



# **D'un modèle à l'autre. Exploration du modèle des liaisons courbes à partir de la réaction de glycosylation**

**Thèse**

**Jean-Francois Parent**

**Doctorat en chimie**  
Philosophiæ doctor (Ph. D.)

Québec, Canada

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**Jean-François Parent**

Sous la direction de :

Jean-François Paquin, directeur

Pierre Deslongchamps, codirecteur



## Résumé

Le modèle de liaison atomique développé par Pauling et Slater dans les années 1930 pour décrire les systèmes insaturés ne fait pas partie de l'attirail standard du chimiste moderne. Pour diverses raisons, les liaisons courbes ont été mises au rancard dans les années 1950 et les connaissances y étant reliées se sont lentement érodées au fil des générations de chercheurs. Elles n'ont pas pour autant été complètement effacées de la mémoire collective : le travail constituant cette thèse contribue à redonner à ce modèle ses lettres de noblesse. Le projet prend racine dans l'aspect le plus singulier du modèle de Pauling, soit la différenciation orbitalaire. C'est-à-dire que les deux orbitales  $\tau$  constituant la liaison multiple sont distinctes l'une de l'autre, en contraste avec le modèle plus popularisé de Hückel où l'orbitale  $\pi$  s'étend sur la face supérieure et inférieure de l'insaturation. Il est néanmoins important d'exploiter cette facette particulière avec une approche méthodologique pouvant aboutir à des applications directes hors du secteur de la chimie fondamentale et ainsi accroître la portée de nouvelles découvertes. Pour ce faire, cette thèse emploie la réaction de glycosylation  $S_N1$  comme transformation clé et utilise comme donnée probante le ratio anomérique résultant d'une attaque sur l'intermédiaire oxocarbenium formé lors du processus réactionnel. Les donneurs de glycosyle sont sursimplifiés et géométriquement rigidifiés afin de limiter les facteurs pouvant moduler la sélectivité au carbone anomérique. Les différents donneurs semblables à des *trans*-décalines (pyranosides) et des *trans*-hydrindanes (furanosides) sont obtenus par des synthèses multi-étapes à partir de l'oxyde de cyclohexène et contiennent uniquement un groupement fonctionnel en position C<sub>2</sub>. La nature électronique et l'orientation spatiale de ces groupements sont contrôlées et la nucléophilicité des accepteurs utilisés est minimisée. La rationalisation des résultats est conduite par l'application du modèle de Pauling en tenant compte de toutes ces contraintes.

## Abstract

The atomic bonding model developed by Slater and Pauling in the 30s describing the unsaturated systems is not part of the modern chemist's toolbox. For diverse reasons, the model was put aside after 1950 and its knowledge slowly eroded as years went by. However, it was never completely forgotten by the community and this thesis aims to bring it back into the light with a modernised fashion. This project takes root in the most particular aspect of the model, which is orbital differentiation. That aspect implies that the two  $\tau$  bonds forming the chemical bond are distinct in their electronic constituent where the more widely used Hückel  $\pi$ - $\sigma$  model contrasts with its orbital laid simultaneously above and below the plane of the central bond. Exploiting the orbital specificity of the bent bond model requires the use of an approach that will show direct application of the model's potential to a field of chemistry other than the fundamental one to increase its reach within the scientific community. With that goal in mind, the thesis utilises the  $S_N1$  glycosylation reaction for which the observed anomeric ratio resulting from the attack on an oxocarbenium intermediate is the rationalised data. The glycosylation donors are both geometrically rigidified and chemically oversimplified to decrease the number of factors modulating the anomeric selectivity. Similar to *trans*-decalins (pyranosides) and *trans*-hidrindans (furanosides), the donors are obtained through multistep synthesis from cyclohexene oxide and are substituted only at the  $C_2$  position. The electronic nature and the orientation of the substituents are controlled and the nucleophilicity of the different acceptors is minimized. The analysis of the results is conducted by applying the Pauling bent bond model while considering all specific constraints.

## Table des matières

Résumé .....	ii
Abstract.....	iii
Table des matières .....	iv
Liste des figures et des tableaux .....	vii
Liste des abréviations .....	xii
Remerciements .....	xv
Avant-propos .....	xvii
Introduction .....	1
Science fondamentale et ses paradigmes .....	1
Pauling, orbitales de valences et liaison courbes .....	6
Modèle dérivé et application en chimie organique .....	9
Objectifs du projet .....	20
Liaisons $\tau$ et glycosylation $S_N1$ .....	20
Les donneurs de liaison glycosidique .....	22
Réactivité générale des furanoses .....	23
Réactivité générale des pyranoses .....	27
La réaction de glycosylation $S_N1$ et ses conditions .....	32
Choix du solvant et des nucléophiles.....	33
Évaluation de la méthode expérimentale .....	38
Perspectives du modèle.....	39
Chapitre 1 Bent Bond ( $\tau$ ) and the antiperiplanar hypothesis, and the reactivity at the anomeric center in pyranosides .....	40
1.1 Avant-Propos .....	40
1.2 Résumé.....	44
1.3 Abstract.....	44
1.4 Specific introduction.....	45
1.5 $\sigma$ - $\pi$ versus $\tau$ bond electronic models.....	48
1.6 Synthesis of bicyclic pyranosides donors 1.1-1.3.....	53
1.7 Glycosylation experiments .....	55
1.8 Rationalization of glycosylation .....	58
1.9 Summary .....	65
Chapitre 2 Applying the Bent Bond / Antiperiplanar Hypothesis to the Stereoselective Glycosylation of Bicyclic Furanosides.....	67
2.1 Avant-Propos .....	67

2.2 Résumé.....	71
2.3 Abstract.....	71
2.4 Specific introduction.....	72
2.5 Synthesis of bicyclic models.....	77
2.6 Glycosylation experiments .....	79
2.7 Summary.....	90
Chapitre 3 Bent Bond/Antiperiplanar Hypothesis: Modulating the Reactivity and the Selectivity in the Glycosylation of Bicyclic Pyranoside Models .....	92
3.1 Avant-Propos .....	92
3.2 Résumé.....	97
3.3 Abstract.....	97
3.4 Specific introduction.....	98
3.5 Results and discussion .....	102
3.6 Glycosylation experiments .....	105
3.7 BBAH analysis of glycosylation results .....	106
3.8 Formation, stability, and reactivity of oxocarbenium ions .....	115
3.9 Summary.....	117
Conclusion.....	119
Bibliographie .....	124
Annexe A Données expérimentales générales.....	139
A.1 Procédure générale de glycosylation.....	139
Annexe B Données expérimentales du chapitre 1 .....	140
B.1 Expériences de contrôles cinétique .....	140
B.2 Protocole de synthèse et caractérisation des composés.....	142
B.3 Glycosylation des donneurs 1.1 .....	153
B.4 Réactions de glycosylation sur les donneurs C <sub>2</sub> -substitués.....	154
B.5 Réactions de glycosylation utilisant les trichloroacetamidates (TAC) .....	158
Annexe C Données expérimentales du chapitre 2 .....	160
C.1 Protocole de synthèse et caractérisation des composés.....	160
C.2 Réactions de C-glycosylation et caractérisation des produits .....	174
C.3 Réactions de O-glycosylation et caractérisation des produits .....	176
Annexe D Données expérimentales du chapitre 3.....	180
D.1 Protocole de synthèse et caractérisation des composés .....	180
D.2 Réactions de C/O-glycosylation et caractérisation des produits.....	195
Annexe E Données spectrales du chapitre 1.....	204

E.1 Spectre RMN des composés caractérisés. ....	204
E.2 Spectres RMN brutes des <i>O</i> et <i>C</i> -glycosylation dans le DCM.....	241
E.3 Spectres RMN brutes des <i>O</i> et <i>C</i> -glycosylation dans le CH <sub>3</sub> CN .....	249
E.4 Spectres RMN brutes des expériences de contrôle cinétique. ....	256
Annexe F Données spectrales et expérimentales du chapitre 2.....	262
F.1 Détails de calculs DFT .....	262
F.2 Expérience de contrôle cinétique.....	268
F.3 Spectres RMN des composés caractérisés.....	270
F.4 Spectres RMN brutes des réactions de glycosylation.....	319
F.5 Spectres RMN brutes des expériences des contrôle cinétique. ....	328
F.6 Spectres RMN du furanose complet et de sa <i>O</i> -glycosylation. ....	330
Annexe G Données spectrales du chapitre 3 .....	332
G.1 Spectres RMN des composés caractérisés .....	332
G.2 Expérience de glycosylation compétitive .....	393
G.3 Spectres RMN brutes des réactions de glycosylation. ....	396
G.4 Données brutes calcule DFT .....	407

## Liste des figures et des tableaux

### Figures

Figure I.1 Formation des liaisons $\sigma$ - $\pi$ et $\tau$ par la combinaison d'orbitales hybridés.....	10
Figure I.2 Hyperconjugaison et liaisons $\tau$ . .....	12
Figure I.3 Modèle d'addition nucléophile sur un aldéhyde substitué par un hétéroatome. .....	13
Figure I.4 Addition contrôlée par $\sigma$ C-H donneur (haut), par $\sigma$ C-C donneur et $\sigma$ C-OR accepteur (centre) et modulé par C <sub>3</sub> -R.(bas). .....	14
Figure I.5 Sélectivité engendrée par la substitution longue distance sur des adamantanones. .....	15
Figure I.6 Stabilité et réactivité relatives des ester Z et E. ....	16
Figure I.7 Différence d'acidité entre la $\delta$ -valerolactone et l'acétate d'éthyle dans le DMSO. .....	17
Figure I.8 Conformation favorisée des éthers d'énol. ....	18
Figure I.9 Conjugaison du cyclobutadiène. ....	18
Figure I.10 Délocalisation et aromaticité du benzène. ....	19
Figure I.11 Oxocarbénium d'un pyranose et d'un furanose. ....	21
Figure I.12 Donneurs de glycosyle préparés. ....	22
Figure I.13 Glycosylation d'un oxocarbénium <sup>3</sup> E bicyclique furanosique. ....	24
Figure I.14 Conformation possible d'un furanosyle. ....	25
Figure I.15 Carte énergétique de l'oxocarbénium du D-ribose et D-arabinose rapportée par Codée. ....	26
Figure I.16 Conformation résultante de l'addition sur l'ion oxocarbénium <sup>4</sup> H <sub>3</sub> . ....	27
Figure I.17 Mécanisme de $\beta$ -mannosylation par préactivation. <sup>44a</sup> .....	28
Figure I.18 1,2- <i>cis</i> mannosylation sans l'intervention d'un triflate ou d'une paire d'ions via la configuration favorisée B <sub>2,5</sub> . ....	29
Figure I.19 C-glycosylation sélective rapportée par Woerpel et interprétation par liaisons courbes. ....	30
Figure I.20 Glycosylation d'un pyranose C <sub>2</sub> -OBn substitué et carte énergétique correspondante reportée par Codée. ....	31
Figure I.21 Sélectivité de la C-glycosylation en fonction de la nucléophilie de l'accepteur (Nu). ....	33
Figure I.22 Sélectivité de la O-glycosylation en fonction de la nucléophilie de l'accepteur (Nu). ....	33

Figure I.23 Sélectivité du 4,6- <i>O</i> -benzylidène mannose en fonction du nucléophile.....	34
Figure I.24 Sélectivité du 2-deoxy-2-azido-4,6- <i>O</i> -benzylidène glucose en fonction du nucléophile. ....	35
Figure I.25 <i>O</i> -glycosylation du mannose en fonction de la nature de la position 7. ....	36
Figure I.26 Sélectivité diminuée par l'insertion d'un atome électroattracteur. ....	37
Figure I.27 État de transition et mécanisme de glycosylation engendré par le solvant en présence d'un contre-ion triflate.....	37
Figure I.28 Conditions de glycosylation générales aux deux types de donneurs. ....	38
Figure 1.1 Synthèse de la lactone bicyclique telle que rapportée par Woerpel. ....	40
Figure 1.2 Insertion direct de l'oxygène en C <sub>2</sub> . ....	41
Figure 1.3 Voie de synthèse initiale pour l'introduction d'un C <sub>2</sub> -OR en α d'une lactone. ..	41
Figure 1.4 Génération de l'α-iodo δ-valérolactone. ....	42
Figure 1.5 A general glycosylation mechanism. ....	46
Figure 1.6 <i>Anti</i> and <i>Syn</i> periplanar addition on s-p and t bond. ....	49
Figure 1.7 Stereoelectronically preferred nucleophilic addition. ....	50
Figure 1.8 <i>Anti</i> and <i>syn</i> periplanar addition on <sup>4</sup> H <sub>3</sub> -oxocarbenium ion.....	51
Figure 1.9 S <sub>N</sub> 1 vs S <sub>N</sub> 2 with t bonds. ....	51
Figure 1.10 Bicyclic pyranoside donors <b>1.1-1.3</b> .....	52
Figure 1.11 Synthesis of donors <b>1.1</b> . ....	54
Figure 1.12 Synthesis of donors <b>1.2</b> and <b>1.3</b> . ....	55
Figure 1.13 α/β-Glycosidation of bicyclic furanosides analogues. ....	58
Figure 1.14 1,2- <i>Cis</i> nucleophilic addition on <b>1.16</b> and <b>1.17</b> . ....	59
Figure 1.15 Glycosidation of 4,6- <i>O</i> -gluco and manno pyranosides.....	61
Figure 1.16 Glycosylation of 4,6- <i>O</i> -benzylidene of glucose and mannose donors.....	62
Figure 1.17 Nucleophilic addition on bicyclic compound 18 (X = O or CH <sub>2</sub> ). ....	63
Figure 1.18 Resonance structures of τ bonds and stereocontrolled nucleophilic addition on <sup>4</sup> H <sub>3</sub> .....	65
Figure 2.1 Préparation d'un donneur C <sub>2</sub> -F. ....	67
Figure 2.2 Préparation initiale du précurseur diol 1,4 pour l'obtention des donneurs C <sub>2</sub> -Me. ....	68
Figure 2.3 Inside and outside attack. ....	72
Figure 2.4 Allylation of furanosides. ....	72
Figure 2.5 1,2- <i>Cis</i> deuteration or allylation of pentafuranoside analogues (Nu = D or allyl). ....	73

Figure 2.6 1,2- <i>cis</i> Glycosylation of arabinose furanoside .....	74
Figure 2.7 Highly <i>cis</i> -selective N-glycosylation of lactols. ....	74
Figure 2.8 Left: Orbital overlap between incoming Nu and antibonding $\tau^*$ orbital of <i>anti</i> C–O $\tau$ bond produces $sp^3$ oxygen lone pair antiperiplanar to bound Nu. Right: facial selectivity modulated by hyperconjugation between C <sub>2</sub> –OR and C <sub>2</sub> –H groups antiperiplanar to their respective $\tau$ bond of the oxocarbenium ion. ....	75
Figure 2.9 Glycosylation donors. LG = OAc or SPh. ....	76
Figure 2.10 Synthesis of unsubstituted donors <b>2.1</b> .....	77
Figure 2.11 Synthesis of donors <b>2.2-2.3</b> .....	78
Figure 2.12 Synthesis of donors <b>2.4-2.5</b> .....	79
Figure 2.13 Reaction Conditions for C and O-Glycosylations Described in Table 2.1 .....	80
Figure 2.14 Steric and conformational factors to the S <sub>N</sub> 1 glycosylation reaction of substituted bicyclic furanosides. ....	83
Figure 2.15 C-Glycosylation of donors <b>2.1-2.5</b> with TMSallyl and TFE in CH <sub>2</sub> Cl <sub>2</sub> and CH <sub>3</sub> CN.....	84
Figure 2.16 Resonance structures of a carbobicyclic oxocarbenium ion. ....	87
Figure 2.17 Remote oxygen effect on selectivity.....	88
Figure 2.18 Merz-Kollman charges for oxocarbenium ion models from on B3LYP/6-31-G* calculation.....	89
Figure 2.19 Glycosylation in the presence of AgOTf/NIS with TFE.....	89
Figure 3.1 Préparation d'un donneur C <sub>2</sub> -CF <sub>3</sub> .....	93
Figure 3.2 Formation de l'intermédiaire énol lors de l'ozonolyse. ....	94
Figure 3.3 Réactivité d'un donneur C <sub>2</sub> -CF <sub>3</sub> . ....	94
Figure 3.4 Glycosylation donors. ....	98
Figure 3.5 Relative reactivity in function of C <sub>2</sub> .....	99
Figure 3.6 C <sub>2</sub> -substituted pyranoside C-glycosylation. ....	100
Figure 3.7 Glycosylation of C <sub>2</sub> -substituted pyranosides with the bent bond approach.....	101
Figure 3.8 Synthesis of donosr <b>3.4</b> and <b>3.5</b> . ....	101
Figure 3.9 Preparation of donors <b>3.6</b> , <b>3.7</b> , <b>3.10</b> and <b>3.11</b> . ....	102
Figure 3.10 Preparation of donors <b>3.8</b> and <b>3.9</b> . ....	104
Figure 3.11 Glycosylation conditions.....	106
Figure 3.12 $\alpha/\beta$ Glycosylation of bicyclic pyranosides. ....	107
Figure 3.13 Proposed mechanism for CH <sub>3</sub> CN solvent participation.....	110
Figure 3.14 Trapping $\beta$ -acetonitrilium ion derived from <b>3.4(SPh)</b> and <b>3.5(SPh)</b> under O-glycosylation conditions. ....	111



Figure 3.15 Glycosylation of 2-methyltetrahydropyranyl acetate from $^4\text{H}_3$ and $^3\text{H}_4$ half-chairs.....	114
Figure 3.16 Competitive glycosylation experiment. ....	115
Figure 3.17 Inductive effect of benzylidene vs cyclohexane fused to pyranosyl donors. ..	116
Figure B.1 Expérience de contrôle cinétique.	141
Figure F.1 C-Glycosylation with TMSAllyl in $\text{CH}_2\text{Cl}_2$ .	265
Figure F.2 O-Glycosylation with $\text{CF}_3\text{CH}_2\text{OH}$ in $\text{CH}_2\text{Cl}_2$ .....	266
Figure F.3 O-Glycosylation with $\text{CF}_3\text{CH}_2\text{OH}$ in $\text{CH}_3\text{CN}$ . ....	267
Figure F.4 Verification for the reaction's kinetic nature with <b>2.5(TFE)</b> . ....	268
Figure F.5 Verification for the reaction's kinetic nature with <b><math>\beta</math>-2.2(TFE)</b> . ....	268
Figure F.6 Thermodynamic control.....	269

## Tableaux

Table 1.1 Glycosylation of bicyclic donors <b>1.1-1.3</b> . .....	57
Table 2.1 Glycosylation of bicyclic donors <b>2.1-2.5</b> . .....	81
Table 3.1 Glycosylation of donors <b>1.1-1.3</b> and <b>3.4-3.11</b> .....	109
Table B.1 Expérience de contrôle cinétique .....	141
Table E.1 XYZ coordinates for geometry optimized (3a <i>S</i> ,7a <i>R</i> )-1-Oxaoctahydroindene oxocarbenium ion. Selected ESP charges (Merz-Kollman) indicated on right column and numbered in structure. ....	262
Table E.2 XYZ coordinates for geometry optimized (3a <i>S</i> ,7a <i>R</i> )-1,4,6-Trioxahexahydroindene oxocarbenium ion. ....	263

## Liste des abréviations

2-ClBzOH: acide 2-chlorobenzoïque

ABNO: 9-Azabicyclo [3.3.1] nonane *N*-oxyl

ADN: acide désoxyribonucléique

Appl: antipériplanaire

AX: axial

AllylBr: bromure d'allyle

BAIB: (diacétoxyiodo)benzen

BBA: liaison courbe antipériplanaire [*antiperiplanar bent bond*]

BBAH: hypothèse antipériplanaire des liaisons courbes [*bent bond antiperiplanar hypothesis*]

BnO: Benzyloxy

CAM: cerium ammonium molybdate

CIP: paire d'ions contact [*contact ion pair*]

ClEtO: 2-chloroéthoxy

dba: dibenzylacétone

DBU: 1,8-diazabicyclo[5.4.0]undéc-7-ène

DCM: dichlorométhane

DIBAL-H: hydrure de diisobutylaluminium

DMAP: 4-diméthylaminopyridine

DMDO: diméthylldioxirane

DME: diméthoxyméthyle

DMF: diméthylformamide

DMP: periodinane de Dess-Martin [*Dess-Martin's periodinane*]

Dnr: donneur [*donnor*]

EDG: groupements électrodonneurs [*electrodonating group*]

EQ: équatorial

ESI: ionisation électrospray [*electrospray ionization*]

EtO: éthoxy

EWG: groupement électroattracteur [*electron withdrawing group*]

FMO: orbitale moléculaire frontière [*Frontier Molecular orbital*]

GEA: groupements électroattracteurs

GP: groupe partant

Gluc: glucose

HRMS: spectrométrie de masse haute résolution [*high resolution mass spectrometry*]

IR: infrarouge

Kcal: Kilocalorie  
KIE: effet isotopique cinétique [*kinetic isotopic effect*]  
KHMDS: bis(triméthylsilyl)amide de potassium  
LDA: diisopropylamide de lithium  
LG: groupement partant [*leaving group*]  
Manno: mannose  
Me: méthyle  
MO-CI: Configuration d'interaction d'orbitales moléculaires [*molecular orbital interactive configuration*]  
m.p.: point de fusion [*melting point*]  
Ms: mésylate  
N.D: non-défini [*not determined*]  
NFSI: *N*-Fluorobenzenesulfonimide  
NIS: *N*-Iodosuccinimide  
NMR: résonance magnétique nucléaire [*nuclear magnetic resonance*]  
NMO: oxyde de *N*-méthylmorpholine [*N*-methylmorpholine oxide]  
NOESY: spectroscopy de l'effet Overhauser nucléaire [*nuclear Overhauser effect spectroscopy*]  
Nu: nucléophile  
OAc: acétoxy  
OBC: organic and Biomolecular Chemistry  
OEt: éthoxy  
OTf: ion triflate  
Ph: Phényle  
PMB: *para*-méthoxybenzyle  
Qnt: quantitatif [*quantitative*]  
RMN: résonance magnétique nucléaire  
r.t.: température pièce [*room temperature*]  
SEt: Thioétyle  
S<sub>N</sub>1: substitution nucléophile unimoléculaire  
S<sub>N</sub>2: substitution nucléophile bimoléculaire  
SPh: thiophényle  
SSIP: pair d'ions séparés par le solvant [*solvent separated ion pair*]  
TAC: trichloroacétimide  
TBAF: fluorure de tétrabutylammonium  
TBSCl: chlorure de *tert*-butyldiméthylsilyle  
TEMPO: 2,2,6,6-tétraméthyl-1-pipéridinyloxy

TFE: 2,2,2-trifluoroéthanol

Tf : triflate

THF: tétrahydrofurane

TLC: chromatographie sur couche mince [*thin layer chromatography*]

TMS: triméthylsilane

TOF: temps de vol [*time of flight*]

Tol: toluène

t.p.: température pièce

Ts : tosylate

*t*-Bu: *tert*-butyle

UV: ultraviolet

VB: liaison de valence [*valence Bound*]

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J'aimerais terminer en remerciant tout particulièrement Catherine Dussault qui partage et embellit avec amour mon quotidien depuis maintenant deux ans. Sa présence apaisante, ses encouragements et son support sans limite m'ont permis d'amener ce laborieux projet à terme. En plus de son aide à la rédaction et à la correction de cette thèse, je tiens à la remercier du fond du cœur pour l'enseignement qu'elle m'a transmis. Ses connaissances, son intelligence hors du commun et sa passion débordante pour la sociologie et la philosophie des sciences m'ont insufflé le désir d'exploiter ces éléments dans l'élaboration de mes travaux de recherche et dans la rédaction de cette thèse. Par le biais de nos nombreuses discussions, j'ai pu m'éveiller à cette vision plus riche de la recherche scientifique à laquelle j'aspirais déjà sans trop la comprendre et qui me servira de boussole dans mes entreprises futures.

J'aimerais également remercier le Fonds de recherche du Québec nature et technologie (FRQNT) et le département de Chimie pour leur soutien financier. Leurs contributions ont contribué à leur manière au succès de cette thèse.

## Avant-propos

Les trois articles présentés dans cette thèse sont le fruit d'un travail expérimental que j'ai élaboré et réalisé dans sa quasi-entièreté. Les trois articles ont été acceptés et publiés dans deux journaux scientifiques bénéficiant d'une importante notoriété. Mon premier article a été publié le 4 novembre 2016 dans le journal *Organic and Biomolecular Chemistry* de la *Royal Society for Chemistry*. Le second et le troisième article, pour leur part, ont été publiés dans le *Journal of Organic Chemistry* de l'*American Chemical Society*, respectivement le 10 décembre 2019 et le 18 février 2020.

Il est à mentionner que les articles ont été intégrés sans aucune modification outre la mise en forme et la disposition des figures dans le texte. Le corps du texte est pour les trois articles en tout point similaire à celui soumis et publié par les journaux scientifiques.

La mise en ligne des deux derniers articles a pu être réalisée grâce à la collaboration du Professeur Ghislain Deslongchamps de l'Université du Nouveau-Brunswick (UNB) qui nous a prêté main forte en agréant nos recherches de calculs théoriques concluants. Sa maîtrise aisée de la langue anglaise nous a également été d'une aide remarquable lors du processus de révision.

Le travail expérimental rapporté au second chapitre a été réalisé avec l'aide de Xavier Bertrand, à l'époque étudiant au baccalauréat en chimie. Son travail consistait à reproduire certaines synthèses de donneurs de liaisons glycosidiques et de dupliquer les résultats de la réaction de glycosylation. Cela nous a donc permis une certaine liberté d'exploration de notre objet d'étude qui n'aurait pas été possible dans ces délais si j'avais été le seul à effectuer le travail en laboratoire. Cela a sans doute été une expérience très formatrice pour un étudiant avec un grand potentiel comme Xavier.

L'information présentée ci-haut est reprise et spécifiée dans l'avant-propos de chacun des chapitres qui présentent, en fait, les articles scientifiques que j'ai publiés dans les revues susmentionnées. Ces avant-propos offrent également le préambule expérimental et rationnel ayant mené à l'obtention des résultats présentés dans chaque article.



## Introduction

*Car la science expérimentale n'est pas tant définie par la quantité à quoi elle s'applique que par la mesure qu'elle introduit dans le réel.*

Jacques Lacan, *Écrits I*, p.286

## Science fondamentale et ses paradigmes

Il semble juste de dire que la citation en exergue de cette thèse lui a été structurante : je pense en effet que les pratiques des scientifiques ont des conséquences réelles sur les manières de voir et de penser la nature et le monde, de manière générale. En d'autres termes, chaque modèle de scientificité propose des instruments, des modèles, des théories sur l'objet à connaître, des exemples pour résoudre certains types de problèmes qui véhiculent forcément une certaine vision du réel. Comment était-il possible de se représenter un trou noir et, de surcroît, le vide, avant les avancées de la physique quantique ? Ou encore, comment était-il possible de se représenter la structure du benzène avant de comprendre ce qu'est la conjugaison ? Ces exemples convergent tous en un même point : la science n'est pas seulement un ensemble de découvertes, il s'agit d'un système de propositions, de présuppositions, de prescriptions et de permissions apprises et transmises par socialisation scientifique. Ce n'est pas d'hier que la science et le développement technique prennent source en ces idéaux. Cette citation de Newton en fait témoignage : « Si j'ai pu voir plus loin, c'est en me juchant sur les épaules de géants<sup>1</sup> ». En d'autres termes, ce que l'on nomme « science », ne regroupe pas uniquement les résultats du travail technoscientifique : il faut également tenir compte des institutions qui la supporte et des chercheurs qui y œuvrent au quotidien qui peuvent à leur tour devenir des « géants » pour d'autres. Ainsi pensée, c'est-à-dire en tenant compte de l'importance de la socialisation scientifique dans la création de résultats expérimentaux, la science s'ouvre à des réflexions philosophiques, historiques et sociologiques. En effet, en remarquant que ce qui est socialement valorisé comme objet de recherche change dans le temps, ou encore ce qui est tenu pour vrai par la communauté suit ces mêmes modifications, il faut bien admettre que les différents modèles de scientificité

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<sup>1</sup> Merton, Robert King. *On the Shoulders of Giants a Shandean Postscript*. New York, Free Press. 1965.

comportent un ensemble de présuppositions et de croyances qui sont tenues pour vraies par une communauté de chercheurs. Un noyau de règles et de procédés fondamentaux sont transmis et appris par chaque nouvelle génération de chercheurs, et il devient difficile d'en déroger car ils constituent un principe de réalité. Les exemples types, les théories, les méthodes et les modèles, entre autres, *créent le réel du chercheur*, pour faire écho à la citation de Jacques Lacan. Par exemple, pour valider la structure d'un composé, tous s'entendent sur la viabilité des données obtenues par une masse haute résolution jumelée à la résonance magnétique nucléaire. C'est ainsi dire qu'il y a des formules et des principes qui sont en quelque sorte admis d'avance pour résoudre un certain type de problème. Les règles de Baldwin en sont un autre exemple.<sup>2</sup>

C'est pourquoi aussi, selon certains philosophes des sciences (Lakatos, Kuhn), penser que seuls les éléments d'observation suffisent à rejeter ou à accepter une théorie est trop restrictif. Il faut également tenir compte de la « communauté de croyants » qui supporte un même paradigme. C'est ainsi dire qu'il y a des éléments plus flexibles que d'autres dans la recherche scientifique. Un peu à l'image de l'atome, où la nature du noyau est solide et immuable, sa périphérie, elle, est plus souple. Le noyau représenterait dans ce cas l'ensemble des théories que si on devait les rejeter, annihileraient le paradigme scientifique. La périphérie, que le chimiste et philosophe des sciences Imre Lakatos nomme brillamment le « glaciaire protecteur », est la couche protégeant le noyau de l'atome – ou le cœur du programme de recherche – qui peut être attaquée, remaniée, modifiée, sans que cela ne porte préjudice audit paradigme. Il s'agit d'un entremêlement de particules élémentaires mobiles et malléables d'une importance moins capitale. Aussi, plus s'approche-t-on du noyau et de la couche périphérique du cœur qui définit par extension la nature de ce dernier, plus il devient difficile d'y apporter une modification importante : il est, rappelons-le, « protégé » par la périphérie. Ainsi, pour véritablement enclencher une révolution scientifique, c'est-à-dire pour remplacer le paradigme dominant admis au sein d'une discipline par un autre qui lui serait incommensurable, il faudrait le faire sur les débris de l'ancien. La fission nucléaire, le démantèlement du noyau paradigmatique, n'a toutefois rien de simple et requiert énormément de temps et d'énergie. À mon avis, toutes ces raisons expliquent, du moins en

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<sup>2</sup> Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

partie, pourquoi le modèle des liaisons courbes ( $\tau$ ) tarde si difficilement à faire son entrée dans les manuels de chimie organique.

Il convient maintenant de définir ce qu'est un paradigme et à quoi il fait référence dans ce contexte. On peut le définir comme un consensus partagé entre les chercheurs. Le consensus porte sur des connaissances structurées par des croyances, des méthodes, des règles, des valeurs et des exemples, servant à faciliter l'assimilation et la transmission du savoir au sein d'une discipline. Le chercheur y trouve refuge et réponse dans des périodes de questionnement, puisqu'il est simultanément la source des problèmes à résoudre et l'origine de la solution. Pour le dire simplement, le paradigme est une spécialité partagée par une communauté de chercheurs, qui donnent tous la même direction à leurs travaux. En chimie organique plus particulièrement, le paradigme par excellence est le modèle  $\sigma$ - $\pi$  de Hückel.<sup>3</sup> Une partie importante de nos connaissances fondamentales en réactivité chimique est à la fois basée et expliquée par ce système. Non pas par des lois physiques observables, palpables et précisément mesurées, mais un modèle aux racines plus ou moins arbitraires. Il s'agit d'une représentation du réel entretenue par de multiples exemples et corroboré par de nombreuses expériences, mais qui ne peut pourtant pas s'affirmer strictement rationnellement comme le « vrai » modèle attestant de la « véritable » représentation d'une liaison multiple. En science, c'est ce que tous les philosophes des sciences tentent de démontrer à leur manière, il y a toujours un fond mythique, arbitraire, duquel il n'est pas possible de s'abstraire absolument. C'est que chaque modèle, dont celui de Hückel, apporte son lot de présuppositions sur l'objet à connaître *qui ne peuvent être démontrées empiriquement hors de tout doute*. Il s'agit certes d'un outil formidable, mais il est enseigné comme seule réponse à la liaison multiple, alors qu'il existe une alternative tout aussi valable, elle également corroborée par des expériences empiriques. En jetant un regard sur les cinquante dernières années, la formidable explosion de connaissance prenant appui sur le modèle de Hückel peut être utilisée comme un argument de taille à l'exploration d'un nouveau modèle, celui des liaisons courbes. De plus, le modèle de Pauling déroge peu du modèle dominant au niveau fondamental. Pour cette raison, son

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<sup>3</sup> (a) Huckel, E. Z. *Phys.* **1930**, *60*, 423-456; (b) Mulliken, R. S. *Phys. Rev.* **1932**, *41*, 49-71.

intégration aux connaissances actuelles serait sans doute fulgurante, et ce, d'autant plus advenant que l'on déciderait d'y dédier une main-d'œuvre importante.

Ce qui rend particulièrement difficile l'intégration du modèle des liaisons courbes et nuit à son ascension, c'est qu'il ne provoque pas pour l'instant d'instabilité au modèle de Hückel qui lui non plus d'ailleurs, ne présente aucune anomalie majeure. Il n'y a pas de problème fondamental qui ne peut être résolu, ne serait-ce qu'en partie, par le paradigme actuel. En d'autres termes, il n'y a aucune anomalie qui forcerait les chercheurs à la découverte de nouvelles solutions au paradigme dominant actuel. Puisque l'implication du changement se situe davantage à un niveau fondamental et théorique – voire philosophique –, la majorité des chercheurs ne se sent pas bousculée dans ses croyances puisqu'elle ne contredit pas les résultats physiques et observables de ses recherches. Il n'est qu'un outil de rationalisation supplémentaire. Néanmoins, il semble que l'ouverture d'esprit et l'exercice même de l'esprit critique contraignent le scientifique à tester, vérifier et considérer toute nouvelle idée ou théorie qui se présente avec une légitimité scientifique. Toutefois, sans bouleversement, il devient difficile de stimuler la recherche dans un axe qui, à première vue, ne répond pas aux préoccupations actuelles. L'aspect très conservateur en général des chercheurs n'aide certainement pas. Des scientifiques ralliés autour de paradigmes communs et de traditions de recherche deviennent à plus forte raison des créatures d'habitudes, ce qui tend à les rendre plutôt perméables au changement. Or, l'histoire est tapissée d'exemples où des propositions aux allures drastiques ont permis l'éclosion de domaines de recherches aux conclusions les plus bouleversantes. La proposition de Kekulé sur la tétravalence du carbone et la structure du benzène a pavé la route aux multiples découvertes et théories sur les structures de résonance et l'hybridation orbitale du carbone.<sup>4</sup> Comment Kekulé en est-il venu à proposer ces conclusions? Outre l'uroboros, un symbole où un serpent mange sa propre queue, qui lui inspira en rêve la forme cyclique du benzène, c'est par un sentiment qu'il y avait une anomalie au sein du paradigme précédent qu'il s'est penché sur la question. Pour que le modèle de liaison courbe développé par Pauling gagne sa place, il serait peut-être préférable qu'on y réagisse par un non catégorique plutôt qu'un oui désengagé. Ce non catégorique émergerait d'un problème crucial, d'une anomalie du paradigme dominant et qui

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<sup>4</sup> Kekulé, A. *Liebigs Ann.* **1866**, 137, 129-196

ne pourrait que se résoudre grâce au paradigme des liaisons courbes. Le sentiment de cette irrégularité du modèle actuel ferait écho dans toutes les sous-sphères de la chimie, de la plus fondamentale à la plus appliquée. Dès lors, le non catégorique se ferait entendre par la communauté scientifique. Parce que comme Bachelard l'a si bien énoncé dans son ouvrage *Le nouvel esprit scientifique*, « la science avance en disant non ».<sup>5</sup>

C'est pourquoi il est impératif de continuer à explorer l'aspect fondamental de la chimie et des sciences en général. Non pas seulement par la recherche de nouvelles connaissances, mais également par la remise en question du savoir établi. C'est ce qui abreuve la recherche appliquée et qui résulte en la progression du savoir technique. Une science fondamentale supportée et florissante est l'organe le plus vital du corps de la recherche appliquée. Malheureusement, il plane une tendance grandissante à faire abstraction de son importance. Ce qui n'aide pas sa cause, c'est que l'ère actuelle est soumise aux injonctions de la production et de l'efficacité. La recherche fondamentale est une entreprise en discordance avec notre époque, car le temps est à la fois sa ressource la plus importante et son produit le plus profitable. L'intérêt économique, qui est l'un des aspects dominants de la recherche académique d'aujourd'hui, n'est pas autant explicite et direct pour une découverte fondamentale. Subventionner une recherche pouvant mener à des retombées économiques immédiates est beaucoup plus séduisant aux yeux d'un comité interdisciplinaire qu'un projet fondamental de longue haleine sans espoir apparent de monétisation rapide. Or, une compréhension supérieure des fondements d'une science ne peut qu'accélérer la transition vers son application technique. Le vrai produit d'une recherche fondamentale est une meilleure recherche appliquée. Les retombées de la recherche fondamentale soutenue ne se limitent pas seulement aux gains de connaissances, mais aussi à la qualité de la formation reçue par ses pratiquants qui, au lieu d'acquérir un savoir essentiellement technique, développent une compréhension riche et aboutie de leur sujet.

Ce que l'on observe plutôt de nos jours, c'est la production de scientifiques que Lakatos décrirait pour la plupart « enclins à ne pas comprendre au sujet de la science beaucoup plus

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<sup>5</sup> Bachelard, Gaston. **2004**. La formation de l'esprit scientifique. Contribution à une psychanalyse de la connaissance. Paris, Vrin.

que les poissons à propos de l'hydrodynamique »<sup>6</sup>. Cette citation nécessite toutefois d'être nuancée. Il serait cynique de prendre cette citation telle quelle et de la généraliser à l'ensemble des chercheurs. Bien évidemment, les scientifiques se doivent de comprendre ce qu'ils font, sans quoi il n'y aurait aucun progrès. C'est pourquoi les plus créatifs sont bien souvent ceux dont les connaissances sont les plus étoffées. Ce qui est malheureux, c'est que la recherche contemporaine ne leur en laisse que très faiblement l'opportunité. Les recherches sont financées souvent par des sources externes à l'université, elles sont industrialisées, entrelacées de coopération, mais surtout de compétition, et sont soumises à de sévères contraintes financières et temporelles. Toutes ces conditions, qui se réunissent sous un argument commun, c'est-à-dire celui de trouver une application immédiate à la recherche, minent la légitimité de l'aspect fondamental dans notre contexte contemporain.

## Pauling, orbitales de valences et liaison courbes

Le sujet de recherche fondamentale exploité dans ce projet de thèse est l'utilisation d'une variante du modèle des liaisons courbes de Pauling, mentionnée ci-haut.<sup>7</sup> Ce modèle est en opposition au  $\sigma$ - $\pi$  de Hückel sur quelques aspects clés de la mécanique quantique derrière la liaison multiple.<sup>8</sup> Alors que les liaisons courbes prennent racine dans la théorie des orbitales de valence sur laquelle Pauling lui-même s'est basé pour décrire la résonance et l'hybridation<sup>9</sup>, le modèle  $\sigma$ - $\pi$  de Hückel et Mulliken s'appuie sur la théorie des orbitales moléculaires qui emprunte certaines de ces notions d'hybridation lors de la formation des dites orbitales.<sup>3</sup> Cette dernière suppose, à l'inverse des orbitales de valence, qu'un électron n'est pas confiné à la liaison à laquelle il participe, mais il serait plutôt distribué au sein de l'entière de la molécule lors de la formation du lien. Or, les deux approches exploitent l'équation de Schrödinger pour décrire le mouvement d'électrons. Cette rationalisation ne s'applique avec précision qu'à des modèles simples comportant peu d'électrons, comme l'hydrogène ou

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<sup>6</sup> Lakatos, I. Histoire et méthodologie des sciences humaines. Paris, Presses Universitaires de France. **1994**. p.85

<sup>7</sup> (a) Wintner, C. E. *J. Chem. Educ.* **1987**, *64*, 587-590; (b) Bernett, W. A. *J. Chem. Educ.* **1967**, *44*, 17-24; Randić, M.; Maksić, Z. *Theor. Chem. Acc.* **1965**, *3*, 59-68.

<sup>8</sup> Haddon, R. C. *J. Mol. Struct. THEOCHEM.* **1988**, *169*, 69-78.

<sup>9</sup> (a) Pauling, L. *J. Am. Chem. Soc.* **1931**, *53*, 1367-1400; (b) Linus Pauling *The Nature of the Chemical Bond and the Structure of Molecules and Crystals; An Introduction to Modern Structural Chemistry*, 3rd edn, Ithaca: Cornell University Press, **1960**, 136-142.

l'hélium. C'est par cette limitation qu'il devient impossible de différencier sur une base purement mathématique les deux approches, car chacune utilise des présupposés et des approximations dont la validité ne peut être démontrée empiriquement et qui, pourtant, permettront d'obtenir réponse qui sera jugée vraie par ceux qui acceptent ce modèle. Ces présupposés influencent donc inévitablement le cours de la recherche. C'est un aspect mis de l'avant par la majorité des chimistes théoriciens de l'époque, dont Messmer et Schultz, qui ont cru bon de nuancer leurs conclusions sur le sujet :

No experiment can possibly distinguish between a  $\sigma$ - $\pi$  double bond and double bent bonds in any system, and therefore neither can be proven to be "right" in an absolute sense; both are approximate descriptions. The potential value of making any such distinction lies in the utility, general applicability, and economy of the concepts which emerge, and whether one variant is superior to another in describing properties determined by the electronic structure.<sup>10</sup>

Ce discours est toujours aussi juste aujourd'hui, et ce, malgré une puissance computationnelle qui dépasse de loin celle dont disposait Messmer et Schultz dans les années 1990. Hiberty et Braïda ont publié récemment une étude comparative entre les deux modèles dans une optique similaire à leurs prédécesseurs. Le mot d'ordre est essentiellement le même:

Even if the VB and MO-CI theories, as well as the delocalized and localized orbital representations are all valid, the examples treated in this work show that it is very useful to possess both cultures and to understand when and why one vision may be more suitable than the other, as the bonding nature of a molecule may be totally blurred in one representation and become crystal clear in the other.<sup>11</sup>

Les deux descriptions ont cohabité pendant plusieurs décennies avant que l'une d'elles, le modèle  $\sigma$ - $\pi$ , devienne majoritairement utilisé, étudié et transmis rigoureusement dans les manuels. Les raisons derrière cette décision – plus ou moins réfléchie – de la communauté de faire abstraction d'un des deux modèles ont des origines sociales, économiques, voire politiques. La littérature en chimie fondamentale de l'époque apparaît déchirée entre les deux descriptions, alors qu'il y a un besoin grandissant d'expliquer les propriétés dans des

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<sup>10</sup> (a) Schultz, P. A.; Messmer, R. P. *J. Am. Chem. Soc.* **1993**, *115*, 10925-10937; (b) Schultz, P. A.; Messmer, R. P. *J. Am. Chem. Soc.* **1993**, *115*, 10938-10942; (c) Schultz, P. A.; Messmer, R. P. *J. Am. Chem. Soc.* **1993**, *115*, 10943-10951.

<sup>11</sup> Hiberty, P. C.; Braïda, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 5994-6002.

systèmes de plus en plus complexes en termes de structure moléculaire.<sup>12</sup> Il n'en reste pas moins que Pauling lui-même ne croyait pas à une survie conjointe des deux modèles, envisageant que l'approche par orbitale moléculaire se ferait vite oublier :

There may be chemists who would contend that one innovation of great significance has been made [in the theory of the chemical bond] - the introduction of the  $\sigma$ - $\pi$  description of the double bond and the triple bond and of conjugated systems, in place of the bent-bond description. I contend that the  $\sigma$ - $\pi$  description is less satisfactory than the bent-bond description, that this innovation is only ephemeral, and that the use of the  $\sigma$ - $\pi$  description will die out before long.<sup>8</sup>

Évidemment, Pauling propose certains arguments à la défense de son modèle. Dans la troisième édition de son livre *Nature of the Chemical Bond*,<sup>9</sup> il fait mention de quelques arguments qu'il juge notables, soit la rationalisation de certaines longueurs de liaison, angles et barrières de rotation interne et la ressemblance à la liaison simple permettant de décrire plus facilement les propriétés de la liaison double. Selon Bursten<sup>12</sup>, la perte de popularité du modèle s'est amorcée dans les années 1950, alors que des chercheurs britanniques, entre autres Hall et Lennard-Jones, ont développé une approche mathématique beaucoup plus simple utilisant les orbitales moléculaires pour décrire le mouvement électronique à travers les orbitales dans des composés de taille importante et comportant des systèmes conjugués.<sup>13</sup> L'intérêt grandissant porté à la chimie organique durant cette période est mû par des découvertes d'envergure, comme la structure de l'ADN. Cette découverte a favorisé l'exploitation du modèle  $\sigma$ - $\pi$ , qui aurait joui d'une plus grande facilité à prédire mathématiquement certaines propriétés physiques des molécules organiques. Pauling a également délaissé la défense de son modèle pendant cette époque afin de concentrer ses activités sur d'autres fronts, par exemple la dénucléarisation des deux puissances mondiales du moment, les É.-U. et l'URSS. Cet engagement politique est possiblement à la source du discrédit dont a fait preuve l'URSS vis-à-vis l'entièreté des travaux du chercheur américain sur les orbitales de valence.<sup>12</sup>

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<sup>12</sup> Bursten, J. R. *Ann. Science* **2012**, 69, 69-90.

<sup>13</sup> Hall, G. G.; Lennard-Jones, J. E. *P. Roy. Soc. A-Math. Phys.* **1951**, 205, 357-374.



## Modèle dérivé et application en chimie organique

Tel que mentionné précédemment, le modèle exploité dans le cadre de cette thèse ne correspond pas exactement au modèle de Pauling. Il y prend plutôt inspiration par la description dérivée que Hall et Lennard-Jones en effectuent.<sup>13</sup> Ces derniers démontrent qu'il est possible de transformer avec une relative simplicité la description d'une liaison multiple décrite par  $\sigma$ - $\pi$  vers une liaison courbe  $\tau$ . La transformation inclut l'hybridation supplémentaire d'une orbitale  $sp^2$  et d'une orbitale  $p$  vers deux orbitales équivalentes  $sp^5$  courbes  $((1/3s + (2/3p + 3/3p) \div 2)$ . Il s'agit d'un jeu d'orbitales conceptuellement similaire à la description de Pauling, résidant à l'intérieur des mêmes règles quantiques de la théorie des orbitales de valence, mais dont le caractère  $s$  et  $p$  diffère. Alors que Hall et Lennard Jones évaluent leur approche comme étant une description énergétiquement similaire au modèle  $\sigma$ - $\pi$ , puisque la combinaison d'orbitales atomiques est essentiellement la même, Pauling réfute cette hypothèse. Selon ses propres calculs, la liaison courbe possède le caractère hybridé  $sp^3$  du carbone avec l'intégration d'orbitales  $d$  hybridés entre elles. Il s'agit donc de deux systèmes non équivalents énergétiquement puisque leur description quantique est distincte.<sup>12</sup>

Les fondements respectifs de la mécanique quantique ne seront toutefois pas étudiés dans le cadre de cette thèse. À toute fin pratique, la description orbitalaire de Pauling et celle de Hall et Lennard-Jones se confondent. C'est toutefois cette dernière qui sera exploitée, non pas parce qu'elle semble plus juste, mais parce que son interprétation est plus simple pour le commun des mortels dont les connaissances en chimie quantique sont limitées. Cela ne change en rien son application dans un contexte expérimental. La littérature fondamentale elle-même ne semble pas faire de distinction particulière entre l'interprétation de Pauling et de Lennard-Jones.<sup>7,12,13</sup> Elle tente simplement d'offrir une comparaison entre les deux modèles,  $\sigma$ - $\pi$  et  $\tau$ , dans un contexte spécifique afin d'en évaluer leur applicabilité respective.<sup>10</sup> Des cas tels que la conjugaison ou la longueur des liaisons dans certains systèmes sont souvent utilisées comme appuis expérimentaux. Le cyclopropane<sup>14,7b,c</sup> et les

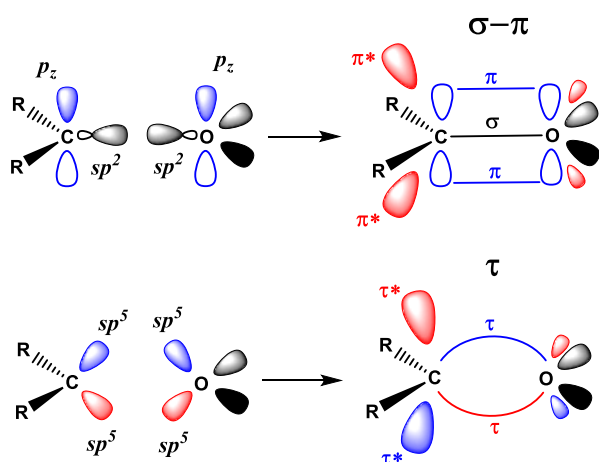
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<sup>14</sup> (a) Messmer, R. P.; Schultz, P. A.; Tatar, R. C.; Freund, H. *J. Chem. Phys. Lett.* **1986**, *126*, 176-180; (b) Messmer, R. P.; Schultz, P. A. *Phys. Rev. Lett.* **1986**, *57*, 2653-2656; (c) Schultz, P. A.; Messmer, R. P. *Phys.*

dérivés de norbornènes,<sup>15</sup> par exemple, font partie de ces composés où la liaison courbe semble répondre aux problèmes fondamentaux d'hybridation des atomes, des angles et des longueurs de liaisons. C'est pourquoi les cyclopropanes sont souvent enseignés en les décrivant comme formés de liaisons bananes, faisant directement référence, sans toutefois les nommer, aux liaisons courbes de Pauling. Sans vouloir être cynique, il y a possiblement un désir d'agréer aux adeptes de  $\sigma$ - $\pi$ , qui forme la majorité de la communauté, ou simplement de diminuer la complexité de la discussion.<sup>16</sup>

L'aspect le plus intéressant du modèle proposé par Pauling, outre la distribution en arc de la densité électronique est que celle-ci est propre à une seule orbitale, qu'il soit question d'alcène ou d'alcyne. L'implication du modèle dans la réactivité des alcynes n'est pas aussi flagrante que dans les alcènes et ses dérivés. Ce point ne sera pas discuté dans le contexte de cette thèse. Il est quand même bien de mentionner que l'alcyne, selon le modèle de Pauling, est formé de trois orbitales  $\tau$  distinctes.<sup>17</sup>

Alors que le modèle de Hückel voit sa formation être le fruit d'une combinaison de deux



orbitales  $p$  générant une seule orbitale  $\pi$  dans le plan d'une liaison  $\sigma$ , la liaison  $\tau$  est formée par l'interaction de 4 lobes distincts de caractère  $sp^5$ , ce qui forme alors deux orbitales individuelles  $\tau$  placées de part et d'autre de l'axe de liaison (*Figure I.1*). Les deux atomes participant à la liaison double possèdent alors un caractère davantage tétraédrique, ce qui laisse place à une interprétation de la réactivité qui inclut l'aspect

**Figure I.1** Formation des liaisons  $\sigma$ - $\pi$  et  $\tau$  par la combinaison d'orbitales hybridés.

*Rev. Lett.* **1987**, 58, 2416-2419; (d) Messmer, R. P. *J. Mol. Struct. THEOCHEM.* **1988**, 169, 137-154; (e) Palke, W. E. *J. Am. Chem. Soc.* **1986**, 108, 6543-6544.

<sup>15</sup> Houk, K. N.; Rondan, N. G.; Brown, F. K.; Jorgensen, W. L.; Madura, J. D.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1983**, 105, 5980-5988.

<sup>16</sup> Palke, W. E. *J. Am. Chem. Soc.* **1986**, 108, 6543-6544.

<sup>17</sup> Pople, J. A. *Q. Rev. Chem. Soc.* **1957**, 11, 273-290.

stéréoélectronique d'une transformation.<sup>18</sup> Cela signifie qu'il est alors possible, par le biais d'hyperconjugaison, de moduler la densité électronique dans un seul de deux liens  $\tau$ . Cette caractéristique est absente du modèle  $\sigma$ - $\pi$  puisque la partie supérieure et inférieure de l'orbitale consiste en un seul et même nuage électronique. Un caractère prochiral peut alors être généré et rationalisé par des phénomènes d'hyperconjugaison dans un alcène ou une cétone. Certaines personnes, plus froides à l'idée, pourraient utiliser comme contre-argument que le nuage d'électrons  $\pi$  peut tout simplement se polariser en fonction des groupements adjacents. Il semble toutefois plus complexe visuellement et contre-intuitif de traiter le modèle  $\sigma$ - $\pi$  sous cet angle.

Les professeurs Pierre et Ghislain Deslongchamps se sont consacrés au cours des dix dernières années à mettre de l'avant la puissance analytique du modèle de Pauling. Par le biais d'une multitude d'effets et de résultats de tout genre tirés de la littérature, ils ont démontré l'aisance avec laquelle les liaisons courbes, jumelées avec l'hypothèse antipériplanaire (*appl*), peuvent rationaliser des phénomènes chimiques peu intuitifs. Ces exemples incluent des analyses de grande justesse sur la conformation d'alcènes et d'éther vinylique, l'effet Cieplak, l'énantiosélectivité des réactions de Diels-Alder, l'isomérisation haute température d'espèces benzéniques et la réactivité des cyclooctatétrènes, pour n'en nommer que certains.<sup>19</sup> Bien que plusieurs pourraient qualifier de raccourci intellectuel l'utilisation de ce modèle, il n'en reste pas moins qu'il est particulièrement facile à intégrer et à appliquer visuellement. Les concepts plus difficiles à saisir sont ceux de

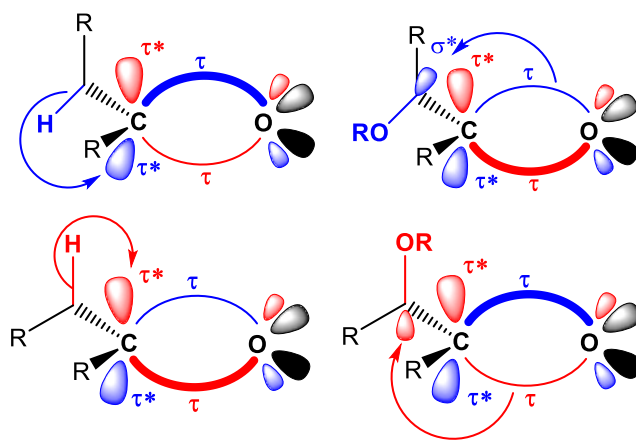
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<sup>18</sup> Deslongchamps, G.; Deslongchamps, P. *Org. Biomol. Chem.* **2011**, *9*, 5321-5333.

<sup>19</sup> (a) Parent, J.-F.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 3299-3304; (b) Deslongchamps, G.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 5751-5755.

l'hyperconjugaison et de l'hypothèse antipériplanaire. Discutés en profondeur dans de nombreux ouvrages,<sup>20</sup> ces phénomènes font le pont entre le modèle de Pauling et le modèle de Hückel. L'hyperconjugaison, qui consiste en un transfert de densité électronique d'une orbitale riche à une orbitale pauvre, est un phénomène établi sur une base d'orbitales de valence, mais également associé aux orbitales moléculaires puisque le mouvement des électrons s'effectue au-delà du noyau électronique auquel ils appartiennent initialement.

L'hypothèse antipériplanaire, quant à elle, décrit simplement la relation géométrique

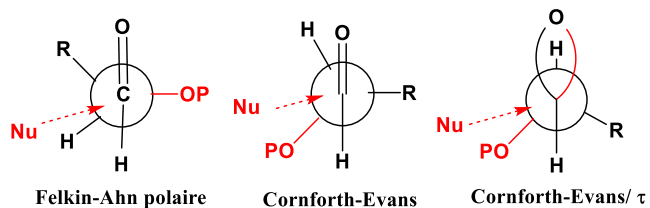


**Figure I.2** Hyperconjugaison et liaisons  $\tau$ .

nécessaire afin de maximiser les interactions hyperconjugantes entre les orbitales lors du bris ou de la formation de celles-ci. L'approche exploitée dans la littérature<sup>19</sup> et dans cette thèse se présente comme un hybride des deux modèles servant à la description de la liaison courbe s'apparentant à la description de Lennard-Jones<sup>13</sup>. Puisque les deux descriptions  $\sigma$ - $\pi$  et  $\tau$  sont plausibles, il semble juste et profitable de tirer avantage de certains principes fondamentaux propres à chacune. La *Figure I.2* illustre la combinaison des deux modèles dans le cas d'un carbonyle  $\alpha$ -substitué où la liaison considérée comme riche ( $\sigma$ -CH ou  $\tau$ ) est dans une orientation antipériplanaire à la liaison pauvre ( $\tau^*$  ou  $\sigma$ -COR). L'hyperconjugaison sera dite positive si la liaison courbe reçoit de la densité électronique et négative si elle en donne. Cela provoque l'asymétrisation de la densité électronique dans les deux liens courbes. Cet effet est représenté par les liaisons en gras dans la *Figure I.2*. Il y aura donc un effet stéréoelectronique à considérer lors d'une réaction d'addition nucléophile ou d'une transformation électrophile qui n'est pas nécessairement possible, ou, du moins, plus difficile à se représenter à travers le modèle  $\sigma$ - $\pi$ .

<sup>20</sup> (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, **1983**, Pergamon Press, Oxford; (b) Alabugin, V. I. *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, **2016**, John Wiley & Sons, Ltd.

Dans le cas de certains types d'additions sur des carbonyles, comme l'addition d'aldol, il est possible de lier cette approche par liaisons courbes au modèle prédictif Cornforth-Evans.<sup>21</sup> Ce dernier est basé sur la minimisation des dipôles entre le groupement électroattracteur



**Figure I.3** Modèle d'addition nucléophile sur un aldéhyde substitué par un hétéroatome.

adjacent et le carbonyle. Lorsque remodelé sous la forme de deux liens  $\tau$ , le modèle prédit habilement l'induction stéréosélective générée par un hétéroatome chiral en  $\alpha$  d'un aldéhyde

(Figure I.3). Selon Evans, le modèle généralement utilisé, celui de Felkin-Ahn polaire, ne prédit pas le produit escompté avec autant de précision.<sup>22</sup> Lorsque seule la taille des substituants est considérée et qu'il n'y a pas d'hétéroatome, les modèles de Cram, de Felkin-Ahn, de Karabatsos ainsi que  $\tau$  prédisent le même résultat.<sup>19a</sup>

Certains exemples d'application mentionnés précédemment méritent d'être davantage élaborés. C'est le cas, entre autres, de l'effet Cieplak<sup>23</sup>, qui s'explique intuitivement avec une approche par liaisons courbes. Cet effet consiste en une tendance d'addition nucléophile en axiale sur des dérivés de cyclohexanone ne trouvant pas réponse à l'intérieur des modèles d'addition courants. Selon Cieplak, la sélectivité faciale est générée par hyperconjugaison stabilisante de la liaison  $\sigma$  C-H dans l'orbitale  $\sigma^*$  de la liaison C-Nu à former, ce qui diminue l'énergie de l'état de transition pour ce produit. Dans le cas où il n'y a pas de liaison C-H, l'hyperconjugaison de la liaison  $\sigma$  C-C domine et mène au produit d'attaque équatorial. Son hypothèse a été fortement critiquée à l'époque, puisque dans le contexte d'orbitales moléculaires, il n'est pas possible de stabiliser une liaison à former par enrichissement de son antiliante.<sup>24</sup> Les résultats obtenus par Cieplak, Noble et plusieurs autres sur la réactivité de cétones cycliques rigidifiées est en parfaite adéquation avec une approche par liaisons

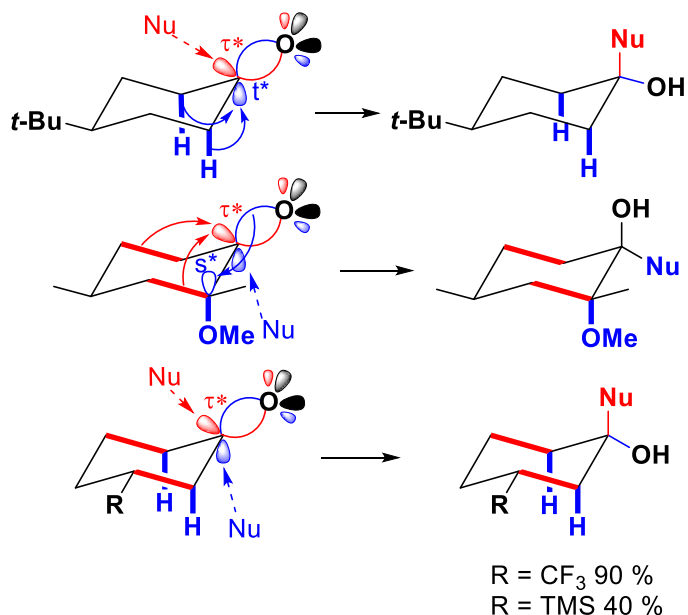
<sup>21</sup> Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1761-1765.

<sup>22</sup> Siska, S. J.; Cee, V. J.; Evans, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9433-9441.

<sup>23</sup> Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552

<sup>24</sup> Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3983-3994.

courbes.<sup>25</sup> En tenant compte que la liaison  $\sigma$ -C-H est la plus donneuse, comme Cieplak le mentionne, cette dernière enrichit la liaison  $\tau$  en bleu dans la *Figure I.4* (haut). Son antiliante sur la face équatoriale devient également plus riche en électrons, ce qui dirige l'attaque par le nucléophile sur la face axiale dans l'antiliante en rouge plus pauvre, générant ainsi l'alcool équatorial. Itoh a démontré que cette hyperconjugation de la liaison C-H est effectivement ce qui guide la

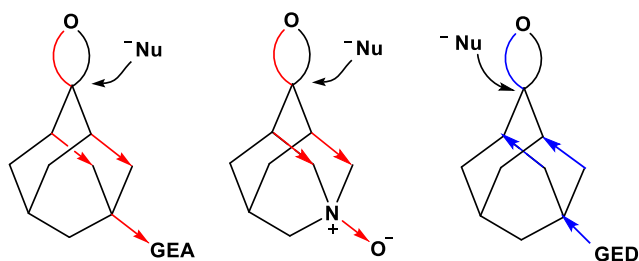


**Figure I.4** Addition contrôlée par  $\sigma$  C-H donneur (haut), par  $\sigma$  C-C donneur et  $\sigma$  C-OR accepteur (centre) et modulé par C<sub>3</sub>-R.(bas).

sélectivité faciale en remplaçant l'un des deux hydrogènes par un groupement électroattracteur.<sup>25c</sup> Cela a pour effet d'affaiblir la densité électronique dans la liaison  $\tau$  en bleu (*Figure I.4*, centre) et de favoriser l'attaque dans l'antiliante  $\tau^*$  correspondante sur la face équatoriale. À cet aspect s'ajoute la contribution des liaisons C-C dans l'orbitale  $\tau^*$  en rouge, ce qui augmente d'autant plus la disparité électronique au sein des deux liens. Favre et Gravel ont d'ailleurs démontré que la contribution des liens C-C à la sélectivité faciale n'est pas à sous-estimer.<sup>25b</sup> L'exemple du bas de la *Figure I.4* en atteste. Un groupement trifluorométhyle en C<sub>3</sub> fortement électroattracteur affecte la capacité d'hyperconjugaison des liens  $\sigma$  C-C par induction, ce qui accroît la participation relative des liens  $\sigma$  C-H.

Les exemples rapportés par le Noble<sup>25c</sup> sur des dérivés adamantanones rigides permettent de réaliser la distance surprenante à laquelle l'hyperconjugaison à travers des liaisons C-C est possible (*Figure I.5*). Des groupements électroattracteurs (GEA) et électrodonneurs (EDG)

<sup>25</sup> (a) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875-5876 (b) Favre, H.; Gravel, D. *Can. J. Chem.* **1961**, *39*, 1548-1552; (c) Kaselj, M.; Chung, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387-1414; (d) Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1009-1010.



**Figure I.5** Sélectivité engendrée par la substitution longue distance sur des adamantanones.

sans avoir à tenir compte des critiques émises par certains à l'endroit de Cieplak et son raisonnement initial.<sup>26</sup>

Dans une optique similaire, la stabilité des esters en fonction de leur conformation peut être rationalisée tout aussi facilement en y appliquant le modèle de Pauling. Cet exemple est l'un des plus éclairants pour illustrer la simplicité du modèle et sa puissance analytique. Il sera donc détaillé davantage. Les esters peuvent se retrouver sous deux conformations, soit E ou Z, la dernière étant celle la plus favorisée et donc adoptée par les esters linéaires sans contrainte géométrique. Quant à la conformation E, elle correspond à la géométrie retrouvée dans une lactone. La différence énergétique est d'une valeur non négligeable de 3.8 kcal mol<sup>-1</sup>.<sup>27</sup> Cette différence est calculée par analyse infrarouge et corroborée par calculs théoriques entre les deux conformations du formate de méthyle. Plusieurs interrogations ont émergé de cette différence énergétique dans la littérature physicochimique, accompagnées bien sûr de leur lot d'explications.<sup>28</sup> Il est d'autant plus intrigant que cette différence en stabilité s'associe d'une variation importante de l'acidité du proton en  $\alpha$  du carbonyle. L'analyse initiale – c'est-à-dire celle qui fait consensus dans la littérature – considère une minimisation des dipôles générée par la conformation Z. Cette diminution générale du moment dipolaire est, sous un angle stéréoelectronique en conservant le modèle  $\sigma$ - $\pi$ , causée par l'hyperconjugaison de deux paires d'électrons non liantes de l'oxygène du carbonyle et l'ester dans la liaison  $\sigma^*$  C-O qui leur est respectivement antipériplanaire. La densité électronique aux deux oxygènes se trouve donc augmentée, diminuant ainsi l'aspect

disposés antipériplanaire aux liaisons C-C influence la sélectivité faciale à travers quatre liaisons jusqu'à l'orbitale du système  $\tau$  qui leur correspond. L'utilisation des orbitales  $\tau$  permet de comprendre aisément les résultats observés pour ces systèmes statiques

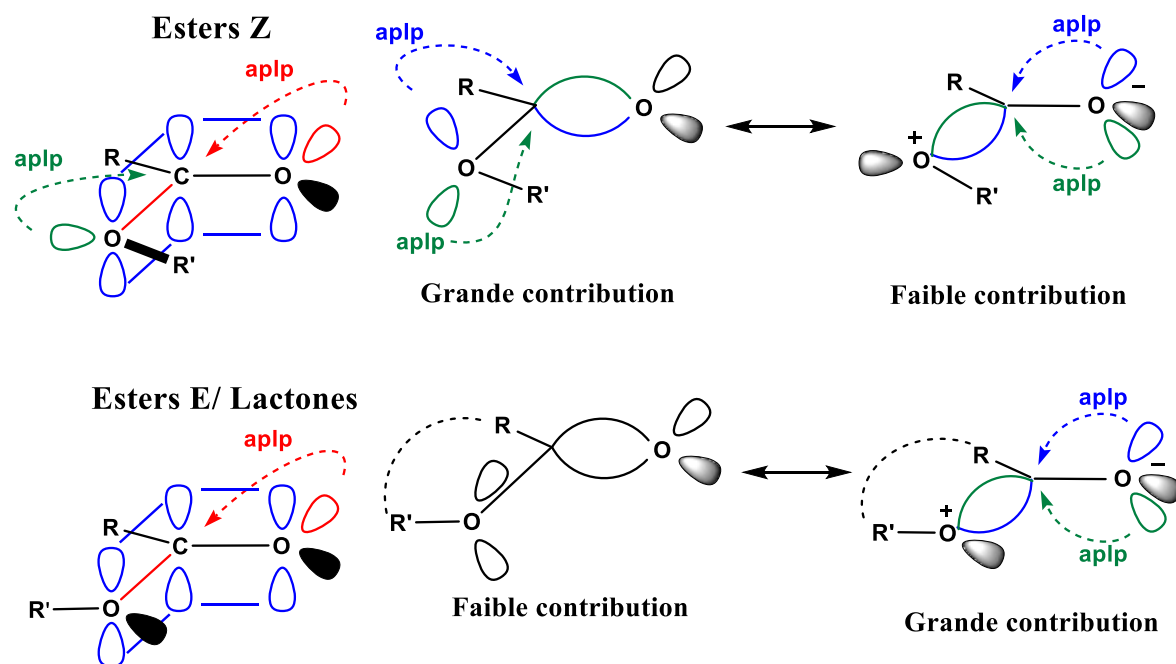
<sup>26</sup> Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 1189-1191.

<sup>27</sup> Blom, C. E.; Günthard, H. H. *Chem. Phys. Lett.* **1981**, *84*, 267-271.

<sup>28</sup> (a) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870-1872; (b) Evanseck, J. D.; Houk, K. N.; Briggs, J. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 23, 10630-10638.

électroattracteur de chacun et du même coup le moment dipolaire. Expérimentalement parlant, cela se traduit, entre autres, par une propension plus importante des lactones à s'hydrolyser en milieu caustique. La  $\delta$ -valerolactone, par exemple, s'hydrolyse 6000 fois plus rapidement que son équivalent linéaire.<sup>29</sup>

Le même argument est utilisé afin de répondre à la question de l'acidité. Houk rapporte par le biais de calcul *ab initio* que le gain énergétique obtenu par une diminution du moment dipolaire plus importante dans la forme énolate de la conformation E suffirait à augmenter l'acidité relative du proton comparément à la conformation Z.<sup>28a</sup> La nucléophilie relative de l'oxygène du carbonyle est une autre caractéristique qui ne semble pas prise en compte dans les discussions, alors que les différences entre les conformères Z et E sont flagrantes. L'oxygène de la lactone est connu comme étant beaucoup plus facile à alkyler, à l'aide d'un sel de Merweein par exemple, et ce, avec une vitesse de réaction 15000 fois supérieure pour certains comparatifs.<sup>30</sup> Cette nucléophilie est également supportée par une augmentation de la valeur  $pK_{HB}$  du carbonyle dans les lactones relativement aux esters acycliques



**Figure I.6** Stabilité et réactivité relatives des ester Z et E.

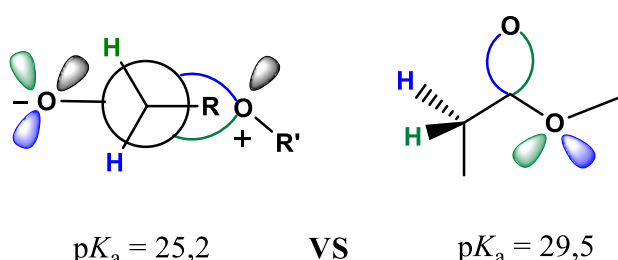
<sup>29</sup> Huisgen, R.; Ott, H. *Tetrahedron* **1959**, 6, 253-267.

<sup>30</sup> Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, 113, 7705-7709.



correspondants.<sup>31</sup> Ces caractéristiques peu communes séparant les deux conformations sont supportées par des arguments valables, bien que peu intuitifs. C'est en palliant ce problème que la liaison courbe surplombe le modèle courant.

En appliquant le visuel permis par le modèle de Pauling et en développant les formes de résonance de chaque intermédiaire (*Figure I.6*), il devient visuellement plus facile de percevoir la contribution des deux paires d'électrons libres de l'oxygène antipériplanaire à chacune des liaisons du carbonyle dans la forme neutre. La même chose est vraie pour la forme de résonance zwitterionique. Il y a toujours deux paires d'électrons respectivement conjuguées dans les liaisons de l'ion oxocarbénium. Évidemment, par sa charge, cette forme de résonance ne contribue que très peu à l'hybride.<sup>19a</sup> C'est cette contribution à la forme de



**Figure I.7** Différence d'acidité entre la  $\delta$ -valerolactone et l'acétate d'éthyle dans le DMSO.

résonance chargée qui explique le gouffre énergétique entre les deux conformères. L'ester E,

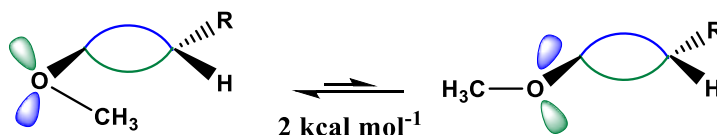
conformationnellement rigide, ne possède pas les deux interactions stabilisantes des paires d'électrons non liantes de l'oxygène. Cette contribution devient disponible seulement sous la forme

chargée. Il est donc possible d'assumer qu'elle contribue davantage à l'hybride de résonance d'un ester E que Z, expliquant alors la différence énergétique entre les deux conformations, une forme *partiellement* chargée étant beaucoup plus haute en énergie. Cette nouvelle vision permet également d'expliquer la tendance des lactones à s'alkyler plus facilement, puisque l'oxygène porte une charge négative plus importante. Pour ce qui concerne le gain en acidité, le rationnel rejoint l'effet Cieplak où les deux hydrogènes sont alignés de manière *app* aux liaisons du carbonyle endocyclique de la forme de résonance chargée (*Figure I.7*). Les liens hautement polarisés de l'oxocarbénium accentuent le caractère acide de chacun des hydrogènes par hyperconjugation. Une approche complémentaire dans le cas d'une lactone serait que l'énolate généré est stabilisé d'une manière plus efficace par les deux paires d'électrons libres de l'oxygène de l'éther, et ce, sans nécessiter la rotation de la liaison O-C.

<sup>31</sup> Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 485-489.

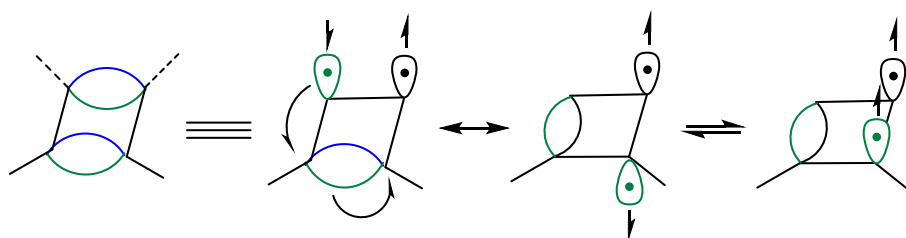
La conformation adoptée rejoint celle reconnue comme plus stable dans les éthers d'énol, où le groupement porté par l'oxygène de l'éther est de conformation gauche entre les deux liaisons courbes de l'alcène. (Figure I.8) Cet aspect est tout aussi vrai pour les esters linéaires, qui existent préférentiellement sous la conformation *cis*. Cette dernière n'explique donc pas la différence en acidité.<sup>32</sup> Cette approche est tout aussi envisageable pour l'analyse de la conformation des amines, des amides et des autres dérivés.<sup>19a</sup> Il est également possible d'analyser la sélectivité dans des systèmes conjugués comme des énones lors des réactions d'addition de Micheal.<sup>19a, 33</sup> Il suffit simplement d'appliquer la relation *appl* à travers deux liaisons  $\tau$  pour rationaliser ou prédire sans difficulté la sélectivité.

C'est cette particularité de lier les représentations de Pauling et de Hückel dans les systèmes conjugués qui rend cette approche particulièrement



**Figure I.8** Conformation favorisée des éthers d'énol.

unique et intéressante en ce qui concerne sa puissance explicative. Puisque le carbone portant l'insaturation possède maintenant un caractère tétraédrique et que chaque double liaison est unique, cela signifie que la conjugaison, selon les règles de ce modèle, est également stéréocontrôlée et s'effectue en respectant l'hypothèse antipériplanaire. La conjugaison se



**Figure I.9** Conjugaison du cyclobutadiène.

décrivait ici, non pas par un mouvement de plusieurs électrons à travers toutes les liaisons, comme dans l'approche  $\sigma$ - $\pi$ , mais plutôt comme le mouvement d'un seul électron à travers plusieurs liaisons courbes subséquentes. (Figure I.9). Dans cette figure, la liaison courbe du haut est développée sous sa forme diradicalaire. L'un des radicaux est ensuite délocalisé dans

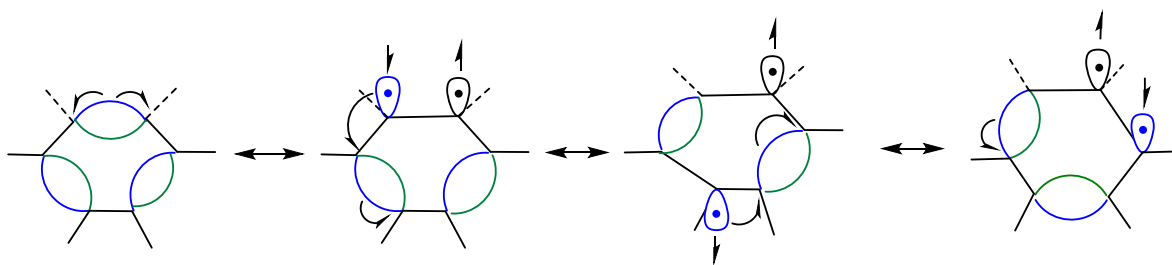
<sup>32</sup> Owen, N. L.; Seip, H. M. *Chem. Phys. Lett.* **1970**, 5, 162-164.

<sup>33</sup> Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, 56, 387-395.

l'orbitale  $\tau^*$  de la liaison  $\tau$  lui étant antipériplanaire. Le nouveau singulet généré se trouve alors sur la face du bas, ce qui rend impossible la formation d'une nouvelle liaison  $\tau$  sans apport énergétique permettant une inversion de Walden.<sup>34</sup> Cette approche explique sans défaut l'antiaromaticité du cyclobutadiène alors qu'à l'inverse, la même démarche effectuée avec le benzène permet une délocalisation pour laquelle le dernier électron singulet généré se trouve dans la phase nécessaire pour reformer la liaison  $\tau$  (Figure I.10).<sup>19c</sup>

Il semble probable que l'une des raisons principales du délaissement progressif du modèle de Pauling soit le développement de la chimie des espèces conjuguées et aromatiques. Par exemple, les réactions de Diels-Alder trouvent leur niche au sein du modèle  $\sigma$ - $\pi$  par la rationalisation d'orbitales moléculaires frontières. Le Professeur Deslongchamps a toutefois démontré que de telles transformations peuvent également être décrites à l'aide du modèle des liaisons courbes. Pour ce faire, il suffit d'utiliser une approche mécanistique considérant l'état de transition diradicaloïde singulet de plus basse énergie en fonction des substituants présents sur le composé.<sup>35</sup>

Sans trop entrer dans les détails, puisque ce type de transformation sort du cadre de cette thèse, cette proposition soulève un aspect particulier qui n'est pas associé en temps normal avec la chimie radicalaire, soit la chiralité. La réactivité de ces radicaux stabilisés ou conjugués dans des liaisons courbes permettent également de proposer des voies



**Figure I.10** Délocalisation et aromaticité du benzène.

mécanistiques pour diverses transformations peu intuitives dont les déplacements sigmatropiques d'hydrogènes<sup>36</sup> et d'alkyles<sup>19c</sup> et les réarrangements thermiques d'espèces conjuguées et aromatiques.<sup>19b</sup> Il s'agit de propositions valant la peine d'être davantage

<sup>34</sup> Maier, G.; Wolf, R.; Kalinowski, H.-O. *Angew. Chem. Int. Ed.* **1992**, *31*, 738-740.

<sup>35</sup> Deslongchamps, G.; Deslongchamps, P. *Tetrahedron* **2013**, *69*, 6022-6033.

<sup>36</sup> Deslongchamps, G.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 10383-10388.

explorées à l'aide des modèles spécifiquement construits afin de mettre en valeur le pouvoir analytique et prédictif apporté par la vision de Pauling.

## Objectifs du projet

### Liaisons $\tau$ et glycosylation $S_N1$

Bien que les exemples tirés de la littérature soient nombreux et qu'il soit facile d'y adapter le modèle de Pauling, on ne retrouve que très peu de travaux expérimentaux conduits dans l'optique unique de démontrer l'applicabilité du modèle. C'est pour pallier ce manque que cette thèse a pour objectif d'étudier la réaction de glycosylation  $S_N1$  dans une définition élargie du terme, à l'aide de composés analogues aux glucides spécialement construits afin de mettre l'accent sur la participation de l'hyperconjugaison et des liaisons courbes.

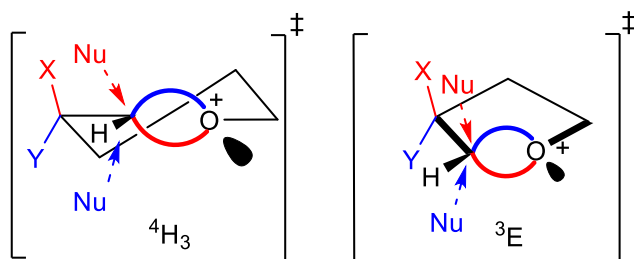
Considérons tout d'abord la réaction de glycosylation  $S_N1$  en elle-même. Cette transformation fait l'objet de nouvelles publications presque quotidiennement, puisque la formation d'une liaison glycosidique est considérée comme le nerf de la guerre en chimie des glucides. Il existe une multitude d'approches permettant de contrôler la stéréochimie au carbone anomérique, mais la complexité moléculaire de mono, poly ou oligosaccharides rend difficile le développement des conditions réactionnelles pouvant être appliquées de manière générale. Il y a donc deux manières d'aborder ce problème. La première est de s'appuyer davantage sur la méthode. Par exemple, certains groupes de recherche tendent à concentrer leurs efforts sur l'élaboration de nouvelles approches synthétiques pouvant exploiter, par exemple, la nature des groupements protecteurs et celle du groupement anomérique ou bien par l'utilisation de réactifs spécifiques.<sup>37</sup>

La deuxième approche consiste à définir les bases fondamentales de réactivités partagées par un plus grand nombre de glucides. C'est-à-dire qu'il faut établir les facteurs structuraux et stéréoélectroniques intrinsèquement liés à la réactivité et, de surcroît, à la sélectivité, pour ensuite les appliquer par extrapolation à des systèmes aux caractéristiques analogues. Plus précisément, cela aboutit à évaluer les différentes conformations adoptées par l'intermédiaire

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<sup>37</sup> (a) Das, R.; Mukhopadhyay, B. *ChemistryOpen* **2016**, 5, 401-433; (b) Ranade, S. C.; Demchenko, A. V. *J. Carbohydr. Chem.* **2013**, 32, 1-43.

oxocarbénium et comment la stabilité et la réactivité de ce dernier sont influencées par les groupements environnants ou les conditions réactionnelles. Il devient ensuite possible d'établir des principes de base à partir desquels la production et la synthèse de glucides complexes gagnent en efficacité.



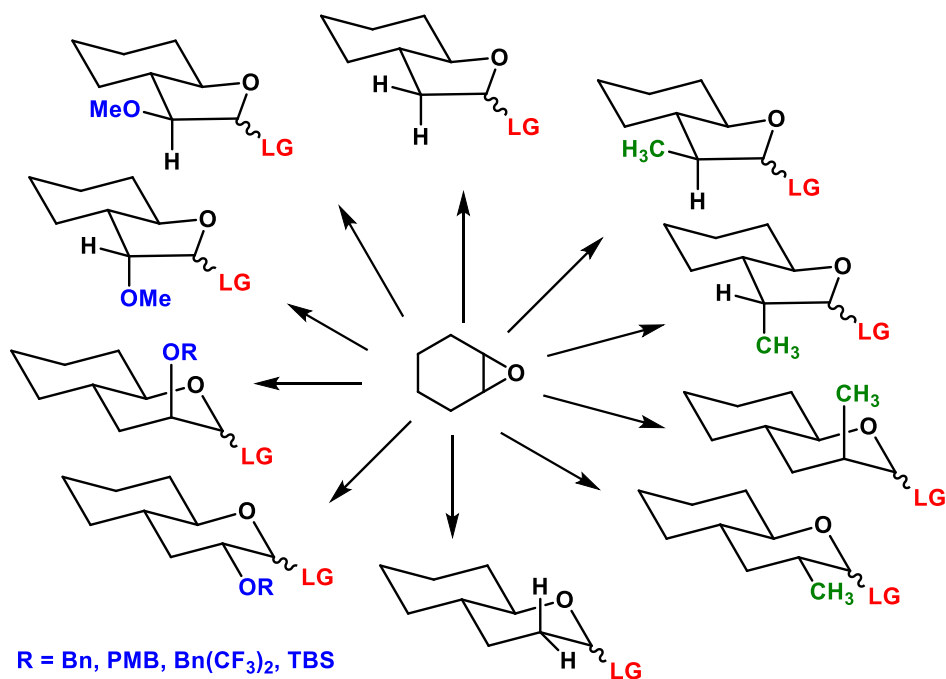
**Figure I.11** Oxocarbénium d'un pyranose et d'un furanose.

La raison justifiant l'exploitation de la glycosylation  $S_N1$  pour démontrer l'utilité du modèle de Pauling réside dans l'intermédiaire oxocarbénium, un analogue endocyclique à la cétone formée à l'état de transition de cette transformation. Cet intermédiaire

possède toutefois une réactivité plus importante étant donné l'oxygène chargé et la géométrie contrainte du cycle. En support à cette approche, l'oxocarbénium, dans le contexte des glucides, est substitué en position deux. Une position qui place les groupements portés par ce carbone parfaitement antipériplanaire à leur liaison  $\tau$  respective formant l'oxocarbénium (Figure I.11). Tel que l'indique cette figure, les deux types de glucides les plus communs ont été mis à l'étude, soit les pyranoses et les furanoses. Ces derniers ont été préparés dans leur appareil le plus simple, c'est-à-dire dans une optique limitant au maximum tout autre facteur pouvant influencer la sélectivité de la réaction de glycosylation. L'accent pourra alors être placé sur la contribution stéréoélectronique aux liaisons courbes d'un seul et unique substituant au sein de la structure, soit celui introduit en position deux, pour ensuite en déterminer l'impact général sur la sélectivité de la réaction en fonction de sa nature et de son orientation. De plus, il va sans dire que la réaction de glycosylation doit être conduite des conditions parfaitement cinétiques.

## Les donneurs de glycosyle

Il est difficile d'isoler spécifiquement la contribution d'une variable dépendante d'une équation qui en comporte plusieurs, comme c'est le cas ici. En tentant d'étudier l'apport d'un seul facteur stéréoelectronique au sein d'une structure aussi complexe que les glucides, les résultats expérimentaux obtenus peuvent rapidement devenir cauchemardesques à interpréter. Cela est sans compter les analyses spectrales, telle que la RMN, qui peuvent induire certaines résistances par l'enchevêtrement de signaux qu'on y retrouve. Une simplification du système à l'étude est donc primordiale afin d'obtenir la réponse la plus juste possible. C'est pourquoi les donneurs illustrés à la *Figure I.12* ont été préparés. Évidemment certains facteurs structuraux intrinsèques peuvent biaiser, voire masquer l'effet stéréoelectronique ciblé. Ceux-ci seront abordés plus en profondeur dans les prochaines sections. En revanche, lorsque ces facteurs sont définis, ce qui était initialement considéré comme une variable devient alors une constante et, de ce fait, l'équation générale se simplifie. De manière plus détaillée, la simplification des donneurs de liaison glycosidique pyranoses et furanoses synthétisés se traduit par l'absence d'oxygènes sur les autres positions du squelette (*Figure I.12*). Le cas inverse demanderait que l'effet engendré par chacun sur la



**Figure I.12** Donneurs de glycosyle préparés.

sélectivité soit considéré, ce qui consisterait en des contributions stéréoélectroniques secondaires, comme une activation plus prononcée de l'intermédiaire oxocarbénium ou une participation directe à la sélectivité par stabilisation électrostatique. La construction en bicyclic *trans* confère également aux donneurs une seule conformation à l'état de transition, sans possibilité d'inversion puisqu'une torsion trop importante dans le cycle cyclohexyle adjacent serait alors induite.

## Réactivité générale des furanoses

L'approche bicyclic pour l'étude de la réaction de glycosylation s'inspire grandement du travail de Keith Woerpel sur la réactivité des glucides. La quasi-totalité de ses publications parues entre 1999 et 2015 vise à comprendre, par des donneurs aux structures simples et adéquates au contexte, les facteurs de sélectivité de la glycosylation  $S_N1$  dans des conditions cinétiques.

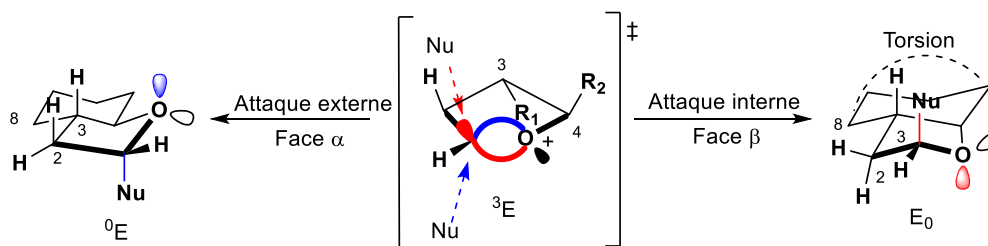
Woerpel est l'un des pionniers de l'analyse conformationnelle des cations oxocarbénium dans les furanoses.<sup>38</sup> Ce dernier a démontré que l'addition d'un nucléophile s'effectue toujours préférentiellement à l'intérieur de l'intermédiaire chargé de conformation  ${}^3E$  (*Figure I.13*).<sup>39</sup> Selon son analyse, l'attaque sur cette face (considérons-la comme la face  $\beta$ ) est favorisée du fait que la conformation  $E_0$  engendrée est moins énergétique, car les carbones deux et trois du cycle sont d'orientation gauche. D'autre part, la face  $\alpha$  est défavorisée, puisque la conformation  ${}^0E$  du produit final voit cette fois-ci les deux mêmes carbones  $C_2$  et  $C_3$  s'éclipser. Cet effet est d'autant plus marqué par la présence du cycle adjacent, alors que les substituants éclipsés ne sont plus deux hydrogènes, mais plutôt un hydrogène et un méthylène en  $C_8$ . Dans un contexte de *C*-glycosylation, Woerpel a démontré que la sélectivité n'est pas parfaite. Le changement de conformation du furanose lors de l'attaque interne induit une torsion du cyclohexyle adjacent, ce qui engendre de l'attaque externe à hauteur de 30 %. En appui à cette proposition, Woerpel a démontré qu'un cycle adjacent dont la taille est supérieure, comme un cyclooctane, permet une plus grande liberté conformationnelle, ce qui

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<sup>38</sup> (a) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152; (b) Lavinda, O.; Tran, V. T.; Woerpel, K. A. *Org. Biomol. Chem.* **2014**, *12*, 7083-7091.

<sup>39</sup> Fuchs, B. *Top. Stereochem.* **1978**, *10*, 1-94.

induit une sélectivité presque aussi élevée (93 % interne) que dans le cas d'un furanose dont la conformation n'est pas rigidifiée à l'état de transition.<sup>38</sup> Bien que son analyse soit tout à fait juste et que la sélectivité soit guidée par les différentes conformations adoptées par les cycles à la suite de l'addition du nucléophile, Woerpel ne propose pas de raisonnement explicite à savoir pourquoi les deux produits d'attaque se présentent dans ces conformations. Comme le dépeint la *Figure I.13*, la formation du produit à la suite de l'attaque du nucléophile inflige une géométrie dans laquelle une paire d'électrons non-liante doit être générée dans une relation antipériplanaire à la liaison formée.<sup>20a</sup> Cette analyse initiale est encore ici facilement représentée par le modèle des liaisons courbes. Comme dans le cas d'une réaction S<sub>N</sub>2, le nucléophile déplace ou brise une liaison et *génère* une paire d'électrons libres. Si l'on considère une attaque externe sur l'enveloppe <sup>3</sup>E, cela signifie une addition du nucléophile dans l'antiliante τ\* en bleu sur la face α et la dissociation de l'orbitale liante τ de même couleur sur la face β générant ainsi la paire d'électrons sur cette même face. La conformation adoptée par le cycle ne peut alors qu'être la <sup>0</sup>E, respectant la relation antipériplanaire. En somme, bien que ce soient des effets conformationnels qui soient ultimement la cause de la sélectivité dans la glycosylation S<sub>N</sub>1 des furanoses, leur existence est invariablement causée par des effets stéréoélectroniques.

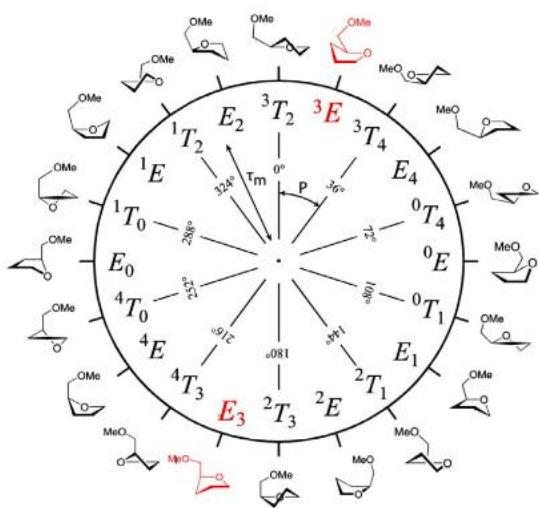


**Figure I.13** Glycosylation d'un oxocarbénium <sup>3</sup>E bicyclique furanosique.

La littérature découlant des travaux de Woerpel par d'autres chercheurs sur le même sujet tend à généraliser la glycosylation S<sub>N</sub>1 de furanoses en fonction des conformations adoptées par l'oxocarbénium. Cette voie semble tout à fait justifiable, puisque le modèle «inside/outside attack» de Woerpel est un facteur prépondérant de la sélectivité.<sup>38</sup> Cependant, il est fort à parier que des effets stéréoélectroniques engendrés par les différents substituants du glucide ont leur place dans l'analyse et mériteraient d'être analysés avec plus de soin.



Les travaux rapportés par Codée sur la conformation des oxocarbéniums furanoses sont substantiels à l'égard d'une combinaison d'effets conformationnels et stéréoélectroniques.<sup>40</sup> Par des études computationnelles extensives d'énergie de conformation de cycle, ses travaux démontrent qu'il est possible de prédire la sélectivité de la glycosylation en déterminant d'avance quelle conformation de l'oxocarbénium est la plus stable, c'est-à-dire celle qui est la plus adaptée à l'état de transition. L'approche utilisée par Codée est d'autant plus robuste que les calculs théoriques sont corroborés en totalité par des résultats expérimentaux. Les expériences sont conduites à l'aide de nucléophiles faibles réagissant préférentiellement via un mécanisme de glycosylation S<sub>N</sub>1.<sup>41</sup> Les cartes topographiques énergétiques obtenues sont exprimées à l'aide du cercle de pseudo-rotation décrivant les conformations possibles d'un furane (*Figure I.14*).<sup>42</sup> Le degré de stabilité de chaque conformation obtenue computationnellement est représenté par un gradient de couleur, distribué au sein du cercle



**Figure I.14** Conformation possible d'un furanosyle.<sup>40a</sup>

de pseudo-rotation (*Figure I.15*). Les zones plus foncées en noir et violet représentent les conformations étant déterminées comme plus stables pour un glucide donné. Bien évidemment, tel que dépeint à la *Figure I.15*, la conformation oscille entre <sup>3</sup>E et E<sub>3</sub> en fonction du furanose étudié, mais la sélectivité suit toujours le principe d'attaque interne proposé par Woerpel. Cette variation entre les deux conformères reste toutefois le fruit d'effets stéréoélectroniques engendrés par les multiples groupements portés par le glucide. Les deux

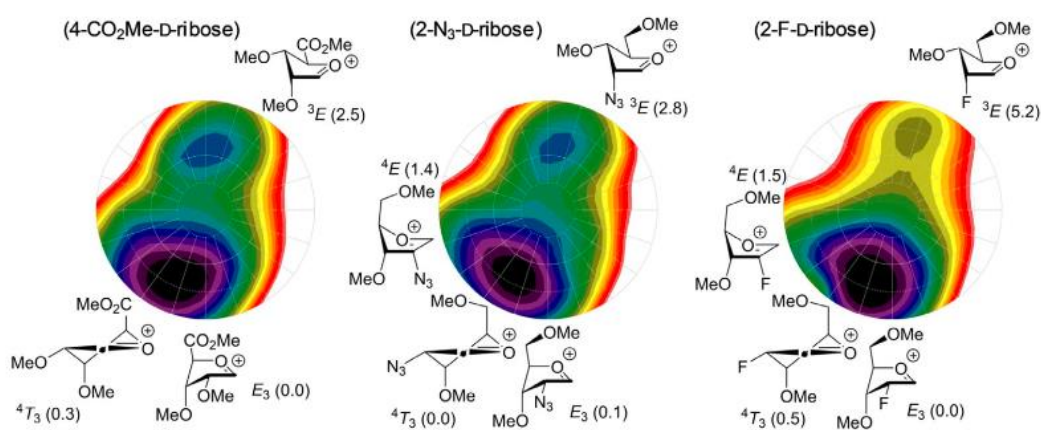
facteurs électroniques prédominant à la stabilisation d'un système donné sont, d'une part, une stabilisation électrostatique du centre anomérique par le groupement en C5 et, de l'autre,

<sup>40</sup> (a) van Rijssel, E. R.; van Delft, P.; van Marle, D. V.; Bijvoets, S. M.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A.; Filippov, D. V.; Codée, J. D. C. *J. Org. Chem.* **2015**, *80*, 4553-4565; (b) Vorm, S. v. d.; Hansen, T.; Rijssel, E. R. v.; Dekkers, R.; Madern, J. M.; Overkleeft, H. S.; Filippov, D. V.; Marel, G. A. v. d.; Codée, J. D. C. *Chem. Eur. J.* **2019**, *25*, 7149-7157.

<sup>41</sup> (a) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907-4910 (b) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 8039-8050.

<sup>42</sup> Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205-8212.

une hyperconjugaison positive du lien C<sub>2</sub>-H. Ce qui est particulièrement intéressant avec les résultats présentés par Codée est que d'une manière indépendante du glucide et de sa fonctionnalisation, la sélectivité est toujours *cis* en relation avec le groupement en position deux. De plus, la conformation favorisée est toujours celle où ce même groupement est disposé dans la partie interne de l'enveloppe. Cette sélectivité est en parfait accord avec ce que prédiraient les liaisons courbes. Il est donc juste de proposer que l'hyperconjugaison du groupement électroattracteur en position deux jumelé à l'aspect conformationnel de l'attaque interne favorise grandement la conversion de l'oxonium le moins réactif en produit glycosylé.



**Figure I.15** Carte énergétique de l'oxocarbénium du D-ribose et D-arabinose rapportée par Codée.<sup>40b</sup>

La vitesse de conversion est donc plus élevée que l'équilibration entre les deux ions oxocarbénium et la conversion du conformère plus énergétique. Ce contexte correspondrait à première vue à un scénario Curtin-Hammett cinétique.<sup>43</sup>

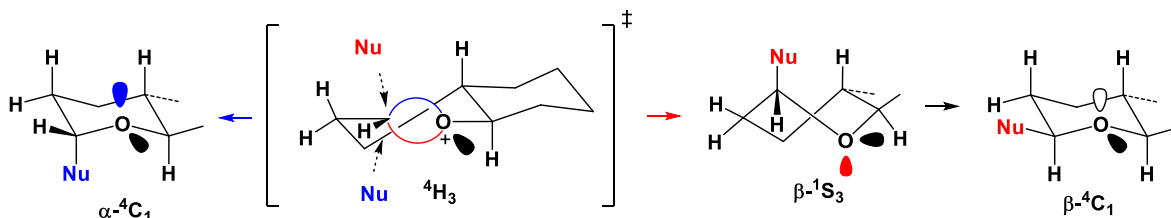
La question qui se pose maintenant est celle de déterminer à quel point les effets stéréoelectroniques peuvent influencer la sélectivité de la réaction dans les furanoses et, implicitement, s'ils peuvent être traduits à l'aide du « langage » de Pauling. En ce qui concerne les donneurs synthétisés, l'utilisation d'un cycle adjacent plus tendu semble contre-intuitive puisqu'elle influence la sélectivité. Or, c'est justement le fait que la réaction de glycosylation ne soit pas parfaitement sélective qui justifie le choix du cyclohexane. En plus d'être plus simple à préparer et moins dispendieux que les cycles de taille supérieure, il est

<sup>43</sup> Chakraborty, S.; Saha, C. *Resonance* **2016**, *21*, 151-171.

plus évident de percevoir une sélectivité induite par une nouvelle substitution lorsque la molécule servant de base comparative, c'est-à-dire le donneur non substitué, n'est pas parfaitement sélective. Le risque inhérent est que les effets électroniques soient complètement surplombés par le caractère conformationnel et stérique intrinsèque aux donneurs. Comme il le sera décrit dans les chapitres à venir, ce n'est toutefois pas le cas, et ce, malgré des apports stériques et conformationnels encore plus importants engendrés par une substitution en C<sub>2</sub>. Ces considérations s'avèrent d'ailleurs un point névralgique dans le cas plus particulier des donneurs furanoses bicycliques.

## Réactivité générale des pyranoses

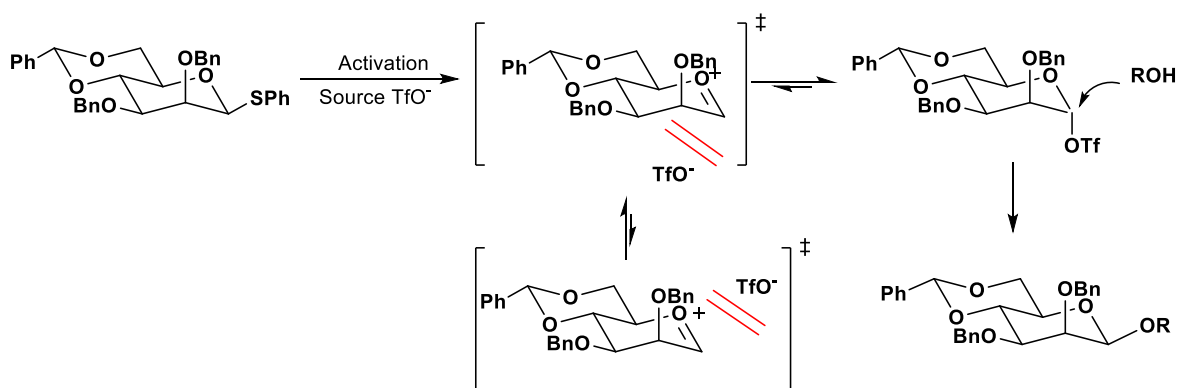
Tout comme les furanoses, les pyranoses présentent certaines restrictions conformationnelles en ce qui concerne leur réactivité. Leur analyse est toutefois plus simple que les furanoses pour une raison particulière, c'est-à-dire la taille du cycle. De manière analogue aux cycles à cinq atomes, l'état de transition oxocarbenium peut exister sous plusieurs conformères dont la stabilité varie en fonction de la géométrie adoptée et des différents facteurs stabilisant engendrés par le patron de substitution. Dans le cas des donneurs présentés à la *Figure I.12*, la jonction *trans* entre les deux cycles ne permet, à première vue, qu'une seule conformation possible à l'état de transition, la demi-chaîse <sup>4</sup>H<sub>3</sub>. L'inversion de la chaise vers la forme <sup>3</sup>H<sub>4</sub>, n'étant évidemment pas envisageable puisque cela signifierait une substitution *trans*-diaxial aux carbones 4 et 5 impossible à adopter pour le cycle adjacent. En suivant le principe porté par l'hypothèse antipériplanaire, une addition nucléophile sur un ion oxocarbenium pyranose <sup>4</sup>H<sub>3</sub> bicyclique s'effectuera préférentiellement sur la face α (sous le plan) pour générer directement la chaise <sup>4</sup>C<sub>1</sub> où la paire d'électrons non liante engendrée est antipériplanaire à la nouvelle liaison formée. L'addition sur la face β (au-dessus du plan), quant à elle, mène à la formation du bateau croisé <sup>1</sup>S<sub>3</sub> pour la même raison. La complétion de la transformation



**Figure I.16** Conformation résultante de l'addition sur l'ion oxocarbenium <sup>4</sup>H<sub>3</sub>.

nécessite donc un passage supplémentaire par la forme  ${}^4H_3$  pour l'obtention du produit final. La face  $\beta$  est donc généralement défavorisée d'un point de vue énergétique (*Figure I.16*). Il est alors normal qu'il soit relativement difficile de glycosyler en  $\beta$  un substrat dérivé d'un mannose par un mécanisme  $S_N1$ , puisqu'il y a un apport stérique défavorisant supplémentaire provenant du substituant en C<sub>2</sub>. La formation d'un lien glycosidique 1,2-*cis* est, de ce fait, sujet de publications récurrentes, et ce, particulièrement dans un contexte de *mannosylation*, mais aussi de *glucosylation*  $S_N1$ .<sup>44</sup> Il existe également quelques méthodes exploitant des stratégies plus spécifiques au mode de substitution du donneur comme la participation de groupements voisins ou de modes de protections orthogonaux particuliers. Ce sont des contextes impliquants plus souvent un mécanisme de type  $S_N2$  et qui sont peu généralisables à d'autres systèmes.<sup>45</sup>

La méthode prédominante pour la synthèse d'un lien 1,2-*cis* mannoside est celle de Crich, où la sélectivité est guidée par la génération d'intermédiaire glycosyles triflates covalents (*Figure I.17*).<sup>46</sup> Cette méthode requiert la rigidification du glucide par un acétal 4,6-*O*-benzylidène afin de limiter les conformations possibles à l'état de transition et de favoriser la formation du triflate anomérique plutôt qu'une paire d'ions en déstabilisant l'ion oxocarbenium par hyperconjugaison négative des liens C<sub>5</sub>-O et C<sub>4</sub>-O.<sup>44a</sup> Il ne s'agit donc pas



**Figure I.17** Mécanisme de  $\beta$ -mannosylation par préactivation.<sup>44a</sup>

<sup>44</sup> (a) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144-1153; (b) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687-2704.

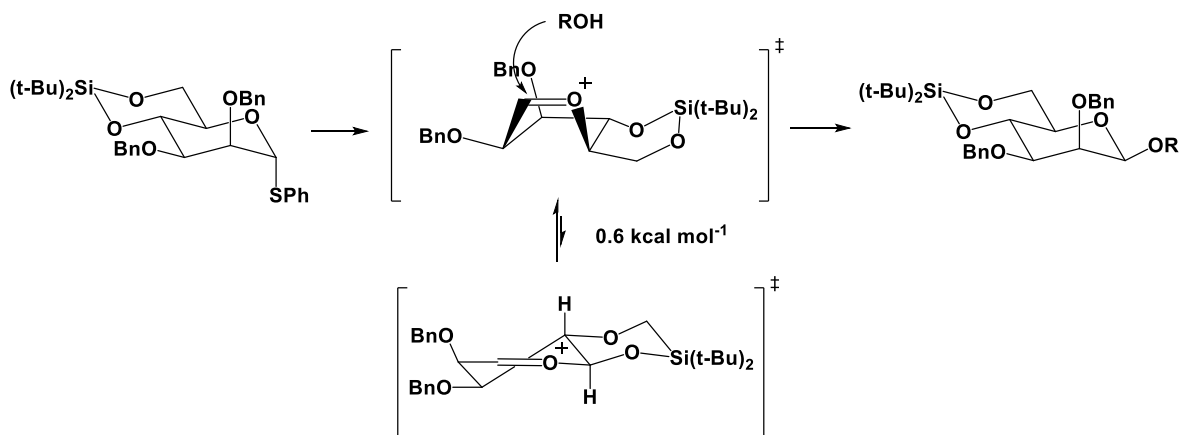
<sup>45</sup> (a) Elferink, H.; Mensink, R. A.; White, P. B.; Boltje, T. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11217-11220; (b) Hashimoto, Y.; Tanikawa, S.; Saito, R.; Sasaki, K. *J. Am. Chem. Soc.* **2016**, *138*, 14840-14843.

<sup>46</sup> Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321-8348; (b) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506-4507.

d'une réaction  $S_N1$  à proprement parler, puisque le lien  $\beta$  dans le cas du mannose est généré par la substitution d'un triflate anomérique par l'alcool.

Bols a toutefois démontré que cette réactivité engendrée par la rigidification du système permet d'obtenir le produit 1,2-*cis* du mannose sans avoir recours à une préactivation ou un triflate, donc par un mécanisme beaucoup plus près d'une réaction  $S_N1$ . L'ion oxocarbénium adopterait préférentiellement une conformation  $B_{2,5}$  qui serait plus faible en énergie de 0.6 à 0.7 kcal mol<sup>-1</sup> (Figure I.18)<sup>47</sup> causé par l'orientation pseudo-axiale du groupement C<sub>3</sub>-OR pouvant stabiliser la charge de l'oxygène anomérique.<sup>48</sup> Le nucléophile attaque donc la face la moins encombrée, soit celle à l'extérieur du bateau. Cette attaque correspond également à ce que prédit le modèle des liaisons courbes, soit *cis* relativement au groupement attracteur C<sub>2</sub>-OBn. L'utilisation ici d'un silylidène plutôt que d'un benzyldène n'aurait aucune influence sur la formation du conformère bateau.

Cette conformation inusitée ne s'applique toutefois pas dans la rationalisation des résultats



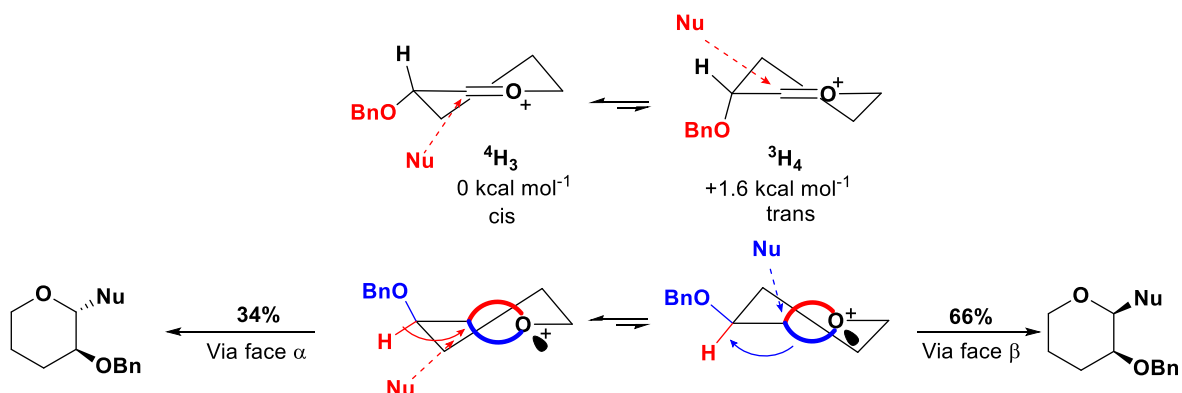
**Figure I.18** 1,2-*cis* mannosylation sans l'intervention d'un triflate ou d'une paire d'ions via la configuration favorisée  $B_{2,5}$ .

obtenus à l'aide des donneurs simplifiés présentés à la Figure I.12, puisque ceux-ci sont dépourvus de substituant à cette position. Il est donc juste de croire que la conformation des états de transition oxocarbénium des donneurs simplifiés existe bel et bien dans une

<sup>47</sup>(a) Heuckendorff, M.; Bendix, J.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2014**, *16*, 1116-1119; (b) Heuckendorff, M.; Bols, P. S.; Barry, C. B.; Frihed, T. G.; Pedersen, C. M.; Bols, M. *Chem. Commun.* **2015**, *51*, 13283-13285.

<sup>48</sup> Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545-553.

conformation  $^4H_3$ . Le raisonnement de Bols est d'ailleurs en accord avec les conclusions rapportées par Woerpel pour un pyranose substitué en C<sub>2</sub> par un groupement benzyle. L'orientation pseudo équatoriale d'un groupement C<sub>2</sub>-OR dans un oxocarbenium serait plus favorisée que l'inverse, puisqu'il y aurait une stabilisation de l'ion par hyperconjugaison positive de la liaison C<sub>2</sub>-H pseudoaxiale. Bien que cet argument soit valide en soi, il semble toutefois appliqué dans le mauvais contexte. Il a été démontré par Alabugin qu'il existe effectivement une différence entre la capacité hyperconjugante d'une liaison C-H<sub>ax</sub> et C-H<sub>eq</sub>.<sup>49</sup> La propension supérieure de la liaison C-H<sub>ax</sub> à concourir à une interaction hyperconjugante a toutefois été établie dans des systèmes étherifiés 1,3-dioxane ou dithiane. Dans ces systèmes, les différentes relations antipériplannaires entre les liaisons C-H et C-X (où X est un hétéroatome) sont établies dans la forme chaise du cyclohexane. Ce raisonnement n'est donc pas applicable aux ions oxocarbeniums, puisque les liaisons C<sub>2</sub>-H et C<sub>2</sub>-OR sont disposées à des angles quasi-similaires à l'insaturation. La contribution de la liaison C<sub>2</sub>-H axiale ou équatoriale n'explique donc pas cette préférence accrue envers le modèle de Woerpel pour le produit d'addition 1,2-*cis* tel que ce dernier le propose, bien qu'il trouve un appui computationnel à ses résultats.<sup>48,50</sup> Cela illustre que les calculs théoriques peuvent être malléables.<sup>51</sup> Une simple réévaluation des conformations à l'état de transition à l'aide des liaisons courbes suffit à comprendre la sélectivité (*Figure I.19*). Il s'agit tout simplement d'un équilibre entre les deux formes demi-chaise où la  $^4H_3$  réagit plus



**Figure I.19** C-glycosylation sélective rapportée par Woerpel et interprétation par liaisons courbes.

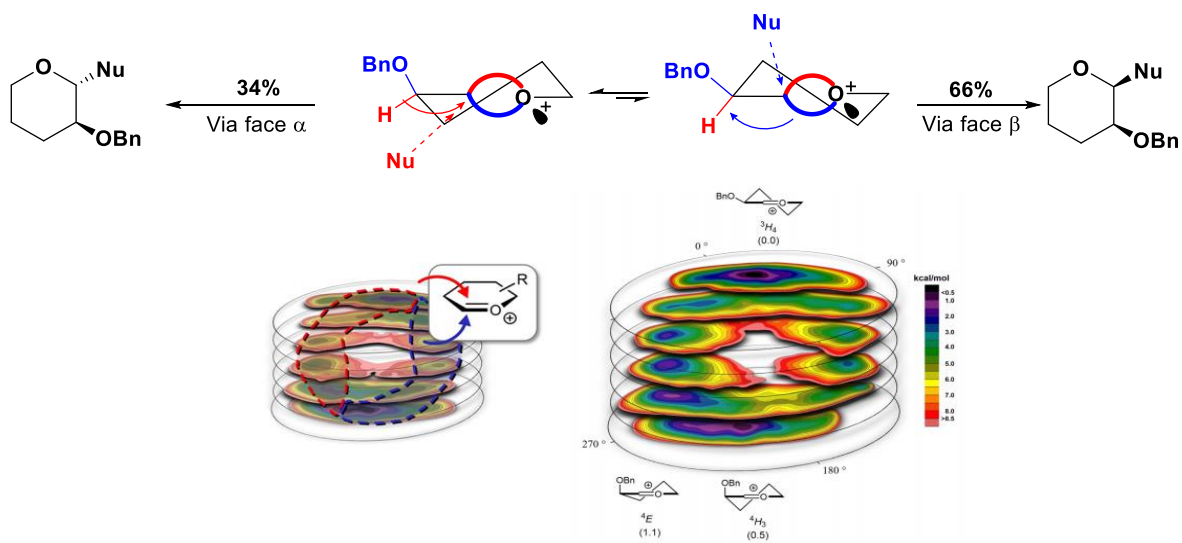
<sup>49</sup> Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910-3919.

<sup>50</sup> Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169.

<sup>51</sup> Plata, R. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 3811-3826.

rapidement, puisque la face  $\alpha$  favorisée énergétiquement est également celle de l'antiliante la plus faible des deux liaisons  $\tau$ . La conversion vers le produit 1,2-*cis* est donc plus rapide que le 1,2-*trans* puisque l'attaque sur la face  $\alpha$  est défavorisée par hyperconjugaison positive de la liaison C<sub>2</sub>-H dans la conformation <sup>3</sup>H<sub>4</sub>.

Ces résultats avec un système mobile simple sont corroborés par Codée et sa méthode somme toute plus complexe de carte topographique de réactivité, mais cette fois-ci appliquée au oxocarbenium pyranosides. Les cartes de réactivité sont légèrement plus élaborées que dans le cas des furanoses, puisqu'elle inclut également la face la plus prône à l'attaque d'un nucléophile en fonction de la conformation. Cette donnée supplémentaire génère donc un graphique énergétique tridimensionnel.<sup>52</sup> Le résultat présenté à la *Figure I.20* est analogue à celui présenté par Woerpel. Puisqu'il s'agit ici de l'énantiomère du composé présenté à la *Figure I.19*, c'est toutefois la demi-chaîne <sup>3</sup>H<sub>4</sub> qui prédomine. La sélectivité favorisant le



**Figure I.20** Glycosylation d'un pyranose C<sub>2</sub>-OBn substitué et carte énergétique correspondante reportée par Codée.<sup>52</sup>

<sup>52</sup> Hansen, T.; Lebedel, L.; Remmerswaal, W. A.; van der Vorm, S.; Wander, D. P. A.; Somers, M.; Overkleeft, H. S.; Filippov, D. V.; Désiré, J.; Mingot, A.; Bleriot, Y.; van der Marel, G. A.; Thibaudeau, S.; Codée, J. D. C. *ACS Cent. Sci.* **2019**, *5*, 781-788.

produit d'addition 1,2-*cis* se décrit à l'aide du même raisonnement que celui énoncé précédemment, c'est-à-dire par le modèle des liaisons courbes.

Les pyranoses consistent donc en un modèle plus précis/riche que peut l'être celui des furanoses en ce qui concerne la perception d'une participation stéréoelectronique des liaisons  $\tau$  dans la sélectivité faciale de la glycosylation  $S_N1$ . Les facteurs intrinsèques à la réactivité d'un pyrane sont plus facilement identifiables et qualitativement évalués par rapport au cas d'un furane. Il devient donc plus simple de rendre compte de ces différents facteurs lorsqu'un rationnel en fonction des liaisons courbes est mis de l'avant.

## La réaction de glycosylation $S_N1$ et ses conditions

En plus des restrictions géométriques et stéréoelectroniques à considérer dans chaque modèle moléculaire, la manière de conduire la réaction de glycosylation influence la sélectivité en soi puisque le choix des conditions peut moduler le ratio d'addition au carbone anomérique. L'implication peut être telle que le mécanisme de la réaction lui-même soit altéré. Le caractère  $S_N1$  de la glycosylation peut facilement être influencé par le choix du solvant, du nucléophile, des additifs présents dans la réaction et par la réactivité du donneur lui-même. Cela signifie donc qu'une réaction de glycosylation puisse difficilement être décrite avec exactitude à l'aide d'un mécanisme  $S_N1$ . La voie réactionnelle d'un ion oxocarbénium hautement réactif en produit de glycosylation s'inscrit davantage au sein d'un large spectre de réactivité oscillant entre  $S_N2$  et  $S_N1$ , et dont la position est dictée par l'agencement de tous les facteurs déterminants dans la réaction.<sup>53</sup> Les prochaines sous-sections serviront donc à décrire brièvement l'apport individuel de chacun de ces facteurs dans l'interprétation du mécanisme et de la sélectivité qui en découle. Cette discussion permettra de présenter la logique se situant derrière le choix des conditions de mise en œuvre des travaux et expériences réalisés dans le cadre de ma thèse.

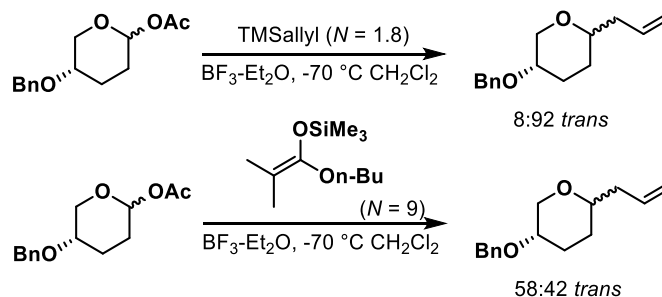
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<sup>53</sup> (a) Adero, P. O.; Amarasekara, H.; Wen, P.; Bohé, L.; Crich, D. *Chem. Rev.* **2018**, *118*, 8242-8284; (b) Bohé, L.; Crich, D. *Carbohydr. Res.* **2015**, *403*, 48-59.



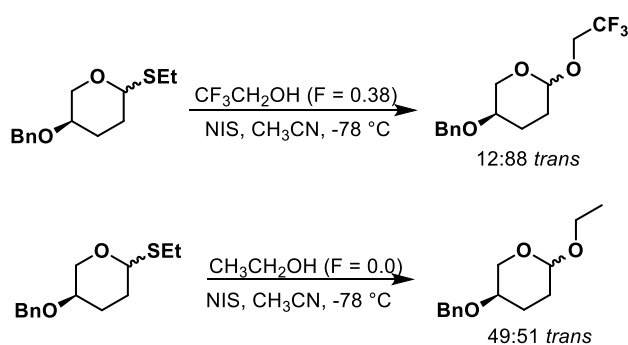
## Choix du solvant et des nucléophiles

Dans un contexte pleinement axé sur la chimie des glucides et la construction d'oligosaccharides complexes, il va de soi que les nucléophiles et les conditions réactionnelles sont adaptés afin de maximiser la sélectivité et le rendement. Les nucléophiles utilisés



**Figure I.21** Sélectivité de la C-glycosylation en fonction de la nucléophilie de l'accepteur (Nu).

sont alors de nature également glucidique et certains additifs sont utilisés afin d'orienter la sélectivité vers un produit spécifique. En revanche, l'approche doit être différente lorsque le but est d'évaluer la réactivité propre à un donneur via une route mécanistique tendant vers la  $S_N1$ . Tout d'abord, la force du nucléophile doit être considérée. Un nucléophile trop puissant tend à réagir dans un état de transition très tôt, c'est-à-dire dont la structure de l'état de transition ressemble davantage au produit de départ qu'au produit final. Dans le contexte où la formation d'un oxocarbénium est souhaité, un état de transition tôt sera plutôt perçu comme un état de transition/mécanisme  $S_N2$  exposé où la sélectivité sera guidée davantage par l'orientation du groupement anomérique que par les différents effets stéréoélectroniques et conformationnels propres au donneur. À l'inverse, la sélectivité d'un état de transition tard

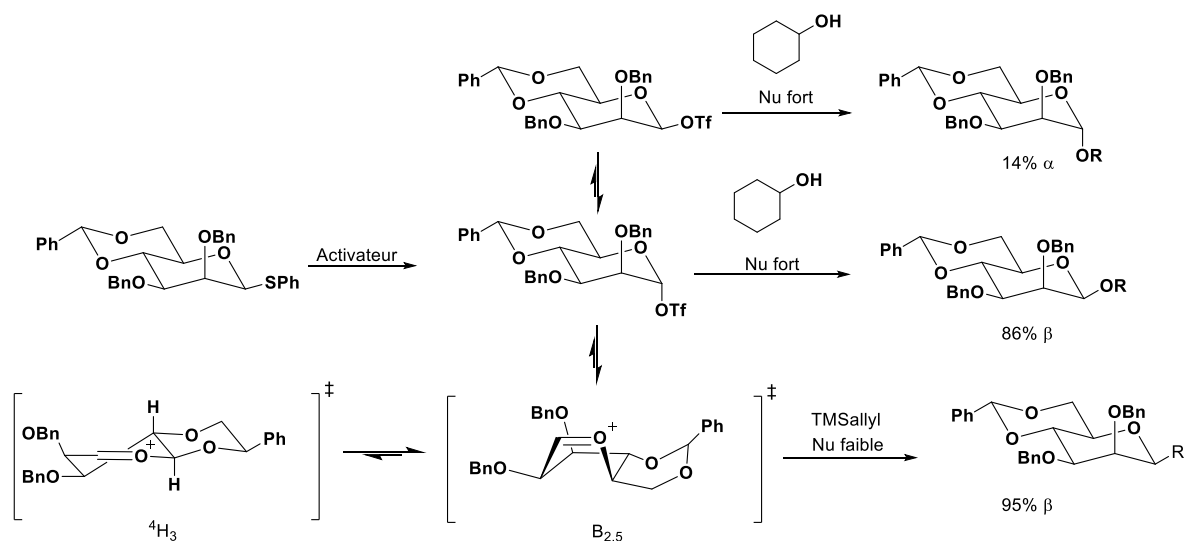


**Figure I.22** Sélectivité de la O-glycosylation en fonction de la nucléophilie de l'accepteur (Nu).

peut s'appliquer.<sup>54</sup> Woerpel a d'ailleurs démontré expérimentalement qu'un gain en nucléophilie mène à une diminution en sélectivité, puisque la vitesse de réaction approche la limite de diffusion des espèces dans le milieu. En d'autres termes, le nucléophile réagit immédiatement au contact d'une espèce glycosidique, qu'elle soit sous forme de

<sup>54</sup> Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497-510.

triflate ou d'ion oxocarbenium, et ce, sans tenir compte des autres facteurs. Cela s'apparente à un état de transition tôt. Les travaux de Woerpel à ce sujet s'étendent de la *C*-glycosylation<sup>41</sup> à la *O*-glycosylation<sup>55</sup> et les conclusions sont similaires pour les deux types de nucléophiles. La *Figure I.21* exemplifie ce cas dans lequel le TMSallyl avec un paramètre de nucléophilie *N* de 1.8 est plus sélectif que l'éther d'énol silylé davantage nucléophile avec un paramètre *N* de 9.<sup>56</sup> Dans le cas de la *O*-glycosylation, les ratios sont très similaires, bien que la nature du nucléophile et des conditions réactionnelles changent. Le nucléophile plus puissant est cependant moins sélectif, puisque l'état de transition est beaucoup plus tôt. Dans ce cas-ci néanmoins, la force du nucléophile est déterminée en extrapolant le paramètre d'induction de champ à la densité électronique de l'alcool (*Figure I.22*).<sup>57</sup> Une analyse similaire, mais plus élaborée a été proposée par Codée sur des glucides plus complexes en effectuant la glycosylation dans des conditions laissant place à la formation d'un triflate anomérique.<sup>58</sup> L'aspect rigide des donneurs étudiés 4,6-*O*-benzylidène glucose et mannose change également la donne en ce qui concerne la conformation adoptée à l'état de transition par l'ion



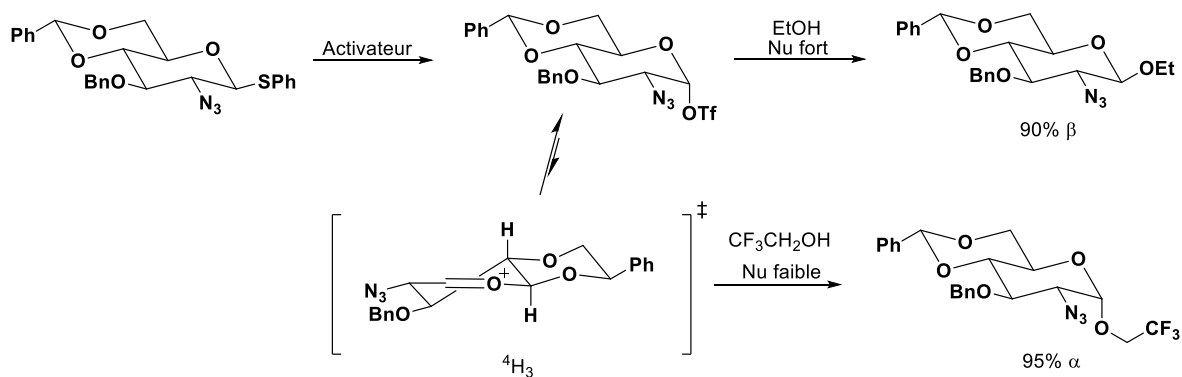
**Figure I.23** Sélectivité du 4,6-*O*-benzylidène mannose en fonction du nucléophile.

<sup>55</sup> Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118.

<sup>56</sup> Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.

<sup>57</sup> Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165-195.

<sup>58</sup> van der Vorm, S.; Hansen, T.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Sci.* **2017**, *8*, 1867-1875.

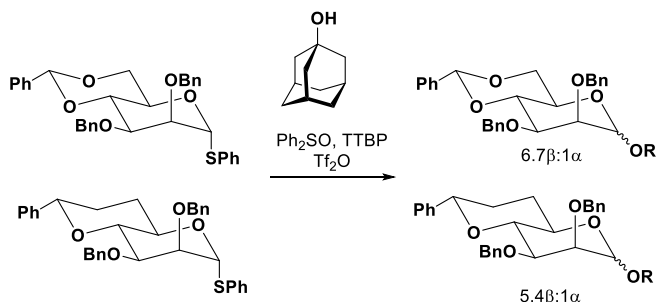


**Figure I.24** Sélectivité du 2-deoxy-2-azido-4,6-*O*-benzylidène glucose en fonction du nucléophile.

oxocarbénium. Dans les cas plus spécifiques des nucléophiles faibles TMSallyl et trifluoroéthanol mentionnés ci-haut, la sélectivité semble suivre l'orientation du groupement C<sub>2</sub>-OBn, menant aux produits de glycosylation 1,2-*cis*. Ces derniers étant trop faibles pour déplacer un triflate anomérique dans une quelconque orientation, la réaction opère plutôt par le biais d'une substitution S<sub>N</sub>1 sur l'ion oxocarbénium respectif de plus faible énergie du glucose (<sup>4</sup>H<sub>3</sub>) et du mannose (B<sub>2,5</sub>). Une sélectivité se traduisant donc par un état de transition tard. À l'opposé, par un état de transition tôt, les nucléophiles forts réagissent par une voie mécanistique plus proche de la S<sub>N</sub>2 en déplaçant un triflate anomérique plus stabilisé en  $\alpha$  par l'effet anomère (*Figure I.23*).<sup>59</sup> Codée a également renchéri sur l'inaptitude des nucléophiles faibles dans ces cas précis, en jouant sur la stabilité de l'état de transition par le biais d'analogues modifiés du glucose. En remplaçant le benzyle par un azoture ou une dinitropyridone, l'aspect fortement électroattracteur de ces groupements augmente la réactivité de l'ion oxocarbénium, ce qui accroît du même coup la propension à former un triflate anomérique.<sup>60</sup> Cela se traduit donc par une inversion complète de la sélectivité en fonction de la force du nucléophile. Un nucléophile fort emprunte alors un état de transition tôt par une réaction S<sub>N</sub>2 pour former le produit d'addition 1,2-*trans* dans un ratio 91:9, alors qu'un nucléophile faible nécessite la formation de la demi-chaîne <sup>4</sup>H<sub>3</sub> et attaque la face  $\alpha$  favorisée conformationnellement pour former le produit d'addition 1,2-*cis* (*Figure I.24*).

<sup>59</sup> Lemieux, R. U. *Pure Appl. Chem.* **1971**, 25, 527-548.

<sup>60</sup> van der Vorm, S.; Hansen, T.; van Hengst, J. M. A.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Soc. Rev.* **2019**, 48, 4688-4706.



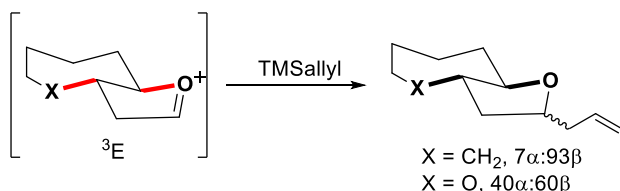
**Figure I.25** *O*-glycosylation du mannose en fonction de la nature de la position 7.

*O*-glycosylation, les donneurs de Codée sont activés par une combinaison beaucoup plus puissante de NIS/TfOH ou de Ph<sub>2</sub>SO/Tf<sub>2</sub>O permettant de générer le triflate. Tel que mentionné précédemment, cela témoigne d'une réactivité accrue des ions oxocarbéniums dans les modèles rigidifiés acétal 4,6, puisque les deux liaisons C-O sont orientées antipériplanaire à la liaison C<sub>5</sub>-O<sup>+</sup> et rend l'ion plus difficile à former. Ces observations sont d'un appui considérable à l'approche simplifiée utilisée avec donneurs de la *Figure I.12*, car en plus de retirer les liaisons dont l'hyperconjugaison est négative, l'ion oxocarbénium est maintenant enrichi par hyperconjugaison positive des liens σ C-C.<sup>61</sup> Une publication de Codée fait d'ailleurs mention d'un gain en stabilité de l'ion oxocarbénium du benzylidène mannose engendré par le remplacement de la liaison polarisée C<sub>6</sub>-O polarisée par un lien C-C (*Figure I.25*).<sup>62</sup> La sélectivité en β se trouve toutefois diminuée alors qu'on s'attendrait à une proportion plus grande de l'oxocarbénium B<sub>2.5</sub> et donc d'anomère β. Il faut cependant souligner que le choix du nucléophile laisse à désirer en raison de sa nature forte et très encombrée stériquement. Ces propriétés influencent fort probablement la sélectivité, particulièrement, lorsqu'elles sont comparées à celles du trifluoroéthanol.

Woerpel a également tenté l'expérience, mais de manière inverse en insérant cette fois un oxygène supplémentaire dans la structure d'un hydrindane.<sup>38b</sup> La sélectivité β très élevée en absence d'hétéroatome correspond au modèle d'attaque interne dans l'enveloppe favorisée <sup>3</sup>E. L'insertion de l'atome d'oxygène engendre de l'hyperconjugaison négative avec la liaison C<sub>5</sub>-O<sup>+</sup> de l'ion oxocarbénium à l'état de transition, le rendant plus réactif et, en bout

<sup>61</sup> Rauk, A.; Sorensen, T. S.; von Ragué Schleyer, P. *J. Chem. Soc., Perkin. Trans. 2* **2001**, 869-874.

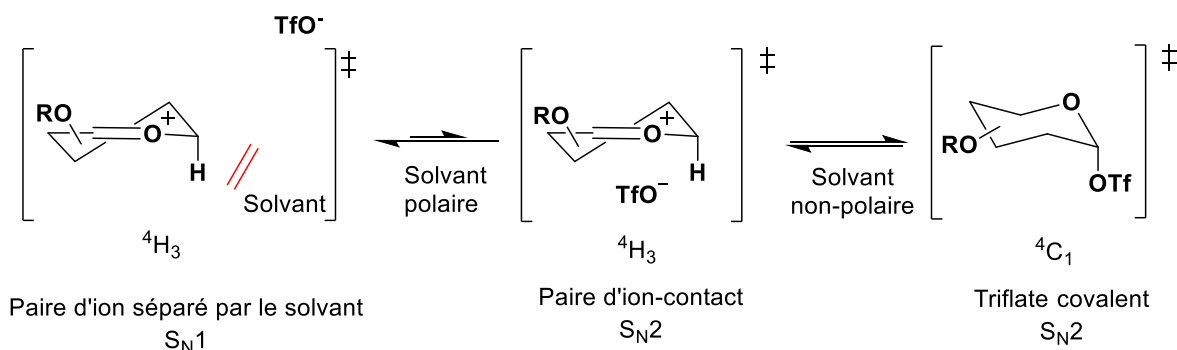
<sup>62</sup> Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.* **2013**, 78, 2191-2205.



**Figure I.26** Sélectivité diminuée par l'insertion d'un atome électroattracteur.

de ligne, diminuant la sélectivité (*Figure I.26*). La réaction procède alors par un état de transition plus tôt où les conformères développés à la suite d'une attaque interne ou externe n'ont plus d'incidence sur la sélectivité faciale.

D'une manière similaire, le solvant utilisé peut également moduler la réactivité de l'ion oxocarbénium. Un solvant plus polaire, comme l'acétonitrile, stabilise l'intermédiaire, ce qui peut induire un état de transition relativement tard. Crich<sup>53a</sup> et Woerpel<sup>63</sup> en décrivent d'ailleurs les effets. Ils ont démontré que le mécanisme de la réaction avoisine une réactivité  $S_N1$  par un intermédiaire se trouvant sous la forme d'une paire d'ions séparée par le solvant (*Figure I.27*). De surcroît, une stabilisation du genre peut également se manifester par une interaction covalente entre le solvant et l'intermédiaire chargé. Cet effet est particulièrement notable pour des glucides complets et rigides pour lesquels l'ion oxocarbénium est plus réactif. L'utilisation de l'acétonitrile y est reconnue pour accroître la sélectivité en  $\beta$  en générant un ion acétonitrilium en  $\alpha$  au carbone anomérique qui est par la suite déplacé par le nucléophile via un mécanisme  $S_N2$ .<sup>64</sup> Cet effet a été observé dans des cas particuliers qui seront décrits dans ce travail. En revanche, la sélectivité observée est inverse à celle généralement mentionnée dans la littérature. Or, l'effet engendré par le solvant dans le contexte de ce travail se décrit par une participation des liaisons courbes et possiblement de l'effet anomère inverse. Ces résultats seront élaborés dans les prochains chapitres.



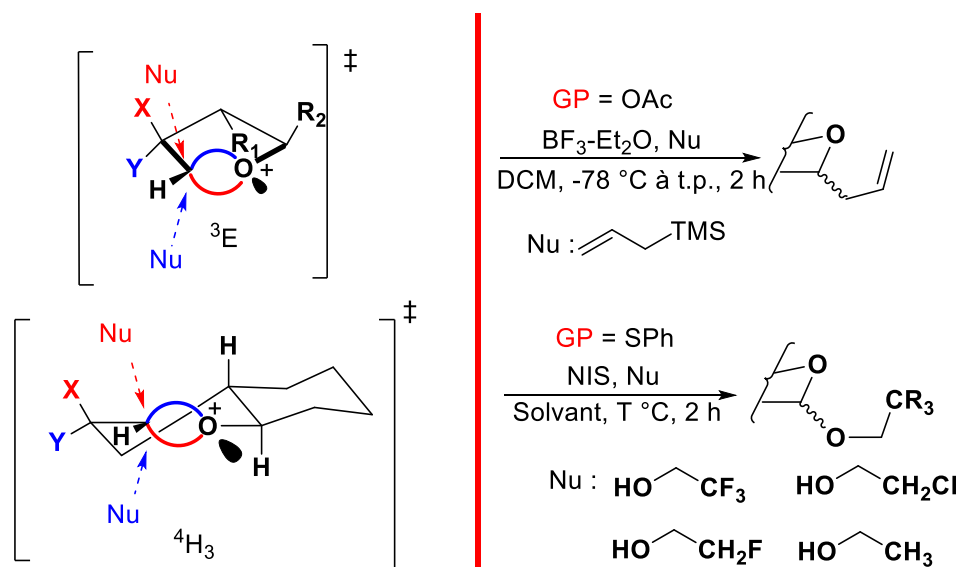
**Figure I.27** État de transition et mécanisme de glycosylation engendré par le solvant en présence d'un contre-ion triflate.

<sup>63</sup> Kendale, J. C.; Valentín, E. M.; Woerpel, K. A. *Org. Lett.* **2014**, *16*, 3684-3687.

<sup>64</sup> Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747-750.

## Évaluation de la méthode expérimentale

En somme, les donneurs présentés à la *Figure I.12* possèdent les propriétés chimiques nécessaires à l'évaluation du modèle de Pauling à l'aide de la réaction de glycosylation  $S_N1$ . Leur structure dépourvue d'oxygène en 3,4 et 6 permet la génération d'un oxocarbénium relativement stable. Cela permet le passage par une voie mécanistique plus proche de la réaction  $S_N1$  par un état de transition relativement tard comparément aux glucides complets. La rigidification du modèle permet toutefois de conserver une certaine réactivité de l'ion oxocarbénium en le contraignant dans une seule conformation à l'état de transition. L'état de transition général ne devrait donc pas être tard à un point tel où la sélectivité faciale est guidée uniquement par les facteurs conformationnels, stériques et stéréoélectroniques intrinsèques aux donneurs, mais également par la participation hyperconjuguante des groupements en  $C_2$  à travers une liaison  $\tau$  spécifique.



**Figure I.28** Conditions de glycosylation générales aux deux types de donneurs.

Les conditions réactionnelles (*Figure I.28*) de la glycosylation ont également été choisies en tenant compte des principes mentionnés ci-haut. C'est-à-dire que l'on omet l'utilisation de triflate pouvant stabiliser l'intermédiaire et induire une substitution  $S_N2$ . Des nucléophiles faibles nécessitant le passage par l'intermédiaire oxocarbénium ont également été utilisés par mécanisme  $S_N1$  cinétique. Il sera d'ailleurs démontré, en accord avec les résultats de Codée et Woerpel, que la sélectivité faciale diminue avec l'utilisation de nucléophiles plus

puissants. De plus, deux solvants de faible et forte polarité ont été utilisés dans le contexte de la *O*-glycosylation afin d'en décrire les effets sur la sélectivité. Les ratios rapportés pour chacune des transformations est établie sur la base du RMN  $^1\text{H}$  et  $^{19}\text{F}$  du mélange brut obtenu après lavage aqueux. La nature de chaque anomère est déterminée sur la base de la constante de couplage du proton anomérique lorsque possible et par expérience de couplage NOESY 1D lorsque nécessaire. La nature cinétique de la transformation est confirmée par des expériences de contrôle thermodynamique sur plusieurs jours et par mise en réaction des produits isolés aux conditions réactionnelles afin de démontrer qu'aucune anomérisation n'y prend initialement place.

## **Perspectives du modèle**

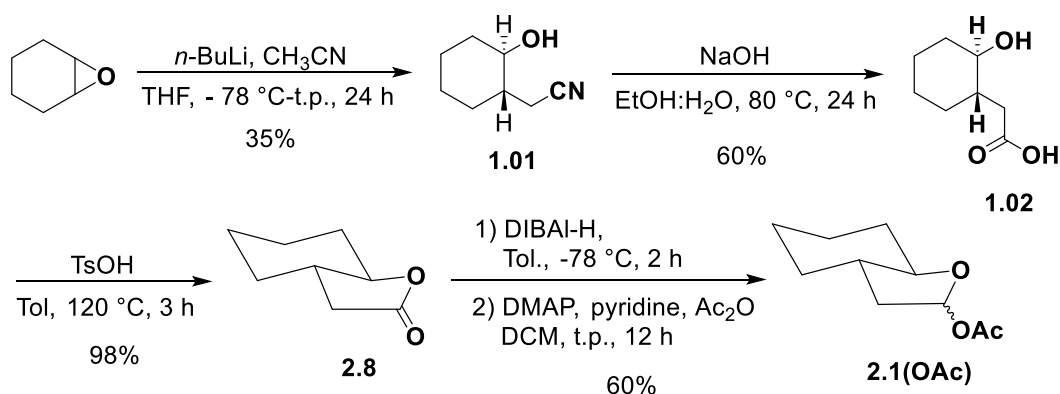
L'objectif ultime derrière la réalisation et la publication de ces travaux de doctorat est d'initier une habitude au sein de la communauté scientifique. Cette habitude est celle d'une ouverture au modèle des liaisons courbes, afin qu'il soit éventuellement appliqué pour résoudre les problèmes quotidiens de la chimie organique. Il pourra ainsi de plus en plus prendre racine dans la discipline, au point d'être un jour enseigné et transmis comme modèle équivalent à  $\sigma$ - $\pi$  plutôt que simple curiosité.

Tel qu'évoqué au début de l'introduction, il serait quelque peu exagéré d'insinuer que la version de la glycosylation présentée dans cette thèse et les résultats expérimentaux se traduisent par une application directe à la chimie des glucides. Évidemment, la simplification des donneurs crée un gouffre entre la réactivité de ces derniers et celle de l'analogue comportant tous ses oxygènes, ce qui rend la comparaison directe plus difficile. Il est néanmoins utile de simplifier un problème et d'en décortiquer chaque variable. Cela permet de déterminer avec une plus grande exactitude la participation individuelle de chacun des facteurs et d'approcher avec des connaissances plus soutenues un problème chimique récalcitrant qui, plus souvent qu'autrement, possède bien plus qu'une seule réponse.

# Chapitre 1 Bent Bond ( $\tau$ ) and the antiperiplanar hypothesis, and the reactivity at the anomeric center in pyranosides

## 1.1 Avant-Propos

Ce premier chapitre contient les travaux réalisés plus tard dans le cheminement de ce projet de thèse. La période d'induction s'est avérée longue et difficile. Les différentes routes de synthèse des donneurs ont pris un certain temps à établir et les conditions de glycosylation optimales pour les donneurs simplifiés ont dû être déterminées par essais et erreurs tout en s'inspirant de la littérature disponible à ce moment. Ce processus est frustrant lorsque la voie synthétique pour l'obtention du donneur est longue et fastidieuse.



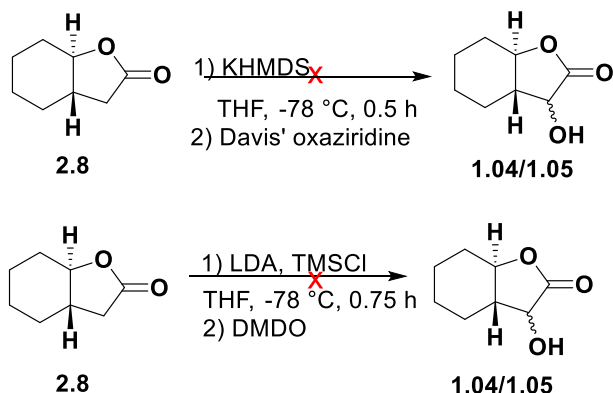
**Figure 1.1** Synthèse de la lactone bicyclique telle que rapportée par Woerpel.<sup>1</sup>

Le plan de synthèse considéré initialement pour l'obtention des donneurs substitués en C<sub>2</sub> a été établi avec l'intention d'exploiter les méthodes rapportées dans les travaux de Woerpel sur le modèle bicyclique furanoside (*Figure 1.3*).<sup>1</sup> Ce dernier sera plus amplement abordé au Chapitre 2. Dès les premières réactions, cette voie synthétique s'est avérée difficile à reproduire. Bien que l'ouverture de l'époxyde du cyclohexène soit la méthode la plus directe à l'obtention d'une jonction bicyclique trans, le produit d'addition de l'acétonitrile **1.01** et l'hydrolyse de ce dernier vers l'acide **1.02** se sont avérés beaucoup moins efficaces qu'attendu. La lactone **2.8** a tout de même été générée en quantité suffisante pour tenter d'introduire un oxygène en C<sub>2</sub>. Pour ce faire, plusieurs méthodes classiques d' $\alpha$ -hydroxylation empruntant

<sup>1</sup> Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152.



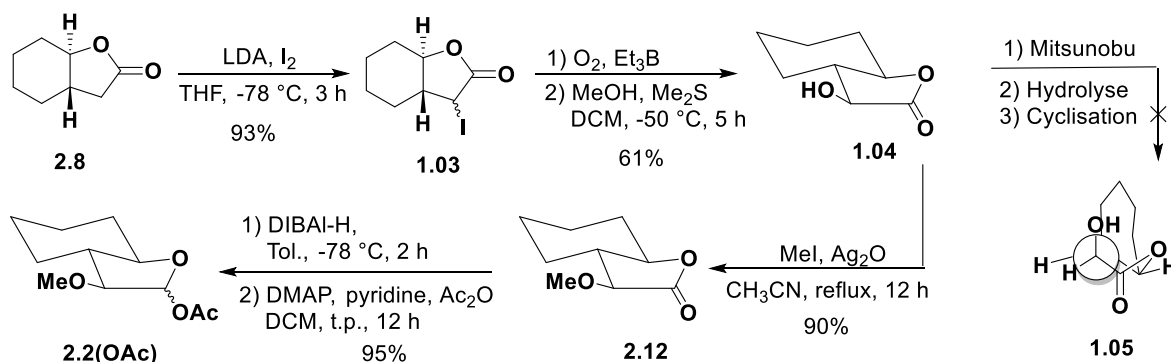
l'intermédiaire énolate ou énolate silylé ont été envisagées, mais sans succès (*Figure 1.2*). C'est finalement l'utilisation de l' $\alpha$ -iodo lactone **1.03** qui a permis la formation de l'alcool **1.04** par la génération du radical piégé en ion hydroperoxyde. Il est ensuite réduit en alcool à l'aide de  $\text{Me}_2\text{S}$  (*Figure 1.3*).<sup>2</sup> Toutefois, cette transformation n'a généré qu'un seul diastéréoisomère de l'alcool et dans des rendements généralement faibles. Une séquence



**Figure 1.2** Insertion direct de l'oxygène en C<sub>2</sub>.

employant la réaction de Mitsunobu a été étudiée, mais sans succès. La préparation d'un donneur de C-glycosylation et de O-glycosylation a alors été entreprise à partir de cette voie de synthèse afin d'obtenir les premiers résultats. Les conditions de glycosylation ont initialement été les mêmes pour les deux types de nucléophiles utilisés.

L'utilisation d'un acide de Lewis fort, le  $\text{BF}_3\text{-Et}_2\text{O}$ , sur un donneur dont le groupe sortant est un acétate est tout à fait appropriée dans le contexte de la C-glycosylation puisqu'il n'y a pas d'anomérisation possible au carbone anomère au cours de la transformation. Les mêmes conditions avec le même donneur ont été employées pour la O-glycosylation avec 2,2,2-trifluoroéthanol, ce qui a généré des composés dont le ratio anomérique était le produit d'un équilibre thermodynamique plutôt que d'une transformation cinétique. L'emploi d'un acide de Lewis venait donc invariablement biaiser le résultat. Pour remédier à ce problème et en

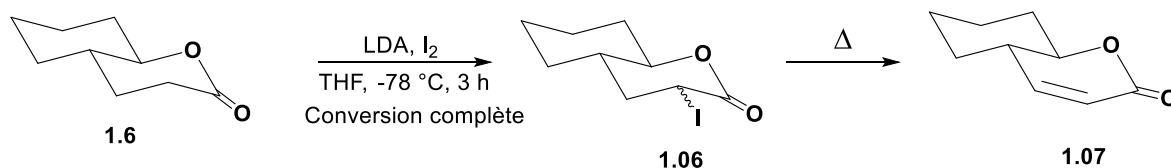


**Figure 1.3** Voie de synthèse initiale pour l'introduction d'un C<sub>2</sub>-OR en  $\alpha$  d'une lactone.

<sup>2</sup> Kihara, N.; Ollivier, C.; Renaud, P. *Org. Lett.* **1999**, *1*, 1419-1422.

s'inspirant encore une fois des travaux de Woerpel, l'utilisation d'un donneur soufré pouvant être activé par du NIS a été préconisée.<sup>3</sup>

Malgré des résultats intéressants, les difficultés rencontrées à la synthèse sur plus grande échelle des donneurs furanosides portant le OMe en C<sub>2</sub> et l'apparente complexité de l'analyse ont fait en sorte que ces substrats ont été mis au rancart pendant quelques années avant d'être réétudiés en profondeur. L'expérience acquise lors de l'étude des autres types de donneurs a permis une compréhension plus étoffée de leur réactivité. C'est pourquoi le premier article présenté dans cette thèse décrit des travaux effectués plus tard dans le cheminement. La synthèse des pyranoses bicycliques a débloqué la voie à une préparation plus efficace des furanoses, puisqu'il s'est avéré impossible d'effectuer la réaction de d'oxy/déhalogénéation radicalaire<sup>2</sup> sur la  $\delta$ -valérolactone **1.6**. En effet, le dérivé iodé **1.06** possédait une propension trop forte à l'élimination et se dégradait rapidement (*Figure 1.4*). Il a donc fallu repenser la stratégie de synthèse en introduisant l'oxygène correspondant plus tôt dans la synthèse et, conséquemment, construire la structure bicyclique avec le groupement C<sub>2</sub>-OR déjà en place.



**Figure 1.4** Génération de l' $\alpha$ -iodo  $\delta$ -valérolactone.

La synthèse élaborée et décrite dans ce chapitre pour les donneurs pyranosides C<sub>2</sub>-OBn a été très utile dans l'obtention des autres donneurs portant un groupement électroattracteur de type OR en C<sub>2</sub> (*Figure 1.12*). De plus, la simplicité et l'efficacité des transformations employées ont permis d'obtenir des quantités suffisantes de matériel pour plusieurs essais. Cela a permis une étude rigoureuse de la réaction de glycosylation et de ses différentes conditions en minimisant la resynthèse des différents donneurs.

Nous avons émis le présupposé selon lequel nous nous adressions à un lectorat connaissant peu – ou pas – le modèle de Pauling. En effet, cet article constitue à plus forte raison une initiation à la matière par le biais d'une étude expérimentale pour de nombreux lecteurs et

<sup>3</sup> Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118.

lectrices. Le ton de l'article se voulait donc dès les premières lignes clair et simple. Il propose également une mise en contexte théorique et historique du modèle, ce qui est peu fréquent dans les articles scientifiques conventionnels. On remarquera ici des croisements et des similitudes avec ce qui a été présenté en introduction à cette thèse. Néanmoins, nous avons jugé nécessaire ce retour à la source, en plus de l'étayer de références exhaustives, puisque, rappelons-le, nous présentons la légitimité d'un paradigme et, ce faisant, d'une nouvelle vision du monde et de la nature.

En ce qui concerne le choix du véhicule de publication, la *Royal Society of Chemistry* (RSC) et l'équipe derrière la mise en presse du journal *Organic and Biomolecular Chemistry* se sont montrées ouvertes dans le passé à la publication d'articles portant sur les liaisons courbes. Il semble donc y avoir une volonté particulière de ce journal et de cet éditeur de publier des recherches au contenu original. Nous avons donc cru bon de soumettre nos travaux à l'évaluation des examinateurs de OBC sous la forme présentée ci-dessous.

## 1.2 Résumé

La stéréosélectivité d'une addition nucléophile sur un oxocarbénium dérivé de bicyclics pyranosides modèles portant ou non un groupement C<sub>2</sub>-OR peut être rationalisée par l'utilisation de liaisons courbes jumelées à l'hypothèse antiperiplanaire en conjonction avec le concept d'hyperconjugaison comme un modèle alternatif d'interprétation de la structure et de la réactivité.

## 1.3 Abstract

The stereoselectivity of nucleophilic addition on oxocarbenium ions derived from bicyclic pyranoside model with or without a C<sub>2</sub>-OR group can be understood through the use of the bent-bond and the antiperiplanar hypothesis in conjunction with the concept of hyperconjugation as an alternative interpretive model of structure and reactivity.

## 1.4 Specific introduction

The reaction of an alcohol for instance, ethanol or a sugar having a free hydroxyl group as a nucleophile (described in the field of carbohydrates as acceptor) at the anomeric center ( $C_1$ ) of a glycoside (described as the donor) is the most important chemical transformation in the field of glycochemistry.<sup>4</sup> Numerous experimental studies<sup>5</sup> indicate that this apparently simple *O*-glycosylation step can take place through a large variety of reaction mechanism which spanned between that of a  $S_N2$ -like nucleophilic substitution in which the alcohol displaces the leaving group of an  $\alpha$  or a  $\beta$ -glycosyl donor and that of a direct  $S_N1$ -like nucleophilic addition of an alcohol on an oxocarbenium ion intermediate. As illustrated in *Figure 1.5*, preactivation of the leaving group of the donor is also necessary and although it can take place by protonation, modern glycosylation procedures which occur at low temperature, avoid such conditions in order to prevent acid equilibration of the final  $\alpha$  or  $\beta$ -glycoside product. In the case of *C*-glycosylation,<sup>6</sup> the reaction is believed to take place by a simple nucleophilic addition to the very reactive oxocarbenium ion because the reagents (allyltrimethylsilane, allyltributylstannane or silyl enol ether,) are poor nucleophiles unable to successfully undergo an  $S_N2$  displacement reaction directly on a glycosyl donor.

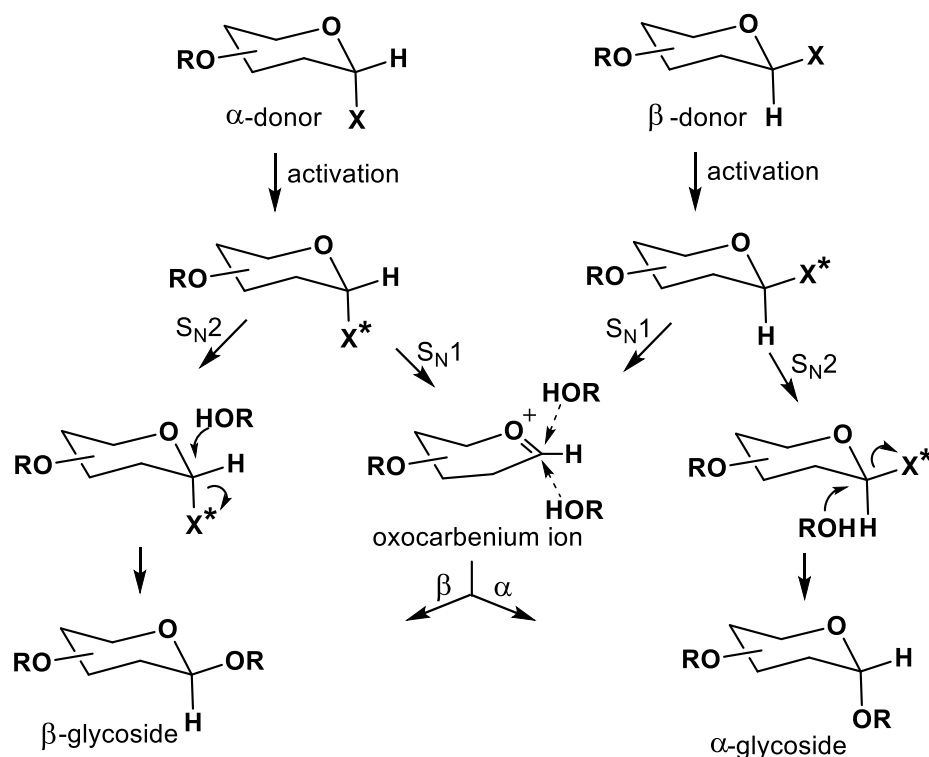
*Figure 1.5* is however an oversimplification of the reality since several other factors need to be considered at the glycosylation step. For instance, there is the possibility that a conformational change is taking place because the reaction may occur on a higher energy conformer than that of the ground state of the glycosyl donor (i.e. chair  ${}^4C_1$ ,  ${}^1C_4$  or twist-boat

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<sup>4</sup> (a) Demchenko, A. V. (Ed.), *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*, Wiley-VCH, **2008**; (b) Horenstein, N. A. *Adv. Phys. Org. Chem.* **2006**, *41*, 275- 314; (c) Miljković, M. *Carbohydrates: Synthesis, Mechanisms and Stereoelectronic Effects*, Springer, New York, **2010**.

<sup>5</sup> (a) Schmidt, R. R. *Angew. Chem., Int. Ed.* **1986**, *25*, 212-235; (b) Ranade, S. C.; Demchenko, A. V. *J. Carbohydr. Chem.* **2013**, *32*, 1-43; (c) Guo, J.; Ye, X.-S. *Molecules* **2010**, *15*, 7235-7265; (d) Zhu, X.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934; (e) Bohé, L.; Crich, D. *Carbohydr. Res.* **2015**, *403*, 48-59; (f) Miljković, M. *Electrostatic and Stereoelectronic Effects in Carbohydrate Chemistry*, Springer, New York, **2014**.

<sup>6</sup> (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169; (b) Ayala, L.; Lucero, C. G.; Antoinette, J.; Romero, C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521-15528; (c) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641-2647; (d) 4c chap. 5



**Figure 1.5** A general glycosylation mechanism.

$^1S_3$ ,  $^0S_2$ , etc)<sup>7</sup> or that of the corresponding oxocarbenium ion (half chair  $^4H_1$  or  $^1H_4$ ). In addition, the various inductive effect<sup>6</sup> resulting from the spatial orientation of the equatorial and axial OH or O-protected groups present at C<sub>3</sub>, C<sub>4</sub> and C<sub>6</sub> in the glycosyl donor or in the oxocarbenium ion can influence the reactivity of the anomeric center. Also, the non-bonding electron pairs of these oxygen substituents located at various positions of the carbohydrate structure, if appropriately oriented in space, can also electrostatically stabilize the positive charge<sup>8,9</sup> and that may induce a conformational change of the oxocarbenium ion ground state. In the case of an  $S_N1$ -like process and even an  $S_N2$ -like process, the angle of attack<sup>10</sup> and the strength of the nucleophile<sup>11</sup> must also be considered and since a given process can take place

<sup>7</sup> (a) Stoddart, J. F. *Stereochemistry of Carbohydrates*, Wiley-Interscience, Toronto, **1971**; (b) Bérces, A.; Whitfield, D.M.; Nukada, T. *Tetrahedron* **2001**, *57*, 477-491; (c) Dixon, H. B. F. *Pure & Appl. Chem.* **1981**, *53*, 1901-1905.

<sup>8</sup> (a) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195-1201; (b) 4c Chap. 4.

<sup>9</sup> Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597-7604.

<sup>10</sup> (a) Bürgi, H. B.; Dunitz J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065-5067; (b) Dunitz J. D.; Winkler, F. K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *31*, 251-263.

<sup>11</sup> Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118.

through an early or a late transition state,<sup>11</sup> this may indicate if steric repulsion between the nucleophile and the neighbouring substituents of the oxocarbenium ion plays a discriminating role favoring the formation of an  $\alpha$  or a  $\beta$ -glycoside.

Of course, polarity of the solvent may also induce a  $S_N1$  or a  $S_N2$  process.<sup>11</sup> The glycosylation reaction can be further complicated because the oxocarbenium ion could exist as a transient glycosyl donor intermediate with a very labile leaving group (e.g. glycosyl triflate) or the more or less equivalent contact-ion pair (CIP). The oxocarbenium ion could exist also as a solvent-separated ion pair (SSIP) and stereoselectivity can thus be analyzed while considering the CIP, transient glycosyl donor or SSIP situation.<sup>5e,12</sup> Stereoelectronic effects have also been proposed for the anomeric effect which in combination with steric effects can explain the relative stability of  $\alpha$  and  $\beta$ -glycosides, they are also useful to rationalize the reaction mechanism of glycosylation.<sup>13</sup> For instance, stereoelectronic factors like the antiperiplanar<sup>13</sup> versus the synperiplanar<sup>14</sup> nucleophilic addition to an oxocarbenium ion can be considered to explain which reaction trajectory will be energetically preferred.

In recent years, FMO based *ab initio* calculation<sup>15</sup> has been used to modulate transition structures of the glycosylation reaction and primary <sup>13</sup>C and <sup>3</sup>H kinetic isotope effects (KIE)<sup>16</sup> has also been carried out to obtain experimental information on the degree of positive charge at C<sub>1</sub> in the glycosylation step. Finally, it should be pointed out that only the well-established  $\sigma$ - $\pi$  bonding orbital model of the oxocarbenium ion has been considered so far in carbohydrate chemistry.

In 2011, we reported that using the Slater-Pauling bent bond model (*tau*-bonds,  $\tau$  bonds) in combination with the antiperiplanar hypothesis (BBAH) is a useful conceptual model to understand the conformation and reactivity of organic molecules containing carbonyl

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<sup>12</sup> Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144-1153.

<sup>13</sup> (a) Beaulieu, N.; Dickinson R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531-2536; (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, **1983**, Pergamon Press, Oxford; (c) Kirby, A. J. *The Anomeric Effect and Associated Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, **1983**.

<sup>14</sup> (a) Deslongchamps, P.; Jones, P. G.; Li, S.; Kirby, A. J.; Kuusela, S.; Ma, Y. *J. Chem. Soc., Perkin Trans. 2*, **1997**, 2621-2626; (b) Li, S.; Deslongchamps, P. *Tetrahedron Lett.* **1993**, *34*, 7757-7758; (c) Li, S.; Deslongchamps, P. *Tetrahedron Lett.* **1993**, *34*, 7759-7762.

<sup>15</sup> Withfield, D. M. *Adv. Carbohydr. Chem. Biom.* **2009**, *62*, 83-159.

<sup>16</sup> Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D. A.; Crich, D. *Nat. Chem.* **2012**, *4*, 663-667.

group.<sup>17</sup> Realizing that oxocarbenium ion are O-alkylated derivative of ketones, we recently became interested to see if the  $\tau$  bond orbital model could be useful as an alternative to the  $\sigma$ - $\pi$  model while providing a new approach to the understanding of the key parameters which govern the glycosylation reaction. The Bent-Bond-Antiperiplanar hypothesis as a new interpretive model in conjunction with the concept of hyperconjugation<sup>18</sup> is discussed next.

## 1.5 $\sigma$ - $\pi$ versus $\tau$ bond electronic models

Carbonyl groups can either be expressed by the familiar Hückel  $\sigma/\pi$  orbital construct<sup>19</sup> or by the Slater-Pauling bent bond model,<sup>20</sup> which is based on two equivalent  $\tau$  bonds (*Figure 1.6*).<sup>21</sup> There is however a fundamental difference between the  $\sigma/\pi$  and the  $\tau$  bond model. In the first model, the  $\pi^*$  antibonding lobes above and below the plane of the carbonyl group correspond to the same  $\pi^*$  orbital. In the second model, the two antibonding orbitals correspond to two different  $\tau^*$  orbitals, one above and one below the plane of the carbonyl group. As a result, the  $\tau$  bond model confers a tetrahedral character to the carbonyl group. By considering the antiperiplanar hypothesis, a nucleophile will add by interacting with a  $\tau^*$  antibonding orbital displacing the corresponding antiperiplanar  $\tau$  bond in the same manner as a  $S_N2$  reaction displaces a leaving group on a saturated system. We previously explained the nucleophilic addition on cyclohexanone and adamantanone derivatives in this manner.<sup>17</sup> The  $\tau$  bond model provides a very simple and clear alternative to the Cieplak effect<sup>22</sup> or the

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<sup>17</sup> Deslongchamps, G.; Deslongchamps, P. *Org. Biomol. Chem.* **2011**, *9*, 5321-5333.

<sup>18</sup> (a) Rauk, A.; Sorensen, T. S.; von Ragué Schleyer, P. *J. Chem. Soc., Perkin. Trans. 2* **2001**, 869-874; (b) Rauk, A.; Sorensen, T. S.; Maerker, C.; Carneiro, J. W. d. M.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1996**, *118*, 3761-3762; (c) von R. Schleyer, P.; de M. Carneiro, W.; Koch, W.; Forsyth, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 3990-3992; (d) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910-3919; (e) Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 3447-3449.

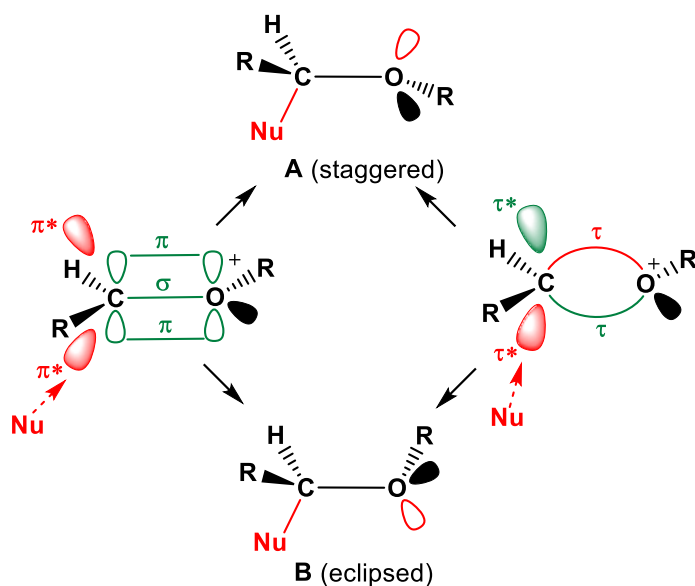
<sup>19</sup> Huckel, E. *Z. Phys.* **1930**, *60*, 423-456.

<sup>20</sup> (a) Slater, J. C. *Phys. Rev.* **1931**, *37*, 481-489; (b) Pauling, L. *J. Am. Chem. Soc.* **1931**, *53*, 1367-1400

<sup>21</sup> Although, the Hückel model has gained wide adoption, both models are quantitatively equivalent from the standpoint of molecular orbital theory, each being interconvertible via unitary transformation of the basic atomic orbital function. The requisite hybridization for forming bent bonds can be rationalized starting from a typical  $sp^2$  hybridized system. Linear combination of one of the  $sp^2$  orbital with the remaining pz orbital produces two orbitals with proper geometries for formation of bent bonds with another atom of similar hybridization. Indeed, re-hybridizing one  $sp^2$  orbital with one p orbital yields 2 hybrids  $\tau$  orbital each with 1/6 s character and 5/6 p character. The bent bond model also accounts for the observed bond length and angles in a wide variety of compounds. (a) Pauling, L. *J. Am. Chem. Soc.* **1931**, *53*, 1367-1400; (b) Robinson, E. A.; Gillespie, R. J. *J. Chem. Educ.* **1980**, *57*, 329-333.

<sup>22</sup> (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552; (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447-8462.





**Figure 1.6** *Anti* and *Syn* periplanar addition on s-p and t bond.

Inomata's *syn* effect.<sup>23</sup> Consequently, the nucleophilic addition yields a product directly in the more stable conformation **A** (Figure 1.6). With the  $\sigma$ - $\pi$  bonding model, one must postulate that the nucleophilic addition on an oxocarbenium ion must develop an oxygen lone pair antiperiplanar to the incoming nucleophile to yield the product in the staggered **A** conformation. The alternative synperiplanar nucleophilic addition

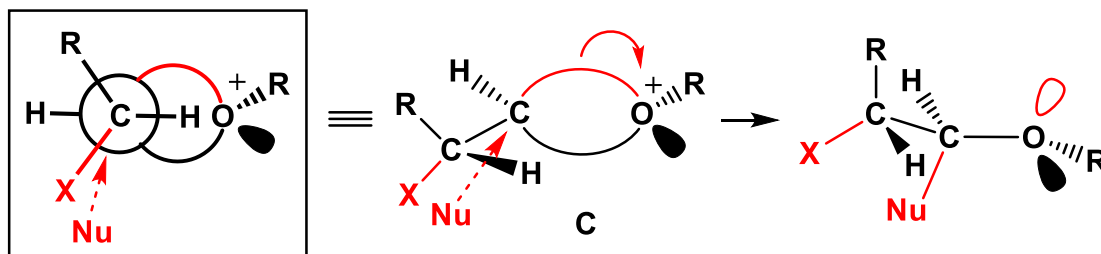
can be eliminated using both electronic bonding models because the product is formed directly in the higher energy eclipsed conformation **B**. A similar situation<sup>17</sup> is occurring in the E<sub>2</sub> elimination reaction forming an olefin. In the *anti* elimination, the reacting molecule is in the lower energy staggered conformation while the *syn* elimination is normally less favorable because the reacting molecule must be in the higher energy eclipsed conformation. While assuming antiperiplanarity of all reaction groups, the *syn* elimination is believed to occur via what is known as a "double inversion pathway" according to Ingold and Sicher<sup>24</sup> in order to avoid the eclipsed conformation. We have also recently shown<sup>25</sup> that product stereoisomers formed in [1,3]-sigmatropic thermal rearrangements can be explained by the preferential formation of staggered over eclipsed conformers of intermediate diradical.

<sup>23</sup> Inomata, K. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 1172-1182 and references therein.

<sup>24</sup> (a) Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1937**, 1208-1236; (b) Sicher, J.; Zavada, J.; Krupicka, J. *Tetrahedron Lett.* **1966**, *7*, 1619-1625

<sup>25</sup> Deslongchamps G.; Deslongchamps, P. *Org. Biomol. Chem.* **2016**, *14*, 7754-7767.

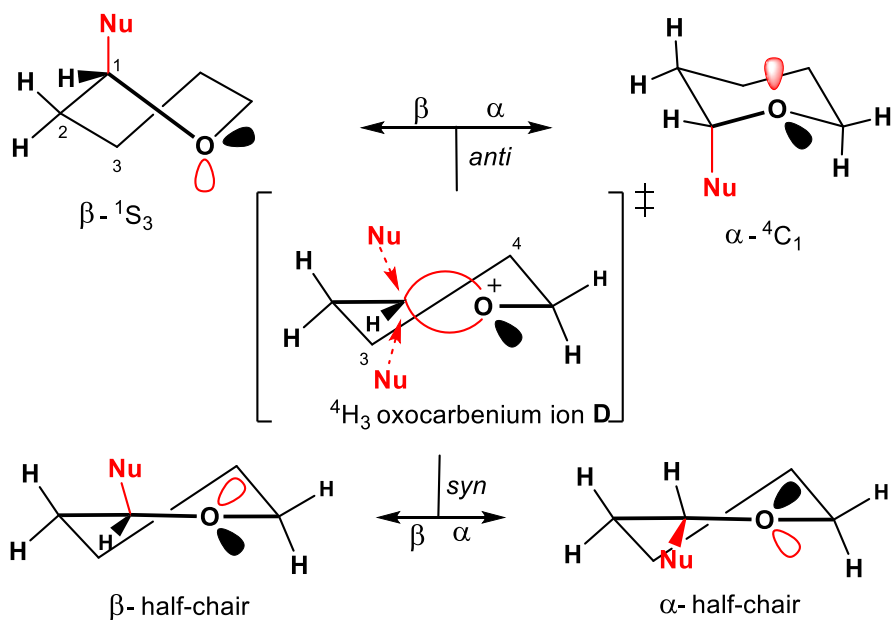
A difference between the  $\sigma$ - $\pi$  and the  $\tau$  bond models appears when the oxocarbenium ion is in a specific chiral environment opening the possibility of face diastereoselectivity. This situation happens when there is an adjacent chiral center at C<sub>2</sub> bearing an electron withdrawing group (EWG) and an electron donating group (EDG). As indicated in the most stable staggered conformation **C** of an oxocarbenium ion (Figure 1.7), the  $\tau$  bond above the plane is oriented antiperiplanar to the polar C-X bond and thus can withdraw electronic



**Figure 1.7** Stereoelectronically preferred nucleophilic addition.

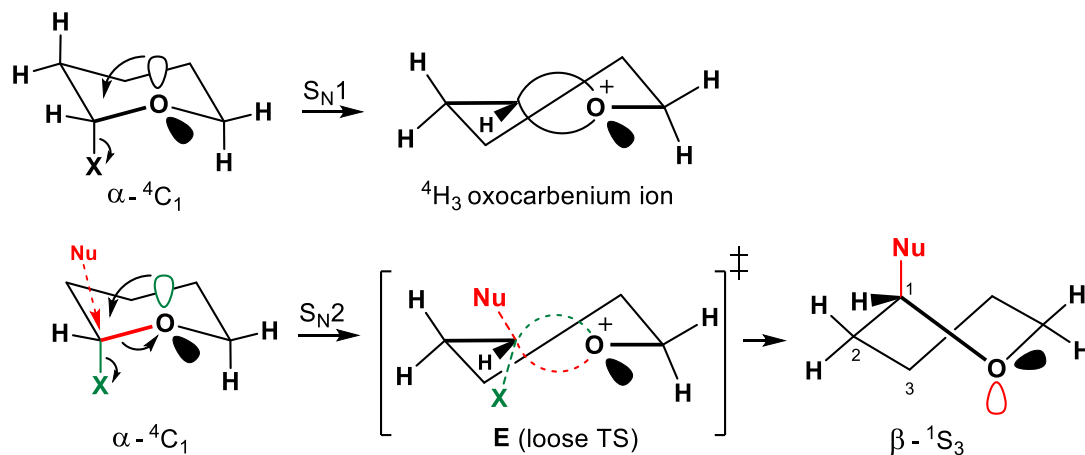
density of that  $\tau$  bond by hyperconjugation.<sup>18</sup> On the other hand, the  $\tau$  bond below is more electron rich because it is antiperiplanar to the C-R bond of the EDG. Consequently, the nucleophile will preferably displace the weaker  $\tau$  bond below the plan as shown. Stereoselective nucleophilic addition on aldehyde or ketone having an  $\alpha$  chiral group with an electron withdrawing group was first observed by Cornforth.<sup>26a</sup> A remarkable experimental and theoretical study of stereocontrol in aldol addition reactions of methyl ketone-derived enolates and aldehydes containing an  $\alpha$ -alkoxy stereocenter was reported by Evans and his co-workers.<sup>26b,c</sup> The Cornforth-Evans transition model which is proposed to rationalize these results corresponds essentially to transition state model **C**.

<sup>26</sup> (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112-127; (b) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1761-1765; (c) Siska, S. J.; Cee, V. J.; Evans, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9433-9441; (d) See Also: <https://youtu.be/h1biL-1o394>.



**Figure 1.8** *Anti* and *syn* periplanar addition on  ${}^4\text{H}_3$ -oxocarbenium ion.

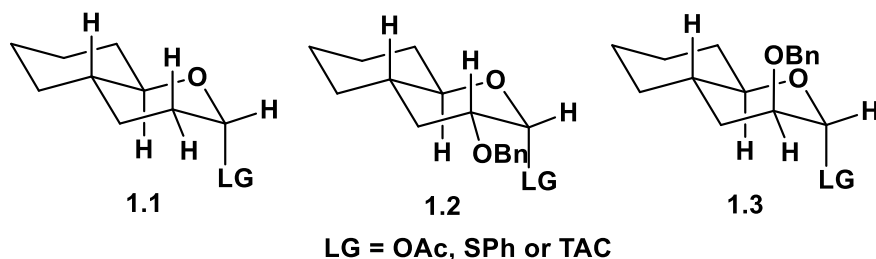
A preferential face selectivity can also occur due to a different conformational environment. This is the case for cyclic intermediate like the  ${}^4\text{H}_3$  six-membered oxocarbenium ion **D** (Figure 1.8). By applying the antiperiplanar hypothesis, the nucleophilic addition below and above the plane leads automatically to the  ${}^4\text{C}_1$  chair and the  ${}^1\text{S}_3$  twist-boat conformers of the  $\alpha$  and  $\beta$ -anomers respectively; the former process being energetically favored for conformational reasons. These two pathways follow a trajectory in which an oxygen lone pair develops antiperiplanar to the attacking nucleophile in the reaction product.<sup>13</sup> Note that



**Figure 1.9**  $\text{S}_{\text{N}}1$  vs  $\text{S}_{\text{N}}2$  with t bonds.

in oxocarbenium **D**, both hydrogens at C<sub>2</sub> are each antiperiplanar to a different  $\tau$  bond contributing equally to the electronic density of the two  $\tau$  bonds. Also, a synperiplanar addition of the nucleophile leads to a half-chair conformation which is energetically higher than the chair or the twist-boat just described. In cyclohexane, the half-chair and the twist-boat are respectively ~10 and ~5-6 kcal/mol higher in energy than the chair conformation. In addition, the nucleophilic trajectory for the  $\tau$  bond model<sup>17</sup> follows exactly the Bürgi-Dunitz angle<sup>10</sup> which was deduced from X-rays experimental studies. It is also pertinent to realize that the  $\tau$  bond model can be used to propose an almost identical geometry for the transition structure of the S<sub>N</sub>1 and the S<sub>N</sub>2 reaction as illustrated in *Figure 1.9*. In S<sub>N</sub>1, the axially oriented leaving group is ejected by an antiperiplanar oxygen lone pair generating the oxocarbenium ion.<sup>17</sup> In the S<sub>N</sub>2 reaction, the nucleophile starts to form a bond prior to the complete ejection of the leaving group by the oxygen lone pair.<sup>17</sup> Thus, the C<sub>1</sub>-O  $\tau$  bond and the oxygen lone pair of the anomeric center are both involved in the transition structure **E** which can be classified a loose transition state.<sup>4(b),27</sup> Note again that the Bürgi-Dunitz angle<sup>10</sup> for the nucleophilic addition and the leaving group ejection is now respected in the S<sub>N</sub>2 process. With the  $\sigma$ - $\pi$  model, the nucleophilic reaction must start by an interaction with the antibonding  $\pi^*$  orbital of the oxocarbenium ion which knowledge of the spatial orientation comes from *ab initio* calculation.

In order to test the validity of the  $\tau$  bond model and in order to limit the number of conformations of the pyranose ring, we have first studied the glycosylation reaction of bicyclic pyranoside donors **1.1-1.3** which exist in their ground state <sup>4</sup>C<sub>1</sub> chair conformation,



**Figure 1.10** Bicyclic pyranoside donors **1.1-1.3**.

<sup>27</sup> (a) Sinnott, M. L. *Chem. Rev.* **1990**, *90*,1171-1202; (b) Zechel D. L; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11-18; (c) Chan, J. F; Sannikova, N; Tang, A; Bennett, A. J. *J. Am. Chem. Soc.* **2014**, *136*, 12225-12228.

the *trans* junction of the two six-membered rings preventing chair inversion (*Figure 1.10*). In addition, the bicyclic models **1.1-1.3** are heavily truncated due to the absence of exocyclic hydroxyl groups or derivatives which are normally present at C<sub>3</sub>, C<sub>4</sub>, and C<sub>6</sub> in carbohydrates. The choice of these models is thus to eliminate the influence of these oxygen substituents so that the  $\tau$  bond model can be tested on a <sup>4</sup>C<sub>1</sub> pyranoside without exocyclic OR groups and only with the presence of an equatorial or axial O-benzyl group at C<sub>2</sub> which could influence the glycosylation step through hyperconjugation. We also felt that pyranoside donors **1.2-1.3** can be considered 3,4,6-deoxy models of 4,6-O-benzylidene<sup>28</sup> (or 4,6-O-silylene)<sup>29</sup> of glucose and mannose donors which on glycosylation are respectively  $\alpha$  and  $\beta$ -selective. Results obtained in the glycosylation of **1.1-1.3** donors could thus be useful to understand several of the factors which control the  $\alpha$ -gluco and  $\beta$ -manno stereoselectivity.

We thus wish to report herein a study on the *C*- and *O*-glycosylation of the three racemic bicyclic pyranoside models **1.1**, **1.2**, and **1.3** having an OAc or a SPh group at the anomeric center. We have also studied pyranosides **1.2** and **1.3** having a trichloroacetimidate (TCA) group.

## 1.6 Synthesis of bicyclic pyranosides donors 1.1-1.3

The model substrates **1.1-1.3** were prepared starting with cyclohexene oxide which gave a direct access to *trans* substituted and easily derivable 2-allylcyclohexanol intermediate **1.4** by epoxide opening (*Figure 1.11*).<sup>30a</sup> In order to obtain the desired unsubstituted bicyclic pyranoside **1.1**, the allylic compound was placed under hydroboration-oxidation conditions to yield 1,5 diol **1.5**. The *trans* fused six membered bicyclic lactone **1.6** was obtained by selective  $\delta$ -oxidative lactonisation of the 1,5 diol using 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) and (Diacetoxyiodo)benzene (BAIB) in 85% yield.<sup>30b</sup> The lactone was further

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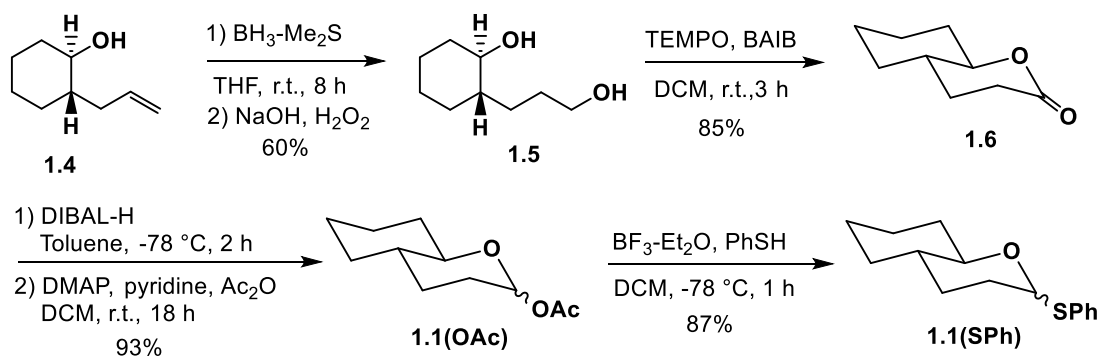
<sup>28</sup> (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506-4507; (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198; (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435; (d) Crich D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926.

<sup>29</sup> (a) Heuckendorff, M.; Bendix, J.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2014**, *16*, 1116-1119; (b) Heuckendorff, M.; Bols, P. S.; Barry, C. B.; Frihed, T. G.; Pedersen, C. M.; Bols, M. *Chem. Commun.* **2015**, *51*, 13283-13285.

<sup>30</sup> (a) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152; (b) Ebine, M.; Suga, Y.; Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2010**, *8*, 39-42; (c) Furukawa, K.; Shibuya, M.; Yamamoto, Y. *Org. Lett.* **2015**, *17*, 2282-2285.

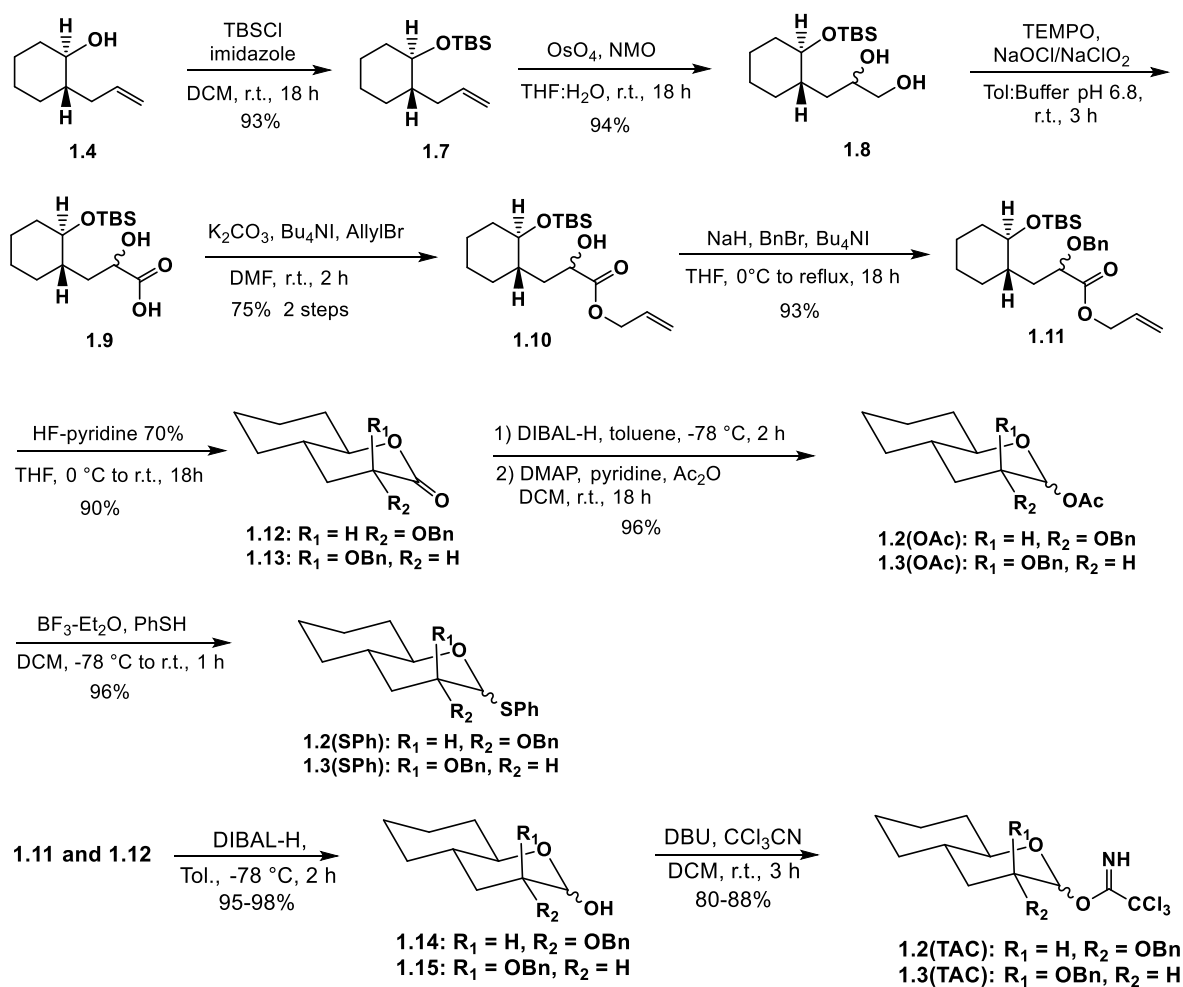
reduced and acetylated in a one-pot reaction using DIBAL-H followed by a standard acetylation procedure to yield acetoxy donor **1.1(OAc)**, which was used to obtain bicyclic donor **1.1(SPh)** ( $\alpha/\beta = 88:12$ ).

Usual  $\alpha$ -hydroxylation methods did not provide C<sub>2</sub> substituted intermediates directly from lactone **1.6**. To access the C<sub>2</sub>-OBn derivatives, a different sequence had to be developed. Compound **1.4** was first protected using TBSCl. The use of this protecting group was helpful for purification of subsequent reactions, decreasing the polarity of products, facilitating their isolation. The silylated alcohol **1.7** was then submitted to dihydroxylation conditions with catalytic OsO<sub>4</sub> to give a high yield of the vicinal diol **1.8** in a 60:40 diastereoisomeric ratio. A selective oxidation of the terminal alcohol using TEMPO in the presence of NaOCl/NaClO<sub>2</sub> in a biphasic media provided efficiently the  $\alpha$ -hydroxy carboxylic acid which was converted into allylic ester **1.10**.<sup>30c</sup> Prior to ring closure, the alcohol was benzylated to compound **1.11**. Deprotection of the silylated secondary alcohol using excess 70% HF-



**Figure 1.11** Synthesis of donors **1.1**.

pyridine carried in 18 h at room temperature provided directly the two  $\alpha$ -benzyloxy **1.12** and **1.13** in a 6:4 diastereomer ratio which were separated by chromatography. Their stereochemistry was established by <sup>1</sup>H NMR spectroscopy. Both isomers **1.12** and **1.13** were either reduced and acetylated to yield the bicyclic acetate donors **1.1(OAc)** and **1.3(OAc)** or reduced to the corresponding lactol **1.14** and **1.15** with DIBAL-H. The **1.2(OAc)** and **1.3(OAc)** donors were converted into the corresponding **1.2(SPh)** and **1.3(SPh)** donors using the reaction conditions for donors **1.1(SPh)**. Lactols **1.14** and **1.15** were converted further to



**Figure 1.12** Synthesis of donors **1.2** and **1.3**.

trichloroacetamide donors **1.2(TAC)** and **1.3(TAC)** efficiently using DBU and trichloroacetonitrile. The synthesis of donor **1.1(TAC)** was not successful, the final product being unstable under the reaction conditions. In 2-deoxy derivatives, the electron donating ability of the ring oxygen is strong and can easily eject a good leaving group like TAC. Accordingly, the acid hydrolysis of methyl-2-deoxy- $\alpha$ -D-glucopyranoside is much faster ( $\sim 2 \times 10^3$ ) than the corresponding glucose derivative.<sup>31</sup>

## 1.7 Glycosylation experiments

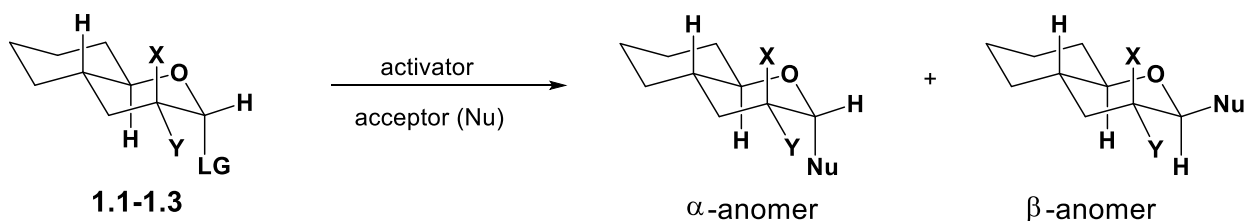
Results of glycosylation of donors **1.1-1.3** are shown in *Table 1.1*. C-Glycosylation was carried out with allyltrimethylsilane in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ .<sup>6</sup> In *O*-

<sup>31</sup> Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429-3440.

glycosylation, donor **1.1(SPh)** was reacted with N-iodosuccinimide in CH<sub>2</sub>Cl<sub>2</sub> at -78°C<sup>6</sup> and in CH<sub>3</sub>CN at -40°C to -20°C.<sup>11</sup> Donors **1.2** and **1.3(SPh)** were reacted at -40°C to -20°C in both CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN using the same conditions. Three alcohols with increasing



**Table 1.1** Glycosylation of bicyclic donors **1.1-1.3**.



<u>Entry</u>	<u>Dnr</u>	<u>LG</u>	<u>Nu</u>	<u>T°C</u>	<u>S</u>	<u>Y</u>	<u><math>\alpha:\beta</math> ratio</u>
1	1.1 (X=Y=H)	OAc	TMSAlyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	88%	$\alpha$ only
2	"	SPh (77 $\alpha$ :23 $\beta$ )	CF <sub>3</sub> CH <sub>2</sub> OH	-78	"	Qnt	88:12
3	"	SPh (60 $\alpha$ :40 $\beta$ )	"	-40	CH <sub>3</sub> CN	Qnt	95:5
4	"	SPh (77 $\alpha$ :23 $\beta$ )	ClCH <sub>2</sub> CH <sub>2</sub> OH	-78	CH <sub>2</sub> Cl <sub>2</sub>	96%	62:38
5	"	SPh (60 $\alpha$ :40 $\beta$ )	"	-40	CH <sub>3</sub> CN	82%	90:10
6	"	SPh (77 $\alpha$ :23 $\beta$ )	CH <sub>3</sub> CH <sub>2</sub> OH	-78	CH <sub>2</sub> Cl <sub>2</sub>	61%	45:55
7	"	SPh (60 $\alpha$ :40 $\beta$ )	"	-40	CH <sub>3</sub> CN	81%	72:28
8	1.2 (X=H, Y=OBn)	OAc	TMSAlyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	96%	$\alpha$ only
9	"	SPh (60 $\alpha$ :40 $\beta$ )	CF <sub>3</sub> CH <sub>2</sub> OH	-40 to -20	"	93%	83:17
10	"	SPh ( $\alpha$ only)	"	"	CH <sub>3</sub> CN	77%	$\alpha$ only
11	"	SPh (60 $\alpha$ :40 $\beta$ )	ClCH <sub>2</sub> CH <sub>2</sub> OH	"	CH <sub>2</sub> Cl <sub>2</sub>	93%	63:34
12	"	SPh ( $\alpha$ only)	"	"	CH <sub>3</sub> CN	87%	60:40
13	"	SPh (60 $\alpha$ :40 $\beta$ )	CH <sub>3</sub> CH <sub>2</sub> OH	"	CH <sub>2</sub> Cl <sub>2</sub>	93%	50:50
14	"	SPh ( $\alpha$ only)	"	"	CH <sub>3</sub> CN	97%	35:65
15	"	TCA (45 $\alpha$ :55 $\beta$ )	CF <sub>3</sub> CH <sub>2</sub> OH	-78	CH <sub>2</sub> Cl <sub>2</sub>	78%	80:20
16	"	"	CH <sub>3</sub> CH <sub>2</sub> OH	"	"	91%	45:55
17	1.3 (X=OBn, Y=H)	OAc ( $\beta$ only)	TMSAlyl	"	CH <sub>2</sub> Cl <sub>2</sub>	93%	95:5
18	"	OAc ( $\alpha$ only)	"	"	"	82%	85:15
19	"	SPh (90 $\alpha$ :10 $\beta$ )	CF <sub>3</sub> CH <sub>2</sub> OH	-40 to -20	"	86%	65:35
20	"	SPh ( $\beta$ only)	"	"	"	85%	68:32
21	"	"	"	"	CH <sub>3</sub> CN	88%	78:22
22	"	SPh ( $\alpha$ only)	"	"	"	88%	82:18
23	"	SPh (90 $\alpha$ :10 $\beta$ )	ClCH <sub>2</sub> CH <sub>2</sub> OH	"	CH <sub>2</sub> Cl <sub>2</sub>	98%	66:34
24	"	SPh ( $\beta$ only)	"	"	CH <sub>3</sub> CN	98%	62:38
25	"	SPh (90 $\alpha$ :10 $\beta$ )	CH <sub>3</sub> CH <sub>2</sub> OH	"	CH <sub>2</sub> Cl <sub>2</sub>	93%	50:50
26	"	SPh ( $\beta$ only)	"	"	CH <sub>3</sub> CN	89%	65:35
27	"	TAC (91 $\alpha$ :9 $\beta$ )	CF <sub>3</sub> CH <sub>2</sub> OH	-78	CH <sub>2</sub> Cl <sub>2</sub>	89%	82:18
28	"	"	CH <sub>3</sub> CH <sub>2</sub> OH	"	"	76%	72:28

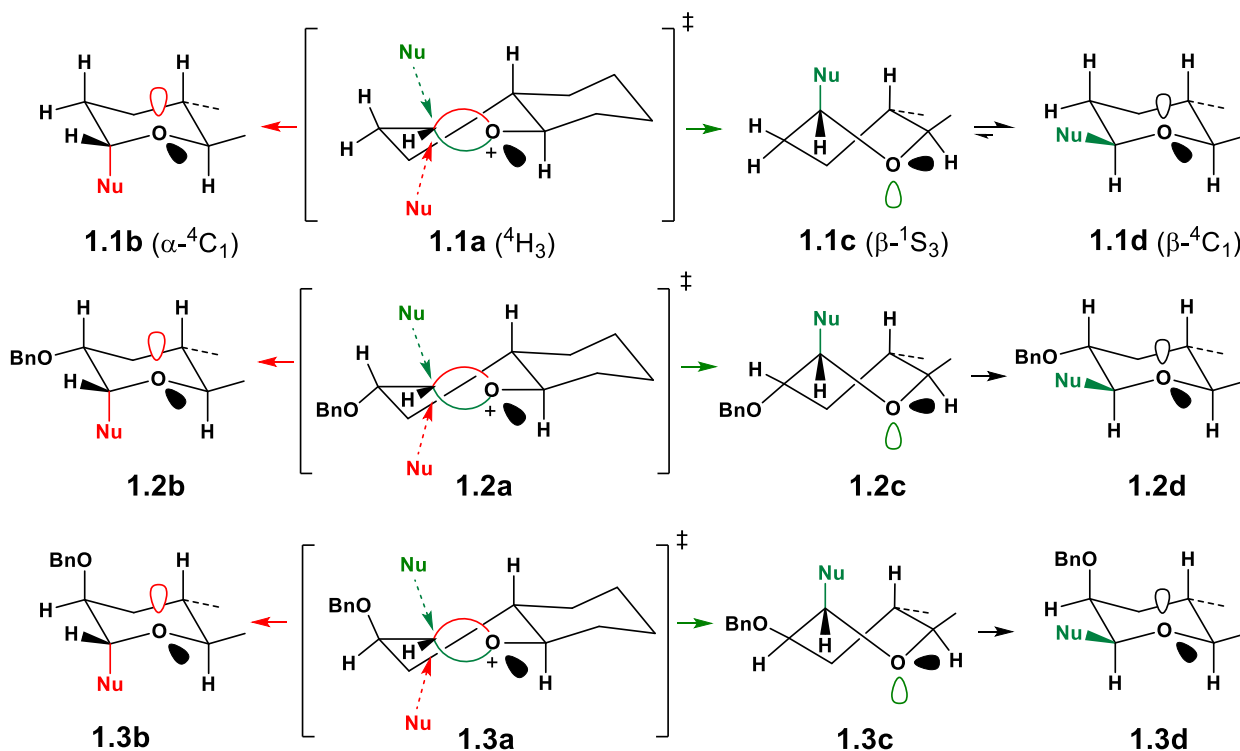
**Dnr:** donor; **Ac:** acceptor; TMSAlyl: allyltrimethylsilane; **S:** solvent; **Y:** yield TCA: trichloroacetimidate (OCNHCCl<sub>3</sub>); Qnt: Quantitative

nucleophilicity,  $\text{CF}_3\text{CH}_2\text{OH}$ ,  $\text{ClCH}_2\text{CH}_2\text{OH}$  and  $\text{CH}_3\text{CH}_2\text{OH}$  were used as acceptors. Donors **1.2** and **1.3(TAC)** were reacted with  $\text{CF}_3\text{CH}_2\text{OH}$  and  $\text{CH}_3\text{CH}_2\text{OH}$  with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv) in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ .

The method developed by Woerpel<sup>11</sup> was used to confirm that the *O*-glycosylation experiments were conducted under kinetic control. Pure  $\alpha$  or  $\beta$ -anomer obtained from donors **1.1-1.3** were resubmitted to the glycosylation reaction conditions of a different donor and nucleophile. Results showed that there was no anomerization or nucleophile incorporation in the  $\alpha$  or  $\beta$ -anomer. Results are described in the ESI.

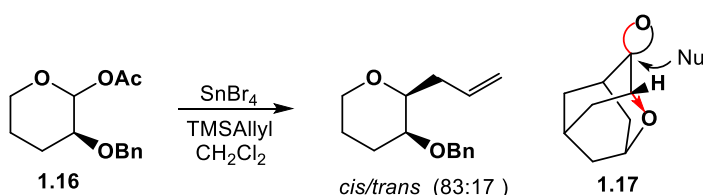
## 1.8 Rationalization of glycosylation

With the  $\tau$  bond model, the bicyclic pyranoside **1.1** must form the oxocarbenium ion in the  $^4\text{H}_3$  half-chair conformation **1.1a** which will preferably react with the nucleophile on the  $\alpha$ -face producing directly the  $\alpha$ -anomer **1.1b** in the  $\alpha$ - $^4\text{C}_1$  chair conformation (Figure 1.13) while the minor  $\beta$ -anomer would be produced in the  $\beta$ - $^1\text{S}_3$  twist-boat conformation **1.1c** which is then converted to the stable  $^4\text{C}_1$  chair form **1.1d**.



**Figure 1.13**  $\alpha/\beta$ -Glycosidation of bicyclic furanosides analogues.

Bicyclic pyranoside **1.2** with the equatorial OBn group will generate an oxocarbenium ion in the  ${}^4\text{H}_3$  conformation **1.2a** having the C<sub>2</sub>-OBn bond antiperiplanar to the  $\tau$  bond above the plane of the carbonyl group. As a result, the  $\tau$  bond above the plane is electron poorer, so, the  $\alpha$  nucleophilic addition should take place to an even larger extent due to the presence of the equatorial C<sub>2</sub>-OR group producing the  $\alpha$ -anomer in the  ${}^4\text{C}_1$  chair conformation **1.2b**. In complete agreement with this analysis, Woerpel and co-workers<sup>11</sup> have previously observed that the C-glycosylation of 2-O-benzyltetrahydropyran donor **1.16** gave the 1,2-*cis* product as the major anomer (ratio 83:17) via a nucleophilic addition on the oxocarbenium ion intermediate (*Figure 1.14*). This analysis is also supported by the reported<sup>32</sup> reactivity of 6-oxo-2-adamantanone **1.17** in which all reagents (alkylation or reduction) react exclusively as shown.



**Figure 1.14** 1,2-*Cis* nucleophilic addition on **1.16** and **1.17**.

Bicyclic pyranoside **1.3** with the axial OBn group will form an oxocarbenium ion in the  ${}^4\text{H}_3$  conformation **1.3a** having a C<sub>2</sub>-OR bond antiperiplanar to the  $\tau$  bond below the plane of the carbonyl

group. The  $\alpha$ -isomer is thus favored by the formation of the  ${}^4\text{C}_1$  chair conformer but the hyperconjugation of the axial OBn group favors the  $\beta$ -isomer although produced in the less stable  ${}^1\text{S}_3$  conformer. These two effects are thus opposing each other.

The glycosylation described in *Table 1.1* can now be examined. The  $\alpha$ -anomers are generally obtained as the major isomer with weak nucleophiles TMSAllyl (entries 1, 8, 17, 18) and  $\text{CF}_3\text{CH}_2\text{OH}$  (entries 2, 3, 9, 10, 15, 19-22) whereas there is almost no stereocontrol with stronger nucleophiles in  $\text{CH}_2\text{Cl}_2$  (entries 4, 6, 11, 13, 16, 23, 25) which is not the case in  $\text{CH}_3\text{CN}$  (entries 5, 7, 12, 14, 21, 22, 24, 26).

C-Glycosylation of donor **1.1(OAc)** (entry 1) shows that the  ${}^4\text{C}_1$  conformer formation is powerful enough that only the  $\alpha$ -isomer is observed. When both parameters, i.e.  ${}^4\text{C}_1$

<sup>32</sup> (a) Subramaniam, R. S.; Fort, R. C. Jr. *J. Org. Chem.* **1984**, *49*, 2891-2896; (b) Kaselj, M.; Chung, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387-1414.

conformation and hyperconjugation of OBn group are working in the same direction as in donor **1.2(OAc)** having an equatorial OBn group (entry 8) only the  $\alpha$ -isomer is again observed. However, when both parameters are in opposition as in donor **1.3(OAc)** (entries 17, 18), the  $\alpha$ -isomer still prevails but the minor formation of the  $\beta$ -isomer indicates that the  ${}^4C_1$  conformation parameter is not completely dominating the hyperconjugation effect of the axial OBn group forming the  $\beta$ -isomer in the  ${}^1S_3$  conformation.

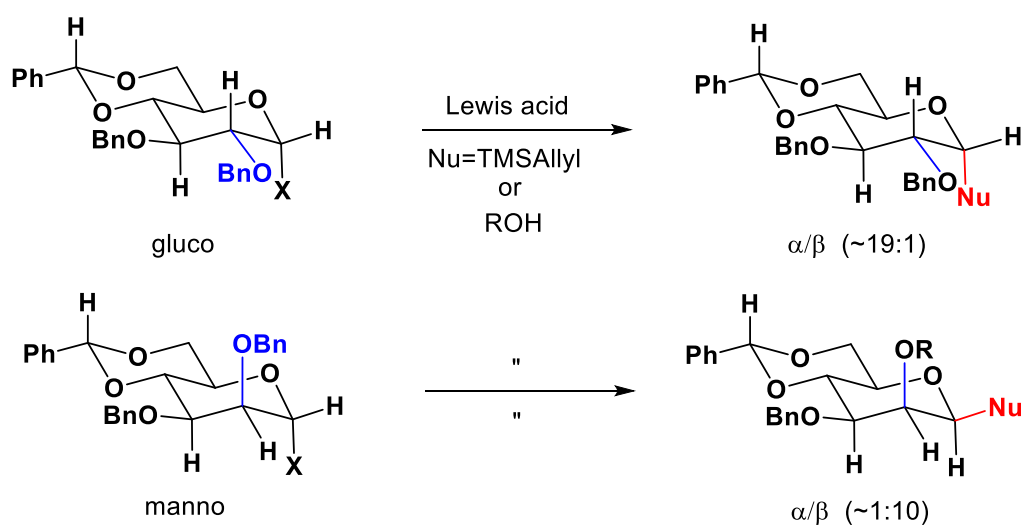
*O*-Glycosylation can now be examined while taking into account Woerpel's finding<sup>11</sup> that stereoselectivity can be greater in CH<sub>3</sub>CN than in CH<sub>2</sub>Cl<sub>2</sub>. Indeed:

Increasing the polarity of the solvent results in stabilization of the cationic intermediate and subsequently reduces the rate of nucleophilic addition. As the rate of nucleophilic addition is decreased from the diffusion limit regime, greater facial selectivity for the stereoelectronically preferred product would be observed.<sup>11</sup>

Thus, it is necessary to take into account the nucleophilicity of the acceptor, the reactivity of the corresponding oxocarbenium ion, and the nature of the solvent. These factors can control the distance of the nucleophile to the oxocarbenium ion at the transition state level, thus strong nucleophiles can lead to a reduction of  $\alpha/\beta$  selectivity in an early transition state. Indeed, according to Woerpel,<sup>11</sup> 2-deoxy-3,4,5-trimethoxy  $\alpha$ -glucosyl donor gives a 91:9  $\alpha/\beta$  ratio with the weak nucleophile allylTMS, a 83:17 ratio with CF<sub>3</sub>CH<sub>2</sub>OH, and a 1:1  $\alpha/\beta$  ratio with EtOH. Consequently, the transition state can be considered earlier in CH<sub>2</sub>Cl<sub>2</sub> than with CH<sub>3</sub>CN to the point that there is a loss of face selectivity in the approach of a good nucleophile.

*O*-glycosylation with CF<sub>3</sub>CH<sub>2</sub>OH in CH<sub>2</sub>Cl<sub>2</sub> and in CH<sub>3</sub>CN of the non-substituted donor **1.1(SPh)** (entries 2 and 3) indicates that the antiperiplanar nucleophilic addition leading to the  $\alpha$ - ${}^4C_1$  conformer is the dominating parameter. The slightly lower  $\alpha$  selectivity in CH<sub>2</sub>Cl<sub>2</sub> can also indicate that CF<sub>3</sub>CH<sub>2</sub>OH might be nucleophilic enough to be near diffusion rate limit which can explain the very minor formation of the  $\beta$ -anomer in this solvent. With the stronger nucleophiles ClCH<sub>2</sub>CH<sub>2</sub>OH and CH<sub>3</sub>CH<sub>2</sub>OH, there is a higher  $\alpha$  selectivity in CH<sub>3</sub>CN (entries 5, 7) contrary to CH<sub>2</sub>Cl<sub>2</sub> (entries 4, 6).

With pyranoside donor **1.2(SPh)**, glycosylation with  $\text{CF}_3\text{CH}_2\text{OH}$  in  $\text{CH}_3\text{CN}$  gives only the  $\alpha$ -anomer (entry 10) in agreement with the  ${}^4\text{C}_1$  conformation and the hyperconjugation of the equatorial OBn group. In  $\text{CH}_2\text{Cl}_2$ , the small quantity (17%) of the  $\beta$ -anomer (entry 9) can be explained in the same manner than donor **1.1(SPh)**. With  $\text{ClCH}_2\text{CH}_2\text{OH}$ , the reaction is low  $\alpha$  selective in  $\text{CH}_3\text{CN}$  and in  $\text{CH}_2\text{Cl}_2$  (entries 11, 12). This alcohol being more nucleophilic than  $\text{CF}_3\text{CH}_2\text{OH}$ , more  $\beta$ -anomer is observed. With  $\text{CH}_3\text{CH}_2\text{OH}$ , there is no selectivity in  $\text{CH}_2\text{Cl}_2$  and it was surprising to see that the  $\beta$ -anomer was even the major product (entries 13, 14).  $\text{CH}_3\text{CH}_2\text{OH}$  being the strongest nucleophile, it can undergo a  $\text{S}_{\text{N}}2$  reaction on the  $\alpha$ -**1.2(SPh)** donor in  $\text{CH}_3\text{CN}$ . This hypothesis is supported by the fact that  $\alpha$ -donor **1.1(SPh)**



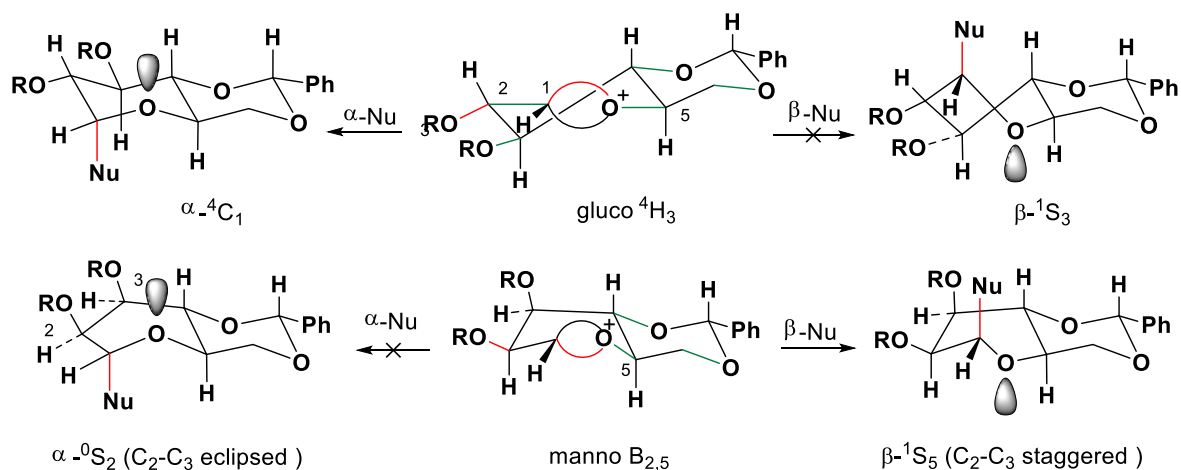
**Figure 1.15** Glycosidation of 4,6-O-gluco and manno pyranosides.

by comparison with  $\alpha$ -donor **1.2(SPh)** is a 2-deoxypyranoside donor which can produce an oxocarbenium ion at a much faster rate.<sup>31</sup> In  $\text{CH}_3\text{CN}$  (and partly in  $\text{CH}_2\text{Cl}_2$ ) and specially with  $\text{CH}_3\text{CH}_2\text{OH}$ , the  $\text{S}_{\text{N}}2$  pathway can be the major process. With donor **1.2(TAC)**, there is again more of the  $\beta$ -anomer with  $\text{CH}_3\text{CH}_2\text{OH}$  than with  $\text{CF}_3\text{CH}_2\text{OH}$  (entries 15, 16).

*O*-Glycosylation of donors **1.3(SPh)** with  $\text{CF}_3\text{CH}_2\text{OH}$  in  $\text{CH}_3\text{CN}$  (entries 21-22) shows an important quantity (18 to 22%) of the  $\beta$ -anomer which is explained by the hyperconjugation of the axial OBn group despite the fact that it is produced in the less stable  ${}^1\text{S}_3$  conformation. Indeed, donor **1.2** under the same conditions yields only the  $\alpha$ -anomer. In  $\text{CH}_2\text{Cl}_2$  (entries 19-20) there is an even larger quantity (32 to 35%) of the  $\beta$ -anomer probably due for the reasons described for donors **1.1** and **1.2**. With  $\text{ClCH}_2\text{CH}_2\text{OH}$  and  $\text{CH}_3\text{CH}_2\text{OH}$ , in  $\text{CH}_3\text{CN}$

donors **1.3(SPh)** (entries 24, 26) gives an important quantity (35 to 38%) of the  $\beta$ -anomer. In  $\text{CH}_2\text{Cl}_2$ , the minor  $\beta$ -anomer is also very important (34% with  $\text{ClCH}_2\text{CH}_2\text{OH}$  and 50% with  $\text{CH}_3\text{CH}_2\text{OH}$ ) (entries 23, 25).

It remains to consider the high  $\alpha$ - and  $\beta$ -glycosylation of glucose and mannose donors in the presence of nucleophiles (*Figure 1.15*). The pathways of these reactions have been studied extensively by the groups of Crich<sup>12,16,33</sup>, Bols-Pedersen<sup>29</sup> and theoretically by Kosma<sup>34</sup>. Their work indicates that the reactive conformation of the oxocarbenium ion corresponds to a  ${}^4\text{H}_3$  half-chair for glucose and equilibrating  ${}^4\text{H}_3$  and  $\text{B}_{2,5}$  conformations for mannose ( $\text{B}_{2,5}$  being major). The  $\text{B}_{2,5}$  conformation in mannose has the  $\text{C}_3\text{-OR}$  group axially oriented and properly located to stabilize the positive charge of the oxocarbenium ion. This conformational electrostatic stabilization has been previously recognized by Woerpel<sup>8b</sup> and us<sup>9</sup>. As a result, the nucleophile would finally preferably on the  $\beta$  side of  $\text{B}_{2,5}$  for mannose. The prefer addition on both sugars is in complete agreement with the  $\tau$  bond model, the nucleophile reacting on the  $\alpha$  side of  ${}^4\text{H}_1$  for glucose and on the  $\beta$  side of  $\text{B}_{2,5}$  for mannose (*Figure 1.16*).



**Figure 1.16** Glycosylation of 4,6-O-benzylidene of glucose and mannose donors.

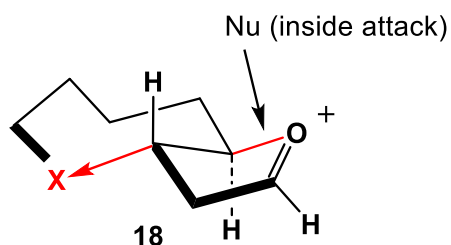
It is however important to point out that the polar  $\text{C}_4\text{-O}$  and  $\text{C}_6\text{-O}$  bond (indicated in green) are perfectly antiperiplanar to the  $\text{C}_5\text{-O}$  bond withdrawing electronic density from the  $\text{C}_5$ -

<sup>33</sup> (a) Huang, M.; Retailleau, P.; Bohé, L.; Crich, D. *J. Am. Chem. Soc.* **2012**, *134*, 14746-14749; (b) Moumé-Pymbock, M.; Furukawa, T.; Mondal, S.; Crich, D. *J. Am. Chem. Soc.* **2013**, *135*, 14249-14255; (c) Bohé, L.; Crich, D. *Carbohydr. Res.* **2015**, *403*, 48-59.

<sup>34</sup> Hosoya, T.; Kosma, P.; Rosenau, T. *Carbohydr. Res.* **2015**, *411*, 64-69.

O<sup>+</sup>=C<sub>1</sub>-unit by hyperconjugation (Figure 1.16). Indeed, the 4,6-*O*-benzylidene group is known to be “disarming”<sup>35</sup> and playing an important role in the stereoselectivity observed. In addition, the polar equatorial C<sub>3</sub>-O bond in the glucose oxocarbenium ion is antiperiplanar to the C<sub>2</sub>-C<sub>1</sub> bond, also withdrawing electronic density in the C<sub>2</sub>-C<sub>1</sub>=O<sup>+</sup>- unit. So, clearly, the electron density of the  $\tau$  bonds of these oxocarbenium ions must be very low due to the hyperconjugation of these oxygen atoms. This means that the glycosylation transition states must be even earlier with these sugars than with the bicyclic models **1.2** and **1.3**, without polar C-O bonds at C<sub>3</sub>, C<sub>4</sub> and C<sub>6</sub>.

This hyperconjugation effect is again strongly supported by Woerpel study<sup>36</sup> on the *C*-glycosylation of a series of bicyclic furanoside donors. For example, when X=CH<sub>2</sub> in the oxocarbenium ion intermediate **1.18**, the inside attack is highly favoured (98:2) but when X=O, the inside attack preference is lost (60:40) (Figure 1.17). These experimental results are supported by calculation, which indicates that the inside attack on **1.18** (X=CH<sub>2</sub>) is favoured over the outside attack by 1.6 kcal/mol whereas the same attack on **1.18** (X=O) is favoured by only 0.2 kcal/mol. We interpret these results by the hyperconjugation caused by the polar C-O bond in **1.18** (X=O) which is antiperiplanar to the C<sub>4</sub>-O<sup>+</sup> bond rendering the oxocarbenium ion electron poorer thus more reactive, causing an early transition state and a loss of selectivity.



**Figure 1.17** Nucleophilic addition on bicyclic compound **18** (X = O or CH<sub>2</sub>).

It remains to explain why 4,6-*O*-benzylidene mannose donors are  $\beta$ -selective while bicyclic donors **1.3** are low  $\alpha$  selective with strong nucleophile and  $\alpha$ -selective with weak nucleophiles in CH<sub>2</sub>Cl<sub>2</sub>. As shown above, glycosylation of glucose and mannose occurs with a transition state considered earlier than that of donors **1.1-1.3**. It appears unlikely that the stereoselectivity observed in mannose and glucose

<sup>35</sup> (a) Fraser-Reid, B.; Wu, Z. C.; Andrews, W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434-1435; (b) Andrews, W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280-5289; (c) Demchenko, A. V.; Mydock, L. K. *Org. Lett.* **2008**, *10*, 2103-2106; (d) Pedersen, C. M.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222-9235.

<sup>36</sup> Kendale, J. C.; Valentín, E. M.; Woerpel, K. A. *Org. Lett.* **2014**, *16*, 3684-3687.

would be controlled only by the  $\tau$  bond electronic density which depends on the hyperconjugation of the equatorial or axial C<sub>2</sub>-OR bond. But if one assumes that, as proposed by Crich<sup>12,16,33</sup> and Bols-Pedersen,<sup>29</sup> the oxocarbenium ions derived from the 4,6-*O*-benzylidenes of glucose and mannose react through their <sup>4</sup>H<sub>1</sub> and B<sub>2,5</sub> conformation respectively, it becomes possible to understand their behavior while taking into account the BBA hypothesis.

A nucleophilic displacement of a  $\tau$  bond is the equivalent of a S<sub>N</sub>2 reaction. In glucose, this reaction on the <sup>4</sup>H<sub>1</sub> conformation of the oxocarbenium ion leads directly to the <sup>4</sup>C<sub>1</sub> conformation of the  $\alpha$ -anomer which is more favourable than a  $\beta$  attack forming the  $\beta$ -anomer in the less stable <sup>1</sup>S<sub>3</sub> conformation. On the other hand, in the case of mannose, a  $\beta$  nucleophilic attack on the B<sub>2,5</sub> conformation produces the  $\beta$ -anomer in the <sup>1</sup>S<sub>5</sub> twist-boat conformation in which the C<sub>2</sub>-OBn and C<sub>3</sub>-OBn bonds remain staggered. This is a lower energy process than an  $\alpha$  attack on B<sub>2,5</sub>, which produces the  $\alpha$ -anomer in the <sup>0</sup>S<sub>2</sub> twist-boat conformation having the OR groups at C<sub>2</sub> and C<sub>3</sub> becoming eclipsed. A similar argument has been used previously by Crich<sup>37</sup> who stated that there is a reduction of the O<sub>2</sub>-C<sub>2</sub>-C<sub>3</sub>-O<sub>3</sub> torsion angle in the B<sub>2,5</sub> oxocarbenium ion of mannose.<sup>38</sup>

Crich and co-workers have also reported<sup>37,39</sup> the *C*- and *O*-glycosylation of 3-deoxy derivatives of 4,6-*O*-benzylidene of glucose and mannose donors. The  $\alpha$  and  $\beta$  selectivity of the 3-deoxy derivatives was found to be similar in the *C*-glycosylation with those of the natural sugars. However, the *O*-glycosylation differs considerably, they were unselective in 3-deoxy glucose and found with a low  $\alpha$  selectivity with 3-deoxy mannose. Interestingly, donor 1.3 which is a good 4,6-deoxy model of 3-deoxy mannose is also  $\alpha$  selective. Thus, in 3-deoxy mannose, the most stable conformer for the oxocarbenium ion can be the <sup>4</sup>H<sub>3</sub> conformer not the B<sub>2,5</sub>. However, further comparison should be made with caution as quite

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<sup>37</sup> Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473-8480.

<sup>38</sup> In the case of mannose, there is also the alternative possibility that synperiplanar attack could take place on the B<sub>2,5</sub> oxocarbenium ion to form directly the corresponding  $\beta$ -anomer in its boat-form ( $\beta$ -B<sub>2,5</sub>) (or indirectly through the Ingold-Sicher double inversion pathway)<sup>24</sup>. Examination of a simple molecular model indicates that a synperiplanar nucleophilic addition on the  $\beta$  face is more likely than an  $\alpha$  addition. It could also be a lower energy process than the antiperiplanar reaction producing the  $\beta$ -<sup>1</sup>S<sub>5</sub> or the  $\alpha$ -<sup>0</sup>S<sub>2</sub> conformer!

<sup>39</sup> Moumé-Pymboc, M.; Crich, D. *J. Org. Chem.* **2012**, *77*, 8905-8912.

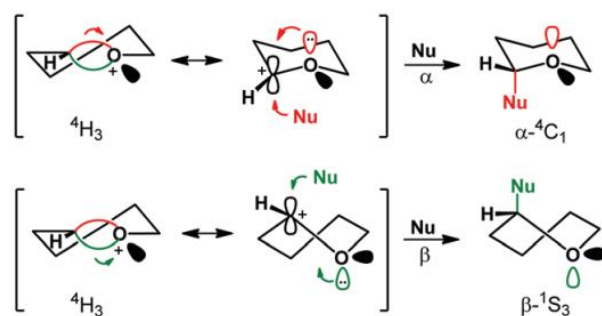


different nucleophiles (1-adamantanol) or bulky sugars (e.g., 1,2,5,6-di-*O*-isopropylidene- $\alpha$ -D-glucopyranose) versus ethanol derivatives) were used in these studies. Conformationally restricted donors related to the 4,6-*O*-benzylidene glycopyranose donors having different orientation for the oxygen at C<sub>6</sub> have been recently investigated.<sup>33b, 35d, 40</sup>

## 1.9 Summary

In conclusion, the  $\tau$  bond model explains why donor **1.1** is  $\alpha$ -selective with weak nucleophiles yielding the product directly in the  ${}^4C_1$  conformation. For the same reason and that of the hyperconjugation effect of the equatorial C<sub>2</sub>-OR group and despite the possible steric repulsion of that group with the nucleophile at the transition state, donor **2** remains  $\alpha$ -selective. This model explains also that the major formation of the  $\alpha$ -anomer with donor **1.3** is due to the fact that it is produced in the  $\alpha$ - ${}^4C_1$  conformation. It also explains that the presence of the  $\beta$ -anomer as an important minor product is due to hyperconjugation of the axial C<sub>2</sub>-OR group despite the fact that it leads to a product in the  $\beta$ - ${}^1S_3$  conformation. In addition, there is an important loss of stereocontrol in CH<sub>2</sub>Cl<sub>2</sub> which is not occurring in CH<sub>3</sub>CN.

The  $\tau$  bond model is also in agreement with the Crich-Bols-Pedersen pathways for the 4,6-*O*-benzylidene derivatives of glucose and mannose. In glucose, the  $\alpha$ -anomer is formed preferably through a nucleophile reacting on the  ${}^4H_3$  conformation of the oxocarbenium ion producing the anomer directly in the  ${}^4C_1$  conformation. In the case of mannose, the  $\beta$ -anomer



**Figure 1.18** Resonance structures of  $\tau$  bonds and stereocontrolled nucleophilic addition on  ${}^4H_3$ .

is preferably formed through a nucleophilic reaction on the B<sub>2,5</sub> conformation of the oxocarbenium ion, producing that anomer in its  ${}^1S_5$  conformation. This process is lower in energy than an  $\alpha$  nucleophilic attack on B<sub>2,5</sub> producing the  $\alpha$ -anomer in the less stable  ${}^0S_2$  conformation in which the

<sup>40</sup> Dharuman, S.; Crich, D. *Chem. Eur. J.* **2016**, *22*, 4535-4552 and references therein.

OR groups at C<sub>2</sub> and C<sub>3</sub> become eclipsed. Finally, the  $\tau$  bond model can also explain the loss of stereoselectivity in the *O*-glycosylation of 3-deoxy-4,6-*O*-benzylidene of glucose and mannose donors. It also provides a rationale for the different behavior of glucose and mannose donors and the bicyclic donors **1-3**.<sup>26d</sup>

Finally, the  $\tau$  bond model combined with the antiperiplanar hypothesis and the concept of hyperconjugation suggests that there are two conformationally different types of resonance structures for a six-membered oxocarbenium ion (*Figure 1.18*). As a consequence, this provides the required information necessary to predict that there are two sterically different stereochemically controlled pathways for the addition of a nucleophile. The pathway having minimal conformational effect is thus expected to be lower in energy. In the example shown (*Figure 1.17*), the nucleophilic addition on the  $\alpha$  side of the <sup>4</sup>H<sub>3</sub> oxocarbenium ion shown should thus prevail and this should be the case even with an early transition state, unless the nucleophile is so strong that it reacts at the diffusion rate.

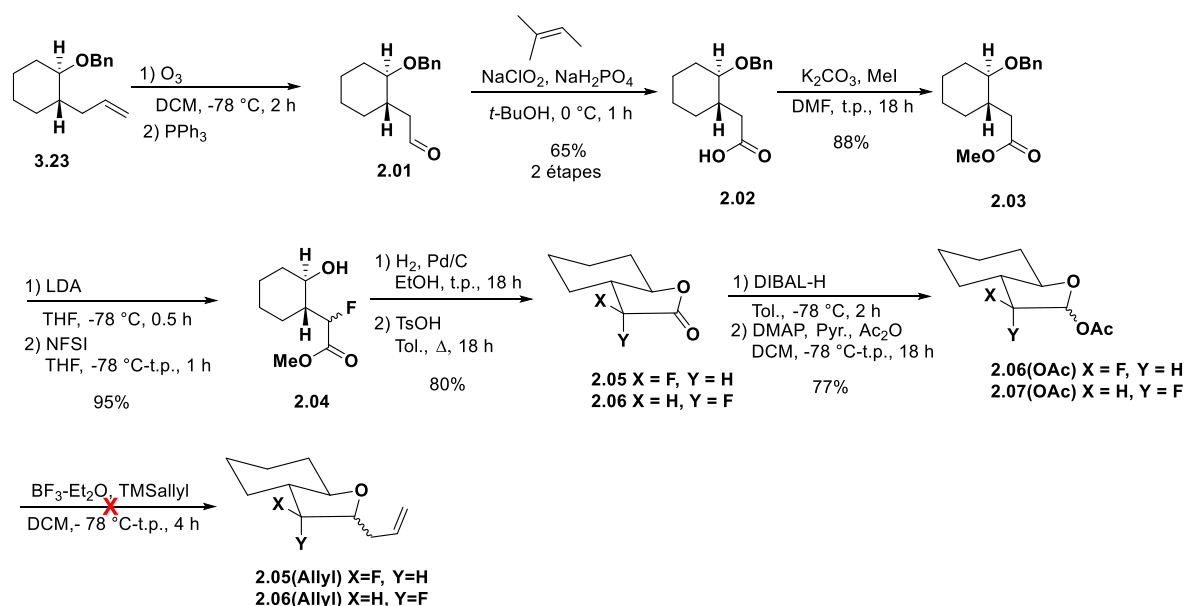
Glycosylation with bicyclic pyranoside models having various EWG and EDG at both C<sub>2</sub> and C<sub>3</sub> is presently being investigated to further confirm the validity of the  $\tau$  bond model. We are also carrying out an analogous study on the glycosylation of bicyclic furanoside donors similar to the above bicyclic pyranosides. Results will be reported in the near future.

# Chapitre 2 Applying the Bent Bond / Antiperiplanar Hypothesis to the Stereoselective Glycosylation of Bicyclic Furanosides

## 2.1 Avant-Propos

Fort d'une compréhension accrue et du support d'une littérature de plus en plus intéressée à la glycosylation  $S_N1$ , l'applicabilité de la liaison courbe sur les intermédiaires oxocarbéniums dans le contexte de glycosylation de furanosides est revenue dans la ligne de mire. Les résultats présentés dans chapitre sont en partie le fruit d'un travail en laboratoire effectué avec l'aide de Xavier Bertrand. Dans le cadre d'un stage de recherche en milieu académique, Xavier a contribué à la resynthèse des donneurs de glycosylation furanoside afin d'obtenir un réplica de chacun des résultats présentés dans le *Tableau 2.1*.

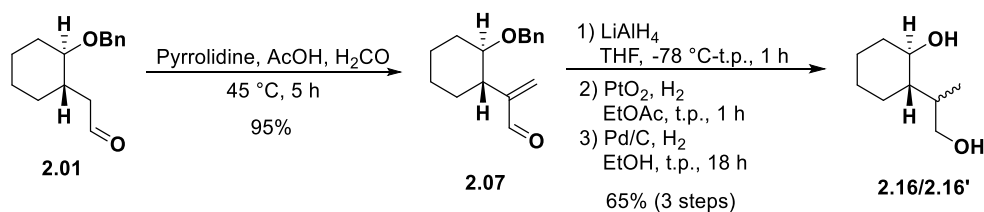
Tel que mentionné dans l'introduction et comme en témoignera ce chapitre, évaluer la participation d'effets stéréoélectroniques dans la glycosylation de composés furanosides est beaucoup plus ardue que dans les pyranosides, puisque ces derniers possèdent plusieurs facteurs concomitants et intrinsèques à la structure pouvant affecter le cours de la réaction de glycosylation.<sup>11</sup> C'est pour cette raison que l'objectif initial de cette partie des travaux incluait la fabrication de donneurs  $C_2$  fluorés en plus d'un groupement  $C_2$ -OR afin de



**Figure 2.1** Préparation d'un donneur  $C_2$ -F.

minimiser la contribution d'effets stériques et de mettre l'accent sur la forte propriété électroattractrice du fluor.

L'insertion de l'atome de fluor, comme l'atome d'oxygène, s'avère plus simple sur un intermédiaire linéaire que sur la forme cyclique. La préparation de l'ester méthylique **2.03** et la formation de l'énolate correspondant permettent d'introduire le fluor de manière électrophile grâce au NFSI<sup>1</sup> pour générer l'intermédiaire **2.04**, cyclisé ensuite en deux étapes. La séparation des deux diastéréoisomères axial et équatorial de la lactone bicyclique **2.05/2.06** ont ensuite été possibles par simple chromatographie. Cependant, c'est la C-glycosylation qui s'est avéré l'aspect le plus problématique de ces donneurs. En effet, la génération d'un intermédiaire oxocarbenium furanoside est apparu impossible en présence d'un C<sub>2</sub>-F, et ce, même en augmentant la température et la quantité d'acide de Lewis. L'effet inducteur de l'halogène serait en somme trop important pour permettre l'expulsion du groupe partant et la génération de l'oxocarbenium. Par cette observation, nous avons donc conclu que la génération d'un ion oxocarbenium de type furanoside ne serait pas envisageable en présence d'un atome de fluor en C<sub>2</sub> dans ces conditions. Notre intérêt s'est alors tourné vers la préparation des donneurs C<sub>2</sub>-Me.



**Figure 2.2** Préparation initiale du précurseur diol 1,4 **2.16** et **2.16'** pour l'obtention des donneurs C<sub>2</sub>-Me.

La stratégie synthétique initialement envisagée ne correspond pas à celle qui est rapportée dans l'article. Elle est plus longue de plusieurs étapes et nécessite l'utilisation d'un groupement protecteur sur l'alcool devant tenir le coup dans des conditions particulièrement difficiles. L'étape clé étant ici encore le passage par les diols 1,4 **2.16** et **2.16'** pouvant être oxydés en lactone par une réaction de cyclisation oxydative rapportée par Stahl.<sup>28</sup> Le passage par le diol est d'autant plus nécessaire qu'il permet la séparation par chromatographie des

<sup>1</sup> Posner, G.; Maio, W.; Kalinda, A.S. *Bioorg. Med. Chem.* **2008**, *16*, 5247-5253

deux diastéréoisomères. Ceci consiste en une tâche beaucoup plus ardue sous la forme cyclisée, bien qu'elle soit possible. La stratégie consistait donc à former l'aldéhyde **2.01** par ozonolyse de l'allyle puis d'effectuer la méthylation de Mannich catalysée par la pyrrolidine, une transformation qui s'est avérée très efficace.<sup>2</sup> Les diols **2.16** pouvaient ensuite être obtenus par des réductions successives de l'aldéhyde à l'aide d'un hydrure. S'en suit l'hydrogénation de l'alcène grâce au platine, puis la libération de l'alcool protégé en benzyle par hydrogénolyse au palladium. L'utilisation du palladium pour réduire à la fois l'alcène et libérer l'alcool secondaire a conduit à l'hydrogénolyse de l'alcool allylique, d'où l'étape supplémentaire d'hydrogénation au platine. La découverte de la réduction de Marshall<sup>27</sup> décrite dans ce chapitre pour la synthèse des donneurs **2.4** et **2.5** a permis de réduire le nombre d'étapes synthétiques en plus d'augmenter le rendement global. La stratégie synthétique initiale n'a toutefois pas été développée en vain, puisqu'elle a nous a guidé dans la préparation des donneurs C<sub>2</sub>-Me présentés dans le chapitre 3.

Afin d'étoffer l'argument utilisé pour rationaliser la sélectivité de la glycosylation, des donneurs complètement oxygénés ont été préparés à l'aide de protocoles rapportés dans la littérature. Également en soutien à l'approche utilisant des donneurs de glycosylation simplifiée, des études computationnelles sur la réactivité des donneurs ont été effectuées par notre collaborateur Ghislain Deslongchamps. Malgré la quantité importante de données expérimentales obtenues et le support computationnel, il s'est avéré difficile de publier l'article présenté dans ce chapitre. Plusieurs soumissions ont été nécessaires, puisque les évaluateurs ne saisissaient tout simplement pas l'objectif de l'expérience et, ce faisant, la portée de la découverte. Ils étaient davantage concernés par la transposition des résultats à de l'application directe en chimie des glucides plutôt que d'en analyser l'impact au niveau fondamental et théorique. Il a donc été nécessaire de remanier les écrits pour nuancer certains propos et en rigidifier d'autres. Enfin, ces réécritures auront permis de recevoir ultimement d'excellents commentaires de la part des évaluateurs.

L'article est présenté ici sous la forme en laquelle il a été soumis au *Journal of Organic Chemistry*. Au cours des deux dernières années, ce journal s'est montré ouvert aux nouvelles

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<sup>2</sup> Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538-2541

propositions du Professeur Pierre Deslongchamps sur la rationalisation des réactions hautes températures de systèmes conjugués. Nous avons donc profité de cet intérêt et de cette ouverture pour publier dans ce journal. Les journaux de l'*American Chemical Society* ont d'ailleurs une grande notoriété qui, je l'espère, permettra à nos travaux de trouver un auditoire plus large et, ultimement, que cela permettra la formation de nouveaux connaisseurs et diffuseurs de connaissances du modèle de Pauling.

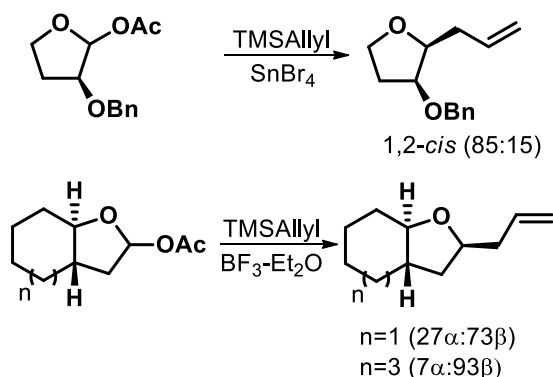
## 2.2 Résumé

La glycosylation stéréosélective d'une série de bicyclic furanosides a été conduite en présence de nucléophiles faibles. Les résultats ont été analysés par l'entremise du modèle orbitalaire liaisons courbes/ hypothèse antiperiplanaire (BBAH) dans l'optique d'en évaluer la validité. Selon le modèle BBAH, le nucléophile déplace l'une des deux liaisons courbes lors de son approche de manière antipériplanaire. La sélectivité de la glycosylation est alors gouvernée par le déplacement de la liaison courbe la plus faible déterminée par la présence d'un groupement électrodonneur ou électroattracteur en C<sub>2</sub>. De manière générale, l'analyse par BBAH supporte et augmente la portée du modèle de glycosylation interne/externe de Woerpel en considérant l'influence stéréoélectronique des groupements électroattracteurs et électrodonneurs voisins dans le contexte d'addition nucléophile sur un intermédiaire oxocarbénium.

## 2.3 Abstract

The glycosylation stereoselectivities for a series of bicyclic furanoside models have been carried out in the presence of weak nucleophiles. These results were analyzed through the bent bond / antiperiplanar hypothesis (BBAH) orbital model in order to test its validity. According to the BBAH, incoming nucleophiles displace one of the two bent bonds of bicyclic oxocarbenium ion intermediates in antiperiplanar fashion. The glycosylation stereoselectivity is then governed by displacement of the weaker bent bond as determined by the presence of electron-withdrawing or donating substituents at C<sub>2</sub>. Overall, the BBAH analysis expands Woerpel's "inside/outside attack" glycosylation model by considering the stereoelectronic influence of neighbouring electron-withdrawing and donating groups on the nucleophilic addition to oxocarbenium ion intermediates.

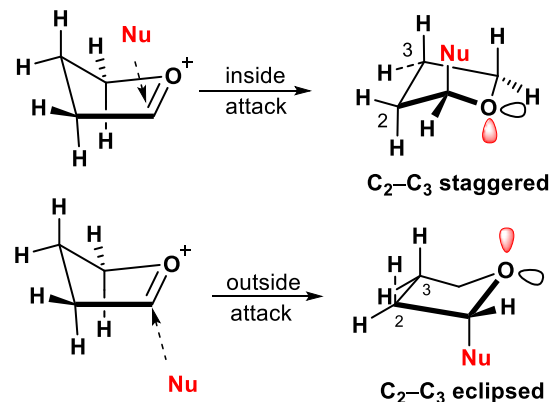
## 2.4 Specific introduction



**Figure 2.4** Allylation of furanosides.

furanosides can also be analyzed in a similar fashion using a series of bicyclic furanoside model compounds.

Woerpel and co-workers<sup>11</sup> previously reported the C-glycosylation of several furanosides with allyltrimethylsilane (TMSallyl) in the presence of Lewis acid. For example, a 2-benzyloxyfuranoside acetate gave the 1,2-*cis* product as a major isomer (*cis:trans* 85:15) (Figure 2.4).<sup>11e</sup> When the OBn group was replaced by a CH<sub>3</sub> group, the reaction became



**Figure 2.3** Inside and outside attack.

<sup>3</sup> Deslongchamps, G.; Deslongchamps, P. *Org. Biomol. Chem.* **2011**, *9*, 5321-5333.

<sup>4</sup> (a) Deslongchamps, G.; Deslongchamps, P. *Tetrahedron* **2013**, *69*, 6022-6033; (b) see also: Chen J.; Wulff J. E. *Org. Biomol. Chem.* **2016**, *14*, 10170-10174.

<sup>5</sup> Deslongchamps G.; Deslongchamps, P. *Org. Biomol. Chem.* **2016**, *14*, 7754-7767.

<sup>6</sup> Parent, J.-F.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 3299-3304.

<sup>7</sup> Deslongchamps, G.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 5751-5755.

<sup>8</sup> Deslongchamps, G.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 10383-10388.

<sup>9</sup> Deslongchamps, G.; Deslongchamps, P. *Org. Biomol. Chem.* **2019**, *17*, 7007-7012.

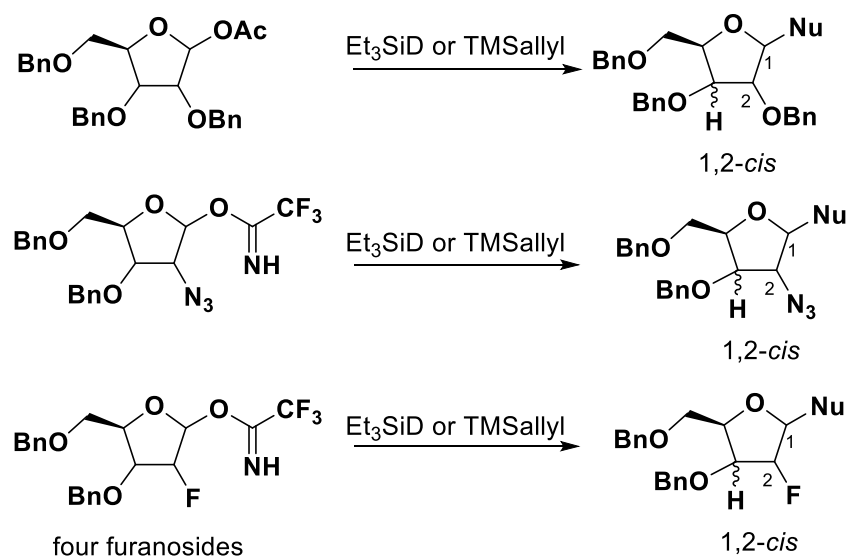
<sup>10</sup> Parent, J.-F.; Deslongchamps, P. *Org. Biomol. Chem.* **2016**, *14*, 11183-11198.

<sup>11</sup> (a) Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 6706-6707. (b) Lavinda, O.; Tran, V. T.; Woerpel, K. A. *Org. Biomol. Chem.* **2014**, *12*, 7083-7091; (c) Larsen, C. H.; Ridgway B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209; (d) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152; (e) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879-10884; (f) Tran, V. T.; Woerpel, K. A. *J. Org. Chem.* **2013**, *78*, 6609-6383.



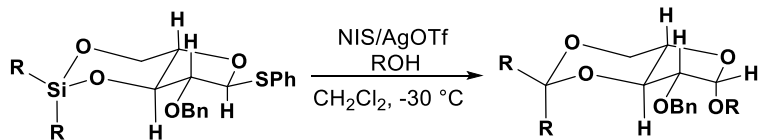
modestly *trans* selective.<sup>12</sup> Woerpel also reported the allylation of a conformationally rigid bicyclic furanoside, which yielded mainly the  $\beta$ -isomer (27 $\alpha$ :73 $\beta$ ).<sup>11b,d,f</sup> From these results, Woerpel postulated that the nucleophile preferably undergoes an "inside attack" on the corresponding oxocarbenium ion intermediate in relation to its <sup>3</sup>E conformation. As illustrated in *Figure 2.3*,<sup>11</sup> the inside attack produces a five-membered product in an initial conformation where the substituents at C<sub>2</sub> and C<sub>3</sub> stagger each other. The alternative "outside attack" produces a five-membered product that eclipses the C<sub>2</sub>–C<sub>3</sub> bond. The inside attack also eclipses the C<sub>3</sub>–C<sub>4</sub> bond, a factor that was used to account for the lower  $\beta$  stereoselectivity for *C*-allylation of the *trans*-fused cyclohexane model (73%) compared to its more conformationally mobile cyclooctane counterpart (93%) as shown in *Figure 2.4*

As will be demonstrated herein, a straightforward application of the BBAH orbital model produces the same general outcome as the Woerpel inside/outside attack model but also accounts for the modulation of glycosylation stereoselectivities due to stereoelectronic interactions between the bent bonds of the oxocarbenium ion intermediates and the substituents at C<sub>2</sub>.



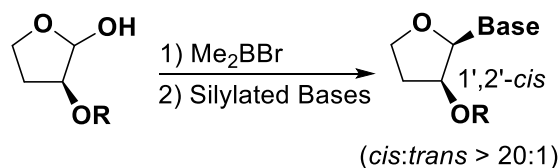
**Figure 2.5** 1,2-*Cis* deuteration or allylation of pentafuranoside analogues (Nu = D or allyl).

<sup>12</sup> (a) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 1169-1174; (b) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.*, **2000**, 3893-3901; (c) Schmitt, A.; Reissig, H.-U. *Chem. Ber.* **1995**, *128*, 871-876; (d) Schmitt, A.; Reissig, H.-U. *Synlett*, **1990**, 40-42.



**Figure 2.6** 1,2-*cis* Glycosylation of arabinose furanoside

analogues of ribose, arabinose, xylose and lyxose bearing different substituents at C<sub>2</sub> (Figure 2.5). The reactions all gave 1,2-*cis* adducts with good (85:15) to excellent (98:2) stereoselectivity. These results were rationalized on the basis of Woerpel's inside attack model by analyzing the most stable conformation of their respective oxocarbenium ions by *ab initio* calculation. In all cases, the major product had the nucleophile *cis* to the C<sub>2</sub> electron-withdrawing group (EWG). Boons and co-workers<sup>13c</sup> also reported the 1,2-*cis* glycosylation of bicyclic 3,5-*O*-di-*tert*-butylsilane arabinose furanoside with several carbohydrate nucleophiles (Figure 2.6). Once again, the nucleophile added *cis* to the C<sub>2</sub> EWG.



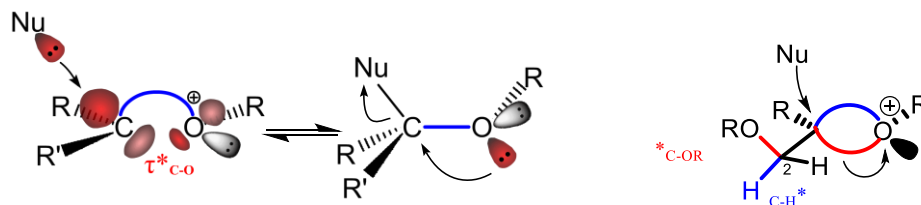
**Figure 2.7** Highly *cis*-selective N-glycosylation of lactols.

Guindon and co-workers<sup>14</sup> reported a highly diastereoselective route to 1',2'-*cis* nucleoside analogues in the D-ribo, D-lyxo, D-xylo and D-arabinoside series. These five-membered ring lactols all underwent highly selective N-glycosylation reactions in the presence of dimethylboron bromide and silylated pyrimidine nucleobases (Figure 2.7). For example, the five-membered lactol having a C<sub>2</sub>-OR group gave the 1',2'-*cis* isomer in high yield (*cis:trans* ratio >20:1). When the OR group at C<sub>2</sub> was replaced by a CH<sub>3</sub> group, the selectivity was completely lost (*cis:trans* ratio 1:1). So, the EWG at C<sub>2</sub> is clearly a dominant factor in the stereoselectivity of furanoside oxocarbenium ion.<sup>11c-d,12b,14,15</sup> These reactions were interpreted through an S<sub>N</sub>1 or an “exploded” transition state model.

<sup>13</sup> (a) van Rijssel, E. R.; van Delft, P.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A.; Fillippov, D. V.; Codée, J. D. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 10381-10385; (b) Vorm, S. v. d.; Hansen, T.; Rijssel, E. R. v.; Dekkers, R.; Madern, J. M.; Overkleeft, H. S.; Filippov, D. V.; Marel, G. A. v. d.; Codée, J. D. C. *Chem. Eur. J.* **2019**, *25*, 7149-7157; (c) Zhu, X.; Kawatkar, S.; Rao, Y.; Boons, G.-J. *J. Am. Chem. Soc.* **2006**, *126*, 11948-11957.

<sup>14</sup> Prévost, M.; St-Jean, O.; Guindon, Y. *J. Am. Chem. Soc.* **2010**, *132*, 12433-12439.

<sup>15</sup> Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553-1565.



**Figure 2.8** Left: Orbital overlap between incoming Nu and antibonding  $\tau^*$  orbital of *anti* C–O  $\tau$  bond produces  $sp^3$  oxygen lone pair antiperiplanar to bound Nu. Right: facial selectivity modulated by hyperconjugation between C<sub>2</sub>–OR and C<sub>2</sub>–H groups antiperiplanar to their respective  $\tau$  bond of the oxocarbenium ion.

As opposed to the Hückel  $\sigma$ - $\pi$  model,<sup>16</sup> the bent bond ( $\tau$  bond) model<sup>17</sup> confers tetrahedral character to the carbon of carbonyl groups and, by extension, to oxocarbenium ions. According to the BBAH, nucleophilic addition to a carbonyl group is viewed as a S<sub>N</sub>2-like process in which the nucleophile specifically displaces the *anti* bent bond, and necessarily generates an antiperiplanar oxygen lone pair on the initial product conformation (*Figure 2.8*).<sup>18</sup> The reverse process, corresponding to the elimination of the nucleophile, must occur by assistance of a strictly antiperiplanar oxygen lone pair to reform the bent bonds of the oxocarbenium ion intermediate. In the furanosyl series, nucleophilic displacement of one of the bent bonds on the <sup>3</sup>E conformation of the oxocarbenium ion yields a product conformation in which the new carbon-nucleophile bond has no choice but to be antiperiplanar to the newly produced oxygen lone pair.

During the addition, a filled orbital on the nucleophile overlaps with the large outer lobe of the antibonding  $\tau^*$  C–O orbital (*Figure 2.8*), and release the  $sp^3$  oxygen lone pair in antiperiplanar fashion.<sup>1-8</sup> The electron density of each  $\tau$  bond can vary independently depending on the stereoelectronic alignment of neighbouring electron-withdrawing or donating groups through hyperconjugation;<sup>19</sup> the BBAH further states that the nucleophile will preferably displace the weaker (i.e. electron poorer)  $\tau$  bond. As shown in *Figure 2.8*,

<sup>16</sup> Huckel, E. *Z. Phys.* **1930**, *60*, 423-456.

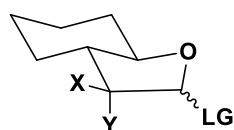
<sup>17</sup> (a) Slater, J. C. *Phys. Rev.* **1931**, *37*, 481-489; (b) Pauling, L. *J. Am. Chem. Soc.* **1931**, *53*, 1367-1400.

<sup>18</sup> (a) Beaulieu, N.; Dickinson R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531-2536; (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, **1983**, Pergamon Press, Oxford; (c) Kirby, A. J. *The Anomeric Effect and Associated Stereoelectronic Effects at Oxygen*, **1983**, Springer-Verlag, Berlin,

<sup>19</sup> Alabugin, V. I. *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, **2016**, John Wiley & Sons, Ltd.; (b) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions. Reference Edition*, John Wiley & Sons, Ltd, **2010**.

one of the oxocarbenium  $\tau$  bonds is electronically enriched by hyperconjugation with an antiperiplanar C–H bond (a  $\sigma_{\text{C-H}} \rightarrow \tau^*$  interaction), while the other  $\tau$  bond is weakened by the antiperiplanar electron-withdrawing OR group (a  $\tau \rightarrow \sigma^*_{\text{C-OR}}$  interaction). As a result, the nucleophile prefers to displace the weaker  $\tau$  bond and adds *cis* to the OR group. One should note that, in the  $\sigma$ - $\pi$  model, the two  $\pi^*$  lobes correspond to the same orbital and cannot be differentiated in this way. The Cieplak effect<sup>20</sup> and Inomata's *syn* effect<sup>21</sup> can thus be easily rationalized using the  $\tau$  bond model. Woerpel does mention possible hyperconjugation between axial C<sub>2</sub>–H bonds in pseudoequatorial pyranosyl oxocarbenium ions.<sup>22</sup>

All the previous results presented in *Figure 2.4-2.7* are readily rationalized by the BBAH orbital model. To further test this model, we synthesized and studied the glycosylation of a series of conformationally rigid *trans* bicyclic furanosides **2.1-2.5** (*Figure 2.9*). Each



<u>Donor</u>	<u>X</u>	<u>Y</u>
2.1	H	H
2.2	OCH <sub>3</sub>	H
2.3	H	OCH <sub>3</sub>
2.4	CH <sub>3</sub>	H
2.5	H	CH <sub>3</sub>

**Figure 2.9**

Glycosylation

donors. LG = OAc or SPh.

compound was prepared with either OAc or SPh group at the anomeric position to allow for both C- and O-glycosylation reactions to be analyzed. Four of these bicyclic models have a OCH<sub>3</sub> or a CH<sub>3</sub> group located either in a  $\beta$ -pseudoequatorial or  $\alpha$ -pseudoaxial orientation at C<sub>2</sub> and a *trans* bicyclic ring fusion that confines their corresponding 5-membered oxocarbenium ions to basically exist in their <sup>3</sup>E conformation. This conformational restriction can potentially affect glycosylation selectivity. Our model compounds do not perfectly reflect the reactivity of fully oxygenated carbohydrates, our goal being to pinpoint the specific stereoelectronic contribution of

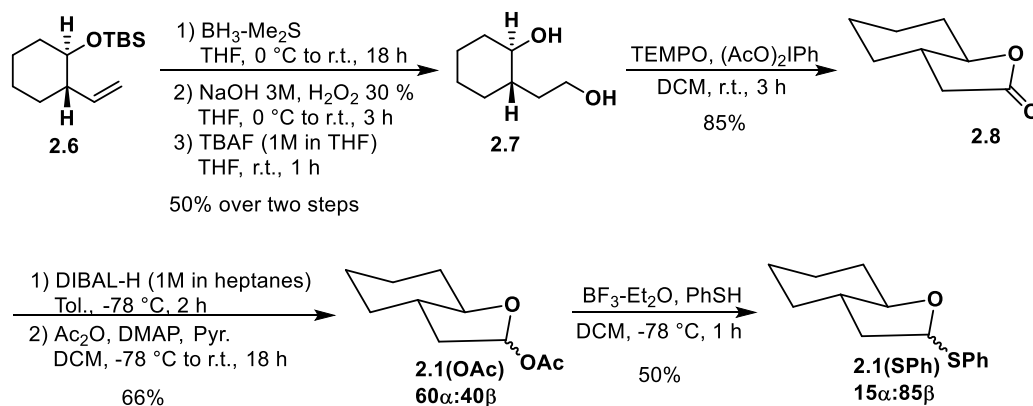
the C<sub>2</sub>-substituents within the BBAH paradigm. This requires simplified carbohydrate donor surrogates in which the oxocarbenium ion is unaffected by other conformational and stereoelectronic factors. Nevertheless, the term glycosylation can still be applied as the conformational limitations of furanoses and the particular reactivity of the anomeric center are two aspects that are shared in our approach.

<sup>20</sup> (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540-4552; (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447-8462.

<sup>21</sup> Inomata, K. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 1172-1182.

<sup>22</sup> Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545-553.

## 2.5 Synthesis of bicyclic models



**Figure 2.10** Synthesis of unsubstituted donors **2.1**

The starting *trans*-fused bicyclic furanosides were obtained by vinyl anion addition to cyclohexene oxide.<sup>23</sup> The non-substituted donors **2.1** (Figure 2.10) were prepared by hydroboration and deprotection of **2.6**, which gave diol **2.7** followed by selective TEMPO oxidation to yield bicyclic lactone **2.8**.<sup>24</sup> The *C*-glycosylation donor **2.1(OAc)** was then prepared from **2.8** through a one-pot reduction-acetylation procedure.<sup>11d</sup> The *O*-glycosylation donor **2.1(SPh)** was obtained from **2.1(OAc)** using a literature procedure.<sup>25</sup>

The preparation of  $\text{C}_2\text{-OCH}_3$  donors **2.2** and **2.3** required a more complex synthetic route, similar to that reported for the synthesis of substituted bicyclic pyranosides (Figure 2.11).<sup>10</sup> Dihydroxylation of **2.6** gave a 2:1 mixture of diols **2.9** in which the primary alcohol was further oxidized to the carboxylic acid using TEMPO followed by a Pinnick oxidation of the aldehyde intermediate.<sup>26</sup> After allyl esterification to yield compound **2.10**, the remaining secondary alcohol was methylated using standard methodology. The resulting diastereoisomers **3.11/3.11'** were separated by chromatography and submitted to a deprotection/cyclization sequence to provide lactones **3.12** and **3.13**. The donors **3.2(OAc)**,

<sup>23</sup> Tobia, D.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 777-782.

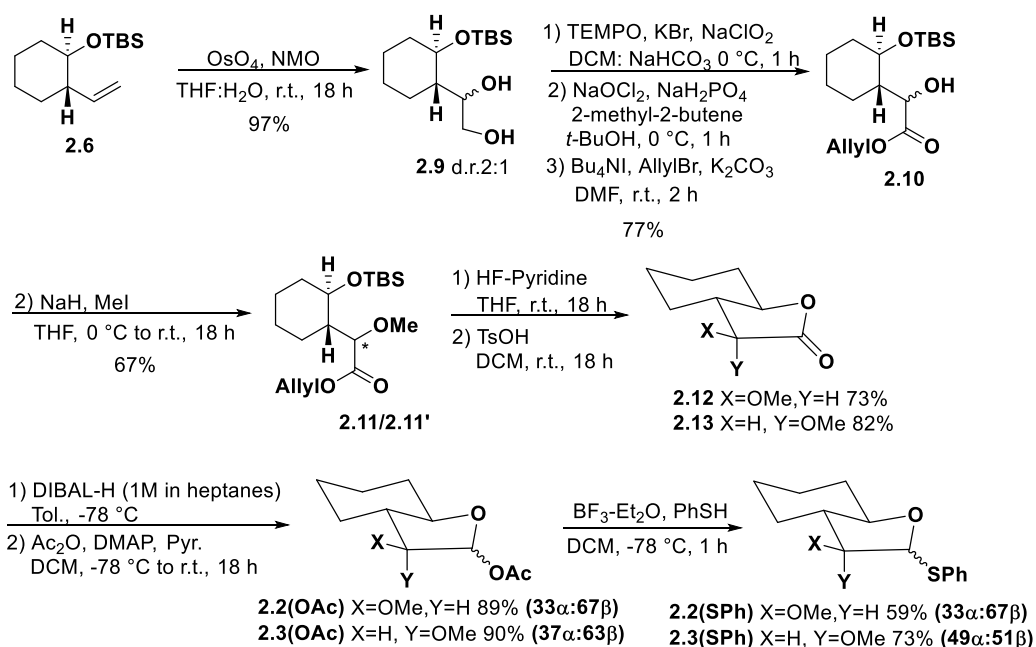
<sup>24</sup> Ebine, M.; Suga, Y.; Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2010**, *8*, 39-42.

<sup>25</sup> Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118.

<sup>26</sup>(a) Yang, T.-F.; Tseng, C.-H.; Wu, K.-I.; Chang, C.-N. *J. Org. Chem.* **2007**, *72*, 7034-7037; (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096.

**3.3(OAc)**, **3.2(SPh)** and **3.3(SPh)** were obtained using the same reaction sequence described above from the corresponding lactone.

The syntheses of donors **2.4** and **2.5** having a methyl group at C<sub>2</sub> began by diethylmalonate anion displacement of cyclohexene oxide, which gave  $\alpha$ -carboxyethylbutyrolactone **2.14** (Figure 2.11). Marshall's reduction protocol<sup>27</sup> then yielded the desired allylic alcohol **2.15**, which was hydrogenated with catalytic platinum(IV) oxide, providing a ~1:1 mixture of diastereoisomeric diols **2.16/2.16'**. Chromatographic separation followed by Stahl oxidation<sup>28</sup> produced corresponding lactones **2.17** and **2.18**. As this reaction is known to use atmospheric oxygen as the external oxidation source, larger scale reactions were speeded-up using pure oxygen gas.<sup>28</sup> These two lactones were obtained in good yields and converted to donors **2.4** and **2.5**. To do so, **2.17** and **2.18** were reduced with DIBAL-H and acetylated to

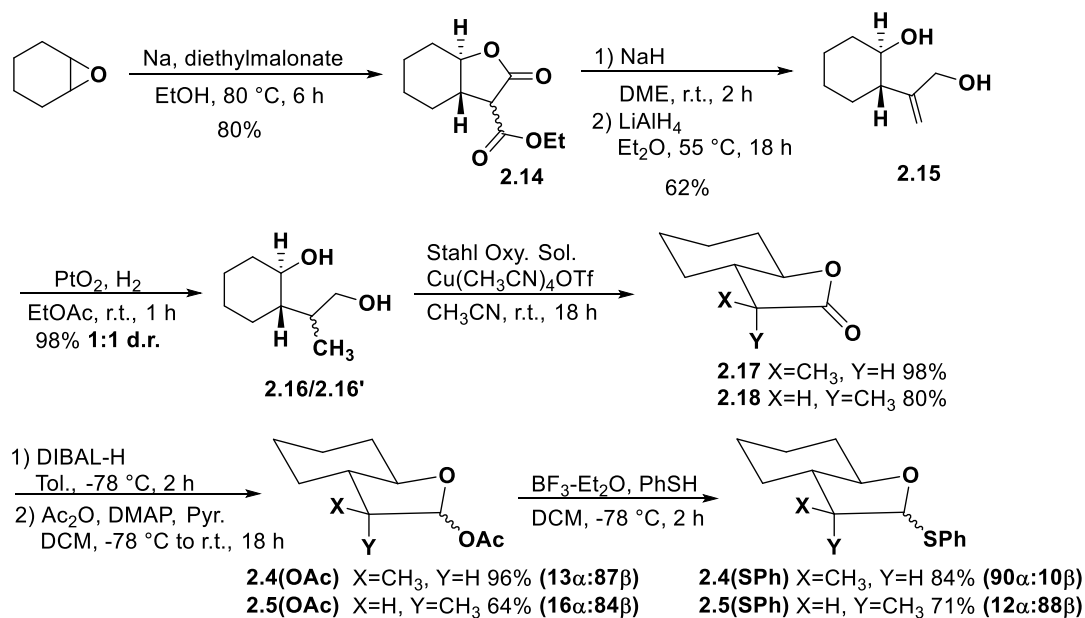


**Figure 2.11** Synthesis of donors **2.2-2.3**.

<sup>27</sup> (a) Marshall, J. A.; Cohen, N.; Arenson, K. R. *J. Org. Chem.* **1965**, *30*, 762-766; (b) Marshall, J. A.; Andersen, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113-118.

<sup>28</sup> (a) Ryland, B. L.; McCann, S. D.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 12166-12173; (b) Xie, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3767-3770.

yield **2.4(OAc)**. (13 $\alpha$ :87 $\beta$ ) and **2.5(OAc)** (16 $\alpha$ :84 $\beta$ ) respectively, providing **2.4(SPh)** (90 $\alpha$ :10 $\beta$ ) and **2.5(SPh)** (12 $\alpha$ :88 $\beta$ ) with PhSH and BF<sub>3</sub>·Et<sub>2</sub>O.

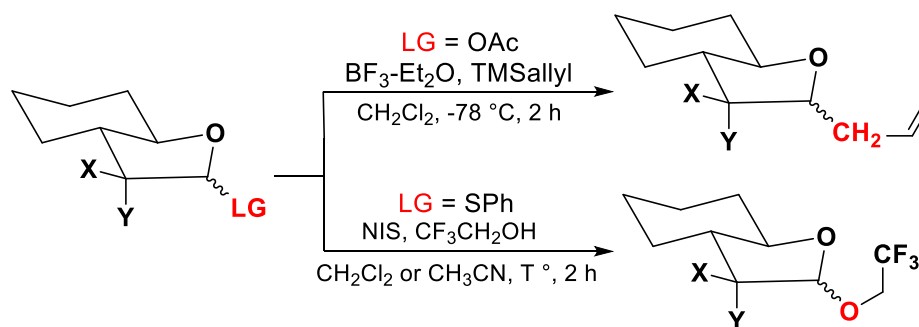


**Figure 2.12** Synthesis of donors **2.4-2.5**.

## 2.6 Glycosylation experiments

Glycosylation experiments were carried out on bicyclic furanosides **2.1-2.5** (Figure 2.9) having OAc or SPh as anomeric leaving groups, allowing for both *C*- and *O*-glycosylation to be investigated. For *C*-glycosylation, the OAc derivatives were reacted with BF<sub>3</sub>·Et<sub>2</sub>O and TMSallyl in CH<sub>2</sub>Cl<sub>2</sub> for 2 h at low temperature. For *O*-glycosylation, the SPh derivatives were reacted with NIS and 2,2,2-trifluoroethanol (TFE) in CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CN for 2 h (Figure 2.13). These conditions were based on the work reported by Woerpel.<sup>25</sup> The *C*-glycosylation conditions do not allow for product epimerization due to the nature of the nucleophile. *O*-glycosylation reaction conditions can, theoretically, lead to product epimerization. However, we showed that this does not occur under the experimental conditions<sup>10</sup>; isolated products resubmitted to glycosylation conditions with a different donor and nucleophile showed no change from their initial anomeric ratio. Thermodynamic conditions were also performed on an isolated product, showing a change in the anomeric ratio over time. This showed that the thioglycosides activated by NIS provided a clean, kinetic glycosylation reaction. All the SPh

donors allowed for the reactions to be carried out without any Lewis acid or stabilizing triflate source, which often can influence the reaction selectivity (*Figure 2.13*). All product ratios reported in *Table 2.1* were duplicated and determined by  $^1\text{H}$  NMR and/or  $^{19}\text{F}$  NMR using the crude mixture of reaction products. The relative configurations at the anomeric center were established by 1D NOESY experiments. Any variation in the reported isolated yields was attributed to the volatility and stability of the glycosylated adduct on silica gel. Crude  $^1\text{H}$  NMR showed a complete conversion to the desired compound in almost every case.<sup>29</sup>



**Figure 2.13** Reaction Conditions for C and O-Glycosylations Described in Table 2.1

<sup>29</sup>Voir Annexe E pour les données spectrales des brutes de réaction.



**Table 2.1** Glycosylation of bicyclic donors **2.1-2.5**.

Entry	Donor	LG	Nu	T °C <sup>d</sup>	Solvent	$\alpha$ : $\beta$ ratio	Yield
1	<b>2.1</b> (X=Y=H)	OAc	TMSallyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	30:70	N.D. <sup>e</sup>
2	"	SPh (15 $\alpha$ :85 $\beta$ )	TFE	-40	"	51:49	37%
3	"	"	"	-40	CH <sub>3</sub> CN	27:73	61%
4	<b>2.2</b> (X=OMe, Y=H)	OAc	TMSallyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	34:66	96%
5 <sup>a</sup>	"	SPh ( $\alpha$ only)	TFE	-40	"	34:66	67%
6 <sup>b</sup>	"	SPh ( $\beta$ only)	"	-78	"	98:2	N.D. <sup>c</sup>
7	"	SPh ( $\alpha$ only)	"	-40	CH <sub>3</sub> CN	34:66	86%
8	"	SPh (69 $\alpha$ :31 $\beta$ )	"	-40	"	33:67	74%
9	<b>2.3</b> (X=H, Y=OMe)	OAc	TMSallyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	6:94	83%
10 <sup>a</sup>	"	SPh (49 $\alpha$ :51 $\beta$ )	TFE	-40	"	18:82	76%
11 <sup>b</sup>	"	"	"	-78	"	13:87	N.D.
12	"	"	"	-40	CH <sub>3</sub> CN	22:78	58%
13	<b>2.4</b> (X=Me, Y=H)	OAc	TMSallyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	60:40	98%
14	"	SPh (90 $\alpha$ :10 $\beta$ )	TFE	-40	"	86:14	73%
15	"	"	"	-40	CH <sub>3</sub> CN	92:8	56%
16	<b>2.5</b> (X=H, Y=Me)	OAc	TMSallyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	>3:97	90%
17	"	SPh (12 $\alpha$ :88 $\beta$ )	TFE	-40	"	7:93	73%
18	"	"	"	-40	CH <sub>3</sub> CN	9:91	56%

<sup>a</sup> The initial temperature was -40 °C and brought to approximately -15 °C. No conversion was observed below -20°C. <sup>b</sup> AgOTf was added as a triflate source and full conversion occurred at -78 °C. <sup>c</sup>No purification performed. Ratio determined using the crude <sup>1</sup>H NMR and/or <sup>19</sup>F NMR. <sup>d</sup> Initial temperature in CH<sub>2</sub>Cl<sub>2</sub> for donor **2.2** and **2.3** was -40 °C and slowly brought to -20 °C over the 2 h reaction period. <sup>e</sup> N.D.: not determined.

## 2.6 Discussion

As demonstrated in our previous work<sup>10</sup> and in other studies,<sup>25,30</sup> stereoselectivity at the anomeric carbon is highly affected by the nature of the nucleophile.<sup>31</sup> Stronger nucleophiles generally exhibit a lower stereoselectivity upon addition to oxocarbenium ion intermediates as a result of earlier glycosylation transition state geometries that are less sensitive to steric and electronic asymmetry near the electrophilic center. However, oxocarbenium ion intermediates may not form easily and, as a result, glycosylations may proceed through an exploded S<sub>N</sub>2-like transition state,<sup>15</sup> especially in the presence of strong nucleophiles or by forming nitrilium ion intermediates.<sup>32</sup> Glycosylations with weak nucleophiles or stabilized glycosyl donors are expected to be more S<sub>N</sub>1-like; the nucleophile addition must then proceed by a later transition state, and be more heavily influenced by steric hindrance and other factors as the nucleophile approaches the electrophilic center. To tease out the factors guiding glycosylation reactions involving oxocarbenium ion intermediates, only the weaker nucleophiles TMSallyl and TFE were considered for this study. Carbon based nucleophiles are believed to react strictly through an S<sub>N</sub>1 mechanism,<sup>31</sup> whereas TFE is generally assumed not to be nucleophilic enough<sup>25</sup> for an S<sub>N</sub>2 mechanism. It is thus anticipated that the anomeric configuration of the donor moiety should not influence the glycosylation stereoselectivity under the reaction conditions described in *Figure 2.13*<sup>33</sup> as they are all assumed to involve oxocarbenium ion intermediates. Results presented for donor **2.2** (entries 7 and 8) support this statement as the initial anomeric orientation of the donor did not influence the selectivity outcome of the reaction.

As shown in donors **2.1-2.3** and **2.5** preferentially formed β-glycosides with the TMSallyl nucleophile (entries 1, 4, 9 and 16) whereas donor **2.4** produced the α-glycoside in slight excess (entry 13). With the TFE nucleophile, *O*-glycosylation in CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CN showed

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<sup>30</sup> van der Vorm, S.; Hansen, T.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Sci.* **2017**, *8*, 1867-1875.

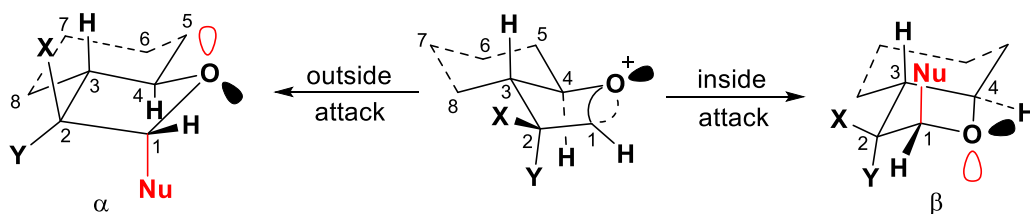
<sup>31</sup> van der Vorm, S.; Hansen, T.; van Hengst, J. M. A.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Soc. Rev.* **2019**, *48*, 4688-4706.

<sup>32</sup> Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747-750.

<sup>33</sup>(a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169; (b) Ayala, L.; Lucero, C. G.; Antoinette, J.; Romero, C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521-15528; (c) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641-2647.

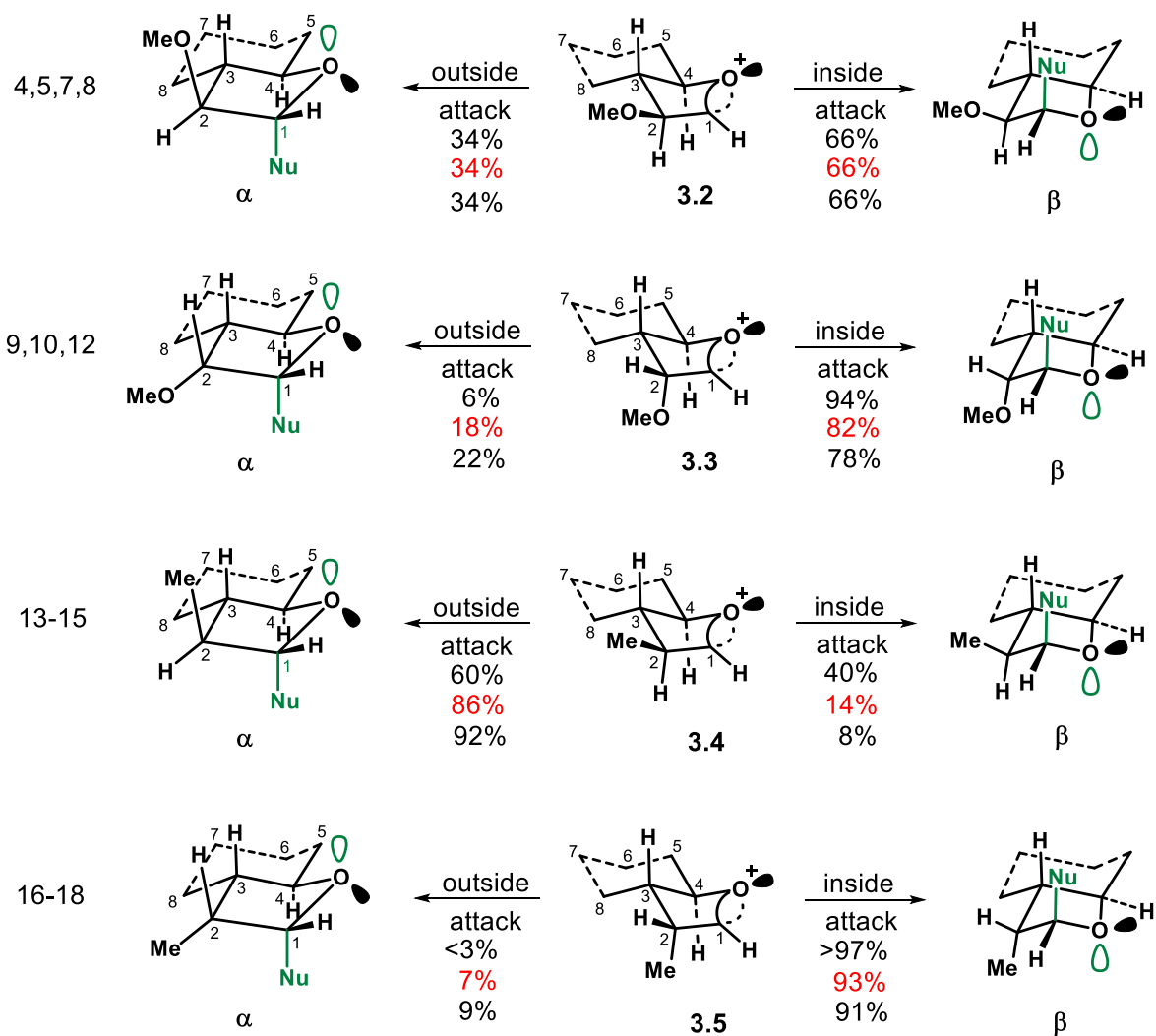
a similar trend in most cases. Donors **2.1-2.3** and **2.5** gave preferentially  $\beta$ -*O*-glycosides (entries 3; 5, 7-8; 10, 12 and 17-18). As above, donor **2.4** gave again mainly  $\alpha$ -*O*-glycosides (entries 14-15).

Overall, the BBAH analysis expands Woerpel's "inside/outside attack" glycosylation model by considering the stereoelectronic influence of neighbouring electron-withdrawing and donating groups on the nucleophilic addition to oxocarbenium ion intermediates. As shown in *Figure 2.14*, inside attack on the fixed  ${}^3E$  conformation of the oxocarbenium ion directly furnishes a  $\beta$ -glycoside in a conformation where the  $C_2$  substituents (X/Y) stagger the  $C_1$  and  $C_3$  groups. Conversely, the outside attack produces an  $\alpha$ -glycoside in a conformation that eclipses the X and Y substituents at  $C_2$  with the axial H and  $C_8$  methylene at  $C_3$ . The BBAH analysis further considers any potential hyperconjugation between  $\tau$  bonds in the oxocarbenium intermediates and the EWG or electron-donating groups (EDG) at  $C_2$  in the glycosylation reactions.



**Figure 2.14** Steric and conformational factors to the  $S_N1$  glycosylation reaction of substituted bicyclic furanosides.

The *C*-glycosylation of donors **2.1-2.5** with TMSallyl in  $CH_2Cl_2$  is illustrated in *Figure 2.15*. As indicated in entry 1 (or *Figure 2.15*) using the carbon-based nucleophile, the bicyclic furanoside **2.1** with no substituent at  $C_2$  gave a 30:70 ratio of the  $\alpha$ - and  $\beta$ -anomers, both under stereoelectronic control. This is in accordance with the results previously reported by Woerpel in which the  $\beta$ -isomer is favored for conformational reasons as a result of the inside attack.<sup>11c</sup> With TFE in  $CH_2Cl_2$  (entry 2), there is an increase in the  $\alpha$ -isomer as the stronger nucleophile predicates an earlier transition state. In  $CH_3CN$  (entry 3), the oxocarbenium ion



**Figure 2.15** C-Glycosylation of donors **2.1-2.5** with TMSallyl and TFE in  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{CN}$ .

more stabilized so the reaction may involve a somewhat later transition state or contact ion pair.<sup>32</sup> The  $\beta$  selectivity is thus observed as with TMSallyl.

In the case of bicyclic oxocarbenium ion **2.2** bearing a  $\beta$ -OCH<sub>3</sub> group, the addition of TMSallyl (entry 4) favors the  $\beta$ -anomer (i.e. inside attack) by favorable displacement of the  $\alpha$ -bent bond that is weakened by hyperconjugation with the antiperiplanar  $\beta$ -OCH<sub>3</sub> group; conversely, the  $\beta$ -bent bond is instead stabilized as it is antiperiplanar to the donating C<sub>2</sub>-H bond.<sup>19,34</sup> Thus,  $\alpha$ -attack is disfavored on stereoelectronic grounds. As for the steric effects,  $\alpha$ -attack should be favored as *trans* addition avoids repulsion between the  $\beta$ -OCH<sub>3</sub> and the incoming nucleophile but is also disfavored because of eclipsing of the C<sub>2</sub>-C<sub>3</sub> bond in the  $\alpha$ -addition product.<sup>35</sup> Overall, *cis* addition to donor **2.2** is slightly favored, and the results with TFE as nucleophile (entries 5, 7-8) are similar to those of TMSallyl (entry 4). The presence of a polar OCH<sub>3</sub> group must produce a more reactive oxocarbenium ion, but TFE is a stronger nucleophile than TMSallyl. As a result, the  $\alpha$ : $\beta$  selectivity remains the same. Interestingly, comparing the reaction of donors **2.1** and **2.2** with TFE in CH<sub>2</sub>Cl<sub>2</sub> (entries 2 and 5) shows an increase of inside attack with donor **2.2** (17%). This indicates that the  $\beta$ -OCH<sub>3</sub> hyperconjugation with the  $\alpha$ -bent bond is more important than the steric repulsion between the nucleophile and the  $\beta$ -OCH<sub>3</sub> during 1,2-*cis* addition. In the more polar CH<sub>3</sub>CN, the inside attack on donor **2.2** (entries 7-8) is slightly less than on donor **2.1** (entry 3).

In the case of donor **2.3** bearing an  $\alpha$ -OCH<sub>3</sub> group (entry 9), the  $\beta$ -anomer through the inside attack is stereoelectronically disfavored by a weakening of the  $\beta$ -bent bond (antiperiplanar to  $\alpha$ -OCH<sub>3</sub>) and concomitant enrichment of the  $\alpha$ -bent bond (antiperiplanar to  $\beta$ -C<sub>2</sub>-H bond). However, the  $\beta$ -attack is sterically favored as it occurs *trans* to the  $\alpha$ -OCH<sub>3</sub> and the inside attack staggers the C<sub>2</sub>-C<sub>3</sub> bond;  $\alpha$ -attack would eclipse the C<sub>2</sub>-C<sub>3</sub> bond including severe repulsion between  $\alpha$ -OCH<sub>3</sub> and C<sub>8</sub>. On the other hand, formation of the  $\alpha$ -isomer is stereoelectronically favored by hyperconjugative effects of the C<sub>2</sub> substituents but is quite sterically disfavored by the outside attack eclipsing the C<sub>2</sub>-C<sub>3</sub> bond, and important repulsion between the OCH<sub>3</sub> and the incoming nucleophile. As a result, the  $\alpha$ -isomer is produced in only 6% with TMSallyl (entry 9). With TFE in CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CN (entries 10 and 12), an

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<sup>34</sup> (a) Laube, T. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 349-350; (b) Rauk, A.; Sorensen, T. S.; von Ragué Schleyer, P. J. *Chem. Soc., Perkin. Trans. 2* **2001**, 869-874.

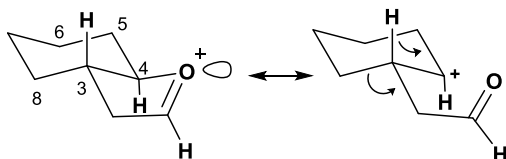
<sup>35</sup> Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, G.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105-1121.

increase of the  $\alpha$ -isomer is observed (~20%) which is probably due to the stronger nucleophile, resulting in a slightly earlier transition state, and lessening the steric selectivity factors.

Donor **2.4** (entry 13) bears a  $\beta$ -Me group at C<sub>2</sub> and is the only one to produce the  $\alpha$ -anomer as major product (60%). In this case, stereoelectronics predict that the  $\beta$ -anomer should be somewhat favored because the  $\beta$ -bent bond is strengthened by hyperconjugation with the antiperiplanar  $\alpha$ -C<sub>2</sub>-H bond (which is assumed to be somewhat more important than the C<sub>2</sub>-CH<sub>3</sub> hyperconjugation) but there is no longer an EWG at C<sub>2</sub> to weaken the antiperiplanar  $\alpha$ -bent bond so the stereoelectronic steering is expected to be less than for entries 4,5,7,8.<sup>34</sup> The  $\alpha$ -anomer should be sterically favored by adding *trans* to the  $\beta$ -CH<sub>3</sub> group but disfavored by this outside attack that eclipses the C<sub>2</sub>-C<sub>3</sub> bond in the  $\alpha$ -anomer.<sup>11d</sup> As a result, reaction of donor **2.4** with the weaker TMSallyl nucleophile (entry 13) should proceed by a later transition state, so the  $\alpha$ -isomer prevails (60%) but formation of the BBAH-favored  $\beta$ -isomer is still important despite the strong steric repulsion. With TFE in CH<sub>2</sub>Cl<sub>2</sub> (entry 14), the major  $\alpha$ -isomer is increased to 86% while in CH<sub>3</sub>CN (entry 15), it is raised to 92%. These two results indicate that increasing the nucleophile reactivity leads to an earlier transition state where the steric aspects prevails, yet not fully, over the hyperconjugation. Again, the percentage of the  $\alpha$ -isomer increases with a more polar solvent and stabilizing solvent.

In the case of donor **2.5**, the  $\beta$ -anomer is strongly favored by both the inside attack and the *trans* addition and is only disfavored by the weak C<sub>2</sub>-H hyperconjugation. Conversely, the  $\alpha$ -anomer is strongly disfavored by the 1,2-*cis* addition and by outside attack which eclipses the C<sub>2</sub>-C<sub>3</sub> bond, including a severe interaction between the  $\alpha$ -CH<sub>3</sub> group and the ring CH<sub>2</sub> group at C<sub>8</sub>. It is only favored by the C<sub>2</sub>-H hyperconjugation. As a result, the  $\beta$ -anomer completely dominates with TMSallyl (entry 16) and is over 90%  $\beta$ -selective with TFE in both solvent (entries 17-18). Again, there is a slight decrease of the  $\beta$ -isomer with the stronger nucleophile TFE, as the earlier transition state is less sensitive to the steric environment. Thus, the BBAH can rationalize correctly all these results at the molecular level using classic organic chemistry principles.

Interestingly, it was also noticed that the electron-donating effect of the CH<sub>3</sub> group can be clearly perceived through the reaction conditions of donors **2.4** and **2.5**, where the glycosylation reaction could be kept at -40 °C for the entire transformation without having to increase the temperature, which was required for donors **2.2** and **2.3** bearing an OCH<sub>3</sub> EWG group. Consequently, the oxocarbenium ion from donors **2.4** and **2.5** would be more stable because of the CH<sub>3</sub> hyperconjugation. This observation led to a realization that the different stereoselectivities observed for donors **2.2-2.5** and those of sugar-furanosides described in *Figure 2.4*, *2.3-2.5* could be explained by the different reactivity of their oxocarbenium ions. In carbohydrates, all the OR groups should destabilize their corresponding oxocarbenium ions through electron-withdrawing inductive effects, rendering



**Figure 2.16** Resonance structures of a carbobicyclic oxocarbenium ion.

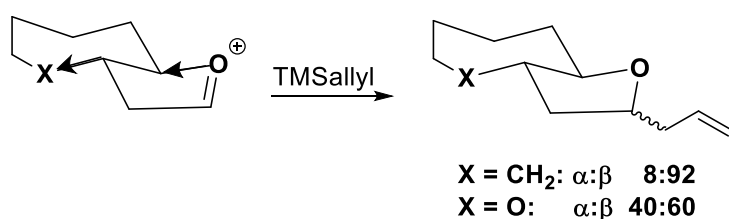
them more reactive, and resulting in earlier transition states for nucleophilic addition. Thus, the favored 1,2-*cis* addition described in *Figure 2.4*, *2.3-2.5* would be the result of an inside attack

and the hyperconjugation effect of the OCH<sub>3</sub> group. In bicyclic donor models **2.1-2.5**, the oxocarbenium ion should be more stable, less reactive, resulting in later transition states for nucleophilic addition. Indeed, for donors **2.1-2.5**, both the C<sub>5</sub>-C<sub>6</sub> and C<sub>3</sub>-C<sub>8</sub> bonds are antiperiplanar to the C<sub>4</sub>-O bond so the oxocarbenium ion should be more stable and less reactive. This hyperconjugation effect can be expressed by the resonance structures indicated in *Figure 2.16*.<sup>34</sup>

As indicated in entries 2 and 3 (*Table 2.1* and *Figure 2.15*), glycosylation of donor **2.1** with TFE occurs even at a steady -40°C, which clearly indicates that the oxocarbenium ion intermediate is easily formed and must be relatively stable. This result is further confirmed by the observation that, on treatment of 3,5-*O*-di-*tert*-butylsilyl arabinose (*Figure 2.6*) with our glycosylation conditions (NIS, CH<sub>3</sub>CN, no Lewis acid), no reaction was observed even at 0°C because the oxocarbenium ion is likely not produced. This highly oxygenated donor was synthesized using reported protocols by Crich<sup>15</sup> and Zhu.<sup>36</sup>

<sup>36</sup> Wang, Y.; Maguire-Boyle, S.; Dere R. T.; Zhu, X. *Carbohydr. Res.* **2008**, *343*, 3100-3106.

Thus, the glycosylation of donors **2.1-2.5**, compared to that of carbohydrate-derived donors, must occur through later transition states because of their increased oxocarbenium ion stability. Conversely, the glycosylation of carbohydrate penta-furanoside derivatives must occur through earlier transition states because of the inductive effect of several neighbouring oxygens. As a result, the known 1,2-*cis* addition observed in the glycosylation of the 4,6-*O*-benzylidene derivatives of glucose and mannose must occur through earlier transition states in which the stereoselectivity is essentially controlled by the orientation of the C<sub>2</sub>-OR group. Supporting the above analysis, Woerpel and co-workers reported<sup>11f</sup> that, in the postulated 7-



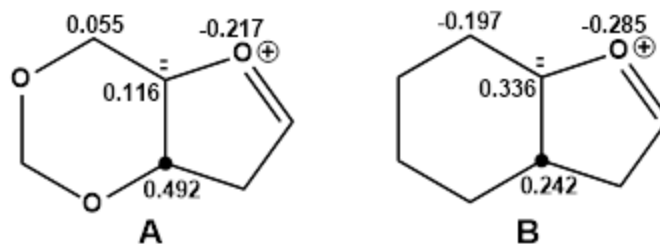
**Figure 2.17** Remote oxygen effect on selectivity.

membered bicyclic furanoside oxocarbenium intermediates, the  $\alpha$ -outside attack is weak (8%) when X=CH<sub>2</sub> and become important (40%) when X=O (Figure 2.17).

The electron-withdrawing effect of benzylidene groups on oxocarbenium ion reactivity was modeled by DFT calculations. B3LYP/6-31G\* calculations were performed on (3a*S*,7a*R*)-1,4,6-trioxahexahydroindene **A** (i.e. model of benzylidene-fused furanosyl oxocarbenium ion) and (3a*S*,7a*R*)-1-oxa-octahydroindene **B** (i.e. cyclohexane-fused furanosyl oxocarbenium ion) from which Merz-Kollman atomic partial charges were derived (Figure 2.18).<sup>37</sup> Partial charges on the oxocarbenium oxygen were found to be -0.217 for the benzylidene model **A**

<sup>37</sup> (a) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.*, **1984**, *5*, 129-145; (b) Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

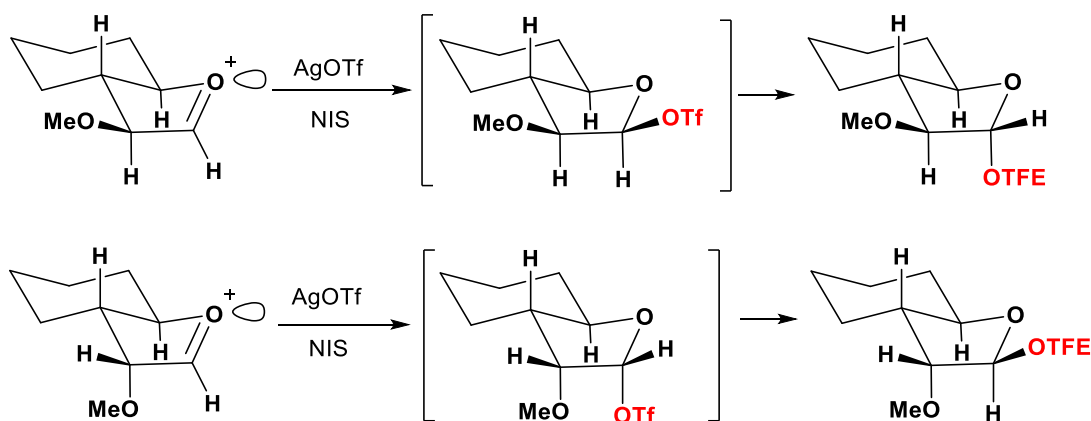




**Figure 2.18** Merz-Kollman charges for oxocarbenium ion models from on B3LYP/6-31-G\* calculation.

and -0.285 for the cyclohexane model **B**, supporting the remote electron-withdrawing effect of the benzylidene oxygens on the oxocarbenium oxygen.

Finally, entries 6 and 11 of *Table 2.1* describe the glycosylation using conditions reported by Crich<sup>15</sup> in which AgOTf was added in catalytic amount to the standard conditions, under the assumption that catalytic triflate might provide insight into the nature of the reaction intermediate. To our surprise, selectivity was inverted in entry 6 for donor **2.2** (98 $\alpha$ :2 $\beta$  vs 34 $\alpha$ :66 $\beta$  initially), whereas donor **2.3** produced a greater  $\beta$ -selective glycosylation (entry 11). The transformations occur rapidly even when maintained at -78°C. One can argue that the triflate may preferentially form a  $\alpha$  or  $\beta$  covalent bond at the anomeric center depending on the orientation at C<sub>2</sub>. Considering the weak nucleophilic nature of TFE, the covalent C<sub>1</sub>-OTf bond would have to be highly labile. Thus, formation of a covalent triflate intermediate could follow the bent bond approach by addition to the weaker  $\tau$  bond followed by S<sub>N</sub>2-like



**Figure 2.19** Glycosylation in the presence of AgOTf/NIS with TFE.

displacement with TFE as illustrated in *Figure 2.19*.<sup>38</sup> A contact ion pair can also be considered, which would stabilize the oxocarbenium ion. The presence of a Lewis acid is also known to activate the NIS, which catalyses the reaction. This would explain the high reactivity observed at lower temperature but not the inversion of selectivity.<sup>39</sup>

## 2.7 Summary

This paper reports the *C*- and *O*-glycosylation of bicyclic furanosides **2.1-2.5** with allyltrimethylsilane and trifluoroethanol, respectively. These reactions were carried out to test whether the bent bond / antiperiplanar hypothesis (BBAH) orbital model could rationalize the stereoselectivity of glycosylation reactions. The analysis expands Woerpel's "inside/outside attack" reaction model by incorporating the stereoelectronic influence of electron-withdrawing (i.e. OCH<sub>3</sub>) and electron-donating (i.e. H or CH<sub>3</sub>) groups at C<sub>2</sub> on the relative nucleophilic displacement of the two  $\tau$  bonds of the oxocarbenium ion intermediates.

Interestingly, the glycosylation stereoselectivities on bicyclic oxocarbenium glycosyl donors **2.1-2.5** (*Figure 2.9*) turned out to be quite different than those reported for five-membered carbohydrates containing multiple OR groups as shown in *Figure 2.5-5*. The glycosylation stereoselectivities for sugar-derived furanosides are rationalized by the Woerpel model with the BBAH-based premise that nucleophilic addition to the oxocarbenium ion intermediates proceeds by early transition states, and that the generally preferred 1,2-*cis* stereoselectivity is due largely to the orientation of the C<sub>2</sub>-OR group relative to the  $\tau$  bonds of the oxocarbenium ion intermediates.

In the case of the bicyclic donors **2.1-2.5**, the glycosylation outcomes are different because the oxocarbenium ion intermediates are stabilized by opposite hyperconjugative effects involving CH<sub>2</sub> groups at C<sub>5</sub> and C<sub>8</sub>. As a result, they form more easily at lower temperatures, whereas their carbohydrate furanoside counterparts were not reactive at the same temperatures under our glycosylation reaction conditions. Thus, nucleophilic addition to the

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<sup>38</sup> van der Vorm, S.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *J. Org. Chem.* **2017**, *82*, 4793-4811.

<sup>39</sup> (a) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331-1334; (b) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769-782.

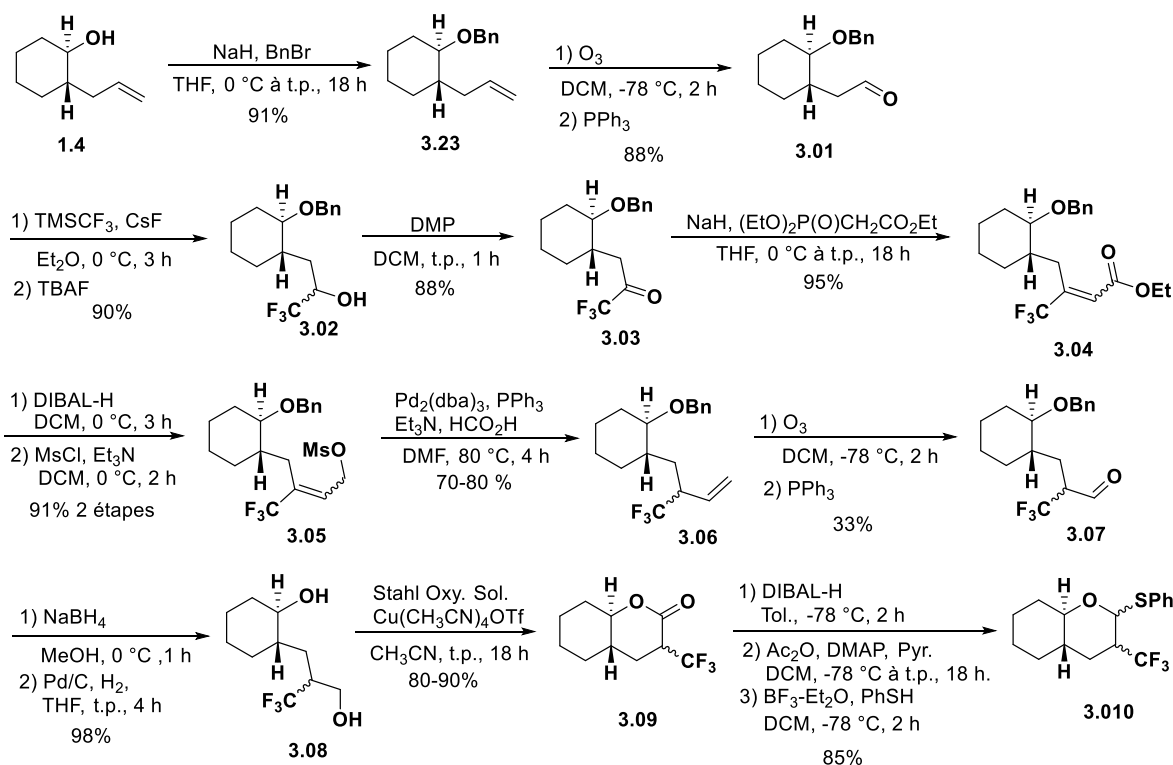
stabilized oxocarbenium ions **2.1-2.5**, must proceed through later transition states than for their carbohydrate counterparts. Consequently, the conformationally preferred inside attack on donors **2.1-2.3** and **2.5** becomes more important, favoring the  $\beta$ -glycosylation. The electron donating  $\text{CH}_3$  group at  $\text{C}_2$  plays both a steric and a stereoelectronic role (stabilizing the adjacent antiperiplanar  $\tau$  bond). Thus, the  $\alpha$ -glycosylation in bicyclic model **2.4** is now favored.

# Chapitre 3 Bent Bond/Antiperiplanar Hypothesis: Modulating the Reactivity and the Selectivity in the Glycosylation of Bicyclic Pyranoside Models

## 3.1 Avant-Propos

Pour donner suite aux résultats intéressants obtenus avec les furanosides C<sub>2</sub>-Me substitués, il est apparu prometteur d'étendre la gamme de substituants en C<sub>2</sub> dans les bicyclics pyranosides. Ces derniers possèdent des caractéristiques géométriques beaucoup moins contraignantes, ce qui permettrait en théorie de percevoir une modulation de la sélectivité beaucoup plus importante en fonction du substituant et de ses différentes propriétés. L'introduction du groupement électrodonneur C<sub>2</sub>-Me s'est donc imposée comme la première étape dans la variation des substituants. Qui plus est, la stratégie de synthèse servant à introduire ce groupement a été développée auparavant dans la préparation des furanosides C<sub>2</sub>-Me (*Figure 2.2*), ce qui en a facilité la synthèse. Pour faire contraste en termes d'électronégativité tout en conservant la gêne stérique provenant de ce type de substitution, l'insertion d'un groupement CF<sub>3</sub> a été tentée. D'un point de vue théorique, une approche comparative des groupements C<sub>2</sub>-CF<sub>3</sub> et CH<sub>3</sub> sur la sélectivité de la réaction de glycosylation peut être un argument de taille à l'utilisation des liaisons courbes si les résultats sont concomitants avec le rationnel du modèle. Il aurait été également très intéressant de faire varier la substitution d'un à trois fluors sur le méthyle du C<sub>2</sub>-CH<sub>3</sub> pour en noter les effets stéréoelectroniques dans l'oxocarbénium. Cette approche a toutefois dû être mise à l'écart pour des raisons synthétiques et pratiques.

D'une manière plus détaillée, l'introduction d'un groupement C<sub>2</sub>-CF<sub>3</sub> s'est avérée lourde en termes d'étapes de synthèse. Comme le dépeint la *Figure 3.1*, douze transformations à partir de l'époxyde du cyclohexène sont nécessaires à la fabrication des différentes formes du donneur. L'étape clé de ce schéma réactionnel est, comme pour plusieurs donneurs présentés jusqu'ici, d'obtenir la forme diol 1,5 avec la substitution désirée au deuxième carbone de la chaîne. La stratégie envisagée initialement a été d'obtenir un vinyle CF<sub>3</sub> pour en faire une hydroboration/oxydation anti-markovnikov. Aucune source de bore ne s'est toutefois avérée efficace pour cette transformation. Il a donc été envisagé d'exploiter une séquence plus

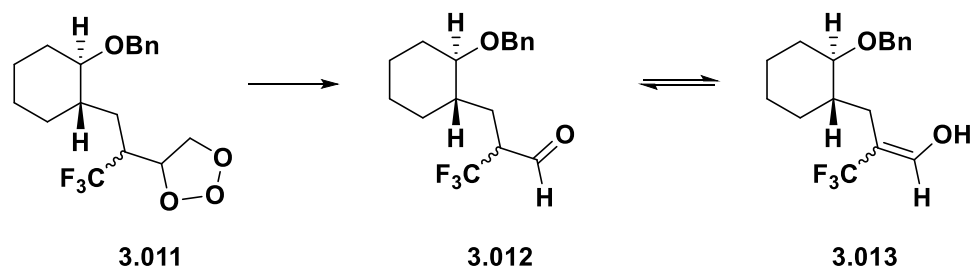


**Figure 3.1** Préparation d'un donneur C<sub>2</sub>-CF<sub>3</sub>.

longue nécessitant l'homologation de deux carbones à l'aide de la réaction de Horner-Wadsworth-Emmons pour ensuite, grâce à une formylation catalysée au palladium, en déplacer l'insaturation en bout de chaîne.<sup>1</sup> Cette séquence donne donc accès à un précurseur du diol **3.08**. Cependant, l'ozonolyse de l'alcène terminal en aldéhyde ou en alcool a posé un problème. Cette méthode toujours très utile n'a pas mené au résultat escompté, mais plutôt à un retour en arrière de plusieurs étapes jusqu'à la cétone CF<sub>3</sub> **3.03**. Une des explications plausibles à cette réactivité inattendue est que le carbonyle formé lors de la décomposition du molozonide est majoritairement l'aldéhyde (**3.13**) substitué.<sup>2</sup> La présence du CF<sub>3</sub> augmentant l'acidité du proton au carbone α, la forme énol de ce même aldéhyde devient donc l'espèce majoritaire dans le milieu réactionnel et peut de nouveau réagir avec l'ozone pour former la cétone α-CF<sub>3</sub> **3.03** ultimement isolée (Figure 3.2). Malgré cet accroc, les diastereoisomères du diol **3.08** ont tout de même été isolés en faible quantité après réduction de l'aldéhyde résultant de l'ozonolyse et de la déprotection de l'alcool secondaire. Le reste

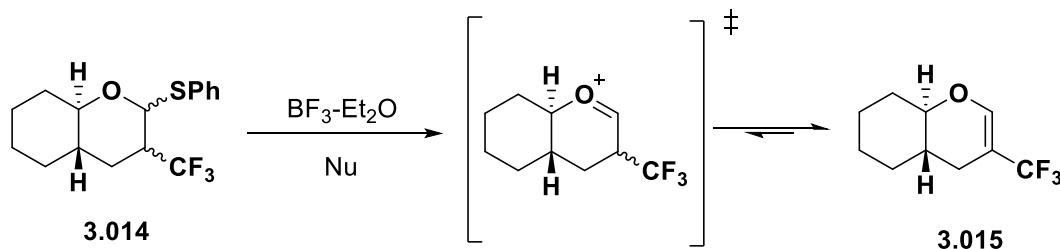
<sup>1</sup> Konno, T.; Takehana, T.; Mishima, M.; Ishihara, T. *J. Org. Chem.* **2006**, *71*, 3545-3550.

<sup>2</sup> Geletneky, C.; Berger, S. *Eur. J. Org. Chem.* **1998**, *1998*, 1625-1627.



**Figure 3.2** Formation de l'intermédiaire énoïl lors de l'ozonolyse.

de la séquence synthétique a donc été explorée pour confirmer la viabilité des donneurs. Malheureusement, la transformation du diol en lactone via l'oxydation de Stahl<sup>3</sup> a causé une épimérisation au carbone portant le groupement CF<sub>3</sub>. Le mécanisme réactionnel de cette transformation inclut une oxydation en deux temps de l'alcool primaire en aldéhyde puis du lactol formé intramoléculairement en lactone. Comme pour l'ozonolyse, il semblerait que la première étape d'oxydation à l'aldéhyde génère l'épimérisation du centre chiral adjacent par une forte propension à générer la forme énoïl par tautomérisation. Le diol 1,5 est somme toute convertit efficacement en lactone. Toutefois, il s'est avéré impossible de séparer les diastéréoisomères correspondants. De nouveau, la suite de la synthèse a été étudiée afin de confirmer la possibilité de générer des donneurs de liaison glycosidique portant un CF<sub>3</sub> et d'en établir la réactivité dans les conditions réactionnelles usuelles. Alors que les furanosides C<sub>2</sub>-F ne montraient aucune propension à former l'oxocarbenium, les tentatives de glycosylation conduites avec le mélange de pyranoses C<sub>2</sub>-CF<sub>3</sub> **3.10** ont plutôt mené au produit d'élimination correspondant. C'est de nouveau l'acidité accrue du proton en C<sub>2</sub> engendrée par la présence du CF<sub>3</sub> qui pose un problème et qui favorise l'élimination lors de l'éjection



**Figure 3.3** Réactivité d'un donneur C<sub>2</sub>-CF<sub>3</sub>.

<sup>3</sup> (a) Ryland, B. L.; McCann, S. D.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 12166-12173;  
 (b) Xie, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3767-3770.

du groupe partant en position anomérique plutôt que la formation d'un oxocarbenium (*Figure 3.3*).

Riche de ces échecs avec les composés fluorés comme groupements directeurs de glycosylation, il a alors été envisagé de modifier la nature électronique du groupement C<sub>2</sub>-OBn préalablement étudié. Cette approche permet de comparer directement l'apport électronique du groupement C<sub>2</sub> à l'une ou l'autre des liaisons  $\tau$  de l'oxocarbenium tout en conservant le même caractère stérique. Les deux variations initialement envisagées sur le cycle aromatique du benzyle étaient le *p*-NO<sub>2</sub> et le *p*-OMe, lesquelles pourraient s'effectuer à partir de la lactone C<sub>2</sub>-OH. La première modification n'a toutefois pas été accomplie malgré de nombreux efforts. L'alkylation directe du bromure correspondant est très peu favorisée, puisque la position benzylique est déstabilisée à la fois par l'effet inducteur du NO<sub>2</sub> et par résonance. L'utilisation de conditions acides par le trichloroacétimide du benzyle *p*-NO<sub>2</sub> ne s'est pas montrée efficace non plus. C'est alors que l'utilisation du 3,5 bistrifluorométhyle a été envisagée comme fonction modulatrice de la densité électronique du benzyle.

Comme en dépeint l'article présenté dans ce chapitre, cette modification a mené à des résultats très particuliers qui ont permis d'explorer davantage un aspect stéréoélectronique débattu par la communauté, c'est-à-dire l'effet anomère inverse. Cet effet est généralement marginalisé et peu mentionné puisqu'il ne pouvait être justifié jusqu'à maintenant que dans un contexte particulier où le groupement anomérique est un composé azoté chargé, par exemple, comme un pyridinium.<sup>4</sup> Ce facteur se juxtapose parfaitement avec le modèle des liaisons courbes lorsque l'oxonium est fortement activé et que le solvant utilisé est l'acétonitrile. Comme quoi, aussi bien faire une pierre deux coups lorsqu'il vient temps de proposer une théorie qui sort des sentiers battus.

Par souci de consistance avec l'article présenté au chapitre 2 sur les furanosides, des études computationnelles ont été effectuées par notre collaborateur Ghislain Deslongchamps sur la réactivité de l'intermédiaire oxocarbenium en fonction des substituants. La synthèse d'un donneur modèle complètement oxygéné a aussi été effectuée afin d'établir un comparatif

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<sup>4</sup> Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527-548.

entre la réactivité des donneurs simplifiés qui sont proposés et celle plus propre à une chimie des glucides. Cela a comme bienfait de démontrer que l'utilisation de donneurs de liaisons glycosidiques dépourvus de facteurs électroniques secondaires permet d'étudier la transformation dans un domaine de réactivité donnant accès à une perception accrue des effets stéréoelectroniques principaux à travers le modèle des liaisons  $\tau$ .

Tout comme pour l'article présenté au *Chapitre 2*, ce manuscrit a été soumis au *Journal of Organic Chemistry* de l'ACS. Cette décision allait de soi, car notre travail sur les furanosides a été bien reçu de la part de l'éditeur et des évaluateurs. Aussi, ces nouveaux résultats s'inscrivent dans la continuité de nos travaux antérieurs, ce qui rend légitime le choix d'un même journal.



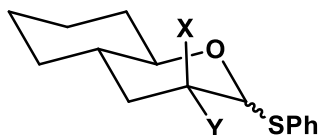
### 3.2 Résumé

Des réactions de glycosylations ont été conduites sur une série de pyranosides bicycliques C<sub>2</sub>-substitués pour en isoler et analyser les facteurs contrôlant la stéréosélectivité lors de la glycosylation d'hydrates de carbone. Le modèle orbitalaire liaison courbe/ hypothèse antipériplanaire (BBAH) rationalise tous les résultats rapportés en considérant des interactions hyperconjugantes entre différents substituants en C<sub>2</sub> et les deux liens tau  $\tau$  (liens courbes) d'intermédiaires oxocarbéniums formés dans les conditions de glycosylation. Selon le modèle BBAH, un nucléophile s'additionne sur l'intermédiaire oxocarbénium par un déplacement S<sub>N</sub>2 antipériplanaire de sa liaison  $\tau$  la plus pauvre.

### 3.3 Abstract

Glycosylation reactions were performed on a series of bicyclic C<sub>2</sub>-substituted pyranoside models to isolate and analyze factors that control the glycosylation stereoselectivities observed in carbohydrates. The bent bond / antiperiplanar hypothesis (BBAH) orbital model rationalizes all these results by considering hyperconjugation interactions between groups at C<sub>2</sub> and the two  $\tau$  bonds (bent bonds) of oxocarbenium ion intermediates formed under the glycosylation conditions. According to the BBAH, nucleophiles add to the oxocarbenium intermediates by S<sub>N</sub>2-like antiperiplanar displacement of the weaker of its two  $\tau$  bonds.

### 3.4 Specific introduction



<u>Donor</u>	<u>X</u>	<u>Y</u>
1.1	H	H
1.3	OBn	H
1.2	H	OBn
3.4	OBn(CF <sub>3</sub> ) <sub>2</sub>	H
3.5	H	OBn(CF <sub>3</sub> ) <sub>2</sub>
3.6	OPMB	H
3.7	H	OPMB
3.8	CH <sub>3</sub>	H
3.9	H	CH <sub>3</sub>
3.10	OTBS	H
3.11	H	OTBS

**Figure 3.4** Glycosylation donors.

Because the glycosylation reaction is a key step for most processes involving carbohydrate synthesis, new methods for improving both the yield and the stereoselectivity of these reactions continue to be reported.<sup>5</sup> Over the last nine years, we have reported on the initial development and multiple applications of the bent bond / antiperiplanar hypothesis (BBAH), a conceptually novel orbital model for rationalizing the reactivity of various types of unsaturated systems.<sup>6,7,8,9,10,11,12</sup> In this regard, we sought to better understand the fundamental principles governing the stereoselectivity of glycosylation reaction at the anomeric center of carbohydrates. We have previously shown that the *O*- and *C*-glycosylation of simplified bicyclic pyranoside<sup>13</sup> and furanoside<sup>14</sup> models under S<sub>N</sub>1 conditions could be rationalized through the BBAH model.<sup>6</sup> We wish to report an important extension of the initial study using bicyclic pyranoside model substrates bearing a wider variety of substituent types at C<sub>2</sub> in terms of electronic and steric properties. The glycosylation stereoselectivity results for glycosyl donors **3.4-3.11** are thus reported and compared to those for the unsubstituted donor **1** and the C<sub>2</sub> *O*-benzylated donors **1.2-1.3**<sup>13</sup> (Figure 3.4).

<sup>5</sup> (a) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144-1153; (b) Moons, S. J.; Mensink, R. A.; Bruekers, J. P. J.; Vercammen, M. L. A.; Jansen, L. M.; Boltje, T. J. *J. Org. Chem.* **2019**, *84*, 4486-4500; (c) Yao, H.; Vu, M. D.; Liu, X.-W. *Carbohydr. Res.* **2019**, *473*, 72-81.

<sup>6</sup> Deslongchamps, G.; Deslongchamps, P. *Org. Biomol. Chem.* **2011**, *9*, 5321-5333.

<sup>7</sup> (a) Deslongchamps, G.; Deslongchamps, P. *Tetrahedron* **2013**, *69*, 6022-6033; (b) Chen J.; Wulff J. E. *Org. Biomol. Chem.* **2016**, *14*, 10170-10174.

<sup>8</sup> Deslongchamps G.; Deslongchamps, P. *Org. Biomol. Chem.* **2016**, *14*, 7754-7767.

<sup>9</sup> Parent, J.-F.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 3299-3304.

<sup>10</sup> Deslongchamps, G.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 5751-5755.

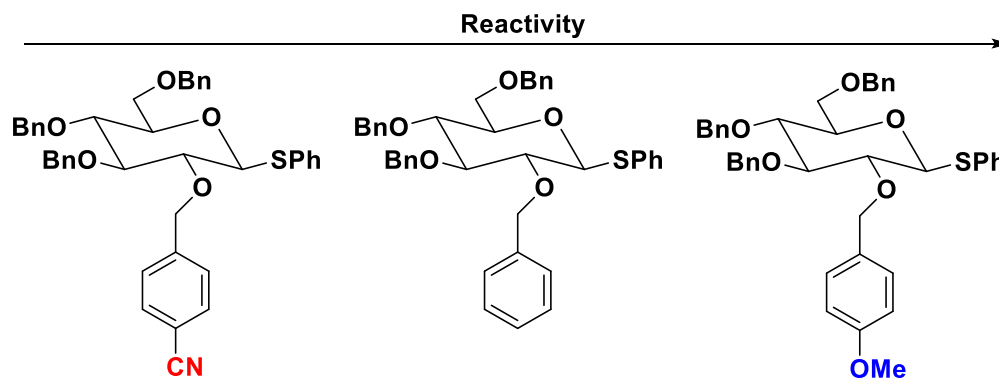
<sup>11</sup> Deslongchamps, G.; Deslongchamps, P. *J. Org. Chem.* **2018**, *83*, 10383-10388.

<sup>12</sup> Deslongchamps; G.; Deslongchamps, P. *Org. Biomol. Chem.* **2019**, *17*, 7007-7012.

<sup>13</sup> Parent, J.-F.; Deslongchamps, P. *Org. Biomol. Chem.* **2016**, *14*, 11183-11198.

<sup>14</sup> Parent, J.-F.; Bertrand, X.; Deslongchamps, P.; Deslongchamps, P. *J. Org. Chem.* **2020**, *85*, 758-773.

In 2016, Jensen group reported that three different benzyl substituents at C<sub>2</sub> influenced the reactivity of 3,4,6-tribenzylated glucosyl donors (*Figure 3.5*).<sup>15</sup> Glycosyl donors with the electron-withdrawing *p*-cyanobenzyl groups at C<sub>2</sub> were found to be less reactive than electron-donating *p*-methoxybenzyloxy (OPMB) group. This gave them the opportunity to perform an armed/disarmed coupling between two glycosylation donors with different protecting groups. Neither the conformational features of the donors nor the specific glycosylation reaction conditions could account for the observed stereoselectivities at the anomeric carbon. However, higher temperatures were required to perform glycosylations on the donors bearing a C<sub>2</sub> electron-withdrawing group (EWG) compared to those bearing an electron-donating group (EDG) at the same position, which in turn could influence the glycosylation stereoselectivities.



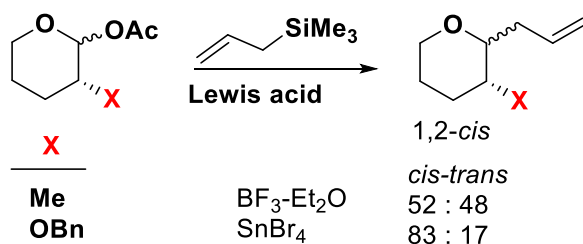
**Figure 3.5** Relative reactivity in function of C<sub>2</sub>.

Woerpel reported on the effect of an EDG or EWG at C<sub>2</sub> using simplified, conformationally mobile pyranoside models (*Figure 3.6*).<sup>16</sup> The *cis* stereoselectivity observed for the C<sub>2</sub>–OBn substituted tetrahydropyran donor was rationalized via an oxocarbenium intermediate in an energetically favored <sup>4</sup>H<sub>3</sub> half-chair conformation stabilized by hyperconjugation with the axial C<sub>2</sub>–H bond.<sup>16c</sup> The nucleophile was then assumed to attack the oxocarbenium intermediate from the face leading directly to the product in a chair conformation.

<sup>15</sup> Heuckendorff, M.; Poulsen, L. T.; Jensen, H. H. *J. Org. Chem.* **2016**, *81*, 4988-5006.

<sup>16</sup> (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169; (b) Ayala, L.; Lucero, C. G.; Antoinette, J.; Romero, C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521-15528; (c) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545-553.

These results can be readily rationalized by the BBAH model,<sup>6,13,14</sup> considering hyperconjugation of the C<sub>2</sub> substituents.<sup>17</sup> In the oxocarbenium intermediate, hyperconjugation between the electron-donating C<sub>2</sub>–H bond and its antiperiplanar τ bond (σ<sub>CH</sub>→τ\* interaction) increases electron density of that bent bond. By the same token,

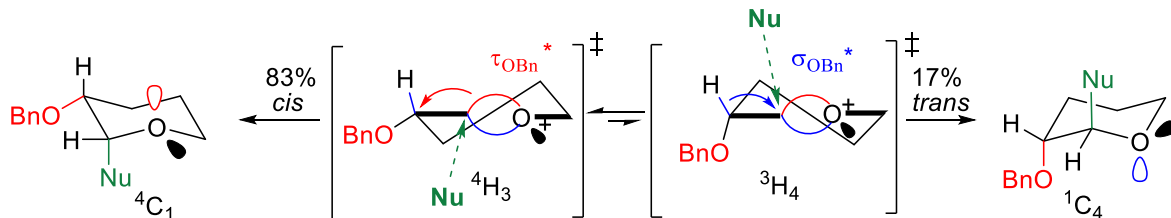


**Figure 3.6** C<sub>2</sub>-substituted pyranoside C-glycosylation.

hyperconjugation between the electron withdrawing C<sub>2</sub>–OBn bond and its antiperiplanar τ bond (τ → σ\*<sub>OBn</sub> interaction) decreases electron density of the latter. As a result, incoming nucleophiles will preferentially displace the weaker of the two τ bonds in S<sub>N</sub>2-like fashion. As shown in

Figure 3.7, the oxocarbenium ion can equilibrate between half-chair <sup>4</sup>H<sub>3</sub> or <sup>3</sup>H<sub>4</sub> conformations, the OBn group being only slightly more hindering in the latter. Nucleophilic attack from the α face of the <sup>4</sup>H<sub>3</sub> conformer displaces the weaker τ bond (shown in red) despite developing steric hindrance with the OBn group to produce the major *cis* product directly in its <sup>4</sup>C<sub>1</sub> chair. Nucleophilic attack from the β face of the <sup>4</sup>H<sub>3</sub> form would initially produce the *trans* adduct but as a high-energy twist-boat (displacing the stronger τ bond shown in blue) and can be dismissed from further analysis. As for the <sup>3</sup>H<sub>4</sub> oxocarbenium conformer, nucleophilic attack from the α face could also form an initial *cis* product but in a twist-boat conformation that can be dismissed by the same argument. Only the β attack is viable, displacing the opposing bent bond (shown in blue) in S<sub>N</sub>2-like fashion to form minor *trans* adduct as a <sup>1</sup>C<sub>4</sub> chair. Thus, a sterically unhindered nucleophilic approach to the β face of the <sup>3</sup>H<sub>4</sub> conformer comes at the expense of displacing a stronger bent bond. Conversely,

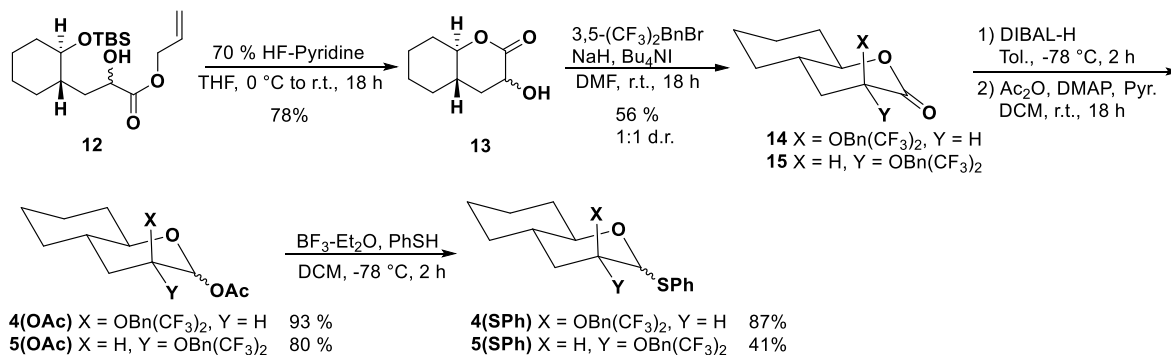
<sup>17</sup> (a) Alabugin, V. I. *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, 2016, John Wiley & Sons, Ltd.; (b) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions. Reference Edition*, 2010, John Wiley & Sons, Ltd.



**Figure 3.7** Glycosylation of C<sub>2</sub>-substituted pyranosides with the bent bond approach.

the sterically hindered nucleophilic approach to the  $\alpha$  face of the <sup>4</sup>H<sub>3</sub> conformer does displace the weaker bent bond and accounts for the major product being *cis*.

Conformational effects were recently studied in great depth by Codée<sup>18</sup> using more than 30 different pyranoside-like glycosyl donors with varying substitution patterns. Conformational energy landscapes for each compound were computed and found to predict with great precision the stereoselectivity of the D-glycosylation reactions based on the global minimum of each donor. For instance, using the enantiomer of the C<sub>2</sub>–OBn donor studied by Woerpel,<sup>16</sup> the transition state for the addition of deuterated triethylsilane was found to be 0.5 kcal/mol



**Figure 3.8** Synthesis of donors 3.4 and 3.5.

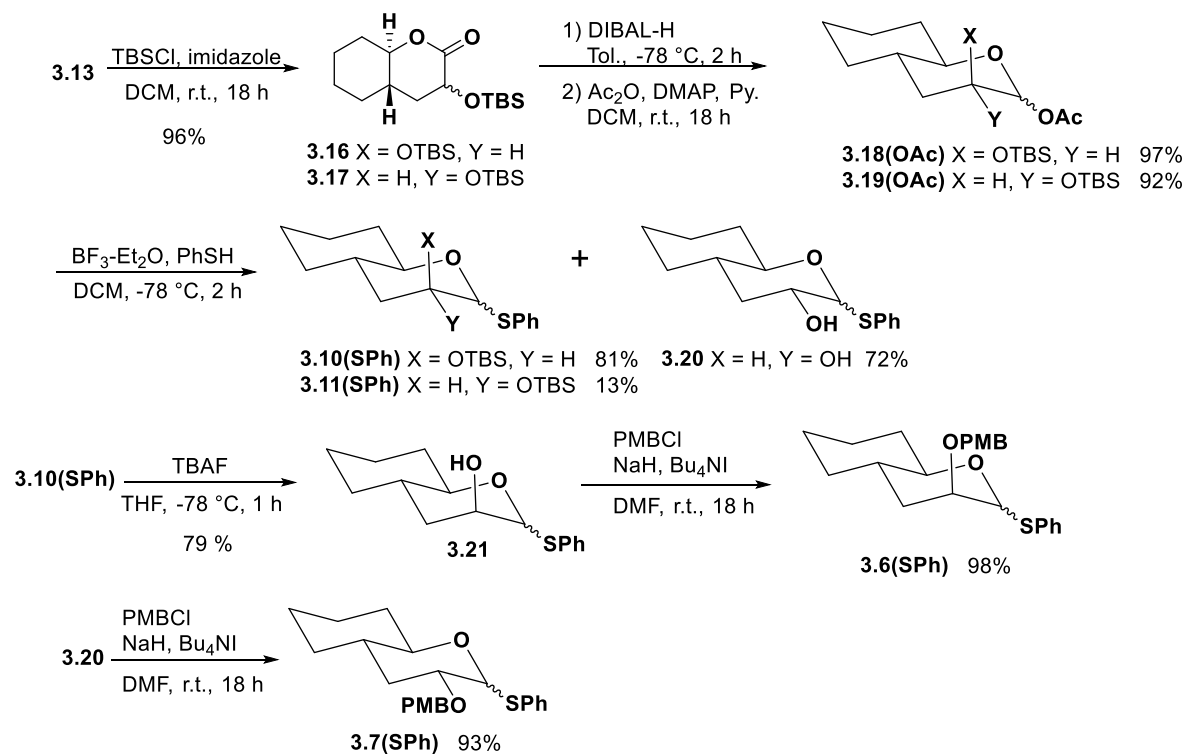
lower for the *cis* addition, in agreement with the experiment (66:34 *cis/trans* ratio). Where the work of Codée and Woerpel shows the factors leading to a selective S<sub>N</sub>1 glycosylation through intermediate pyranosyl cations, our work aims to explain how those very reactive intermediates can be tamed through hyperconjugative effects predicated by the BBAH model.<sup>6,13,14</sup> In similar fashion to the work of Jensen,<sup>15</sup> the reactivities of our bicyclic glycosylation donors were studied by modifying the nature of their substituents. In this work,

<sup>18</sup> Hansen, T.; Lebedel, L.; Remmerswaal, W. A.; van der Vorm, S.; Wander, D. P. A.; Somers, M.; Overkleeft, H. S.; Filippov, D. V.; Désiré, J.; Mingot, A.; Blierot, Y.; van der Marel, G. A.; Thibaudeau, S.; Codée, J. D. *C. ACS Cent. Sci.* **2019**, *5*, 781-788.

the donors listed in *Figure 3.4* were specifically designed not to have any oxygenated substituent, other than the one at C<sub>2</sub>, to isolate the stereoelectronic contribution of the C<sub>2</sub> substituents on modulating glycosylation reactivity.

### 3.5 Results and discussion

Bicyclic donors **3.4** and **3.5** were synthesized from intermediate **3.12** (*Figure 3.8*), which was prepared by our previously described approach.<sup>13</sup> Deprotection and lactonization of **3.12** afforded  $\alpha$ -hydroxylactone **3.13** in a 1:1 diastereoisomeric ratio. Benzylation with 3,5-bis(trifluoromethyl)benzyl bromide afforded diastereoisomers **3.14/3.15** that were separated by column chromatography. The remaining three steps leading to donors **3.4** and **3.5** are identical to these previously reported for the preparation of donors **3.2** and **3.3**.<sup>13</sup>



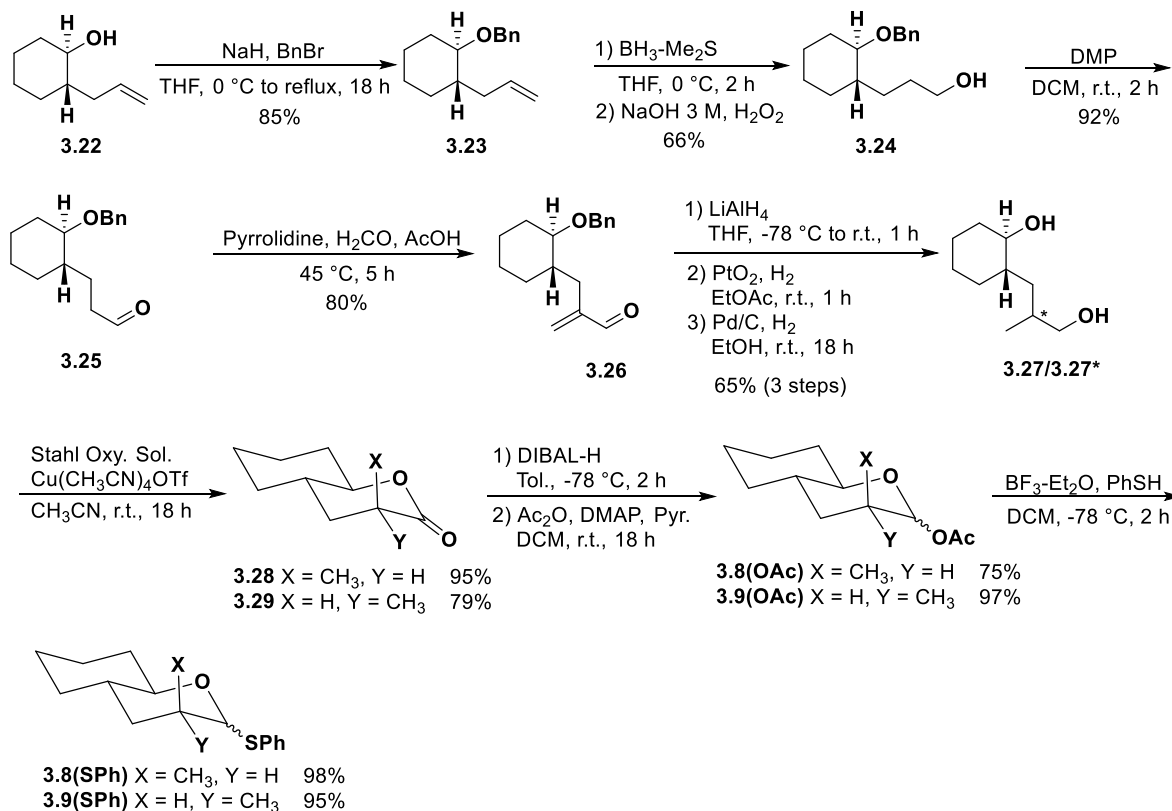
**Figure 3.9** Preparation of donors **3.6**, **3.7**, **3.10** and **3.11**.

Preparation of donors **3.6** and **3.7** proved to be less straightforward because of the inherent lability of OPMB ethers under Lewis acid conditions (*Figure 3.9*).<sup>19</sup> Because of this, C-

<sup>19</sup> Bouzide, A.; Sauv , G. *Synlett* **1997**, 1153-1154.

glycosylation reactions could not be carried out and only *O*-glycosylation of the thiophenyl donors were further investigated. The PMB ethers were also installed at the very end of the synthetic sequence because conditions for converting anomeric acetates (*C*-glycosylation donors) into their corresponding thioethers (*O*-glycosylation donors) also require a strong Lewis acid. To this effect, silylation of hydroxylactones **3.13** with *tert*-butyldimethylchlorosilane (TBSCl) produced **3.16** and **3.17**, which were separated by chromatography and reduced with DIBAL-H and acetylated to obtain **3.18** and **3.19**, which were converted to thioglycoside donors **3.10(SPh)** and **3.11(SPh)**. Partial deprotection of the equatorial OTBS group during thioglycosylation yielded 20% of the free alcohol intermediate **3.20**, which was judiciously recovered to produce donor **3.7(SPh)**. Donor **3.6(SPh)** was obtained by deprotection of **3.10(SPh)**, followed by standard benzylation of **3.21** with PMBCl.

The preparation of donors **3.8** and **3.9** described in *Figure 3.10* is obtained again from opening the cyclohexene oxide using allyl cuprate.<sup>20</sup> Further protection of the alcohol **3.22** as benzyl ether allowed the homologation of the allyl moiety to the aldehyde **3.25** by a



**Figure 3.10** Preparation of donors **3.8** and **3.9**.

hydroboration oxidation reaction followed by DMP oxidation. The Mannich methylation yielded the  $\alpha,\beta$ -unsaturated aldehyde **3.26**.<sup>21</sup> After reduction of the aldehyde to the corresponding allylic alcohol, the methyl substituent was generated in a 1:1 diastereoisomeric ratio by hydrogenation of the olefin using PtO<sub>2</sub> and H<sub>2</sub> gas. Traditional Pd/C did not provide the expected fully hydrogenated/deprotected diol, but rather over reduction of the allylic C–O bond from hydrogenolysis. Upon reduction of the olefin, Pd/C was then used to remove the benzyl ether. Using Stahl's oxidation reaction with the commercially available ABNO

<sup>20</sup> Tobia, D.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 777-782.

<sup>21</sup> Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538-2541.



solution,<sup>22</sup> each 1,5-diol diastereoisomers **3.27/3.27\*** was separated by chromatography and converted into their corresponding lactone **3.28** and **3.29**. Using the same sequence reported for the synthesis of *C/O*-glycosylation donors **1.1-1.3**, the donors **3.8** and **3.9** were obtained.

### 3.6 Glycosylation experiments

Weak nucleophiles with a compatible activating agent were employed for both *C*- and *O*-glyco-sylations (*Figure 3.11*). *C*-glycosylations were carried out on the anomeric acetate donors using Woerpel's procedure of allyltrimethylsilane (TMSallyl) and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in DCM (provided the  $\text{C}_2$ -substituents were chemically compatible). *O*-glycosylations were carried out on the anomeric thiophenyl donors using 2,2,2-trifluoroethanol (TFE) in  $\text{CH}_2\text{Cl}_2$  or  $\text{CH}_3\text{CN}$  in the presence of NIS as the activating agent.<sup>16,23</sup> All glycosylation results are reported in the *Table 3.1*, including some previously published results. All glycosylation conditions exclude any triflate source to avoid any intermediate formation of covalent anomeric triflates that could muddle interpretation of the results. Indeed, triflated intermediates could undergo glycosylation under  $\text{S}_{\text{N}}2$  conditions while the current analysis hinges on reactions that are under strictly  $\text{S}_{\text{N}}1$  conditions. The possibility of post-glycosylation anomerization of the TFE *O*-glycosides was dismissed as shown in our previous work.<sup>13,14</sup> Different donor anomers showed little or no difference in glycosylation

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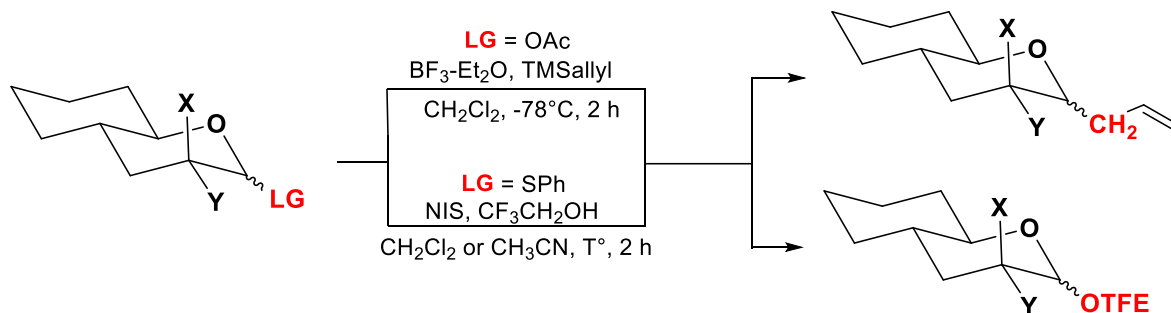
<sup>22</sup> (a) Ryland, B. L.; McCann, S. D.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 12166-12173; (b) Xie, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3767-3770.

<sup>23</sup> Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118.

reactivities. Finally, resubmission of isolated glycosylated compounds under the original glycosylation conditions showed no anomerization.

### 3.7 BBAH analysis of glycosylation results

Table 3.1 entries 1-9 compare the previously reported *C*- and *O*-glycosylation results for donors **1.1** (unsubstituted), **1.2** (equatorial C<sub>2</sub>-OBn), and **1.3** (axial C<sub>2</sub>-OBn),<sup>13</sup> It was observed that the more polar solvent CH<sub>3</sub>CN increased the S<sub>N</sub>1 glycosylation selectivity



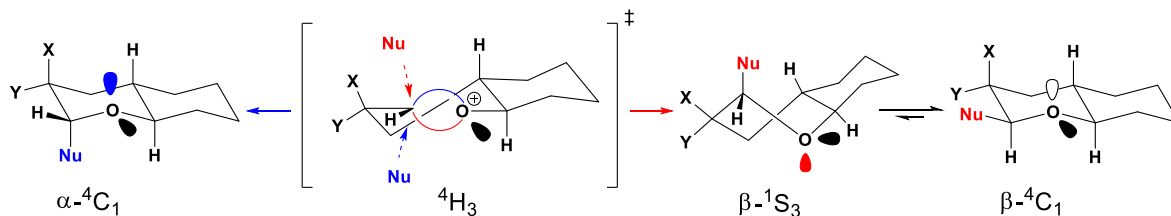
**Figure 3.11** Glycosylation conditions.

compared to CH<sub>2</sub>Cl<sub>2</sub>.<sup>23</sup> It was further reported that the stronger nucleophile EtOH led to a loss in selectivity.<sup>13,23</sup> The new glycosylation results reported in entries 10-27 pertain to donors **3.4-3.11** with different C<sub>2</sub> substituents (OBn(CF<sub>3</sub>)<sub>2</sub>, OPMB, OTBS and CH<sub>3</sub>) and only weak glycosylation nucleophiles (TMSallyl and TFE). Anomeric ratios were determined by <sup>1</sup>H NMR of the crude reaction mixtures while the anomeric identities were determined by 1D NOESY experiments and <sup>3</sup>J<sub>H1-H2</sub> coupling constants whenever possible.

**Donors 1.1-1.3:** Analyzing the glycosylation results for reactions involving *trans* fused-bicyclic pyranosyl oxocarbenium ions require the consideration of two possible reaction trajectories (*Figure 3.12*). For all cases, nucleophilic attack from the α-face (bottom face) of the <sup>4</sup>H<sub>3</sub> half-chair conformer would directly generate the α-<sup>4</sup>C<sub>1</sub> chair product. This follows from the antiperiplanar hypothesis that states that nucleophilic displacement of any bent bond on the oxocarbenium ion must release a lone pair antiperiplanar to the newly formed covalent

bond,<sup>24</sup> a stereoelectronic requirement that can be justified on the basis of microscopic reversibility. The corresponding nucleophilic attack from the  $\beta$ -face of the  ${}^4H_3$  conformer leads necessarily to a product in a higher-energy  $S_3$  twist-boat conformation that subsequently reverts to the  $\beta$ - ${}^4C_1$  chair.<sup>5</sup> The  $\alpha$ -glycosylation thus prevails, based on stereoelectronic grounds.

Further to this stereoelectronic aspect, hyperconjugation effects implicating the bent bonds



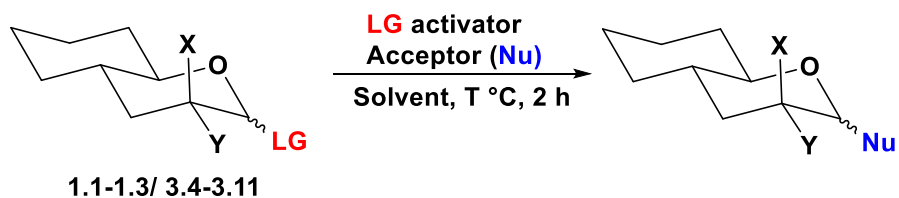
**Figure 3.12**  $\alpha/\beta$  Glycosylation of bicyclic pyranosides.

and substituents at  $C_2$  will be seen to modulate glycosylation stereoselectivity based on the nature of the substituents. As depicted in *Figure 3.12*, the X group in the  ${}^4H_3$  oxocarbenium ion is antiperiplanar to the red  $\tau$  bond. If X is an EWG,  $\tau \rightarrow \sigma^*$  hyperconjugation will weaken the opposing bent bond (shown in red) while the C–H group will strengthen the other bent bond (shown in blue) via  $\sigma \rightarrow \tau^*$  hyperconjugation; both groups at  $C_2$  would steer nucleophilic attack from the  $\beta$  face, displacing the weaker  $\tau$  bond. However, the initial product would be in a strained  $\beta$ - ${}^1S_3$  twist-boat conformation. Conversely, nucleophilic attack from the  $\alpha$ -face leads directly to a stable  $\alpha$ - ${}^4C_1$  chair geometry but necessitates displacing the stronger of the two bent bonds if X=EWG. Thus, forming the  $\alpha$ - ${}^4C_1$  product opposes the bias involving  $C_2$  substituent hyperconjugation. This model accounts for the results of entries 4-6 involving OBn donor **1.2** in which the  $\alpha$ -anomer prevails for both *C*- and *O*-glycosylation reactions. However, when the EWG is switched to the Y position, both the stereoelectronic steering for nucleophilic attack and the hyperconjugation effects work in the same direction favoring nucleophilic addition from the  $\alpha$ -face to yield a 1,2-*cis* addition product. This corresponds exactly to entries 7-9 involving OBn donor **1.3** where the  $\alpha/\beta$  ratios are uniformly higher

<sup>24</sup> (a) Beaulieu, N.; Dickinson R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531-2536; (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, **1983**, Pergamon Press, Oxford; (c) Kirby, A. J. *The Anomeric Effect and Associated Stereoelectronic Effects at Oxygen*, **1983**, Springer-Verlag, Berlin.

than for donor **1.2** (entries 4-6). Of course, the situation is predicted to be different with EDGs at C<sub>2</sub>. Thus, placement of a methyl group at C<sub>2</sub> should, in principle, invert the stereoselectivity as will be discussed later.

**Donors 3.4-3.7:** For the present study, two types of benzyl ethers (donors **3.4-3.5** and **3.6-3.7**) with opposing inductive properties were investigated (see *Table 3.1*). Donors **3.4** and **3.5** possess a 3,5-bis(trifluoromethyl) group to increase the electron-withdrawing properties of the benzyl ether moiety. Those C<sub>2</sub> groups should further weaken their respective *anti* bent bond in the corresponding oxocarbenium ion intermediates, therefore inducing greater facial selectivity for nucleophilic addition (*Figure 3.12*). For the C-glycosylation of donor **3.4(OAc)** (entry 10, 86 $\alpha$ :14 $\beta$ ), the proportion of  $\beta$ -glycosylated product increases by 10% relative to the reaction performed with donor **1.2(OAc)** (entry 4, 95 $\alpha$ :5 $\beta$ ), consistent with the BBAH model. As expected, C-glycosylation of epimeric donor **3.5(OAc)** (Y=OBn(CF<sub>3</sub>)<sub>2</sub>) remains essentially  $\alpha$ -selective (entry 13, 97 $\alpha$ :3 $\beta$ ). O-glycosylations performed on donors **3.4(SPh)/3.5(SPh)** (entries 11 and 14) were shown to be less selective than their C-glycosylation counterparts. In the same CH<sub>2</sub>Cl<sub>2</sub> solvent, O-glycosylations using donors **3.4(SPh)** (entry 11, 67 $\alpha$ :33 $\beta$ ) and **3.5(SPh)** (entry 14, 85 $\alpha$ :15 $\beta$ ) gave ratios similar to those using donors **1.2(SPh)** (entry 5, 68 $\alpha$ :32 $\beta$ ) and **1.3(SPh)** (entry 8, 83 $\alpha$ :17 $\beta$ ), respectively. The OBn(CF<sub>3</sub>)<sub>2</sub> groups on the oxocarbenium ions derived from donors **3.4** and **3.5** should induce greater steering of stereoselectivity. However, these oxocarbenium ions become more reactive due to inductive effects and must have earlier O-glycosylation transition states to the extent that BBAH-imposed stereoelectronic control cannot further influence facial selectivity. This is especially relevant for the more reactive TFE nucleophile. Based on this, **3.4(SPh)** and **3.5(SPh)** should require a higher temperature to expel the leaving group to form the oxocarbenium ion; indeed, the glycosylations were observed to occur at no less than 0°C.

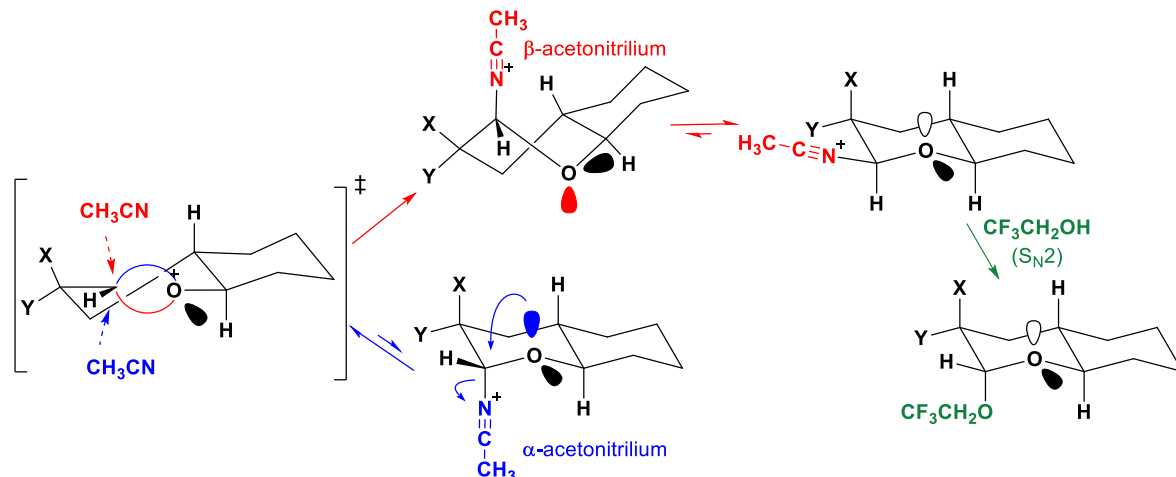
**Table 3.1** Glycosylation of donors **1.1-1.3** and **3.4-3.11**.<sup>13</sup>

Entry	Donor	LG	Nu	T °C	Solvent	$\alpha:\beta^a$	Yield <sup>b</sup>
1 <sup>c</sup>	<b>1.1</b> (X=Y=H)	OAc	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	>97:3	88%
2 <sup>c</sup>	"	SPh (77 $\alpha$ :23 $\beta$ )	TFE	-40 <sup>d</sup>	"	88:12	Quant.
3 <sup>c</sup>	"	SPh (77 $\alpha$ :23 $\beta$ )	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	95:5	Quant.
4 <sup>c</sup>	<b>1.3</b> (X=OBn, Y=H)	OAc ( $\beta$ only)	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	95:5	93%
5 <sup>c</sup>	"	SPh ( $\beta$ only)	TFE	-40 <sup>d</sup>	"	68:32	76%
6 <sup>c</sup>	"	"	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	78:22	88%
7 <sup>c</sup>	<b>1.2</b> (X=H, Y=OBn)	OAc	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	>97:3	96%
8 <sup>c</sup>	"	SPh (77 $\alpha$ :23 $\beta$ )	TFE	-40 <sup>d</sup>	"	83:17	93%
9 <sup>c</sup>	"	SPh ( $\alpha$ only)	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	>97:3	77%
10	<b>3.4</b> (X=OBn(CF <sub>3</sub> ) <sub>2</sub> , Y=H)	OAc ( $\beta$ only)	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	86:14	87%
11	"	SPh ( $\alpha/\beta$ only) <sup>f</sup>	TFE	-40 <sup>d</sup>	"	67:33	71%
12	"	"	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	91:9	70%
13	<b>3.5</b> (X=H, Y=OBn(CF <sub>3</sub> ) <sub>2</sub> )	OAc (27 $\alpha$ :73 $\beta$ )	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	>97:3	79%
14	"	SPh (35 $\alpha$ :65 $\beta$ )	TFE	-40 <sup>d</sup>	"	85:15	85%
15	"	"	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	92:8	82%
16	<b>3.6</b> (X=OPMB, Y=H)	SPh (27 $\alpha$ :73 $\beta$ )	TFE	-40 <sup>e</sup>	CH <sub>2</sub> Cl <sub>2</sub>	71:29	85%
17	"	"	"	-40 <sup>e</sup>	CH <sub>3</sub> CN	75:25	71%
18	<b>3.7</b> (X=H, Y=OPMB)	SPh ( $\alpha$ only)	TFE	-40 <sup>e</sup>	CH <sub>2</sub> Cl <sub>2</sub>	82:18	61%
19	"	"	"	-40 <sup>e</sup>	CH <sub>3</sub> CN	>97:3	48%
20	<b>3.8</b> (X=CH <sub>3</sub> , Y=H)	OAc (50 $\alpha$ :50 $\beta$ )	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	>97:3	88%
21	"	SPh ( $\alpha$ only)	TFE	-40 <sup>d</sup>	"	97:3	79%
22	"	"	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	93:7	71%
23	<b>3.9</b> (X=H, Y=CH <sub>3</sub> )	OAc ( $\beta$ only)	Allyl	-78	CH <sub>2</sub> Cl <sub>2</sub>	>3:97	88%
24	"	SPh ( $\alpha$ only)	TFE	-40 <sup>d</sup>	"	91:9	60%
25	"	"	"	-40 <sup>d</sup>	CH <sub>3</sub> CN	83:17	54%
26	<b>3.10</b> (X=OTBS, Y=H)	SPh (54 $\alpha$ :47 $\beta$ )	TFE	-40 <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	87:13	69%
27	<b>3.11</b> (X=H, Y=OTBS)	SPh (50 $\alpha$ :50 $\beta$ )	TFE	-40 <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	80:20	51%

a) Ratios were obtained from crude reaction mixture <sup>1</sup>H NMR; b) In some cases, isolated yields might not be representative of the efficiency of the transformation as the final product could be partly lost during purification; c) Previously reported results for the glycosylation of donor **1.1-1.3**; d) The initial temperature was -40 °C and the reaction was brought to 0 °C over the course of 2 h; e) Conversion was recorded above -30 °C; f) the nature of the donor's anomeric ratio does not affect the reaction outcome. See SI.

As for the *O*-glycosylations performed in CH<sub>3</sub>CN, both donors **3.4**(SPh) and **3.5**(SPh) showed greater  $\alpha$ -selectivity (entries 12 and 15) than in CH<sub>2</sub>Cl<sub>2</sub> (entries 11 and 14). At first glance, the presence of the stronger electron-withdrawing groups at C<sub>2</sub> should have favored

more *cis* nucleophilic attack according to the BBAH model, as was the case for the *C*-glycosylations, but the results revealed very high  $\alpha$ -selectivities. For example, donor **3.4(SPh)** yielded mainly  $\alpha$ -product (entry 12, 91 $\alpha$ :9 $\beta$ ) compared to donor **1.3(SPh)** (entry 6, 78 $\alpha$ :22 $\beta$ ). This apparent anomaly could be ascribed to the higher reaction temperature, but the solvent itself may have had the most critical effect on glycosylation selectivity. Indeed, CH<sub>3</sub>CN can add to the oxocarbenium ion derived from **3.4(SPh)** to form acetonitrilium intermediates. According to the BBAH, CH<sub>3</sub>CN should prefer to add *cis* to the C<sub>2</sub>-OBn(CF<sub>3</sub>)<sub>2</sub>



**Figure 3.13** Proposed mechanism for CH<sub>3</sub>CN solvent participation.

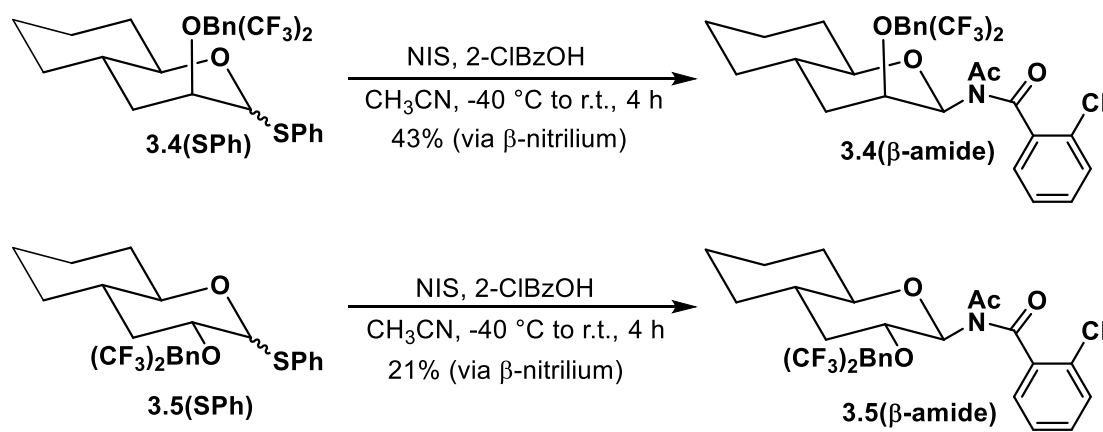
group (displacing the weaker  $\tau$  bond) and form a  $\beta$ -acetonitrilium ion. This ion can then undergo facile S<sub>N</sub>2-like substitution<sup>2</sup> by trifluoroethanol to yield the final product as its  $\alpha$ -anomer (*Figure 3.13*). Any  $\alpha$ -acetonitrilium adduct should be unstable and poised to eject CH<sub>3</sub>CN by stereoelectronic participation of the ring oxygen's antiperiplanar lone pair and revert to the oxocarbenium ion. Overall, a greater proportion of  $\alpha$ -glycosylation product should be observed.

To test this hypothesis, an experiment originally devised by Fraser-Reid was performed, consisting of trapping acetonitrilium intermediates with 2-chlorobenzoic acid.<sup>25</sup> Accordingly, treating donor **3.4(SPh)** under those conditions yielded benzamide adduct **3.4( $\beta$ -amide)** determined by 1D-NOESY experiment, confirming the formation of a transient acetonitrilium intermediate and establishing its  $\beta$  configuration (*Figure 3.14*). The Fraser-

<sup>25</sup> Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747-750.

Reid original experiment was performed on a polybenzylated glucose and found the acetonitrilium to be  $\alpha$ -oriented, a result that concords with the BBAH model (i.e. C<sub>2</sub>-equatorial OBn group).

The solvent hypothesis also supports the findings for donor **3.5(SPh)** (entry 15, 92 $\alpha$ :8 $\beta$ ), where a slightly greater portion of  $\beta$ -anomer is obtained compared to donor **1.2** (entry 9, >97 $\alpha$ :3 $\beta$ ). Performing the same acetonitrilium trapping experiment using donor **3.5(SPh)** also afforded product **3.5( $\beta$ -amide)** but in a lower 21% yield (*Figure 3.14*).



**Figure 3.14** Trapping  $\beta$ -acetonitrilium ion derived from **3.4(SPh)** and **3.5(SPh)** under *O*-glycosylation conditions.

At this point, the reverse anomeric effect must be brought into the discussion. It originates from the observation that positively charged anomeric substituents prefer the equatorial configuration, in apparent opposition to the anomeric effect.<sup>4</sup> Equatorial substituents at C<sub>1</sub> are staggered between the two lone pairs of the ring oxygen (Y = OBn(CF<sub>3</sub>)<sub>2</sub>, X = H, *Figure 3.13*). If positively charged, these substituents will prefer to be equatorial due to electrostatic stabilization between the two lone pairs, thus reversing the usual anomeric trend.<sup>26</sup> In the current context, the reverse anomeric effect must contribute to stabilizing  $\beta$ -acetonitrilium adducts, allowing for subsequent trapping by the Fraser-Reid method. Accordingly, the formation of any  $\beta$ -acetonitrilium anomer should be further enhanced by the reverse anomeric effect. The BBAH model also predicts a greater proportion of  $\beta$ -acetonitrilium intermediate derived from donor **3.4(SPh)** compared to donor **3.5(SPh)**, which is supported

<sup>26</sup> Grein, F.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1562-1572.

by the trapping experiments. The  $\alpha$ -acetonitrilium adducts do not benefit from this electrostatic stabilization, and must lose  $\text{CH}_3\text{CN}$ , assisted by the antiperiplanar lone pair, and revert to the oxocarbenium ion. To study this further, DFT calculations (B3LYP/6-31G\*) were performed on the  $\alpha$ - and  $\beta$ -acetonitrilium adducts derived from donor **1.1**. Geometry optimization of the  $\beta$ -acetonitrilium anomer produced a stable structure in which the  $\text{CH}_3\text{CN}$  group remaining covalently bonded to the anomeric carbon ( $\text{C}_1\text{-N}$  distance: 1.46Å). However, all attempts to geometry optimize the  $\alpha$ -acetonitrilium anomer resulted in a structure in which the  $\text{CH}_3\text{CN}$  group had dissociated ( $\text{C}_1\cdots\text{N}$  distance: 2.53Å), a result that supports the inherent instability of the axial  $\alpha$ -acetonitrilium adduct. Overall, this reactivity appears to be particular to donors **3.4** and **3.5**, as their oxocarbenium ions are much more reactive than the other donors studied.

**Donors 3.6-3.7:** Donors **3.6** and **3.7** have a weak electron-donating *p*-methoxybenzyl ether at  $\text{C}_2$ . So the glycosylation results in both  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{CN}$  should be similar to those for unsubstituted benzyl ether donors **1.2** and **1.3**. Indeed, *O*-glycosylation results for donor **3.6(SPh)** in  $\text{CH}_2\text{Cl}_2$  (entry 16, 71 $\alpha$ :29 $\beta$ ) and  $\text{CH}_3\text{CN}$  (entry 17, 75 $\alpha$ :25 $\beta$ ) are very similar to those for the simpler donor **1.3(SPh)** in  $\text{CH}_2\text{Cl}_2$  (entry 5, 68 $\alpha$ :32 $\beta$ ) and  $\text{CH}_3\text{CN}$  (entry 6, 78 $\alpha$ :22 $\beta$ ). Similarly, *O*-glycosylation of donor **3.7(SPh)** in  $\text{CH}_2\text{Cl}_2$  (entry 18, 84 $\alpha$ :16 $\beta$ ) and  $\text{CH}_3\text{CN}$  (entry 19, 97 $\alpha$ :3 $\beta$ ) correspond to those of donor **1.2(SPh)** in  $\text{CH}_2\text{Cl}_2$  (entry 8, 83 $\alpha$ :17 $\beta$ ) and  $\text{CH}_3\text{CN}$  (entry 9, 97 $\alpha$ :3 $\beta$ ). However, donors **3.4** and **3.5** with a  $\text{OBn}(\text{CF}_3)_2$  in  $\text{CH}_3\text{CN}$  showed reactivity somewhat different to that of **3.6** and **3.7** with a OPMB as they are more reactive. These results are not surprising as the electron-donating character of the OPMB is probably not as prominent as the electron-withdrawing effect of the two trifluoromethyl groups in donors **3.4/3.5**. The required temperatures for the glycosylation reactions support this conclusion (see *Table 3.1* footnotes d and e).

**Donors 3.10-3.11:** Donors **3.10(SPh)** (X= OTBS, Y=H) and **3.11(SPh)** (X=H, Y=OTBS) were also investigated as they were obtained as intermediates in the synthesis of donors **3.6** and **3.7**. These donors could tease out information regarding the steric contribution of  $\text{C}_2$  substituents on glycosylation selectivity since the stereoelectronic effect of OTBS groups should be similar to that of OBn groups. One would assume that nucleophilic approach from the same face as the OTBS group could be somewhat hindered, especially if that  $\text{C}_2$  group



were axial. The *O*-glycosylation result for donor **3.10(SPh)** (entry 26, 87 $\alpha$ :13 $\beta$ ) showed a noticeable increase in *trans* addition compared to donor **1.2(SPh)** (entry 5, 68 $\alpha$ :32 $\beta$ ) whereas the addition to **3.11(SPh)** (entry 27, 80 $\alpha$ :20 $\beta$ ) gave similar results to **1.2(SPh)** (entry 8, 83 $\alpha$ :17 $\beta$ ). The results are completely consistent with the above analysis.

**Donors 3.8-3.9:** The *C*- and *O*-glycosylation of donors **3.8** (X=CH<sub>3</sub>, Y=H) and **3.9** (X=H, Y=CH<sub>3</sub>) bearing an electron-donating CH<sub>3</sub> group at C<sub>2</sub> was also carried out to test the BBAH model. The CH<sub>3</sub>-C  $\sigma$  bond is known to be electron-donating *via* hyperconjugation, although it is known experimentally to be slightly less donating than its H-C  $\sigma$  bond counterpart.<sup>27</sup> This implies that the bent bonds in oxocarbenium ions derived from donors **3.8** and **3.9** are more stereoelectronic influenced by hyperconjugation with the H-C  $\sigma$  bond than the CH<sub>3</sub>-C  $\sigma$  bond at C<sub>2</sub>. Both *C*- and *O*-glycosylations of **3.8** were found to be mainly *trans* selective (entries 20-22). In comparison to the donors bearing C<sub>2</sub>-OR groups, the oxocarbenium ions derived from donors **3.8** and **3.9** must be less reactive due to hyperconjugation; the glycosylation reactions of **3.8/3.9** must then involve later transition states in which the nucleophiles are closer to the oxocarbenium group of the donors. Steric influence of neighboring groups (in this case the C<sub>2</sub>-CH<sub>3</sub> groups) becomes more important in controlling facial selectivity. In the case of donor **3.8**, *trans* addition leads directly to the conformationally favored  $\alpha$ -anomer as a <sup>4</sup>C<sub>1</sub> chair (*Figure 3.12*). This anomer was formed exclusively with the weaker and bulkier TMSallyl nucleophile (entry 20, >97 $\alpha$ :3 $\beta$ ). Because the 1,2-*cis* addition must initially generate a high energy twist-boat conformer, C<sub>2</sub>-H hyperconjugation contribution cannot compete to sway TMSallyl addition from the  $\beta$  face. However, with the stronger nucleophile TFE, a slight increase in  $\beta$ -anomer is observed from *O*-glycosylation in both solvents (entry 21, 97 $\alpha$ :3 $\beta$  and entry 22, 93 $\alpha$ :7 $\beta$ ). The *O*-glycosylations are assumed to involve earlier transition states because of the more reactive nucleophile, and as a result, must be less sensitive to developing steric interactions. The influence of  $\sigma$  C-H hyperconjugation on the facial selectivity during the nucleophilic

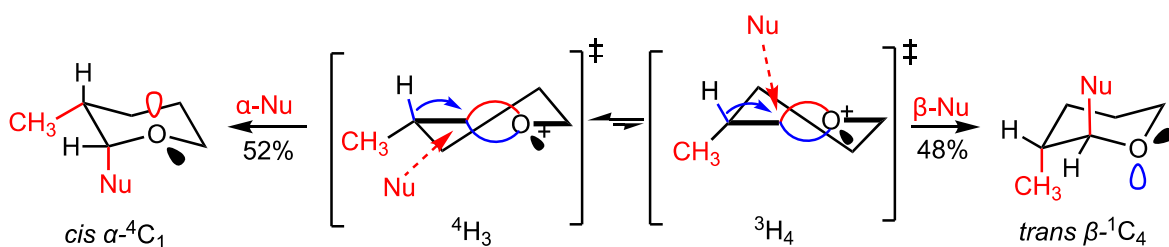
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<sup>27</sup> (a) Laube, T. *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 349-35.; (b) Rauk, A.; Sorensen, T. S.; von Ragué Schleyer, P. J. *Chem. Soc., Perkin. Trans. 2* **2001**, 869-874.

addition of TFE to the oxocarbenium intermediates should be more noticeable, which corresponds to the observed results.

In sharp contrast, the *C*-glycosylation of donor **3.9(OAc)** with TMSallyl was found to be exclusively  $\beta$ -selective (entry 23,  $>3\alpha:97\beta$ ). With TMSallyl, *trans* addition is thus preferred regardless of the fact that the  $\beta$ -addition leads to a twist-boat. Steric hindrance between the bulky TMSallyl nucleophile and the  $C_2$ -CH<sub>3</sub> group of **3.9** must be more prominent due to the later *C*-glycosylation transition state, overcoming any stabilizing hyperconjugation of  $C_2$ -H that would steer the addition from the other face. As for *O*-glycosylation with TFE, the stereoselectivity is reversed with *cis* addition to **3.9** predominating both in CH<sub>2</sub>Cl<sub>2</sub> (entry 24, 91 $\alpha$ :9 $\beta$ ) and CH<sub>3</sub>CN (entry 25, 83 $\alpha$ :17 $\beta$ ). This is also consistent with an earlier transition state for *O*-glycosylation in which the addition of TFE to donor **3.9** can occur *cis* to the  $C_2$ -CH<sub>3</sub> group to form some of the  $\alpha$ -<sup>4</sup>C<sub>1</sub> isomer. In this case, the  $C_2$ -H hyperconjugation indicates preferential opening of the  $\alpha$ -bent bond to produce some of the  $\beta$ -anomer *via* the energetic twist-boat conformation.

The *C*-glycosylation of 2-methyltetrahydropyranyl acetate with TMSallyl reported in *Figure 3.6* can now be re-examined.<sup>16</sup> According to the BBAH, the *cis*  $\alpha$ -<sup>4</sup>C<sub>1</sub> and *trans*  $\beta$ -<sup>1</sup>C<sub>4</sub> isomers are produced from half-chairs <sup>4</sup>H<sub>3</sub> and <sup>3</sup>H<sub>4</sub>, respectively, which are not conformationally locked and can easily interconvert as shown in *Figure 3.15*. Forming the *cis*  $\alpha$ -<sup>4</sup>C<sub>1</sub> isomer is disfavored at the transition state by steric repulsion between the  $\alpha$ -CH<sub>3</sub> group and the entering nucleophile but is favored by the formation of a more stable equatorial CH<sub>3</sub> group in the final *cis*  $\alpha$ -<sup>4</sup>C<sub>1</sub> product and by  $C_2$ -H hyperconjugation. On the other hand, formation of the *trans*  $\beta$ -<sup>1</sup>C<sub>4</sub> isomer is sterically favored by the *trans* addition but is disfavored by the axial orientation of the CH<sub>3</sub> group in the final  $\beta$ -<sup>1</sup>C<sub>4</sub> product and also by  $C_2$ -H hyperconjugation.

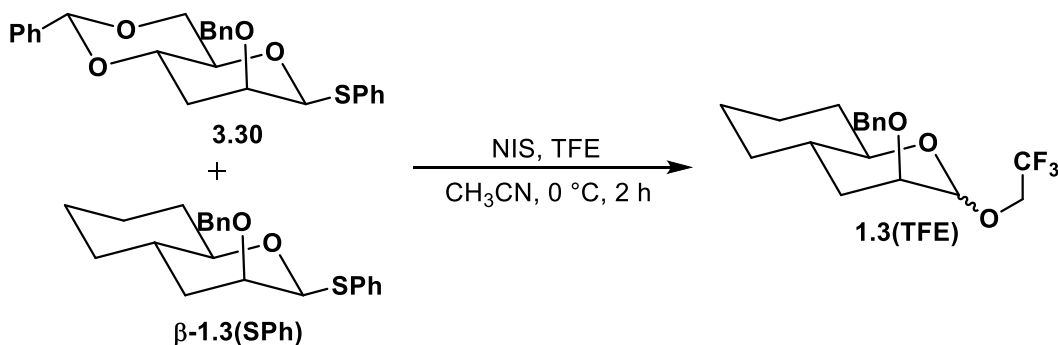


**Figure 3.15** Glycosylation of 2-methyltetrahydropyranyl acetate from <sup>4</sup>H<sub>3</sub> and <sup>3</sup>H<sub>4</sub> half-chairs.

The *C*-glycosylation results from *Figure 3.6* can thus be completely understood by assuming a relatively late transition state in which the Nu $\cdots$ CH $_3$  (and Nu $\cdots$ OBn) steric repulsion is a key stereoselectivity parameter but with further modulation due to hyperconjugation. As shown in *Figure 3.15*, hyperconjugation involving the C $_2$ -H bond stabilizes the  $\alpha$ -bent bond in the oxocarbenium ion (shown in blue) such that nucleophilic attack to the  $^4H_3$  conformer is stereoelectronically predisposed to displace the weaker  $\beta$  bent bond to form the *cis*  $\alpha$ - $^4C_1$  product despite developing steric interactions with the C $_2$ -CH $_3$  group. Conversely, nucleophilic attack to the  $^3H_4$  conformer faces induces no steric hindrance from the C $_2$ -CH $_3$  group but must displace the stronger  $\alpha$  bent bond.

### 3.8 Formation, stability, and reactivity of oxocarbenium ions

With an EWG at C $_2$ , these oxocarbenium ions should be less stable and more reactive than those with an EDG at C $_2$ . In addition, with an EDG at C $_2$ , these ions should form more easily; this can be shown experimentally by observing the ease of disappearance of the starting donors as a function of temperature during the course of the *O*-glycosylation with TFE. Indeed, the *O*-glycosylation of **3.8(SPh)**/**3.9(SPh)** occurred instantaneously at -40°C whereas donors **1.2-3.7** (EWG at C $_2$ ) required more time or higher temperatures, going from -30 °C for the C $_2$ -OPMB donors to -20 °C for the C $_2$ -OBn donors, and 0°C for the C $_2$ -OBn(CF $_3$ ) $_2$  donors. The silylated ethers **3.10/3.11** also reacted at a steady -40 °C, but at a slower rate than their C $_2$ -methylated counterparts **3.8/3.9**. Furthermore, these observations provide some hints concerning the relative position of the transition states along the nucleophilic addition reaction paths. To further support the above analysis, we prepared the

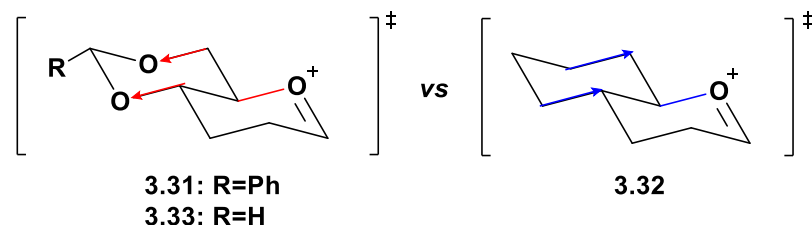


**Figure 3.16** Competitive glycosylation experiment.

3-deoxy-4,6-*O*-benzylidene thiomannoside **3.30** described by Crich<sup>28</sup> and performed a competition experiment in which a mixture of donors **3.30** and **β-1.3(SPh)** was submitted to our *O*-glycosylation conditions with excess TFE and 2 equivalents of NIS (*Figure 3.16*).

As expected, only the electron rich donor **β-1.3(SPh)** reacted and oxygenated substrate **3.30** was fully recovered. Donor **3.30** would require a stronger activating agent in the presence of stabilizing counter ions such as triflates.<sup>29</sup> This demonstrates that simplifying of our donors as carbobicyclic substrates allows us to work within an unusual reactivity domain for the S<sub>N</sub>1 glycosylation reaction. Replacing the benzylidene oxygens of **3.31** with methylenes in **3.32** stabilizes the oxocarbenium ion by inductive effects (*Figure 3.17*). The two C<sub>4</sub>–C<sub>8</sub> and C<sub>6</sub>–C<sub>7</sub> bonds can thus contribute stabilizing hyperconjugation<sup>27</sup> with the oxocarbenium ion intermediate. This effect was also observed by Codée, where replacement of the C<sub>6</sub> oxygen of a polybenzylated mannoside by a methylene group decreased its reactivity.<sup>30</sup>

Finally, Woerpel showed that a more polar solvent like CH<sub>3</sub>CN can also contribute to the stabilization of oxocarbenium intermediates,<sup>29</sup> inducing later reaction transition states. For instance, the *O*-glycosylation of donor **3.9(SPh)** in CH<sub>3</sub>CN (entry 25, 83α:17β) produced more β-product compared to CH<sub>2</sub>Cl<sub>2</sub> (entry 24, 91α:9β). By decreasing the reactivity of the



**Figure 3.17** Inductive effect of benzylidene vs cyclohexane fused to pyranosyl donors.

oxocarbenium ion intermediate, the glycosylation transition state is later, favoring direct formation of the α-anomer in its α-<sup>4</sup>C<sub>1</sub> conformation (*Figure 3.12*). Hirshfeld atomic charges<sup>31</sup> were computed from geometry optimized oxocarbenium ions **3.32** and **3.33**

<sup>28</sup> Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473-8480.

<sup>29</sup> Kendale, J. C.; Valentín, E. M.; Woerpel, K. A. *Org. Lett.* **2014**, *16*, 3684-3687.

<sup>30</sup> Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.* **2013**, *78*, 2191-2205.

<sup>31</sup> De Proft, F.; Van Alsenoy, C.; Peeters, A.; Langenaeker, W. & Geerlings, P. *J. Comput. Chem.* **2002**, *23*, 1198-1209.

(B3LYP/6-31G\*) and, as expected, the oxocarbenium oxygen in **3.32** had a greater negative charge (-0.00768) than in **3.33** (-0.00165).

### 3.9 Summary

This work reports the *O* and *C*-glycosylation of conformationally restricted bicyclic pyranosides containing either an EWG or an EDG at the C<sub>2</sub> position. Various bicyclic donors **3.4-3.11** were prepared and submitted to glycosylation reactions in the presence of the weak nucleophiles TMSallyl and trifluoroethanol in CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN. The results were interpreted according to the BBAH model,<sup>13</sup> which views oxocarbenium ion intermediates as having two bent bonds; the additions of nucleophiles to oxocarbenium ions are viewed as S<sub>N</sub>2-like displacements at the anomeric carbon with selective displacement of one of the two bent bonds. The model further considers hyperconjugation between C<sub>2</sub>-substituents and their antiperiplanar oxocarbenium bent bond as an influencing factor on glycosylation stereoselectivity.

The glycosylation stereoelectivity results for donors **3.4-3.7** and **3.10-3.11**, having modified benzyl or *t*-butylsilyl ether at C<sub>2</sub>, differ from the results obtained for donors **1.2-1.3** having a simple C<sub>2</sub> benzyl ether. For instance, donors **3.4/3.5** (3,5-(CF<sub>3</sub>)<sub>2</sub>benzyloxy group at C<sub>2</sub>) showed different glycosylation stereoselectivity than donors **1.2/1.3** (C<sub>2</sub>-OBn group) due to differential hyperconjugation with one of the bent bonds of the oxocarbenium ion intermediate. In addition, *O*-glycosylations using CH<sub>3</sub>CN as solvent support the formation of acetonitrilium intermediates that can further react with TFE in S<sub>N</sub>2 manner, accounting for the formation of β-glycosylated products. Such acetonitrilium ions were confirmed by trapping experiments with 2-chlorobenzoic acid producing β-N-acetyl-1-chlorobenzamide products. donors **3.6/3.7** (C<sub>2</sub>-OPMB group) showed slight differences in terms of selectivity compared to **1.2/1.3**, whereas the presence of the larger TBS ether in donors **3.10/3.11** appears to affect the *O*-glycosylation through steric hindrance, forcing the nucleophile to attack in a slightly more *trans* fashion.

The most notable results pertain to donors **3.8/3.9** (C<sub>2</sub>-CH<sub>3</sub>) for which the glycosylation stereoelectivities conform exactly with the BBAH predictive model. Indeed, *O*-glycosylation reactions of **3.8/3.9** with the stronger TFE nucleophile should proceed through a relatively

early transition state and were consistent with the stereoelectronic premise that a C<sub>2</sub>-H bond is a better electron donor than a C<sub>2</sub>-CH<sub>3</sub> bond for hyperconjugation with its antiperiplanar bent bond. C-glycosylation of **3.8/3.9** with the weaker TMSallyl nucleophile should proceed through a later transition state and appear to be more sensitive to steric effects as TMSallyl must be closer to the oxocarbenium ion at the transition state. In essence, stronger nucleophiles add to oxocarbenium ions via earlier transition states such that hyperconjugation effects predicted by the BBAH model are more easily perceptible.

Finally, it was observed that the glycosylation of donors having a C<sub>2</sub>-EWG proceed at higher temperatures (-30 to 0°C) than those with a C<sub>2</sub>-EDG (-40°C), indicating that the oxocarbenium ion does not form as easily with a C<sub>2</sub>-EWG. With an EWG at C<sub>2</sub>, the oxocarbenium ion must be less stable, hence more reactive, and that the transition state for nucleophilic addition must be earlier than for a donor with a C<sub>2</sub>-EDG. The higher stability of the oxocarbenium ion generated in our bicyclic donors was also demonstrated by a competitive glycosylation in the presence of fully oxygenated 4,6-benzylated donors. The unreacted armed donor advocates for the very unusual reactivity domain of our glycosylation substrates.

Other than the BBAH, we know of no other mechanistic model that can account for the detailed glycosylation fingerprints reported in the present study at the molecular level. We recognize the potential applications of the BBAH model to carbohydrate chemistry in general and will report further findings in due course.

## Conclusion

L'objectif central de cette thèse était d'illustrer à l'aide d'exemples concrets l'applicabilité des liaisons courbes comme modèle de représentation de la liaison multiple. Grâce à diverses expérimentations, nous avons pu montrer que dans le cas des réactions de glycosylation, le modèle de Pauling semble fournir des éléments explicatifs valides, voire supérieurs à ceux du modèle de Huckel traditionnellement accepté dans la discipline. Nos trois articles, en effet, l'ont tous illustré à leur manière : d'abord en démontrant qu'il est possible de rationaliser par liaisons  $\tau$  la variation dans la sélectivité de la réaction de glycosylation  $S_N1$  sur des bicycles rigides de type pyranose; ensuite en transposant cette idée générale de donneurs sursimplifiés dépourvus d'éléments stéréoélectroniques secondaires à un modèle analogue aux furanoses; et, enfin, en étendant notre approche à l'étude de l'effet engendré par la modulation de la nature électronique du groupement en  $C_2$  sur les pyranoses.

De manière plus détaillée, le premier article et chapitre de cette thèse expose l'importance des conditions réactionnelles utilisées, ce qui inclut le choix du nucléophile, du solvant et des autres paramètres de la réaction de glycosylation. Cela permet de mettre en évidence l'un des points forts de notre approche qui est l'aisance avec laquelle nos modèles de glucides simplifiés s'imbriquent dans le contexte particulier de ce genre de transformation. Il devient immensément plus simple de percevoir les variations de réactivité engendrées par des changements minimes aux conditions réactionnelles puisque que l'on a conscience des facteurs intrinsèques géométriques et stéréoélectroniques à la réactivité des donneurs de liaison glycosidique.

Cet article est beaucoup plus exploratoire que ne le sont les suivants et, conséquemment, il est davantage modeste dans les thèses qu'il avance. Nous tentons simplement d'y mettre en lumière la possibilité d'utiliser le modèle des liens  $\tau$  dans un contexte réactionnel dont la nature décomplexifiée augmente la possibilité d'apporter un raisonnement dans lequel notre modèle s'insère. C'est toutefois un travail qui n'aurait pu être accompli sans l'aide d'une littérature de plus en plus étoffée sur le sujet.

Nous avons montré qu'il est possible de générer un ion oxacarbénium dans un modèle *trans* décaline sous forme demi-chaise  ${}^4H_3$  et que l'hypothèse antipériplanaire est l'aspect clé

gouvernant la formation des deux anomères du produit. La décaline non substituée **1.1** obéit, à peu de chose près, à cette règle puisque les substituants en C<sub>2</sub> sont d'une nature stérique et électronique similaire. La force du nucléophile et la polarité du solvant provoquent évidemment certains changements. C'est toutefois par la mise en équivalence des différents donneurs C<sub>2</sub>-OBn **1.2** et **1.3** dans des conditions réactionnelles similaires que peuvent être interprétés les résultats à l'aide du modèle. D'ailleurs, la variation des ratios anomériques et l'analyse qui en découle ne peut prendre assise uniquement sur les facteurs stériques et géométriques. Par exemple, le gain en sélectivité *cis*, ou β lors de la C-glycosylation du donneur **1.3** va à l'encontre du rationnel géométrique et stérique. Il se justifie cependant sans problème en considérant une désymétrisation de la densité électronique des deux liens τ par hyperconjugaison.

L'objectif du deuxième article était de transposer le savoir acquis à la glycosylation des furanoses rigides. Tel que mentionné au second chapitre, cette famille de donneurs se prête moins bien à une analyse des effets stéréoélectroniques puisque la géométrie de la structure moléculaire est plus contraignante. Cependant, ayant déjà développé l'approche réactionnelle, il allait de soi qu'un effort supplémentaire devait être consacré à l'introduction de groupements directeurs en C<sub>2</sub> qui diffèrent d'un éther. C'est pourquoi la synthèse de donneurs C<sub>2</sub>-CH<sub>3</sub> a été effectuée. Nous avons pu démontrer que l'effet donneur de la liaison C-H est supérieur à la liaison C-C. Il influence le cours de la réaction et peut même surclasser le *inside attack* favorisé dans les furanoses conjointement à une contribution stérique du méthyle. Les résultats obtenus avec les donneurs **2.4** et **2.5** avec les deux types de nucléophiles en témoignent. L'effet participatif de la liaison courbe est toutefois plus difficile à inclure dans les donneurs **2.2** et **2.3** puisque la géométrie des intermédiaires semble masquer en grande partie les autres facteurs jouant sur la réactivité.

Or, nous avons démontré hors du contexte des liens τ que la stabilité de l'oxocarbénium est grandement influencée lors de la modification de la nature électronique du groupement en C<sub>2</sub>. Dans le cas de nos donneurs, lorsque comparés à un glucide standard, l'activation du groupement partant et la génération de l'intermédiaire réactif est plus facile. L'intermédiaire est plus stabilisé ce qui signifie que l'état de transition sera généralement plus tard avec nos donneurs simplifiés qu'il ne l'est avec un glucide complet. Cette proposition est soutenue à



la fois expérimentalement et par des calculs théoriques. Dès lors, si on considère la participation d'effets stéréoelectroniques émanant de l'hyperconjugaison de liens courbes, il est juste de croire qu'ils seront perceptibles dans un état de transition relativement tard, plus que tôt.

Comme nous l'avons présupposé, l'utilisation de donneur rigides et simplifié s'avère un outil plus qu'adéquat dans l'atteinte de notre objectif. Toutefois, malgré les résultats très intéressants obtenus avec les furanoses au chapitre deux, les différents facteurs géométriques présents limitent la réalisation complète de cet objectif. L'utilisation d'une structure pyranosique s'avère beaucoup moins contraignante et c'est pour cette raison que nous en avons étoffé l'étude dans les travaux du troisième chapitre.

La modification de la nature des groupement directeurs en C<sub>2</sub> a été beaucoup plus instructive qu'elle ne l'apparaissait d'emblée. L'objectif spécifique guidant la réalisation de cette partie des travaux était de provoquer une variation dans la sélectivité au carbone anomérique en utilisant les mêmes conditions réactionnelles. Par exemple, la synthèse des donneurs benzyle bistrifluorométhyle **3.4** et **3.5** devait en théorie engendrer une sélectivité 1,2-*cis* plus importante que les donneurs **1.2** et **1.3** C<sub>2</sub>-OBn, puisque ce groupement fluoré est davantage électroattracteur. Toutefois, nous n'avions pas anticipé que toute modification apportée au caractère électronique du donneur joue également sur la réactivité générale de l'intermédiaire oxocarbénium et ainsi sur l'interaction entre ce dernier et l'accepteur (nucléophile) à l'état de transition. Cet énoncé est tout aussi vrai dans le cas du groupement méthyle stabilisant. Tel que démontré dans l'article du chapitre deux et plus explicitement dans le chapitre trois, ces gains et pertes en réactivité se traduisent par des températures d'activation différentes et vont, par le fait même, influencer le résultat de la transformation. Cela signifie donc, à toute fin pratique, qu'une comparaison parfaite ne peut être établie entre différents donneurs. Il faut donc considérer et évaluer les facteurs influençant la sélectivité de la réaction de glycosylation, et ce, pour chaque donneur en tenant compte des conditions plutôt que de chercher à en définir un ensemble de lois, de méthodes et d'explications s'appliquant à toutes les situations. L'expérience de captation de l'adduit acétonitrilium par l'acide 2-chlorobenzoïque sur les donneurs **3.4** et **3.5** confirme cet énoncé. Puisque cette réactivité particulière ne corroborait pas tout à fait notre raisonnement général, nous avons décidé de

l'explorer davantage. Nous avons conclu que l'explication répondant aux données expérimentales était celle qui faisait intervenir à la fois l'hyperconjugaison de liens  $\tau$  et l'effet anomère inverse. L'interaction particulière du solvant dans cette réaction de glycosylation nous a mené à nuancer notre proposition vers l'analyse d'une sélectivité qui est bel et bien guidée par les facteurs stéréoélectroniques (hyperconjugaison, liaisons courbes, hypothèse antipériplanaire) et structuraux (conformation, encombrement stérique). Elle se trouve toutefois chapeauté par la résultante de l'ensemble de ces facteurs, soit la réactivité de l'intermédiaire oxocarbénium à l'état de transition.

Nous devons maintenant pointer les limites à notre recherche. Malgré qu'il y ait toujours une contribution à différents degrés d'hyperconjugaison  $\sigma\text{-}\tau^*/\tau\text{-}\sigma^*$ , la fenêtre de réactivité où les liaisons courbes sont perceptibles est très mince, du moins dans le cas d'une réaction de glycosylation. Elle s'entremêle à d'autres facteurs, prend plus ou moins de place dans le cours de la réaction selon le contexte, mais reste toujours présente indépendamment des préférences des chercheurs et chercheuses.

Bien que nous ayons montré l'efficacité et, par là, les limites possibles du modèle des liaisons courbes dans le cas de la réaction de glycosylation, nous ne pouvons soutenir que ce modèle s'applique – et s'appliquera – à toutes les situations. En d'autres termes, si le modèle explique les cas que nous avons étudiés, un autre pourra néanmoins, dans un futur plus ou moins lointain, en pointer les faiblesses. En effet, depuis Popper<sup>1</sup>, la philosophie des sciences nous a montré que les énoncés scientifiques ne sont, en réalité, que des *conjectures*. Cela veut dire qu'un énoncé est jugé valide et vrai jusqu'à preuve du contraire, c'est-à-dire lorsqu'il sera falsifié par un autre. En d'autres termes, un énoncé scientifique ne peut jamais être prouvé hors de tout doute, il ne peut qu'être *corroboré* par des expériences et des tests qui en montrent la validité.

Ainsi, nous soutenons, à la manière de Popper, que nos expériences corroborent le modèle de Pauling : il peut donc être utilisé pour expliquer nos résultats, bien que nous sachions qu'il pourrait être réfuté un jour. Mais encore, c'est bien cette qualité d'être réfutable qui donne à ce modèle son caractère de scientificité : il peut être testé, travaillé, discuté, soumis à de

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<sup>1</sup> Popper, Karl Raimund. *La logique de la découverte scientifique*. 1982, Paris, Payot.

nombreux tests et épreuves. Nous lançons donc l'invitation à la communauté de chercheuses et chercheurs en chimie organique à travailler davantage ce modèle, pour le corroborer ou le falsifier, mais surtout dans l'espoir de promouvoir un plus grand pluralisme au sein de notre discipline. Cela n'insinue évidemment pas que l'on doive complètement abandonner le modèle de Hückel, mais que l'on doit plutôt exploiter, comme Hiberty, Messmer et plusieurs autres le proposent, les forces de chacun et les utiliser de manière complémentaire. Nous pourrions donc dire que la thèse transversale de ce travail est que le pluralisme scientifique, c'est-à-dire que plusieurs théories et modèles coexistent au sein d'une même discipline, est bénéfique au progrès de la science.

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## Annexe A Données expérimentales générales

The following section includes the spectroscopic data of newly synthesized compounds. Transformation requiring inert and anhydrous conditions were carried out within an argon atmosphere with dry solvents and oven dried/flame dried glassware. Dry DCM, Et<sub>2</sub>O, toluene and THF was obtained from a Vacuum Atmosphere Inc; Solvent Purification System. CH<sub>3</sub>CN was distilled over CaH<sub>2</sub>. All commercially available reagents were used as received without further purification. Thin – layer chromatography analysis of reaction mixtures were performed using Silicycle’s Silica alumina backed TLC plates and analysed using UV light and/or by staining with either potassium permanganate, cerium ammonium molybdate (CAM) or p – anisaldehyde. Flash column chromatography purification was carried out on Silicycle silica gel 60 Å, 230 – 400 mesh. NMR spectroscopic data for <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F and NOESY 1D were recorded at ambient temperature in neutralized CDCl<sub>3</sub> using an Agilent DD2 500, Bruker 300 MHz and Varian Inova 400 spectrometers. High – resolution mass spectra were obtained on a LC/MS – TOF Agilent 6210 using electrospray ionization (ESI). Infrared spectra were obtained using an Aminco Bowman Adrid Zone infrared spectrometer with a NaCl crystal matrix. Melting point values were determined using a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected.

### A.1 Procédure générale de glycosylation

#### C-glycosylation: Procédure Générale A

A solution of an acetate donor in DCM (0.1M) under N<sub>2</sub> was brought to -78 °C and allyltrimethylsilane (4 equiv.) was added. The mixture was then treated with BF<sub>3</sub> – Et<sub>2</sub>O (1.2 equiv) and brought to ambient temperature over 2 hours before quenching with saturated NaHCO<sub>3</sub>. Organic phase was separated and the aqueous washed with DCM (3x), dried over MgSO<sub>4</sub> and condensed *in vacuo*. Crude mixtures were analysed by <sup>1</sup>H NMR spectroscopy and purified as described

#### O- glycosylation: Procédure générale B

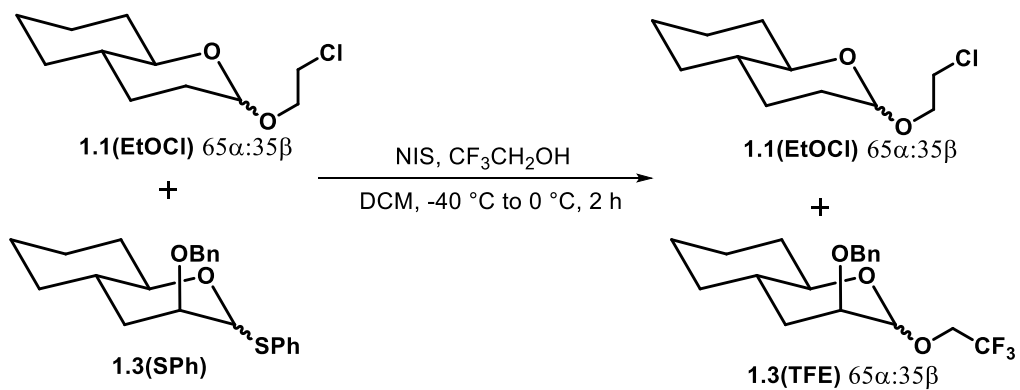
A solution of a thiophenylacetal donor in dry DCM or CH<sub>3</sub>CN (0.1M) with the nucleophile (4 equiv.) under N<sub>2</sub> was brought to -40 °C The mixture was then treated with NIS (2 equiv)

and brought to -20 °C over 1.5 hours before quenching with a saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. Using CH<sub>3</sub>CN as solvent requires flame dried material and dropwise addition of a NIS/CH<sub>3</sub>CN solution in order to maintain inert atmosphere. The organic phase was separated and the aqueous phase washed with DCM (3x). Organic fractions were combined, dried over MgSO<sub>4</sub> and condensed *in vacuo*. Crude mixtures were analysed by <sup>1</sup>H NMR spectroscopy and purified as described. Special care was is to be taken for the removal of solvent with those compounds as they appeared to be slightly volatile. To be noted that the characterization of some O-glycosylated products by any HRMS method available to us would often only provide the corresponding oxocarbenium ion after the loss of the trifluoroethyl moiety.

## **Annexe B Données expérimentales du chapitre 1**

### **B.1 Expériences de contrôles cinétique**

The kinetic pathway of the glycosylation reactions studied were confirmed using control experiment based on the method reported by Woerpel.<sup>11</sup> These experiments are valuable in the context of the O-glycosylation, whereas anomerisation cannot occur in the case of C-glycosylation. Purified compounds from previous nucleophilic addition were resubmitted to the reaction conditions in the presence of a different donor. As shown in the figure below compound **1.1(CIEtO)** submitted with **1.3(SPh)** and TFE as nucleophile did not undergo anomerization as the initial anomeric ratio was found to be the same in the crude mixture at 65α:35β. No incorporation of 2-chloroethanol was observed on donor **1.3** as only **1.1(CIEtO)** and **1.3(TFE)** were observed.



**Figure B.1** Expérience de contrôle cinétique.

**Table B.1** Expérience de contrôle cinétique

Entry	Compound	Donor	Initial ratio ( $\alpha$ : $\beta$ )	Observed <sup>a</sup> ( $\alpha$ : $\beta$ )	Incorporation product
1	1.1(ClEtO)	1.3(SPh)	65:35	65:35	None
2	1.2(TFE) <sup>b</sup>	1.1(SPh)	65:35	65:35	None
3	1.3(TFE) <sup>b</sup>	1.1(SPh)	70:30	75:25	None
4	$\beta$ -1.2(TFE)	1.1(SPh)	0:100	0:100	None

<sup>a</sup>determined by <sup>1</sup>H NMR and <sup>19</sup>F NMR of the crude mixtures; <sup>b</sup>Ethanol was used as nucleophile

## B.2 Protocole de synthèse et caractérisation des composés

**2-Allylcyclohexanol (1.4).** The compound was obtained following the Woerpel *et al.* described procedure with comparative yield and similar spectral data;<sup>1</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.90 – 1.01 (m, 1H), 1.12 – 1.22 (m, 1H), 1.23 – 1.29 (m, 1H), 1.33 (dddt, *J* = 11.7, 9.4, 7.8, 4.0 Hz, 1H), 1.59 – 1.69 (m, 2H), 1.70 – 1.83 (m, 2H), 1.93 – 2.04 (m, 2H), 2.46 (dddt, *J* = 14.1, 7.1, 4.5, 1.4 Hz, 1H), 3.27 (td, *J* = 9.8, 4.5 Hz, 1H), 5.00 – 5.04 (m, 1H), 5.05 – 5.10 (m, 2H), 5.87 (dddd, *J* = 17.0, 10.1, 7.6, 6.8 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 24.9, 25.5, 30.4, 35.6, 37.5, 44.9, 74.7, 116.0, 137.5; HRMS (ESI) Calculated for C<sub>9</sub>H<sub>17</sub>O<sup>+</sup> (M+H)<sup>+</sup>: 141.1273; Found: 141.1277.

**2-(3-Hydroxypropyl)cyclohexanol (1.5).** To a solution of olefin **1.4** (1.0 g 7.13 mmol) in dry THF (5 mL) at 0°C under nitrogen atmosphere was added over 10 min BH<sub>3</sub>-Me<sub>2</sub>S 2M solution in THF (8.56 mmol, 4.28 mL). The reaction was then brought slowly to ambient temperature and stirred for 8 hours. The mixture was treated with a 3M sodium hydroxide at 0°C until the pH was basic and H<sub>2</sub>O<sub>2</sub> (14.26 mmol, 1.61 mL) was added. The reaction was stirred for 3 hours until completion and was diluted with EtOAc. Organic layer was separated and the aqueous layer washed with EtOAc (3x) The organic layers were combined and washed with brine (1x), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (60% EtOAc/hexanes, *R<sub>f</sub>* = 0.22, TLC stained with *p*-anisaldehyde) to obtain diol **1.5** (676 mg, 60%) as a colorless thick oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.86 – 0.99 (m, 1H), 1.09 – 1.29 (m, 5H), 1.43 – 1.57 (m, 1H), 1.59 – 1.76 (m, 3H), 1.76 – 1.87 (m, 2H), 1.91 – 1.99 (m, 1H), 2.17 (s, 2H), 3.22 (td, *J* = 9.4, 4.5 Hz, 1H), 3.64 (td, *J* = 6.3, 1.1 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 24.9, 25.6, 28.2, 29.4, 30.4, 35.8, 44.6, 62.9, 74.6; HRMS (ESI) Calculated for C<sub>9</sub>H<sub>19</sub>O<sub>2</sub><sup>+</sup> (M+H)<sup>+</sup>: 159.1379; Found: 159.1378.

**Octahydro 2H-chromen-2-one (1.6).** To a solution of diol **1.5** (1.13 g, 7.14 mmol) in dry DCM (50 mL) under N<sub>2</sub> was added Bis(acetoxy)iodobenzene (6.90 g, 21.42 mmol) and TEMPO (0.223 g, 1.43 mmol). The reaction was stirred for 3 hours at ambient temperature and quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The organic layer was separated and aqueous

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<sup>1</sup> Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152.

washed with EtOAc (2x). The combined organic were washed sequentially with saturated NaHCO<sub>3</sub> (1x), water (1x), dried over MgSO<sub>4</sub> and condensed *in vacuo*. The orange residue was purified by silica gel column chromatography (20% EtOAc/hexane, *R<sub>f</sub>* = 0.28, TLC stained with CAM) to obtain the lactone **1.6** as a yellowish oil (0.940 g, 85%); IR (NaCl)  $\nu_{\max}$  2934, 2861, 1736, 1229, 1179, 1038 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.02 – 1.11 (m, 1H), 1.22 – 1.35 (m, 2H), 1.40 – 1.57 (m, 3H), 1.68 – 1.75 (m, 1H), 1.80 – 1.89 (m, 3H), 2.08 – 2.14 (m, 1H), 2.5 – 2.58 (m, 1H), 2.67 (ddd, *J* = 18.1, 7.4, 3.4 Hz, 1H), 3.88 (ddd, *J* = 11.0, 10.5, 4.3 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  24.1, 25.1, 26.5, 29.9, 31.1, 32.3, 38.8, 83.4, 171.6; HRMS (ESI) Calculated for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub><sup>+</sup> (M+H)<sup>+</sup>: 155.1066; Found: 155.1075.

**Octahydro-2H-chromen-2-yl acetate (1.1(OAc)).** To a -78°C solution of **1.6** (0.1 g 0.648 mmol) in dry toluene (3 mL) under N<sub>2</sub> atmosphere was added dropwise DIBAL-H 1M in heptanes (0.778 mL, 0.778 mmol). The reaction was stirred at -78°C for 2 hours and pyridine (0.061 mL, 0.778 mmol), was slowly added at -78°C, followed by DMAP (0.095 g, 0.778 mmol) in 1 mL of dry DCM, stirred 10 minutes and Ac<sub>2</sub>O (0.356 mL, 3.89 mmol) was added dropwise. The reaction was let to reach ambient temperature and stirred 12 hours. The mixture was quenched with saturated NH<sub>4</sub>Cl and diluted with EtOAc. The extracted organic phase was washed with 1N NaHSO<sub>4</sub> (2x), saturated NaHCO<sub>3</sub> (2x), brine (1x), dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes with 2% Et<sub>3</sub>N, *R<sub>f</sub>* = 0.44, TLC stained with CAM) to obtain a mixture of two diastereoisomeric acetates (0.118 g, 93%, 16 $\alpha$ :84 $\beta$ ) **1.1(OAc)** as a colorless oil; IR (NaCl)  $\nu_{\max}$  2931, 2859, 1748, 1353, 1370, 1225, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, TMS)  $\delta$  0.90 – 1.08 (m, 1H), 1.15 – 1.41 (m, 5H), 1.45 – 1.61 (m, 1H), 1.62 – 1.66 (m, 2H), 1.74 – 1.81 (m, 2H), 1.82 – 1.84 (m, 1H), 1.91 – 1.94 (m, 1H), 2.10 (s, 3H), 3.13 (ddd, *J* = 10.7, 10.2, 4.1 Hz, 0.86H), 3.44 (ddd, *J* = 10.2, 10.1, 3.9 Hz, 0.18H), 5.67 (dd, *J* = 10.0, 2.4 Hz, 0.84H), 6.14 (d, *J* = 2.9 Hz, 0.16H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  21.3, 21.3, 24.7, 24.8, 25.0, 25.6, 25.7, 29.1, 29.4, 30.7, 31.0, 31.7, 32.1, 32.1, 40.7, 41.2, 75.4, 80.6, 92.5, 94.8, 169.4; HRMS (ESI) Calculated for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub>K<sup>+</sup> (M+K)<sup>+</sup>: 237.0887; Found: 237.0888.

Characteristic peaks for the minor  $\alpha$ -isomer:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  3.44 (ddd,  $J = 10.2, 10.1, 3.9$  Hz, 0.18H), 6.14 (d,  $J = 2.9$  Hz, 0.16H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  21.3, 21.3, 24.8, 25.0, 25.7, 29.4, 31.7, 32.1, 41.2, 75.4, 92.5.

**2-(Phenylthio)octahydro-2H-chromene (1.1(SPh)).** To a solution of diastereoisomeric acetate **1.1(OAc)** (0.2 g, 1.08 mmol) in dry DCM (3 mL) under  $\text{N}_2$  atmosphere was added PhSH (0.124 mL, 1.21 mmol). The mixture was cooled to  $-78^\circ\text{C}$  and  $\text{BF}_3\cdot\text{Et}_2\text{O}$  (0.136 mL, 1.11 mmol) was slowly added. After 1 hour of stirring at  $-78^\circ\text{C}$ , the reaction was quenched with  $\text{Et}_3\text{N}$ , brought to ambient temperature and diluted with DCM. The organic phase was isolated and the aqueous washed with DCM (3x). The organic phases were combined, dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The residue was purified by silica gel column chromatography (2% EtOAc/hexanes,  $R_f = 0.44$  at 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give two diastereoisomeric thioacetal **1.1(SPh)** (0.232 g, 87%, 77 $\alpha$ :23 $\beta$ ) as a white solid which was characterised as a mixture; mp: 45.8-49.3  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 – 0.99 (m, 0.2H), 1.10 (tdd,  $J = 12.9, 11.3, 3.8$  Hz, 0.8H), 1.18 – 1.48 (m, 5H), 1.48 – 1.57 (m, 1H), 1.58 – 1.75 (m, 3H), 1.76 – 1.85 (m, 2H), 1.92 – 1.99 (m, 0.5H), 2.03 (dddd,  $J = 13.9, 4.0, 2.7, 1.1$  Hz, 1H), 2.17 (tt,  $J = 13.5, 5.0$  Hz, 1H), 3.05 (ddd,  $J = 11.0, 9.0, 4.1$  Hz, 0.23H), 3.86 (ddd,  $J = 10.1, 10.0, 3.6$  Hz, 0.77H), 4.83 (dd,  $J = 11.4, 2.2$  Hz, 0.23H), 5.63 (d,  $J = 5.3$  Hz, 0.77H), 7.17 – 7.24 (m, 1H), 7.25 – 7.32 (m, 3H), 7.46 – 7.51 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9, 25.1, 25.6, 25.8, 26.7, 31.5, 31.6, 31.9, 32.1, 32.2, 32.4, 40.8, 42.1, 47.5, 73.7, 82.8, 84.8, 85.6, 126.4, 126.6, 128.7, 128.8, 130.5, 130.7, 135.3, 136.2; HRMS (ESI) Calculated for  $\text{C}_{15}\text{H}_{21}\text{OS}^+$  (M+H) $^+$ : 249.1307; Found: 249.1320.

Characteristic peaks for the minor  $\beta$ -isomer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89–0.99 (m, 0.2H), 3.05 (ddd,  $J = 11.0, 9.0, 4.1$  Hz, 0.23H), 4.83 (dd,  $J = 11.4, 2.2$  Hz, 0.23H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9, 25.6, 31.5, 32.2, 32.4, 40.8, 82.8, 84.8, 126.6, 128.7, 130.5, 135.3.

**2-Allyl-tert-butyldimethylsilyloxy cyclohexane (1.7).** To a solution of **1.4** (2.0 g, 14.26 mmol) in DCM (20 mL) was added imidazole (3.88 g, 57.05 mmol) followed by *tert*-butyldimethylsilylchloride (2.58 g, 17.11 mmol). The solution was stirred for 12 hours and diluted with hexane. The mixture was condensed under reduced pressure and the resulting



slurry was filtered with hexane through a large silica pad to remove imidazole. The mixture was then purified by silica gel column chromatography (2% Et<sub>2</sub>O/hexanes, *R<sub>f</sub>* = 0.55, TLC stained with KMnO<sub>4</sub>) to yield **7** as a colorless oil (3.37 g, 93%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.06 (s, 6H), 0.81 – 0.90 (m, 1H), 0.90 (s, 9H), 1.09 – 1.37 (m, 4H), 1.55 – 1.63 (m, 1H), 1.68 – 1.83 (m, 3H), 1.84 – 1.91 (m, 1H), 2.56 (dddt, *J* = 13.2, 6.5, 3.3, 1.6 Hz, 1H), 3.23 (td, *J* = 9.6, 4.1 Hz, 1H), 4.97 – 5.03 (m, 2H), 5.77 (dddd, *J* = 16.7, 10.4, 8.2, 6.2 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ -4.7, -3.9, 18.1, 25.0, 25.4, 25.9, 29.9, 36.0, 37.0, 45.0, 75.1, 115.5, 137.7; HRMS (ESI) Calculated for C<sub>15</sub>H<sub>31</sub>O<sub>2</sub>Si<sup>+</sup> (M+H)<sup>+</sup>: 255.2138; Found: 255.2130.

**3-(2-((*tert*-Butyldimethylsilyloxy)cyclohexyl)propane-1,2-diol (1.8).** To a solution of **1.7** (3.0 g, 11.8 mmol) in THF (30 mL) and water (10 mL) was added *N*-methylmorpholine oxide (2.76 g, 23.6 mmol) followed by OsO<sub>4</sub> (4% in H<sub>2</sub>O) (5 mol%, 3.8 mL). The reaction was stirred for 18h with the flask wrapped in aluminum foil. It was then diluted with water and EtOAc. The phases were separated and the aqueous mixture was washed with EtOAc (5x), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (35% EtOAc/hexanes, *R<sub>f</sub>* = 0.33, TLC stained with CAM) to give two diastereoisomeric diols **1.8** (3.18 g, 94%) isolated as a thick colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.06 – 0.11 (m, 6H), 0.86 – 0.95 (m, 9H), 0.99 – 1.11 (m, 1H), 1.13 – 1.34 (m, 4H), 1.35 – 1.44 (m, 0.5H), 1.44 – 1.54 (m, 0.5H), 1.57 – 1.66 (m, 1H), 1.69 – 1.87 (m, 3H), 1.87 – 1.94 (m, 1H), 3.18 – 3.28 (m, 1H), 3.41 (ddd, *J* = 14.9, 11.1, 7.2 Hz, 1H), 3.61 (ddd, *J* = 11.0, 4.7, 3.3 Hz, 1H), 3.73 (ddt, *J* = 10.7, 6.5, 3.1 Hz, 0.5H), 3.86 (dtd, *J* = 7.7, 6.5, 3.2 Hz, 0.5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ -4.4, -4.2, -4.2, -3.9, 18.1, 24.8, 24.8, 25.5, 25.6, 25.9, 25.9, 32.2, 32.5, 36.0, 37.1, 41.9, 42.4, 66.8, 67.6, 70.7, 70.7, 76.5, 76.9; HRMS (ESI) Calculated for C<sub>15</sub>H<sub>33</sub>O<sub>3</sub>Si<sup>+</sup> (M+H)<sup>+</sup>: 289.2193; Found : 289.2184.

**3-(2-((*tert*-Butyldimethylsilyloxy)cyclohexyl)-2-hydroxypropanoic acid (1.9).** To a solution of **1.8** (2.0 g, 6.93 mmol) in toluene (40 mL) and pH 6.8 phosphate buffer (32 mL) was added TEMPO (0.270 g, 1.73 mmol). The reaction was stirred rapidly while a 0.128M solution of NaOCl (13.53 mL, 1.73 mmol) and a 3.5M solution of NaOCl<sub>2</sub> (7.1 mL, 20.79 mmol) were added simultaneously over 1 minute. The dark red reaction was stirred for 2 hours until its color faded to a pale orange and then brought to pH 4 by a slow addition of 1M HCl. The phases were separated and the aqueous washed with EtOAc (3x). The combine

organic phases were dried over MgSO<sub>4</sub> and condensed *in vacuo*. The resulting mixture was rapidly purified with silica gel column chromatography (35% EtOAc/hexanes with 2% AcOH, *R<sub>f</sub>* = 0.35 (strikes), TLC stained with CAM) to yield the two diastereoisomeric acids **1.9** as a thick yellowish oil which was directly submitted to the next step.

**Allyl-3-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-hydroxypropanoate (1.10).** To a solution of **1.9** (2.0 g, 6.61 mmol) in DMF (14 mL) was added K<sub>2</sub>CO<sub>3</sub> (1.37 g, 9.91 mmol), tetrabutylammonium iodide (0.487 g, 1.32 mmol) and allyl bromide (2.28 mL, 36.4 mmol) dropwise. The reaction was stirred for 2 hours at ambient temperature and then diluted in water and Et<sub>2</sub>O. The aqueous phase was washed with Et<sub>2</sub>O (3x). The combined organic phases were washed with 1N HCl (1x) and saturated NaHCO<sub>3</sub> (1x). Organic phase was dried over MgSO<sub>4</sub> and condensed *in vacuo*. The resulting mixture was purified with silica gel column chromatography (5% EtOAc /hexanes, *R<sub>f</sub>* = 0.22, TLC stained with CAM) to yield compound **1.10** (1.45 g, 75% over two steps) as a yellowish oil; IR (NaCl)  $\nu_{\max}$  3485, 2930, 2857, 1736, 1256, 1092, 835, 774 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, TMS)  $\delta$  0.04 – 0.08 (m, 6H), 0.88 – 0.90 (m, 9H), 0.94 – 1.06 (m, 1H), 1.15 – 1.37 (m, 4H), 1.40 – 1.49 (m, 1H), 1.50 – 1.68 (m, 3H), 1.69 – 1.77 (m, 1H), 1.88 (ddt, *J* = 9.7, 4.3, 1.6 Hz, 1H), 1.91 – 1.99 (m, 1H), 2.04 (ddd, *J* = 14.2, 11.1, 3.4 Hz, 1H), 2.18 (dt, *J* = 14.0, 4.8 Hz, 0.25H), 2.92 (d, *J* = 6.2 Hz, 1H), 3.09 (d, *J* = 6.2 Hz, 0.2H), 3.22 (td, *J* = 9.6, 4.0 Hz, 1H), 3.25 – 3.28 (m, 0.1H), 4.24 (ddd, *J* = 11.0, 6.1, 3.1 Hz, 1H), 4.33 (q, *J* = 6.0 Hz, 0.25H), 4.63 – 4.74 (m, 2H), 5.16 – 5.39 (m, 2H), 5.92 (ddt, *J* = 17.2, 10.5, 5.9 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  -4.6, -4.5, -4.0, -3.9, 0.0, 18.1, 24.7, 25.3, 25.4, 25.9, 25.9, 30.2, 35.8, 37.7, 38.3, 41.4, 42.2, 65.9, 65.9, 68.7, 70.4, 75.8, 118.8, 119.0, 131.6, 175.5; HRMS (ESI) Calculated for C<sub>18</sub>H<sub>35</sub>O<sub>4</sub>Si<sup>+</sup> (M+H)<sup>+</sup>: 343.2291; Found : 343.2293.

**Allyl 2-(benzyloxy)-3-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-propanoate (1.11).** To a solution of **1.10** (1.728 g, 5.04 mmol) in a two necks flask with dry THF (15 mL) under N<sub>2</sub> was added Bu<sub>4</sub>NI (0.186 g, 0.503 mmol) and benzyl bromide (1.2 mL, 10.08 mmol). The mixture was brought to 0°C and NaH 60% in oil (0.295 g, 6.05 mmol) was slowly added. The reaction was stirred at 0°C for 1 hour then brought to reflux and stirred for 16 hours. The mixture was then quenched with saturated NH<sub>4</sub>Cl<sub>aq</sub>, diluted with water and Et<sub>2</sub>O. The organic

phase was separated and the aqueous washed with Et<sub>2</sub>O (3x). The combined organic phase was dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography (0 to 5% EtOAc /hexanes, *R<sub>f</sub>* = 0.44 at 5% EtOAc /hexanes, TLC stained with CAM) to yield the two diastereoisomers of compound **2.11** (2.03 g, *d.r.*: 3:2, 93%) as a colorless thick oil; IR (NaCl)  $\nu_{\max}$  2929, 2856, 1750, 1256, 1091, 835, 774 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.03 – 0.10 (m, 6H), 0.83 – 0.90 (m, 9H), 0.94 – 1.40 (m, 3H), 1.41 – 1.74 (m, 4.5H), 1.78 – 1.94 (m, 1.5H), 2.15 – 2.23 (m, 0.45H), 2.29 (ddd, *J* = 13.6, 10.3, 3.2 Hz, 0.55H), 3.15 – 3.27 (m, 1H), 4.03 (dd, *J* = 10.3, 3.6 Hz, 0.56H), 4.11 (dd, *J* = 7.7, 5.2 Hz, 0.4H), 4.37, 4.73 (ABq, *J<sub>AB</sub>* = 11.8 Hz, 1.1H), 4.43, 4.67 (ABq, *J<sub>AB</sub>* = 11.6 Hz, 0.8H), 4.64 (m, 2H), 5.12 – 5.22 (m, 0.26H), 5.25 (ddt, *J* = 10.4, 2.0, 1.2 Hz, 0.8H), 5.30 – 5.38 (m, 0.8H), 5.86 – 5.98 (m, 1H), 7.26 – 7.39 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  – 4.6, – 4.6, – 4.0, – 4.0, 18.0, 18.1, 24.6, 24.7, 25.0, 25.4, 25.9, 26.0, 29.2, 31.3, 35.6, 35.6, 35.9, 36.3, 40.9, 42.6, 65.2, 65.3, 71.9, 72.3, 75.4, 75.7, 75.8, 78.4, 118.5, 118.7, 127.7, 128.0, 128.1, 128.3, 131.9, 137.7, 172.8, 173.3; HRMS (ESI) Calculated for C<sub>25</sub>H<sub>41</sub>O<sub>4</sub>Si<sup>+</sup> (M+H)<sup>+</sup>: 433.2768; Found: 433.2760.

**3 $\alpha$ -(Benzyloxy)octahydro-2H-chromen-2-one (1.12 and 1.13).** To a solution of **1.11** (2.0 g, 4.62 mmol) in dry THF (20 mL) at 0°C under N<sub>2</sub> was added dropwise excess HF 70% in pyridine (1 mL, 38 mmol). The reaction was brought to room temperature over 1 hour and stirred for an additional 15 hours and was quenched slowly with saturated aqueous NaHCO<sub>3</sub>. The mixture of the two diastereoisomers was purified a first time by silica gel flash chromatography at 10% EtOAc to obtain a white solid residue (1.083 g, 90%) and a second time using a Biotage Isolera 1 with a Teledyne Isco 80 g RediSepRf column at 25 mL/min using a linear gradient of 0 to 10% EtOAc/hexanes to obtain pure fractions of the two diastereoisomers **1.12** (*R<sub>f</sub>* = 0.5 at 20% EtOAc/hexanes) **1.13** (*R<sub>f</sub>* = 0.45 at 20% EtOAc/hexanes) and mixed fractions.

**1.12:** White solid; mp: 77.8-81.6 °C; IR (NaCl)  $\nu_{\max}$  2936, 2863, 1739, 1451, 1022, 737 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, TMS)  $\delta$  1.14 (tdd, *J* = 12.8, 11.3, 3.1 Hz, 1H), 1.19 – 1.35 (m, 3H), 1.36 – 1.46 (m, 1H), 1.54 – 1.64 (m, 1H), 1.66 – 1.73 (m, 2H), 1.79 – 1.88 (m, 2H), 2.12 (ddtd, *J* = 11.9, 4.2, 3.0, 1.5 Hz, 1H), 2.19 (ddd, *J* = 13.2, 6.9, 4.5 Hz, 1H), 4.01 (dd, *J* = 8.7,

6.8 Hz, 1H), 4.06 (ddd,  $J = 11.3, 11.3, 4.3$  Hz, 1H), 4.71, 4.96 (ABq,  $J_{AB} = 11.9$  Hz, 2H), 7.30 – 7.33 (m, 1H), 7.35 – 7.40 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.0, 25.0, 31.0, 32.0, 34.8, 38.8, 72.8, 74.1, 83.2, 127.9, 128.0, 128.4, 137.5, 171.3; HRMS (ESI) Calculated for  $\text{C}_{16}\text{H}_{21}\text{O}_3^+$  (M+H) $^+$ : 261.1485; Found 261.1490.

**1.13:** White solid; mp: 116.1-120.5; IR (NaCl)  $\nu_{\text{max}}$  2932, 2881, 1729, 1136, 741, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.08 (tdd,  $J = 12.7, 11.5, 3.5$  Hz, 1H), 1.17 – 1.33 (m, 2H), 1.43 (tdd,  $J = 12.2, 10.9, 3.7$  Hz, 1H), 1.63 – 1.92 (m, 4H), 2.03 (dt,  $J = 13.4, 7.8$  Hz, 1H), 2.08 – 2.17 (m, 1H), 3.89 (ddd,  $J = 10.7, 10.7, 4.4$  Hz, 1H), 4.10 (dd,  $J = 8.6, 7.7$  Hz, 1H), 4.61, 4.95 (ABq,  $J_{AB} = 12.0$  Hz, 2H) 7.27 – 7.40 (m, 5H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  23.9, 24.9, 31.5, 31.9, 33.2, 36.9, 71.5, 72.3, 81.0, 127.9, 128.0, 128.5, 128.5, 137.5, 171.8; HRMS (ESI) Calculated for  $\text{C}_{16}\text{H}_{21}\text{O}_3^+$  (M+H) $^+$ : 261.1485; Found 261.1498.

**3-(Benzyloxy)octahydro-2H-chromen-2-y-acetate (1.2(OAc)).** From the lactone **1.12** (0.280 g, 1.079 mmol) using the method used for **1.1(OAc)**, the residue was purified by silica gel column chromatography (20%  $\text{Et}_2\text{O}$ /hexanes,  $R_f = 0.28$ , TLC stained with CAM) to yield a diastereoisomeric mixture of **1.2(OAc)** (14 $\alpha$ :86 $\beta$ , 0.297 g, 90%) as a white solid; mp: 57.4-64.6  $^\circ\text{C}$ ; IR (NaCl):  $\nu_{\text{max}}$  2930, 2861, 1756, 1453, 1368, 1226, 1041, 738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.98–1.08 (m, 1H), 1.13 – 1.36 (m, 5H), 1.63 – 1.68 (m, 2H), 1.75 – 1.89 (m, 1H), 1.94 – 1.99 (m, 1H), 2.09 – 2.13 (m, 1H), 2.12 (s, 2.4H), 2.17 (s, 0.29H), 3.14 (ddd,  $J = 10.5, 9.0, 4.1$  Hz, 0.85H), 3.38 (ddd,  $J = 10.6, 4.1$  Hz, 0.15H), 3.44 (ddd,  $J = 10.8, 8.0, 5.1$  Hz, 0.84H), 3.62 (ddd,  $J = 11.8, 4.8, 3.3$  Hz, 0.15H), 4.54, 4.62 (ABq,  $J_{AB} = 12.0$  Hz, 0.23H), 4.62, 4.65 (ABq,  $J_{AB} = 15$  Hz, 1.76H), 5.60 (d,  $J = 8.0$  Hz, 0.86H), 6.34 (d,  $J = 3.4, 0.13$ H), 7.27–7.37 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 24.5, 24.9, 25.2, 25.3, 30.9, 31.3, 31.5, 31.5, 31.5, 31.6, 36.0, 40.4, 40.6, 70.9, 72.0, 74.1, 74.6, 75.7, 79.9, 90.2, 96.2, 127.5, 127.6, 127.7, 127.7, 128.4, 128.4, 138.4, 169.5; HRMS (ESI) Calculated for  $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}^+$  (M+Na) $^+$ : 327.1566; Found: 327.1559.

Characteristic peaks of the minor  $\alpha$ -**1.2(OAc)** anomer :  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (s, 0.29H), 3.38 (ddd,  $J = 10.6, 4.1$  Hz, 0.15H), 3.62 (ddd,  $J = 11.8, 4.8, 3.3$  Hz, 0.15H), 6.34 (d,  $J = 3.4, 0.13$ H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9, 25.3, 31.3, 31.5, 31.6, 40.6, 70.9, 74.1, 74.6, 79.9, 90.2, 127.7, 127.7, 128.4, 138.0.

**3 $\alpha$ -(Benzyloxy)octahydro-2H-chromen-2-yl- $\beta$ -acetate ( $\beta$ -1.3(OAc)).** Using the same one pot method described for **1.1(OAc)** starting with lactone **1.13** (0.1 g, 0.387 mmol). Purification by silica gel column chromatography (10% EtOAc/hexanes,  $R_f$  = 0.22, TLC stained with CAM) yields only the  $\beta$ -anomer of **1.3(OAc)** (0.113 g, 96%) as a colorless oil; IR (NaCl)  $\nu_{\max}$  2931, 2857, 1756, 1451, 1354, 1229, 1043, 730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.92 (tdd,  $J$  = 13.1, 3.9 Hz, 1H), 1.18 – 1.33 (m, 3H), 1.47 (tdd,  $J$  = 12.5, 12.0, 3.7 Hz, 1H), 1.57 – 1.74 (m, 2H), 1.76 – 1.82 (m 1H), 1.90 – 2.00 (m, 2H), 2.10 (s, 2H), 3.17 (ddd,  $J$  = 11.0, 9.8, 4.1 Hz, 1H), 3.59 – 3.61 (m, 1H), 4.65, 4.70 (ABq,  $J_{AB}$  = 12.6 Hz, 3H), 5.63 (d,  $J$  = 1.4 Hz, 1H), 7.24 – 7.41 (m, 5H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  21.2, 24.6, 25.5, 30.9, 31.7, 34.1, 35.1, 71.9, 72.1, 81.0, 94.8, 127.6, 127.8, 128.2, 138.5, 169.3; HRMS (ESI) Calculated for  $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 327.1566; Found: 327.1555.

**3 $\alpha$ -(Benzyloxy)octahydro-2H-chromen-2-yl- $\alpha$ -acetate ( $\alpha$ -1.3(OAc)).** From a sequence where the lactol **1.15** resulting of the reduction of **1.13** was not converted directly to an acetate in a one pot sequence, the acetylation on **1.15** (0.260 g, 1.00 mmol) provided after silica gel column chromatography (10% EtOAc/hexanes,  $R_f$  = 0.34, TLC stained with CAM) the  $\alpha$ -**1.3(OAc)** anomer (0.284 g, 0.933 mmol, 93%) as a colorless oil; IR (NaCl):  $\nu_{\max}$  2930, 2857, 1752, 1451, 1370, 1233, 737, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.99 (qd,  $J$  = 12.5, 12.4, 3.7 Hz, 1H), 1.21 – 1.44 (m, 3H), 1.47 – 1.69 (m, 3H), 1.70 – 1.88 (m, 4H), 2.08 (s, 3H), 3.40 – 3.50 (m, 2H), 4.59, 4.68 (ABq,  $J_{AB}$  = 12.3 Hz, 2H), 6.15 (d,  $J$  = 1.4 Hz, 1H), 7.25 – 7.39 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3, 25.0, 25.6, 30.6, 31.5, 31.8, 35.1, 71.0, 72.3, 75.6, 92.0, 127.6, 127.7, 128.4, 138.2, 169.5; HRMS (ESI) Calculated for  $\text{C}_{18}\text{H}_{25}\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$ : 305.1747; Found: 305.1744.

**3 $\alpha/\beta$ -(Benzyloxy)-2-(phenylthio)octahydro-2H-chromene (**1.2(SPh)** and **1.3(SPh)**).** Using the same protocol as for **1.1(SPh)**, **1.3(OAc)** (0.1 g, 0.328 mmol) was converted into **1.3(SPh)** (0.075 g, 90 $\alpha$ :10 $\beta$ , 0.032 g  $\beta$ -only, 95%) and **1.2(OAc)** (0.1 g, 0.328 mmol) converted to **1.2(SPh)** (0.109 g, 60 $\alpha$ :40 $\beta$ , 94%). All compounds were purified by silica gel column chromatography (10%  $\text{Et}_2\text{O}$ /hexanes,  $R_f$  =  $\alpha$ -**1.3(SPh)**: 0.37;  $\beta$ -**1.3(SPh)**: 0.3 and  $R_f$  of **1.2(SPh)**: 0.55 at 10% EtOAc/hexanes, TLC stained with CAM).

**1.2(SPh):** mp: 87.0-102.3 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.97 – 1.08 (m, 0.55H), 1.12 – 1.43 (m, 5H), 1.49–1.60 (m, 1H), 1.61 – 1.71 (m, 2H), 1.82 (dddd, *J* = 13.2, 8.4, 4.7, 1.9 Hz, 1.6H), 1.89 (dddd, *J* = 12.6, 4.6, 3.5, 1.3 Hz, 0.6H), 1.95 – 2.03 (m, 0.45H), 2.15 – 2.22 (m, 0.42H), 3.01 (ddd, *J* = 10.9, 9.1, 4.1 Hz, 0.4H), 3.40 (ddd, *J* = 10.4, 9.4, 4.9 Hz, 0.4H), 3.81 – 3.90 (m, 1.2H), 4.63 (ABq, *J* = 11.5 Hz, 1.2H), 4.66 (Abq, *J* = 5.0 Hz, 0.8H), 4.71 (d, *J* = 9.5 Hz, 0.4H) 7.21 – 7.42 (m, 8H), 7.52 – 7.59 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 24.7, 25.0, 25.2, 25.4, 31.2, 31.3, 31.5, 31.9, 33.3, 37.7, 40.5, 40.9, 70.3, 72.0, 73.2, 75.1, 75.7, 82.3, 88.4, 89.2, 126.6, 126.9, 127.7, 127.7, 127.8, 127.9, 128.3, 128.4, 128.7, 128.8, 131.4, 131.4, 134.6, 135.5, 138.0, 138.3; HRMS (ESI) Calculated for C<sub>22</sub>H<sub>27</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup>: 355.1726; Found: 355.1721.

**1.3(SPh):** (90α:10β); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.01–1.12 (m, 1H), 1.22–1.51 (m, 4H), 1.53 – 1.72 (m, 3H), 1.77– 1.91 (m, 4H), 3.08 (ddd, *J* = 11.1, 9.8, 4.1 Hz, 0.1), 3.77 (ddd, *J* = 2.8, 1.1 Hz, 0.9H), 3.79 –3.80 (m,0.1), 3.84 (ddd, *J* = 10.5, 10.4, 3.9 Hz, 0.9H), 4.55, 4.65 (ABq, *J*<sub>AB</sub> = 12.2 Hz, 1.8H), 4.61, 4.75 (ABq, *J*<sub>AB</sub> = 12.1 Hz, 0.2H ), 4.87 (d, *J* = 1.5 Hz, 0.1H), 5.64 (s, 0.9H), 7.21–7.41 (m, 8H), 7.45–7.58 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 24.9, 25.1, 25.6, 25.7, 31.3, 31.5, 31.7, 31.9, 32.0, 35.9, 70.7, 74.2, 75.2, 82.9, 86.5, 126.6, 126.8, 127.6, 127.6, 128.0, 128.2, 128.4, 128.7, 128.9, 130.3, 130.8, 135.5, 138.2; HRMS (ESI) Calculated for C<sub>22</sub>H<sub>27</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup>: 355.1726; Found: 355.1709.

**β-1.3(SPh):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.81 – 0.99 (m, 1H), 1.25 (q, *J* = 14.7, 12.5 Hz, 4H), 1.47 – 1.86 (m, 3H), 1.89 – 2.01 (m, 1H), 2.05 (dt, *J* = 13.9, 3.3 Hz, 1H), 3.06 (td, *J* = 10.4, 4.1 Hz, 1H), 3.74 – 3.81 (m, 1H), 4.60, 4.74 (ABq, *J* = 12.1 Hz) 4.86 (d, *J* = 1.6 Hz, 1H), 7.16 – 7.23 (m, 1H), 7.26 (s, 1H), 7.33 – 7.39 (m, 2H), 7.44 – 7.52 (m, 4H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 24.9, 25.6, 31.3, 32.0, 34.5, 35.0, 71.5, 75.3., 82.9, 89.0, 126.5, 127.6, 128.0, 128.2, 128.7, 130.3, 136.6, 138.2; HRMS (ESI) Calculated for C<sub>22</sub>H<sub>27</sub>O<sub>2</sub>S<sup>+</sup> (M+H)<sup>+</sup>: 355.1726; Found: 355.1717.

**3α-(Benzyloxy) octahydro-2H-chromen-2-ol (1.15).** In a solution of **1.13** (0.1 g 0.387 mmol) in dry THF under N<sub>2</sub> at -78°C was added DIBAL-H 1M in hexanes (0.464 mL, 0.464 mmol). The mixture was stirred for 1.5 hours at -78°C and quenched at -78°C with a saturated

aqueous solution of sodium potassium tartrate. After 1 hour of stirring at ambient temperature, the organic phase was separated and the aqueous phase washed with EtOAc (3x). The combine organic phases were dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography (30% EtOAc/hexanes, *R<sub>f</sub>* = 0.48, TLC stained with CAM) to yield a mixture of **1.15** (0.091 g, 90%, 80 $\alpha$ :20 $\beta$ ) as a white solid; mp: 83.1-89.9 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.80 – 1.06 (m, 1H), 1.17 – 1.47 (m, 3H), 1.50 – 1.86 (m, 6.6H), 1.90 – 1.99 (m, 0.2H), 2.05 (dt, *J* = 14.3, 3.2 Hz, 0.2H), 3.06 (ddd, *J* = 11.0, 9.9, 4.2 Hz, 0.2H), 3.35 (d, *J* = 3.1 Hz, 0.8H), 3.48 (td, *J* = 2.7, 1.4 Hz, 0.2H), 3.53 – 3.55 (m, 0.2H), 3.62 (td, *J* = 10.5, 3.8 Hz, 0.8H), 3.97 (d, *J* = 12.1 Hz, 0.8H), 4.49, 7.73 (Abq, *J<sub>AB</sub>* = 11.9 Hz, 0.4H), 4.56, 4.62 (d, *J<sub>AB</sub>* = 12.4 Hz, 1.4H), 4.66 (dd, *J* = 12.1, 1.8 Hz, 0.2H), 5.18 (dd, *J* = 3.1, 1.5 Hz, 0.8H), 7.24 – 7.38 (m, 5H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  24.7, 25.1, 25.6, 25.7, 29.6, 30.9, 31.5, 31.9, 33.0, 34.9, 35.5, 70.8, 71.2, 73.1, 73.6, 74.3, 79.6, 92.6, 94.6, 127.6, 127.6, 127.9, 127.9, 128.3, 128.5, 137.8, 138.4; HRMS (ESI) Calculated for C<sub>16</sub>H<sub>22</sub>O<sub>3</sub>Na<sup>+</sup> (M+Na)<sup>+</sup>:285.1461; Found: 285.1457.

**3 $\beta$ -(Benzyloxy) octahydro-2H-chromen-2-ol (1.14).** Using the same protocol as for **1.15** on lactone **1.12** (0.1 g, 0.387 mmol) and purified by silica gel column chromatography (30% EtOAc/hexanes, *R<sub>f</sub>* = 0.48, TLC stained with CAM), a mixture of **1.14** (0.98 g, 97% (35 $\alpha$ :65 $\beta$ ) was isolated as a white solid; mp: 76.6-83.0° C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.93 – 1.42 (m, 6H), 1.46 – 1.70 (m, 2.5H), 1.72 – 1.90 (m, 2H), 1.90 – 1.97 (m, 0.65H), 2.00 – 2.08 (m, 0.65H), 3.03 (ddd, *J* = 10.7, 9.1, 4.1 Hz, 0.6H), 3.14 (br s, 0.35H), 3.24 (ddd, *J* = 10.7, 7.4, 4.9 Hz, 0.6H), 3.51 – 3.60 (m, 0.8H), 3.67 (br s, 0.5H), 4.57, 4.62 (ABq, *J<sub>AB</sub>* = 12.0 Hz, 0.8H), 4.65 (m, 0.65H), 4.67, 4.76 (ABq, *J<sub>AB</sub>* = 12.0 Hz, 1.2H), 5.20 – 5.47 (m, 0.35H), 7.25 – 7.37 (m, 5H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  24.6, 24.9, 25.3, 25.4, 30.5, 30.9, 31.4, 31.6, 31.7, 35.9, 40.5, 40.6, 70.4, 72.0, 72.2, 75.1, 76.7, 77.0, 77.4, 78.1, 79.2, 91.2, 99.0, 127.6, 127.7, 127.8, 127.8, 128.4, 128.5, 138.0, 138.6; HRMS (ESI) Calculated for C<sub>16</sub>H<sub>22</sub>O<sub>3</sub>Na<sup>+</sup> (M+Na)<sup>+</sup>:285.1461; Found: 285.1457.

**3 $\beta$ -(Benzyloxy)octahydro-2H-chromen-2-yl 2,2,2-trichloroacetimidate (1.2(TAC)).** In a solution of **1.14** (0.1 g, 0.385 mmol) in dry DCM (3.5 mL) under N<sub>2</sub> was added trichloroacetonitrile (0.156 mL, 1.54 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.077

mmol, 0.015mL). The reaction was stirred for 3 hours at ambient temperature. After completion, the mixture was condensed and purified by silica gel column chromatography (10% EtOAc/hexanes, 3% Et<sub>3</sub>N, *R<sub>f</sub>*=0.40, TLC stained with CAM) to yield **1.2(TAC)** (0.138 g, 88%, 45 $\alpha$ :55 $\beta$ ) as a colorless oil; IR (NaCl):  $\nu_{\max}$  3341, 2932, 2861, 1669, 1295, 1057, 795 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.97 – 1.43 (m, 6H), 1.61 – 1.75 (m, 3H), 1.76 – 1.84 (m, 1H), 1.84 – 1.94 (m, 1H), 1.96 – 2.03 (m, 0.5H), 2.11 (dd, *J* = 9.3, 5.1 Hz, 0.5H), 3.13 – 3.24 (m, 0.55H), 3.50 (td, *J* = 10.4, 4.0 Hz, 0.45H), 3.55 – 3.62 (m, 0.55H), 3.72 (ddd, *J* = 11.8, 4.8, 3.2 Hz, 0.45H), 4.58, 4.66 (ABq, *J<sub>AB</sub>* = 11.9 Hz, 1.1H), 4.67, 4.78 (d, *J* = 11.9 Hz, 0.9H), 5.75 (d, *J* = 7.9 Hz, 0.55H), 6.47 (d, *J* = 3.1 Hz, 0.45H), 7.25 – 7.38 (m, 5H), 8.52 (s, 0.45H), 8.63 (s, 0.55H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  24.5, 24.9, 25.2, 25.3, 30.9, 31.3, 31.5, 31.5, 31.5, 36.3, 40.2, 40.5, 70.6, 72.4, 74.5, 75.1, 75.6, 80.0, 94.6, 100.7, 127.5, 127.6, 127.7, 128.3, 128.4, 138.2, 138.4, 161.5, 161.6; HRMS (ESI) Calculated for C<sub>18</sub>H<sub>23</sub>Cl<sub>3</sub>NO<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup>: 406.0738; Found: 406.0729.

**3 $\alpha$ -(Benzyloxy)octahydro-2H-chromen-2-yl 2,2,2-trichloroacetimidate (1.3(TAC)).** In a solution of **1.14** (0.08 g, 0.308 mmol) in dry DCM (3 mL) under N<sub>2</sub> was added trichloroacetonitrile (0.123 mL, 1.23 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.061 mmol, 0.012 mL). The reaction was stirred for 3 hours at ambient temperature. After completion, the mixture was condensed and purified by silica gel column chromatography (10% EtOAc/hexanes, 3% Et<sub>3</sub>N, *R<sub>f</sub>*=0.38, TLC stained with CAM) to yield **1.3(TAC)** (0.100 g, 80%, 91 $\alpha$ :9 $\beta$ ) as a colorless oil; IR (NaCl):  $\nu_{\max}$  3341, 2931, 2858, 1285, 1072 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.94 – 1.09 (m, 1H), 1.21 – 1.47 (m, 3H), 1.56 – 1.72 (m, 3H), 1.75 – 1.94 (m, 4H), 3.40 (td, *J* = 10.6, 4.0 Hz, 0.08H), 3.57 (td, *J* = 10.5, 4.1 Hz, 0.92H), 3.65 (td, *J* = 2.7, 1.6 Hz, 1H), 4.63, 4.71 (ABq, *J<sub>AB</sub>* = 12.2 Hz, 2H), 5.60 (s, 0.08H), 6.29 (s, 0.92H), 7.27 – 7.41 (m, 5H), 8.50 (s, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  24.8, 25.0, 25.4, 25.6, 30.1, 30.7, 31.3, 31.5, 31.6, 31.7, 34.9, 35.1, 71.1, 71.3, 72.0, 72.4, 75.9, 76.0, 96.1, 96.9, 127.6, 127.6, 127.7, 127.9, 128.4, 128.5, 137.7, 138.2, 159.5, 160.7; HRMS (ESI) Calculated for C<sub>18</sub>H<sub>23</sub>Cl<sub>3</sub>NO<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup>: 406.0738; Found: 406.0745.



### B.3 Glycosylation des donneurs 1.1

**2-Allyloctahydro-2H-chromene (1.1(Allyl)).** From **1.1(OAc)** (0.055 g, 0.277 mmol) using general procedure A, only pure  **$\alpha$ -1.1(Allyl)** (0.044 g, 86%) was obtained without purification. Lower yield can be explained by the compound volatility;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  0.99 (qd,  $J = 12.8, 11.7, 3.5$  Hz, 1H), 1.14–1.40 (m, 5H), 1.47–1.53 (m, 1H), 1.54–1.68 (m, 3H), 1.72–1.80 (m, 2H), 1.86 (tdd,  $J = 13.5, 5.8, 4.4$  Hz, 1H), 2.26–2.34 (m, 1H), 2.60 (ddd,  $J = 14.3, 8.0, 6.6, 1.4$  Hz, 1H), 3.17 (ddd,  $J = 10.1, 3.7$  Hz, 1H), 3.98 (ddt,  $J = 7.0$  Hz, 1H), 5.04 (dt,  $J = 2.2, 1.2$  Hz, 0.5H), 5.05–5.08 (m, 1H), 5.10 (dt,  $J = 2.1, 1.5$  Hz, 0.5H), 5.81 (dddd,  $J = 16.9, 10.2, 7.4, 6.7$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  25.2, 25.6, 25.9, 28.0, 31.8, 32.8, 35.0, 42.3, 72.8, 73.6, 116.4, 135.7; HRMS (ESI) Calculated for  $\text{C}_{12}\text{H}_{21}\text{O}^+$  (M+H) $^+$ : 181.1586; Found: 181.1593.

**2-(2,2,2-Trifluoroethoxy)octahydro-2H-chromene (1.1(TFE)).** From **1.1(SPh)** (0.032 g, 0.128 mmol) using general procedure B in DCM, only  **$\alpha$ -1.1(TFE)** (0.011 g, 36%) could be obtained by flash column chromatography (2% EtOAc/pentanes, 2%  $\text{Et}_3\text{N}$ ,  $R_f = 0.4$  at 5% EtOAc/hexanes, TLC stained with CAM) as a colorless oil. The low yield can be attributed to the compound low stability towards silica gel and volatility. Crude  $^1\text{H}$  NMR showed a 90 $\alpha$ :10 $\beta$  ratio and complete conversion of the starting material to the desired product;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  1.01 (qd,  $J = 12.6, 12.37, 3.3$  Hz, 1H), 1.16 – 1.37 (m, 4H), 1.42 – 1.54 (m, 2H), 1.54 – 1.71 (m, 1H), 1.71 – 1.93 (m, 5H), 3.33 (ddd,  $J = 10.3, 10.3, 3.6$  Hz, 1H), 3.80 – 4.01 (m, 2H), 4.90 (d,  $J = 2.8$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.8, 25.0, 25.7, 29.9, 31.6, 32.1, 41.3, 63.1, 63.5, 63.8, 64.2, 73.5, 97.8, 122.8, 125.6;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  – 74.18 (t,  $J = 9.0$  Hz); HRMS: Because of the compound low stability towards any kind of ionisation source available, the only molecular ion that could be observed was (M-TFE) $^+$  Calculated for 139.1100; Found 139.1116.

**2-(2-Chloroethoxy)octahydro-2H-chromene (1.1(CIEtO)).** From **1.1(SPh)** (0.02 g, 0.0805 mmol) using general procedure B in DCM, crude  $^1\text{H}$  NMR showed a 60 $\alpha$ :40 $\beta$  of **1.1(CIEtO)** which was purified by flash column chromatography (10%  $\text{Et}_2\text{O}$ /hexanes, 2%  $\text{Et}_3\text{N}$ ,  $R_f = 0.37$  at 10%  $\text{Et}_2\text{O}$ /hexanes, TLC stained with CAM) to yield a mixture of  **$\alpha$ : $\beta$ -1.1(CIEtO)** as a colorless oil (0.017 g, 96%);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.83 – 1.09 (m, 1H), 1.09 – 1.40

(m, 4H), 1.41 – 1.68 (m, 4H), 1.69 – 1.93 (m, 4H), 2.97 (ddd,  $J = 11.0, 9.1, 4.1$  Hz, 0.35H), 3.39 (td,  $J = 10.1, 3.6$  Hz, 0.65H), 3.62 – 3.78 (m, 3H), 3.84 – 3.96 (m, 0.65H), 4.10 (ddd,  $J = 11.0, 6.0, 5.2$  Hz, 0.35H), 4.46 (dd,  $J = 9.7, 2.3$  Hz, 0.35H), 4.86 (dd,  $J = 3.3, 1.6$  Hz, 0.65H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.8, 25.1, 25.1, 25.6, 25.8, 29.5, 30.3, 31.1, 31.7, 32.2, 32.2, 40.9, 41.5, 42.9, 43.2, 67.1, 68.8, 73.1, 79.6, 97.6, 102.5; HRMS (ESI) Calculated for  $\text{C}_{11}\text{H}_{19}\text{ClO}_2\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$ : 241.0965; Found: 241.0976.

**2-Ethoxyoctahydro-2H-chromene (1.1(EtO)).** From **1.1(SPh)** (0.06 g, 0.241 mmol) using general procedure B in DCM, crude  $^1\text{H}$  NMR showed a 45 $\alpha$ :55 $\beta$  ratio of **1.1(EtOH)** which was purified by silica gel column chromatography (5% EtOAc/hexanes, 3%  $\text{Et}_3\text{N}$ ,  $R_f = 0.4$  at 15% EtOAc/hexanes, TLC stained with CAM) to yield a pure mixture (70 $\alpha$ :30 $\beta$ ) of **1.1(EtOH)** as a colorless oil (0.027 g, 61%);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.83 – 1.06 (m, 1H), 1.12 – 1.31 (m, 7H), 1.32 – 1.57 (m, 2H), 1.57 – 1.66 (m, 1H), 1.67 – 1.84 (m, 3H), 1.87 (ddt,  $J = 11.2, 3.8, 2.1$  Hz, 1H), 2.95 (ddd,  $J = 11.0, 9.0, 4.1$  Hz, 0.7H), 3.35 (td,  $J = 10.1, 3.7$  Hz, 0.3H), 3.39 – 3.55 (m, 1H), 3.71 (dq,  $J = 9.8, 7.1$  Hz, 0.3H), 3.94 (dq,  $J = 9.5, 7.1$  Hz, 0.7H), 4.40 (dd,  $J = 9.7, 2.2$  Hz, 0.7H), 4.81 (dd,  $J = 2.4$  Hz, 0.3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  15.2, 15.2, 24.8, 25.2, 25.3, 25.7, 25.8, 29.7, 30.6, 31.2, 31.7, 32.0, 32.2, 32.2, 41.0, 41.7, 62.1, 64.0, 72.6, 79.4, 96.9, 101.9; HRMS (ESI) Calculated for  $\text{C}_{11}\text{H}_{21}\text{O}_2^+$  ( $\text{M}+\text{H}$ ) $^+$ : 185.1536; Found: 185.1532.

## B.4 Réactions de glycosylation sur les donneurs C<sub>2</sub>-substitués

**2-Allyl-3 $\beta$ -(benzyloxy) octahydro-2H-chromene (1.2(Allyl)).** Using general procedure A from **1.2(OAc)** (0.030, 0.0985 mmol, 14 $\alpha$ :86 $\beta$ ), was obtained without purification, pure  $\alpha$ -**1.2(Allyl)** as a colorless oil (0.027 g, 96%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.02 – 1.14 (m, 1H), 1.14 – 1.41 (m, 5H), 1.58 – 1.68 (m, 2H), 1.76 – 1.83 (m, 2H), 1.86 (dt,  $J = 12.3, 4.0$  Hz, 1H), 2.36 (dddt,  $J = 15.1, 5.1, 3.7, 1.3$  Hz, 1H), 2.58 – 2.66 (m, 1H), 3.10 (td,  $J = 10.2, 3.9$  Hz, 1H), 3.77 (dddd,  $J = 11.4, 5.5, 4.6, 0.8$  Hz, 1H), 4.14 (dt,  $J = 10.5, 4.5$  Hz, 1H), 4.53, 4.57 (ABq,  $J_{AB} = 15$  Hz, 2H), 5.07 – 5.16 (m, 2H), 5.79 – 6.02 (m, 1H), 7.28 – 7.37 (m, 5H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  25.1, 25.5, 28.9, 31.5, 31.9, 32.1, 41.5, 70.6, 72.4, 74.6, 75.6, 116.4, 127.5, 127.6, 128.4, 135.6, 138.6; HRMS (ESI) Calculated for  $\text{C}_{19}\text{H}_{26}\text{O}_2^+$  ( $\text{M}+\text{H}$ ) $^+$ : 287.2005; Found: 287.1991.

**3 $\beta$ -(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene (1.2(TFE)).** Using general procedure B in DCM from **1.2(SPh)** (0.05 g, 0.141 mmol, 60 $\alpha$ :40 $\beta$ ) gave after column chromatography (5% EtOAc/hexanes  $R_f$  = 0.51 ( $\alpha$ ) and 0.57( $\beta$ ) at 10% EtOAc/hexanes, stained with CAM) pure  $\alpha$  (38 mg) and  $\beta$  (7.0 mg) isomers of **1.2(TFE)** (0.045 g, 93%) isolated and characterised separately.  $^1\text{H}$  NMR study on the crude before purification showed a 83 $\alpha$ :17 $\beta$  ratio of isomers.

**$\alpha$ -1.2(TFE):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.01 – 1.37 (m, 5H), 1.56 – 1.70 (m, 3H), 1.74 – 1.87 (m, 3H), 3.30 (td,  $J$  = 10.4, 3.9 Hz, 1H), 3.57 (ddd,  $J$  = 11.9, 4.8, 3.4 Hz, 1H), 3.86 – 4.06 (m, 2H), 4.57, 4.62 (ABq,  $J_{AB}$  = 12.1 Hz, 2H), 4.91 (d,  $J$  = 3.3 Hz, 1H), 7.26 – 7.37 (m, 5H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9, 25.3, 30.8, 31.2, 31.4, 40.8, 63.6, 64.0, 64.3, 64.7, 70.6, 72.9, 75.0, 97.5, 122.7, 125.4, 127.7, 127.7, 128.4, 138.3;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  – 73.66 (t,  $J$  = 8.9 Hz); HRMS (ESI): Calculated for  $\text{C}_{18}\text{H}_{23}\text{F}_3\text{O}_3\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 367.1491; Found: 367.1476.

**$\beta$ -1.2(TFE):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.91 – 1.05 (m, 1H), 1.11 – 1.40 (m, 4H), 1.59 – 1.69 (m, 2H), 1.76 – 1.84 (m, 1H), 1.87 – 1.96 (m, 1H), 1.98 – 2.04 (m, 1H), 2.96 (td,  $J$  = 9.5, 4.0 Hz, 1H), 3.31 (ddd,  $J$  = 11.0, 7.5, 5.3 Hz, 1H), 3.97 (dq,  $J$  = 12.3, 8.6 Hz, 1H), 4.21 (dq,  $J$  = 12.3, 8.8 Hz, 1H), 4.44 (d,  $J$  = 7.5 Hz, 1H), 4.63, 4.82 (ABq,  $J_{AB}$  = 11.7 Hz, 2H), 7.25 – 7.37 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  24.6, 25.2, 30.8, 31.5, 36.4, 40.5, 65.3, 65.6, 65.8, 66.1, 72.8, 76.1, 79.2, 105.7, 127.5, 127.9, 128.3, 138.6;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  – 74.17 (t,  $J$  = 8.9 Hz); HRMS (ESI): Calculated for  $\text{C}_{18}\text{H}_{23}\text{F}_3\text{O}_3\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 367.1491; Found: 367.1471.

**3 $\beta$ -(Benzyloxy)-2-(2-chloroethoxy)octahydro-2H-chromene (1.2(CIEtO)).** Using general procedure B in DCM from **1.2(SPh)** (0.02 g, 0.0564 mmol, 60 $\alpha$ :40 $\beta$ ), crude  $^1\text{H}$  NMR showed a 63 $\alpha$ :34 $\beta$  ratio of anomers. After column chromatography (10%  $\text{Et}_2\text{O}$ /hexanes  $R_f$  = 0.18( $\alpha$ ) and 0.30( $\beta$ ) at 10% EtOAc/hexanes), a mixture of  $\alpha/\beta$ -**1.2(CIEtO)** (0.017 g, 93%, 65 $\alpha$ :35 $\beta$ ) was isolated and characterised together as a colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94 – 1.39 (m, 6H), 1.60 – 1.70 (m, 2.1H), 1.75 – 1.86 (m, 2.1H), 1.90 – 1.96 (m, 0.4H), 2.01 (dd,  $J$  = 9.4, 5.1 Hz, 0.4H), 2.96 (ddd,  $J$  = 10.7, 8.9, 4.1 Hz, 0.4H), 3.28 – 3.34 (m, 0.4H), 3.39 (td,  $J$  = 10.8, 3.9 Hz, 0.6H), 3.55 (ddd,  $J$  = 11.9, 4.7, 3.4 Hz, 0.6H), 3.69 – 3.74 (m,

2H), 3.75 – 3.86 (m, 1H), 3.92 (dt,  $J = 10.9, 6.2$  Hz, 0.6H), 4.16 (dt,  $J = 10.9, 5.5$  Hz, 0.4H), 4.40, (d,  $J = 7.5$  Hz, 0.35H) 4.58, 4.65 (ABq,  $J_{AB} = 12.3$  Hz, 1.2H), 4.68, 4.88 (ABq,  $J_{AB} = 11.9$  Hz, 0.8H), 4.86 (s, 0.65H), 7.24 – 7.40 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  24.6, 25.0, 25.3, 25.4, 30.9, 31.1, 31.3, 31.5, 31.6, 36.6, 40.6, 41.0, 42.8, 42.9, 67.8, 69.4, 70.6, 72.5, 72.8, 75.3, 76.4, 79.0, 97.4, 105.9, 127.4, 127.7, 127.8, 127.8, 128.3, 128.4, 138.5, 138.9; HRMS (ESI): Calculated for  $\text{C}_{18}\text{H}_{25}\text{O}_3\text{ClNa}^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 347.1384; Found: 347.1387.

**3 $\beta$ -(Benzyloxy)-2-ethoxyoctahydro-2H-chromene (1.2(EtO))**. Using general procedure B in DCM from **1.2(SPh)** (0.02 g, 0.0564 mmol, 60 $\alpha$ :40 $\beta$ ), crude  $^1\text{H}$  NMR showed a 50 $\alpha$ :50 $\beta$  ratio of anomers. After column chromatography (10%  $\text{Et}_2\text{O}$ /hexanes,  $R_f = 0.23$ , TLC stained with CAM), a mixture of  $\alpha/\beta$ -**1.2(EtO)** (0.015 g, 93%, 45 $\alpha$ :55 $\beta$ ) was isolated as a colorless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 – 1.15 (m, 1.5H), 1.15 – 1.41 (m, 7H), 1.60 – 1.69 (m, 2H), 1.74 – 1.85 (m, 1.5H), 1.90 – 1.96 (m, 0.5H), 1.96 – 2.02 (m, 0.5H), 2.95 (ddd,  $J = 10.8, 9.0, 4.0$  Hz, 0.55H) 3.26 – 3.36 (m, 0.88H), 3.51 – 3.59 (m, 0.7H), 3.62 (dq,  $J = 9.5, 7.1$  Hz, 0.55H), 3.77 (dq,  $J = 10.0, 7.1$  Hz, 0.45H), 4.00 (dq,  $J = 9.4, 7.1$  Hz, 0.55H) 4.36 (d,  $J = 7.5$  Hz, 0.55H), 4.57, 4.64 (ABq,  $J_{AB} = 12.4$  Hz, 0.7H), 4.67, 4.84 (ABq,  $J_{AB} = 12.0$  Hz, 1.3H), 4.84 (d,  $J = 0.6$  Hz, 1H), 4.85 (s, 0.45H), 7.25 – 7.38 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  15.2, 15.4, 24.7, 25.0, 25.3, 25.5, 31.0, 31.1, 31.3, 31.6, 31.7, 36.7, 40.7, 41.1, 62.8, 65.0, 70.5, 72.0, 72.7, 75.3, 76.7, 78.8, 96.6, 105.5, 127.4, 127.6, 127.7, 127.7, 128.3, 128.3, 138.6, 139.1; HRMS (ESI): Calculated for  $\text{C}_{18}\text{H}_{26}\text{O}_3\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 313.1774; Found: 313.1770.

**2-Allyl-3 $\alpha$ -(benzyloxy) octahydro-2H-chromene (1.3(allyl))**. From pure  $\beta$ -**1.3(OAc)** (0.056 g, 0.184 mmol) using general procedure A, crude  $^1\text{H}$  NMR showed a 95 $\alpha$ :5 $\beta$  ratio of anomers. After purification by silica gel column chromatography (10%  $\text{Et}_2\text{O}$ /hexanes,  $R_f = 0.35$ , TLC stained with CAM), compounds were isolated as colorless oils (0.049 g, 93%). From  $\alpha$ -**2.3(OAc)**, 82% yield on similar scale.

$\alpha$ -**1.3(Allyl)**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.95 (ddd,  $J = 12.6, 12.5, 3.8$  Hz, 1H), 1.19–1.46 (m, 4H), 1.53–1.86 (m, 6H), 2.17–2.28 (m, 1H), 2.52 (dddt,  $J = 14.3, 7.9, 6.4, 1.5$  Hz, 1H), 3.18 (ddd,  $J = 10.1, 3.7$  Hz, 1H), 3.37 (td,  $J = 2.9, 1.1$  Hz, 1H), 4.03 (tt,  $J = 7.7, 1.3$  Hz, 1H), 4.54 (d,  $J = 12.5$  Hz, 1H), 4.59 (d,  $J = 12.5$  Hz, 1H), 5.01–5.09 (m, 2H), 5.77 (dddd,  $J =$

16.8, 10.2, 7.5, 6.4 Hz, 1H), 7.24–7.29 (m, 1H), 7.30–7.39 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  25.2, 25.8, 30.7, 31.6, 32.4, 34.6, 36.0, 70.2, 73.8, 75.2, 116.8, 127.4, 127.6, 128.3, 134.8, 134.8, 138.8; HRMS (ESI) Calculated for  $\text{C}_{19}\text{H}_{27}\text{O}_2^+$  ( $\text{M}+\text{H}$ ) $^+$ : 287.2005; Found: 287.1997.

**$\beta$ -1.3(Allyl)**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90 – 1.00 (m, 1H), 1.15 (ddd,  $J = 13.8, 12.2, 2.6$  Hz, 1H), 1.20 – 1.35 (m, 3H), 1.42 (dddd,  $J = 14.6, 12.1, 9.5, 3.9$  Hz, 1H), 1.54 – 1.70 (m, 2H), 1.77 – 1.92 (m, 2H), 2.05 (dt,  $J = 13.9, 3.2$  Hz, 1H), 2.32 – 2.50 (m, 2H), 2.97 (ddd,  $J = 11.0, 9.5, 4.1$  Hz, 1H), 3.35 – 3.42 (m, 2H), 4.43, 4.68 (ABq,  $J_{AB} = 12.1$  Hz, 2H), 4.97 – 5.06 (m, 2H), 5.73 (dddd,  $J = 16.8, 10.1, 7.8, 6.4$  Hz, 1H), 7.28 – 7.41 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  25.1, 25.8, 31.5, 32.2, 33.8, 35.8, 36.2, 70.6, 72.6, 79.7, 82.3, 116.7, 127.5, 128.0, 128.2, 135.2, 138.7; HRMS (ESI) Calculated for  $\text{C}_{19}\text{H}_{27}\text{O}_2^+$  ( $\text{M}+\text{H}$ ) $^+$ : 287.2005; Found: 287.2002.

**$3\alpha$ -(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene (1.3(TFE))**. Using general procedure B in DCM from **1.3(SPh)** (0.06 g, 0.169 mmol, 90 $\alpha$ :10 $\beta$ ) gave after column chromatography (10% EtOAc/hexanes  $R_f = 0.38$ ) a 70 $\alpha$ :30 $\beta$  ratio of **1.3(TFE)** (0.05 g, 86%) isolated and characterised as a mixture.  $^1\text{H}$  NMR study on the crude before purification showed a 65 $\alpha$ :35 $\beta$  ratio of anomers. Similar result was obtained from pure  **$\beta$ -1.3(SPh)**;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.82 – 1.06 (m, 1H), 1.16 – 1.45 (m, 3H), 1.46 – 1.96 (m, 8H), 3.02 (ddd,  $J = 11.1, 9.8, 4.1$  Hz, 0.3H), 3.33 (td,  $J = 10.6, 3.8$  Hz, 0.7H), 3.52 (td,  $J = 2.7, 1.4$  Hz, 0.7H), 3.62 (td,  $J = 2.8, 1.5$  Hz, 0.3H), 3.82 – 4.05 (m, 1.7H), 4.16 – 4.31 (m, 0.3H), 4.53 (s, 0.3H), 4.57, 4.61 (ABq,  $J = 12.3$  Hz, 1.4H), 4.71, 7.76 (d,  $J = 12.9$  Hz, 0.6H), 4.85 (s, 0.7H), 7.24 – 7.43 (m, 5H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.7, 25.0, 25.5, 25.6, 30.1, 30.9, 31.4, 31.6, 31.7, 34.9, 35.2, 35.3, 63.5, 64.8, 65.1, 65.4, 65.8, 71.0, 72.4, 72.5, 73.0, 73.8, 80.4, 98.2, 102.5, 122.6, 125.4, 127.4, 127.6, 127.7, 127.8, 128.2, 128.4, 138.2, 138.8;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  – 74.32 (t,  $J = 8.9$  Hz), – 74.21 (t,  $J = 8.8$  Hz); HRMS (ESI): Calculated for  $\text{C}_{18}\text{H}_{23}\text{F}_3\text{O}_3\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$ : 367.1491; Found :367.1479.

**$3\alpha$ -(Benzyloxy)-2-(2-chloroethoxy)octahydro-2H-chromene (1.3(CIEtO))**. From **1.3(SPh)** (0.02 g, 0.056 mmol) using general procedure B in DCM, the crude  $^1\text{H}$  NMR showed a ratio of isomers of 6 $\alpha$ :34 $\beta$ . Purification by silica gel column chromatography (10%

Et<sub>2</sub>O/hexanes, *R<sub>f</sub>* = 0.23, TLC stained with CAM) yielded **1.3(CIEtO)** as a colorless oil (0.018 g, 98%); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.83 – 1.03 (m, 1H), 1.15 – 1.44 (m, 3H), 1.48 – 1.74 (m, 4H), 1.74 – 1.83 (m, 2.2H), 1.86 – 1.93 (m, 0.66H), 3.01 (ddd, *J* = 11.2, 9.8, 4.1 Hz, 0.33H), 3.40 (td, *J* = 11.2, 10.8, 3.8 Hz, 0.66H), 3.49 (td, *J* = 2.8, 1.4 Hz, 0.66H), 3.60 (td, *J* = 3.0, 1.1 Hz, 0.33H), 3.64 – 3.68 (m, 1.2H), 3.69 – 3.76 (m, 1.4H), 3.90 – 3.97 (m, 0.66H), 4.14 – 4.24 (m, 0.33H), 4.47 (d, *J* = 1.2 Hz, 0.26H), 4.58, 4.62 (ABq, *J<sub>AB</sub>* = 12.4 Hz, 1.3H), 4.75, 4.83 (ABq, *J<sub>AB</sub>* = 13.0 Hz, 0.6H), 4.82 (s, 0.66H) 7.24 – 7.43 (m, 5H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 24.8, 25.1, 25.6, 25.7, 30.4, 31.0, 31.5, 35.1, 35.4, 35.4, 43.1, 67.2, 69.1, 70.9, 72.4, 72.8, 73.3, 73.5, 80.1, 98.1, 102.9, 127.3, 127.6, 127.6, 127.8, 128.2, 128.4, 138.4, 139.1; HRMS (ESI): Calculated for C<sub>18</sub>H<sub>25</sub>O<sub>3</sub>ClNa<sup>+</sup> (M+Na)<sup>+</sup>: 347.1384; Found: 347.1395.

**3α-(Benzyloxy)-2-ethoxyoctahydro-2H-chromene (1.3(EtO))**. From **1.3(SPh)** (0.02 g, 0.056 mmol) using general procedure B in DCM, the crude <sup>1</sup>H NMR showed a ratio of anomers of 50α:50β. Purification by silica gel column chromatography, (5% Et<sub>2</sub>O/hexanes, *R<sub>f</sub>* = 0.48 at 10 EtOAc/hexanes, TLC stained with CAM) yielded **1.3(EtO)** as a colorless oil (0.011 g, 93% 50α:50β); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.83 – 1.02 (m, 1H), 1.16 – 1.43 (m, 3H) 1.21 (t, *J* = 7.1 Hz, 1.5H), 1.27 (t, *J* = 7.0 Hz, 1.5H), 1.47 – 1.71 (m, 4H), 1.73 – 1.84 (m, 2H), 1.85 – 1.94 (m, 1H), 3.00 (ddd, *J* = 11.1, 9.7, 4.1 Hz, 0.5H), 3.37 (td, *J* = 10.4, 3.9 Hz, 0.5H), 3.44 (td, *J* = 3.0, 1.5 Hz, 0.5H), 3.45 – 3.53 (m, 1H), 3.55 (td, *J* = 3.0, 1.0 Hz, 0.5H), 3.76 (dq, *J* = 9.8, 7.1 Hz, 0.5H), 4.01 (dq, *J* = 9.4, 7.1 Hz, 0.5H), 4.41 (d, *J* = 1.1 Hz, 0.5H), 4.59, 4.62 (ABq, *J<sub>Ab</sub>* = 1.3 Hz, 1H), 4.73, 4.85 (ABq, *J<sub>AB</sub>* = 12.9 Hz, 1H) 7.24 – 7.44 (m, 5H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 15.1, 15.3, 24.8, 25.2, 25.7, 25.7, 30.5, 31.1, 31.5, 31.9, 35.3, 35.5, 35.6, 62.4, 64.5, 70.8, 72.3, 72.9, 73.2, 73.8, 79.9, 97.5, 102.5, 127.2, 127.5, 127.6, 127.7, 128.1, 128.3, 138.6, 139.4; HRMS (ESI): Calculated for C<sub>18</sub>H<sub>27</sub>O<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup>: 291.1954; Found: 291.1953.

## B.5 Réactions de glycosylation utilisant les trichloroacetamidates (TAC)

**3β-(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene (1.2(TFE))**. From **1.2(TAC)** (0.065 g, 0.160 mmol, 45α:55β) using general procedure A, the crude <sup>1</sup>H NMR showed a ratio of anomers of 80α:20β. Purification by silica gel column chromatography,

(10% Et<sub>2</sub>O/hexanes, TLC stained with CAM) gave pure mixture of  **$\alpha$ : $\beta$ -1.2(TFE)** as a colorless oil (0.043 g, 78%, 65 $\alpha$ :35 $\beta$ ). Spectral data are similar to the ones obtained from **1.2(SPh)**.

**3 $\beta$ -(Benzyloxy)-2-ethoxyoctahydro-2H-chromene (1.2(EtO))**. From **1.2(TAC)** (0.03 g, 0.074 mmol, 45 $\alpha$ :55 $\beta$ ) using general procedure A, the crude <sup>1</sup>H NMR showed a ratio of anomers of 45 $\alpha$ :55 $\beta$ . Purification by silica gel column chromatography, (10% Et<sub>2</sub>O/hexanes, TLC stained with CAM) gave pure mixture of  **$\alpha$ / $\beta$ -1.2(EtO)** as a colorless oil (0.020 g, 91%, 60 $\alpha$ :40 $\beta$ ). Spectral data are similar to the ones obtained from **1.2(SPh)**.

**3 $\alpha$ -(Benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene (1.3(TFE))**. From **1.3(TAC)** (0.04 g, 0.04 mmol, 91 $\alpha$ :9 $\beta$ ) using general procedure A, the crude <sup>1</sup>H NMR showed a ratio of anomers of 82 $\alpha$ :18 $\beta$ . Purification by silica gel column chromatography, (10% Et<sub>2</sub>O/hexanes, TLC stained with CAM) gave pure mixture of  **$\alpha$ / $\beta$ -1.3(TFE)** as a colorless oil (0.022 g, 76%, 85 $\alpha$ :15 $\beta$ ). Spectral data are similar to the ones obtained from **1.3(SPh)**.

**3 $\alpha$ -(Benzyloxy)-2-ethoxyoctahydro-2H-chromene (1.3(EtO))**. From **1.3(TAC)** (0.04 g, 0.04 mmol, 91 $\alpha$ :9 $\beta$ ) using general procedure A, the crude <sup>1</sup>H NMR showed a ratio of anomers of 72 $\alpha$ :28 $\beta$ . Purification by silica gel column chromatography, (10% Et<sub>2</sub>O/hexanes, TLC stained with CAM) gave pure mixture of  **$\alpha$ / $\beta$ -1.3(EtO)** as a colorless oil (0.022 g, 76%, 72 $\alpha$ :28 $\beta$ ). Spectral data are similar to the ones obtained from **1.3(SPh)**.

## Annexe C Données expérimentales du chapitre 2

### C.1 Protocole de synthèse et caractérisation des composés

**tert-Butyldimethyl((2-vinylcyclohexyl)oxy)silane (2.6):** To the allyl alcohol (3.5 g, 27.7 mmol) in dry DCM (30 mL) under argon was added imidazole (3.77 g, 55.5 mmol) followed by TBSCl (5.02 g, 33.3 mmol). The mixture was stirred overnight at ambient temperature. Silica was added and the mixture condensed to a powdered blend. The desired compound was recovered by filtration through a fritted glass funnel filled with 10 cm of silica gel using hexanes to yield after evaporation 6.27 g (94 %) of **2.6** as colourless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.82 (ddd,  $J = 17.6, 10.4, 7.4$  Hz, 1H), 5.04 – 4.96 (m, 2H), 3.28 (td,  $J = 9.6, 4.2$  Hz, 1H), 2.01 – 1.92 (m, 1H), 1.91 – 1.85 (m, 1H), 1.78 – 1.70 (m, 2H), 1.67 – 1.61 (m, 1H), 1.37 – 1.13 (m, 4H), 0.88 (s, 8H), 0.04 (s, 3H), 0.03 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  142.1, 113.9, 74.9, 49.8, 35.8, 30.5, 25.9, 25.0, 24.8, 18.2, -0.02, -4.2, -4.5; HRMS (ESI-TOF)  $M/Z$ :  $[\text{M}+\text{K}]^+$  Calcd for  $\text{C}_{14}\text{H}_{28}\text{OSiK}$  279.1546; Found; 279.1532.

**2-(2-Hydroxyethyl)cyclohexan-1-ol (2.7):** To a solution of OTBS protected olefin **2.6** (1.3 g, 5.4 mmol) in dry THF (10 mL) at 0 °C under an argon atmosphere was added 2 M  $\text{BH}_3\text{-Me}_2\text{S}$  solution in THF (10.81 mmol, 5.41 mL) over 10 min. The reaction was then brought slowly to ambient temperature and stirred for 18 h. The mixture was treated with 3 M NaOH at 0 °C until the pH was basic and excess 30%  $\text{H}_2\text{O}_2$  was added. The reaction was stirred for 3 h until completion and was diluted with water and DCM. The organic layer was separated, and the aqueous layer washed with DCM (3 $\times$ ). The organic layers were combined, dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The crude residue was rapidly eluted on a silica gel pad with 50:50 EtOAc/hexanes, condensed *in vacuo* then diluted in dry THF (5 mL). 1 M TBAF solution in THF (5.4 mL, 5.4 mmol) was then added. The reaction was stirred 1 h at ambient temperature and quenched with saturated  $\text{NH}_4\text{Cl}_{(\text{aq})}$ . The reaction was diluted with DCM, the phases separated, and the aqueous portion washed with DCM (3 $\times$ ), dried over  $\text{MgSO}_4$ , filtered and condensed *in vacuo*. The crude mixture was purified by silica gel column chromatography (50% EtOAc/hexanes, TLC stained with *p*-anisaldehyde) to obtain 0.430 g (50 % over two steps) of the diol **2.7** as a colourless thick oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.21 (s, 1H), 3.75 (dt,  $J = 10.6, 4.7$  Hz, 1H), 3.59 (ddd,  $J = 10.7, 9.5, 3.5$  Hz, 1H), 3.19 (td,  $J$



= 9.8, 4.4 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.77 – 1.64 (m, 3H), 1.64 – 1.56 (m, 1H), 1.51 (dtd,  $J = 14.7, 4.8, 3.6$  Hz, 1H), 1.36 – 1.09 (m, 4H), 1.07 – 0.97 (m, 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ , 74.9, 61.4, 44.4, 44.37, 38.1, 35.5, 32.7, 25.6, 24.9; HRMS (ESI-TOF)  $M/Z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_8\text{H}_{17}\text{O}_2$  145.1223; Found 145.1212.

**Hexahydrobenzofuran-2(3H)-one (2.8):** To a solution of diol **2.7** (0.219 g, 1.51 mmol) in dry DCM (3 mL) under argon was added [bis(acetoxy)iodo]benzene (1.46 g, 4.53 mmol) followed by TEMPO (0.070 g, 0.453 mmol). The reaction was stirred for 3 h at ambient temperature and quenched with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The organic layer was isolated and washed with DCM (3 $\times$ ). Combined phases were dried over  $\text{MgSO}_4$ , filtered and condensed under reduce pressure. The crude mixture was purified by flash chromatography (20% EtOAc/hexanes, TLC stained with CAM) to yield 0.180 g (85%) of a colourless oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.78 (td,  $J = 10.9, 3.8$  Hz, 1H), 2.50 (ddd,  $J = 16.1, 6.8, 2.2$  Hz, 1H), 2.22 (tt,  $J = 13.1, 4.8$  Hz, 2H), 2.02 – 1.86 (m, 3H), 1.82 – 1.76 (m, 1H), 1.53 (qd,  $J = 11.8, 3.4$  Hz, 1H), 1.46 – 1.24 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.6, 85.2, 44.8, 35.9, 30.2, 28.3, 25.3, 24.1; IR (NaCl)  $\nu_{\text{max}}$  2939, 2865, 1781, 1447, 1189, 1030, 931  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_8\text{H}_{13}\text{O}_2$  141.0910; Found 141.0905.

**Octahydrobenzofuran-2-yl acetate (2.1(OAc)):** To a  $-78$   $^\circ\text{C}$  solution of lactone **2.8** (0.900 g, 6.42 mmol) in dry toluene (20 mL) under an argon atmosphere was added dropwise 1 M DIBAL-H in heptanes (7.70 mL, 7.70 mmol). The reaction was stirred at  $-78$   $^\circ\text{C}$  for 2 h. Once the reaction completed by TLC monitoring, pyridine (0.620 mL, 7.70 mmol), was slowly added at  $-78$   $^\circ\text{C}$ , followed by DMAP (0.941 g, 7.70 mmol) in 6 mL of dry DCM, stirred for 10 min and  $\text{Ac}_2\text{O}$  (3.03 mL, 32.1 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and stirred for 12 h. The mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with EtOAc. The extracted organic phase was washed with 1 N  $\text{NaHSO}_4$  (2 $\times$ ), saturated  $\text{NaHCO}_3$  (2 $\times$ ), brine (1 $\times$ ), dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes with 2%  $\text{Et}_3\text{N}$ , TLC stained with CAM) to obtain a mixture of two diastereoisomeric acetates **2.1(OAc)** (0.778 g, 60 $\alpha$ :40 $\beta$ , 66 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.24 (dd,  $J = 6.0, 4.7$  Hz, 0.6H), 6.19 (d,  $J = 5.2$  Hz, 0.4H), 3.37 (td,  $J = 10.4, 3.8$  Hz, 0.6H), 3.19 (td,  $J = 10.7, 3.8$  Hz, 0.4H), 2.42 (ddd,  $J = 13.0, 7.1, 6.1$  Hz, 0.6H), 2.19 – 2.10 (m, 1H), 2.05 (s, 1.8H), 2.03 (s,

1.2H), 2.00 (dd,  $J = 12.5, 5.4$  Hz, 1H), 1.96 – 1.88 (m, 1H), 1.87– 1.80 (m, 1H), 1.79 – 1.66 (m, 2H), 1.57 (ddd,  $J = 12.8, 11.9, 4.7$  Hz, 1H), 1.47 – 1.34 (m, 1.4H), 1.33 – 1.02 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 170.4, 98.2, 97.5, 85.4, 82.9, 45.2, 41.9, 37.9, 37.8, 31.5, 30.5, 28.5, 28.4, 25.6, 25.5, 24.2, 24.1, 21.4, 21.3.; IR (NaCl)  $\nu_{\text{max}}$  2936, 2860, 1749, 1450, 1376, 1234, 1036, 963, 864  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) M/Z:  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}_3\text{Na}$ : 207.0991; Found: 207.0992.

**2-(Phenylthio)octahydrobenzofuran (2.1(SPh)):** To a solution of diastereoisomeric acetate **2.1(OAc)** (0.778 g, 4.22 mmol) in dry DCM (20 mL) under an argon atmosphere was added PhSH (1.72 mL, 16.9 mmol). The mixture was cooled to  $-78$  °C and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (0.570 mL, 4.64 mmol) was slowly added. After 1 h of stirring at  $-78$  °C, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$ , brought to ambient temperature and diluted with DCM. The organic phase was isolated and the aqueous one was washed with DCM (3 $\times$ ). The organic phases were combined, dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The residue was purified by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give two diastereoisomeric thioacetals **2.1(SPh)** (0.500 g, 50 %, 15 $\alpha$ :85 $\beta$ ) as colourless oils;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 – 7.49 (m, 2H), 7.35 – 7.16 (m, 3H), 5.63 (t,  $J = 7.2$  Hz, 0.85H), 5.50 (dd,  $J = 7.8, 2.7$  Hz, 0.15H), 3.39 (td,  $J = 10.2, 3.8$  Hz, 0.85H), 3.17 (td,  $J = 10.6, 3.8$  Hz, 0.15H), 2.55 (dt,  $J = 12.2, 6.8$  Hz, 1H), 2.20 – 2.10 (m, 1H), 1.98 – 1.89 (m, 1H), 1.88 – 1.79 (m, 1H), 1.73 – 1.67 (m, 1H), 1.53 (td,  $J = 11.9, 7.3$  Hz, 1H), 1.45 – 1.03 (m, 5H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  131.5, 130.2, 128.7, 126.9, 126.5, 85.6, 84.8, 81.4, 45.1, 44.2, 38.9, 38.5, 31.5, 30.6, 28.7, 25.6, 24.2; HRMS (ESI-TOF) M/Z:  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{14}\text{H}_{19}\text{OS}$ : 235.1151; Found 235.1148.

**1-(2-((tert-Butyldimethylsilyl)oxy)cyclohexyl)ethane-1,2-diol (2.9):** To a solution of **2.6** (6.27 g, 26.1 mmol) in THF (36 mL) and water (12 mL) at  $0$  °C was added N-methylmorpholine oxide (6.41 g, 54.6 mmol) followed by catalytic  $\text{OsO}_4$  (4% in  $\text{H}_2\text{O}$ , 2 mL). The reaction was stirred for 18 h at ambient temperature. It was then diluted with water and EtOAc. The phases were separated, and the aqueous mixture was washed with EtOAc (5 $\times$ ), dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (35% EtOAc/hexanes, TLC stained with CAM) to give two

diastereoisomeric diols **2.9** (6.9 g, 97%) isolated as a thick yellowish oil (ratio ~2:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.69 – 3.53 (m, 4H), 1.98 – 1.87 (m, 1H), 1.80 – 1.51 (m, 5H), 1.40 – 1.10 (m, 5H), 0.91 (s, 5.5H), 0.90 (s, 3.5H), 0.14 (d,  $J = 8.2$  Hz, 3.5H), 0.11 (d,  $J = 4.1$  Hz, 2.5H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  78.6, 76.0, 73.6, 73.4, 64.7, 63.9, 47.6, 46.8, 36.4, 36.2, 26.6, 26.2, 25.87, 25.82, 25.78, 25.45, 25.11, 24.7, 24.6, 17.95, 17.87, -3.4, -3.6, -4.69, -4.73; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{14}\text{H}_{31}\text{O}_3\text{Si}$  275.2037; Found 275.2013.

**Allyl 2-(2-((*tert*-butyldimethylsilyloxy)cyclohexyl)-2-hydroxyacetate (2.10):** To a solution of diol **2.9** (4.0 g, 14.6 mmol) in DCM (69 mL) and saturated  $\text{NaHCO}_{3(\text{aq})}$  (17 mL) was added TEMPO (0.09 g, 0.583 mmol) and KBr (1.91 g, 16.0 mmol). The reaction was stirred rapidly while a 0.435 M solution of NaOCl (36.8 mL, 16.0 mmol) was added at 0 °C. The dark-red reaction was stirred for 1 h until its colour faded to a pale orange. Once completion reached, a  $\text{Na}_2\text{S}_2\text{O}_3$  aqueous solution was added and the phases were separated and the aqueous one was washed with DCM (3 $\times$ ). The combine organic phases were dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The crude aldehyde was directly submitted to the next step. The intermediary aldehyde was put in solution in *t*-BuOH (120 mL) and water (40 mL),  $\text{NaH}_2\text{PO}_4$  (3.49 g, 29.1 mmol). Once the salt completely dissolved, the reaction was brought to 0 °C and 2-methyl-2-butene 2 M solution in THF (14.6 mL) was added to the mixture followed by solid  $\text{NaOCl}_2$  pellets (80 % w/w, 3.29 g, 29.1 mmol) The reaction was stirred at 0 °C for 1 h. Following completion, the mixture was slowly acidified to pH 4 using 1 N HCl. The mixture was extracted using DCM (4 $\times$ ), dried with  $\text{MgSO}_4$ , filtered and condensed under reduced pressure. The crude product was dissolved in minimal amount of DCM and quickly purified through an acid/base workup using 1 N NaOH and 1 N HCl. After reacidification, the desired acid was extracted using DCM (5 $\times$ ), dried over  $\text{MgSO}_4$  and condensed. The resulting thick yellow oil was put in solution in DMF (25 mL) followed by the addition of  $\text{K}_2\text{CO}_3$  (3.10 g, 22.49 mmol), tetrabutylammonium iodide (1.66 g, 4.49 mmol) and allyl bromide (1.94 mL, 22.49 mmol) dropwise. The reaction was stirred for 2 h at ambient temperature and then diluted in water and  $\text{Et}_2\text{O}$ . The aqueous phase was washed with  $\text{Et}_2\text{O}$  (3 $\times$ ). The combined organic phases were washed with 1 N HCl (1 $\times$ ) and saturated  $\text{NaHCO}_3$  (1 $\times$ ). The organic phase was dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The resulting crude was purified by silica gel column chromatography (5% EtOAc/hexanes, TLC stained with

CAM) to yield compound **2.10** (3.72 g, 77 % over three steps) as a yellowish oily mixture of the two diastereoisomers (2.3:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.01 – 5.81 (m, 1H), 5.43 – 5.17 (m, 2H), 4.77 – 4.56 (m, 3H), 4.27 (q,  $J = 3.4$  Hz, 0.77H), 3.68 (ddd,  $J = 9.7, 3.5$  Hz, 0.77H), 3.60 (ddd,  $J = 9.9, 3.8$  Hz, 0.33H), 3.25 (d,  $J = 4.1$  Hz, 0.77H), 2.73 (d,  $J = 5.5$  Hz, 0.33H), 1.97 – 1.80 (m, 2H), 1.78 – 1.59 (m, 3H), 1.35 – 1.00 (m, 4H), 0.88 (s, 3H), 0.86 (s, 6H), 0.08, (s, 1H), 0.07, (s, 1H), 0.05 (s, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  1757, 174.1, 131.7, 131.6, 119.1, 118.8, 69.8, 66.0, 65.9, 49.5, 48.7, 36.2, 36.1, 27.5, 26.0, 25.9, 25.4, 25.2, 24.8, 24.7, 23.8, 18.04, 18.03, -4.00, -4.1, -4.3, -5.0; IR (NaCl)  $\nu_{\text{max}}$  3529, 2931, 2857, 1733, 1250, 1086  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{17}\text{H}_{33}\text{O}_4\text{Si}$  329.2142; Found 329.2141.

**Allyl 2-(2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-2-methoxyacetate (2.11/2.11')**: To a solution of **2.10** (3.12 g, 9.48 mmol) in dry THF (11 mL) was added at 0 °C under argon NaH (60 % in mineral oil, 0.430 g, 10.08 mmol). The mixture was stirred for 15 min after which iodomethane (2.53 mL, 40.6 mmol) was slowly added. Reaction was stirred overnight and quenched with saturated  $\text{NH}_4\text{Cl}$ , diluted with water and  $\text{Et}_2\text{O}$ . The organic phase was isolated, and the aqueous portion extracted with  $\text{Et}_2\text{O}$  (3 $\times$ ). The combined organic phases were dried with  $\text{MgSO}_4$ , filtered and condensed under reduced pressure. The resulting crude was purified by silica gel column chromatography (5%  $\text{Et}_2\text{O}$ /hexanes, TLC stained with CAM) to yield each compound **2.11** (minor) (0.815 g, 25 %) and **2.11'** (major) (1.362 g, 42 %) as pale yellowish oils.

#### **Minor 2.11:**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.93 (ddt,  $J = 17.3, 10.5, 5.7$  Hz, 1H), 5.33 (dq,  $J = 17.2, 1.5$  Hz, 1H), 5.24 (dq,  $J = 10.4, 1.3$  Hz, 1H), 4.66 (ddd,  $J = 30.1, 13.3, 5.7, 1.5$  Hz, 2H), 4.26 (d,  $J = 2.3$  Hz, 1H), 3.61 (ddd,  $J = 10.0, 4.4$  Hz, 1H), 3.39 (s, 3H), 1.95 (dt,  $J = 8.6, 3.0$  Hz, 1H), 1.75 – 1.58 (m, 2H), 1.45 – 1.18 (m, 4H), 1.17 – 1.02 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07(s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.9, 132.1, 118.3, 79.0, 70.5, 65.1, 58.5, 48.8, 36.1, 26.0, 25.4, 24.7, 24.3, 18.0, -3.6, -4.7; IR (NaCl)  $\nu_{\text{max}}$  2933, 2857, 1750, 1257, 1086, 835  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{18}\text{H}_{38}\text{NO}_4\text{Si}$  360.2564; Found 360.2549.

### Major 2.11':

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.00 – 5.88 (m, 1H), 5.35 (dq,  $J = 17.2, 1.5$  Hz, 1H), 5.26 (dq,  $J = 10.4, 1.1$  Hz, 1H), 4.65 (dt,  $J = 6.0, 1.2$  Hz, 2H), 4.13 (d,  $J = 2.9$  Hz, 1H), 3.61 (ddd,  $J = 9.9, 9.8, 4.4$  Hz, 1H), 3.39 (s, 3H), 1.93 – 1.85 (m, 2H), 1.80 (ddt,  $J = 12.1, 9.7, 3.2$  Hz, 1H), 1.71 – 1.58 (m, 2H), 1.30 – 1.22 (m, 1H), 1.19 – 1.13 (m, 2H), 0.95 – 0.90 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 132.1, 119.0, 80.4, 70.6, 65.1, 58.3, 49.2, 36.1, 26.1, 26.0, 25.1, 24.4, 181, -3.9, -4.7; IR (NaCl)  $\nu_{\text{max}}$  2930, 2857, 1752, 1450, 1090, 836  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{18}\text{H}_{35}\text{O}_4\text{Si}$  343.2298; Found 343.2296.

**3-Methoxyhexahydrobenzofuran-2(3H)-one (2.12):** To a solution of ester **2.11'** (1.32 g, 3.97 mmol) in a scintillation vial with dry THF (10 mL) at 0 °C under an argon atmosphere was slowly added HF (70 % in pyridine) in excess (1 mL). The reaction was left to reach ambient temperature overnight. A saturated solution of  $\text{NaHCO}_3$  was then added slowly to the mixture until fizzing would stop and further diluted with water and EtOAc. The organic phase was isolated, and the aqueous portion extracted with EtOAc (3 $\times$ ). Combined organic phases were further washed with a small portion of 1 N HCl, then dried over  $\text{MgSO}_4$ , filtered, and condensed under reduced pressure. As only a fraction of the desired cyclisation occurred, the crude mixture was additionally diluted in dry DCM (10 mL) and TsOH (0.068 g, 0.397 mmol) was added. The mixture was stirred overnight and quenched with saturated  $\text{NaHCO}_{3(\text{aq})}$ . The organic layer was isolated, and the aqueous portion extracted with EtOAc (3 $\times$ ). Combined organic phases were dried over  $\text{MgSO}_4$ , filtered, and condensed under reduced pressure. The crude was isolated by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) to yield compound **2.12** (0.494 g, 73%) as a slightly yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.79 (d,  $J = 11.6$  Hz, 1H), 3.73 (ddd,  $J = 10.9, 3.9$  Hz, 1H), 3.61 (s, 3H), 2.19 (dt,  $J = 10.9, 3.3$  Hz, 1H), 2.08 (dt,  $J = 9.1, 3.2$  Hz, 1H), 2.01 – 1.83 (m, 2H), 1.83 – 1.72 (m, 1H), 1.58 – 1.42 (m, 1H), 1.40 – 1.21 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  175.1, 80.8, 79.1, 58.7, 50.1, 30.3, 27.2, 24.9, 23.8; IR (NaCl)  $\nu_{\text{max}}$  2940, 1785, 1457, 1197, 1022  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_9\text{H}_{15}\text{O}_3$  171.1015; Found 171.1018.

**3-Methoxyhexahydrobenzofuran-2(3H)-one (2.13):** To a solution of ester **2.11** (0.815 g, 2.37 mmol) in a scintillation vial with dry THF (10 mL) at 0 °C under an argon atmosphere was slowly added HF (70 % in pyridine) in excess (1 mL). The reaction was left to reach ambient temperature overnight. A saturated solution of NaHCO<sub>3(aq)</sub> was then added slowly to the mixture until fizzing would stop and further diluted with water and EtOAc. The organic phase was isolated, and the aqueous portion extracted with EtOAc (3×). Combined organic phases were further washed with a small portion of 1 N HCl, then dried over MgSO<sub>4</sub>, filtered, and condensed under reduced pressure. As only a fraction of the desired cyclisation occurred, the crude mixture was additionally diluted in dry DCM (10 mL) and TsOH (0.040 g, 0.237 mmol) was added. The mixture was stirred overnight and quenched with saturated NaHCO<sub>3(aq)</sub>. The organic layer was isolated, and the aqueous portion extracted with EtOAc (3×). Combined organic phases were dried over MgSO<sub>4</sub>, filtered, and condensed under reduced pressure. The crude was isolated by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) to yield compound **2.13** (0.333 g, 82 %) as a slightly yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.20 (ddd, *J* = 10.9, 3.9 Hz, 1H), 3.67 (d, *J* = 4.7 Hz, 1H), 3.49 (s, 3H), 2.26 – 2.20 (m, 1H), 1.91 – 1.68 (m, 4H), 1.61 – 1.22 (m, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ 173.7, 82.5, 78.1, 58.2, 49.5, 30.6, 25.2, 23.8, 22.8; IR (NaCl) ν<sub>max</sub> 2942, 1785, 1456, 1198, 1026 cm<sup>-1</sup>; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>9</sub>H<sub>15</sub>O<sub>3</sub> 171.1015; Found 171.1012.

**3-Methoxyoctahydrobenzofuran-2-yl acetate (2.2(OAc)):** Using the same one-pot reduction acetylation reaction as described for compound **2.1(OAc)**, from lactone **2.12** (0.333 mg, 1.94 mmol) using 1 M DIBAL-H in heptanes (2.33 mL, 2.33 mmol), pyridine (0.187 mL, 2.33 mmol), DMAP (0.284 g, 2.33 mmol), Ac<sub>2</sub>O (1.10 mL, 11.6 mmol) were isolated and separated the two acetylated anomers by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) **α-2.2(OAc)** (0.125 g, 30 %) and **β-2.2(OAc)** (0.247 g, 59 %) as colourless oils. Anomers were identified by analogy with **2.2(SPh)** NMR for which the NOESY shows the more downfield anomeric proton to be the one corresponding to the β-anomer.

**Minor  $\alpha$ -isomer:**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.67 (dd,  $J = 9.1, 2.7$  Hz, 1H), 3.55 (ddd,  $J = 11.1, 11.0, 4.1$  Hz, 1H), 3.39 (s, 3H), 2.10 (s, 3H), 2.15 – 2.03 (m, 2H), 1.86 – 1.80 (m, 1H), 1.76 – 1.72 (m, 1H), 1.56 (dt,  $J = 14.3, 9.6$  Hz, 1H), 1.42 (ddd,  $J = 11.6, 11.4, 3.9$  Hz, 1H), 1.31 – 1.16 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 101.3, 89.6, 81.3, 58.3, 51.3, 30.9, 27.4, 25.3, 23.7, 21.3; IR (NaCl)  $\nu_{\text{max}}$  2938, 2863, 1748, 1456, 1231  $\text{cm}^{-1}$ , HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{Na}]^+$ : Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}$  237.1097; Found 237.1097.

**Major  $\beta$ -isomer:**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.27 (d,  $J = 4.5$  Hz, 1H), 3.56 (dd,  $J = 11.0, 4.5$  Hz, 1H), 3.41 (s, 3H), 3.30 (td,  $J = 11.1, 3.9$  Hz, 1H), 2.10 – 2.15 (m, 2H), 2.11 (s, 3H), 1.89 – 1.80 (m, 1H), 1.79 – 1.66 (m, 2H), 1.42 (ddd,  $J = 11.6, 11.4, 3.9$  Hz, 1H), 1.31 – 1.08 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 93.3, 84.0, 80.8, 59.0, 46.3, 31.9, 27.1, 25.1, 24.1, 21.4; IR (NaCl)  $\nu_{\text{max}}$  2938, 2863, 1748, 1237, 1007  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{Na}]^+$ : Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}$ : 237.1097; Found 237.1097.

**3-Methoxyoctahydrobenzofuran-2-yl acetate (2.3(OAc)):** Using the same one-pot reduction acetylation reaction as described for compound **2.1(OAc)**, from lactone **2.15** (0.494 g, 2.88 mmol) using 1 M DIBAL-H in heptanes (3.45 mL, 3.45 mmol), pyridine (0.278 mL, 3.45 mmol), DMAP (0.421 g, 3.45 mmol),  $\text{Ac}_2\text{O}$  (1.36 mL, 14.4 mmol) were isolated and separated the two acetylated anomers by silica gel column chromatography (20 % EtOAc/hexanes, TLC stained with CAM) to yield major  **$\beta$ -2.3(OAc)** (0.348 g, 56 %) and minor  **$\alpha$ -2.3(OAc)** (0.208 g, 34 %) as colourless oils respectively. Anomers were identified by analogy with **2.3(SPh)** NMR for which the NOESY shows the more downfield anomeric proton to be the one corresponding to the  $\alpha$ -anomer. The matching coupling constant  $^3J_{\text{H}_1-\text{H}_2}$  of about 4.2 Hz in both cases also confirms the orientation of each anomer.

**Major  $\beta$ -isomer:**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.09 (s, 1H), 3.68 (ddd,  $J = 11.0, 10.9, 3.9$  Hz, 1H), 3.61 (d,  $J = 4.0$  Hz, 1H), 3.44 (s, 3H), 2.24 – 2.17 (m, 1H), 2.06 (s, 3H), 1.91 – 1.73 (m, 3H), 1.58 – 1.47 (m, 1H), 1.48 – 1.29 (m, 2H), 1.28 – 1.17 (m, 2H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$

169.9, 99.1, 85.5, 82.4, 57.9, 46.6, 32.1, 25.6, 24.0, 23.5, 21.3; IR (NaCl)  $\nu_{\max}$  2938, 1748, 1373, 1234, 1011  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{Na}]^+$ : Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}$ : 237.1097; Found 237.1093.

**Minor  $\alpha$ -isomer:**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.19 (d,  $J = 4.2$  Hz, 1H), 3.87 (dd,  $J = 4.3, 5.0$  Hz, 1H), 3.71 (ddd,  $J = 10.4, 10.4, 4.0$  Hz, 1H), 3.40 (s, 3H), 2.15 (s, 1H), 2.13 (s, 3H), 1.91 – 1.73 (m, 3H), 1.54 – 1.37 (m, 2H), 1.35 – 1.14 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 99.2, 81.4, 80.9, 60.3, 49.8, 31.1, 25.3, 23.8, 23.6, 21.1; IR (NaCl)  $\nu_{\max}$  2937, 1733, 1375, 1253, 1026  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{Na}]^+$ : Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}$  237.1097; Found 237.1094.

**3-Methoxy-2-(phenylthio)octahydrobenzofuran (2.2(SPh)):** Using the same procedure as described for **2.1(SPh)** from **2.2(OAc)** (0.300 g, 1.40 mmol) using PhSH (0.571 mL, 5.60 mmol) and  $\text{BF}_3\text{-Et}_2\text{O}$  (0.190 mL, 1.54 mmol), the desired compound was isolated by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield the major  $\alpha$ -**2.2(SPh)** (0.151 g, 40 %) and  $\beta$ -**2.2(SPh)** (0.066 g, 19 %) as a colourless oil and a white solid (mp: 48.7-55.0  $^\circ\text{C}$ ) respectively. NOESY experiments showed a coupling between H1 and H4 of the minor isomer, thus confirming the  $\beta$ -SPh orientation.

**Major  $\alpha$ -2.2(SPh):**

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (d,  $J = 7.3$  Hz, 2H), 7.40 – 7.14 (m, 3H), 5.45 (d,  $J = 4.5$  Hz, 1H), 3.67 – 3.52 (m, 2H), 3.51 (s, 3H), 2.21 – 2.06 (m, 2H), 1.94 – 1.80 (m, 1H), 1.79 (d,  $J = 4.4$  Hz, 1H), 1.52 (dddd,  $J = 26.7, 23.3, 11.5, 3.5$  Hz, 2H), 1.39 – 1.18 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.7, 130.4, 128.9, 126.8, 90.5, 90.4, 79.5, 58.8, 51.4, 31.0, 27.7, 25.4, 23.9; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2\text{S}$  265.1256; Found 265.1261.

**Minor  $\beta$ -2.2(SPh):**

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J = 7.0$  Hz, 1H), 7.40 – 7.17 (m, 3H), 5.65 (d,  $J = 6.5$  Hz, 1H), 3.87 (dd,  $J = 10.0, 6.5$  Hz, 1H), 3.53 (s, 3H), 3.29 (td,  $J = 11.0, 3.9$  Hz, 1H), 2.14



(td,  $J = 10.2, 8.9, 4.1$  Hz, 2H), 1.91 – 1.66 (m, 1H), 1.52 (ddd,  $J = 11.6, 3.7$  Hz, 1H), 1.34 – 1.09 (m, 2H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  13C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  135.4, 131.3, 128.8, 126.7, 88.6, 85.6, 81.0, 59.1, 49.7, 32.0, 27.7, 25.3, 24.2; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2\text{S}$  265.1256; Found 265.1265.

**3-Methoxy-2-(phenylthio)octahydrobenzofuran (2.3(SPh))**: Using the same procedure as described for **2.1(SPh)** from **2.3(OAc)** (0.134 g, 0.625 mmol) using PhSH (0.255 mL, 2.5 mmol) and  $\text{BF}_3\text{-Et}_2\text{O}$  (0.092 mL, 0.75 mmol), the desired compound was isolated by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give the mixture of thioacetals **2.3(SPh)** (49 $\alpha$ :51 $\beta$ , 0.090 g, 54 %). NOESY experiments showed a coupling between the more downfield H1 and H2 and not H4, thus confirming that the downfield signal belongs to the  $\alpha$ -SPh.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 – 7.51 (m, 1H), 7.34 – 7.23 (m, 2.5H), 7.21 – 7.16 (m, 0.5H), 5.79 (d,  $J = 4.7$  Hz, 0.5H), 5.28 (s, 0.5H), 3.95 (t,  $J = 4.6$  Hz, 0.5H), 3.77 (d,  $J = 4.1$  Hz, 0.5H), 3.73 (td,  $J = 10.3, 4.2$  Hz, 0.5H), 3.57 (td,  $J = 10.8, 4.1$  Hz, 0.5H), 3.53 (s, 1.5H), 3.31 (s, 1.5H), 2.24 – 2.13 (m, 1H), 1.93 – 1.71 (m, 4H), 1.56 – 1.08 (m, 6H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  132.1, 130.4, 129.0, 128.8, 127.4, 126.3, 92.1, 89.2, 87.9, 84.0, 82.5, 79.3, 60.9, 57.6, 50.6, 48.7, 32.1, 31.4, 25.6, 25.52, 24.0, 23.99, 23.91; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2\text{S}$  265.1256; Found 265.1261.

**Ethyl-2-oxooctahydrobenzofuran-3-carboxylate (2.14)**: In a flame dried bicol, solid sodium chunks (0.561 g, 24.4 mmol) were added to 30 mL of dry ethanol at 0 °C under argon. Once the sodium dissolved, diethylmalonate (3.73 mL, 24.4 mmol) was slowly added and the reaction stirred at ambient temperature for 0.5 h followed by cyclohexene oxide (2.47 mL, 20.4 mmol). The reaction was refluxed overnight, and a white precipitate was formed, indicative of reaction completion. The mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with EtOAc. The organic layer was isolated, and the aqueous phase washed with EtOAc (3 $\times$ ). Combined organic phases were washed with brine, dried with  $\text{MgSO}_4$ , filtered and condensed under reduced pressure. The crude residue was purified by flash chromatography (8% EtOAc/hexanes, TLC stained with  $\text{KMnO}_4$ ) to yield **2.14** (3.61 g, 80%) of colourless viscous oil containing the two diastereoisomers (88eq: 12ax) of the ethyl ester and characterized as such;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.31 – 4.18 (m, 2H), 3.81 (ddd,  $J$

= 11.5, 10.7, 3.9 Hz, 1H), 3.48 (d,  $J = 8.4$  Hz, 0.12H), 3.24 (d,  $J = 12.9$  Hz, 0.88H), 2.39 – 2.20 (m, 2H), 2.00 – 1.88 (m, 3H), 1.86 – 1.76 (m, 1H), 1.58 (qd,  $J = 11.7, 3.9$  Hz, 1H), 1.44 – 1.23 (m, 6H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.5, 167.5, 166.7, 83.2, 83.0, 61.9, 61.8, 53.0, 51.5, 48.1, 47.7, 30.4, 30.0, 27.4, 25.4, 25.2, 25.0, 24.0, 23.85, 23.8, 14.2, 14.1; IR (NaCl)  $\nu_{\text{max}}$  2942, 2867, 1786, 1734, 1165, 1019  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{11}\text{H}_{17}\text{O}_4$  214.1155; Found 214.1152.

**2-(3-Hydroxyprop-1-en-2-yl)cyclohexan-1-ol (2.15):** To 20 mL of dimethoxymethane in a flame dried bicol under argon was added NaH (0.795 g, 19.9 mmol, 60% dispersed in mineral oil). A 20 mL solution of **2.14** (2 g, 9.03 mmol) in dimethoxymethane was slowly added and stirred for 2 h at ambient temperature upon which the mixture turned to a white slurry. Solid  $\text{LiAlH}_4$  (0.939 g, 24.8 mmol) was put in solution with 30 mL of dried  $\text{Et}_2\text{O}$  and added to the reaction mixture. The reaction was refluxed overnight and quenched slowly with aqueous saturated Rochelle's salt. After 2 h of stirring, organic layer was isolated, and the aqueous layer washed with  $\text{EtOAc}$  (3 $\times$ ). The organic phases were combined, washed with brine, dried with  $\text{MgSO}_4$  and condensed under reduced pressure. Crude mixture was purified by flash chromatography (45%  $\text{EtOAc}$ /hexanes, TLC stained with CAM) to yield **2.15** (0.870 g 62 %) of the desired diol as a white solid (mp: 63.2-66.0  $^\circ\text{C}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.20 (s, 1H), 5.05 (s, 1H), 4.15, 4.09 (ABq,  $J_{AB} = 12.9$  Hz, 2H), 3.51 (td,  $J = 10.1, 4.2$  Hz, 1H), 2.46 (s, br, 1H), 2.07 – 2.03 (m, 1H), 2.00 (td,  $J = 11.4, 10.3, 3.4$  Hz, 1H), 1.82 – 1.67 (m, 3H), 1.39 – 1.16 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  150.9, 112.6, 73.6, 65.7, 50.5, 34.9, 31.8, 25.8, 24.9; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_9\text{H}_{17}\text{O}_2$  157.1223; Found 157.1201.

**2-(1-Hydroxypropan-2-yl)cyclohexan-1-ol (2.16/2.16')**: To a solution of allylic alcohol (0.125 g, 0.768 mmol) in  $\text{EtOAc}$  (8 mL) was added  $\text{PtO}_2$  (0.0174 g, 10 mol%). The reaction was stirred 1 h under  $\text{H}_2$  atmosphere using a rubber balloon and filtered on celite upon completion. The solvent was evaporated and the diastereoisomers isolated by flash chromatography as a thick oil for the least polar **2.16** (0.05 g, 48.0 %) and a white solid (0.061 g, 50%, mp: 78.3-81.3) for the most polar isomer **2.16'**.

**Diol 2.16:**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.81 (br s, 1H), 3.64, 3.57 (d of ABq,  $J_d = 5.4$  Hz  $J_{AB} = 10.7$ , 2H), 3.40 (td,  $J = 9.9, 4.4$  Hz, 1H), 2.02 – 1.94 (m, 1H), 1.80 (m, 1H), 2.75 – 1.68 (m, 1H), 1.67 – 1.61 (m, 1H), 1.61 – 1.53 (m, 1H), 1.44 – 1.34 (m, 1H), 1.30 – 1.10 (m, 4H), 0.95 (d,  $J = 7.3$ , 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  70.5, 67.0, 49.0, 38.9, 35.9, 30.0, 25.9, 24.9, 11.9; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_9\text{H}_{19}\text{O}_2$  159.1379; Found 159.1377.

**Diol 2.16':**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.58, 3.50 (d of ABq,  $J_d = 5.5$  Hz,  $J_{AB} = 10.6$  Hz, 2H), 3.41 (ddd,  $J = 10.1, 10.1, 4.3$  Hz, 1H), 2.38 (br s, 2H), 2.11 – 1.97 (m, 2H), 1.77 – 1.70 (m, 1H), 1.70 – 1.60 (m, 2H), 1.40 (ddt,  $J = 11.9, 10.0, 3.6$  Hz, 1H), 1.32 – 1.10 (m, 3H), 0.98 (qd,  $J = 13.2, 3.8$  Hz, 1H), 0.87 (d,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  72.0, 66.6, 46.1, 36.5, 35.8, 25.8, 25.7, 25.0, 12.6; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_9\text{H}_{19}\text{O}_2$  159.1379; Found 159.1375.

**3-Methylhexahydrobenzofuran-2(3H)-one (2.17):** To a solution of the most polar diol **2.16'** (0.433 g, 2.73 mmol) in 13 mL of  $\text{CH}_3\text{CN}$  was added tetrakisacetonitrile copper(I) triflate 0.045 g, 0.121 mmol) followed by commercial 0.04 M Stahl Aerobic Oxidation ABNO solution (0.121 mmol, 1.81 mL). The reaction was stirred overnight at ambient temperature. As the reaction reached completion, the mixture colour changed from dark brown to blue. Reaction was diluted with  $\text{H}_2\text{O}$ , extracted with 3 $\times$  DCM, dried with  $\text{MgSO}_4$ , filtered and condensed under reduced pressure. The crude was purified by silica gel flash chromatography (10% EtOAc/hexanes, TLC stained with CAM) to yield 0.420 g (98 %) of the desired lactone **2.17** as a yellowish oil. Positive NOESY between H4 and H2 and the absence of coupling between H4 and the  $\text{CH}_3$  group confirmed the pseudo-equatorial orientation of the  $\text{CH}_3$  group;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.72 (td,  $J = 10.8, 3.9$  Hz, 1H), 2.31 – 2.16 (m, 2H), 1.96 – 1.87 (m, 2H), 1.86 – 1.74 (m, 1H), 1.56 – 1.22 (m, 5H), 1.19 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  179.4, 82.8, 51.7, 41.4, 30.1, 27.4, 25.2, 24.1, 12.5; IR (NaCl)  $\nu_{\text{max}}$  2937, 2865, 1785, 1457, 1178, 1015  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_9\text{H}_{15}\text{O}_2$  156.1100; Found 156.1093.

**3-Methylhexahydrobenzofuran-2(3H)-one (2.18):** To a solution of the diol **2.16** (0.733 g, 4.62 mmol) in 27 mL of CH<sub>3</sub>CN was added tetrakisacetonitrile copper(I) triflate (0.055 g, 0.136 mmol) followed by commercial 0.04 M Stahl Aerobic Oxidation ABNO solution (0.081 mmol, 2.04 mL). The reaction was stirred overnight at ambient temperature. As reaction reached completion, the mixture color changed from dark brown to blue. Reaction was diluted with H<sub>2</sub>O, extracted with DCM (3×), dried with MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude was purified by silica gel flash chromatography (10 % EtOAc/hexanes, TLC stained with CAM) to yield 0.576 g (80 %) of desired lactone **2.18** as a yellowish oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.97 (td, *J* = 11.1, 3.9 Hz, 1H), 2.62 (p, *J* = 7.6 Hz, 1H), 2.24 (dt, *J* = 11.2, 3.4 Hz, 1H), 1.97 (dddd, *J* = 11.8, 10.8, 7.5, 3.3 Hz, 1H), 1.93 – 1.88 (m, 1H), 1.84 – 1.75 (m, 2H), 1.52 (qd, *J* = 12.0, 11.6, 4.0 Hz, 1H), 1.44 – 1.23 (m, 3H), 1.15 (d, *J* = 7.7 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 180.1, 81.8, 47.3, 38.8, 30.6, 25.2, 24.6, 24.0, 9.6; IR (NaCl) *v*<sub>max</sub> 2940, 2866, 1779, 1391, 1194, 1017 cm<sup>-1</sup>; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub> 156.1100; Found 156.1094.

**3-Methyloctahydrobenzofuran-2-yl acetate 2.4(OAc):** From lactone **2.17** (0.250 g, 1.64 mmol) using the same one-pot reduction acetylation reaction with 1 M DIBAL-H in heptanes (1.97 mL, 1.97 mmol), pyridine (0.157 mL, 1.97 mmol), DMAP (0.241 g, 1.97 mmol), Ac<sub>2</sub>O (0.775 mL, 8.2 mmol), the desired compound was isolated by silica gel column chromatography (10 % EtOAc/hexanes, TLC stained with CAM) to yield a mixture of acetylated compounds **2.4(OAc)** characterized as such (13α:87β, 0.313 g, 96 %). Positive answer in the 1D NOESY experiment between H4 and the H1 confirmed the β as the major anomer in the mixture; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.17 (d, *J* = 5.2 Hz, 0.13H), 5.83 (d, *J* = 4.6 Hz, 0.87H), 3.47 (ddd, *J* = 10.8, 9.6, 3.9 Hz, 0.87H), 3.25 (td, *J* = 10.7, 3.8 Hz, 0.13H), 2.13 – 2.06 (m, 1H), 2.05 (s, 2.6H), 2.04 (s, 0.4H), 1.95 – 1.84 (m, 1H), 1.82 (s, 1H), 1.77 – 1.69 (m, 1H), 1.42 – 1.15 (m, 4H), 1.15 – 1.02 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 2.6H), 0.96 (d, *J* = 6.8 Hz, 0.4H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 170.9, 170.5, 104.2, 98.6, 85.1, 83.3, 52.6, 48.1, 45.1, 42.3, 31.7, 30.7, 27.2, 27.0, 25.5, 25.4, 24.3, 24.0, 21.4, 21.3, 14.7, 10.4; IR (NaCl) *v*<sub>max</sub> 2934, 2862, 1745, 1234, 979 cm<sup>-1</sup>; HRMS (ESI-TOF) *M/Z* [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>11</sub>H<sub>22</sub>O<sub>3</sub>N 216.1594; Found 216.1591.

**3-Methyloctahydrobenzofuran-2-yl acetate (2.5(OAc)):** From lactone **2.18** ( 0.253 g, 1.64 mmol) using the same one-pot reduction acetylation reaction with 1 M DIBAL-H in heptanes (1.97 mL, 1.97 mmol), pyridine (0.157 mL, 1.97 mmol), DMAP (0.241 g, 1.97 mmol), Ac<sub>2</sub>O (0.775 mL, 8.2 mmol), the desired compound was isolated by silica gel column chromatography (10 % EtOAc/hexanes, TLC stained with CAM) to yield a mixture of acetylated compounds **2.5(OAc)** as a colourless oil and characterized as such (16 $\alpha$ :84 $\beta$ , 0.200 g, 64 %). The nature of the major anomer was determined by analogy with the **2.5(SPh)** NOESY experiment; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.31 (d, *J* = 6.0 Hz, 0.15H), 5.84 (s, 0.85H), 3.52 (td, *J* = 10.9, 3.8 Hz, 1H), 2.60 (h, *J* = 7.4 Hz, 0.25H), 2.27 – 2.18 (m, 2H), 2.10 (s, 0.4H), 2.05 (s, 2.6H), 1.87 – 1.70 (m, 4H), 1.41 (dddd, *J* = 11.6, 11.41, 11.41, 3.9 Hz, 1H), 1.31 – 1.15 (m, 3H), 0.98 (d, *J* = 7.5 Hz, 2.6H), 0.89 (d, *J* = 7.5 Hz, 0.4H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 170.5, 103.7, 100.0, 82.2, 79.7, 48.1, 45.2, 41.8, 38.2, 32.2, 31.1, 25.6, 25.5, 25.1, 24.8, 24.2, 24.1, 21.5, 21.2, 10.8, 9.2; IR (NaCl)  $\nu_{\max}$  2936, 2862, 1740, 1453, 1373, 1239, 973 cm<sup>-1</sup>; HRMS (ESI-TOF) M/Z [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>11</sub>H<sub>22</sub>O<sub>3</sub>N 216.1594; Found 216.1592.

**3-Methyl-2-(phenylthio)octahydrobenzofuran (2.4(SPh)):** With the same procedure as described for **2.1(SPh)** from **2.4(OAc)** (0.690 g, 3.48 mmol) using PhSH ( 1.42 mL, 13.9 mmol) and BF<sub>3</sub>-Et<sub>2</sub>O (0.471 mL, 3.82 mmol), the desired compound was isolated by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield a mixture of thiofuranoside **2.4(SPh)** characterized as such (90 $\alpha$ :10 $\beta$ , 0.725 g, 84 %); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.16 (m, 1H), 5.61 (d, *J* = 7.5 Hz, 0.1H), 5.14 (d, *J* = 7.5 Hz, 0.9H), 3.46 (td, *J* = 10.7, 10.3, 3.9 Hz, 0.9H), 3.26 (td, *J* = 10.7, 3.8 Hz, 0.1H), 2.33 – 2.20 (m, 0.1H), 2.18 – 2.10 (m, 1H), 1.97 – 1.72 (m, 4H), 1.48 – 1.14 (m, 4H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.13 – 0.97 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  136.7, 131.2, 130.2, 128.8, 128.76, 126.5, 126.4, 93.3, 91.6, 84.7, 82.1, 52.4, 50.6, 46.2, 43.4, 31.9, 30.9, 27.5, 27.4, 25.5, 24.4, 24.1, 15.7, 13.6; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>15</sub>H<sub>21</sub>OS 249.1307; Found 249.1310.

**3-Methyl-2-(phenylthio)octahydrobenzofuran (2.5(SPh)):** With the same procedure as described for **2.1(SPh)** from **2.5(OAc)** (0.454 g, 2.23 mmol) using PhSH (0.910 mL, 8.92

mmol) and  $\text{BF}_3\text{-Et}_2\text{O}$  (0.302 mL, 2.45 mmol), the desired compound was isolated by the residue was purified by silica gel column chromatography (2% EtOAc/hexanes to 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield a mixture of thiofuranoside **2.5(SPh)** characterized as such (ratio  $12\alpha:88\beta$ , 0.394 g, 71 %). The major  $\beta$  anomer was confirmed by 1D NOESY correlation between H4 and H1;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.48 (m, 2H), 7.34 – 7.16 (m, 3H), 5.74 (d,  $J = 6.4$  Hz, 0.13H), 5.01 (d,  $J = 2.6$  Hz, 0.87H), 3.61 (td,  $J = 10.5, 3.9$  Hz, 0.13H), 3.40 (td,  $J = 10.9, 3.9$  Hz, 0.87H), 2.70 (h,  $J = 7.3$  Hz, 0.12H), 2.35 (pd,  $J = 7.4, 2.6$  Hz, 0.83H), 2.19 (dq,  $J = 11.3, 3.2$  Hz, 1H), 1.89 – 1.77 (m, 1H), 1.78 – 1.70 (m, 2H), 1.68 – 1.53 (m, 1H), 1.49 – 1.36 (m, 1H), 1.35 – 1.07 (m, 4H), 1.11(d,  $J = 7.4, 0.3$ H) 1.02 (d,  $J = 7.3$  Hz, 2.7H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  136.6, 135.4, 131.2, 130.7, 128.8, 128.8, 128.7, 126.8, 126.3, 92.4, 91.5, 82.2, 79.1, 48.7, 47.4, 42.8, 39.5, 32.1, 31.7, 25.6, 25.4, 25.1, 24.2, 24.1, 11.1; HRMS (ESI-TOF)  $M/Z$   $[M+H]^+$ : Calcd for  $\text{C}_{15}\text{H}_{21}\text{OS}$  249.1307; Found 249.1310.

## C.2 Réactions de C-glycosylation et caractérisation des produits

**2-Allyloctahydrobenzofuran (2.1(allyl))**: Similar result and spectral data as reported by Woerpel and co-workers.<sup>9e</sup>

**2-Allyl-3-methoxyoctahydrobenzofuran (2.2(allyl))**: From **2.2(OAc)** (0.04 g, 0.187 mmol) using general procedure A with  $\text{BF}_3\text{-Et}_2\text{O}$  (0.028 mL, 0.224 mmol) and allylTMS (0.118 mL and 0.748 mmol) in DCM (1.9 mL), the crude  $^1\text{H}$  NMR showed a ration of  $34\alpha:66\beta$ . Compound was purified by silica gel chromatography (5% EtOAc/hexanes, TLC stained with  $\text{KMnO}_4$ ) to yield **2.2(allyl)** (0.035 g, 96 %) as a colourless oily mixture of anomers;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.99 – 5.81 (m, 1H), 5.18 – 5.02 (m, 2H), 3.99 (ddd,  $J = 8.5, 7.5, 4.5$  Hz, 0.65H), 3.87 (dt,  $J = 6.9, 5.8$  Hz, 0.35H), 3.61 (dd,  $J = 8.6, 7.5$  Hz, 0.65H), 3.39 (s, 1H), 3.38 (s, 2H), 3.38 – 3.33 (m, 0.35H), 3.27 (td,  $J = 10.9, 4.0$  Hz, 0.35H), 3.04 (td,  $J = 10.8, 3.9$  Hz, 0.65H), 2.41 – 2.32 (m, 1.3H), 2.31 – 2.21 (m, 0.7H), 2.13 – 2.02 (m, 2H), 1.85 – 1.64 (m, 2H), 1.58 (tdd,  $J = 11.5, 8.9, 3.2$  Hz, 0.35H), 1.46 – 1.31 (m, 1.65H), 1.30 – 1.12 (m, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  136.0, 134.8, 117.1, 116.3, 88.9, 85.7, 81.7, 80.0, 79.7, 79.1, 58.8, 58.3, 51.9, 51.3, 39.3, 35.0, 31.6, 31.5, 28.6, 28.4, 25.7, 25.4, 24.1, 23.9; HRMS (ESI-TOF)  $M/Z$   $[M+H]^+$ : Calcd for  $\text{C}_{12}\text{H}_{21}\text{O}_2$  197.1536; Found 197.1528.

**2-Allyl-3-methoxyoctahydrobenzofuran (2.3(allyl)):** From **2.3(OAc)** (0.05 g, 0.233 mmol) using general procedure A with BF<sub>3</sub>-Et<sub>2</sub>O (0.034 mL, 0.279 mmol) and allylTMS (0.148 mL and 0.932 mmol) in DCM (2.3 mL), a mixture of 6 $\alpha$ :94 $\beta$  compound was obtained according to the crude <sup>1</sup>H NMR. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM) to yield **2.3(allyl)** as a colourless oil (6 $\alpha$ :94 $\beta$ , 0.038 g, 83 %). The major  $\beta$ -anomer was identified by NOESY where the OCH<sub>3</sub> couples with the major anomeric proton, therefore confirming the  $\beta$ -orientation of the substituent; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.83 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.06 (td, *J* = 7.2, 4.2 Hz, 0.06H), 3.89 (ddd, *J* = 7.3, 5.7, 1.4 Hz, 0.94H), 3.61 (dt, *J* = 3.8, 1.6 Hz, 0.06H), 3.46 – 3.35 (m, 2H), 3.29 (s, 3H), 2.42 – 2.30 (m, 1H), 2.29 – 2.16 (m, 1H), 2.17 – 2.10 (m, 1H), 1.88 – 1.70 (m, 3H), 1.40 (dddd, *J* = 12.4, 3.5 Hz, 1H), 1.32 – 1.11 (m, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  134.4, 117.4, 85.5, 83.76, 80.4, 57.4, 49.2, 39.3, 31.8, 25.7, 24.0, 23.96; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>12</sub>H<sub>21</sub>O<sub>2</sub> 197.1536; Found 197.1528.

**2-Allyl-3-methyloctahydrobenzofuran (2.4(allyl)):** From **2.4(OAc)** (0.03 g, 0.151 mmol) using general procedure A with BF<sub>3</sub>-Et<sub>2</sub>O (0.023 mL, 0.181 mmol) and allylTMS (0.096 mL and 0.604 mmol) in DCM (1.5 mL), a mixture of 60 $\alpha$ :40 $\beta$  was obtained according to the <sup>1</sup>H NMR. The mixture was characterized as a colourless oil without the need for additional purification **2.4(allyl)** (0.027 g, 98 %). 1D NOESY showed correlation between the major H1 signal and the CH<sub>3</sub> at the C2 position, confirming the major  $\alpha$ -anomer; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.97 – 5.82 (m, 1H), 5.16 – 5.00 (m, 2H), 4.05 (td, *J* = 8.9, 4.5 Hz, 0.4H), 3.61 (ddd, *J* = 8.3, 6.7, 5.0 Hz, 0.6H), 3.21 (td, *J* = 10.1, 3.8 Hz, 0.6H), 3.07 (td, *J* = 10.5, 3.9 Hz, 0.4H), 2.41 – 2.25 (m, 1H), 2.25 – 2.03 (m, 2H), 1.99 – 1.65 (m, 4H), 1.61 – 1.47 (m, 1H), 1.35 – 1.02 (m, 7H), 0.99 (d, *J* = 6.5 Hz, 1.8H), 0.96 (d, *J* = 7.0 Hz, 1.2H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  136.3, 135.3, 116.7, 116.2, 85.0, 82.5, 82.4, 80.0, 53.2, 51.5, 43.8, 40.7, 39.5, 36.8, 31.7, 31.6, 27.9, 27.5, 25.7, 25.6, 24.4, 24.3, 15.4, 12.7; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>12</sub>H<sub>21</sub>O 181.1586; Found: 197.1571.

**2-Allyl-3-methyloctahydrobenzofuran (2.5(allyl)):** From **2.5(OAc)** (0.03 g, 0.151 mmol) using general procedure A with BF<sub>3</sub>-Et<sub>2</sub>O (0.023 mL, 0.181 mmol) and allylTMS (0.096 mL and 0.604 mmol) in DCM (1.5 mL), only pure  $\beta$ -anomer was obtained according to the <sup>1</sup>H NMR and 1D NOESY experiment where and coupling between C<sub>1</sub>-H and C<sub>4</sub>-H was observed. The desired

compound **2.5(allyl)** was characterized as a colourless oil without the need for additional purification (0.025 g, 90 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.83 (ddtd,  $J = 17.2, 10.2, 7.0, 1.2$  Hz, 1H), 5.12 – 5.02 (m, 2H), 3.53 (dddd,  $J = 6.8, 5.7, 3.4, 1.0$  Hz, 1H), 3.21 (td,  $J = 10.5, 3.9$  Hz, 1H), 2.36 (dddq,  $J = 13.9, 7.0, 5.8, 1.3$  Hz, 1H), 2.26 (dtq,  $J = 14.0, 7.0, 1.2$  Hz, 1H), 2.17 – 2.10 (m, 1H), 2.02 – 1.89 (m, 1H), 1.82 – 1.66 (m, 3H), 1.45 – 1.07 (m, 5H), 0.88 (dd,  $J = 7.2, 1.1$  Hz, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  135.0, 116.9, 86.1, 80.3, 47.6, 40.5, 38.9, 31.8, 25.8, 25.0, 24.2, 15.3; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{Na}]^+$ : Calcd for  $\text{C}_{12}\text{H}_{20}\text{ONa}$  203.1406; Found 203.1398.

### C.3 Réactions de O-glycosylation et caractérisation des produits

**2-(2,2,2-Trifluoroethoxy)octahydrobenzofuran (2.1(TFE))**: Using general procedure B with NIS (0.096 g, 0.426 mmol) and 2,2,2 trifluoroethanol (0.062 mL, 0.852 mmol) in  $\text{CH}_3\text{CN}$  (2.1 mL) from **2.1(SPh)** (0.05 g, 0.213 mmol, 15 $\alpha$ :85 $\beta$ ), crude  $^1\text{H}$  NMR showed a 22 $\alpha$ :78 $\beta$  ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of  $\alpha/\beta$ -**2.1(TFE)** (0.033 g, 69 %, 21 $\alpha$ :79 $\beta$ ) was isolated and characterized together as a colourless oil. NOESY experiment showed a coupling between  $\text{C}_1\text{-H}$  and  $\text{C}_4\text{-H}$  as the major anomeric proton was irradiated, meaning that the major anomer is the  $\beta$ -**2.1(TFE)**;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.22 (dd,  $J = 5.7, 4.3$  Hz, 0.79H), 5.14 (d,  $J = 4.7$  Hz, 0.21H), 4.06 (dq,  $J = 12.4, 9.1$  Hz, 0.79H), 4.05 – 3.95 (m, 0.21H), 3.86 (dq,  $J = 12.3, 8.7$  Hz, 0.79H), 3.80 (dt,  $J = 12.2, 8.7$  Hz, 0.21H), 3.34 (td,  $J = 10.4, 3.9$  Hz, 0.79H), 3.21 (ddd,  $J = 11.1, 9.8, 3.8$  Hz, 0.21H), 2.35 (ddd,  $J = 13.2, 7.4, 5.8$  Hz, 1H), 2.15 – 2.01 (m, 1H), 1.98 – 1.79 (m, 2H), 1.76 – 1.60 (m, 2H), 1.54 (ddd,  $J = 13.1, 11.7, 4.3$  Hz, 1H), 1.43 – 1.01 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  124.0 (q,  $J = 278$  Hz), 104.3, 103.3, 85.3, 81.4, 65.0 (q,  $J = 34.2$  Hz), 45.6, 42.1, 38.4, 38.3, 31.7, 30.55, 28.5, 28.5, 25.6, 24.3, 24.2;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.22 (t,  $J = 8.7$  Hz, 084F), -74.27 (t,  $J = 8.9$  Hz, 2.16F); HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+ - [\text{H}_2\text{O}]$ : Calcd for  $\text{C}_{10}\text{H}_{17}\text{F}_3\text{ON}$  224.1262; Found 224.1243.

**3-Methoxy-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (2.2(TFE))**: Using general procedure B with NIS (0.059 g and 0.264 mmol) and 2,2,2 trifluoroethanol (0.038 mL, 0.528 mmol) in  $\text{CH}_3\text{CN}$  (1.3 mL) from **2.2(SPh)** (0.035 g, 0.132 mmol, 32 $\alpha$ :68 $\beta$ ), crude  $^1\text{H}$  NMR showed a 34 $\alpha$ :66 $\beta$  ratio of anomers. After column chromatography (100 % hexanes then 10



% EtOAc/hexanes, TLC stained with CAM),  $\alpha$ -**2.2(TFE)** (0.010 mg, 30 %) and the more polar  $\beta$ -**2.2(TFE)** (0.019, 56 %) were obtained and characterized as colourless volatile oils. NOESY experiment on the major  $\beta$ -**2.2(TFE)** isomer showed a coupling between C<sub>1</sub>-H and C<sub>4</sub>-H, thus confirming the orientation at the anomeric center.

**Minor  $\alpha$ -2.2(TFE):**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.02 (s, 1H), 4.02 (dq,  $J = 12.3, 8.7$  Hz, 1H), 3.88 (dq,  $J = 12.6, 8.6$  Hz, 1H), 3.55 (d,  $J = 9.1$  Hz, 1H), 3.54 – 3.48 (m, 1H), 3.42 (s, 3H), 2.12 – 2.00 (m, 2H), 1.85 – 1.80 (m, 1H), 1.73 (d,  $J = 8.8$  Hz, 1H), 1.54 – 1.46 (m, 1H), 1.44 – 1.35 (m, 1H), 1.30 – 1.15 (m, 4H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$  -74.25 (t,  $J = 8.7$  Hz, 3F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  123.9 (q,  $J = 282.8$  Hz), 108.0, 90.3, 80.3, 64.7 (q,  $J = 34.3$  Hz) 58.3, 51.6, 30.9, 27.3, 25.3, 23.8; HRMS (ESI-TOF) M/Z [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>11</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>3</sub> 272.1468; Found 272.1478.

**Major  $\beta$ -2.2(TFE):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.11 (s, 1H), 4.00 (dq,  $J = 20.6, 11.3, 10.8$  Hz, 2H), 3.52 (dd,  $J = 10.9, 4.4$  Hz, 1H), 3.45 (s, 3H), 3.30 (td,  $J = 12.7, 11.9, 5.4$  Hz, 1H), 2.12 – 2.02 (m, 2H), 1.88 – 1.77 (m, 1H), 1.74 (ddt,  $J = 10.6, 8.2, 2.4$  Hz, 2H), 1.46 – 1.32 (m, 1H), 1.32 – 1.04 (m, 3H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -73.92 (t,  $J = 8.9$  Hz, 3F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  124.1 (q,  $J = 277.8$  Hz), 99.6, 84.2, 80.4, 63.8 (q,  $J = 34.3$  Hz), 57.9, 46.4, 32.0, 27.1, 25.2, 24.2; HRMS (ESI-TOF) M/Z [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>11</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>3</sub> 272.1468; Found 272.1451.

**3-Methoxy-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (2.3(TFE)):** Using general procedure B with NIS (0.085 g, 0.378 mmol) and 2,2,2 trifluoroethanol (0.056 mL, 0.756 mmol) in CH<sub>3</sub>CN ( 1.9 mL) from **2.3(SPh)** (0.05 g, 0.189 mmol, 50 $\alpha$ :50 $\beta$ ), crude <sup>1</sup>H NMR showed a 22 $\alpha$ :78 $\beta$  ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of  $\alpha/\beta$ -**2.3(TFE)** (0.028 g, 58%, 26 $\alpha$ :74 $\beta$ ) was isolated and characterized as a colourless oil. The anomeric ratio was determined by analogy with **2.3(SPh)** NOESY where the more downfield signal corresponds to the  $\beta$ -oriented anomeric hydrogen; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.28 (d,  $J = 3.9$  Hz, 0.22H), 5.02 (s, 0.78H), 4.15 (dq,  $J = 12.7, 9.0$  Hz, 0.22H), 4.04 (dq,  $J = 12.3, 9.0$  Hz, 0.83H),

3.85 (dq,  $J = 12.3, 8.6$  Hz, 0.83H), 3.79 (dd,  $J = 5.4, 3.9$  Hz, 0.22H), 3.68 (td,  $J = 11.0, 3.9$  Hz, 1H), 3.64 (d,  $J = 4.1$  Hz, 0.8H), 3.48 (s, 0.6H), 3.41 (s, 2.4H), 2.20 – 2.11 (m, 1H), 1.89 – 1.73 (m, 3H), 1.58 (dddd,  $J = 12.2, 10.9, 4.1, 3.1$  Hz, 1H), 1.51 – 1.14 (m, 4H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.27 (t,  $J = 8.6$  Hz, 3F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  125.2, 123.9 (q,  $J = 278.2$  Hz), 122.2, 105.2, 104.9, 85.9, 82.2, 81.7, 79.8, 65.3 (q,  $J = 34.3$  Hz), 64.1 (q,  $J = 34.4$  Hz), 60.1, 57.9, 49.9, 46.7, 32.3, 31.3, 25.6, 25.4, 24.1, 24.1, 23.9, 23.7, 23.6; HRMS (ESI-TOF)  $M/Z$ : calcd for  $\text{C}_{11}\text{H}_{21}\text{F}_3\text{NO}_3$   $[\text{M}+\text{NH}_4]^+$ : 272.1468; Found 272.1464.

**3-Methyl-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (2.4(TFE))**: Using general procedure B with NIS (0.054 g, 0.242 mmol) and 2,2,2 trifluoroethanol (0.035 mL, 0.484 mmol) in  $\text{CH}_3\text{CN}$  (1.2 mL) from **2.4(SPh)** (0.03 g, 0.121 mmol), crude  $^1\text{H}$  NMR showed a 91 $\alpha$ :9 $\beta$  ratio of anomers. After column chromatography (100 % hexanes then 10 % EtOAc/hexanes, TLC stained with CAM), a mixture of  $\alpha/\beta$ -**2.4(TFE)** (0.017 g, 56 %, 91 $\alpha$ :9 $\beta$ ) was isolated and characterized as a colourless oil. The crude NMR showed a complete conversion to the desired compound. The low yield can be explained by the volatile nature of the compound. Irradiation of the minor isomer  $\text{C}_4\text{-H}$  under NOESY experiment showed a positive coupling with  $\text{C}_1\text{-H}$  whereas the same experiment performed on the major anomer  $\text{C}_4\text{-H}$  did not show the same correlation, which confirms the nature of the minor  $\beta$ -anomer;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.96 (d,  $J = 5.1$  Hz, 0.08H), 4.77 (d,  $J = 4.3$  Hz, 0.92H), 4.05 (dq,  $J = 12.3, 9.0$  Hz, 1H), 3.84 (dq,  $J = 12.4, 8.7$  Hz, 1H), 3.45 (ddd,  $J = 10.9, 9.7, 4.0$  Hz, 0.92H), 3.26 (td,  $J = 10.5, 3.7$  Hz, 0.08H), 2.11 – 2.05 (m, 1H), 1.91 – 1.77 (m, 3H), 1.79 – 1.70 (m, 1H), 1.38 – 0.97 (m, 8H), 1.11 (d,  $J = 6.9$  Hz, 2.7H), 1.02 (d,  $J = 6.8$  Hz, 0.3H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.32 (t,  $J = 8.9$  Hz, 0.3F), -74.35 (t,  $J = 8.8$  Hz, 2.7F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  124.0 (q,  $J = 279.8$  Hz), 111.2, 105.0, 84.9, 82.1, 65.3 (q  $J = 34.3$  Hz), 52.9, 48.0, 45.7, 43.1, 31.9, 30.8, 27.2, 27.1, 25.5, 25.45, 24.4, 24.0, 14.9, 10.2; HRMS (ESI-TOF)  $M/Z$   $[\text{M}-\text{CF}_3\text{CH}_2\text{O}]^+$ : Calcd for  $\text{C}_9\text{H}_{15}\text{O}$  139.1122; Found 139.1115.

**3-Methyl-2-(2,2,2-trifluoroethoxy)octahydrobenzofuran (2.5(TFE))**: Using general procedure B with NIS (0.054 g, 0.240 mmol) and 2,2,2 trifluoroethanol (0.035 mL, 0.480 mmol) in  $\text{CH}_3\text{CN}$  (1.2 mL) from **2.5(SPh)** (0.03 g, 0.120 mmol), crude  $^1\text{H}$  NMR showed a 9 $\alpha$ :91 $\beta$  ratio of anomers. After column chromatography (100 % hexanes then 10 %

EtOAc/hexanes, TLC stained with CAM), a mixture of  $\alpha/\beta$ -**2.5(TFE)** (0.016 g, 55 %, 9 $\alpha$ :91 $\beta$ ) was isolated and characterized together as a colourless oil. Irradiation of the major isomer C<sub>4</sub>-H under NOESY experiment showed a positive coupling with C<sub>1</sub>-H, thus confirming the nature of the major  $\beta$ -anomer; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.21 (d, *J* = 5.9 Hz, 0.09H), 4.76 (s, 0.91H), 4.07 (dq, *J* = 12.3, 9.0 Hz, 0.09H), 4.00 (dq, *J* = 12.2, 9.1 Hz, 0.91H), 3.85 (dt, *J* = 12.2, 8.6 Hz, 0.09H), 3.79 (dq, *J* = 12.2, 8.7 Hz, 0.91H), 3.52 (td, *J* = 11.0, 3.9 Hz, 0.91H), 3.45 (td, *J* = 10.5, 4.0 Hz, 0.09H), 2.51 (pd, *J* = 7.6, 5.9 Hz, 0.09H), 2.25 (p, *J* = 7.4 Hz, 0.91H), 2.14 (dq, *J* = 10.1, 3.4 Hz, 1H), 1.84 – 1.72 (m, 4H), 1.36 (qd, *J* = 11.4, 3.9 Hz, 1H), 1.30 – 1.10 (m, 4H), 0.92 (d, *J* = 7.5 Hz, 2.7H), 0.90 (d, *J* = 7.5 Hz, 0.3H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -74.18 (t, *J* = 9.0 Hz, 2.7F), -74.35 (t, *J* = 8.6 Hz, 0.3F); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  124.1 (q, *J* = 278.4 Hz), 109.5, 105.6, 82.1, 63.9 (q, *J* = 34 Hz), 48.5, 45.3, 42.0, 38.8, 32.4, 31.1, 29.7, 25.6, 25.5, 25.0, 24.8, 24.3, 24.2, 10.9, 8.9; HRMS (ESI-TOF) *M/Z* [M-CF<sub>3</sub>CH<sub>2</sub>O]<sup>+</sup>: Calcd for C<sub>9</sub>H<sub>15</sub>O 139.1122; Found 139.1117.

## Annexe D Données expérimentales du chapitre 3

### D.1 Protocole de synthèse et caractérisation des composés

**3-Hydroxyoctahydro-2*H*-chromen-2-one (3.13):** The diastereoisomeric allylic ester **3.12** (5.8 g, 16.9 mmol) was put in solution in dry THF (40 mL) under argon at 0 °C in a Teflon round bottomed flask. Excess 70% HF-pyridine (3 mL) was slowly syringed with the needle submerged in the solution and the reaction was allowed to reach ambient temperature overnight. As TLC showed complete conversion, the reaction was quenched slowly with saturated NaHCO<sub>3(aq)</sub>, diluted in water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×). The combined organic phase was dried with MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude mixture was purified by flash chromatography (20% EtOAc/hexanes, TLC stained with CAM) to yield a diastereoisomeric mixture of the two α-hydroxylactones **3.13** (2.25 g, 78% in a d.r. ratio of 1:1) as a white powder. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.41 (dd, *J* = 10.2, 8.8 Hz, 0.5H), 4.19 (dd, *J* = 11.2, 6.8 Hz, 0.5H), 3.98 (td, *J* = 10.7, 4.4 Hz, 0.5H), 3.89 (td, *J* = 10.5, 4.1 Hz, 0.5H), 3.48 (s, 1H), 2.23 – 1.95 (m, 2H), 1.92 – 1.74 (m, 2H), 1.74 – 1.61 (m, 3H), 1.48 – 1.30 (m, 1H), 1.32 – 1.07 (m, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 176.1, 174.6, 85.7, 80.3, 68.2, 65.0, 39.0, 37.4, 35.3, 33.5, 31.9, 31.7, 30.5, 24.9, 24.9, 24.9, 24.1, 23.8; IR (NaCl) ν<sub>max</sub> 3444, 2935, 2862, 1732, 1239, 1061 cm<sup>-1</sup>; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>9</sub>H<sub>15</sub>O<sub>3</sub> 171.1016; Found 171.1023.

**3β/3α-(3,5-bis(Trifluoromethyl)benzyloxy)octahydro-2*H*-chromen-2-one (3.14/3.15):** The diastereoisomeric α-hydroxylactone **3.13** (0.6 g, 3.53 mmol), 60% NaH in mineral oil (0.171, 4.24 mmol) and tetrabutylammonium iodide (0.130 g, 0.353 mmol) were dissolved with dry DMF (7 mL) under argon and stirred for 15 min. 3,5-bis(Trifluoromethyl)benzyl bromide (1.19 g, 3.88 mmol) was then added dropwise and the reaction left to stirred overnight at ambient temperature. The reaction was quenched with saturated NH<sub>4</sub>Cl<sub>(aq)</sub> and diluted with large portion of water. The aqueous phase was extracted with Et<sub>2</sub>O (5×) and the combined organic phases dried with MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude mixture was purified and the diastereoisomers separated by flash chromatography (15% EtOAc/hexanes, TLC stained with CAM) to yield the minor least polar equatorial α-

benzyloxy lactone **3.15** (0.158 g, 11%) as a thick colorless oil and the major most polar lactone **3.14** as a white solid (0.467 g, 45%, mp: 77.6-82.8 °C).

**Major 3.14:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (s, 2H), 7.79 (s, 1H), 5.09, 4.65 (ABq,  $J_{AB}$  = 12.3 Hz, 2H), 4.17 (dd,  $J$  = 8.9, 7.7 Hz, 1H), 3.95 (td,  $J$  = 10.8, 4.4 Hz, 1H), 2.18 – 2.02 (m, 2H), 1.99 – 1.65 (m, 5H), 1.43 (tdd,  $J$  = 12.3, 11.0, 3.7 Hz, 1H), 1.36 – 1.19 (m, 2H), 1.18 – 1.06 (m, 1H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.93 (s, 6F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 140.4, 131.6 (q,  $J$  = 33.3 Hz), 127.5, 124.63, 121.59 (td,  $J$  = 5.6, 4.1, 1.8 Hz), 119.2, 81.1, 72.8, 71.0, 36.9, 33.0, 31.8, 31.5, 24.9, 23.81; IR (NaCl)  $\nu_{\text{max}}$  2940, 2865, 1754, 1279, 1177, 1133  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{18}\text{H}_{19}\text{F}_6\text{O}_3$  397.1233; Found 397.1221.

**Minor 3.15:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (s, 2H), 7.79 (s, 1H), 5.17, 4.77 (ABq,  $J_{AB}$  = 12.5 Hz, 2H), 4.04 (dd,  $J$  = 9.6, 6.8 Hz, 1H), 4.00 (ddd,  $J$  = 10.9, 4.1 Hz, 1H), 2.24 (ddd,  $J$  = 12.9, 6.9, 3.7 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.89 – 1.80 (m, 2H), 1.75 (ddd,  $J$  = 12.9, 11.9, 9.6 Hz, 2H), 1.63 (tdt,  $J$  = 11.8, 10.4, 3.6 Hz, 1H), 1.49 – 1.08 (m, 4H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.92 (s, 6F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 140.5, 131.7 (q,  $J$  = 33.3 Hz), 127.6, 127.5, 124.6, 121.9 – 121.6 (m), 119.2, 83.9, 75.2, 71.6, 38.9, 34.9, 32.0, 30.8, 24.9, 24.0; IR (NaCl)  $\nu_{\text{max}}$  2940, 2866, 1744, 1279, 1173, 1131  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{18}\text{H}_{19}\text{F}_6\text{O}_3$  397.1233; Found 397.1222.

**3 $\beta$ -(3,5-bis(Trifluoromethyl)benzyloxy)octahydro-2H-chromen-2 $\beta$ -yl acetate (3.4(OAc)):** To a -78 °C solution of lactone **3.14** (0.298 g, 0.752 mmol) in dry toluene (7.5 mL) under an argon atmosphere was added dropwise 1 M DIBAL-H in heptanes (0.902 mL, 0.902 mmol). The reaction was stirred at -78 °C for 2 h. Upon completion shown by TLC monitoring, pyridine (0.071 mL, 0.902 mmol), was slowly added at -78 °C, followed by DMAP (0.110 g, 0.902 mmol) in 2 mL of dry  $\text{CH}_2\text{Cl}_2$ , stirred for 10 min and  $\text{Ac}_2\text{O}$  (0.355 mL, 3.76 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and stirred for 12 h. The mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with EtOAc. The extracted organic phase was washed with 1 N  $\text{NaHSO}_4$  (2 $\times$ ), saturated  $\text{NaHCO}_3$  (2 $\times$ ), brine (1 $\times$ ), dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes, TLC stained with CAM) to obtain the single  $\beta$ -**3.4(OAc)** anomer (0.307 g, 93%) as a white solid (mp: 80.1-84.9 °C) The nature

of the anomer was confirmed using a 1D NOESY experiment where C<sub>4</sub>-H coupled with the anomeric C<sub>1</sub>-H signal, confirming the β orientation of the acetate. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.87 (s, 2H), 7.79 (s, 1H), 5.68 (d, *J* = 1.3 Hz, 1H), 4.82, 4.76 (ABq, *J*<sub>AB</sub> = 13.4 Hz, 2H), 3.64 (s, br, 1H), 3.22 (ddd, *J* = 11.0, 9.6, 4.1 Hz, 1H), 2.13 (s, 3H), 2.03 (dt, *J* = 14.3, 3.4 Hz, 1H), 1.99 – 1.93 (m, 1H), 1.80 (d, *J* = 7.4 Hz, 1H), 1.74 – 1.62 (m, 3H), 1.47 (qd, *J* = 12.3, 3.8 Hz, 1H), 1.41 – 1.20 (m, 3H), 0.96 (qd, *J* = 13.6, 12.9, 4.2 Hz, 1H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -62.84 (s, 6H); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 169.4, 141.4, 131.6 (q, *J* = 33.1 Hz), 127.3, 124.4, 124.4, 122.3, 121.6 – 121.4 (m), 94.3, 81.0, 73.8, 70.4, 35.1, 34.0, 31.7, 30.8, 25.5, 24.6, 21.0; IR (NaCl) ν<sub>max</sub> 2934, 2860, 1760, 1279, 1174, 1132 cm<sup>-1</sup>; HRMS (ESI-TOF) *M/Z* [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>20</sub>H<sub>26</sub>F<sub>6</sub>O<sub>4</sub>N 458.1761; Found 458.1742.

**3α-(3,5-bis(Trifluoromethyl)benzyloxy)octahydro-2*H*-chromen-2-yl acetate (3.5(OAc))**: Using the same one-pot procedure and purification described for **3.4(OAc)**, from lactone **3.15** (0.191 g, 0.482 mmol) in toluene (4.82 mL) with 1 M DIBAL-H in heptanes (0.578 mL, 0.578 mmol), pyridine (0.045 mL, 0.578 mmol), DMAP (0.070 g, 0.578 mmol, in 4.82 mL of CH<sub>2</sub>Cl<sub>2</sub>) and Ac<sub>2</sub>O (0.227 mL, 2.41 mmol), **3.5(OAc)** was obtained as a slight yellow oil containing the two anomers (0.170 g, 80%, ~27α:73β). Here the major anomer shows a coupling constant of 8 Hz, characteristic of a *trans* diaxial orientation. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.79 (s, 1H), 7.76 (s, 2H), 6.40 (d, *J* = 2.7 Hz, 0.3H), 5.62 (d, *J* = 8.0 Hz, 0.7H), 4.77, 4.70 (ABq, *J*<sub>AB</sub> = 13.2 Hz, 1.4H), 4.74, 4.61 (ABq, *J*<sub>AB</sub> = 11.9 Hz, 0.6H), 3.68 (ddd, *J* = 11.8, 4.9, 3.3 Hz, 0.3H), 3.48 – 3.38 (m, 1H), 3.16 (td, *J* = 10.4, 4.2 Hz, 0.7H), 2.15 (s, 1H), 2.13 (s, 2H), 2.00 – 1.95 (m, 1H), 1.91 – 1.77 (m, 2H), 1.72 – 1.63 (m, 2H), 1.41 – 0.99 (m, 6H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -62.89 (s, 4.3F), -62.93 (s, 1.7F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 170.0, 169.4, 141.2, 140.8, 131.7 (q, *J* = 33.2 Hz), 131.7 (q, *J* = 33.2 Hz), 127.4 – 127.2 (m), 127.1 – 126.9 (m), 124.6, 121.9, 121.6 – 121.3 (m), 95.8, 89.9, 80.0, 76.5, 75.5, 74.7, 70.0, 69.5, 40.5, 40.3, 35.6, 31.5, 31.4, 31.4, 31.3, 30.8, 25.3, 25.2, 24.8, 24.5, 21.1, 21.1; IR (NaCl) ν<sub>max</sub> 2935, 2864, 1757, 1368, 1279, 1133 cm<sup>-1</sup>; HRMS (ESI-TOF) *M/Z* [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>20</sub>H<sub>26</sub>F<sub>6</sub>O<sub>4</sub>N 458.1761; Found 458.1764.

**3β-(3,5-bis(Trifluoromethyl)benzyloxy)-2-(phenylthio)octahydro-2*H*-chromene (3.4(SPh))**: To a solution of acetate β-**3.4(OAc)** (0.120 g, 0.270 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL) under an argon atmosphere was added PhSH (0.033 mL, 0.324 mmol). The mixture was

cooled to  $-78\text{ }^{\circ}\text{C}$  and  $\text{BF}_3\text{-Et}_2\text{O}$  (0.034 mL, 0.324 mmol) was slowly added. After 1 h of stirring at  $-78\text{ }^{\circ}\text{C}$ , the reaction was quenched with  $\text{Et}_3\text{N}$ , brought to ambient temperature and diluted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was isolated, and the aqueous portion was extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ ). The organic phases were combined, dried over  $\text{MgSO}_4$  and condensed *in vacuo*. The residue was purified by silica gel column chromatography (100% hexanes until all left over PhSH eluted then 5% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to yield partially separated anomers at an approximate 1:1 ratio in mass. The more polar  $\beta$ -anomer was confirmed by NOE correlation between  $\text{C}_4\text{-H}$  and  $\text{C}_1\text{-H}$ .  $\alpha$ -**3.4(SPh)** (0.144 g, 42%, 10% in mass of  $\beta$ -**3.4(SPh)**) was isolated as a colorless thick oil and  $\beta$ -**3.4(SPh)** (0.154 g, 45%, 5% in mass of  $\alpha$ -**3.4(SPh)**) as a white solid. The minor anomer will not be reported in each of the following characterizations.

**Major  $\alpha$ -anomer characteristic peaks:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (s, 2H), 7.81 (s, 1H), 7.53 – 7.49 (m, 2H), 7.35 – 7.22 (m, 3H), 5.64 (d,  $J = 1.9$  Hz, 1H), 4.73, 4.64 (ABq,  $J_{AB}=12.8$  Hz, 2H), 3.88 (td,  $J = 10.5, 3.7$  Hz, 1H), 3.83 (s, 1H), 1.94 – 1.77 (m, 3H), 1.74 – 1.61 (m, 3H), 1.50 – 1.26 (m, 4H), 1.16 – 1.04 (m, 1H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.99 (s, 6F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  141.1, 135.1, 131.7 (q,  $J = 33.3$  Hz), 131.1, 129.0, 127.3 – 127.2 (m), 127.1, 124.4, 122.2, 121.5 (p,  $J = 3.8$  Hz), 86.3, 76.5, 74.2, 70.3, 36.0, 31.8, 31.9, 31.4, 25.6, 25.1; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{24}\text{H}_{28}\text{F}_6\text{NO}_2\text{S}$  509.1771; Found 509.1772.

**$\beta$ -Anomer:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (s, 2H), 7.82 (s, 1H), 7.52 – 7.48 (m, 2H), 7.31 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 4.89 (s, 1H), 4.84, 4.69 (ABq,  $J_{AB}= 12.8$  Hz, 2H), 3.83 (s, 1H), 3.11 (td,  $J = 10.3, 4.0$  Hz, 2H), 2.09 (dt,  $J = 14.0, 3.0$  Hz, 1H), 2.02 – 1.96 (m, 1H), 1.89 – 1.80 (m, 1H), 1.79 – 1.50 (m, 4H), 1.41 – 1.25 (m, 3H), 1.01 – 0.91 (m, 1H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.81 (s, 5.4F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  140.9, 136.1, 131.6 (q,  $J = 33.3$  Hz), 130.3, 128.8, 127.9 – 127.8 (m), 124.5, 122.3, 121.9 – 121.5 (m), 88.8, 83.0, 76.8, 70.3, 35.1, 34.5, 32.0, 31.2, 25.5, 24.8; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{24}\text{H}_{28}\text{F}_6\text{NO}_2\text{S}$  509.1771; Found 509.1772.

### **3 $\alpha$ -(3,5-bis(Trifluoromethyl)benzyloxy)-2-(phenylthio)octahydro-2H-chromene**

**(3.5(SPh)):** Following the same protocol and purification described for **3.4(SPh)**, from **3.5(OAc)** (0.130 g, 0.295 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) with PhSH (0.036 mL, 0.354 mmol) and

BF<sub>3</sub>-Et<sub>2</sub>O (0.044 mL, 0.354 mmol) was obtained the donor **3.5(SPh)** as a mixture of anomer (0.06 g, 41%, 40 $\alpha$ :60 $\beta$ , yellowish oil). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.86 (s, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.57 – 7.52 (m, 2H), 7.33 – 7.21 (m, 3H), 5.79 (d,  $J$  = 4.9 Hz, 0.4H), 4.80, 4.61 (ABq,  $J_{AB}$  = 12.3 Hz, 0.8H), 4.75 (s, 1H), 4.71 (d,  $J$  = 9.5, 0.6H), 3.94 (dt,  $J$  = 11.7, 4.7 Hz, 0.4H), 3.85 (td,  $J$  = 10.3, 3.9 Hz, 0.4H), 3.42 (td,  $J$  = 9.7, 5.3 Hz, 0.6H), 3.04 (td,  $J$  = 10.1, 4.1 Hz, 0.6H), 2.27 – 2.19 (m, 0.6H), 2.07 – 2.00 (m, 0.6H), 1.98 – 1.91 (m, 0.4H), 1.90 – 1.78 (m, 1.6H), 1.75 – 1.63 (m, 2H), 1.46 – 1.16 (m, 5.4H), 1.12 – 0.99 (m, 0.6H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -62.85 (s, 3.6F), -62.86 (s, 2.4F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  141.1, 140.8, 135.1, 134.4, 131.6 (q,  $J$  = 33.1 Hz), 131.6 (q,  $J$  = 33.1 Hz), 131.4, 131.4, 128.9, 128.8, 127.6 – 127.3 (m), 127.1, 126.9, 124.7, 124.7, 122.0 – 121.9 (m), 121.5 (dt,  $J$  = 8.0, 4.0 Hz), 89.3, 88.2, 82.4, 76.7, 76.4, 73.3, 70.5, 68.8, 40.9, 40.5, 37.7, 33.3, 31.9, 31.4, 31.2, 31.2, 25.4, 25.2, 25.0, 24.7; HRMS (ESI-TOF)  $M/Z$  [M+H]<sup>+</sup>: Calcd for C<sub>24</sub>H<sub>25</sub>F<sub>6</sub>O<sub>2</sub>S 491.1474; Found 491.1496.

**3 $\beta$ /3 $\alpha$ -((*tert*-Butyldimethylsilyloxy)octahydro-2H-chromen-2-one (3.16/3.17):** To a solution of  $\alpha$ -hydroxylactone **3.13** (0.240 g, 1.40 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) under argon was added imidazole (0.381 g, 5.6 mmol) followed by *tert*-butyldimethylchlorosilane (0.232 g, 1.54 mmol). The reaction was stirred overnight and quenched with saturated NH<sub>4</sub>Cl<sub>(aq)</sub> and diluted in CH<sub>2</sub>Cl<sub>2</sub>. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 $\times$ ), dried with MgSO<sub>4</sub>, filtered and condensed under reduced pressure. Purification though silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM) yielded the less polar isomer **3.17** (0.176 g, 44%, mp: 78.8-81.1 °C) and the more polar isomer **3.16** (0.206 g, 52%, mp: 78.5-82.3 °C) both as white solids.

**Major isomer 3.16 (Axial OTBS):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.38 (dd,  $J$  = 8.9, 7.7 Hz, 1H), 3.90 (td,  $J$  = 10.7, 4.4 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.98 – 1.78 (m, 4H), 1.74 – 1.62 (m, 2H), 1.45 – 1.33 (m, 1H), 1.31 – 1.18 (m, 2H), 1.18 – 1.04 (m, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  172.9, 80.4, 66.8, 36.9, 35.9, 31.9, 31.7, 25.7, 25.0, 23.9, 18.3, -4.7, -5.6; IR (NaCl)  $\nu_{max}$  2934, 2857, 1754, 1254, 1143, 838 cm<sup>-1</sup>; HRMS (ESI-TOF)  $M/Z$  [M+H]<sup>+</sup>: Calcd for C<sub>15</sub>H<sub>29</sub>O<sub>3</sub>Si 285.1880; Found 285.1882.

**Minor isomer 3.17 (Eq. OTBS):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.18 (dd,  $J$  = 9.5, 6.6 Hz, 1H), 3.92 (ddd,  $J$  = 11.2, 9.8, 4.2 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.84 – 1.74 (m, 2H), 1.72 –



1.53 (m, 3H), 1.43 – 1.02 (m, 4H), 0.87 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 83.7, 69.5, 39.0, 37.6, 32.0, 30.9, 25.7, 25.7, 25.0, 24.0, 18.2, -4.7, -5.6; IR (NaCl)  $\nu_{\text{max}}$  2937, 2856, 1749, 1252, 1152, 836  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{15}\text{H}_{29}\text{O}_3\text{Si}$  286.1906; Found 286.1924.

**3 $\beta$ -((*tert*-Butyldimethylsilyl)oxy)octahydro-2*H*-chromen-2-yl acetate (3.18):** Using the same one-pot procedure and purification described for **3.4(OAc)**, from lactone **3.16** (0.205 g, 0.720 mmol) in toluene (7.2 mL) with 1 M DIBAL-H in heptanes (0.864 mL, 0.864 mmol), pyridine (0.069 mL, 0.864 mmol), DMAP (0.105 g, 0.864 mmol, in 2.5 mL of  $\text{CH}_2\text{Cl}_2$ ) and  $\text{Ac}_2\text{O}$  (0.289 mL, 3.6 mmol), **3.18** was obtained as a colorless oil containing the two anomers (0.230 g, 97%,  $\sim 10\alpha:90\beta$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.81 (s, 0.1H), 5.57 (s, 0.9H), 3.88 (t,  $J = 3.5$  Hz, 0.1H), 3.71 (q,  $J = 2.5$  Hz, 0.9H), 3.39 (td,  $J = 10.5, 4.1$  Hz, 0.1H), 3.14 (td,  $J = 10.6, 4.1$  Hz, 0.9H), 2.11 (s, 2.6H), 2.09 (s, 0.4H), 1.96 – 1.89 (m, 1H), 1.84 – 1.53 (m, 6H), 1.49 – 1.19 (m, 4H), 0.92 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 169.5, 94.8, 81.0, 77.2, 76.3, 75.6, 66.8, 66.5, 37.9, 34.5, 34.5, 33.7, 31.9, 31.8, 31.5, 30.9, 25.84, 25.8, 25.7, 25.6, 25.0, 24.7, 21.3, 18.3, 18.1, -4.6, -4.8, -4.9, -5.0; IR (NaCl)  $\nu_{\text{max}}$  2930, 2856, 1759, 1059, 1043, 832  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{17}\text{H}_{36}\text{NO}_4\text{Si}$  346.2408; Found 346.2411.

**3 $\alpha$ -((*tert*-Butyldimethylsilyl)oxy)octahydro-2*H*-chromen-2-yl acetate (3.19):** Using the same one-pot procedure and purification described for **3.4(OAc)**, from lactone **3.17** (0.173 g, 0.608 mmol) in toluene (6.08 mL) with 1 M DIBAL-H in heptanes (0.730 mL, 0.730 mmol), pyridine (0.045 mL, 0.730 mmol), DMAP (0.089 g, 0.730 mmol, in 3 mL of  $\text{CH}_2\text{Cl}_2$ ) and  $\text{Ac}_2\text{O}$  (0.244 mL, 3.04 mmol), **3.19** was obtained as a colorless oil containing the two anomers (0.183 g, 92%,  $\sim 25\alpha:75\beta$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.07 (d,  $J = 3.5$  Hz, 0.25H), 5.44 (d,  $J = 7.8$  Hz, 0.75H), 3.88 – 3.80 (m, 0.25H), 3.58 (ddd,  $J = 10.0, 7.5, 4.8$  Hz, 0.75H), 3.33 (td,  $J = 10.5, 4.0$  Hz, 0.25H), 3.12 (td,  $J = 10.2, 4.0$  Hz, 0.75H), 2.10 (s, 3H), 1.98 – 1.89 (m, 1.6H), 1.82 – 1.74 (m, 1.4H), 1.68 – 1.59 (m, 1.75H), 1.54 (q,  $J = 12.0$  Hz, 0.25H), 1.36 – 1.11 (m, 5H), 1.10 – 0.94 (m, 1H), 0.85 (s, 6H), 0.84 (s, 3H), 0.06 (s, 2.3H), 0.05 (d,  $J = 0.7$  Hz, 0.7H), 0.04 (d,  $J = 0.6$  Hz, 2.3H), 0.03 (d,  $J = 0.7$  Hz, 0.7H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 169.6, 96.7, 92.2, 80.0, 74.4, 69.7, 68.5, 40.5, 40.4, 39.3, 34.4, 31.6, 31.5, 31.3, 30.9, 25.7, 25.6, 25.3, 25.2, 24.9, 24.5, 21.2, 21.1, 18.0, 17.95, -4.6, -

4.8, -4.79, -4.9; IR (NaCl)  $\nu_{\max}$  2930, 2857, 1758, 1226, 1116, 837  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{17}\text{H}_{36}\text{NO}_4\text{Si}$  346.2408; Found 346.2408.

**3 $\beta$ -((*tert*-Butyldimethylsilyloxy)-2-(phenylthio)octahydro-2*H*-chromene (3.10(SPh)):**

Following the same protocol and purification described for **3.4(SPh)**, from **3.18** (0.230 g, 0.700 mmol) in  $\text{CH}_2\text{Cl}_2$  (7 mL) with PhSH (0.085 mL, 0.840 mmol) and  $\text{BF}_3\text{-Et}_2\text{O}$  (0.103 mL, 0.840 mmol) was obtained the donor **3.10(SPh)** as a mixture of anomer (0.224 g, 81%, 53 $\alpha$ :47 $\beta$ , yellowish oil).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (dt,  $J = 8.0, 1.3$  Hz, 0.5H), 7.32 – 7.16 (m, 0.5H), 5.32 (s, 0.5H), 4.82 (d,  $J = 1.4$  Hz, 0.5H), 4.12 – 4.06 (m, 0.5H), 4.07 – 4.01 (m, 0.5H), 3.77 (td,  $J = 10.1, 3.0$  Hz, 0.5H), 3.06 (td,  $J = 10.3, 4.1$  Hz, 0.5H), 2.02 – 1.94 (m, 0.5H), 1.88 – 1.70 (m, 2.5H), 1.71 – 1.45 (m, 5H), 1.45 – 1.20 (m, 2.5H), 1.06 (td,  $J = 12.4, 3.6$  Hz, 0.5H), 0.96 (s, 4.5H), 0.89 (s, 4.5H), 0.19 (s, 1.5H), 0.11 (s, 1.5H), 0.05 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  137.0, 135.4, 131.1, 129.7, 128.9, 128.7, 126.8, 126.3, 90.0, 89.9, 82.9, 74.1, 69.9, 69.1, 39.6, 35.4, 34.9, 34.6, 32.2, 31.8, 31.5, 31.3, 26.0, 25.8, 25.7, 25.6, 25.1, 24.9, 18.3, 18.1, -4.5, -4.7, -4.8, -4.9; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{21}\text{H}_{38}\text{NO}_2\text{SSi}$  396.2287; Found 396.2289.

**3 $\alpha$ -((*tert*-Butyldimethylsilyloxy)-2-(phenylthio)octahydro-2*H*-chromene (3.11(SPh)**

**and 2-(phenylthio)octahydro-2*H*-chromen-3 $\alpha$ -ol (3.20):** Following the same protocol and purification described for **3.4(SPh)**, from **3.19** (0.183 g, 0.557 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.7 mL) with PhSH (0.068 mL, 0.668 mmol) and  $\text{BF}_3\text{-Et}_2\text{O}$  (0.082 mL, 0.668 mmol) was obtained the donor **3.11(SPh)** as a mixture of anomer (0.030 g, 13%, 96 $\alpha$ :4 $\beta$ ) and intermediate **3.20** (0.112 g, 72%, 70 $\alpha$ :30 $\beta$ , colorless oil) as a white solid.

**3.11(SPh):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 – 7.47 (m, 2H), 7.31 – 7.25 (m, 2H), 7.24 – 7.18 (m, 1H), 5.50 (d,  $J = 5.1$  Hz, 0.7H), 4.58 (d,  $J = 9.3$  Hz, 0.3H), 4.09 (dt,  $J = 11.2, 4.9$  Hz, 0.7H), 3.78 (td,  $J = 10.1, 3.3$  Hz, 0.7H), 3.62 (td,  $J = 9.9, 9.4, 4.9$  Hz, 0.3H), 2.98 (td,  $J = 10.0, 4.0$  Hz, 0.3H), 2.08 – 1.94 (m, 0.7H), 1.89 – 1.77 (m, 2H), 1.77 – 1.48 (m, 3.3H), 1.44 – 1.11 (m, 5H), 0.91 (d,  $J = 1.5$  Hz, 9H), 0.14 (s, 1H), 0.09 (s, 1H), 0.07 (s, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  135.9, 131.6, 130.7, 128.7, 128.6, 126.5, 126.4, 91.5, 91.2, 82.2, 72.7, 69.9, 69.89, 41.5, 40.9, 40.6, 36.4, 31.9, 31.5, 31.3, 31.25, 25.9, 25.8, 25.4, 25.3, 25.0, 24.8, 18.1, 18.1, -4.2, -4.5, -4.7; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{21}\text{H}_{38}\text{NO}_2\text{SSi}$  396.2287; Found 396.2400.

**2-(Phenylthio)octahydro-2H-chromen-3 $\alpha$ -ol (3.20):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 – 7.50 (m, 2H), 7.35 – 7.24 (m, 3H), 5.55 (dd,  $J = 4.9, 1.3$  Hz, 0.96H), 4.50 (d,  $J = 9.5$  Hz, 0.04H), 3.99 (dt,  $J = 11.4, 4.7$  Hz, 1H), 3.68 (td,  $J = 10.2, 4.1$  Hz, 1H), 3.49 (ddd,  $J = 10.5, 9.4, 4.8$  Hz, 0.04H), 3.07 – 3.00 (m, 0.04H), 2.19 – 1.95 (m, 1H), 1.95 – 1.80 (m, 3H), 1.66 (tdd,  $J = 8.6, 6.9, 3.6$  Hz, 2H), 1.45 – 1.05 (m, 6H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  135.0, 132.0, 131.7, 129.0, 128.9, 127.6, 127.2, 94.4, 91.8, 82.8, 74.0, 69.0, 68.4, 40.7, 40.6, 38.4, 36.5, 31.9, 31.5, 31.3, 31.2, 25.3, 25.3, 25.0, 24.8; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2\text{S}$  265.1257; Found 265.1255.

**2-(Phenylthio)octahydro-2H-chromen-3 $\beta$ -ol (3.21):** To a solution of **3.10(SPh)** (0.100 g, 0.255 mmol) in dry THF (2 mL) at  $-78$  °C under argon was added TBAF (1 M in THF, 0.382 mL, 0.382 mmol). The reaction was stirred for 1 h and left to reach room temperature, upon which TLC showed completion. The reaction was quenched with saturated  $\text{NaHCO}_3(\text{aq})$  and diluted with water and  $\text{CH}_2\text{Cl}_2$ . The aqueous mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ ), dried with  $\text{MgSO}_4$ , filtered, and condensed under reduced pressure. The crude mixture was purified by silica gel flash chromatography (15% EtOAc/hexanes, TLC stained with CAM) to yield **3.21** (0.056 g, 79%, 56 $\alpha$ :44 $\beta$ ) as an oily colorless mixture of the two anomers.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 – 7.45 (m, 2H), 7.31 – 7.20 (m, 3H), 5.41 (t,  $J = 1.3$  Hz, 0.6H), 4.89 (d,  $J = 1.2$  Hz, 0.4H), 4.08 – 4.02 (s, 0.6H), 4.00 (s, 0.4H), 3.87 (td,  $J = 10.0, 3.7$  Hz, 0.6H), 3.09 (ddd,  $J = 11.1, 9.6, 4.2$  Hz, 0.4H), 2.56 (s, br, 1H), 1.97 (dt,  $J = 13.9, 3.3$  Hz, 1H), 1.89 – 1.72 (m, 2H), 1.72 – 1.56 (m, 3H), 1.53 – 1.18 (m, 4H), 1.17 – 0.86 (m, 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  135.1, 134.9, 131.1, 130.7, 128.9, 128.9, 127.03, 127.0, 89.5, 89.4, 83.4, 74.1, 68.9, 68.7, 38.2, 35.8, 35.1, 33.6, 32.1, 31.7, 31.4, 31.1, 25.7, 25.6, 25.0, 24.8; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_2\text{S}$  265.1257; Found 265.1251.

**3 $\beta$ -((4-Methoxybenzyl)oxy)-2-(phenylthio)octahydro-2H-chromene (3.6(SPh)):** To a solution of **3.20** (0.056 g, 0.201 mmol) in dry DMF (1 mL) under argon was added  $\text{Bu}_4\text{NI}$  (0.007 g, 0.02 mmol) followed by 60%  $\text{NaH}$  in mineral oil (0.010 g, 0.241 mmol). The reaction was stirred for 5 min after which  $\text{PMBCl}$  (0.033 mL, 0.241 mmol) was added. The reaction was stirred overnight at room temperature. Upon completion, the reaction was diluted with water and  $\text{Et}_2\text{O}$ . The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 $\times$ ). The combined organic phases were dried with  $\text{MgSO}_4$ , filtered and condensed under reduced pressure. The

crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM) to yield **3.6(SPh)** (0.075 g, 98%, 56 $\alpha$ :44 $\beta$ ) as a colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 – 7.46 (m, 2H), 7.40 (d,  $J$  = 8.6 Hz, 1H), 7.34 – 7.19 (m, 4H), 6.91 (d,  $J$  = 8.7 Hz, 1H), 6.88 (d,  $J$  = 8.7 Hz, 1H), 5.61 (s, 0.56H), 4.86 (d,  $J$  = 1.5 Hz, 0.44H), 4.70, 4.55 (ABq,  $J_{AB}$  = 11.8 Hz, 1H), 4.58, 4.49 (ABq,  $J_{AB}$  = 11.8 Hz, 1H), 3.85 – 3.82 (m, 0.5H) 3.83 (s, 1.3H), 3.81 (s, 1.7H), 3.77 – 3.74 (m, 1H), 3.07 (ddd,  $J$  = 11.1, 9.7, 4.1 Hz, 0.5H), 2.04 (dt,  $J$  = 14.1, 3.2 Hz, 0.5H), 2.00 – 1.93 (m, 0.5H), 1.90 – 1.75 (m, 3H), 1.73 – 1.64 (m, 1H), 1.63 – 1.51 (m, 2H), 1.50 – 1.34 (m, 3H), 1.06 (qd,  $J$  = 12.7, 3.6 Hz, 0.5H), 0.99 – 0.88 (m, 0.5H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2, 159.2, 136.7, 135.6, 130.9, 130.3, 129.6, 129.3, 128.9, 128.7, 126.8, 126.6, 113.8, 113.7, 89.1, 86.6, 82.9, 74.8, 74.8, 74.2, 71.1, 70.4, 55.3, 55.28, 35.9, 35.0, 34.5, 32.06, 31.9, 31.7, 31.5, 31.3, 25.7, 25.6, 25.1, 24.9; HRMS (ESI-TOF)  $M/Z$   $[M+H]^+$ : Calcd for  $\text{C}_{23}\text{H}_{29}\text{O}_3\text{S}$  385.1832; Found 385.1853.

**3 $\alpha$ -((4-Methoxybenzyl)oxy)-2-(phenylthio)octahydro-2H-chromene (3.7(SPh))**: To a solution of **3.21** (0.050 g, 0.179 mmol) in dry DMF (1 mL) under argon was added  $\text{Bu}_4\text{NI}$  (0.006 g, 0.018 mmol) followed by 60% NaH in mineral oil (0.009 g, 0.215 mmol). The reaction was stirred for 5 min after which PMBCl (0.029 mL, 0.215 mmol) was added. The reaction was stirred overnight at room temperature. Upon completion, the reaction was diluted with water and  $\text{Et}_2\text{O}$ . The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 $\times$ ). The combined organic phases were dried with  $\text{MgSO}_4$ , filtered and condensed under reduced pressure. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM) to yield **3.7(SPh)** (0.064 g, 93%, 95 $\alpha$ :5 $\beta$ ) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (d,  $J$  = 8.3 Hz, 2H), 7.35 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 6.87 (d,  $J$  = 8.0 Hz, 2H), 5.71 (d,  $J$  = 4.9 Hz, 0.95H), 4.70 (d,  $J$  = 9.6 Hz, 0.05H), 4.64, 4.49 (ABq,  $J_{AB}$  = 11.4 Hz, 1.90H), 4.57, 4.61 (ABq,  $J_{AB}$  = 11.2 Hz, 0.10H), 3.89 – 3.81 (m, 1.8H), 3.80 (s, 3H), 3.38 (td,  $J$  = 9.5, 4.9 Hz, 0.05H), 3.00 (td,  $J$  = 9.7, 4.0 Hz, 0.05H), 1.89 – 1.77 (m, 3H), 1.73 – 1.61 (m, 2H), 1.53 (q,  $J$  = 12.1 Hz, 1H), 1.43 – 1.09 (m, 5H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3, 135.6, 131.4, 131.3, 130.1, 129.6, 129.5, 129.4, 128.8, 128.7, 126.6, 113.8, 113.8, 89.2, 88.5, 82.3, 75.3, 74.9, 73.2, 71.6, 71.5, 70.0, 55.3, 41.0, 40.5, 37.8, 33.4, 31.9, 31.5, 31.3, 25.4, 25.3, 25.0, 24.8; HRMS (ESI-TOF)  $M/Z$   $[M+H]^+$ : Calcd for  $\text{C}_{23}\text{H}_{29}\text{O}_3\text{S}$  385.1832; Found 385.1840.

**2-(((Allylcyclohexyl)oxy)methyl)benzene (3.23):** A solution of the alcohol **3.22** (4.0 g, 28.54 mmol) in dry THF (60 mL) under argon was brought to 0 °C. NaH (60% in mineral oil, 1.37 g, 34.25 mmol) was added slowly and stirred 15 min upon which benzyl bromide (3.45 mL, 29.11 mmol) was added slowly. The reaction was brought to reflux using an oil bath and stirred overnight. The mixture was quenched with NH<sub>4</sub>Cl, diluted with water and Et<sub>2</sub>O. The phases were separated, and the aqueous layer extracted with Et<sub>2</sub>O (3×). Combined organic phases were dried over MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude residue was purified by silica gel chromatography (100% hexanes then 5% EtOAc/hexanes, TLC stained with KMnO<sub>4</sub>) to yield **3.23** (5.5 g, 85%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.31 (m, 4H), 7.30 – 7.25 (m, 1H), 5.78 (dddd, *J* = 16.7, 10.2, 8.3, 6.2 Hz, 1H), 5.04 – 4.95 (m, 2H), 4.64, 4.43 (ABq, *J*<sub>AB</sub> = 11.5 Hz, 2H), 3.03 (td, *J* = 9.7, 4.2 Hz, 1H), 2.58 (dddt, *J* = 11.4, 5.3, 3.4, 1.6 Hz, 1H), 2.17 (ddd, *J* = 7.6, 5.4, 3.6 Hz, 1H), 1.93 (dt, *J* = 13.7, 8.5 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.67 – 1.59 (m, 1H), 1.55 – 1.43 (m, 1H), 1.31 – 1.11 (m, 3H), 1.02 – 0.89 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 139.1, 137.3, 128.3, 127.8, 127.4, 115.8, 81.3, 70.6, 42.9, 36.8, 31.1, 30.2, 25.4, 24.8; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>16</sub>H<sub>23</sub>O 231.1743; Found 231.1724.

**2-(Benzyloxy)cyclohexylpropan-1-ol (3.24):** To a solution of OBn protected olefin **3.23** (1.35 g, 5.8 mmol) in dry THF (14 mL) at 0 °C under an argon atmosphere was added 2M BH<sub>3</sub>-Me<sub>2</sub>S solution in THF (14.67 mmol, 7.35 mL) over 10 min. The reaction was then brought slowly to ambient temperature and stirred for 18 h. The mixture was treated with 3M NaOH at 0 °C until the pH was basic and excess 30% H<sub>2</sub>O<sub>2</sub> was added. The reaction was stirred for 3 h until completion and was diluted with water and CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated, and the aqueous layer washed with CH<sub>2</sub>Cl<sub>2</sub> (3×). The organic layers were combined, dried over MgSO<sub>4</sub> and condensed *in vacuo*. The crude was purified using silica gel chromatography (35% EtOAc in hexanes, TLC stained with CAM) to yield the terminal alcohol **3.24** (1.25 g, 69%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.31 (m, 4H), 7.30 – 7.24 (m, 1H), 4.64, 4.42 (ABq *J*<sub>AB</sub> = 88, 11.6 Hz, 2H), 3.60 (tt, *J* = 6.7, 2.0 Hz, 2H), 3.01 (td, *J* = 9.5, 4.4 Hz, 1H), 2.15 (dtd, *J* = 7.7, 4.3, 1.7 Hz, 1H), 1.89 – 1.55 (m, 6H), 1.54 (m, 2H), 1.29 – 1.09 (m, 4H), 0.95 (ddd, *J* = 11.8, 3.7 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 139.0, 128.3, 127.9, 127.5, 81.8, 70.6, 63.2, 42.7, 31.1, 30.6, 29.8, 28.3, 25.5, 24.7; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>16</sub>H<sub>25</sub>O<sub>2</sub> 249.1849; Found 249.1842.

**3-(2-(Benzyloxy)cyclohexyl)propanal (3.25):** To a solution of the alcohol **3.24** (1.25 g, 5.03 mmol in dry CH<sub>2</sub>Cl<sub>2</sub> (15mL) under argon at 0 °C was added Dess-Martin periodinane (2.35 g, 5.53 mmol) The mixture was stirred for 2 h at room temperature. Upon completion, the reaction was quenched with a saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. Once separated, the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the combine organic phases washed with saturated NaHCO<sub>3</sub>. Organic phase was dried over MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude mixture was eluted through a 5 cm silica pad using 10% EtOAc/hexanes to yield **3.25** (1.14 g, 92%) as a clear oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.72 (t, *J* = 1.9 Hz, 1H), 7.34 (d, *J* = 4.4 Hz, 3H), 7.31 – 7.25 (m, 1H), 4.65, 4.40 (ABq, *J*<sub>AB</sub> = 60, 11.5 Hz, 2H), 3.01 (td, *J* = 9.5, 4.2 Hz, 1H), 2.41 (ddd, *J* = 9.2, 7.1, 1.9 Hz, 2H), 2.22 – 2.04 (m, 2H), 1.81 – 1.73 (m, 2H), 1.69 – 1.60 (m, 1H), 1.52 – 1.36 (m, 2H), 1.28 – 1.14 (m, 3H), 1.02 – 0.87 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 203.2, 138.9, 128.4, 127.8, 127.5, 81.6, 70.5, 42.7, 41.6, 31.0, 30.5, 25.4, 24.9, 24.6; IR (NaCl) ν<sub>max</sub> 2928, 2857, 1726, 1451, 1094, 698 cm<sup>-1</sup>; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>16</sub>H<sub>23</sub>O<sub>2</sub> 247.1693; Found 247.1706.

**2-((2-(Benzyloxy)cyclohexyl)methyl)acrylaldehyde (3.26):** To a solution of aldehyde **3.25** (1.136 g, 4.61 mmol) in pyrrolidine (0.038 mL, 0.461 mmol) and formaldehyde (0.140 g, 0.465 mmol) was added acetic acid (0.028 g, 0.026 mL). The reaction was stirred at 45 °C for 5 h using an oil bath and quenched with saturated NaHCO<sub>3</sub> and diluted in Et<sub>2</sub>O. The aqueous phase was extracted twice with Et<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude mixture was eluted through a 5 cm silica pad with a 10% EtOAc/Hexanes to yield 0.952 g (80%) of the desired compound **3.26** as a colorless oil. IR (NaCl): ν<sub>max</sub> 2928, 2855, 1692, 1449, 1094 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.52 (s, 1H), 7.39 – 7.24 (m, 5H), 6.23 (s, 1H), 6.01 (s, 1H), 4.66, 4.42 (ABq, *J*<sub>AB</sub> = 11.6 Hz, 2H), 3.04 (ddd, *J* = 9.6, 9.5, 4.1 Hz, 1H), 2.82 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.19 – 2.13 (m, 1H), 2.05 (dd, *J* = 14.0, 9.3 Hz, 1H), 1.76 (dd, *J* = 9.2, 3.6 Hz, 1H), 1.70 – 1.55 (m, 3H), 1.34 – 1.08 (m, 3H), 0.94 – 0.81 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 194.9, 149.2, 139.0, 135.0, 128.3, 127.7, 127.4, 81.7, 70.2, 42.3, 30.9, 30.4, 30.2, 25.2, 24.6; HRMS (ESI-TOF) M/Z [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>N 276.1958; Found 276.1940.

**2-(3-Hydroxy-2-methylpropyl)cyclohexan-1-ol (3.27/3.27'):** To a solution of the acrylaldehyde **3.26** (0.952 g, 3.68 mmol) in dry THF (10 mL) under argon atmosphere at -78

°C was added LiAlH<sub>4</sub> (3.87 mL, 1 M in THF). Reaction was stirred 0.5 h and quenched slowly using saturated Rochelle's salt and stirred at room temperature for 1 h. Reaction mixture was dilute with water and EtOAc and the organic phase separated. The aqueous layer was extracted with EtOAc twice and the combined organic phases dried over MgSO<sub>4</sub>, filtered and condense under reduced pressure. To the crude solution of allylic alcohol in EtOAc (10 mL) was added PtO<sub>2</sub> (0.082 g, 0.368 mmol). The solution was stirred under H<sub>2</sub> atmosphere by the mean of a rubber balloon for 1 h. Upon completion, the slurry mixture was filter on celite and washed with EtOAc. The resulting mixture was condensed under reduced pressure and diluted in dry THF (10 mL). 10% Pd/C (0.39 g, 0.368 mmol) was added and the reaction stirred overnight under H<sub>2</sub> atmosphere by the mean of a rubber balloon. The mixture was filtered on celite, washed with EtOAc and condensed under reduced pressure. The diastereoisomeric mixture was purified by silica gel chromatography (40% EtOAc/hexanes, TLC stained with CAM) to yield 0.271 g of **3.27** and 0.120 g of **3.27'** as thick oils (65% over 3 steps).

**Major diastereoisomer 3.27:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.50 – 3.35 (m, 2H), 3.19 (ddd, *J* = 10.0, 9.8, 4.2 Hz, 1H), 2.54 (br, s, 2H), 1.98 – 1.89 (m, 1H), 1.84 – 1.67 (m, 3H), 1.66 – 1.52 (m, 2H), 1.36 – 1.08 (m, 5H), 0.98 – 0.84 (m, 1H), 0.85 (d, *J* = 6.7 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 75.0, 68.5, 41.7, 35.8, 35.7, 32.5, 31.0, 25.6, 24.9, 16.4; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>10</sub>H<sub>21</sub>O<sub>2</sub> 173.1536; Found 173.1536.

**Minor diastereoisomer 3.27':** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.56 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.42 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.17 (td, *J* = 9.9, 4.3 Hz, 1H), 2.86 (br, s, 2H), 1.97 – 1.88 (m, 1H), 1.88 – 1.76 (m, 2H), 1.78 – 1.67 (m, 2H), 1.65 – 1.56 (m, 1H), 1.35 – 1.07 (m, 4H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.81 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 75.7, 66.6, 42.8, 36.8, 35.8, 33.3, 31.9, 25.6, 24.9, 18.7; HRMS (ESI-TOF) *M/Z* [M+H]<sup>+</sup>: Calcd for C<sub>10</sub>H<sub>21</sub>O<sub>2</sub> 173.1536; Found 173.1534.

**3β-Methyloctahydro-2H-chromen-2-one (3.28):** To a solution of the diol **3.27** (0.271 g, 1.57 mmol) in 10 mL of CH<sub>3</sub>CN was added tetrakisacetonitrile copper(I) triflate (0.029 g, 0.0785 mmol) followed by commercial 0.04 M Stahl Aerobic Oxidation ABNO solution (0.0472 mmol, 1.18 mL). The reaction was stirred overnight at ambient temperature. As reaction reached completion, the mixture color changed from dark brown to blue.

Reaction was diluted with H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×), dried with MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude was purified on flash chromatography (20% EtOAc/hexanes, TLC stained with CAM) to yield 0.250 g (95%) of desired lactone **3.28** as a white solid. 1D NOESY experiment confirmed the orientation of the C<sub>2</sub>-substituent. Mp: 43.6-45.6 °C; IR (NaCl)  $\nu_{\max}$  2933, 2865, 1741, 1455, 1178, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.92 (td,  $J$  = 10.5, 4.4 Hz, 1H), 2.77 – 2.59 (m, 1H), 2.18 – 2.08 (m, 1H), 1.88 – 1.79 (m, 2H), 1.76 – 1.51 (m, 4H), 1.42 (dddd,  $J$  = 13.5, 12.1, 10.9, 3.7 Hz, 1H), 1.36 – 1.17 (m, 2H), 1.22 (d,  $J$  = 6.9 Hz, 3H), 1.18 – 1.02 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  176.2, 80.9, 37.79, 33.7, 33.2, 31.9, 31.7, 25.2, 24.0, 16.8; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>10</sub>H<sub>17</sub>O<sub>2</sub> 169.1223; Found 169.1221.

**3 $\beta$ -Methyloctahydro-2H-chromen-2-one (3.29):** To a solution of the diol **3.27'** (0.120 g, 0.697 mmol) in 5 mL of CH<sub>3</sub>CN was added tetrakisacetonitrile copper(I) triflate (0.013 g, 0.035 mmol) followed by commercial 0.04 M Stahl Aerobic Oxidation ABNO solution (0.0209 mmol, 0.522 mL). The reaction was stirred overnight at ambient temperature. As reaction reached completion, the mixture color changed from dark brown to blue. Reaction was diluted with H<sub>2</sub>O, extracted with 3× CH<sub>2</sub>Cl<sub>2</sub>, dried with MgSO<sub>4</sub>, filtered and condensed under reduced pressure. The crude was purified on flash chromatography (20% EtOAc/hexanes, TLC stained with CAM) to yield 0.093 g (79%) of desired lactone **3.29** as a slightly yellow oil. IR (NaCl)  $\nu_{\max}$  2932, 2861, 1732, 1465, 1180, 163 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.84 (ddd,  $J$  = 10.8, 10.7, 4.3 Hz, 1H), 2.57 (dp,  $J$  = 12.2, 7.1 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.89 (ddd,  $J$  = 13.2, 6.8, 3.0 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.73 – 1.65 (m, 1H), 1.55 (tdt,  $J$  = 11.7, 10.2, 3.3 Hz, 1H), 1.42 (qd,  $J$  = 12.5, 12.0, 3.7 Hz, 1H), 1.35 – 1.20 (m, 3H), 1.29 (d,  $J$  = 7.2 Hz, 3H), 1.04 (qd,  $J$  = 13.0, 3.7 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  174.4, 84.6, 77.4, 77.0, 76.7, 39.8, 36.7, 36.3, 32.3, 30.7, 25.1, 24.1, 17.7; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>10</sub>H<sub>17</sub>O<sub>2</sub> 169.1223; Found 169.1219.

**3 $\beta$ -Methyloctahydro-2H-chromen-2-yl-acetate (3.8(OAc)):** To a -78 °C solution of **3.28** (0.246 g, 1.48 mmol) in dry toluene (15 mL) under an argon atmosphere was added dropwise 1 M DIBAL-H in heptanes (1.78 mL, 1.78 mmol). The reaction was stirred at -78 °C for 2 h and pyridine (0.141 mL, 1.78 mmol), was slowly added at -78 °C, followed by DMAP (0.182 g, 1.78 mmol) in 3 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, stirred for 10 min and Ac<sub>2</sub>O (0.840



mL, 7.43 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and stirred for 12 h. The mixture was quenched with saturated NH<sub>4</sub>Cl and diluted with EtOAc. The extracted organic phase was washed with 1 N NaHSO<sub>4</sub> (2×), saturated NaHCO<sub>3</sub> (2×), brine (1×), dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes, TLC stained with CAM) to obtain a mixture two diastereoisomeric acetates (0.236 g, 93%, 50α:50β) **3.8(OAc)** as a colorless oil. IR (NaCl)  $\nu_{\max}$  2928, 2857, 1748, 1235, 1048 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.82 (s, 0.5H), 5.73 (d, *J* = 2.6 Hz, 0.5H), 3.40 (dt, *J* = 10.3, 5.1 Hz, 0.5H), 3.12 (ddd, *J* = 11.0, 9.4, 4.1 Hz, 0.5H), 2.10 (s, 1.5H), 2.09 (s, 1.5H), 2.05 – 1.97 (m, 0.6H), 1.96 – 1.84 (m, 1H), 1.85 – 1.73 (m, 1.5H), 1.72 – 1.17 (m, 8H), 1.13 (d, *J* = 7.3 Hz, 1.5H), 1.06 (d, *J* = 7.0 Hz, 1.5H), 1.06 – 0.85 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  169.9, 169.5, 96.5, 96.3, 81.3, 75.6, 36.1, 35.4, 35.4, 32.0, 31.96, 31.8, 31.7, 31.7, 31.3, 31.1, 25.7, 25.65, 25.0, 24.7, 21.3, 21.2, 16.8, 11.7; HRMS (ESI-TOF) *M/Z* [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>12</sub>H<sub>24</sub>NO<sub>3</sub> 230.1751; Found 230.1744.

**3α-Methyloctahydro-2H-chromen-2-yl-β-acetate (3.9(OAc))**: To a -78 °C solution of **3.29** (0.070 g, 0.416 mmol) in dry toluene (4 mL) under argon atmosphere was added dropwise 1 M DIBAL-H in heptanes (0.500 mL, 0.500 mmol). The reaction was stirred at -78 °C for 2 h and pyridine (0.040 mL, 0.500 mmol), was slowly added at -78 °C, followed by DMAP (0.051 g, 0.500 mmol) in 1 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, stirred for 10 min and Ac<sub>2</sub>O (0.235 mL, 2.08 mmol) was added dropwise. The reaction was allowed to reach ambient temperature and stirred for 12 h. The mixture was quenched with saturated NH<sub>4</sub>Cl and diluted with EtOAc. The extracted organic phase was washed with 1 N NaHSO<sub>4</sub> (2×), saturated NaHCO<sub>3</sub> (2×), brine (1×), dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes, TLC stained with CAM) to obtain the acetate (0.086 g, 97%) **β-3.9(OAc)** as a colorless oil. IR (NaCl)  $\nu_{\max}$  2929, 2861, 1754, 1228, 1063, 1046 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.34 (d, *J* = 8.8 Hz, 1H), 3.11 (td, *J* = 10.2, 4.1 Hz, 1H), 2.11 (s, 3H), 1.97 – 1.89 (m, 1H), 1.81 – 1.69 (m, 3H), 1.66 – 1.58 (m, 2H), 1.41 – 1.16 (m, 4H), 1.05 – 0.88 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  169.9, 98.6, 80.5, 41.3, 38.2, 35.4, 31.9, 30.9, 25.5, 24.7, 21.2, 16.1; HRMS (ESI-TOF) *M/Z* [M-OAc]<sup>+</sup>: Calcd for C<sub>10</sub>H<sub>17</sub>O 153.1279; Found 153.1308.

**3 $\beta$ -Methyl-2 $\alpha$ -(phenylthio)octahydro-2H-chromene (3.8(SPh)):** To a solution of diastereoisomeric acetate **3.8(OAc)** (0.190 g, 0.895 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (8 mL) under an Argon atmosphere was added PhSH (0.1 mL 0.985 mmol). The mixture was cooled to -78 °C and BF<sub>3</sub>-Et<sub>2</sub>O (0.125 mL, 0.985 mmol) was slowly added. After 1 h of stirring at -78 °C, the reaction was quenched with Et<sub>3</sub>N, brought to ambient temperature and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was isolated and the aqueous one was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 $\times$ ). The organic phases were combined, dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography (100% hexanes until leftover PhSH was eluted then 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give thioacetal  **$\alpha$ -3.8(SPh)** (0.230 g, 98%) as a colorless oil. The nature of the  $\alpha$ -anomer was confirmed by 1D NOESY where irradiation of H<sub>1</sub> showed a coupling with the axial C<sub>2</sub>-CH<sub>3</sub>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.51 – 7.44 (m, 2H), 7.32 – 7.23 (m, 2H), 7.24 – 7.17 (m, 1H), 5.31 (s, 1H), 3.86 (td,  $J$  = 10.1, 3.9 Hz, 1H), 2.19 (dddd,  $J$  = 11.8, 7.1, 5.8, 2.2 Hz, 1H), 1.84 – 1.65 (m, 2H), 1.74 – 1.63 (m, 2H), 1.63 – 1.51 (m, 2H), 1.45 – 1.31 (m, 3H), 1.28-1.17 (m, 1H), 1.23 (d,  $J$  = 7.2 Hz, 3H), (dtd,  $J$  = 13.6, 12.1, 3.5 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  136.3, 130.7, 128.8, 126.4, 90.1, 74.0, 36.2, 34.5, 32.9, 31.9, 31.7, 25.8, 25.2, 19.4; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>16</sub>H<sub>23</sub>OS 263.1464; Found 263.1454.

**3 $\alpha$ -Methyl-2-(phenylthio)octahydro-2H-chromene (3.9(SPh)):** To a solution of diastereoisomeric acetate **3.4(OAc)** (0.034 g, 0.160 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL) under an argon atmosphere was added PhSH (0.018 mL, 176 mmol). The mixture was cooled to -78 °C and BF<sub>3</sub>-Et<sub>2</sub>O (0.022 mL, 0.176 mmol) was slowly added. After 1 h of stirring at -78 °C, the reaction was quenched with Et<sub>3</sub>N, brought to ambient temperature and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was isolated and the aqueous one was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 $\times$ ). The organic phases were combined, dried over MgSO<sub>4</sub> and condensed *in vacuo*. The residue was purified by silica gel column chromatography 100% hexanes until leftover PhSH was eluted then 10% EtOAc/hexanes, TLC revealed by UV light and stained with CAM) to give a mixture of thioacetals **3.9(SPh)** (0.040 g, 95%, 96 $\alpha$ :4 $\beta$ ) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.50 (d,  $J$  = 7.4 Hz, 2H), 7.27 (t,  $J$  = 7.4 Hz, 2H), 7.20 (t,  $J$  = 7.3 Hz, 1H), 5.44 (d,  $J$  = 4.6 Hz, 0.96H), 4.44 (d,  $J$  = 9.9 Hz, 0.04H), 3.82 (td,  $J$  = 10.2, 3.5 Hz, 0.96H), 3.00 (td,  $J$  = 10.3, 4.2 Hz, 0.04H), 2.34 – 2.21 (m, 1H), 1.86 – 1.76 (m, 2H), 1.72 – 1.57 (m, 2H), 1.58 – 1.49 (m, 1H), 1.46 – 1.06 (m, 6H), 1.04 (d,  $J$  = 6.9 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$

136.1, 131.1, 128.8, 126.4, 92.1, 73.3, 42.3, 36.9, 35.0, 31.9, 31.5, 25.7, 25.2, 18.9; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>16</sub>H<sub>23</sub>OS 263.1464; Found 263.1453.

## D.2 Réactions de C/O-glycosylation et caractérisation des produits

### 2-Allyl-3 $\beta$ -(3,5-bis(trifluoromethyl)benzyloxy)octahydro-2H-chromene (3.4(Allyl)):

Following the C-glycosylation general procedure on  $\beta$ -3.4(OAc) (0.04 g, 0.090 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) with AllylTMS (0.057 mL, 0.360 mmol) and BF<sub>3</sub>-Et<sub>2</sub>O (0.016 mL, 0.108 mmol), the purification on silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM), the less polar  $\beta$ -3.4(Allyl) (0.003 g, 8%, traces of hexanes in the <sup>1</sup>H NMR) and more polar  $\alpha$ -3.4(Allyl) (0.033 g, 87%, contains 5% traces of the  $\beta$ -anomer) were partially separated as colorless oils. 1D NOESY experiment on the H<sub>4</sub> signal of the major anomer showed positive coupling with the allylic CH<sub>2</sub>, thus confirming the  $\alpha$ -oriented nature of the major anomer.

**Minor  $\beta$ -3.4(Allyl):** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, TMS)  $\delta$  7.86 – 7.77 (m, 3H), 5.83 – 5.71 (m, 1H), 5.11 – 5.01 (m, 2H), 4.75, 4.51 (ABq,  $J_{AB}$  = 12.6 Hz, 2H), 3.47 (s, 1H), 3.45 – 3.43 (m, 1H), 3.00 (td,  $J$  = 10.2, 4.1 Hz, 1H), 2.49 (dt,  $J$  = 14.1, 6.3 Hz, 1H), 2.40 (dt,  $J$  = 14.4, 7.7 Hz, 1H), 2.03 (dt,  $J$  = 14.1, 3.2 Hz, 1H), 1.94 – 1.75 (m, 2H), 1.72 – 1.46 (m, 4H), 1.46 – 1.34 (m, 3H), 1.04 – 0.91 (m, 1H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$  -62.87 (s, 6F); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  141.5, 134.7, 131.4, 127.7 – 127.5 (m), 121.5 – 121.2 (m), 117.0, 82.4, 79.3, 74.4, 69.7, 36.2, 35.9, 33.9, 32.1, 31.5, 29.7, 25.7, 25.0; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>21</sub>H<sub>25</sub>F<sub>6</sub>O<sub>2</sub> 423.1753; Found 423.1730.

**Major  $\alpha$ -3.4(Allyl):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.82 (s, 2H), 7.78 (s, 1H), 5.79 (dddd,  $J$  = 16.6, 10.2, 7.7, 6.3 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.67, 4.63 (ABq,  $J_{AB}$  = 13.2 Hz, 2H), 4.04 (t,  $J$  = 7.7 Hz, 1H), 3.44 – 3.40 (m, 1H), 3.20 (td,  $J$  = 10.0, 3.5 Hz, 1H), 2.55 (ddd,  $J$  = 14.1, 7.8, 6.2 Hz, 1H), 2.28 (dt,  $J$  = 14.7, 7.7 Hz, 1H), 1.87 – 1.76 (m, 3H), 1.74 – 1.55 (m, 3H), 1.48 (ddd,  $J$  = 14.8, 12.5, 2.9 Hz, 1H), 1.42 – 1.18 (m, 3H), 0.97 (dddd,  $J$  = 12.5, 3.9 Hz, 1H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -62.87 (s, 6F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  141.6, 134.5, 131.6 (q,  $J$  = 31.9 Hz), 127.4 – 127.2 (m), 124.8, 121.5 – 121.2 (m), 117.2, 75.2, 75.0, 73.9, 69.0, 36.0, 34.6, 32.4, 31.6, 30.6, 25.7, 25.1; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>21</sub>H<sub>25</sub>F<sub>6</sub>O<sub>2</sub> 423.1753; Found 423.1725.

**2-Allyl-3 $\alpha$ -(3,5-bis(trifluoromethyl)benzyloxy)octahydro-2H-chromene (3.5(Allyl)):**

Following the C-glycosylation general procedure on **3.5(OAc)** (0.04 g, 0.090 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) with AllylTMS (0.057 mL, 0.360 mmol) and BF<sub>3</sub>-Et<sub>2</sub>O (0.016 mL, 0.108 mmol), the purification on silica gel chromatography (5% EtOAc/hexanes, TLC stained with CAM), yielded  **$\alpha$ -3.5(Allyl)** (0.030 g, 79%). The nature of the anomer was confirmed by analysis of the coupling constant for the H<sub>2</sub> signal at 3.79 ppm, where there is only one of the three coupling constants showing a *trans* diaxial value. Two *trans* diaxial relation (H<sub>2</sub>-H<sub>1</sub> and H<sub>2</sub>-H<sub>3</sub>) would be characteristic of the  $\beta$ -anomer. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (s, 1H), 7.77 (s, 2H), 5.90 (ddt,  $J$  = 17.1, 10.1, 6.9 Hz, 1H), 5.18 – 5.07 (m, 2H), 4.67, 4.63 (ABq,  $J_{AB}$  = 12.9 Hz, 2H), 4.16 (dt,  $J$  = 10.2, 4.8 Hz, 1H), 3.79 (ddd,  $J$  = 11.6, 5.6, 4.6 Hz, 1H), 3.12 (td,  $J$  = 10.1, 3.9 Hz, 1H), 2.63 (dddt,  $J$  = 15.1, 10.8, 7.2, 1.3 Hz, 1H), 2.34 (dddt,  $J$  = 15.1, 6.9, 4.0, 1.5 Hz, 1H), 1.89 (dddd,  $J$  = 12.2, 4.4, 3.3, 1.0 Hz, 1H), 1.86 – 1.76 (m, 2H), 1.72 – 1.60 (m, 2H), 1.40 (q,  $J$  = 12.0 Hz, 1H), 1.34 – 1.03 (m, 5H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -62.90 (s, 6F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  141.3, 135.2, 131.6 (q,  $J$  = 33.2 Hz), 127.3 – 126.8 (m), 124.7, 121.9, 121.6 – 121.1 (m), 116.6, 74.4, 72.6, 69.1, 41.4, 32.0, 31.7, 31.4, 29.2, 25.5, 25.0; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>21</sub>H<sub>25</sub>F<sub>6</sub>O<sub>2</sub> 423.1753; Found 423.1761.

**3 $\beta$ -(3,5-bis(Trifluoromethyl)benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-**

**chromene (3.4(TFE)):** Following the general procedure for O-glycosylation starting with  **$\beta$ -3.4(SPh)** (0.044 g, 0.088 mmol) in DCM (0.8 mL) with NIS (0.026 g, 0.116 mmol) and 2,2,2-trifluoroethanol (0.017 mL, 0.232 mmol), silica gel column chromatography (100% hexanes to remove the thiolated byproduct then 5% EtOAc/hexanes, TLC stained with CAM) afforded an  $\alpha/\beta$  mixture of **3.4(TFE)** (0.030 g, 71%, 67 $\alpha$ :33 $\beta$ ) as a colorless strong smelling oil. The anomeric ratio was determined by comparison with previously reported C<sub>2</sub>-OBn donors. <sup>13</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.86 (s, 0.5H), 7.82 – 7.74 (m, 2.5H), 4.91, 4.80 (ABq,  $J_{AB}$  = 17.4 Hz, 0.6H), 4.90 (s, 0.7H), 4.71, 4.66 (ABq,  $J_{AB}$  = 12.9 Hz, 1.4H), 4.58 (s, 0.3H), 4.19 (dq,  $J$  = 12.6, 9.0 Hz, 0.4H), 4.05 – 3.86 (m, 1.6H), 3.65 (td,  $J$  = 3.0, 1.1 Hz, 0.3H), 3.57 (td,  $J$  = 2.8, 1.4 Hz, 0.7H), 3.36 (td,  $J$  = 10.5, 3.9 Hz, 0.7H), 3.05 (ddd,  $J$  = 11.2, 9.6, 4.1 Hz, 0.3H), 1.95 (dt,  $J$  = 14.2, 3.4 Hz, 0.7H), 1.86 – 1.76 (m, 2.3H), 1.71 – 1.56 (m, 3H), 1.51 (tdd,  $J$  = 12.6, 11.1, 3.9 Hz, 0.7H), 1.42 – 1.21 (m, 3.3H), 1.05 – 0.88 (m, 1H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$  -62.90 (s, 4.2F), -62.91 (s, 1.8F), -74.23 (t,  $J$  = 8.6 Hz, 2.2F), -74.40 (t,  $J$  = 9.0 Hz,

0.8F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  141.7, 141.0, 131.7 (q,  $J = 33.3$  Hz), 129.0, 127.4, 127.2, 125.1, 125.0, 124.5, 124.4, 122.9, 122.8, 122.3, 122.2, 121.7 – 121.4 (m), 121.4 – 121.1 (m), 102.2, 97.8, 86.3, 80.5, 74.4, 74.2, 74.0, 73.9, 71.3, 69.7, 69.4, 65.2 (q,  $J = 34.2$  Hz), 63.7 (q,  $J = 34.5$  Hz), 36.0, 35.4, 35.2, 35.0, 31.7, 31.6, 31.3, 30.9, 30.0, 25.6, 25.5, 24.96, 24.6; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{20}\text{H}_{25}\text{F}_9\text{NO}_3$  498.1685; Found 498.1687.

**3 $\alpha$ -(3,5-bis(Trifluoromethyl)benzyloxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-**

**chromene (3.5(TFE))**: Following the general procedure B for O-glycosylation in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) starting with **3.5(SPh)** (0.030 g, 0.0612 mmol) with NIS (0.028 g, 0.124 mmol) and 2,2,2-trifluoroethanol (0.018 mL, 0.248 mmol), silica gel column chromatography (100% hexanes to remove the thiolated byproduct then 5% EtOAc/hexanes, TLC stained with CAM) afforded an  $\alpha/\beta$  mixture of **3.5(TFE)** (0.025 g, 85%, 83 $\alpha$ :17 $\beta$ ) as a colorless strong smelling oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 (s, 2H), 7.79 (s, 1H), 5.04 (d,  $J = 3.4$  Hz, 0.83H), 4.92, 4.74 (ABq,  $J_{AB} = 12.7$  Hz, 0.3H), 4.71, 4.66 (ABq,  $J_{AB} = 12.5$  Hz, 1.7H), 4.47 (d,  $J = 7.5$  Hz, 0.17H), 4.20 (dq,  $J = 12.4, 8.8$  Hz, 0.2H), 4.06 – 3.93 (m, 2H), 3.65 (ddd,  $J = 11.9, 4.9, 3.4$  Hz, 0.83H), 3.33 (td,  $J = 10.4, 4.0$  Hz, 0.83H), 2.99 (td,  $J = 10.1, 4.1$  Hz, 0.17H), 2.11 – 2.04 (m, 0.3H), 1.98 – 1.90 (m, 0.3H), 1.89 – 1.77 (m, 3H), 1.75 – 1.62 (m, 3.4H), 1.42 – 1.00 (m, 4H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.95 (s, 1F), -62.97 (s, 5F), -73.91 (t,  $J = 8.8$  Hz, 2.5F), -74.32 (t,  $J = 8.6$  Hz, 0.5F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  141.4, 141.0, 131.7, 131.65 (q,  $J = 33.3$  Hz), 131.4, 127.4 – 127.3 (m), 127.3 – 127.1 (m), 126.6, 125.2, 125.0, 124.4, 122.9, 122.2, 121.5 (p,  $J = 3.8$  Hz), 121.4, 105.4, 97.2, 79.3, 76.0, 73.0, 71.3, 68.8, 65.5 (q,  $J = 35.3$  Hz), 64.0 (q,  $J = 34.4$  Hz), 40.7, 36.2, 31.4, 30.8, 30.7, 29.7, 25.3, 25.2, 24.9, 24.5; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{NH}_4]^+$ : Calcd for  $\text{C}_{20}\text{H}_{25}\text{F}_9\text{NO}_3$  498.1685; Found 498.1682.

**3 $\beta$ -((4-Methoxybenzyl)oxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene**

**(3.6(TFE))**: Following the general procedure A for O-glycosylation starting with **3.6(SPh)** (0.042 g, 0.109 mmol) in  $\text{CH}_3\text{CN}$  (1 mL) with NIS (0.049 g, 0.218 mmol) and 2,2,2-trifluoroethanol (0.032 mL, 0.436 mmol), silica gel column chromatography (100% hexanes to remove the thiolated byproduct then 5% EtOAc/Hexanes, TLC stained with CAM) afforded an  $\alpha/\beta$  mixture of **3.6(TFE)** (0.029 g, 71%, 87 $\alpha$ :13 $\beta$ ) as a slightly yellow oil. The

anomeric ratio was determined by comparison with previously reported C<sub>2</sub>-OBn donors. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32 (d, *J* = 8.6 Hz, 0.3H), 7.29 – 7.26 (m, 1.7H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.82 (s, 0.87H), 4.74, 4.66 (ABq, *J*<sub>AB</sub> = 12.5 Hz, 0.26H), 4.54, 4.51 (ABq, *J*<sub>AB</sub> = 11.9 Hz, 1.74H), 4.24 (dq, *J* = 12.4, 9.0 Hz, 0.13H), 3.99 (dq, *J* = 12.3, 9.0 Hz, 1H), 3.88 (dq, *J* = 12.4, 8.7 Hz, 1H), 3.82 (d, *J* = 0.6 Hz, 3H), 3.61 (t, *J* = 3.1 Hz, 0.13H), 3.51 (q, *J* = 2.4 Hz, 0.87H), 3.33 (td, *J* = 10.5, 3.8 Hz, 0.87H), 3.01 (td, *J* = 10.2, 4.1 Hz, 0.13H), 1.88 – 1.62 (m, 5H), 1.59 – 1.46 (m, 2H), 1.44 – 1.33 (m, 1H), 1.32 – 1.23 (m, 2H), 0.98 (qd, *J* = 12.5, 3.7 Hz, 0.8H), 0.90-0.82 (m, 0.20H); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ -74.19 (t, *J* = 8.8 Hz, 2.6F), -74.29 (t, *J* = 8.9 Hz, 0.4F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 159.2, 159.2, 130.9, 130.5, 130.3, 129.4, 129.4, 124.0 (q, 279.8 Hz), 113.8, 113.6, 102.5, 98.3, 80.4, 73.8, 72.7, 72.1, 71.9, 71.5, 70.7, 65.3 (q, *J* = 34.1 Hz), 63.7 (q, *J* = 34.6 Hz), 55.3, 55.2, 35.3, 35.2, 35.0, 31.7, 31.7, 31.4, 30.9, 30.1, 25.6, 25.5, 25.0, 24.7; HRMS (ESI-TOF) M/Z [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>19</sub>H<sub>29</sub>F<sub>3</sub>NO<sub>4</sub> 392.2043; Found 392.2051.

### **3α-((4-Methoxybenzyl)oxy)-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene**

**(3.7(TFE))**: Following the general procedure A for O-glycosylation starting with **α-3.7(SPh)** (0.032 g, 0.084 mmol) in CH<sub>3</sub>CN (1 mL) with NIS (0.038 g, 0.168 mmol) and 2,2,2-trifluoroethanol (0.025 mL, 0.336 mmol), silica gel column chromatography (100% hexanes to remove the thiolated byproduct then 5% EtOAc/Hexanes, TLC stained with CAM) afforded an α/β mixture of **3.7(TFE)** (0.019 g, 61%, 87α:13β) as a slightly yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.88 (d, *J* = 3.3 Hz, 0.87H), 4.75, 4.55 (ABq, *J*<sub>AB</sub> = 11.3 Hz, 0.26H), 4.54, 4.50 (ABq, *J*<sub>AB</sub> = 11.8 Hz, 1.74H), 4.43 (d, *J* = 7.5 Hz, 0.13H), 4.21 (dq, *J* = 12.3, 8.8 Hz, 0.07H), 3.95 (qd, *J* = 8.9, 5.0 Hz, 2H), 3.81 (s, 0.4H), 3.80 (s, 2.6H), 3.55 (ddd, *J* = 11.9, 4.8, 3.4 Hz, 0.87H), 3.33 – 3.24 (m, 1H), 2.95 (ddd, *J* = 10.5, 9.3, 3.9 Hz, 0.13H), 1.86 – 1.71 (m, 3H), 1.71 – 1.56 (m, 3H), 1.37 – 1.01 (m, 5H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -73.63 (t, *J* = 8.7 Hz, 2.39F), -74.15 (t, *J* = 8.7 Hz, 0.41F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 159.3, 159.2, 130.7, 130.4, 129.6, 129.4, 129.3, 124.1 (q, *J* = 286.0 Hz), 113.8, 113.8, 113.7, 105.8, 97.6, 75.7, 74.6, 72.9, 72.4, 71.5, 70.2, 64.2 (q, *J* = 34.6 Hz), 55.3, 40.8, 40.5, 36.5, 31.5, 31.3, 30.9, 30.8, 25.3, 25.2, 24.9, 24.6; HRMS (ESI-TOF) M/Z [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>19</sub>H<sub>29</sub>F<sub>3</sub>NO<sub>4</sub> 392.2043; Found 392.2051.

***tert*-Butyldimethyl((2-(2,2,2-trifluoroethoxy)octahydro-2*H*-chromen-3 $\beta$ -yl)oxy)silane (3.10(TFE))**: Following the general procedure A for O-glycosylation starting with **3.10(SPh)** (0.040 g, 0.105 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) with NIS (0.053 g, 0.236 mmol) and 2,2,2-trifluoroethanol (0.034 mL, 0.472 mmol), silica gel column chromatography (100% hexanes to remove the thiolated byproduct then 5% EtOAc/hexanes, TLC stained with CAM) afforded an  $\alpha/\beta$  mixture of **3.10(TFE)** (0.030 g, 69%, 78 $\alpha$ :22 $\beta$ ) as a colorless oil. The anomeric ratio was determined by comparison with previously reported C<sub>2</sub>-OBn donors.<sup>13</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.62 (s, 0.8H), 4.40 (s, 0.2H), 4.16 (dq,  $J$  = 12.5, 9.0 Hz, 0.1H), 4.03 – 3.83 (m, 2.1H), 3.78 (td,  $J$  = 2.7, 1.4 Hz, 0.8H), 3.28 (td,  $J$  = 10.2, 3.8 Hz, 0.8H), 2.97 (ddd,  $J$  = 11.1, 9.5, 4.0 Hz, 0.2H), 1.84 – 1.77 (m, 2H), 1.75 – 1.45 (m, 5H), 1.44 – 1.15 (m, 3H), 1.05 – 0.92 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -74.27 (t,  $J$  = 8.7 Hz, 0.7F), -74.29 (t,  $J$  = 8.9 Hz, 2.3F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  124.1 (q,  $J$  = 278.3 Hz), 124.0 (q,  $J$  = 278.8 Hz), 102.0, 100.6, 80.3, 73.8, 67.3, 67.0, 65.2 (q,  $J$  = 34.4 Hz), 63.6 (q,  $J$  = 34.5 Hz), 38.1, 34.7, 34.7, 33.6, 31.8, 31.4, 31.0, 29.7, 25.9, 25.8, 25.7, 25.6, 25.0, 24.8, 18.4, 18.1, -4.7, -4.9, -5.0, -5.3; HRMS (ESI-TOF)  $M/Z$  [M+NH<sub>4</sub>]<sup>+</sup>: Calcd for C<sub>17</sub>H<sub>35</sub>F<sub>3</sub>NO<sub>3</sub>Si 386.2341; Found 386.2333.

***tert*-Butyldimethyl((2-(2,2,2-trifluoroethoxy)octahydro-2*H*-chromen-3 $\alpha$ -yl)oxy)silane (3.11(TFE))**: Following the general procedure A for O-glycosylation starting with **3.11(SPh)** (0.032 g, 0.0845 mmol) in CH<sub>2</sub>Cl<sub>2</sub>(1.2 mL) with NIS (0.053 g, 0.236 mmol) and 2,2,2-trifluoroethanol (0.034 mL, 0.472 mmol), silica gel column chromatography (100% hexanes to remove the thiolated byproduct then 5% EtOAc/hexanes, TLC stained with CAM) afforded an  $\alpha/\beta$  mixture of **3.11(TFE)** (0.018 g, 51%, 85 $\alpha$ :15 $\beta$ ) as a slightly yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.75 (d,  $J$  = 3.4 Hz, 0.85H), 4.25 (d,  $J$  = 7.4 Hz, 0.15H), 4.14 (dddd,  $J$  = 12.9, 10.4, 9.4, 8.3 Hz, 0.15H), 3.97 (qd,  $J$  = 8.9, 1.3 Hz, 1.7H), 3.92 – 3.85 (m, 0.15H), 3.81 (tdd,  $J$  = 8.1, 3.9, 1.2 Hz, 0.85H), 3.49 (dt,  $J$  = 11.3, 6.1 Hz, 0.15H), 3.27 (td,  $J$  = 10.4, 4.0 Hz, 0.85H), 2.95 (td,  $J$  = 9.8, 4.0 Hz, 0.15H), 1.89 – 1.75 (m, 2H), 1.70 – 1.55 (m, 4H), 1.42 – 1.02 (m, 5H), 0.88 (s, 9H), 0.06 (s, 6H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -73.77 (t,  $J$  = 8.8 Hz, 0.86F), -73.94 (t,  $J$  = 8.8 Hz, 0.14F); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  124.7 (q, 279.8 Hz), 105.5, 99.9, 79.3, 72.6, 70.5, 65.6 (q,  $J$  = 34.9 Hz), 64.3 (q,  $J$  = 34.4 Hz), 40.9, 40.5, 39.3, 34.0, 31.5, 31.2, 30.8, 29.7, 29.7, 25.7, 25.3, 25.2, 25.0, 24.6, 18.1, -4.7, -4.8, -4.9, -5.1; HRMS (ESI-TOF)  $M/Z$  [M+H]<sup>+</sup>: Calcd for C<sub>17</sub>H<sub>32</sub>F<sub>3</sub>O<sub>3</sub>Si 369.2067; Found 369.2070.

**2 $\alpha$ -Allyl-3 $\beta$ -methyloctahydro-2H-chromene (3.8(Allyl)):** From **3.8(OAc)** (0.40 g, 0.188 mmol) using general procedure A in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) with TMSallyl (0.119 mL, 0.752 mmol) and BF<sub>3</sub>-Et<sub>2</sub>O (0.028 mL, 0.226 mmol), only pure  **$\alpha$ -3.8(allyl)** (0.032 g, 88%) was obtained without the need for purification as a colorless oil. 1D NOESY confirms the  $\alpha$ -orientation of the anomer as irradiation of the C<sub>6</sub>-H showed a positive coupling with the allylic protons of the acceptor and no coupling with the anomeric signal. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.81 (ddt,  $J$  = 17.2, 10.1, 7.0 Hz, 1H), 5.09 (q,  $J$  = 1.7 Hz, 0.5H), 5.04 (dd,  $J$  = 2.0, 1.3 Hz, 1H), 5.02 (dt,  $J$  = 2.2, 1.1 Hz, 0.5H), 3.60 (t,  $J$  = 7.5 Hz, 1H), 3.12 (td,  $J$  = 9.8, 3.9 Hz, 1H), 2.62 (dddt,  $J$  = 14.4, 8.1, 6.6, 1.5 Hz, 1H), 2.28 (dtt,  $J$  = 14.3, 7.2, 1.3 Hz, 1H), 1.82 – 1.65 (m, 3H), 1.68 – 1.54 (m, 1H), 1.58 – 1.36 (m, 3H), 1.36 – 1.18 (m, 4H), 1.16 (d,  $J$  = 7.1 Hz, 3H), 1.04 – 0.85 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  135.9, 116.2, 78.3, 73.8, 36.2, 36.1, 32.7, 32.1, 31.9, 30.4, 25.9, 25.2, 19.6; HRMS (ESI-TOF) M/Z [M+H]<sup>+</sup>: Calcd for C<sub>13</sub>H<sub>23</sub>O 195.1743; Found 195.1740.

**2 $\beta$ -Allyl-3 $\alpha$ -methyloctahydro-2H-chromene (3.9(Allyl)):** From **3.9(OAc)** (0.040 g, 0.188 mmol) using general procedure A in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) with TMSallyl (0.119 mL, 0.752 mmol) and BF<sub>3</sub>-Et<sub>2</sub>O (0.028 mL, 0.226 mmol), only pure  **$\beta$ -3.9(allyl)** (0.032 g, 88%) was obtained without purification as a slight yellow oil. Positive coupling between the irradiated C<sub>5</sub>-H and the anomeric proton from the 1D NOESY experiment confirms the  $\beta$ -orientation. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.87 (ddt,  $J$  = 17.1, 10.2, 6.9 Hz, 1H), 5.10 (dt,  $J$  = 2.0, 1.5 Hz, 0.5H), 5.06 (dd,  $J$  = 2.5, 1.1 Hz, 1H), 5.03 (dt,  $J$  = 2.2, 1.2 Hz, 0.5H), 3.83 (dt,  $J$  = 11.2, 4.7 Hz, 1H), 3.05 (td,  $J$  = 10.0, 3.6 Hz, 1H), 2.53 (dddt,  $J$  = 14.5, 11.2, 7.1, 1.3 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.79 – 1.73 (m, 2H), 1.68 – 1.52 (m, 2H), 1.44 (dt,  $J$  = 12.9, 3.6 Hz, 1H), 1.35 – 1.14 (m, 4H), 1.13 – 0.85 (m, 2H), 0.81 (d,  $J$  = 7.0 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  136.0, 115.9, 77.3, 72.5, 42.6, 34.3, 34.3, 32.5, 31.7, 29.4, 25.8, 25.2, 17.9; HRMS (ESI-TOF) M/Z [M+H-H<sub>2</sub>O]<sup>+</sup>: Calcd for C<sub>13</sub>H<sub>21</sub> 177.1638; Found 177.1628.

**3 $\beta$ -Methyl-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene (3.8(TFE)):** From  **$\alpha$ -3.8(SPh)** (0.050 g, 0.190 mmol) using general procedure A in CH<sub>3</sub>CN (1.9 mL) with NIS (0.085 g, 0.380 mmol) and 2,2,2-trifluoroethanol (0.055 mL, 0.760 mmol), a mixture of  **$\alpha/\beta$ -3.8(TFE)** (0.034 g, 71%, 96 $\alpha$ :4 $\beta$ ) was obtained after silica gel column chromatography (100% hexanes then 5% EtOAc/hexanes, TLC stained with CAM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.57 (s, 1H), 4.11



(dq,  $J = 12.6, 9.1$  Hz, 0.03H), 3.94 (dq,  $J = 12.4, 8.6$  Hz, 1H), 3.85 (dq,  $J = 12.4, 8.6$  Hz, 1H), 3.29 (td,  $J = 10.5, 3.5$  Hz, 1H), 2.95 (ddd,  $J = 11.2, 9.1, 4.1$  Hz, 0.03H), 1.97 (m, 1H), 1.78 (m, 2H), 1.74 – 1.57 (m, 2H), 1.58 – 1.38 (m, 2H), 1.38 – 1.16 (m, 3H), 1.09 (d,  $J = 7.4$  Hz, 3H), 1.04 – 0.82 (m, 2H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.17 (t,  $J = 8.9$  Hz, 2.9F), -74.37 (t,  $J = 8.9$  Hz, 0.1F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  124.2 (q,  $J = 278.3$  Hz), 103.6, 102.4, 80.6, 73.7, 63.7 (q,  $J = 34.2$  Hz), 36.3, 35.6, 35.4, 32.8, 32.0, 31.9, 31.6, 31.1, 29.7, 25.8, 25.7, 25.1, 24.8, 17.0, 14.1, 11.4; HRMS (ESI-TOF)  $M/Z$   $[\text{M}-\text{CF}_3\text{CH}_2\text{OH}]^+$ : Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}$  152.1201; Found 152.1277. The very labile nature of the anomeric group did not allow a precise HMRS of the hole compound, but rather the product of a  $\beta$ -elimination within the instrument, even at a lower fragmentation voltage.

**3 $\alpha$ -Methyl-2-(2,2,2-trifluoroethoxy)octahydro-2H-chromene (3.9(TFE)):** From **3.9(SPh)** (0.070 g, 0.267 mmol) using general procedure A in  $\text{CH}_3\text{CN}$  (2.67 mL) with NIS (0.120 g, 0.534 mmol) and 2,2,2-trifluoroethanol (0.077 mL, 1.07 mmol), a mixture of  $\alpha/\beta$ -**3.9(TFE)** (0.038 g, 54%, 83 $\alpha$ :17 $\beta$ ) was obtained after silica gel column chromatography (100% hexanes then 5% EtOAc/hexanes, TLC stained with CAM). The position of the anomeric signal in both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR confirm the major product to be the  $\alpha$ -**3.9(TFE)**. Also, 1D NOESY experiment did not show positive coupling between the  $\text{C}_1\text{-H}$  and  $\text{C}_5\text{-H}$ , indicating again the major anomer to be  $\alpha$  oriented.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.67 (d,  $J = 3.3$  Hz, 0.83H), 4.57 (s, 0.17H), 4.01 – 3.79 (m, 2H), 3.34 – 3.21 (m, 1H), 2.00-1.76 (m, 3H) 1.70 – 1.56 (m, 3H), 1.44 – 1.14 (m, 4H), 1.09 (d,  $J = 7.4$  Hz, 0.6H), 1.06 – 0.84 (m, 2H), 0.91 (d,  $J = 7.0$  Hz, 2.4H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.18 (t,  $J = 9.0$  Hz, 0.55F), -74.24 (t,  $J = 8.9$  Hz, 2.45F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  124.2 (q,  $J = 278.6$  Hz), 102.4, 101.4, 73.7, 72.9, 64.1 (q,  $J = 34.2$  Hz), 41.7, 35.4, 35.1, 33.0, 32.0, 31.9, 31.89, 31.6, 31.4, 31.3, 25.7, 25.6, 25.5, 25.1, 17.0, 16.4; HRMS (ESI-TOF)  $M/Z$   $[\text{M}-\text{CF}_3\text{CH}_2\text{OH}]^+$ : Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}$  152.1201; Found 152.1278. The very labile nature of the anomeric group did not allow a precise HMRS of the hole compound, but rather the product of a  $\beta$ -elimination within the instrument, even at a lower fragmentation voltage.

**N-Acetyl-N-3 $\beta$ -(3,5-bis(trifluoromethyl)benzyloxy)octahydro-2H-chromen-2-yl)-2 $\beta$  chlorobenzamide (3.4( $\beta$ -amide)):** To a solution of  $\beta$ -**3.4(SPh)** (0.05 g, 0.1019 mmol) in dry  $\text{CH}_3\text{CN}$  (2 mL) with 4 $\text{\AA}$  MS and 2-chlorobenzoic acid (0.017 g, 0.112 mmol) under argon at

-40 °C was rapidly added NIS (0.06 g, 0.265 mmol) as a powder. The mixture was allowed to reach room temperature and stirred for 4 h, quenched with saturated  $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$  and diluted with  $\text{CH}_2\text{Cl}_2$ . Organic phase was separated, and the aqueous portion extracted with  $\text{CH}_2\text{Cl}_2$  (2 $\times$ ). Combined organic phases were dried with  $\text{MgSO}_4$ , filtered and condensed *in vacuo*. Compound **3.4( $\beta$ -amide)** was obtained after silica gel column chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes, TLC stained with CAM) as yellowish thick oil (0.025 g, 43%). The nature of the anomer was confirmed by 1D NOESY where a positive coupling between  $\text{H}_1$  and  $\text{H}_5$  was observed.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (s, 1H), 7.74 (s, 2H), 7.46 (d,  $J = 7.8$  Hz, 1H), 7.43 – 7.37 (m, 2H), 7.31 (ddd,  $J = 8.2, 5.6, 2.8$  Hz, 1H), 5.38 (d,  $J = 5.0$  Hz, 1H), 4.69, 4.61 (ABq,  $J_{AB} = 12.6$  Hz, 2H), 4.42 (q,  $J = 5.5$  Hz, 1H), 3.54 (td,  $J = 10.6, 4.1$  Hz, 1H), 2.33 (s, 3H), 1.94 (ddd,  $J = 13.8, 10.0, 5.8$  Hz, 1H), 1.85 – 1.68 (m, 2H), 1.67 – 1.53 (m, 3H), 1.32 – 1.10 (m, 4H), 1.04 (qd,  $J = 12.4, 3.3$  Hz, 1H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.81 (s, 6F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8, 171.7, 140.9, 135.1, 132.0, 131.6 (q,  $J = 33.4$  Hz), 131.4, 130.4, 129.7, 127.4 – 127.2 (m), 127.1, 124.4, 122.2, 121.5 (p,  $J = 3.8$  Hz), 85.8, 76.3, 74.6, 69.9, 36.3, 32.4, 32.3, 32.1, 26.2, 25.5, 24.5; IR (NaCl)  $\nu_{\text{max}}$  2932, 2860, 1681, 1279, 1174, 1134  $\text{cm}^{-1}$ ; HRMS (ESI-TOF)  $M/Z$   $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{27}\text{H}_{27}\text{ClF}_6\text{NO}_4$  578.1527; Found 578.1558.

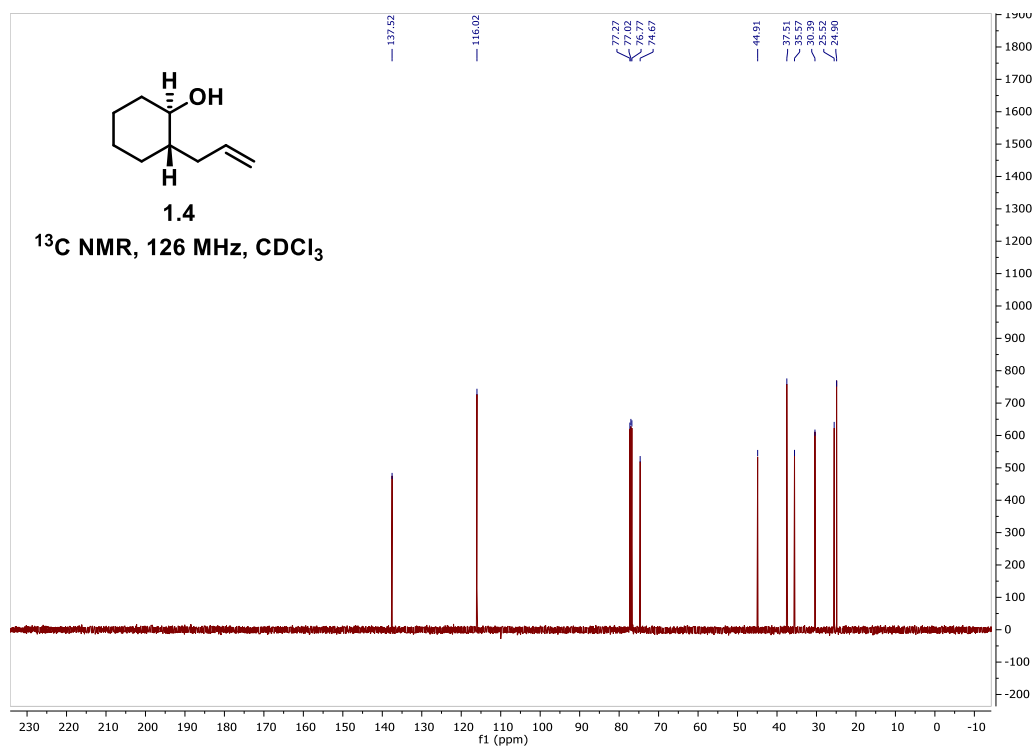
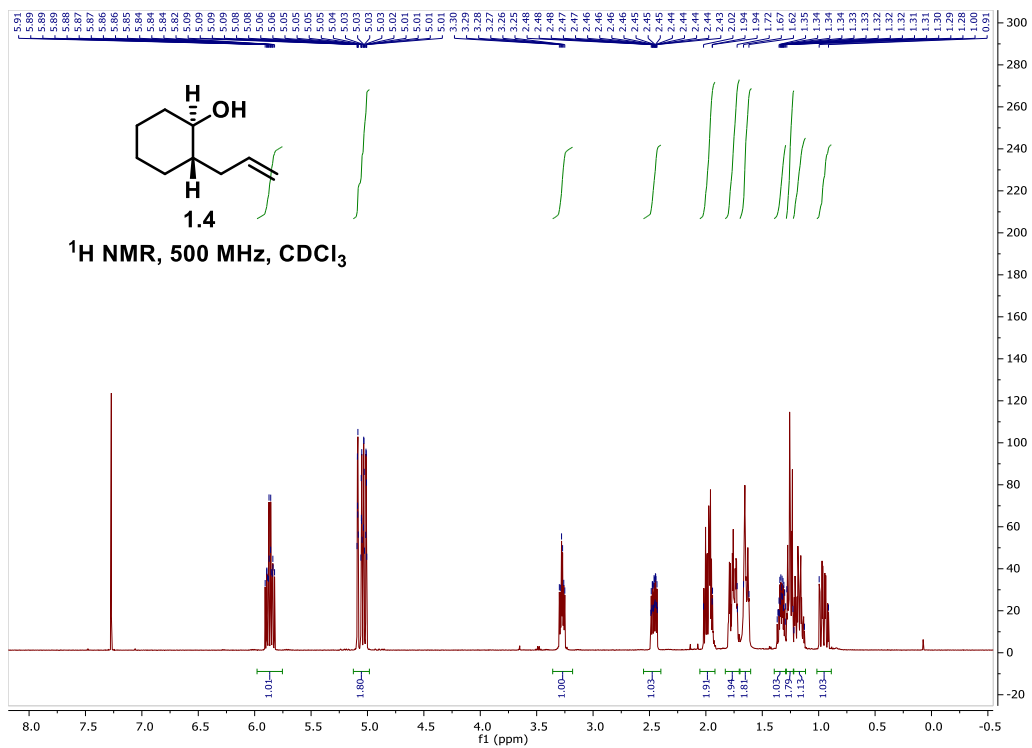
**N-Acetyl-N-3 $\alpha$ -(3,5-Bis(trifluoromethyl)benzyloxy)octahydro-2H-chromen-2-yl)-2 $\beta$ -chlorobenzamide (3.5( $\beta$ -amide)):** To a solution of  $\alpha/\beta$ -**3.5(SPh)** (0.06 g, 0.121 mmol) in dry  $\text{CH}_3\text{CN}$  (2 mL) with 4Å MS and 2-chlorobenzoic acid (0.020 g, 0.133 mmol) under argon at -40 °C was rapidly added NIS (0.072 g, 0.320 mmol) as a powder. The mixture was allowed to reach room temperature and stirred for 4 h, quenched with saturated  $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$  and diluted with  $\text{CH}_2\text{Cl}_2$ . Organic phase was separated, and the aqueous portion extracted with  $\text{CH}_2\text{Cl}_2$  (2 $\times$ ). Combined organic phases were dried with  $\text{MgSO}_4$ , filtered and condensed *in vacuo*. Compound **3.5( $\beta$ -amide)** was obtained after silica gel column chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes, TLC stained with CAM) as yellowish thick oil (0.015 g, 21%).  $^{19}\text{F}$  NMR showed only one fluorinated compound. The nature of the anomer was confirmed by 1D NOESY where a positive coupling between  $\text{H}_1$  and  $\text{H}_5$  was observed.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (s, 1H), 7.73 (d,  $J = 1.7$  Hz, 2H), 7.43 – 7.32 (m, 3H), 7.17 (td,  $J = 7.5, 1.3$  Hz, 1H), 5.93 (d,  $J = 6.7$  Hz, 1H), 4.70, 4.63 (ABq,  $J_{AB} = 12.1$  Hz, 2H), 4.04 (dtd,  $J = 10.3, 6.8, 3.2$  Hz, 1H), 3.85 (td,  $J = 10.5, 4.2$  Hz, 1H), 2.19 (s, 3H),

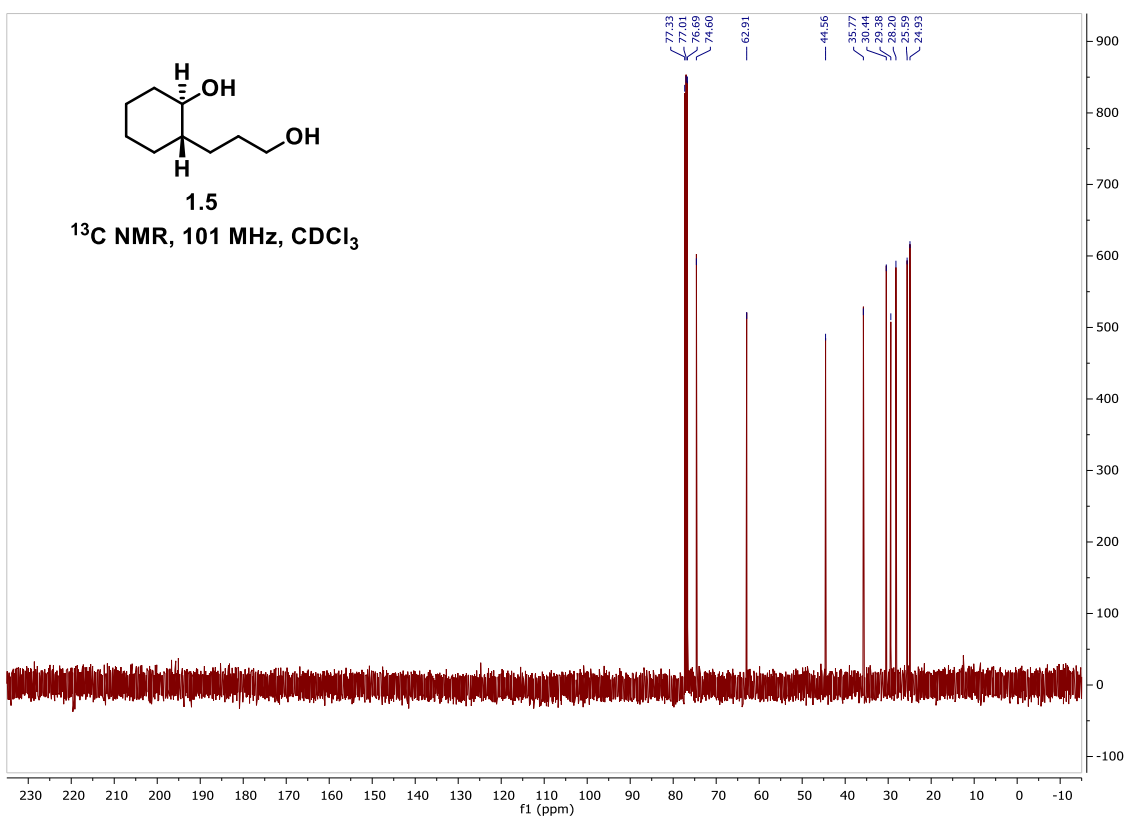
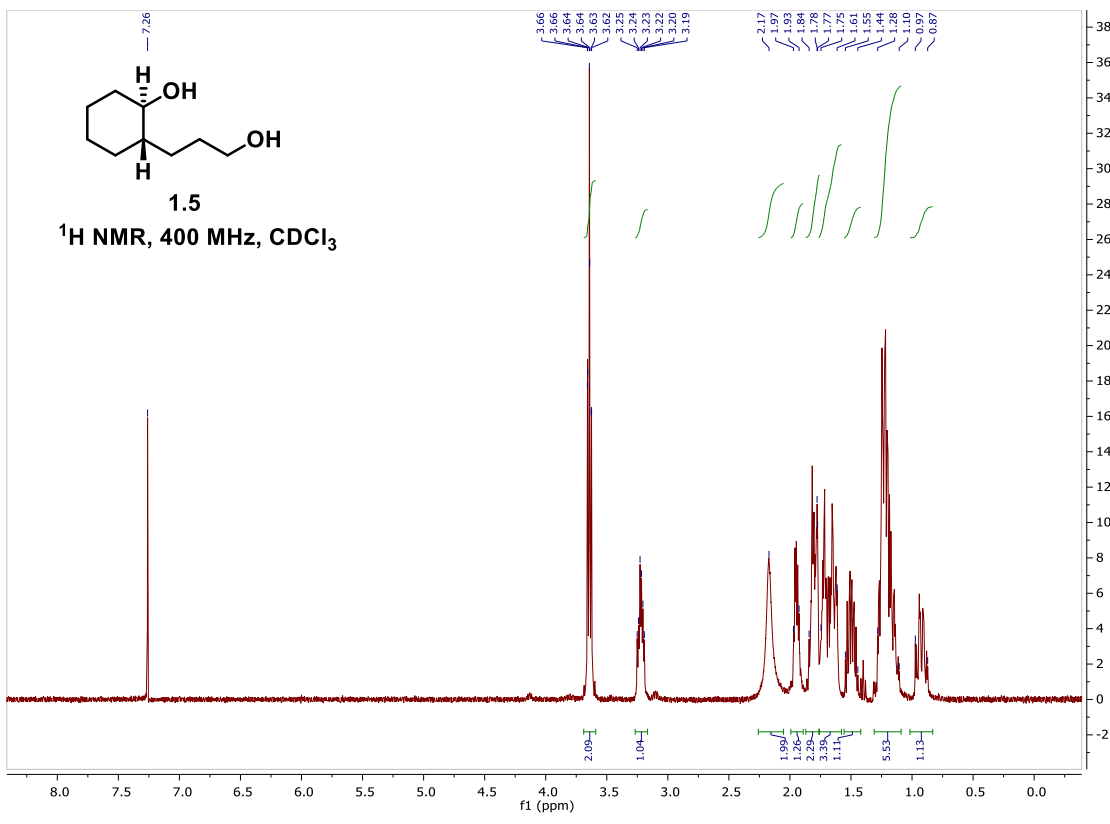
2.02 – 1.91 (m, 2H), 1.90 – 1.75 (m, 3H), 1.75 – 1.65 (m, 2H), 1.42 – 1.12 (m, 4H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.86 (s, 6F);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  176.0, 172.2, 140.3, 135.6, 131.9, 131.6, 131.5, 131.45, 130.3, 129.7, 127.6 – 127.3 (m), 126.7, 121.8 – 121.5 (m), 81.7, 74.7, 74.4, 69.5, 39.5, 32.3, 31.7, 31.2, 26.7, 25.5, 24.7; IR (NaCl)  $\nu_{\text{max}}$  2933, 2861, 1743, 1680, 1279, 1175, 1134  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) M/Z  $[\text{M}+\text{H}]^+$ : Calcd for  $\text{C}_{27}\text{H}_{27}\text{ClF}_6\text{NO}_4$  578.1527; Found 578.1514.

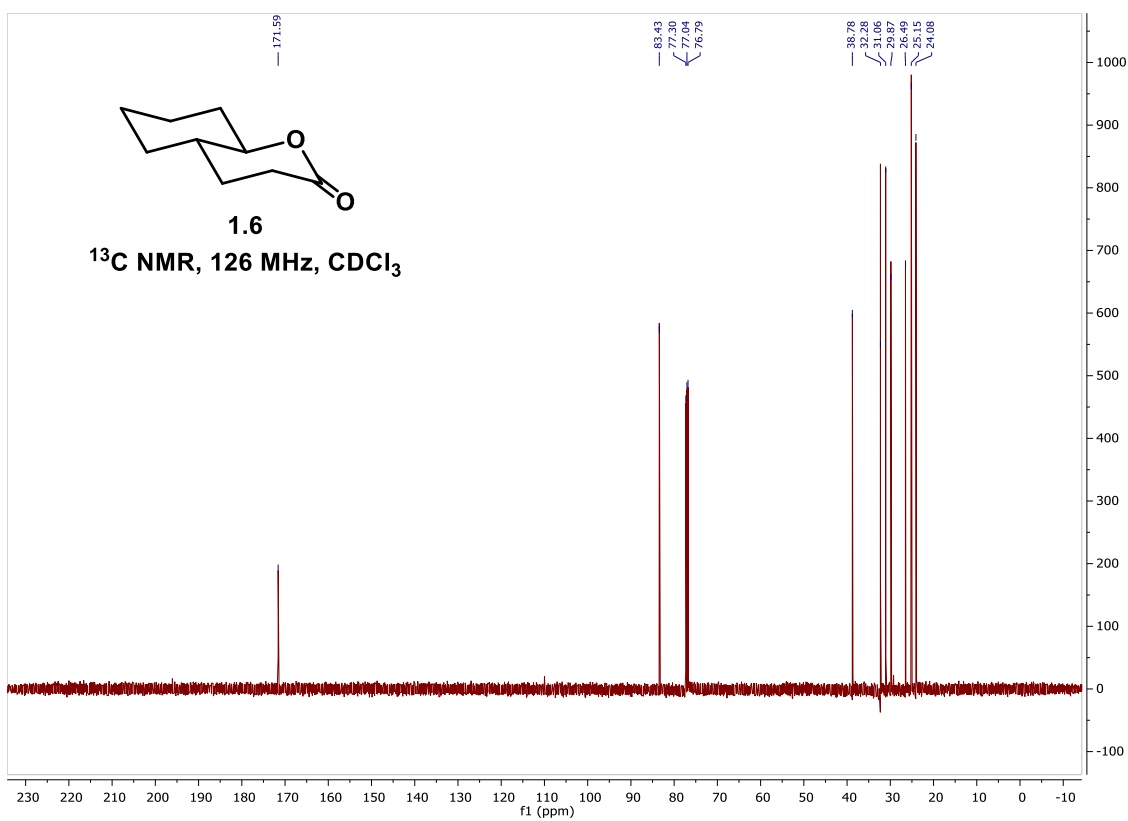
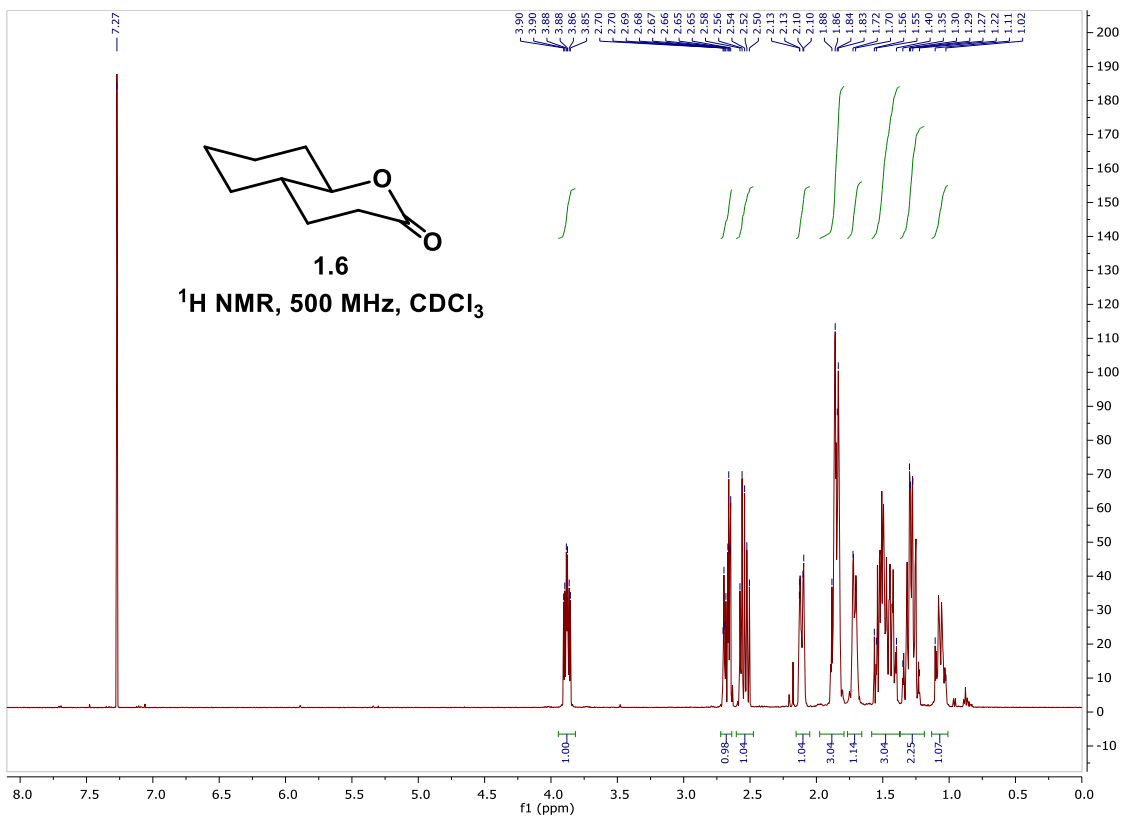
**S-Phenyl 2-O-benzyl-4,6-O-benzylidene-3-deoxy- $\beta$ -D-arabino-thiohexopyranoside (3.30):** Compound **3.30** was prepared using the method reported by Crich with similar results and spectral data.<sup>28</sup>

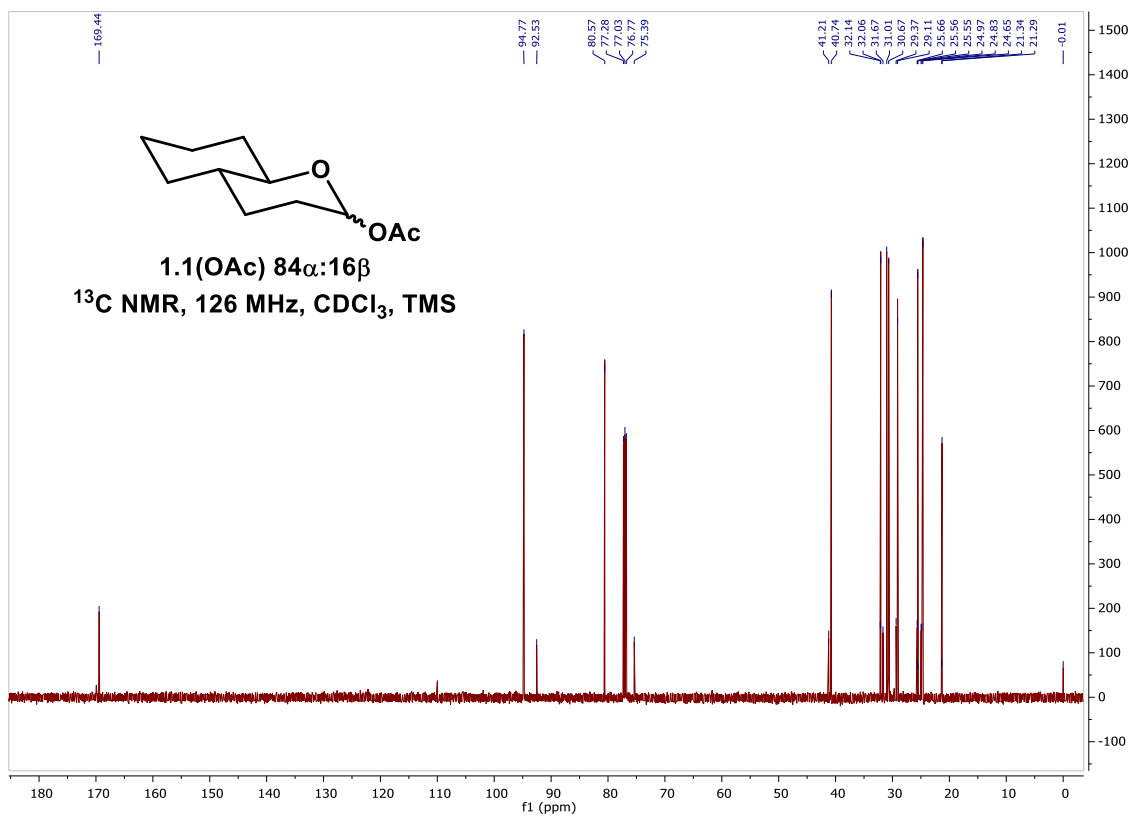
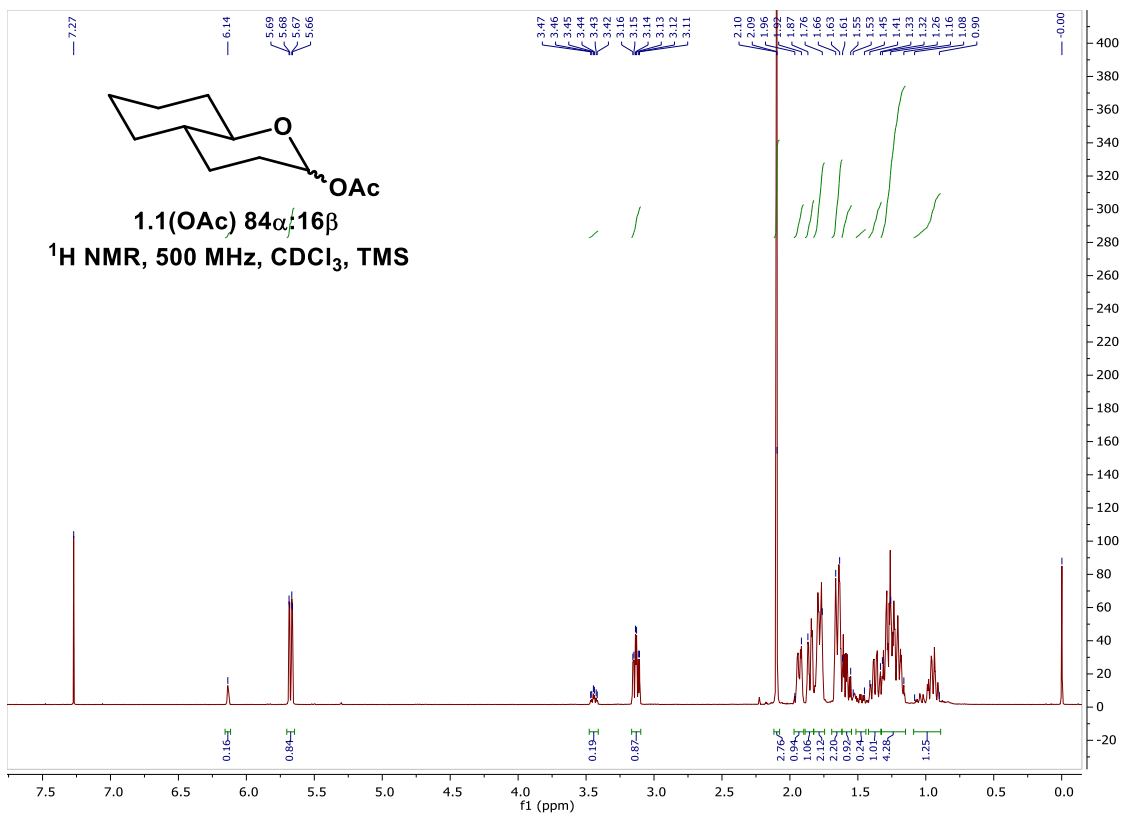
# Annexe E Données spectrales du chapitre 1

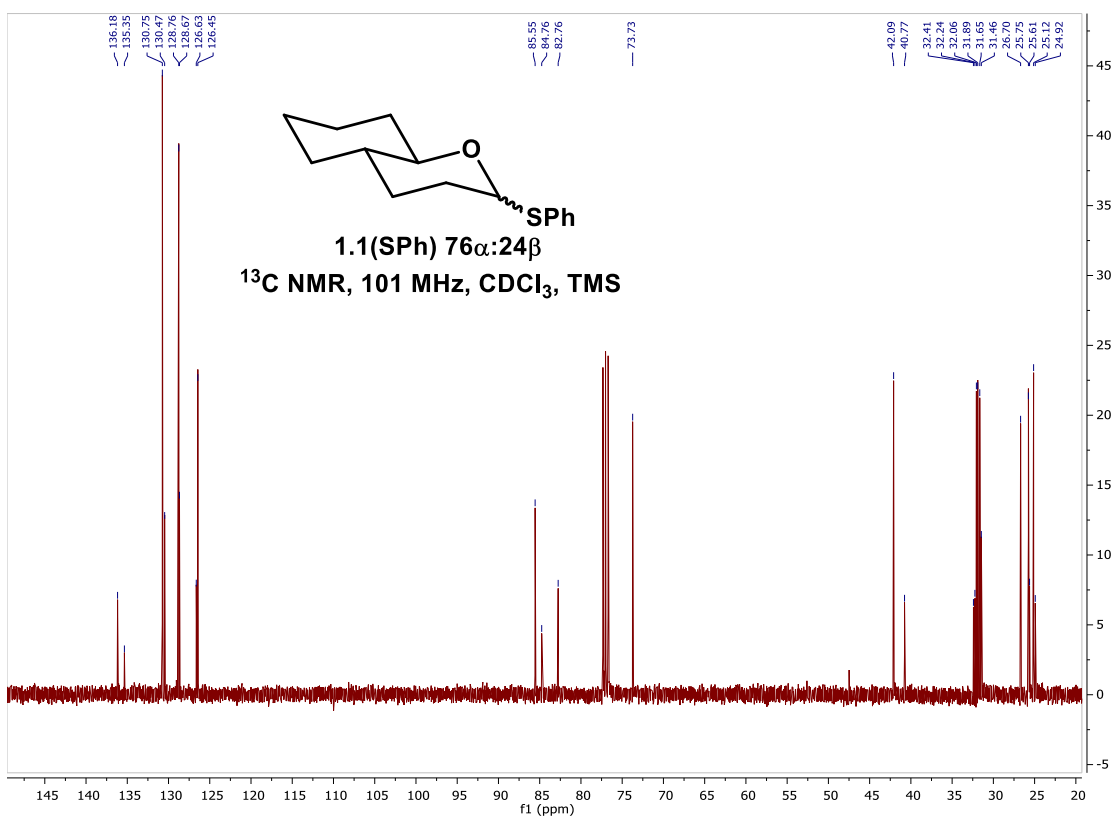
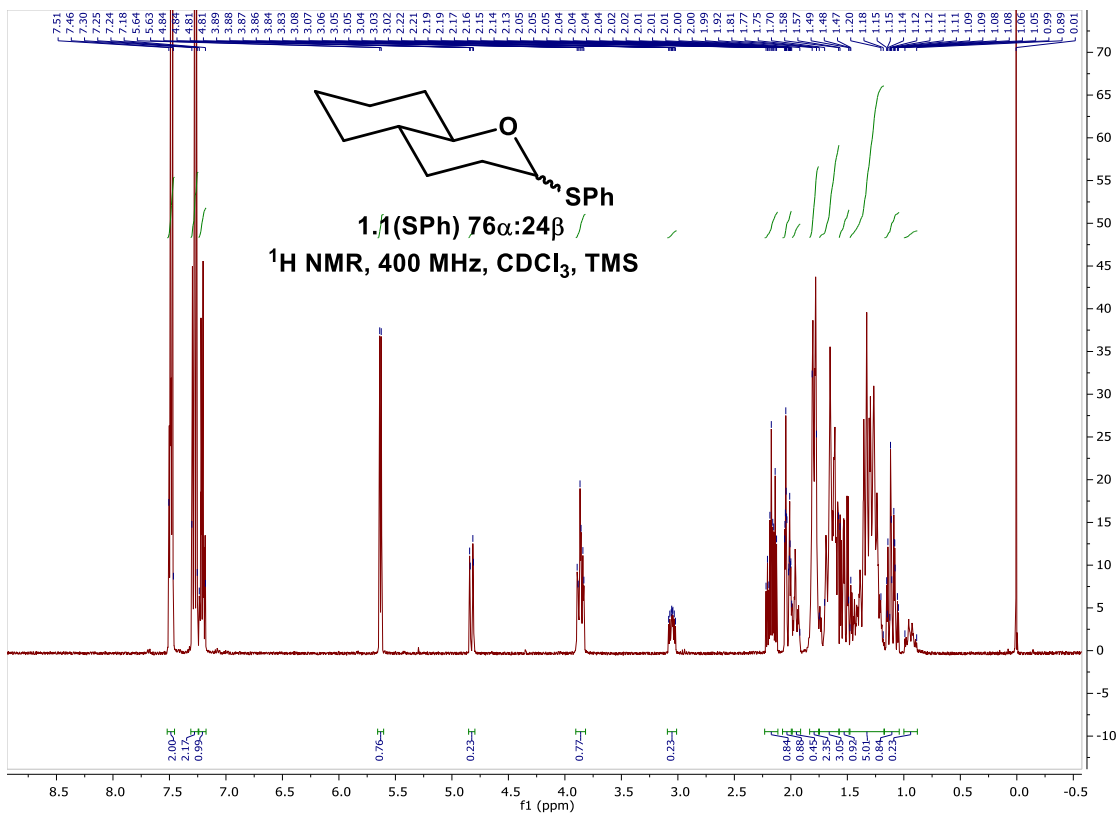
## E.1 Spectre RMN des composés caractérisés.



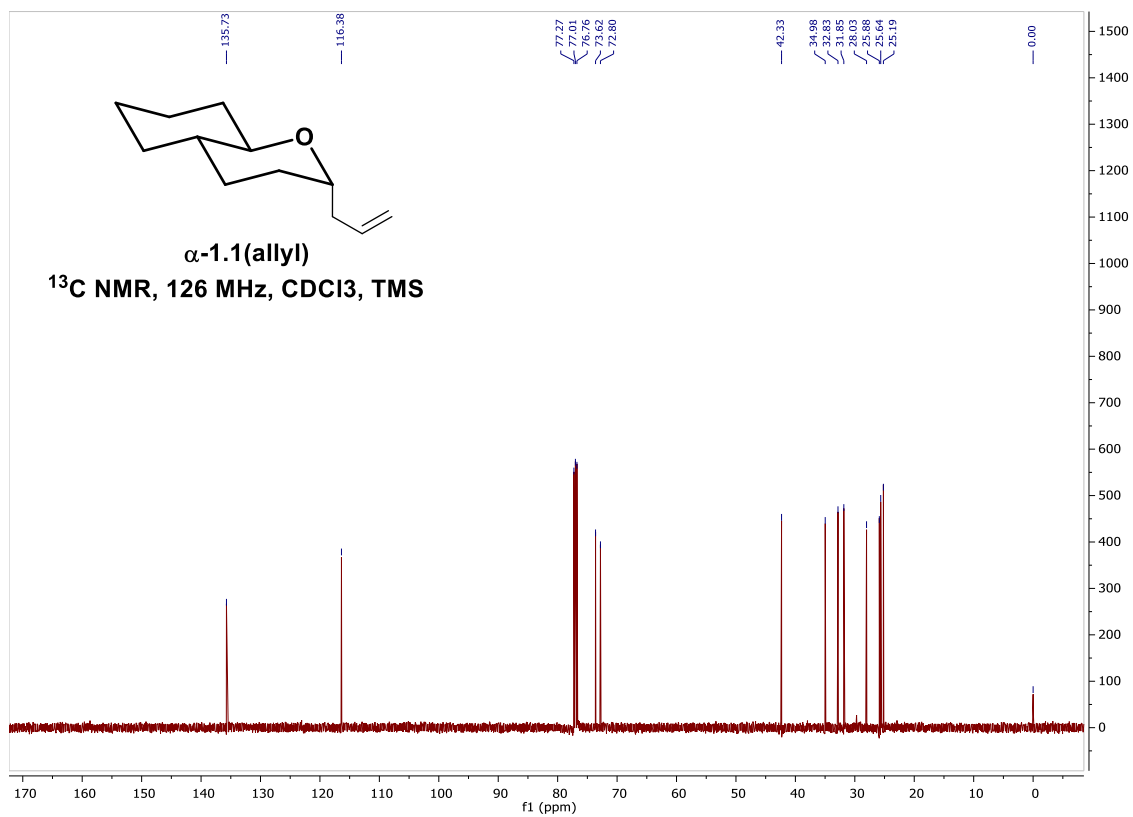
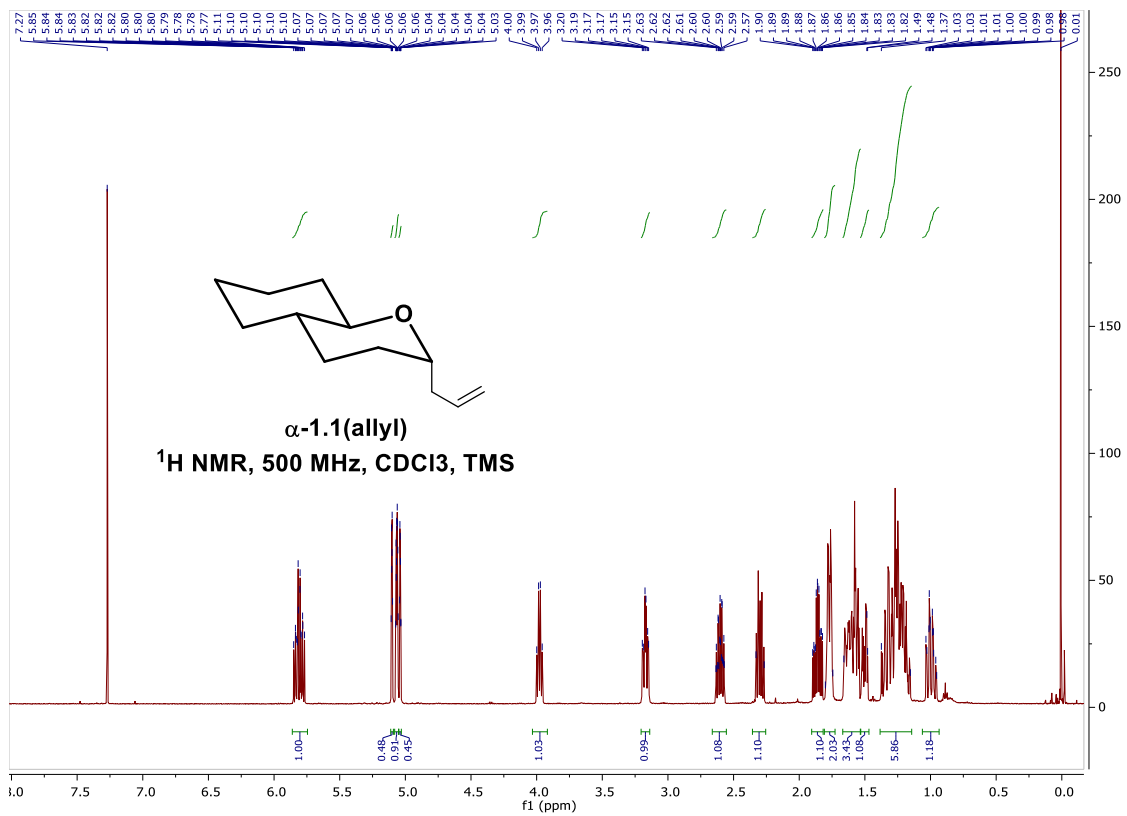


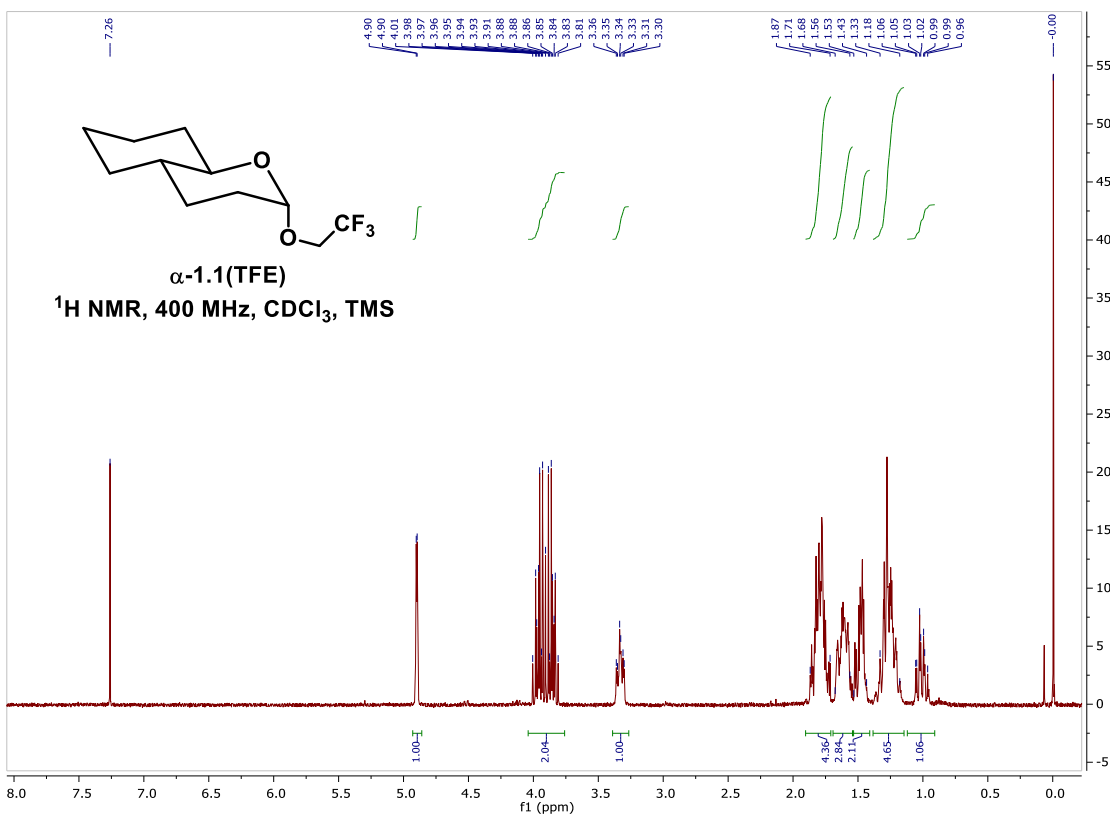
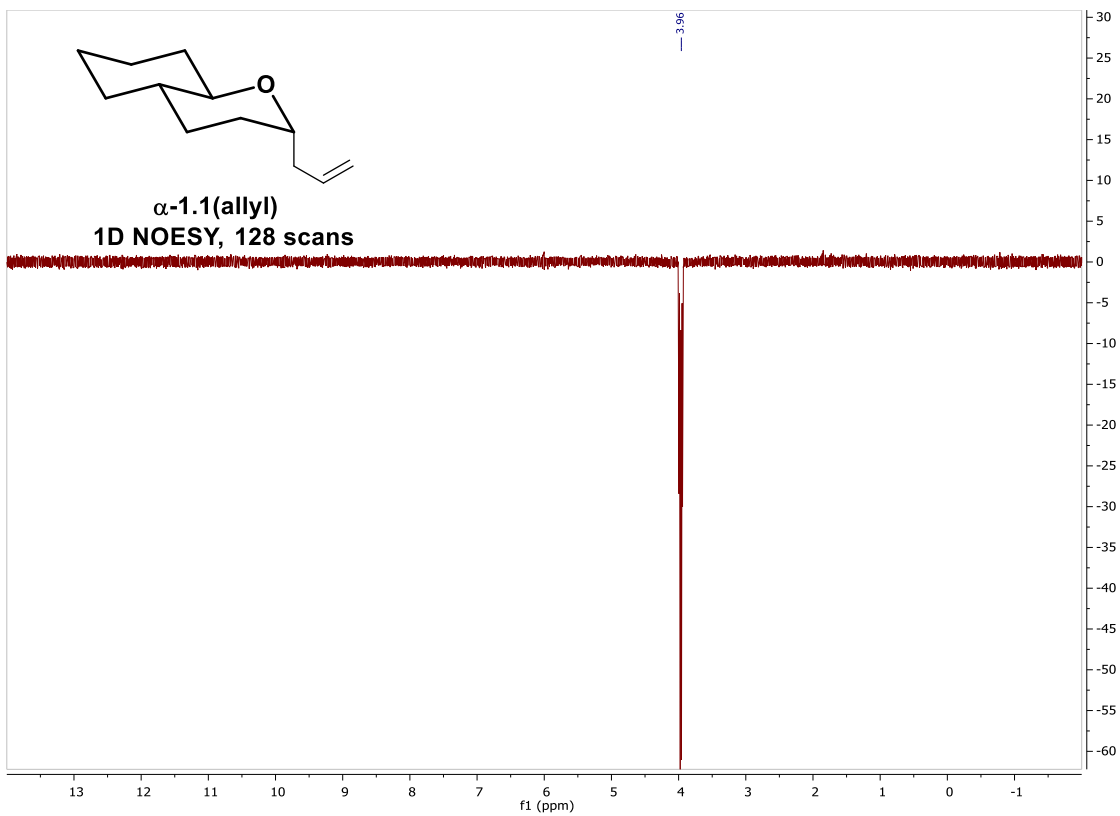


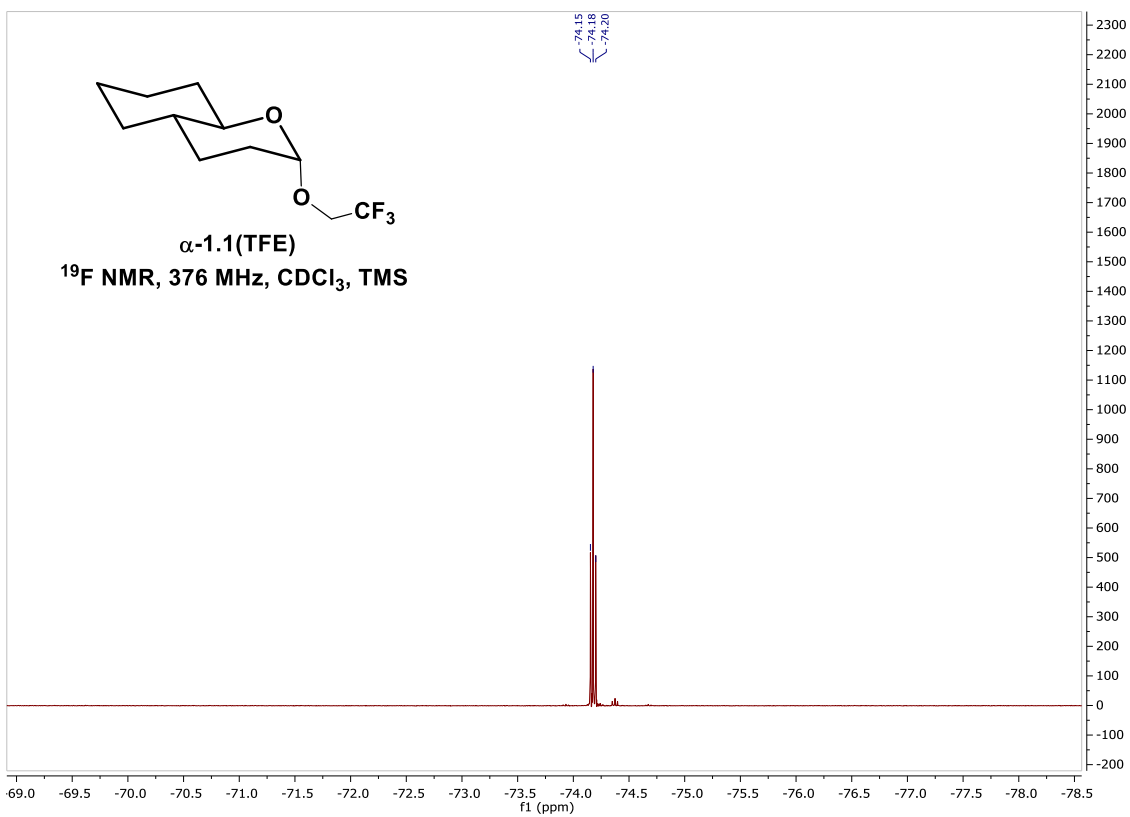
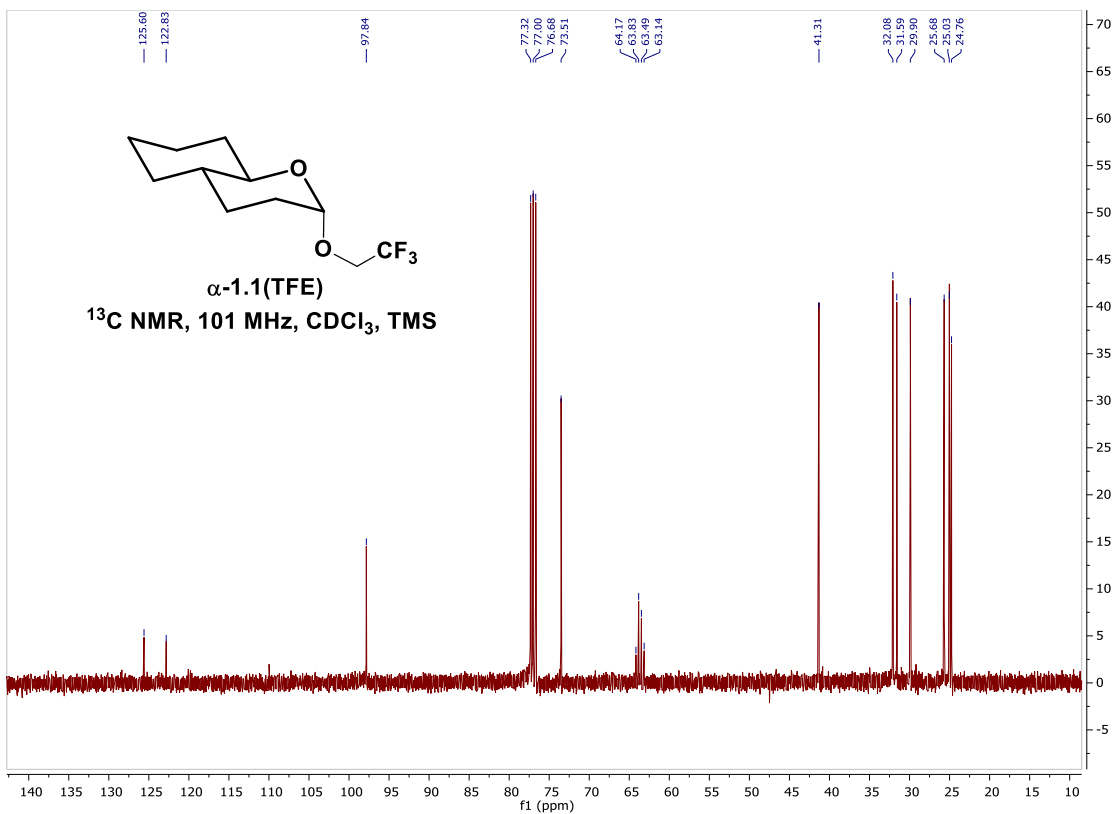


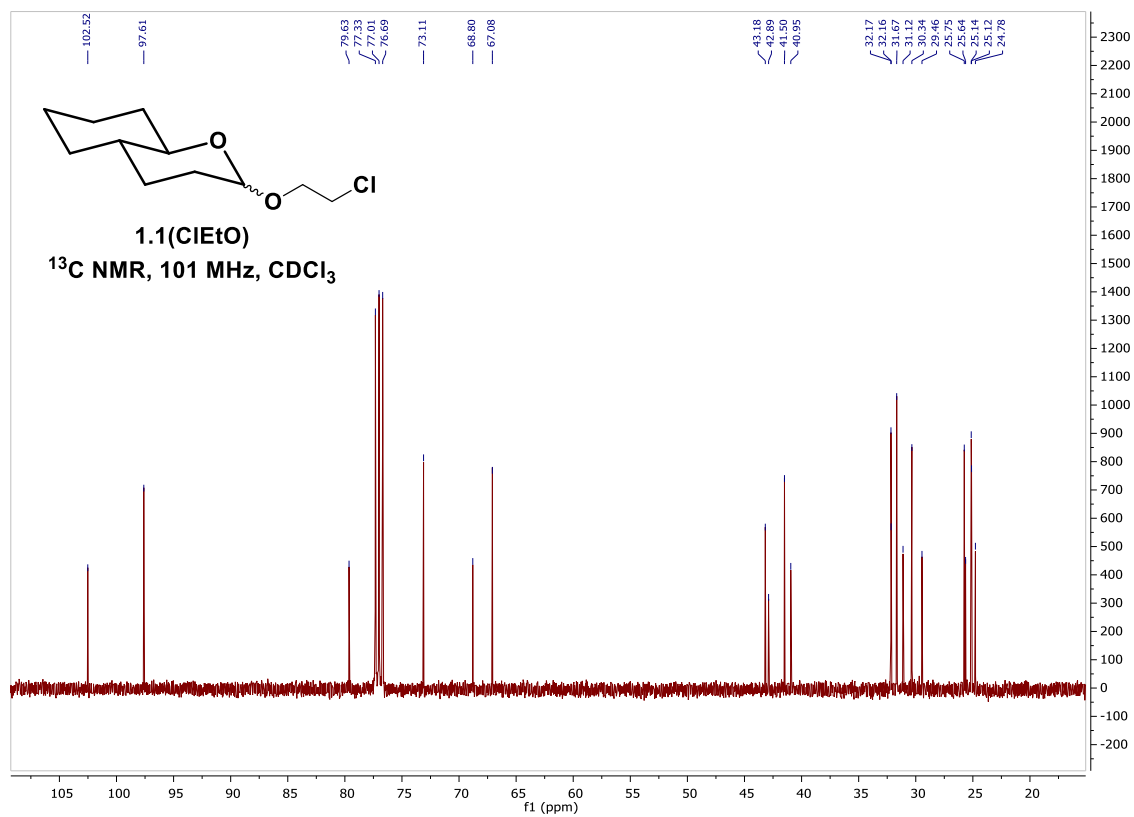
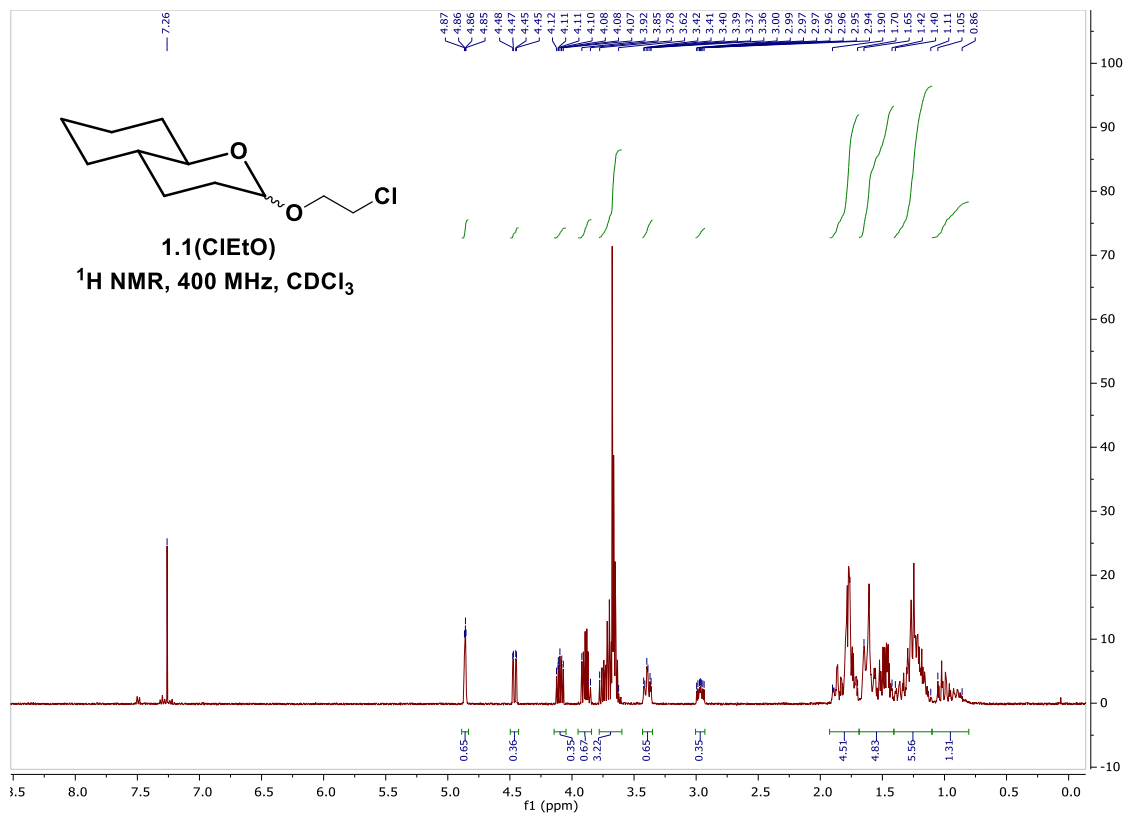


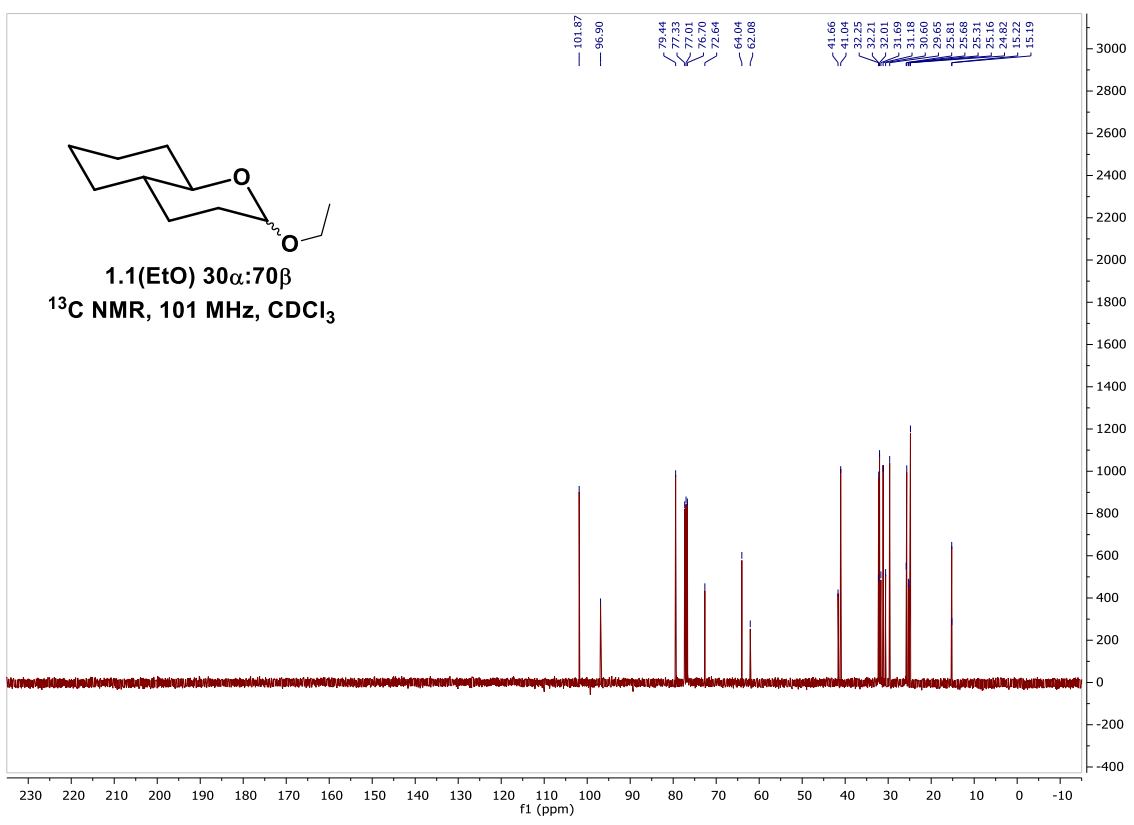
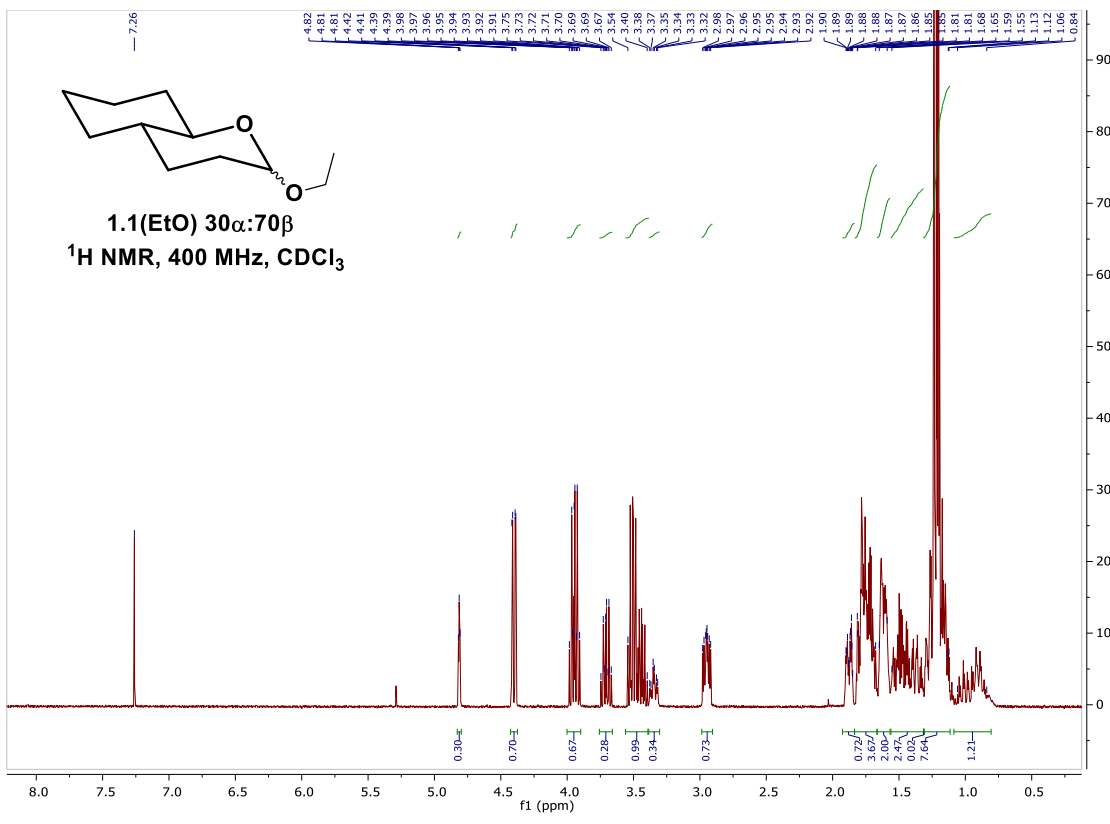


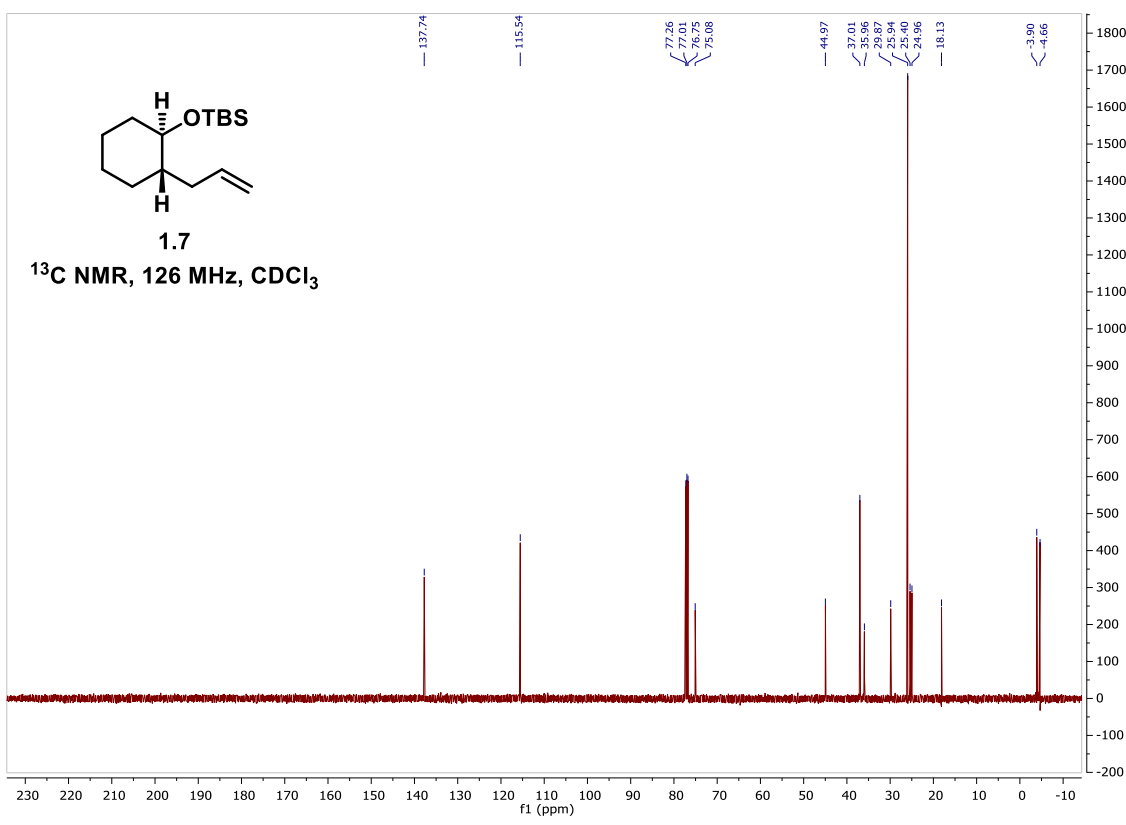
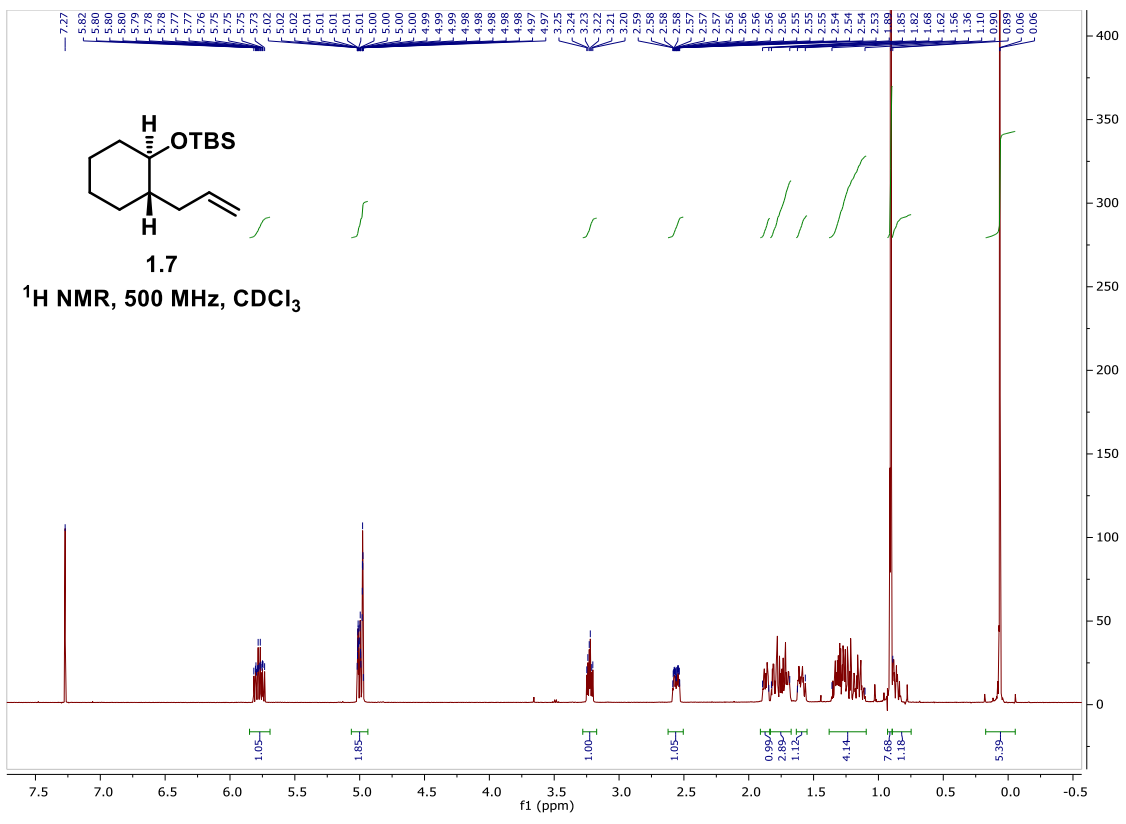


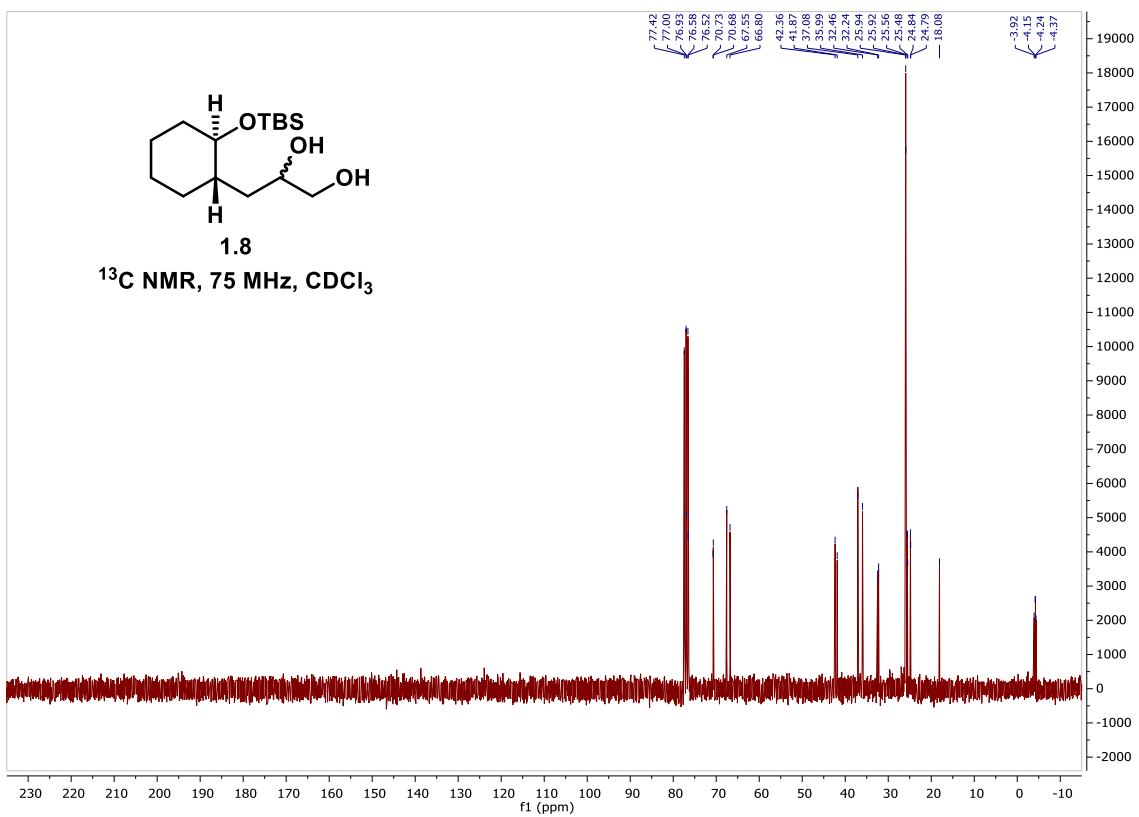
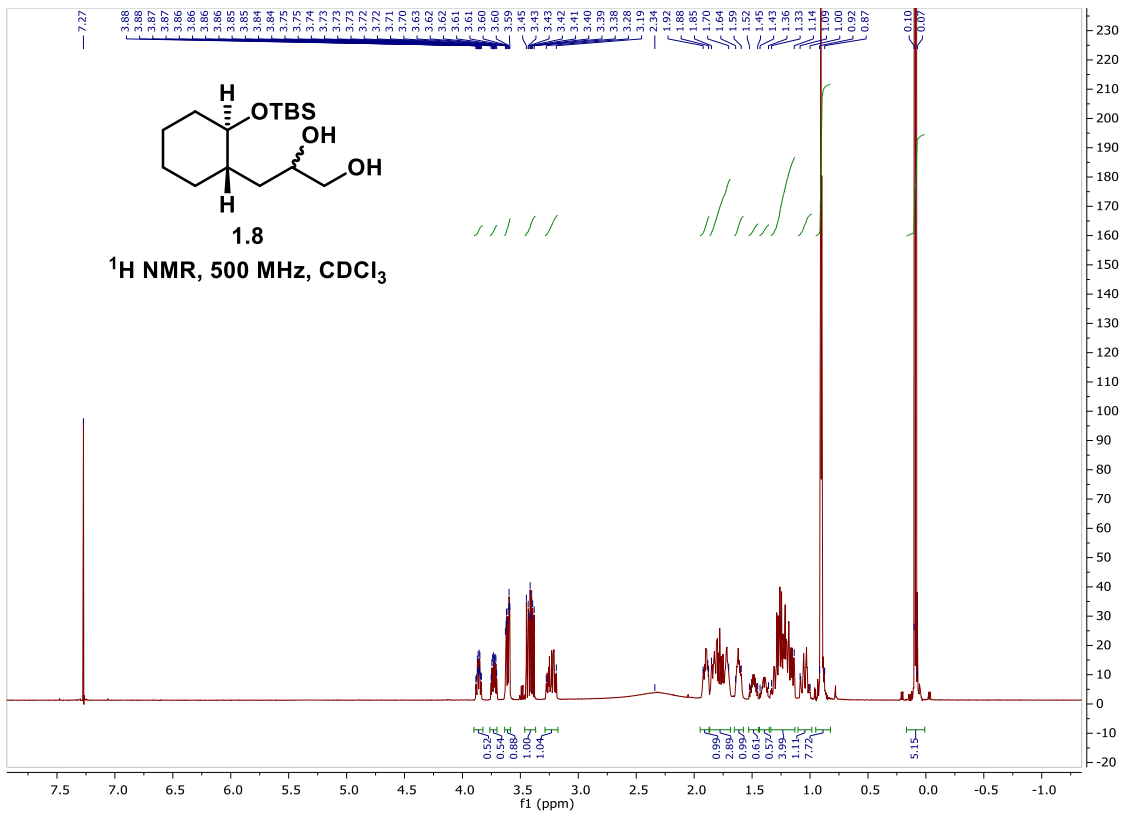


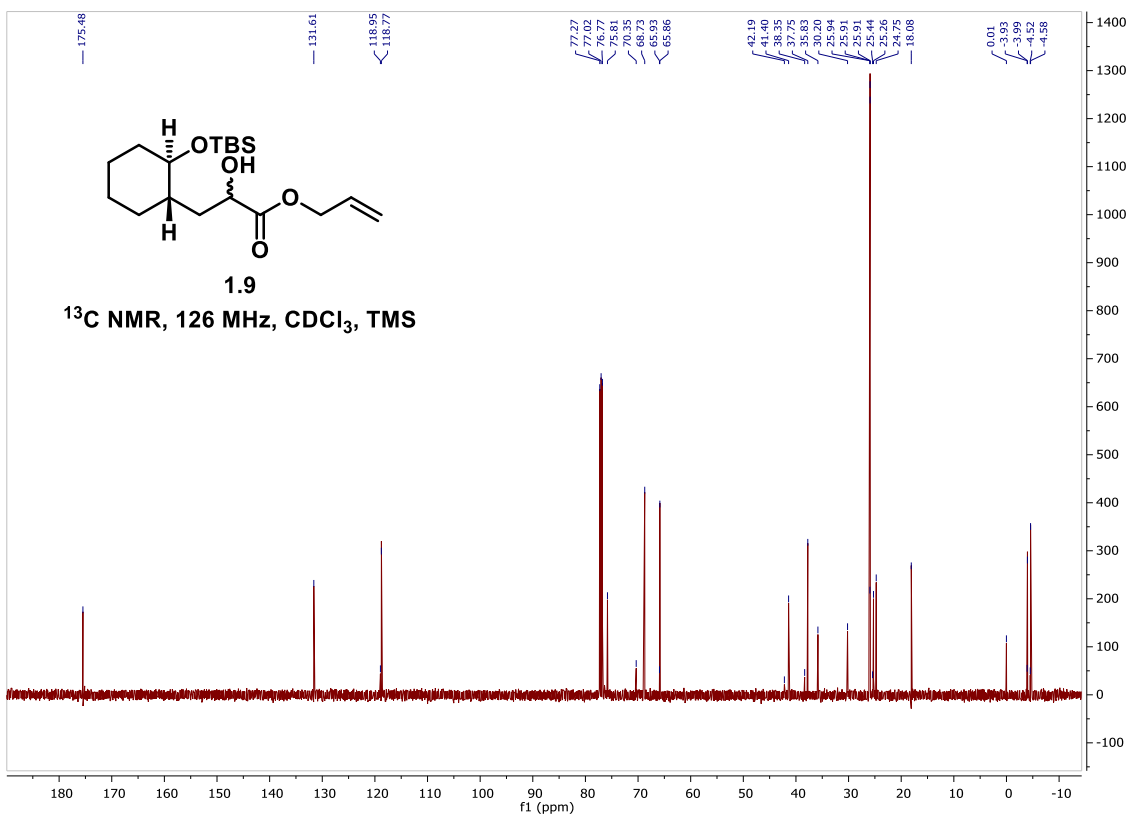
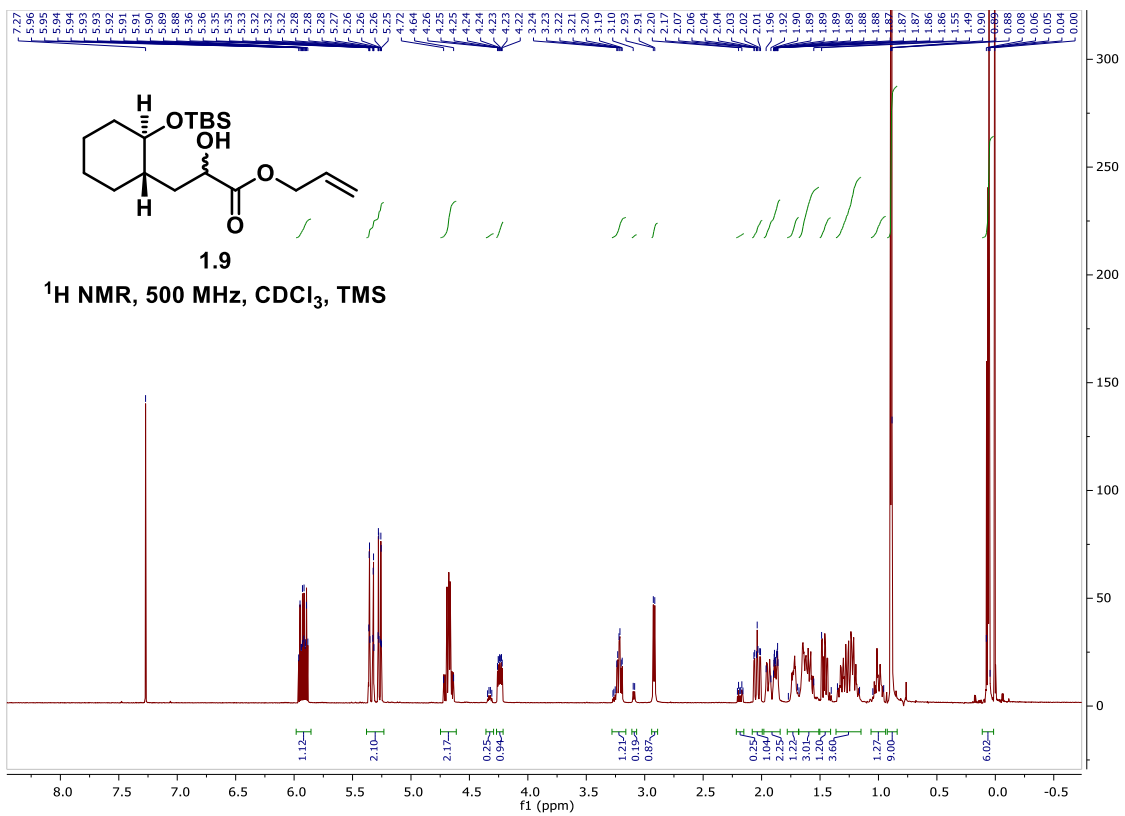




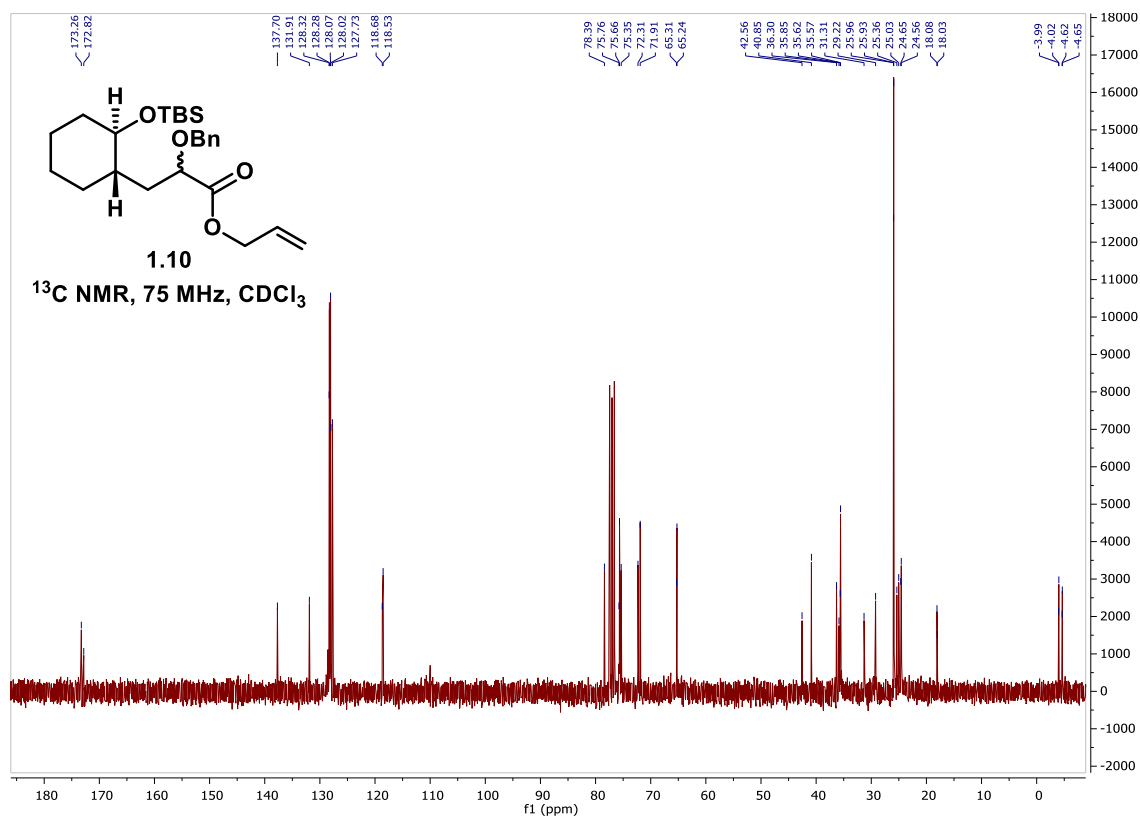
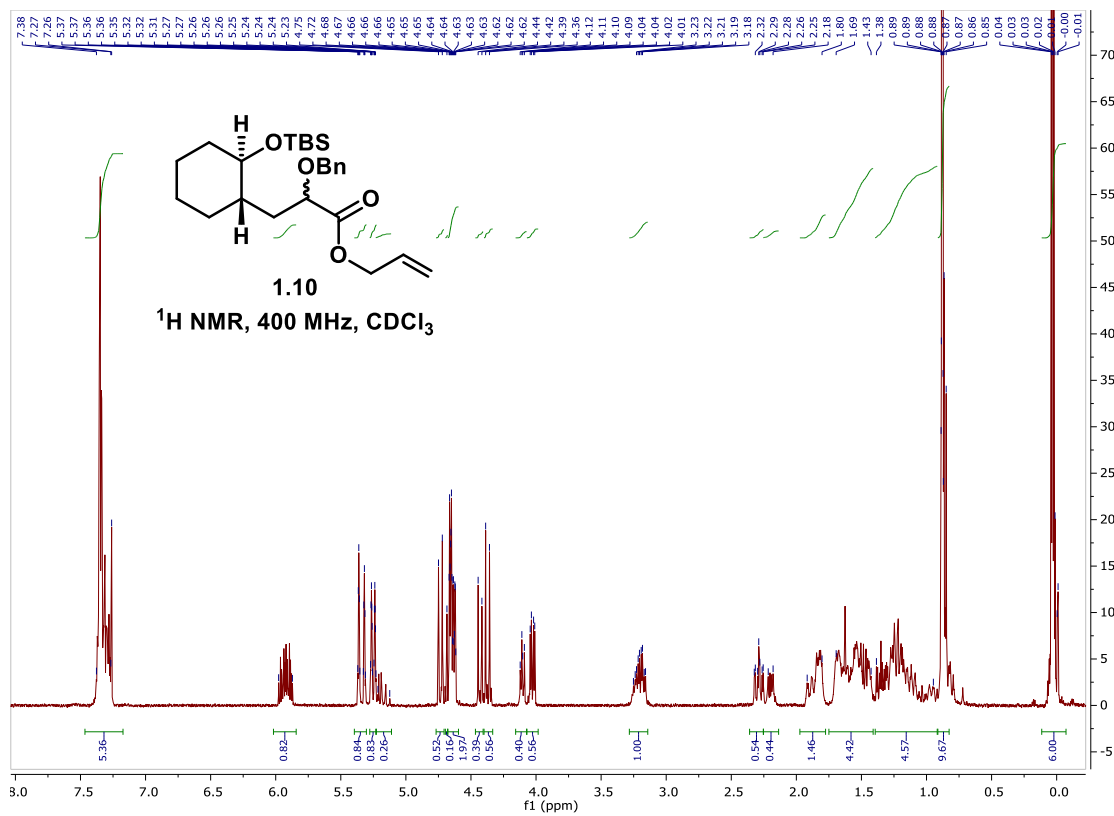


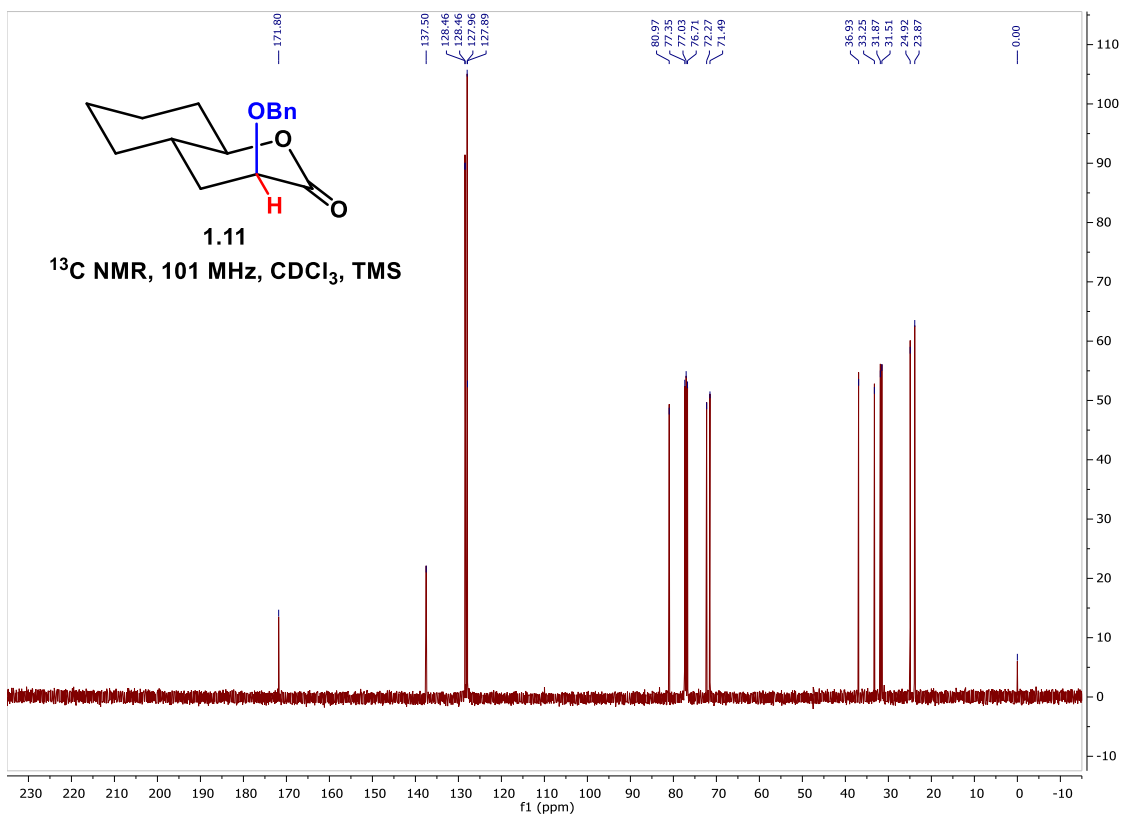
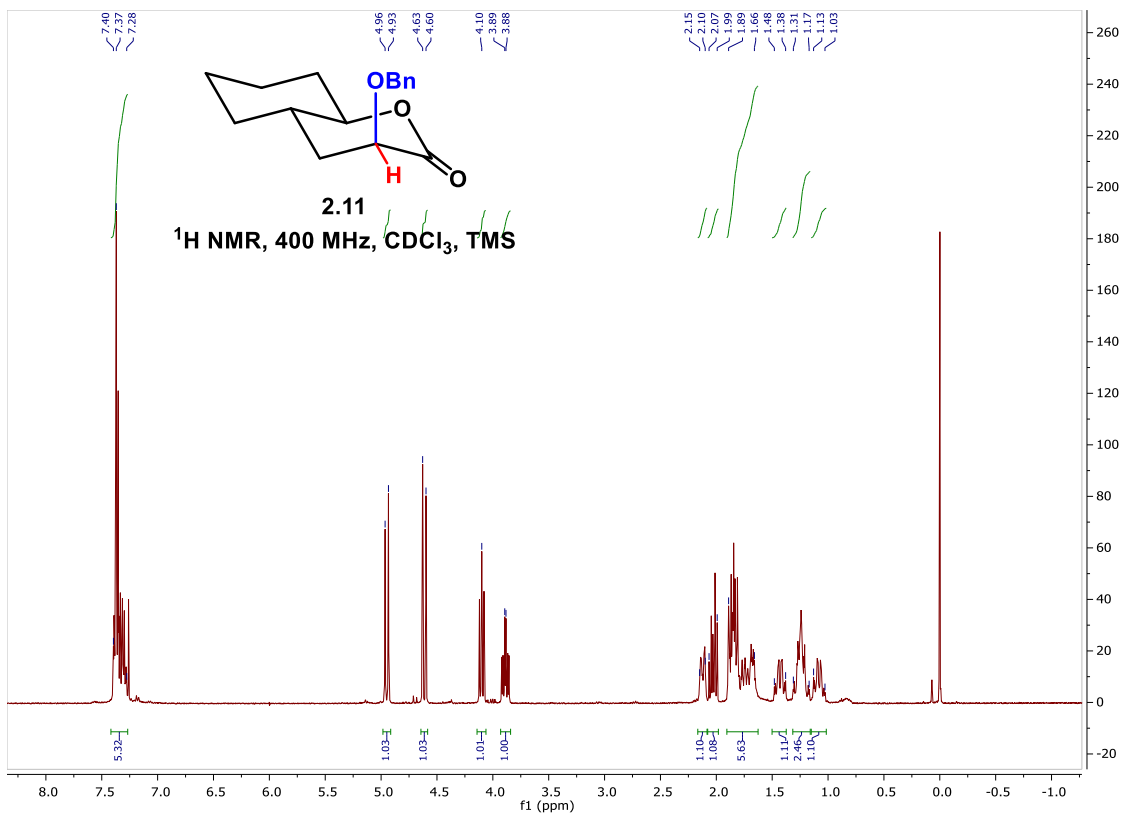


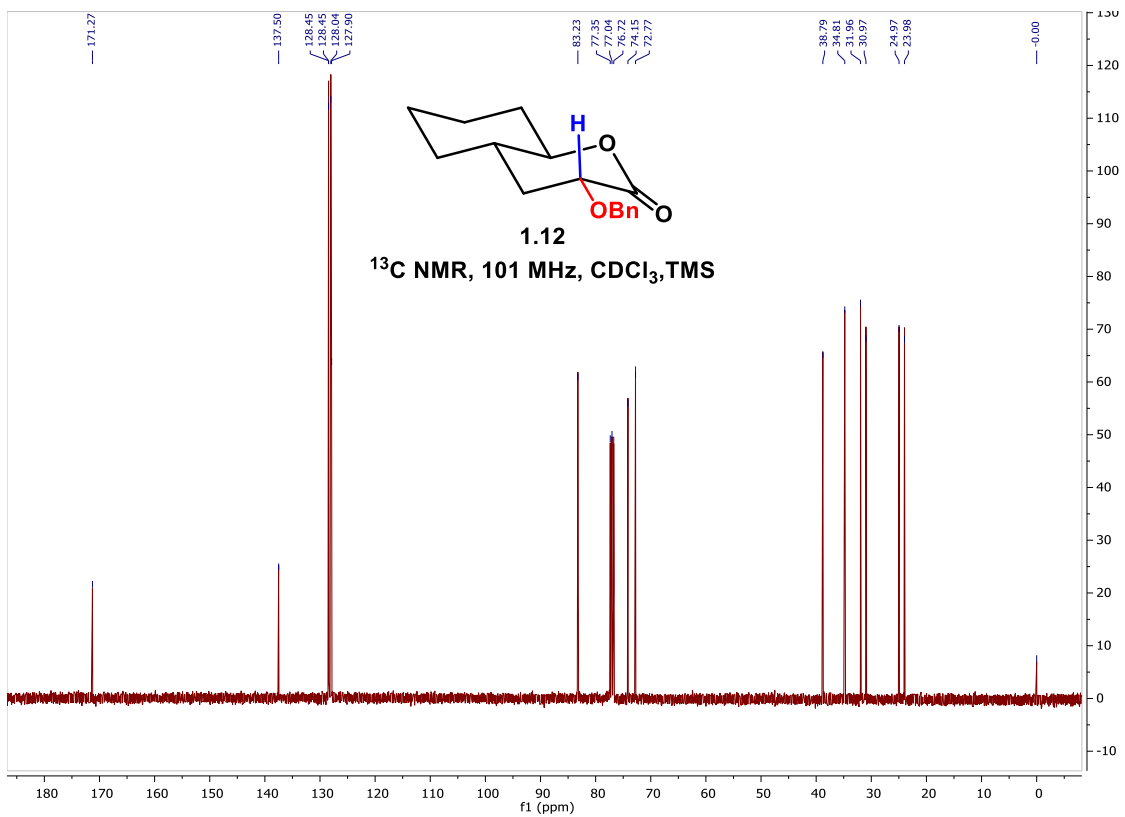
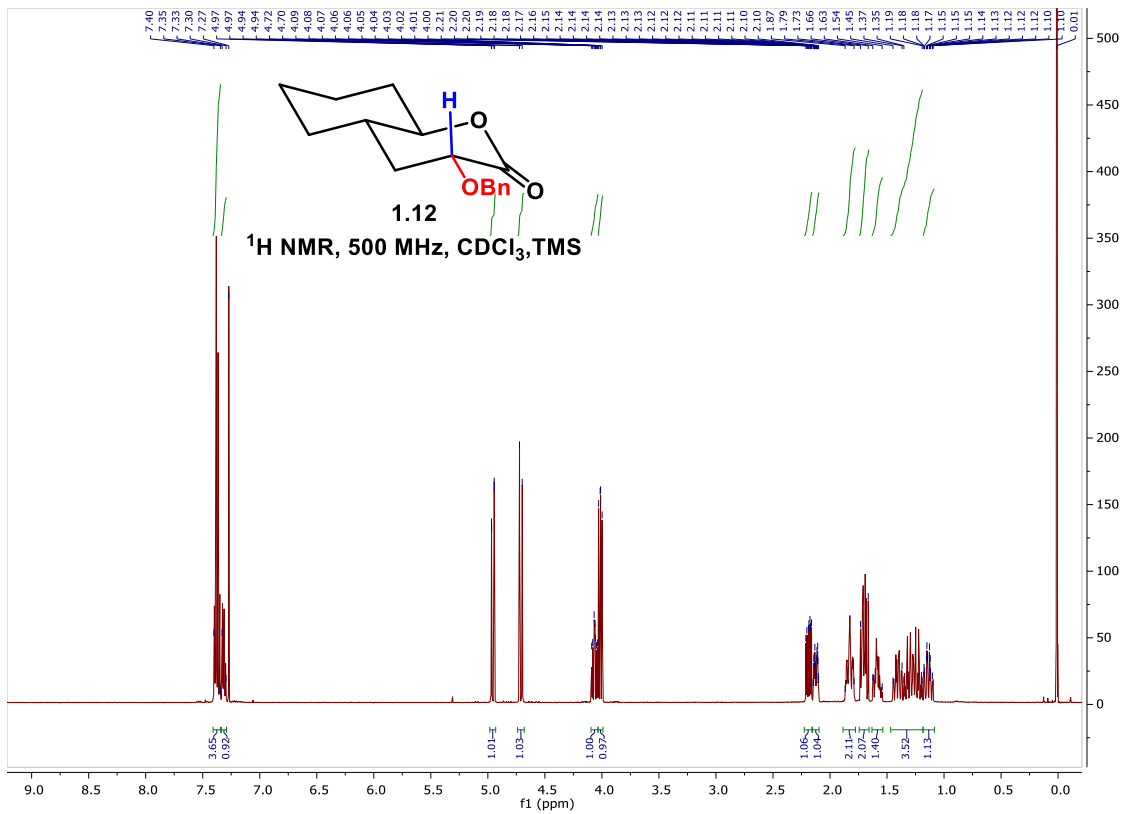


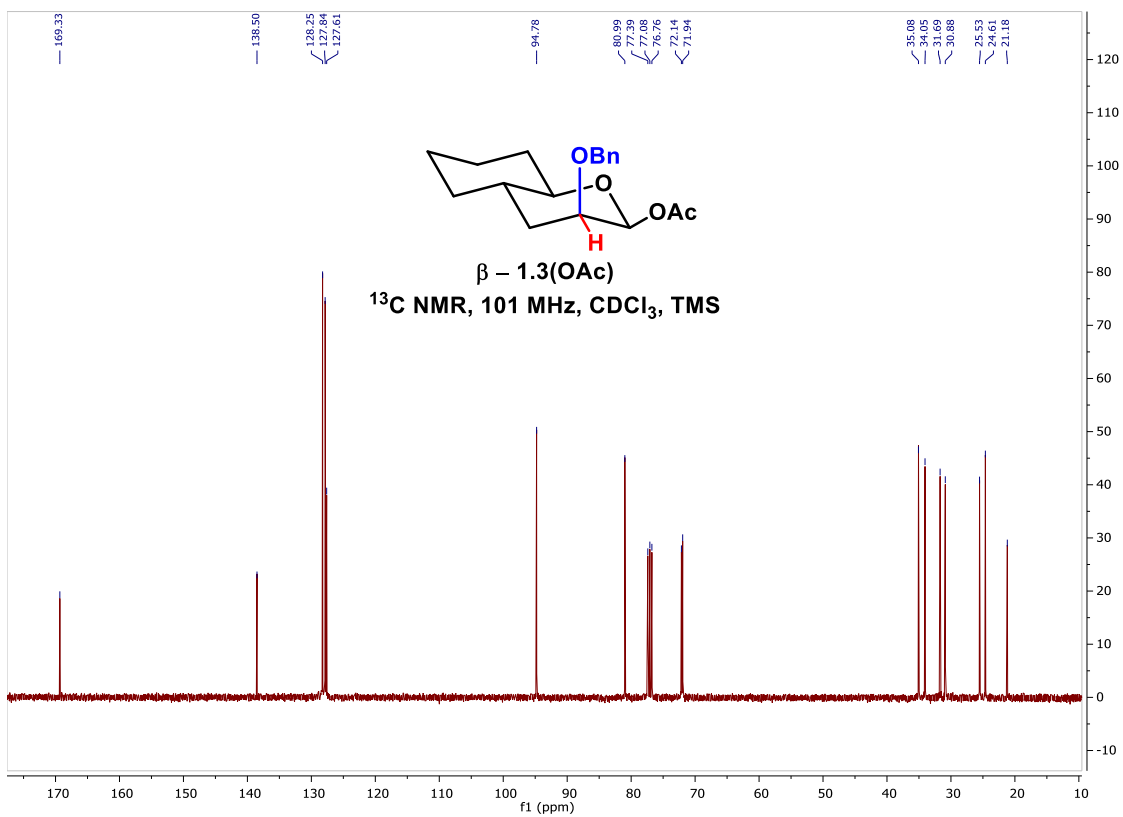
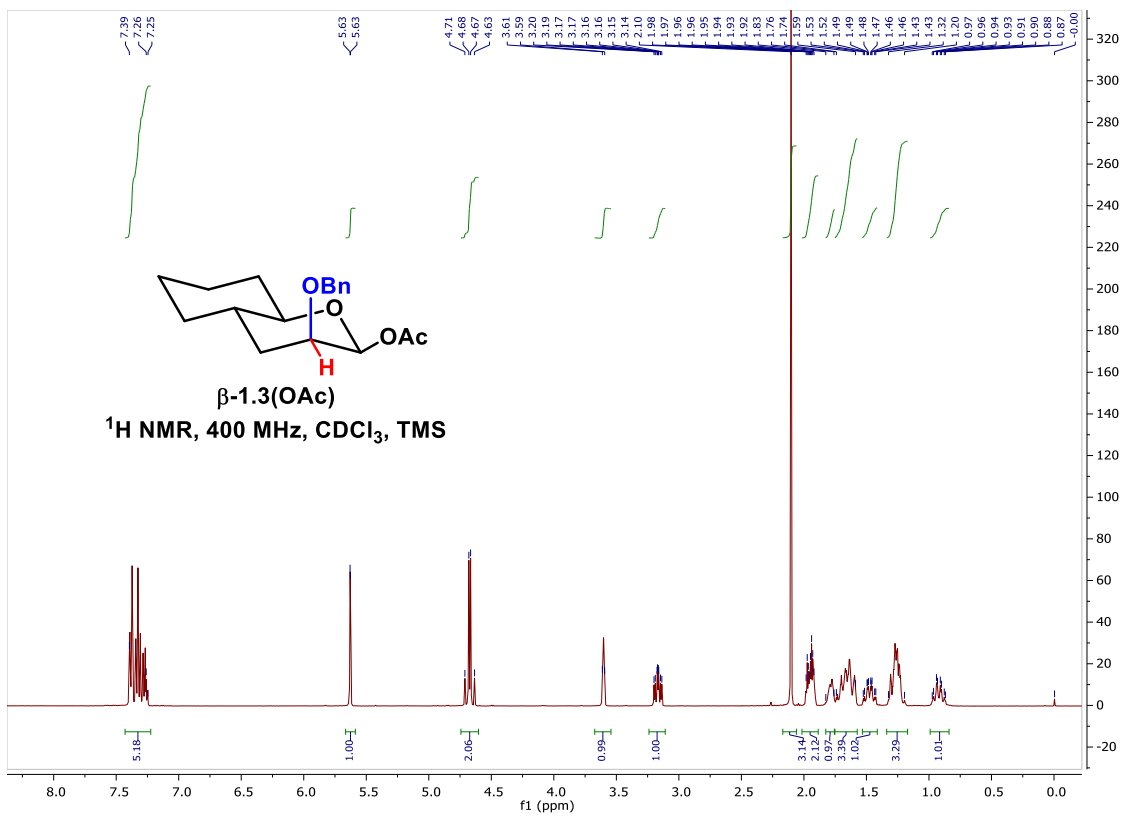


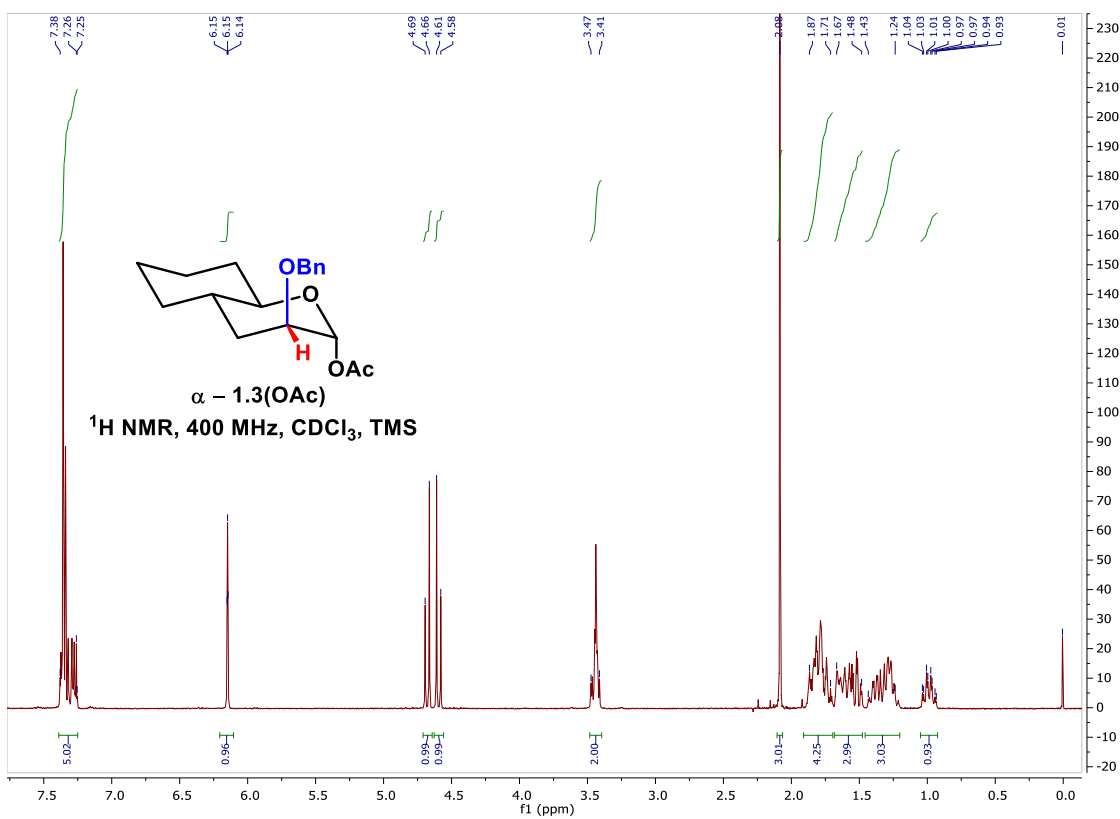
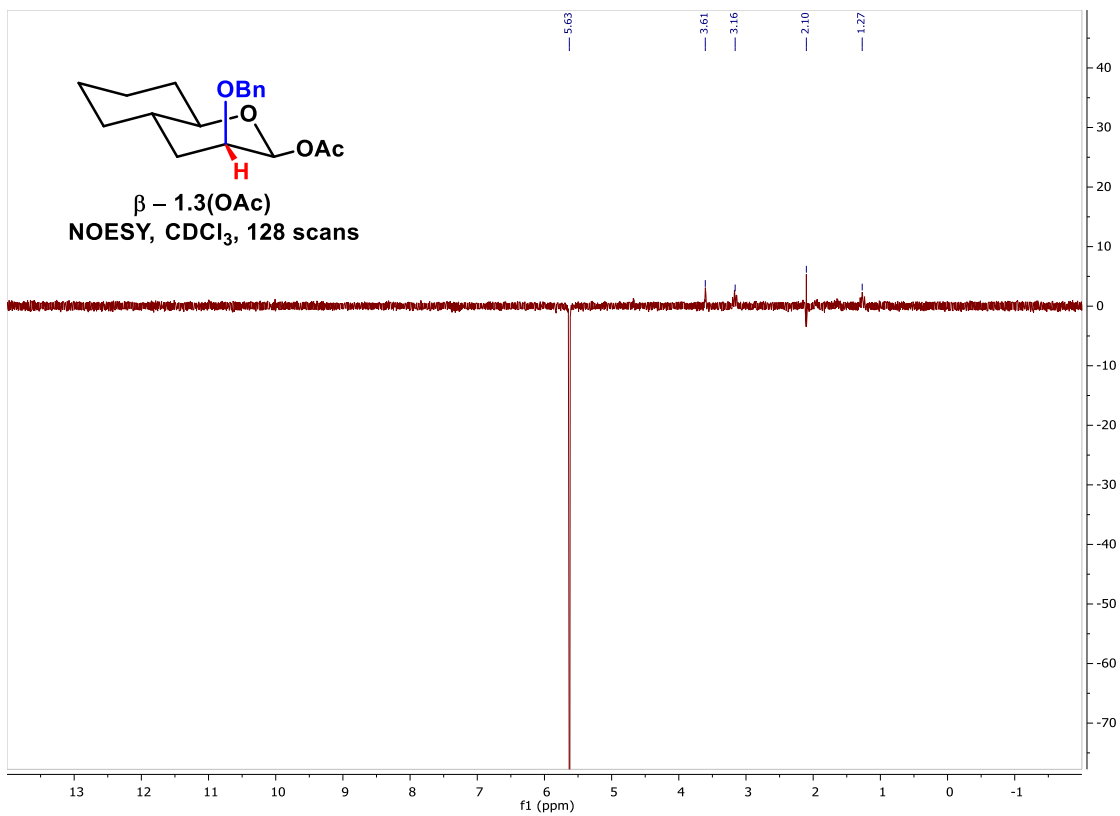


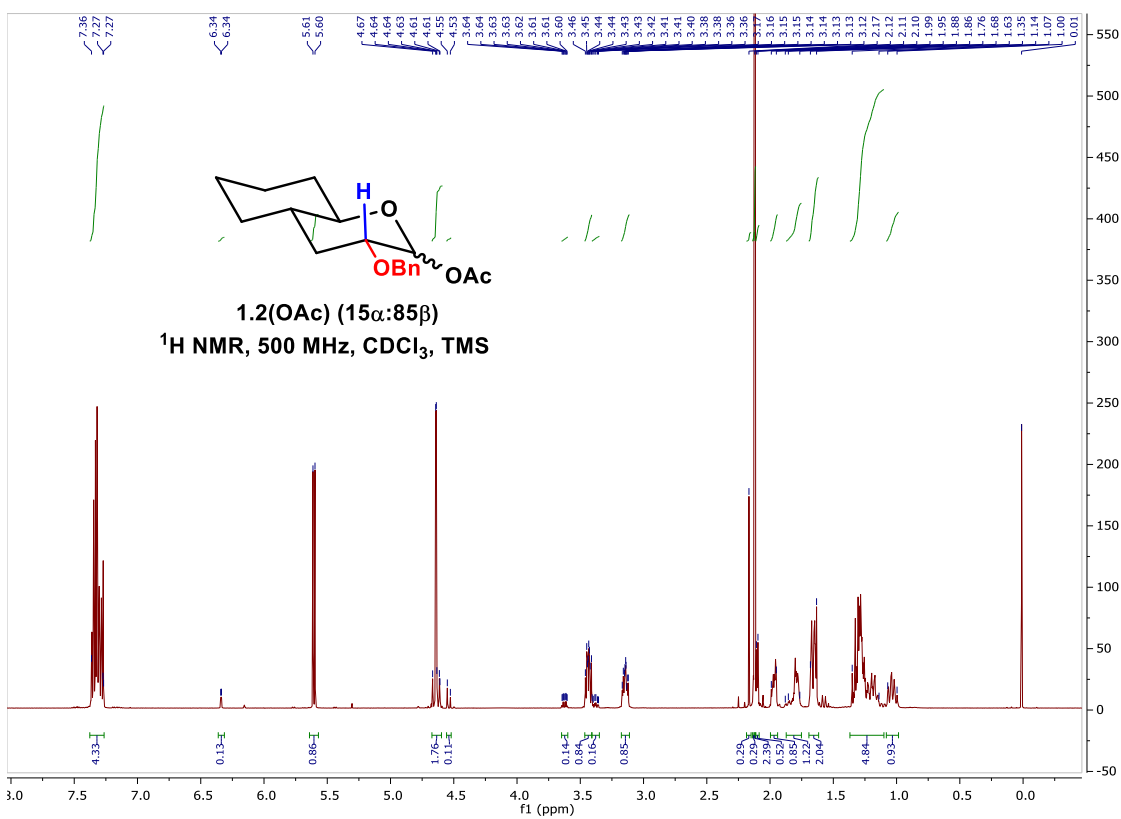
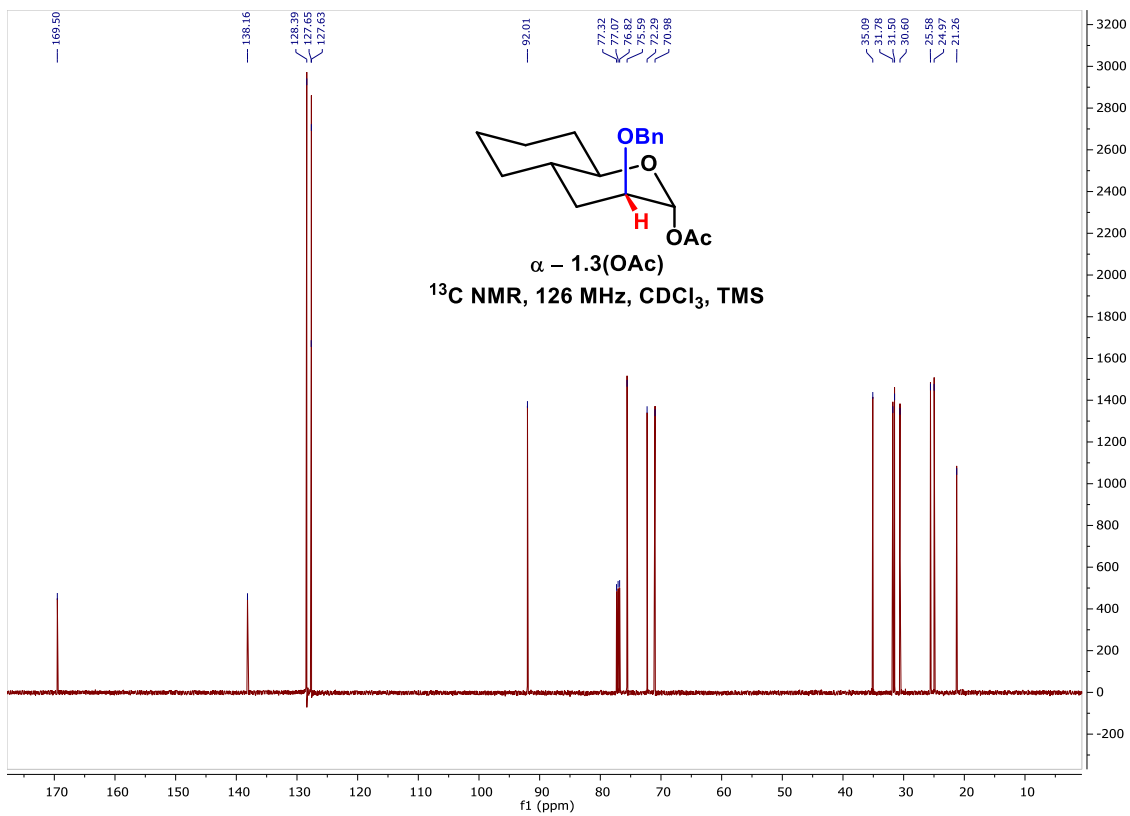


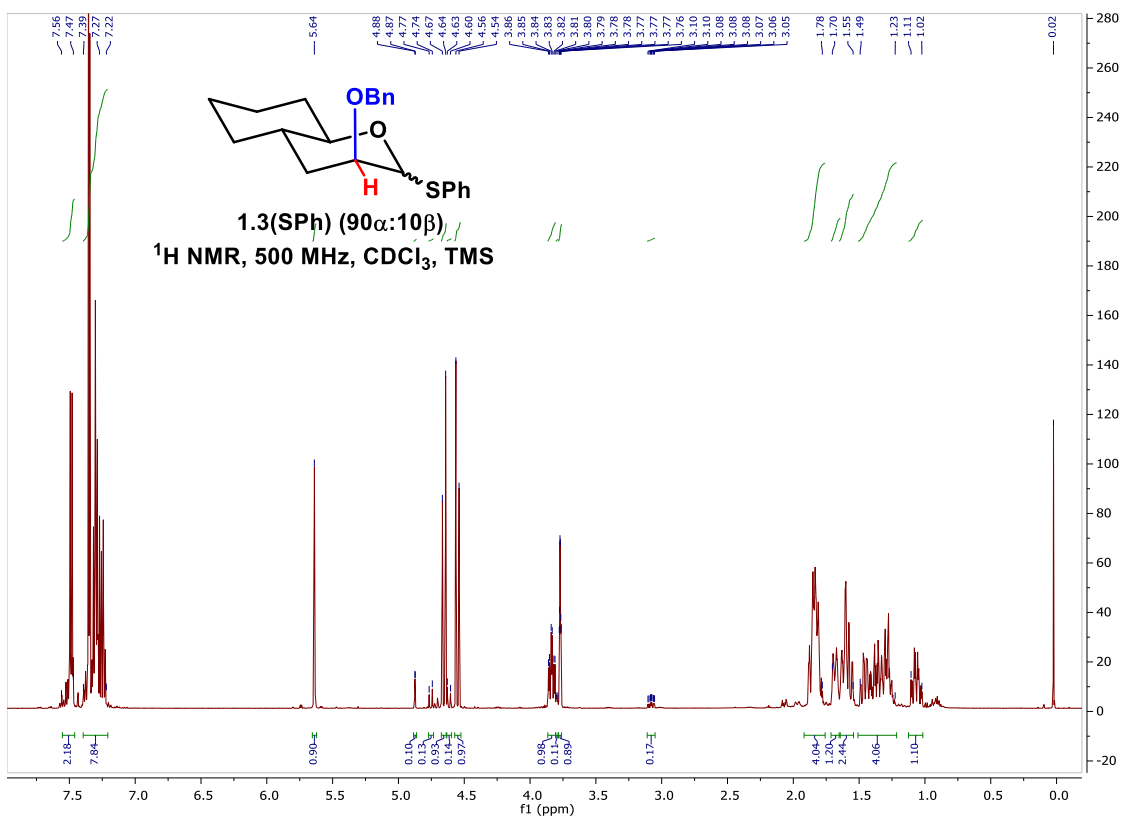
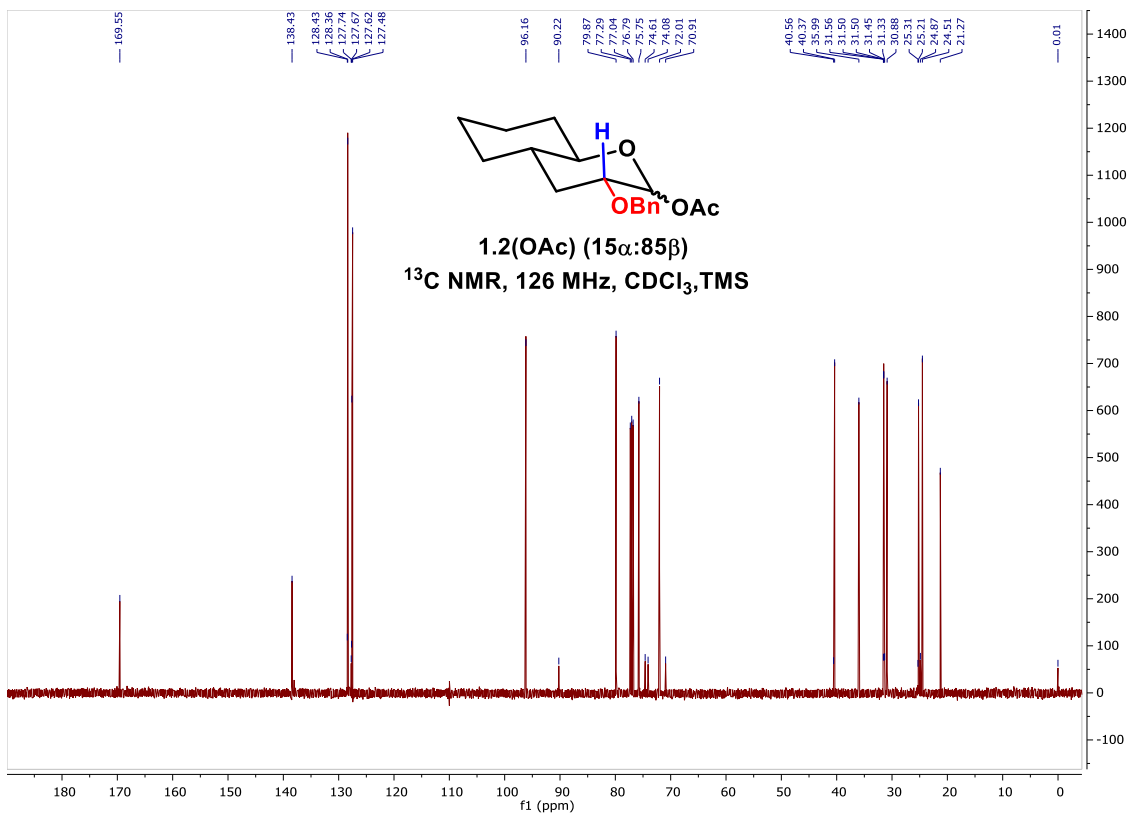


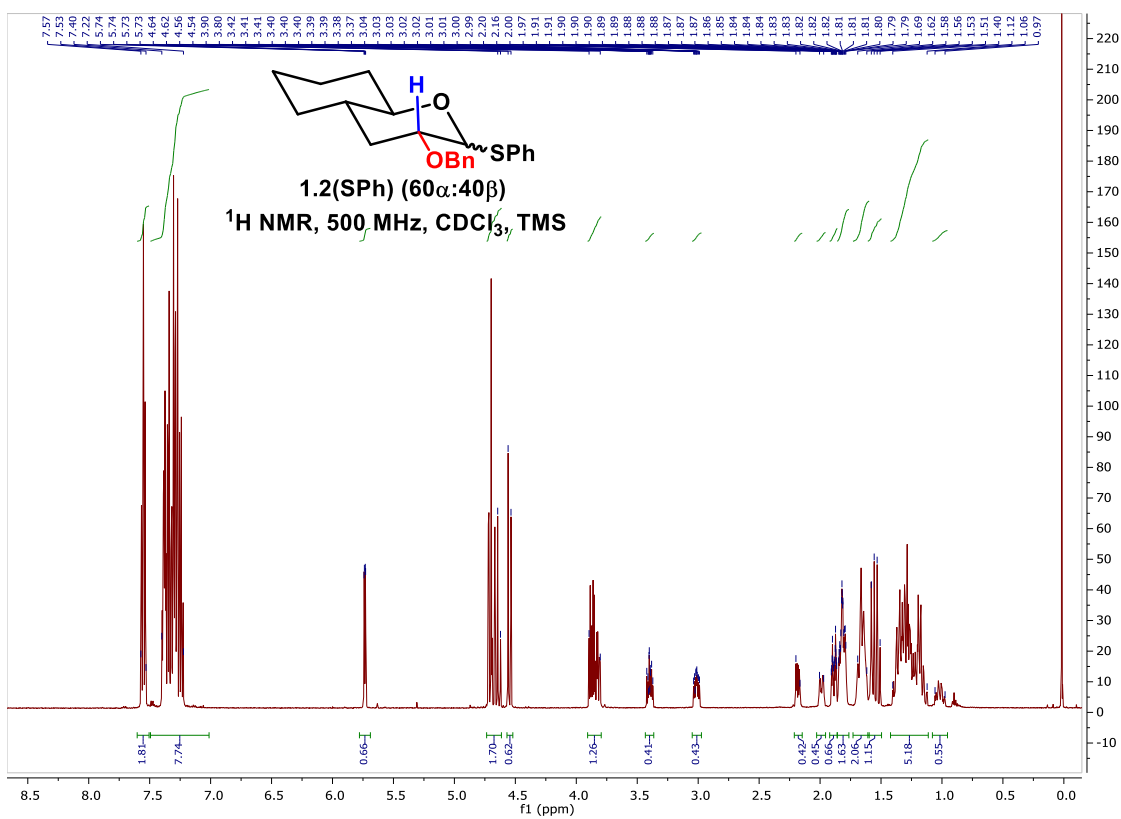
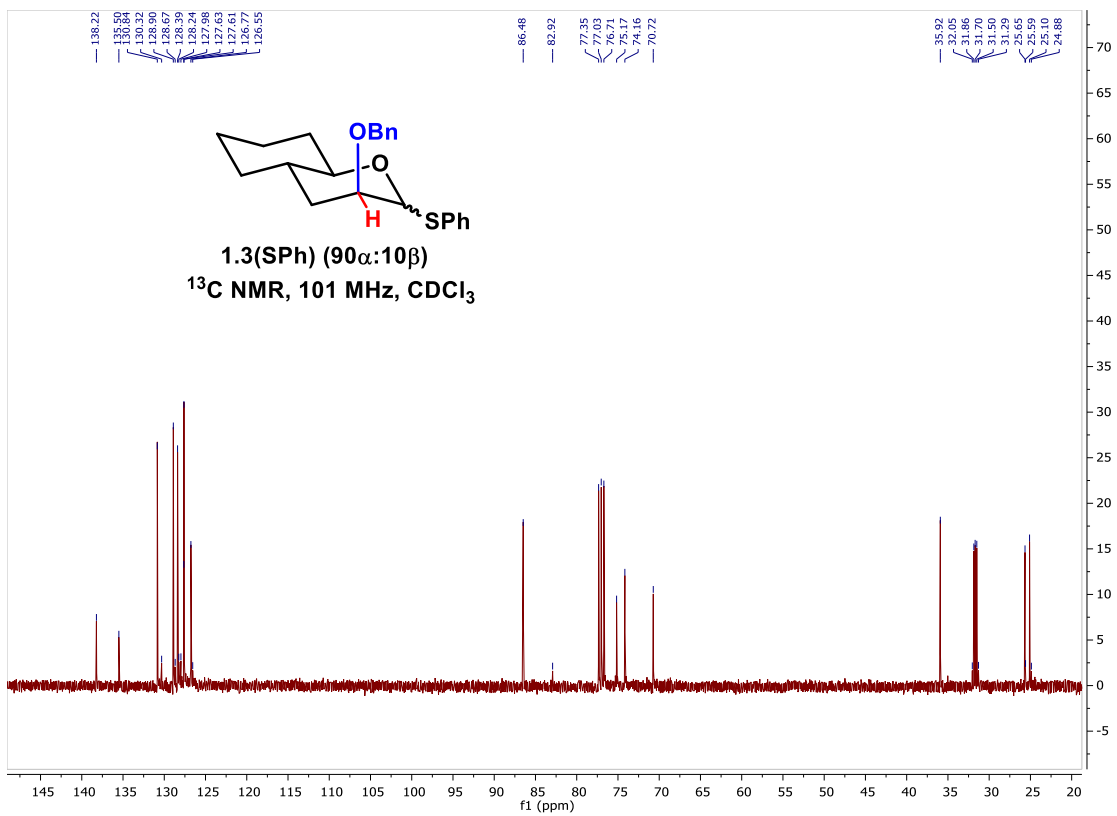




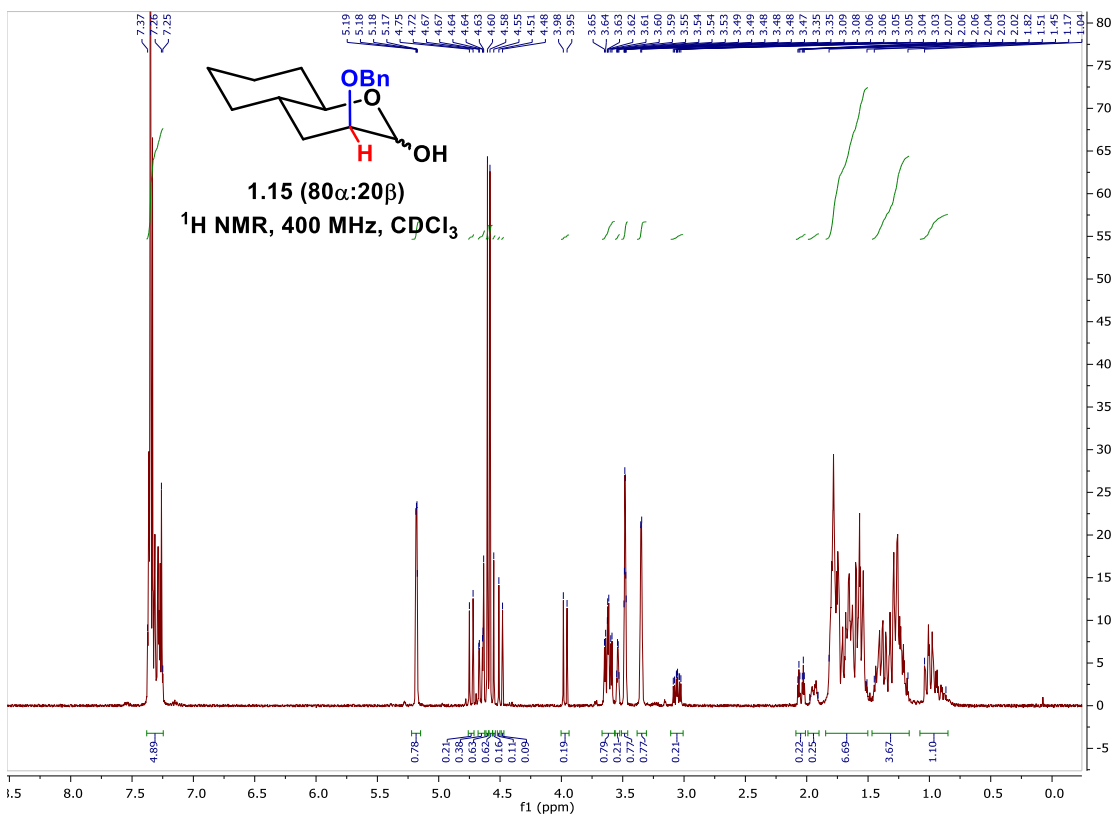
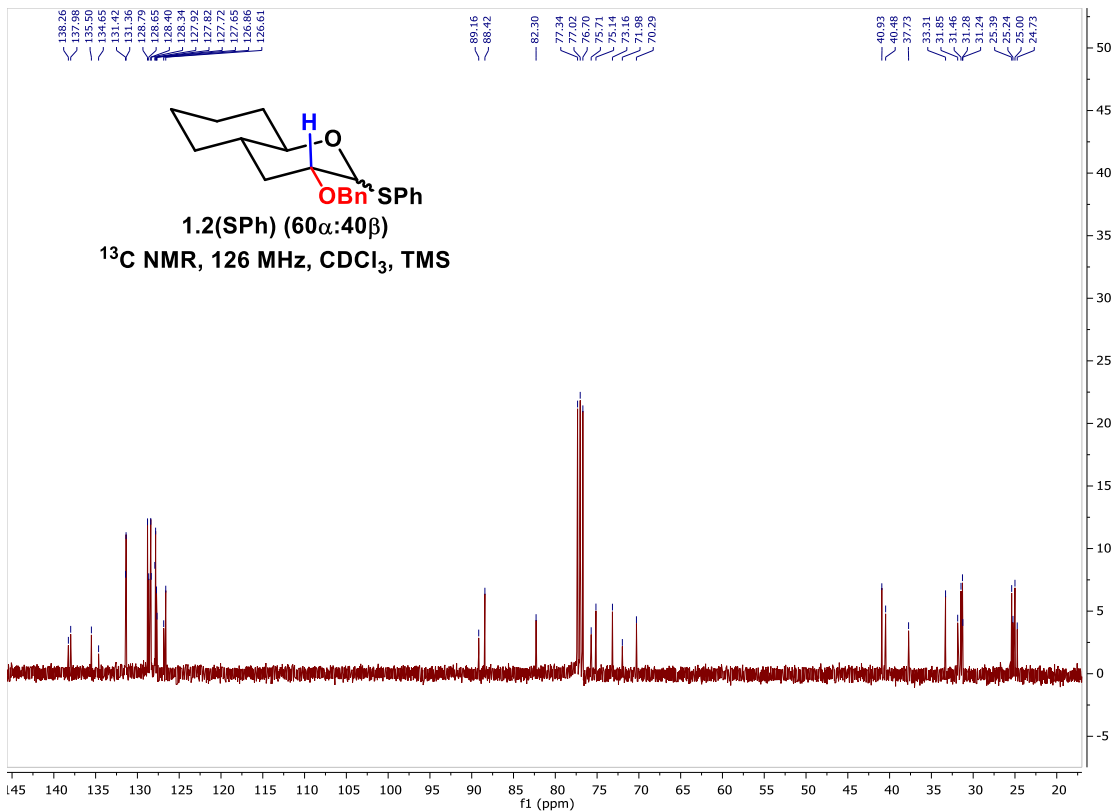


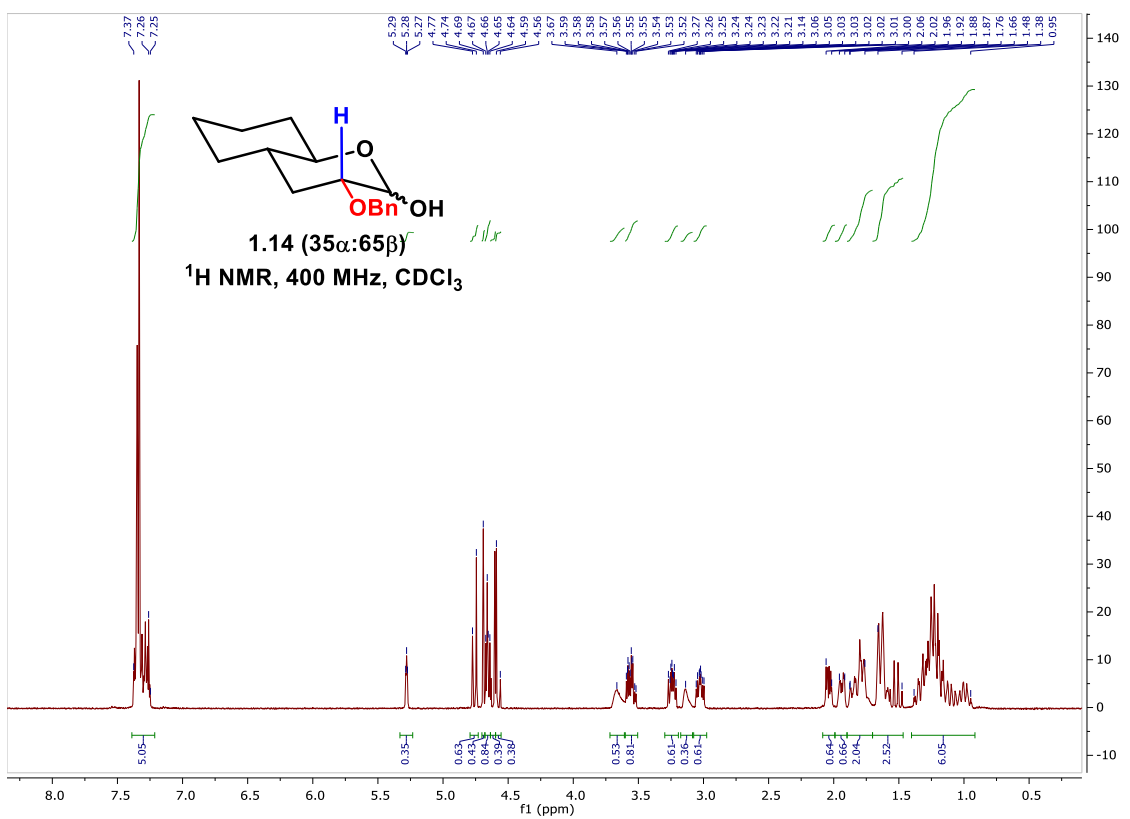
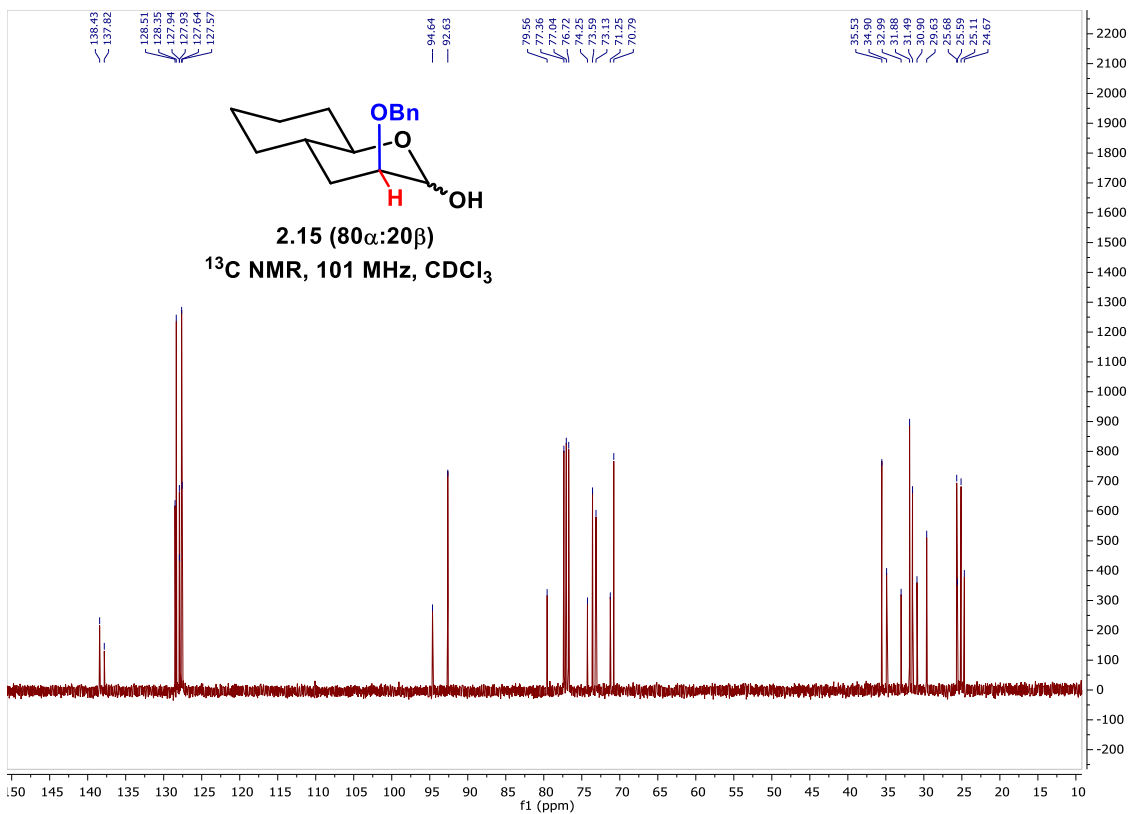


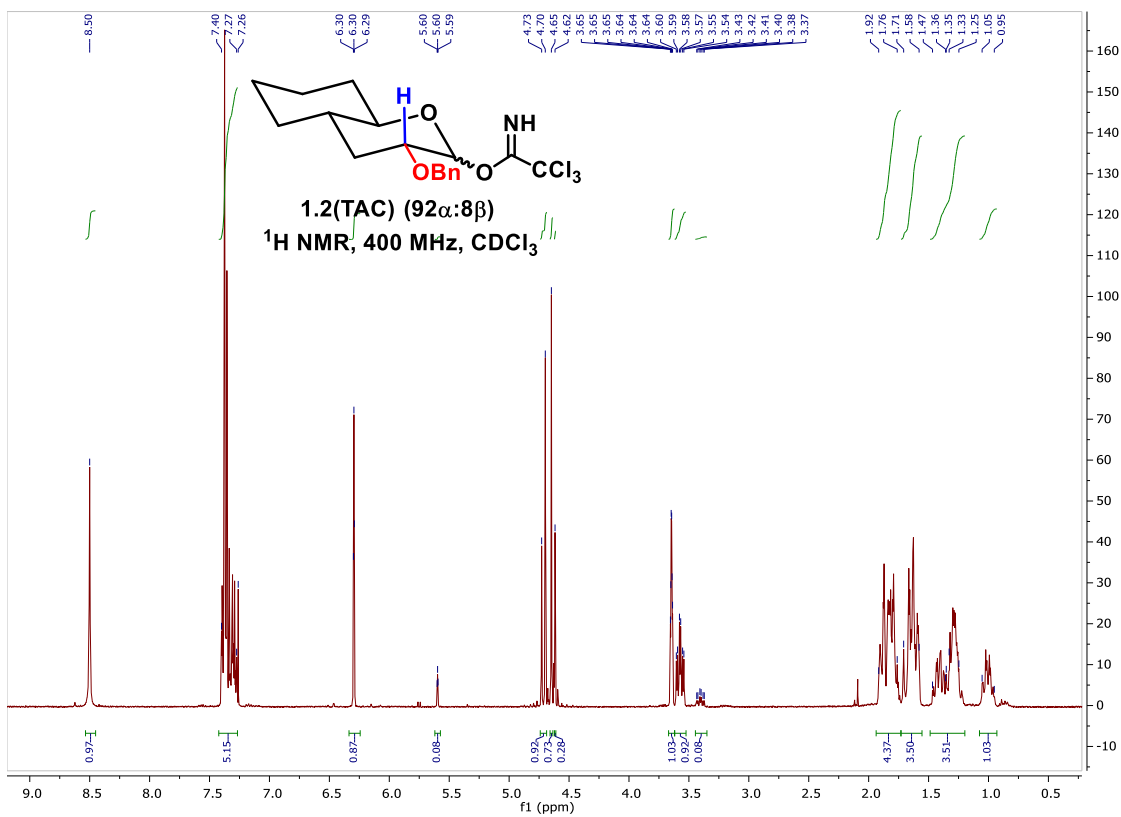
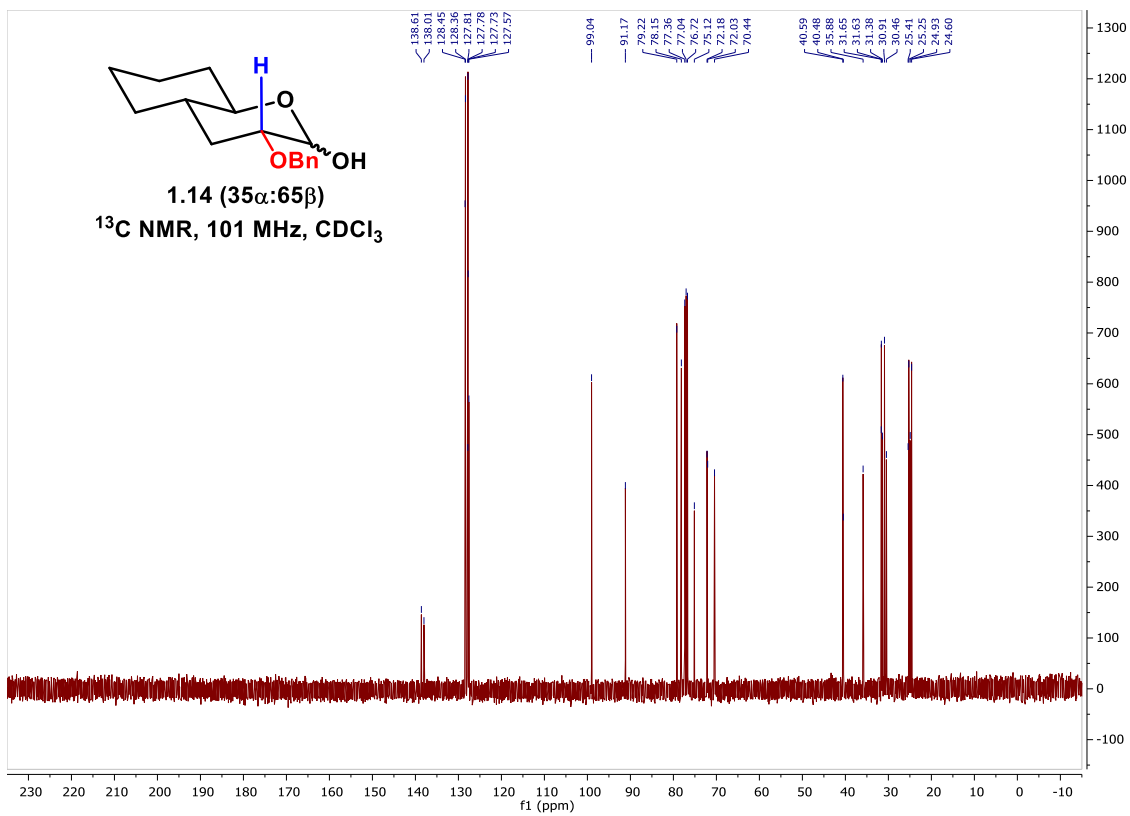


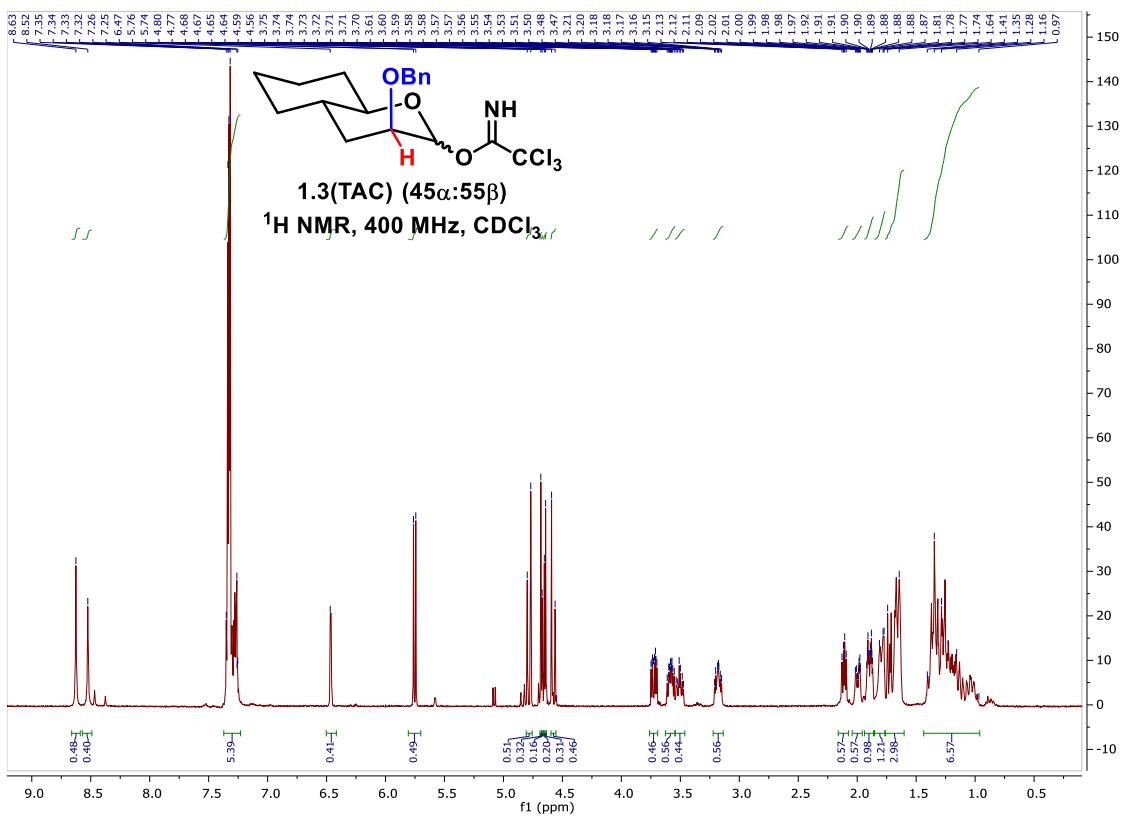
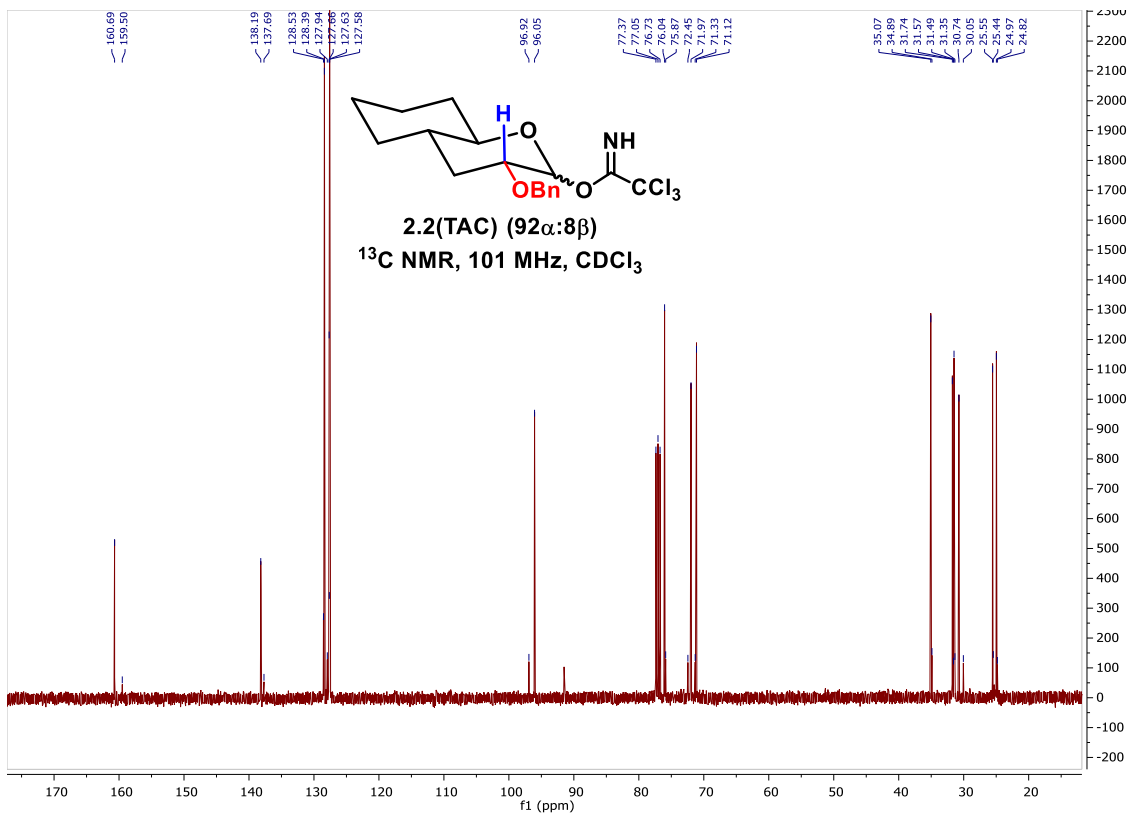


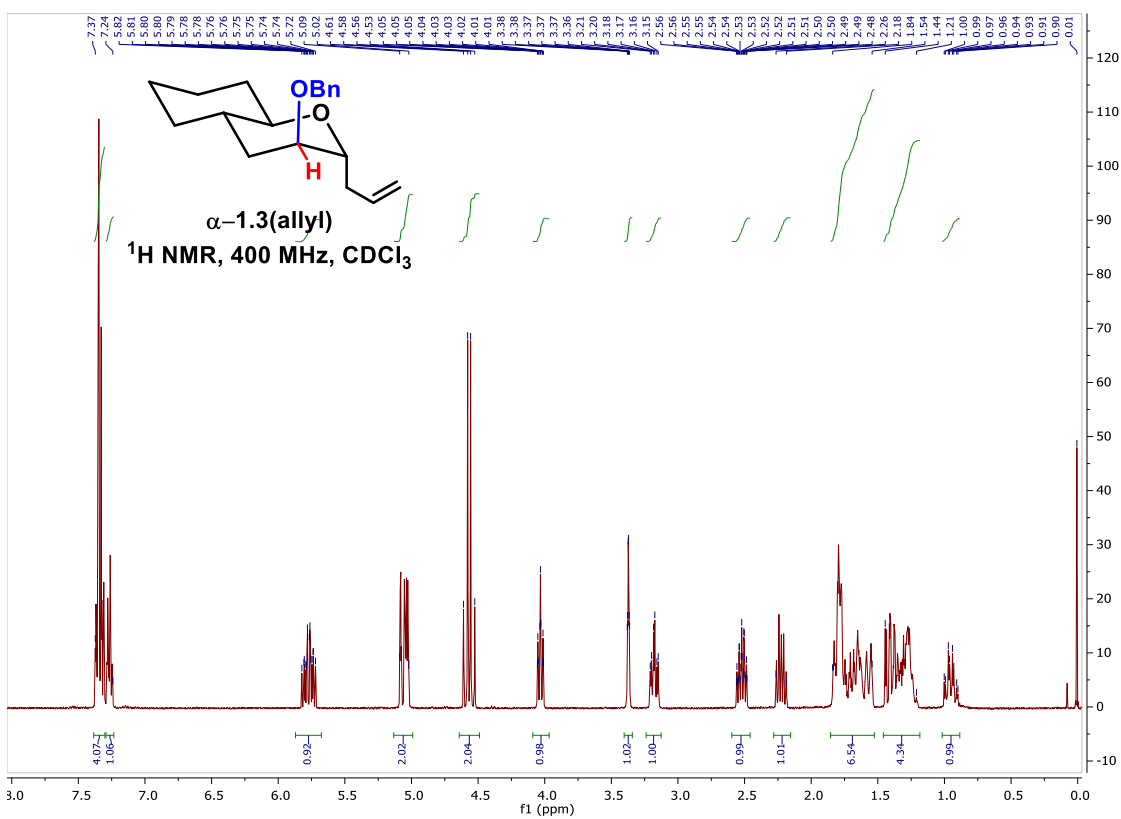
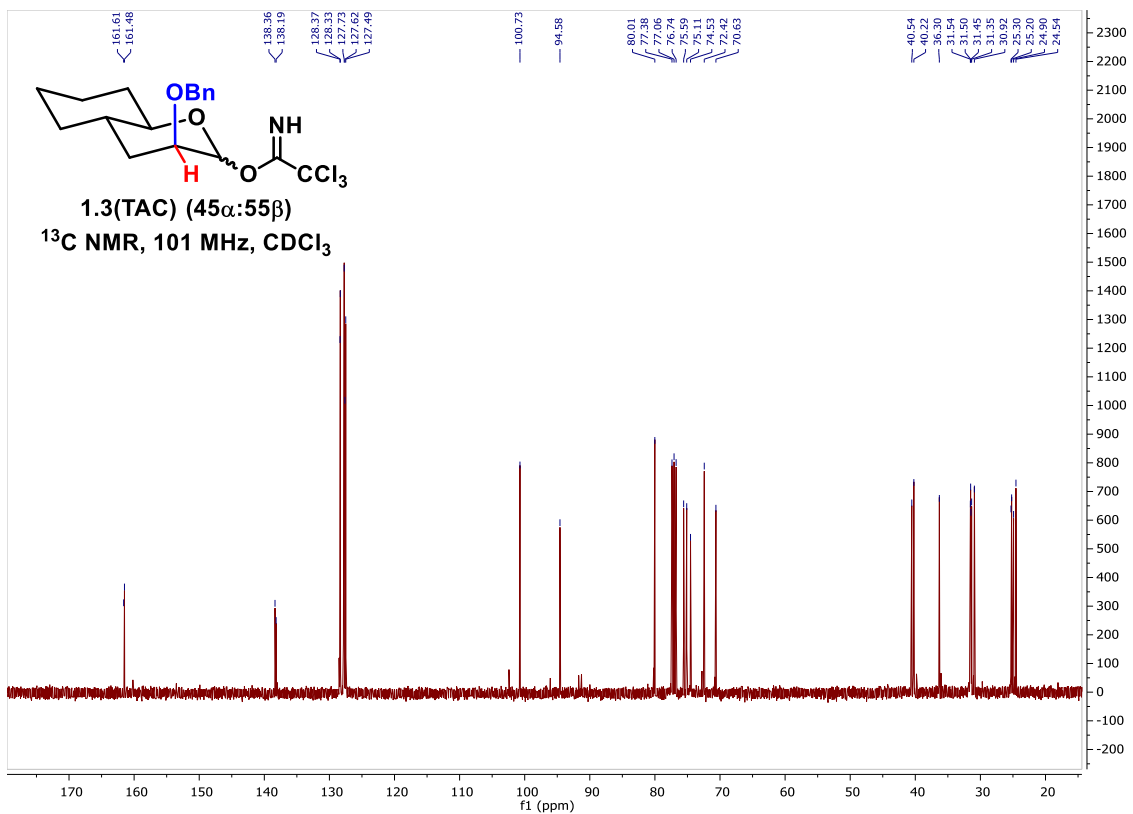


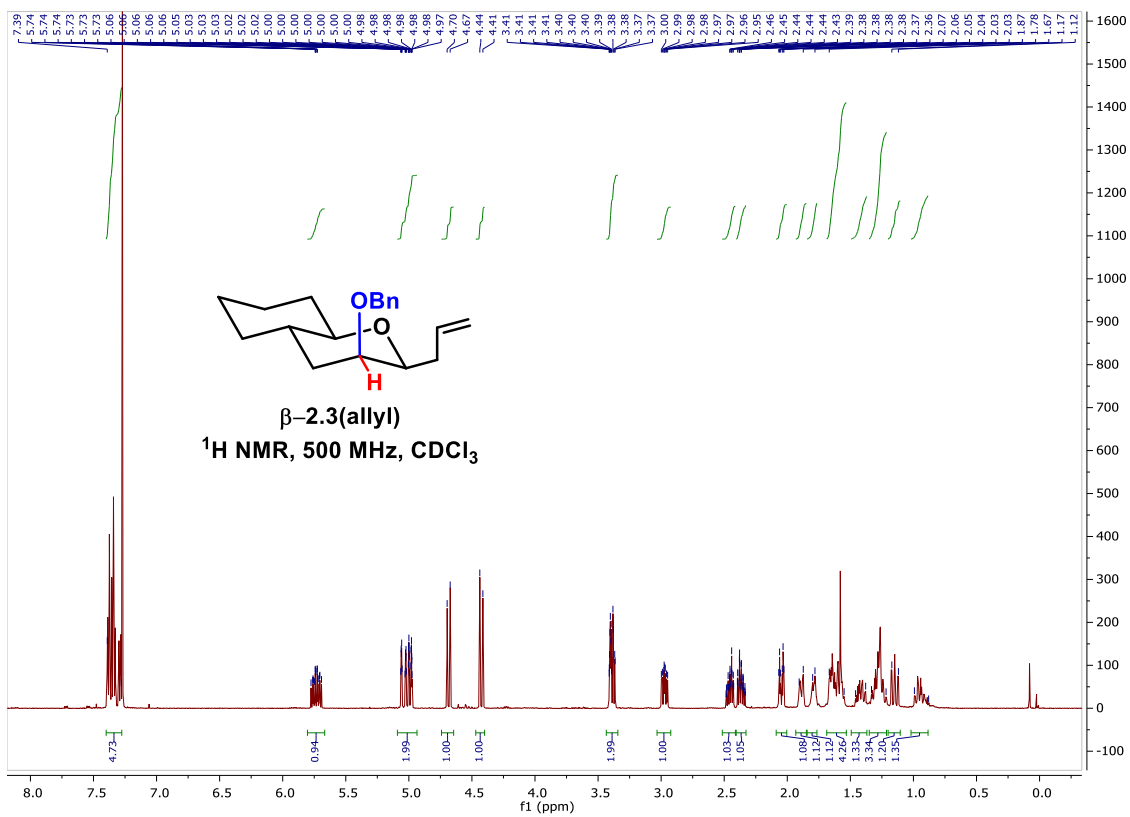
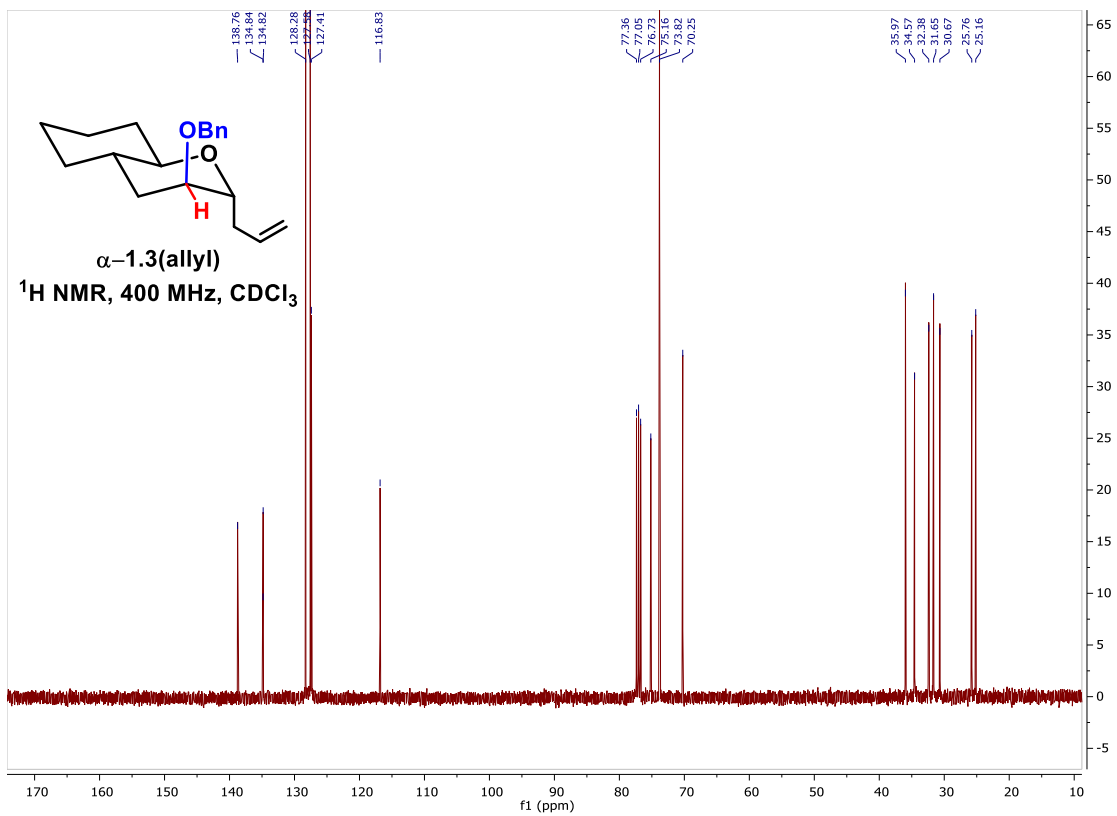


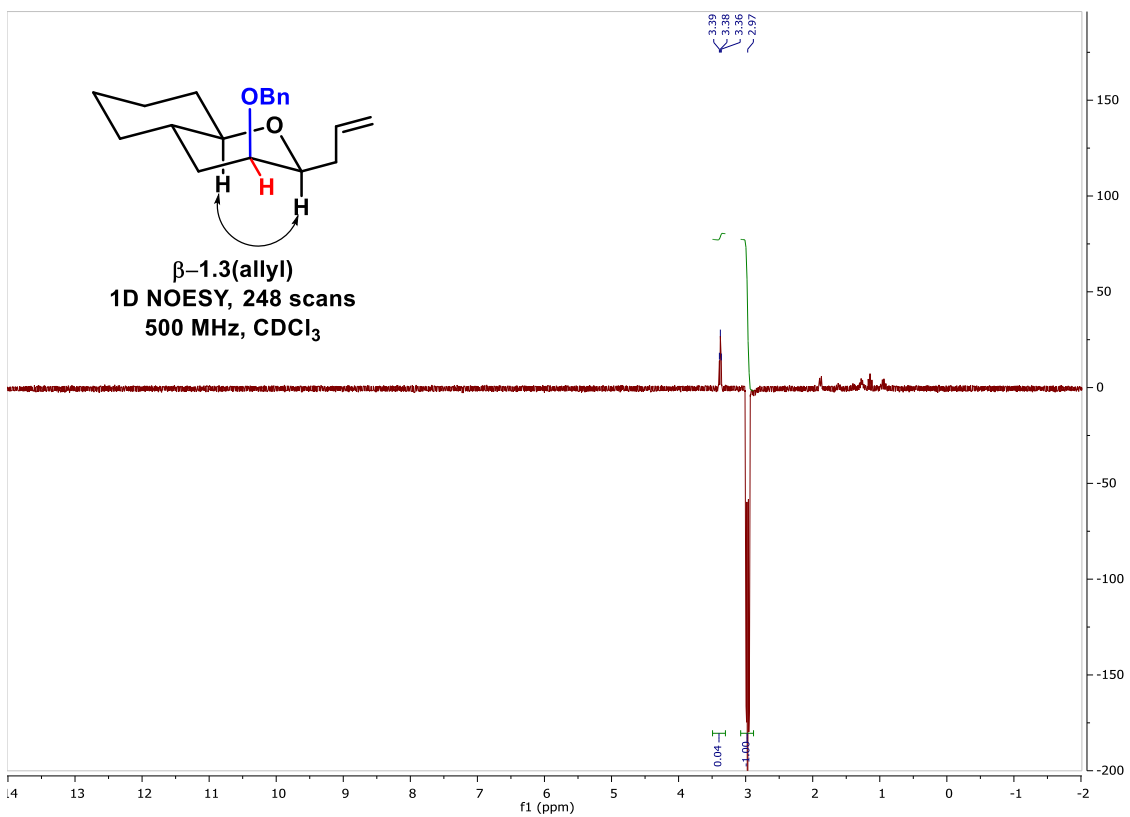
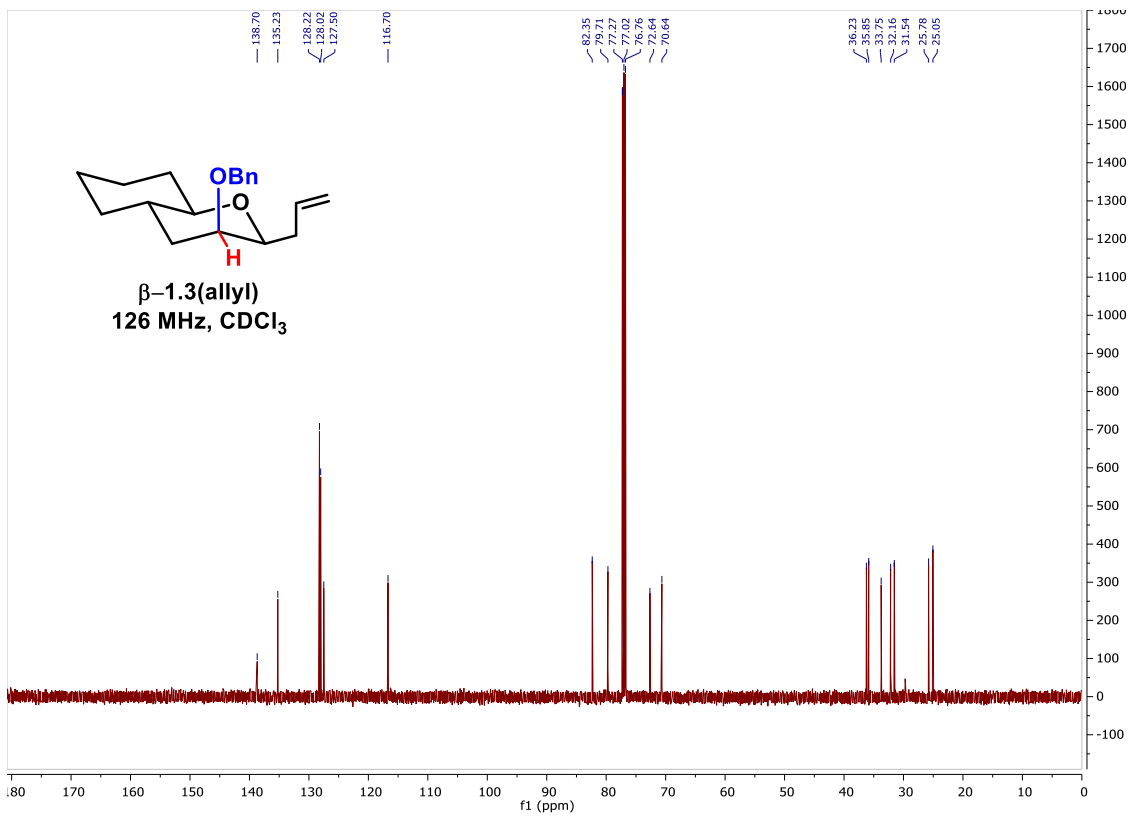


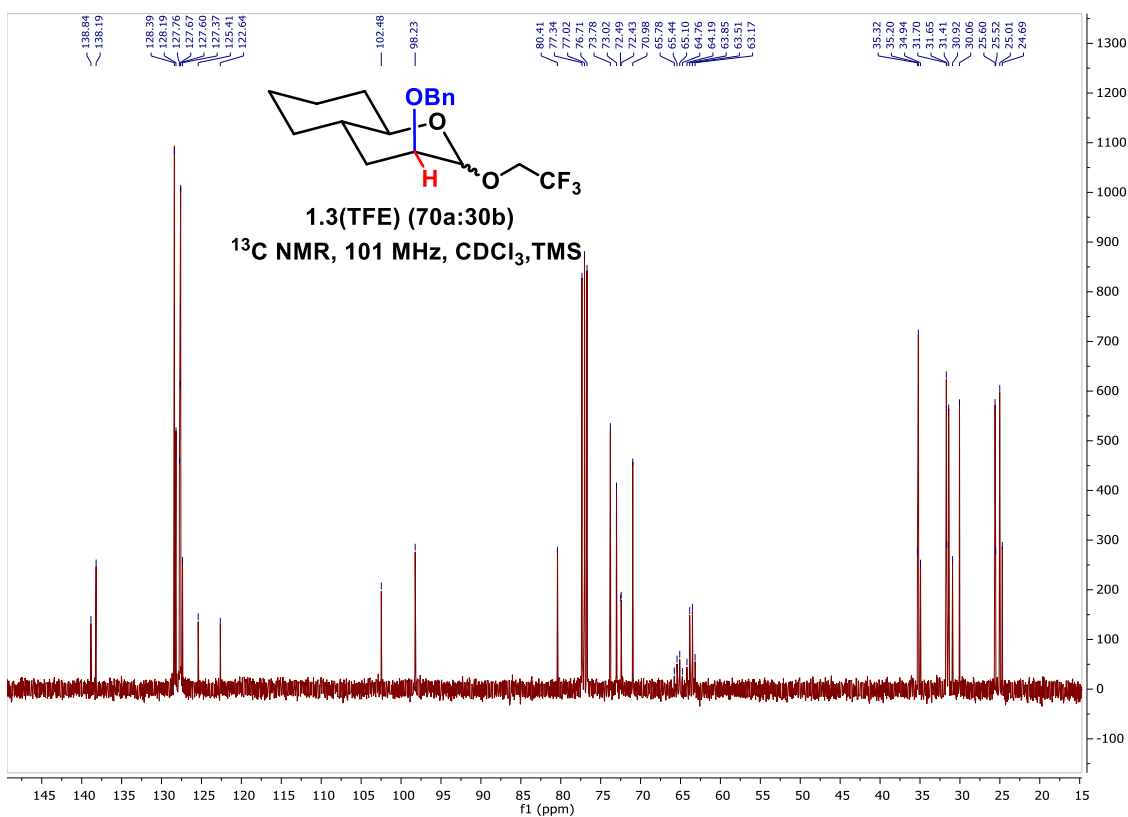
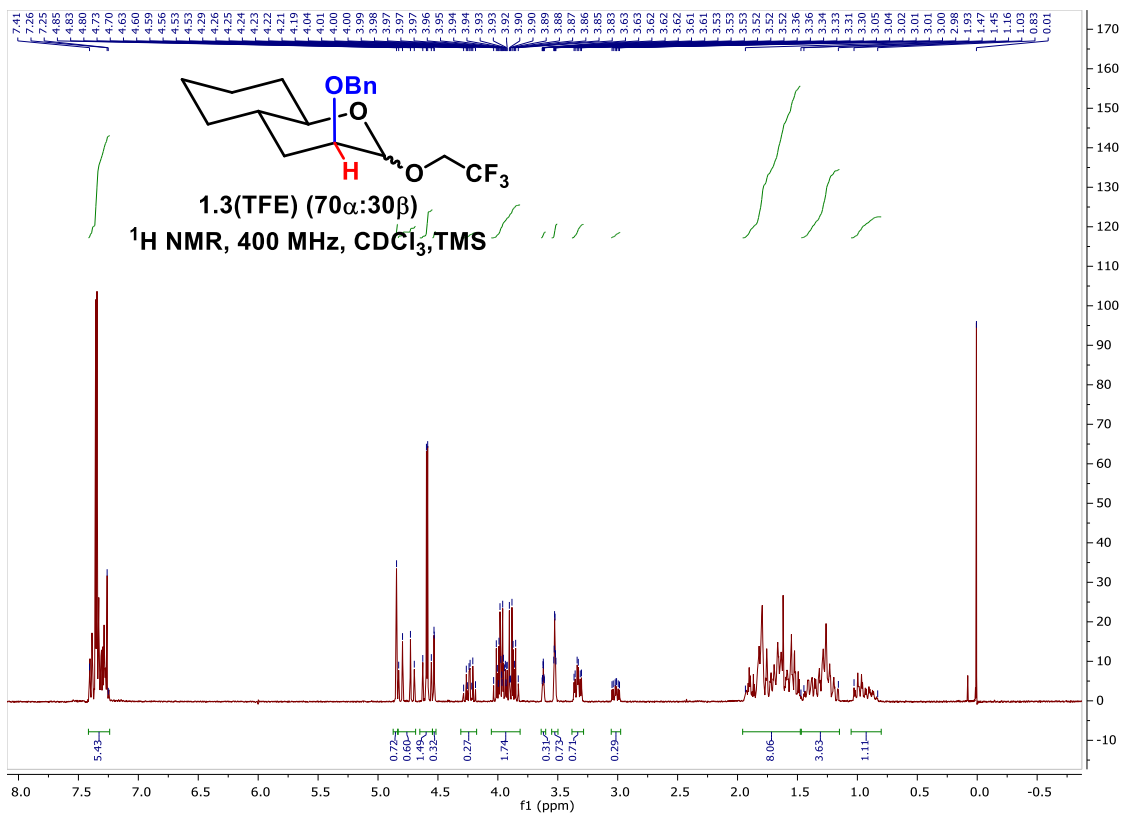




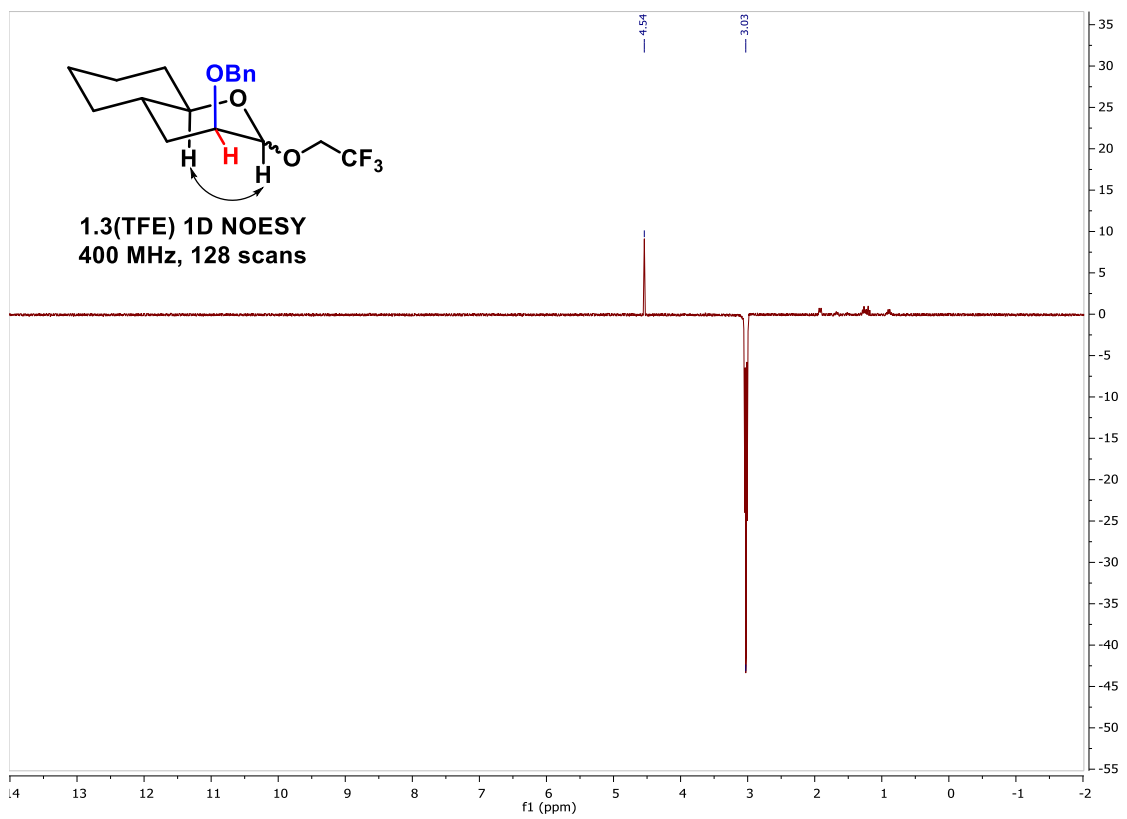
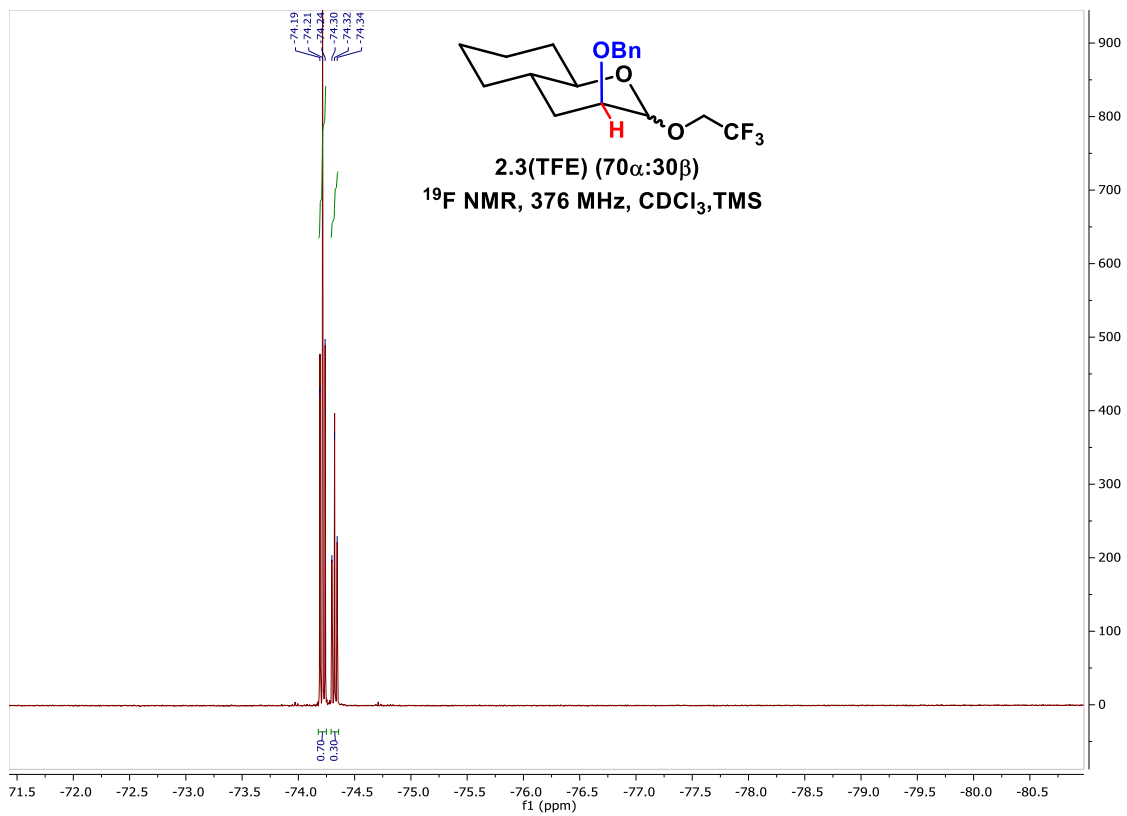


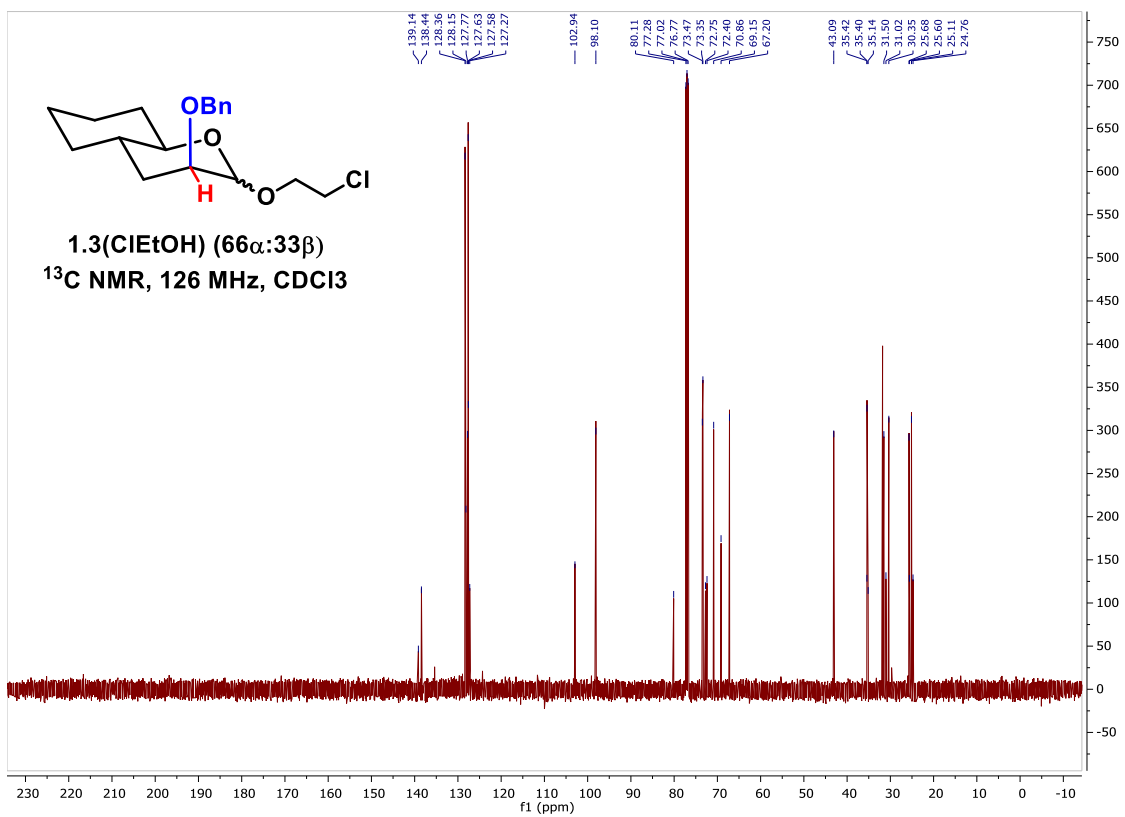
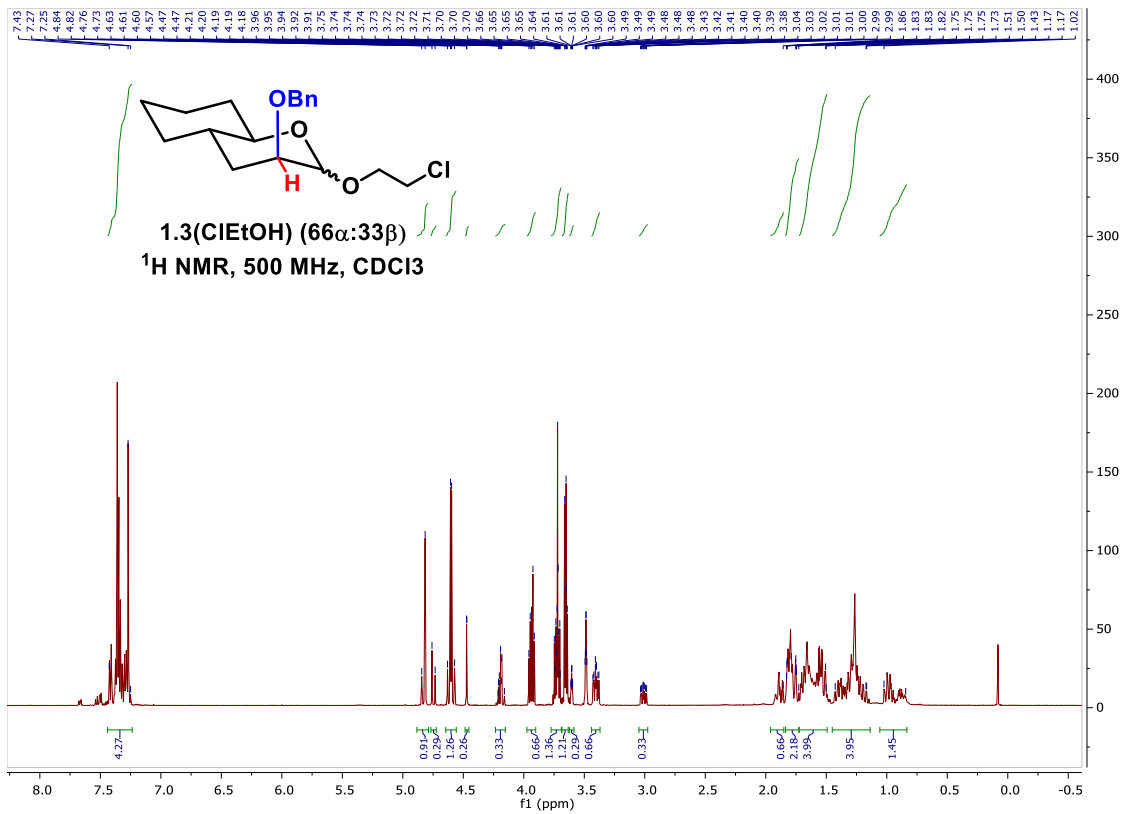


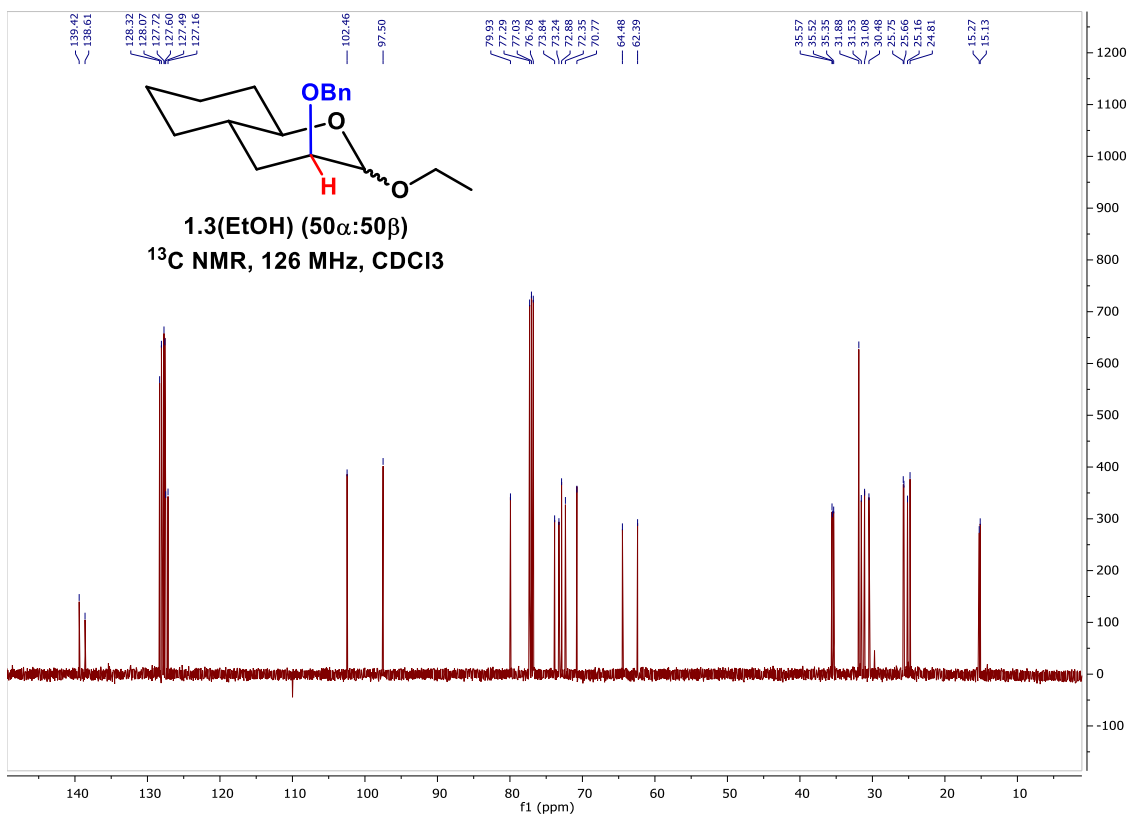
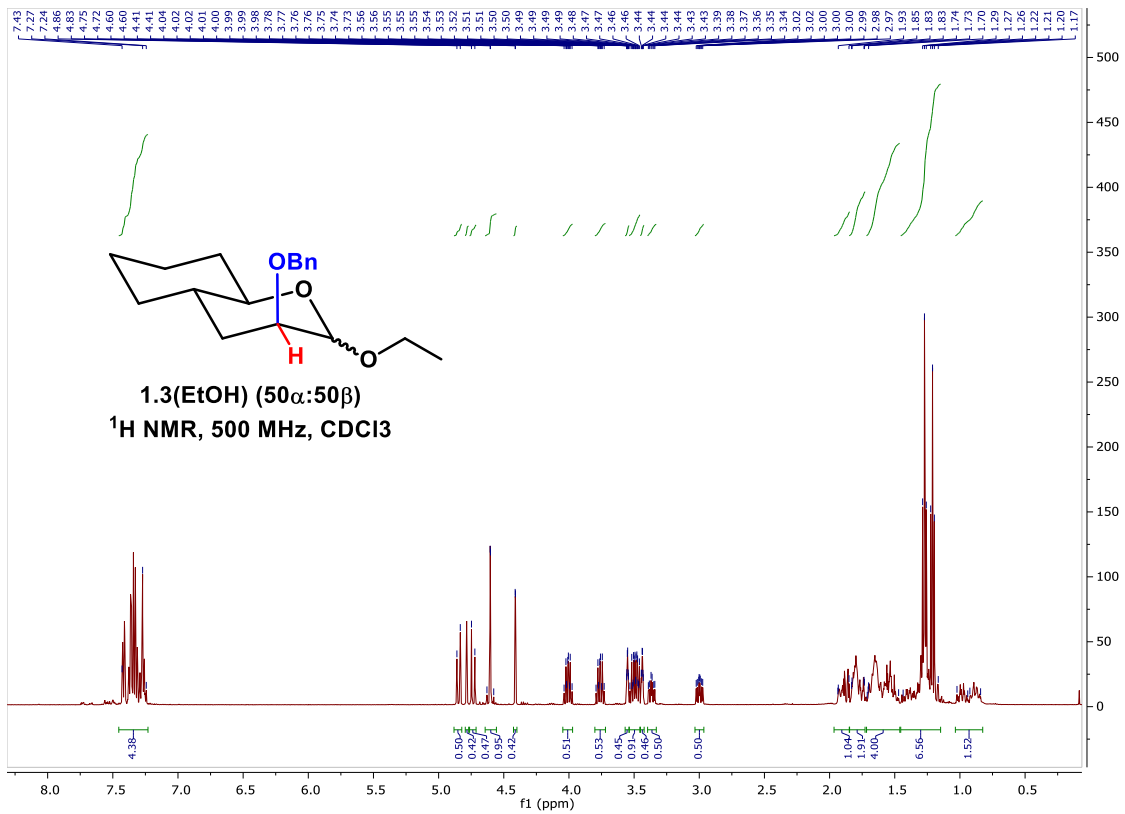


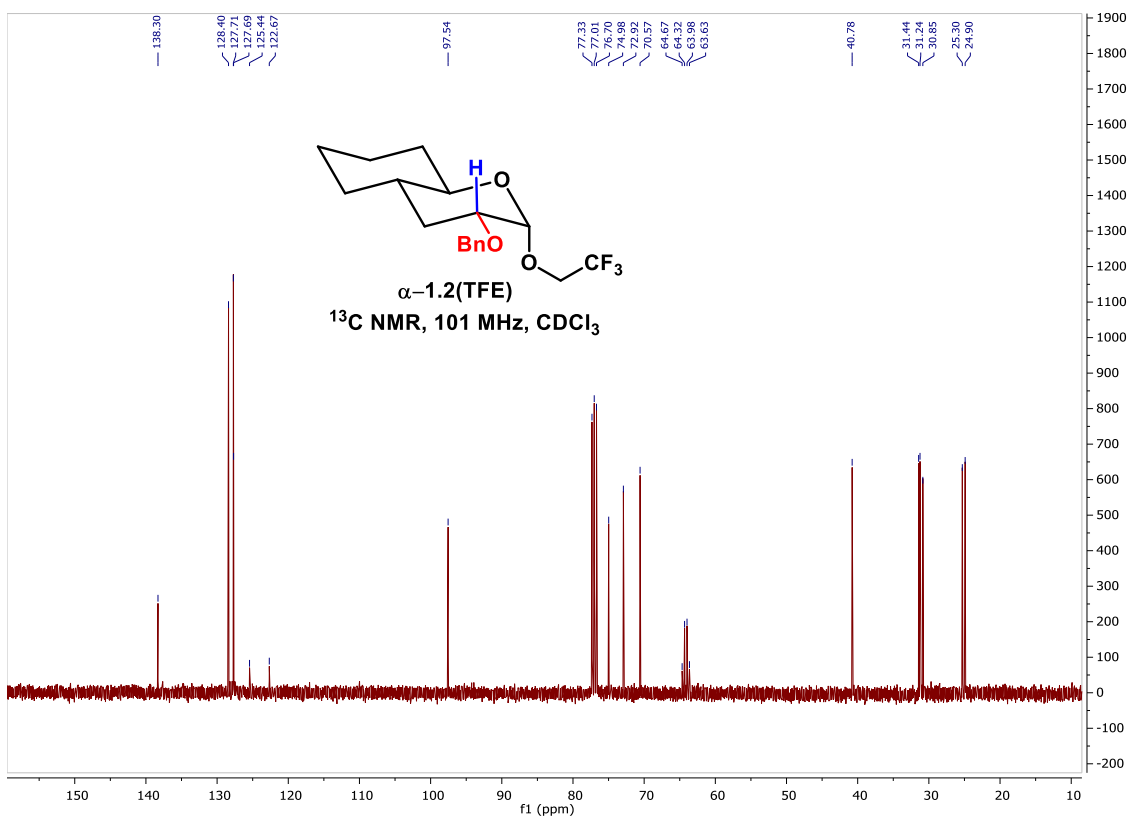
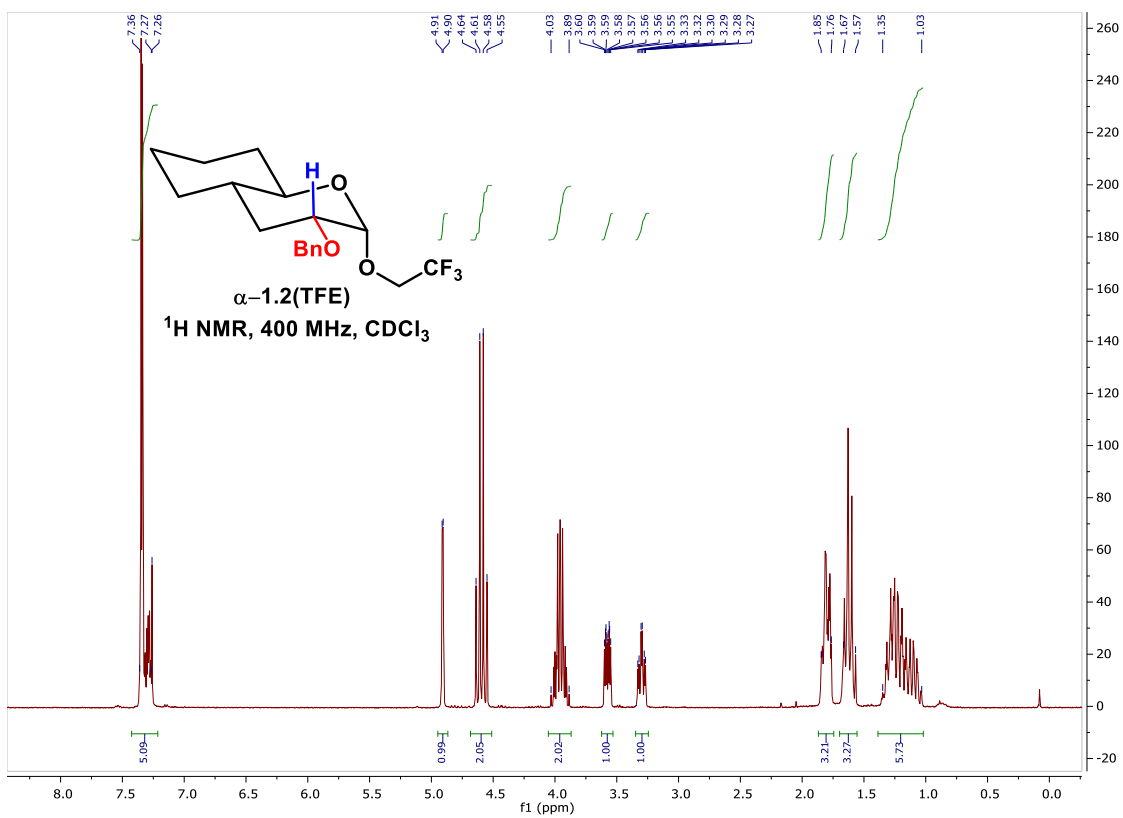


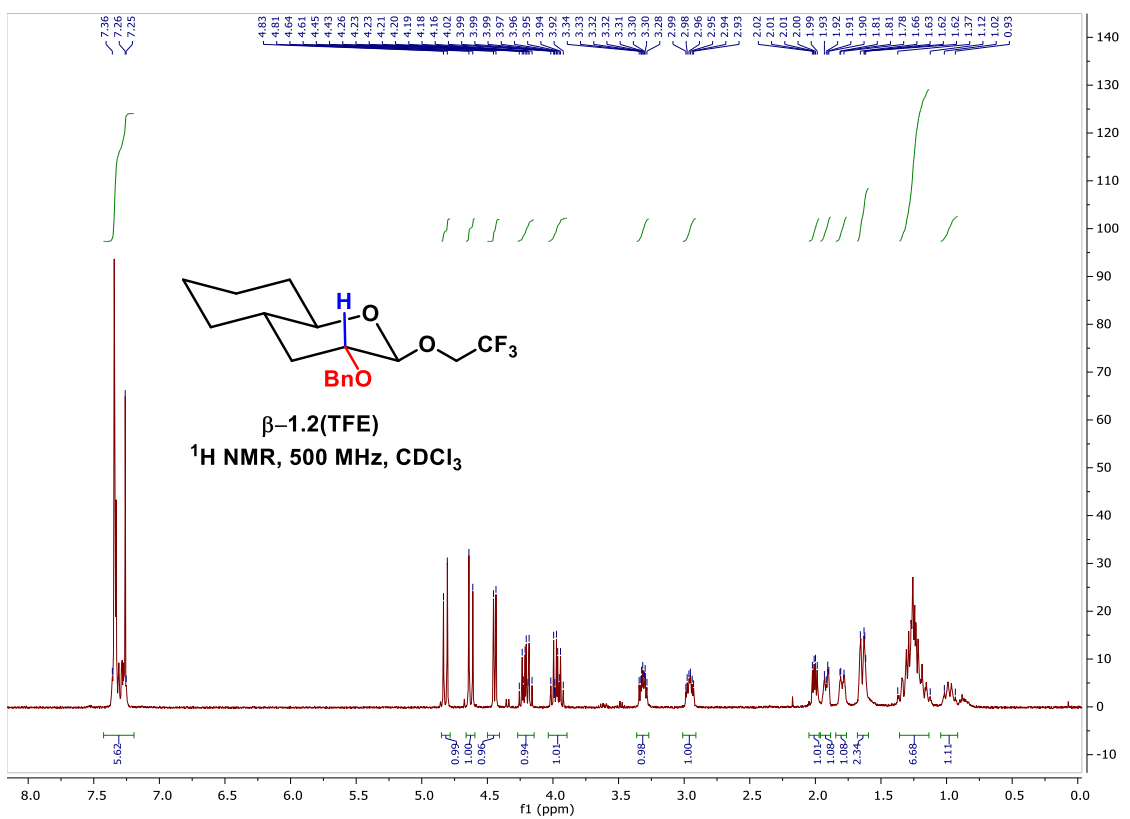
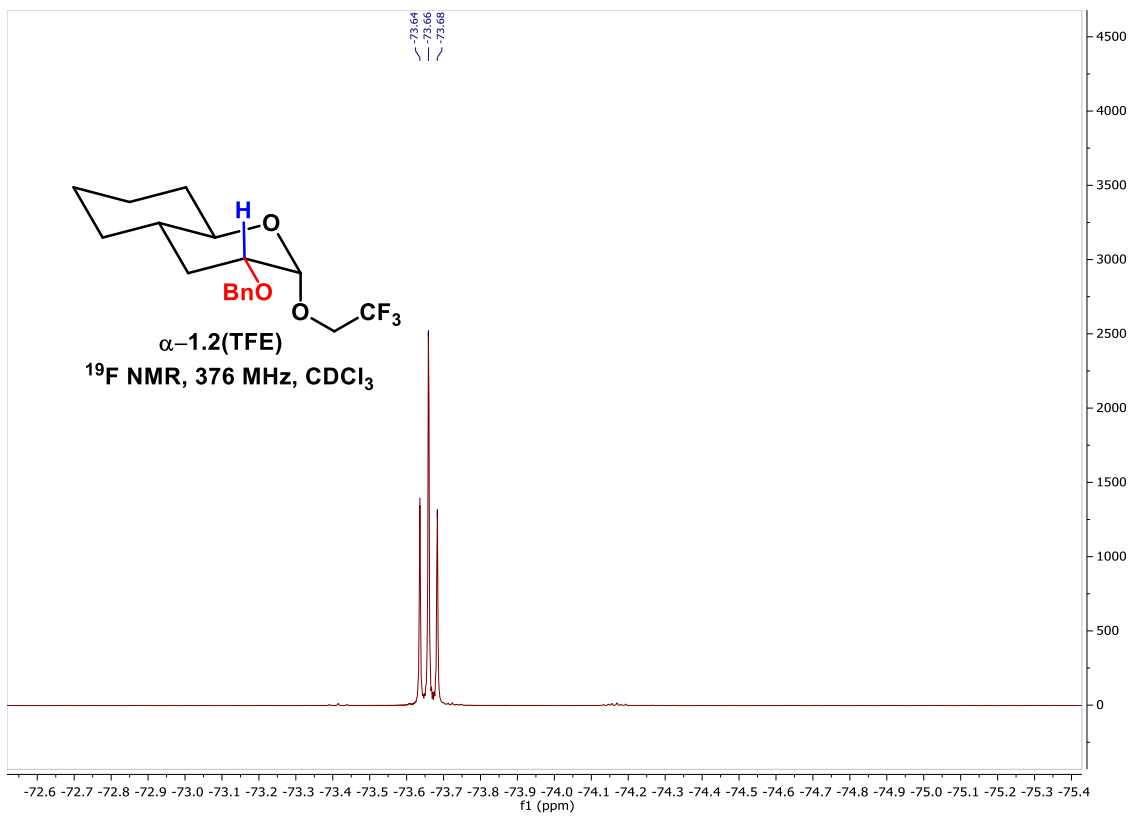


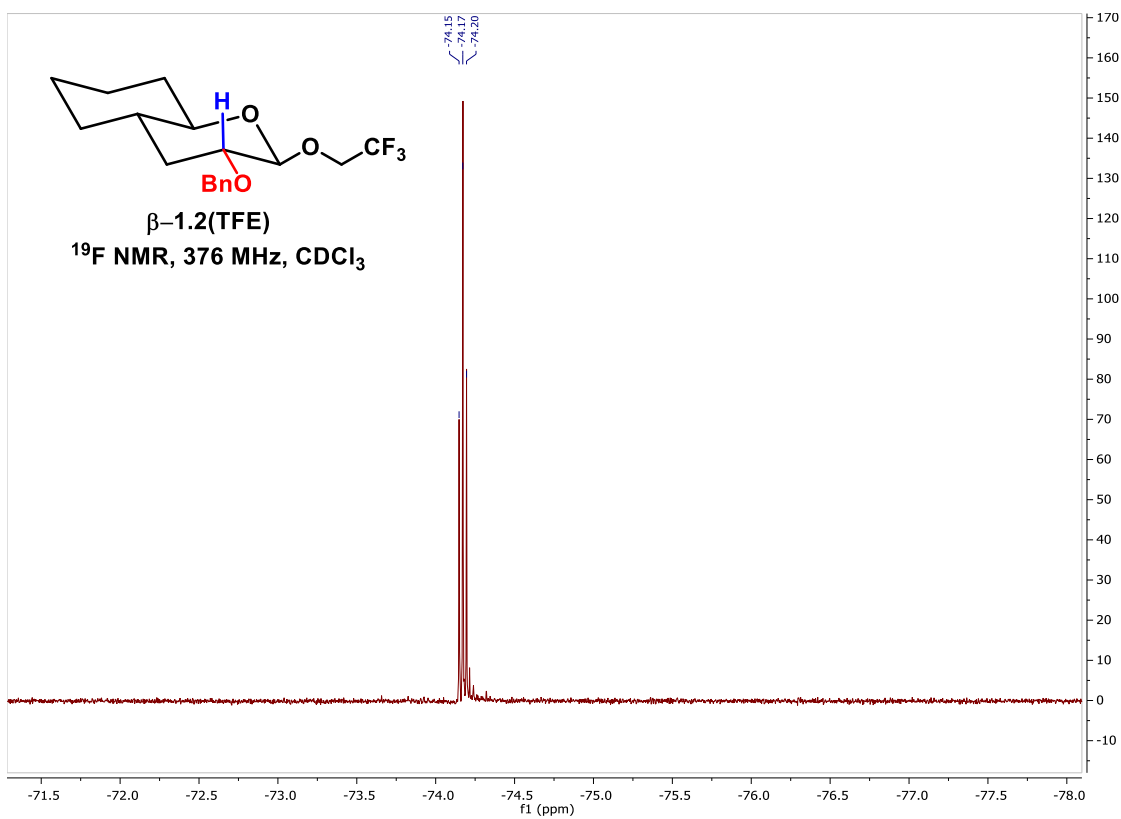
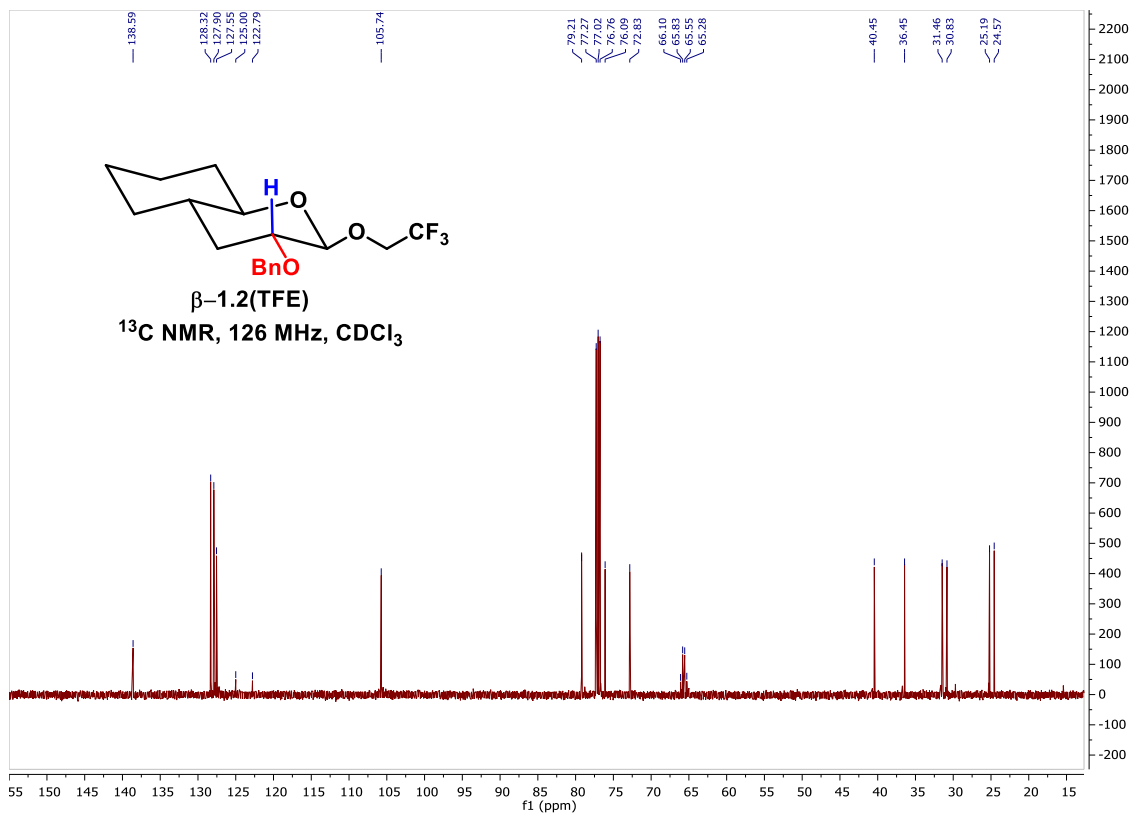


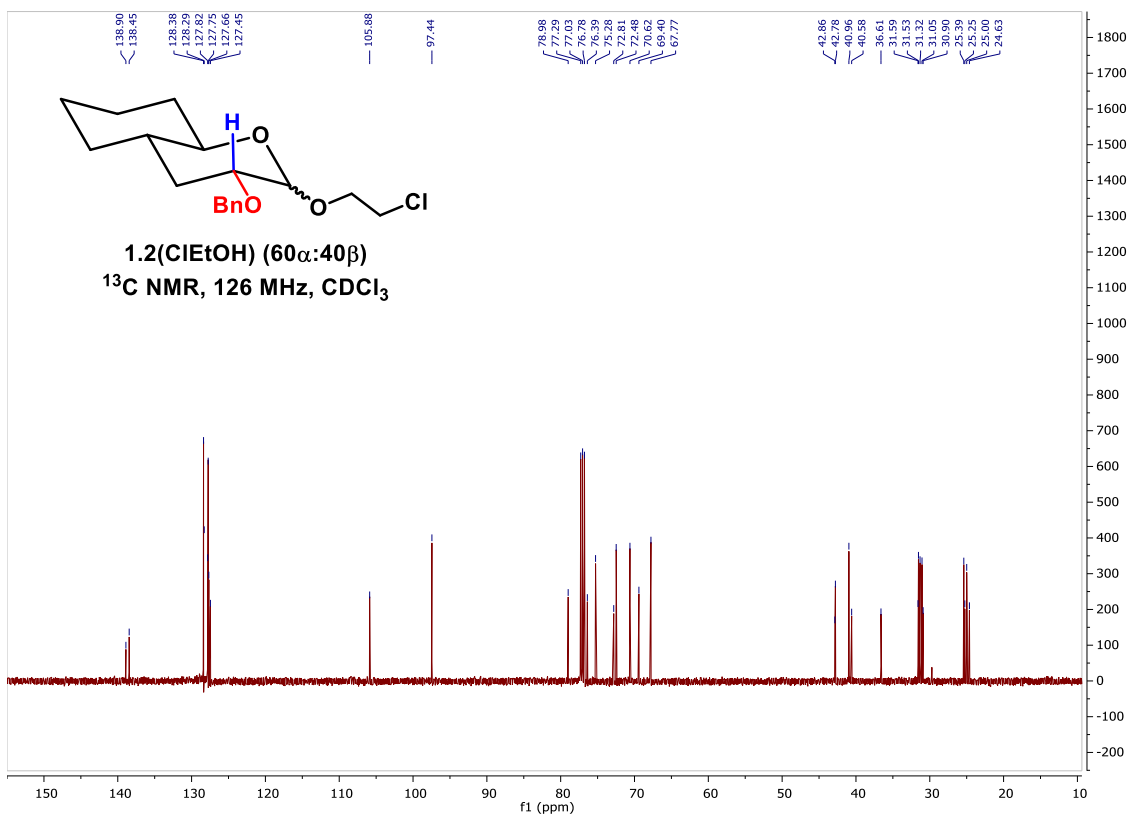
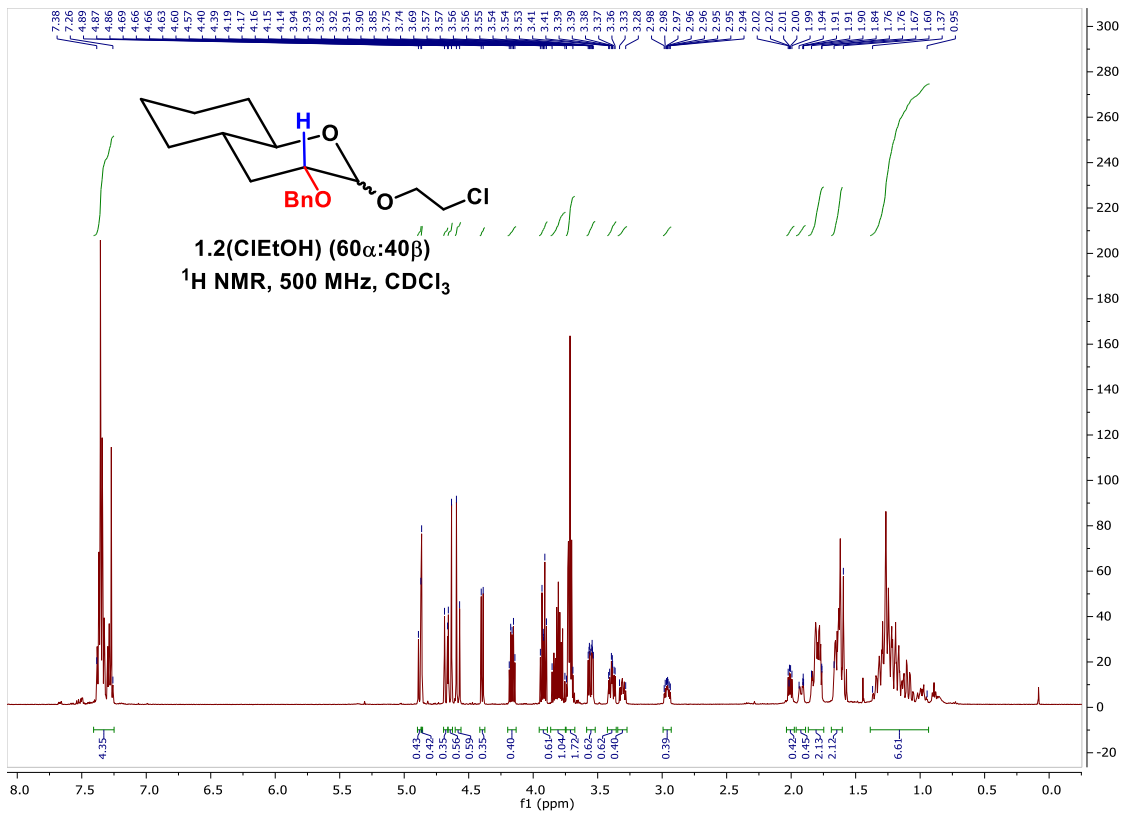


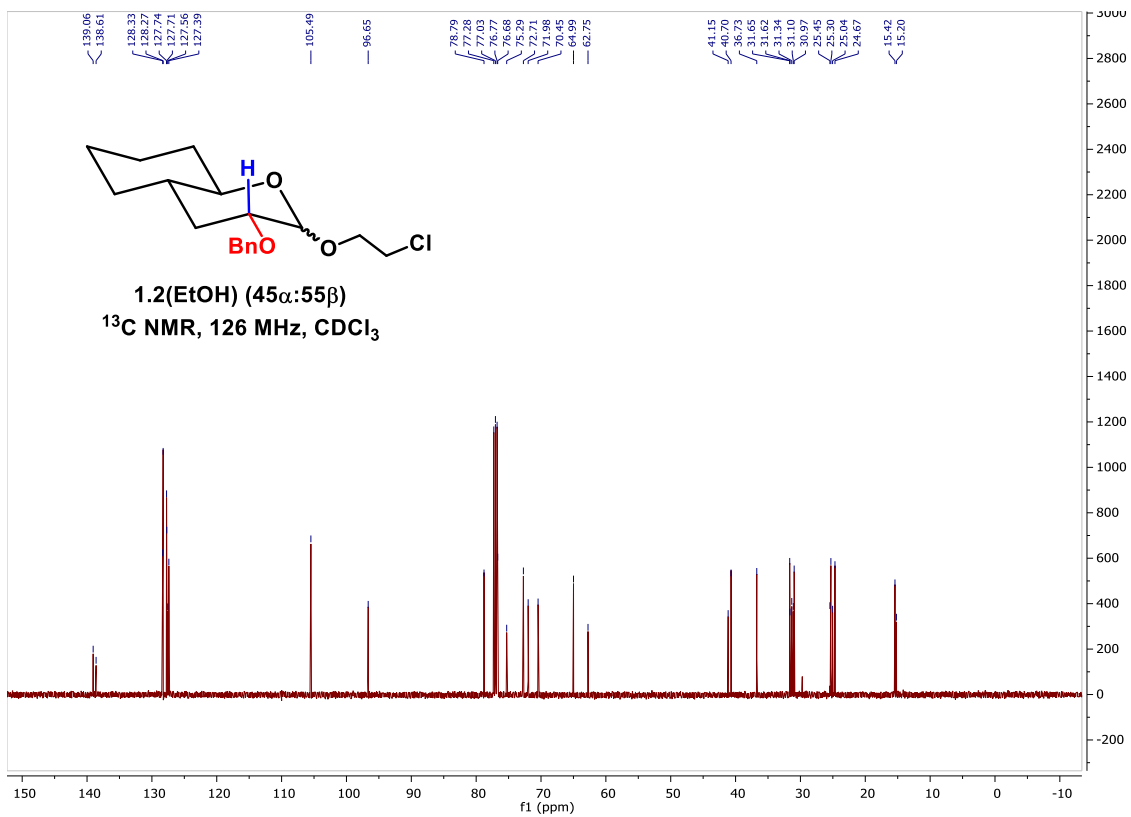
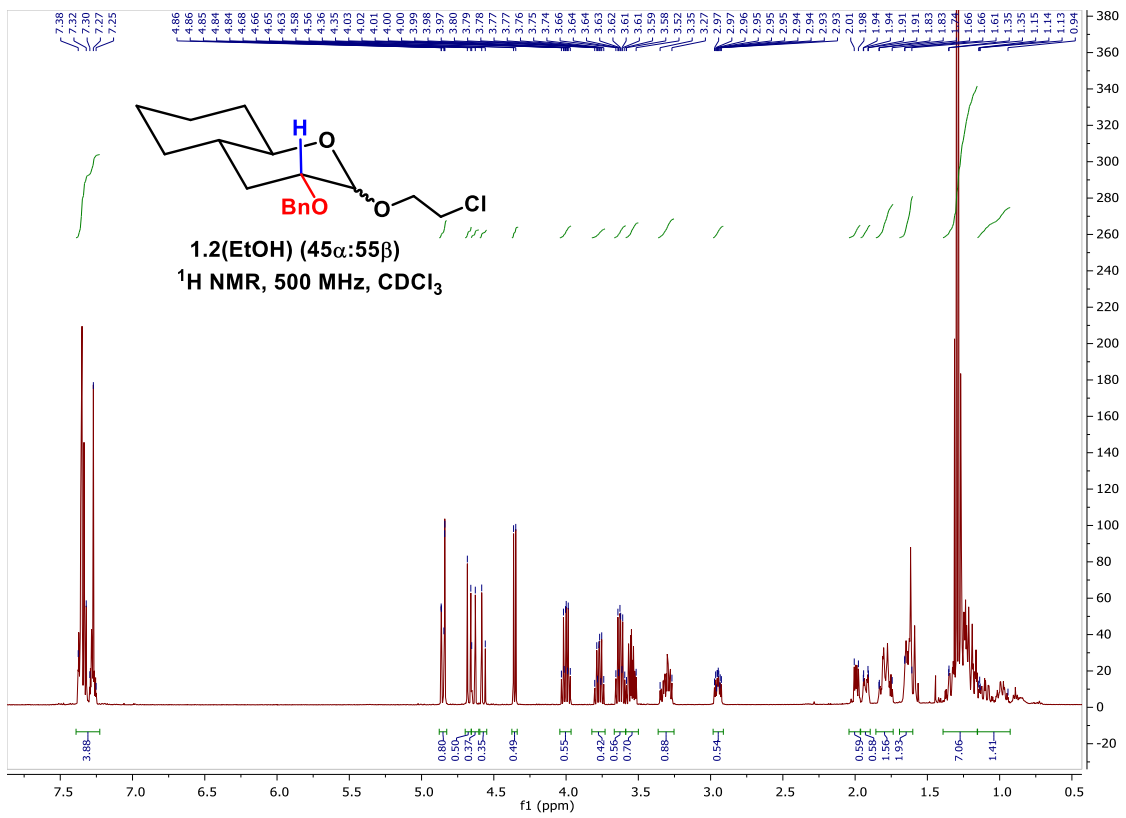






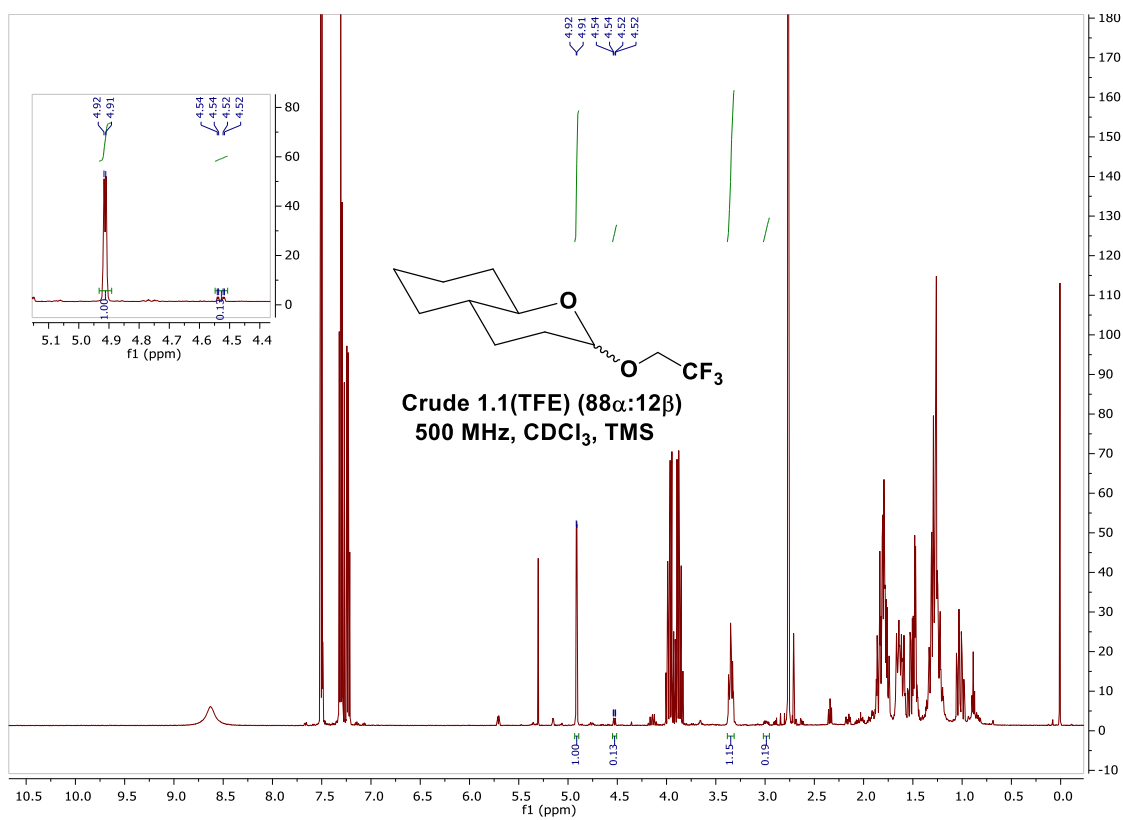
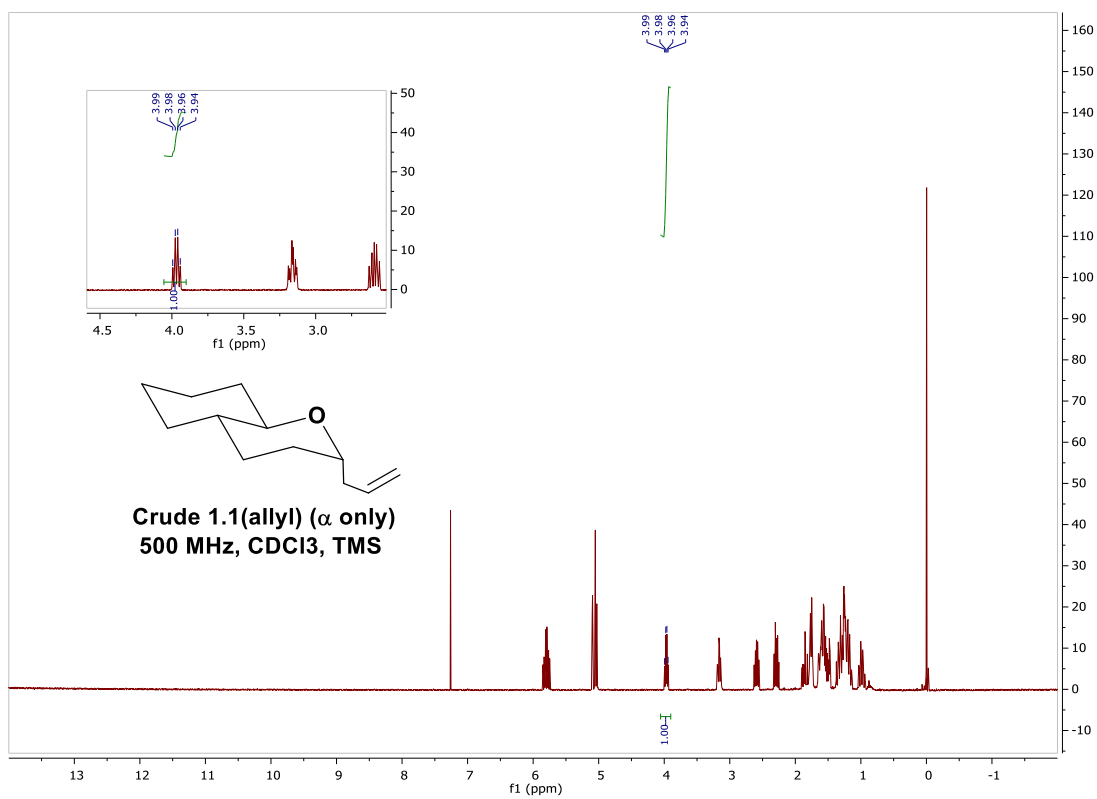


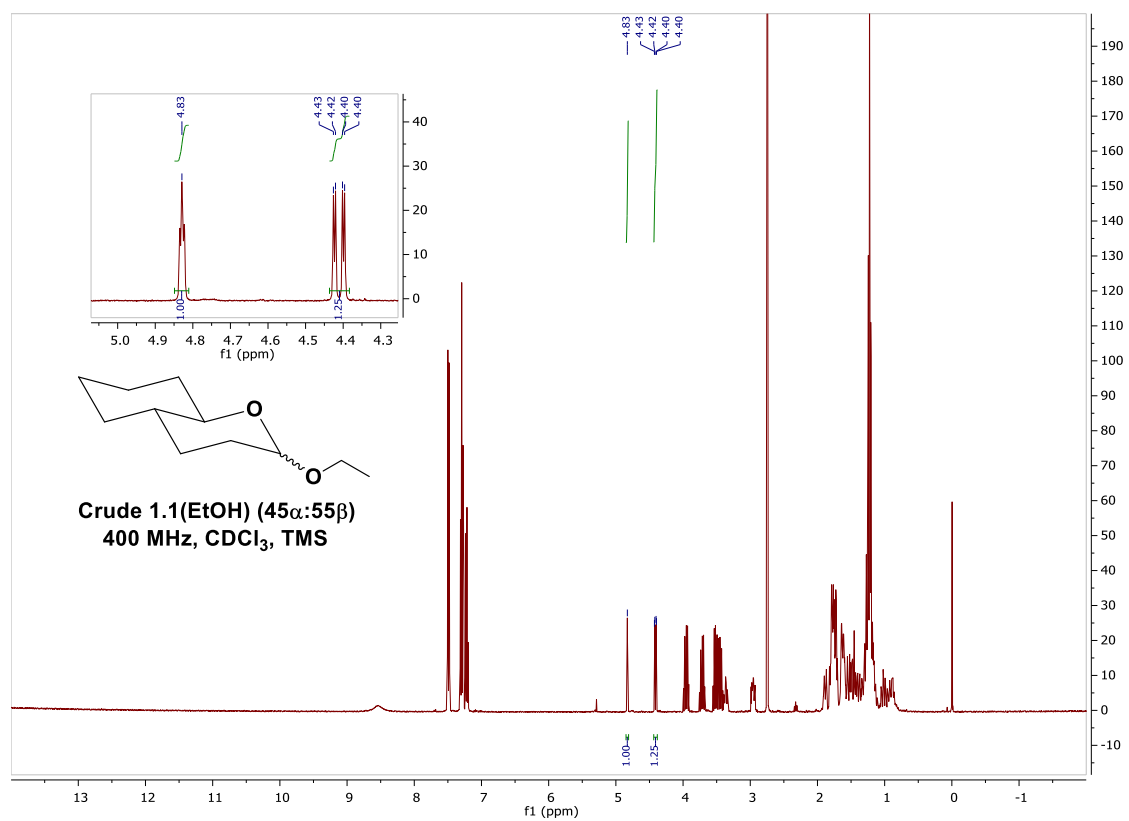
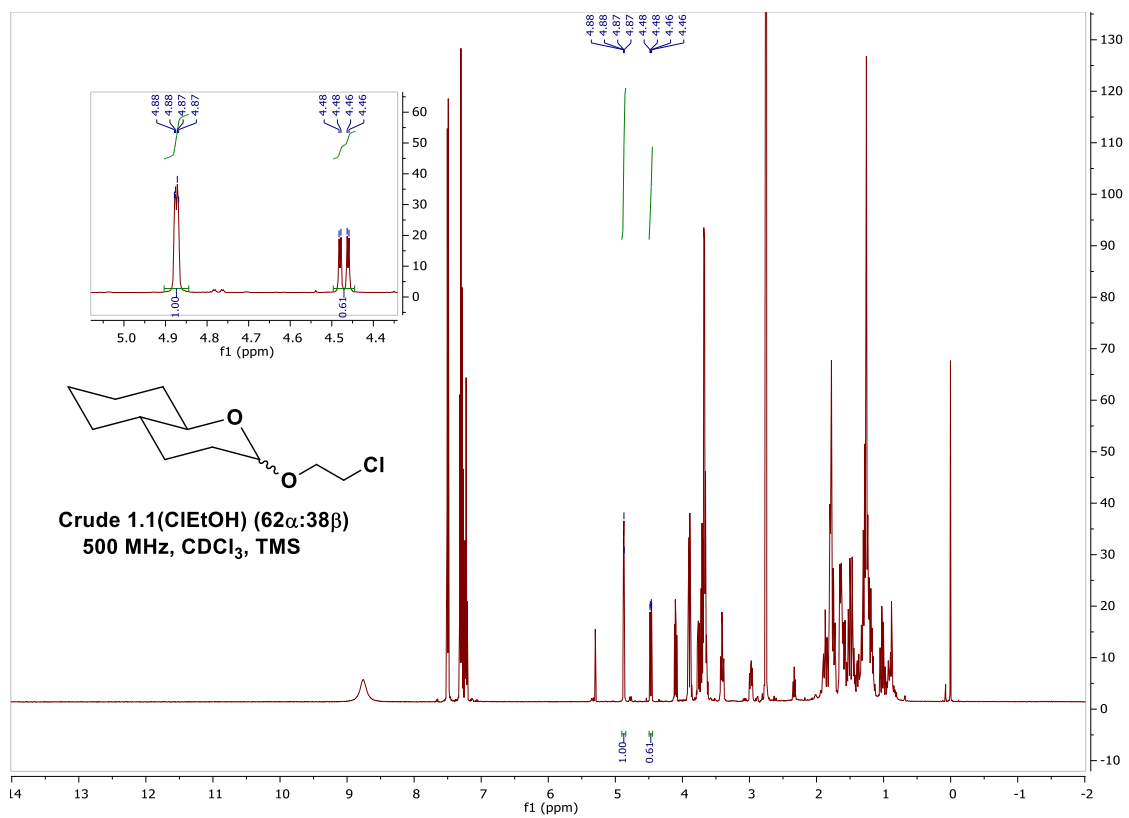


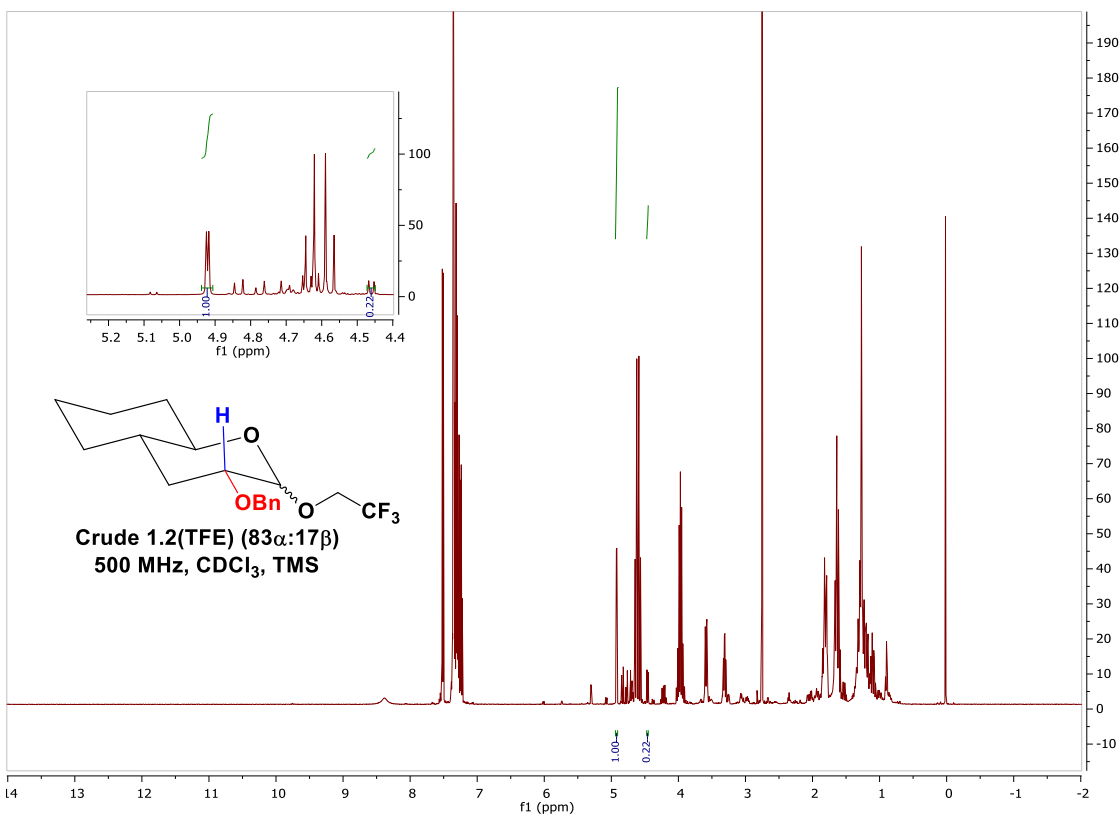
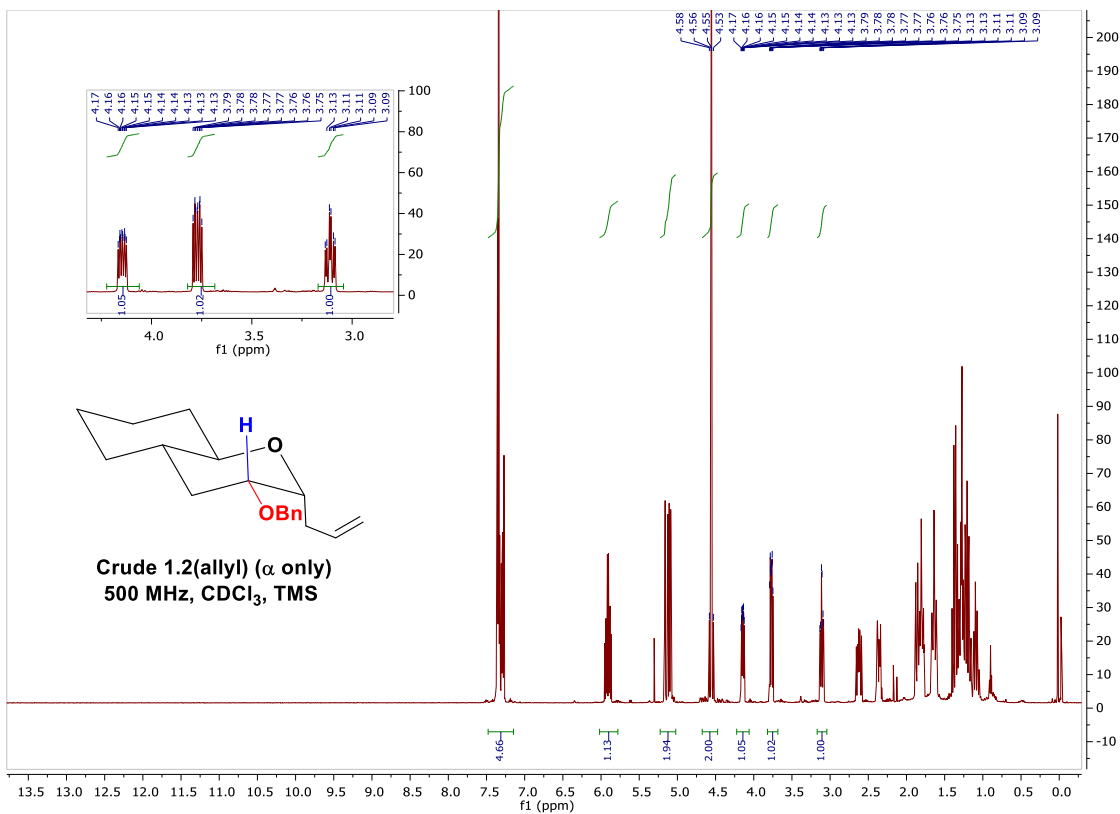


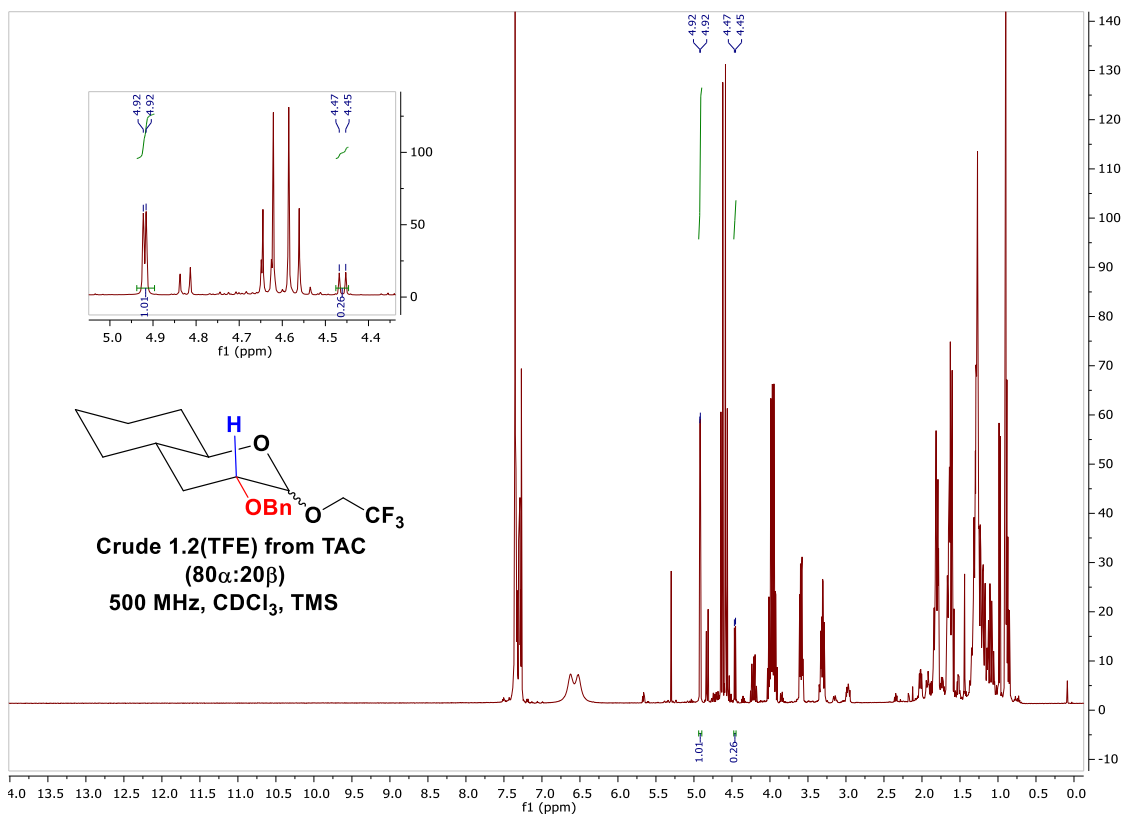
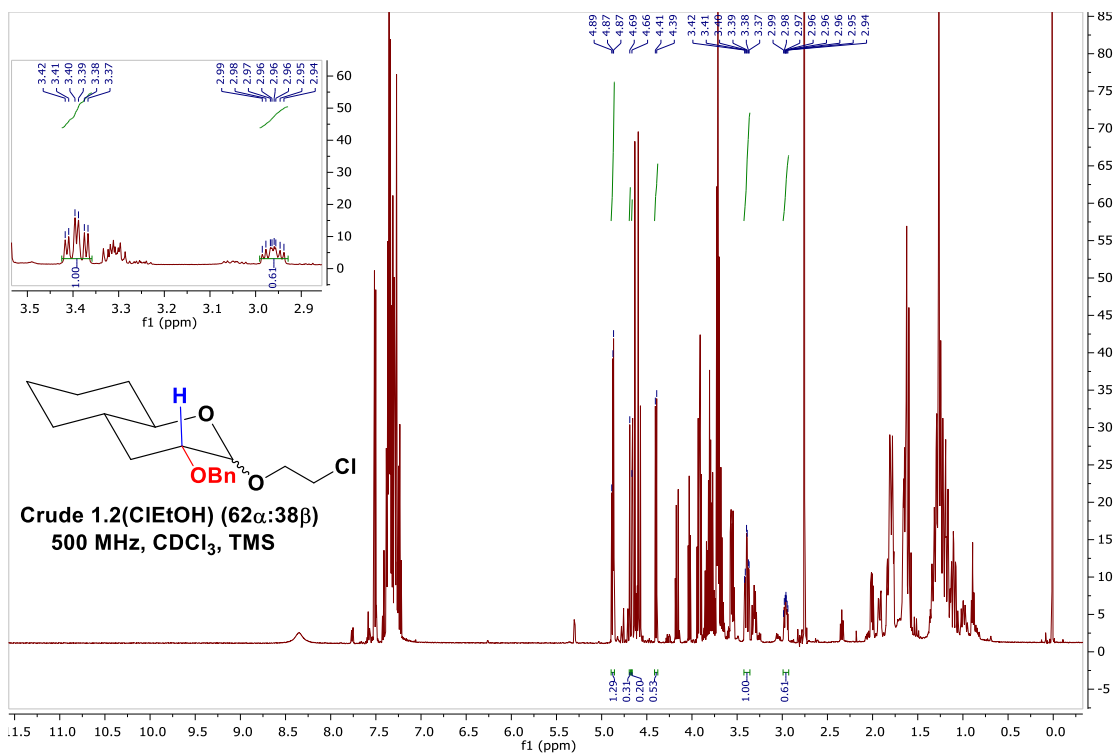


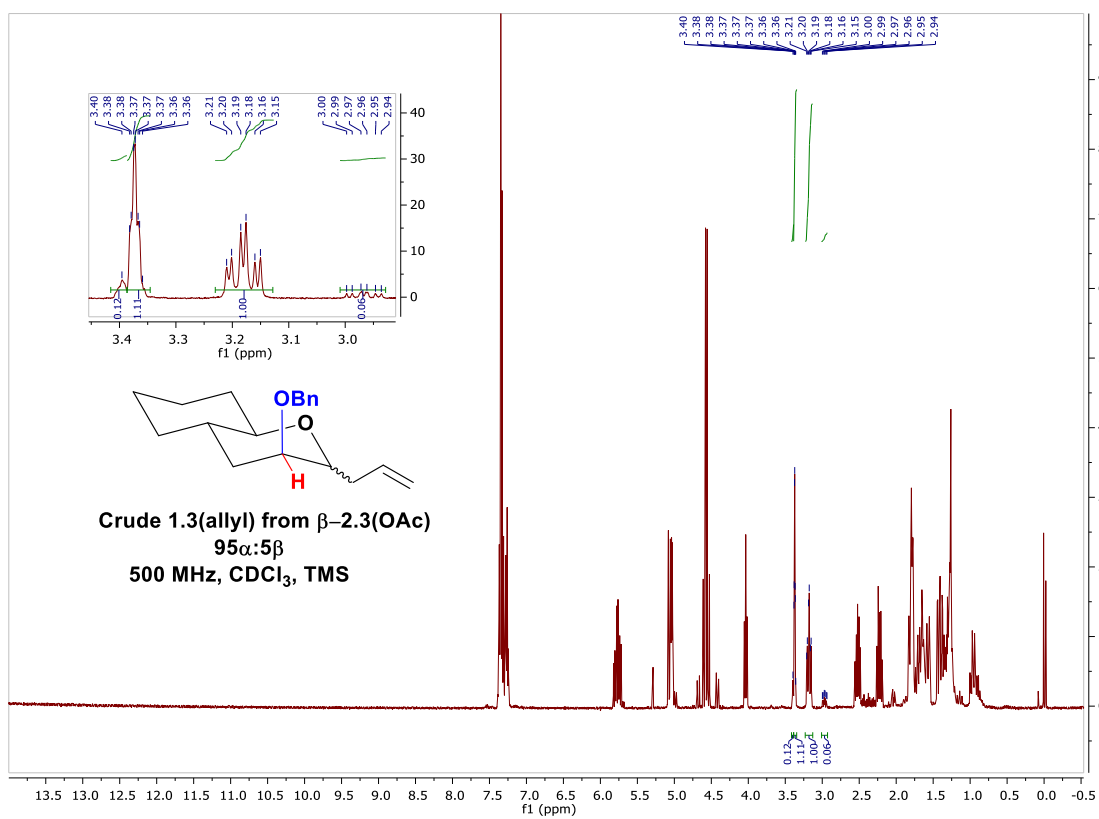
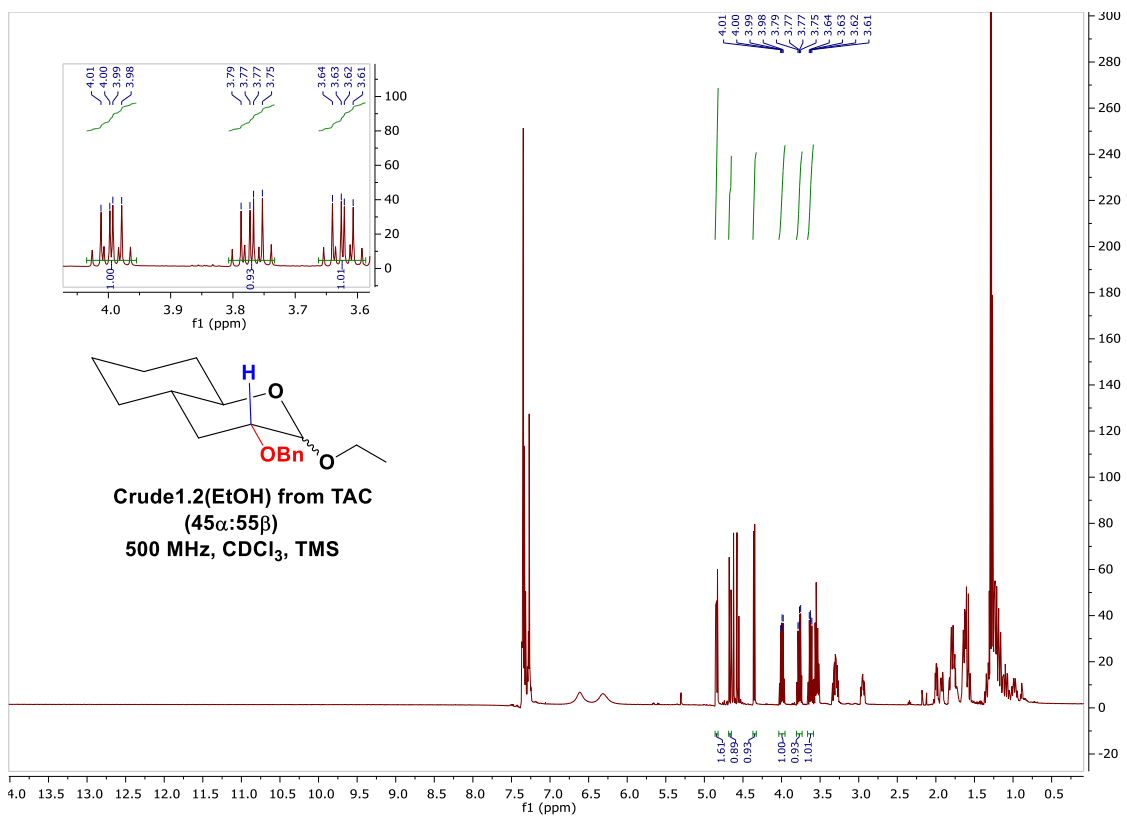
## E.2 Spectres RMN brutes des O et C-glycosylation dans le DCM

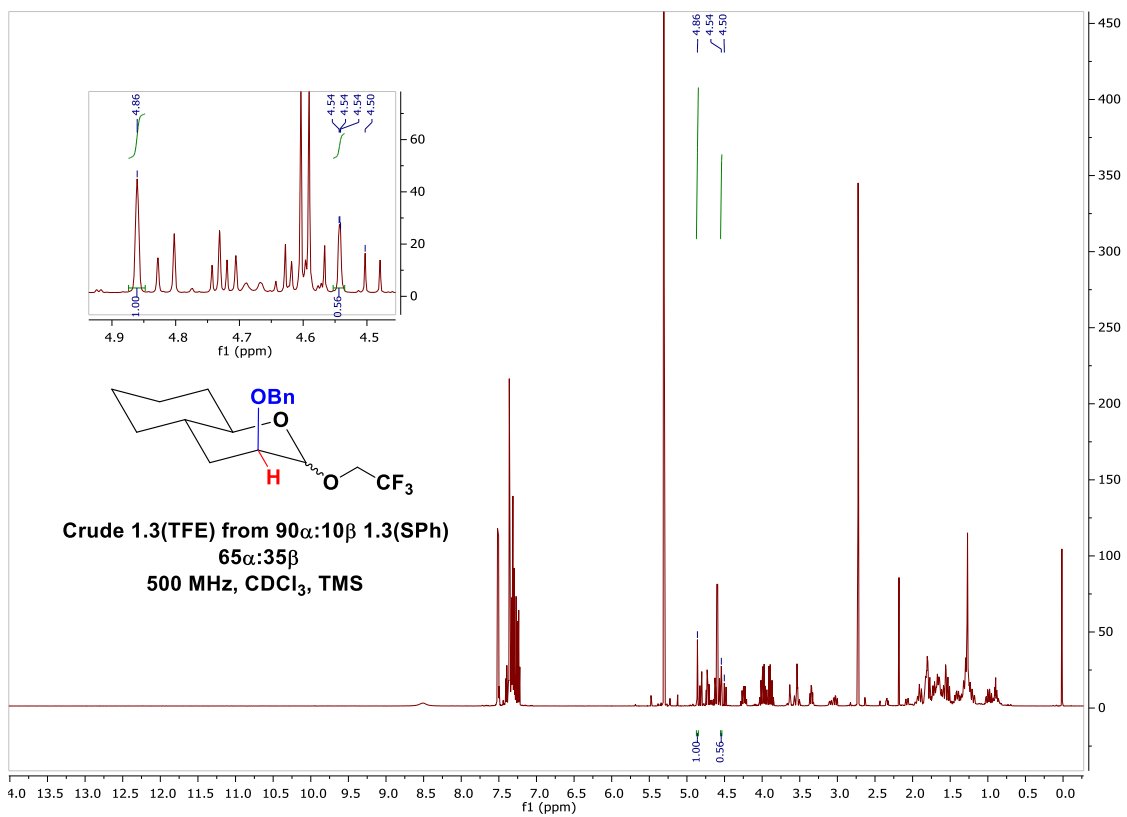
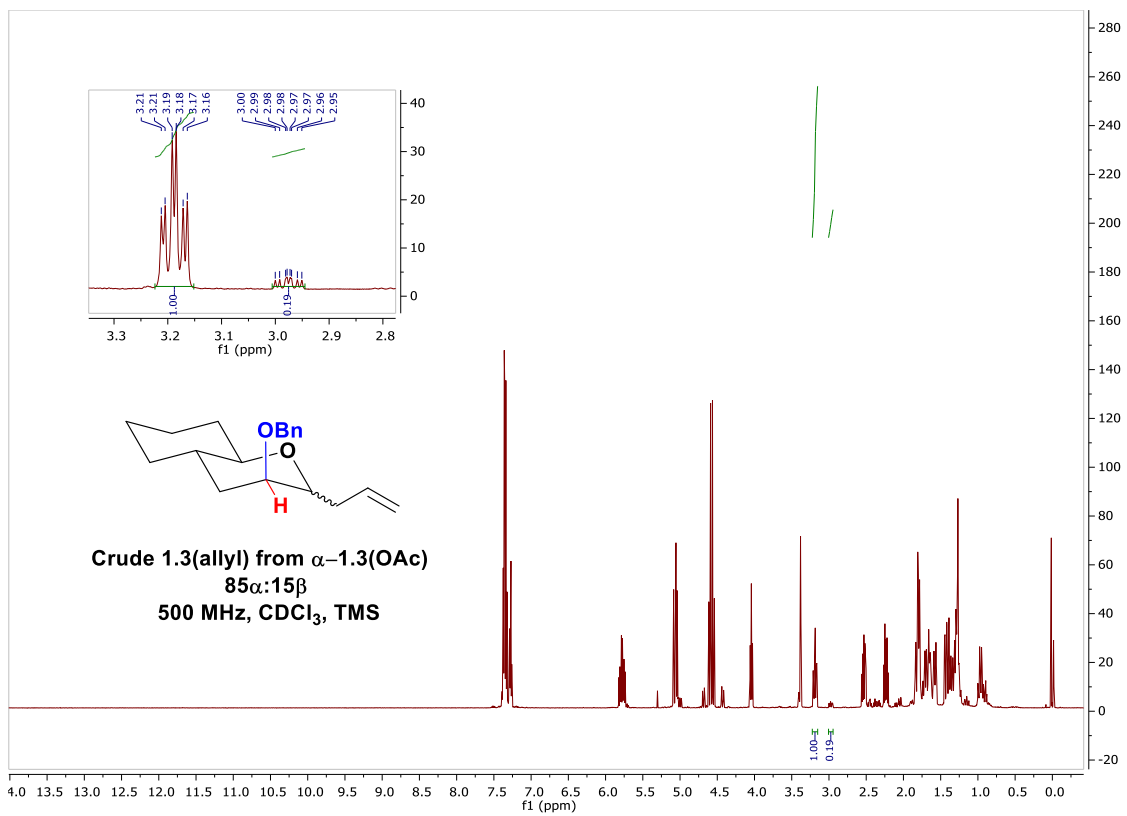


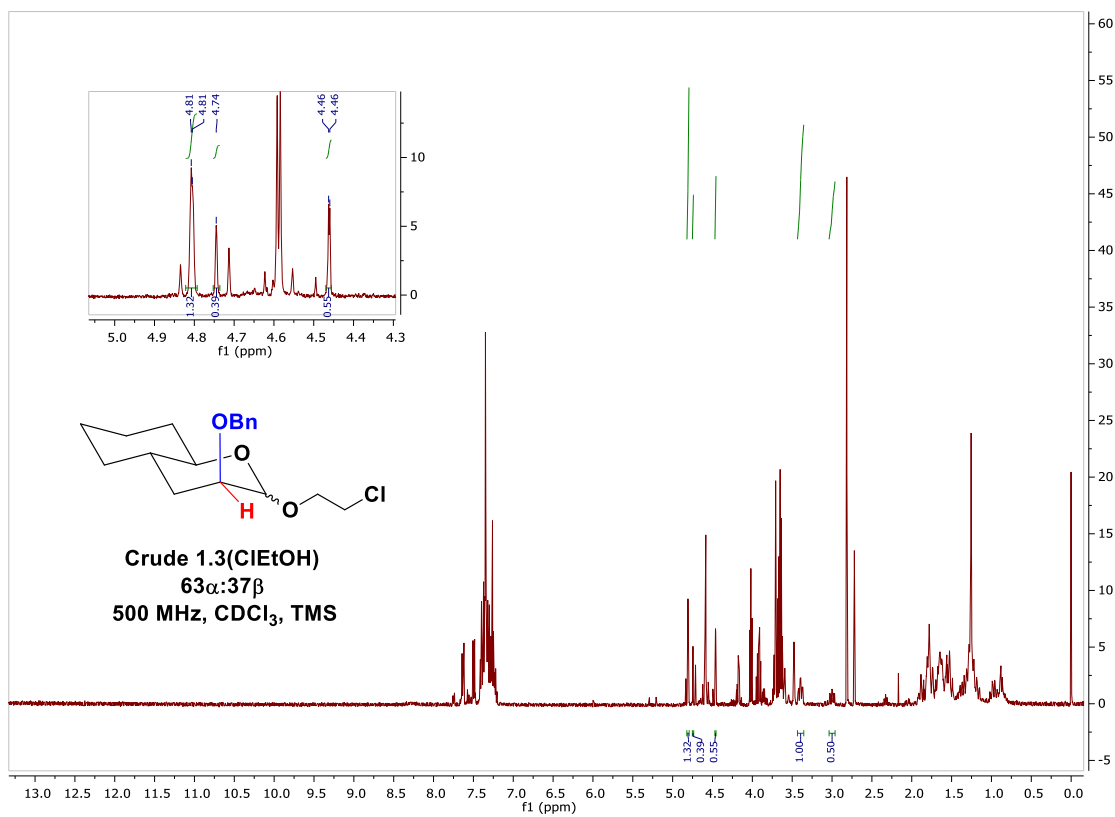
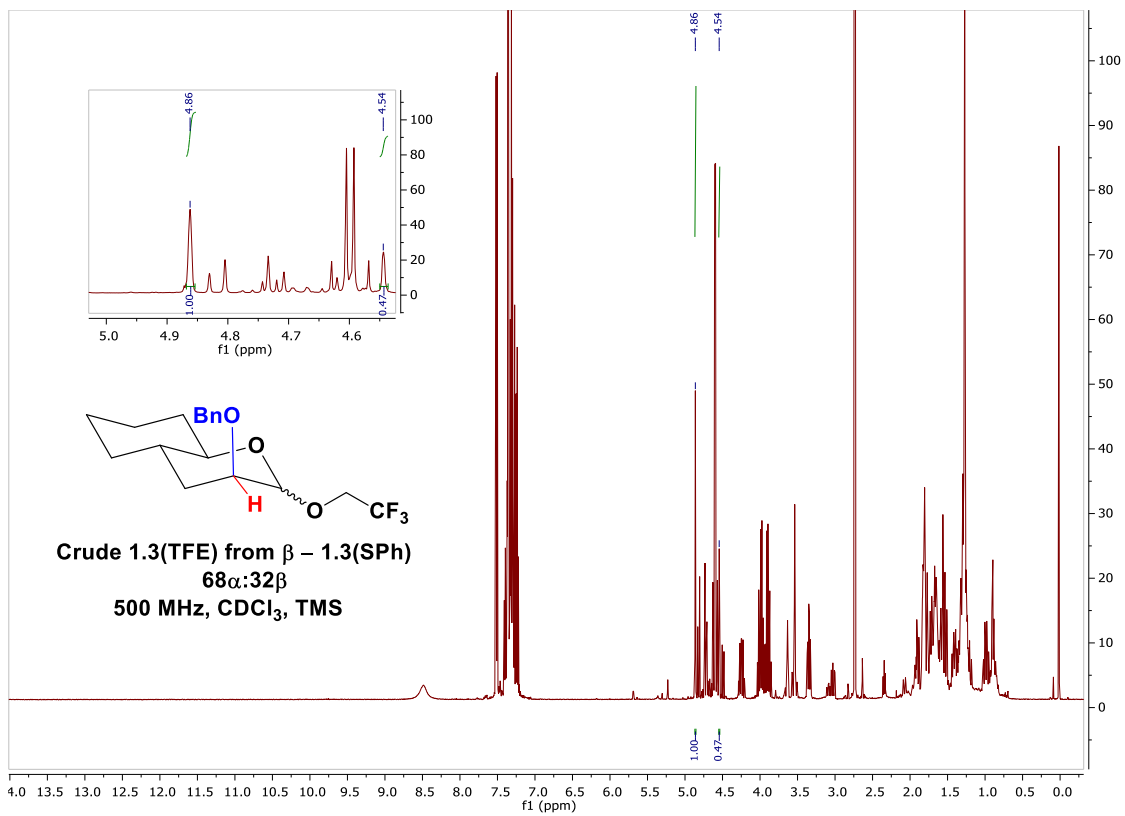


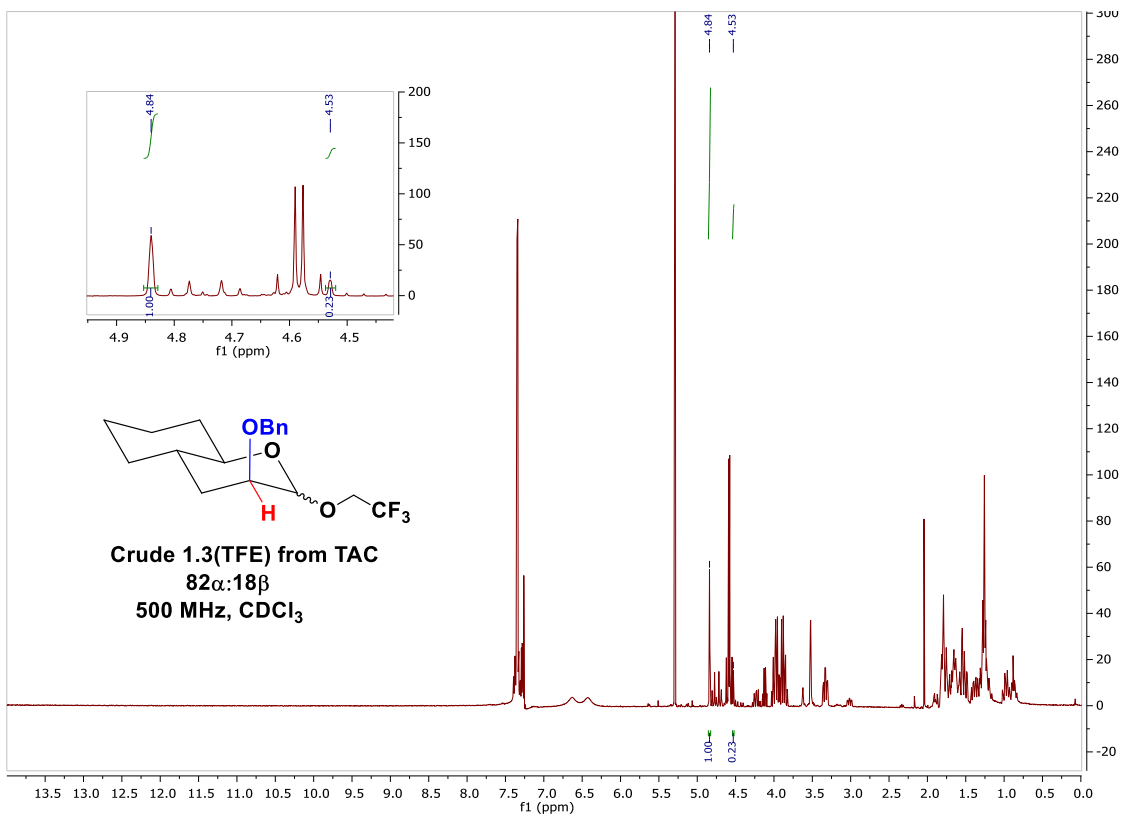
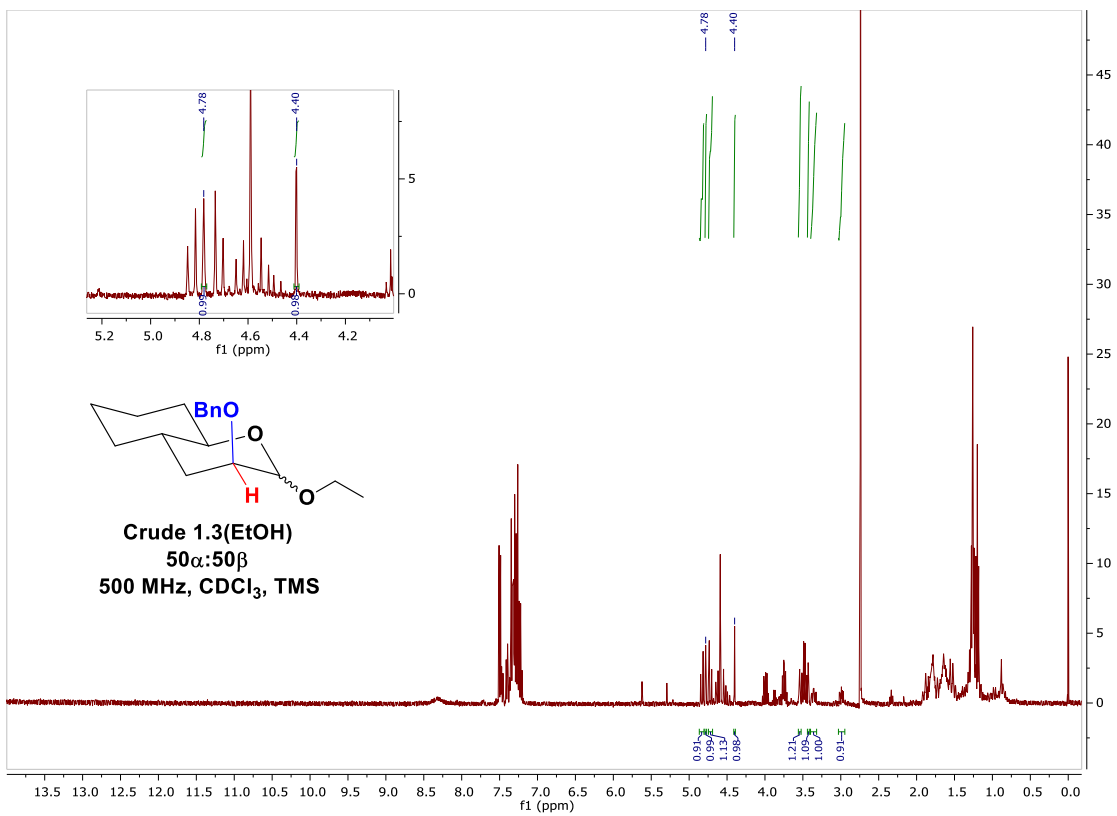




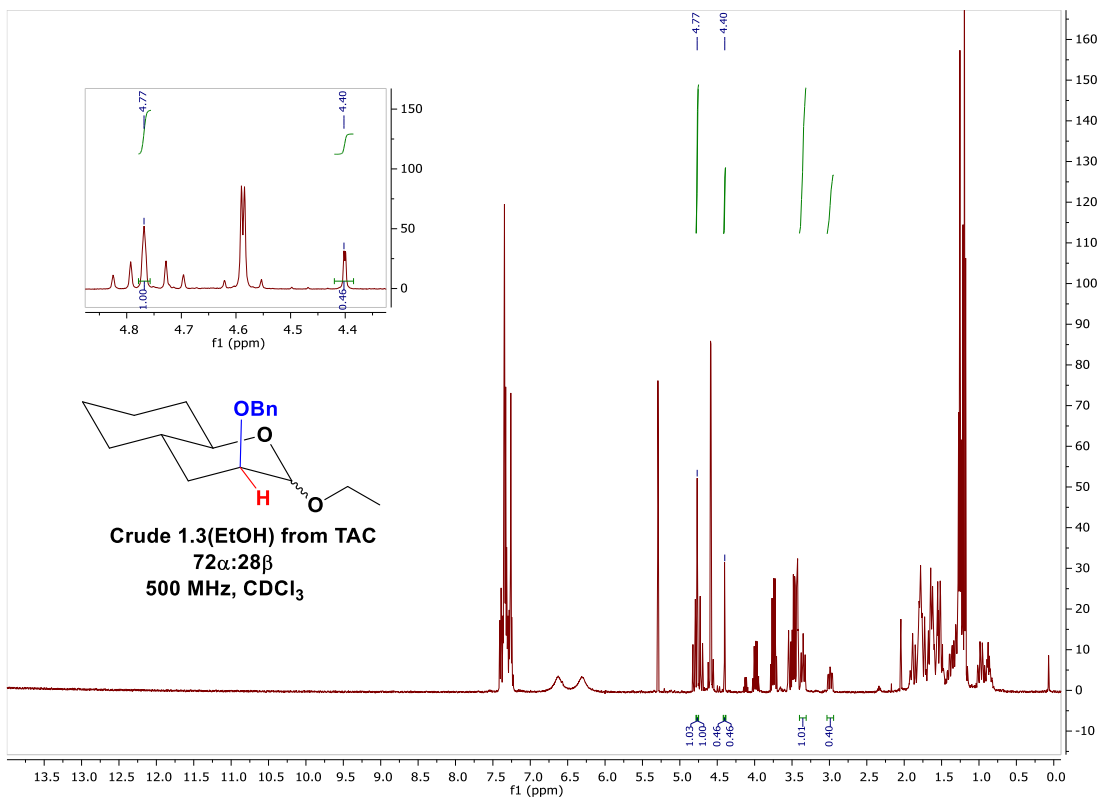




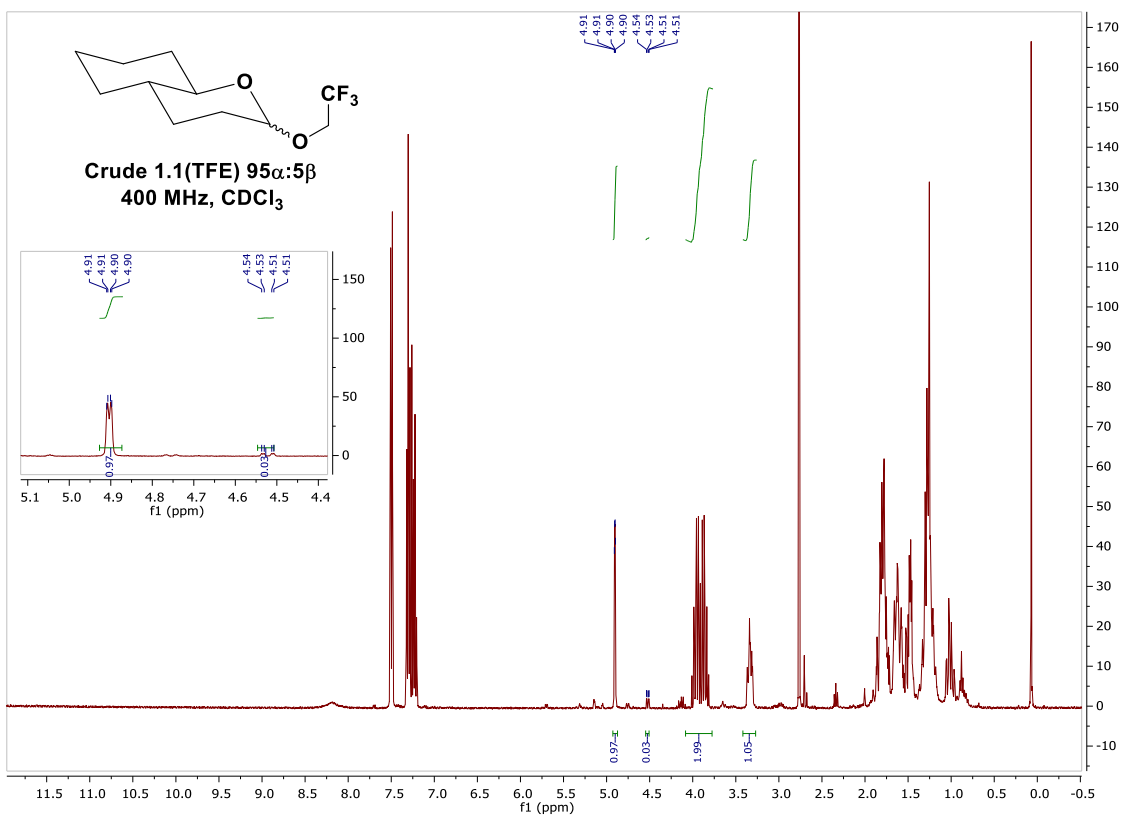


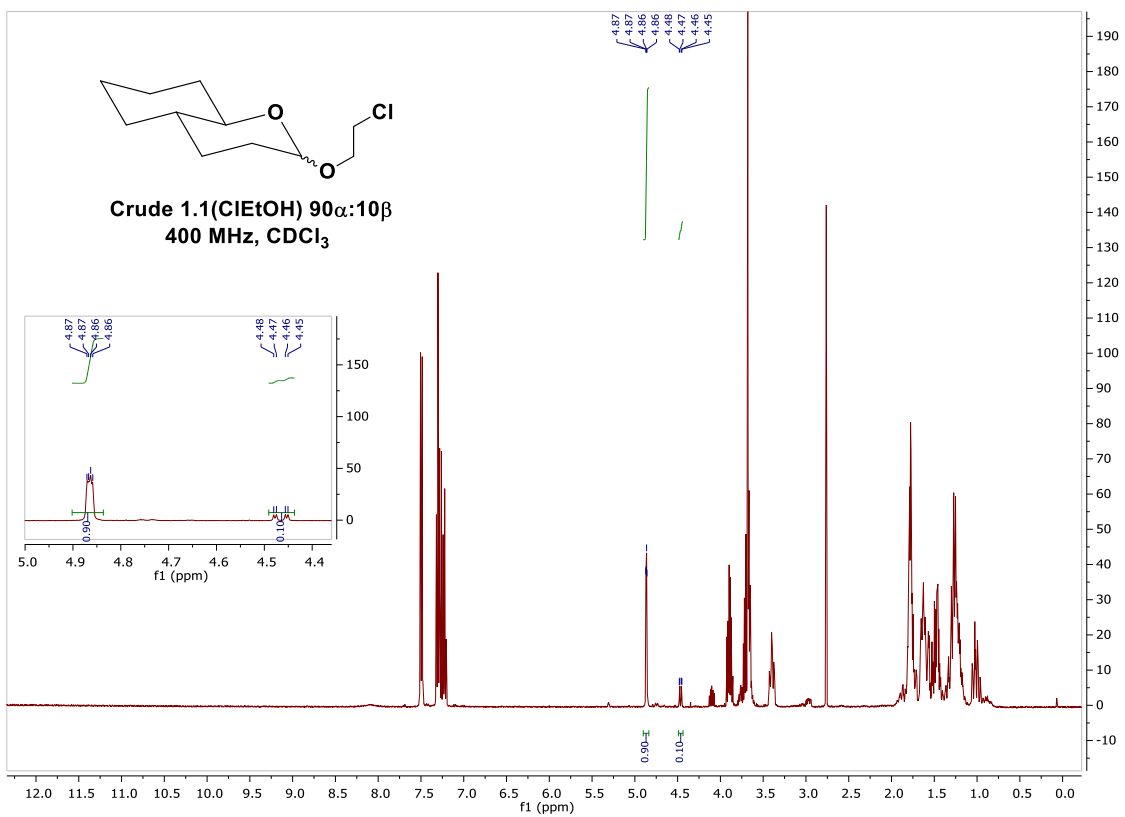
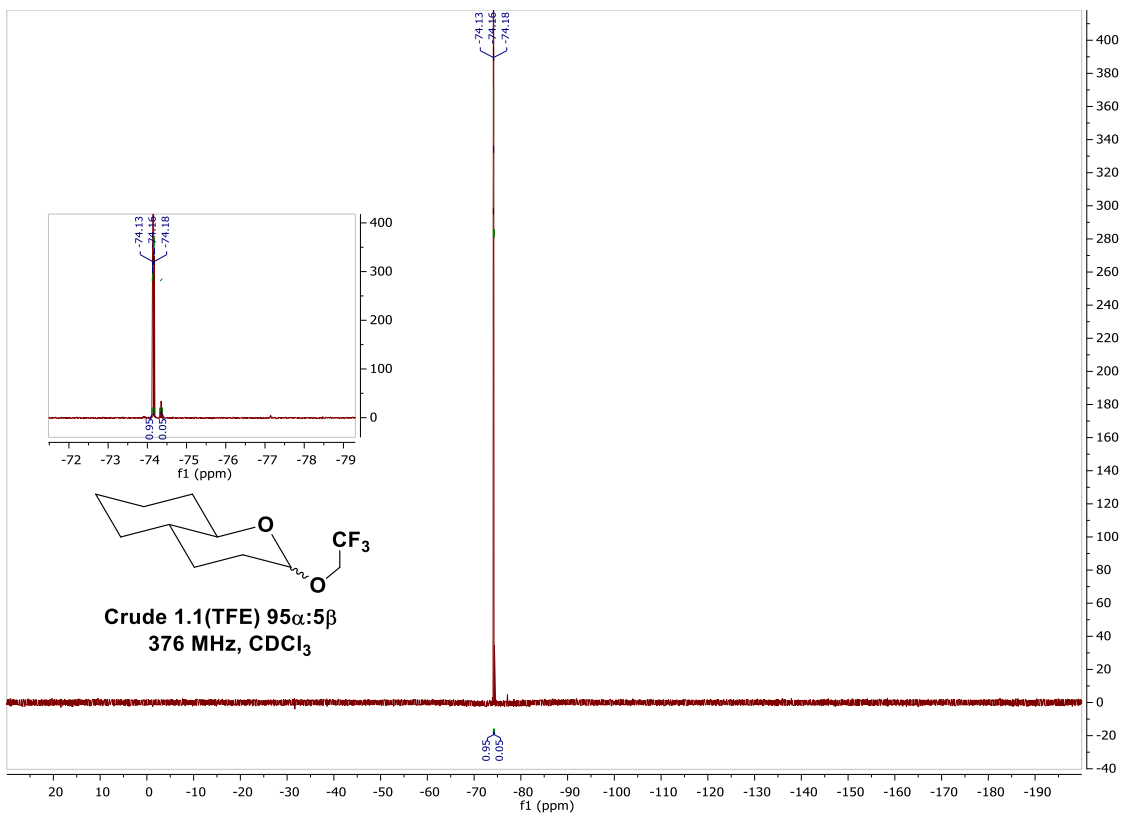


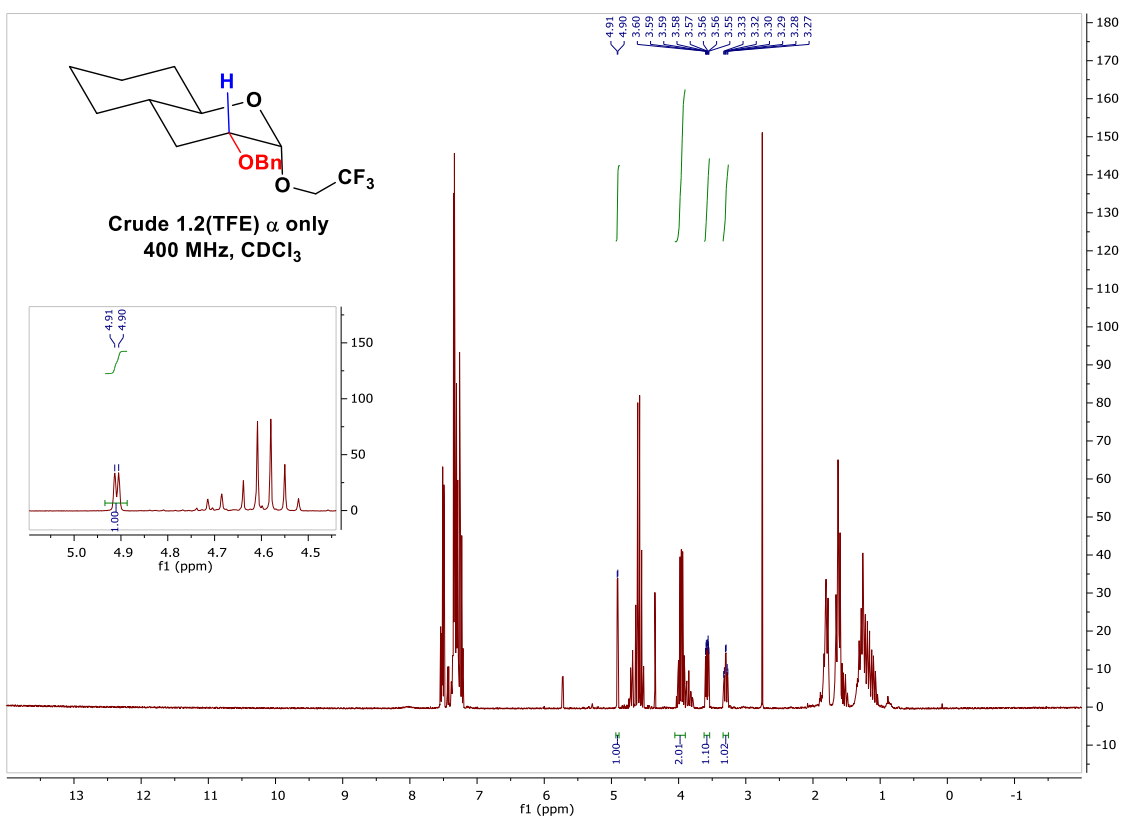
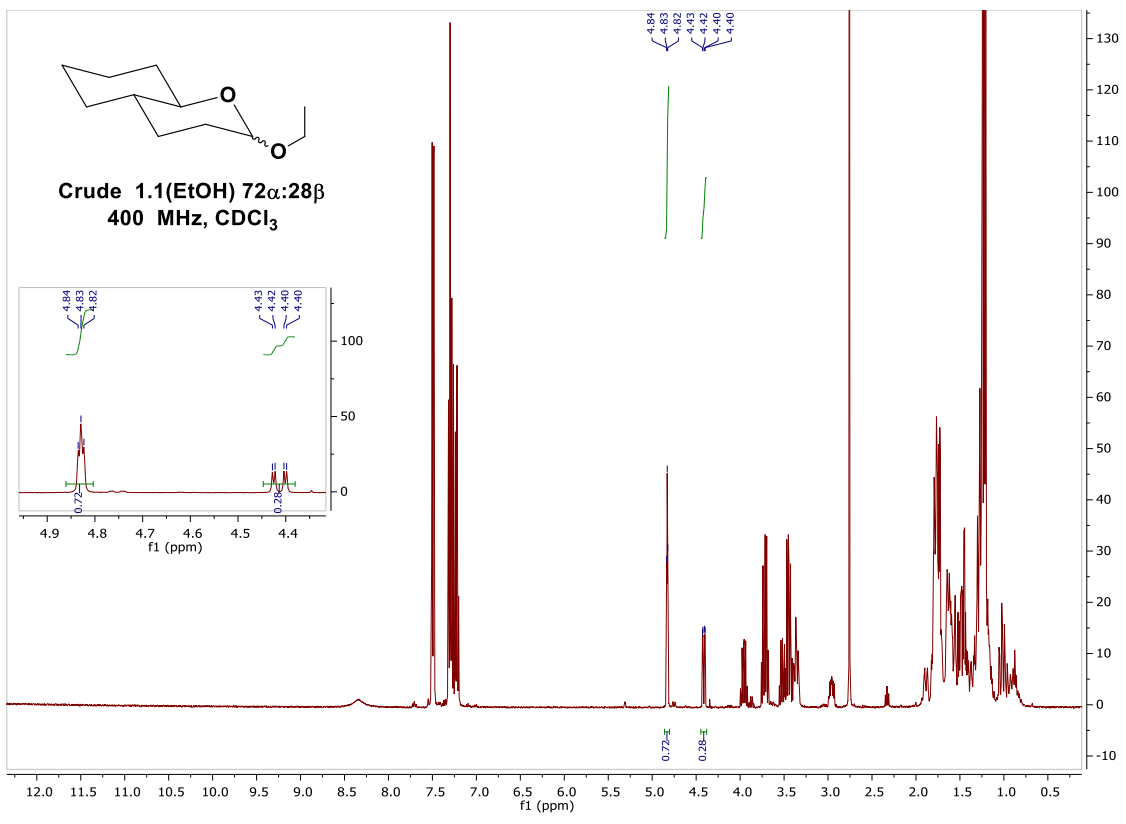


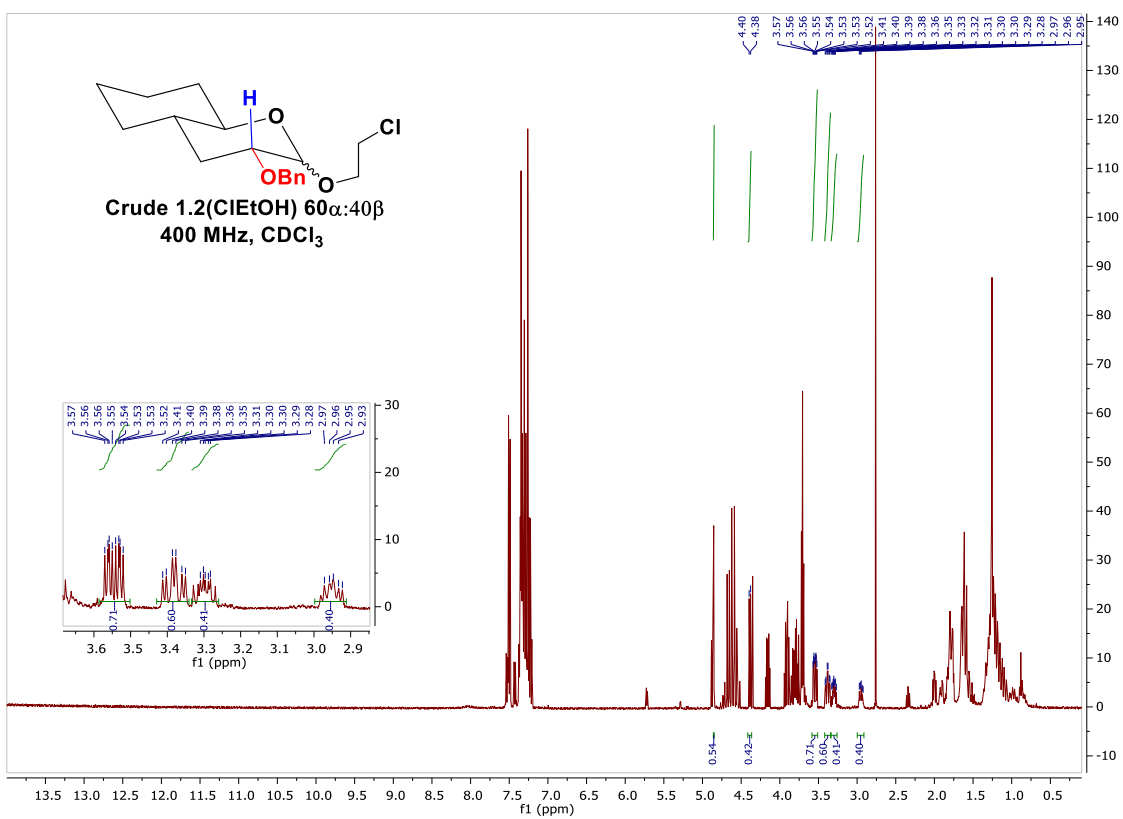
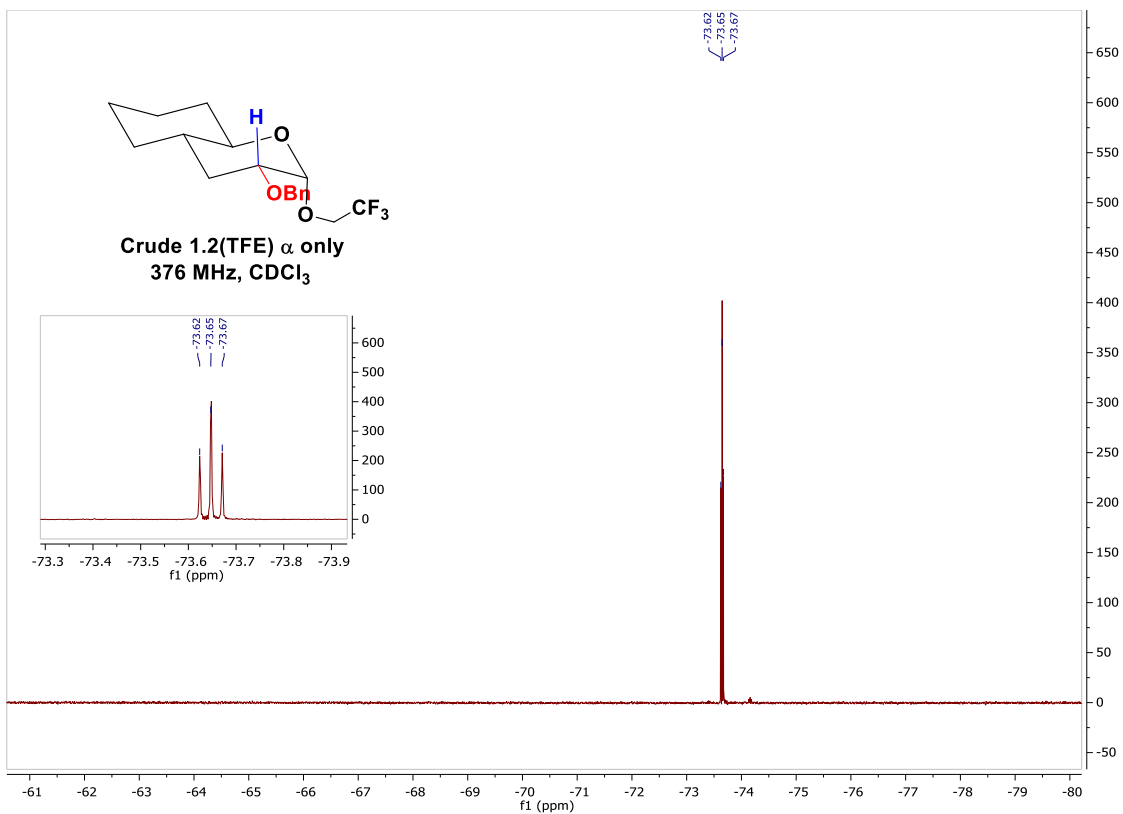


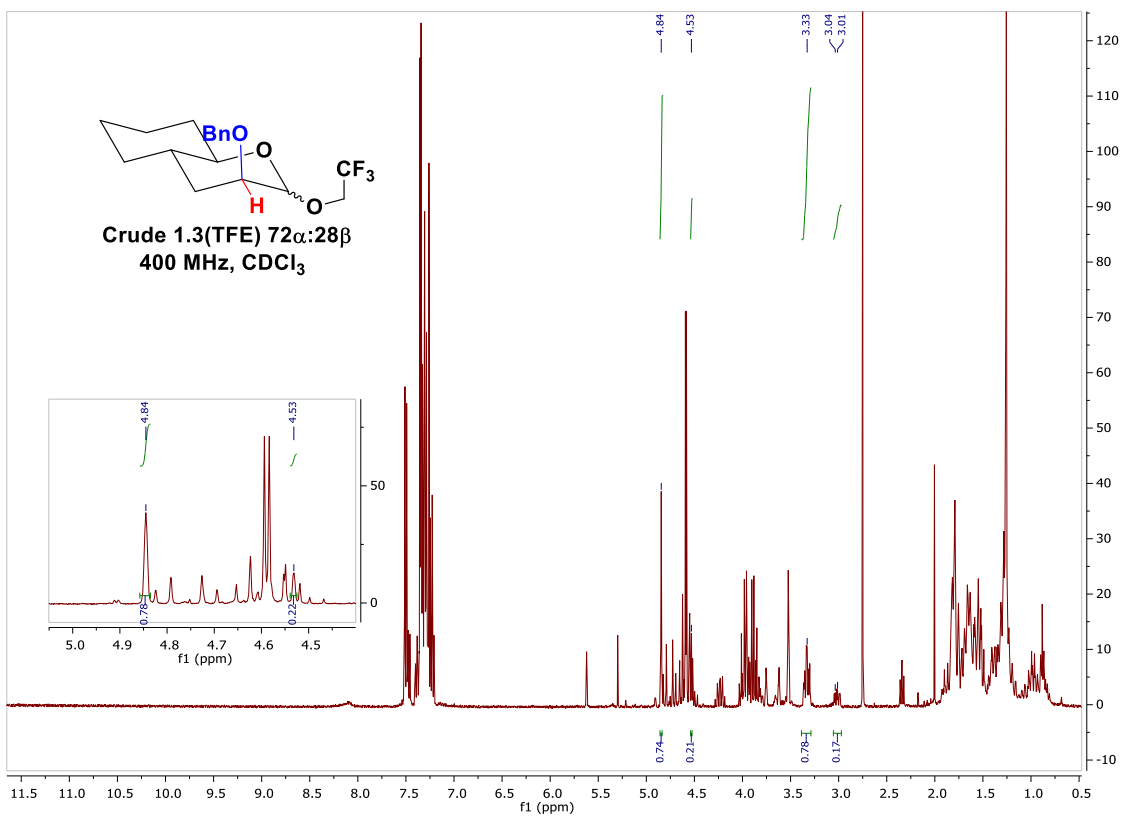
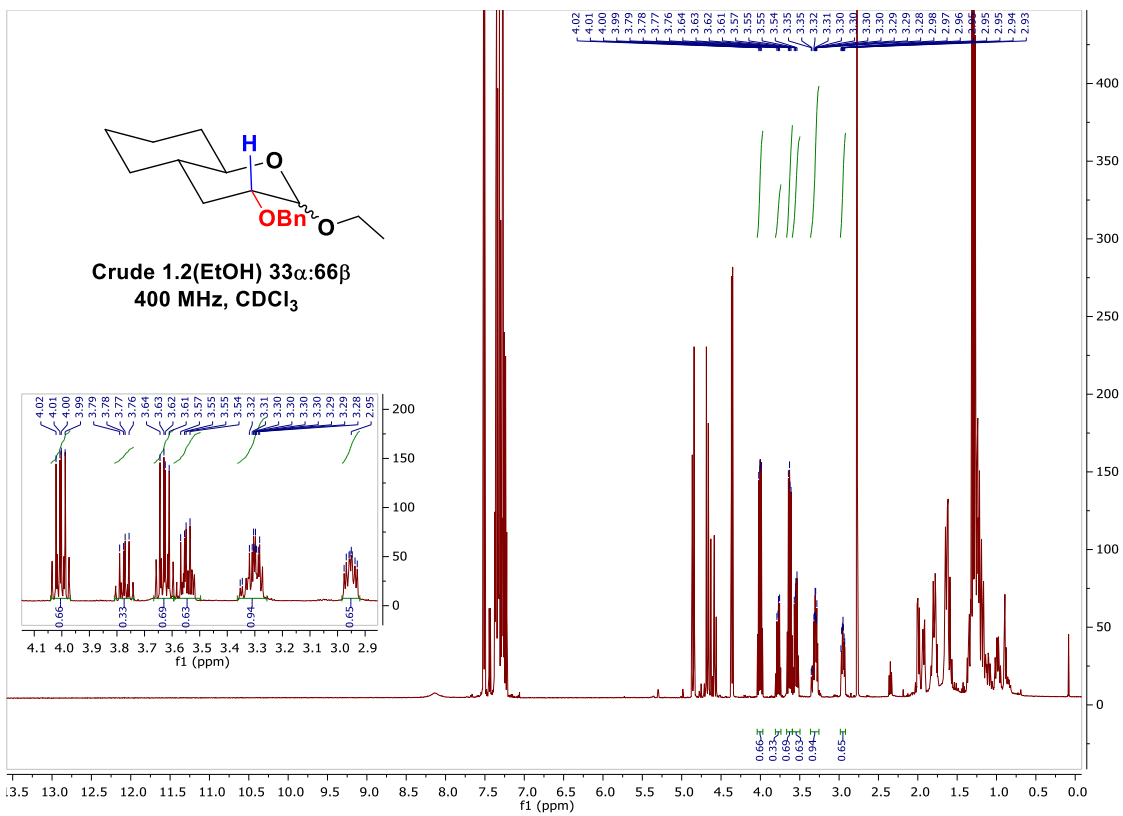
### E.3 Spectres RMN brutes des O et C-glycosylation dans le CH<sub>3</sub>CN

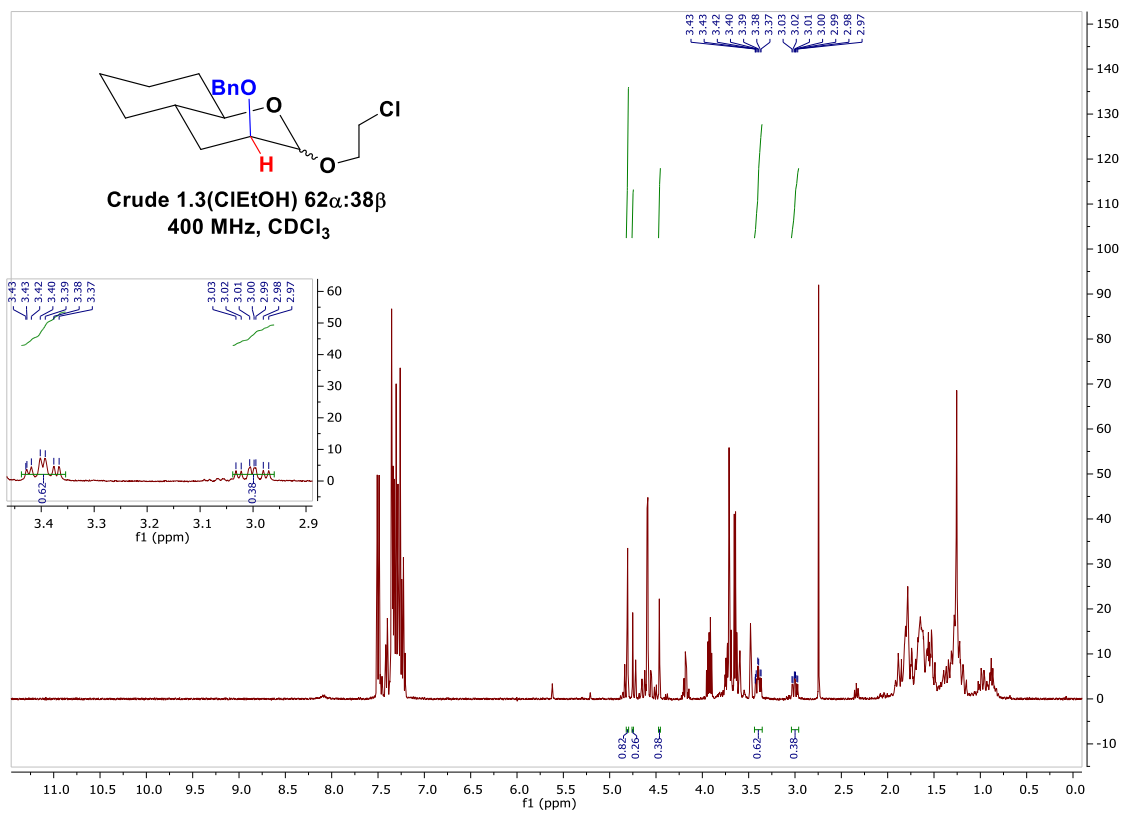
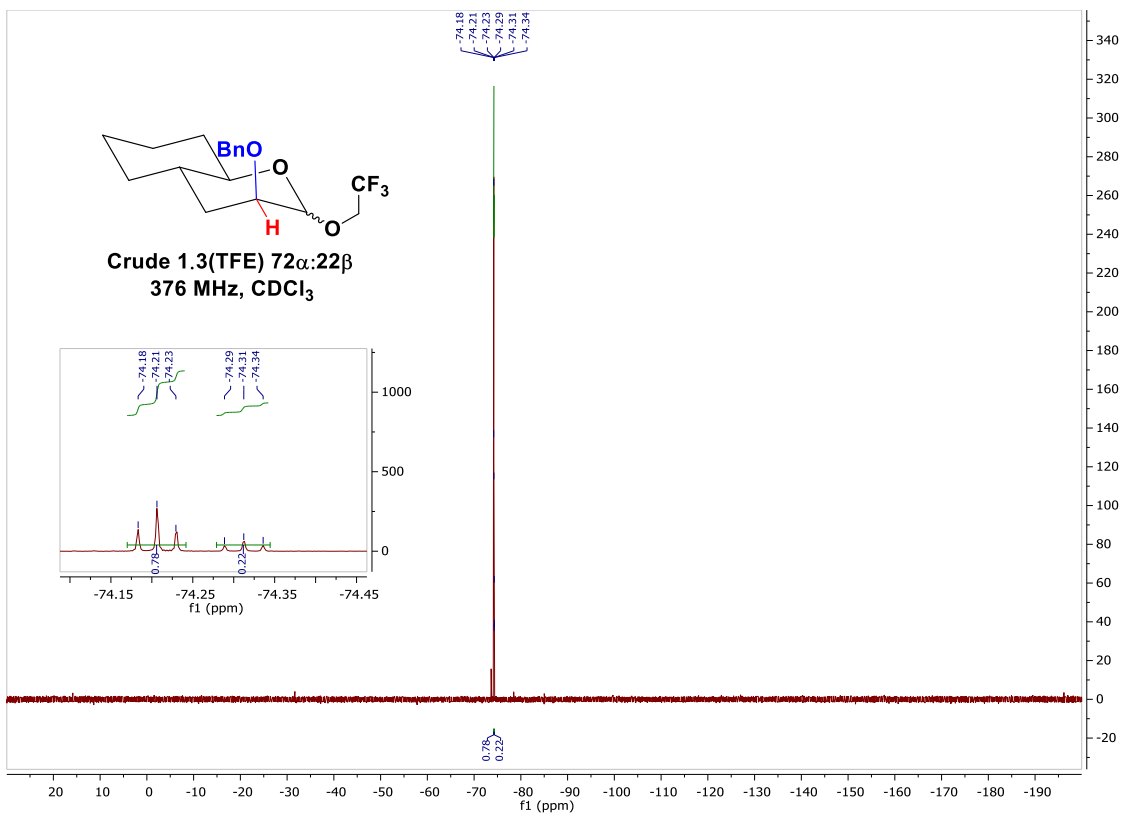


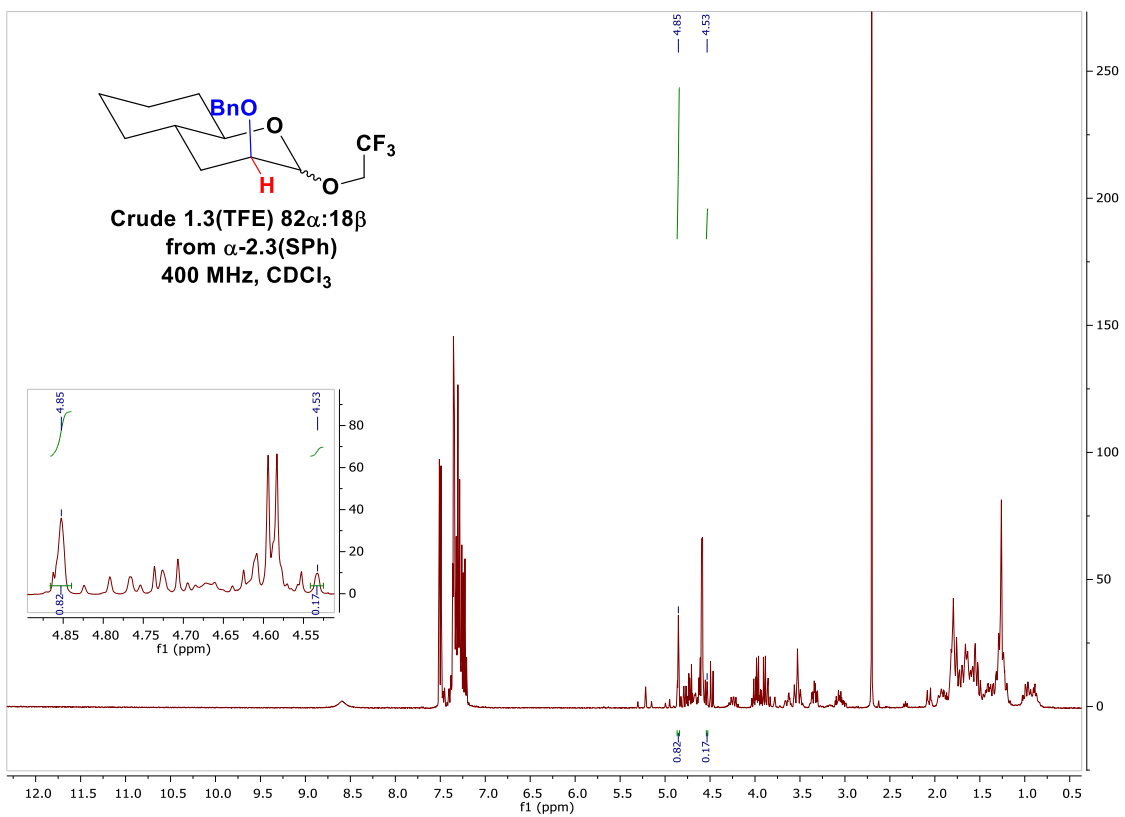
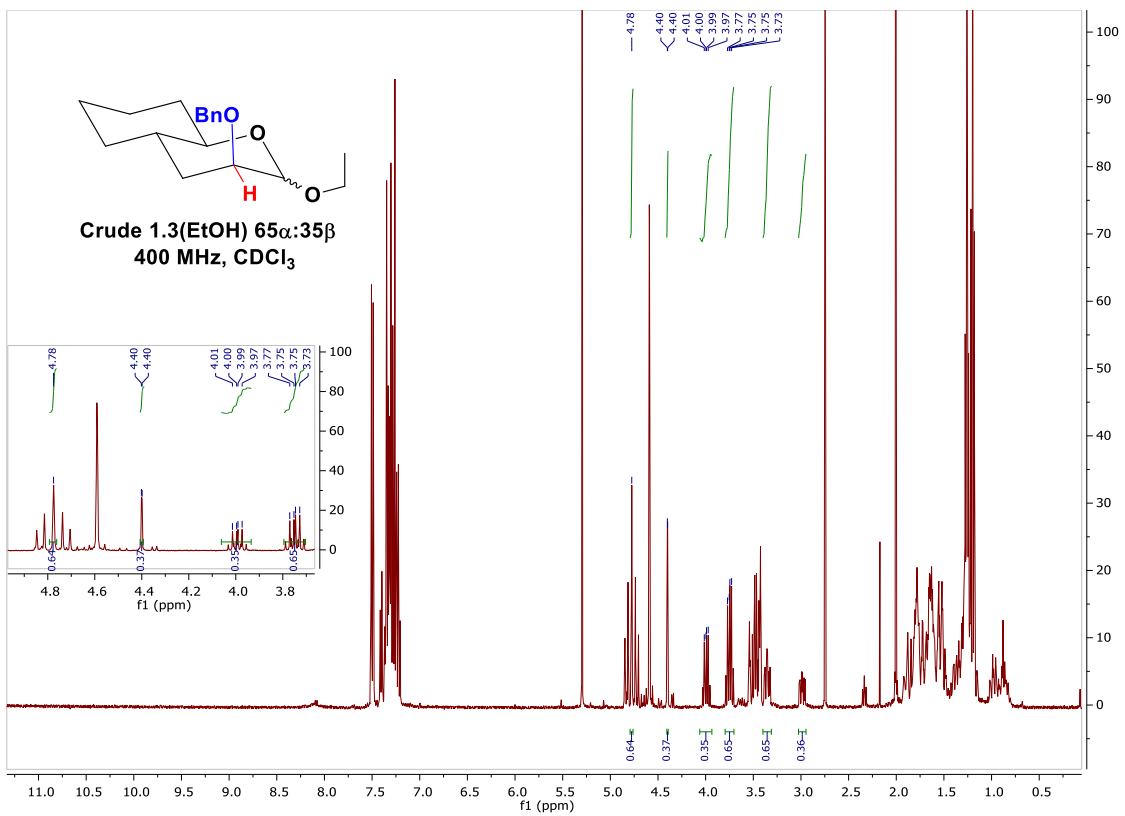


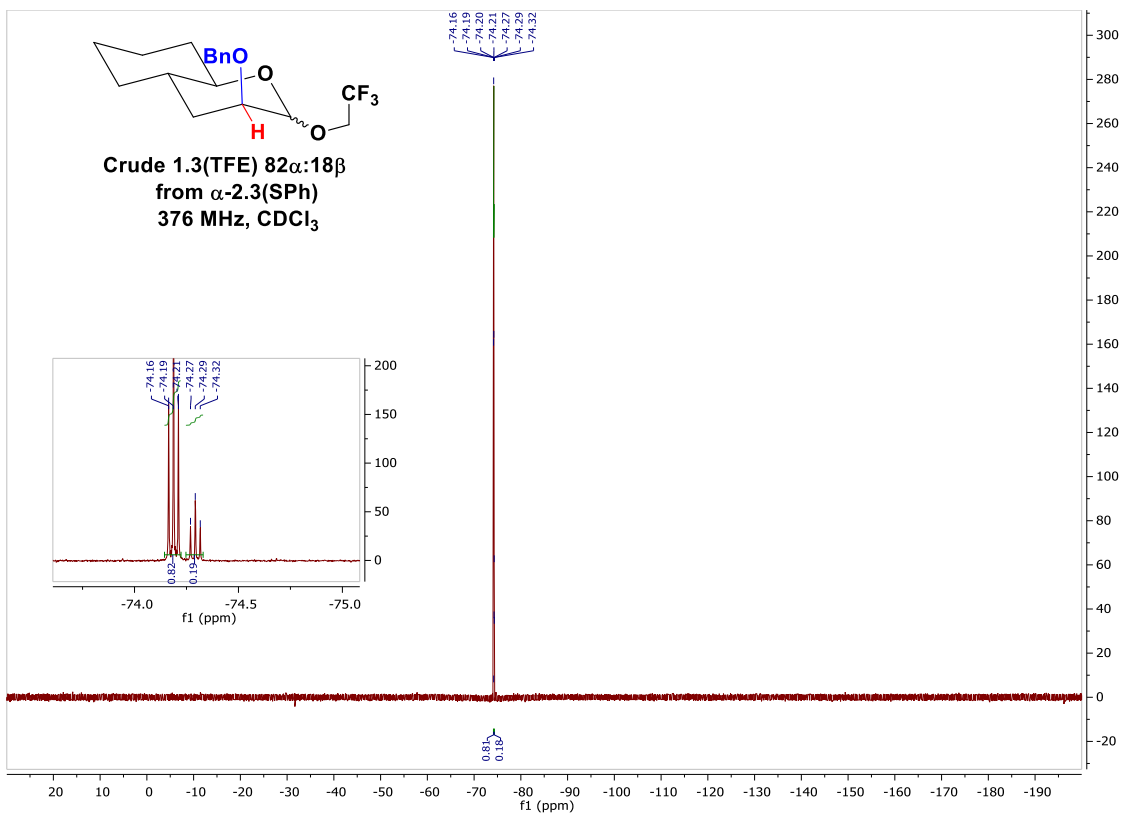




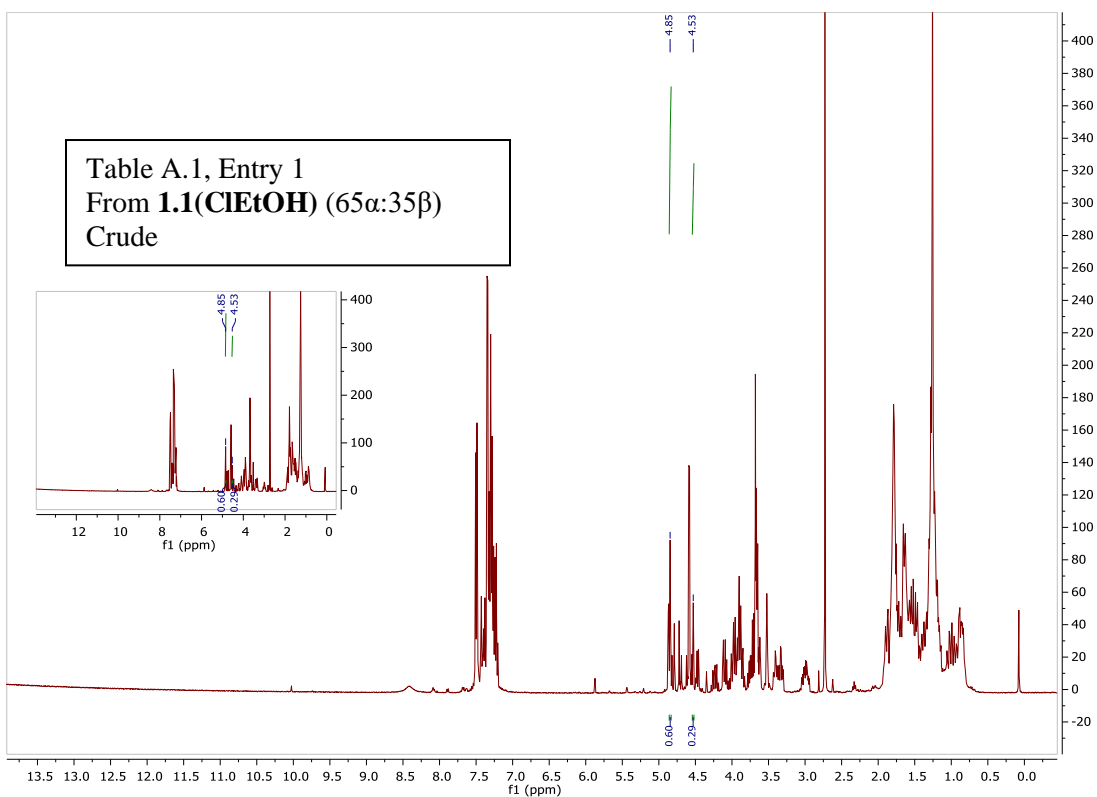




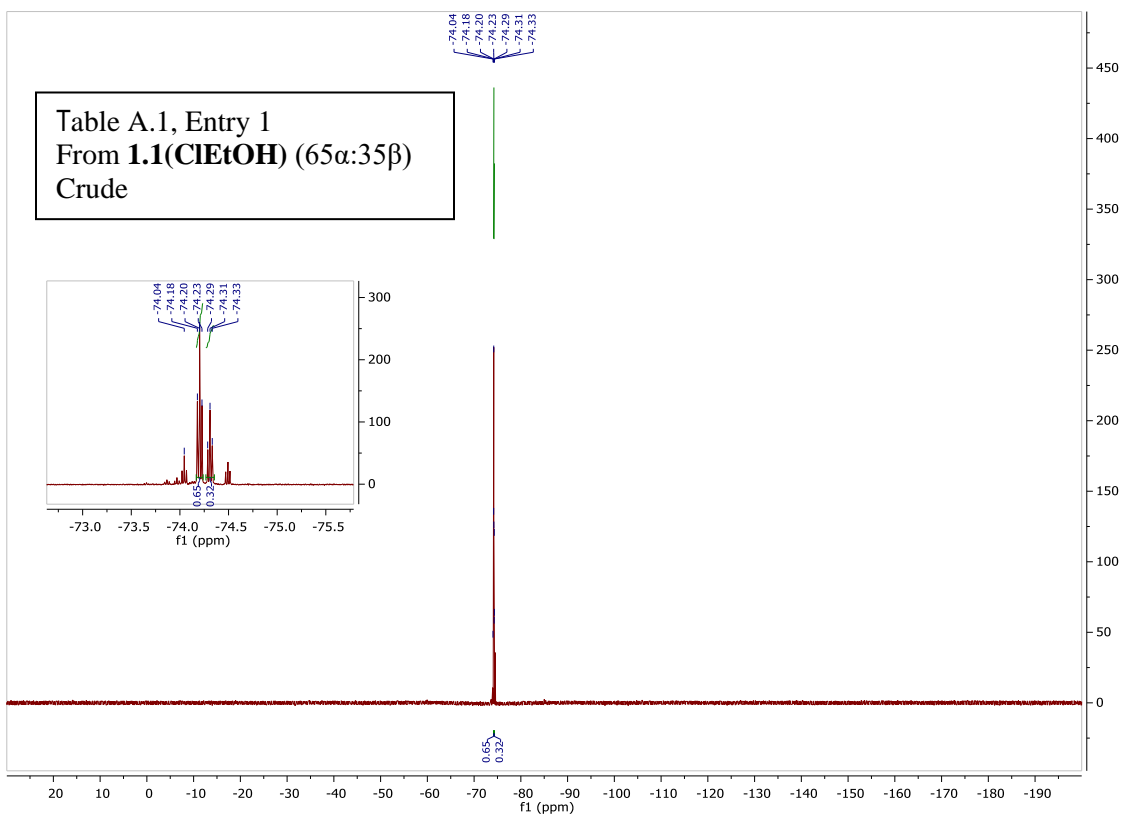
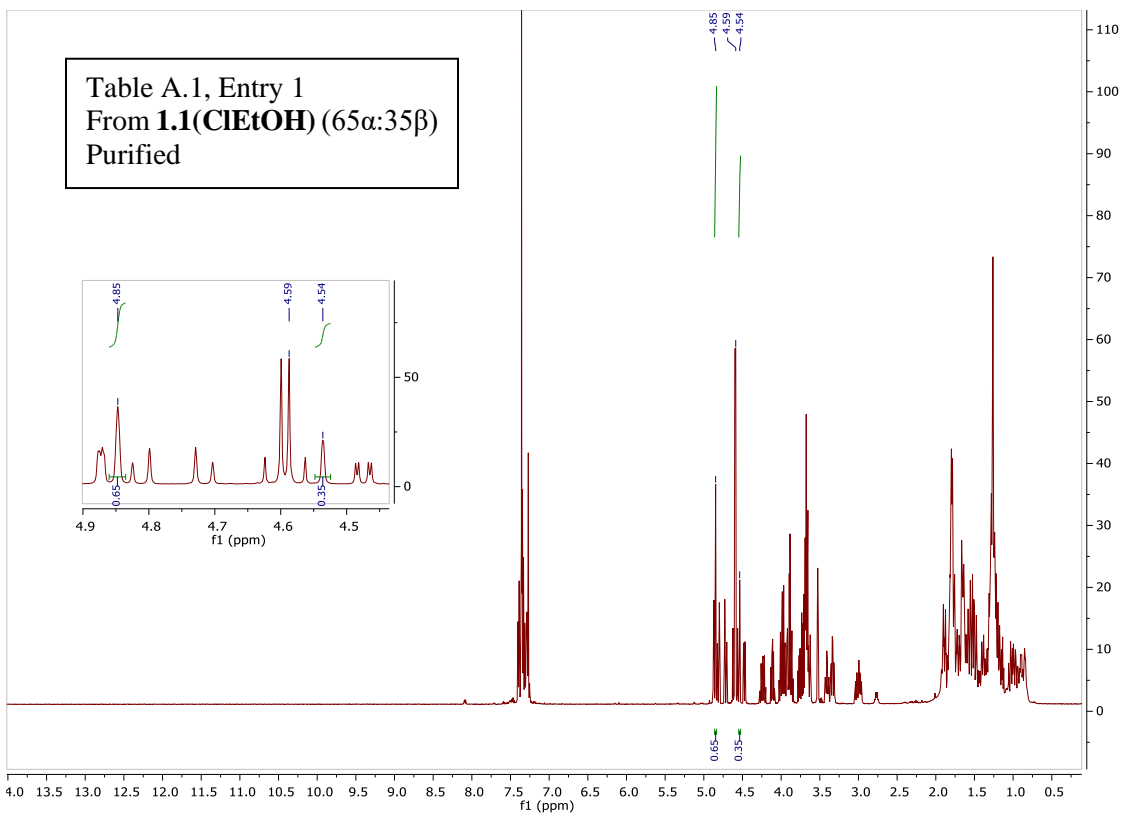


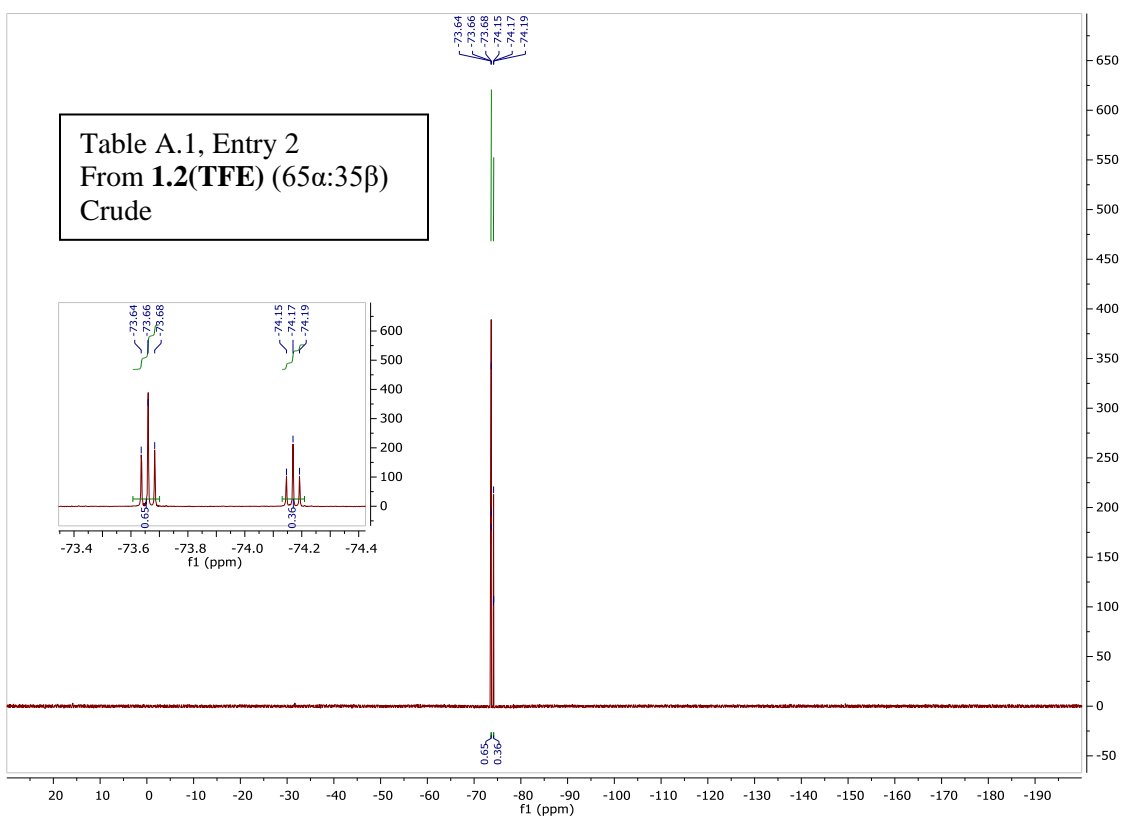
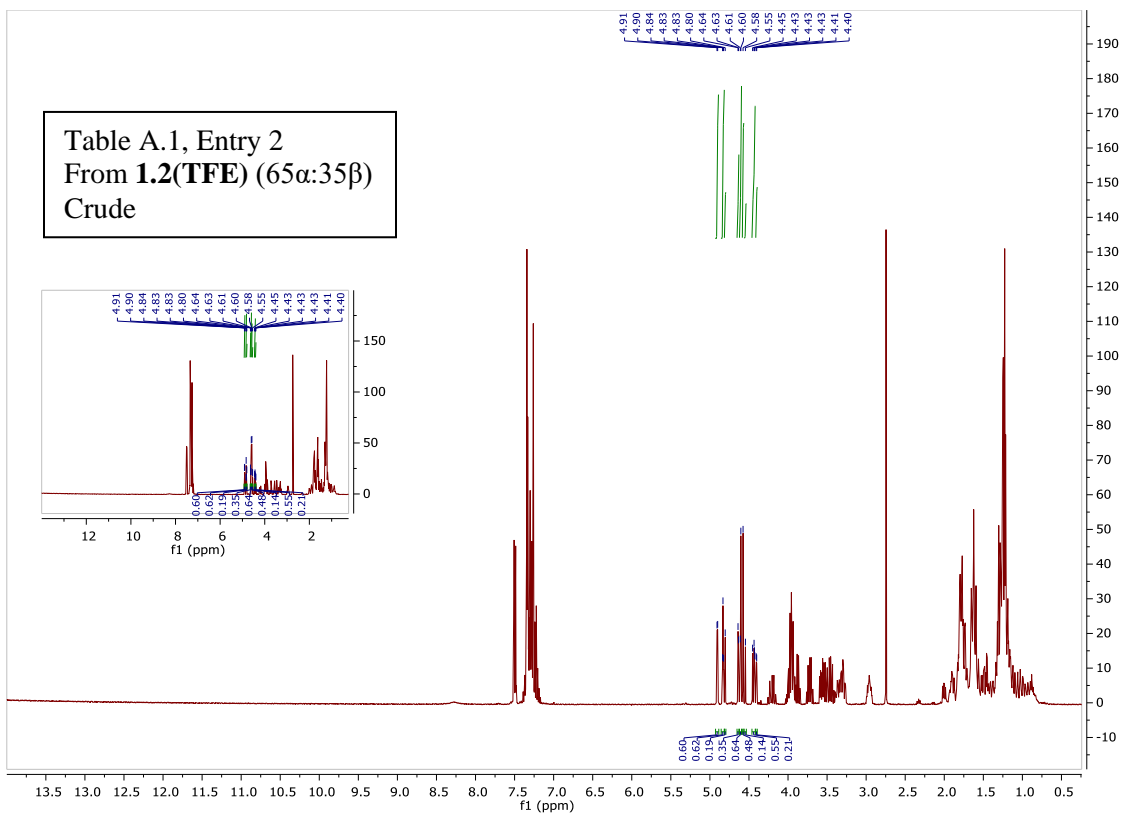


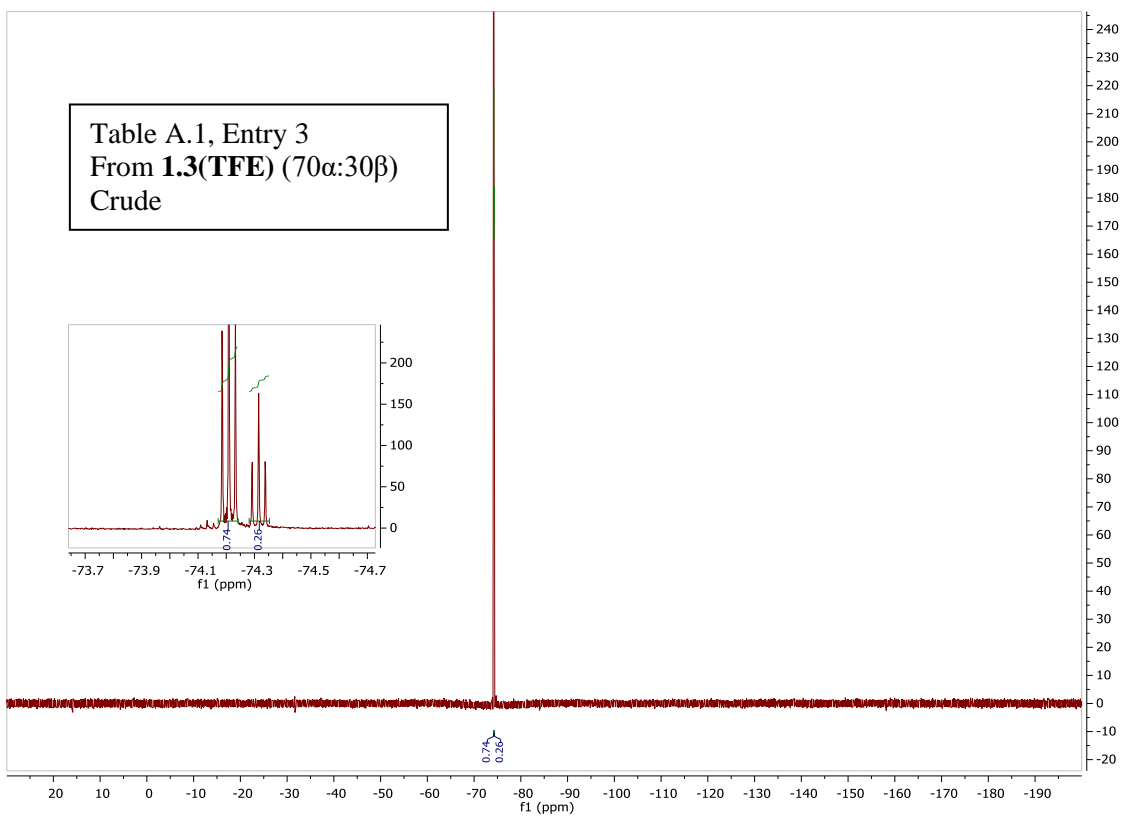
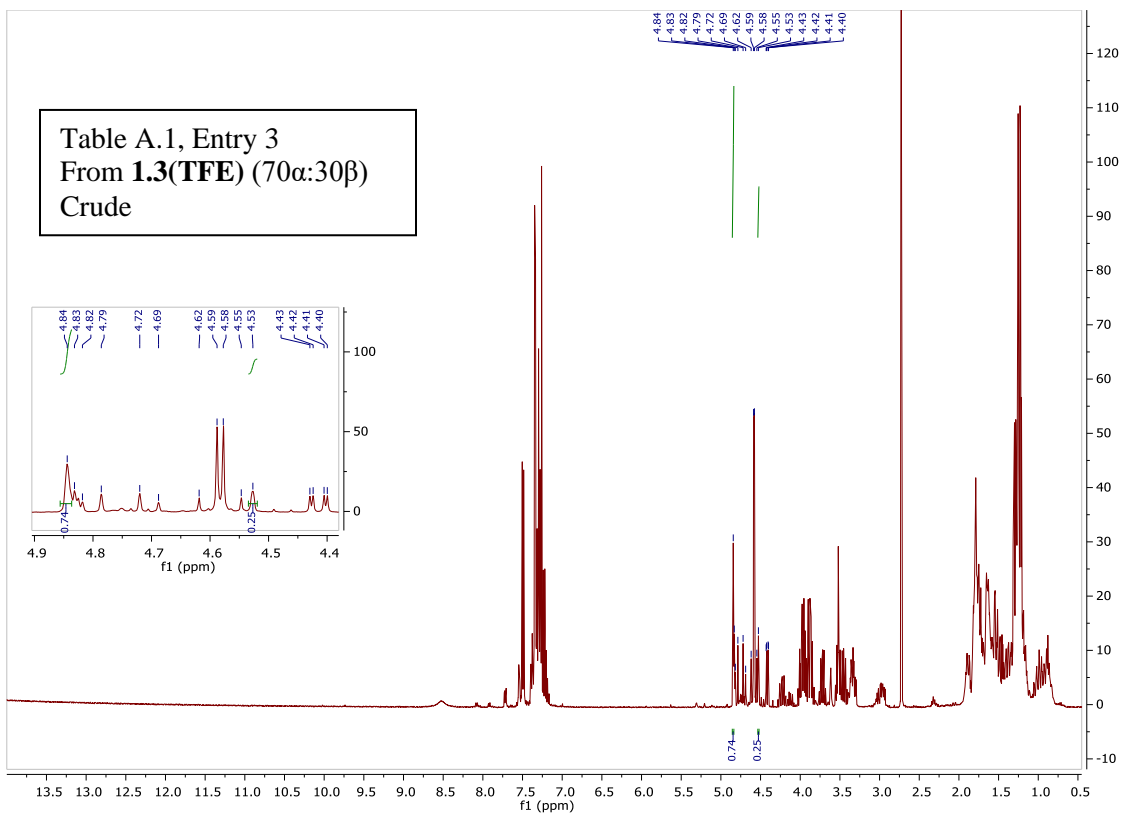
#### E.4 Spectres RMN brutes des expériences de contrôle cinétique.

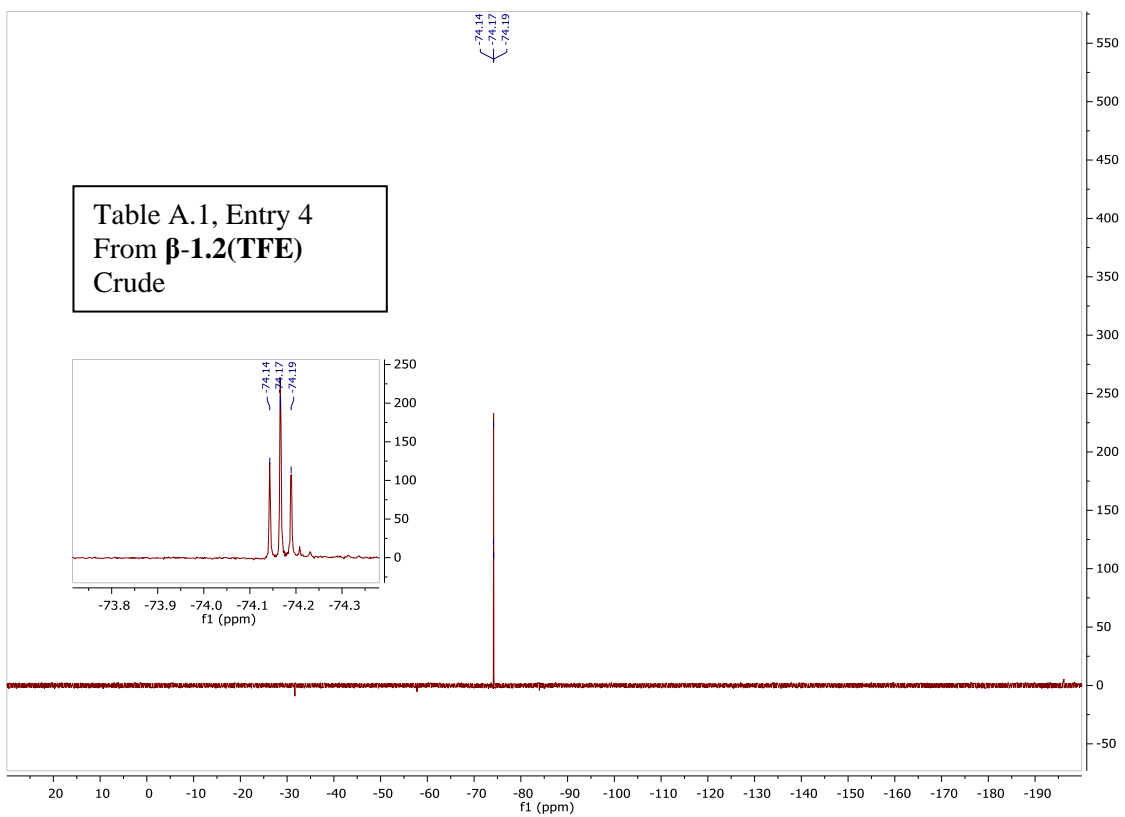
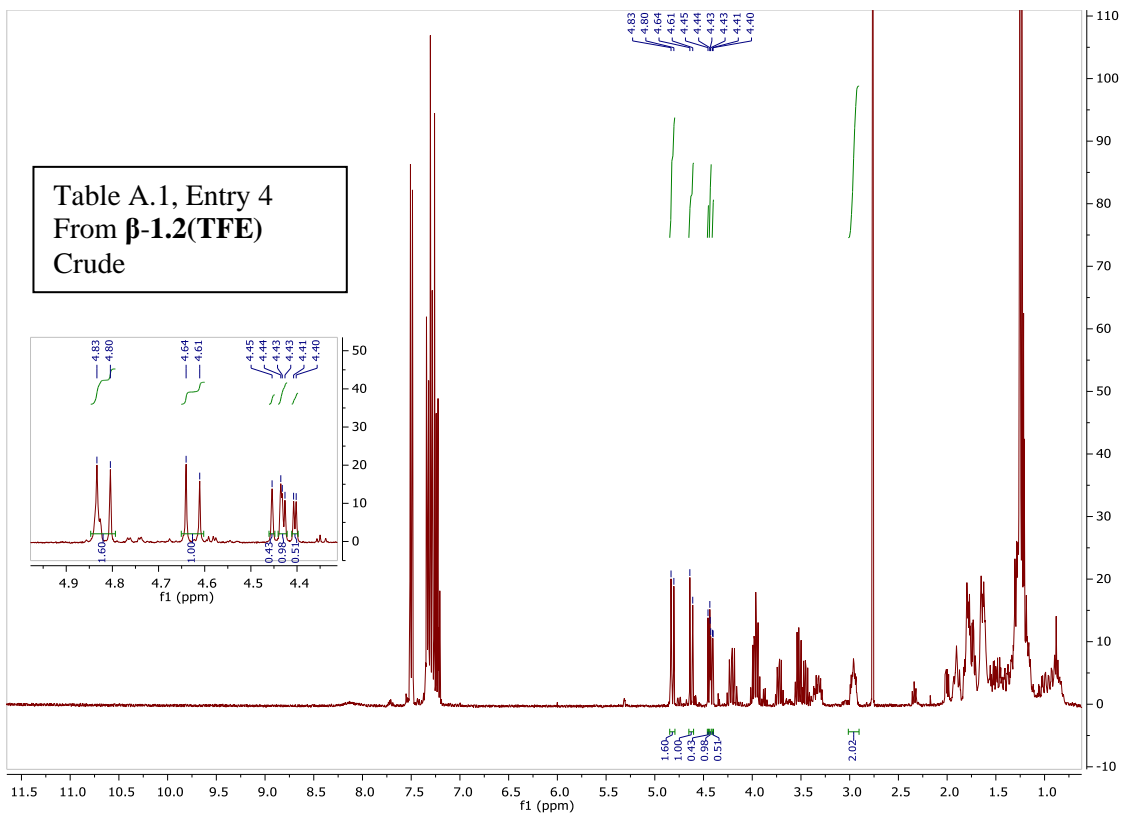










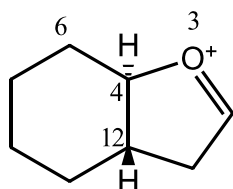




## Annexe F Données spectrales et expérimentales du chapitre 2

### F.1 Détails de calculs DFT

**Table E.1** XYZ coordinates for geometry optimized (3a*S*,7a*R*)-1-Oxaoctahydroindene oxocarbenium ion. Selected ESP charges (Merz-Kollman) indicated on right column and numbered in structure.



E= -387.6322559 Hartree (G16,<sup>2</sup> B3LYP/6-31G\*)

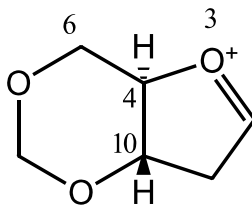
<u>Atom</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>Merz-Kollman</u>
C	2.430461	-0.155678	-0.067084	
H	3.493641	-0.344767	-0.197954	
O	1.686795	-1.150954	0.016663	O3: -0.285
C	0.264876	-0.660654	0.304102	C4: 0.336
H	0.258013	-0.642463	1.396742	
C	-0.848591	-1.503658	-0.224935	C6: -0.197
H	-0.838166	-2.507204	0.195959	
H	-0.789933	-1.578965	-1.311808	
C	-1.129764	-0.749206	0.202379	
H	-2.990665	-1.267754	-0.215171	

<sup>2</sup> (a) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.*, **1984**, *5*, 129-145; (b) Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

H	-1.227578	-0.813996	1.289118	
C	0.310622	0.73023	-0.282262	C12: 0.242
C	-0.902206	1.504326	0.211196	
H	-0.870288	1.600936	1.299826	
H	-0.915031	2.510706	-0.204558	
C	-1.150077	0.722657	-0.22835	
H	-1.233626	0.780244	-1.316674	
H	-3.040789	1.201843	0.17482	
H	0.230152	0.634455	-1.370047	
C	1.749771	1.15081	0.030577	
H	1.877585	1.499137	1.067251	
H	1.201777	1.902494	-0.614543	

**Table F.2** XYZ coordinates for geometry optimized (3a*S*,7a*R*)-1,4,6-Trioxahexahydroindene oxocarbenium ion.

Selected ESP charges (Merz-Kollman) indicated on right column and numbered in structure.



**-459.**

**E= -459.3919477 Hartree (G16, B3LYP, 6-31G\*)**

<u>Atom</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>Merz-Kollman</u>
<u>charge</u>				
C	1.35882	0.135532	0.06616	
H	3.42285	0.307762	0.21113	
O	1.625959	1.149901	0.02193	O3: -0.217
C	0.233339	0.695491	-0.31016	C4: 0.116
H	0.214709	0.672681	-1.39962	
C	-0.973831	1.44161	0.20739	C6: 0.055
H	-1.108621	2.42838	-0.22551	
H	-0.979801	1.50988	1.30003	
O	-2.016131	0.615379	-0.28333	
C	0.24899	-0.703679	0.28101	C10: 0.492
O	-0.83064	-1.41184	-0.20492	
C	-2.01075	-0.70546	0.17886	
H	-2.09398	-0.729111	1.27321	
H	-2.84454	-1.211751	-0.2933	
H	0.18833	-0.617549	1.37806	
C	1.66343	-1.159269	-0.07558	
H	1.7356	-1.468639	-1.12987	
H	1.111951	-1.944519	0.53035	



(Table 2.1)  
Entry

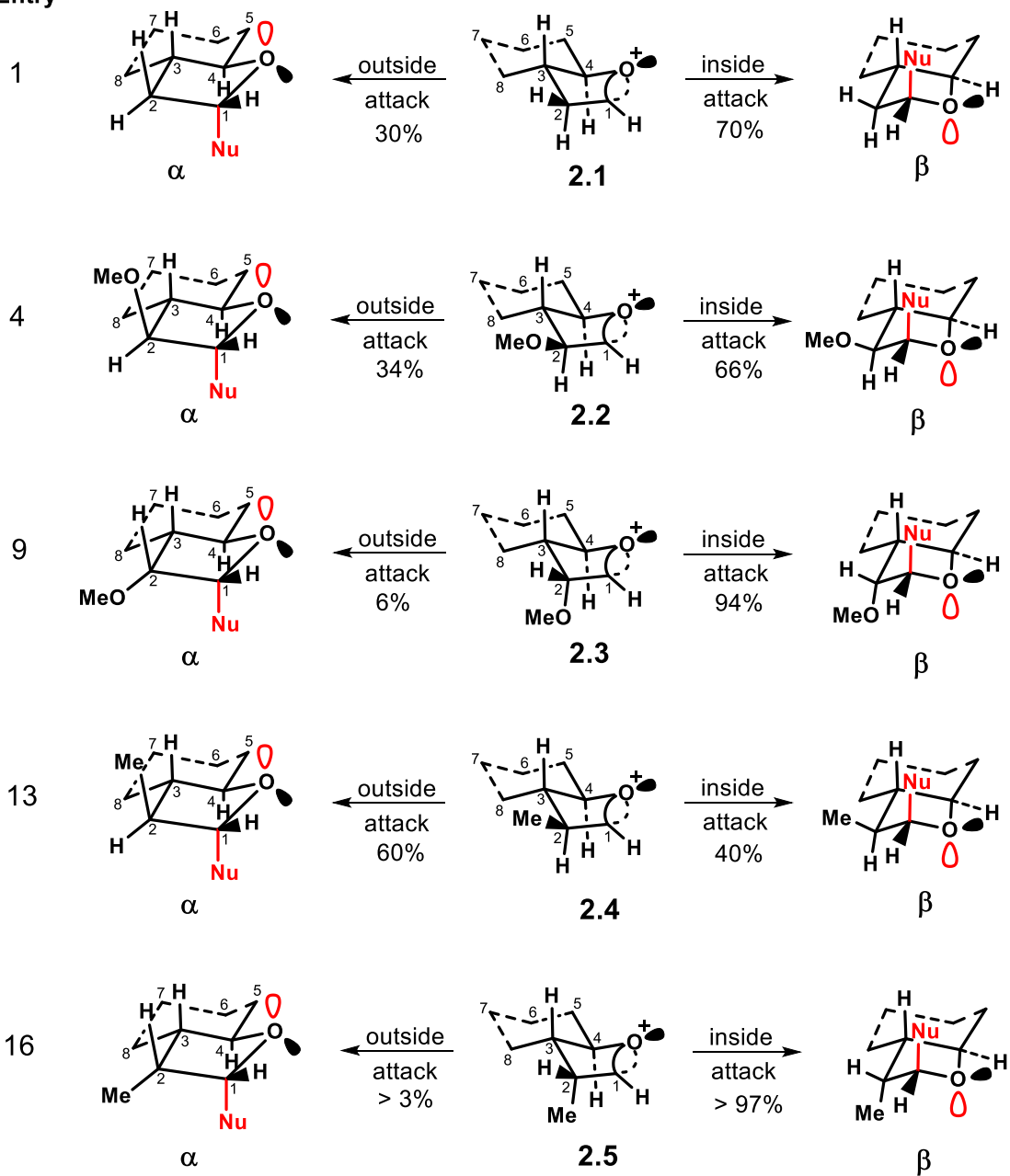
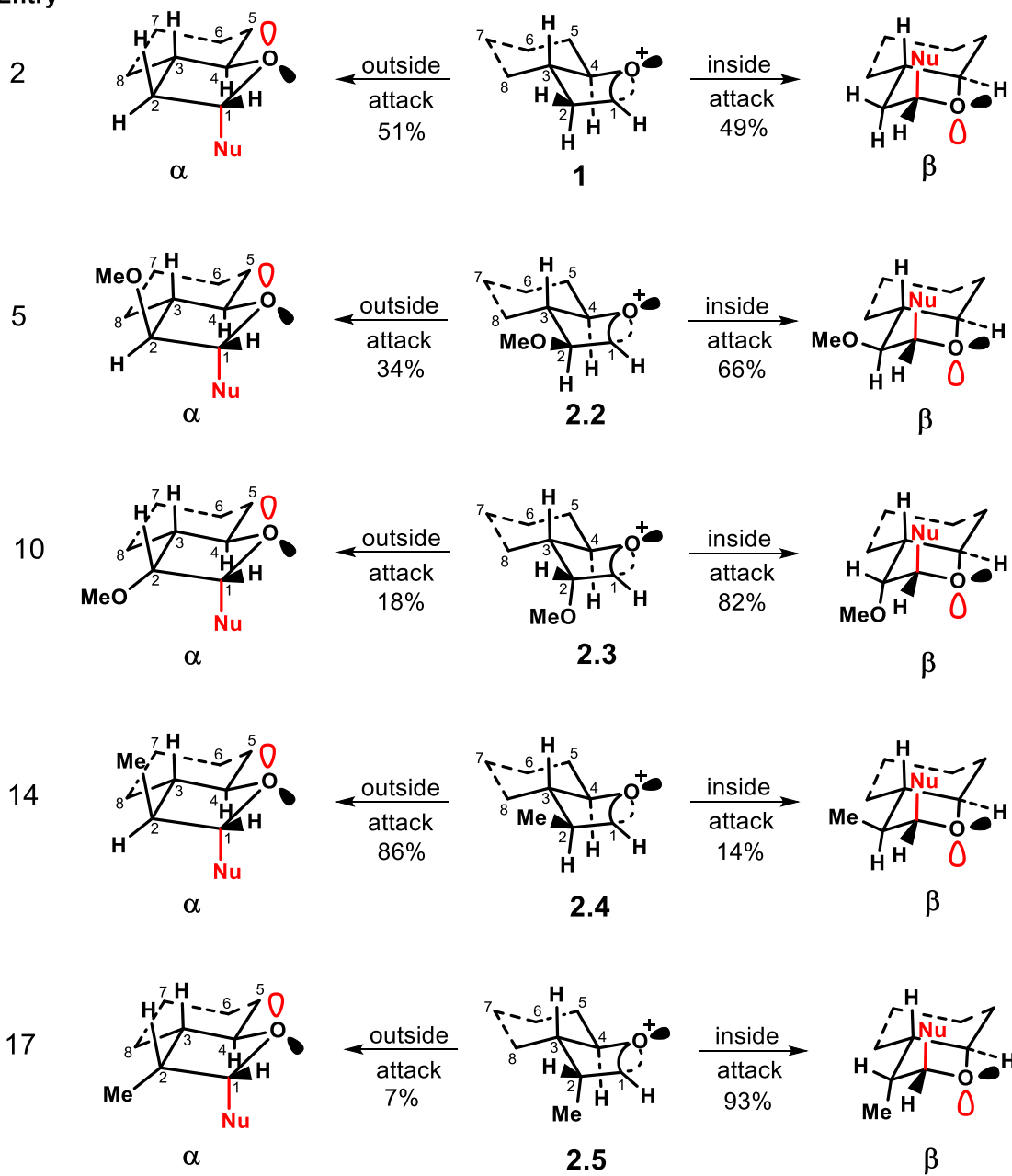


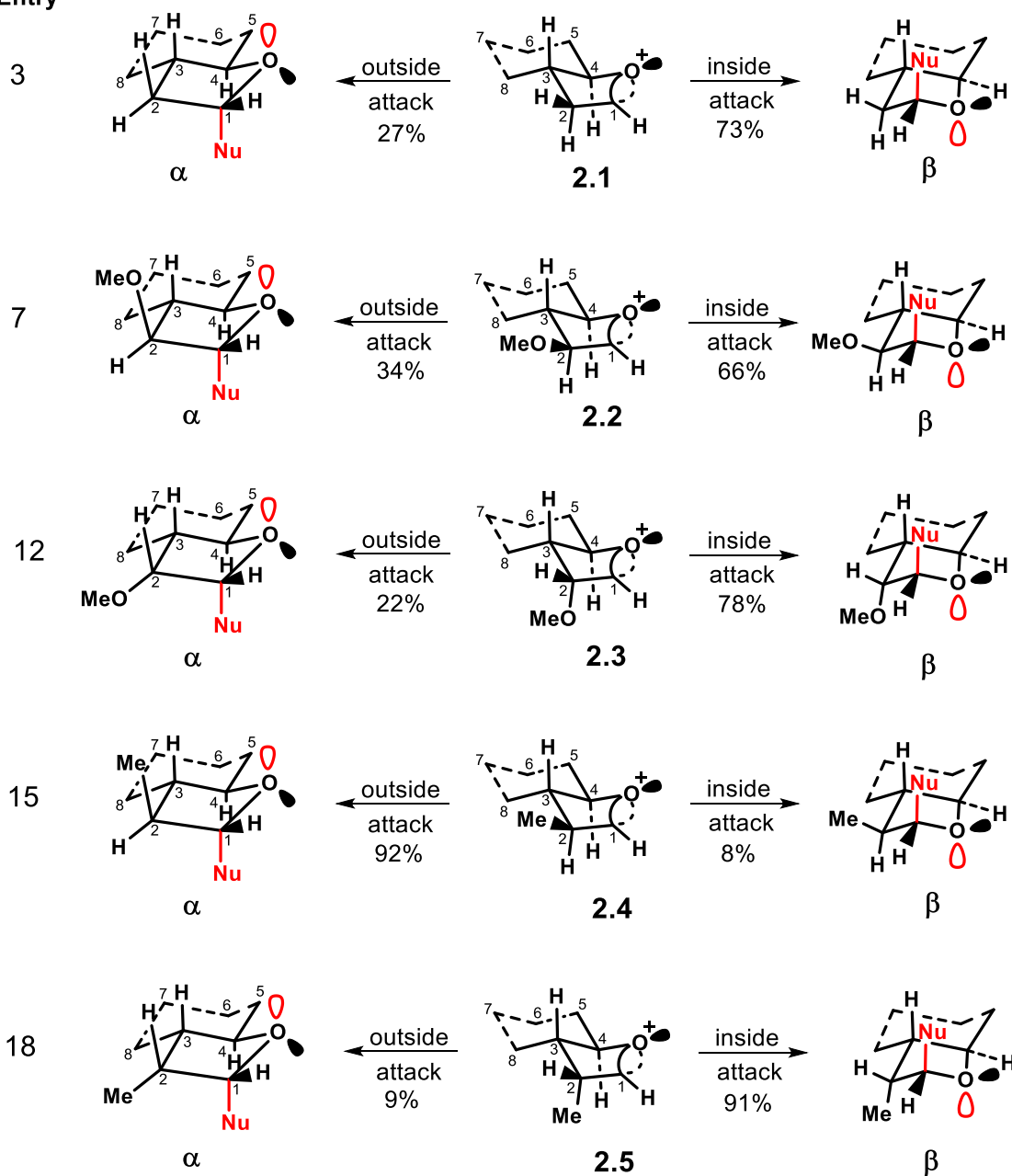
Figure F.1 C-Glycosylation with TMSallyl in CH<sub>2</sub>Cl<sub>2</sub>.

(Table 2.1)  
Entry



**Figure F.2** *O*-Glycosylation with  $\text{CF}_3\text{CH}_2\text{OH}$  in  $\text{CH}_2\text{Cl}_2$ .

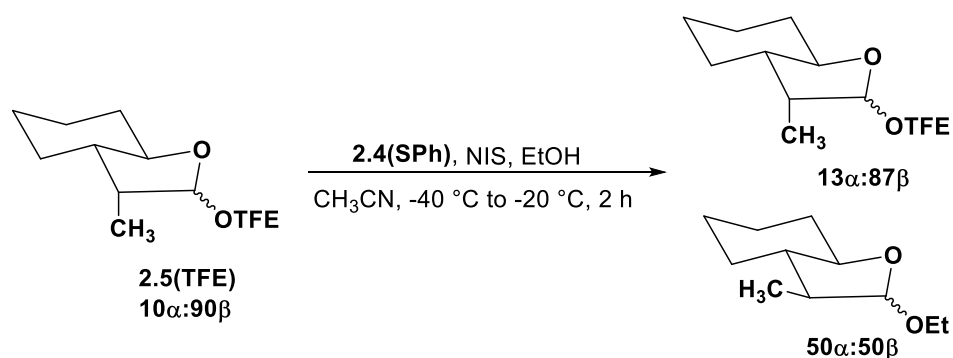
(Table 2.1)  
Entry



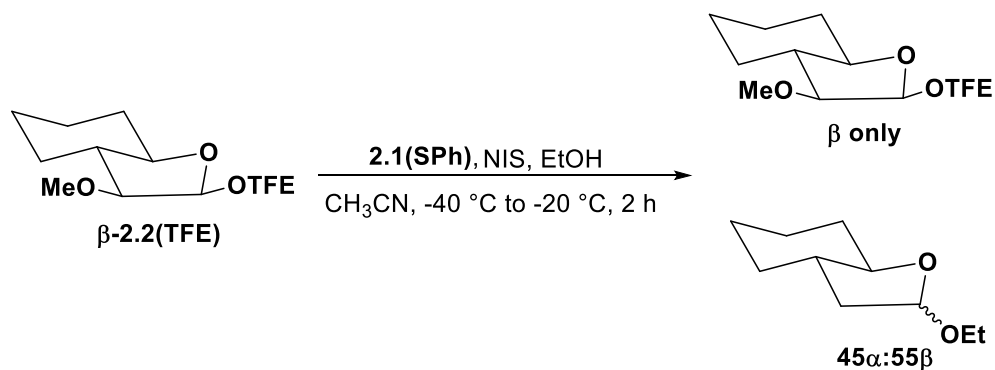
**Figure F.3** *O*-Glycosylation with  $\text{CF}_3\text{CH}_2\text{OH}$  in  $\text{CH}_3\text{CN}$ .

## F.2 Expérience de contrôle cinétique.

The kinetic pathway of the glycosylation reactions studied were confirmed using control experiments based on the method reported by Woerpel.<sup>3</sup> These experiments are valuable in the context of the *O*-glycosylation, whereas anomerization cannot occur in the case of *C*-glycosylation. Purified compounds from previous nucleophilic addition were resubmitted to the reaction conditions in the presence of a different donor and reanalyzed by <sup>1</sup>H NMR to record any change in the anomeric ratio. Even though there is a small variation in Scheme S1 in the anomeric ratios, the 3 % difference is negligible and within the error margin of an NMR analysis. A purified donor was also submitted to thermodynamic equilibration conditions to confirm the initial kinetic nature of the reaction with an increase proportion of  $\alpha$ -anomer.

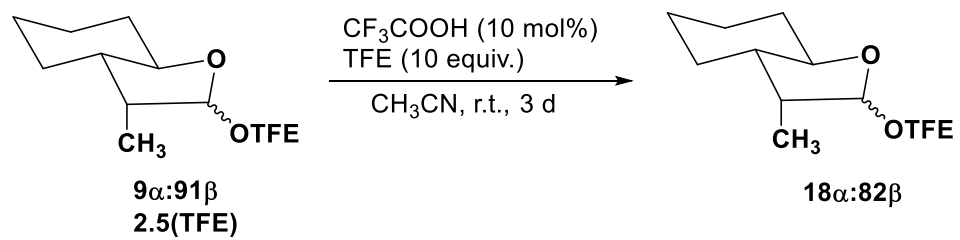


**Figure F.4** Verification for the reaction's kinetic nature with 2.5(TFE).



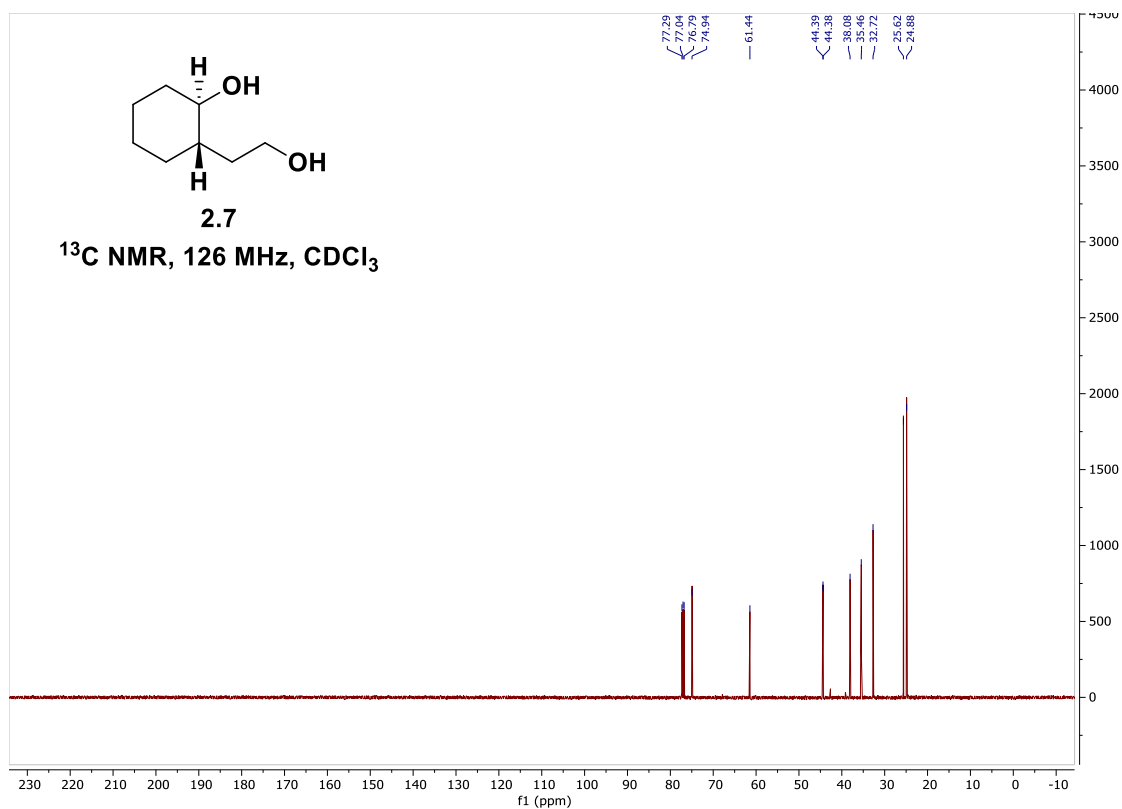
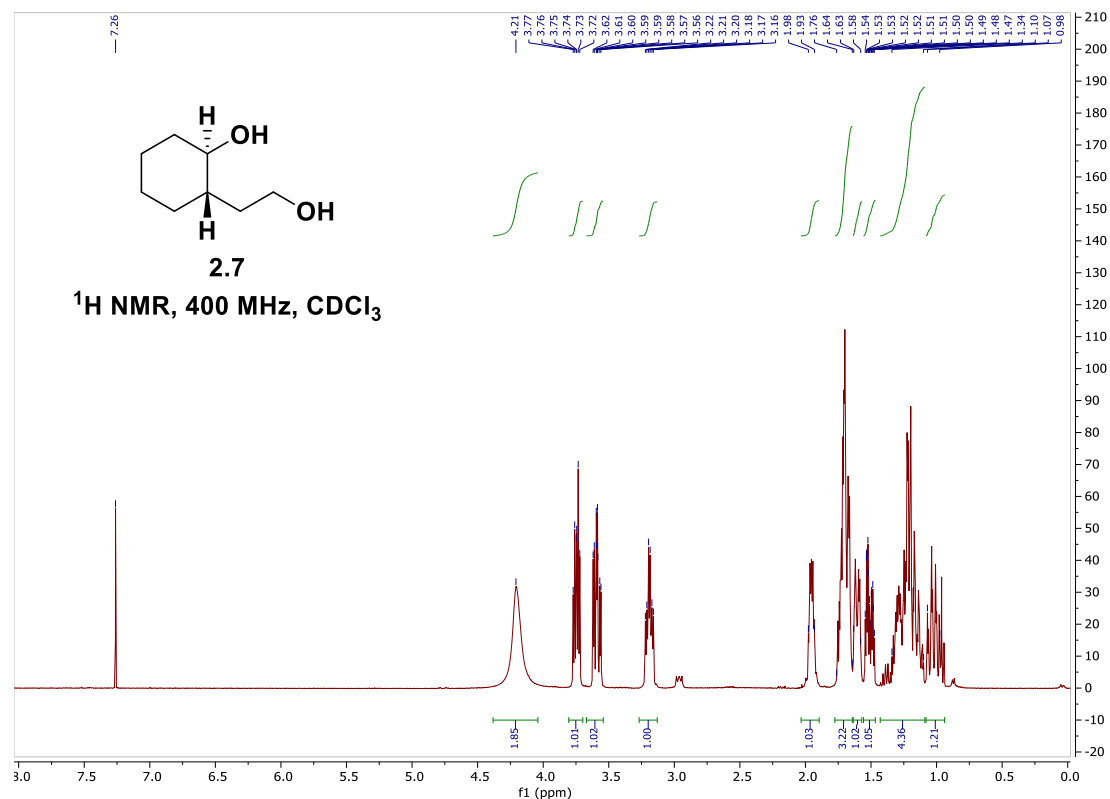
**Figure F.5** Verification for the reaction's kinetic nature with  $\beta$ -2.2(TFE).

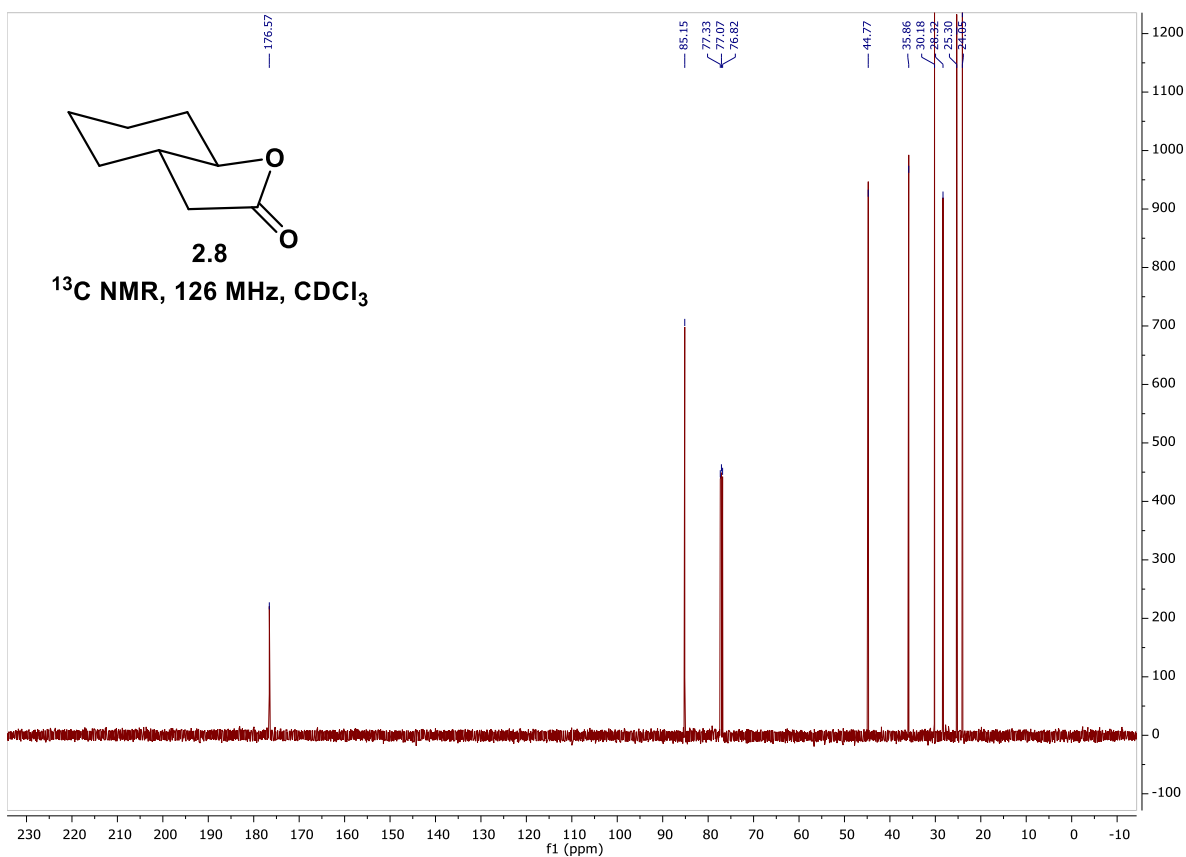
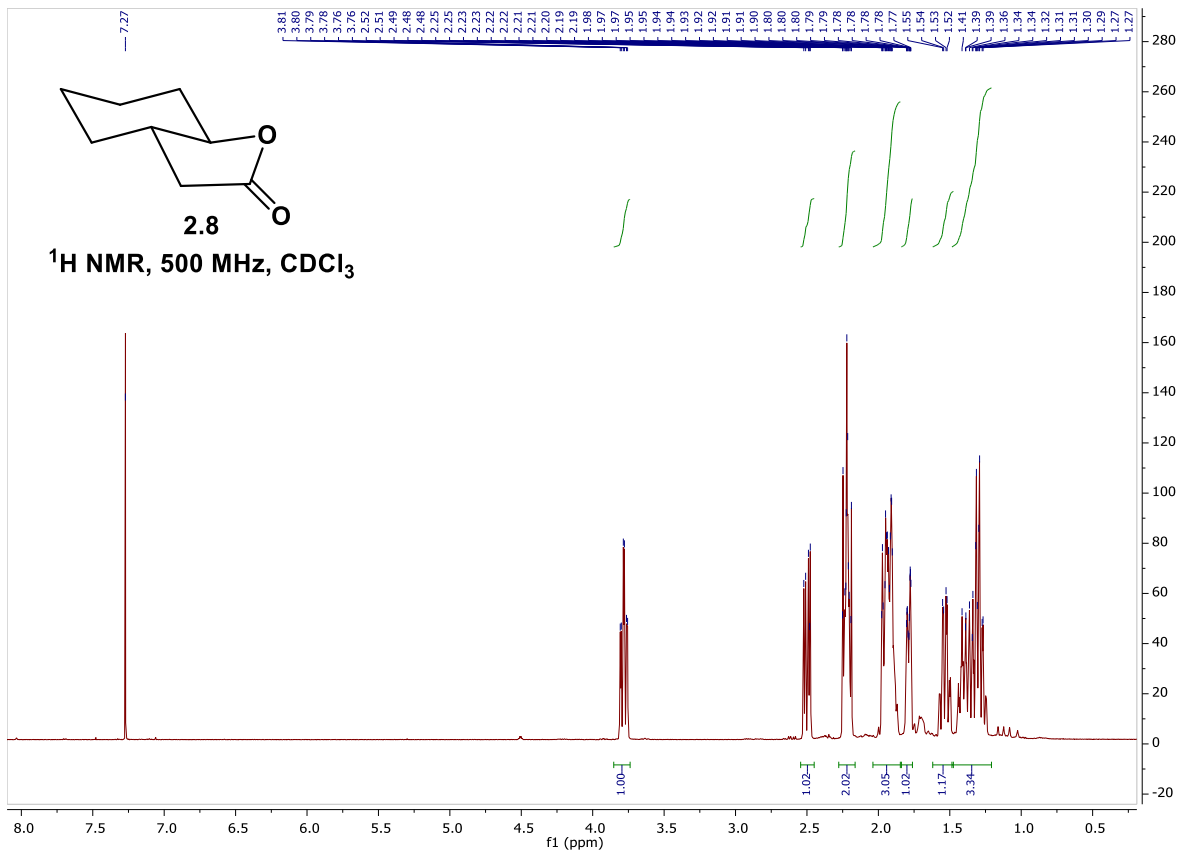
<sup>3</sup> Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107-1118.

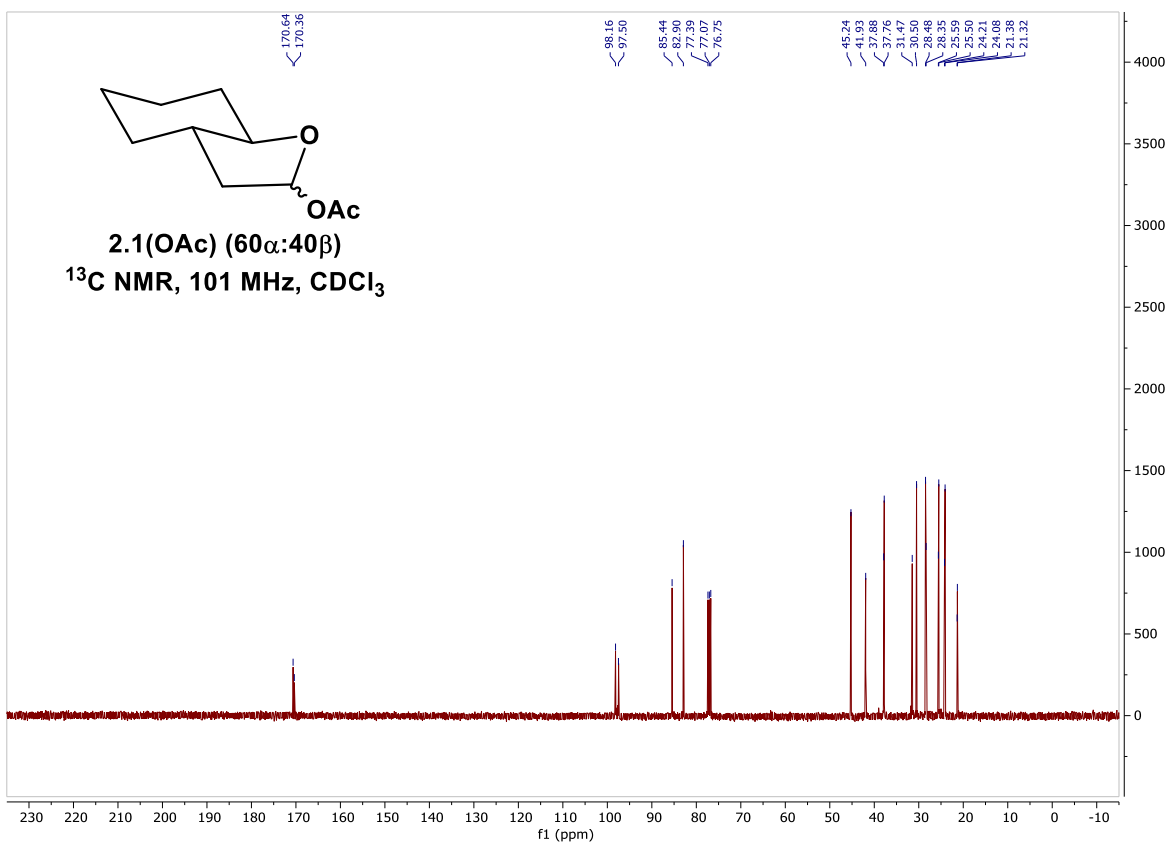
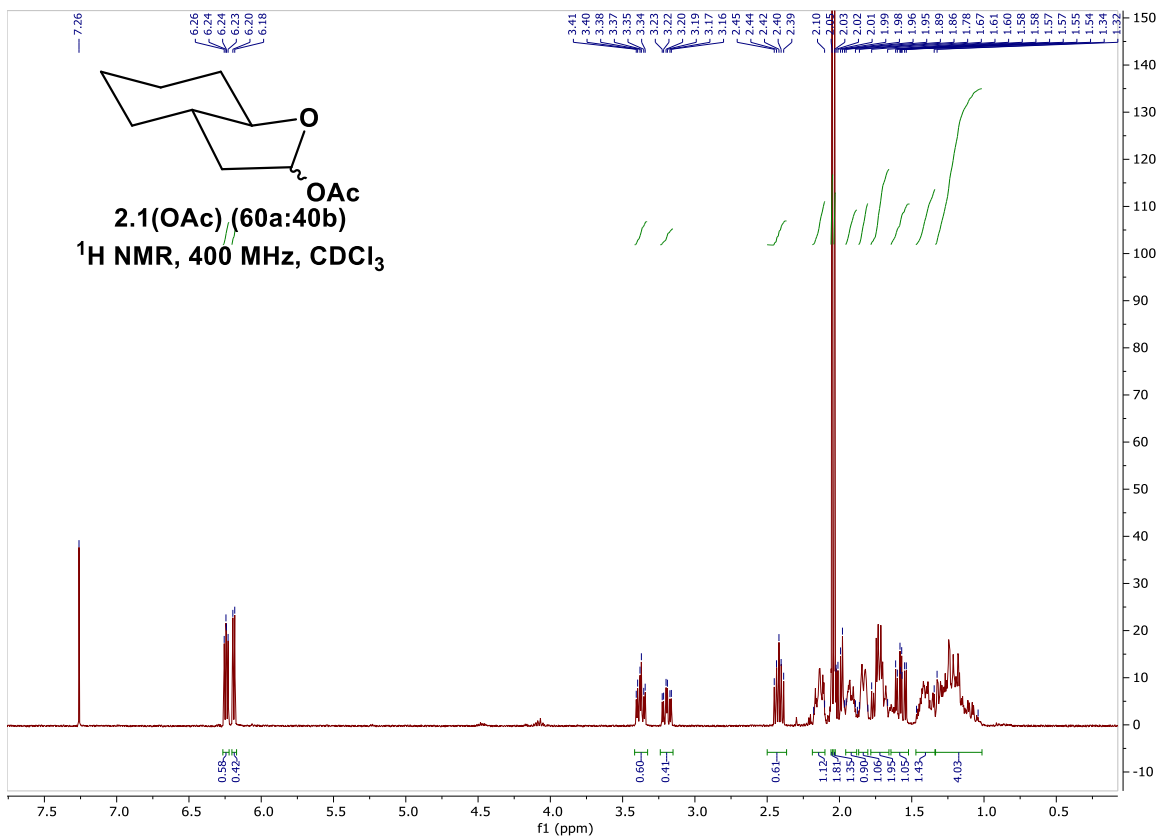


**Figure F.6** Thermodynamic control.

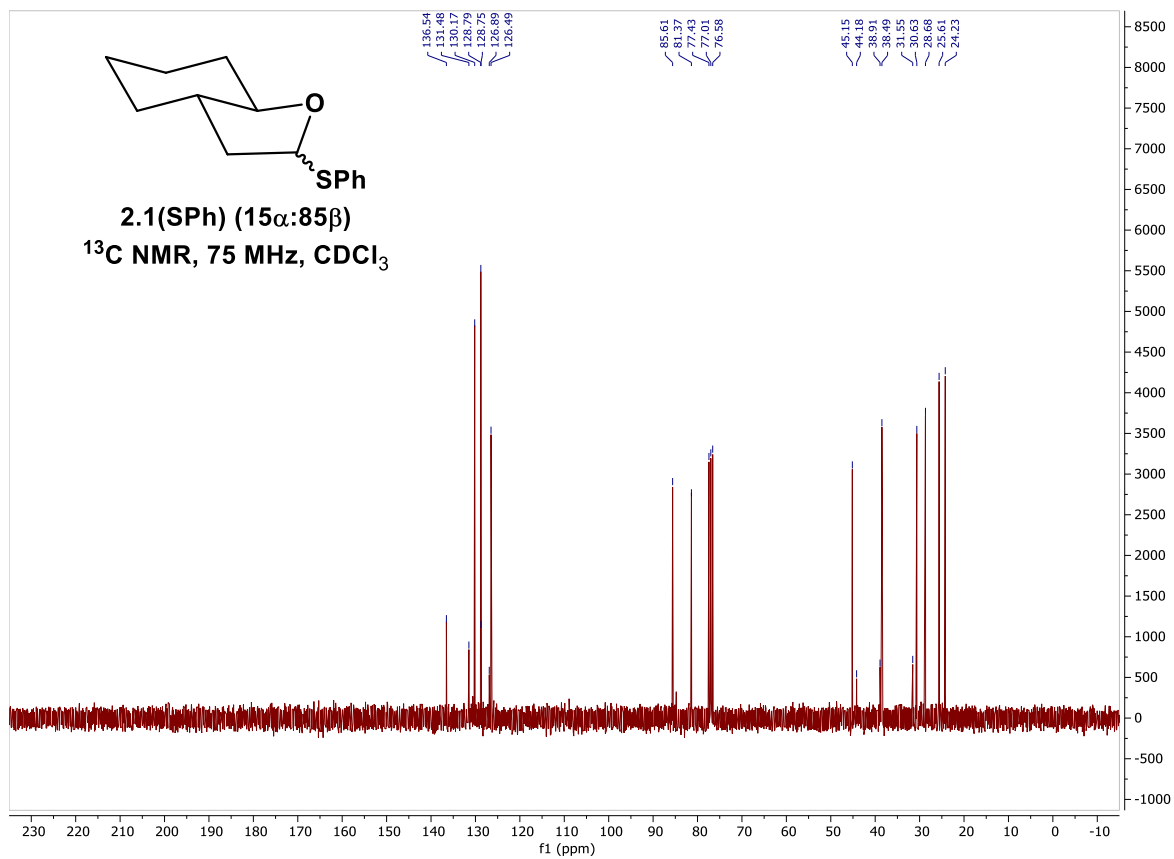
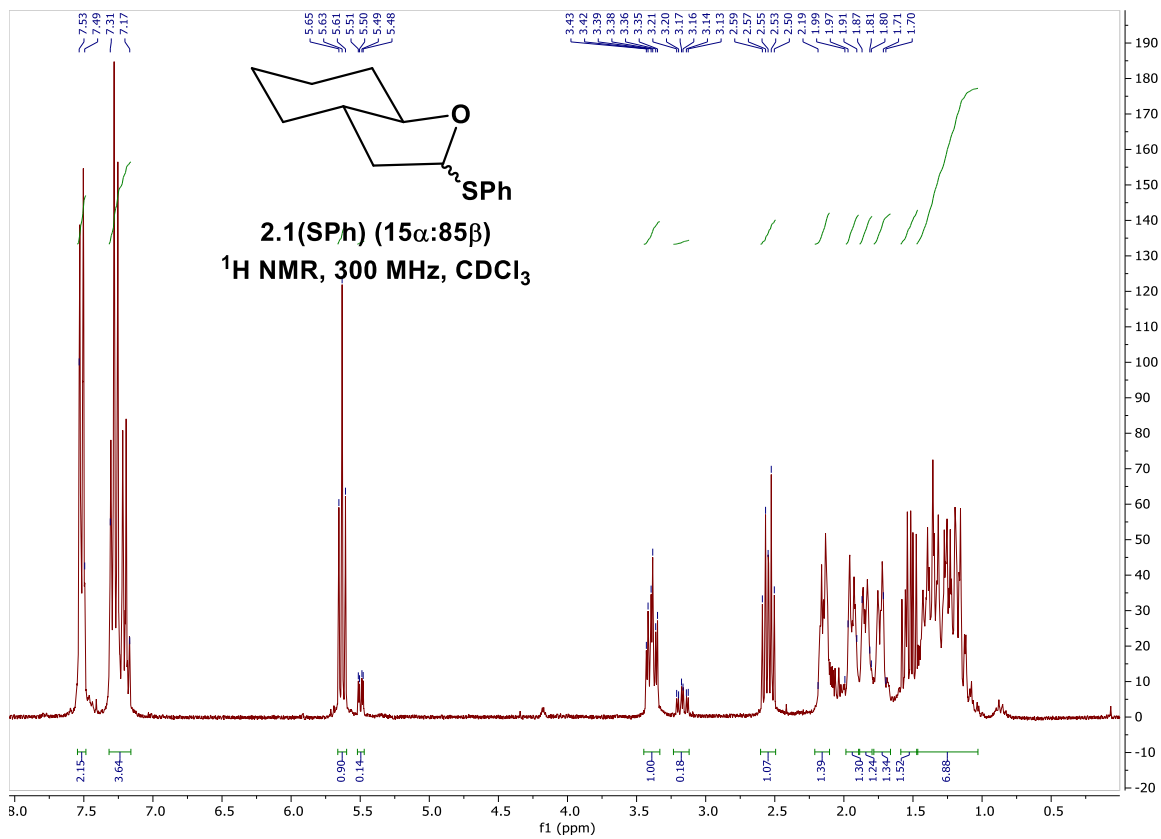
### F.3 Spectres RMN des composés caractérisés.

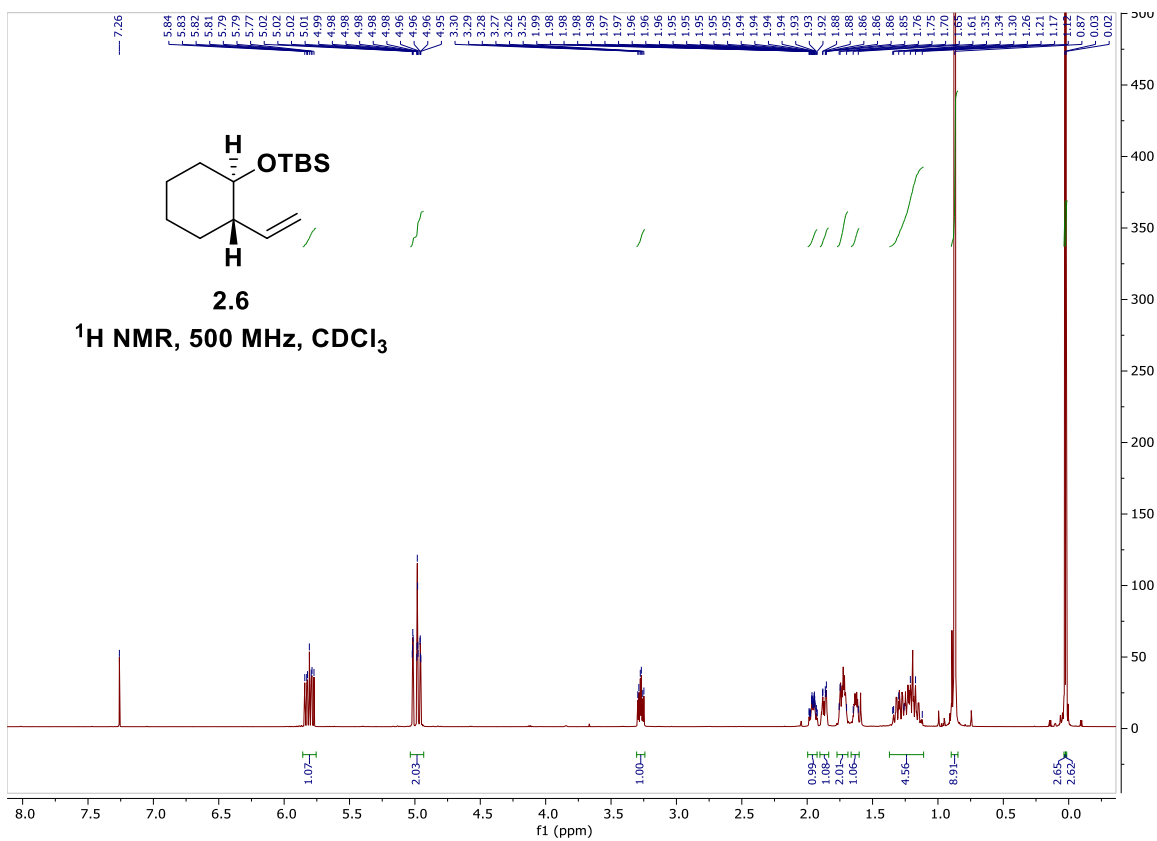
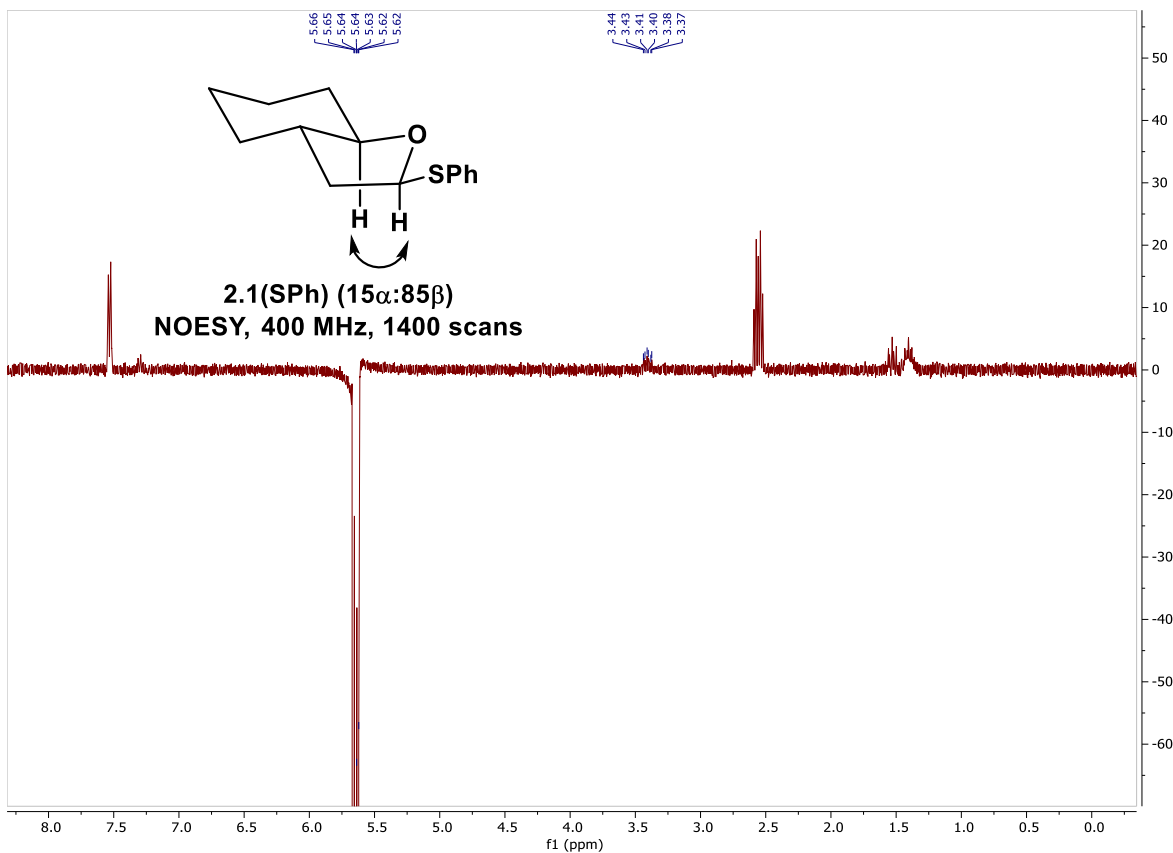


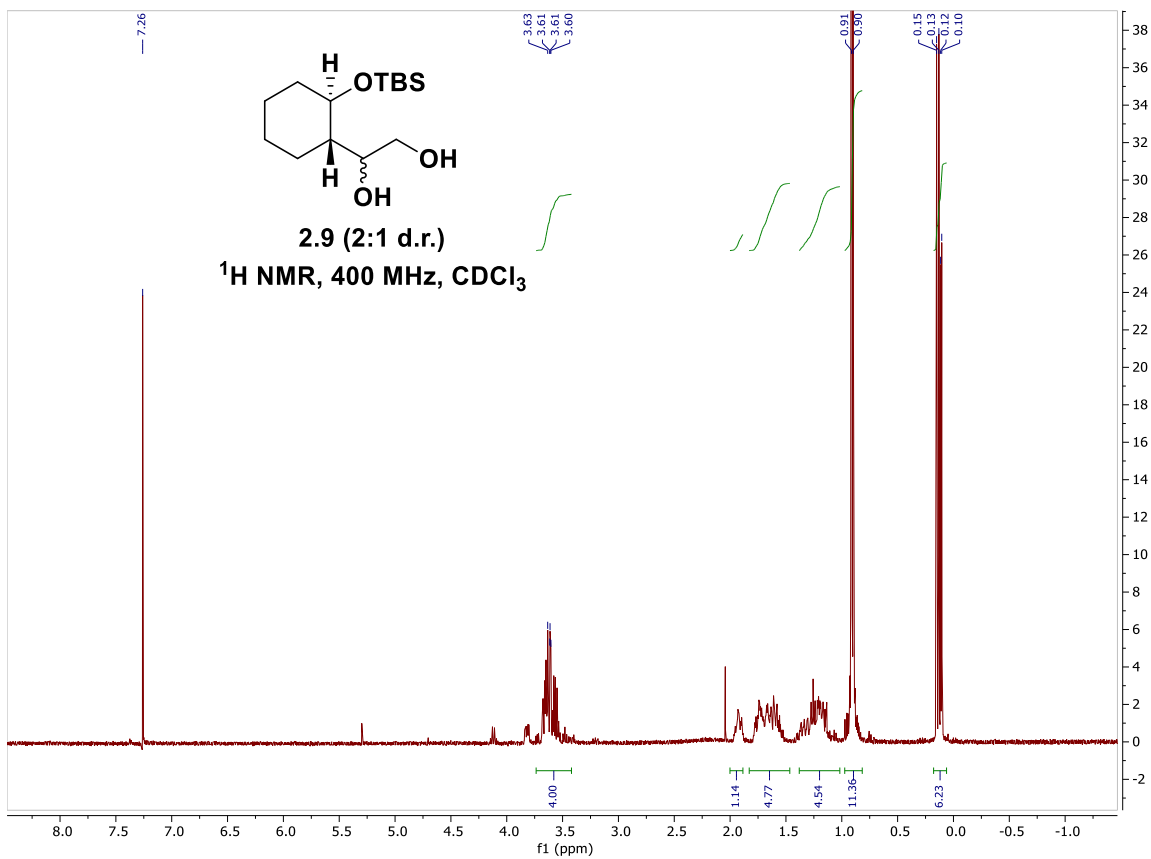
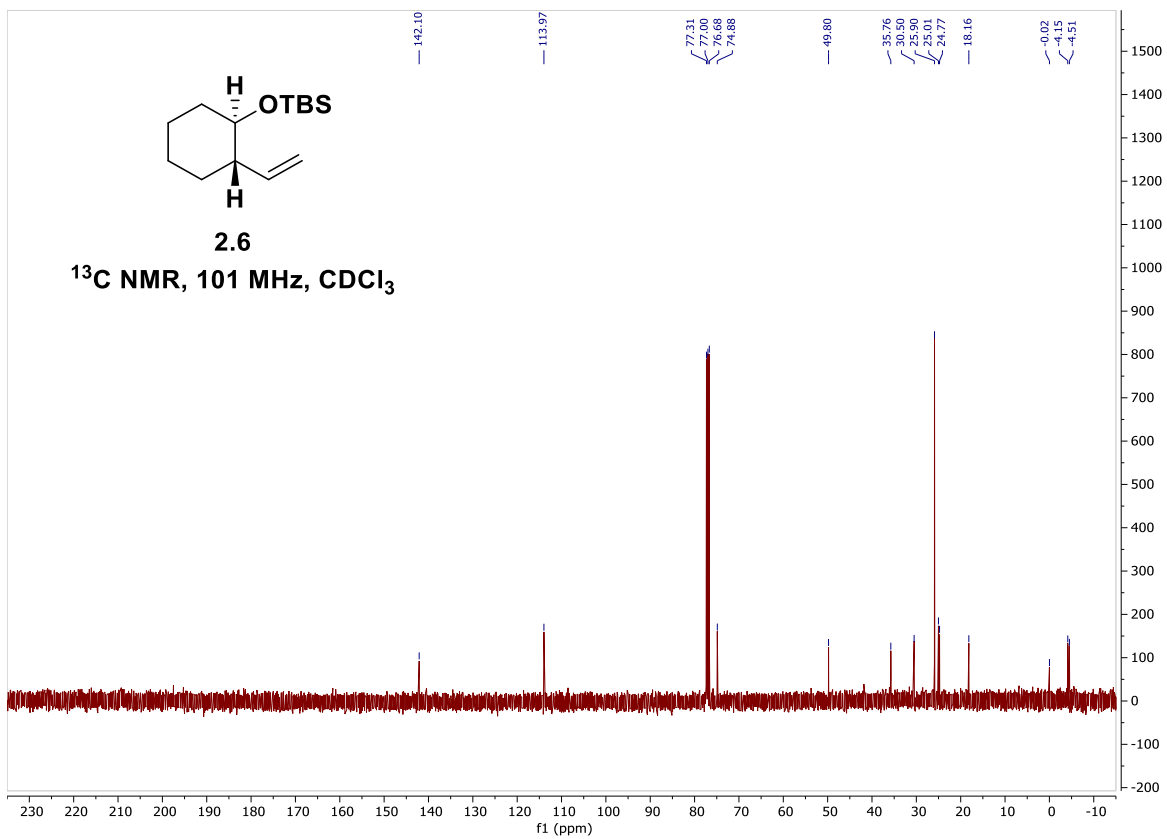


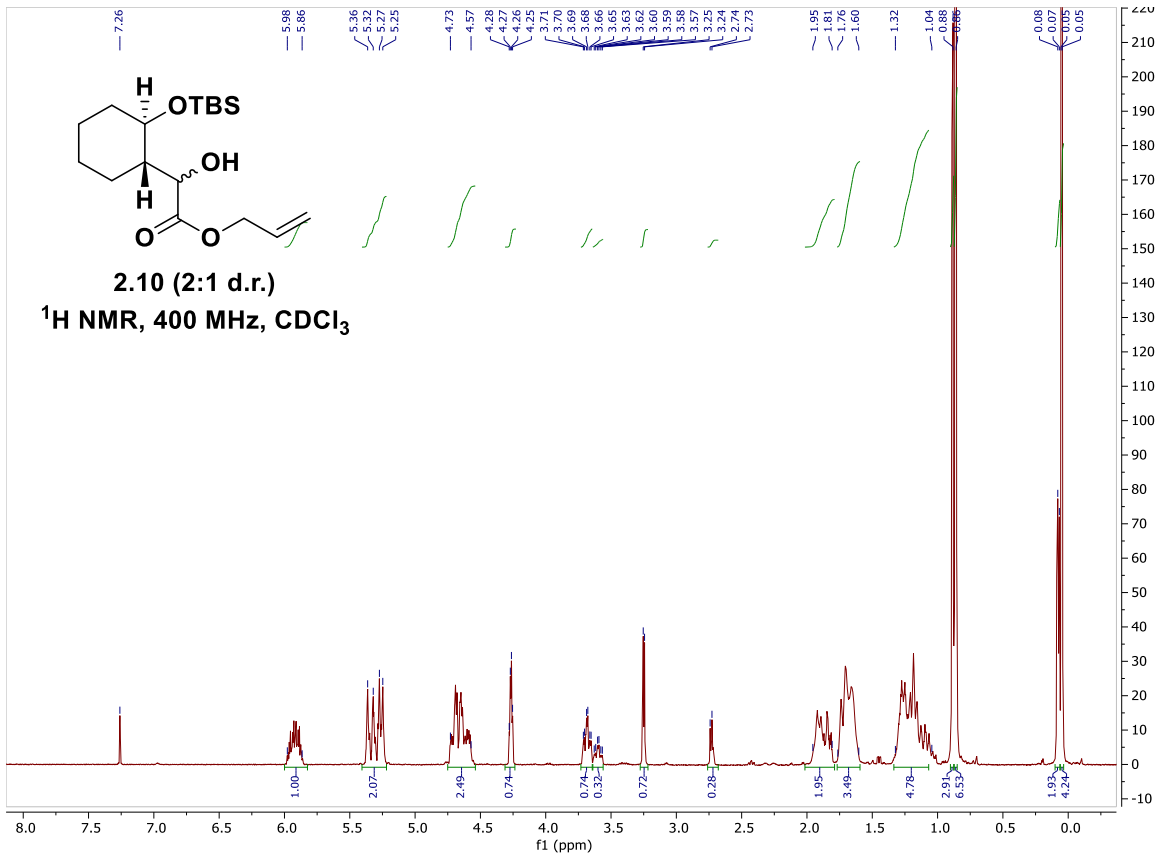
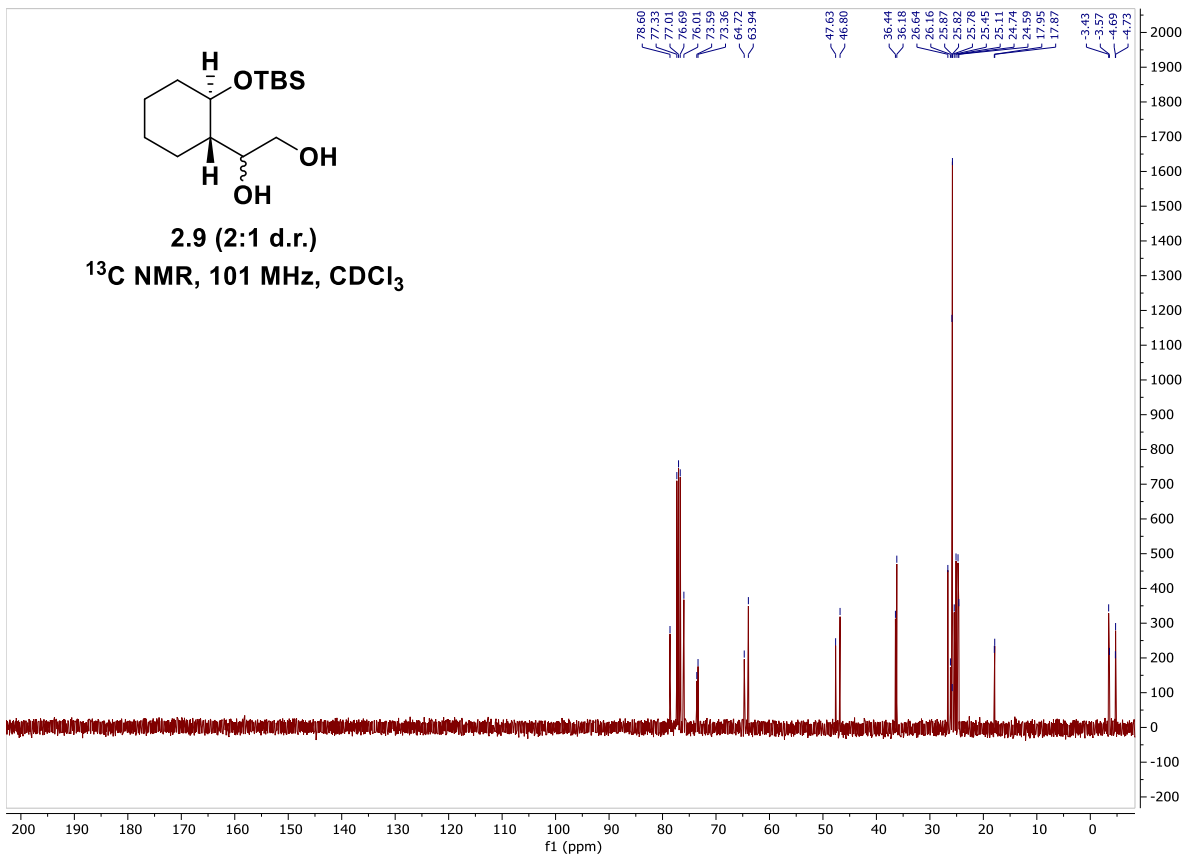


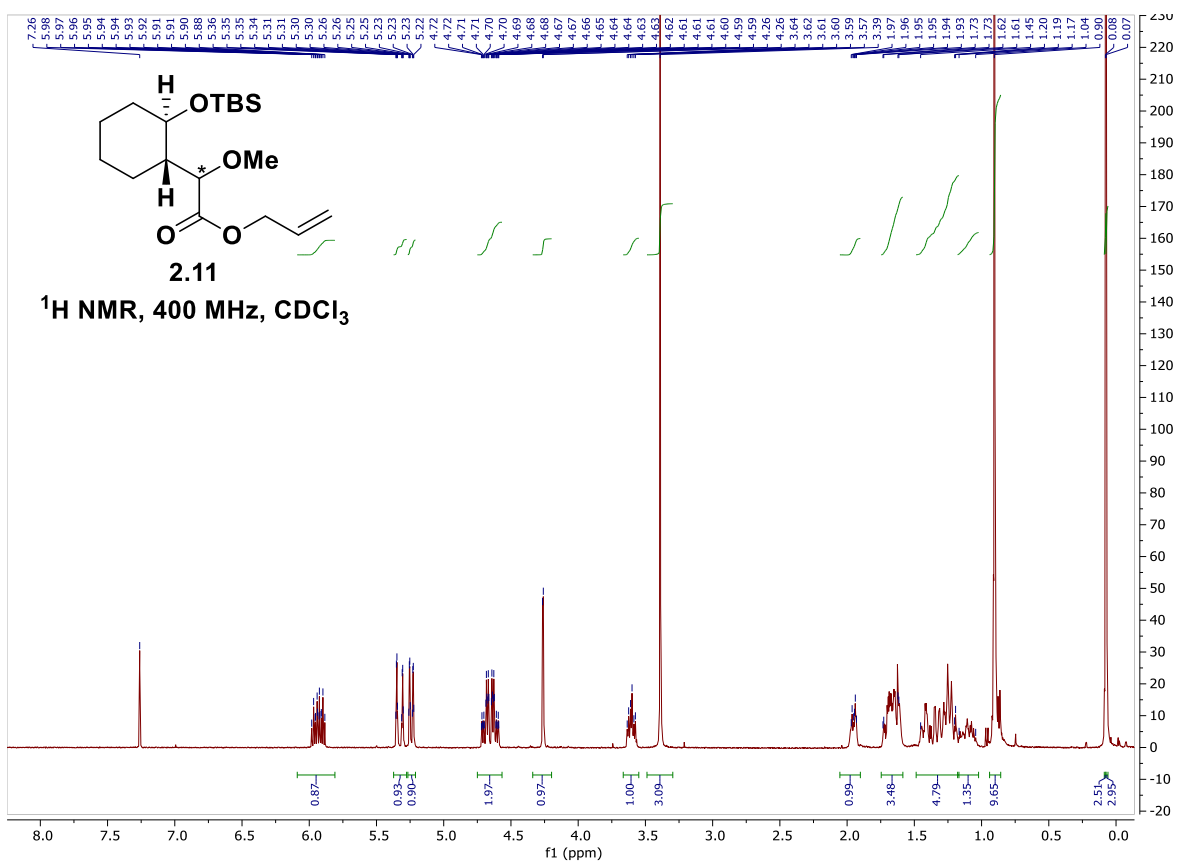
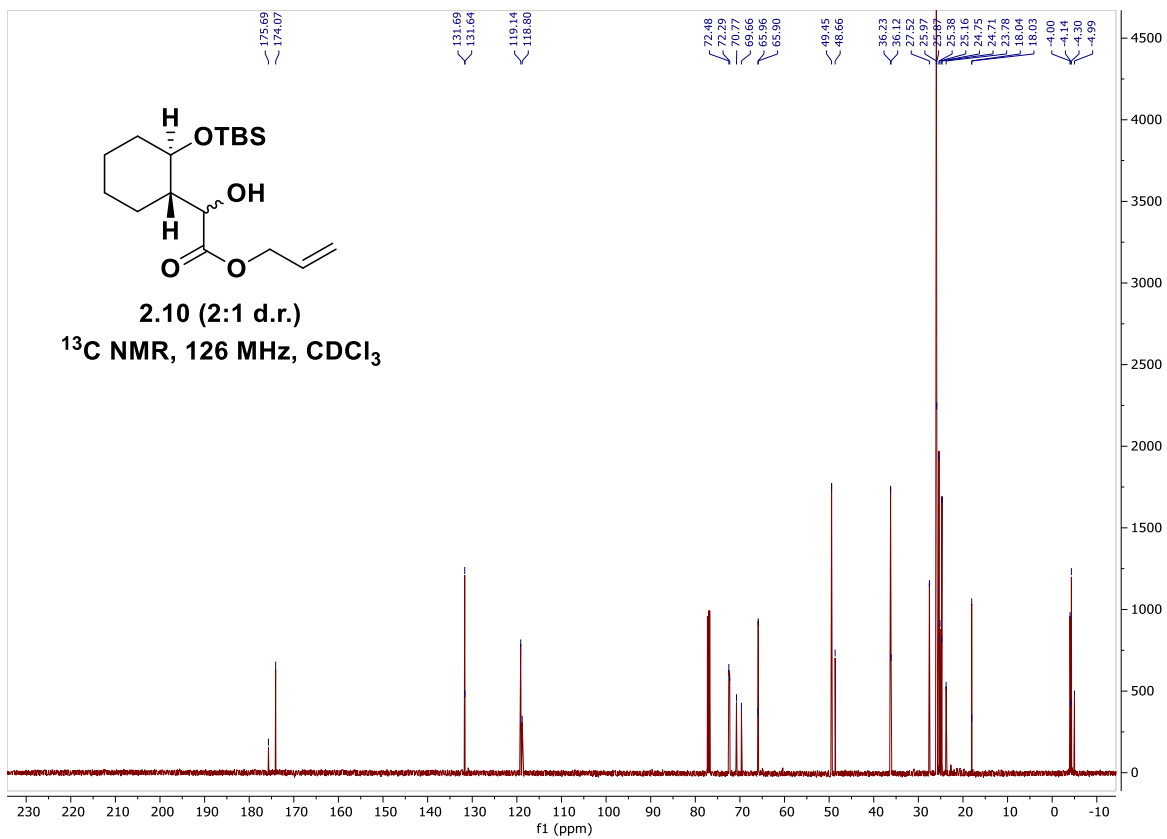


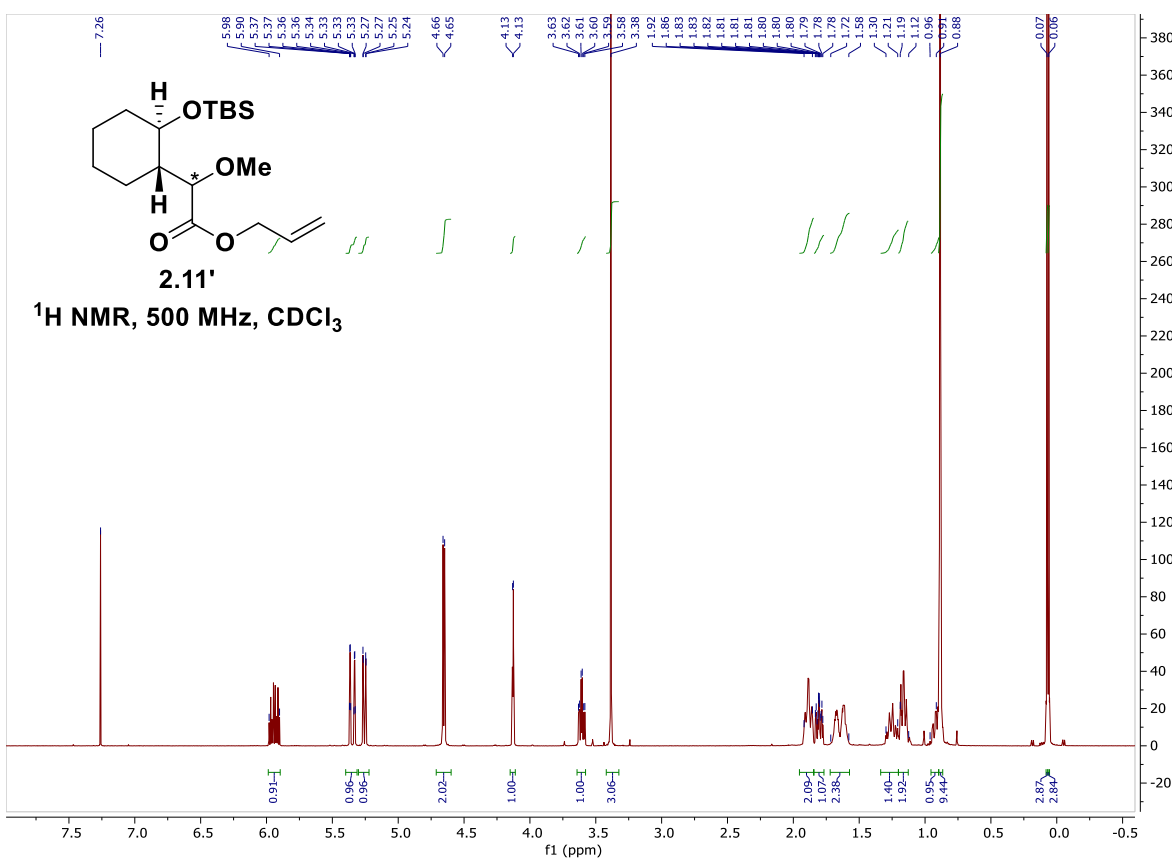
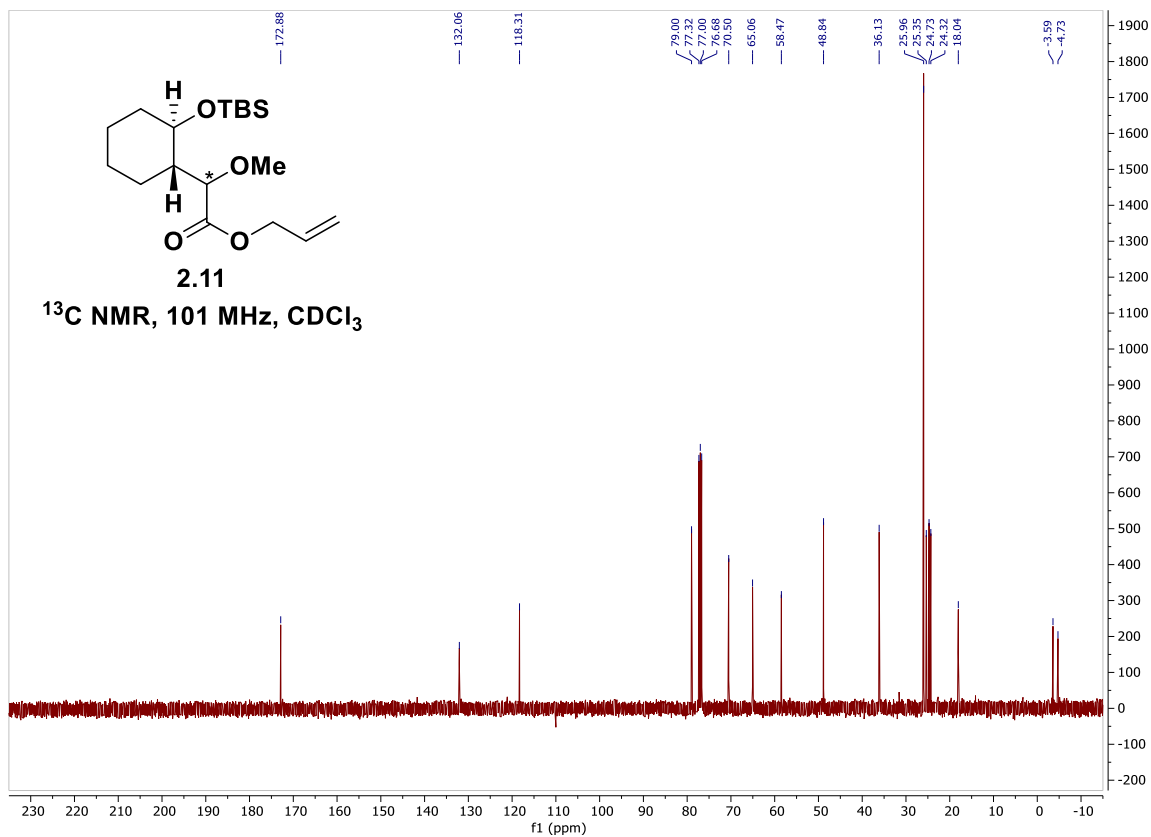


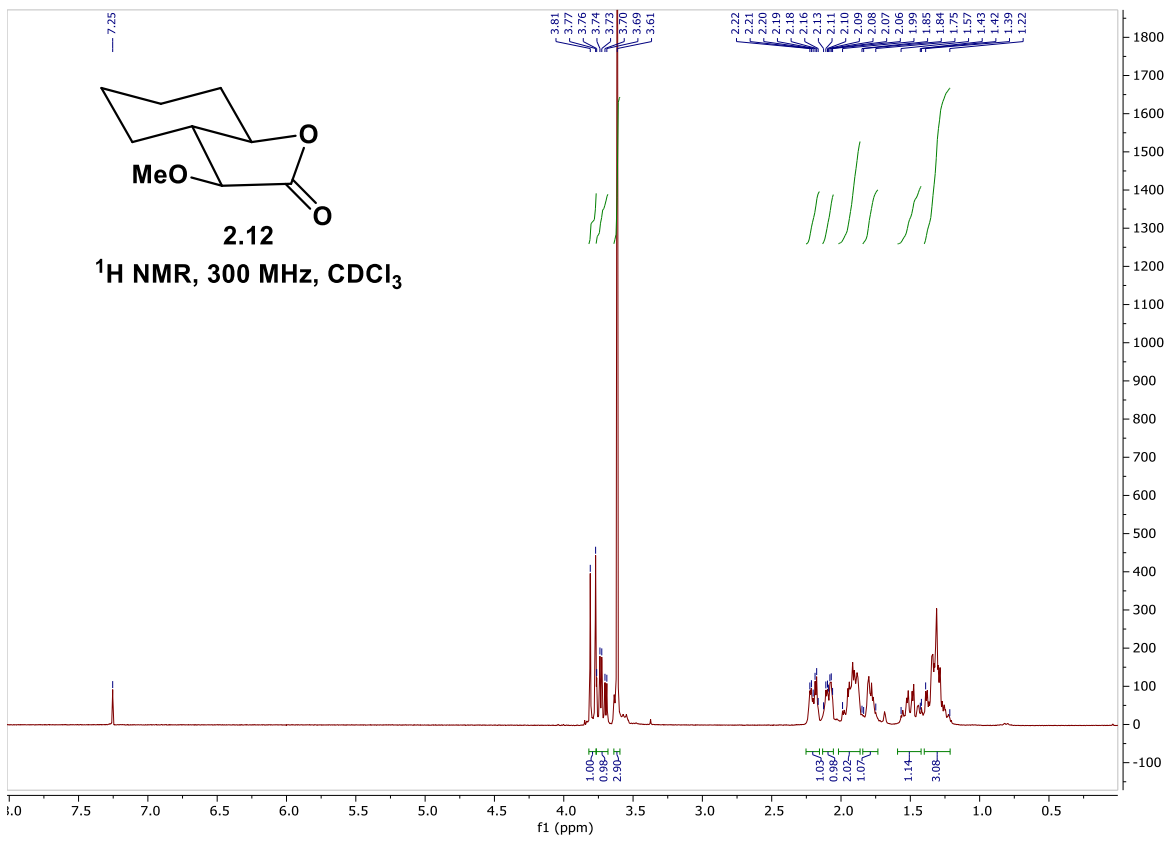
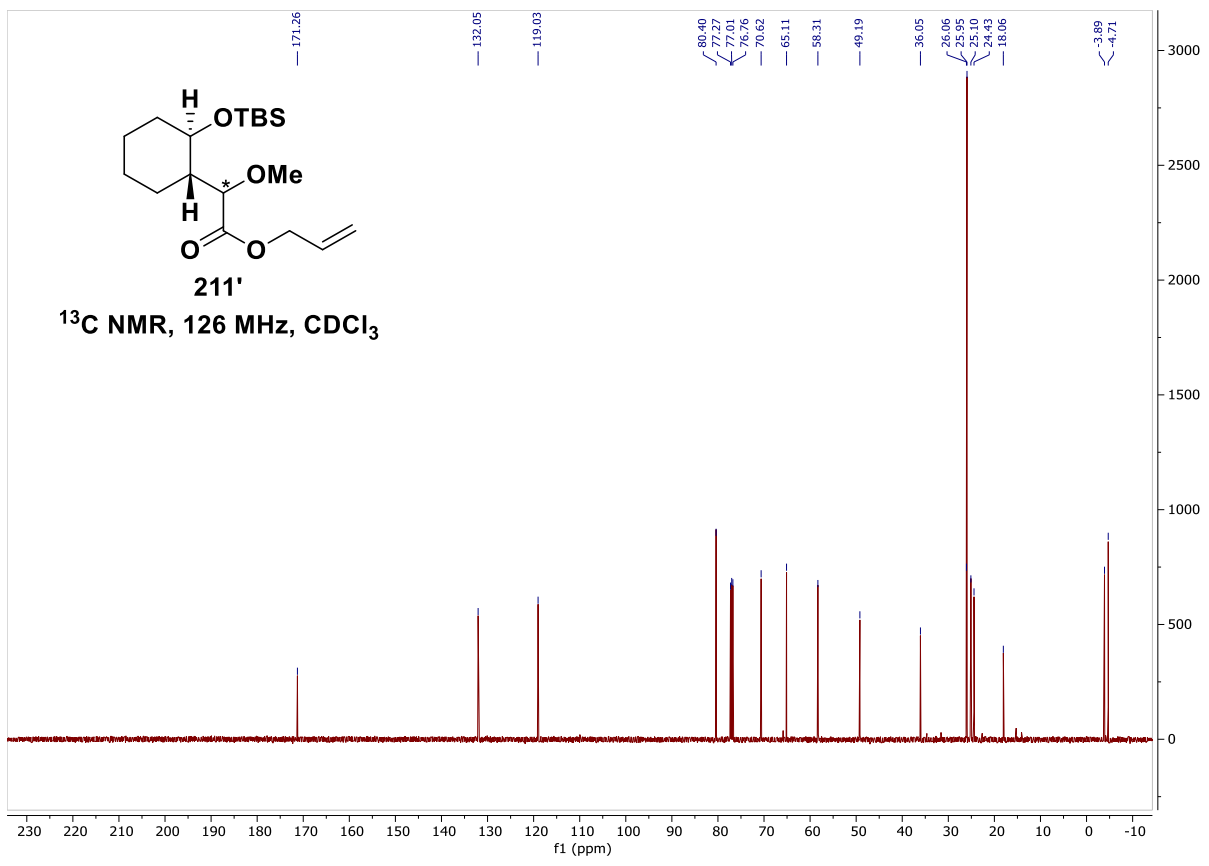


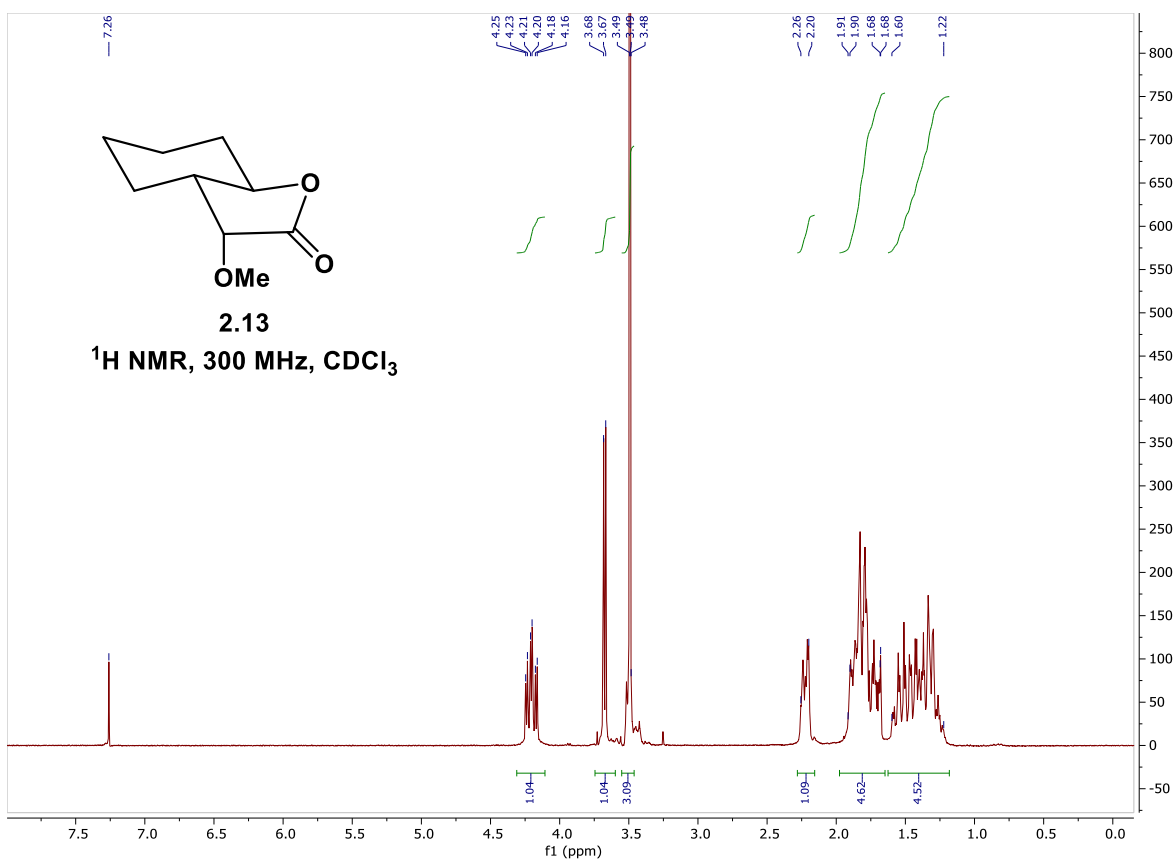
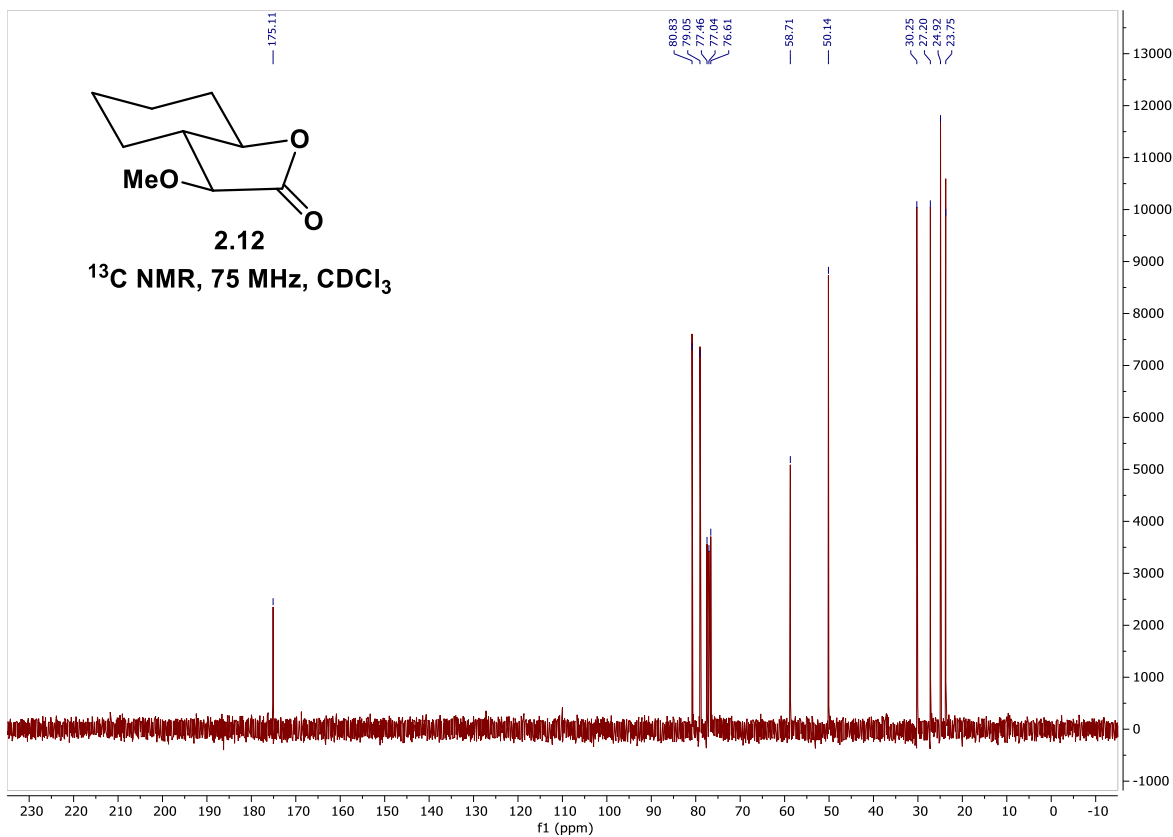




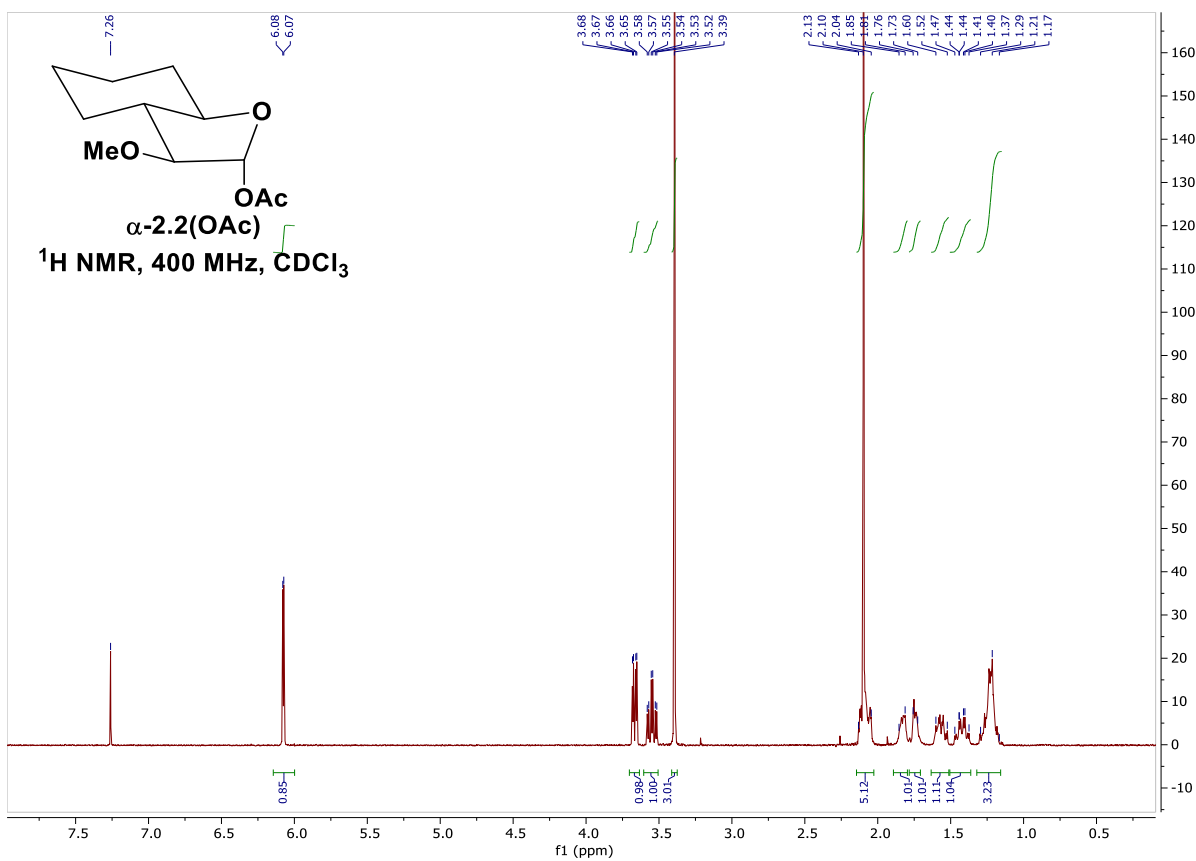
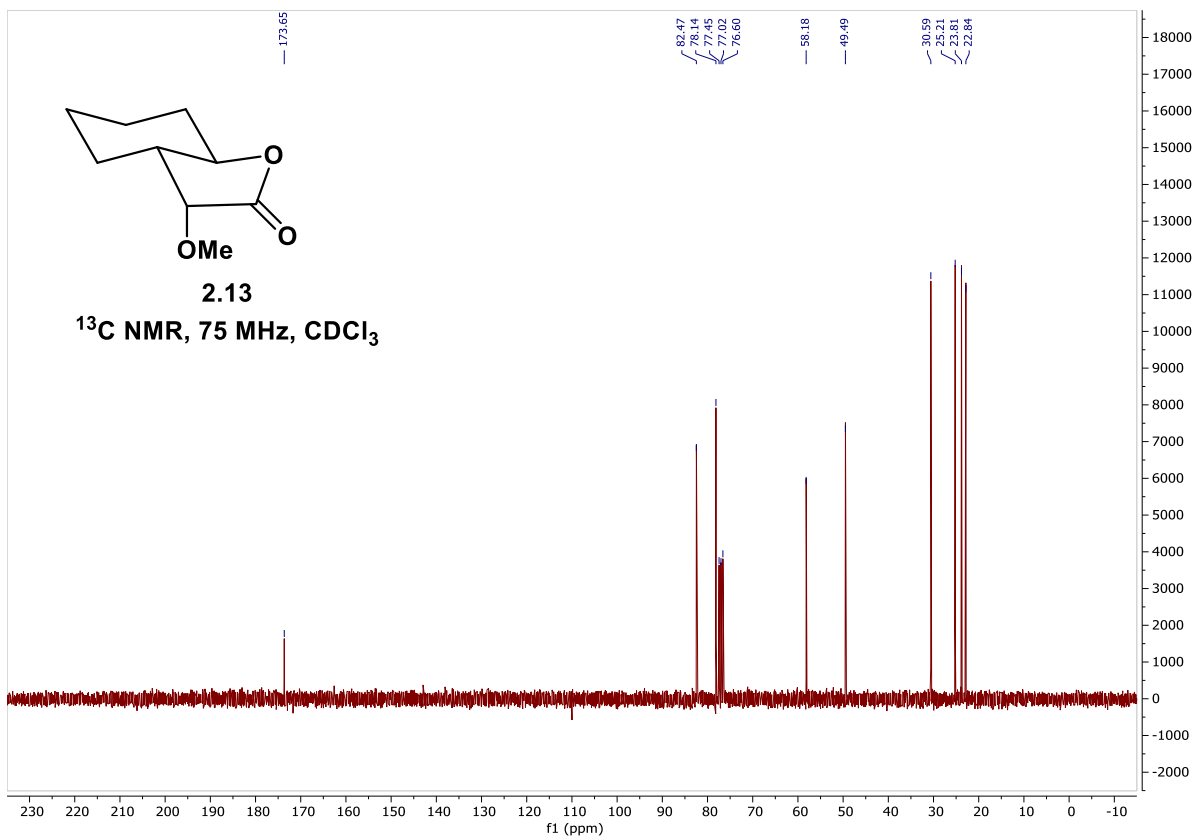


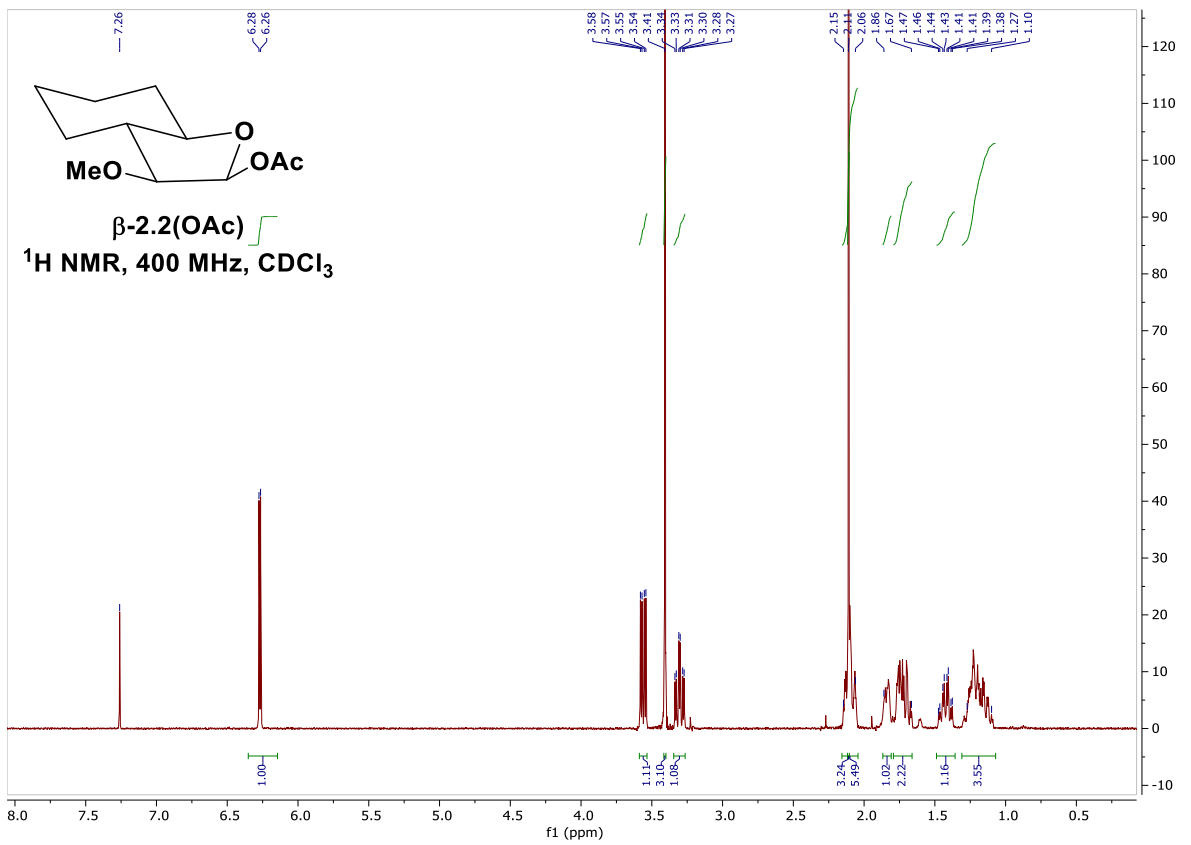
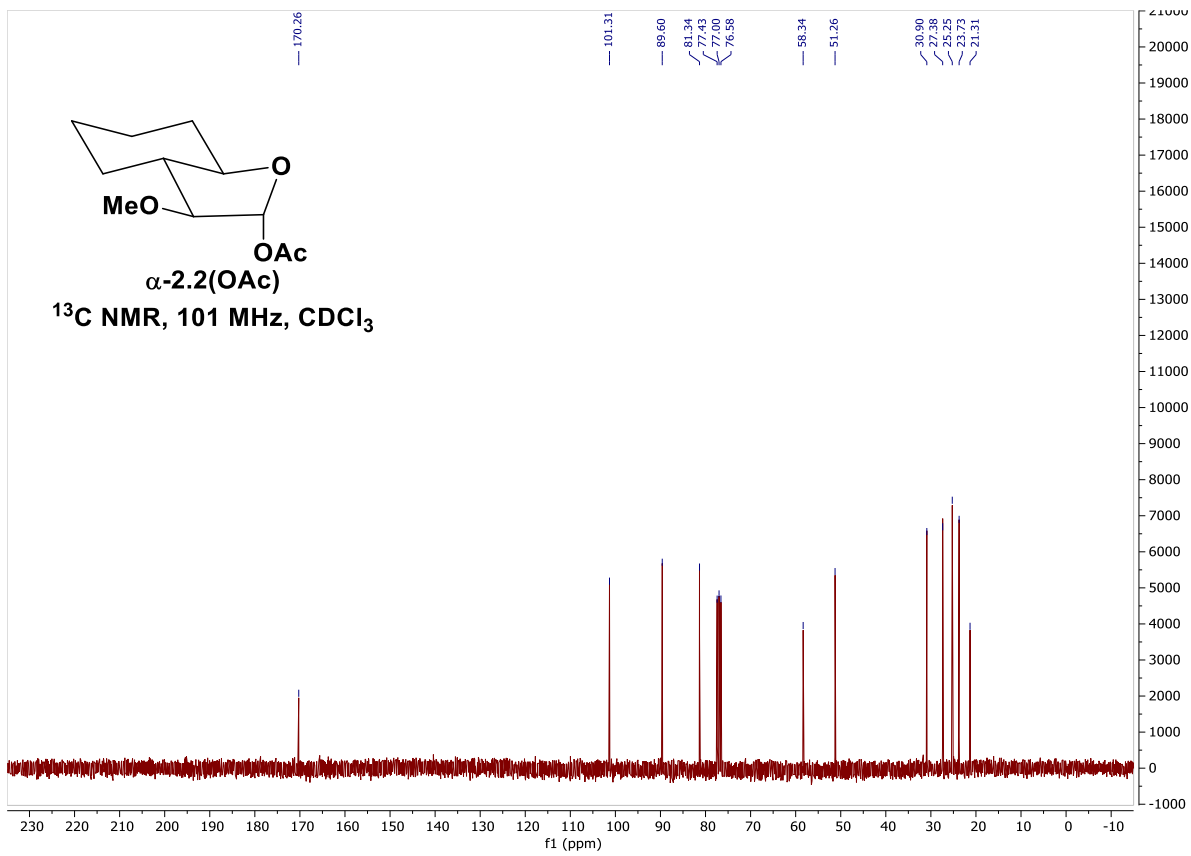


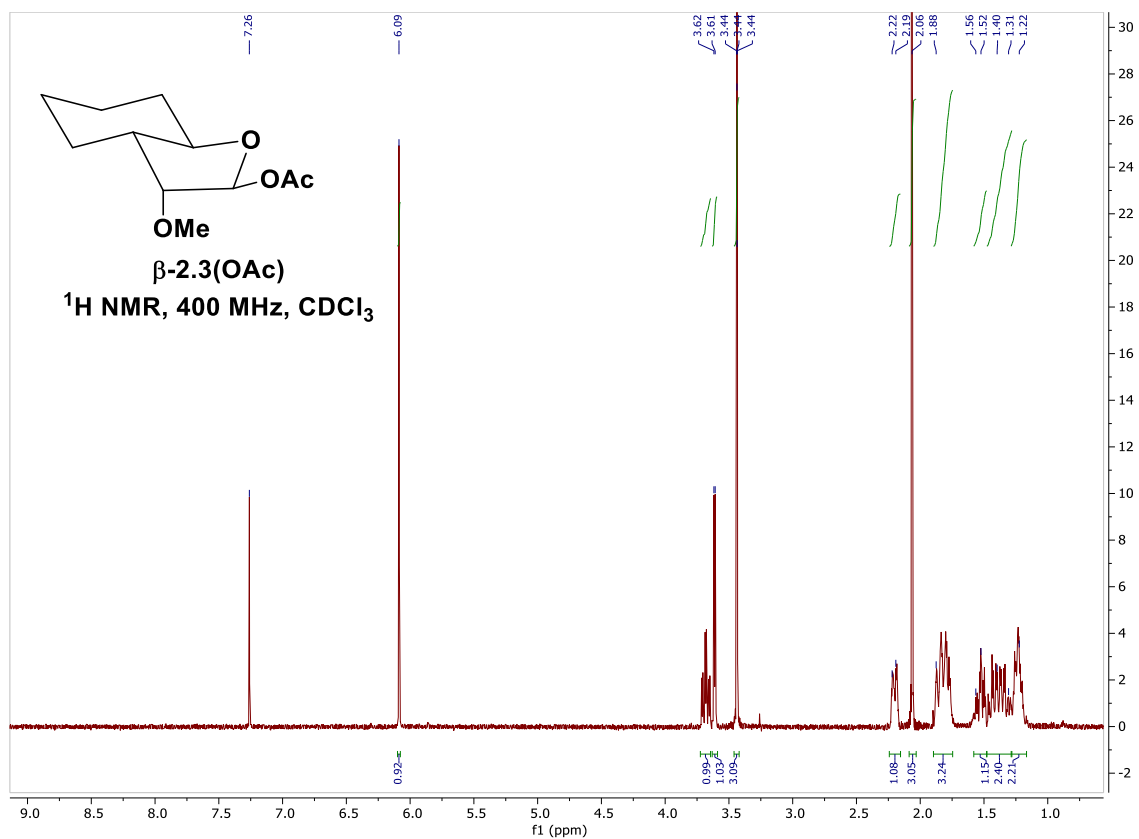
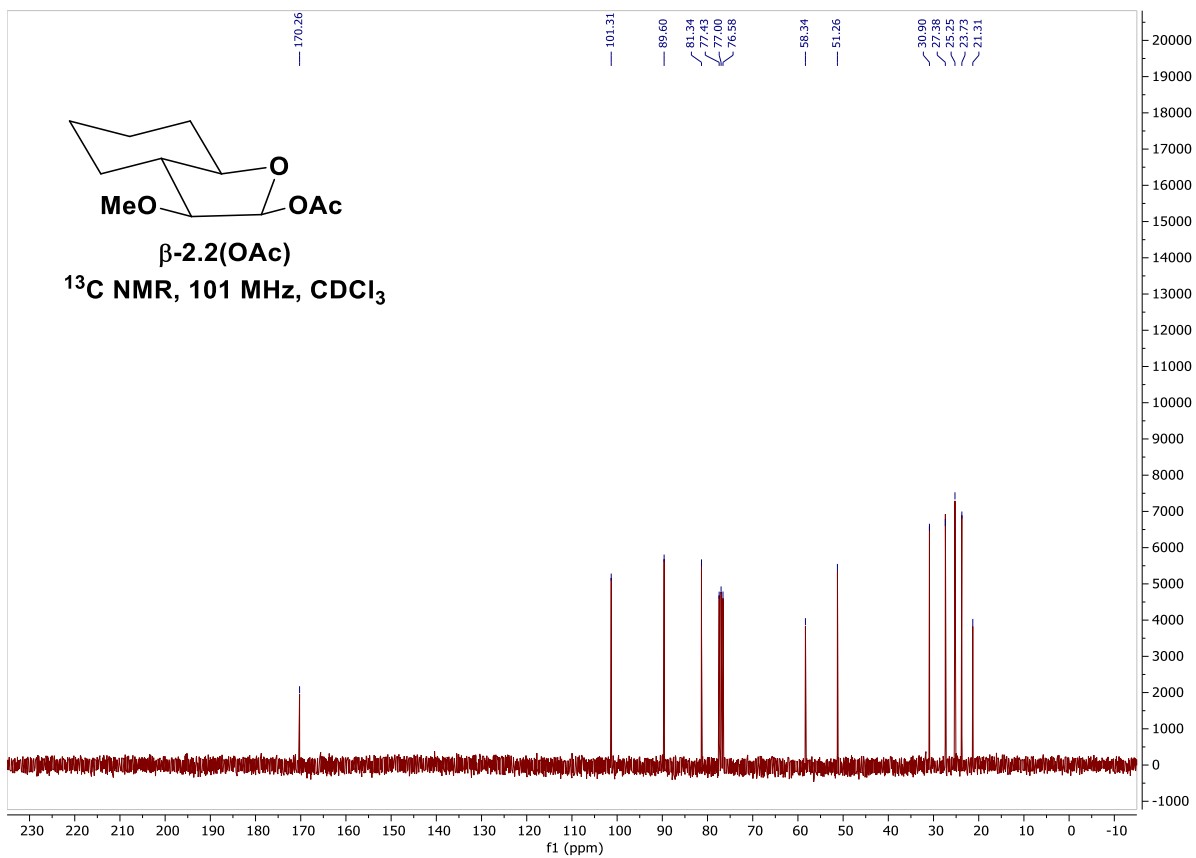


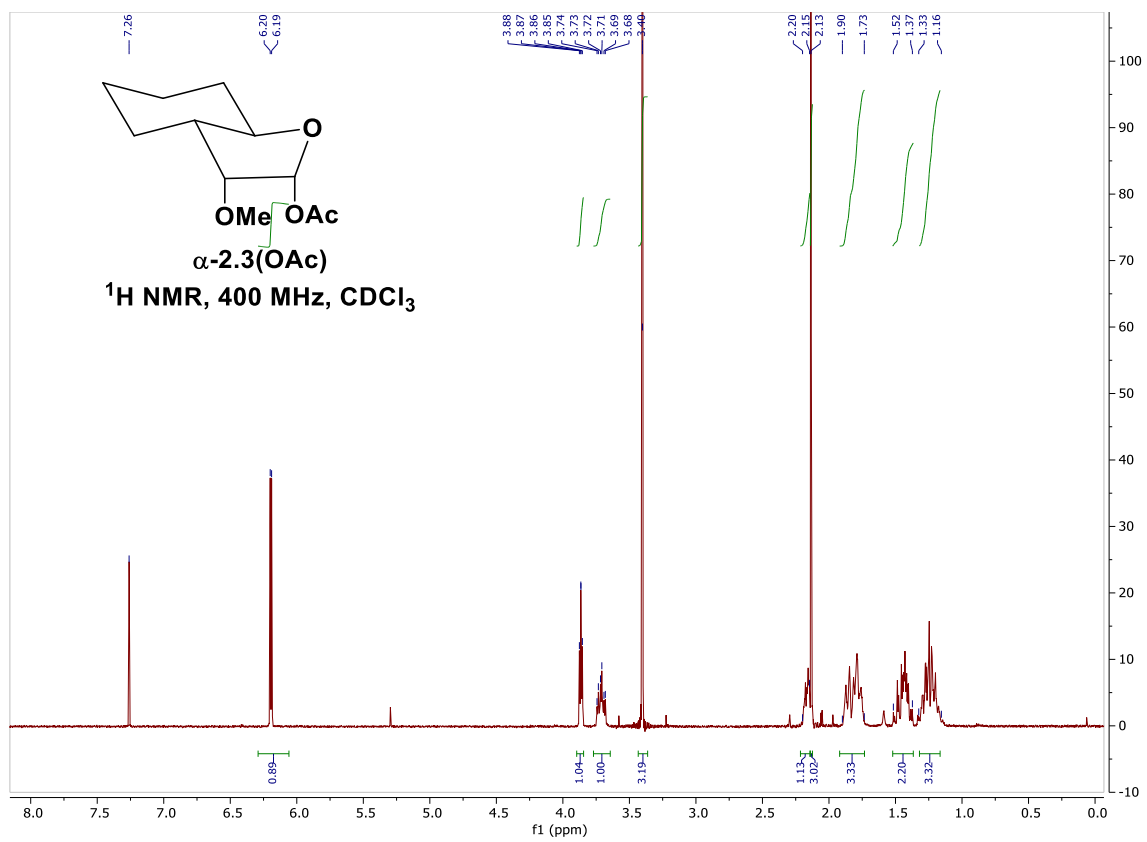
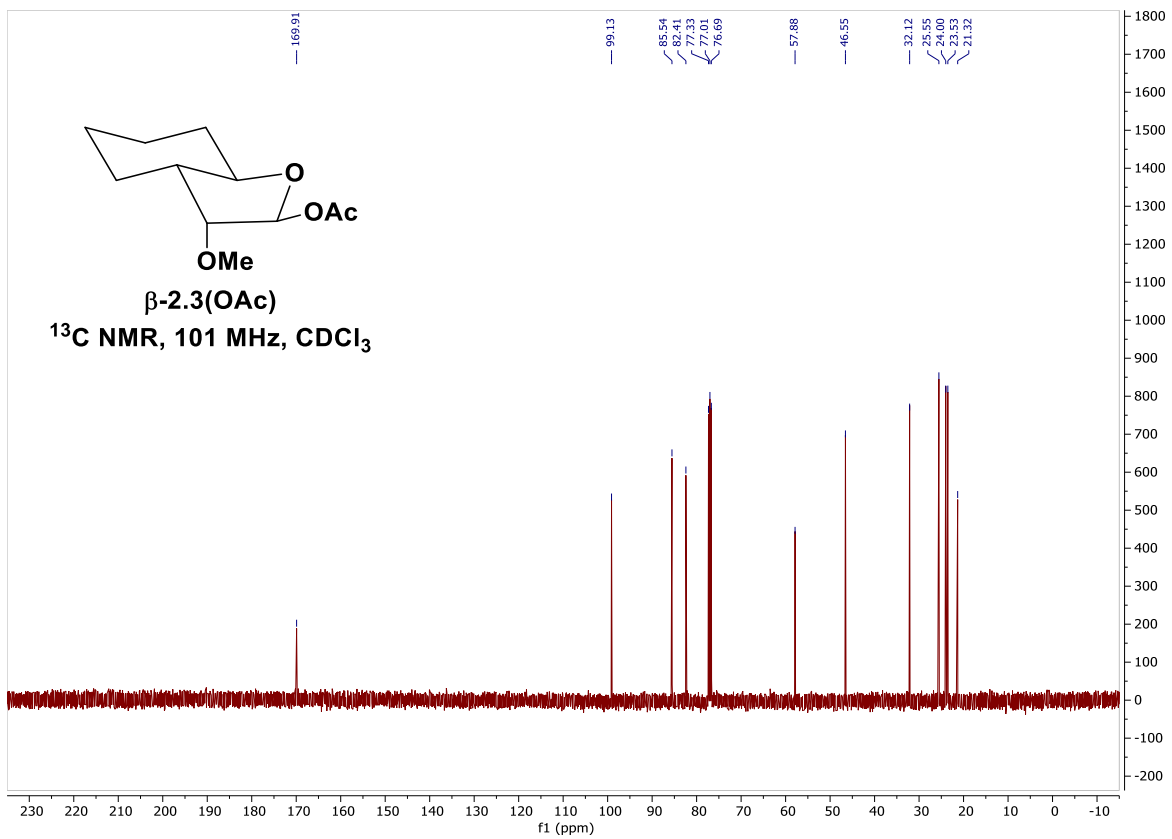


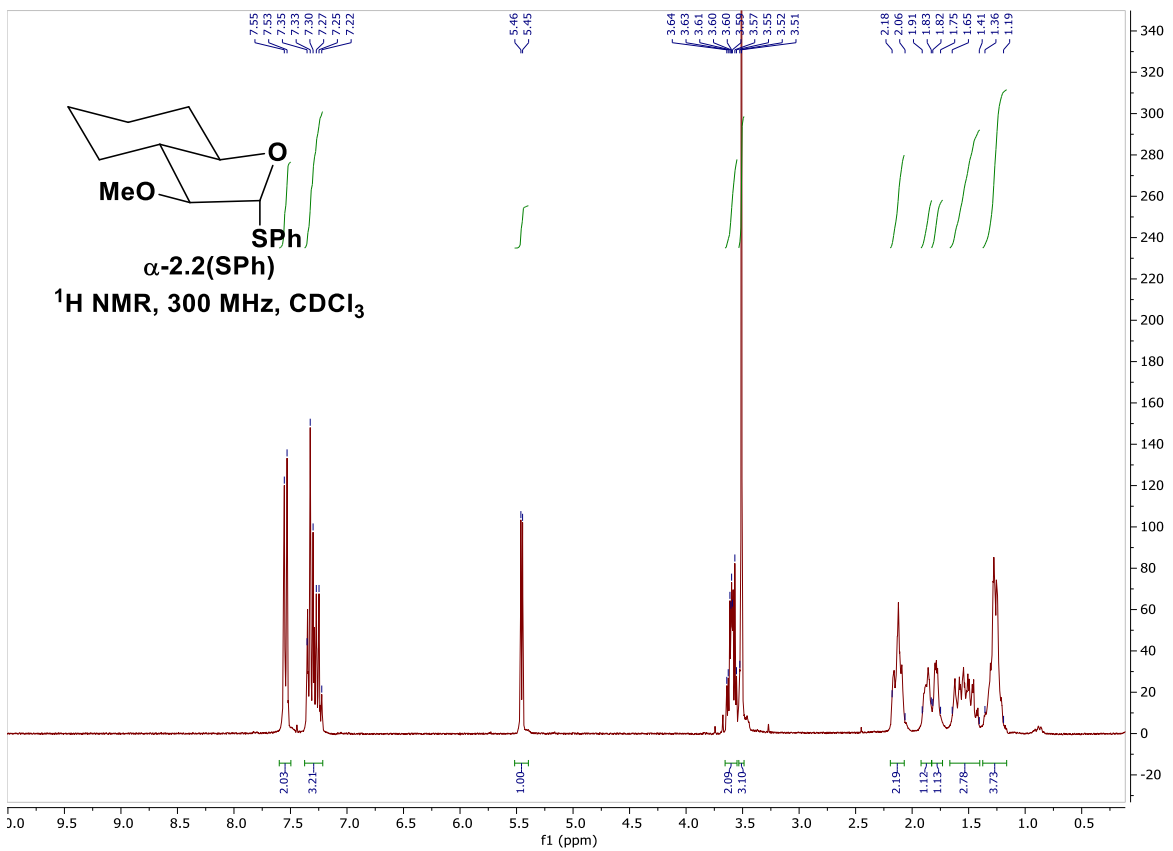
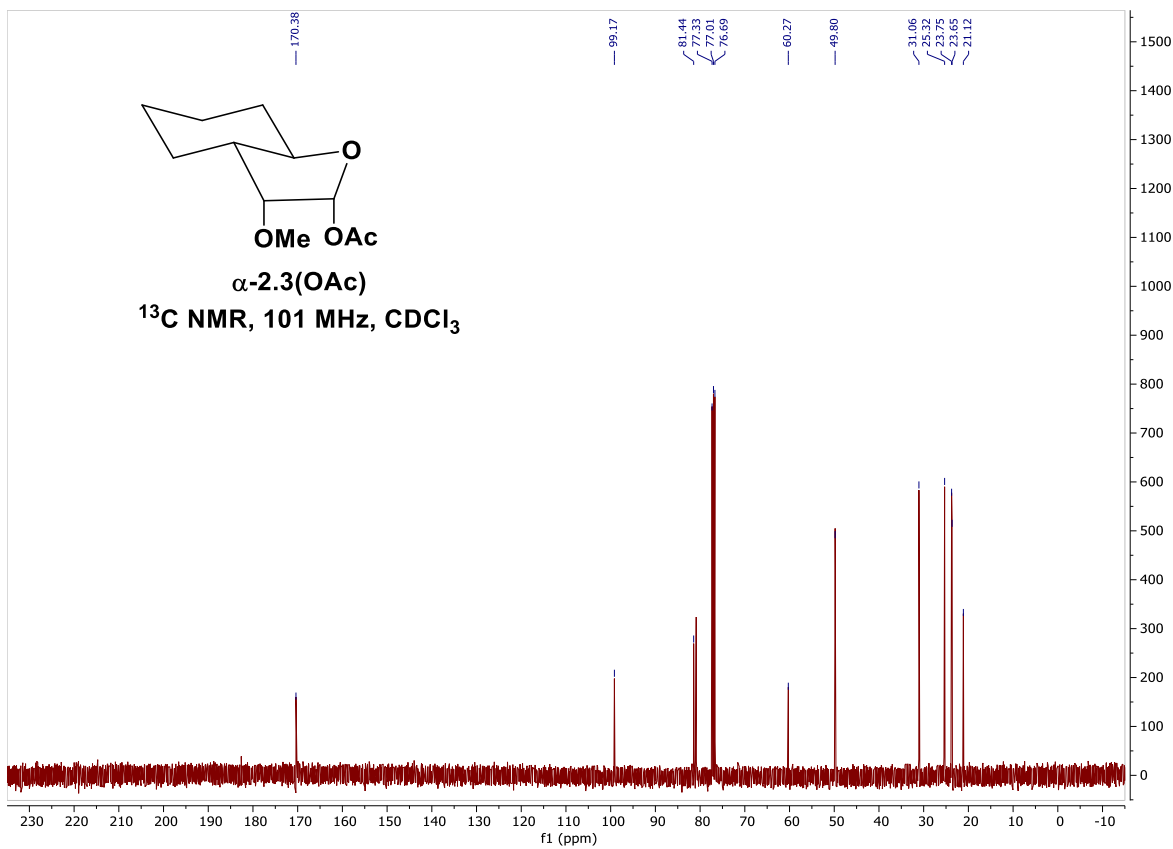


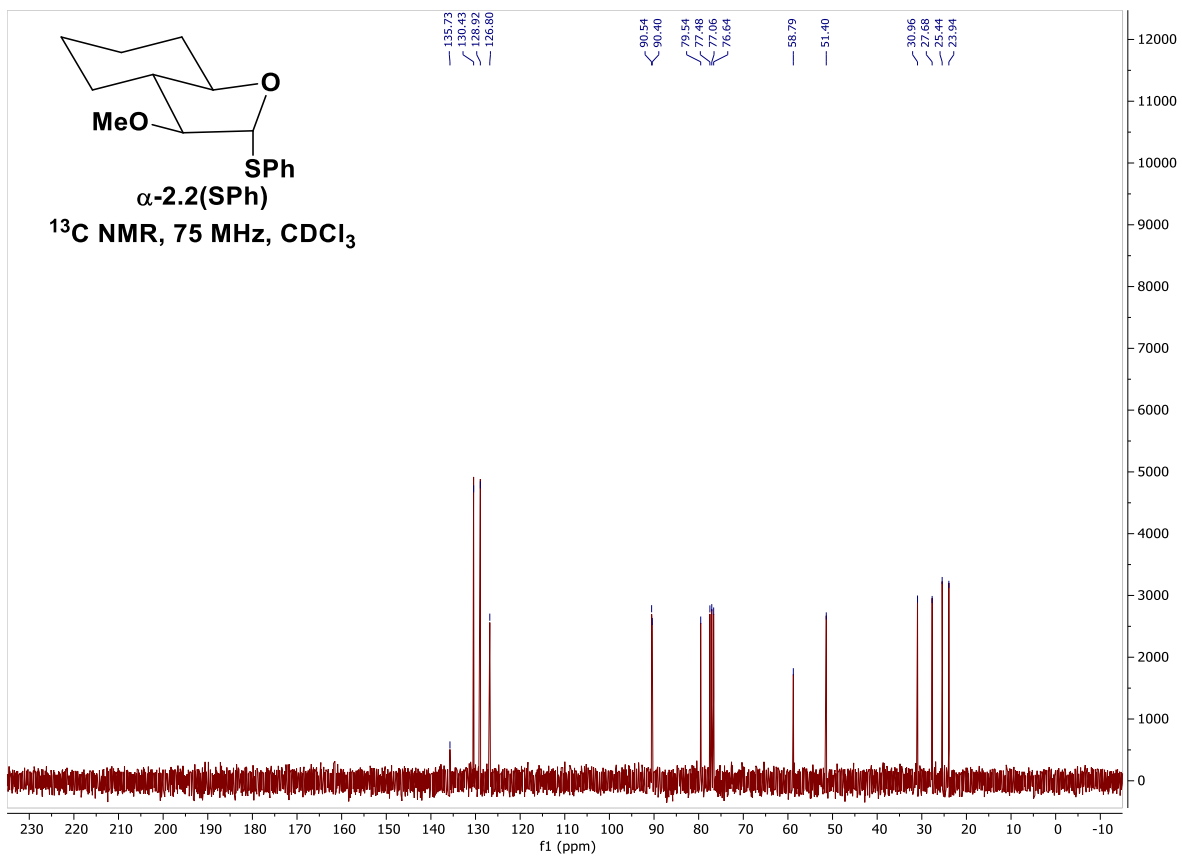


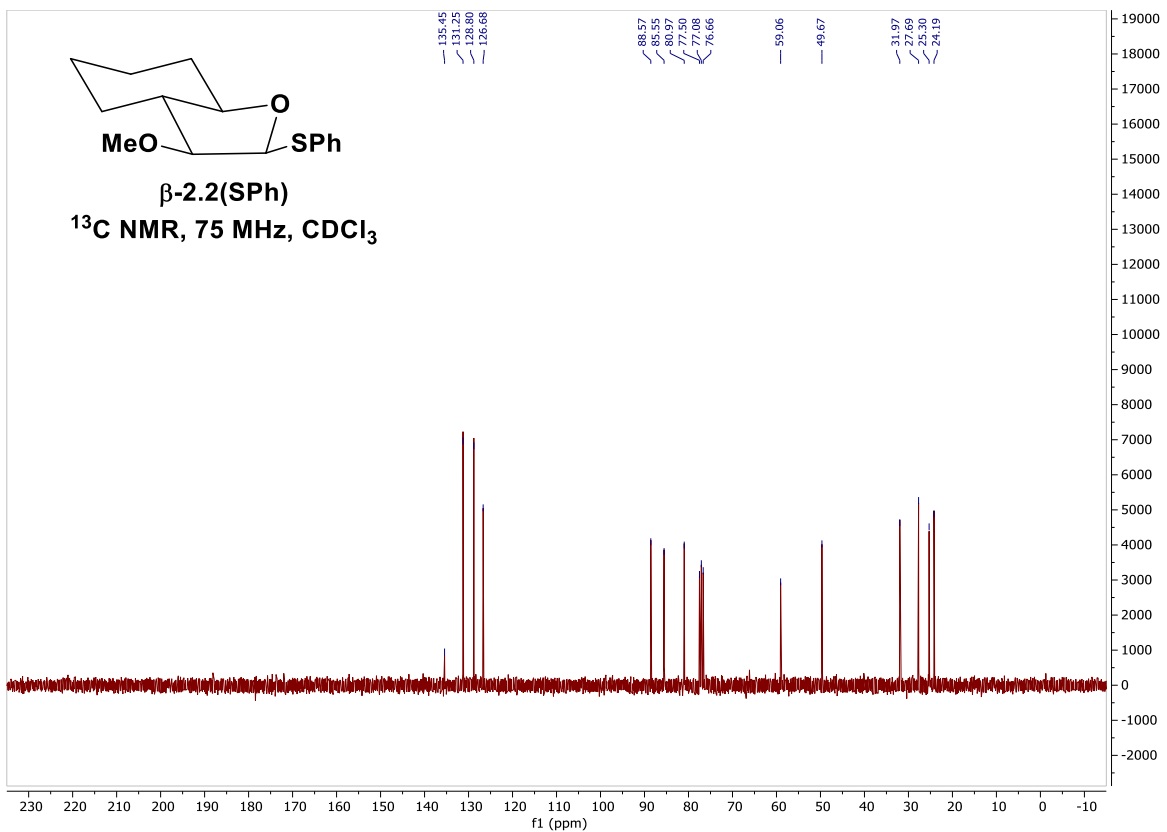
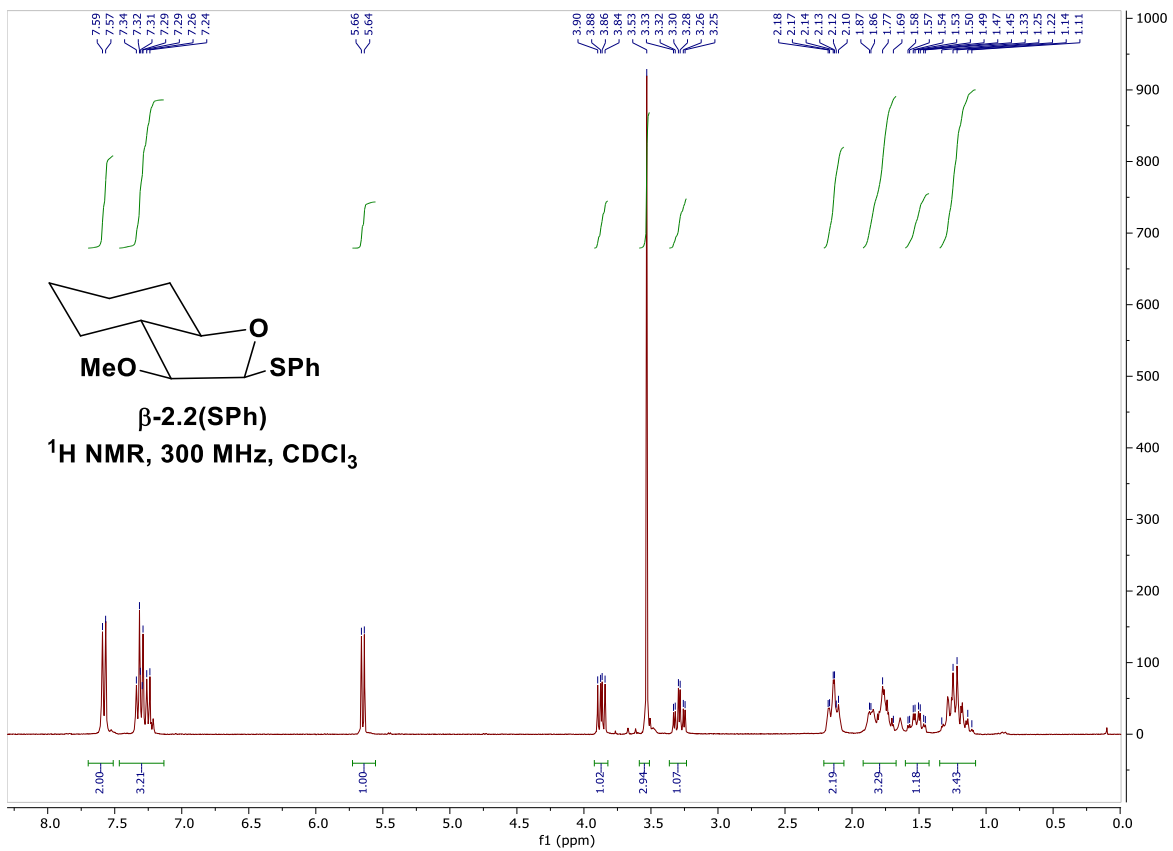


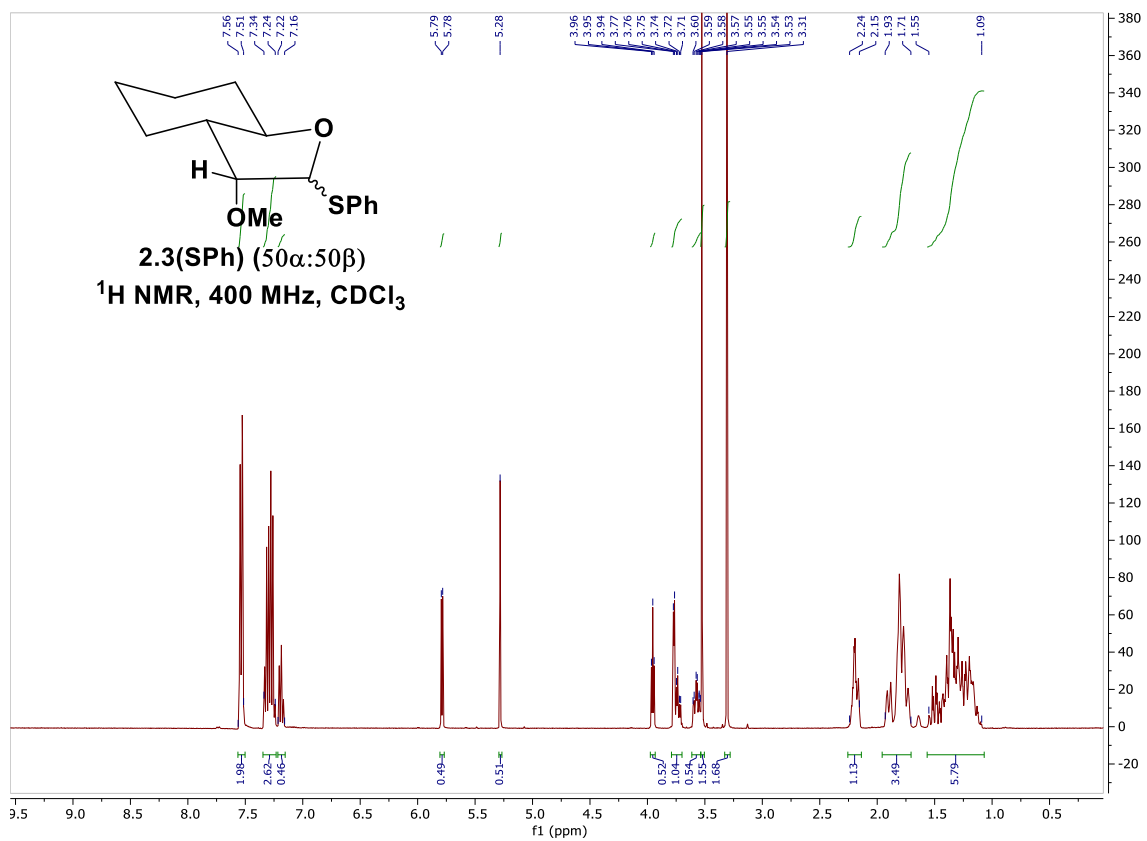
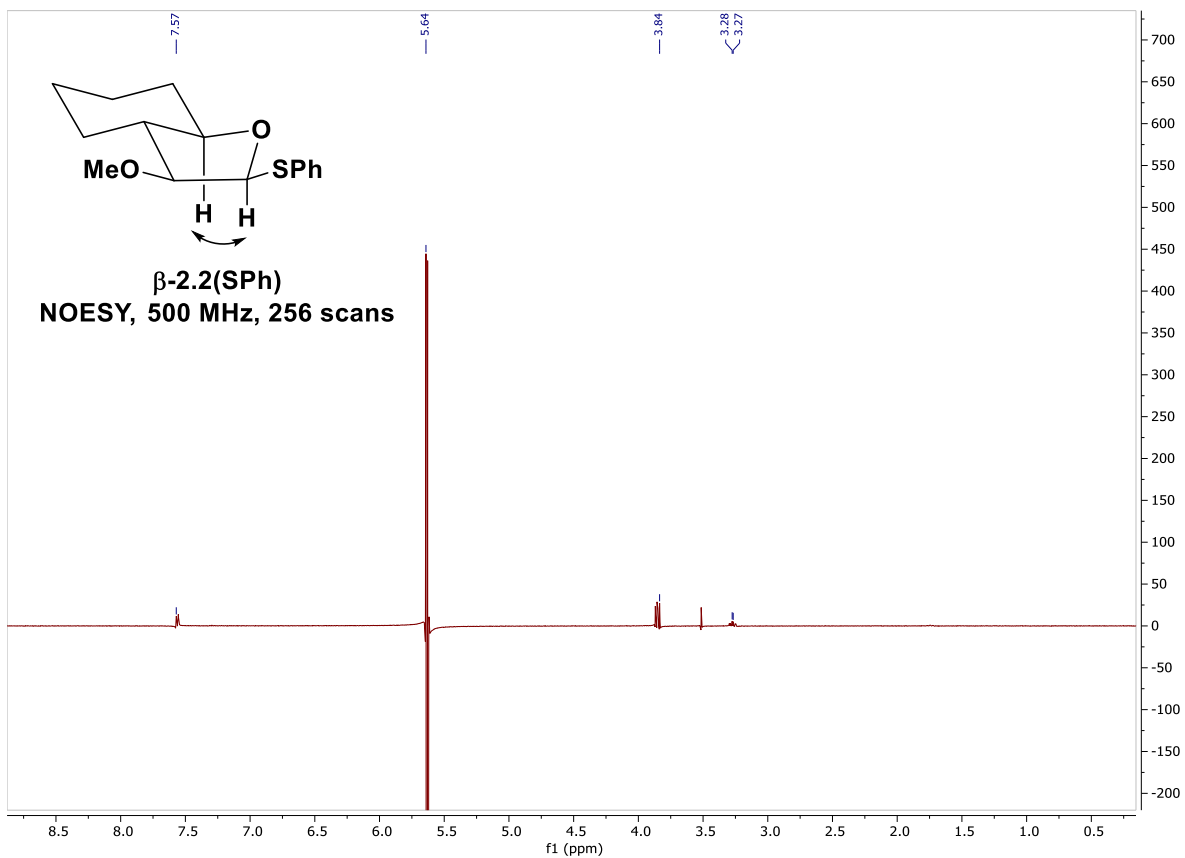




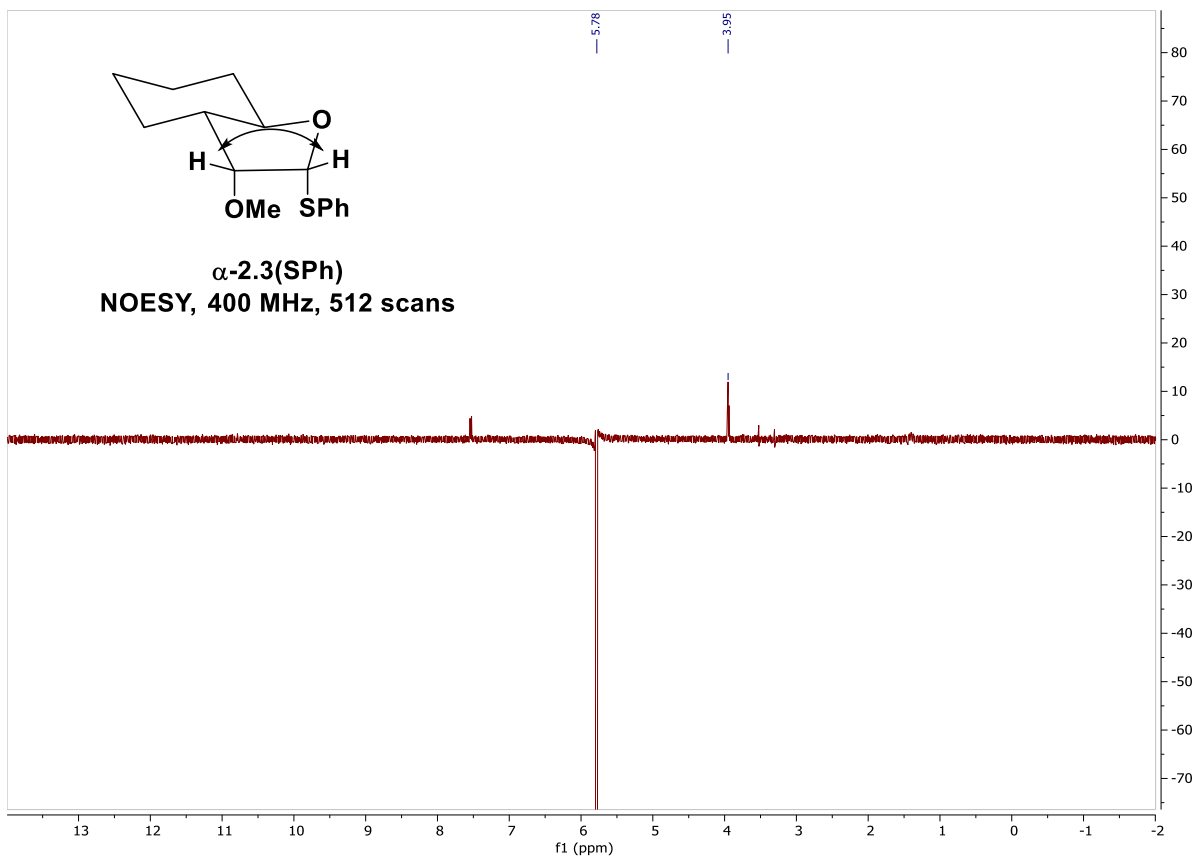
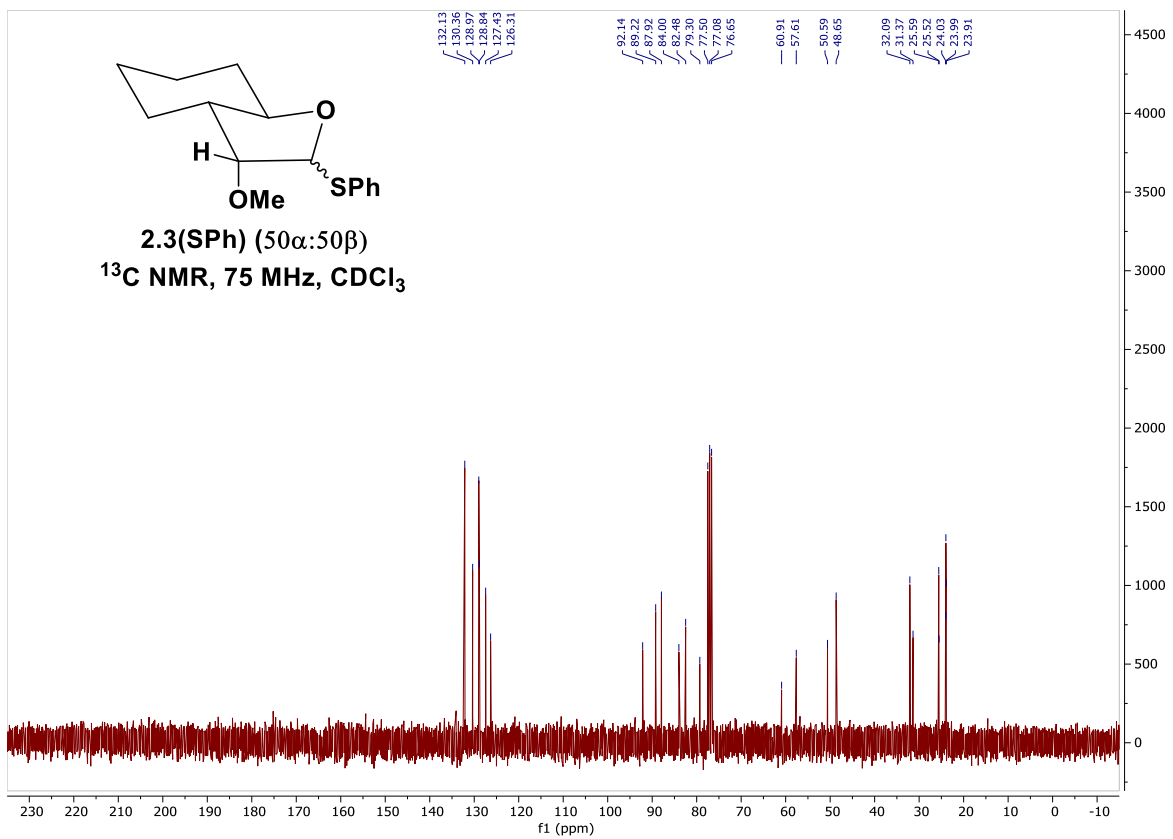


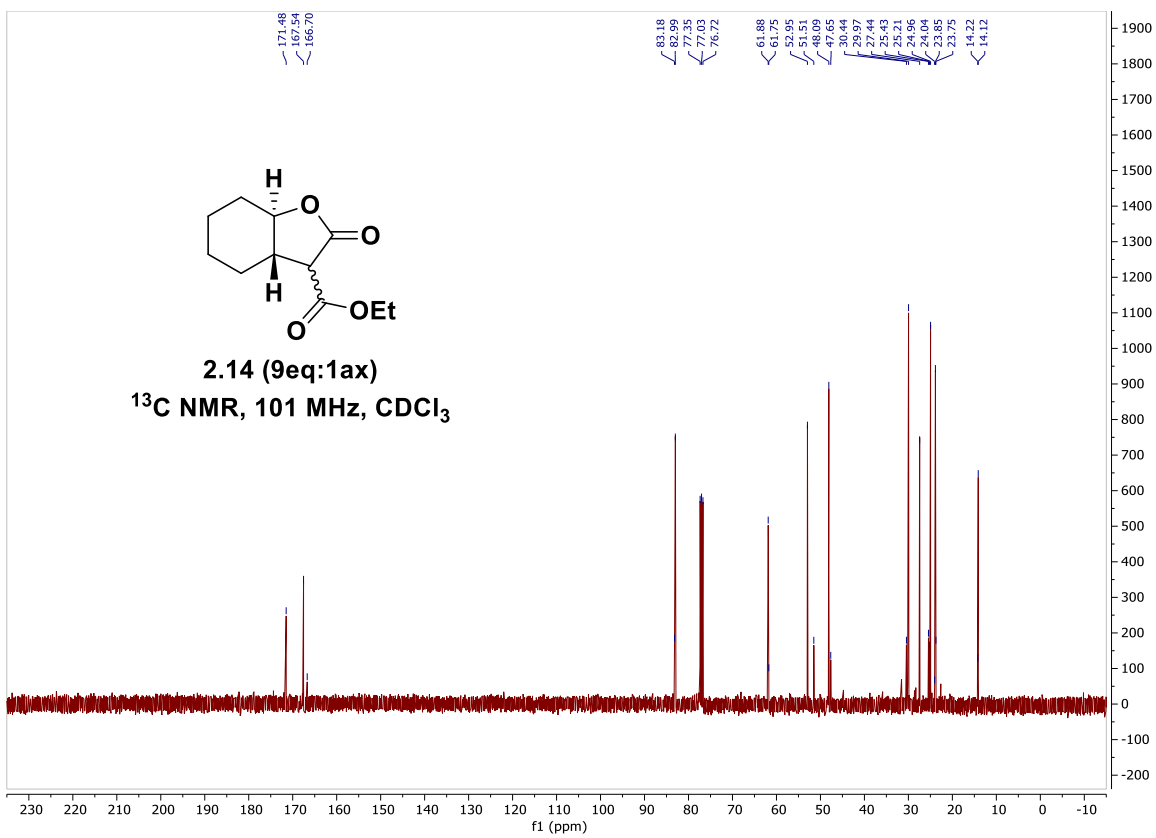
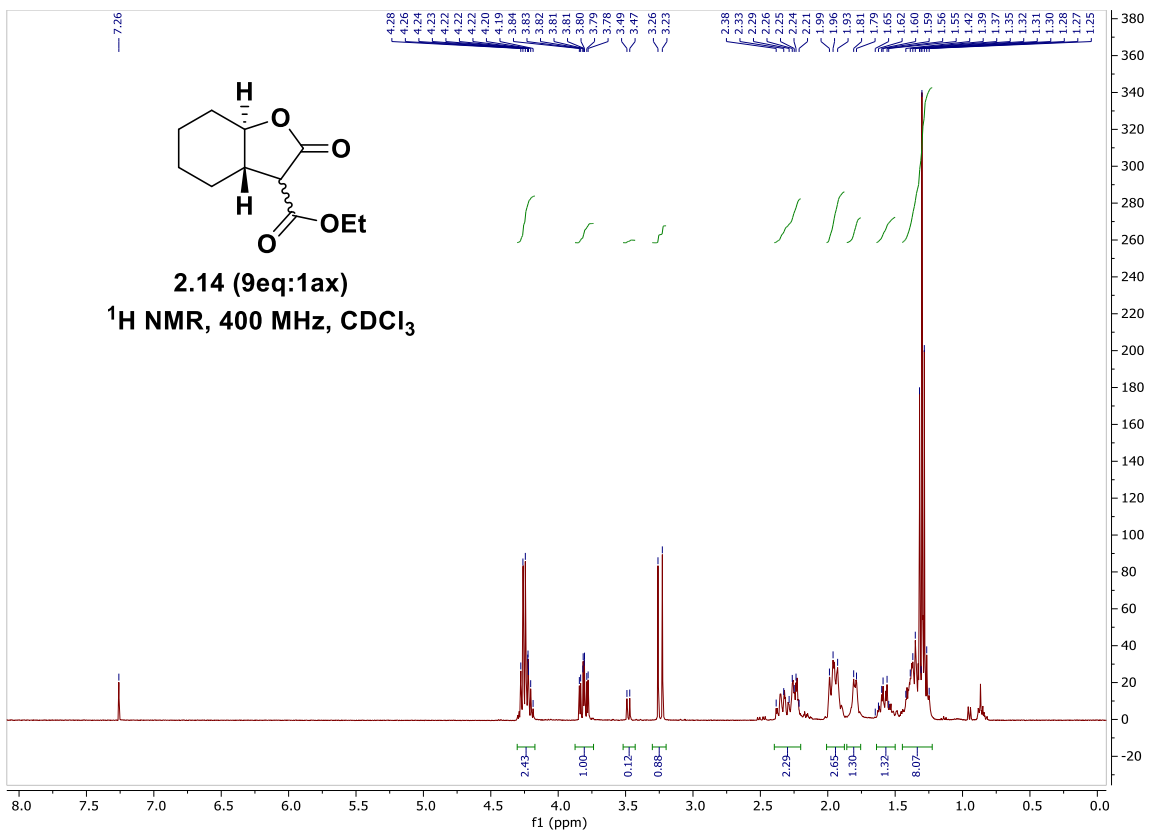


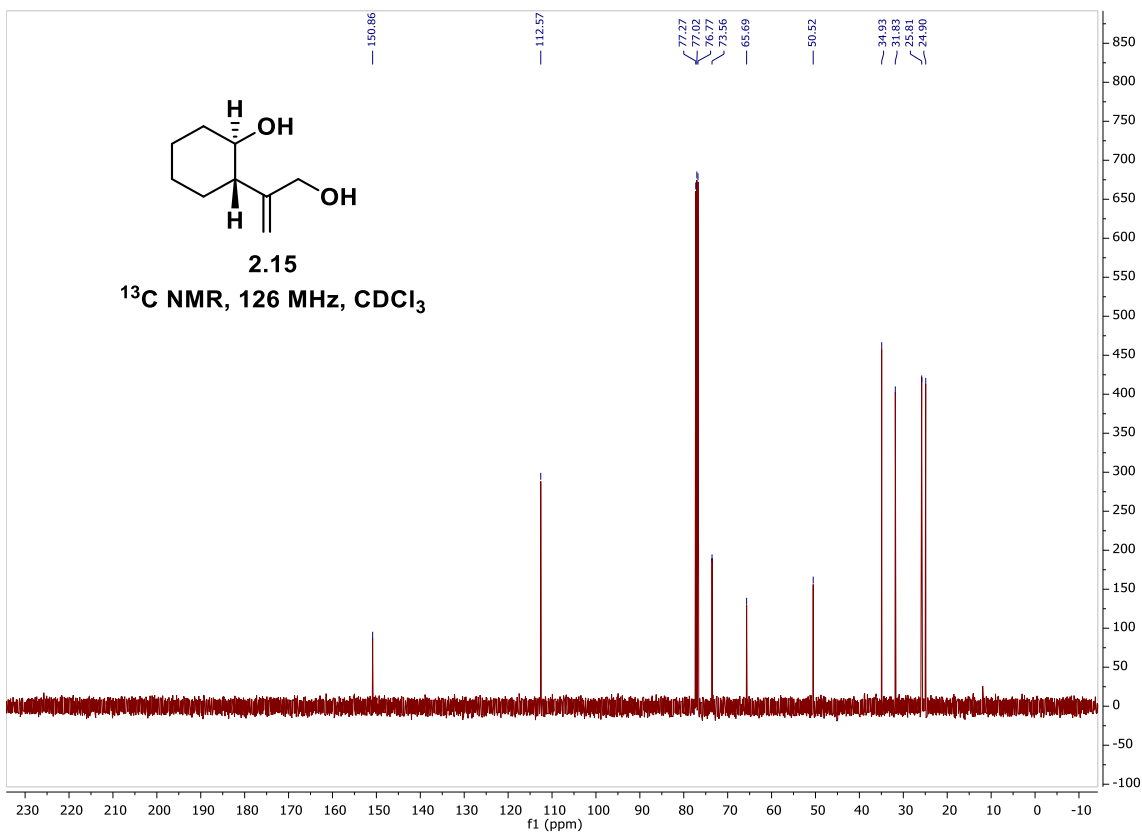
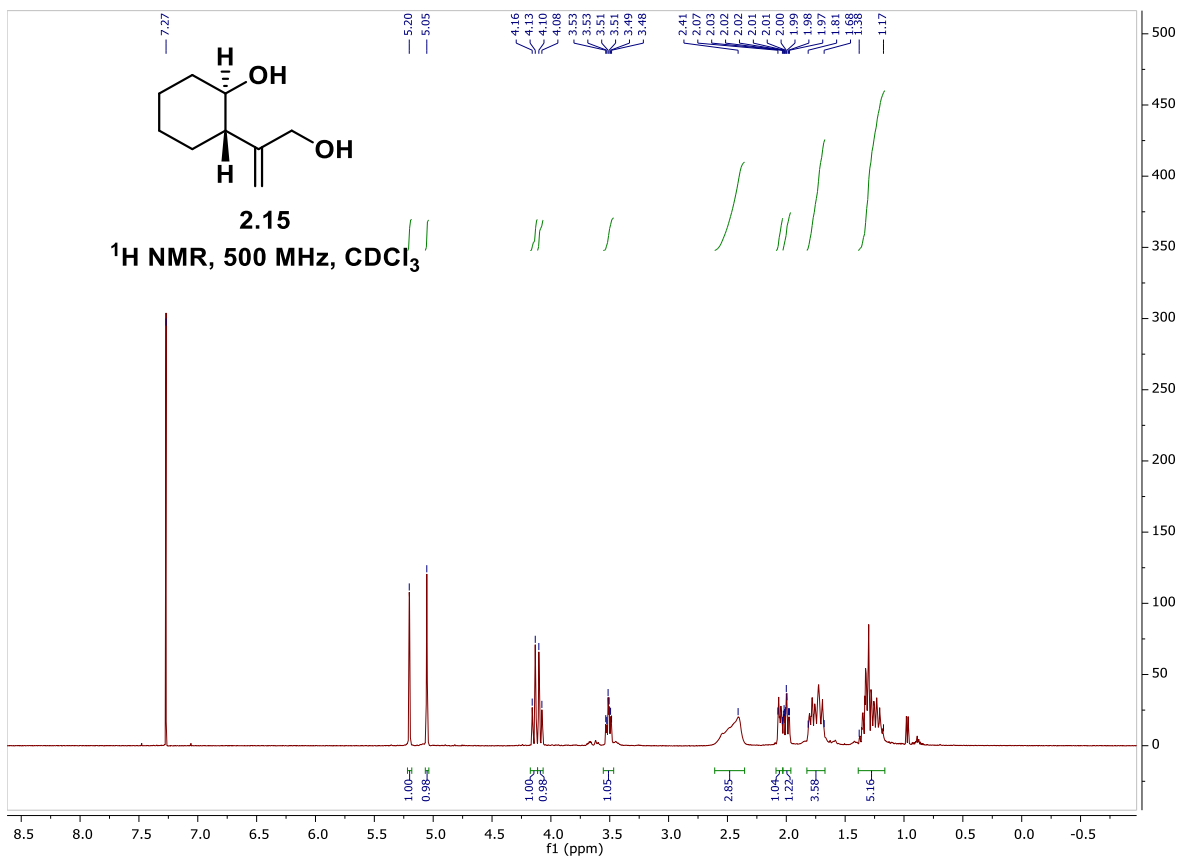


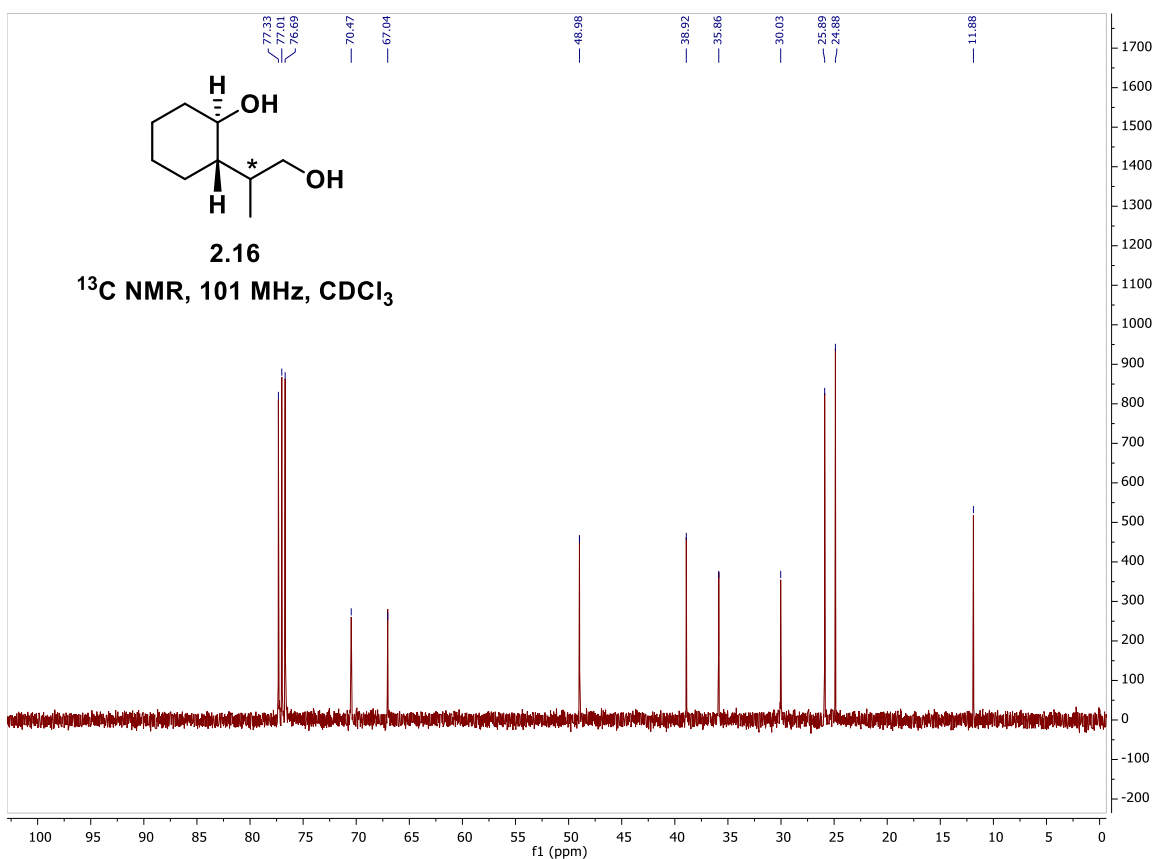
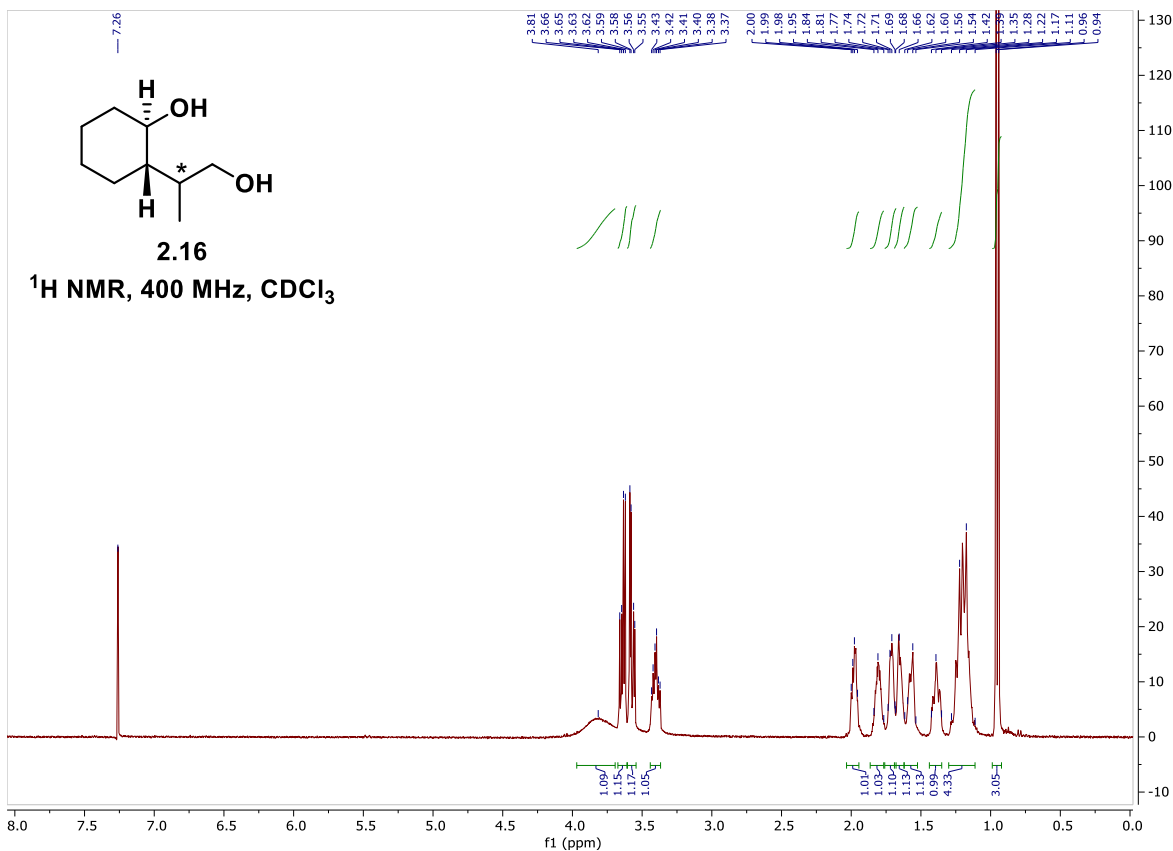


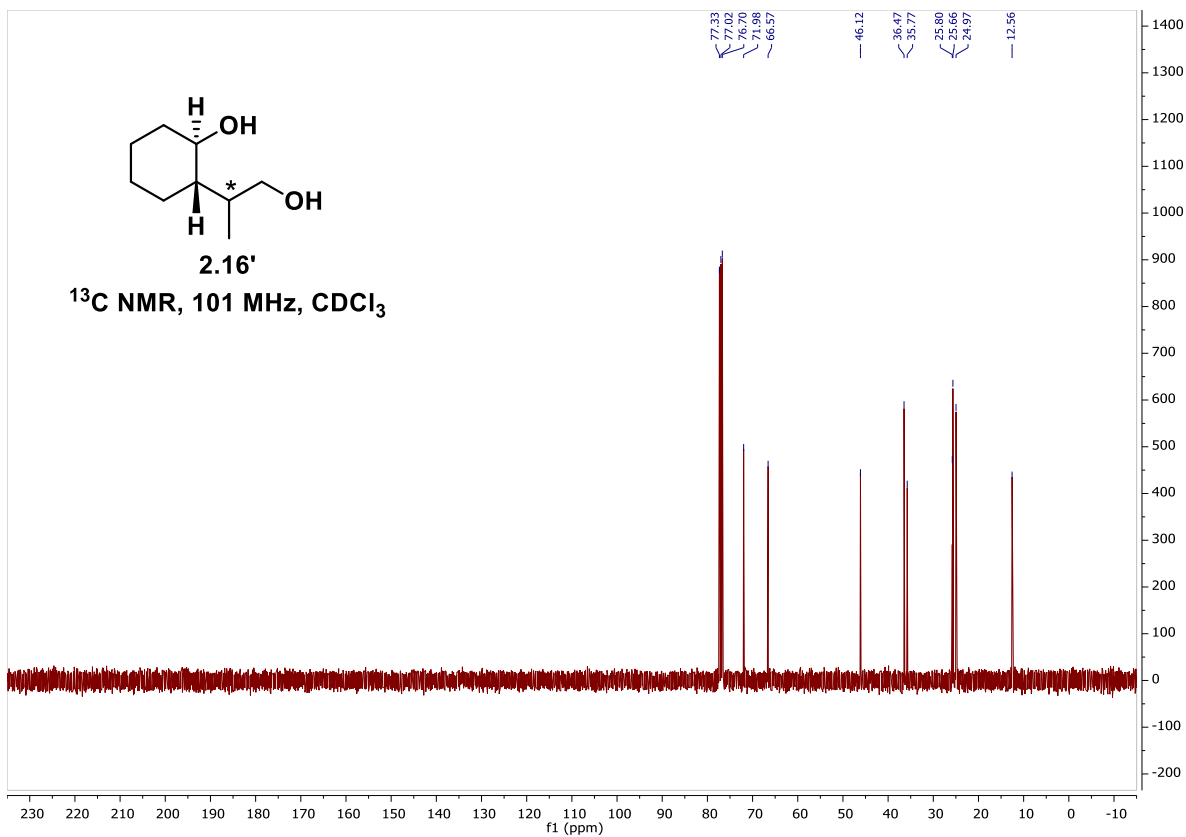
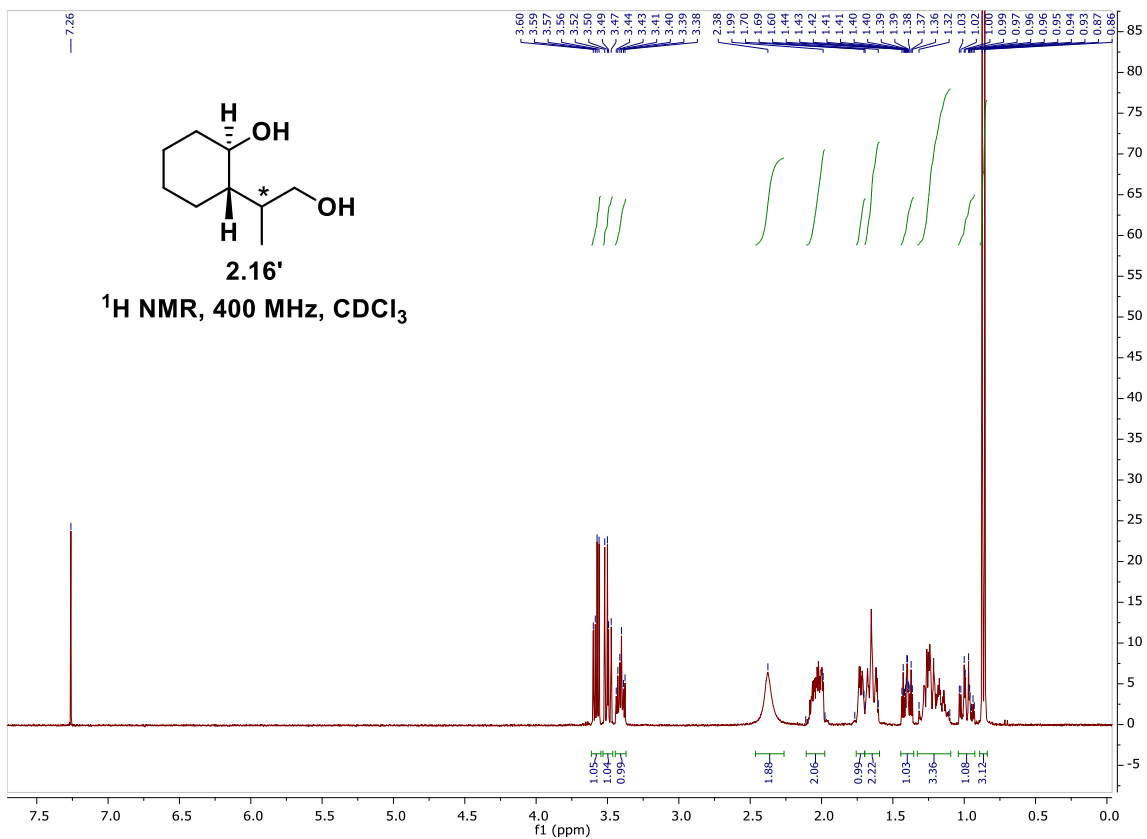


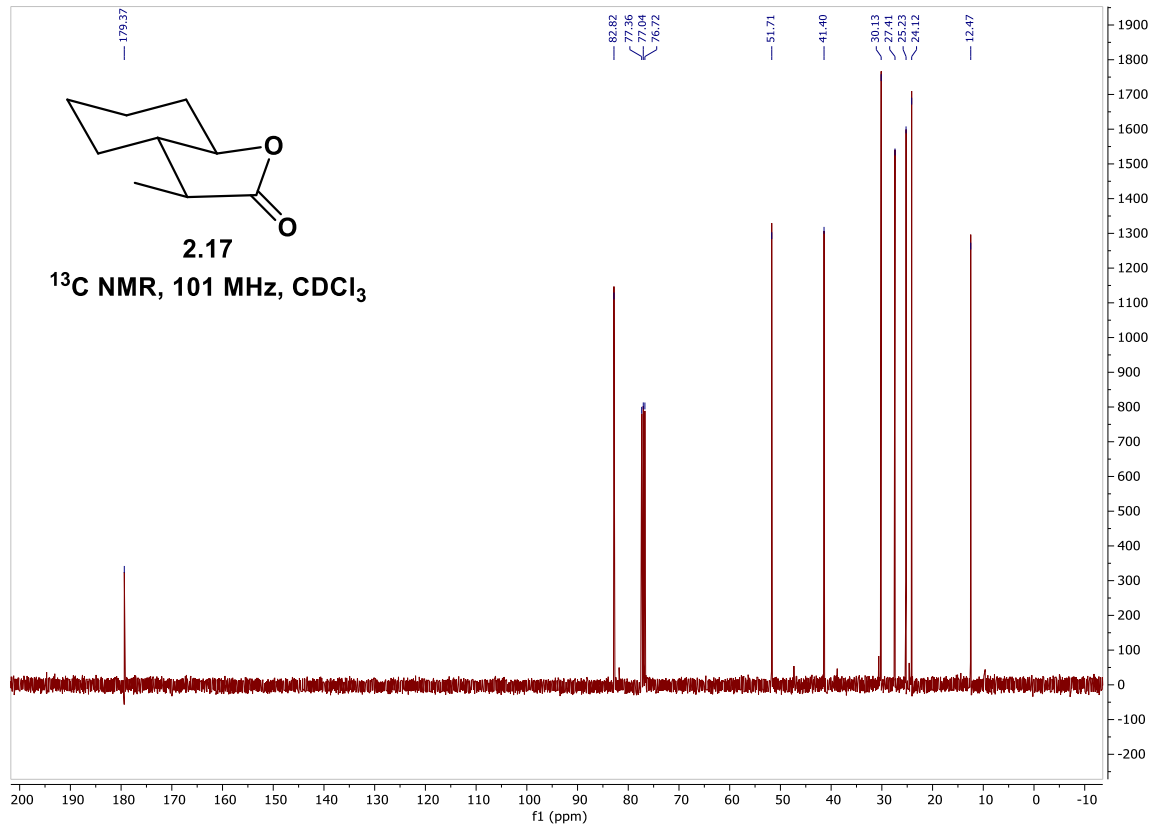
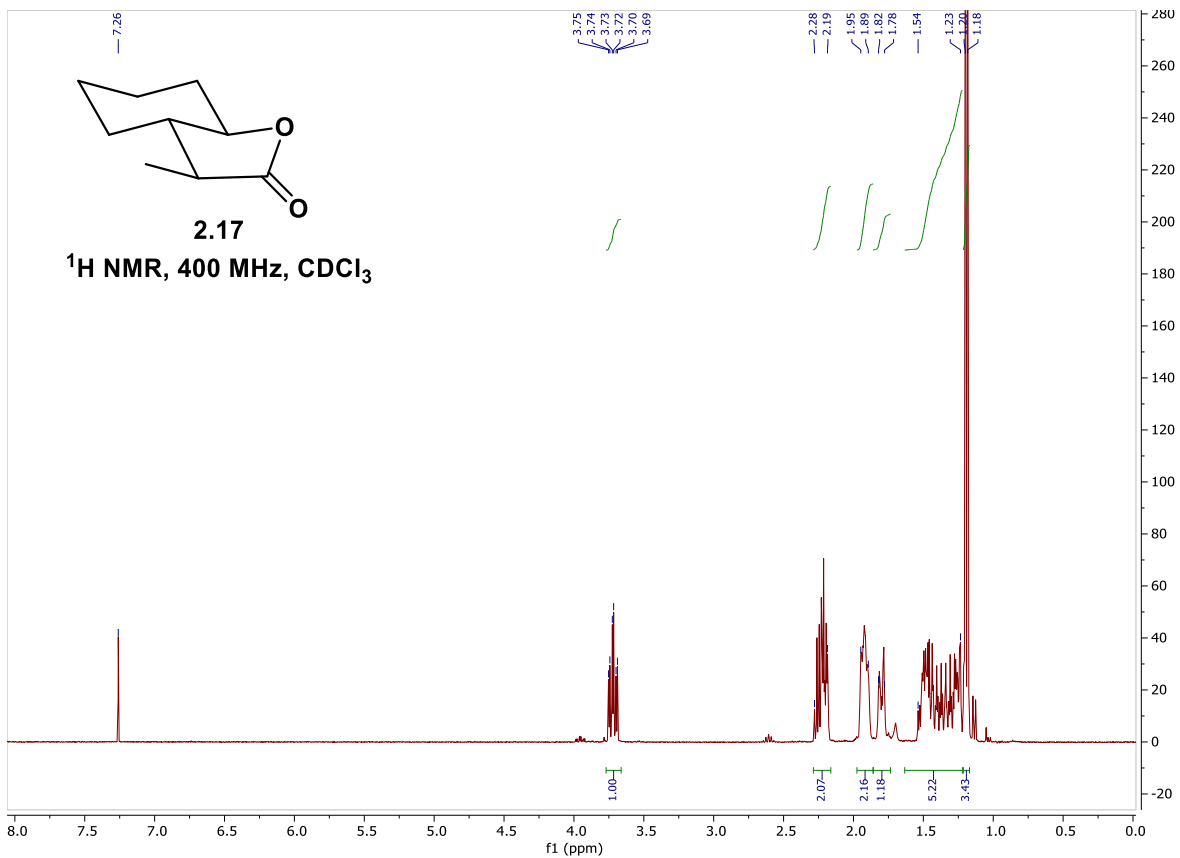


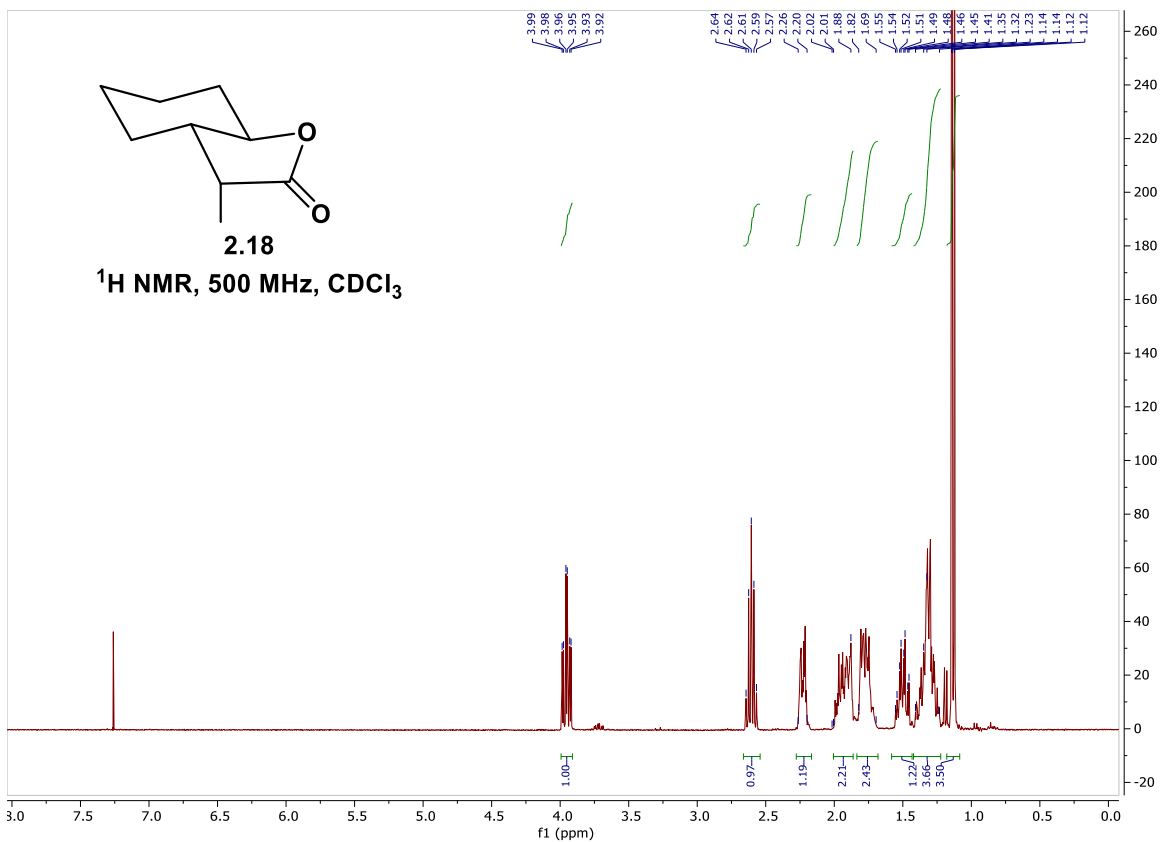
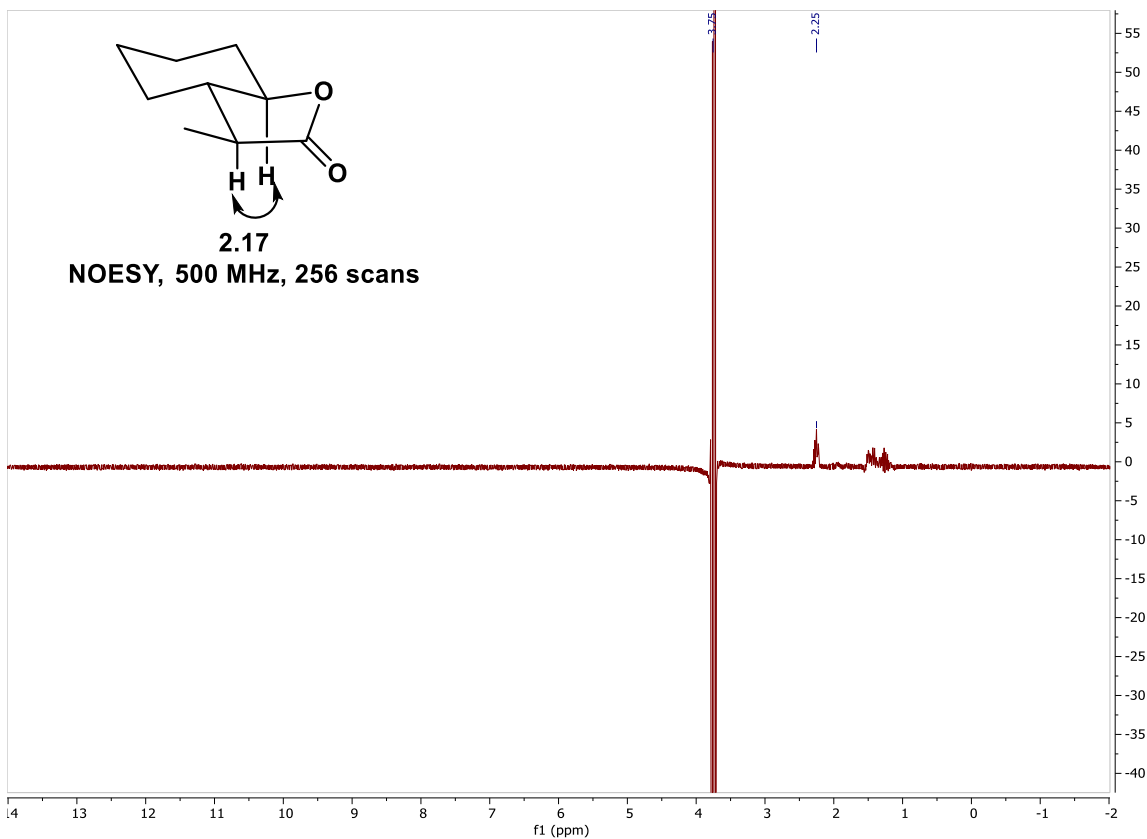


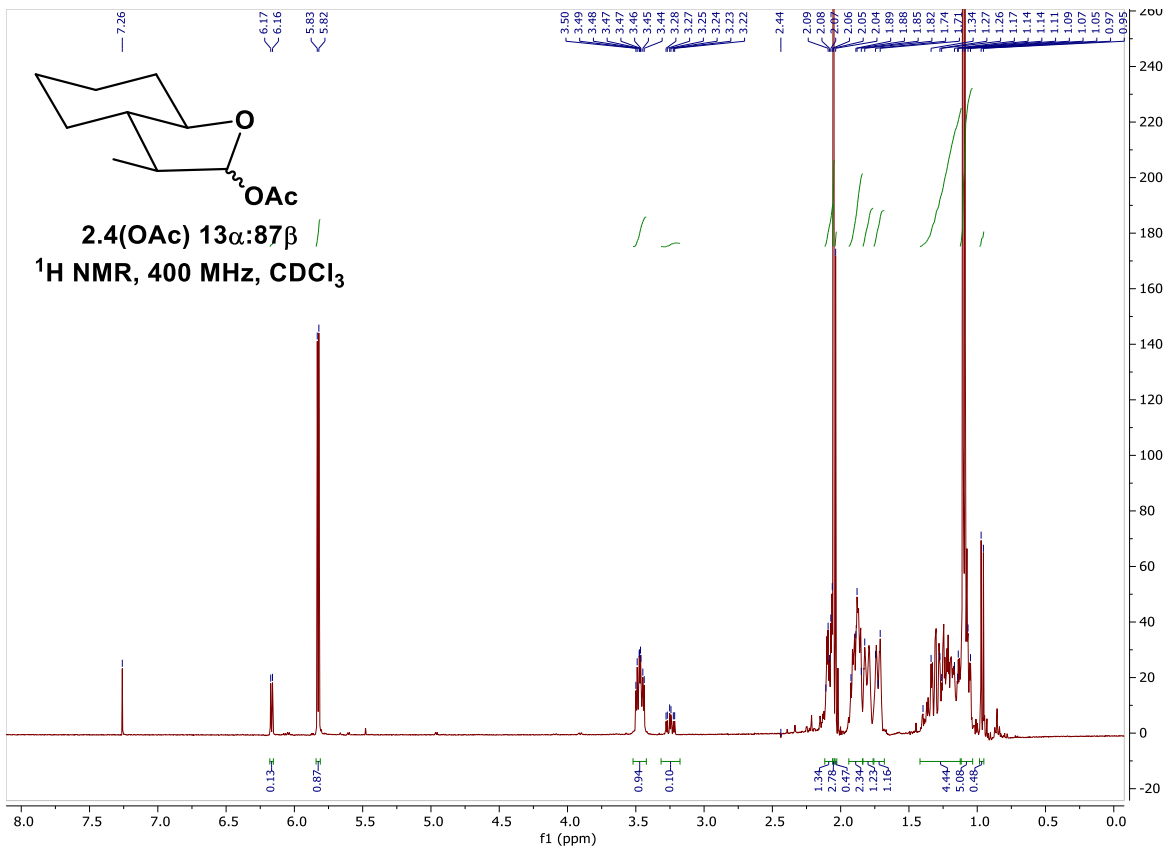
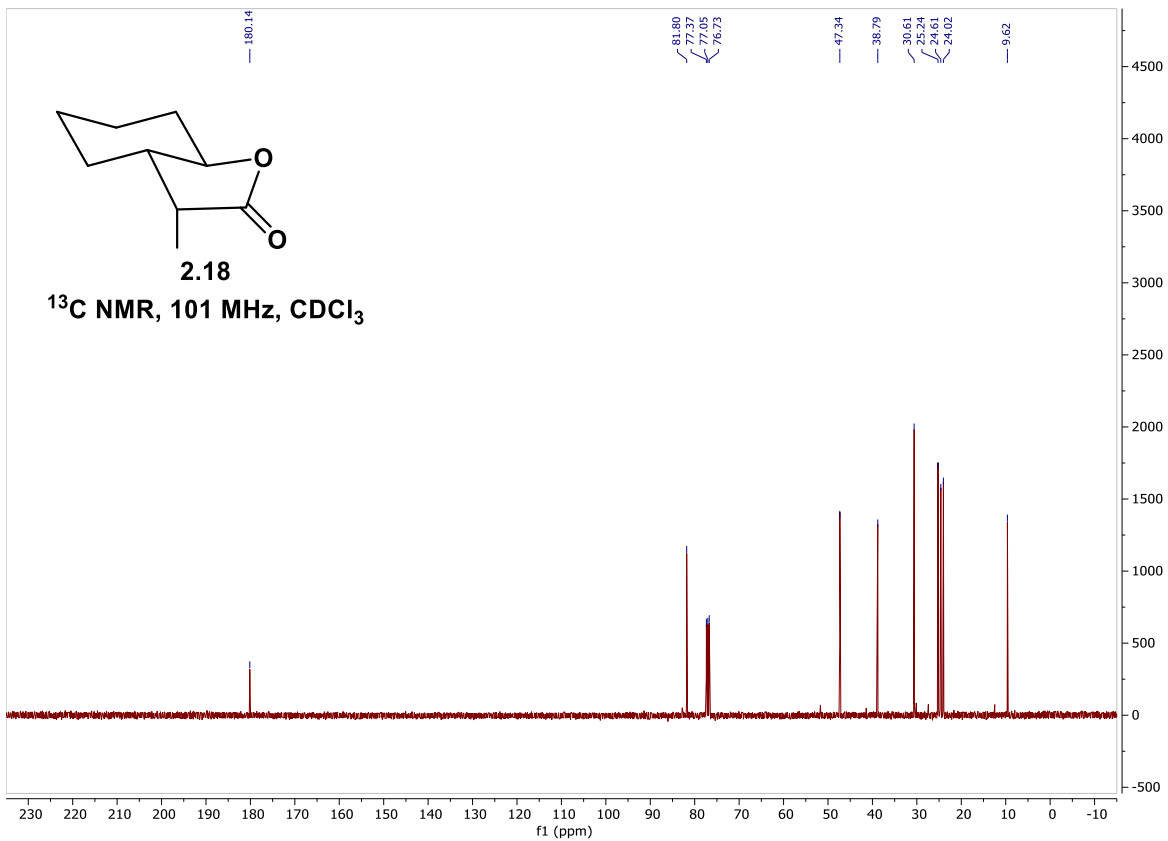




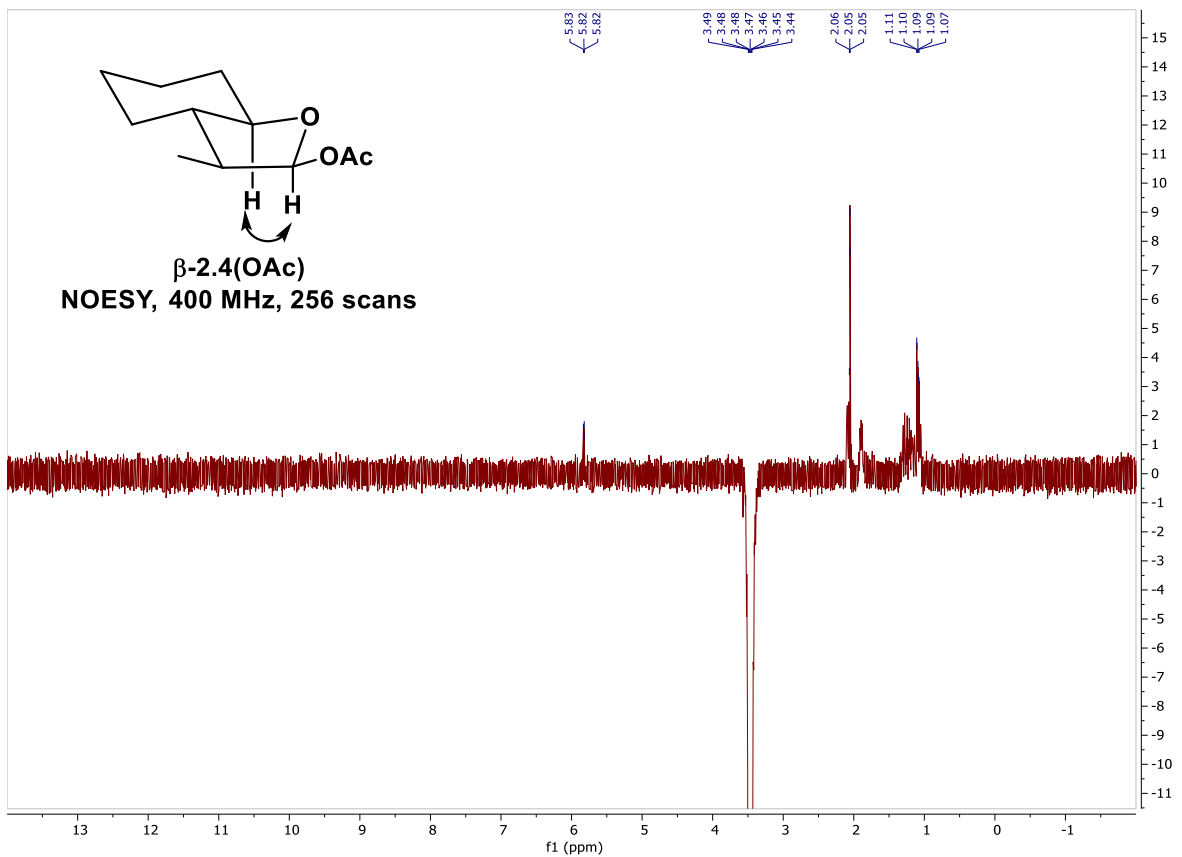
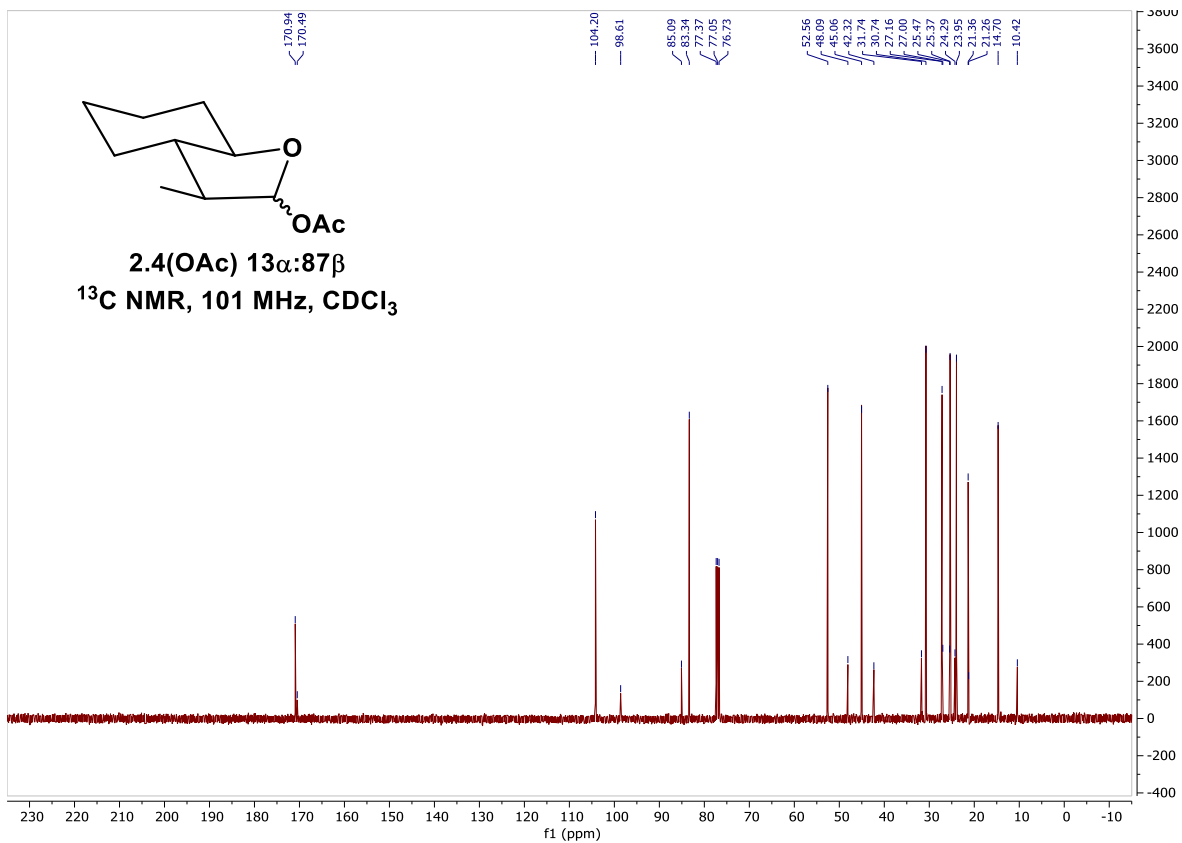


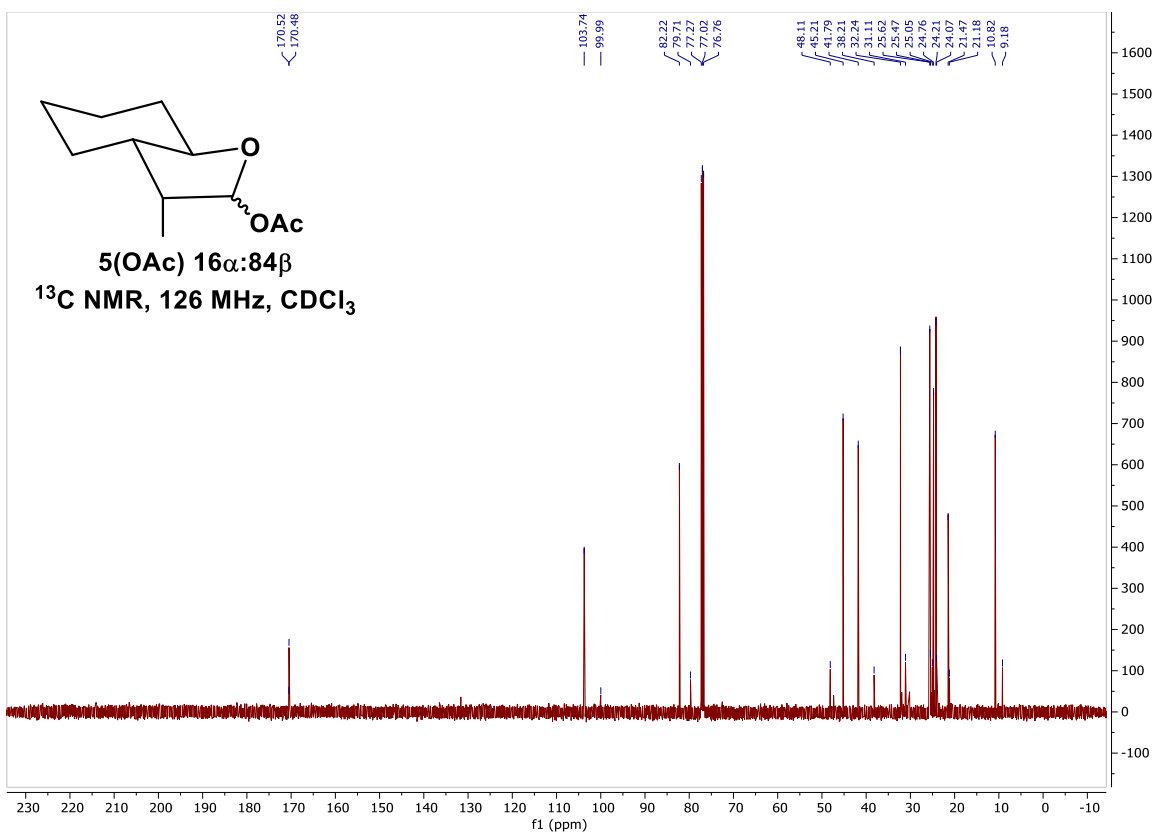
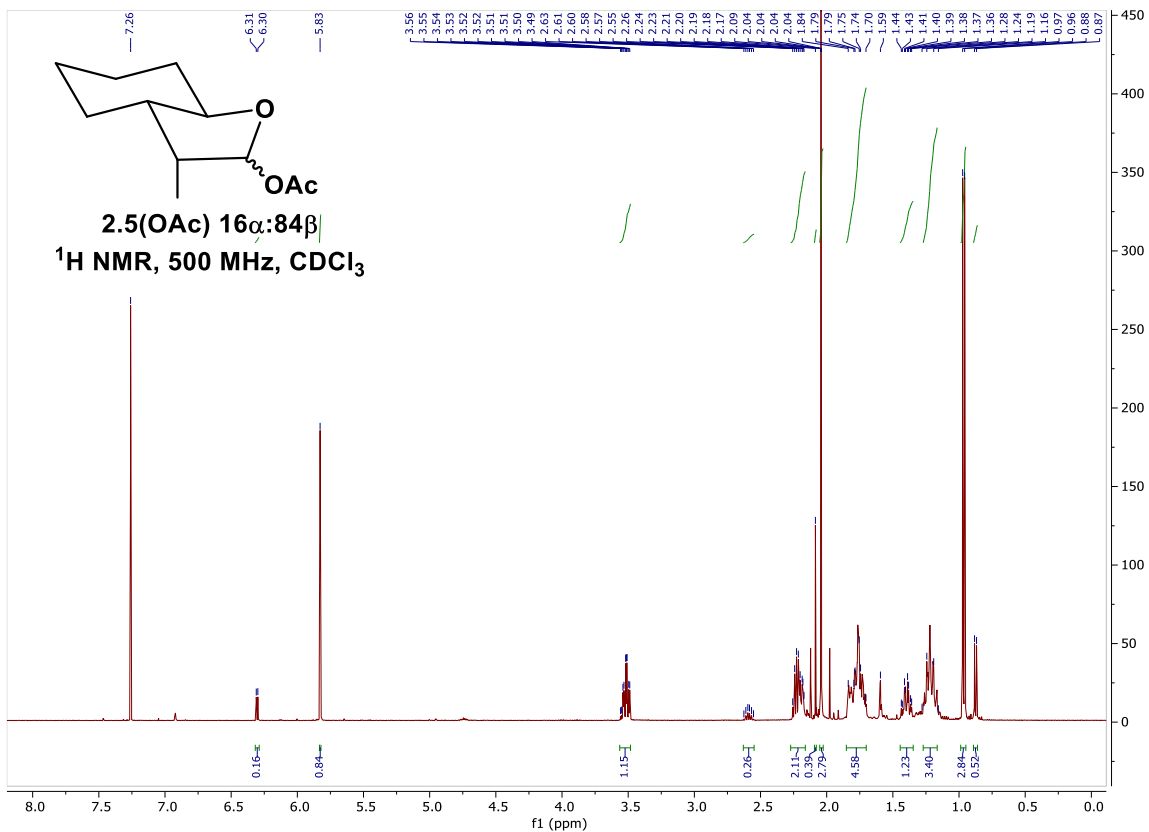


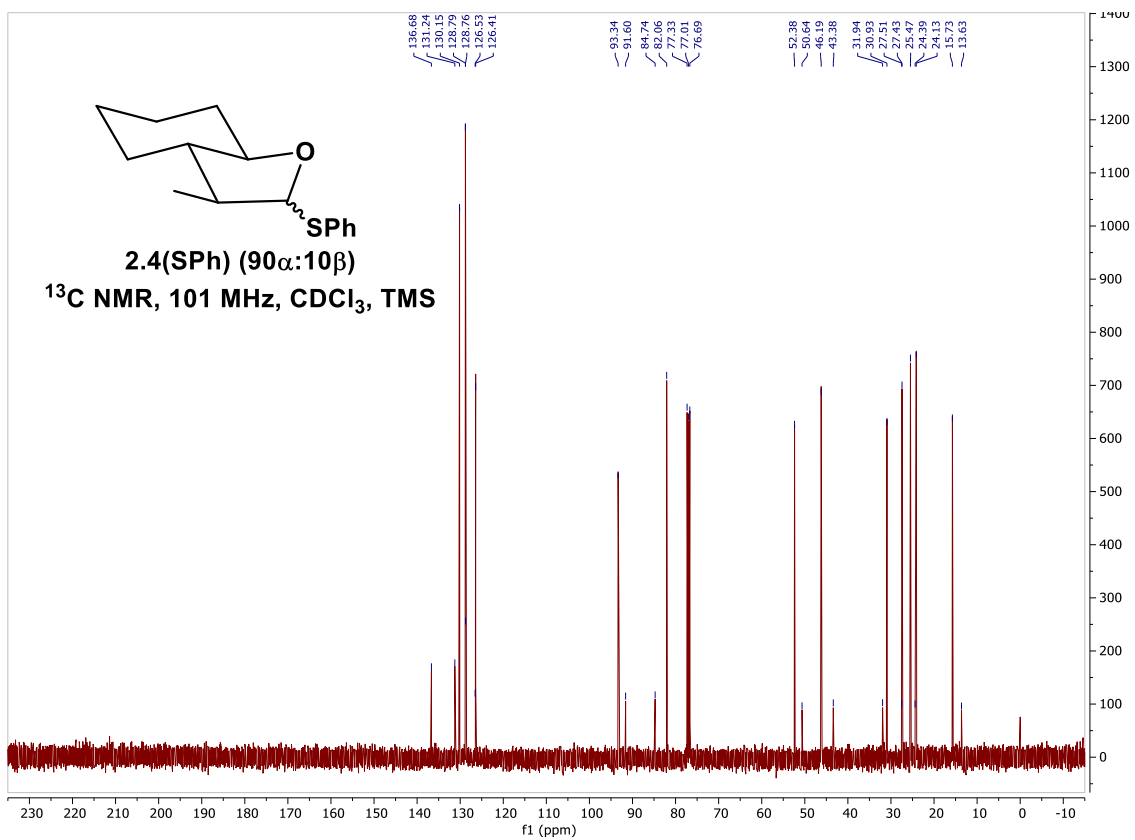
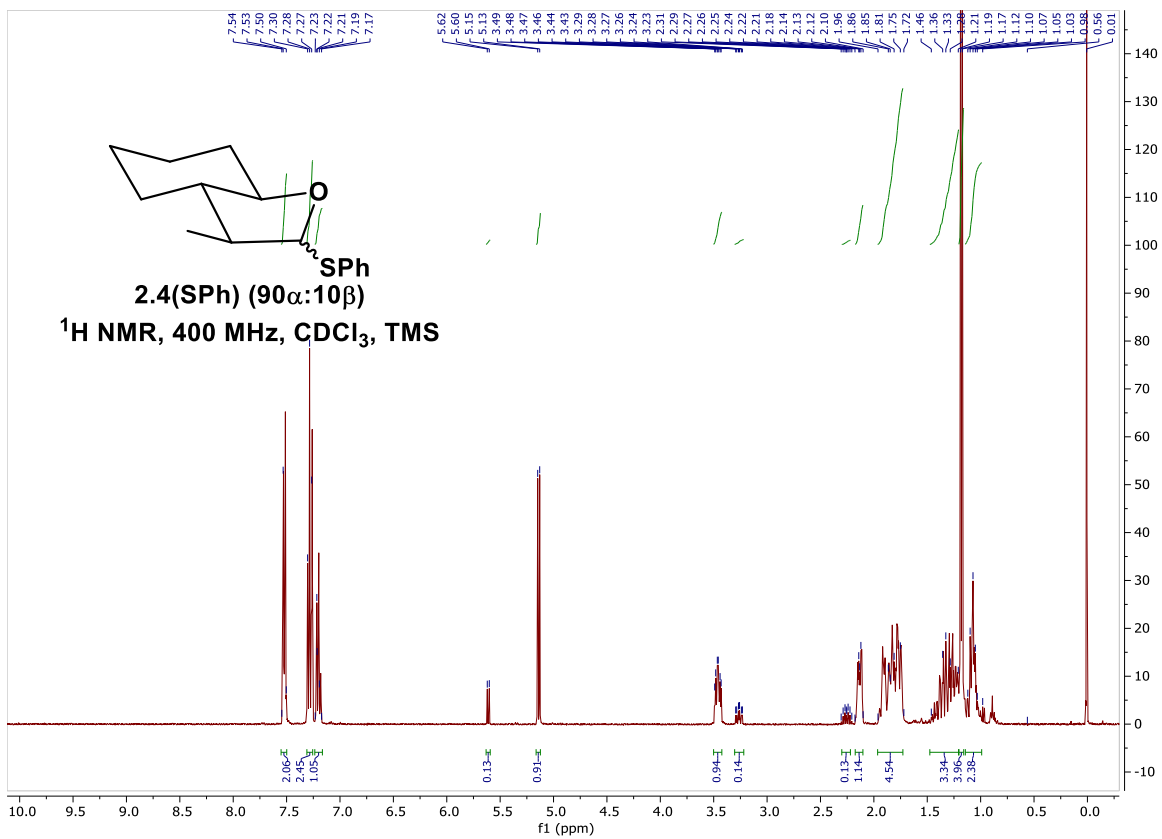


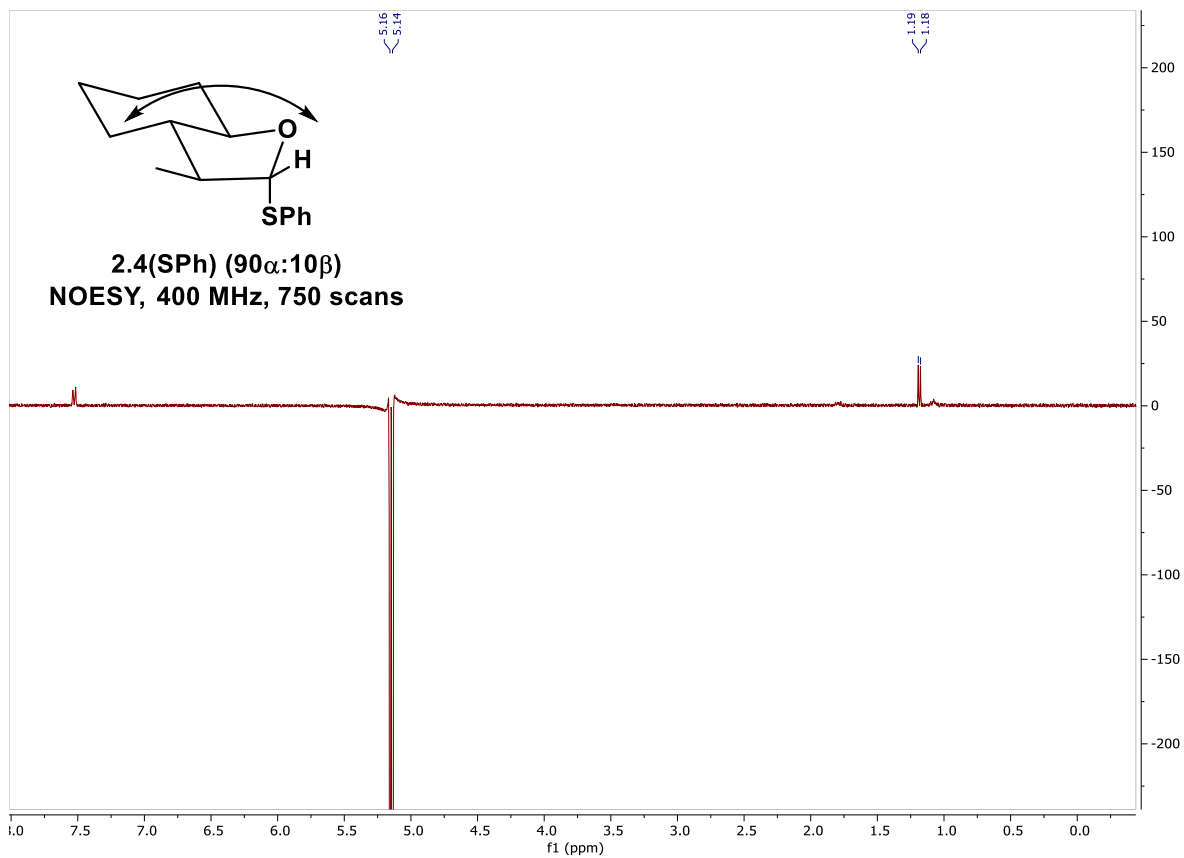


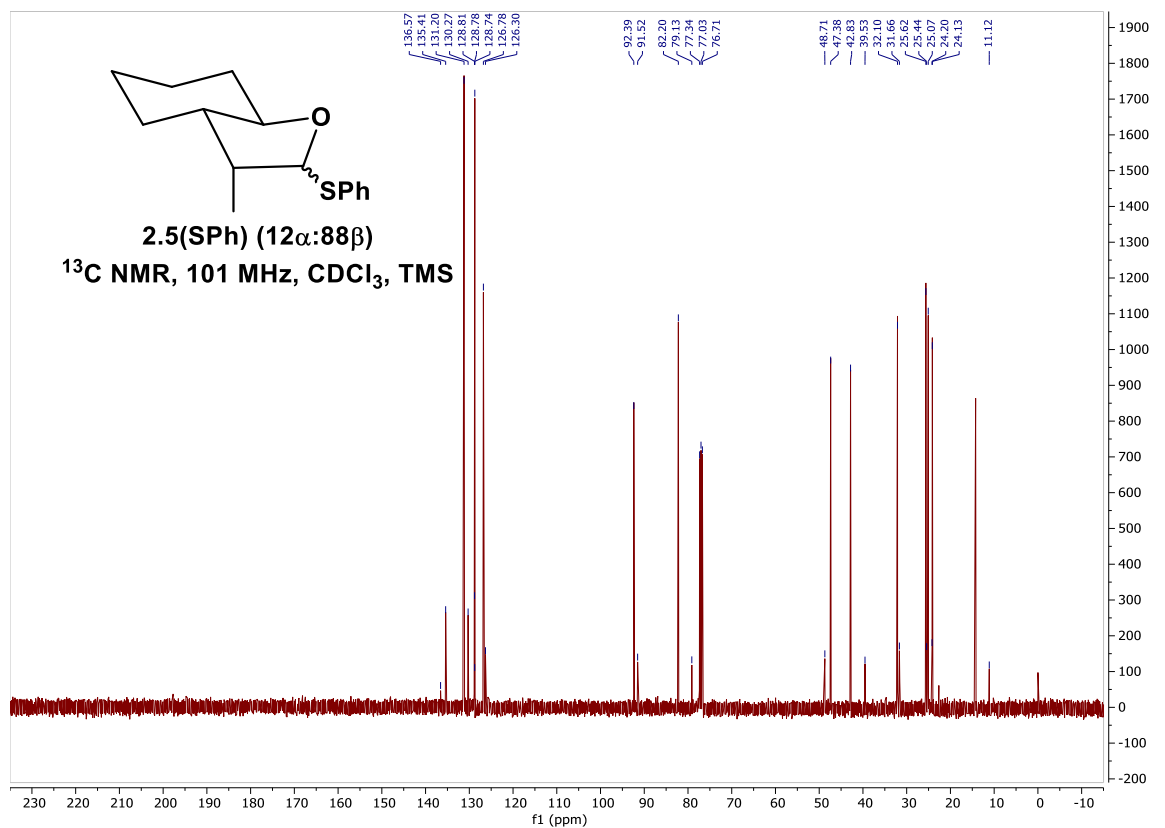
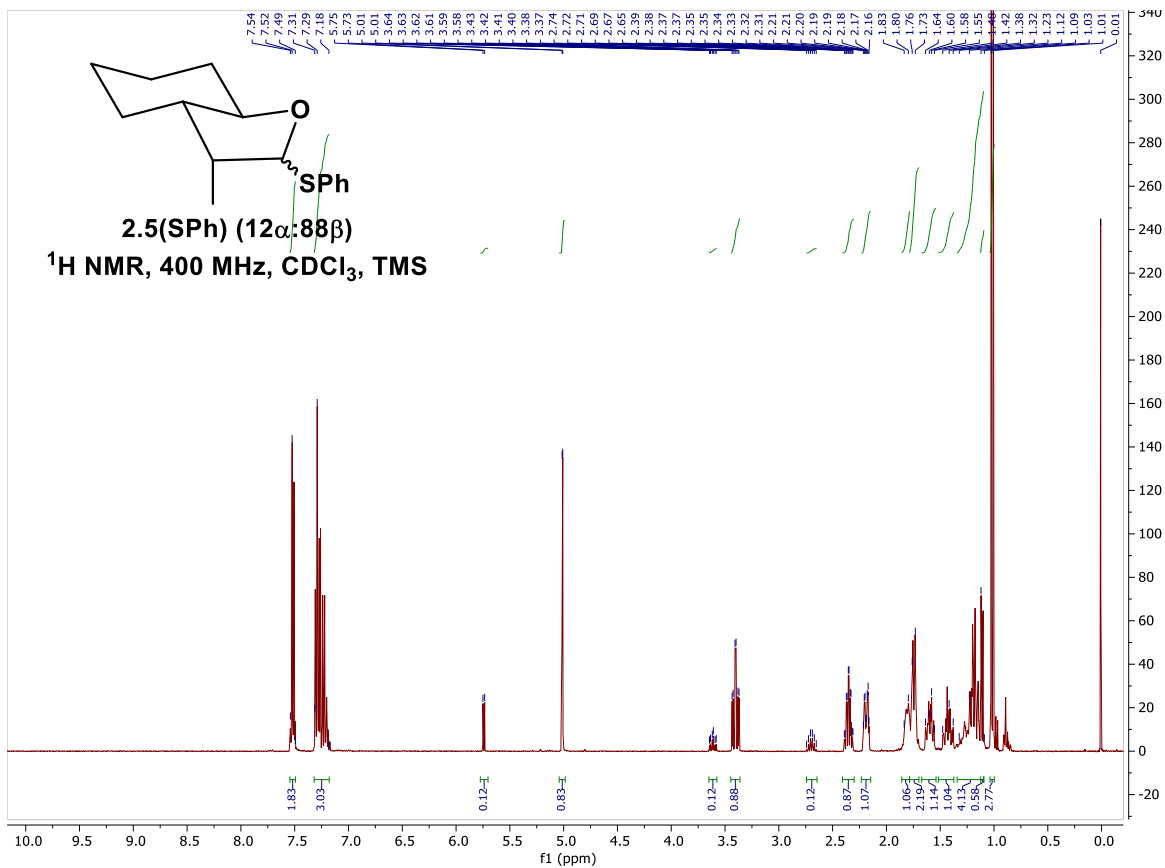


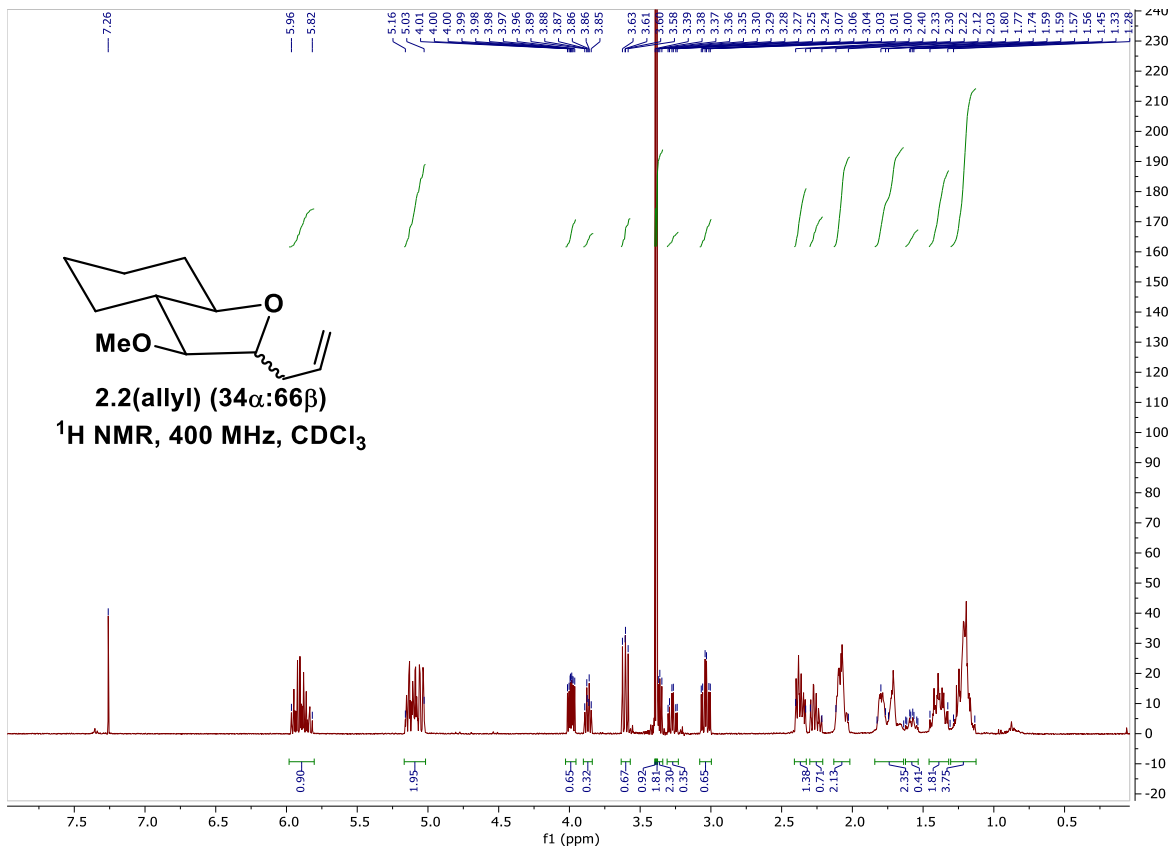
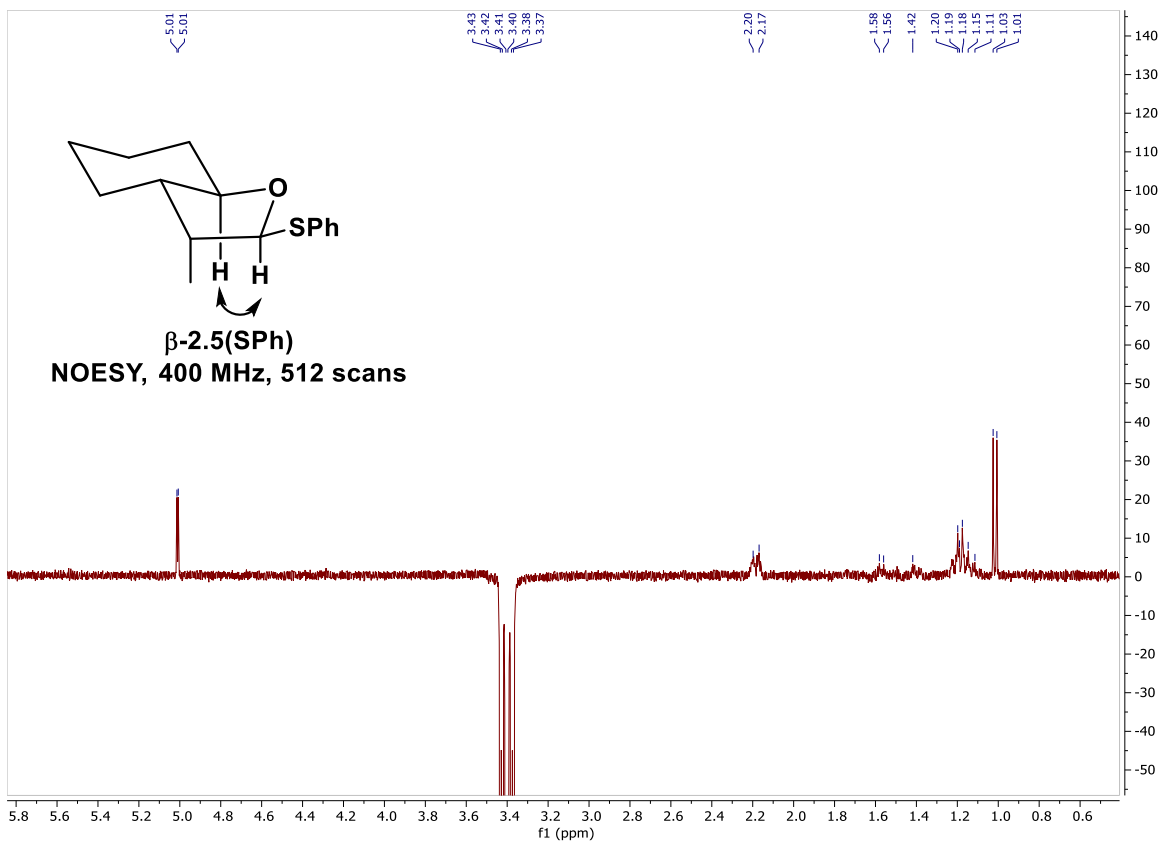


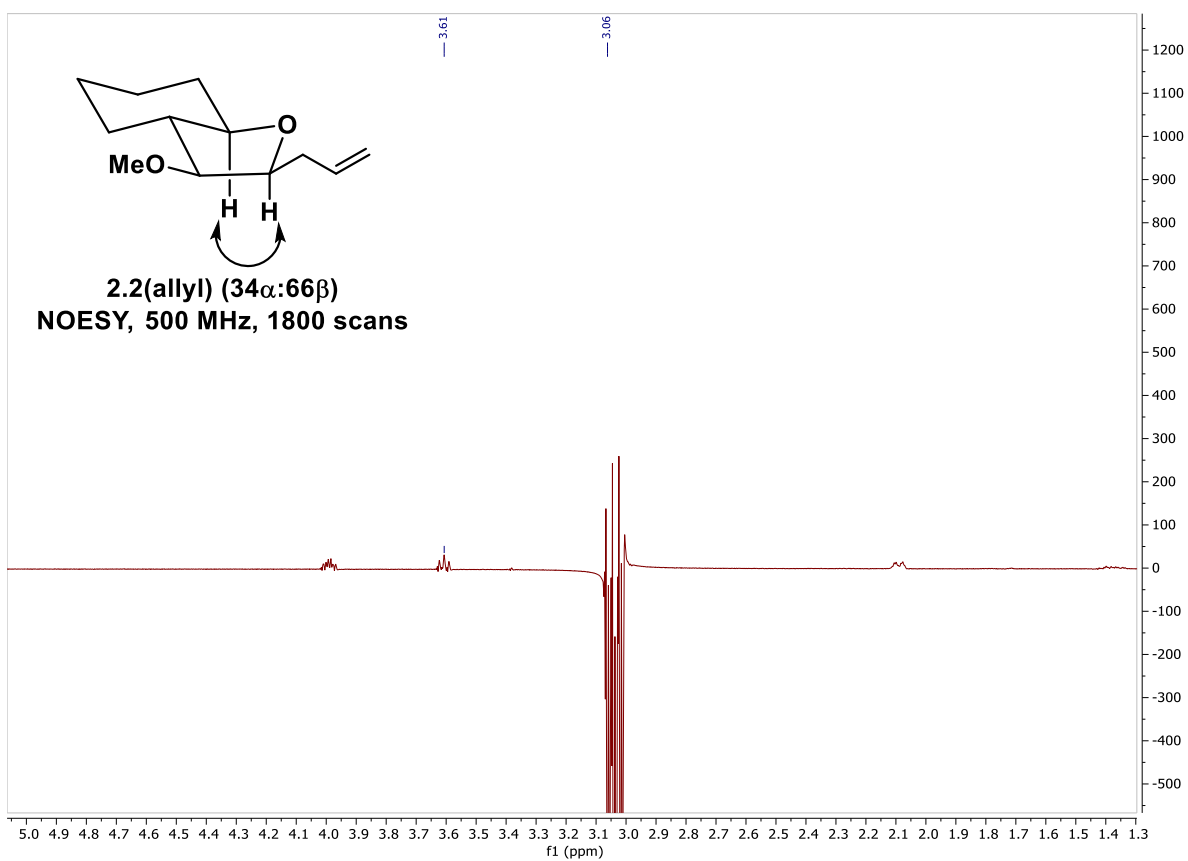
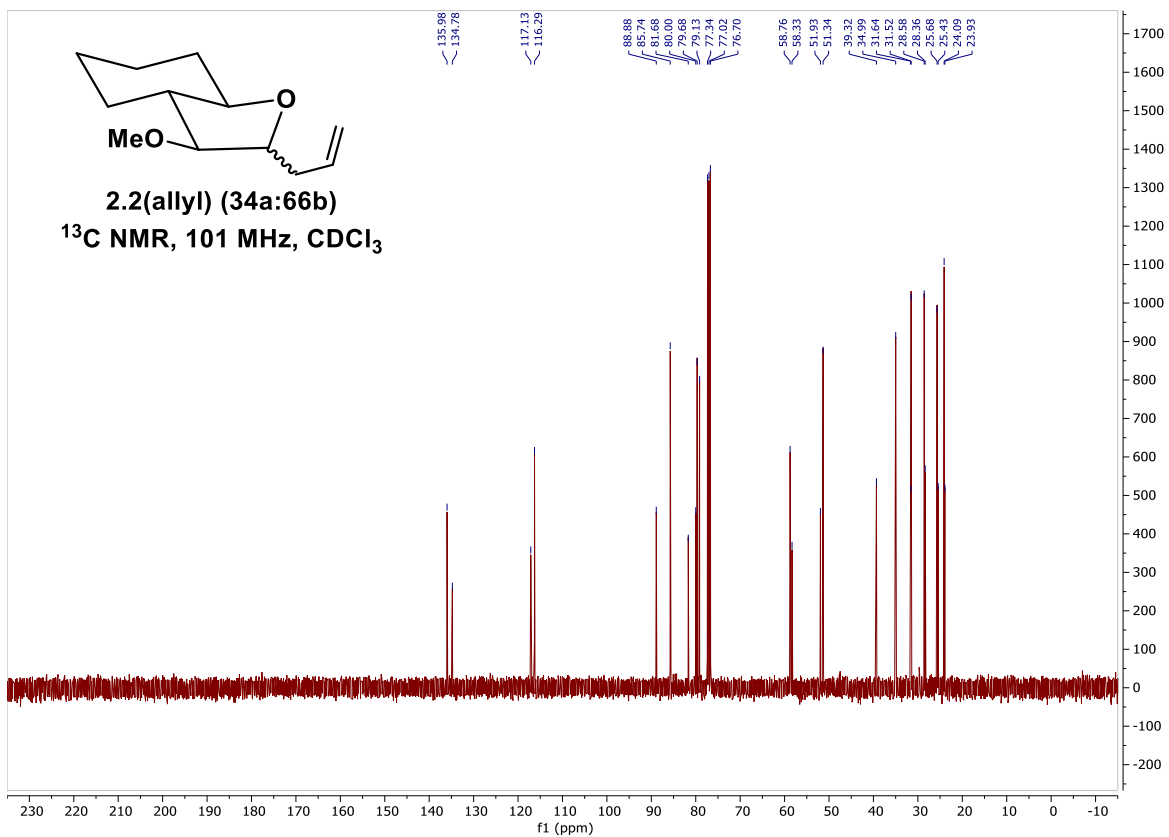


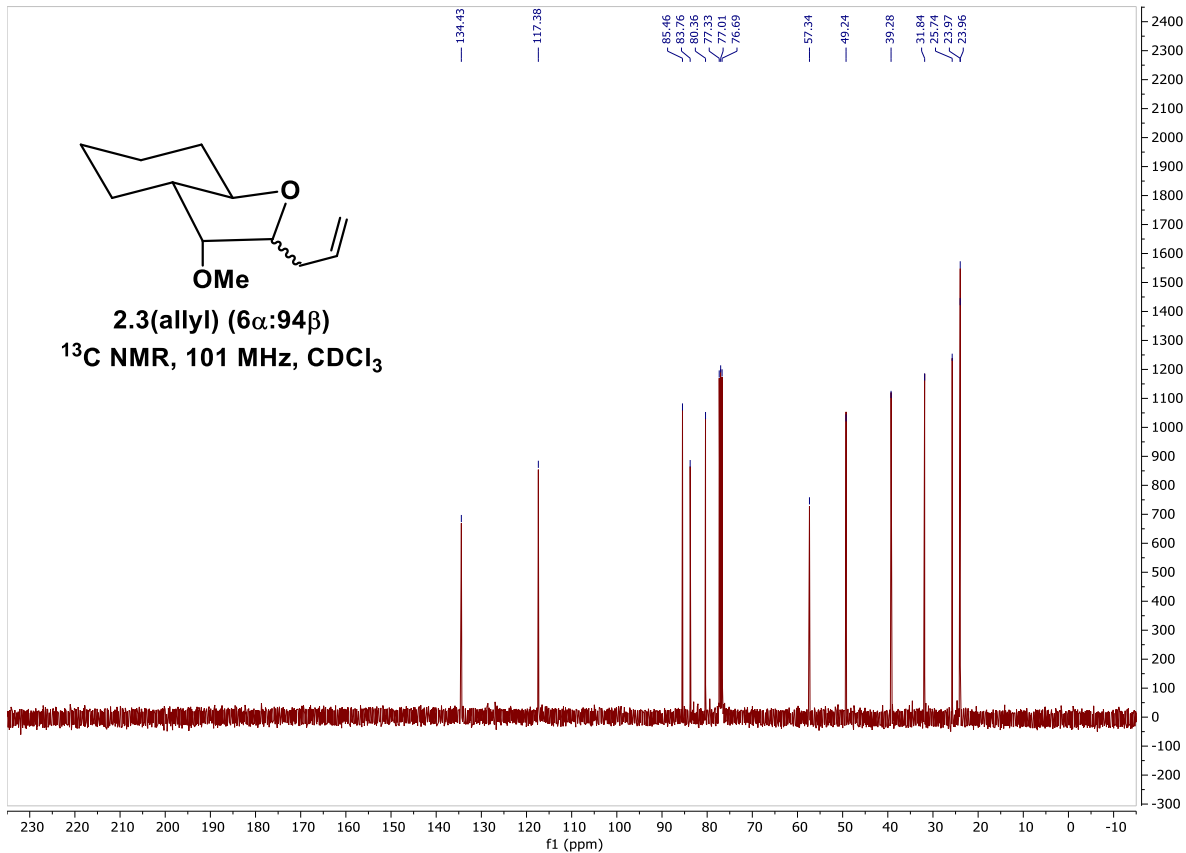
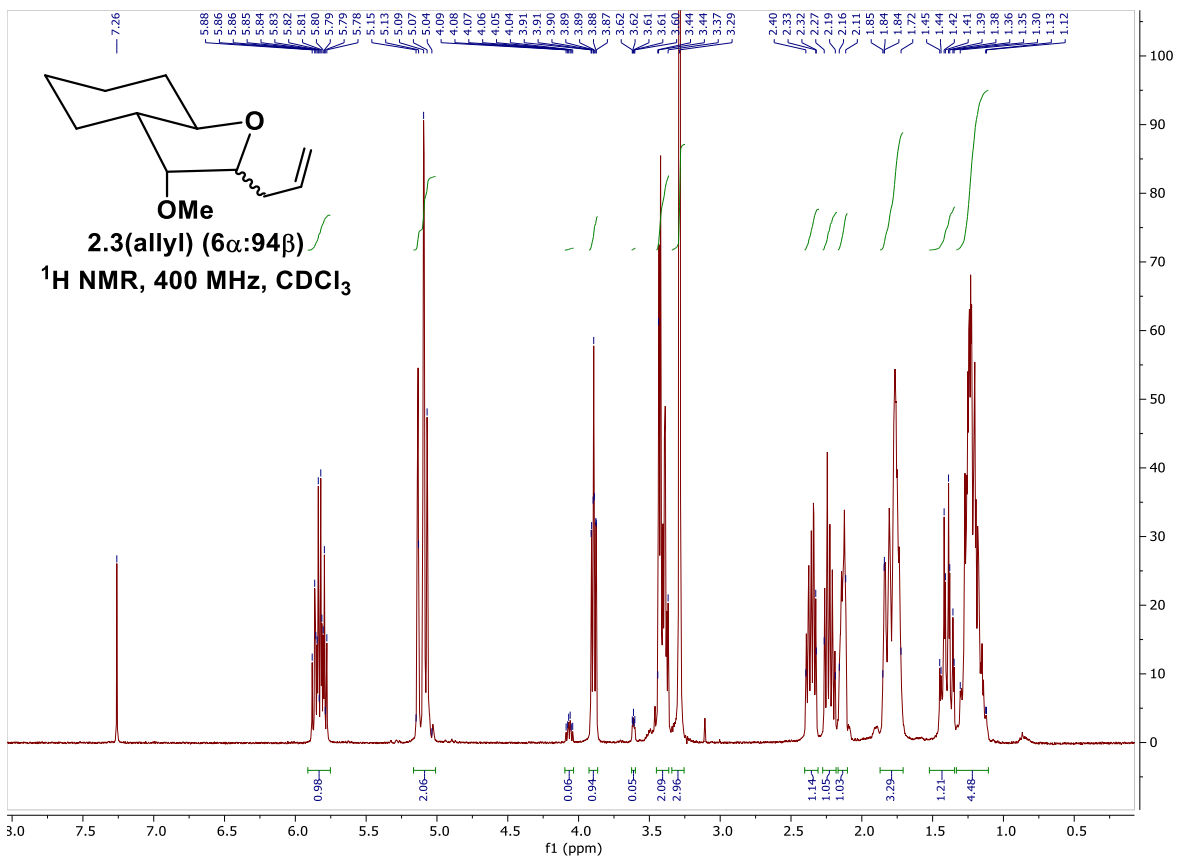




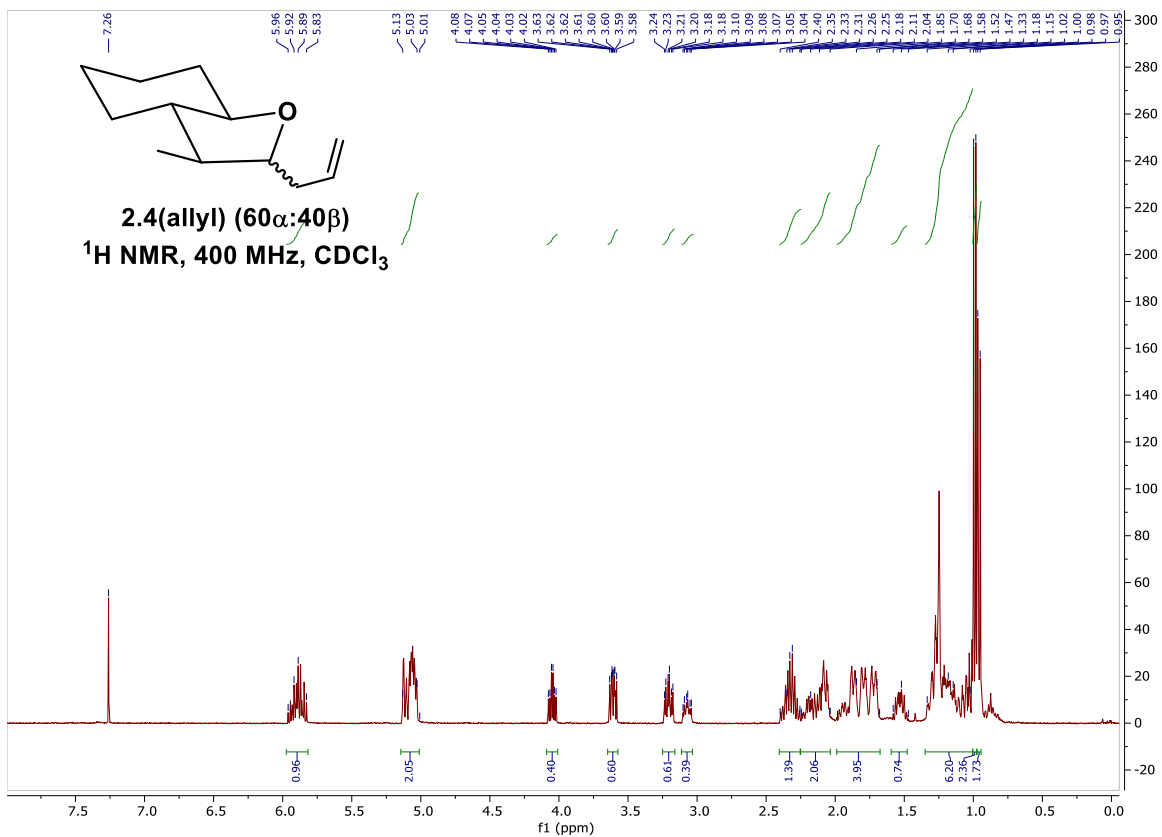
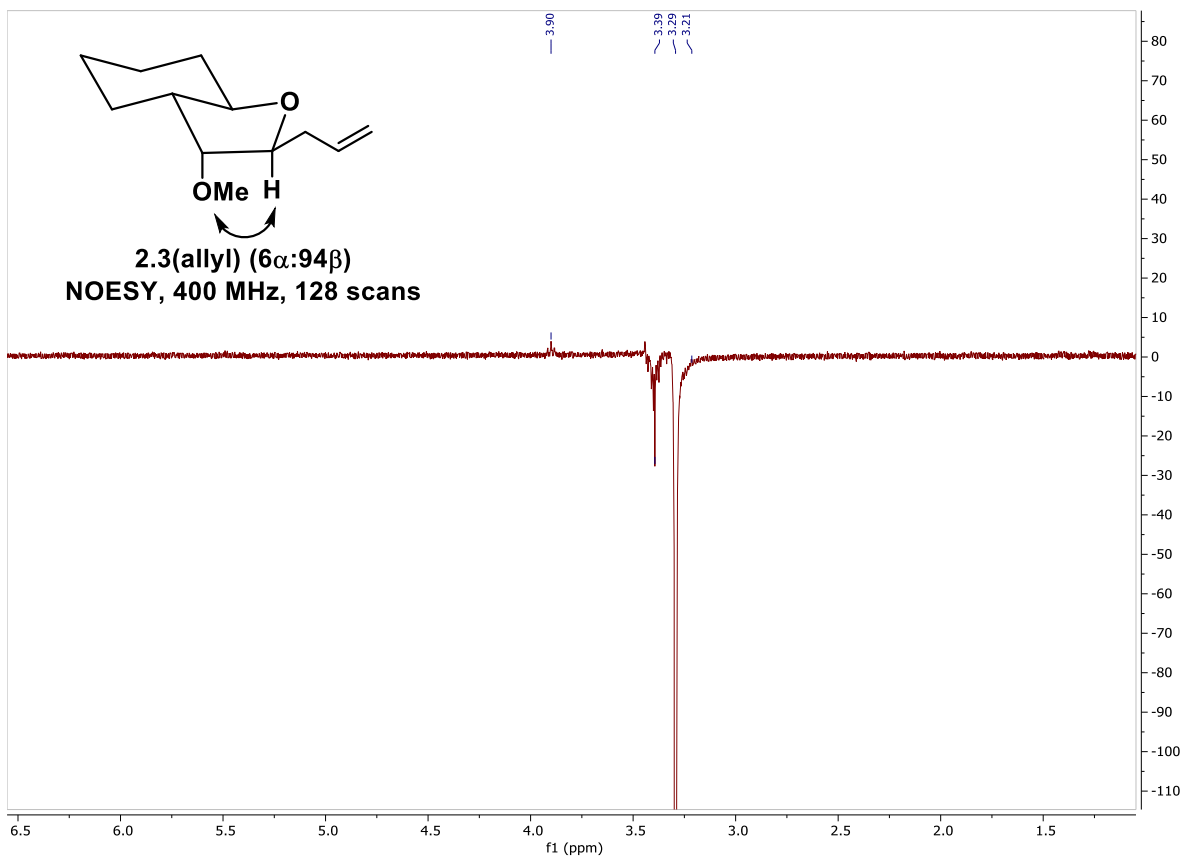


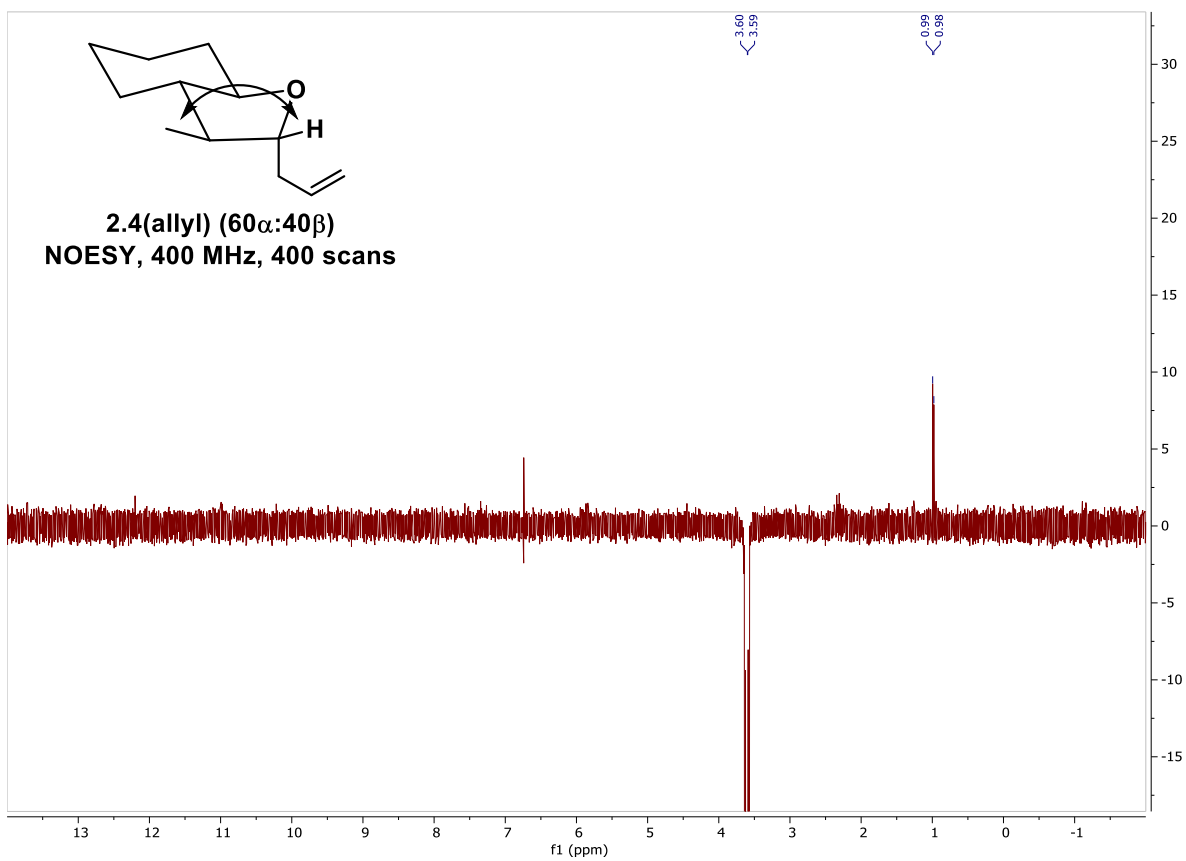
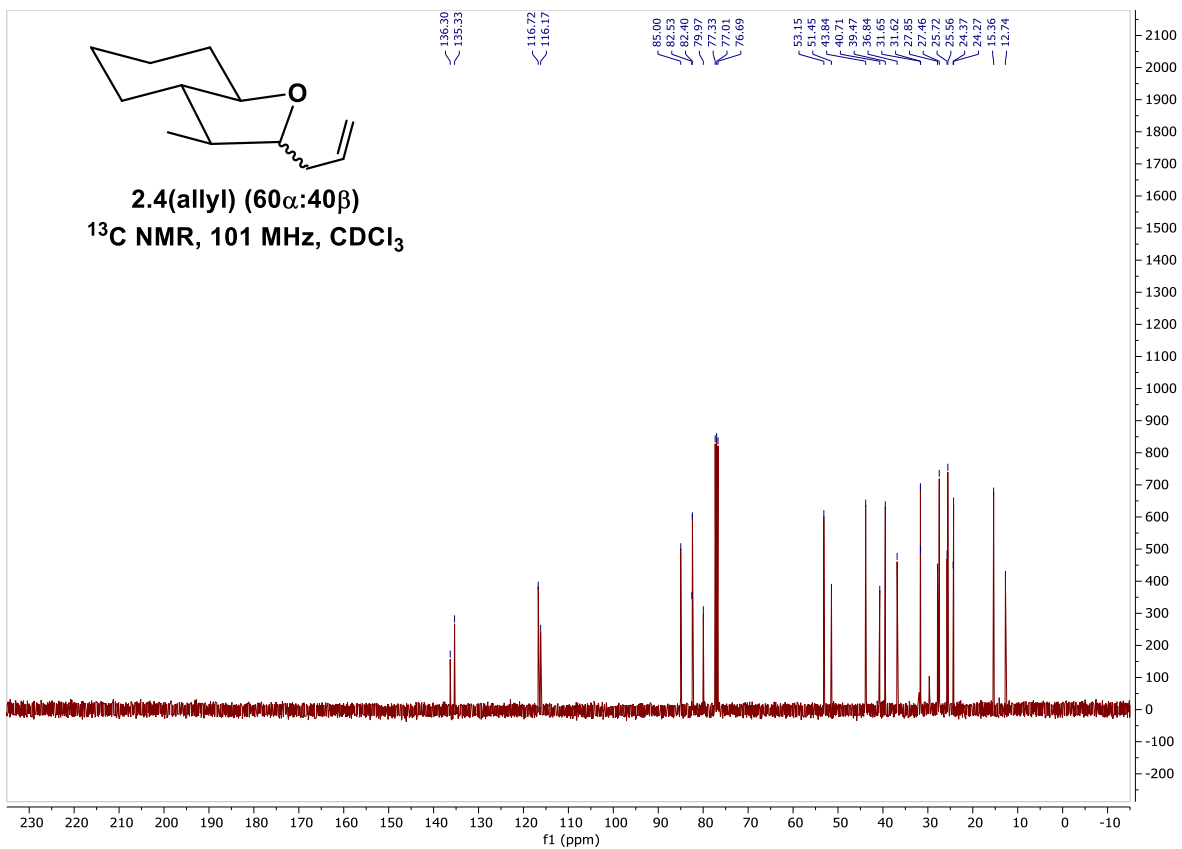


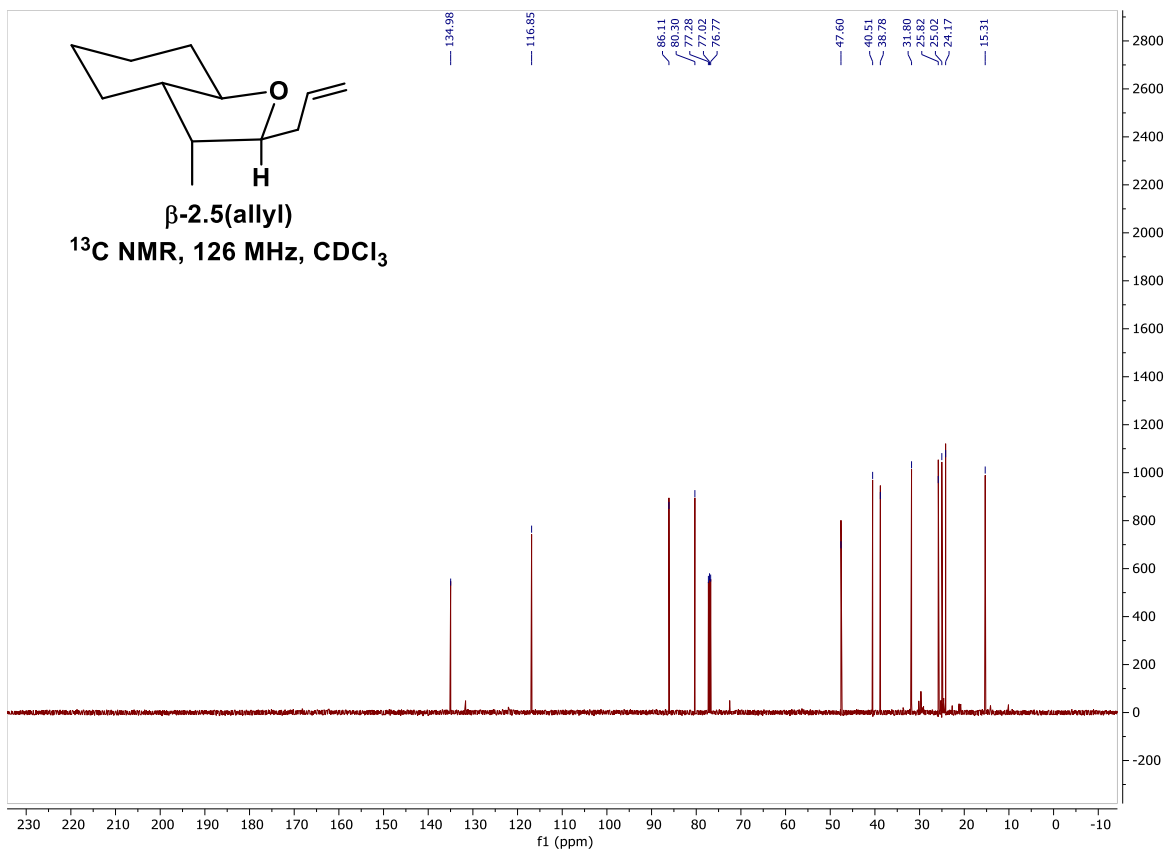
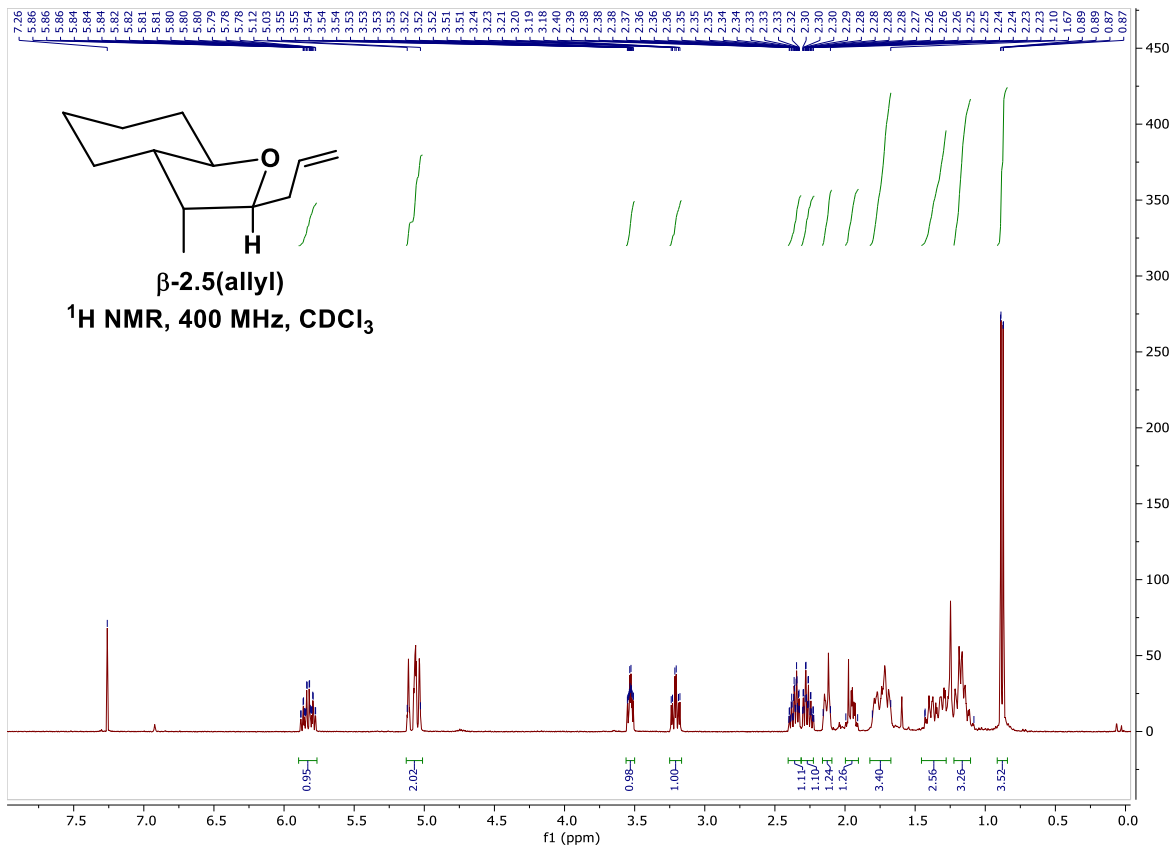


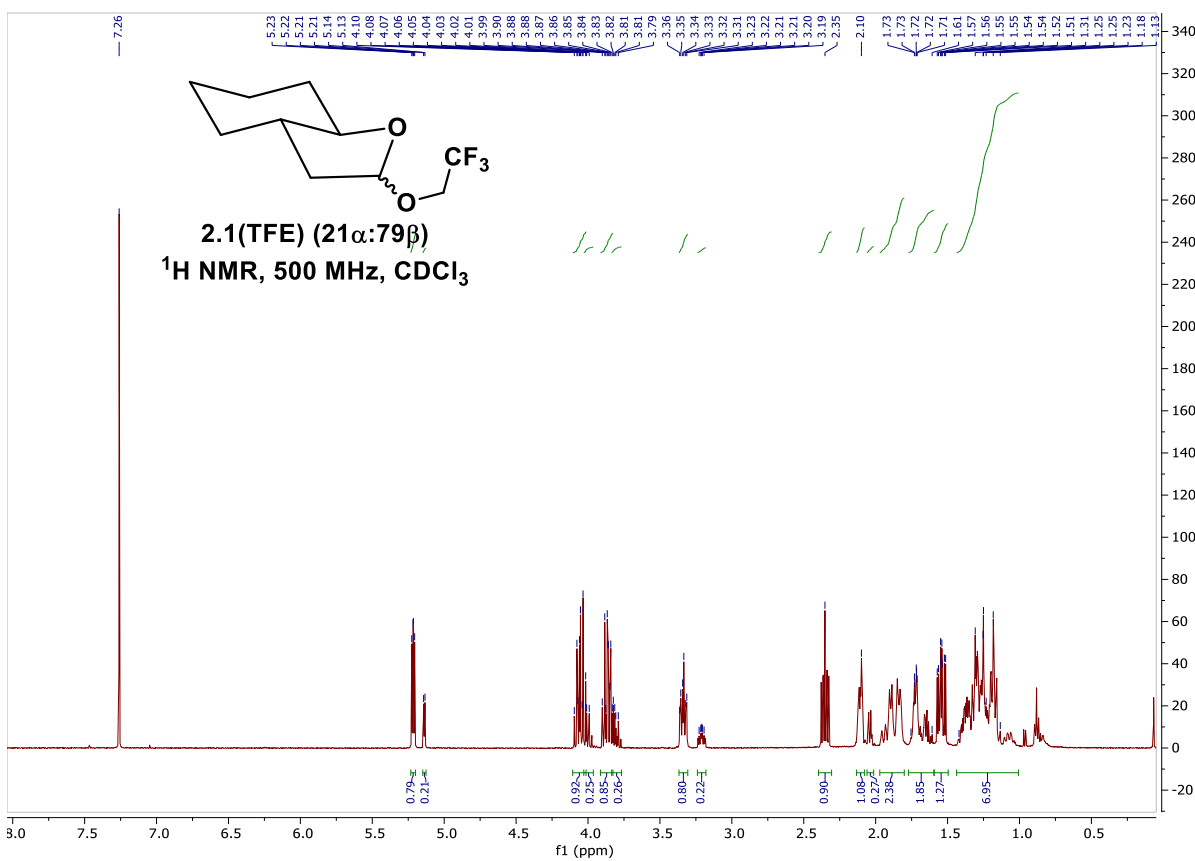
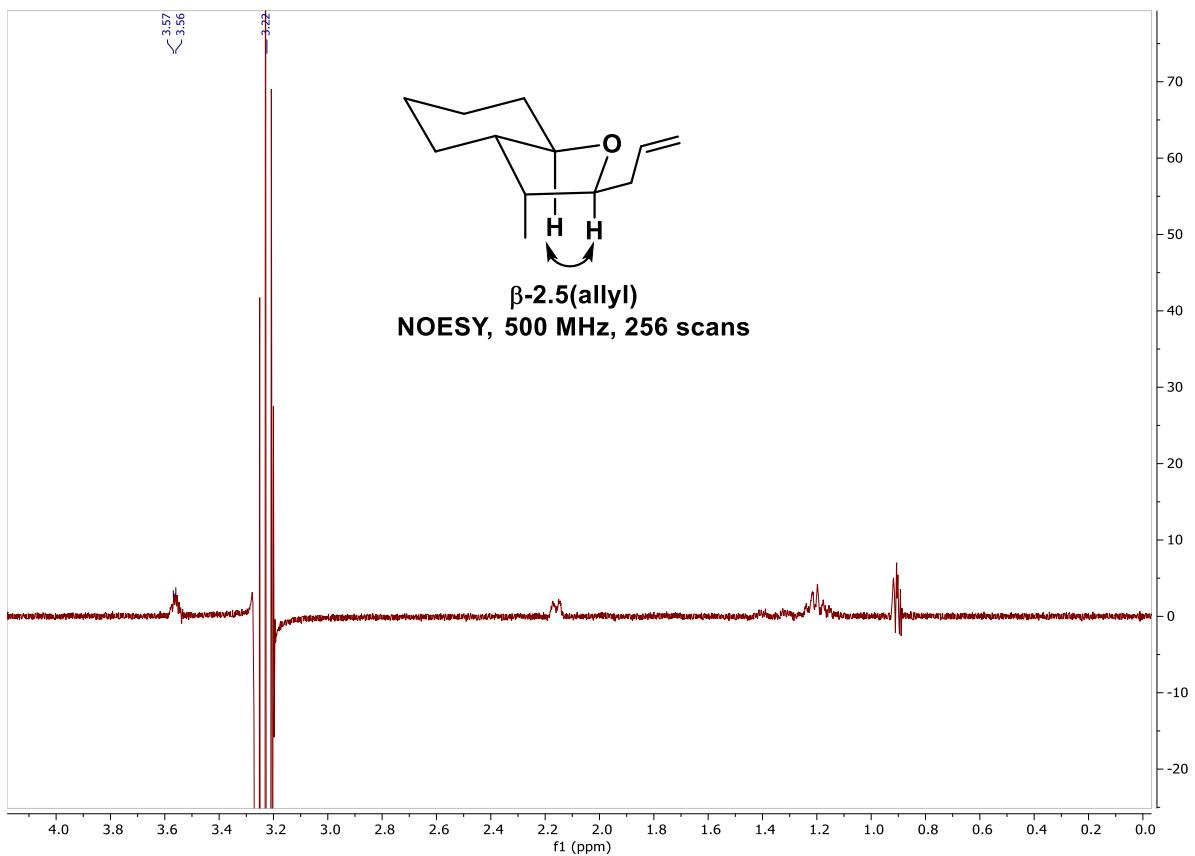


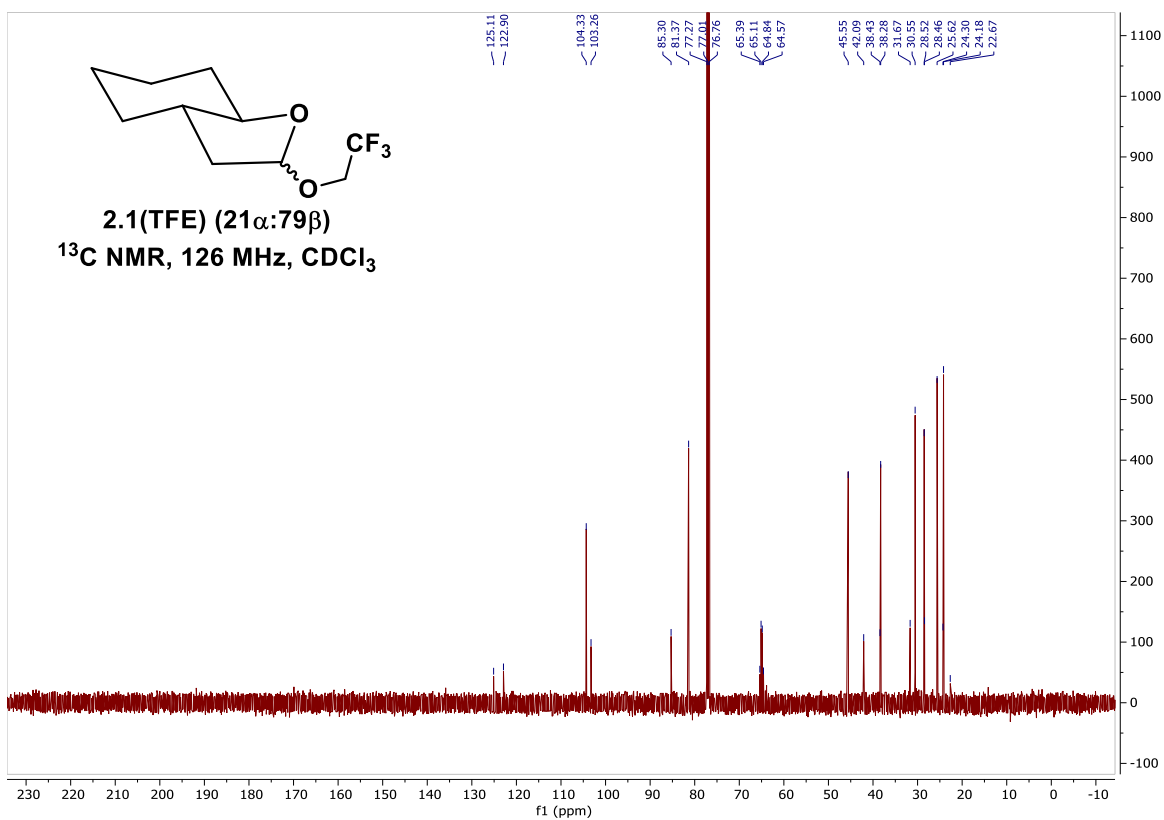
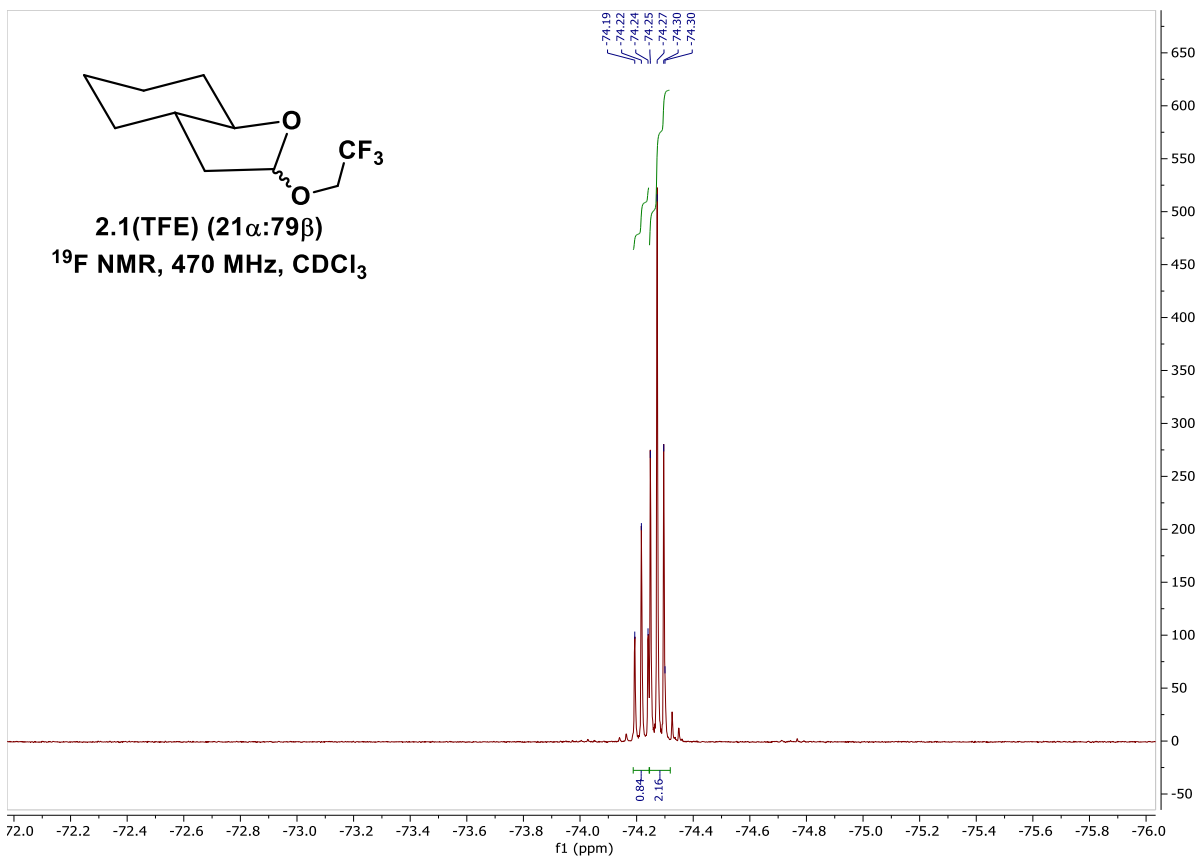


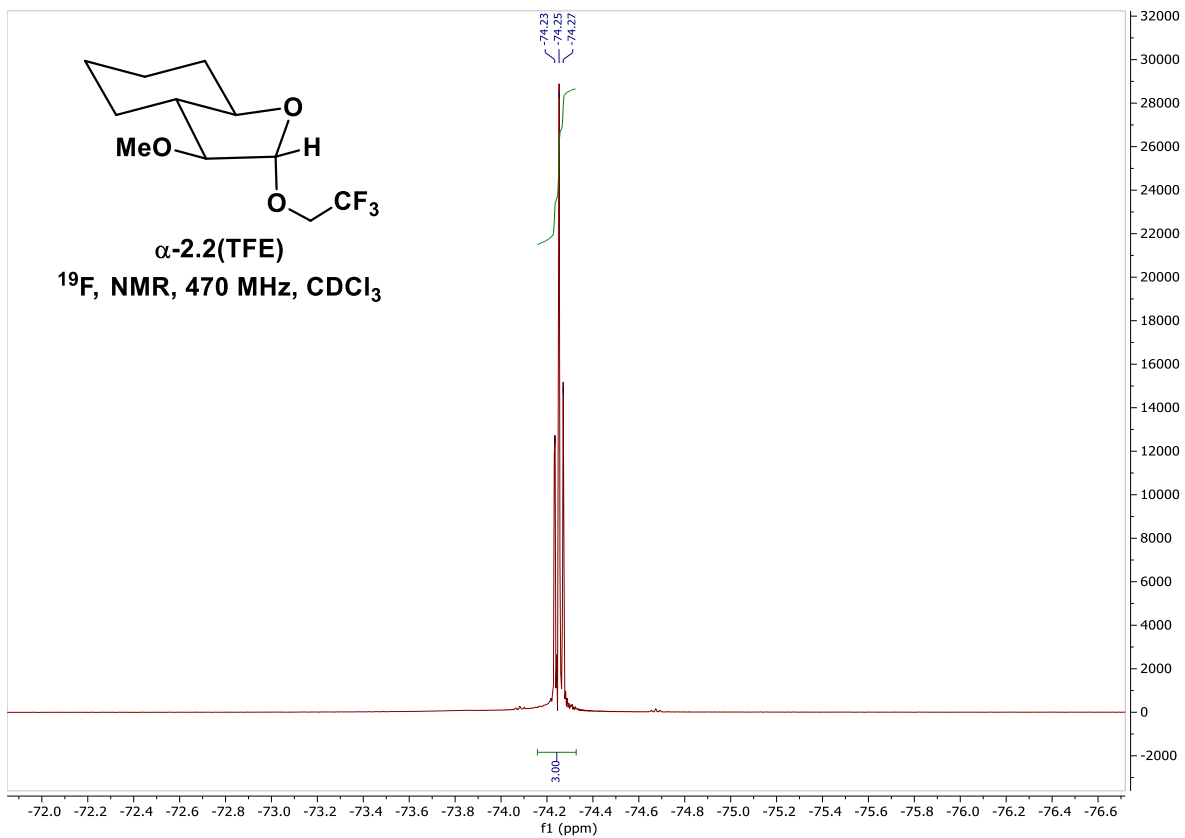
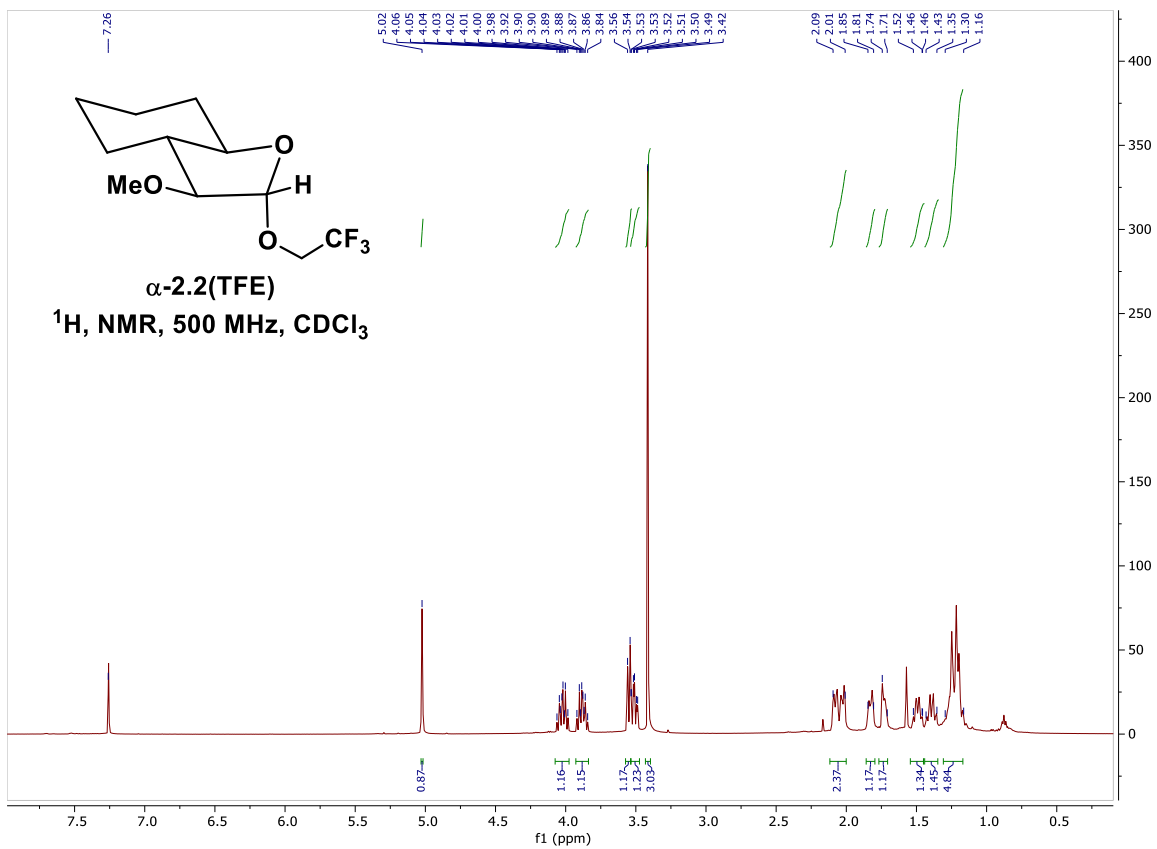


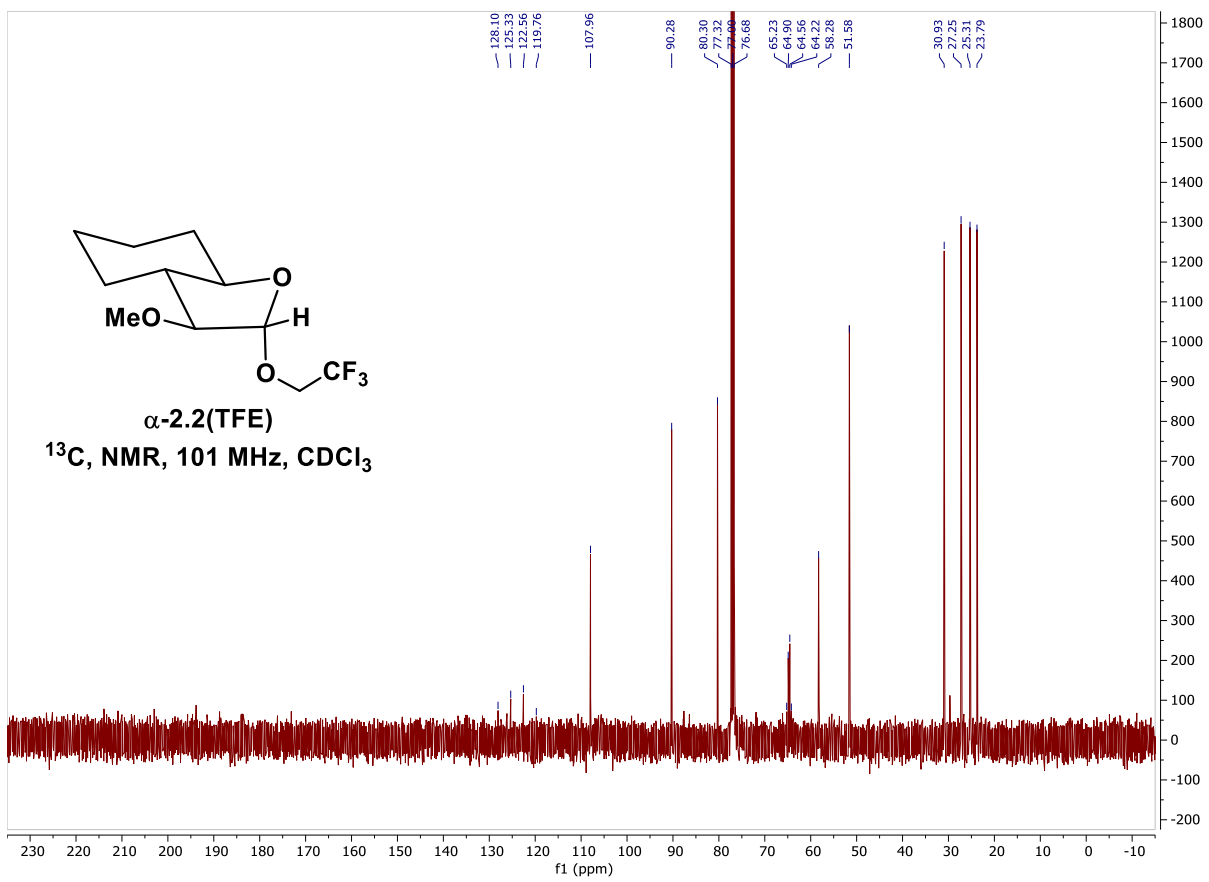
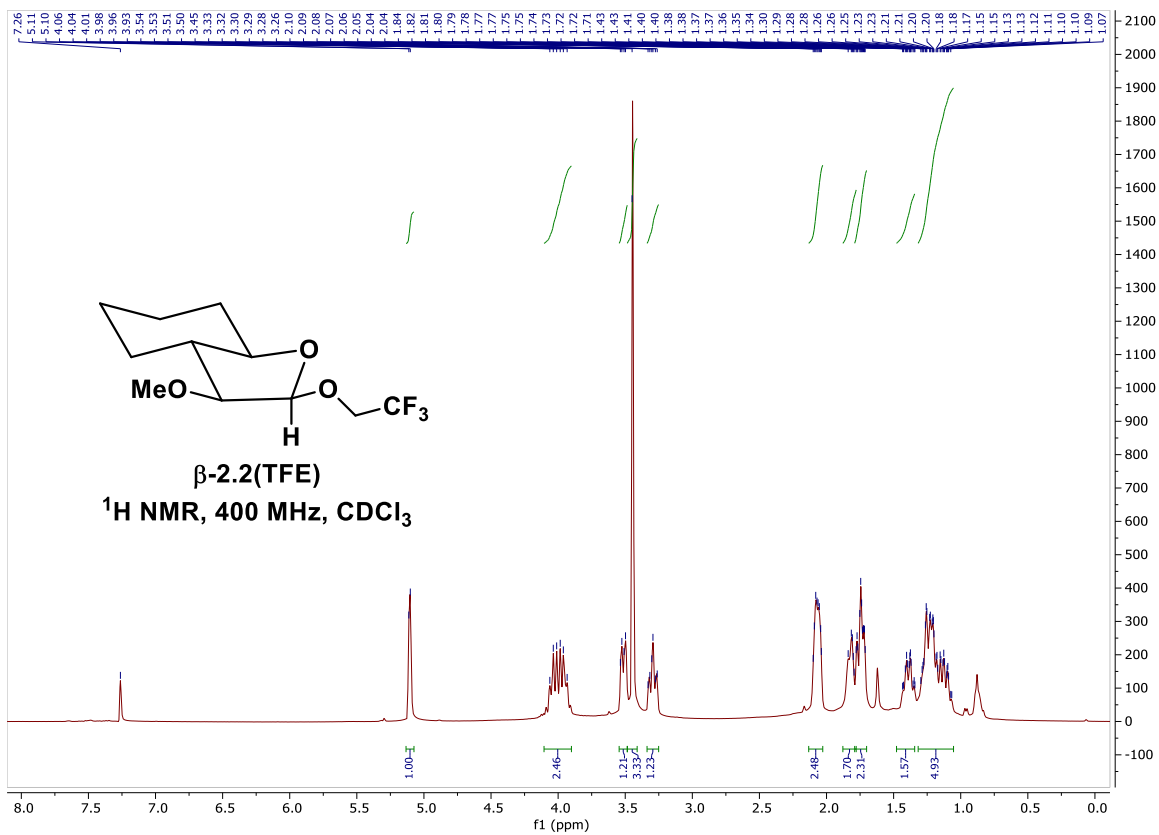


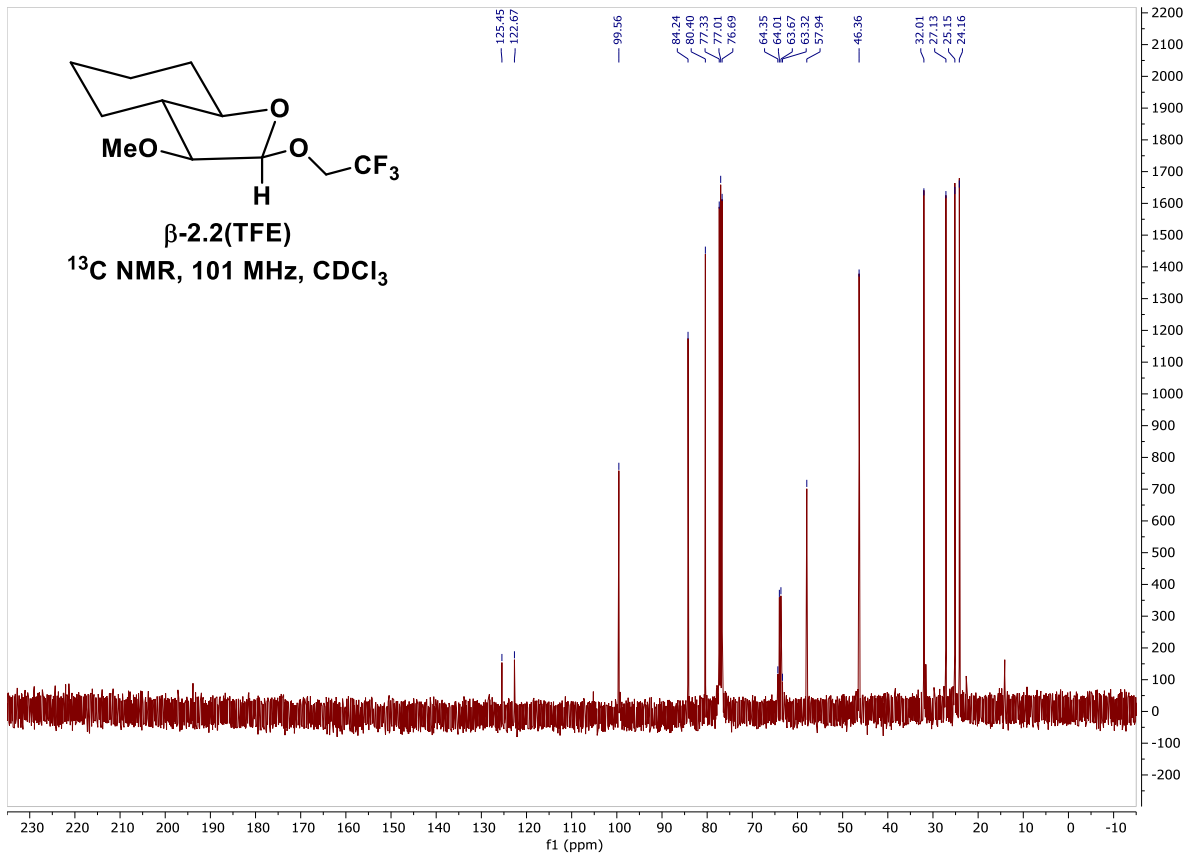
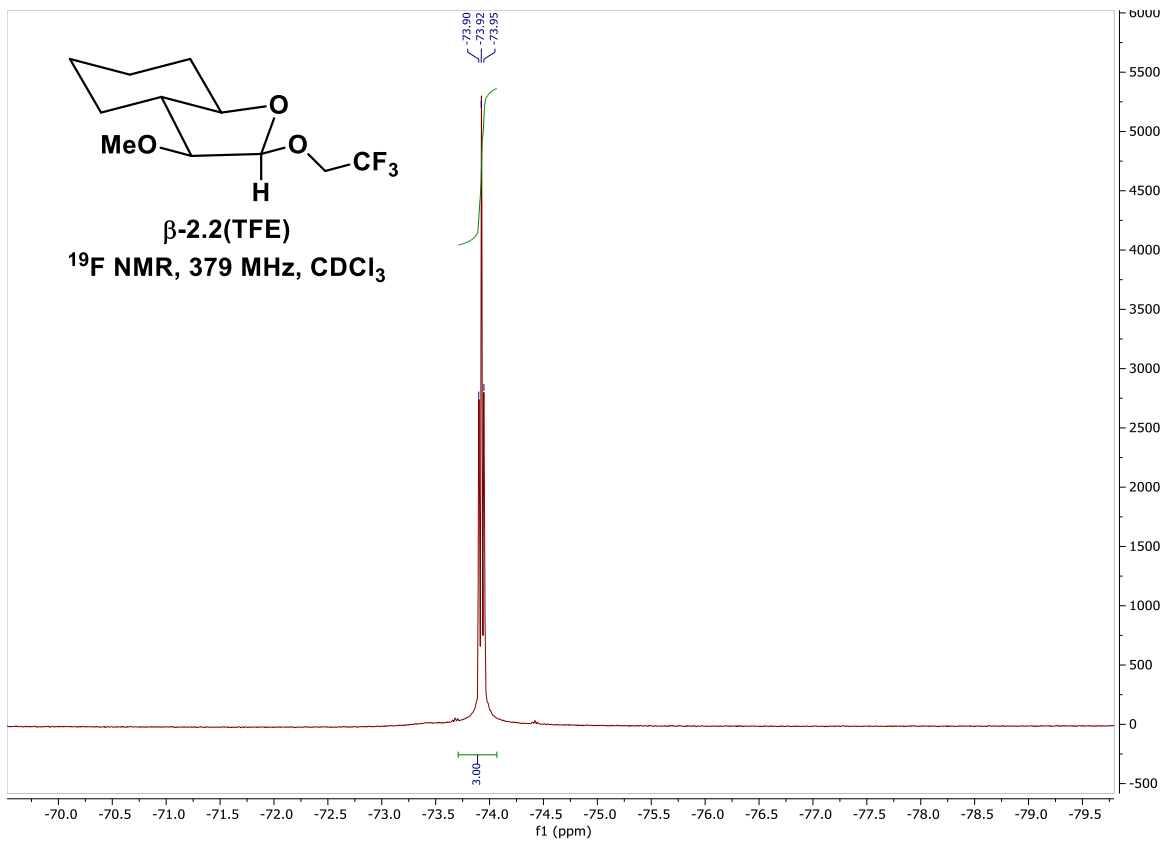




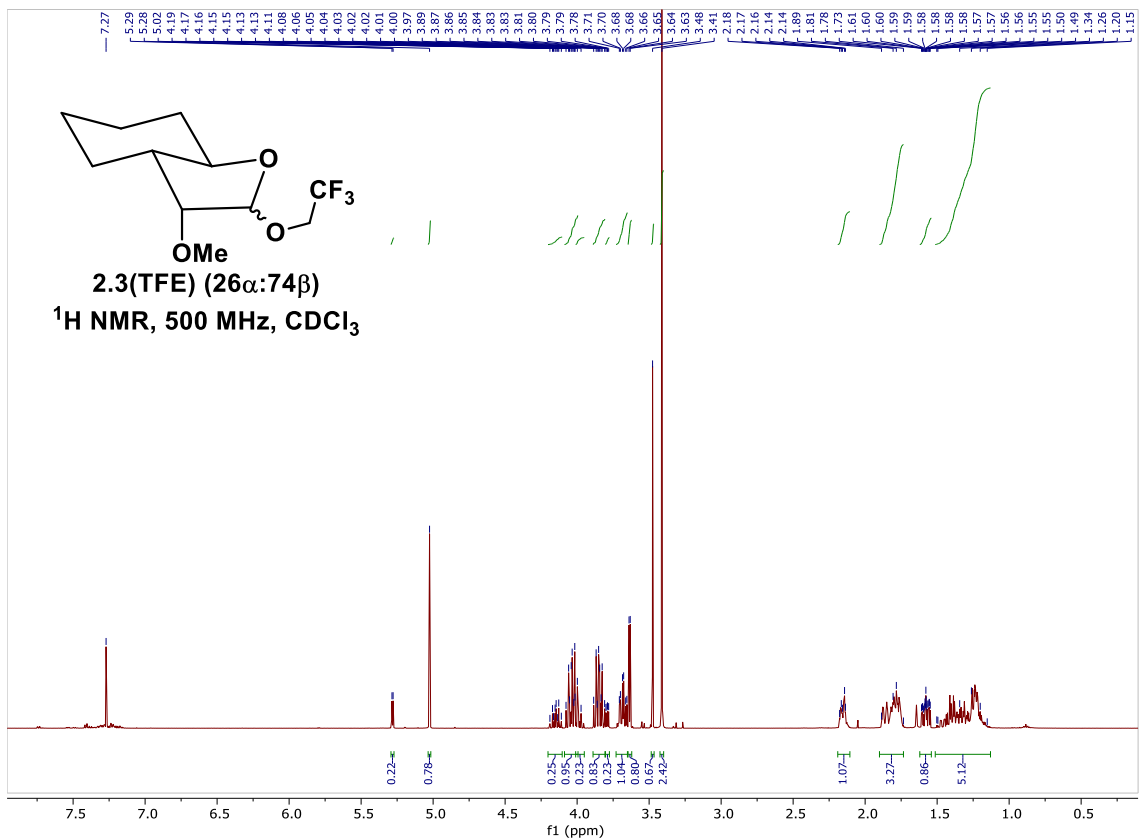
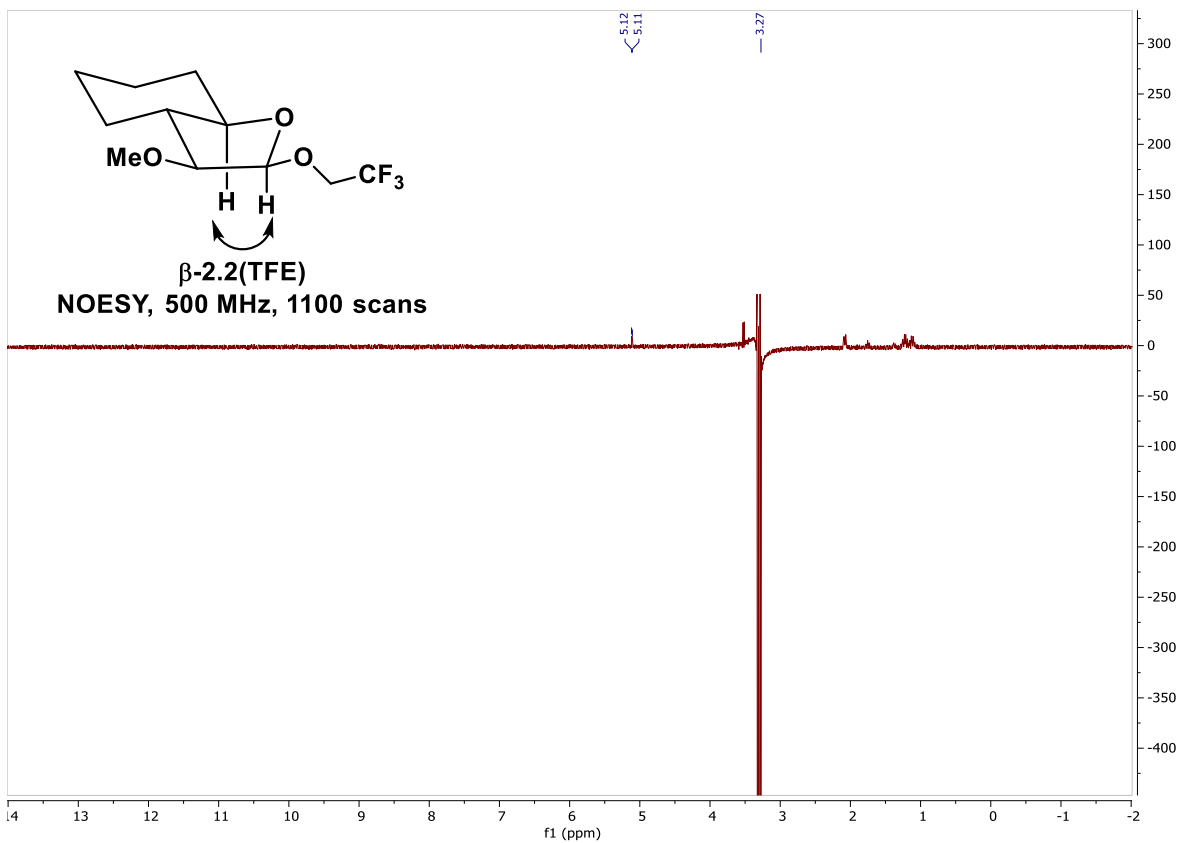


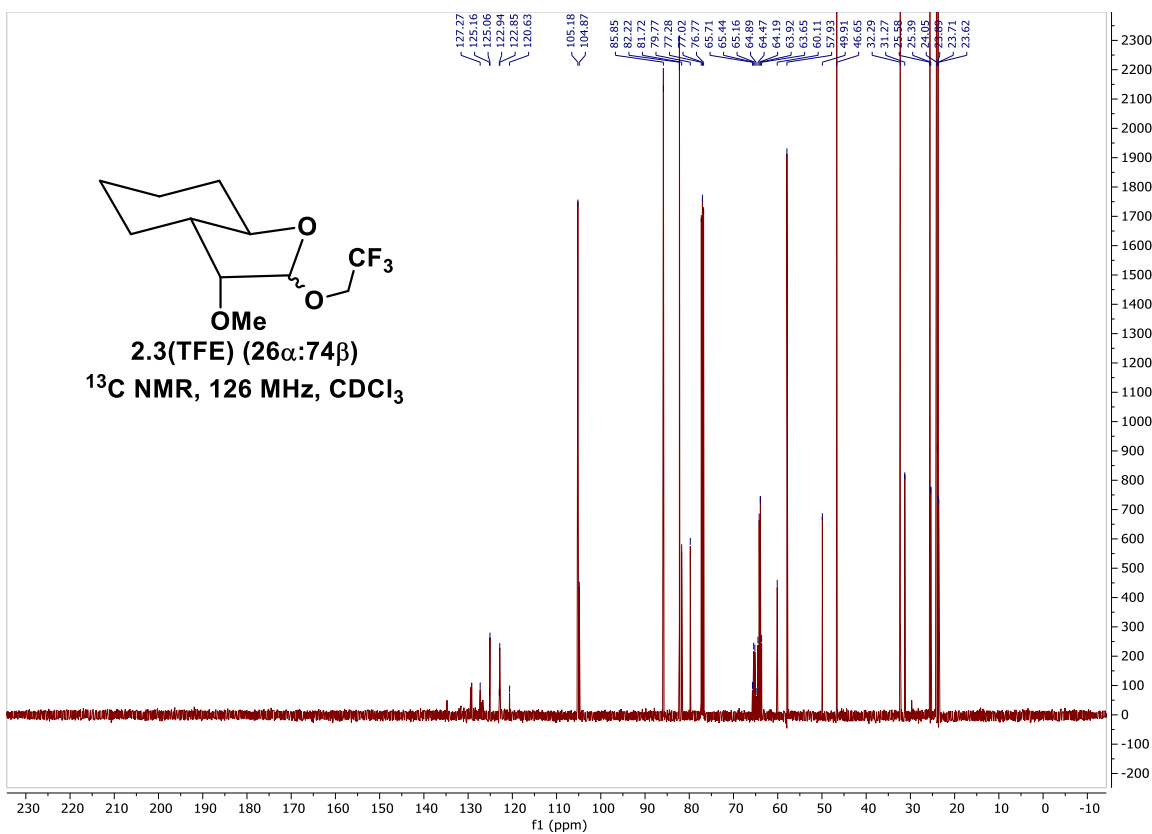
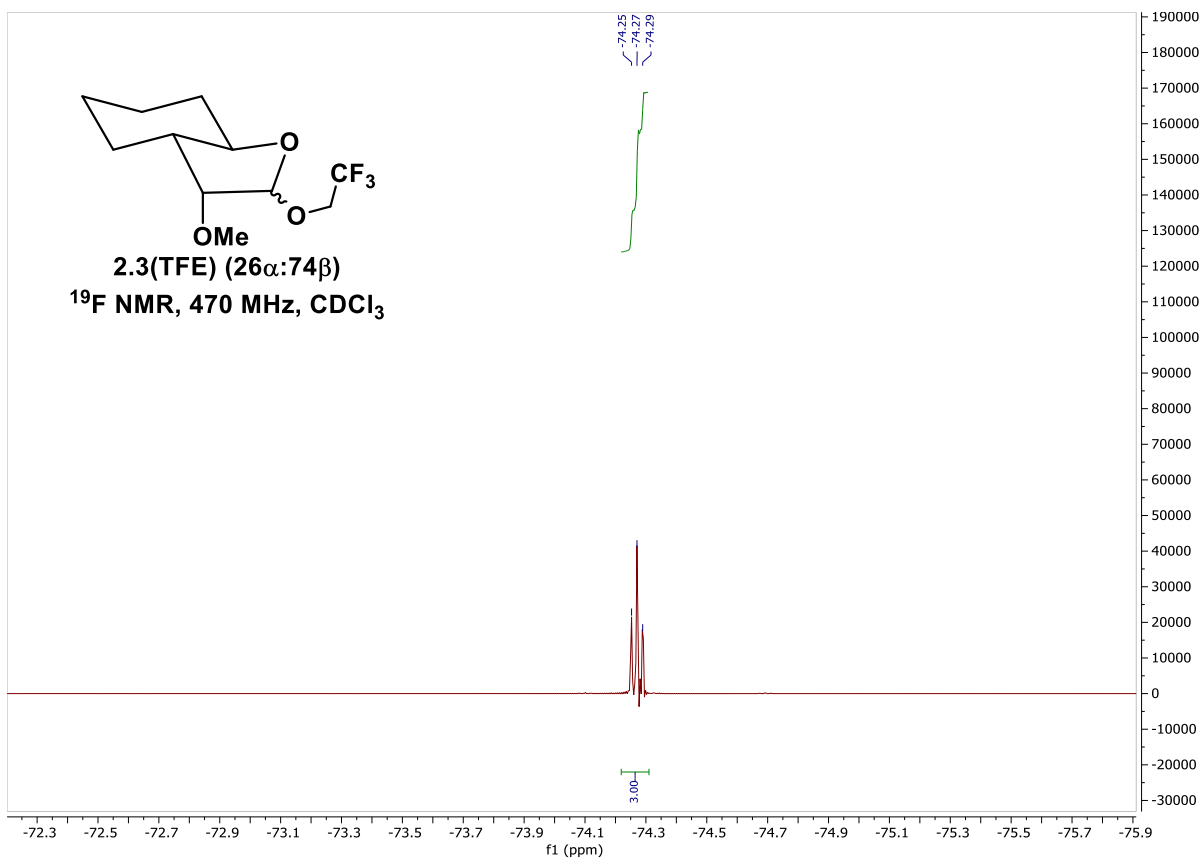


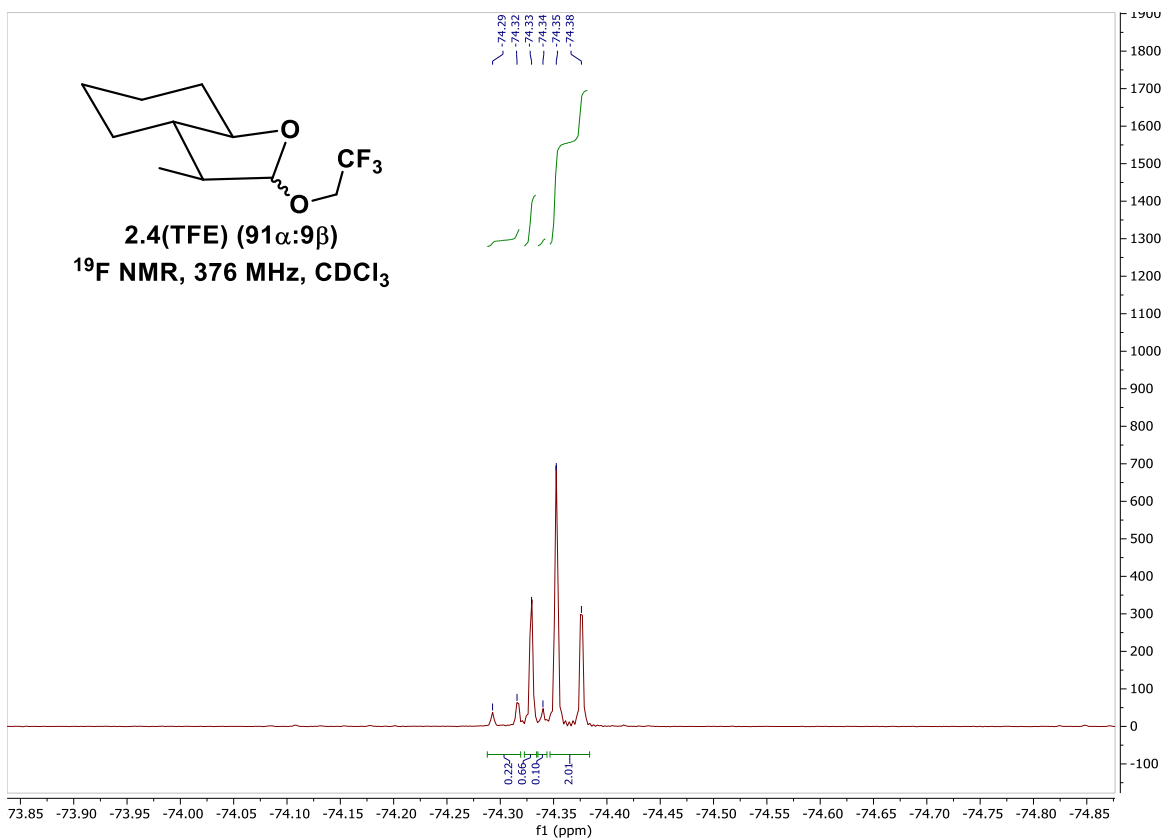
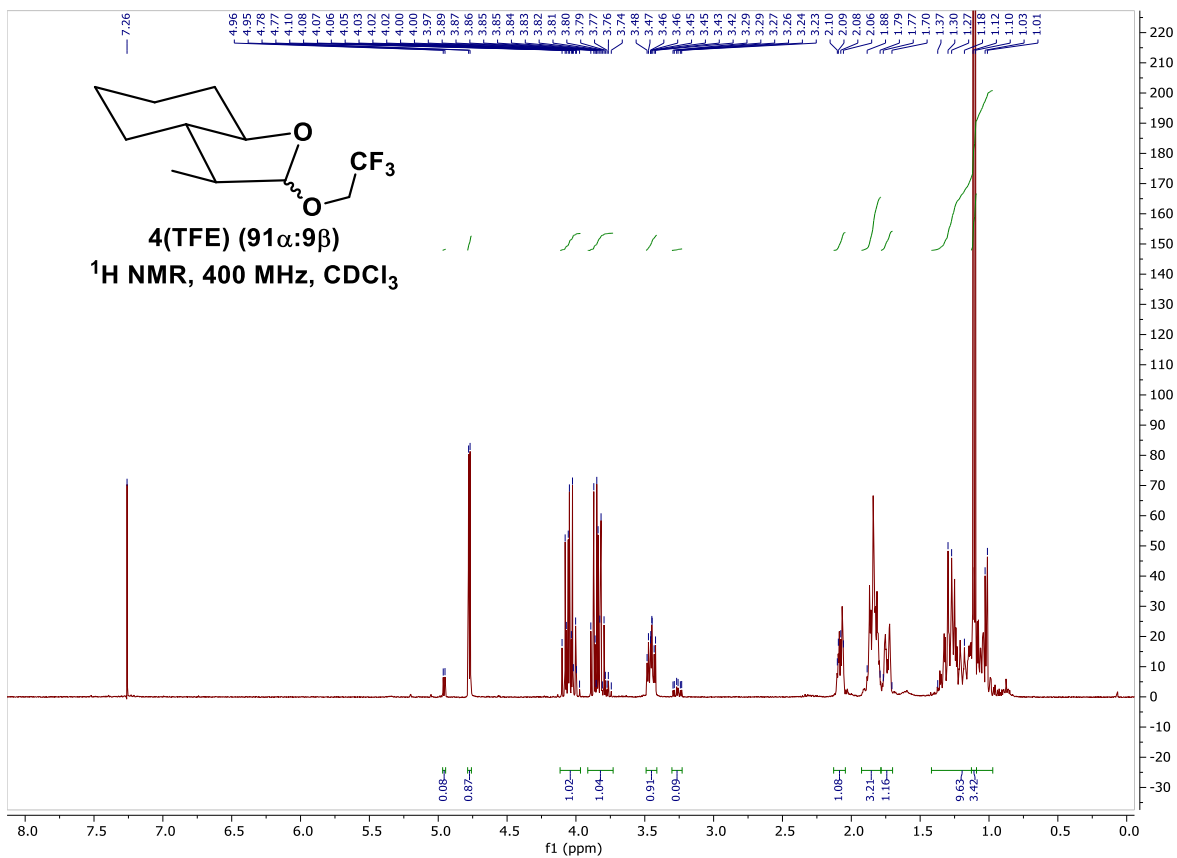


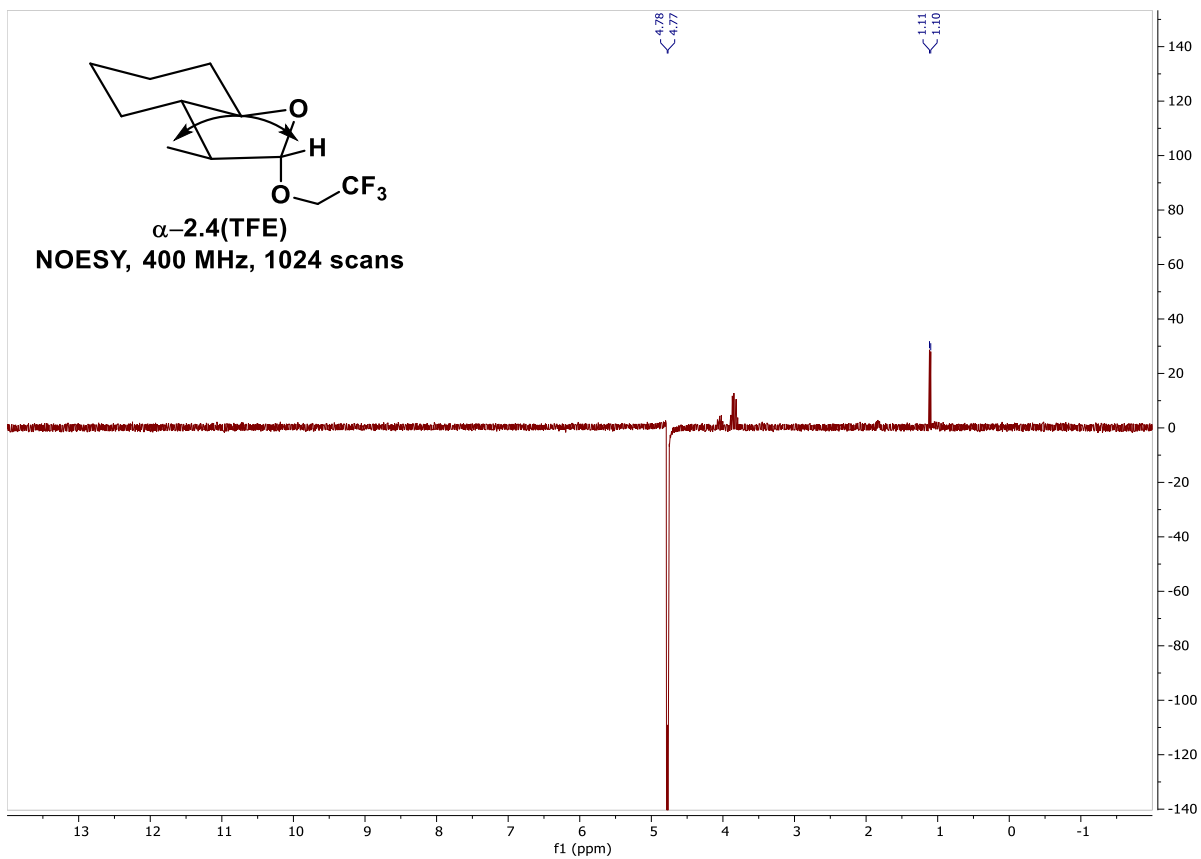
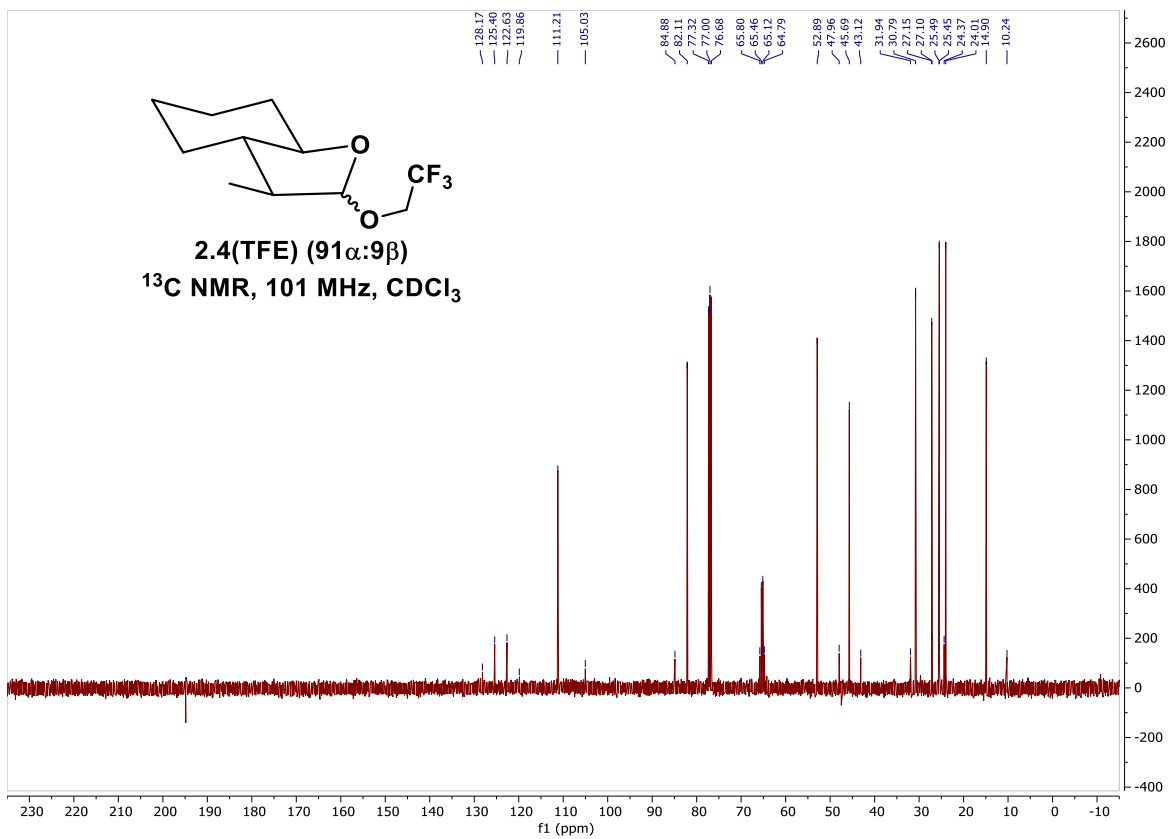


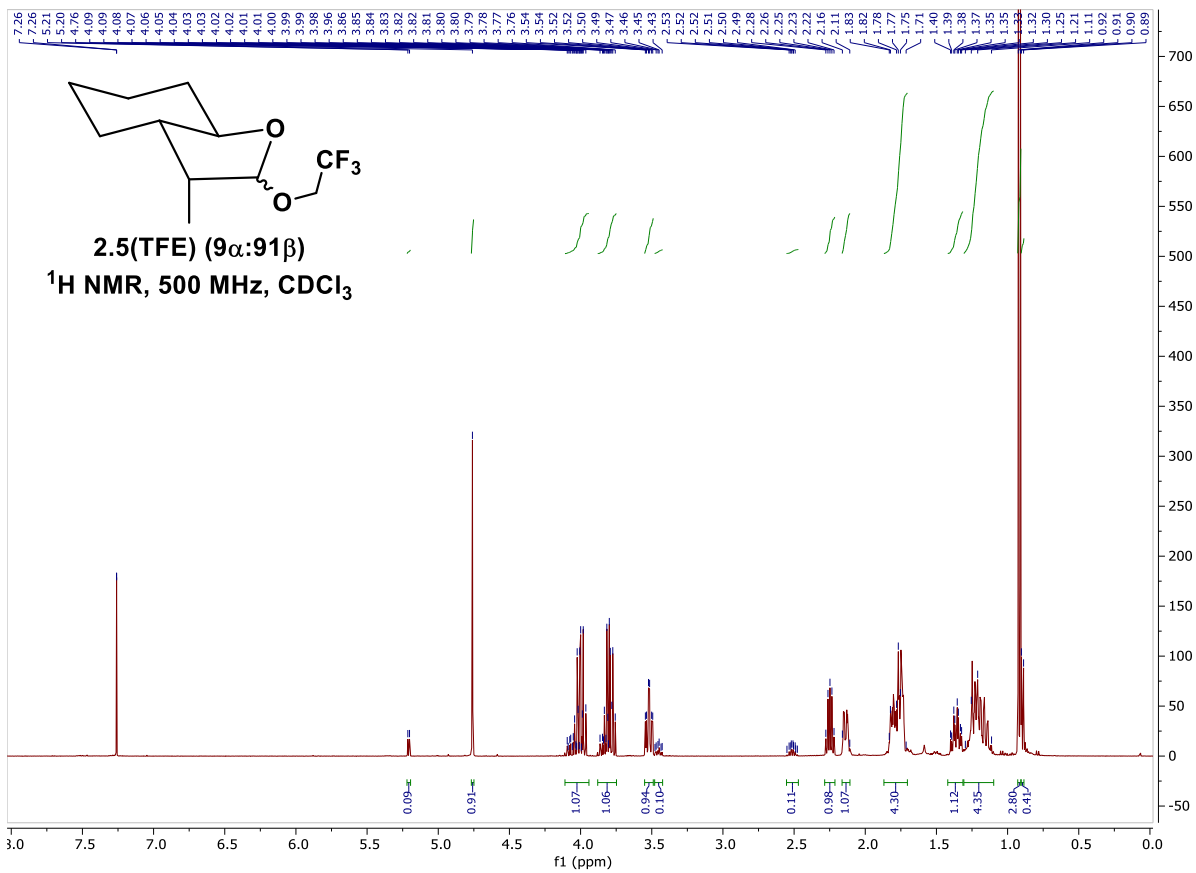
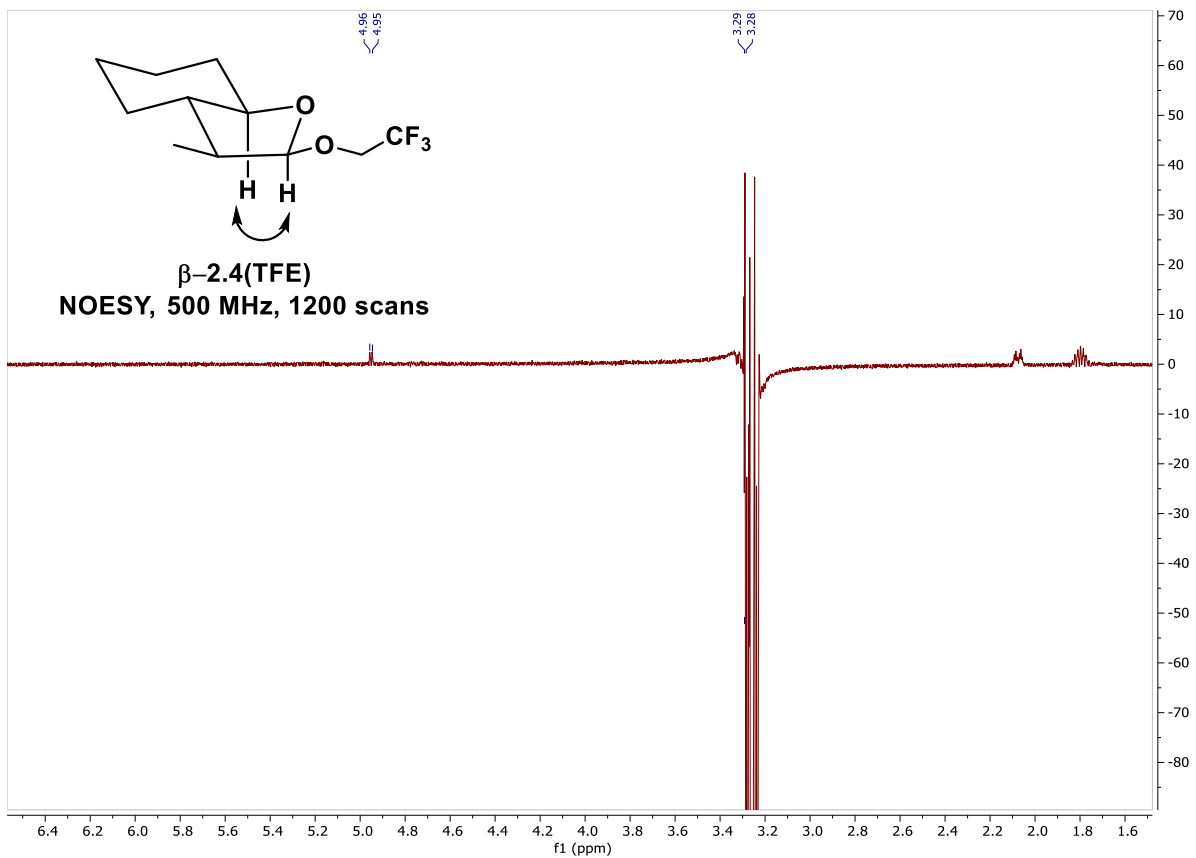


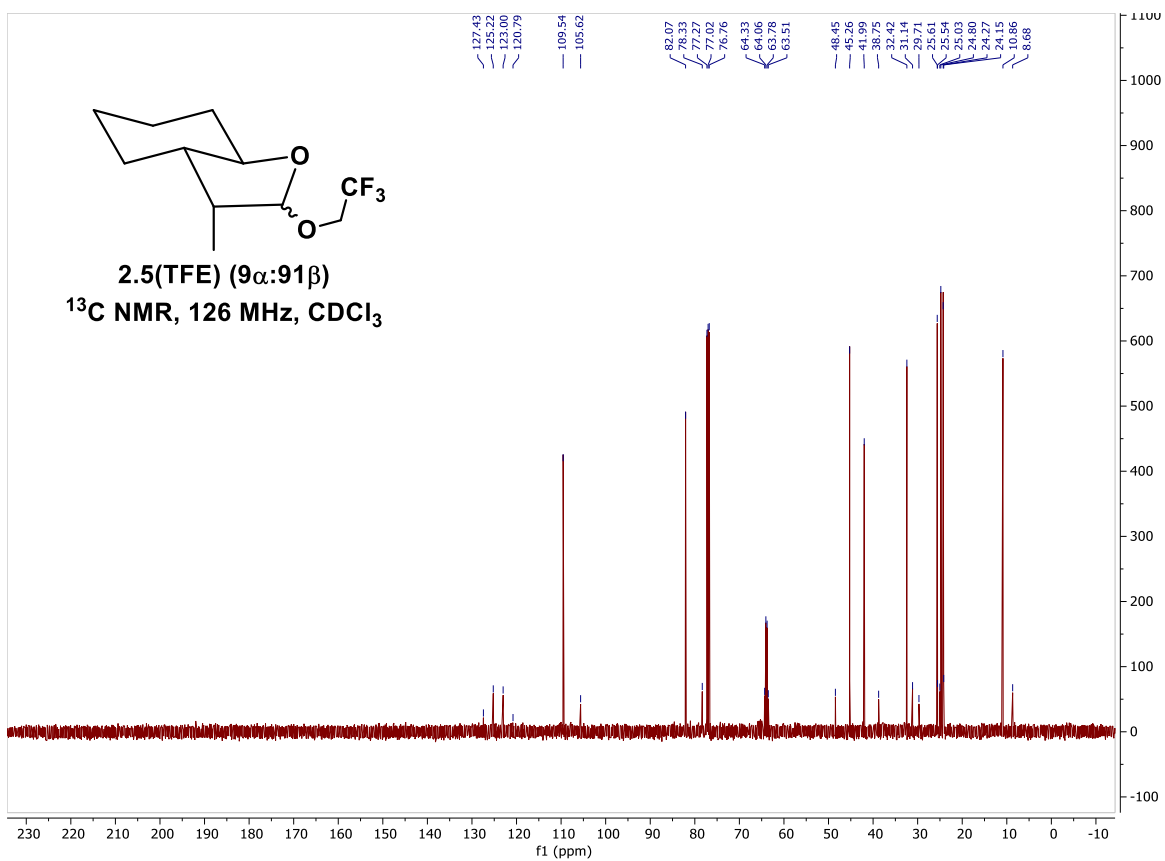
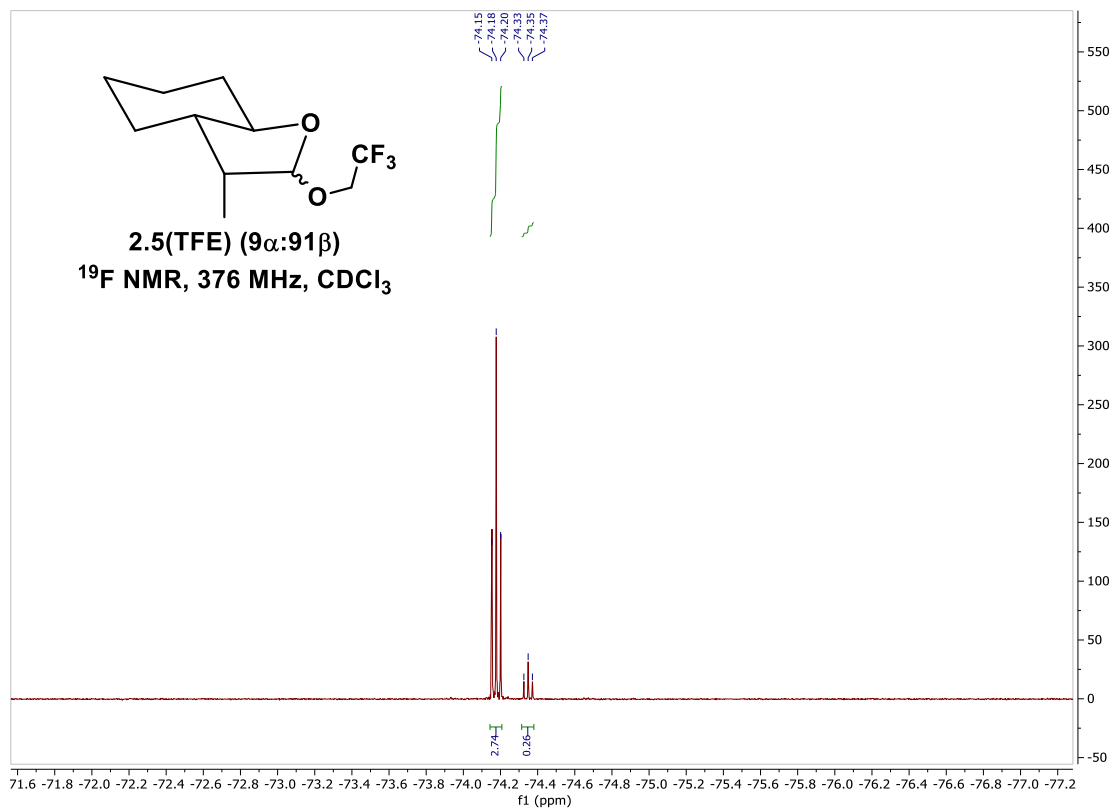


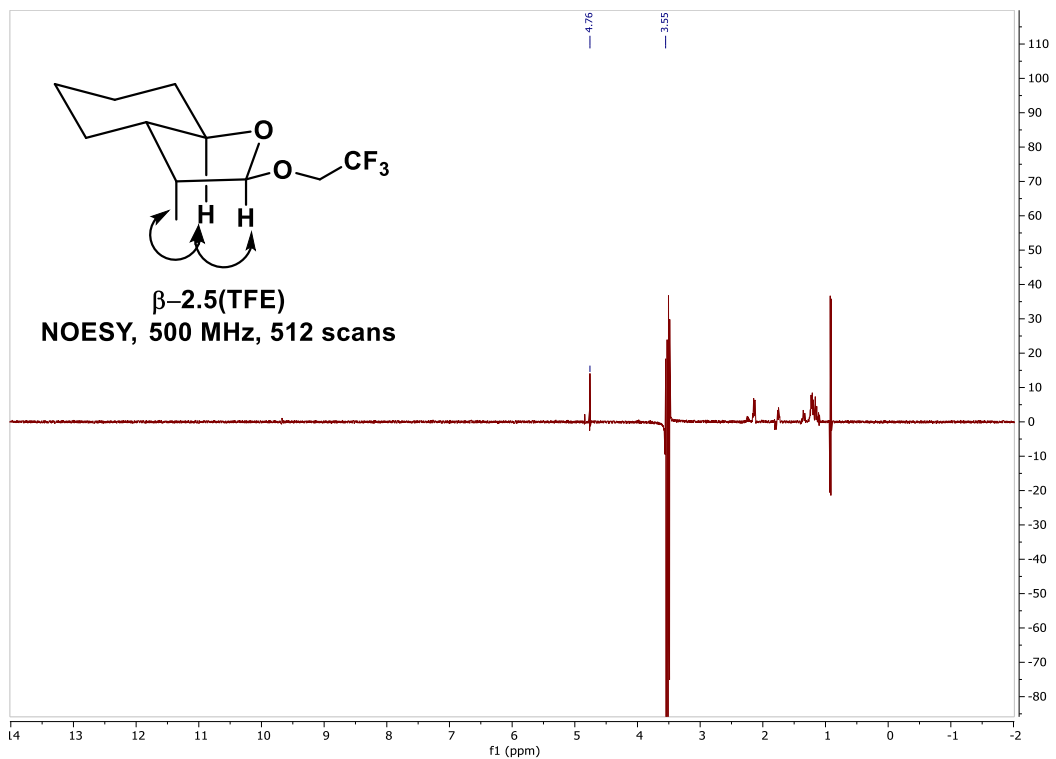




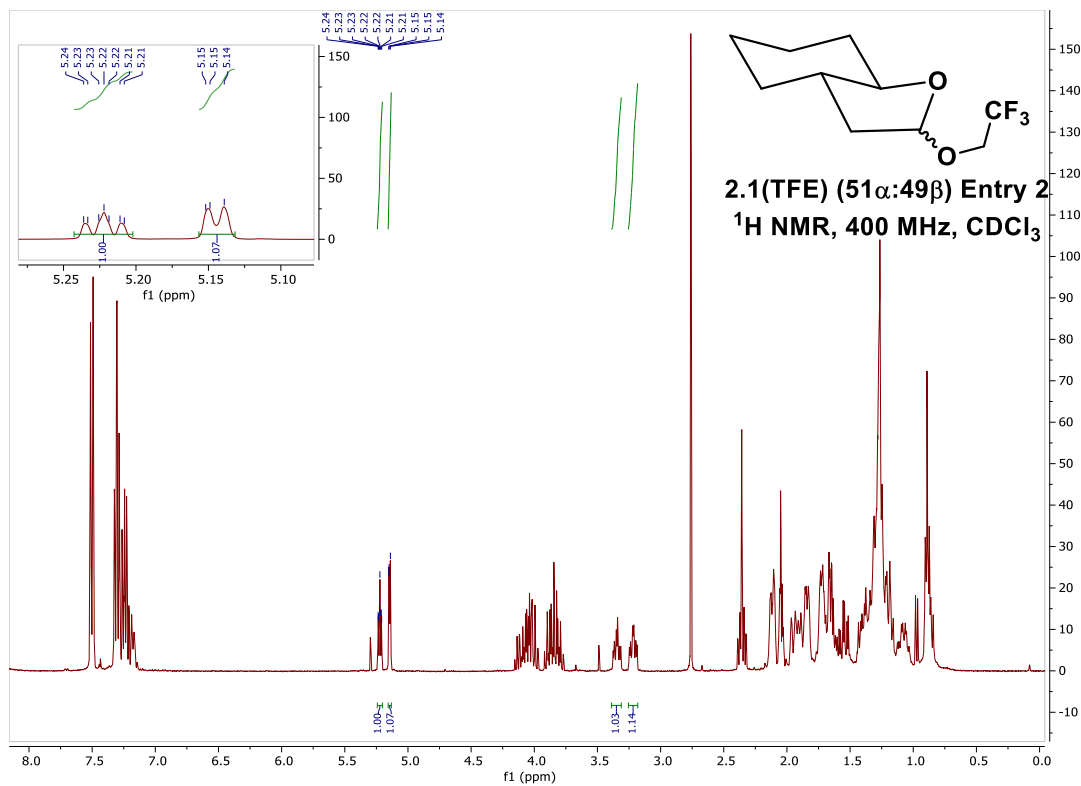


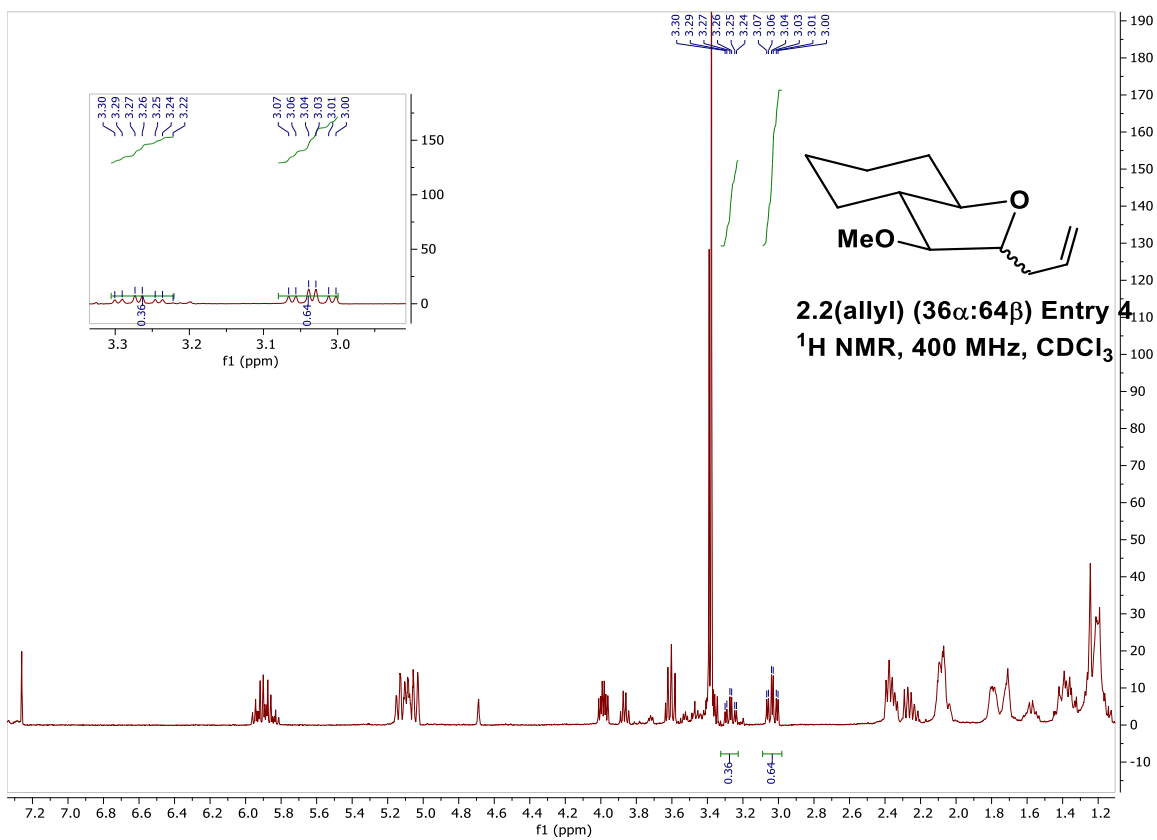
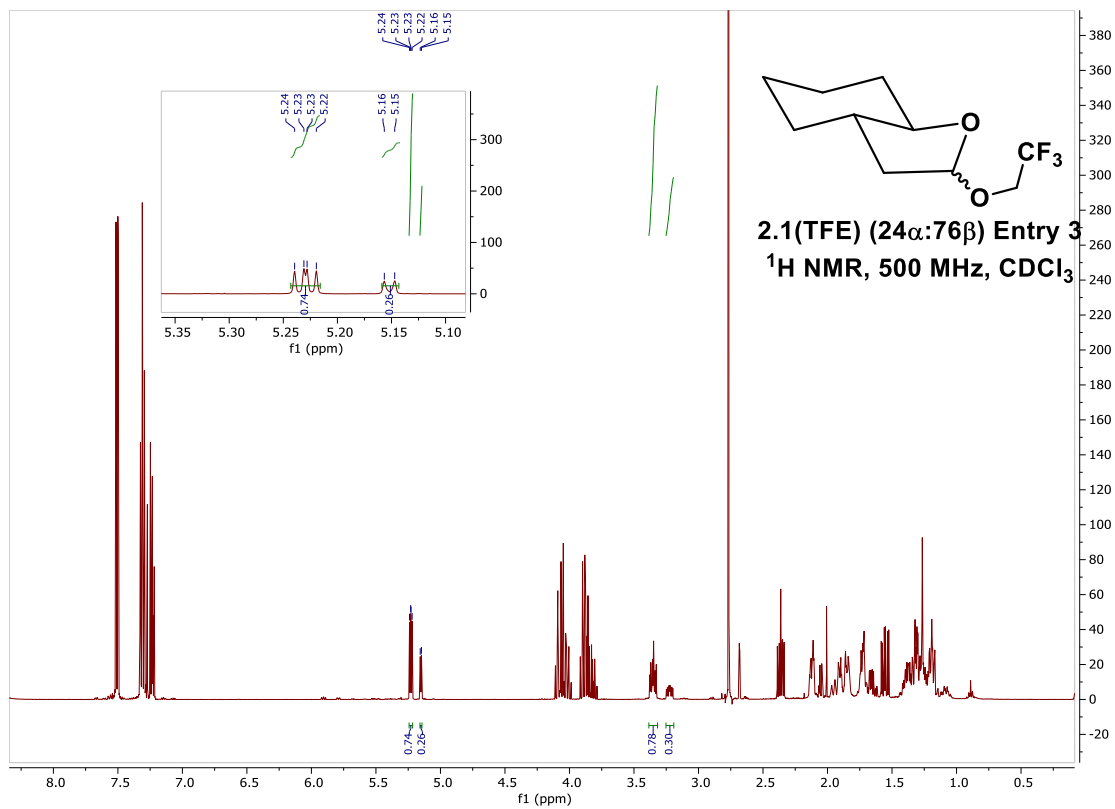




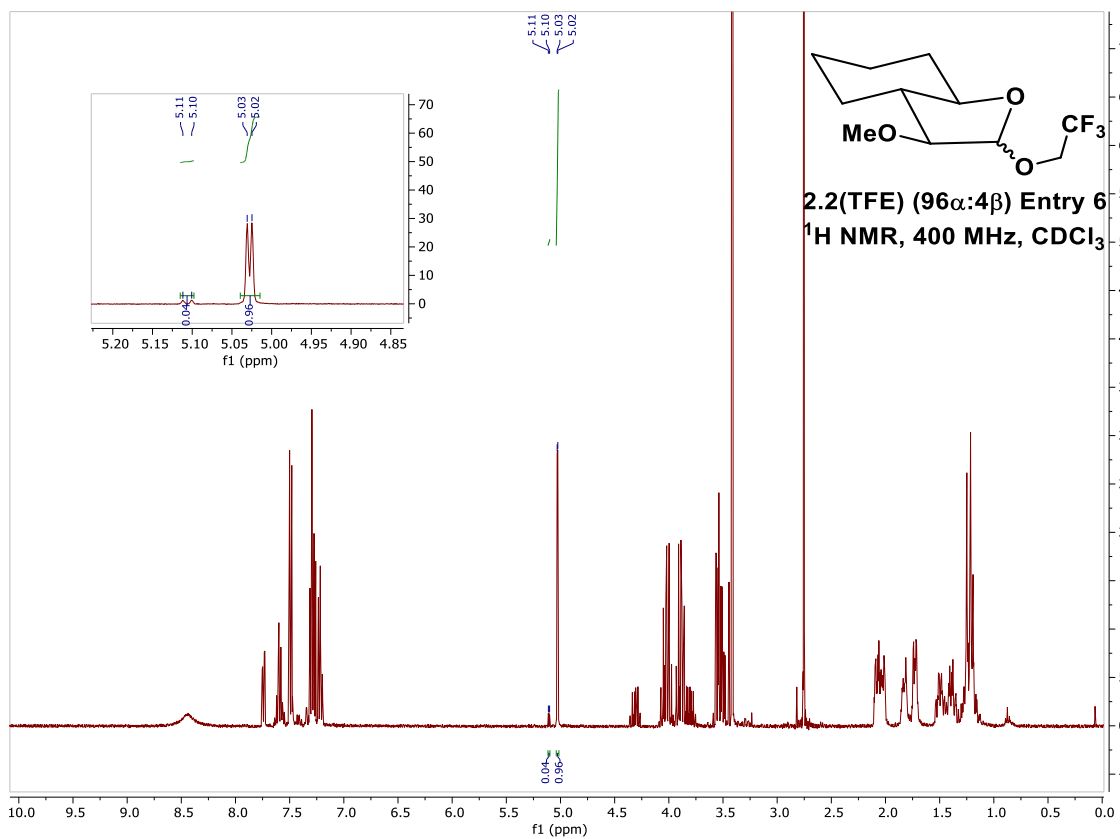
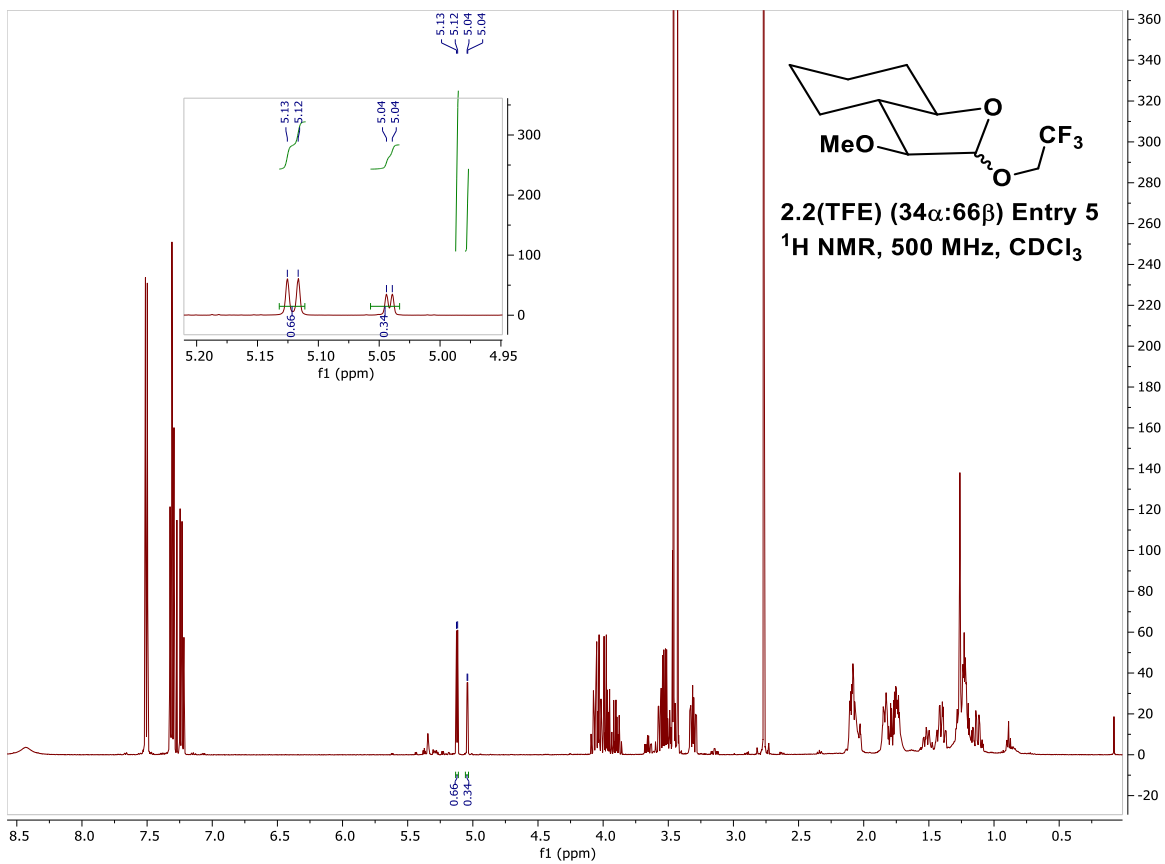


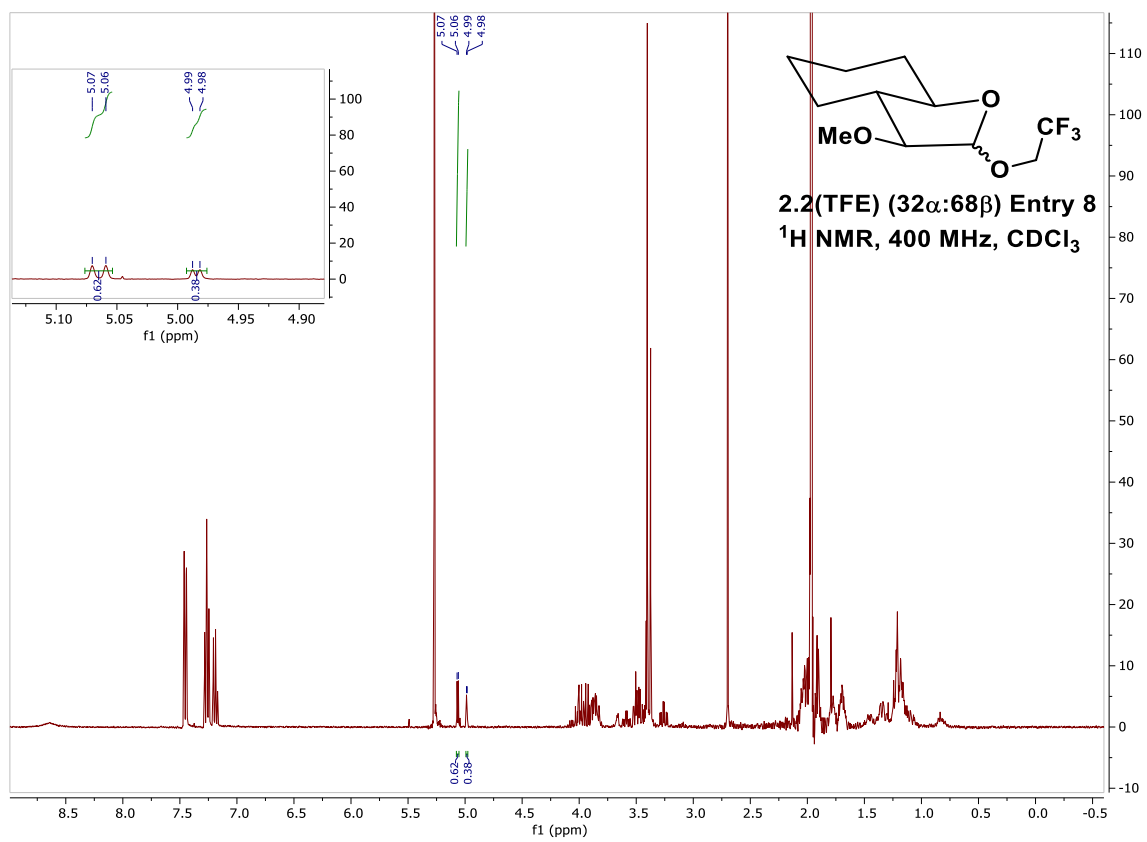
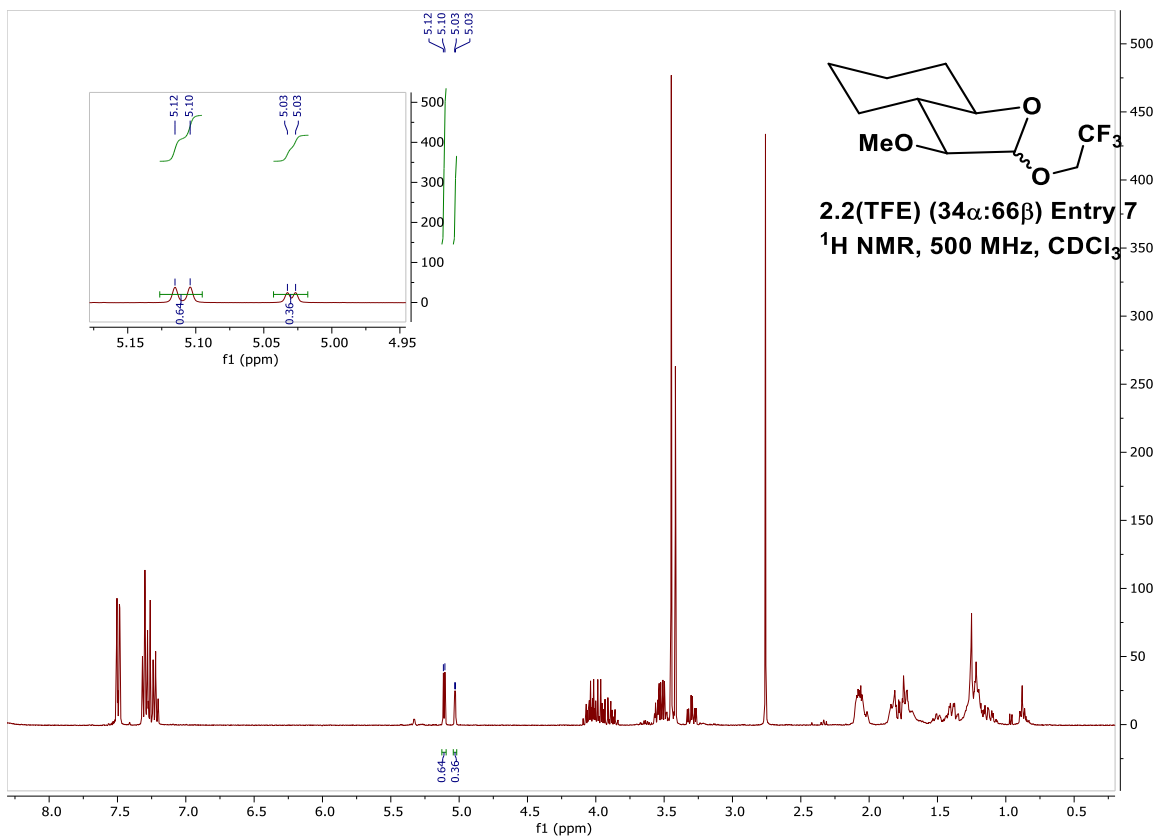
#### F.4 Spectres RMN brutes des réactions de glycosylation.

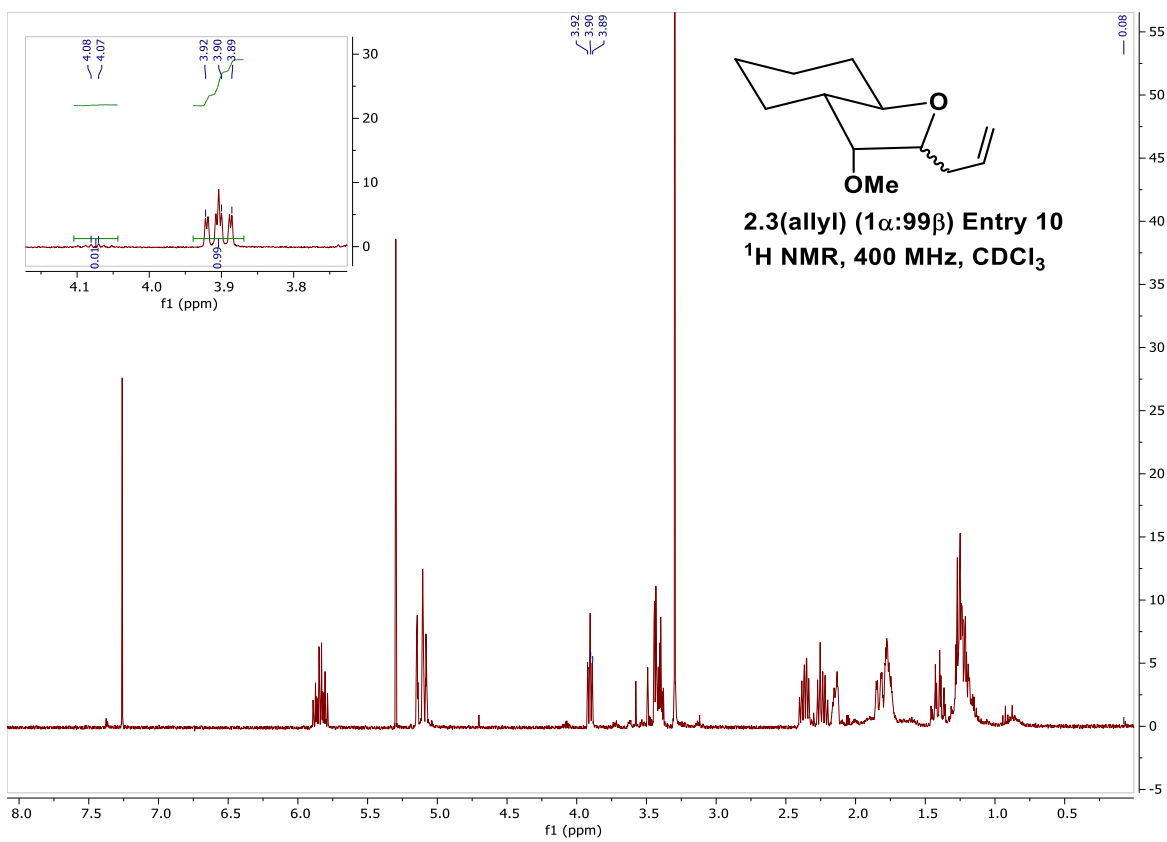
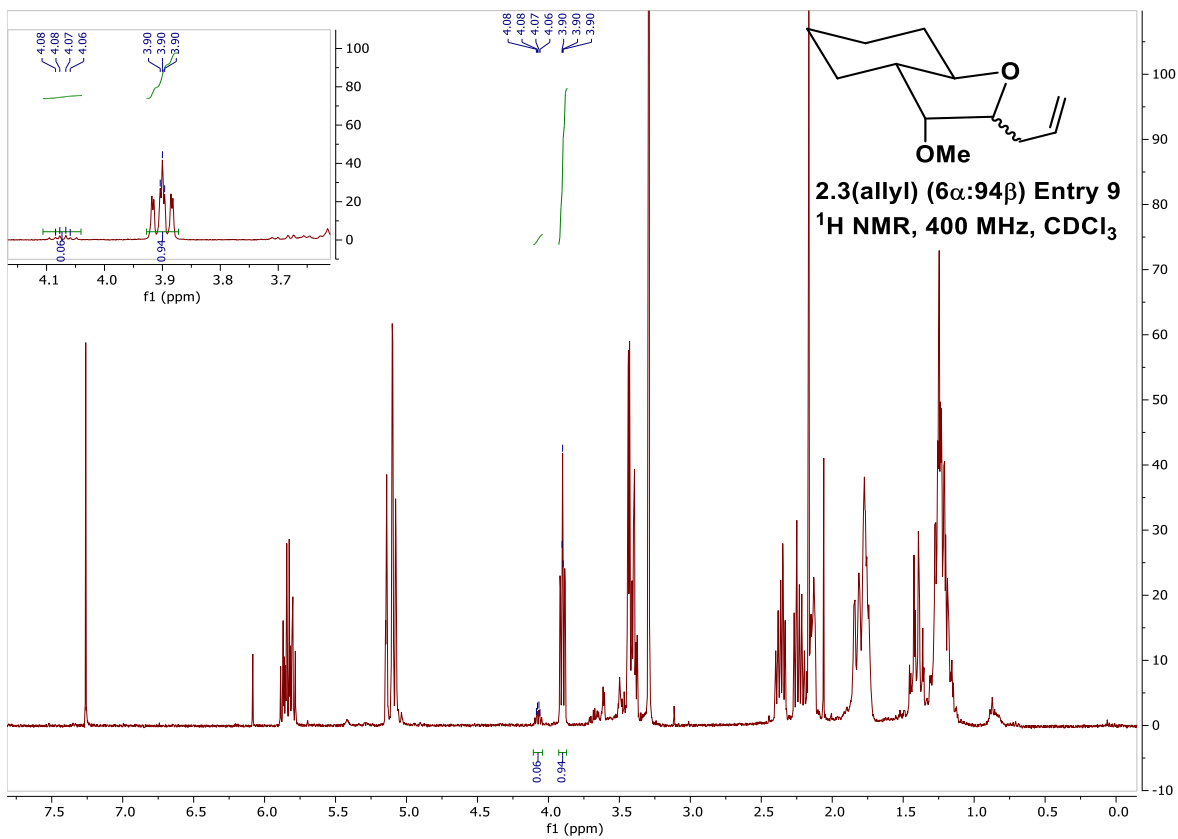


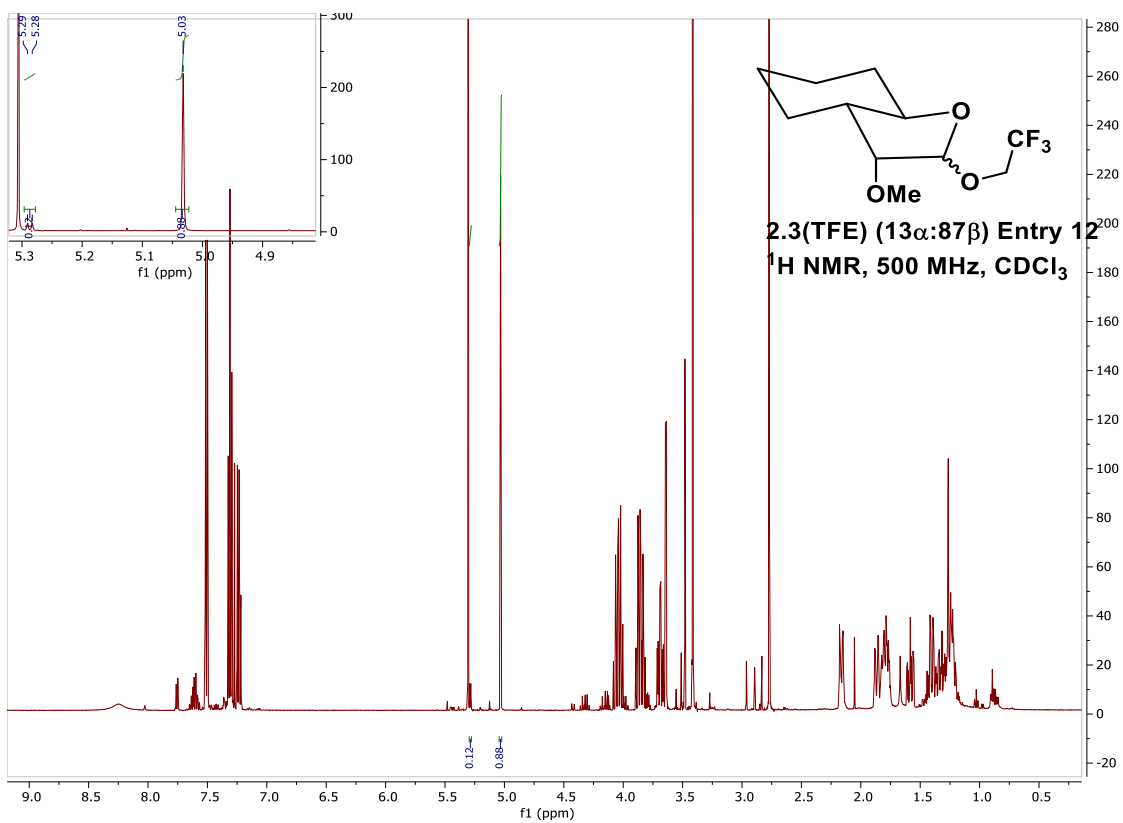
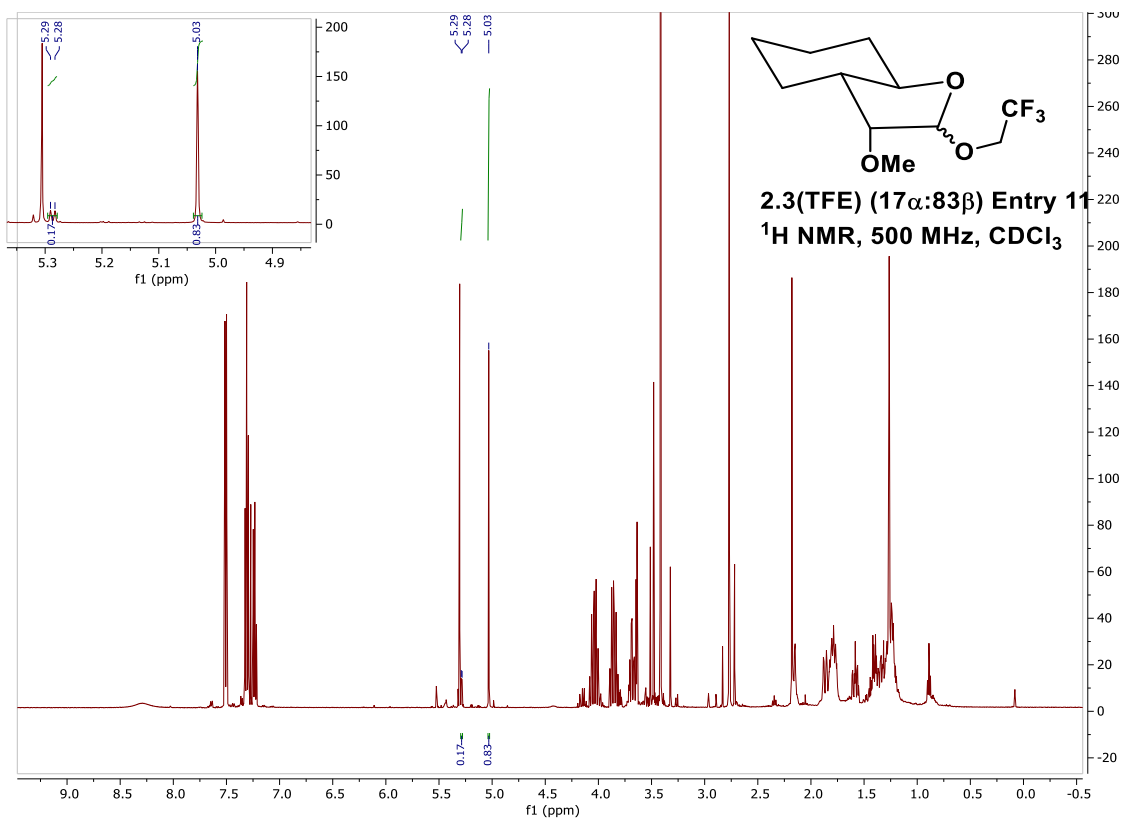


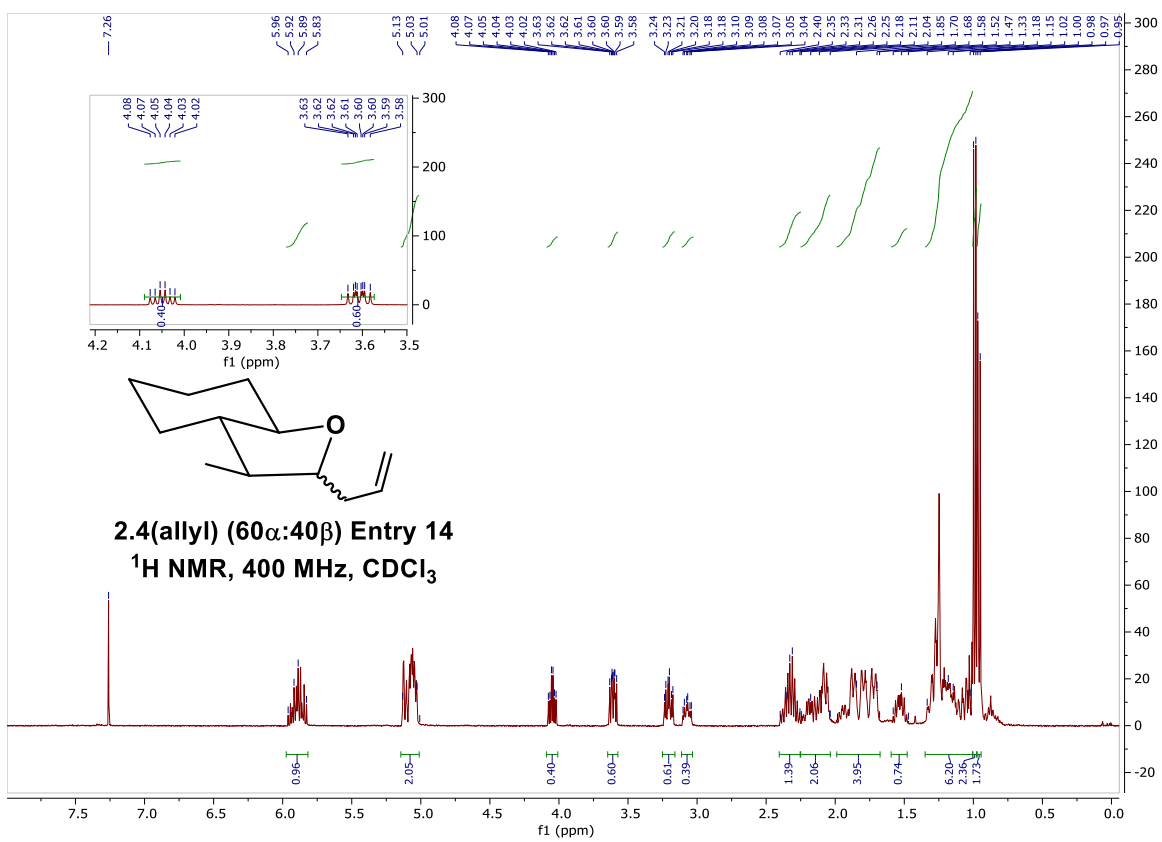
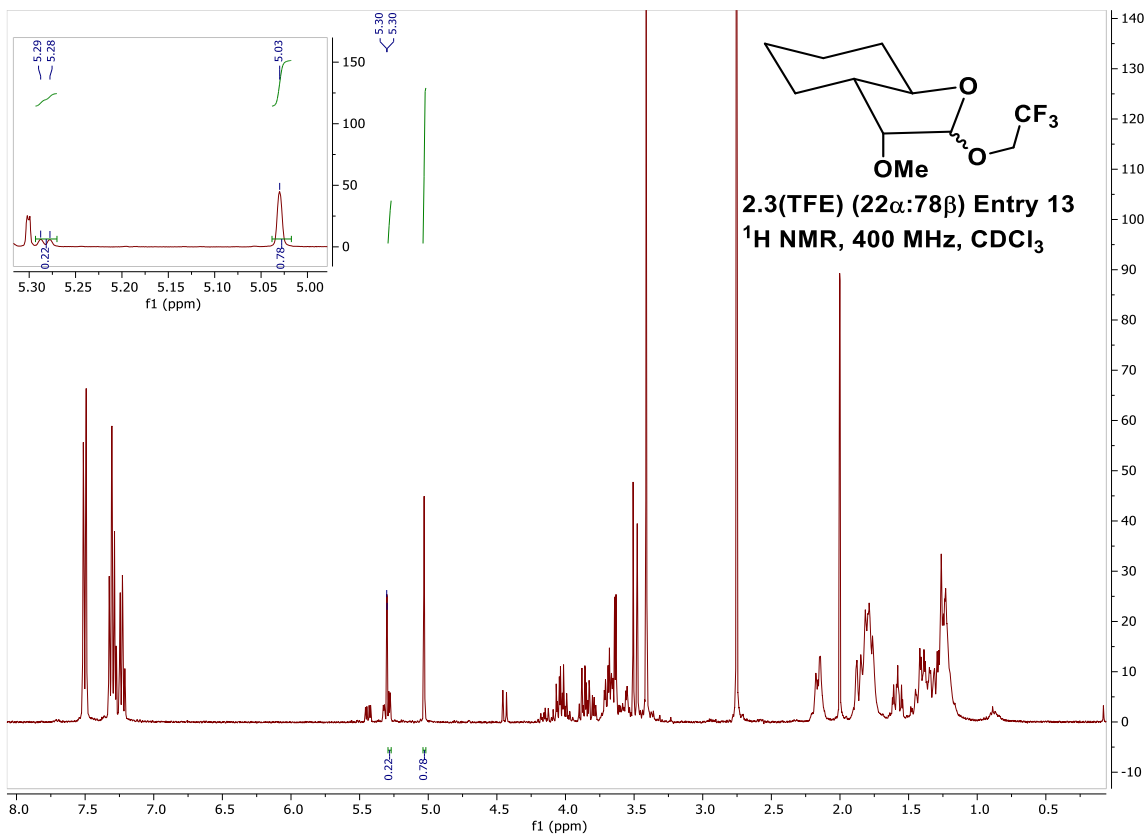


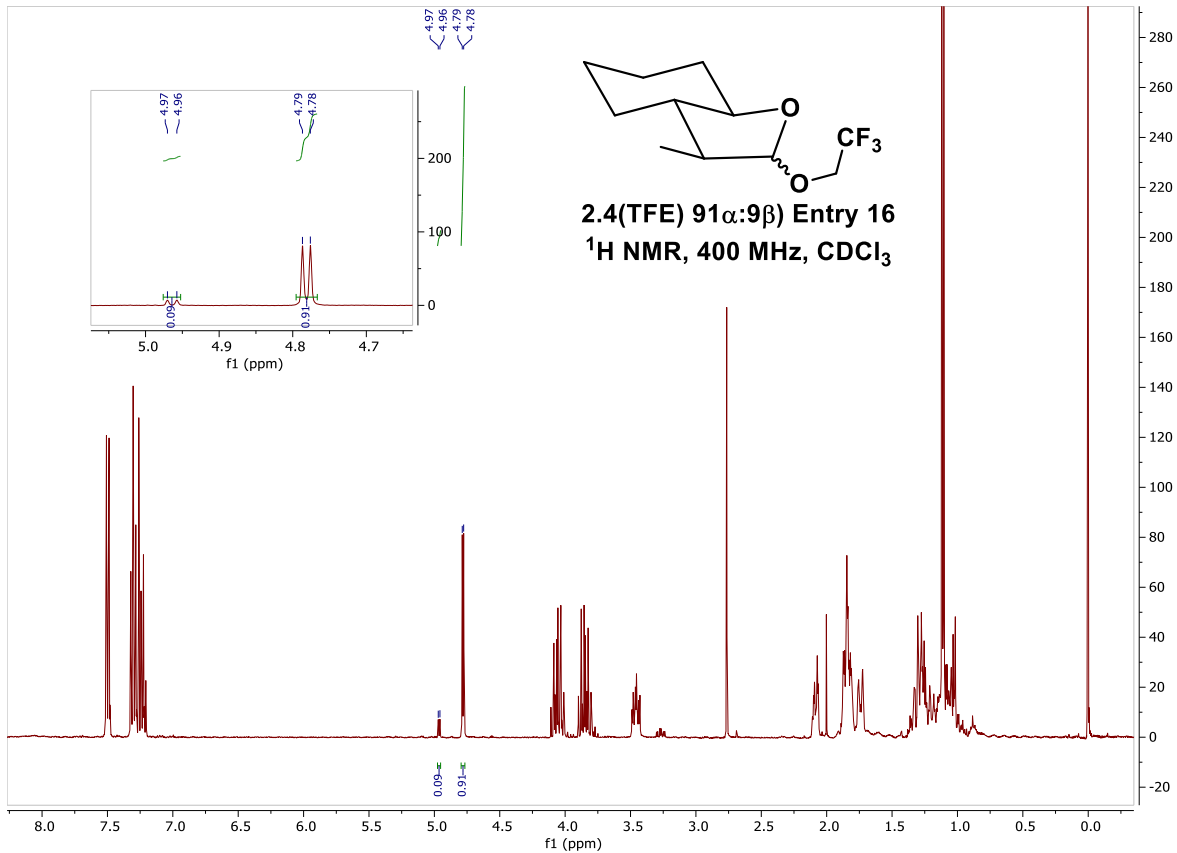
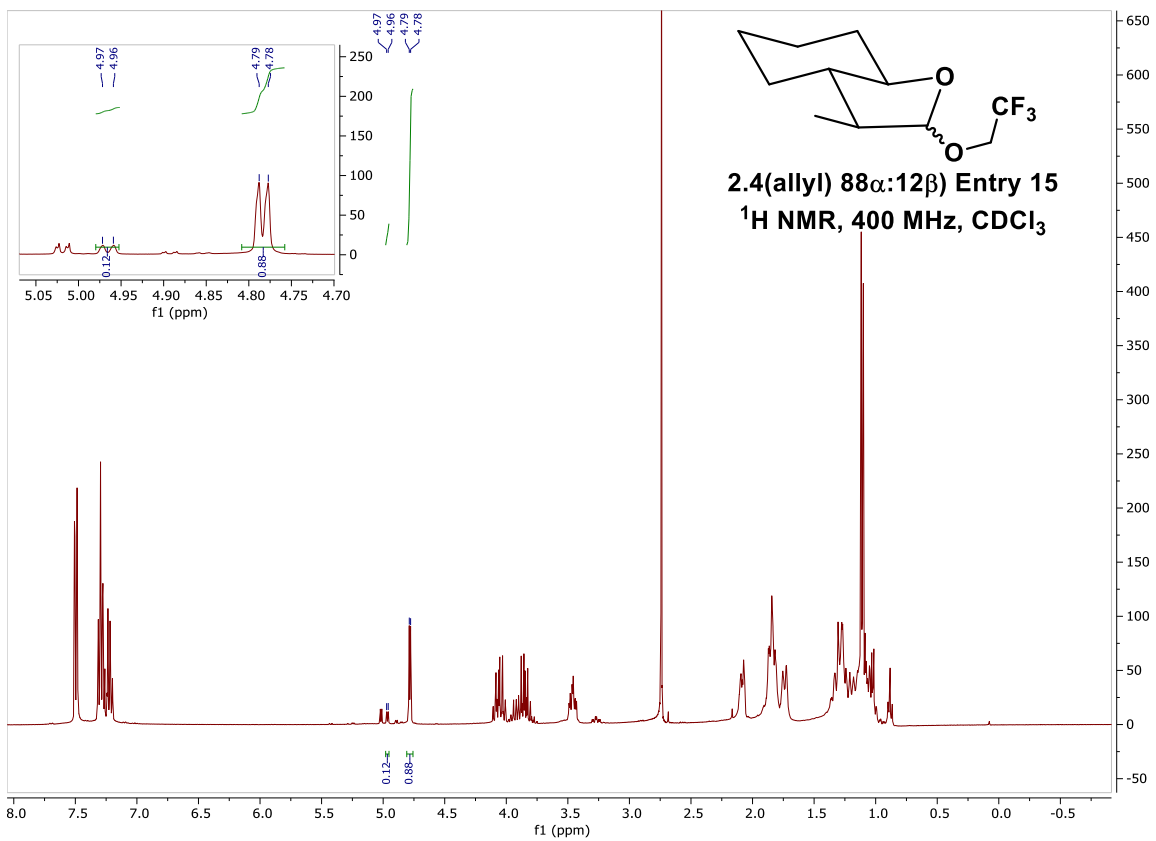


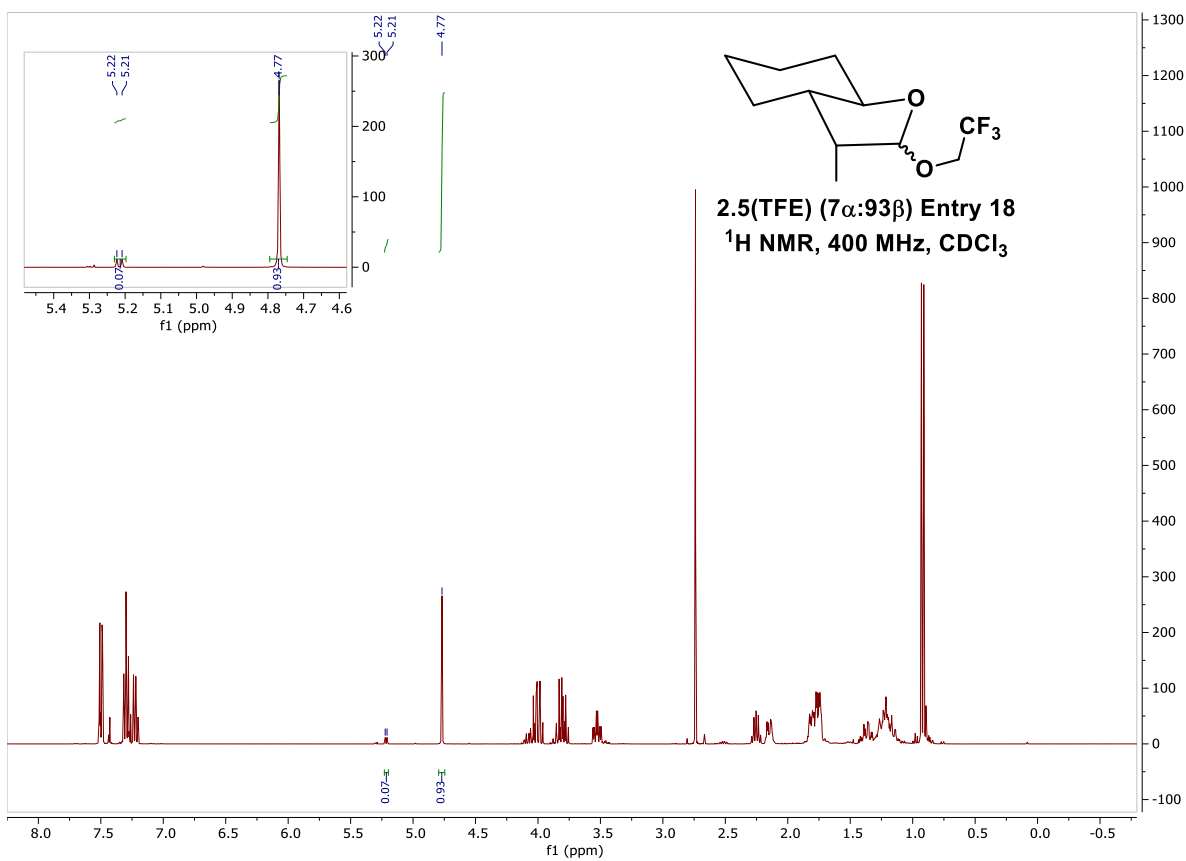
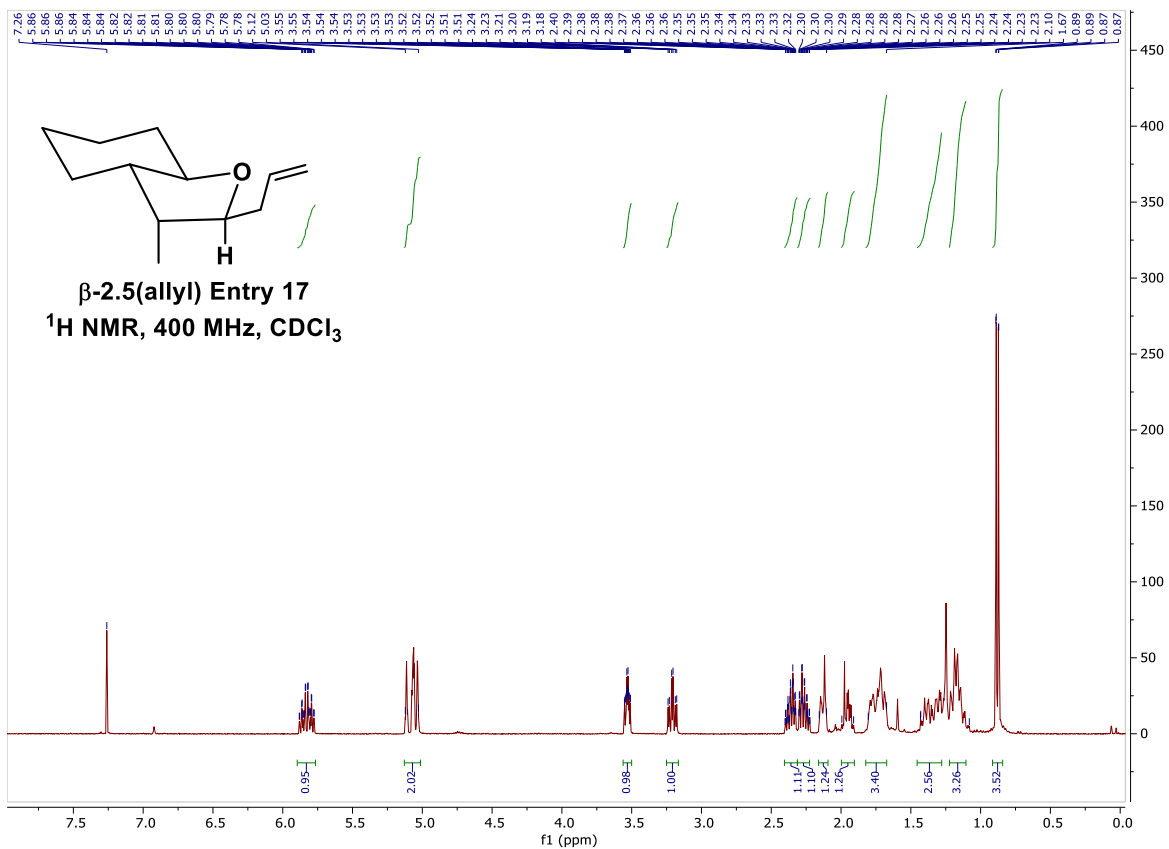


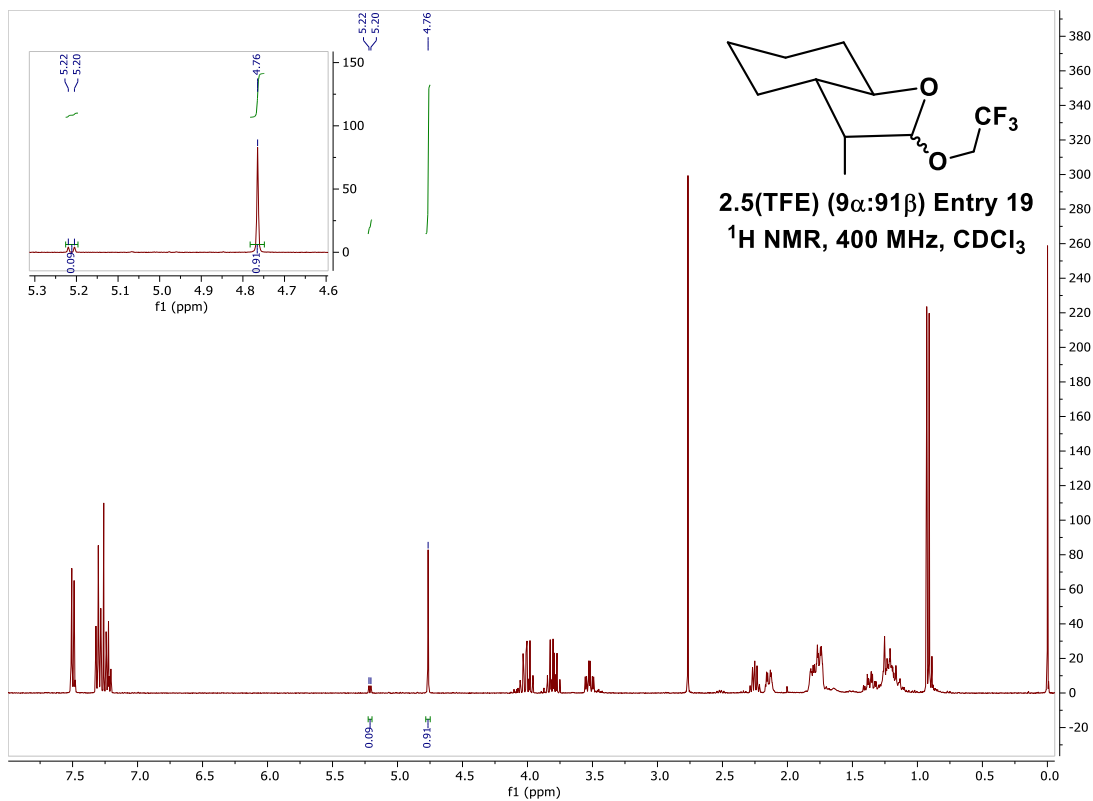




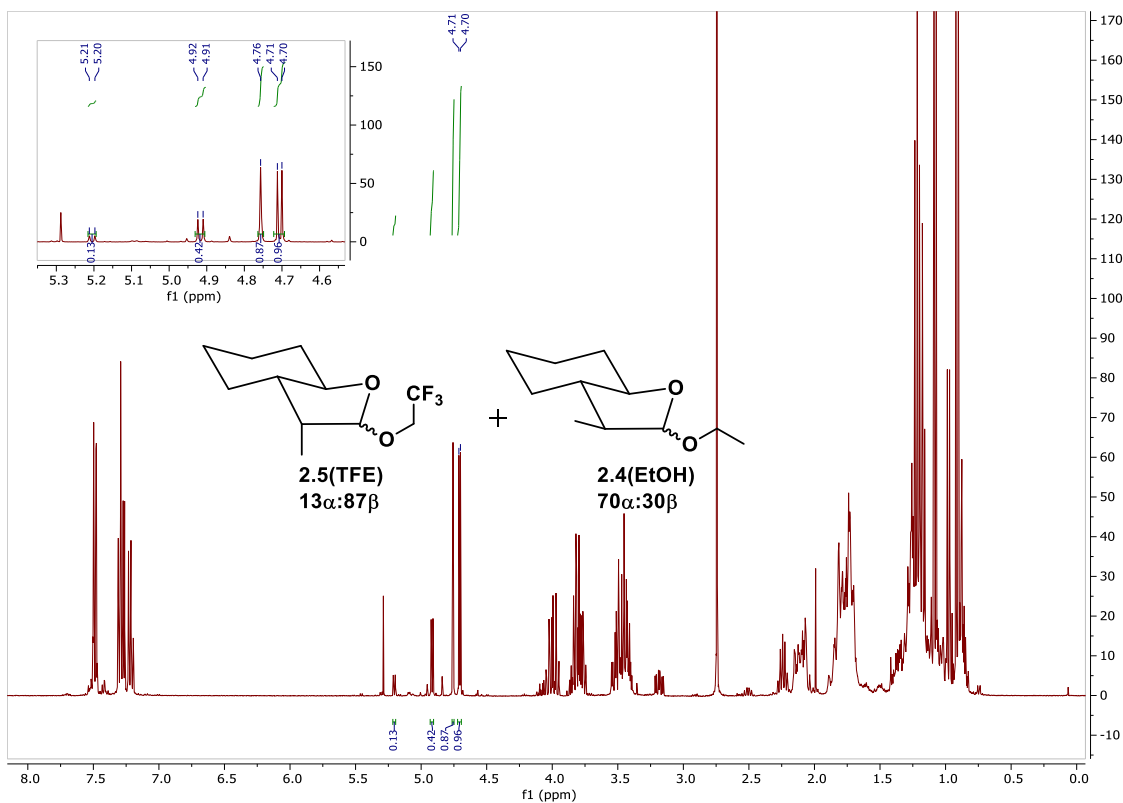




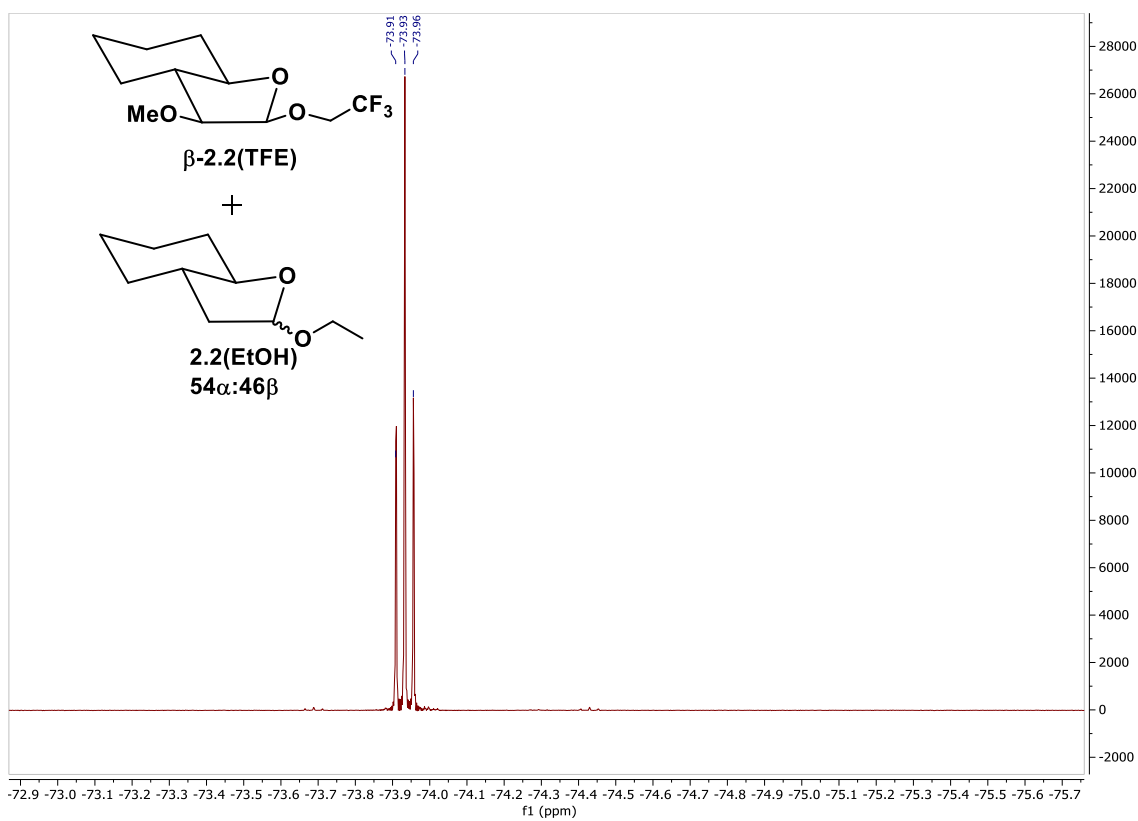
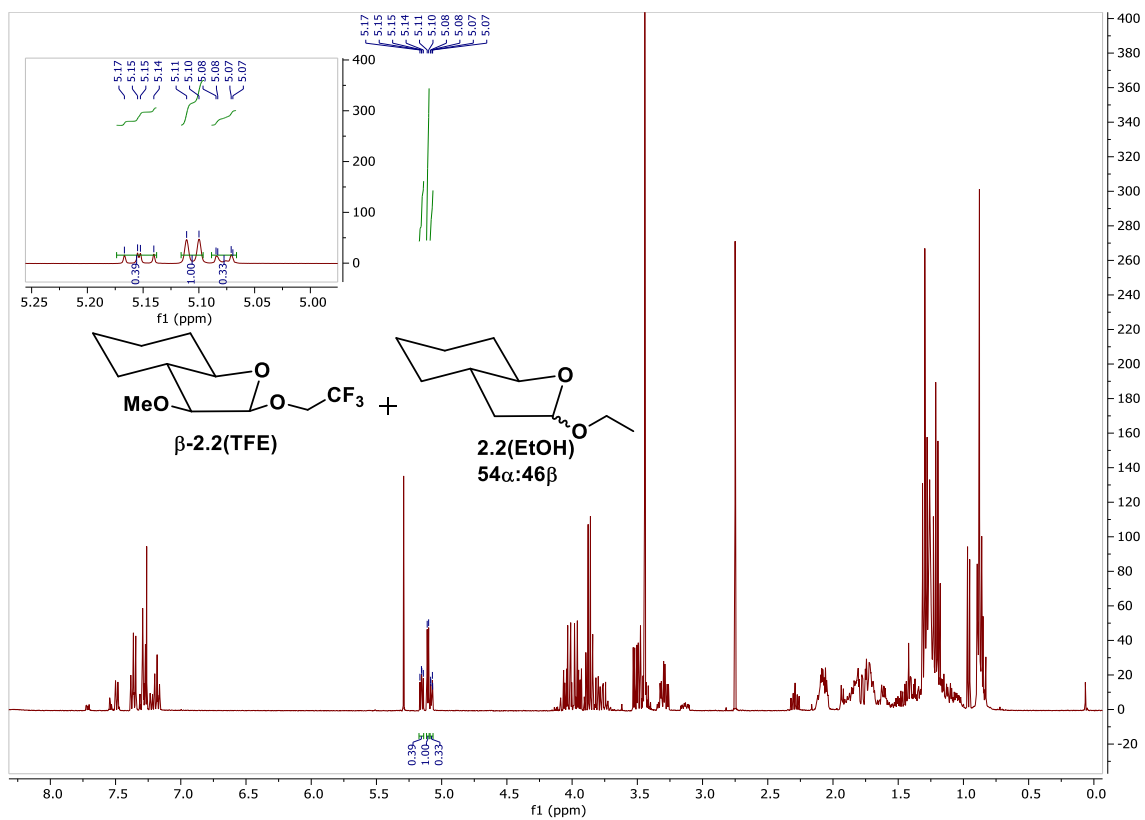


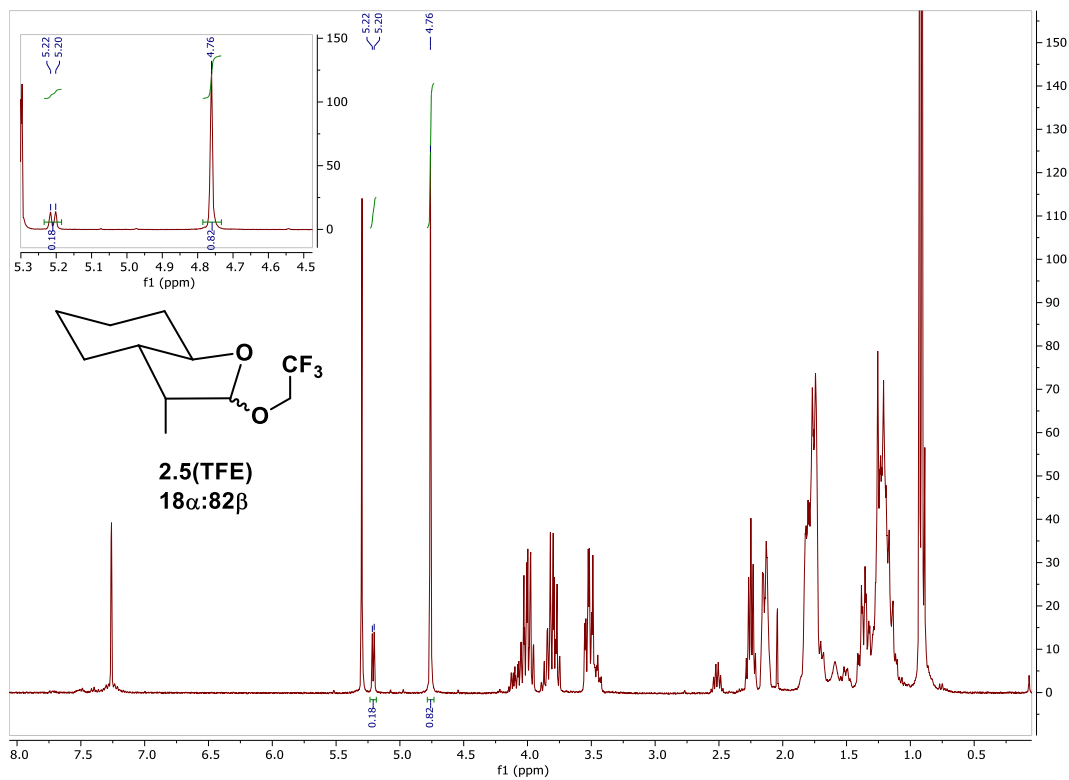


## F.5 Spectres RMN brutes des expériences des contrôle cinétique.

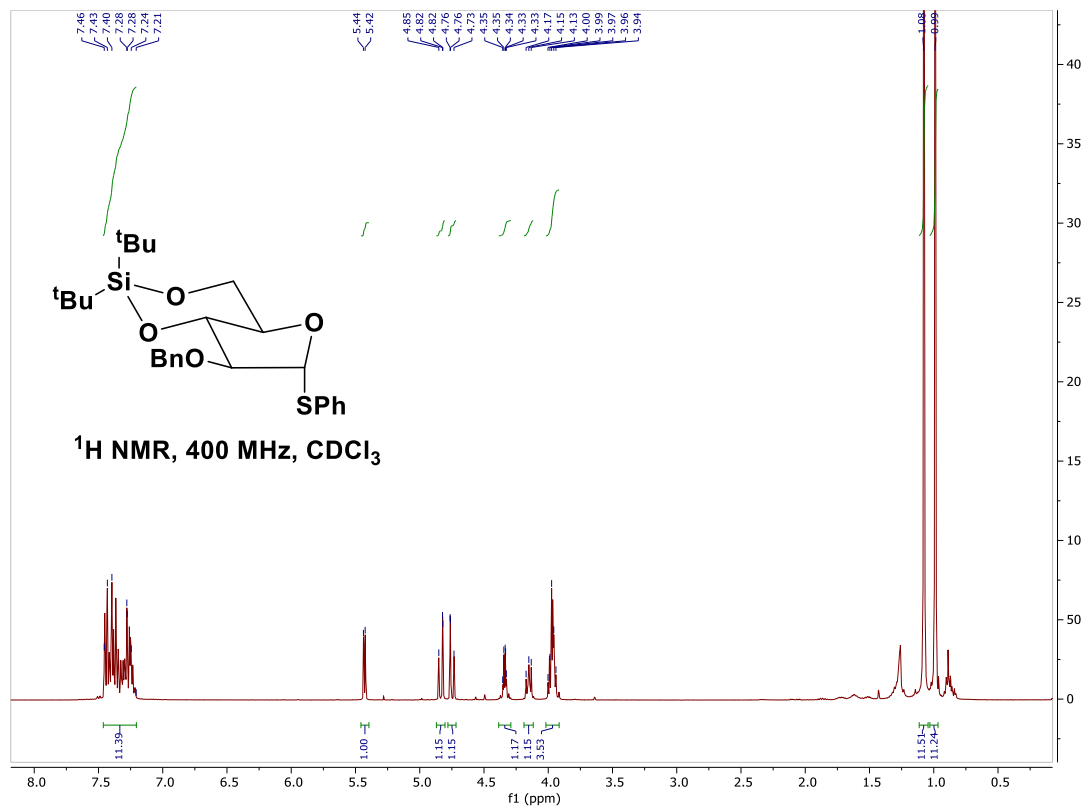


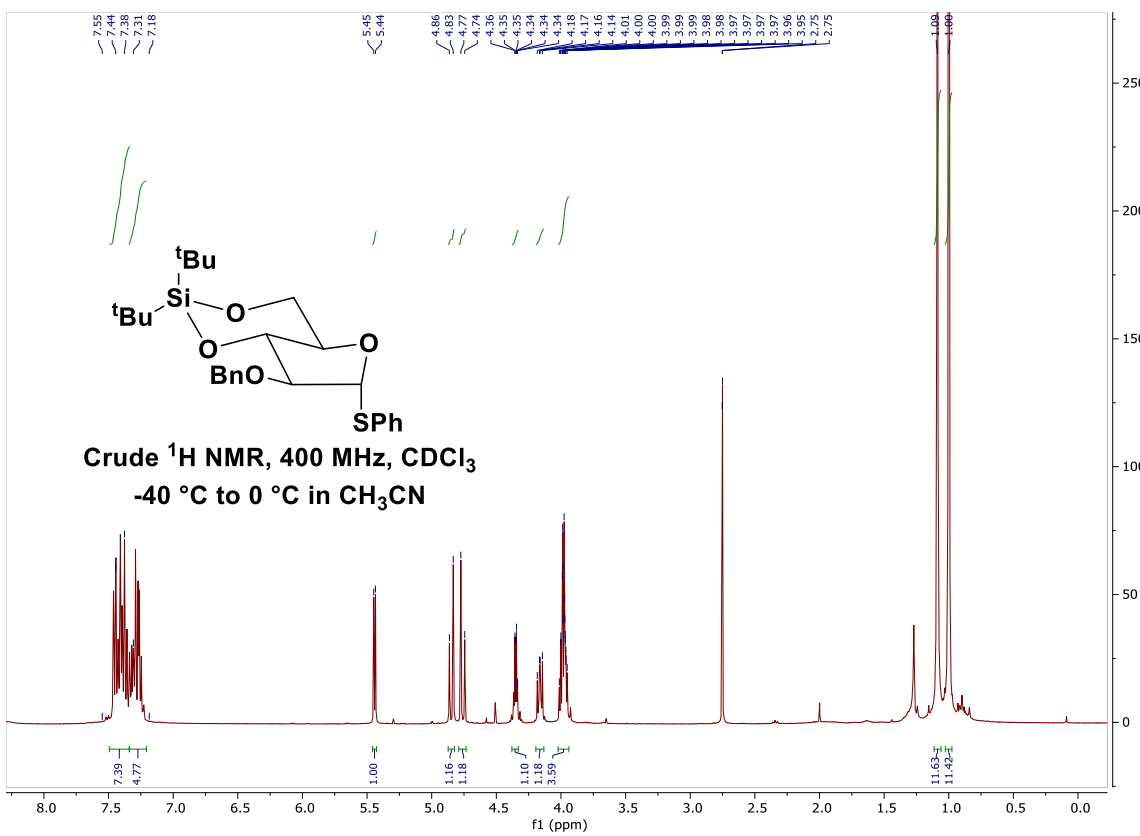
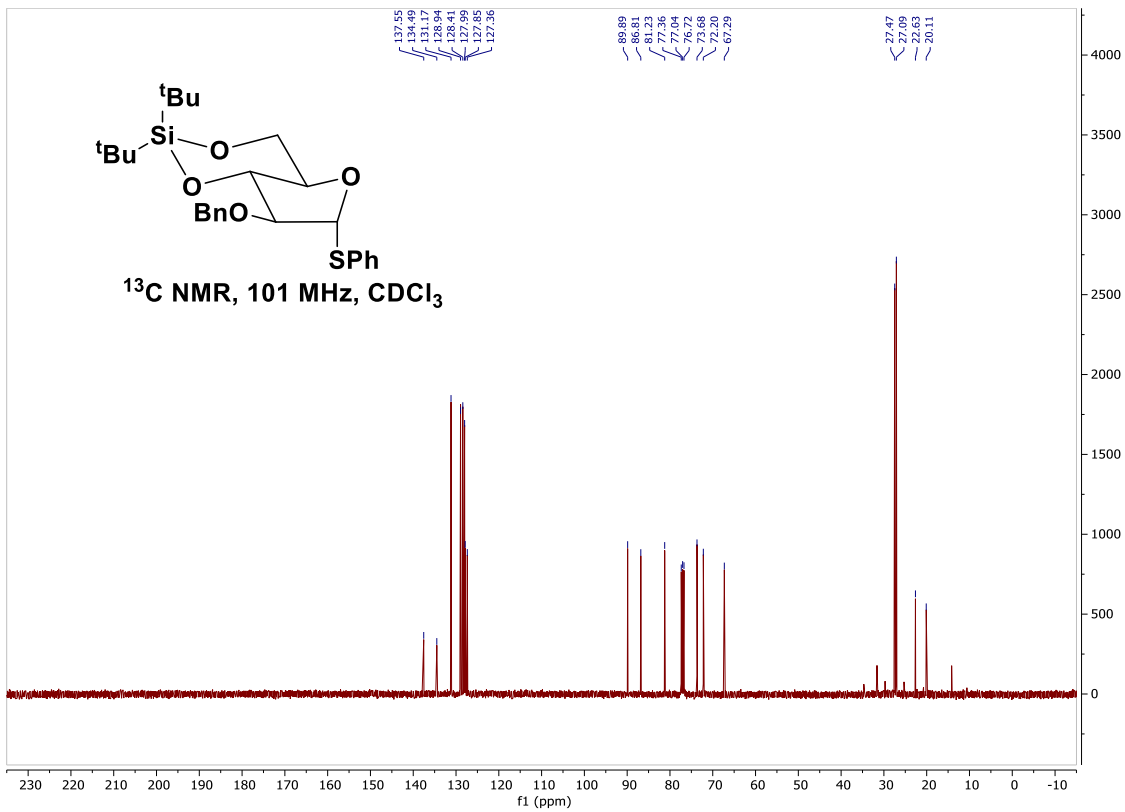






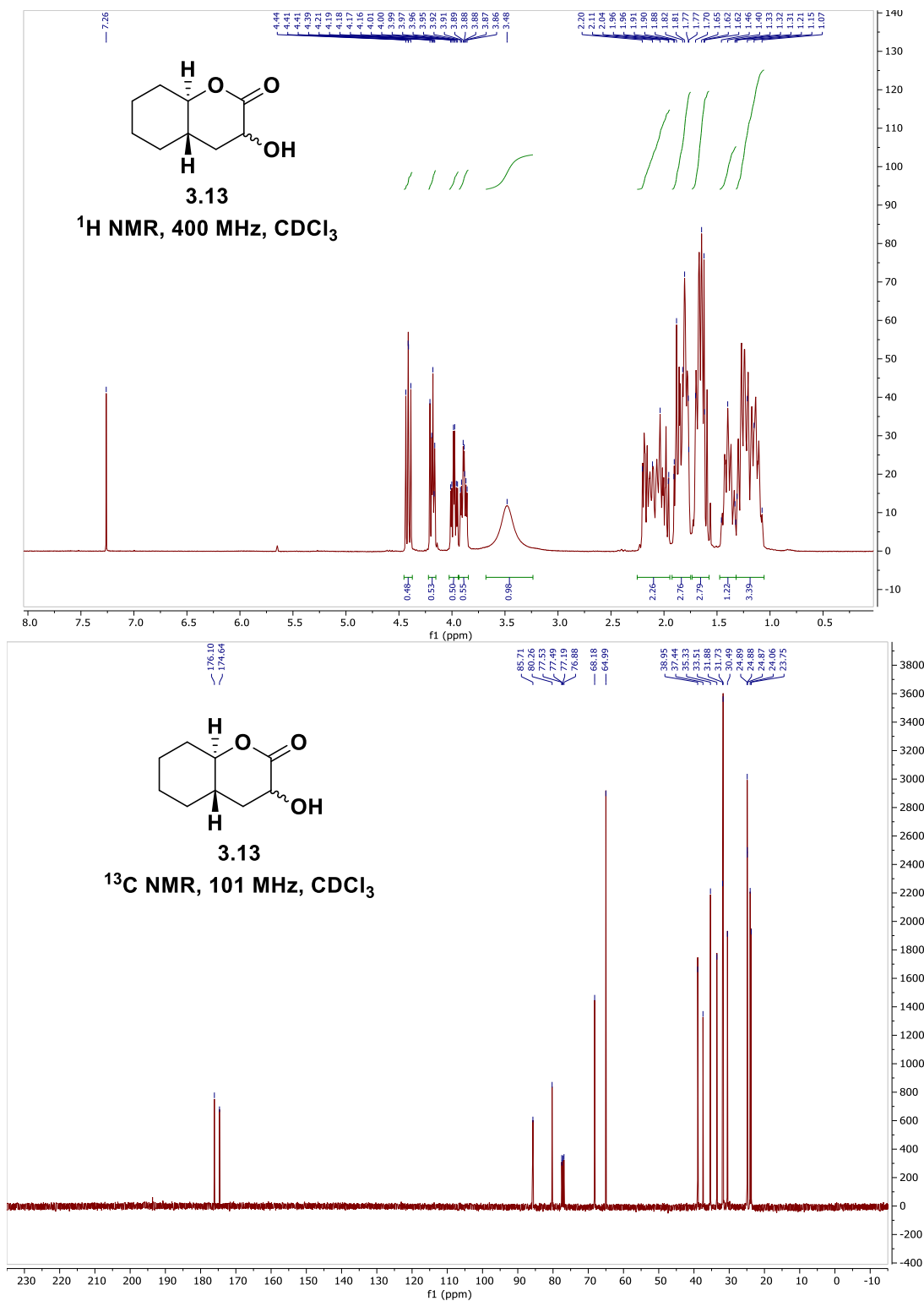
## F.6 Spectres RMN du furanose complet et de sa *O*-glycosylation.

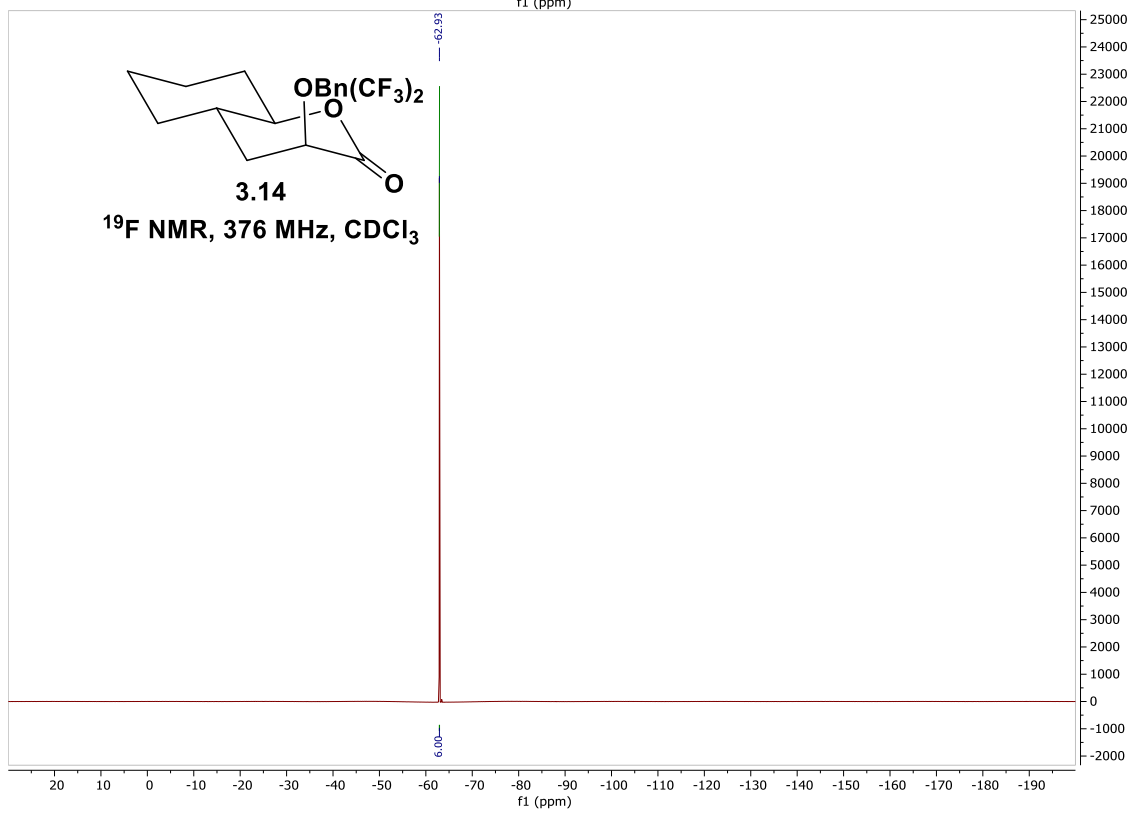
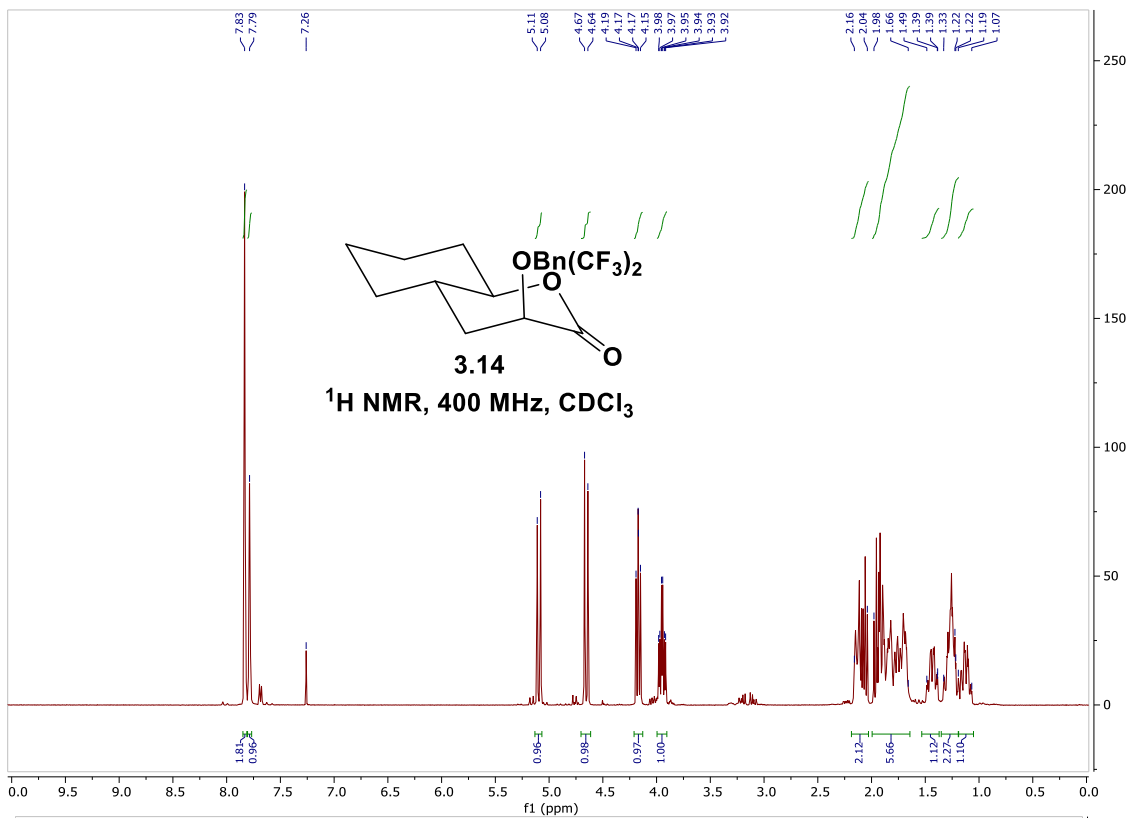


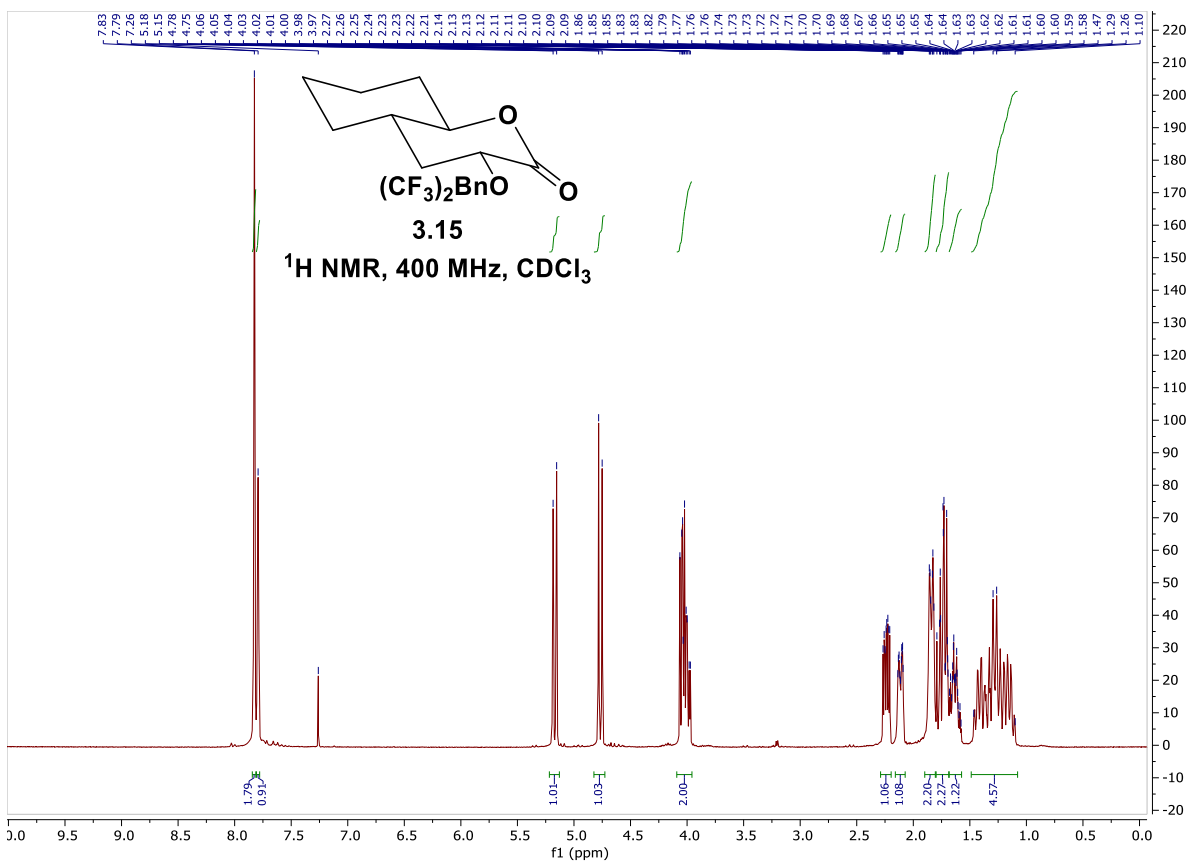
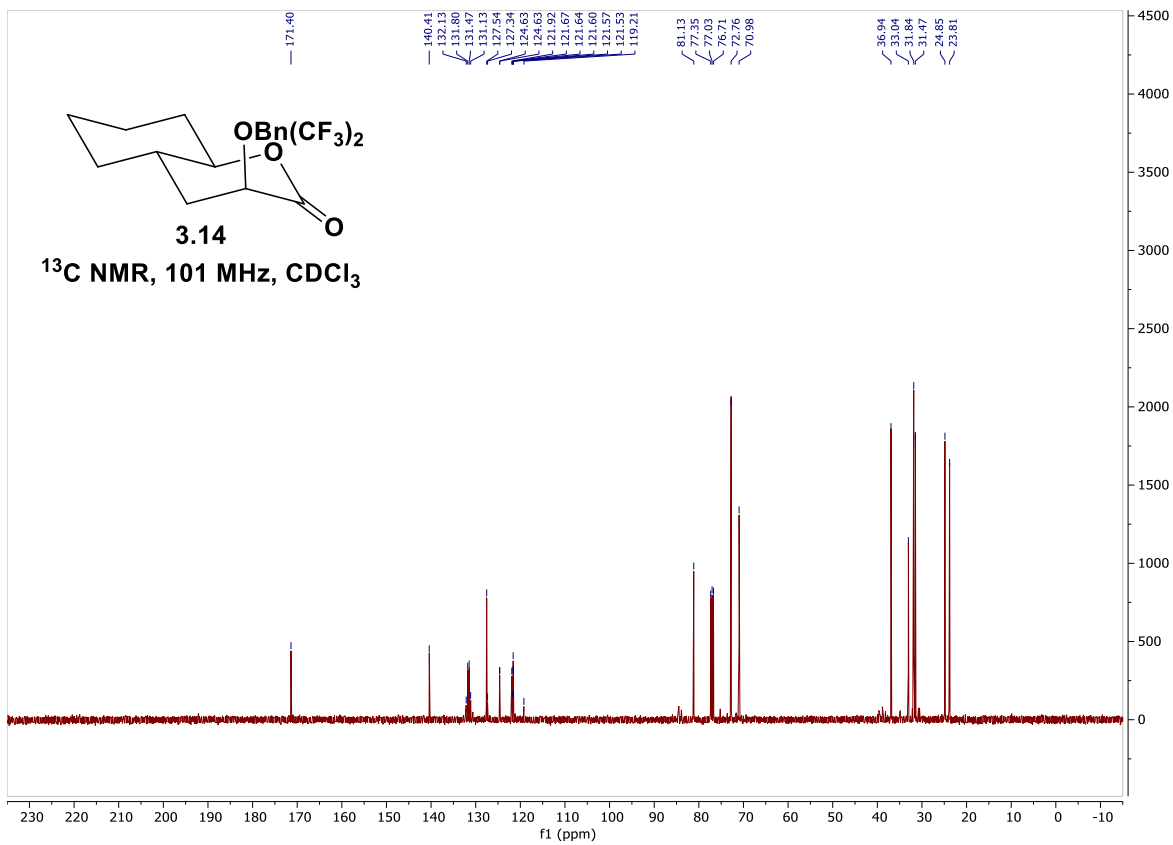


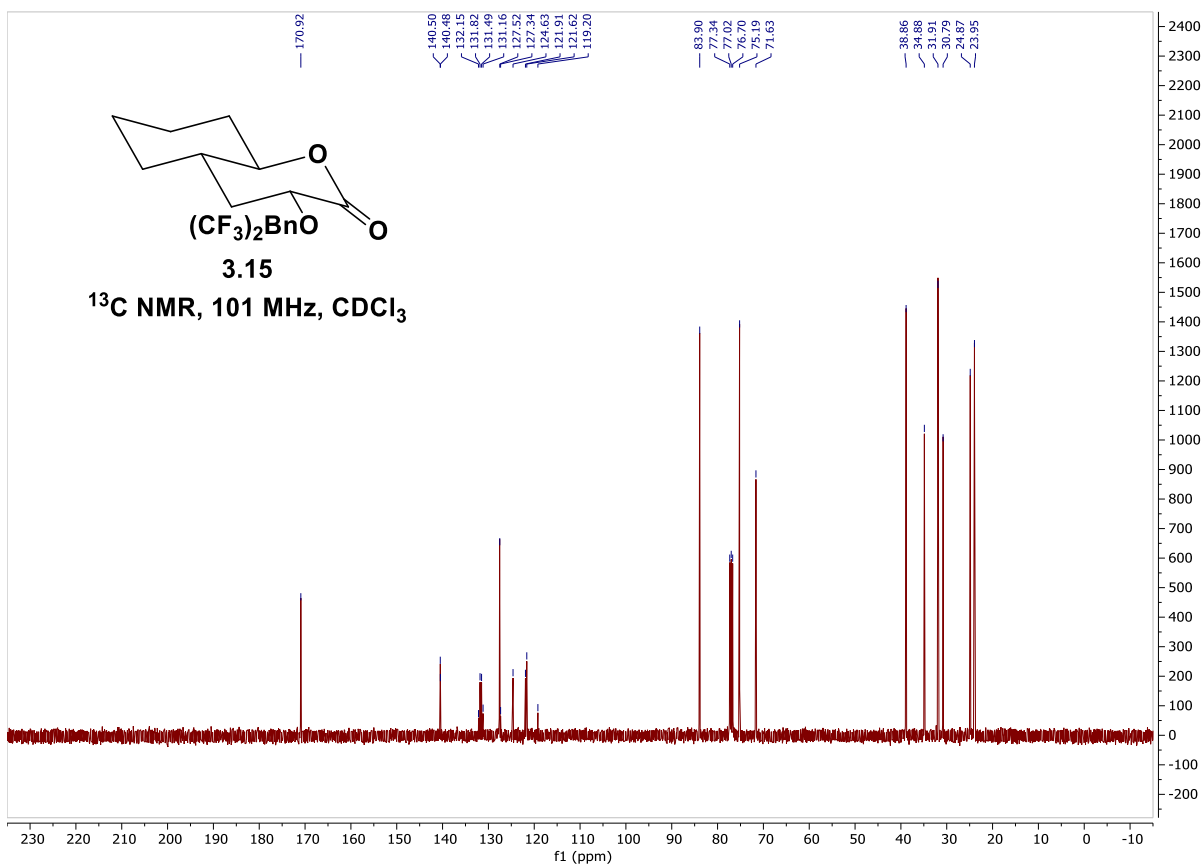
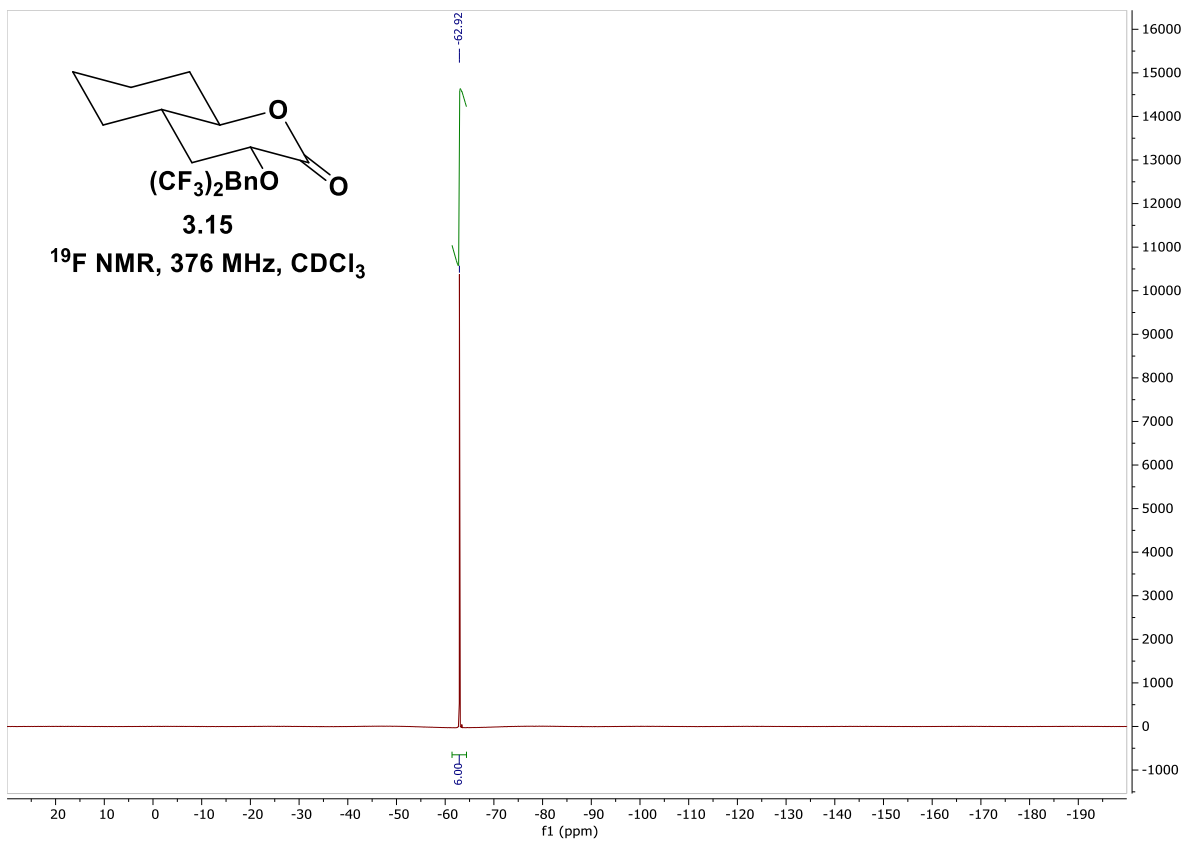
# Annexe G Données spectrales du chapitre 3

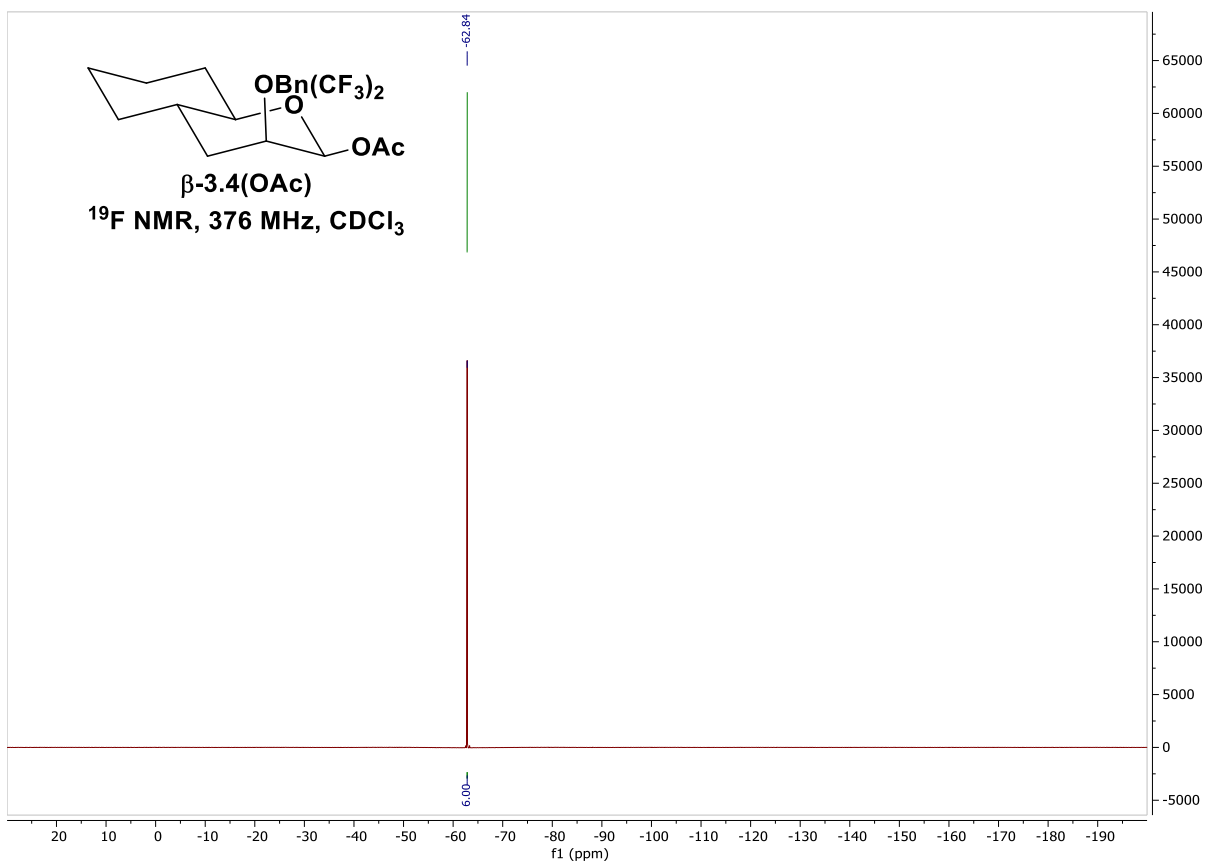
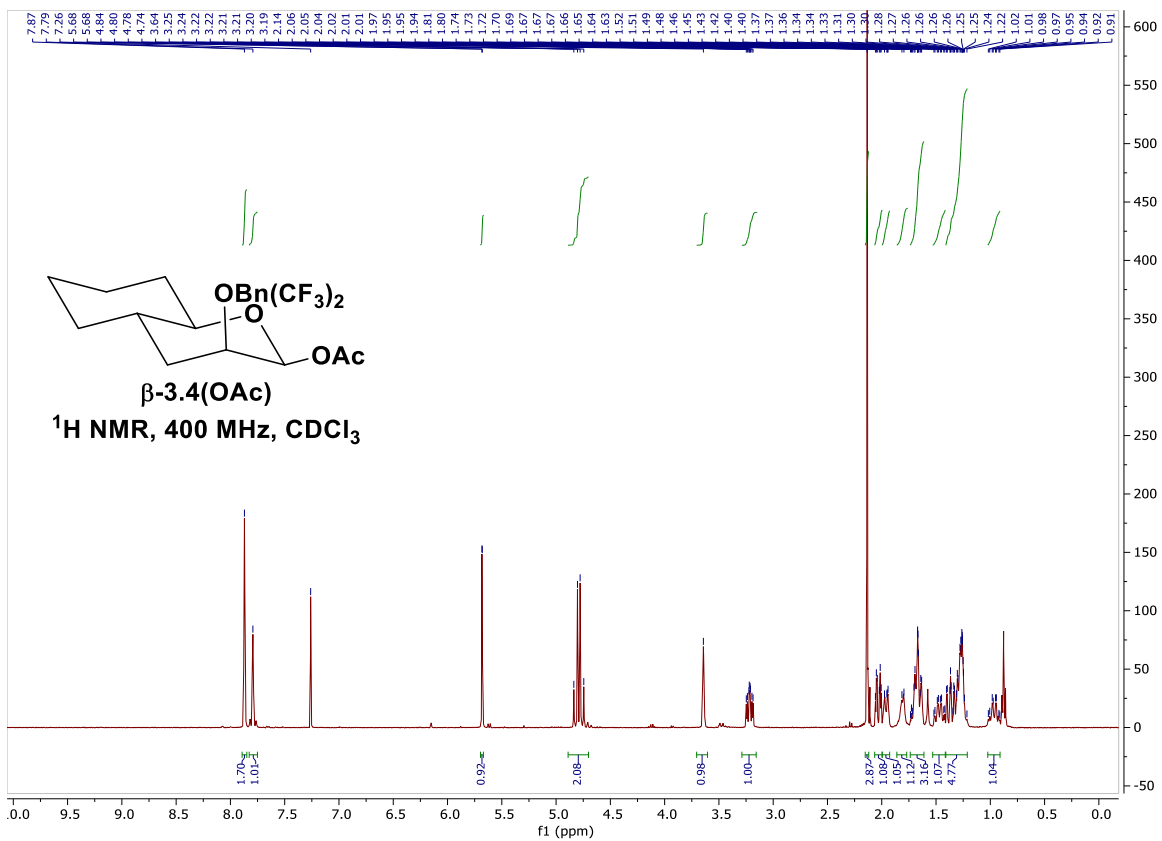
## G.1 Spectres RMN des composés caractérisés



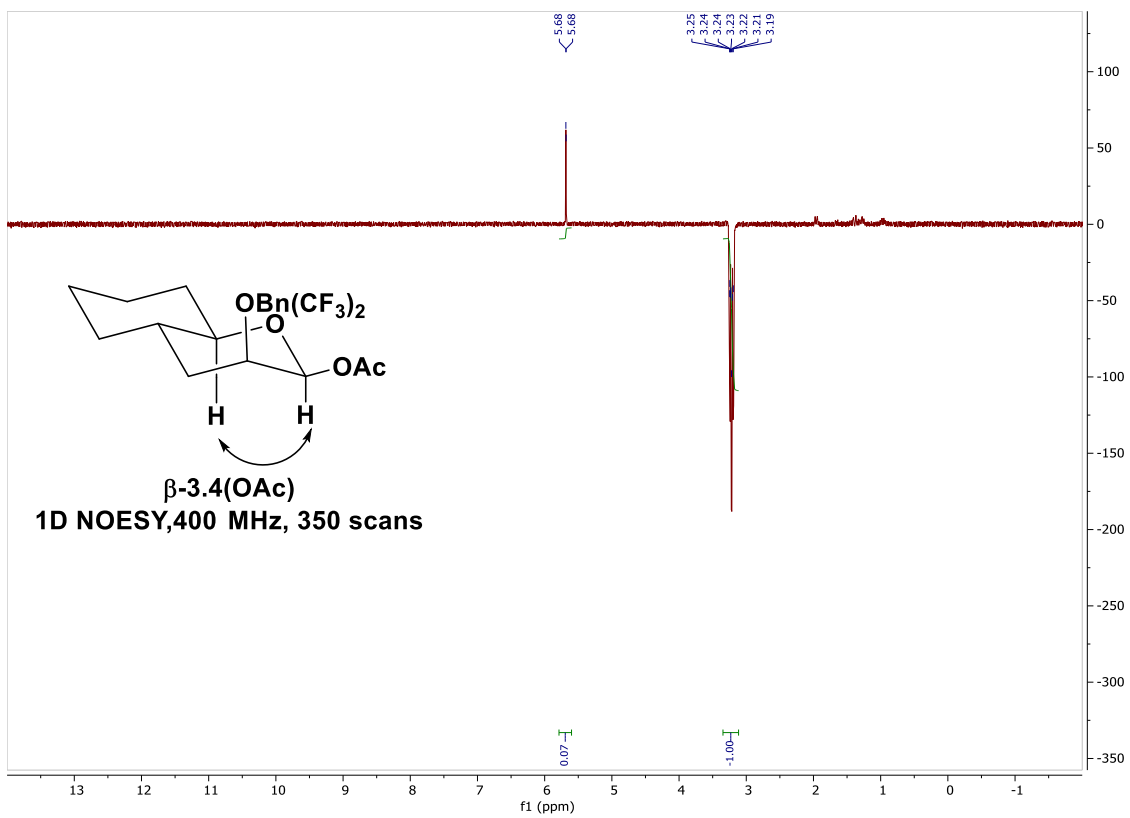
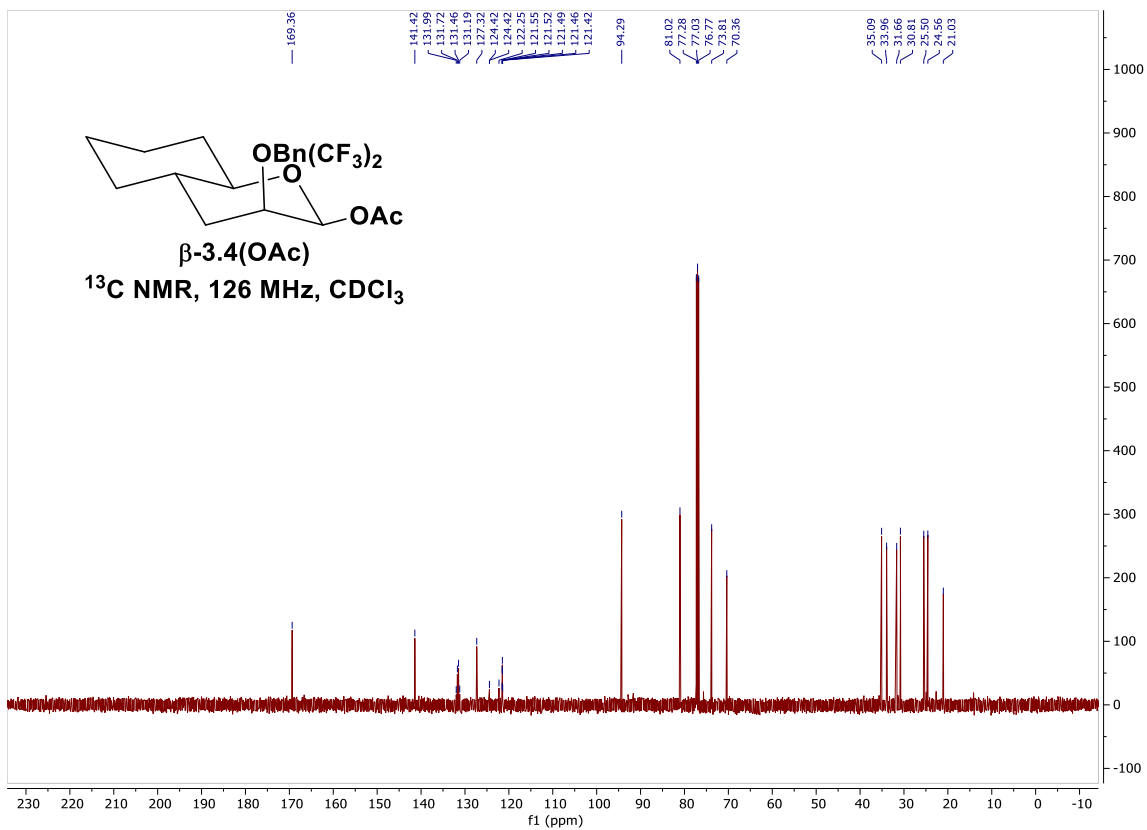


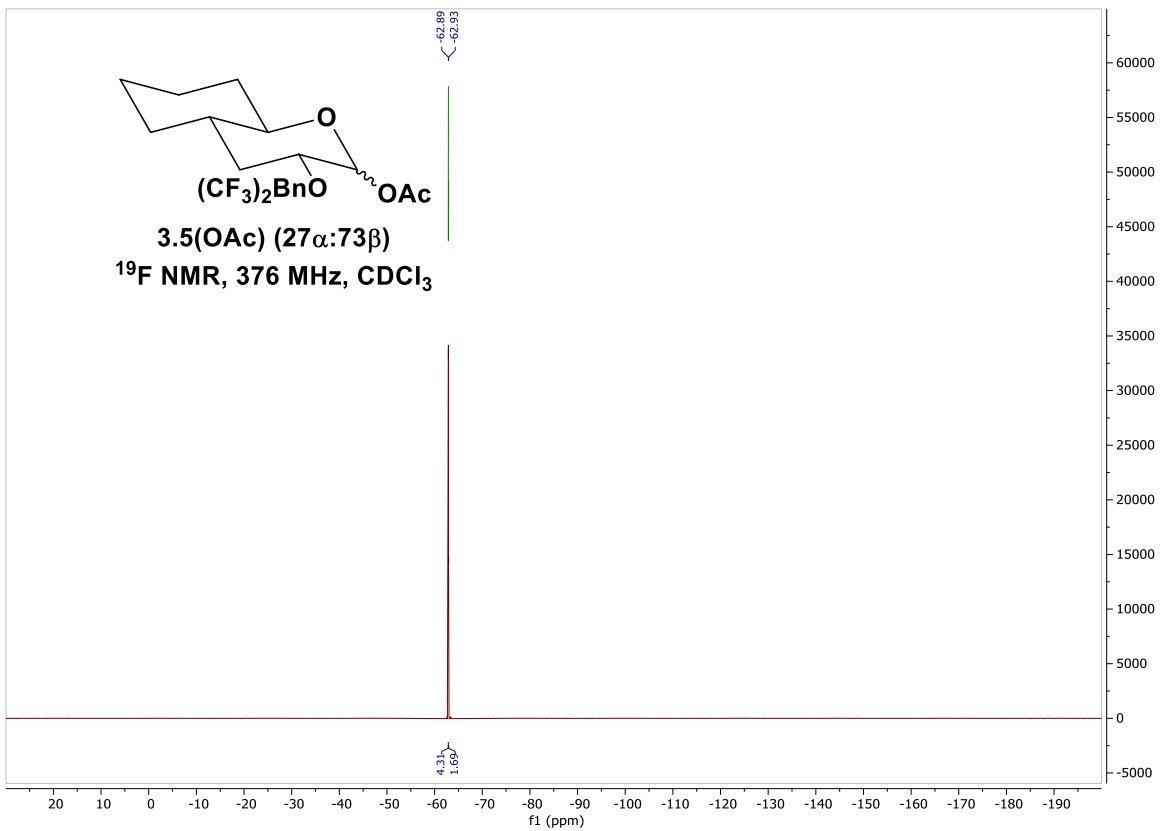
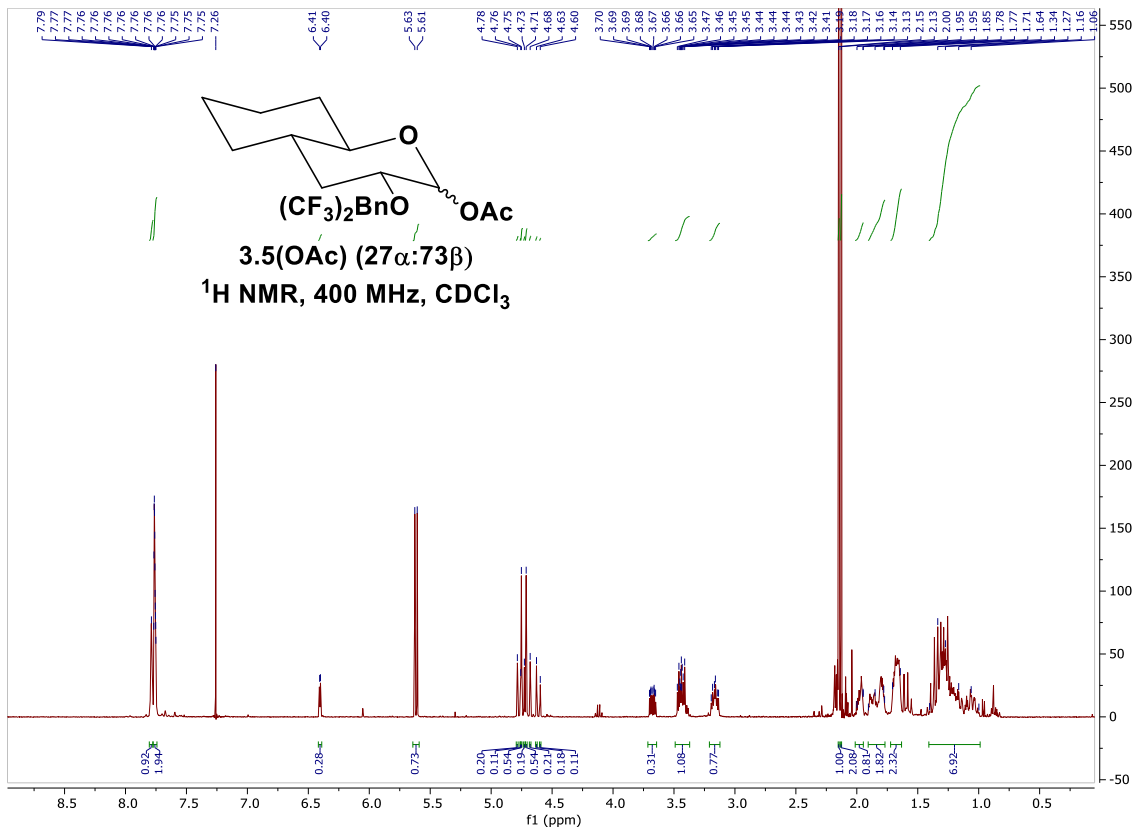


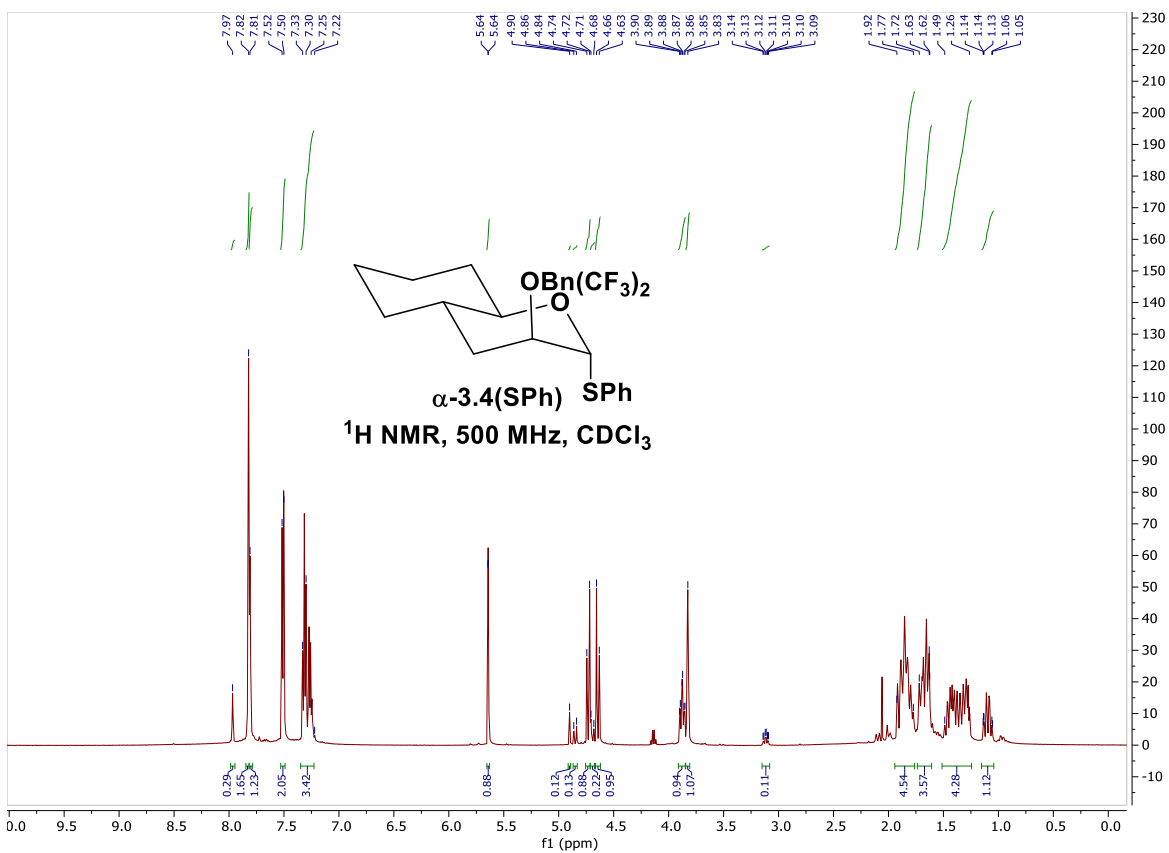
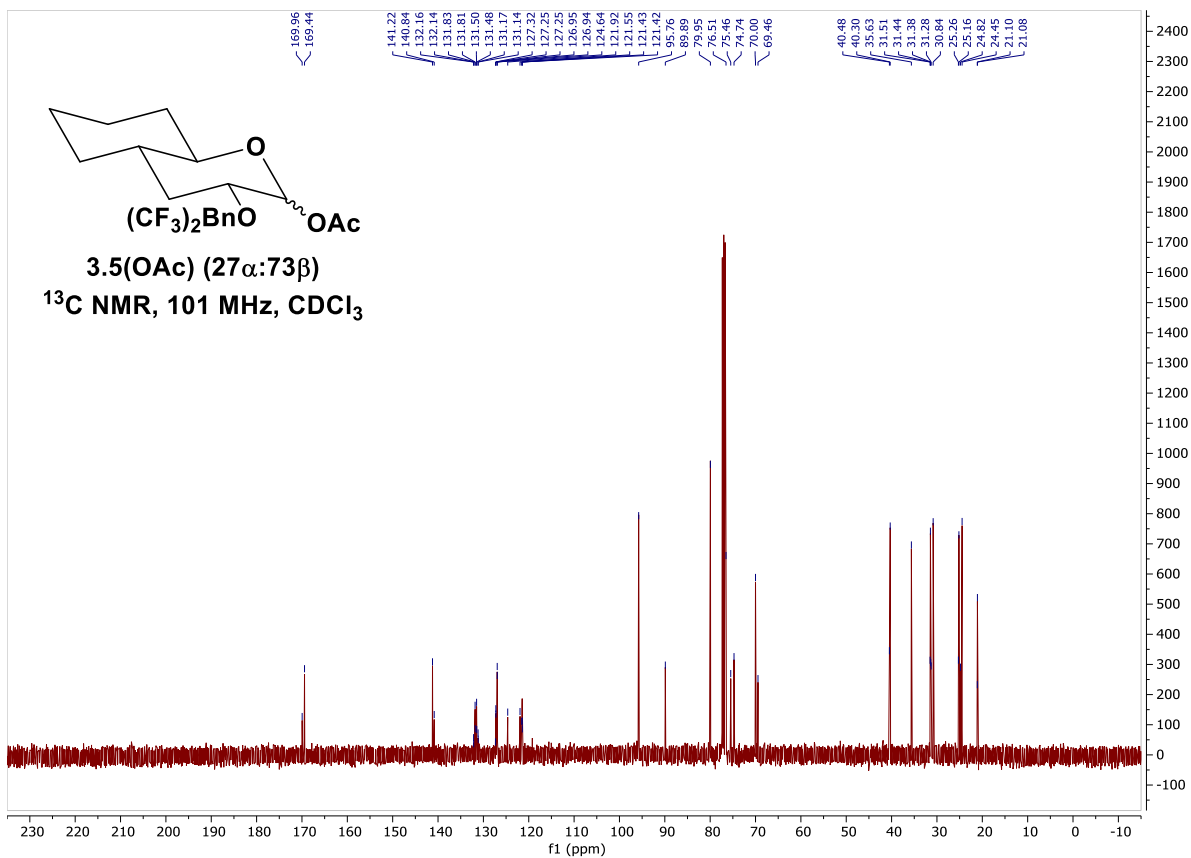


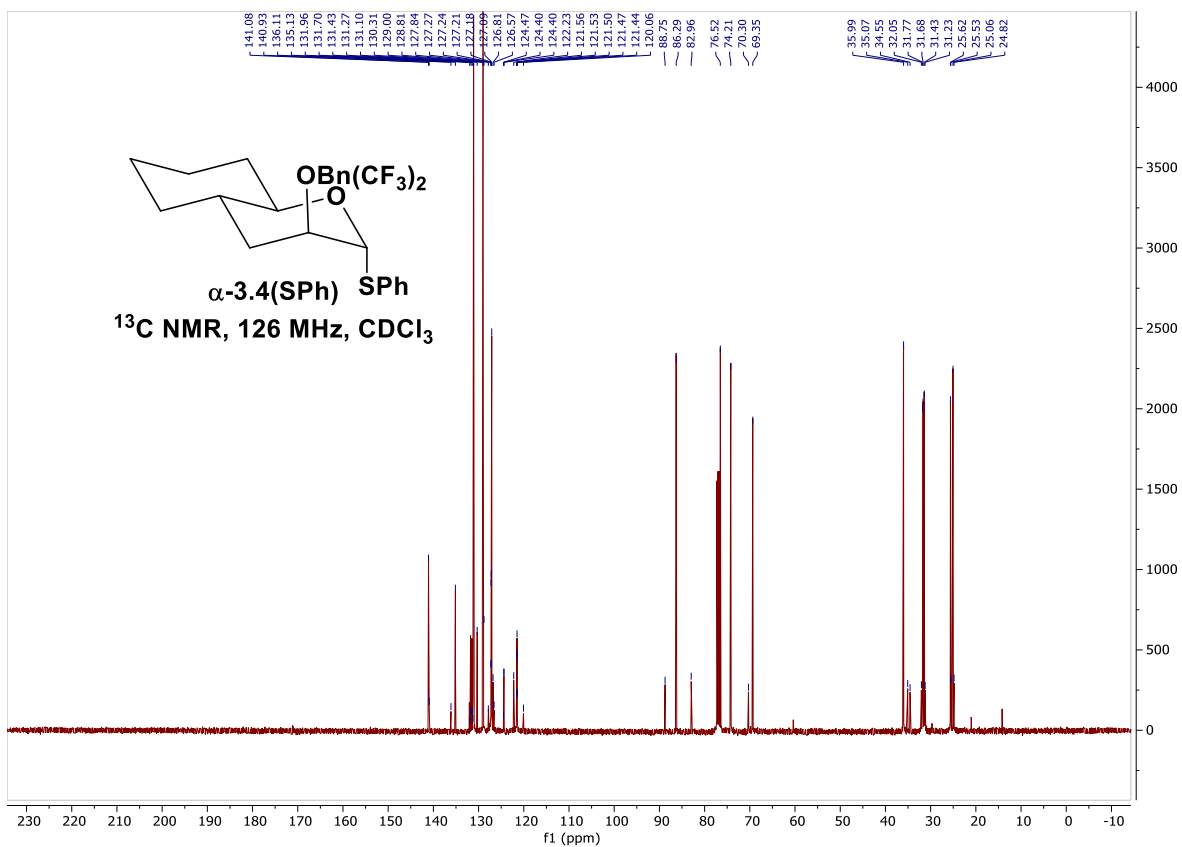
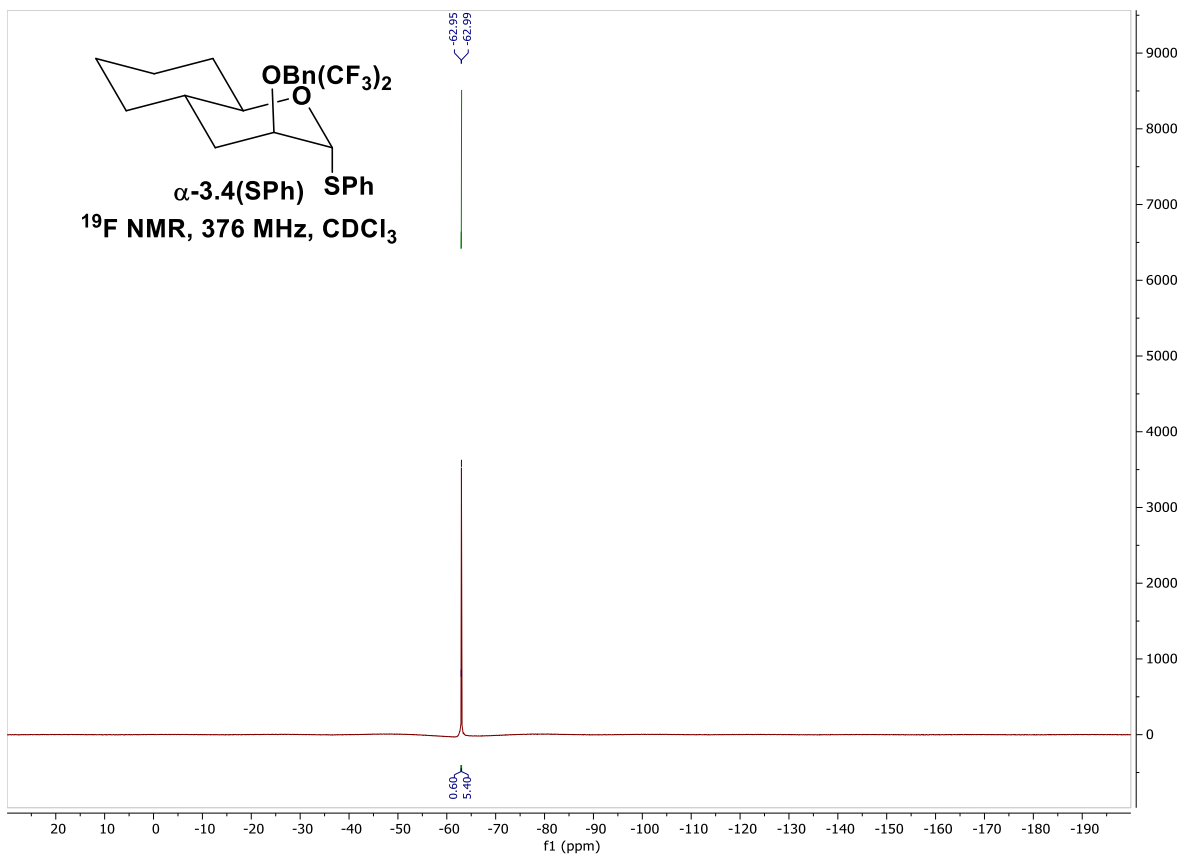


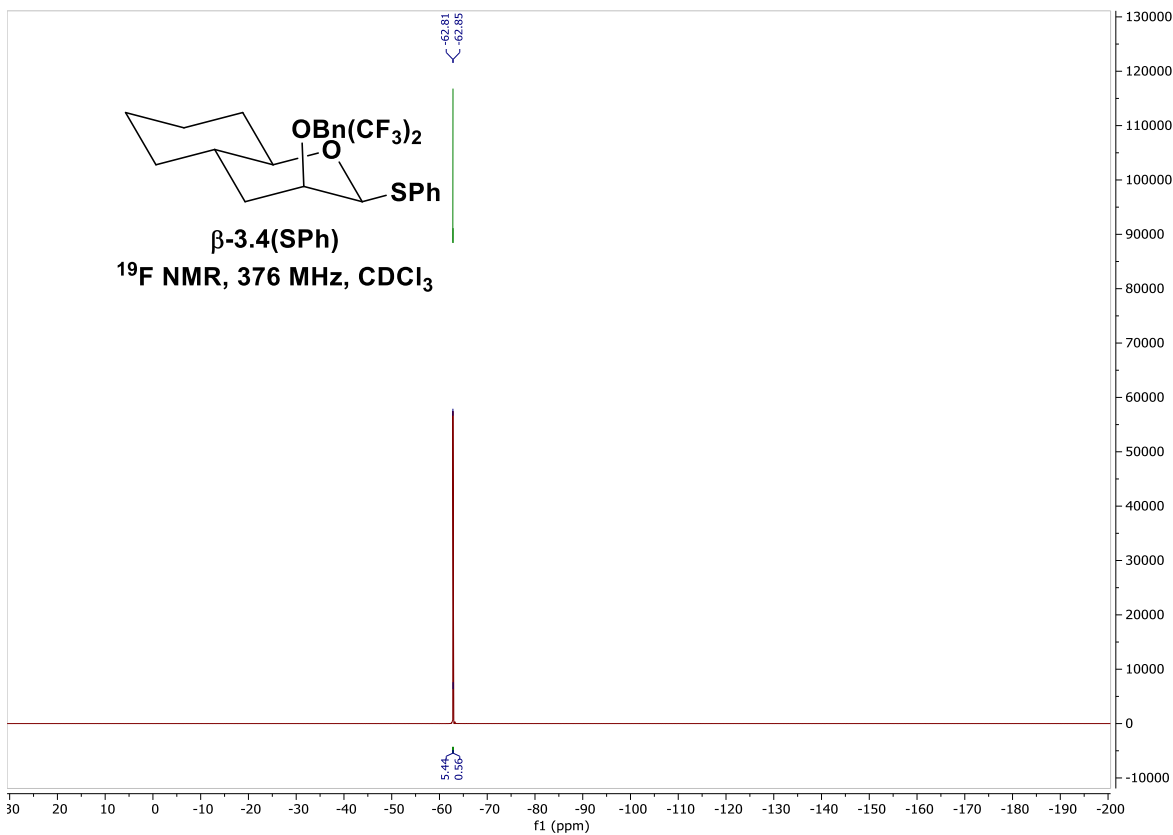
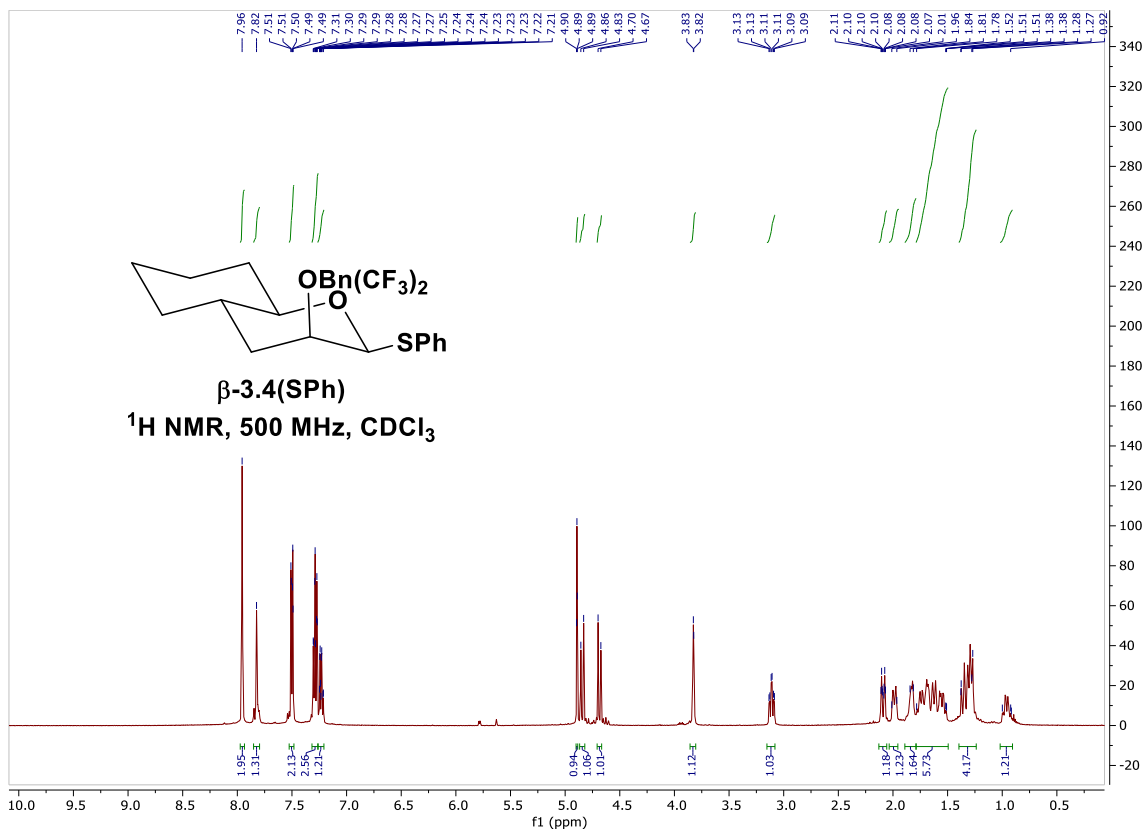




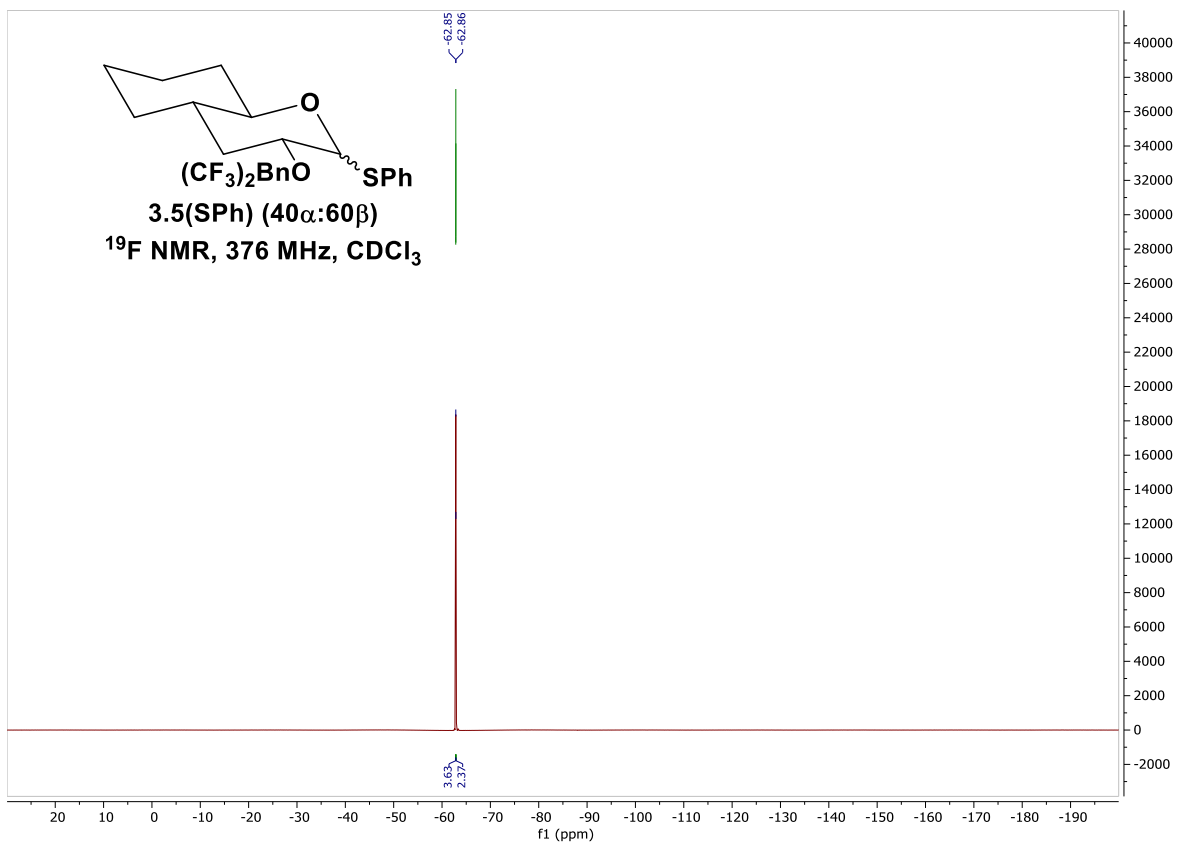
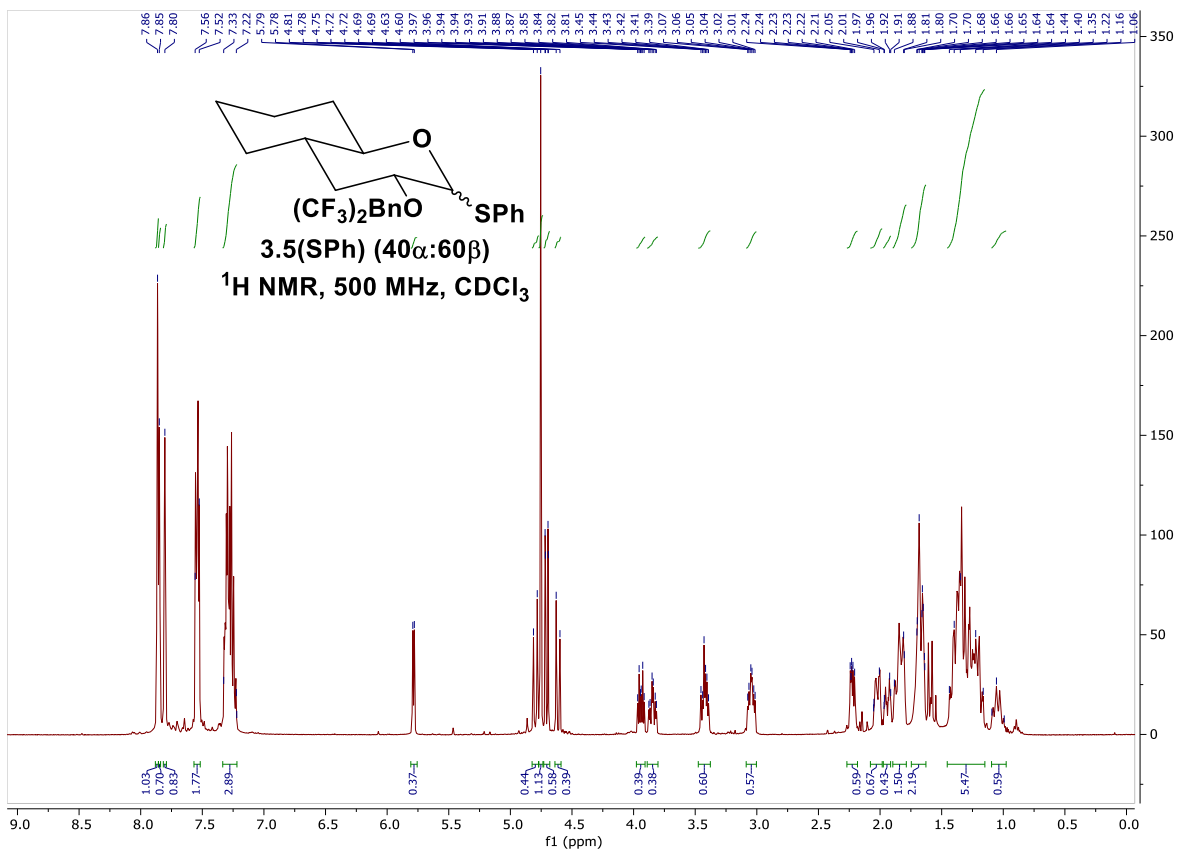


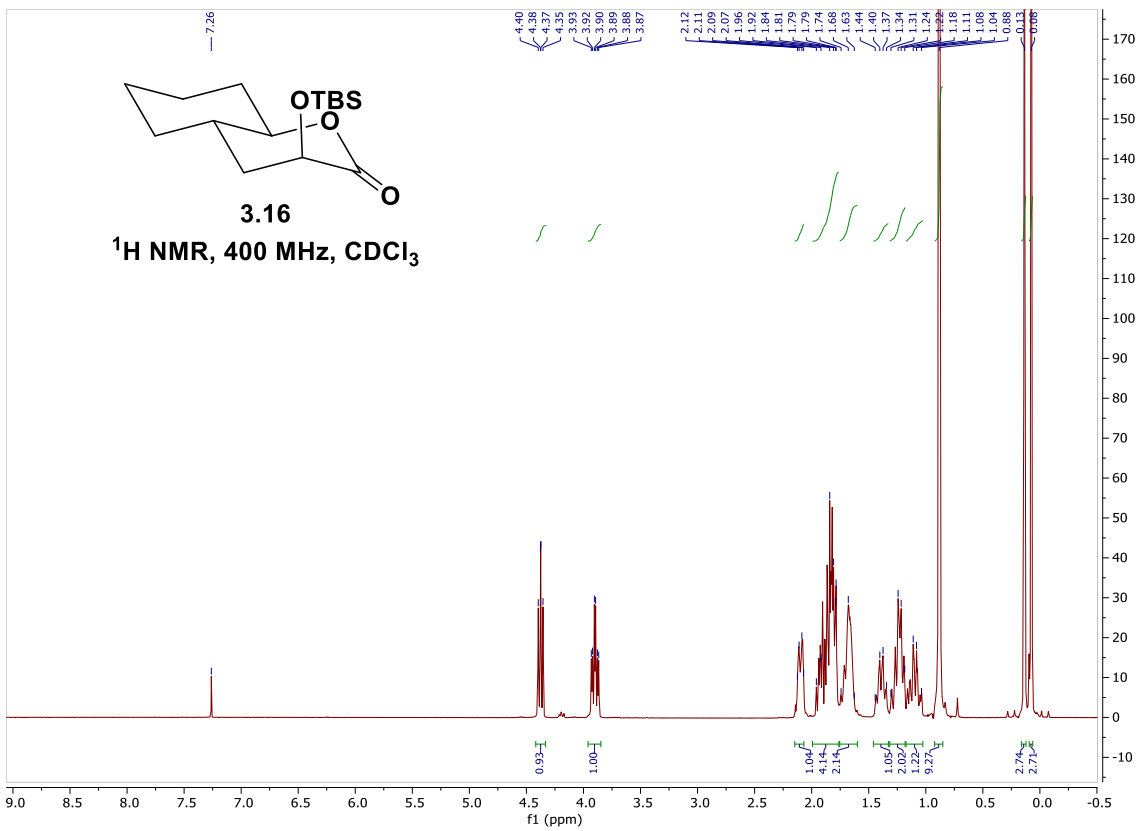
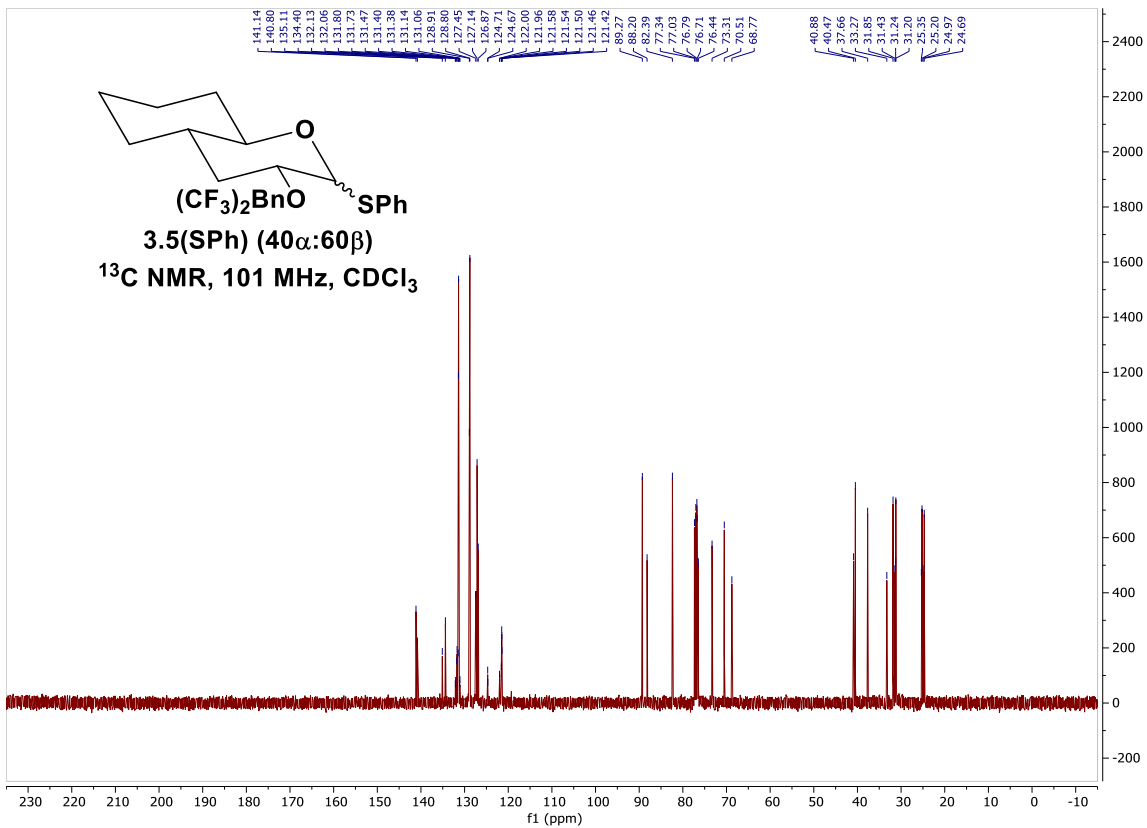




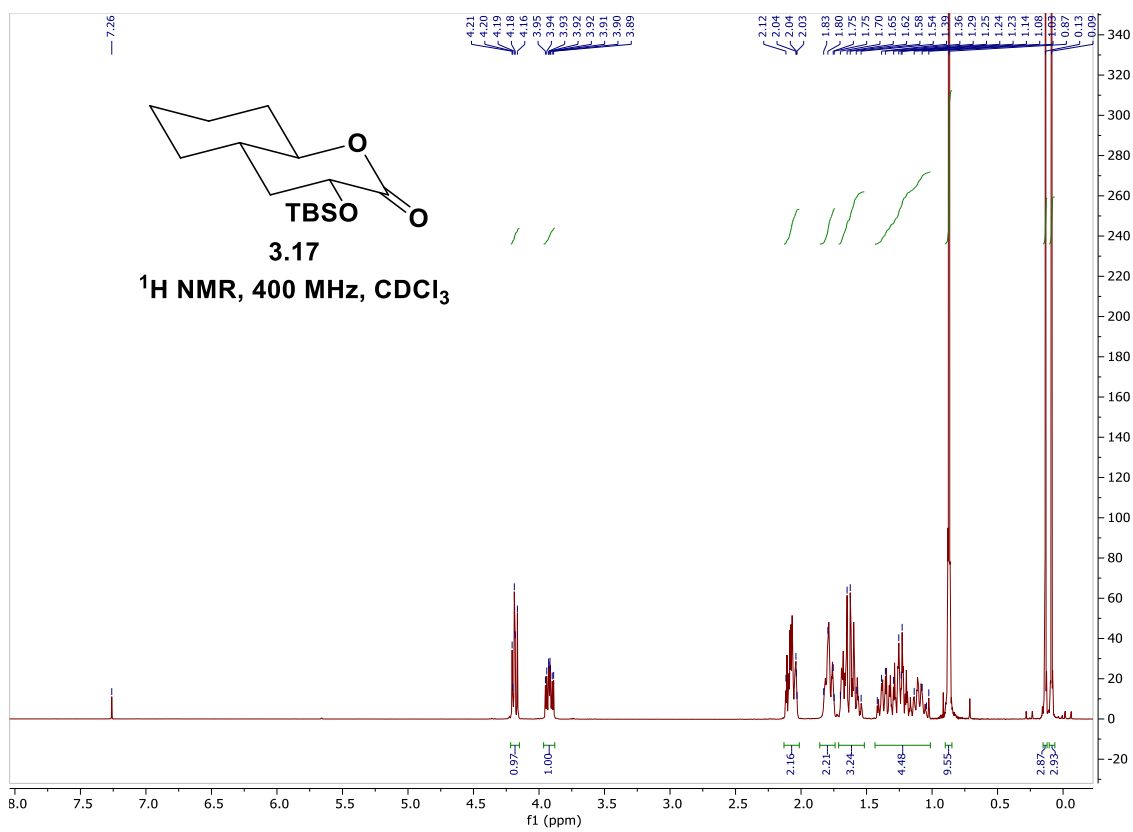
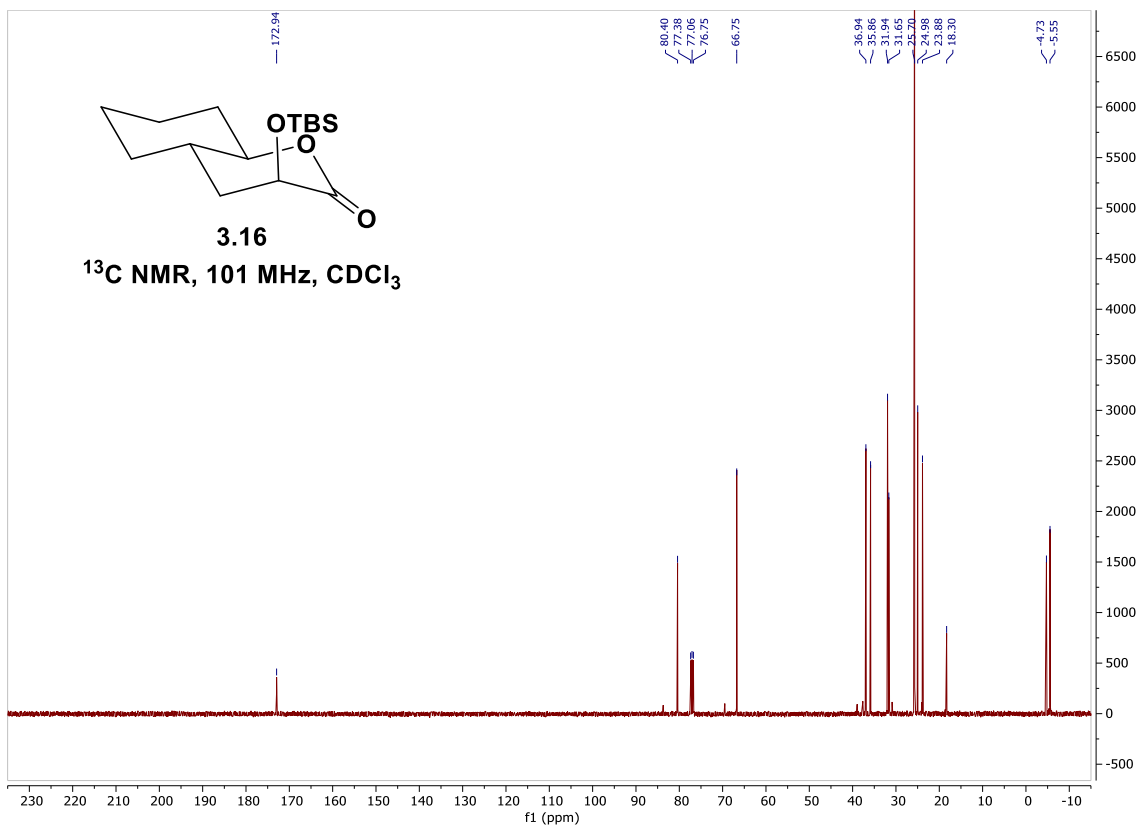


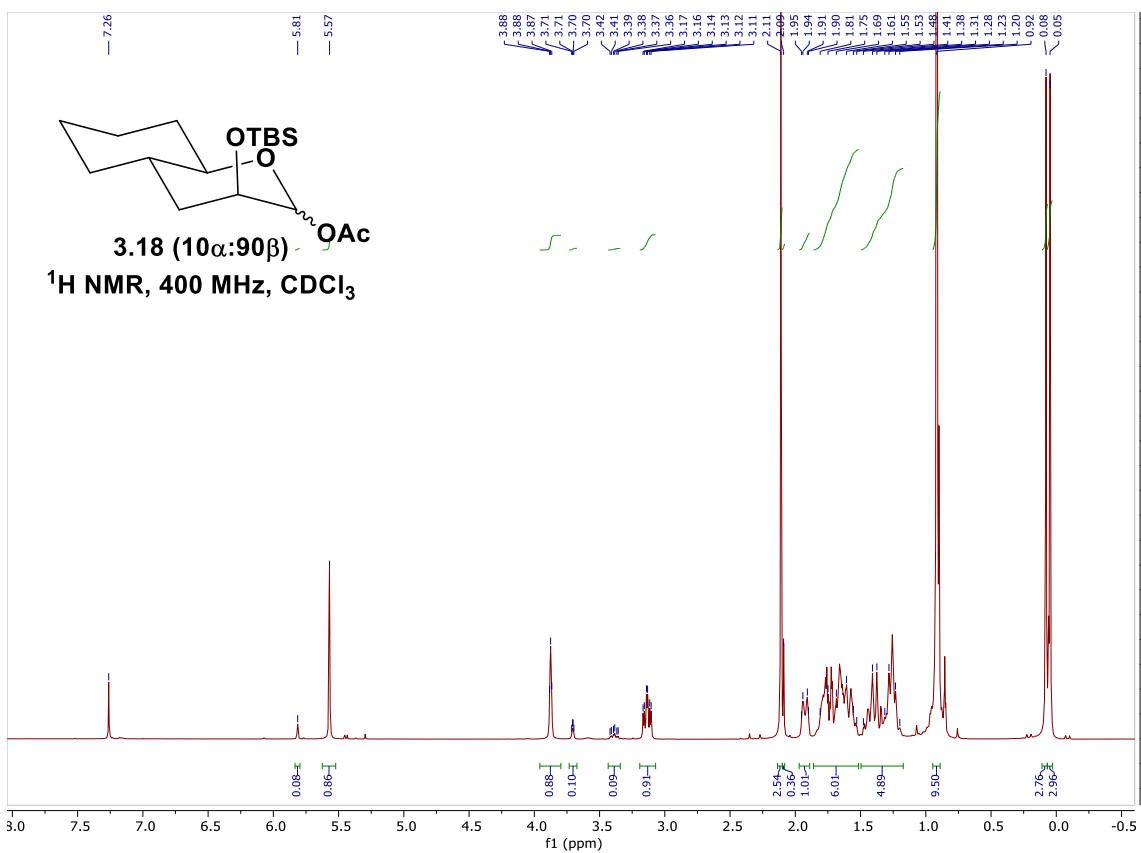
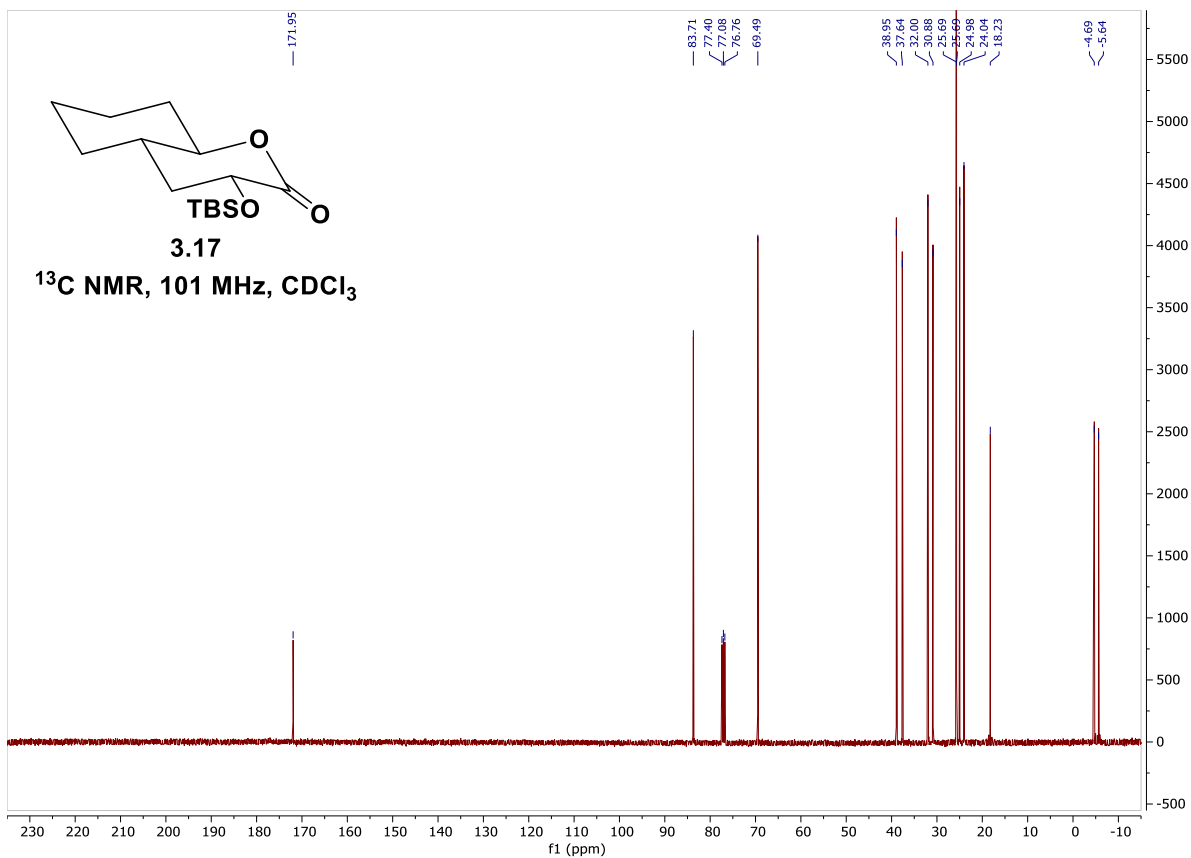




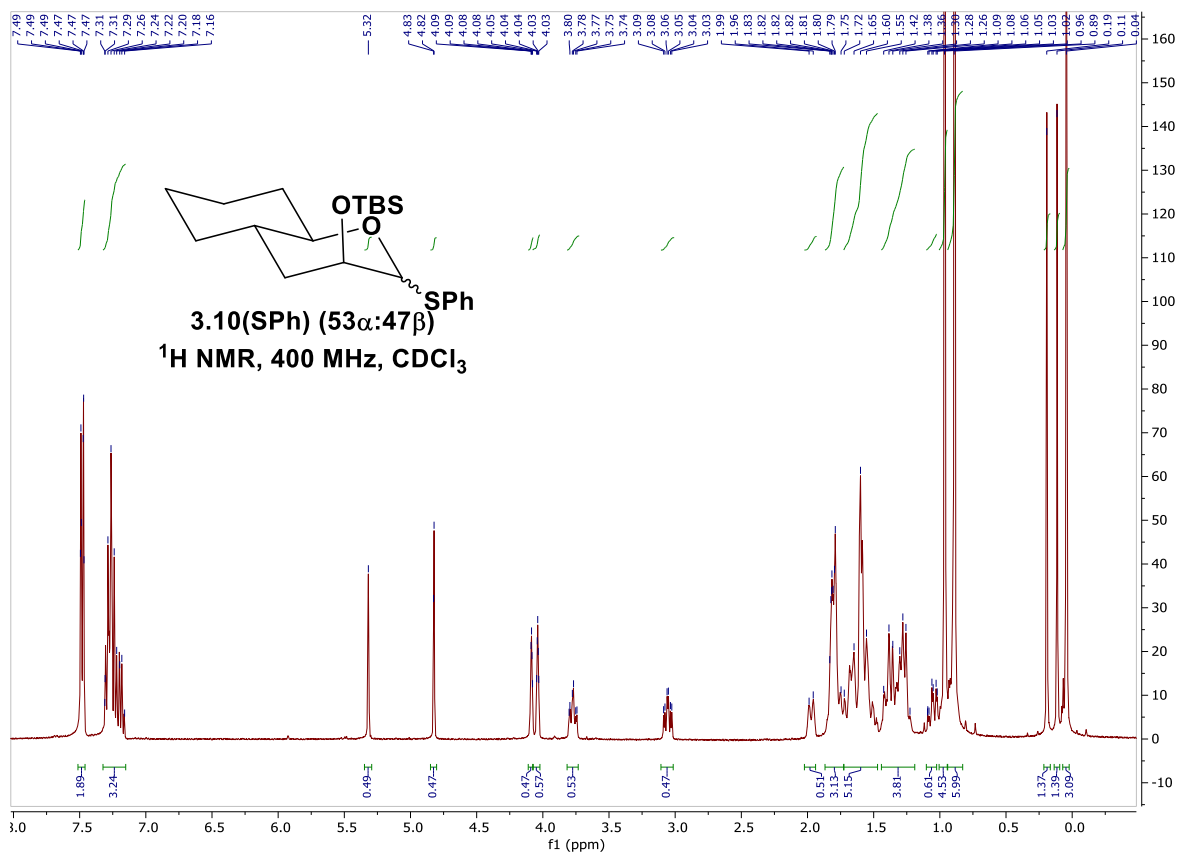
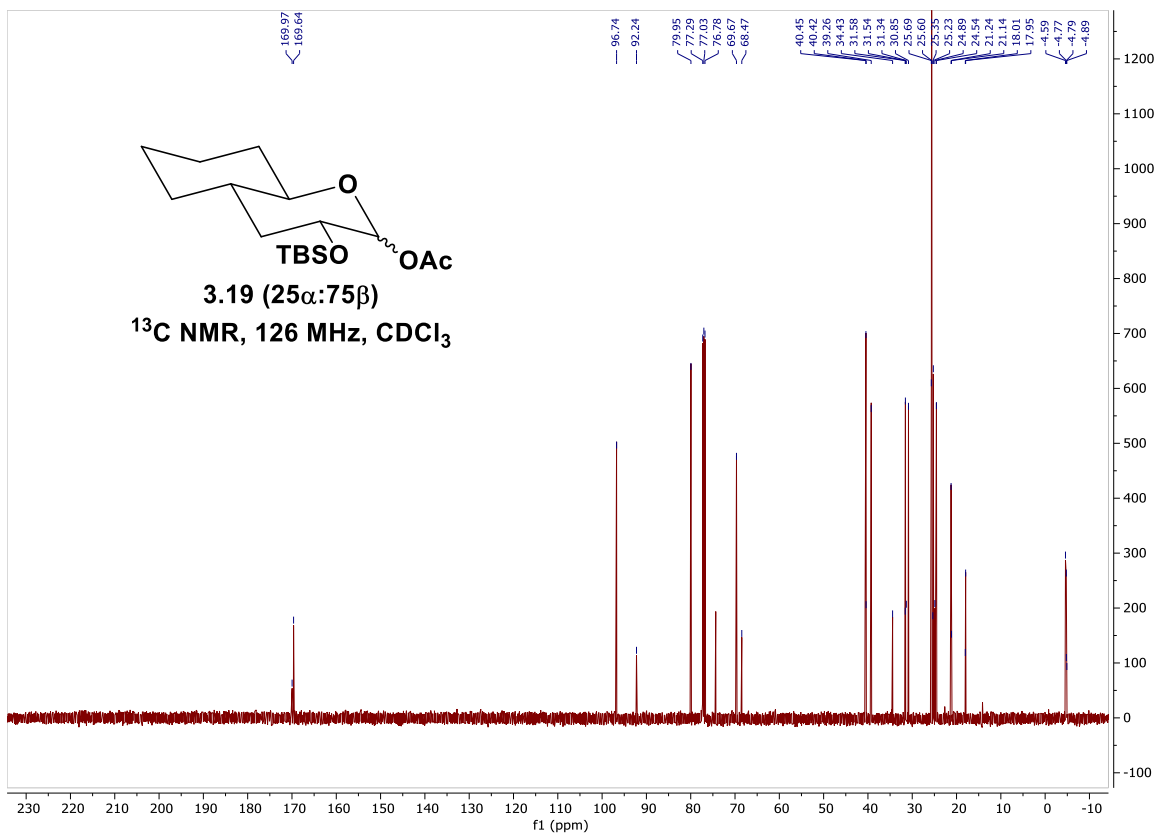


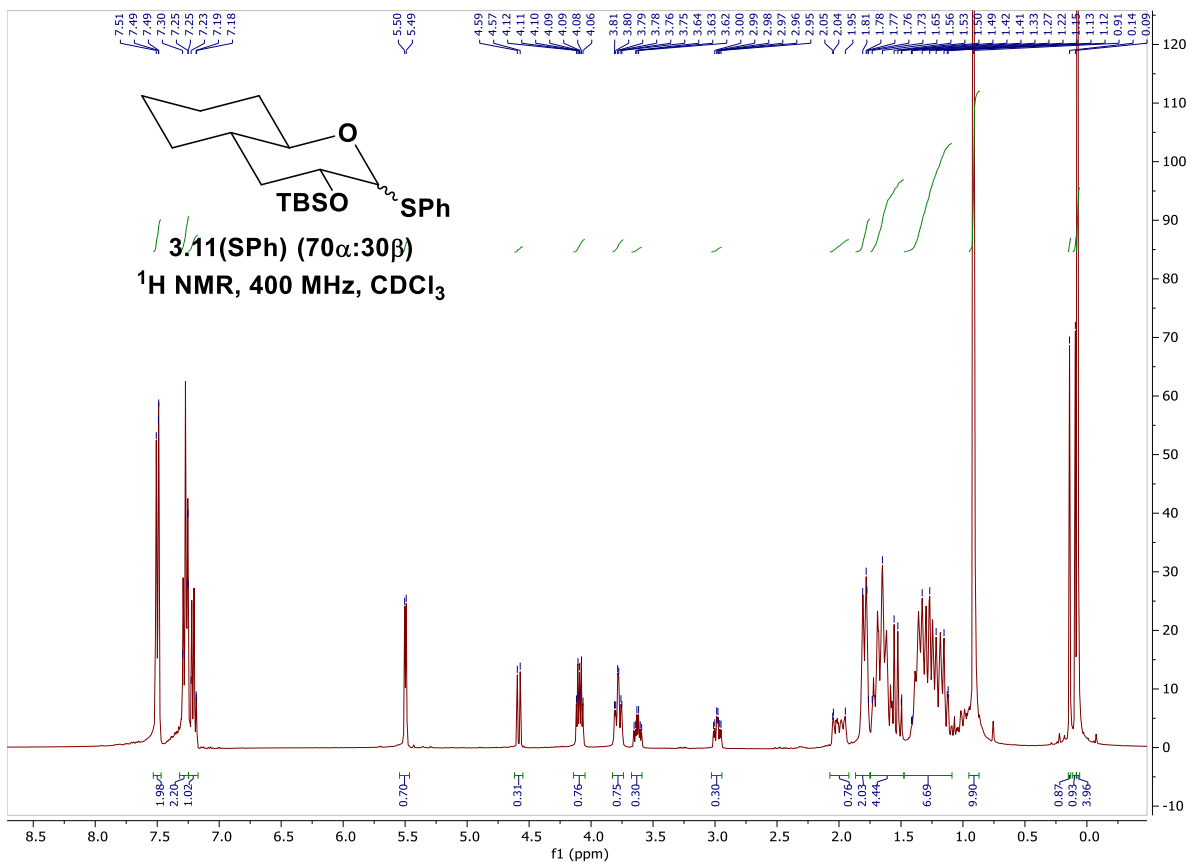
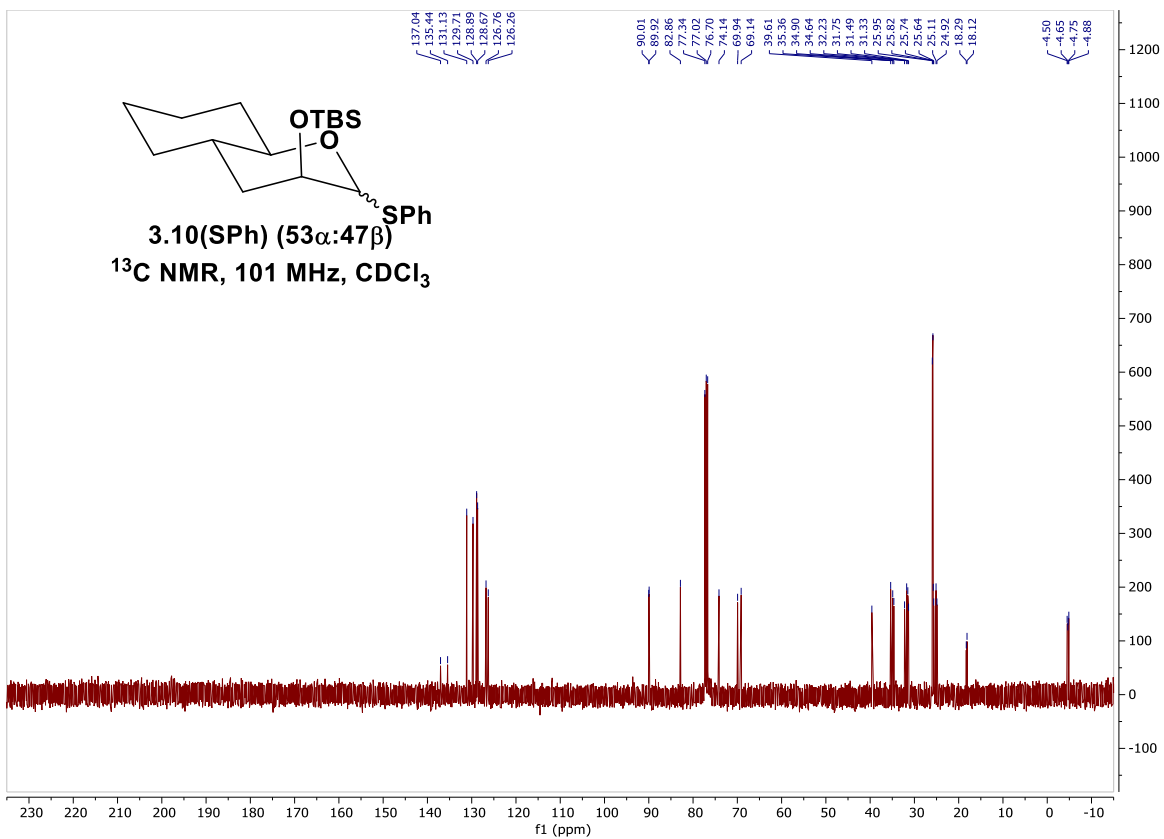


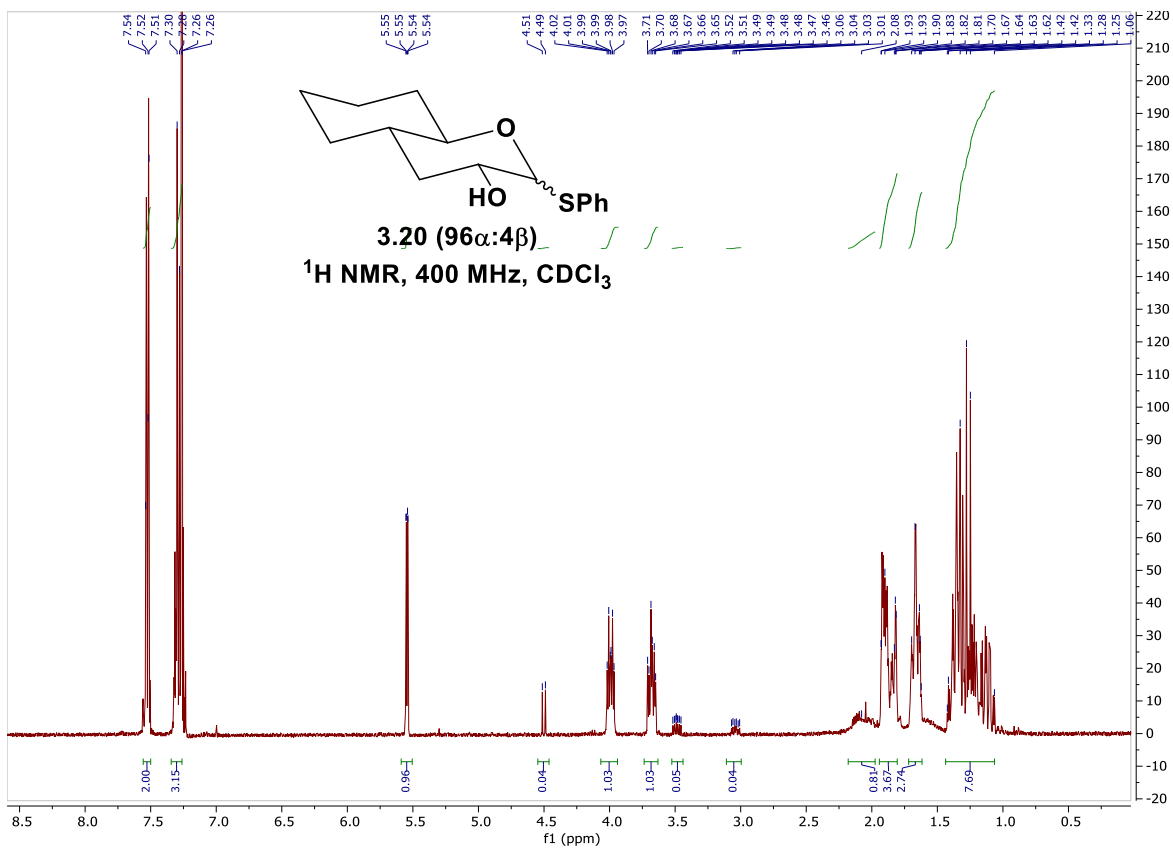
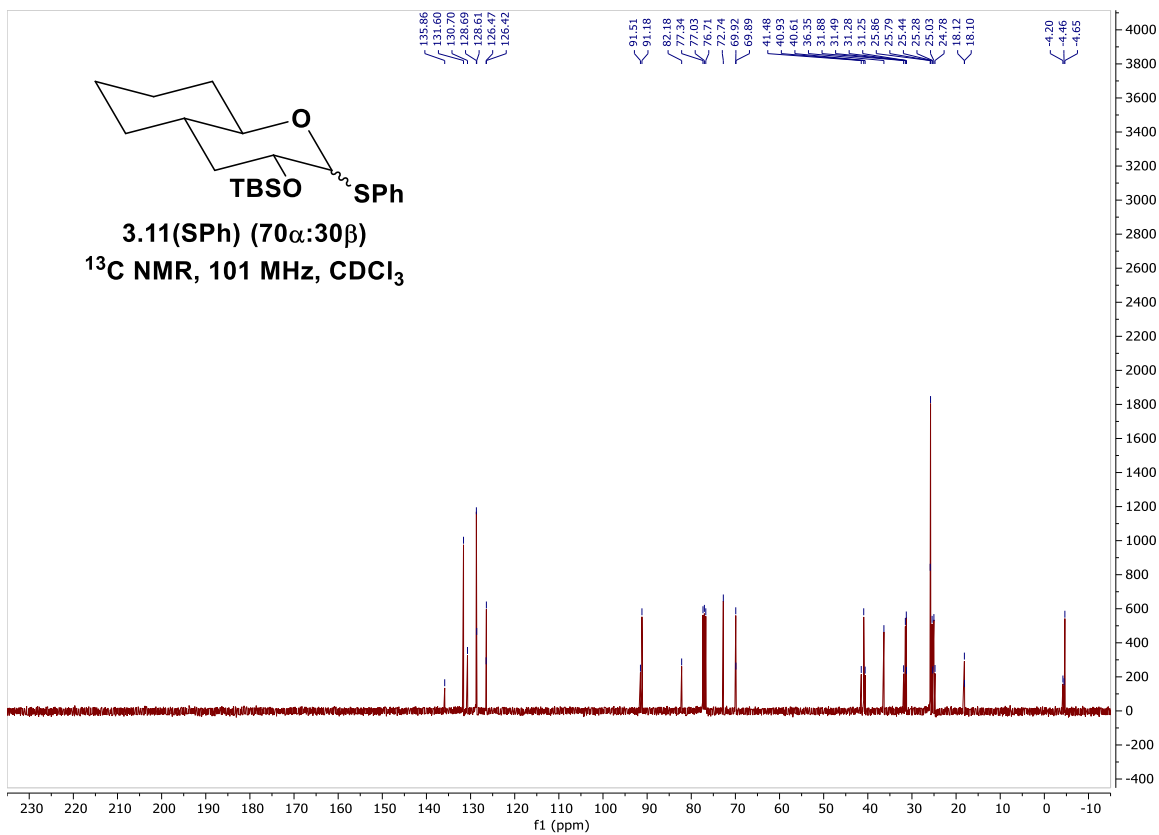


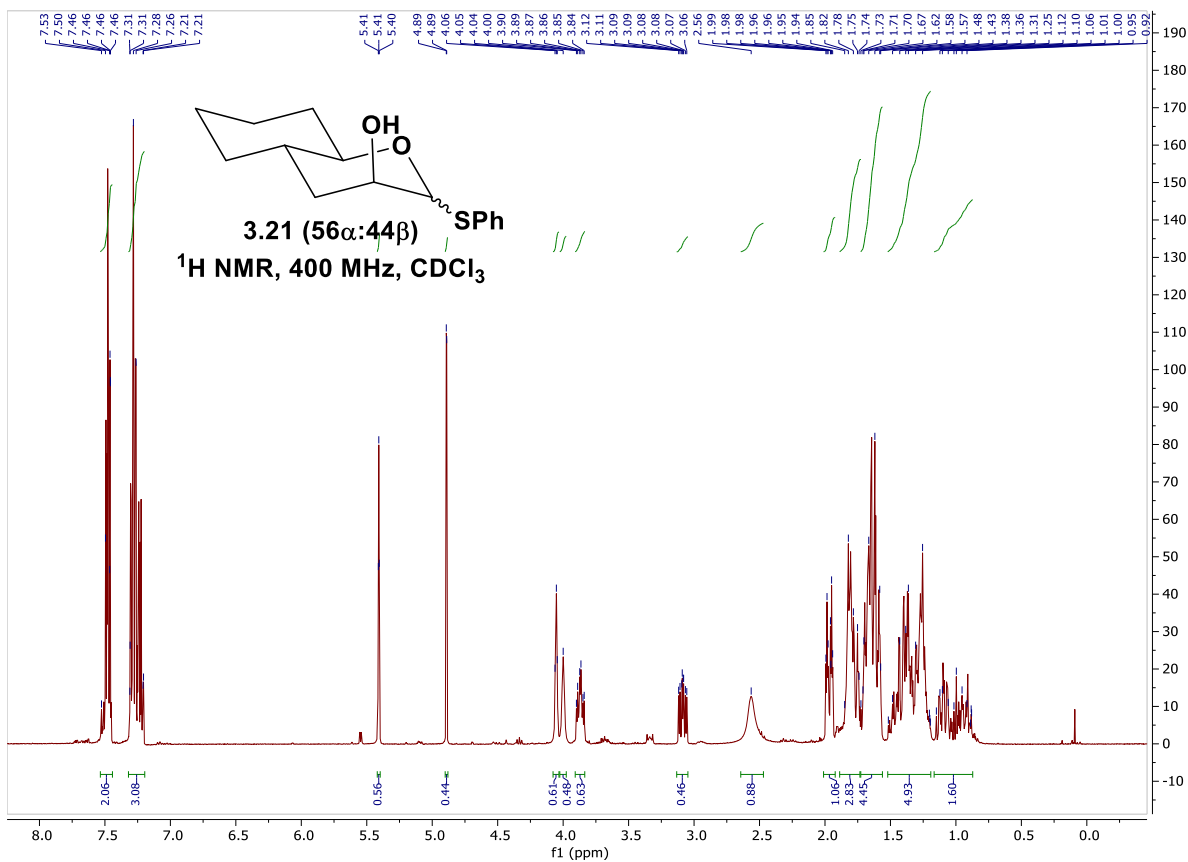
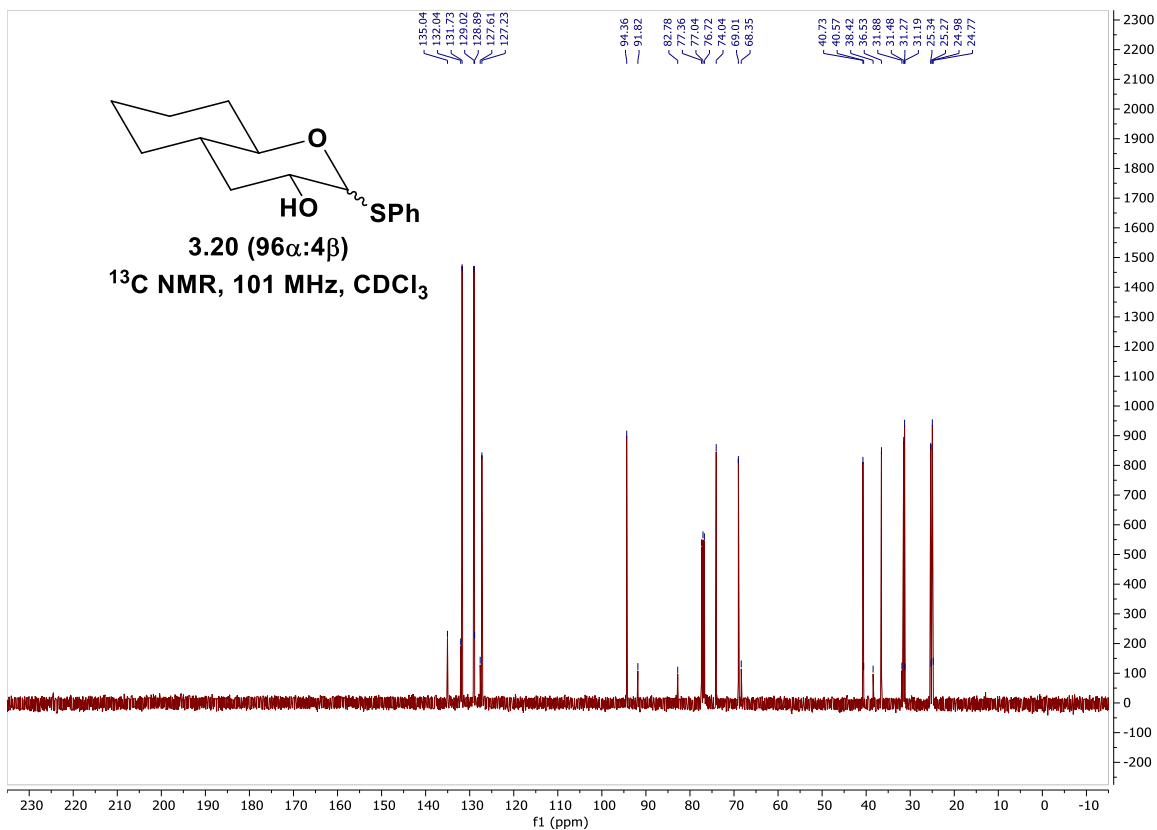


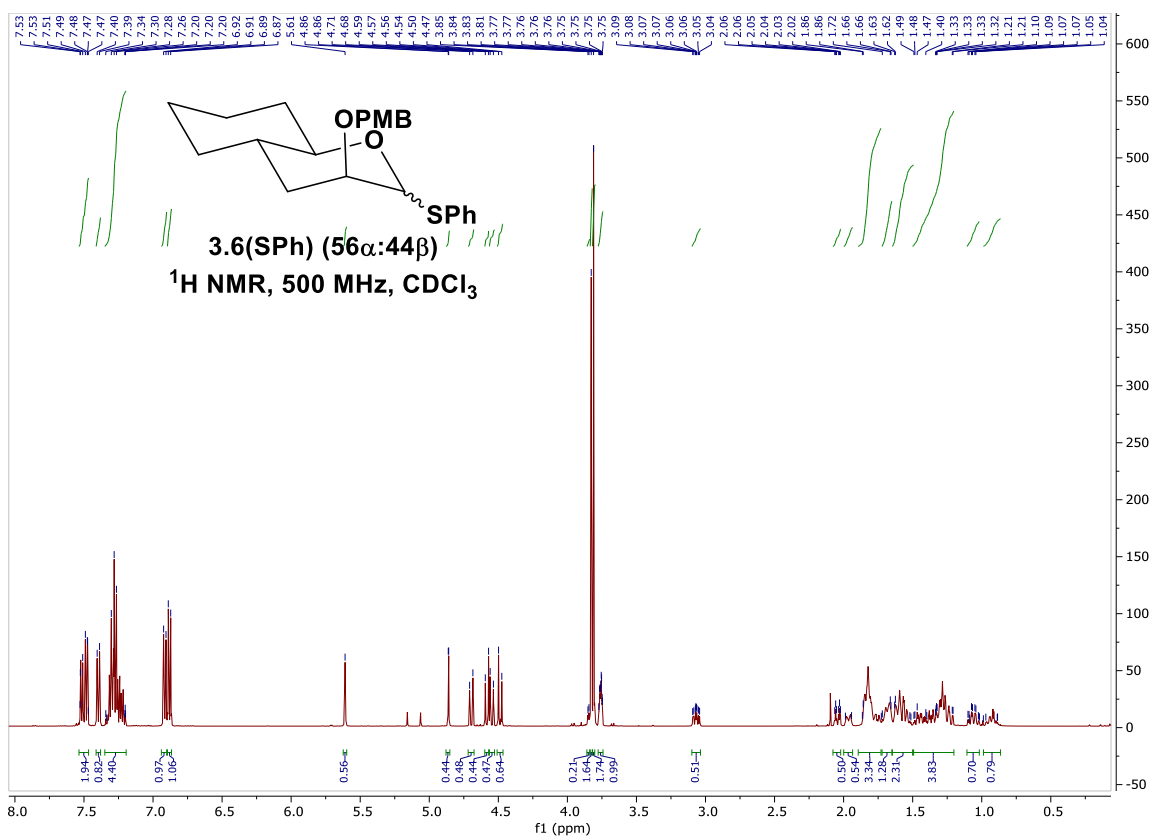
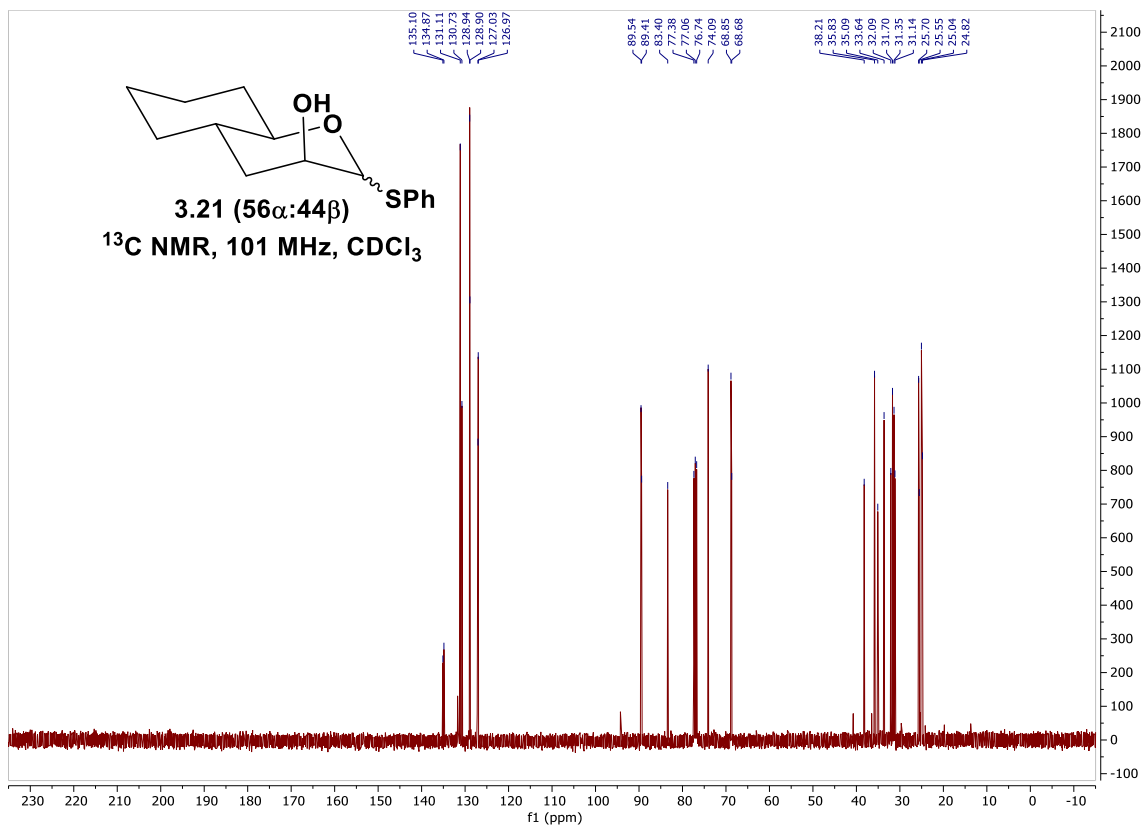




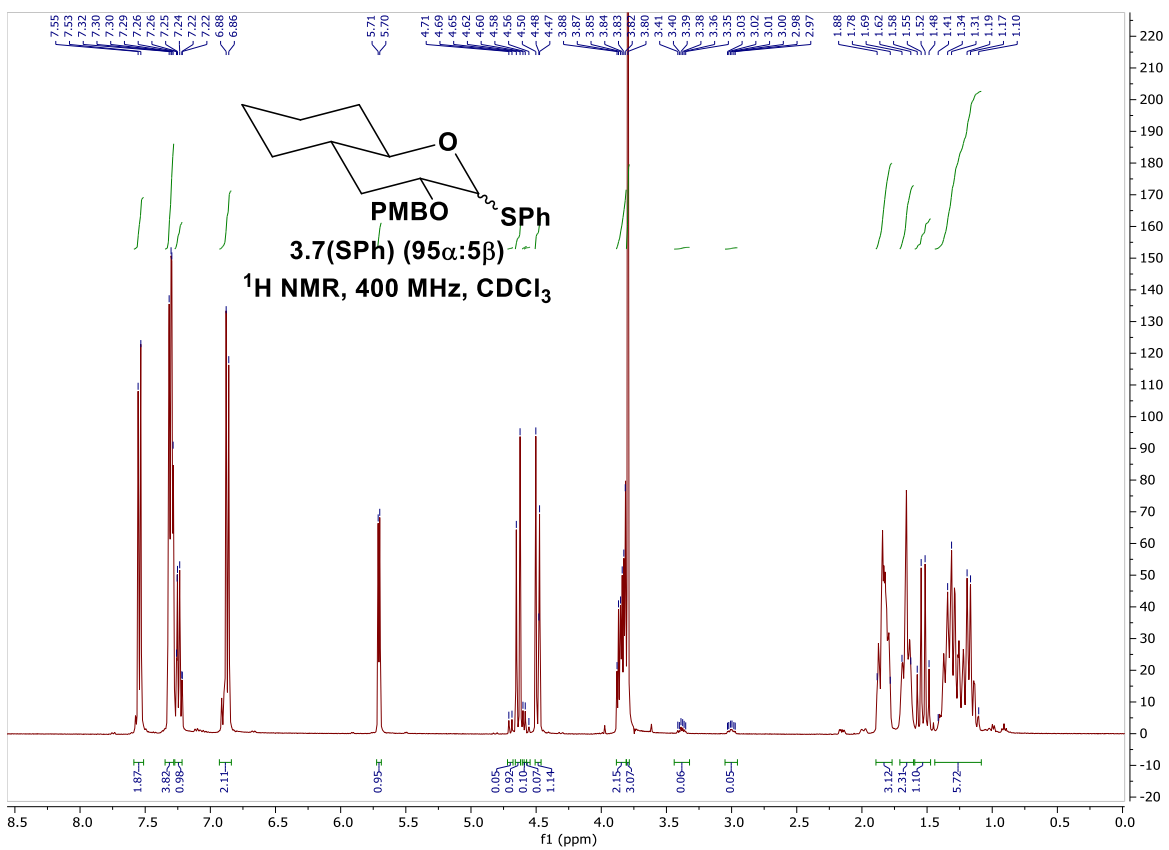
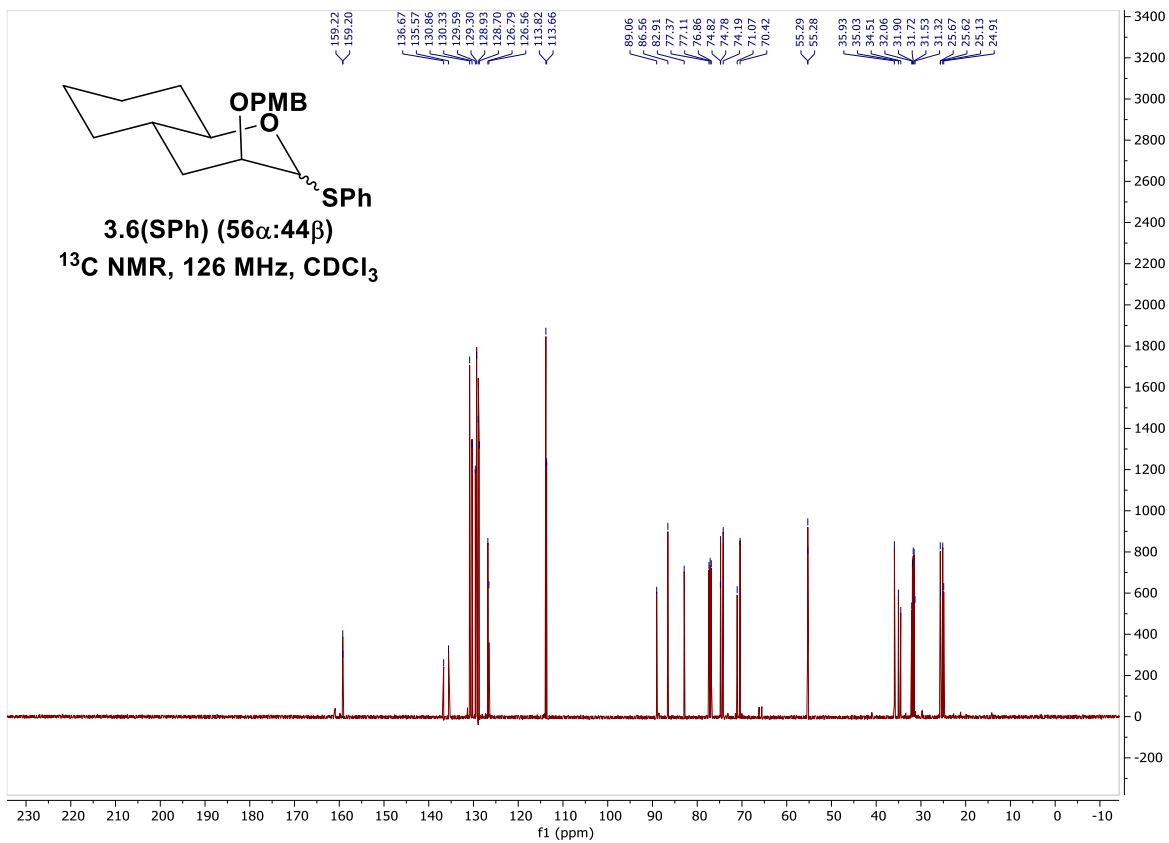


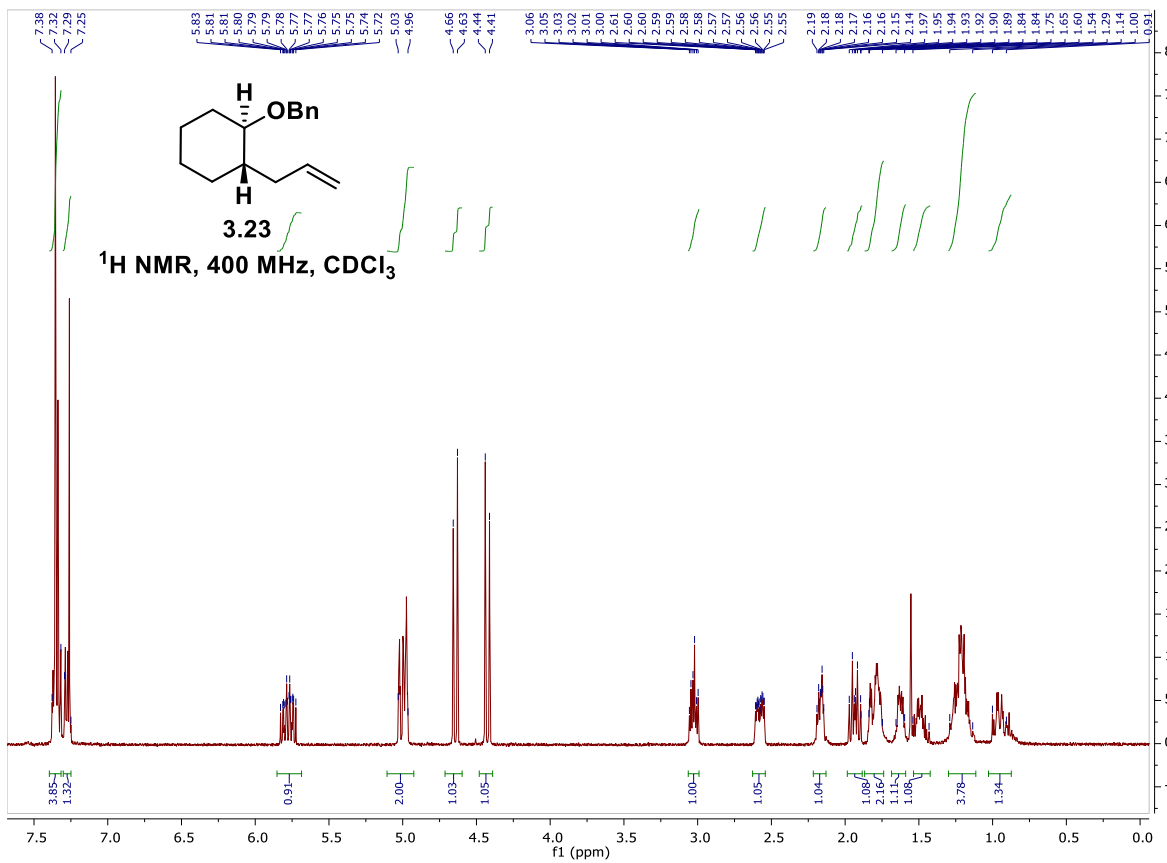
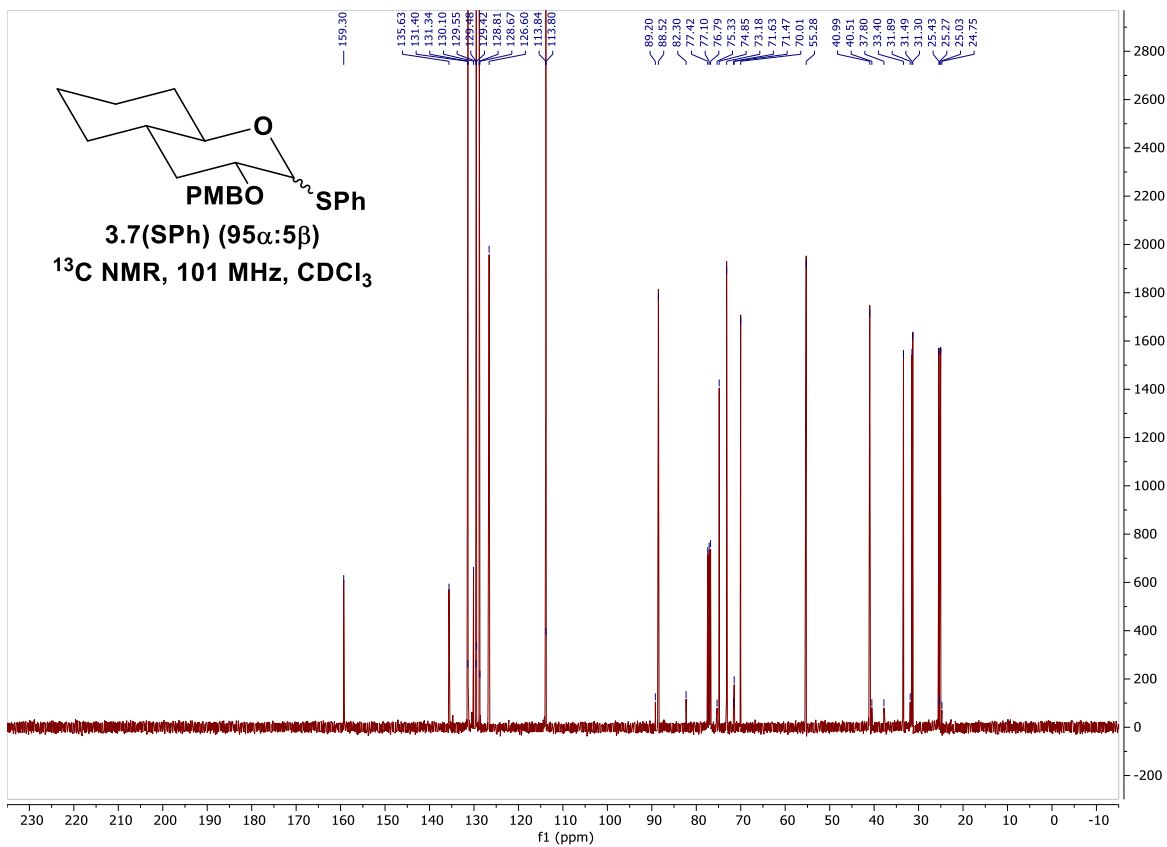




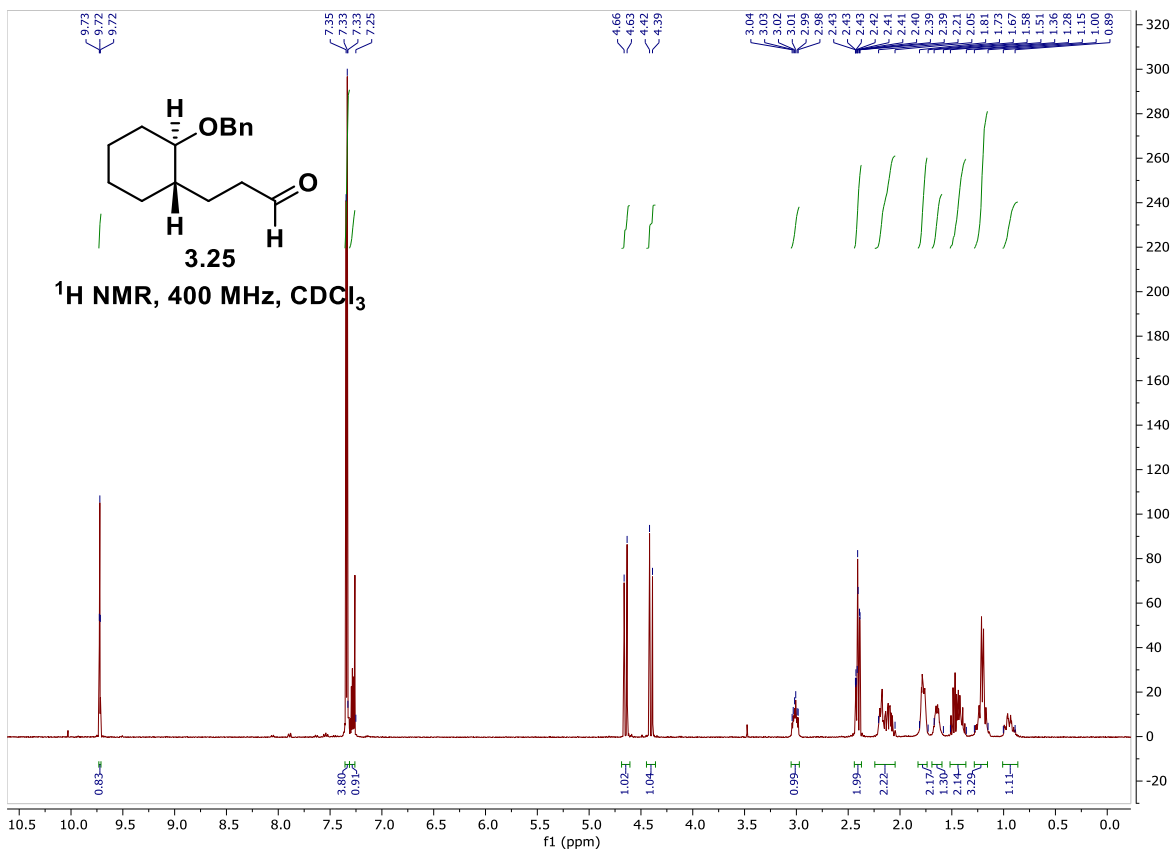
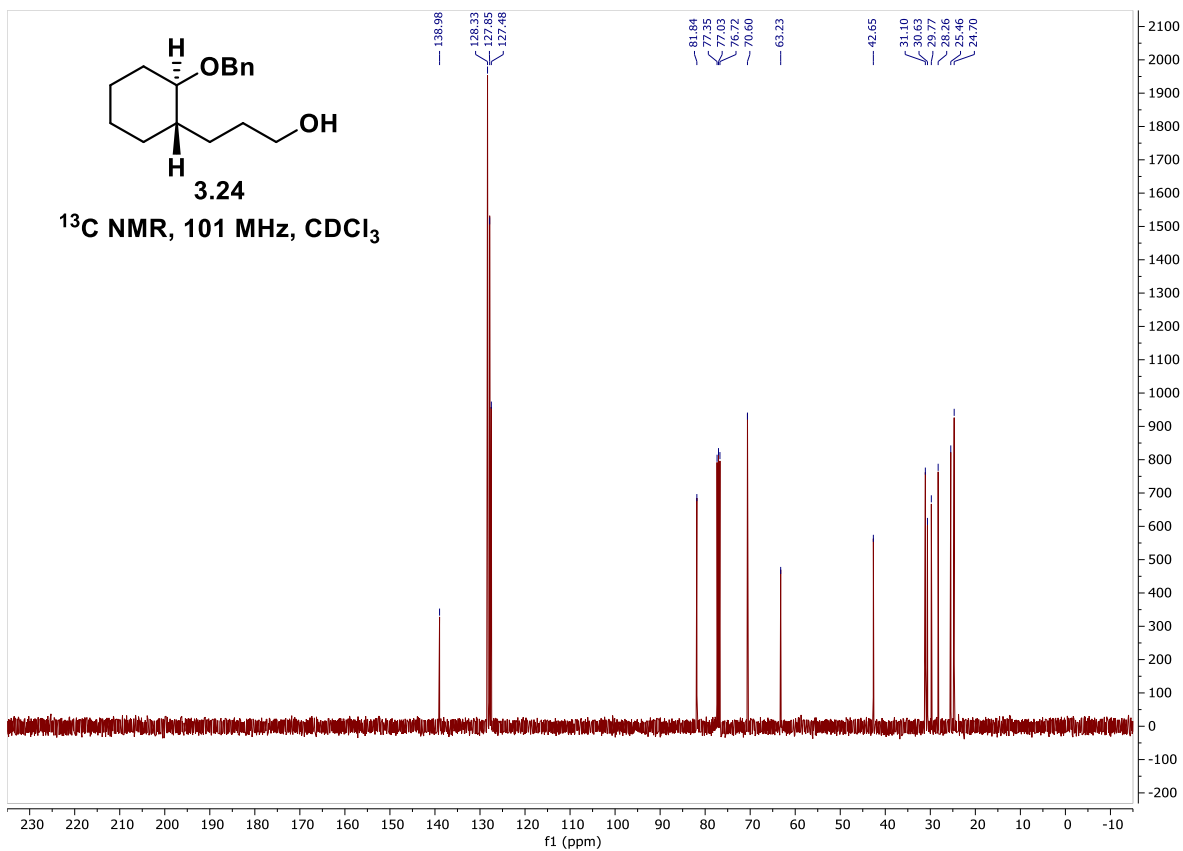


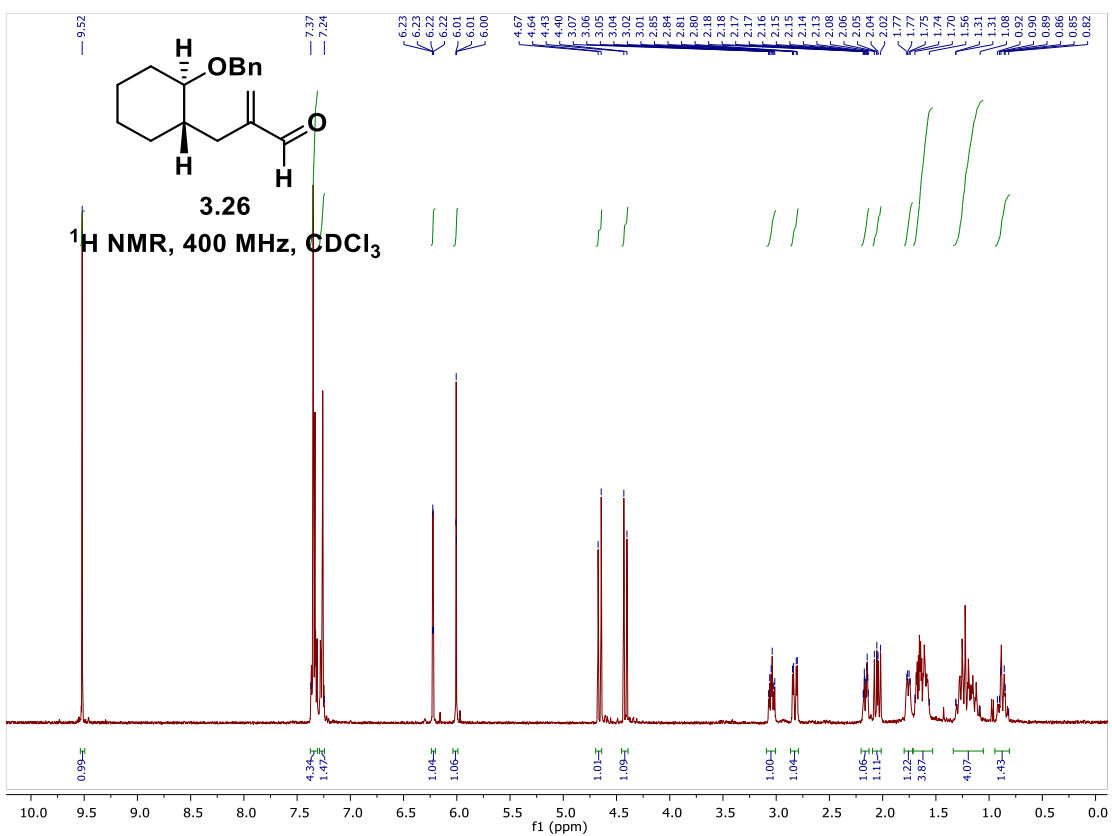
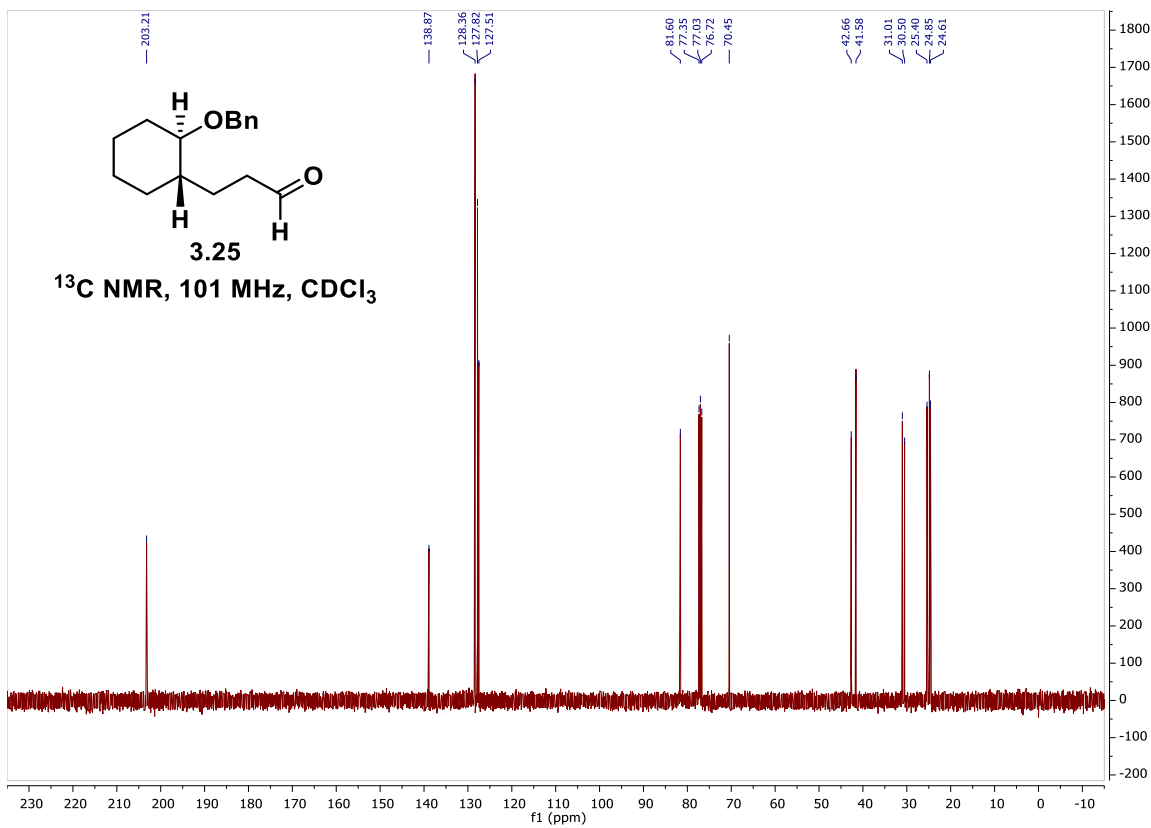


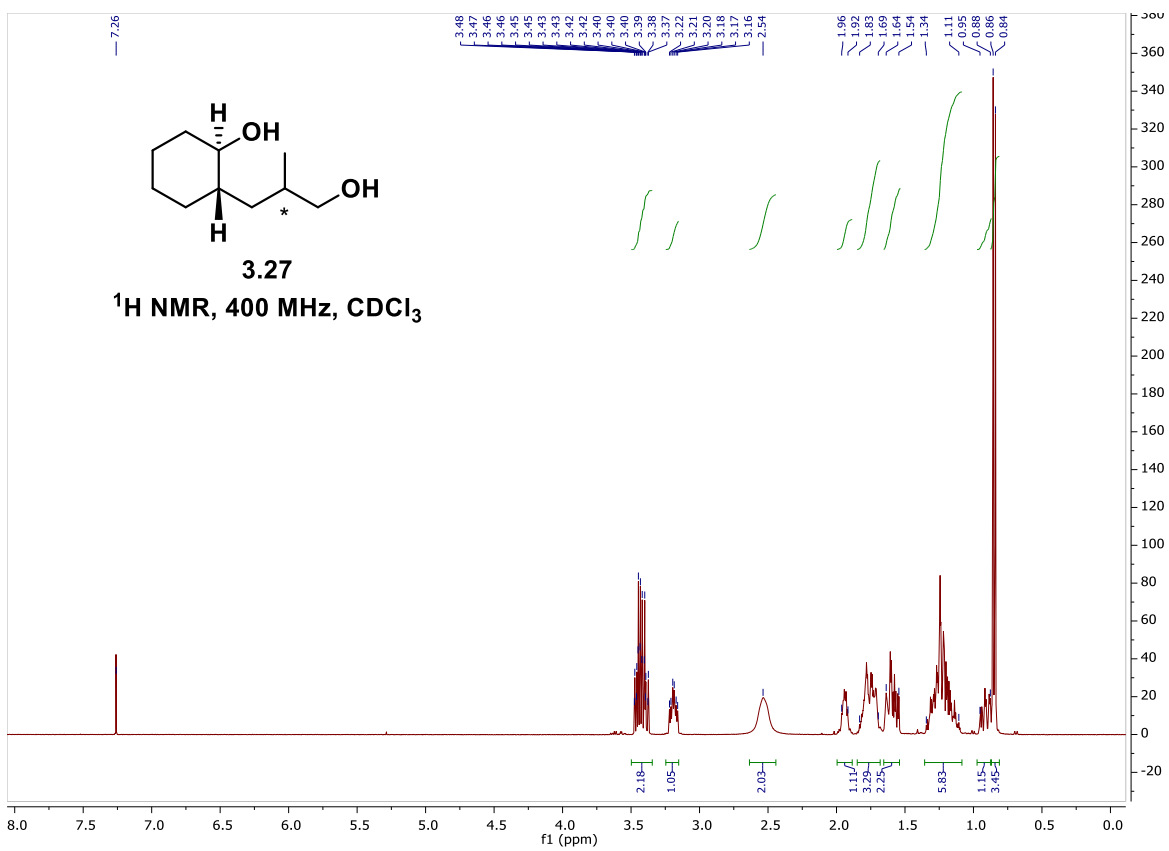
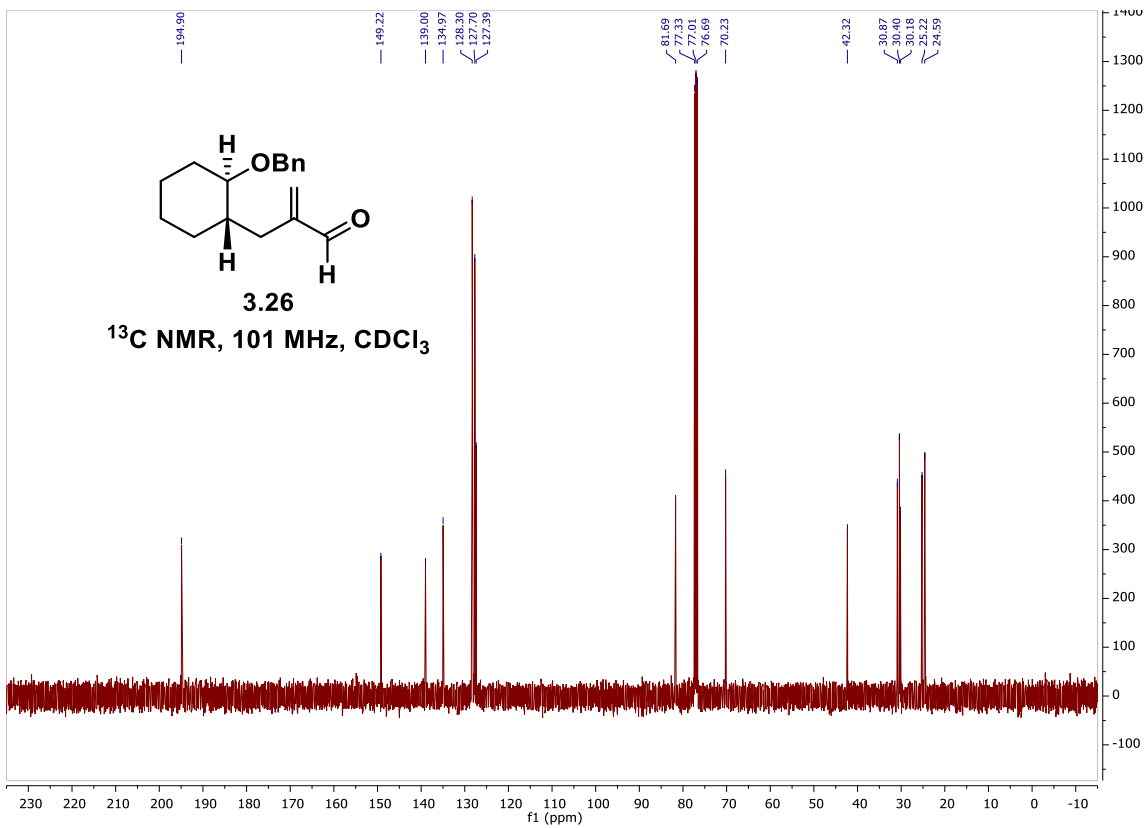


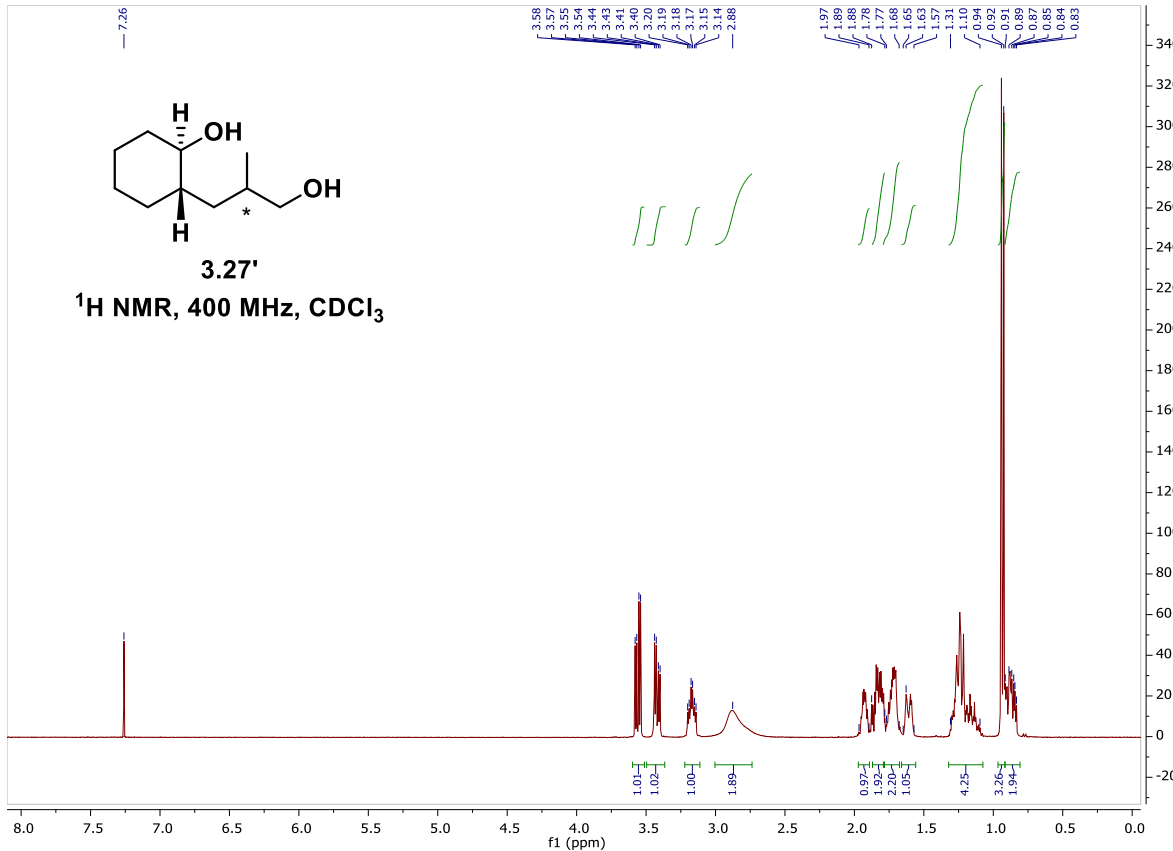
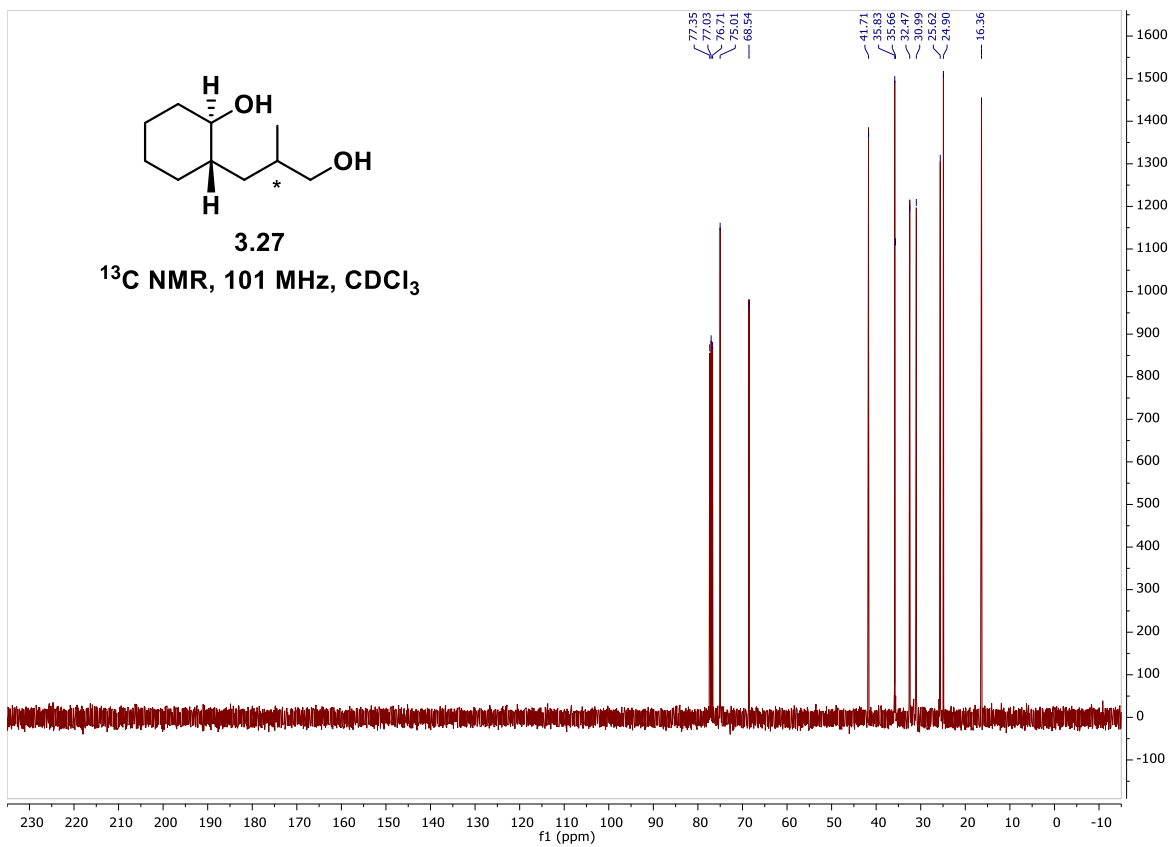


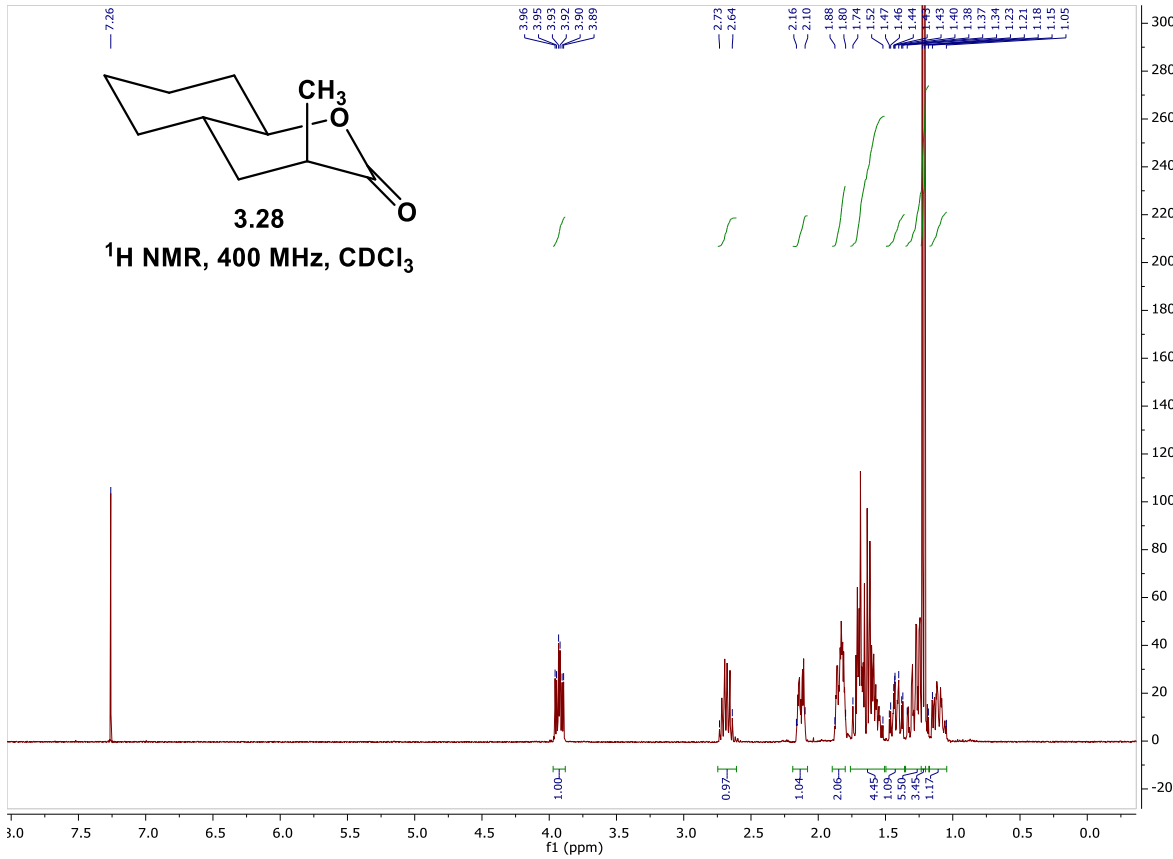
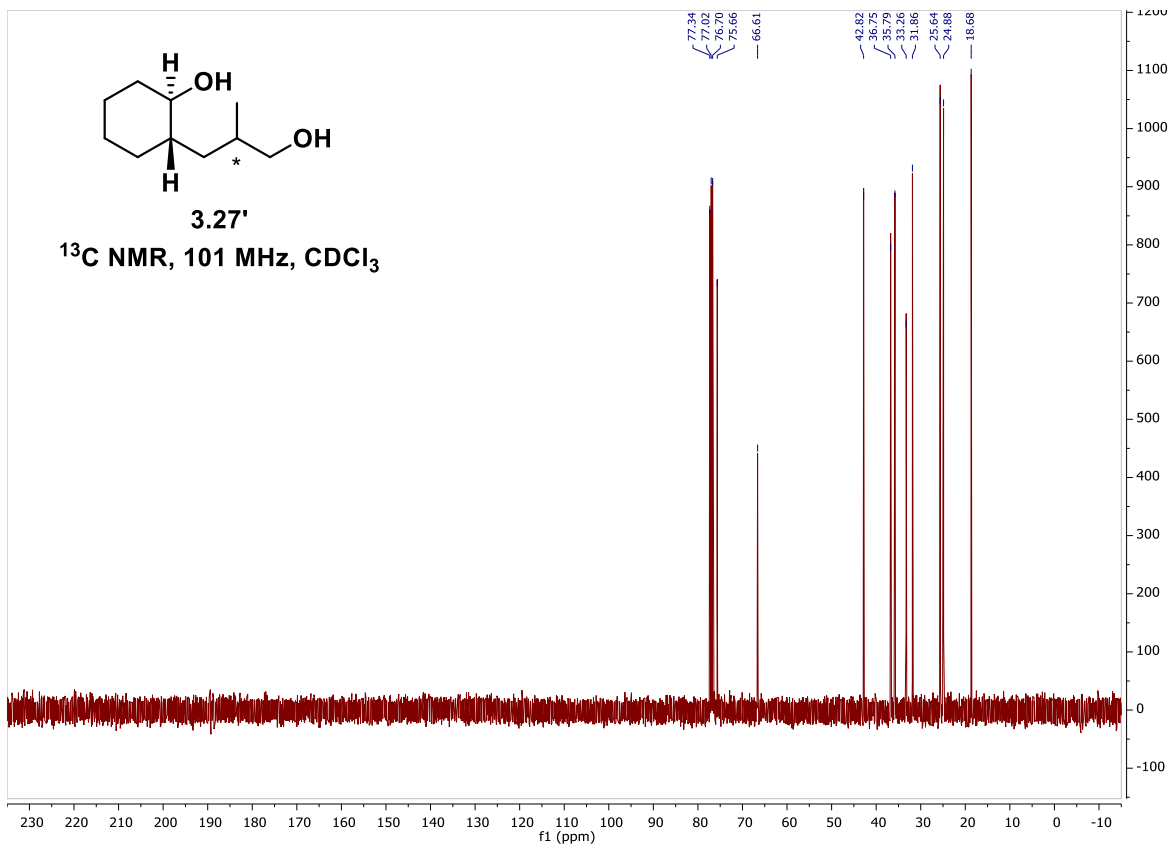




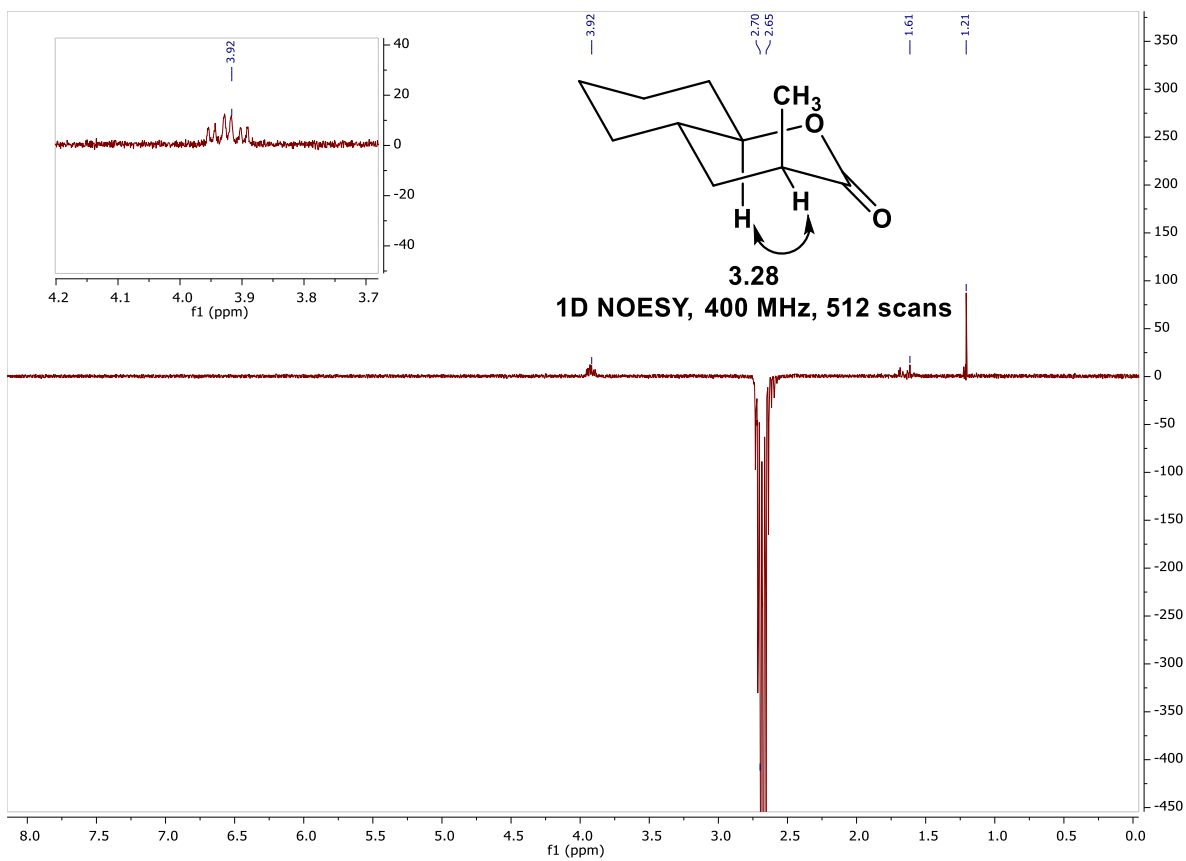
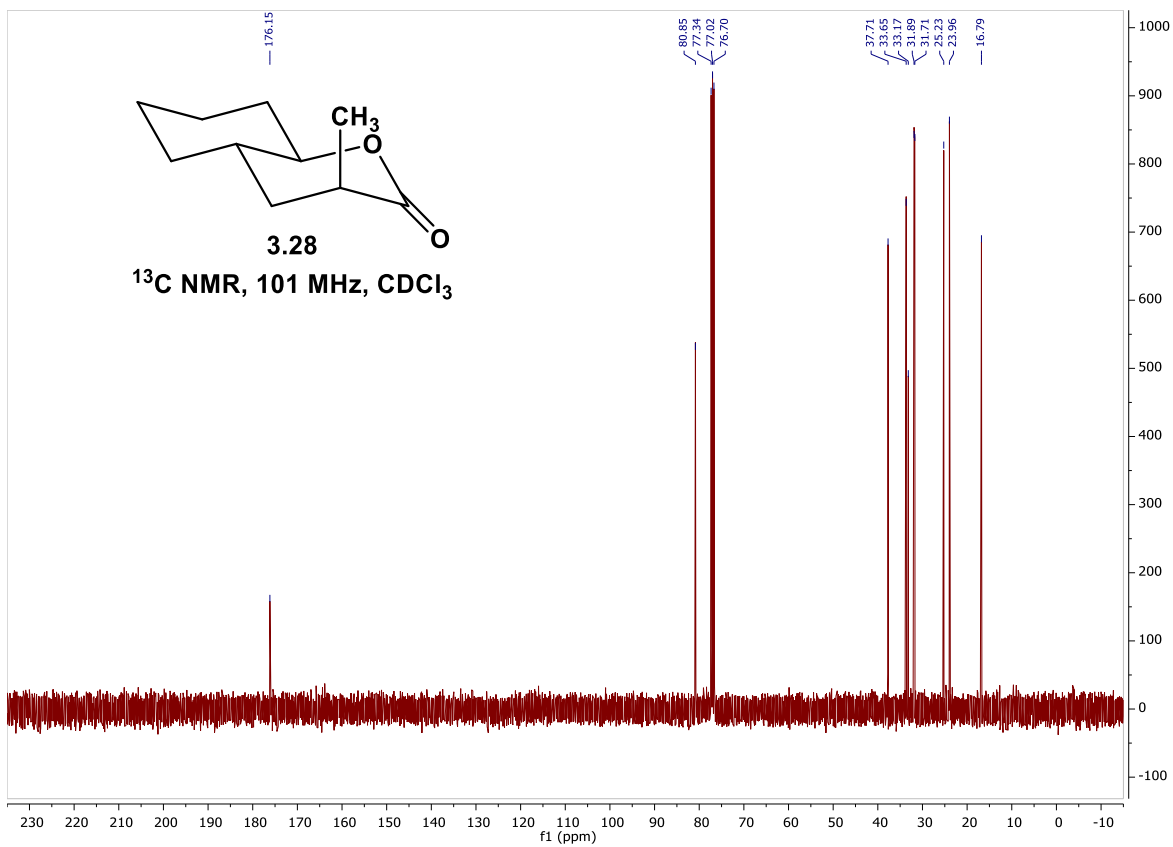


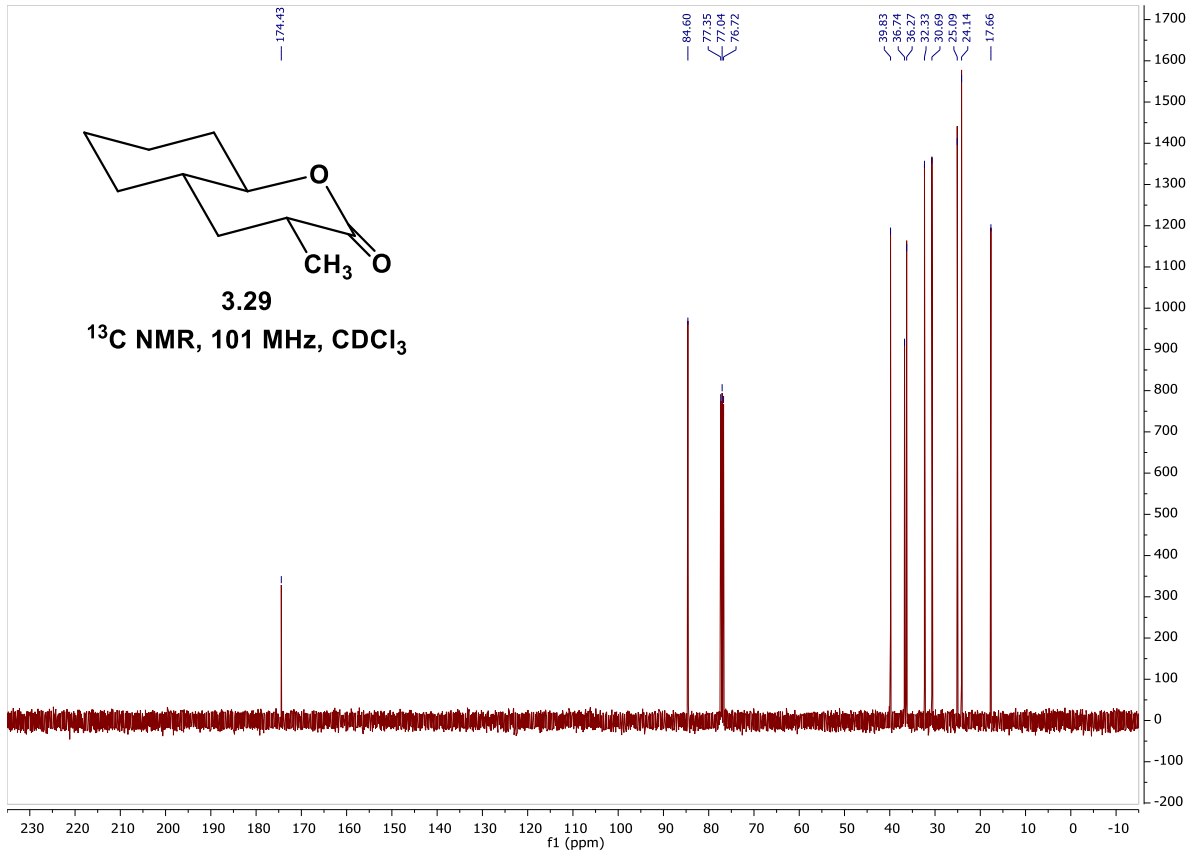
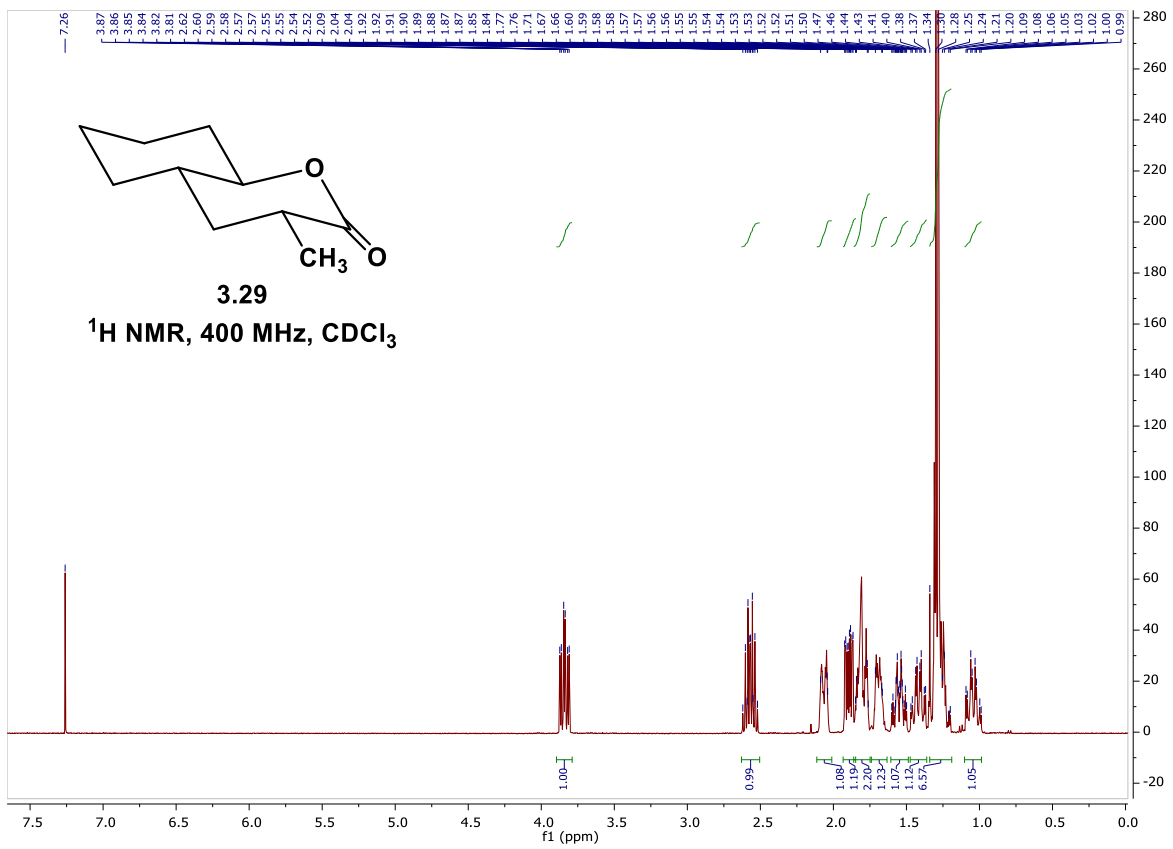


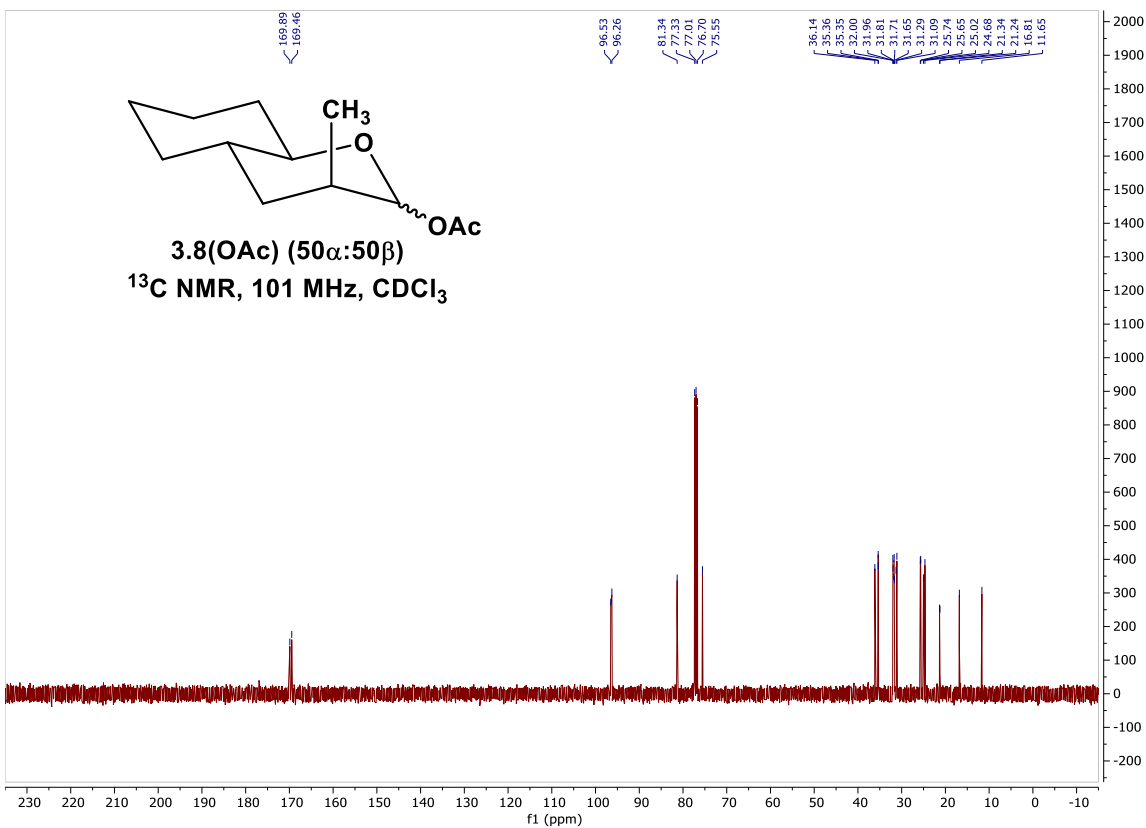
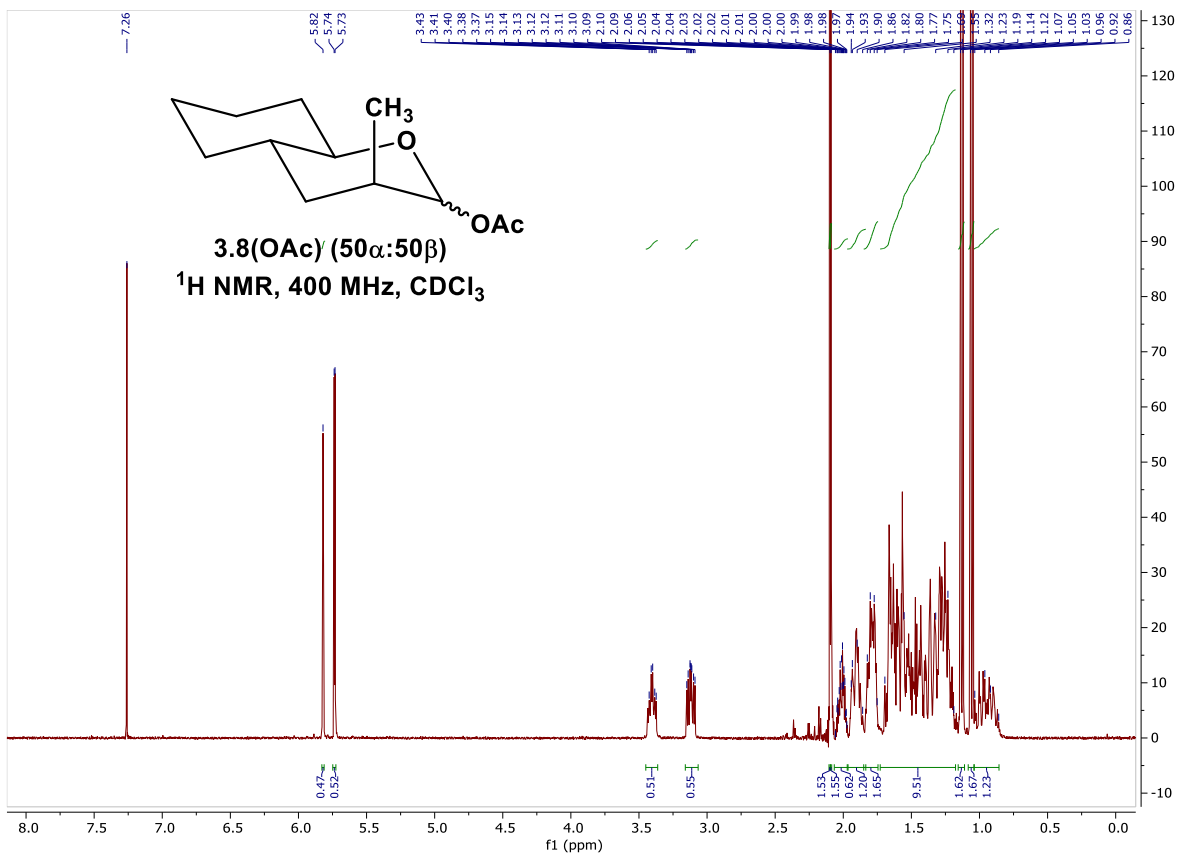


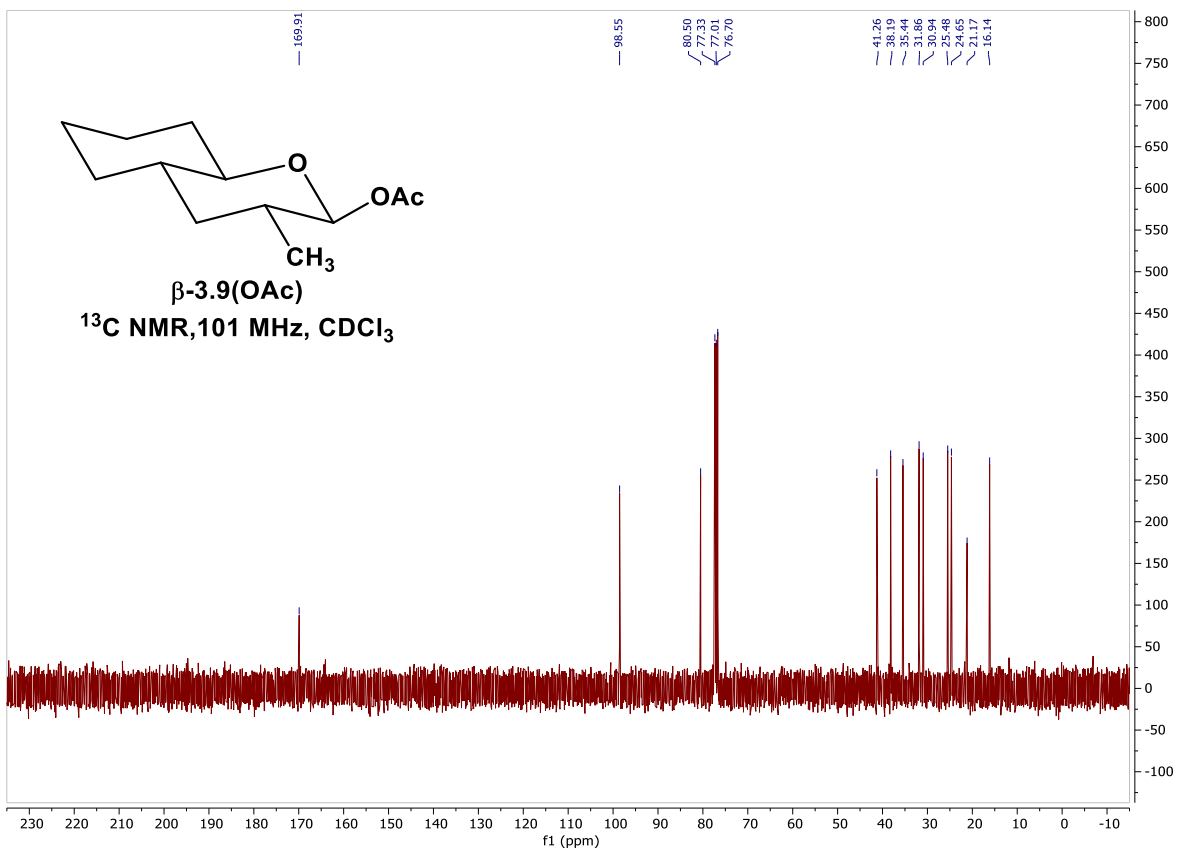
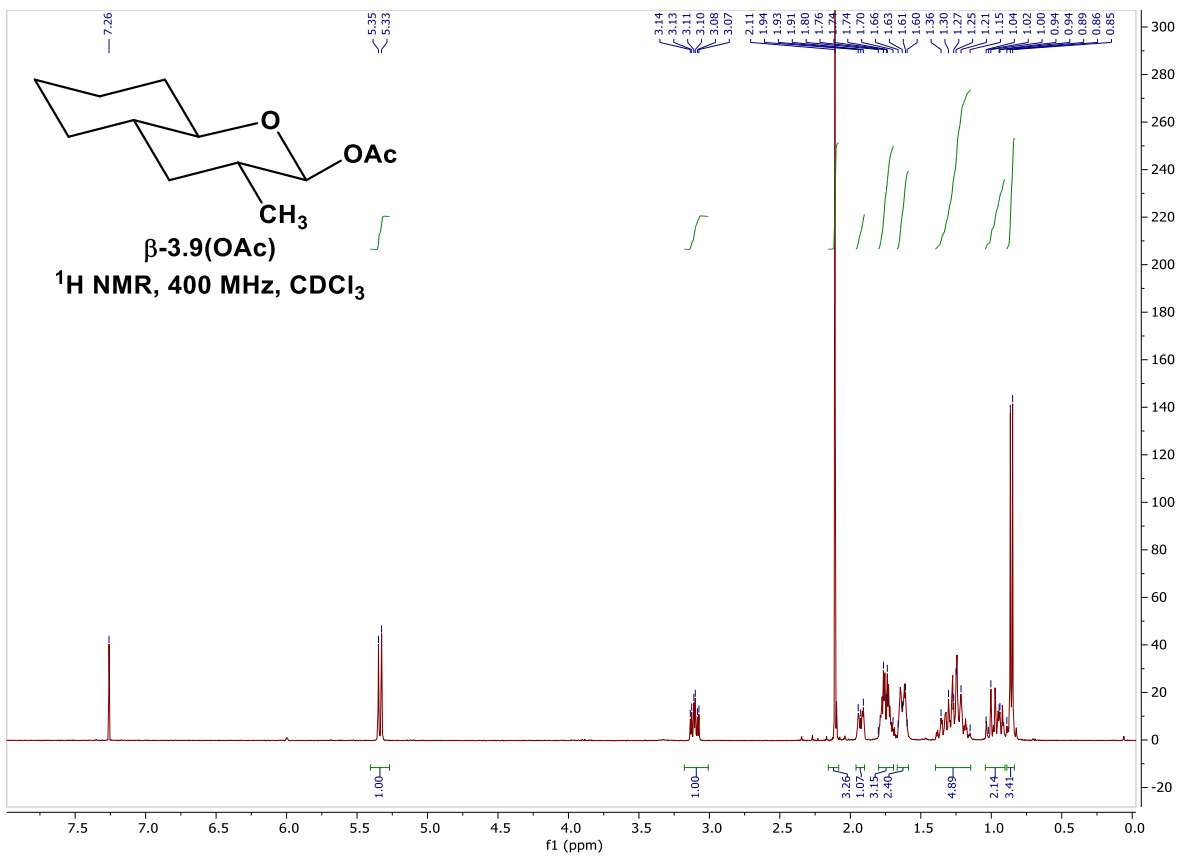


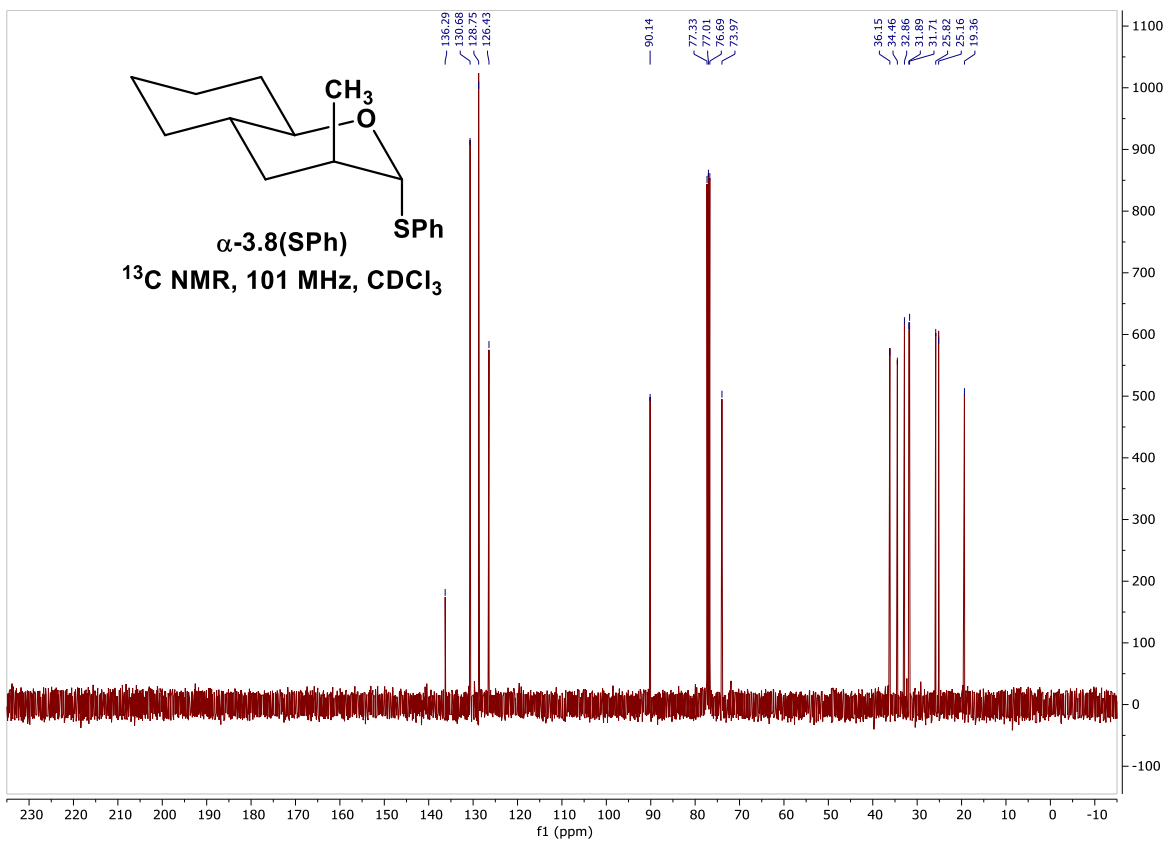
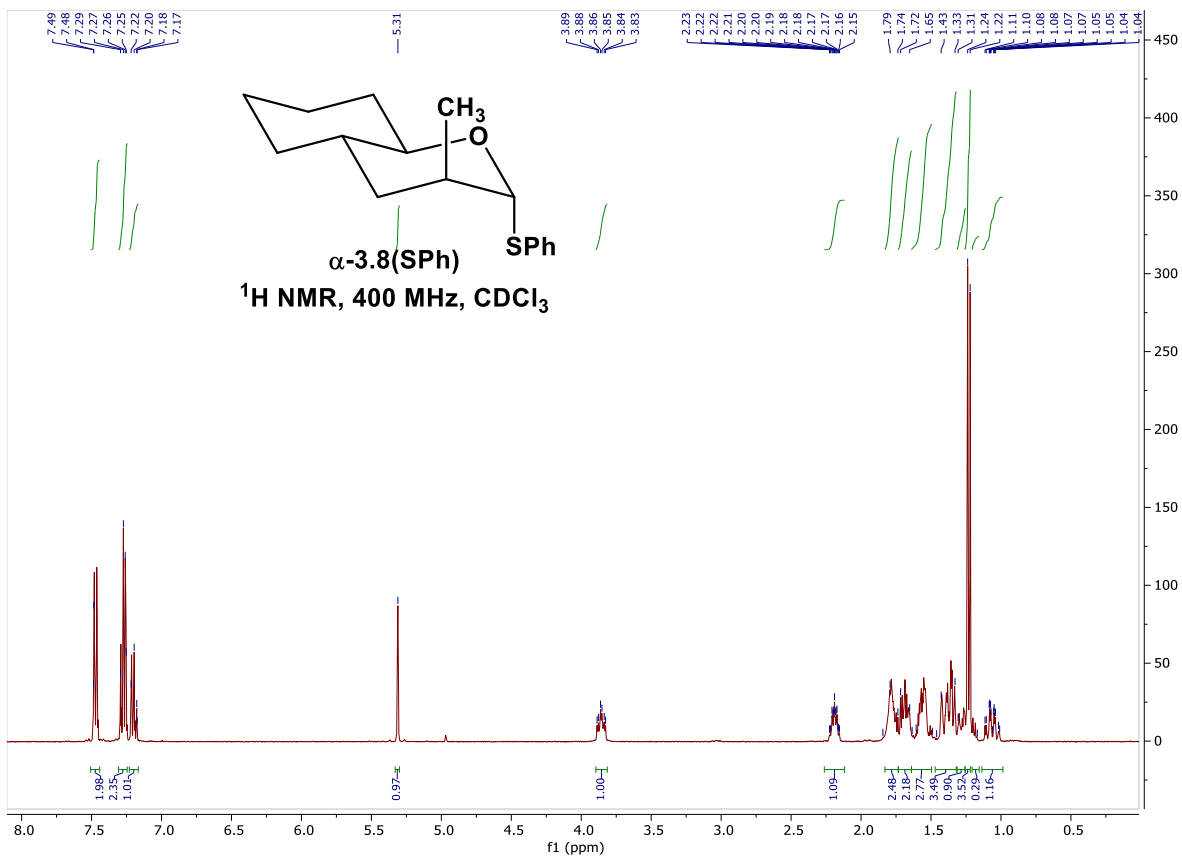


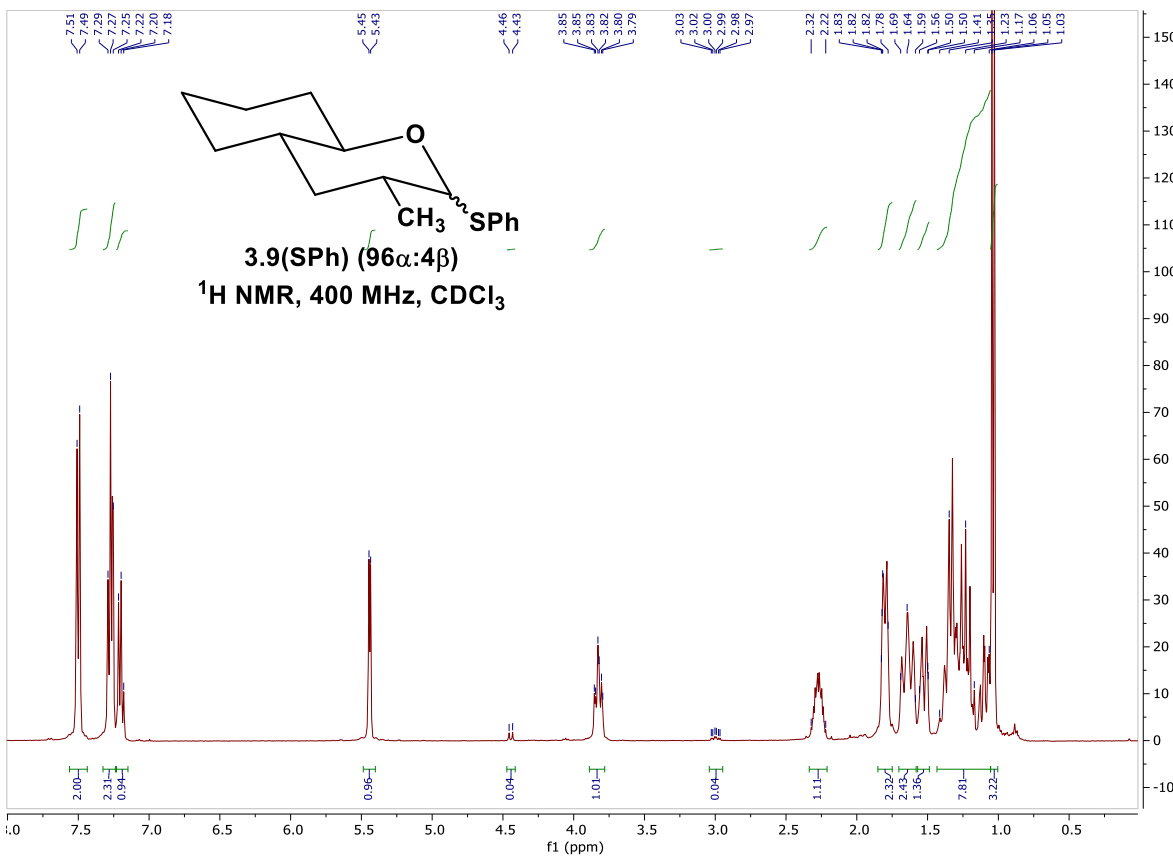
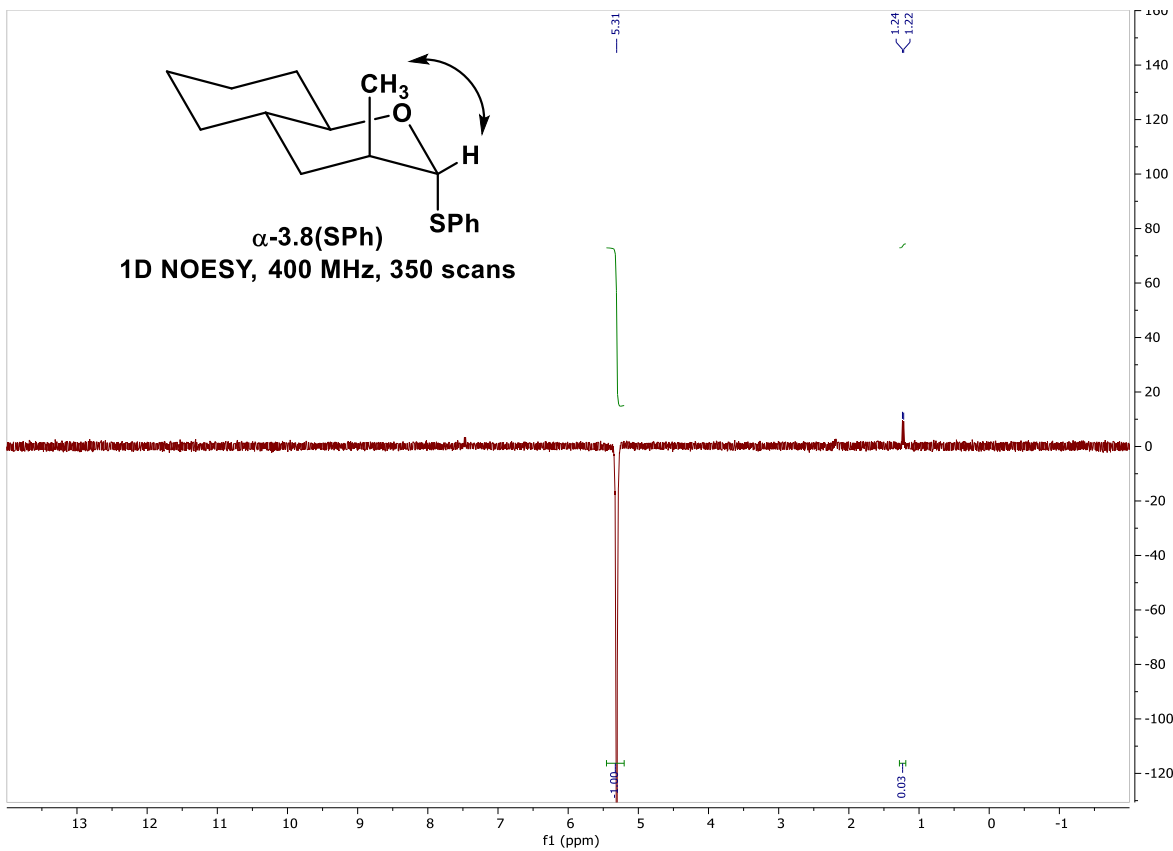


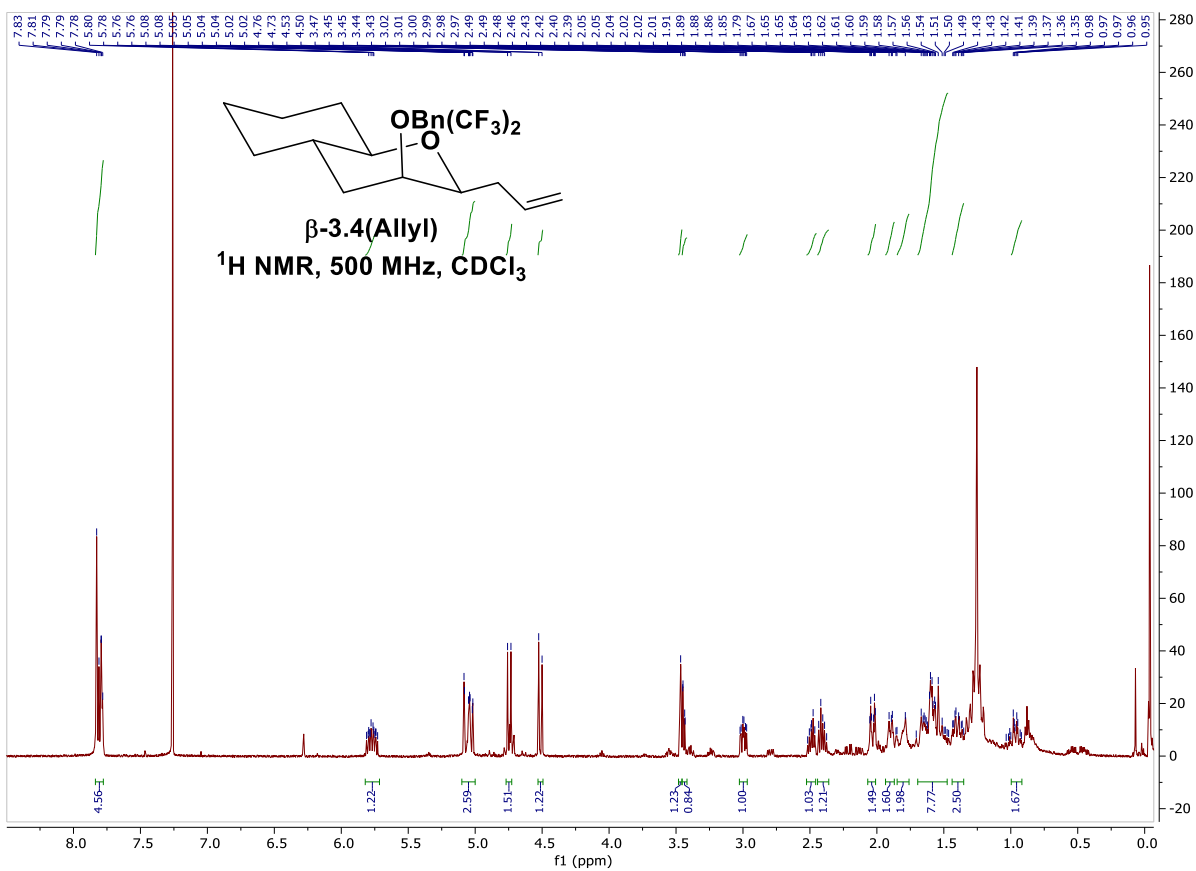
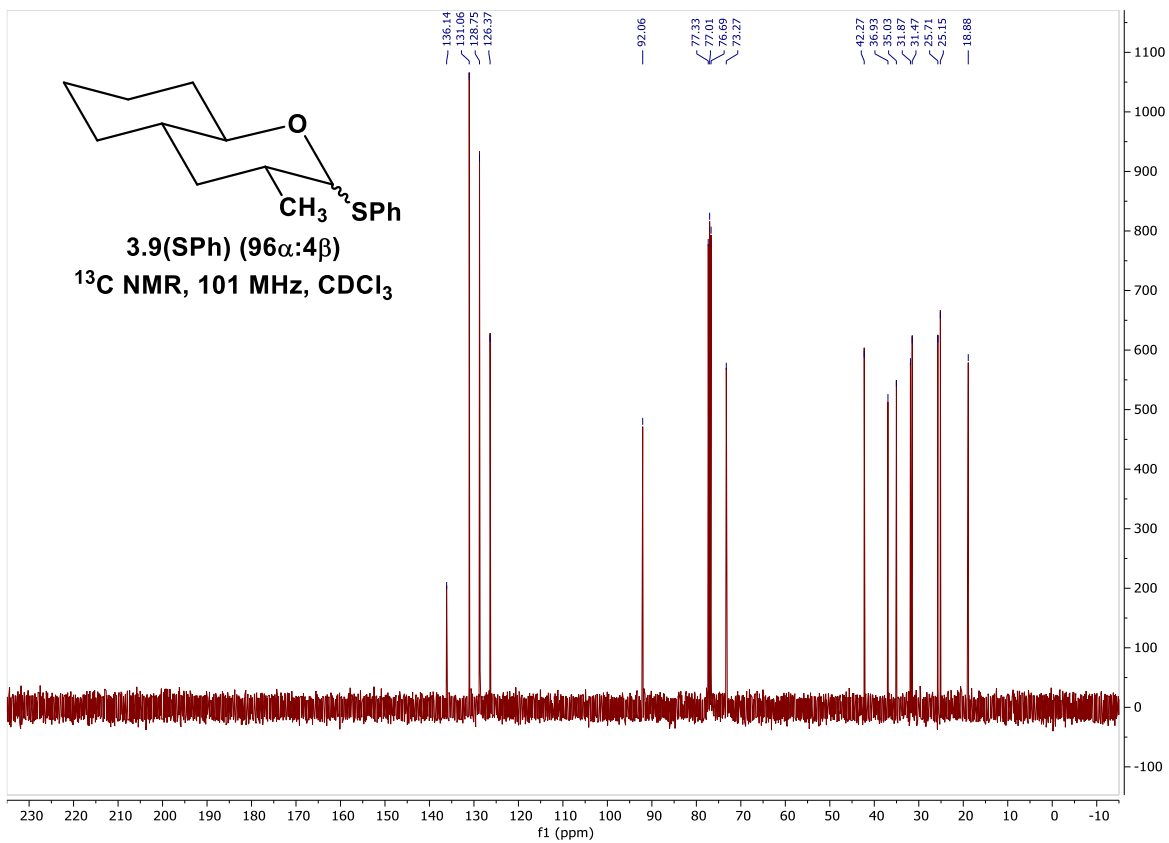


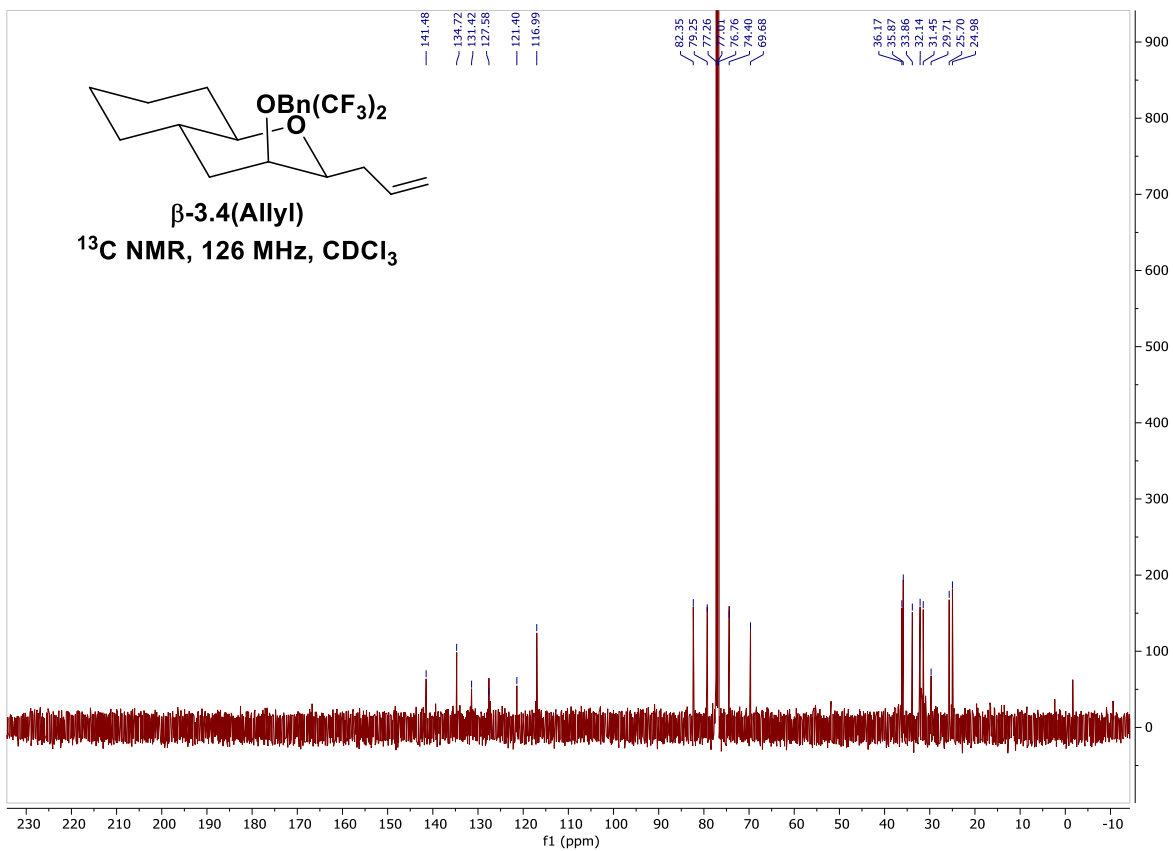
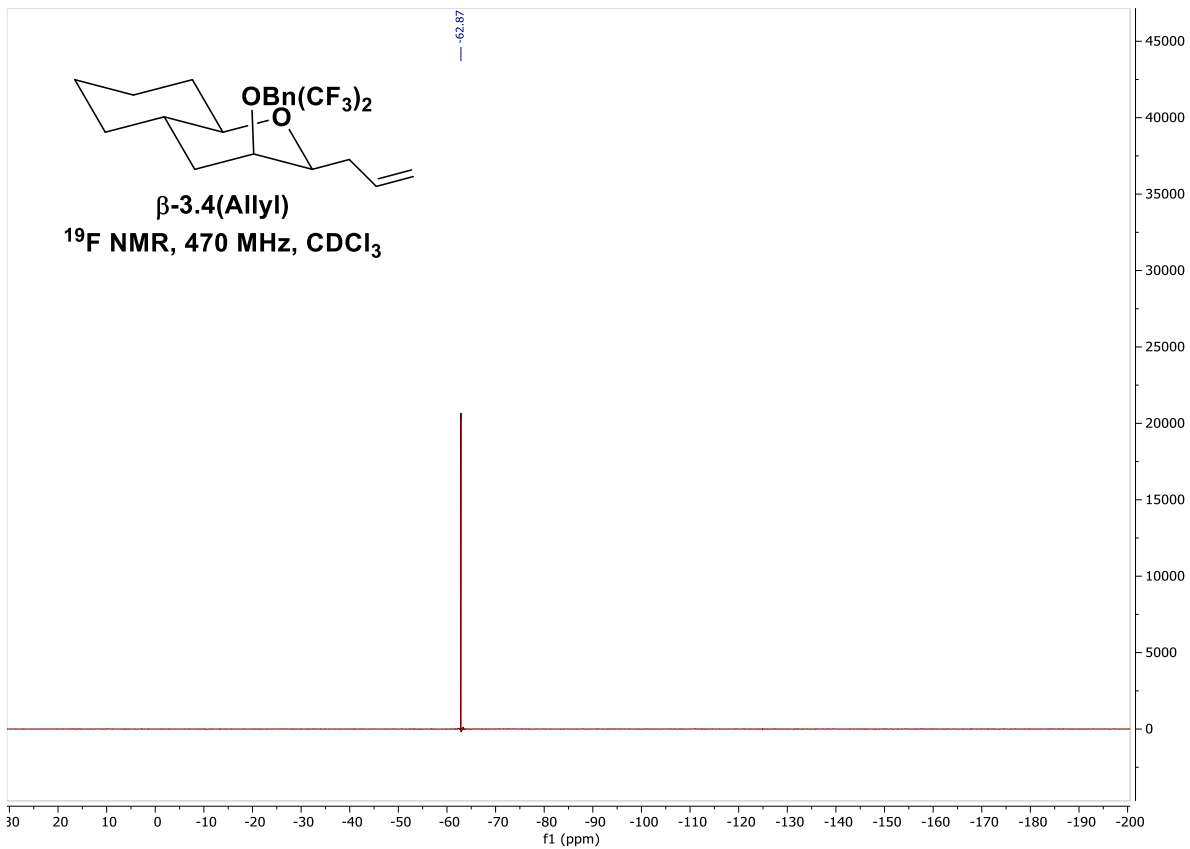




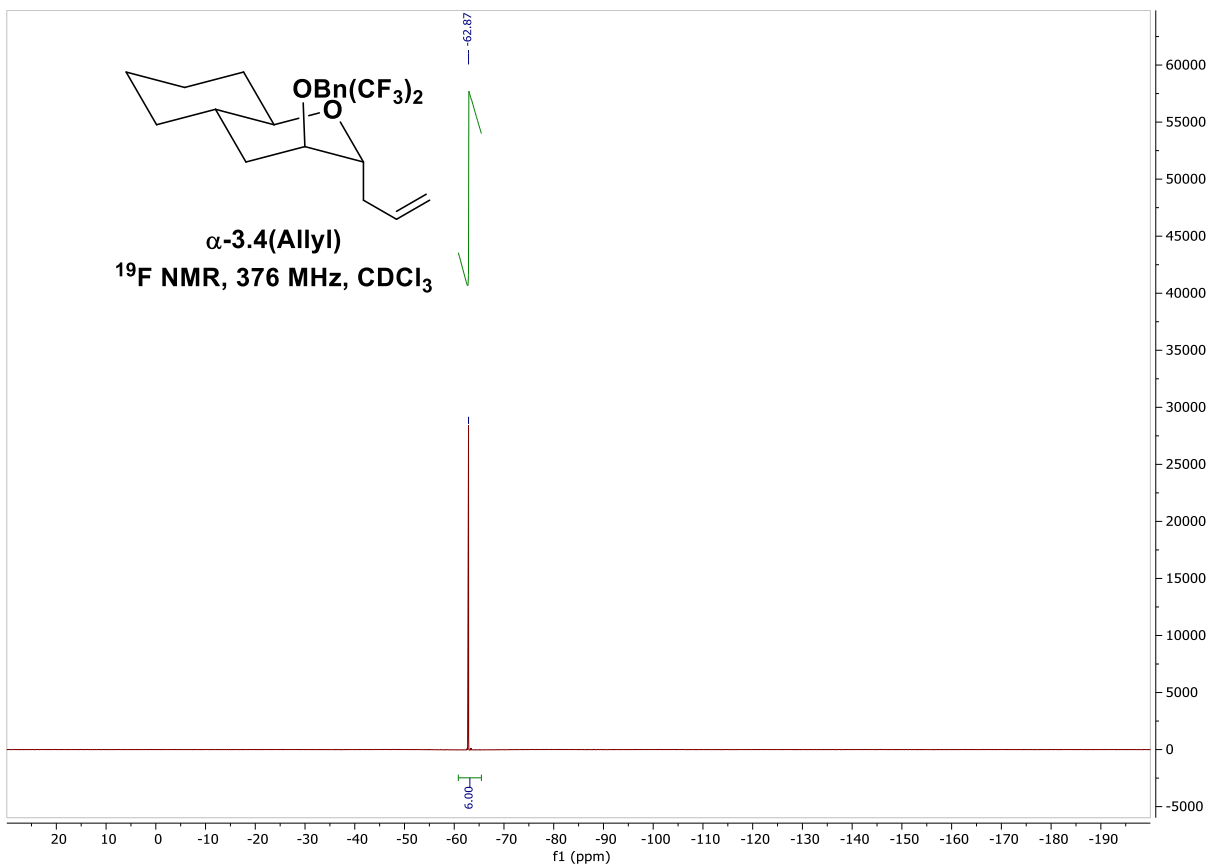
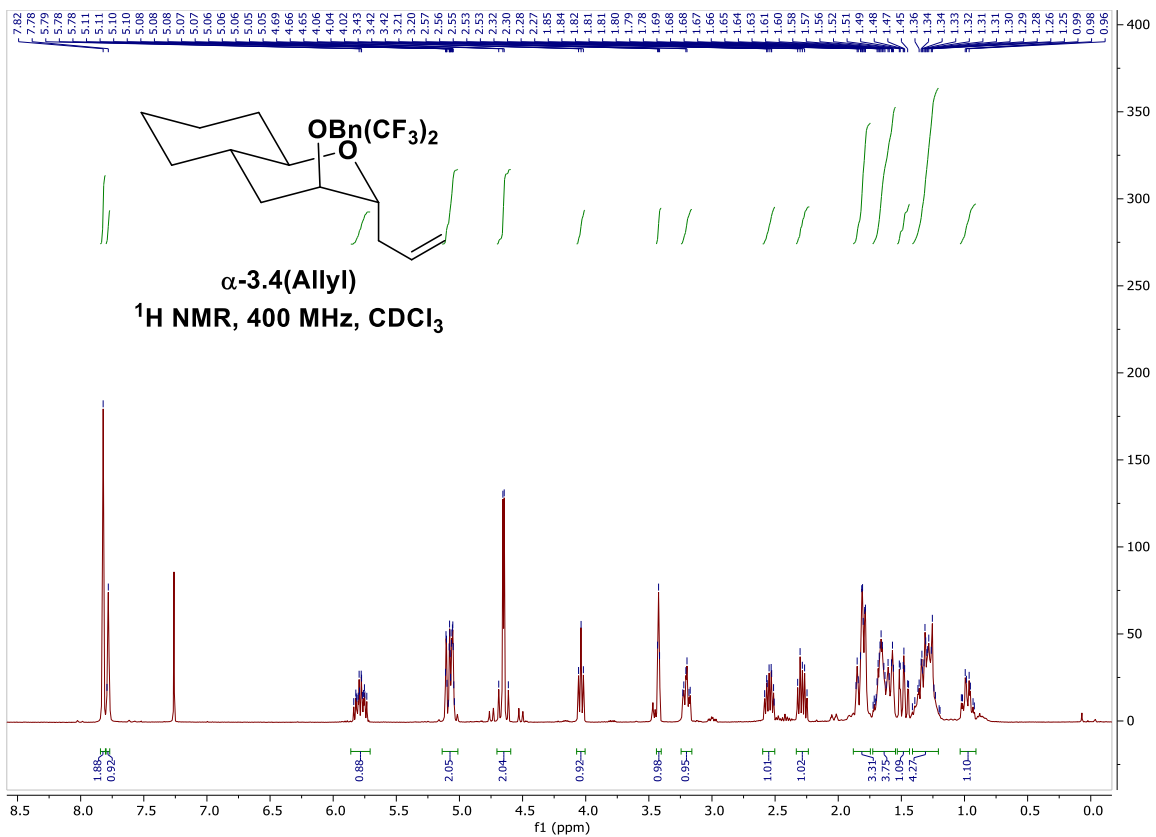


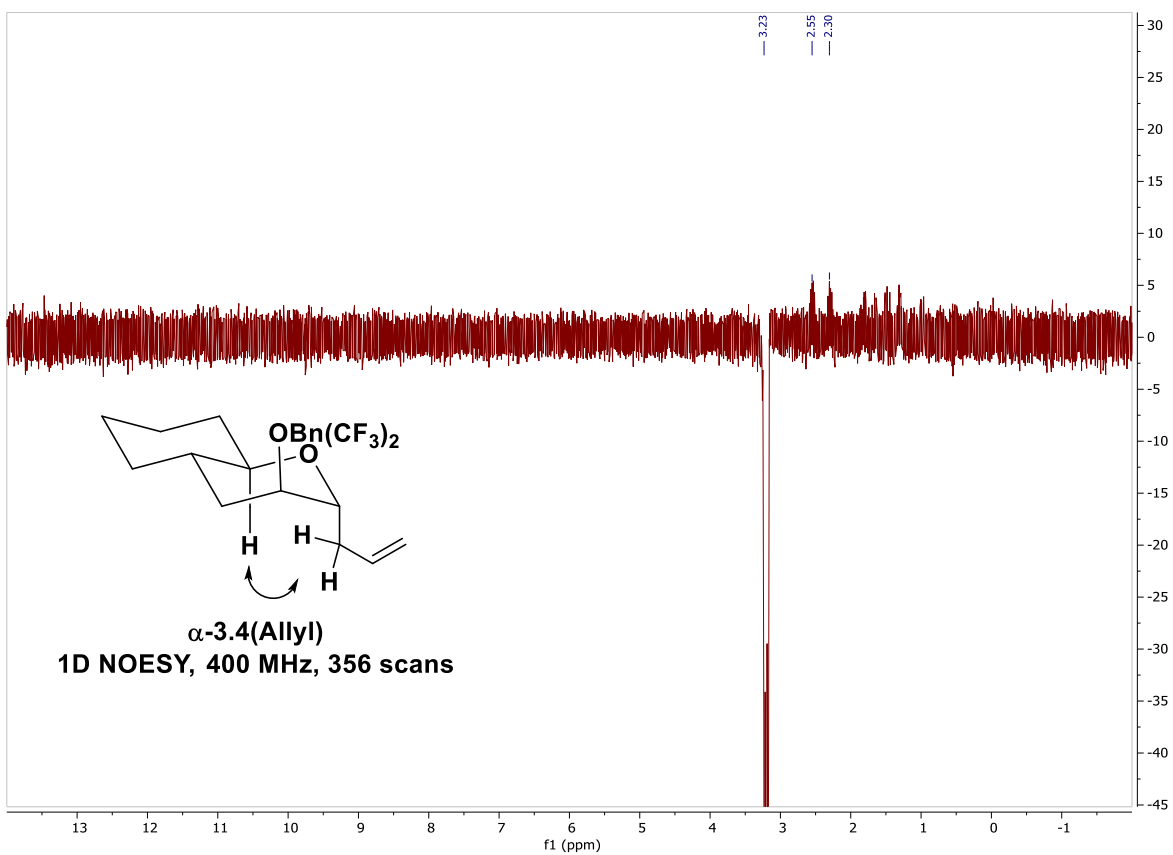
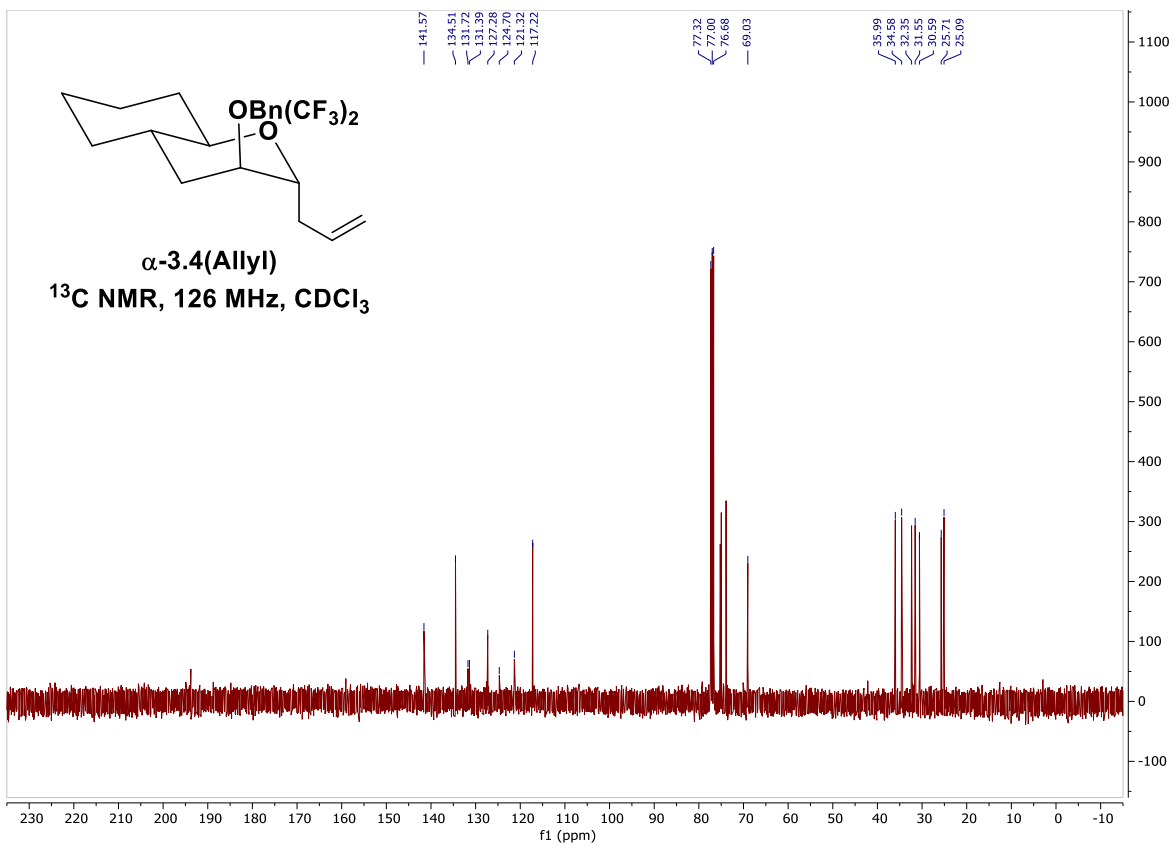


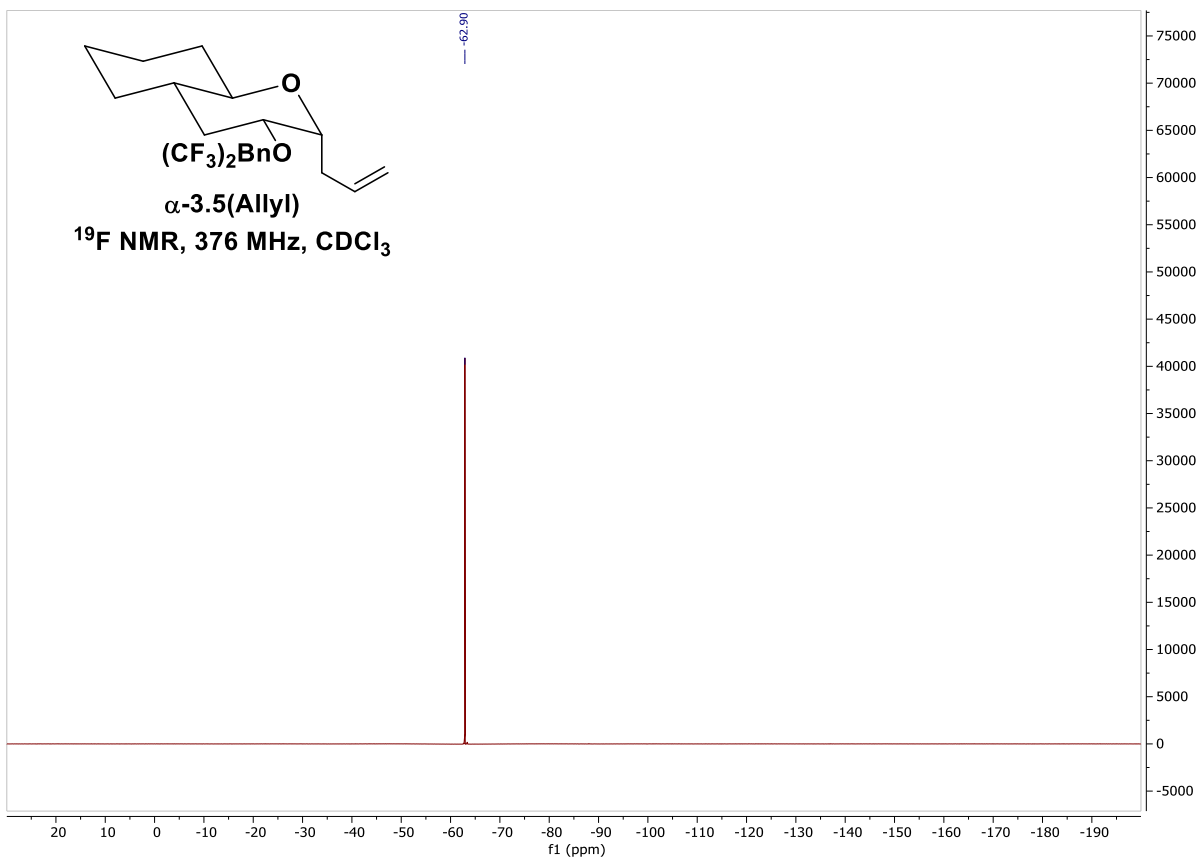
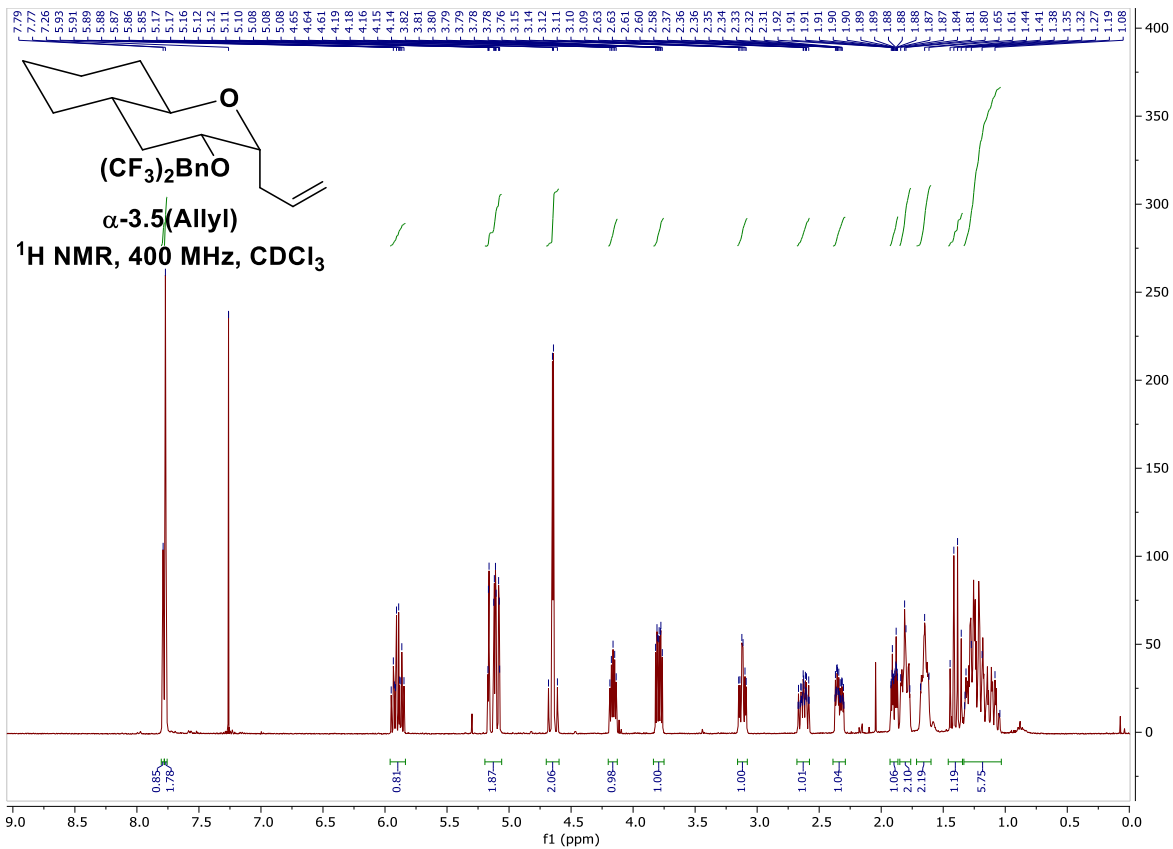


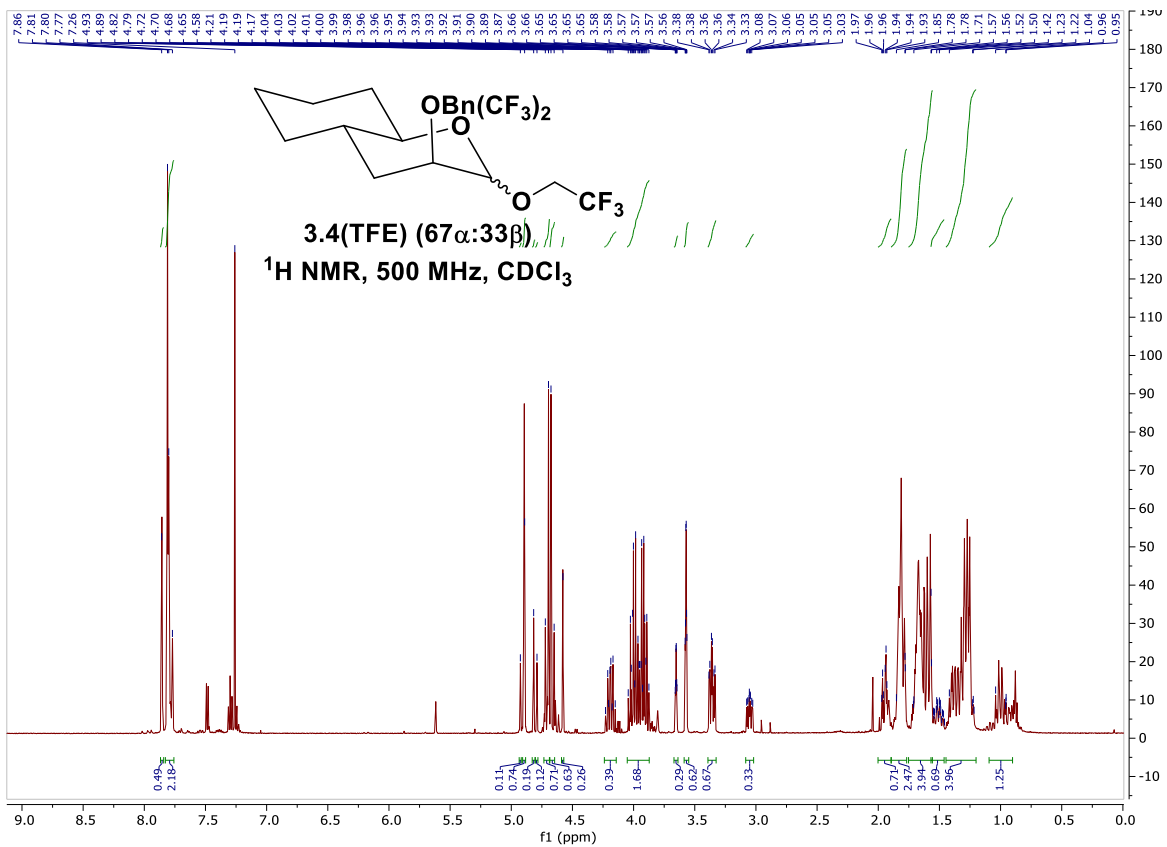
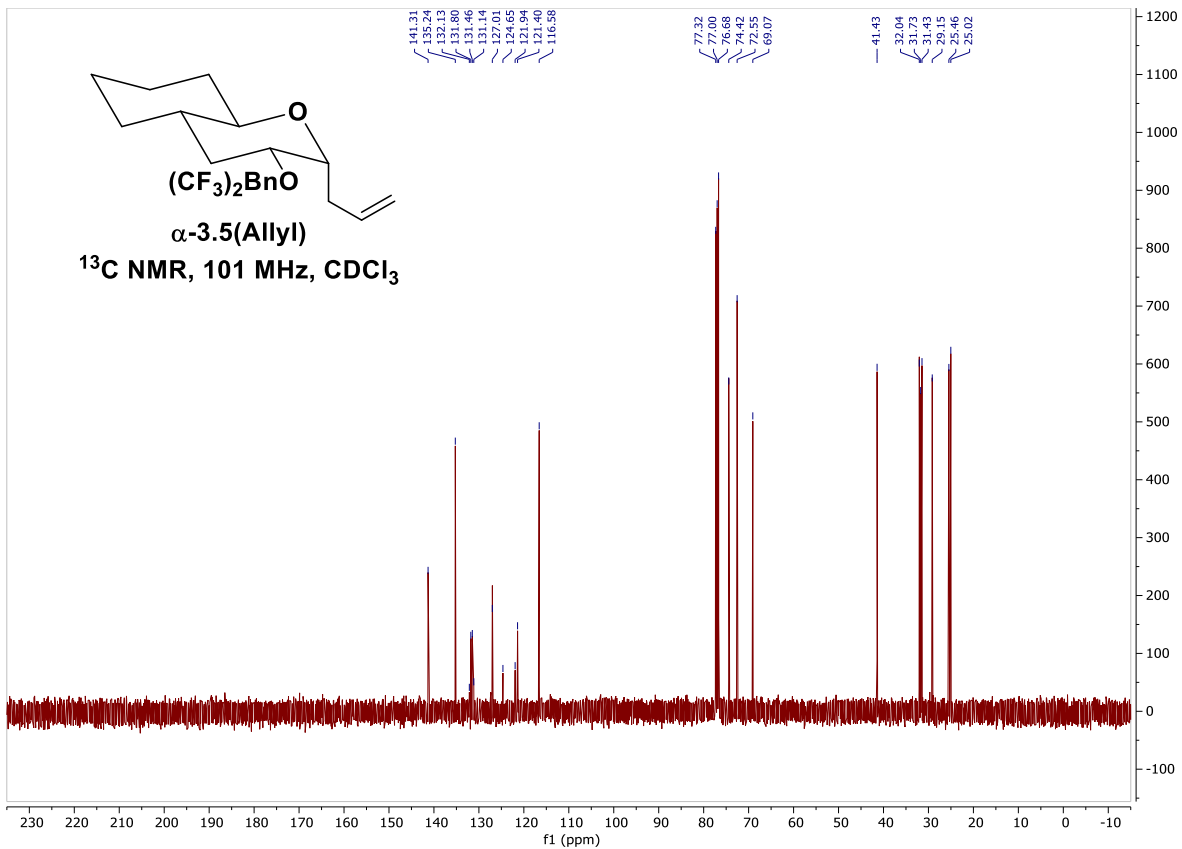


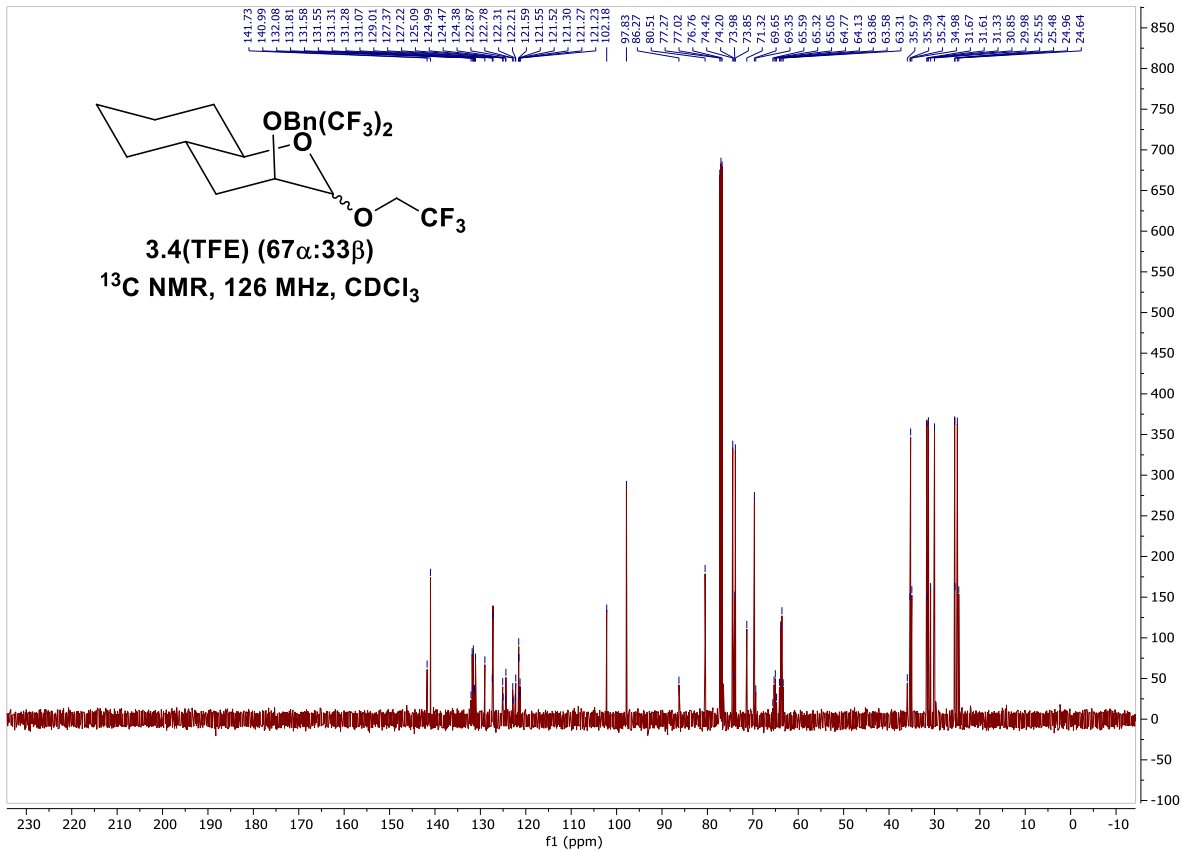
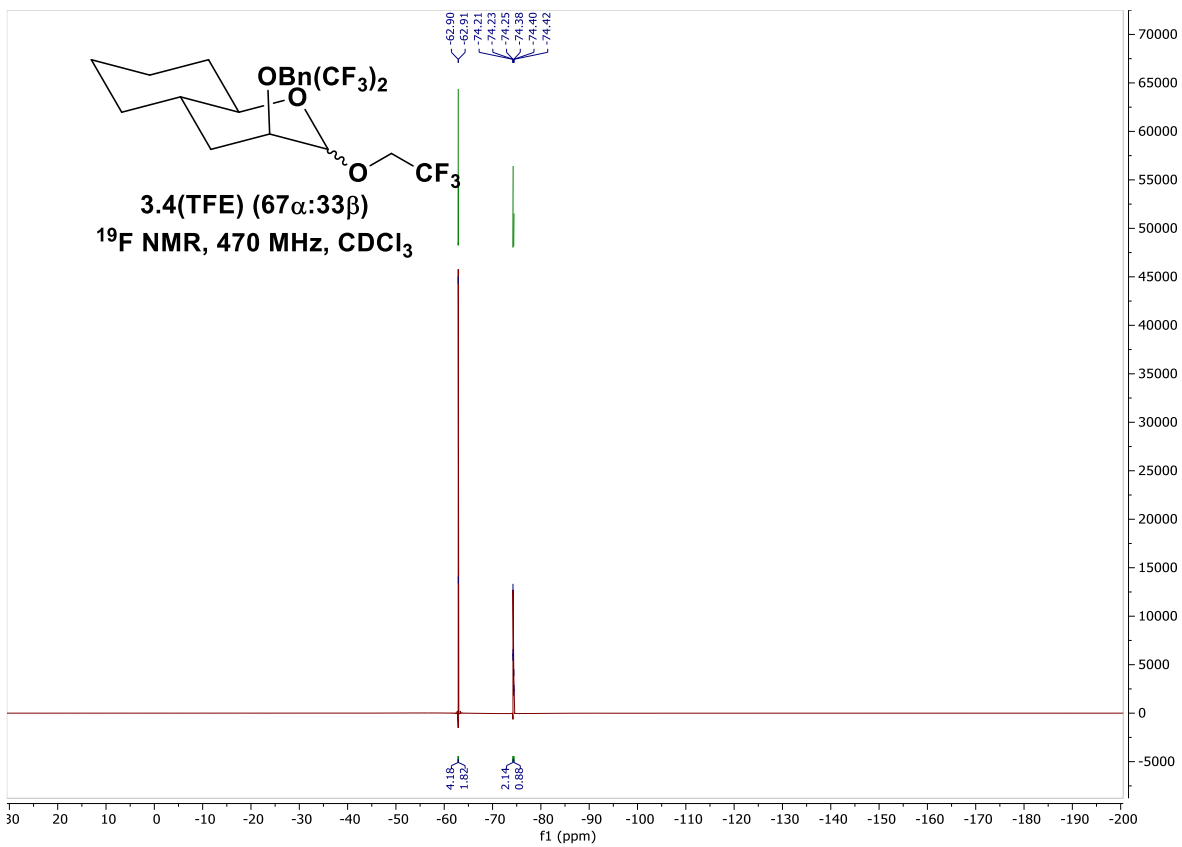


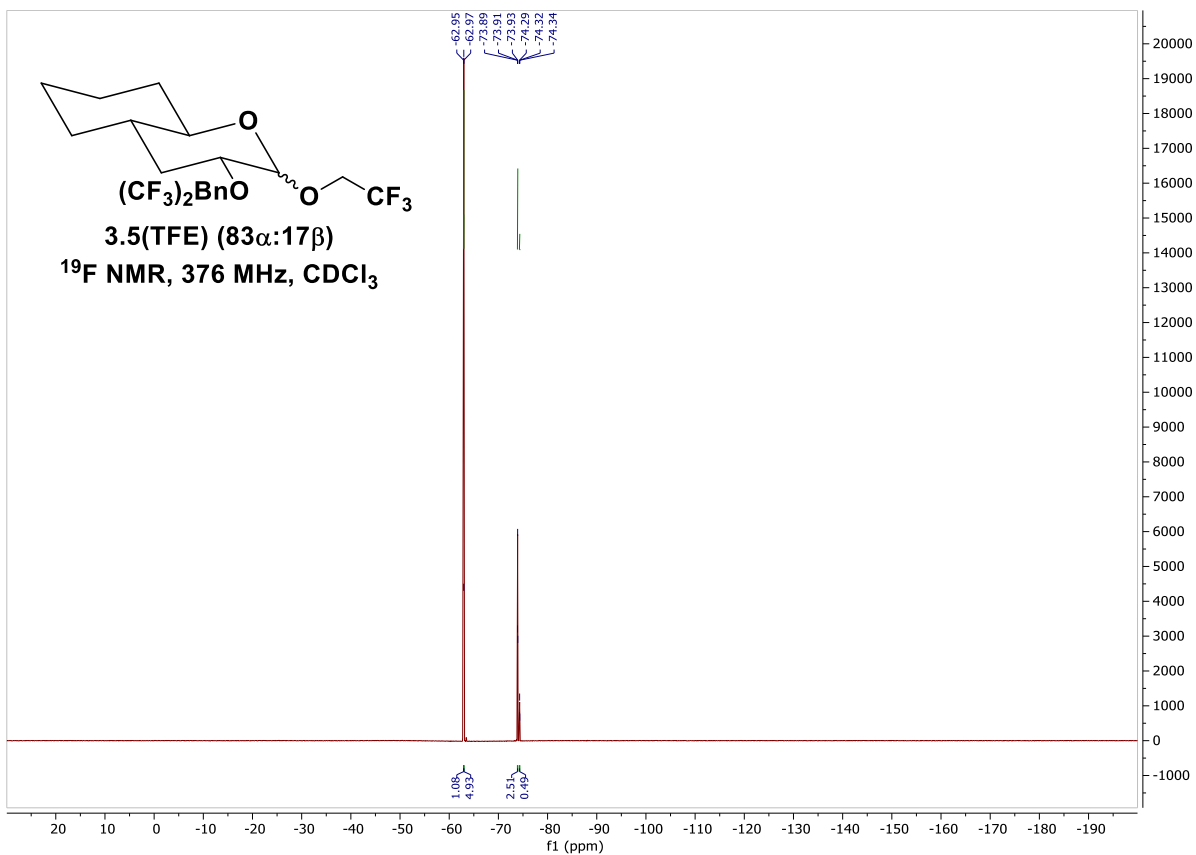
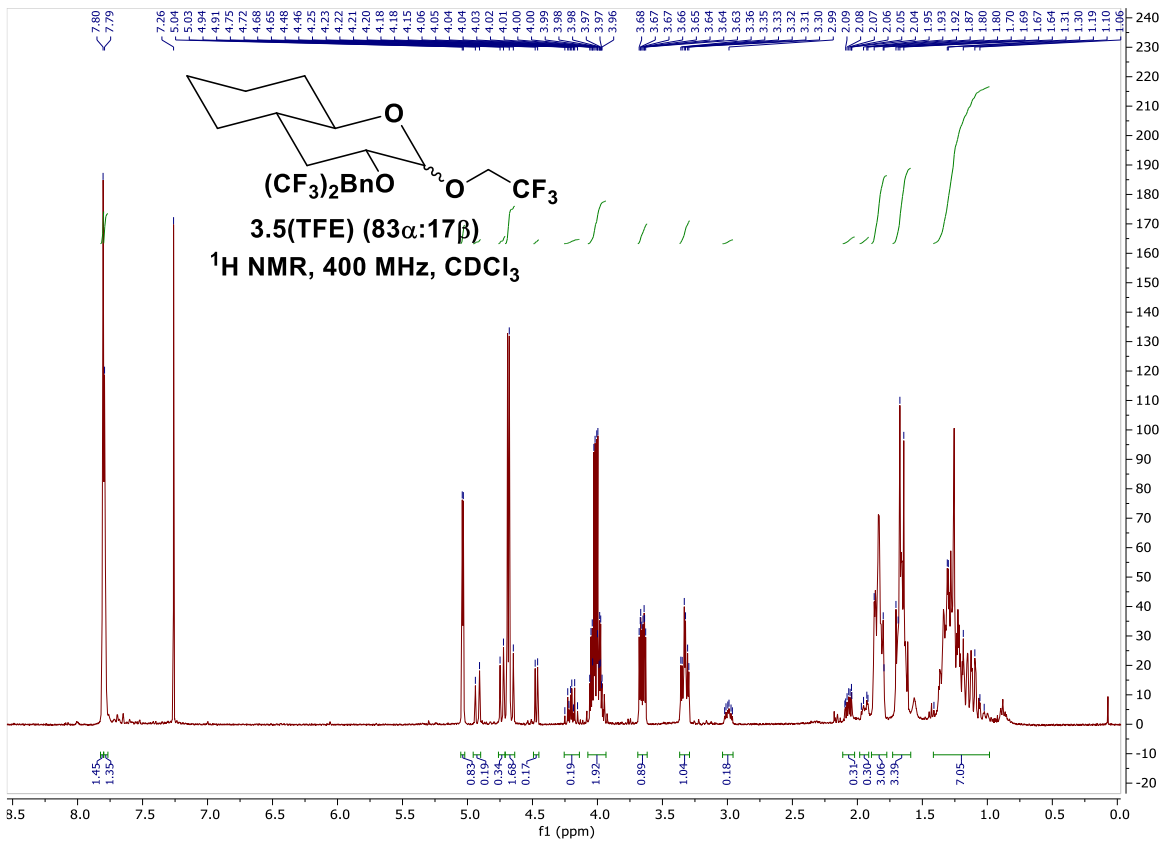


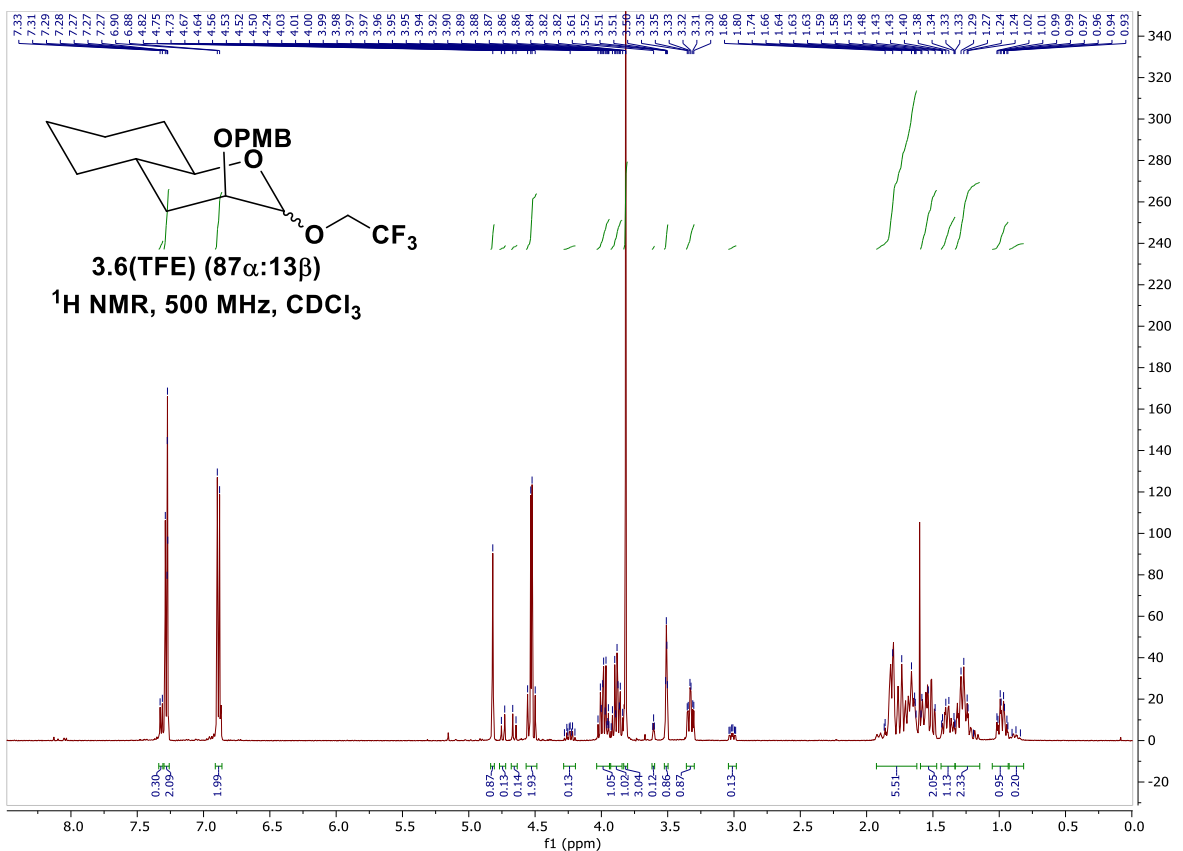
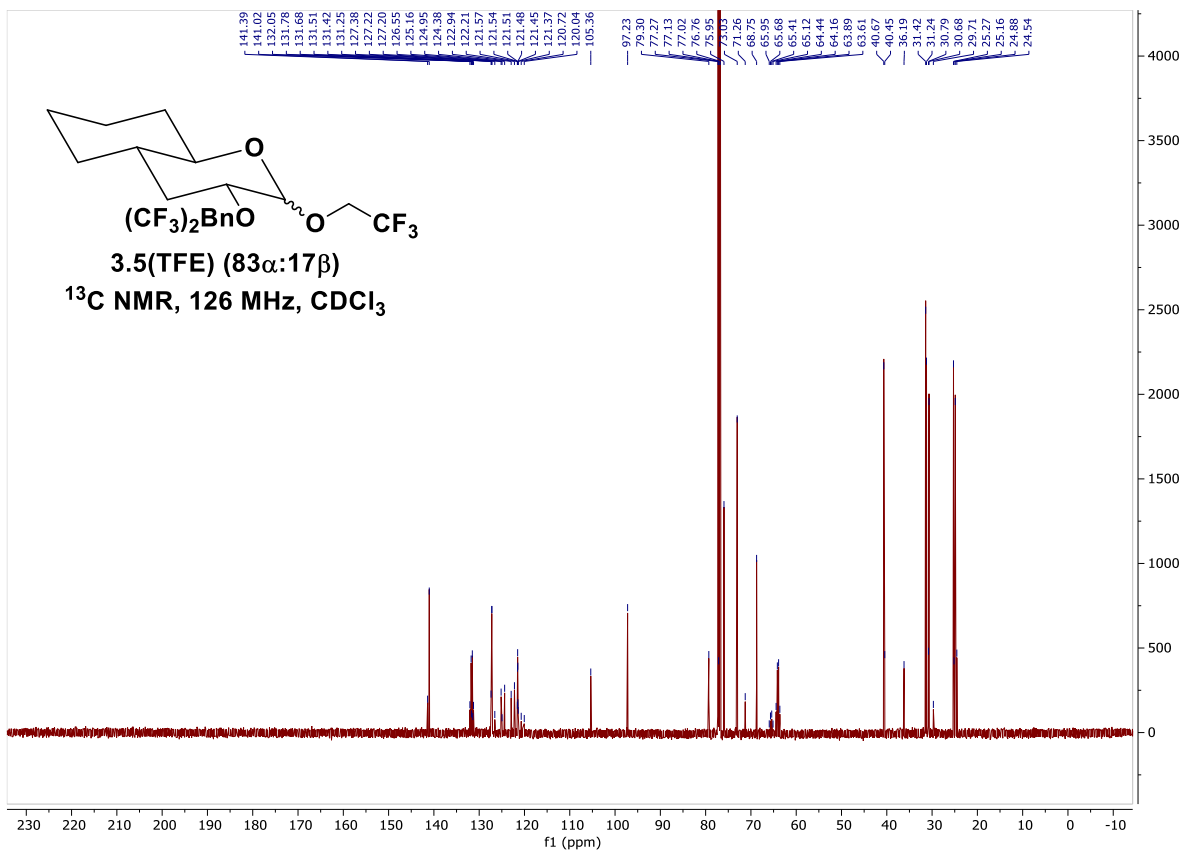


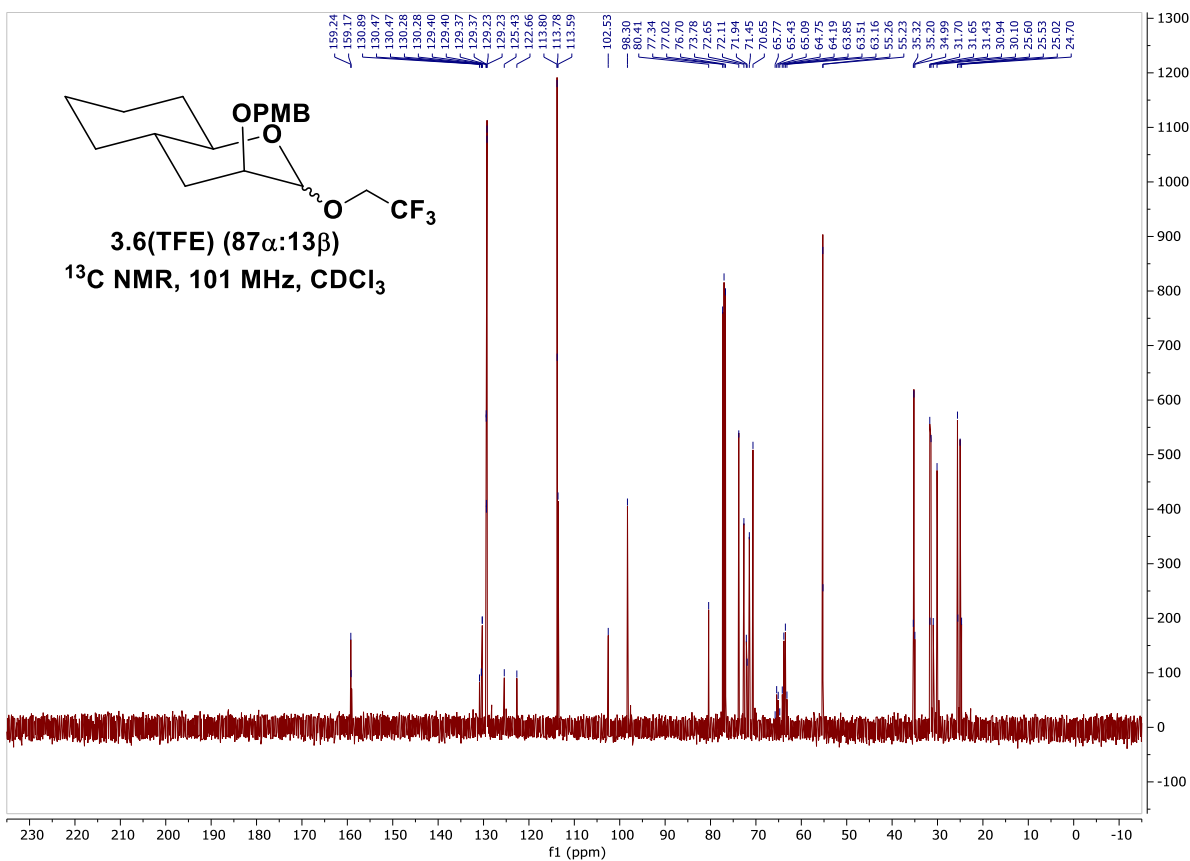
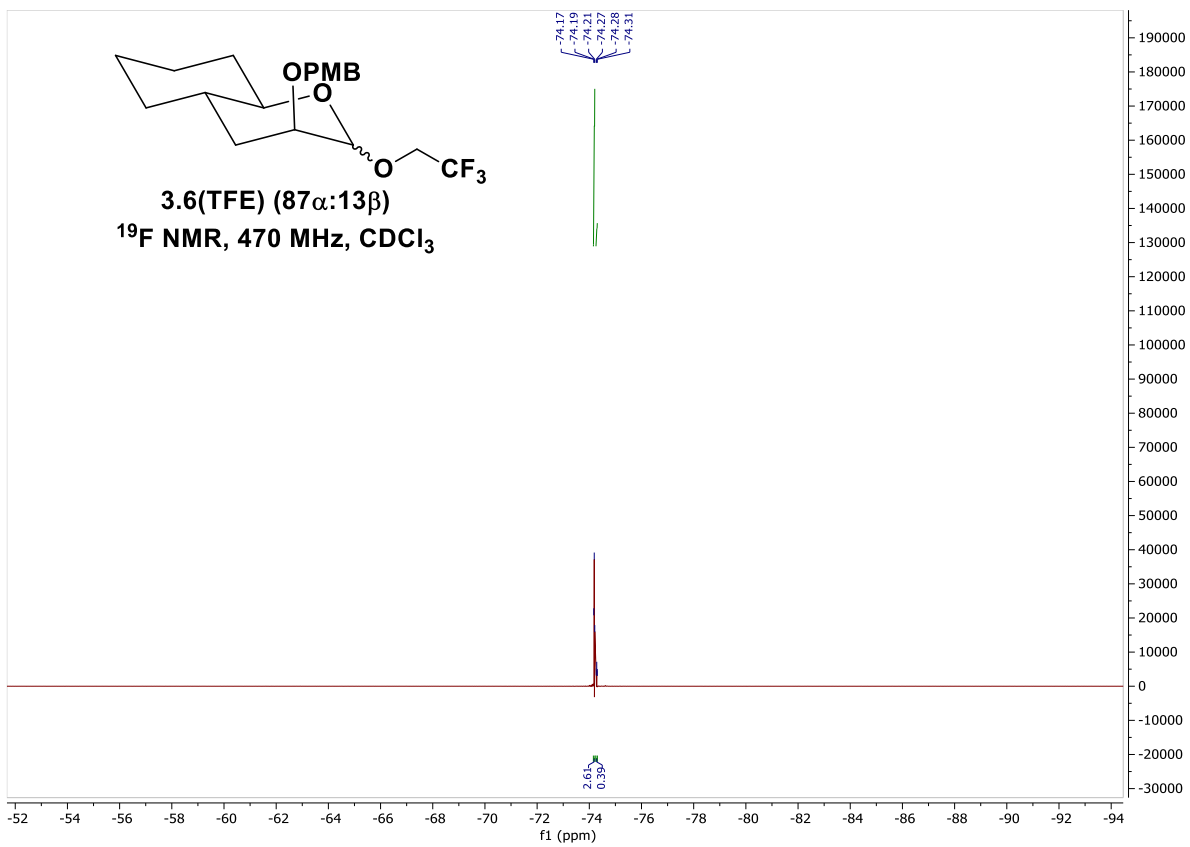




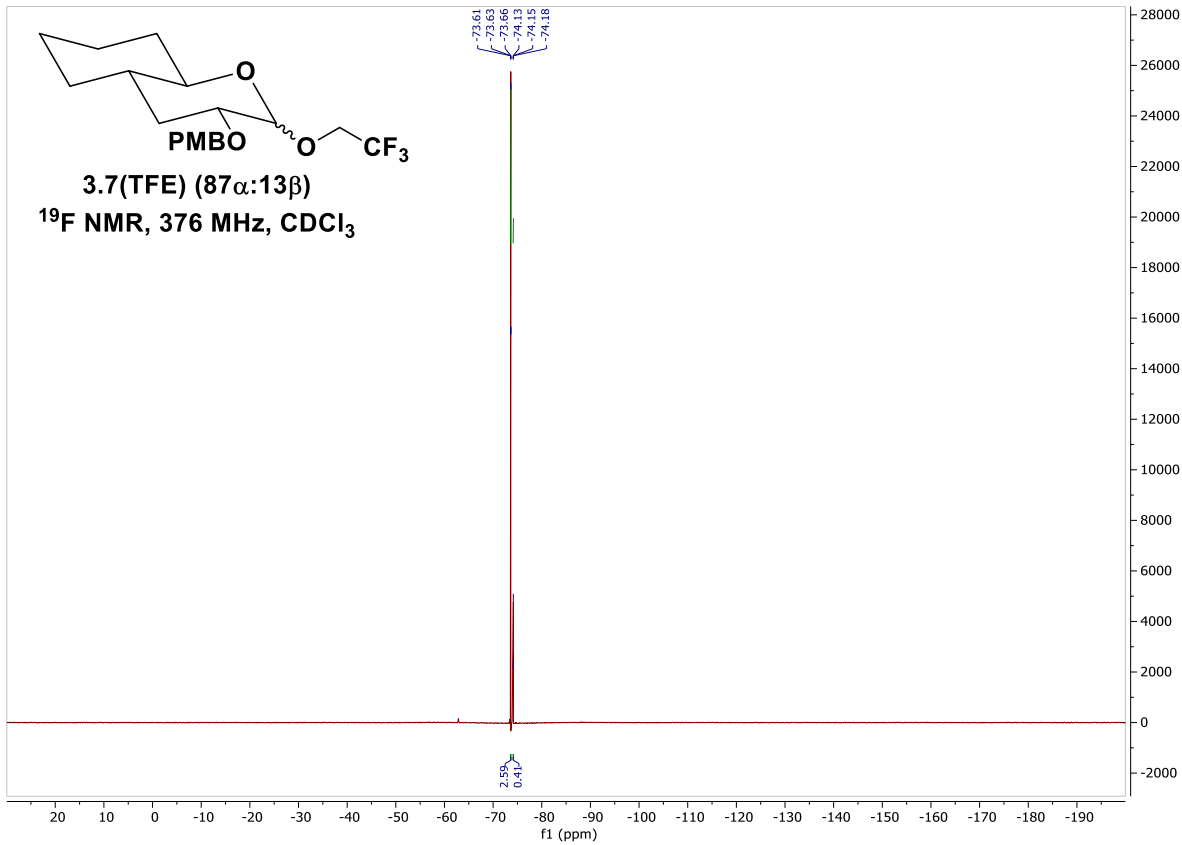
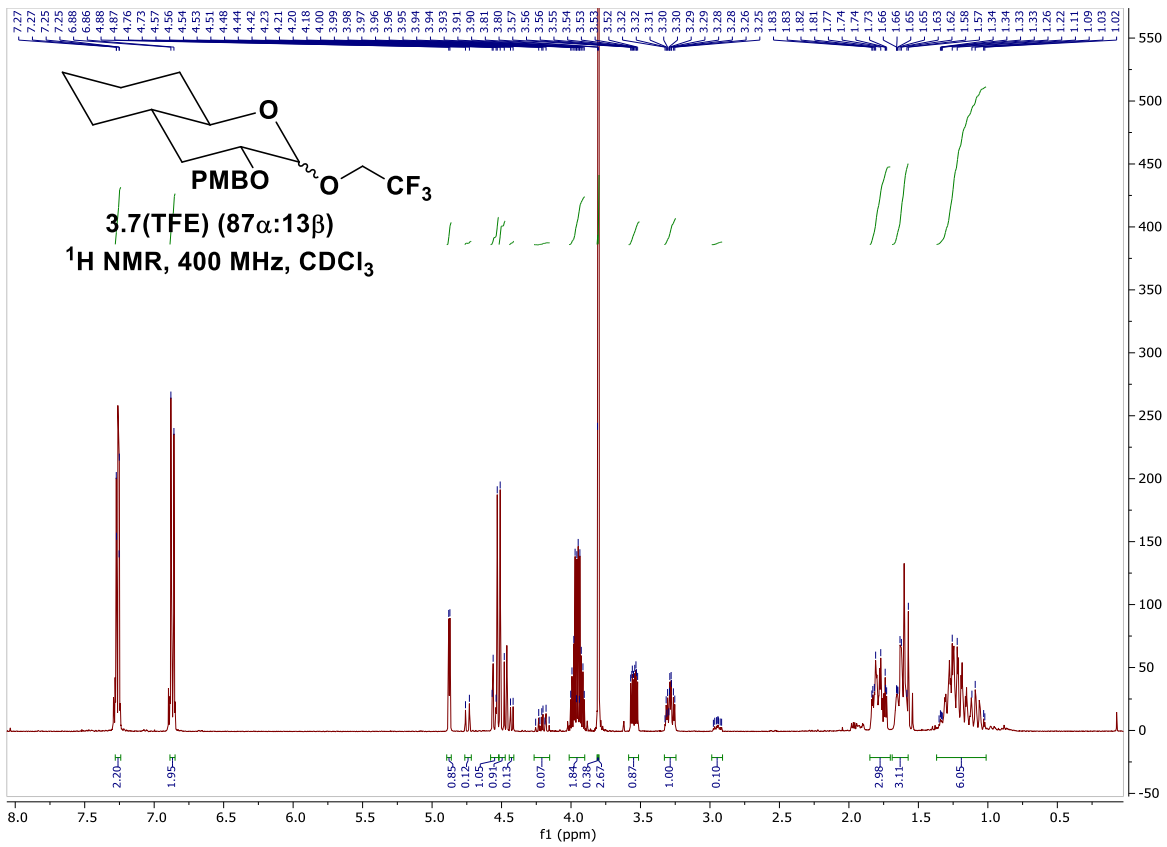


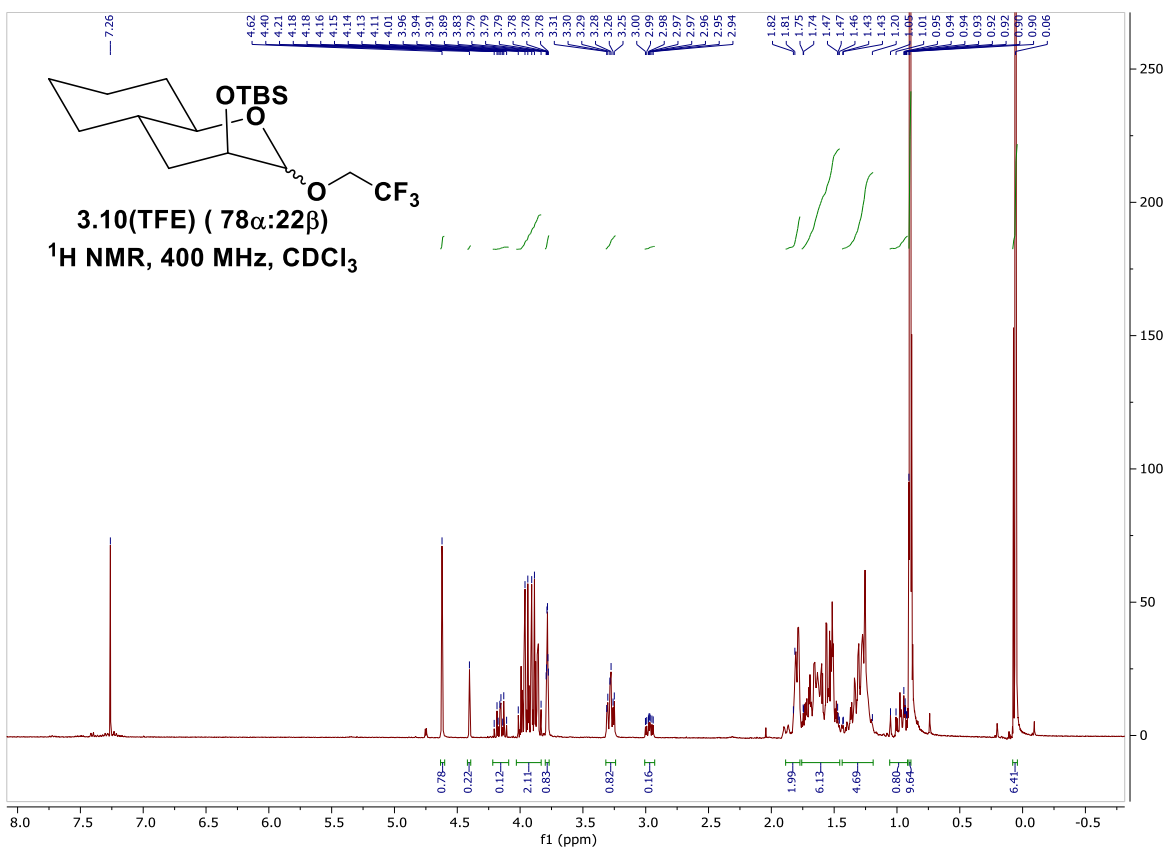
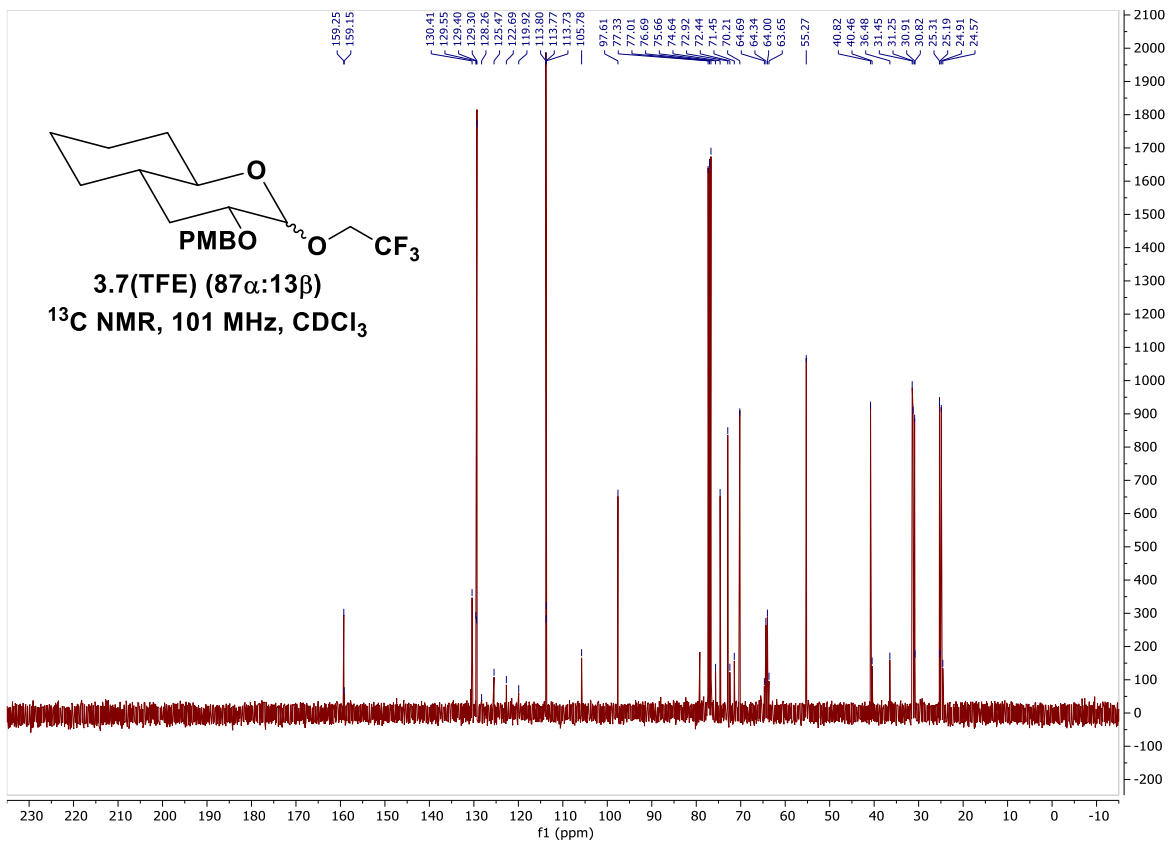


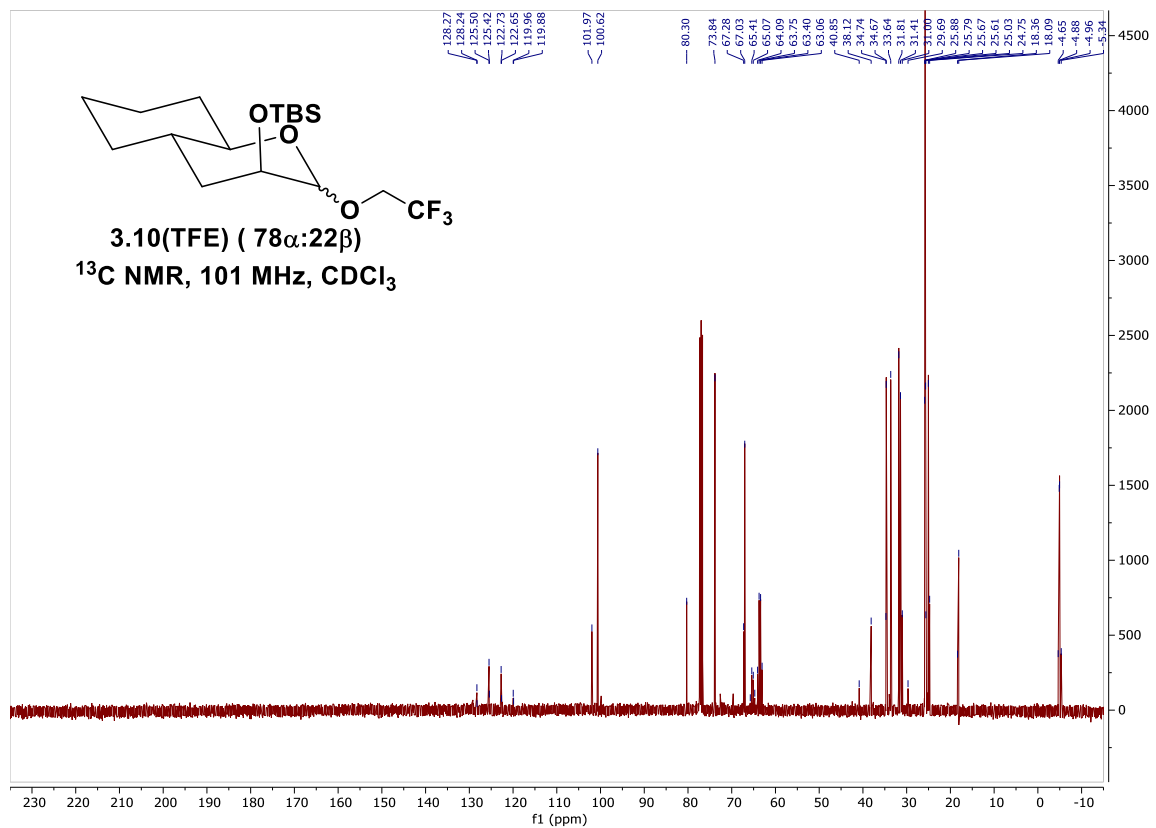
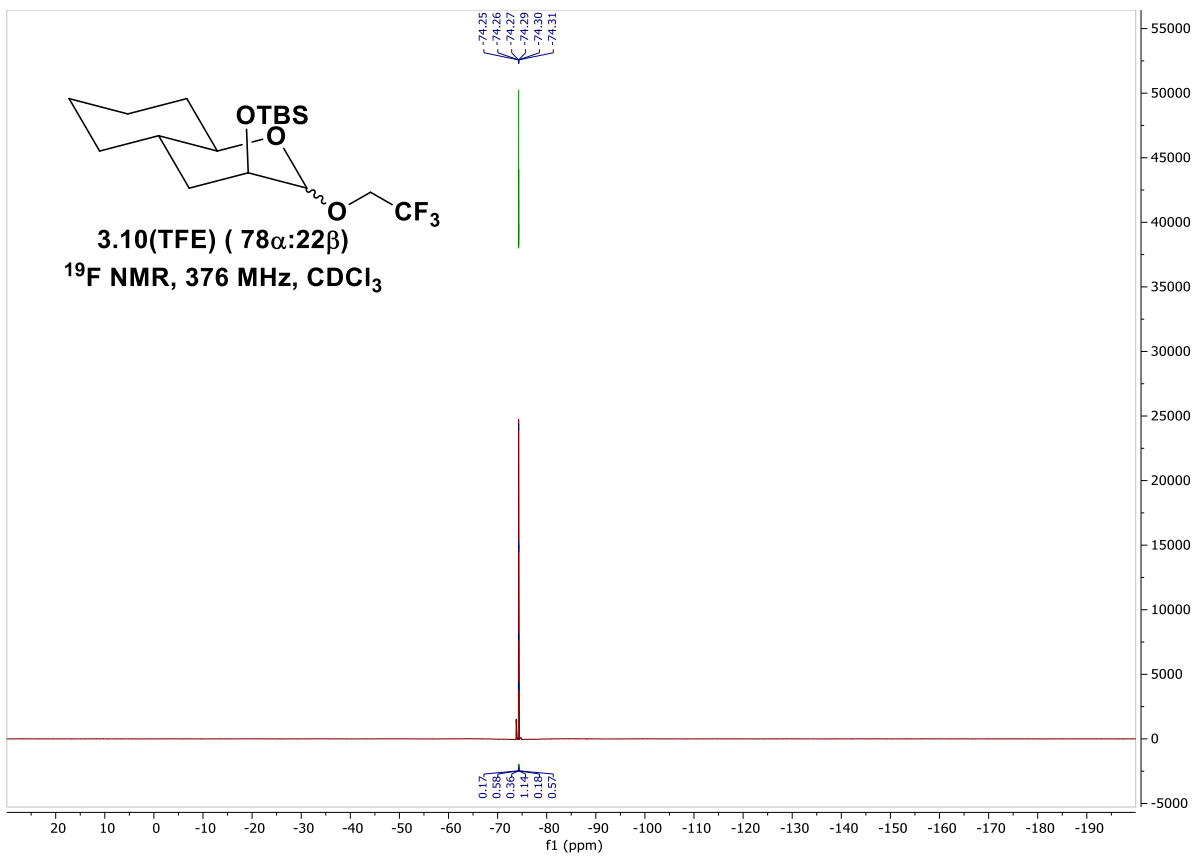




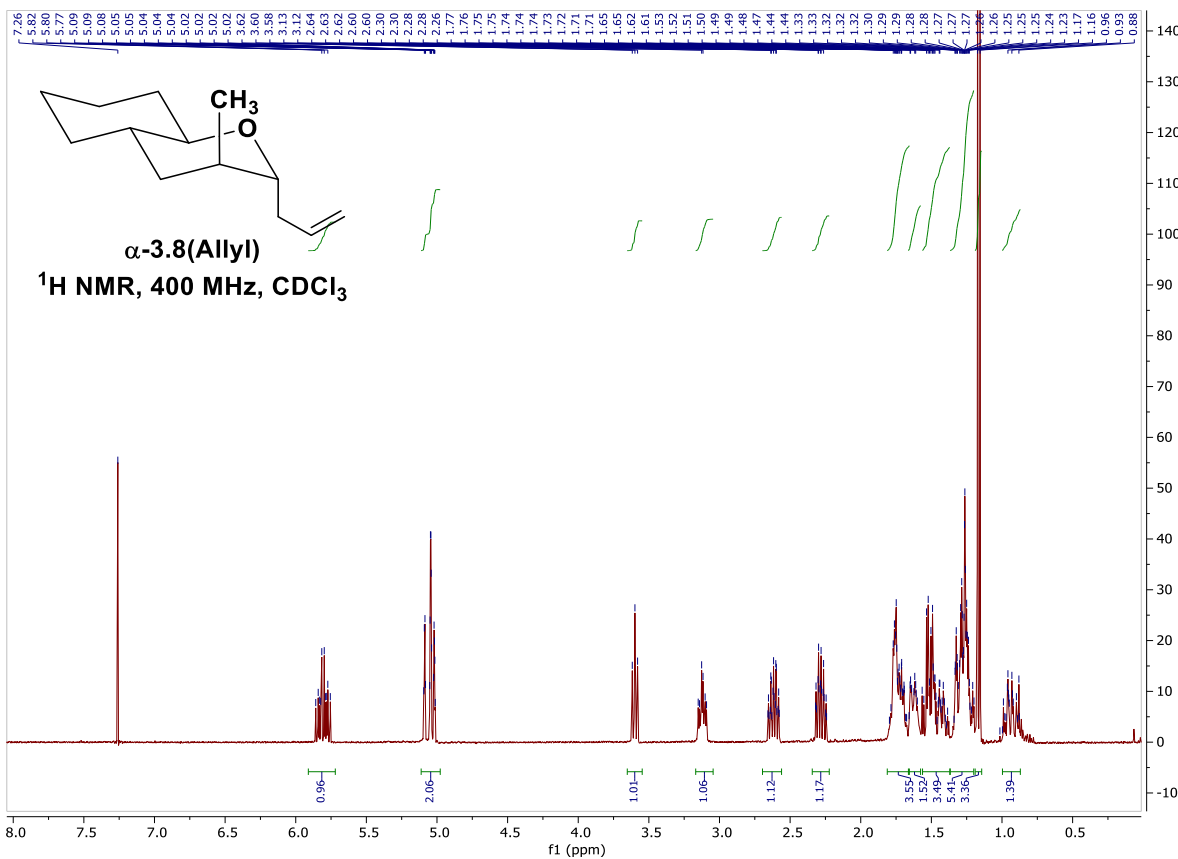
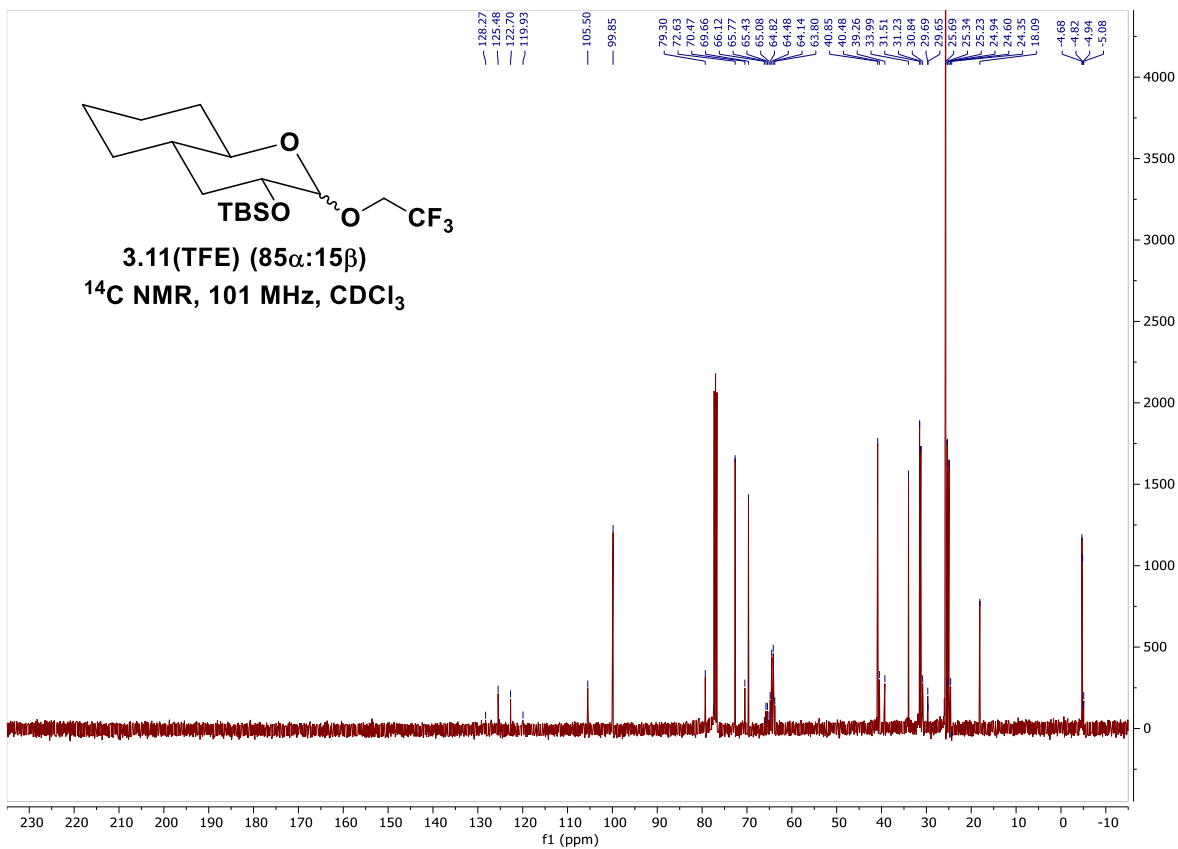


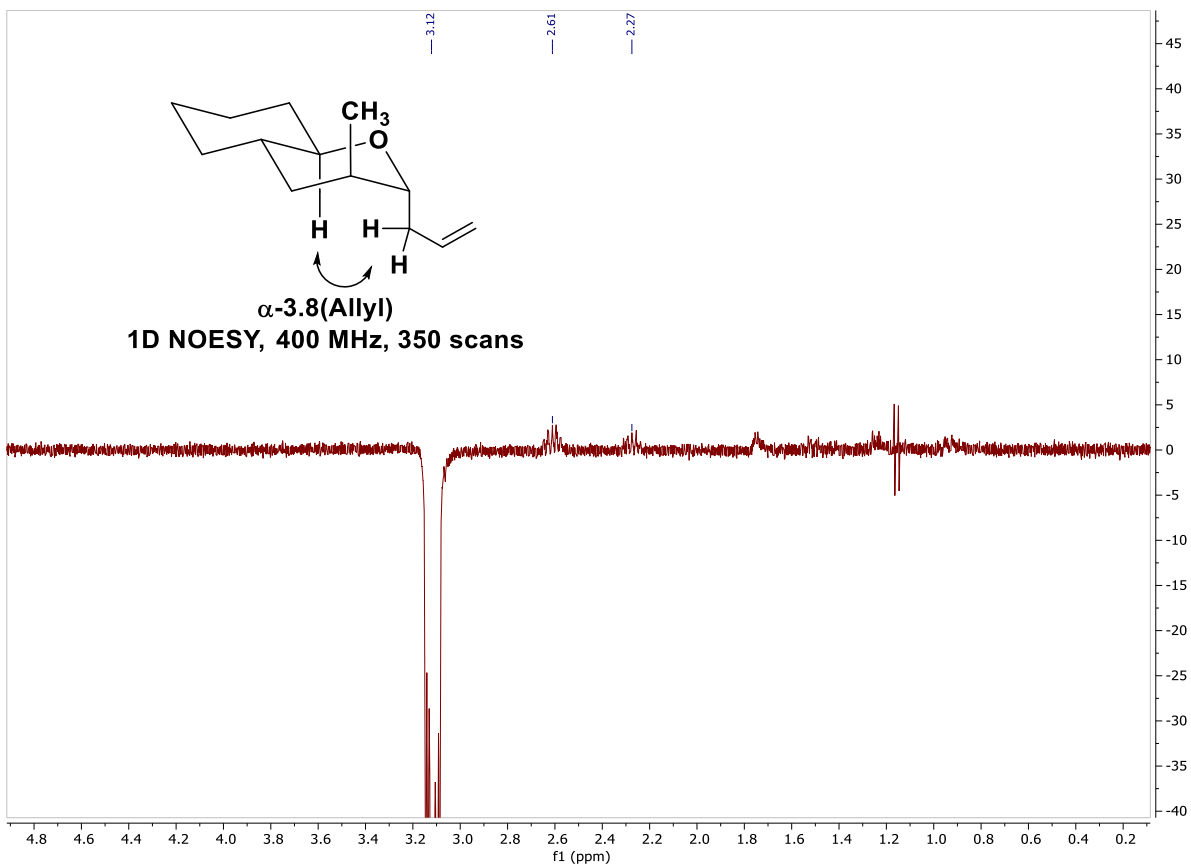
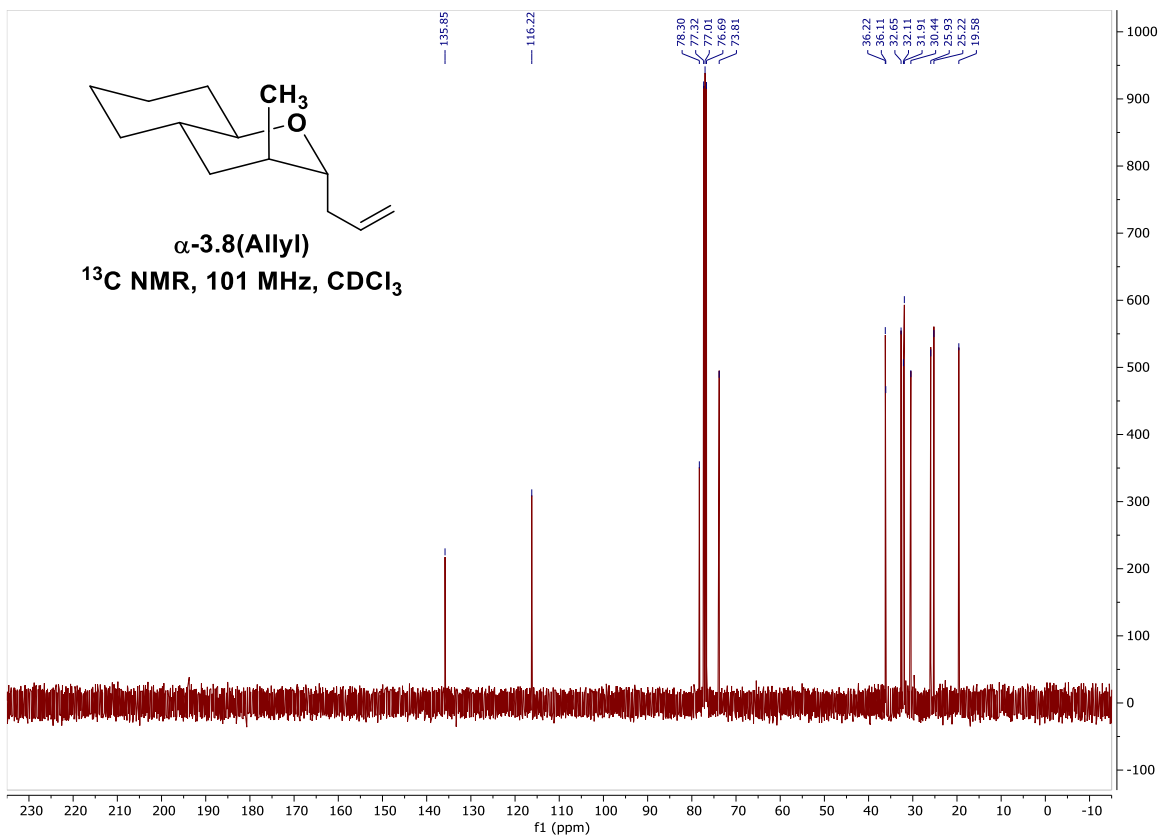


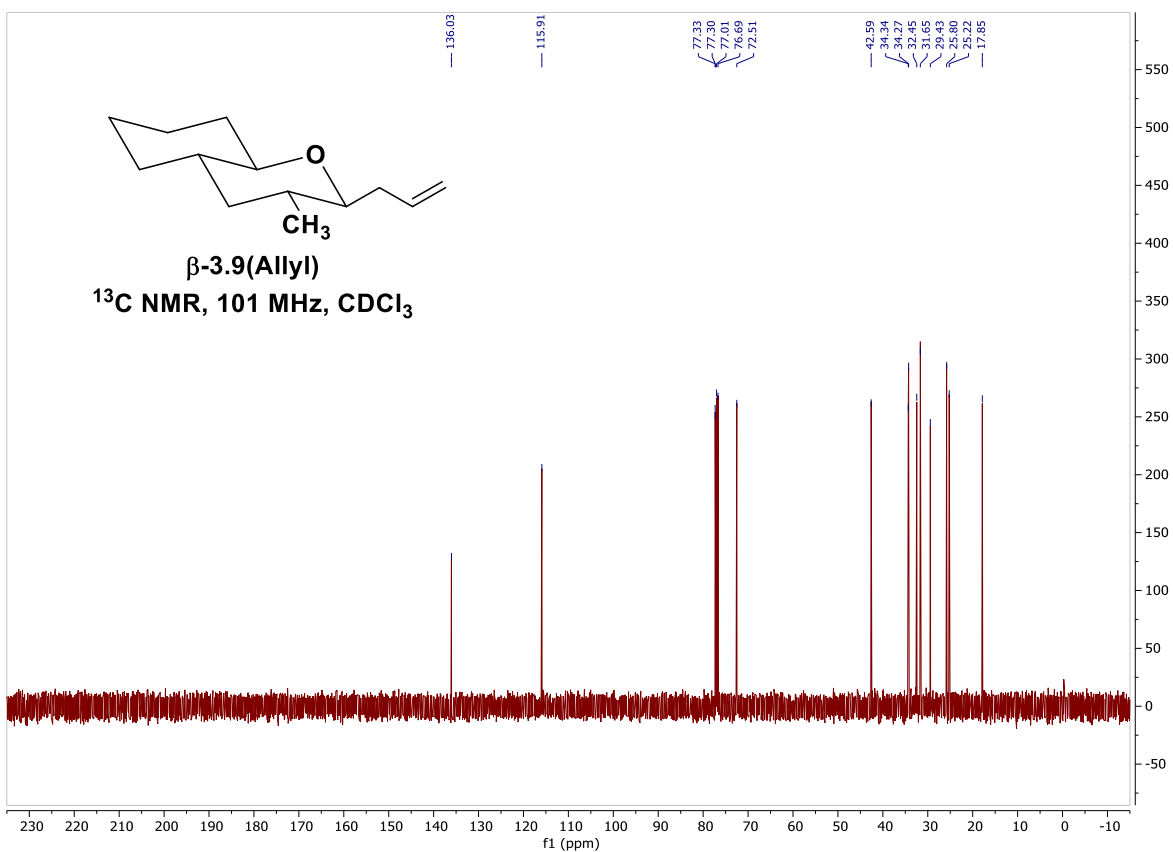
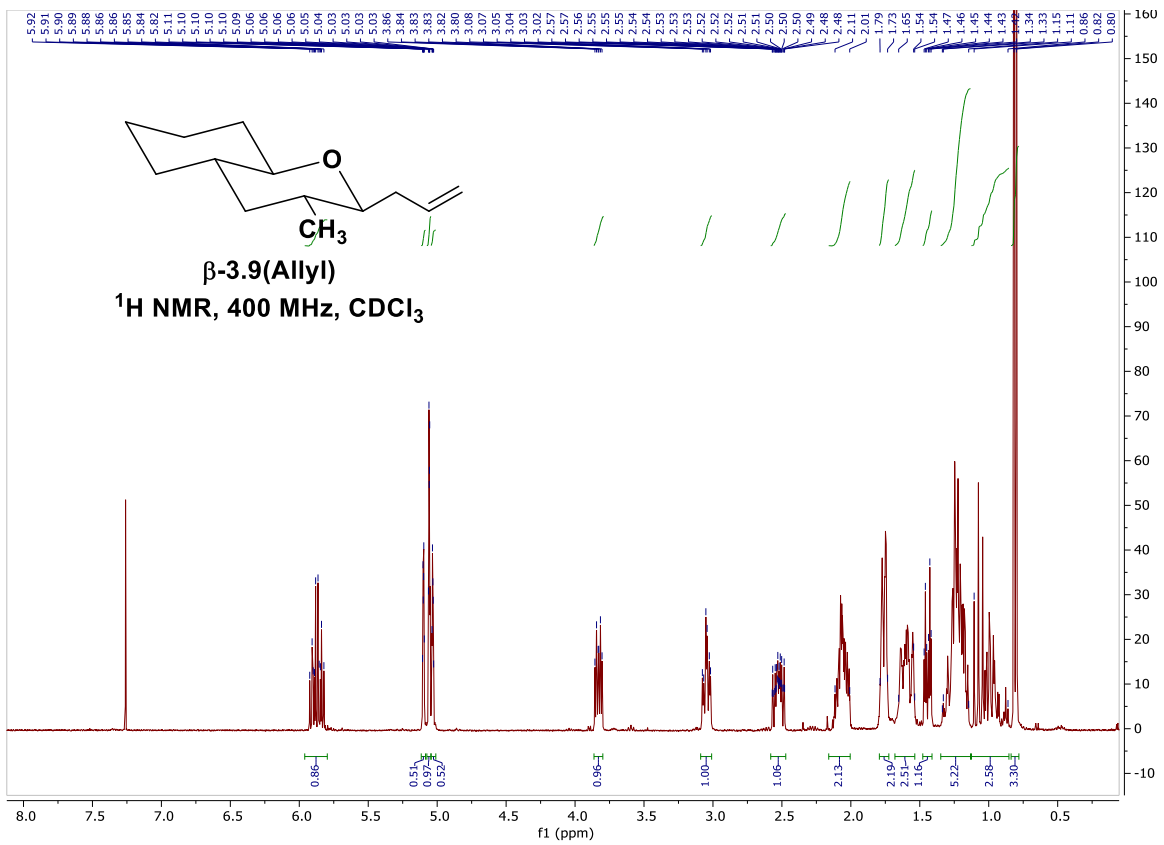


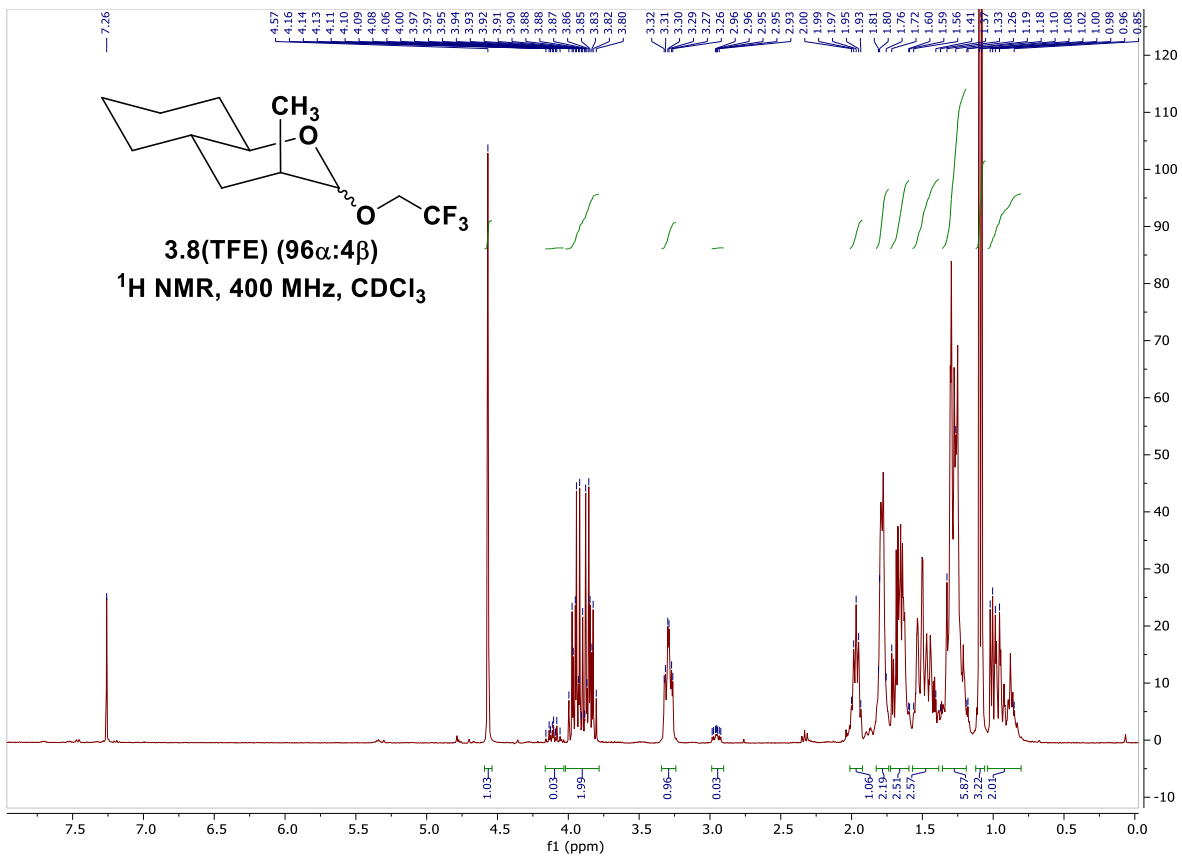
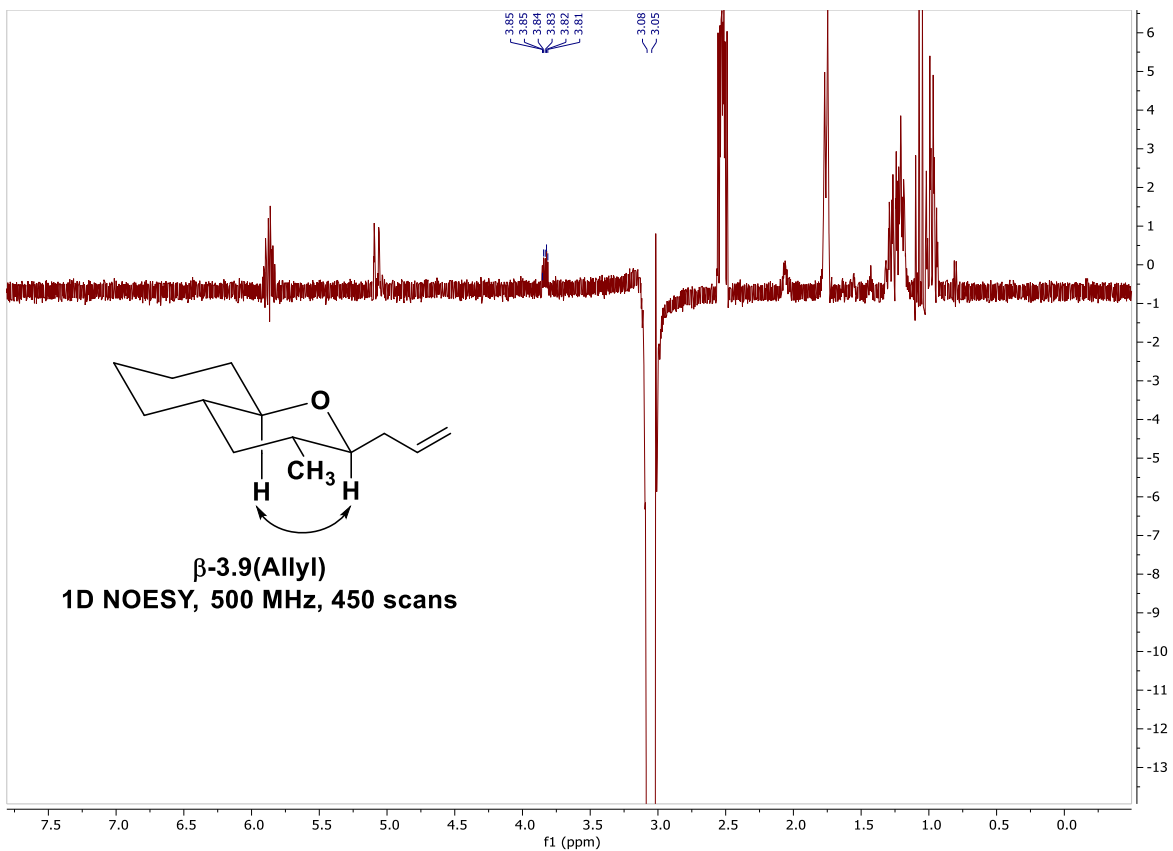




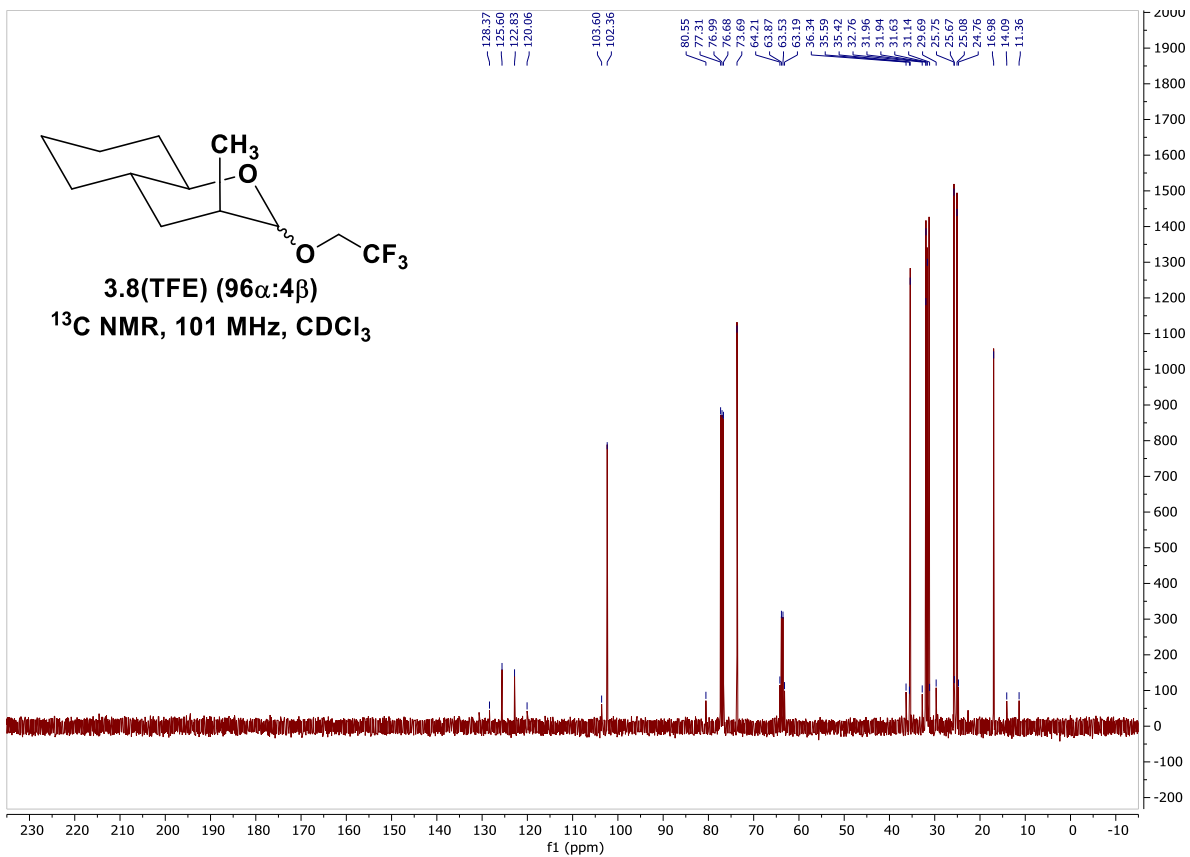
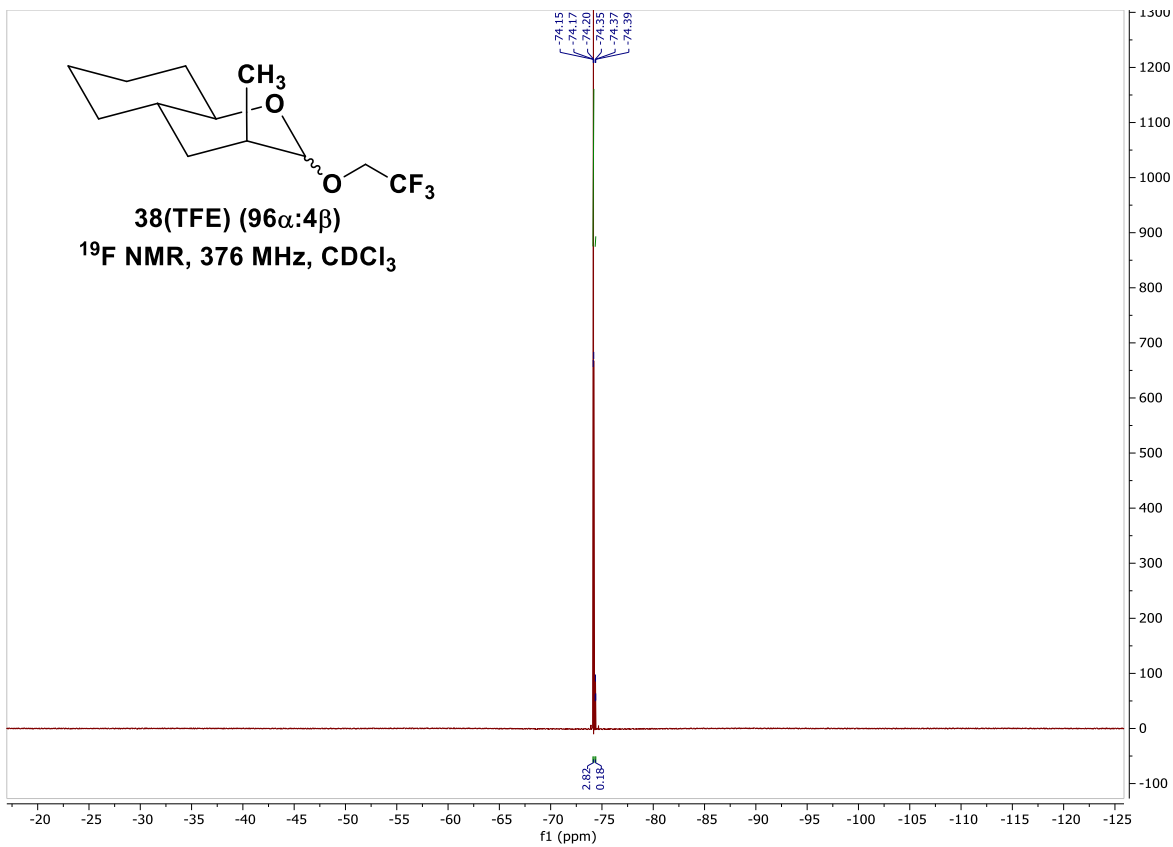


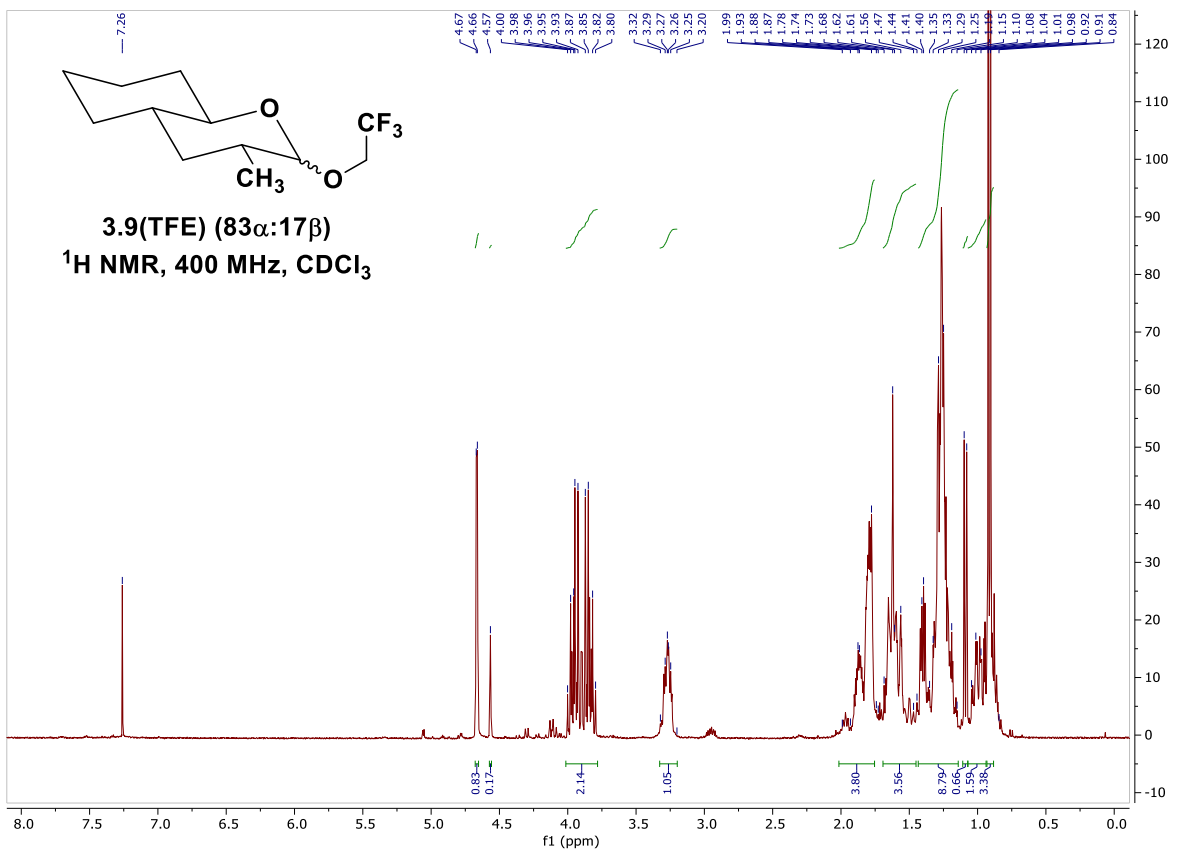
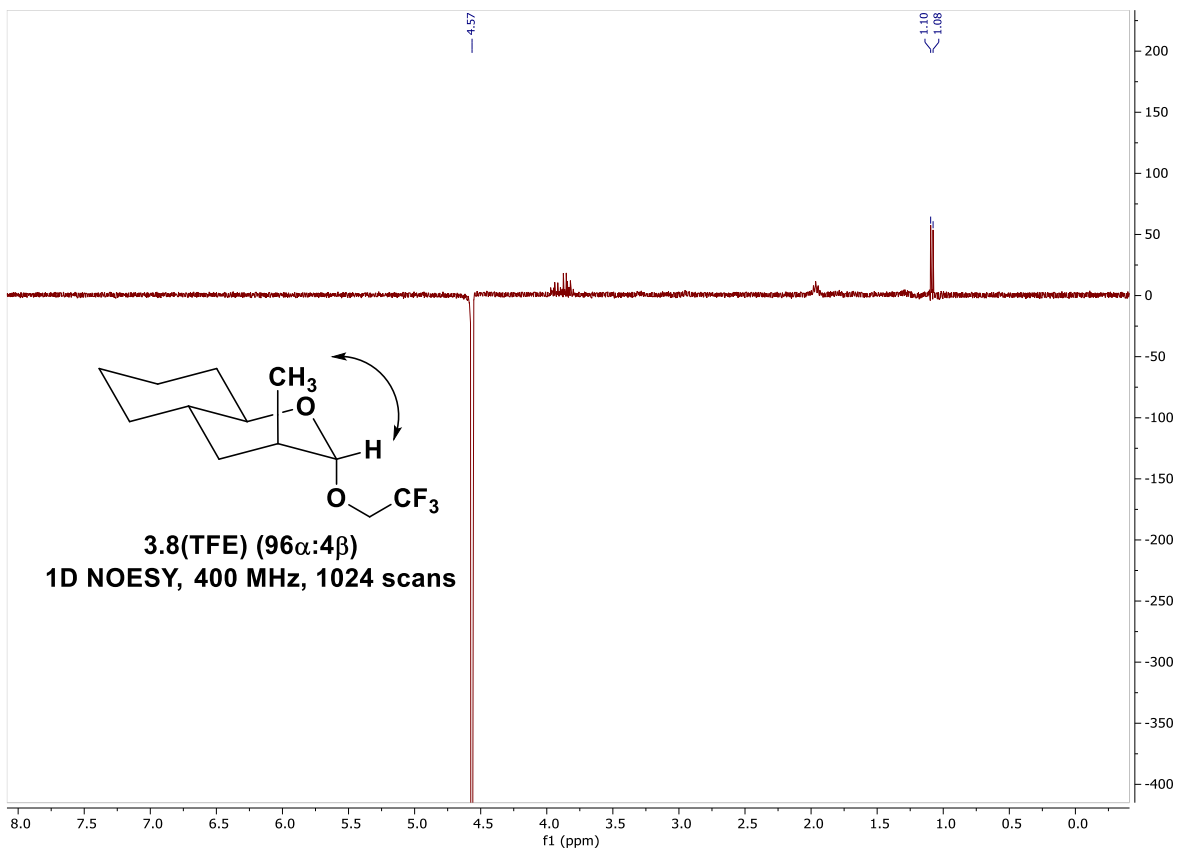


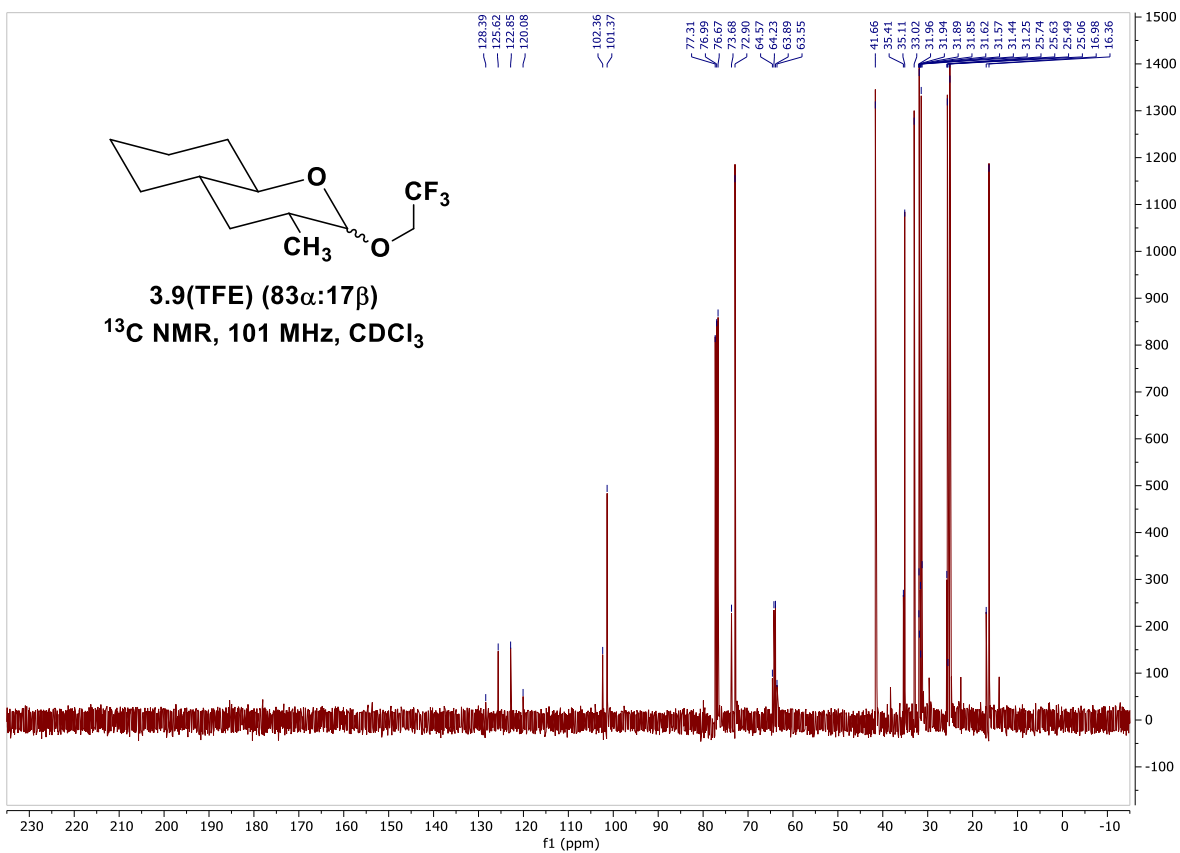
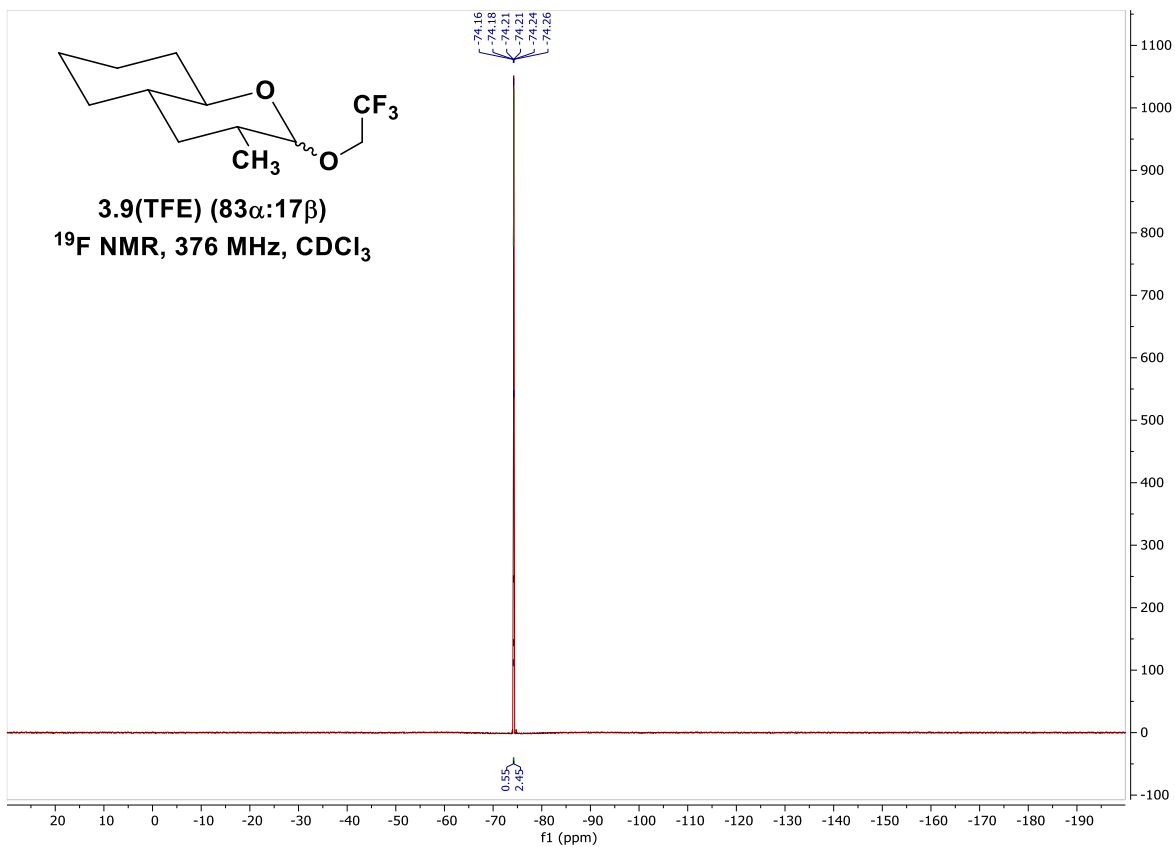


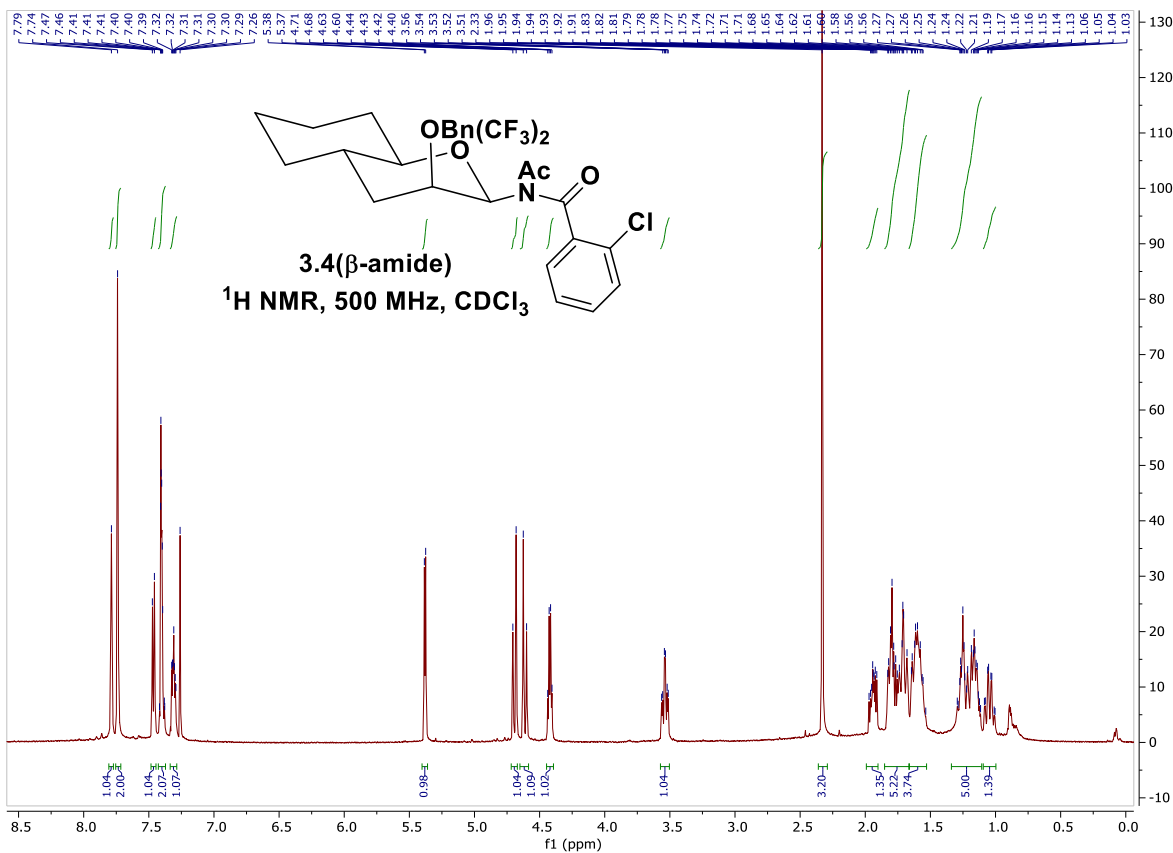
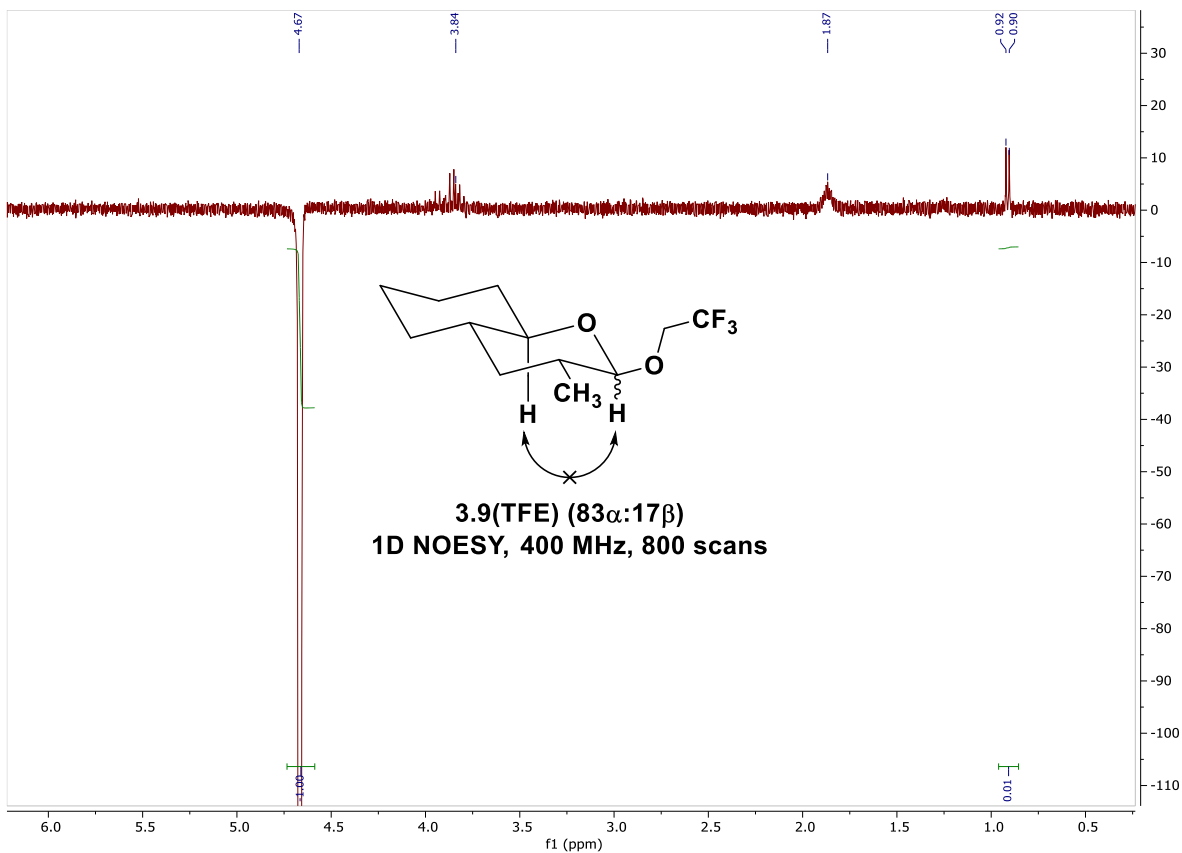


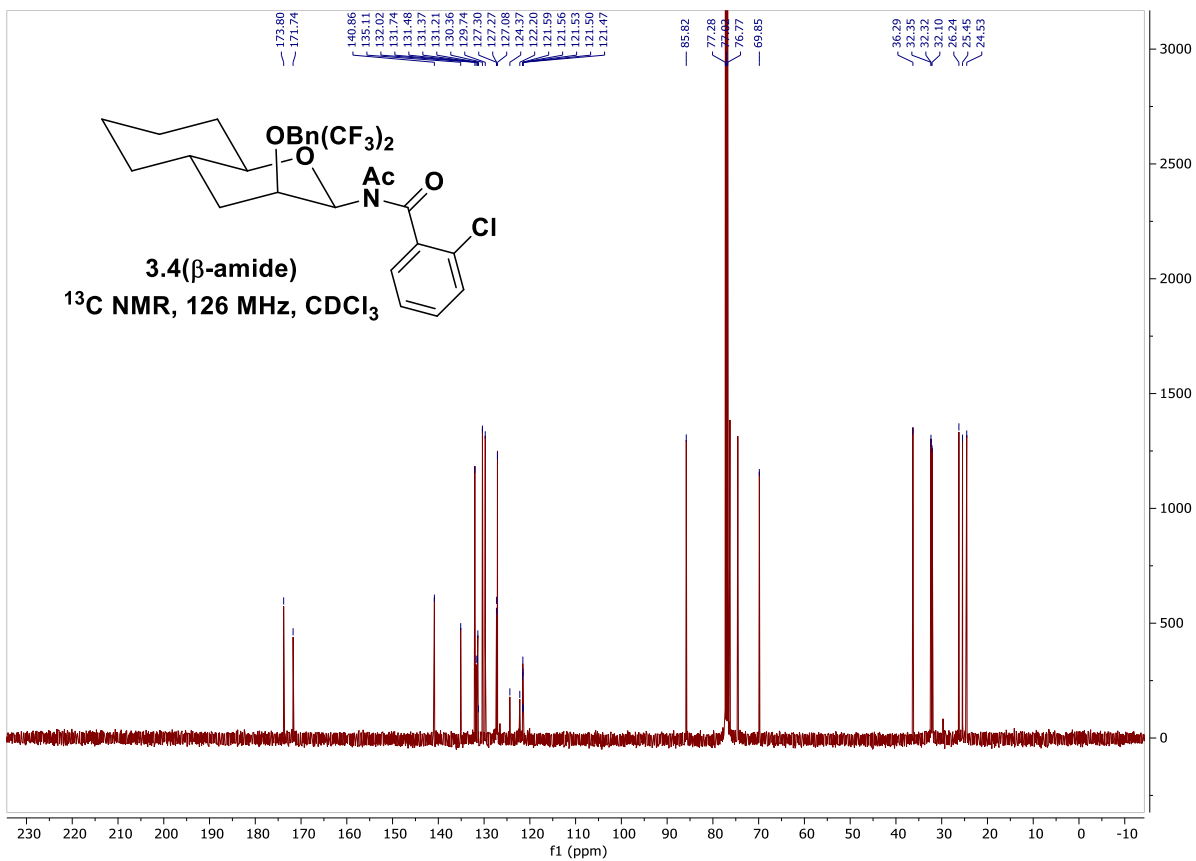
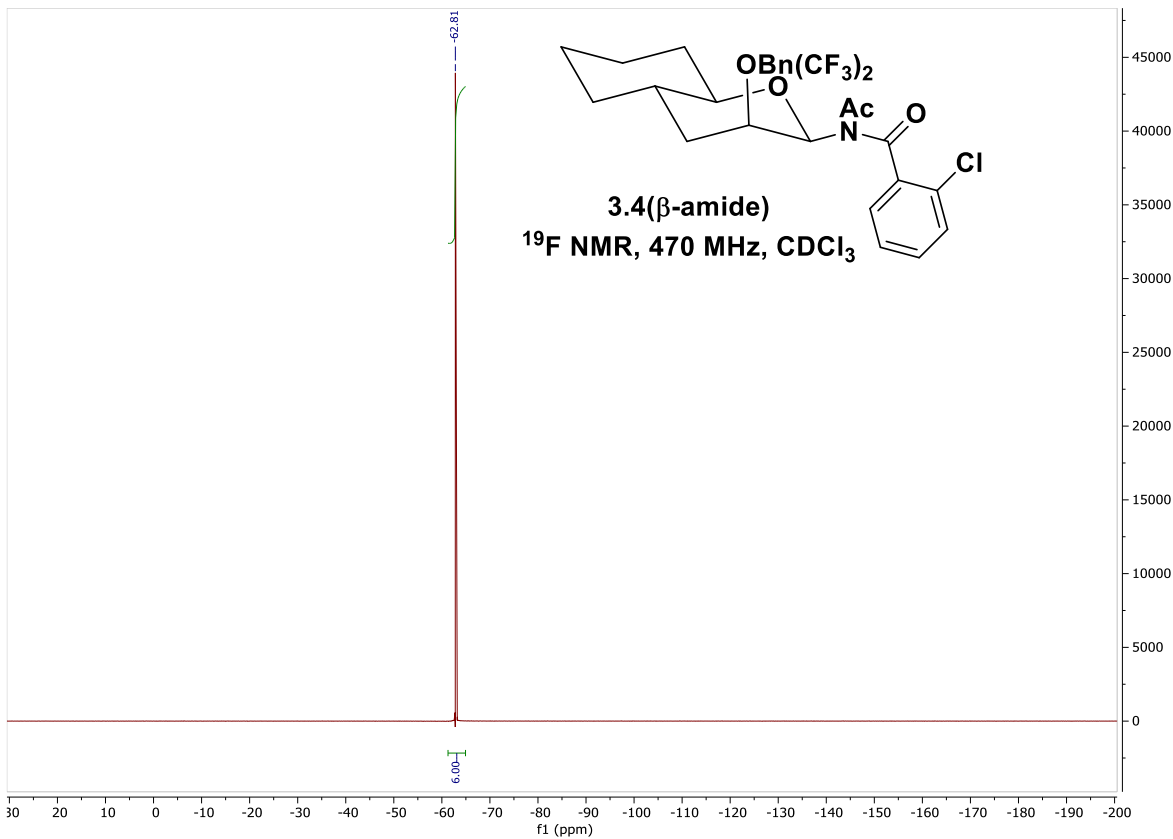


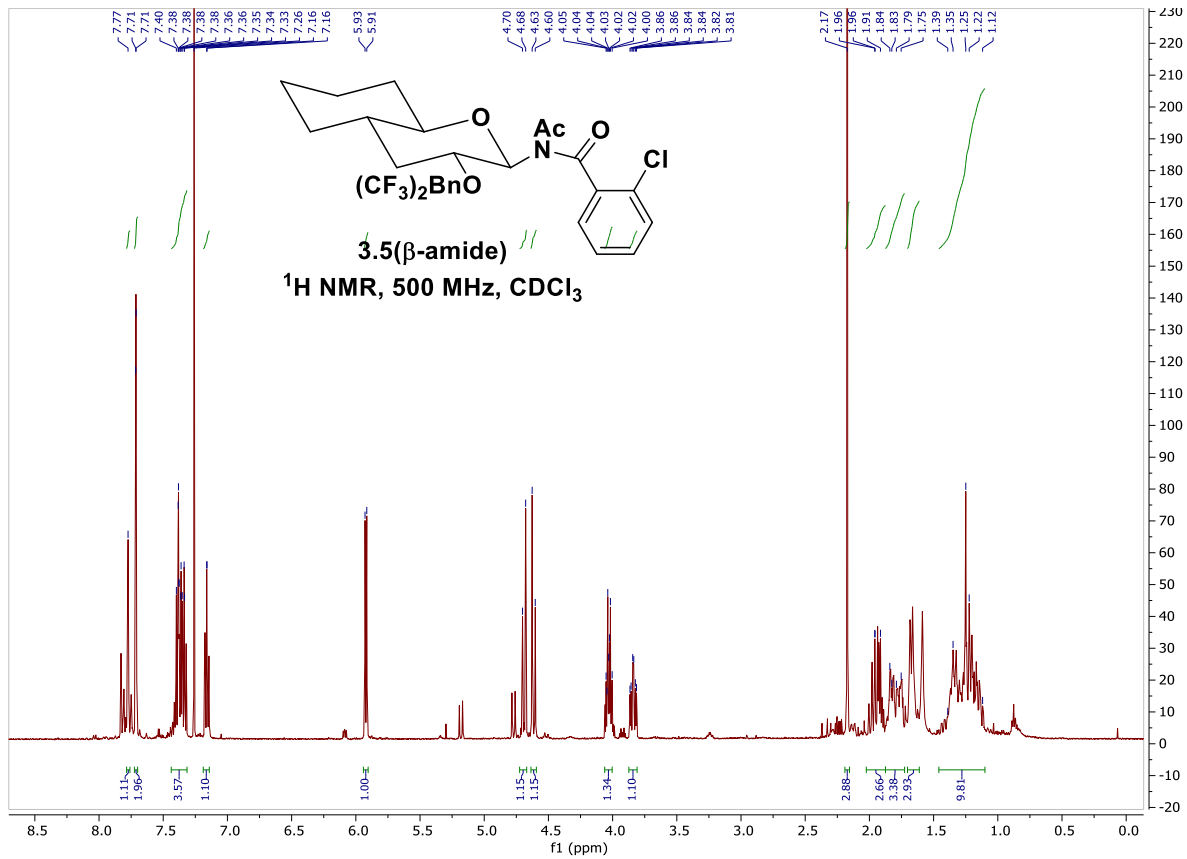
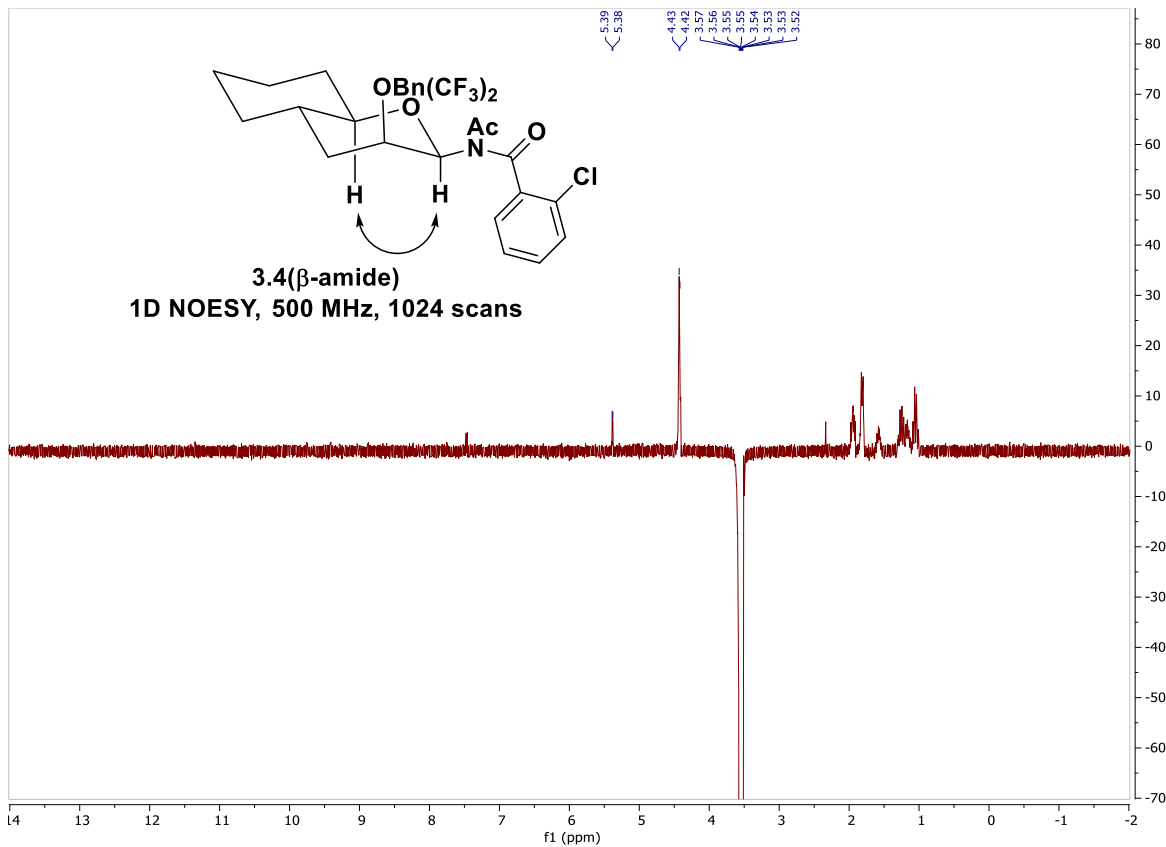


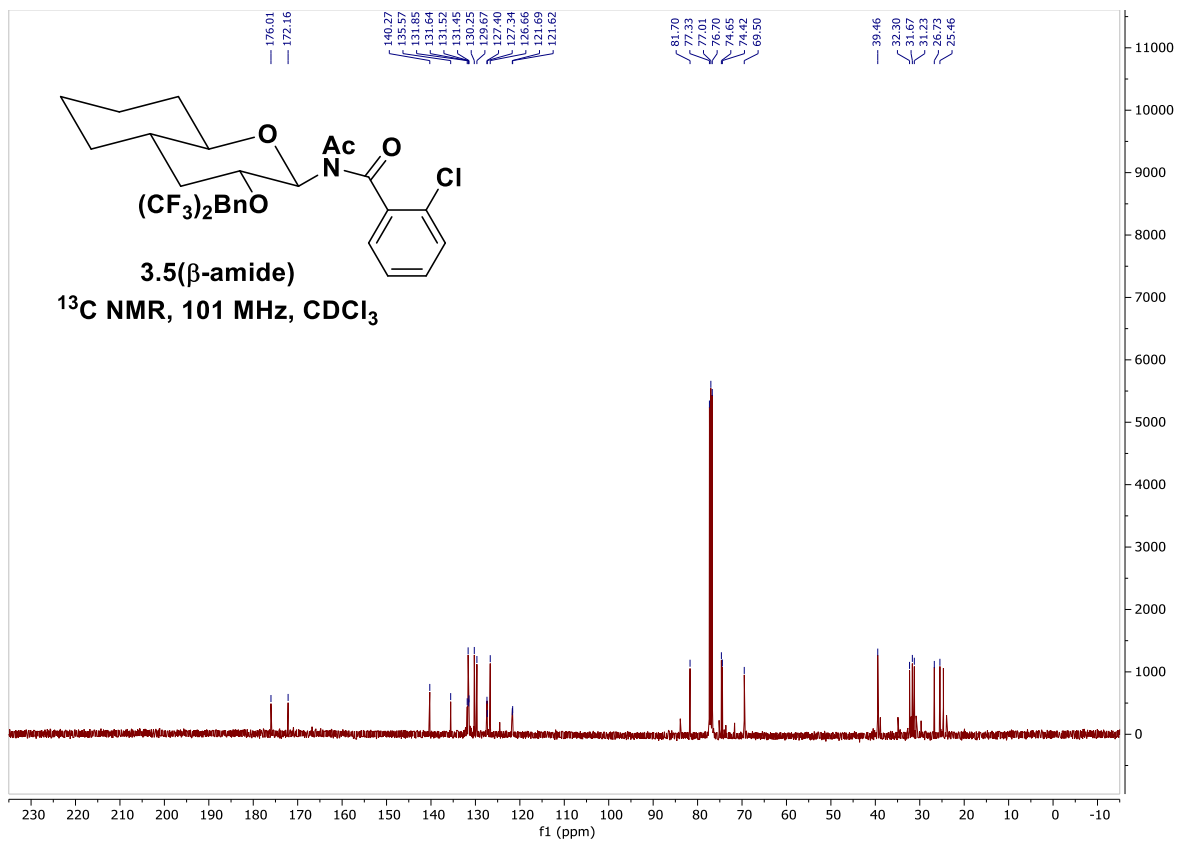
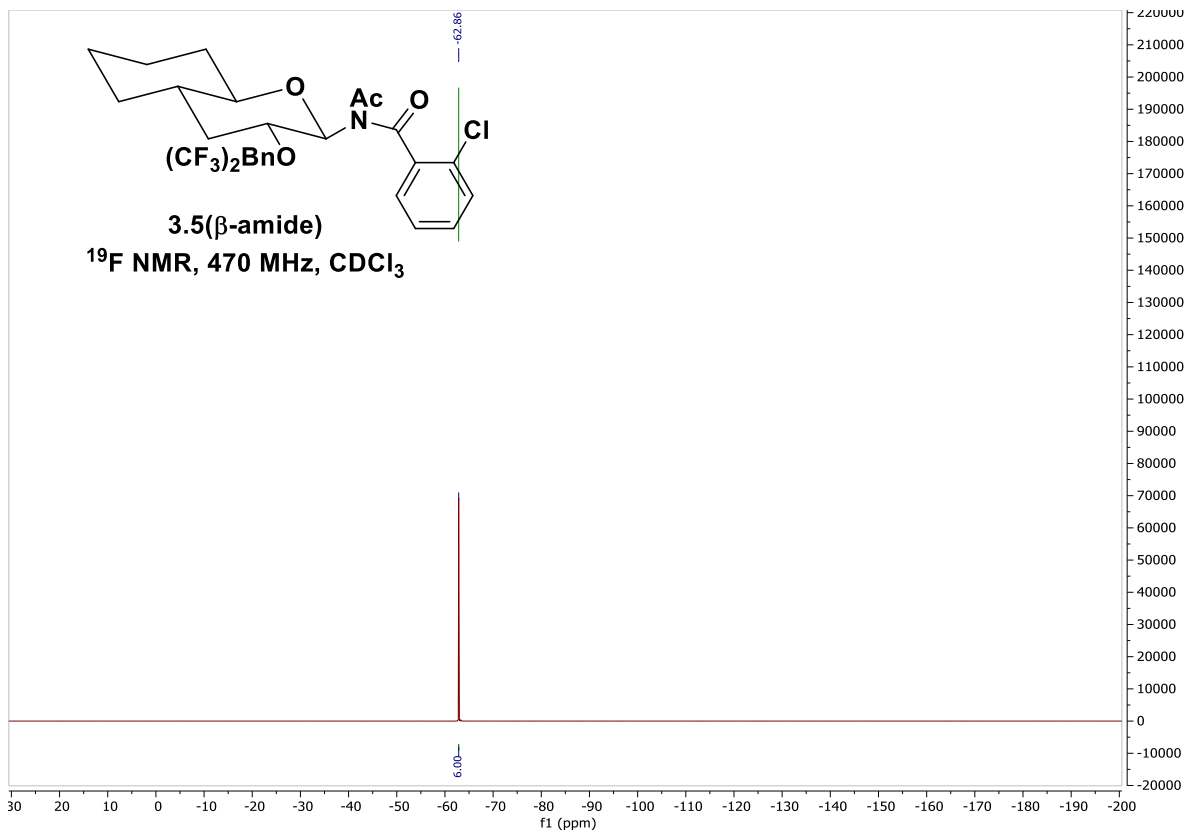


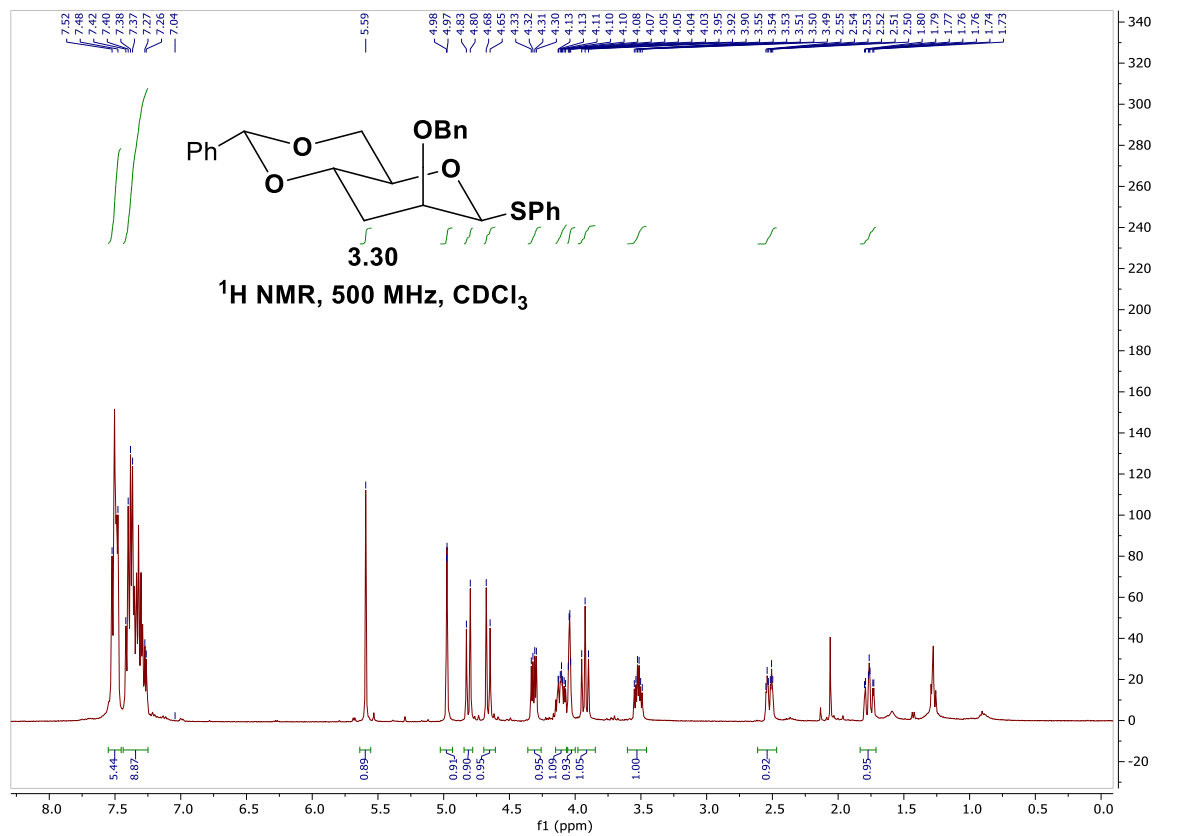
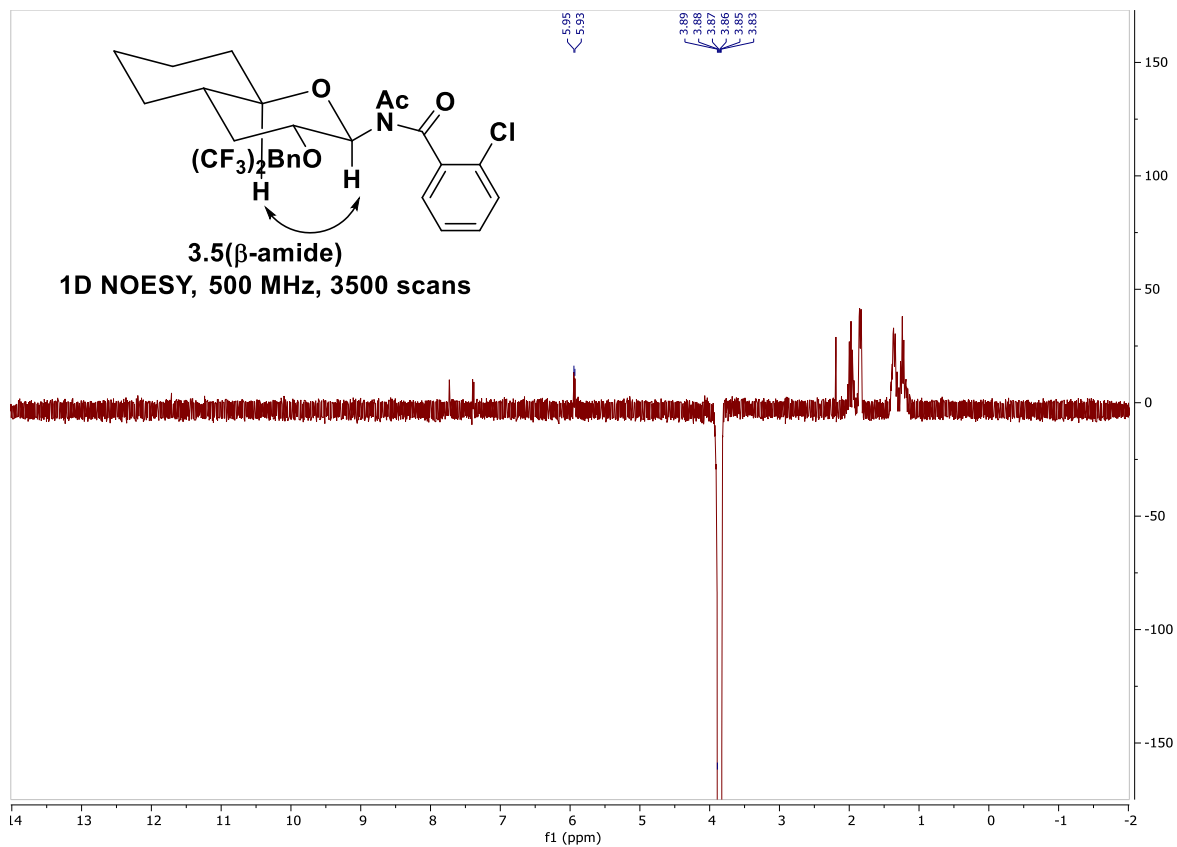








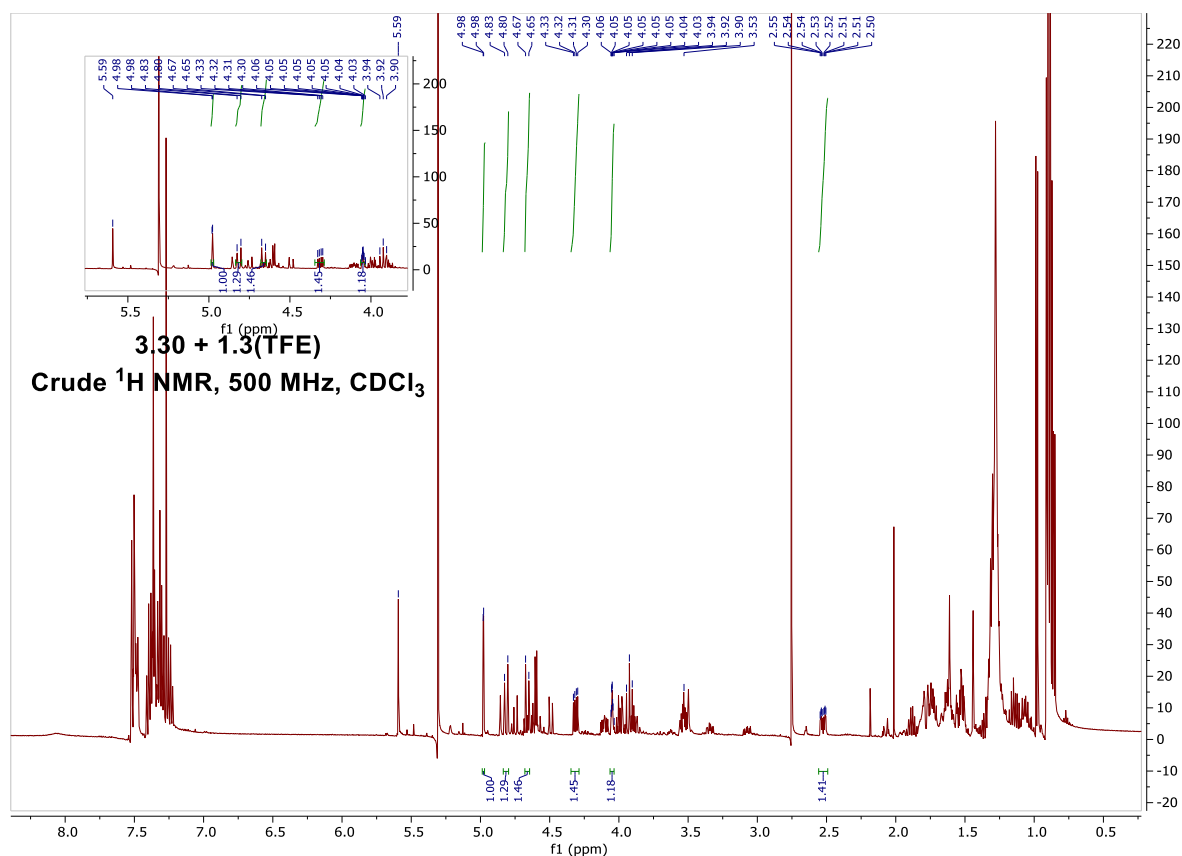


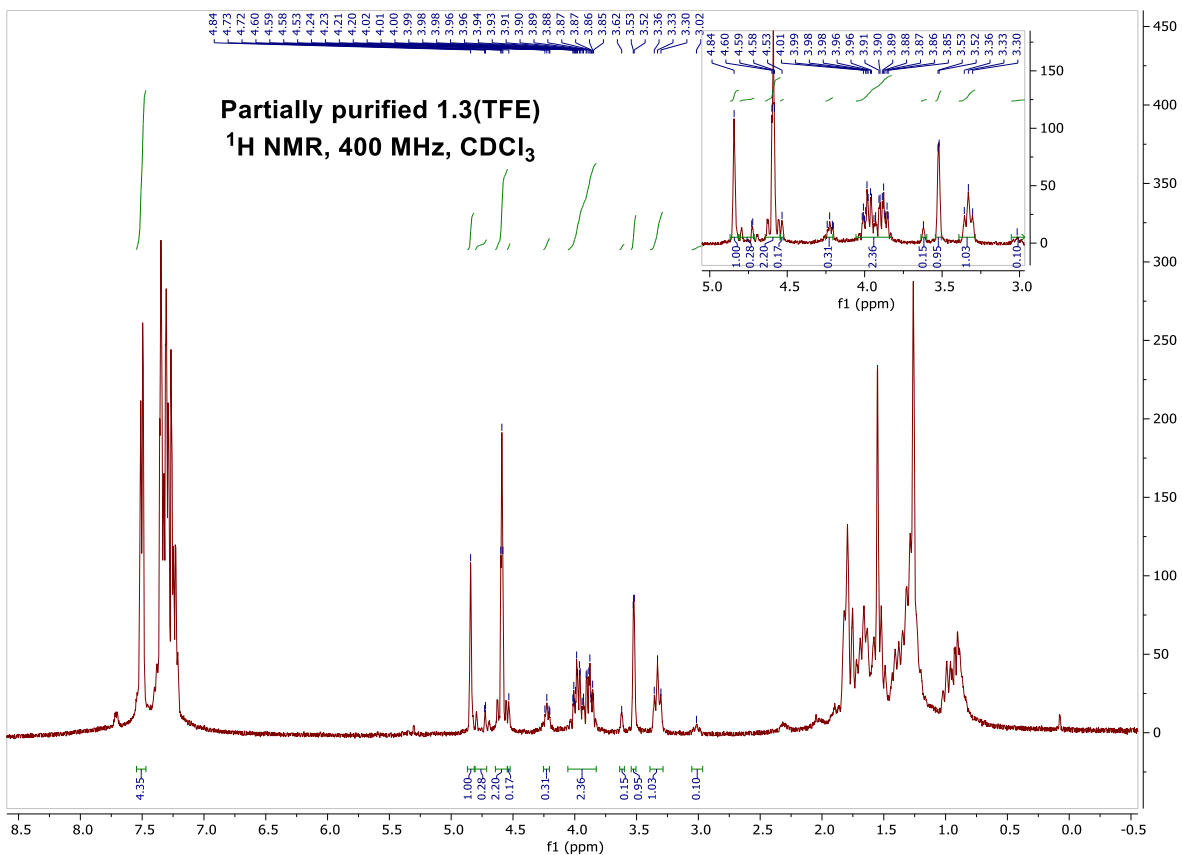
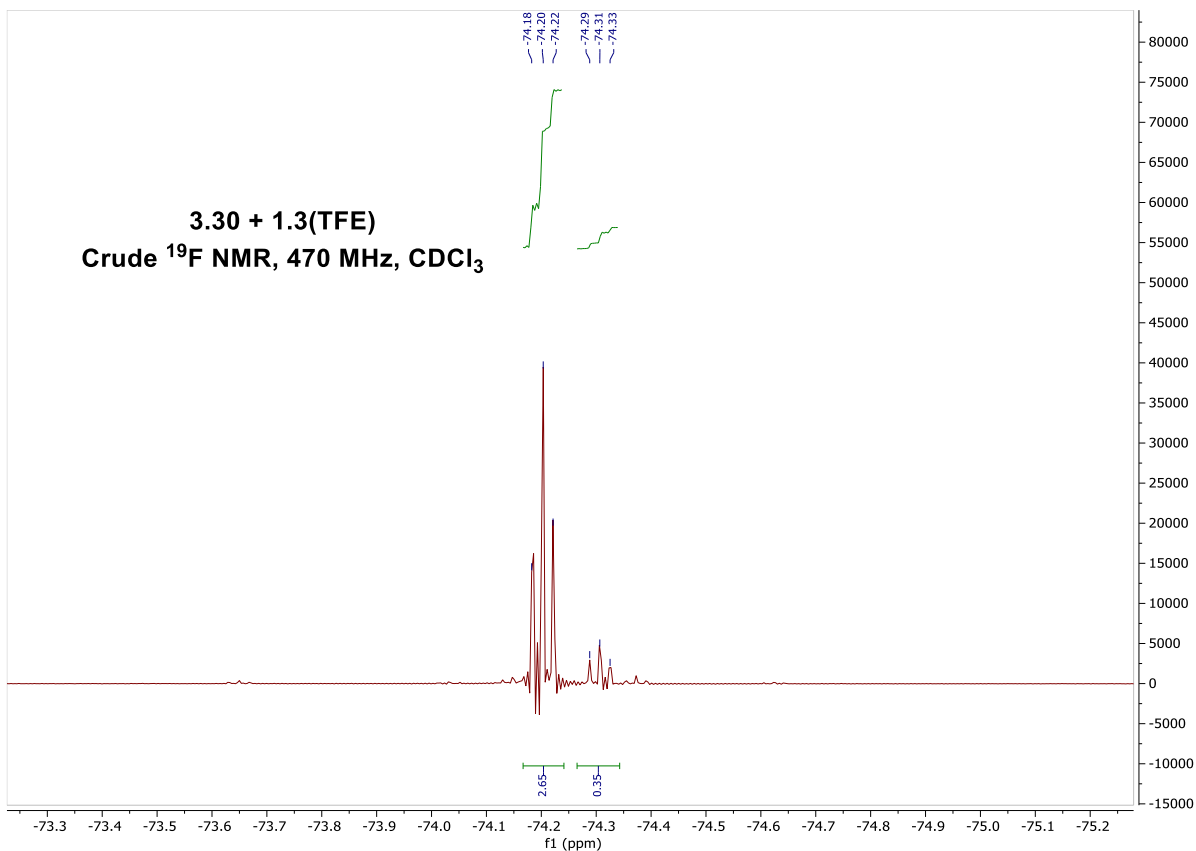




## G.2 Expérience de glycosylation compétitive

Compound **3.30** (0,006 g, 0.0138 mmol) and  **$\beta$ -1.3(SPh)** (0.005 g, 0.0138 mmol) were put in solution with dry CH<sub>3</sub>CN (0.5 mL) with 4Å molecular sieves. 2,2,2-trifluoroethanol (0.004 mL, 0.055 mmol) was added and the solution brought to 0 °C. NIS (0.006 g, 0.028 mmol) was then added in solution with dry CH<sub>3</sub>CN (0.250 mL). The reaction was stirred 2 hours at 0 °C upon which it was quenched with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3(aq)</sub> and diluted with DCM. The organic phase was separated, and the aqueous portion extracted with DCM (3x). Combined organic phase was dried with MgSO<sub>4</sub>, filtered and condensed *in vacuo*. Crude <sup>1</sup>H NMR and <sup>19</sup>F NMR showed conversion of only  **$\beta$ -1.3(SPh)** to a mixture of  **$\alpha/\beta$ -1.3(TFE)**. After silica gel column chromatography (5% EtOAc to 15 % EtOAc/hexanes, TLC stained with CAM), compound **3.30** was recovered (0.005 g, 83%).





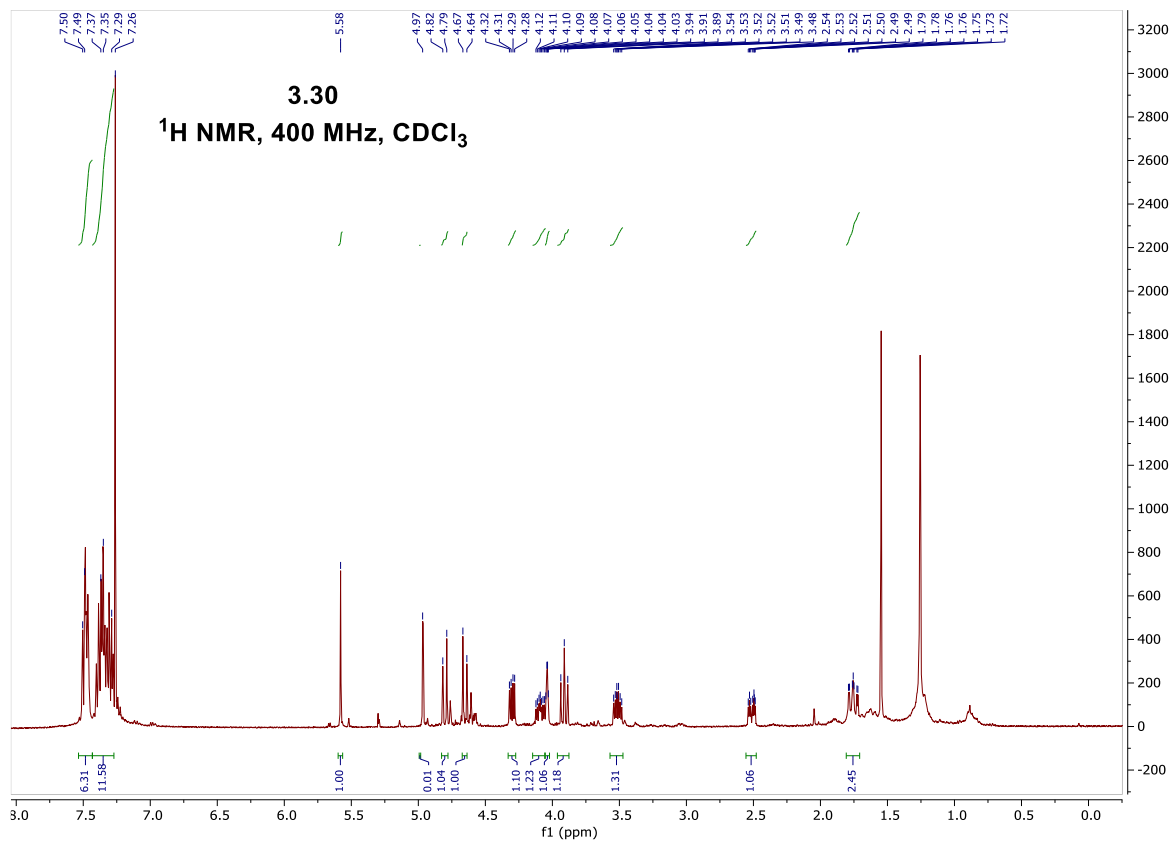




Table 3.1 entry 12: **3.4(TFE)** in CH<sub>3</sub>CN; 91 $\alpha$ :9 $\beta$  from  $\alpha$ -**3.4(TFE)**

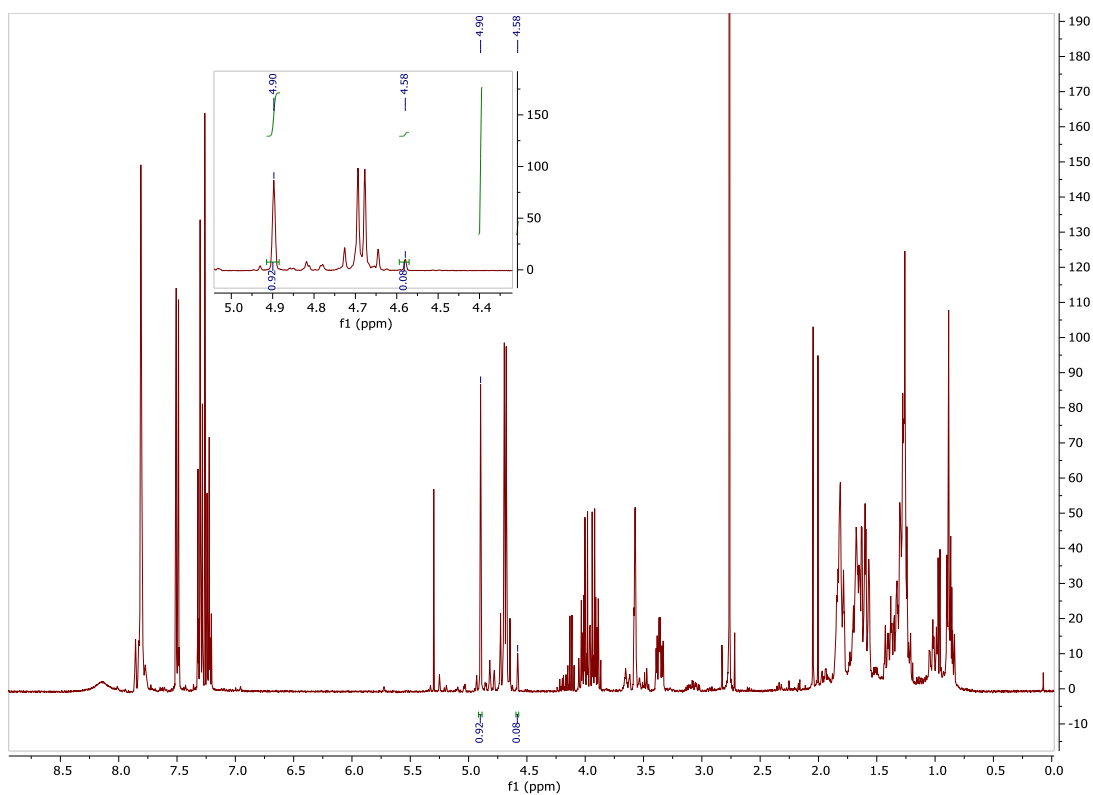


Table 3.1 entry 12: **3.4(TFE)** in CH<sub>3</sub>CN; 88 $\alpha$ :12 $\beta$  from  $\beta$ -**3.4(TFE)**

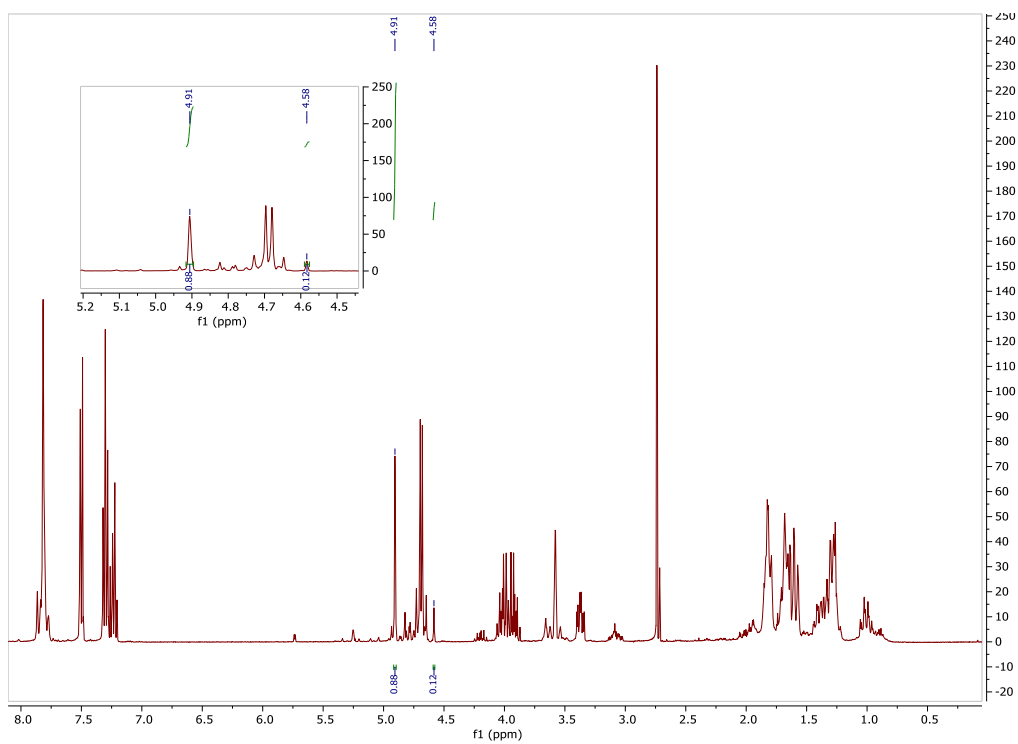


Table 3.1 entry 13: **3.5(Allyl)** in CH<sub>2</sub>Cl<sub>2</sub>; >97α:3β

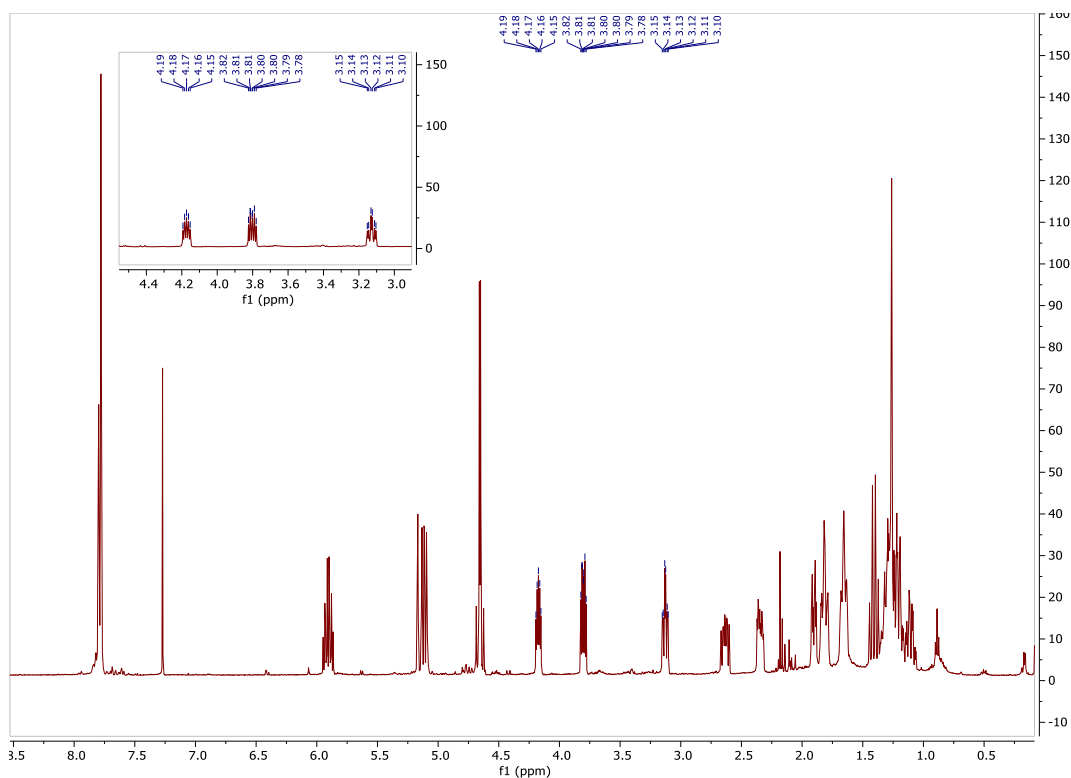


Table 3.1 entry 14: **3.5(TFE)** in CH<sub>2</sub>Cl<sub>2</sub>; 85α:15β

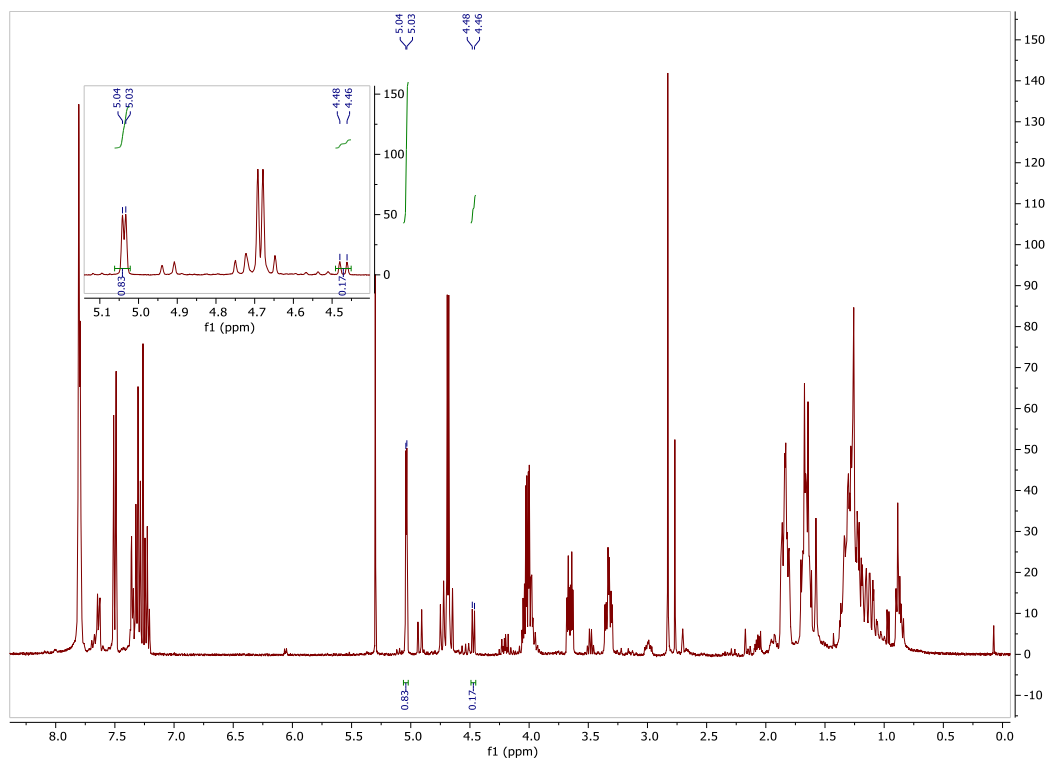


Table 3.1 entry 15: **3.5(TFE)** in CH<sub>3</sub>CN; 92 $\alpha$ :8 $\beta$

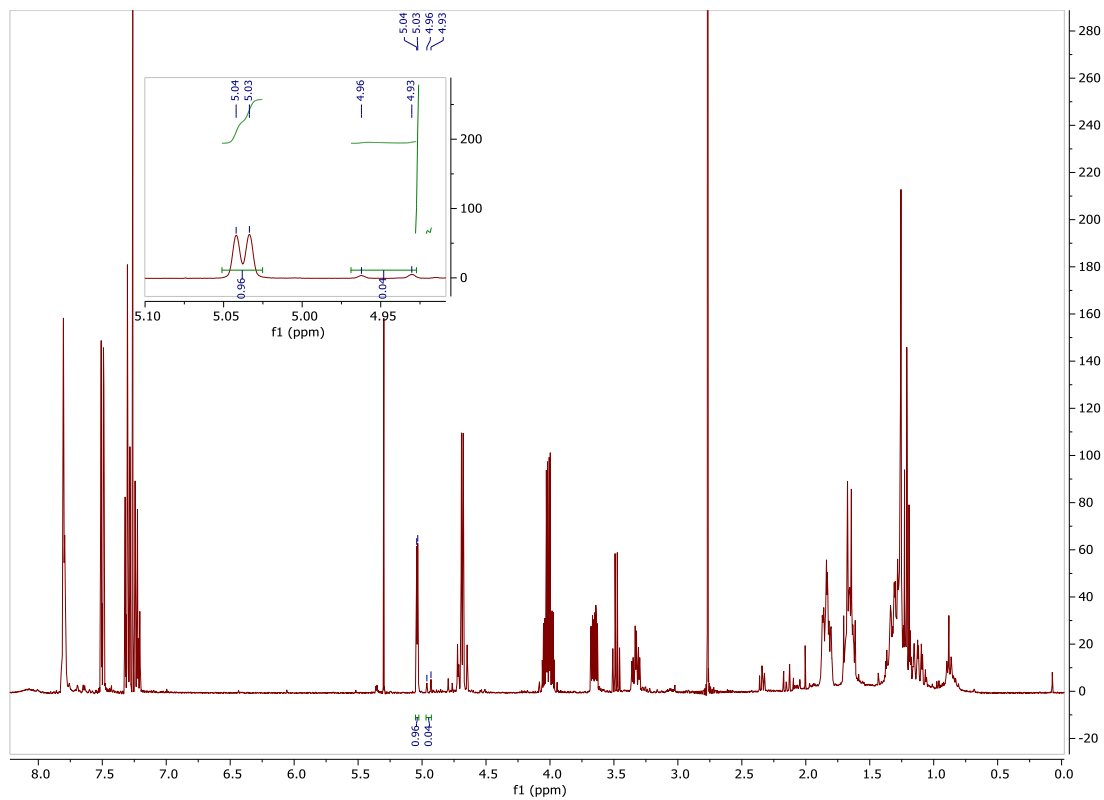


Table 3.1 entry 16: **3.6(TFE)** in CH<sub>2</sub>Cl<sub>2</sub>; 71 $\alpha$ :29 $\beta$

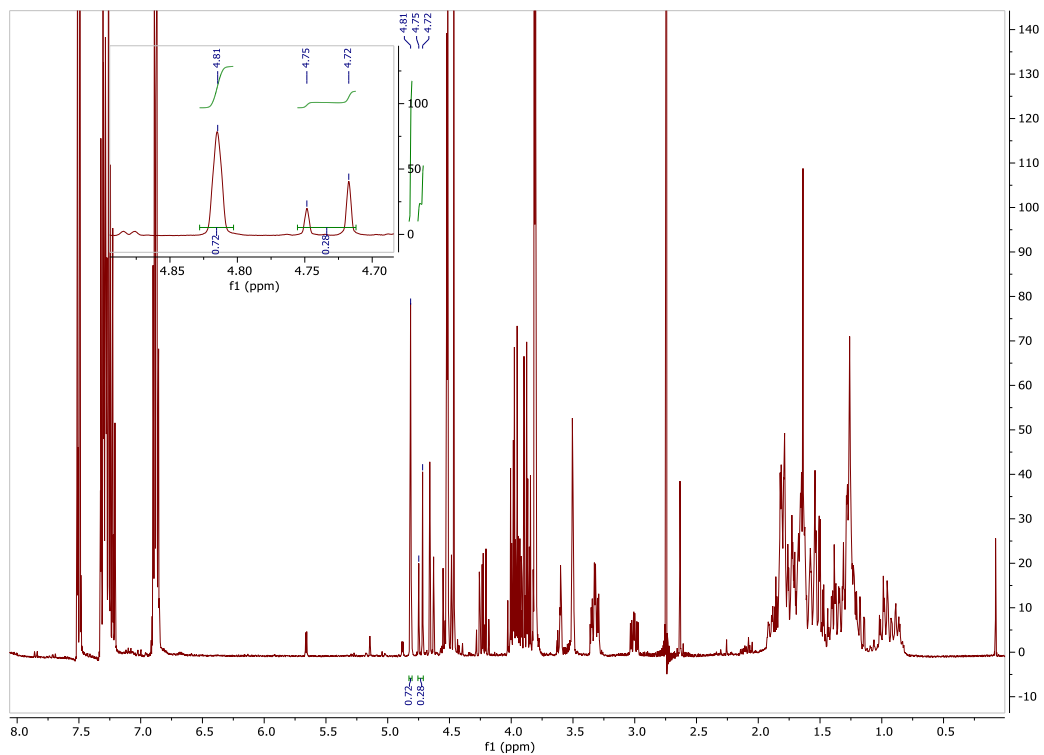


Table 3.1 entry 17: **3.6(TFE)** in CH<sub>3</sub>CN; 75 $\alpha$ :25 $\beta$

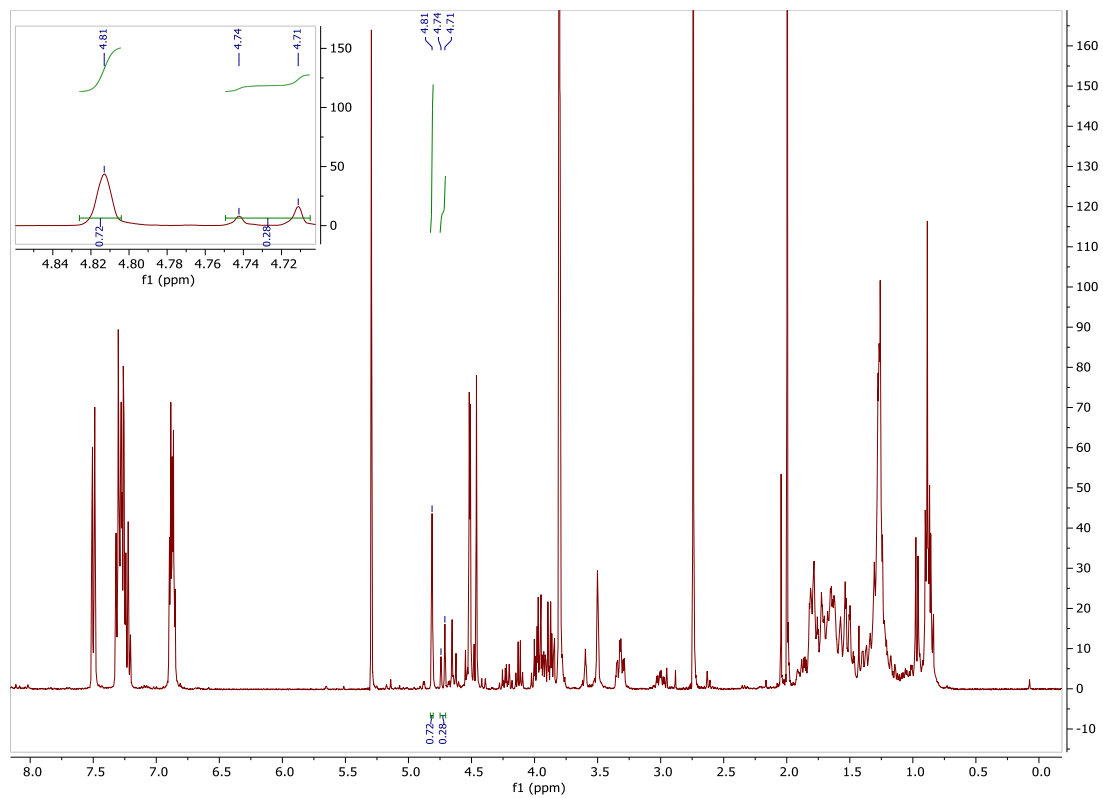


Table 3.1 entry 18: **3.7(TFE)** in CH<sub>2</sub>Cl<sub>2</sub>; 82 $\alpha$ :18 $\beta$

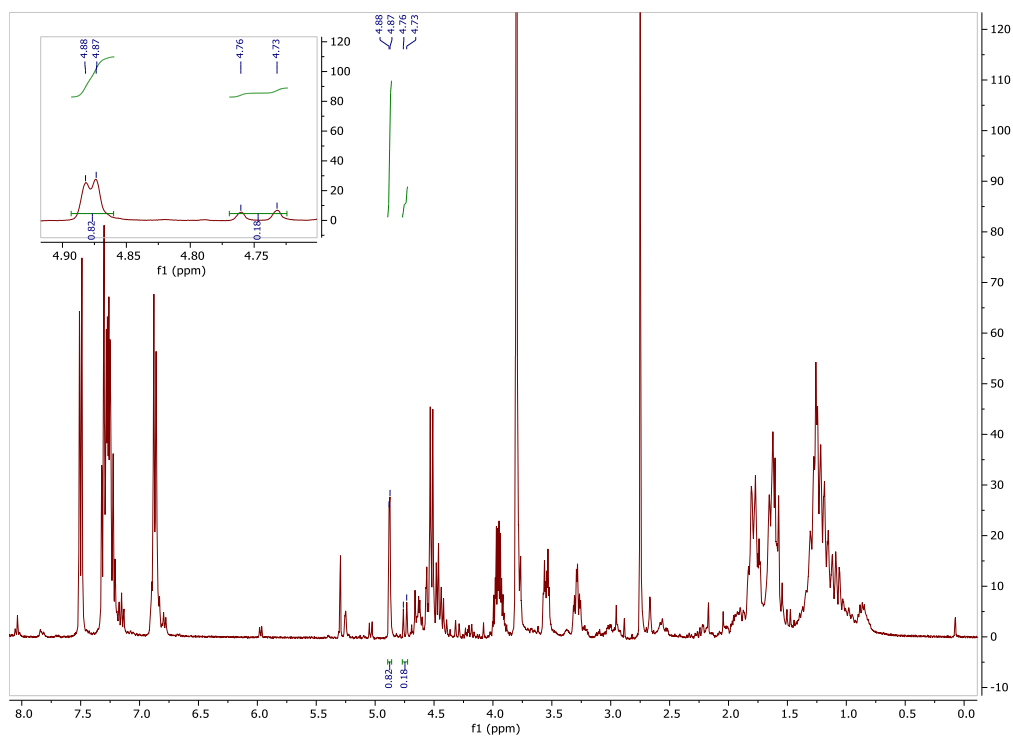




Table 3.1 entry 19: **3.7(TFE)** in CH<sub>3</sub>CN; >97 $\alpha$ :3 $\beta$

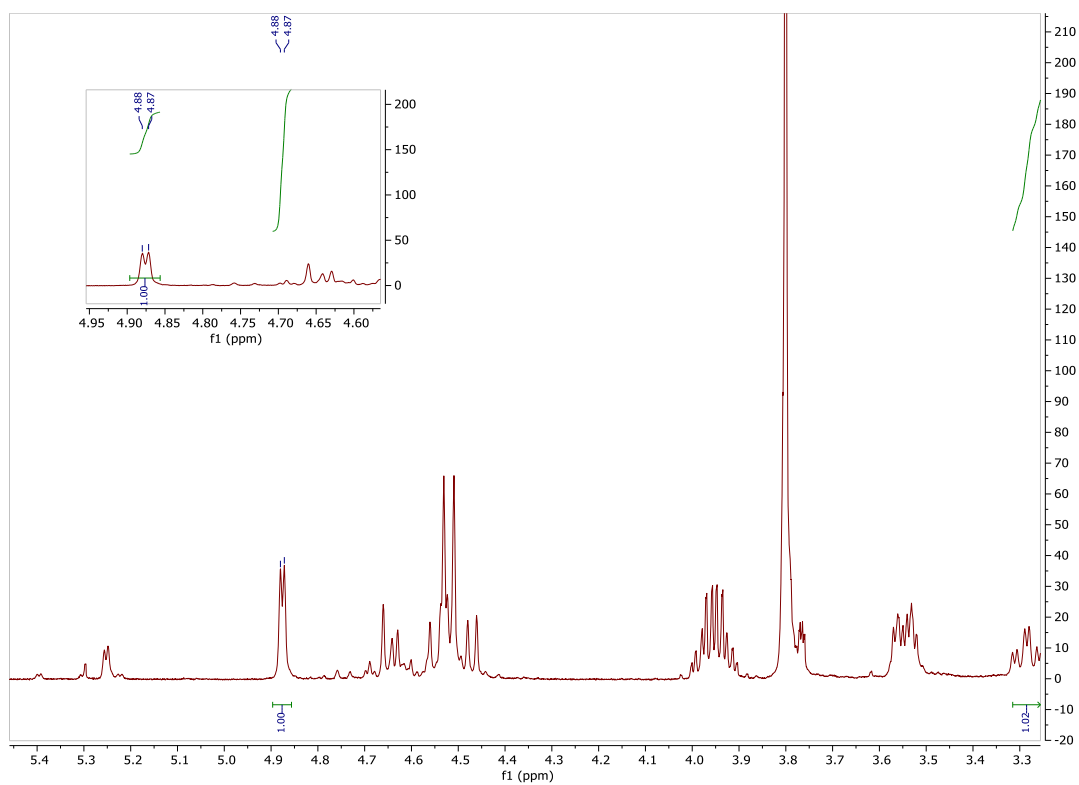


Table 3.1 entry 19: **3.7(TFE)** in CH<sub>3</sub>CN; >97 $\alpha$ :3 $\beta$ ; <sup>19</sup>F NMR

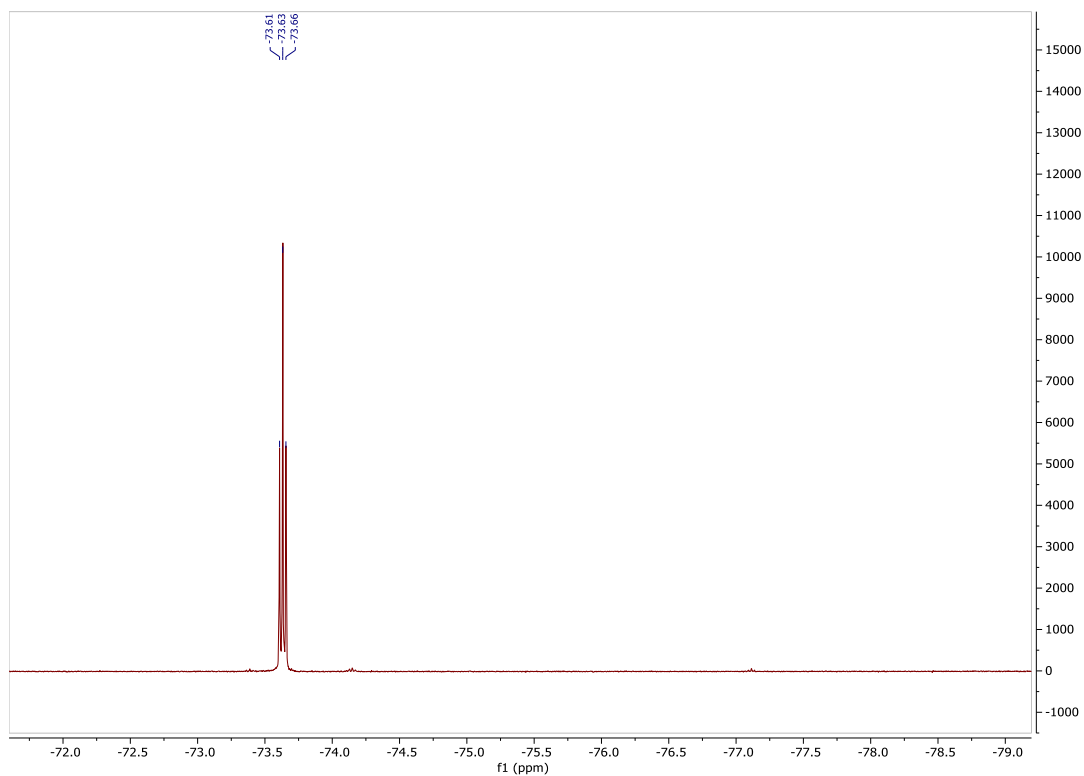


Table 3.1 entry 20: **3.8(Allyl)** in CH<sub>2</sub>Cl<sub>2</sub>; >97α:3β

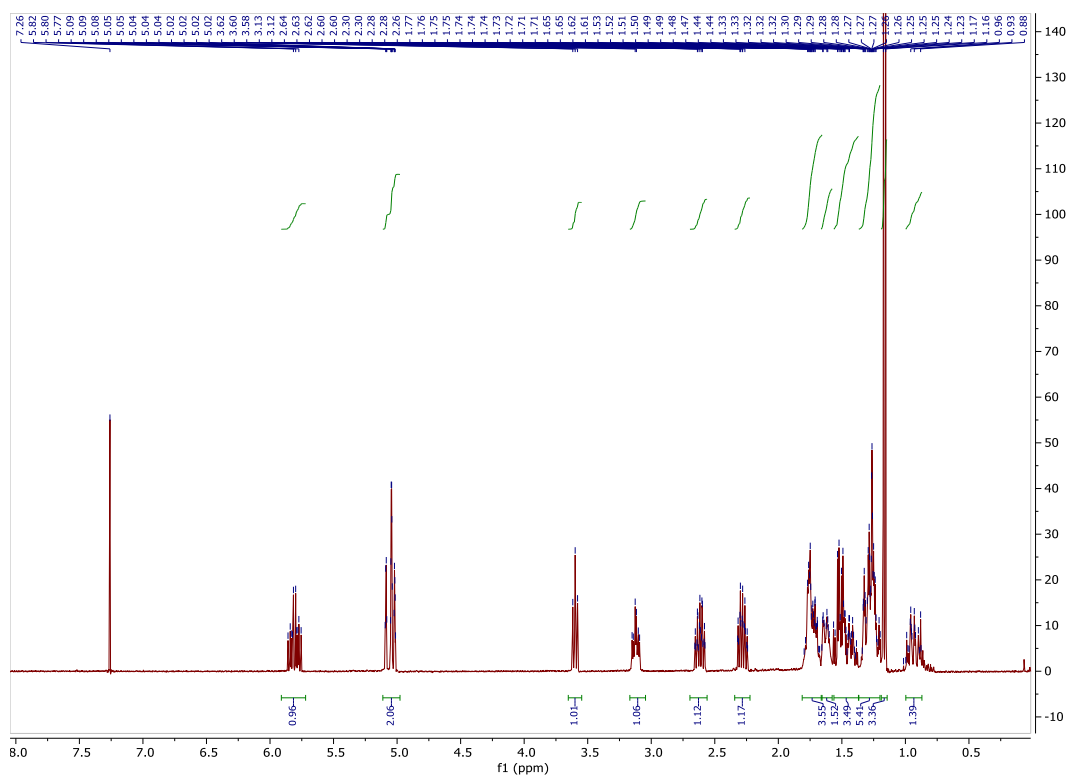


Table 3.1 entry 21: **3.8(TFE)** in CH<sub>2</sub>Cl<sub>2</sub>; 97α:3β

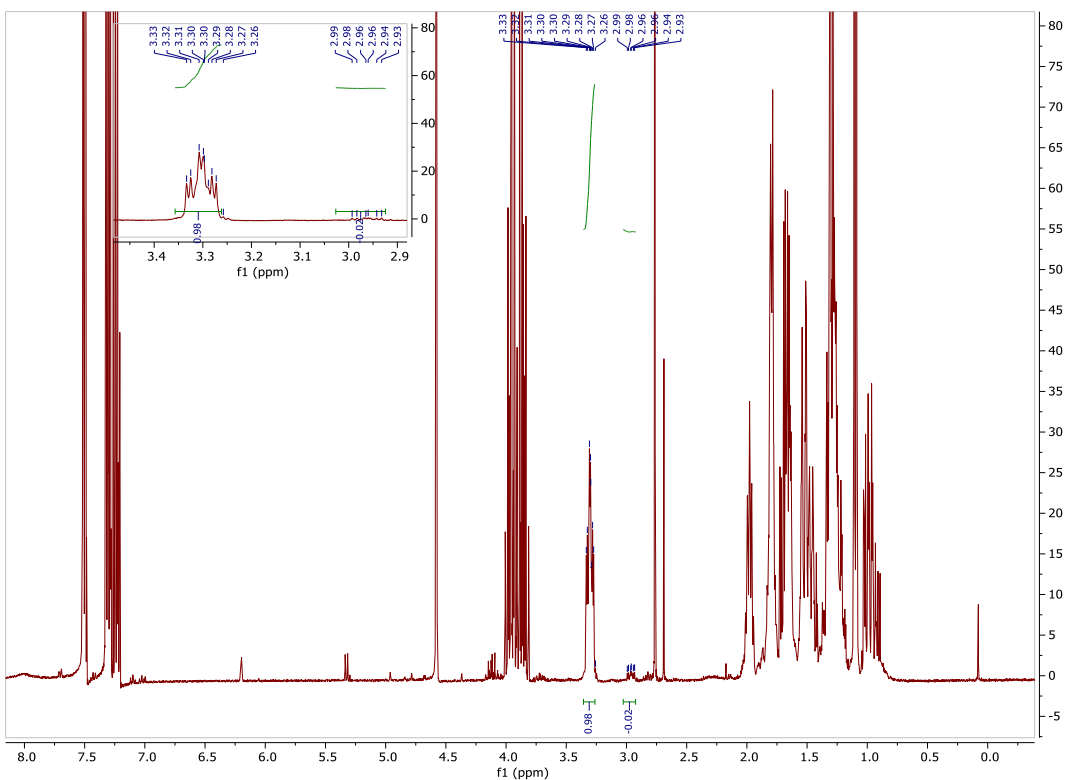


Table 3.1 entry 21: **3.8(TFE)** in CH<sub>2</sub>Cl<sub>2</sub>; 97 $\alpha$ :3 $\beta$ ; <sup>19</sup>F NMR

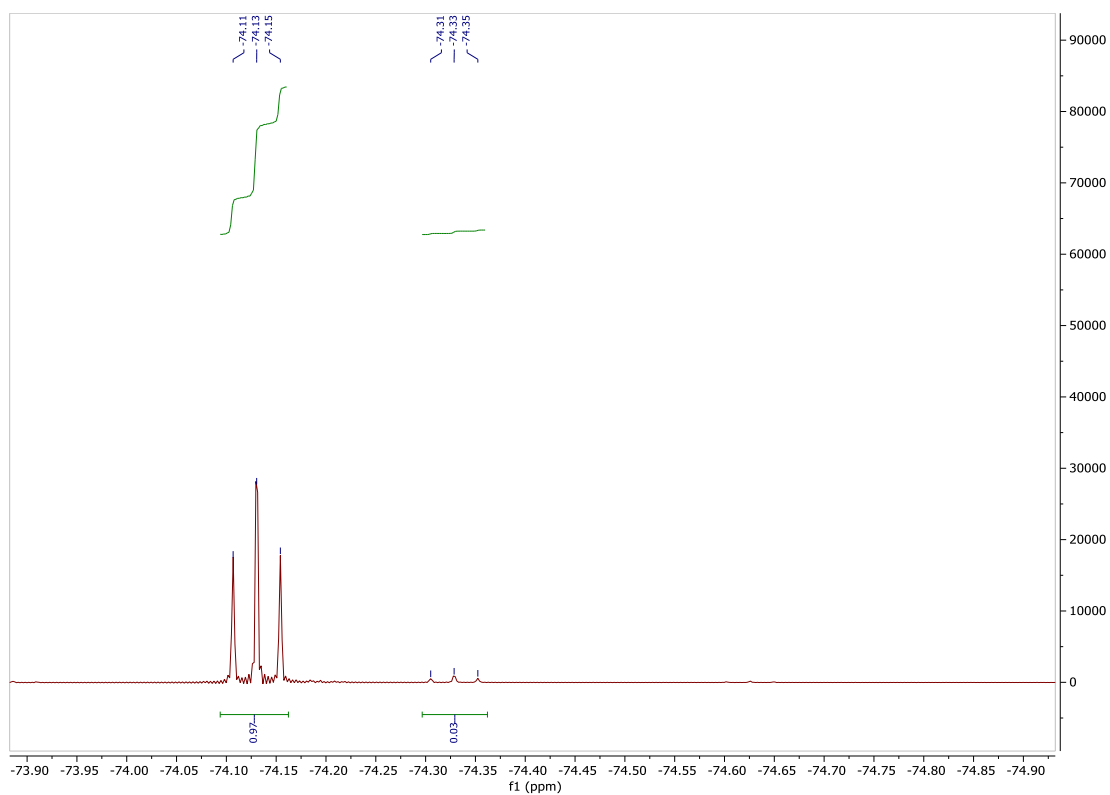


Table 3.1 entry 22: **3.8(TFE)** in CH<sub>3</sub>CN; 93 $\alpha$ :7 $\beta$

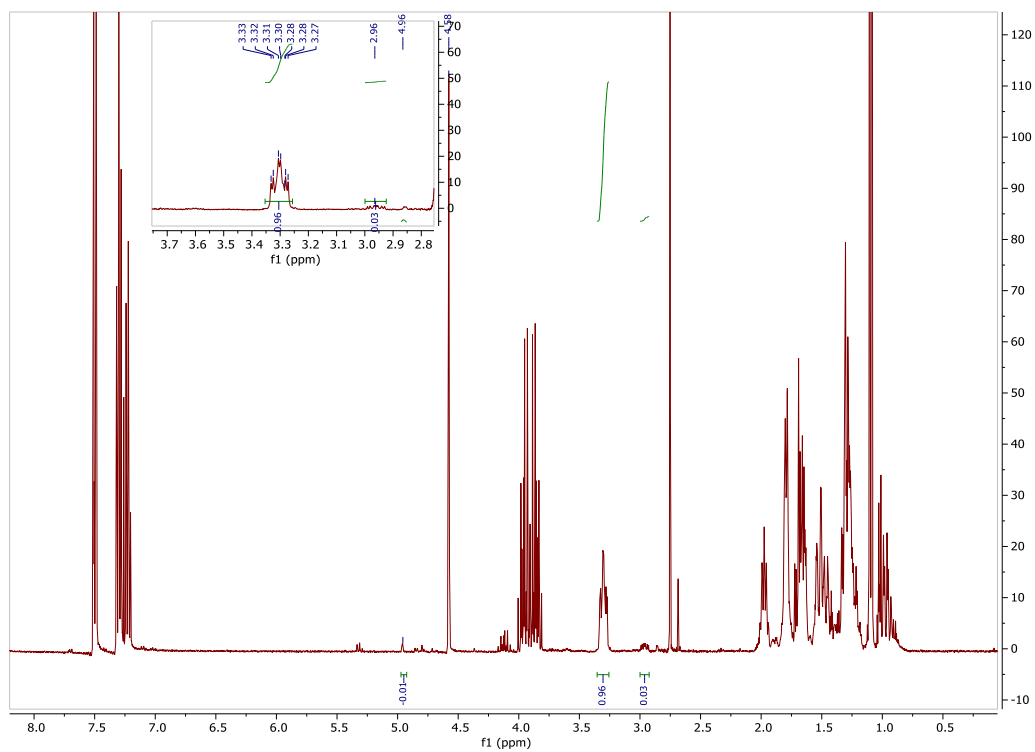


Table 3.1 entry 22: **3.8(TFE)** in CH<sub>3</sub>CN; 93 $\alpha$ :7 $\beta$ ; <sup>19</sup>F NMR

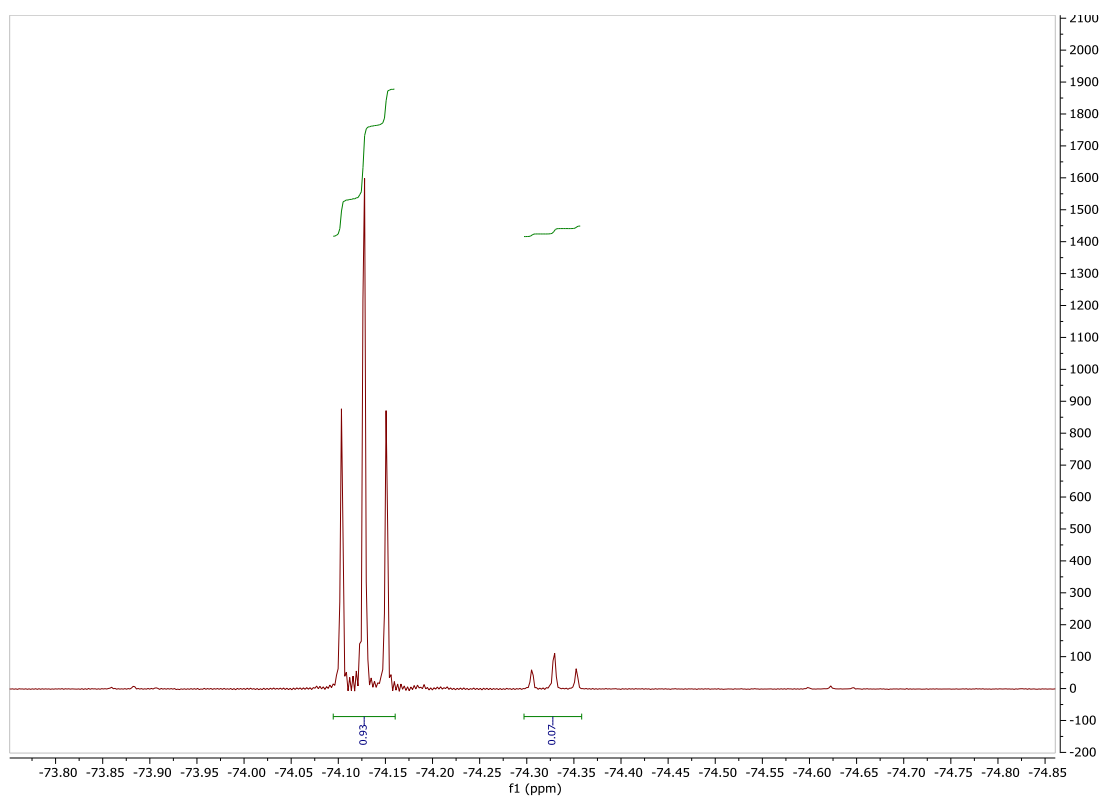


Table 3.1 entry 23: **3.9(Allyl)** in CH<sub>2</sub>Cl<sub>2</sub>; >3 $\alpha$ :97 $\beta$

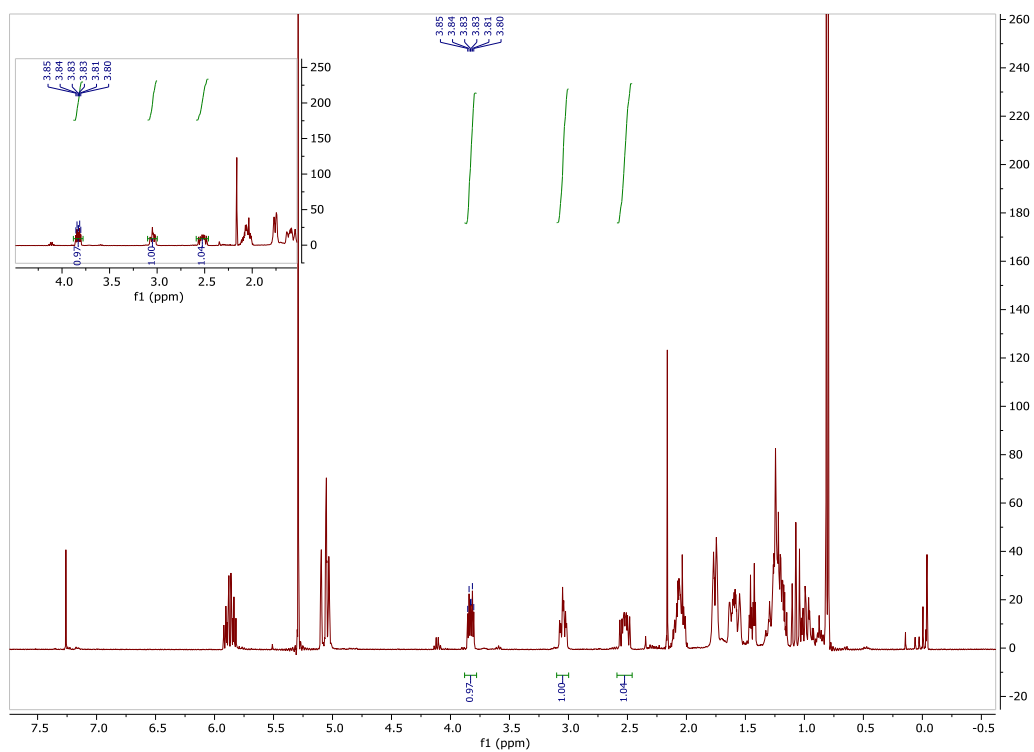


Table 3.1 entry 24: **3.9(TFE)** in CH<sub>2</sub>Cl<sub>2</sub>; 91 $\alpha$ :9 $\beta$

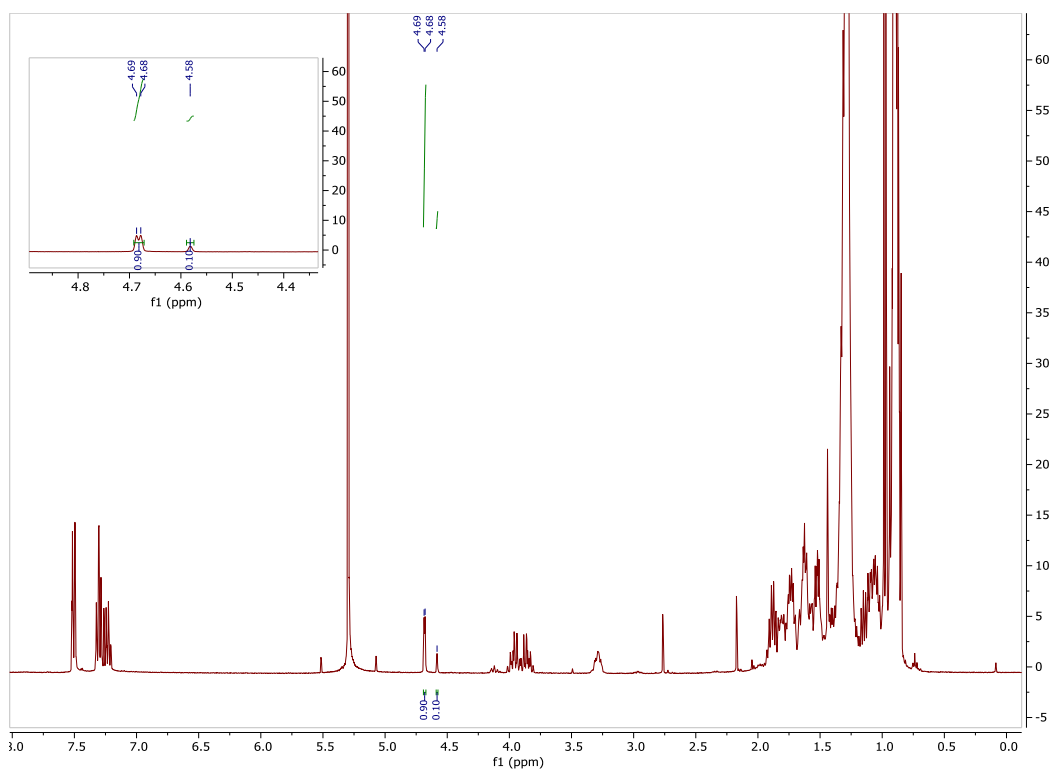


Table 3.1 entry 25: **3.9(TFE)** in CH<sub>3</sub>CN; 83 $\alpha$ :17 $\beta$

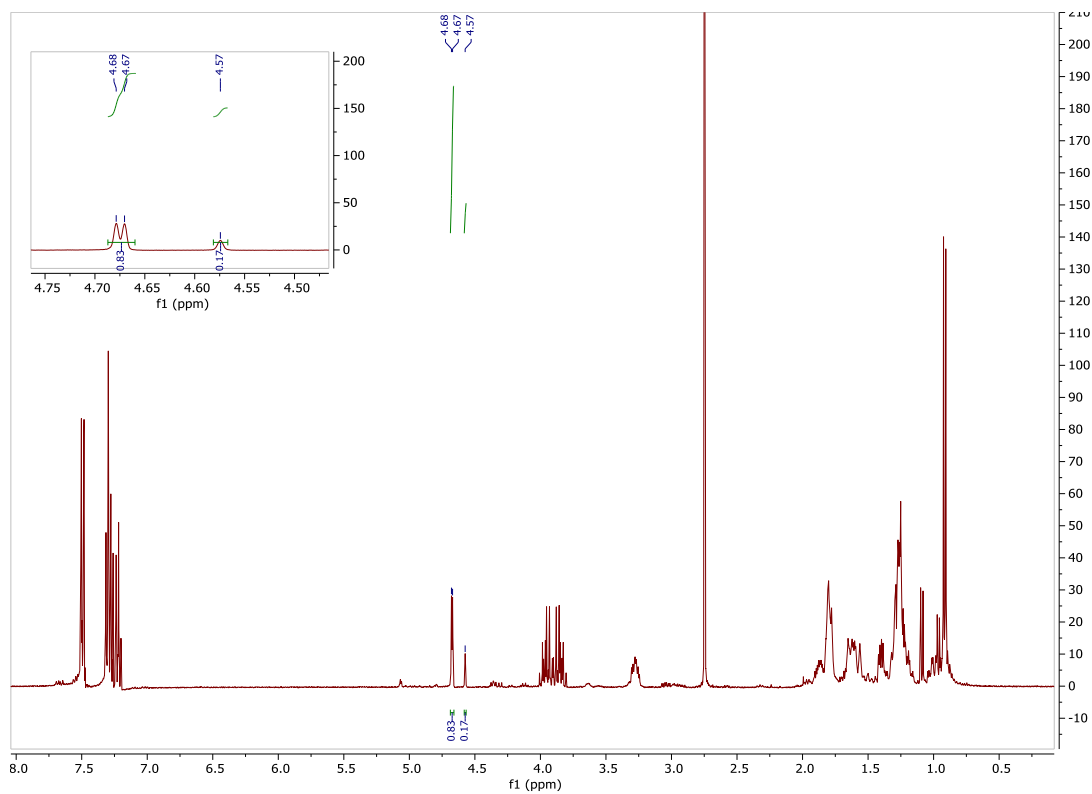


Table 3.1 entry 26: **3.10**(TFE) in CH<sub>2</sub>Cl<sub>2</sub>; 87 $\alpha$ :13 $\beta$

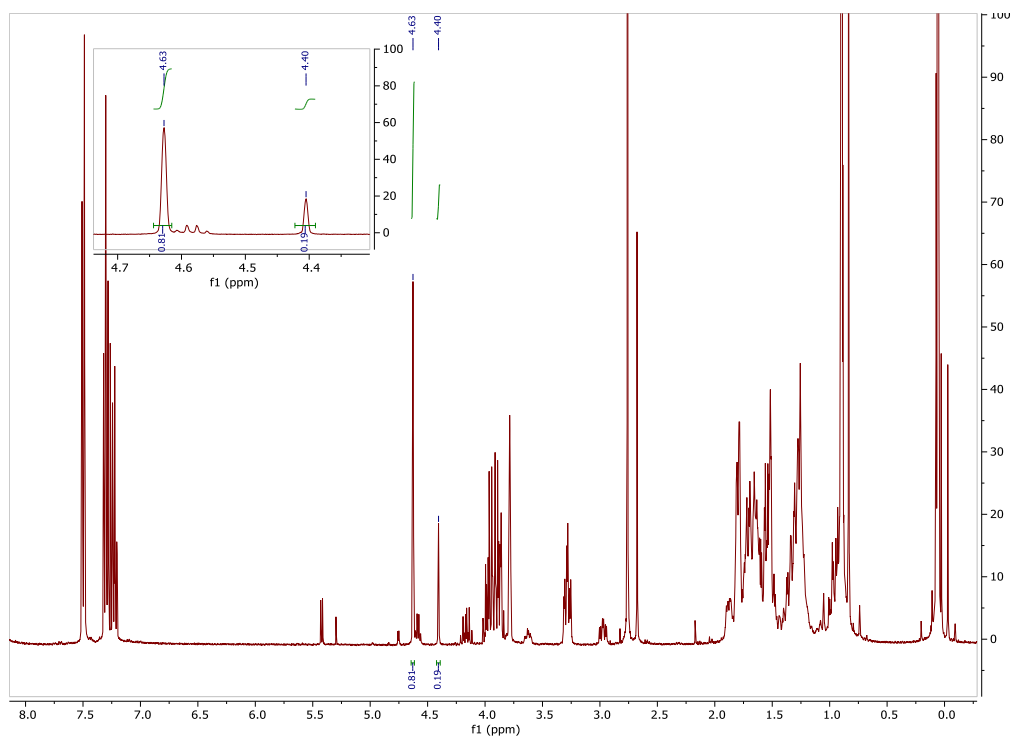
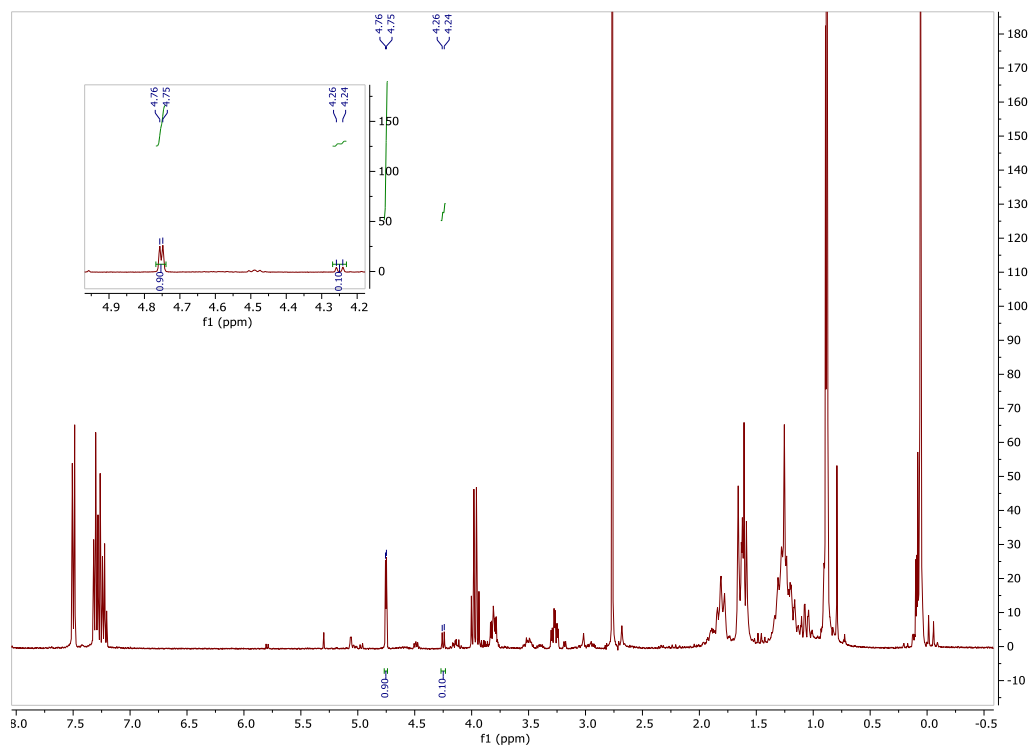


Table 3.1 entry 27: **3.11**(TFE) in CH<sub>2</sub>Cl<sub>2</sub>; 80 $\alpha$ :20 $\beta$



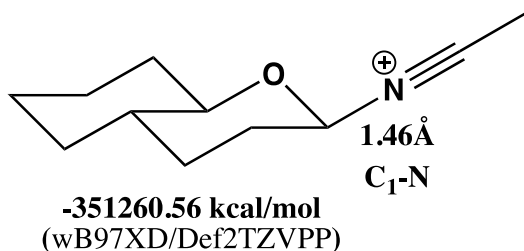
## G.4 Données brutes calcule DFT

Geometry optimizations of acetonitrilium adducts were carried out with Gaussian 16<sup>4</sup> using B3LYP/6-31G\* and reoptimized by wB97XD/Def2TZVPP. Atomic coordinates from B3LYP/6-31G\* geometries are reported.

---

<sup>4</sup> Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

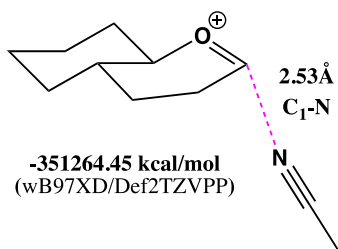
**Donor 3.1( $\beta$ -acetonitrilium):**



<b>Atom</b>	<b>X</b>	<b>Y</b>	<b>Z</b>
C	1.324775	0.370768	0.544412
H	1.304717	0.47707	1.637908
N	2.697476	-0.025003	0.236365
C	3.742195	-0.36964	-0.047759
C	5.067562	-0.808483	-0.403357
H	4.993156	-1.774112	-0.904953
H	5.667513	-0.908207	0.501413
H	5.521222	-0.07805	-1.073398
O	0.557637	-0.686888	0.113743
C	-0.848743	-0.471787	0.377774
H	-0.96096	-0.344612	1.464688
C	-1.602698	-1.705282	-0.06407
C	-3.098701	-1.515447	0.19015
H	-3.278165	-1.463379	1.26804
H	-3.641601	-1.38763	-0.17233
H	-1.225149	-2.579256	0.466933
H	-1.419746	-1.863448	-1.130024
C	-1.335262	0.790455	-0.322377
C	-2.824924	0.981886	-0.046821
H	-3.179722	1.872785	-0.567141
H	-2.972811	1.164888	1.022809
C	-3.626314	-0.245432	-0.473532
H	-3.56794	-0.352969	-1.560458
H	-4.679269	-0.10587	-0.229799
H	-1.199657	0.631671	-1.398393
C	-0.483291	1.982515	0.101476
H	-0.65469	1.199496	1.160433
H	-0.768255	2.876679	-0.451853
C	0.999769	1.694415	-0.133526
H	1.632053	2.485891	0.269295
H	1.199672	1.595357	-1.20189

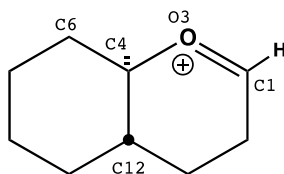


**Donor 3.1( $\alpha$ -acetonitrilium):**



Atom	X	Y	Z
C	-0.943982	0.887977	1.34499
H	-1.687983	0.947967	1.13999
N	-2.865968	-0.092049	0.01699
C	-3.840962	-0.585062	-0.37201
C	-5.066953	-1.203079	-0.86501
H	-5.937961	-0.669091	-0.47501
H	-5.115939	-1.24708	-0.54001
H	-5.090954	-1.170079	-1.95901
O	-0.220968	-0.142013	1.41199
C	0.841036	-0.436999	0.35999
H	0.261044	-0.996007	-0.38201
C	1.891048	-1.315984	1.01099
C	2.949053	-1.67297	-0.05601
H	2.491062	-1.323976	-0.81301
H	3.745061	-1.258959	0.41599
H	1.42906	-1.217991	1.42399
H	1.360041	-0.769978	1.83999
C	1.389019	0.855009	-0.22701
C	2.425024	0.482023	-1.30801
H	2.852011	1.402029	-1.72301
H	1.915031	-0.028984	-1.13801
C	3.529036	-0.419962	-0.73201
H	4.118028	0.151046	-0.00101
H	4.22104	-0.712953	-1.52901
H	1.920011	1.387016	0.57799
C	0.235007	1.735993	-0.72301
H	-0.310986	1.224986	-1.52601
H	0.612994	2.674998	-1.13701
C	-0.726997	2.03398	0.43399
H	-1.707002	1.398967	0.11199
H	-0.327008	2.822985	1.09699

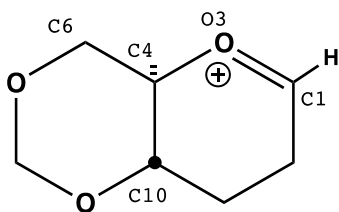
Merz-Kollman charges were computed in Gaussian 16 from B3LYP/6-31G\* geometry optimized structures.

**Structure 3.32:****Merz-Kollman charges**

C1: 0.453  
O3: -0.275  
C4: 0.322  
C6: -0.225  
C12: -0.055

<b>Atom</b>	<b>X</b>	<b>Y</b>	<b>Z</b>
C	1.33626	-0.854288	-0.148569
H	3.15821	-1.534797	-0.372999
O	1.25557	-1.428068	0.064611
C	-0.01412	-0.652829	0.369631
H	-0.00676	-0.620129	1.460771
C	-1.16983	-1.47099	-0.142209
H	-1.165499	-2.46117	0.311541
H	-1.07647	-1.59376	-1.223739
C	-2.46478	-0.7195	0.191871
H	-2.59998	-0.70004	1.276721
H	-3.30853	-1.273181	-0.216119
C	0.071819	0.733451	-0.224639
C	-1.217901	1.47668	0.132851
H	-1.185412	2.47273	-0.309109
H	-1.264381	1.61475	1.217551
C	-2.445821	0.70799	-0.349869
H	-2.450271	0.68396	-1.442939
H	-3.350931	1.232129	-0.046389
H	0.109479	0.626231	-1.315599
C	1.343239	1.424072	0.252211
H	1.311639	1.550272	1.335901
C	2.560089	0.592652	-0.138429
H	3.443689	0.769673	0.485241
H	2.919219	0.815353	-1.154599
H	1.427698	2.419092	-0.180189

Structure 3.33:



Merz-Kollman charges

C1: 0.473  
O3: -0.261  
C4: 0.199  
C6: 0.001  
C10: 0.164

Atom	X	Y	Z
C	1.264431	0.850129	0.16536
H	3.085832	1.518908	0.42202
O	1.180661	1.44	-0.01637
C	-0.037259	0.671551	-0.38542
H	-0.020629	0.621731	-1.47332
C	-1.275449	1.405662	0.10032
H	-1.404308	1.366992	-0.39106
H	-1.226108	1.559492	1.18616
O	-1.358639	0.587783	-0.25921
C	0.02788	-0.717599	0.23492
O	-1.137681	-1.388028	-0.12943
C	-1.28738	-0.690287	0.30153
H	-1.2819	-0.623347	1.39883
H	-3.146861	-1.248277	-0.05268
H	0.07349	-0.599569	1.33135
C	1.262079	-1.44384	-0.25303
H	1.185479	-1.60153	-1.32854
C	2.48829	-0.593561	0.08395
H	3.32513	-0.734882	-0.61174
H	2.93435	-0.848732	1.05674
H	1.345248	-2.42113	0.21651