Université du Québec
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Centre Armand-Frappier Santé Biotechnologie

En route vers la synthèse totale des agminosides : glycolipides partiellement acétylés issus de l'éponge de mer *Raspailia agminata*

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Thèse présentée pour l'obtention du grade de
Philosophiæ Doctor, Ph.D.
en biologie

Date de dépôt initial : 2022-07-10
Date de dépôt final : 2022-12-01

Jury d'évaluation

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« La vie n'est facile pour aucun de nous. Mais quoi, il faut avoir de la persévérance, et surtout de la confiance en soi.[...] *»*

- Marie Curie, physicienne et chimiste polonnaise, prix Nobel de physique (1903) et prix Nobel de chimie (1911)

Résumé

Récemment, Wojnar et Northcote de la *Victoria University of Wellington* ont décrit l'isolation et la caractérisation structurale d'une nouvelle famille de glycolipides issus de l'éponge de mer *Raspailia agminata* qu'ils ont nommés agminosides **A**–**E**. Il s'est avéré que les agminosides sont des glycolipides comportant une structure très particulière composée d'un hexaglucoside (ou pentaglucoside pour l'agminoside **E**) pour partie glycosidique et d'une chaîne lipidique comportant un acide carboxylique libre et une unité glycérol. Les congénères se différencient par leur motif d'acétylation partielle. L'isolation n'ayant conduit qu'à de très faibles quantités de glycolipides, seule une activité cytotoxique de l'agminoside **A** a été mise en évidence contre les cellules cancéreuses HeLa. Le potentiel biopharmaceutique des agminosides reste donc à explorer.

L'objectif principal du projet de thèse consiste à établir une voie de synthèse totale vers les agminosides **A**–**E** ainsi que leurs dérivés afin de mettre en évidence leur activité biologique. Ce tour de force a été dans un premier temps réalisé par la synthèse d'un glycolipide dérivé des agminosides comportant la partie glycosidique de ces derniers, glycosylée sur l'acide (*R*)-3-hydroxydécanoique typiquement retrouvé dans la structure de rhamnolipides bactériens. La synthèse de la partie glycosidique a été effectuée selon une stratégie [3 + 2] mettant en jeu un donneur trisaccharidique *N*-phényltrifluoroacétimidate et un accepteur diglucolipidique encombré. Les unités glycosidiques ont été assemblées entre elles *via* des thioglycosylations catalysées par le couple de promoteurs NIS/Yb(OTf)$_3$. Ceci a permis le développement d'une voie de synthèse totale vers un glycolipide chimérique avec un rendement de 0,5% en 39 étapes, ainsi que la confirmation du motif d'acétylation de l'agminoside **E**. Cette méthode de synthèse pourra ensuite être adaptée afin de permettre la synthèse totale des agminosides.

De surcroît, la chaîne lipidique des agminosides a été rétrosynthétiquement déconnectée, par le lien éther en deux fragments : une chaîne carbonée en C_{20} et un dérivé glycérol. Ces deux fragments possédant un centre chiral, les synthétiser en évitant toute épimérisation des centres stéréogéniques a été un défi. Ainsi, le dérivé glycérol a été obtenu avec un rendement global de 34% sur cinq étapes et la chaîne carbonée a été obtenue avec un rendement global de 8% sur quatre étapes dont une étape de transmétallation d'un organomagnésien en organocuprate. La formation du lien éther entre ces deux fragments n'a malheureusement pas pu être réalisée, mais des voies alternatives vers l'obtention de la chaîne lipidique ont été imaginées et restent à explorer.

Une fois cette dernière en main, la méthode de synthèse de la partie glycosidique développée au cours de ce travail de recherche permettra l'obtention des agminosides **A**–**E** ainsi que de dérivés désacétylés, peracétylés ou encore macrolactonisés. Enfin, ce document décrit la première synthèse de la partie glycosidique des agminosides, mais il s'agit également de la première étude sur les agminosides depuis leur découverte en 2011.

Abstract

Recently, Wojnar and Northcote from Victoria University of Wellington described the isolation and structural characterization of a new family of glycolipids from the marine sponge *Raspailia agminata,* which they named agminosides **A**–**E**. Agminosides are glycolipids featuring a very atypical structure composed of a hexaglucoside (or pentaglucoside for agminoside **E**) for the glycosidic part and a lipidic chain comprising a free carboxylic acid and a glycerol unit. Congeners are differentiated by their partially acetylated pattern. As the isolation only led to very small amounts of glycolipids, among all agminosides, only agminoside **A** was biologically evaluated and exhibited a cytotoxic activity against HeLa cancer cells. The biopharmaceutical potential of agminosides therefore remains to be explored.

The ultimate objective of the thesis project was to establish a total synthesis of agminosides **A**–**E** as well as their derivatives in order to enable their biological evaluation. This goal was initially achieved by the synthesis of a glycolipid derived from agminosides comprising the glycosidic part of the latter, glycosylated on the (*R*)-3-hydroxydecanoic acid typically found in the structure of bacterial rhamnolipids. The synthesis of the glycosidic part was carried out according to a [3 + 2] strategy involving a trisaccharidic *N*-phenyltrifluoroacetimidate donor and a hindered diglucolipid acceptor. The glycosidic units were assembled together *via* thioglycosylations catalyzed by the promoters NIS/$Yb(OTf)_3$. This has allowed the development of a total synthesis of a chimeric glycolipid with an overall yield of 0.5% over 39 steps, as well as the confirmation of the acetylation pattern of agminoside **E**. This synthetic route could be further adapted for the total synthesis of agminosides.

In addition, the lipid chain of agminosides was retrosynthetically disconnected, by the ether bond into two fragments: a C_{20} carbon chain and a glycerol unit. These two fragments bearing a chiral center, synthesizing them avoiding any epimerization of the stereogenic centers was a challenge. Thus, the glycerol derivative was obtained with an overall yield of 34% over five steps and the carbon chain was obtained with an overall yield of 8% over four steps, including a transmetallation step from an organomagnesium into an organocuprate. The formation of the ether bond between these two fragments has not yet been accomplished, but alternative ways to obtain the lipid chain have been devised and remain to be explored.

Once this synthesis of the lipid is achieved, the route developed during this research work will make it possible to obtain agminosides **A**–**E** as well as deacetylated, peracetylated or even

macrolactonized derivatives. Finally, this document describes the first synthesis of the glycosidic part of agminosides, but it is also the first study on agminosides since their discovery in 2011.

Remerciements

Ce projet, financé par le Conseil de recherches en sciences naturelles et en génie du Canada (CRSNG), a été effectué sous la direction du Professeur Charles Gauthier que je me dois de remercier pour la confiance qu'il m'a accordée pour mener à bien ce projet dans son laboratoire ainsi que pour ses précieux conseils. Aussi, merci à Annie Castonguay pour m'avoir permis de commencer mon doctorat en bénéficiant de ses intallations ainsi que d'avoir accepté de m'accorder son temps en faisant partie de mon jury depuis le début.

Je voudrais également remercier Maude Cloutier, Emmanilo Delar, Paul Gormand, Mathilde Grosset et Dr Floriane Heis pour tous ces beaux moments et fous rires passés au et en dehors du laboratoire. Mais aussi à tous les stagiaires qui ont participé à l'avancement du projet, Arianne Provost-Savard, Sabrina Di Cintio, Océane Burton et Justin Cordeil.

Je tiens cependant à ne pas oublier tous les autres membres du laboratoire, Gokulakrishnan Ravicoularamin, Oscar Gamboa, Dr Nazar Hussain, Samar Hadj Amor, Dr Arasakumar Thangaraj, Dr Nitish Verma, Dr Sujit Manmode, Dr Sateesh Dubbu et Sheida Moghadasi ainsi que les stagiaires Nassima Ameur, Robert Hoyeck, Seynabou Ndong, Gayetri Shrestha, Marie-Joëlle Prévost, Armand Caulet, Shawn Tripodi, Fatma Boujenoui, Gérard Yapi, Floriane Cardinaud, Anne-Sophie Doyon et Mingyu Zhang.

Je remercie tous les amis que je me suis faits durant cette aventure, Robin Vidal et ses précieux conseils quant à la chimie des organomagnésiens, mais aussi Jacinthe Gagnon, Marie-Aude Pinoteau et Philippe Egesborg pour leur amitié et leur soutien.

Je n'oublie pas non plus toutes ces belles personnes qui m'ont marqué au cours de cette aventure, Myriam Létourneau, Marianne Piochon, Louise Roux, Selma Metaane, Mehdi Haghdoost, Golara Golbaghi, Mustafa Iddir et Richard Boulon.

Je tiens tout particulièrement à remercier Isabelle Queval, psychologue de l'INRS, et Chloé Godbout, orthopédagogue de l'INRS, sans qui la fin de ce travail aurait été compromise.

Et enfin, je réserve mes derniers remerciements à ma famille, mes parents et mon frère sans qui je ne serais évidemment pas là aujourd'hui, mais aussi à Sabrina Delahais, ma fiancée, pour m'avoir suivi au Québec et soutenu tout au long de mon doctorat.

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Liste des Abréviations

All : Allyle

AZMB : *ortho*-Azidométhylbenzoyle

Bt : Butanoyle

CAN : Nitrate de cérium et d'ammonium

CCM : Chromatographie sur couche mince

COSY : *Correlation spectroscopy*

CSA : Acide camphosulfonique

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

DCC : Dicyclohexylcarbodiimide

DCE : 1,2-Dichloroéthane

DCM : Dichlorométhane

DDQ : 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEPT : *Distortionless enhanced polarization transfert*

DIPEA : Diisopropyléthylamine

DMAP : 4-Diméthylaminopyridine

DMF : Diméthylformamide

2,2-DMP : 2,2-Diméthoxypropane

DMSO : Diméthylsulfoxyde

DMTST : Triflate de diméthyl(méthylthio)sulfonium

équiv : Équivalent

ESI : *Electrospray ionisation*

Et : Éthyle

GGL : Glycoglycérolipide

GSL : Glycosphingolipide

HDTC : Hydrazine dithiocarbonate

HeLa : Henrietta Lacks

HMBC : *Heteronuclear Multiple Bond Correlation*

HRMS : *High Resolution Mass Spectrometry*

HSQC : *Heteronuclear Singular Quantum Coherence*

LECCD : *Liposomial exciton-coupling circular dichroism*

Lev : Lévulinoyle

MALDI : *Matrix-assisted laser desorption/ionisation*

Me : Méthyle

MOM : Méthoxyméthyle

MS : Tamis moléculaire (*Molecular Sieves*)

MTPA : Acide α-méthyl-α-trifluorométhylphénylacétique

NBS : *N*-Bromosuccinimide

NIS : *N*-Iodosuccinimide

NOESY : *Nuclear overhauser effect spectroscopy*

Phth : Phtalimide

PMB : *para*-Méthoxybenzyle

PTFA : *N*-Phényl trifluoroacétimidoyle

PTSA : Acide *p*-toluènesulfonique

Pyr : Pyridine

Quin : 2-Quinolinecarbonyle

rdt : Rendement

R_f : Rapport frontal

RMN : Résonance magnétique nucléaire

ROESY : *Rotating frame overhauser effect spectroscopy*

t.a. : Température ambiante

TBAB : Bromure de tétrabutylammonium

TBAF : Fluorure de tétrabutylammonium

TBAHS : Hydrogénosulfate de tétrabutylammonium

TBAI : Iodure de tétrabutylammonium

TBS: *tert*-Butyldiméthylsilyle

*t*Bu : *tert*-Butyle

TOF : *Time of flight*

TCA : Trichloroacétimidoyle

Tf : Trifluorométhanesulfonyle

THF : Tétrahydrofurane

TMS : Triméthylsilyle

TOCSY : *Total correlation spectroscopy*

Tol : Toluène

TEA·HF : Triéthylamine fluorure d'hydrogène

Ts : *para*-Méthylphénylsulfonyle

TTBP : 2,4,6-Tri-*tert*-butylpyridine

Abréviations signaux RMN

br s : singulet large

br d : doublet large

br t : triplet large

d : doublet

dd : doublet dédoublé

ddd : doublet dédoublé dédoublé

ddt : doublet dédoublé triplé

dt : doublet triplé

m : multiplet

s : singulet

t : triplet

td : triplet dédoublé

q : quadruplet

-Chapitre I-

Introduction Générale

1.1 Intérêts des glycolipides

Les glycolipides sont des composants des membranes cellulaires et sont présents dans tout le domaine du vivant, que ce soient les bactéries, les champignons, les plantes ou les animaux, incluant l'homme. Ils offrent une large gamme d'applications dans les domaines pharmaceutique et cosmétique et peuvent rivaliser avec les tensioactifs les plus communs.

Ils sont également impliqués dans une grande variété de fonctions biologiques essentielles telles que la communication intercellulaire, le transport photosynthétique d'électrons ou encore la modulation de la réponse immunitaire. De plus, certains microorganismes pourraient utiliser des glycolipides pour se protéger du stress oxydatif pouvant être induit par des peroxydes ou par la chaleur.[1,2,3]

C'est pourquoi les glycolipides sont des cibles pertinentes pour l'immunothérapie, mais aussi à la base du développement de certains vaccins et médicaments avec des résultats prometteurs en essais cliniques.[4,5] La capacité des glycolipides à former des gels, des niosomes, des hexosomes ou des cubosomes dont la structure est directement reliée à leurs propriétés lyotropiques[6] permet la solubilisation et le piégeage de médicaments. De plus, les glycolipides sont également utilisés pour améliorer le ciblage des médicaments du fait de leur partie glycosidique capable de reconnaître spécifiquement les protéines présentes à la surface des cellules. Aussi, ils peuvent servir à la synthèse de molécules bioactives. Au cours des 25 dernières années, l'intérêt pour les glycolipides dans les domaines cosmétique et pharmaceutique a grandement augmenté.

1.2 Structures et catégories de glycolipides

Les glycolipides sont composés d'une partie glycosidique [constituée d'une ou plusieurs unité(s) glycosidique(s)] reliée au groupement hydroxyle d'un alcool gras ou d'un acide gras, ou encore au groupement carboxyle d'un acide gras.[7] Ces derniers font partie de la grande famille des glycoconjugués parmi laquelle on retrouve, en plus des glycolipides, les glycoprotéines, les glycopeptides, les peptidoglycanes et les lipopolysaccharides. Ils proviennent du transfert d'une ou plusieurs unité(s) glycosidique(s) vers un glycérol acylé, une sphingosine acylée (céramide), un stérol ou alcool gras de structures diverses par les glycosyltransférases.[4] Ils sont catégorisés en fonction de la structure de leur partie aglycone.

Le terme glycoglycérolipide (GGL) désigne les glycolipides comportant une ou plusieurs unité(s) glycérol(s) sur lesquelles peuvent être acylés un ou plusieurs acides gras (Figure 1). Ils

sont plus largement répandus chez les microbes et les plantes. Quant aux glycosphingolipides (GSLs), leur aglycone est une sphingosine (longue chaîne aliphatique amino alcool) ou un céramide (sphingosine *N*-acylée) (Figure 1). Ils sont particulièrement présents chez les invertébrés marins[8] et sont classifiés en fonction de la composition de leur chaîne glycosidique : les GSLs neutres qui comportent une (cérébroside) ou plusieurs unité(s) glycosidique(s) non chargée(s) (dont les vespariosides), les GSLs acides comportant une partie glycosidique substituée par une ou plusieurs fonction(s) ionisée(s), comme des acides sialiques (gangliosides) ou des sulfates (sulfatides) par exemple, les GSLs basiques et les GSLs amphotères.[9]

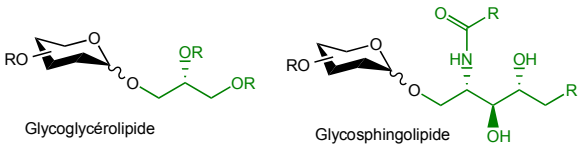

Figure 1 – Structures types des GGLs et GSLs

Les rhamnolipides sont des glycolipides tensioactifs qui ont beaucoup été étudiés dans la littérature[10] principalement pour leurs propriétés biosurfactantes et possèdent de nombreuses applications industrielles.[11] Les rhamnolipides sont structuralement caractérisés par une partie glycosidique constituée d'une ou deux unités α-L-rhamnopyranoside glycosylée(s) sur une ou deux unités β-hydroxyacide(s). Initialement, ces glycolipides ont été isolés à partir de *Pseudomonas aeruginosa* sous la forme d'un mélange de quatre congénères (Figure 2). Depuis, une soixantaine de congénères variant par la longueur de la chaîne lipidique ont été isolés à partir d'autres espèces du genre *Pseudomonas* mais aussi d'autres familles de bactéries comme *Burkholderia* ou *Pantoea*.[10] L'intérêt pour les rhamnolipides ne se limite pas à leurs propriétés biosurfactantes. Il s'étend à leurs effets sur la santé grâce à leurs propriétés antitumorales[12,13] et antimicrobiennes,[14,15] mais aussi à leurs propriétés immunomodulatrices et comme facteurs de virulence. Enfin, bien que la biosynthèse des rhamnolipides ait été et continue à être optimisée,[16] plusieurs aspects limitent encore la production industrielle. D'une part, les coûts de production ainsi que les difficultés de purification restent importants. D'autre part, le choix de la souche bactérienne, duquel dépend les rendements et congénères de rhamnolipides obtenus, ainsi que la pathogénicité de *Pseudomonas aeruginosa*, qui est aujourd'hui la plus utilisée, demeurent des points critiques dans la production à grande échelle.[17] Il est intéressant de noter que la chaîne acide (*R*)-3-hydroxydécanoique des rhamnolipides possède des propriétés immunomodulatrices en elle-même.[18]

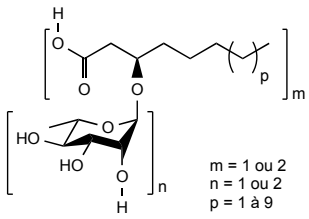

Figure 2 – Structures des congénères des rhamnolipides

Il existe d'autres catégories, bien que moins fréquentes, comme les stéryl glycolipides, glycosylés à un stérol, les phosphoglycolipides, avec un groupement phosphate inséré entre l'aglycone et la partie glycosidique, les glycolipides phénoliques, glycosylés à un groupement phénol, et, enfin, certains glycolipides qui sont glycosylés à des glycols (Figure 3). Cependant, malgré toutes ces catégories de glycolipides, il existe tout de même d'autres glycolipides n'appartenant à aucune d'entre elles. Ces derniers seront détaillés dans le chapitre 2.

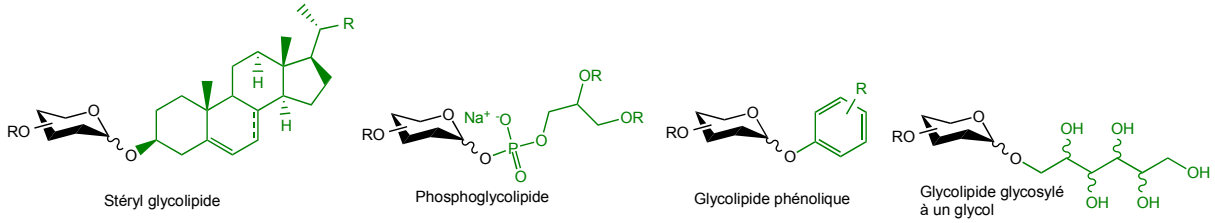

Figure 3 – Structures types de glycolipides divers

Les structures dans lesquelles l'acide gras est directement connecté au sucre par une autre position que la position anomérique sont appelées saccharolipides ou acylaminosucres du fait du remplacement d'un groupement hydroxyle de l'unité glycosidique par une fonction amine dans la plupart des cas. Au sein de ces dérivés glycolipidiques, une unité glycosidique remplace le groupement glycérol des glycoglycérolipides et des glycoglycérophospholipides. Des composés bien connus de cette catégorie sont les précurseurs du lipide A qui se retrouve sur la membrane externe des bactéries Gram négatives.

1.3 Présentation du sujet de thèse et plan

Le sujet de ce travail de recherche porte sur la synthèse des agminosides (Figure 4), une famille de glycolipides ne correspondant à aucune des catégories mentionnées ci-dessus. Les agminosides sont des glycolipides issus de l'éponge de mer *Raspailia agminata* endémique de la Nouvelle-Zélande. Isolés et décrits pour la première fois en 2008 dans la thèse de doctorat de

Joanna M. Wojnar,[19] la structure et l'isolation de ces composés seront abordés plus en détails dans le chapitre 2.

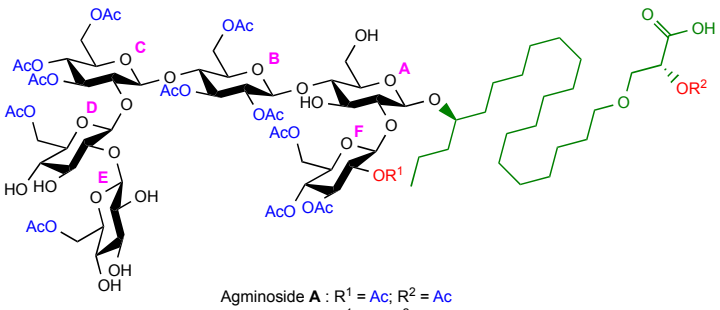

Figure 4 – Structures des agminosides A–E

Il est cependant nécessaire de préciser ici que parmi les particularités structurales inhabituelles des agminosides figurent un motif d'acétylation partiel bien défini ainsi que la présence de cinq à six unités β-D-glucopyranosides. De plus, le faible rendement d'isolation impose d'établir une méthode de synthèse totale de ces glycolipides. L'obtention d'une méthode de synthèse pourra permettre de confirmer le motif d'acétylation partielle établi par Northcote *et al.*, et de facilement synthétiser des dérivés (désacétylé, peracétylé, macrolactonisé, etc.), accessibles uniquement par synthèse. La synthèse des agminosides permettra également d'améliorer les rendements d'obtention et de déterminer les activités biologiques des agminosides **A**–**E** et de leurs dérivés. Ce projet de recherche constitue un défi synthétique de taille. Ainsi, seront discutés dans ce document la synthèse d'un glycolipide dérivé de l'agminoside **E** comportant la partie glycosidique de ce dernier glycosylée sur un aglycone communément retrouvé dans les rhamnolipides, l'acide (*R*)-3-hydroxydécanoique,(*cf* chapitre 4) ainsi que le travail effectué jusqu'à présent dans le cadre de la synthèse de la chaîne lipidique native des agminosides (*cf* chapitre 5).

Ainsi, ce document sera articulé en six chapitres. Le chapitre 1 correspond à l'introduction générale qui présente les glycolipides, leurs provenances, leurs structures et leurs catégorisations ainsi que les agminosides qui sont le sujet de ce projet. Le chapitre 2 comprend une revue de littérature centrée sur les glycolipides d'origine marine et notamment les glycolipides partiellement *O*-acétylés dont les agminosides. Sont discutés dans ce chapitre l'intérêt du milieu marin comme source de composés biologiquement actifs, ainsi que les découverte, provenance et structure de divers glycolipides marins. Certaines synthèses totales y sont discutées ainsi que d'autres familles

de glycolipides qui, comme les agminosides, ne peuvent être classées dans aucune des catégories présentées ci-dessus. Tous les détails connus sur les agminosides seront discutés avant de présenter les objectifs de ce travail. Le chapitre 3 consiste en un article publié dans *The Chemical Record* traitant des travaux de synthèse précédemment effectués par le groupe du Pr Charles Gauthier. Ce chapitre traite de différentes stratégies de synthèse largement répandues en glycochimie telles que l'utilisation de groupements protecteurs ainsi que plusieurs méthodes de glycosylation courantes et efficaces. Cette revue de littérature exemplifie l'expertise du Pr Charles Gauthier. Celle-ci m'a permis de progresser au sein du vaste domaine de la chimie des hydrates de carbone et de mettre au point les différentes synthèses du chapitre 4 de mon projet de doctorat. Par ailleurs, le chapitre 4 comprend un article publié dans *The Journal of Organic Chemistry* discutant du travail de synthèse du glycolipide dérivé des agminosides. Plusieurs méthodes de glycosylation et stratégies de synthèse ont été explorées au cours de ce travail de recherche. À la suite de cet article se trouve une section complémentaire à l'article qui discute des stratégies de synthèse alternatives qui ont été tentées au cours de ce travail de recherche sans toutefois faire partie de la publication. Cette section présente également le détail de la synthèse des précurseurs connus de l'article. Le chapitre 5 est constitué de l'état de la synthèse de la chaîne lipidique native des agminosides ainsi que des pistes à explorer pour finaliser la synthèse. Il discute des difficultés rencontrées lors de la synthèse et des solutions envisagées pour les résoudre. Le chapitre 6 correspond à la conclusion générale de ce travail de recherche, résumant les résultats obtenus ainsi que les perspectives en vue d'établir la voie de synthèse totale vers les agminosides **A**–**E** et leurs dérivés. Enfin, se trouvent en annexes les spectres RMN des composés synthétisés organisés par chapitre ainsi qu'un tableau comparatif de la RMN ^{1}H de la partie glycosidique du glycolipide chimérique synthétisé avec celle de l'agminoside **E** isolé. Les références sont notées à la fin de chaque section du manuscrit de la thèse.

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-Chapitre II-

Revue de la littérature sur les glycolipides d'origine marine

2.1 Intérêt biologique de composés issus du milieu marin

Dans le domaine de la chimie des produits naturels, l'environnement marin représente une source inestimable de composés biologiquement actifs et structurellement différents. Bon nombre de nouveaux squelettes carbonés propres à certaines espèces marines ont été décrits.[1]

Principalement produits par des invertébrés comme moyen de défense chimique,[2] les métabolites secondaires marins se doivent d'être très puissants car ils sont rejetés dans l'eau et se retrouvent ainsi sous une forme diluée.[3] De plus, l'immense diversité biologique de l'environnement marin augmente le nombre de composés biologiquement actifs issus d'espèces marines pouvant potentiellement être utilisés pour traiter diverses pathologies humaines.[4]

Un bon exemple concerne l'isolation de la maïtotoxine (Figure 1) à partir du dinophyte *Gambierdiscus toxicus*. Il s'agit du métabolite secondaire le plus toxique et avec le plus haut poids moléculaire n'ayant jamais été isolé.[5]

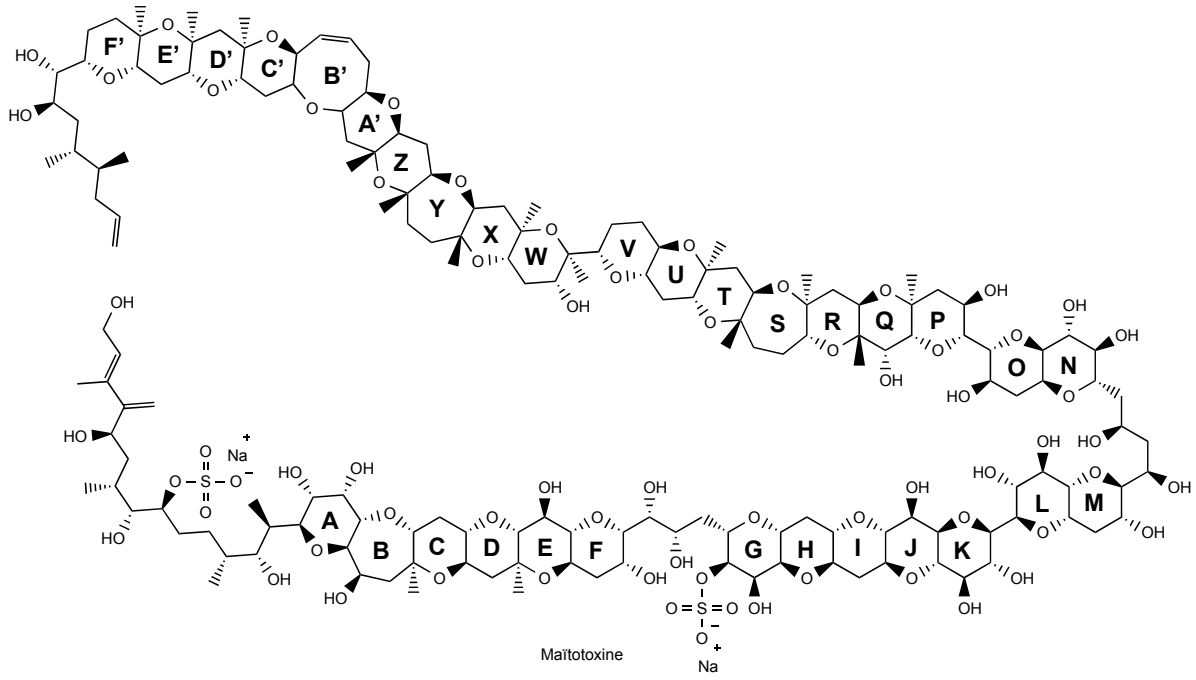

Figure 1 – Structure de la maïtotoxine

Depuis 1996, le groupe de Nicolaou *et al.* a travaillé sur la synthèse de la maïtotoxine, morceau par morceau.[6] Après la synthèse de certains fragments[7] et plusieurs études structurales visant à préciser la structure exacte de la maïtotoxine[8] (en parallèle de nombreuses autres équipes), il publie en 2007[9] puis en 2008[10] la synthèse du fragment GHIJKLMNO. Quelques années plus tard, ce sont les synthèses des fragments ABCDEFG,[11] QRSTU,[12] C'D'E'F',[13] et WXYZA'[14] qui

sont décrites. En 2014, la synthèse du fragment QRSTUVWXYZA'[15] est établie pour ne laisser, après 20 années de travaux, à synthétiser que les cycles P et B' ainsi que les deux chaînes aux extrémités.[16]

Bien que l'élaboration d'une voie de synthèse totale soit un procédé long et coûteux, elle n'en demeure pas moins pertinente. En effet, celle-ci permet non seulement de préciser ou confirmer la structure des molécules extraites, ouvre également la voie vers la synthèse de dérivés non naturels. Ceux-ci permettent également d'effectuer des études de relation structure/activité pouvant améliorer la compréhension de certains mécanismes biologiques ainsi que facilitant l'accès à de potentiels médicaments.

2.2 Les glycolipides issus d'invertébrés marins

Les deux plus grandes sources de glycolipides d'origine marine sont les *Porifera* (spongiaires) et les *Echinodermata*.[17] Dans les années 50, les travaux de Bergmann et Feeney[18] dans le domaine des produits naturels marins ont mené à la découverte de la spongothymidine et de la spongouridine (Figure 2) à partir de l'éponge marine *Cryptotethya crypta*. Deux dérivés de ces composés, la Vidarabine® (Ara-A) et la Cytarabine® (Ara-C) ont été synthétisés pour leurs intérêts biologiques et sont encore utilisés en clinique aujourd'hui en tant qu'agents antiviraux et anticancéreux respectivement.[19,20,21] Depuis, plus de 5 000 nouveaux composés ont été isolés à partir d'éponges marines et bon nombre de ces composés montrent de puissantes activités pharmaceutiques telles qu'anti-inflammatoires, anticancéreuses, antivirales ou encore antibactériennes.[19]

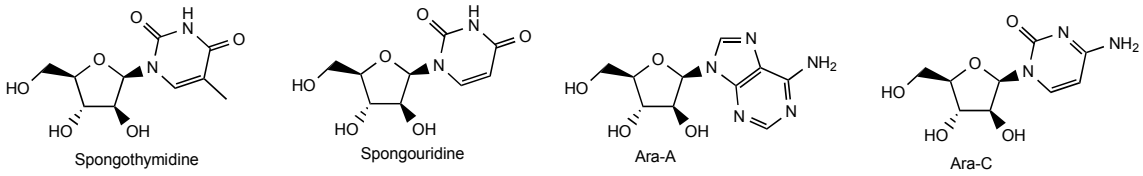

Figure 2 – Structures des glyconucléosides issus de *Cryptotethya crypta* et de leurs dérivés

En 1993, Natori *et al.* ont découvert de nouveaux glycosphingolipides, plus précisément des α-galactosylcéramides, issus de l'éponge marine *Agelas mauritianus* qu'ils ont nommé les agelasphins (Figure 3).[22] La particularité de ces composés est la présence d'une liaison glycosidique de type α alors que les liaisons de type β sont présentes dans la quasi-totalité des glycosphingolipides naturels.[23] Les agelasphins s'avèrent exercer des activités biologiques importantes en lien avec la réponse immunitaire ainsi que des propriétés anti-métastatiques.[24] Ainsi,

des analogues de ces composés ont vu le jour : KRN7000 et OCH (Figure 3). Ces composés sont capables de stimuler le système inné humain en interagissant avec les anticorps et les lymphocytes T (NKT).[25,26,27] De plus, ces glycosphingolipides possèdent des propriétés immunostimulantes, ils peuvent donc être utilisés en tant qu'adjuvants pour la vaccination thérapeutique.

En 2001, Borbone *et al.* ont isolé plusieurs glycosphingolipides de structures apparentées (Figure 3) à partir de l'éponge marine *Aplysinella rhax* issue des eaux peu profondes de la Nouvelle Calédonie.[28] La partie glycosidique de ces glycosphingolipides est une chaîne trisaccharidique branchée ayant la structure suivante : β-D-GalNAc*p*-(1→4)-[α-D-Fuc*p*-(1→3)]-β-D-GlcNAc*p*. C'était la première fois qu'un glycolipide comportant une unité D-fucopyranoside était répertorié. La chaîne lipidique est de type céramide et varie en longueur en fonction des composés (m = 18, n = 10 ; m = 19, n = 11 ; m = 22, n = 10 ; avec n et m, nombre de CH_2 sur chacune des chaînes carbonées du céramide). Borbone *et al.* ont également mis en évidence les propriétés inhibitrices de la synthèse d'oxydes nitriques dont la production excessive est impliquée dans la pathogénèse des réponses inflammatoires. Au vu de ces propriétés biologiques, Hada *et al.* ont décidé de synthétiser des analogues de ces composés naturels dans le but de bonifier leurs propriétés biologiques.[29] Ainsi, en 2007, cinq analogues de ces glycosphingolipides ont été synthétisés : la chaîne céramide a été remplacée par un alcool gras ou par un groupement triméthylsilyléthyl, l'unité D-fucopyranose a été remplacée par le L-fucopyranose ou a été éliminée, et l'unité *N*-acétylgalactosamine a été remplacée par le D-galactopyranose. Ainsi, Hada *et al.* ont pu déterminer que : 1) la chaîne lipidique n'est pas nécessaire à l'activité biologique ; 2) l'unité fucopyranose préférentiellement en série D est essentielle ; et 3) le groupement acétamido de la galactosamine améliore l'activité inhibitrice.

En 2004, Pettit *et al*. ont isolé et identifié la turbostatine (**1**-**4**), un β-glycosphingolipide issu, cette fois-ci, non pas d'une éponge de mer, mais d'un mollusque marin, *Turbo stenogyrus*, endémique de Taïwan (Figure 3).[30] La partie glycosidique des turbostatines est un monoglycoside qui peut varier : c'est un D-glucopyranoside pour les turbostatines **1** et **2** alors que pour les turbostatines **3** et **4**, il s'agit d'un D-galactopyranoside. Il a été observé que cette famille de glycolipides possède des propriétés inhibitrices de la croissance des cellules cancéreuses sur différents cancers humains (leucémie lymphocytique, adénocarcinome du pancréas, adénocarcinome du sein, glioblastome du système nerveux central, cancer du poumon à grandes cellules, adénocarcinome du colon et carcinome de la prostate).[30]

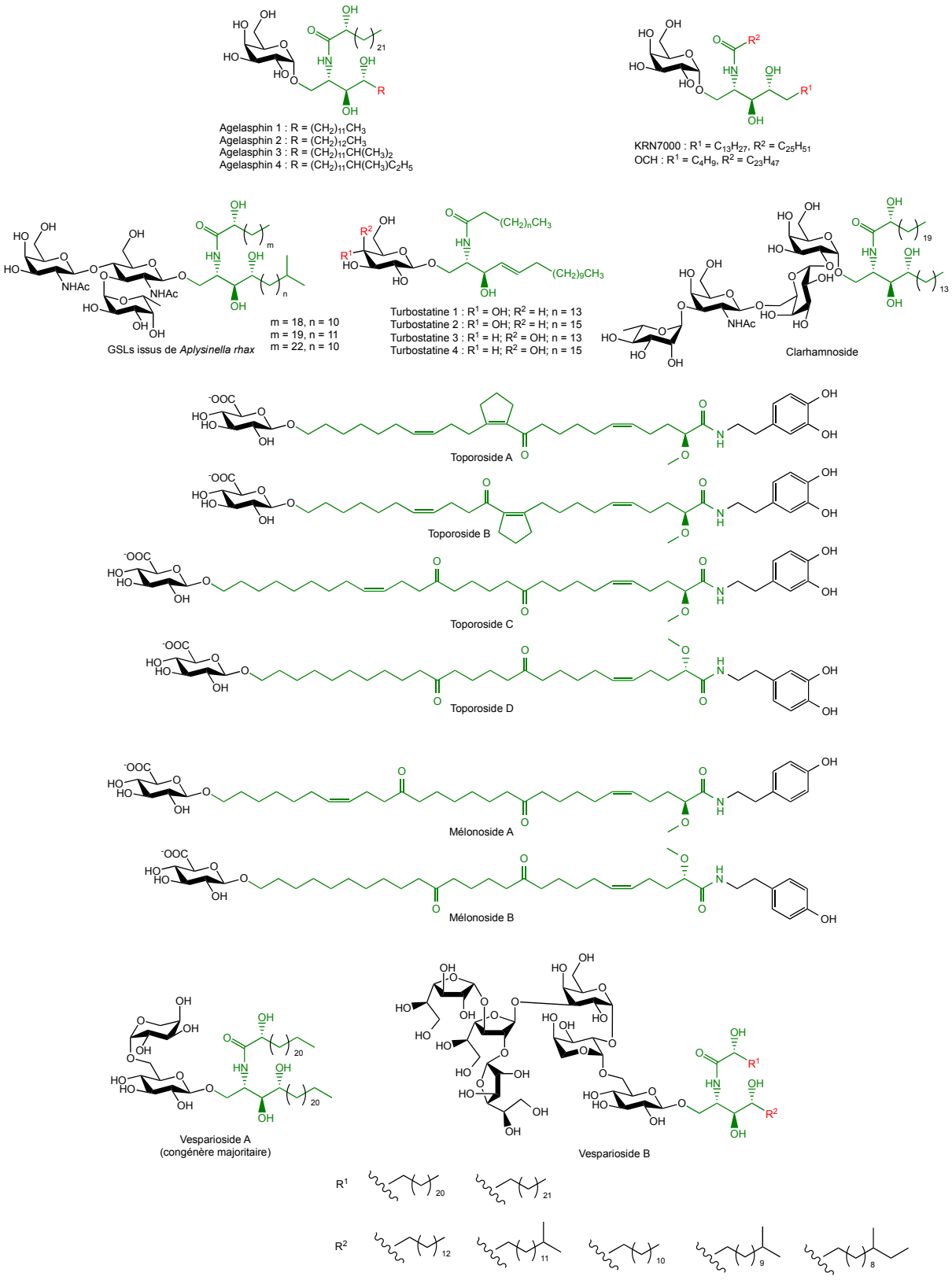

Figure 3 – Structures de différents glycolipides marins

La même année, Costantino *et al.* ont découvert les clarhamnosides, une nouvelle famille de glycosphingolipides issus de l'éponge marine *Agelas clathrodes* (Figure 3).[31] La partie glycosidique du clarhamnoside est un tétrasaccharide comportant trois unités D-galactopyranoses et une unité L-rhamnopyranose. Les liaisons glycosidiques sont principalement de type 1,2-*cis* (α), et les unités se succèdent comme suit : α-L-Rha*p*-(1→3)-β-D-GalNAc*p*-(1→6)-α-D-Gal*p*-(1→2)-α-D-Gal*p*. Il est à noter qu'il s'agit du seul α-galactoglycosphingolipide rapporté jusqu'à maintenant comportant une unité L-rhamnopyranose à son extrémité non-réductrice.[31] À partir de 2006, le groupe de Yingxia Li s'est intéressé à la synthèse des clarhamnosides. Son groupe a réalisé, dans un premier temps, la synthèse de la chaîne tétrasaccharidique glycosylée à un groupement propyl (allyl avant la réduction finale) selon une approche de glycosylation [2 + 2].[32] En 2007, ils ont publié la synthèse totale du clarhamnoside selon la même approche [2 + 2], mais en remplaçant le groupement allyl par une sphingosine qui a été acylée juste avant la déprotection finale (Figure 4).[33]

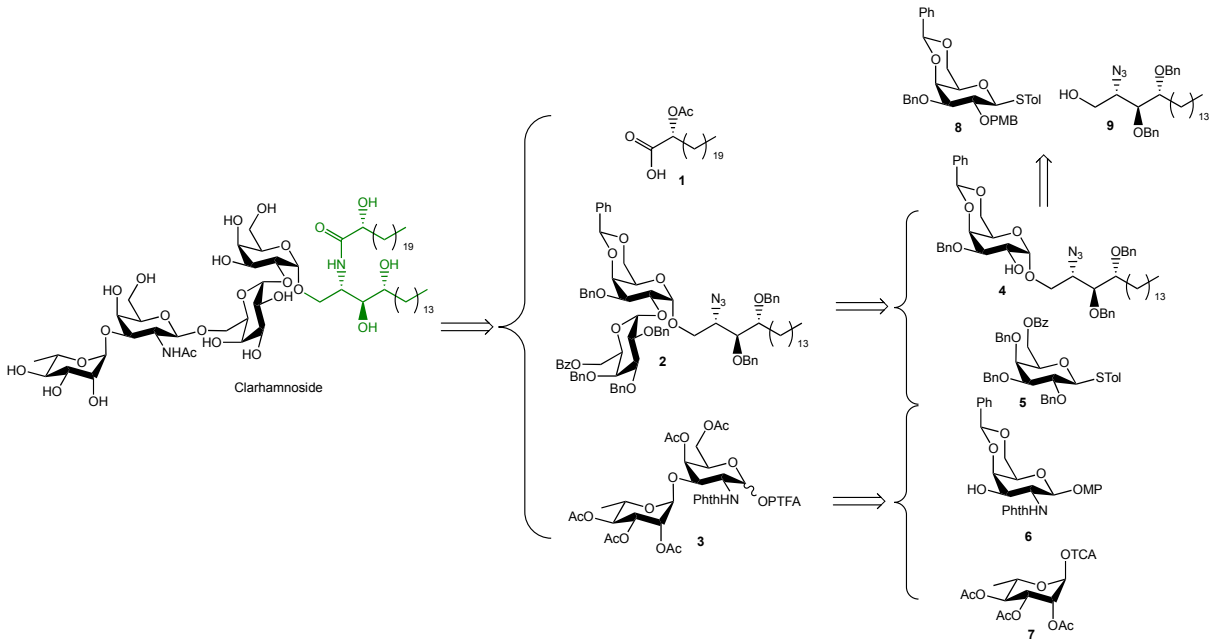

Figure 4 – Stratégie de synthèse du clarhamnoside

Plus récemment, en 2022, Guzii *et al.* ont mis en évidence les toporosides A–D.[34] Issus de l'éponge de mer *Stelodoryx toporoki* originaire de la mer du pacifique nord-ouest, ils possèdent un fragment D-glucuronide lié à une chaine carbonée linaire insaturée et pouvant comporter un fragment carbonyl α,β-insaturé cyclopentényle pour les toporosides A et B. L'extrémité de la chaîne est constituée d'un amide substitué par une unité dopamine (Figure 3). Les toporosides A,

C et D ont montré des effets cardioprotecteurs contre les dommages induits par TNF-α. Il est à noter que le toporoside D possède la même structure que le mélonoside B à cela près que l'unité dopamine est une tyramine (comportant un phénol en moins).

Ces derniers ont été caractérisés quelques années plus tôt, en 2018, également par Guzii *et al.* et sont issus de l'éponge de mer *Melonanchora kobjakovae* originaire de la mer d'Okhotsk, au large de l'île de Sakaline.[35] Les mélonosides présentent donc une structure très similaire à celle des toporosides (Figure 3). L'étude de l'activité biologique de ces composés n'a montré aucun impact sur les activités transcriptionnelles de AP-1 et NF-κB. Cependant, les mélonosines A et B, leurs versions déglucuronylées, ont montré de bonnes propriétés inhibitrices de ces deux facteurs.

En 2008, Costantino *et al.* ont isolé le vesparioside B à partir de l'éponge de mer *Spheciospongia vesparia* sous la forme d'un mélange de congénères différenciés par l'extrémité de la partie céramide.[36] Il s'agit d'un glycosphingolipide complexe comportant une partie glycosidique allongée par rapport à celle du vesparioside A (Figure 3), isolé en 2005 par la même équipe et qualifié par celle-ci de premier diglycosylcéramide comportant une unité pentose.[37]

En 2016, Gao *et al.* ont publié la synthèse du vesparioside B[38] dont la partie glycosidique constitue le principal défi. Celle-ci contient un trisaccharide branché en 2,3 à l'extrémité réductrice qui est constitué de trois unités furanoses glycosylées de façon 1,2-*cis*. Les auteurs ont décidé de former le lien α-galactosidique en dernier *via* une glycosylation [4 + 2] entre le thioglycoside **10** et l'accepteur **11** (Figure 5). Le tétraglycoside **10** a été obtenu par glycosylations successives des furanosides **12**, **13** et **14** ainsi que du galactoside **15**. D'autre part, le glycolipide **11** a été obtenu par glycosylation des dérivés **16** et **17** puis avec le céramide **18**. Les synthèses de ces composés ne seront pas détaillées ici. Ne seront traités que les points cruciaux.

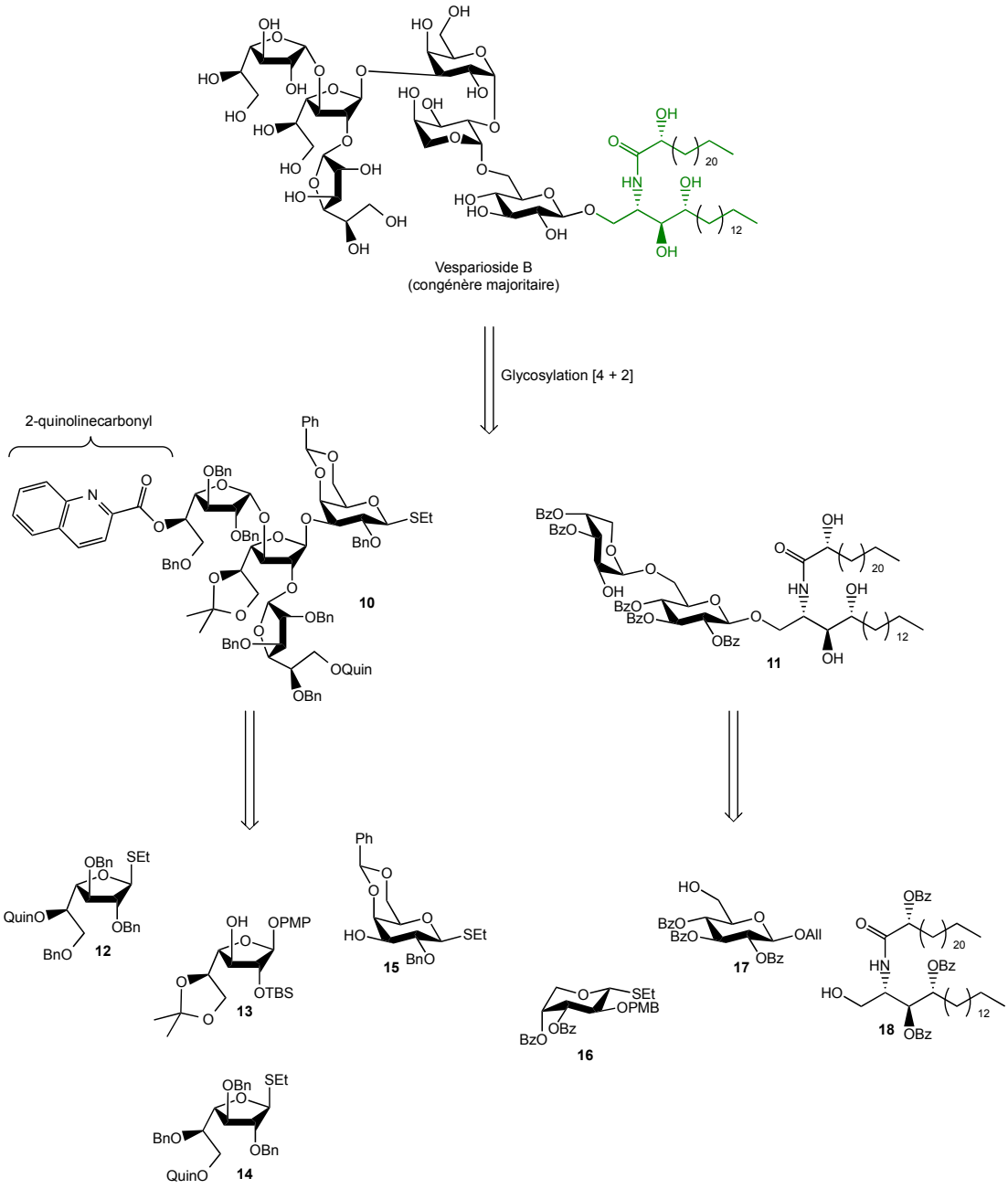

Figure 5 – Rétrosynthèse du congénère majoritaire du vesparioside B

Comme décrit dans le schéma 1, les liens α-galactofuranosyles présents sur le trisaccharide **21** ont été obtenus par la présence d'un groupement 2-quinolinecarbonyle (Quin) encombrant la face inférieure des donneurs **12** et **14**. Les auteurs ont montré que le groupement Quin en position 5 permettait une meilleure sélectivité α:β qu'en position 6. Cependant, lors de la seconde glycosylation, le groupement Quin du donneur s'est avéré plus labile qu'en position primaire.

Enfin, la β-sélectivité lors de l'obtention du tétrasaccharide **10** a été attribuée par un effet bouclier du fragment 2-*O*-galactofuranosyle sur la face inférieure.

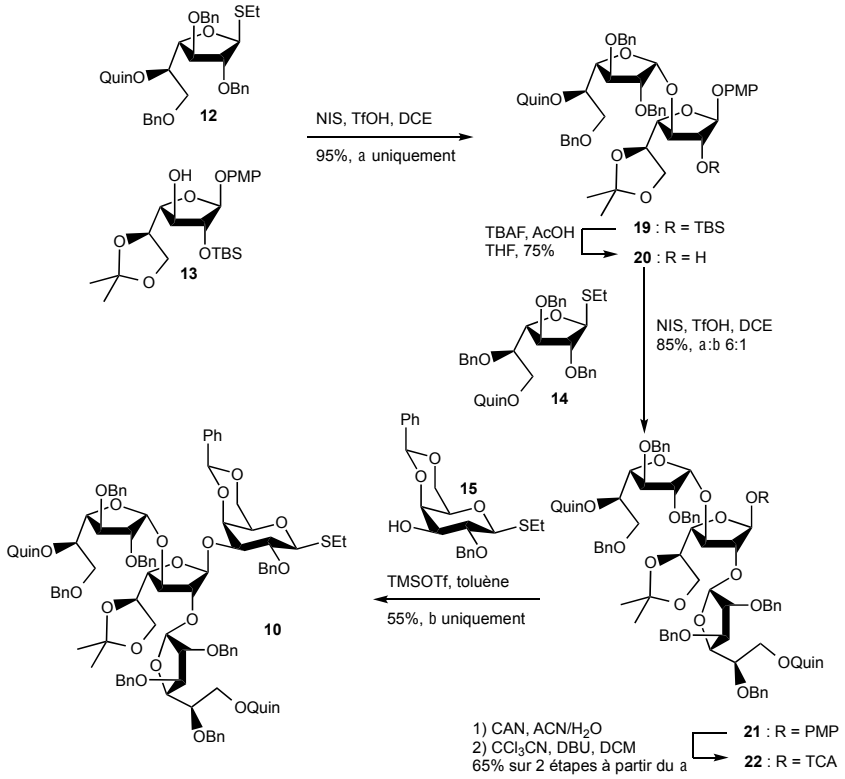

Schéma 1 – Synthèse du tétraglycoside 4

Lors de la synthèse du glycolipide **11** (Schéma 2), c'est le lien β-D-arabinopyranosyl qui a été le plus difficile à obtenir. Dans un premier temps, les auteurs ont essayé la glycosylation avec un donneur 3,4-*O*-isopropylidène ou 3,4-di-*O*-benzylé permettant l'obtention du disaccharide correspondant avec un rendement de 75% et un ratio α:β de 1:3. Mais c'est le composé **16** 2,3-di-*O*-benzoylé qui a permis la formation exclusive du lien β avec un rendement de 95%.

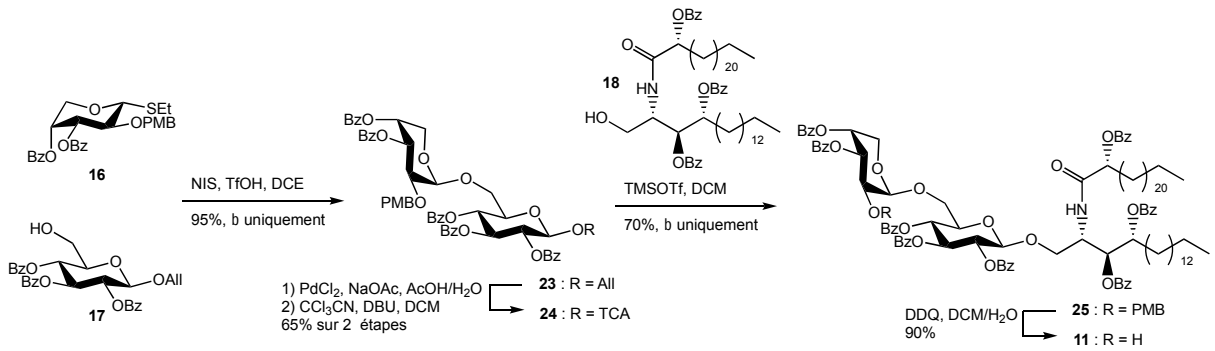

Schéma 2 – Synthèse du diglycolipide 5

Enfin, la glycosylation présentée dans le schéma 3 a été un défi du fait de l'encombrement stérique de l'alcool en 2 du résidu arabinopyranosyle. De fait, la glycosylation des partenaires **10** et **11** catalysée par NIS/TfOH n'a permis l'obtention de l'hexaglycolipide **26** qu'avec un faible rendement de 16%. C'est l'application d'une méthode de glycosylation inverse, où l'accepteur (**11**) est dissout dans le solvant avec le couple de promoteurs (ici NIS/TfOH) et où une solution du donneur (**10**) est ajoutée lentement à 0 °C, qui a permis l'amélioration du rendement de glycosylation jusqu'à 80% avec formation exclusive de l'isomère α. Les auteurs ont attribué la stéréosélectivité de cette glycosylation à la présence du benzylidène encombrant la face supérieure du fragment galactopyranosyle.

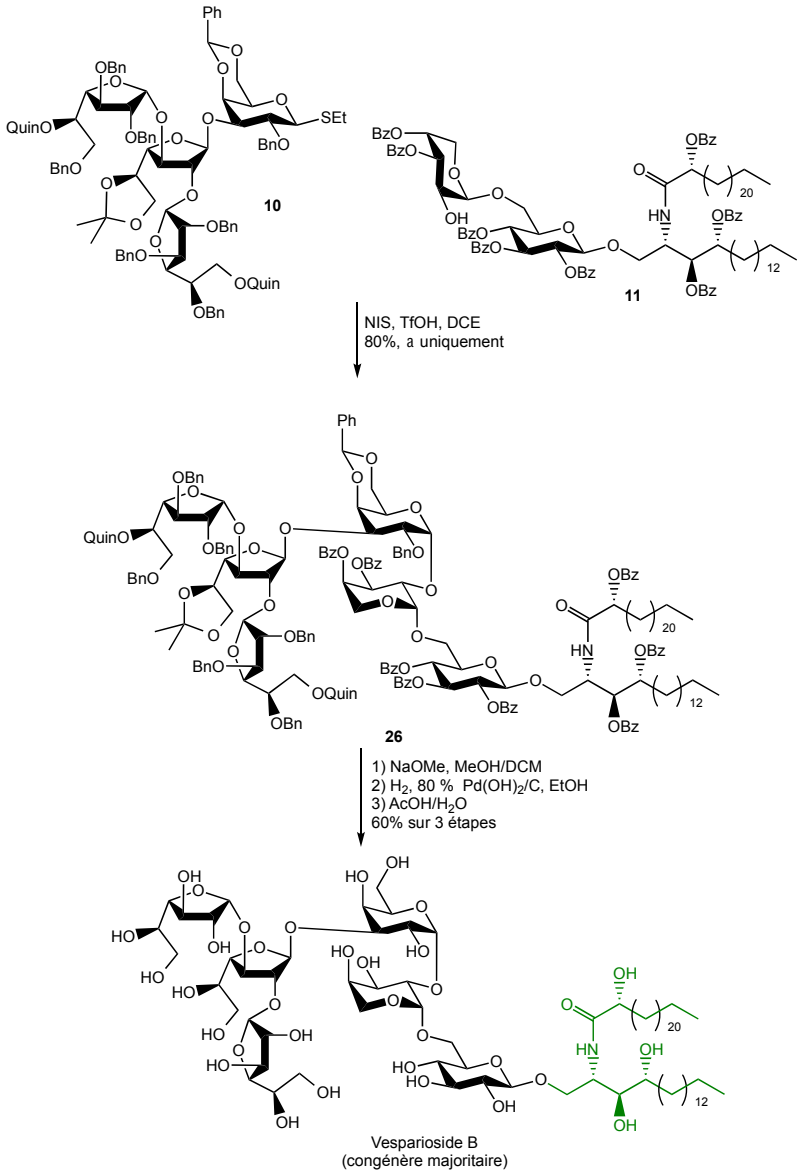

Schéma 3 – Glycosylation [4 + 2] et déprotections pour obtenir le congénère majoritaire du vesparioside B

2.3 Les familles de glycolipides d'origine marine partiellement *O*-acétylés

Les glycolipides partiellement acétylés ne peuvent être classifiés dans aucune des grandes catégories de glycolipides. Ils ne sont pas fréquents dans la nature et seulement quelques structures glycolipidiques possédant une chaîne glycosidique acétylée ont été actuellement décrites : les agminosides, les caminosides, les erylusamines, les erylusamides, les rosélipins, les stellettosides et les pachymosides. Certains composés communs de ces glycolipides acétylés atypiques sont représentés à la figure 6.

L'erylusamine **B** a été isolé en 1993 par Fusetani *et al.*[39] à partir de l'éponge marine *Erylus placenta*, une espèce endémique du Japon. Structuralement, l'erylusamine **B** est un tétrasaccharide branché partiellement acétylé, contenant des unités L-arabinopyranoses et D-xylopyranoses et relié à un alcool gras dérivé d'amide se terminant par une unité *N*,*N*-diméthylpentanediamine. Les erylusamines et leurs dérivés sont de puissants antagonistes cytotoxiques des récepteurs multifonctionnels des interleukines-6 et pourraient être utilisés comme agents anti-inflammatoires.[39,40] En 1996, les travaux de Goobes *et al.*[41] ajoutent aux glycolipides acétylés du genre *Erylus* deux nouveaux composés : l'erylusamine TA et l'erylusine, qui comportent une chaîne lipidique, similaire à celle des erylusamines, glycosylée à un trisaccharide branché constitué de deux unités D-galactopyarnoses et une unité D-glucopyranose, le galactose de l'extrémité réductrice étant acétylé sur la position primaire.

Plus récemment, en 2016, Gaspar *et al.* ont isolé une nouvelle variété de glycolipides issue de *Erylus deficiens*, originaire des côtes portugaises, complétant encore la chimiothèque issue du genre *Erylus* : les erylusamides (Figure 6).[42] Ils sont composés d'une chaîne pentasaccharidique branchée et partiellement acétylée comportant trois unités D-glucopyranoses, une unité D-galactopyranose ainsi qu'une unité D-xylopyranose toutes liées par des liaisons glycosidiques de type β. La chaîne lipidique quant à elle ne diffère de celle des pachymosides que par la longueur de la chaîne carbonée. Ces glycolipides auraient des propriétés inhibitrices de l'enzyme indoleamine 2,3-dioxygénase (IDO1) qui joue un rôle dans le contrôle des infections ainsi que dans le processus de rejet immunitaire dû aux lymphocytes T. En sachant que l'IDO1 est surexprimée dans une grande variété de cellules cancéreuses et agit contre les lymphocytes T permettant ainsi la prolifération de la tumeur,[43] les erylusamides possèdent un potentiel thérapeutique à explorer.

En 2015, les stellettosides ont été isolés d'éponges de mer du genre *Stelletta*, originaires du Japon, par Peddie *et al.*[44] sous la forme de deux fractions : les stellettosides A composés de deux

isomères (A1 et A2) et les stellettosides B composés de quatre isomères (B1 – 4) (Figure 6). Tous ces isomères sont des triglycolipides composés d'un trisaccharide linéaire de L-arabinopyranoside glycosylé en 1,2-*trans* avec l'unité de l'extrémité réductrice complètement acétylée, ainsi que d'un alcool gras dérivé d'amide similaire à celui des erylusamines se terminant par une unité *N*,*N*-diméthylputrescine au lieu de l'unité *N*,*N*-diméthylcadavérine. Il est à noter que le motif *threo* de dioxygénation présent sur l'aglycone des erylusamines est remplacé ici par un motif *erythro*. Les isomères de stellettosides se différencient par la longueur de la chaîne et la position des substituants sur celle-ci. Là où les stellettosides A n'ont montré aucune activité contre les cellules HeLa à 10 μM, les stellettosides B ont montré une valeur d'IC_{50} de 9 μM.

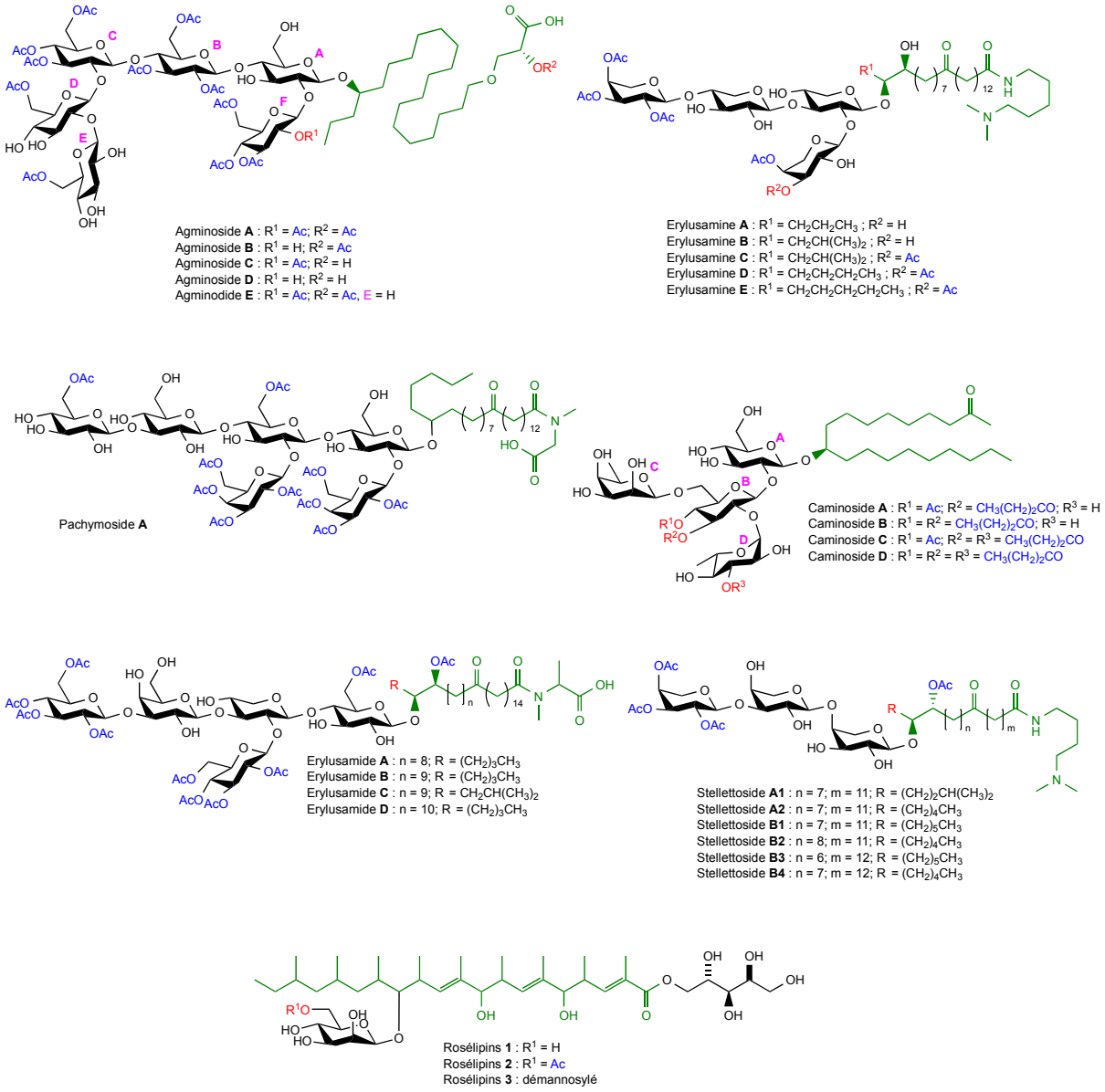

Figure 6 – Structures chimiques de glycolipides polyacétylés issus d'éponges marines.

En 2004, le groupe de R. J. Andersen a rapporté une méthode d'isolation du pachymoside **A** guidée par des essais biologiques[45] à partir de *Pachymatisma johnstonia*, une éponge marine présente en Mer du Nord. Les extraits de cette éponge se sont avérés être des inhibiteurs de la production de sécrétions bactériennes de type III. Les pachymosides (Figure 6) sont composés d'une chaîne hexasaccharidique branchée et partiellement acétylée contenant des unités D-glucopyranoses et D-galactopyranoses. La chaîne lipidique est similaire à celle des erylusamines à l'exception de l'unité terminale qui contient ici un acide carboxylique.

Une autre famille de composés ayant été très étudiée est la famille des rosélipins. D'abord isolée à partir du champignon marin *Gliocladium roseum* et caractérisée en 1999 par Tomoda *et al*.,[46] cette famille a été découverte grâce à ses propriétés inhibitrices contre la diacylglycérol acyltransférase (DGAT) dans le cadre de la lutte contre le diabète, mais possède également des propriétés antibactérienne, cytotoxique, antiparasitaire ainsi qu'inhibitrice de l'enzyme HIV-1-intégrase.[47,48,49,50,51] Les rosélipins (Figure 6) sont constitués d'un acide gras hautement méthylé acylé à un fragment D-arabinitol et glycosylé à une unité D-mannopyranose (rosélipins 1A et 1B) pouvant être acétylée en position primaire (rosélipins 2A et 2B).[52] Aussi, la configuration absolue des trois alcools présents sur cette chaîne méthylée n'a pas été déterminée par les auteurs. Il est à noter que des dérivés démannosylés (rosélipins 3A et 3B) ont été synthétisés par voie enzymatique[53,54] et ont montré de meilleures propriétés inhibitrices de DGAT.

Les caminosides sont une autre famille de glycolipides partiellement acétylés issus d'éponges marines. Ils ont également été isolés par l'équipe de R. J. Andersen en 2002 à partir de *Caminus sphaeroconia*, une éponge marine issue des Grottes de la Baie de Toucari en République Dominicaine.[55,56] Cependant, bien que la structure du caminoside **A** (Figure 6) ait été déterminée en 2002, la configuration absolue du C10 reliant la chaîne lipidique à la partie oligosaccharidique n'a été déterminée qu'en 2004 par dichroïsme circulaire liposomial avec couplage d'exciton (LECCD).[57] Il a ensuite fallu attendre 2006 pour que les structures des caminosides **B**–**D** soient déterminées.[56] Tous les caminosides (**A**–**D**) partagent la même structure de chaîne tétrasaccharidique composée de deux unités D-glucopyranoses, une unité L-quinovopyranose et une unité 6-désoxy-L-talopyranose. La chaîne lipidique est une chaîne linéaire en C_{19} portant une méthyl cétone en bout de chaîne. Les différences structurales entre les caminosides **A**–**D** sont liées aux positions des groupements acétates et butyrates de la partie glycosidique. Les caminosides sont de puissants inhibiteurs du système de sécrétion de type III d'*Escherichia coli*, ce qui fait de cette

famille de glycolipides des agents antibiotiques prometteurs. Les caractéristiques structurales uniques des caminosides couplées à leurs activités biologiques intéressantes ont inspiré les chimistes organiciens pour les synthétiser à partir de produits commerciaux. Le groupe de Biao Yu a été le premier à prendre part à ce défi en rapportant la synthèse totale du caminoside **A** en 2005.[58] Cependant, la synthèse totale proposée par Biao Yu ne tient pas compte de la configuration absolue de la chaîne lipidique, les travaux de Molinski ayant été menés en parallèle.

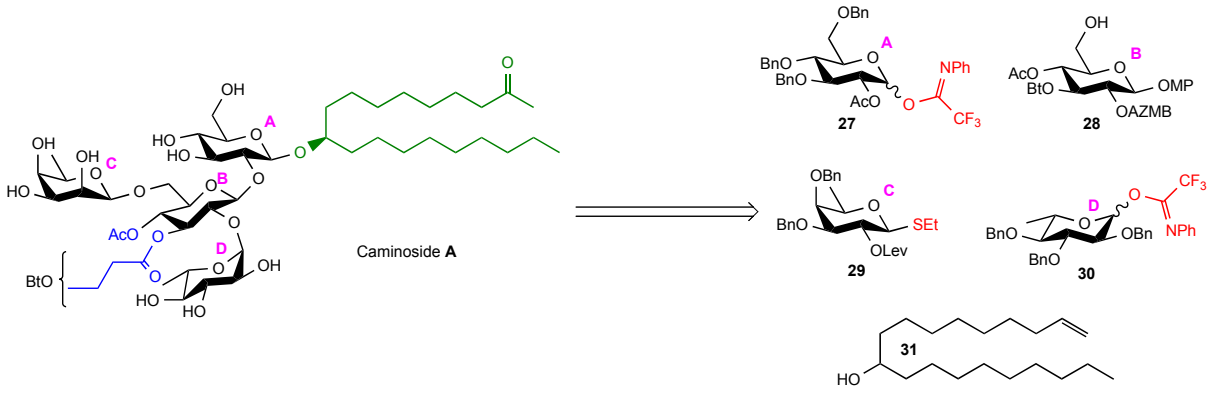

Figure 7 – Analyse rétrosynthétique du caminoside A

D'après leur approche synthétique (Figure 7), qui compte 57 étapes au total, les différentes unités glycosidiques ont été synthétisées selon des séquences standards de protection/déprotection à partir du D-glucopyranose, du D-galactopyranose et du L-rhamnopyranose. Les étapes clés de ces synthèses sont détaillées ci-dessous (Schéma 4). La conversion du dérivé D-galactopyranose à la position C6 permettant l'obtention d'un dérivé D-fucopyranose **29** a été effectuée par réduction du dérivé iodé issu du dérivé tosylé **32**.[59,60] Par la suite, l'épimérisation en C2 du L-rhamnopyranose permettant l'obtention du L-quinovopyranose a été produite par l'action de l'acide molybdique dans l'eau.[61,62] Ces synthèses comportent entre sept et 14 étapes par glycoside et ont des rendements globaux allant de 21% à 38%.

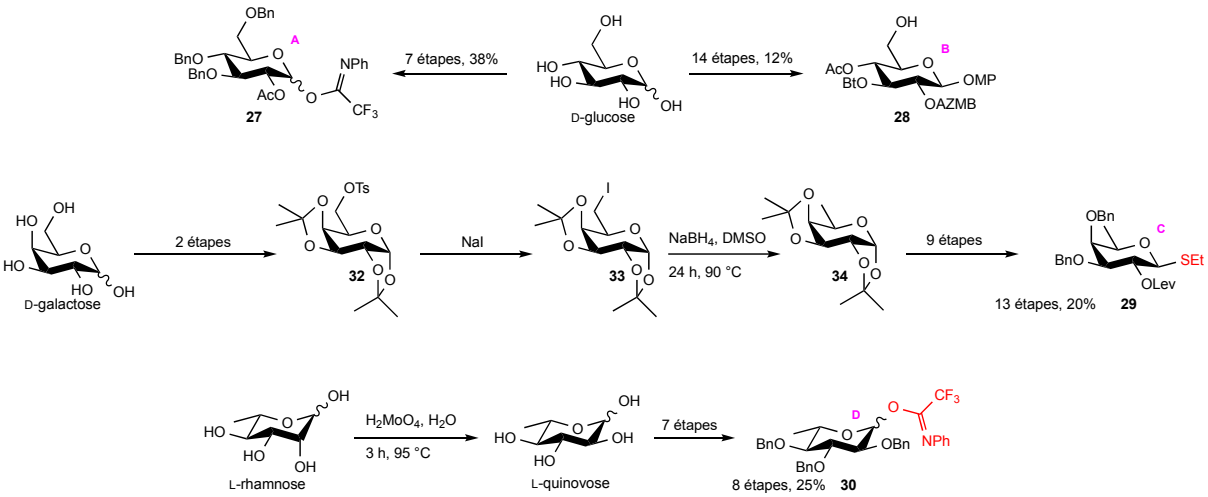

Schéma 4 – Synthèse des unités glycosidiques du caminoside A

La suite de leur approche était basée sur une séquence de glycosylation [2 + 2 + 1] (Schéma 5). Ainsi, les premières glycosylations ont été celles entre les synthons **27** et **31** et entre les synthons **28** et **29** permettant l'obtention des dérivés **35** et **38**. Au cours de la synthèse, une épimérisation de la position C2 de l'unité D-fucopyranoside du disaccharide **36** a été effectuée par une séquence d'oxydation-réduction afin d'obtenir l'unité D-talopyranoside souhaitée sur le disaccharide **37**.[63,64] Ensuite a eu lieu la glycosylation entre les composés **35** et **38** générant le trisaccharide lipidique **39** qui a par la suite été glycosylé avec le donneur **30** afin d'obtenir le caminoside **A**, ainsi que son dérivé peracétylé **40**. Les auteurs ont observé un mélange de diastéréoisomères dû à l'utilisation de l'alcool racémique **31** lors de leur synthèse, mais les trop faibles différences des signaux RMN ^{1}H et ^{13}C n'ont pas permis de déteminer la configuration absolue de l'aglycone.

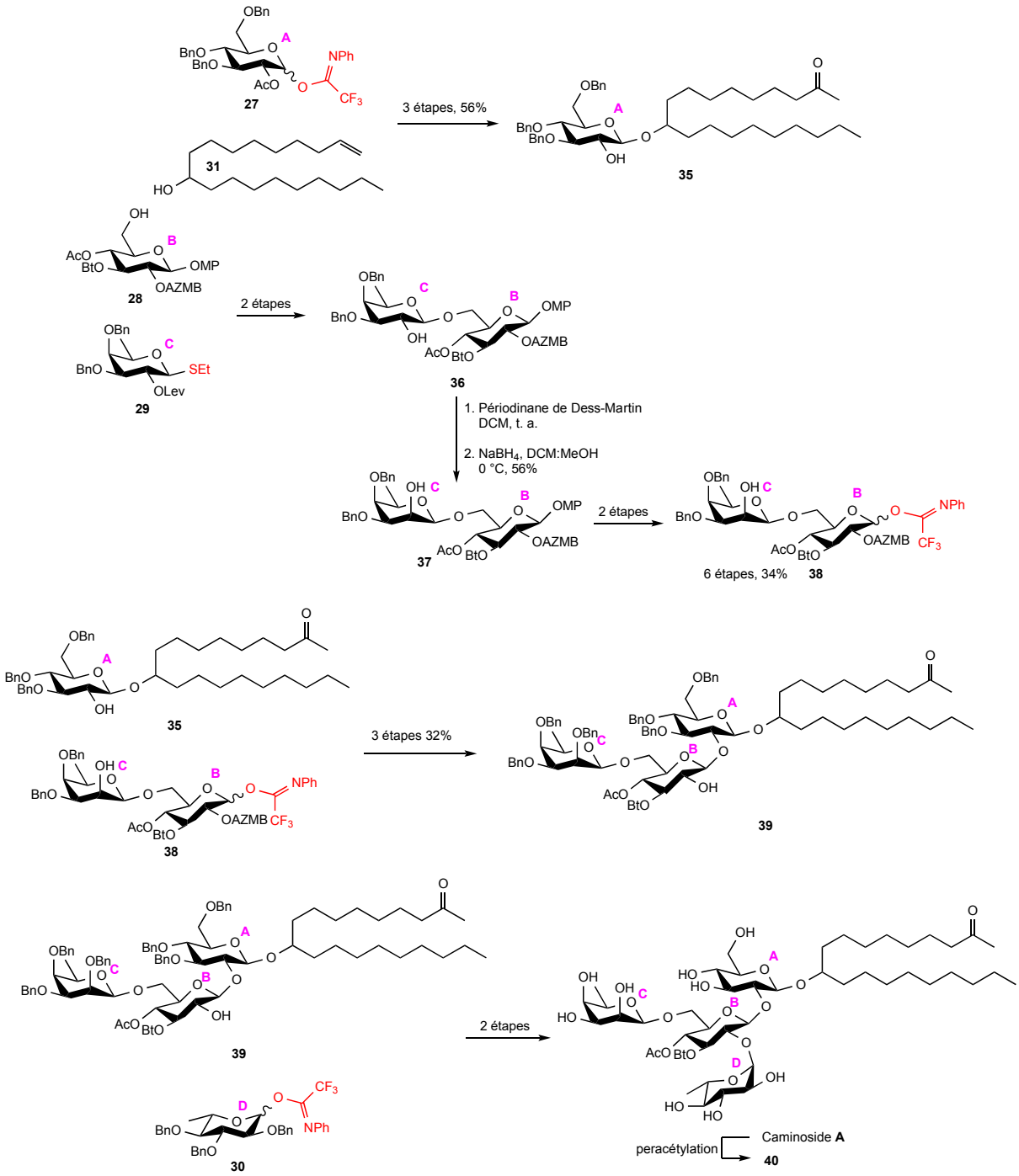

Schéma 5 – Glycosylations de la synthèse du caminoside A

Cinq ans plus tard, le groupe de Yingxia Li a rapporté la synthèse totale du caminoside **B** selon une approche similaire, tout en prenant en compte la stéréochimie *R* de la chaîne lipidique (Figure 8).[65] Leur synthèse faisant également intervenir les classiques de la chimie des carbohydrates, *i.e.*, les unités glycosidiques et le squelette oligosaccharidique ont été préparés par des réactions de protection/déprotection et les intermédiaires ont été purifiés à chaque étape sur gel

de silice. Ces derniers ont tout de même trouvé de nouvelles voies de synthèse des unités glycosidiques qui améliorent les rendements globaux. Cependant, leurs produits de départ sont plus élaborés et donc plus coûteux. En effet, afin de respecter la stéréoselectivité de la chaîne lipidique, l'alcool **43** a été obtenu à partir du composé chiral commercial **47**. Aussi, l'unité talopyranoside a été obtenue à partir du α-acétobromofucose *via* l'unité fucoside **45** tandis que, dans la synthèse du caminoside **A** par Biao Yu, elle a été obtenue à partir du D-galactopyranose *via* l'unité fucose **29**. Les synthèses des autres synthons n'ont pas non plus été décrites à partir des sucres déprotégés mais à partir des intermédiaires déjà partiellement protégés **44** et **46**. Leurs données RMN ont pu confirmer la structure du caminoside B.

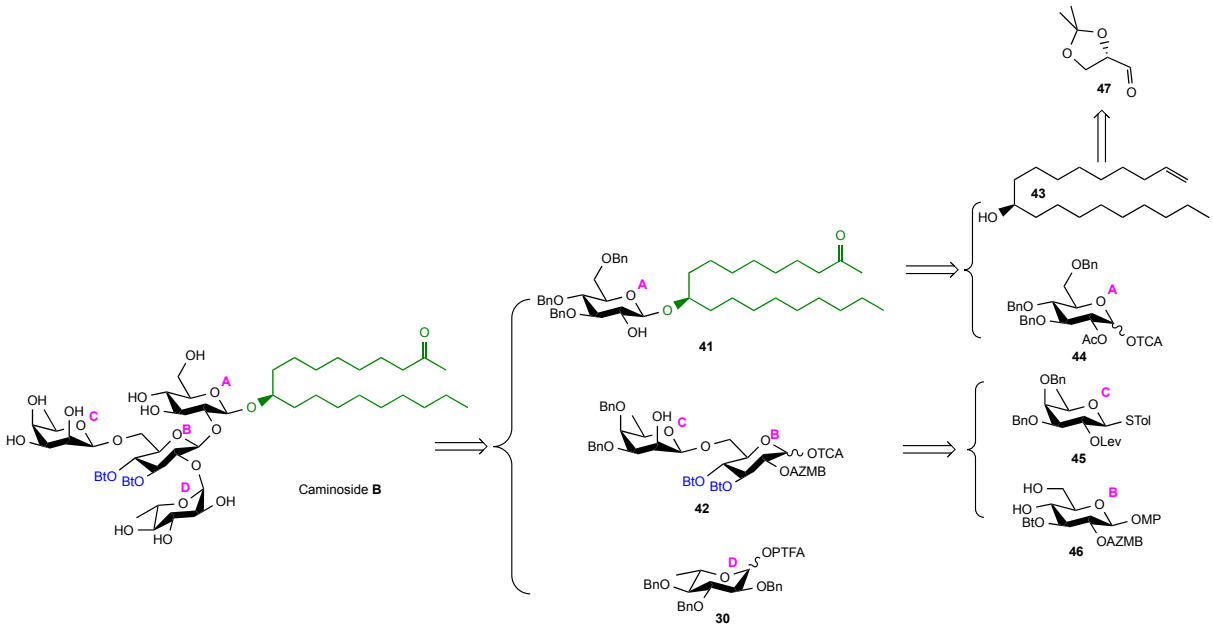

Figure 8 – Stratégie de synthèse du caminoside B par Yingxia *et al.*

2.4 Les agminosides : isolation, structure et activités biologiques

En 2008 puis en 2011, J. Wojnar et P. Northcote de la *Victoria University of Wellington* ont décrit pour la première fois une méthode d'isolation des agminosides (**A**–**E**) (Figure 3), une famille de glycolipides à structure inhabituelle issue de l'éponge marine *Raspailia agminata*, une espèce endémique de la Nouvelle-Zélande. Dans leur article publié dans *Journal of Natural Products*, ils décrivent les étapes de purification des agminosides et détaillent tout le processus d'identification structurale. Ainsi, l'isolation des agminosides a débuté par l'extraction des éponges dans le MeOH suivie par une purification en phase inverse sur HP20 en utilisant un gradient croissant d'acétone dans l'eau. Il s'est avéré que la fraction à 60% d'acétone dans l'eau possédait les signaux RMN les

plus intéressants (des signaux correspondant à des protons glycosidiques entre 3.0 et 5.5 ppm, des groupements acétyles aux alentours de 2.1 ppm ainsi que des multiplets, correspondants aux CH_2 de la chaîne lipidique, entre 1.2 et 1.7 ppm). Ensuite, ils ont procédé à la purification sur une colonne d'exclusion stérique (LH20). Les premières fractions ont par la suite été purifiées sur colonne de gel de silice avec des mélanges d'éluants ternaires (DCM:MeOH:H_2O) qui ont été les seuls à fournir de bons résultats, signe d'une molécule amphiphile telle qu'un glycolipide. Ceci a été confirmé par RMN *via* la présence d'un carbone sp^2 d'ester ainsi que par un massif de CH_2. La suite de la purification en HPLC a été guidée par spectrométrie de masse en ESI en mode négatif.

Une fois isolé, la masse de l'ion pseudomoléculaire de l'agminoside **A** a été déterminé en MALDI-TOF puis les structures des agminosides ont été déterminées par RMN (^1H, ^{13}C, HSQC-DEPT, HSQC-TOCSY, HSQC, COSY, HMBC et ROESY). Cependant, les analyses RMN n'ont pas permis de déterminer hors de tout doute la structure de la partie aglycone des agminosides. Pour ce faire, ils ont hydrolysé la chaîne lipidique de la partie oligosaccharidique par l'action de HCl dans le MeOH à chaud pendant 48 h. De cette façon, la structure du lipide a pu être déterminée par spectrométrie de masse haute résolution en ESI en mode positif et par RMN (^1H, ^{13}C, COSY et HMBC). Enfin, en vue de confirmer la présence d'un groupement acide carboxylique libre au bout de la chaîne lipidique, une méthylation des agminosides par le triméthylsilyldiazométhane a été effectuée. La formation d'un méthylester a été confirmée par RMN (^1H, ^{13}C et HMBC). Cependant, *quid* des deux centres stéréogènes de la chaîne lipidique ? Après avoir estérifié les deux positions du lipide par le (*R*)-MTPA, dans un premier temps, et le (*S*)-MTPA dans un second temps, la RMN (^1H, ^{13}C et ^{19}F) a permis de déterminer, selon la méthode de Mosher,[66] la configuration *R*,*R* du lipide.

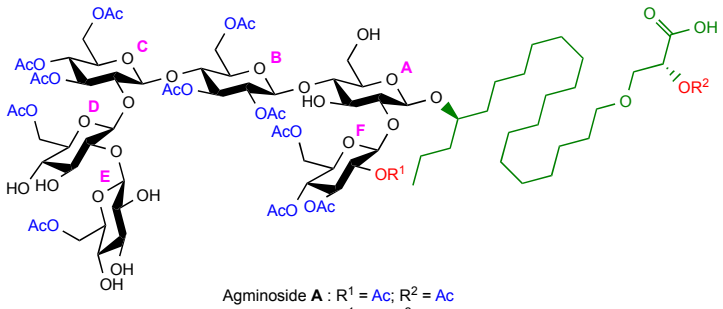

Figure 9 – Structures des agminosides A–E

Les agminosides **A**–**E** (Figure 9) présentent des caractéristiques structurales uniques en comparaison des autres glycolipides naturels comme une chaîne oligosaccharidique branchée composée de cinq (agminoside **E**) à six (agminosides **A**–**D**) unités D-glucopyranoses connectées aussi bien avec des liaisons β-(1→4) que β-(1→2). De plus, tous les agminosides possèdent une chaîne lipidique similaire comportant un groupement acide carboxylique et une unité glycérol. Cependant, la partie aglycone est glycosylée sur la partie lipidique et non sur l'unité glycérol. En outre, les différences entre les agminosides consistent en la répartition des groupements acétyles et le nombre d'unités glycosidiques (seulement cinq pour l'agminoside **E** contre six pour les agminosides **A**–**D**). Par ailleurs, bien que les agminosides **A**–**E** diffèrent par leur motif d'acétylation, pour tous, l'alcool primaire du sucre à l'extrémité réductrice de la partie saccharidique n'est pas acétylé. Ainsi, il est possible de supposer qu'une version macrolactonisée des agminosides pourrait exister au sein de l'éponge mais que cette dernière n'a pas été isolée par les auteurs ou alors que la macrolactone s'est ouverte pendant le fastidieux processus de purification.

Il est important de mentionner qu'une trop faible quantité a été isolée, *i.e.*, 11 mg, 3,1 mg, 2,5 mg, 1,3 mg, et 0,5 mg respectivement pour les agminosides **A**, **D**, **B**, **C** et **E** à partir de 250 g d'éponge (rendement < 0,0044%) pour prétendre effectuer des tests biologiques approfondis et un criblage complet des activités pharmacologiques. Ainsi, nous savons très peu de choses concernant l'activité biologique des agminosides, si ce n'est que l'agminoside **A** a montré une activité sur les cellules cancéreuses de la lignée HeLa. Cependant, les autres agminosides n'ont pas été testés. En outre, les potentielles applications des agminosides et de leurs dérivés pourraient toucher de nombreux domaines (surfactant, cosmétologie, agroalimentaire, délivrance de médicaments, etc.).

Au vu des activités biologiques déjà rapportées dans la littérature pour les glycolipides dérivés d'éponge marine, il est fort probable que les agminosides et leurs dérivés puissent représenter des agents thérapeutiques prometteurs. Cependant, depuis de nombreuses années, les récifs coralliens se détériorent et reculent petit à petit. Cette diminution de son habitat ralentit le renouvellement des ressources.[67,68] En conséquence, l'étude des agminosides ne peut pas se baser sur la récolte des éponges. Ainsi, en vue de déterminer l'activité biologique des agminosides **A**–**E**, la synthèse totale semble être le moyen privilégié pour obtenir ces molécules en quantités suffisantes. Cela permettrait également d'évaluer l'impact de la répartition des groupements

acétyles pour l'activité biologique des agminosides par le biais de la synthèse de dérivés non-acétylé, peracétylé et/ou macrolactonisé.

Ainsi, afin d'établir une voie de synthèse vers les agminosides, nous avons décidé de commencer par la synthèse de l'agminoside le plus simple : l'agminoside **E**. Aussi, afin de mener à bien cet objectif principal, nous avons fait l'hypothèse qu'il est possible de synthétiser ce glycolipide *via* une méthode de glycosylation [3 + 2] mettant en œuvre des synthons glycosidiques préacétylés. Alors, afin de remplir l'objectif principal, deux sous-objectifs ont été formulés. D'abord, établir une voie de synthèse de la partie glycosidique de l'agminoside **E** *via* la synthèse d'un glycolipide chimérique comprenant l'acide β-hydroxydécanoïque natif des rhamnolipides. Ensuite, établir une voie de synthèse de la chaîne lipidique native des agminosides *via* la formation tardive du lien éther séparant la chaîne carbonée du fragment glycérol. La synthèse de la partie glycosidique des agminosides sera présentée dans le chapitre 4 tandis que les travaux sur la chaîne lipidique seront discutés dans le chapitre 5.

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-Chapitre III-

Glycosylation and Protecting Group Strategies Towards the Synthesis of Saponins and Bacterial Oligosaccharides: A Personal Account

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(Article publié dans *The Chemical Record* 2021, *21*, 2990-3004)

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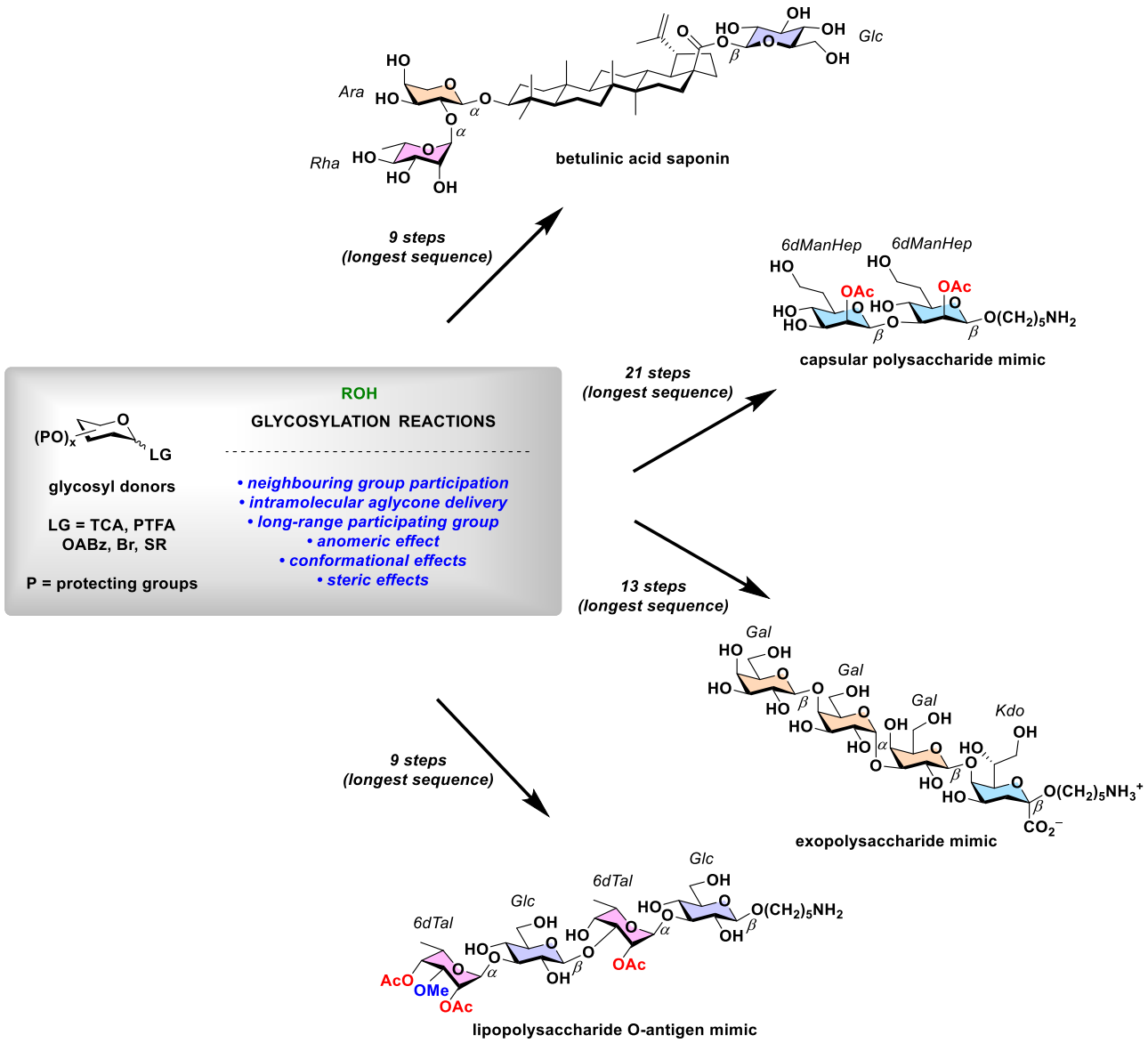
Contribution des auteurs

K. Muru a contribué à ce manuscrit par la création de figures et schémas et par la relecture attentive et correction du manuscrit. C. Gauthier a été le directeur de recherche des projets présentés dans cet article. Il a contribué à la rédaction de l'article.

Résumé

Depuis plus de 50 ans, l'intérêt des sucres, des glycolipides et, plus largement, des glycoconjugués, n'a cessé de croître. En effet, ces composés ne sont pas seulement impliqués dans d'importants processus biologiques, mais sont aussi considérés comme des agents thérapeutiques et prophylactiques prometteurs. Plusieurs groupes protecteurs, donneurs de glycosyle et méthodologies de glycosylation ont été développés et certains d'entre eux ont trouvé de larges applications synthétiques en chimie des carbohydrates. Dans ce « compte rendu personnel », nous décrivons les travaux du Pr Charles Gauthier dans le domaine de la glycochimie en présentant différentes stratégies de groupements protecteurs et de glycosylations mises en oeuvre au cours de sa carrière pour synthétiser des glycanes bioactifs, plus spécifiquement des saponines naturelles de type lupane, ainsi que des oligosaccharides liés aux espèces du genre *Burkholderia*.

Résumé graphique



Abstract: Carbohydrates and their conjugates are not only involved in important biological processes but are also regarded as promising therapeutics and prophylactics. Over the last century, several glycosylation methodologies, glycosyl donors, and protecting groups have been developed and some of them have found broad synthetic applications in carbohydrate chemistry. In this Personal Account, we describe how glycosylation and protecting group strategies have been implemented in our as well as in other research groups as to synthesize bioactive glycans, more specifically naturally occurring lupane-type saponins as well as oligosaccharides related to *Burkholderia* species.

1. Introduction

Carbohydrates are a class of primary metabolites that are ubiquitous in Nature. Long considered only as source of energy and structural polymers,[1] it is now well documented that carbohydrates, *i.e.*, mono-, oligo-, and polysaccharides, and their conjugates, *i.e.*, glycoproteins, glycolipids, and peptidoglycans, represent a class of biomolecules involved in central biological processes such as cell adhesion and migration, tumor and metastasis development, angiogenesis and inflammation, modulation of the immune response as well as microbial infections.[2] Furthermore, secondary metabolites from natural organisms, such as terpenes, polyphenols, and alkaloids, are often found under their glycosylated counterparts.[3] The biological activity of these glycosylated natural products (GNP) is generally correlated with the presence of the saccharide portion of the molecule.[4] To decipher the molecular mechanisms underlying glycan-mediated biological processes, but also to develop sugar-based therapeutics and prophylactics, it is a requisite to access pure and structurally well-defined molecules.[5]

Contrasting with the linear sequence of nucleotides in deoxyribonucleic acid and amino acids in proteins, the polyfunctional character of carbohydrates serves as a lever to reach an unparallel level of molecular complexity.[6] This structural diversity nevertheless represents a major hurdle to access these biomolecules. Glycoconjugates are naturally occurring in the form of complex mixtures of related structures, often at very low concentrations, which complicates their purification and characterization from biological sources.[7] In this context, carbohydrate chemistry has established itself as a preferred field for accessing homogeneous glycoconjugates free from biological contaminants. Advances in carbohydrate chemistry have enabled the synthesis of complex glycans, glycoconjugates, GNP or related mimetics, some of which have been clinically approved as drugs and vaccines.[5a]

Notwithstanding the remarkable advances in the field of glycosciences,[8] the synthesis of carbohydrate-derived compounds remains a tedious process calling for the implementation of important human and technical resources. Carbohydrate chemists of the 21st century are still facing many challenges, the main one being to develop general synthetic methodologies for the stereoselective formation of glycosidic bonds.[9] Hence, much work remains to be done in chemical glycosciences, which is a very active and burgeoning area of research.[10]

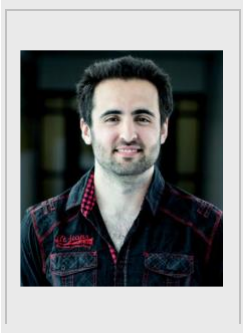
1.1. Glycosyl Donors

The O-glycosylation reaction stands as a corner stone in carbohydrate chemistry.[11] During the last century, a plethora of leaving groups has been developed for the activation of the anomeric position of the so-called glycosyl donors.[12] Notwithstanding the diversity of these leaving groups, only few of them have found broad application for the synthesis of complex oligosaccharides and GNP (Figure 1A).

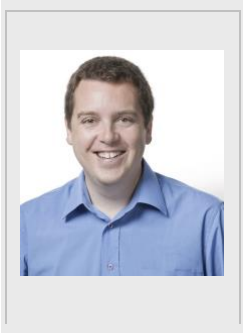
Schmidt's trichloroacetimidates (TCA) are one of the most widely used glycosyl donors owing to their efficiency in glycosylation reactions with a large variety of glycosyl acceptors including aliphatic and aromatic alcohols.[13] TCA can be activated either using catalytic amounts of Lewis or Bronsted acids. However, their somewhat low stability together with their possible Overman rearrangement into *N*-trichloroacetamides prompted the Yu group to develop *N*-phenyl-2,2,2-trifluoroacetimidates (PTFA) as an alternative to TCA.[14] PTFA donors are generally more stable than their TCA homologues, they do not undergo rearrangement into *N*-acetamides because of the presence of the bulky *N*-phenyl group, and they can be activated using catalytic amounts of acid.

In some specific cases where the glycosyl acceptors or aglycones are acid-sensitive, the activation of TCA and PTFA glycosyl donors can be troublesome. To solve this issue, the Yu group reported the *ortho*-alkynylbenzoate (OABz) leaving group,[15] which can be activated under neutral conditions using gold catalysts such as PPh_3AuNTf_2 and PPh_3AuOTf. These OABz donors have found wide application in the chemical glycosylation of complex acid-sensitive substrates.[16]

Kevin Muru received his B.Sc. (chemistry) in 2014 from the University of Le Havre. He then obtained his M.Sc. (organic chemistry) in 2016 from the University of Orsay studying one-pot tandem glycosylation-cycloaddition reactions. Kevin is now pursuing his Ph.D. studies at the Institut National de la Recherche Scientifique (INRS) in the field of carbohydrate chemistry under the guidance of Prof. C. Gauthier, working on the total synthesis of natural glycolipids.



Charles Gauthier received his Ph.D. (chemistry) in 2009 from the Université du Québec à Chicoutimi (UQAC). Following postdoctoral studies at the Institut Pasteur in Paris (Dr. L. A. Mulard) and at the University of Oxford (Prof. B. G. Davis), he was a Senior Lecturer at the University of Poitiers in France (2011-2016). He joined INRS as an Assistant Professor in 2016, working on carbohydrate and natural product chemistry, and has been promoted to the rank of Associate Professor in 2020.



Glycosyl bromides are another class of glycosyl donors that have found broad application. First reported by Michael[17] for phenolates and further extended by Koenigs and Knorr[18] to aliphatic alcohols, glycosyl bromides have been recently reinvestigated by the Demchenko group.[19] Typically activated with stoichiometric amounts of silver salts,[18] the Koenigs-Knorr glycosylation can be significantly accelerated when adding catalytic amounts of TMSOTf in the presence of Ag_2O.[19] These conditions were proved to be mild while maintaining neutral pH as well as providing excellent reaction yields. Furthermore, glycosyl bromides can be successfully employed for the synthesis of acyl glycosides under phase-transfer conditions.[20]

Thioglycosides are arguably the most widely used glycosyl donors because they present several advantages over other donors.[21] First applied in glycosylation reactions by Ferrier and co-workers in 1973,[22] thioglycosides are readily accessible from peracylated or bromide substrates, they can be selectively activated under very mild conditions through soft electrophiles and are thus suitable donors for the glycosylation of a wide range of substrates. In addition, they remain stable under several reaction conditions allowing orthogonal protecting group strategies. The main disadvantage of using thioglycosides is that their activation usually requires stoichiometric amounts of promotors,[21a] although some catalytic systems have been sporadically reported.[23]

1,2-Unsaturated sugar derivatives, the so-called glycals, have also found vast application in carbohydrate chemistry.[24] Their great versatility makes them privileged substrates for chemical diversification based on the sugar scaffold. Indeed, glycals are not only used for the synthesis of O, S, and C-glycosides but also for conducting various transformations including epoxidation, cyclopropanation, Ferrier rearrangement as well as alkene functionalization, to name a few examples.[24]

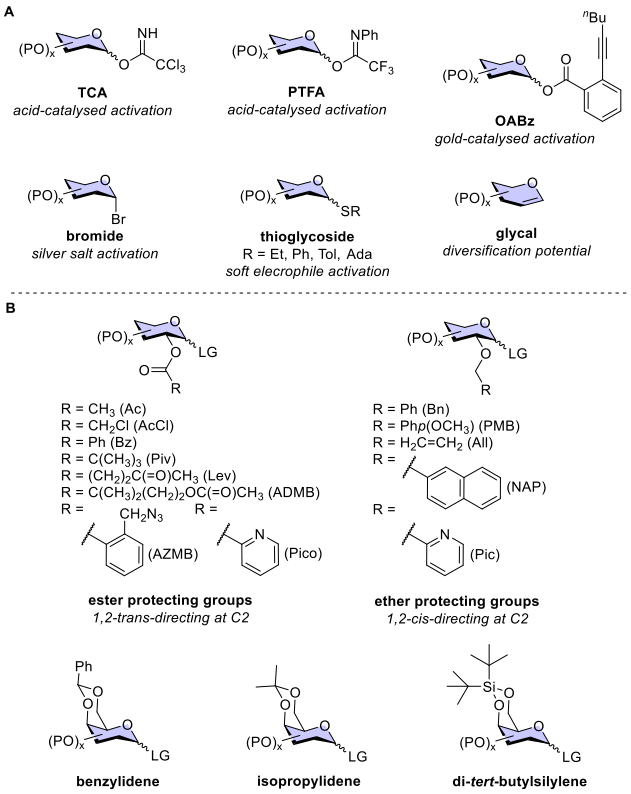


Figure 1. Glycosylation methodologies (**A**) and protecting groups (**B**) commonly used in oligosaccharide and natural product synthesis. Ac: acetyl; AcCl: chloroacetyl; Ada: adamantyl; ADMB: 4-acetoxy-2,2-dimethylbutanoate; All: allyl; Bn: benzyl; Bz: benzoyl; Lev: levulinoyl; LG: leaving group; NAP: 2-naphthylmethyl; OABz: *ortho*-alkynylbenzoyl; P: protecting group; Pic: picolinyl; Pico: picoloyl; Piv: pivaloyl; PMB: *para*-methoxybenzoyl; PTFA: *N*-phenyl-2,2,2-trifluoroacetimidate; TCA: trichloroacetimidate; Tol: tolyl.

1.2. Protecting Groups

As glycans bear numerous hydroxyl groups on their heterocyclic scaffold, protecting groups are a prerequisite in carbohydrate chemistry to conduct selective transformation of these reactive functionalities (Figure 1B).[25] The presence of protecting groups can significantly alter the reactivity of glycosyl donors. As a general empirical rule, ester protecting groups tend to deactivate the anomeric position (disarmed sugars) while ether protecting groups tend to activate it (armed sugars).[26] The armed/disarmed effect in glycosyl donors is a concept that was first introduced by Fraser-Reid more than thirty years ago.[27] Since then, this concept has been implemented for the programmable one-pot glycosylation[28] and automated oligosaccharide synthesis[29] of complex glycans.

The presence of an ester protecting group (*e.g.*, Ac, AcCl, Bz, Piv, Lev, ADMB, AZMB) at the C2 position of a glycosyl donor has been shown to allow the stereoselective formation of 1,2-*trans*-glycosides *via* the so-called neighbouring group participation (NGP)

effect involving the formation of a transient dioxolenium ion.[30] In contrast, the presence of an ether protecting group (*e.g.*, Bn, PMB, All, NAP) at C2 generally favors the formation of 1,2-*cis*-glycosides through putative oxocarbenium species,[31] which are favorably attacked at their bottom face leading to the more thermodynamically stable axial glycosides.[32] However, as recently emphasized by Crich,[33] there is an accumulation of experimental evidences rather supporting S_N2-like bimolecular mechanisms for glycosylation reactions proceeding under strict kinetic control. Under these Curtin-Hammett scenario, loosely associated counteranions (usually triflates) rapidly equilibrate in the form of anomeric pairs of activated donors and, as such, the nature of counterions and reaction concentration are important factors to take into consideration for stereoselectivity optimization. The presence of an ether at C2 such as NAP and PMB groups can also be applied to the formation of 1,2-*cis*-glycosides through the intramolecular aglycone delivery (IAD) strategy,[34] which delivers the aglycone on the same side than the C2 tether. Long-range participating effects[35] are also possible using, for instance, the recently developed picoloyl (Pico) and picolinyl (Pic) groups.[36] These pyridine-containing groups have been shown to be of great value for the synthesis of 1,2-*cis*-glycosides, such as *α*-glucosides and *β*-D-mannosides,[37] through a strategy pioneered by the Demchenko group and coined hydrogen-bond-mediated aglycone delivery (HAD).[36]

Protecting groups suitable for vicinal diols such as benzylidene, isopropylidene, and di-*tert*-butylsilylene (DTBS) are also commonly employed in carbohydrate chemistry. By locking the pyranose ring into a specific conformation (usually the $^4C_1$), these groups strongly interfere on the stereoselective outcome of the glycosylation reaction.[12b, 38] For instance, the 4,6-*O*-benzylidene[39] and DTBS[40] groups have been shown to favor the formation of *α*-galactosides through steric effects.

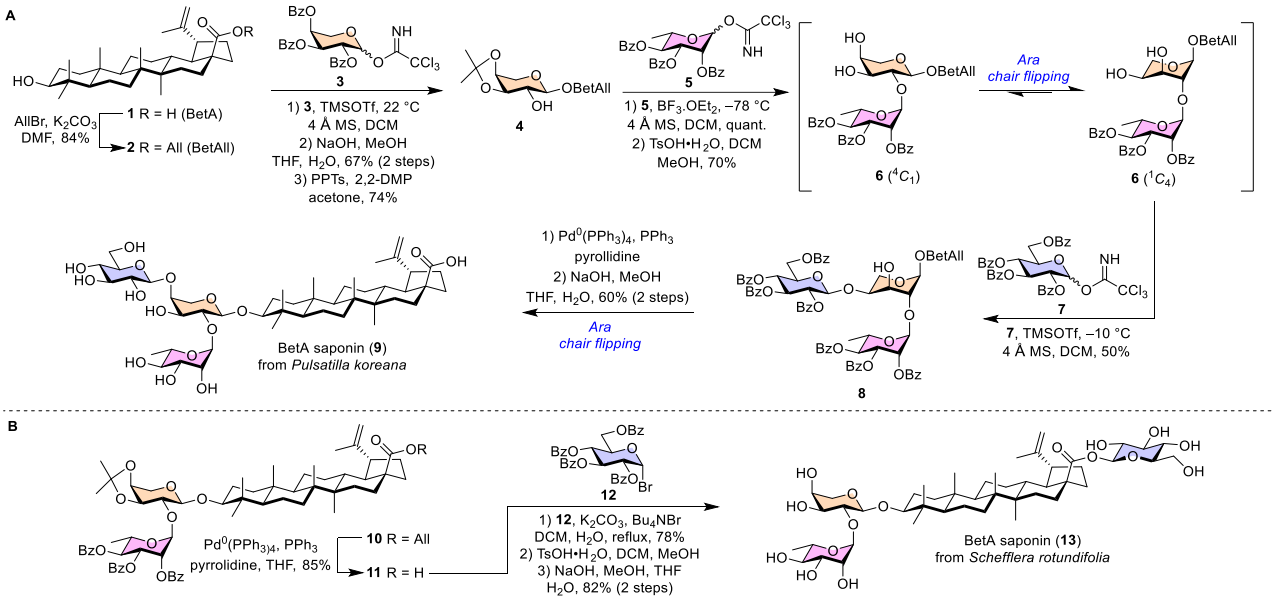
In this Personal Account, we discuss how some of the aforementioned glycosylation and protecting group strategies have been implemented in our as well as in other research groups as to synthesize bioactive GNP (*i.e.*, lupane-type saponins) and microbial polysaccharides mimics − especially those related to *Burkholderia* species − which could find application as therapeutics and prophylactics. We describe approaches allowing the stereoselective synthesis of specific glycosidic linkages found in plants and bacterial glycoconjugates including *α*-L-arabinosides (Ara), *α*-L-rhamnosides (Rha), *β*-D-glucosides (Glc), *α*- and *β*-D-galactosides (Gal), 6-deoxy-*α*-L-talosides (6dTal), 6-deoxy-*β*-D-*manno*-heptosides (ManHep) as well as 3-deoxy-*β*-D-*manno*-oct-2-ulosonic acid (Kdo) glycosides.

2. Synthesis of Lupane-Type Saponins

Lupane-type triterpenoids, such as betulinic acid (**1**, BetA), are bioactive natural products mainly isolated from the bark of paper birch trees[41] but are also found in numerous plants and medicinal herbs.[42] Because of their low toxicity and broad spectrum of pharmacological properties (anticancer, antiviral, antimalarial), lupane-type triterpenoids stand as promising scaffolds for drug discovery. However, their low aqueous solubility (0.02 μg•mL^{-1} for BetA)[43] and poor biodisponibility represents major hurdles for their clinical development. As to improve the hydrosolubility and modulate the medicinal properties of betulinic acid (**1**), we[20b, 44] and others[45] have become interested in appending sugar moieties at the C3 and/or C28 position(s) of the pentacyclic lupane-type triterpenoid scaffold.

As a first step into the realm of carbohydrate chemistry, we chose to target two naturally occurring betulinic acid saponins (**9** and **13**, Scheme 1),[44c] which were previously isolated from medicinal plants from Traditional Chinese Medicine (TCM).[42] As depicted in Scheme 1A, the synthesis commenced with the protection of betulinic acid (**1**) carboxylic function in the form of an allyl ester. A perbenzoylated L-arabinose residue activated into a TCA derivative was then appended at the C3 position of allyl betulinate (**2**) under the catalytic promotion of TMSOTf and the benzoyl groups were saponified. Insertion of an isopropylidene group at the C3/C4 positions allowed to couple a perbenzoylated L-rhamnose residue specifically at the C2 position. Once again, a TCA donor was successfully used, however the glycosylation reaction was conducted at cryogenic temperature in the presence of $BF_3.OEt_2$ as to avoid side reactions.

Following cleavage of the isopropylidene group, we were intrigued to find that the arabinose moiety in saponin **6** underwent a ring-flipping, switching from the usual $^4C_1$ to the atypical $^1C_4$ conformation. Because of the presence of three substituents in the axial position, this chemical behavior was counterintuitive. We hypothesized that this conformation was predominantly formed to keep as far apart as possible the two bulky substituents at C1 and C2, *i.e.*, the perbenzoylated rhamnose and the lupane algycone. We took advantage of the equatorial and thus more reactive hydroxyl group at the C4 position in saponin **6** ($^1C_4$) to conduct a regioselective glycosylation using a perbenzoylated TCA glucose donor. Pd(0)-mediated deallylation followed by saponification of the resulting trisaccharide-containing triterpenoid **8** led to the formation of betulinic acid saponin **9**, which was previously isolated from the roots of the TCM plant *Pulsatilla koreana*.[46] Interestingly, the arabinose moiety retrieved its usual $^4C_1$ conformation in naturally occurring saponin **9**.

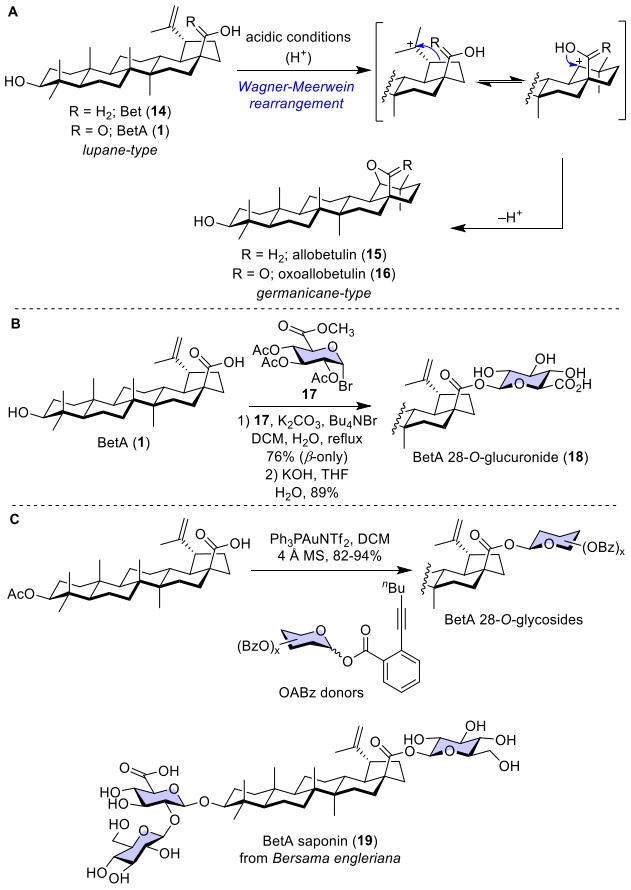


Scheme 1. Synthesis of naturally occurring arabinose-containing betulinic acid saponins **9** and **13**. (**A**) Monodesmosidic saponin **9** from the roots of *Pulsatilla koreana*; (**B**) Bidesmosidic saponin **13** from the leaves of *Schefflera rotundifolia*. Pink: L-rhamnose (Rha); purple: D-glucose (Glc); yellow: L-arabinose (Ara).

The disaccharide-containing derivative **10** of the previous sequence was used to complete the total synthesis of betulinic acid saponin **13** (Scheme 1B).[44c] Accordingly, the allyl group at the C28 position of compound **10** was removed providing free carboxylic acid **11**. The next glycosylation reaction was challenging because of the propensity of lupane-type triterpenoids **14** and **1** to undergo acid-catalyzed Wagner-Meerwein rearrangement into germanicane-type triterpenoids **15** and **16**, respectively (Scheme 2A). The use of TCA derivatives was thus precluded. As an alternative, perbenzoylated glucose bromide **12** was efficiently and stereoselectively transformed into an acyl glycoside when phase-transfer conditions were investigated (K_2CO_3, DCM/H_2O, reflux). Cleavage of the isopropylidene group followed by saponification readily led to betulinic acid saponin **13**, previously isolated from the leaves of *Schefflera rotundifolia*.[47]

We took advantage of phase-transfer conditions to synthesize betulinate 28-*O*-*β*-D-glucuronide (**18**),[20b] which is a plausible human metabolite of betulinic acid (**1**) and thus an important compound to have in hand when conducting clinical investigations in humans with betulinic acid (**1**) or related derivatives such as the anti-HIV bevirimat.[48] As shown in Scheme 2B, the synthesis was expeditious and only involved commercially available substrates.[20b] Interestingly, saponification of the acetyl and methyl ester groups with aqueous KOH did not affect the sterically hindered C28 acyl glycoside functionality. We further demonstrated that acyl glucuronide **18** could be used as an anticancer agent in a prodrug monotherapy strategy, *i.e.*, it is more hydrosoluble than the parent aglycone, not cytotoxic nor hemolytic, and can be enzymatically hydrolyzed in the presence of *β*-glucuronidase.

The synthesis of betulinic acid saponins bearing sugar moieties at the C28 position was also investigated by Yu and co-workers who capitalized on their newly developed OABz donors.[45b] Under the promotion of a gold catalyst (PPh_3AuNTf_2), a series of betulinate 28-*O*-glycosides were synthesized in high yields without any trace of germanicane rearrangement products, owing to the neutrality of the reaction conditions (Scheme 2C). They further extended their approach to the synthesis of glucuronide-containing bidesmosidic saponin **19**, previously isolated from the stem bark of *Bersama engleriana*,[49] a tree used in Africa for its diverse medicinal properties.



Scheme 2. (**A**) Acid-catalyzed Wagner-Meerwein rearrangement of lupanes; (**B**) Synthesis of betulinate acyl glucuronide **18** through phase-transfer conditions; (**C**) Synthesis of betulinate acyl glycosides through gold-catalyzed glycosylation. Purple: D-glucose (Glc) and D-glucuronic acid (GlcA).

3. Synthetic Oligosaccharides Related to *Burkholderia* Species

Burkholderia species are a vast group of Gram-negative bacteria (GNB) found in diverse ecological niches.[50] Among them, some are highly pathogenic for humans such as *Burkholderia pseudomallei*, the causative agent of the neglected tropical disease melioidosis and a potential bioterrorism threat.[51] Because of its high morbidity and mortality rates and its resistance to clinically used antibiotics, there is an increased interest in developing therapeutic and prophylactic countermeasures against *B. pseudomallei*.[52]

B. pseudomallei expresses diverse surface polysaccharides including capsular polysaccharide (CPS), lipopolysaccharide O-antigen (LPS OAg), and exopolysaccharide (EPS) (Figure 2). These biopolymers are one of the main targets of immune response and thus represent attractive antigens for vaccine development and diagnostic tools against melioidosis.[50] In the last years, we have become interested in synthesizing oligosaccharide mimics of *B. pseudomallei* polysaccharides.[53] The presence of uncommon and challenging glycosidic bonds within these polysaccharides such as 6-deoxy-*β*-ManHep, 6-deoxy-*α*-Tal, and *β*-Kdo glycosides was especially appealing to us.

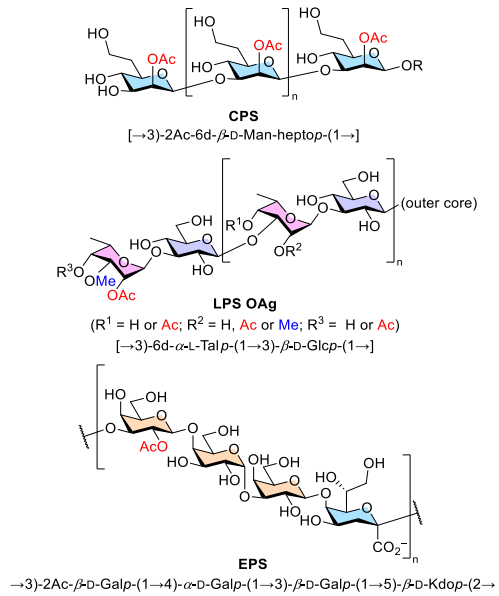
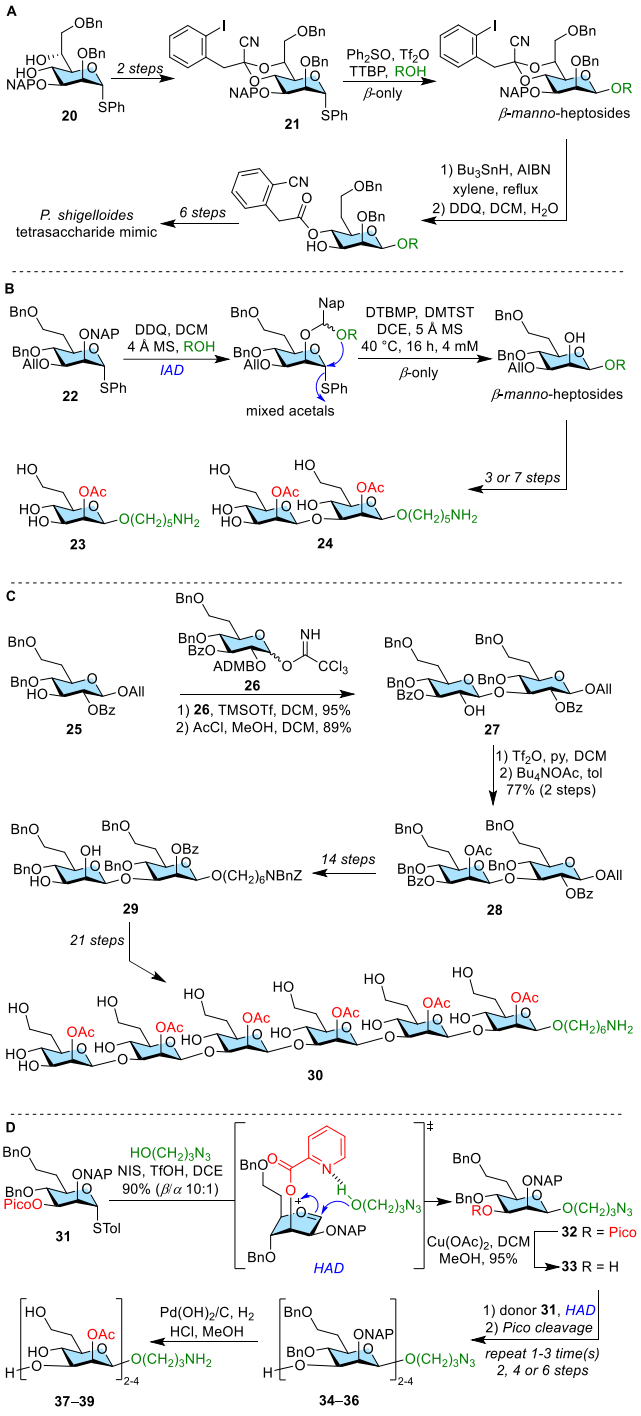


Figure 2. Main surface polysaccharides produced by *B. pseudomallei*. Blue: 6-deoxy-D-*manno*-heptose (6dManHep) and 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo); pink: 6-deoxy-L-talose (6dTal); purple: D-glucose (Glc); yellow: D-galactose (Gal).

3.1. Synthesis of 6-Deoxy-β-D-*manno*-heptosides

The CPS of *B. pseudomallei* is a linear homopolymer featuring (1→3)-linked 2-*O*-acetyl-6-deoxy-β-D-ManHep residues as the repeating unit (Figure 2).[54] We identified two main challenges that needed to be addressed to synthesize mimics of this CPS. First, the presence of an acetyl group at C2, which is labile and prone to migration.[55] Second, the synthesis of glycosides in the *β-manno* configuration, which still stands as a hot topic in carbohydrate chemistry.[56] As for the second challenge, the absence of a hydroxyl group at C6 hampers the insertion of a 4,6-*O*-benzylidene protecting group, which is a prerequisite to the formation of *β*-mannosides through a transient *α*-triflate intermediate under S_N2-like Crich mannosylation.[57]

Crich and Banerjee[58] were the first to report the stereoselective synthesis of 6dManHep glycosides in the *β*-configuration (Scheme 3A). Their approach relied on the use of a 4,6-*O*-[1-cyano-2-(2-iodophenyl)ethylidene] acetal protected thioglycoside (**21**), which was obtained in two steps from corresponding diol **20**. Under the promotion of Ph_2SO/Tf_2O in the presence of a hindered based (2,4,6-tri-*tert*-butylpyrimidine, TTBP), a series of *β-manno*-heptosides were obtained in excellent yields and selectivities when using the conformationally locked thioglycoside **21**. Radical fragmentation of the acetal by treatment with tributyltin hydride and azoisobutyronitrile cleanly led to the formation of target 6-deoxy-*β-manno*-heptosides. Subsequent removal of the NAP ether with DDQ provided a free hydroxyl group at C3. This pioneering chemistry was then further applied to the synthesis of a tetrasaccharide, which mimics the LPS of *Plesimonas shigelloides*, an infectious GNB that contaminates surface water and causes diarrhea.



Scheme 3. Synthesis of 6-deoxy-*β*-D-*manno*-heptosides through radical fragmentation (**A**); NAP-mediated intramolecular aglycone delivery (IAD) (**B**); *gluco*-heptoside epimerization (**C**); and hydrogen-bonded-mediated aglycone delivery (HAD) (**D**).

Our research group also embarked on the project of synthesizing 6d-*β-manno*-heptosides with the idea in mind of developing a CPS-based glycoconjugate vaccine against melioidosis.[53a] As depicted in Scheme 3B, our approach relied on

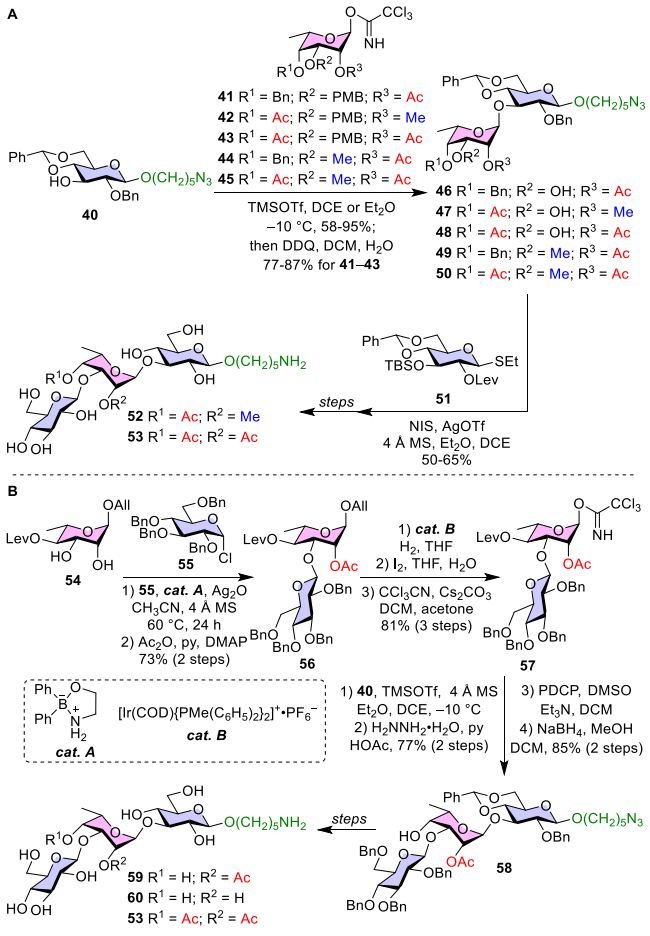
the use of naphthyl-assisted IAD for generating the *β*-mannoside bonds. Thioglycoside donor **22** bearing a NAP group at C2 was reacted with different alcohol acceptors in the presence of DDQ. A mixture of (*R*)- and (*S*)-acetals was obtained and directly subjected to intramolecular glycosylation using dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) as the promotion system under diluted conditions. Pleasingly, this approach yielded a series of 6d-*β*-*manno*-heptosides with full control of stereoselectivity. We took advantage of the presence of a free hydroxyl group at C2 to acetylate this position as naturally found in the 6-deoxyheptan CPS of *B. pseudomallei*. Finally, deallylation and subsequent Pd-catalysed hydrogenolysis under microfluidic conditions[59] led to the formation of monosaccharide **23** and disaccharide **24**, which represent respectively one and two repeating units of the native CPS.

Following our seminal publication, Scott and co-workers[60] reported two years later the challenging synthesis of an hexasaccharide related to *B. pseudomallei* CPS (Scheme 3C). Instead of using *manno*-heptoside donors, they rather designed *gluco*-heptose building blocks **25** and **26**, which were coupled together under the promotion of TMSOTf. Owing to the NGP of a 4-acetoxy-2,2-dimethylbutanoate (ADMB)[61] at C2, a *β*-glucosidic bond was exclusively formed. The ADMB group was subsequently cleaved by treatment with AcCl/MeOH, which generated HCl *in situ*. The C2 position of disaccharide **27** was then epimerized from the *gluco*- to the *manno*-configuration by formation of a triflate and S_N2 displacement with tetrabutylammonium acetate to afford disaccharide **28**. Protecting group manipulation and epimerization of the *gluco*-heptose residue at the reducing end led to diol **29**. Iteration of the previous glucosylation/epimerization sequence provided target hexasaccharide **30** after 21 steps. The presence of an aminolinker at the reducing end of oligosaccharide **30** allowed its covalent coupling with a carrier protein (TetHc). The resulting glycoconjugate vaccine was shown to protect mice against melioidosis infections.

Recently, Gu and co-workers[62] reported the synthesis of di- to tetrasaccharide mimics of *B. pseudomallei* CPS (Scheme 3D). Their approach relied on the use of a picoloyl (Pico) group at the C3 position of a 6-deoxy-*manno*-heptose thioglycoside donor, which provided high *β*-stereoselectivity *via* HAD. Theoretically, once thioglycoside donor **31** was activated, the alcohol acceptor formed a hydrogen bond with the Pico group allowing the delivery of the aglycone on the *β*-face of the transient oxocarbenium intermediate. The Pico group in heptoside **32** was then selectively removed by treatment with copper(II) acetate to give alcohol **33**. Iteration of the HAD/Pico cleavage approach followed by subsequent protecting group manipulation, and acetylation provided di-, tri-, and tetrasaccharide **37**-**39**, which were coupled with a carrier protein (CRM197) and evaluated *in vivo* for immunogenicity. The trisaccharide conjugate induced the strongest immune response among the tested glycovaccines.

3.2. Synthesis of 6-Deoxy-*α*-L-talopyranosides

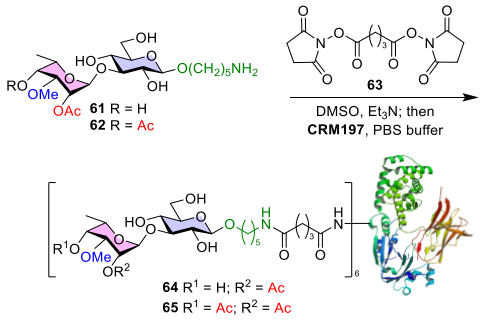
The repeating unit of the LPS OAg from *B. pseudomallei* is a (1→3)-linked disaccharide featuring *β*-D-glucopyranose and 6-deoxy-*α*-L-talopyranose as the sugar residues (Figure 2).[63] Interestingly, the intrachain 6dTal residues are non-stoichiometrically substituted with acetyl groups at the C2 and/or C4 positions, and methyl groups at C2. Additionally, the terminal 6dTal residue features a methyl group at C3 as well as acetyl groups at both the C2 and C4 positions. The LPS OAg of the genetically related *B. mallei* is of similar structure although the acetyl groups at C4 are absent.[63] As these structural modifications could modulate the interactions of these OAgs with the immune system, we were interested in synthesizing oligosaccharides featuring all of the reported epitopes of *B. pseudomallei* and *B. mallei* LPS OAgs (Scheme 4).[53c] Prior to the publication of our work, Zhang and co-workers[64] reported the preparation of di-, tri-, and tetrasaccharides related to the LPS OAg of *B. pseudomallei*, however these oligosaccharides were lacking the substitution epitopes.



Scheme 4. First (**A**) and second (**B**) generation synthesis of trisaccharides related to the lipopolysaccharide O-antigen from *Burkholderia* species. Pink: L-rhamnose and 6-deoxy-L-talose; purple: D-glucose. PDCP: phenyl dichlorophosphate.

As shown in Scheme 4A, we first opted to include the substitution epitopes directly on the all-*cis* 6dTal scaffold.[53c] Therefore, the 6dTal donors **41**−**45**, obtained *via* the C4 epimerization of the corresponding Rha residues, were activated as Schmidt's TCAs. TMSOTf-promoted glycosylation of 6dTal donors **41**−**45** with Glc acceptor **40**, followed by PMB deprotection (if needed), generated five differently substituted disaccharides (**46**−**50**) with full control of *α*-stereoselectivity even when an NPG was lacking at C2 (as for disaccharide **47**). Subsequent coupling of thioglucoside **51** with glycosyl acceptors **47** and **48** under the action of NIS/AgOTf furnished trisaccharides **52** and **53**, respectively, in convenient yields and complete *β*-stereoselectivity. Unfortunately, all our attempts to glucosylate the C3 position of disaccharide **46** were fruitless, which we believed was due to steric crowding generated by the presence of a benzyl group at C4.

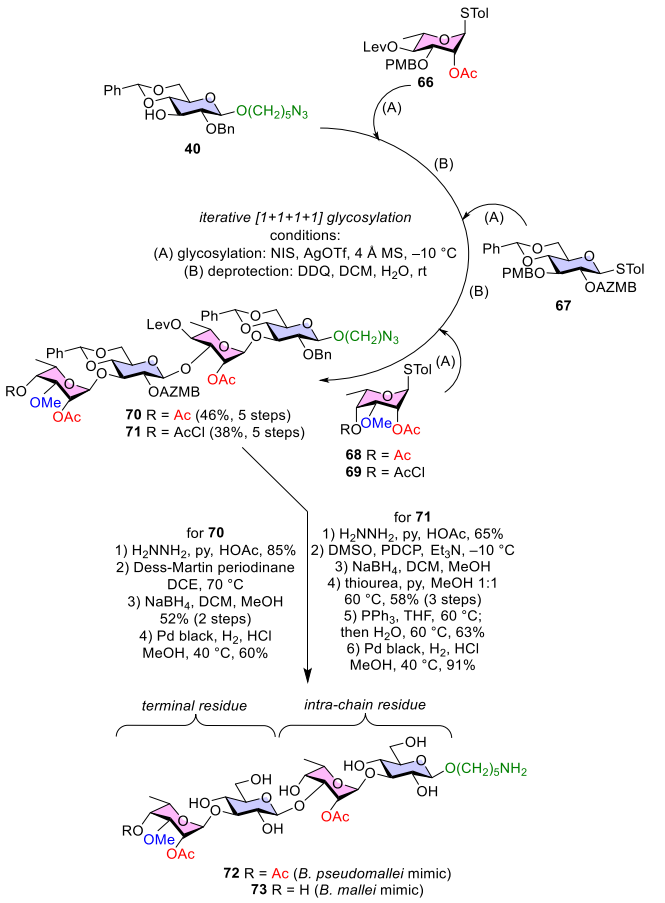
A second-generation synthesis was thus devised (Scheme 4B) in which a rhamnose acceptor was instead used and subsequently epimerized at a later stage of the synthetic route.[53c] Rha diol **54** was subjected to regioselective glycosylation at C3 with perbenzylated glucose chloride **55** in the presence of Ag_2O and Taylor's catalyst (*i.e.*, 2-aminoethyl diphenylborinate).[65] Following acetylation, resulting disaccharide **56** was deallylated and transformed into TCA donor **57**. This activated disaccharide was then coupled with acceptor **40** and the Lev group was cleaved under the action of hydrazine hydrate revealing the C4 hydroxyl group. Then, epimerization of the C4 position, which allowed the conversion of the *rhamno*- into the 6d-*talo*-configuration, generated trisaccharide **58**. Protecting group manipulation and subsequent Pd-catalyzed hydrogenolysis led to target trisaccharides **53**, **59**, and **60**. Target disaccharides **61** and **62** (Scheme 5) were obtained *via* hydrogenolysis of precursors **49** and **50**, respectively.



Scheme 5. Synthesis of disaccharide:CRM197 conjugate vaccines. Pink: 6-deoxy-L-talose; purple: D-glucose.

With these seven oligosaccharides in hand, we studied their interaction with monoclonal antibodies (mAbs) that differentially recognize *B. pseudomallei* and *B. mallei* antigens.[53c] Using ELISA assays and biophysical technics such as surface plasmon resonance (SPR) and saturation transfer difference (STD)-NMR, we demonstrated that these mAbs were specifically directed towards disaccharides **61** and **62**, which represent the terminal epitopes of LPS OAgs from *B. mallei* and *B. pseudomallei*, respectively. Disaccharides **61** and **62** were then covalently linked with a carrier protein (CRM197) through NHS ester chemistry using disuccinimidyl glutarate (**63**) (Scheme 5). The immunogenicity of the resulting glycoconjugates **64** and **65** were evaluated in mice. Mice immunized with glycoconjugate **64** produced high-titer IgG responses that crossreacted with *B. mallei*-like OAgs (endpoint titers ranging from 1:400 to 1:64,000 relative to control).

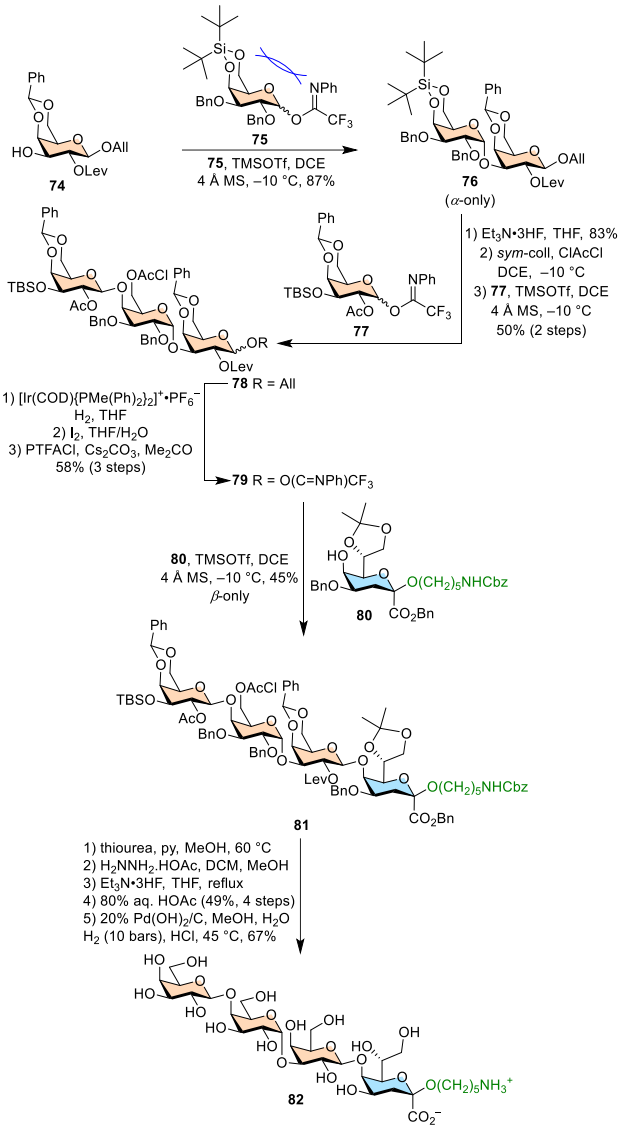
In a subsequent study,[53d] we hypothesized that tetrasaccharides **72** and **73** (Scheme 6) featuring both terminal and intrachain epitopes of LPS OAgs from *B. pseudomallei* and *B. mallei*, respectively, could represent exquisite candidates for vaccine development. Our successful approach was based on the epimerization of the inner Rha residue once the protected tetrasaccharide is obtained. Three novel building blocks were designed capitalizing this time on thioglycoside chemistry and using PMB as temporary protecting groups. Following an uneventful and iterative [1+1+1+1] glycosylation sequence relying on NIS/AgOTf promotion system, tetrasaccharides **70** and **71** were obtained, which featured either an acetyl or a chloroacetyl group at the C4 position of the terminal 6dTal residue. The Lev group was then cleaved and the resulting C4 hydroxyl epimerized upon a stereoselective oxidation/reduction sequence. The orthogonal cleavage of each protecting group, *i.e.*, AcCl, AZMB, benzylidene, and Bn, concomitantly with the reduction of the azido group into an amine, allowed the formation of target tetrasaccharides **72** and **73**. These compounds strongly reacted with culture-confirmed Thai melioidosis patient serum and closely mimicked the antigenicity of native *B. pseudomallei* LPS OAg. Tetrasaccharides **72** and **73** thus represent exquisite candidates to be tested in melioidosis vaccination studies.



Scheme 6. Synthesis of tetrasaccharide mimics of *B. pseudomallei* and *B. mallei* LPS OAg. Pink: L-rhamnose and 6-deoxy-L-talose; purple: D-glucose. PDCP: phenyl dichlorophosphate.

3.3. Synthesis of *β*-Kdo Glycosides

One of the main polysaccharides to be produced by *B. pseudomallei* is a *β*-Kdo-containing EPS (Figure 2).[66] This EPS strongly reacts with melioidosis patient serum[67] and as such is seen as a promising antigen for the development of glycovaccines and diagnostics against *Burkholderia* infections. Structurally, this EPS is a linear heteropolymer composed of a tetrasaccharide repeating unit featuring a *β*,*α*,*β*-configured trigalactoside linked at the C5 position of a *β*-Kdo residue. In addition, one acetyl group is found at the C2 position of the terminal Gal residue. The structure of the biological repeating unit of this EPS, *i.e.*, prior to its elongation and flipping at the outer membrane, was solved and consisted in a tetrasaccharide having the Kdo residue at the reducing end.[66]



Scheme 7. Synthesis of the biological tetrasaccharide repeating unit of the *β*-Kdo-containing exopolysaccharide from *B. pseudomallei*. Blue: 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo); yellow: D-galactose.

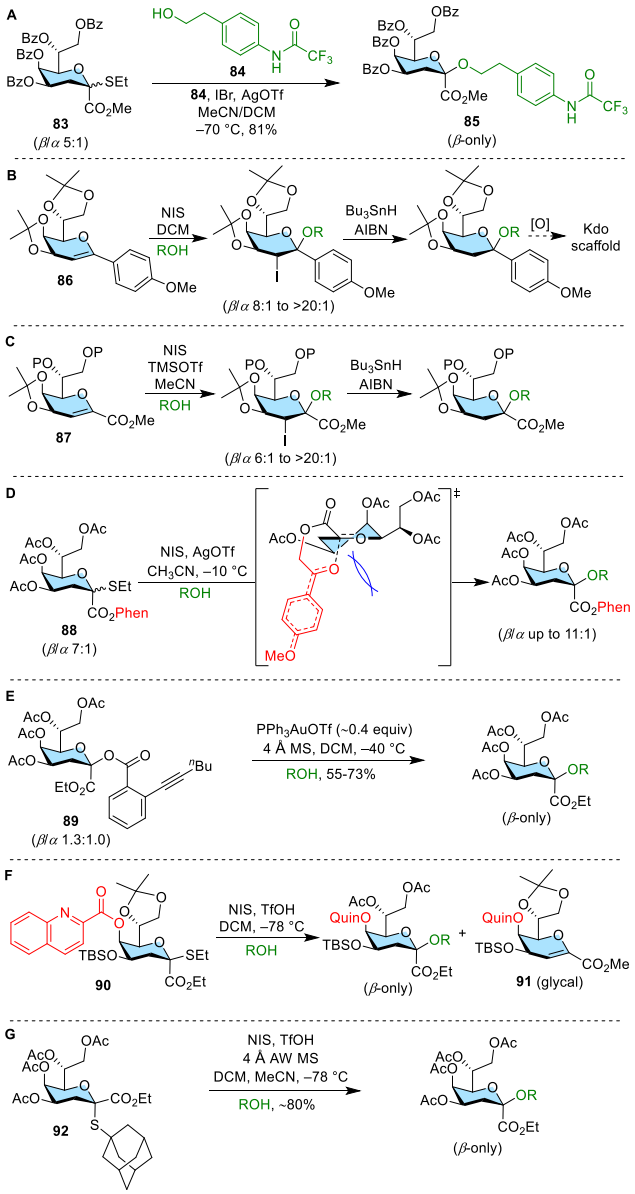
As part of our research program towards the development of *Burkholderia* glycovaccines, we were interested in devising a synthetic route allowing access to this *β*-Kdo-containing tetrasaccharide (Scheme 7).[53b] We first targeted the challenging *α*-galactoside linkage. To do so, we devised Gal donor **75** bearing a DTBS group at the C4 and C6 positions, which was activated in the form of a PTFA. Because of its steric hindrance at the *β*-face, the DTBS group, first reported in 2003 by Imamaru and co-workers,[40a] is known to be *α*-directive when a non-participating group is installed at C2. As planned, coupling between glycosyl acceptor **74** and PTFA donor **75** provided disaccharide **76** in excellent yield with full control of *α*-stereoselectivity. The DTBS group was then removed using $Et_3N.3HF$ and the primary alcohol was regioselectively chloroacetylated using Yamamoto's conditions.[68] The resulting

disaccharide was glycosylated with PTFA donor **77** generating trisaccharide **78** having the requested *β*-galactoside linkage. The anomeric position was deallylated and activated into a PTFA. Trisaccharide donor **79** was reacted with Kdo acceptor **80** bearing a *β*-linker at the reducing end. TMSOTf-promoted glycosylation yielded tetrasaccharide **81** in the exclusive *β-galacto*-configuration. A global deprotection strategy was then deployed in which the AcCl, Lev, TBS, and isopropylidene groups of tetrasaccharide **81** were orthogonally cleaved one after the other. A hydrogenolysis reaction using microfluidic conditions in the presence of Pearlman's catalyst allowed the simultaneous removal of two benzylidenes, three benzyl ethers, one benzyl ester, and one benzyl carbamate, which finally yielded target tetrasaccharide **82** ready for coupling with a carrier protein. The immunological investigation of this relevant bacterial oligosaccharide is still pending in our research group.

Kdo residues are mainly found in the surface polysaccharides of virtually all GNB.[69] In the LPS core region of GNB, Kdo residues are attached to the lipid A through *α*-glycosidic linkages. A lot of efforts have thus been devoted to develop efficient glycosylation methodologies towards *α*-Kdo glycosides in pure anomeric forms, as recently reviewed by Kosma.[70] Although less common, Kdo glycosides are also found in their *β*-configuration in surface polysaccharides of GNB[69b] such as, for instance, in the poly-Kdo linker at the reducing end of CPS[71] and in the EPS of pathogenic *Burkholderia* species, as previously described. Innovative synthetic methodologies have thus been implemented in recent years in our and other research groups in order to access *β*-Kdo glycosides (Scheme 8). Importantly, the synthesis of Kdo glycosides is not a trivial task for two main reasons: 1) the absence of a hydroxyl group at C3 hampering the use of NGP; and 2) the presence of an electron-withdrawing carboxylic acid at C1, which deactivates and hinders the anomeric position, and eases the formation of undesired 2,3-glycals.

The first synthesis of a *β*-Kdo glycoside was reported by the van Boom group in 1992.[72] They showed that when a peracetylated *β*-Kdo thioglycoside was activated with NIS/TfOH in the presence of a primary alcohol-containing linker, the resulting *β*-glycoside was exclusively formed. In 2007, the Oscarson group[73] revisited the use of Kdo thioglycosides as glycosyl donors. They showed that a high *β*-selectivity can be reached when perbenzoylated Kdo thioglycoside **83** was reacted with primary alcohol **84** under the promotion of IBr/AgOTf in a MeCN/DCM mixture at low temperature (Scheme 8A).

Inspired by the pioneering work of Takahashi,[74] the Ling group[75] reported the use of a 4,5:7,8-di-*O*-isopropylidene-containing 1-*C*-arylglycal donor (**86**). Upon treatment with NIS, a series of 3-iodo-Kdo glycosides were generated with good to exclusive *β*-selectivities (Scheme 8B). The presence of the 4,5-*O*-isopropylidene locking the pyranose ring into a skew-boat conformation was a prerequisite to reach this level of *β*-selectivity as the opposite *α*-anomer was formed using peracetylated donors under similar conditions.[73] Subsequent radical deiodination with Bu_3SnH/AIBN followed by oxidative transformation finally led to Kdo glycosides. The Mong group[76] investigated a similar strategy in which Kdo glycal donors, such as compound **87**, bearing a preinstalled carboxylate at C1 were synthesized (Scheme 8C). NIS-mediated glycosylation with these newly developed glycals in the presence of several acceptors yielded Kdo glycosides in *β*/*α* ratios of up to 20:1 following deiodination. Once again, the authors showed that the presence of a 4,5-*O*-isopropylidene group was needed to reach such level of *β*-stereoselectivity.



Scheme 8. Synthesis of *β*-Kdo glycosides using: a perbenzoylated thioglycoside (**A**); glycal functionalization (**B** and **C**); a 4'-methoxyphenacyl auxiliary group (**D**); gold-catalyzed glycosylation (**E**); hydrogen-bonded-mediated algycon delivery (**F**); a peracetylated thioadamantane glycoside (**G**).

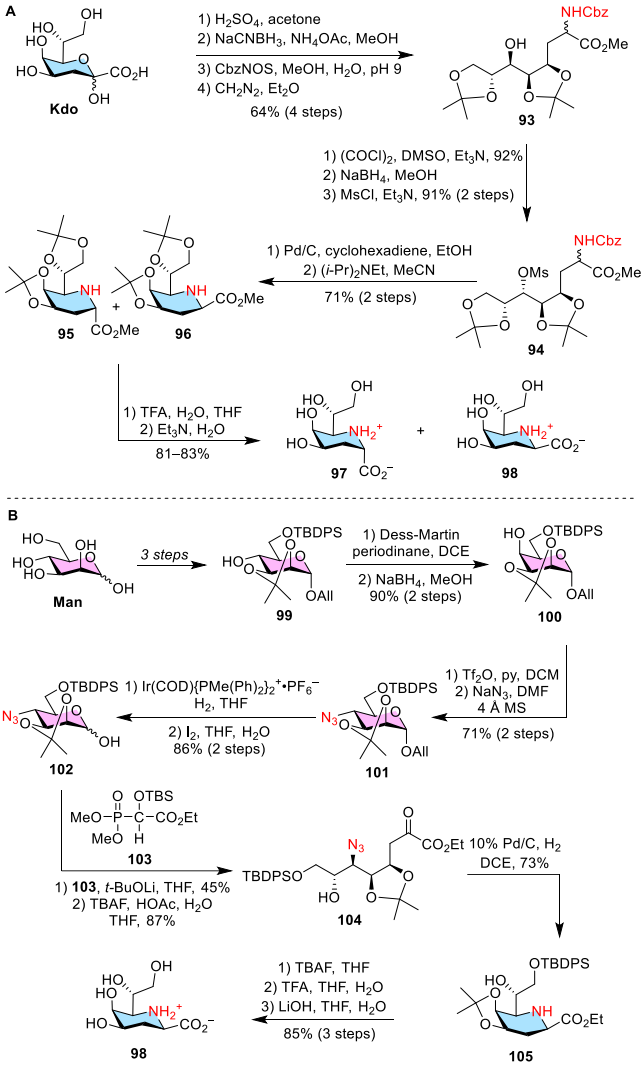
Our research group was also interested in developing a synthetic approach to reach *β*-Kdo glycosides (Scheme 8D).[77] To do so, we took advantage of a 4'-methoxyphenacyl (Phen) auxiliary group at the C1 position of peracetylated thioglycoside donor **88**. Our hypothesis was that, once activated, the long-range participation of the Phen group could stabilized the oxocarbenium

ion through the formation of an *α*-spirophenacylium intermediate that would be thermodynamically favoured over its *β*-counterpart.[78] Attack from the aglycone would thus come from the *β*-face of the Kdo ring. Using this approach, a series of Kdo glycosides were synthesized with *β*/*α* ratios up to 11:1 and, notably, by minimizing the formation of undesirable glycals.

In 2017, Mi and co-workers[79] reported a highly stereoselective approach towards the synthesis of *β*-Kdo glycosides (Scheme 8E). They equipped a Kdo glycosyl donor with an OABz group at the anomeric position. When subjected to gold(I)-catazed glycosylation in DCM at −40 °C, OABz donor **89** provided an exclusive *β*-selectivity with a series of primary, secondary, and tertiary alcohols. No mechanistic explanations were given by the authors to account for these intriguing results.

Demchenko's HAD methodology was applied to the field of Kdo glycosides by the Yang group (Scheme 8F).[80] They devised a Kdo donor equipped with a 2-quinolinecarbonyl (Quin) group at the axial C5 position. Through standard NIS/TfOH activation of thioglycoside **90**, *β*-Kdo glycosides were generated in the presence of several glycosyl acceptors. However, one of the main drawbacks of this methodology is that two equivalents of Kdo donor **90** were needed as to compensate the substantial formation of glycal **91**. Their methodology was further extended to the synthesis of a *β*-Kdo-containing trisaccharide found in the LPS of the marine bacterium *Alteromonas macleodii*.

Recently, the Crich group[81] also reported a stereoselective methodology for the synthesis of *β*-Kdo glycosides (Scheme 8G). They hypothesized that suitably protected Kdo donors adopt the *trans*,*gauche* conformation of their side chain, which would consequently favour equatorial anomers when the glycosylation reaction is conducted at low temperature. Therefore, using peracetylated or penbenzylated *S*-adamantanyl Kdo donors, such as derivative **92**, in conjunction with NIS/TfOH as the promotion system in a DCM/MeCN mixture at −78 °C, they managed to generate a series of Kdo glycosides with exclusive *β*-selectivity. As expected, the presence of a DTBS group at the C5/C7 positions reversed the selectivity toward the *α*-anomer, which was explained by the shielding effect of the DTBS group imposing a *gauche*,*gauche* conformation to the Kdo side chain.



Scheme 9. Total synthesis of 6-amino-2,6-dideoxy-Kdo from Kdo (**A**) and D-mannose (**B**). Blue: Kdo; pink: Man.

3.4. Synthesis of 6-Amino-2,6-Dideoxy-Kdo Derivatives

Because of the importance of Kdo-processing enzymes in the biosynthesis of bacterial polysaccharides, the Kdo biosynthetic pathway has been recognized as a promising target in drug discovery[82] as well as for the live imaging of bacterial membranes through metabolic glycan labeling.[83] As such, the Kdo scaffold has been the subject of diverse synthetic modifications over the last 35 years, mainly as to develop potential inhibitors of LPS biosynthetic machinery.[84] Owing to the recent discovery of previously undisclosed Kdo-processing enzymes involved in the biosynthesis of the CPS of GNB,[71] we and others have been interested in modifying the Kdo scaffold as to obtain potent enzymatic inhibitors.

Iminosugars, *i.e.*, sugars in which the endocyclic oxygen atom is replaced with a nitrogen, have been shown efficient for inhibiting sugar-processing enzymes such as glycosidases and glycosyltransferases.[85] We have thus become interested in synthesizing 6-amino-2,6-dideoxy-Kdo derivatives as potential inhibitors of Kdo-processing enzymes.[86] As depicted in Scheme 9A, the synthesis of Kdo iminosugars was first reported by Norbeck and Kramer[87] in 1987 starting from ammonium Kdo. Briefly, Kdo was subjected to ketal formation followed by a reductive amination, which allowed to introduce a nitrogen atom on the Kdo scaffold. Then, protection of the resulting amine followed by carboxylic acid esterification gave acyclic derivative **93**. The free alcohol at C6 was then epimerized and converted into mesylate **94**. Phase-transfer conditions allowed the removal of the carbamate substituent. Then, the ring closure reaction was performed by heating substrate **94** in a sealed tube at 100 °C in MeCN in the presence of diisopropylethylamine. A separable mixture of anomers **95** (*β*) and

96 (*α*) was obtained, which were finally deprotected into target derivatives **97** and **98**, respectively.

Our own approach[86] relied on the insertion of the nitrogen atom at the C6 rather than at the C2 position and started with the commercially available and inexpensive D-mannose. As shown in Scheme 9B, derivative **99**, obtained in three steps from D-mannose, was subjected to a two-step oxidation/reduction sequence to afford compound **100** in which the C4 position was epimerized. Then, the free alcohol was transformed into a triflate, which was displaced by azide ions *via* an S_N2 reaction. The anomeric position of derivative **101** was deallylated and the resulting hemiacetal **102** was subjected to Horner-Wadsworth-Emmons (HWE)[88] homologation using phosphine **103** in the presence of lithium *tert*-butoxide. Removal of the TBS group under buffered conditions allowed the formation of ketoester **104**, which was ready for the 6-*exo*-*trig* ring closure. Following optimization, we found that Pd-catalyzed reductive cyclization of derivative **104** enabled the *α*-stereoselective formation of Kdo-like azacyclic derivative **105**. Alternatively, derivative **105** was obtained through a tandem Staudinger/aza-Wittig reaction[89] (PPh_3, THF, 60 °C) followed by an *in situ α*-iminoester reduction with $NaBH_3CN$. Global deprotection of derivative **105** was uneventful leading to target Kdo iminosugar **98**. We are currently taking advantage of the iminoester intermediate for the late-stage diversification of the Kdo scaffold. The evaluation of these derivatives against Kdo-processing enzymes is still pending in our research group.

4. Summary and Outlook

In summary, we have shown that, according to the nature of the glycosidic bonds to be formed and the arrangement of saccharide residues, one can take advantage of a vast repertoire of glycosylation methodologies, glycosyl donors, and protecting group strategies to enable the synthesis of complex GNP and oligosaccharides. Glycosylation approaches such as NGP of esters at C2, IAD, HAD, as well as conformational, steric, and anomeric effects can be judiciously employed to access, with great efficiency and stereoselectivity, important glycan-based molecular targets. In this Personal Account, we have described the recent implementation of some of these approaches in our research group, which empowered the synthesis of naturally occurring lupane-type saponins as well as bacterial oligosaccharides associated with pathogenic *Burkholderia* species. Specifically, we have devised stereoselective methods for the synthesis of rare bacterial sugars including *β*-Kdo, 6d-*β*-ManHep, and 6d-*α*-Tal glycosides. We strongly believe that the best days of the burgeoning field of chemical glycosciences are still ahead of us and that synthetic research efforts will one day be rewarded by the discovery of more general glycosylation methodologies. The advancement of synthetic technologies in carbohydrate chemistry will be beneficial not only in fundamental sciences but also for real-life clinical applications such as for the development of therapeutic agents, vaccines, and adjuvants.

Acknowledgements

This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC) under Award No. RGPIN-2016-04950, the Fonds de recherche du Québec (FRQ) – Fonds de la recherche scientifique (F.R.S./FNRS), the Fonds de recherche du Québec – Nature et technologies (FRQNT) under Award No. 2021-PR-283932, the Institut Pasteur International Network (IPIN) under Award No. PTR-380-20, and the Réseau québécois de la recherche sur les médicaments (RQRM). C.G. was supported by a Research Scholar Junior 2 Salary Award from the Fonds de recherche du Québec – Santé (FRQS).

Keywords: Oligosaccharides • carbohydrate chemistry • glycosyl donors • saponins • protecting groups

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-Chapitre IV-

Total Synthesis of a Chimeric Glycolipid Bearing the Partially Acetylated Backbone of Sponge-Derived Agminoside E

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(Article publié dans *The Journal of Organic Chemistry* 2021, *86*, 15357-15375)

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4.1 Article publié

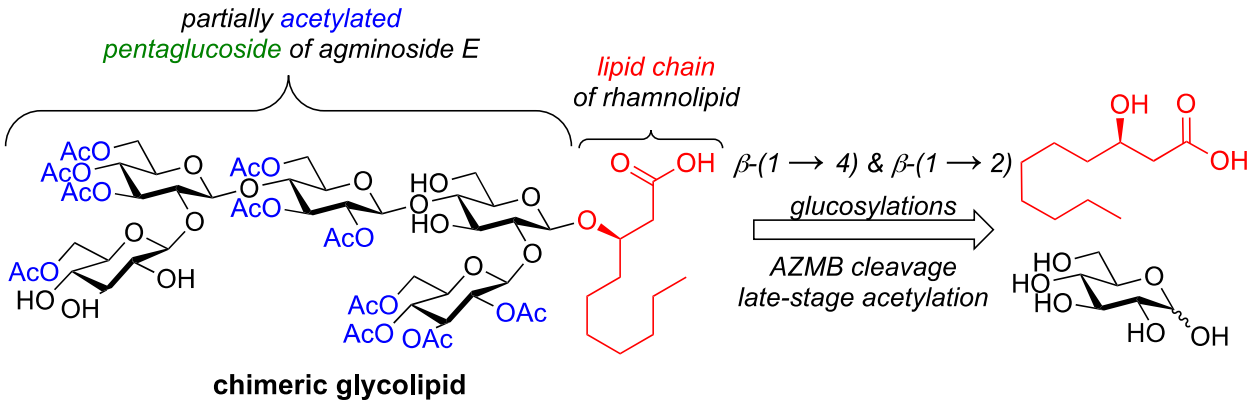
Contribution des auteurs

L'auteur principal de cet article (K. Muru) a rédigé une partie du manuscrit en plus d'effectuer la synthèse et la purification de tous les composés. M. Cloutier a contribué à la synthèse de certains composés ainsi qu'à la relecture du manuscrit. A. Provost-Savard, S. Di Cintio, O. Burton et J. Cordeil ont participé, dans le cadre de stages de recherche de premier cycle, à la synthèse organique et la purification de composés aussi bien ici que dans le chapitre suivant (*cf* chapitre 5). M.-C. Groleau, J. Legault et É. Déziel ont participé à l'évaluation biologique du composé final. Enfin, C. Gauthier, directeur de ce projet de recherche, a contribué à l'analyse des résultats et à la rédaction de l'article.

Résumé

Nous décrivons la synthèse totale d'un glycolipide chimérique portant à la fois le squelette partiellement acétylé de l'agminoside E dérivé de l'éponge de mer *Raspailia agminata* et la chaîne acide (*R*)-3-hydroxydécanoïque des rhamnolipides bactériens. Le squelette pentaglucolipidique ramifié a été obtenu en utilisant une approche de déconnexion [3 + 2]. Les liaisons glycosidiques β-(1 $\rightarrow$ 2) et β-(1 $\rightarrow$ 4) ont été synthétisées par une combinaison de glycosylations stéréosélectives *via* l'utilisation de donneurs thiotolyl activé par NIS/Yb(OTf)$_3$ et de donneurs *N*-phényl-2,2,2-trifluoroacétimidate et trichloroacétimidate activé par le TMSOTf. La synthèse totale du glycolipide structurellement simplifié, dont le motif d'acétylation partielle sur la partie glycane est identique à l'agminoside E, a été complétée par pentaacétylation, réduction de Staudinger d'un groupe (2-azidométhyl)benzoyle suivie d'une hydrogénolyse microfluidique en flux continu. Notre étude servira de pierre fondatrice pour la synthèse totale des agminosides vers la compréhension de leurs fonctions biologiques chez les éponges.

Résumé graphique



ABSTRACT: We describe the total synthesis of a chimeric glycolipid bearing both the partially acetylated backbone of sponge-derived agminoside E and the (*R*)-3-hydroxydecanoic acid chain of bacterial rhamnolipids. The branched pentaglucolipid skeleton was achieved using a [3 + 2] disconnection approach. The β-(1 $\rightarrow$ 2) and β-(1 $\rightarrow$ 4)-glycosidic bonds were synthesized through a combination of NIS/Yb(OTf)$_3$- and TMSOTf-mediated stereoselective glycosylations of thiotolyl, *N*-phenyltrifluoroacetimidate, and trichloroacetimidate donors. Late-stage pentaacetylation, Staudinger reduction of a (2-azidomethyl)benzoyl group followed by continuous-flow microfluidic hydrogenolysis completed the total synthesis of the structurally simplified glycolipid, whose partial acetylation pattern on the glycan part was identical to agminoside E. Our study lays the foundation for the total synthesis of sponge-derived agminosides and the understanding of their biological functions in sponges.

INTRODUCTION

In the field of natural product chemistry, the marine environment has proven to be a rich source of structurally diverse and biologically active compounds including glycolipids.[1–3] In 2011, Wojnar and Northcote described the isolation of agminosides A–E (Figure 1), a group of structurally related, complex, and unusual glycolipids, from the marine sponge *Raspailia agminata*.[4,5] Sponge specimens of *R. agminata* were collected by hand from Taheke Reef in the Cavalli Islands, New Zealand. MS-guided fractionation of a MeOH extract from 251 g of wet sponges led to the isolation of agminosides in minute quantities (0.5–11 mg).[5] The agminosides show unique structural features compared to other sponge-derived glycolipids, including a branched oligosaccharidic chain composed of five to six D-glucopyranose residues connected by both β-(1 $\rightarrow$ 4) and β-(1 $\rightarrow$ 2) linkages, a single aglycone glycosylated on the lipid rather than on the glycerol unit, and, importantly, a partial acetylation of the hydroxyl groups, which slightly differs from one congener to the other (Figure 1).

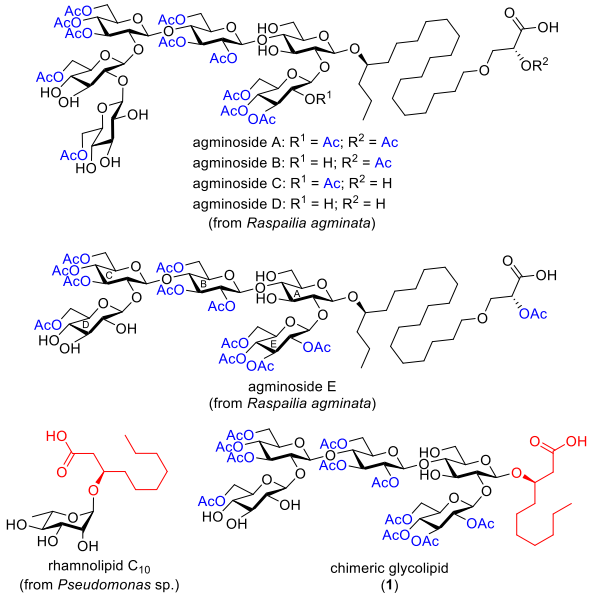


Figure 1. Structure of agminosides A–E, rhamnolipid C_{10}, and target chimeric glycolipid **1**.

Partially acetylated glycolipids have been infrequently described in the literature.[3] To the best of our knowledge, agminosides A–E,[5] caminosides A–D,[6,7] erylusamine B,[8] pachymoside A,[9] stellettosides,[10] and erylusamides A–D[11] are the only partially acetylated glycolipids to have been isolated from marine sponges until now. Because of the global degradation of coral reefs,[12] scarcity of the natural resource, and very low isolation yields from sponge extracts, pure and homogeneous samples of these acetylated glycolipids are only available in limited quantities. The greater availability of these glycolipids and their derivatives would help the understanding of their biological functions in sponges and enable the study of their therapeutic potential.[3] As such, even if agminosides are major metabolites of the *R. agminata* MeOH extract,[4] their biological roles remain to be explored. Only the main congener, that is, agminoside A, was biologically evaluated and showed a moderate cytotoxic activity against cervical cancer cell lines (HeLa, IC_{50} = 32 μM).[4]

Total synthesis stands as a tantalizing tool to access these acetylated glycolipids.[3] The Yu and Li groups have been involved in this challenge by reporting the total synthesis of caminosides A[13] and B,[14] respectively, which are two diacylated glycolipids identified from the marine sponge *Caminus sphaeroconia*. These compounds are potent inhibitors of *Escherichia coli* type II secretion system, which makes them promising antibiotic agents.[6,7] In line with our expertise with the synthesis of partially acetylated oligosaccharides[15–18] together with the structural complexity and biological importance of these sponge-derived glycolipids,[5] we have become interested in developing a synthetic access to agminosides and their derivatives. As the chiral lipidic chain of agminosides would represent an important challenge to synthesize, we first planned to use the readily available (*R*)-3-hydroxydecanoic acid chain of rhamnolipids produced by *Pseudomonas* sp.[19,20] (Figure 1). We reasoned that this structural simplification would allow to focus our efforts first on the equally synthetically challenging, partially acetylated pentasaccharidic backbone of agminoside E. The presence of a terminal carboxylic acid, which is also found on the lipid chain of agminosides, could enable further chemical diversification at the lipid tail to generate additional derivatives. From a biological point of view, we hypothesized that the chimeric glycolipid exhibits biological properties similar to both agminosides and rhamnolipids, including cytotoxic, antimicrobial, and

antibiofilm activities, coming from its "chimeric" nature. Therefore, we herein report the convergent synthesis of a structurally simplified chimeric glycolipid (**1**, Figure 1) bearing both the partially acetylated pentaglucosidic backbone of agminoside E and a (*R*)-3-hydroxydecanoic acid chain, reminiscent of the monolipidic tail of bacterial rhamnolipids. Preliminary biological investigation of the target glycolipid (**1**) is also presented.

RESULTS AND DISCUSSION

First Synthetic Approach. Several disconnection strategies would be theoretically possible for the elaboration of the branched pentaglucosidic scaffold of agminoside E-like glycolipid **1**. To benefit from the so-called neighboring group participation (NGP) of C2 esters through putative dioxolenium-ion intermediates,[21,22] which, in the case of D-glucose, would lead to the formation of β-(or 1,2-*trans*) glycosides, the two (1 $\rightarrow$ 2) bonds attaching residues D–C and E–A would have to be synthesized subsequently to the C–B (1 $\rightarrow$ 4) and A–aglycone bonds. Importantly, one would consider two options for the introduction of the partial acetylation pattern, that is, using building blocks bearing pre-installed acetyl groups or *via* a regioselective deprotection/acetylation sequence in the last steps. We first opted for the former approach being cognizant that preactivation conditions[23] would be needed for coupling between glycosidic partners of a similar reactivity. As retrosynthetically depicted in Figure 2, chimeric glycolipid **1** would come from a [3 + 2] glycosylation between trisaccharide **2**, in the form of a thiotolyl (STol) glycoside,[24, 25] and branched glucolipid **3**. These oligosaccharides would be obtained from five conveniently functionalized STol or trichloroacetimidate (TCA)[26] building blocks (**4a**, **5a**, **6**, **7a**, and **8**) and benzyl ester **9**.[27] The presence of a (2-azidomethyl)benzoyl (AZMB)[28] group at the C2 position of residues **4a**, **6**, and **7a** would ensure the formation of β-glucosidic bonds *via* NGP. The AZMB group would be orthogonally cleaved through hydrogenolysis or Staudinger reduction, hence preserving the integrity of the acetylation pattern.[27] The AZMB group would be favored over a chloroacetyl group because of the basic conditions needed to remove the latter that could trigger acetyl migration. In addition, the presence of a levulinoyl (Lev)[29] ester in building block **7a** would allow the selective unmasking of the C4 hydroxyl position prior to the formation of the final β-(1 $\rightarrow$ 4)-glucosidic bond between residues B and A. The remaining alcohols would be protected with benzyl groups, cleavable through Pd-catalyzed hydrogenolysis.

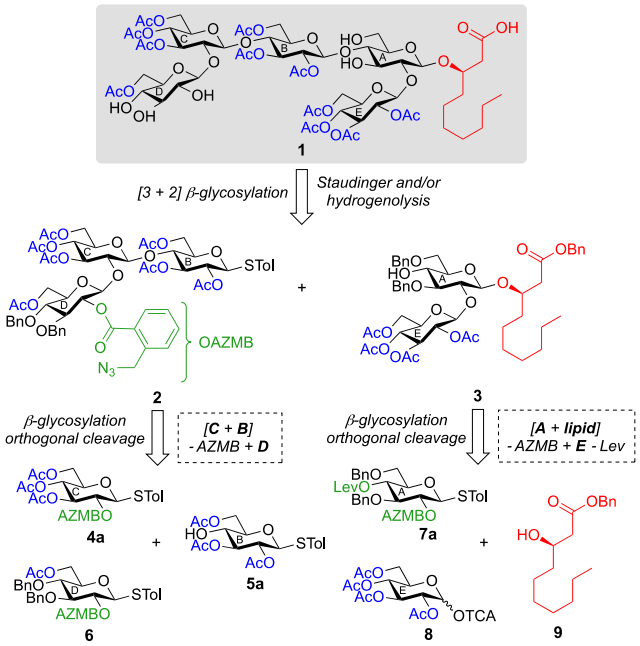
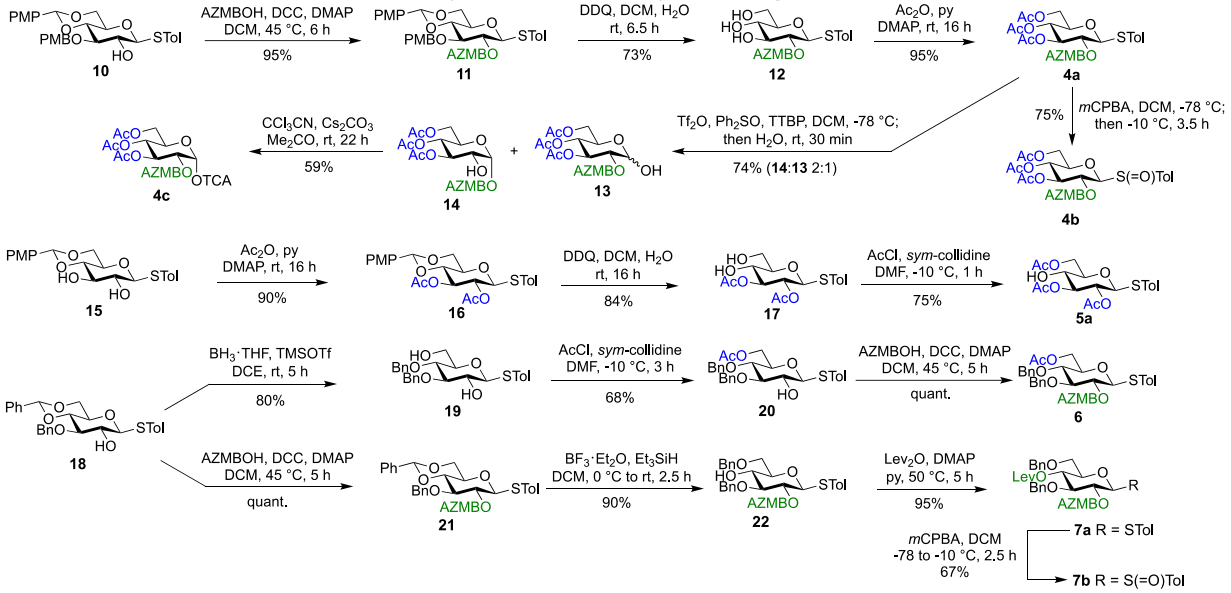


Figure 2. Retrosynthetic strategy of chimeric glycolipid **1** *via* building blocks bearing pre-installed acetyl groups.

The synthesis of the glucosyl building blocks was straightforward (Scheme 1). Briefly, STol derivative **10**,[30] protected with a *para*-methoxybenzylidene group at C4/C6 along with a PMB group at C3, was substituted with an AZMB group at C2. The treatment of compound **11** with DDQ gave triol **12**. Subsequent peracetylation led to target STol donor **4a**.

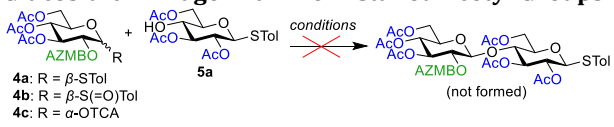
Scheme 1. Synthesis of Glucosyl Building Blocks 4-7.

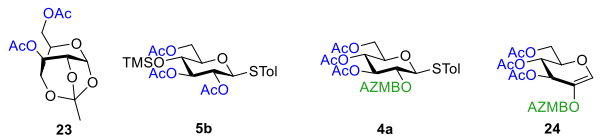


Activation of STol derivative **4a** using Tf_2O, Ph_2SO, and 2,4,6-tri-*tert*-butylpyridine (TTBP) followed by hydrolysis led to an inseparable mixture of hemiacetal **13** and migration product **14**. Other more standard conditions were tried for activation, that is, using NBS or NIS, but thioglycoside **4a** was resistant toward them. The mixture of alcohols **13** and **14** was treated with CCl_3CN in the presence of Cs_2CO_3 overnight providing TCA donor **4c**. In parallel, STol donor **4a** was converted into sulfoxide donor **4b** by treatment with *m*CPBA.[31,32] Regarding the synthesis of acceptor **5a**, STol diol **15**[33] was acetylated to give derivative **16**, which was reacted with DDQ to generate diol **17**.[34] Regioselective acetylation at the primary position using Yamamoto's conditions[35] provided target alcohol **5a**. Glucosyl donors **6, 7a**, and **7b** were obtained from known derivative **18**.[36] Regioselective opening of the benzylidene under the action of BH_3·THF/TMSOTf[37] provided compound **19**[38] bearing a free alcohol at C6, which was selectively acetylated. The resulting derivative **20**[38] was then protected at the C2 position with an AZMB group to afford STol donor **6**. In parallel, an AZMB group was appended at the C2 position of compound **18**. Regioselective benzylidene opening of fully protected derivative **21** using Et_3SiH in the presence of BF_3·OEt_2 led to compound **22** bearing a free alcohol at C4. Importantly, the AZMB group was stable under these conditions.[39] Treatment of alcohol **22** with levulinic anhydride generated STol derivative **7a**, which was converted into sulfoxide **7b** through the action of *m*CPBA.

With STol donor **4a** and acceptor **5a** in hand, several glycosylation conditions were screened for the formation of the β-(1→4) linkage between residues C and B (Table 1, see Table S1 for additional entries). Pre-activation of donor **4a** using three different promoter systems (TolSCl/AgOTf,[40] NIS/TMSOTf,[41] and DMTST[42]) did not provide any trace of disaccharide while activation with Ph_2SO/Tf_2O[43] generated the corresponding hydrolyzed hemiacetal. Activation of the more reactive sulfoxide **4b** with Tf_2O in the presence of TTBP, used as an acid scavenger, led to α-D-glucopyranose 1,2,4-orthoacetate (**23**),[44] whose formation can be rationalized by the intramolecular self-condensation of glycosyl acceptor **5a** following its activation with *in situ* generated TolSOTf. Interestingly, STol donor **4a** was equally formed from sulfoxide **4b** during this process (see Figure 3 for a mechanistic hypothesis). Adding equimolar amounts of 4-allyl-1,2-dimethoxybenzene[45] to scavenge TolSOTf did not lead to any improvement. The last attempts were performed with TCA derivative **4c** using three different triflate catalysts, that is, TMSOTf, AgOTf, or TBSOTf.[15] Unfortunately, these reactions were unsuccessful as well, providing glycal **24** and silylated acceptor **5b** as the main by-products.

Table 1. Attempts to Construct the C-B β-(1→4)-Glucosidic Linkage with Pre-Installed Acetyl Groups.





23 5b 4a 24

entry[a]	donor	conditions[b]	by-product (s)
1	**4a**	NIS, AgOTf, DCM, −10 °C, 1.5 h	**23**
2	**4b**	Tf_2O, TTBP, DCM, −78 °C to rt, 2 h	**23** + **4a**
3	**4c**	TMSOTf, DCE, rt, 8 h	**5b** + **4a**
4	**4c**	TBSOTf, tol, 80 °C, 2 h	**24**

[a]See Table S1 for additional entries. [b]Reactions were performed in anhydrous solvents in the presence of 4 Å MS using 1.3 equiv of donor **4** and 1.0 equiv of acceptor **5a**.

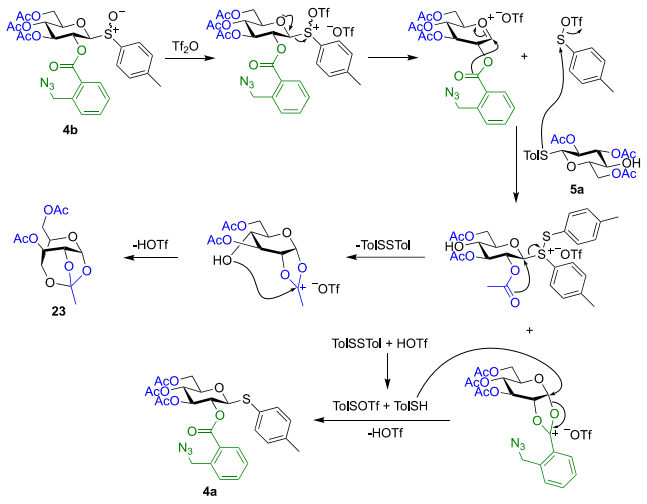


Figure 3. Proposed mechanism for the concomitant formation of thioglycoside **4a** and orthoester **23** from the reaction between sulfoxide **4b** and acceptor **5a** in the presence of triflic anhydride (reference to Table 1, entry 2).

Second Synthetic Approach. These unsuccessful attempts prompted us to follow an alternative strategy in which trisaccharide **2** was replaced with trisaccharide **25** (Figure 4). We reasoned that substituting five acetyl groups by one *para*-methoxybenzylidene and three PMB groups in residues C and B would improve the reactivity of both glycosyl donor **11** and acceptor **26** according to the Fraser-Reid armed-disarmed concept.[46,47] Moreover, the presence of an allyl group instead of an STol glycoside at the anomeric position of glycosyl acceptor **26** would prevent its self-condensation. The allyl group would then be readily removed at the trisaccharide level prior to the activation of the resulting hemiacetal into an *N*-phenyl-2,2,2-trifluoroacetimidate (PTFA)[48] donor followed by subsequent [3 + 2] glycosylation with glycolipid **3**, which would remain the same as in the first approach. We hypothesized that the acetylation pattern of agminoside E would be reached at the pentaglucolipid level through the orthogonal cleavage of the *para*-methoxybenzylidene and PMB groups and subsequent pentaacetylation. STol donor **11** is an intermediate in the synthesis of donor **4a** (see previous Scheme 1) while allylated derivative **26** was obtained in a six-step sequence from α-allylglucose **27**[49] (Scheme 2). Briefly, tetraol **27** was protected with a *para*-methoxybenzylidene. The resulting diol **28** was converted into PMB ether **29** *via* a one-pot three-step sequence.[50] Acetylation of alcohol **29** gave compound **30**, which was regioselectively opened under the combined action of $NaBH_3CN/HCl{\cdot}Et_2O$,[51] providing glycosyl acceptor **26** bearing a free hydroxyl group at C4.

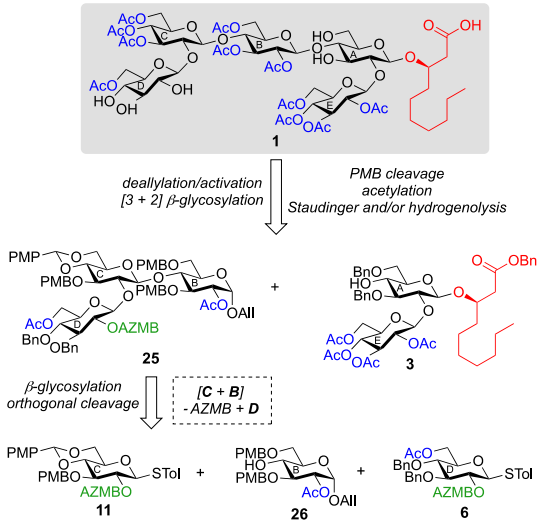
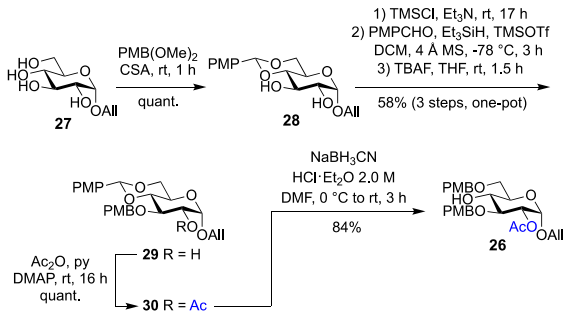


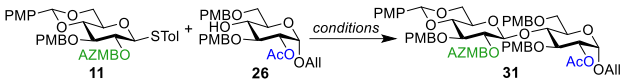
Figure 4. Retrosynthetic strategy of chimeric glycolipid **1** via late-stage acetylation using PMB-protected trisaccharide **25**.

Scheme 2. Synthesis of Glucosyl Building Block 26.



Moving forward with this second synthetic plan, we reinvestigated the formation of the challenging C-B β-(1 → 4)-glucosidic bond using more reactive STol donor **11** and allylated glycosyl acceptor **26**. Several promoters were screened for the formation of disaccharide **31** (Table 2). Glycosylation with Ph_2SO/Tf_2O at −78 °C led to the degradation of the reaction mixture (entry 1), whereas a moderate yield of disaccharide **31** (28%) was obtained using NIS/TMSOTf in DCE (entry 2). Replacing DCE with MeCN or toluene did not improve the reaction yield (entries 3 and 4). We then studied the impact of the promoter counterion (entries 5 and 6). We were pleased to find that using AgOTf instead of TMSOTf provided disaccharide **31** in 68% yield. Further improvements were obtained using $Yb(OTf)_3$, which almost quantitatively yielded disaccharide **31**. As far as we are aware, although the NIS/$Yb(OTf)_3$ promotion system was successfully implemented by Fraser-Reid and co-workers for the activation of *n*-pentenyl orthoesters,[52,53] it has only been sporadically reported for thioglycosides.[27,52,54,55]

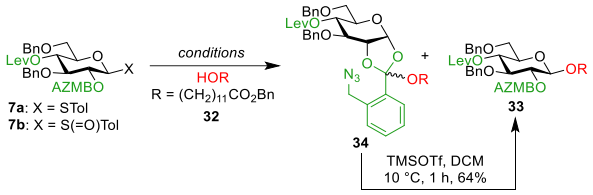
Table 2. Optimization of the Formation of the C-B *β*-(1→4)-Glucosidic Linkage.



entry	conditions[a]	solvent	temp (°C)	yield (%)[b]
1	Ph_2SO, Tf_2O, TTBP	DCM	−78	nd[c]
2	NIS, TMSOTf	DCE	0	28
3	NIS, TMSOTf	MeCN	−10	nd[d]
4	NIS, TMSOTf	tol	−10	nd[c]
5	NIS, AgOTf	DCE	0	68
6	NIS, $Yb(OTf)_3$	DCE	0	96

[a]Reactions were performed in anhydrous solvents in the presence of 4 Å MS using 1.3 equiv of donor **11**. [b]Isolated yields. [c]Degradation. [d]Donor hydrolysis.

Table 3. Optimization of the Formation of the A-Aglycon *β*-Glucosidic Linkage.



entry	donor	conditions[a]	yield, %[b]
1	**7a**	TolSCl, AgOTf, DCM, −78 °C to rt	nd[c]
2	**7a**	NIS, TfOH, DCM, −10 °C	nd[c]
3	**7a**	NIS, AgOTf, DCM, −10 to 0 °C	nd[c]
4	**7a**	NIS, TMSOTf, DCM, −10 to 10 °C	34 (0)
5	**7a**	NIS, $Yb(OTf)_3$, DCM, 0 °C	50 (40)
6	**7a**	Ph_2SO, Tf_2O, TTBP, tol, −78 °C to rt	25 (75)
7	**7a**	Ph_2SO, Tf_2O, TTBP, DCM, rt	31 (68)
8	**7b**	Tf_2O, TTBP, tol, −70 to −40 °C	12 (20)

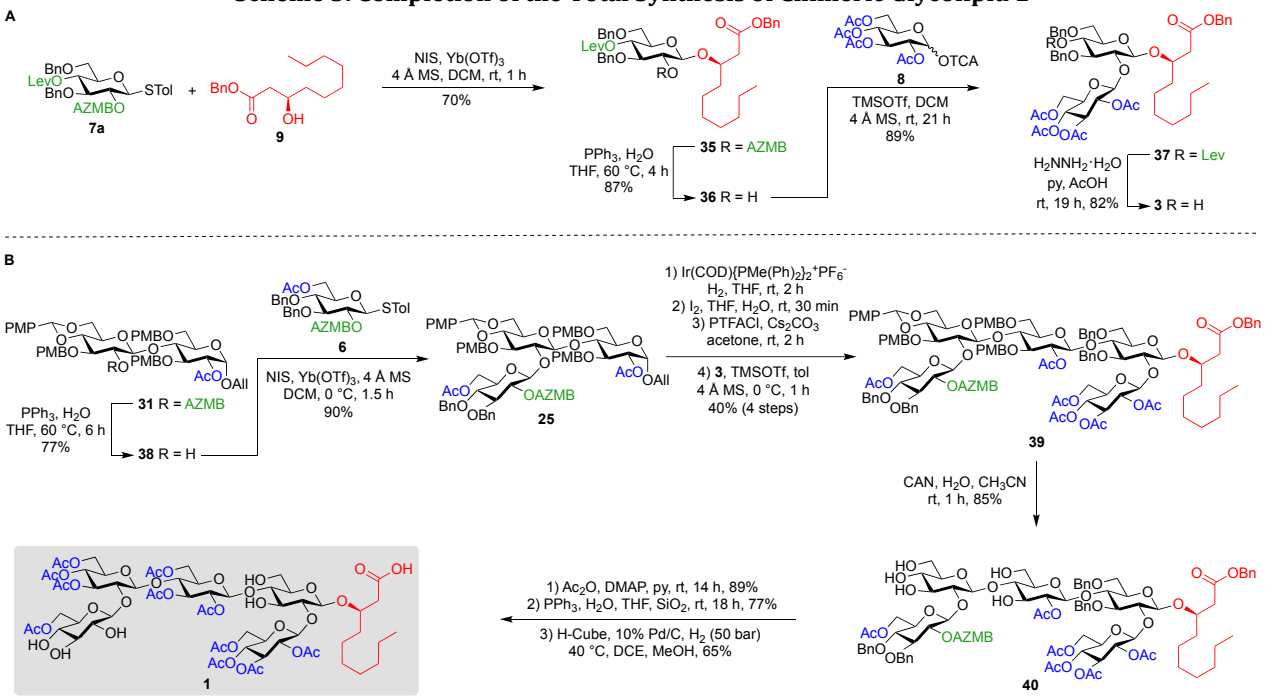
[a]Reactions were performed in anhydrous solvents in the presence of 4 Å MS using 1.2 equiv of lipid **32**. [b]Isolated yields of **33**. Isolated yields of **34** are written in brackets. [c]Degradation.

Having achieved the synthesis of the "western" disaccharide **31**, we then focused our attention on the synthesis of the "eastern" glycolipid **3**, also involving the formation of a *β*-(1 → 4) linkage. As a first step, we sought to study the glycosylation behavior of our newly developed STol donor **7a** using benzyl 12-hydroxydodecanoate (**32**) as a model glycosyl acceptor (Table 3). Promotors, such as TolSCl/AgOTf, NIS/TfOH, and NIS/AgOTf in dichloromethane (DCM), only led to the degradation of the reaction mixture (entries 1–3), whereas the use of NIS/TMSOTf did allow the formation of glycolipid **33**, although in a moderate yield (34%, entry 4). Pleasingly, NIS/$Yb(OTf)_3$ conditions provided 50% yield of glycolipid **33** along with 40% of the corresponding orthoester **34** (entry 5), which was readily converted into *β*-glucoside **33** through the action of TMSOTf.[56] Switching to Ph_2SO/Tf_2O as the activation system provided increased yields of orthoester **34** (entries 6 and 7) while using sulfoxide **7b** as the donor did not allow to improve the reaction outcome (entry 8).

We were pleased to find that applying our optimized NIS/$Yb(OTf)_3$ conditions for the coupling between glycosyl donor **7a** and benzyl (*R*)-3-hydroxydecanoate (**9**)[27] furnished glycolipid **35** in 70% yield without. a noticeable formation of the orthoester (Scheme 3A). The AZMB group was then removed *via* Staudinger reduction giving C2 alcohol **36** (87%) ready for the formation of the (1 → 2)-branched linkage. This was achieved uneventfully using peracetylated glucose TCA **8** under the promotion of TMSOTf,[17] providing disaccharide **37** in 89% yield. Orthogonal cleavage of the Lev group under the action of hydrazine acetate finally generated eastern glycolipid **3** (82%) ready for the elongation to the pentasaccharide level.

We then went on with the final sequence of our synthetic journey toward chimeric glycolipid **1** (Scheme 3B). Staudinger reduction of the AZMB group in C-B disaccharide **31** afforded C2 alcohol **38** (77%). NIS/$Yb(OTf)_3$-promoted glycosylation of STol donor **6** with glycosyl acceptor **38** stereoselectively provided trisaccharide **25** in excellent yield (90%). The allyl group at the reducing end of trisaccharide **25** was then isomerized into the corresponding 1-propenyl ether using an iridium-based catalyst.[57] Subsequent iodine-mediated hydrolysis[58] of the latter derivative provided an hemiacetal, which was activated into a PTFA donor. TMSOTf-promoted [3 + 2] glycosylation of the PTFA donor with glycolipid **3** allowed the formation of the pentaglucolipid backbone **39** in 40% yield over four steps from trisaccharide **25**. The proper acetylation pattern was installed uneventfully (89%) following ceric ammonium nitrate (CAN)-mediated cleavage of the *para*-methoxybenzylidene group as well as the three PMB groups providing pentaol **40** (85%). Thereafter, the AZMB group at the C2 position of residue D was selectively cleaved in 77% yield using slightly modified Staudinger conditions.[15] At this step, size-exclusion chromatography (LH-20) was performed to remove the excess of phosphine derivatives. Final cleavage of the four benzyl ethers altogether with the benzyl ester was problematic under conventional heterogeneous conditions (Pd-based catalysts, 1 atm of H_2) leading to incomplete hydrogenolysis and degradation of the target compound over a prolonged reaction time. Gratifyingly, continuous-flow microfluidic hydrogenolysis[59] using a H-Cube reactor provided target chimeric glycolipid **1** in a pure and homogeneous form. Extensive 1D and 2D NMR analyse and comparison with the reported spectral data confirmed that glycolipid **1** bears the same partially acetylated pentaglucosidic backbone as agminoside E (see Table S2 for a detailed comparison of ^1H and ^{13}C chemical shifts).

Scheme 3. Completion of the Total Synthesis of Chimeric Glycolipid 1



Preliminary Biological Evaluation. As the biological properties of agminosides are mainly unknown, chimeric glycolipid **1** was preliminarily evaluated for its potential cytotoxic and antimicrobial activities; however, it was not active at the maximum tested concentrations against cancer cells nor against a range of bacteria and fungus. Biofilm assays were also conducted, and it turns out that glycolipid **1** significantly enhances the production of the biofilm in *Pseudomonas aeruginosa* (Figure 5). Additional biological experiments are however needed to understand the exact mechanism by which this occurs.

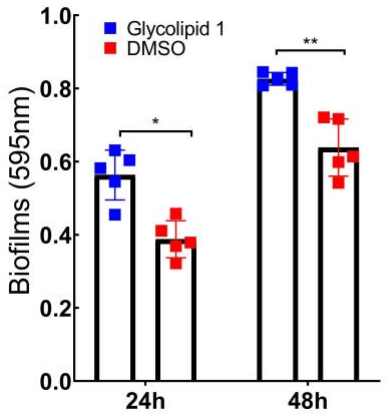


Figure 5. Biofilm formation of *P. aeruginosa* PA14 in the presence of 100 μM of glycolipid **1**. DMSO was in controls. Error bars represent standard deviation. Values that are significantly different (*t*-test) are indicated by asterisks (**, $P < 0.001$; *, $P < 0.01$).

CONCLUSIONS

In summary, we have reported the total synthesis of a structurally simplified glycolipid (**1**) bearing the partially acetylated pentaglucosidic scaffold of agminoside E together with the monolipid chain of bacterial rhamnolipids. The chimeric pentaglucolipid was built via the blockwise [3 + 2] glycosylation of a PTFA-activated trisaccharide with a (1 → 2)-branched glycolipid. Three of the β-glucosidic bonds were efficiently achieved using thiotolyl donors under the activation of NIS/Yb(OTf)$_3$ in the presence of an orthogonal AZMB group at C2. Introduced at a late stage of the synthetic sequence, the partial acetylation pattern of target chimeric glycolipid **1** was identical to that of sponge-derived agminoside E. A comparison of the NMR data of our synthetic compound with agminoside E has confirmed the proposed structure of the pentaglucosidic backbone of the natural product. Our pioneering study lays the foundation for the total synthesis of agminosides A–E, which would allow highlighting their therapeutic potential as well as to understand their biological functions in sponges. Work is currently in progress in our laboratory on the synthesis of the lipid tail of agminosides, which should enable the total synthesis of these marine natural products.

EXPERIMENTAL SECTION

General Methods. All starting materials and reagents were purchased from commercial sources and used as received without further purification. Unless otherwise stated, all reactions were performed under an Ar atmosphere using anhydrous solvents that were prepared from commercial solvents and dried over heat-gun activated 4 Å molecular sieves. Reagents were introduced *via* an anhydrous syringe. When required, reaction mixtures were heated using an oil bath. Powdered 4 Å molecular sieves were activated before use by heating with a heat gun for 15 min under high vacuum. Thin-layer chromatographies were performed with silica gel (60 F_{254} 0.25 mm) pre-coated aluminum foil plates. Compounds were visualized by using an UV_{254} lamp and/or by staining with an orcinol solution (1 mg•mL^{-1} in 10% aq. H_2SO_4) with heating. Normal-phase column chromatography was performed on silica gel 60 Å (15–40 μm). Size exclusion chromatography was performed on GE Healthcare Sephadex LH-20 resin (70 μm). NMR spectra were recorded at 297 K in the indicated solvent ($CDCl_3$ or CD_3OD) with 400 or 600 MHz instruments, employing standard software given by the manufacturer. ^1H spectra were referenced to tetramethylsilane (TMS, δ_H = 0.00 ppm) as an internal reference and ^{13}C NMR spectra were referenced to a solvent residual peak ($CDCl_3$, δ_C = 77.16 ppm; MeOD, δ_C = 49.00 ppm). Assignments were based on ^1H, ^{13}C, COSY, and HSQC experiments and additional HMBC, undecoupled HSQC, and 2D TOCSY experiments when required. Interchangeable assignments are marked with an asterisk (*). High-resolution mass spectra (HRMS) were recorded on an ESI-Q-TOF mass spectrometer. Optical rotation $[\alpha]_D^{20}$ data were measured on an Anton Paar polarimeter.

*4-Methylphenyl 2-O-(2-Azidomethylbenzoyl)-3-O-(4-methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-β-D-thioglucopyranoside (**11**).* To a solution of compound **10**[30] (4.21 g, 8.03 mmol, 1.0 equiv) in dry DCM (80 mL) were successively added *N*,*N*'-dicylcohexylcarbodiimide (DCC) (3.33 g, 16.1 mmol, 2.0 equiv), 4-dimethylaminopyridine (DMAP) (983 mg, 8.05 mmol, 1.0 equiv), and 2-azidomethylbenzoic acid[28] (2.13 g, 12.0 mmol, 1.5 equiv), and the mixture was refluxed for 6 h. After complete conversion, the suspension was cooled to 0 °C, filtered over Celite, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 7:3) gave the desired compound **11** (5.20 g, 95%) as a white amorphous solid: R_f 0.3 (Hex/EtOAc 7:3); $[\alpha]_D^{20}$ +27 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.88–7.85 (m, 1H, C*H*^{AZMB}), 7.63–7.54 (m, 2H, 2 × C*H*^{AZMB}), 7.44–7.37 (m, 3H, 3 × C*H*^{Ar}), 7.37–7.32 (m, 2H, 2 × C*H*^{Ar}), 7.11–7.06 (m, 2H, 2 × C*H*^{Ar}), 7.06–7.01 (m, 2H, C*H*^{Ar}), 6.93–6.88 (m, 2H, 2 × C*H*^{Ar}), 6.62–6.57 (m, 2H, 2 × C*H*^{Ar}), 5.55 (s, 1H, PMPC*H*O_2), 5.19 (dd, 1H, *J* = 10.0 Hz, *J* = 8.6 Hz, H-2), 4.80 (d, 1H, *J* = 15.0 Hz, CH*H*^{AZMB}), 4.77 (d, 1H, *J* = 10.1 Hz, H-1), 4.75 (d, 1H, *J* = 11.5 Hz, CH*H*^{PMB}), 4.74 (d, 1H, *J* = 15.0 Hz, C*H*H^{AZMB}), 4.56 (d, 1H, *J* = 11.5 Hz, C*H*H^{PMB}), 4.39 (dd, 1H, *J* = 10.5 Hz, *J* = 4.9 Hz, H-6a), 3.88–3.72 (m, 3H, H-3, H-6b, H-4), 3.81 (s, 3H, CH_3^{OMe}), 3.69 (s, 3H, CH_3^{OMe}), 3.53 (ddd, 1H, *J* = *J* = 9.9 Hz, *J* = 5.0 Hz, H-5), 2.33 (s, 3H, CH_3^{STol}); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm): 165.0 (O*C*=O), 160.2 (C^{Ar}), 159.3 (C^{Ar}), 138.8 (C^{Ar}), 137.8 (C^{Ar}), 133.7 (2C, 2 ×C*H*^{Ar}), 133.0 (*C*H^{AZMB}), 131.2 (*C*H^{AZMB}), 130.0 (C^{Ar}), 129.9 (2C, 2 × *C*H^{Ar}), 129.82 (2C, 2 × *C*H^{Ar}), 129.77 (C^{Ar}), 129.5 (*C*H^{AZMB}), 128.6 (C^{Ar}), 128.1, 128.0 (C^{Ar}, *C*H^{AZMB}), 127.5 (2C, 2 × *C*H^{Ar}), 113.8 (2C, 2 × *C*H^{Ar}), 113.7 (2C, 2 × *C*H^{Ar}), 101.4 (PMP*C*HO_2), 87.1 (C-1), 81.6, 79.2 (2C, C-3, C-4), 74.1 (*C*H_2^{PMB}), 72.1 (C-2), 70.8 (C-5), 68.7 (C-6), 55.5 (*C*H_3^{OMe}), 55.3 (*C*H_3^{OMe}), 53.0 (*C*H_2^{AZMB}), 21.3 (*C*H_3^{STol}); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{37}H_{37}N_3NaO_8S$ 706.2194; found 706.2190; *m*/*z*: [M + K]$^+$ calcd for $C_{37}H_{37}N_3KO_8S$ 722.1933; found 722.1926.

*4-Methylphenyl 2-O-(2-Azidomethylbenzoyl)-β-D-thioglucopyranoside (**12**).* To a solution of compound **11** (209 mg, 0.305 mmol, 1.0 equiv) in DCM/H_2O (10:1, 6.7 mL) was added DDQ (279 mg, 1.23 mmol, 4.0 equiv), and the mixture was stirred at rt for 6.5 h. After complete conversion of the starting material, saturated aq. $NaHCO_3$ (8.0 mL) was added and the solution was stirred for an additional 10 min (organic layer turned bright yellow). Next, the aqueous layer was extracted three times with DCM (3 × 15 mL) and the combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 3:7 followed by DCM/MeOH 9:1) gave the desired compound **12** (99 mg, 73%) as a white amorphous solid: R_f 0.3 (DCM/MeOH 9:1); $[\alpha]_D^{20}$ –23 (*c* 0.8, $CHCl_3$); ^1H NMR (600 MHz, MeOD) δ (ppm): 8.04–8.02 (m, 1H, C*H*^{AZMB}), 7.63–7.60 (m, 1H, C*H*^{AZMB}), 7.55–7.54 (m, 1H, C*H*^{AZMB}), 7.47–7.45 (m, 1H, C*H*^{AZMB}), 7.39–7.37 (m, 2H, 2 × C*H*^{STol}), 7.10–7.08 (m, 2H, 2 × C*H*^{STol}), 4.98 (dd, 1H, *J* = 9.9 Hz, *J* = 9.4 Hz, H-2), 4.86–4.84 (m, 1H, H-1), 4.82 (d, 1H, *J* = 14.3 Hz, CH*H*^{AZMB}), 4.76 (d, 1H, *J* = 14.3 Hz, C*H*H^{AZMB}), 3.92 (dd, 1H, *J* = 12.1 Hz, *J* = 1.9 Hz, H-6a), 3.73 (dd, 1H, *J* = 12.0 Hz, *J* = 5.6 Hz, H-6b), 3.71 (dd, 1H, *J* = *J* = 8.9 Hz, H-3), 3.45 (t, 1H, *J* = *J* = 9.7 Hz, H-4), 3.41 (ddd, 1H, *J* = 9.5 Hz, *J* = 5.4 Hz, *J* = 2.0 Hz, H-5), 2.29 (s, 3H, CH_3^{STol}); $^{13}C\{^1H\}$ NMR (150 MHz, MeOD) δ (ppm): 167.2 (O*C*=O), 139.1 (C^{Ar}), 138.3 (C^{Ar}), 133.8 (*C*H^{AZMB}), 133.5 (2C, 2 × *C*H^{STol}), 132.0 (*C*H^{AZMB}), 131.2 (*C*H^{AZMB}), 131.84 (C^{Ar}), 130.80 (C^{Ar}), 130.6 (2C, 2 × *C*H^{STol}), 129.3 (*C*H^{AZMB}), 87.7 (C-1), 82.3 (C-5), 77.5 (C-3), 74.6 (C-2), 71.5 (C-4), 62.7 (C-6), 53.6 (*C*H_2^{AZMB}), 21.1 (*C*H_3^{STol}); HRMS (ESI-TOF) *m*/*z*: [M + NH_4]$^+$ calcd for $C_{21}H_{27}N_4O_6S$ 463.1646; found 463.1629; *m*/*z*: [M + Na]$^+$ calcd for $C_{21}H_{23}N_3NaO_6S$ 468.1200; found 468.1184.

*4-Methylphenyl 3,4,6-Tri-O-acetyl-2-O-(2-azidomethylbenzoyl)-β-D-thioglucopyranoside (**4a**).* To a solution of compound **12** (1.64 g, 3.69 mmol, 1.0 equiv) in dry pyridine (19 mL) and Ac_2O (19 mL) was added DMAP (45 mg, 0.37 mmol, 0.1 equiv). The mixture was stirred at rt for 16 h. After complete conversion of the starting material, the crude was concentrated under reduced pressure and co-evaporated with toluene. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 7:3) gave the desired compound **4a** (2.00 g, 95%) as a white amorphous solid: R_f 0.25 (Hex/EtOAc 7:3); $[\alpha]_D^{20}$ +35 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.97–7.96 (m, 1H, C*H*^{AZMB}), 7.61–7.58 (m, 1H, C*H*^{AZMB}), 7.53–7.52 (m, 1H, C*H*^{AZMB}), 7.45–7.42 (m, 1H, C*H*^{AZMB}), 7.38–7.37 (m, 2H, 2 × C*H*^{STol}), 7.11–7.10 (m, 2H, 2 × C*H*^{STol}), 5.39 (t, 1H, *J* = 9.4 Hz, H-3), 5.19 (t, 1H, *J* = 9.7 Hz, H-2), 5.10 (t, 1H, *J* = 9.8 Hz, H-4), 4.84 (d, 1H, *J* = 14.4 Hz, CH*H*^{AZMB}), 4.78 (d, 1H, *J* = 10.1 Hz, H-1), 4.73 (d, 1H, *J* = 14.4 Hz, C*H*H^{AZMB}), 4.26 (dd, 1H, *J* = 12.2 Hz, *J* = 5.0 Hz, H-6a), 4.22 (dd, 1H, *J* = 12.2 Hz, *J* = 2.5 Hz, H-6b), 3.78 (ddd, 1H, *J* = 10.1 Hz, *J* = 5.0 Hz, *J* = 2.5 Hz, H-5), 2.34 (s, 3H, CH_3^{STol}), 2.11 (s, 3H, CH_3^{Ac}), 2.03 (s, 3H, CH_3^{Ac}), 1.94 (s, 3H, CH_3^{Ac}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 170.6 (O*C*=O), 170.2 (O*C*=O), 169.4 (O*C*=O), 164.9 (O*C*=O), 138.9 (C^{Ar}), 137.5 (C^{Ar}), 133.9 (2C, 2 × *C*H^{STol}), 133.1 (*C*H^{AZMB}), 131.1 (*C*H^{AZMB}), 129.9 (*C*H^{AZMB}), 129.7 (2C, 2 × *C*H^{STol}), 128.4 (*C*H^{AZMB}), 128.1 (C^{Ar}), 127.4 (C^{Ar}), 85.9 (C-1), 75.9 (C-5), 73.9 (C-3), 70.4 (C-2), 68.3 (C-4), 62.2 (C-6), 52.8 (*C*H_2^{AZMB}), 21.2 (*C*H_3^{STol}), 20.8 (*C*H_3^{Ac}), 20.60 (*C*H_3^{Ac}), 20.57 (*C*H_3^{Ac}); HRMS (ESI-TOF) *m*/*z*: [M + NH_4]$^+$ calcd for $C_{27}H_{33}N_4O_9S$ 589.1963; found 589.1957; *m*/*z*: [M + Na]$^+$ calcd for $C_{27}H_{29}N_3NaO_9S$ 594.1517; found 594.1510.

*4-Methylphenyl 3,4,6-Tri-O-acetyl-2-O-(2-azidomethylbenzoyl)-β-D-glucopyranosyl Sulfoxide (**4b**).* To a solution of thioglycoside **4a** (103 mg, 0.181 mmol, 1.0 equiv) in dry DCM (875 μL) cooled to –78 °C was added *m*CPBA (37 mg, 0.21 mmol, 1.2 equiv), and the mixture was immediately placed in a –10 °C bath and stirred for 3.5 h. Then, the crude was washed with saturated aq. $NaHCO_3$ (3 mL) and extracted three times with DCM (3 × 3 mL). The combined organic layers were washed with brine (10 mL), filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 7:3 to 4:6) gave the desired compound **4b** (80 mg, 75%, 2:1 mixture of diastereoisomers) as a white amorphous solid: R_f 0.2 (Hex/EtOAc

1:1); major compound data: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.77–7.76 (m, 1H, C*H*^{AZMB}), 7.61–7.49 (m, 4H, 4 × C*H*^{Ar}), 7.38–7.35 (m, 1H, C*H*^{AZMB}), 7.20–7.19 (m, 2H, 2 × C*H*^{SOTol}), 5.50 (t, 1H, *J* = 9.5 Hz, H-2), 5.43 (t, 1H, *J* = 9.2 Hz, H-3), 5.04 (dd, 1H, *J* = 10.0 Hz, *J* = 9.2 Hz, H-4), 4.83 (d, 1H, *J* = 14.6 Hz, CH*H*^{AZMB}), 4.70 (d, 1H, *J* = 14.6 Hz, C*H*H^{AZMB}), 4.54 (d, 1H, *J* = 9.7 Hz, H-1), 4.21–4.15 (m, 2H, H-6a, H-6b), 3.78 (ddd, 1H, *J* = 10.0 Hz, *J* = 4.4 Hz, *J* = 2.7 Hz, H-5), 2.31 (s, 3H, C*H*$_3^{SOTol}$), 2.03 (s, 3H, C*H*$_3^{Ac}$), 2.02 (s, 3H, C*H*$_3^{Ac}$), 1.95 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 170.5 (O*C*=O), 170.3 (O*C*=O), 169.4 (O*C*=O), 164.8 (O*C*=O^{AZMB}), 142.4 (C^{Ar}), 137.9 (C^{Ar}), 135.7 (C^{Ar}), 133.4 (*C*H^{AZMB}), 131.3 (*C*H^{AZMB}), 129.9 (*C*H^{AZMB}), 129.7 (2C, 2 × *C*H^{SOTol}), 128.3 (*C*H^{AZMB}), 127.4 (C^{Ar}), 125.8 (2C, 2 × *C*H^{SOTol}), 92.6 (C-1), 76.6 (C-5), 73.6 (C-3), 68.1 (C-2), 67.7 (C-4), 61.6 (C-6), 53.0 (*C*H^{AZMB}), 21.5 (*C*H$_3^{SOTol}$), 20.8 (*C*H$_3^{Ac}$), 20.7 (*C*H$_3^{Ac}$), 20.6 (*C*H$_3^{Ac}$); minor compound data: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.96–7.95 (m, 1H, C*H*^{AZMB}), 7.61–7.49 (m, 4H, 4 × C*H*^{Ar}), 7.44–7.42 (m, 1H, C*H*^{AZMB}), 7.30–7.28 (m, 2H, 2 × C*H*^{SOTol}), 5.56 (t, 1H, *J* = 9.5 Hz, H-2), 5.45 (t, 1H, *J* = 9.3 Hz, H-3), 5.08 (t, 1H, *J* = 9.7 Hz, H-4), 4.87 (d, 1H, *J* = 14.6 Hz, CH*H*^{AZMB}), 4.72 (d, 1H, *J* = 14.6 Hz, C*H*H^{AZMB}), 4.41 (d, 1H, *J* = 9.8 Hz, H-1), 4.21–4.15 (m, 1H, H-6a), 4.10 (dd, 1H, *J* = 12.3 Hz, *J* = 2.4 Hz, H-6b), 3.72 (ddd, 1H, *J* = 10.0 Hz, *J* = 5.6 Hz, *J* = 2.4 Hz, H-5), 2.38 (s, 3H, C*H*$_3^{SOTol}$), 2.02 (s, 3H, C*H*$_3^{Ac}$), 2.00 (s, 3H, C*H*$_3^{Ac}$), 1.96 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 170.5 (O*C*=O), 170.4 (O*C*=O), 169.4 (O*C*=O), 164.7 (O*C*=O^{AZMB}), 142.5 (C^{Ar}), 137.8 (C^{Ar}), 135.5 (C^{Ar}), 133.4 (*C*H^{AZMB}), 131.4 (*C*H^{AZMB}), 130.0 (*C*H^{AZMB}), 129.8 (2C, 2 × *C*H^{SOTol}), 128.4 (*C*H^{AZMB}), 127.7 (C^{Ar}), 126.0 (2C, 2 × *C*H^{SOTol}), 90.2 (C-1), 76.8 (C-5), 73.8 (C-3), 68.2 (C-2), 68.0 (C-4), 61.9 (C-6), 53.0 (*C*H^{AZMB}), 21.6 (*C*H$_3^{SOTol}$), 20.7 (*C*H$_3^{Ac}$), 20.67 (*C*H$_3^{Ac}$), 20.66 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{27}H_{29}N_3NaO_{10}S$ 610.1449; found 610.1466.

*3,4,6-Tri-O-acetyl-2-O-(2-azidomethylbenzoyl)-α-D-glucopyranose (**13**) and 3,4,6-Tri-O-acetyl-1-O-(2-azidomethylbenzoyl)-α-D-glucopyranose (**14**).* To a solution of thioglycoside **4a** (200 mg, 0.350 mmol, 1.0 equiv) in DCM (4.0 mL) were added tri-*tert*-butylpyridine (209 mg, 0.839 mmol, 2.4 equiv) and Ph_2SO (105 mg, 0.464 mmol, 1.3 equiv) and the mixture was cooled to −78 °C before the addition of Tf_2O (78 μL, 0.46 mmol, 1.3 equiv). Next, water (400 μL) was added and the reaction was stirred at rt for 30 min. Then, the crude was washed with saturated aq. $NaHCO_3$ (2 mL), the organic layer was filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 7:3 to 6:4) gave an inseparable mixture of compounds **13** and **14** (120 mg, 74%, 1:2 **13**/**14** ratio) as a white amorphous solid: R_f 0.4 (Hex/EtOAc 1:1); compound **14** data: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.10–8.09 (m, 1H, C*H*^{AZMB}), 7.65–7.63 (m, 1H, C*H*^{AZMB}), 7.53–7.47 (m, 2H, 2 × C*H*^{AZMB}), 6.50 (d, 1H, *J* = 3.8 Hz, H-1), 5.38 (t, 1H, *J* = 9.8 Hz, H-3), 5.17 (t, 1H, *J* = 9.8 Hz, H-4), 4.86 (d, 1H, *J* = 14.4 Hz, CH*H*^{AZMB}), 4.71 (d, 1H, *J* = 14.4 Hz, C*H*H^{AZMB}), 4.30 (dd, 1H, *J* = 12.3 Hz, *J* = 4.0 Hz, H-6a), 4.11–4.06 (m, 2H, H-5, H-6b), 4.03–3.99 (m, 1H, H-2), 2.89 (br d, 1H, *J* = 8.6 Hz, O*H*), 2.13 (s, 3H, C*H*$_3^{Ac}$), 2.08 (s, 3H, C*H*$_3^{Ac}$), 2.05 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 171.6 (O*C*=O), 170.8 (O*C*=O), 169.6 (O*C*=O), 165.0 (O*C*=O^{AZMB}), 137.4 (C^{AZMB}), 133.7 (*C*H^{AZMB}), 131.8 (*C*H^{AZMB}), 130.7 (*C*H^{AZMB}), 128.9 (*C*H^{AZMB}), 128.1 (C^{AZMB}), 92.5 (C-1), 73.4 (C-3), 70.29 (C-5*), 70.27 (C-2*), 67.5 (C-4), 61.7 (C-6), 53.7 (*C*H$_2^{AZMB}$), 21.0 (*C*H$_3^{Ac}$), 20.83 (*C*H$_3^{Ac}$), 20.76 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{23}N_3NaO_{10}$ 488.1276; found 488.1290 (as a mixture with compound **13**); compound **13** data: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.04–8.02 (m, 1H, C*H*^{AZMB}), 7.60–7.57 (m, 1H, C*H*^{AZMB}), 7.53–7.47 (m, 1H, C*H*^{AZMB}), 7.45–7.43 (m, 1H, C*H*^{AZMB}), 5.73 (t, 1H, *J* = 9.8 Hz, H-3), 5.61 (br s, 1H, H-1), 5.17 (t, 1H, *J* = 9.9 Hz, H-4), 5.14 (dd, 1H, *J* = 10.1 Hz, *J* = 3.7 Hz, H-2), 4.82 (d, 1H, *J* = 14.4 Hz, CH*H*^{AZMB}), 4.73 (d, 1H, *J* = 14.4 Hz, C*H*H^{AZMB}), 4.34 (ddd, 1H, *J* = 10.2 Hz, *J* = 4.3 Hz, *J* = 2.3 Hz, H-5), 4.29 (dd, 1H, *J* = 12.3 Hz, *J* = 4.3 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.3 Hz, *J* = 2.3 Hz, H-6b), 3.57 (br s, 1H, O*H*), 2.12 (s, 3H, C*H*$_3^{Ac}$), 2.06 (s, 3H, C*H*$_3^{Ac}$), 1.98 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 170.9 (O*C*=O), 170.4 (O*C*=O), 169.8 (O*C*=O), 165.7 (O*C*=O^{AZMB}), 137.5 (C^{AZMB}), 133.6 (*C*H^{AZMB}), 132.0 (*C*H^{AZMB}), 130.4 (*C*H^{AZMB}), 128.8 (*C*H^{AZMB}), 127.8 (C^{AZMB}), 90.3 (C-1), 72.2 (C-2), 70.0 (C-3), 68.5 (C-4), 67.6 (C-5), 62.1 (C-6), 53.5 (*C*H$_2^{AZMB}$), 20.92 (*C*H$_3^{Ac}$), 20.86 (*C*H$_3^{Ac}$), 20.8 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{23}N_3NaO_{10}$ 488.1276; found 488.1290 (as a mixture with compound **14**).

*Trichloroacetimidate 3,4,6-Tri-O-acetyl-2-O-(2-azidomethylbenzoyl)-α-D-glucopyranoside (**4c**).* To a solution of compounds **13** and **14** (104 mg, 0.223 mmol, 1.0 equiv) in acetone (3.6 mL) were added Cs_2CO_3 (205 mg, 0.630 mmol, 2.8 equiv) and CCl_3CN (315 μL, 2.65 mmol, 12 equiv) and the mixture was stirred at rt for 22 h. Then, the crude was filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 7:3) gave the desired compound **4c** (80 mg, 59%) as a colorless oil: R_f 0.5 (Hex/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 1H, N*H*), 7.95–7.94 (m, 1H, C*H*^{AZMB}), 7.59–7.56 (m, 1H, C*H*^{AZMB}), 7.51–7.50 (m, 1H, C*H*^{AZMB}), 7.39–7.36 (m, 1H, C*H*^{AZMB}), 6.71 (d, 1H, *J* = 3.7 Hz, H-1), 5.77 (t, 1H, *J* = 9.8 Hz, H-3), 5.37 (dd, 1H, *J* = 10.2 Hz, *J* = 3.7 Hz, H-2), 5.28 (t, 1H, *J* = 9.8 Hz, H-4), 4.85 (d, 1H, *J* = 14.8 Hz, CH*H*^{AZMB}), 4.76 (d, 1H, *J* = 14.8 Hz, C*H*H^{AZMB}), 4.33–4.27 (m, 2H, H-5, H-6a), 4.18 (dd, 1H, *J* = 12.0 Hz, *J* = 1.6 Hz, H-6b), 2.10 (s, 3H, C*H*$_3^{Ac}$), 2.08 (s, 3H, C*H*$_3^{Ac}$), 2.00 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 170.8 (O*C*=O), 170.2 (O*C*=O), 169.6 (O*C*=O), 165.2 (O*C*=O^{AZMB}), 160.6 (*C*=N), 138.3 (C^{AZMB}), 133.7 (*C*H^{AZMB}), 131.6 (*C*H^{AZMB}), 129.9 (*C*H^{AZMB}), 128.4 (*C*H^{AZMB}), 127.0 (C^{AZMB}), 93.0 (C-1), 90.7 (*C*Cl$_3$), 70.4 (C-2), 70.3 (C-5), 69.9 (C-3), 67.8 (C-4), 61.5 (C-6), 53.1 (*C*H$_2^{AZMB}$), 20.83 (*C*H$_3^{Ac}$), 29.79 (*C*H$_3^{Ac}$), 20.7 (*C*H$_3^{Ac}$); this compound was too unstable to obtain an HRMS.

*4-Methylphenyl 2,3-Di-O-acetyl-4,6-O-(4-methoxybenzylidene)-β-D-thioglucopyranoside (**16**).* To a solution of compound **15**[33] (651 mg, 1.61 mmol, 1.0 equiv) in dry pyridine (4.0 mL) and Ac_2O (4.0 mL) was added DMAP (20 mg, 0.16 mmol, 0.1 equiv), and the mixture was stirred at rt for 16 h. After complete conversion of the starting material, the solution was concentrated under reduced pressure and co-evaporated with toluene. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 5:5) gave the desired compound **16** (703 mg, 90%) as a white amorphous solid: R_f 0.2 (Hex/EtOAc 8:2); $[\alpha]_D^{20}$ −40 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39–7.36 (m, 2H, 2 × C*H*^{Ar}), 7.35–7.32 (m, 2H, 2 × C*H*^{Ar}), 7.16–7.13 (m, 2H, 2 × C*H*^{Ar}), 6.89–6.84 (m, 2H, 2 × C*H*^{Ar}), 5.44 (s, 1H, PMPC*H*O$_2$), 5.31 (t, 1H, *J* = 9.2 Hz, H-3), 4.96 (dd, 1H, *J* = 9.9 Hz, *J* = 9.1 Hz, H-2), 4.73 (d, 1H, *J* = 10.0 Hz, H-1), 4.35 (dd, 1H, *J* = 10.6 Hz, *J* = 5.0 Hz, H-6a), 3.79 (s, 3H, C*H*$_3^{OMe}$), 3.76 (t, 1H, *J* = 10.3 Hz, H-6b), 3.62 (t, 1H, *J* = 9.6 Hz, H-4), 3.53 (td, 1H, *J* = *J* = 9.7 Hz, *J* = 5.0 Hz, H-5), 2.36 (s, 3H, C*H*$_3^{STol}$), 2.10 (s, 3H, C*H*$_3^{Ac}$), 2.02 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ (ppm): 170.3 (O*C*=O), 169.7 (O*C*=O), 160.3 (C^{Ar}), 138.9 (C^{Ar}), 133.8 (2C, 2 × *C*H^{Ar}), 129.9 (2C, 2 × *C*H^{Ar}), 129.4 (C^{Ar}), 127.9 (C^{Ar}), 127.6 (2C, 2 × *C*H^{Ar}), 113.7 (2C, 2 × *C*H^{Ar}), 101.6 (PMP*C*HO$_2$), 86.9 (C-1), 78.2 (C-4), 73.1 (C-3), 71.0 (C-2), 70.8 (C-5), 68.5 (C-6), 55.4 (*C*H$_3^{OMe}$), 21.3 (*C*H$_3^{STol}$), 21. 0 (*C*H$_3^{Ac}$), 20.9 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{29}O_8S$ 489.1578; found 489.1577; *m/z*: [M + Na]$^+$ calcd for $C_{25}H_{28}NaO_8S$ 511.1397; found 511.1399.

*4-Methylphenyl 2,3-Di-O-acetyl-β-D-thioglucopyranoside (**17**).* To a solution of compound **16** (2.06 g, 4.22 mmol, 10 equiv) in DCM/H_2O (10:1, 90 mL) was added DDQ (2.80 g, 12.4 mmol, 2.9 equiv), and the mixture was stirred at rt for 16 h. After complete conversion of the starting material, saturated aq. $NaHCO_3$ (80 mL) was added, and the solution was stirred for an additional 10 min (organic layer turned bright yellow). Next, the aqueous layer was extracted three times with DCM (3 × 40 mL) and the combined organic layers were successively washed with saturated aq.

$NaHCO_3$ (80 mL), brine (80 mL), filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 3:7) gave the desired compound **17** (1.31 g, 84%) as a white foaming oil: R_f 0.2 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[34]

*4-Methylphenyl 2,3,6-Tri-O-acetyl-β-D-thioglucopyranoside (**5a**).* To a cooled solution of compound **17** (547 mg, 1.48 mmol, 1.0 equiv) in dry DMF (6.7 mL) and dry *sym*-collidine (6.7 mL) at −10 °C was added AcCl (210 μL, 2.96 mmol, 2.0 equiv) dropwise. After stirring at this temperature for 1 h, MeOH (7.0 mL) was added to quench the reaction. The mixture was then concentrated under reduced pressure, resolubilized in EtOAc (15 mL), and washed with 1.0 M HCl (3 × 15 mL) and saturated aq. $NaHCO_3$ (15 mL). Finally, the organic layer was filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 7:3 to 3:7) gave the desired compound **5a** (457 mg, 75%) as a white amorphous solid: R_f 0.5 (Hex/EtOAc 3:7). Physical and analytical data agreed with those published.[60]

*4-Methylphenyl 3,4-Di-O-benzyl-β-D-thioglucopyranoside (**19**).* To a cooled solution of compound **18**[36] (2.27 g, 4.89 mmol, 1.0 equiv) in dry DCE (50 mL) at 0 °C was added BH_3·THF (1.0 M in THF, 25 mL, 25 mmol, 5.0 equiv) followed by TMSOTf (135 μL, 0.744 mmol, 0.15 equiv). The mixture was stirred for 5 h at rt, after which Et_3N (1.0 mL, 14 mmol, 2.8 equiv) and MeOH (5.0 mL) were successively added to quench the reaction. Finally, the mixture was concentrated under reduced pressure and co-evaporated with MeOH. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 6:4) gave the desired compound **19** (1.83 mg, 80%) as a white amorphous solid: R_f 0.5 (Hex/EtOAc 6:4). Physical and analytical data agreed with those published.[38]

*4-Methylphenyl 6-O-Acetyl-3,4-di-O-benzyl-β-D-thioglucopyranoside (**20**).* To a cooled solution of compound **19** (1.04 g, 2.24 mmol, 1.0 equiv) in dry DMF (10 mL) and dry pyridine (10 mL) at −10 °C was added AcCl (310 μL, 4.48 mmol, 2.0 equiv) dropwise. The mixture was stirred at −10 °C for 1 h, after which additional AcCl (160 μL, 2.25 mmol, 1.0 equiv) was added. The mixture was stirred for an additional 30 min at −10 °C then quenched with MeOH (2.0 mL, 79 mmol, 35 equiv). Next, the mixture was concentrated under reduced pressure, resolubilized in EtOAc (20 mL), and washed with 1.0 M aq HCl (3 × 20 mL) and saturated aq. $NaHCO_3$ (20 mL). The organic layer was filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 8:2) gave the desired compound **20** (770 mg, 68%) as a white amorphous solid: R_f 0.4 (Hex/EtOAc 7:3). Physical and analytical data agreed with those published.[38]

*4-Methylphenyl 6-O-Acetyl-2-O-(2-azidomethylbenzoyl)-3,4-di-O-benzyl-β-D-thioglucopyranoside (**6**).* To a solution of compound **20** (655 mg, 1.29 mmol, 1.0 equiv) in dry DCM (13 mL) were successively added DCC (532 mg, 2.58 mmol, 2.0 equiv), DMAP (158 mg, 1.29 mmol, 1.0 equiv), and 2-azidomethylbenzoic acid[28] (342 mg, 1.93 mmol, 1.5 equiv) and the mixture was refluxed for 5 h. After complete conversion of the starting material, the suspension was cooled to 0 °C, filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 8:2) gave the desired compound **6** (869 mg, quant.) as a white amorphous solid: R_f 0.3 (Hex/EtOAc 7:3); $[\alpha]_D^{20}$ +26 (*c* 0.8, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.95–7.94 (m, 1H, C*H*^{AZMB}), 7.60–7.57 (m, 1H, C*H*^{AZMB}), 7.55–7.53 (m, 1H, C*H*^{AZMB}), 7.41–7.38 (m, 1H, C*H*^{AZMB}), 7.37–7.25 (m, 7H, 7 × C*H*^{Ar}), 7.16–7.12 (m, 5H, 5 × C*H*^{Ar}), 7.08–7.07 (m, 2H, 2 × C*H*^{Ar}), 5.20 (t, 1H, *J* = 9.6 Hz, H-2), 4.84 (d, 1H, *J* = 10.9 Hz, CH*H*^{Bn}), 4.82 (d, 1H, *J* = 14.7 Hz, CH*H*^{AZMB}), 4.77 (d, 1H, *J* = 11.3 Hz, CH*H*^{Bn}), 4.71 (d, 1H, *J* = 9.9 Hz, H-1), 4.69 (d, 1H, *J* = 14.7 Hz, C*H*H^{AZMB}), 4.63 (d, 1H, *J* = 11.3 Hz, C*H*H^{Bn}), 4.59 (d, 1H, *J* = 10.9 Hz, C*H*H^{Bn}), 4.45 (dd, 1H, *J* = 11.6 Hz, *J* = 1.6 Hz, H-6a), 4.20 (dd, 1H, *J* = 11.6 Hz, *J* = 4.6 Hz, H-6b), 3.83 (t, 1H, *J* = 8.7 Hz, H-3), 3.65–3.60 (m, 2H, H-4, H-5), 2.32 (s, 3H, C*H*$_3^{STol}$), 2.06 (s, 3H, C*H*$_3^{Ac}$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 170.7 (O*C*=O), 165.1 (O*C*=O), 138.5 (C^{Ar}), 137.9 (C^{Ar}), 137.7 (C^{Ar}), 137.5 (C^{Ar}), 133.6 (2C, 2 × *C*H^{STol}), 133.1 (*C*H^{AZMB}), 131.1 (*C*H^{AZMB}), 129.7 (2C, 2 × *C*H^{STol}), 129.6 (*C*H^{AZMB}), 128.7 (2C, 2 × *C*H^{Bn}), 128.5 (C^{Ar}), 128.43, 128.40 (3C, 2 × *C*H^{Bn}, C^{Ar}*), 128.3, 128.2 (3C, 3 × *C*H^{Bn}*), 128.1 (*C*H^{AZMB}), 127.94, 127.92 (3C, 3 × *C*H^{Bn}), 86.2 (C-1), 84.5 (C-3), 77.6, 77.3 (C-4, C-5), 75.5, 75.3 (2C, 2 × *C*H$_2^{Bn}$), 72.3 (C-2), 63.0 (C-6), 53.0 (*C*H$_2^{AZMB}$), 21.3 (*C*H$_3$), 21.0 (*C*H$_3$); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{37}H_{41}N_4O_7S$ 685.2690; found 685.2693.

*4-Methylphenyl 2-O-(2-Azidomethylbenzoyl)-3-O-benzyl-4,6-O-benzylidene-β-D-thioglucopyranoside (**21**).* To a solution of compound **18** (504 mg, 1.09 mmol, 1.0 equiv) in dry DCM (10 mL) were successively added DCC (467 mg, 2.26 mmol, 2.1 equiv), DMAP (130 mg, 1.07 mmol, 1.0 equiv), and 2-azidomethylbenzoic acid[28] (272 mg, 1.54 mmol, 1.4 equiv) and the mixture was refluxed for 5 h. After complete conversion of the starting material, the suspension was cooled to 0 °C, filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 95:5 to 8:2) gave thedesired compound **21** (678 mg, quant.) as a white amorphous solid: R_f 0.4 (Hex/EtOAc 8:2); $[\alpha]_D^{20}$ +15 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91–7.88 (m, 1H, C*H*^{AZMB}), 7.63–7.54 (m, 2H, 2 × C*H*^{Ar}), 7.51–7.47 (m, 2H, 2 × C*H*^{Ar}), 7.42–7.33 (m, 6H, 6 × C*H*^{Ar}), 7.16–7.06 (m, 7H, 7 × C*H*^{Ar}), 5.60 (s, 1H, PhC*H*O$_2$), 5.19 (dd, 1H, *J* = 10.0 Hz, *J* = 8.6 Hz, H-2), 4.85 (d, 1H, *J* = 11.9 Hz, CH*H*^{Ar}), 4.81 (d, 1H, *J* = 14.9 Hz, CH*H*^{Ar}), 4.79 (d, 1H, *J* = 10.0 Hz, H-1), 4.71 (d, 1H, *J* = 14.9 Hz, C*H*H^{Ar}), 4.64 (d, 1H, *J* = 11.9 Hz, C*H*H^{Ar}), 4.39 (dd, 1H, *J* = 10.5 Hz, *J* = 5.0 Hz, H^{6a}), 3.88 (dd, 1H, *J* = 9.2 Hz, *J* = 8.6 Hz, H-3), 3.85 (dd, 1H, *J* = 10.5 Hz, *J* = 7.5 Hz, H-6b), 3.80 (dd, 1H, *J* = 9.2 Hz, *J* = 9.1 Hz, H-4), 3.56 (ddd, 1H, *J* = 9.8 Hz, *J* = 9.1 Hz, *J* = 5.0 Hz, H-5), 2.33 (s, 3H, C*H*$_3^{STol}$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1 (O*C*=O), 138.8 (C^{Ar}), 137.9 (C^{Ar}), 137.8 (C^{Ar}), 137.3 (C^{Ar}), 133.8 (2C, 2 × *C*H^{Ar}), 133.0 (*C*H^{AZMB}), 131.1 (*C*H^{AZMB}), 129.9 (2C, 2 × *C*H^{Ar}), 129.6 (*C*H^{Ar}), 129.2 (*C*H^{Ar}), 128.6 (C^{Ar}), 128.5 (2C, 2 × *C*H^{Ar}), 128.3 (2C, 2 × *C*H^{Ar}), 128.1 (3C, 3 × *C*H^{Ar}), 128.0 (C^{Ar}), 127.8 (*C*H^{Ar}), 126.1 (2C, 2 × *C*H^{Ar}), 101.4 (Ph*C*HO$_2$), 87.1 (C-1), 81.7 (C-4), 79.8 (C-3), 74.5 (*C*H$_2^{Bn}$), 72.1 (C-2), 70.7 (C-5), 68.7 (C-6), 53.0 (*C*H$_2^{AZMB}$), 21.3 (*C*H$_3^{STol}$); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{35}H_{33}N_3NaO_6S$ 646.1982; found 646.1939; *m/z*: $[M + Ag]^+$ calcd for $C_{35}H_{33}AgN_3O_6S$ 730.1136; found 730.1099.

*4-Methylphenyl 2-O-(2-Azidomethylbenzoyl)-3,6-di-O-benzyl-β-D-thioglucopyranoside (**22**).* Compound **21** (799 mg, 1.28 mmol, 1.0 equiv) was dissolved in dry DCM (13 mL). The solution was cooled at 0 °C and Et_3SiH (2.5 mL, 15 mmol, 12.0 equiv) and BF_3·Et_2O (320 μL, 2.56 mmol, 2.0 equiv) were successively added. The solution was stirred while being allowed to gradually warm to rt during 2.5 h. The solution was diluted with DCM (20 mL) and washed with saturated aq. $NaHCO_3$ (20 mL). The organic layer was filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 7:3) gave the desired compound **22** (724 mg, 90%) as a white amorphous solid: R_f 0.3 (Hex/EtOAc 7:3); $[\alpha]_D^{20}$ −7 (*c* 0.9, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.97–7.95 (m, 1H, C*H*^{AZMB}), 7.60–7.58 (m, 1H, C*H*^{AZMB}), 7.55–7.54 (m, 1H, C*H*^{AZMB}), 7.42–7.39 (m, 1H, C*H*^{AZMB}), 7.38–7.30 (m, 7H, 7 × C*H*^{Ar}), 7.19–7.16 (m, 5H, 5 × C*H*^{Ar}), 7.05–7.02 (m, 2H, 2 × C*H*^{Ar}), 5.20 (t, 1H, *J* = 9.6 Hz, H-2), 4.82 (d, 1H, *J* = 14.8 Hz, CH*H*^{AZMB}), 4.74 (d, 1H, *J* = 9.8 Hz, H-1), 4.73 (d, 1H, *J* = 14.8 Hz, C*H*H^{AZMB}), 4.71 (d, 1H, *J* = 11.8 Hz, CH*H*^{Bn}), 4.69 (d, 1H, *J* = 11.8 Hz, C*H*H^{Bn}), 4.60 (d, 1H, *J* = 11.8 Hz, CH*H*^{Bn}), 4.57 (d, 1H, *J* = 11.8 Hz, C*H*H^{Bn}), 3.81 (d, 2H, *J* = 4.7 Hz, H-6a, H-6b), 3.78 (t, 1H, *J* = 9.2 Hz, H-4), 3.68 (t, 1H, *J* = 9.0 Hz, H-3), 3.57 (dt, 1H, *J* = 9.6 Hz, *J* = 4.7 Hz,

H-5), 2.79 (br s, 1H, O*H*), 2.30 (s, 3H, CH_3^{STol}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 165.2 (O*C*=O), 138.4 (C^{Ar}), 138.0 (C^{Ar}), 137.9 (C^{Ar}), 137.8 (C^{Ar}), 133.4 (2C, 2 × *C*H^{Ar}), 133.0 (*C*H^{AZMB}), 131.1 (*C*H^{AZMB}), 129.8 (2C, 2 × *C*H^{Ar}), 129.6 (*C*H^{AZMB}), 128.68 (C^{Ar}), 128.65 (C^{Ar}), 128.6 (2C, 2 × *C*H^{Ar}), 128.5 (2C, 2 × *C*H^{Ar}), 128.1 (*C*H^{AZMB}), 127.98 (2C, 2 × *C*H^{Ar}), 127.97 (2C, 2 × *C*H^{Ar}), 127.9 (2C, 2 × *C*H^{Ar}), 86.5 (C-1), 83.9 (C-3), 78.4 (C-5), 74.8 (*C*H_2^{Bn}), 73.8 (*C*H_2^{Bn}), 72.2 (C-4), 72.1 (C-2), 70.5 (C-6), 53.0 (*C*H_2^{AZMB}), 21.3 (*C*H_3^{STol}); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{35}H_{35}N_3NaO_6S$ 648.2139; found 648.2138.

*4-Methylphenyl 2-O-(2-Azidomethylbenzoyl)-3,6-di-O-benzyl-4-O-levulinoyl-β-D-thioglucopyranoside (**7a**).* To a solution of compound **22** (887 mg, 1.42 mmol, 1.0 equiv) in dry pyridine (13 mL) were successively added DMAP (433 mg, 3.55 mmol, 2.5 equiv) and a solution of levulinic anhydride[61] in dry pyridine (0.5 M, 13.0 mL, 6.46 mmol, 1.0 equiv). The mixture was stirred at 50 °C for 5 h. After complete conversion of the starting material, the solution was concentrated under reduced pressure. Purification by silica gel flash chromatography (Tol/EtOAc 95:5) gave the desired compound **7a** (978 mg, 95%) as a white amorphous solid: R_f 0.3 (Tol/EtOAc 9:1); $[\alpha]_D^{20}$ +16 (*c* 3.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.94–7.92 (m, 1H, C*H*^{AZMB}), 7.60–7.57 (m, 1H, C*H*^{AZMB}), 7.55–7.53 (m, 1H, C*H*^{AZMB}), 7.41–7.37 (m, 3H, 3 × C*H*^{Ar}), 7.34–7.34 (m, 4H, 4 × C*H*^{Ar}), 7.31–7.28 (m, 1H, C*H*^{Ar}), 7.15–7.10 (m, 5H, C*H*^{Ar}), 7.02–7.00 (m, 2H, 2 × C*H*^{Ar}), 5.25 (dd, 1H, *J* = 9.8 Hz, *J* = 9.3 Hz, H-2), 5.11 (dd, 1H, *J* = 9.8 Hz, *J* = 9.4 Hz, H-4), 4.80 (d, 1H, *J* = 14.9 Hz, CH*H*^{AZMB}), 4.77 (d, 1H, *J* = 10.0 Hz, H-1), 4.69 (d, 1H, *J* = 14.9 Hz, CH*H*^{AZMB}), 4.60 (d, 1H, *J* = 11.5 Hz, CH*H*^{Bn}), 4.55 (d, 1H, *J* = 11.5 Hz, C*H*H^{Bn}), 4.54 (d, 1H, *J* = 11.6 Hz, CH*H*^{Bn}), 4.53 (d, 1H, *J* = 11.6 Hz, C*H*H^{Bn}), 3.87 (t, 1H, *J* = 9.1 Hz, H-3), 3.70 (ddd, 1H, *J* = 9.4 Hz, *J* = 5.7 Hz, *J* = 3.5 Hz, H-5), 3.66–3.62 (m, 2H, H-6a, H-6b), 2.67–2.55 (m, 2H, C*H*^{Lev}), 2.44 (ddd, 1H, *J* = 17.3 Hz, *J* = 7.6 Hz, *J* = 5.8 Hz, C*H*^{Lev}), 2.34 (dt, 1H, *J* = 17.4 Hz, *J* = 6.4 Hz, C*H*^{Lev}), 2.29 (s, 3H, CH_3^{STol}), 2.12 (s, 3H, CH_3^{Lev}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 206.3 (*C*=O^{Lev}), 171.6(O*C*=O), 165.0 (O*C*=O), 138.4 (C^{Ar}), 138.3 (C^{Ar}), 137.84 (C^{Ar}), 137.79 (C^{Ar}), 133.2 (2C, 2 × *C*H^{STol}), 133.1 (*C*H^{AZMB}), 131.1 (*C*H^{AZMB}), 129.8 (2C, 2 × *C*H^{STol}), 129.6 (*C*H^{AZMB}), 128.7 (C^{Ar}), 128.6 (C^{Ar}), 128.5 (2C, 2 × *C*H^{Bn}), 128.4 (2C, 2 × *C*H^{Bn}), 128.1 (*C*H^{AZMB}), 127.91 (2C, 2 × *C*H^{Bn}), 127.85 (2C, 2 × *C*H^{Bn}), 127.8 (*C*H^{Bn}), 127.7 (*C*H^{Bn}), 86.5 (C-1), 81.7 (C-3), 78.0 (C-5), 74.2 (*C*H_2^{Bn}), 73.7 (*C*H_2^{Bn}), 72.1 (C-2), 71.1 (C-4), 69.8 (C-6), 52.9 (*C*H_2^{AZMB}), 37.8 (*C*H_2^{Lev}), 29.9 (*C*H_3^{Lev}), 28.0 (*C*H_2^{Lev}), 21.3 (*C*H_3^{STol}); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{40}H_{45}N_4O_8S$ 741.2953; found 741.2966; *m/z*: $[M + Na]^+$ calcd for $C_{40}H_{41}N_3NaO_6S$ 746.2507; found 746.2519.

*4-Methylphenyl 2-O-(2-Azidomethylbenzoyl)-3,6-di-O-benzyl-4-levulinoyl-β-D-glucopyranosyl Sulfoxide (**7b**).* To a solution of thioglycoside **7a** (52 mg, 72 μmol, 1.0 equiv) in dry DCM (350 μL) cooled to −78 °C was added *m*CPBA (15 mg, 85 μmol, 1.1 equiv), and the mixture was allowed to slowly warm up to −10 °C in 2.5 h. Then, the crude material was washed with saturated aq. $NaHCO_3$ (2 mL) and extracted with DCM (3 × 5.0 mL). The combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 7:3 to 1:1) gave the desired compound **7b** (36 mg, 67%, 2:1 mixture of diastereoisomers) as a white amorphous solid: R_f 0.2 (Hex/EtOAc 1:1); major compound data: ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.79–7.77 (m, 1H, C*H*^{AZMB}), 7.60–7.51 (m, 4H, 4 × C*H*^{Ar}), 7.36–7.25 (m, 6H, 6 × C*H*^{Ar}), 7.16–7.10 (m, 7H, 7 × C*H*^{Ar}), 5.54–5.51 (m, 1H, H-2), 5.08–5.03 (m, 1H, H-4), 4.80–4.76 (m, 1H, CH*H*^{AZMB}), 4.71–4.68 (m, 1H, C*H*H^{AZMB}), 4.64–4.53 (m, 2H, CH_2^{Bn}), 4.53 (d, 1H, *J* = 9.4 Hz, H-1), 4.44–4.35 (m, 2H, CH_2^{Bn}), 3.96–3.92 (m, 1H, H-3), 3.74–3.68 (m, 1H, H-5), 3.62–3.54 (m, 2H, H-6a, H-6b), 2.66–2.54 (m, 2H, CH_2^{Lev}), 2.45–2.38 (m, 1H, CH*H*^{Lev}), 2.35–2.30 (m, 1H, C*H*H^{Lev}), 2.24 (s, 3H, CH_3^{STol}), 2.10 (s, 3H, CH_3^{Lev}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 206.2 (*C*=O^{Lev}), 171.4 (O*C*=O), 164.7 (O*C*=O^{AZMB}), 142.2 (C^{Ar}), 138.2 (C^{Ar}), 138.1 (C^{Ar}), 137.5 (C^{Ar}), 135.9 (C^{Ar}), 133.3 (*C*H^{AZMB}), 131.2 (*C*H^{AZMB}), 129.6 (2C, 2 × *C*H^{Ar}), 129.5 (*C*H^{AZMB}), 128.5 (2C, 2 × *C*H^{Ar}), 128.4 (2C, 2 × *C*H^{Ar}), 128.1–127.6 (8C, C^{Ar}, 7 × *C*H^{Ar}), 125.9 (2C, 2 × *C*H^{Ar}), 93.0 (C-1), 80.8 (C-3), 78.4 (C-5), 74.2 (*C*H_2^{Bn}), 73.8 (*C*H_2^{Bn}), 70.3 (C-4), 69.27, 69.26 (2C, C-2, C-6), 53.0 (*C*H_2^{AZMB}), 37.8 (*C*H_2^{Lev}), 29.8 (*C*H_3^{Lev}), 27.9 (*C*H_2^{Lev}), 21.5 (*C*H_2^{STol}); minor compound data: ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.92–7.91 (m, 1H, C*H*^{AZMB}), 7.60–7.51 (m, 4H, 4 × C*H*^{Ar}), 7.40–7.38 (m, 1H, C*H*^{AZMB}), 7.36–7.25 (m, 5H, 5 × C*H*^{Ar}), 7.16–7.10 (m, 7H, 7 × C*H*^{Ar}), 5.54–5.51 (m, 1H, H-2), 5.08–5.03 (m, 1H, H-4), 4.80–4.76 (m, 1H, CH*H*^{AZMB}), 4.71–4.68 (m, 1H, C*H*H^{AZMB}), 4.64–4.53 (m, 2H, CH_2^{Bn}), 4.46 (d, 1H, *J* = 9.7 Hz, H-1), 4.44–4.35 (m, 2H, CH_2^{Bn}), 3.96–3.92 (m, 1H, H-3), 3.74–3.68 (m, 1H, H-5), 3.62–3.54 (m, 2H, H-6a, H-6b), 2.66–2.54 (m, 2H, CH_2^{Lev}), 2.45–2.38 (m, 1H, CH*H*^{Lev}), 2.35–2.30 (m, 1H, C*H*H^{Lev}), 2.27 (s, 3H, CH_3^{STol}), 2.11 (s, 3H, CH_3^{Lev}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 206.2 (*C*=O^{Lev}), 171.5 (O*C*=O), 164.5 (O*C*=O^{AZMB}), 142.4 (C^{Ar}), 138.11 (C^{Ar}), 138.09 (C^{Ar}), 137.6 (C^{Ar}), 135.6 (C^{Ar}), 133.2 (*C*H^{AZMB}), 131.3 (*C*H^{AZMB}), 129.8 (2C, 2 × *C*H^{Ar}), 129.6 (*C*H^{AZMB}), 128.5 (2C, 2 × *C*H^{Ar}), 128.4 (2C, 2 × *C*H^{Ar}), 128.1–127.6 (8C, C^{Ar}, 7 × *C*H^{Ar}), 126.0 (2C, 2 × *C*H^{Ar}), 90.4 (C-1), 81.3 (C-3), 79.0 (C-5), 74.0 (*C*H_2^{Bn}), 73.7 (*C*H_2^{Bn}), 70.4 (C-4), 69.5 (C-2), 69.1 (C-6), 53.0 (*C*H_2^{AZMB}), 37.8 (*C*H_2^{Lev}), 29.8 (*C*H_3^{Lev}), 27.9 (*C*H_2^{Lev}), 21.5 (*C*H_2^{STol}); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{40}H_{41}N_3NaO_9S$ 762.2456; found 762.2471.

*3,6-Di-O-acetyl-1,2,4-O-ortho-acetyl-α-D-glucopyranose (**23**).* To a round-bottom flask were added glycosyl donor **4a** (16 mg, 29 μmol, 1.2 equiv), and NIS (7.7 mg, 36 μmol, 1.5 equiv), and the mixture was dried under high vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (70 mg, 4.4 mass equiv) and dry DCM (500 μL) were added and the mixture was stirred for 1 h at rt under an Ar atmosphere. The suspension was cooled to −10 °C and were added AgOTf (0.7 mg, 2 μmol, 0.1 equiv) followed by glycosyl acceptor **5a** (12 mg, 24 μmol, 1.0 equiv). The mixture was stirred at 0 °C for 2 h, after which Et_3N (100 μL, 718 μmol, 30 equiv) was added to quench the reaction. The suspension was filtered over Celite, and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 7:3) gave the undesired compound **23** (13 mg, 60%) as a white amorphous solid: R_f 0.5 (Hex/EtOAc 1:1); $[\alpha]_D^{20}$ +25 (*c* 1.4, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.80 (d, 1H, *J* = 4.8 Hz, H-1), 5.20 (ddd, 1H, *J* = 4.7 Hz, *J* = 1.5 Hz, *J* = 1.2 Hz, H-3), 4.64 (br t, 1H, *J* = 6.9 Hz, H-5), 4.52 (dt, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz, H-2), 4.32 (dd, 1H, *J* = 12.3 Hz, *J* = 7.4 Hz, H-6a), 4.24–4.21 (m, 2H, H-4, H-6b), 2.13 (s, 3H, CH_3^{Ac}), 2.10 (s, 3H, CH_3^{Ac}), 1.66 (s, 3H, C$H_3^{orthoAc}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 170.7 (O*C*=O), 169.6 (O*C*=O), 119.5 (*C*^{orthoAc}), 97.6 (C-1), 75.0 (C-5), 72.2 (C-2), 70.5 (C-4), 64.9 (C-3), 63.8 (C-6), 21.0 (*C*H_3^{Ac}), 20.9 (*C*H_3^{Ac}), 20.2 (*C*$H_3^{orthoAc}$); this compound was too instable to obtain an HRMS.

*4-Methylphenyl 2,3,6-Tri-O-acetyl-4-O-trimethylsilyl-β-D-thioglucopyranoside (**5b**).* To a round-bottom flask were added glycosyl donor **4c** (20 mg, 33 μmol, 1.0 equiv) and glycosyl acceptor **5a** (16 mg, 39 μmol, 1.2 equiv), and the mixture was dried under high vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (82 mg, 4.0 mass equiv) and dry DCE (330 μL) were added, and the mixture was stirred for 1 h at rt under an Ar atmosphere. The suspension was cooled to −10 °C and TMSOTf (2 μL, 10 μmol, 0.3 equiv) was added. The mixture was stirred at rt for 16 h, after which Et_3N (50 μL, 359 μmol, 11 equiv) was added to quench the reaction. The suspension was filtered over Celite and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 80:20 to 75:25) gave the undesired compound **5b** (7 mg, 40%) as a white amorphous solid: R_f 0.6 (Hex/EtOAc 1:1); $[\alpha]_D^{20}$ −12 (*c* 0.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.38–7.36 (m, 2H, 2 × C*H*^{STol}), 7.12–7.11 (m, 2H, 2 × C*H*^{STol}), 5.08 (t, 1H, *J* = 9.2 Hz, H-3), 4.83 (dd, 1H, *J* = 9.8 Hz, *J* = 9.4

Hz, H-2), 4.62 (d, 1H, *J* = 10.0 Hz, H-1), 4.42 (dd, 1H, *J* = 12.1 Hz, *J* = 4.1 Hz, H-6a), 4.10 (dd, 1H, *J* = 12.1 Hz, *J* = 1.0 Hz, H-6b), 3.74 (t, 1H, *J* = 9.3 Hz, H-4), 3.52 (ddd, 1H, *J* = 9.6 Hz, *J* = 5.0 Hz, *J* = 2.1 Hz, H-5), 2.34 (s, 3H, CH_3^{STol}), 2.09 (s, 3H, CH_3^{Ac}), 2.08 (s, 3H, CH_3^{Ac}), 2.04 (s, 3H, CH_3^{Ac}), 0.08 (s, 9H, 3 × CH_3^{TMS}). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{32}NaO_8SSi$ 507.1479; found 507.1502.

3,4,6-Tri-O-acetyl-2-O-(2-azidomethylbenzoyl)-D-glucal (**24**). To a round-bottom flask were added glycosyl donor **4c** (33 mg, 55 µmol, 1.0 equiv), freshly activated 4 Å molecular sieves (100 mg, 3.0 mass equiv), and dry toluene (4.4 mL), and the mixture was stirred for 1 h at rt under an Ar atmosphere. Then, AgOTf (4.2 mg, 16 μmol, 0.3 equiv) was added and the solution was heated to 80 °C. After 5 min, glycosyl acceptor **5a** (33.3 mg, 82 μmol, 1.5 equiv) and additional dry toluene (2.2 mL) were added. The mixture was stirred at 80 °C for 2 h, TBSOTf (4 μL, 16 μmol, 0.3 equiv) was added, and the solution was stirred for an additional 2 h at 80 °C after which Et_3N (100 μL, 718 μmol, 13 equiv) was added to quench the reaction. The suspension was filtered over Celite and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 85:15 to 75:25) gave the undesired compound **24** (9 mg, 19%) as a white amorphous solid: R_f 0.5 (Hex/EtOAc 1:1); $[\alpha]_D^{20}$ +0.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.02–8.01 (m, 1H, CH^{AZMB}), 7.61–7.59 (m, 1H, CH^{AZMB}), 67.54–7.53 (m, 1H, CH^{AZMB}), 7.44–7.41 (m, 1H, CH^{AZMB}), 6.81 (s, 1H, H-1), 5.73 (d, 1H, *J* = 4.3 Hz, H-3), 5.30 (dd, 1H, *J* = 5.5 Hz, *J* = 4.4 Hz, H-4), 4.83 (d, 1H, *J* = 14.7 Hz, CHH^{AZMB}), 4.78 (d, 1H, *J* = 14.7 Hz, CHH^{AZMB}), 4.50 (dd, 1H, *J* = 12.0 Hz, *J* = 6.7 Hz, H-6a), 4.46–4.43 (m, 1H, H-5), 4.29 (dd, 1H, *J* = 12.0 Hz, *J* = 3.4 Hz, H-6b), 2.14 (s, 3H, CH_3^{Ac}), 2.12 (s, 3H, CH_3^{Ac}), 2.02 (s, 3H, CH_3^{Ac}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 170.6 (O*C*=O), 170.1 (O*C*=O), 169.7 (O*C*=O), 165.2 (O*C*=O^{AZMB}), 139.8 (C-1), 138.2 (C^{AZMB}), 133.6 (*C*H^{AZMB}), 131.6 (*C*H^{AZMB}), 129.9 (*C*H^{AZMB}), 128.4 (*C*H^{AZMB}), 127.6 (C-2*), 127.5 (C^{AZMB}*), 74.4 (C-5), 67.7 (C-4), 66.5 (C-3), 61.1 (C-6), 53.0 (*C*H$_2^{AZMB}$), 20.94 (*C*H$_3^{Ac}$), 20.87 (*C*H$_3^{Ac}$), 20.8 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{22}N_3O_9$ 448.1351; found 448.1351.

Benzyl 12-O-[2-O-(2-Azidomethylbenzoyl)-3,6-di-O-benzyl-4-O-levulinoyl-β-D-glucopyranosyl]dodecanoate (**33**) *and 1,2-O-[(Benzyldodecanoate-12-oxy)-(2-Azidomethylphenyl)Methylene-3,6-di-O-benzyl-4-O-levulinoyl-α-D-glucopyranose* (**34**). **Route A.** To a round-bottom flask were added donor **7a** (20 mg, 28 μmol, 1.0 equiv), lipid **32**[62] (11 mg, 35 μmol, 1.2 equiv), TTBP (25 mg, 99 μmol, 3.5 equiv), and Ph_2SO (10 mg, 46 μmol, 1.6 equiv), and the flask was dried under high vacuum for 1.5 h. Then, freshly activated 4 Å molecular sieves (150 mg, 7.5 massic equiv) and dry toluene (500 μL) were added, and the mixture was stirred for 1.5 h at rt under an Ar atmosphere. Next, the flask was cooled to −78 °C and Tf_2O (7 μL, 0.04 mmol, 1.5 equiv) was added. After 15 min, the cooling bath was removed, and the mixture was stirred at rt for an additional 1 h. Then, an excess of Et_3N was added to quench the reaction, and the mixture was filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 6:3) gave the desired compound **33** (6 mg, 25%) as a white amorphous solid along with the corresponding orthoester **34** (19 mg, 75%) as a white amorphous solid. Orthoester **34** data: R_f 0.55 (Hex/EtOAc 1:1); $[\alpha]_D^{20}$ +42 (*c* 2.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.80–7.79 (m, 1H, CH^{AZMB}), 7.66–7.23 (m, 18H, 18 × CH^{Ar}), 5.93 (d, 1H, *J* = 5.1 Hz, H-1), 5.11–5.09 (m, 3H, CH_2^{Bn}, H-4), 4.83 (d, 1H, *J* = 12.0 Hz, CHH^{Bn}), 4.76 (d, 1H, *J* = 14.4 Hz, CHH^{AZMB}), 4.69 (d, 1H, *J* = 14.4 Hz, CHH^{AZMB}), 4.66 (d, 1H, *J* = 12.0 Hz, CHH^{Bn}), 4.54 (ddd, 1H, *J* = 4.6 Hz, *J* = 3.2 Hz, *J* = 0.8 Hz, H-2), 4.47 (d, 1H, *J* = 12.0 Hz, CHH^{Bn}), 4.42 (d, 1H, *J* = 12.0 Hz, CHH^{Bn}), 3.87 (dd, 1H, *J* = 2.9 Hz, *J* = 2.0 Hz, H-3), 3.66–3.62 (m, 1H, H-5), 3.47–3.42 (m, 2H, H-6a, H-6b), 3.20 (t, 2H, *J* = 6.7 Hz, C$H_2^{12'}$), 2.68–2.58 (m, 2H, CH_2^{Lev}), 2.52–2.45 (m, 1H, CHH^{Lev}), 2.40–2.32 (m, 3H, CHH^{Lev}, C$H_2^{2'}$), 2.10 (s, 3H, CH_3^{Lev}), 1.65–1.60 (m, 2H, C$H_2^{3'}$), 1.48–1.43 (m, 2H, C$H_2^{11'}$), 1.34–1.24 (m, 14H, C$H_2^{4'}$ to C$H_2^{10'}$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 206.3 (*C*=O^{Lev}), 173.8 (C-1'), 171.9 (O*C*=O^{Lev}), 145.7 (2C, 2 × CH^{Ar}), 138.2 (C^{Ar}), 137.7 (C^{Ar}), 136.2 (C^{Ar}), 134.5 (C^{Ar}), 134.4 (C^{Ar}), 131.2 (2C, 2 × CH^{Ar}), 129.5 (2C, 2 × CH^{Ar}), 128.7 (2C, 2 × CH^{Ar}), 128.5 (CH^{Ar}), 128.3 (2C, 2 × CH^{Ar}), 128.1 (CH^{Ar}), 128.0 (CH^{Ar}), 127.8 (CH^{Ar}), 127.6 (CH^{Ar}), 127.4 (CH^{Ar}), 126.9 (CH^{AZMB}), 124.9 (2C, 2 × CH^{Ar}), 120.5 (OCOO^{AZMB}), 97.7 (C-1), 75.2 (C-3), 73.9 (C-2), 73.2 (CH_2^{Bn}), 71.9 (CH_2^{Bn}), 69.7 (C-6), 68.5 (C-5), 68.2 (C-4), 66.2 (CH_2^{Bn}), 64.0 (C-12'), 51.8 (CH_2^{AZMB}), 37.9 (CH_2^{Lev}), 34.5 (C-2'), 29.8 (CH_3^{Lev}), 29.7 (CH_2^{alkyl}), 29.6 (CH_2^{alkyl}), 29.5 (C-11'), 29.4 (CH_2^{alkyl}), 29.3 (CH_2^{alkyl}), 29.2 (CH_2^{alkyl}), 28.1 (CH_2^{Lev}), 20.2 (CH_2^{alkyl}), 25.9 (CH_2^{alkyl}), 25.1 (C-3'); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{52}H_{67}N_4O_{11}$ 923.4800; found 923.4782. Glycolipid **33** data: R_f 0.5 (Hex/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.90–7.88 (m, 1H, CH^{AZMB}), 7.66–7.64 (m, 2H, 2 × CH^{Ar}), 7.58–7.55 (m, 1H, CH^{AZMB}), 7.53–7.51 (m, 1H, CH^{AZMB}), 7.48–7.44 (m, 3H, 3 × CH^{Ar}), 7.39–7.36 (m, 1H, CH^{AZMB}), 7.36–7.30 (m, 5H, 5 × CH^{Ar}), 7.17–7.14 (m, 5H, 5 × CH^{Ar}), 5.27 (dd, 1H, *J* = 9.5 Hz, *J* = 7.9 Hz, H-2), 5.15 (t, 1H, *J* = 9.5 Hz, H-4), 5.11 (s, 2H, CH_2^{Bn}), 4.74 (d, 1H, *J* = 14.9 Hz, CHH^{AZMB}), 4.71 (d, 1H, *J* = 14.9 Hz, CHH^{AZMB}), 4.63 (d, 1H, *J* = 11.6 Hz, CHH^{Bn}), 4.58–4.53 (m, 4H, H-1, CHH^{Bn}, CHH^{Bn}, CHH^{Bn}), 3.90–3.85 (m, 2H, H-3, H-12'a), 3.67 (ddd, 1H, *J* = 9.4 Hz, *J* = 5.8 Hz, *J* = 3.2 Hz, H-5), 3.64 (dd, 1H, *J* = 10.7 Hz, *J* = 3.2 Hz, H-6a), 3.61 (dd, 1H, *J* = 10.7 Hz, *J* = 5.8 Hz, H-6b), 3.46 (dt, 1H, *J* = 9.6 Hz, *J* = 6.8 Hz, H-12'b), 2.66–2.55 (m, 2H, CH_2^{Lev}), 2.46–2.41 (m, 1H, CHH^{Lev}), 2.39–2.33 (m, 3H, CHH^{Lev}, C$H_2^{2'}$), 2.13 (s, 3H, CH_3^{Lev}), 1.65–1.60 (m, 2H, C$H_2^{3'}$), 1.54–1.46 (m, 2H, C$H_2^{11'}$), 1.23–1.04 (m, 14H, C$H_2^{4'}$ to C$H_2^{10'}$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 206.3 (*C*=O^{Lev}), 173.9 (C-1'), 171.7 (O*C*=O^{Lev}), 165.1 (O*C*=O^{AZMB}), 138.2 (C^{Ar}), 137.9 (C^{Ar}), 137.8 (C^{Ar}), 136.3 (C^{Ar}), 132.9 (*C*H^{AZMB}), 130.9 (*C*H^{AZMB}), 129.50 (*C*H^{AZMB}), 129.48 (*C*H^{Ar}), 128.7 (2C, 2 × CH^{Ar}, 128.5 (2C, 2 × CH^{Ar}), 128.4 (2C, 2 × CH^{Ar}), 128.3 (2C, 2 × CH^{Ar}), 128.00 (CH^{Ar}), 127.95 (2C, 2 × CH^{Ar}), 127.9 (2C, 2 × CH^{Ar}), 127.78 (C^{Ar}), 127.76 (CH^{AZMB}), 125.0 (CH^{Ar}), 101.1 (C-1), 80.2 (C-3), 73.84 (C-5), 73.77 (CH_2^{Bn}), 73.7 (CH_2^{Bn}), 73.4 (C-2), 71.4 (C-4), 70.1 (C-12'), 69.8 (C-6), 66.2 (CH_2^{Bn}), 53.0 (CH_2^{AZMB}), 37.9 (CH_2^{Lev}), 34.5 (C-2'), 29.91 (CH_2^{alkyl}), 29.85 (CH_3^{Lev}), 29.6 (CH_2^{alkyl}), 29.5 (CH_2^{alkyl}), 29.44 (CH_2^{alkyl}), 29.35 (CH_2^{alkyl}), 29.3 (CH_2^{alkyl}), 28.0 (CH_2^{Lev}), 26.0 (CH_2^{alkyl}), 25.1 (C-3'), 22.8 (CH_2^{alkyl}). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{52}H_{67}N_4O_{11}$ 923.4800; found 923.4784. **Route B.** To a solution of orthoester **34** (11 mg, 12 μmol, 1.0 equiv) in dry DCM (625 μL) cooled at 10 °C was added TMSOTf (0.6 μL, 3 μmol, 0.25 equiv), and the mixture was stirred at 10 °C for 1 h under an Ar atmosphere. Then, Et_3N was added to quench the reaction and the mixture was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 7:3) gave the desired compound **33** (7 mg, 64%) as a white amorphous solid.

Allyl 4,6-O-(4-Methoxybenzylidene)-α-D-glucopyranoside (**28**). To a solution of allyl D-glucopyranoside **27**[49] (α/β 75:25) (2.95 g, 13.4 mmol, 1.0 equiv) in dry CH_3CN (135 mL) were successively added anisaldehyde dimethylacetal (4.5 mL, 28 mmol, 2.1 equiv) and CSA (314 mg, 1.35 mmol, 0.1 equiv). The solution was stirred at rt for 1 h, after which Et_3N (2.0 mL, 14 mmol, 1.1 equiv) was added to quench the reaction. The solution was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 5:5 to 2:8) gave the desired compound **28** (1.38 g, 97%, α/β 75:25) as a white amorphous solid: R_f 0.5 (DCM/MeOH 9:1). Physical and analytical data agreed with those published.[63]

Allyl 3-O-(4-Methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-α-D-glucopyranoside (**29**). To a solution of compound **28** (α/β 75:25) (3.05 g, 8.67 mol, 1.0 equiv) in dry CH_3CN (35 mL) were successively added Et_3N (12.0 mL, 86.1 mmol, 9.9 equiv) and TMSCl (4.4 mL, 35 mmol, 4.0 equiv), and the mixture was stirred for 14 h at rt. Then, the solution was concentrated under reduced

pressure before the addition of hexanes and filtration over Celite. The filtrate was concentrated under reduced pressure and dried under high vacuum for 2 h. The resulting crude material was dissolved in dry DCM (52 mL) and anisaldehyde (1.4 mL, 11 mmol, 1.3 equiv), Et_3SiH (1.8 mL, 11 mmol, 1.3 equiv) and freshly activated 4 Å molecular sieves (4.4 g, 1.0 mass equiv) were added to the solution. The mixture was then stirred for 30 min at rt. Then, the reaction mixture was cooled to −78 °C, TMSOTf (165 μL, 0.912 mmol, 0.1 equiv) was added, and the solution was stirred for 1.5 h at −78 °C. Additional TMSOTf (165 μL, 0.912 mmol, 0.1 equiv) was added, and the reaction mixture was again stirred for 1.5 h at −78 °C. After. the complete conversion of the starting material, TBAF (1.0 M in THF, 18 mL, 18 mmol, 2.1 equiv) was added at −78 °C, and the mixture was stirred for 90 min at rt. Finally, the suspension was filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 7:3) gave the desired compound **29** (3.06 g, 58% over three steps, α/β 75:25) as a white amorphous solid: R_f 0.2 (Hex/EtOAc 6:4); α-anomer data: $[\alpha]_D^{20}$ +67 (*c* 2.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.43–7.41 (m, 2H, 2 × C*H*^{Ar}), 7.31–7.28 (m, 2H, 2 × C*H*^{Ar}), 6.92–6.89 (m, 2H, 2 × C*H*^{Ar}), 6.86–6.84 (m, 2H, 2 × C*H*^{Ar}), 5.93 (dddd, 1H, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz, *J* = 5.5 Hz, H-2^{Allyl}), 5.53 (s, 1H, PMPC*H*O$_2$), 5.32 (dt, 1H, *J* = 17.1 Hz, *J* = 1.5 Hz, H-3cis^{Allyl}), 5.24 (dt, 1H, *J* = 10.4 Hz, *J* = 1.2 Hz, H-3trans^{Allyl}), 4.95 (d, 1H, *J* = 4.0 Hz, H-1), 4.88 (d, 1H, *J* = 11.1 Hz, CH*H*^{PMB}), 4.72 (d, 1H, *J* = 11.1 Hz, C*H*H^{PMB}), 4.26 (dd, 1H, *J* = 10.3 Hz, *J* = 4.8 Hz, H-6a), 4.23 (ddt, 1H, *J* = 12.8 Hz, *J* = 5.4 Hz, *J* = 1.4 Hz, H-1a^{Allyl}), 4.07 (ddt, 1H, *J* = 12.8 Hz, *J* = 6.3 Hz, *J* = 1.2 Hz, H-1b^{Allyl}), 3.87 (td, 1H, *J* = 10.0 Hz, *J* = 4.9 Hz, H-5), 3.82 (t, 1H, *J* = 9.1 Hz, H-3), 3.82 (s, 3H, C*H*$_3^{OMe}$), 3.79 (s, 3H, C*H*$_3^{OMe}$), 3.73 (t, 1H, *J* = 10.3 Hz, H-6b), 3.73–3.68 (m, 1H, H-2), 3.61 (t, 1H, *J* = 9.4 Hz, H-4), 2.25 (d, 1H, 7.5 Hz, O*H*); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 160.2 (C^{Ar}), 159.4 (C^{Ar}), 133.6 (C-2^{Allyl}), 130.8 (C^{Ar}), 130.0 (C^{Ar}), 129.8 (2C, 2 × *C*H^{Ar}), 127.5 (2C, 2 × *C*H^{Ar}), 118.4 (C-3^{Allyl}), 113.9 (2C, 2 × *C*H^{Ar}), 113.7 (2C, 2 × *C*H^{Ar}), 101.4 (PMP*C*HO$_2$), 98.1 (C-1), 82.1 (C-4), 78.8 (C-3), 74.7 (*C*H$_2^{PMB}$), 72.5 (C-2), 69.1 (C-6), 68.9 (C-1^{Allyl}), 63.0 (C-5), 55.44 (*C*H$_3^{OMe}$), 55.42 (*C*H$_3^{OMe}$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{31}O_8$ 459.2013; found 459.2025.

*Allyl 2-O-Acetyl-3-O-(4-methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-α-D-glucopyranoside (**30**).* To a solution of compound **29** (α/β 75:25) (1.02 g, 2.22 mmol, 1.0 equiv) in dry pyridine (5.5 mL) and Ac_2O (5.5 mL) was added DMAP (27 mg, 0.22 mmol, 0.1 equiv). The mixture was stirred at rt for 16 h. After the complete conversion of the starting material, the solution was concentrated under reduced pressure and co-evaporated with toluene. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 8:2) gave the desired compound **30** (1.09 g, 98%, α/β 75:25) as a white amorphous solid: R_f 0.3 (Hex/EtOAc 7:3); α-anomer data: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.43–7.40 (m, 2H, 2 × C*H*^{Ar}), 7.24–7.21 (m, 2H, 2 × C*H*^{Ar}), 6.92–6.89 (m, 2H, 2 × C*H*^{Ar}), 6.84–6.82 (m, 2H, 2 × C*H*^{Ar}), 5.88 (dddd, 1H, *J* = 17.0 Hz, *J* = 10.6 Hz, *J* = 6.2 Hz, *J* = 5.3 Hz, H-2^{Allyl}), 5.54 (s, 1H, PMPC*H*O$_2$), 5.30 (dt, 1H, *J* = 17.1 Hz, *J* = 1.6 Hz, H-3cis^{Allyl}), 5.22 (dt, 1H, *J* = 10.4 Hz, *J* = 1.3 Hz, H-3trans^{Allyl}), 5.07 (d, 1H, *J* = 3.9 Hz, H-1), 4.85 (dd, 1H, *J* = 9.8 Hz, *J* = 3.9 Hz, H-2), 4.80 (d, 1H, *J* = 11.4 Hz, CH*H*^{PMB}), 4.64 (d, 1H, *J* = 11.3 Hz, C*H*H^{PMB}), 4.26 (dd, 1H, *J* = 10.3 Hz, *J* = 4.9 Hz, H-6a), 4.18 (ddt, 1H, *J* = 13.1 Hz, *J* = 5.2 Hz, *J* = 1.5 Hz, H-1a^{Allyl}), 4.04 (t, 1H, *J* = 9.5 Hz, H-3), 4.01 (ddt, 1H, *J* = 13.1 Hz, *J* = 6.2 Hz, *J* = 1.2 Hz, H-1b^{Allyl}), 3.90 (td, 1H, *J* =10.9 Hz, *J* = 4.9 Hz, H-5), 3.82 (s, 3H, C*H*$_3^{OMe}$), 3.79 (s, 3H, C*H*$_3^{OMe}$), 3.74 (t, 1H, *J* = 10.3 Hz, H-6b), 3.68 (t, 1H, *J* = 9.3 Hz, H-4), 2.09 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 170.5 (O*C*=O), 160.2 (C^{Ar}), 159.3 (C^{Ar}), 133.6 (C-2^{Allyl}), 130.8 (C^{Ar}), 130.0 (C^{Ar}), 129.5 (2C, 2 × *C*H^{Ar}), 127.5 (2C, 2 × *C*H^{Ar}), 118.2 (C-3^{Allyl}), 113.8 (2C, 2 × *C*H^{Ar}), 113.7 (2C, 2 × *C*H^{Ar}), 101.4 (PMP*C*HO$_2$), 96.0 (C-1), 82.2 (C-4), 76.0 (C-3), 74.7 (*C*H$_2^{PMB}$), 73.2 (C-2), 69.0 (C-6), 68.7 (C-1^{Allyl}), 62.7 (C-5), 55.5 (*C*H$_3^{OMe}$), 55.4 (*C*H$_3^{OMe}$), 21.1 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{27}H_{32}NaO_9$ 523.1939; found 523.1936.

*Allyl 2-O-Acetyl-3,6-di-O-(4-methoxybenzyl)-α-D-glucopyranoside (**26**).* To a solution of compound **30** (α/β 87:13) (1.54 g, 3.07 mmol, 1.0 equiv) in dry DMF (31 mL) was added freshly activated 4 Å molecular sieves (9.27 g, 5.0 mass equiv), and the mixture was stirred for 1 h at rt. The suspension was then cooled to 0 °C and $NaBH_3CN$ (1.96 g, 31.2 mmol, 10.2 equiv) was added. After stirring at 0 °C for 15 min, HCl (2.0 M in Et_2O, 12.3 mL, 24.6 mmol, 8.0 equiv) was added dropwise over a period of 5 min. The mixture was stirred at 0 °C for 1.3 h, after which additional HCl (2.0 M in Et_2O, 6.2 mL, 12 mmol, 4.0 equiv) was added, and the mixture was allowed to gradually warm up to rt for 2 h. The suspension was then filtered through a sintered glass, and the filtrate was washed with saturated aq. $NaHCO_3$ (200 mL). The aqueous layer was extracted with DCM (5 × 100 mL), and the combined organic layers were washed with brine (200 mL), filtered over $MgSO_4$, concentrated under reduced pressure, and co-evaporated with toluene (8×). Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 6:4) gave the desired compound **26** (1.30 g, 84%, pure α) as a white amorphous solid: R_f 0.3 (Tol/EtOAc 8:2); $[\alpha]_D^{20}$ +63 (*c* 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.26–7.24 (m, 4H, 4 × CH^{Ar}), 6.89–6.86 (m, 4H, 4 × CH^{Ar}), 5.88 (ddt, 1H, *J* = 17.1 Hz, *J* = 10.7 Hz, *J* = 5.8 Hz, H-2^{Allyl}), 5.29 (dq, 1H, *J* = 17.2 Hz, ^2J = ^4J = 1.6 Hz, H-3cis^{Allyl}), 5.20 (dq, 1H, *J* = 10.5 Hz, ^2J = ^4J = 1.4 Hz, H-3trans^{Allyl}), 5.06 (d, 1H, *J* = 3.7 Hz, H-1), 4.81 (dd, 1H, *J* = 10.0 Hz, *J* = 3.7 Hz, H-2), 4.74 (d, 1H, *J* = 11.3 Hz, CH*H*^{PMB}), 4.65 (d, 1H, *J* = 11.3 Hz, C*H*H^{PMB}), 4.53 (d, 1H, *J* = 11.7 Hz, CH*H*^{PMB}), 4.48 (d, 1H, *J* = 11.7 Hz, C*H*H^{PMB}), 4.17 (ddt, 1H, *J* = 13.2 Hz, *J* = 5.1 Hz, *J* = 1.5 Hz, H-1a^{Allyl}), 4.00 (ddt, 1H, *J* = 13.2 Hz, *J* = 6.2 Hz, *J* = 1.3 Hz, H-1b^{Allyl}), 3.86 (t, 1H, *J* = 9.6 Hz, H-3), 3.80 (s, 3H, C*H*$_3^{OMe}$), 3.79 (s, 3H, C*H*$_3^{OMe}$), 3.81–3.78 (m, 1H, H-5), 3.70–3.64 (m, 3H, H-4, H-6a, H-6b), 2.60–2.48 (br s, 1H, O*H*), 2.09 (s, 3H, C*H*$_3^{Ac}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 170.5 (O*C*=O), 159.5 (C^{Ar}), 159.4 (C^{Ar}), 133.8 (C-2^{Allyl}), 130.8 (C^{Ar}), 130.1 (C^{Ar}), 129.45 (2C, 2 × *C*H^{PMB}), 129.44 (2C, 2 × *C*H^{PMB}), 117.9 (C-3^{Allyl}), 114.1 (2C, 2 × *C*H^{PMB}), 114.0 (2C, 2 × *C*H^{PMB}), 95.3 (C-1), 79.5 (C-3), 74.9 (*C*H$_2^{PMB}$), 73.5 (C-2), 73.4 (*C*H$_2^{PMB}$), 71.6 (C-5), 70.1 (C-4), 69.6 (C-6), 68.4 (C-1^{Allyl}), 55.43 (*C*H$_3^{OMe}$), 55.42 (*C*H$_3^{OMe}$), 21.1 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + NH_4]$^+$ calcd for $C_{27}H_{38}NO_9$ 520.2541; found 520.2545; *m/z*: [M + Na]$^+$ calcd for $C_{27}H_{34}NaO_9$ 525.2095; found 525.2104.

*Allyl 2-O-(2-Azidomethylbenzoyl)-3-O-(4-methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-β-D-glucopyranosyl-(1 → 4)-2-O-acetyl-3,6-di-O-(4-methoxybenzyl)-α-D-glucopyranoside (**31**).* To a round-bottom flask were added donor **11** (1.08 g, 1.58 mmol, 1.0 equiv), acceptor **26** (545 mg, 1.09 mmol, 0.7 equiv), and NIS (590 mg, 2.62 mmol, 1.7 equiv), and the mixture was dried under high vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (4.47 g, 4.0 mass equiv) and dry DCM (24 mL) were added, and the mixture was stirred for 1 h at rt under an Ar atmosphere. The suspension was cooled to 0 °C and $Yb(OTf)_3$ (199 mg, 0.321 mmol, 0.2 equiv) was added. The mixture was stirred at 0 °C for 1.5 h, after which Et_3N (400 μL, 2.87 mmol, 1.8 equiv) was added to quench the reaction. The suspension was filtered over Celite, and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 65:35) gave the desired compound **31** (885 mg, 77%) as a white amorphous solid: R_f 0.3 (Tol/EtOAc 8:2); $[\alpha]_D^{20}$ +22 (*c* 0.7, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.73–7.72 (m, 1H, C*H*^{AZMB}), 7.62–7.59 (m, 1H, C*H*^{AZMB}), 7.55–7.53 (m, 1H, C*H*^{AZMB}), 7.44–7.42 (m, 2H, 2 × C*H*^{Ar}), 7.41–7.38 (m, 1H, C*H*^{AZMB}), 7.25–7.23 (m, 2H, 2 × C*H*^{Ar}), 7.22–7.19 (m, 2H, 2 × C*H*^{Ar}), 7.07–7.04 (m, 2H, 2 × C*H*^{Ar}), 6.94–6.91 (m, 2H, 2 × C*H*^{Ar}), 6.91–6.89 (m, 2H, 2 × C*H*^{Ar}), 6.88–6.86 (m, 2H, 2 × C*H*^{Ar}), 6.65–6.63 (m, 2H, 2 × C*H*^{Ar}), 5.79 (dddd, 1H, *J* = 17.1 Hz, *J* = 10.8 Hz, *J* = 6.1 Hz, *J* = 5.3 Hz, H-2^{Allyl}), 5.50 (s, 1H, PMPC*H*O$_2$), 5.22 (dt, 1H, *J*

= 17.2 Hz, *J* = 1.5 Hz, H-3cis^{Allyl}), 5.15–5.12 (m, 2H, H-3trans^{Allyl},H-2C), 4.99 (d, 1H, *J* = 3.8 Hz, H-1B), 4.89 (d, 1H, *J* = 14.8 Hz, CH*H*^{AZMB}), 4.82 (d, 1H, *J* = 10.8 Hz, CH*H*^{PMB}), 4.77 (dd, 1H, *J* = 10.0 Hz, *J* = 3.8 Hz, H-2B), 4.76 (d, 1H, *J* = 11.6 Hz, CH*H*^{PMB}), 4.69 (d, 1H, *J* = 14.8 Hz, C*H*H^{AZMB}), 4.59 (d, 1H, *J* = 11.9 Hz, CH*H*^{PMB}), 4.56 (d, 1H, *J* = 10.8 Hz, C*H*H^{PMB}), 4.53 (d, 1H, *J* = 11.8 Hz, C*H*H^{PMB}), 4.46 (d, 1H, *J* = 8.0 Hz, H-1C), 4.22 (dd, 1H, *J* = 10.6 Hz, *J* = 4.9 Hz, H-6aC), 4.14 (d, 1H, *J* = 12.0 Hz, C*H*H^{PMB}), 4.05 (ddt, 1H, *J* = 13.1 Hz, *J* = 5.1 Hz, *J* = 1.3 Hz, H-1a^{Allyl}), 3.95 (t, 1H, *J* = 9.4 Hz, H-4B), 3.89 (ddt, 1H, *J* = 13.1 Hz, *J* = 6.1 Hz, *J* = 1.1 Hz, H-1b^{Allyl}), 3.85 (dd, 1H, *J* = 9.8 Hz, *J* = 9.0 Hz, H-3B), 3.83 (s, 3H, C*H*$_3^{OMe}$), 3.80 (s, 3H, C*H*$_3^{OMe}$), 3.74 (s, 3H, C*H*$_3^{OMe}$), 3.71 (s, 3H, C*H*$_3^{OMe}$), 3.71–3.68 (m, 1H, H-4C), 3.59–3.53 (m, 4H, H-3C, H-5B, H-6aB, H-6bC), 3.31 (dd, 1H, *J* = 10.5 Hz, *J* = 1.2 Hz, H-6bB), 3.19 (td, 1H, *J* = 9.7 Hz, *J* = 5.0 Hz, H-5C), 2.01 (s, 3H, C*H*$_3^{Ac}$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 170.4 (O*C*=O), 164.7 (O*C*=O), 160.2 (C^{Ar}), 159.6 (C^{Ar}), 159.2 (C^{Ar}), 159.1 (C^{Ar}), 138.4 (C^{Ar}), 133.6 (C-2^{Allyl}), 133.1 (*C*H^{AZMB}), 131.4 (C^{Ar}), 130.8 (*C*H^{AZMB}), 130.3 (C^{Ar}), 130.1 (C^{Ar}), 130.0 (2C, 2 × *C*H^{Ar}), 129.9 (C^{Ar}), 129.8 (*C*H^{AZMB}), 129.6 (2C, 2 × *C*H^{Ar}), 129.2 (2C, 2 × *C*H^{Ar}), 128.2 (C^{Ar}), 127.9 (*C*H^{AZMB}), 127.5 (2C, 2 × *C*H^{Ar}), 117.8 (C-3^{Allyl}), 114.1 (2C, 2 × *C*H^{Ar}), 113.72 (2C, 2 × *C*H^{Ar}), 113.70 (2C, 2 × *C*H^{Ar}), 113.69 (2C, 2 × *C*H^{Ar}), 101.3 (PMP*C*HO$_2$), 100.8 (C-1C), 95.1 (C-1B), 82.0 (C-4C), 78.3 (C-3C*), 77.6 (C-3B), 76.7 (C-4B), 75.1 (*C*H$_2^{PMB}$), 74.0 (*C*H$_2^{PMB}$), 73.9 (C-2C), 73.1 (*C*H$_2^{PMB}$), 72.9 (C-2B), 70.2 (C-5B*), 68.8 (C-6C), 68.5 (C-1^{Allyl}), 67.0 (C-6B), 66.1 (C-5C), 55.5 (*C*H$_3^{OMe}$), 55.44 (*C*H$_3^{OMe}$), 55.39 (*C*H$_3^{OMe}$), 55.3 (*C*H$_3^{OMe}$), 53.1 (*C*H$_2^{AZMB}$), 21.0 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{57}H_{64}N_3O_{17}$ 1062.4230; found 1062.4219; *m/z*: [M + Na]$^+$ calcd for $C_{57}H_{63}NaN_3O_{17}$ 1084.4050; found 1084.4046.

*Allyl 3-O-(4-Methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-β-D-glucopyranosyl-(1→4)-2-O-acetyl-3,6-di-O-(4-methoxybenzyl)-α-D-glucopyranoside (**38**).* To a solution of compound **31** (860 mg, 0.810 mmol, 1.0 equiv) in dry THF (25 mL) was added PPh_3 (345 mg, 1.31 mmol, 1.6 equiv). The solution was stirred at 60 °C for 2 h, after which H_2O (3.2 mL) was added and the mixture was stirred for an additional 4 h at 60 °C. The mixture was then concentrated under reduced pressure and co-evaporated with toluene. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 6:4) gave the desired compound **38** (566 mg, 77%) as a white amorphous solid: R_f 0.2 (Tol/EtOAc 8:2); $[\alpha]_D^{20}$ +31 (*c* 1.6, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.41–7.39 (m, 2H, 2 × C*H*^{Ar}), 7.30–7.27 (m, 4H, 4 × C*H*^{Ar}), 7.22–7.19 (m, 2H, 2 × C*H*^{Ar}), 6.92–6.89 (m, 2H, 2 × C*H*^{Ar}), 6.89–6.87 (m, 2H, 2 × C*H*^{Ar}), 6.87–6.84 (m, 4H, 4 × C*H*^{Ar}), 5.86 (ddt, 1H, *J* = 17.0 Hz, *J* = 10.5 Hz, *J* = 5.7 Hz, H-2^{Allyl}), 5.45 (s, 1H, PMP*C*HO$_2$), 5.28 (br d, 1H, *J* = 17.2 Hz, H-3cis^{Allyl}), 5.19 (br d, 1H, *J* = 10.4 Hz, H-3trans^{Allyl}), 5.06 (br s, 1H, H-1B), 4.86–4.78 (m, 3H, CH*H*^{PMB}, H-2B, CH*H*^{PMB}), 4.68 (d, 1H, *J* = 11.3 Hz, C*H*H^{PMB}), 4.65 (d, 1H, *J* = 11.9 Hz, CH*H*^{PMB}), 4.61 (d, 1H, *J* = 10.8 Hz, C*H*H^{PMB}), 4.49 (d, 1H, *J* = 7.1 Hz, H-1C), 4.42 (d, 1H, *J* = 11.6 Hz, C*H*H^{PMB}), 4.13 (dd, 1H, *J* = 13.2 Hz, *J* = 5.2 Hz, H-1a^{Allyl}), 4.10 (dd, 1H, *J* = 10.6 Hz, *J* = 4.9 Hz, H-6aC), 4.04–3.93 (m, 4H, H-5B, H-6aB, H-1b^{Allyl}, H-3B), 3.85–3.82 (m, 1H, H-4B), 3.81 (s, 3H, C*H*$_3^{OMe}$), 3.783 (s, 3H, C*H*$_3^{OMe}$), 3.781 (s, 3H, C*H*$_3^{OMe}$), 3.75 (s, 3H, C*H*$_3^{OMe}$), 3.65 (br d, 1H, *J* = 11.3 Hz, H-6bB), 3.58–3.53 (m, 2H, H-6bC, H-4C), 3.44–3.39 (m, 2H, H-2C, H-3C), 3.10 (td, 1H, *J* = 9.7 Hz, *J* = 4.7 Hz, H-5C), 3.03 (br d, 1H, *J* = 7.1 Hz, O*H*), 2.03 (s, 3H, C*H*$_3^{Ac}$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 170.4 (O*C*=O), 160.1 (C^{Ar}), 159.5 (C^{Ar}), 159.4 (C^{Ar}), 159.2 (C^{Ar}), 133.6 (C-2^{Allyl}), 131.2 (C^{Ar}), 130.7 (C^{Ar}), 130.00 (2C, 2 × *C*H^{Ar}), 129.98 (2C, 2 × *C*H^{Ar}), 129.84 (C^{Ar}), 129.75 (C^{Ar}), 128.7 (2C, 2 × *C*H^{Ar}), 127.5 (2C, 2 × *C*H^{Ar}), 117.9 (C-3^{Allyl}), 113.99 (2C, 2 × *C*H^{Ar}), 113.95 (2C, 2 × *C*H^{Ar}), 113.8 (2C, 2 × *C*H^{Ar}), 113.7 (2C, 2 × *C*H^{Ar}), 103.5 (C-1C), 101.3 (PMP*C*HO$_2$), 95.2 (C-1B), 81.4 (C-4C), 80.2 (C-3C), 78.6 (C-3B), 77.5 (C-5B), 75.2 (C-2C), 74.8 (*C*H$_2^{PMB}$), 74.4 (*C*H$_2^{PMB}$), 73.3 (2C, C-2B, *C*H$_2^{PMB}$), 70.2 (C-4B), 68.8 (C-6C), 68.5 (C-1^{Allyl}), 67.9 (C-6B), 66.4 (C-5C), 55.44 (*C*H$_3^{OMe}$), 55.41 (*C*H$_3^{OMe}$), 55.38 (*C*H$_3^{OMe}$), 55.36 (*C*H$_3^{OMe}$), 21.0 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{49}H_{59}O_{16}$ 903.3798; found 903.3803; *m/z*: [M + Na]$^+$ calcd for $C_{49}H_{58}NaO_{16}$ 925.3617; found 925.3628.

*Allyl 6-O-Acetyl-2-O-(2-azidomethylbenzoyl)-3,4-di-O-benzyl-β-D-glucopyranosyl-(1 → 2)-3-O-(4-methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-β-D-glucopyranosyl-(1 → 4)-2-O-acetyl-3,6-di-O-(4-methoxybenzyl)-α-D-glucopyranoside (**25**).* To a round-bottom flask were added donor **6** (440 mg, 0.659 mmol, 1.0 equiv), acceptor **38** (396 mg, 0.439 mmol, 0.7 equiv), and NIS (239 mg, 1.06 mmol, 1.6 equiv), and the mixture was dried under high vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (1.76 g, 4.0 mass equiv) and dry DCM (10 mL) were added, and the mixture was stirred for 1 h at rt under an Ar atmosphere. Next, the suspension was cooled to 0 °C and $Yb(OTf)_3$ (85 mg, 0.14 mmol, 0.2 equiv) was added. The mixture was stirred at 0 °C for 1.5 h, after which Et_3N (150 μL, 1.08 mmol, 1.6 equiv) was added to quench the reaction. The suspension was then filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 65:35) gave the desired compound **25** (532 mg, 84%) as a white amorphous solid: R_f 0.25 (Tol/EtOAc 8:2); $[\alpha]_D^{20}$ +17 (*c* 0.4, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.85–7.84 (m, 1H, C*H*^{AZMB}), 7.55–7.51 (m, 2H, 2 × C*H*^{AZMB}), 7.37–7.30 (m, 7H, 7 × C*H*^{Ar}), 7.22–7.12 (m, 12H, 12 × C*H*^{Ar}), 6.87–6.82 (m, 6H, 6 × C*H*^{Ar}), 6.71–6.69 (m, 2H, 2 × C*H*^{Ar}), 5.87 (dddd, 1H, *J* = 16.8 Hz, *J* = 10.8 Hz, *J* = 5.9 Hz, *J* = 5.3 Hz, H-2^{Allyl}), 5.38 (s, 1H, PMPC*H*O$_2$), 5.31 (dd, 1H, *J* = 17.3 Hz, *J* = 1.5 Hz, H-3cis^{Allyl}), 5.27 (dd, 1H, *J* = 9.2 Hz, *J* = 8.1 Hz, H-2D), 5.20 (dd, 1H, *J* = 10.5 Hz, *J* = 1.2 Hz, H-3trans^{Allyl}), 5.09 (d, 1H, *J* = 8.0 Hz, H-1D), 5.07 (d, 1H, *J* = 3.8 Hz, H-1B), 4.85–4.78 (m, 4H, CH*H*^{Ar}, CH*H*^{Ar}, CH*H*^{Ar}, H-2B), 4.76 (d, 1H, *J* = 14.8 Hz, CH*H*^{AZMB}) , 4.74 (d, 1H, *J* = 14.8 Hz, C*H*H^{AZMB}), 4.71 (d, 1H, *J* = 10.8 Hz, CH*H*^{Ar}), 4.65 (d, 1H, *J* = 11.0 Hz, C*H*H^{Ar}), 4.64 (d, 1H, *J* = 11.5 Hz, CH*H*^{Ar}), 4.59 (d, 1H, *J* = 10.7 Hz, C*H*H^{Ar}), 4.51 (d, 1H, *J* = 10.7 Hz, C*H*H^{Ar}), 4.40 (dd, 1H, *J* = 11.4 Hz, *J* = 2.1 Hz, H-6aD), 4.39 (d, 1H, *J* = 11.7 Hz, C*H*H^{Ar}), 4.37 (d, 1H, *J* = 10.7 Hz, C*H*H^{Ar}), 4.29 (d, 1H, *J* = 7.6 Hz, H-1C), 4.21–4.16 (m, 2H, H-6bD, H-1a^{Allyl}), 4.16–4.11 (m, 2H, H-6aB, H-6aC), 4.01 (ddt, 1H, *J* = 13.3 Hz, *J* = 6.1 Hz, *J* = 1.2 Hz, H-1b^{Allyl}), 3.95 (t, 1H, *J* = 9.4 Hz, H-4B), 3.83–3.72 (m, 4H, H-3B, H-3D, H-5B, H-6bB), 3.81 (s, 3H, C*H*$_3^{OMe}$), 3.80 (s, 3H, C*H*$_3^{OMe}$), 3.78 (s, 3H, C*H*$_3^{OMe}$), 3.70 (t, 1H, *J* = 8.1 Hz, H-2C), 3.65 (t, 1H, *J* = 9.3 Hz, H-4D), 3.63 (s, 3H, C*H*$_3^{OMe}$), 3.52–3.48 (m, 1H, H-5D), 3.49 (t, 1H, *J* = 9.3 Hz, H-4C), 3.44 (t, 1H, *J* = 10.4 Hz, H-6bC), 3.37 (t, 1H, *J* = 8.9 Hz, H-3C), 2.96 (td, 1H, *J* = 9.6 Hz, *J* = 5.0 Hz, H-5C), 2.021 (s, 3H, C*H*$_3^{Ac}$), 2.015 (s, 3H, C*H*$_3^{Ac}$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 170.6 (O*C*=O), 170.4 (O*C*=O), 164.9 (O*C*=O), 160.1 (C^{Ar}), 159.4 (C^{Ar}), 159.2 (C^{Ar}), 159.1 (C^{Ar}), 138.5 (C^{Ar}), 137.6 (C^{Ar}), 137.5 (C^{Ar}), 133.9 (C-2^{Allyl}), 133.6 (C^{Ar}), 133.3 (*C*H^{AZMB}), 131.5 (C^{Ar}), 130.73 (*C*H^{AZMB}), 130.69 (C^{Ar}), 130.00 (C^{Ar}), 129.98 (C^{Ar}), 129.9 (*C*H^{AZMB}), 129.7 (2C, 2 × *C*H^{Ar}), 129.1 (2C, 2 × *C*H^{Ar}), 129.0 (2C, 2 × *C*H^{Ar}), 128.7 (2C, 2 × *C*H^{Ar}), 128.5 (2C, 2 × *C*H^{Ar}), 128.3 (3C, 3 × *C*H^{Ar}), 128.03 (*C*H^{Ar}), 128.01 (2C, 2 × *C*H^{Ar}), 127.7 (*C*H^{Ar}), 127.4 (2C, 2 × *C*H^{Ar}), 117.8 (C-3^{Allyl}), 114.0 (2C, 2 × *C*H^{Ar}), 113.8 (2C, 2 × *C*H^{Ar}), 113.64 (2C, 2 × *C*H^{Ar}), 113.60 (2C, 2 × *C*H^{Ar}), 101.3 (PMP*C*HO$_2$), 101.1 (C-1C), 100.1 (C-1D), 95.2 (C-1B), 83.2 (C-3D), 82.0 (C-3C), 81.9 (C-4C), 78.3 (C-4D), 78.0 (C-3B), 77.9 (C-2C), 77.1 (C-4B), 75.5 (*C*H$_2^{Ar}$), 75.2 (*C*H$_2^{Ar}$), 74.8 (*C*H$_2^{Ar}$), 74.3 (*C*H$_2^{Ar}$), 74.0 (C-2D), 73.1 (C-5D), 72.9 (C-2B), 72.8 (*C*H$_2^{Ar}$), 70.7 (C-5B), 68.9 (C-6C), 68.6 (C-1^{Allyl}), 67.8 (C-6B), 65.4 (C-5C), 62.9 (C-6D), 55.43 (*C*H$_3^{OMe}$), 55.42 (*C*H$_3^{OMe}$), 55.39 (*C*H$_3^{OMe}$), 55.3 (*C*H$_3^{OMe}$), 53.0 (*C*H$_2^{AZMB}$), 21.00 (*C*H$_3^{Ac}$), 20.99 (*C*H$_3^{Ac}$); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{79}H_{87}NaN_3O_{23}$ 1468.5623; found 1468.5610; *m/z*: [M + K]$^+$ calcd for $C_{79}H_{87}KN_3O_{23}$ 1484.5362; found 1484.5447.

*Benzyl (R)-3'-O-[2-O-(2-Azidomethylbenzoyl)-3,6-di-O-benzyl-4-O-levulinoyl-β-D-glucopyranosyl]decanoate (**35**).* To a round-bottom flask were added donor **7a** (525 mg, 0.726 mmol, 1.0 equiv), acceptor **9**[27] (162 mg, 0.581 mmol, 0.8 equiv), and NIS (262 mg, 1.16 mmol, 1.6 equiv), and the mixture was dried under high

vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (2.9 g, 4.0 mass equiv) and dry DCE (7.5 mL) were added, and the mixture was stirred for 1 h at rt. The mixture was then cooled to 0 °C and $Yb(OTf)_3$ (90 mg, 0.15 mmol, 0.2 equiv) was added. The reaction mixture was brought back to rt and stirred at this temperature for 1 h. Then, Et_3N (200 μL, 1.45 mmol, 2.0 equiv) was added to quench the reaction, which was then filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2) gave the desired compound **35** (359 mg, 70%) as a colorless oil: R_f 0.25 (Hex/EtOAc 7:3); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.94–7.92 (m, 1H, C*H*^{AZMB}), 7.58–7.52 (m, 2H, 2 × C*H*^{AZMB}), 7.38–7.35 (m, 1H, C*H*^{AZMB}), 7.34–7.25 (m, 10H, 10 × C*H*^{Ar}), 7.14–7.12 (m, 5H, 5 × C*H*^{Ar}), 5.24 (dd, 1H, *J* = 9.4 Hz, *J* = 8.0 Hz, H-2), 5.15 (t, 1H, *J* = 9.4 Hz, H-4), 5.09 (d, 1H, *J* = 12.4 Hz, CH*H*^{Bn}), 4.99 (d, 1H, *J* = 12.4 Hz, C*H*H^{Bn}), 4.77 (d, 1H, *J* = 15.1 Hz, CH*H*^{AZMB}), 4.75 (d, 1H, *J* = 15.1 Hz, C*H*H^{AZMB}), 4.67 (d, 1H, *J* = 8.1 Hz, H-1), 4.62 (d, 1H, *J* = 11.6 Hz, CH*H*^{Bn}), 4.54 (d, 1H, *J* = 11.6 Hz, C*H*H^{Bn}), 4.48 (s, 2H, C*H*$_2^{Bn}$), 4.05–4.01 (m, 1H, H-3'), 3.84 (t, 1H, *J* = 9.4 Hz, H-3), 3.62–3.52 (m, 3H, H-5, H-6a, H-6b), 2.92 (dd, 1H, *J* = 16.0 Hz, *J* = 5.8 Hz, H-2'a), 2.64–2.55 (m, 2H, C*H*$_2^{Lev}$), 2.49 (dd, 1H, *J* = 16.0 Hz, *J* = 6.9 Hz, H-2'b), 2.44–2.34 (m, 2H, C*H*$_2^{Lev}$), 2.12 (s, 3H, C*H*$_3^{Lev}$), 1.46–1.39 (m, 1H, H-4'a), 1.36–1.30 (m, 1H, H-4'b), 1.17–1.09 (m, 3H, C*H*$_2^{alkyl}$, CH*H*^{alkyl}), 1.01–0.92 (m, 5H, C*H*H^{alkyl}, 2 × C*H*$_2^{alkyl}$), 0.86–0.77 (m, 5H, C*H*$_2^{alkyl}$, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 206.3 (*C*=O^{Lev}), 171.6 (O*C*=O), 171.4 (O*C*=O), 164.7 (O*C*=O), 138.4 (C^{Ar}), 138.2 (C^{Ar}), 137.9 (C^{Ar}), 136.0 (C^{Ar}), 133.1 (*C*H^{AZMB}), 131.0 (*C*H^{AZMB}), 129.4 (*C*H^{AZMB}), 128.7 (2C, 2 × *C*H^{Bn}), 128.5 (2C, 2 × *C*H^{Bn}), 128.33 (2C, 2 × *C*H^{Bn}), 128.32 (*C*H^{Bn}), 128.27 (2C, 2 × *C*H^{Bn}), 128.02 (C^{Ar}), 127.95 (2C, 2 × *C*H^{Bn}), 127.9 (3C, 2 × *C*H^{Bn}, *C*H^{AZMB}), 127.8 (*C*H^{Bn}), 127.7 (*C*H^{Bn}), 101.7 (C-1), 80.1 (C-3), 78.2 (C-3'), 73.7 (*C*H$_2^{Bn}$), 73.6 (*C*H$_2^{Bn}$), 73.4 (C-5), 73.3 (C-2), 71.4 (C-4), 69.7 (C-6), 66.3 (*C*H$_2^{Bn}$), 53.1 (*C*H$_2^{AZMB}$), 41.2 (C-2'), 37.8 (*C*H$_2^{Lev}$), 35.2 (C-4'), 31.8 (*C*H$_2^{alkyl}$), 29.9 (*C*H$_3^{Lev}$), 29.5 (*C*H$_2^{alkyl}$), 29.1 (*C*H$_2^{alkyl}$), 28.0 (*C*H$_2^{Lev}$), 25.3 (*C*H$_2^{alkyl}$), 22.7 (*C*H$_2^{alkyl}$), 14.2 (*C*H$_3^{alkyl}$); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{50}H_{63}N_4O_{11}$ 895.4488; found 895.4488; *m/z*: $[M + Na]^+$ calcd for $C_{50}H_{59}NaN_3O_{11}$ 900.4042; found 900.4035.

*Benzyl (R)-3'-O-(3,6-Di-O-benzyl-4-O-levulinoyl-β-D-glucopyranosyl)decanoate (**36**).* To a solution of glycolipid **35** (359 mg, 0.409 mmol, 1.0 equiv) in dry THF (12.5 mL) was added PPh_3 (172 mg, 0.656 mmol, 1.6 equiv). The solution was stirred at 60 °C for 2 h, after which H_2O (1.6 mL) was added. The mixture was stirred for an additional 2 h at 60 °C before being concentrated under reduced pressure and co-evaporated with toluene. Purification by silica gel flash chromatography (Tol/EtOAc 9:1) gave the desired compound **36** (256 mg, 87%) as a colorless oil: R_f 0.25 (Tol/EtOAc 8.2); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.34–7.21 (m, 15H, 15 × C*H*^{Bn}), 5.10 (d, 1H, *J* = 12.3 Hz, CH*H*^{Bn}), 5.05 (d, 1H, *J* = 12.3 Hz, C*H*H^{Bn}), 5.00 (t, 1H, *J* = 9.2 Hz, H-4), 4.82 (d, 1H, *J* = 11.8 Hz, CH*H*^{Bn}), 4.70 (d, 1H, *J* = 11.8 Hz, C*H*H^{Bn}), 4.46 (s, 2H, C*H*$_2^{Bn}$), 4.67 (d, 1H, *J* = 7.4 Hz, H-1), 4.15–4.11 (m, 1H, H-3'), 3.57–3.47 (m, 5H, H-2, H-3, H-5, H-6a, H-6b), 2.85 (dd, 1H, *J* = 15.7 Hz, *J* = 6.4 Hz, H-2'a), 2.63–2.52 (m, 3H, C*H*$_2^{Lev}$, H-2'b), 2.47 (br s, 1H, O*H*), 2.42–2.31 (m, 2H, C*H*$_2^{Lev}$), 2.11 (s, 3H, C*H*$_3^{Lev}$), 1.65–1.59 (m, 1H, H-4'a), 1.55–1.49 (m, 1H, H-4'b), 1.42–1.38 (m, 1H, CH*H*^{alkyl}), 1.33–1.25 (m, 9H, CH*H*^{alkyl}, 4 × C*H*$_2^{alkyl}$), 0.88 (t, 3H, *J* = 7.0 Hz, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 206.4 (*C*=O^{Lev}), 171.8 (O*C*=O), 171.4 (O*C*=O), 138.7 (C^{Ar}), 138.3 (C^{Ar}), 136.0 (C^{Ar}), 128.7 (2C, 2 × *C*H^{Bn}), 128.5 (2C, 2 × *C*H^{Bn}), 128.42 (2C, 2 × *C*H^{Bn}), 128.37 (*C*H^{Bn}), 128.35 (2C, 2 × *C*H^{Bn}), 127.93 (2C, 2 × *C*H^{Bn}), 127.87 (2C, 2 × *C*H^{Bn}), 127.74 (*C*H^{Bn}), 127.67 (*C*H^{Bn}), 102.6 (C-1), 81.6 (C-3), 77.1 (C-3'), 74.5 (C-2), 74.4 (*C*H$_2^{Bn}$), 73.7 (*C*H$_2^{Bn}$), 73.6 (C-5), 70.9 (C-4), 69.7 (C-6), 66.4 (*C*H$_2^{Bn}$), 41.0 (C-2'), 37.9 (*C*H$_2^{Lev}$), 34.9 (C-4'), 31.9 (*C*H$_2^{alkyl}$), 29.9 (*C*H$_3^{Lev}$), 29.6 (*C*H$_2^{alkyl}$), 29.3 (*C*H$_2^{alkyl}$), 28.0 (*C*H$_2^{Lev}$), 25.4 (*C*H$_2^{alkyl}$), 22.8 (*C*H$_2^{alkyl}$), 14.2 (*C*H$_3^{alkyl}$); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{42}H_{58}NO_{10}$ 736.4055; found 736.4053.

*Benzyl (R)-3'-O-[2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl-(1 → 2)-3,6-di-O-benzyl-4-O-levulinoyl-β-D-glucopyranosyl]decanoate (**37**).* To a round-bottomed flask were added acetimidate **8**[64] (238 mg, 0.483 mmol, 1.0 equiv) and glycolipid **36** (256 mg, 0.357 mmol, 0.8 equiv), and the mixture was dried under high vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (1.0 g, 4.0 mass equiv) and dry DCM (5.0 mL) were added and the mixture was stirred for 1 h at rt under an Ar atmosphere. Next, TMSOTf (24.5 μL, 0.135 mmol, 0.3 equiv) was added. The suspension was stirred at rt for 21 h, after which Et_3N (200 μL, 1.45 mmol, 3.0 equiv) was added to quench the reaction. The suspension was filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 6:4) gave the desired compound **37** (332 mg, 89%) as a colorless oil: R_f 0.4 (Hex/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.37–7.21 (m, 15H, 15 × C*H*^{Bn}), 5.13–5.08 (m, 3H, CH*H*^{Bn}, H-4E, H-2E*), 5.04 (d, 1H, *J* = 12.4 Hz, C*H*H^{Bn}), 5.00–4.94 (m, 3H, H-4A, H-1E, H-3E*), 4.73 (d, 1H, *J* = 11.2 Hz, CH*H*^{Bn}), 4.54 (d, 1H, *J* = 11.2 Hz, C*H*H^{Bn}), 4.49 (d, 1H, *J* = 7.6 Hz, H-1A), 4.44 (s, 2H, C*H*$_2^{Bn}$), 4.27 (dd, 1H, *J* = 12.3 Hz, *J* = 4.3 Hz, H-6aE), 4.15–4.11 (m, 1H, H-3'), 4.03 (dd, 1H, *J* = 12.3 Hz, *J* = 2.2 Hz, H-6bE), 3.65 (dd, 1H, *J* = 9.2 Hz, *J* = 7.6 Hz, H-2A), 3.62–3.57 (m, 2H, H-5E, H-3A), 3.52–3.44 (m, 3H, H-5A, H-6aA, H-6bA), 2.80 (dd, 1H, *J* = 15.6 Hz, *J* = 6.4 Hz, H-2'a), 2.57–2.45 (m, 3H, C*H*$_2^{Lev}$, H-2'b), 2.31 (ddd, 1H, *J* = 17.4 Hz, *J* = 7.5 Hz, *J* = 6.0 Hz, CH*H*^{Lev}), 2.17 (dt, 1H, *J* = 17.4 Hz, *J* = 6.4 Hz, C*H*H^{Lev}), 2.09 (s, 3H, C*H*$_3^{Lev}$), 2.05 (s, 3H, C*H*$_3^{Ac}$), 2.01 (s, 3H, C*H*$_3^{Ac}$), 1.98 (s, 3H, C*H*$_3^{Ac}$), 1.96 (s, 3H, C*H*$_3^{Ac}$), 1.64–1.58 (m, 1H, H-4'a), 1.53–1.48 (m, 1H, H-4'b), 1.45–1.38 (m, 2H, C*H*$_2^{alkyl}$), 1.34–1.28 (m, 8H, 4 × C*H*$_2^{alkyl}$), 0.90 (t, 3H, *J* = 6.9 Hz, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 206.3 (*C*=O^{Lev}), 171.8 (O*C*=O), 171.3 (O*C*=O), 170.8 (O*C*=O), 170.4 (O*C*=O), 169.43 (O*C*=O), 169.39 (O*C*=O), 138.2 (C^{Ar}), 138.1 (C^{Ar}), 136.0 (C^{Ar}), 128.64 (2C, 2 × *C*H^{Bn}), 128.58 (2C, 2 × *C*H^{Bn}), 128.39 (2C, 2 × *C*H^{Bn}), 128.35 (2C, 2 × *C*H^{Bn}), 128.3 (*C*H^{Bn}), 128.0 (2C, 2 × *C*H^{Bn}), 127.9 (*C*H^{Bn}), 127.8 (2C, 2 × *C*H^{Bn}), 127.7 (*C*H^{Bn}), 101.3 (C-1A), 100.1 (C-1E, $^1J_{C\text{-}H}$ = 164.4 Hz), 82.6 (C-3A), 79.3 (C-2A), 76.9 (C-3'), 75.7 (*C*H$_2^{Bn}$), 73.6 (*C*H$_2^{Bn}$), 73.3 (C-4E*), 73.1 (C-5A), 72.5 (C-4A*), 72.0 (C-5E), 71.6 (C-3E*), 69.6 (C-6A), 68.2 (C-2E*), 66.3 (*C*H$_2^{Bn}$), 62.0 (C-6E), 40.9 (C-2'), 37.8 (*C*H$_2^{Lev}$), 34.5 (C-4'), 32.0 (*C*H$_2^{alkyl}$), 29.84 (*C*H$_3^{Lev}$), 29.77 (*C*H$_2^{alkyl}$), 29.5 (*C*H$_2^{alkyl}$), 27.9 (*C*H$_2^{Lev}$), 24.9 (*C*H$_2^{alkyl}$), 22.8 (*C*H$_2^{alkyl}$), 20.9 (*C*H$_3^{Ac}$), 20.8 (*C*H$_3^{Ac}$), 20.7 (2C, 2 × *C*H$_3^{Ac}$), 14.2 (*C*H$_3^{alkyl}$); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{56}H_{76}NO_{19}$ 1066.5006; found 1066.4992; *m/z*: $[M + Na]^+$ calcd for $C_{56}H_{72}NaO_{19}$ 1071.4560; found 1071.4552.

*Benzyl (R)-3'-O-[2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl-(1 → 2)-3,6-di-O-benzyl-β-D-glucopyranosyl]decanoate (**3**).* Compound **37** (291 mg, 0.277 mmol, 1.0 equiv) was solubilized in dry pyridine (1.8 mL), and the solution was cooled to 0 °C. Glacial AcOH (1.2 mL) and hydrazine monohydrate (70 μL, 1.4 mmol, 5.2 equiv) were successively added. The solution was stirred for 19 h at rt before being concentrated under reduced pressure and co-evaporated with toluene (10×). Purification by silica gel flash chromatography (Tol/EtOAc 85:15 to 8:2) gave the desired compound **3** (216 mg, 82%) as a colorless oil: R_f 0.25 (Tol/EtOAc 85:15); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.42–7.25 (m, 15H, 15 × C*H*^{Bn}), 5.16–5.09 (m, 3H, CH*H*^{Bn}, H-4E, H-2E*), 5.04 (d, 1H, *J* = 12.4 Hz, C*H*H^{Bn}), 5.02–4.98 (m, 2H, H-1E, H-3E*), 4.77 (d, 1H, *J* = 11.1 Hz, CH*H*^{Bn}), 4.74 (d, 1H, *J* = 11.1 Hz, C*H*H^{Bn}), 4.53 (d, 1H, *J* = 12.1 Hz, CH*H*^{Bn}), 4.48 (d, 1H, *J* = 12.1 Hz, C*H*H^{Bn}), 4.45 (d, 1H, *J* = 7.7 Hz, H-1A), 4.28 (dd, 1H, *J* = 12.3 Hz, *J* = 4.3 Hz, H-6aE), 4.13–4.09 (m, 1H, H-3'), 4.03 (dd, 1H, *J* = 12.3 Hz, *J* = 2.2 Hz, H-6bE), 3.66 (dd, 1H, *J* = 10.2 Hz, *J* = 4.7 Hz, H-6aA), 3.63–3.57 (m, 4H, H-2A, H-4A, H-5E, H-6bA), 3.43 (t, 1H, *J* = 9.0 Hz, H-3A), 3.32 (dt, 1H, *J* = 9.6 Hz, *J* = 4.8 Hz, H-5A), 2.76 (dd, 1H, *J* = 15.7 Hz, *J* = 6.5 Hz, H-2'a), 2.65 (br s, 1H, O*H*), 2.53 (dd, 1H, *J* = 15.7 Hz, *J* = 6.0 Hz, 1H, H-2'b), 2.04 (s, 3H,

CH_3^{Ac}), 2.010 (s, 3H, CH_3^{Ac}), 2.006 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.63–1.57 (m, 1H, H-4'a), 1.53–1.47 (m, 1H, H-4'b), 1.45–1.38 (m, 2H, CH_2^{alkyl}), 1.34–1.26 (m, 8H, 4 × CH_2^{alkyl}), 0.90 (t, 3H, *J* = 6.9 Hz, CH_3^{alkyl}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 171.2 (O*C*=O), 170.7 (O*C*=O), 170.3 (O*C*=O), 169.36 (O*C*=O), 169.35 (O*C*=O), 138.4 (C^{Ar}), 137.6 (C^{Ar}), 135.9 (C^{Ar}), 128.8 (2C, 2 × *C*H^{Bn}), 128.6 (2C, 2 × *C*H^{Bn}), 128.5 (2C, 2 × *C*H^{Bn}), 128.3 (2C, 2 × *C*H^{Bn}), 128.23 (*C*H^{Bn}), 128.19 (2C, 2 × *C*H^{Bn}), 128.1 (*C*H^{Bn}), 127.9 (*C*H^{Bn}), 127.7 (2C, 2 × *C*H^{Bn}), 101.5 (C-1A), 100.1 (C-1E), 84.7 (C-3A), 78.9 (C-2A*), 76.8 (C-3'), 75.6 (*C*H$_2^{Bn}$), 73.7 (*C*H$_2^{Bn}$), 73.3 (C-5A), 73.2 (C-4E*), 72.8 (C-4A*), 72.5 (C-3E), 71.8 (C-5E*), 70.5 (C-6A), 68.2 (C-2E*), 66.1 (*C*H$_2^{Bn}$), 62.0 (C-6E), 40.9 (C-2'), 34.5 (C-4'), 31.9 (*C*H$_2^{alkyl}$), 29.7 (*C*H$_2^{alkyl}$), 29.5 (*C*H$_2^{alkyl}$), 24.8 (*C*H$_2^{alkyl}$), 22.7 (*C*H$_2^{alkyl}$), 20.8 (*C*H$_3^{Ac}$), 20.7 (*C*H$_3^{Ac}$), 20.62 (*C*H$_3^{Ac}$), 20.60 (*C*H$_3^{Ac}$), 14.1 (*C*H$_3^{alkyl}$); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{51}H_{70}NO_{17}$ 968.4638; found 968.4664; *m/z*: [M + Na]$^+$ calcd for $C_{51}H_{66}NaO_{17}$ 973.4192; found 973.4217.

*Benzyl (R)-3'-O-[6-O-Acetyl-2-O-(2-azidomethylbenzoyl)-3,4-di-O-benzyl-β-D-glucopyranosyl-(1→2)-3-O-(4-methoxybenzyl)-4,6-O-(4-methoxybenzylidene)-β-D-glucopyranosyl-(1 → 4)-2-O-acetyl-3,6-di-O-(4-methoxybenzyl)-β-D-glucopyranosyl-(1 → 4)-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,6-di-O-benzyl-β-D-glucopyranosyl]decanoate (**39**).* In a 5 mL round-bottom flask filled with an Ar atmosphere, 1,5-cyclooctadiene-bis(methyldiphenylphosphine)iridium(I) (14 mg, 0.016 mmol, 0.005 equiv) was suspended in dry THF (1.5 mL). The atmosphere was replaced three times with hydrogen gas. The mixture appearance changed color from a red suspension to a light-yellow solution. The atmosphere was then turned back to Ar three times. The resulting iridium solution was then added to a solution of compound **25** (430 mg, 0.297 mmol, 1.0 equiv) in dry THF (1.5 mL). The mixture was stirred at rt for 2 h, after which was added a solution of iodine (153 mg, 0.602 mmol, 2.0 equiv) in THF (1.5 mL) and water (400 μL). The mixture was stirred at rt for another 30 min. Then, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (15 mL), and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. The mixture was filtered through silica gel (Tol/EtOAc 7:3) to remove the majority of impurities yielding 378 mg of partially pure hemiacetal: R_f 0.3 (Tol/EtOAc 6:4); HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{76}H_{87}N_4O_{23}$ 1423.5756; found 1423.5720; *m/z*: [M + Na]$^+$ calcd for $C_{76}H_{83}NaN_3O_{23}$ 1428.5310; found 1428.5285. Next, a portion of the hemiacetal (103 mg, 73.0 μmol, 1.0 equiv) was dissolved in acetone (1.0 mL) and Cs_2CO_3 (37 mg, 0.11 mmol, 1.5 equiv) and phenyl trifluoroacetimidoyl chloride (148 mg, 0.712 mmol, 10 equiv) were successively added. The mixture was stirred at rt for 2 h, then filtered over Celite and concentrated under reduced pressure. The mixture was once again filtered through silica gel (Tol/EtOAc 9:1 with 1% of Et_3N) to give 103 mg of partially pure *N*-phenyltrifluoroacetimidate: R_f 0.65 (Tol/EtOAc 75:25 + 1% Et_3N). The latter *N*-phenyltrifluoroacetimidate (103 mg, 65.2 μmol, 1.0 equiv) was mixed with compound **3** (51 mg, 54 μmol, 0.8 equiv) in a round-bottom flask and dried under high vacuum for 1 h. Then, freshly activated 4 Å molecular sieves (453 mg, 4.0 mass equiv) and dry toluene (2.0 mL) were added. The suspension was stirred at rt for 1 h under an Ar atmosphere. Then, the mixture was cooled to 0 °C and a 10% *v/v* solution of TMSOTf in dry toluene (23 μL, 13 μmol, 0.2 equiv) was added. The suspension was stirred at 0 °C for 1 h. Finally, the reaction was quenched with 50 μL of Et_3N, filtered over Celite, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 6:4) gave the desired compound **39** (75 mg, 40% over four steps) as a colorless oil: R_f 0.15 (Hex/EtOAc 6:4); ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.83–7.82 (m, 1H, C*H*^{AZMB}), 7.54–7.47 (m, 3H, 3 × C*H*^{Ar}), 7.34–7.25 (m, 21H, 21 × C*H*^{Ar}), 7.19–7.14 (m, 10H, 10 × C*H*^{Ar}), 7.08–7.07 (m, 2H, 2 × C*H*^{Ar}), 6.87–6.83 (m, 6H, 6 × C*H*^{Ar}), 6.68–6.66 (m, 2H, 2 × C*H*^{Ar}), 5.34 (s, 1H, PMPC*H*O$_2$), 5.28 (dd, 1H, *J* = 9.6 Hz, *J* = 8.1 Hz, H-2D), 5.23 (d, 1H, *J* = 10.1 Hz, CH*H*^{Ar}), 5.10 (d, 1H, *J* = 12.4 Hz, CH*H*^{Ar}), 5.09 (d, 1H, *J* = 8.0 Hz, H-1D), 5.05–5.00 (m, 4H, H-1E, H-2E, H-4E, C*H*H^{Ar}), 4.93–4.89 (m, 2H, H-2B, H-3E), 4.82 (d, 1H, *J* = 10.9 Hz, CH*H*^{Ar}), 4.80 (d, 1H, *J* = 10.6 Hz, CH*H*^{Ar}), 4.77 (d, 1H, *J* = 15.0 Hz, CH*H*^{AZMB}), 4.76 (d, 1H, *J* = 10.6 Hz, CH*H*^{Ar}), 4.73 (d, 1H, *J* = 15.0 Hz, C*H*H^{AZMB}), 4.69–4.66 (m, 3H, C*H*H^{Ar}, CH*H*^{Ar}, CH*H*^{Ar}), 4.57 (d, 1H, *J* = 8.2 Hz, H-1B), 4.50 (d, 1H, *J* = 11.0 Hz, CH*H*^{Ar}), 4.49 (d, 1H, *J* = 12.2 Hz, C*H*H^{Ar}), 4.46 (d, 1H, *J* = 10.1 Hz, C*H*H^{Ar}), 4.43 (d, 1H, *J* = 12.2 Hz, C*H*H^{Ar}), 4.42 (d, 1H, *J* = 10.6 Hz, CH*H*^{Ar}), 4.40 (d, 1H, *J* = 7.6 Hz, H-1C), 4.34 (d, 1H, *J* = 7.7 Hz, H-1A), 4.31 (d, 1H, *J* = 10.6 Hz, C*H*H^{Ar}), 4.31–4.28 (m, 1H, H-6aD), 4.27 (d, 1H, *J* = 10.7 Hz, C*H*H^{Ar}), 4.24 (dd, 1H, *J* = 11.9 Hz, *J* = 5.5 Hz, H-6bD), 4.21 (dd, 1H, *J* = 12.1 Hz, *J* = 4.4 Hz, H-6aE), 4.05–3.97 (m, 6H, H-3', H-4A, H-4B, H-6aB[a], H-6aC, H-6aE), 3.90 (dd, 1H, *J* = 10.5 Hz, *J* = 1.5 Hz, H-6bB)[a], 3.80 (s, 3H, CH_3^{OMe}), 3.79 (s, 3H, CH_3^{OMe}), 3.78 (s, 3H, CH_3^{OMe}), 3.78–3.75 (m, 1H, H-3D), 3.73–3.61 (m, 4H, H-2A, H-2C, H-6aA[a], H-6bA[a]), 3.63 (s, 3H, CH_3^{OMe}), 3.57 (dd, 1H, *J* = 10.0 Hz, *J* = 8.8 Hz, H-4D), 3.51 (t, 1H, *J* = 8.9 Hz, H-3A), 3.47 (t, 1H, *J* = 9.2 Hz, H-4C), 3.47–3.45 (m, 1H, H-5D), 3.43 (t, 1H, *J* = 9.2 Hz, H-3B), 3.43–3.40 (m, 1H, H-5E), 3.39 (t, 1H, *J* = 8.9 Hz, H-3C), 3.35 (d, 1H, *J* = 10.3 Hz, H-6bC), 3.35–3.32 (m, 1H, H-5B)[b], 3.21 (ddd, 1H, *J* = 9.6 Hz, *J* = 3.0 Hz, *J* = 2.0 Hz, H-5A)[b], 2.87 (td, 1H, *J* = 9.7 Hz, *J* = 5.1 Hz, H-5C), 2.85 (dd, 1H, *J* = 15.7 Hz, *J* = 6.1 Hz, H-2'a), 2.50 (dd, 1H, *J* = 15.7 Hz, *J* = 6.9 Hz, H-2'b), 2.02 (s, 3H, CH_3^{Ac}), 2.01 (s, 3H, CH_3^{Ac}), 1.99 (s, 3H, CH_3^{Ac}), 1.98 (s, 3H, CH_3^{Ac}), 1.91 (s, 3H, CH_3^{Ac}), 1.88 (s, 3H, CH_3^{Ac}), 1.56–1.51 (m, 1H, H-4'a), 1.47–1.42 (m, 3H, H-4'b, CH_2^{alkyl}), 1.34–1.28 (m, 8H, 4 × CH_2^{alkyl}), 0.90 (t, 3H, *J* = 6.7 Hz, CH_3^{alkyl}); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ (ppm): 171.5 (C-1'), 170.8 (O*C*=O), 170.5 (O*C*=O), 170.3 (O*C*=O), 169.5 (O*C*=O), 169.3 (2C, 2 × O*C*=O), 164.9 (O*C*=O^{AZMB}), 160.1 (C^{Ar}), 159.4 (C^{Ar}), 159.1 (C^{Ar}), 159.0 (C^{Ar}), 138.7 (C^{Ar}), 138.5 (C^{Ar}), 138.3 (C^{Ar}), 137.7 (C^{Ar}), 137.6 (C^{Ar}), 136.1 (C^{Ar}), 133.3 (*C*H^{AZMB}), 131.3 (C^{Ar}), 131.1 (C^{Ar}), 130.8 (*C*H^{AZMB}), 130.6 (C^{Ar}), 130.0 (*C*H^{AZMB}), 129.9 (C^{Ar}), 129.6 (C^{Ar}), 129.04 (2C, 2 × *C*H^{Ar}), 129.02 (2C, 2 × *C*H^{Ar}), 128.9 (2C, 2 × *C*H^{Ar}), 128.8 (*C*H^{AZMB}), 128.74 (2C, 2 × *C*H^{Ar}), 128.67 (4C, 4 × *C*H^{Ar}), 128.54 (2C, 2 × *C*H^{Ar}), 128.52 (2C, 2 × *C*H^{Ar}), 128.32 (4C, 4 × *C*H^{Ar}), 128.30 (*C*H^{Ar}), 128.2 (2C, 2 × *C*H^{Ar}), 128.10 (*C*H^{Ar}), 128.05 (*C*H^{Ar}), 128.03 (*C*H^{Ar}), 128.02 (2C, 2 × *C*H^{Ar}), 127.95 (2C, 2 × *C*H^{Ar}), 127.8 (*C*H^{Ar}), 127.4 (2C, 2 × *C*H^{Ar}), 114.0 (2C, 2 × *C*H^{Ar}), 113.73 (2C, 2 × *C*H^{Ar}), 113.71 (2C, 2 × *C*H^{Ar}), 113.6 (2C, 2 × *C*H^{Ar}), 101.4 (C-1A), 102.1 (C-1C), 101.1 (PMP*C*HO$_2$), 100.3 (C-1D), 100.2 (C-1B), 99.7 (C-1E), 84.1 (C-3A), 83.1 (C-3D), 82.2 (C-3C), 81.9 (C-4C), 81.0 (C-3B), 78.4 (C-4D), 78.1 (C-2A)[c], 77.8 (C-2C)[c], 77.6 (C-3'), 77.3 (C-4A)[d], 76.3 (C-4B)[d], 75.7 (*C*H$_2^{Ar}$), 75.5 (*C*H$_2^{Ar}$), 75.32 (C-5B)[e], 75.29 (*C*H$_2^{Ar}$), 75.0 (C-5A)[e], 74.33 (*C*H$_2^{Ar}$), 74.29 (*C*H$_2^{Ar}$), 73.9 (C-2D), 73.6 (*C*H$_2^{Ar}$), 73.5 (C-5D), 73.3 (C-2B)[f], 73.2 (C-2E)[g], 72.3 (*C*H$_2^{Ar}$), 71.9 (C-3E)[f, g], 71.6 (C-5E), 68.8 (C-6C), 68.6 (C-4E)[g], 68.2 (C-6B), 67.7 (C-6A), 66.2 (*C*H$_2^{Ar}$), 65.2 (C-5C), 62.8 (C-6D), 62.2 (C-6E), 55.5 (*C*H$_3^{OMe}$), 55.44 (*C*H$_3^{OMe}$), 55.42 (*C*H$_3^{OMe}$), 55.3 (*C*H$_3^{OMe}$), 53.0 (*C*H$_2^{AZMB}$), 41.3 (C-2'), 35.1 (C-4'), 32.1 (*C*H$_2^{alkyl}$), 29.8 (*C*H$_2^{alkyl}$), 29.7 (*C*H$_2^{alkyl}$), 24.8 (*C*H$_2^{alkyl}$), 22.8 (*C*H$_2^{alkyl}$), 21.02 (*C*H$_3^{Ac}$), 21.01 (*C*H$_3^{Ac}$), 21.0 (*C*H$_3^{Ac}$), 20.8 (*C*H$_3^{Ac}$), 20.74 (*C*H$_3^{Ac}$), 20.73 (*C*H$_3^{Ac}$), 14.3 (*C*H$_3^{alkyl}$). [a, b, c, d, e, f, g]: interchangeable; HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{127}H_{151}N_4O_{39}$ 2355.9950; found 2355.9901.

*Benzyl (R)-3'-O-[6-O-Acetyl-2-O-(2-azidomethylbenzoyl)-3,4-di-O-benzyl-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranosyl-(1 → 4)-2-O-acetyl-β-D-glucopyranoside-(1 → 4)-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,6-di-O-benzyl-β-D-glucopyranosyl]decanoate (**40**).* To a solution of compound **39** (93 mg, 40 μmol, 1.0 equiv) in CH_3CN (1.4 mL) and water (160 μL) was added CAN (169 mg, 0.307 mmol, 7.7 equiv), and the solution was stirred at rt for 1 h. Then, saturated aq. $NaHCO_3$ (3.0 mL) was added, and the mixture was stirred for an additional 30 min before being diluted with saturated aq. $NaHCO_3$ (10 mL) and extracted

with DCM (3 × 15 mL). The organic layer was concentrated under reduced pressure and co-evaporated with toluene (6×). Purification by silica gel flash chromatography (DCM/MeOH 10:0 to 97:3) gave the desired compound **40** (64 mg, 85%) as a colorless oil: R_f 0.2 (DCM/MeOH 95:5); $[\alpha]_D^{20}$ +4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.96–7.94 (m, 1H, C*H*^{AZMB}), 7.54–7.51 (m, 1H, C*H*^{AZMB}), 7.46–7.40 (m, 5H, 5 × C*H*^{Ar}), 7.36–7.23 (m, 17H, 17 × C*H*^{Ar}), 7.18–7.13 (m, 5H, 5 × C*H*^{Ar}), 5.24 (dd, 1H, *J* = 8.6 Hz, *J* = 7.8 Hz, H-2D), 5.11 (d, 1H, *J* = 12.2 Hz, CH*H*^{Bn}), 5.08–5.03 (m, 4H, C*H*H^{Bn}, H-1D, H-2E, H-4E), 5.01 (dd, 1H, *J* = 10.4 Hz, CH*H*^{Bn}), 4.98–4.93 (m, 2H, H-1E, H-3E), 4.84 (d, 1H, *J* = 11.0 Hz, CH*H*^{Bn}), 4.82 (d, 1H, *J* = 14.4 Hz, CH*H*^{AZMB}), 4.79 (d, 1H, *J* = 11.3 Hz, CH*H*^{Bn}), 4.74 (dd, 1H, *J* = 9.2 Hz, *J* = 8.4 Hz, H-2B), 4.66 (d, 1H, *J* = 14.4 Hz, C*H*H^{AZMB}), 4.65 (d, 1H, *J* = 11.2 Hz, C*H*H^{Bn}), 4.64 (d, 1H, *J* = 12.2 Hz, CH*H*^{Bn}), 4.60 (d, 1H, *J* = 11.0 Hz, C*H*H^{Bn}), 4.58 (d, 1H, *J* = 10.4 Hz, C*H*H^{BBn}), 4.50 (d, 1H, *J* = 12.3 Hz, C*H*H^{Bn}), 4.44 (d, 1H, *J* = 8.2 Hz, H-1B), 4.38 (dd, 1H, *J* = 12.0 Hz, *J* = 2.2 Hz, H-6aD), 4.36 (d, 1H, *J* = 7.8 Hz, H-1A), 4.33 (d, 1H, *J* = 7.7 Hz, H-1C), 4.27 (dd, 1H, *J* = 12.3 Hz, *J* = 4.6 Hz, H-6aE), 4.21 (dd, 1H, *J* = 12.0 Hz, *J* = 4.1 Hz, H-6bD), 4.13 (br s, 1H, O*H*), 4.07–4.03 (m, 1H, H-3'), 4.03 (dd, 1H, *J* = 12.3 Hz, *J* = 2.3 Hz, H-6bE), 3.85 (t, 2H, *J* = 8.9 Hz, H-3D, H-4A), 3.78 (dd, 1H, *J* = 12.2 Hz, *J* = 3.1 Hz, H-6aB), 3.74 (dd, 1H, *J* = 9.7 Hz, *J* = 8.6 Hz, H-3A), 3.70–3.65 (m, 3H, H-6aA, H-6aC, H-6bB), 3.64–3.58 (m, 4H, H-2A, H-5D, H-6bA, H-6bC), 3.55 (ddd, 1H, *J* = 9.5 Hz, *J* = 4.4 Hz, *J* = 2.4 Hz, H-5E), 3.53 (dd, 1H, *J* = 8.7 Hz, *J* = 7.7 Hz, H-2C), 3.48 (t, 1H, *J* = 9.1 Hz, H-4D), 3.45 (t, 1H, *J* = 9.3 Hz, H-4C), 3.43–3.39 (m, 3H, H-3B, H-3C, H-4B), 3.34 (br s, 1H, O*H*), 3.28–3.20 (m, 2H, H-5A, H-5B), 3.03–2.96 (m, 2H, O*H*, H-5C), 2.83 (dd, 1H, *J* = 15.6 Hz, *J* = 6.2 Hz, H-2'a), 2.83–2.76 (br s, 1H, O*H*), 2.51 (dd, 1H, *J* = 15.6 Hz, *J* = 6.7 Hz, H-2'b), 2.04 (s, 3H, C*H*$_3^{Ac}$), 2.02 (s, 3H, C*H*$_3^{Ac}$), 2.22 (s, 3H, C*H*$_3^{Ac}$), 1.99 (s, 3H, C*H*$_3^{Ac}$), 1.97 (s, 3H, C*H*$_3^{Ac}$), 1.96 (s, 3H, C*H*$_3^{Ac}$), 1.58–1.53 (m, 1H, H-4'a), 1.49–1.41 (m, 3H, H-4'b, C*H*$_2^{alkyl}$), 1.36–1.28 (m, 8H, 4 × C*H*$_2^{alkyl}$), 0.91 (t, 3H, *J* = 6.9 Hz, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 171.5 (O*C*=O), 170.83 (O*C*=O), 170.82 (O*C*=O), 170.4 (O*C*=O), 169.9 (O*C*=O), 169.5 (O*C*=O), 169.3 (O*C*=O), 165.3 (O*C*=O^{AZMB}), 138.6 (C^{Ar}), 138.1 (C^{Ar}), 138.0 (C^{Ar}), 137.52 (C^{Ar}), 137.47 (C^{Ar}), 136.1 (C^{Ar}), 133.4 (*C*H^{AZMB}), 131.3 (*C*H^{AZMB}), 130.2 (*C*H^{AZMB}), 128.8 (2C, 2 × *C*H^{Ar}), 128.72 (2C, 2 × *C*H^{Ar}), 128.68 (3C, 3 × *C*H^{Ar}), 128.6 (2C, 2 × *C*H^{Ar}), 128.5 (2C, 2 × *C*H^{Ar}), 128.44 (C^{Ar})^a, 128.35 (*C*H^{Ar})^a, 128.32 (3C, 3 × *C*H^{Ar})^a, 128.30 (*C*H^{Ar})^a, 128.25 (2C, 2 × *C*H^{Ar}), 128.11 (2C, 2 × *C*H^{Ar}), 128.09 (*C*H^{Ar})^a, 128.0 (2C, 2 × *C*H^{Ar}), 127.9 (*C*H^{Ar})^a, 127.6 (2C, 2 × *C*H^{Ar}), 101.9 (C-1A), 101.1 (C-1C), 100.2 (C-1D), 100.03 (C-1B), 99.97 (C-1E), 83.4 (C-4D), 82.8 (C-3D)^b, 80.1 (C-4C), 79.0 (C-2C), 78.1 (C-2A), 77.6 (C-3'), 77.5 (C-3A), 76.70 (C-4A)^b, 76.67 (C-4B)^c, 75.6 (C-5B), 75.3 (2C, 2 × *C*H$_2^{Bn}$), 75.2 (*C*H$_2^{Bn}$), 74.83 (C-5A), 74.81 (C-5C), 73.7 (*C*H$_2^{Bn}$), 73.6 (C-2B), 73.4 (2C, C-2D, C-5D), 73.3 (C-2E), 72.9 (C-3B)^c, 72.0 (C-3E), 71.6 (C-5F), 70.4 (C-3C)^c, 68.6 (C-4E), 67.6 (C-6A), 66.2 (*C*H$_2^{Bn}$), 62.4 (C-6D), 62.2 (C-6E), 62.0 (C-6B), 61.1 (C-6C), 53.2 (*C*H$_2^{AZMB}$), 41.3 (C-2'), 35.0 (C-4'), 32.1 (*C*H$_2^{alkyl}$), 29.8 (*C*H$_2^{alkyl}$), 29.7 (*C*H$_2^{alkyl}$), 24.9 (*C*H$_2^{alkyl}$), 22.8 (*C*H$_2^{alkyl}$), 21.1 (*C*H$_3^{Ac}$), 21.0 (*C*H$_3^{Ac}$), 20.9 (2C, 2 × *C*H$_3^{Ac}$), 20.74 (*C*H$_3^{Ac}$), 20.71 (*C*H$_3^{Ac}$), 14.3 (*C*H$_3^{alkyl}$). $^{a, b, c}$: interchangeable; HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{95}H_{121}N_4O_{35}$ 1877.7806; found 1877.7850.

*(R)-3'-O-[6-O-Acetyl-β-D-glucopyranosyl-(1 → 2)-3,4,6-tri-O-acetyl-β-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl-(1 → 4)-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl]decanoic Acid (**1**).* To a solution of pentaol **40** (52 mg, 28 μmol, 1.0 equiv) in pyridine (2.1 mL) and Ac_2O (2.1 mL) was added a 1% *w/v* solution of DMAP in pyridine (17 μL, 14 μmol, 0.05 equiv), and the solution was stirred at rt for 14 h. Then, the mixture was concentrated under reduced pressure and co-evaporated with toluene (4×). Purification by silica gel flash chromatography (Tol/EtOAc 8:2 to 7:3) gave benzyl (*R*)-3'-*O*-[6-*O*-acetyl-2-*O*-(2-azidomethylbenzoyl)-3,4-di-*O*-benzyl-*β*-D-glucopyranosyl-(1 → 2)-3,4,6-tri-*O*-acetyl-*β*-D-glucopyranosyl-(1 → 4)-2,3,6-tri-*O*-acetyl-*β*-D-glucopyranosyl-(1 → 4)-2-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-3,6-di-*O*-benzyl-*β*-D-glucopyranosyl]decanoate (51 mg, 89%) as a colorless oil: R_f 0.50 (Tol/EtOAc 1:1); $[\alpha]_D^{20}$ –16 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.76–7.75 (m, 1H, CH^{AZMB}), 7.57–7.53 (m, 2H, 2 × CH^{AZMB}), 7.43–7.25 (m, 21H, 21 × H^{Ar}), 7.18–7.13 (m, 5H, 5 × H^{Ar}), 5.16–5.10 (m, 4H, 2 × CH*H*^{Bn}, H-2D, H-3E), 5.03 (d, 1H, *J* = 12.3 Hz, C*H*H^{Bn}), 5.02 (t, 1H, *J* = 9.4 Hz, H-4E), 5.00–4.95 (m, 2H, H-3B, H-3C), 4.92–4.85 (m, 3H, H-1E, H-2B, H-4C), 4.85–4.82 (m, 3H, CH*H*^{AZMB}, CH*H*^{Bn}, H-2E), 4.79 (d, 1H, *J* = 11.3 Hz, CH*H*^{Bn}), 4.73 (d, 1H, *J* = 8.2 Hz, H-1B), 4.70 (d, 1H, *J* = 15.5 Hz, C*H*H^{AZMB}), 4.68 (d, 1H, *J* = 11.8 Hz, C*H*H^{Bn}), 4.66 (d, 1H, *J* = 12.7 Hz, CH*H*^{Bn}), 4.65 (d, 1H, *J* = 7.9 Hz, H-1D), 4.58 (d, 1H, *J* = 10.8 Hz, C*H*H^{Bn}), 4.52 (d, 1H, *J* = 12.3 Hz, C*H*H^{Bn}), 4.47 (d, 1H, *J* = 10.6 Hz, C*H*H^{Bn}), 4.45–4.43 (m, 2H, H-6aB, H-6aD), 4.41 (d, 1H, *J* = 7.1 Hz, H-1C), 4.36 (dd, 1H, *J* = 12.2 Hz, *J* = 6.0 Hz, H-6bD), 4.35 (d, 1H, *J* = 7.8 Hz, H-1A), 4.28–4.25 (m, 2H, H-6aC, H-6bB), 4.21 (dd, 1H, *J* = 12.4 Hz, *J* = 4.4 Hz, H-6aE), 4.06–4.02 (m, 1H, H-3'), 3.99 (t, 1H, *J* = 9.1 Hz, H-4A), 3.98 (dd, 1H, *J* = 12.4 Hz, *J* = 2.5 Hz, H-6bE), 3.94 (dd, 1H, *J* = 12.2 Hz, *J* = 2.2 Hz, H-6bC), 3.80 (t, 1H, *J* = 9.3 Hz, H-3D), 3.79 (t, 1H, *J* = 9.3 Hz, H-4D), 3.71 (dd, 1H, *J* = 11.2 Hz, *J* = 3.4 Hz, H-6aA), 3.68 (dd, 1H, *J* = 8.4 Hz, *J* = 7.3 Hz, H-2C), 3.65 (dd, 1H, *J* = 9.7 Hz, *J* = 8.7 Hz, H-4B), 3.64–3.60 (m, 2H, H-2A, H-6bA), 3.56–3.52 (m, 3H, H-5B, H-5C, H-5D), 3.48 (t, 1H, *J* = 8.9 Hz, H-3A), 3.40 (ddd, 1H, *J* = 9.7 Hz, *J* = 4.3 Hz, *J* = 2.5 Hz, H-5E), 3.20 (ddd, 1H, *J* = 9.7 Hz, *J* = 3.0 Hz, *J* = 1.9 Hz, H-5A), 2.83 (dd, 1H, *J* = 15.6 Hz, *J* = 6.1 Hz, H-2'a), 2.51 (dd, 1H, *J* = 15.6 Hz, *J* = 6.6 Hz, H-2'b), 2.08 (s, 3H, C*H*$_3^{Ac}$), 2.03 (s, 3H, C*H*$_3^{Ac}$), 2.02 (s, 3H, C*H*$_3^{Ac}$), 1.993 (s, 3H, C*H*$_3^{Ac}$), 1.987 (s, 3H, C*H*$_3^{Ac}$), 1.973 (s, 3H, C*H*$_3^{Ac}$), 1.969 (s, 3H, C*H*$_3^{Ac}$), 1.94 (s, 6H, 2 × C*H*$_3^{Ac}$), 1.87 (s, 3H, C*H*$_3^{Ac}$), 1.78 (s, 3H, C*H*$_3^{Ac}$), 1.57–1.52 (m, 1H, H-4'a), 1.49–1.39 (m, 3H, H-4'b, C*H*$_2^{alkyl}$), 1.34–1.27 (m, 8H, 4 × C*H*$_2^{alkyl}$), 0.90 (t, 3H, *J* = 6.9 Hz, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 171.5 (O*C*=O), 170.8 (O*C*=O), 170.7 (O*C*=O), 170.6 (O*C*=O), 170.5 (O*C*=O), 170.3 (O*C*=O), 169.9 (O*C*=O), 169.8 (O*C*=O), 169.7 (O*C*=O), 169.5 (O*C*=O), 169.4 (O*C*=O), 169.3 (O*C*=O), 164.7 (O*C*=O^{AZMB}), 138.7 (C^{Ar}), 138.6 (C^{Ar}), 138.1 (C^{Ar}), 137.8 (C^{Ar}), 137.6 (C^{Ar}), 136.1 (C^{Ar}), 133.0 (*C*H^{AZMB}), 130.6 (*C*H^{AZMB}), 129.5 (*C*H^{AZMB}), 128.70 (4C, 4 × *C*H^{Ar}), 128.68 (2C, 2 × *C*H^{Ar}), 128.6 (*C*H^{Ar}), 128.54 (2C, 2 × *C*H^{Ar}), 128.46 (2C, 2 × *C*H^{Ar}), 128.4 (C^{Ar})^a, 128.3 (2C, 2 × *C*H^{Ar}), 128.24 (*C*H^{Ar})^a, 128.20 (*C*H^{Ar})^a, 128.13 (2C, 2 × *C*H^{Ar}), 128.12 (2C, 2 × *C*H^{Ar}), 128.09 (*C*H^{Ar})^a, 128.0 (2C, 2 × *C*H^{Ar})^a, 127.9 (*C*H^{Ar})^a, 127.8 (*C*H^{Ar})^a, 127.7 (*C*H^{Ar})^a, 101.9 (C-1A), 101.6 (C-1C), 100.7 (C-1D), 99.6 (C-1B), 99.5 (C-1E), 83.6 (C-3A), 83.0 (C-3D), 77.91 (C-2A), 77.90 (C-4B), 77.5 (C-3'), 77.0 (C-4D), 76.7 (C-2C), 76.6 (C-4A), 75.24 (*C*H$_2^{Bn}$), 75.20 (*C*H$_2^{Bn}$), 75.0 (*C*H$_2^{Bn}$), 74.8 (C-3C)^b, 74.7 (C-5A), 74.0 (C-3E)^c, 73.8 (*C*H$_2^{Bn}$), 73.6 (C-2D)^c, 73.5 (C-5D)^e, 73.2 (C-3B)^b, 72.7 (C-2E), 72.6 (C-5B)^e, 72.0 (C-2B)^d, 71.6 (C-5E), 71.5 (C-5C)^e, 68.5 (C-4E), 68.2 (C-4C)^d, 67.6 (C-6A), 66.2 (*C*H$_2^{Bn}$), 62.8 (C-6B)^f, 62.7 (C-6D)^f, 62.1 (C-6E), 61.8 (C-6C)^f, 52.9 (*C*H$_2^{AZMB}$), 41.2 (C-2'), 35.0 (C-4'), 32.1 (*C*H$_2^{alkyl}$), 29.8 (*C*H$_2^{alkyl}$), 29.6 (*C*H$_2^{alkyl}$), 24.9 (*C*H$_2^{alkyl}$), 22.8 (*C*H$_2^{alkyl}$), 21.03 (*C*H$_3^{Ac}$), 20.95 (*C*H$_3^{Ac}$), 20.91 (*C*H$_3^{Ac}$), 20.86 (*C*H$_3^{Ac}$), 20.85 (2C, 2 × *C*H$_3^{Ac}$), 20.78 (*C*H$_3^{Ac}$), 20.73 (2C, 2 × *C*H$_3^{Ac}$), 20.72 (*C*H$_3^{Ac}$), 20.65 (*C*H$_3^{Ac}$), 14.3 (*C*H$_3^{alkyl}$). $^{a, b, c, d, e, f}$: interchangeable; HRMS (ESI-TOF) *m/z:* $[M + NH_4]^+$ calcd for $C_{105}H_{131}N_4O_{40}$ 2088.8367; found 2088.8283; *m/z*: $[M + 2(NH_4)]^{2+}$ calcd for $C_{105}H_{135}N_5O_{40}$ 1052.9336; found 1052.9387. To a solution of the latter compound (27 mg, 13 μmol, 1.0 equiv) in THF (1.2 mL) and water (130 μL) were added PPh_3 (36 mg, 0.14 mmol, 10 equiv) and SiO_2 (6.7 mg, 500 mg mmol^{-1}), and the solution was stirred at rt for 18 h. Then, the mixture was concentrated under reduced pressure. Purification by size exclusion chromatography using Sephadex LH-20 in DCM followed by silica gel flash chromatography (Tol/EtOAc 8:2 to 6:4) gave benzyl (*R*)-3'-*O*-[6-*O*-acetyl-3,4-di-*O*-benzyl-*β*-D-glucopyranosyl-(1 → 2)-3,4,6-tri-*O*-acetyl-*β*-D-glucopyranosyl-(1 → 4)-2,3,6-tri-*O*-

acetyl-*β*-D-glucopyranosyl-(1 → 4)-2-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-3,6-di-*O*-benzyl-*β*-D-glucopyranosyl]decanoate (20 mg, 77%) as a colorless oil: R_f 0.25 (Tol/EtOAc 6:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.39–7.25 (m, 25H, 25 × H^{Ar}), 5.18 (t, 1H, *J* = 9.4 Hz, H-3B), 5.14 (d, 1H, *J* = 10.6 Hz, CH*H*^{Bn}), 5.13 (t, 1H, *J* = 9.5 Hz, H-3C), 5.10 (d, 1H, *J* = 12.3 Hz, CH*H*^{Bn}), 5.03–4.99 (m, 2H, C*H*H^{Bn}, H-4E), 4.97–4.92 (m, 3H, C*H*H^{Bn}, H-3E, H-4C), 4.90–4.86 (m, 4H, CH*H*^{Bn}, H-1E^a, H-2E, H-2B), 4.79 (d, 1H, *J* = 10.9 Hz, C*H*H^{Bn}), 4.78 (d, 1H, *J* = 8.5 Hz, H-1B^a), 4.62 (d, 1H, *J* = 12.4 Hz, CH*H*^{Bn}), 4.56 (d, 1H, *J* = 12.8 Hz, C*H*H^{Bn}), 4.54 (d, 1H, *J* = 10.9 Hz, CH*H*^{Bn}), 4.46 (d, 1H, *J* = 10.6 Hz, C*H*H^{Bn}), 4.43 (dd, 1H, *J* = 12.1 Hz, *J* = 3.9 Hz, H-6aB), 4.35 (d, 1H, *J* = 7.7 Hz, H-1A^b), 4.33–4.28 (m, 3H, H-6aC, H-6aD, H-6bB), 4.25 (d, 1H, *J* = 7.6 Hz, H-1C^b), 4.22 (d, 1H, *J* = 7.4 Hz, H-1D), 4.21 (dd, 1H, *J* = 12.5 Hz, *J* = 4.4 Hz, H-6aE), 4.13 (dd, 1H, *J* = 11.8 Hz, *J* = 1.9 Hz, H-6bD), 4.05–4.02 (m, 1H, H-3'), 4.01–3.97 (m, 2H, H-6bC, H-6bE), 3.96 (t, 1H, *J* = 9.3 Hz, H-4A), 3.72 (t, 1H, *J* = 9.5 Hz, H-4B), 3.68 (dd, 1H, *J* = 11.1 Hz, *J* = 3.7 Hz, H-6aA), 3.63–3.59 (m, 4H, H-2A, H-2C, H-5B, H-6bA), 3.57 (ddd, 1H, *J* = 9.8 Hz, *J* = 3.8 Hz, *J* = 2.1 Hz, H-5C), 3.51–3.44 (m, 3H, H-2D, H-3A, H-3D), 3.42–3.37 (m, 2H, H-5D, H-5E), 3.34 (dd, 1H, *J* = 9.7 Hz, *J* = 8.3 Hz, H-4D), 3.21 (ddd, 1H, *J* = 9.8 Hz, *J* = 3.4 Hz, *J* = 2.0 Hz, H-5A), 2.83 (dd, 1H, *J* = 15.6 Hz, *J* = 6.1 Hz, H-2'a), 2.50 (dd, 1H, *J* = 15.6 Hz, *J* = 6.8 Hz, H-2'b), 2.06 (s, 3H, C*H*$_3^{Ac}$), 2.05 (s, 3H, C*H*$_3^{Ac}$), 2.02 (s, 3H, C*H*$_3^{Ac}$), 2.01 (s, 3H, C*H*$_3^{Ac}$), 1.99 (s, 3H, C*H*$_3^{Ac}$), 1.983 (s, 3H, C*H*$_3^{Ac}$), 1.981 (s, 3H, C*H*$_3^{Ac}$), 1.977 (s, 3H, C*H*$_3^{Ac}$), 1.96 (s, 3H, C*H*$_3^{Ac}$), 1.94 (s, 3H, C*H*$_3^{Ac}$), 1.86 (s, 3H, C*H*$_3^{Ac}$), 1.55–1.51 (m, 1H, H-4'a), 1.47–1.45 (m, 1H, H-4'b), 1.39–1.29 (m, 10H, 5 × C*H*$_2^{alkyl}$), 0.89 (t, 3H, *J* = 6.8 Hz, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ (ppm): 171.4 (O*C*=O), 170.9 (O*C*=O), 170.8 (O*C*=O), 170.7 (O*C*=O), 170.61 (O*C*=O), 170.58 (O*C*=O), 170.3 (O*C*=O), 170.0 (O*C*=O), 169.7 (O*C*=O), 169.6 (O*C*=O), 169.5 (O*C*=O), 169.2 (O*C*=O), 138.8 (C^{Ar}), 138.6 (C^{Ar}), 138.2 (C^{Ar}), 137.9 (C^{Ar}), 136.1 (C^{Ar}), 128.7 (2C, 2 × *C*H^{Bn}), 128.62 (2C, 2 × *C*H^{Bn}), 128.58 (2C, 2 × *C*H^{Bn}), 128.56 (2C, 2 × *C*H^{Bn}), 128.5 (2C, 2 × *C*H^{Bn}), 128.31 (*C*H^{Bn}), 128.30 (2C, 2 × *C*H^{Bn}), 128.18 (2C, 2 × *C*H^{Bn}), 128.1 (3C, 3 × *C*H^{Bn}), 127.89 (2C, 2 × *C*H^{Bn}), 127.88 (2C, 2 × *C*H^{Bn}), 127.87 (2C, 2 × *C*H^{Bn}), 127.8 (*C*H^{Bn}), 103.9 (C-1D), 102.5 (C-1C), 101.9 (C-1A), 99.8 (C-1B), 99.6 (C-1E), 84.3 (C-3A)^c, 83.7 (C-3D)^c, 78.7 (C-2A)^d, 77.9 (C-2C)^d, 77.8 (C-4B), 77.5 (C-3'), 77.4 (C-4D), 77.0 (C-4A), 75.2 (*C*H$_2^{Bn}$), 75.1 (2C, 2 × *C*H$_2^{Bn}$), 74.64 (C-5A), 74.58 (C-2D), 74.4 (C-3C), 73.7 (C-5D)^e, 73.5 (*C*H$_2^{Bn}$), 73.2 (C-3E)^f, 73.1 (C-3B), 72.5 (C-5B)^d, 72.4 (C-2B)^g, 72.0 (C-2E)^g, 71.8 (C-5C), 71.6 (C-5E)^e, 68.5 (C-4E), 67.9 (C-4C)^f, 67.6 (C-6A), 66.2 (*C*H$_2^{Bn}$), 62.8 (C-6B), 62.7 (C-6D)^h, 62.1 (C-6F)^h, 61.8 (C-6C), 41.2 (C-2'), 34.9 (C-4'), 32.1 (*C*H$_2^{alkyl}$), 29.8 (*C*H$_2^{alkyl}$), 29.7 (*C*H$_2^{alkyl}$), 29.6 (*C*H$_2^{alkyl}$), 22.8 (*C*H$_2^{alkyl}$), 21.1 (*C*H$_3^{Ac}$), 21.0 (2C, 2 × *C*H$_3^{Ac}$), 20.9 (*C*H$_3^{Ac}$), 20.82 (*C*H$_3^{Ac}$), 20.78 (2C, 2 × *C*H$_3^{Ac}$), 20.70 (2C, 2 × *C*H$_3^{Ac}$), 20.68 (*C*H$_3^{Ac}$), 20.66 (*C*H$_3^{Ac}$), 14.3 (*C*H$_3^{alkyl}$). [a, b, c, d, e, f, g, h]: interchangeable; HRMS (ESI-TOF) *m/z*: [M + 2(NH_4)]$^{2+}$ calcd for $C_{97}H_{130}N_2O_{39}$ 973.4120; found 913.4117. Continuous-flow microfluidic hydrogenolysis was achieved using an H-Cube apparatus equipped with a 10% Pd/C cartridge. Temperature and H_2 pressure were set to 40 °C and 50 bar, respectively. The latter compound (20 mg, 10 μmol, 1.0 equiv) was dissolved in DCE/MeOH 7:3 (5 mL) and injected in the apparatus with a 1 mL min^{-1} flow using a DCE/MeOH 1:1 mixture. All collected fractions were combined and concentrated under reduced pressure. Purification by silica gel flash chromatography (DCM/MeOH 8:2 to 6:4) gave the desired glycolipid **1** (9.5 mg, 0.07 mmol, 65%) as a colorless oil: R_f 0.7 (DCM/MeOH 85:15); $[\alpha]_D^{20}$ +1.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, MeOD) δ (ppm): 5.23 (dd, 1H, *J* = 9.4 Hz, *J* = 5.5 Hz, H-3B), 5.21 (dd, 1H, *J* = 9.5 Hz, *J* = 5.7 Hz, H-3C), 5.18 (t, 1H, *J* = 9.6 Hz, H-3E), 5.07 (d, 1H, *J* = 8.1 Hz, H-1E), 5.02 (t, 1H, *J* = 9.7 Hz, H-4E), 4.89 (dd, 1H, *J* = 9.7 Hz, *J* = 8.0 Hz, H-2E), 4.89–4.86 (m, 2H, H-2B, H-4C), 4.77 (d, 1H, *J* = 8.0 Hz, H-1B), 4.75 (dd, 1H, *J* = 11.7 Hz, *J* = 2.0 Hz, H-6aB), 4.52 (d, 1H, *J* = 7.7 Hz, H-1C), 4.45 (dd, 1H, *J* = 11.9 Hz, *J* = 6.9 Hz, H-6aD), 4.42 (d, 1H, *J* = 7.8 Hz, H-1A), 4.34 (dd, 1H, *J* = 12.6 Hz, *J* = 4.1 Hz, H-6aC), 4.33–4.30 (m, 3H, H-1D, H-6aE, H-6bB), 4.29 (dd, 1H, *J* = 11.9 Hz, *J* = 1.8 Hz, H-3B), 4.09 (dd, 1H, *J* = 12.3 Hz, *J* = 2.4 Hz, H-6bE), 4.04 (dd, 1H, *J* = 12.5 Hz, *J* = 2.2 Hz, H-6bC), 4.04–4.00 (m, 1H, H-3'), 3.92 (ddd, 1H, *J* = 9.7 Hz, *J* = 7.1 Hz, *J* = 2.1 Hz, H-5B), 3.81 (ddd, 1H, *J* = 10.1 Hz, *J* = 3.9 Hz, *J* = 2.2 Hz, H-5C), 3.78 (dd, 1H, *J* = 9.7 Hz, *J* = 8.9 Hz, H-4B), 3.77–3.75 (m, 2H, H-5E, H-6aA), 3.60–3.57 (m, 1H, H-6bA), 3.56 (dd, 1H, *J* = 9.4 Hz, *J* = 7.8 Hz, H-2C), 3.55 (t, 1H, *J* = 8.7 Hz, H-3A), 3.50 (t, 1H, *J* = 9.1 Hz, H-4A), 3.45 (dd, 1H, *J* = 8.7 Hz, *J* = 7.8 Hz, H-2A), 3.44–3.42 (m, 1H, H-5D), 3.30 (t, 1H, *J* = 9.1 Hz, H-3D), 3.29–3.27 (m, 1H, H-5A), 3.19 (t, 1H, *J* = 9.4 Hz, H-4D), 3.10 (dd, 1H, *J* = 9.2 Hz, *J* = 7.9 Hz, H-2D), 2.74–2.66 (br s, 1H, O*H*), 2.47–2.39 (br s, 1H, O*H*), 2.20 (s, 3H, C*H*$_3^{Ac}$), 2.19 (s, 3H, C*H*$_3^{Ac}$), 2.054 (s, 3H, C*H*$_3^{Ac}$), 2.051 (s, 3H, C*H*$_3^{Ac}$), 2.04 (s, 3H, C*H*$_3^{Ac}$), 2.018 (s, 3H, C*H*$_3^{Ac}$), 2.016 (s, 3H, C*H*$_3^{Ac}$), 2.00 (s, 6H, 2 × C*H*$_3^{Ac}$), 1.96 (s, 6H, 2 × C*H*$_3^{Ac}$), 1.60–1.49 (m, 4H, H-2'a, H-2'b, H-4'a, H-4'b), 1.49–1.29 (m, 10H, 5 × C*H*$_2^{alkyl}$), 0.93 (t, 3H, *J* = 6.8 Hz, C*H*$_3^{alkyl}$); ^{13}C{^{1}H} NMR (150 MHz, MeOD) δ (ppm): 173.0 (O*C*=O), 172.6 (O*C*=O), 172.3 (O*C*=O), 172.18 (O*C*=O), 172.17 (O*C*=O), 171.8 (O*C*=O), 171.6 (O*C*=O), 171.4 (O*C*=O), 171.3 (O*C*=O), 171.19 (O*C*=O), 171.16 (O*C*=O), 106.0 (C-1D), 103.6 (C-1C), 102.7 (C-1A), 102.2 (C-1B), 102.1 (C-1E), 82.4 (C-4A), 80.9 (C-2C)^a, 80.7 (C-2A), 79.3 (C-4B), 79.2 (C-3'), 77.8 (C-3D), 77.3 (C-3A)^a, 76.0 (C-3C), 75.6 (C-5A), 75.4 (C-5D), 74.7 (C-2D), 74.4 (C-3B)^b, 74.3 (2C, C-3E^b, C-5B^b), 73.3 (C-2E), 73.0 (C-2B)^c, 72.8 (C-5E), 72.7 (C-5C), 71.6 (C-4D), 69.9 (C-4E), 69.6 (C-4C)^c, 64.7 (C-6D), 64.2 (C-6B), 63.3 (C-6E), 63.0 (C-6C), 61.5 (C-6A), 36.2 (C-4')^d, 33.2 (*C*H$_2^{alkyl}$), 31.0 (*C*H$_2^{alkyl}$), 30.9 (*C*H$_2^{alkyl}$), 30.8 (*C*H$_2^{alkyl}$), 26.0 (C-2')^d, 23.9 (*C*H$_2^{alkyl}$), 21.4 (*C*H$_3^{Ac}$), 21.11 (*C*H$_3^{Ac}$), 21.07 (*C*H$_3^{Ac}$), 20.9 (*C*H$_3^{Ac}$), 20.83 (*C*H$_3^{Ac}$), 20.78 (*C*H$_3^{Ac}$), 20.7 (*C*H$_3^{Ac}$), 20.64 (*C*H$_3^{Ac}$), 20.62 (*C*H$_3^{Ac}$), 20.55 (*C*H$_3^{Ac}$), 20.5 (*C*H$_3^{Ac}$), 14.6 (*C*H$_3^{alkyl}$). [a, b, c, d]: interchangeable; HRMS (ESI-TOF) *m/z*: [M + NH_4]$^+$ calcd for $C_{62}H_{96}NO_{39}$ 1478.5554; found 1478.5552; *m/z*: [M + Na]$^+$ calcd for $C_{62}H_{92}NaO_{39}$ 1483.5108; found 1483.5097.

Cell Culture. Human lung carcinoma (A549), human colorectal adenocarcinoma (DLD-1), and human normal skin fibroblast (WS1) cell lines were obtained from the American Type Culture Collection (ATCC). All cell lines were cultured in minimum essential medium containing Earle's salts and L-glutamine (Mediatech Cellgro, VA), to which were added 10% fetal bovine serum (Hyclone), vitamins (1×), penicillin (100 IU mL^{-1}), streptomycin (100 μg•mL^{-1}), essential amino acids (1×), and sodium pyruvate (1×) (Mediatech Cellgro, VA). Cells were kept at 37 °C in a humidified environment containing 5% CO_2.

Cytotoxicity Assay. Exponentially growing A549, DLD-1, or WS1 cells were plated into 96-well microplates (Costar, Corning Inc.) at a density of 5 × 10^3 cells per well in 100 μL of the culture medium and were allowed to adhere for 16 h prior treatment. Increasing concentrations of each compound in biotech DMSO (Sigma-Aldrich) were then added (100 μL per well), and the cells were incubated for 48 h. The final concentration of DMSO in the culture medium was maintained at 0.5% (*v/v*) to avoid solvent toxicity. Cytotoxicity was assessed using resazurin on an automated 96-well Fluoroskan Ascent F1™ plate reader (Labsystems) using excitation and emission wavelengths of 530 and 590 nm, respectively. Fluorescence was proportional to the cellular metabolic activity in each well. Survival percentage was defined as the fluorescence in experimental wells as compared to that in control wells after the subtraction of blank values. Each experiment was carried out three times in triplicate. IC_{50} results were expressed as means ± standard deviation.

Antimicrobial Activity. Antimicrobial activity was measured by broth microdilutions and disk susceptibility tests (Kirby-Bauer) on *Pseudomonas aeruginosa* PA14, *Klebsiella pneumoniae* ATCC 4352, *Escherichia coli* CFT073, *Staphylococcus aureus* Newman, *Bacillus subtilis* PY79, and *Candida albicans* ATCC 90028. A stock of the glycolipid was prepared at 10 mM in DMSO. For broth microdilution assays, serial dilutions from the stock were

performed in the Mueller–Hinton broth to reach concentrations ranging from 100 to 0.78 μM. DMSO was used as a control. Bacteria were added from an overnight culture in the tryptic soy broth (TSB) at a final OD_{600} of 0.01. The plates were incubated for 24 h at 37 °C with shaking at 250 rpm. Growth was measured by adding resazurin and incubating for 30 min at 37 °C with shaking before measuring fluorescence (excitation 530 nm, emission 590 nm) in a Cytation microplate reader (BioTek, USA). For Kirby–Bauer experiments, 10 μL of the stock solution was deposited on a blank susceptibility disk. Bacteria were spread on the surface of a Mueller–Hinton agar plate from an overnight culture in TSB using a sterile swab. The disk was then placed on the surface of the plate. A disk with DMSO was used as a control. Plates were incubated at 37 °C for 24 h.

Biofilm Assay. Bacteria were diluted in sterile TSB 1:10, 0.5% casamino acids containing 100 μM of the tested compound from a 10 mM stock in DMSO or 1% DMSO at an OD_{600} of 0.05. 100 μL was added to the wells of a polystyrene 96-well plate. Five wells per condition were used. Plates were placed in a sealed bag and incubated at 37 °C for 24 and 48 h. Then, the cells were removed, and the wells were washed twice with water. 100 μL of a 1% crystal violet solution was added to each well and left for 10 min. The plate was then washed at least three times with water and air-dried. 100 μL of 30% acetic acid was added to the wells to dissolve the crystal violet and the absorbance at 595 nm was measured using a Cytation microplate reader.

ASSOCIATED CONTENT

Supporting Information

Experimental details for unsuccessful glycosylations with acetylated building blocks, NMR data comparison of synthetic glycolipid **1** with agminoside E, and 1D and 2D NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by a Discovery grant from the Natural Sciences and Engineering Research Council of Canada (NSERC) under award number RGPIN-2016-04950. C.-G. was supported by a Fonds de recherche du Québec—Santé (FRQS) Research Scholars Junior 2 Career Award. M. C. thanks NSERC and Fonds de recherche du Québec—Nature et technologies (FRQNT) for Ph.D. scholarships. A.P.S. thanks NSERC for an undergraduate scholarship.

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4.2 Voies alternatives

Mis à part les deux approches synthétiques présentées dans l'article ci-dessus, deux autres voies de synthèse ont été explorées pour obtenir la partie oligosaccharidique des agminosides. Ces deux voies de synthèse seront détaillées ici, suivies des synthèses, non détaillées dans l'article, des précurseurs utilisés lors de la synthèse finale.

4.2.1 Stratégie de synthèse latente-active

Au vu des résultats présentés précédemment (Tableau 1, chapitre 4, page 51), il a fallu se rendre à l'évidence que non seulement l'accepteur **5a** entrait en compétition avec les donneurs **4a** puisque tous deux sont des thioglycosides mais également que le composé **5a** était plus réactif que le donneur **4a**.

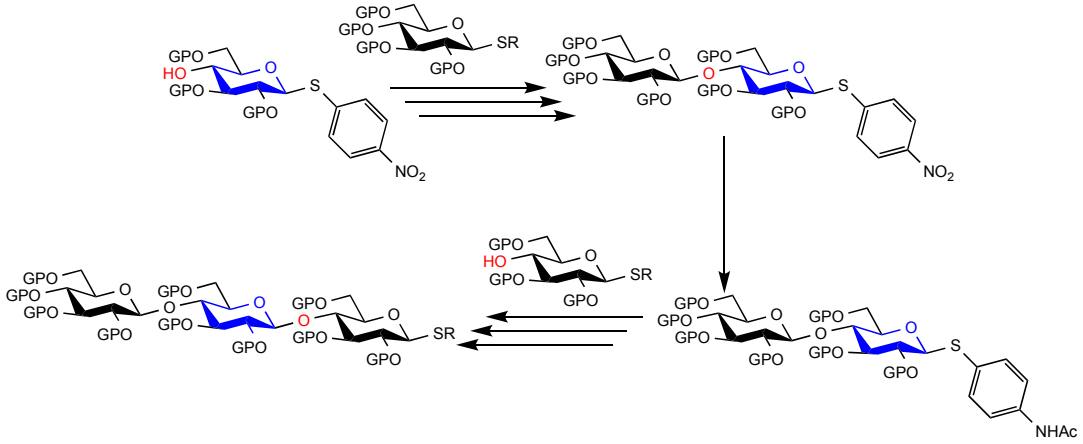

Figure 6 – Principe de la stratégie latente-active

Ainsi, il a été décidé de remanier l'accepteur **5a**. Dans un premier temps, l'application de la stratégie latente-active développée entre autres par le Pr René Roy[l] a été envisagée. Cette stratégie décrite dans la figure 6 consiste à utiliser un groupement *para*-nitro sur le thioglycoside accepteur. L'effet électroattracteur du groupement *para*-nitro fait que ce dernier devient donc moins réactif que le donneur et n'entre plus en compétition avec celui-ci. Une fois la glycosylation effectuée, le groupement *para*-nitro peut être réduit en *para*-amino puis protégé par un acétyle, ce qui permet de grandement améliorer la réactivité du sucre du fait de l'effet électrodonneur du groupement *para*-acétylamine et favorise la glycosylation subséquente.

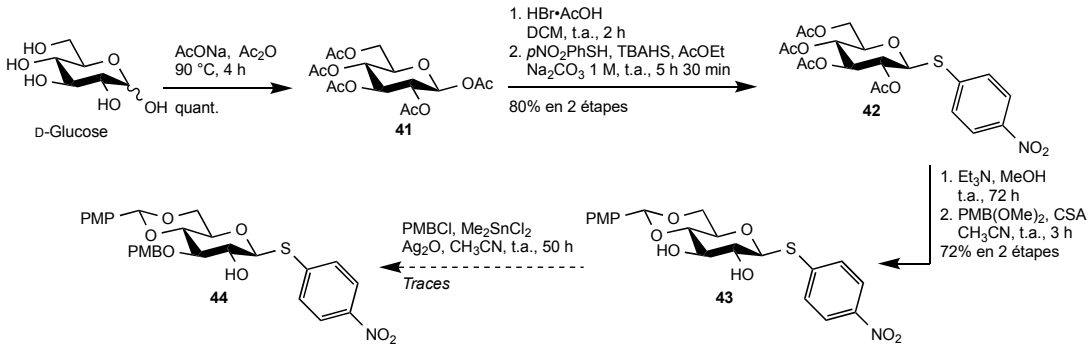

Schéma 4 – Synthèse du donneur 44 pour la stratégie latente-active

Ainsi, tel qu'indiqué dans le schéma 4, le glucose pentacétylé **41** a été bromé en position anomérique par l'action du HBr dans l'AcOH puis immédiatement converti en *para*-nitrothioglycoside sous des conditions de transfert de phase. Le composé **42** ainsi obtenu a ensuite été désacétylé dans le MeOH en présence de Et_3N avant d'insérer un *para*-méthoxybenzylidène en position 4,6 permettant l'obtention de l'acétale **43** avec un rendement de 58% en quatre étapes. La réaction suivante dans la voie de synthèse prévue était la protection régiosélective de la position 3 avec un groupement PMB par l'action d'un acétal stannique menant à l'alcool **44**. Malheureusement, la désactivation du groupement *para*-nitro n'a permis d'obtenir que des traces du composé désiré. Il a donc été décidé d'envisager une route alternative afin de résoudre les problèmes inhérents à cette glycosylation.

4.2.2 Stratégie de la cellobiose

Une autre possibilité pour obtenir le disaccharide B–C lié en β-(1 → 4) est d'utiliser comme produit de départ un composé commercial, la D-cellobiose, un disaccharide comportant déjà ce lien glycosidique. La structure **45** issue de la cellobiose a donc été imaginée (Figure 7), comportant un groupement acétyle à la position 2 de l'extrémité réductrice afin de permettre la formation d'un lien 1,2-*trans* lors d'une future glycosylation. De surcroît, la position 2 de l'extrémité non réductrice demeure libre afin d'intervenir comme accepteur lors de la prochaine glycosylation. Toutes les autres positions sont acétylées ou protégées par des groupements orthogonaux à l'AZMB et au benzyle afin d'y installer, ultérieurement, des groupements acétyles.

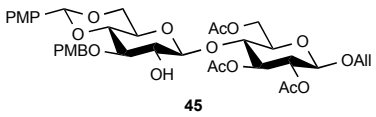

Figure 7 – Structure cible du disaccharide 45

Ainsi, comme décrit dans le schéma 5, la D-cellobiose a été peracétylée par l'action de AcONa dans l'Ac_2O à 90 °C permettant la formation du disaccharide protégé **46**. La position anomérique a ensuite été protégée par un groupement allyle afin de prévenir toute compétition lors des prochaines glycosylations à l'aide de $BF_3 \cdot Et_2O$.[2] Lors de cette réaction, une partie des acétyles ont été clivés, il a donc été entrepris d'effectuer une réacétylation pour faciliter la purification du composé **47**. Malheureusement, cette étape a révélé que seulement 18% du composé avait été allylé. La synthèse a cependant été poursuivie afin d'évaluer sa viabilité avant d'optimiser chaque étape. Le composé a donc été désacétylé et protégé en 4,6 par un *para*-méthoxybenzylidène pour obtenir le pentaol **48**. Cependant, après 11 jours de réaction, seuls 21% de conversion ont été obtenu sur ces deux étapes en raison du manque de solubilité du composé désacétylé dans les solvants organiques. Ainsi, étant donné que la régiosélectivité des étapes suivantes pouvait s'annoncer problématique, il a été décidé que cette voie de synthèse n'était pas viable.

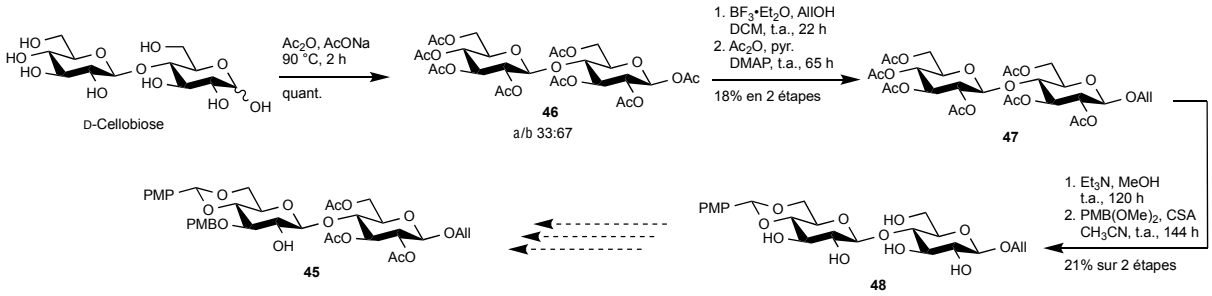

Schéma 5 – Synthèse du disaccharide 45 à partir de la D-cellobiose commerciale

À la vue de ces résultats, il a été admis que notre postulat de départ selon lequel les glycosylations pourraient être effectuées avec des synthons comportant des groupements acétyles pré-installés était erroné. Nous avons ainsi remanié les synthons afin d'essayer la seconde approche synthétique au cours de laquelle les groupements acétyles ont été installés pour la plupart en fin de synthèse. Il s'agit de la méthode présentée dans l'article de ce chapitre (*cf* section 4.1).

4.3 Synthèse des précurseurs de la synthèse finale

Lors de la synthèse détaillée dans l'article, seule la préparation des composés préalablement non-connus a été détaillée. Ainsi, les synthèses des précurseurs, à savoir le trichloroacétimidate **8** utilisé comme précurseur du sucre E, le diol **15** utilisé comme précurseur du sucre B et les alcools **10** et **18** utilisés comme précurseurs des sucres C, et A et D respectivement (Figure 8), seront détaillées dans cette section.

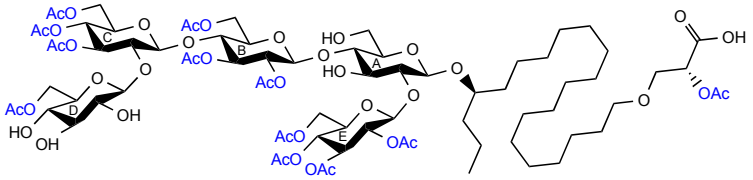

Figure 8 – Structure de l'agminoside E

Dans un premier temps, le donneur **8** a été obtenu par peracétylation du D-glucose[3] à l'aide de AcONa dans l'Ac_2O permettant l'obtention du composé pentaacétylé **41** sans étape de purification. Après clivage régiosélectif de l'acétyle anomérique avec benzylamine,[4] l'hémiacétal **49** a été obtenu avec un rendement de 89%. Le trichloroacétimidate **8** a ensuite été synthétisé à partir du précurseur **49** à l'aide de CCl_3CN en présence d'une base et a été directement utilisé sans purification (schéma 6).

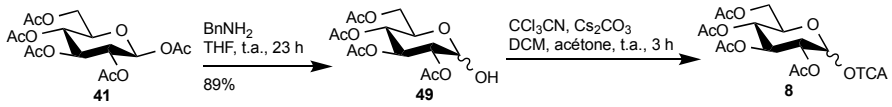

Schéma 6 – Synthèse du trichloroacétimidate 8

Les composés **15** et **10** ont pu être obtenus par bromination du pentaacétyle **41** en position anomérique avec HBr·AcOH 33% suivi de la glycosylation avec TolSH dans des conditions de transfert de phase.[5] Ces réactions ont permis l'obtention du thioglycoside **50** avec un rendement de 83% sur deux étapes. Après désacétylation complète avec Et_3N dans MeOH,[6] le tétraol **51** a été protégé aux positions 4 et 6 par un *para*-méthoxybenzylidène sans étape de purification intermédiaire pour obtenir le diol **15** avec un rendement quantitatif. Ce dernier a ensuite réagi avec Bu_2SnO puis PMBCl afin de mettre à profit la chimie des acétals stanniques[7,8,9] et protéger sélectivement la position 3 pour obtenir l'alcool **10** avec 72% de rendement (schéma 7).

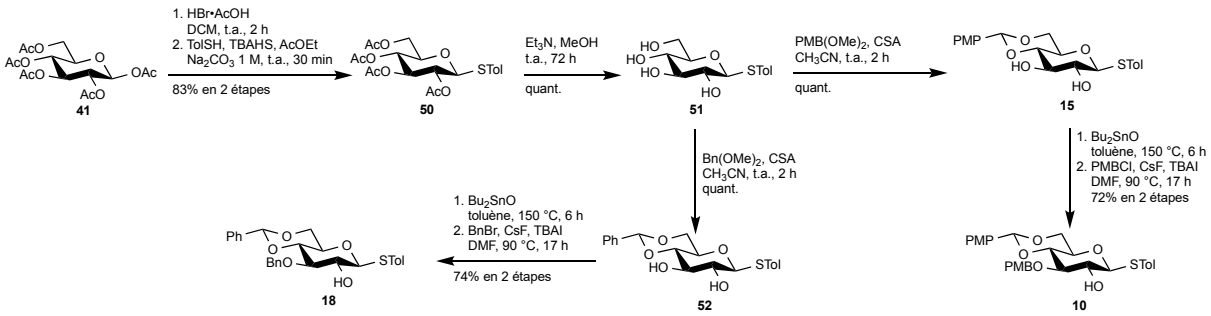

Schéma 7 – Synthèse de l'alcool 10 *via* le diol 15 et de l'alcool 18

De même, l'alcool **18** a été obtenu à partir du tétraol **51** par protection régiosélective en 4 et 6 par un benzylidène pour obtenir le diol **52** avec un rendement quantitatif qui a ensuite été benzylé régiosélectivement selon la même logique que précédemment pour obtenir l'alcool **18** avec 74% de rendement (schéma 7).

Les procédures détaillées des synthèses des composés présentés dans les sections 4.2 et 4.3 apparaissent dans la section 4.4.

4.4 Partie expérimentale (Anglais)

The general methods are the same as presented in the article (p. 55).

1,2,3,4,6-Penta-*O*-acetyl-*β*-D-glucopyranose (41)

To a solution of D-glucose (50.10 g, 0.2781 mol, 1.0 equiv) in Ac_2O (250 mL) was added AcONa (22.77 g, 0.2776 mol, 1.0 equiv). Then, the mixture was warmed to 90 °C for 4 h. After complete conversion, saturated aq. $NaHCO_3$ (3 L) was added at 0 °C to quench the reaction. Next, the aqueous layer was extracted twice with DCM (2 × 500 mL). Finally, the combined organic layers were successively washed with saturated aq. $NaHCO_3$ (500 mL), H_2O (200 mL) and brine (200 mL), filtered over anhydrous $MgSO_4$ and concentrated under reduced pressure to give desired compound **41** (103.3 g, 95%, α/β ratio 25:75) as a white amorphous solid: R_f 0.4 (Hex/EtOAc 1:1). This compound was used without any further purification. Physical and analytical data agreed with those published.[10]

4-Nitrophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (42)

Compound **41** (1.01 g, 2.54 mmol, 1.0 equiv) was dissolved in dry DCM (30 mL) and the solution was cooled to 0 °C prior to the dropwise addition of HBr 33% in AcOH (7.6 mL). The mixture was then warmed up to room temperature for 2 h. After complete conversion, MTBE (20 mL) was added and the solution was washed four times with concentrated aq. $NaHCO_3$ (4 × 20 mL). Finally, the organic layer was filtered over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 2,3,4,6-penta-*O*-acetyl-1-bromoglucopyranose as a white amorphous solid.

The resulting crude bromide donor (2.54 mmol, 1.0 equiv) was dissolved in EtOAc (10 mL) and TBAHS (874 mg, 2.54 mmol, 1.0 equiv), 1 M aq. Na_2CO_3 (10 mL), and 4-nitrophenylthiol (596 mg, 3.81 mmol, 1.5 equiv) were successively added. The mixture was then vigorously stirred for 5.5 h at room temperature prior to the addition of iodine (547 mg, 2.16 mmol, 0.9 equiv). Then, the solution was successively washed twice with saturated aq. $Na_2S_2O_3$ (2 × 20 mL), saturated aq. $NaHCO_3$ (20 mL) and brine (20 mL) and the organic layer was filtered over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 6:4) gave desired compound **46** (1.01 g, 80% over two steps) as a yellow solid: R_f 0.4 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[11]

4-Nitrophenyl 4,6-*O*-(4-methoxybenzylidene)-1-thio-*β*-D-glucopyranoside (43)

To a solution of compound **42** (959 mg, 1.98 mmol, 1.0 equiv) in MeOH (15 mL) was added Et_3N (1.70 mL, 11.9 mol, 6.0 equiv) at room temperature. After 72 h, the mixture was concentrated under reduced pressure and the crude was co-evaporated with toluene twice giving the desired tetraol intermediate as a yellow amorphous solid.

To a solution of the latter compound (1.98 mmol, 1.0 equiv) in dry CH_3CN (20 mL) was successively added anisaldehyde dimethylacetal (480 μL, 3.95 mmol, 2.0 equiv) and CSA (45 mg, 0.20 mmol, 0.1 equiv). After 3 h at room temperature, Et_3N (250 μL, 1.80 mmol, 0.9 equiv) was added to quench the reaction and the mixture was concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to DCM/MeOH 8:2) gave desired diol **43** (616 mg, 72% over two steps) as a yellowish amorphous solid: R_f 0.15 (Hex/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.18–8.14 (m, 2H, 2 × C*H*^{Ar}), 7.79–7.75 (m, 2H, 2 × C*H*^{Ar}), 7.70–7.66 (m, 2H, 2 × C*H*^{Ar}), 7.05–7.01 (m, 2H, 2 × C*H*^{Ar}), 5.82 (s, 1H, PMPC*H*O_2), 4.62 (d, 1H, J = 9.8 Hz, H-1), 4.56 (dd, 1H, J = 10.0 Hz, J = 4.4 Hz, H-6a), 4.45 (t, 1H, J = 8.5 Hz, H-3), 4.23 (dd, 1H, J = 9.7 Hz, J = 8.4 Hz, H-2), 4.07–4.00 (m, 2H, H-4, H-5), 3.98–3.94 (m, 1H, H-6b), 3.68 (s, 3H, C*H*$_3^{OMe}$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 161.0 (*C*^{Ar}), 146.5 (*C*^{Ar}), 146.2 (*C*^{Ar}), 131.4 (*C*^{Ar}), 129.3 (2C, 2 × *C*H^{Ar}), 128.8 (2C, 2 × *C*H^{Ar}), 124.6 (2C, 2 × *C*H^{Ar}), 114.3 (2C, 2 × *C*H^{Ar}), 102.5 (PMP*C*HO_2), 88.2 (C-1), 82.2 (C-4), 76.4 (C-3), 74.6 (C-2), 71.6 (C-5), 69.3 (C-6), 55.6 (*C*H$_3^{OMe}$).

2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl-(1 → 4)-1,2,3,6-tetra-*O*-acetyl-*β*-D-glucopyranoside (46)

To a solution of D-cellobiose (1.00 g, 2.92 mmol, 1.0 equiv) in Ac_2O (5.4 mL) was added AcONa (244 mg, 2.97 mmol, 1.0 equiv). Then, the mixture was warmed to 90 °C for 6 h and AcCl (1.70 mL, 23.8 mmol, 8.2 equiv) was added. After additional 2 h, the crude was washed with saturated aq. $NaHCO_3$ (80 mL) and extracted twice with DCM (2 × 50 mL). The combined organic layers were washed again with saturated aq. $NaHCO_3$ (50 mL) and extracted again with DCM (50 mL). Finally, all organic layers were combined, filtered over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 4:6) gave

desired compound **46** (1.45 g, 73%) as a white amorphous solid: R_f 0.15 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[12]

Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (47)

To a solution of compound **46** (1.72 g, 2.53 mmol, 1.0 equiv) in DCM (13 mL) was added AllOH (1.05 mL, 15.4 mmol, 6.1 equiv). The mixture was cooled to 0 °C prior to the dropwise addition of $BF_3{\cdot}Et_2O$ (500 μL, 4.05 mmol, 1.6 equiv) and stirred at room temperature for 22 h. Then, the crude was washed with saturated aq. $NaHCO_3$ (50 mL) and extracted three times with DCM (3 × 50 mL). The combined organic layers were filtered over anhydrous $MgSO_4$ and concentrated under reduced pressure.

The crude (2.53 mmol, 1.0 equiv) was dissolved in pyridine (6.4 mL). Ac_2O (6.4 mL) and DMAP (33 mg, 0.27 mmol, 0.1 equiv) were added. After stirring at room temperature for 65 h, the mixture was concentrated under reduced pressure and co-evaporated four times with toluene. Purification by silica gel flash chromatography (Hex/EtOAc 6:4 to 1:1) gave desired compound **47** (317 mg, 18% over two steps) as a white amorphous solid: R_f 0.1 (Hex/EtOAc 1:1). Some starting material (compound **46**) was also retrieved (80%). Physical and analytical data agreed with those published.[13]

Allyl 4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranoside (48)

To a solution of compound **47** (1.44 g, 2.13 mmol, 1.0 equiv) in MeOH (17 mL) was added Et_3N (3.2 mL, 23 mmol, 10.8 equiv) at room temperature. After 120 h, the mixture was concentrated under reduced pressure and the crude was co-evaporated with toluene twice giving the desired heptaol intermediate as a white amorphous solid.

To a solution of the latter compound (2.13 mmol, 1.0 equiv) in dry DMF (22 mL) was successively added anisaldehyde dimethylacetal (700 μL, 4.30 mmol, 2.0 equiv) and CSA (51 mg, 0.21 mmol, 0.1 equiv). After stirring for 144 h at room temperature, Et_3N (1.00 mL, 7.17 mmol, 3.4 equiv) was added to quench the reaction and the mixture was concentrated under reduced pressure and co-evaporated five times with toluene. Purification by silica gel flash chromatography (DCM/MeOH 98:2. To. 95:5) gave desired pentaol **48** (226 mg, 21% over two steps) as a white amorphous solid: R_f 0.4 (DCM/MeOH 9:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.43–7. 40 (m, 2H, 2 × CH^{PMP}),

6.90–6.87 (m, 2H, 2 × C*H*^{PMP}), 5.97 (ddt, 1H, *J* = 16.5 Hz, *J* = 10.6 Hz, *J* = 5.5 Hz, H-2^{Allyl}), 5.53 (s, 1H, PMPC*H*O$_2$), 5.36–5.31 (m, 2H, H-3a^{PMP}), 5.19–5.15 (m, 2H, H-3b^{PMP}), 4.56 (d, 1H, *J* = 7.9 Hz, H-1C), 4.37 (ddt, 1H, *J* = 12.9 Hz, *J* = 5.2 Hz, *J* = 1.4 Hz, H-1a^{Allyl}), 4.33 (d, 1H, *J* = 7.8 Hz, H-1B), 4.30–4.26 (m, 1H, H-6aC), 4.15 (ddt, 1H, *J* = 12.9 Hz, *J* = 6.1 Hz, *J* = 1.3 Hz, H-1b^{Allyl}), 3.91 (dd, 1H, *J* = 12.2 Hz, *J* = 2.5 Hz, H-6aB), 3.86 (dd, 1H, *J* = 12.2 Hz, *J* = 4.3 Hz, H-6bB), 3.79 (s, 3H, C*H*$_3$), 3.78–3.75 (m, 1H, H-6bC), 3.64 (t, 1H, *J* = 8.9 Hz, H-3C), 3.59 (t, 1H, *J* = 9.3 Hz, H-4B), 3.52–3.47 (m, 3H, H-3B, H-4C, H-5C), 3.40 (ddd, 1H, *J* = 9.7 Hz, *J* = 4.1 Hz, *J* = 2.5 Hz, H-5B), 3.33 (dd, 1H, *J* = 8.9 Hz, *J* = 8.1 Hz, H-2C), 3.27 (dd, 1H, *J* = 9.1 Hz, *J* = 7.9 Hz, H-2B); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 161.6 (*C*^{Ar}), 135.7 (C-2^{Allyl}), 131.4 (*C*^{Ar}), 128.8 (2C, 2 × *C*H^{PMP}), 117.5 (C-3^{Allyl}), 114.3 (2C, 2 × *C*H^{PMP}), 105.1 (C-1C), 103.2 (C-1B), 103.0 (PMP*C*HO$_2$), 82.0 (C-4C*), 80.7 (C-4B), 76.4 (C-5B), 76.1 (C-3B*), 75.8 (C-2C), 74.9 (C-2B), 74.5 (C-3C), 71.1 (C-1^{Allyl}), 69.4 (C-6C), 67.8 (C-5C*), 61.8 (C-6B), 55.7 (*C*H$_3$).

2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (49)

To a solution of compound **41** (1.02 g, 2.61 mmol, 1.0 equiv) in THF (10.2 mL) was added $BnNH_2$ (450 mg, 3.85 mmol, 1.5 equiv) and the mixture was stirred at room temperature for 23 h. After complete conversion, the mixture was diluted with EtOAc (100 mL) and washed three times with 1 M aq. HCl (3 x 100 mL) and with saturated aq. $NaHCO_3$ (50 mL). The basic aqueous layer was extracted with DCM (50 mL) while the acidic one was extracted three times with DCM (3 x 50 mL). The latter was washed with saturated aq. $NaHCO_3$ (100 mL). Next, all the organic layers were combined and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 7:3 to 4:6) gave desired compound **49** (796 mg, 89%) as a white amorphous solid: R_f 0.2 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[14]

Trichloroacetimidate 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (8)

To a solution of hemiacetal **49** (796 mg, 2.30 mmol, 1.0 equiv) in DCM (29 mL) and acetone (5.6 mL) were added Cs_2CO_3 (151 mg, 0.463 mmol, 0.2 equiv) and CCl_3CN (1.20 mL, 11.5 mmol, 5.0 equiv) and the mixture was stirred at room temperature for 3 h. Then, the crude was filtered over Celite and concentrated under reduced pressure giving crude compound **8** used without any further purification.

4-Methylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (50)

Compound **41** (7.76 g, 19.9 mmol, 1.0 equiv) was dissolved in dry DCM (30 mL) and the solution was cooled to 0 °C prior to the dropwise addition of HBr 33% in AcOH (60 mL). The mixture was then warmed up to room temperature for 2 h. After complete conversion, MTBE (300 mL) was added and the solution was washed five times with concentrated aq. $NaHCO_3$ (5 × 300 mL). Finally, the organic layer was filtered over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 2,3,4,6-pentaacetyl-1-bromoglucopyranoside as a white amorphous solid.

The resulting crude bromide donor (19.9 mmol, 1.0 equiv) was dissolved in EtOAc (80 mL). TBAHS (6.74 g, 19.9 mmol, 1.0 equiv), 1 M aq. Na_2CO_3 (80 mL), and 4-methylphenylthiol (3.74 g, 29.8 mmol, 1.5 equiv) were successively added. The mixture was then vigorously stirred for 30 min at room temperature prior to being diluted with EtOAc (200 mL). Then, the solution was successively washed with saturated aq. $NaHCO_3$ (200 mL) and brine (200 mL) and the organic layer was filtered over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 8:2 to 75:25) gave desired compound **50** (7.48 g, 83% over two steps) as a white amorphous solid: R_f 0.2 (Hex/EtOAc 7:3). Physical and analytical data agreed with those published.[15]

4-Methylphenyl 1-thio-β-D-glucopyranoside (51)

To a solution of compound **50** (21.5 g, 47.3 mmol, 1.0 equiv) in MeOH (380 mL) was added Et_3N (40 mL, 0.28 mol, 6.0 equiv) at room temperature. After 64 h, the mixture was concentrated under reduced pressure and the crude was co-evaporated with toluene four times giving desired compound **51** (13.76 g, quantitative) as a white yellowish amorphous solid: R_f 0.2 (DCM/MeOH 9:1). The compound was used without any further purification. Physical and analytical data agreed with those published.[15]

4-Methylphenyl 4,6-*O*-(4-methoxybenzylidene)-1-thio-β-D-glucopyranoside (15)

To a solution of tetraol **51** (1.01 g, 3.49 mmol, 1.0 equiv) in dry CH_3CN (35 mL) was successively added anisaldehyde dimethylacetal (1.10 mL, 6.99 mmol, 2.0 equiv) and CSA (81 mg, 0.35 mmol, 0.1 equiv). After 2 h at room temperature, Et_3N (0.5 mL, 3.6 mmol, 1.0 equiv) was added to quench the reaction and the mixture was concentrated under reduced pressure. Purification by silica gel flash chromatography (DCM/MeOH 10:0 to 9:1) gave desired compound **15** (1.38 g, 97%) as a

white amorphous solid: R_f 0.2 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[16]

4-Methylphenyl 3-*O*-(4-methoxybenzyl)-4,6-*O*-(4-methoxybenzylidene)-1-thio-*β*-D-glucopyranoside (10)

To a solution of diol **15** (1.30 g, 3.21 mmol, 1.0 equiv) in toluene (40 mL) was added Bu_2SnO (758 mg, 3.05 mmol, 0.9 equiv). The flask was equipped with a Dean-Stark device and the mixture was warmed up to 150 °C for 6 h. The reaction was then cooled to room temperature and concentrated under reduced pressure. Next, dry DMF (40 mL) was added to the crude and CsF (818 mg, 5.39 mmol, 1.7 equiv), TBAI (1.81 g, 4.90 mmol, 1.5 equiv), and PMBCl (1.00 mL, 7.41 mmol, 2.3 equiv) were successively added to the solution. The solution was then warmed up to 90 °C for 17 h. Finally, the mixture was cooled to 0 °C, filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 3:7) gave desired compound **10** (1.21 g, 72%) as a white amorphous solid: R_f 0.5 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.

4-Methylphenyl 4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside (52)

To a solution of tetraol **51** (2.00 g, 6.99 mmol, 1.0 equiv) in dry CH_3CN (70 mL) were successively added benzaldehyde dimethylacetal (2.4 mL, 14 mmol, 2.0 equiv) and CSA (162 mg, 0.697 mmol, 0.1 equiv). After 2 h at room temperature, Et_3N (1.0 mL, 7.8 mmol, 1.0 equiv) was added to quench the reaction and the mixture was concentrated under reduced pressure. Purification by silica gel flash chromatography (DCM/MeOH 10:0 to 95:5) gave desired compound **52** (2.52 g, 96%) as a white amorphous solid: R_f 0.25 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[15]

4-Methylphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside (18)

To a solution of diol **52** (2.46 g, 6.56 mmol 1.0 equiv) in toluene (80 mL) was added Bu_2SnO (1.49 g, 5.98 mmol, 0.9 equiv). The flask was equipped with a Dean-Stark device and the mixture was warmed up to 150 °C for 6 h. The reaction was then cooled to room temperature and concentrated under reduced pressure. Next, dry DMF (80 mL) was added to the crude and CsF (1.52 g, 9.84 mmol, 1.5 equiv), TBAI (3.75 g, 9.84 mmol, 1.5 equiv), and BnBr (1.90 mL, 15.8 mmol, 2.4 equiv)

were successively added to the solution. The solution was then warmed up to 90 °C for 17 h. Finally, the mixture was cooled to 0 °C, filtered over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex:EtOAc 9:1 to 3:7) gave desired compound **18** (2.27 g, 74%) as a white amorphous solid: R_f 0.6 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[17]

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-Chapitre V-

Progrès vers la Synthèse de la Chaîne Lipidique des Agminosides

5.1 Introduction

À l'instar de la structure des agminosides, la chaîne lipidique de ces glycolipides est unique au niveau de sa structure[1,2] (Figure 1). Il s'agit d'un glycérolipide lié à la partie oligosaccharidique non pas par l'alcool de la partie glycérol mais par celui de la chaîne carbonée. Il existe deux versions de cet aglycone : une version acétylée sur la partie glycérol, présente sur les agminosides A, B et E et une version comportant cet alcool libre sur les agminosides C et D. La chaîne lipidique comporte également une fonction acide carboxylique terminale libre.

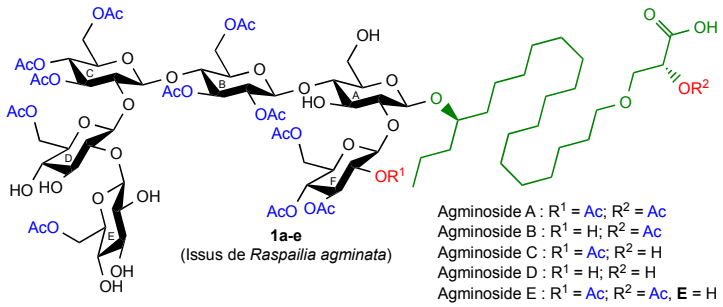


Figure 1 – Structures des agminosides A–E

Là où la plupart des glycolipides marins comportent des chaînes sphingolipidiques,[3] d'autres comportent des glycérolipides, mais, contrairement aux agminosides, leur chaîne est glycosylée sur l'unité glycérol. Aussi, il existe d'autres glycolipides comportant une fonction acide carboxylique terminale. Cependant, pour ceux-ci, la fonction se trouve sur une unité aminoacide. Ainsi, la chaîne lipidique des agminosides est unique en son genre et n'a, de fait, jamais été synthétisée.

Parmi les différentes façons de rétrosynthétiquement disconnecter la chaîne lipidique des agminosides, la formation du lien éther entre la chaîne carbonée et la partie glycérol a été jugée comme la plus évidente. Ainsi, la chaîne carbonée a pu être obtenue par élongation d'un composé commercial, et la partie glycérol a pu être obtenue par aménagement fonctionnel d'un composé commercial de structure similaire. Les principaux défis anticipés de cette synthèse sont donc la synthèse des deux parties tout en respectant leur configuration absolue (*R*, *R*) ainsi que la formation du lien éther en fin de synthèse.

Dans ce chapitre, seront décrits les progrès réalisés sur la synthèse de la chaîne lipidique (sections 5.2.2–5.2.4) ainsi que les alternatives de synthèse pour la poursuite du projet (section 5.3).

5.2 Résultats et discussion

5.2.1 Rétrosynthèse

Comme il a été présenté précédemment, les agminosides possèdent une chaîne lipidique de structure connue possédant un alcool pouvant être acétylé ou non en α de l'acide carboxylique. Dans la figure 2 ci-dessous est présentée l'analyse rétrosynthétique de l'ester de benzyl **1**, un précurseur de cette chaîne.

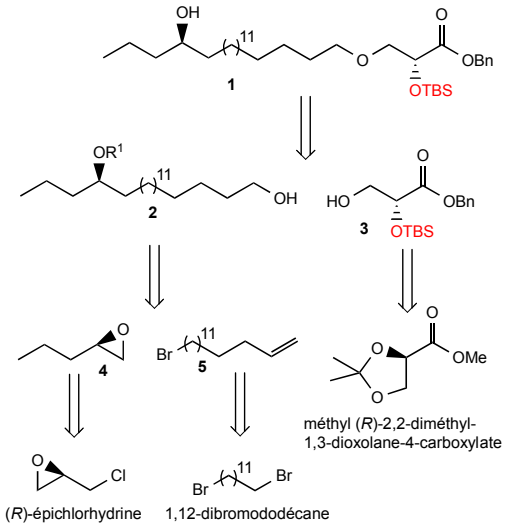


Figure 2 – Analyse rétrosynthétique du lipide 1 *via* formation du lien éther

Le composé **1** a été disconnecté dans un premier temps par le lien éther donnant la chaîne **2** et le glycérol **3**. Ce dernier peut être obtenu à partir du méthyl (*R*)-2,2-diméthyl-1,3-dioxolane-4-carboxylate commercial en cinq étapes d'aménagement fonctionnel. Dans un second temps, la chaîne **2** peut être formée par couplage de Grignard entre l'époxyde chiral **4** et le composé bromé **5** qui peuvent être respectivement obtenus à partir de la (*R*)-épichlorhydrine et du 1,12-dibromododécane, tous deux commerciaux, en deux et une étape(s), respectivement.

5.2.2 Synthèse du glycérol 3

La synthèse du composé **3** a été effectuée comme présentée dans le schéma 1 selon une voie réactionnelle linéaire en cinq étapes. L'ester de benzyle **6** a été obtenu par *trans*-estérification du

méthylester commercial dans l'alcool benzylique en présence de sels d'étain[4] avec un rendement de 69%. Après déprotection de l'isopropylidène en milieu acide permettant l'obtention du diol **7** avec un rendement de 82%, la tritylation régiosélective de l'alcool primaire a mené à l'alcool **8** avec un rendement de 86%.[4]

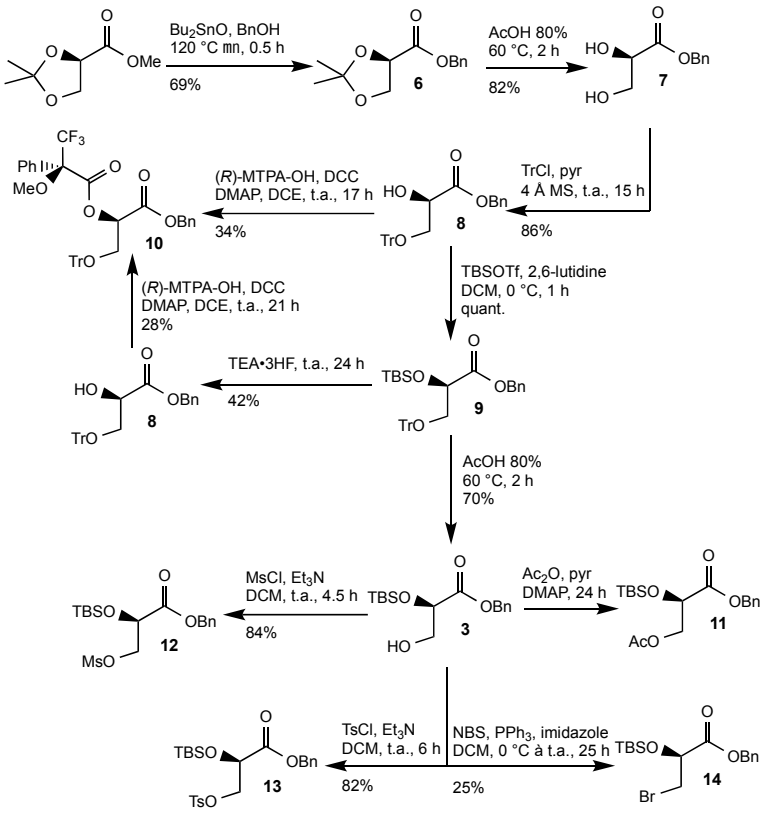


Schéma 1 – Synthèse du composé 3 ainsi que des électrophiles 12, 13 et 14

La silylation de l'alcool **8** s'est montrée plus laborieuse que prévue (Tableau 1). En effet, l'utilisation de TBSCl avec différentes bases (DMAP, *t*BuOK, pyridine et Et_3N) n'a pas mené à la formation du produit désiré (entrées 1–4), seule l'imidazole a permis d'obtenir le composé **9** avec un rendement de 28% (entrée 5) mais ce résultat était difficilement reproductible. En utilisant TBSOTf plutôt que TBSCl, avec Et_3N en chauffant à 50 °C, un rendement de 60% a pu être obtenu (entrée 6), mais la reproductibilité de ces conditions n'était pas suffisante. Enfin, l'utilisation de lutidine[5,6] dans le DCM a permis en 1 h à 0 °C d'obtenir le composé complètement protégé **9** avec un rendement quantitatif (entrée 7).

Tableau 1 – Optimisation de la silylation de l'alcool 8

entrée	agent silylant	base	solvant	température (°C)	temps (h)	rendement (%)[a]
1	TBSCl	DMAP	DMF	20	16	n.d.[b]
2	TBSCl	*t*BUOK	DMF	80	8	n.d.[b]
3	TBSCl	pyridine	DMF	140	16	n.d.[b]
4	TBSCl	Et_3N	DMF	70	18	traces
5	TBSCl	imidazole	DMF	20	24	28
6	TBSOTf	Et_3N	DCE	50	4.5	60
7	TBSOTf	lutidine	DCM	0	1	quant.

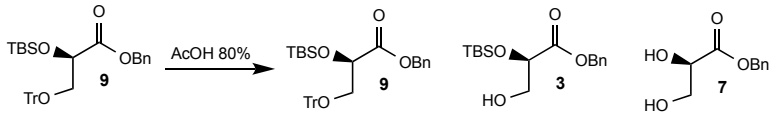
[a] Rendement isolé. [b] Pas de réaction.

À cette étape, il a été décidé de vérifier qu'aucune racémisation du composé n'avait eu lieu. Pour ce faire, l'acide (*R*)-MTPA, dit acide de Mosher,[7] a été couplé à l'alcool **8** pour obtenir l'ester **10**. L'analyse RMN de ce dernier a mis en évidence la présence d'un seul composé. L'absence de diastéréoisomère montre qu'aucune racémisation n'a eu lieu et donc que l'énantiomérie du composé commercial avait été conservée.

Une fois la bonne configuration du composé **9** établie, la déprotection sélective du trityle en milieu acide a pu commencer. Cependant, le TBS étant lui aussi sensible en milieu acide, il a fallu optimiser les conditions pour limiter son hydrolyse (Tableau 2). Les réactions ont eu lieu dans l'AcOH 80% aqueux[8] à différentes températures. D'abord, à 30 °C pendant 3 h, aucune conversion n'a été observée en RMN (entrée 1). En augmentant le temps réactionnel à 20 h, 40% de conversion ont été observés (entrée 2) mais le ratio 3:2 entre l'alcool **3** voulu et le diol **7** issu de l'hydrolyse du TBS indique que celui-ci se déprotège rapidement après le trityle. Nous avons donc décidé d'augmenter la température à 45 °C en diminuant le temps de réaction à quatre heures afin de limiter le départ du TBS (entrée 3), ce qui a permis une meilleure conversion (de 86%) dans un ratio de 3:1. Selon la même logique, les conditions ont été modifiées à 60 °C pendant trois heures (entrée 4) et ont permis une conversion de 94% pour le même ratio. Une dernière condition a été

testée à 60 °C pendant deux heures (entrée 5) mais aucune amélioration n'a été notée. Une autre condition mettant en scène une quantité catalytique de $TsOH \cdot H_2O$ (20 mol%) dans le MeOH[9] a permis une conversion de 71% avec seulement 49% de l'alcool **3** et 22% du diol **7**, soit un ratio de 2:1. Selon ces derniers résultats, les conditions décrites dans l'entrée 5 ont été choisies comme optimales et reproduites à plus grande échelle (entrée 6). Après purification, l'alcool **3** a été obtenu avec un rendement de 70%.

Tableau 2 – Déprotection sélective du trityle



entrée	température (°C)	temps (h)	rendement (%)[a] **9** (%)	**3** (%)	**7** (%)
1	30	3	100	0	0
2	30	20	61	23	16
3	45	4	14	67	19
4	60	3	6	71	23
5	60	2	0	68	32
6	60	2	n.d.[b]	70[c]	21[c]

[a] Rendements observés avec la RMN du brut. [b] Non isolé. [c] Rendements isolés.

Bien que l'utilisation de résine acide DOWEX en vue de déprotéger l'alcool primaire sélectivement n'a pas été concluante, d'autres acides supportés pourraient être pertinents à essayer comme le $HClO_4$ supporté sur gel de silice[10] ou le Nafion-H[11].

Après clivage du trityle, l'alcool primaire a été acétylé afin de vérifier que le TBS n'avait pas migré lors de cette étape. D'après l'analyse RMN, le CH_2 de l'alcool primaire **3** correspond au massif de deux protons entre 3.75 et 3.86 ppm, après acétylation, le CH_2 du composé **11** correspond à deux doublets dédoublés à 4.24 ppm et 4.35 ppm. Ce déblindage indique que l'acétyle a bien réagi sur l'alcool primaire et donc que le TBS n'a pas migré. L'alcool **3** a donc pu être obtenu avec un rendement de 34% en cinq étapes.

Par ailleurs, trois alternatives à l'alcool **3** pour l'étape de formation du lien éther ont été synthétisées : le mésyle[12] **12** obtenu avec un rendement de 84%, le tosyle[12] **13** obtenu avec un

rendement de 82%, et le composé bromé[13,14,15] **14** obtenu avec un rendement de 25%. Bien que ce dernier rendement soit faible, la réaction n'a jamais été optimisée puisque le couplage avec ce composé n'a pas fonctionné (voir les détails dans la section 5.2.4).

5.2.3 Synthèse de la chaîne carbonée 2

Une fois la synthèse du glycérol **3** terminée, celle de la chaîne **2** a commencé. Il s'agit d'une synthèse convergente dont la séquence linéaire la plus longue comporte cinq étapes.

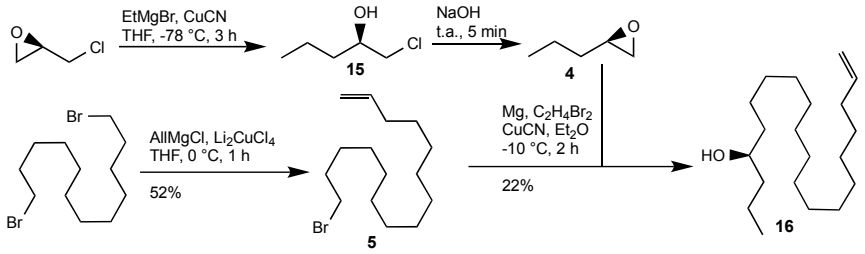
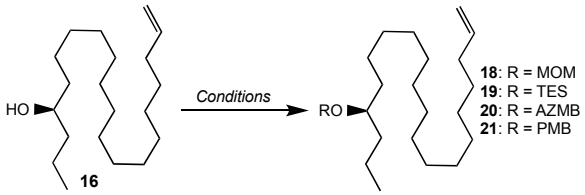


Schéma 2 – Synthèse de l'alcool 13

À partir du 1,12-dibromododécane commercial, le composé bromé **5** a pu être obtenu par allylation partielle[16] par l'action de AllMgCl et Li_2CuCl_4 généré *in situ* à partir de LiCl et de $CuCl_2$ avec un rendement de 52% (Schéma 2). D'un autre côté, à partir de la (*R*)-épichlorhydrine, une réaction avec EtMgBr et CuCN a permis d'allonger la chaîne carbonée[12] pour obtenir l'alcool **15** qui a ensuite été versé goutte à goutte sur du NaOH pulvérisé[17] pour obtenir l'époxyde **4**. Cette synthèse, bien que présentant d'excellentes conversions, a montré des rendements non-reproductibles du fait de la grande volatilité des composés. En effet, l'alcool **15** s'évapore en partie avec le THF à l'évaporateur rotatif et l'époxyde **4** s'évapore avec le Et_2O utilisé pour rincer le NaOH de la réaction. Lors de ces réactions, les rinçages ont donc été effectués avec le minimum de solvant possible et les bruts réactionnels ont été sommairement concentrés pour limiter les pertes de produits. Le couplage de l'époxyde **4** sur le composé bromé **5** a été effectué avec du Mg^0 sous forme de copeaux et du 1,2-dibromoéthane qui, dans un premier temps, génère un organomagnésien qui est utilisé par échange métal-halogène pour former l'organomagnésien dérivé de **5**. Ce dernier a été ajouté goutte à goutte sur l'époxyde **4** en solution dans l'Et_2O pour finalement obtenir l'alcool **16** avec 22% de rendement. Toutefois, après l'avoir fait réagir avec l'acide de Mosher tel que montré précédemment, la présence de deux diastéréoisomères distincts en RMN ^1H montre qu'il y a eu épimérisation de l'alcool lors de la réaction. Il a été supposé que cette racémisation n'avait eu lieu qu'à l'étape de couplage du magnésien et non avant puisque les

réactions précédentes se basent sur des travaux publiés.[12] De ce fait, du CuCN a été ajouté à la solution d'époxyde **4** lors du couplage pour générer *in situ*, par transmétalllation,[16] un organocuprate à partir de l'organomagnésien qui est plus basique que son analogue cuivré. De cette façon, il a été possible d'obtenir l'alcool **16** avec un rendement de 22% qui, après réaction avec l'acide de Mosher pour former l'ester **17**, a bien montré en RMN la présence d'un seul diastéréoisomère, ce qui indique l'absence de racémisation de l'alcool lors de la réaction. Le rendement de ce couplage reste à optimiser puisque la réaction n'a été, à l'heure actuelle, effectuée qu'une seule fois.

Tableau 3 – Protection de l'alcool 13



entrées	groupement protecteur	conditions	temps (h)	température (°C)	rendement (%)[a]
1	MOMCl	DIPEA, DMAP, DCM	3	20	19
2	TESCl	imidazole, DMAP, DMF	5	20	76
3	AZMBOH	DMAP, DCC, DCM	6.5	60	75
4	PMBCl	*t*BuOK, THF	6.75	40	73

[a] Rendements isolés.

Le groupement protecteur initialement prévu pour l'alcool était le MOM. Cependant, comme présenté au Tableau 3 (entrée 1), la réaction de protection avec du MOMCl[18] n'a formé l'éther **18** qu'avec 19% de rendement. Le groupement TES a ensuite été envisagé avec un rendement de 76% pour l'obtention du silyléther **19** (entrée 2). Cependant, craignant que la labilité de ce groupement puisse être un problème pour la suite, nous avons décidé de chercher un autre groupement protecteur plus stable. L'AZMB[19,20], bien que facile à coupler à l'alcool pour former l'ester **20** avec 75% de rendement (entrée 3), ne convenait pas car sensible en milieu basique et donc incompatible avec l'hydroboration-oxydation qui serait la prochaine étape. Enfin, le PMB a été envisagé, bien que nécessitant une base forte pour réagir sur l'alcool. Dans un premier temps, l'utilisation de NaH n'a étonnamment mené à aucune conversion. Cependant, le *t*BuOK a permis

l'obtention de l'éther **21** avec un rendement de 73% (entrée 4). Avant de continuer, le groupement PMB a été clivé par l'action du DDQ[21] (Schéma 3) afin de pouvoir vérifier, grâce à l'ester de Mosher et à la RMN ^{1}H, la présence d'un seul diastéréoisomère **17** et donc qu'aucune racémisation n'avait eu lieu lors de la protection en milieu basique fort.

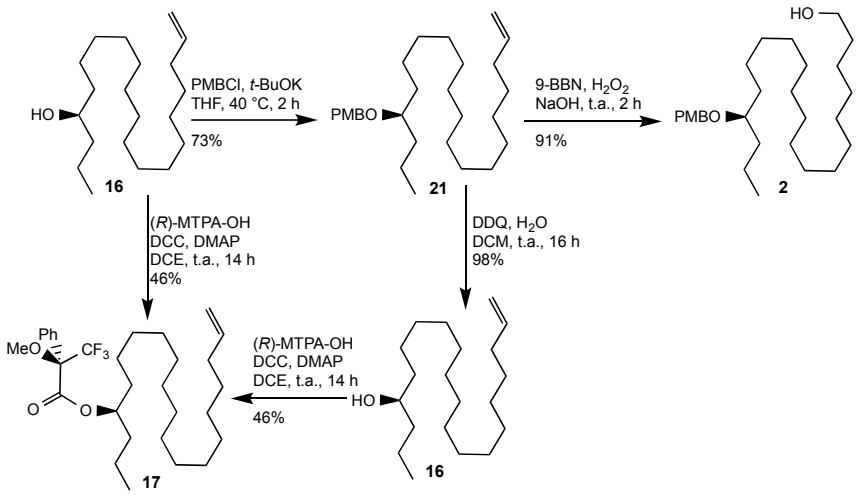


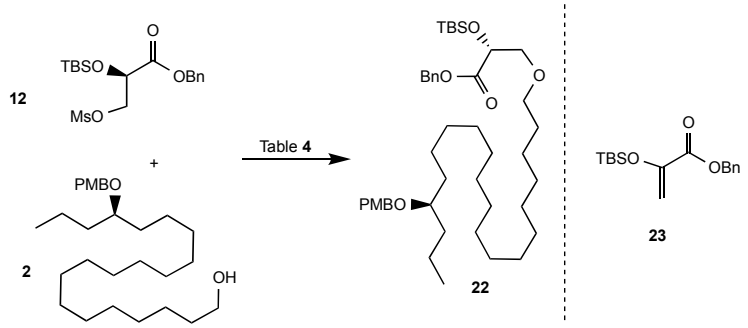
Schéma 3 – Synthèse de l'ester de Mosher 18 et de l'alcool 2

Une fois l'alcène **21** en main, l'hydroboration-oxydation a pu avoir lieu en vue d'obtenir l'alcool primaire **2**. Pour ce faire, le $BH_3 \cdot THF$[22] a été utilisé, dans un premier temps, suivi d'une oxydation par H_2O_2 dans NaOH. Cependant, le composé **2** n'a été obtenu qu'avec un rendement de 46%. Par la suite, le $BH_3 \cdot THF$ a été avantageusement remplacé par du 9-BBN[23] permettant un rendement de 91%, finalisant la synthèse de la chaîne carbonée **2** avec un rendement global de 8% sur quatre étapes.

5.2.4 Couplages

Après avoir finalisé les synthèses des synthons **2** et **3**, plusieurs essais de couplage ont été effectués. Dans un premier temps, l'alcool **2** et le mésyle **12** ont été mis en solution avec une base faible (DIPEA[24] ou lutidine) (Tableau 4, entrées 1 et 2) mais seule l'élimination du mésyle formant l'ester α,β-insaturé **23** a été observée. Dans le cas d'une base forte comme NaH (entrée 3), seule une dégradation a été observée.

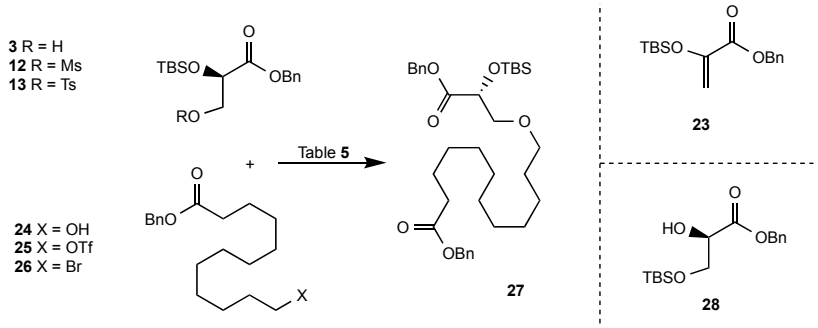
Tableau 4 – Couplage entre le glycérol 12 et la chaîne 2



entrée	base	solvant	température (°C)	résultat
1	DIPEA	toluène	110	élimination (71%)
2	lutidine	-	160	élimination
3	NaH	DCM	20	dégradation

La synthèse de la chaîne **2** étant laborieuse et à faible rendement pour l'instant, elle a été remplacée par l'alcool primaire **24** (Tableau 5), déjà utilisé lors des premiers essais de glycosylation (*cf* chapitre 4).

Tableau 5 – Formation du lien éther avec la chaîne carbonée type



entrée	chaîne	glycérol	base	solvant	température (°C)	résultat
1	**24**	**12**	NaH	DMF	20	n.d.[a]
2	**24**	**13**	DIPEA	toluène	110	n.d.[b]
3	**24**	**13**	lutidine	-	160	n.d.[b]
4	**25**	**3**	Et_3N	DCM[c]	-78 à 20	n.d.[a]
5	**25**	**3**	DIPEA	DMF[c]	20	n.d.[a]
6	**25**	**3**	DBU	DMF	-78	n.d.[a]
7	**25**	**3**	DBU	DMF[c]	-78	**28** (30%)[d]
8	**25**	**3**	K_2CO_3	DMF	0	n.d.[a]
9	**26**	**3**	NaH	DMF	20	n.d.[a]
10	**26**	**3**	*t*BuOK	DMF	20	n.d.[a]
11	**26**	**3**	TBAHS, NaOH 1.0 M	DCE	20	n.d.[e]
12	**26**	**3**	Ag_2O, TMSOTf	DCE	20 à 60	n.d.[f]

[a] Dégradation. [b] Élimination. [c] Ajout de tamis moléculaire 4 Å. [d] Rendement isolé. [e] Pas de réaction. [f] Des traces d'un composé ont été détectées mais qui n'a pu être caractérisé.

Le DMF étant réputé pour accélérer les réactions de type S_N2[25], les dernières conditions utilisant le NaH ont été reproduites en remplaçant le DCM par du DMF (entrée 1), mais cela a malgré tout mené à la dégradation du milieu. L'utilisation du tosyle **13**, plus réactif que le mésyle **12** en présence de DIPEA ou de lutidine (entrées 2 et 3), a, comme précédemment, mené au produit

d'élimination **23**. Il a donc été conclu que la partie glycérol ne pouvait pas jouer le rôle d'électrophile lors de ce couplage puisque trop sensible à l'élimination.

Le triflate **25**[26] a donc été synthétisé à partir de l'alcool **24** et mis en solution avec le nucléophile **3** en présence de Et_3N[27], de DIPEA ou de DBU (entrées 4–6) mais seule la dégradation de **25** a été observée. Aussi, l'ajout de tamis moléculaire 4 Å avec le DBU (entrée 7) a également mené au produit de migration du TBS **28**. Enfin, une base inorganique comme le K_2CO_3[28] (entrée 8) n'a également mené qu'à la dégradation du milieu.

Le triflate **25** étant trop fragile, le composé bromé **26** a été synthétisé. L'utilisation de base forte comme NaH et *t*BuOK (entrées 9–10) ont mené à la dégradation du milieu et l'utilisation de conditions plus douces en transfert de phase[29] (entrée 11) n'a mené à aucune réaction. Enfin, des conditions utilisant Ag_2O avec une catalyse au TMSOTf ont entraîné la dégradation de l'alcool **3**. Cependant, des traces d'un composé ont été détectées, mais ce dernier n'a pas pu être caractérisé.

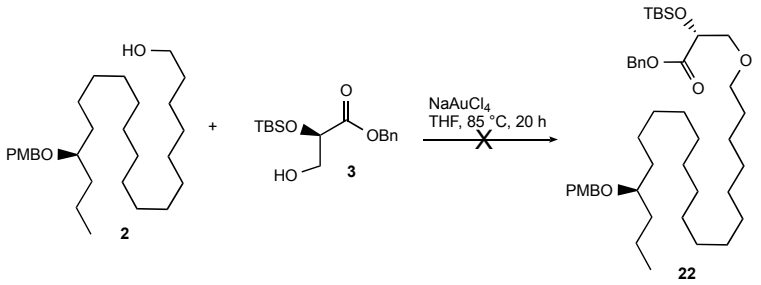


Schéma 4 – Tentative de couplage des alcools 2 et 3 avec une catalyse à $NaAuCl_4$

Enfin, selon les travaux de Medio-Simón[30], une catalyse à l'or pourrait permettre la création d'un lien éther entre deux alcools directement. Comme montré dans le schéma 4, les alcools **2** et **3** ont été mis en présence de $NaAuCl_4$, mais seule la dégradation des composés de départ a été remarquée.

Ainsi, aucune méthode efficace n'a été trouvée pour la formation de ce lien éther et les résultats obtenus jusqu'à maintenant nous encouragent à établir une nouvelle voie de synthèse pour la poursuite du projet (voir section 5.3).

5.3 Alternatives et perspectives

Du fait des résultats obtenus jusque-là, nous avons décidé de revoir l'analyse rétrosynthétique. Telle que présentée à la figure 3, une alternative de synthèse serait d'imaginer un

précurseur **29** au lipide protégé **1** comportant une double liaison pouvant être réduite *via* une réaction d'hydrogénolyse. Ce lien double pourrait être formé par métathèse de la chaîne **30** avec le glycérol **31**. Cette chaîne serait accessible par couplage entre l'époxyde **4** déjà synthétisé avec le composé bromé **32** synthétisable de la même manière que son homologue **5** à partir du 1,11-dibromoundécane commercial. D'autre part, le glycérol **31** pourrait être obtenu par allylation régiosélective du diol **7** suivie par la protection de l'alcool secondaire par un groupement TBS ou par allylation de l'alcool **3** déjà synthétisé.

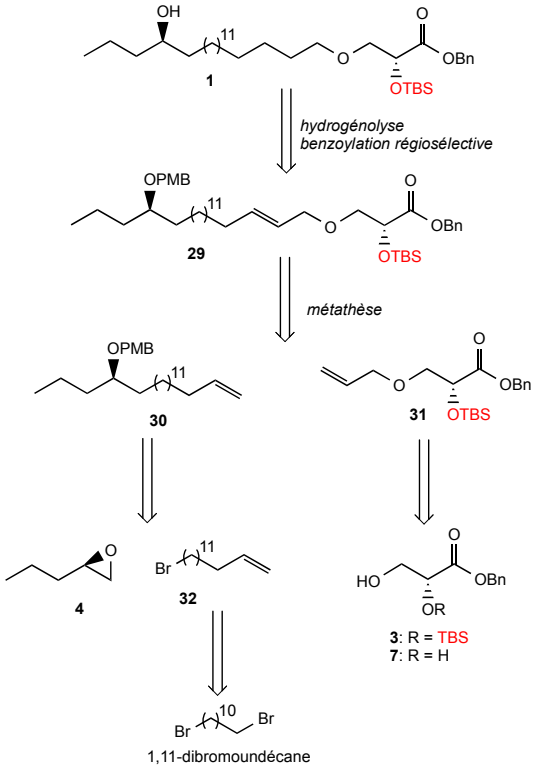


Figure 3 – Analyse rétrosynthétique du lipide 1 *via* métathèse

De manière analogue à la synthèse du composé **2**, la chaîne **30** pourrait être obtenue par monoallylation du 1,11-dibromoundécane suivie par le couplage avec l'époxyde **4** dans les mêmes conditions que celles présentées précédemment. La protection de l'alcool **33** avec un groupement PMB permettra d'obtenir la chaîne **30** (Schéma 5).

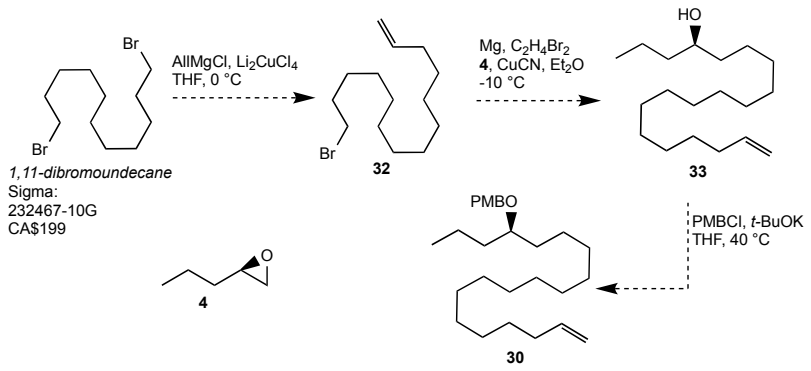


Schéma 5 – Synthèse possible de l'alcène 27

Bien que la formation du lien éther entre les composés **2** et **3** nous a posé problème, nous envisageons que la protection de l'alcool primaire **3** à l'aide d'un groupement allyle pourrait ouvrir tout un éventail de conditions pour accéder au précurseur lipidique **29**. Il serait possible d'utiliser l'acétate d'allyle[31] avec une catalyse au Pd^{II} ou du chlorure d'allyle en transfert de phase,[32] pour obtenir l'alcène **31** (Schéma 6). La métathèse pourrait ensuite avoir lieu entre ce dernier et la chaîne **30** à l'aide d'un catalyseur de Grubbs à base de ruthénium. Enfin, l'hydrogénolyse de l'alcène **29** suivie par la benzylation régiosélective de l'acide **34** permettrait l'obtention du composé **1** cible.

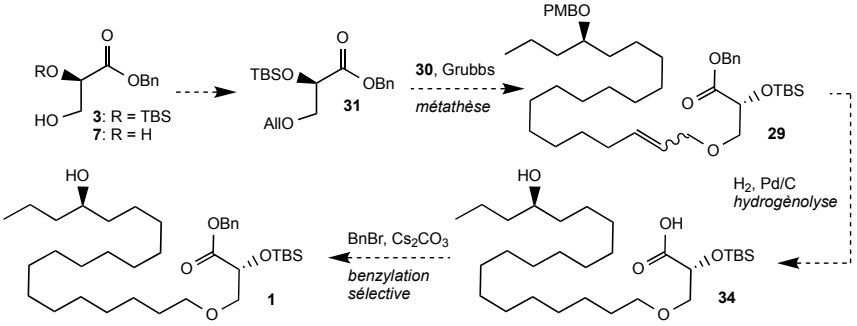


Schéma 6 – Synthèse alternative du lipide 1

5.4 Partie expérimentale (Anglais)

The general methods are the same as presented in the the previous chapter (Chap IV, 4.1 Article publié, p. 55).

(4*R*)-4-Benzoxycarbonyl-2,2-dimethyl-1,3-dioxolane (6)

In a microwavable tube (4*R*)-4-methoxycarbonyl-2,2-dimethyl-1,3-dioxolane (3.66 g, 25.3 mmol, 1.0 equiv), and Bu_2SnO (630 mg, 2.53 mmol, 0.1 equiv) were dissolved in BnOH (35 mL). The mixture was heated using a microwave at 120 °C for 30 min. Then, saturated aq. $NaHCO_3$ (200 mL) was added and the aqueous layer was extracted three times with EtOAc (3 × 250 mL) and the combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 95:5 to 8:2) gave desired compound **6** (4.11 g, 69%) as a yellow oil: R_f 0.4 (Hex/EtOAc 8:2). Physical and analytical data agreed with those published.[4]

Benzyl (2*R*)-2,3-dihydroxypropanoate (7)

In a round-bottom flask, compound **6** (3.89 g, 17.3 mmol, 1.0 equiv) was dissolved in water (6.6 mL) and AcOH (26.4 mL). The mixture was heated at 60 °C for 3 h. Then, water (200 mL) was added and the aqueous layer was extracted five times with DCM (5 × 250 mL) and the combined organic layers were washed with brine (150 mL), filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 6:4 to 4:6) gave desired compound **7** (2.87 g, 82%) as a yellow oil: R_f 0.2 (Hex/EtOAc 1:1). Physical and analytical data agreed with those published.[33]

Benzyl (2*R*)-2-hydroxy-3-triphenylmethoxypropanoate (8)

In a round-bottom flask, compound **7** (1.63 g, 8.32 mmol, 1.0 equiv) was dissolved in DCM (83 mL), and freshly activated 4 Å molecular sieves (6.7 g, 4.1 massic equiv), pyridine (1.5 mL, 18 mmol, 2.2 equiv), and TrCl (2.55 g, 9.15 mmol, 1.1 equiv) were successively added. The mixture was stirred at room temperature for 15 h, then filtered over Celite, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 98:2 to 7:3) gave desired compound **8** (3.13 g, 86%) as a white amorphous solid: R_f 0.4 (Hex/EtOAc 7:3). Physical and analytical data agreed with those published.[4]

Benzyl (2*R*)-2-*tert*-butyldimethylsilyloxy-3-triphenylmethoxypropanoate (9)

In a round-bottom flask, compound **8** (2.00 g, 4.56 mmol, 1.0 equiv) was dissolved in DCE (9.1 mL), and 2,6-lutidine (2.1 mL, 18 mmol, 4.0 equiv) was added. The mixture was cooled the 0 °C prior to the addition of TBSOTf (1.8 mL, 9.1 mmol, 2.0 equiv) and was stirred at 0 °C for 70 min. Then, DCM (40 mL) and saturated aq. $NaHCO_3$ (150 mL) were added, the aqueous layer was extracted with DCM (5 × 50 mL), and the combined organic layers were washed with brine (10 mL), filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 95:5) gave desired compound **9** (2.53 g, quantitative) as a white amorphous solid: R_f 0.5 (Hex/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.43–7.40 (m, 6H, 6 × C*H*^{Ph}), 7.29–7.19 (m, 14H, 14 × C*H*^{Ph}), 5.20 (d, 1H, J = 12.3 Hz, C*H*H^{Bn}), 5.08 (d, 1H, J = 12.3 Hz, CH*H*^{Bn}), 4.37 (dd, 1H, J = 5.1 Hz, J = 4.2 Hz, H-2), 3.38 (dd, 1H, J = 9.2 Hz, J = 4.1 Hz, H-3a), 3.29 (dd, 1H, J = 9.2 Hz, J = 5.3 Hz, H-3b), 0.91 (s, 9H, *t*Bu), 0.07 (s, 3H, C*H*$_3$), 0.05 (s, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.9 (O*C*=O), 144.0 (6C, 6 × *C*^{Ph}), 135.7 (*C*^{Bn}), 128.9 (6C, 6 × *C*H^{Ph}), 128.6 (2C, 2 × *C*H^{Bn}), 128.5 (2C, 2 × *C*H^{Bn}), 128.3 (*C*H^{Bn}), 127.9 (6C, 6 × *C*H^{Ph}), 127.1 (3C, 3 × *C*H^{Ph}), 86.7 (*C*Ph$_3$), 72.6 (C-3), 66.7 (2C, C-2, *C*H$_2^{Bn}$), 25.9 (3C, C(*C*H$_3$)$_3^{TBS}$), 18.5 (*C*(CH$_3$)$_3^{TBS}$), –4.9 (*C*H$_3^{TBS}$), –5.0 (*C*H$_3^{TBS}$); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{40}NaO_4Si$ 575.2588; found 575.2610; *m*/*z* [M + K]$^+$ calcd for $C_{35}H_{40}KO_4Si$ 591.2327; found 591.2340.

Benzyl (2*R*)-2-*tert*-butyldimethylsilyloxy-3-hydroxypropanoate (3)

In a round-bottom flask, compound **9** (559 mg, 1.01 mmol, 1.0 equiv) was dissolved in water (1.4 mL) and AcOH (5.6 mL). The mixture was heated at 60 °C for 2 h. Then, saturated aq. $NaHCO_3$ (200 mL) was added and the aqueous layer was extracted three times with DCM (3 × 150 mL), and the combined organic layers were filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 95:5 to 4:6) gave desired compound **3** (221 mg, 70%) as a colorless oil: R_f 0.3 (Hex/EtOAc 8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.41–7.30 (m, 5H, 5 × C*H*^{Bn}), 5.21 (d, 1H, J = 12.2 Hz, C*H*H^{Bn}), 5.17 (d, 1H, J = 12.2 Hz, CH*H*^{Bn}), 4.33 (t, 1H, J = 4.6 Hz, H-2), 3.86–3.75 (m, 2H, H-3a, H-3b), 2.26–2.19 (br s, 1H, O*H*), 0.90 (s, 9H, *t*Bu), 0.09 (s, 3H, C*H*$_3$), 0.06 (s, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.7 (O*C*=O), 135.5 (*C*^{Bn}), 128.7 (2C, 2 × *C*H^{Bn}), 128.5 (*C*H^{Bn}), 128.4 (2C, 2 × *C*H^{Bn}), 73.0 (C-2), 67.0

(CH_2^{Bn}), 65.1 (C-3), 25.8 (3C, C(CH_3)$_3^{TBS}$), 18.4 (C(CH_3)$_3^{TBS}$), –4.8 (CH_3^{TBS}), –5.3 (CH_3^{TBS}); HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{27}O_4Si$ 311.1673; found 311.1677; *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{27}NaO_4Si$ 333.1493; found 333.1498.

Benzyl 3-acetyloxy-(2*R*)-2-*tert*-butyldimethylsilyloxypropanoate (11)

In a 1.0 mL vial, compound **3** (0.60 mg, 16 μmol, 1.0 equiv) was dissolved in pyridine (40 μL) and Ac_2O (40 μL), and a cristal of DMAP was added. The mixture was stirred at room temperature for 64 h. Then, the solution was concentrated under reduced pressure. The crude was analysed by NMR without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.39–7.33 (m, 5H, 5 × CH^{Bn}), 5.22 (d, 1H, J = 12.2 Hz, CHH^{Bn}), 5.15 (d, 1H, J = 12.2 Hz, CHH^{Bn}), 4.46 (dd, 1H, J = 6.5 Hz, J = 4.0 Hz, H-2), 4.36 (dd, 1H, J = 11.2 Hz, J = 4.0 Hz, H-3a), 4.24 (dd, 1H, J = 11.2 Hz, J = 6.5 Hz, H-3b), 2.25 (s, 3H, CH_3^{Ac}), 0.88 (s, 9H, *t*Bu), 0.08 (s, 3H, CH_3), 0.06 (s, 3H, CH_3).

Benzyl (2*R*)-2-*tert*-butyldimethylsilyloxy-3-methanesulfonyloxypropanoate (12)

In a round-bottom flask, compound **3** (101 mg, 0.325 mmol, 1.0 equiv) was dissolved in DCM (1.0 mL). The mixture was cooled the 0 °C prior to the addition of Et_3N (50 μL, 0.35 mmol, 1.1 equiv), and MsCl (50 μL, 0.64 mmol, 2.0 equiv) and was stirred at room temperature for 4 h. Then, additional Et_3N (50 μL, 0.35 mmol, 1.1 equiv) and MsCl (25 μL, 0.32 mmol, 1.0 equiv) were added and the mixture was stirred at room temperature for an additional 30 min prior to being concentrated under reduced pressure. Purification by silica gel flash chromatography (toluene/EtOAc 98:2 to 9:1) gave desired compound **12** (105 mg, 84%) as a yellow oil: R_f 0.5 (toluene/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.39–7.32 (m, 5H, 5 × CH^{Bn}), 5.20 (s, 1H, CH_2^{Bn}), 4.52–4.48 (m, 2H, H-2, H-3a), 4.38–4.35 (m, 1H, H-3b), 2.98 (s, 3H, CH_3^{Ms}), 0.89 (s, 9H, *t*Bu), 0.092 (s, 3H, CH_3^{TBS}), 0.086 (s, 3H, CH_3^{TBS}); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 169.8 (OC=O), 135.1 (C^{Bn}), 128.8 (2C, 2 × CH^{Bn}), 128.74 (CH^{Bn}), 128.68 (2C, 2 × CH^{Bn}), 71.12, 71.08 (2C, C-2, C-3), 67.5 (CH_2^{Bn}), 37.7 (CH_3^{Ms}), 25.7 (3C, C(CH_3)$_3^{Lev}$), 18.4 (C(CH_3)$_3^{TBS}$), –4.9 (CH_3^{TBS}), –5.3 (CH_3^{TBS}); HRMS (ESI-TOF) *m*/*z* [M + NH_4]$^+$ calcd for $C_{17}H_{32}O_6NSSi$ 406.1714; found 406.1734; *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{28}NaO_6SSi$ 411.1268; found 411.1287.

Benzyl (2*R*)-2-*tert*-butyldimethylsilyloxy-3-(4-methylphenyl)sulfonyloxypropanoate (13)

In a round-bottom flask, compound **3** (43 mg, 0.14 mmol, 1.0 equiv) was dissolved in DCM (1.0 mL). The mixture was cooled the 0 °C prior to the addition of Et_3N (21 μL, 0.18 mmol, 1.1 equiv) and TsCl (55 mg, 0.32 mmol, 2.0 equiv) and was stirred at room temperature for 2.5 h. Then, additional Et_3N (22 μL, 0.18 mmol, 1.1 equiv) and TsCl (29 mg, 0.16 mmol, 1.0 equiv) were added and the mixture was stirred at room temperature for an additional 3.5 h prior to being concentrated under reduced pressure. Purification by silica gel flash chromatography (toluene/EtOAc 98:2) gave desired compound **13** (54 mg, 82%) as a yellow oil: R_f 0.7 (toluene/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.77–7.74 (m, 2H, 2 × C*H*^{Ts}), 7.37–7.29 (m, 7H, 7 × C*H*^{Ar}), 5.13 (s, 1H, C*H*$_2^{Bn}$), 4.44 (dd, 1H, J = 6.8 Hz, J = 3.8 Hz, H-2), 4.28 (dd, 1H, J = 10.1 Hz, J = 3.8 Hz, H-3a), 4.11 (dd, 1H, J = 10.1 Hz, J = 6.8 Hz, H-3b), 2.43 (s, 3H, C*H*$_3^{Ts}$), 0.83 (s, 9H, *t*Bu), 0.030 (s, 3H, C*H*$_3^{TBS}$), 0.027 (s, 3H, C*H*$_3^{TBS}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 169.8 (O*C*=O), 145.1 (*C*^{Ar}), 135.2 (*C*^{Ar}), 132.8 (*C*^{Ar}), 130.0 (2C, 2 × *C*H^{Ts}), 128.72 (2C, 2 × *C*H^{Bn}), 128.65 (*C*H^{Bn}), 128.6 (2C, 2 × *C*H^{Bn}), 128.1 (2C, 2 × *C*H^{Ts}), 71.1 (C-3), 70.9 (C-2), 67.4 (*C*H$_2^{Bn}$), 25.6 (3C, C(*C*H$_3$)$_3^{Lev}$), 21.8 (*C*H$_3^{Ts}$), 18.3 (*C*(CH$_3$)$_3^{TBS}$), –5.0 (*C*H$_3^{TBS}$), –5.32 (*C*H$_3^{TBS}$); HRMS (ESI-TOF) m/z [M + NH_4]$^+$ calcd for $C_{23}H_{36}O_6NSSi$ 482.2027; found 482.2032; m/z [M + Na]$^+$ calcd for $C_{23}H_{32}NaO_6SSi$ 487.1581; found 487.1583.

Benzyl (2*R*)-3-bromo-2-*tert*-butyldimethylsilyloxy-propanoate (14)

In a round-bottom flask, PPh_3 (16 mg, 0.18 mmol, 1.1 equiv), imidazole (5 mg, 0.2 mmol, 1.1 equiv), and NBS (14 mg, 0.18 mmol, 1.1 equiv) were dissolved in DCM (270 μL). The mixture was cooled the 0 °C and after 10 min, compound **3** (15 mg, 0.16 mmol, 1.0 equiv) was added and the solution was allowed to warm to room temperature for 25 h. Then, the crude was concentrated under reduced pressure. Purification by silica gel flash chromatography (toluene/EtOAc 95:5 to 9:1) gave desired compound **14** (5 mg, 25%) as a yellow oil: R_f 0.4 (toluene/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.37–7.32 (m, 5H, 5 × C*H*^{Bn}), 5.21 (d, 1H, J = 12.2 Hz, C*H*H^{Bn}), 5.17 (d, 1H, J = 12.2 Hz, CH*H*^{Bn}), 4.46 (dd, 1H, J = 6.4 Hz, J = 4.8 Hz, H-2), 3.61 (dd, 1H, J = 10.3 Hz, J = 4.7 Hz, H-3a), 3.51 (dd, 1H, J = 10.3 Hz, J = 6.4 Hz, H-3b), 0.90 (s, 9H, *t*Bu), 0.09 (s, 3H, C*H*$_3^{TBS}$), 0.07 (s, 3H, C*H*$_3^{TBS}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 170.5 (O*C*=O), 135.3 (*C*^{Ar}), 128.73 (2C, 2 × *C*H^{Bn}), 128.65 (3C, 3 × *C*H^{Bn}), 72.7 (C-2), 67.3 (*C*H$_2^{Bn}$), 34.2 (C-3), 25.8

($C(CH_3)_3^{TBS}$), –4.8 (CH_3^{TBS}), –5.1 (CH_3^{TBS}); HRMS (ESI-TOF) *m*/*z* [M + NH_4]$^+$ calcd for $C_{16}H_{29}[^{79}Br]O_3NSi$ 390.1095; found 390.1106.

(2*R*)-1-Chloropentan-2-ol (15)

In a round-bottom flask, (*R*)-epichlorohydrin (2.7 mL, 34.44 mmol, 1.0 equiv) was dissolved in THF (46 mL) and CuCN (343 mg, 3.83 mmol, 0.1 equiv) was added. The mixture was cooled to –78 °C prior to the dropwise addition of EtMgBr (1.0 M in THF) (52 mL, 52 mmol, 1.5 equiv) over an hour and the solution was allowed to slowly warm up to –20 °C over 3.5 h. Then, saturated aq. NH_4Cl (50 mL) was added, the aqueous layer was extracted twice with Et_2O (2 × 50 mL), and the combined organic layers were filtered over $MgSO_4$ and slightly concentrated under reduced pressure to afford desired compound **15** (3.14 g, 74% NMR yield) as a yellowish oil: R_f 0.5 (Hex/EtOAc 7:3). Physical and analytical data agreed with those published.[12]

(2*R*)-2-Propyloxirane (4)

In a round-bottom flask, compound **12** (3.0 g, 24.47 mmol, 1.0 equiv) was added dropwise to powdered NaOH (9.8 g, 245 mmol, 10 equiv) at room temperature over 10 min. The mixture was rinced with DCM and the crude was distilled at atmospheric pressure affording desired compound **4** (1.84 g, 75% NMR yield) as a yellowish oil. Physical and analytical data agreed with those published.[12]

15-Bromo-1-pentadecene (5)

In a round-bottom flask, LiCl (318 mg, 7.41 mmol, 0.4 equiv) and $CuCl_2$ (505 mg, 3.70 mmol, 0.2. equiv) were dissolved in THF (28 mL). The mixture was stirred at room temperature for 16 h. Then, 1,12-dibromododecane. (6.00 g, 18.29 mmol, 1.0 equiv) was added and the solution was cooled to 0 °C prior to the dropwise addition of AllMgCl (2.0 M in THF) (11.0 mL, 22.0 mmol, 1.2 equiv) over 10 min and the mixture was stirred at 0 °C for 1 h. Next, 1.0 M aq. HCl. (30 mL) was added and the crude was stirred at room temperature for 1 h. The aqueous layer was then extracted three times with Et_2O (3 × 30 mL) and the combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (100% Hex to Hex/EtOAc 9:1) gave desired compound **5** (2.38 g, 45% with 20% of recovered

starting material) as a colorless oil: R_f 0.5 (pure Hex). Physical and analytical data agreed with those published.[34]

(4*R*)-4-Hydroxy-19-eicosene (16)

In a round-bottom flask, magnesium (323 mg, 9.54 mmol, 2.3 equiv) was heated with a heat gun for 10 min. Then, dry Et_2O (6.0 mL) and 1,2-dibromoethane (4 to 5 drops) were added and the dispersion was stirred at room temperature for 20 min. Then, a solution of compound **5** (1.19 g, 4.15 mmol, 1 equiv) in dry Et_2O (3.0 mL) was added dropwise to the latter over 20 min and the mixture was heated to 45 °C and stirred for 3 h. In another round-bottom flask, epoxide **4** (889 mg, 10.3 mmol, 2.5 equiv) and CuCN (69 mg, 0.77 mmol, 0.2 equiv) were mixed in Et_2O (10.4 mL) and the dispersion was cooled to –10 °C. Next, the magnesium solution was added dropwise to the latter over 8 min and the resulting mixture was stirred at room temperature for 2 h. Then, saturated aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted twice with Et_2O (2 × 20 mL), and the combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (100% Hex to Hex/EtOAc 9:1) gave desired compound **16** (211 mg, 22%) as a white amorphous solid: R_f 0.25 (Hex/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.81 (ddt, 1H, J = 17.1 Hz, J = 10.2 Hz, J = 6.7 Hz, H-19), 4.99 (ddt, 1H, J = 17.1 Hz, J = 2.8 Hz, J = 1.5 Hz, H-20a), 4.93 (ddt, 1H, J = 10.2 Hz, J = 2.8 Hz, J = 1.0 Hz, H-20b), 3.62–3.58 (m, 1H, H-4), 2.06–2.02 (m, 2H, H-18), 1.47–1.40 (m, 4H, H-3, H-5), 1.40–1.33 (m, 4H, H-2, H-17), 1.33–1.24 (m, 22H, 11 × CH_2), 0.95–0.91 (m, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 139.4 (C-19), 114.2 (C-20), 71.9 (C-4), 44.4, 42.1, 39.8, 37.7 (4C, 4 × CH_2), 34.0 (C-18), 30.4, 29.81, 29.79, 29.77, 29.7, 29.3, 29.1, 27.1, 25.8, 24.1, 19.0 (11C, 11 × CH_2), 14.3 (CH_3); HRMS (ESI-TOF) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{44}ON$ 314.3417; found 314.3418; m/z $[M + Na]^+$ calcd for $C_{20}H_{40}NaO$ 319.2971; found 319.2972.

(4*R*)-4-Methoxymethyloxy-19-eicosene (18)

In a round-bottom flask, compound **16** (22 mg, 0.07 mmol, 1.0 equiv) was dissolved in DCE (375 μL), and DIPEA (26 μL, 0.15 mmol, 2.0 equiv), DMAP (1 cristal), and MOMCl (43 mg, 0.23 mmol, 3.3 equiv) were added and the mixture was stirred at room temperature for 90 min. Then, water (3 mL) was added and the aqueous layer was extracted three times with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), filtered over $MgSO_4$ and

concentrated under reduced pressure. Purification by silica gel flash chromatography (100% Hex to Hex/EtOAc 8:2) gave desired compound **18** (5 mg, 19%) as a colorless oil: R_f 0.6 (Hex/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.81 (ddt, 1H, J = 17.1 Hz, J = 10.2 Hz, J = 6.7 Hz, H-19), 4.99 (ddt, 1H, J = 17.1 Hz, J = 2.8 Hz, J = 1.5 Hz, H-20a), 4.93 (ddt, 1H, J = 10.2 Hz, J = 2.8 Hz, J = 1.0 Hz, H-20b), 4.65 (s, 2H, CH_2^{MOM}), 3.55–3.50 (m, 1H, H-4), 3.38 (s, 3H, CH_3^{MOM}), 2.06–2.02 (m, 2H, H-18), 1.51–1.44 (m, 4H, H-3, H-5), 1.40–1.24 (m, 26H, 13 × CH_2), 0.93–0.88 (m, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 139.4 (C-19), 114.2 (C-20), 95.5 (CH_2^{MOM}), 77.4 (C-4), 55.6 (CH_3^{MOM}), 41.7, 39.4, 36.8, 34.5 (4C, 4 × CH_2), 34.0 (C-18), 30.4, 30.0, 29.9, 29.82, 29.77, 29.7, 29.3, 29.1, 25.5, 24.1, 18.7 (11C, 11 × CH_2), 14.4 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{44}NaO_2$ 363.3234; found 363.3222.

(4*R*)-4-Triethylsilyloxy-19-eicosene (19)

In a round-bottom flask, compound **16** (9 mg, 0.03 mmol, 1.0 equiv) was dissolved in DMF (330 μL) and imidazole (14 mg, 0.21 mmol, 7.0 equiv), DMAP (1 mg, 0.01 mmol, 01 equiv), and TESCl (11 μL, 0.07 mmol, 2.0 equiv) were added and the mixture was stirred at room temperature for 5 h. Then, the mixture was concentrated under reduced pressure. Purification by silica gel flash chromatography (100% toluene to toluene/EtOAc 8:2) gave desired compound **19** (10 mg, 76%) as a colorless oil: R_f 0.8 (Hex/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.81 (ddt, 1H, J = 17.1 Hz, J = 10.2 Hz, J = 6.7 Hz, H-19), 4.99 (ddt, 1H, J = 17.1 Hz, J = 2.8 Hz, J = 1.5 Hz, H-20a), 4.93 (ddt, 1H, J = 10.2 Hz, J = 2.8 Hz, J = 1.0 Hz, H-20b), 3.65–3.60 (m, 1H, H-4), 2.06–2.01 (m, 2H, H-18), 1.44–1.22 (m, 30H, 15 × CH_2), 0.96 (t, 9H, J = 7.9 Hz, 3 × CH_3^{TES}), 0.89 (t, 3H, J = 6.8 Hz, CH_3), 0.59 (q, 6H, J = 7.9 Hz, 3 × CH_2^{TES}); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 139.4 (C-19), 114.2 (C-20), 72.6 (C-4), 39.7 (CH_2), 37.5 (CH_2), 37.1 (CH_2), 34.0 (C-18), 30.0 (CH_2), 29.9 (CH_2), 29.83 (2C, 2 × CH_2), 29.79 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 18.8 (CH_2), 14.3 (CH_3), 7.1 (3C, 3 × CH_3^{TES}), 5.3 (3C, 3 × CH_2^{TES}); HRMS (ESI-TOF) m/z $[M + K - TES]^+$ calcd for $C_{20}H_{40}KO$ 335.2716; found 335.2433.

(4*R*)-4-(2-Azidomethylbenzoyl)oxy-19-eicosene (20)

In a round-bottom flask, compound **16** (10 mg, 0.03 mmol, 1.0 equiv) was dissolved in DCM (340 μL) and DMAP (1 cristal), DCC (14 mg, 0.07 mmol, 2.0 equiv), and AZMBOH (9 mg, 0.05 mmol, 1.5 equiv) were added and the mixture was stirred at 60 °C for 6.5 h. Then, the mixture was filtered

over Celite and concentrated under reduced pressure. Purification by silica gel flash chromatography (100% Hex to Hex/EtOAc 8:2) gave desired compound **20** (11 mg, 75%) as a colorless oil: R_f 0.7 (Hex/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.01–7.98 (m, 1H, C*H*^{AZMB}), 7.56–7.52 (m, 1H, C*H*^{AZMB}), 7.51–7.48 (m, 1H, C*H*^{AZMB}), 7.42–7.38 (m, 1H, C*H*^{AZMB}), 5.81 (ddt, 1H, J = 17.1 Hz, J = 10.2 Hz, J = 6.7 Hz, H-19), 5.17–5.11 (m, 1H, H-4), 4.99 (ddt, 1H, J = 17.1 Hz, J = 2.8 Hz, J = 1.5 Hz, H-20a), 4.92 (ddt, 1H, J = 10.2 Hz, J = 2.8 Hz, J = 1.0 Hz, H-20b), 4.83 (s, 2H, C*H*$_2^{AZMB}$), 2.06–2.01 (m, 2H, H-18), 1.73–1.60 (m, 4H, H-3, H-5), 1.44–1.23 (m, 26H, 13 × C*H*$_2$), 0.92–0.87 (m, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 166.7 (O*C*=O), 139.4 (C-19), 137.3 (*C*^{AZMB}), 132.5 (*C*H^{AZMB}), 131.0 (*C*H^{AZMB}), 129.83, 129.82 (2C, *C*^{AZMB}, *C*H^{AZMB}), 128.2 (*C*H^{AZMB}), 114.2 (C-20), 75.7 (C-4), 53.2 (*C*H$_2^{AZMB}$), 34.3, 34.01, 33.97 (3C, C-18, C-3, C-5), 29.9 (*C*H$_2$), 29.80 (*C*H$_2$), 29.77 (*C*H$_2$), 29.76 (*C*H$_2$), 29.72 (*C*H$_2$), 29.71 (*C*H$_2$), 29.67 (*C*H$_2$), 29.66 (*C*H$_2$), 29.3 (*C*H$_2$), 29.1 (*C*H$_2$), 27.7 (*C*H$_2$), 25.6 (*C*H$_2$), 22.8 (*C*H$_2$), 14.2 (*C*H$_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{28}H_{45}NaO_2N_3$ 478.3404; found 478.3395.

(4*R*)-4-(4-Methoxybenzyl)oxy-19-eicosene (21)

In a round-bottom flask, compound **16** (79 mg, 0.27 mmol, 1.0 equiv) was dissolved in THF (2.6 mL) and PMBCl (110 μL, 0.80 mmol, 3.0 equiv), and *t*BuOK (120 mg, 1.07 mmol, 4.0 equiv) were added and the mixture was stirred at 40 °C for 7 h. Then, saturated aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted three times with DCM (3 × 10 mL), and the combined organic layers were filtered over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash chromatography (100% Hex to Hex/EtOAc 8:2) gave desired compound **21** (81 mg, 73%) as a colorless oil: R_f 0.6 (Hex/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.28–7.24 (m, 2H, 2 × C*H*^{PMB}), 6.88–6.85 (m, 2H, 2 × C*H*^{PMB}), 5.81 (ddt, 1H, J = 17.1 Hz, J = 10.2 Hz, J = 6.7 Hz, H-19), 5.02–4.97 (m, 1H, H-20a), 4.94–4.91 (m, 1H, H-20b), 4.43 (s, 2H, C*H*$_2^{PMB}$), 3.80 (s, 3H, C*H*$_3^{PMB}$), 3.37–3.31 (m, 1H, H-4), 2.06–2.01 (m, 2H, H-18), 1.54–1.24 (m, 30H, 15 × C*H*$_2$), 0.93–0.87 (m, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 159.2 (*C*^{PMB}), 139.4 (C-19), 131.5 (*C*^{PMB}), 129.4 (2C, 2 × *C*H^{PMB}), 114.2 (C-20), 113.8 (2C, 2 × *C*H^{PMB}), 78.9 (C-4), 70.5 (*C*H$_2^{PMB}$), 55.4 (*C*H$_3^{OMe}$), 36.4 (*C*H$_2$), 34.1, 34.0, 33.8 (3C, C-18, 2 × *C*H$_2$), 30.0 (*C*H$_2$), 29.9 (*C*H$_2$), 29.83 (*C*H$_2$), 29.81 (*C*H$_2$), 29.78 (*C*H$_2$), 29.7 (*C*H$_2$), 29.3 (*C*H$_2$), 29.1 (*C*H$_2$), 27.8 (*C*H$_2$), 25.5 (*C*H$_2$), 23.1 (*C*H$_2$), 18.8 (*C*H$_2$), 14.3 (*C*H$_3$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{28}H_{48}NaO_2$ 439.3547; found 439.3541; m/z [M + K]$^+$ calcd for $C_{28}H_{48}KO_2$ 455.3286; found 455.3272.

(17*R*)-1-Hydroxy-17-(4-methoxybenzyl)-eicosene (2)

In a round-bottom flask, compound **21** (73 mg, 0.18 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and the mixture was cooled to 0 °C prior to the addition of 9-BBN (0.5 M in THF) (790 μL, 0.39 mmol, 2.2 equiv). After stirring at 0 °C for 2.5 h, EtOH (200 μL), 3.0 M aq. NaOH (290 μL, 0.87 mmol, 5.0 equiv), and 30% aq. H_2O_2 (360 μL, 3.51 mmol, 20.0 equiv) were successively added. Then, saturated aq. NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (15 mL), and the combined organic layers were filtered over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel flash chromatography (Hex/EtOAc 9:1 to 85:15) gave desired compound **2** (69 mg, 91%) as a white amorphous solid: R_f 0.2 (toluene/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.28–7.24 (m, 2H, 2 × C*H*^{PMB}), 6.89–6.84 (m, 2H, 2 × C*H*^{PMB}), 4.43 (s, 2H, C*H*$_2^{PMB}$), 3.79 (s, 3H, C*H*$_3^{PMB}$), 3.62 (t, 2H, J = 6.6 Hz, H-20), 3.36–3.31 (m, 1H, H-17), 1.58–1.24 (m, 34H, 17 × C*H*$_2$), 0.92–0.88 (m, 3H, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 159.1 (*C*^{PMB}), 131.5 (*C*^{PMB}), 129.4 (2C, 2 × *C*H^{PMB}), 113.8 (2C, 2 × *C*H^{PMB}), 78.8 (C-17), 70.5 (*C*H$_2^{PMB}$), 63.2 (C-1), 55.4 (*C*H$_3^{PMB}$), 36.3 (*C*H$_2$), 34.0 (*C*H$_2$), 33.7 (*C*H$_2$), 32.9 (*C*H$_2$), 30.0 (*C*H$_2$), 29.81 (*C*H$_2$), 29.80 (*C*H$_2$), 29.79 (*C*H$_2$), 29.77 (*C*H$_2$), 29.75 (*C*H$_2$), 29.7 (*C*H$_2$), 29.6 (*C*H$_2$), 27.7 (*C*H$_2$), 25.9 (*C*H$_2$), 25.5 (*C*H$_2$), 23.0 (*C*H$_2$), 18.8 (*C*H$_2$), 14.3 (*C*H$_3$); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{50}NaO_3$ 457.3652; found 457.3655; *m*/*z* [M + K]$^+$ calcd for $C_{28}H_{50}KO_3$ 473.3392; found 473.3391.

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-Chapitre VI-

Conclusions et perspectives

Ce travail a constitué un premier pas vers la synthèse totale des agminosides. En effet, plusieurs voies de synthèses ont été explorées en vue d'obtenir, dans un premier temps, l'agminoside **E**. D'abord, l'utilisation d'unités glycosidiques possédant des groupements acétyles pré-installés a été étudiée, mais les essais de glycosylation formant le premier lien β-(1,4) dans la structure de la molécule cible ont montré une forte compétition entre les glycosyles donneur et accepteur. Afin de pallier ce problème, l'application de la stratégie latente-active, ainsi que l'utilisation d'un fragment cellobiose présentant déjà le lien β-(1,4) difficile à obtenir jusque-là ont été envisagées. Malheureusement, les synthèses de ces synthons ont montré de très faibles rendements. Finalement, une refonte de la voie de synthèse et de la structure des unités glycosidiques a été nécessaire afin d'aboutir à la synthèse présentée dans l'article (*cf* chapitre 4).

Afin de développer cette synthèse, et en parallèle de la synthèse de la chaîne lipidique des agminosides, nous avons imaginé un glycolipide chimérique comportant la partie glycosidique partiellement acétylée de l'agminoside **E** avec la chaîne monolipidique des rhamnolipides bactériens. Celui-ci a été obtenu selon une méthode de glycosylation [3 + 2], *i.e.*, le donneur trisaccharidique activé par le PTFA avec un glycolipide ramifié en (1 $\rightarrow$ 2). Les liaisons glycosidiques 1,2-*trans* ont pu être obtenues par la participation d'un groupement AZMB lors de glycosylations mettant en jeu des donneurs thiotolyles. Bien que ce genre de donneurs soient classiquement activés avec des couples de promoteurs comme NIS/TMSOTf ou NIS/AgOTf, de meilleurs résultats ont été obtenus en utilisant NIS/$Yb(OTf)_3$. Ainsi, le glycolipide chimérique ciblé a pu être obtenu avec un rendement global de 0.5% sur 39 étapes de synthèse à partir du D-glucose (Schéma 1), avec une séquence linéaire la plus longue de 19 étapes. Il s'agit donc de la première synthèse de la partie glycosidique des agminosides qui ait été répertoriée dans la littérature. Une comparaison des données RMN de notre composé synthétique aux données RMN des agminosides isolés disponibles dans la littérature a confirmé que le squelette pentaglucosidique et le schéma d'acétylation partielle du glycolipide chimérique ciblé étaient identiques à ceux de l'agminoside **E** isolé.

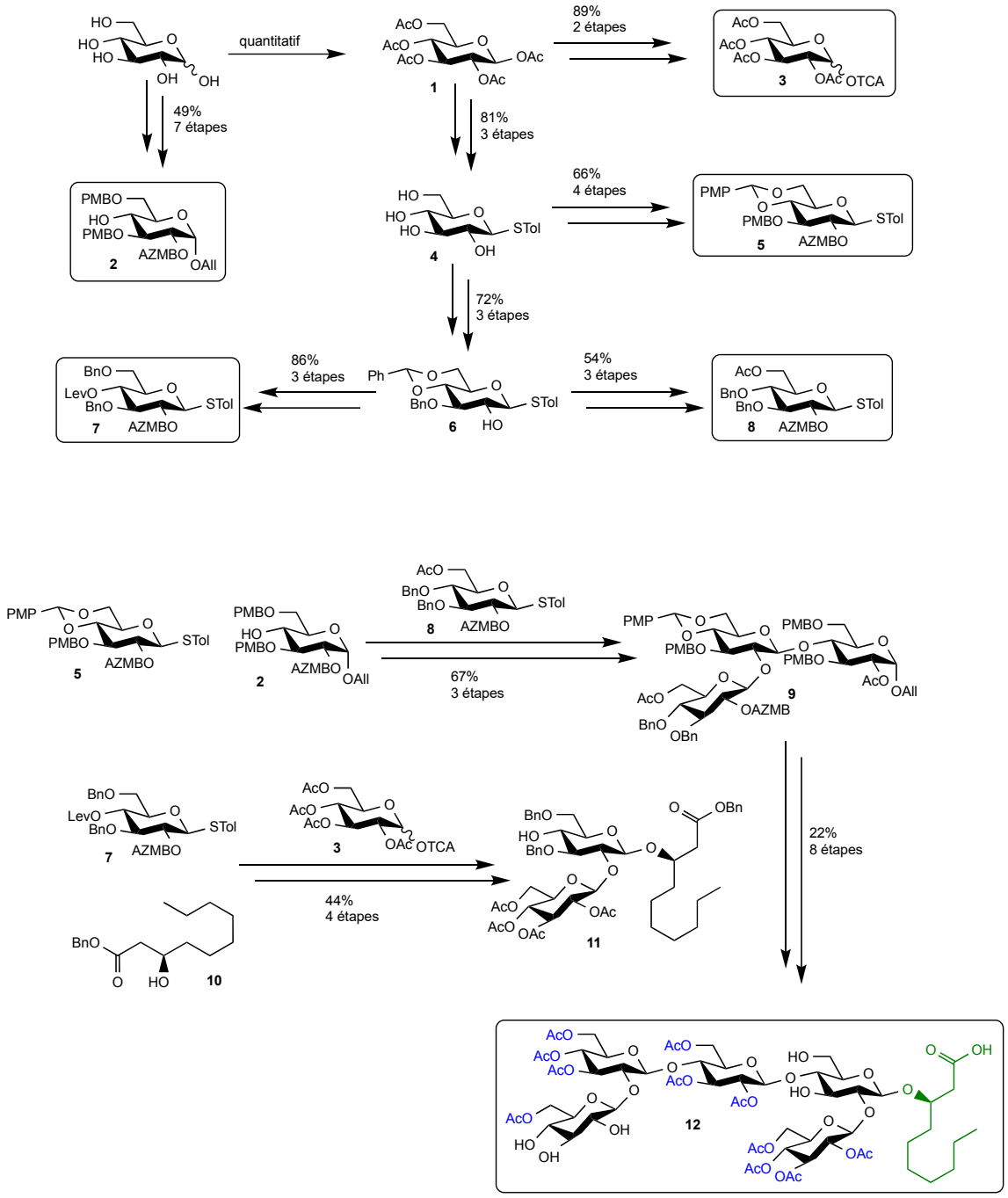

Schéma 1 – Résumé de la synthèse du glycolipide chimérique dérivé de l'agminoside E

Pour ce qui est de la chaîne lipidique native des agminosides, l'analyse rétrosynthétique s'est articulée autour de la formation du lien éther entre la chaîne grasse **15** et l'unité glycérol **16**. Le fragment glycérol a été obtenu par aménagement structural du méthylester chiral commercial mais la synthèse de la chaîne carbonée s'est avérée être plus difficile. L'étape clé de cette synthèse a été la formation d'un organomagnésien à partir du 15-bromopentadécène et le couplage de celui-

ci avec un époxyde chiral volatil issu de la (*R*)-épichlorohydrine *via* la transmétallation du magnésien par un cuprate afin de ne pas épimériser l'alcool chiral. Les deux blocs ont été synthétisés avec succès en respectant les centres stéréogéniques avec des rendements globaux de 34% sur cinq étapes pour le fragment glycérol et 8% sur quatre étapes pour la chaîne carbonée (Schéma 2). Les conditions pour la formation du lien éther restent encore à développer (*cf* chapitre 5).

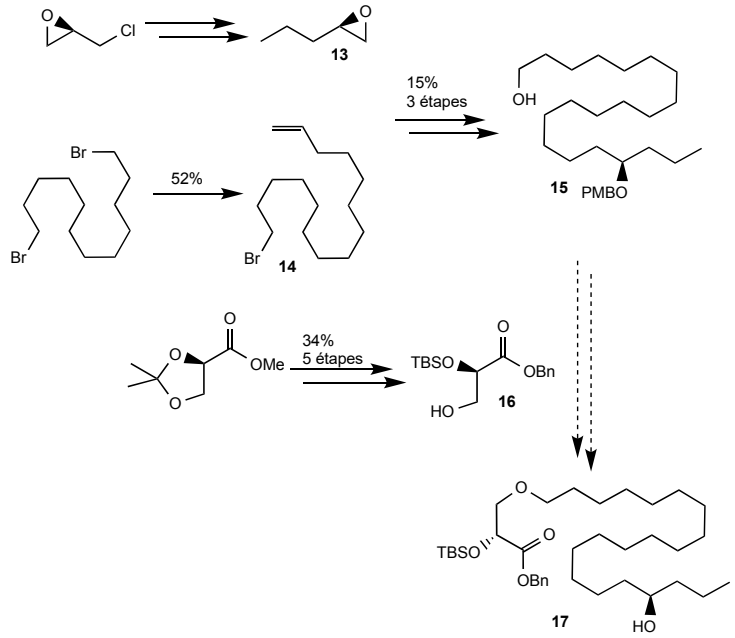

Schéma 4 – Résumé de la synthèse de la chaîne lipidique des agminosides

Une voie de synthèse alternative pouvant permettre l'obtention de l'aglycone natif des agminosides *via* une étape de métathèse croisée entre un alcène linéaire et un allyl lié au fragment glycérol formant le lien éther au préalable a également été imaginée et détaillée dans le chapitre 5.

Une fois la chaîne lipidique **17** synthétisée, elle pourra être glycosylée de façon analogue à celle décrite lors de la synthèse du glycolipide chimérique (Schéma 3) avec les donneurs **7** puis **3** afin d'obtenir le diglycolipide **18** qui pourra ensuite être glycosylé au trisaccharide **9** précédemment synthétisé ou au tétrasaccharide **19** obtenu par élongation du trisaccharide **9** *via* la déprotection de l'AZMB puis glycosylation du donneur **8**. Le TBS sera ensuite clivé par TEA·3HF puis les PMB clivés avec du CAN avant de procéder à une peracétylation pour obtenir, après déprotection, les agminosides **A** (à partir du tétrasaccharide **19**) et **E** (à partir du trisaccharide **9**).

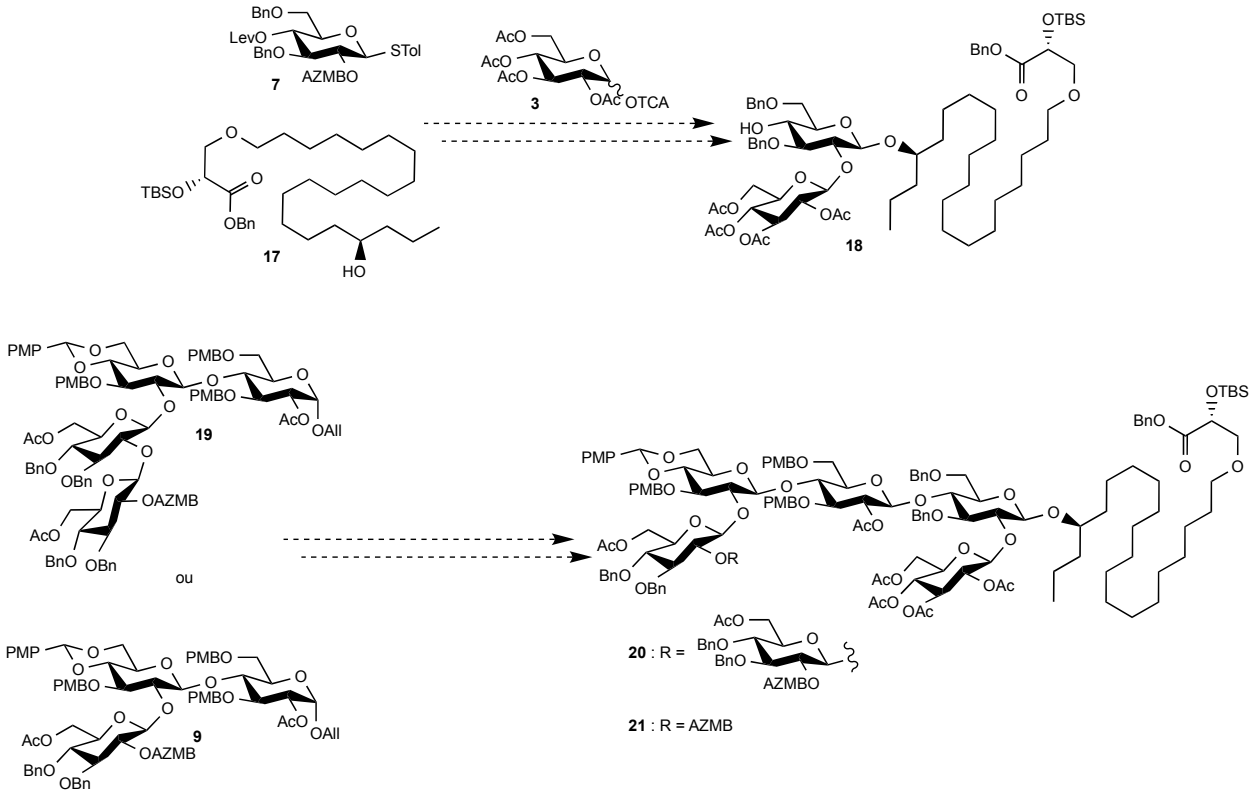

Schéma 5 – Perspectives de synthèse des agminosides A et E

Enfin, il sera nécessaire de différencier la voie de synthèse pour respecter les variations d'acétylation observables sur les différents agminosides. Pour ce faire, le groupement acétyle en 2 de l'unité F (en 2 de l'extrémité réductrice) pourrait être remplacé par un groupement chloroacétyle afin de pouvoir le cliver orthogonalement aux autres groupements protecteurs afin de différencier les synthèses des différents agminosides (Schéma 4). En effet, à partir de l'hexaglucolipide protégé **23**, les agminosides **A**–**D** pourraient être obtenus en modifiant l'ordre des réactions des séquences de déprotection. Ainsi, le clivage des groupements chloroacétyle et TBS par l'action du TBAF, puis, comme pour le glycolipide chimérique, la déprotection des PMB et du *para*-méthoxybenzylidène avec l'aide du CAN, la peracétylation puis le clivage de l'AZMB dans les conditions de Staudinger et, enfin, l'hydrogénolyse permettront l'obtention des agminosides **A** (à partir du composé **22**) et **E** (à partir du composé **23**). Selon la même logique, l'utilisation de TEA·3HF permettra de déprotéger uniquement le groupement TBS avant d'utiliser le CAN et de peracétyler. Après déprotection du groupement chloroacétyle par l'action de l'hydrazinedithiocarbonate (HDTC),[1] l'hydrogénolyse des groupements AZMB et benzyles permettra l'obtention de l'agminoside **B**. Les agminosides **C** et **D** pourront également être obtenus

en modifiant simplement l'ordre de ces réactions : l'utilisation de l'HDTC avant l'acétylation mènera à l'agminoside **C** tandis que l'utilisation de la TEA•3HF et de l'HDTC après l'acétylation permettra l'obtention de l'agminoside **D**.

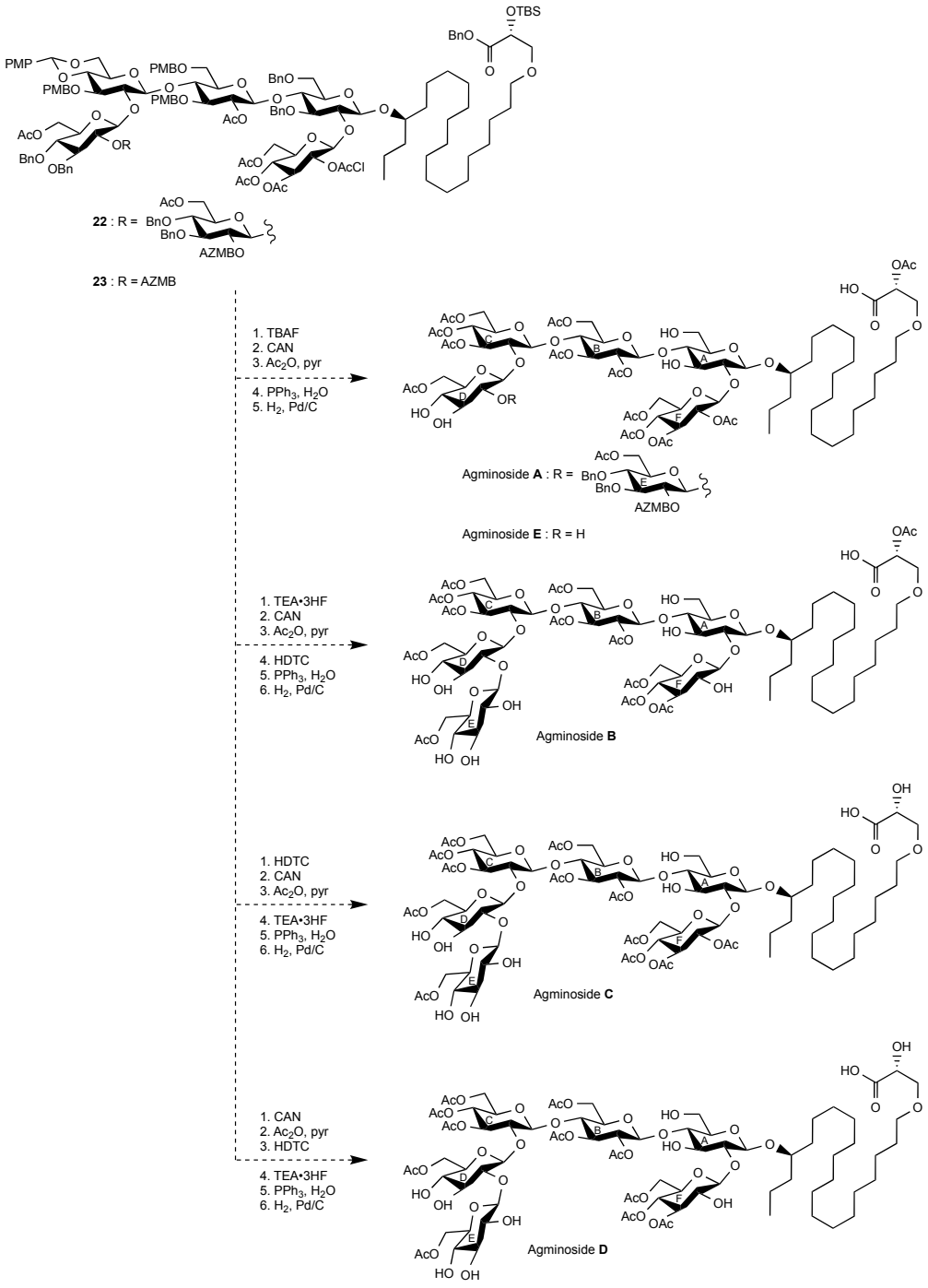

Schéma 6 – Étapes de déprotections permettant la différenciation tardive des agminosides A–E selon leur motif d'acétylation

Des analogues peracétylés et désacétylés pourront également être obtenus et un dérivé macrolactonisé pourrait être obtenu par voie chimique par l'action du DCC ou par voie enzymatique avec la novozyme 435, une lipase très répandue dans la littérature pour les réactions d'estérification.[2] Ces dérivés permettront de comprendre l'impact du motif d'acétylation partielle des agminosides.

Cette étude a donc permis de confirmer le motif d'acétylation de l'agminoside **E** ainsi que la structure de la partie glycosidique de ces composés. Il s'agit d'un premier pas vers la synthèse totale des agminosides ainsi que de la première occurrence d'un travail de recherche à leur sujet depuis leur découverte en 2008. La poursuite du projet pourrait permettre de mettre en évidence leur potentiel thérapeutique ainsi que de comprendre leurs fonctions biologiques chez les éponges.

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[1] Van Boeckel, C. A. A.; Beetz, T. *Tetrahedron Lett.* **1983**, *24*, 3775-3778
[2] Ortiz, C.; Ferreira, M. L.; Barbosa, O.; dos Santos, J. C. S.; Rodrigues, R. C.; Berenguer-Murcia, Á.; Briand, L. E.; Fernandez-Lafuente, R. *Catal. Sci. Technol.* **2019**, *9*, 2380-2420

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Publications :

6. **Muru, K.**; Cloutier, M.; Provost-Savard, A.; Di Cintio, S.; Burton, O.; Cordeil, J.; Groleau, M.-C.; Legault, J.; Déziel, E.; Gauthier, C. Total synthesis of a chimeric glycolipid bearing the partially acetylated backbone of sponge-derived agminoside E. *J. Org. Chem.* **2021**, *86*, 15357-15375.

5. **Muru, K.**; Gauthier, C. Glycosylation and protecting group strategies towards the synthesis of saponins and bacterial oligosaccharides: a personal account. *Chem. Rec.* **2021**, *21*, 2990-3004.

4. St-Gelais, J.; Denavit, V.; Lainé, D.; Giguère, D.; **Muru, K.** Alternative synthesis of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-α,β-D-glucopyranose. In: *Carbohydrate Chemistry: Proven Methods*, Volume 5, Ed.: Kosma, P.; Wrodnigg, T.; Stütz, A.; **2021**, CRC Press, 173-182. (contribution invitee)

3. Cloutier, M.; **Muru, K.**; Gauthier, C. Synthesis of oligosaccharides related to potential bioterrorist pathogens. In: *Recent Trends in Carbohydrate Chemistry*, 1st edition, Ed.: Rauter, A. P.; Christensen, B.; Somsak, L.; Kosma, P.; Adamo, R.; Elsevier, **2020**, 143-206.

2. Cloutier, M.; Delar, E.; **Muru, K.**; Ndong, S.; Hoyeck, R. R.; Kaewarpai, T.; Chantratita, N.; Burtnick, M. N.; Brett, P. J.; Gauthier, C. Melioidosis patient serum-reactive synthetic tetrasaccharides bearing the predominant epitopes of *Burkholderia pseudomallei* and *Burkholderia mallei* O-antigens. *Org. Biomol. Chem.* **2019**, *17*, 8878-8901.

1. Cloutier, M.; **Muru, K.**; Ravicoularamin, G.; Gauthier, C. Polysaccharides from *Burkholderia* species as targets for vaccine development, immunomodulation and chemical synthesis. *Nat. Prod. Rep.* **2018**, *35*, 1251-1293. (page de couverture)

Présentations :

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11. Cloutier, M.; Delar, E.; **Muru, K.**; Gauthier, C. *Burkholderia pseudomallei* and *Burkholderia mallei* synthetic lipopolysaccharide mimics as potential vaccine candidates. *EuroCarb 2019*, 30 juin au 4 juillet **2019**, Leiden, Pays-Bas, (présentation orale)

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9. **Muru, K.**; Di Cintio, S.; Provost-Savard, A.; Gauthier, C. *En route* to agminosides synthesis, natural and polyacetylated glycolipids. *102nd Canadian Chemistry Conference and Exhibition (CCCE2019)*, 3 au 7 juin **2019**, Ville de Québec (Québec), Canada. (affiche)

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7. Cloutier, M.; Delar, E.; Ndong, S.; Hoyeck, R. R.; **Muru, K.**; Gauthier, C. *Burkholderia pseudomallei* and *Burkholderia mallei* synthetic lipopolysaccharide mimics as potential vaccine candidates. *21st Chemistry and Biochemistry Graduate Research Conference*, 9 novembre **2018**, Montréal (Québec), Canada. (présentation orale)

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5. **Muru, K.**; Di Cintio, S.; Provost-Savard, A.; Gauthier, C. En route vers la synthèse des agminosides, glycolipides naturels polyacétylés. *Rassemblement de l'axe microbiologie et Biotechnologie (INRS-IAF)*, 26 octobre **2018**, Laval (Québec), Canada. (présentation orale)

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1. **Muru, K.**; Gauthier, C. Synthèse totale de glycolipides d'origine marine d'intérêt biologique. *10e édition du Congrès Armand-Frappier*, 10 novembre **2017**, Orford (Québec), Canada. (affiche)

-Annexes-

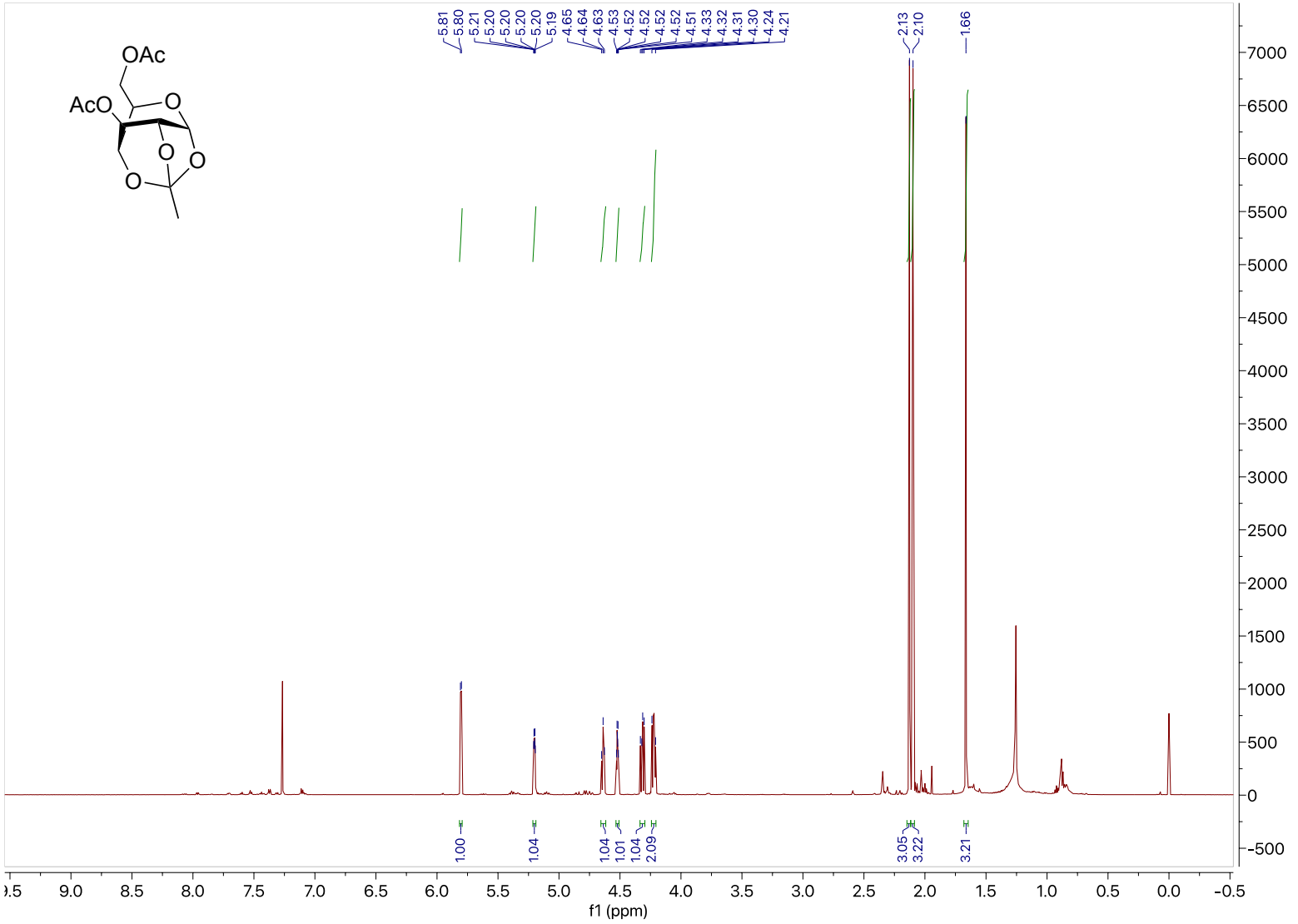
1. Annexes du chapitre IV

Table S2. Comparison Table of Synthesized Compound 3 and Isolated Agminoside E

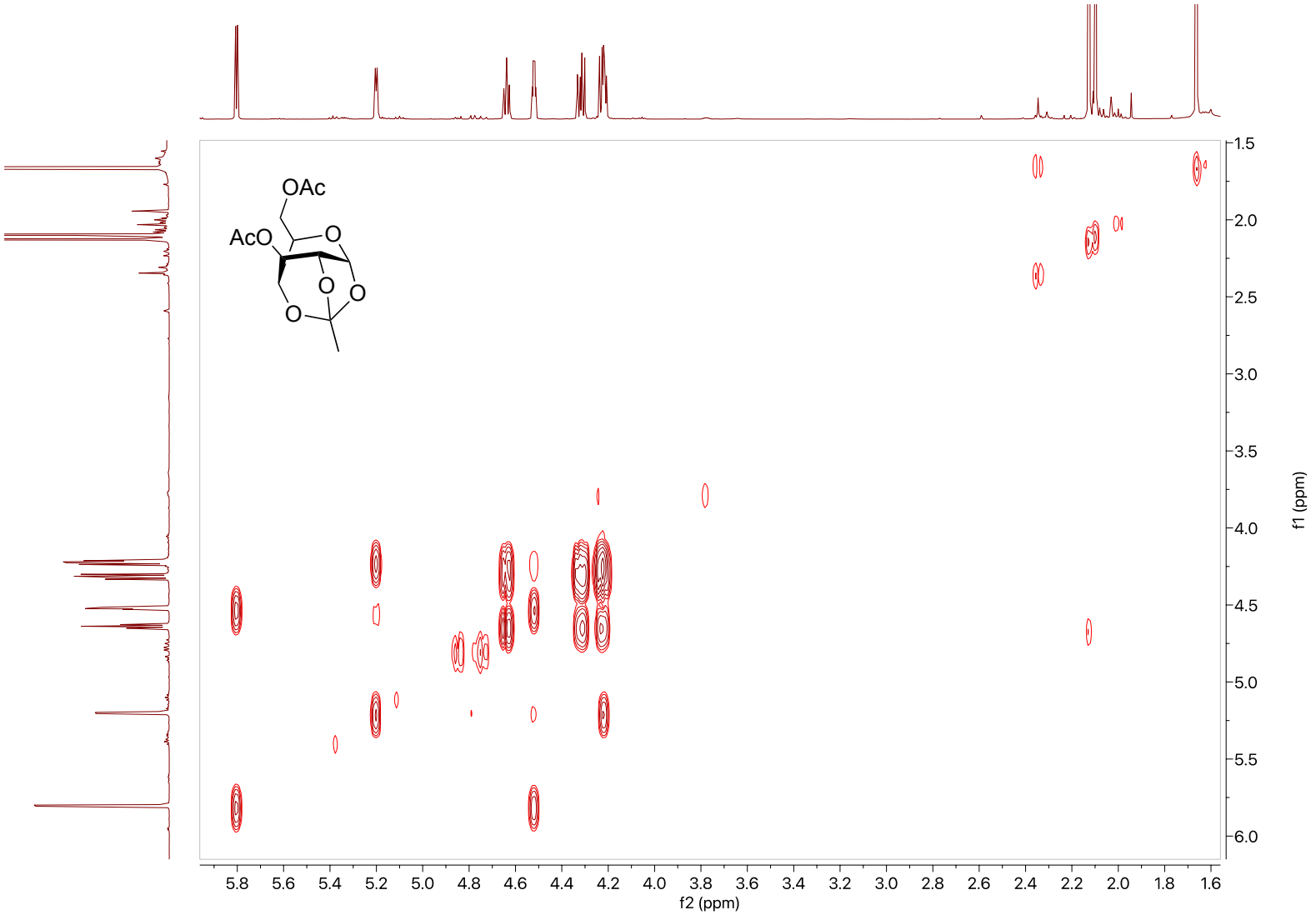
Position	Agminoside E	Compound **3**	Agminoside E	Compound **3**
A1	4.38 d (7.5)	4.42 d (7.8)	101.9	102.7
A2	3.45	3.45 dd (8.7, 7.8)	81.1	80.7
A3	3.55	3.55 t (8.7)	77.3	77.3
A4	3.53	3.50 t (9.1)	82.4	82.4
A5	3.30	3.29 - 3.27	75.7	75.6
A6a	3.75	3.77 – 3.75	61.6	61.5
A6b	3.61	3.60 - 3.57		
B1	4.78	4.77 d (8.0)	102.1	102.2
B2	4.86	4.89 – 4.86	73.0	73.0
B3	5.23	5.23 dd (9.4, 5.5)	74.4	74.4
B4	3.78	3.78 dd (9.7, 8.9)	79.3	79.3
B5	3.92	3.92 ddd (9.7, 7.1, 2.1)	74.2	74.3
B6a	4.75	4.75 dd (11.7, 2.0)	64.3	64.2
B6b	4.30	4.33 – 4.30		
B2-Ac	2.06	2.05[a]	171.2 – 20.6	171.16[b] - 20.62[c]
B3-Ac	2.00	2.00[a]	171.8 – 20.6	172.3[b] - 20.64[c]
B6-Ac	2.19	2.19[a]	172.6 – 21.1	172.6 – 21.11[c]
C1	4.52 d (7.7)	4.52 d (7.7)	103.6	103.6
C2	3.56	3.56 dd (9.4, 7.8)	80.9	80.9
C3	5.22	5.21 dd (9.5, 5.7)	76.1	76.0
C4	4.87	4.89 – 4.86	69.7	69.6
C5	3.81	3.81 ddd (10.1, 3.9, 2.2)	72.6	72.7
C6a	4.35 dd (12.5, 3.9)	4.34 dd (12.6, 4.1)	63.0	63.0
C6b	4.03 dd (12.3, 2.0)	4.04 dd (12.5, 2.2)		
C3-Ac	2.02	2.02[a]	171.6 – 20.8	171.6[b] - 20.7[c]
C4-Ac	1.96	1.96[a]	171.4 – 20.6	171.3[b] - 20.55[c]
C6-Ac	2.04	2.05[a]	172.2 – 20.8	172.17[d] - 20.78[c]
D1	4.31 d (8.0)	4.33-4.30	106.0	106.0
D2	3.09 dd (9.4, 8.4)	3.10 dd (9.2, 7.9)	74.7	74.7
D3	3.29	3.30 t (9.1)	77.7	77.8
D4	3.19 t (9.4)	3.19 t (9.4)	71.6	71.6
D5	3.44	3.44 – 3.42	75.4	75.4
D6a	4.46 dd (11.8, 6.9)	4.45 dd (11.9, 6.9)	69.6	64.7
D6b	4.29	4.29 dd (11.9, 1.8)		
D6-Ac	2.20	2.20[a]	173.0 – 21.4	173.0 – 21.4[c]
F1	5.07 d (8.1)	5.07 d (8.1)	102.1	102.1
F2	4.85	4.89 dd (9.7, 8.0)	73.3	73.3
F3	5.17 t (9.6)	5.18 t (9.6)	74.2	74.3
F4	4.99 t (9.6)	5.02 t (9.7)	69.8	69.9
F5	3.78	3.77 – 3.75	76.7	72.8
F6a	4.29	4.33 – 4.30	63.2	63.3
F6b	4.10 dd (12.1, 2.2)	4.09 dd (12.3, 2.4)		
F2-Ac	2.02	2.02[a]	171.4 – 21.0	171.8[b] - 21.07[c]
F3-Ac	1.97	1.96[a]	171.6 – 20.5	171.4[b] - 20.5[c]
F4-Ac	2.00	2.00[a]	171.3 – 20.9	171.19[b] - 20.9[c]
F6-Ac	2.03	2.04[a]	172.2 – 20.7	172.18[b] - 20.83[c]

[a, b, c, d] : interchangeable

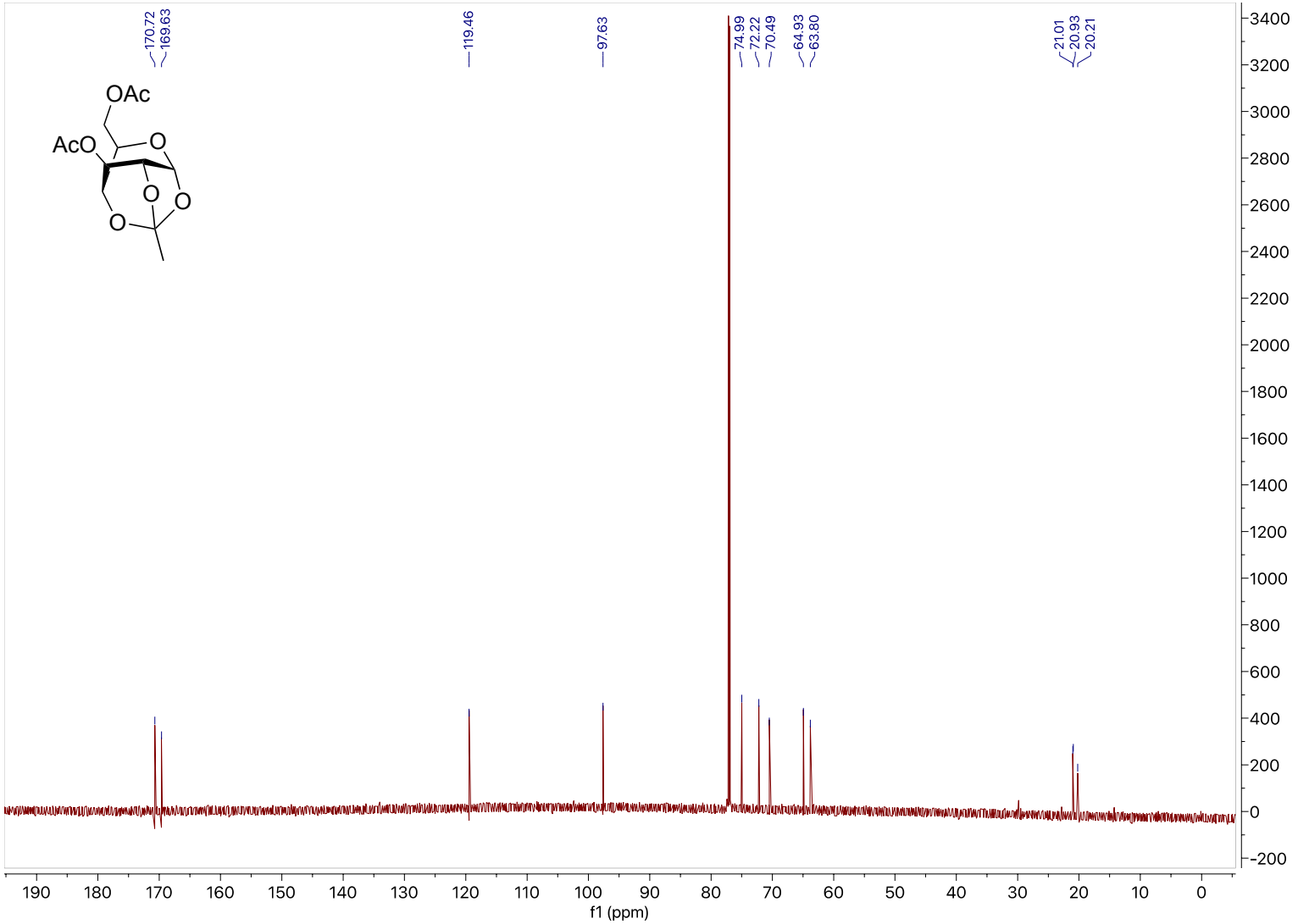
Supplementary figure 1 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 23



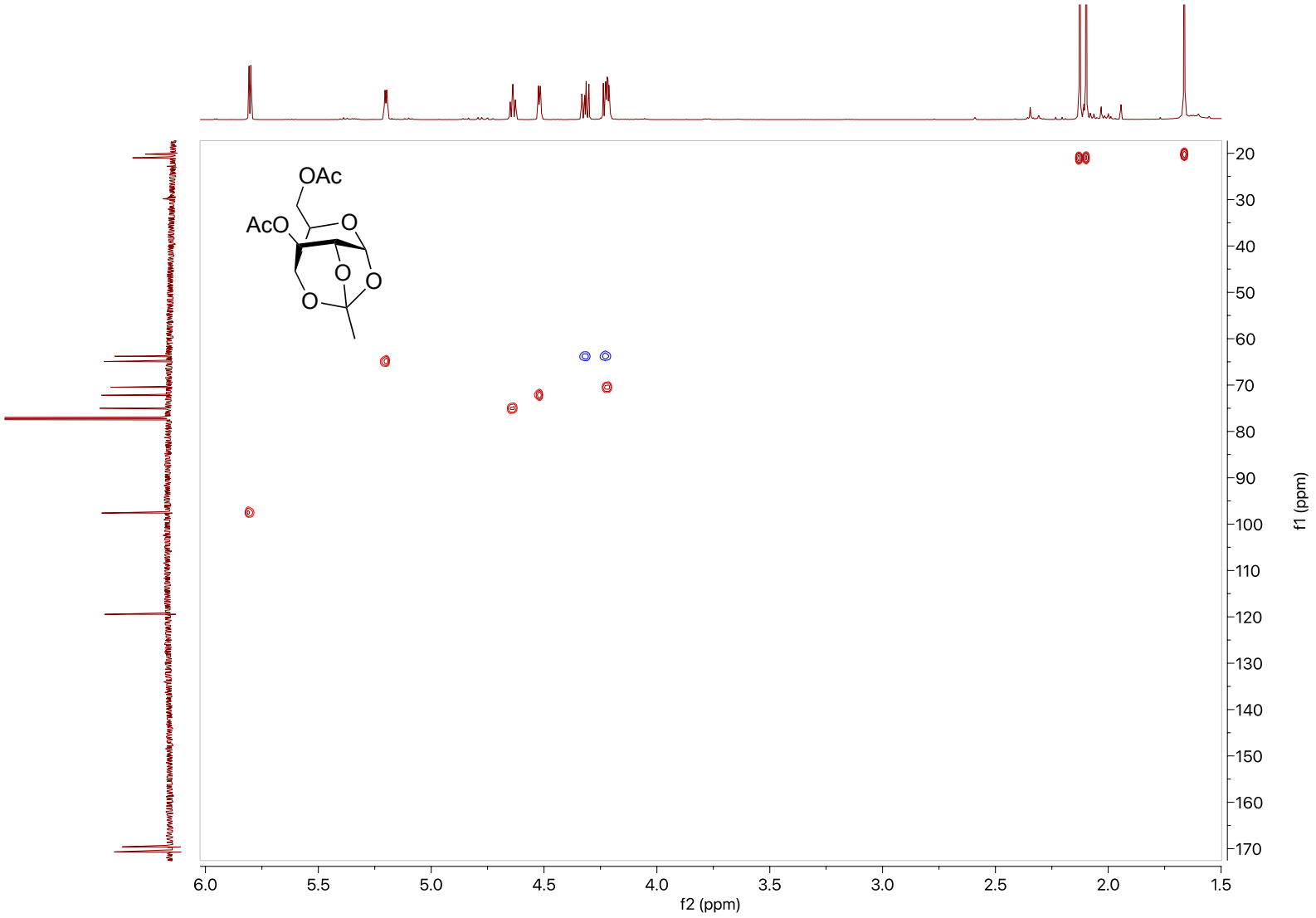
Supplementary figure 2 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 23



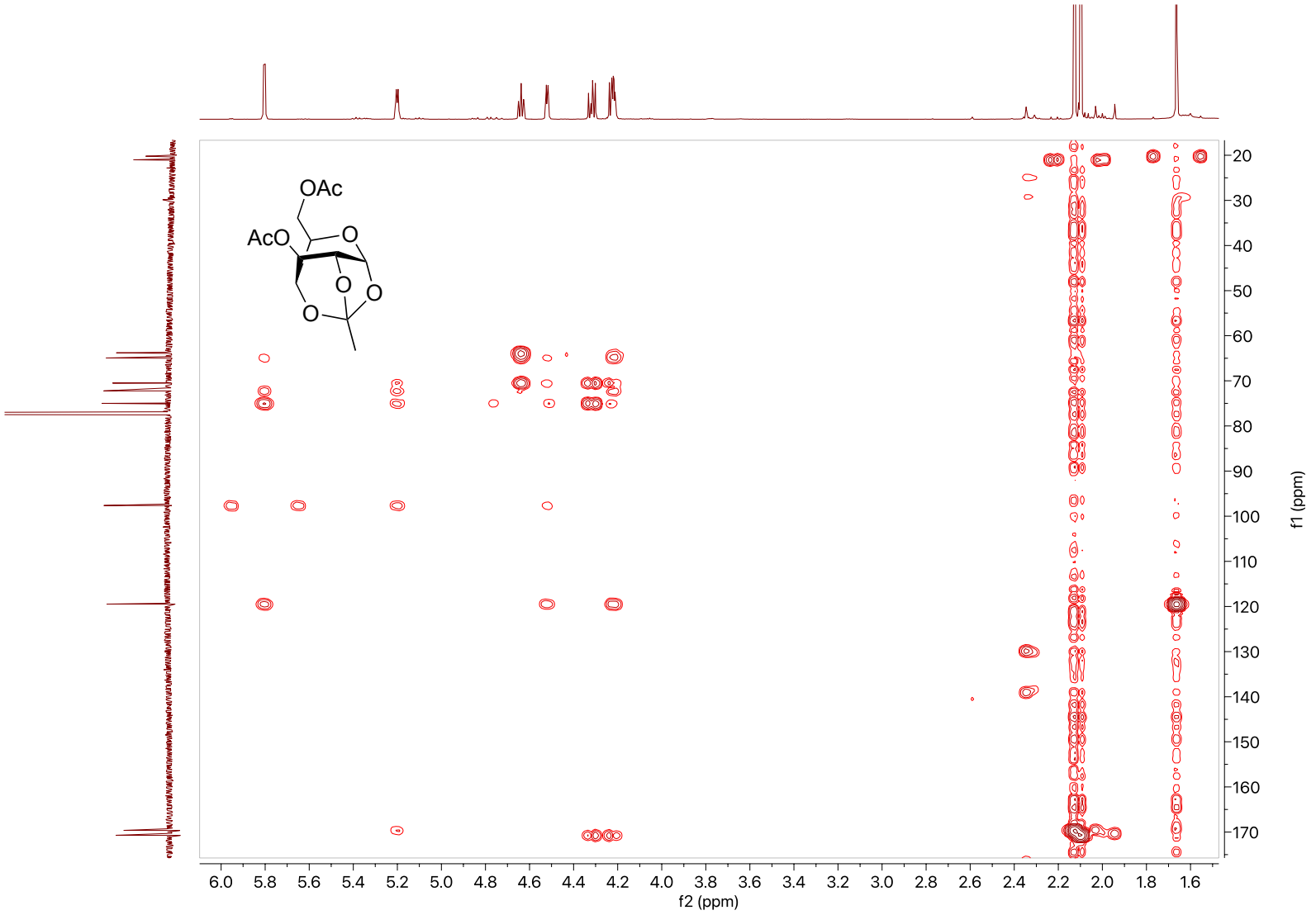
Supplementary figure 3 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 23



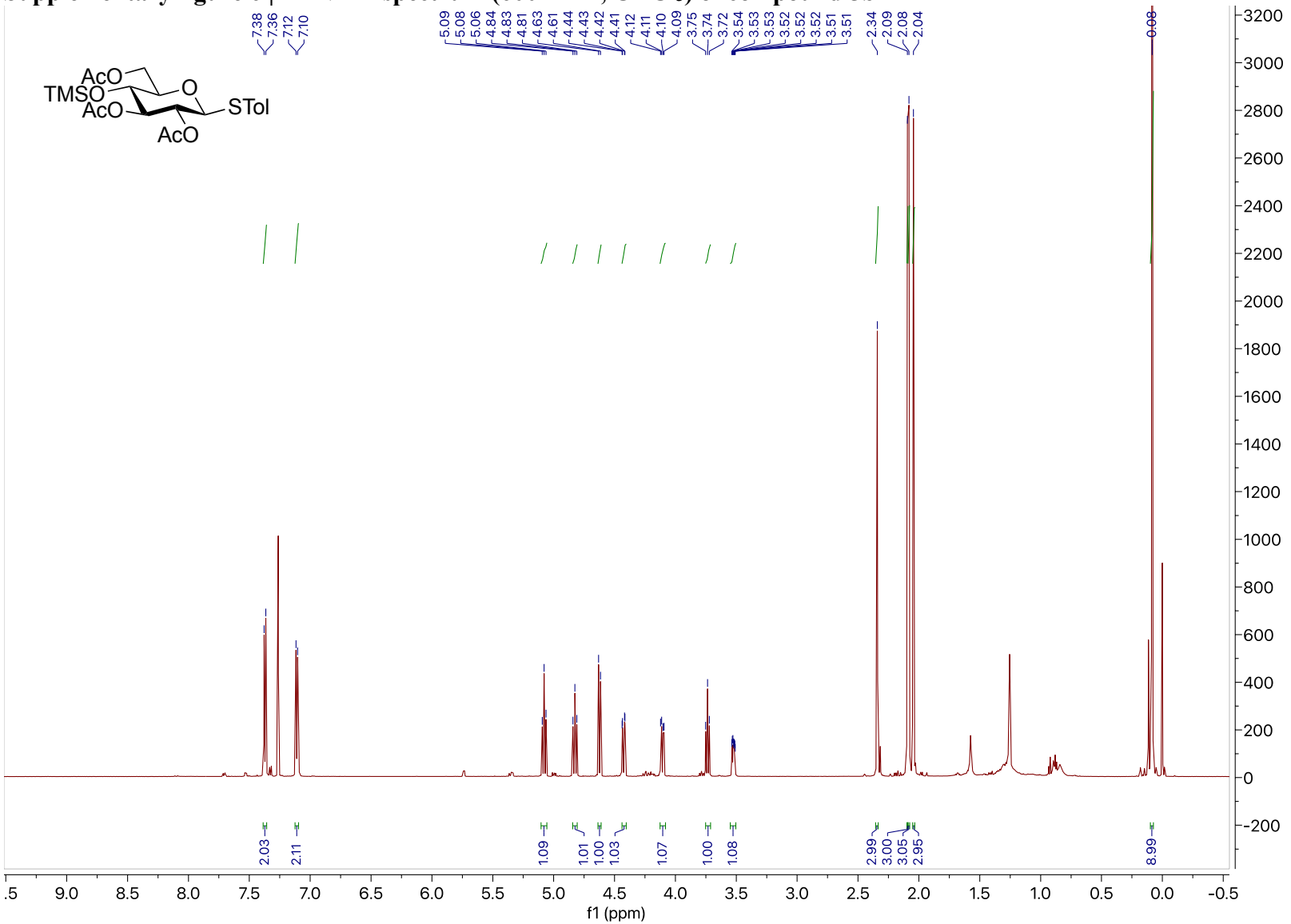
Supplementary figure 4 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 23



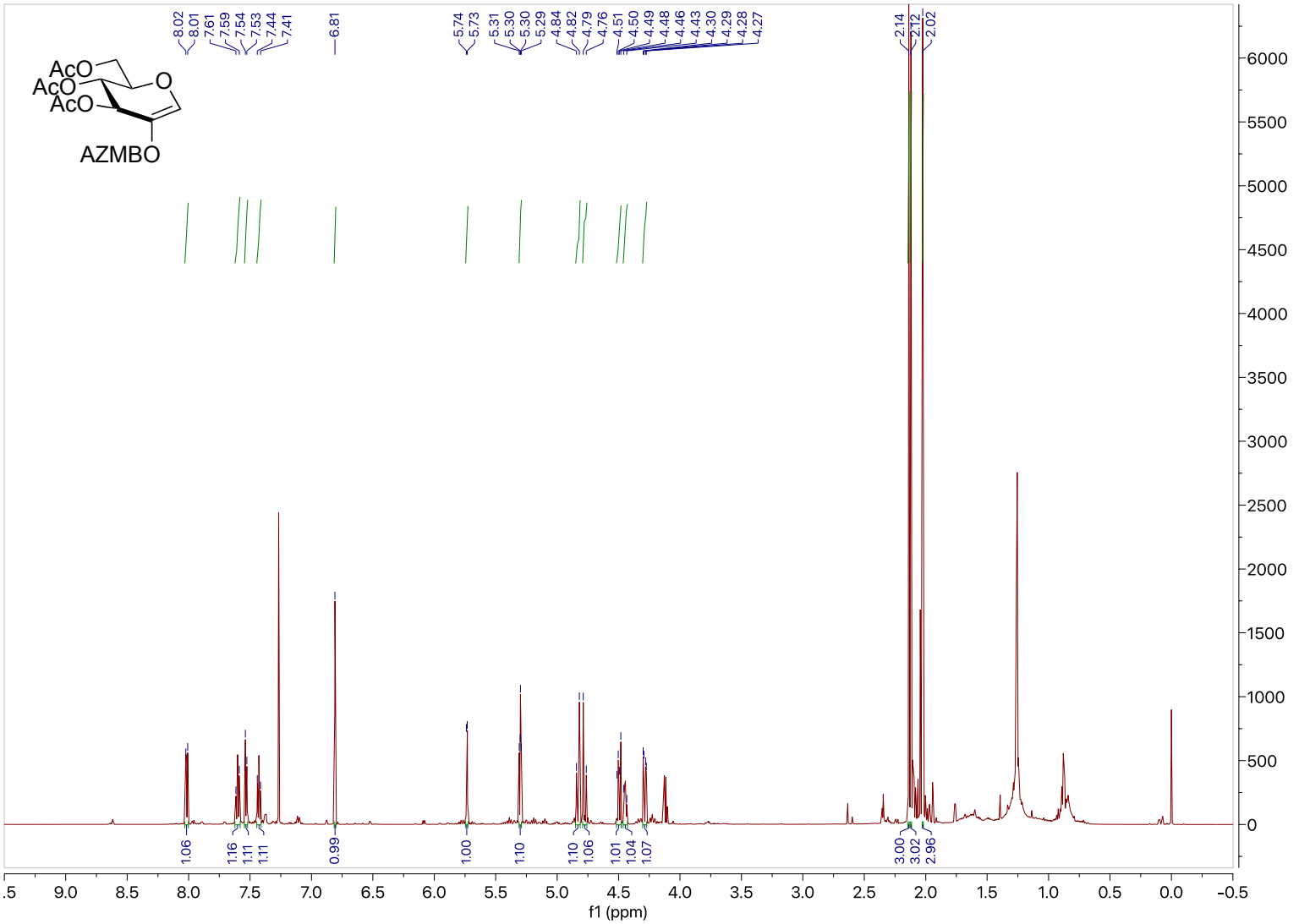
Supplementary figure 5 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 23



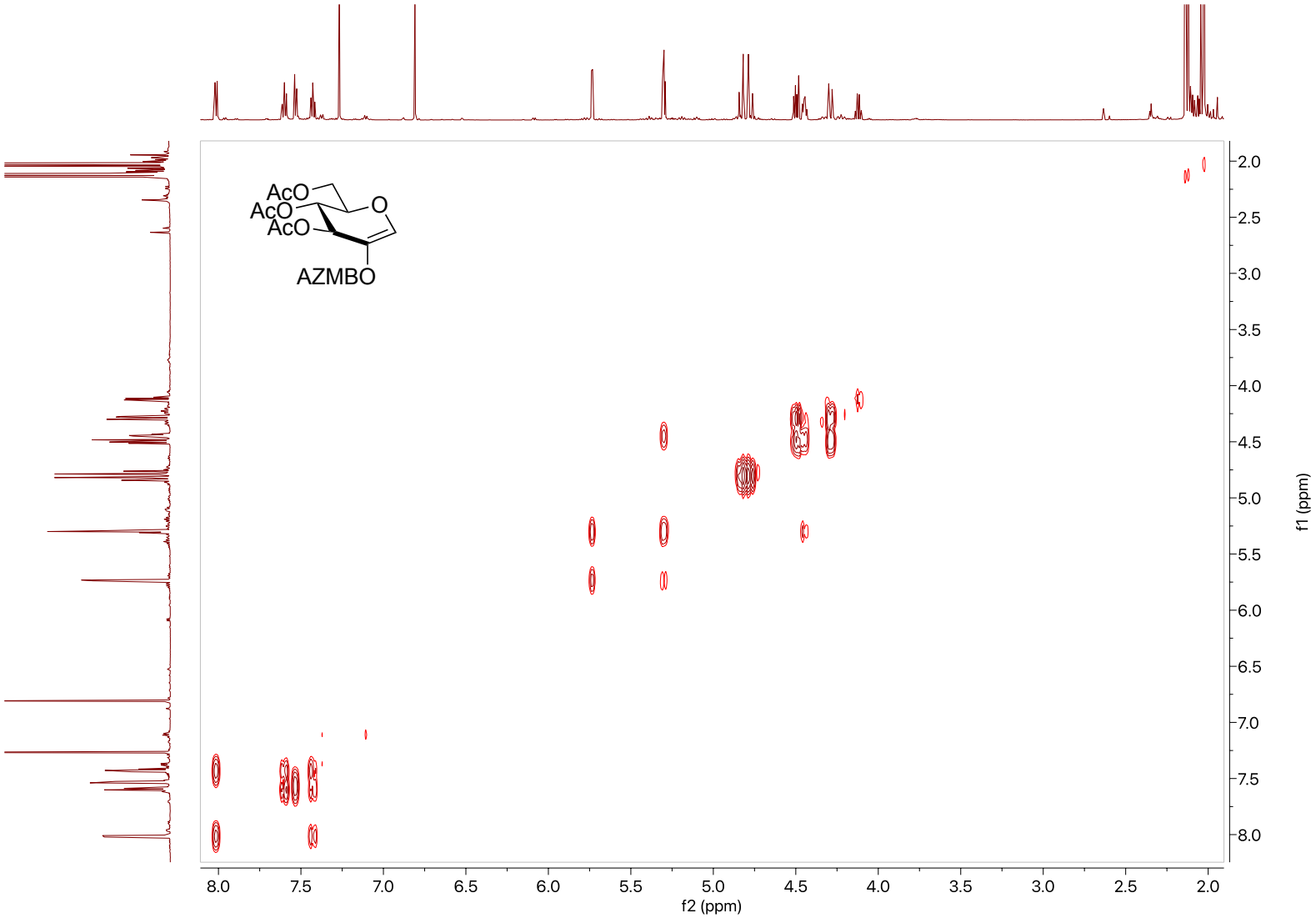
Supplementary figure 6 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 5b



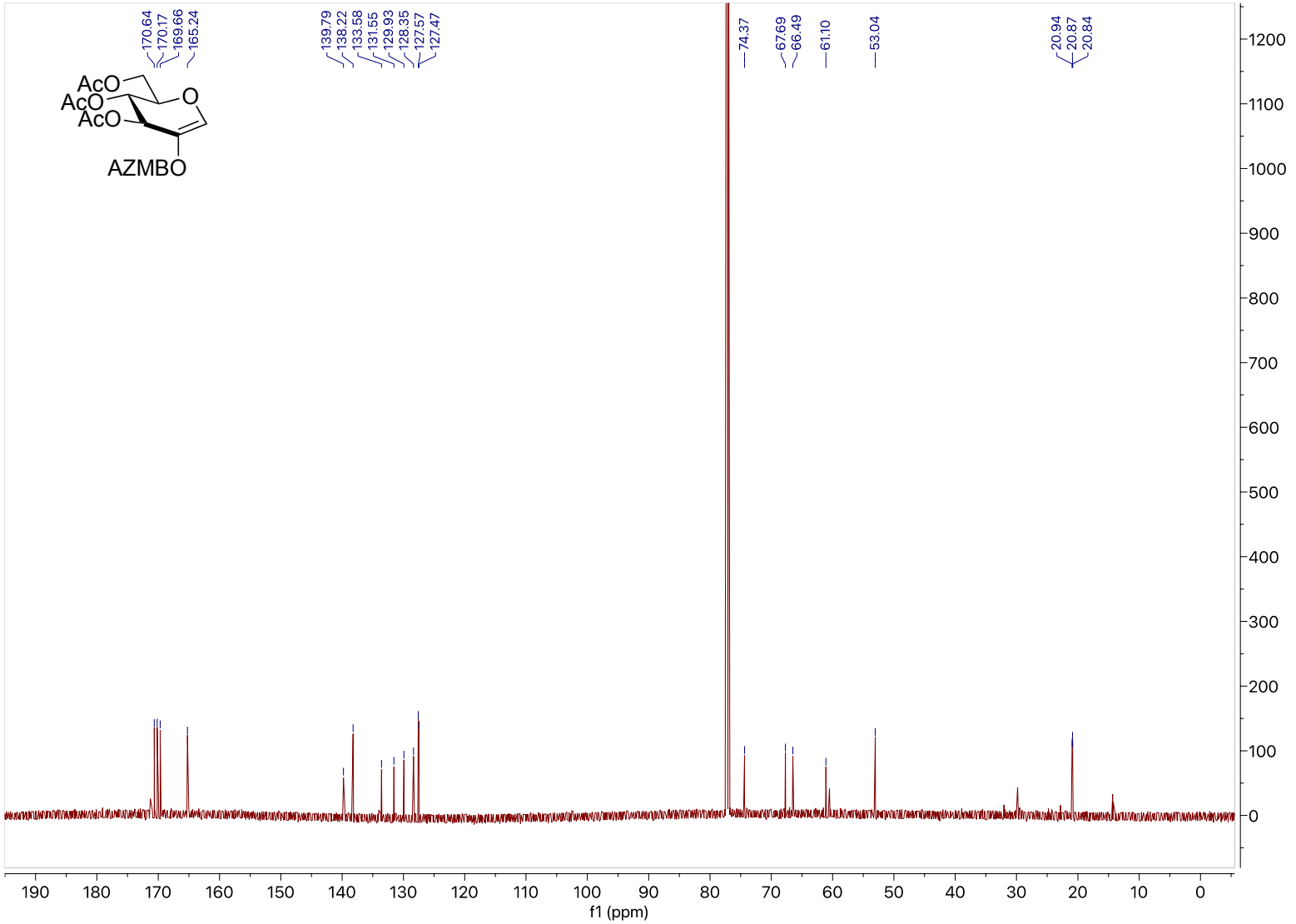
Supplementary figure 7 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 24



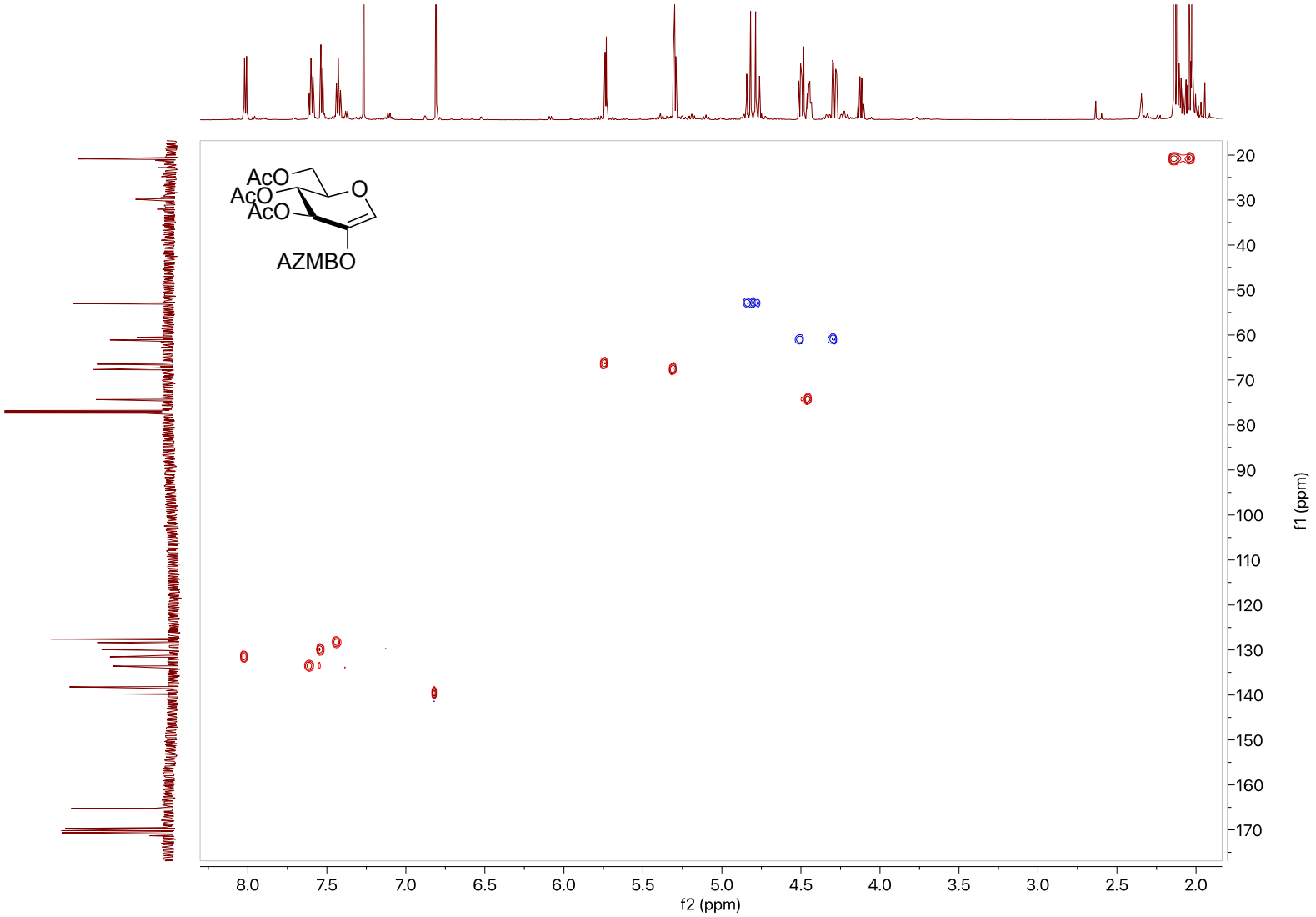
Supplementary figure 8 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 24



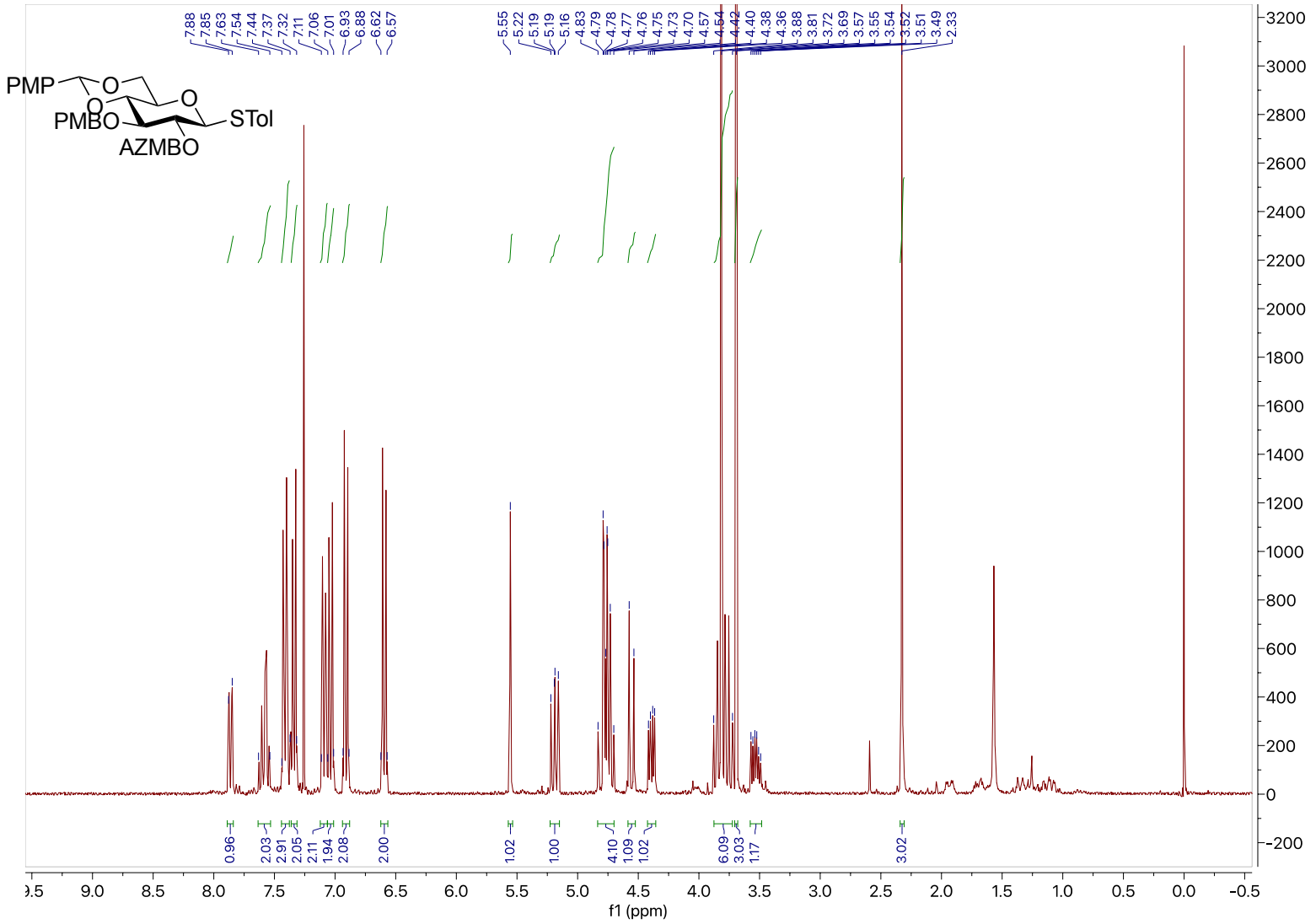
Supplementary figure 9 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 24



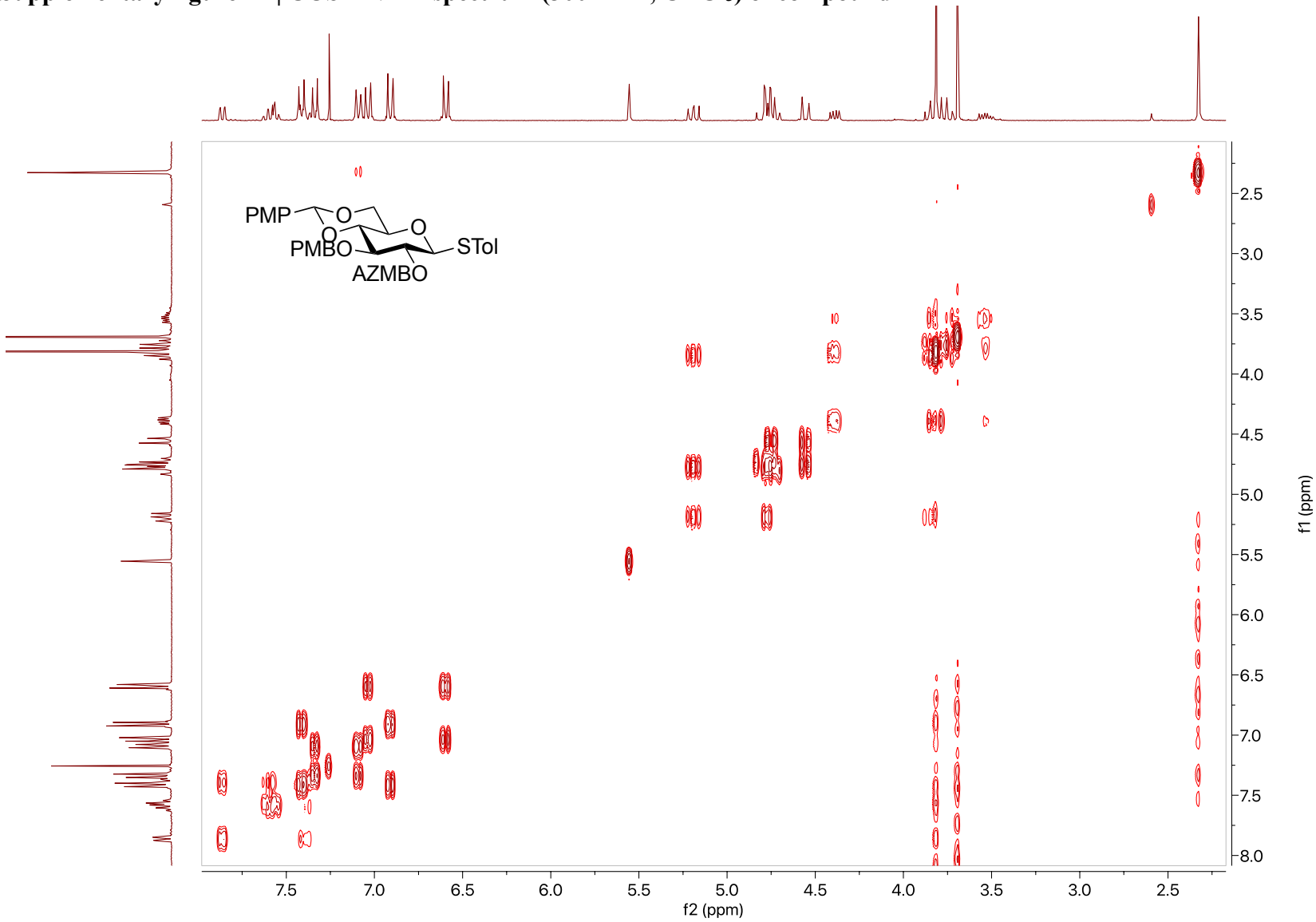
Supplementary figure 10 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 24



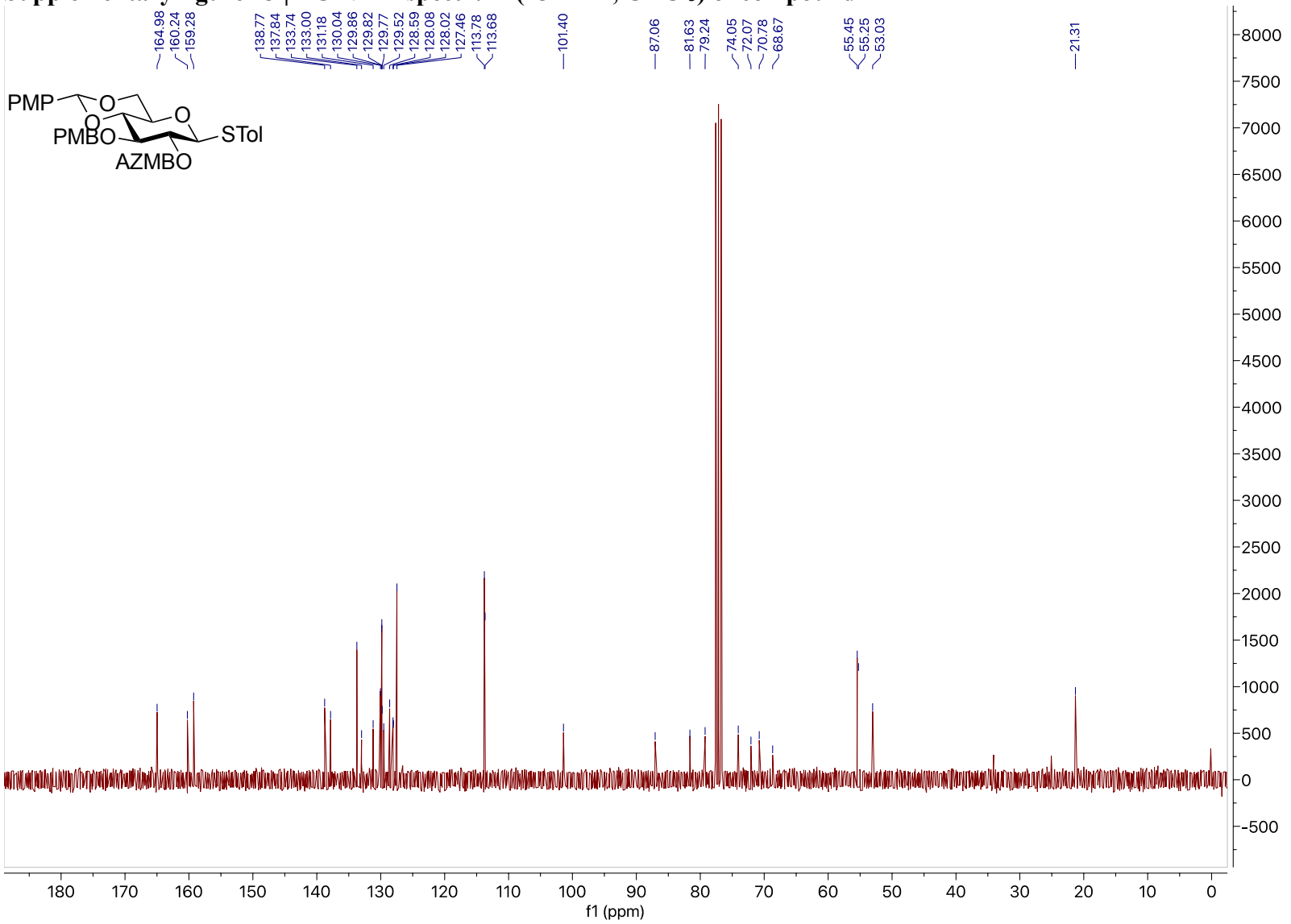
Supplementary Figure 11 | ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound 11



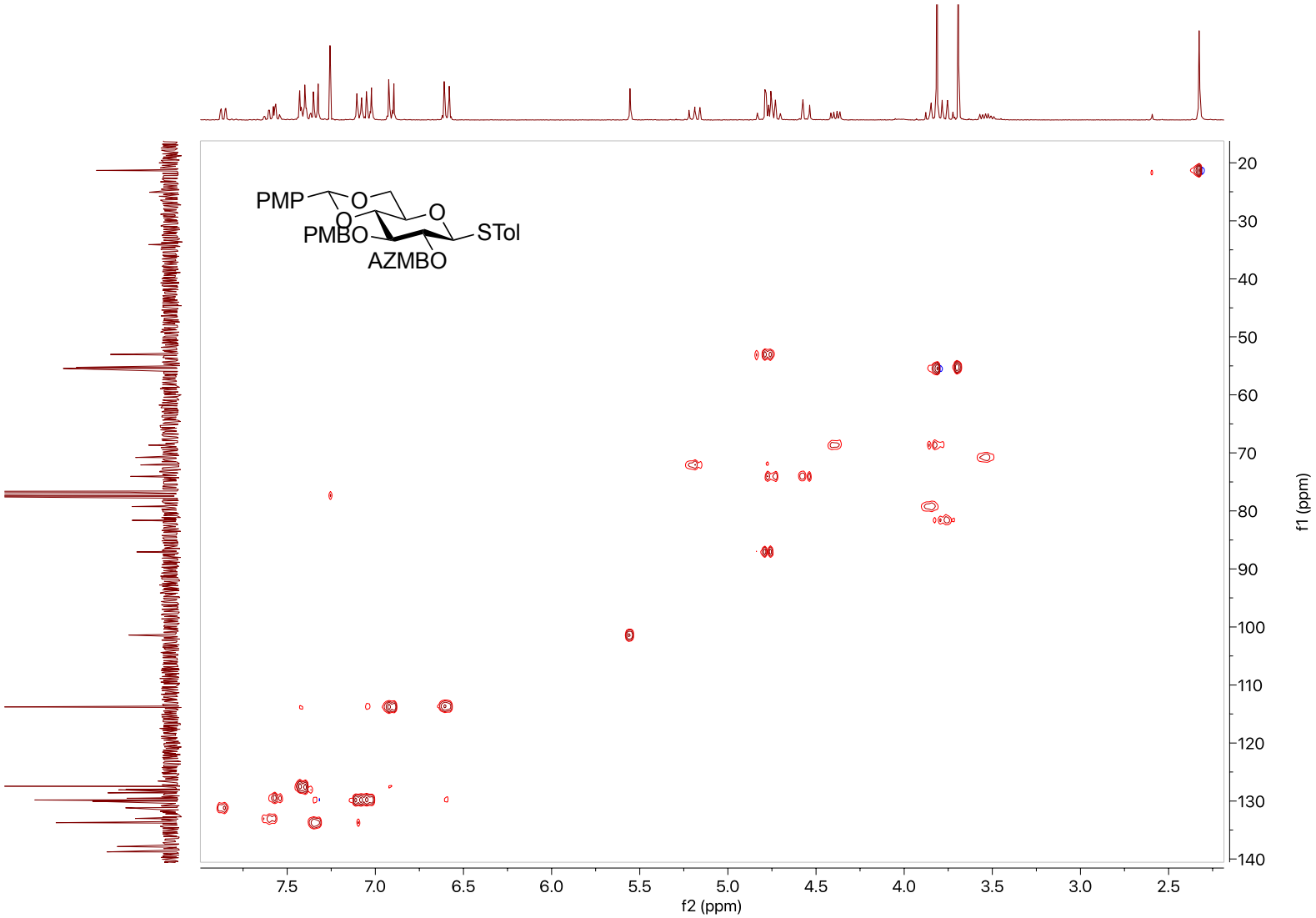
Supplementary figure 12 | COSY NMR spectrum (300 MHz, $CDCl_3$) of compound 11



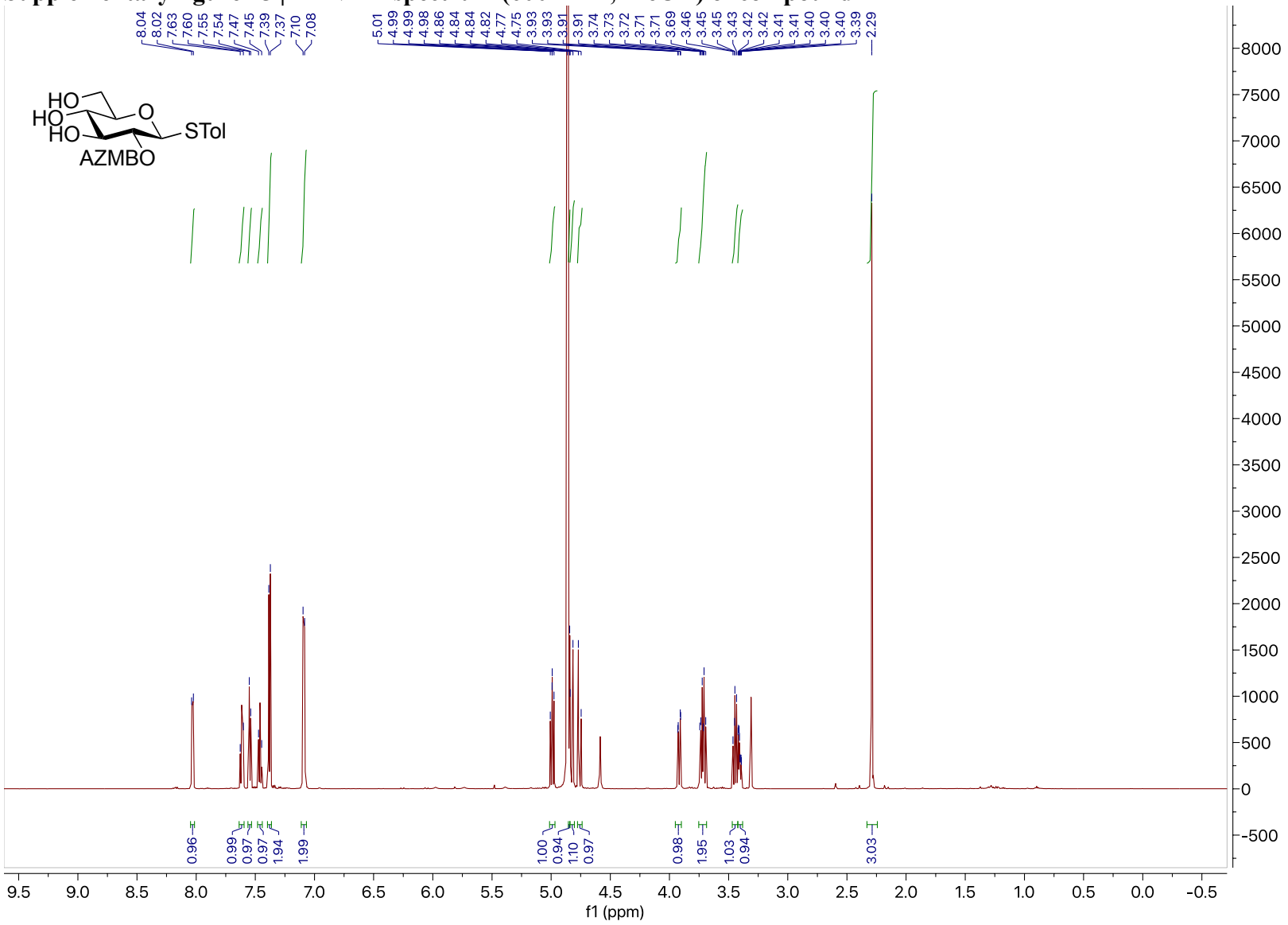
Supplementary figure 13 | ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound 11



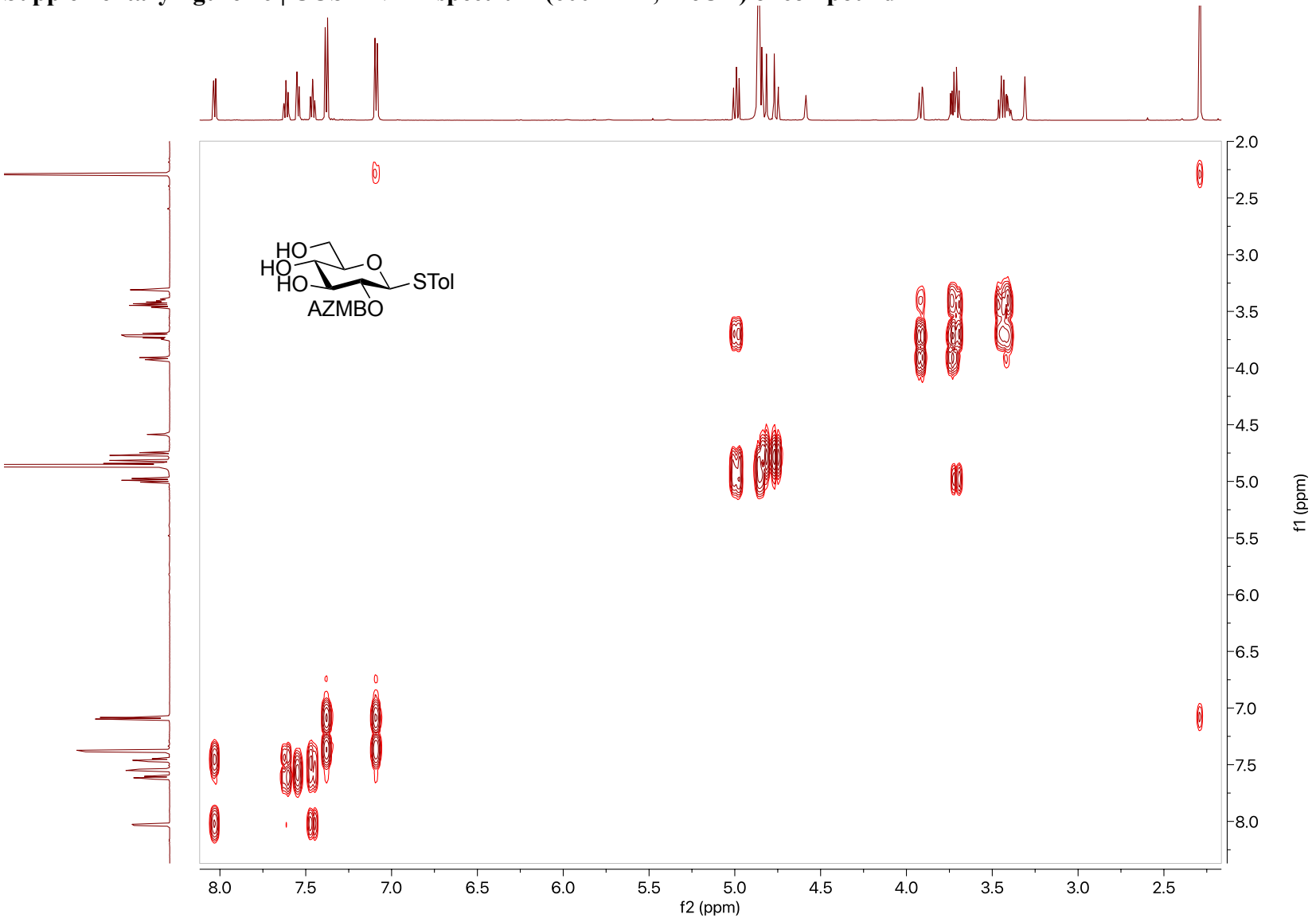
Supplementary figure 14 | HSQC NMR spectrum (300 MHz, $CDCl_3$) of compound 11



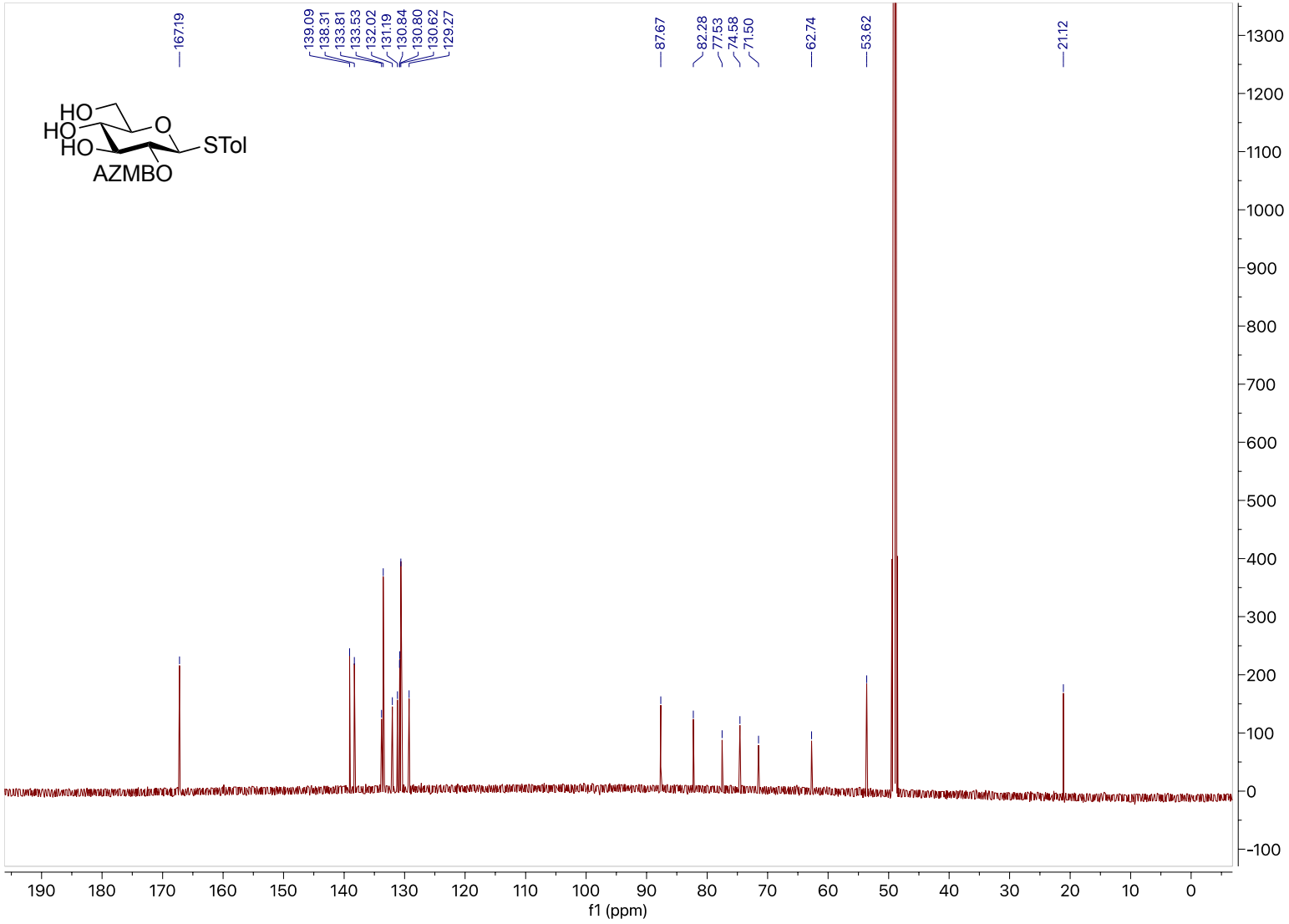
Supplementary figure 15 | ^{1}H NMR spectrum (600 MHz, MeOD) of compound 12



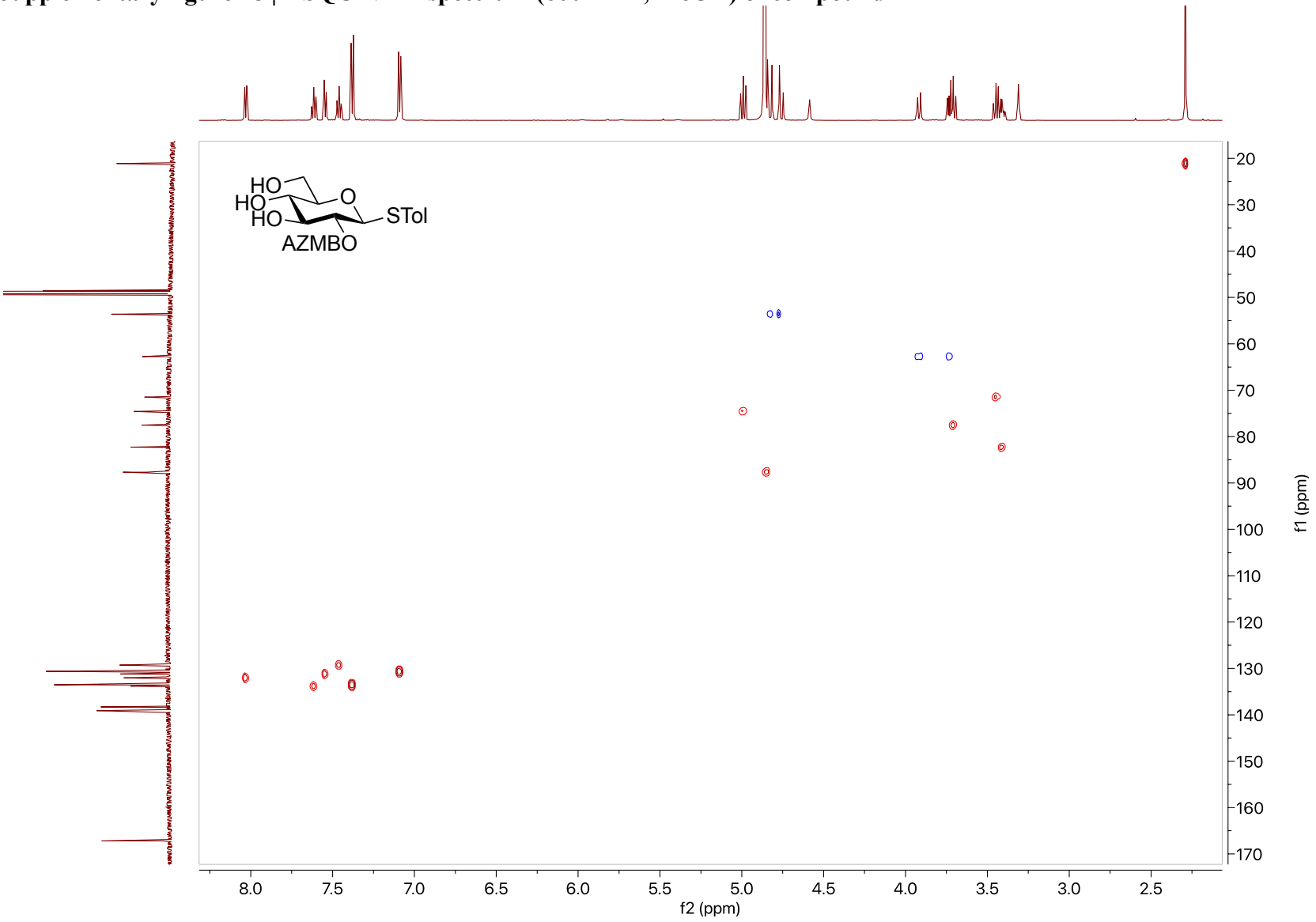
Supplementary figure 16 | COSY NMR spectrum (600 MHz, MeOD) of compound 12



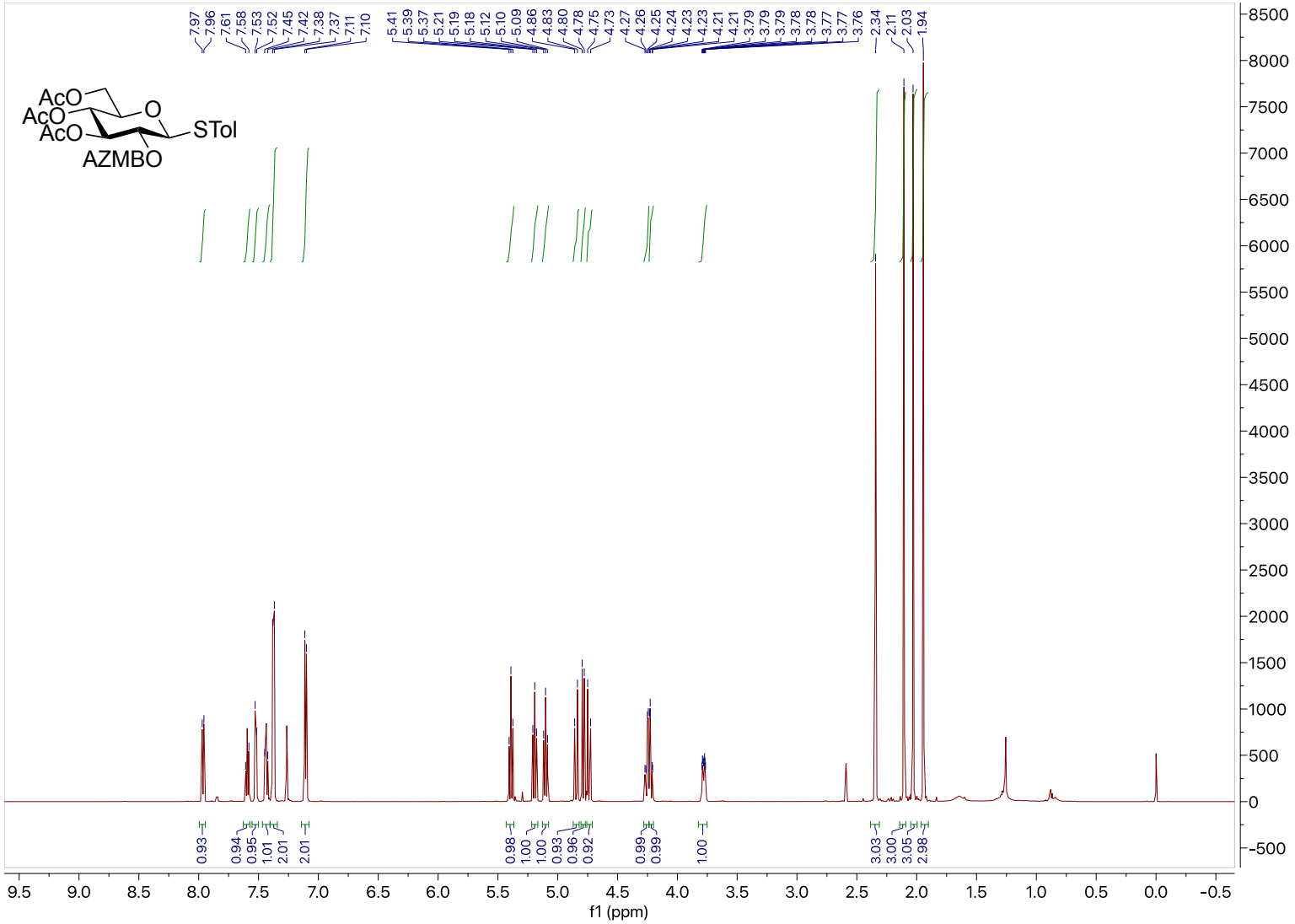
Supplementary figure 17 | ^{13}C NMR spectrum (150 MHz, MeOD) of compound 12



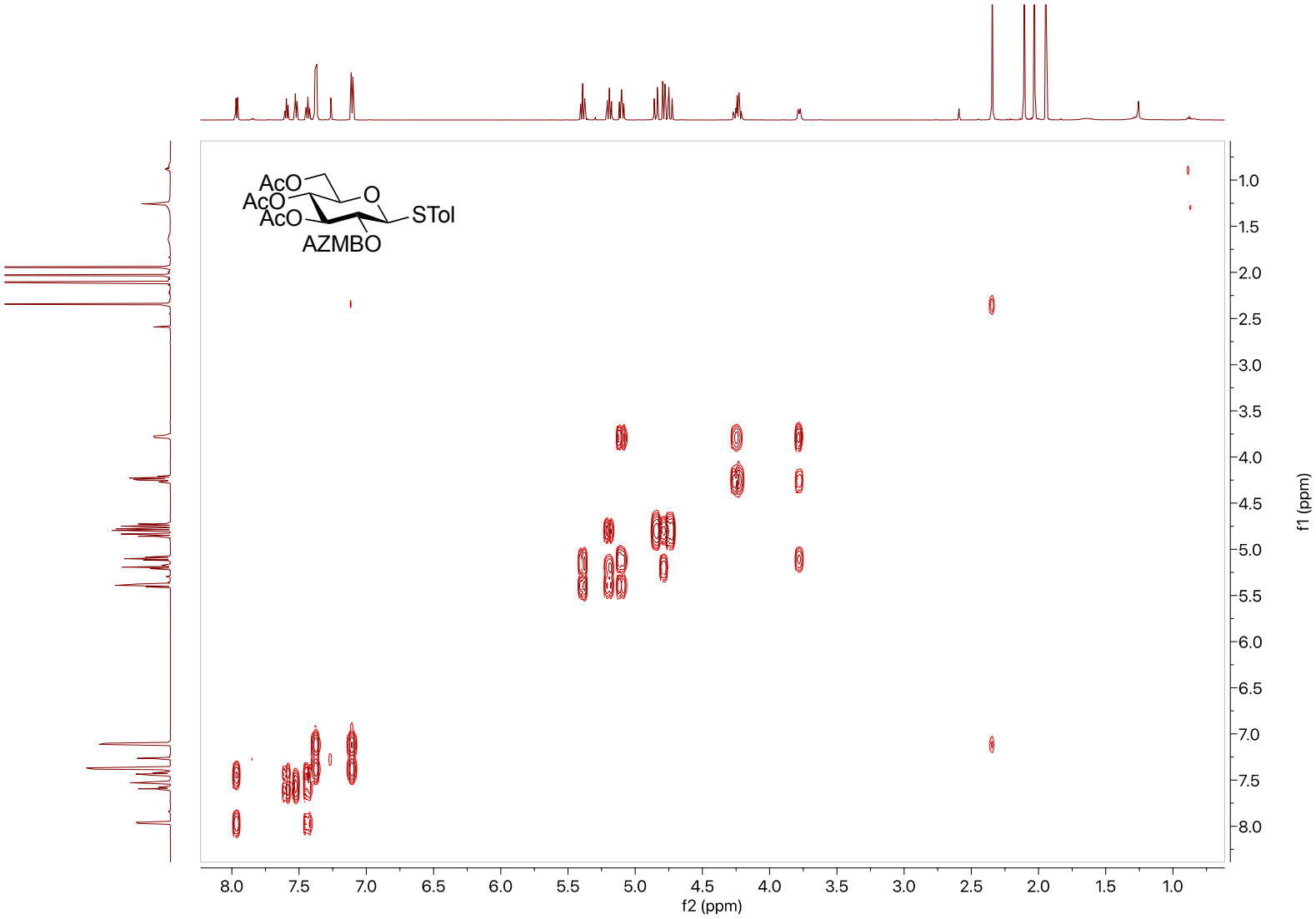
Supplementary figure 18 | HSQC NMR spectrum (600 MHz, MeOD) of compound 12



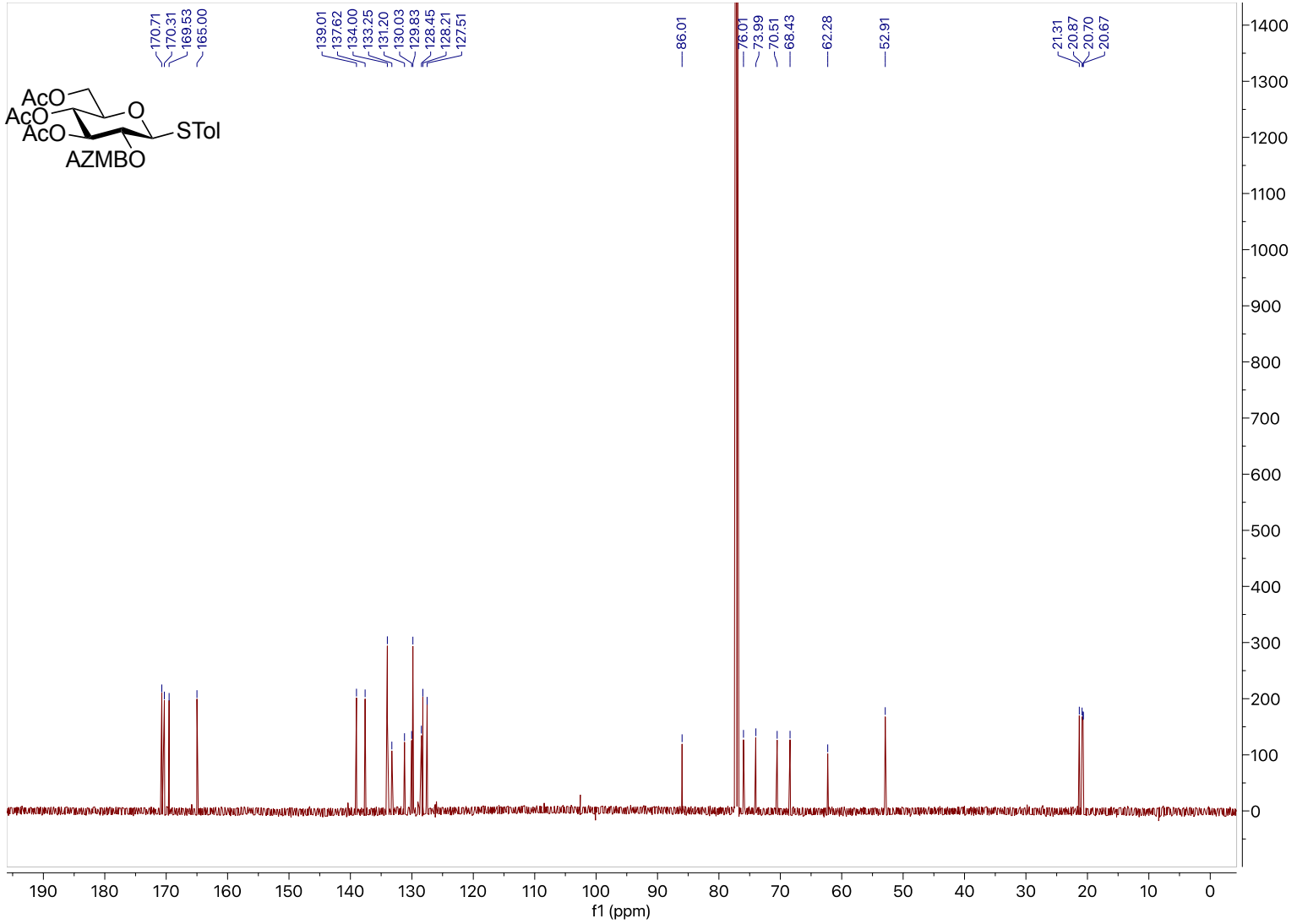
Supplementary figure 19 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 4a



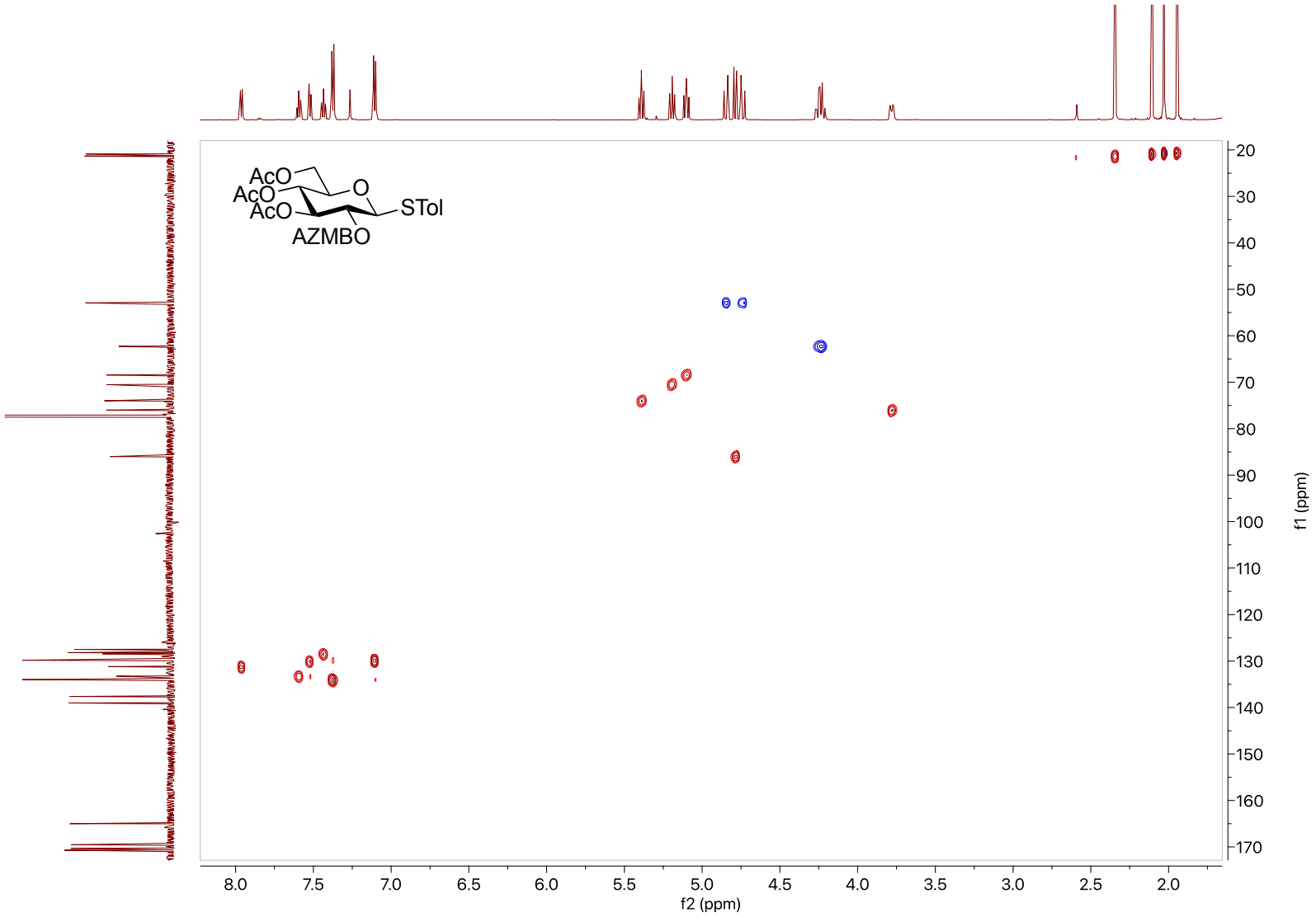
Supplementary figure 20 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 4a



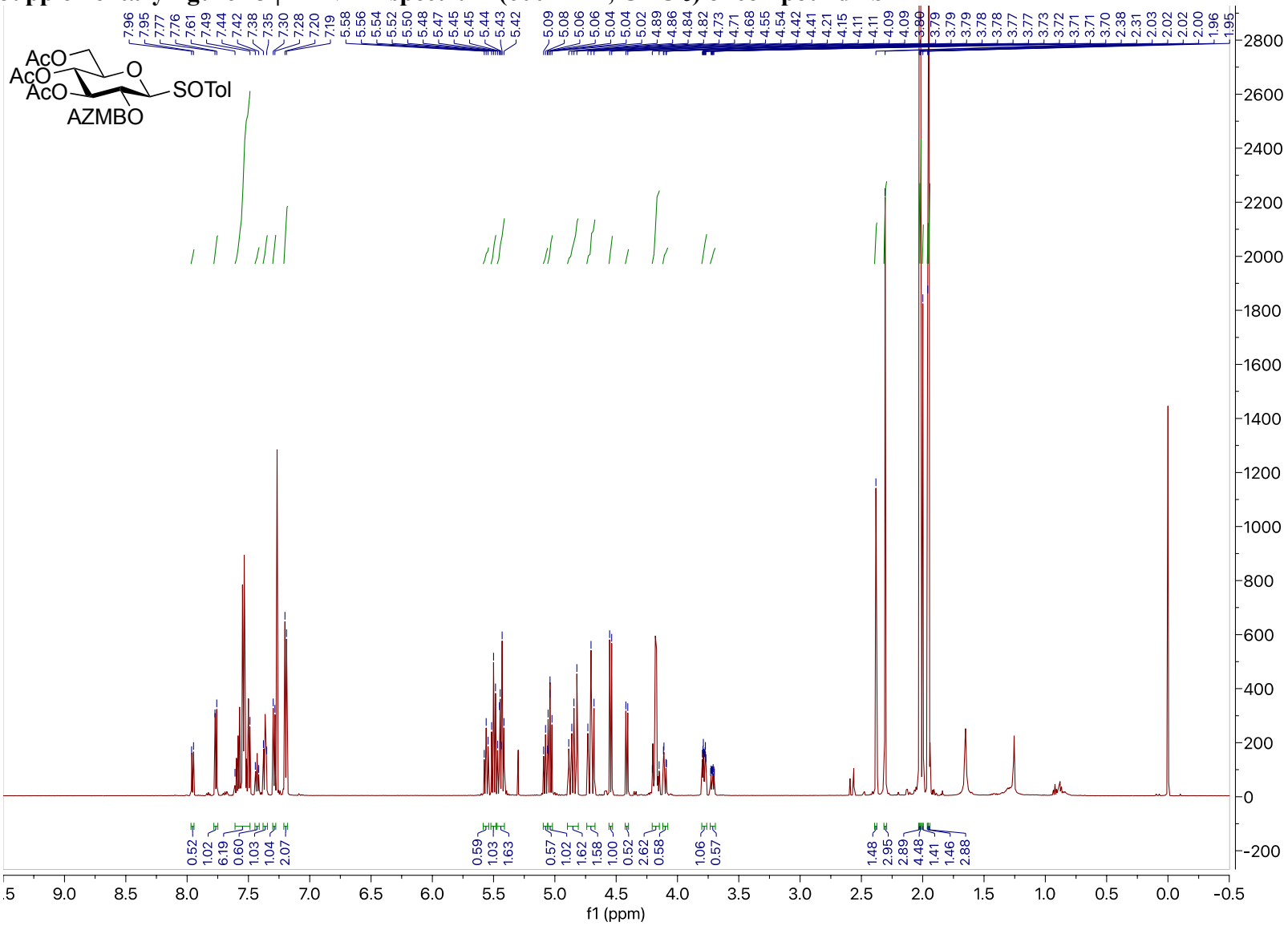
Supplementary figure 21 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 4a



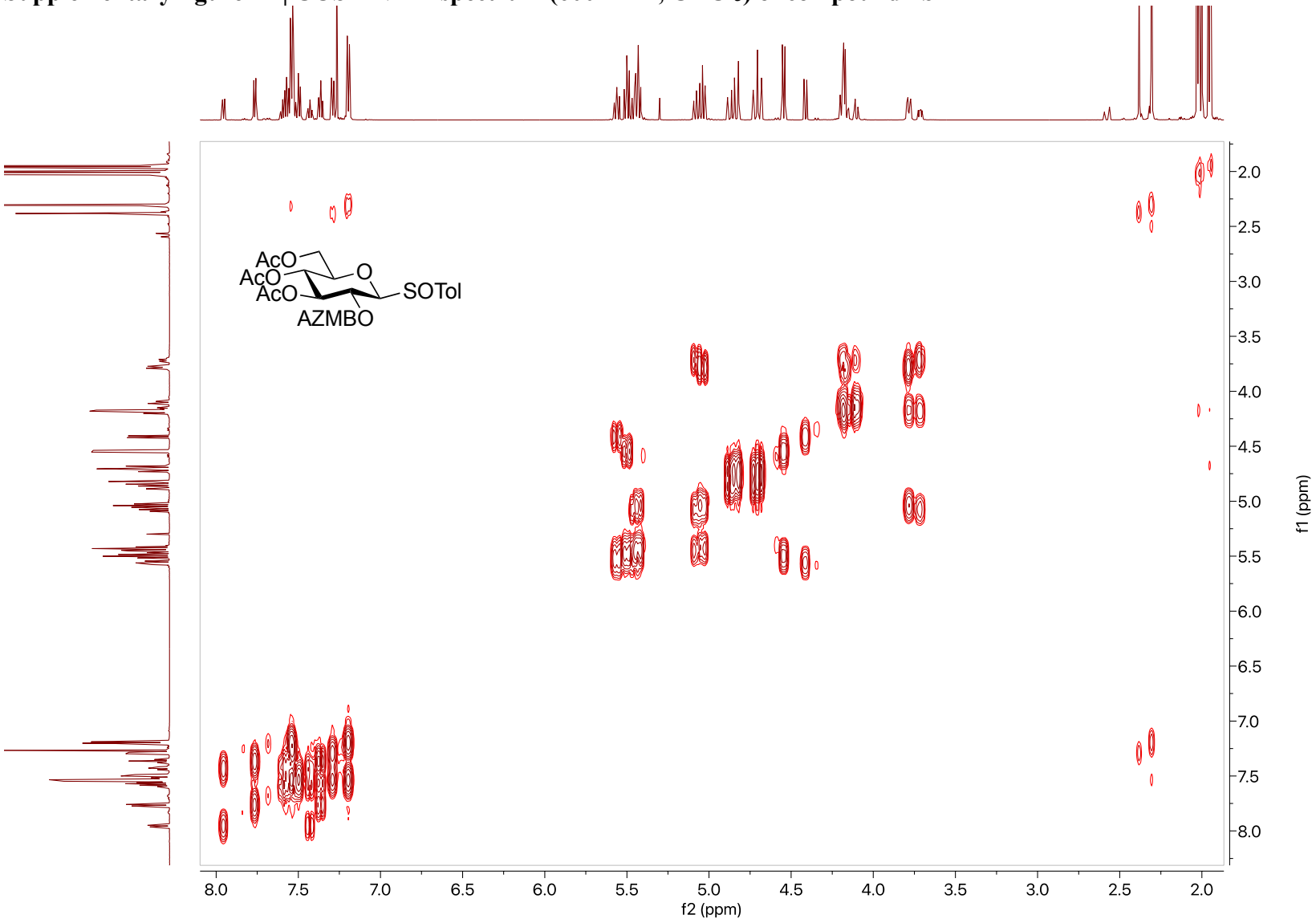
Supplementary figure 22 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 4a



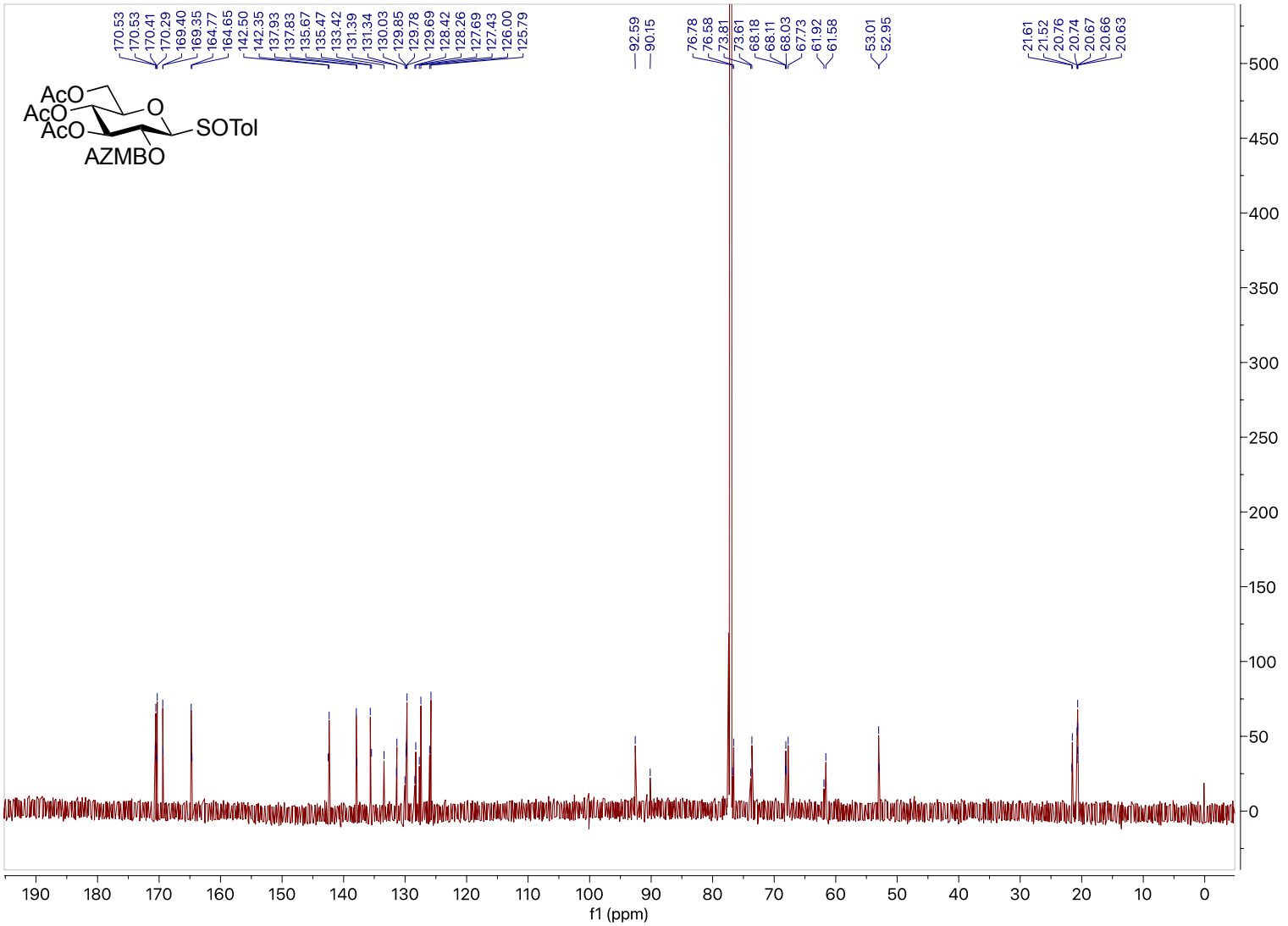
Supplementary figure 23 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 4b



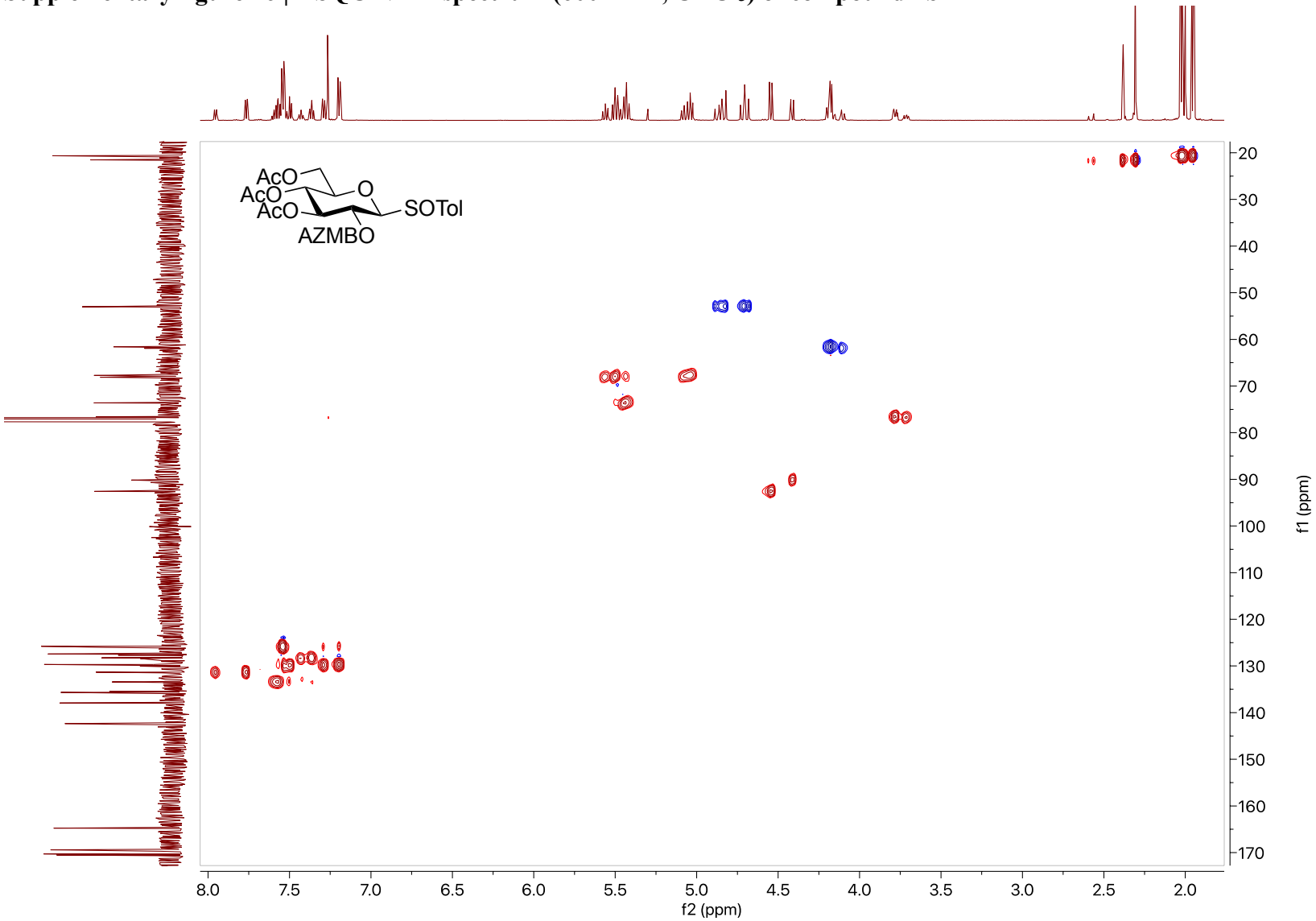
Supplementary figure 24 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 4b



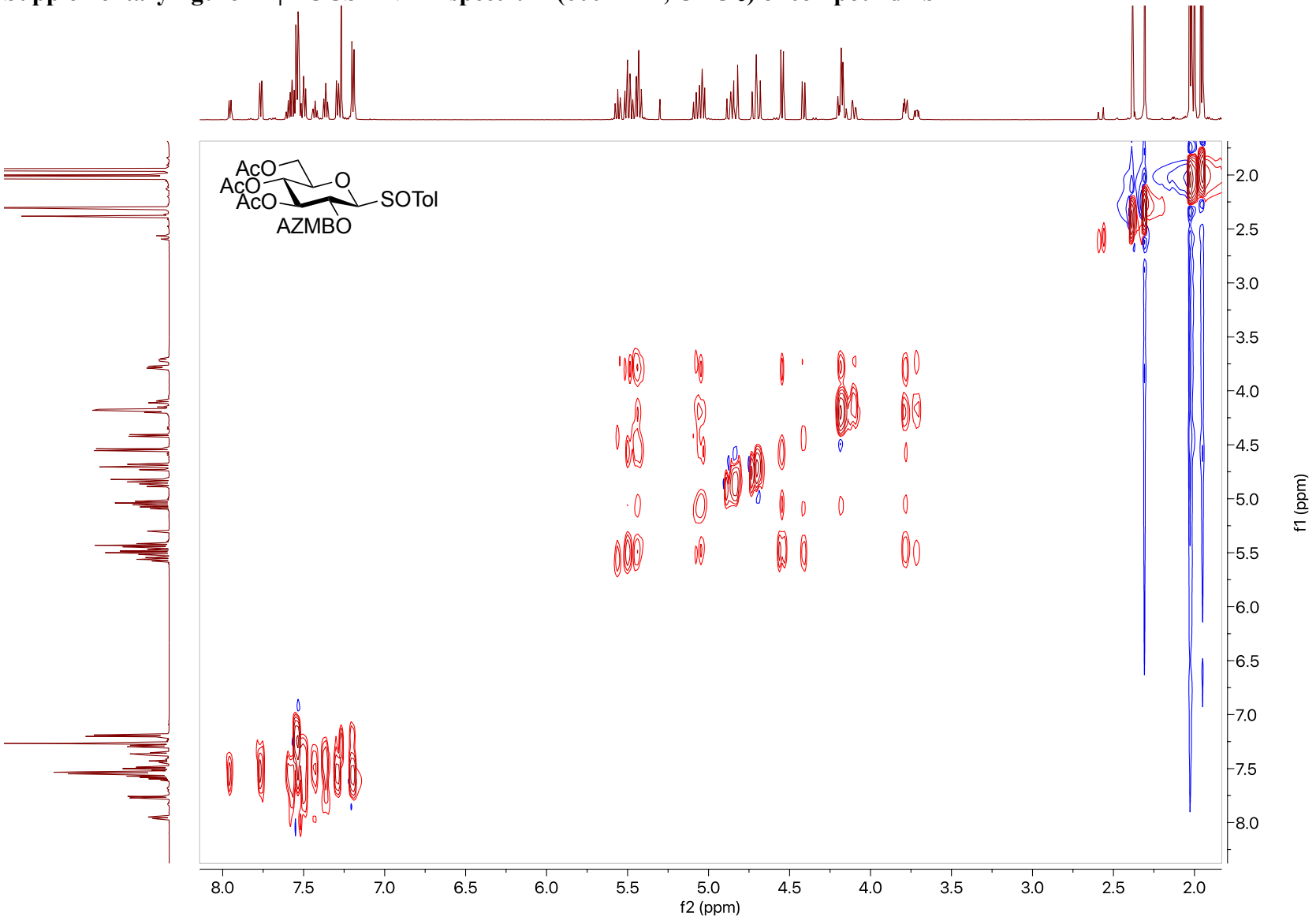
Supplementary figure 25 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 4b



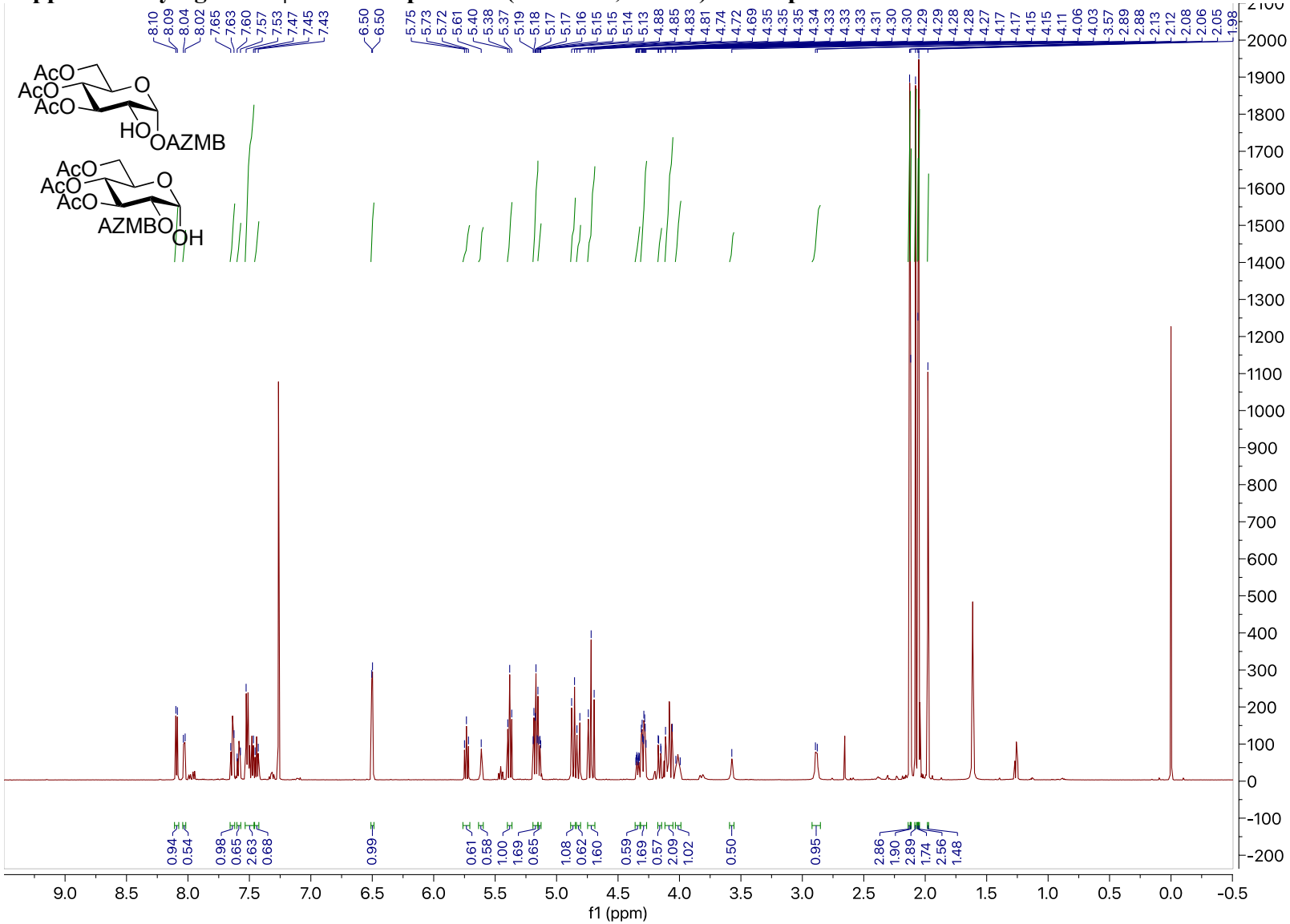
Supplementary figure 26 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 4b



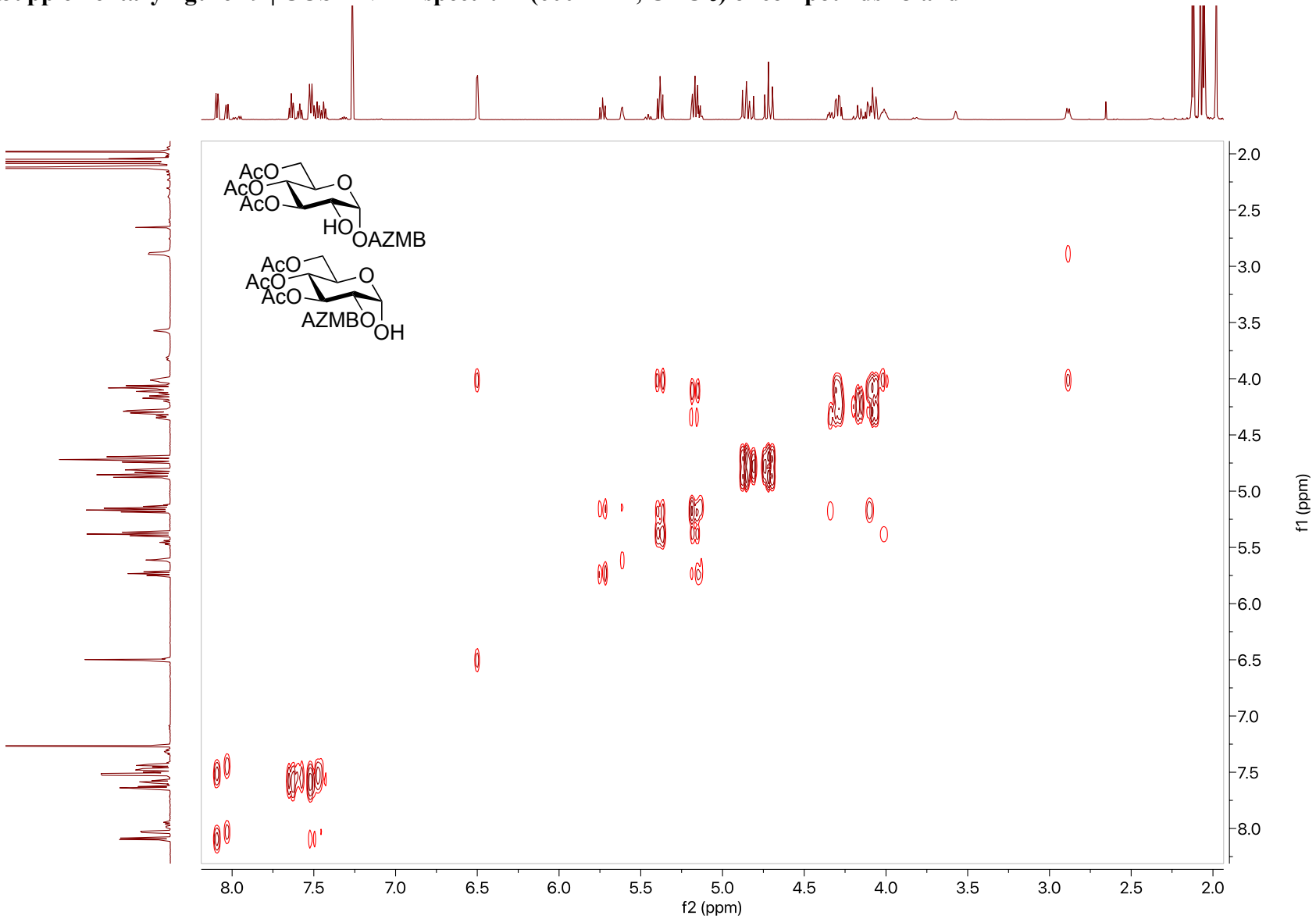
Supplementary figure 27 | TOCSY NMR spectrum (600 MHz, $CDCl_3$) of compound 4b



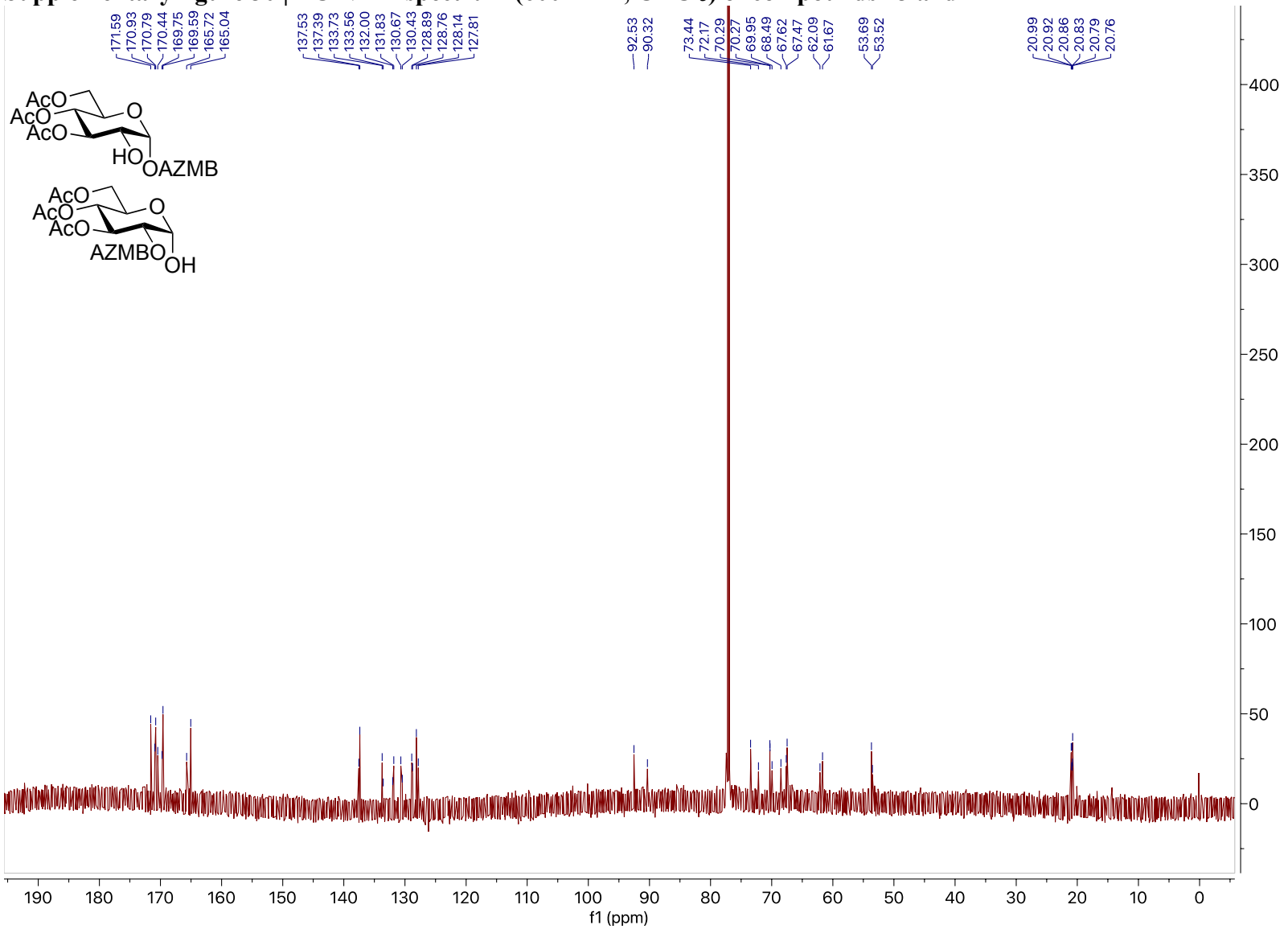
Supplementary figure 28 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compounds 13 and 14



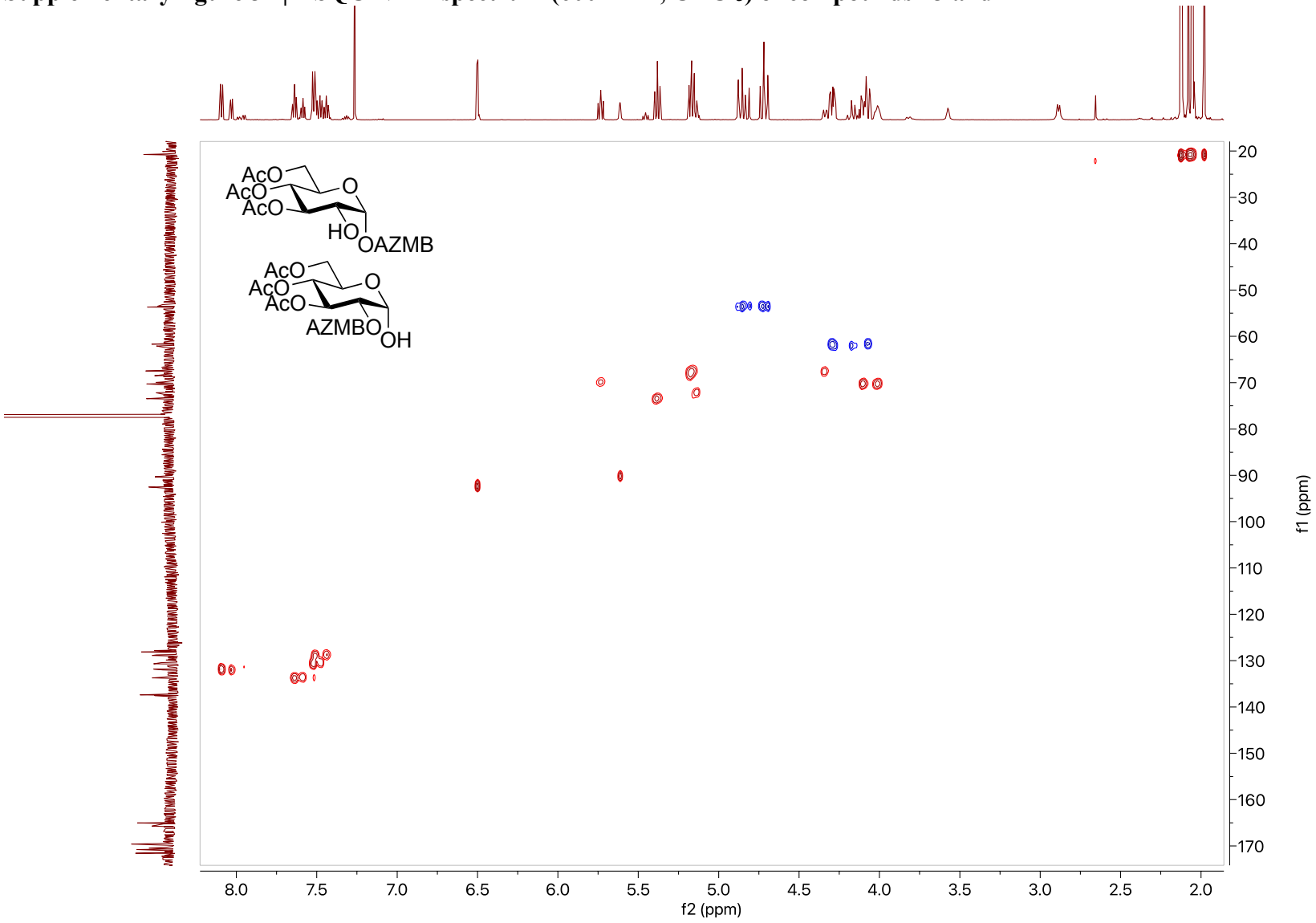
Supplementary figure 29 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compounds 13 and 14



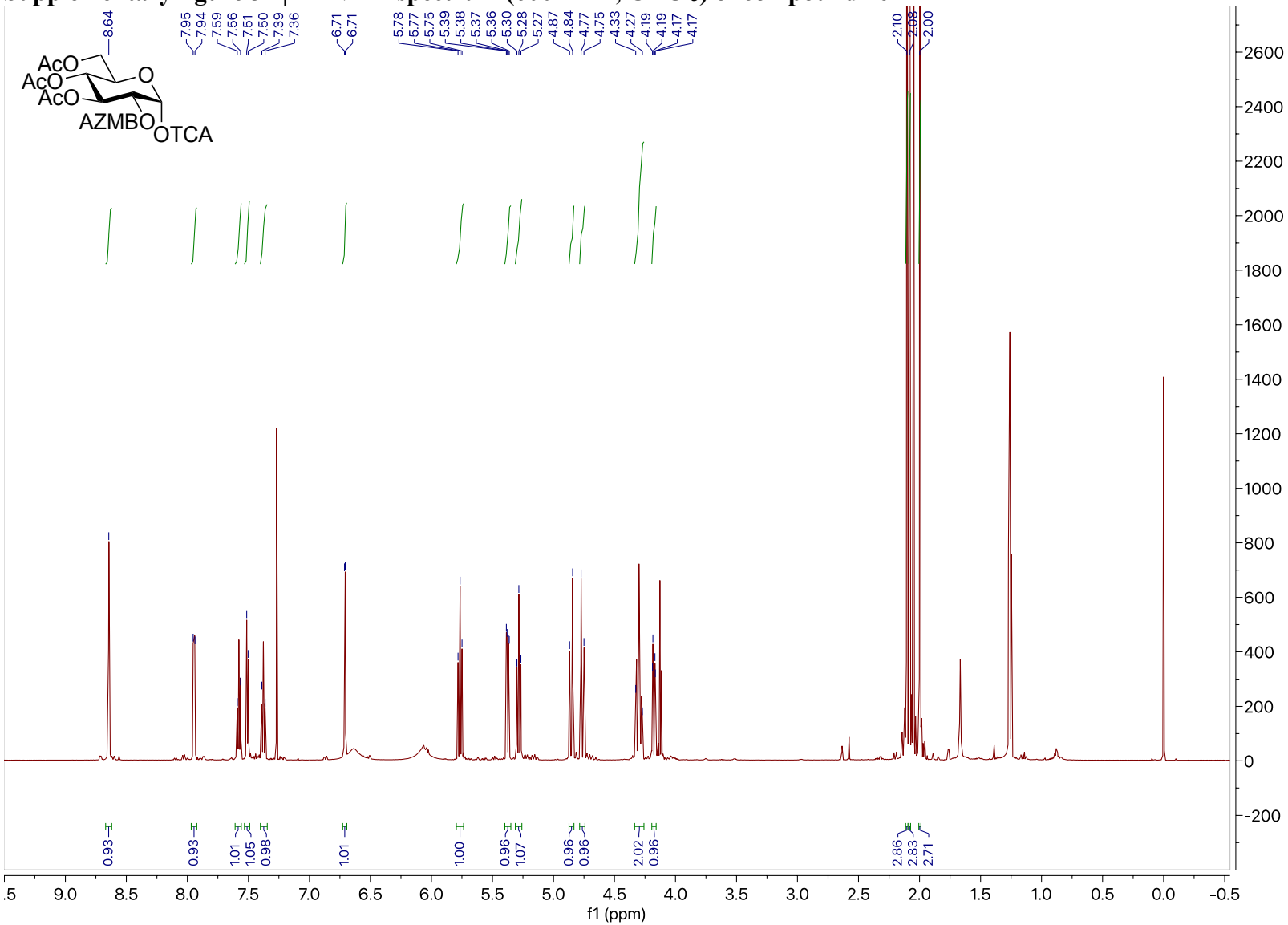
Supplementary figure 30 | ^{13}C NMR spectrum (600 MHz, $CDCl_3$) of compounds 13 and 14



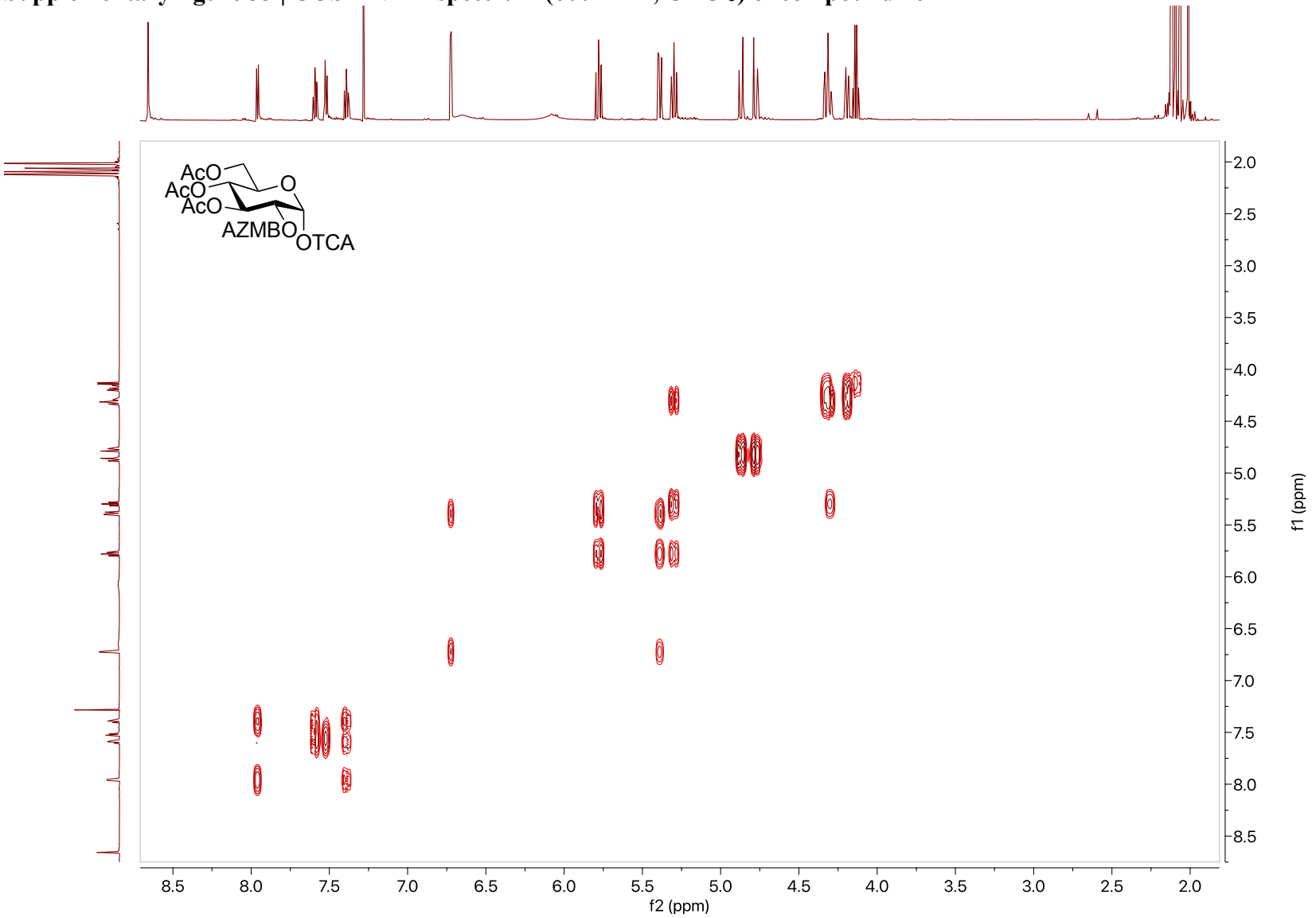
Supplementary figure 31 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compounds 13 and 14



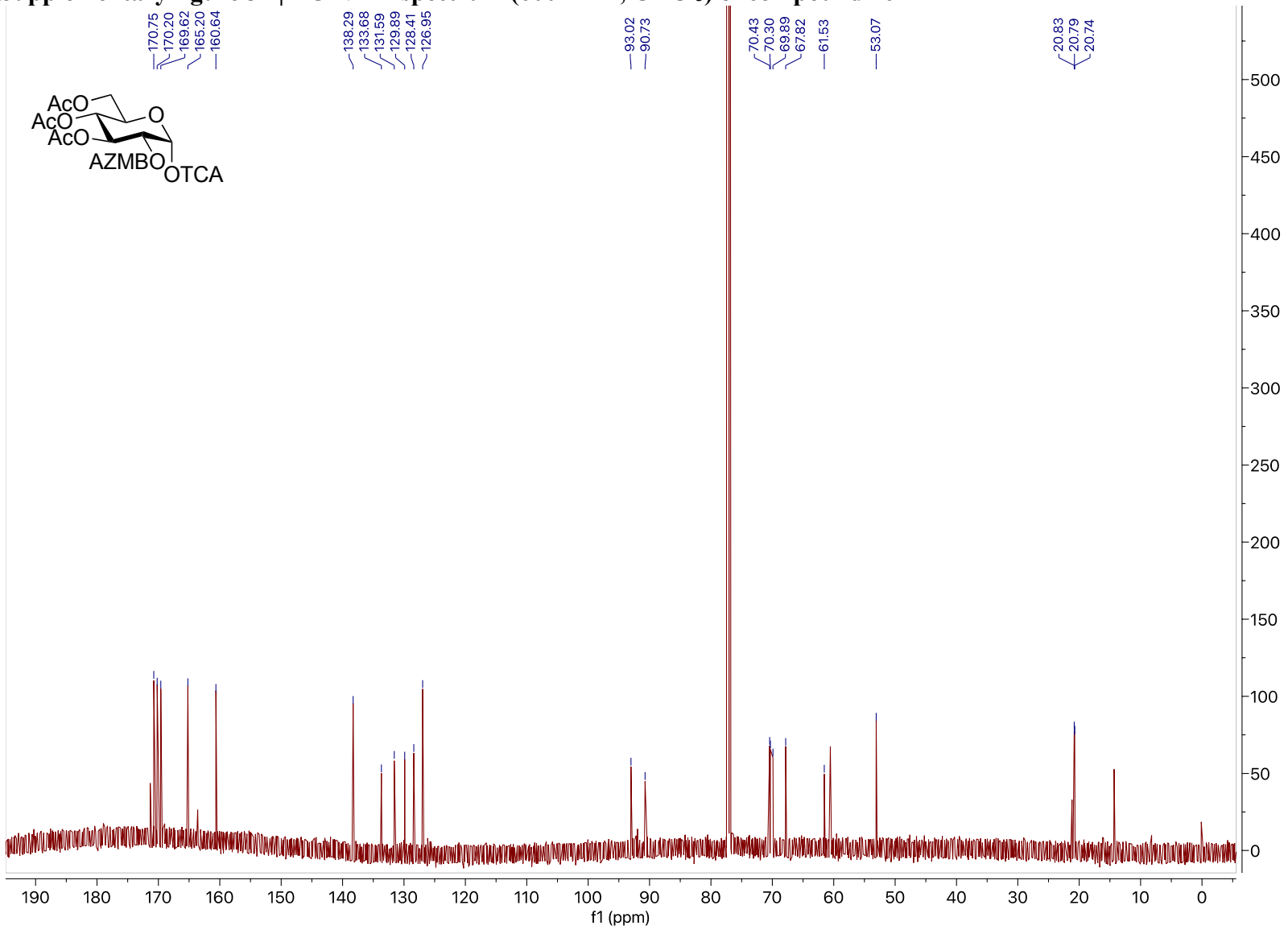
Supplementary figure 32 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 4c



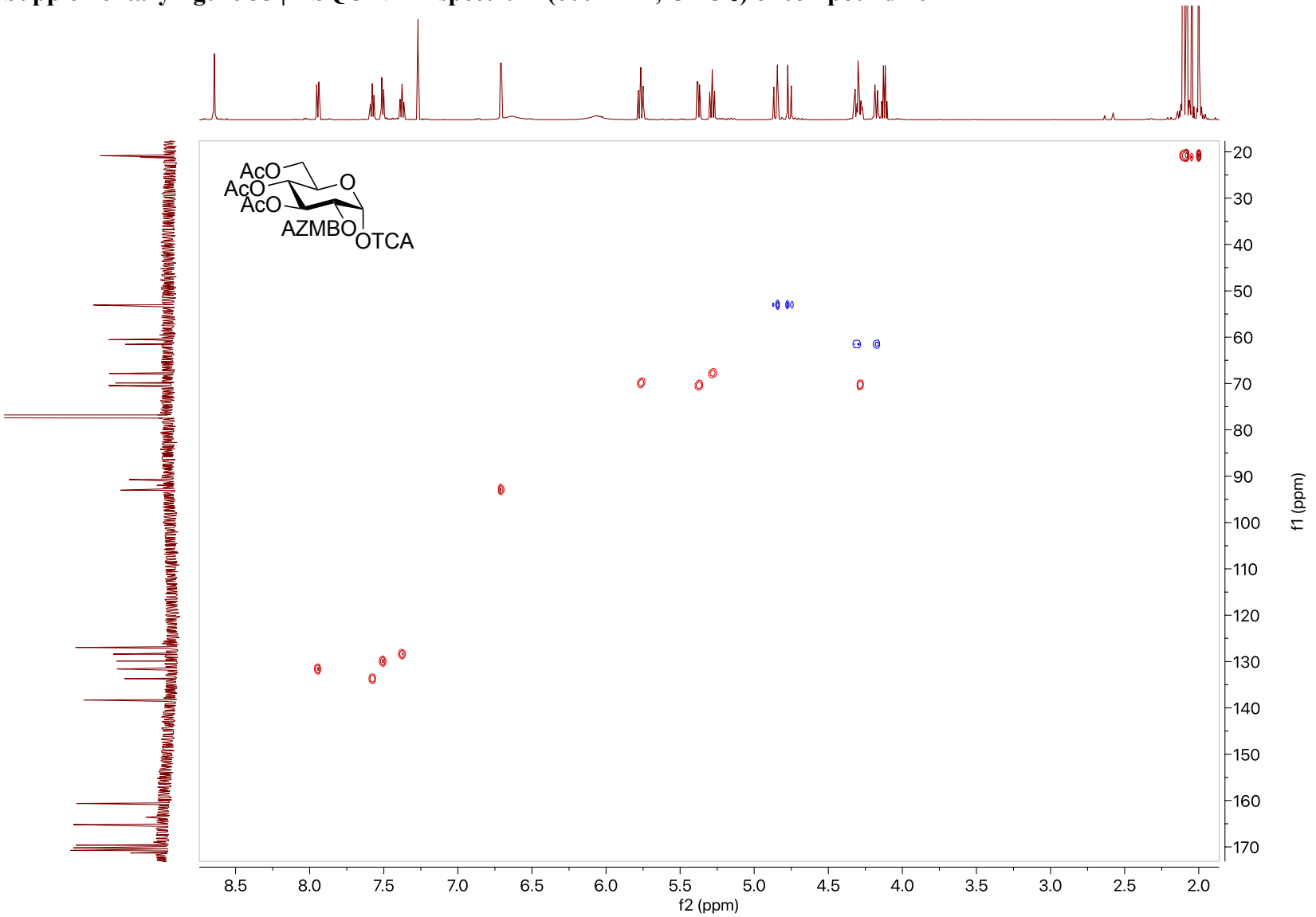
Supplementary figure 33 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 4c



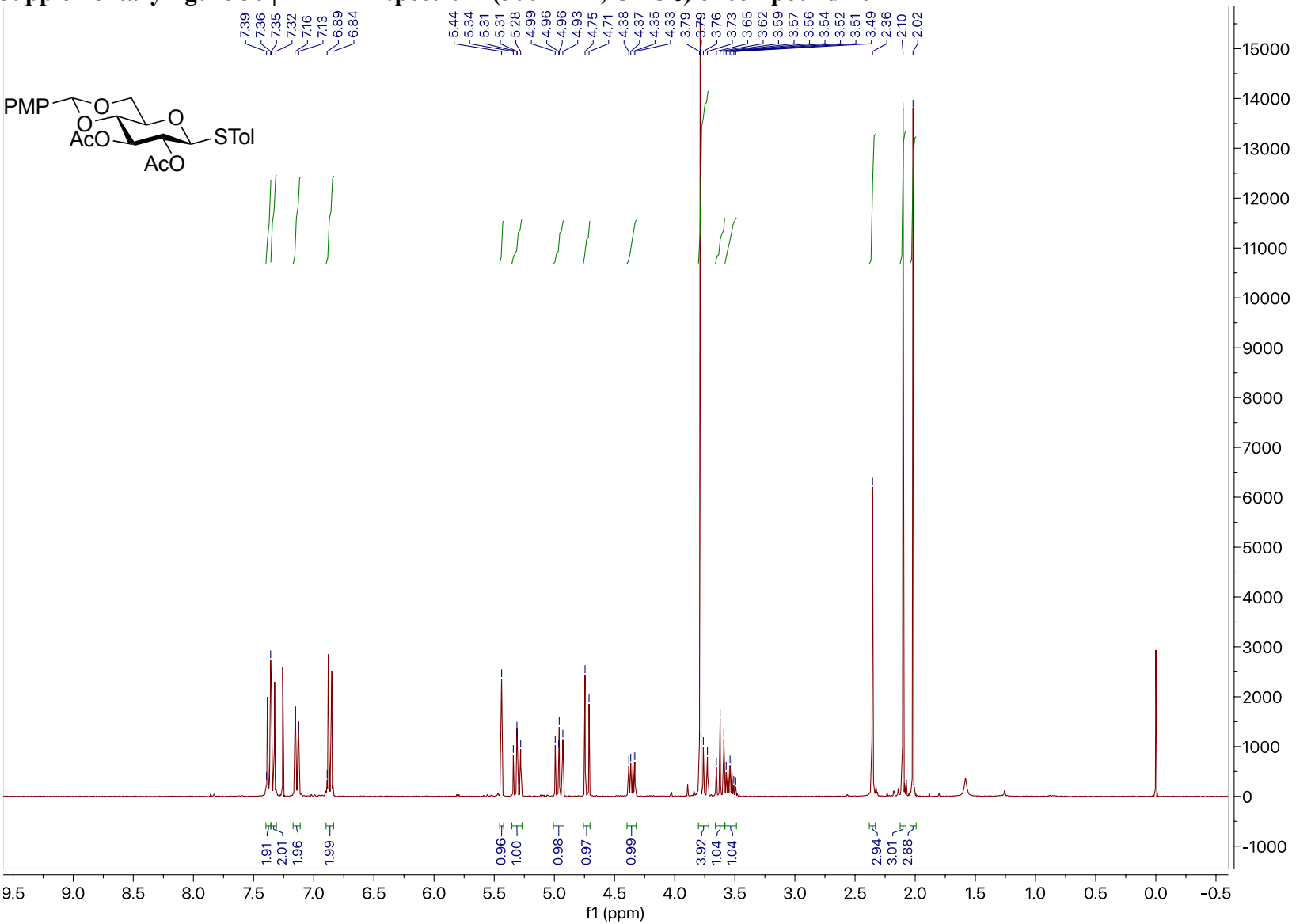
Supplementary figure 34 | ^{13}C NMR spectrum (600 MHz, $CDCl_3$) of compound 4c



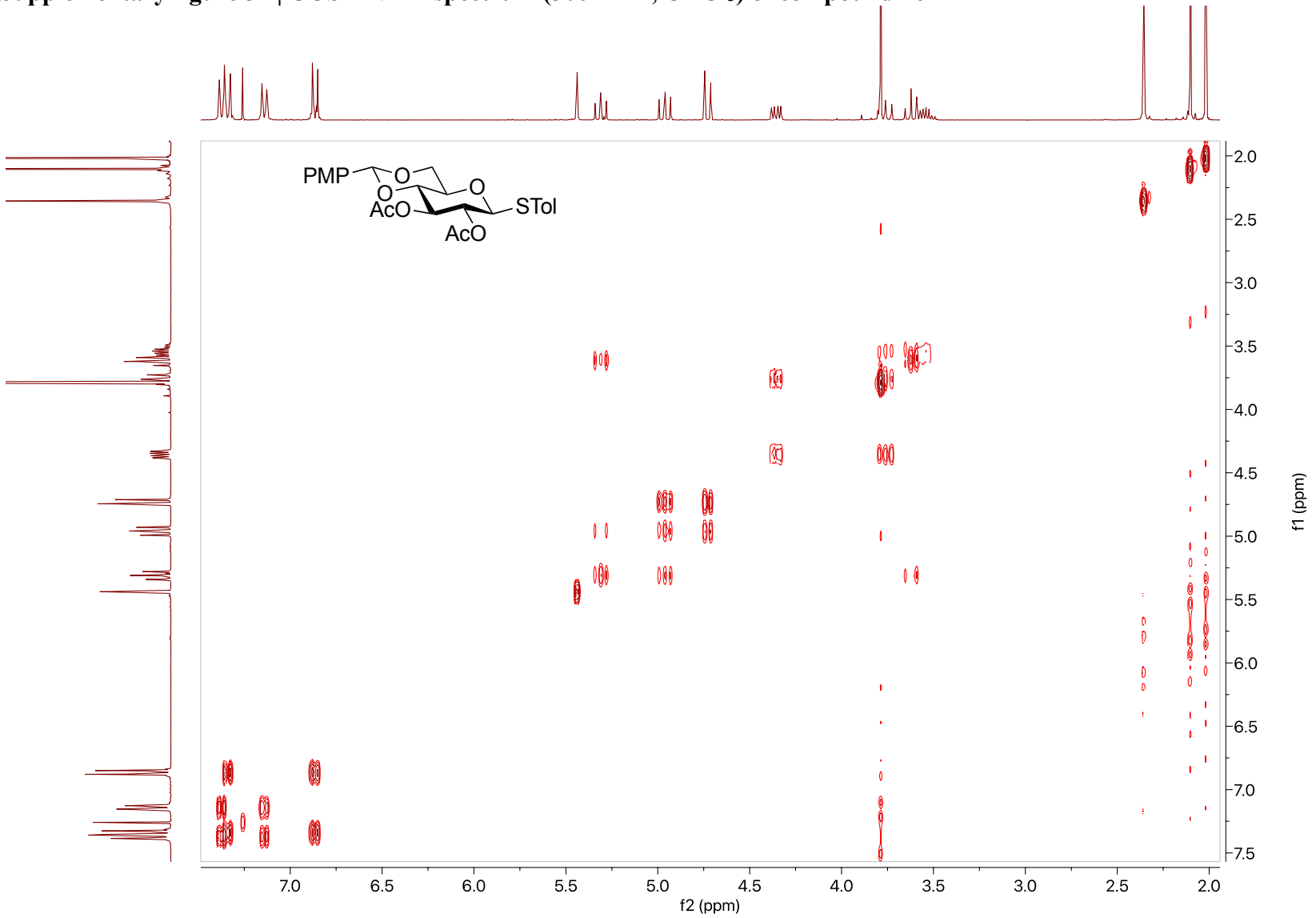
Supplementary figure 35 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 4c



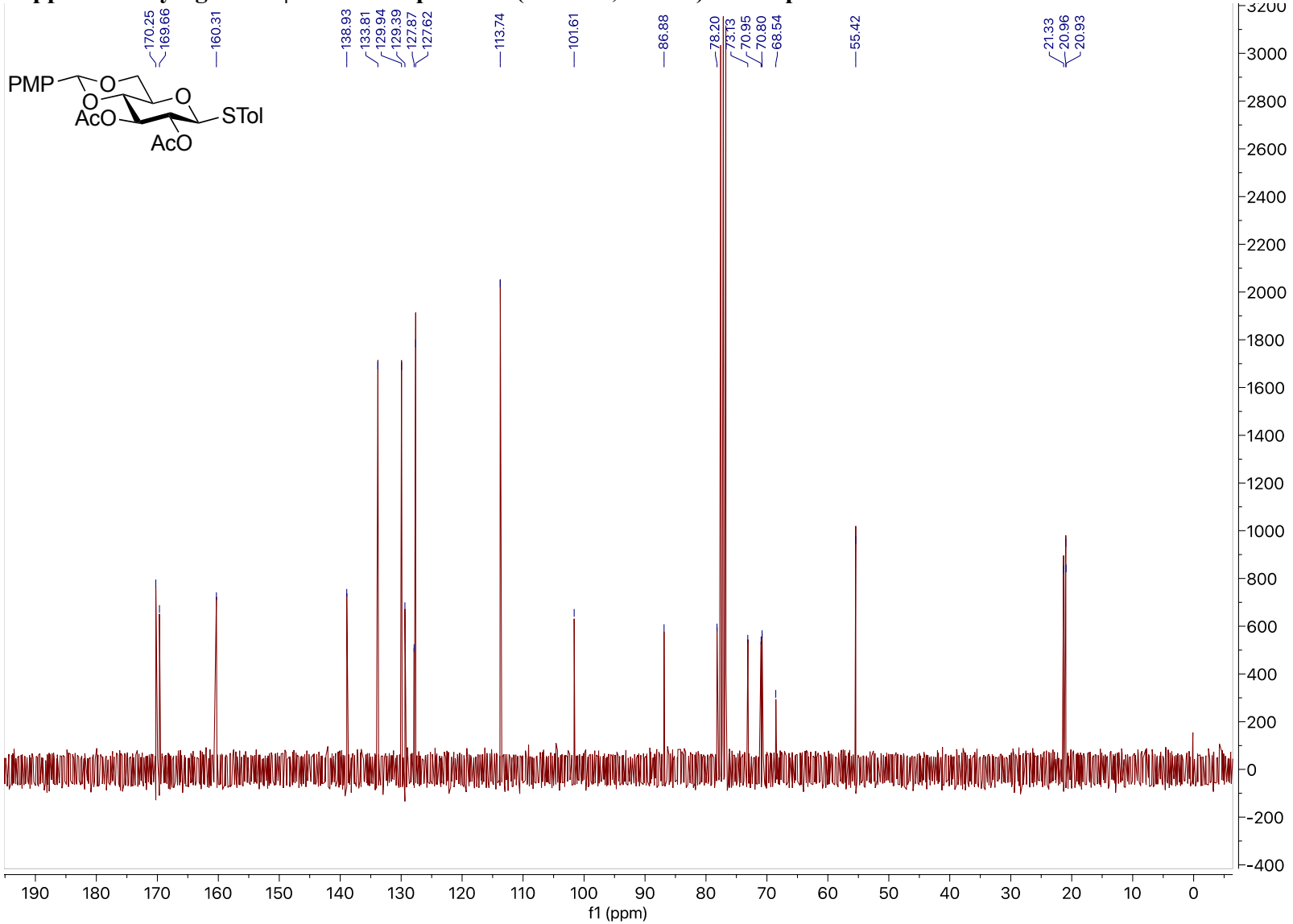
Supplementary figure 36 | ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound 16



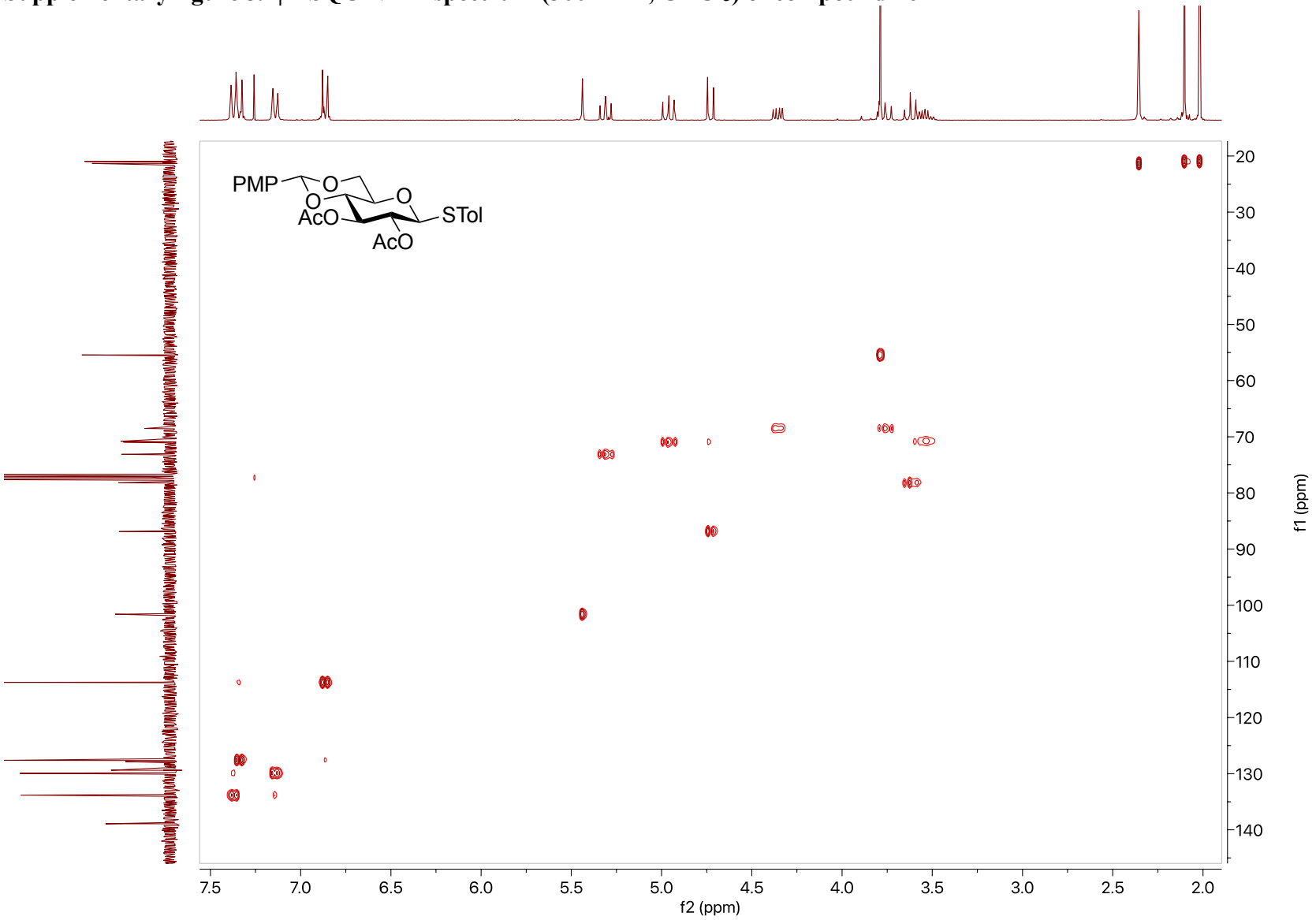
Supplementary figure 37 | COSY NMR spectrum (300 MHz, $CDCl_3$) of compound 16



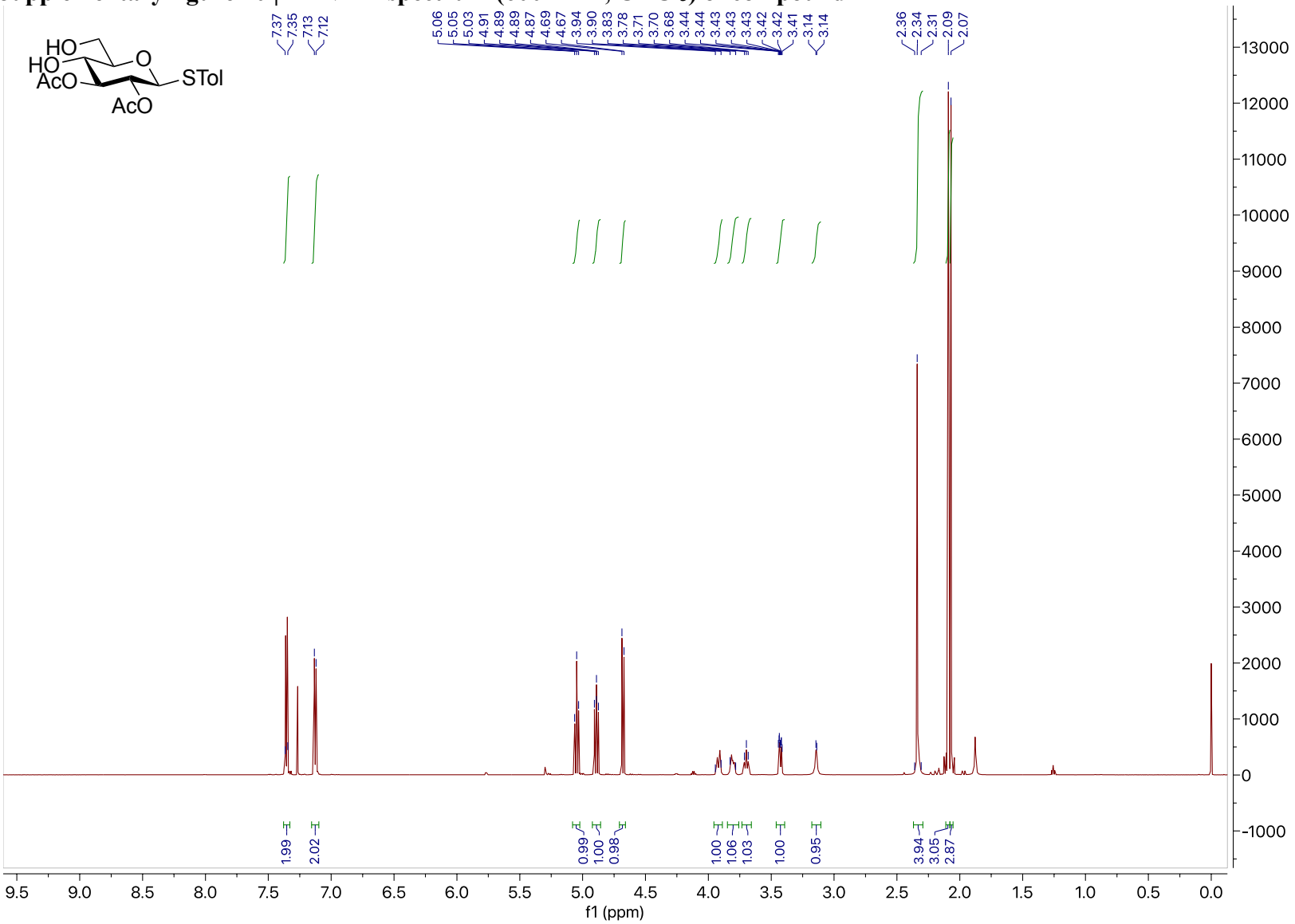
Supplementary figure 38 | ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound 16



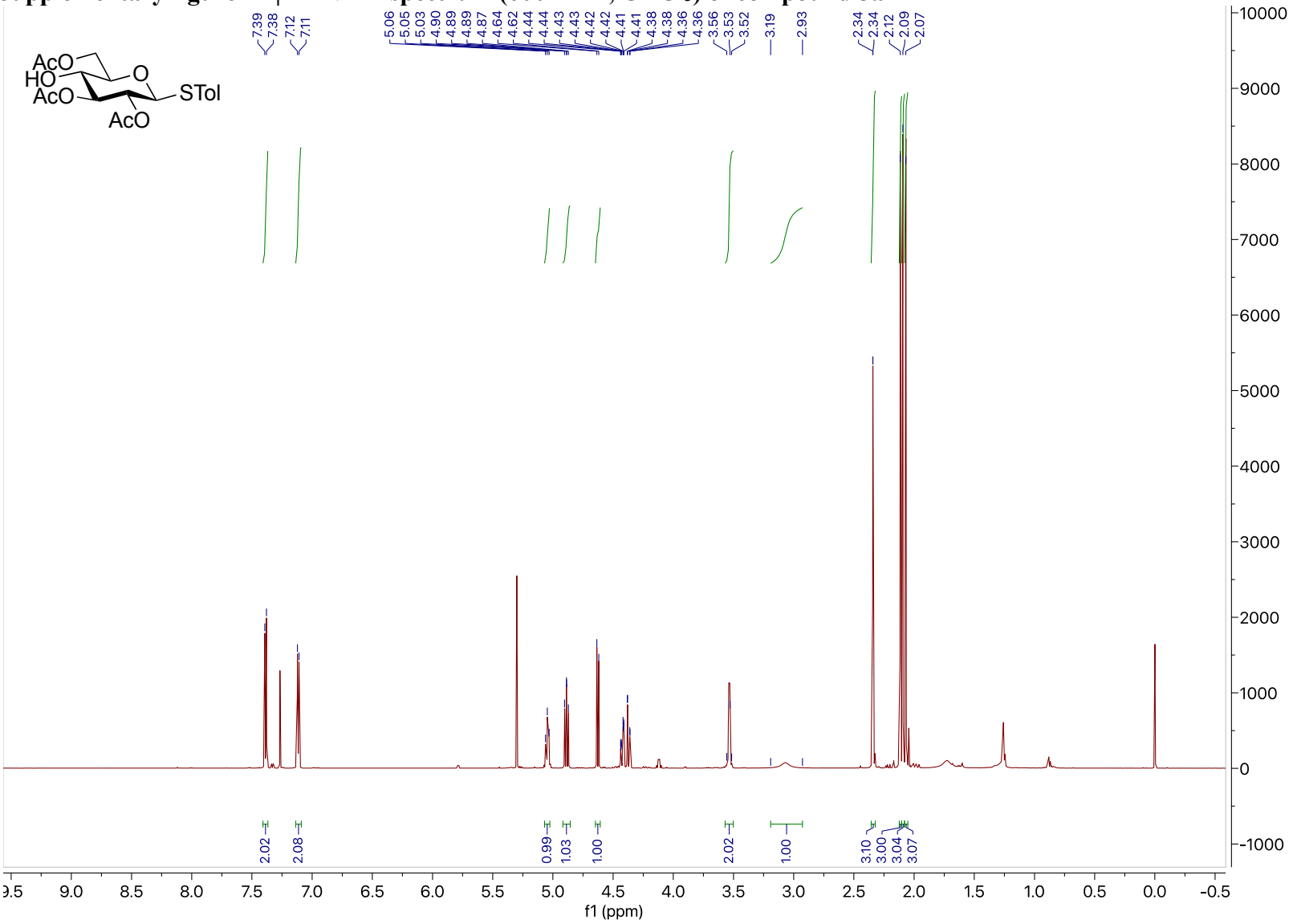
Supplementary figure 39 | HSQC NMR spectrum (300 MHz, $CDCl_3$) of compound 16



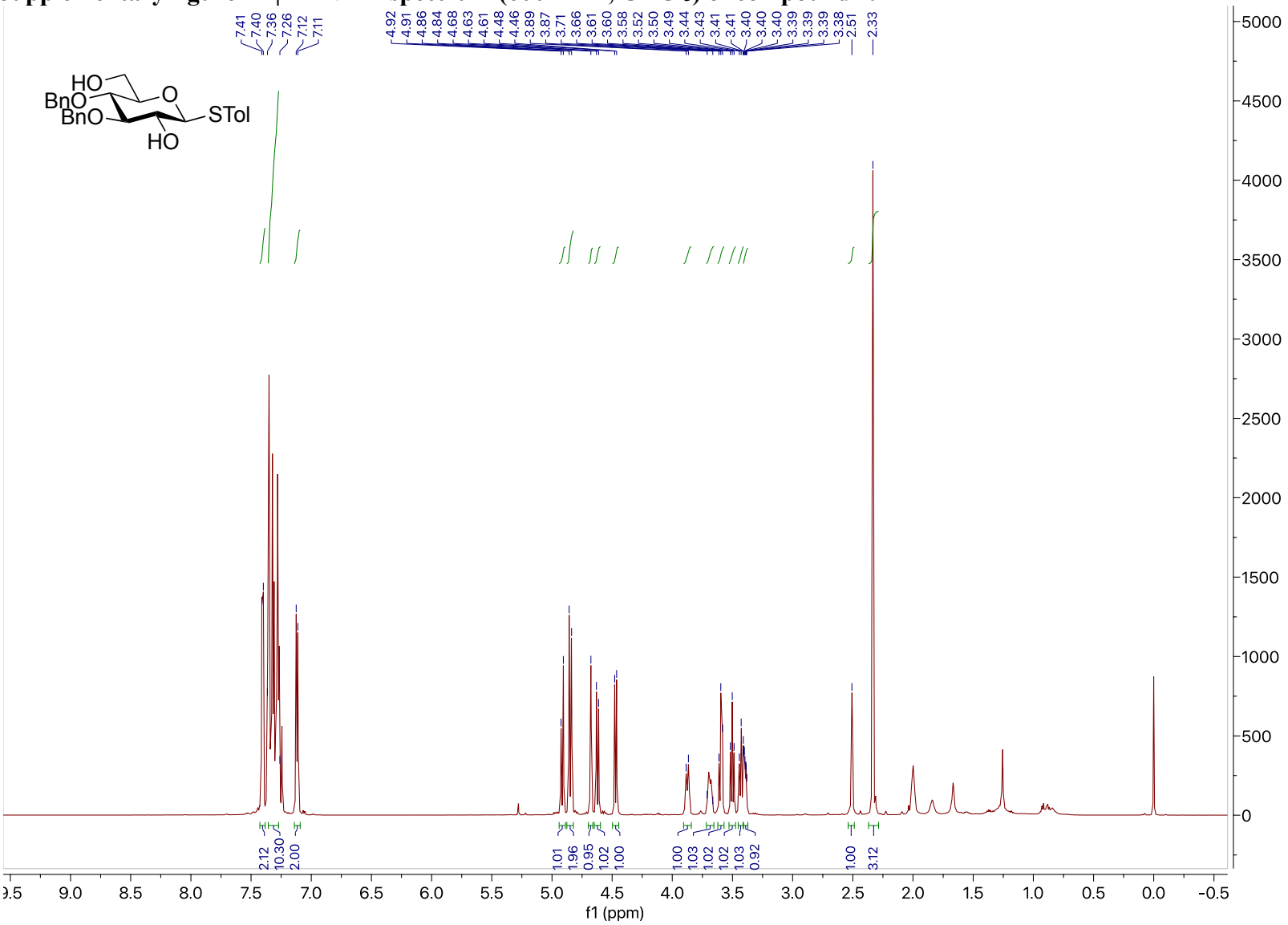
Supplementary figure 40 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 17



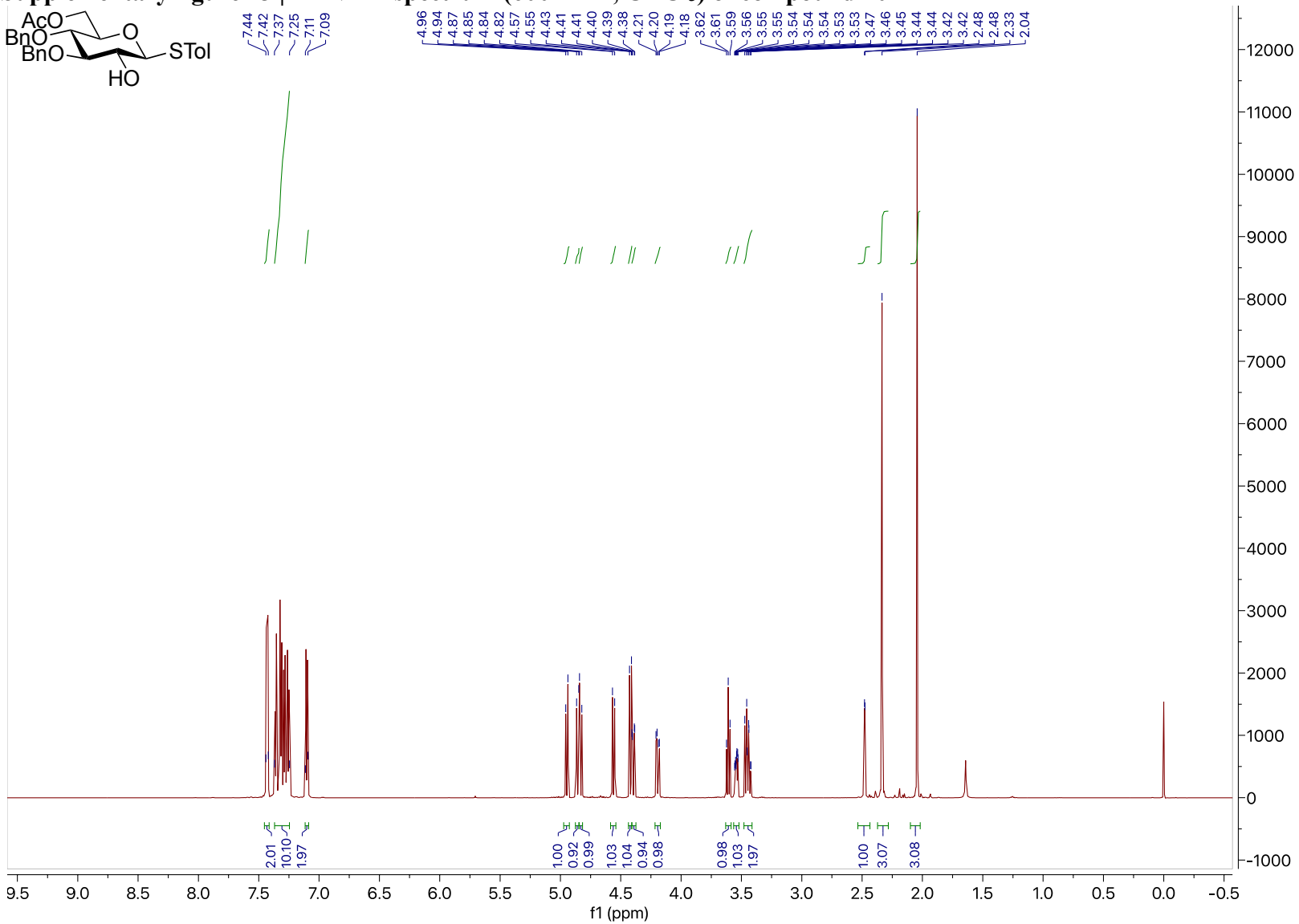
Supplementary figure 41 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 5a



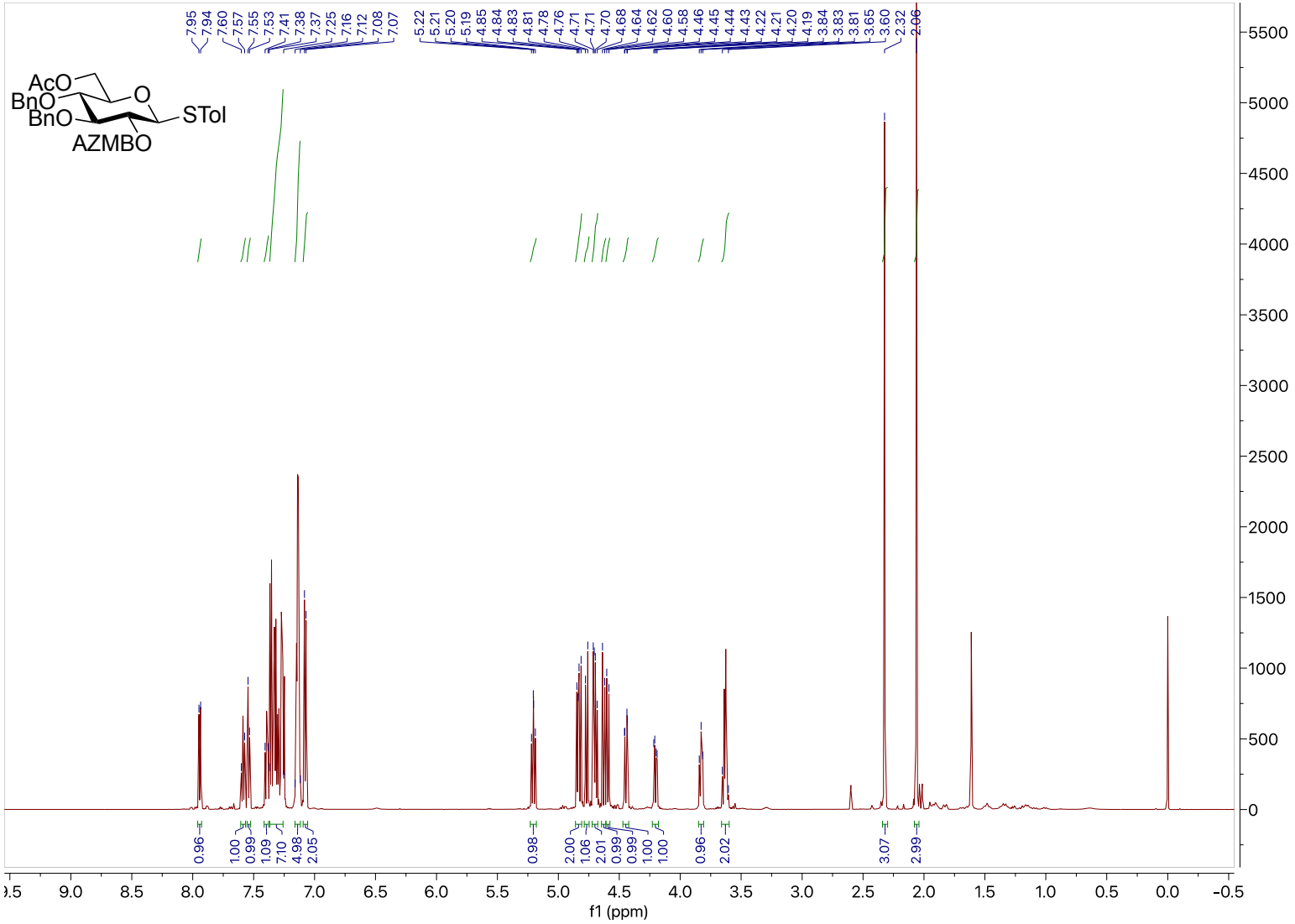
Supplementary figure 42 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 19



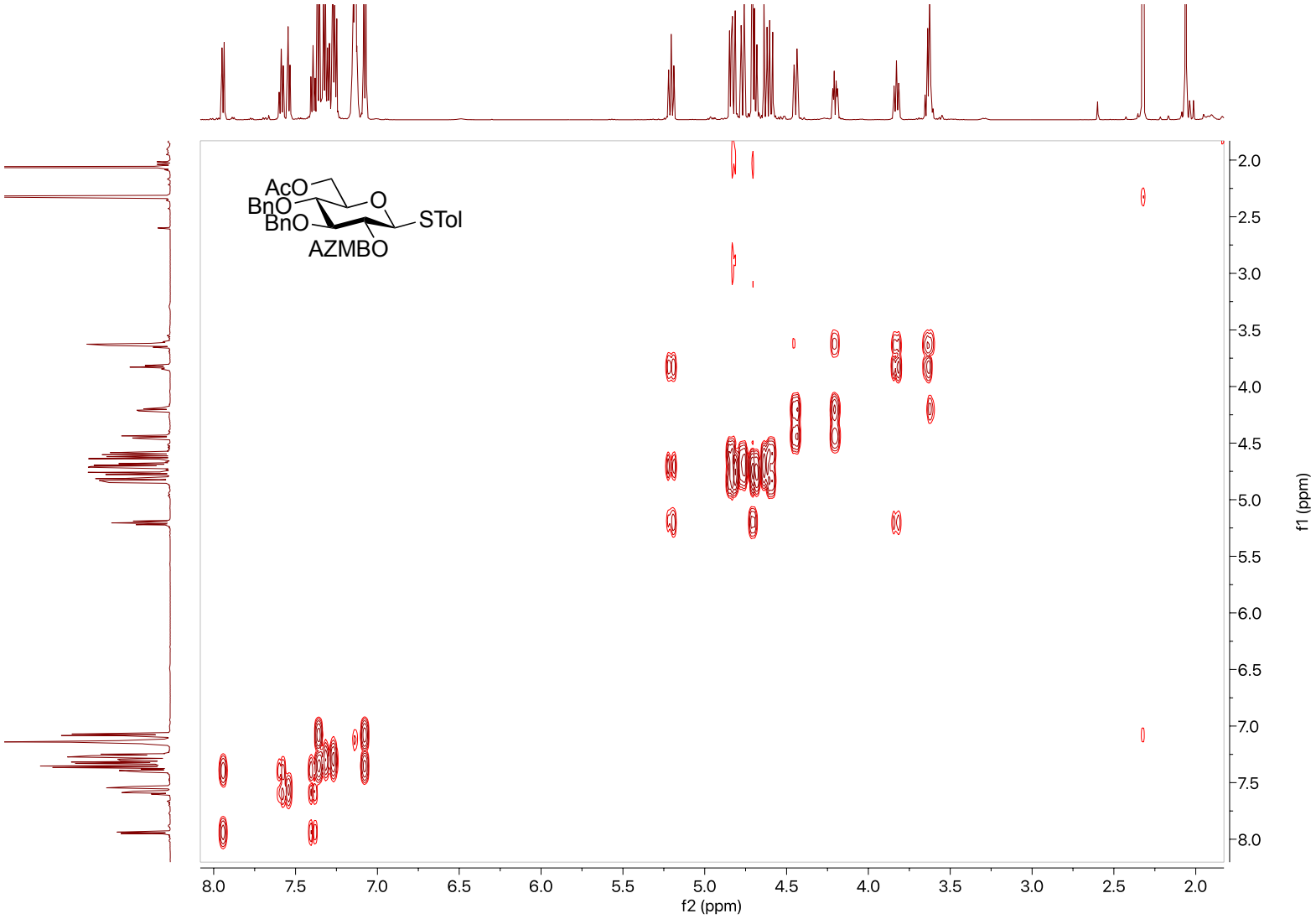
Supplementary figure 43 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 20



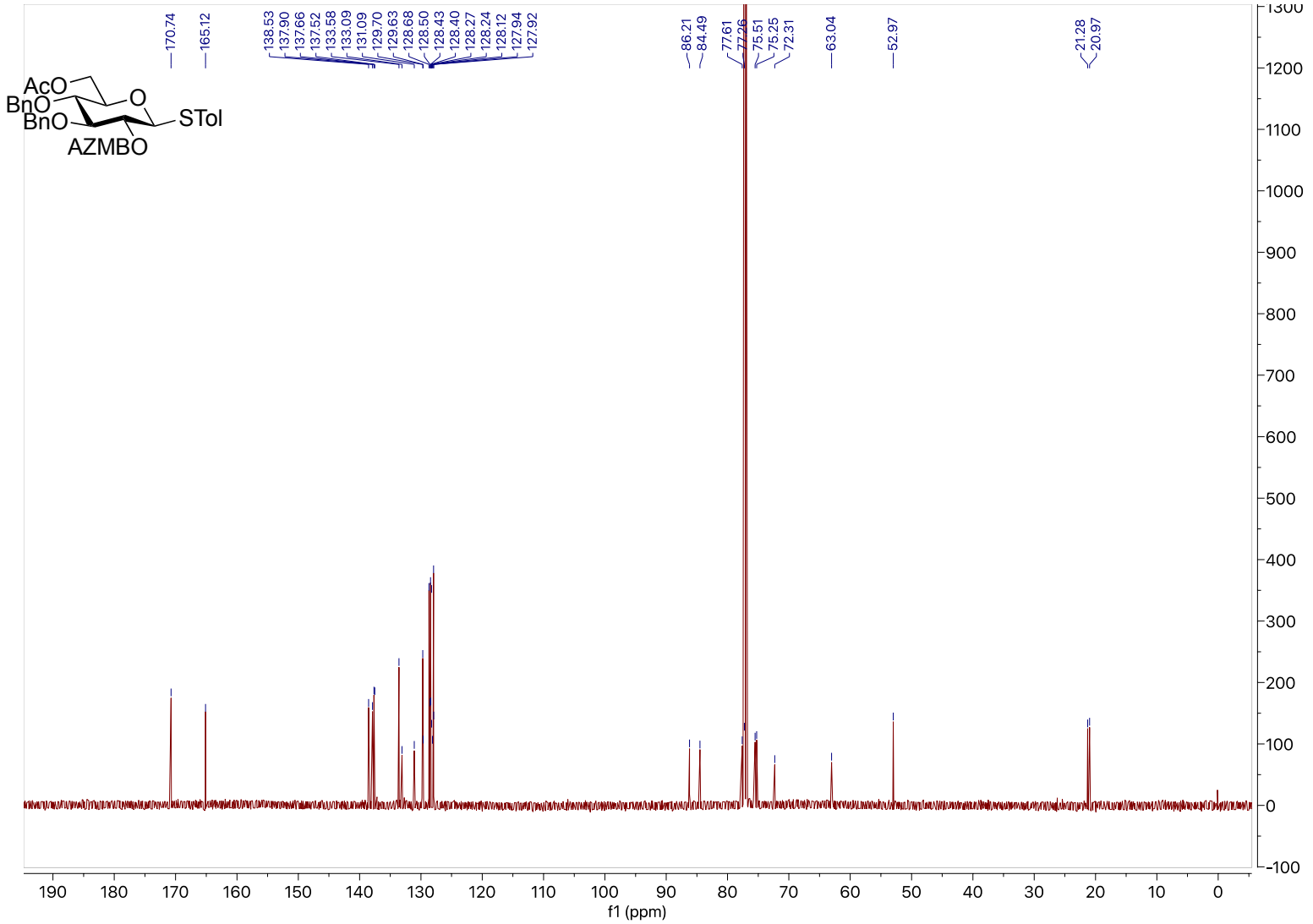
Supplementary figure 44 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 6



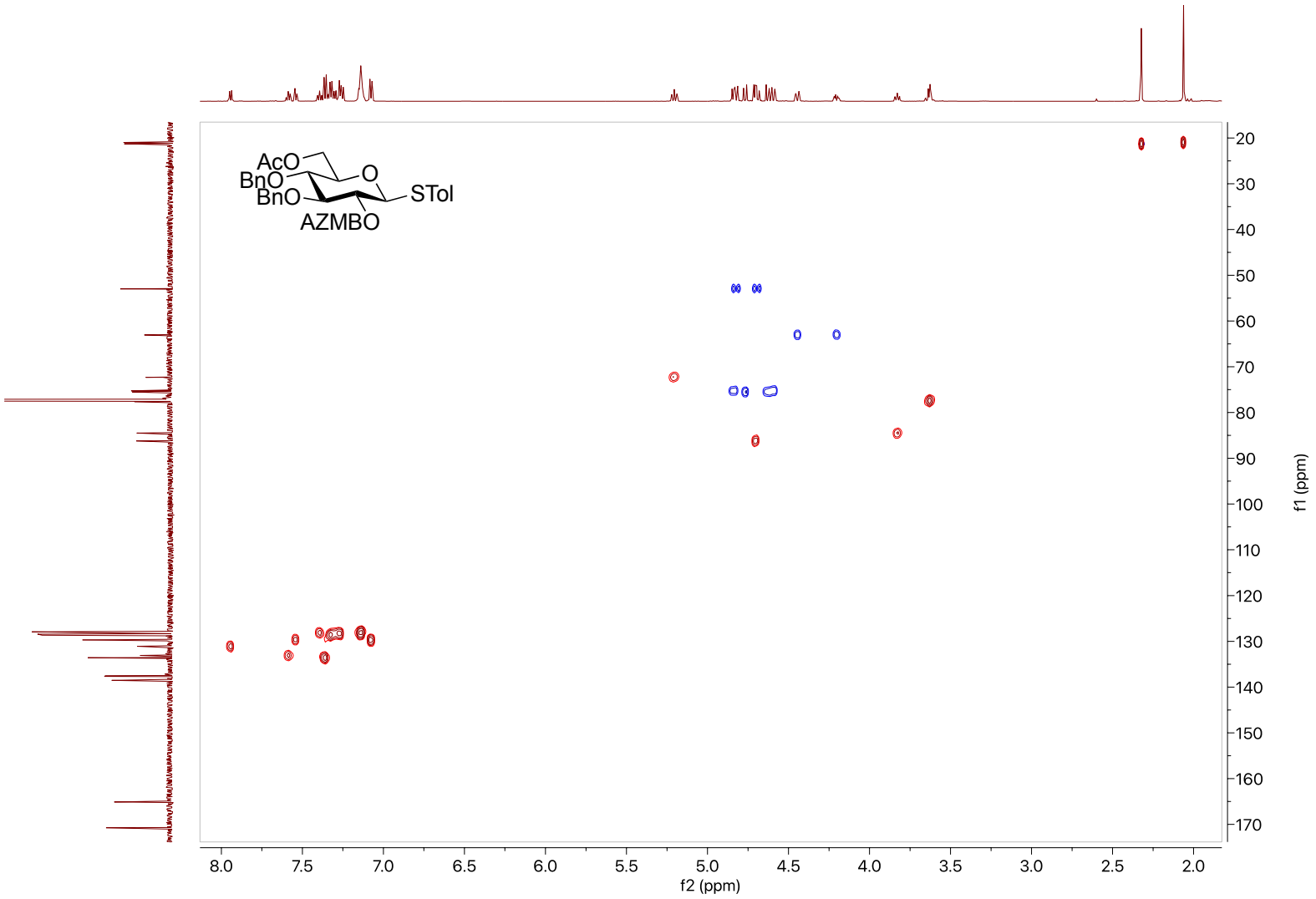
Supplementary figure 45 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 6



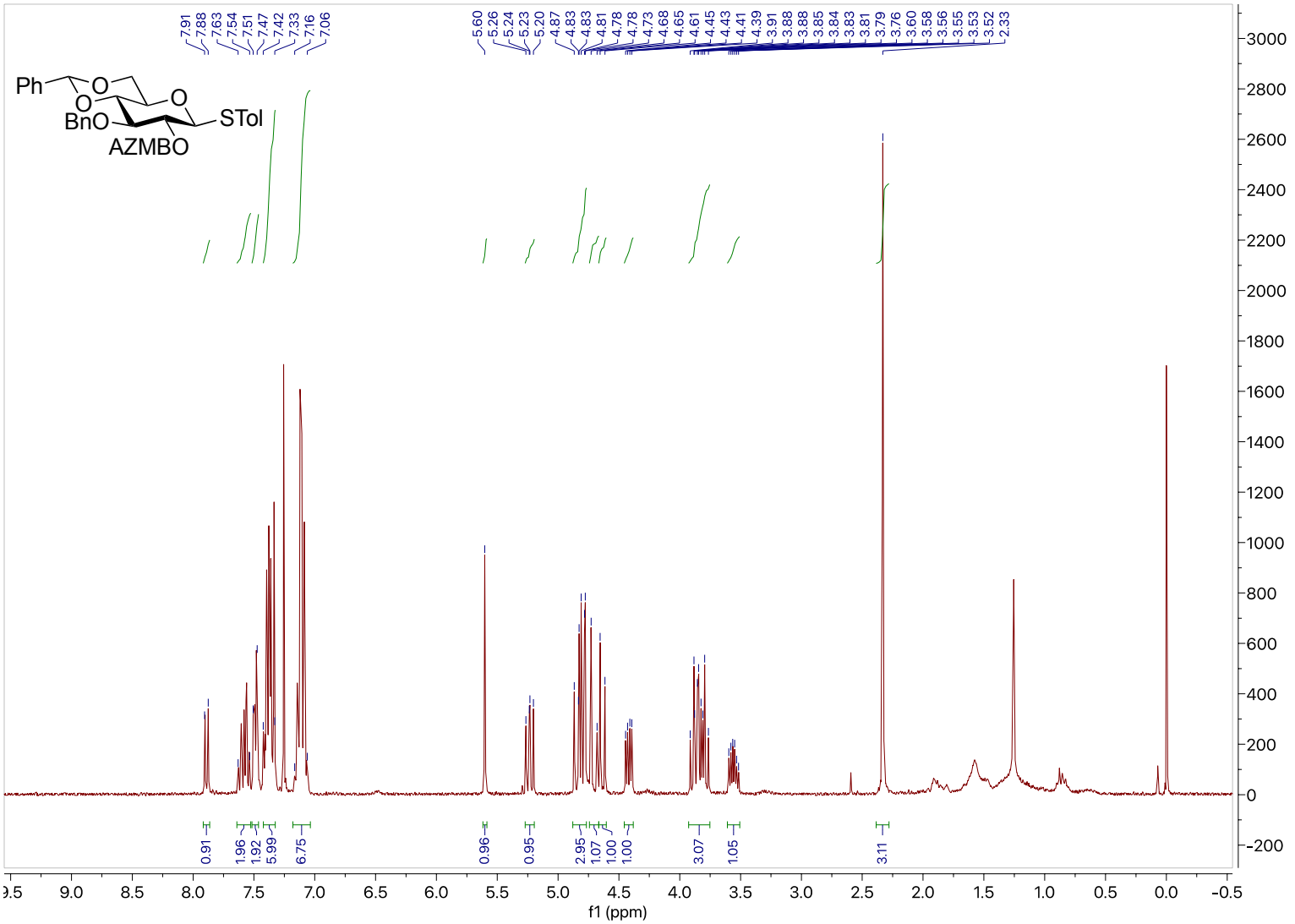
Supplementary figure 46 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 6



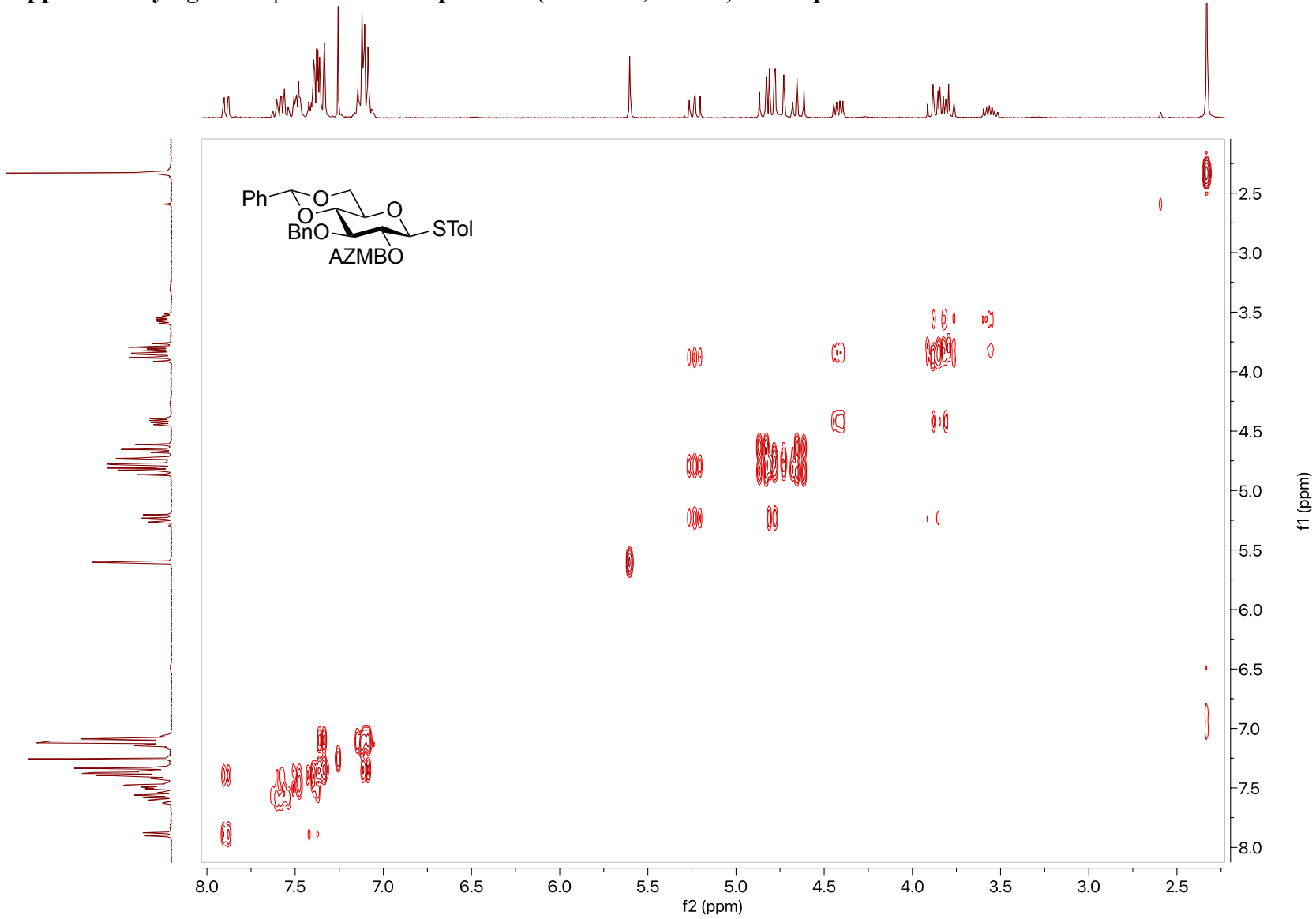
Supplementary figure 47 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 6



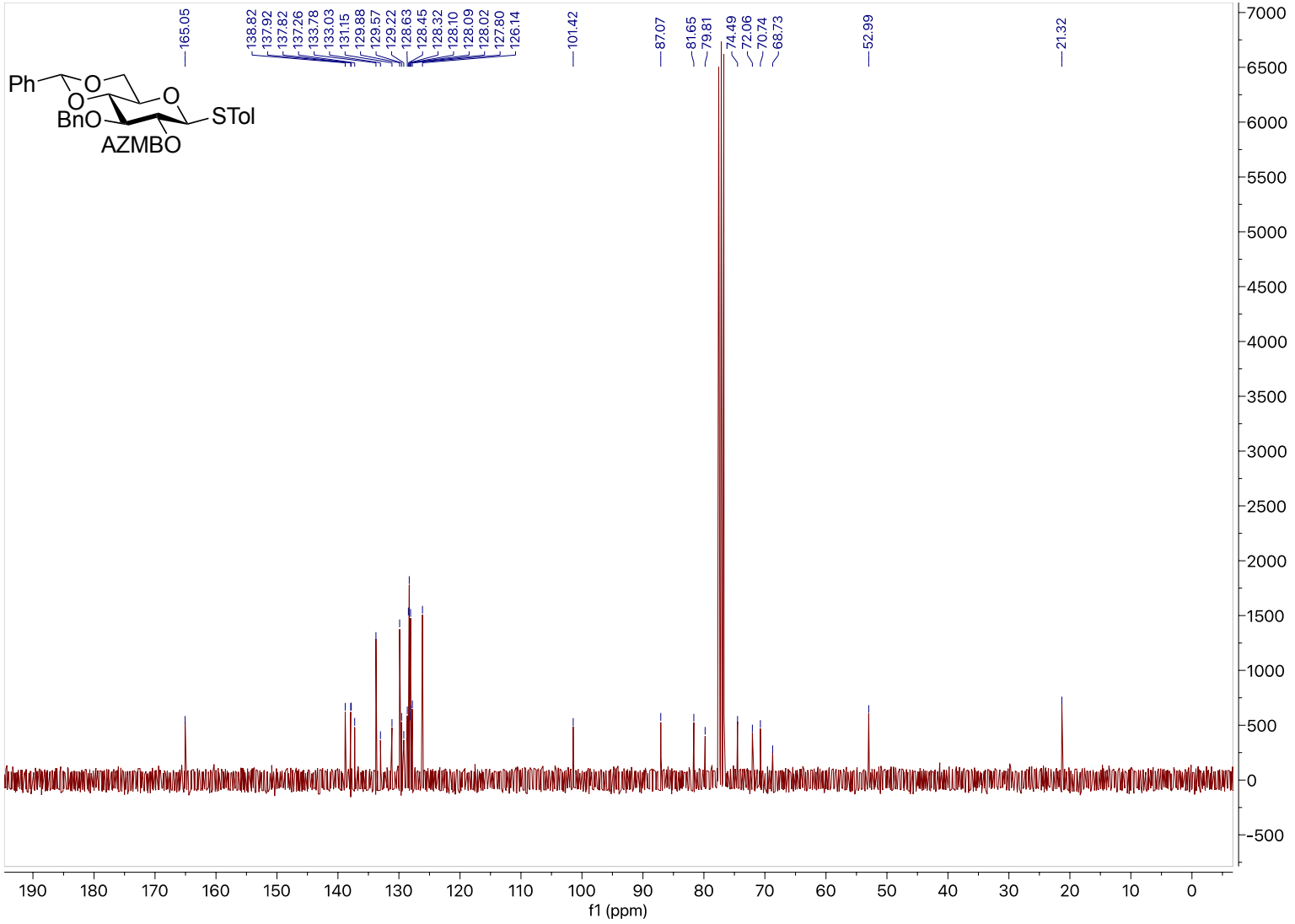
Supplementary figure 48 | ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound 21



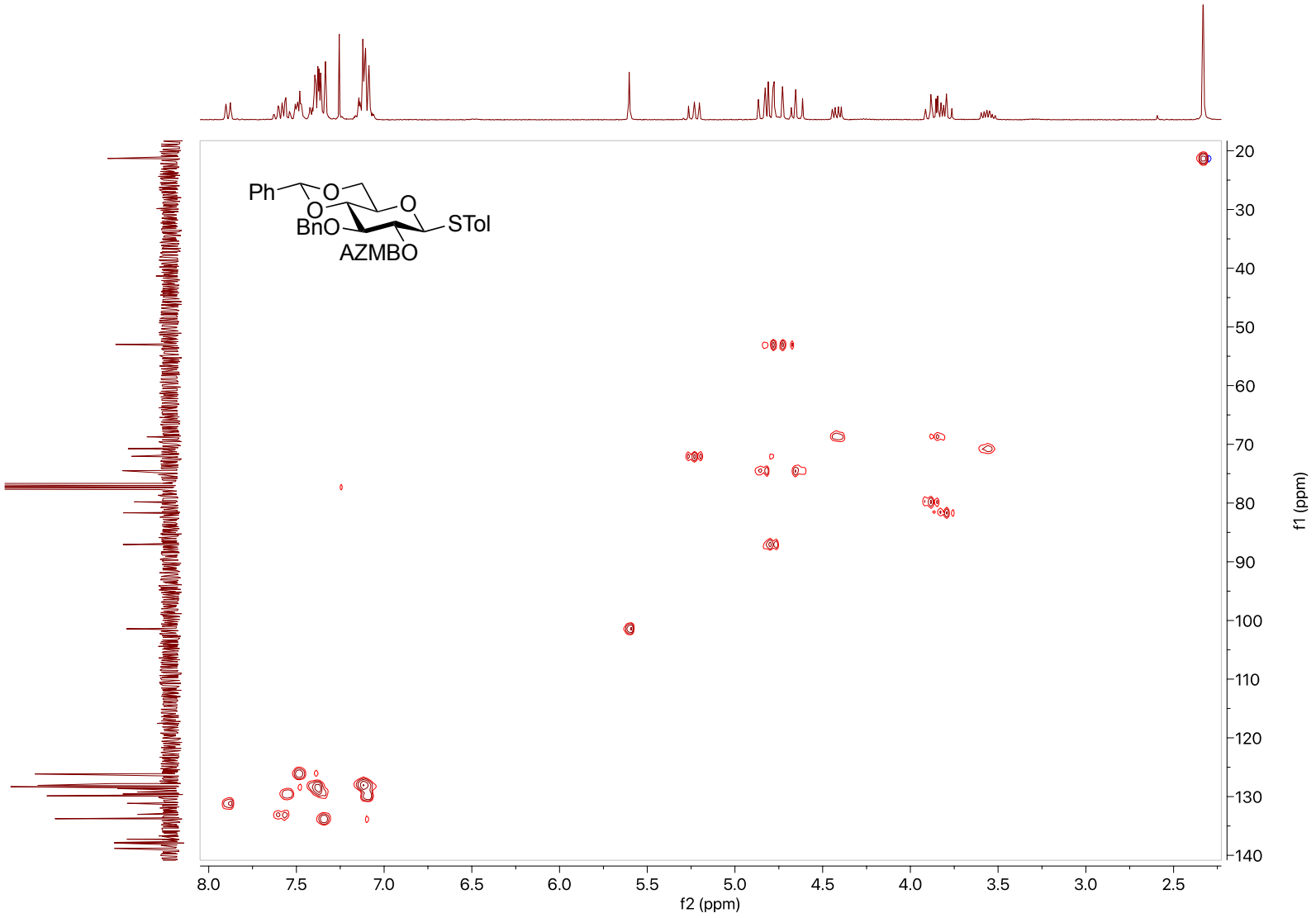
Supplementary figure 49 | COSY NMR spectrum (300 MHz, $CDCl_3$) of compound 21



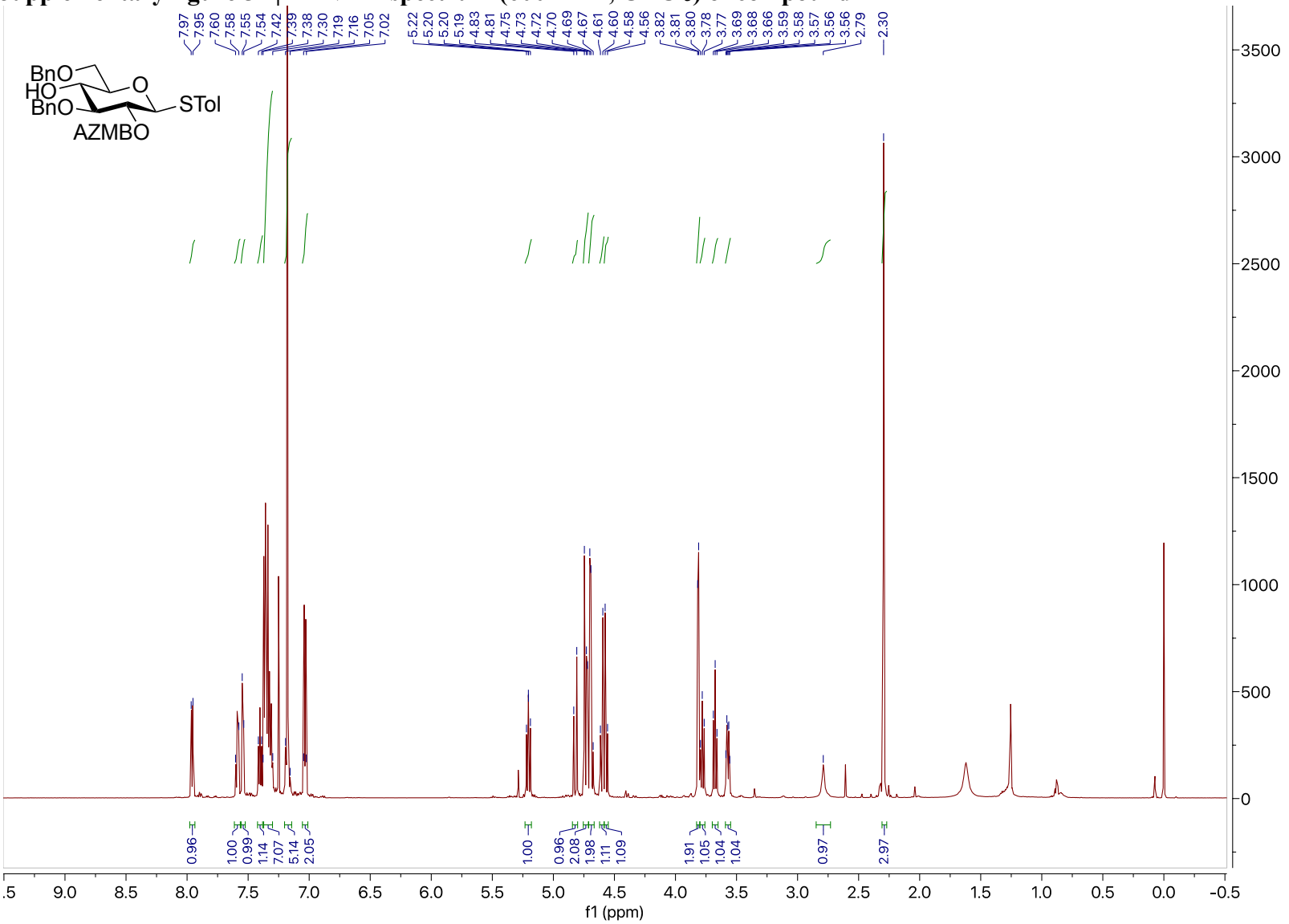
Supplementary figure 50 | ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound 21



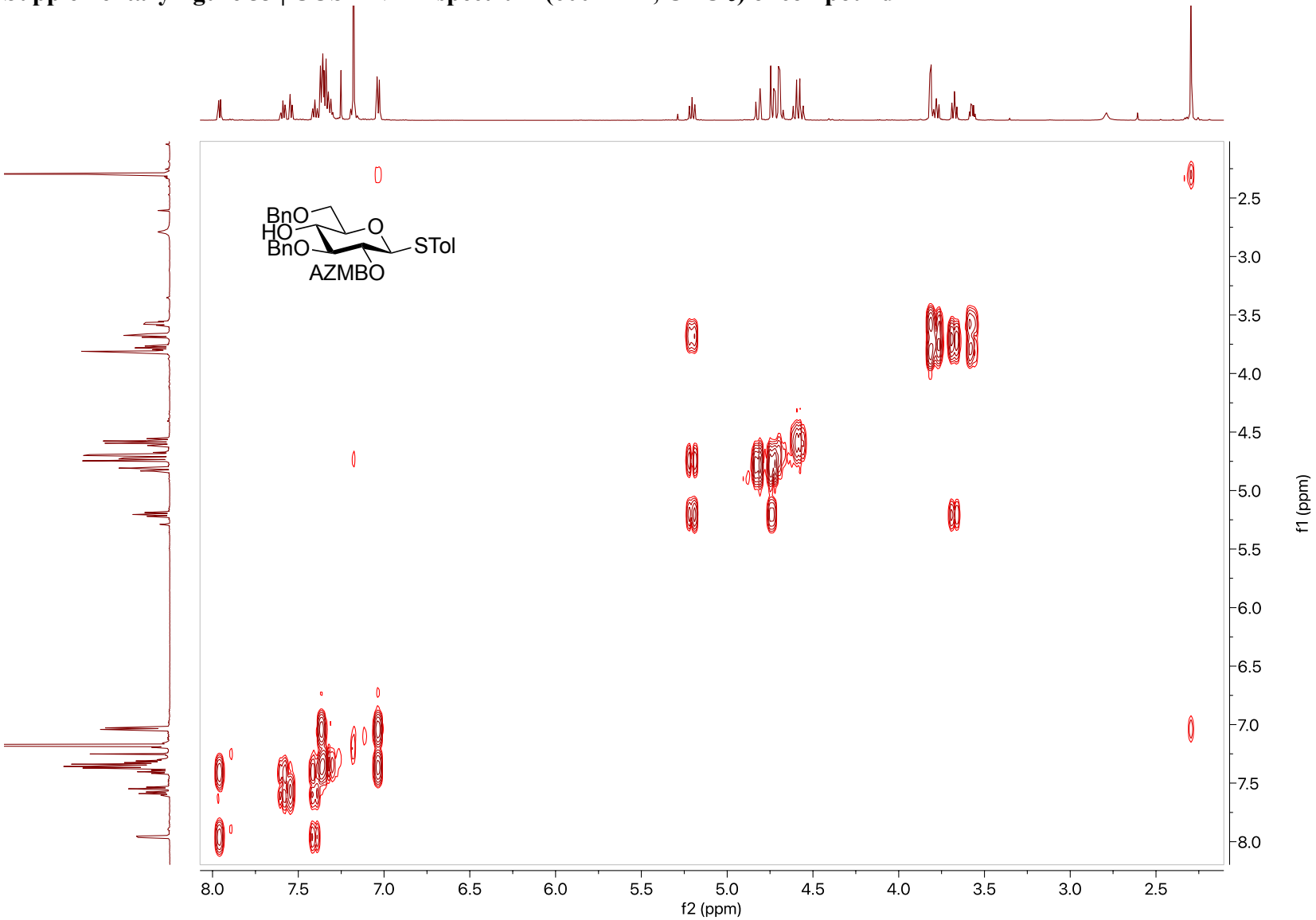
Supplementary figure 51 | HSQC NMR spectrum (300 MHz, $CDCl_3$) of compound 21



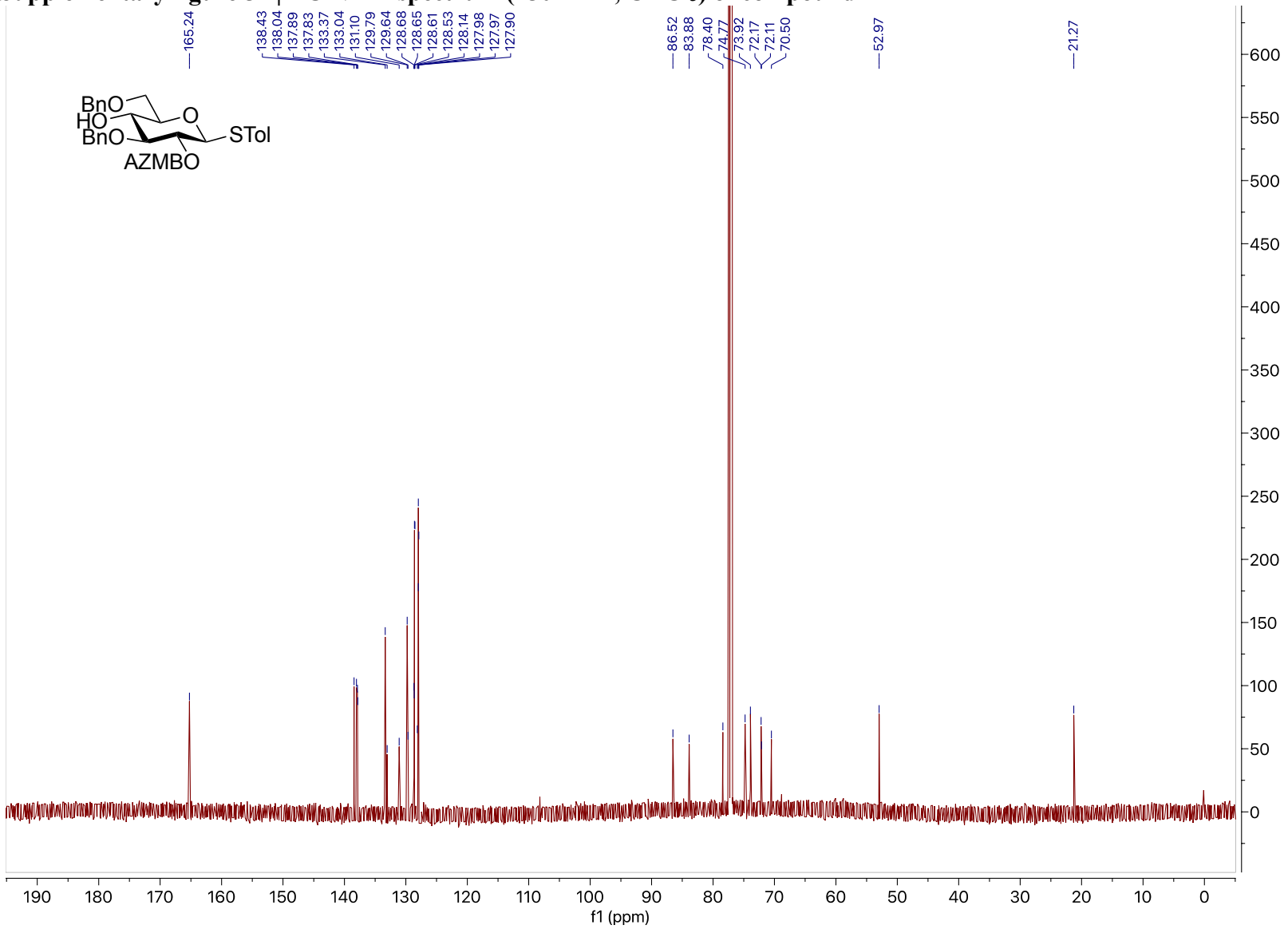
Supplementary figure 52 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 22



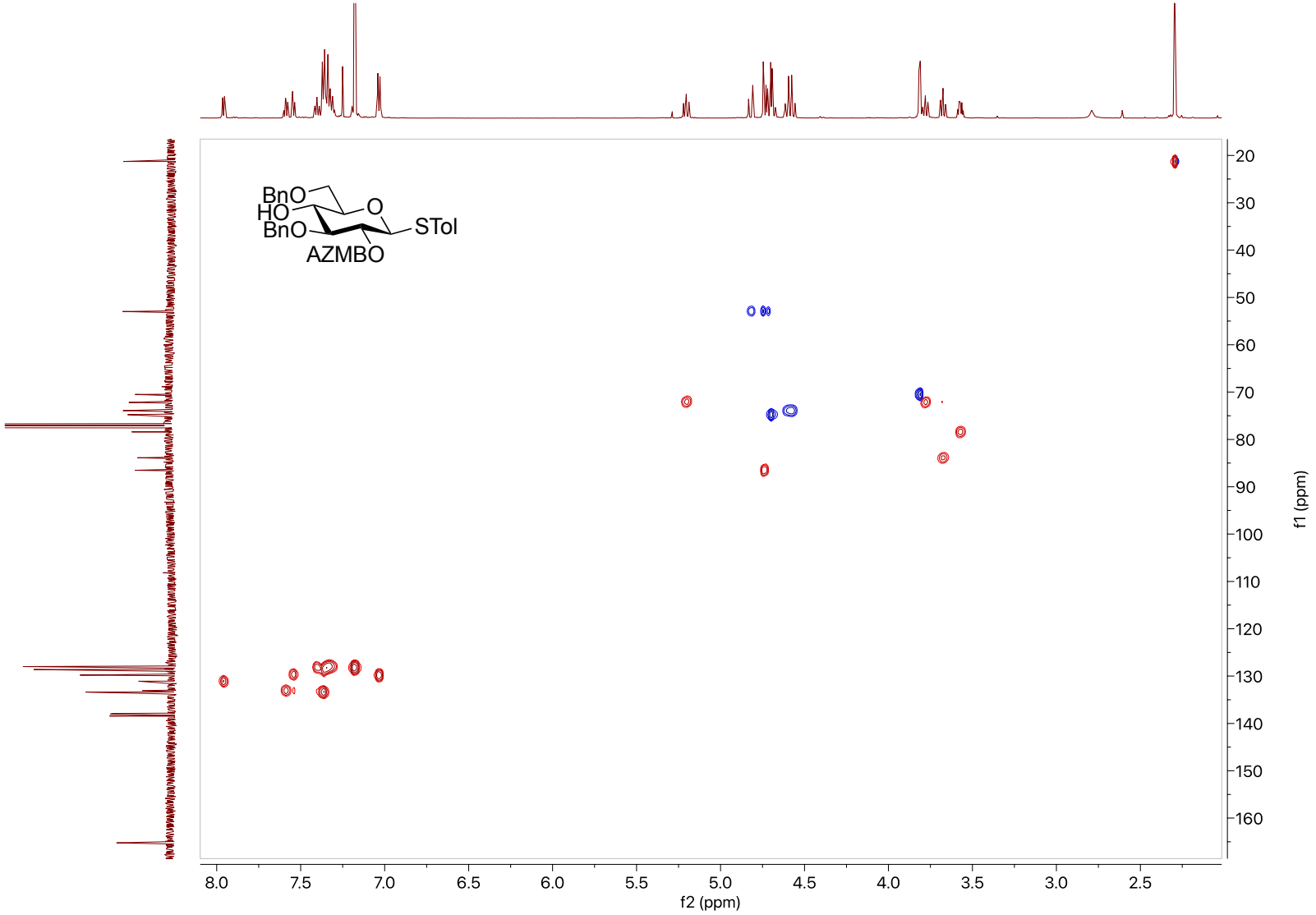
Supplementary figure 53 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 22



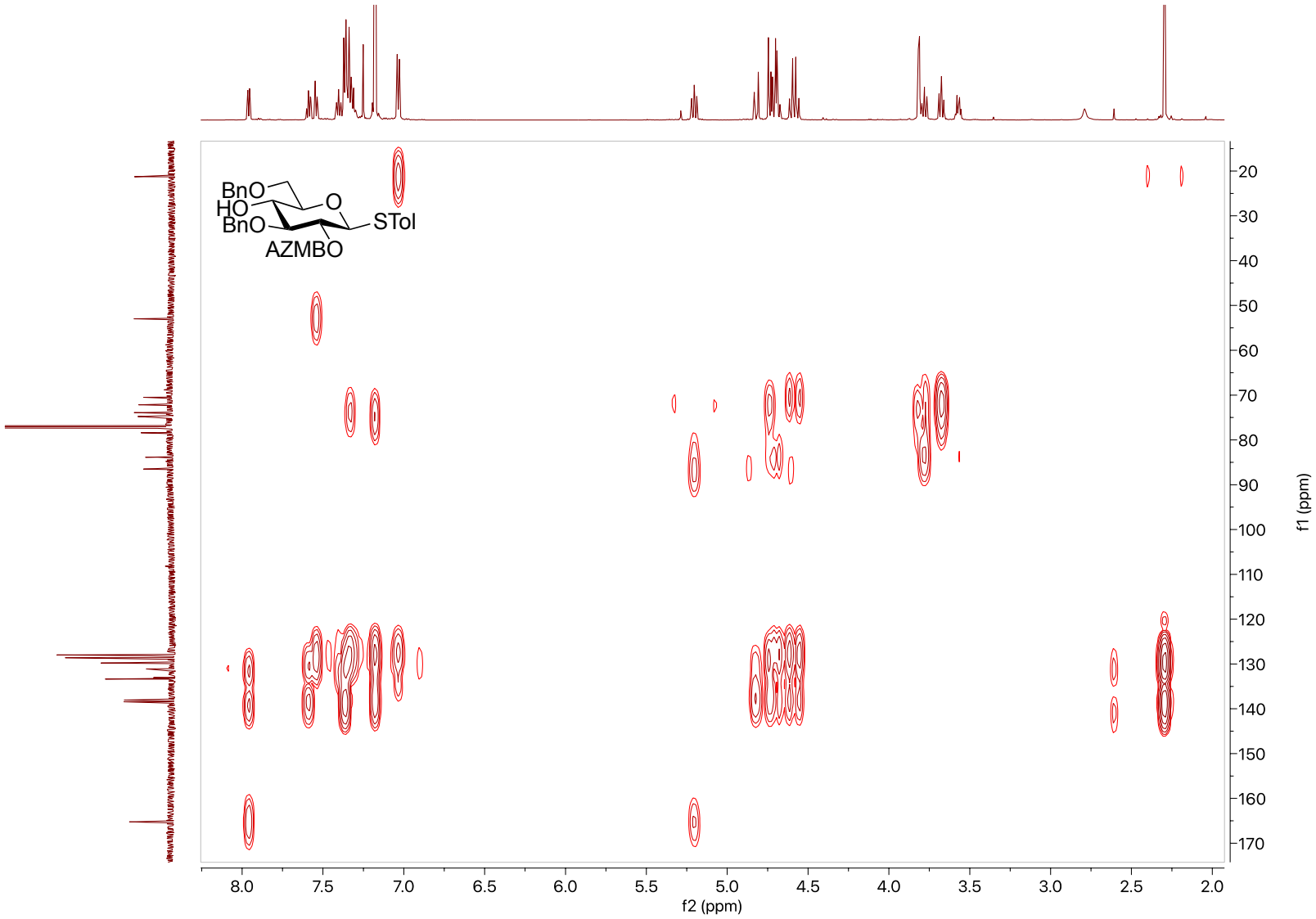
Supplementary figure 54 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 22



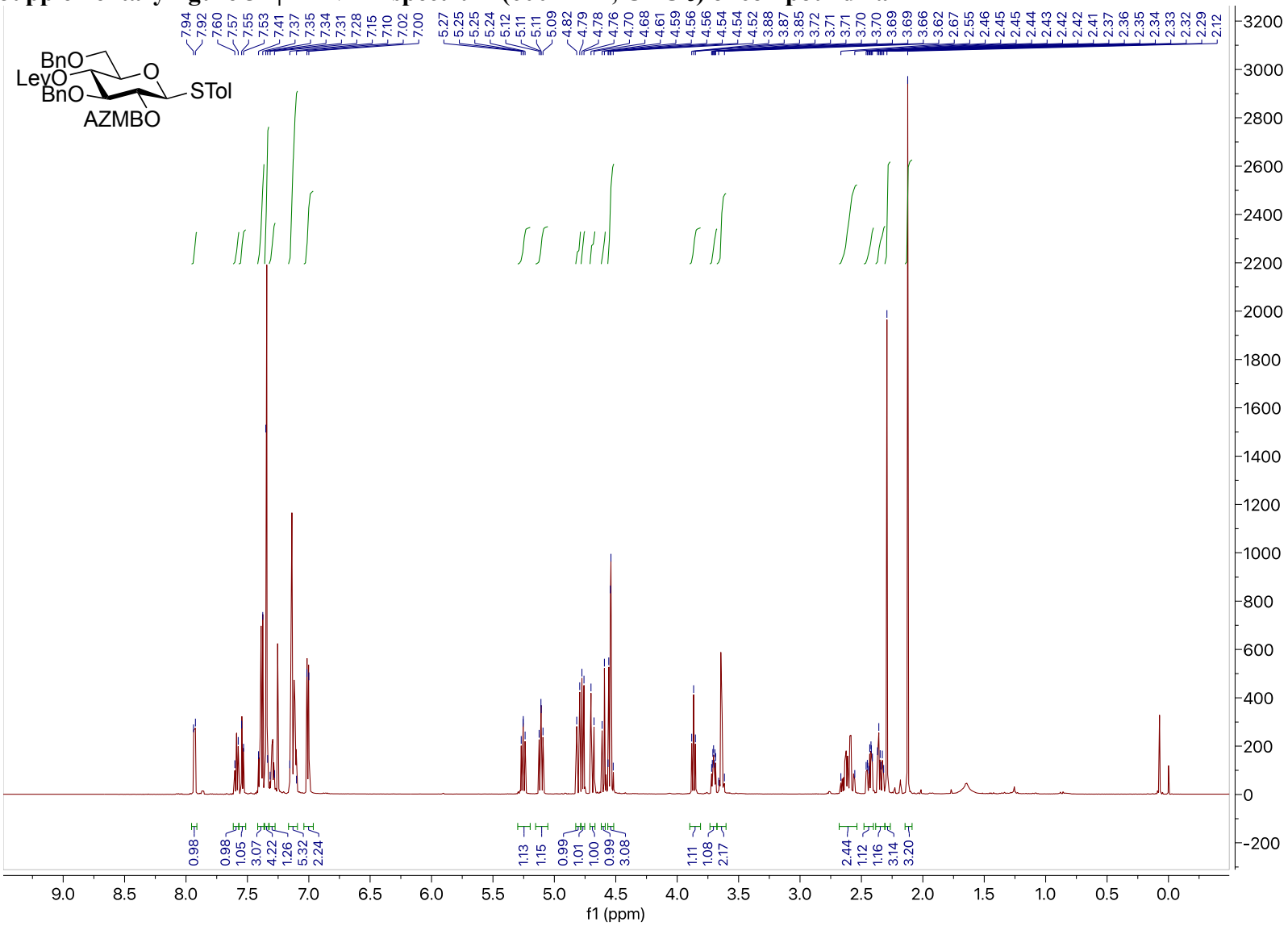
Supplementary figure 55 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 22



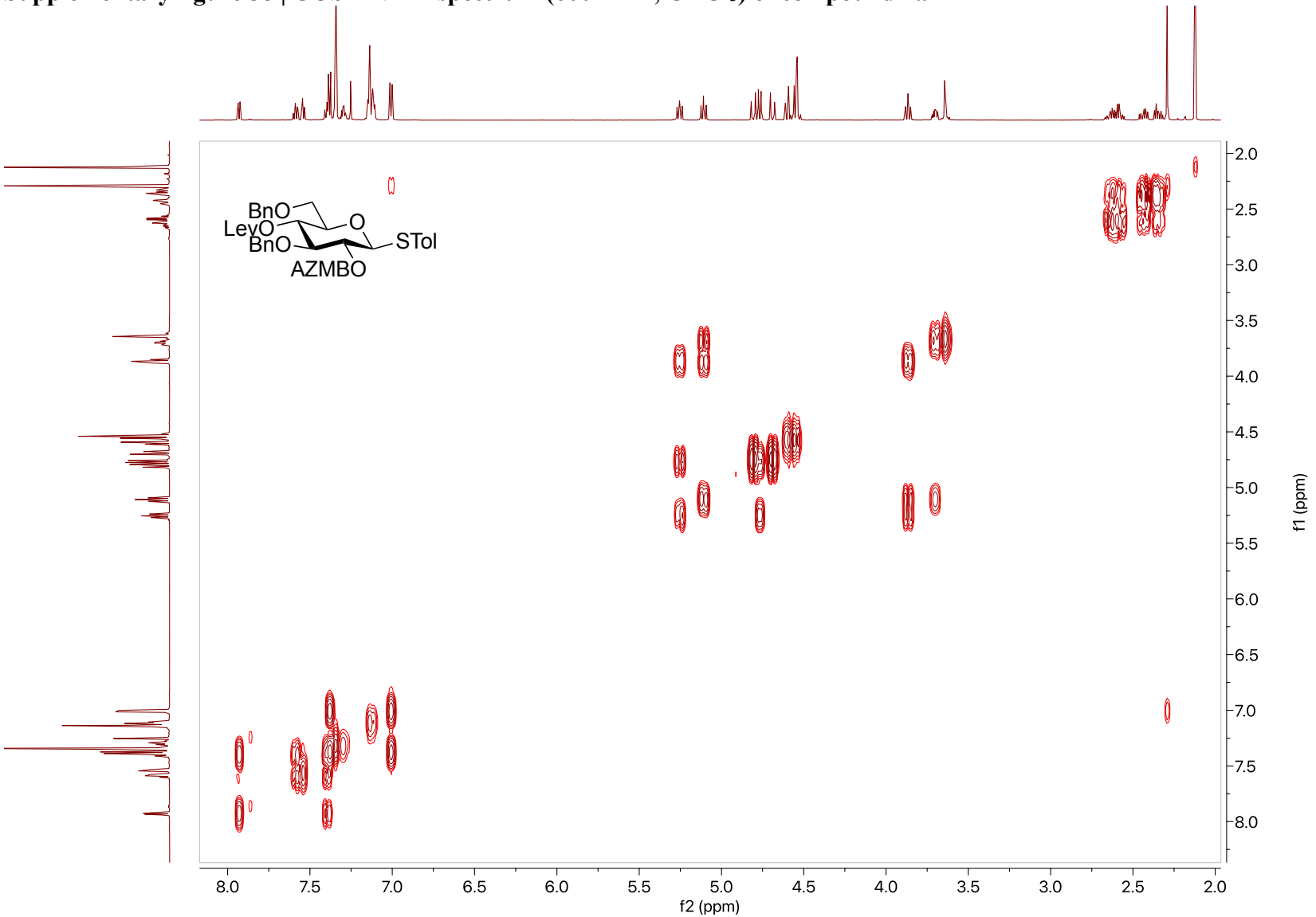
Supplementary figure 56 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 22



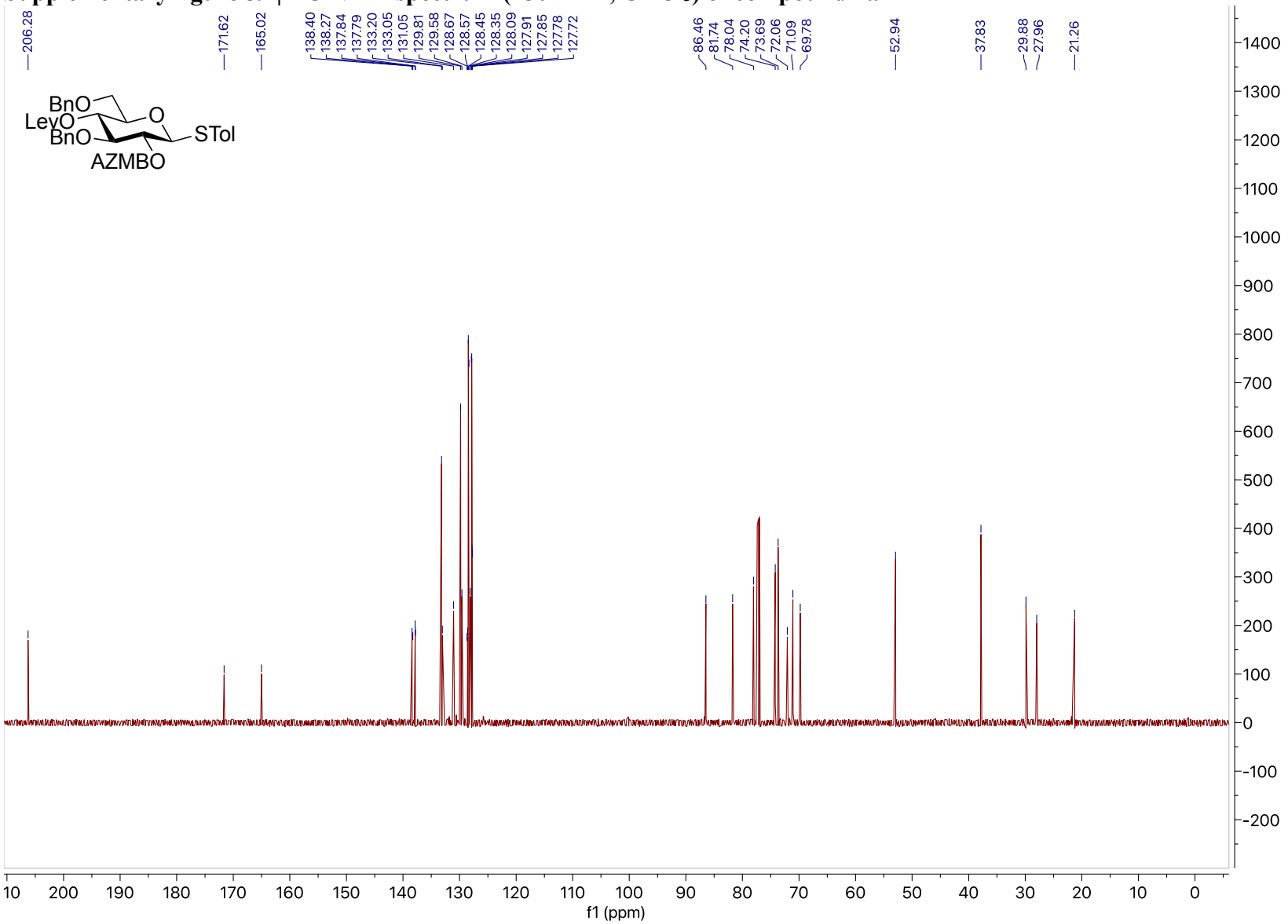
Supplementary figure 57 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 7a



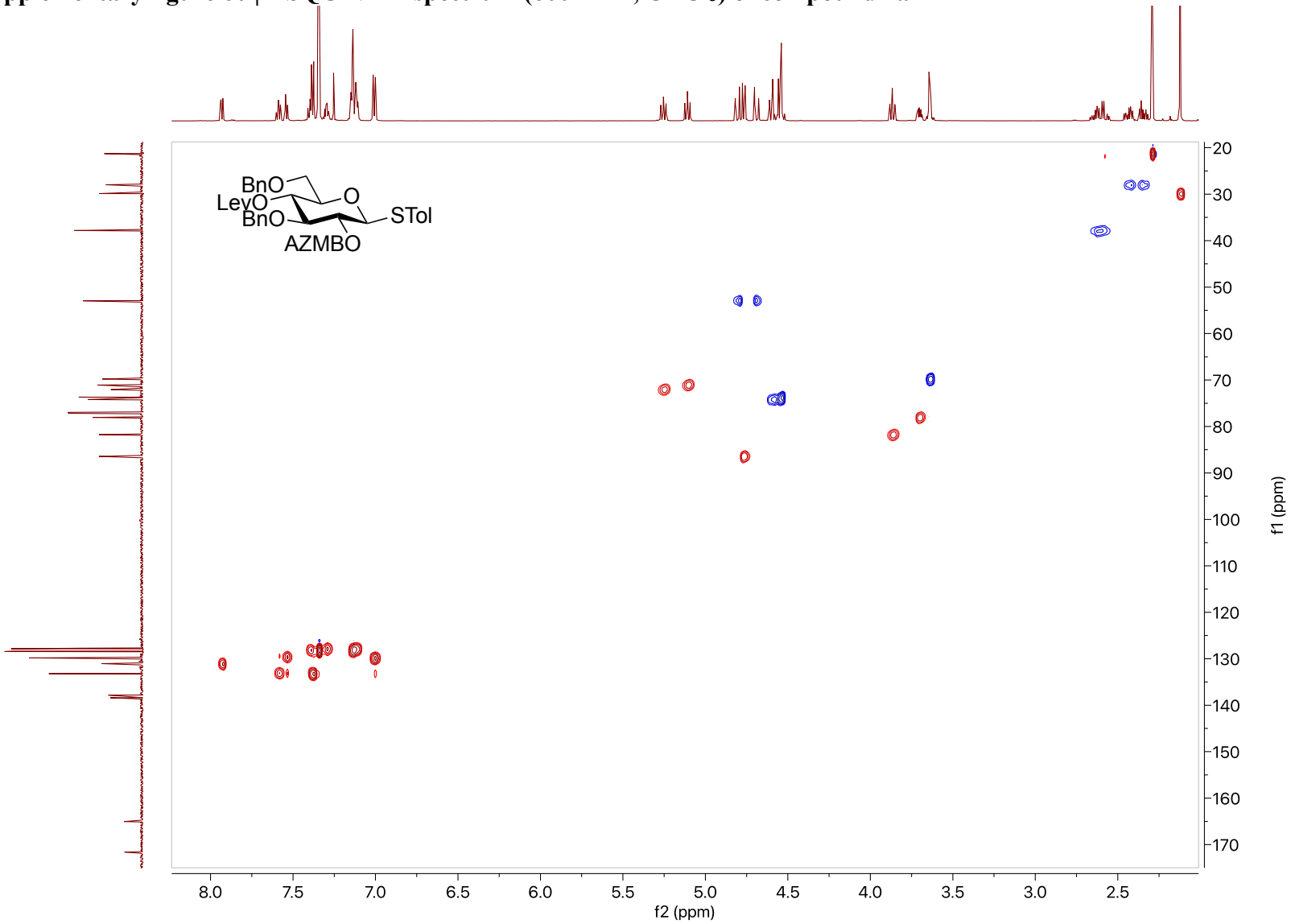
Supplementary figure 58 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 7a



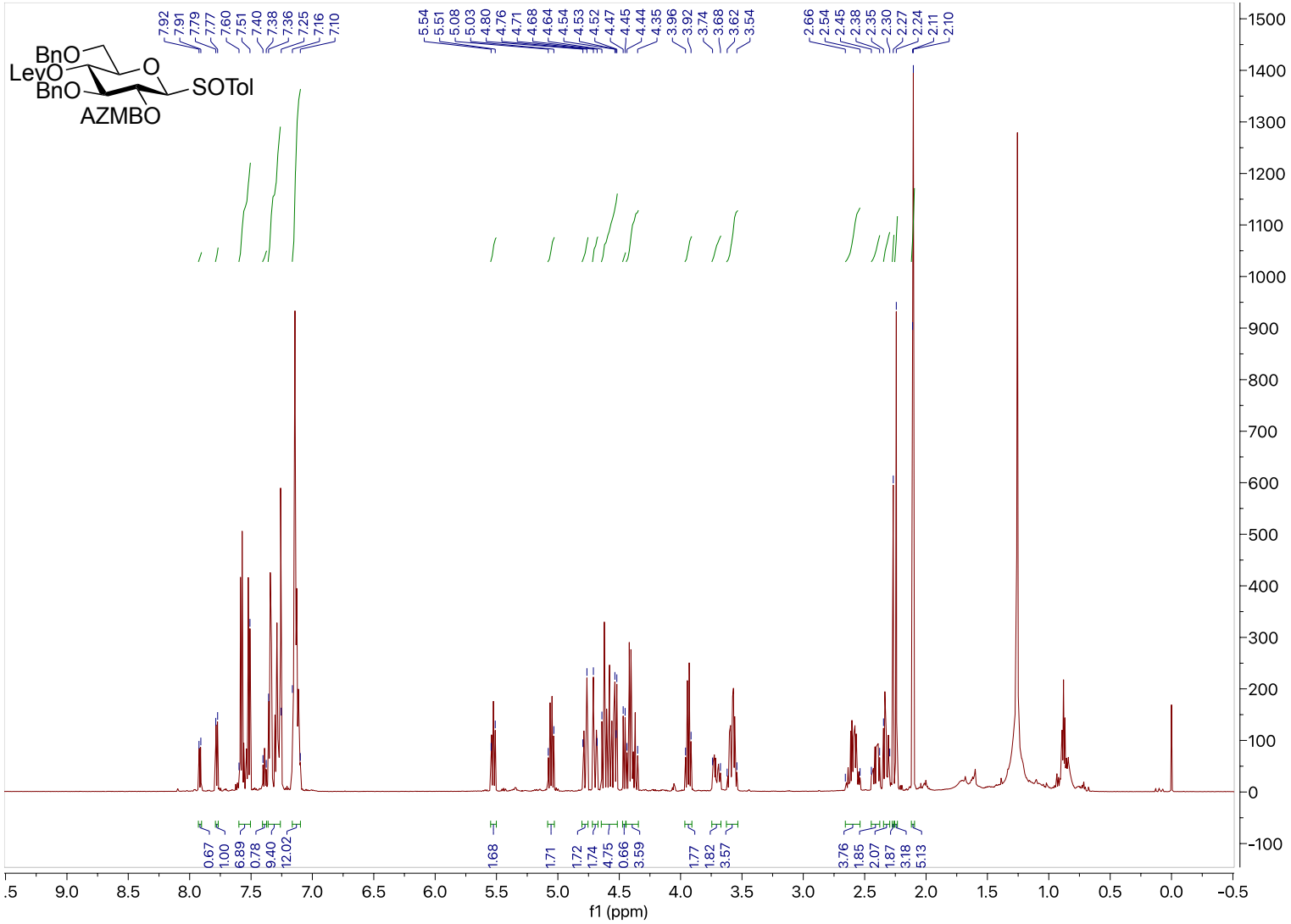
Supplementary figure 59 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 7a



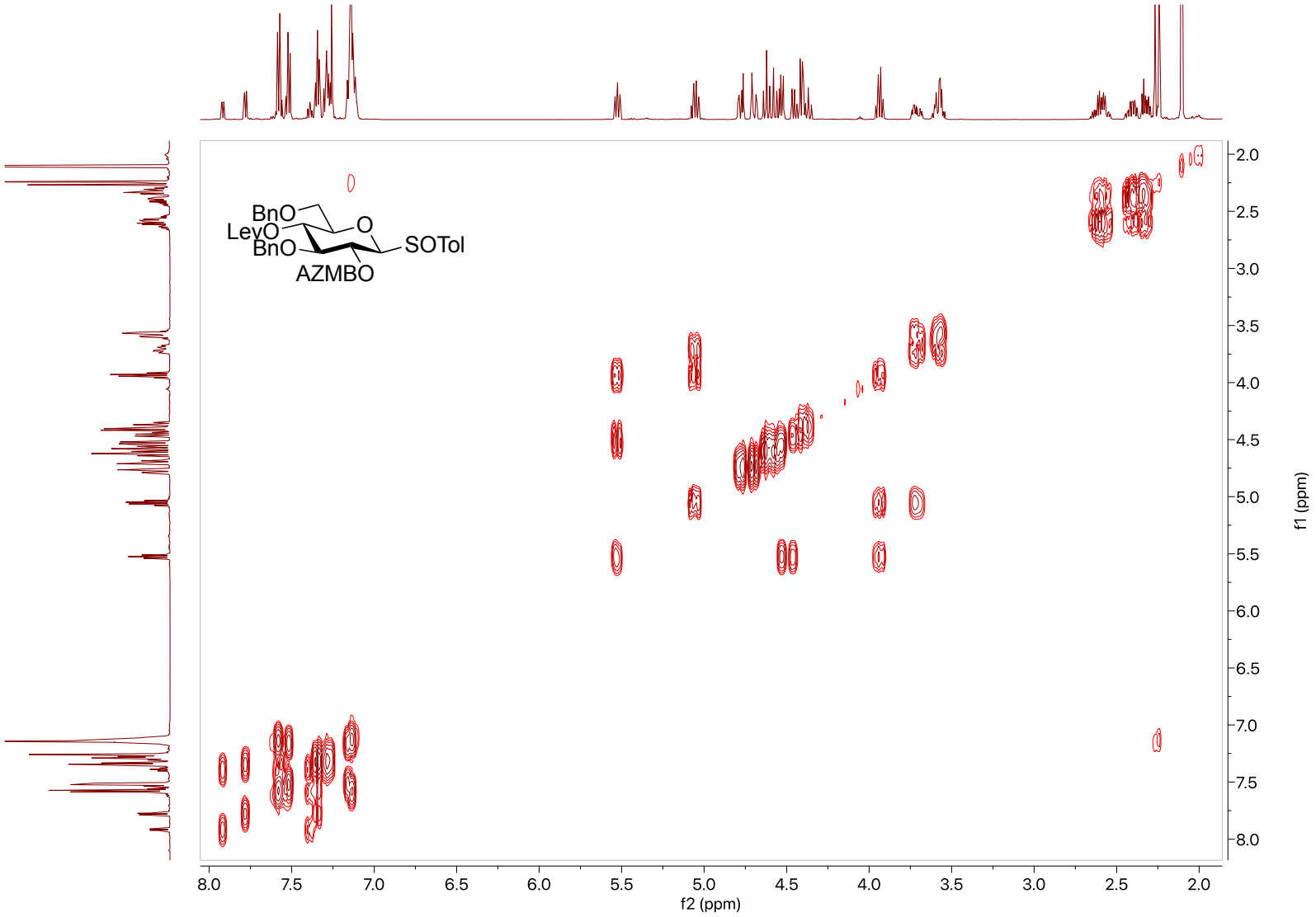
Supplementary figure 60 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 7a



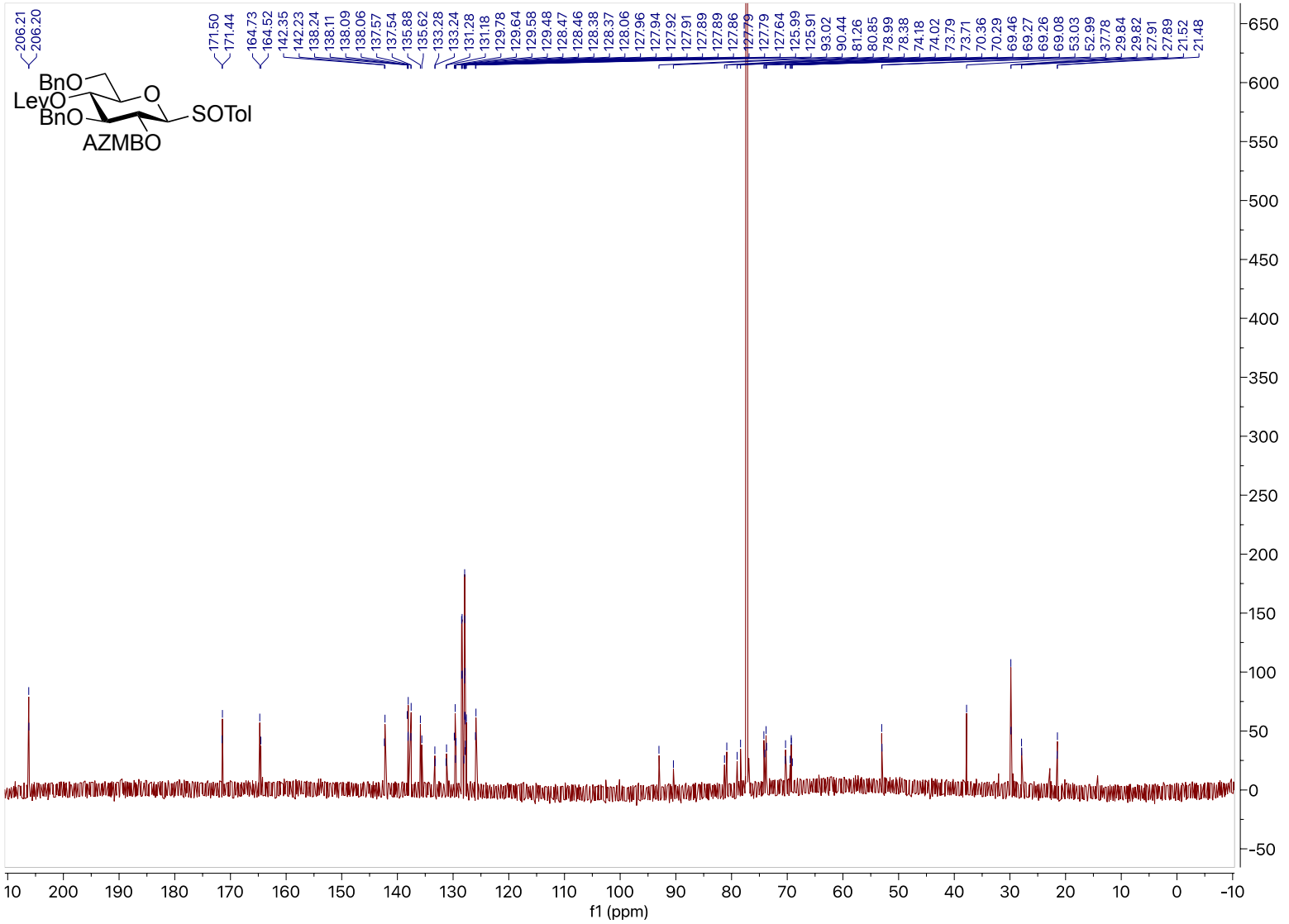
Supplementary figure 61 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 7b



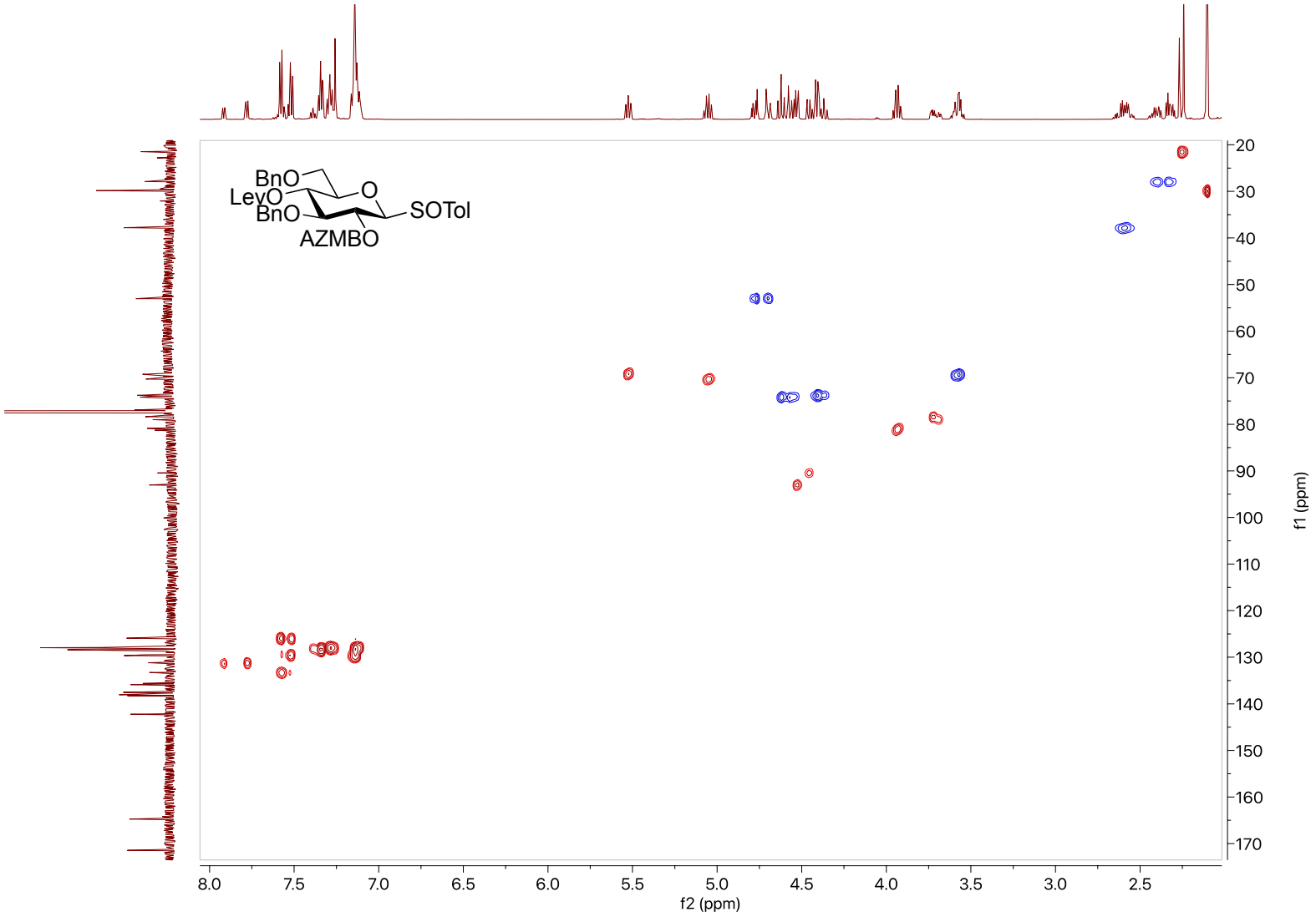
Supplementary figure 62 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 7b



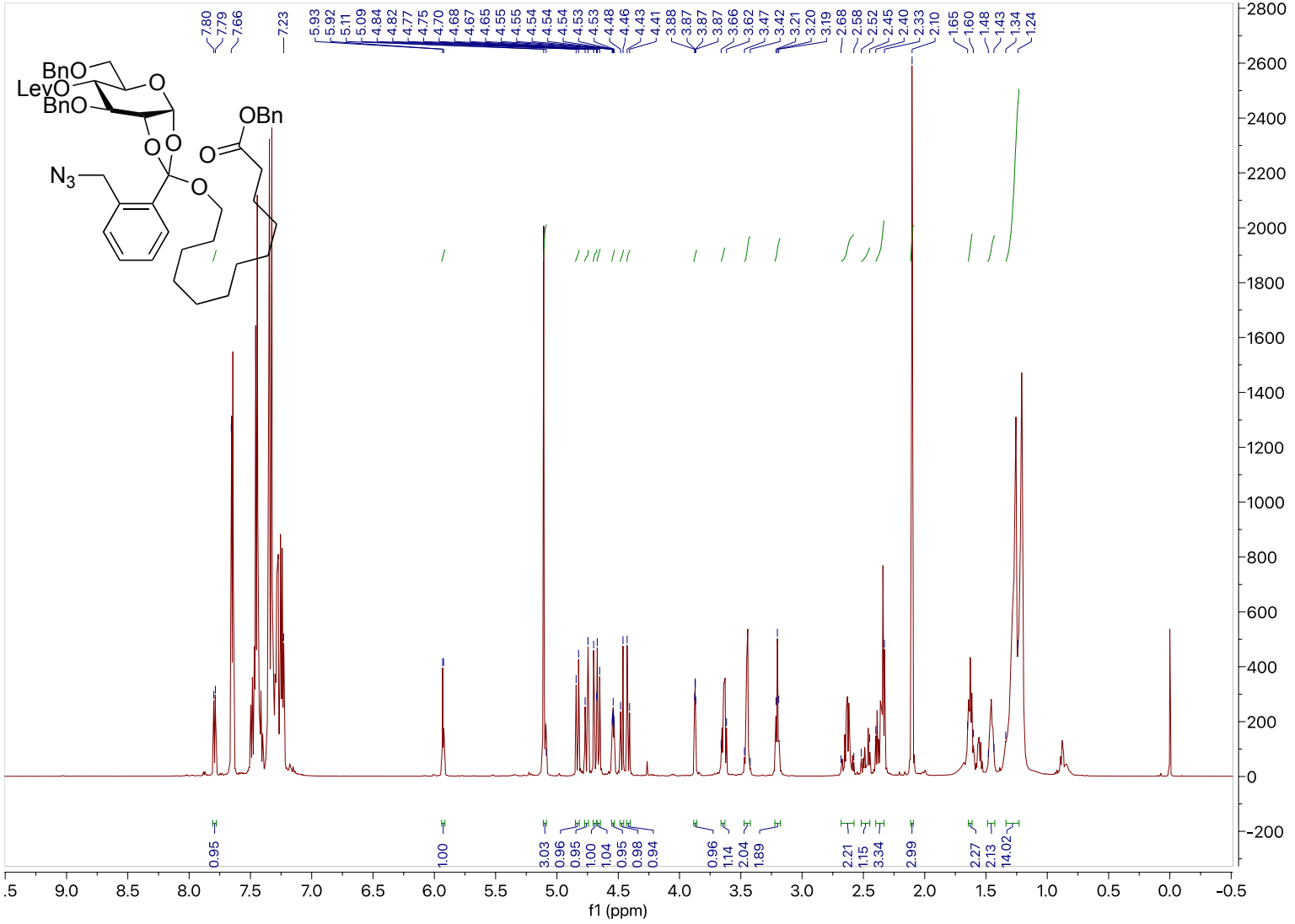
Supplementary figure 63 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 7b



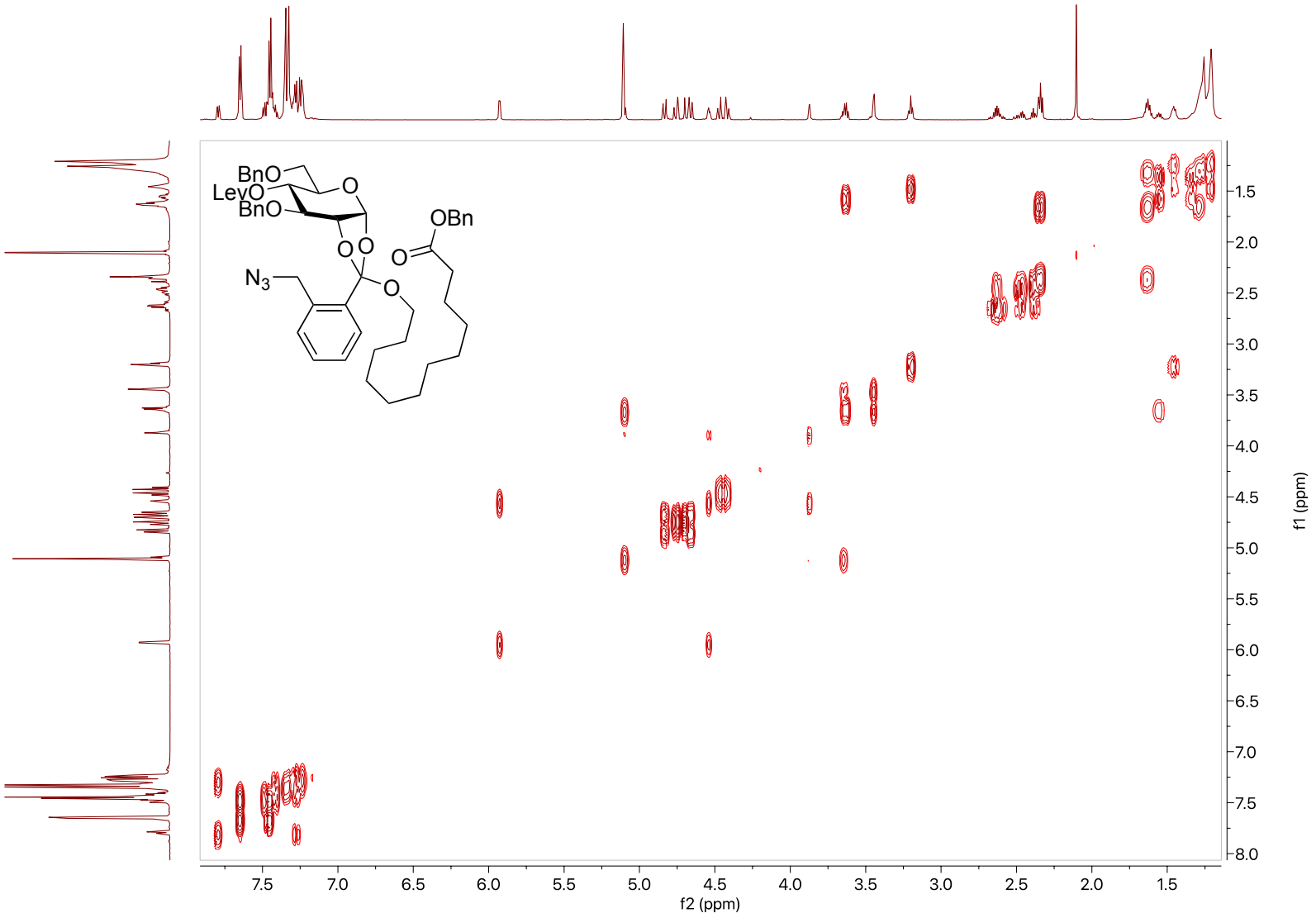
Supplementary figure 64 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 7b



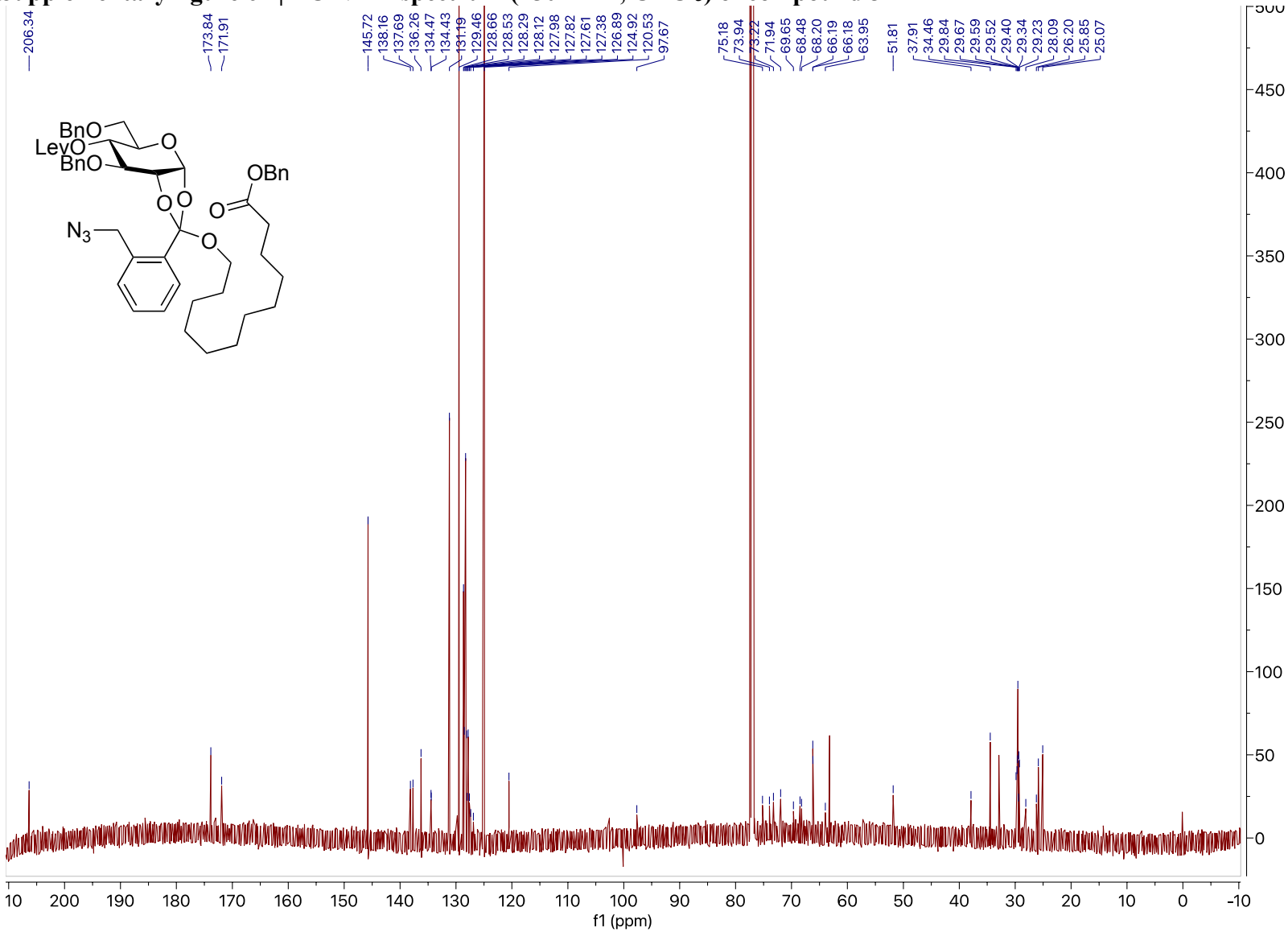
Supplementary figure 65 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 34



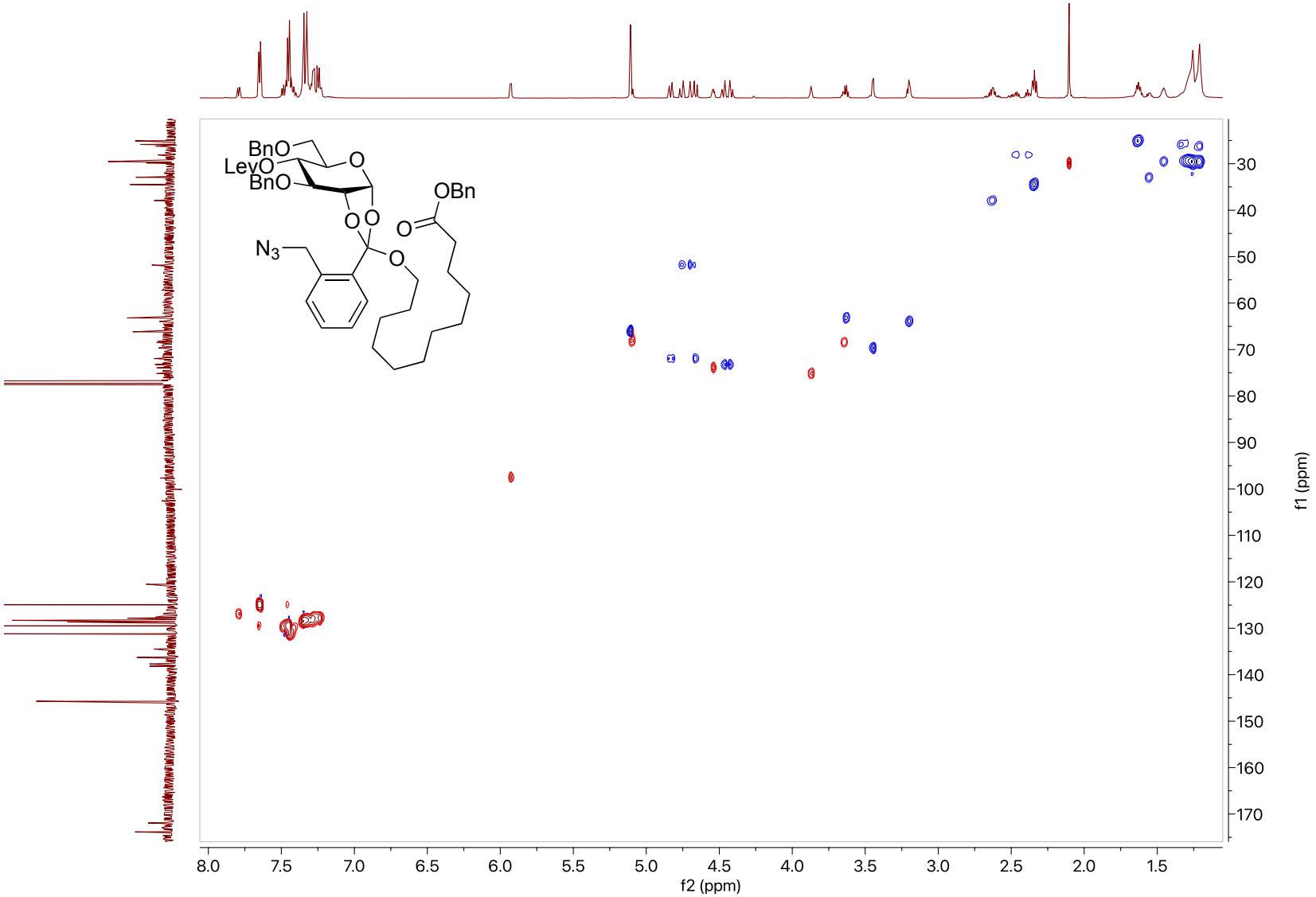
Supplementary figure 66 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 34



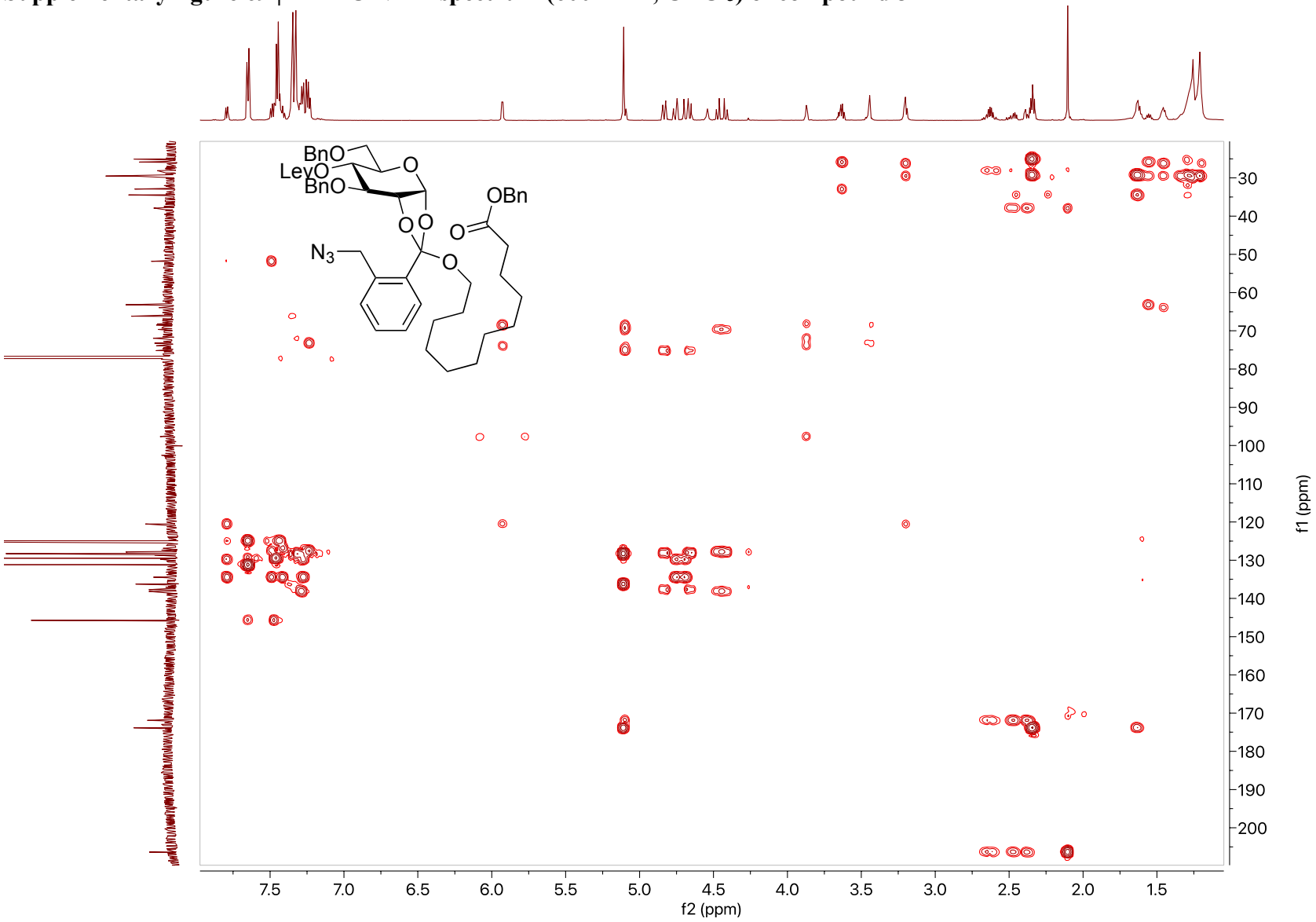
Supplementary figure 67 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 34



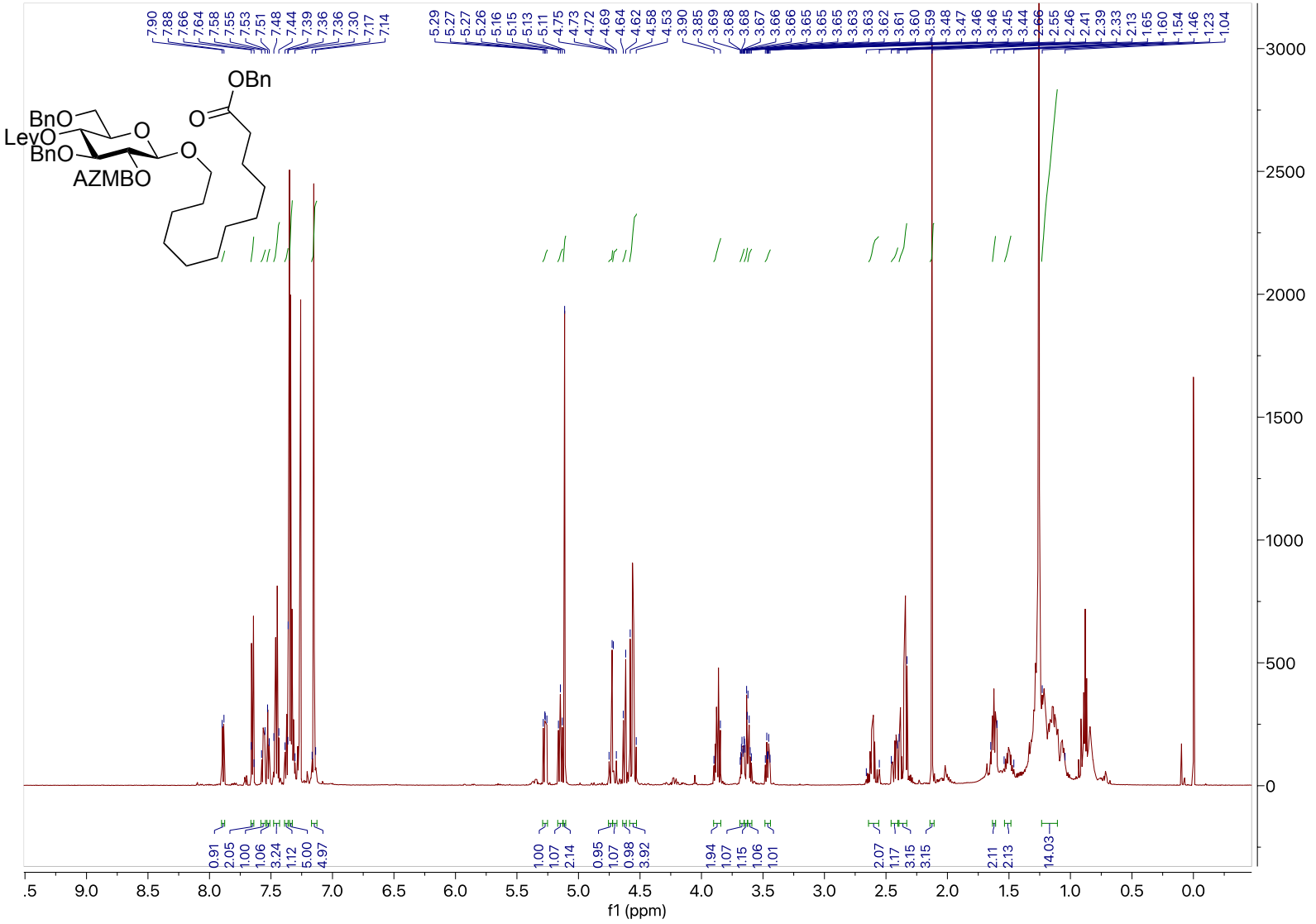
Supplementary figure 68 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 34



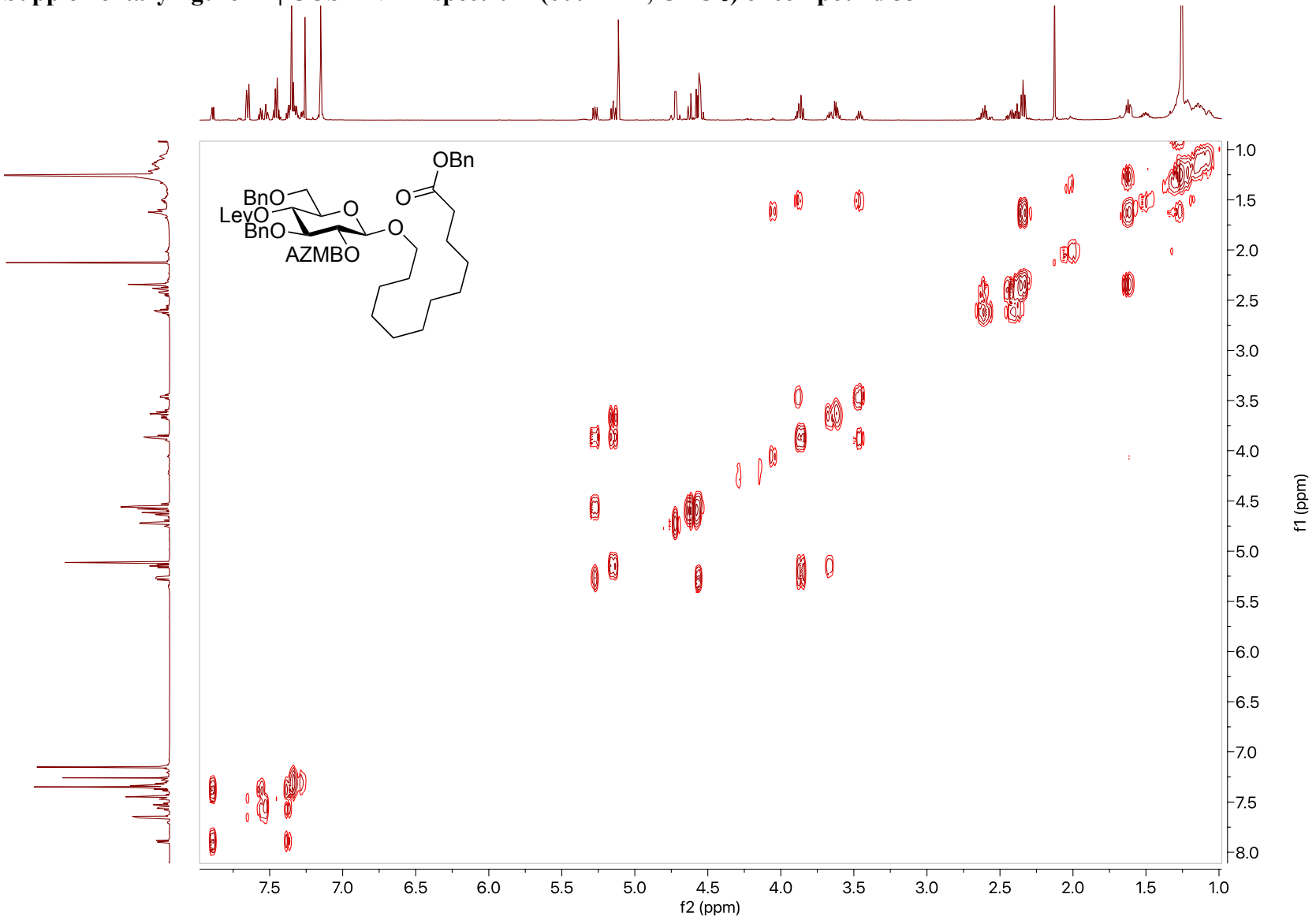
Supplementary figure 69 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 34



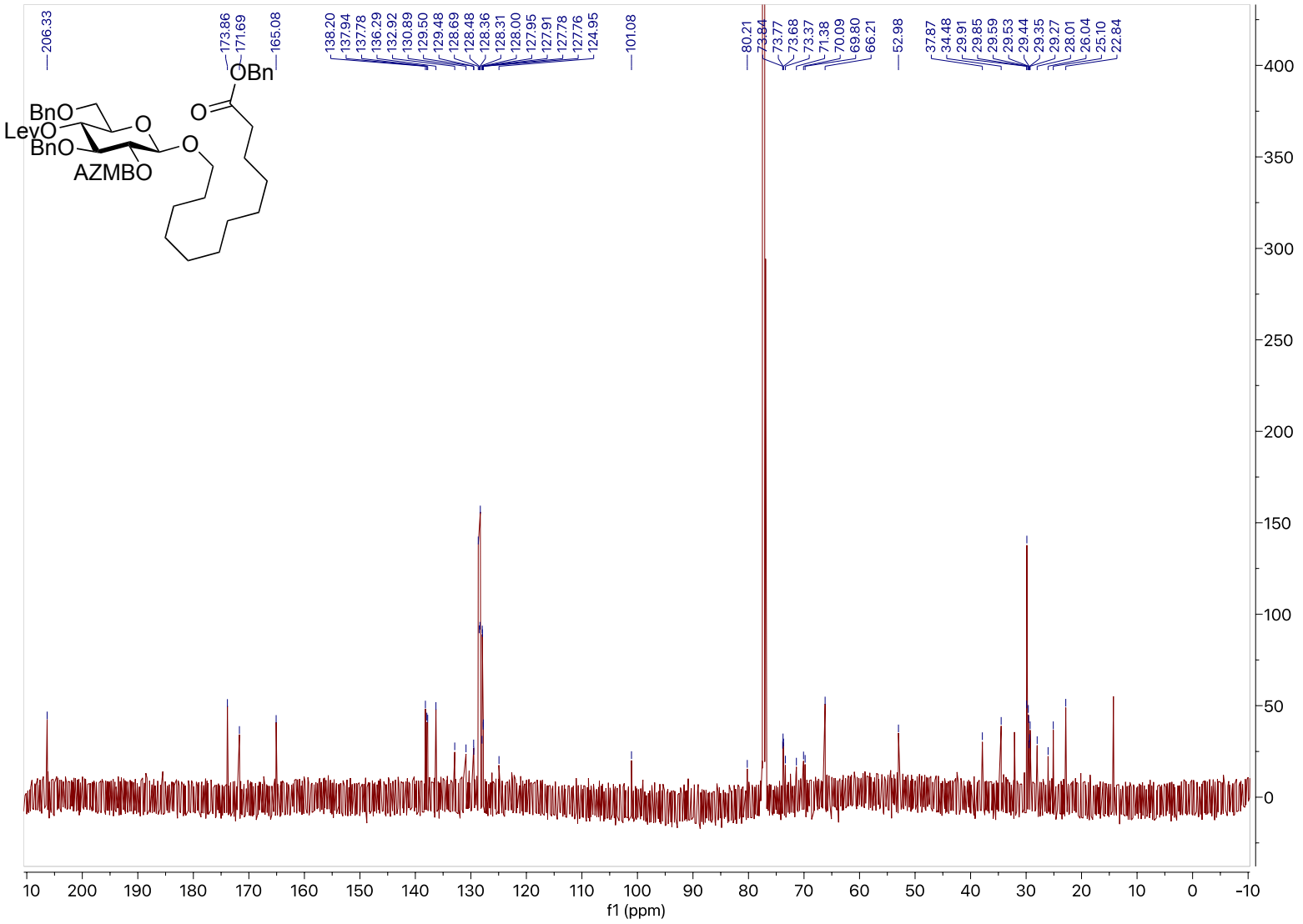
Supplementary figure 70 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 33



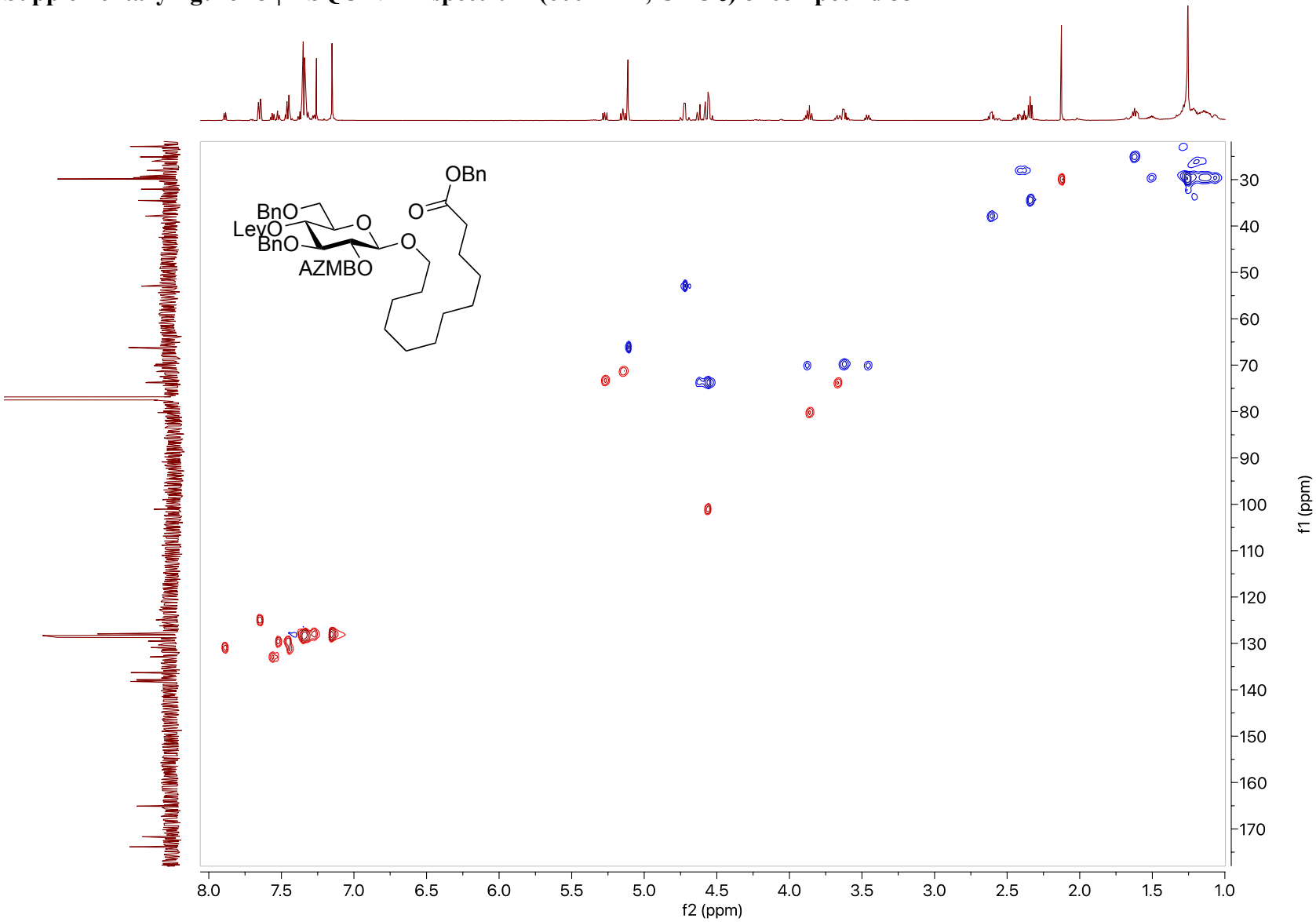
Supplementary figure 71 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 33



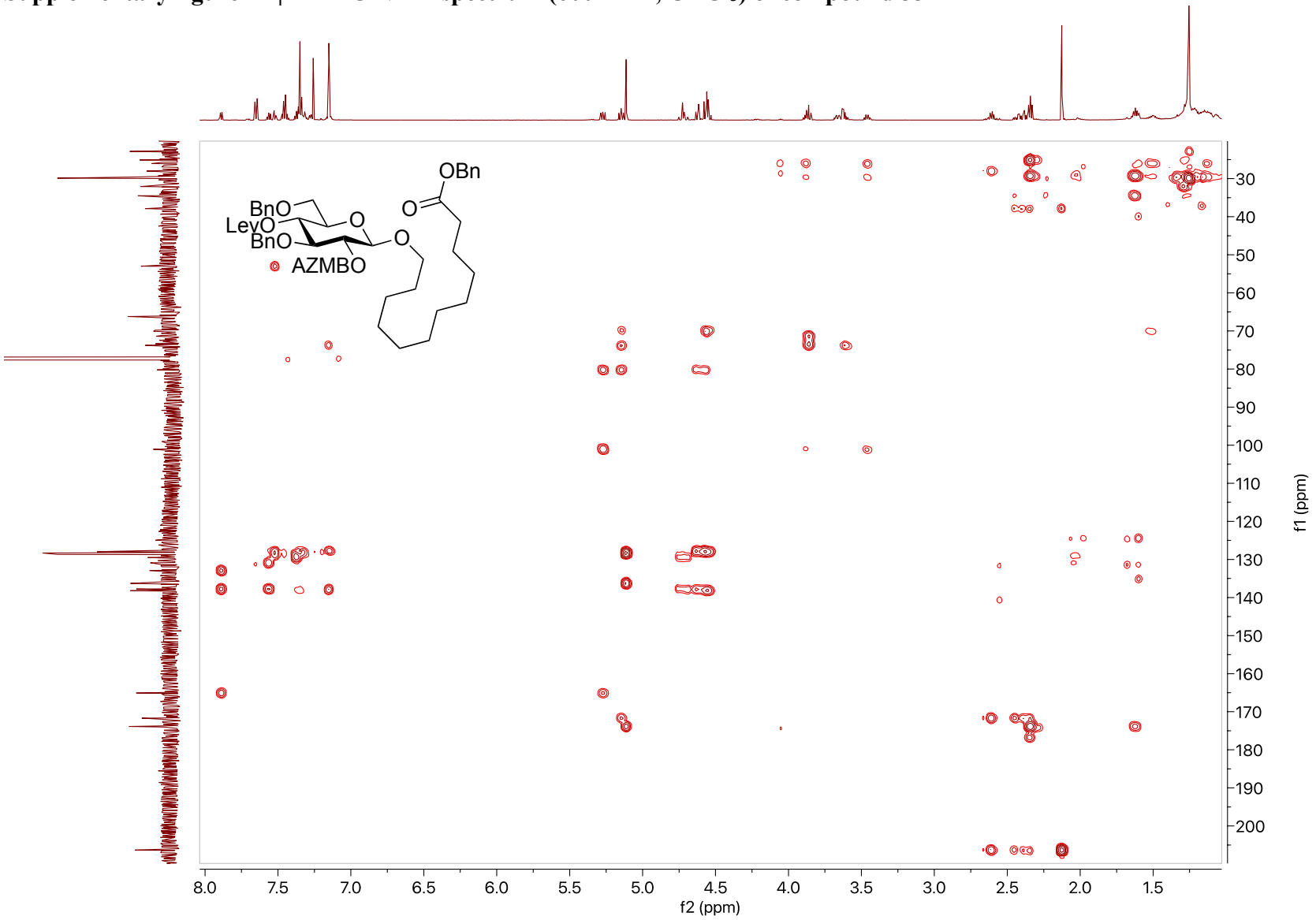
Supplementary figure 72 | ^{13}C NMR spectrum (600 MHz, $CDCl_3$) of compound 33



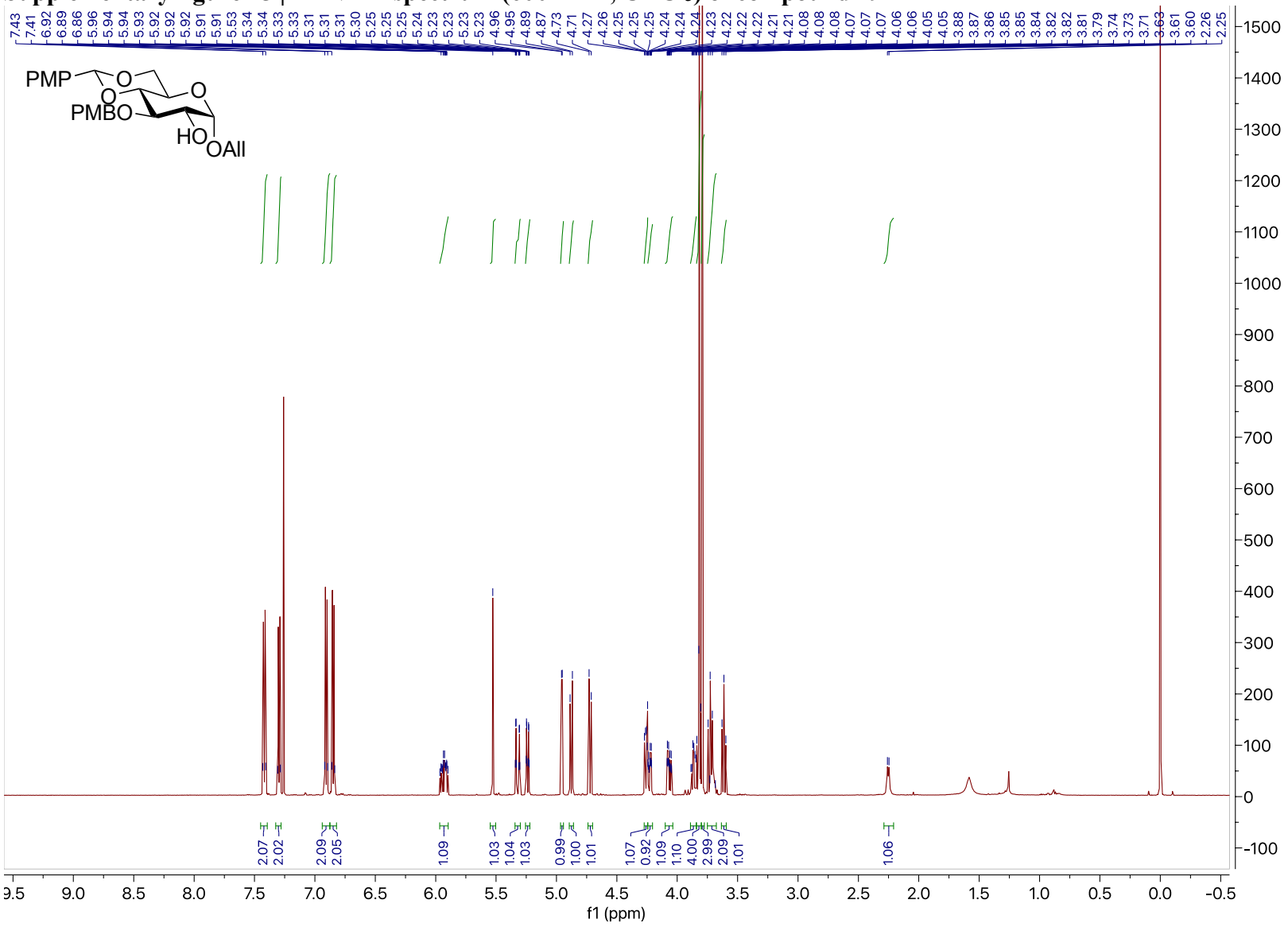
Supplementary figure 73 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 33



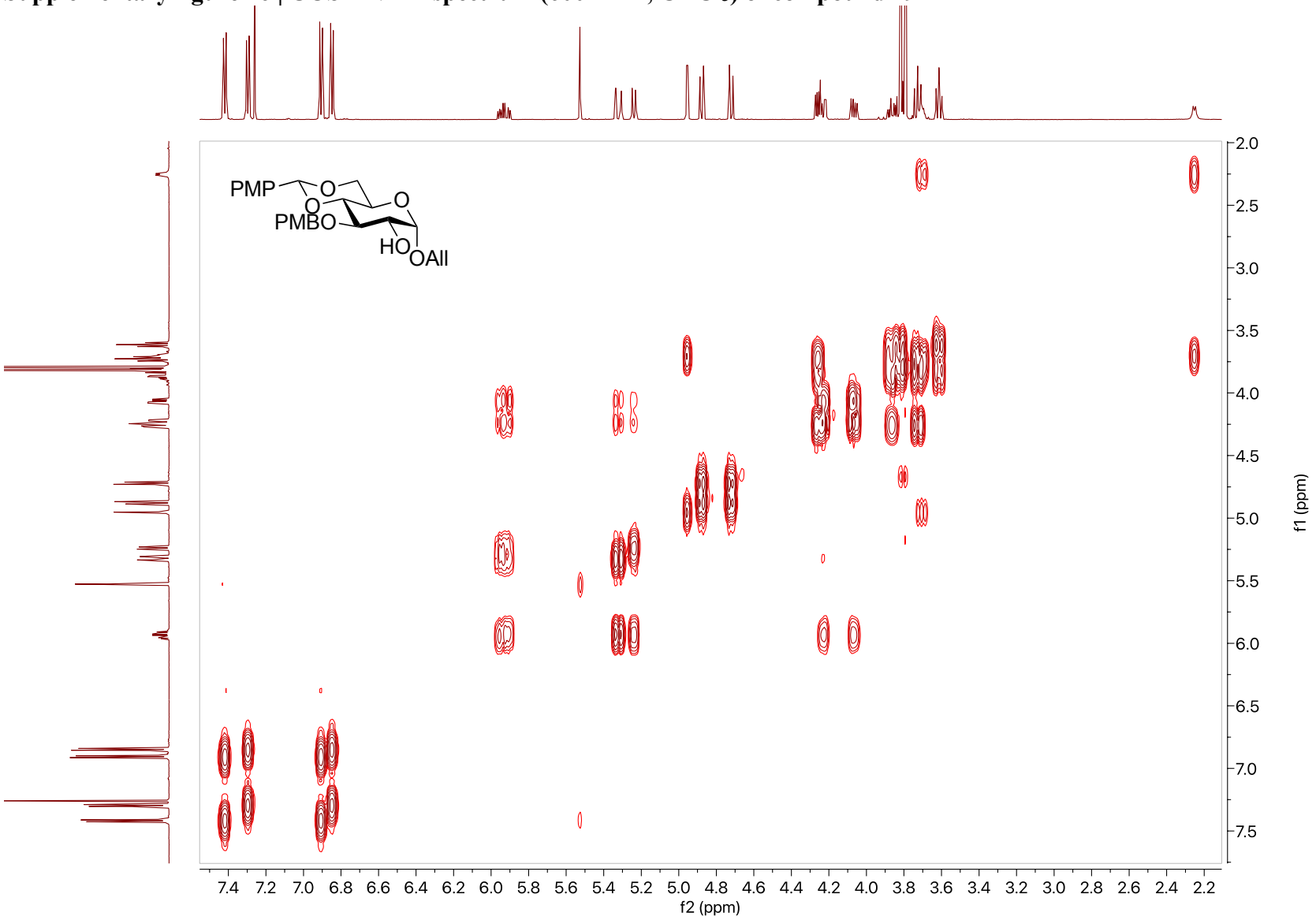
Supplementary figure 74 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 33



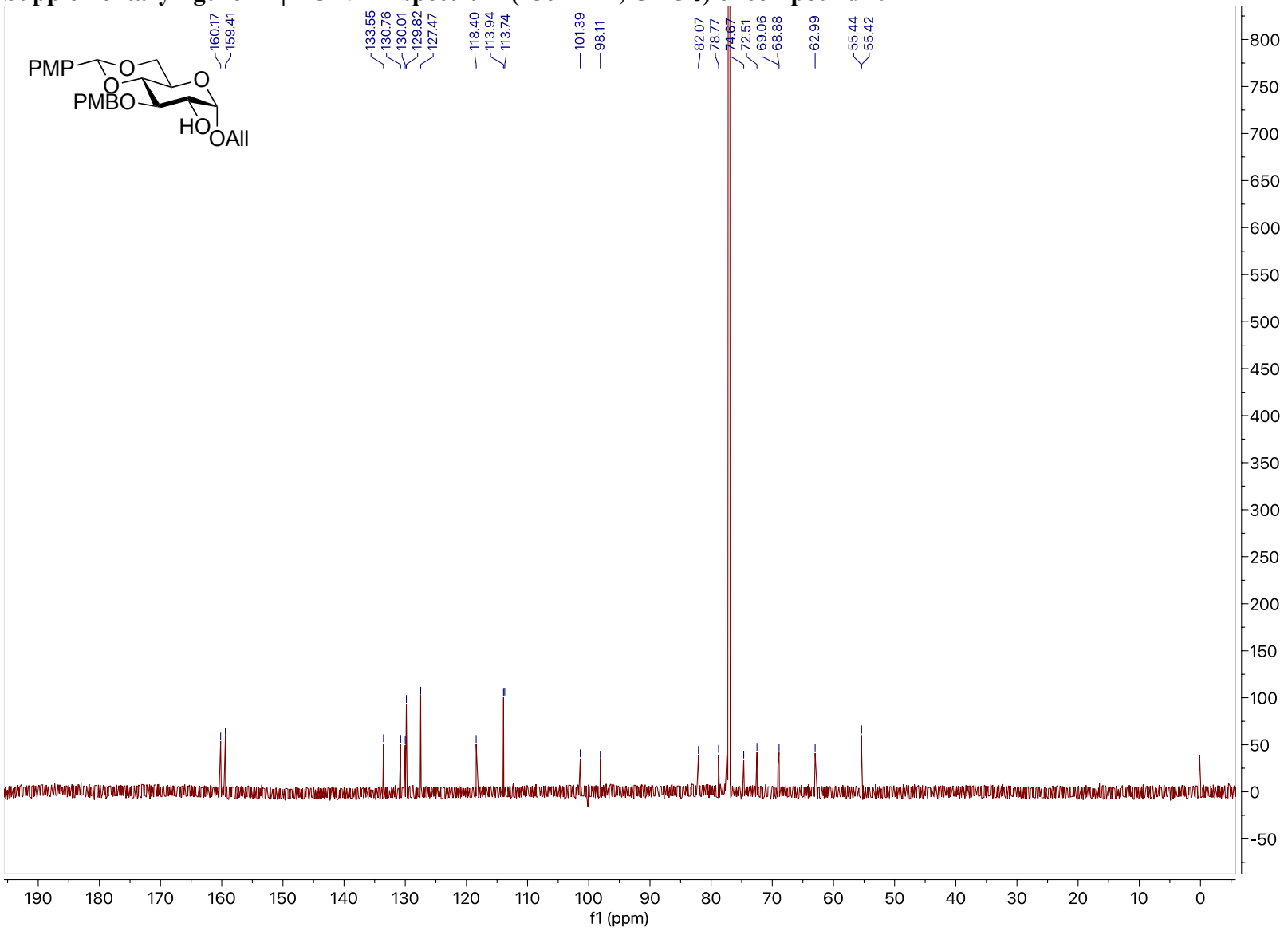
Supplementary figure 75 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 29



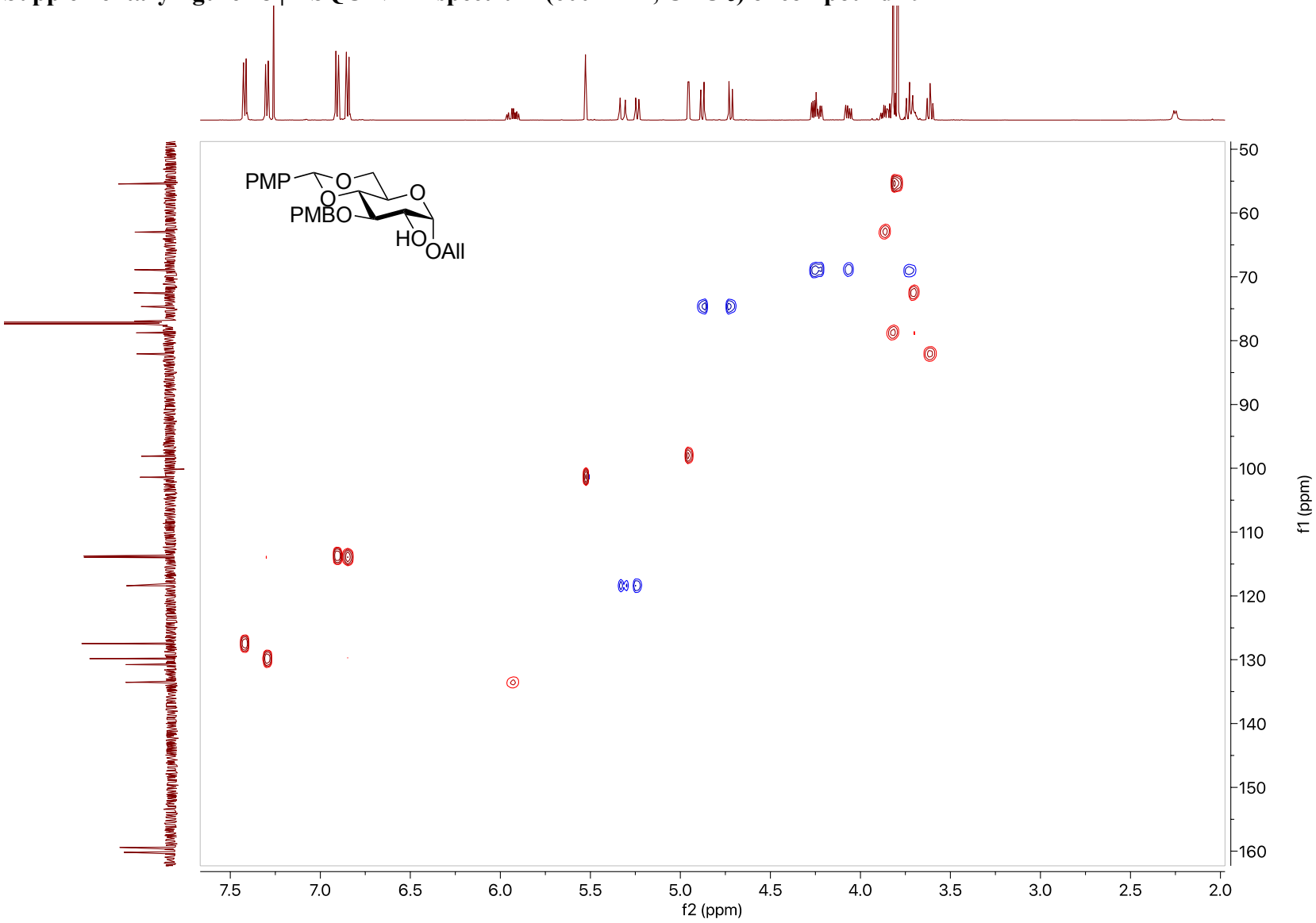
Supplementary figure 76 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 29



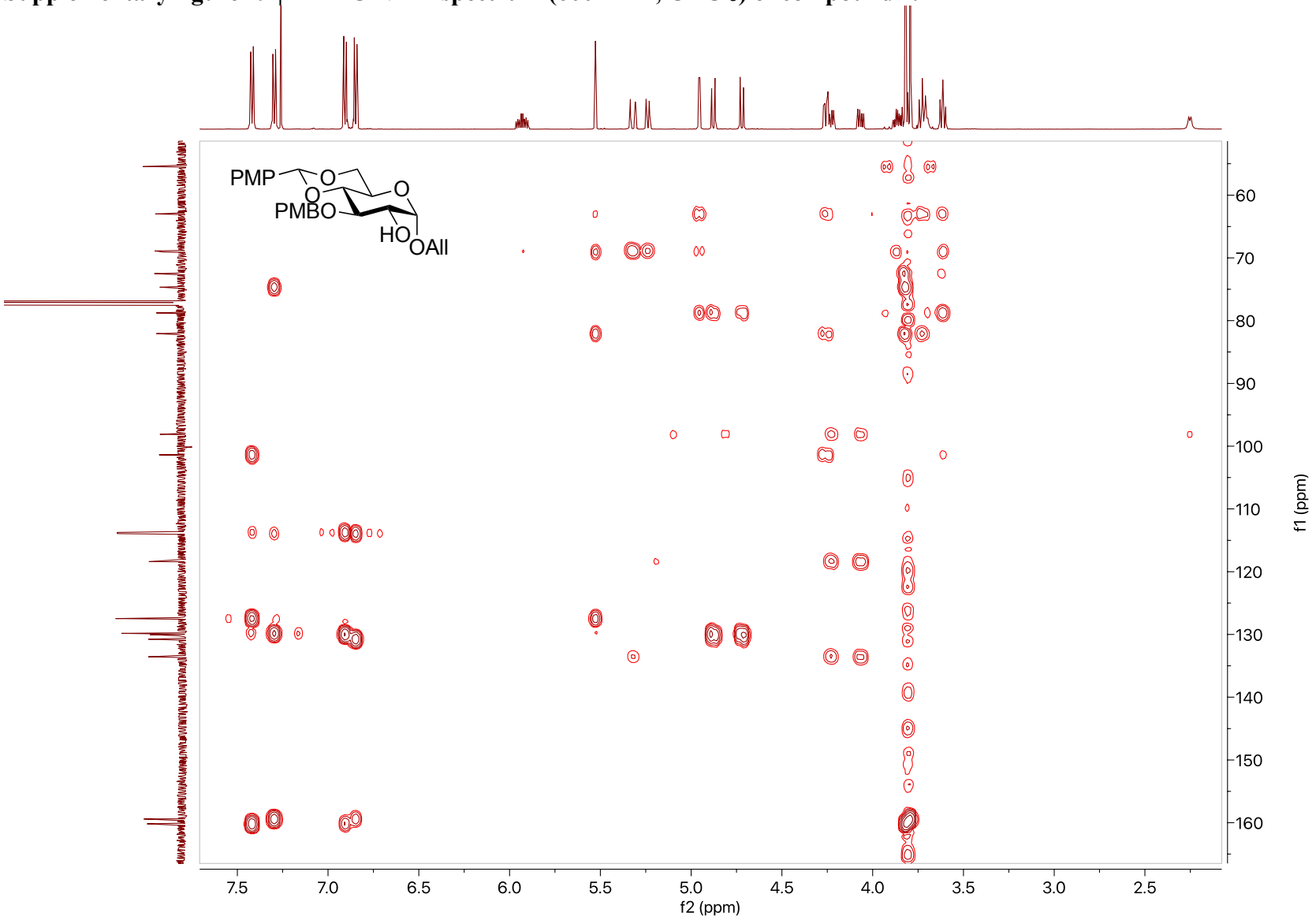
Supplementary figure 77 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 29



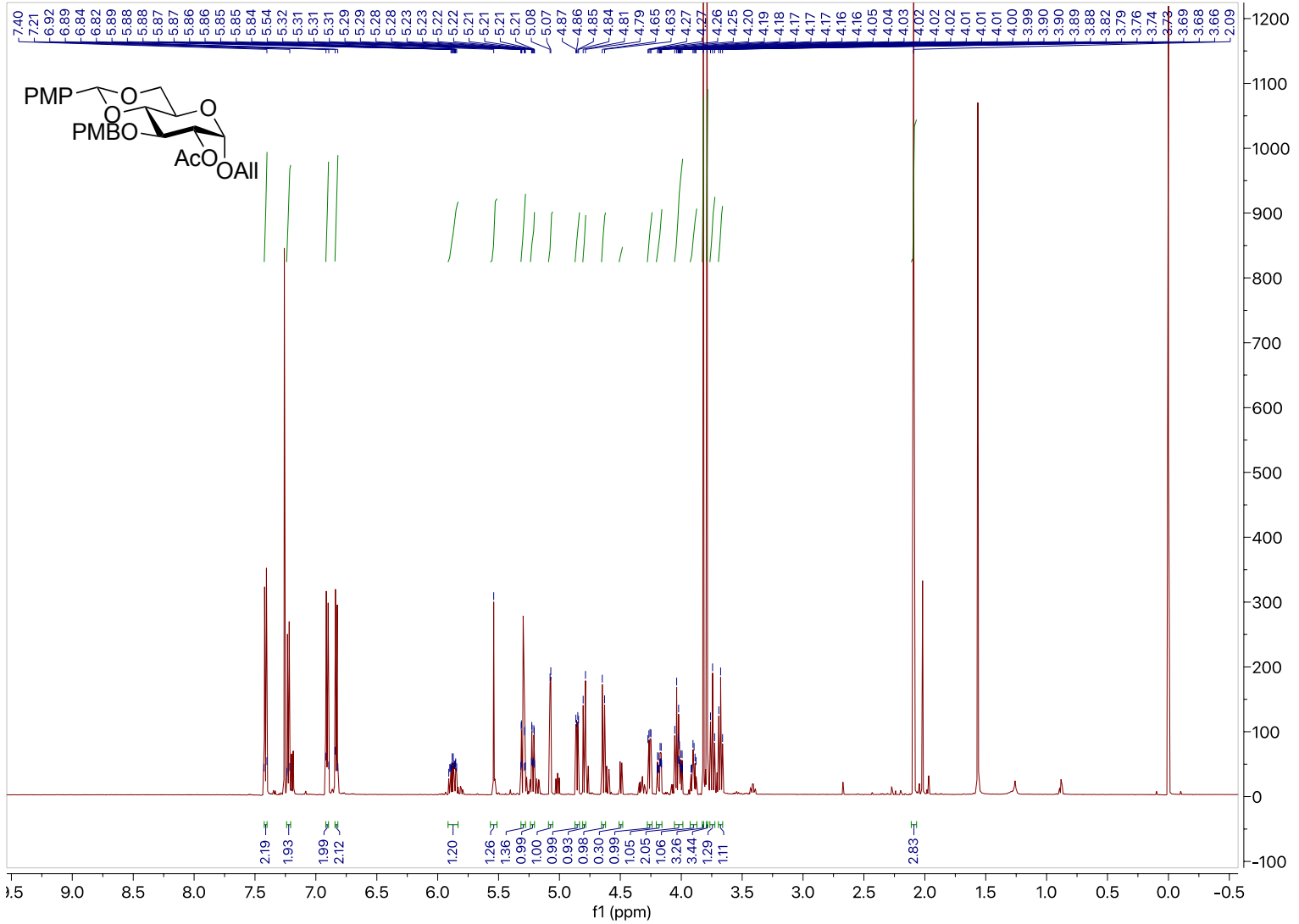
Supplementary figure 78 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 29



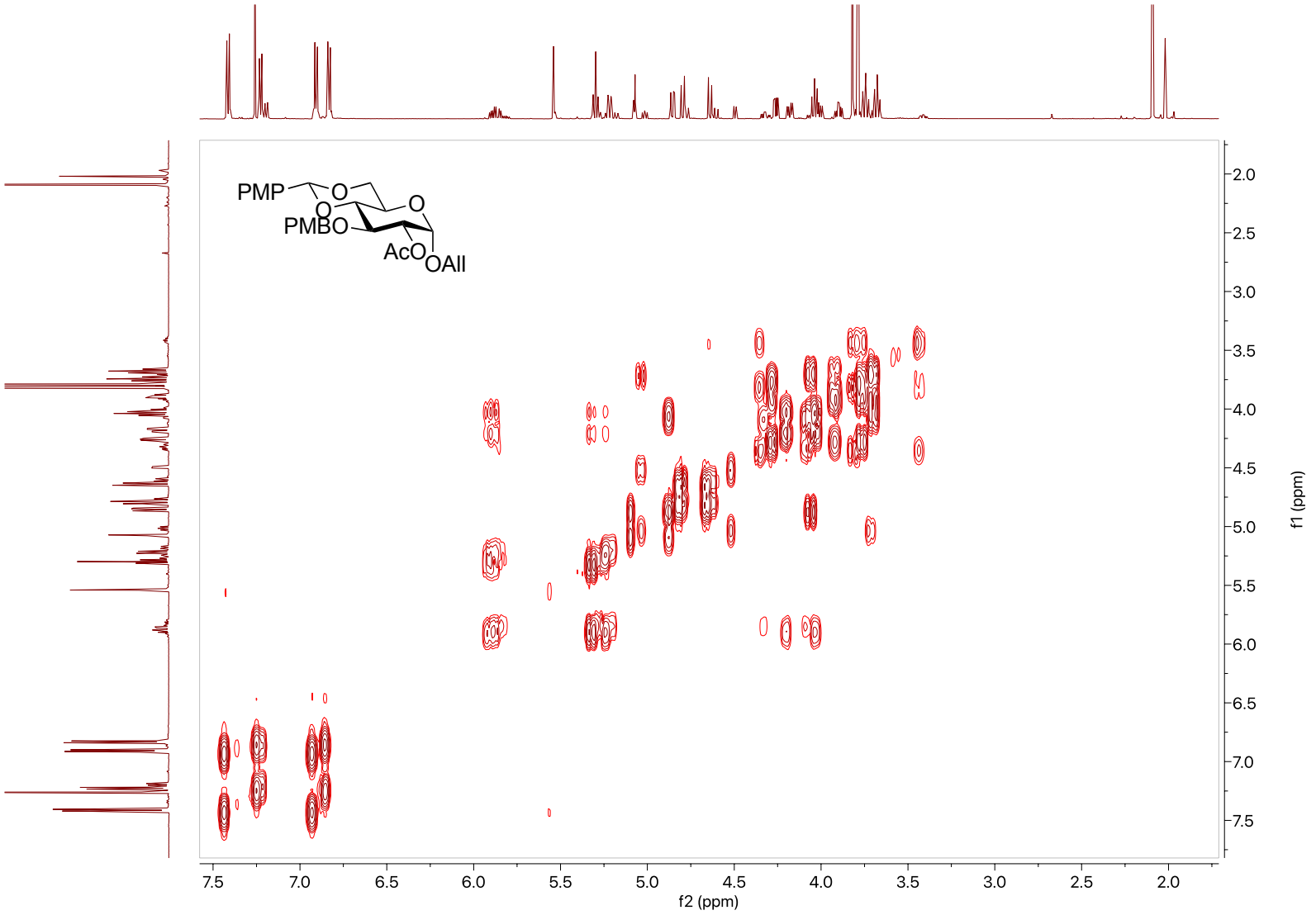
Supplementary figure 79 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 29



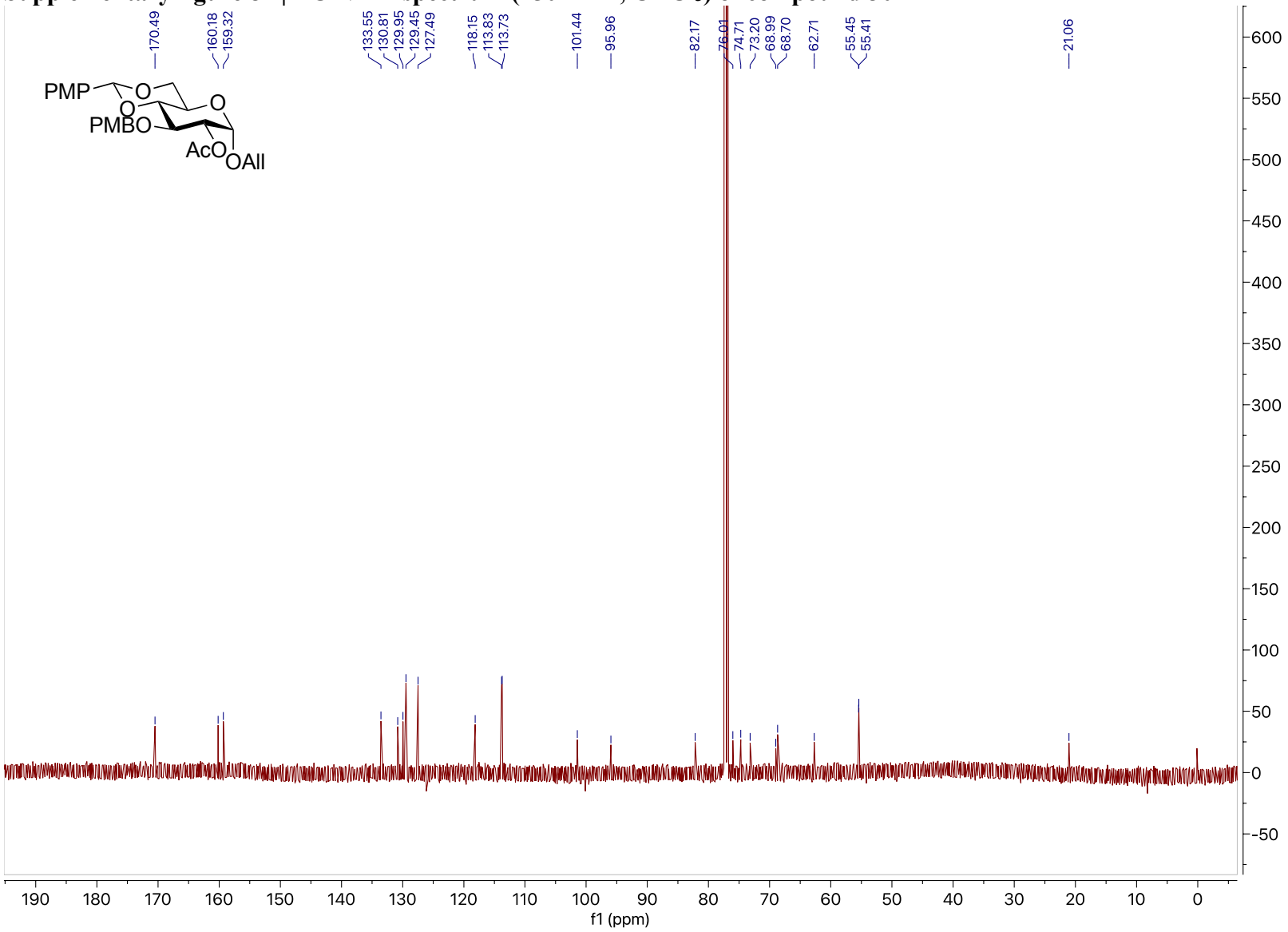
Supplementary figure 80 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 30



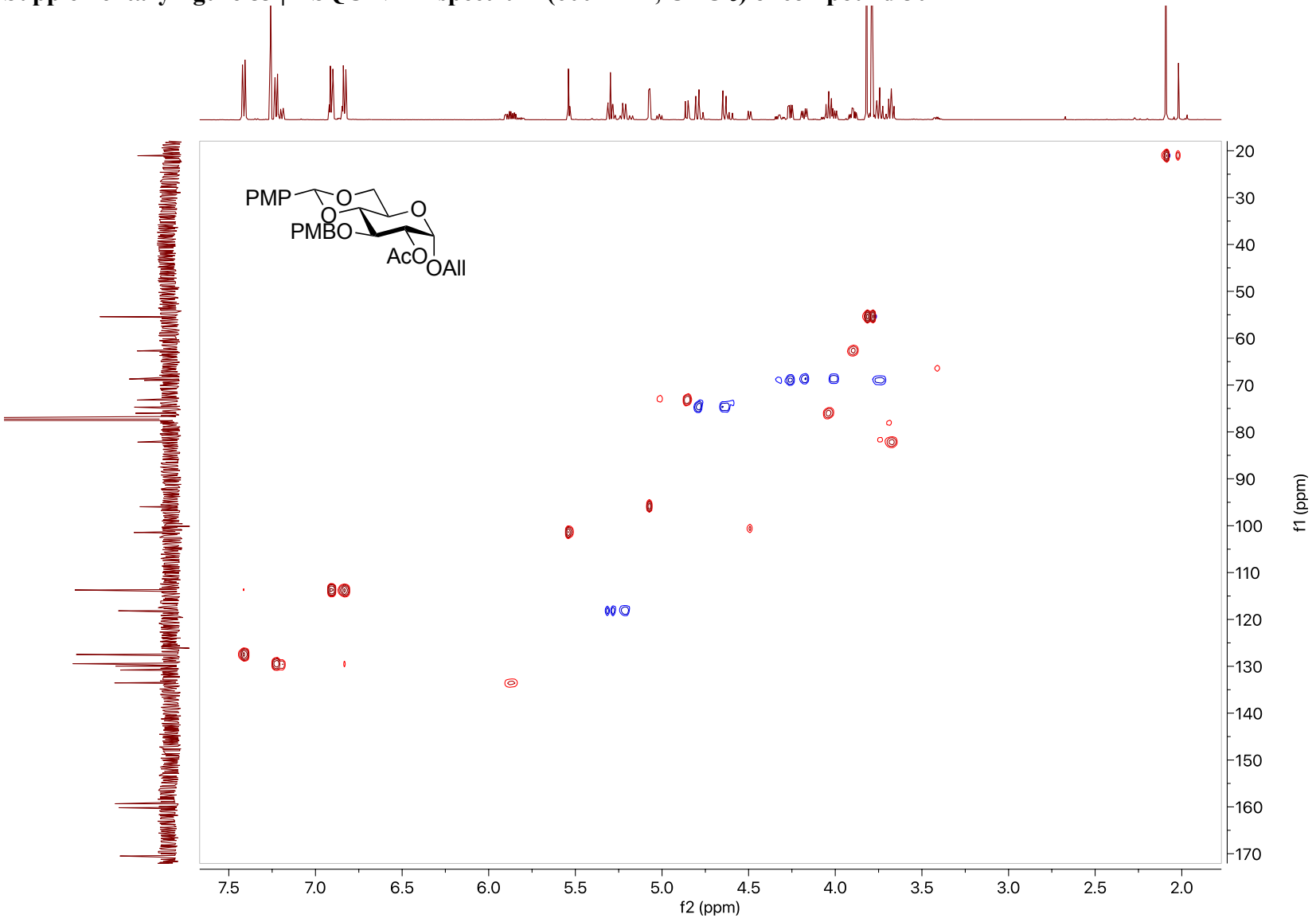
Supplementary figure 81 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 30



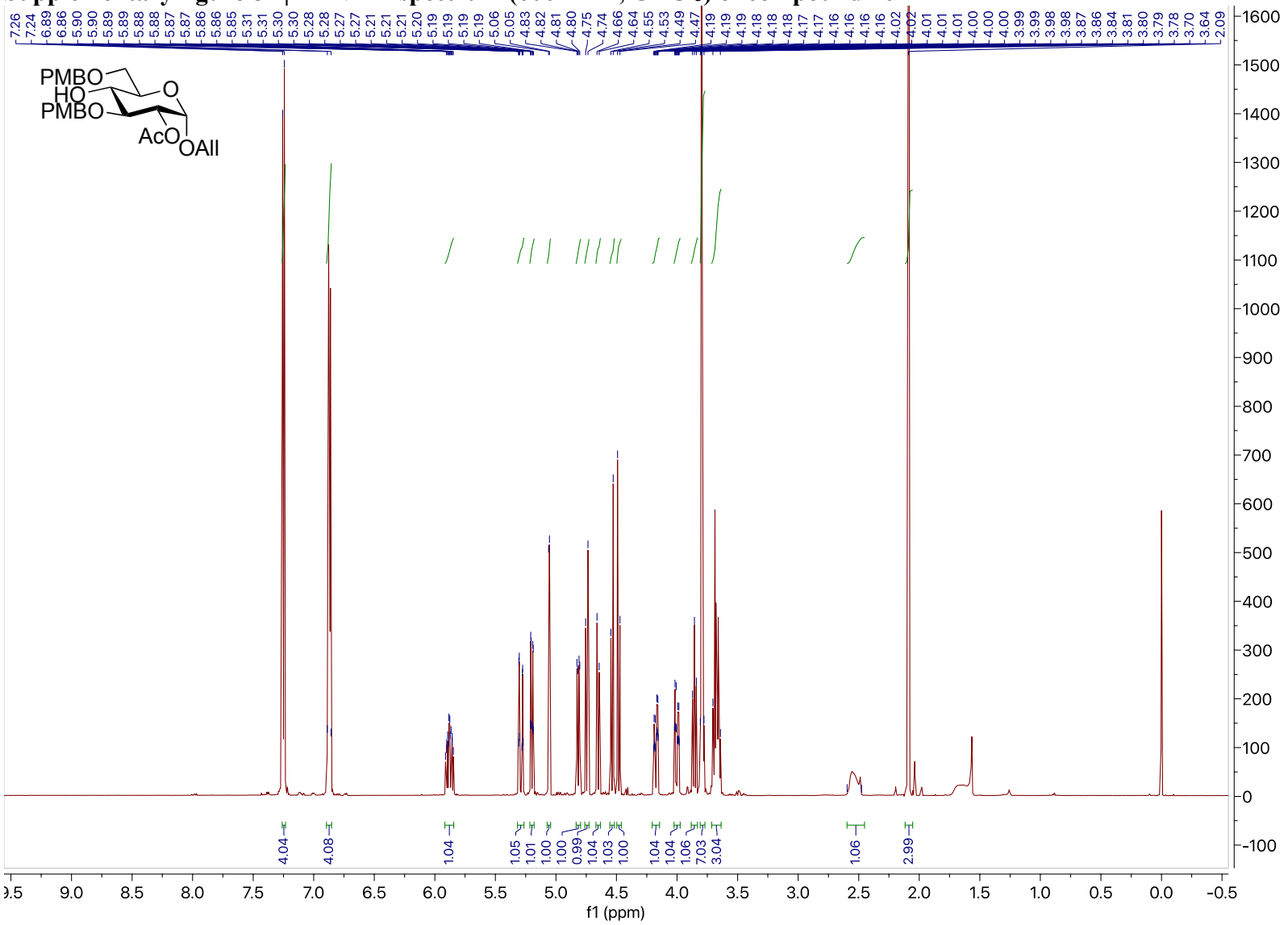
Supplementary figure 82 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 30



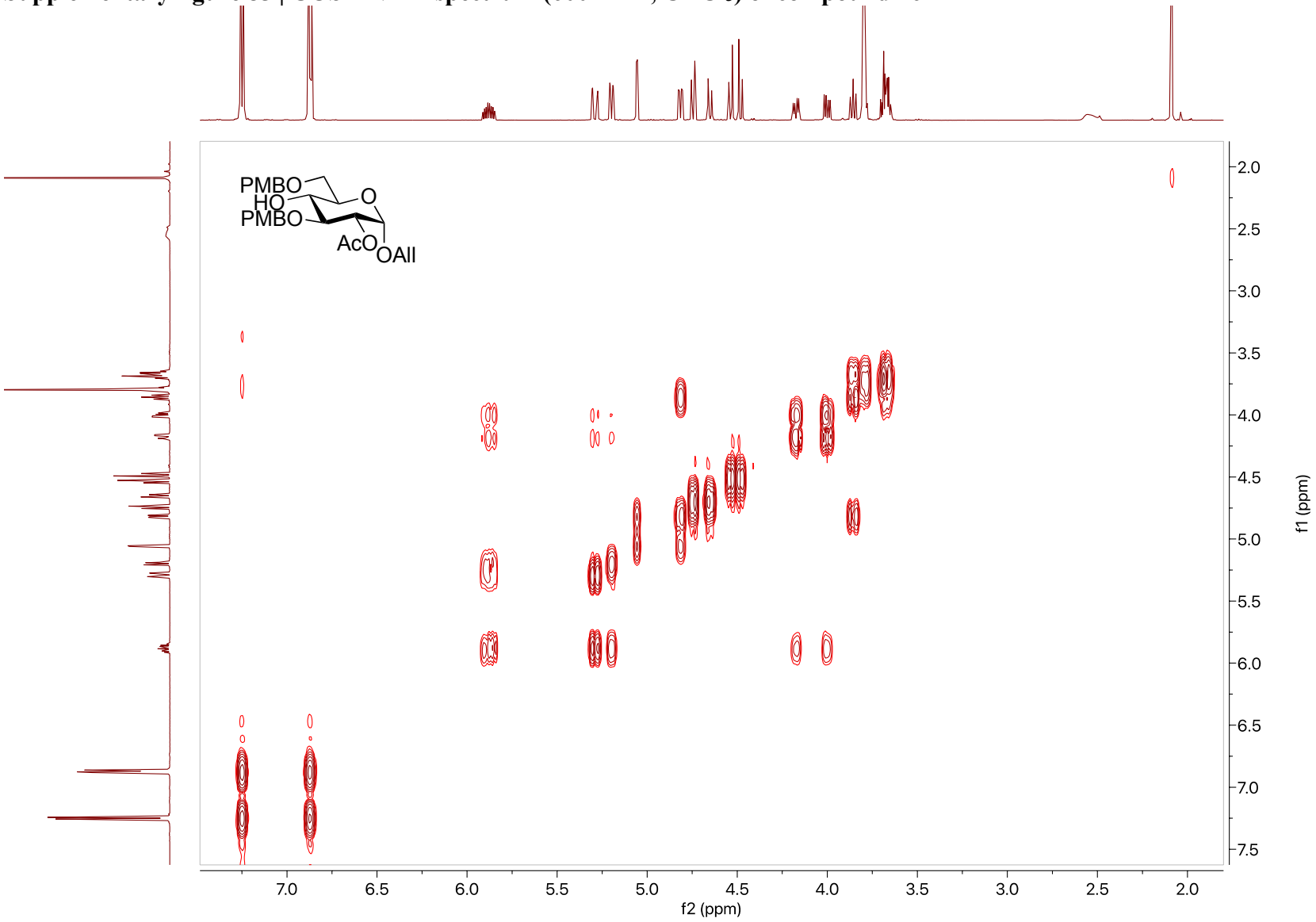
Supplementary figure 83 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 30



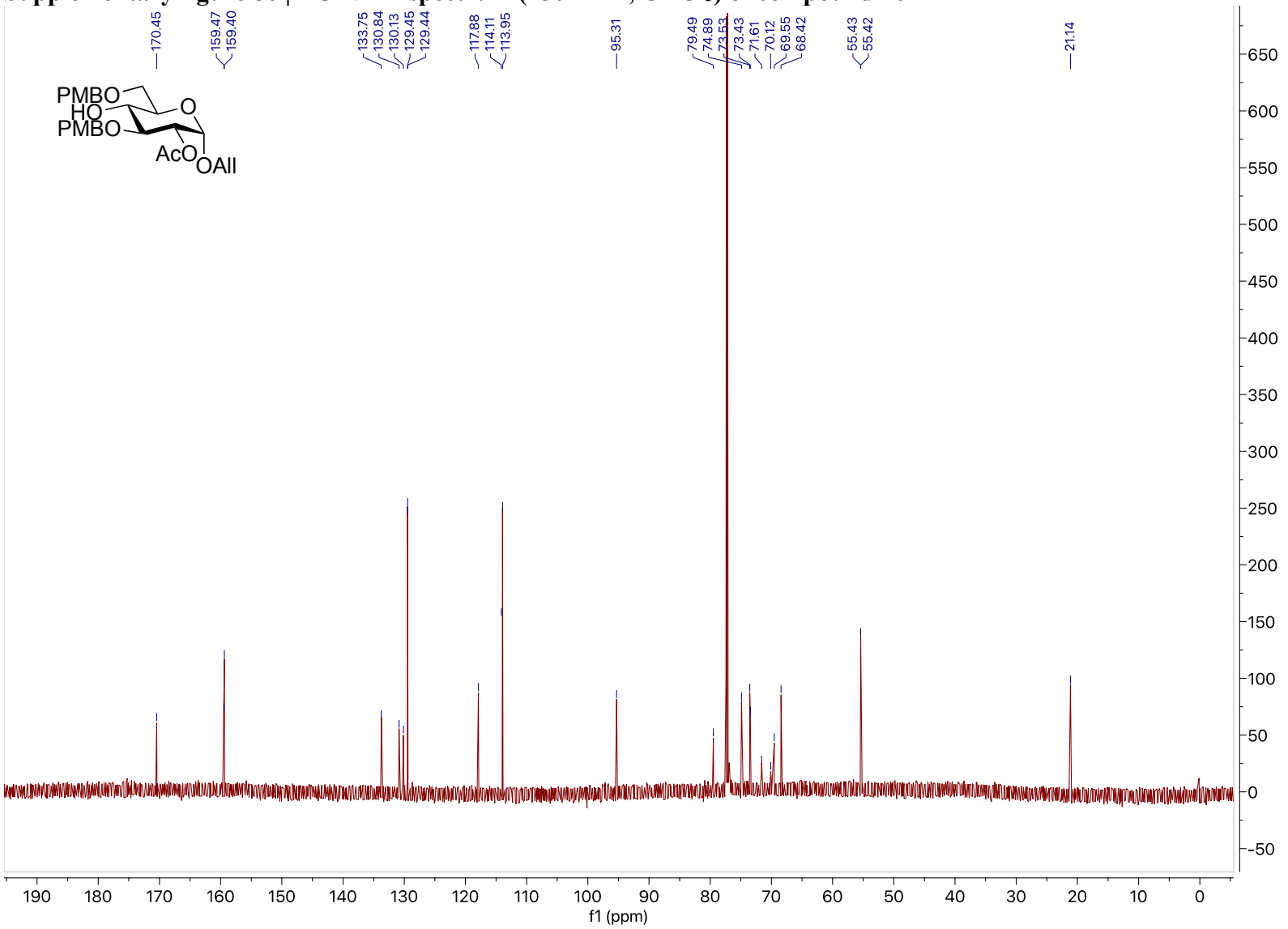
Supplementary figure 84 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 26



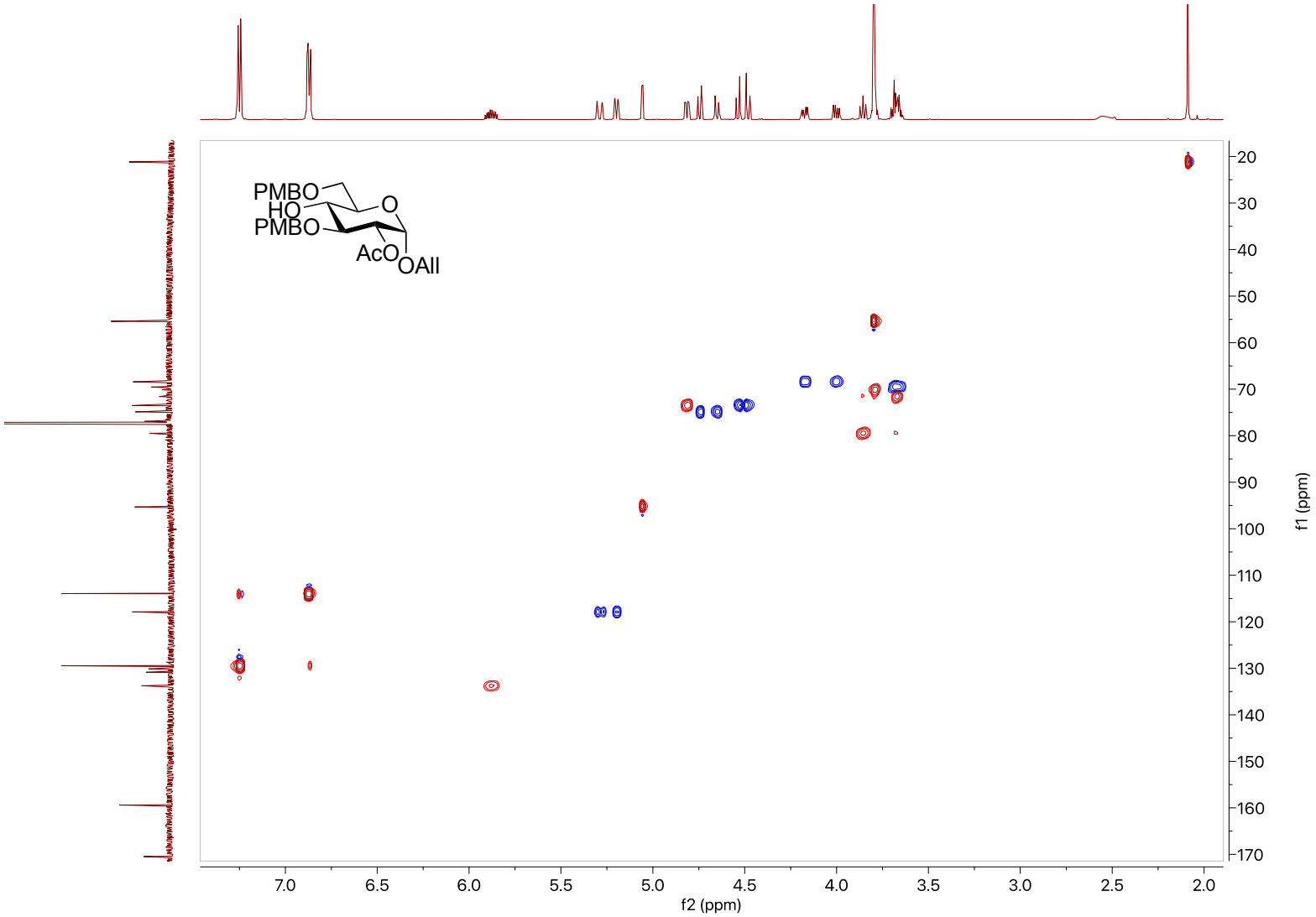
Supplementary figure 85 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 26



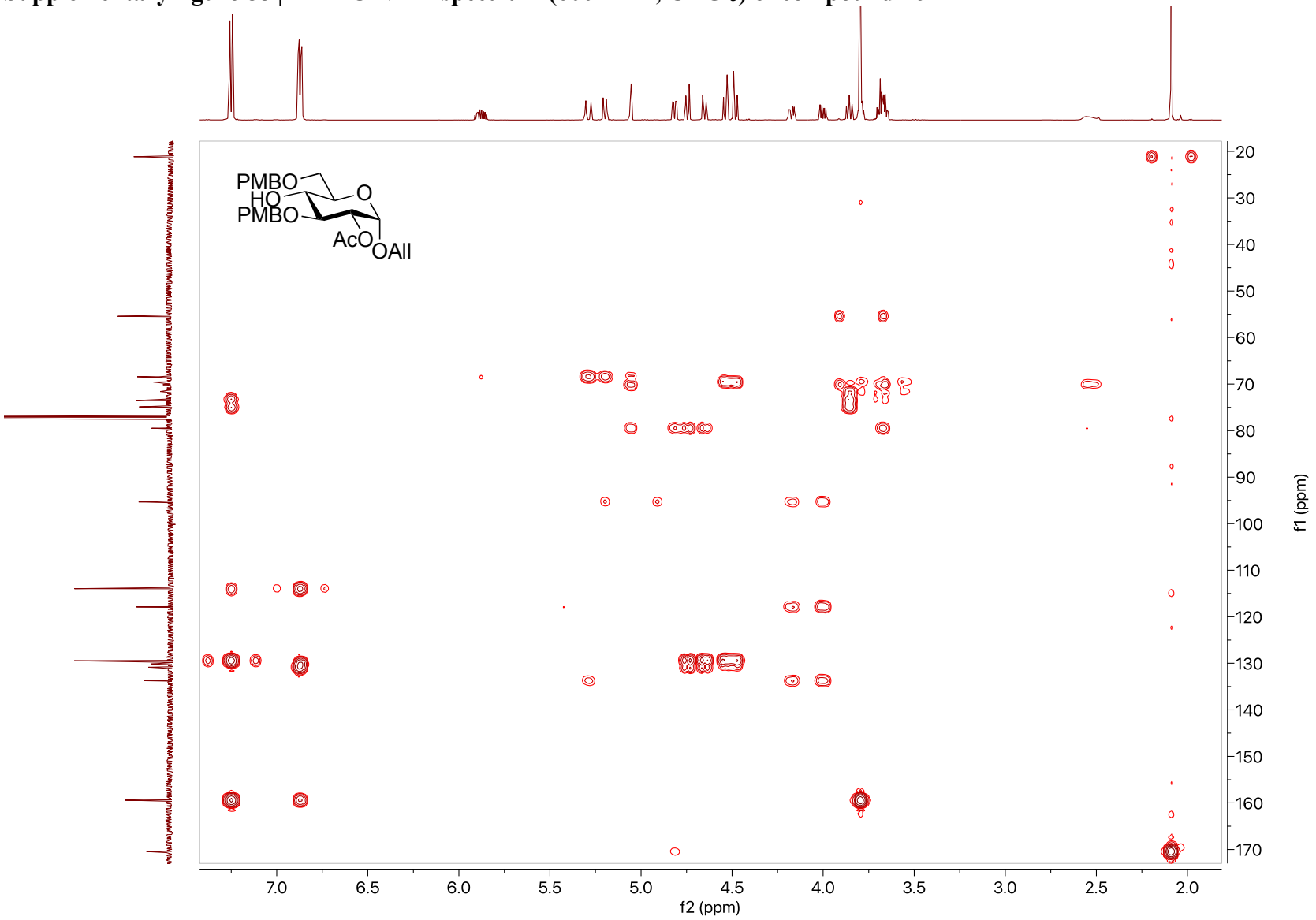
Supplementary figure 86 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 26



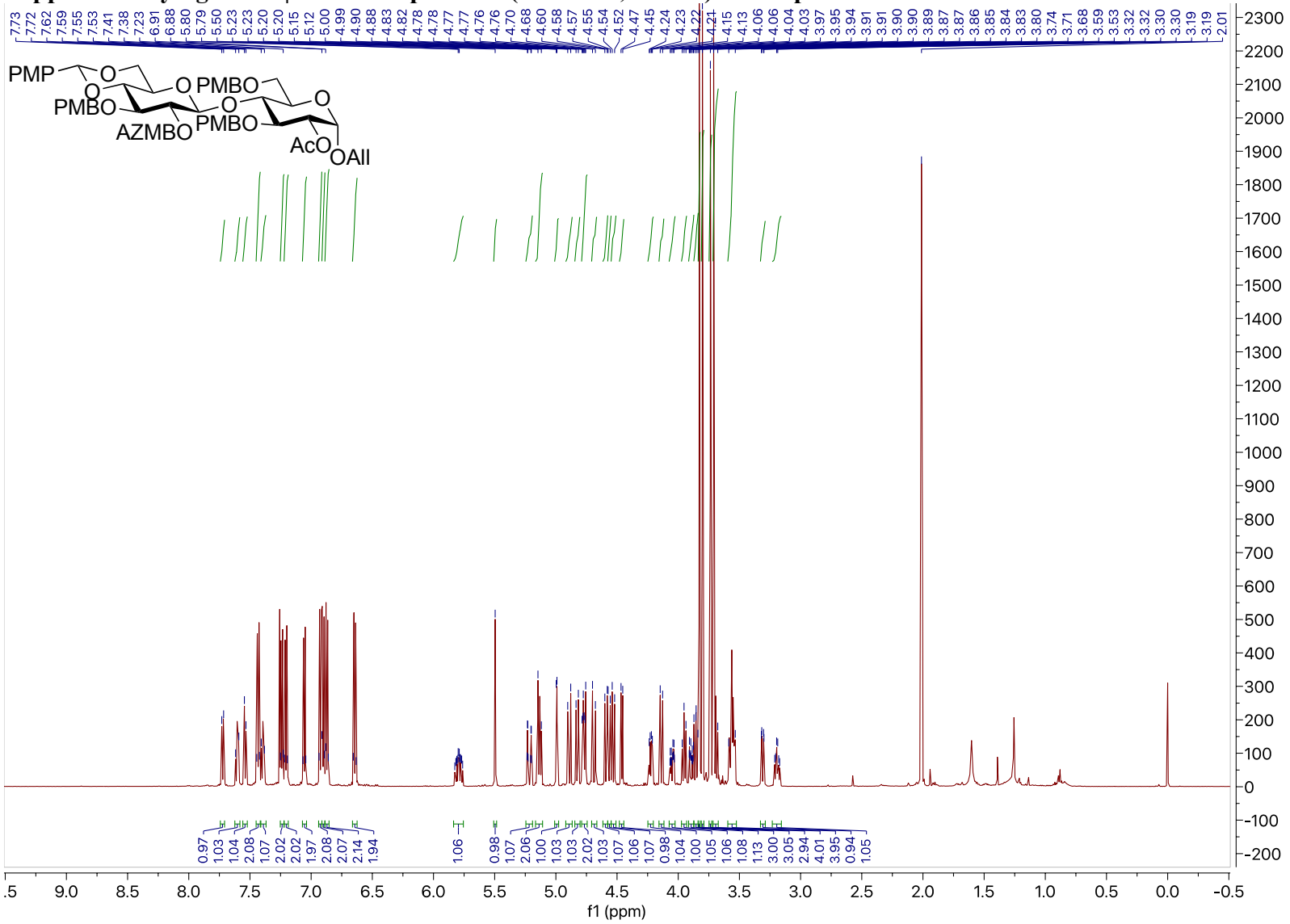
Supplementary figure 87 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 26



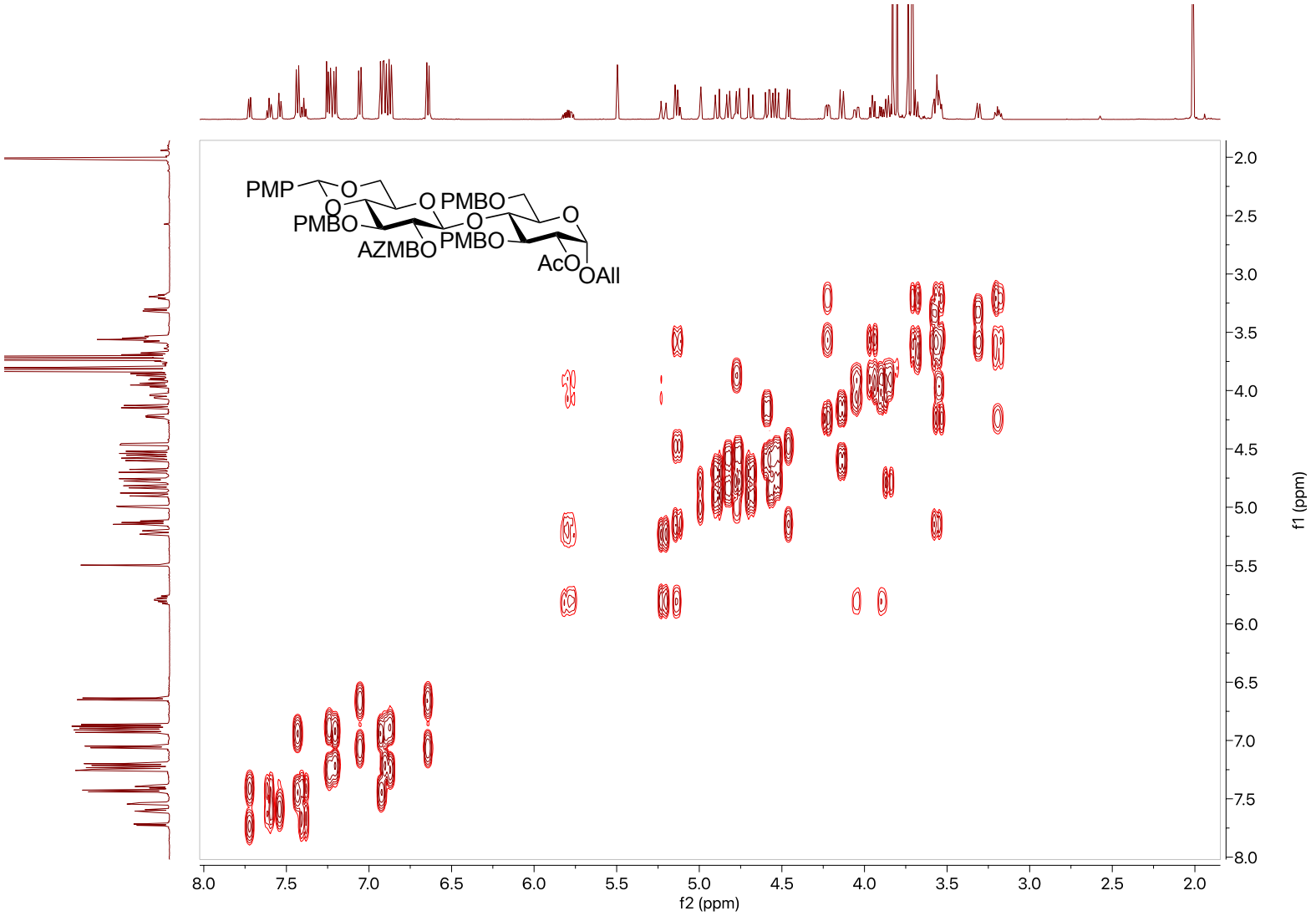
Supplementary figure 88 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 26



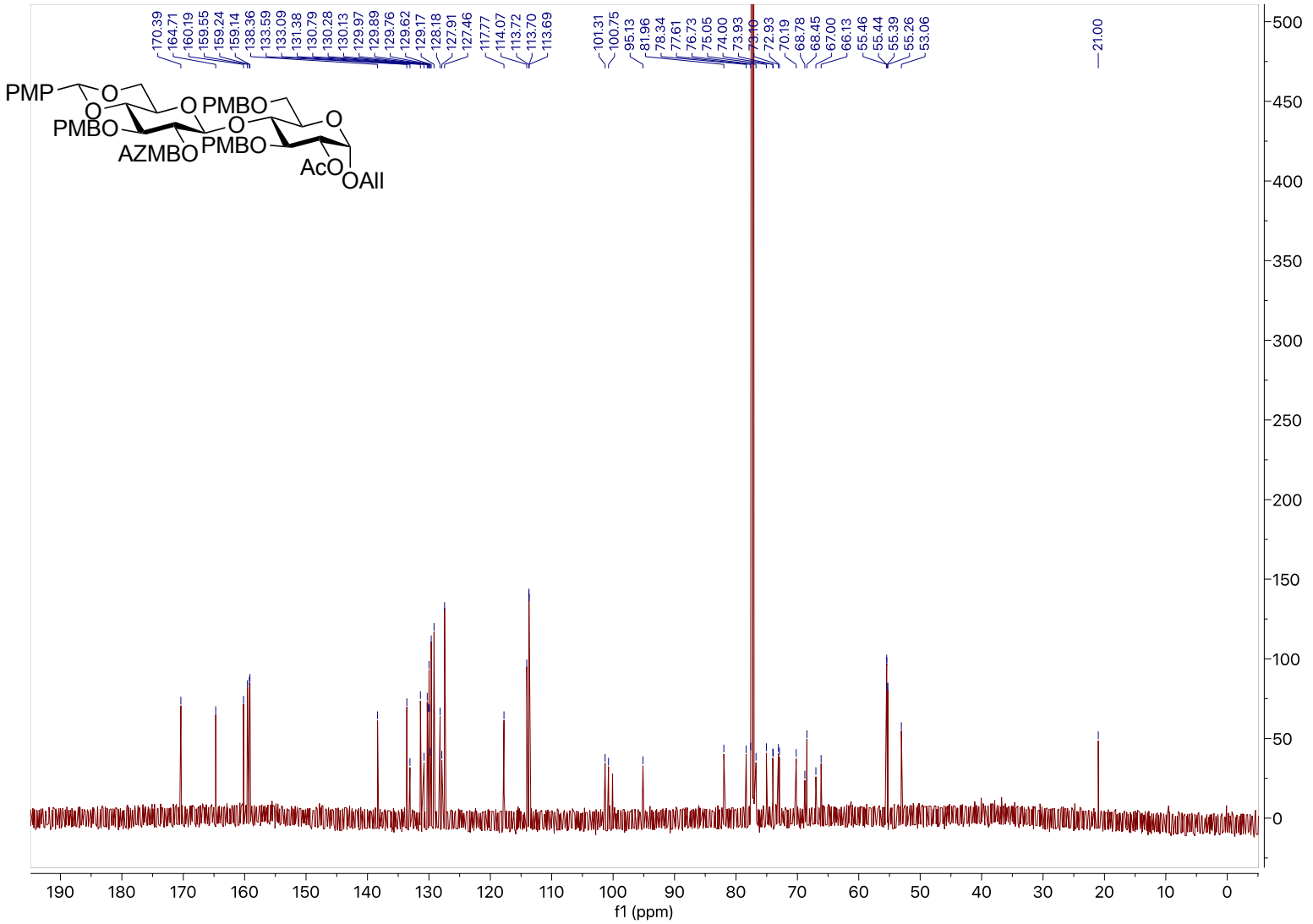
Supplementary figure 89 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 31



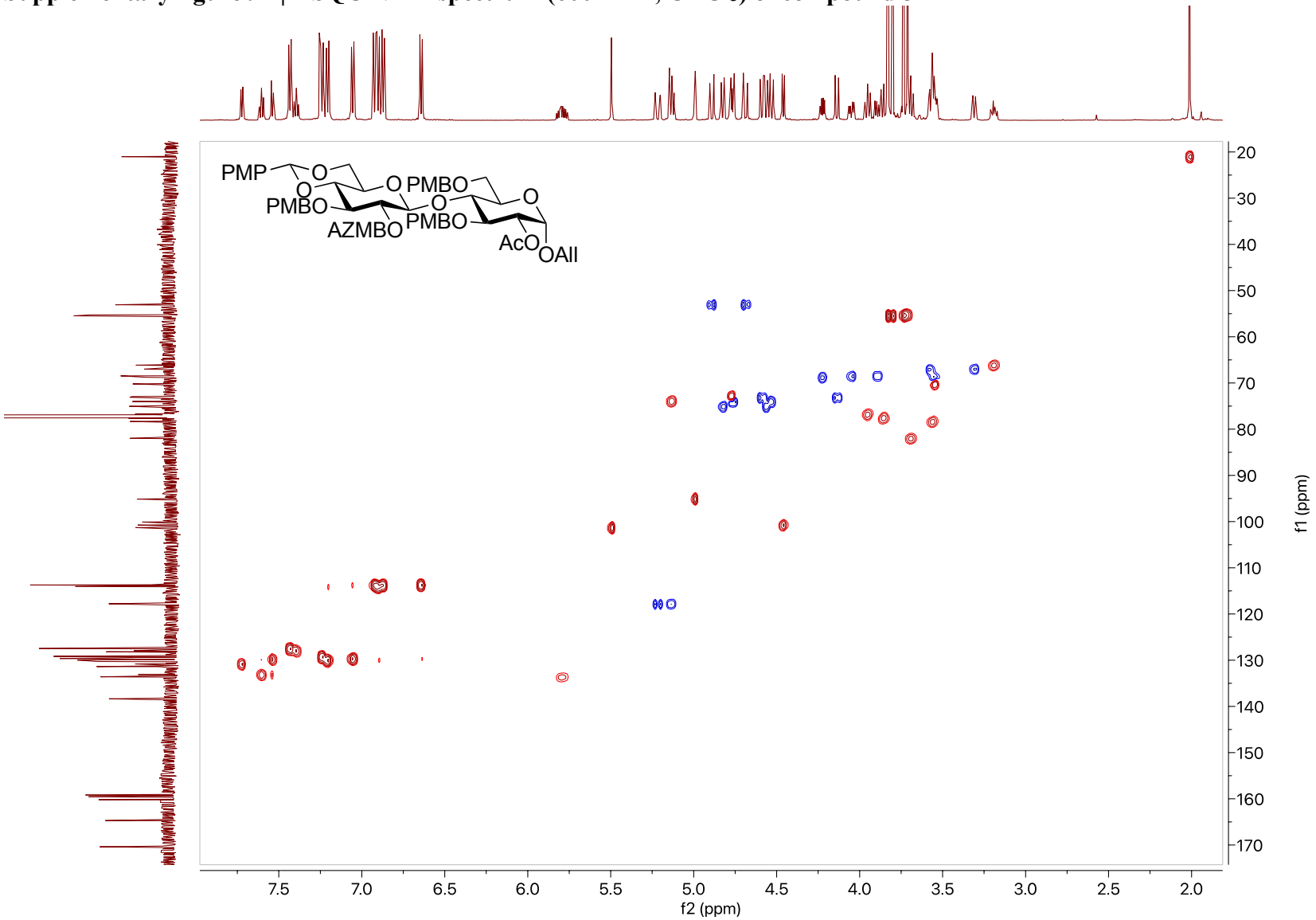
Supplementary figure 90 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 31



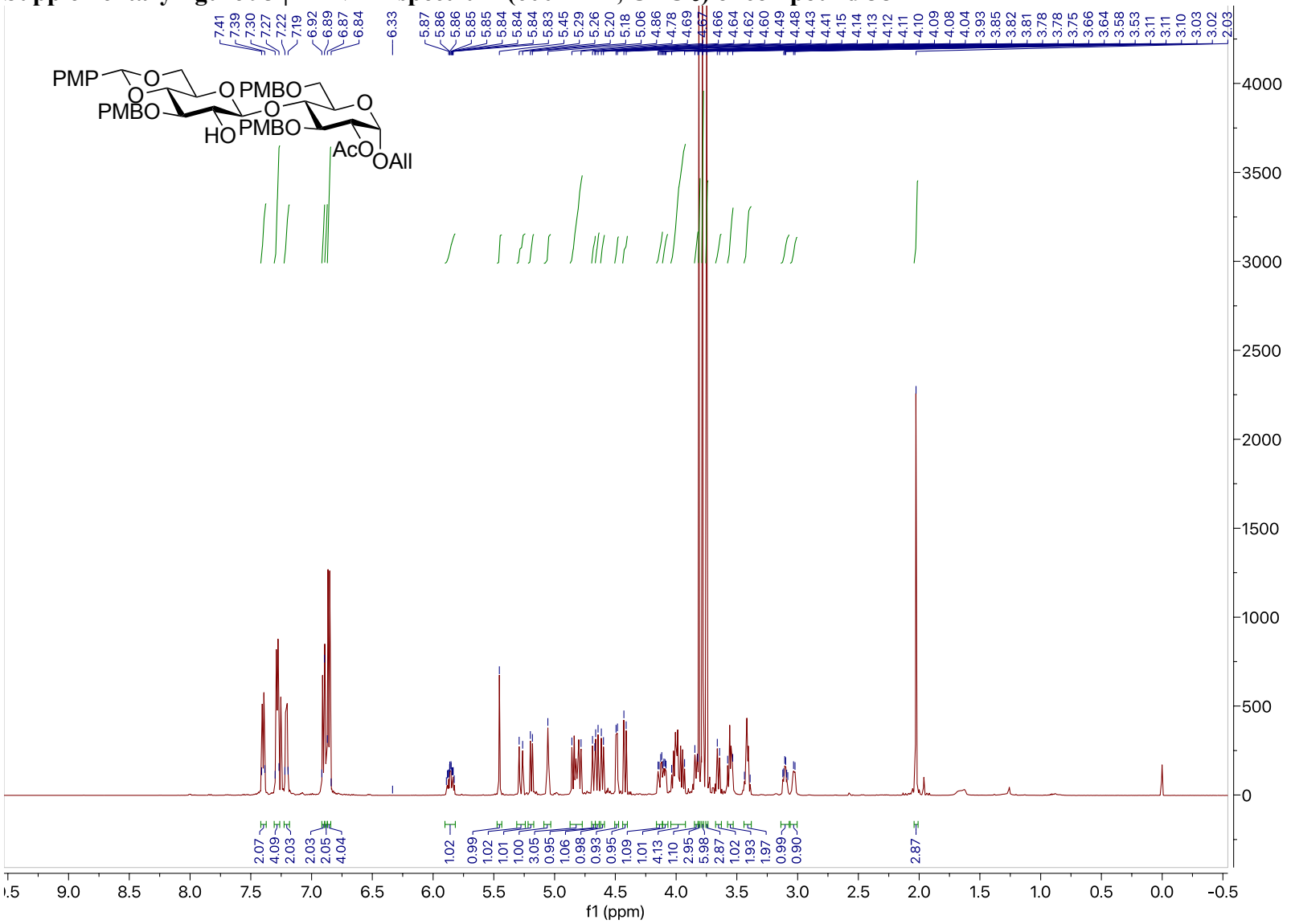
Supplementary figure 91 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 31



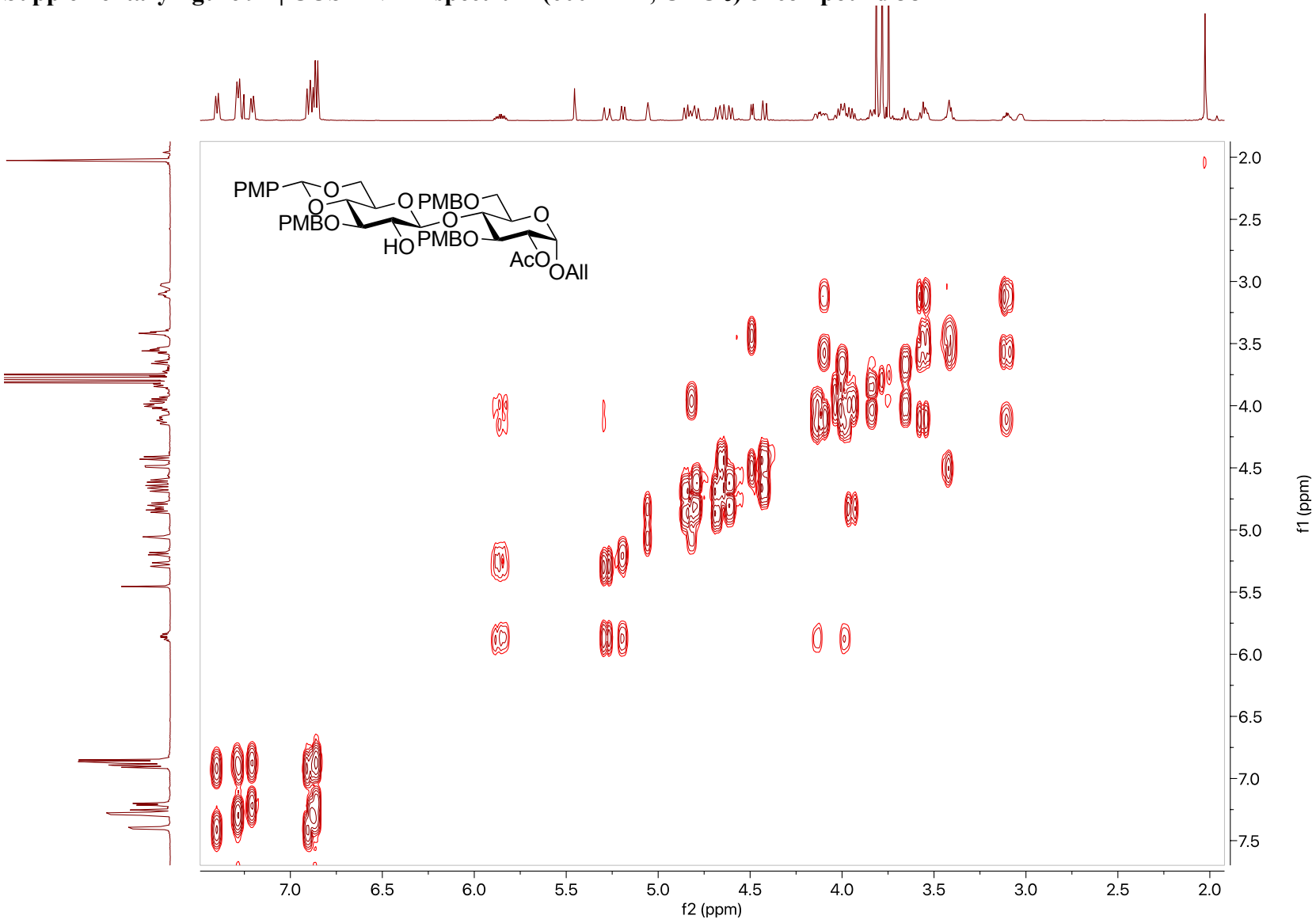
Supplementary figure 92 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 31



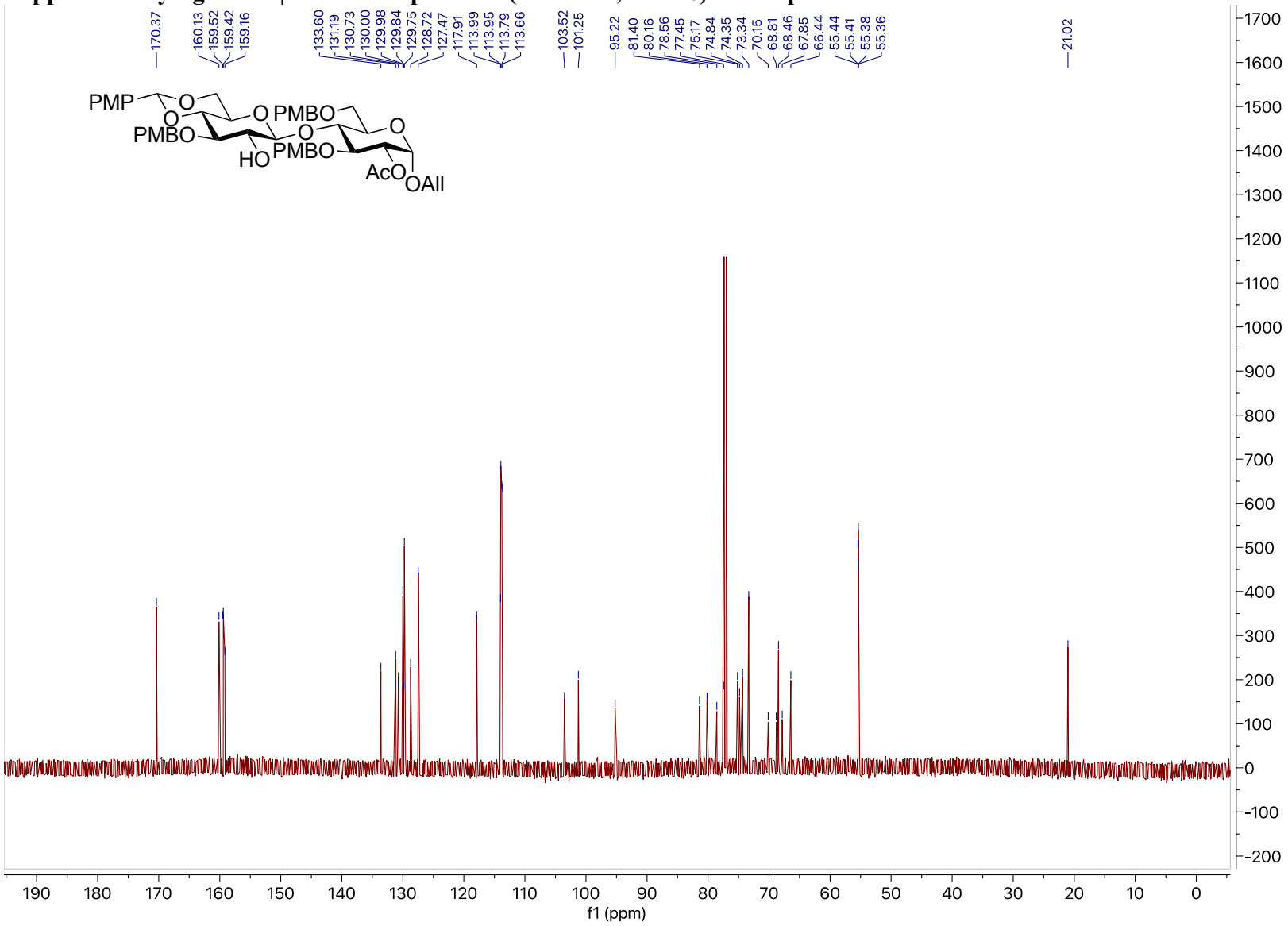
Supplementary figure 93 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 38



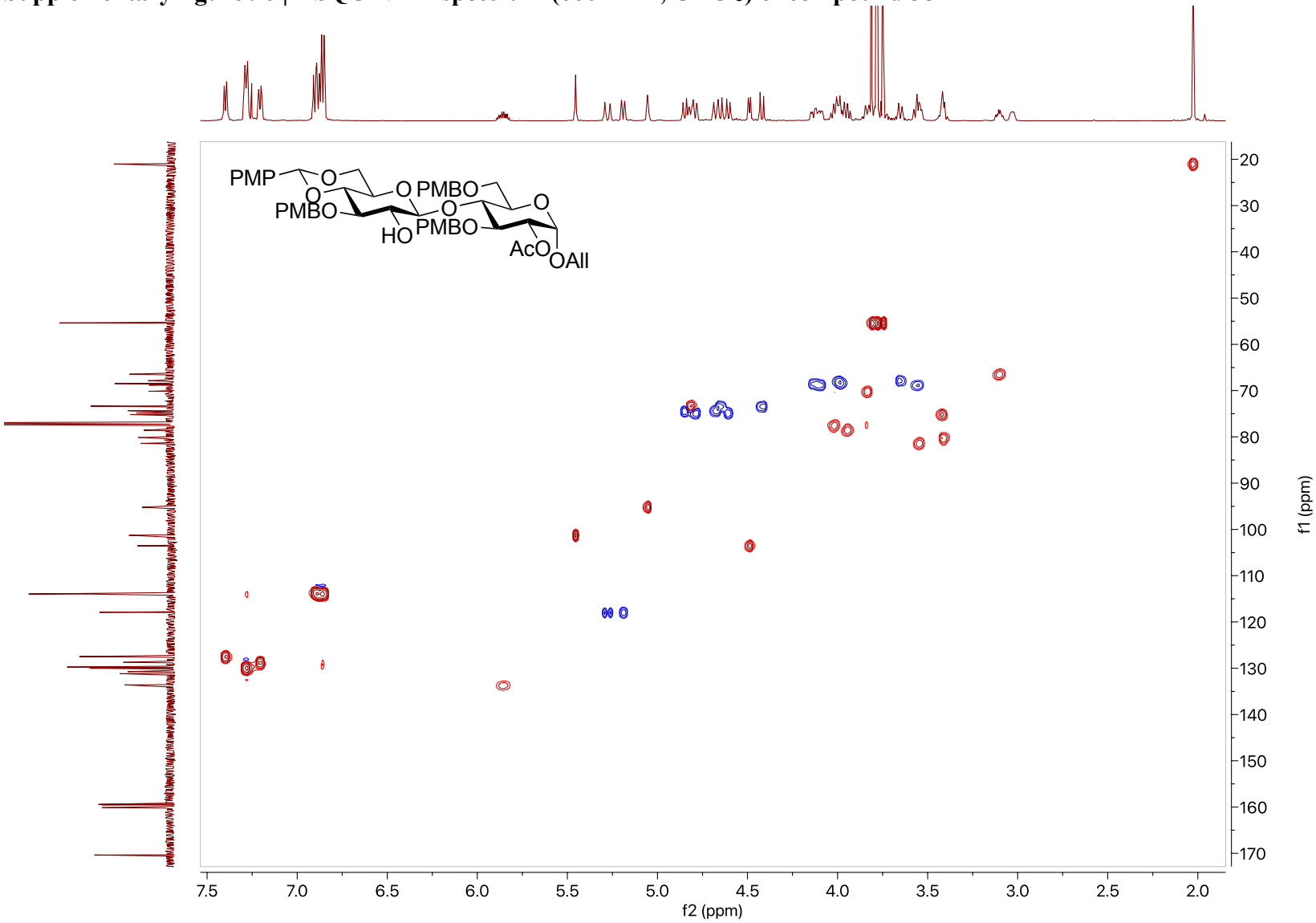
Supplementary figure 94 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 38



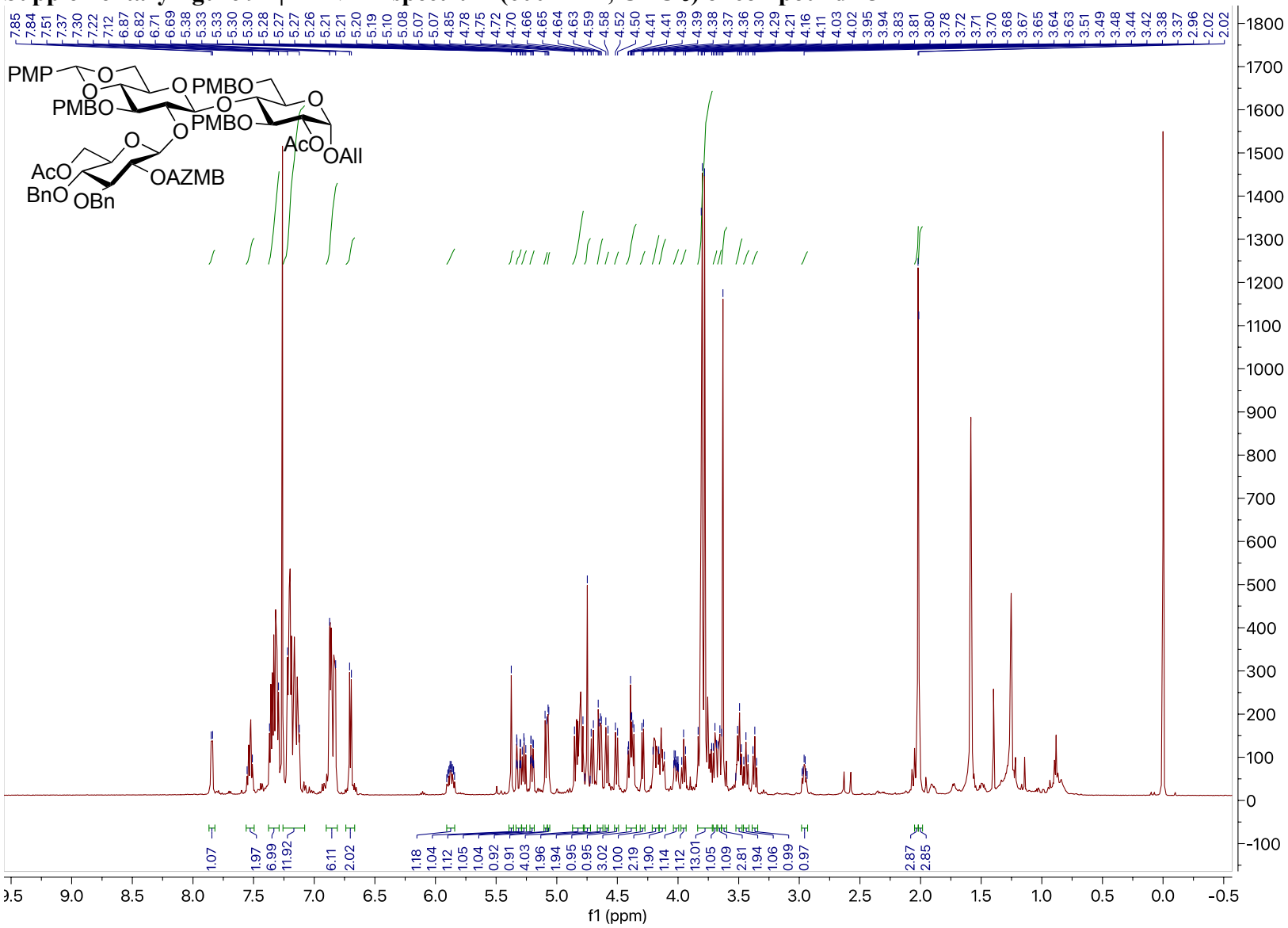
Supplementary figure 95 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 38



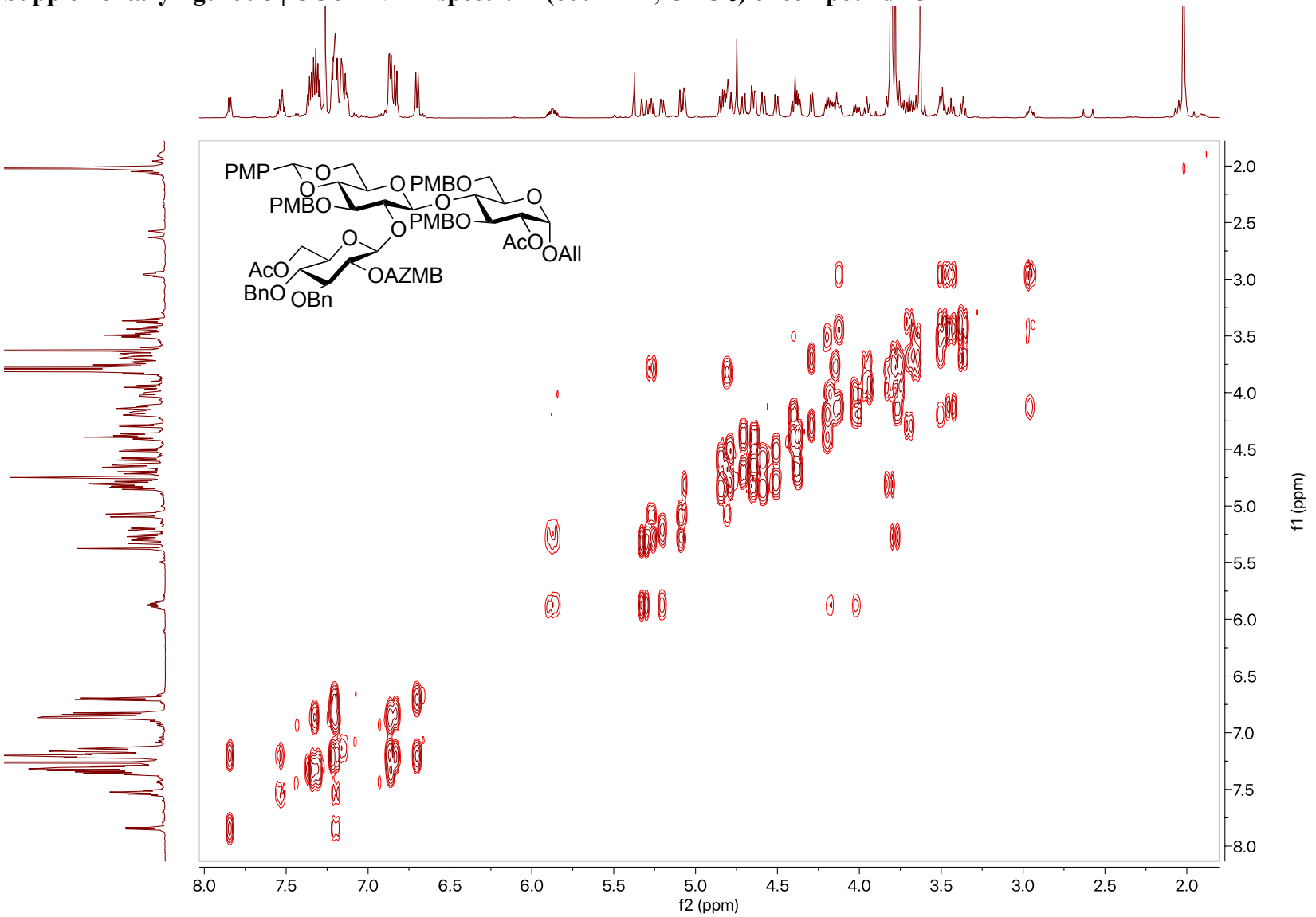
Supplementary figure 96 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 38



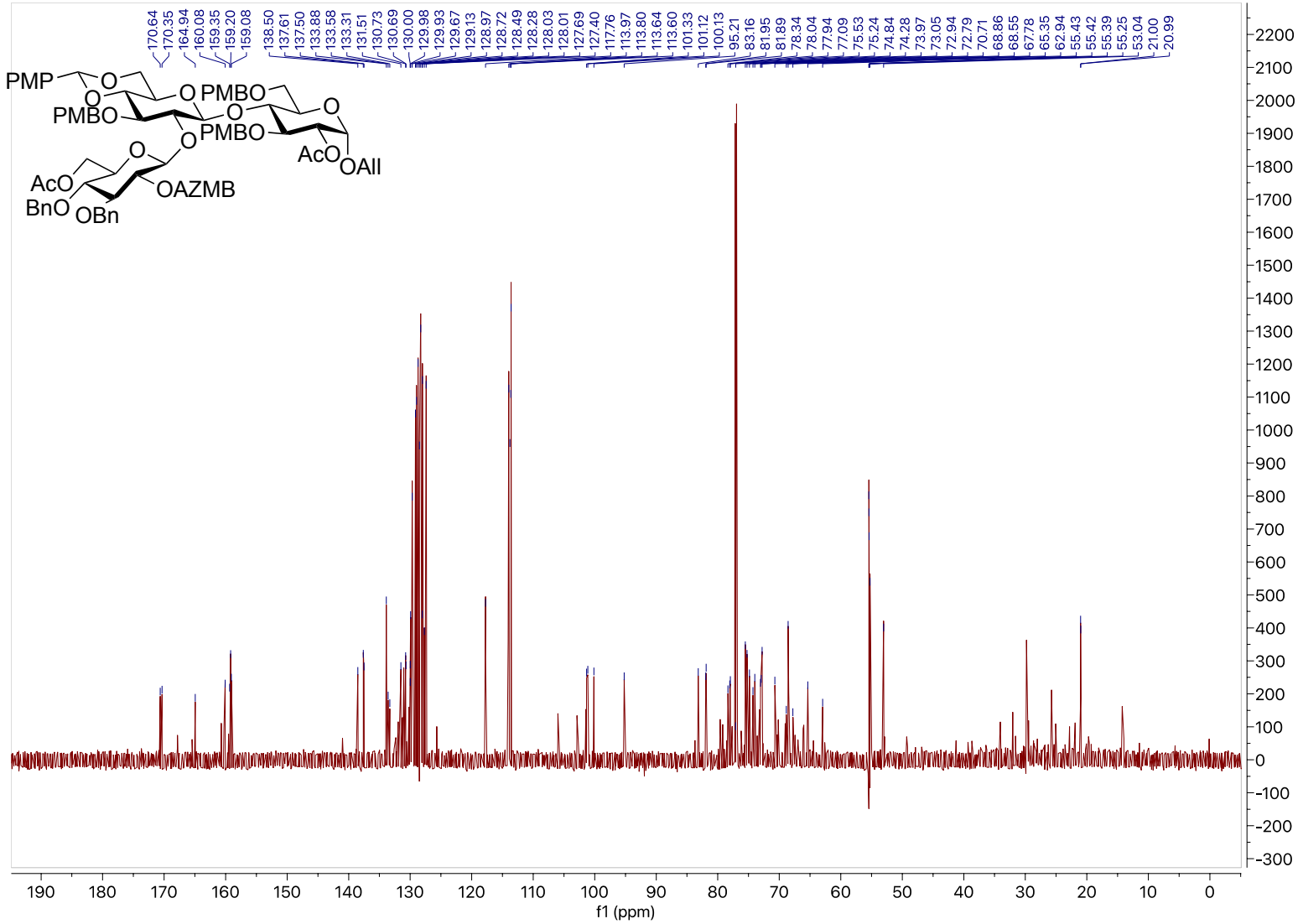
Supplementary figure 97 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 25



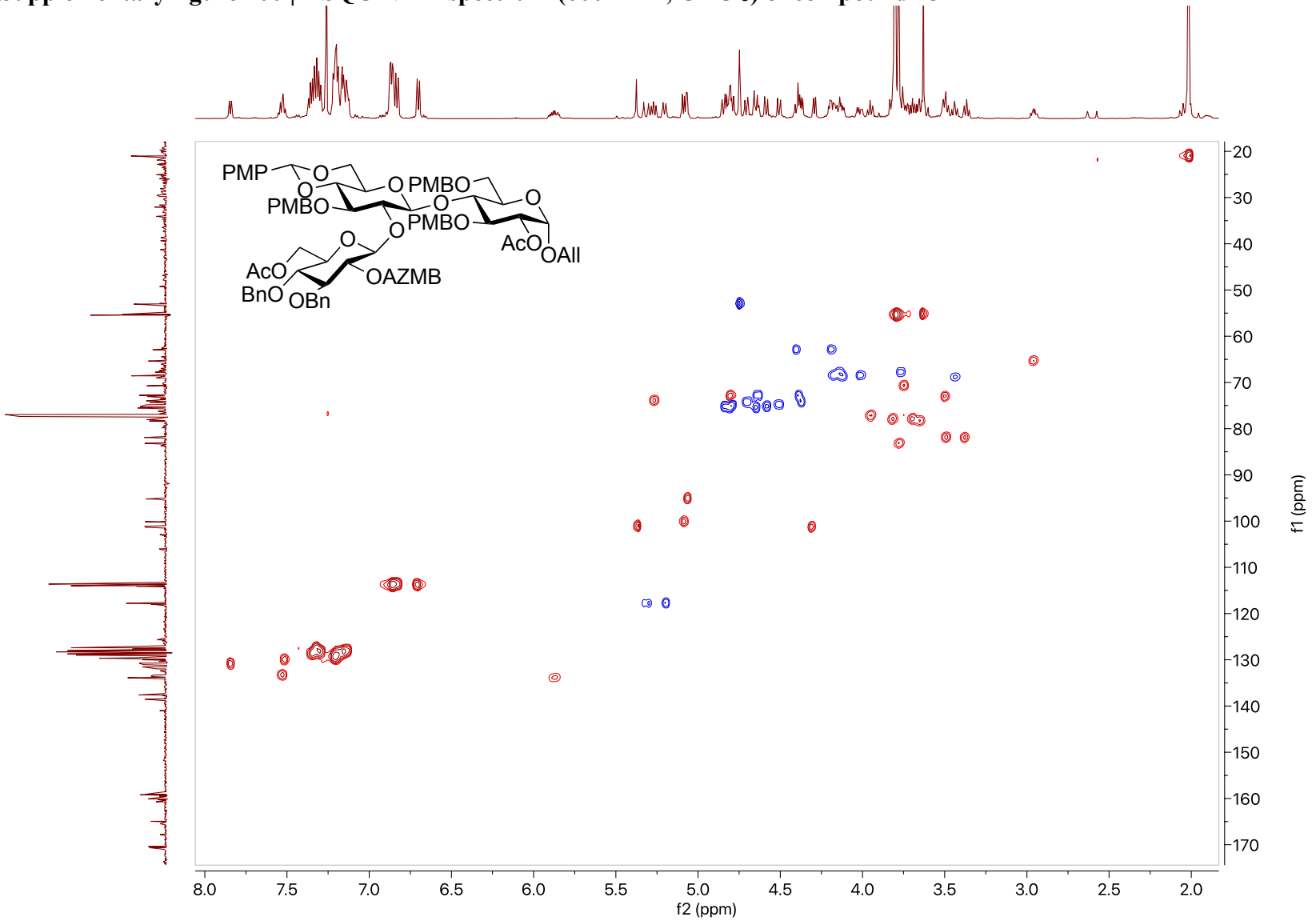
Supplementary figure 98 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 25



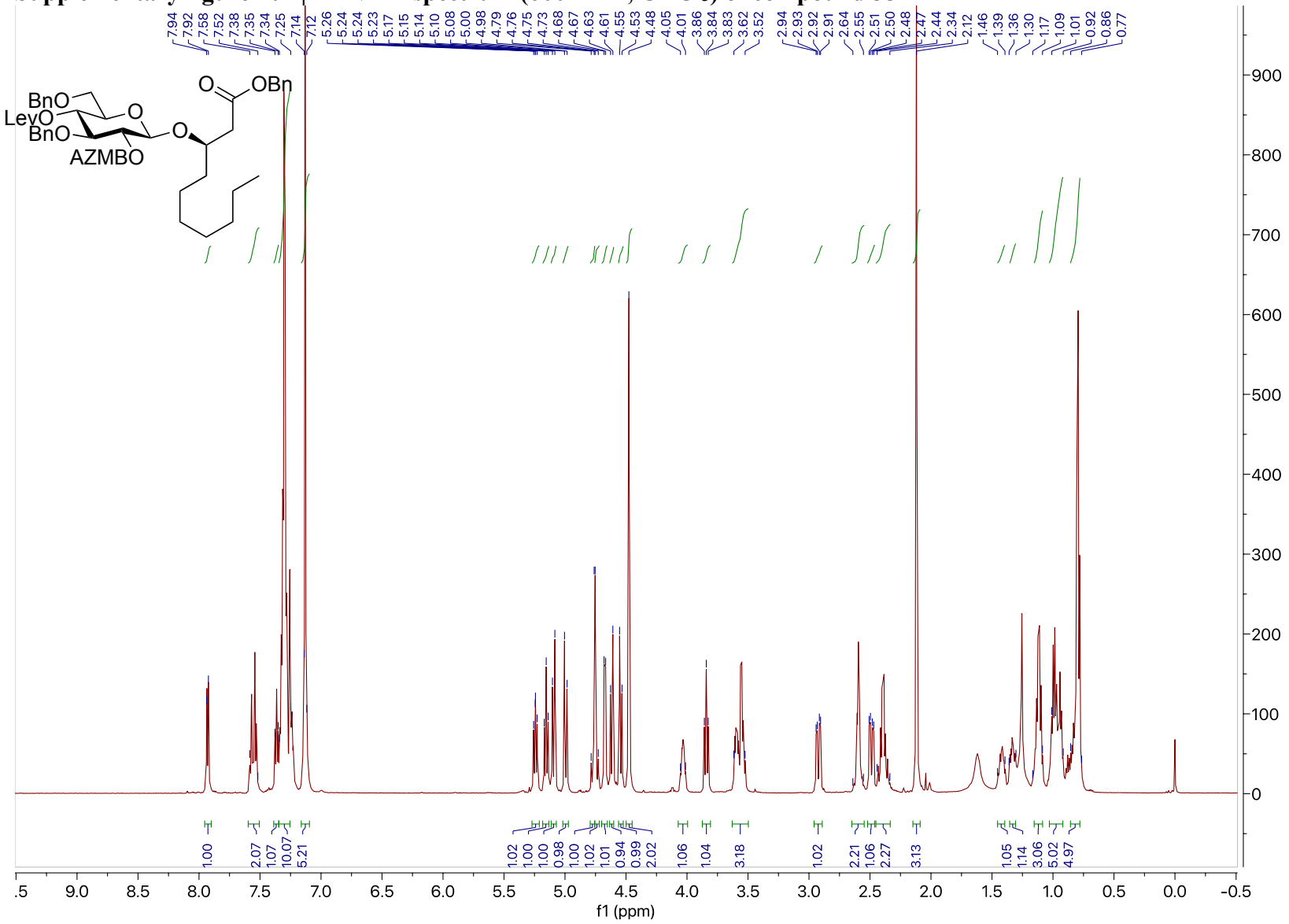
Supplementary figure 99 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 25



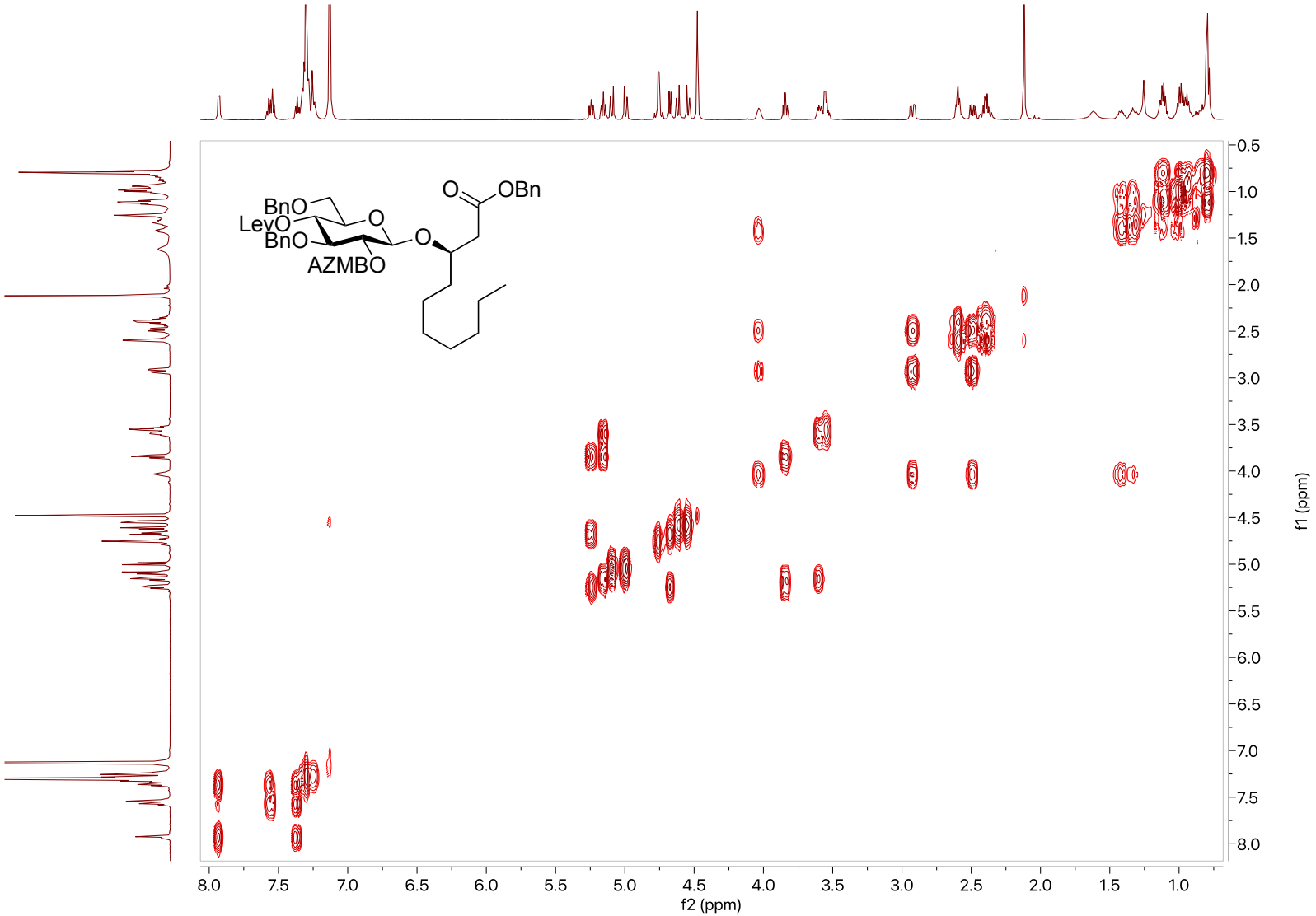
Supplementary figure 100 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 25



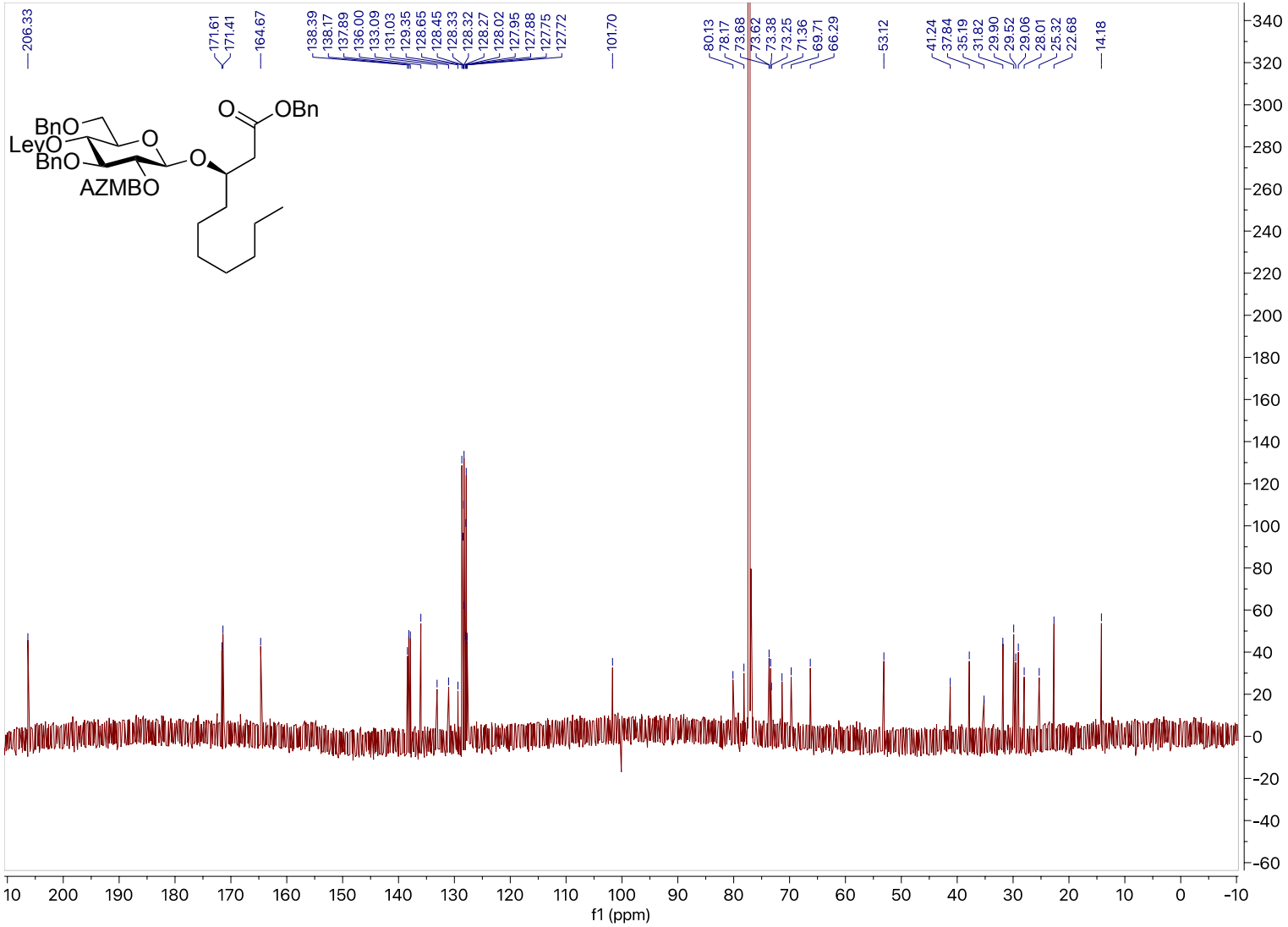
Supplementary figure 101 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 35



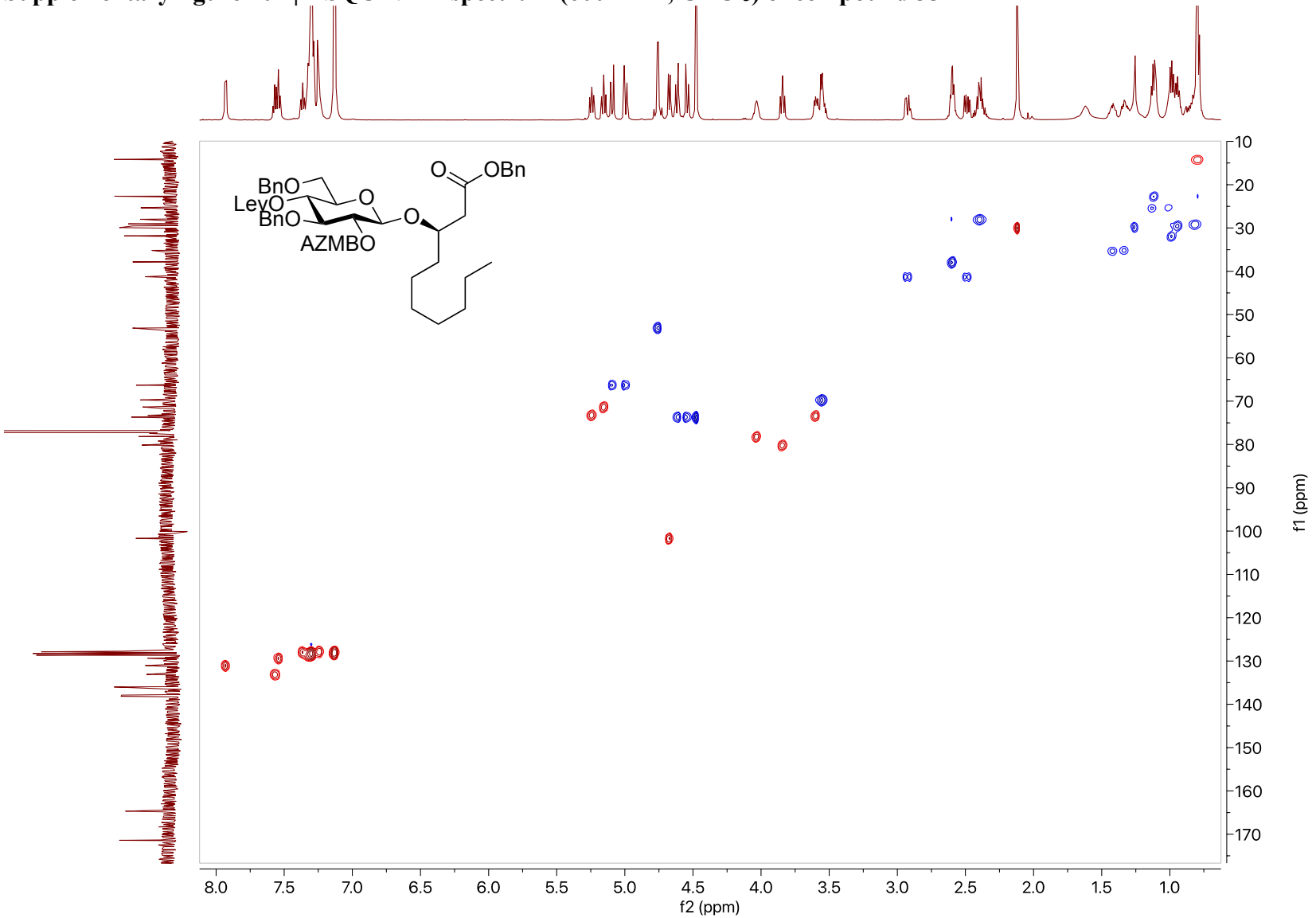
Supplementary figure 102 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 35



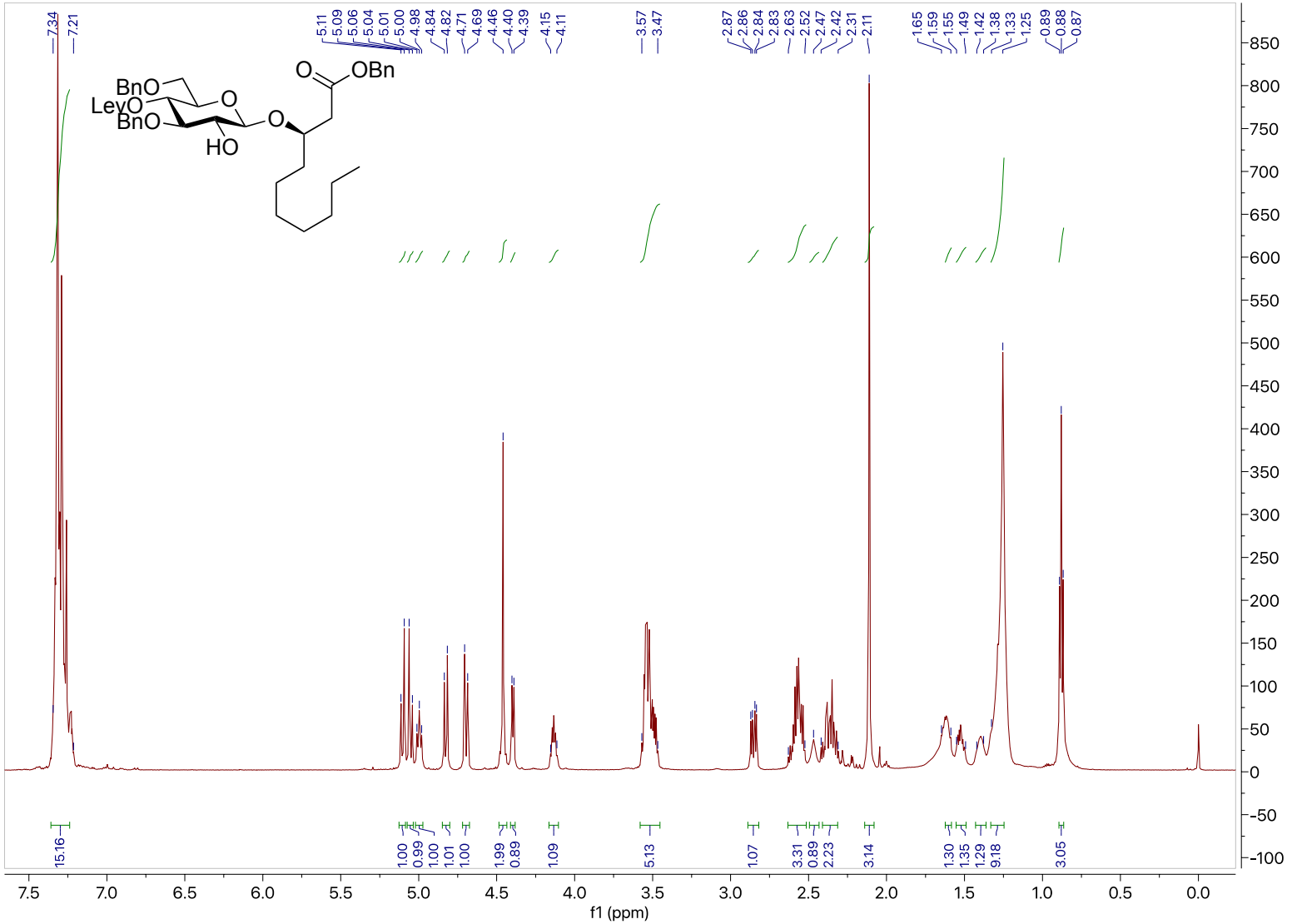
Supplementary figure 103 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 35



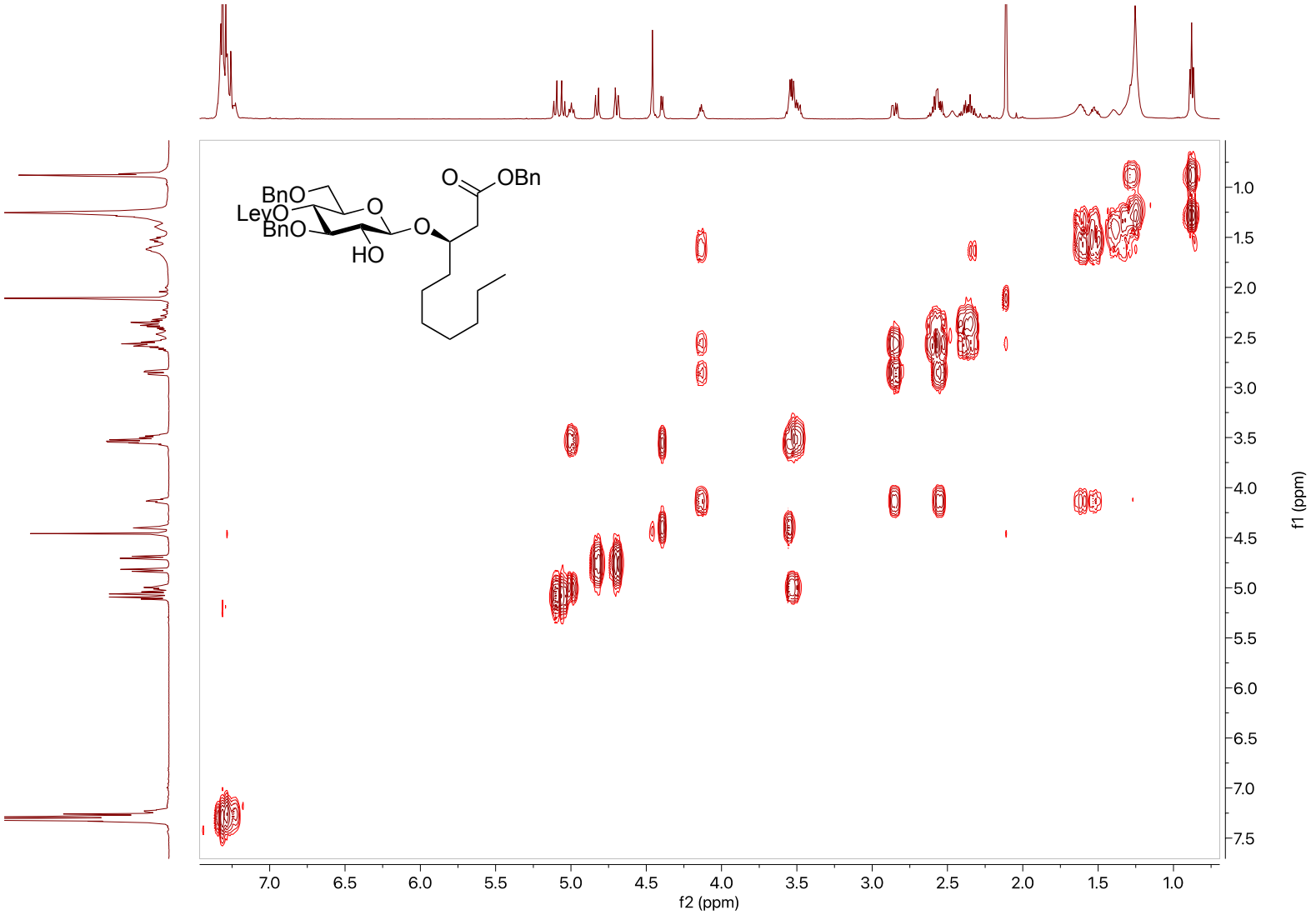
Supplementary figure 104 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 35



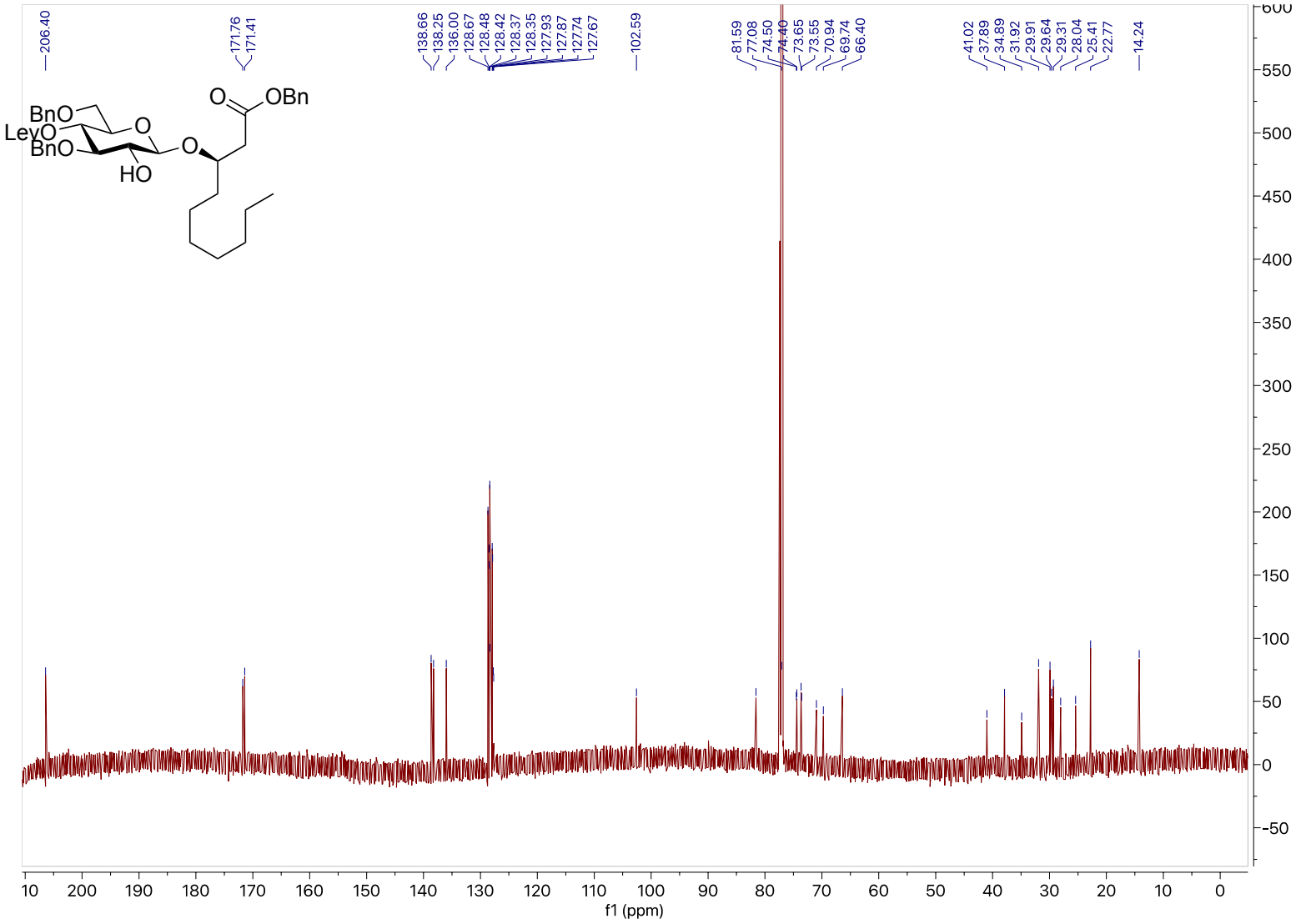
Supplementary figure 105 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 36



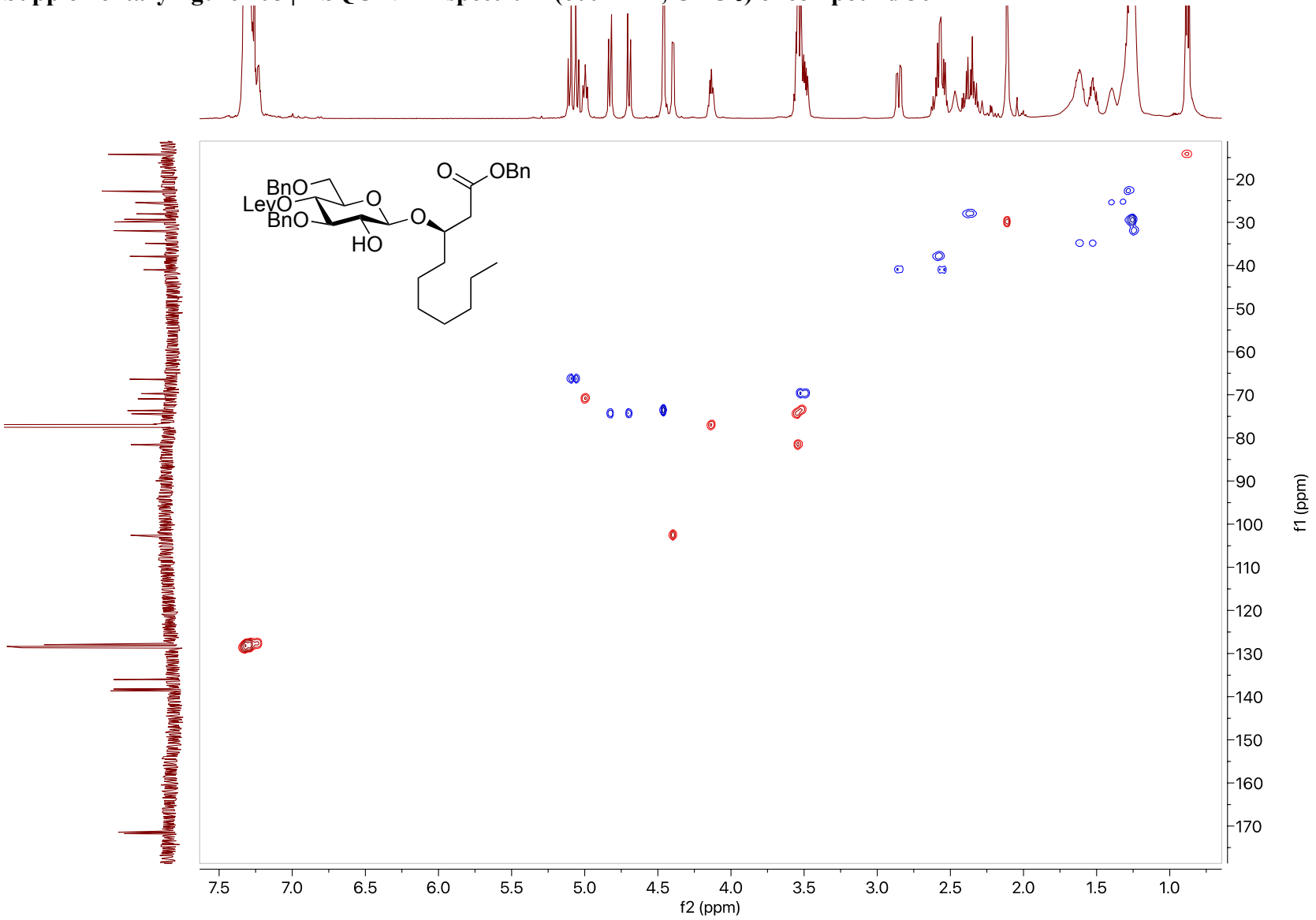
Supplementary figure 106 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 36



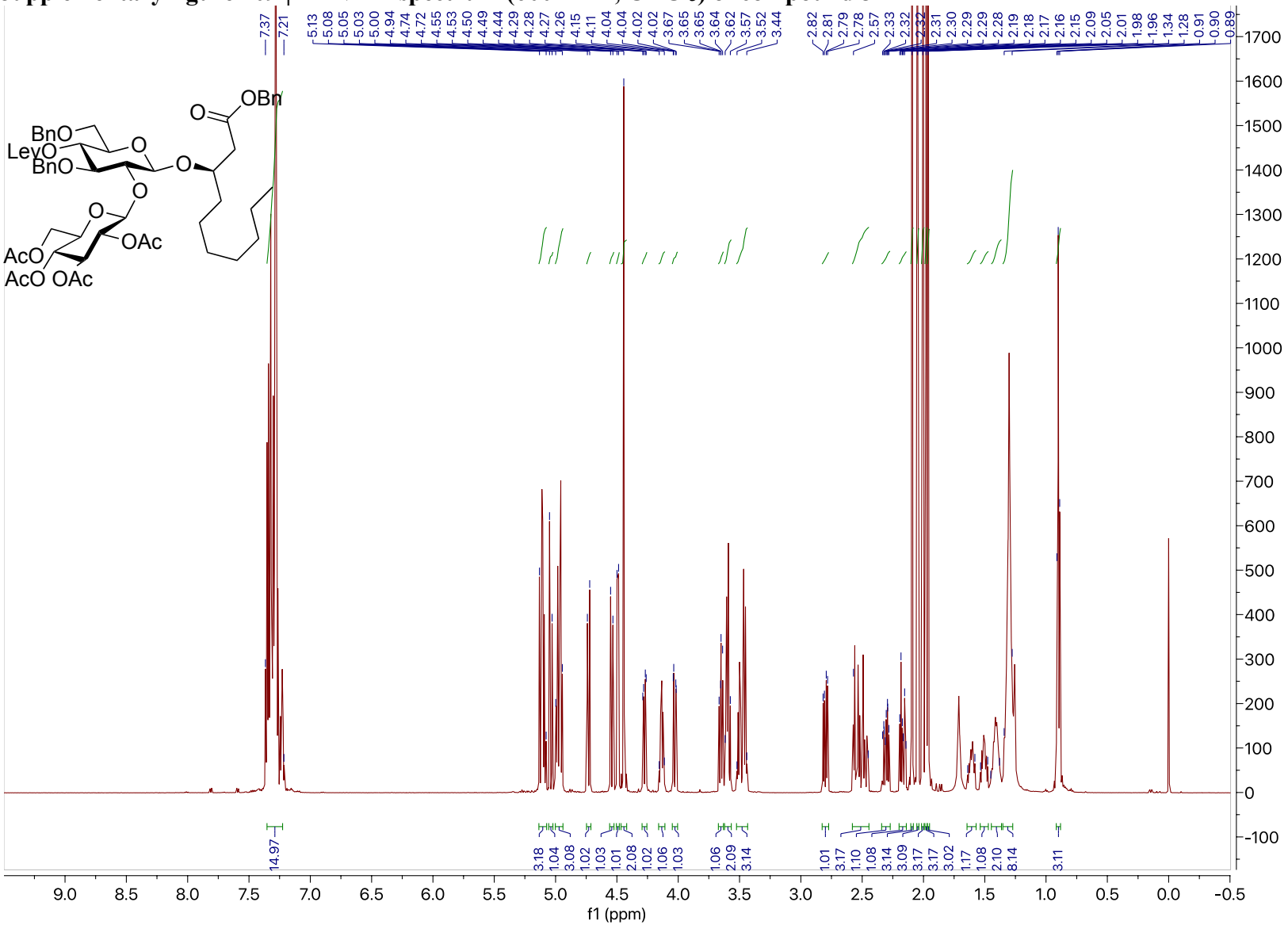
Supplementary figure 107 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 36



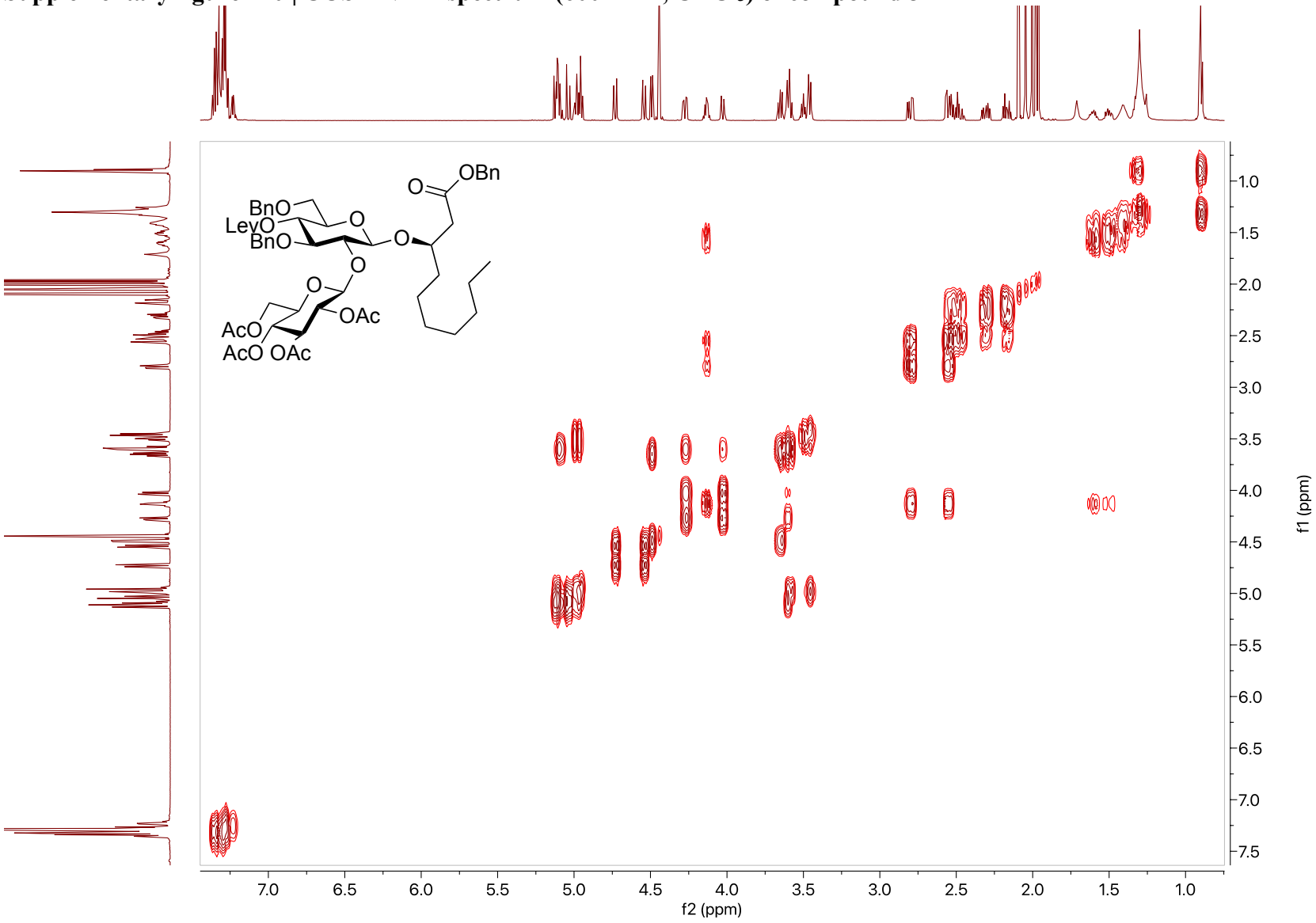
Supplementary figure 108 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 36



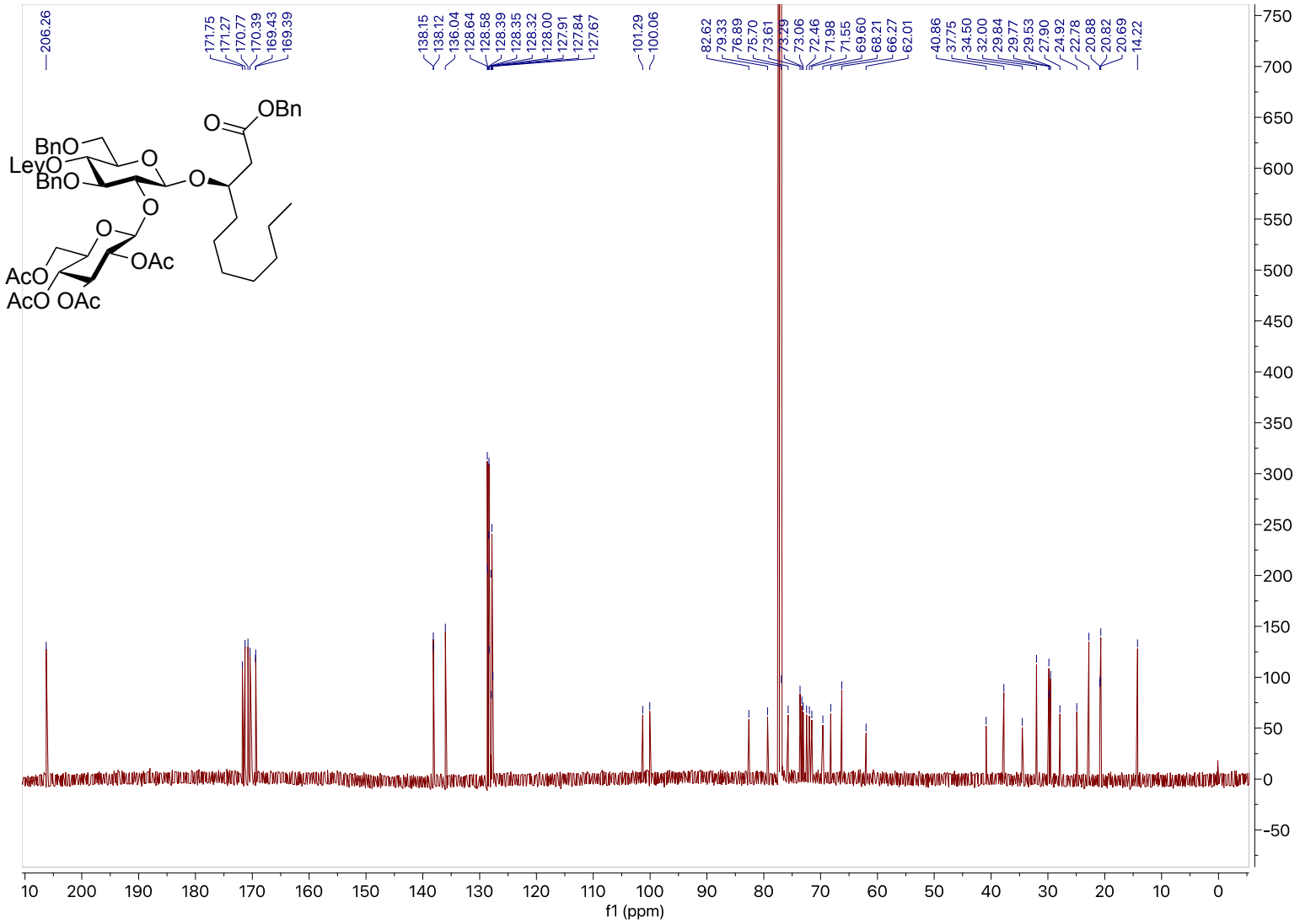
Supplementary figure 109 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 37



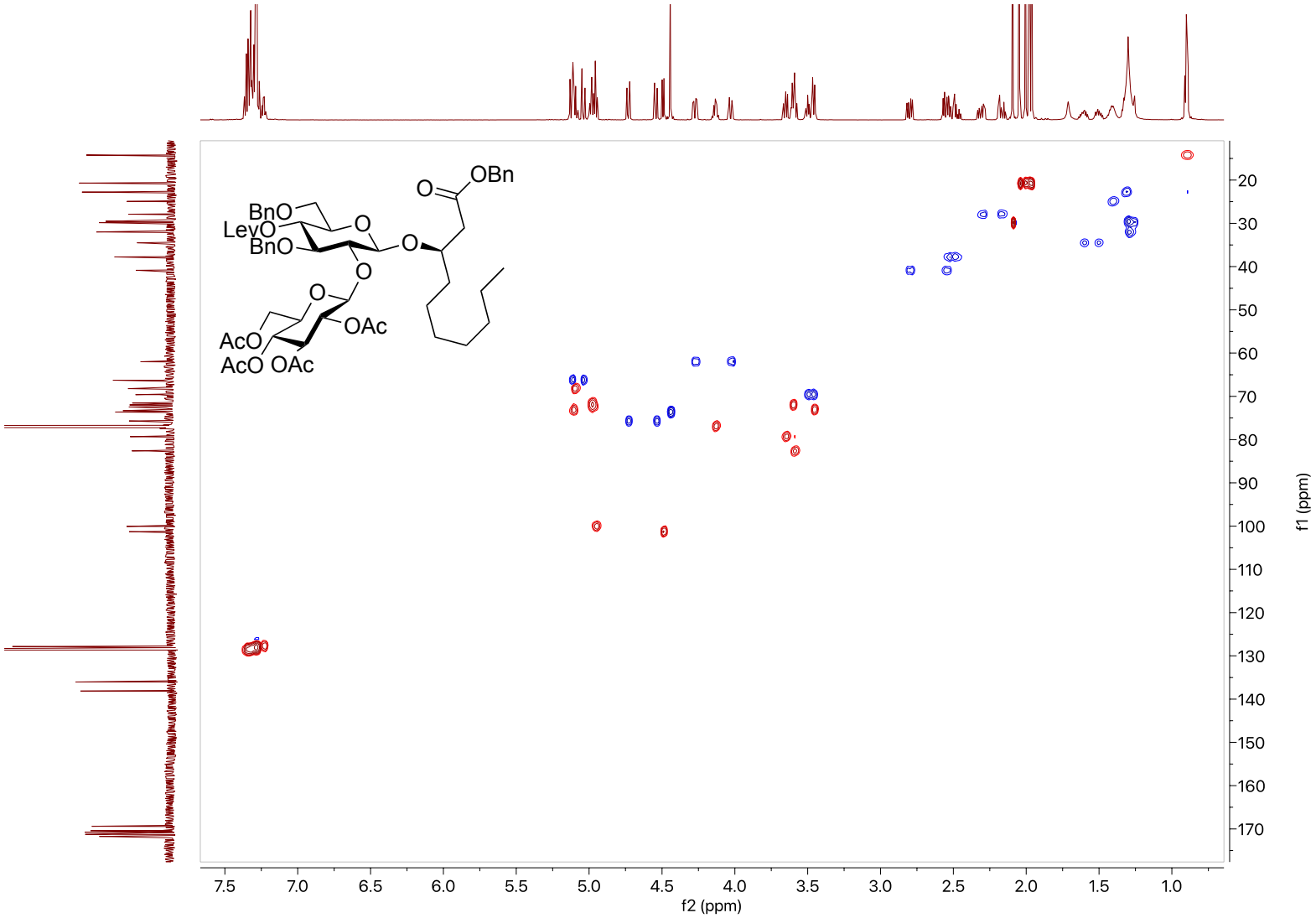
Supplementary figure 110 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 37



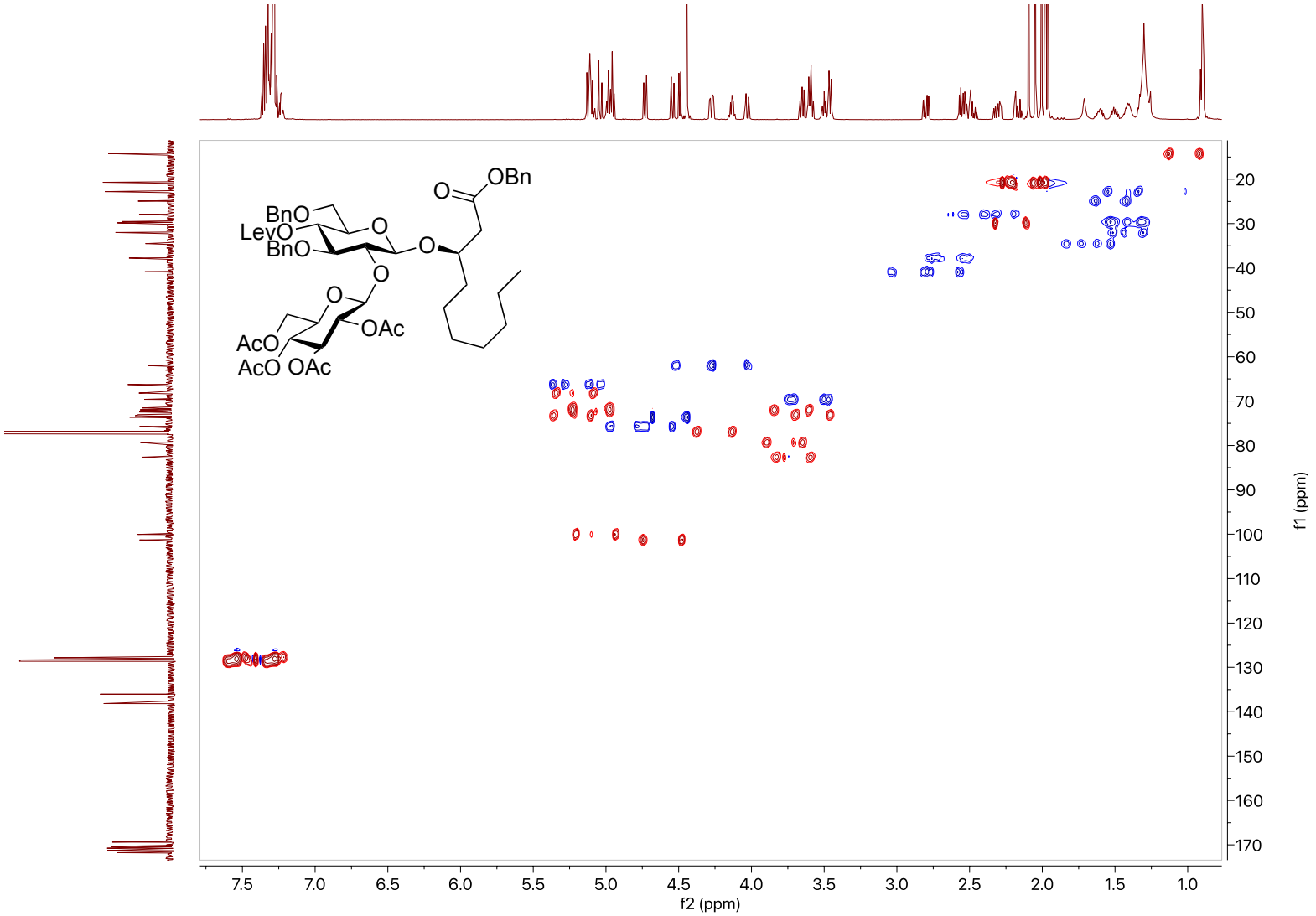
Supplementary figure 111 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 37



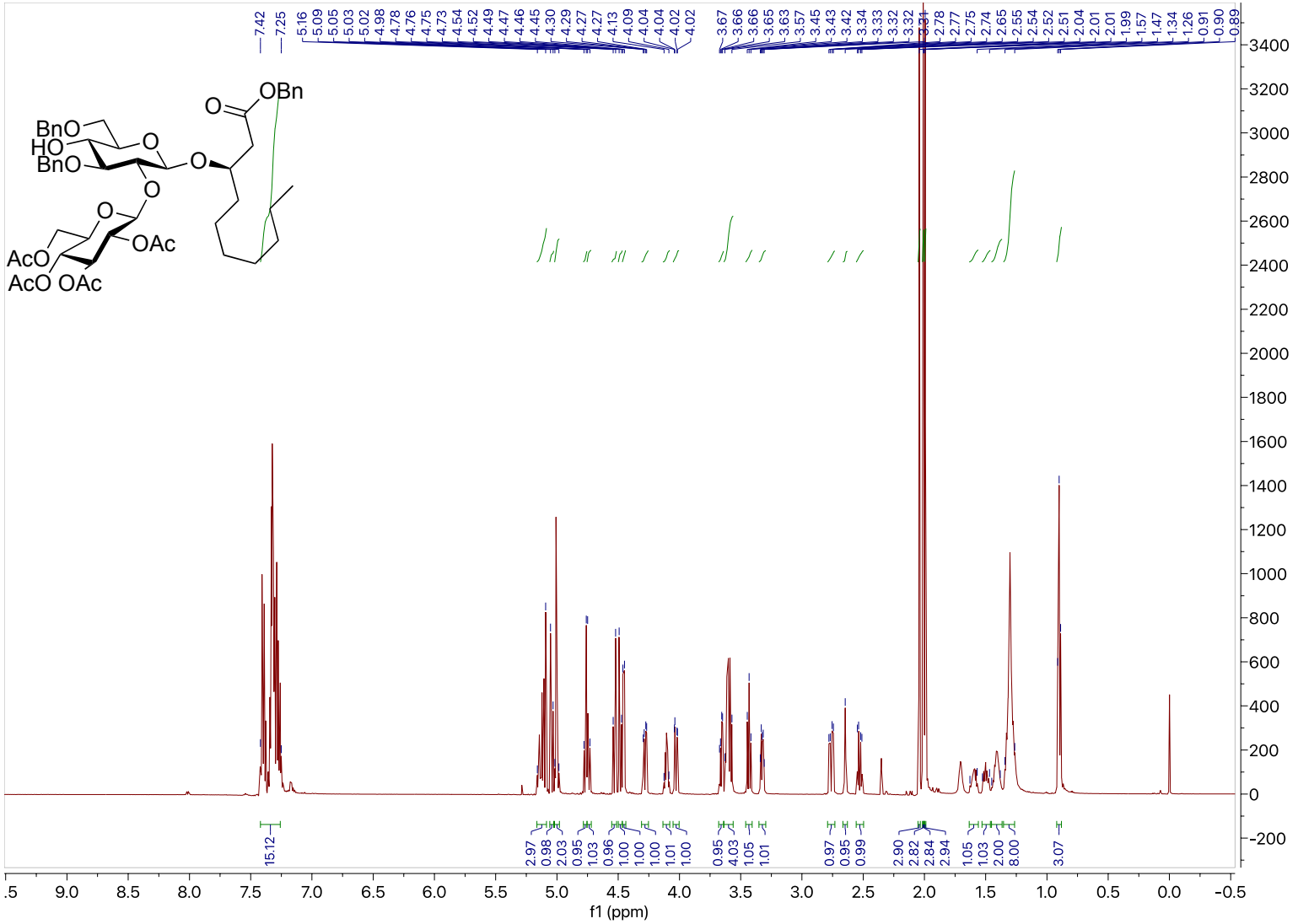
Supplementary figure 112 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 37



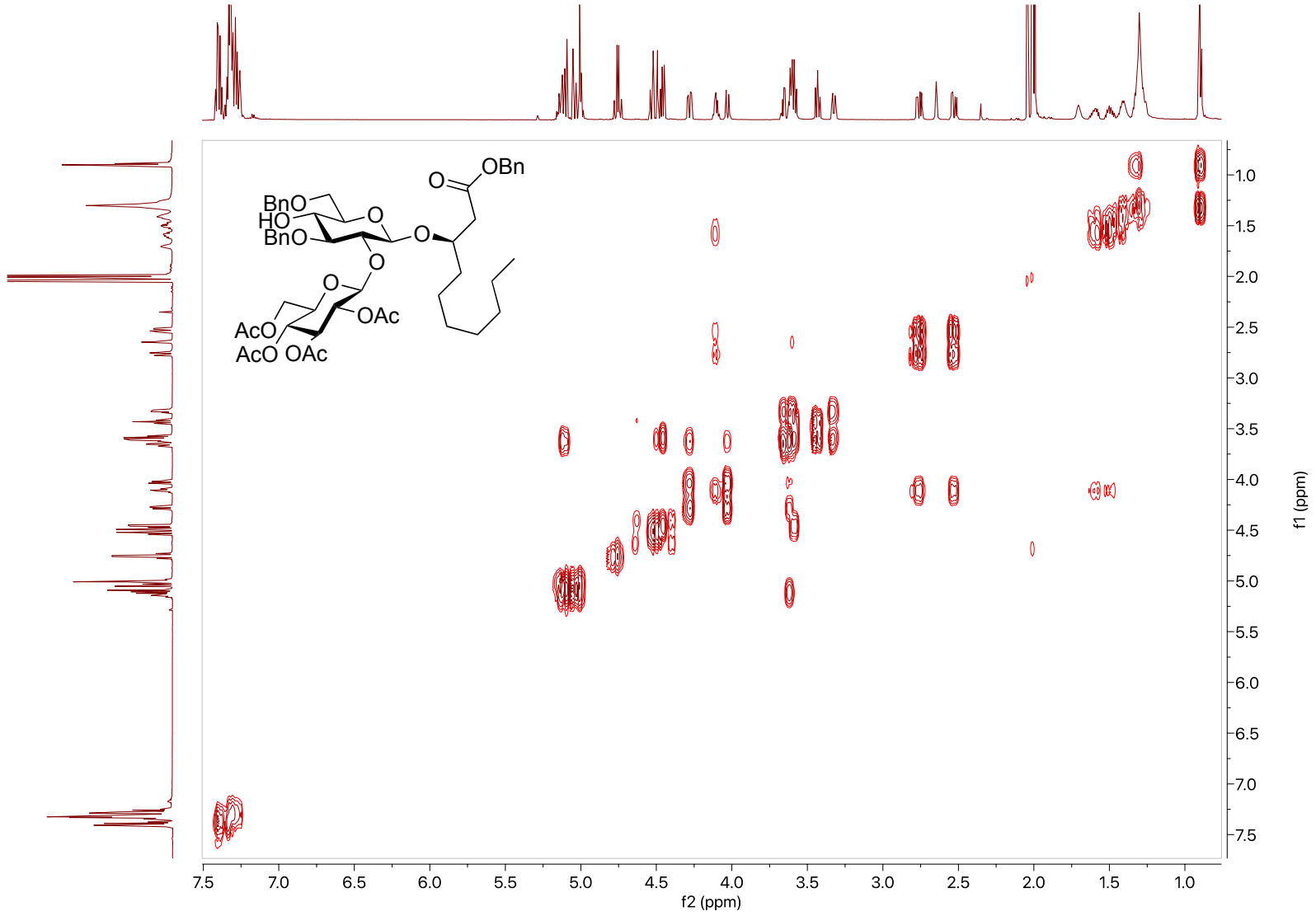
Supplementary figure 113 | undecoupled-HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 37



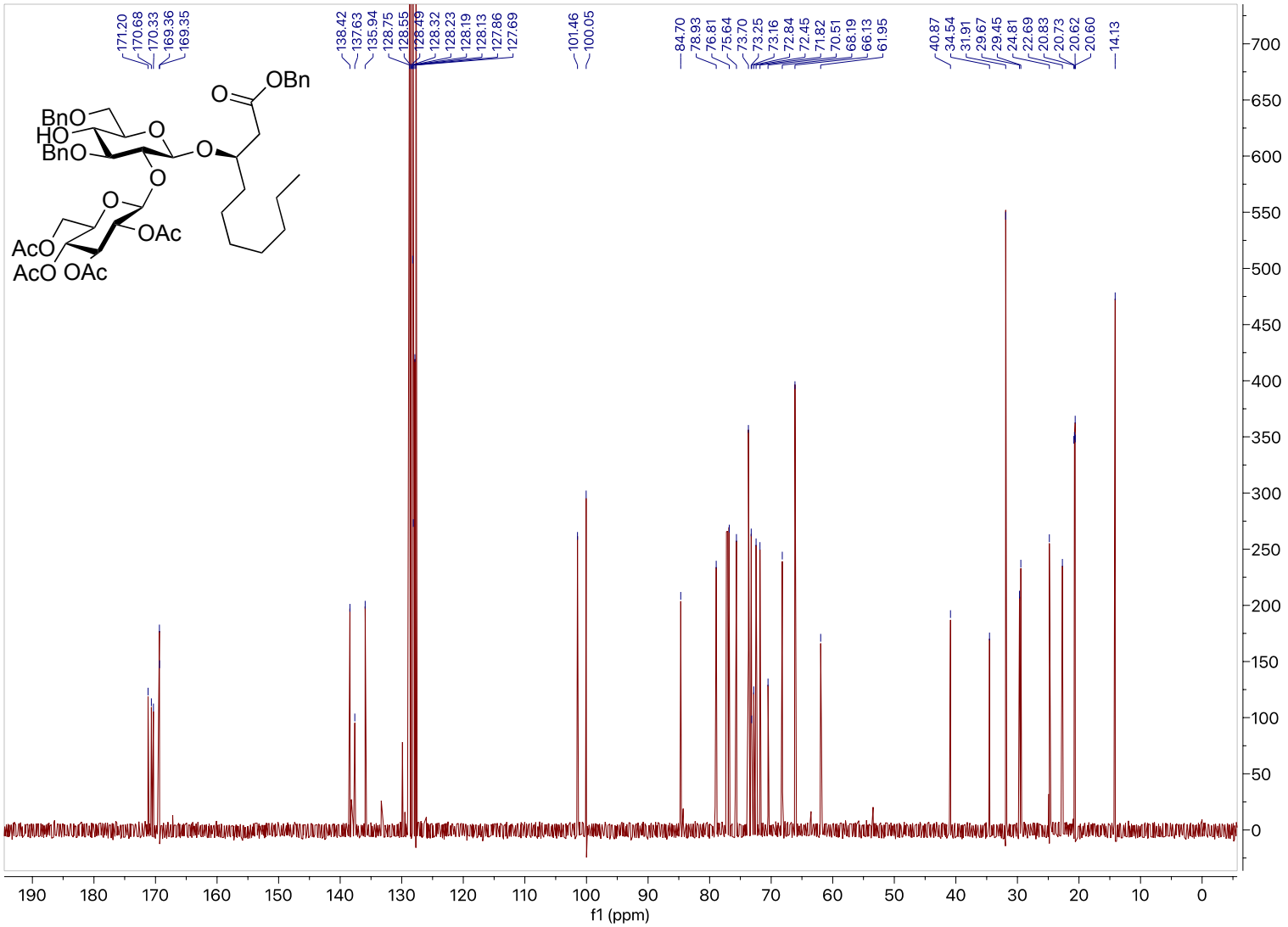
Supplementary figure 114 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 3



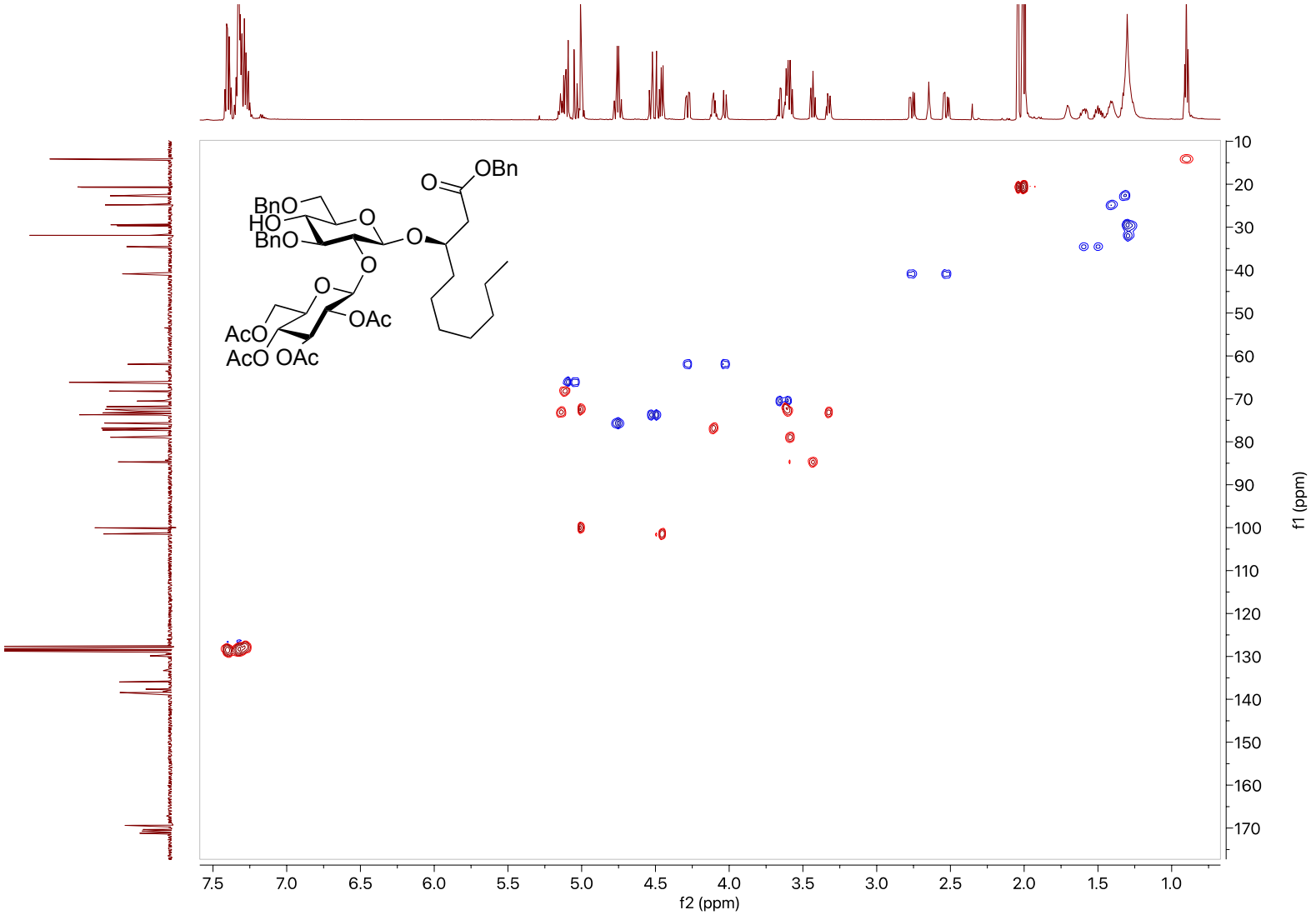
Supplementary figure 115 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 3



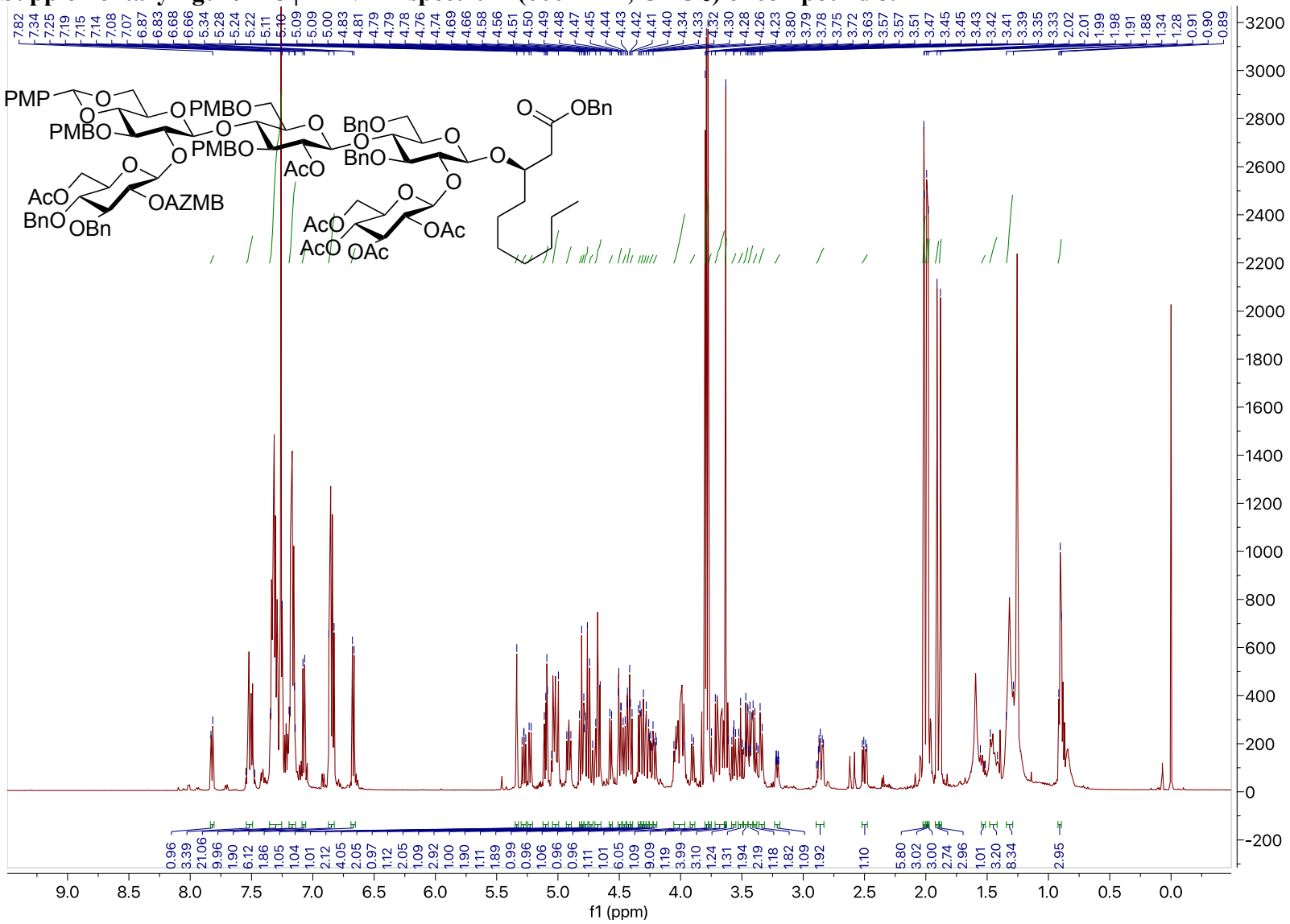
Supplementary figure 116 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 3



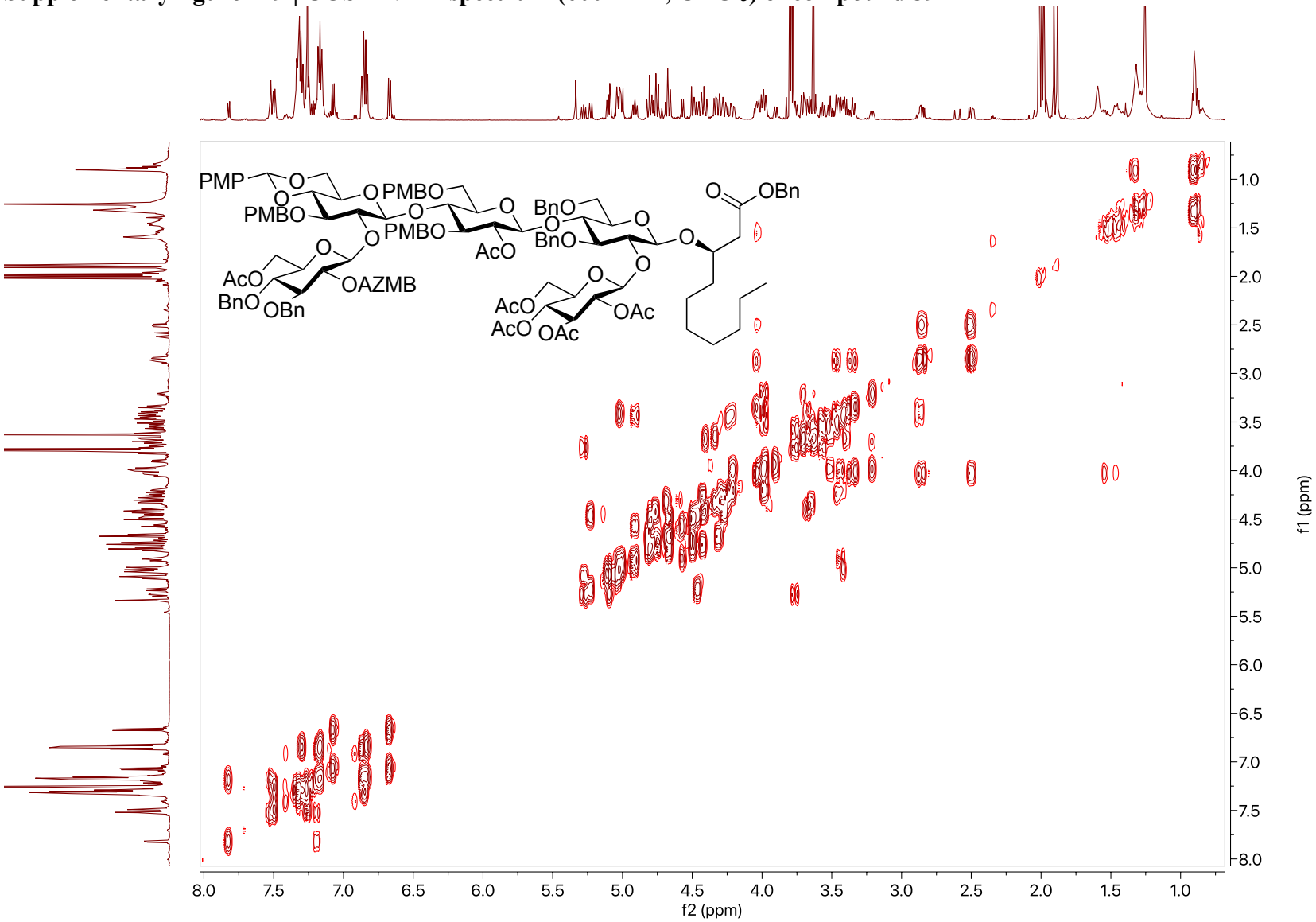
Supplementary figure 117 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 3



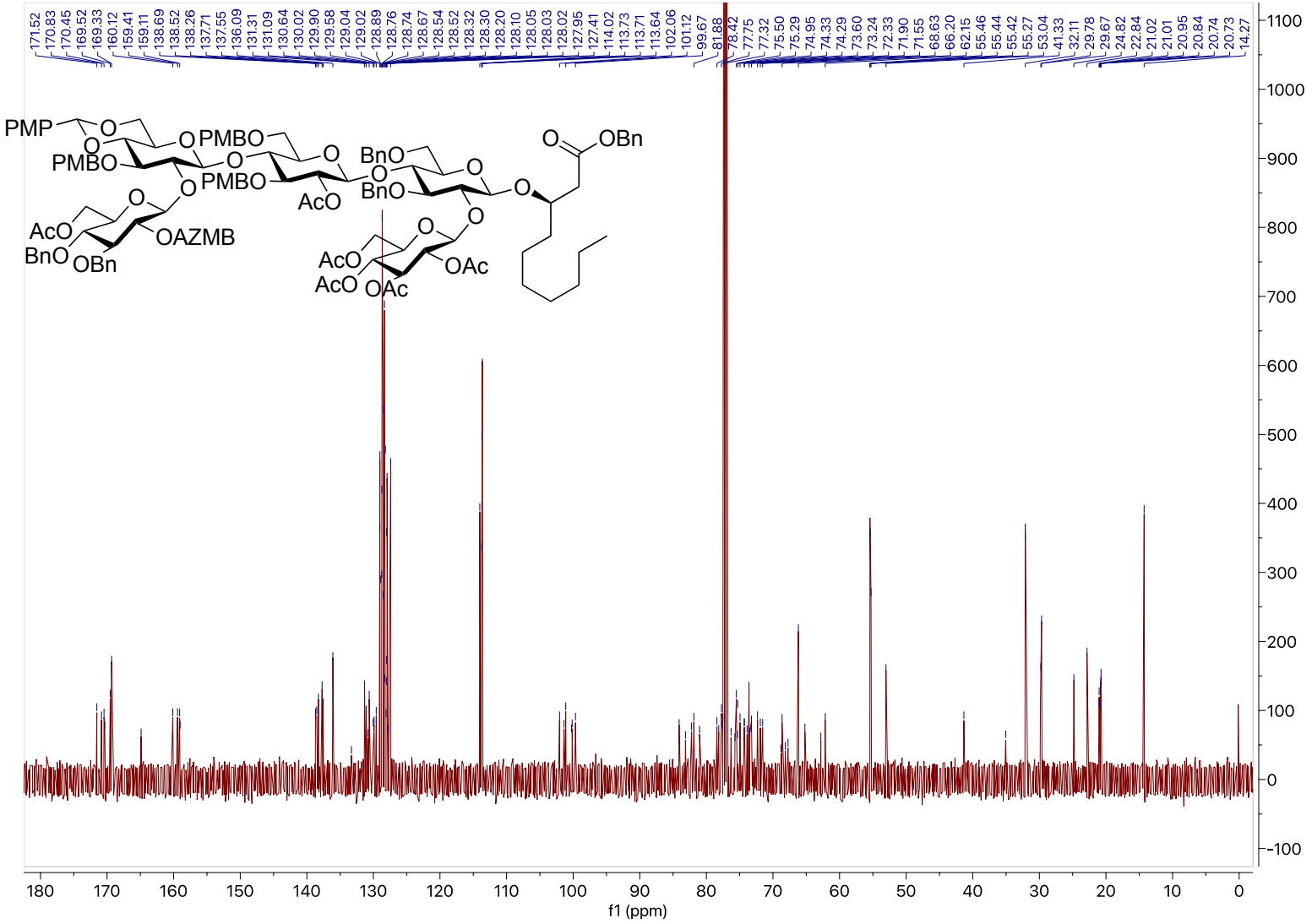
Supplementary figure 118 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 39



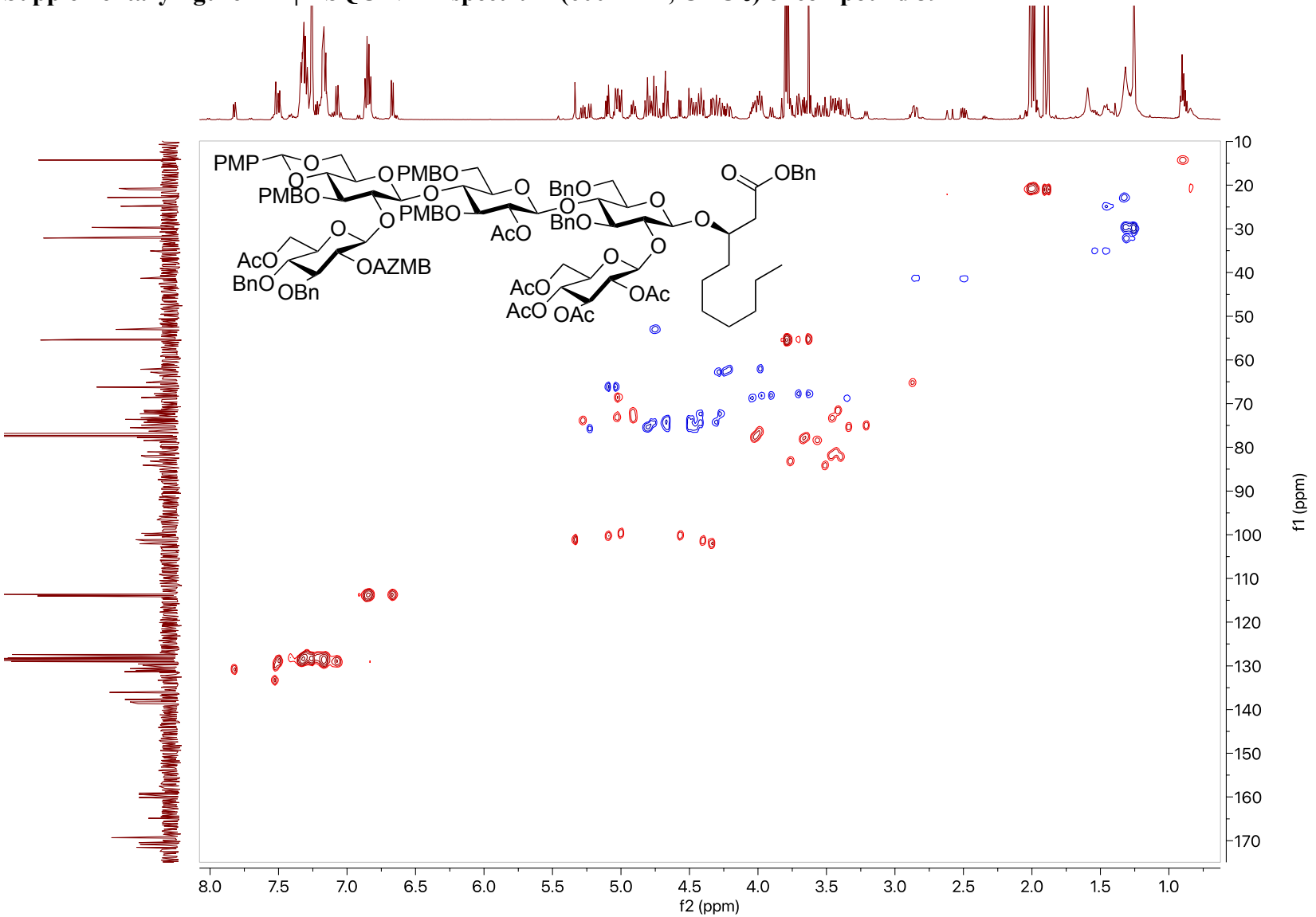
Supplementary figure 119 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 39



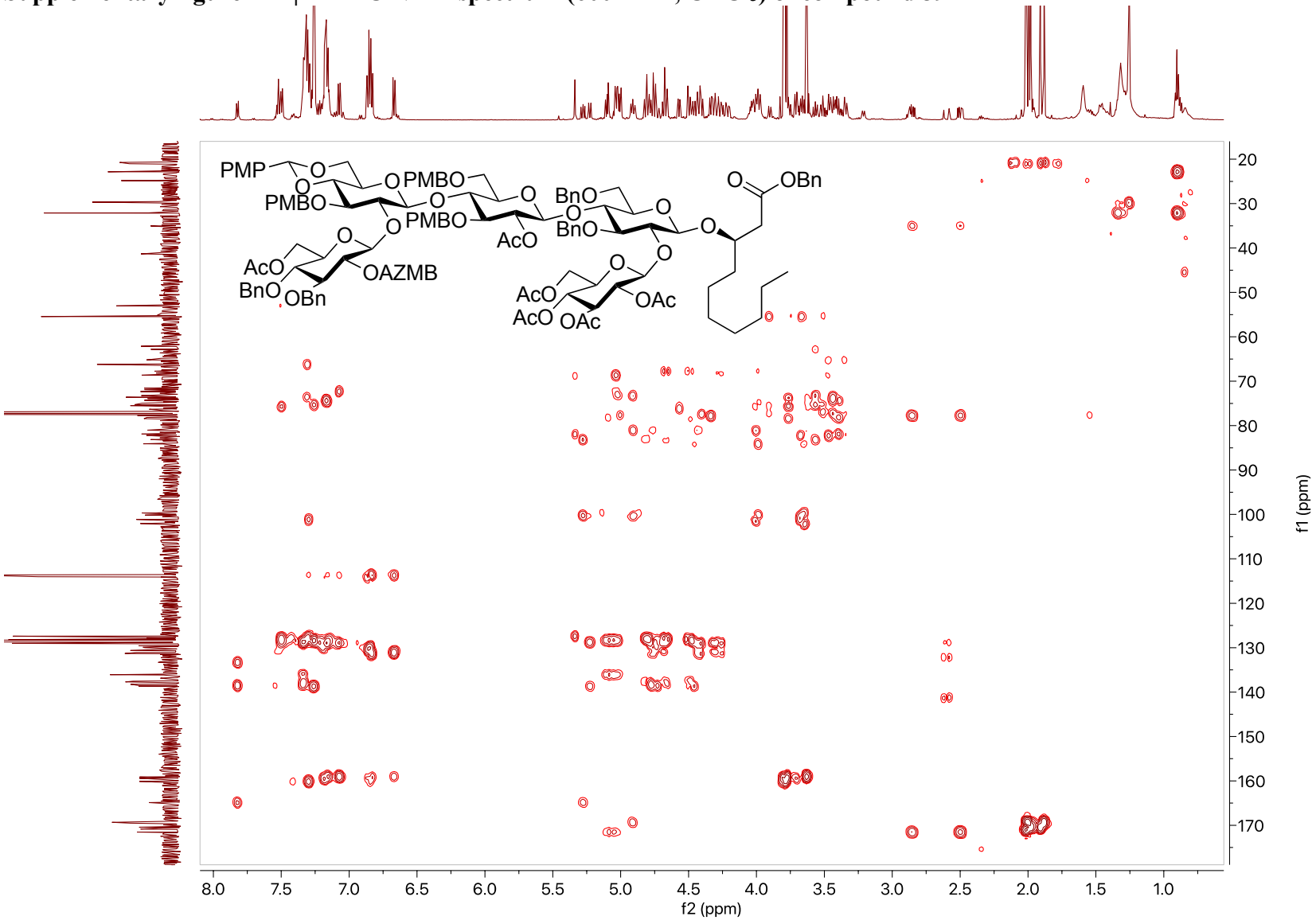
Supplementary figure 120 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 39



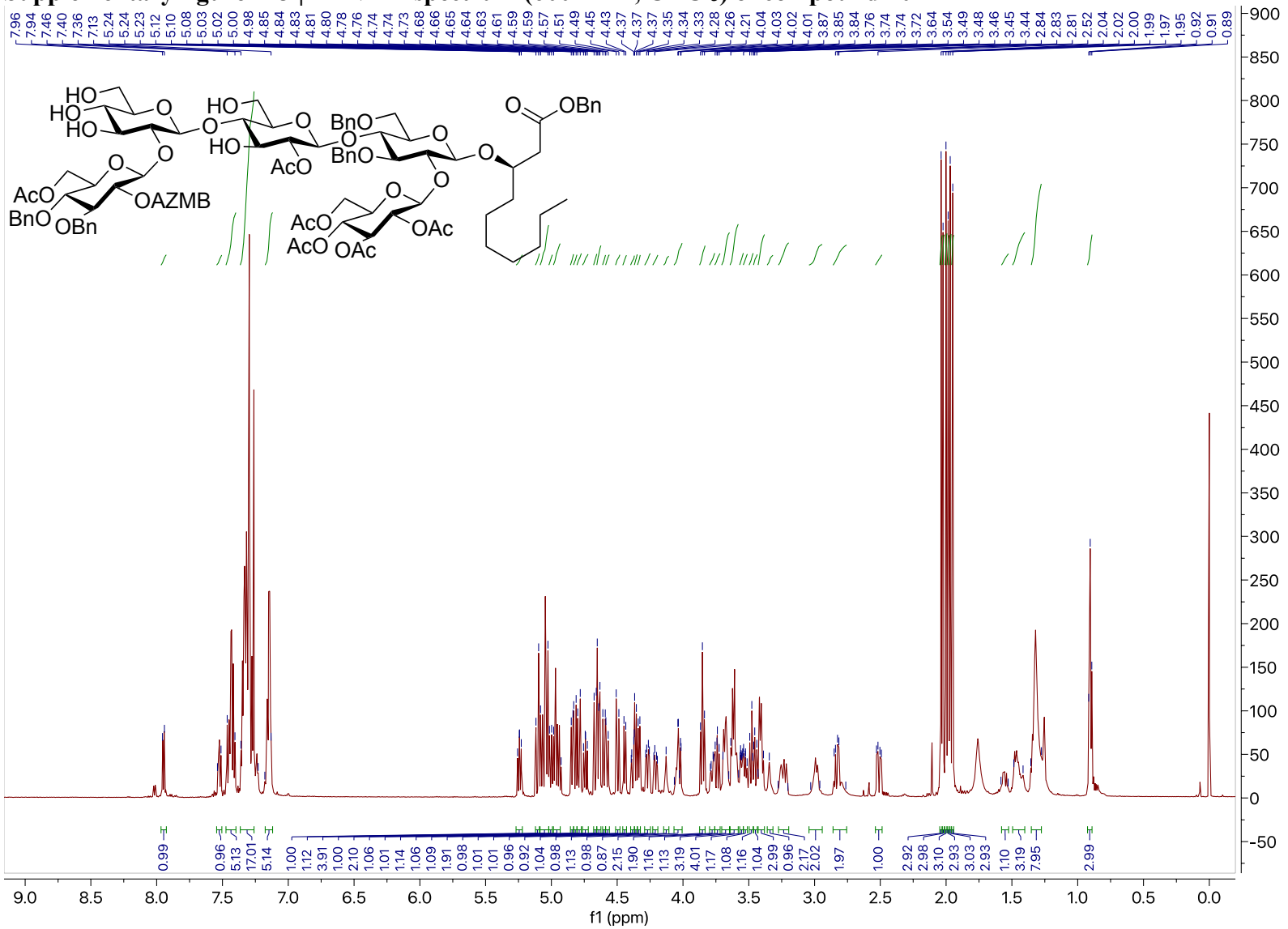
Supplementary figure 121 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 39



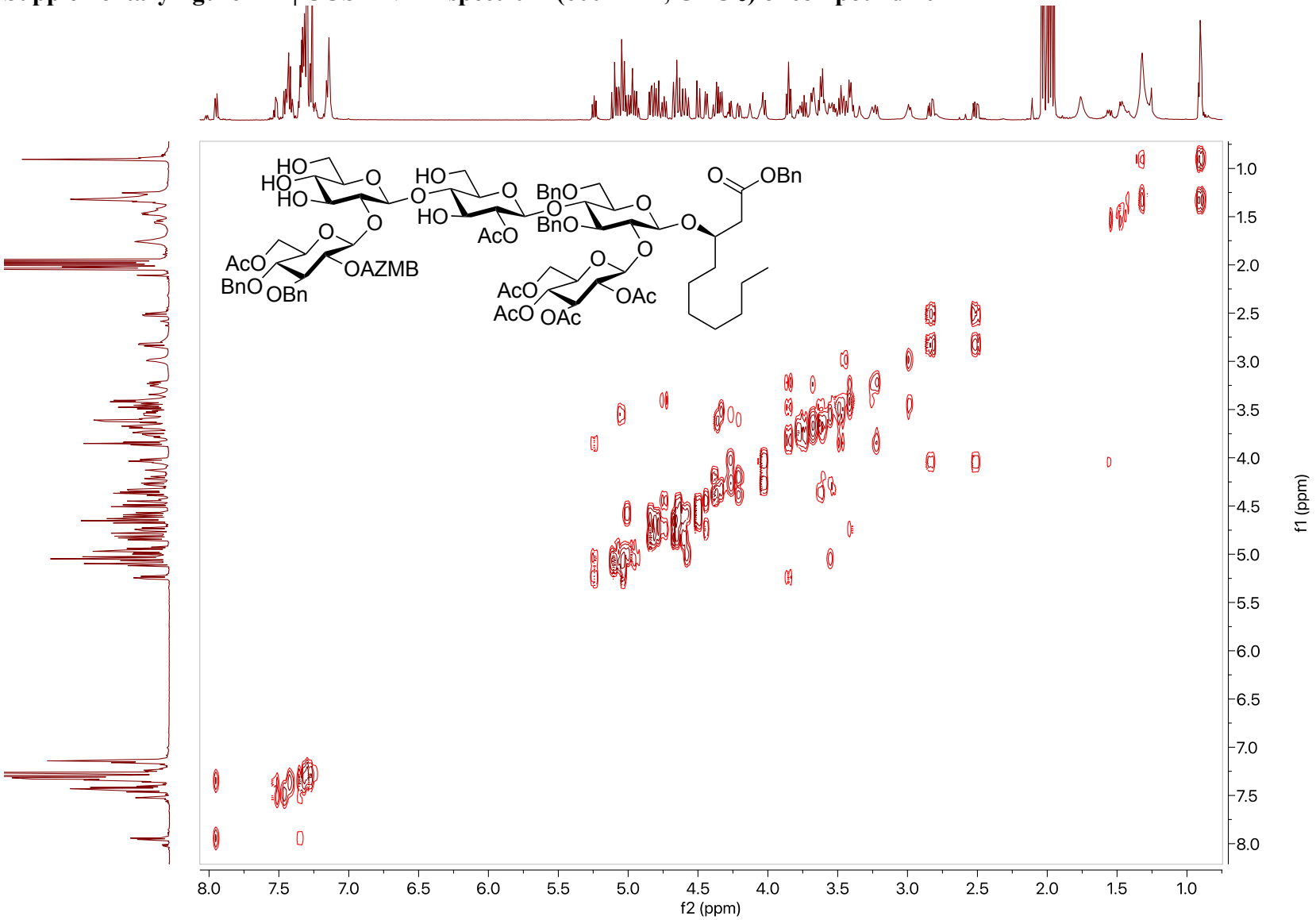
Supplementary figure 122 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 39



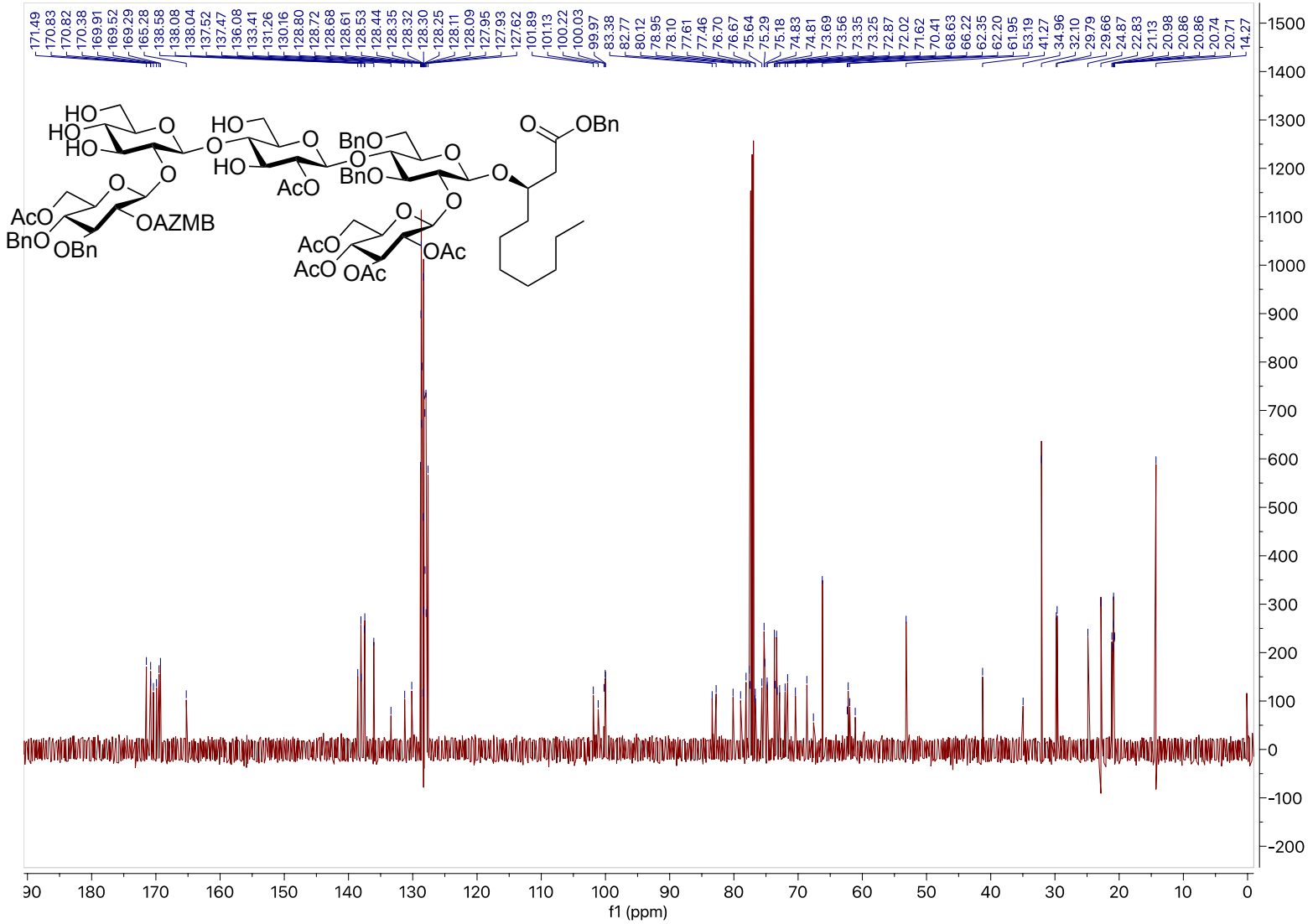
Supplementary figure 123 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 40



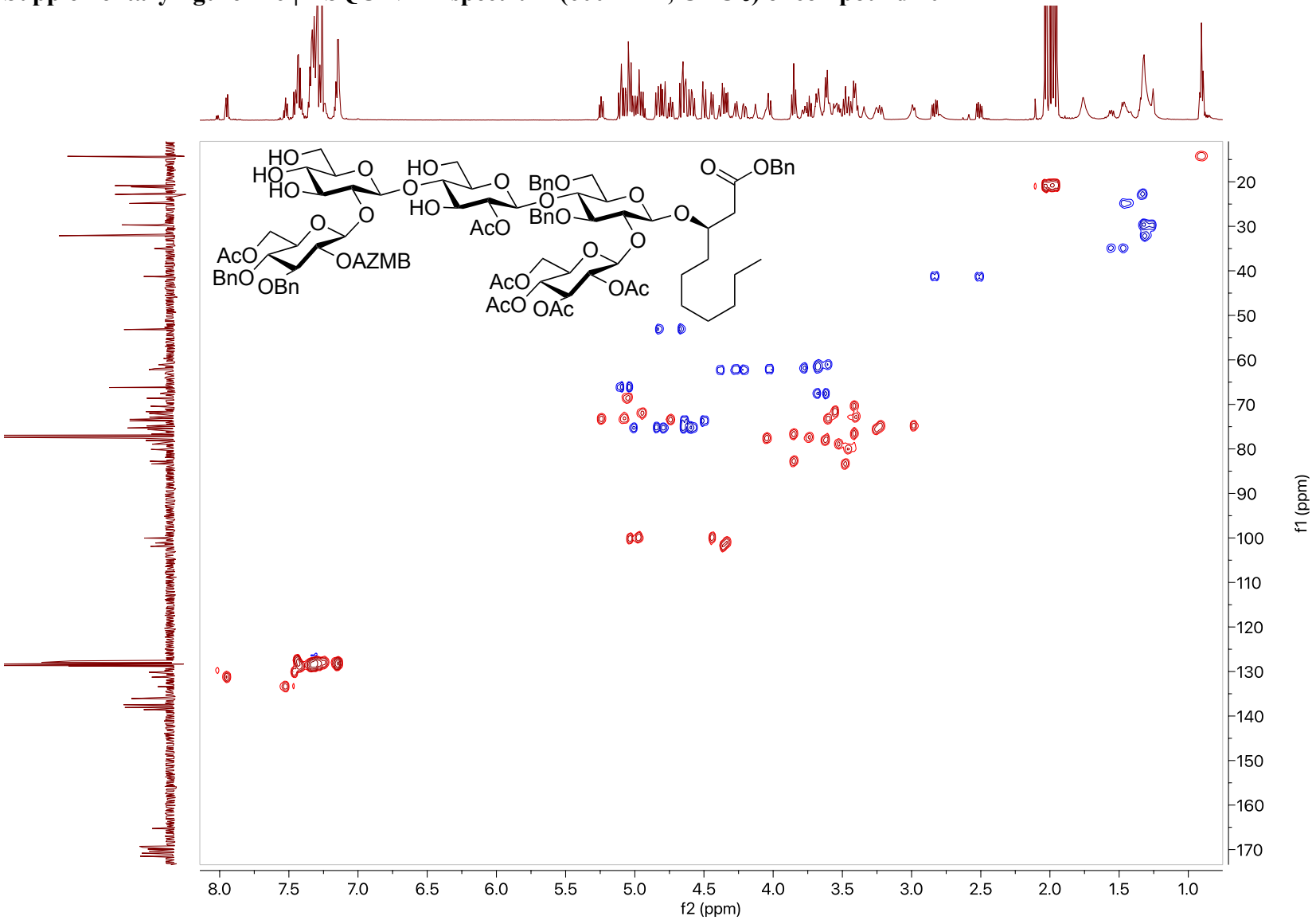
Supplementary figure 124 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 40



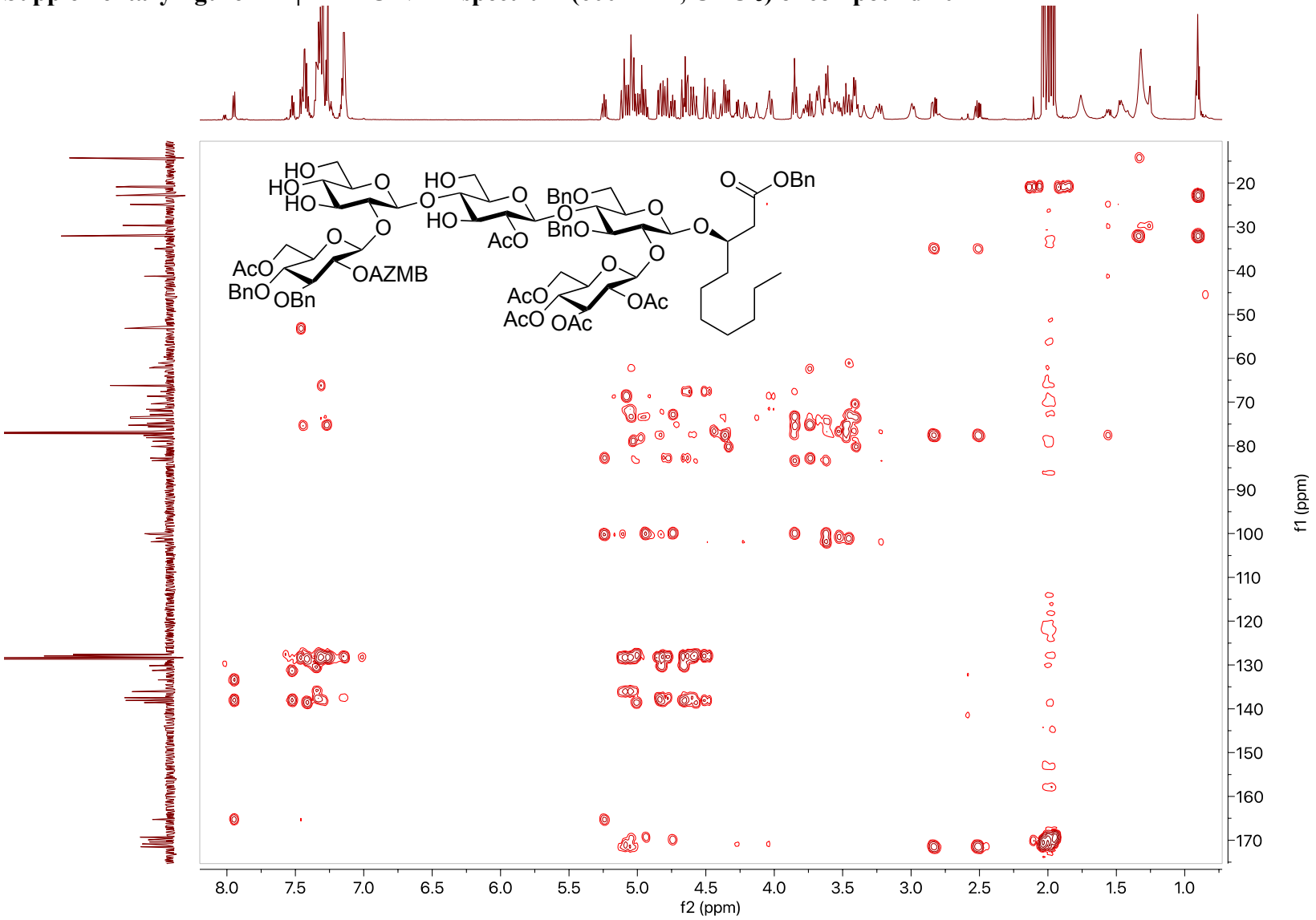
Supplementary figure 125 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 40



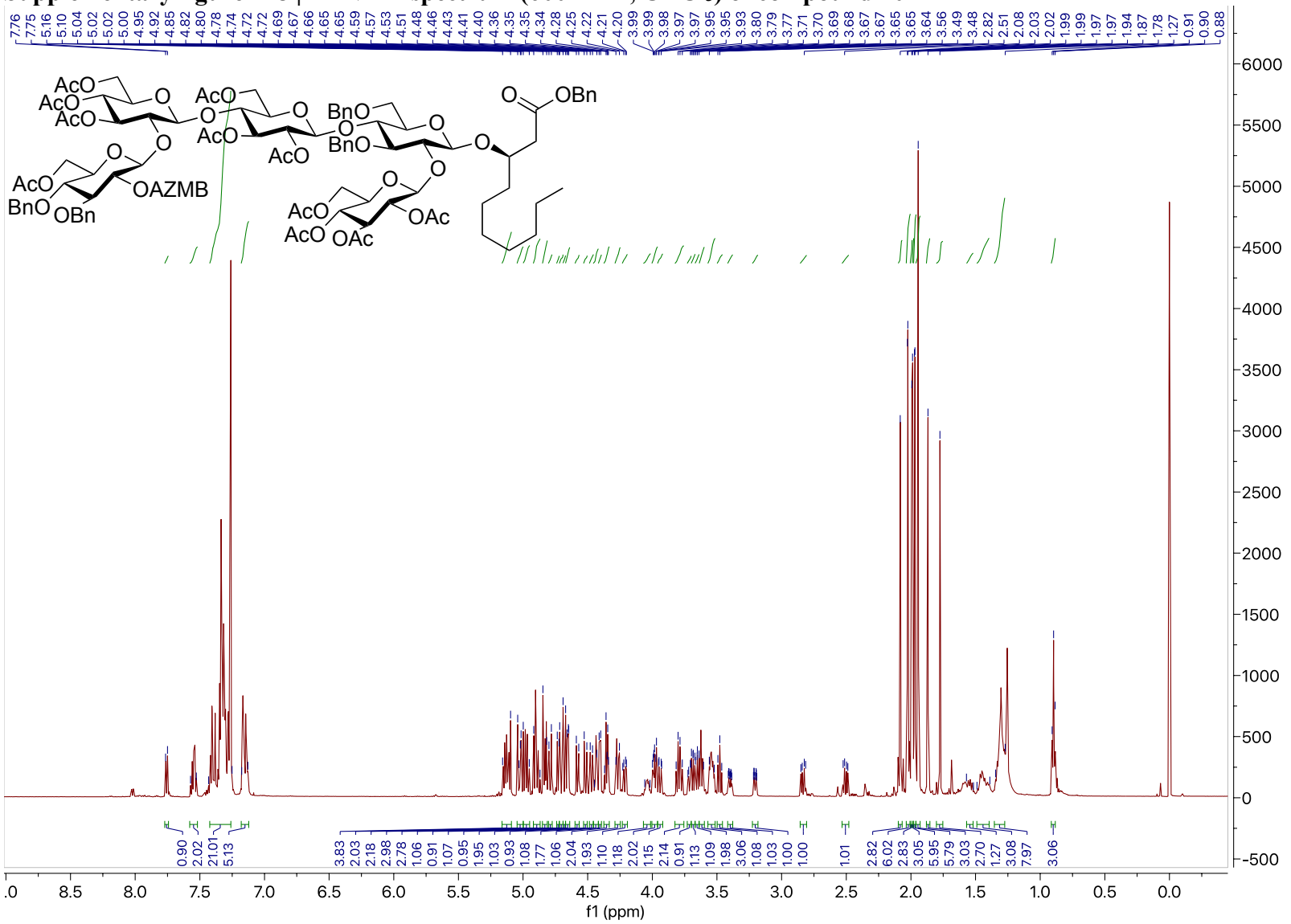
Supplementary figure 126 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 40



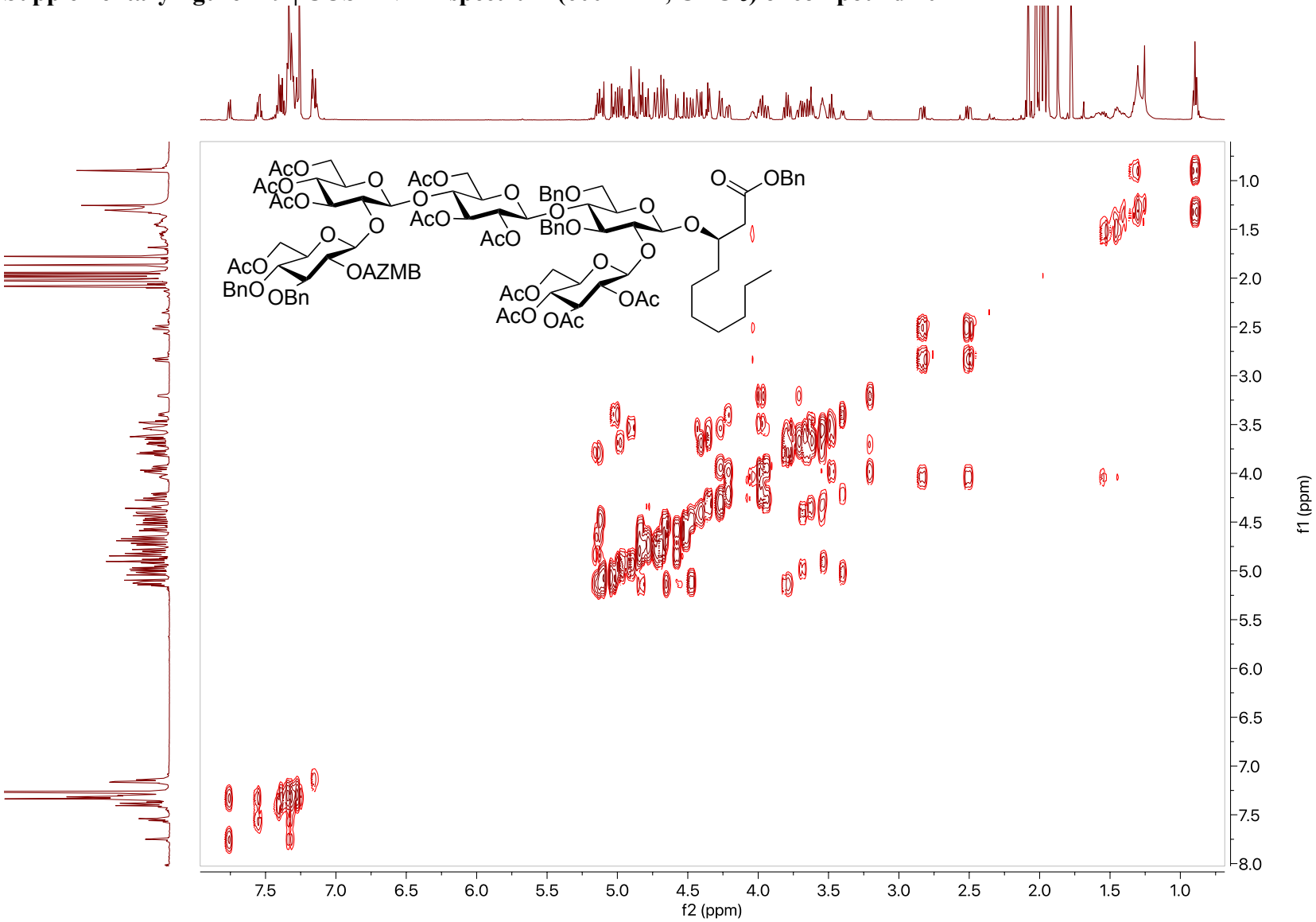
Supplementary figure 127 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 40



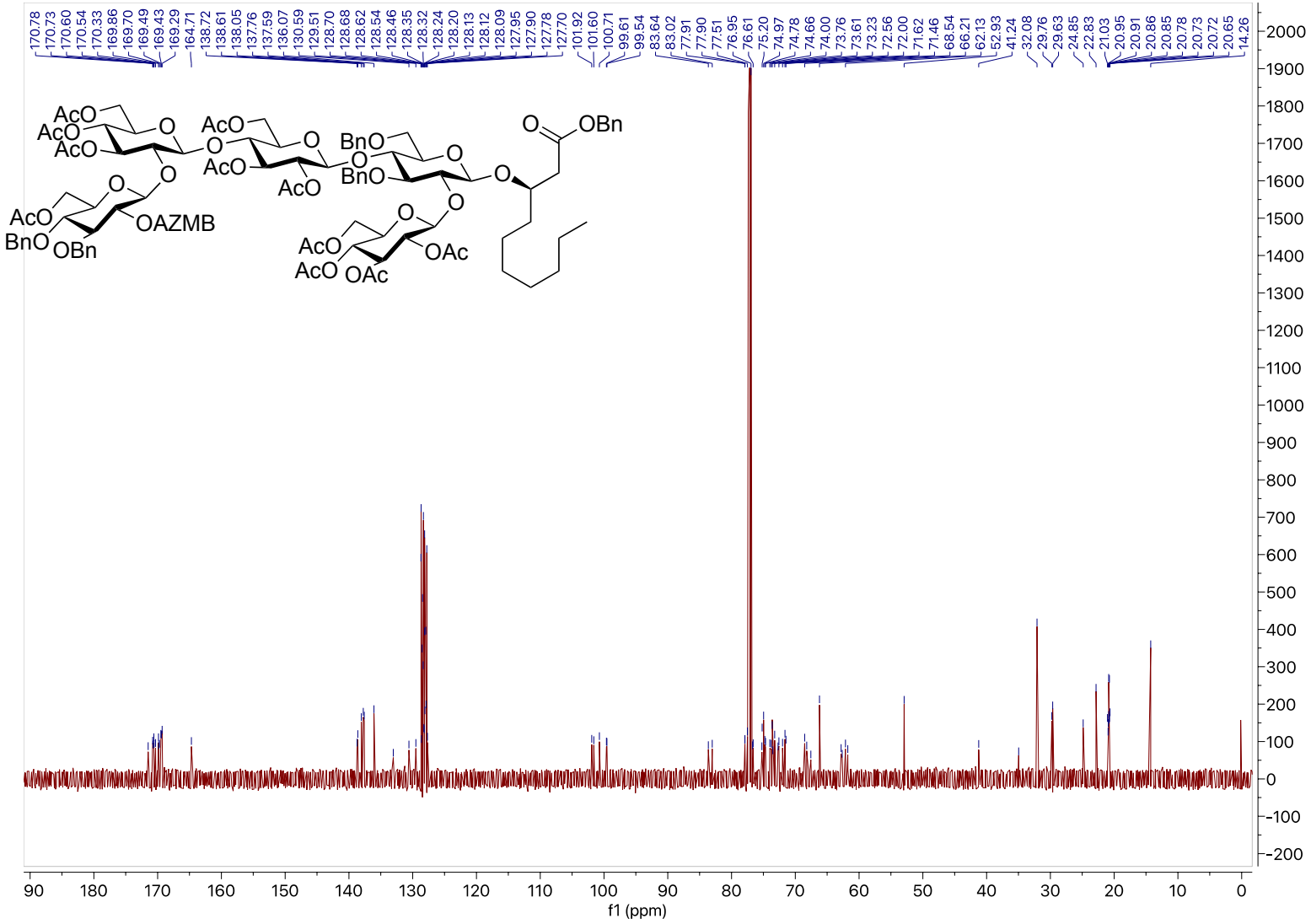
Supplementary figure 128 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 40-1



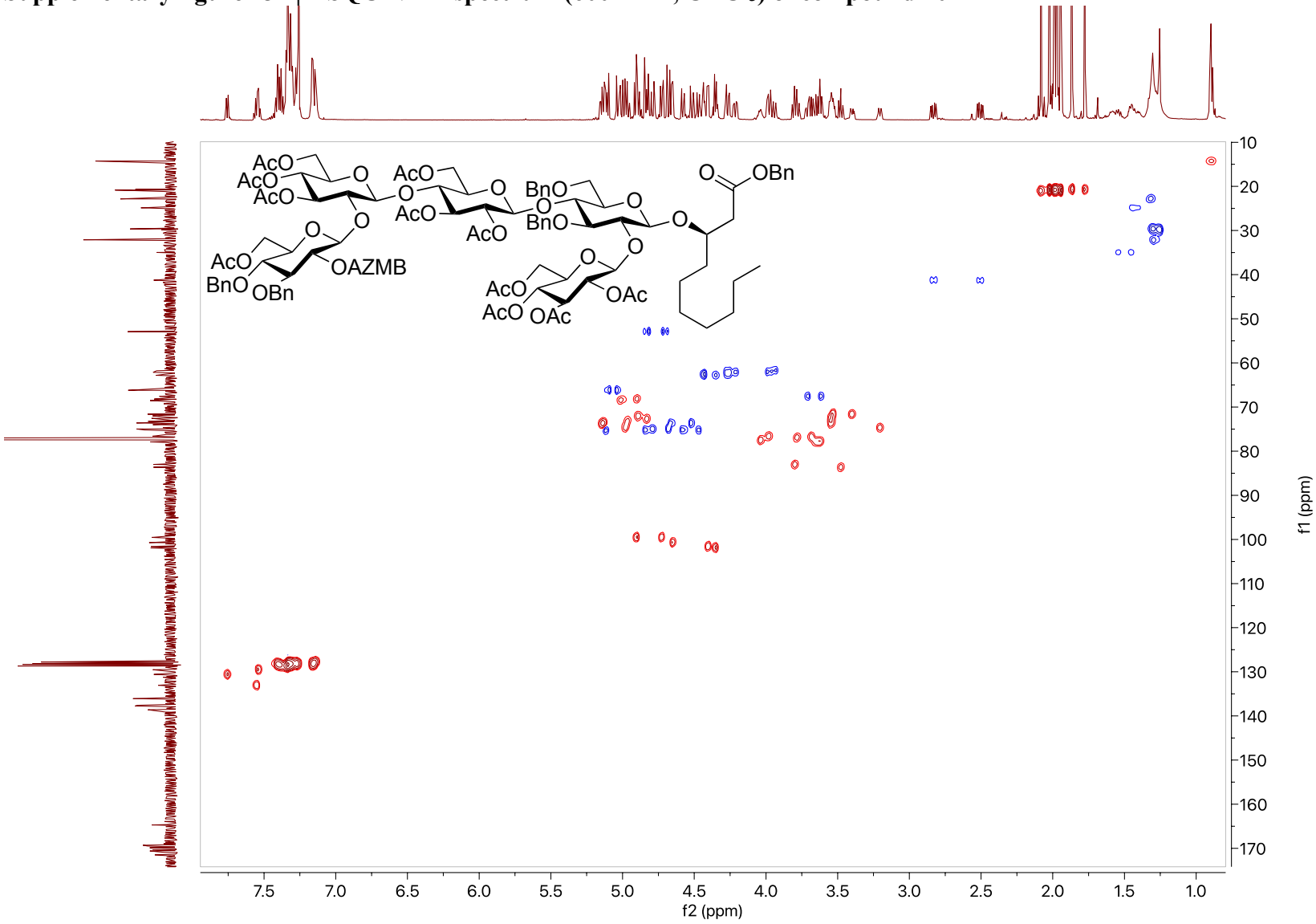
Supplementary figure 129 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 40-1



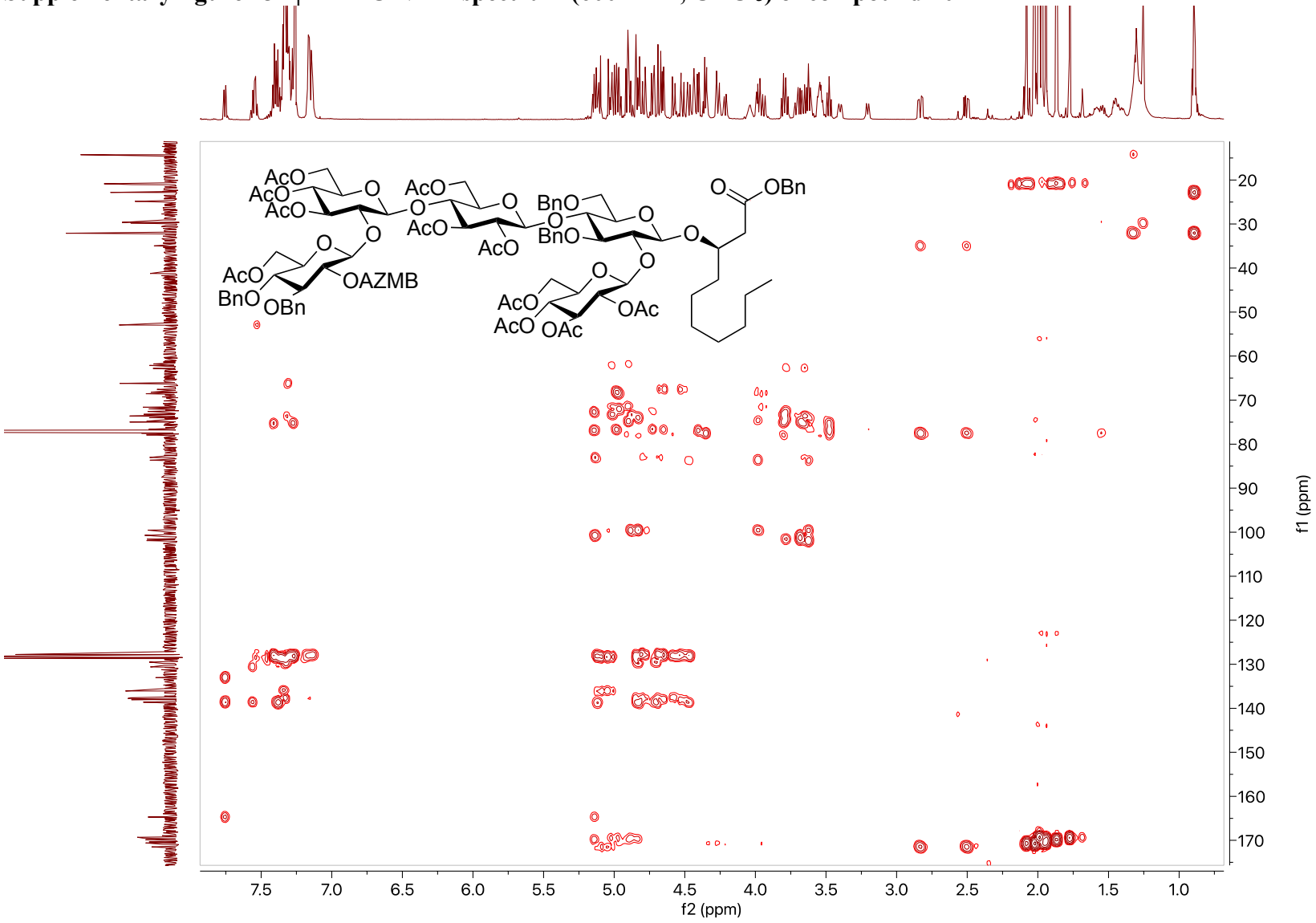
Supplementary figure 130 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 40-1



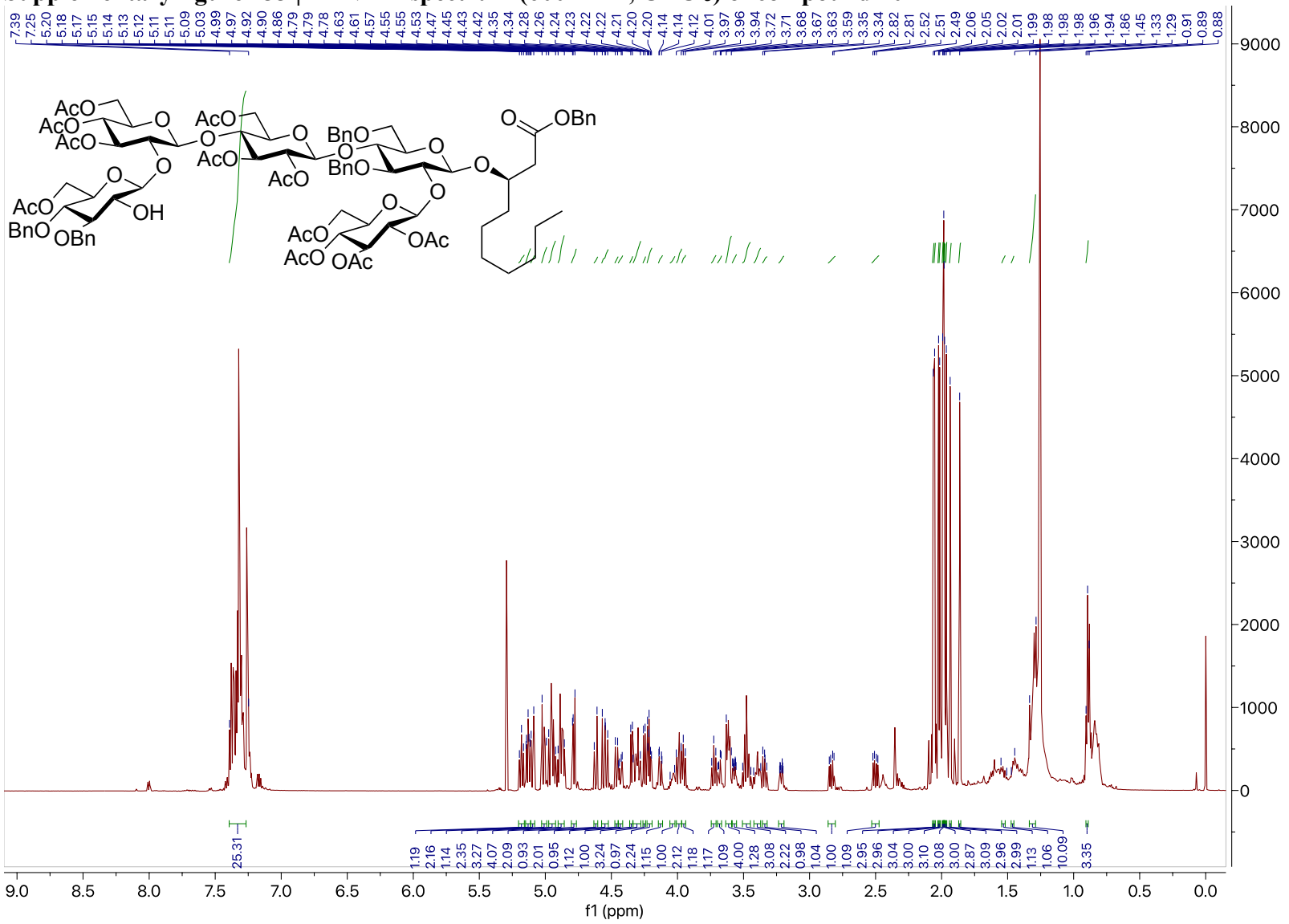
Supplementary figure 131 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 40-1



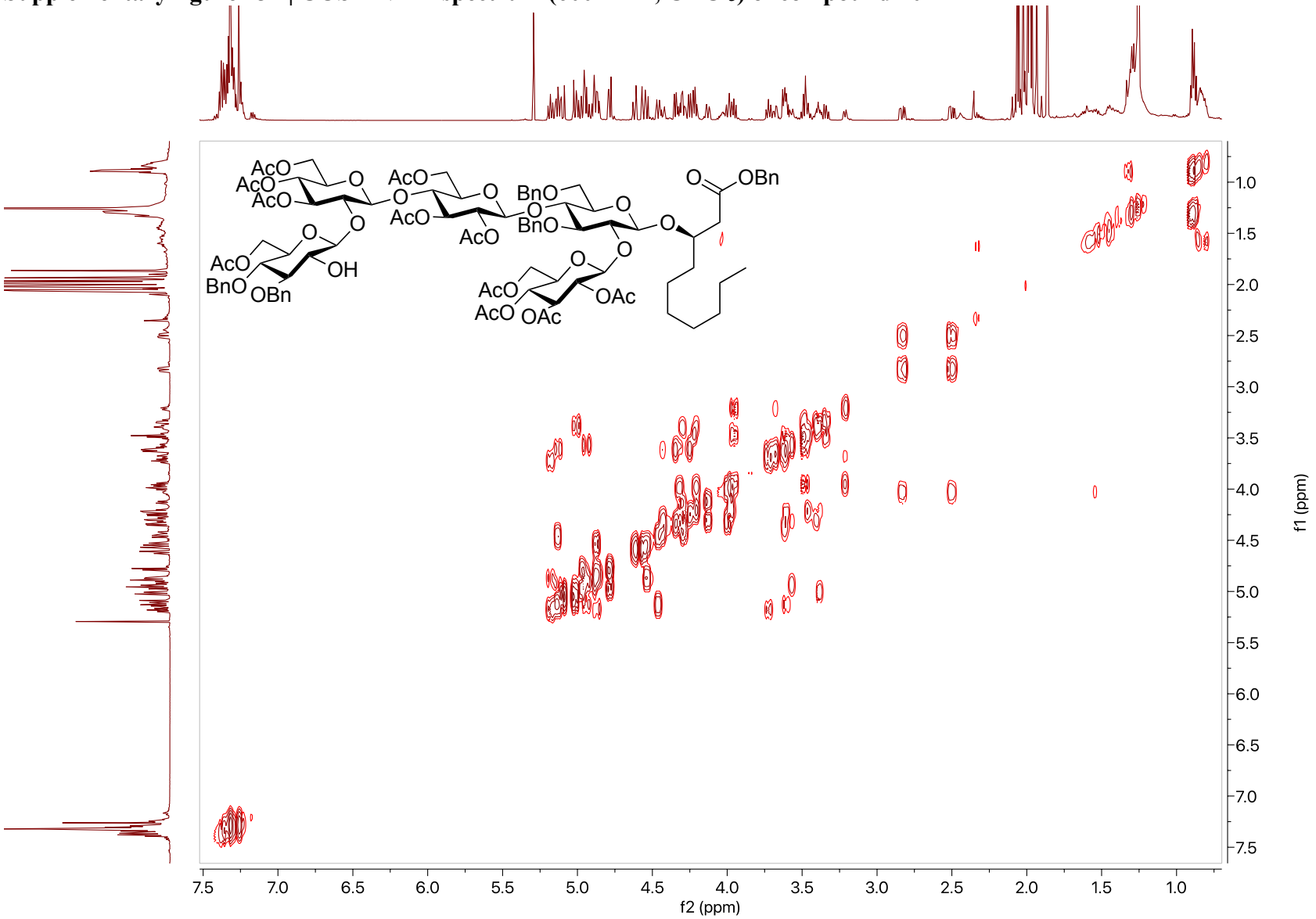
Supplementary figure 132 | HMBC NMR spectrum (600 MHz, $CDCl_3$) of compound 40-1



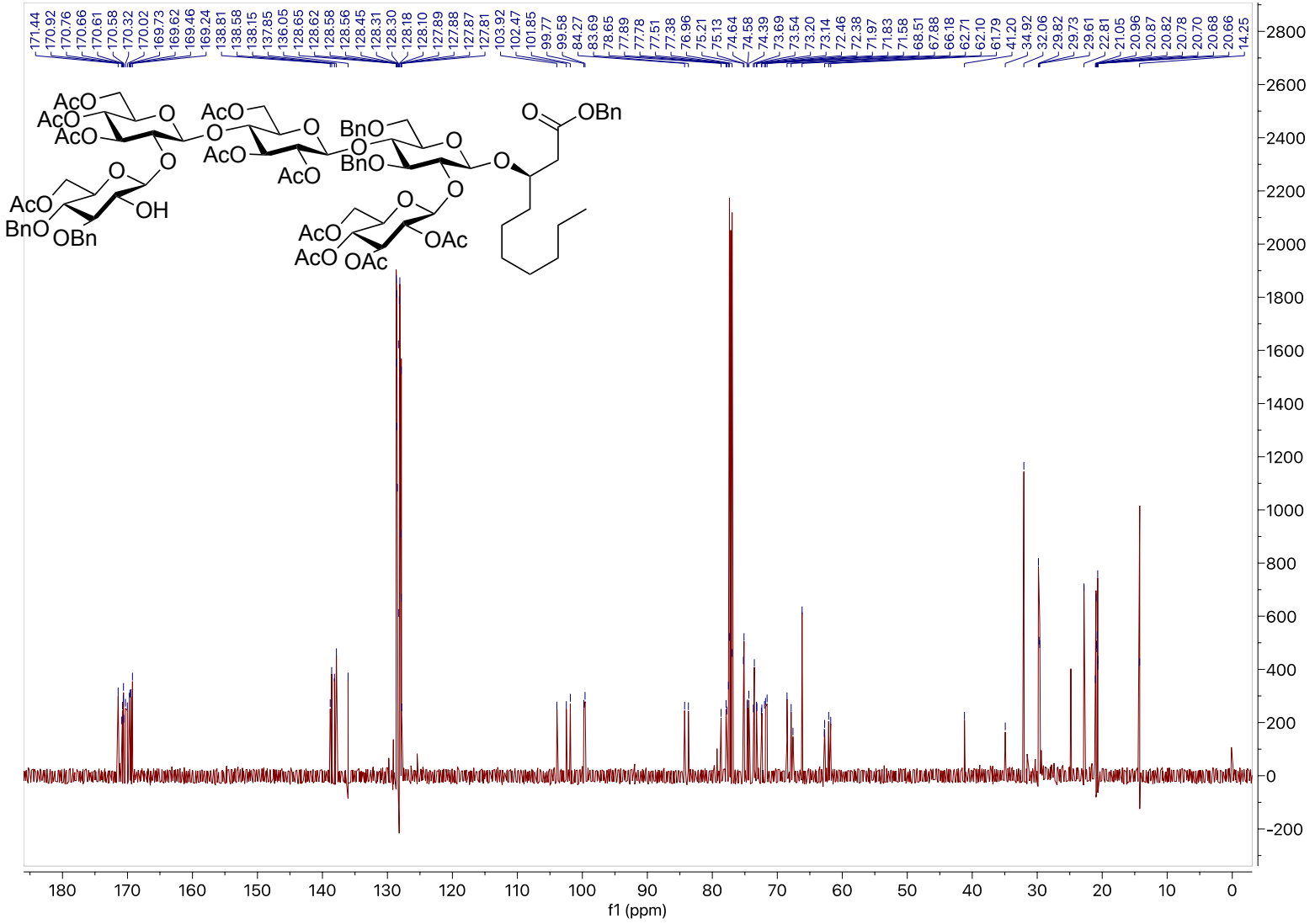
Supplementary figure 133 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 40-2



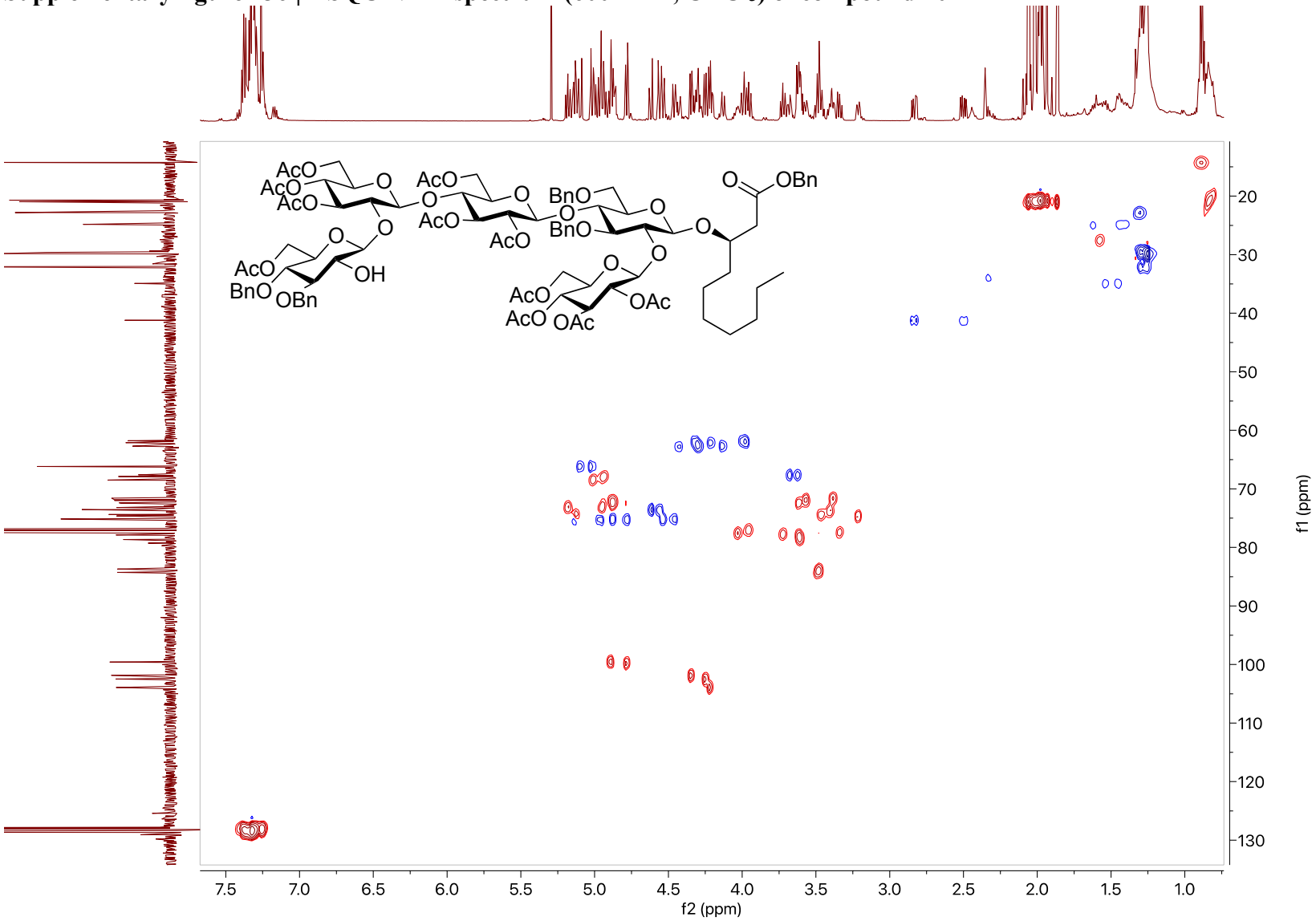
Supplementary figure 134 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 40-2



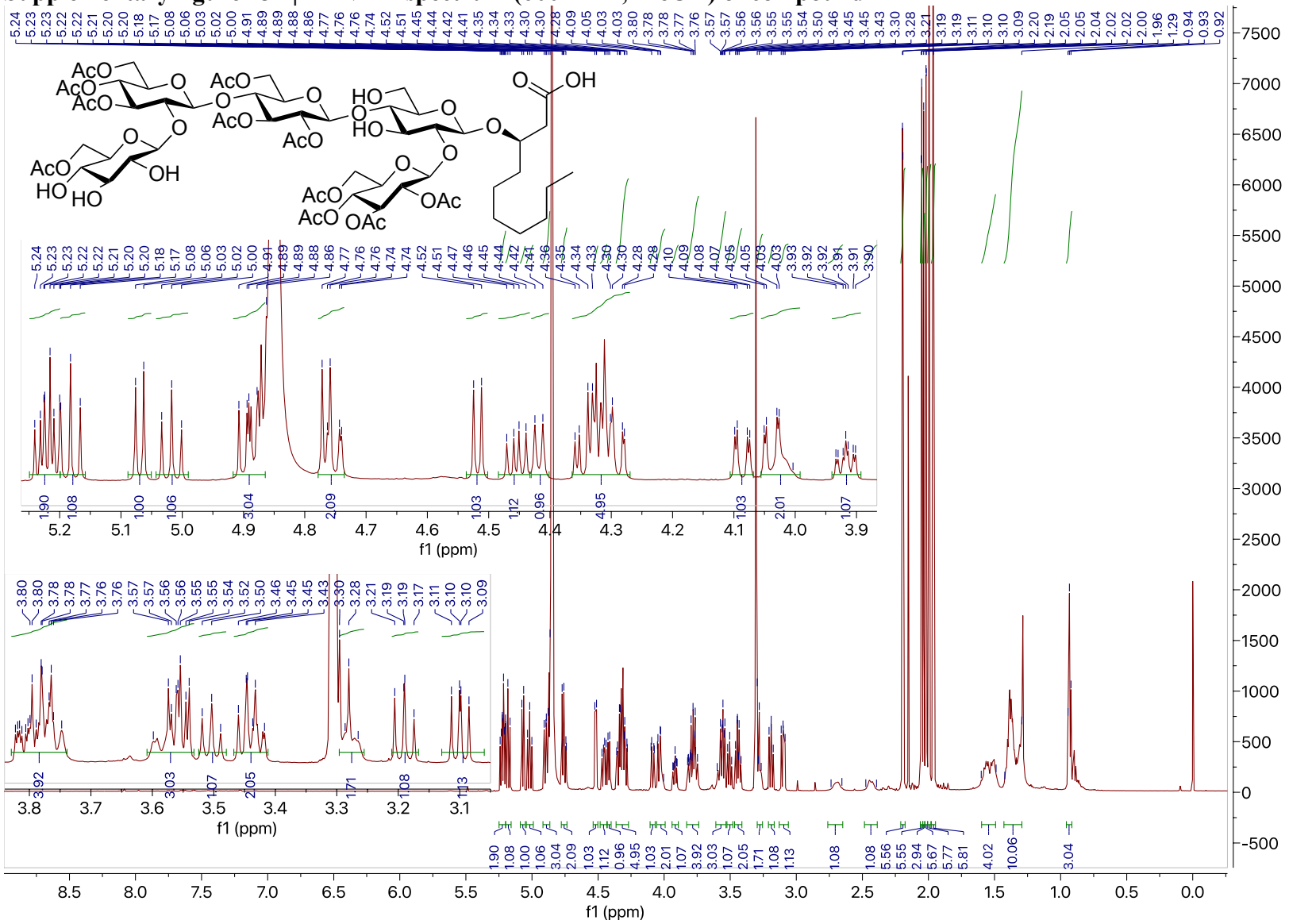
Supplementary figure 135 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 40-2



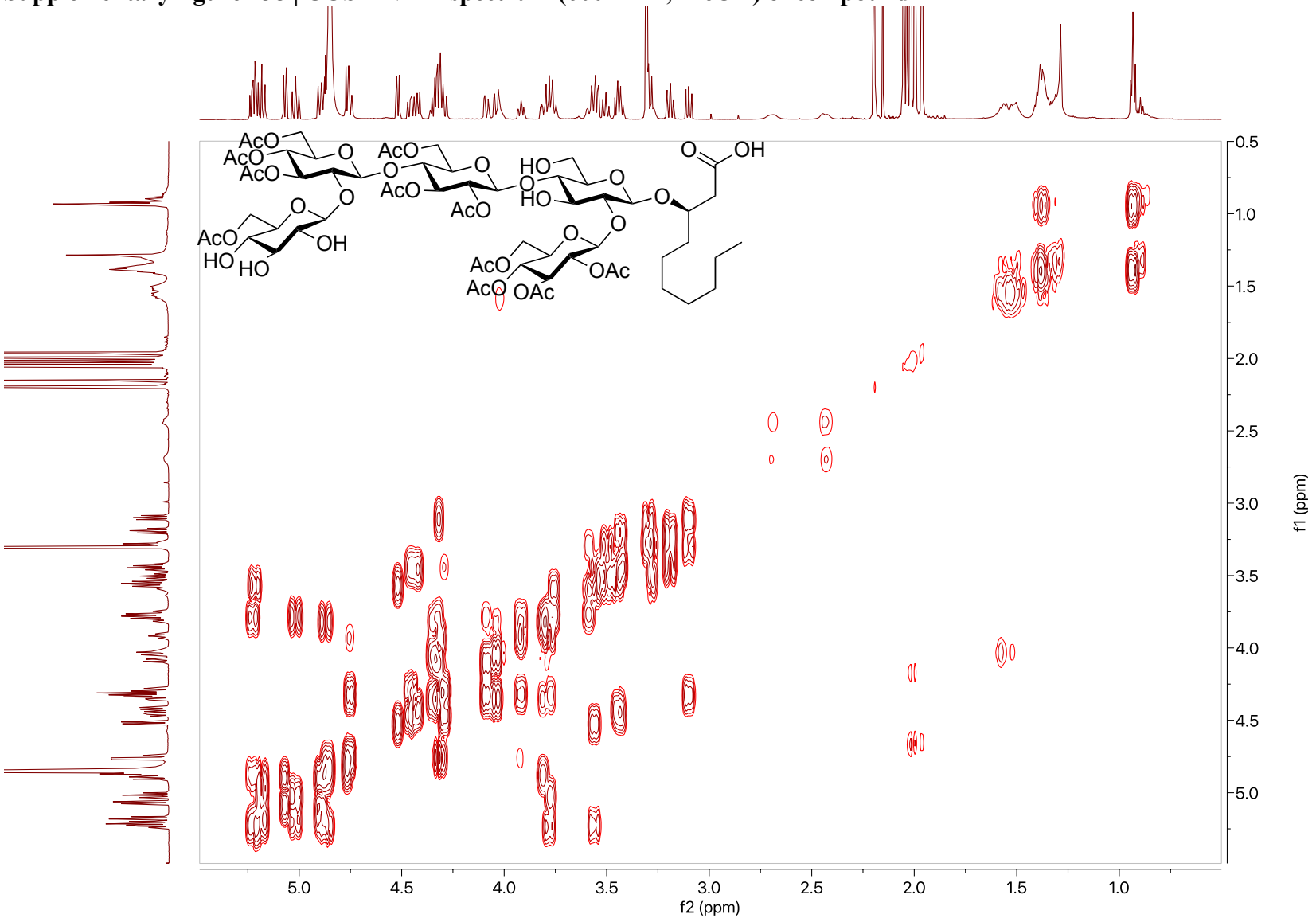
Supplementary figure 136 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 40-2



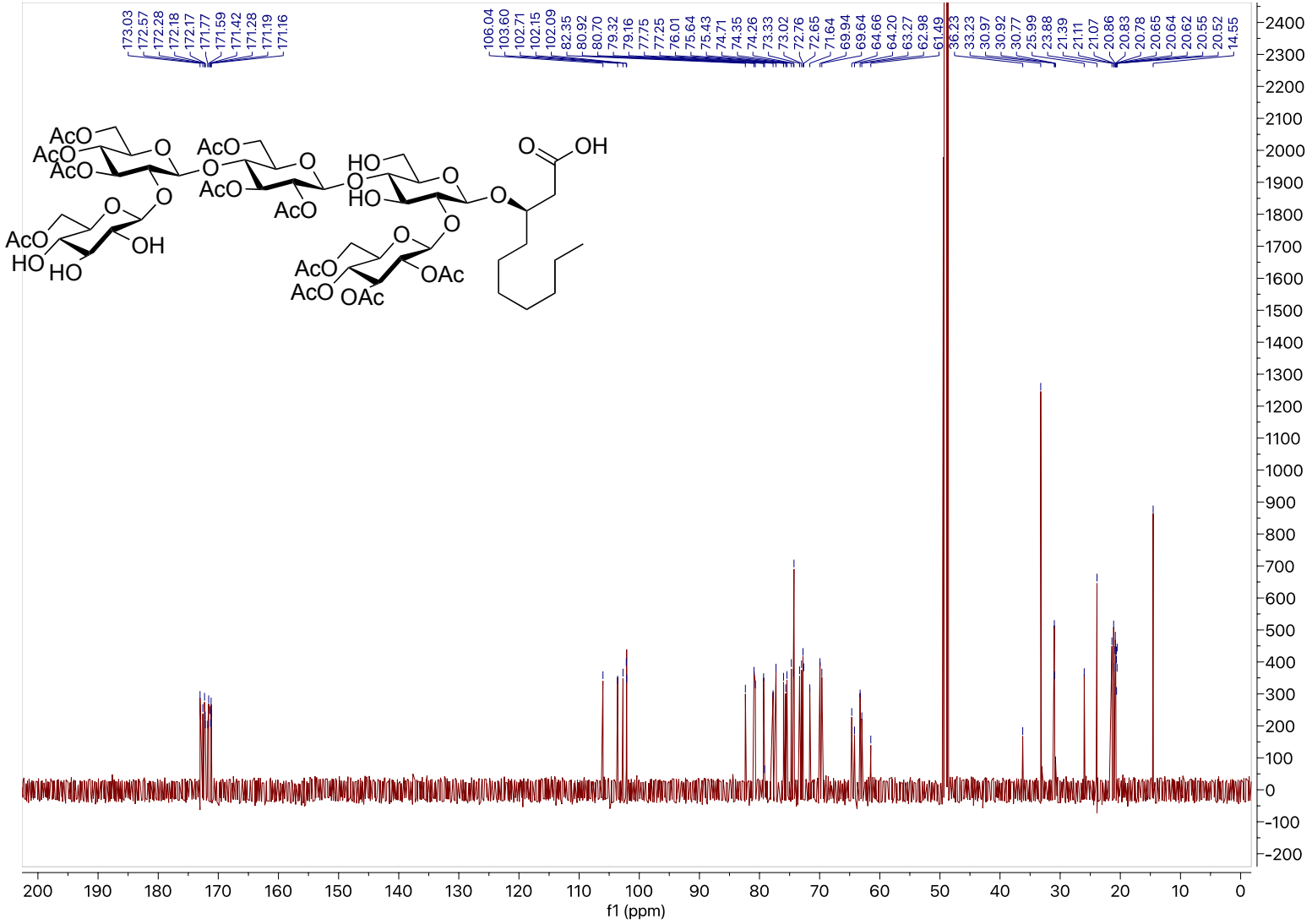
Supplementary figure 137 | ^{1}H NMR spectrum (600 MHz, MeOD) of compound 1



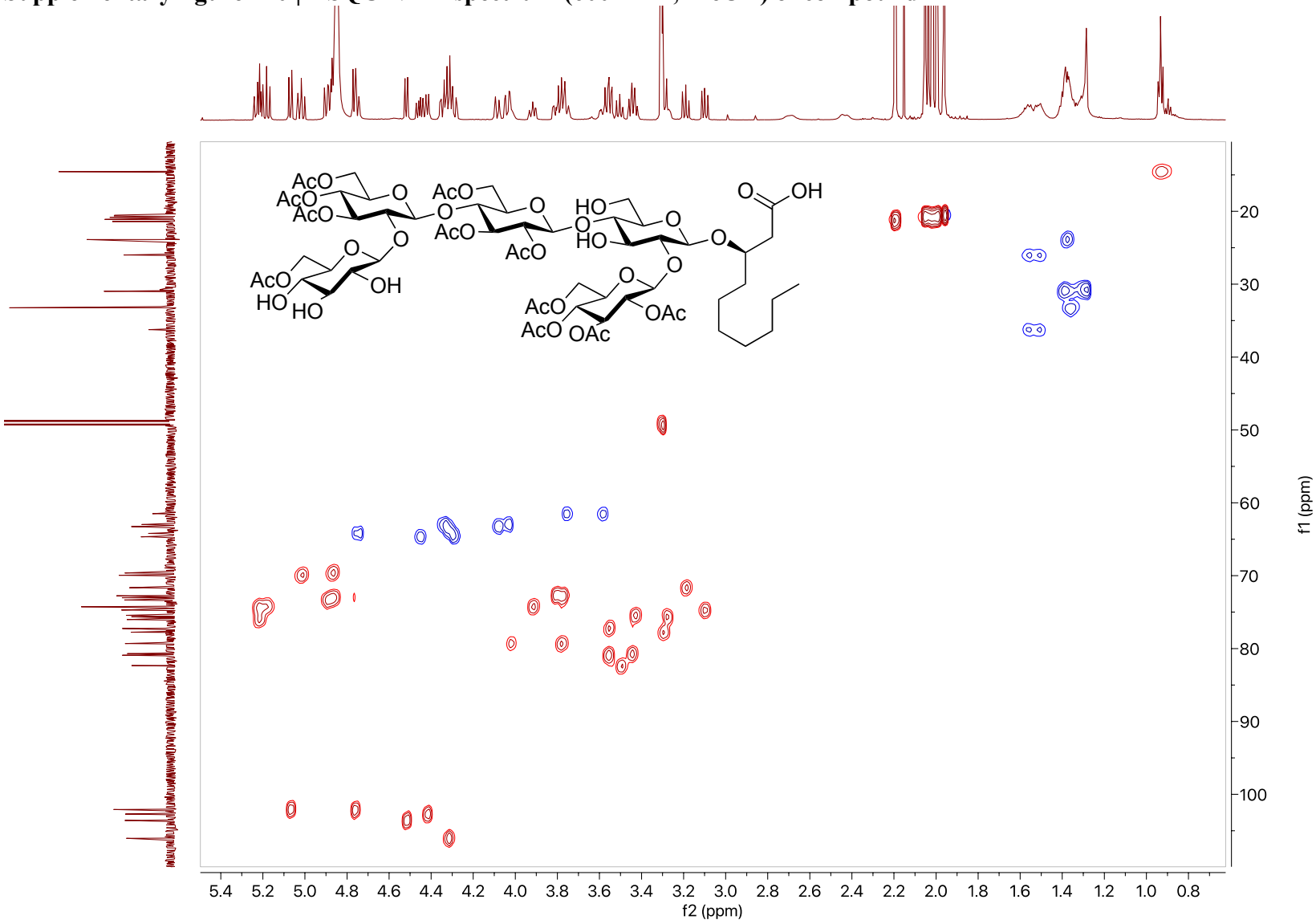
Supplementary figure 138 | COSY NMR spectrum (600 MHz, MeOD) of compound 1



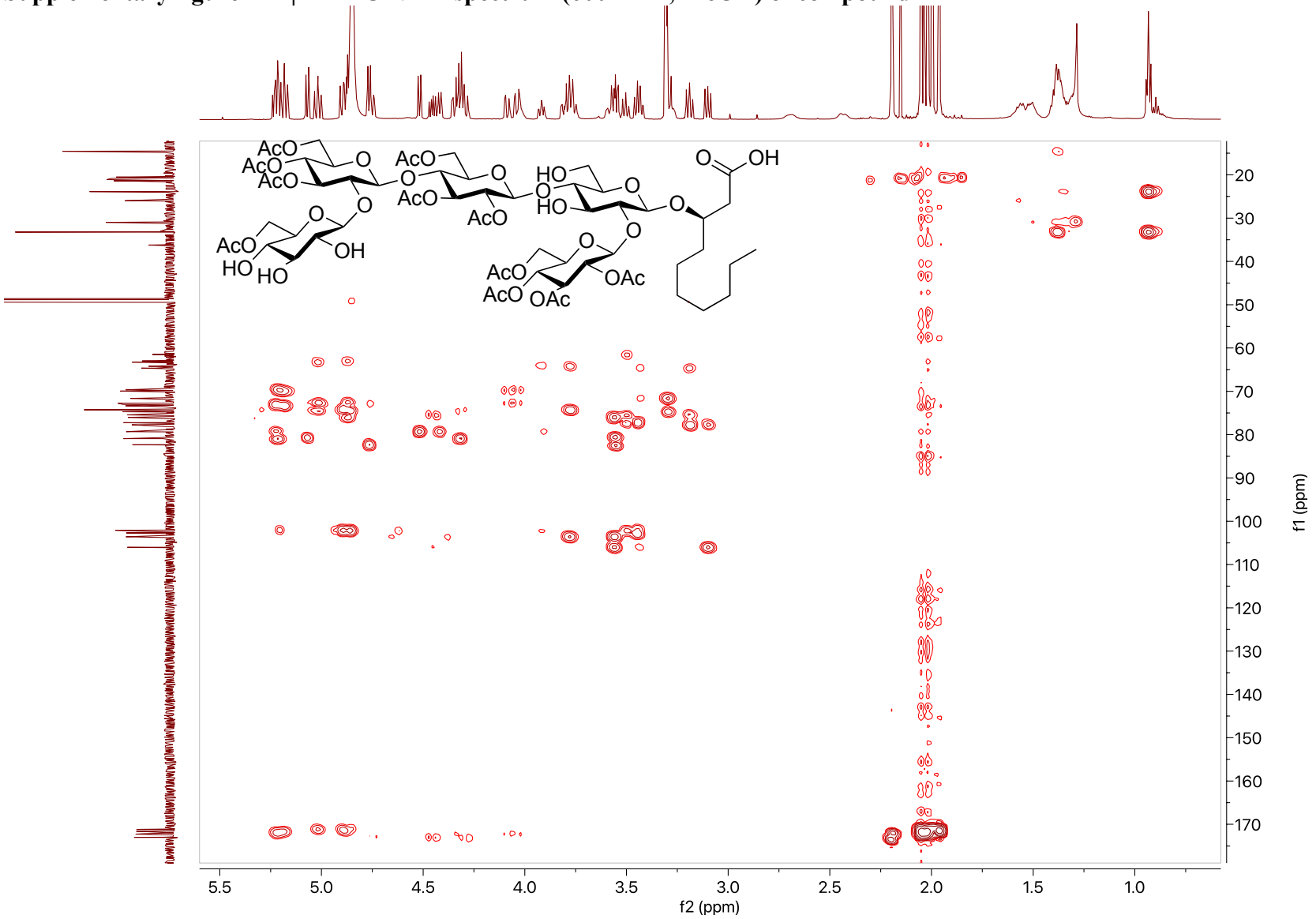
Supplementary figure 139 | ^{13}C NMR spectrum (150 MHz, MeOD) of compound 1



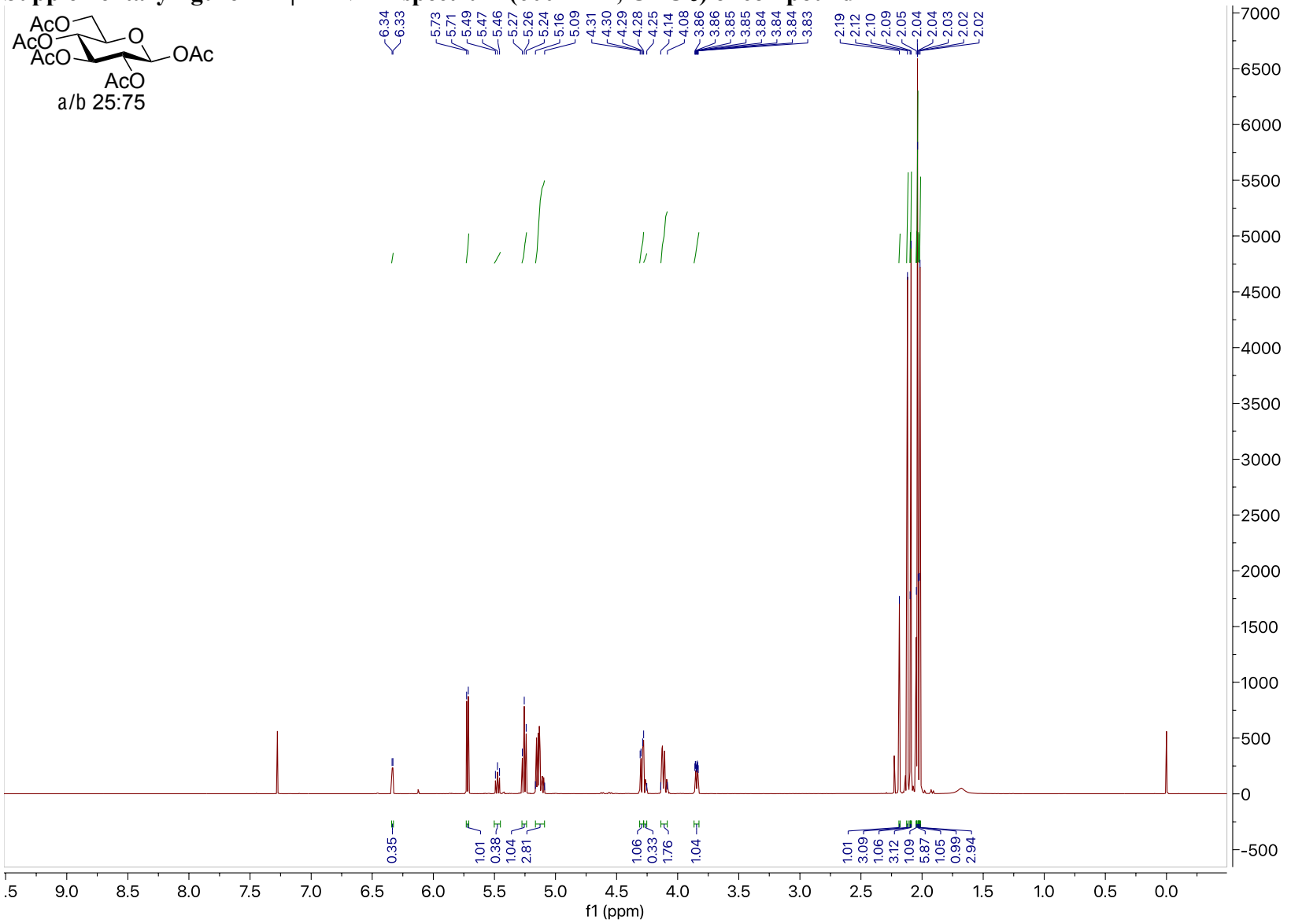
Supplementary figure 140 | HSQC NMR spectrum (600 MHz, MeOD) of compound 1



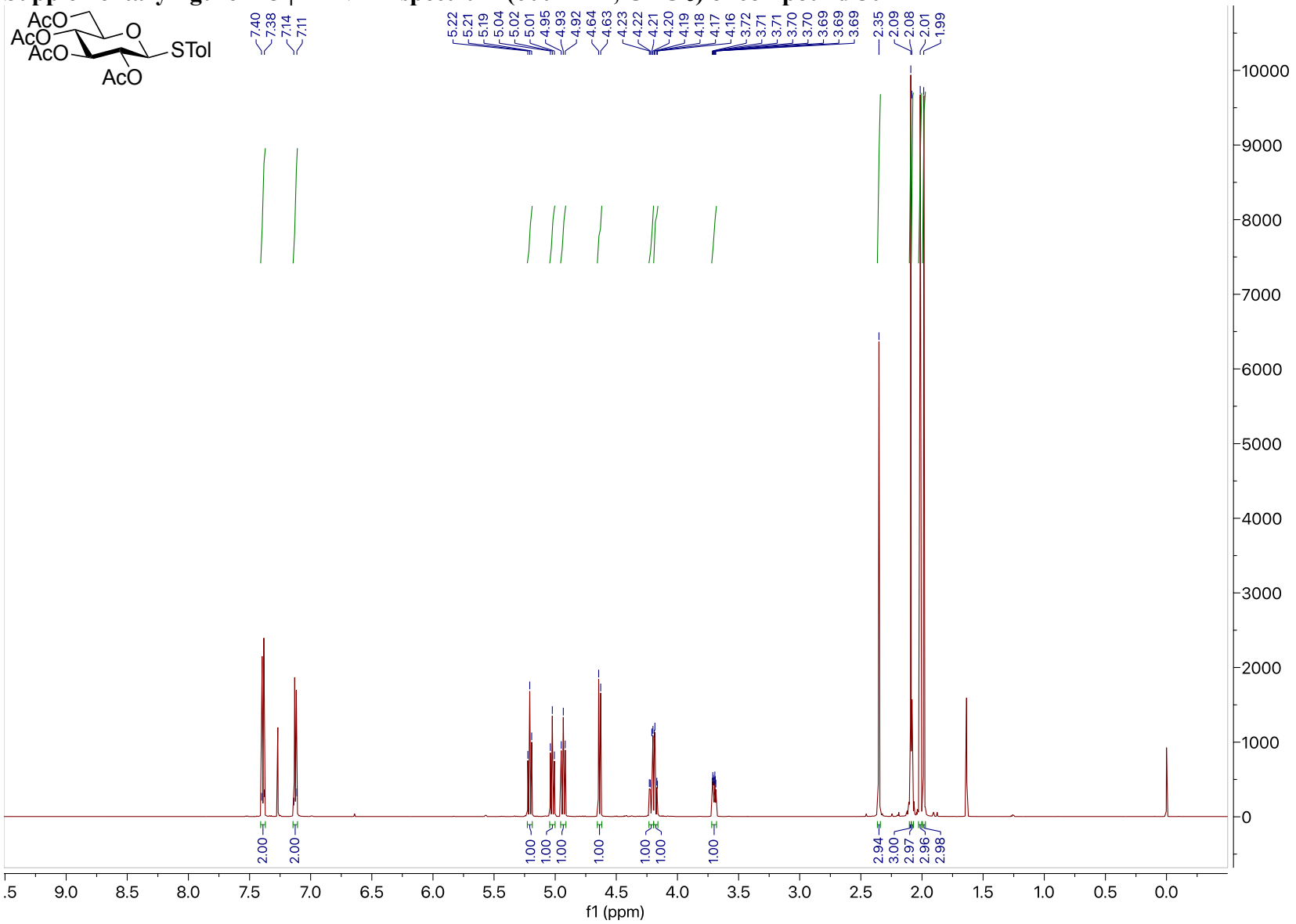
Supplementary figure 141 | HMBC NMR spectrum (600 MHz, MeOD) of compound 1



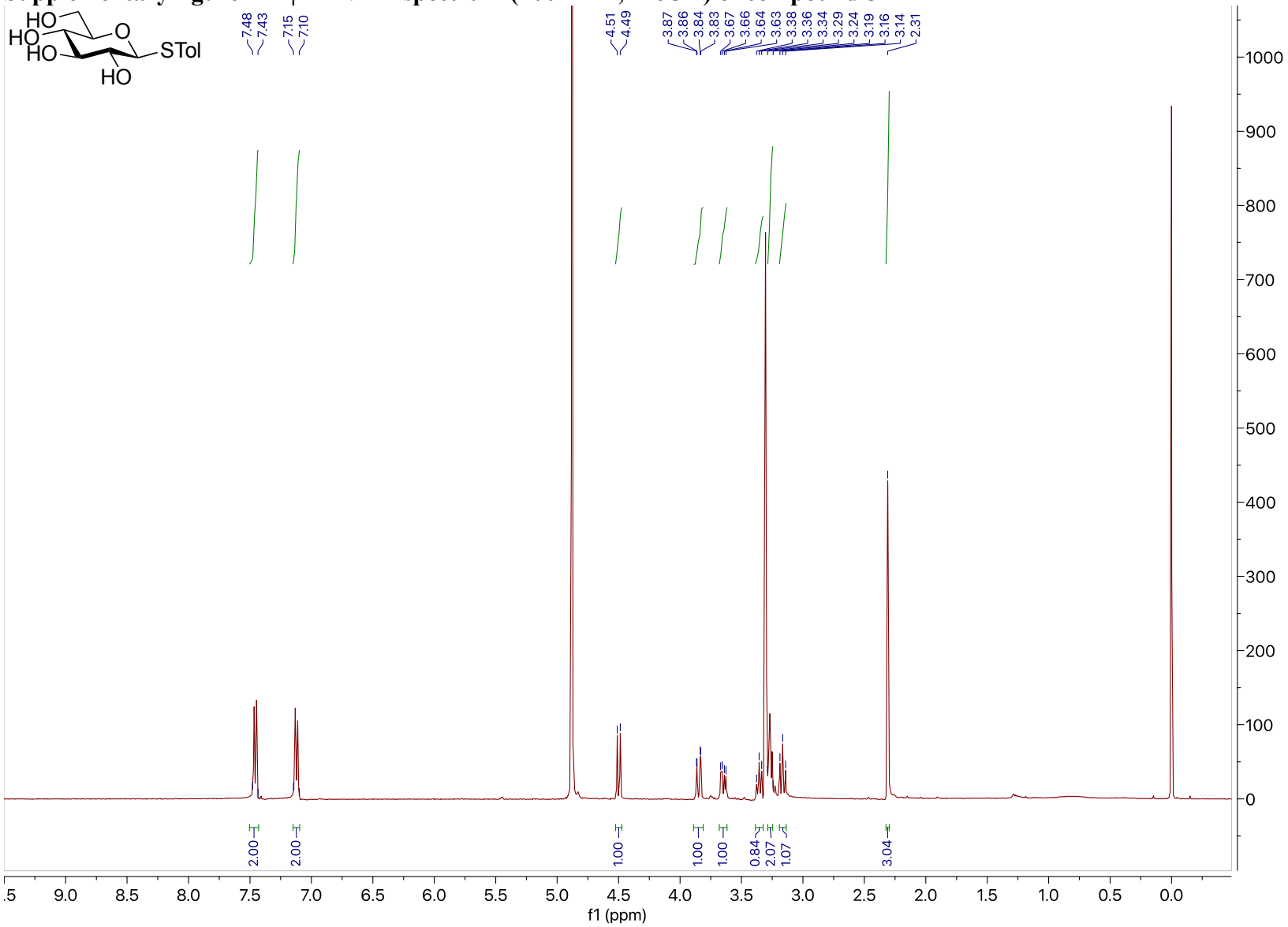
Supplementary figure 142 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 41



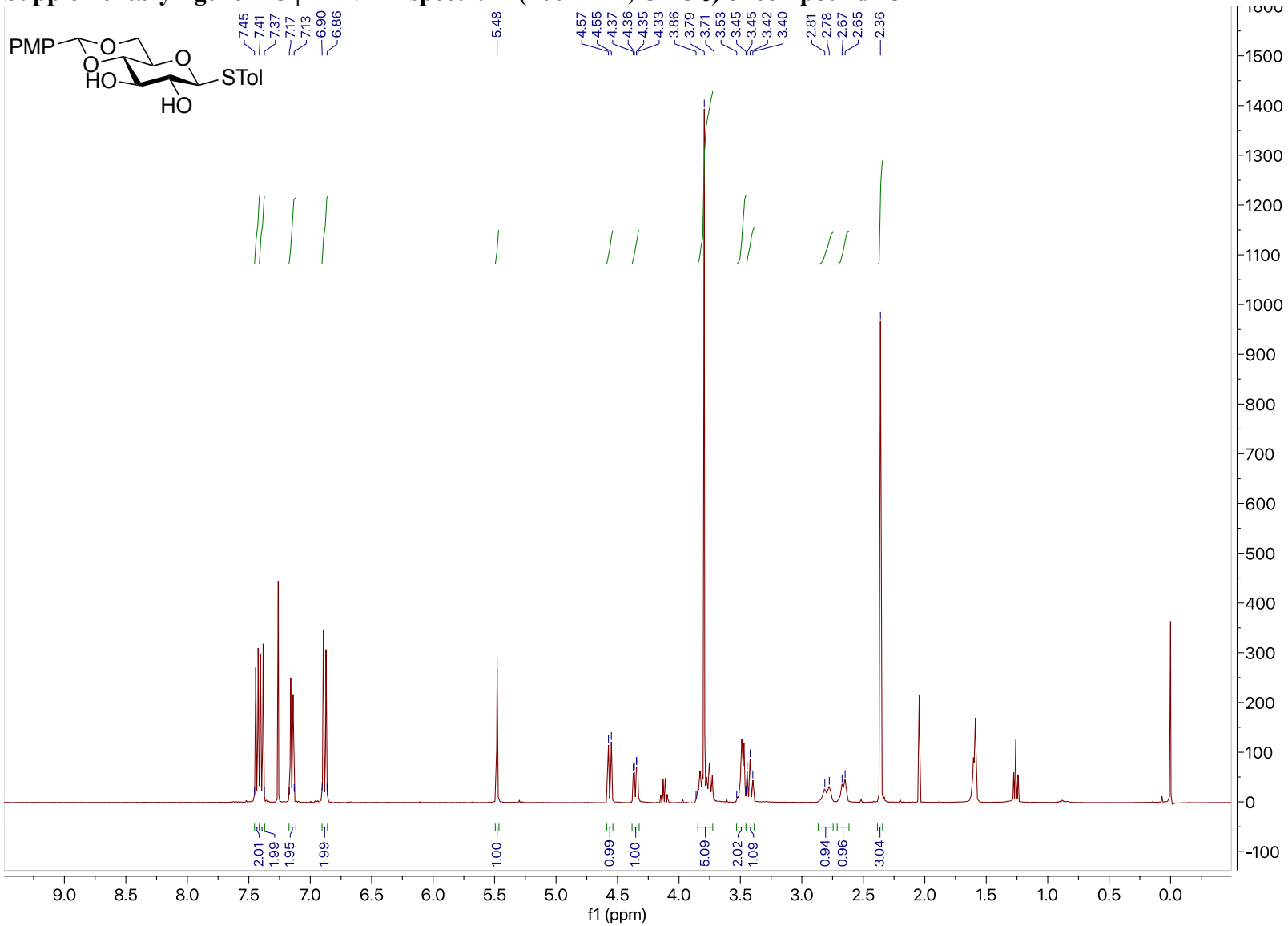
Supplementary figure 143 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 50



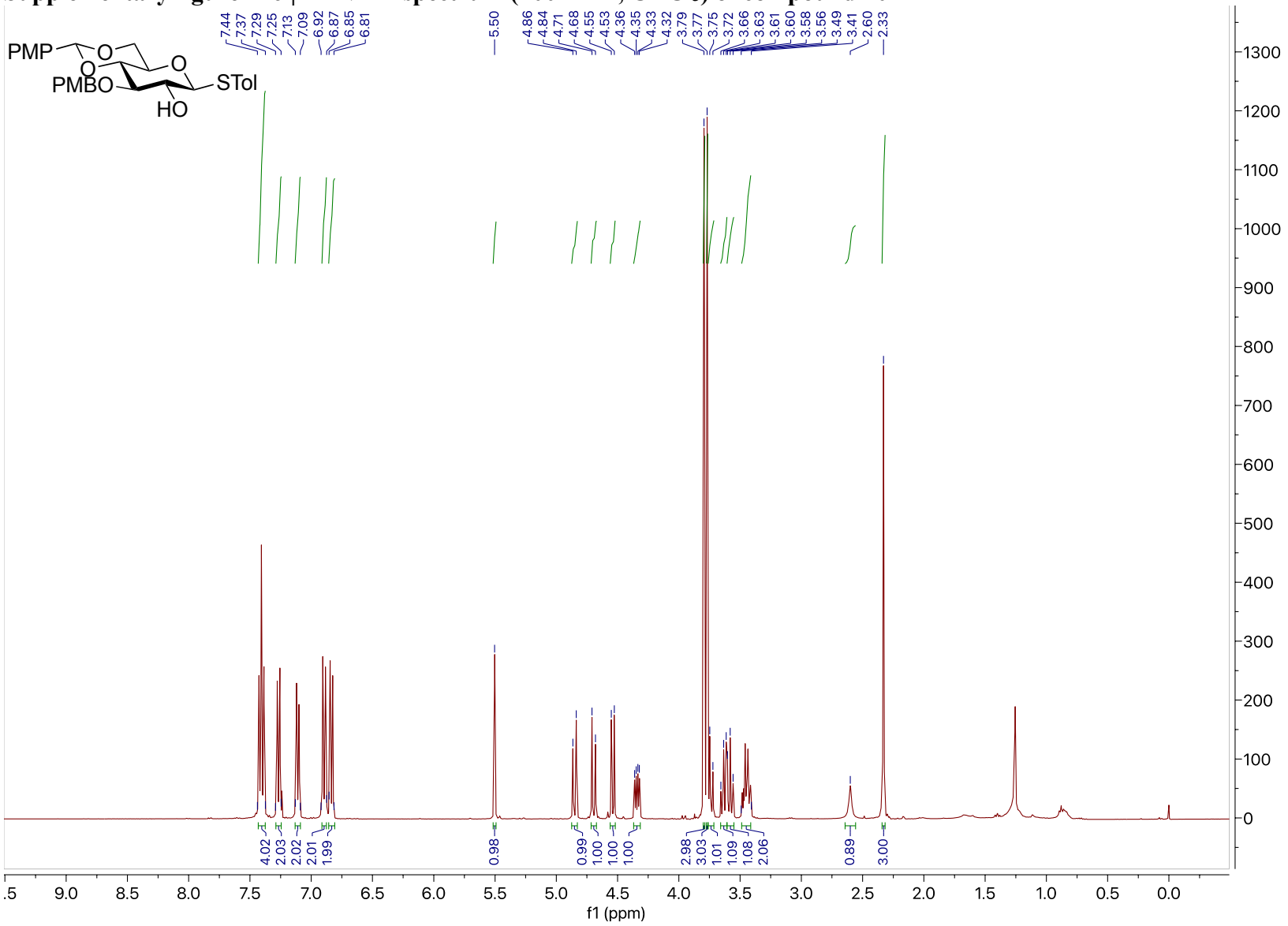
Supplementary figure 144 | ^{1}H NMR spectrum (400 MHz, MeOD) of compound 51



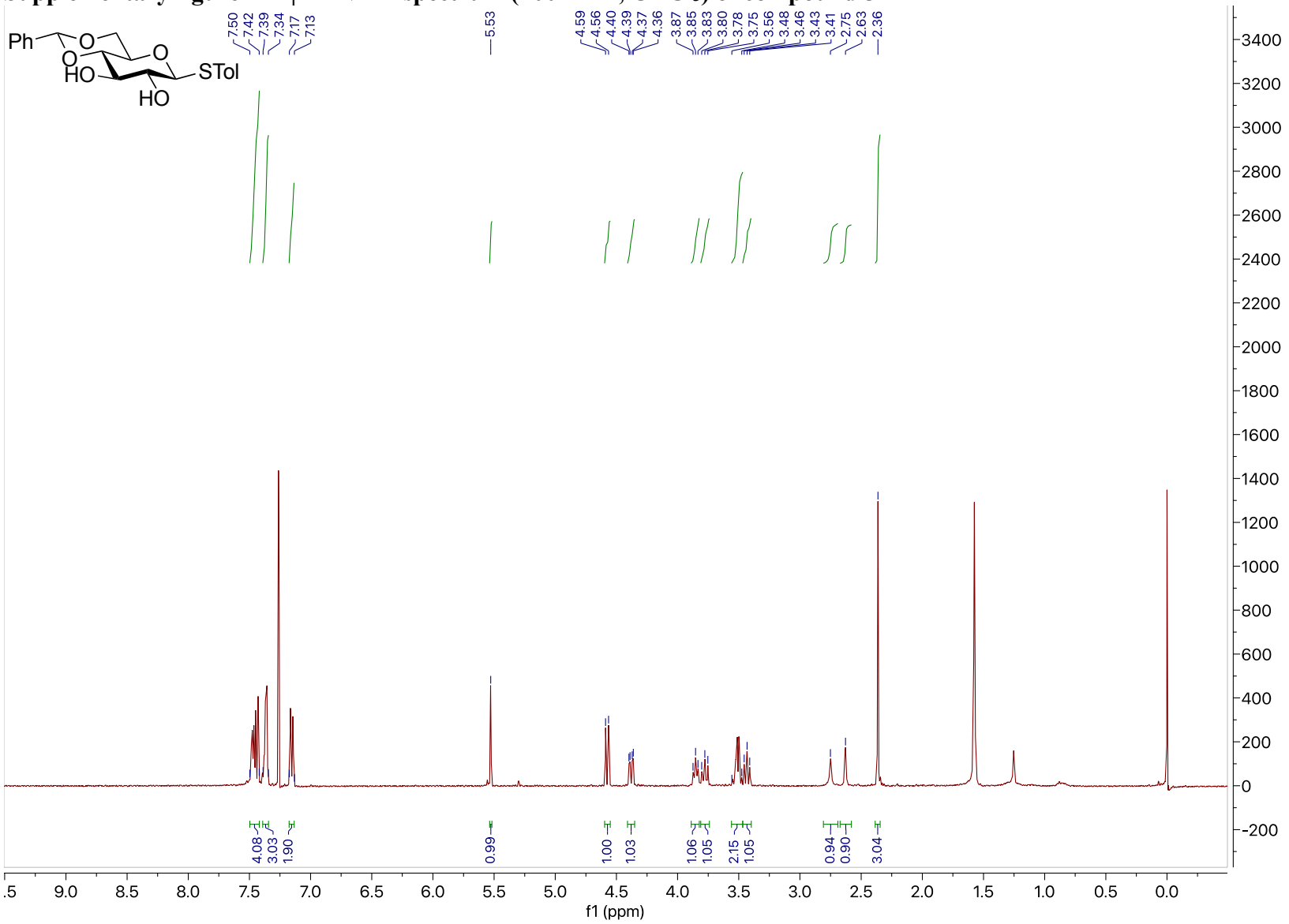
Supplementary figure 145 | ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound 15



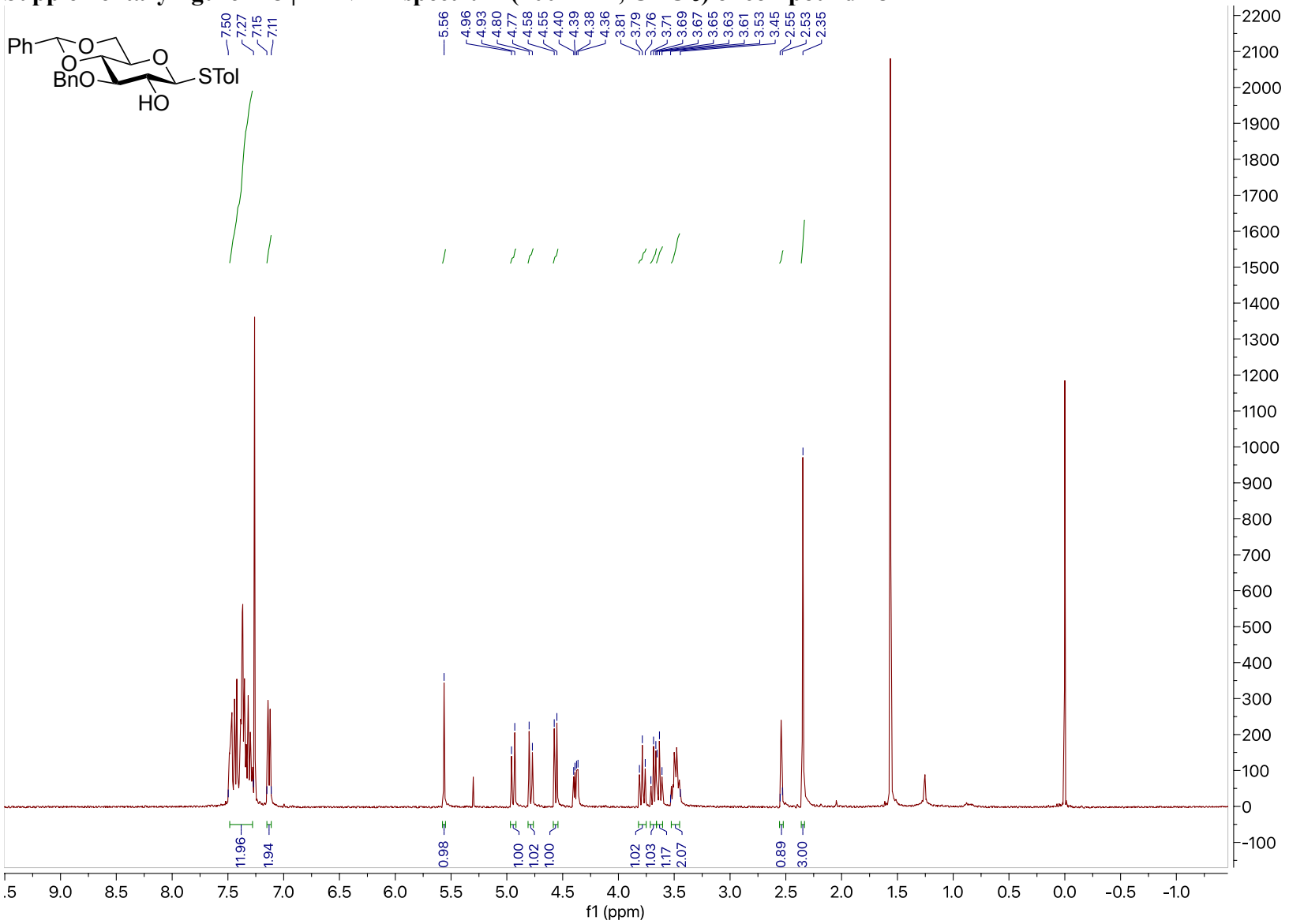
Supplementary figure 146 | ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound 10



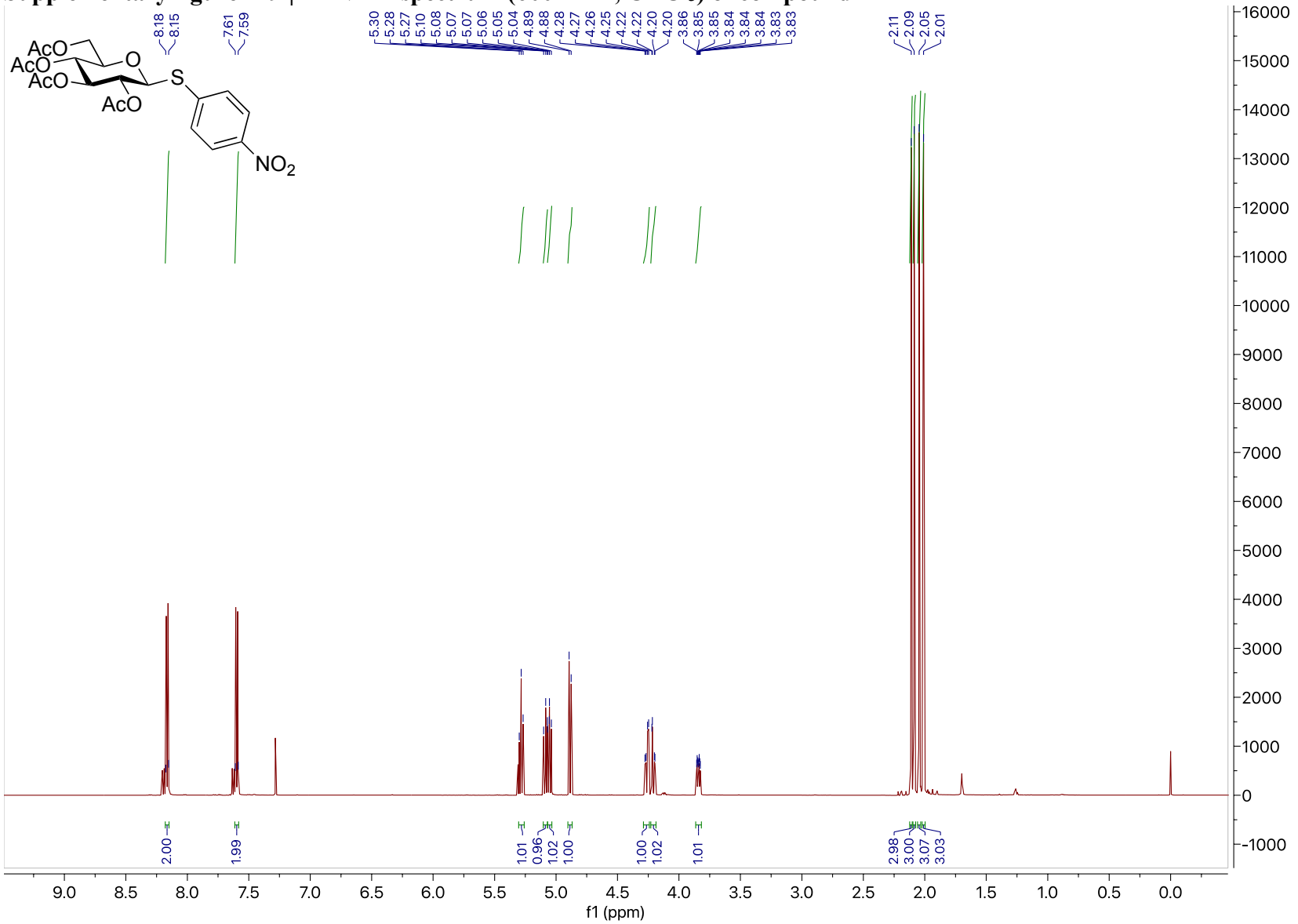
Supplementary figure 147 | ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound 52



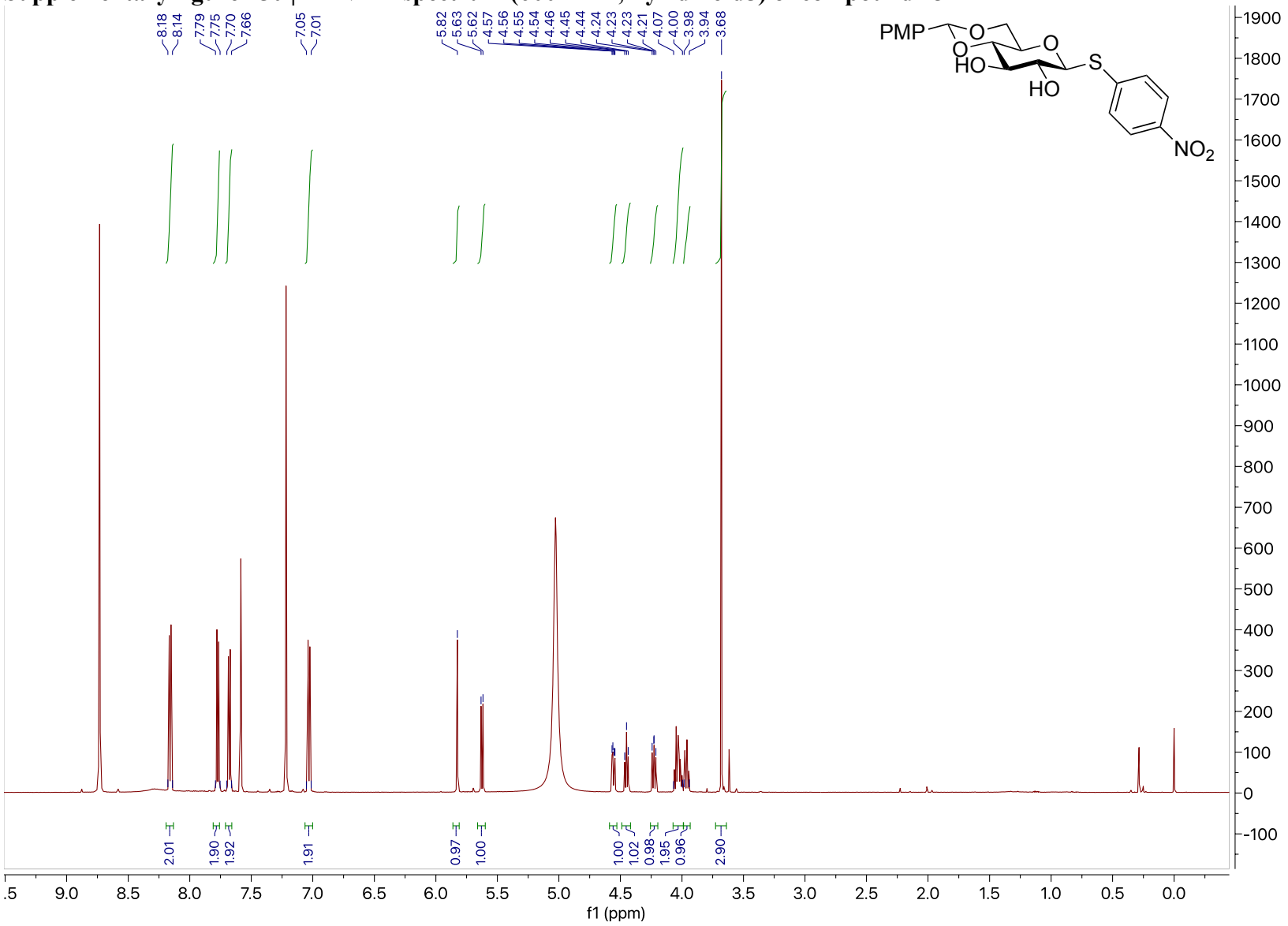
Supplementary figure 148 | ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound 18



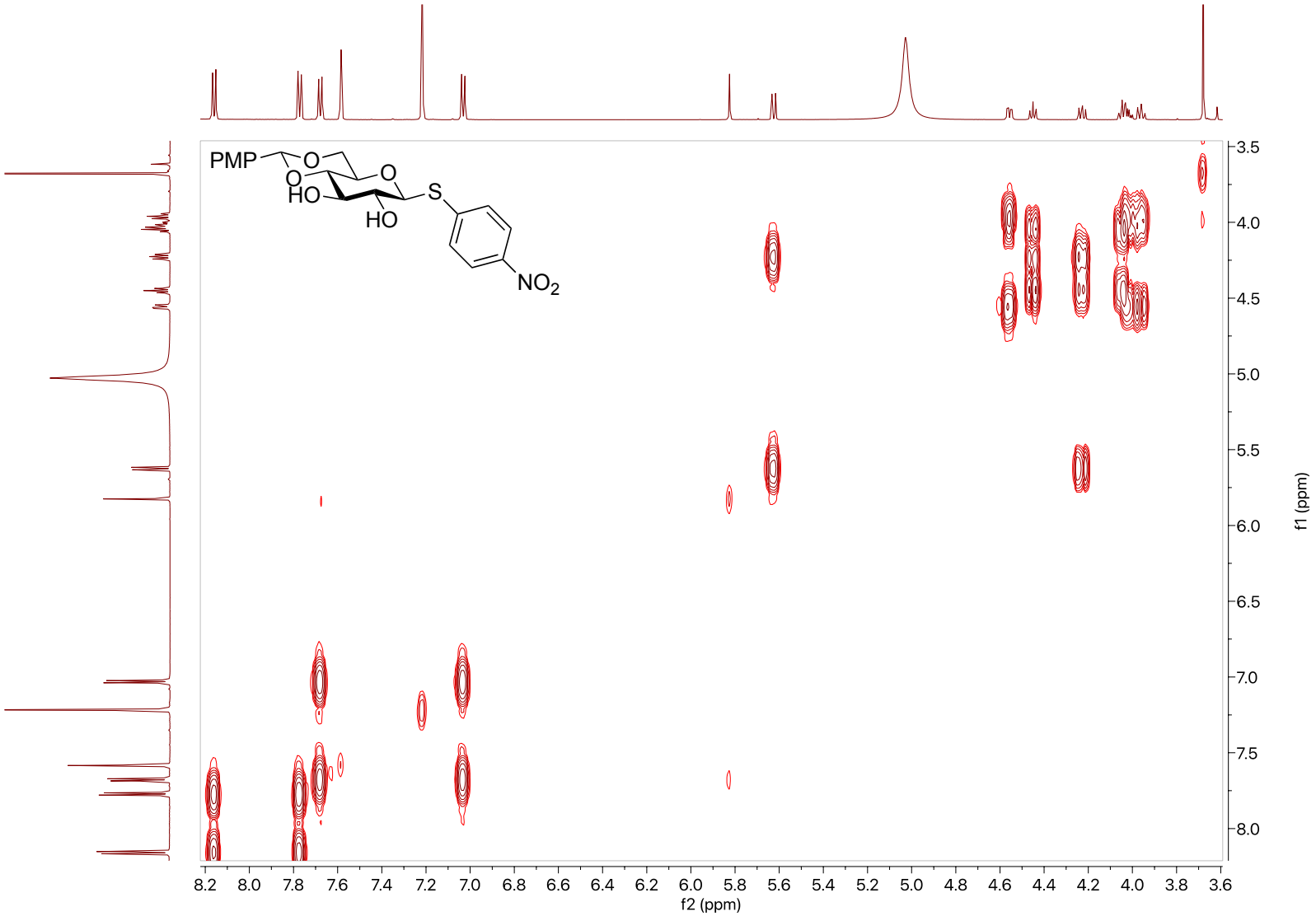
Supplementary figure 149 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 42



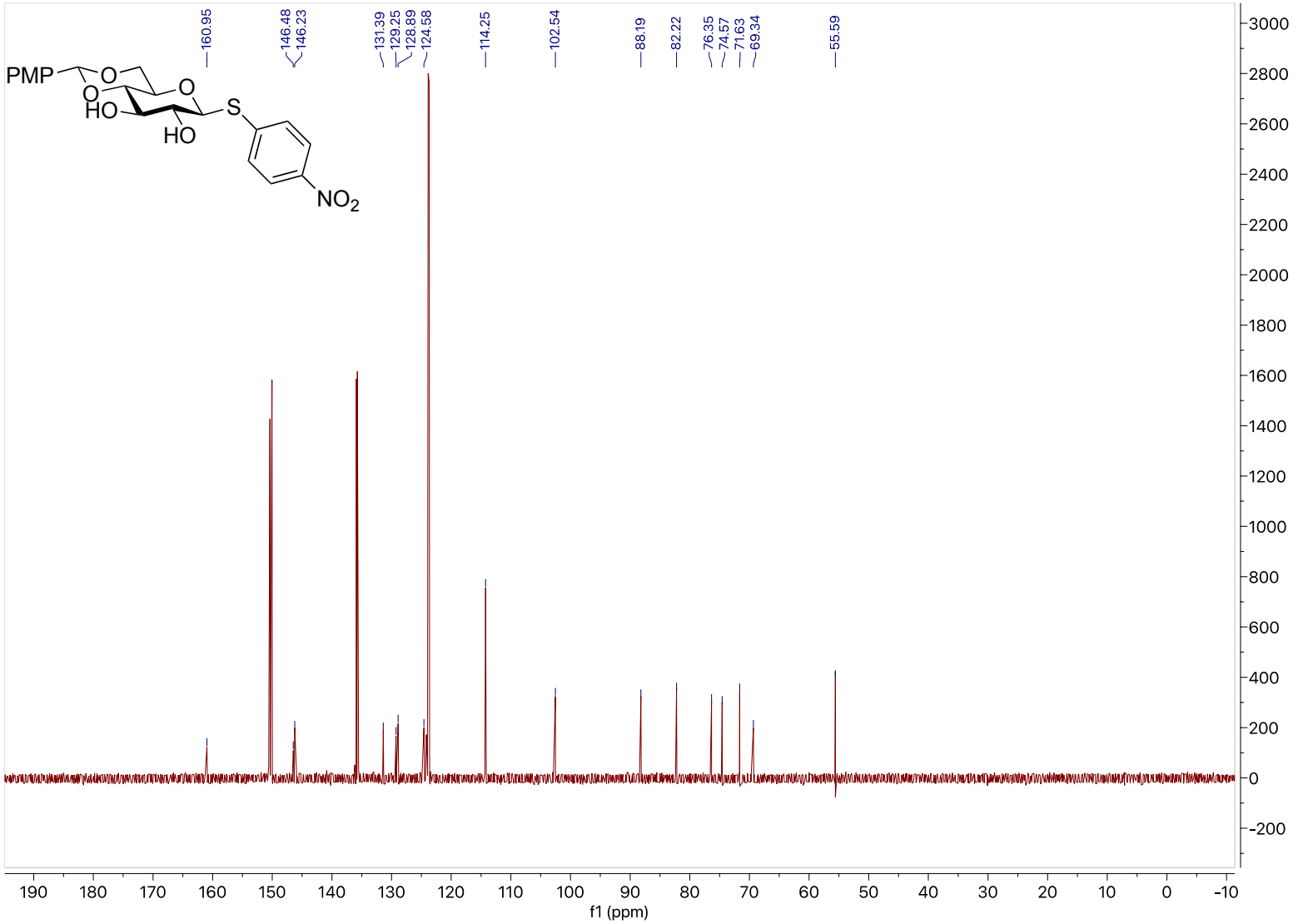
Supplementary figure 150 | ^{1}H NMR spectrum (600 MHz, Pyridine-d5) of compound 43



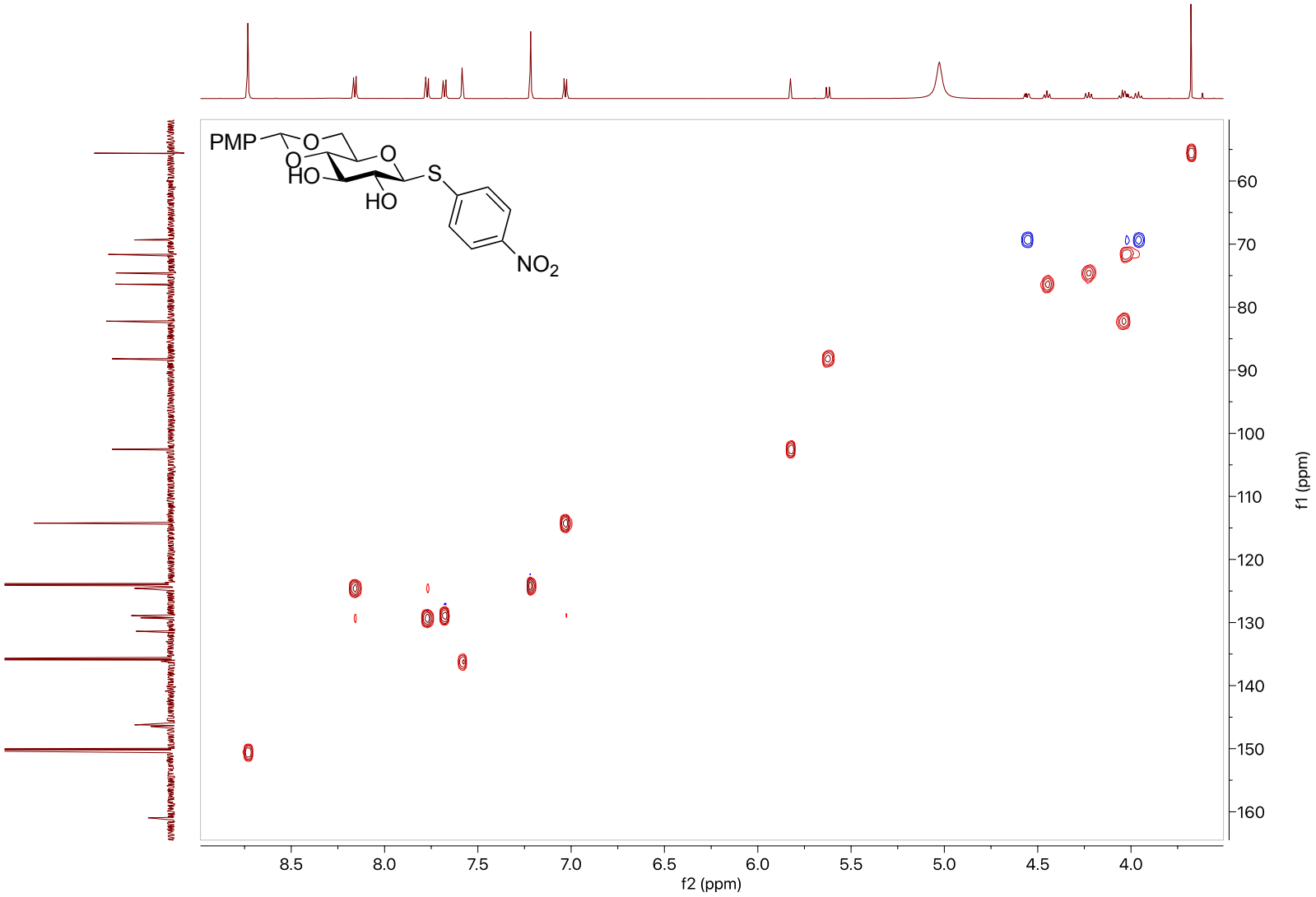
Supplementary figure 151 | COSY NMR spectrum (600 MHz, Pyridine-d5) of compound 43



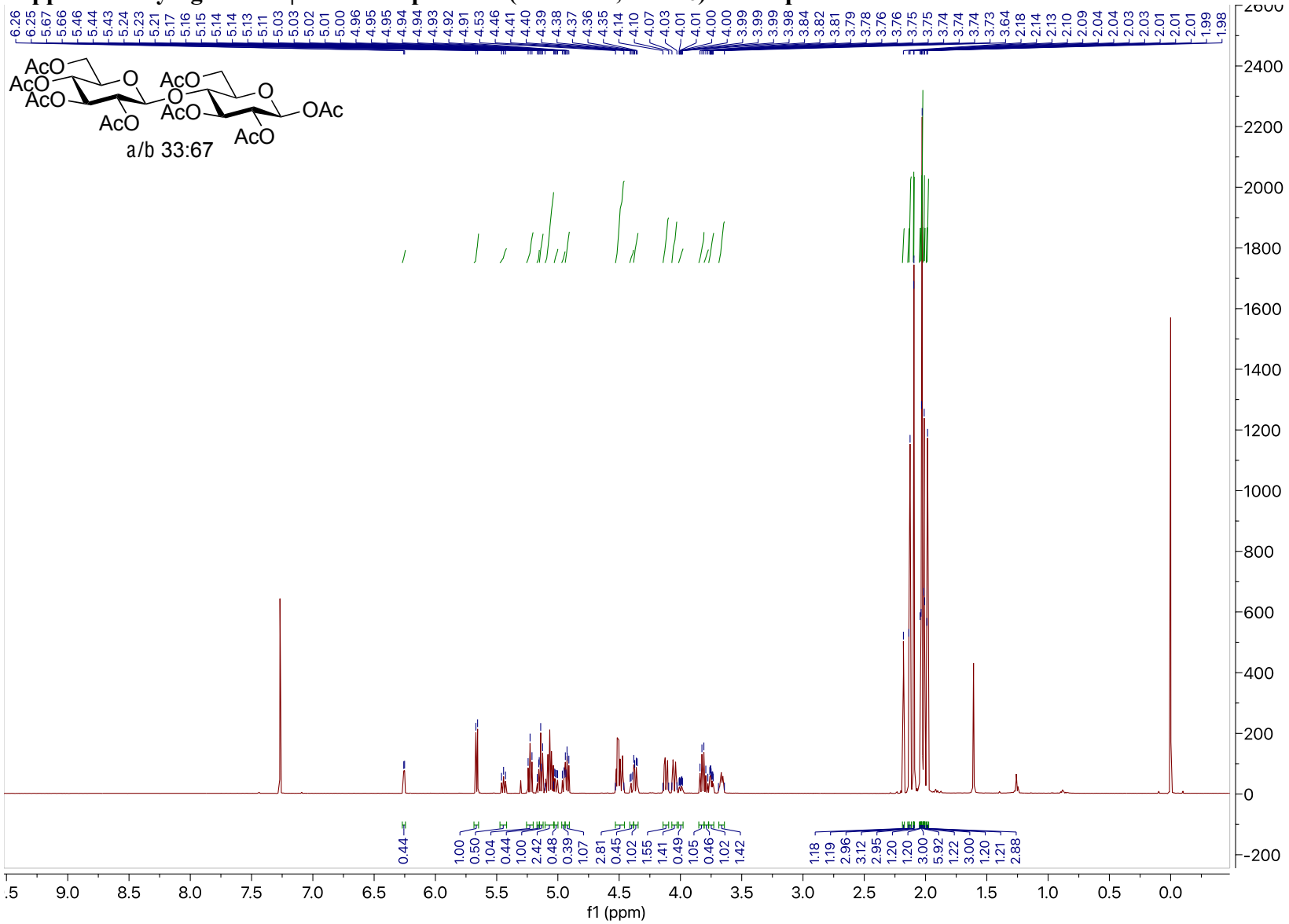
Supplementary figure 152 | ^{13}C NMR spectrum (150 MHz, Pyridine-d5) of compound 43



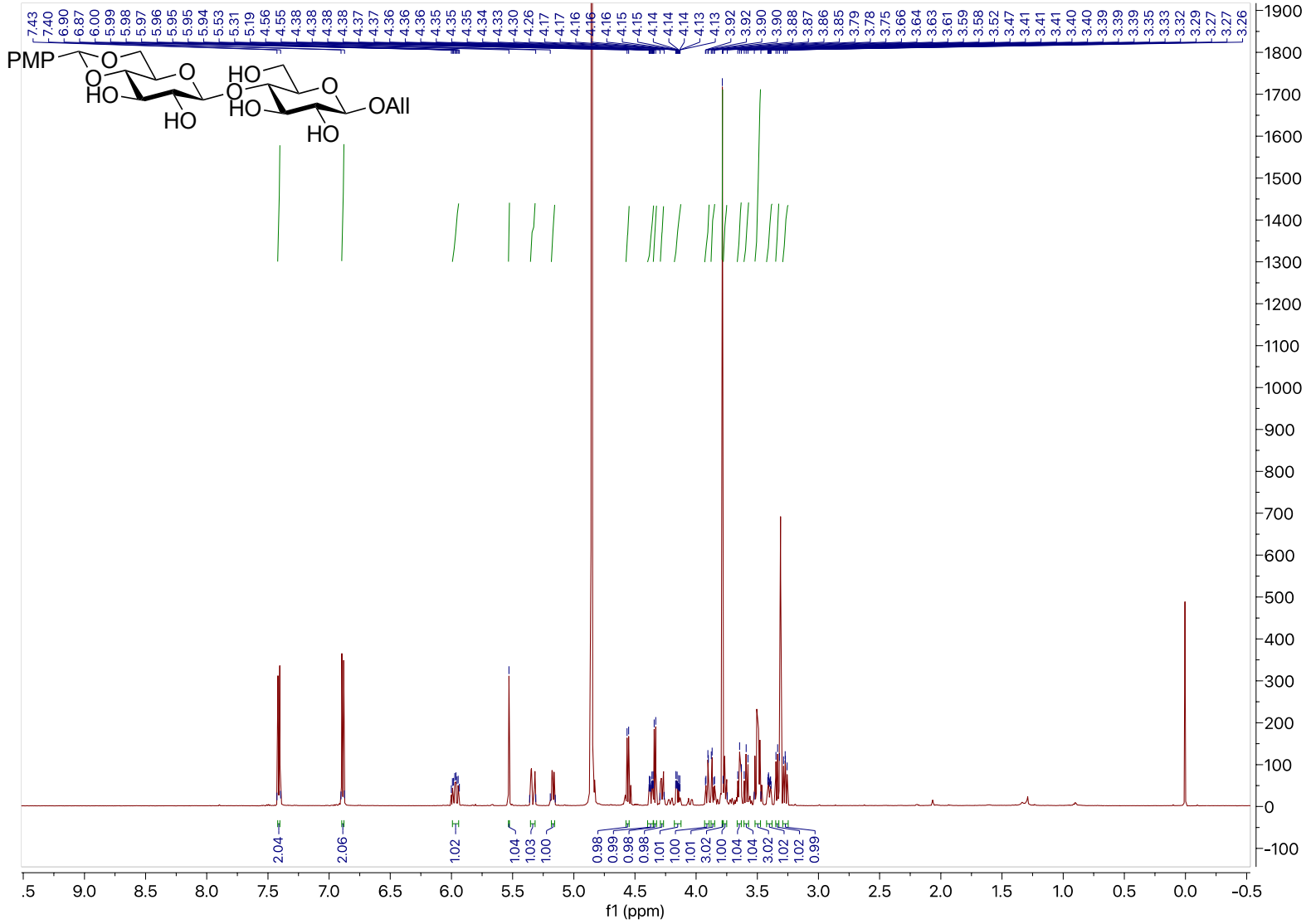
Supplementary figure 153 | HSQC NMR spectrum (600 MHz, Pyridine-d5) of compound 43



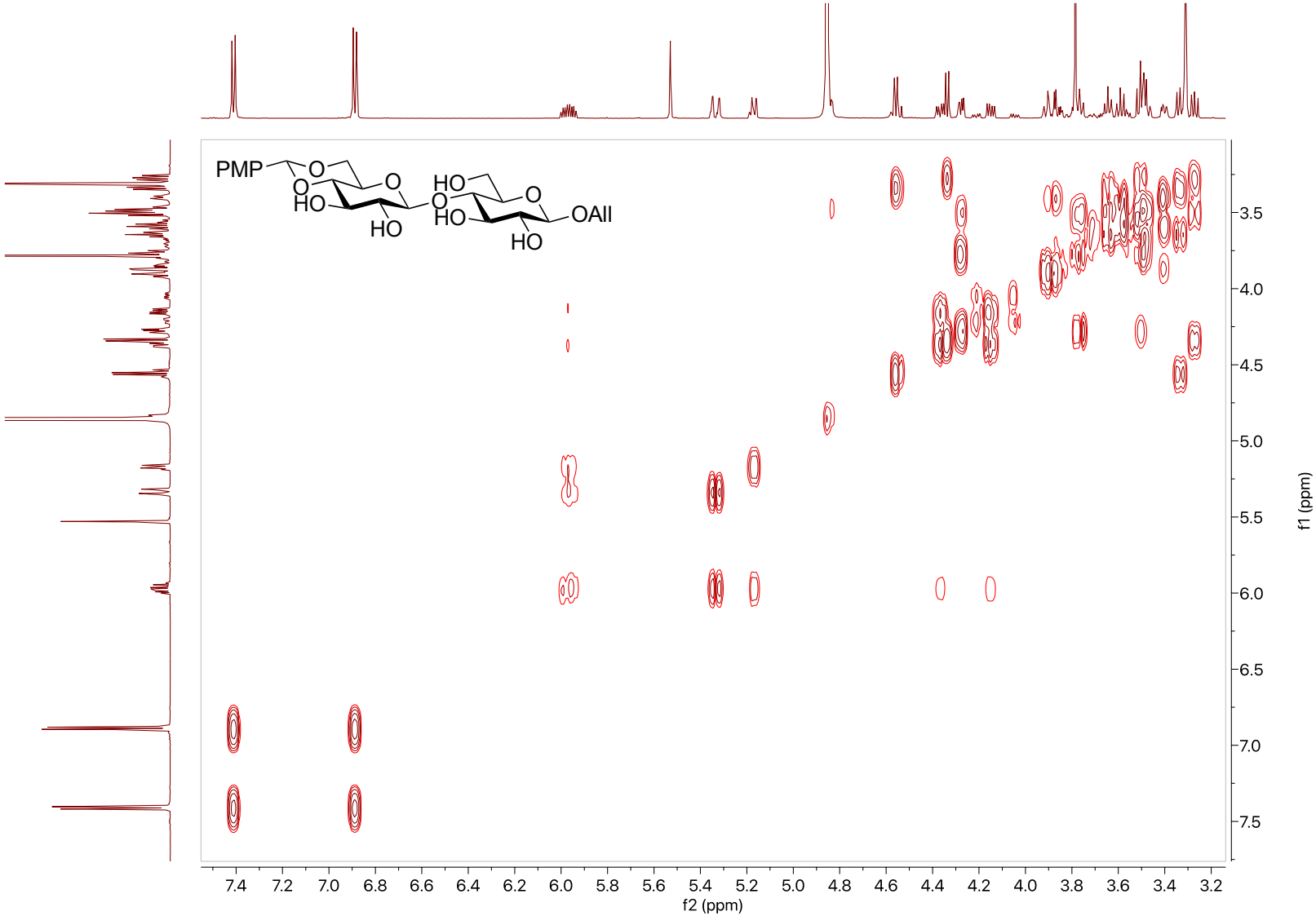
Supplementary figure 154 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 46



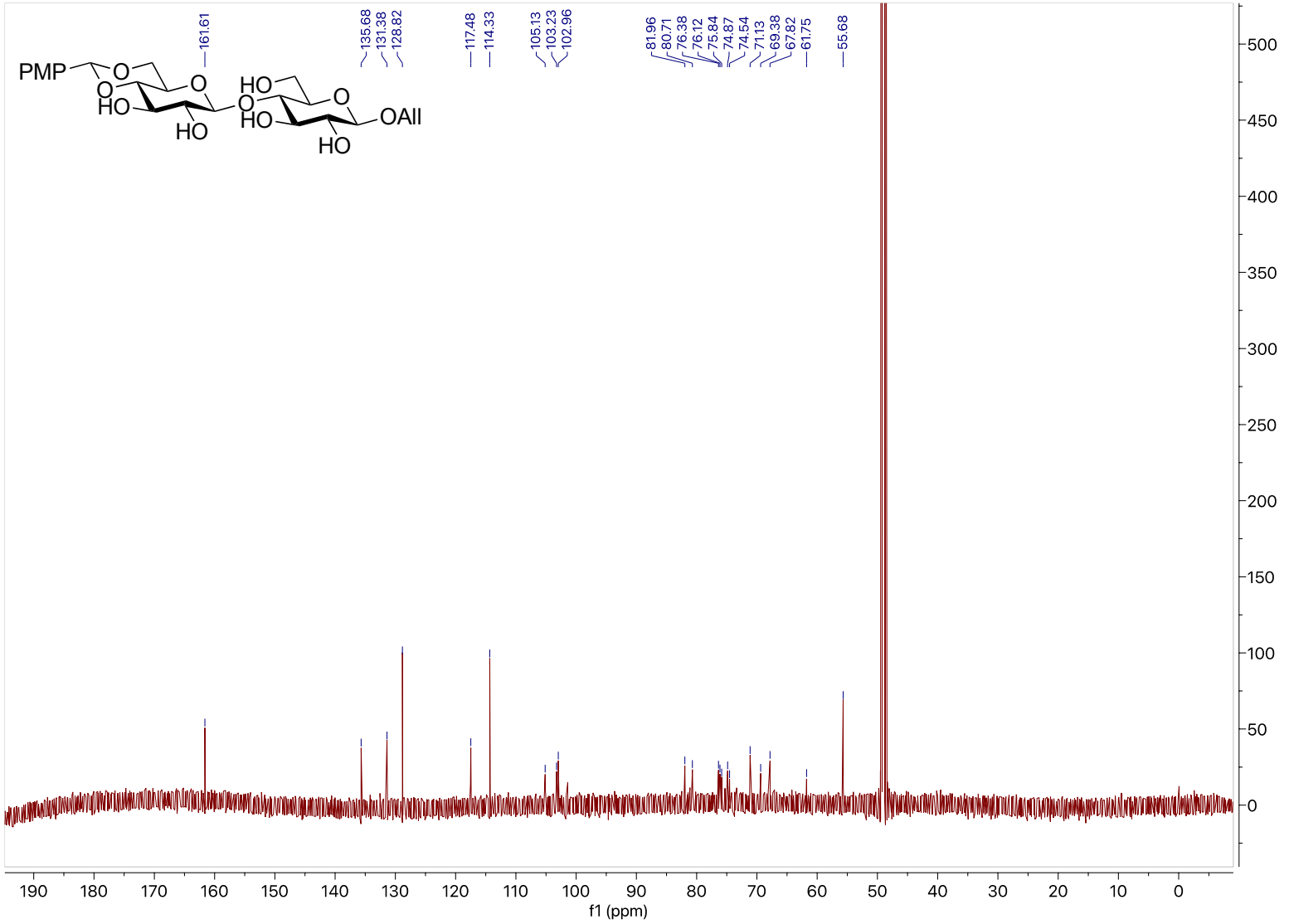
Supplementary figure 155 | ^{1}H NMR spectrum (600 MHz, MeOD) of compound 48



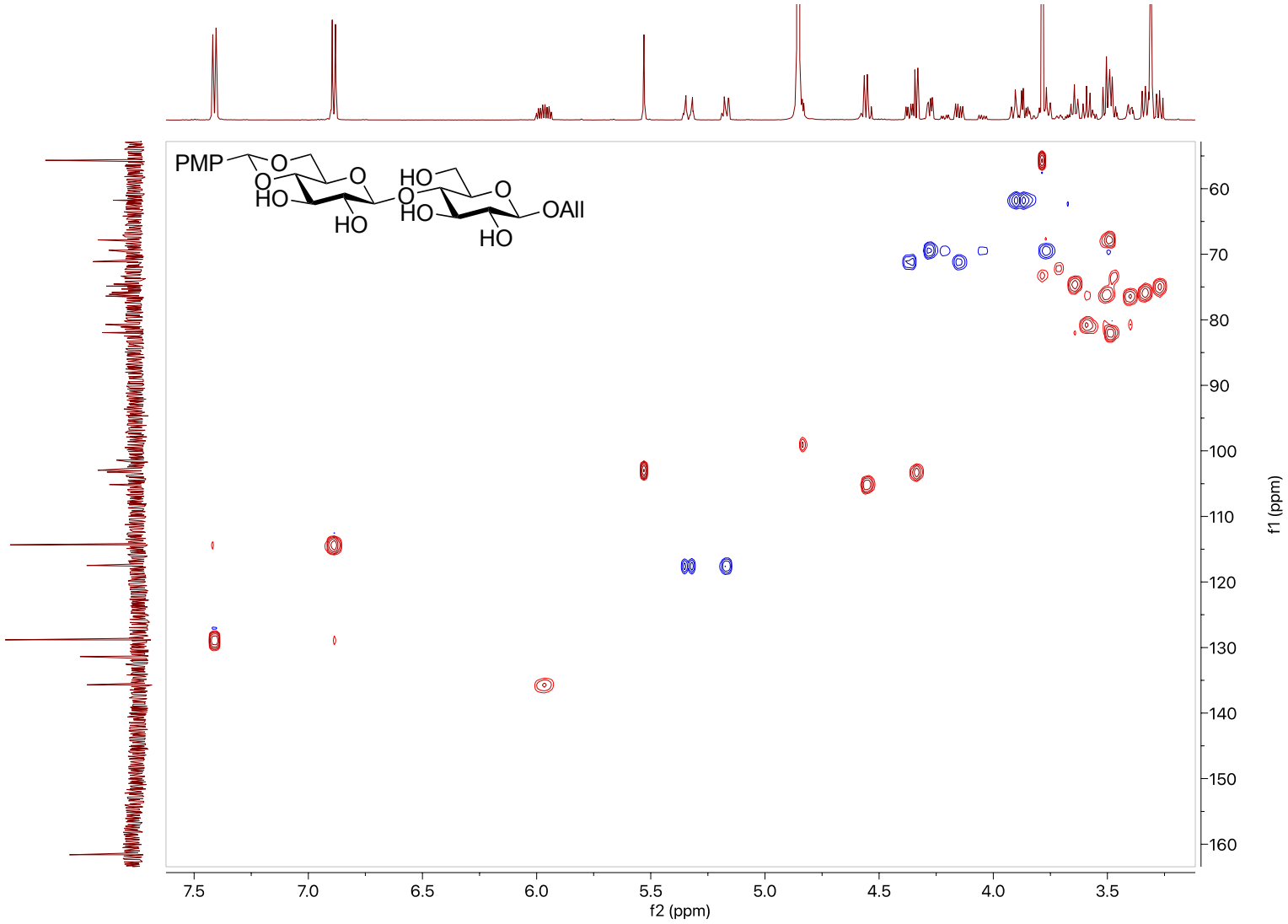
Supplementary figure 156 | COSY NMR spectrum (600 MHz, MeOD) of compound 48



Supplementary figure 157 | ^{13}C NMR spectrum (150 MHz, MeOD) of compound 48

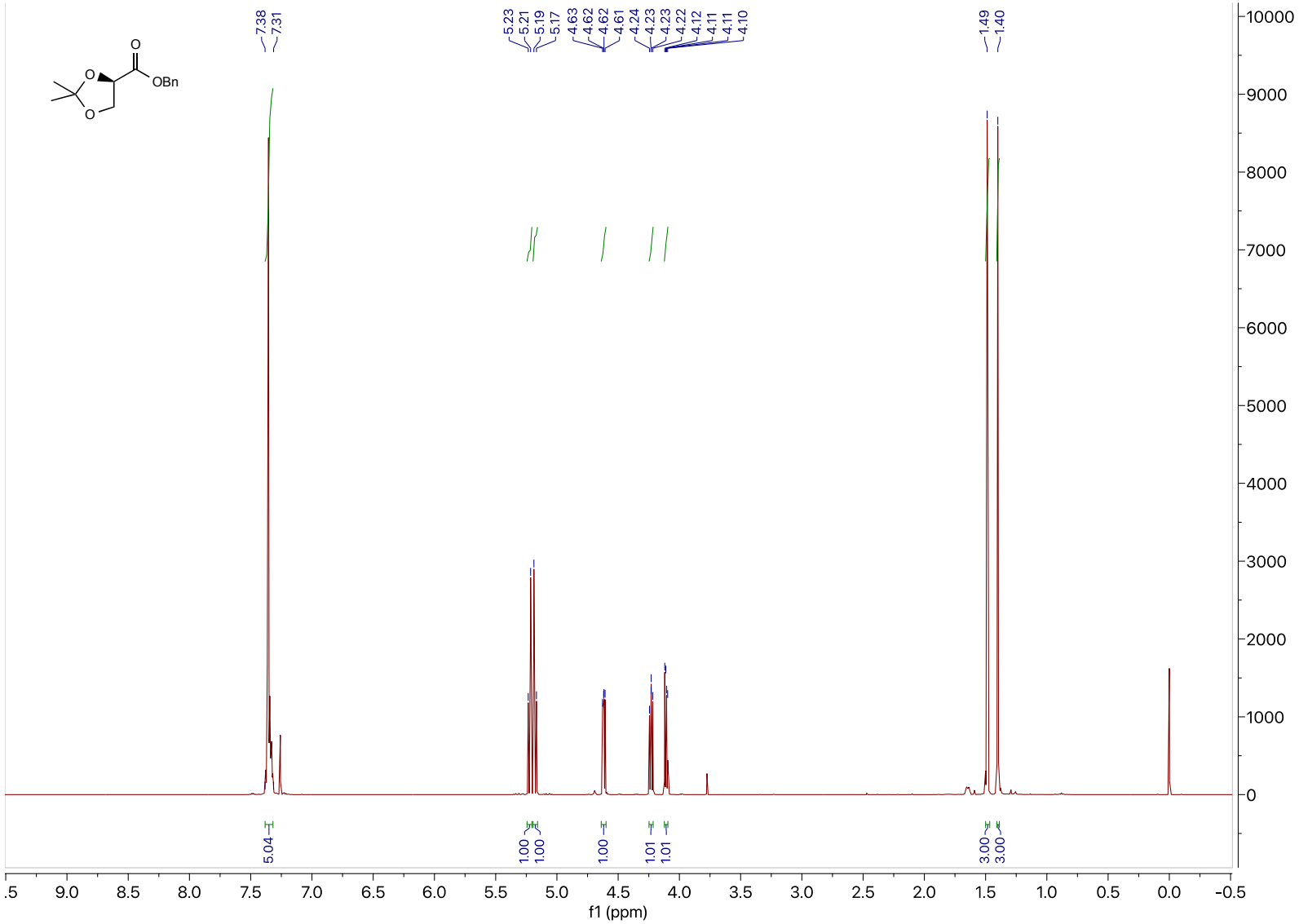


Supplementary figure 158 | HSQC NMR spectrum (600 MHz, MeOD) of compound 48

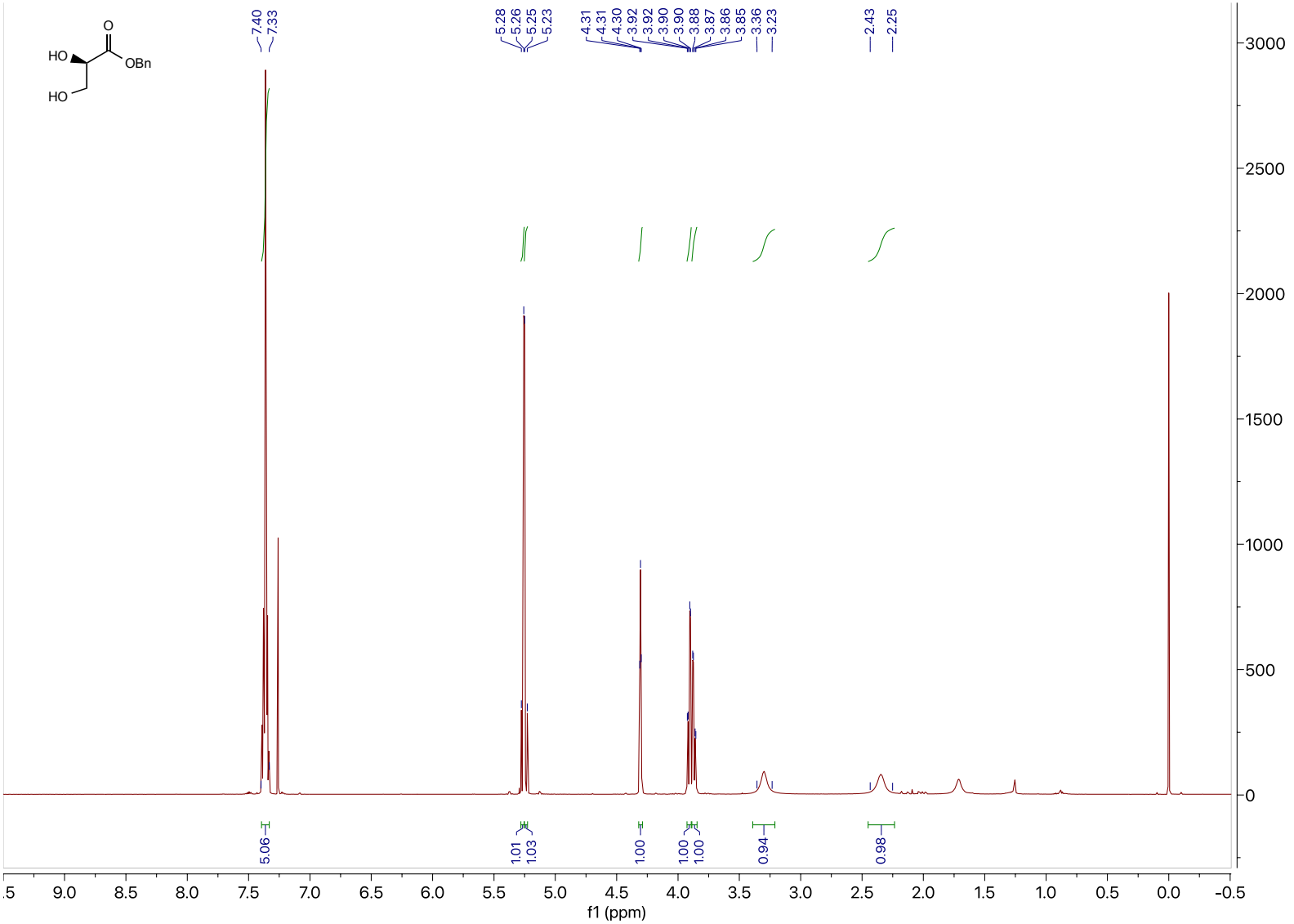


2. Annexes du chapitre V

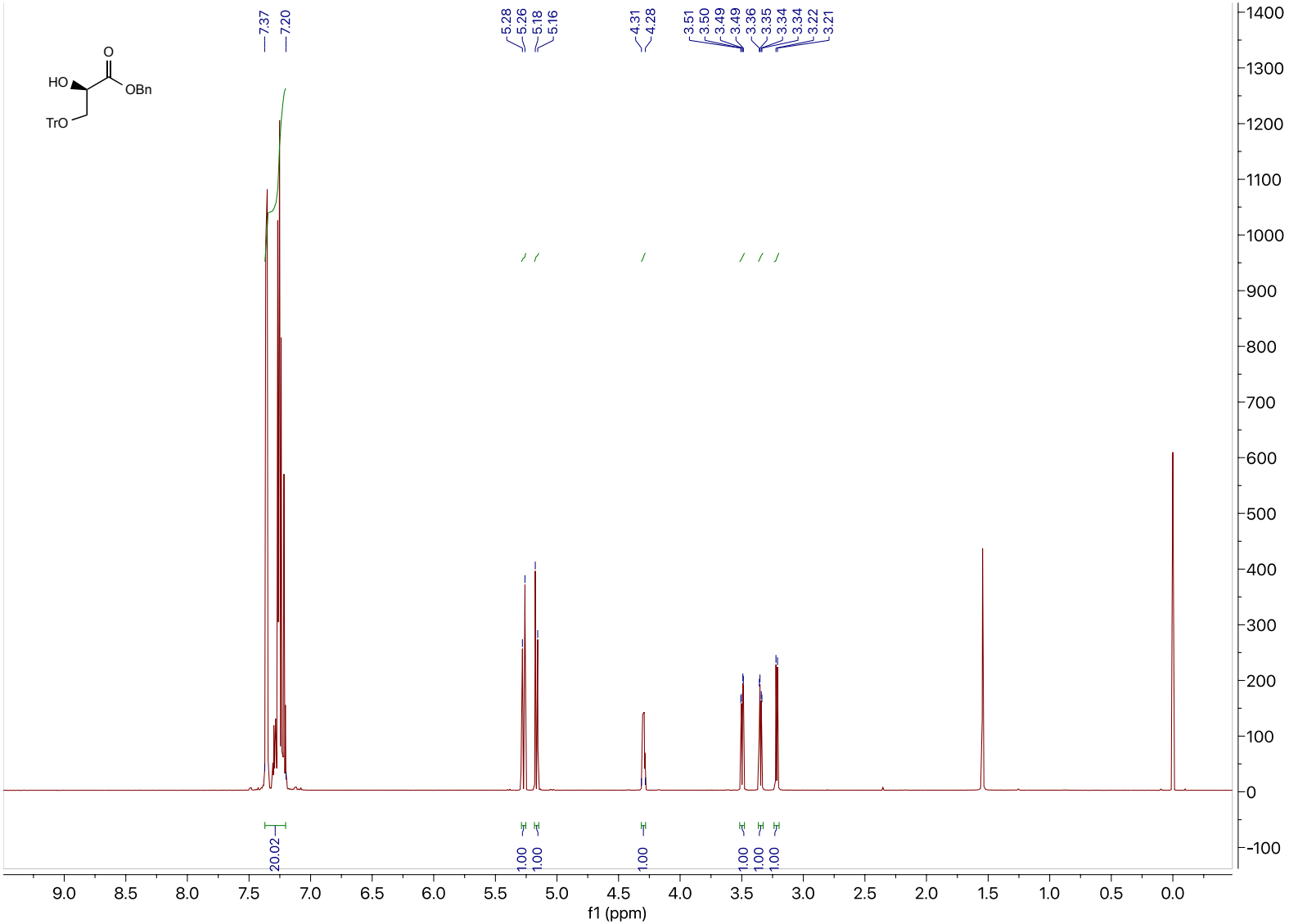
Supplementary figure 159 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 6



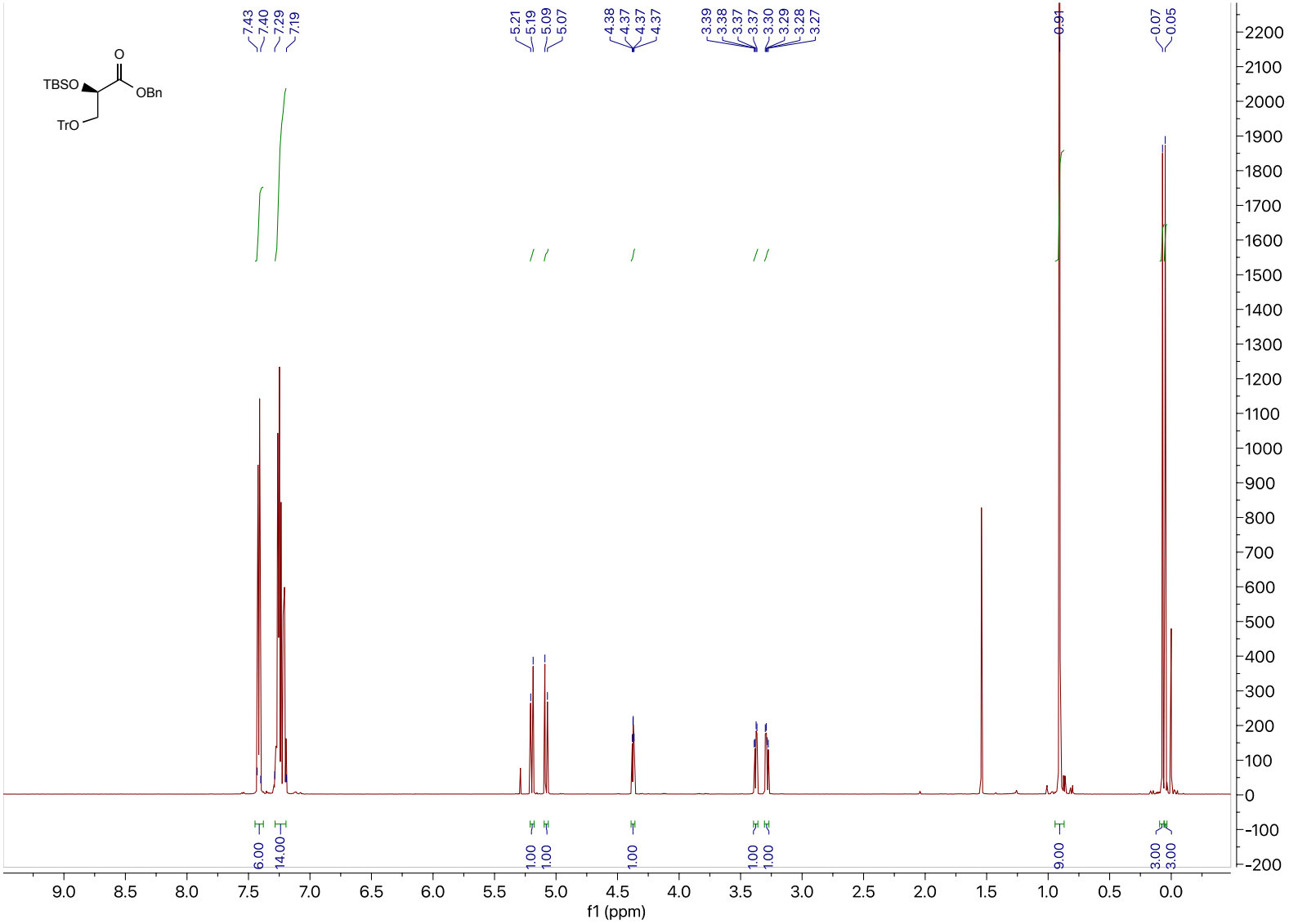
Supplementary figure 160 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 7



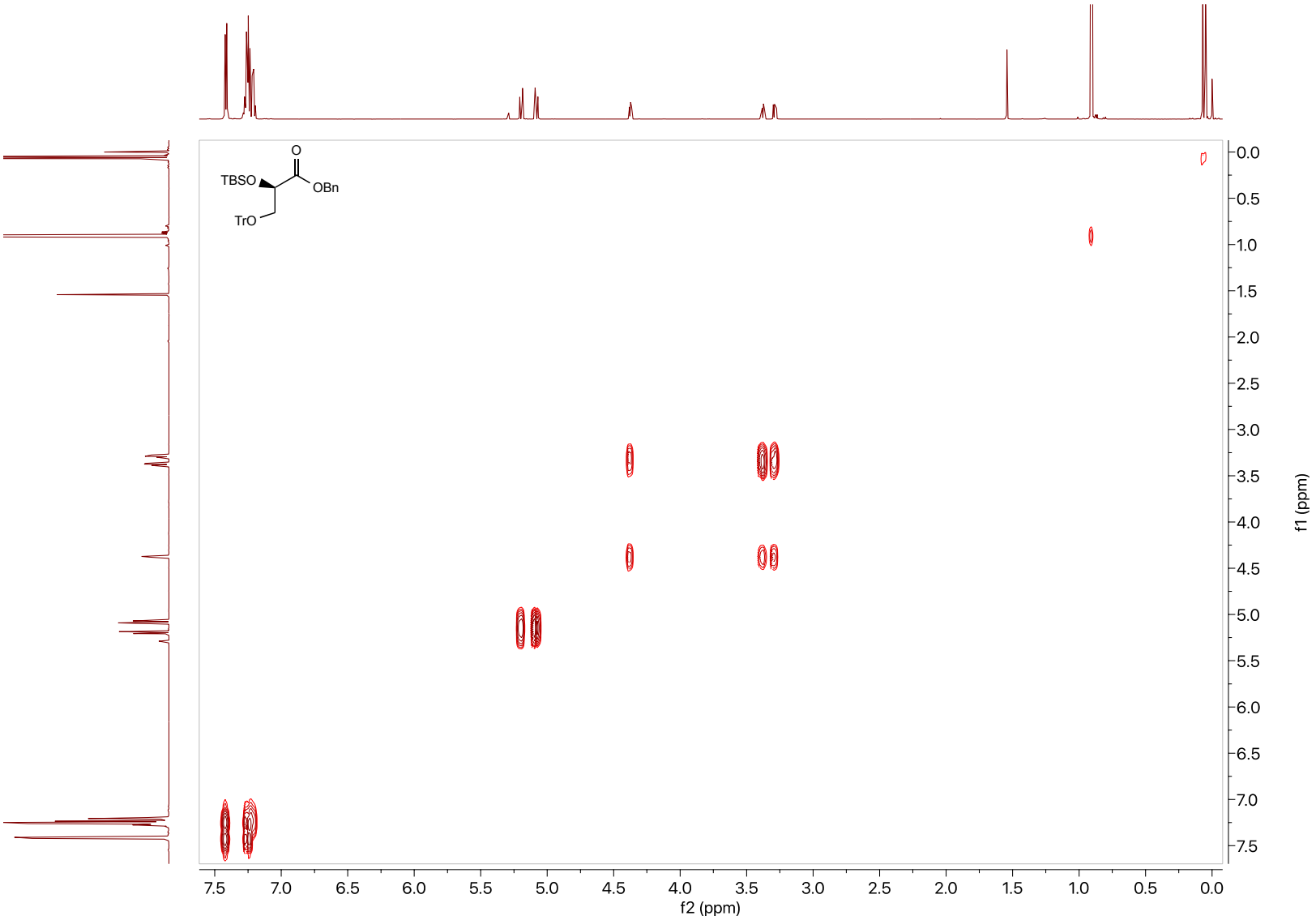
Supplementary figure 161 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 8



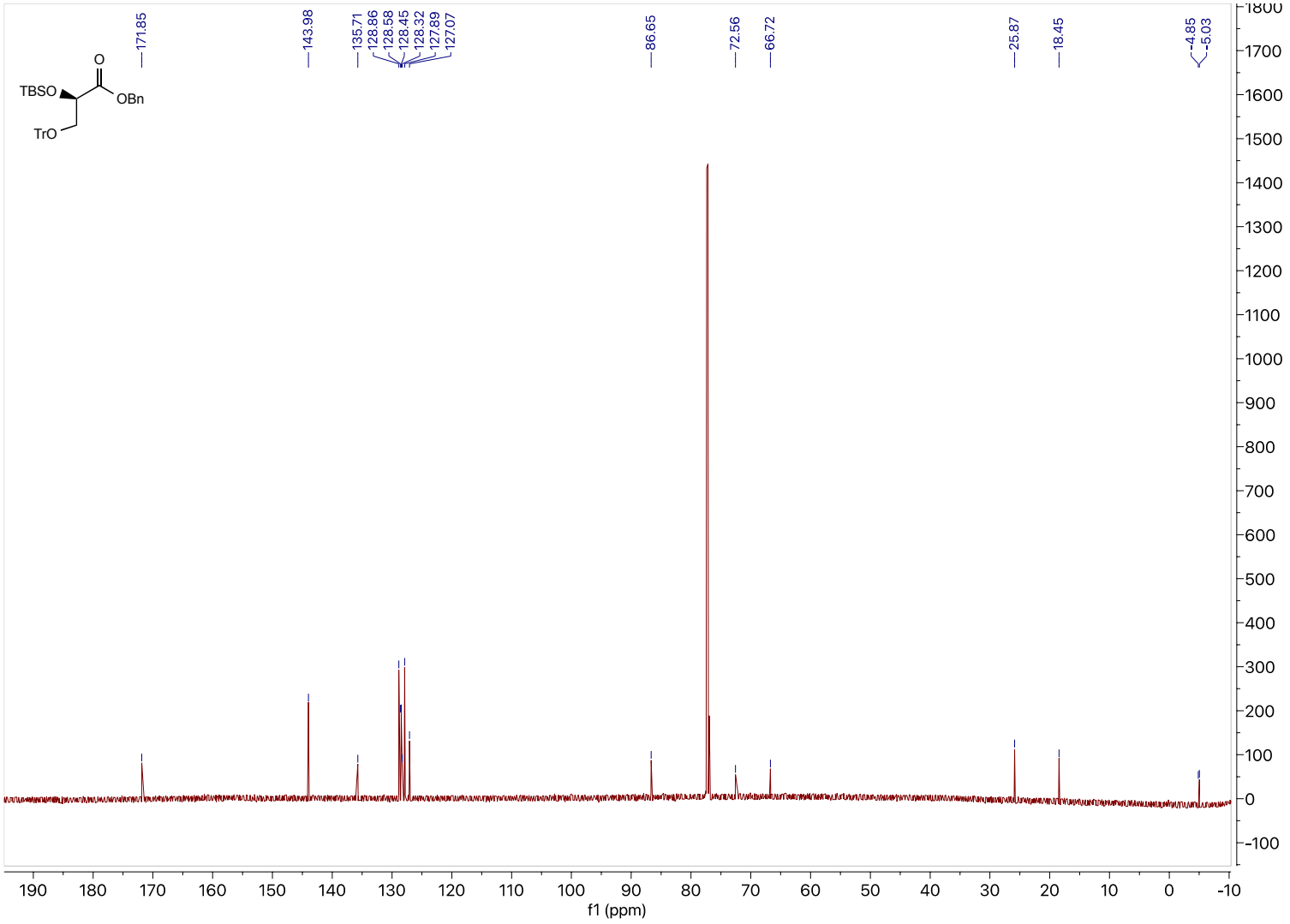
Supplementary figure 162 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 9



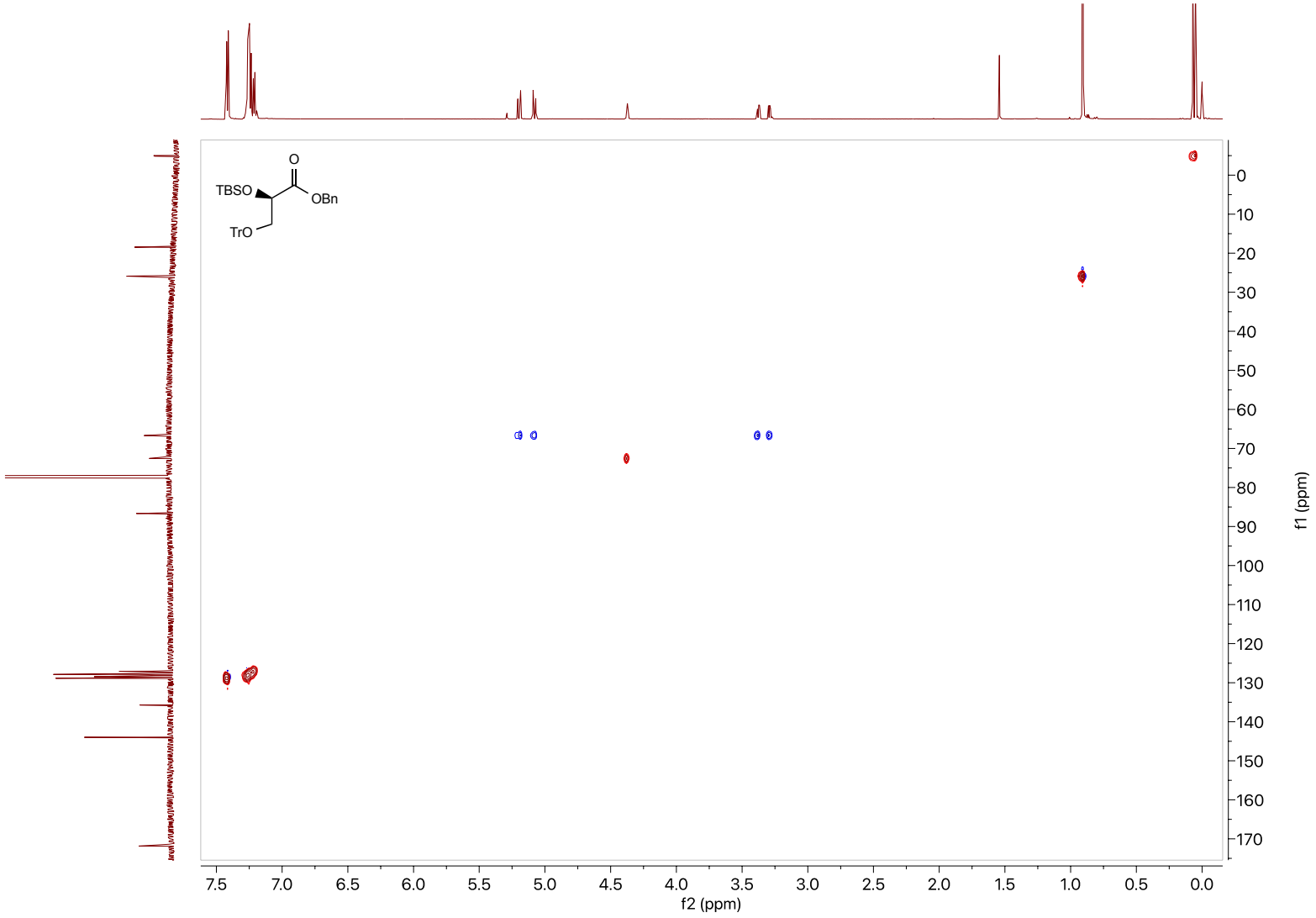
Supplementary figure 163 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 9



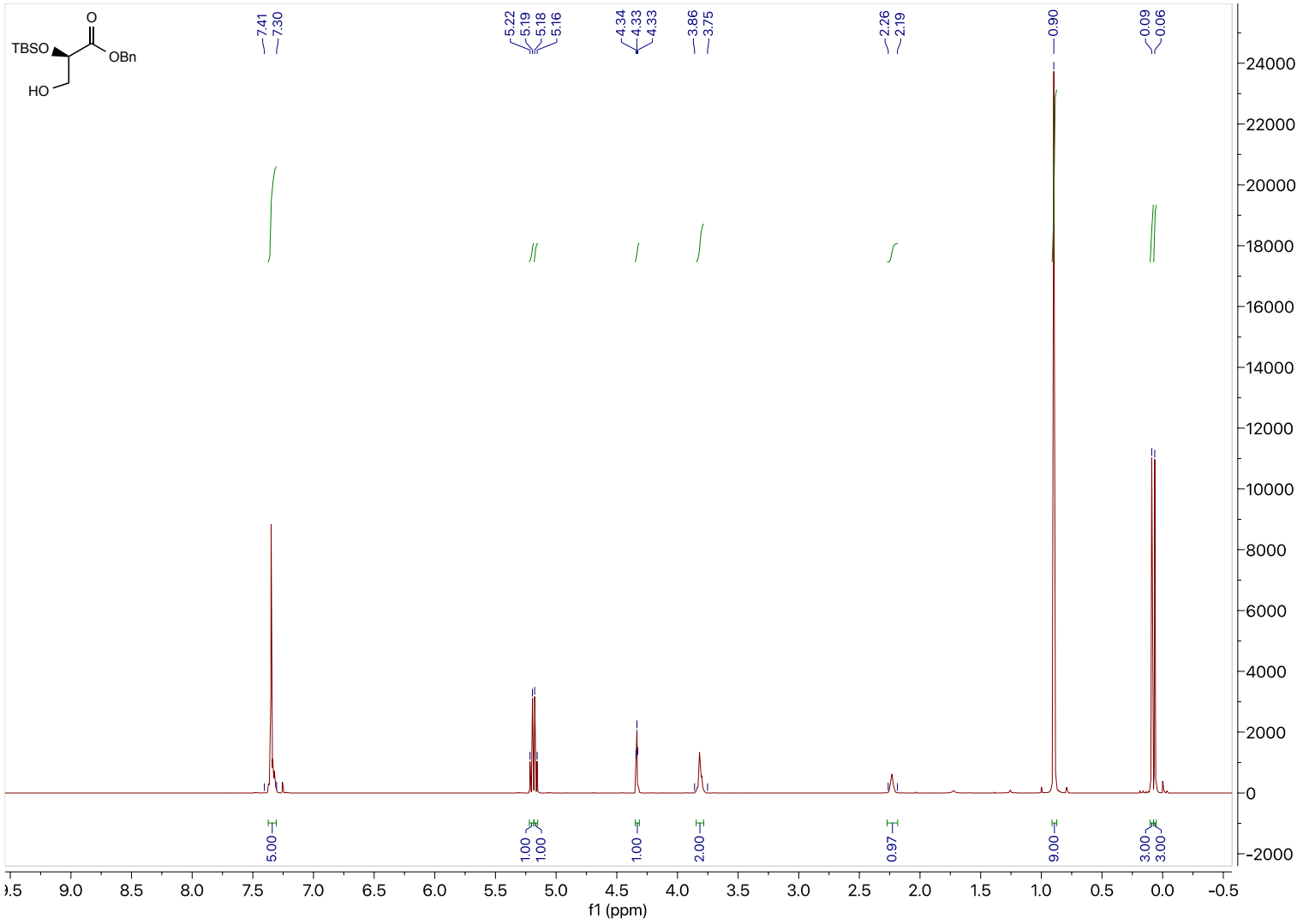
Supplementary figure 164 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 9



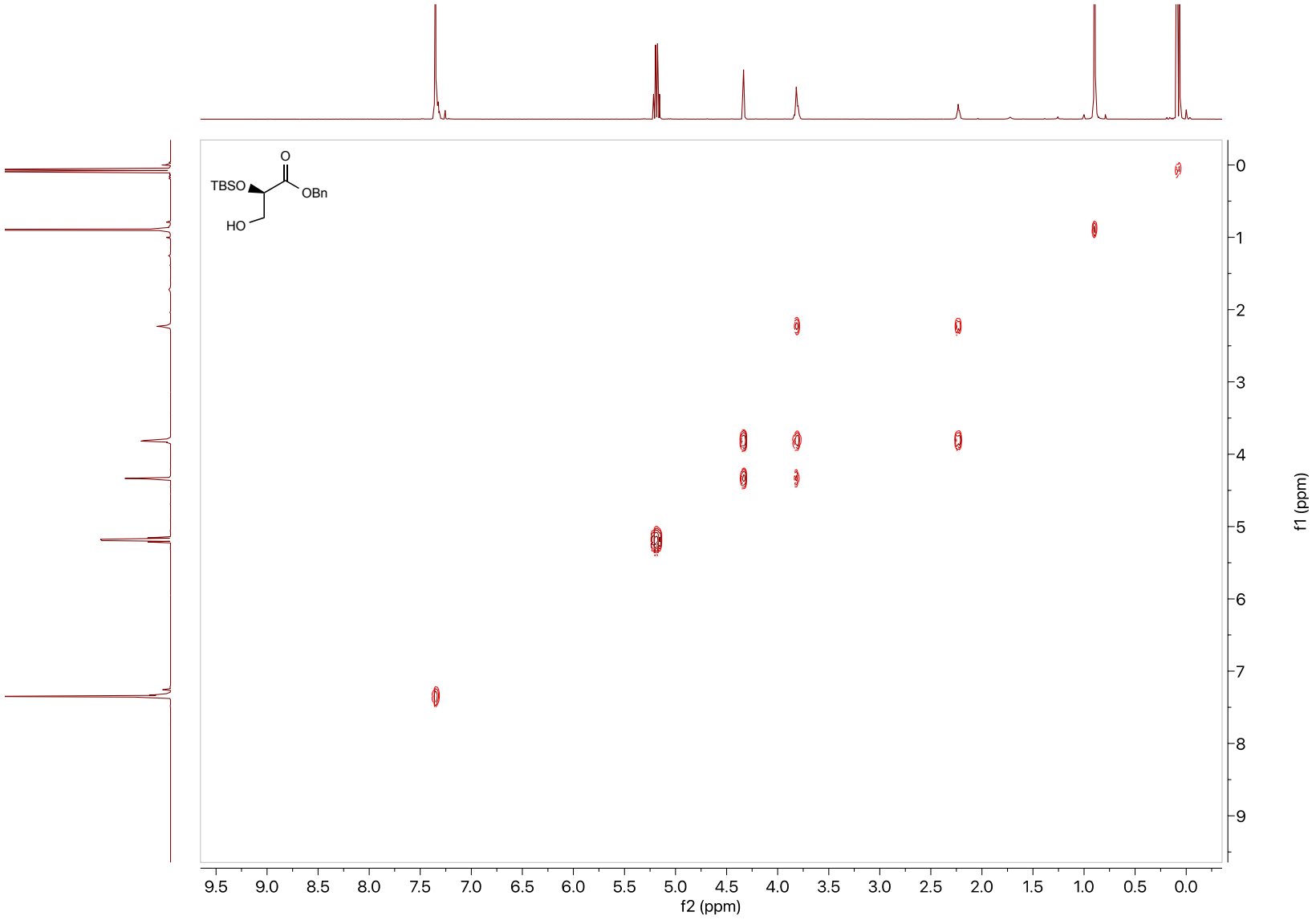
Supplementary figure 165 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 9



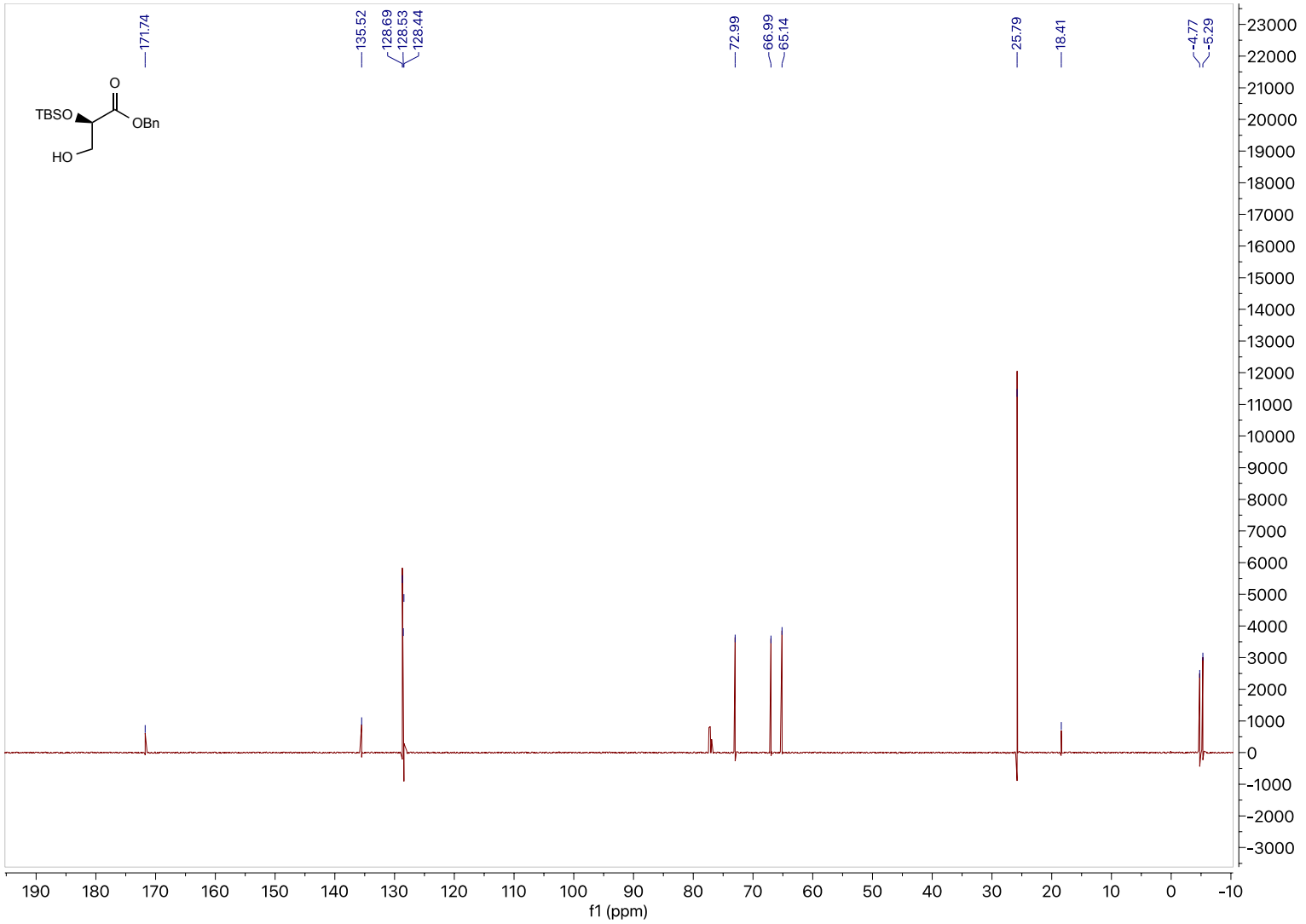
Supplementary figure 166 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 3



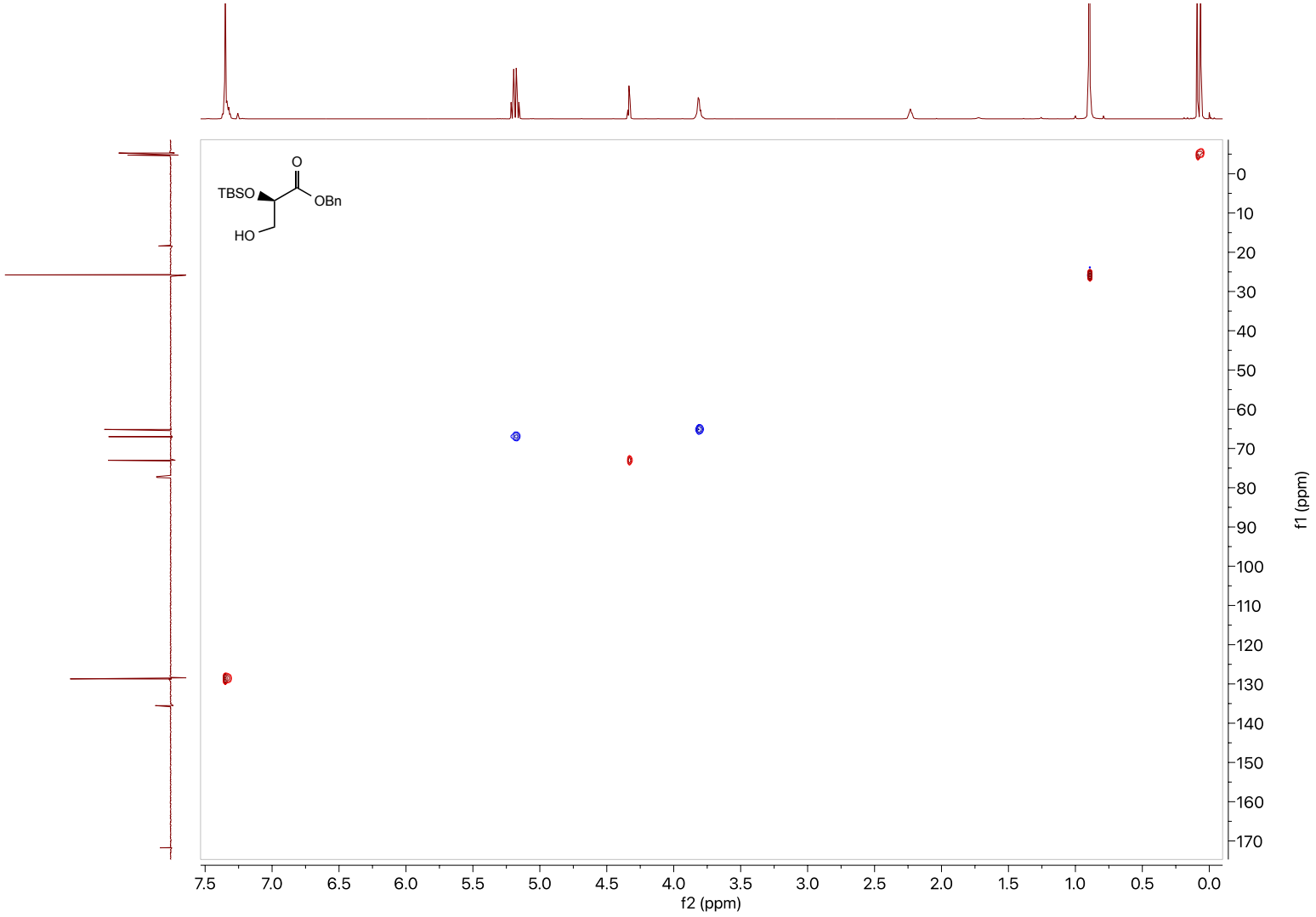
Supplementary figure 167 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 3



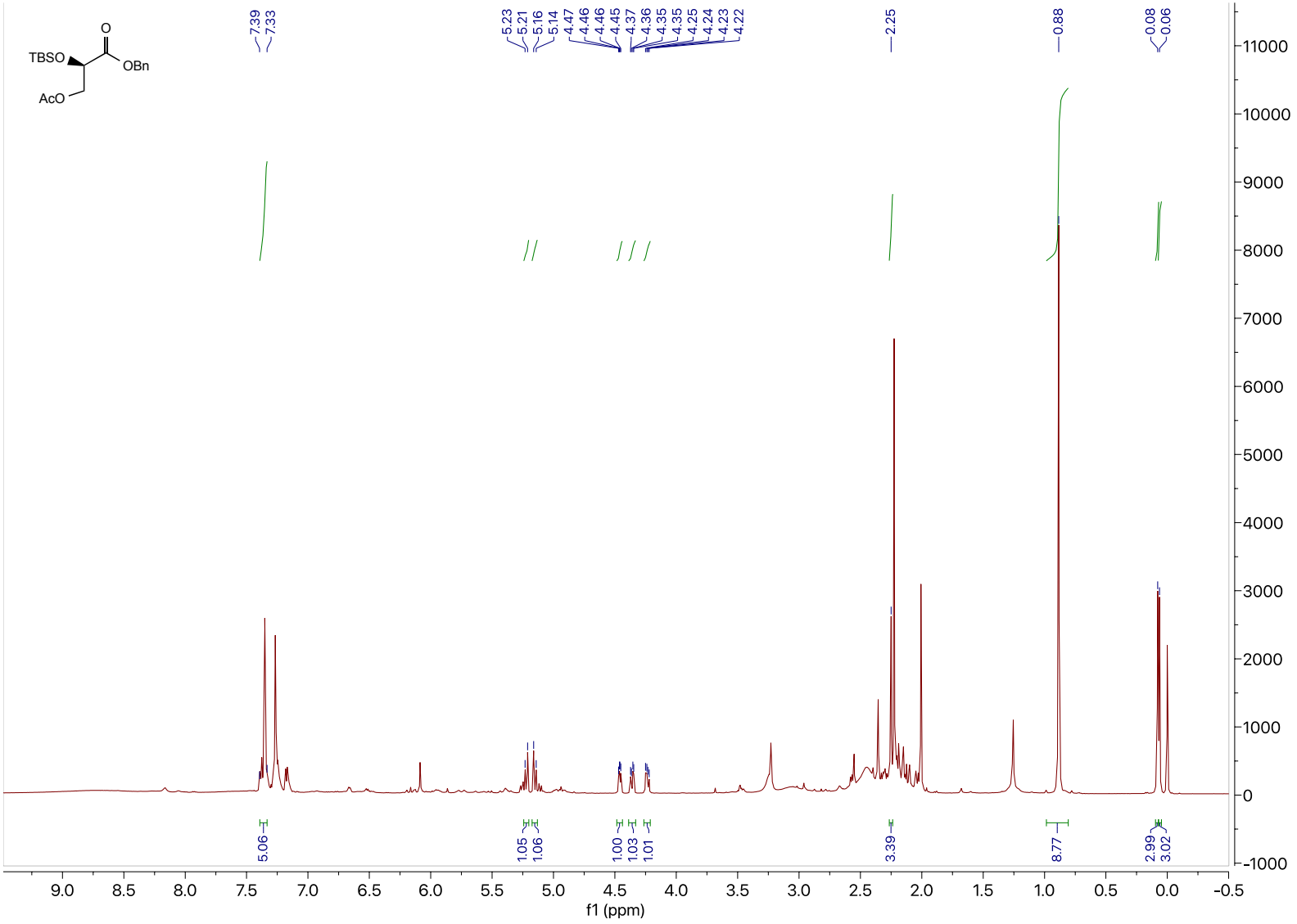
Supplementary figure 168 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 3



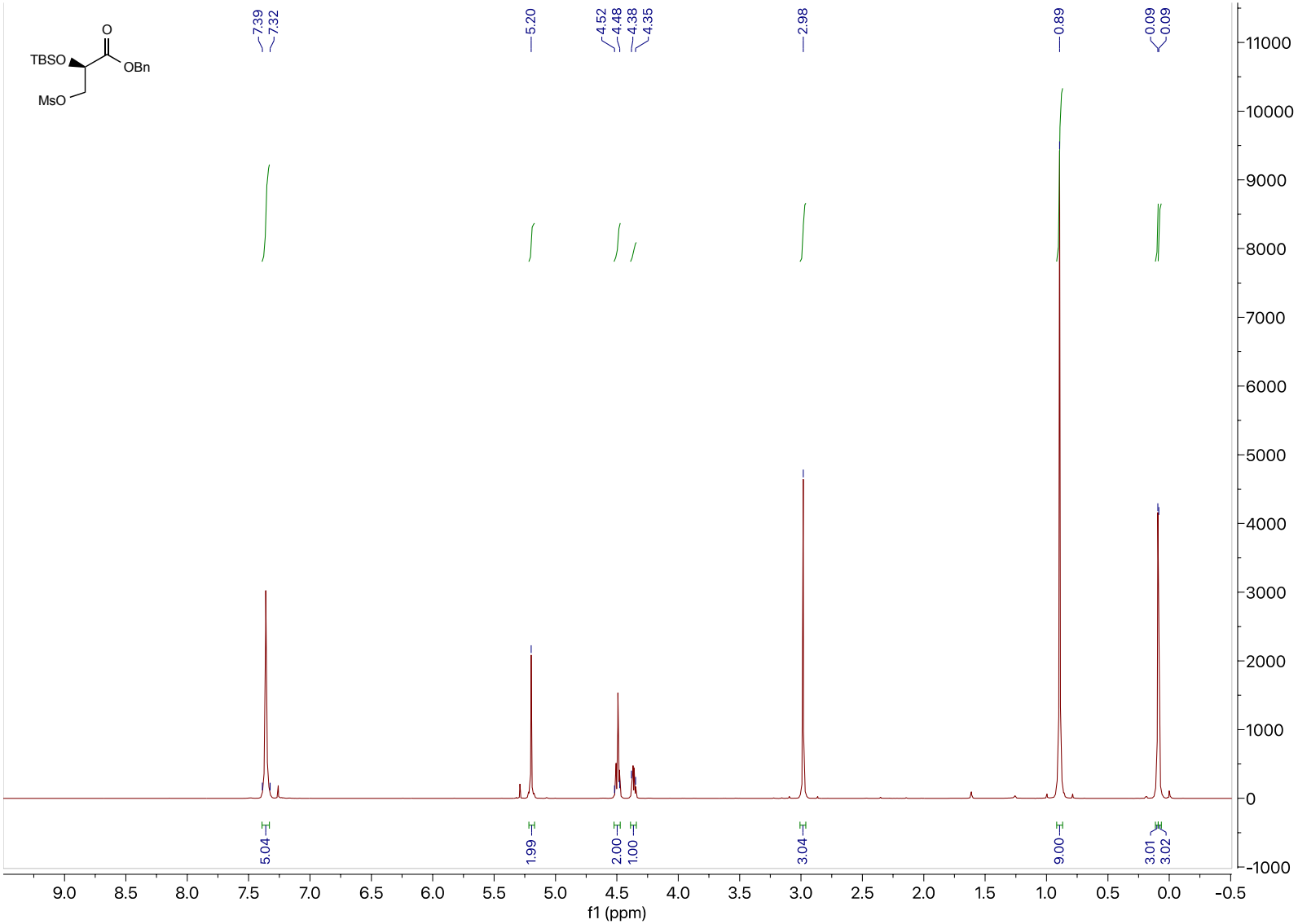
Supplementary figure 169 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 3



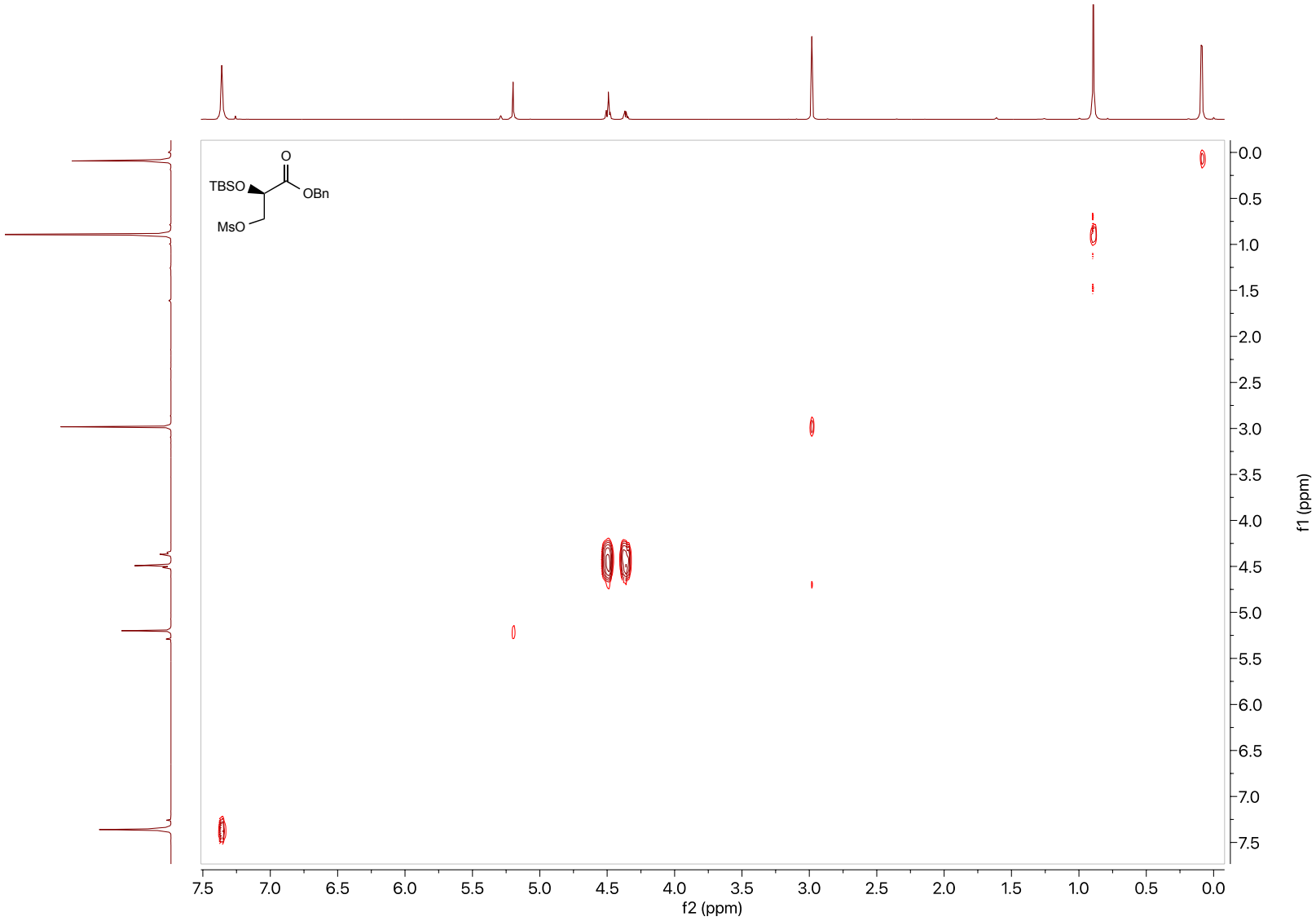
Supplementary figure 170 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 11



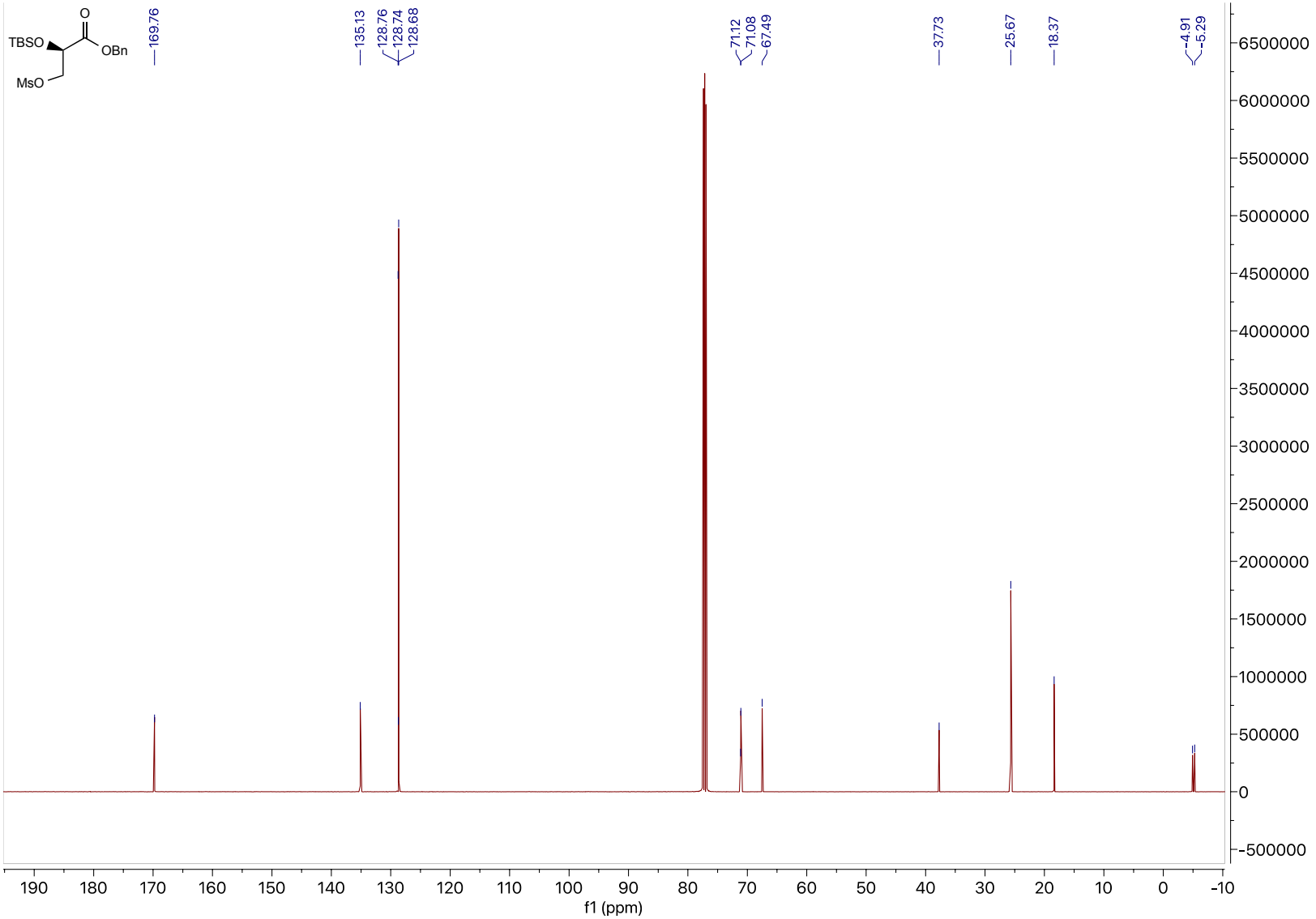
Supplementary figure 171 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 12



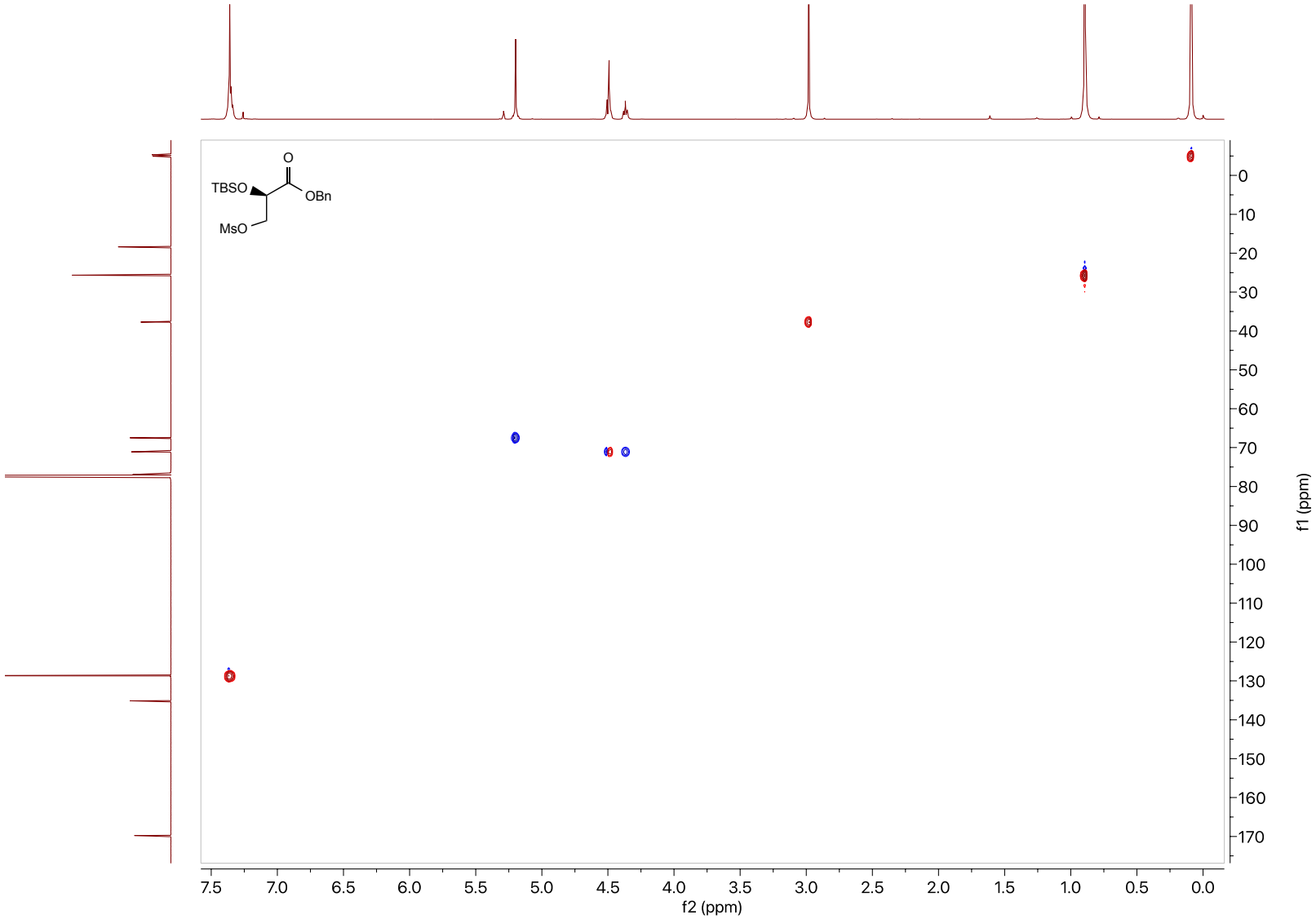
Supplementary figure 172 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 12



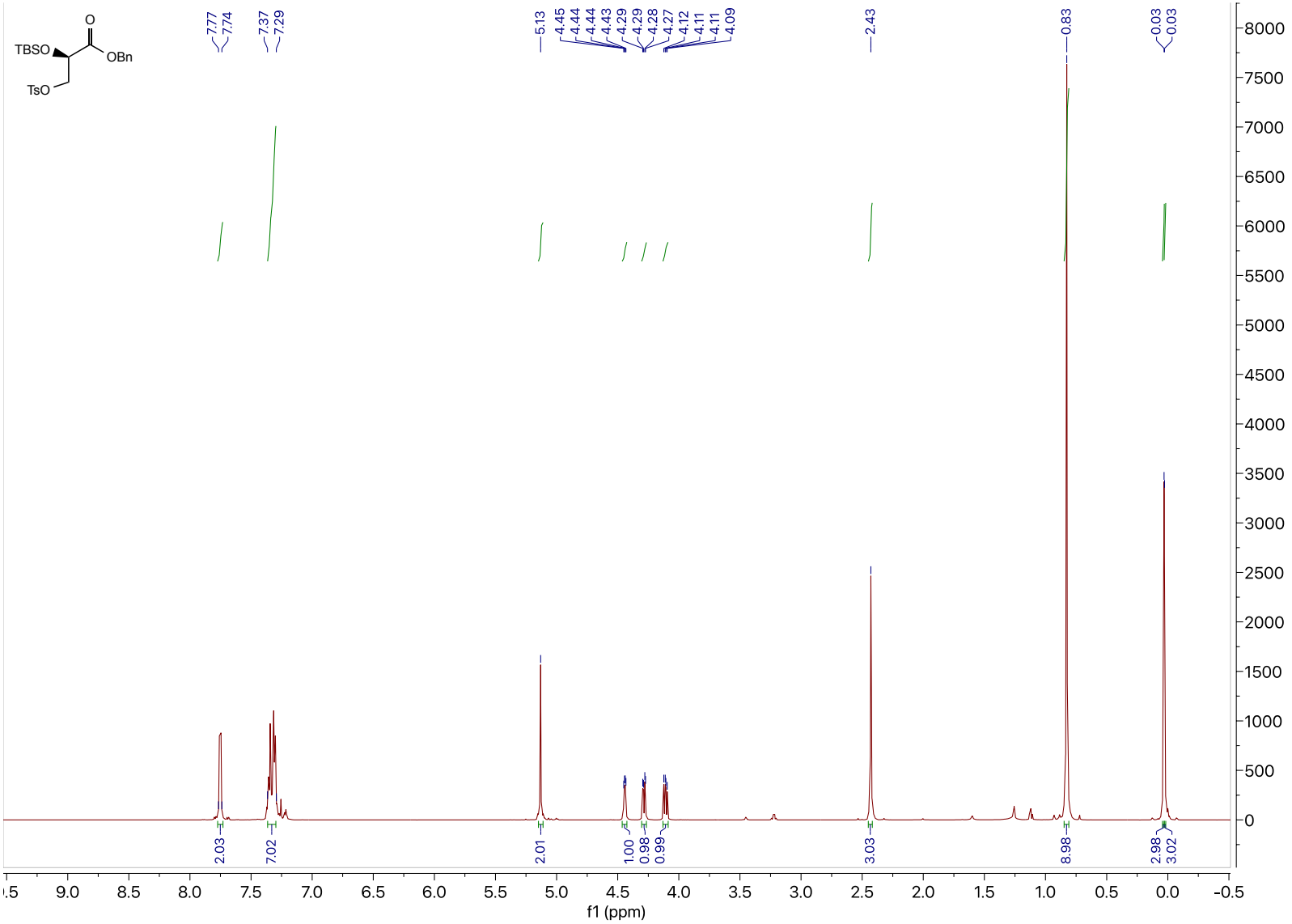
Supplementary figure 173 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 12



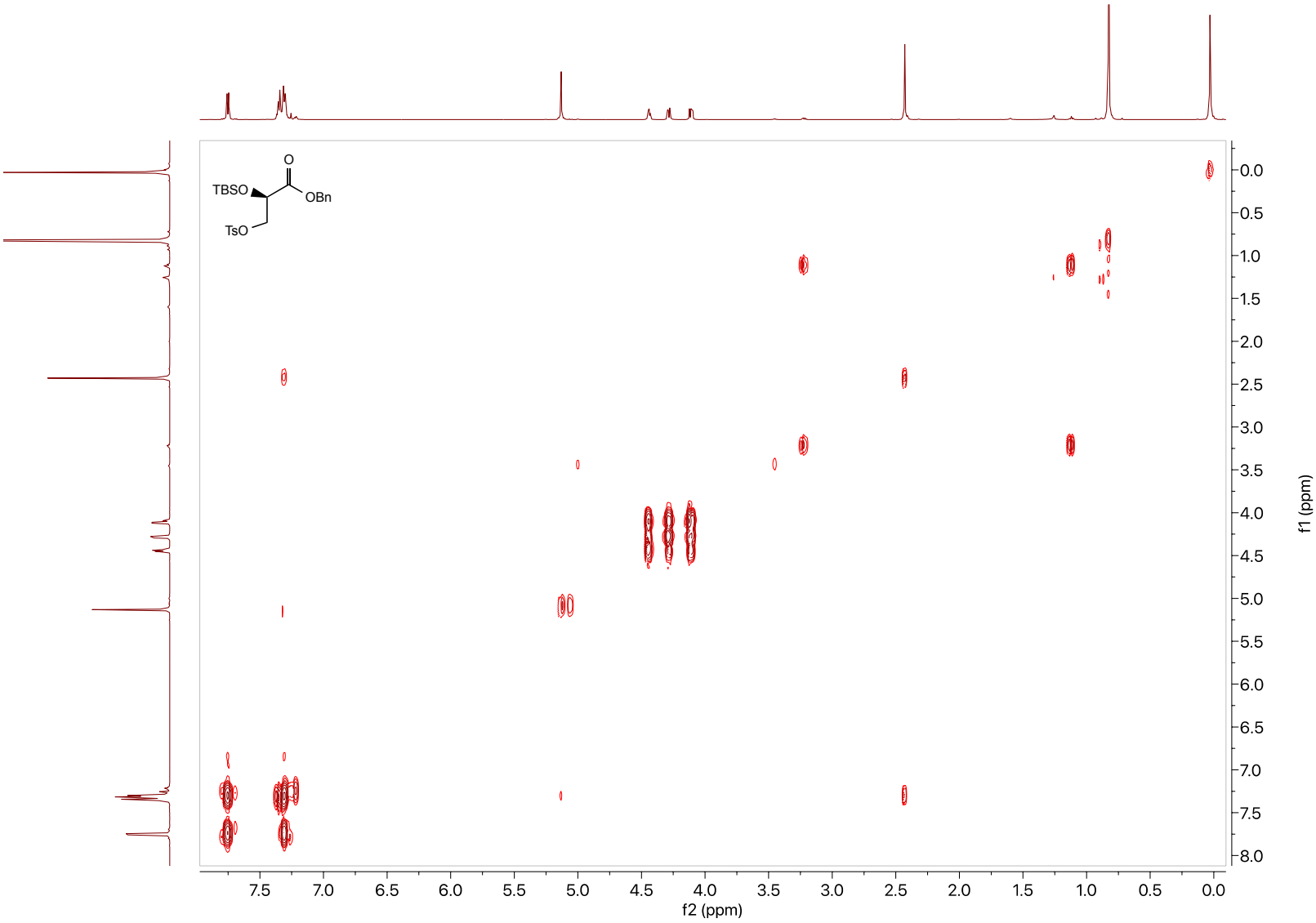
Supplementary figure 174 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 12



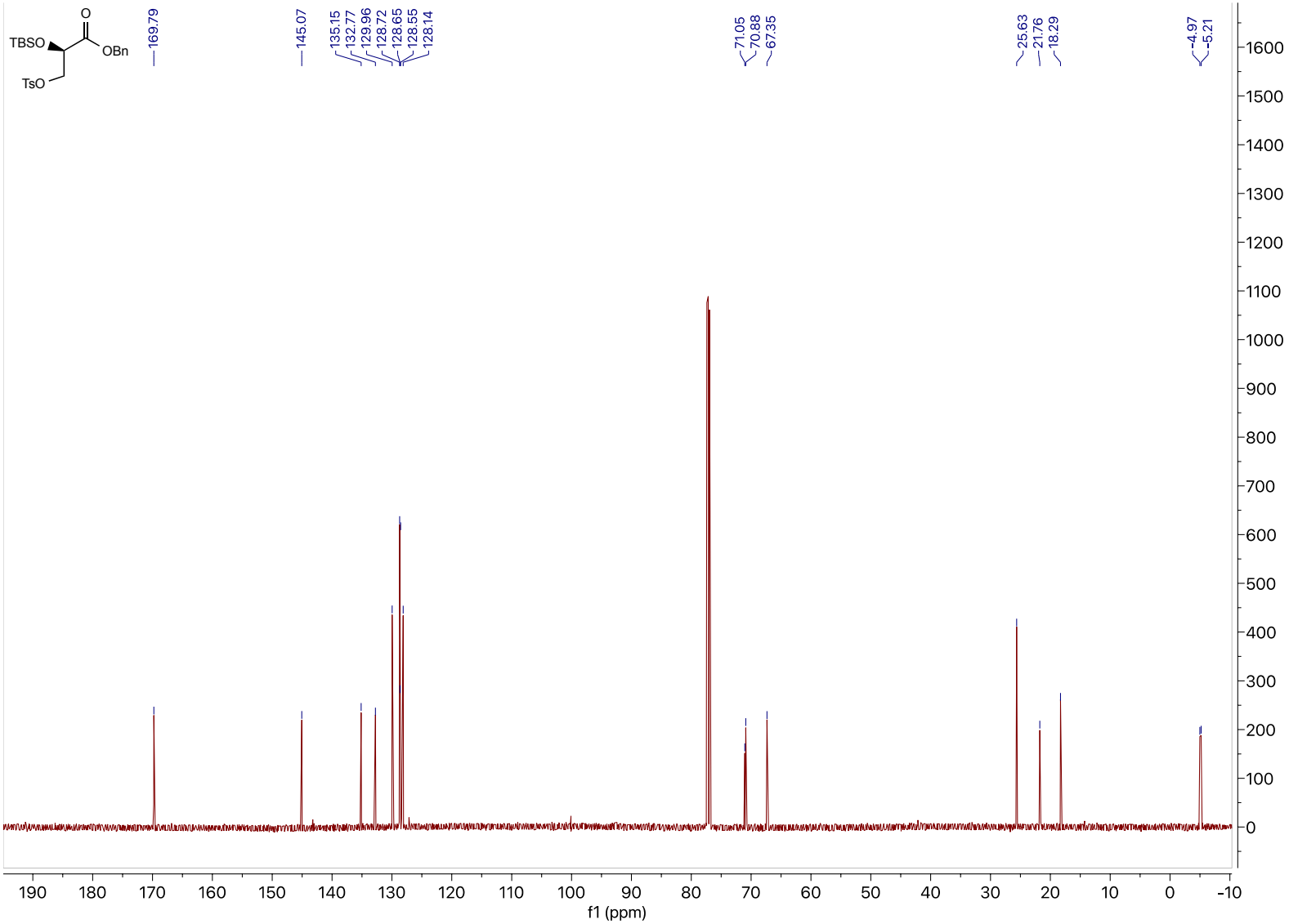
Supplementary figure 175 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 13



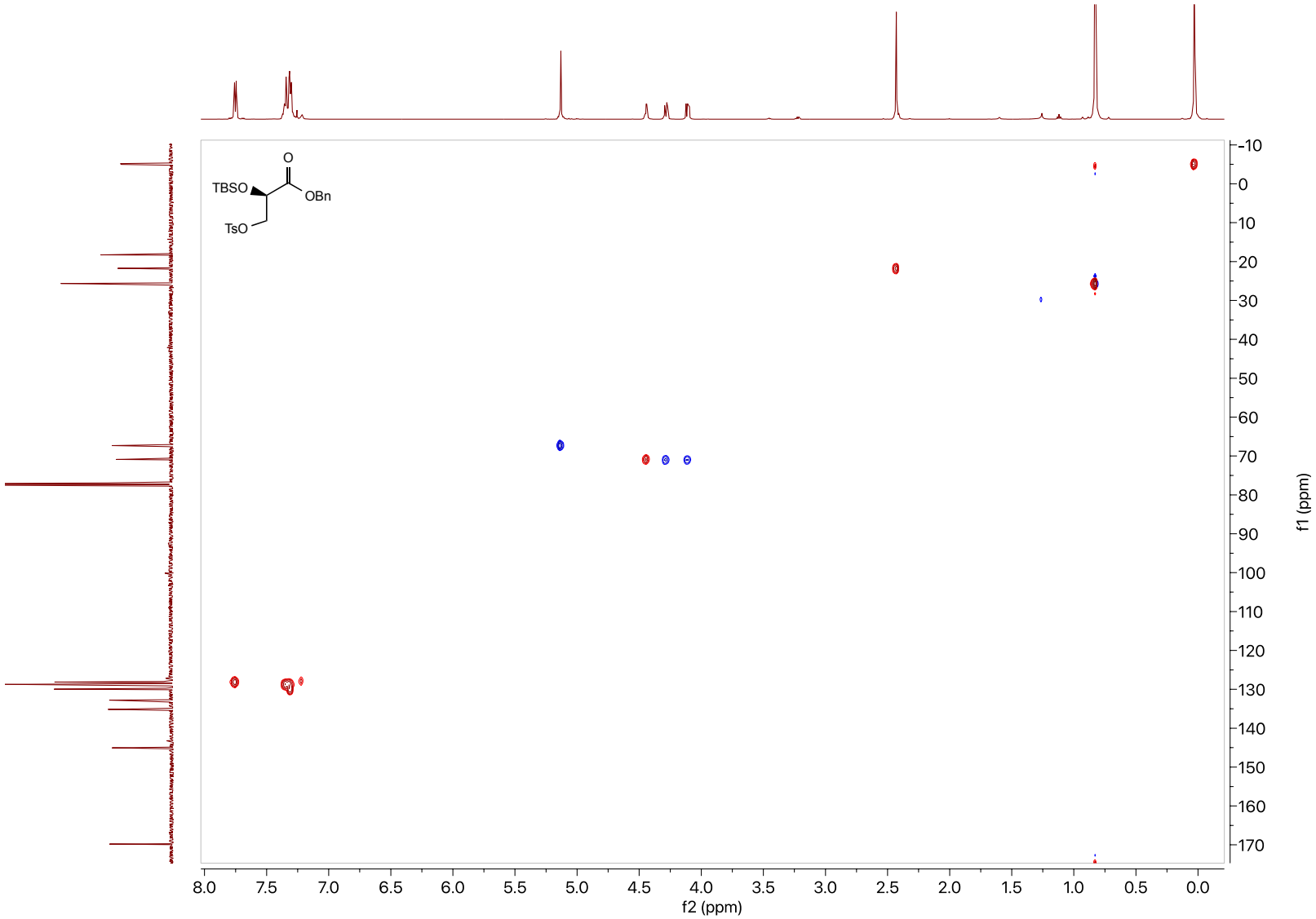
Supplementary figure 176 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 13



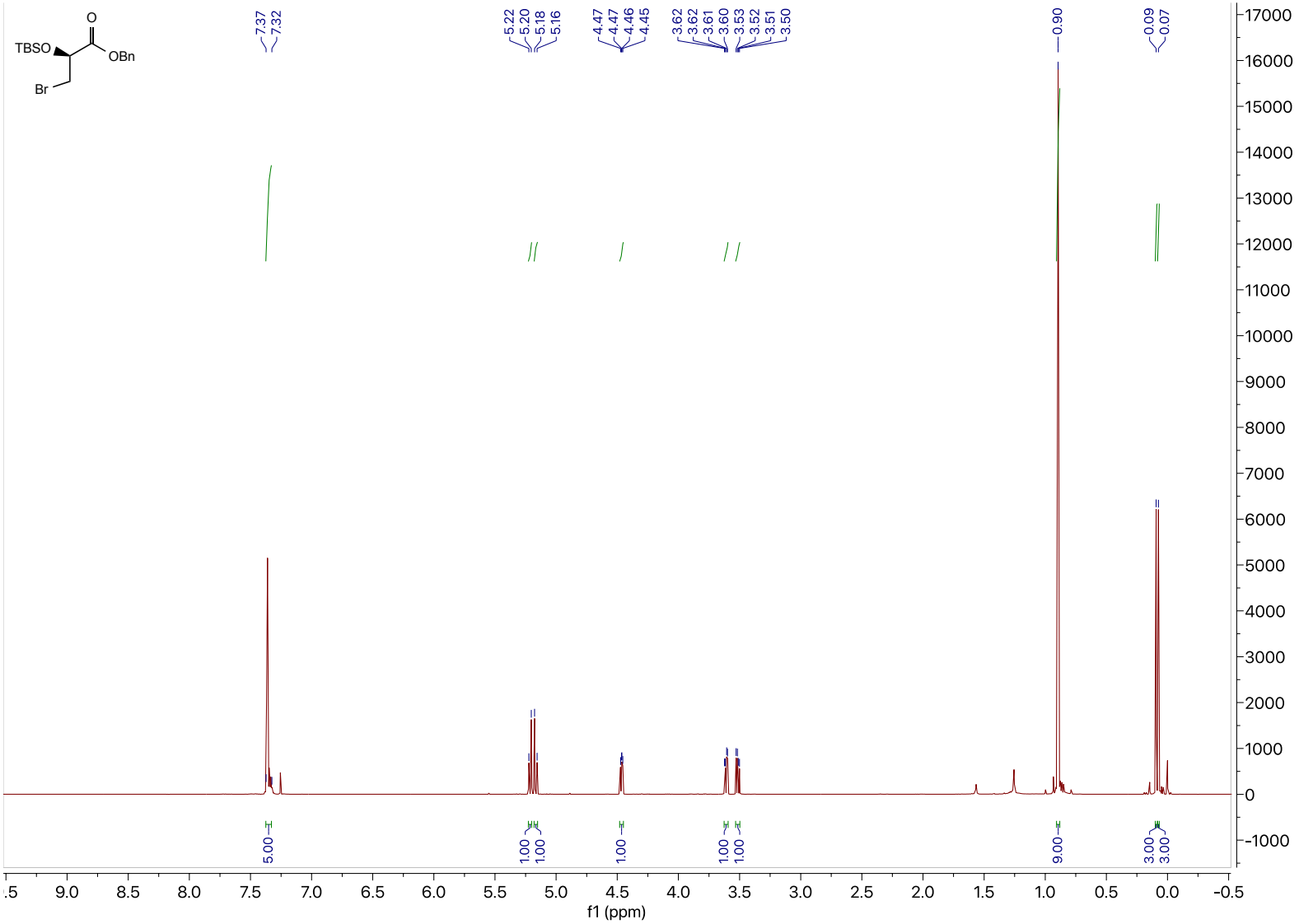
Supplementary figure 177 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 13



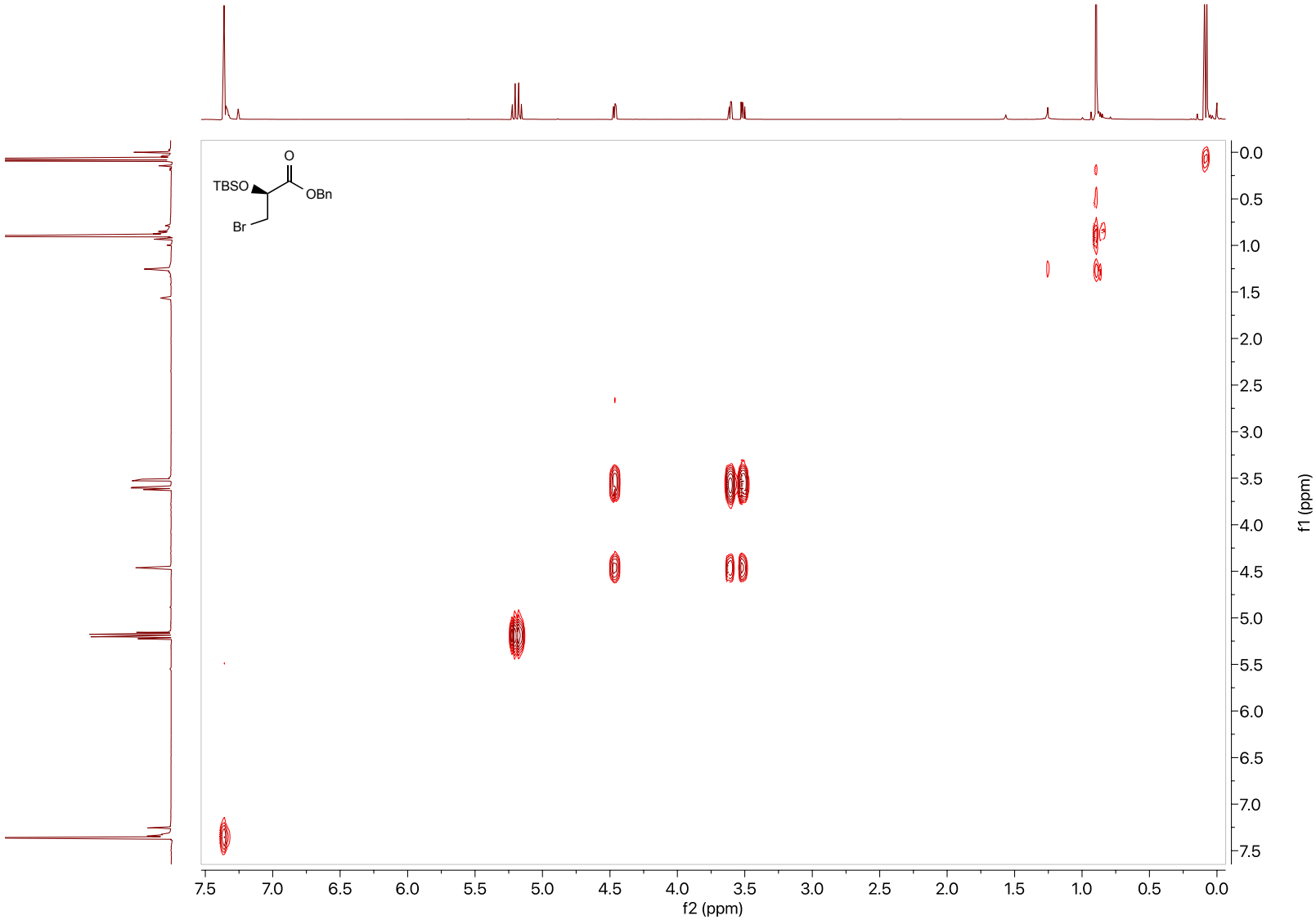
Supplementary figure 178 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 13



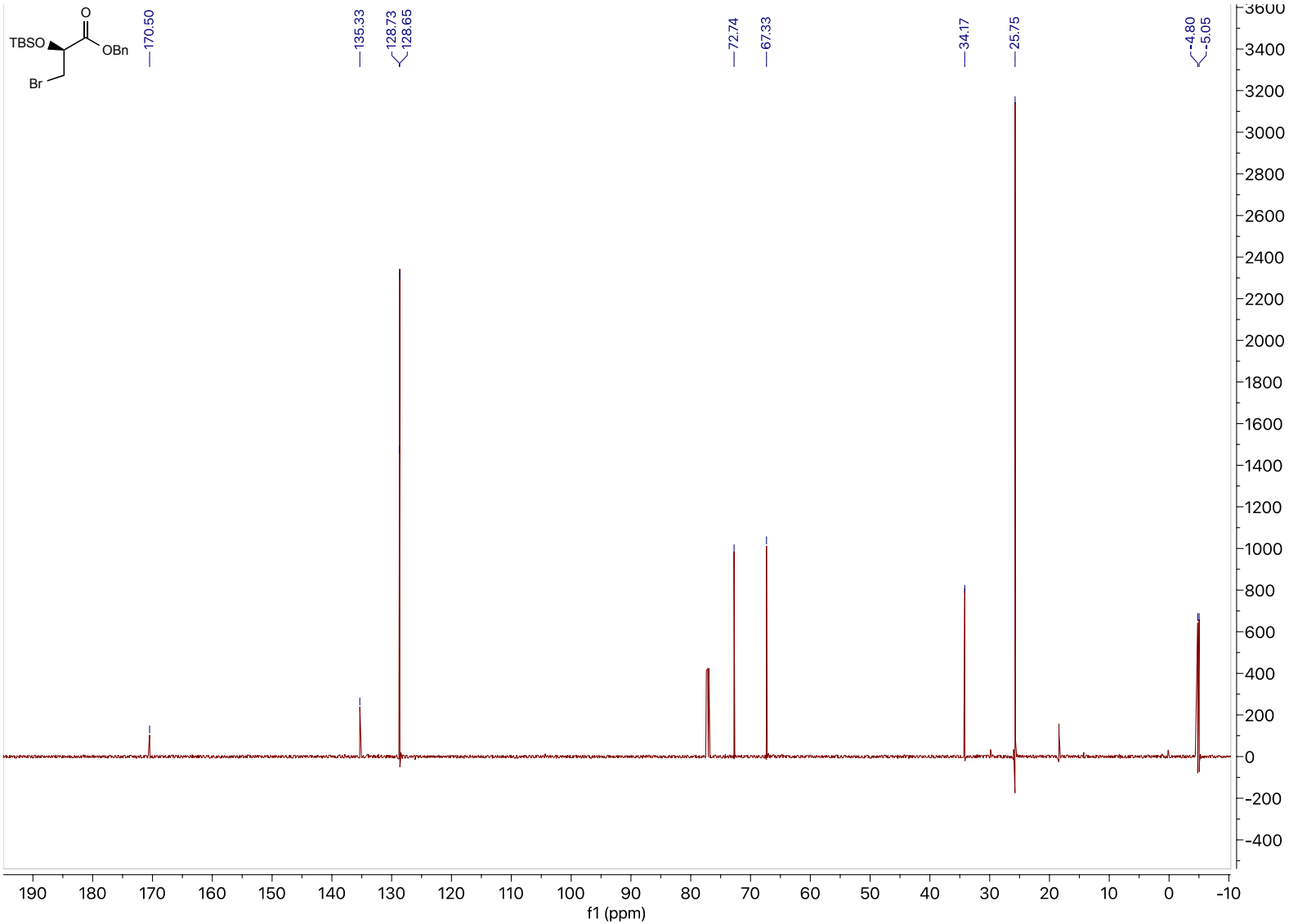
Supplementary figure 179 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 14



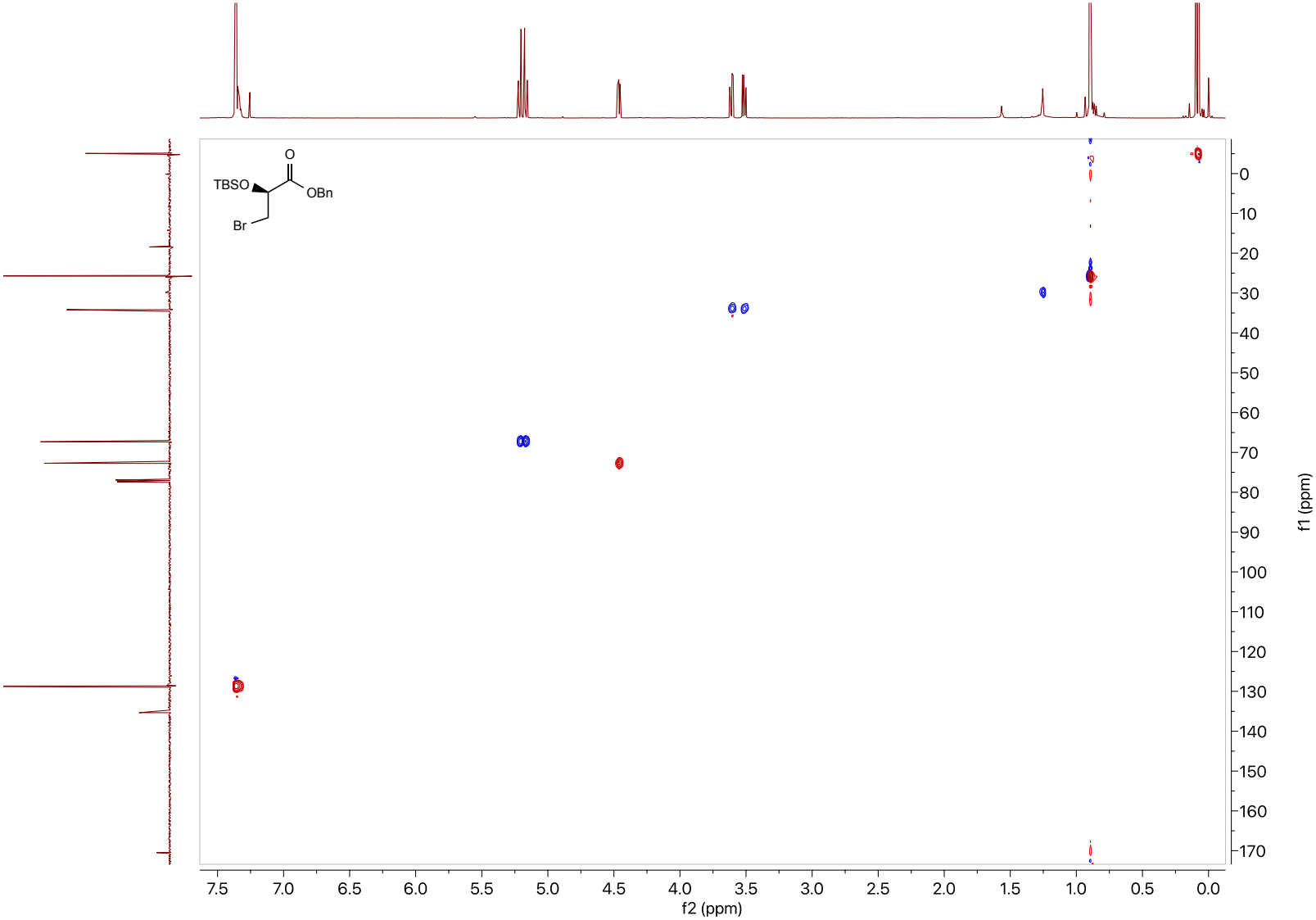
Supplementary figure 180 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 14



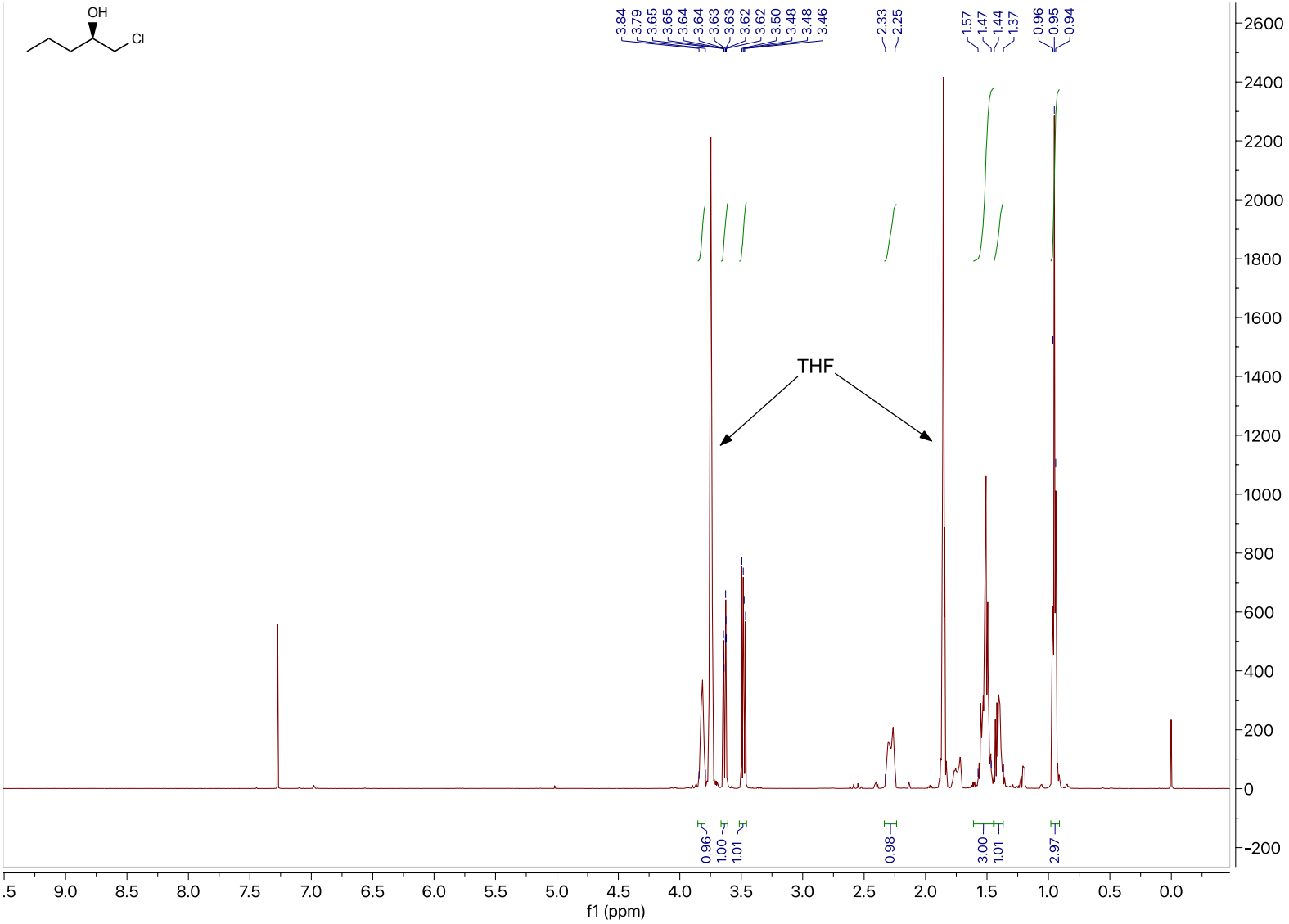
Supplementary figure 181 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 14



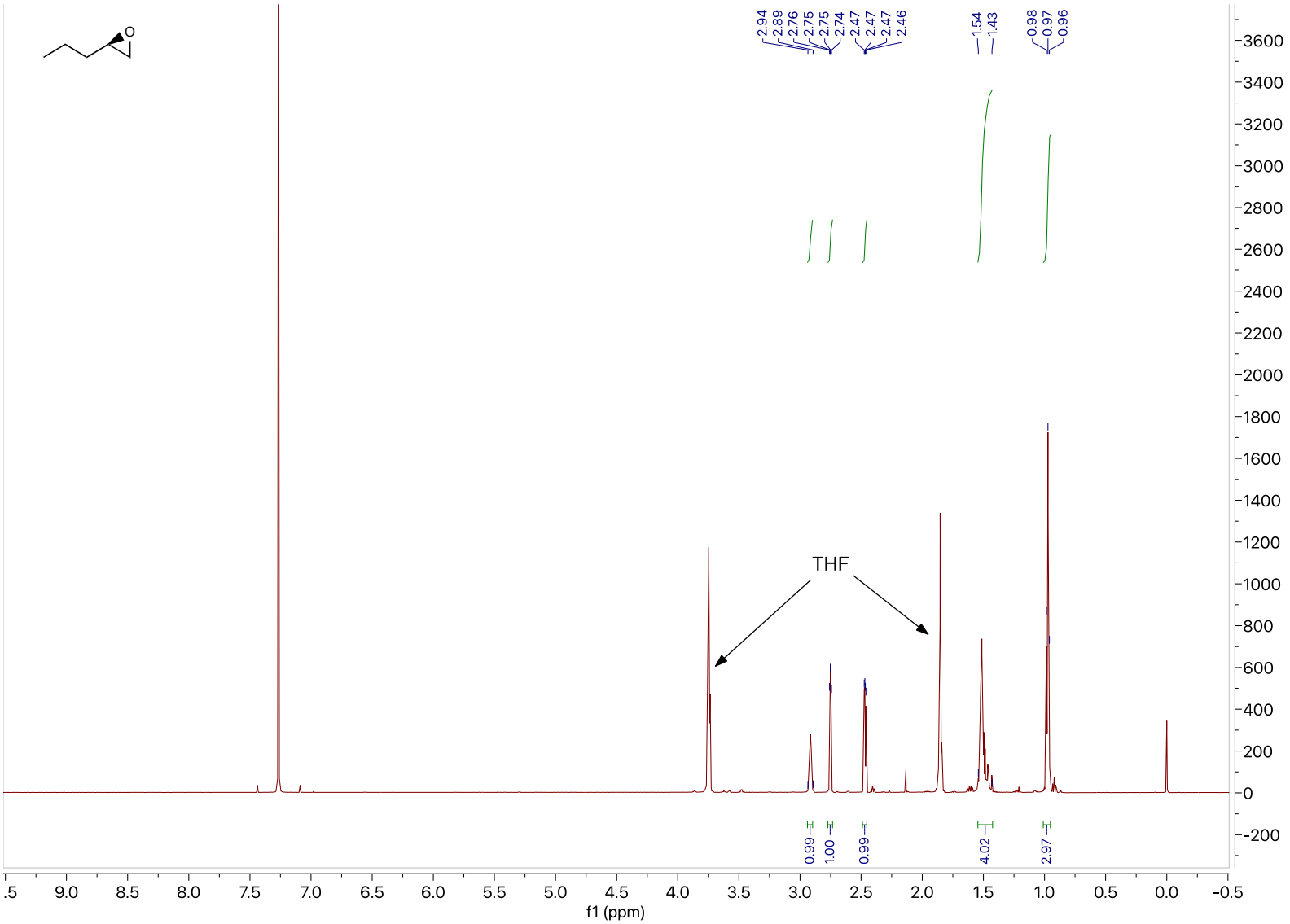
Supplementary figure 182 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 14



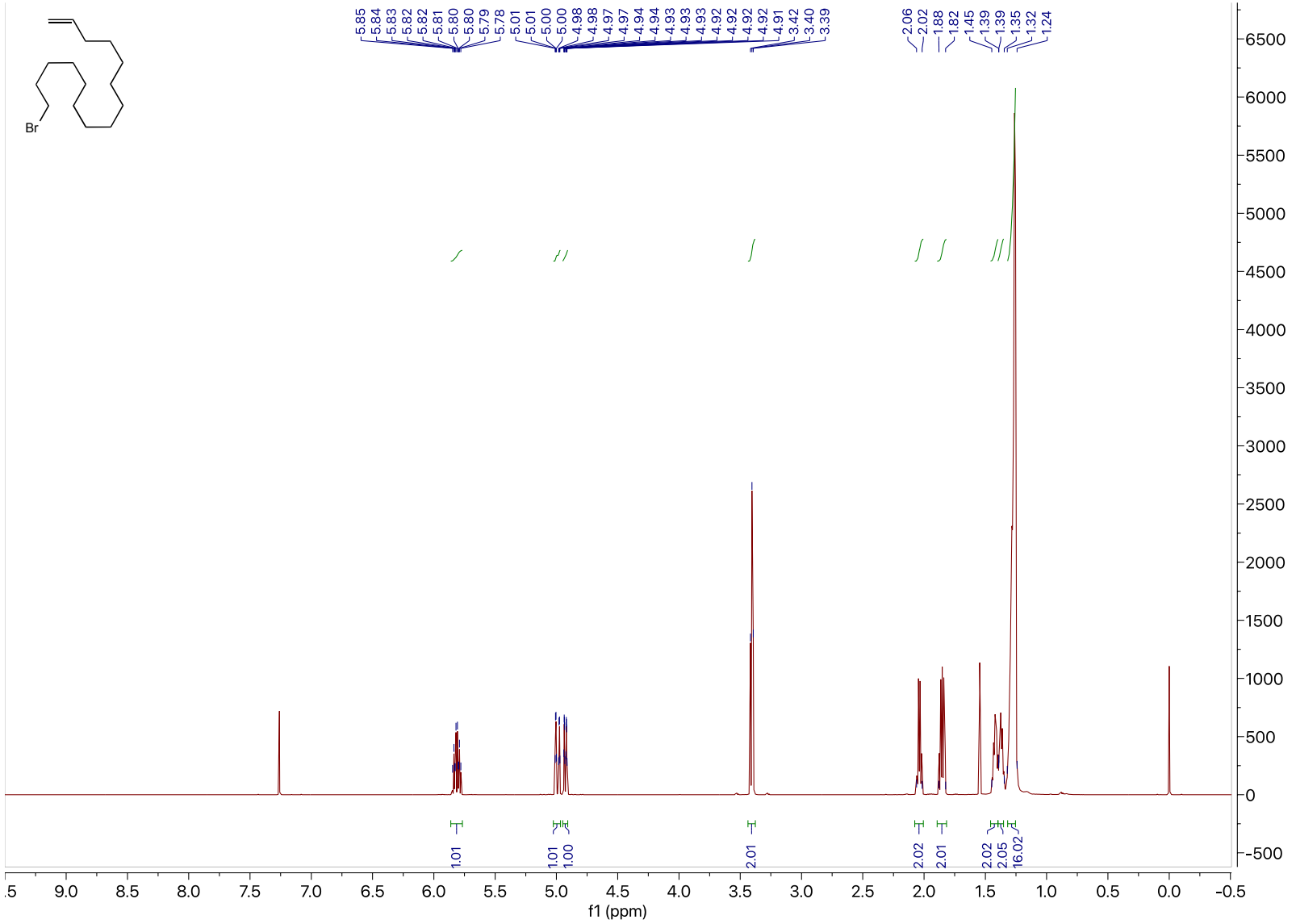
Supplementary figure 183 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 15



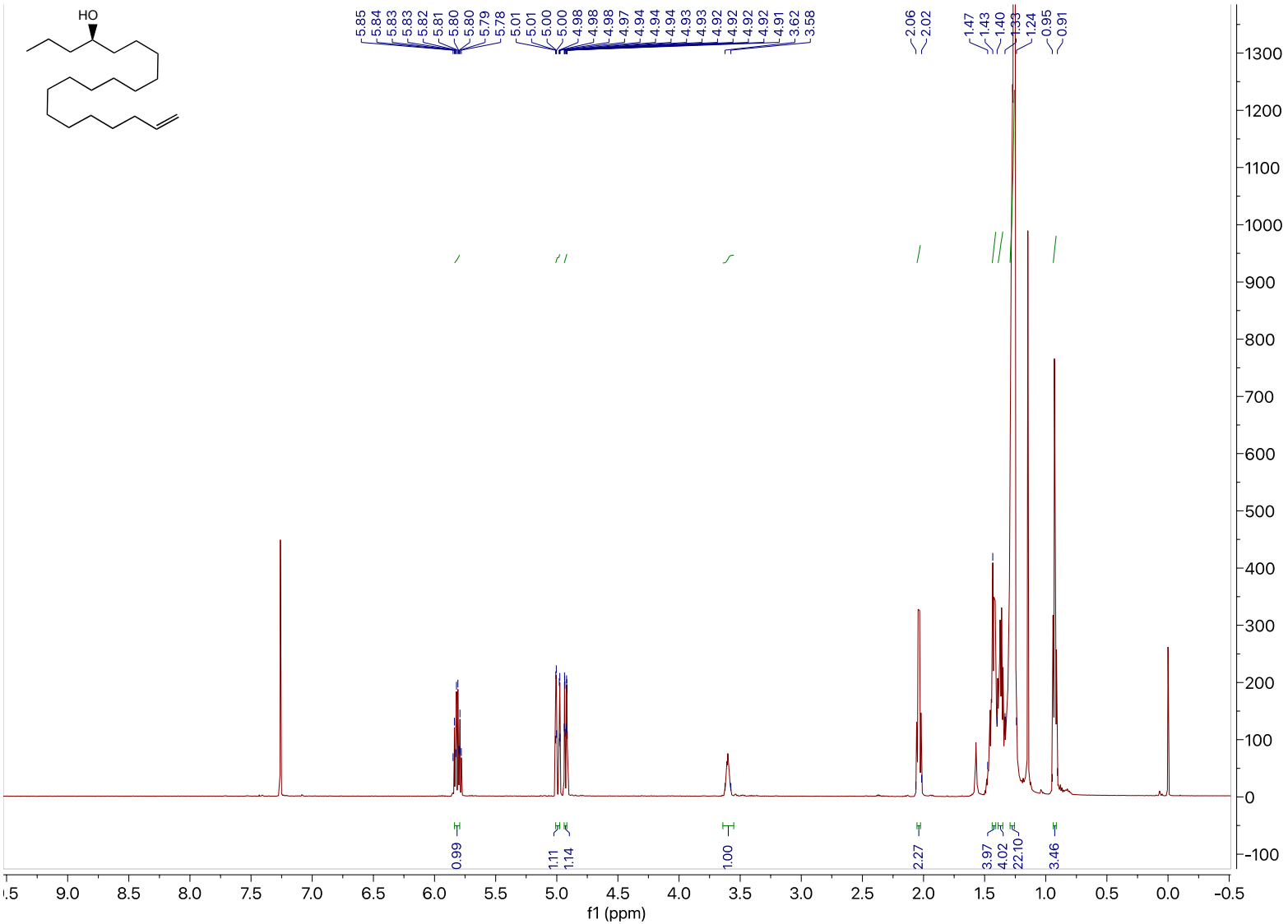
Supplementary figure 184 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 4



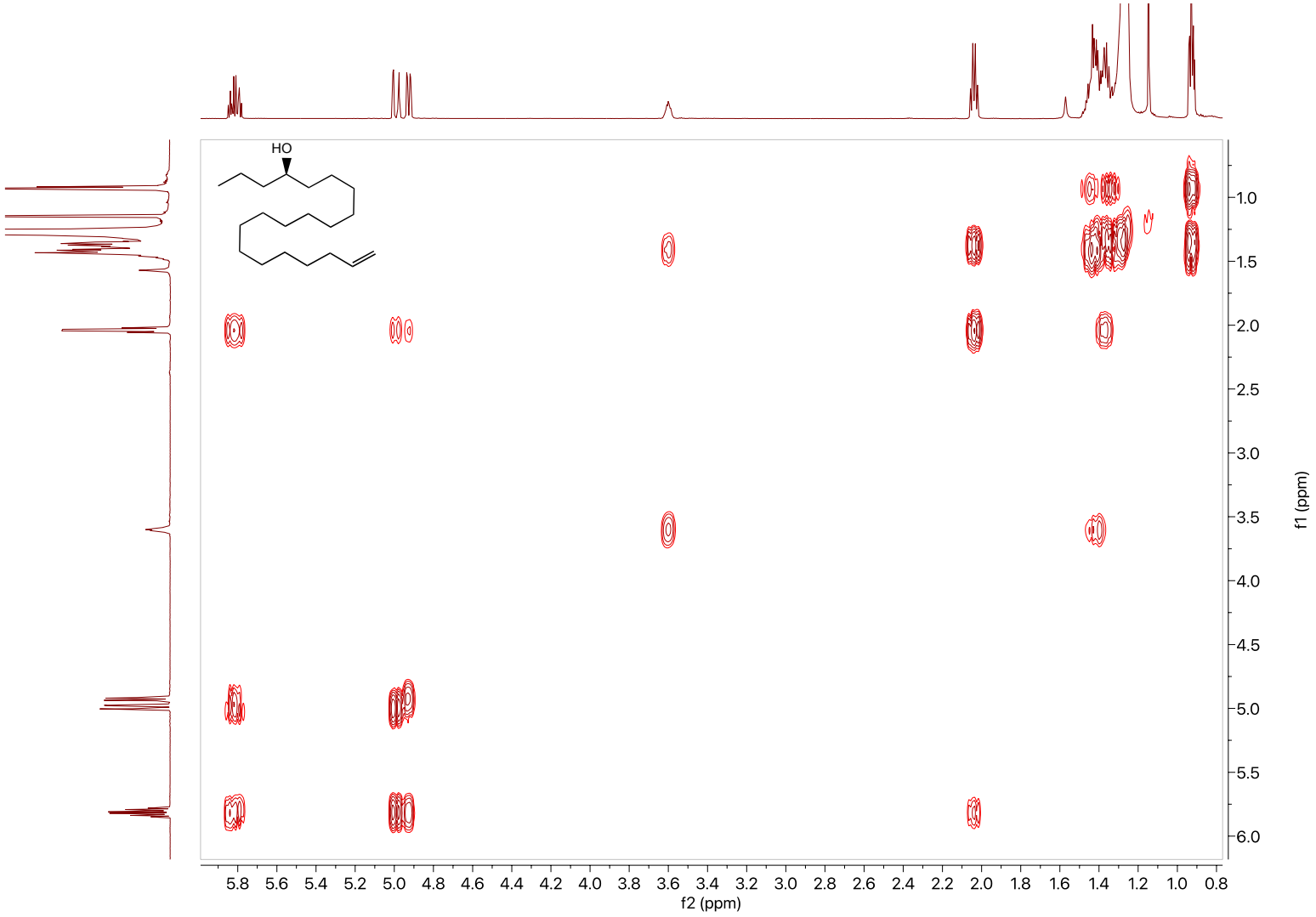
Supplementary figure 185 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 5



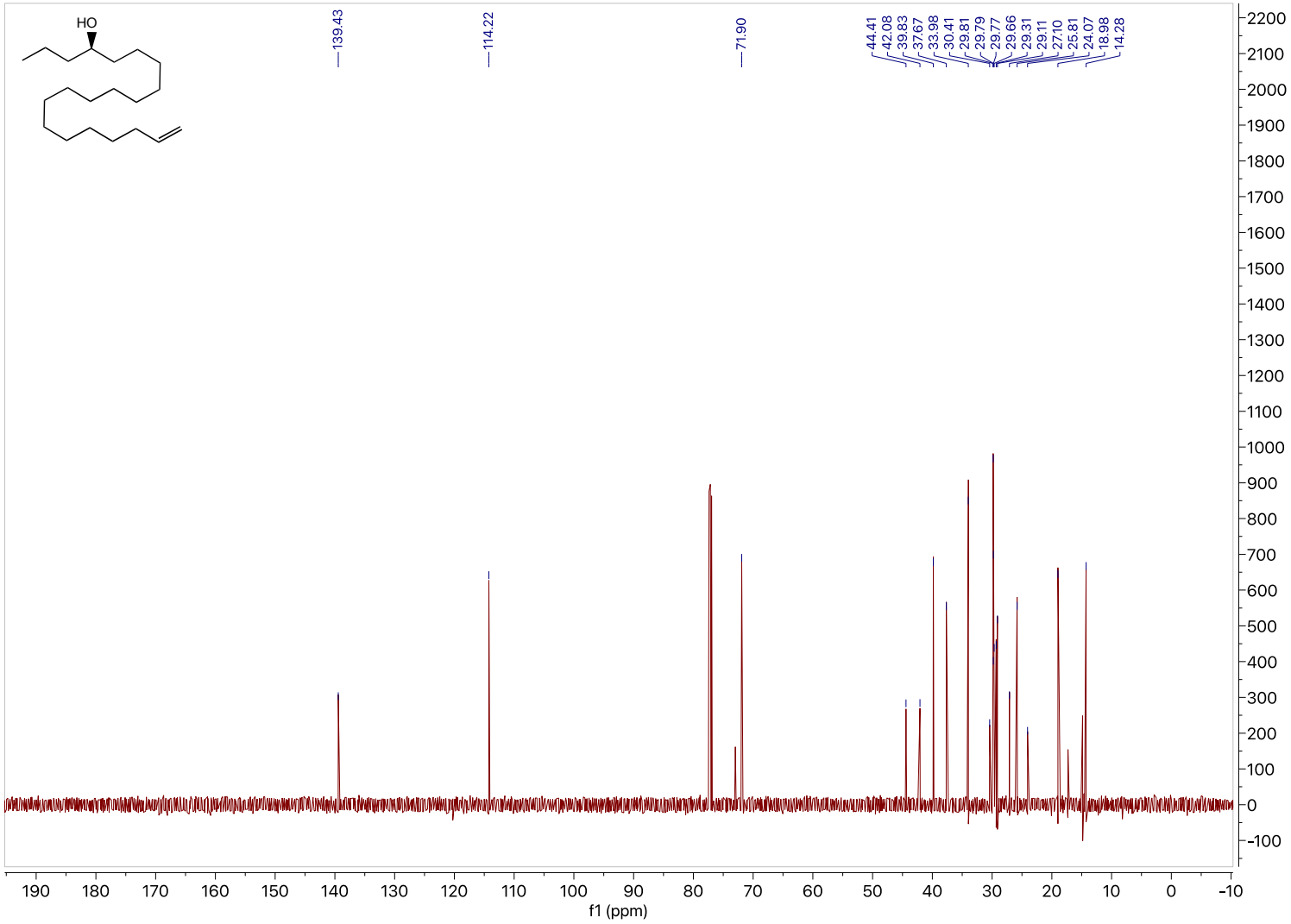
Supplementary figure 186 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 16



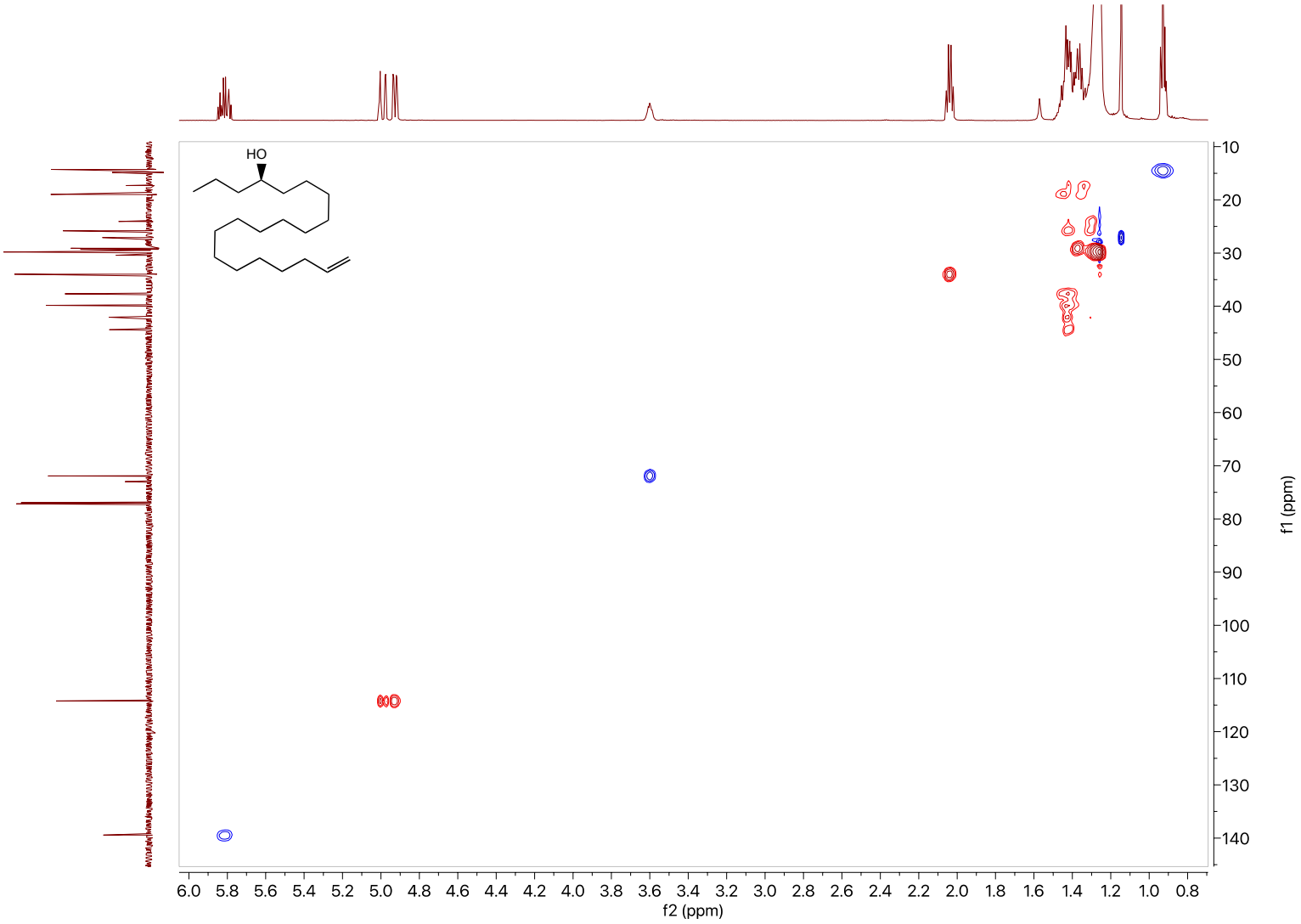
Supplementary figure 187 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 16



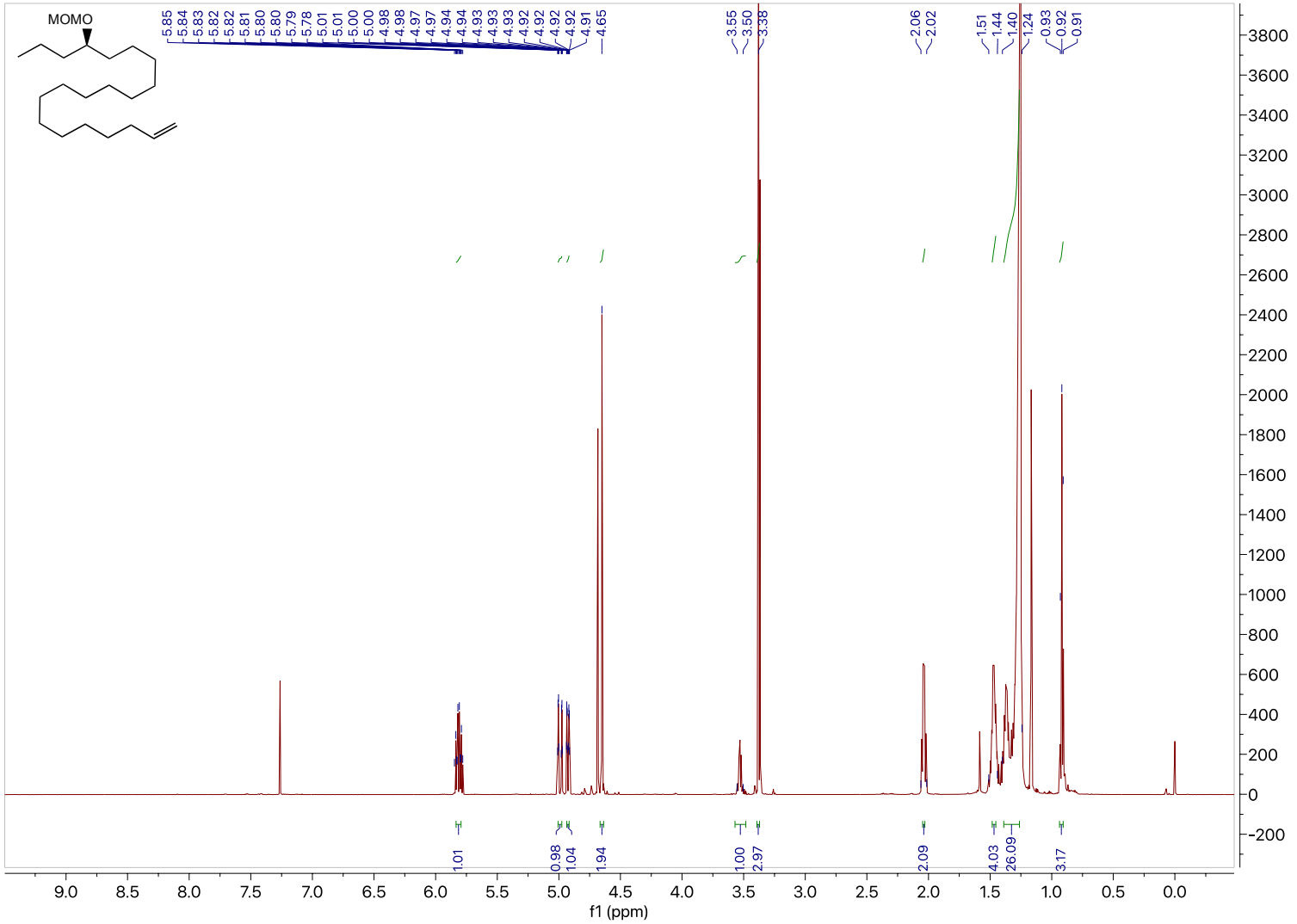
Supplementary figure 188 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 16



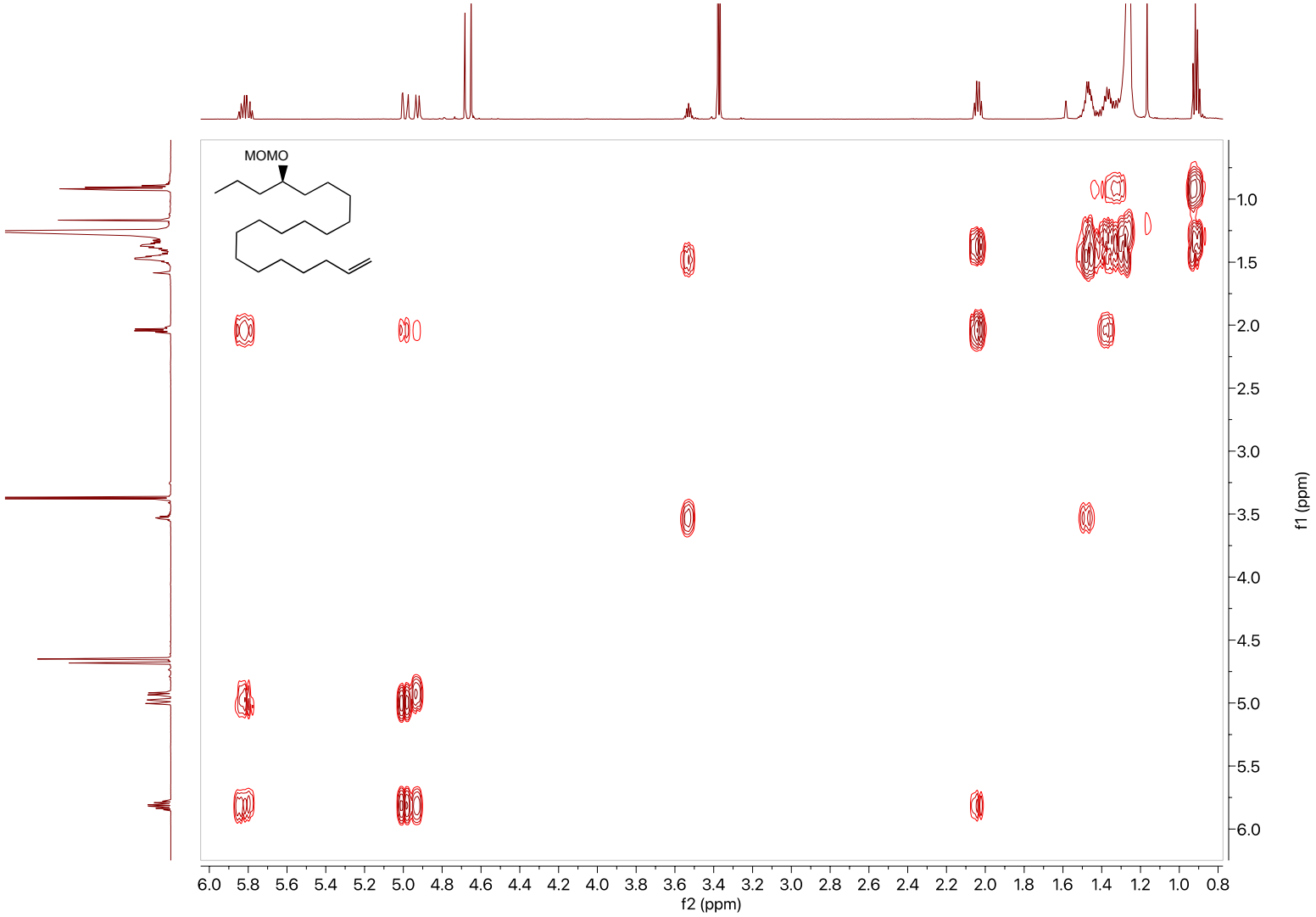
Supplementary figure 189 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 16



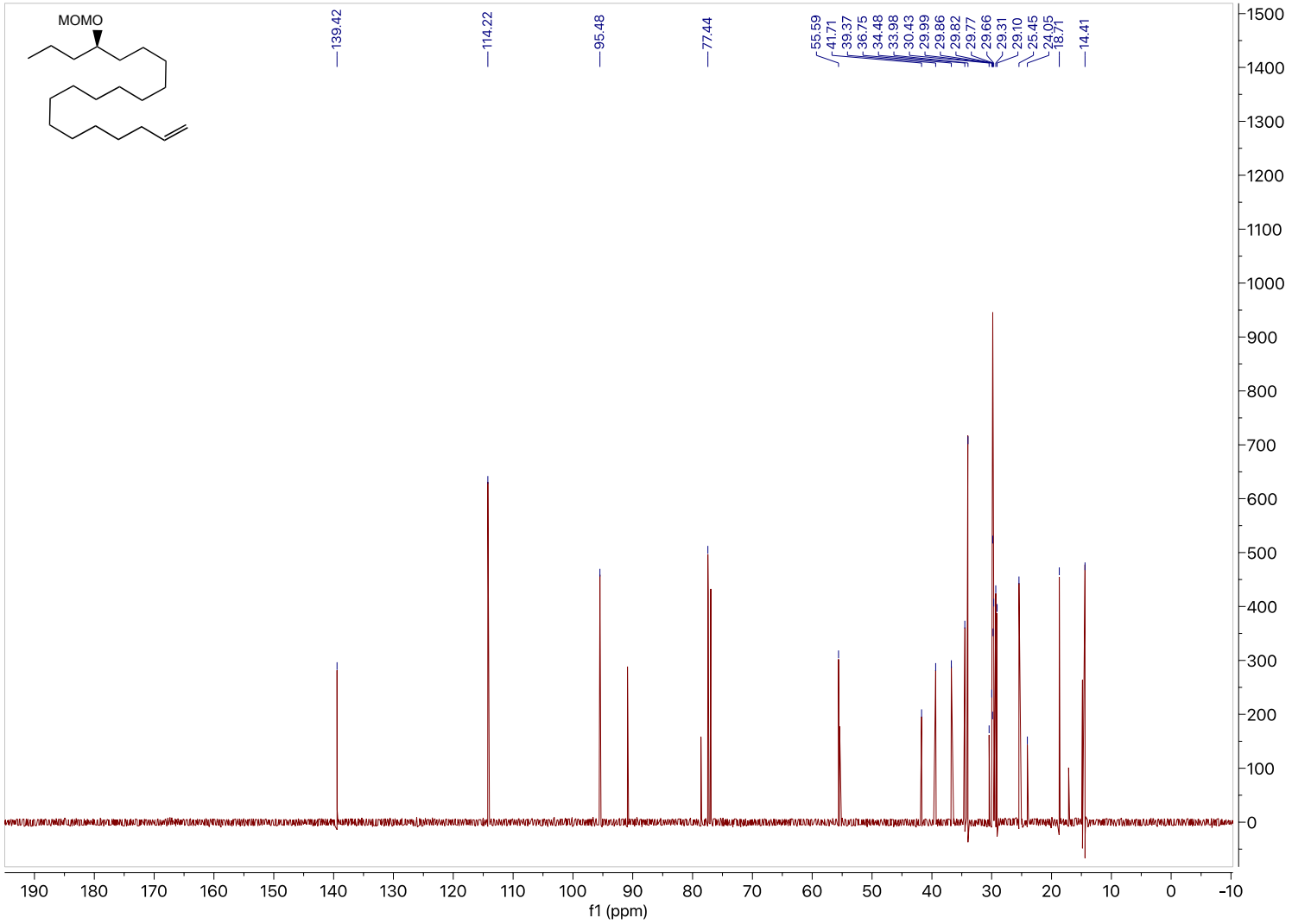
Supplementary figure 190 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 18



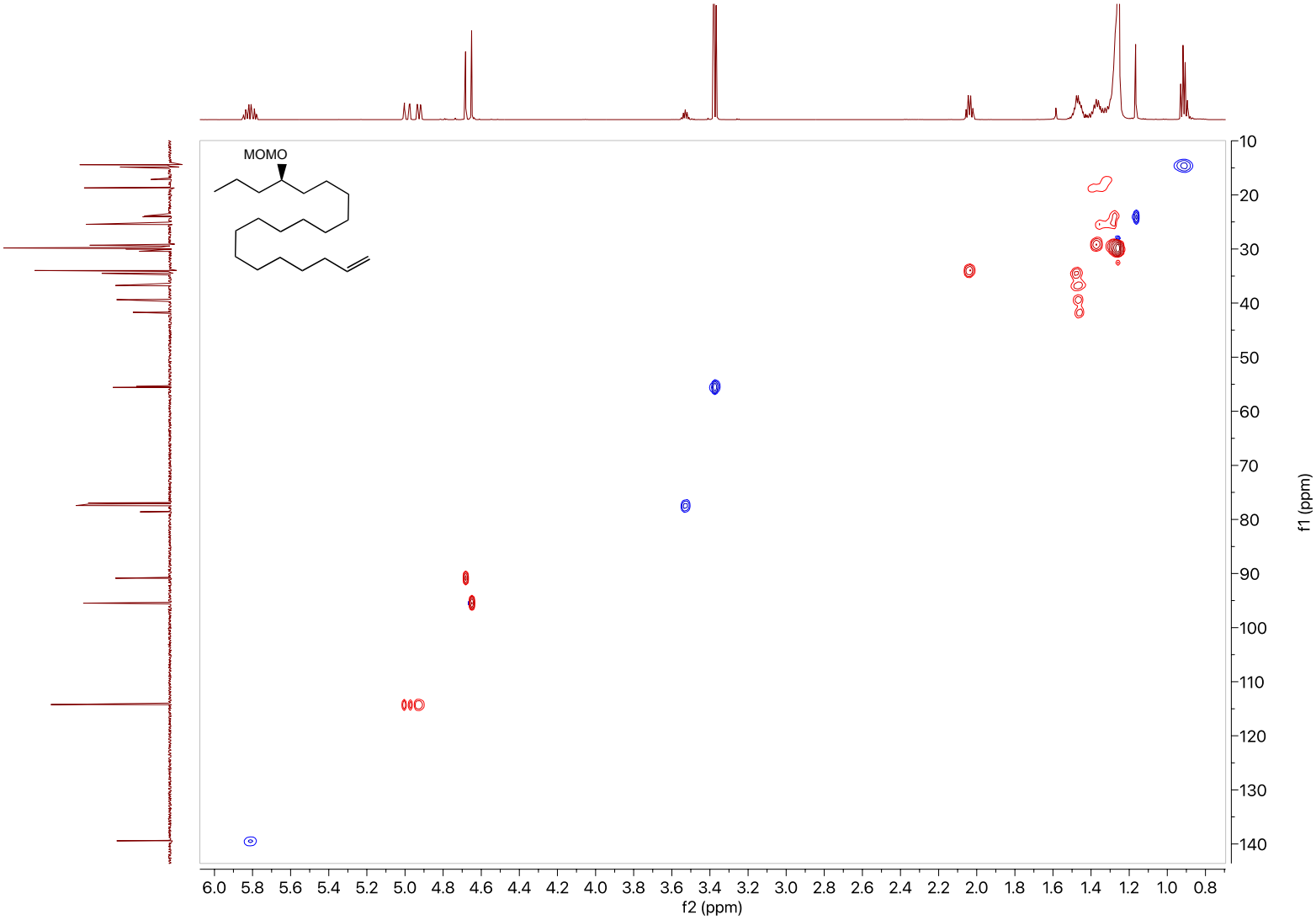
Supplementary figure 191 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 18



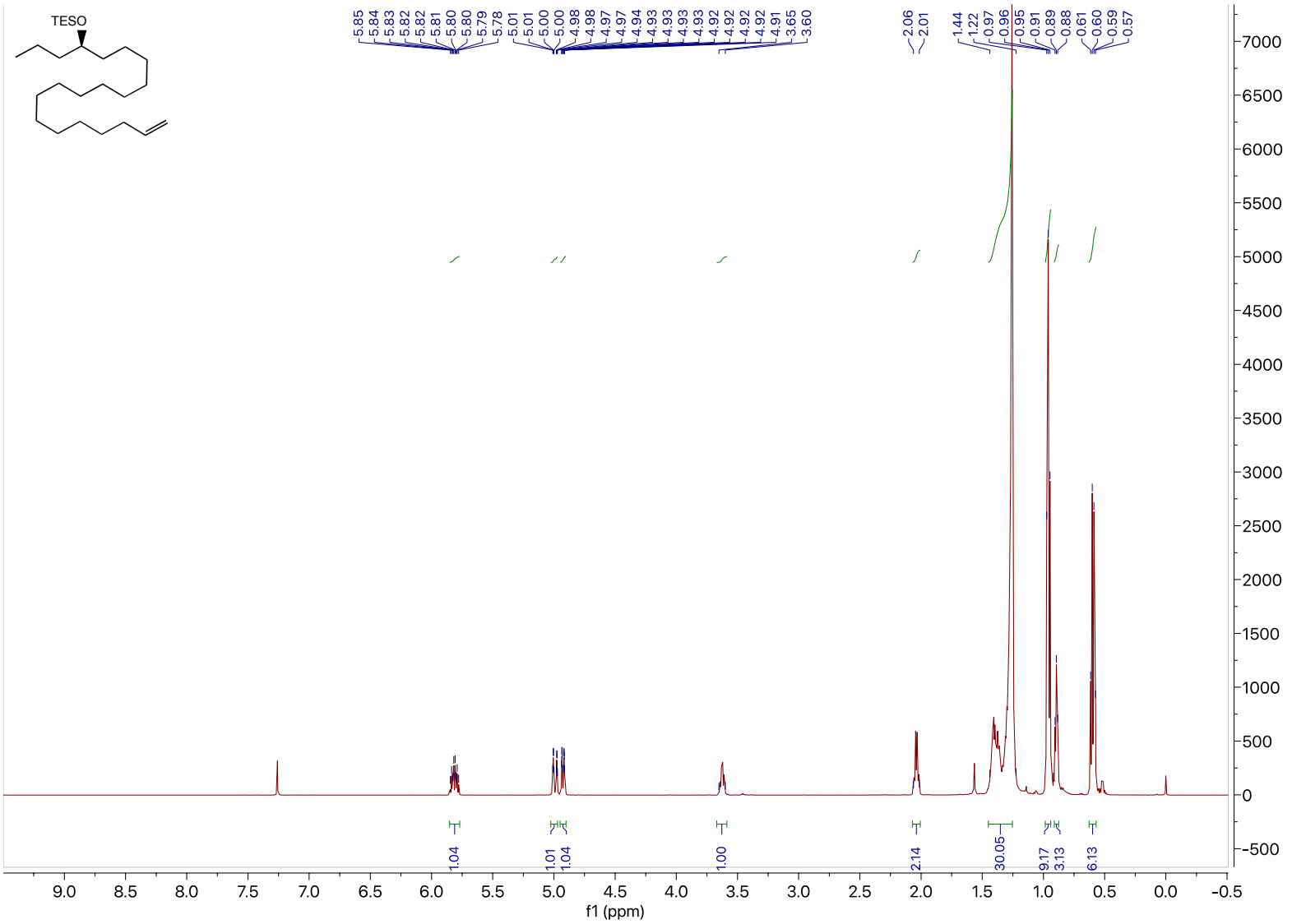
Supplementary figure 192 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 18



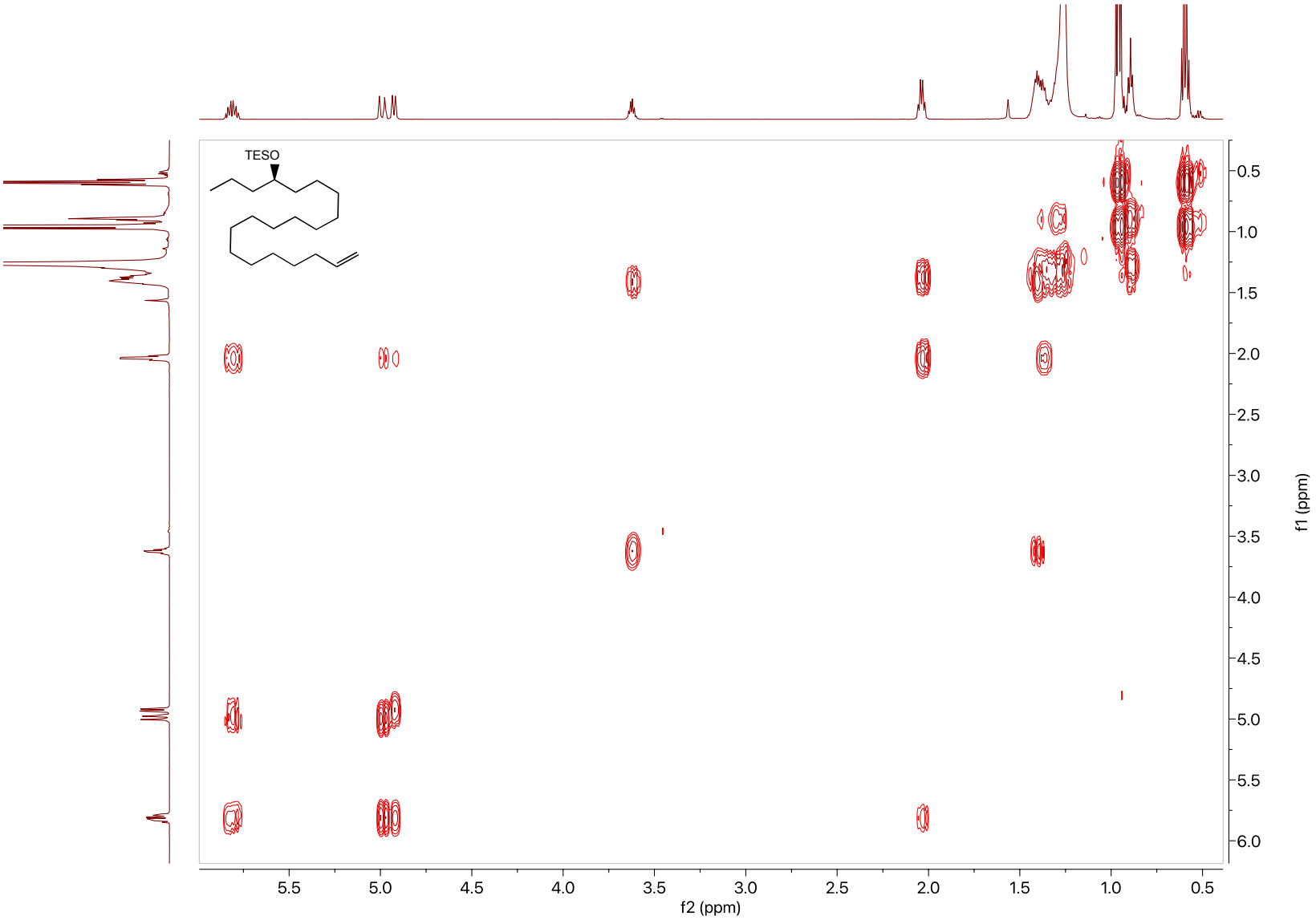
Supplementary figure 193 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 18



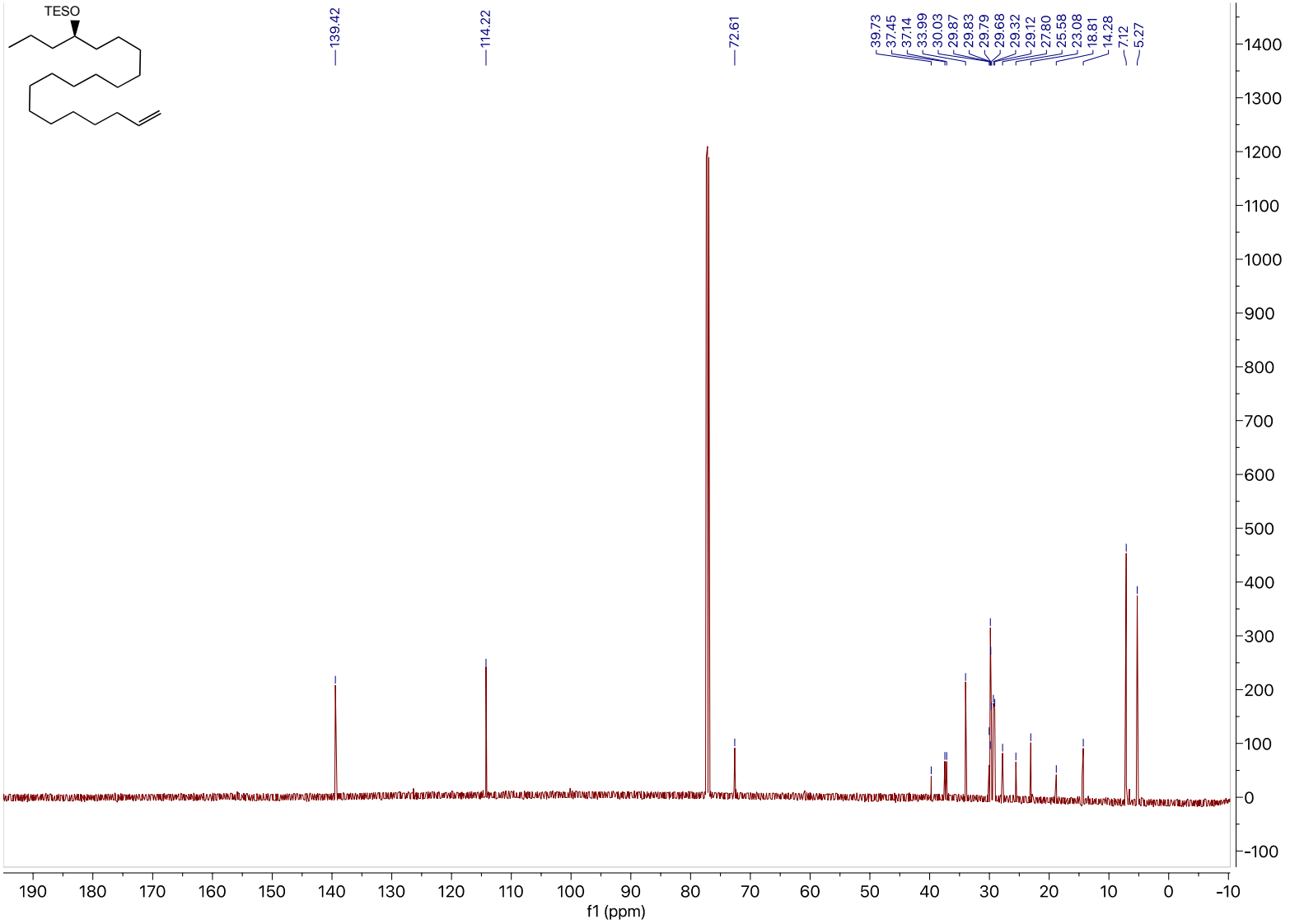
Supplementary figure 194 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 19



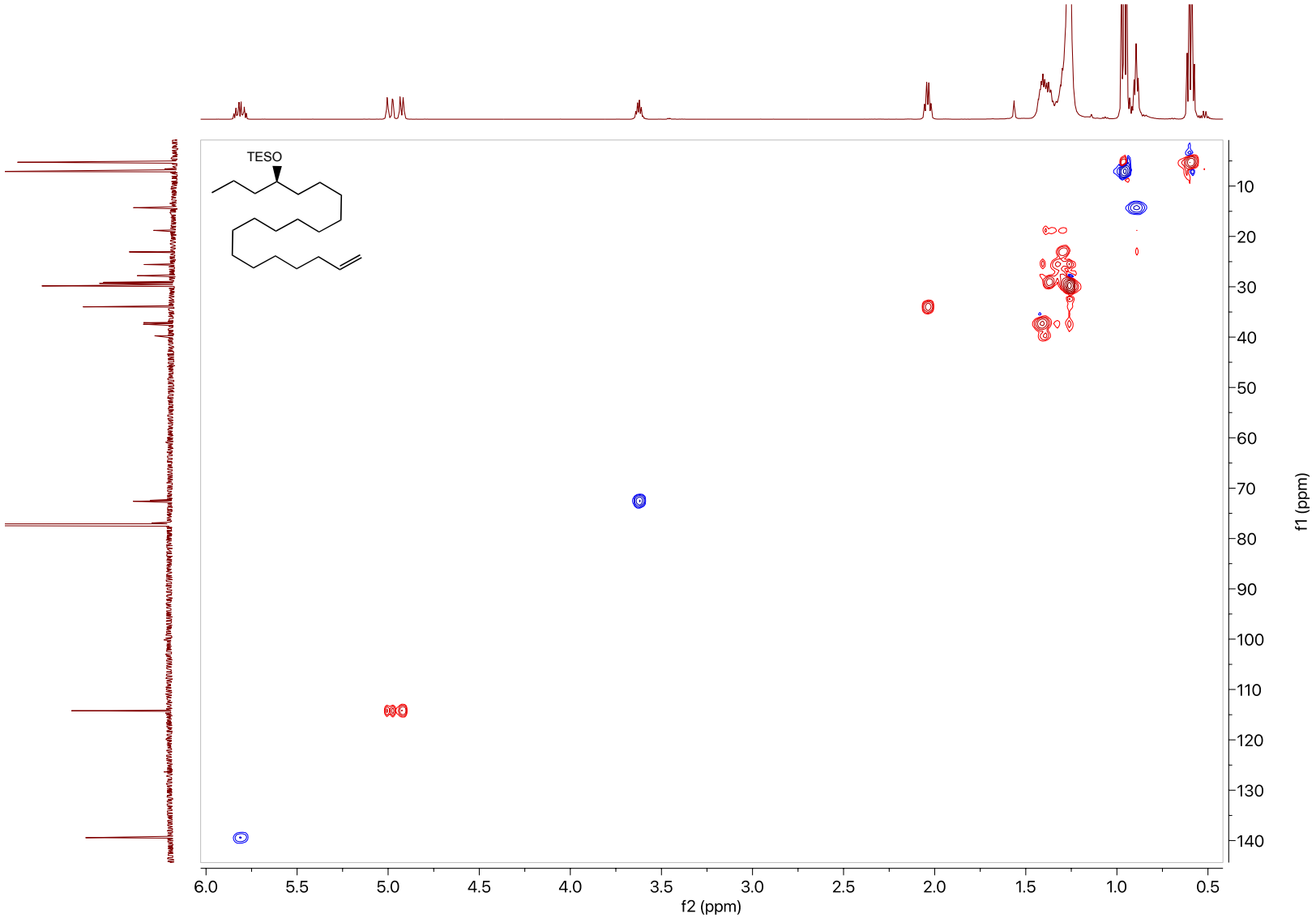
Supplementary figure 195 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 19



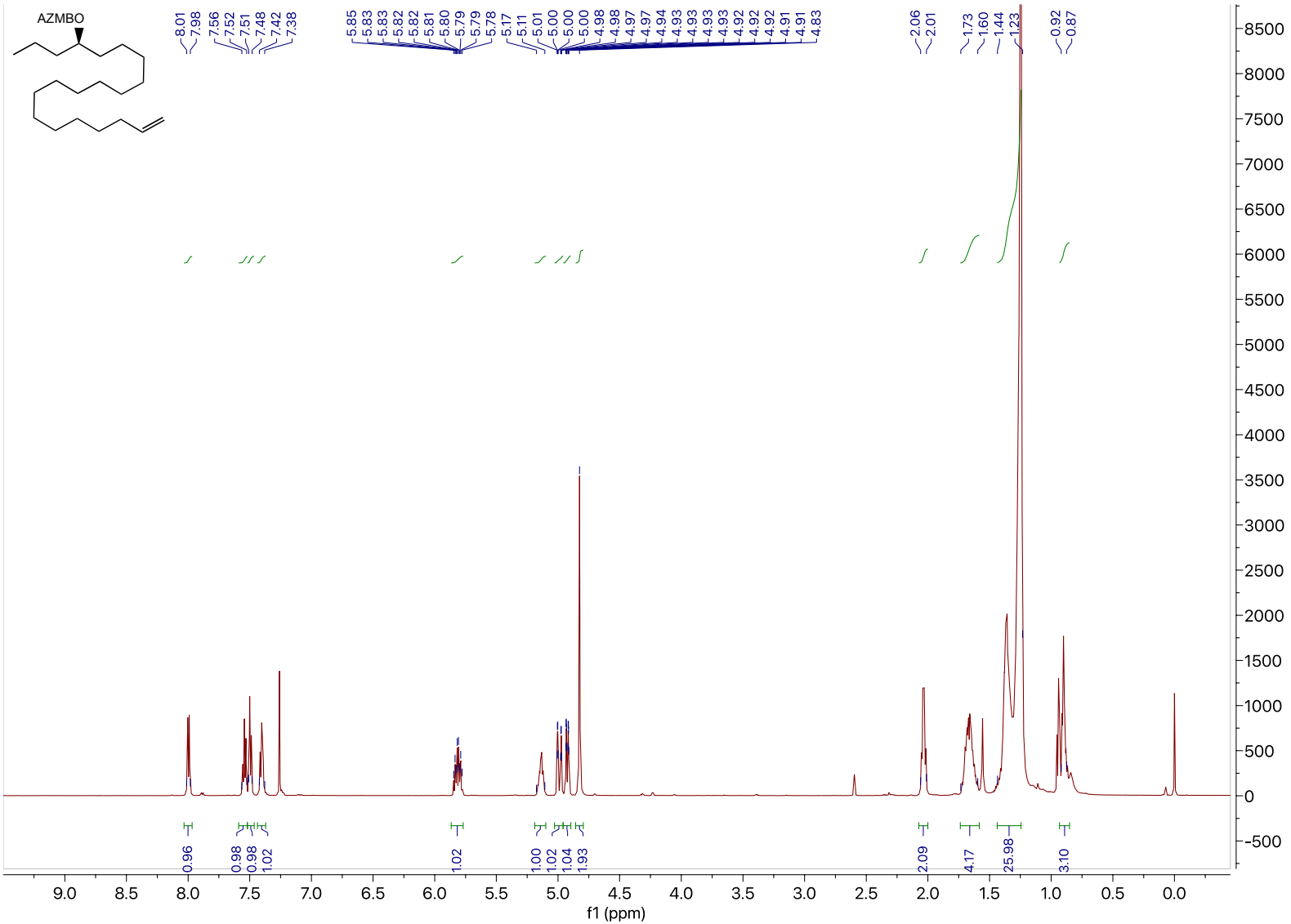
Supplementary figure 196 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 19



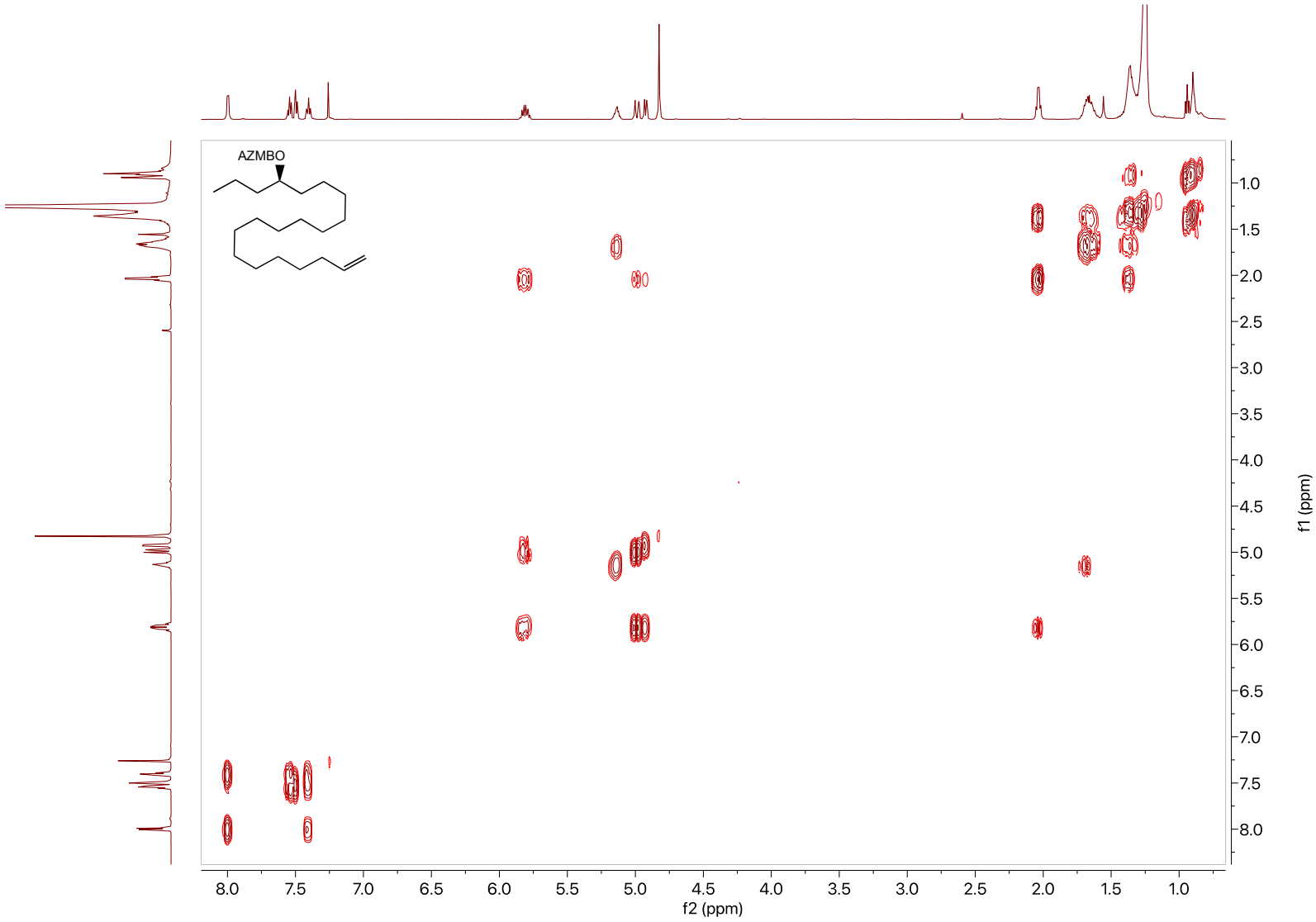
Supplementary figure 197 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 19



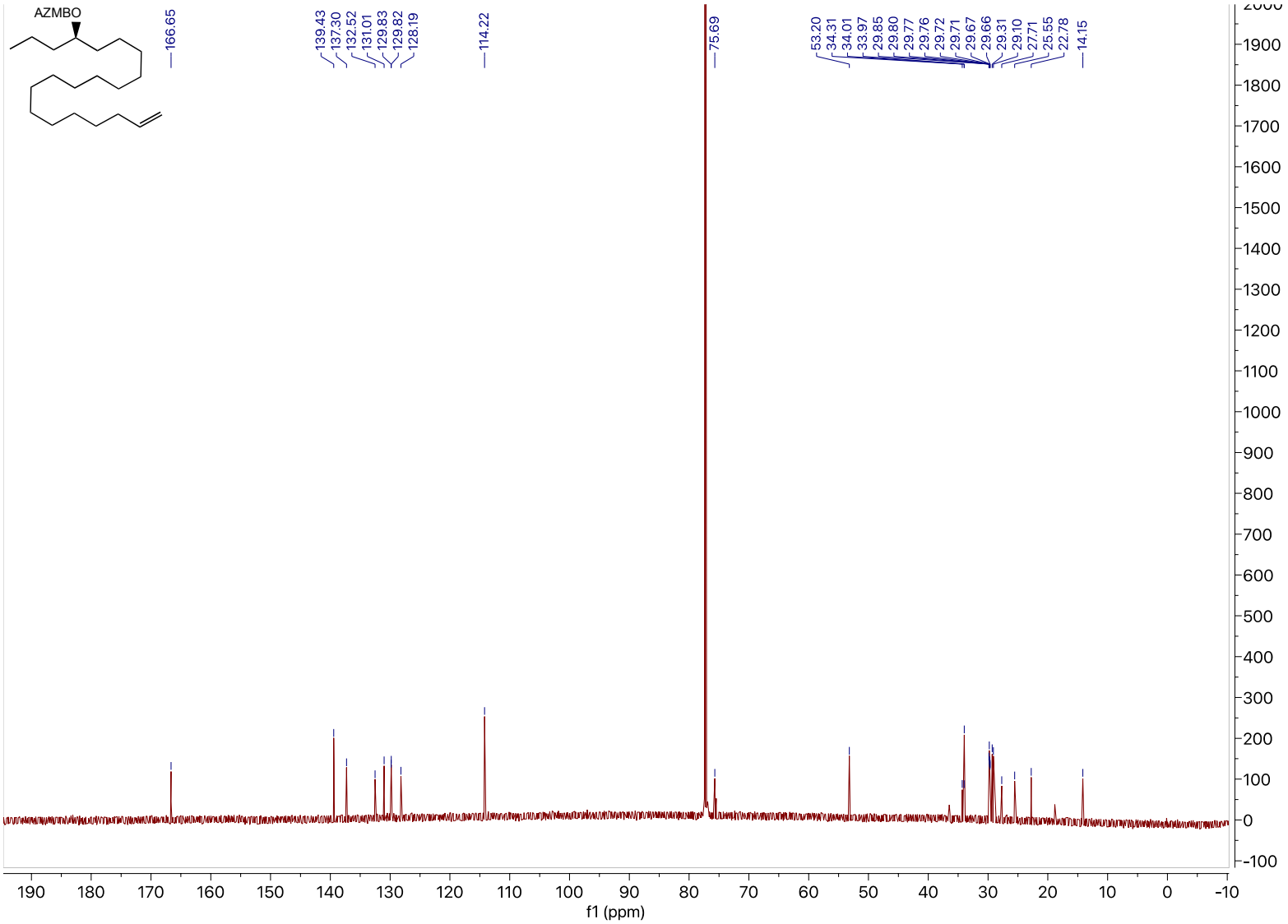
Supplementary figure 198 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 20



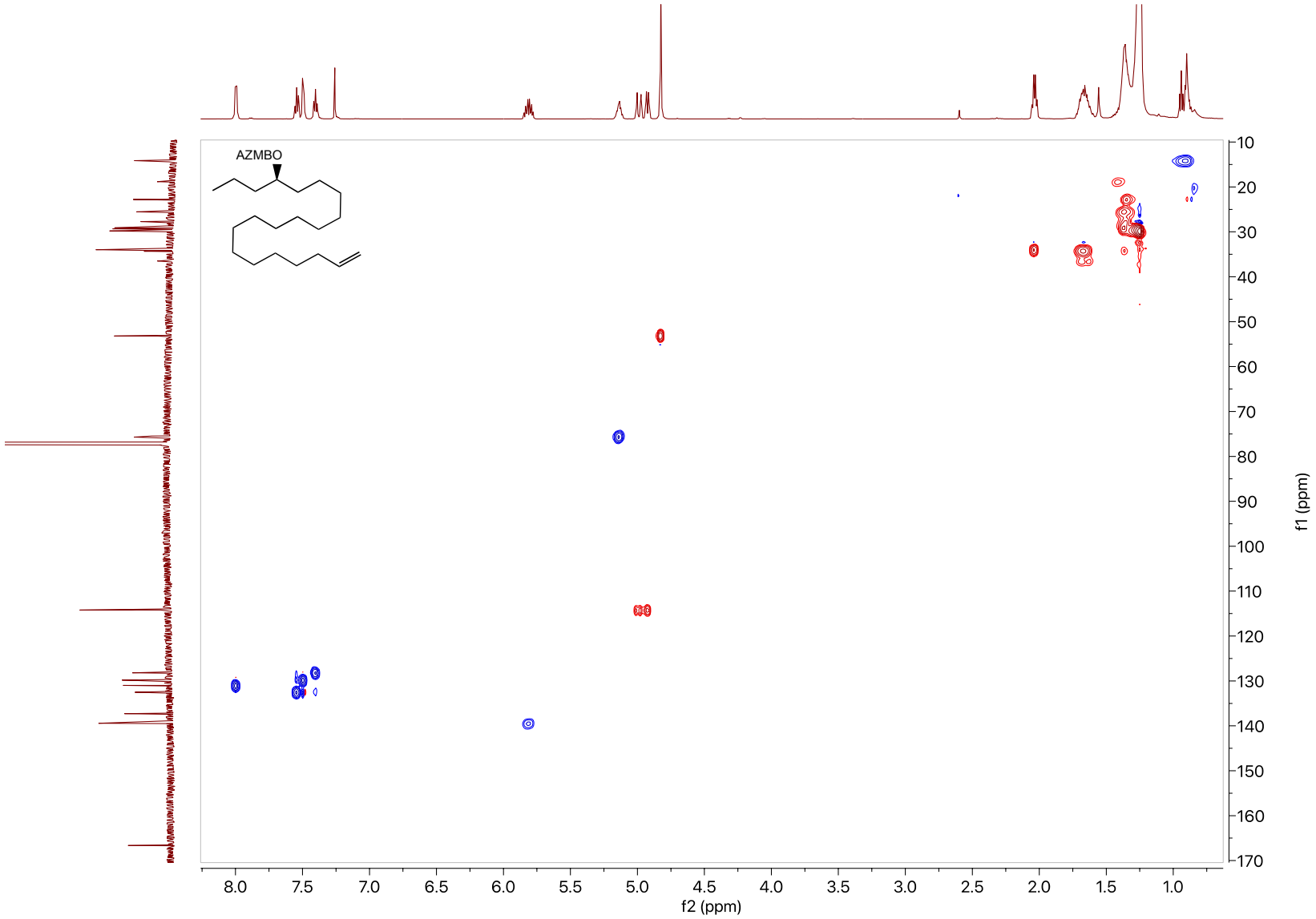
Supplementary figure 199 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 20



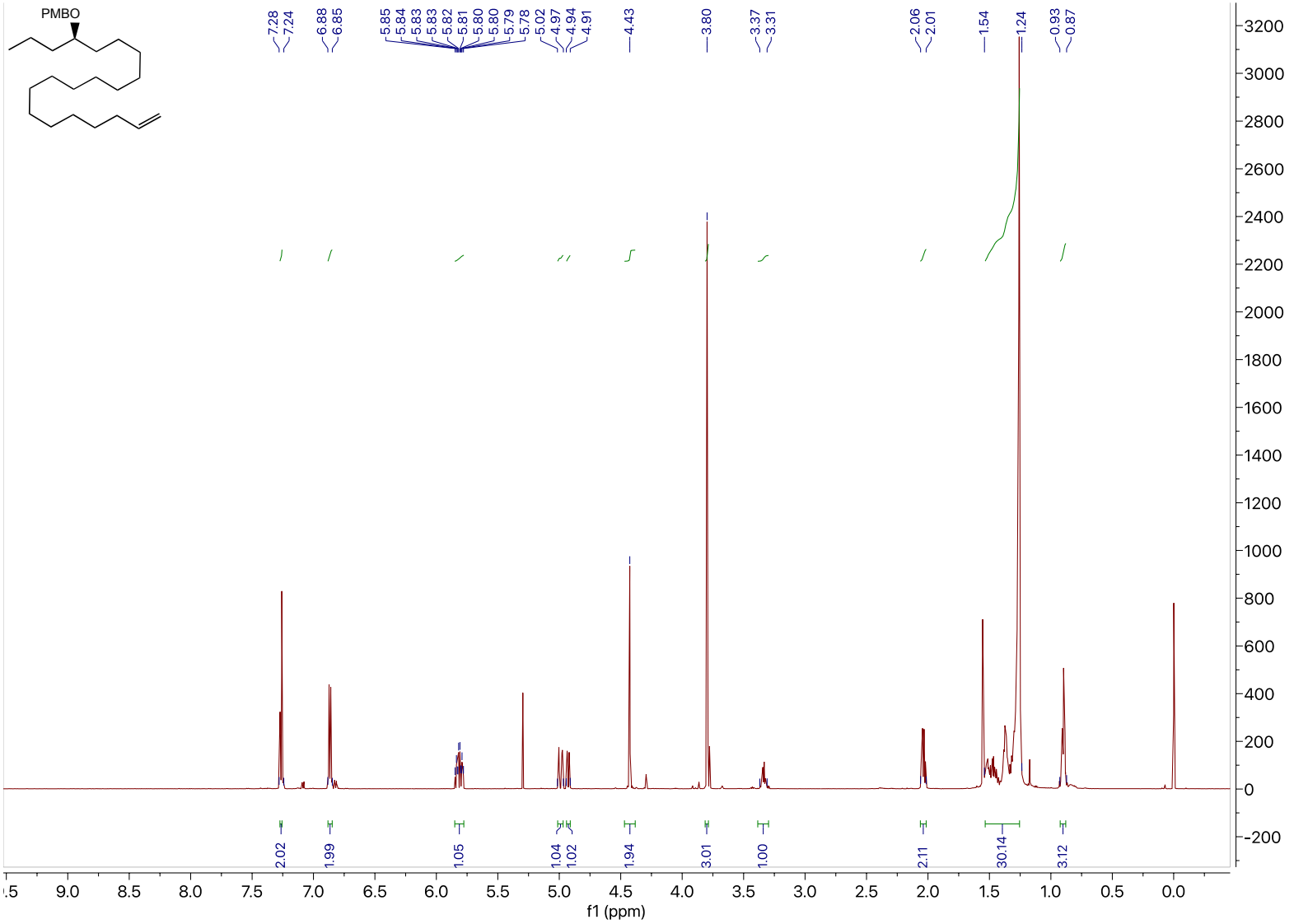
Supplementary figure 200 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 20



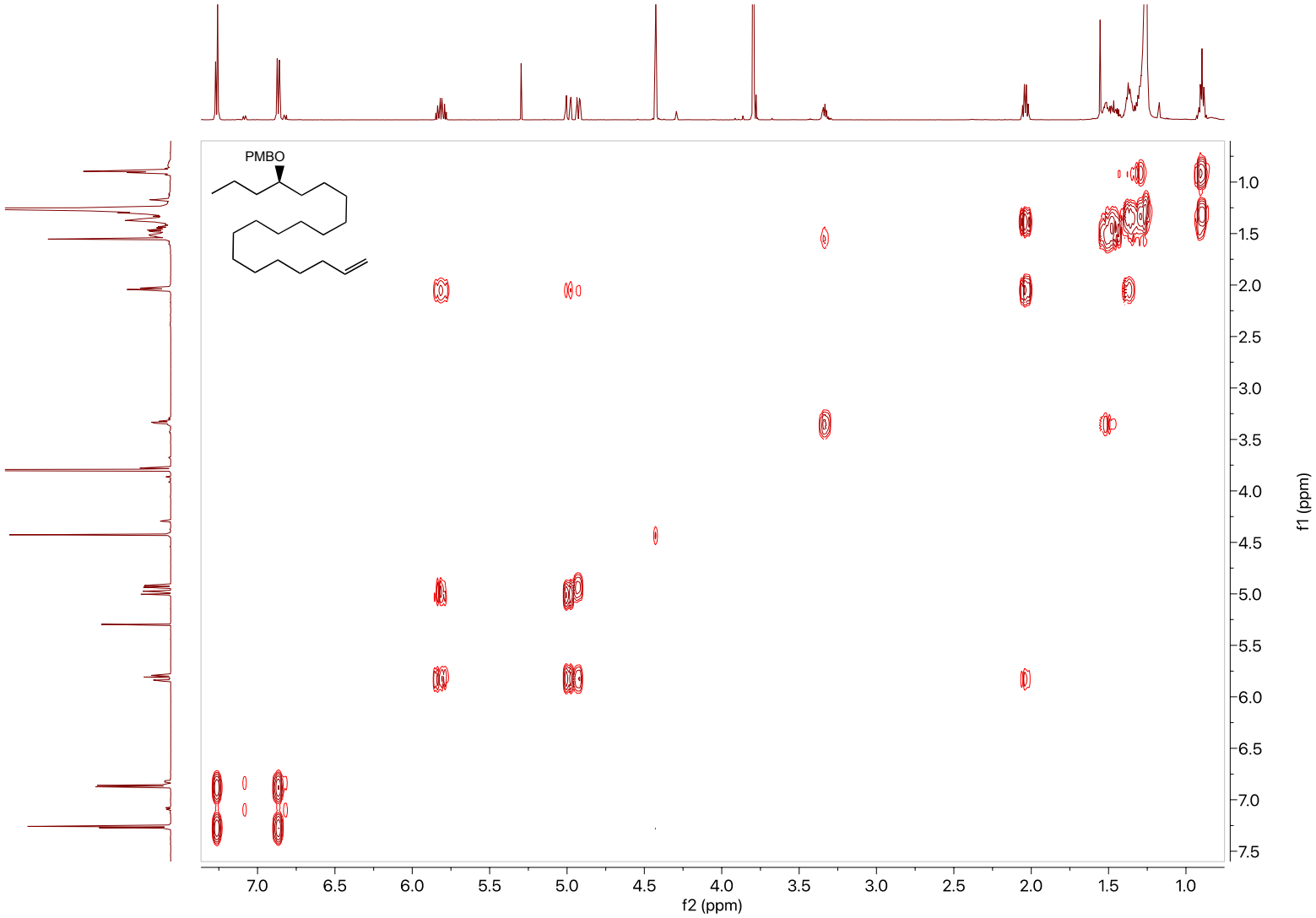
Supplementary figure 201 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 20



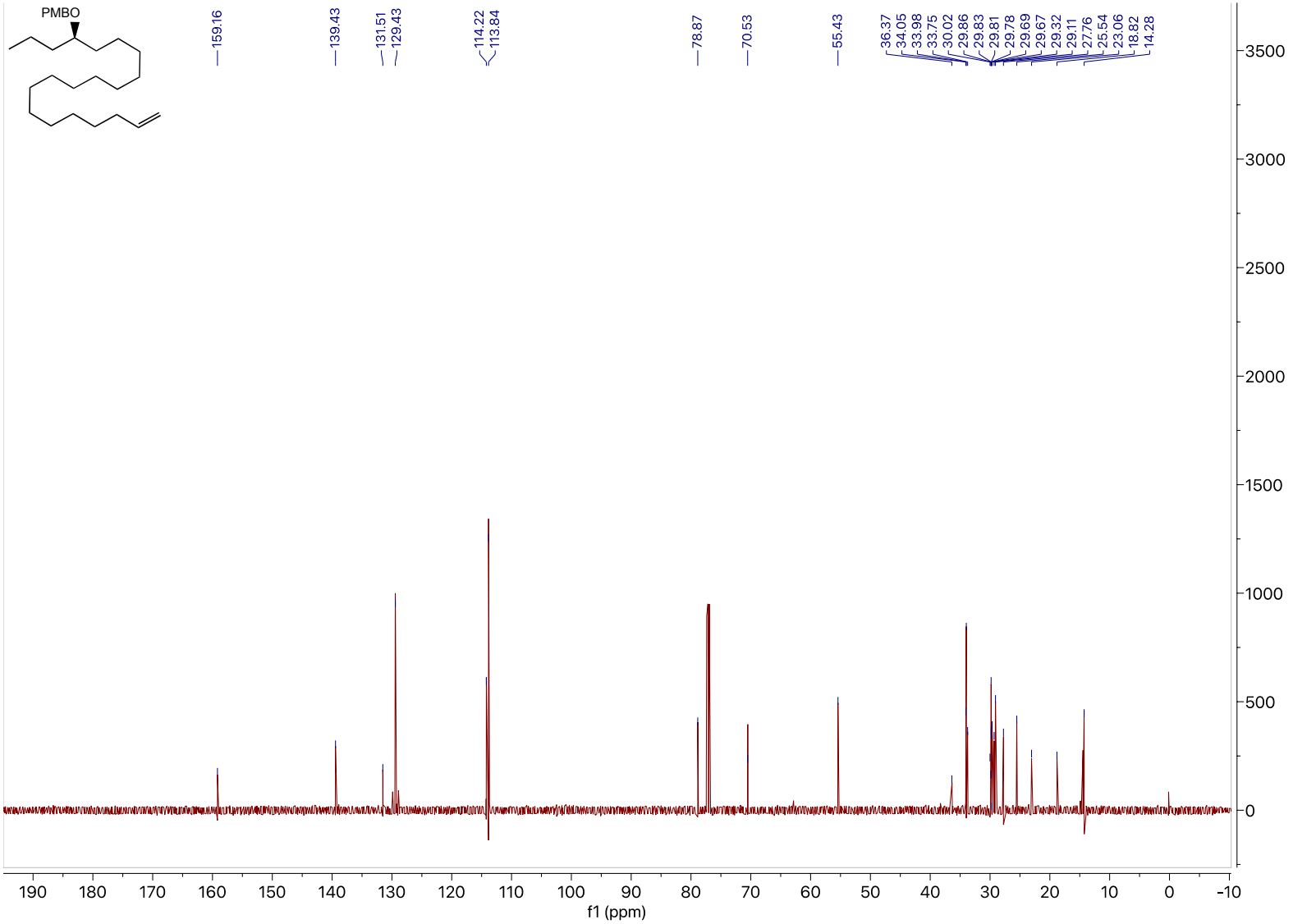
Supplementary figure 202 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 21



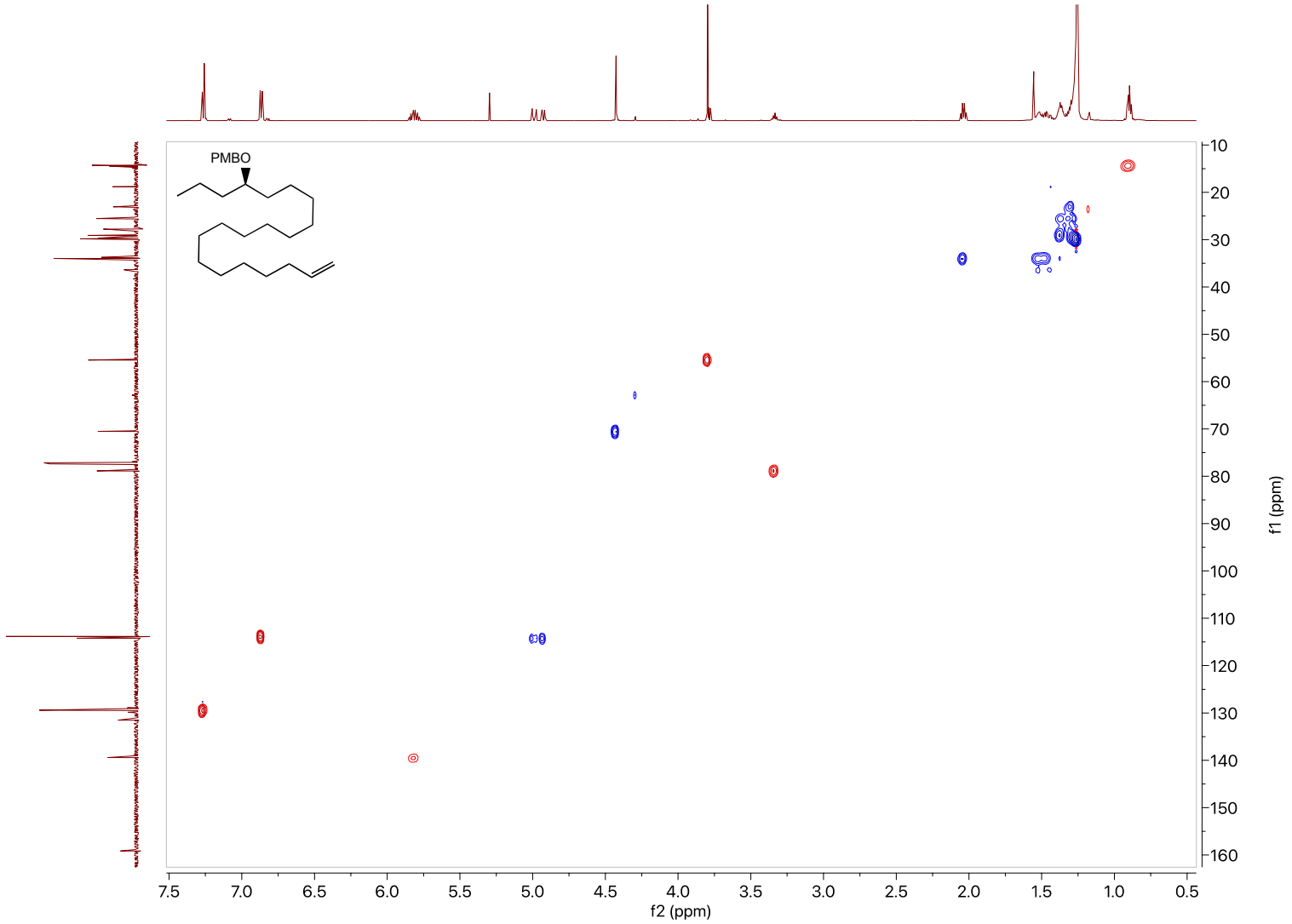
Supplementary figure 203 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 21



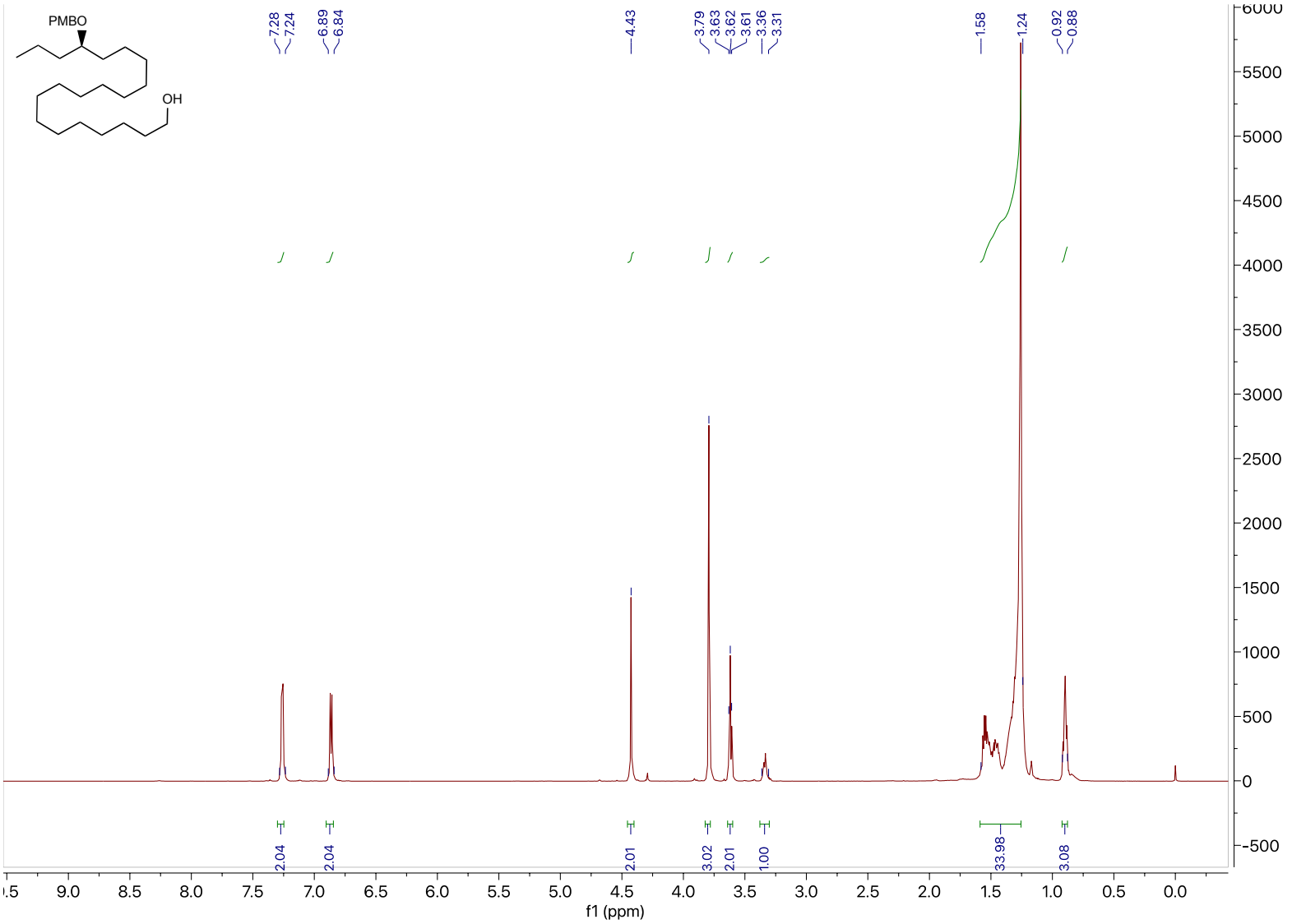
Supplementary figure 204 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 21



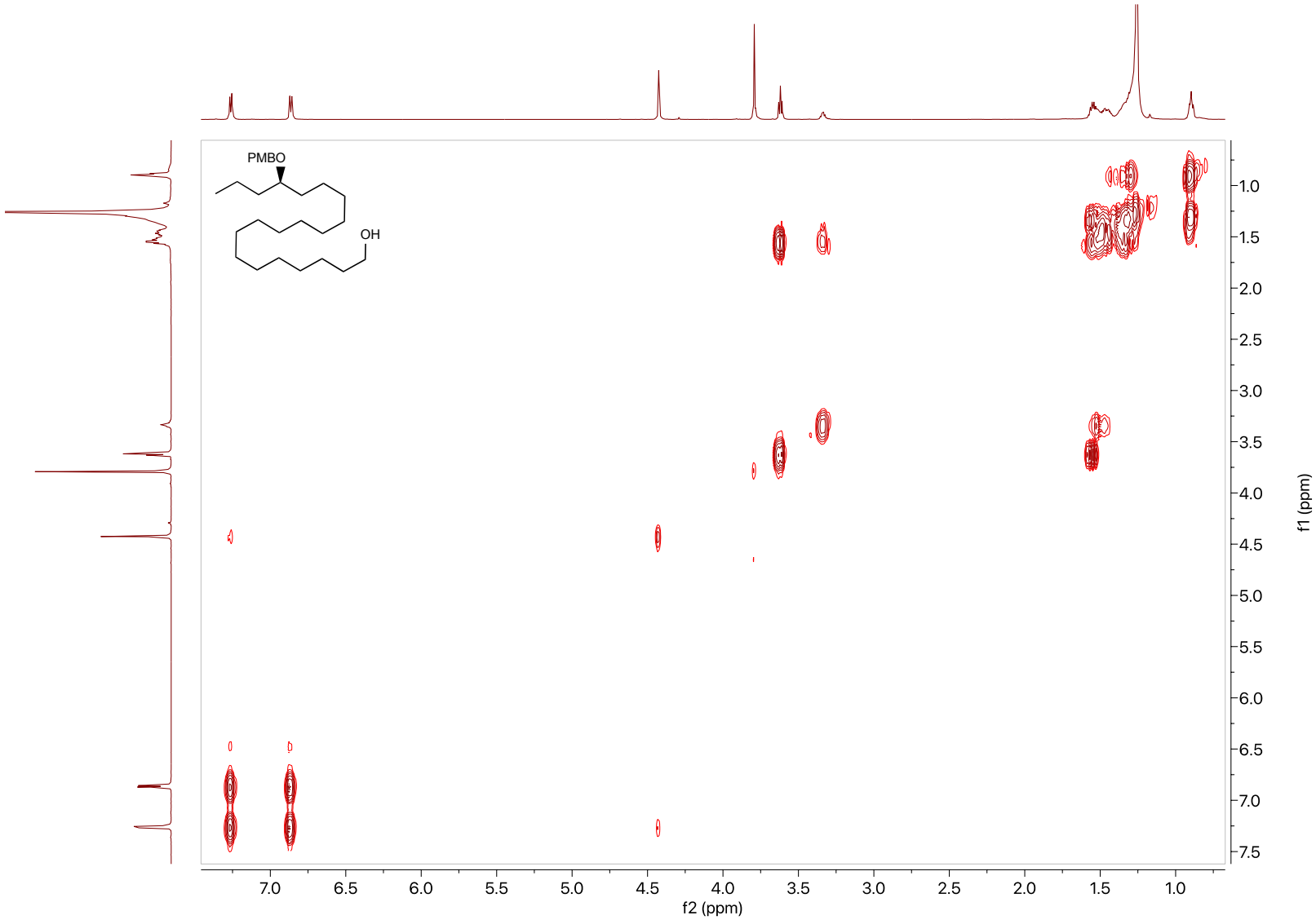
Supplementary figure 205 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 21



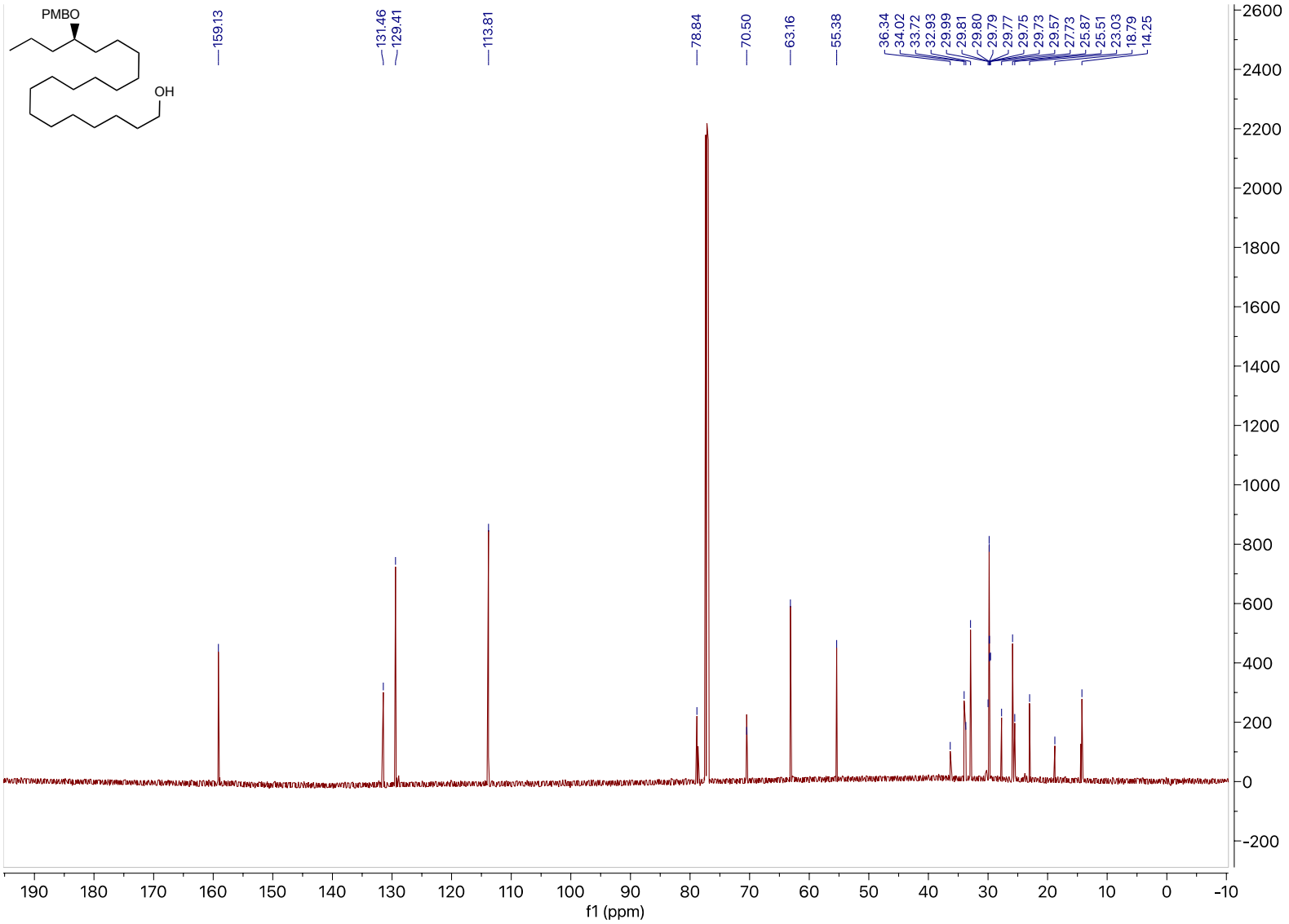
Supplementary figure 206 | ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound 2



Supplementary figure 207 | COSY NMR spectrum (600 MHz, $CDCl_3$) of compound 2



Supplementary figure 208 | ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound 2



Supplementary figure 209 | HSQC NMR spectrum (600 MHz, $CDCl_3$) of compound 2