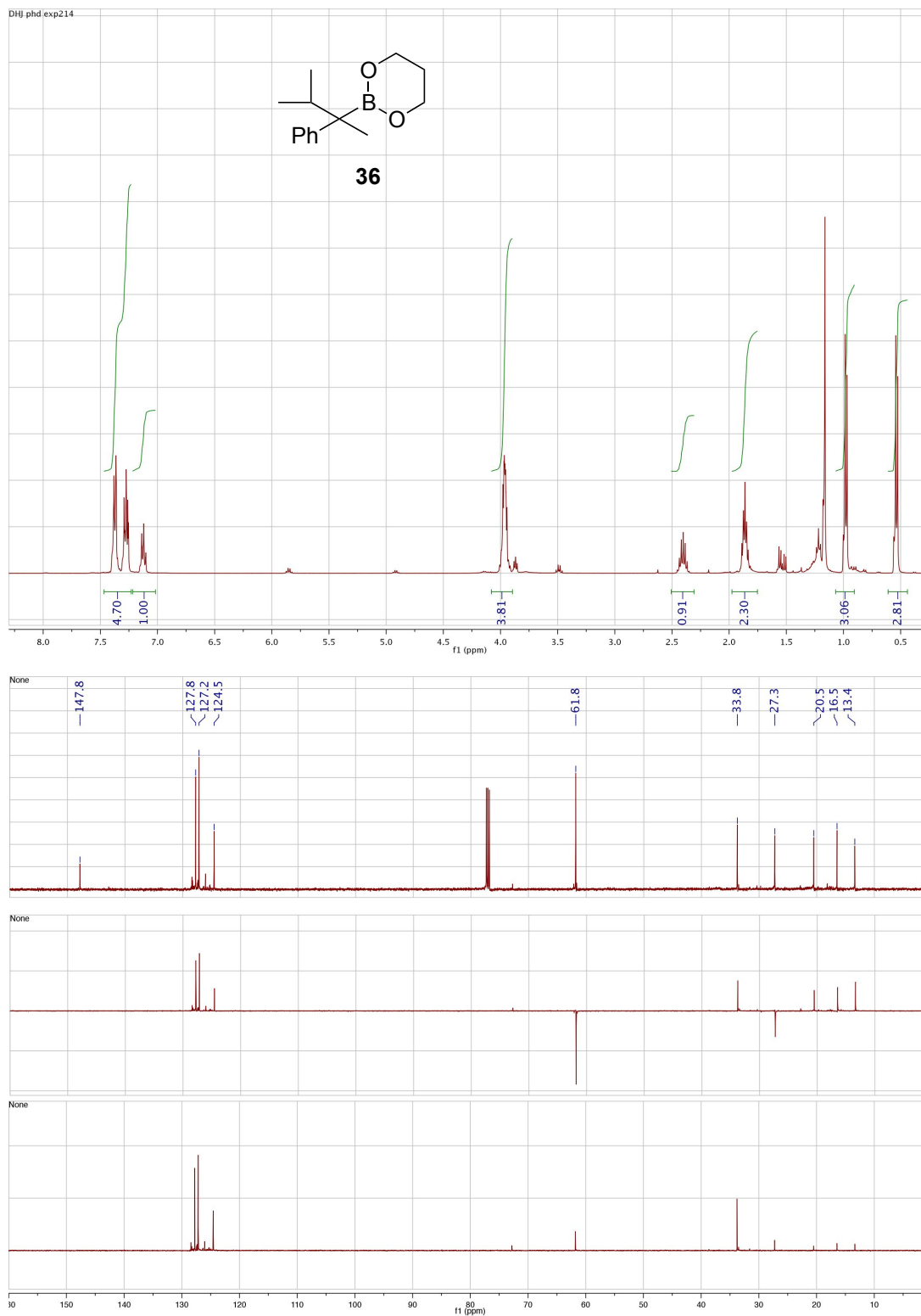
DHJ phd exp229fp/11

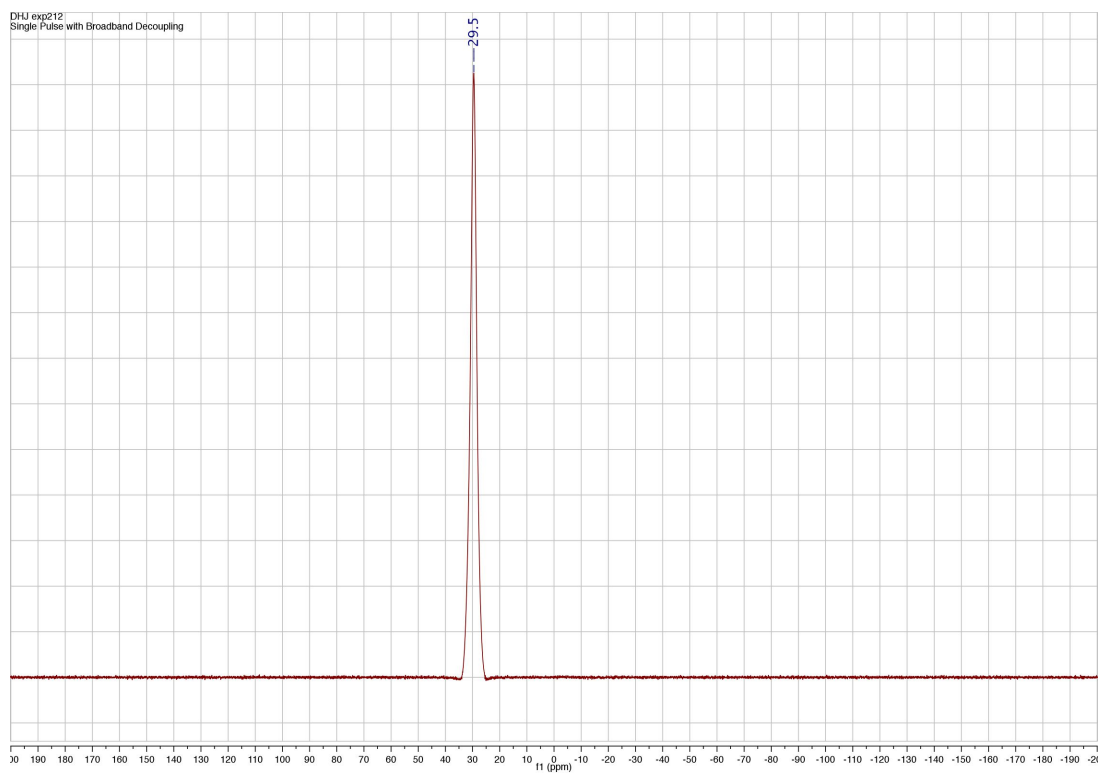


DHJ phd exp229 pure
Single Pulse with Broadband Decoupling

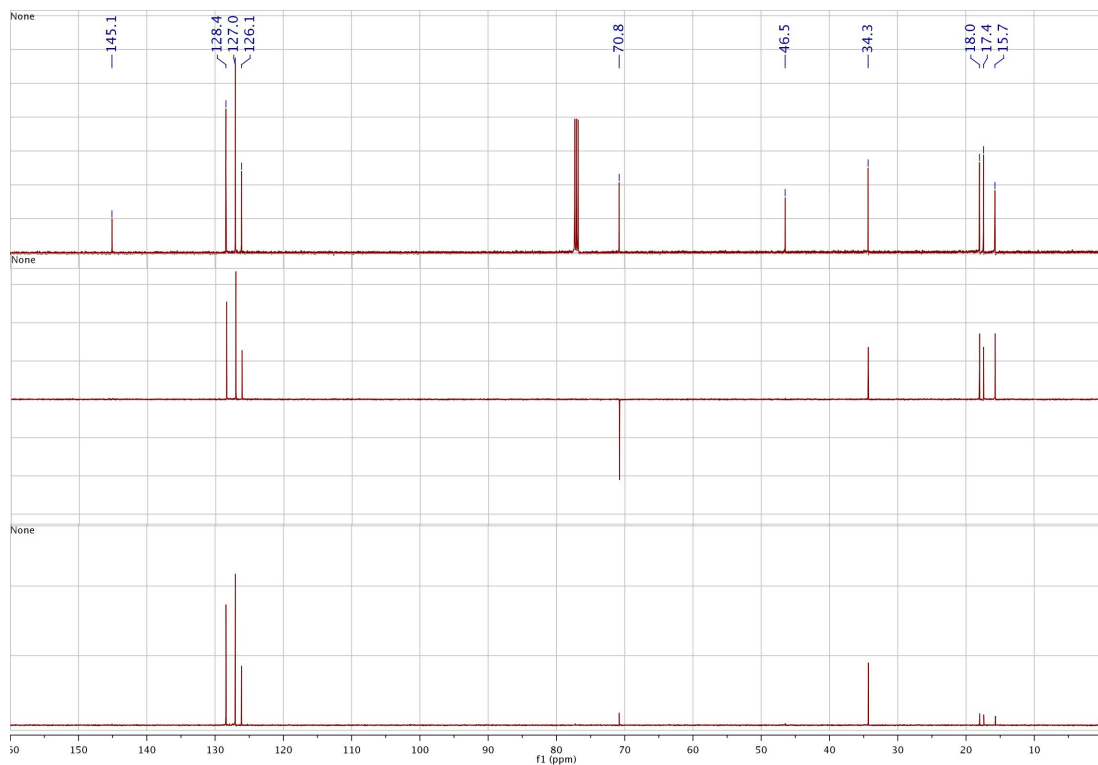
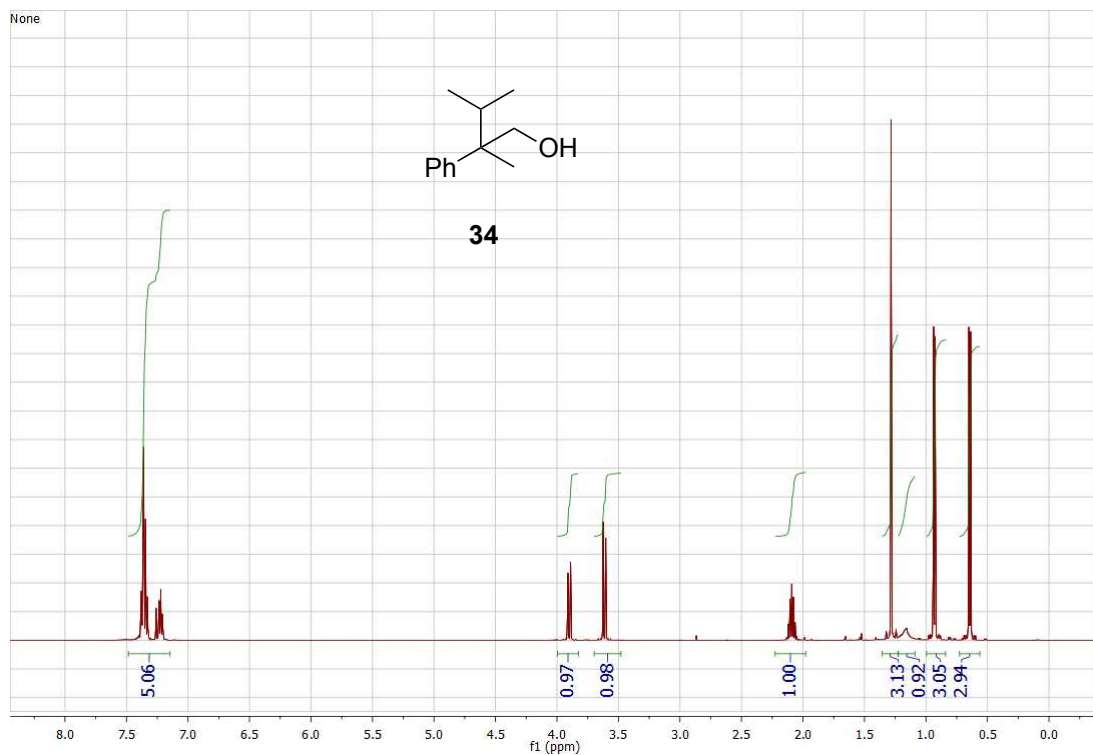


(±)-2-(3-Methyl-2-phenylbutan-2-yl)-1,3,2-dioxaborinane (36)

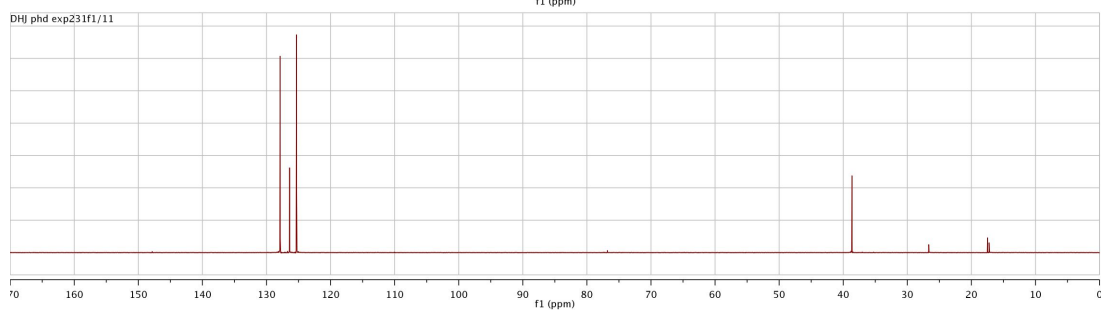
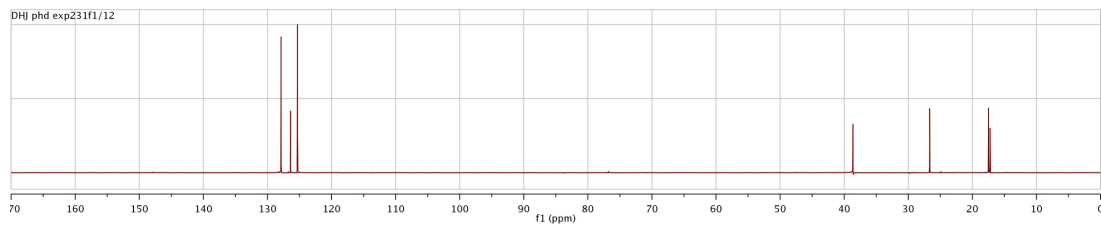
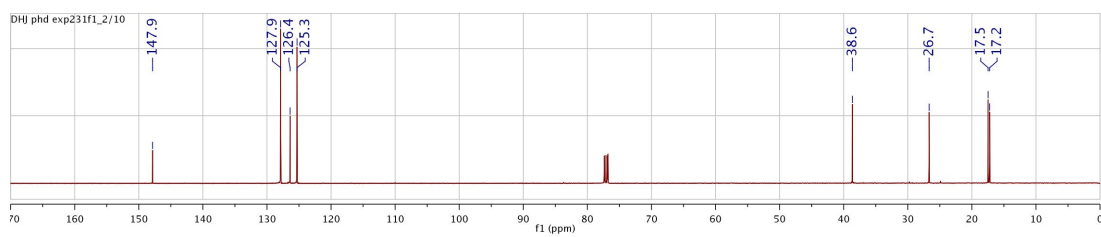
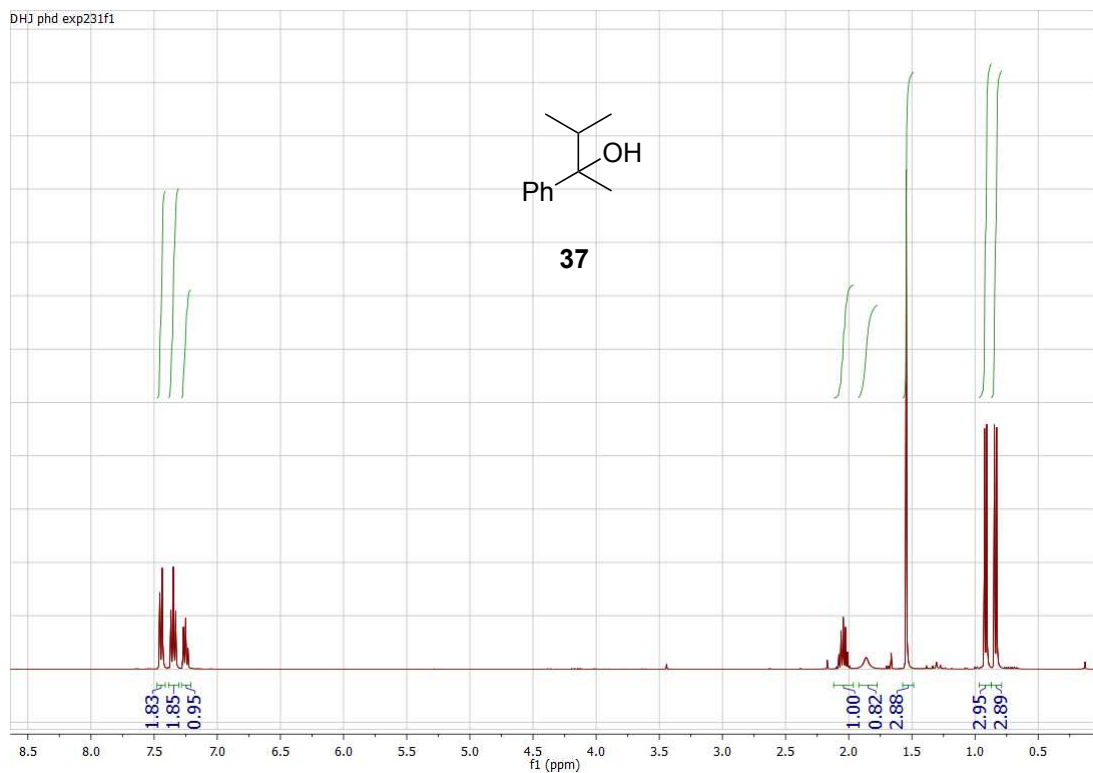




2,3-Dimethyl-2-phenyl-1-butanol (34)



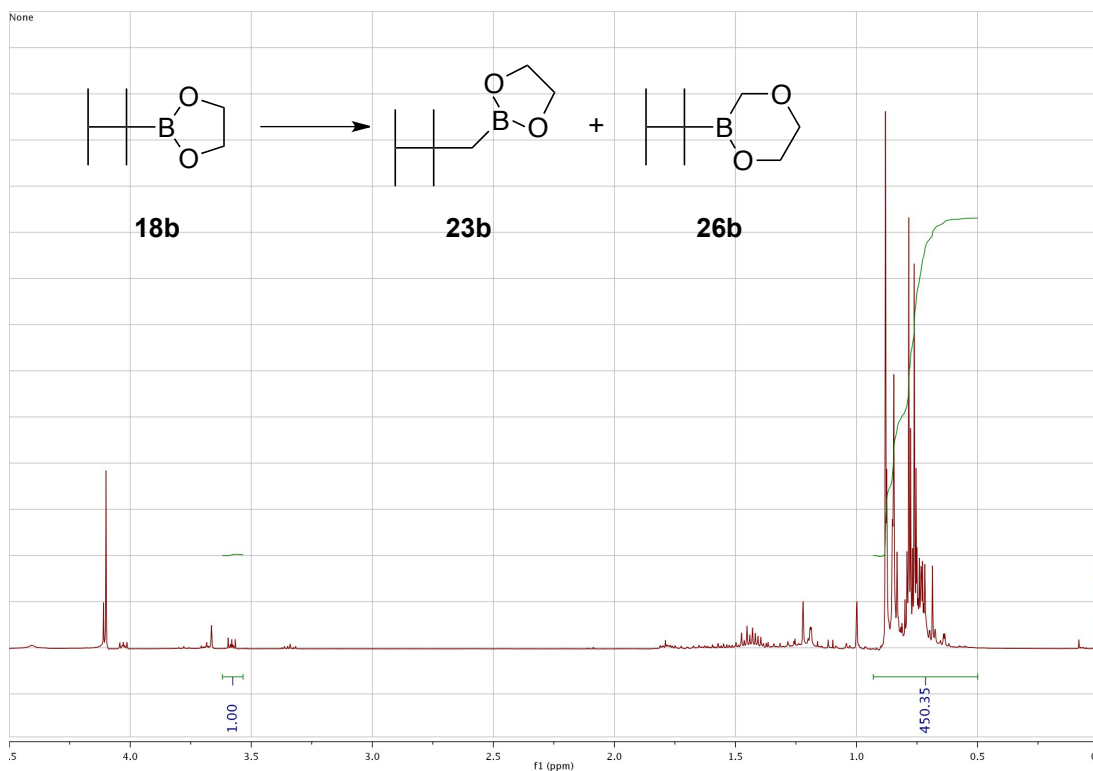
3-Methyl-2-phenyl-2-butanol (37)



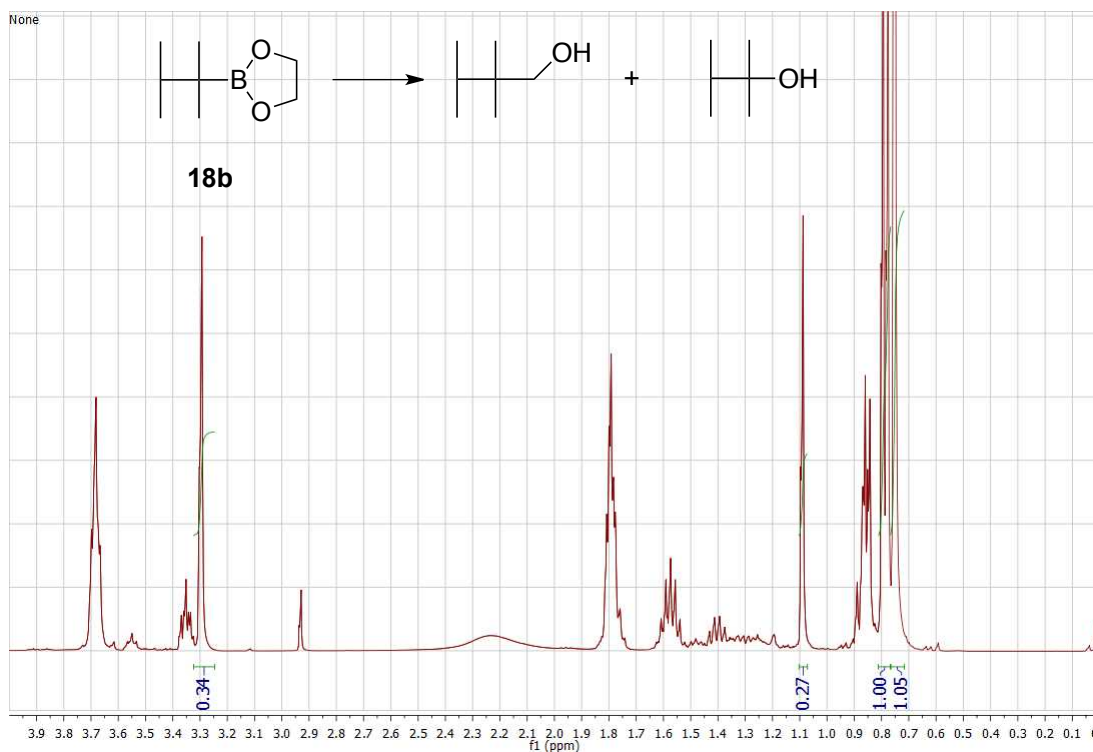
Spectroscopic Study

Experiment 1: 2-*Thexyl*-1,3,2-dioxaborolane (18b) + dibromomethane (1.2 equiv.) + *n*-BuLi (1.1 equiv.)

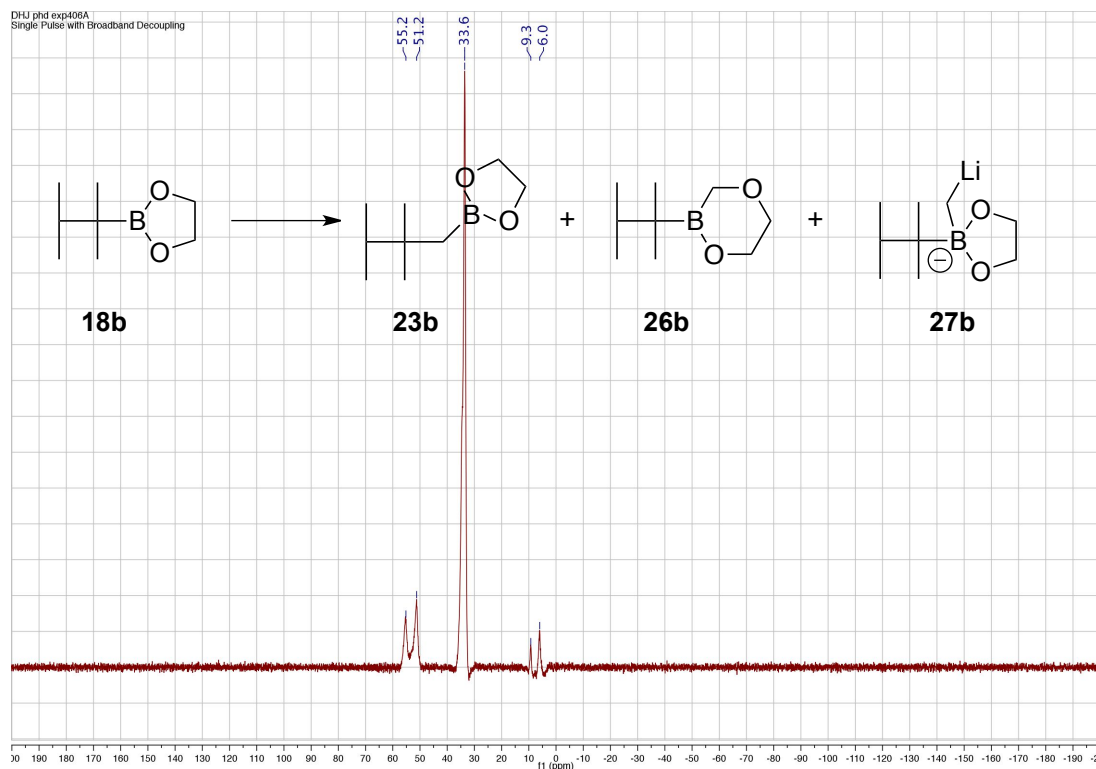
(a) ^1H NMR spectrum after a quick wash with water (reaction mixture not oxidized). The *O*-migration product is visible around 3.6 and 4.1 ppm ($\text{OCH}_2\text{CH}_2\text{O}$). Based on the 'total *thexyl*' integration, the *O*-migration product corresponds to < 2%.



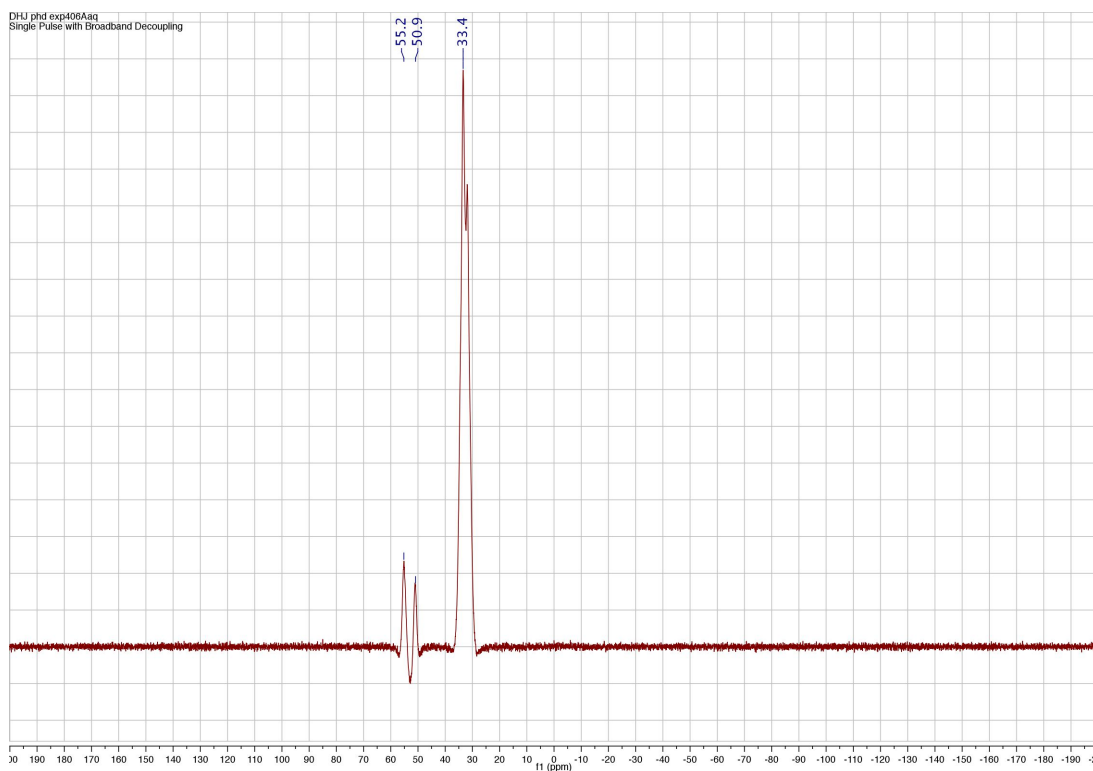
(b) ^1H NMR spectrum after normal oxidative work-up. Significant amounts of THF are present, due to the careful evaporation so that no products were lost.



(c) ^{11}B NMR spectrum after warming and careful evaporation of solvent under a stream of nitrogen. There are two distinct 'borinic' peaks around 50 ppm, as well as a significant peak at 6 ppm, which is tentatively assigned as borate **27b**. The peak at 9 ppm may be a similar species (e.g. solvated or aggregated).

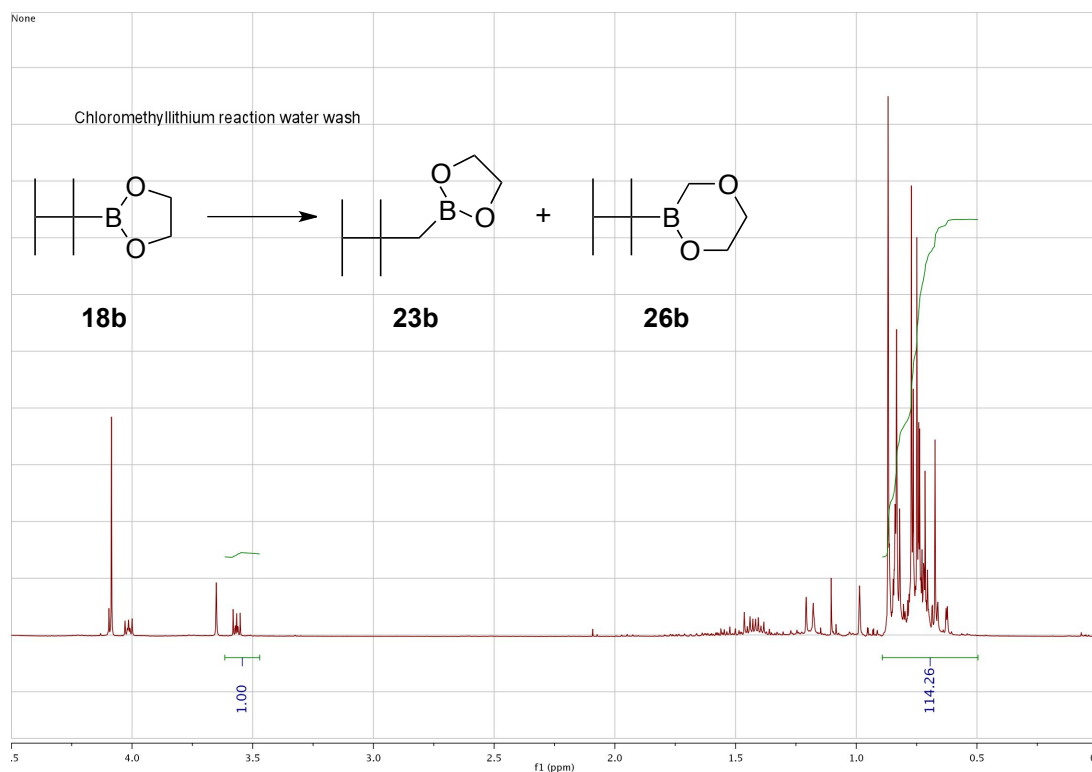


(d) ^{11}B NMR spectrum after washing with water. The peak at 6 ppm has been removed, and the peak at 55.2 ppm has increased in intensity.

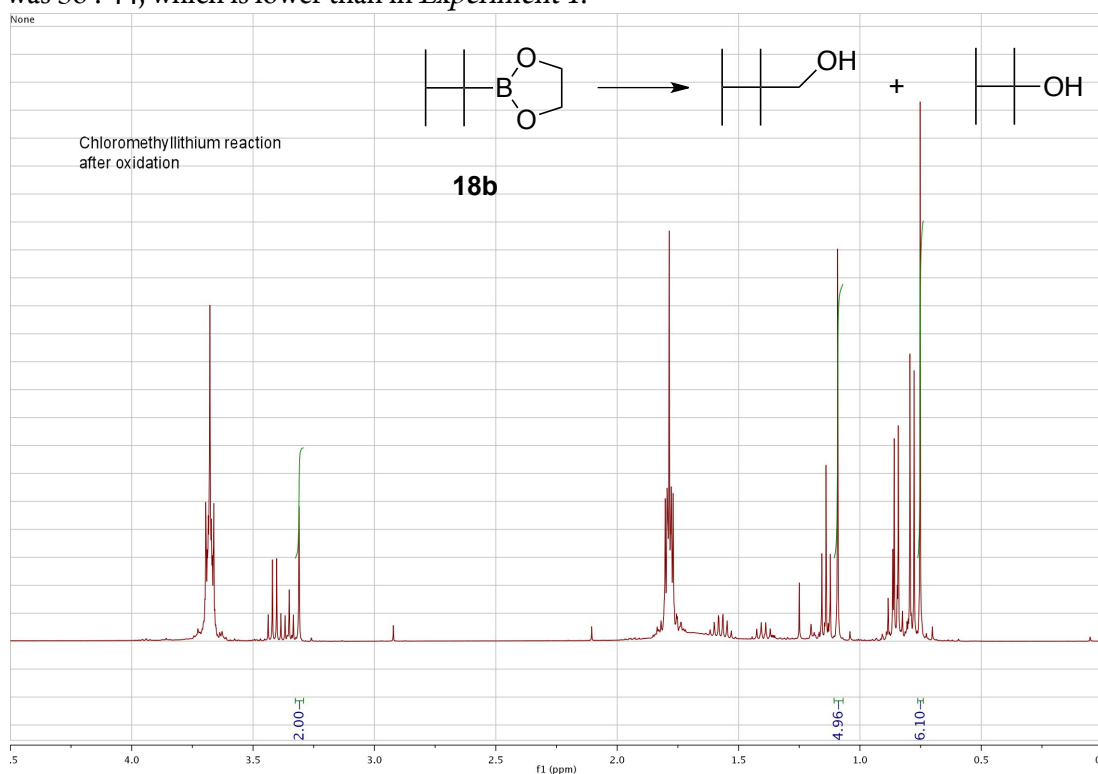


Experiment 2: 2-Thexyl-1,3,2-dioxaborolane (18b) + bromochloromethane (1.2 equiv.) + *n*-BuLi (1.1 equiv.)

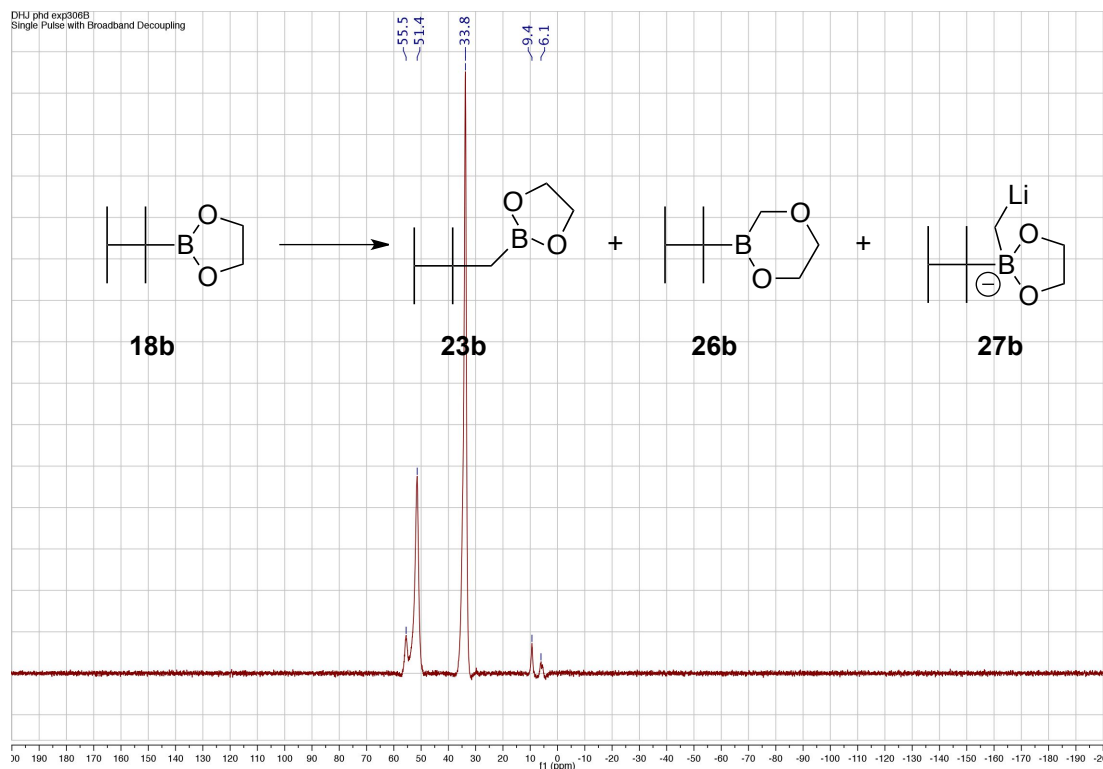
(a) ^1H NMR spectrum after a quick wash with water (reaction mixture not oxidized). The *O*-migration product is visible around 3.6 and 4.1 ppm ($\text{OCH}_2\text{CH}_2\text{O}$). There is clearly more of the *O*-migration product (ca. 5% in this case) compared to *Experiment 1*.



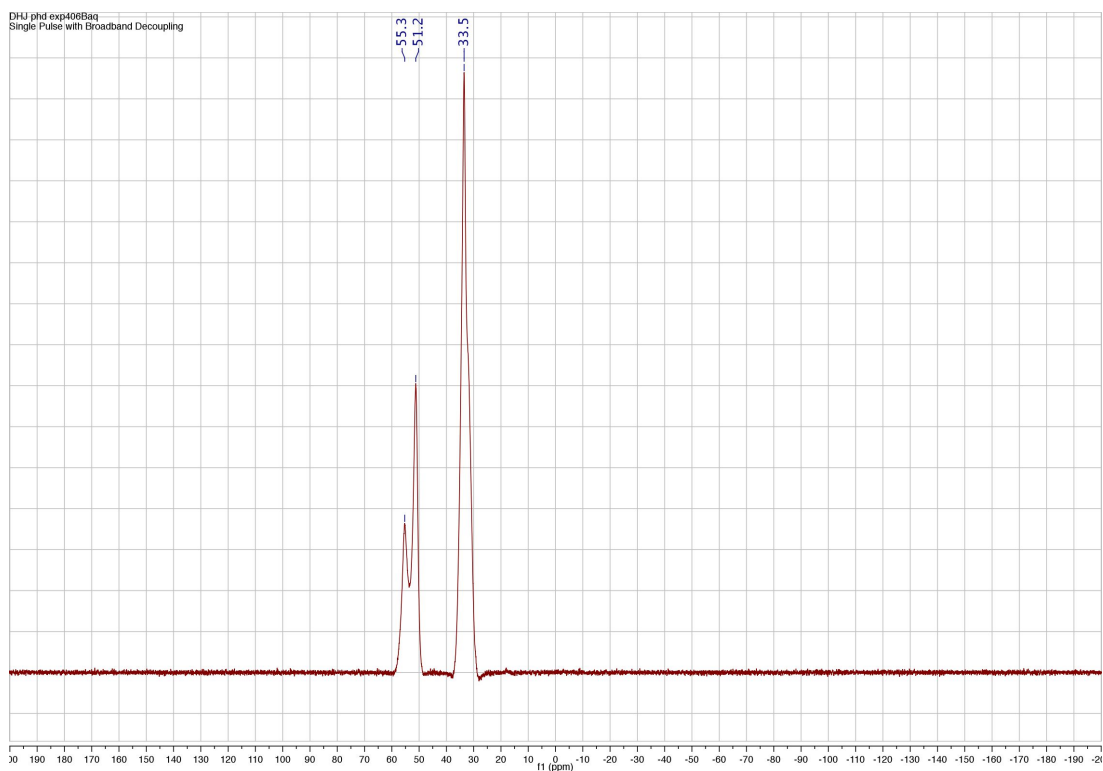
(b) ^1H NMR spectrum after normal oxidative work-up. Significant amounts of THF are present, due to the careful evaporation so that no products are lost. On this occasion, the ratio of thexylmethanol : thexanol was 56 : 44, which is lower than in *Experiment 1*.



(c) ^{11}B NMR spectrum after warming and careful evaporation of solvent under a stream of nitrogen. There are two distinct 'borinic' peaks around 50 ppm, with the peak at 51.4 ppm (attributed to the *O*-migrated product) increased in relative intensity.

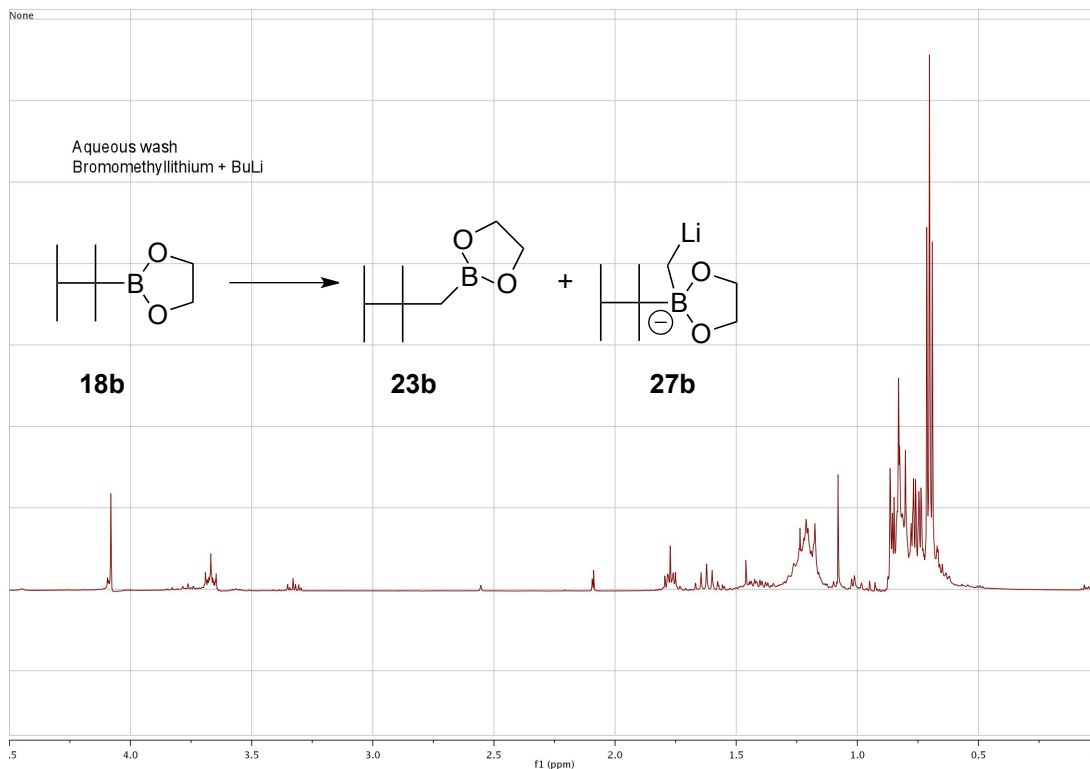


(d) ^{11}B NMR spectrum after washing with water. The peak at 55.7 ppm has increased in intensity at the expense of the 6 ppm and 9 ppm peaks.

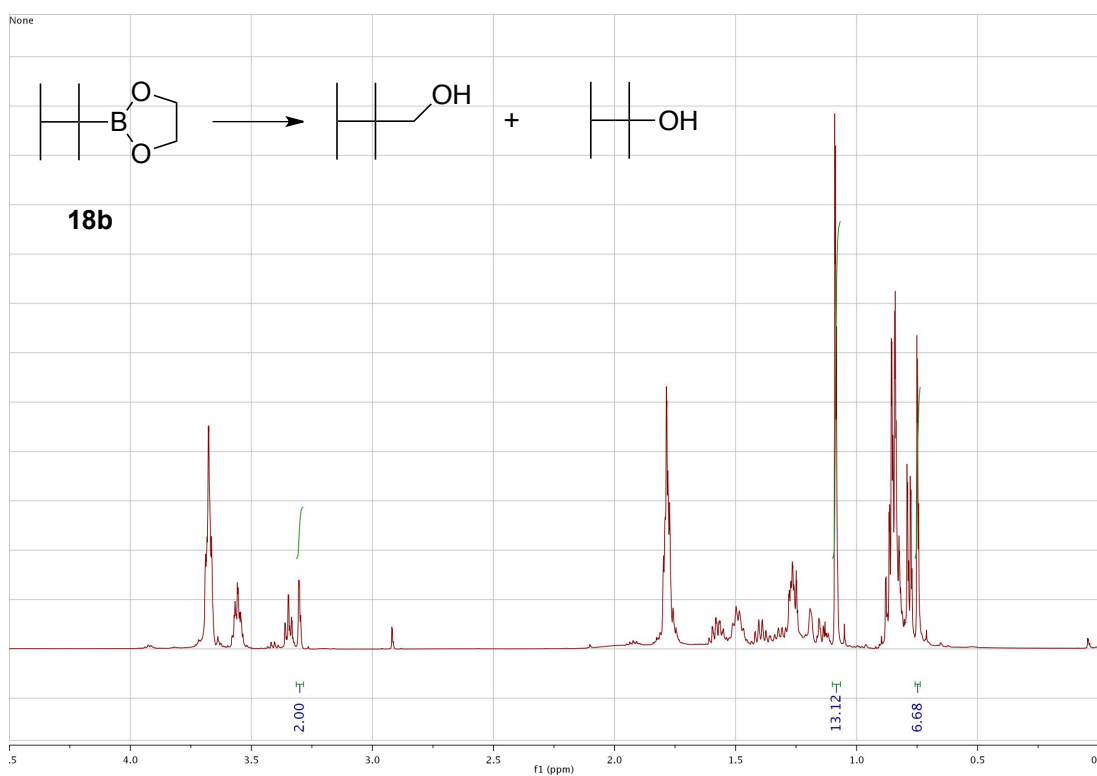


Experiment 3: 2-Thexyl-1,3,2-dioxaborolane (18b) + dibromomethane (1.2 equiv.) and *n*-BuLi (2.2 equiv.)

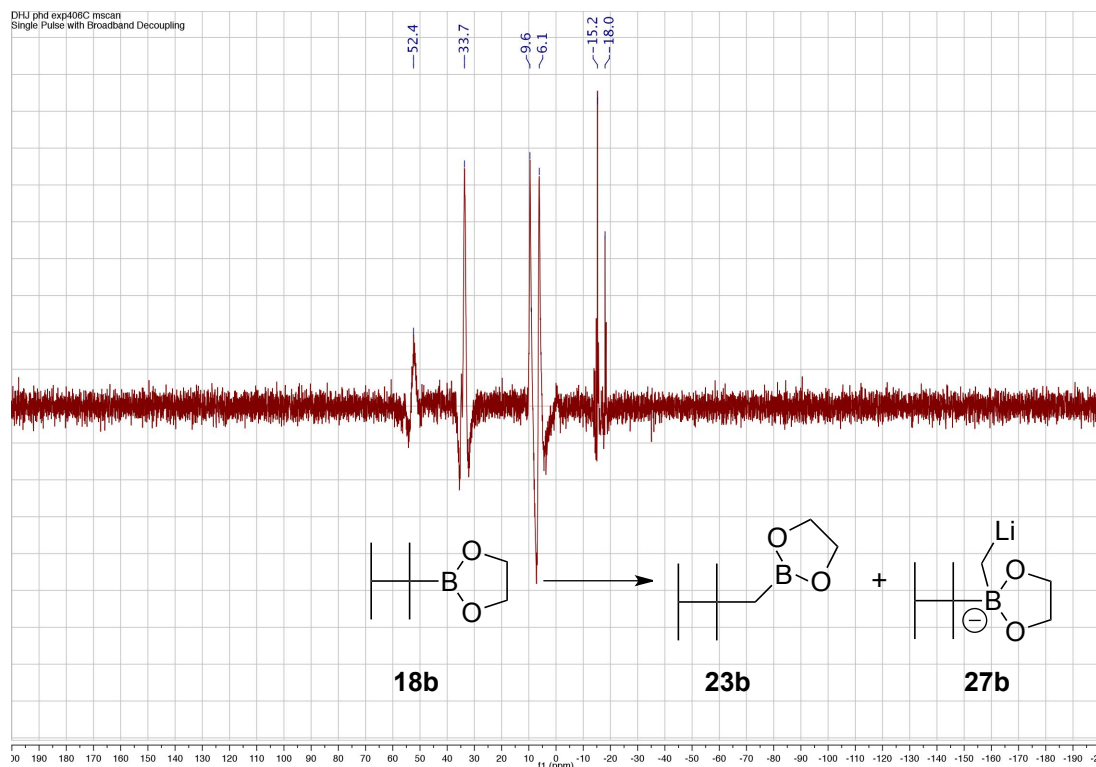
(a) ^1H NMR spectrum after a quick wash with water (reaction mixture not oxidized). In this case, formation of the *O*-migration product has been suppressed, speculated to be a result of lithium-bromine exchange to form **27b** preventing migration.



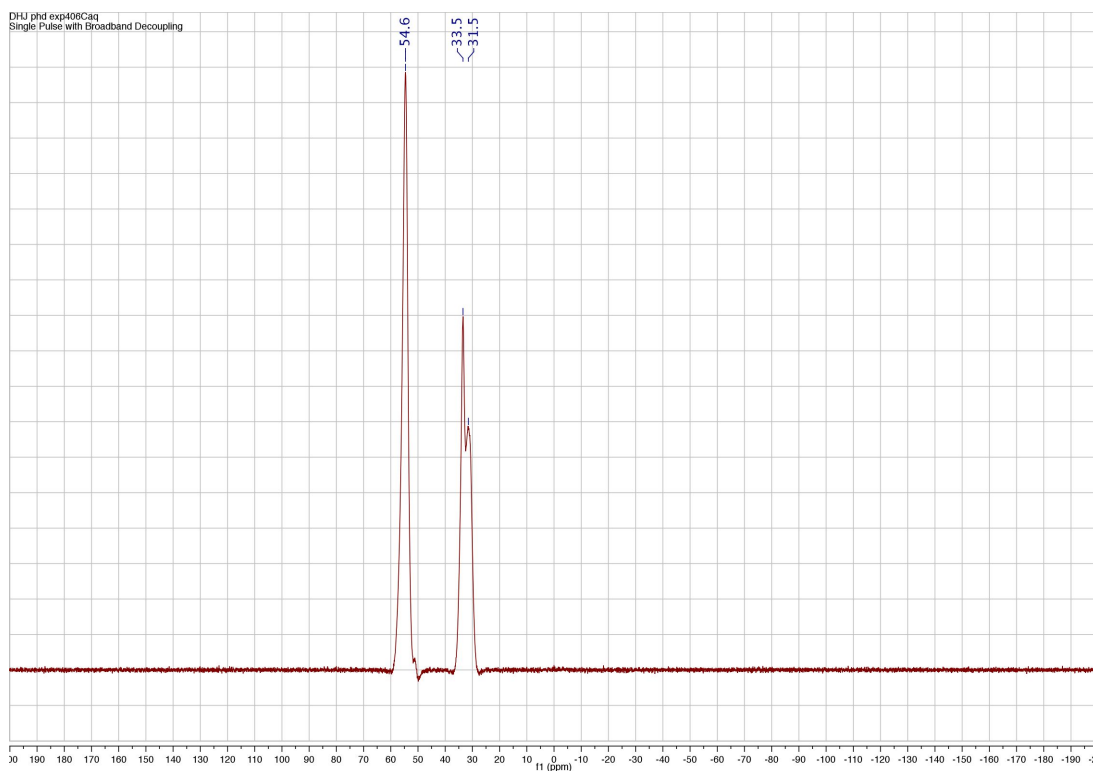
(b) ^1H NMR spectrum after normal oxidative work-up. Some (34%) *C*-migration is still observed, but this is significantly suppressed.



(c) ^{11}B NMR spectrum after warming and careful evaporation of solvent under a stream of nitrogen. Only one 'borinic' peak is now observed (52.4 ppm). The peaks at 6.1 ppm and 9.6 ppm have increased intensity at the expense of the peak at 33.7 ppm.

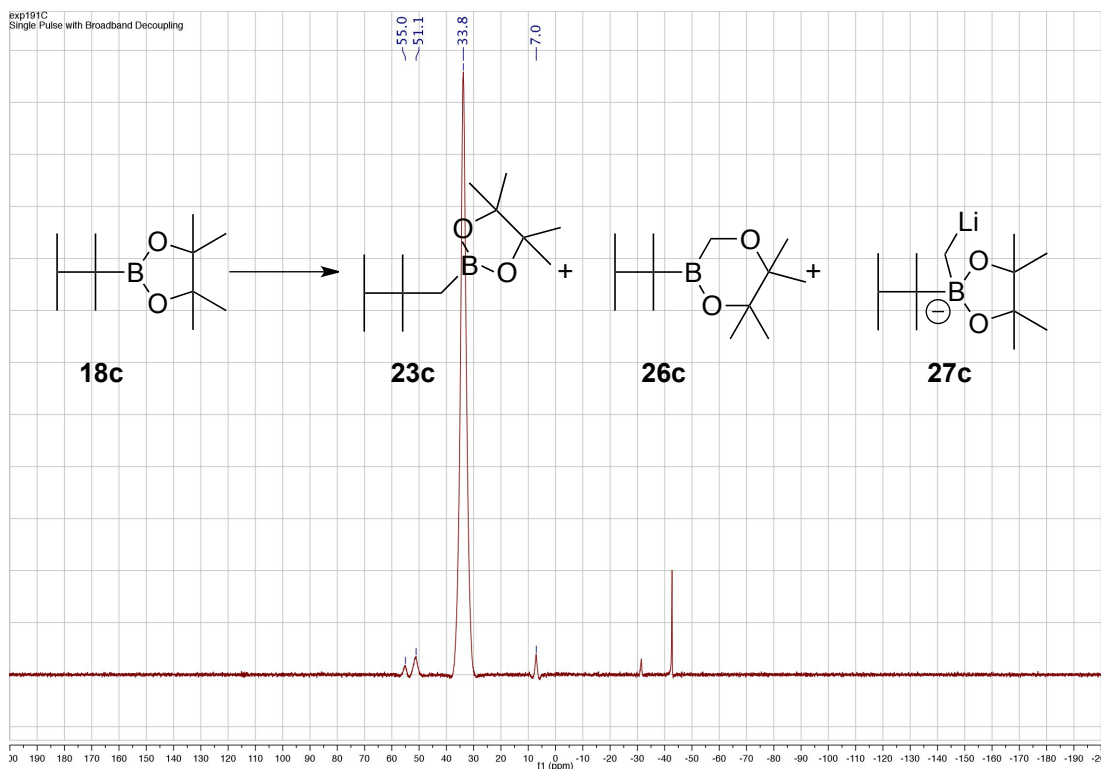


(d) ^{11}B NMR spectrum after washing with water. The peaks around 6 ppm and 9 ppm have been converted into borinic (54.6 ppm) species.



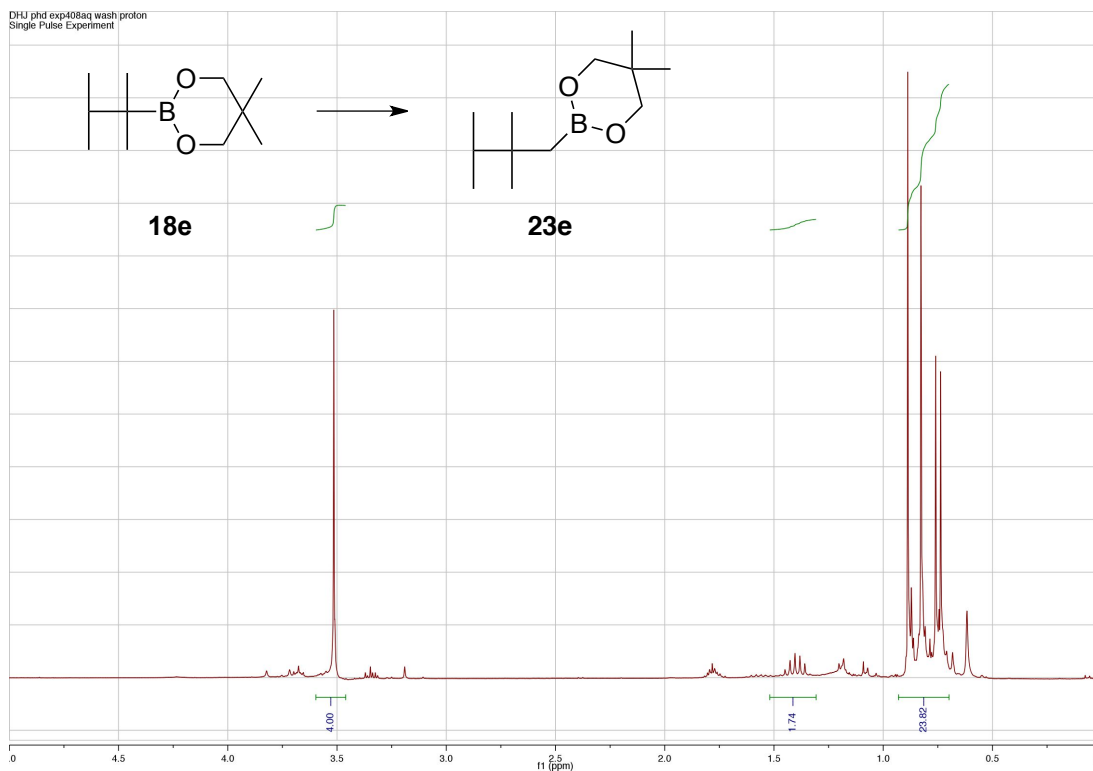
Experiment 4: 2-*Thexyl*-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18c) + dibromomethane (1.2 equiv.) + *n*-BuLi (1.1 equiv.)

(a) ^{11}B NMR spectrum of the crude reaction mixture after warming. Very similar to that obtained from **18b**, although possibly slightly less Li-Br exchange is taking place (the peak at 7.0 ppm is somewhat smaller). It is clear that *O*-migration (51.1 ppm) is still a (minor) competing reaction.

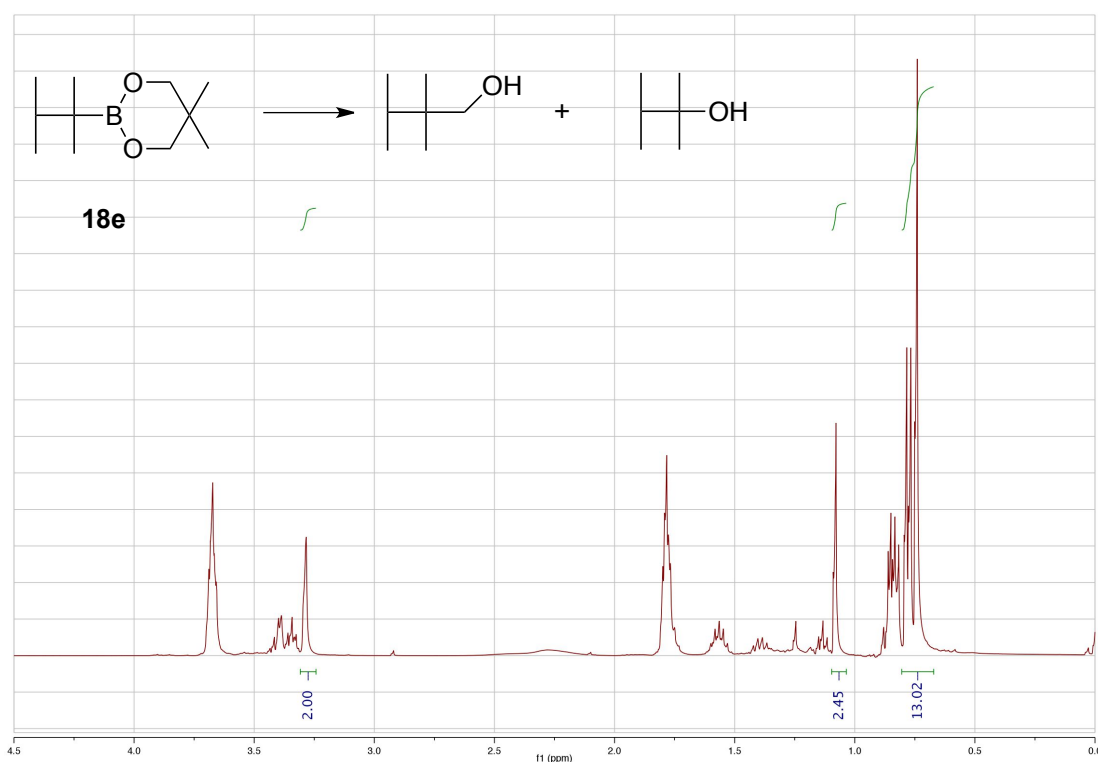


Experiment 5: 2-*Thexyl*-5,5-dimethyl-1,3,2-dioxaborinane (18e) + dibromomethane (1.2 equiv.) + *n*-BuLi (2.2 equiv.)

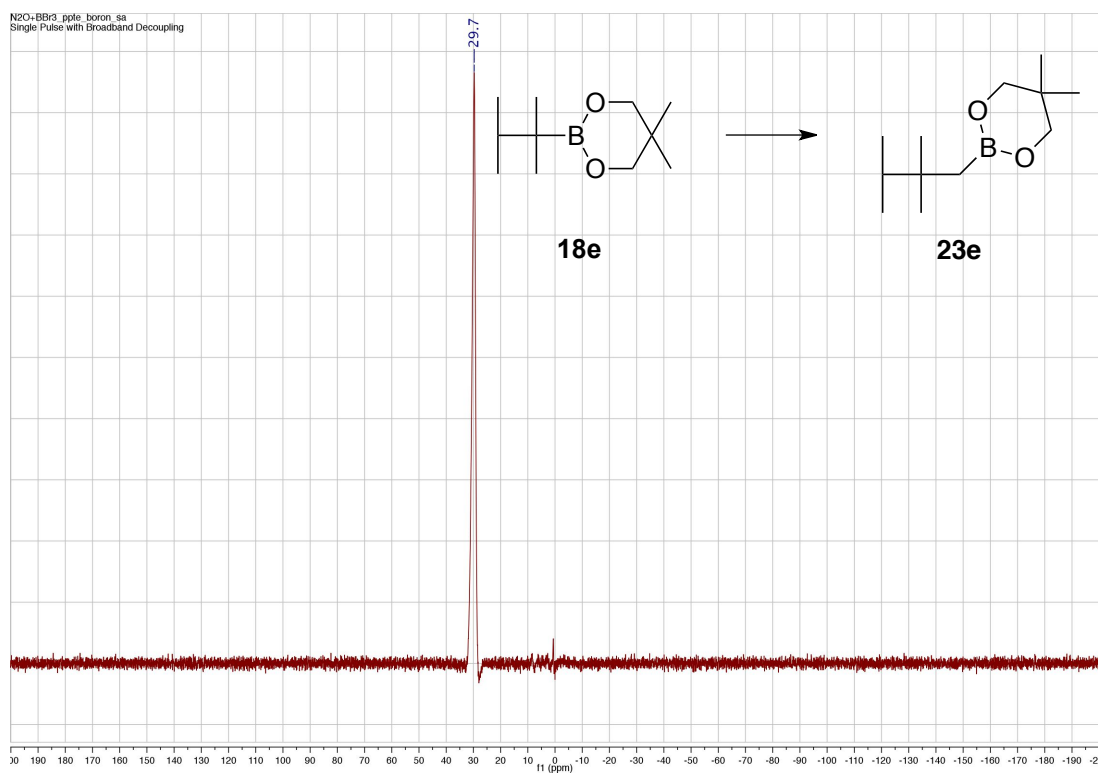
(a) ^1H NMR spectrum after a quick wash with water. Despite the use of excess *n*-BuLi, this appears to be a single species. It is not clear whether any *O*-migration product is present, although this would be conceivable if Li-Br exchange does not occur, and is only there in minute quantities if at all.



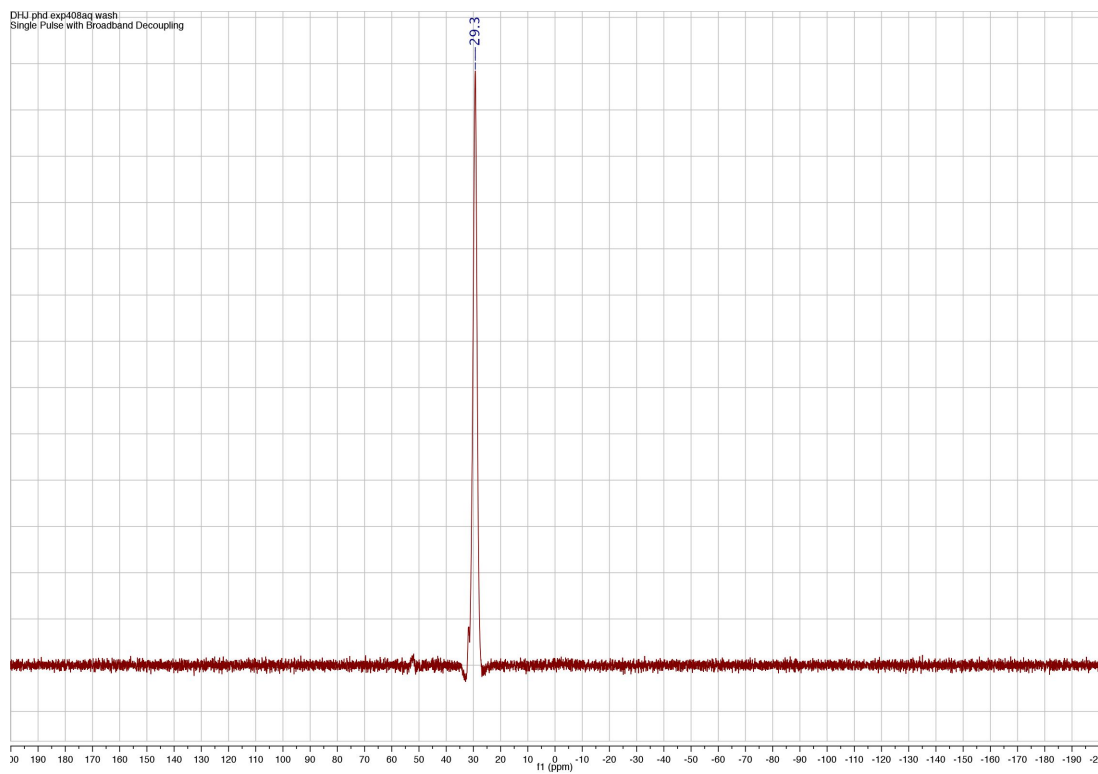
(b) ^1H NMR spectrum after oxidation, showing a very clean approximately 71:29 mixture of homologated:non-homologated products.



(c) ^{11}B NMR spectrum immediately after warming. There is no evidence of lithium-halogen exchange, or borinic species. This is particularly significant since an excess of $n\text{-BuLi}$ was used.



(d) ^{11}B NMR spectrum after washing with water. The spectrum remains clean. There is now a small borinic peak, but the main product corresponds to boronic ester/acid species.



Experiment 6: 2-*Thexyl*-1,3,2-dioxaborolane (18b) + *n*-BuLi (1.1 equiv.)

(a) ^{11}B NMR spectrum after warming to room temperature. A single sharp peak is shown, corresponding to the borate **17**.

