Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

From Nucleosides to Alkaloids and Polyketides:

Total Synthesis of Herbicidin C and Studies Toward Stephadiamine and Divergolides

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aus

Feuchtwangen

2012

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. D. Trauner betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 02.11.2012

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(Dominik Hager)

Dissertation eingereicht am 02.11.2012

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2. Gutachter: Prof. Wolfgang Steglich

Mündliche Prüfung am 17.12.2012.

Abstract

This dissertation describes the synthetic work on several natural products including nucleosides, alkaloids, and polyketides.

The first and main part of this thesis focuses on the total synthesis of the nucleoside antibiotics herbicidin C and its hydrolysis product aureonuclemycin. Due to their diverse biological activity, the herbicidins are considered as promising herbicides for agricultural application. In cooperation with Bayer CropScience AG, a flexible and efficient access to the herbicidins was developed and the challenges and successes of this synthesis are described in detail. More specifically, the route to the undecose moiety integrates a stereoselective *C*-glycosylation with several reagent-controlled stereoselective transformations. The nucleobase was introduced by a surprisingly facile and highly diastereoselective late-stage *N*-glycosylation. In addition to that, natural herbicidin A was transformed into promising derivatives and all compounds, including the intermediates of the total synthesis, were provided to Bayer CropScience AG for a structure activity relationship study (SAR). A list of all provided derivatives is given at the end of the thesis.

The progress toward the synthesis of stephadiamine is described in the second chapter of this thesis. The natural product is the first example of a *C*-norhasubanan alkaloid natural product and despite its structural beauty, no total synthesis of stephadiamine has been reported to date. The proposed racemic retrosynthetic analysis of stephadiamine makes use of a Curtius rearrangement and a late lactonization. The propellane skeleton of this alkaloid was envisioned to be made by means of a homoconjugated addition/Mannich cascade of the key enamine in an extremely efficient manner. An alternative strategy is proposed for future work, which includes a Tsuji-Trost allylation arising the potential for an enantioselective synthesis of stephadiamine.

In chapter III, the progress toward the divergolides C and D is presented. Attention was focused on the large scale preparation of the volatile side chain, and its unusual isolation method is pointed out in detail. In addition, the assembly of the three main building blocks is discussed.

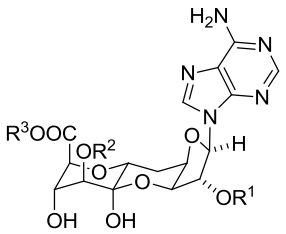
The preparation of *Legionella* autoinducer 1 (LAI-1) is described in chapter IV. The bacterial signaling molecule LAI-1 belongs to the class of α-hydroxyketones (AHKs). Given the effects of LAI-1 on virulence and motility of the bacteria *L. pneumophila*, this signaling molecule has the potential for clinical or technical applications. For a deeper understanding of the signaling circuit in *L. pneumophila* and in order to gain more insight in the mechanism of cell-cell communication, synthetic LAI-1 was prepared and provided to the research group of H. Hilbi, who investigates the gene regulation by AHK-mediated signaling.

Chapter V includes the experimental procedures for the preparation of all compounds, backed up by full analytical characterization. In addition, ^{1}H- and ^{13}C-NMR spectra as well as crystallographic details are given.

Summary

Chapter I: The Total Synthesis of Herbicidin C and Aureonuclemycin

The herbicidins, congener of the large family of nucleoside antibiotics,[1] show a high diversity of biological activity. These molecules are not only promising lead structures in search of new herbicides and the development of biological tools, but have been the focus of synthetic interest for the last decades.[2] Thus, several approaches towards the herbicidins were described in the literature. T. Gallagher and co-workers provided by far the most thorough investigation of the herbicidins.[3] However other research groups, such as the groups of D. A. Whiting,[4] A. H. Haines,[5] P. Sinaÿ,[6] and P. Vogel[7] published different approaches toward the herbicidin skeleton. Despite considerable efforts, only one completed total synthesis of a herbicidin has been reported to date by the group of S. Ichikawa.[8]



	R_1	R_2	R_3
herbicidin A (**Ia**)	Me	$CH_3CH=C(CH_2OH)CO$	Me
herbicidin B (**Ib**)	Me	H	Me
herbicidin C (**Ic**)	H	H	Me
herbicidin E (**Id**)	Me	$(CH_3)_2CHCO$	Me
herbicidin F (**Ie**)	Me	$CH_3CH=C(CH_3)CO$	Me
herbicidin G (**If**)	H	$CH_3CH=C(CH_3)CO$	H
herbicidin H (**Ig**)	Me	$CH_3CH=C(CH_2OH)CO$	H
SI2245 (**Ih**)	Me	CH_3CO	Me
aureonuclemycin (**Ii**)	H	H	H

The biological and structural features render the herbicidins challenging targets for both lead compound research and total synthesis. Thus, scientific collaboration between our research group and Bayer CropScience AG was established to investigate the relationship between the structure and the biological activity of the herbicidins (SAR study).[9] In particular, we developed a synthetic route to two members of this family, namely herbicidin C (**Ic**) and aureonuclemycin (**Ii**),[10] which offered the possibility to gain access to a broad range of potentially bioactive derivatives. These compounds were further investigated by Bayer CropScience AG in the course of bioactivity testings.

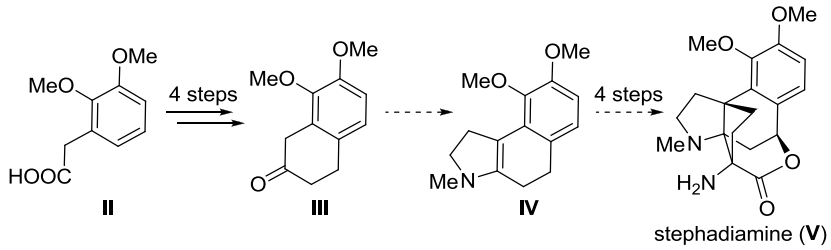
Furthermore, herbicidin A (**Ia**), provided by Bayer CropScience AG, was transformed into promising derivatives in the course of this thesis.

With this work, we contribute to expand the chemistry of the herbicidins and provide a platform for the preparation of structurally related, potentially bioactive derivatives thereof.

Chapter II: Synthesis Toward the Alkaloid Stephadiamine

The natural product stephadiamine (**V**) is the first example of a *C*-norhasubanan alkaloid natural product, originally isolated from *stephania japonica* in 1984.[11] Its pentacyclic skeleton, which structurally resembles the more famous class of hasubanan alkaloids, and the bridging lactone moiety, makes stephadiamine (**V**) a challenging target for total synthesis. Despite its structural beauty, no total synthesis of **V** has been reported to date.

The proposed racemic retrosynthetic analysis of **V** makes use of a Curtius rearrangement and a late lactonization. The propellane skeleton of **V** could be made by means of a cyclopropane opening through key enamine **IV**, which will ultimately be derived from carboxylic acid **II**.



In the forward sense, starting from acid **II**, tetralone **III** was readily prepared on gram scale, including an elegant aryl C–H olefination step.[12] We anticipated that enamine **IV** should be accessible through alkylation and reaction with methylamine.[13] The remaining steps will include installation of the final five-membered ring and the formation of the lactone moiety to yield stephadiamine (**V**) in an extremely efficient manner.

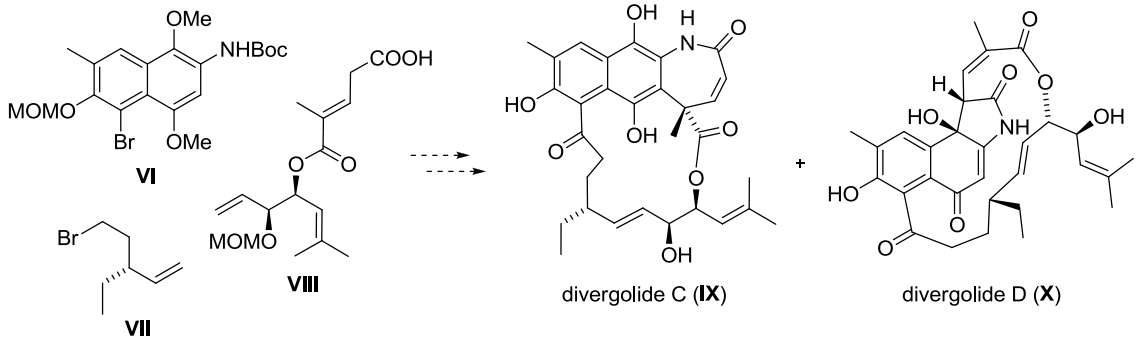
An alternative strategy was proposed, which includes a Tsuji-Trost allylation arising the potential for an enantioselective synthesis of stephadiamine **V**. For this route, the previously prepared tetralone **III** could be applied.

Chapter III: Synthetic Studies Toward Divergolides C and D

Divergolides C (**IX**) and D (**X**) were isolated by C. Hertweck and co-workers in 2011 from an endophyte (*Streptomyces* sp. HKI0576) of the mangrove tree *Bruguiera gymnorrhiza*.[14] Although being structurally different, the divergolides show remarkable biological activities to be potent lead structures for anti-infective and antitumor drugs. Hertweck and co-workers suggested that divergolides C (**IX**) and D (**X**) originate from a common biological precursor. We envisioned a total synthesis of this intermediate followed by a biomimetic conversion to both divergolides C (**IX**) and D (**X**).

This part of the thesis was focused on the preparation of side chain **VII** in large quantities, as well as its assembly with the previously synthesized building blocks **VI** and **VIII**. Towards

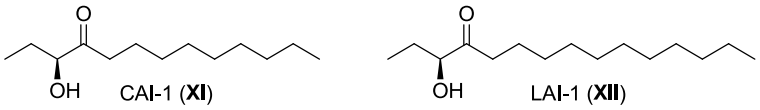
this end, we were successful in coupling all three intermediates. The closure of the macrocycle and the final biomimetic conversion to divergolides C (**IX**) and D (**X**) have not been accomplished, but are currently under investigation in the Trauner group.



Chapter IV: Synthesis of a Bacterial Signaling Molecule

The signaling molecules cholera autoinducer-1 (CAI-1) (**XI**) and *Legionella* autoinducer 1 (LAI-1) (**XII**) belong to the class of α-hydroxyketones (AHKs). Given the effects of CAI-1 (**XI**) and LAI-1 (**XII**) on virulence, biofilm formation and extracellular filaments of *V. cholerae* or *L. pneumophila*, these signaling molecules or derivatives thereof have the potential for clinical or technical applications.

For a deeper understanding of the signaling circuit and in order to gain more insight in the mechanism of cell-cell communication, the research group of H. Hilbi investigates the gene regulation by AHK-mediated signaling in *L. pneumophila*. For this research, synthetic LAI-1 (**XII**) is needed in pure form. The project aimed at providing the Hilbi group with pure LAI-1 (**XII**) for further investigation of the biochemical effects in signaling circuits of bacteria.



Chapter V: Experimental Procedures and Analytical Data

Chapter V includes the experimental procedures for the preparation of all compounds, backed up by full analytical characterization. In addition, ^{1}H- and ^{13}C-NMR spectra as well as crystallographic details are given there.

Acknowledgements

First I would like to thank Prof. D. Trauner for giving me the opportunity and pleasure to work under his supervision. I am extremely grateful for the scientific freedom that was given to me. Dirk's boundless enthusiasm and his interest im my projects contributed the most to my learning.

I also wish to thank my cooperation partners Jörg Tiebes and Christian Paulitz from Bayer CropScience AG for their support throughout my herbicidin project.

Concerning the preparation of this thesis, I am indebted to the following people for their critical reading and helpful advises: Sebastian Strych, Pascal Ellerbrock, Elena Herrero-Gómez, Michael Pangerl, Anastasia Hager, and Daniel Hog.

Nevertheless, the four years in the Trauner group would not have been the same without all the people, who shared their talents and passion with me. It would be difficult to mention them all here, but I must thank at least a few of them for having fun times working and celebrating together: Vilius Franckevičius, Albert Schröckeneder, Pascal Ellerbrock, Florian Löbermann, Michael Pangerl, Daniel Hog, Philipp Stawski, Sebastian Strych, Desiree Stichnoth, Johannes Broichhagen, Arunas Damijonaitis, and Elena Herrero-Gómez. Thank you all in the 'Blue Lab' for having a perfect working atmosphere and good music.

I am deeply grateful for the support provided by the Trauner staff Heike Traub, Martin Sumser, and Carrie Louis.

Thanks to my undergraduate students Maximilian Reindl, Martin Härtel, Felix Fahrnbauer, Shu-An Liu, Nina Vrielink, Gökcen Savasci and Daniel W. Terwilliger for pushing my projects forward.

Finally, I owe my thanks to my wife Anastasia, my sister Johanna, and my family who have always encouraged and supported me.

Abbreviations

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
Å	angstrom
Ac	acetyl
$[\alpha]_D$	specific rotation
AD	asymmetric dihydroxylation
AHBA	3-amino-5-hydroxy-benzoic acid
AHK	α-hydroxyketone
AIBN	azobisisobutyronitrile
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
aq.	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
Bu	butyl
Bz	benzoyl
c	concentration
CAI-1	cholera autoinducer-1
calcd.	calculated
CAM	ceric ammonium molybdate(IV)
cat.	catalytical
CBS	Corey-Bakshi-Shibata
CCDC	Cambridge crystallographic data center
CDI	1,1'-carbonyldiimidazole
CSA	camphorsulfonic acid
CoA	coenzyme A
conc.	concentrated
COSY	^{1}H correlation spectroscopy (NMR)
d	day(s)
d	deutero
δ	chemical shift (NMR)
Δ	delta, heat
DAIB	(diacetoxyiodo)benzene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	*N,N'*-dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
deg	degree(s)
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
d.r.	diastereomeric ratio
E	entgegen (opposite, *trans*)
EBTHI	ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	electron ionization (mass spectrometry)
eq	equivalent(s)
ESI	electrospray ionization (HRMS)
Et	ethyl
FT	Fourier transform (IR)
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond connectivity (NMR)
HMDS	hexamethyldisilazide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HSP	heat shock protein(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence (NMR)
Hz	hertz (frequency)
i	iso (isomer)
IC_{50}	half maximal inhibitory concentration
im	imidazole
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry

J	coupling constant (NMR)
K	Kelvin
λ	lambda, wave length unit
L	litre(s)
l	length
LAI-1	*Legionella* autoinducer-1
LC	liquid chromatography
LDA	lithium *N*,*N*-diisopropylamide
LDBB	lithium 4,4'-di-*tert*-butyldiphenyl
m	meter(s)
m	meta
M	molar (*c*)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry, molecular sieves
MTM	methylthiomethyl
µw	microwave
n	normal (isomer)
N	normal (*c*)
$\tilde{\nu}$	frequency (IR)
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy (NMR)
NTC	nitrogen containing tetrasubstituted carbon
o	ortho
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PE	petrol ether

Ph	phenyl
Piv	pivaloyl
PKS	polyketide synthase
ppm	parts per million (NMR)
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
py	pyridine
quant.	quantitative(ly)
R	undefined substituent
RCM	ring closing metathesis
R_f	retention factor (TLC)
RNA	ribonucleic acid
RP	reversed phase
RT	room temperature
SAR	structure activity relationship
sec	secondary (isomer)
T	temperature
t	(*tert*) tertiary (isomer)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCDD	2,3,7,8-tetrachlorobenzodioxin
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl
TPAP	tetra-*n*-propylammonium perruthenate
t_R	retention time (HPLC)
UV	ultra-violet
W	watt
wt	weight
Z	zusammen (together, *cis*)

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Chapter I: The Total Synthesis of Herbicidin C and Aureonuclemycin

1. Introduction

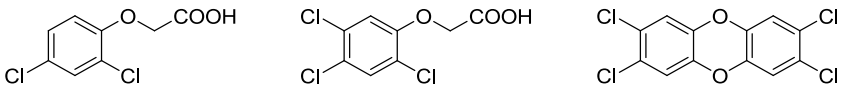
Already at the beginning of plant cultivation, humans were looking for methods to enhance plant growth and protect their seeds and crops in order to secure their sustentation. The Egyptians, for example, made use of remaining Nile slurry after floods to manure their fields. In the ancient world, farmers of many cultures employed stall manure and dung as primitive 'fertilizers' to increase their harvest.[15] As early as in the 8th century BC, Homer mentioned such habits in his epic 'Odyssey',[16] where *'men should come and draw it (heaps of mule and cow dung) away to manure the great close.'*

Around 350 BC, philosophers like Aristotle started to develop theories concerning the reason for the positive effects of soil on plant growth.[15] More than 2000 years later in 1809, the final version of the 'humus theory' was written down by Albrecht Thaer:[17] *'Die Fruchtbarkeit des Bodens hängt eigentlich ganz vom Humus ab; denn außer Wasser ist er es allein, der den Pflanzen die Nahrung gibt. So wie Humus eine Erzeugung des Lebens ist, ist er auch die Bedingung des Lebens. Er gibt die Nahrung dem Organismus, ohne ihn läßt sich daher kein Leben, wenigstens der vollkommenen Tiere und Pflanzen, auf dem Erdboden denken'* - thus, the fertility of soil is just dependent on the humus; only humus and water give nutriment to the plants. Humus is both, creation and precondition of life and it allows survival of the organism; without humus, no life on earth is imaginable, at least for animal and plants.

This view was refined when people realized that inorganic salts, as in guano and Chile saltpeter, can improve their agricultural yields. From 1840 onwards, Justus von Liebig systematically investigated the influence of mineral salts such as nitrates, phosphates, and sulfates on the growth of plants and finally published his 'mineral salt theory'.[18] His work is often connected to the beginning of modern science of plant nutrition. As a result of this research, superphosphate was produced in England and Germany and applied as mineral fertilizer besides guano and Chile saltpeter. With the knowledge that ammonium sulfate can be used as nitrogenous fertilizer and with the development of the Haber-Bosch process in 1909, the way has been opened for the production of fertilizers in large amounts.[19]

Apart from fertilization, weed control is another very effective method to increase the harvest. Already in the middle of the 18th century, people started to use iron sulfate, copper sulfate, and sulfuric acid to kill weeds, later sodium chlorate and dinitro-*ortho*-cresol followed.[20] Altering the soil's pH value, fertility, and salinity as well as mechanical control like tilling and manual removal of unwanted plants, were and still are efficient practices to control weeds.

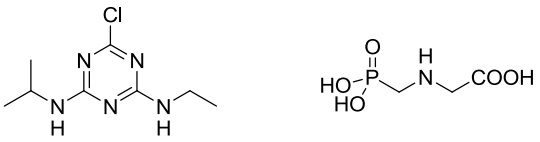
The first and widely applied herbicide was 2,4-dichlorophenoxyacetic acid (**1**) (2,4-D, Figure 1), which was used to selectively kill dicotyledons (dicots, plants whose seed has two embryonic leaves) and keep the monocotyledons (monocots, plants whose seed has one embryonic leave) alive. Thus 2,4-D (**1**) became very successful to protect wheat, corn, rice, and other cereal grasses.[21] Originally, it was developed during World War II to secure the crop production for war periods,[22] but in the Vietnam War it was abused by the U.S. military as defoliant for forests. It became famous as 'Agent Orange', a term which turned into a collective name for all the different herbicide mixtures consisting of the free acids and different alkyl esters of 2,4-D (**1**) and 2,4,5-trichlorophenoxyacetic acid (**2**) (2,4,5-T) in varying compositions. The fatal effects on humans, however, were not caused by the herbicide itself, but by an impurity of the 2,4,5-T (**2**) production, namely 2,3,7,8-tetrachlorobenzodioxin (**3**) (TCDD, Figure 1). The latter is highly toxic and cost the health and lives of hundreds of thousands of people.[23]



2,4-D (**1**) 2,4,5-T (**2**) 2,3,7,8-TCDD (**3**)

Figure 1. Structures of 2,4-D (**1**), 2,4,5-T (**2**) and 2,3,7,8-TCDD (**3**).

In the middle of the 20th century other, important classes of synthetic herbicides were developed, such as the triazines. A famous member of this family is atrazine (**4**) (Figure 2), which can inhibit the photosynthesis of plants and thus destroy unwanted weed.[24] Its use is controversial, since atrazine (**4**) does not decompose within a few weeks after application, therefore leading to accumulation in the ground water.[25] Nevertheless, atrazine (**4**) is still one of the most widely used herbicides in the world, although forbidden in Europe.



atrazine (**4**) glyphosate (**5**)

Figure 2. Structures of the synthetic herbicides atrazine (**4**) and glyphosate (**5**).

Another example from the 1970s is glyphosate (**5**) (Figure 2), which is commercially available under the trade name *Roundup* and is used for nonselective weed control. However, due to the development of resistant crop plants, it is increasingly applied in selective weed control.[26] Glyphosate (**5**) acts as an inhibitor of the shikimic acid pathway and, as a result, the

plant's biosynthesis of amino acids is blocked leading to its death.[27] Since the shikimic acid pathway does not exist in animals, glyphosate (**5**) shows only weak toxicity compared to other herbicides. Additionally, the fact that compound **5** has only a short life time in the soil makes it the most used herbicide in the U.S.A.[24a,28]

The number of different herbicide classes is enormous and the variety of chemical structures and their mode of action extremely large. Hence, the search for new active agents is mainly based on empirical ways and only few herbicides were designed by a completely non-empirical method, which was developed based on the knowledge of the active site of the target enzyme. In fact, the exact molecular target is known only for some herbicide classes. Nevertheless, some general modes of action were determined by physiological and biochemical testing. Herbicides can prevent amino acid, lipid, or carotenoid biosynthesis, and in addition to that, they can interfere with the photosynthesis, disrupt cell division or cause rapid photobleaching.[24]

On the way to new herbicides, natural products can serve as lead structures for new active ingredients.[29] In this sense, the herbicidins are promising nucleoside antibiotics[1] with interesting biological activities (Figure 3).[30] Amongst others, it was found that congeners of this class selectively kill dicots and are non-toxic towards fish.[30a-d,30g-i] Especially this selectivity in the biological activity makes the herbicidins promising herbicides for agricultural application.

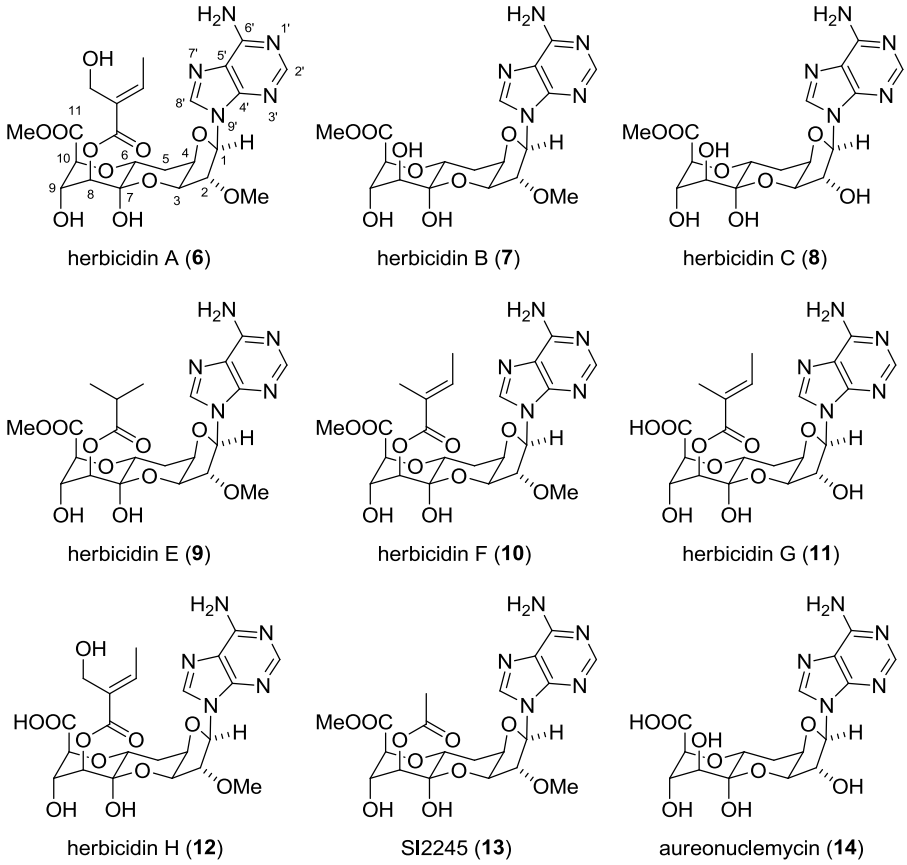


Figure 3. The class of herbicidins.

The herbicidins are not only promising lead structures in search of new herbicides and the development of biological tools, but have been the focus of synthetic interest for the last decades.[2] Thus, several approaches towards the herbicidins were described in the literature. T. Gallagher and co-workers provided by far the most thorough investigation of the herbicidins,[3] however other research groups, such as the groups of D. A. Whiting,[4] A. H. Haines,[5] P. Sinaÿ,[6] and P. Vogel[7] published different approaches toward the herbicidin skeleton. Despite considerable efforts, only one completed total synthesis of a herbicidin by the group of S. Ichikawa has been reported to date.[8]

In order to find a flexible synthetic access to this class of natural products and to provide unnatural derivatives thereof, collaboration between the Trauner research group and Bayer CropScience AG was established. At the beginning of this project, no study on the biological mode of action, binding site or target enzyme of the herbicidins was published. The main focus of our work was the investigation of the relationship between structure and biological activity of the herbicidins (SAR = structure activity relationship study).[9] With this study, we hoped to improve the compounds herbicidal activity against weeds and to be non-toxic to agricultural crops, like corn or rice.

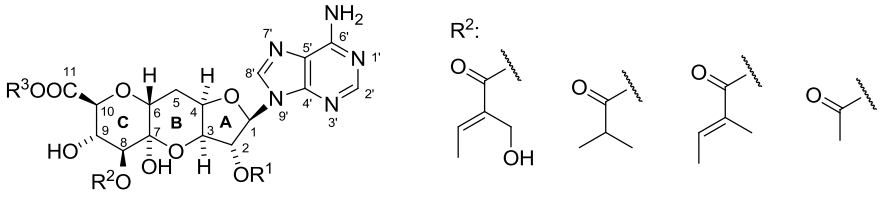
Hence, this project was focused on the following main aspects:

- development of a efficient and flexible total synthesis of the herbicidin skeleton;
- providing synthetic intermediates to Bayer CropScience AG for biological activity testing;
- derivatization of herbicidin A (**6**).[i]

[1] Herbicidin A (**6**) was provided by Bayer CropScience AG in gram quantities.

2. Isolation, Biology and Structural Features of the Herbicidin Family

The herbicidins (**6**–**12**), SI2245 (**13**), and aureonuclemycin (**14**) belong to the same class of nucleoside antibiotics and have been isolated from different strains of bacteria *Streptomyces* (Figure 4).[30] Although all of these natural products have the same skeleton, different names were given to SI2245 (**13**)[30g] and aureonuclemycin (**14**).[30h] However, in this thesis the term 'herbicidins' is used to describe all of these structurally related natural products (**6**–**14**).



	R_1	R_2	R_3	isolated from *Streptomyces* in year	
herbicidin A (**6**)	Me	$CH_3CH=C(CH_2OH)CO$	Me	*S. saganonensis*	1976
herbicidin B (**7**)	Me	H	Me	*S. saganonensis*	1976
herbicidin C (**8**)	H	H	Me	*S. saganonensis*	1979
herbicidin E (**9**)	Me	$(CH_3)_2CHCO$	Me	*S. saganonensis*	1979
herbicidin F (**10**)	Me	$CH_3CH=C(CH_3)CO$	Me	*S. saganonensis*	1979
herbicidin G (**11**)	H	$CH_3CH=C(CH_3)CO$	H	*S. saganonensis*	1979
herbicidin H (**12**)	Me	$CH_3CH=C(CH_2OH)CO$	H	*S. sp.*	1998
SI2245 (**13**)	Me	CH_3CO	Me	*S. sp.*	1988
aureonuclemycin (**14**)	H	H	H	*S. aureus suzhouneusian*	1989

Figure 4. The herbicidin family.

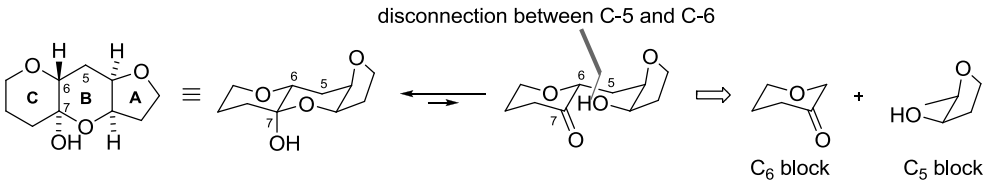
Due to their interesting biological activity, the herbicidins have come under scrutiny of many research groups. For example, herbicidins A (**6**) and B (**7**) are efficient inhibitors of *Xanthomonas oryzae*, a bacterium that causes leaf blight infection in rice crops. Furthermore, reduced seed germination and diminished algal growth as well as selective toxicity towards dicotyledonous plants, but no toxicity against animals, was observed.[30a-d,30g-i]

Structurally, the herbicidins show a number of intriguing characteristics (Figure 4). Their common carbohydrate moiety contains a linear chain of eleven carbon atom, which is folded into a tricyclic furano-pyrano-pyran skeleton to from the three rings **A**, **B**, and **C**. This tricyclic backbone includes nine stereogenic centers. Adenine as the nucleobase resides in a sterically congested concave position. In addition, the hemiketal at C-7 fuses the pyrano-pyran system in such a way that all of its substituents adopt axial orientations. The individual members of the herbicidin family differ in three positions, namely C-2, C-8 and C-11. While residues R^1 and R^3 are either a proton or methyl group, side chain R^2 can be a proton or an ester derived from (*E*)-2-(hydroxymethyl)-2-butenoic acid, isobutyric acid, tiglic acid, and acetic acid.

3. Previous Work on Herbicidins

As a consequence of their structural beauty and their potent biological activities, the herbicidins have attracted much attention from the synthetic community in the past decades.[3-8] In general, two different strategies regarding the *N*-glycosylation were discussed: the nucleobase could be introduced either prior to or subsequent to the formation of the tricyclic carbohydrate moiety. Thus these strategies are called 'early-' or 'late-stage' glycosylation respectively.[1-2,3b] The majority of all groups chose a late-stage adenylation strategy, but never succeeded up to now.[3-7] The only successful approach to herbicidin B (**7**) was accomplished by the group of S. Ichikawa. They started with adenosine and carried the purine base through the whole synthesis.[2,8,31]

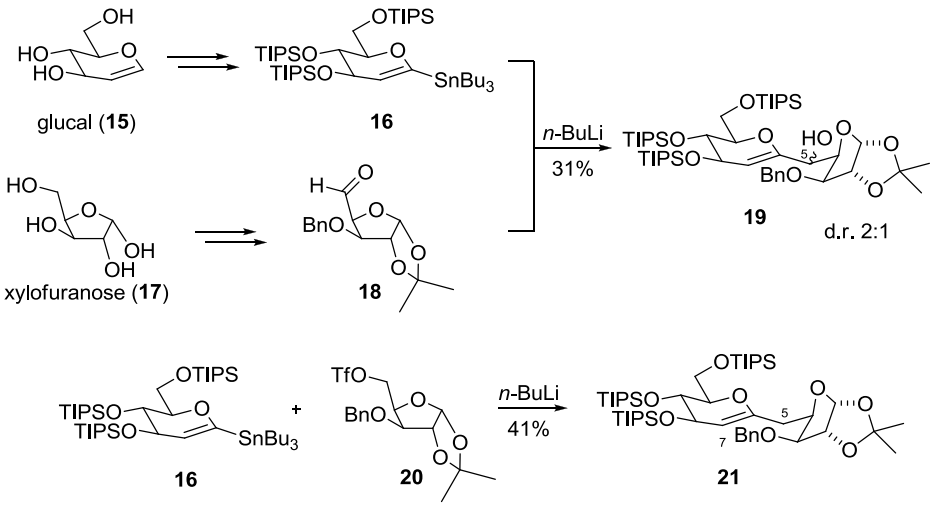
Retrosynthetically, it was reasoned that the hemiacetal at C-7 would occur spontaneously to form ring **B** of the tricyclic skeleton (Scheme 1). The published studies mainly focused on the combination of C_6- plus C_5-building blocks, a strategy, which includes the most obvious and logical disconnection between C-5 and C-6 for the herbicidin undecose.[3-6,8]



Scheme 1. Spontaneous formation of hemiacetal at C-7 and retrosynthetic disconnection to C_6- and C_5-building blocks.

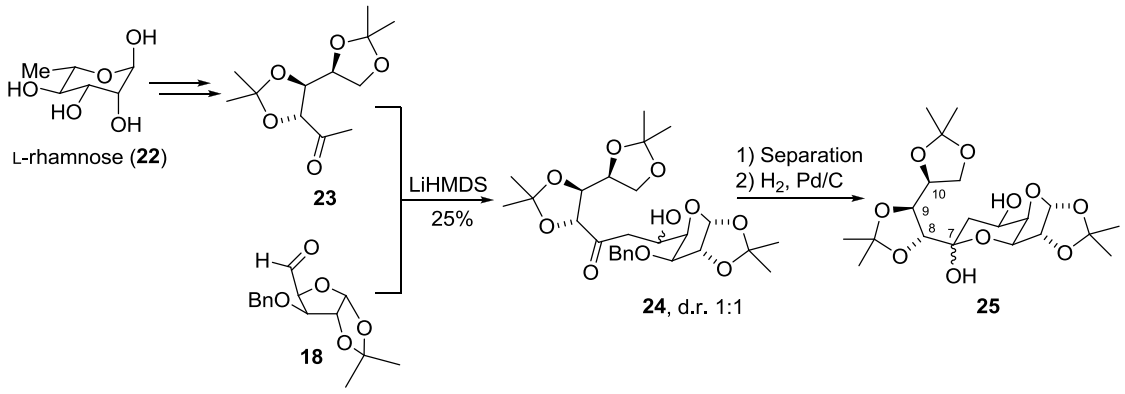
3.1. Unsuccessful C_6 plus C_5 Approaches Toward the Herbicidin Backbone

Between 1988 and 1999, six different groups published on the synthesis of the herbicidins.[3-8] The strategies toward the undecose moiety are very similar and often the *C*-glycosylation was realized through an addition of a C_6- to a xylofuranose-derived C_5-building block. For example, D. A. Whiting and co-workers employed stannane **16**, prepared from glucal **15**, for a transmetallation with *n*-BuLi (Scheme 2).[4] The resulting organolithium species reacted further with aldehyde **18** to give alcohol **19** in low yields and as a 2:1 mixture of separable diastereomers. Further attempts to deoxygenate the C-5 position failed, which led to an alternative plan to alkylate **16** with triflate **20** through a nucleophilic substitution reaction, furnishing compound **21** directly. The reaction occurred in slightly better yields than the addition to the aldehyde **8**. However the installation of the ketone at C-7 was not successful. Hence, the rings **A** and **C** of the herbicidins' undecose sugar were assembled, but the position C-7 remained to be oxidized.



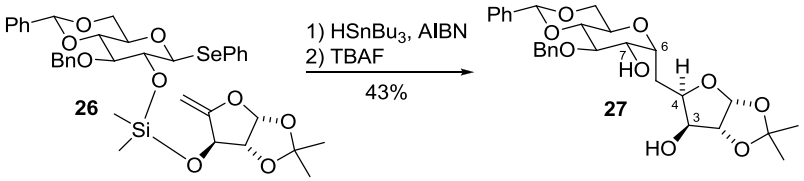
Scheme 2. D. A. Whiting's approach toward the herbicidin backbone.

The very same aldehyde **18** was later used as C_5-building block by A. H. Haines and co-workers.[5] Their aim was to link it with ketone **23** derived from L-rhamnose (**22**) by an aldol addition reaction. Remarkably, this is the only example that made use of an open-chain C_6-carbohydrate building block to access the undecose moiety. However, the reaction with LiHMDS was low-yielding and gave a 1:1 mixture of diastereomers **24**. After separation, one isomer was deprotected resulting in the formation of ring **B** by spontaneous hemiacetal formation at C-7 (Scheme 3). The resulting stereochemistry at C-7 was not determined and further investigations towards the formation of ring **C** were not published. It is worth mentioning that the stereochemistry at C-8, C-9 and C-10 of diol **25** was the opposite configuration as in the herbicidins. This was attributed to the availability of the starting materials: 1-deoxy-L-fructose derivative **23** prepared from naturally occurring L-rhamnose (**22**) was easier accessible than the respective 1-deoxy-D-fructose derivative, which would be needed for the assembly of the herbicidin undecose with the correct stereochemistry.



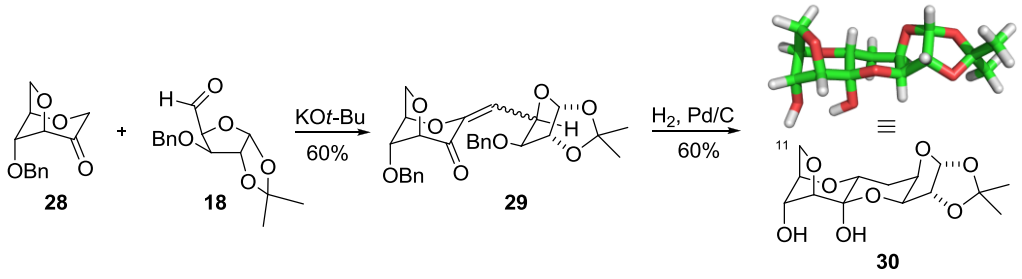
Scheme 3. A. H. Haines' approach toward the herbicidin backbone.

A molecular tethering approach followed by a radical cyclization was investigated by P. Sinaÿ and co-workers (Scheme 4). In this case, silaketal **26** was prepared by linkage of the respective D-glucose- and D-xylose-derived precursors. This intermediate underwent radical 8-*endo*-*trig* cyclization and after removal of the silyl tether with TBAF, compound **27** with the complete rings **A** and **C** was obtained. Luckily, *C*-glycoside **27**, which bears the correct stereochemistry at C-4 and C-6, was isolated as the main diastereomer in surprisingly high yield of 43%.[6] Further transformations towards the closure of ring **B** were not reported. Since both alcohols at C-3 and C-7 in **27** are secondary, it might be challenging to distinguish them in order to set different oxidation states in the further course of the synthesis.



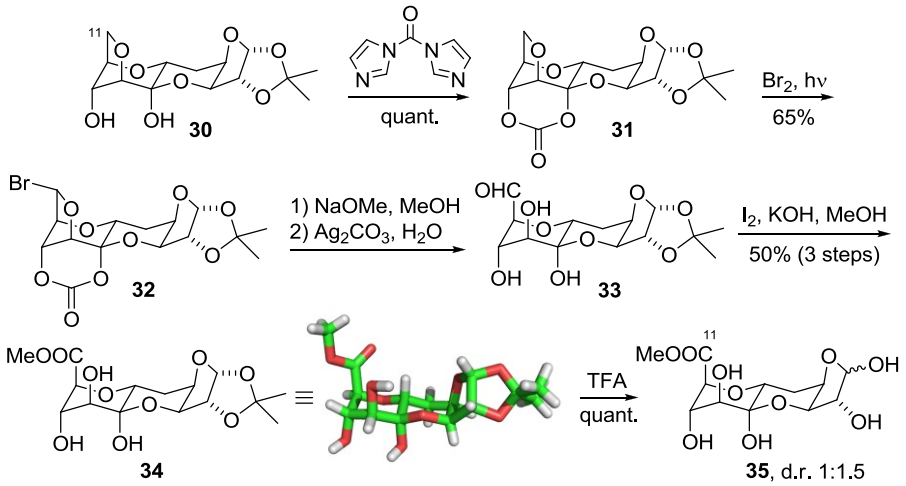
Scheme 4. P. Sinaÿ's approach toward the herbicidin backbone.

In contrast to the approaches described so far, the investigations on the synthesis of the herbicidins by the group of T. Gallagher were more thorough and they date back to 1988.[3] Strategically, the very same aldehyde **18**, which was later used by D. A. Whiting and A. H. Haines (*vide supra*, Scheme 2 and Scheme 3), was combined with the enolate derived from C_6-building block **28** to yield the aldol condensation product **29** as a single diastereomer with an unknown double bond configuration. The hydrogenation of the alkene and concomitant debenzylation yielded hemiacetal **30**, a key compound for further investigations. This intermediate already possessed all three rings **A**, **B**, and **C** of the herbicidin skeleton and only adjustment of the oxidation state at C-11 and cleavage of the ether bridge were needed. However, the reason for the *face*-stereoselective reduction of the double bond remained unclear.[3e]



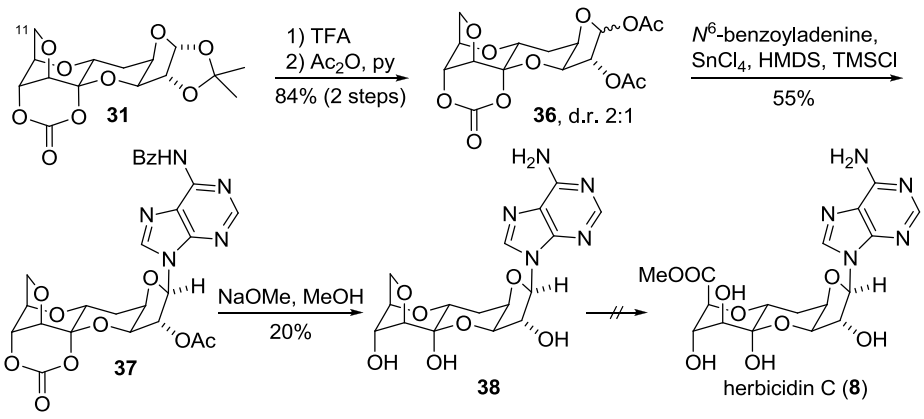
Scheme 5. T. Gallagher's synthesis of key building block **30**.

In order to install the right oxidation state at C-11, diol **30** was protected as carbonate to yield **31** and the bridgehead was brominated selectively (→**32**). Methoxide-induced cleavage of carbonate **32** and silver(I)-mediated hydrolysis of the resulting α-bromoether provided aldehyde **33**, which was further oxidized to ester **34**. Deprotection of the acetonide gave the free undecose **35**, corresponding to herbicidin C. However, its glycosylation was not described.[3e]



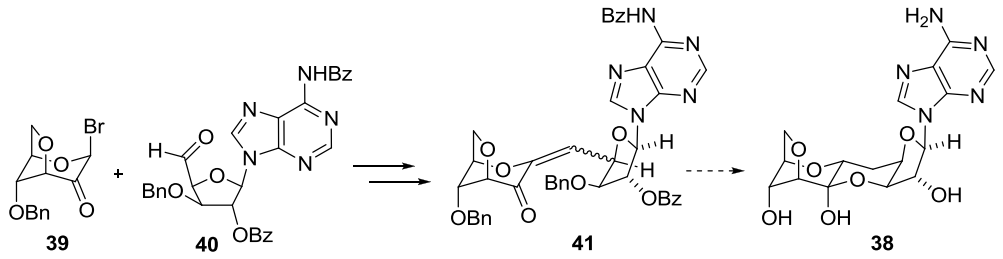
Scheme 6. T. Gallagher's adjustment of the oxidation state at C-11.

In a further attempt, an alternative route from key compound **30** to herbicidin C (**8**) was envisioned employing the glycosylation at an earlier stage.[3b] Thus, the acetonide in **31** was swapped to acetate protecting groups and the resulting diastereomeric mixture of **36** was glycosylated under Lewis acidic conditions (→**37**, Scheme 7). The following deprotection of the base-labile substrate **37** under Zemplén conditions afforded **38** in low yield (20%). The remaining functionalization at C-11 with the previously established radical-mediated bromination and the following ring opening (as used for the synthesis of **34**) to herbicidin C (**8**) was unsuccessful.



Scheme 7. Attempts of T. Gallagher and co-workers towards the synthesis of herbicidin C (**8**).

So far, only late-stage glycosylation attempts were considered by the Gallagher group. In a second, early-stage glycosylation approach to the ether bridged analog **38**, α-bromoketone **39** prepared from D-glucose, was connected to xylo-nucleoside aldehyde **40**, and transformed into a single isomer of **41** with unknown double bond configuration (Scheme 8).[3a] Further investigations to **38** have not been reported so far.



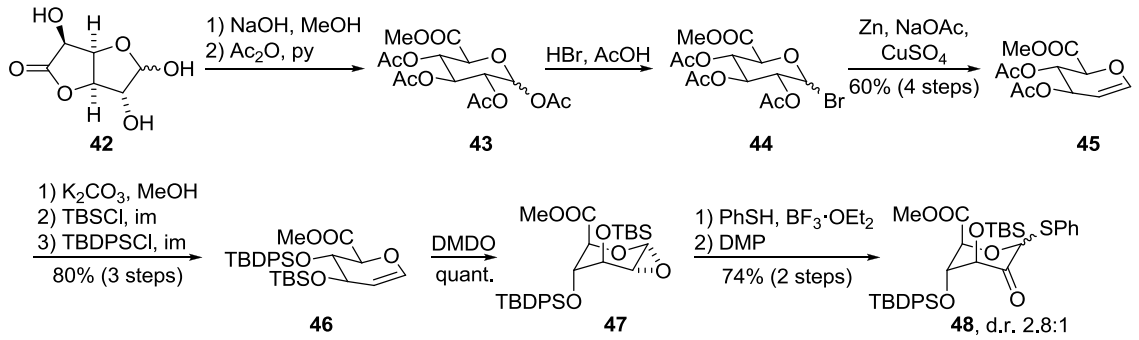
Scheme 8. T. Gallagher's early-stage glycosylation attempt.

In summary, a variety of different studies toward the synthesis of the herbicidins have been published, with strategies that were limited mainly to early-stage glycosylations. The respective undecose sugars were targeted by coupling of C_6- and C_5-precursors. While the groups of D. A. Whiting, A. H. Haines, and P. Sinaÿ were only able to establish two rings of the furano-pyrano-pyran skeleton, the Gallagher group prepared the whole tricyclic undecose sugar moiety. Its glycosylation with adenine has not been met with success so far.

3.2. Ichikawa's Total Synthesis of Herbicidin B Through Early-Stage Glycosylation

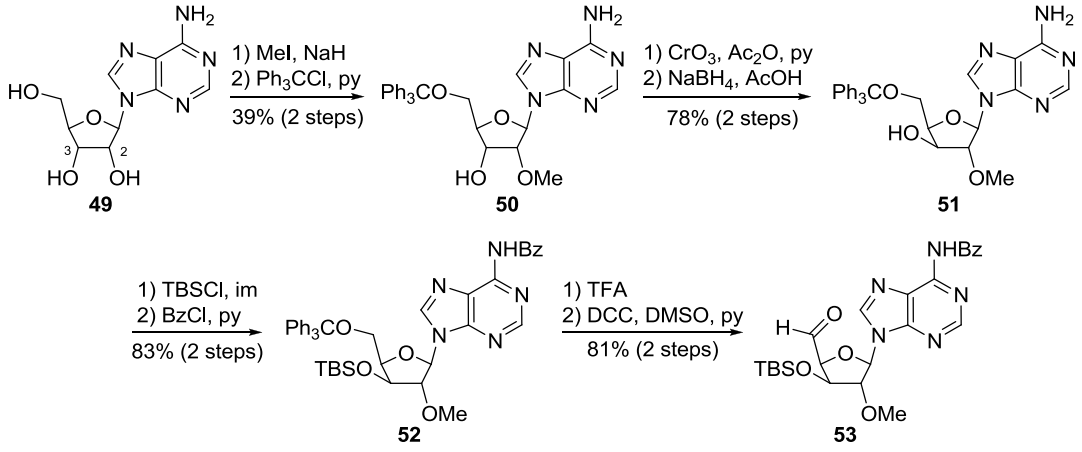
The main difference of S. Ichikawa's route compared to other attempts is the early introduction of the adenine nucleobase.[8] Analogously to other groups, two different building blocks were prepared separately and eventually connected through a samarium diiodide aldol-type *C*-glycosylation. The synthesis of the C_6-building block **48** started with glucurono-lactone (**42**) that was rearranged and acetylated to carbohydrate derivative **43**. Further transformation with HBr to compound **44** and elimination of the bromine gave glycal **45** (Scheme 9).[32] The subsequent change to the right silyl protecting groups was crucial for the success of the whole synthesis. Two TBS-protecting groups did not result in the required axial orientation of the substituents due to too little steric repulsion, while TIPS groups could not be removed later. As a result, the acetates of **45** were cleaved and the resulting diol was treated with TBSCl followed by TBDPSCl (→**46**). Epoxidation of glycal **46** with DMDO gave bicycle **47** as single diastereomer. Opening of the resulting oxirane with thiophenol and subsequent

Dess-Martin periodinane oxidation provided phenylthioulose **48**, in which all substituents are already oriented in an axial manner.



Scheme 9. S. Ichikawa's synthesis of C_6-building block **48**.

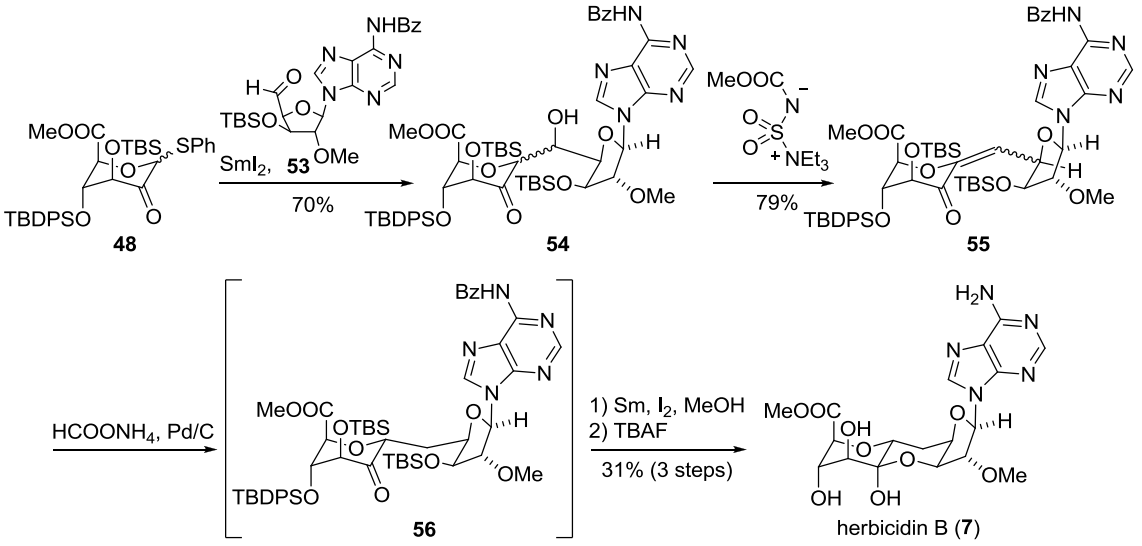
Adenosine (**49**) served as the starting material for the synthesis of the C_5-nucleoside **53** as second building block (Scheme 10). In order to establish the right stereochemistry at C-3, the respective alcohol had to be inverted. Thus, adenosine (**49**) was protected with MeI regioselectively at the sterically less accessible secondary C-2 position in 42% yield.[33] Protection of the primary alcohol with a trityl group gave compound **50**, and an oxidation/reduction sequence inverted the configuration of the alcohol at C-3 (→**51**). Subsequent protection afforded **52**, which was transformed into aldehyde **53**.



Scheme 10. S. Ichikawa's synthesis of C_5-building block **53**.

The coupling of phenylthioulose **48** with aldehyde **53** was achieved through a samarium diiodide mediated aldol-type *C*-glycosylation to give **54** as a mixture of only two diastereomers with unknown stereochemistry (Scheme 11). Dehydration with Burgess' inner salt provided **55** as a single isomer. The stereochemistry of the double bond was not assigned. Reduction of the

alkene occurred *face*-selective with $HCOONH_4$ as dihydrogen donor in presence of palladium on charcoal (→**56**). Final deprotection with SmI_2 and TBAF afforded herbicidin B (**7**).



Scheme 11. S. Ichikawa's connection of **48** with **53** and transformation to herbicidin B (**7**).

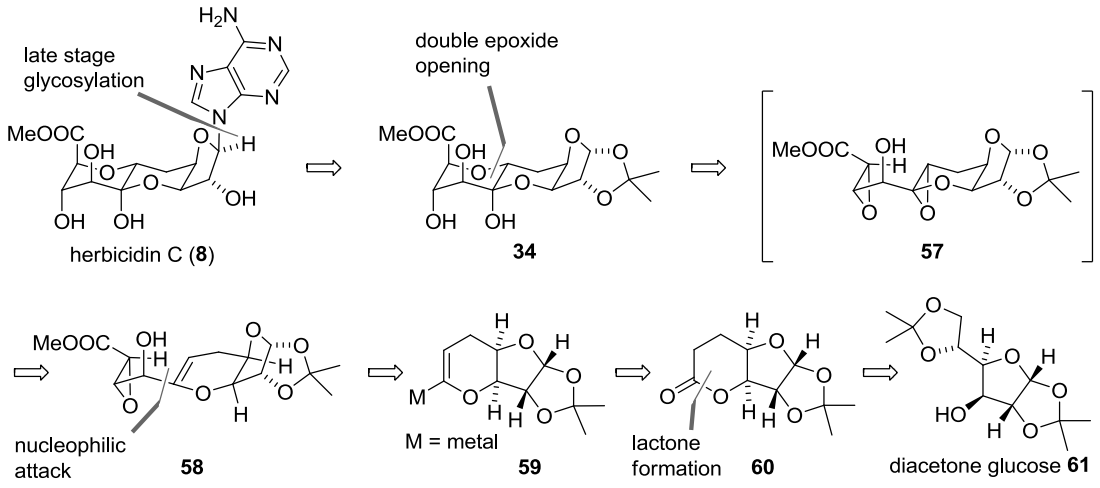
In summary, the first and until then only total synthesis of a member of the herbicidin family was accomplished by S. Ichikawa and co-workers based on an early-stage glycosylation strategy. It required a heavy optimization of the protecting groups in order to achieve a 'conformational flip' in the C_6-building block **48** so that a *face*-stereoselective reduction of the double bond in **55** could be realized.

4. The Right Side Approach: A Preliminary Study

4.1. Retrosynthetic Analysis and Strategy of the Right Side Approach

The strategy we have chosen for the synthesis of the herbicidin skeleton is novel in its building blocks, as we did not envision a C_6 plus C_5 approach. One major aim was to provide a flexible synthesis with respect to potential derivatives for SAR studies. Based on the fact that the common C_6 plus C_5 strategy entailed low-yielding or unselective aldol or *C*-glycosylation reactions, a novel and more efficient approach was necessary.

Retrosynthetically, we expected that herbicidin C (**8**) should be accessible through a challenging late-stage glycosylation from the sterically congestive concave side of the undecose sugar **34** (Scheme 12). In the construction of the latter, we decided not to combine two separately prepared sugar units, but to start with the synthesis of ring **A** of the herbicidins undecose and to install rings **B** and **C** successively. Thus, compound **34**, which had already been synthesized by T. Gallagher and co-workers, could be prepared in a more straight forward fashion by double epoxide opening from compound **58**, *via* intermediate **57**. Alcohol **58** was proposed to stem from dihydropyran **59** and the respective α,β-epoxyaldehyde by a stereoselective organometallic mediated addition. Prior to this, the organometal compound **59** would be prepared from lactone **60**, which could be derived from diacetone glucose **61**, a glucose derivative.

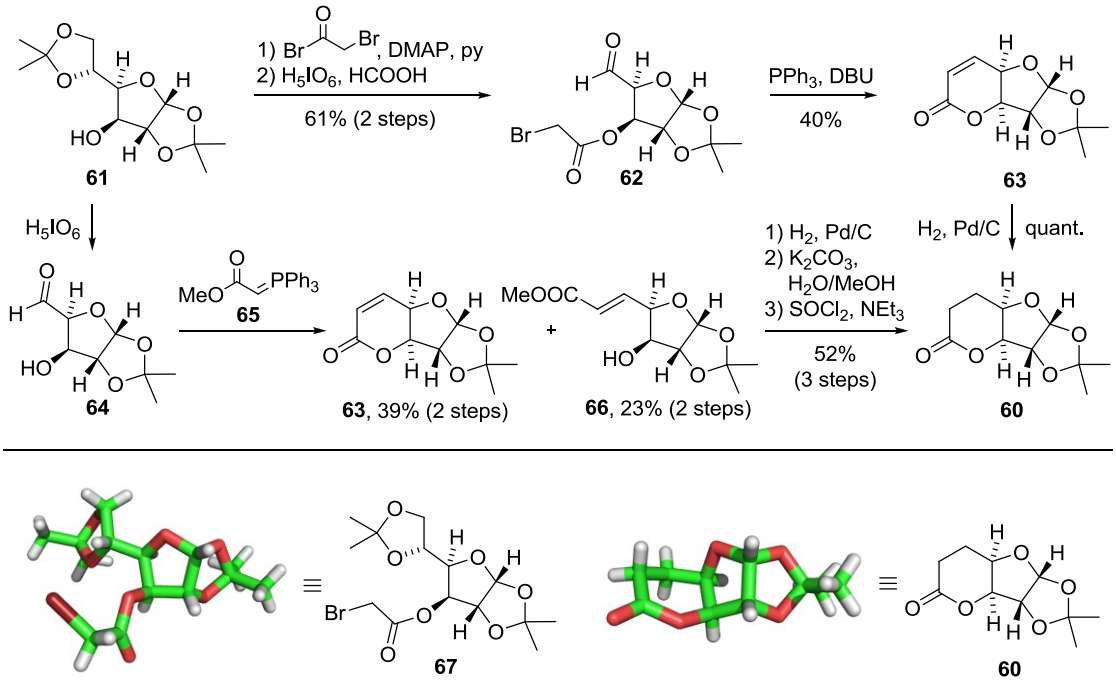


Scheme 12. Retrosynthetic analysis for the right side approach of herbicidin C (**8**).

This fast and efficient synthesis should give access to undecose **34** under complete stereocontrol. A high flexibility would be ensured by the potential to alter the steps and by the late introduction of the nucleobase.

4.2. Results and Discussion of the Right Side Approach – Synthesis of the Carbohydrate Backbone

Initially, the preparation of lactone **60** from commercially available diacetone glucose **61** was the main focus (Scheme 13, top). It has been described that the unsaturated lactone **63** can be prepared by initial esterification of diacetone glucose **61** with 2-bromoacetyl bromide (→**67**) and subsequent regioselective acetonide deprotection/diol cleavage with H_5IO_6.[34] Intramolecular Wittig reaction with the resulting aldehyde **62** afforded the unsaturated lactone **63**. The reported low yield of 22% was improved to 40% by using DBU as a base instead of propylene oxide. The structure of intermediate **67** was confirmed by X-ray crystallography (Scheme 13, bottom). However, the reason for the selective cleavage of only one acetonide with H_5IO_6 remained unclear.[ii] It was speculated that primary acetonides react more readily than secondary acetonides because they are less sterically hindered.[35] Subsequent hydrogenation with hydrogen gas and palladium on charcoal gave key lactone **60** in quantitative yield.



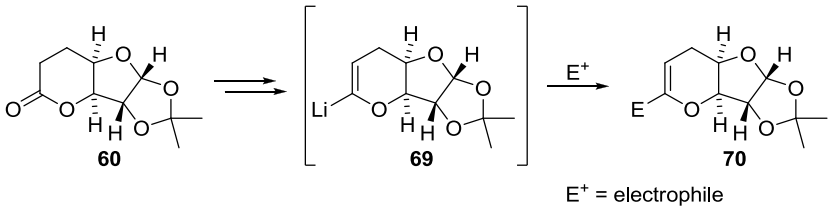
Scheme 13. Synthesis of the key intermediate lactone **60** (top) and X-ray analysis of compounds **67** and **60** (bottom).

In order to improve the total yield of this sequence, the order of steps was altered: selective deprotection of one acetonide and following diol cleavage with H_5IO_6 resulted in aldehyde **64**,

[ii] Selective deprotection of diacetone glucose **61** was also achieved with AcOH to yield triol **68** (see Experimental Section).

which was subjected to intermolecular Wittig reaction with ylide **65** (Scheme 13, top).[36] The resulting *Z*-ester was isolated as the unsaturated lactone **63** in 39% yield, but in addition to that, 23% of *E*-ester **66** was also formed. The latter could be transformed into the desired lactone **60** by a short reduction/saponification/lactonization sequence. Finally, the overall yield from diacetone glucose **61** to lactone **60** was improved from 24% (intramolecular Wittig route) to 51% (intermolecular Wittig route). In addition, the identity of key compound **60** was confirmed by X-ray analysis (Scheme 13, bottom). The only drawback was that the yield of the overall sequence was too low to efficiently prepare decagrams of material, which would be required for the completion of the synthesis of herbicidin C (**8**). Nevertheless, rings **A** and **B** of the herbicidin undecose were successfully installed at that stage of the route and only ring **C** remained to be assembled.

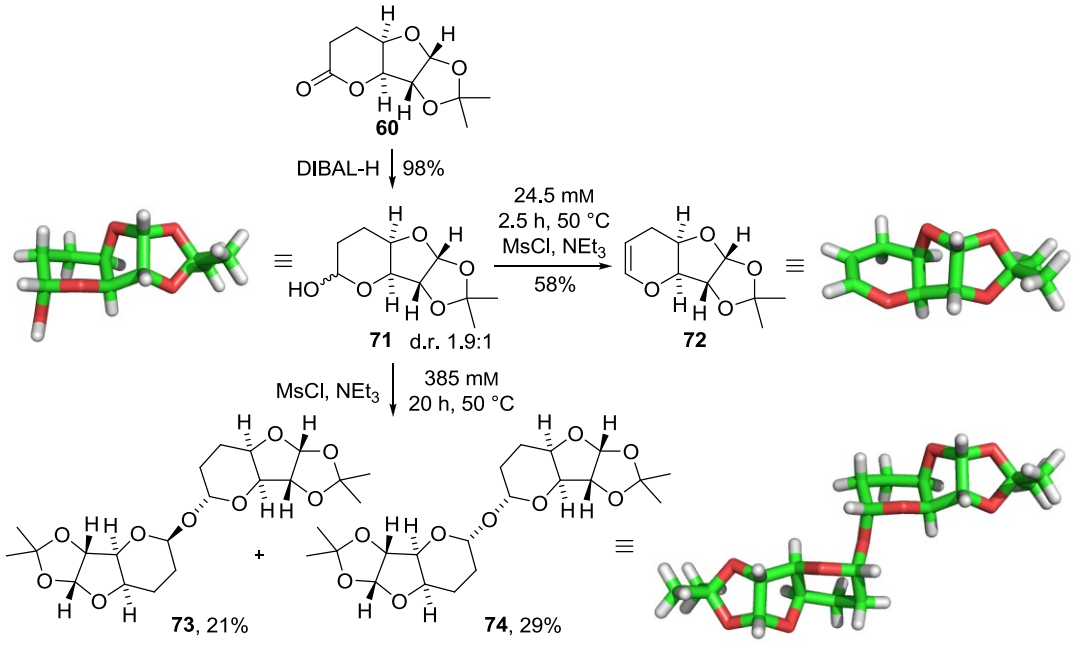
The conceptual next level of the synthesis was the transformation of lactone **60** into a lithiated glycal species **69**, which could be trapped with electrophiles to yield substituted dihydropyrans **70** (Scheme 14).



Scheme 14. Conceptual transformation of lactone **60** to dihydropyran **70**.

The synthesis of organometallic compounds like **69** have been achieved by direct deprotonation of glycals.[37] Thus, lactone **60** was reduced with DIBAL-H to the corresponding lactol **71** as a 2:1 mixture of diastereomers. The major isomer could be analyzed X-ray crystallography (Scheme 15). We expected the elimination to take place readily due to the thermodynamic stability of the dihydropyran thus formed. Even though **71** was isolated as diastereomeric mixture, elimination of both of these isomers should result in the desired product **72**.

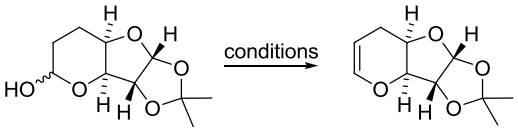
A range of dehydrating conditions was screened (Table 1). It was found that both, *p*-toluenesulfonic acid and phosphorus pentoxide led to decomposition of the substrate **71** (Table 1, entries 1 and 2). No or minute amounts of the desired product **72** were observed with oxalic acid (Table 1, entry 3) as well as tosyl chloride (Table 1, entries 4 and 5) and mesyl chloride at room temperature (Table 1, entry 6). It was pleasing to find that the use of mesyl chloride at elevated temperature raised the amount of product **72**. The reaction could be optimized up to 58% yield after adjusting the temperature and reaction time (Table 1, entries 7–9).



Scheme 15. Preparation of dihydropyran **72** from lactone **60** and undesired dimerization of lactol **71**.

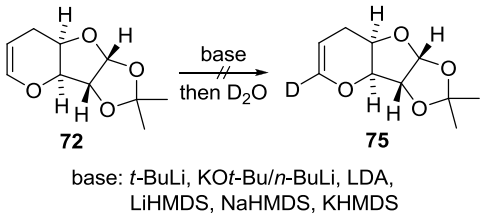
An undesired dimerization of lactol **71** occurred when the elimination reaction with mesyl chloride was carried out under high concentration (Scheme 15). After 20 h at 50 °C and a concentration of 385 mM, two of three possible diastereomeric dimers were isolated, namely unsymmetrical dimer **73** and C_2-symmetric dimer **74**. As expected, the ^{1}H-NMR spectrum of **74** shows only half of the signals compared to that of **73**. The structure of the major product **74** was confirmed by X-ray crystallography, but the second possible C_2-symmetric diastereomer could not be identified.

Table 1. Conditions of the elimination to dihydropyran **72**.



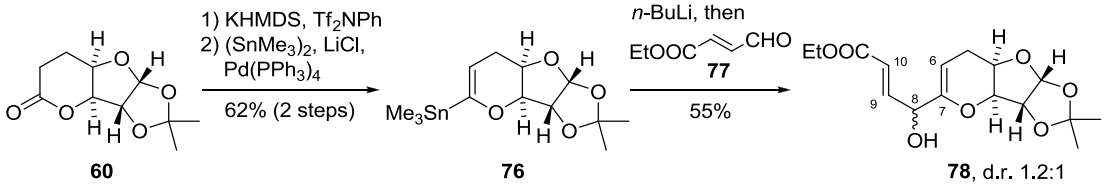
Entry	reaction conditins	Isolated yield
1	*p*-TsOH·H_2O, toluene, RT, 24 h	decomposition
2	P_4O_{10}, toluene, 60 °C, 24 h	decomposition
3	$(COOH)_2$, toluene, 60 °C, 24 h	no reaction
4	TsCl, py, RT, 3 d	no reaction
5	TsCl, py, DMAP, 80 °C, 15 h	5%
6	MsCl, NEt_3, CH_2Cl_2, RT, 2 d	no reaction
7	MsCl, py, 80 °C, 24 h	22%
8	MsCl, NEt_3, CH_2Cl_2, 50 °C, 24 h	42%
9	MsCl, NEt_3, CH_2Cl_2, 50 °C, 3 h	58%

With glycal **72** in hand, deprotonation with several bases was attempted (Scheme 16). Disappointingly, only protonated starting material **72** was recovered after treatment with *t*-BuLi, Schlosser's base, LDA, and HMDS bases and subsequent D_2O-quench.



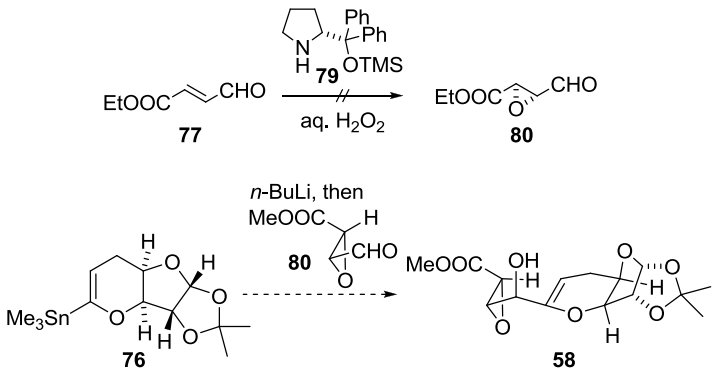
Scheme 16. Unsuccessful deprotonation attempts of glycal **72**.

At this time, another common route to prepare organolithium species **69** from lactone **60** *via* the stannane **76** was pursued (Scheme 17). Initial attempts to deprotonated **60** resulted in the opening of the lactone ring, and the respective carboxylic acid was isolated. However, when the enolate was trapped with *N*-phenyl-bis(trifluoromethanesulfonimide) as soon as it was generated, the resulting sensitive lactone triflate could be converted directly into stannane **76** through Stille cross-coupling reaction. The trimethyl tin group was then exchanged to lithium and the organometallic species reacted further with aldehyde **77** to afford the sensitive alcohol **78** as a 1.2:1 mixture of diastereomers. It is worth pointing out that compound **78** already possesses all carbon atoms, which are needed for the undecose moiety of the herbicidins. The remaining steps would be ring closure and installation of oxygen functionalities at C-6, C-7, C-9, and C-10.



Scheme 17. Synthesis of stannane **76** and organolithium addition to aldehyde **77**.

For this purpose, the synthetic route should be slightly modified. The first epoxide should be introduced by employing the α,β-epoxyaldehyde **80** instead of unsaturated aldehyde **77** with. The synthesis of **80** was described by K. A. Jørgensen and A. Córdova,[38] but due to its instability and volatility, the isolation in preparative amounts was not possible. Therefore, the desired addition of stannane **76** to α,β-epoxyaldehyde **80** could not be further investigated (Scheme 18).



Scheme 18. Attempts of the preparation of alcohol **58**.

At this stage of the synthesis, it was questionable if compound **78** could be converted to the herbicidin framework in an efficient and stereochemical distinct manner. Although all eleven carbon atoms of the undecose skeleton have been assembled and two of three rings were installed, stereoselective functionalization of C-6, C-7, C-8, C-9, and C-10 remained. In addition, the preparation of large amounts of material, especially at the beginning of the sequence, was not practical. Thus, a new retrosynthetic analysis was developed.

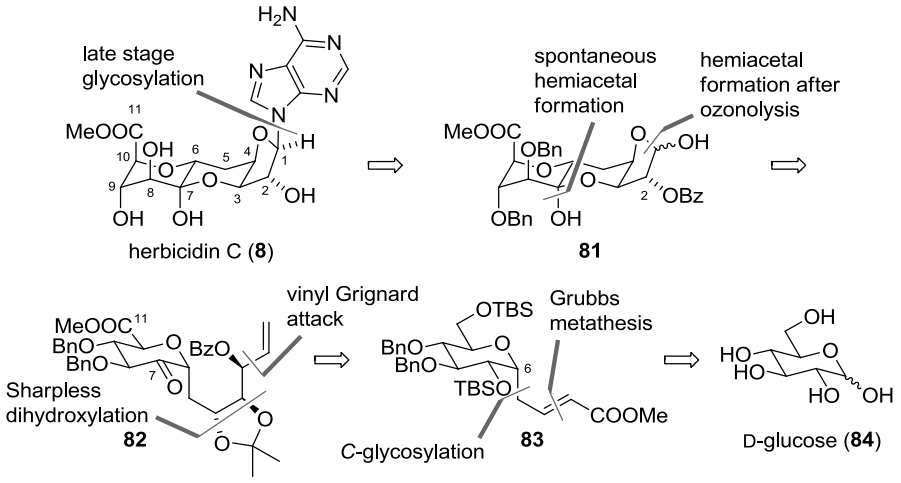
5. The Left Side Approach

5.1. Retrosynthetic Analysis and Strategy of the Left Side Approach

For our second retrosynthetic analysis of herbicidin C (**8**), we considered that the stereochemistry at C-6, C-8, C-9, and C-10 should be set at an early stage of the synthesis, because the functionalization at an advanced point of the reaction sequence might be difficult. Preferentially, the C-6 asymmetric center had to be selectively established, since the early stereocontrol of this position seemed to be crucial for the whole synthesis.

Thus, we reasoned that the challenging late-stage glycosylation could be stereochemically controlled by a neighboring benzoate at C-2, thereby yielding hemiacetal **81** as a logical precursor. This intermediate, in turn, could be traced back to *C*-glycoside **82**, wherein C-7 and C-11 already possess the correct oxidation state. Further retrosynthetic simplification of the side chain would give ester **83**, which could ultimately be derived from D-glucose (**84**).

This novel strategy started with the synthesis of the ring **C** of the herbicidin skeleton and installed rings **B** and **A** at a later stage. Hence it was named 'the left side approach'.

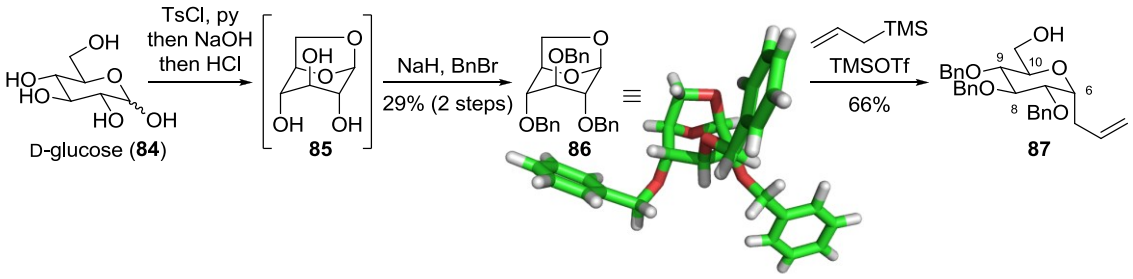


Scheme 19. Retrosynthetic analysis for the left side approach of herbicidin C (**8**).

5.2. Results and Discussion of the Left Side Approach – Total Synthesis of Herbicidin C and Aureonuclemycin

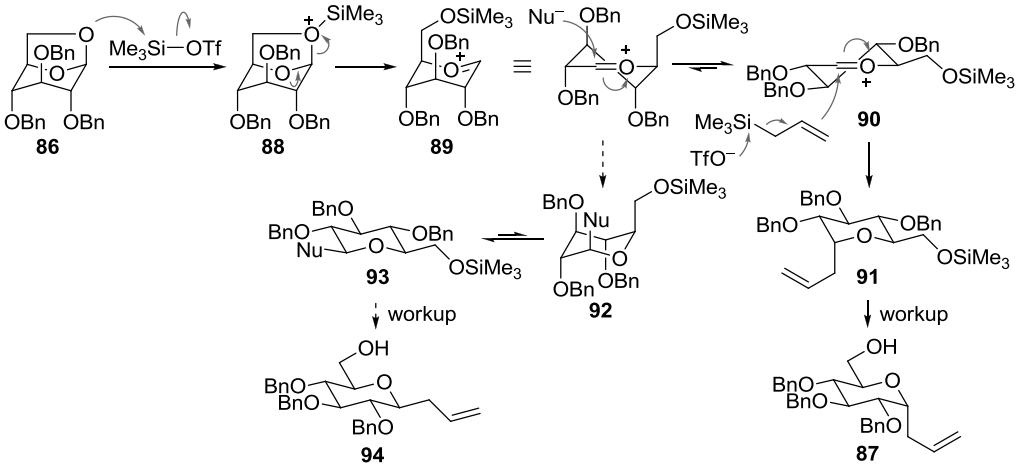
Following our new approach, D-glucose (**84**) was converted into the protected anhydro sugar **86** by combining a practical, large-scale synthesis for 1,6-anhydrohexopyranoses (→**85**)[39] with a standard benzylation protocol (Scheme 20).[40] Reaction of compound **86** with allyltrimethylsilane in the presence of a Lewis acid[41] gave the known α-allyl-*C*-glycoside **87** in 66% yield.[40,42] A second compound was isolated in impure form that was more likely the β-allyl-*C*-glycoside. At this early stage, glycoside **87** already has the C-6 position in the correct

axial orientation and the right stereochemistry at C-8, C-9, and C-10 (herbicidin nomenclature). In course of the synthesis, the ring will have to be inverted.



Scheme 20. Synthesis of *C*-glycoside **87**.

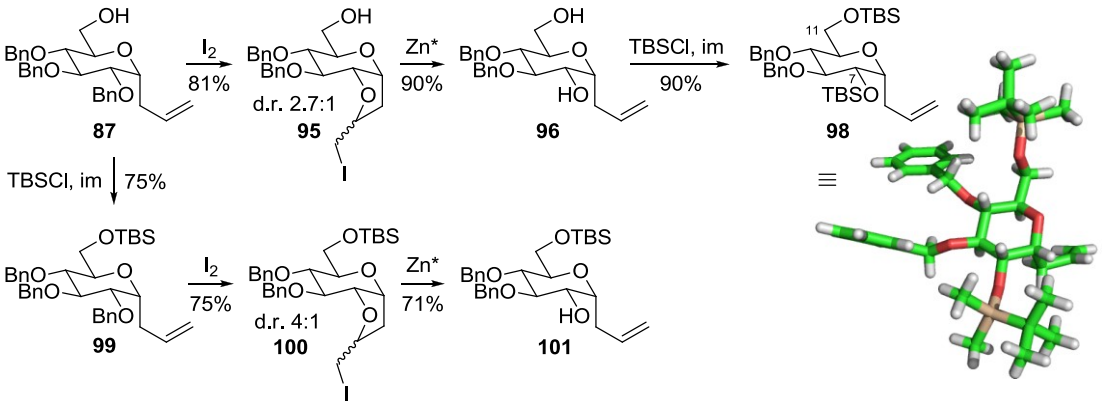
Mechanistically it was anticipated that the selective axial allylation of anhydro sugar **86** would proceed *via* the oxonium ion **89**, since it was reported that the leaving group has no influence on the selectivity of the *C*-glycosylation.[43] Therefore it is reasonable that TMSOTf activates the primary alcohol as a leaving group so that the oxonium ion **89** is formed (Scheme 21). The conformation of this intermediate is presumably unfavored, since all substituents are in axial orientations, thus a conformational flip to the more favored all-equatorial conformation **90** should occur. This in turn, could be attacked by the nucleophile allyltrimethylsilane in an axial orientation, following the rules of the half-chair model[44] to provide **91**.[42-43] The primary TMS group is then presumably cleaved during aqueous work-up to give the desired α-allyl-*C*-glycoside **87**. The corresponding β-isomer **94** could thus be formed by nucleophilic axial attack at the unfavored conformer **89**, resulting in the all-axial intermediate **92**, which would immediately adopt the favored all-equatorial position (→**93**). Compound **94** would then be obtained after deprotection through aqueous work-up.



Scheme 21. Mechanism of the axial *C*-glycosylation to form α- and β-allyl-glucopyranosides **87** and **94**.

The next stage of the synthesis was the preparation of the bissilyl ether **98**, in order to orthogonally protect the remaining C-7 and C-11 alcohols (Scheme 22). These positions would later be oxidized in the herbicidins undecose. Therefore, compound **87** was selectively debenzylated through a two-step protocol[45] involving the formation of iodo ether **95** and subsequent elimination to diol **96**.[iii] After TBS protection, the desired intermediate **98** was obtained.

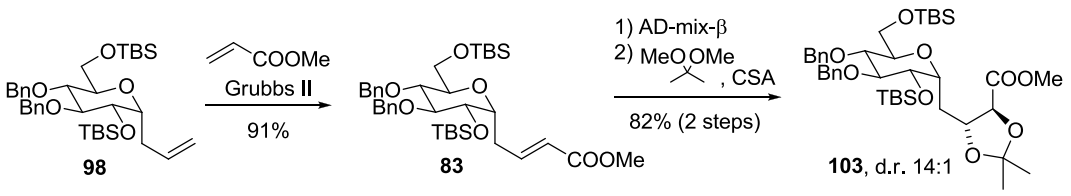
During these investigations, we found that, by permutation of the steps (TBS protection $\rightarrow$**99** followed by formation of iodo ether **100** and elimination), the sequence gives rise to carbohydrate building block **101**, which could be protected, as e.g. acetate, to have three out of four alcohols orthogonally protected (Scheme 22). This building block might find further applications in carbohydrate chemistry.



Scheme 22. Preparation of the silyl ether **98** and carbohydrate building block **101**.

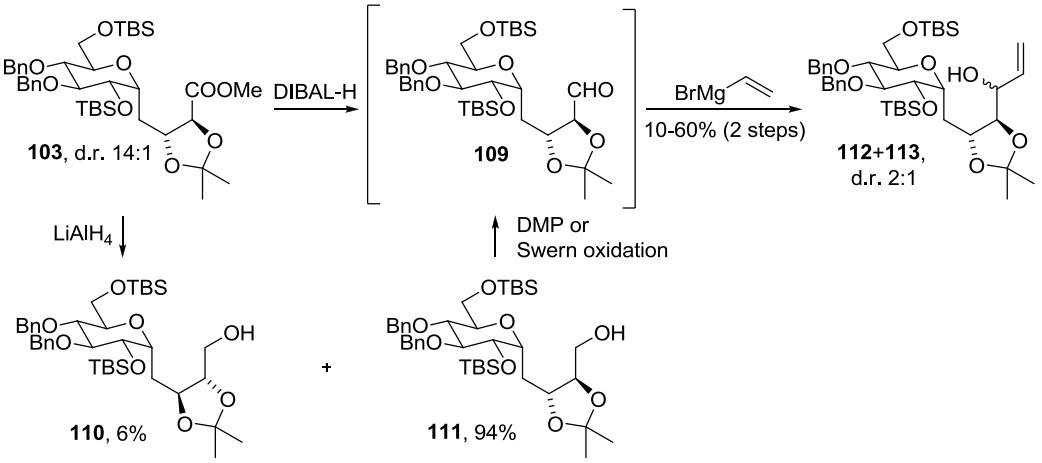
After modification of ring **C** of the herbicidin backbone, we sought to establish the framework of ring **A**. Thus, the allyl side chain of intermediate **98** was elongated by Grubbs' cross-metathesis with methyl acrylate,[47] which afforded unsaturated ester **83** in excellent yield.[iv] The initially reluctant Sharpless dihydroxylation[48] of the electron deficient double bond in **83** was finally forced to completion by a fourfold increased osmium tetroxide concentration. Subsequent acetonide formation yielded methyl ester **103** in a high diastereomeric ratio (Scheme 23).[v] The reaction time of the diol protection under acidic conditions was highly optimized since the primary TBS ether is also cleaved in acidic media.

[iii] As a side product the primary TMS ether **97** was observed since Zn was activated with TMSCl and 1,2-dibromoethane (see Experimental Section).[46]
[iv] *Cis*-ester **102** was observed in 4% yield (see Experimental Section).
[v] In addition to minor diastereomer **104**, both intermediate diols **105** and **106**, as well as the side products free primary alcohol **107** and acetal **108** have been fully characterized (see Experimental Section).



Scheme 23. Synthesis of ester **103**.

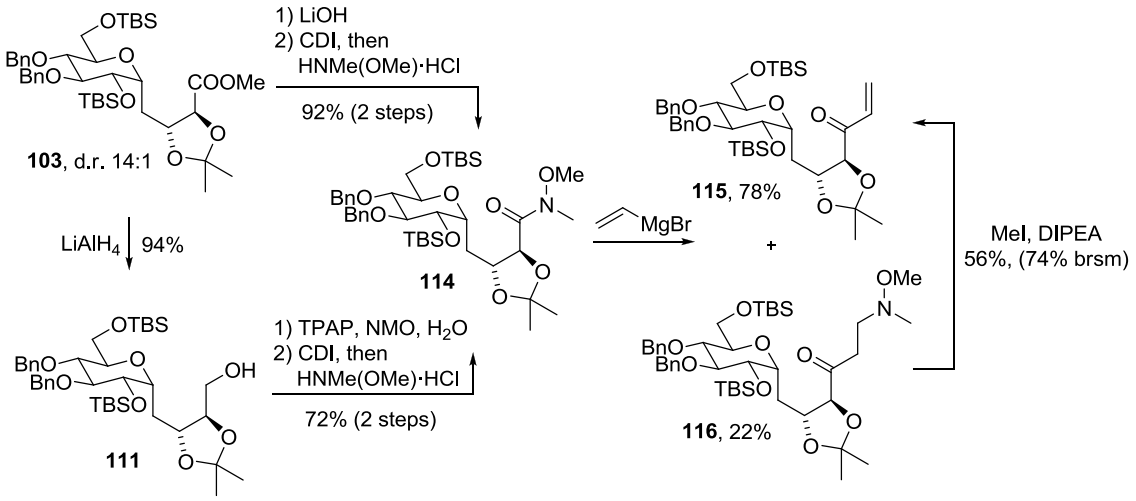
In order to attach the remaining carbon atoms and to install an additional stereocenter, ester **103** was converted into aldehyde **109** with DIBAL-H. As a side reaction, over-reduction with DIBAL-H was observed, so we decided to fully reduce ester **103** with $LiAlH_4$. At the stage of the corresponding alcohols **110** and **111**, it was possible to separate the diastereomers resulting from Sharpless dihydroxylation. Addition of vinylmagnesium bromide to aldehyde **109** gave a mixture of two separable allyl alcohols **112** and **113** in low diastereomeric ratios and unreliable yields (Scheme 24).



Scheme 24. Attempts to synthesize vinyl alcohols **112** and **113**.

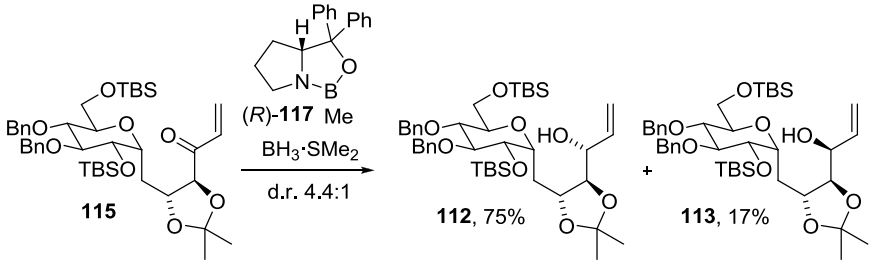
In search of a more efficient transformation of ester **103**, we found that the most practical method was the conversion of **103** to vinyl ketone **105**, which should be reduced by reagent controlled reactions like the Corey-Bakshi-Shibata (CBS) reduction. The double bond in **115** is intended to serve as a carbonyl equivalent later. Thus, saponification of the diastereomeric mixture of ester **103**, obtained after Sharpless dihydroxylation, provided the corresponding acid, which was immediately converted into Weinreb amide **114** (Scheme 25). In order to access isomerically pure material for analytical reasons, the diastereomers were separated after reduction with $LiAlH_4$ at the stage of alcohol **111**, as described above. Ley oxidation and subsequent formation of the Weinreb amide provided another practical route to **114**, however this resolution step was not mandatory for further scale-up of the synthesis. Reaction with vinylmagnesium bromide then provided vinyl ketone **115** and ketone **116** in good yields. This

route becomes even more efficient due to the fact that side product **116** could be recycled to the desired ketone **115** by means of a Hofmann-type elimination.



Scheme 25. Transformation of ester **103** into vinyl ketone **115**.

Installation of the next stereocenter (C-2 in herbicidin) proved to be more challenging than anticipated. Reduction of the carbonyl group in **115** with stoichiometric amounts of the *R*-configured CBS reagent (*R*)-**117** gave again a mixture of the separable alcohols **112** and **113**, this time in high and reliable yields, and moderate diastereomeric ratios (Scheme 26). Unfortunately, we eventually established that the undesired diastereomer **112** was formed as a major product under these conditions (*vide infra*).

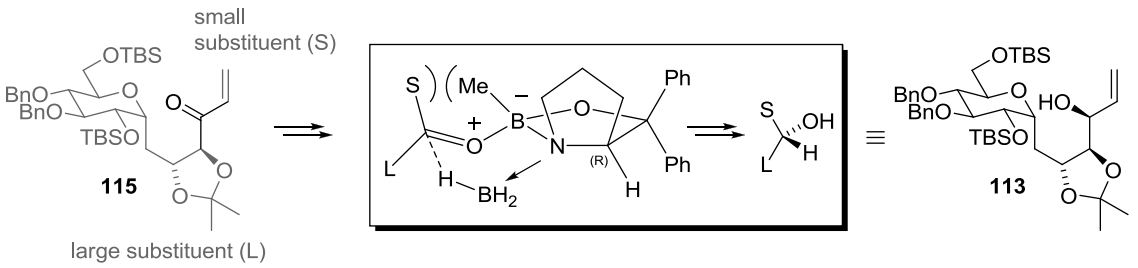


Scheme 26. Synthesis of the undesired diastereomer **112**.

This result was unexpected, since the generally accepted transition-state model for CBS reductions with (*R*)-CBS-Me reagent predicts the opposite configuration of alcohol **112** (Scheme 27). According to the established model, the vinyl group in unsaturated ketone **115** was regarded as the 'small substituent (S)', whereas the acetonide including the whole carbohydrate moiety was defined as 'large substituent (L)'. In the CBS transition-state model, ketone **115** is orientated in such a way that the steric repulsion of the methyl group of the

catalyst (*R*)-**117** and the substituents of **115** is diminished. The reduction will then occur face-selectively from one side of the ketone, which would result in the desired diastereomer **113**. This prediction, however, does not correspond to our experimental findings.

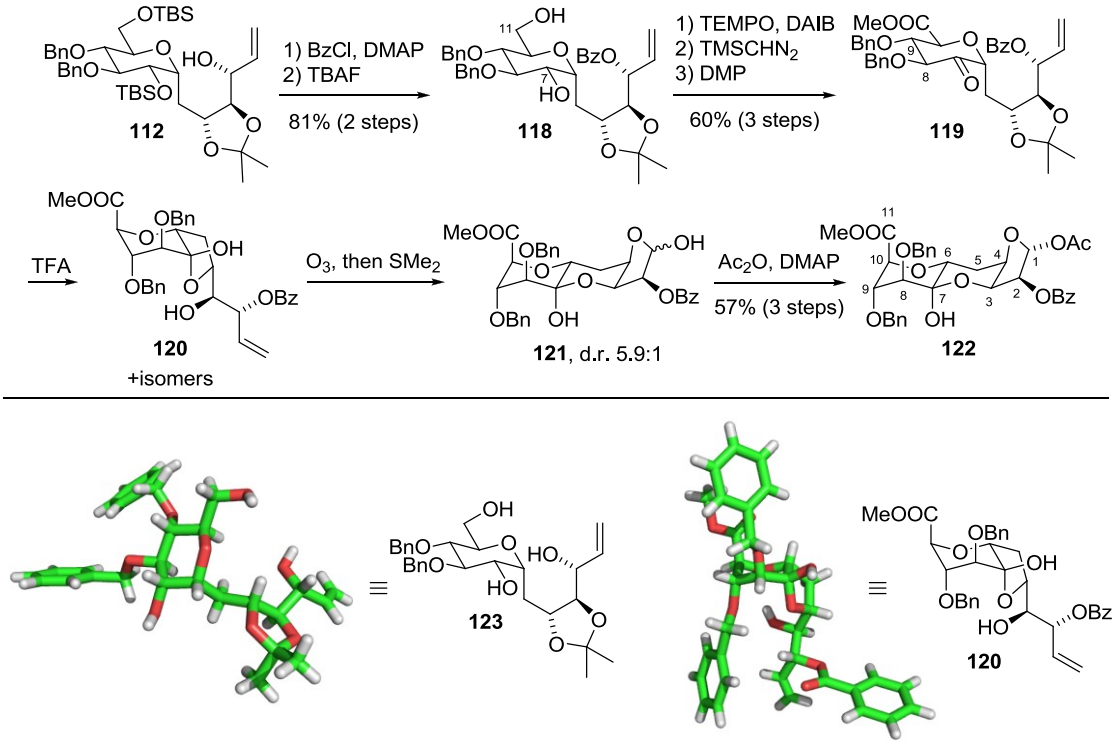
Since this transition-state model seemed not to be applicable to our reaction, it was considered that the CBS reagent was coordinated unexpectedly to our substrate **115** due to substrate constrains. As a result, the validity of the CBS model was overcome.



Scheme 27. Stereochemical consideration of the transition-state model for the diastereoselective Corey-Bakshi-Shibata reduction predicts the desired diastereomer **113**.

The structure of the major isomer **112** was only established after further synthetic transformations, which also served as training ground for our eventually successful synthesis. Benzoylation of alcohol **112** followed by removal of the silyl groups afforded diol **118** (Scheme 28, top). In order to oxidize C-7 and C-11, diol **118** was subjected to a variety of common oxidation methods, such as Dess-Martin periodinane oxidation (DMP), Pinnick oxidation, pyridinium dichromate oxidation (PDC), pyridinium chlorochromate oxidation (PCC), and Ley oxidation. Most of these methods furnished intractable mixtures with little or no desired product. Only oxidation with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and (diacetoxyiodo)benzene (DAIB) in the presence of water proved efficient. Notably, under these conditions, only the primary hydroxy group was oxidized to the corresponding carboxylic acid, whilst the secondary alcohol remained unaffected. Ester formation with (trimethylsilyl)diazomethane followed by oxidation with DMP then provided ketone **119**. Cleavage of the acetonide with trifluoroacetic acid resulted in a mixture of isomeric hemiacetals with compound **120** as the major isomer. When this mixture was subjected to ozonolysis, the whole carbohydrate moiety rearranged and gave the tricyclic herbicidin core **121**. Acetylation of the more accessible hemiacetal yielded undecose **122** as a single diastereomer in 57% yield over three steps. The undesired stereochemistry at C-2 resulting from the CBS reduction (*vide supra*) was indicated by a clear cross-signal of protons H-2 and H-4 in the 2D-NOESY-NMR spectrum of tricycle **122** and was later confirmed by the X-ray structures of the deprotected triol **123** and intermediate **120** (Scheme 28, bottom). However, conformational investigations showed that the 6-membered ring in **119** flipped during the cyclization process to **122**. Whereas the coupling

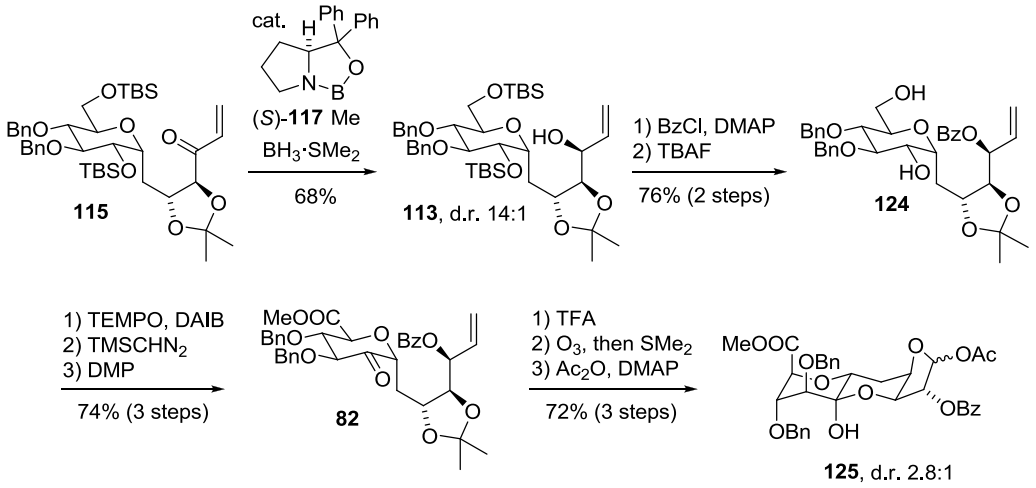
constant of proton H-8 to H-9 in **119** is $J = 7.1$ Hz, the corresponding coupling in tricycle **122** has a size of $J = 3.4$ Hz, indicating that both protons, H-8 and H-9, now adopt equatorial positions.



Scheme 28. Establishment of the tricyclic core **122** (top) and X-ray structures of compounds **120** and **123** (bottom).

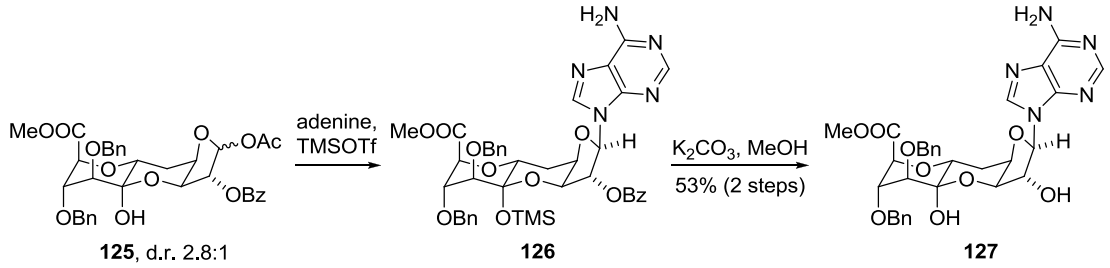
In order to correct the stereochemistry at C-2, we revisited the diastereoselective reduction of ketone **115** (Scheme 29). Simple reduction with $BH_3{\cdot}SMe_2$ gave a 1.4:1 mixture of diastereomers in favor of the desired diastereomer **113**. However, use of the *S*-configured CBS-Me enantiomer (*S*)-**117** in stoichiometric amounts provided the desired alcohol **113** in d.r. = 14:1. These results suggested a matched case of substrate **115** and the (*S*)-CBS-Me reagent. Notably, the amount of (*S*)-**117** could be reduced to catalytic quantities (10 mol-%) while keeping the d.r. value at 14:1.

With our stereochemical problem solved, we could proceed with the total synthesis (Scheme 29). First, a benzoyl group was installed at C-2 to assist the late-stage glycosylation. Subsequent deprotection with TBAF yielded diol **124**, which was converted into ketoester **82** by using the previously established oxidation/esterification sequence. Reiteration of our cyclization conditions (TFA, O_3, Ac_2O) provided undecose **125** as a mixture of diastereomers in 72% yield over three steps. Tricycle **125** contains all three rings **A**, **B**, and **C** of the herbicidin framework as well as the right stereochemistry in all positions. Glycosylation of adenine and final deprotection remained to be performed.



Scheme 29. Establishment of the undecose skeleton **125**.

With compound **125** in hand, we proceeded to investigate the crucial late-stage glycosylation. Much to our satisfaction, the reaction was successful by using a modification of the silyl-Hilbert-Johnson (or Vorbrüggen) protocol. Under these conditions, glycosylamine **126** was obtained. After deprotection with potassium carbonate, **127** was isolated in 53% yield over two steps (Scheme 30).

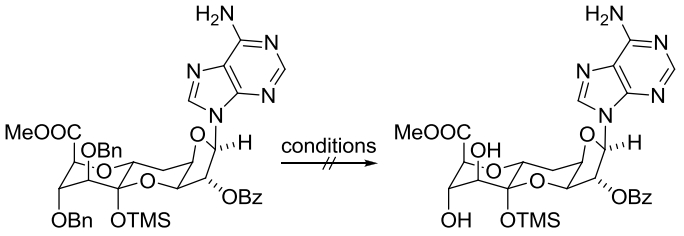


Scheme 30. Glycosylation of compound **125**.

In order to complete the total synthesis of herbicidin C (**8**), the benzyl protecting groups had to be cleaved off. However, this transformation was more difficult than initially expected. First, intermediate **126** was subjected to a variety of debenzylation conditions to potentially yield glycoside **128** (Table 2). Hydrogenation with different palladium catalysts proved to be unsuccessful and only starting material was recovered (Table 2, entries 1–3). This is not surprising since it was described that amines,[49] as well as nucleobases[50] can poison and thus inactivate the palladium catalyst. However other examples show that depending on the substrate, the hydrogenation can be successful in presence of a nucleobase.[50-51] On the other hand, transfer hydrogenation with $HCOONH_4$ as a hydrogen source and reduction with Raney nickel led to decomposition of **126** (Table 2, entries 4 and 5). The same results were obtained

with Lewis acids (Table 2, entries 6 and 7) and radical deprotection conditions (Table 2, entries 8 and 9), since only intractable mixtures were isolated.

Table 2. Conditions to debenzylate intermediate **126**.

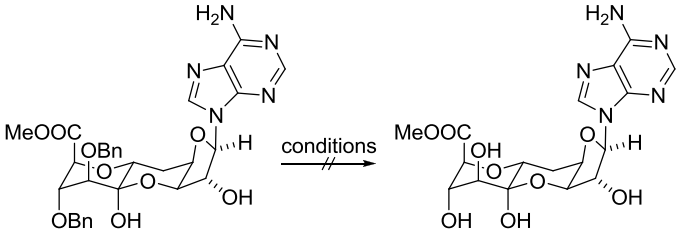


126 **128**

Entry	reaction conditions	Isolated yield
1	H_2 (6 bar), Pd/C, MeOH, RT, 18 h	no reaction
2	H_2 (8 bar), $Pd(OH)_2$/C, MeOH, RT, 15 h	no reaction
3	H_2 (8 bar), $Pd(OH)_2$/C, AcOH, RT, 15 h	no reaction
4	$HCOONH_4$, $Pd(OH)_2$/C, MeOH, RT, 15 h	decomposition
5	H_2, Raney-Ni, MeOH, RT, 15 d	decomposition
6	$FeCl_3$, CH_2Cl_2, RT, 12 h	decomposition
7	BBr_3, CH_2Cl_2, –78 °C to RT, 3 h	decomposition
8	DDQ, CH_2Cl_2, H_2O, RT, 8 d	decomposition
9	Li, NH_3, EtOH, –78 °C	decomposition

Next, we investigated the deprotection of compound **127**. Again, no reaction was observed with palladium as catalyst (Table 3, entries 1–3). Only 20% of a not further characterized monobenzylated product was isolated when substrate **127** was applied to radical lithium 4,4'-di-*tert*-butyldiphenyl (LDBB) deprotection conditions (as indicated by ^{1}H-NMR spectroscopy and mass spectrometry) (Table 3, entry 4).

Table 3. Conditions to debenzylate compound **127**.

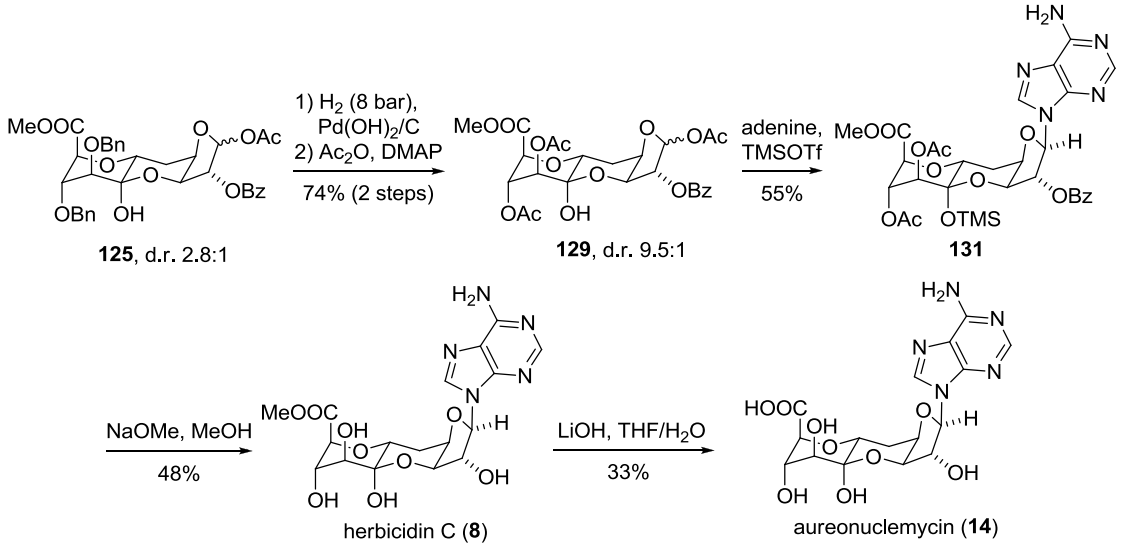


127 herbicidin C (**8**)

Entry	reaction conditins	Isolated yield
1	H_2, Pd/C, MeOH, RT, 17 h	no reaction
2	H_2, Pd/C, EtOAc, RT, 16 h	no reaction
3	H_2, PtO_2, MeOH, RT, 5 h	no reaction
4	LDBB, THF, -78 °C	20% monodebenzylation

Since debenzylation was found to be impossible at the end of the synthesis, the two remaining benzyl protecting groups in **127** had to be swapped for acetyl groups at this stage

yielding tricyclic intermediate **129** (Scheme 31).[vi] Glycosylation under the previously established conditions were also successful with substrate **129**, and glycosylamine **131** was isolated in 55% yield. Global deprotection under Zemplén conditions gave herbicidin C (**8**) as a colorless solid. The identity of our synthetic material was confirmed by detailed spectroscopic studies, including NMR titration with an authentic sample of the natural product. Saponification of the base-labile herbicidin C (**8**) under mild conditions yielded aureonuclemycin (**14**), the third member of the herbicidin class.



Scheme 31. Total syntheses of herbicidin C (**8**) and aureonuclemycin (**14**).

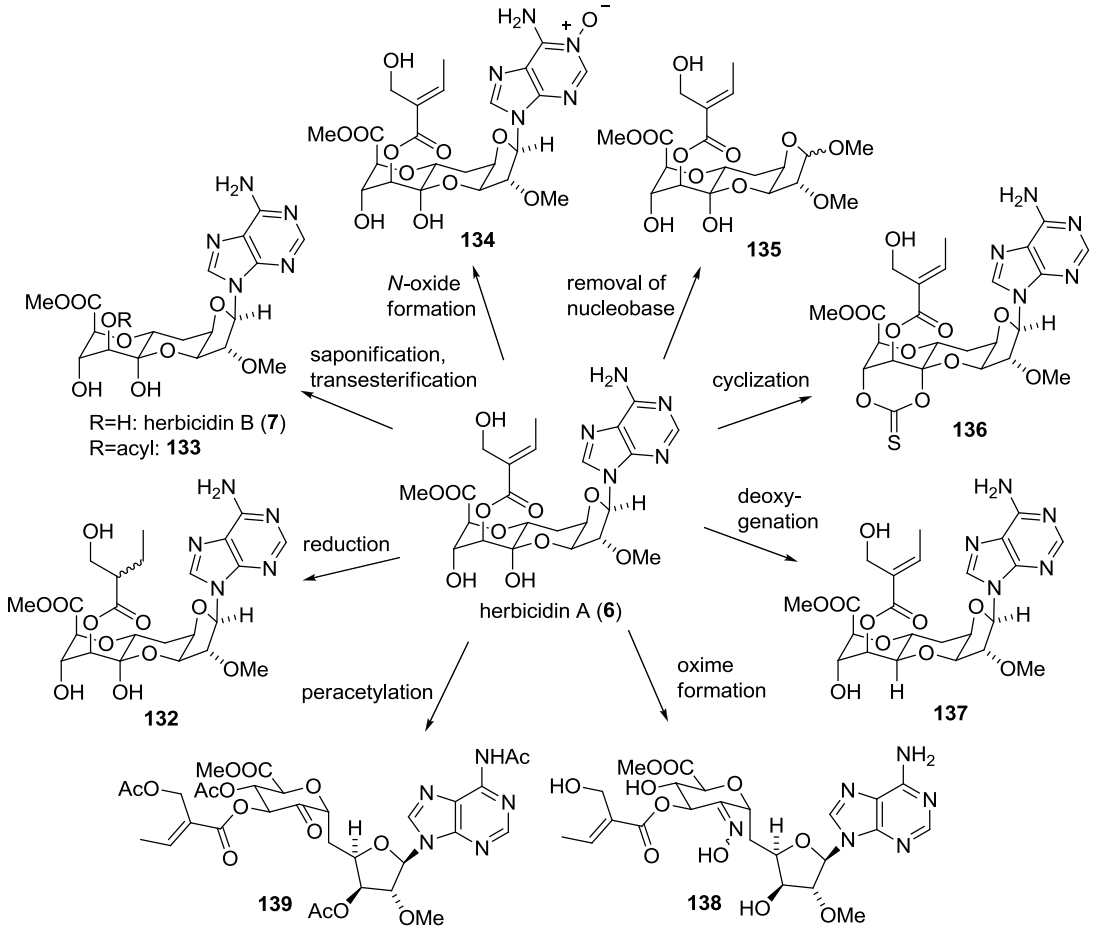
Overall, we developed an efficient and flexible total synthesis of two complex undecose nucleoside antibiotics, namely herbicidin C (**8**) and aureonuclemycin (**14**). Our route integrates a stereoselective *C*-glycosylation with several reagent-controlled stereoselective transformations and a surprisingly facile and highly diastereoselective late-stage *N*-glycosylation. Our synthetic strategy could give rise to several other members of the class and opens the opportunity to prepare a wide range of derivatives, which could be investigated in course of the SAR study.

[vi] Monobenzylated compound **130** was observed as a side product of the reductive double debenzylation (see Experimental Section).

6. Preparation of Compounds for SAR Study with Bayer CropScience AG

The biological and structural features make the herbicidins interesting targets for both, total synthesis and lead structure search. Every isolated intermediate of the synthetic route developed was sent to Bayer CropScience AG for biological activity testing, regardless of its structurally resemblance to the natural product. A list of all the compounds that were prepared for testing is attached in the appendices.

In addition, herbicidin A (**6**) was provided by Bayer CropScience AG for derivatization of the actual natural product. Different one- or two-step transformations were envisioned for the derivatization of herbicidin A (**6**) to furnish potentially bioactive compounds (Scheme 32).



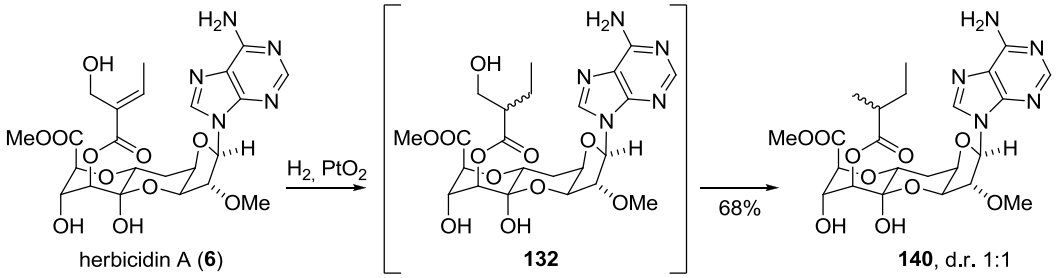
Scheme 32. Envisioned derivatives of herbicidin A (**6**) for structure-activity relationship (SAR) study.

First, we focused on the ester side chain. Reduction of the double bond should give saturated ester **132**, while saponification would provide herbicidin B (**7**), which itself could be esterified with alkyl carboxylic acids to yield herbicidin analogs of type **133**. Next, we

envisioned modifications of the nucleobase, such as *N*-oxide formation (→**134**) or its removal (→**135**). Further transformation could target the hemiaminal at C-7 by converting the free hydroxy group to a cyclic thiocarbonate **136** or by removing the latter (→**137**). Finally, the more flexible ring-opened derivatives **138** and **139**, derived from oxide formation and peracetylation, would complete the attempt to modify most of the structural skeleton of herbicidin A (**6**), although much more derivatives are conceivable.

6.1. Derivatization of Herbicidin A

First, hydrogenation of herbicidin A (**6**) was expected to give alcohol **132**. After reduction with hydrogen gas and Adams' catalyst (PtO_2), saturated ester **140** was isolated as a 1:1 mixture of diastereomers (Scheme 33). Mechanistically, it was anticipated that intermediate **132** undergoes elimination of water and is again subjected to reduction.

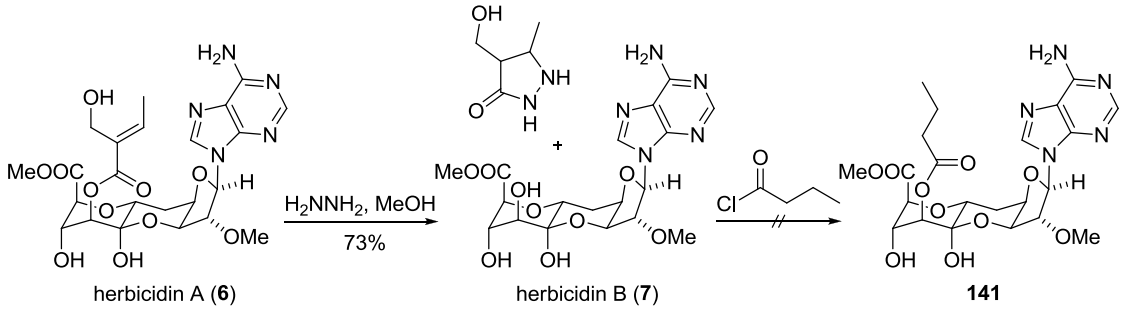


Scheme 33. Hydrogenation of herbicidin A (**6**).

The saponification of herbicidin A (**6**) to herbicidin B (**7**) in high yields was a challenge. The herbicidins, like other nucleoside natural products, are sensitive towards even mild basic reaction conditions (such as NaOMe or NH_3 in MeOH).[3b,8,10,52] The transformation of herbicidin A (**6**) to herbicidin B (**7**) described in the literature were typically carried out with phosphate buffer under careful control of the pH value, but even in these cases the reported yields were only 49%.[30b,30f]

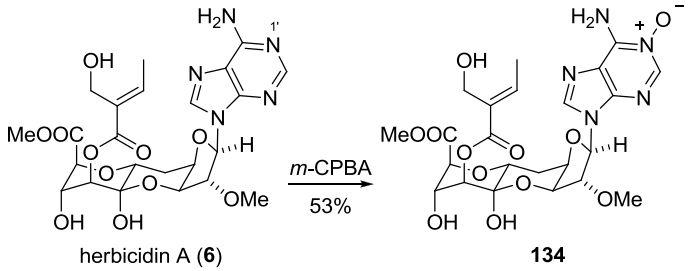
We reasoned that removal of the ester side chain of herbicidin A (**6**) might be more efficient, when hydrazine was used as a nucleophile since the formation of a 5-membered pyrazolidinone ring from the Michael system and hydrazine is feasible. Indeed, the yield of herbicidin B (**7**) was increased to 73% under these conditions. However, no byproduct derived from the side chain and hydrazine was detected (Scheme 34).

Further attempts to acylate herbicidin B (**7**) with butyric acid chloride failed and only intractable mixtures of products were obtained.



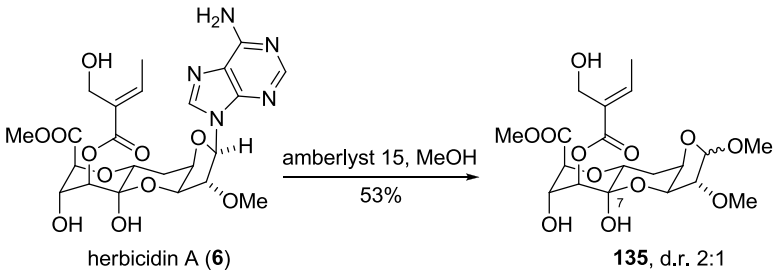
Scheme 34. Saponification of herbicidin A (**6**) to herbicidin B (**7**)

Next, we modified the nucleobase of herbicidin A (**6**) to afford derivatives for the bioactivity screening. The *N*-oxidation of adenine and adenosine with peracids is known to be regioselective for the 1'-position.[53] Thus, oxidation of herbicidin A (**6**) with *m*-CPBA afforded herbicidin *N*-oxide **134** in 53% yield (Scheme 35).



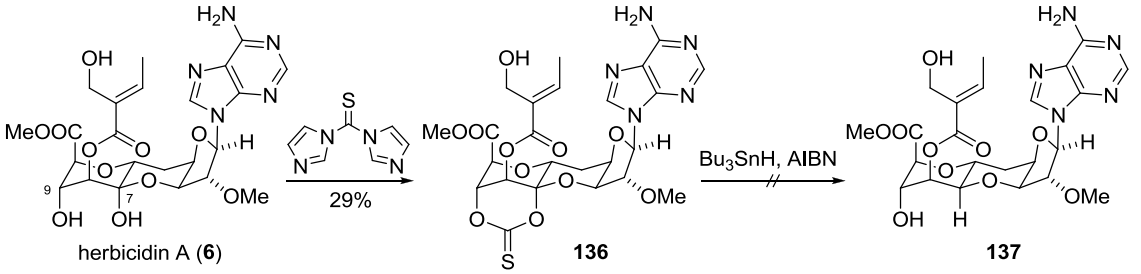
Scheme 35. Formation of *N*-oxide **134** from herbicidin A (**6**).

To prove that the bioactivity of herbicidin A (**6**) is based on the nucleobase, the latter was removed by methanolysis with amberlyst 15 at room temperature in 53% yield and 2:1 d.r. and the resulting derivative **135** was subjected to biological activity tests (Scheme 36). The methanolysis of herbicidin A (**6**) under harsher conditions (amberlyst 15, MeOH, 90 °C) was described in the literature.[30e] However, not only adenine was removed, but also the hemiacetal at C-7 was transformed into the respective methoxy ketal.



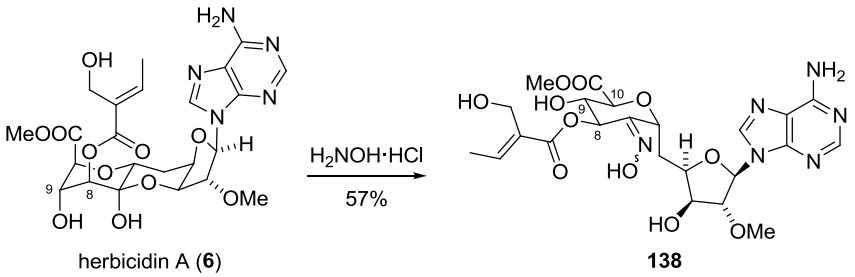
Scheme 36. Removal of the nucleobase of herbicidin A (**6**).

In order to prepare a cyclized derivative of herbicidin A (**6**), the hemiacetal at C-7 and the free alcohol at C-9 were converted into thiocarbonate **136**. This intermediate could potentially be deoxygenated under Barton-McCombie conditions. However, attempts to obtain the desired product **137** failed, presumably due to the poor solubility of substrate **136** in most organic solvents.



Scheme 37. Cyclization and unsuccessful deoxygenation of herbicidin A (**6**).

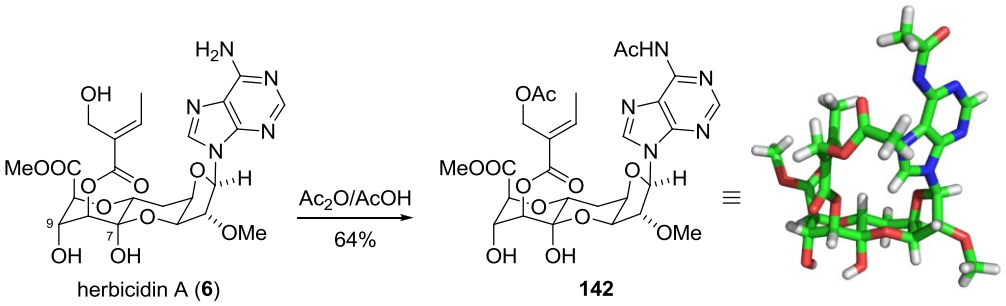
Due to its tricyclic undecose core, the herbicidin skeleton is relatively stiff. A more flexible derivative would be herbicidin oxime **138**, which was prepared from herbicidin A (**6**) and hydroxylamine (Scheme 38). By comparison of the coupling constants of the respective ^{1}H-NMR signals, it was shown that the 6-membered ring in **138** was inverted in order to have the substituents at C-8, C-9, and C-10 in equatorial position. Whereas the coupling constant of proton H-8 to H-9 in **6** has a size of $J = 3.3$ Hz, the corresponding coupling constant in oxime **138** is $J = 9.1$ Hz, indicating an axial-axial coupling of H-8 and H-9. This ring-opened derivative should provide information on the importance of the tricyclic undecose core on the bioactivity.



Scheme 38. Preparation of herbicidin oxime **138**.

According to our plans (*vide supra*, Scheme 32), we expected the peracetylation of herbicidin A (**6**) to give a second ring-opened compound **139**. Interestingly, only bisacetylation was observed yielding derivative **142**, although the reaction was carried out in a mixture of Ac_2O and AcOH as solvent (Scheme 39). It was speculated that the hydroxy group at C-9 is less reactive and/or sterically less accessible towards electrophiles. If the hemiketal at C-7 was

acetylated during the reaction and hydrolyzed back to the hemiketal during aqueous work-up remained unclear. The structure of **142** was also confirmed by X-ray crystallography.

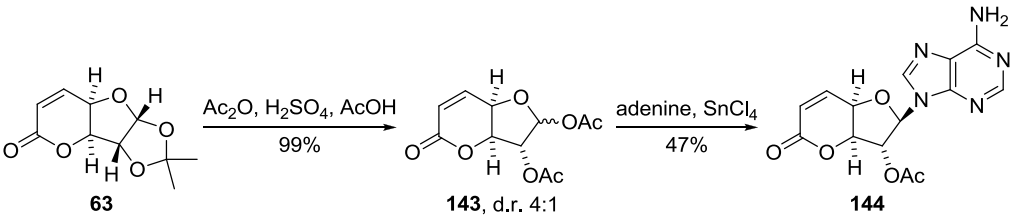


Scheme 39. Acetylation of herbicidin A (**6**).

Overall, herbicidin A (**6**) was derivatized at different positions of the molecule. Variations at the ester side chain, the nucleobase, the hemiketal, and the ring **B** provided a few derivatives which were sent to Bayer CropScience AG to give first insights of the relationship between the structure and the activity of the herbicidins.

6.2. Derivatives from the Right Side Approach

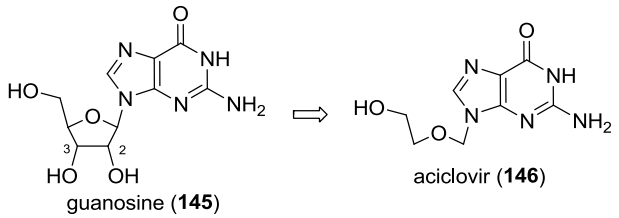
Our synthesis of the herbicidins possesses the potential to afford interesting derivatives for SAR study. Although these intermediates are structurally far away from the actual natural products, it was considered interesting to prepare compounds that have reduced complexity compared to the herbicidin skeleton to further investigate their bioactivity. Thus, cleavage of the acetonide in unsaturated lactone **63** and concomitant acetylation gave acetate **143** as a 4:1 mixture of diastereomers. Stereoselective *N*-glycosylation provided derivative **144**. This glycosylamine represents a reduced form of the herbicidin framework with ring **C** of the herbicidins undecose being completely absent.



Scheme 40. Preparation of derivative **144** from unsaturated lactone **63**, an intermediate from the right side approach.

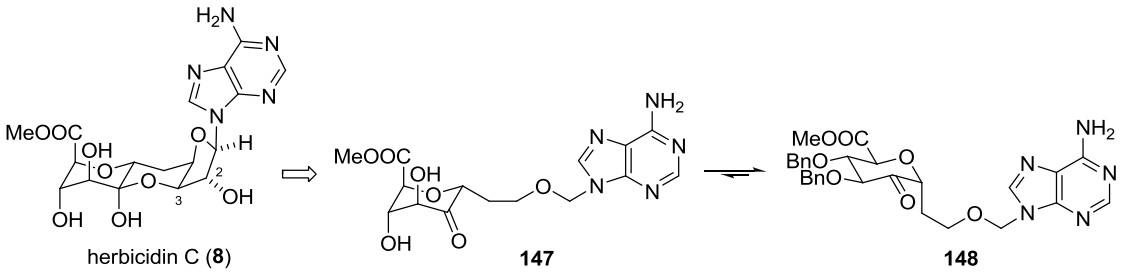
6.3. Derivatives from the Left Side Approach

In search for interesting derivatives for SAR testing, we were inspired by the antiviral drug aciclovir (**146**) (Scheme 41). The selective antiherpetic agent was discovered in the late 1970s and due to its extreme selectivity and low cytotoxicity, it was considered as the beginning of a new era in antiviral chemotherapy. Structurally, the carbohydrate moiety of guanosine (**145**) was reduced by the two carbon atoms C-2 and C-3.



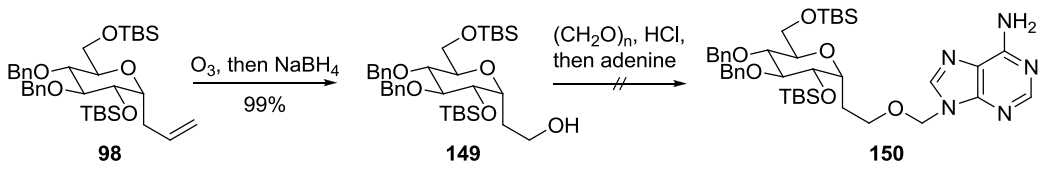
Scheme 41. Structural relationship of guanosine (**145**) and the antiviral drug aciclovir (**146**).

In analogy, we designed a herbicidin derivative lacking two of its carbon atoms, namely C-2 and C-3. The resulting compound **147** should immediately flip to its presumably more stable conformer **148**. This derivative should be accessible from the left side approach of the total synthesis.



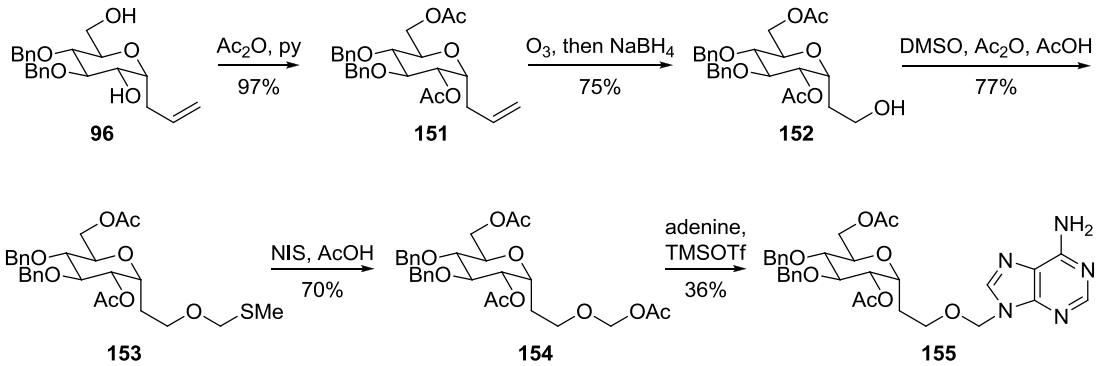
Scheme 42. Structural relationship of herbicidin C (**8**) and derivative **148**.

TBS ether **98** was chosen as a potential precursor to **148**. Its double bond was ozonolyzed and the secondary ozonide was reduced to afford alcohol **149** (Scheme 43). The chain elongation through formation of a chloromethyl ether with paraformaldehyde under acidic conditions and following reaction with adenine failed, due to the instability of the TBS ethers under these conditions.



Scheme 43. Attempts to synthesize TBS-protected glycosylamine **150**.

Therefore we decided to change the TBS ethers to more stable acetate groups (Scheme 44). Thus, diol **96** was protected with acetic anhydride and the resulting diacetate **151** was again ozonolyzed and subsequent reductive work-up gave alcohol **152**. Unfortunately, the formation of a chloromethyl ether with paraformaldehyde and HCl or trimethylsilyl chloride was again unsuccessful and we decided to elongate the chain with the help of a Pummerer reaction to methylthiomethyl (MTM) ether **153**. Direct coupling of **153** with adenine and sulfuryl chloride, as well as silylated adenine in the presence of *N*-bromosuccinimide were not successful and only decomposition of the substrate was observed. Therefore we converted thioether **153** with *N*-iodosuccinimide in the presence of acetic acid to acetate **154**, which was then *N*-glycosylated under our previously established conditions to provide glycosylamine **155**.



Scheme 44. Synthesis of glycosylamine **155**.

At this stage of the synthesis, we realized that further transformation toward the desired derivative **148** would be more challenging than initially anticipated. The yields of the glycosylation were lower than expected and the purification was only efficient with HPLC. We decided to stop the preparation of the herbicidin derivative **148** at this point since compound **96** was needed for the ongoing total synthesis. Nevertheless, compound **155** is still an interesting intermediate which was sent to Bayer CropScience AG for activity testing.

Finally, we were able to utilize both routes of our total synthesis to prepare interesting intermediates for SAR testing. Although derivative **148** was not completed, progress was made towards finishing this analog and only adjustment of the oxidation states remained.

7. Conclusions

In summary, we have achieved the first total synthesis of two complex undecose nucleoside antibiotics, namely herbicidin C (**8**) and aureonuclemycin (**14**). The first approach converged from the ring **A** of the herbicidin undecose. Establishment of the second ring **B** was achieved by following literature protocols. However, the route was not efficient enough to prepare decagram quantities of material and was thus abandoned. Nevertheless, we eventually assembled all carbon atoms of the undecose moiety although the right oxidation states and stereochemistry at several atoms were not established. Furthermore, the closure of the last ring **C** was not realized.

In our second attempt to synthesize the undecose sugar, ring **C** was first constructed already with the right stereochemistry of its substituents. The advanced intermediate **98** was elongated with an open chained form of ring **A**. Thereby, we had to overcome unexpected stereochemical problems, but finally the whole undecose carbohydrate was arranged into the desired tricyclic herbicidin core **129**. The challenging late-stage glycosylation from the sterically more congestive concave side proceeded surprisingly facile and was stereochemically controlled by a neighboring group. Global deprotection then provided the natural products herbicidin C (**8**) and aureonuclemycin (**14**).

In further synthetic investigations, we prepared a range of simple derivatives of herbicidin A (**6**) for SAR study on the herbicidins in cooperation with Bayer CropScience AG. These synthetic transformations included variation of the ester side chain, modification of the nucleobase, derivatization of the hemiketal, and synthesis of a ring-opened derivative of herbicidin A (**6**).

In addition, our synthetic approaches were used in order to prepare structurally less complex derivates of the herbicidin framework. From the right side approach, derivative **144** was prepared, which lacks ring **C** but has the complete adenine moiety established at ring **A**. The left side approach afforded the incomplete derivative **155**, which also has the adenine attached. However, the oxidation states and the final deprotection remained to be established.

With this work, we contribute to expand the chemistry of the herbicidins and provide a platform for the preparation of structurally related, potentially bioactive derivatives thereof.

Chapter II: Synthesis Toward the Alkaloid Stephadiamine[vii]

8. Introduction

The history of alkaloid natural products and their connection to humankind is long and ambivalent. Mostly isolated from plant sources,[55] these natural products and their parent organisms have been and are still used as food spices, currency, ritual tools, hallucinogenic drugs and poison.[56] One of the most prominent and early applications of an alkaloidal poison is reported in the context of the execution of Socrates in 399 BC by means of drinking an extract of poison hemlock (*Conium maculatum*), the main biologically active compound of which is coniine (**156**).[57] Other poisonous alkaloid containing plants and the corresponding natural products have also been misused by humankind. Curare for example, with its main neurotoxic ingredient tubocurarine (**157**), was used as an arrow poison by South American indigenous people.[58] Strychnine (**158**), gained from *Strychnos nux-vomica*, was applied as doping agent, analgesic and poison.[59] Furthermore, the addictive effect of tobacco and the hallucinogenic nature of *Atropa belladonna* are based on the biologically active alkaloids nicotine (**159**)[60] and atropine (**160**)[58] respectively (Figure 5).

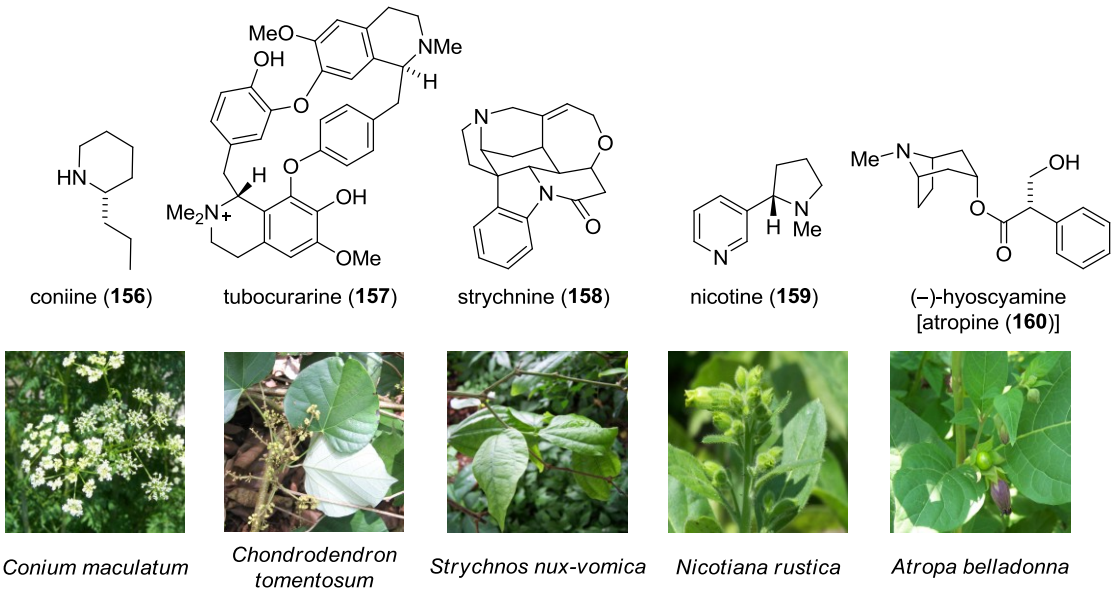


Figure 5. Famous alkaloid structures: coniine (**156**), tubocurarine (**167**), strychnine (**158**), nicotine (**159**), and atropine (**160**), as well as their natural sources: *Conium maculatum*,[61] *Chondrodendron tomentosum*,[62] *Strychnos nux-vomica*,[61] *Nicotiana rustica*,[61] *Atropa belladonna*.[61]

[vii] This project was performed in cooperation with A. Hager, a PhD student in the Trauner group. The chapter was written together and can be found also in her PhD thesis.[54] Both authors contributed equally to this work.

Although only a limited number of simple amino acid derived building blocks are involved in the biogenesis of alkaloids, the incorporation of other polyketide and terpenoid structures allow for a broad structural diversity and complexity within these natural products.[55,58] As a result, a variety of biological activities are known among alkaloids. For example, they can activate, block or deactivate several ion channels, or alternatively bind to DNA affecting protein biosynthesis.[63]

One of the most famous and historically important alkaloids is (–)-morphine (**161**), the main component of opium (Figure 6).[64] Its ambiguous biological activities are both, blessing and curse to mankind: on one hand alkaloid **161** releases pain, on the other it makes addictive. Most likely, opium poppy (*Papaver somniferum*), the main source of (–)-morphine (**161**), was cultivated and used by Sumerians as medicine and hallucinogenic drug already more than 4000 years ago.[65] In the following centuries, the use of opium, the dry milky juice of the opium poppy fruit, became widely common in China, the Arabian countries, and throughout the whole world. The addiction to (–)-morphine (**161**) provoked wars and is still one of the major problems worldwide. However, (–)-morphine (**161**) is used as one of the most potent analgesic drugs up to date.[64]

Although *Papaver somniferum* has been cultivated for centuries, it was only in 1804 that (–)-morphine (**161**) was isolated and identified as the main biologically active ingredient of opium poppy by F. Sertürner (Figure 6).[66] Since then, several biological studies and chemical syntheses of morphine and its analogs have been performed.[67] In fact, this natural product and its intriguing structure is still an inspiration for synthetic chemists even nowadays.

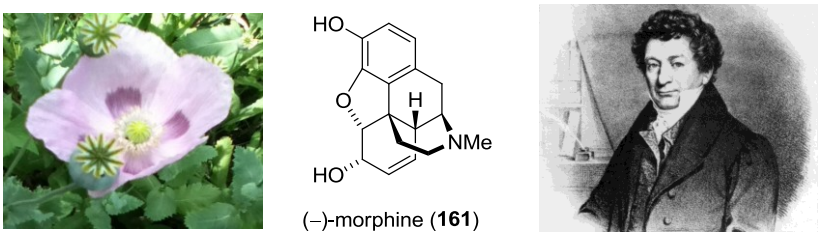


Figure 6. *Papaver somniferum* (left),[61] the natural source of (–)-morphine (**161**) (middle) and a portrait of its discoverer F. Sertürner (right).[68]

During the last centuries many other alkaloids with the common morphinan skeleton have been isolated and characterized (Figure 7).[69] The backbone features a benzylic all carbon quaternary center in C-13 and a nitrogen containing stereocenter with (*R*)-configuration at C-9. In 1964, Y. Inubushi and co-workers were able to isolate a new alkaloid showing a modified morphinan skeleton.[70] Hasubanonine (**162**) eventually turned out to be the parent compound of the new class of hasubanan natural products, all possessing the typical hasubanan skeleton, isomeric to the morphinans. Mostly isolated from various *Stephania* species, which were also

used in traditional Chinese medicine, more than 40 hasubanans have been identified to date.[69a] In contrast to the morphinans, the nitrogen substituent in the hasubanan skeleton is moved from C-9 to the C-14 position, forming a 5-membered ring, which now incorporates a nitrogen containing tetrasubstituted carbon center (NTC). The resulting aza-propellane skeleton can vary in its oxidation states. In addition, the hasubanans differ from morphinans in their absolute stereochemistry since they represent the opposite enantiomeric series of the skeleton.[71] Although the biological activities of hasubanan alkaloids are not as remarkable as those of the morphine derived structures, they have been the subject of extensive chemical research since the 1970s, culminating in various total syntheses of these natural products.[72]

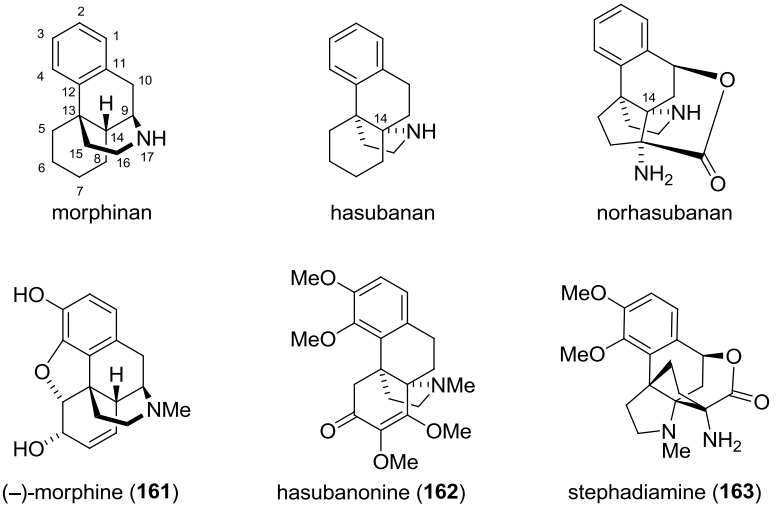


Figure 7. The structures of morphinan, hasubanan and norhasubanan skeletons, as well as the corresponding parent compounds morphine (**161**), hasubanonine (**162**) and stephadiamine (**163**).

Along with the investigation of *Stephania* species, another new alkaloid type related to the morphinans was discovered. Thus far, the only identified representative of these norhasubanan alkaloids is stephadiamine (**163**).[11] As in the case of hasubanans, the norhasubanan core possesses the opposite configuration of the morphinan skeleton and an NTC center at C-14 position. Additionally, one of the rings is rearranged forming a pentacyclic system with a second NTC center, featuring a primary amine (Figure 7).

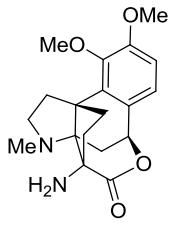
Many synthetic routes to morphinan and hasubanan structures have been developed in the last century and still a huge synthetic interest in this type of compounds exists. Thus, it is surprising that no synthetic approach to the norhasubanan stephadiamine (**163**) has yet been published, despite its structural beauty. Therefore, the goal of this work was the development of the first and efficient total synthesis of stephadiamine (**163**) with the potential of an enantioselective NTC installation.

9. Isolation, Biology and Properties of Stephadiamine

9.1. Isolation and Structure

The common scrambler *Stephania japonica*, often found in south-east Asia and the Pacific region, is known to possess various medicinal properties. Parts of this plant and its extracts are used in the Chinese and Taiwanese folk medicine as anti-diarrheal, anti-febrile drugs, and as a remedy against malaria and cholera.[11,73] Biological investigations of alcoholic extracts of this species have shown that *S. japonica* is a rich source of hasubanan alkaloids.[69b,74] In the course of metabolome investigations of *S. japonica* in 1984, T. Ibuka and co-workers were able to isolate and characterize a minor component of the ethanolic plant extract representing a novel type of alkaloidal structure, the pentacyclic stephadiamine (**163**), which was isolated as a colorless solid (Figure 8).[11]

Stephania japonica



stephadiamine (**163**)

Figure 8. Leaves of *Stephania japonica* (left)[75] and the structure of stephadiamine (**163**) (right).

The quantity of the obtained novel natural product was not adequate for chemical degradation studies. Nevertheless, T. Ibuka and co-workers established the structure of the molecule using IR and ^{1}H-NMR spectroscopic analysis as well as mass spectrometry. Eventually, they were able to obtain X-ray structures of stephadiamine (**163**) and its derivative *N*-*p*-bromobenzoyl stephadiamine (**164**), clarifying the connectivity and the absolute stereochemistry of the compound (Figure 9).[11] Strictly, the lactonic *C*-norhasubanan **163** is not a member of hasubanan the alkaloid family. This type of skeleton has not been previously found in nature and to our knowledge, stephadiamine (**163**) is the only representative of norhasubanan alkaloids identified thus far.

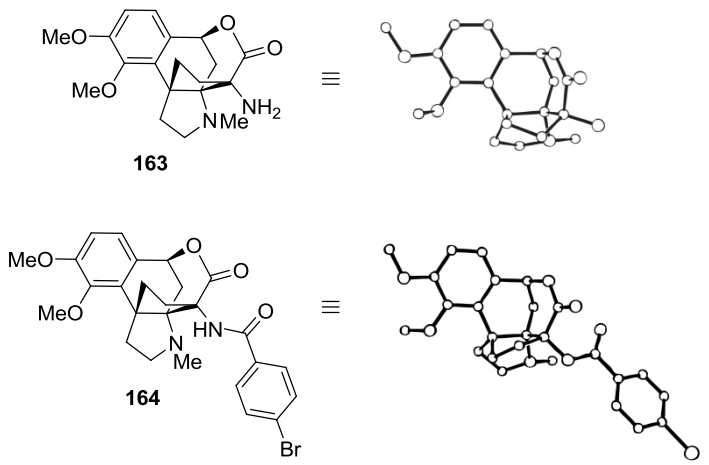


Figure 9. Structure and X-ray analysis of stephadiamine (**163**) (top) and *N*-*p*-bromobenzoyl stephadiamine (**164**) (bottom).

The basic pentacyclic core of the natural product **163** features a tetralin system, which is bridged by a 6-membered lactone moiety and connected to a pyrrolidine ring further bridged by two methylene groups forming a propellane structure (Figure 10). Stephadiamine (**163**) possesses four stereogenic centers, two of which are benzylic. An all-carbon quaternary stereocenter at C-13 and an oxygen containing chiral center at C-10 are joined by two NTCs at the C-7 and C-14 position. One of the latter includes a tertiary amine portion (C-14), whereas the second (C-7) bears a primary amine as the nitrogen substituent. However, in contrast to hasubanan alkaloids, the former ring **C** is rearranged to a 5-membered system and the 6-membered lactone moiety forms the new ring **E** (Figure 8). In addition, hasubanan alkaloids show only one nitrogen atom, whereas stephadiamine (**163**) possesses two nitrogen functionalities.

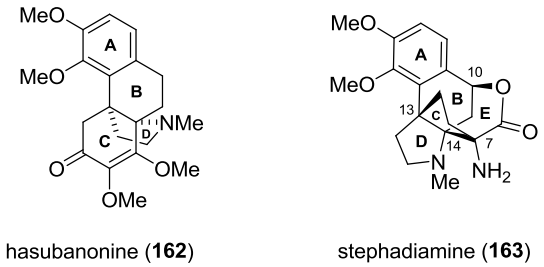
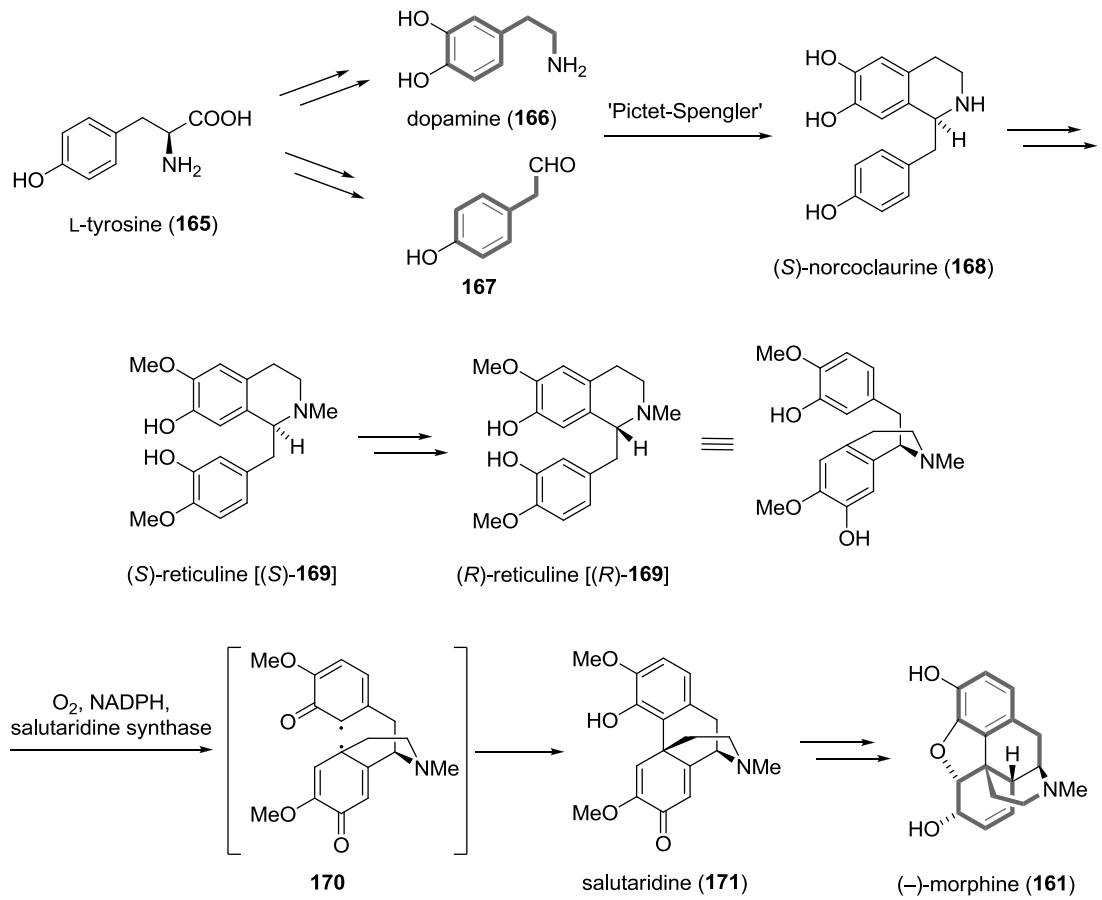


Figure 10. Skeletons of hasubanonine (**162**) and stephadiamine (**163**).

The synthetic challenge presented by the complex structure of stephadiamine (**163**) with two contiguous NTC centers and the fact that it has not been synthesized thus far prompted us to develop a total synthesis of this natural product.

9.2. Biosynthetic Considerations

The structural resemblance of the morphinan, hasubanan and norhasubanan skeleton discloses a connection of the biogenesis of the natural products belonging to these three classes of alkaloids. The broad interest in morphine (**161**) culminated in extensive studies on the biosyntheses of several benzyltetrahydroisoquinoline alkaloids.[76] It was shown that in nature, (–)-morphine (**161**) is derived from dopamine (**166**) and 4-hydroxyphenylacetaldehyde (**167**), two simple building blocks originating from the amino acid tyrosine (**165**) (Scheme 45).[58]

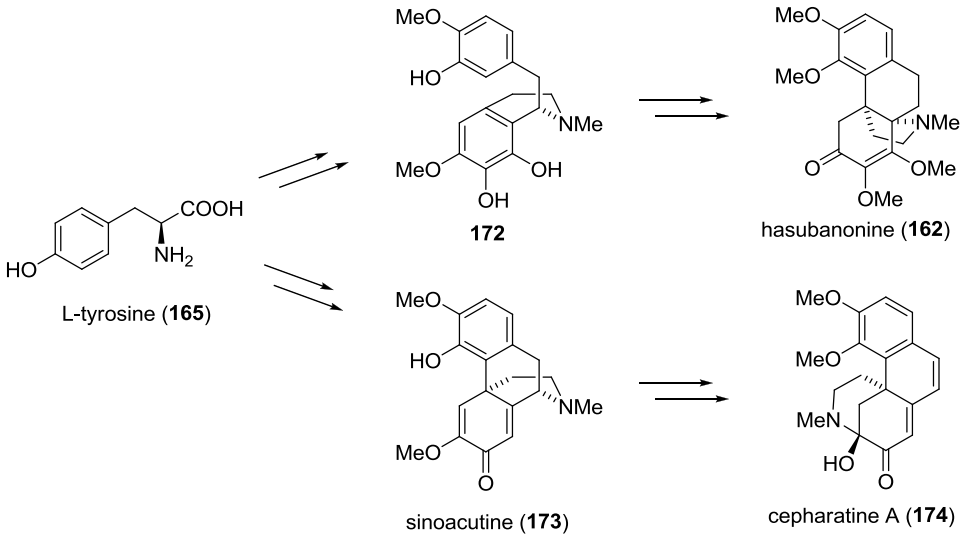


Scheme 45. Biosynthesis of (–)-morphine (**161**).

It was suggested that both building blocks are combined in an enzyme promoted Pictet-Spengler-type reaction to the benzyltetrahydroisoquinoline core of (*S*)-norcoclaurine (**168**), which is then oxidized and methylated to yield (*S*)-reticuline [(*S*)-**169**]. An enzyme catalyzed oxidation/reduction process forms its (*R*)-enantiomer (*R*)-**169**, a key compound in all morphinan alkaloid biosyntheses. Compound (*R*)-**169** is cyclized *via* an enzymatically formed diradical **170** to salutaridine (**171**), by a selective intramolecular *o*,*p*-phenoloxidative coupling, which is one of the most important reactions in the morphinan biosyntheses. In tetracycle **171**, the major

framework of (–)-morphine (**161**) is already established.[77] Finally, further enzyme catalyzed transformations afford **161**.[58]

In the case of the parent hasubanan alkaloid hasubanonine (**162**), the biogenesis was investigated less thoroughly. Feeding experiments of ^{14}C-labelled isoquinolines to *S. japonica* performed by A. R. Battersby in the early 1980s led to the proposal that, in analogy to morphine biogenesis, phenoloxidative coupling of tyrosine derived isoquinoline **172**, an oxidized version of (*R*)-reticuline [(*R*)-**169**], is involved in the formation of hasubanonine (**162**) (Scheme 46).[78] However, the detailed sequence of the transformations involved in the biosynthesis of hasubanonine (**162**), especially the installation of the 5-membered pyrrolidine moiety was yet to be explained. In the case of cepharatine A (**174**), another hasubanan alkaloid, Y.-H. Zhang and co-workers suggested the incorporation of sinoacutine (**173**), the enantiomer of salutaridine (**171**), which is involved in morphine biosynthesis (Scheme 46).[73]



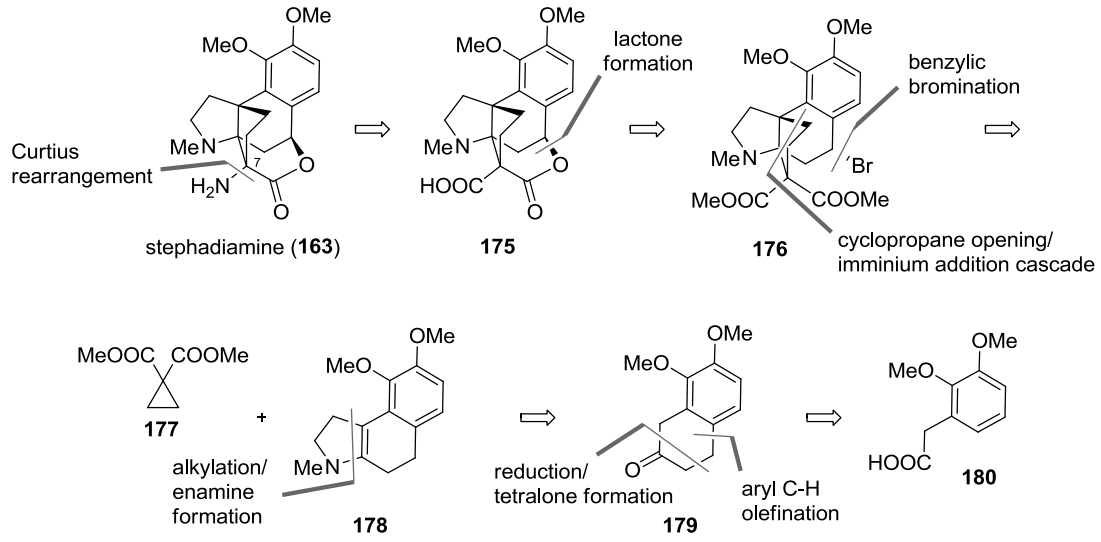
Scheme 46. Proposed biosyntheses of hasubanan alkaloids hasubanonine (**162**) and cepharatine A (**174**).

Unfortunately, the biogenesis of our target compound stephadiamine (**163**) was not investigated. However, its resemblance to the morphinan and hasubanan structures again suggests the incorporation of L-tyrosine (**165**). Further speculation along these lines would result in the assumption that a Pictet-Spengler-type reaction and a phenoloxidative coupling are also involved in stephadiamine biosynthesis. In addition, a skeletal rearrangement leading to dearomatization and ring contraction to form rings **C** and **E** would have to take place.

10. Results and Discussion – Toward Stephadiamine[viii]

10.1. Strategy and Retrosynthetic Analysis of Stephadiamine

One of the major challenges posed by the envisioned total synthesis of stephadiamine (**163**) is the assembly of the two contiguous NTC centers. Among many methods for the synthesis of NTC centers, Curtius rearrangement is a powerful tool and has been applied successfully in total syntheses of various alkaloids, even in sterically hindered cases.[79] The retrosynthetic strategy we have chosen involves a Curtius rearrangement, which would introduce the NTC center at C-7 position comprising a primary amine as substituent. Thus, stephadiamine **163** could be traced back to carboxylic acid **175** (Scheme 47). At this stage, we envisaged to introduce the lactone moiety in **175** by means of an intramolecular bromine replacement leading to diester **176** as a logical precursor. The propellane skeleton of bromide **176** could be assembled by means of a benzylic bromination and a homoconjugated addition/Mannich cascade, involving dimethyl cyclopropane-1,1-dicarboxylate (**177**) and enamine **178** as reaction partners. In turn, enamine **178** could be derived from β-tetralone **179** through a stepwise enamine formation/alkylation sequence. The tetralone system **179** is known to be accessible from the simple commercially available building block 2-(2,3-dimethoxyphenyl)acetic acid (**180**) in several steps involving a C–H activation process and a cyclization reaction.[12]



Scheme 47. Retrosynthetic analysis of stephadiamine (**163**).

The synthetic approach toward stephadiamine (**163**) is both novel and challenging in its nature. Not only does it involve a cyclopropane opening/aminoalkylation cascade, which is

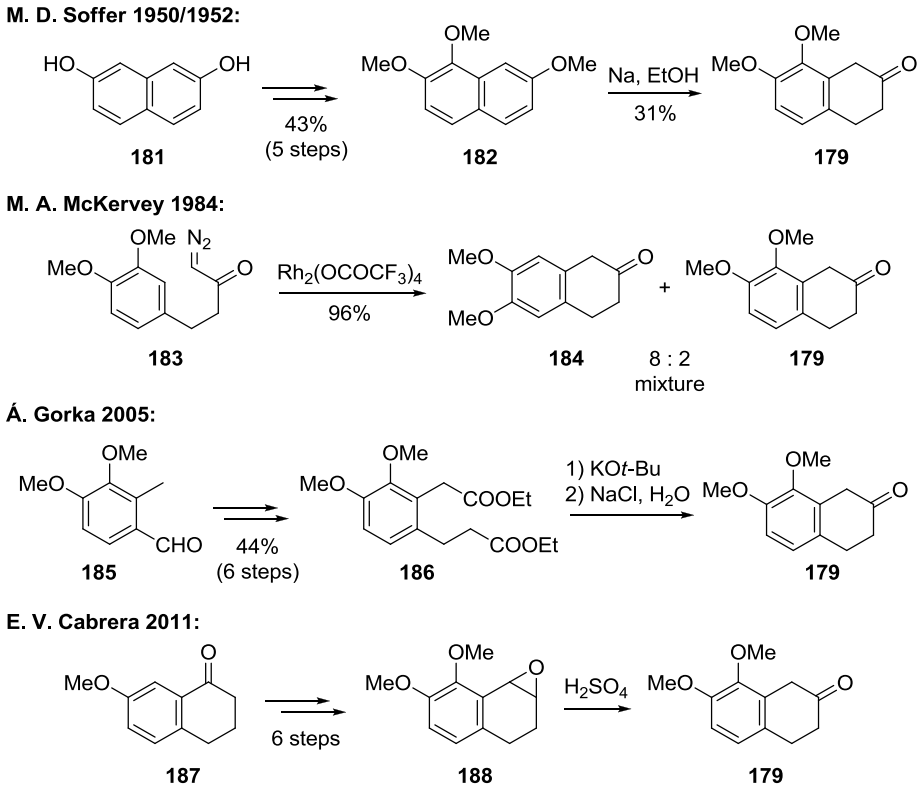
[viii] The experimental work of this chapter was performed together with N. Vrielink, an undergraduate researcher in the Trauner group.

scarcely represented in literature and, to our knowledge, has never been used in total synthesis thus far. The strategy also requires the formation of known enamine **178** as one of the intermediates, which is has been described to be oxygen and temperature sensitive.[13c] In addition, the assembly of tetralone **179** relies on a novel type of chemistry involving a C–H activation process.

Despite its challenging nature, the envisioned approach offers a high flexibility. For example, β-tetralone **179** represents a key intermediate, which could function as a branching point for various synthetic approaches toward the total synthesis of stephadiamine (**163**). Furthermore, the assembly of enamine **178** starting from β-tetralone **179** can proceed through several different approaches by interchanging alkylation and enamine formation processes. Finally, the cyclopropane opening reaction (→**176**) requires an activation of dimethyl cyclopropane-1,1-dicarboxylate **177** with a Lewis acid.[80] At this stage, the use of a chiral Lewis acid could hold promise to even access **163** in enantioenriched form.

10.2. Assembly of β-tetralone

Our first goal in the total synthesis of stephadiamine (**163**) was to access dimethoxy β-tetralone **179**. Several syntheses of this compound have been described in the literature, which will be shortly discussed herein (Scheme 48).

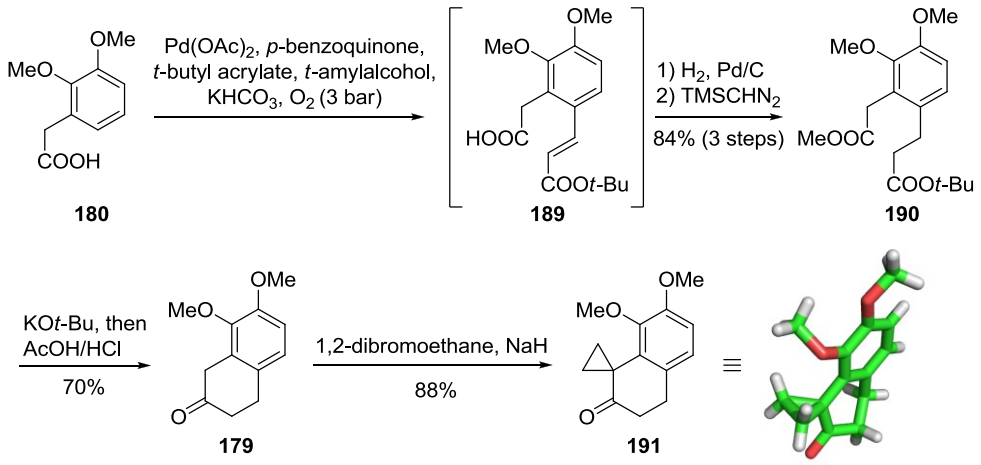


Scheme 48. Literature known syntheses of β-tetralone **179**.

The earliest synthesis was published in 1950/1952 by M. D. Soffer and co-workers along the lines of their work toward morphine. It focused on the dearomatization of trimethoxynaphthalene **182** under Birch conditions as a key step.[81] Unfortunately, they needed 5 steps to synthesize **182** starting from dihydroxynaphthalene **181** and the final dearomatization step provided the desired tetralone **179** in unsatisfactory yield of only 31%. More than 30 years later, M. A. McKervey and co-workers published a rhodium(II) catalyzed C–H insertion of diazoketone **183** providing the desired 5,6-dimethoxytetralone (**179**) only as a minor regioisomer and mostly the undesired *para*-cyclized product **184**.[82] In 2005, Á. Gorka and co-workers synthesized **179** starting from benzaldehyde derivative **185**.[83] First, they assembled the diester **186** in 6 steps and then cyclized it in a low yielding two step protocol to **179**. A shorter route to β-tetralone **179** was developed by E. V. Cabrera and co-workers in 2011, who converted the commercially available 7-methoxy-1-tetralone (**187**) to epoxide **188** in four steps. In the final step, under strongly acidic conditions, the epoxide **188** was opened to β-tetralone **179**.[84]

All described routes described thus far are lengthy, include low yielding steps, and/or employ expensive catalysts. In addition, the starting materials are not easily available and the key intermediates have to be prepared over several steps. Eventually, it seemed that the best, shortest and most elegant way to assemble **179** would be a synthesis based on a procedure published by J.-Q. Yu and co-workers in 2010 (Scheme 49).[12] The synthesis commences with a elegant palladium catalyzed aryl C–H olefination of dimethoxyphenylacetic acid **180** with *tert*-butyl acrylate as a coupling partner. This step necessitated careful optimization as the procedure reported by J.-Q. Yu and co-workers lead only to mixtures of starting material and traces of product. However, application of oxygen overpressure of 3 bar in an autoclave apparatus furnished the corresponding unsaturated ester **189** exclusively. Without further purification, a reduction/esterification sequence was performed providing the diester **190** in 84% over three steps. The synthesis of β-tetralone **179** was accomplished by means of a cyclization/decarboxylation process, which gave **179** in 70% yield. This short protocol provided the desired β-tetralone **179** in only four steps, three of which were carried out without column chromatography, in an overall yield of 59% on multigram scale.

Next, β-tetralone **179** was converted to the corresponding cyclopropane **191** in 88% yield, which could serve as an alternative precursor for the assembly of enamine **178** (*vide supra*, Scheme 47). The structure of **191** was confirmed by X-ray crystallography (Scheme 49).

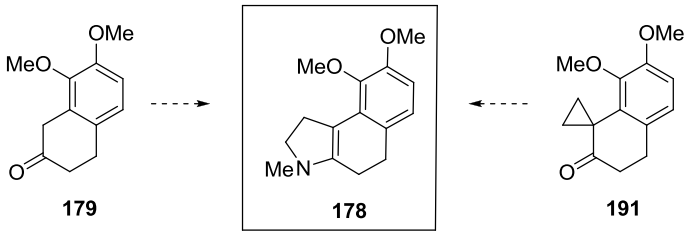


Scheme 49. Synthesis of β-tetralone **179**,[12] the assembly of the corresponding cyclopropane **191**, and X-ray structure of **191**.

With β-tetralone **179** and cyclopropane **191** in hand, first attempts toward the synthesis of enamine structure **178** were undertaken.

10.3. Toward Tricyclic Enamine

As outlined in the retrosynthetic analysis, the preparation of enamine **178**, a key intermediate in the total synthesis of stephadiamine (**163**), could start directly from tetralone **179** with a subsequent amination/alkylation sequence (Scheme 50). Alternatively, it is also reasonable that the formation of **178** could be achieved by means of a cyclopropane-opening reaction of **191**, followed by a cyclization with methylamine as nucleophile.

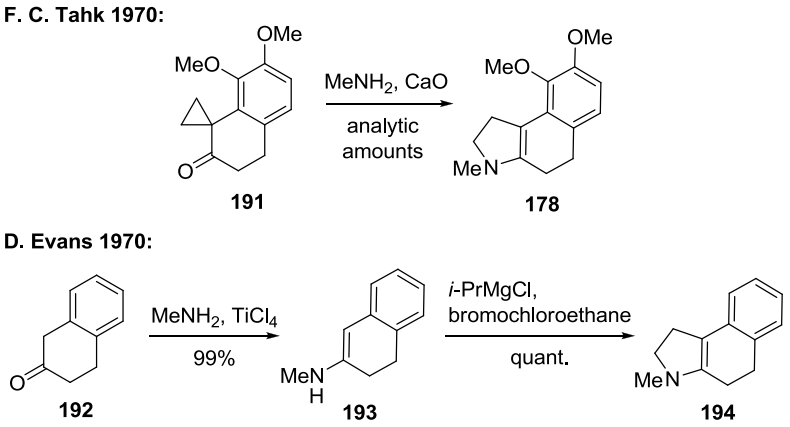


Scheme 50. Envisioned assembly of the tricyclic enamine structure **178**.

10.3.1. Previous Work on the Formation of the Key Enamine

Enamine **178** presents a methoxy substitution pattern, typical for morphinan and hasubanan alkaloids (*vide supra*, Figure 10). Thus, the synthesis of this portion was of great interest to synthetic chemists. It is therefore astonishing that compound **178** was synthesized only once by F. C. Tahk and co-workers in 1970 in the context of their work on cepharamine (Scheme 51).[13c] The enamine **178**, which was described as air sensitive, was made from cyclopropane **191** by means of a homoconjugated addition of methylamine followed by cyclization. To

achieve this transformation, Tahk and co-workers had to apply harsh conditions including heating as well as high pressure and long reaction times. Unfortunately, only analytical amounts of the product **178** could be isolated and characterized despite the fact that 1 gram of starting material was employed in this reaction.



Scheme 51. Literature known syntheses of enamine **178** and its derivatives.

In the same year D. A. Evans and co-workers published their work on the synthesis of the hasubanan carbocyclic system (Scheme 51).[13b,85] One of the key intermediates used in this approach was enamine **194**, which lacked the two methoxy groups present in **178**. Starting from tetralone **192**, Evans *et al*. achieved the assembly of tricycle **194** *via* enamine **193** by a two step protocol involving amination of tetralone **192** and alkylation of enamine **193** with bromochloroethane. This procedure is high yielding and could be performed on gram scale.

In addition to the described protocols, the formation of enamines of type **178** was the subject of two other publications.[86] Both are based on the sequence established by Evans and co-workers. Yet, the synthesis of a system containing two methoxy groups as present in **178** using the Evans protocol has not been reported to date.

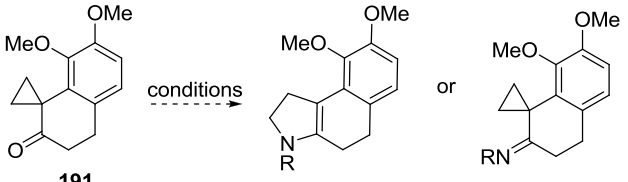
With this information in background, the synthesis enamine **178** was attempted following one of the described procedures or variations of them.

10.3.2. Studies toward Enamine System

Initially, attempts in the synthesis of enamine **178** focused on the homoconjugated addition of amine nucleophiles to cyclopropane **191** as described by Tahk and co-workers (*vide supra*, Scheme 51). In order to improve the yield of the transformation, cyclopropane **191** was subjected to several reaction conditions involving methylamine or benzylamine as nucleophiles with the expectation that enamines **178** and **195** or the corresponding imines **196** and **197** would be formed (Table 4). First, reaction conditions including methylamine solutions and methyl amine hydrochloride salt were investigated (Table 4, entries 1–7). As it is known that acids such as ytterbium(III) triflate or *p*-toluenesulfonic acid can activate cyclopropane substituted ketones

and force the cyclopropane opening, they were also explored as additives.[80] Despite the variation of temperature and solvents only starting material was re-isolated in most cases without observing the formation of the desired products. In the presence of acidic additives, decomposition and formation of complex mixtures occurred (Table 4, entries 1 and 2).

Table 4. Screening conditions applied for synthesis of enamine **178** and **195** and corresponding imines **196** and **197**.



191

R = Me **178**
R = Bn **195**

R = Me **196**
R = Bn **197**

Entry	reaction conditins	Observation
1	$MeNH_2$ in THF, MeCN, $Yb(OTf)_3$, 80 °C	complex mixture
2	$MeNH_2$ in THF, toluene, *p*-TsOH, 80 °C	decomposition
3	$MeNH_2$ in THF, THF, RT	no reaction
4	$MeNH_2$ in THF, THF, µw, 100 °C	no reaction
5	$MeNH_2$ in THF, xylene, 140 °C	no reaction
6	$MeNH_2$·HCl, benzene, µw, 100 °C	no reaction
7	$MeNH_2$·HCl, benzene, 150 °C	no reaction
8	$MeNH_2$ (gas), toluene, $Yb(OTf)_3$, 80 °C	complex mixture
9	$MeNH_2$ (gas), 100 °C	**196**:**191** (1.5:1)[a]
10	$BnNH_2$, Et_2O, RT	no reaction
11	$BnNH_2$, xylene, 140 °C	decomposition
12	$BnNH_2$, benzene, 4Å MS, 90 °C	complex mixture
13	$BnNH_2$, Et_2O, $TiCl_4$, –15 °C	no reaction

[a] As determined by ^{1}H-NMR spectroscopy.

As Tahk and co-workers used freshly condensed methylamine gas, a closer examination of these conditions was undertaken (Table 4, entries 8 and 9). Methylamine gas was condensed at −78 °C in a high pressure vessel and cyclopropane **191** was dissolved therein. Heating in the presence of ytterbium(III) triflate with toluene as solvent lead to the formation of complex mixtures (Table 4, entry 8). However, when methylamine was used as solvent without any additives at 100 °C over several days, a 1.5:1 mixture of a new compound and starting material **191** was obtained (Table 4, entry 9). ^{1}H-NMR spectroscopy suggested the formation of imine **196**. Unfortunately, we were not able to fully characterize the new component as all separation attempts lead to decomposition of the material. Figure 11 shows ^{1}H-NMR spectrum of the crude mixture of **196** and **191**.

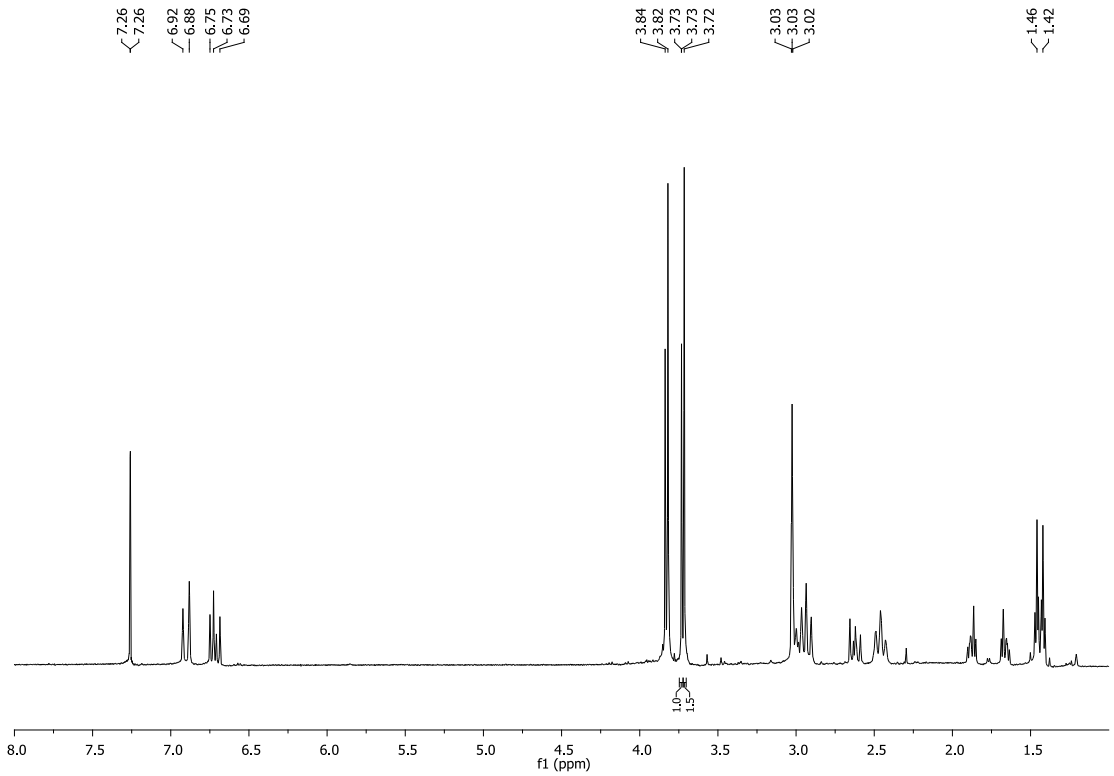
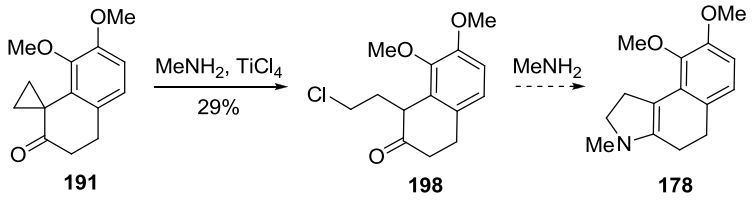


Figure 11. ^{1}H-NMR spectrum (200 MHz, $CDCl_3$) of the crude mixture of **196** and **191**.

At this point, the suitability of benzylamine as nucleophilic reaction partner was investigated, since the corresponding products might be more stable than the methylated derivatives (Table 4, entries 10–13). Similar conditions as used in the methylamine screening were applied. In most cases, either decomposition or recovery of starting material was observed.

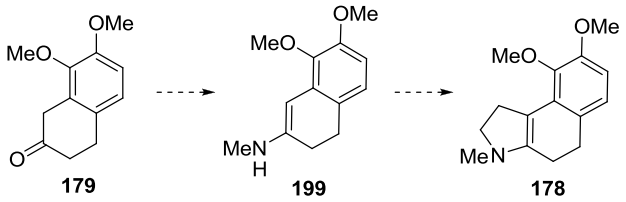
As mentioned above, Tahk and co-workers were able to obtain only analytical amounts of the desired enamine **178** even though they performed the reaction with large quantities of starting material **191**. In our case, isolation of the desired enamine **178** following the same strategy was not met with success. Supposedly, the envisioned cyclopropane opening might be hindered due to the presence of two adjacent methoxy substituents, which cause compound **191** to be sterically hindered and also to be a more electron rich system disfavoring nucleophilic attack.

Although these first attempts were unsuccessful, one interesting and promising result was obtained, when cyclopropane **191** was treated with methylamine in the presence of titanium(IV) chloride at room temperature (Scheme 52). Under these conditions, the cyclopropane ring was opened by a chlorine anion, presumably after the activation of the keto group by titanium(IV) chloride. Methyl amine is most likely not involved in the formation of compound **198**. Further development and optimization of this reaction could prove chloride **198** as a building block for the synthesis of enamine **178**. Furthermore, treatment of **198** with methyl amine could force an intramolecular ring closure to occur providing an elegant entry to enamine **178** (Scheme 52).



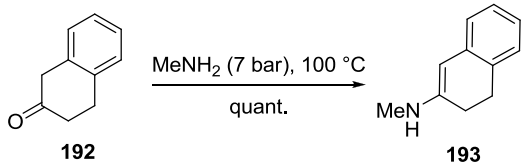
Scheme 52. Cyclopropane opening reaction leading to the formation of chloride **198** and envisioned formation of enamine **178**.

At this stage of the synthesis, we decided to test the conditions for the enamine formation published by Evans and co-workers.[85] In this context, we first aimed for enamine **199**, which should then be alkylated to afford the desired compound **178** (Scheme 53).



Scheme 53. Envisioned stepwise formation of **178** *via* enamine **199** as possible precursor.

Following this strategy, we tried to reproduce the reaction of unsubstituted β-tetralone **192** to enamine **193** as described by Evans *et al.* (*vide supra*, Scheme 51). Unfortunately, treatment of commercially available **192** with methylamine solution in the presence of titanium(IV) chloride at room temperature did not lead to the formation of the desired enamine **193**. In addition, conditions such as $MeNH_2$/amberlyst-15/toluene/ΔT,[87] $MeNH_2/TiCl_4/NEt_3/CH_2Cl_2$,[88] and $MeNH_2 \cdot HCl$/*p*-TsOH/toluene/ΔT[89] proved unsuccessful as only starting material was recovered. Eventually, we found that heating of β-tetralone **192** with neat methylamine at 100 °C in an autoclave apparatus (7 bar) furnished the desired enamine **193** in quantitative yields (Scheme 54).



Scheme 54. Formation of the enamine structure **193**.

The conversion of tetralone **192** was monitored by ^{1}H-NMR spectroscopy. A comparison of the crude reaction spectrum with the starting material indicated the formation of enamine **193**.

The signal of benzylic proton (H-2) disappeared at the expense of a new proton signal at 5.25 ppm (enamine-H). Furthermore, a new methyl group (H-11) attached to a nitrogen atom was detected at 2.80 ppm in the ^{1}H-NMR spectrum. All of these new signals suggested the quantitative formation of the desired enamine **193**. Due to the instability of the compound, further characterization attempts were not performed.

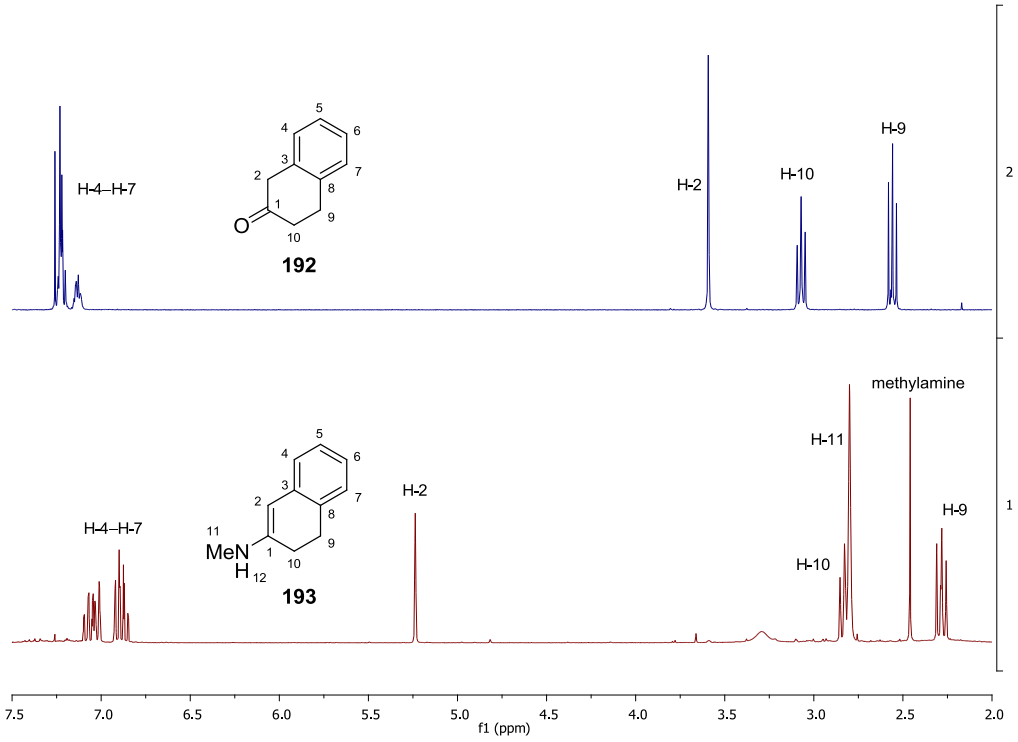
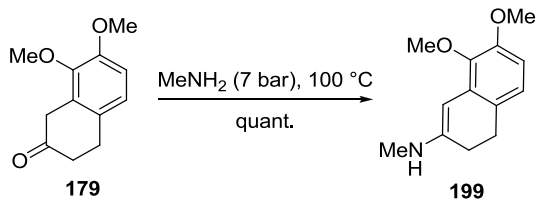


Figure 12. ^{1}H-NMR spectra ($CDCl_3$) of β-tetralone **192** and the desired enamine **193**.

Having successfully established conditions for the enamine formation, the same procedure was applied to the dimethoxytetralone system **179**. Treatment of tetralone **179** with methylamine at high temperatures in an autoclave apparatus led to the quantitative formation of the desired dimethoxyenamine **199** (Scheme 55).



Scheme 55. Formation of enamine **199**.

As in the test reaction, the conversion of **179** was monitored by ^{1}H-NMR spectroscopy (Figure 13). Comparison of the spectra again revealed quantitative formation of enamine **199**. In

analogy to the spectrum of enamine **193**, the ^{1}H-spectrum of **199** shows a new peak at 5.47 ppm corresponding to the enamine proton H-2 and lacks a methylene group, which is present in the starting material (peak H-2 in the spectrum of **179**). In addition, another new peak suggesting the presence of a methyl group attached to a nitrogen atom appeared (peak H-13). Hence, the crude proton spectrum of the reaction indicated the formation of the desired compound **199**. No further characterization could be performed due to the instability of the product.

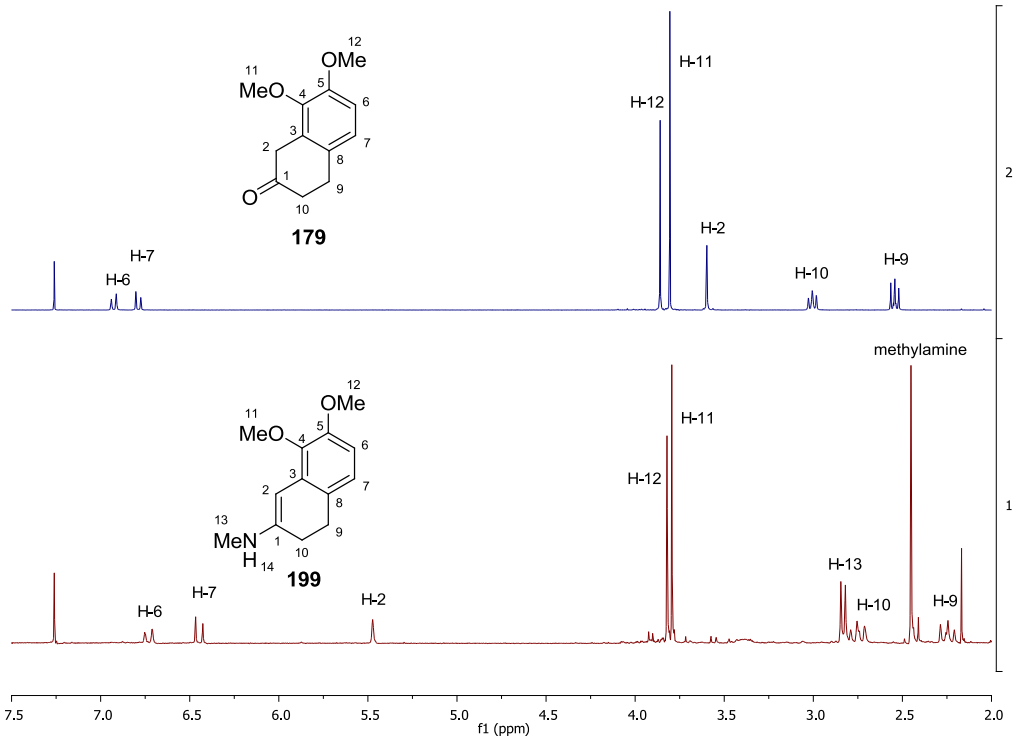
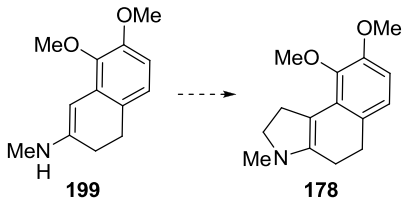


Figure 13. ^{1}H-NMR spectra (in $CDCl_3$) of β-tetralone **179** and crude enamine **199**.

At this point, we envisioned the alkylation of enamine **199** to access the tricyclic enamine **178**, a key intermediate in the total synthesis of stephadiamine **163** (Scheme 56). Several conditions, among them the alkylation condition developed by Evans, were investigated using the crude enamine **199**. Thus far, no conclusive results were obtained. This topic is currently being investigated by N. Vrielink as a part of her Master project in the Trauner laboratories.



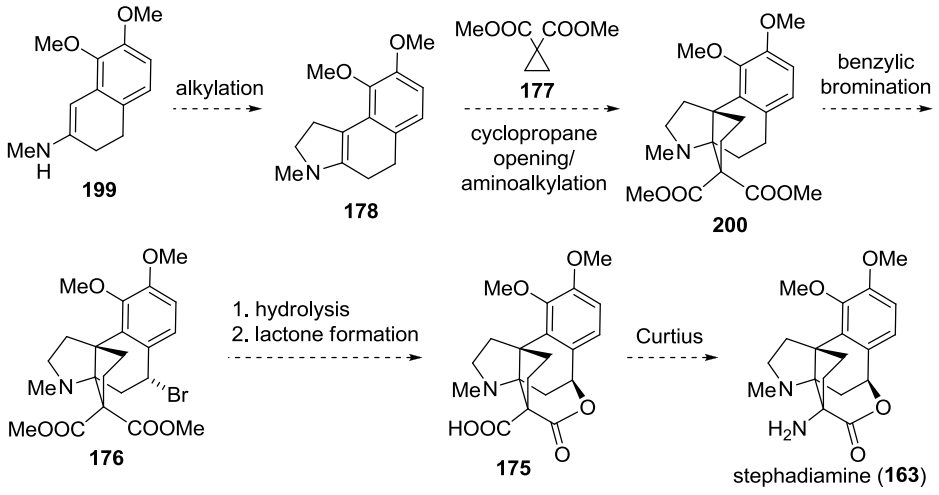
Scheme 56. Envisioned installation of the ethylene bridge forming enamine **178**.

11. Summary, Conclusions and Future Directions

In summary, first attempts toward the total synthesis of the norhasubanan stephadiamine (**163**) have been made. The literature known synthetic route to β-tetralone **179**, one of the key intermediates in the envisioned synthesis, was optimized. Following these high yielding and reliable procedures, compound **179** could be synthesized in multigram quantities in 59% yield over four steps. In addition, the cyclopropane system **191** was prepared, which could possibly serve as a valuable precursor for the formation of enamine **178**.

Furthermore, first experiments aiming at the formation of the tricyclic enamine system **178** were performed. Although these attempts remained unsuccessful, some promising results were obtained implying the formation of imine **196** as mixture with starting material **191**. Additionally, cyclopropane **196** could be opened with titanium(IV) chloride presumably forming the primary chloride **198**, which in future could open alternative routes for the synthesis of enamine **178**. Finally, we were able to accomplish the syntheses of rather unstable bicyclic enamine structures **193** and **199**, precursors for the formation of the desired tricyclic enamine systems **178** and **194**. Alkylation reactions of enamine **199** were performed to install the ethylene bridge, unfortunately with no success so far.

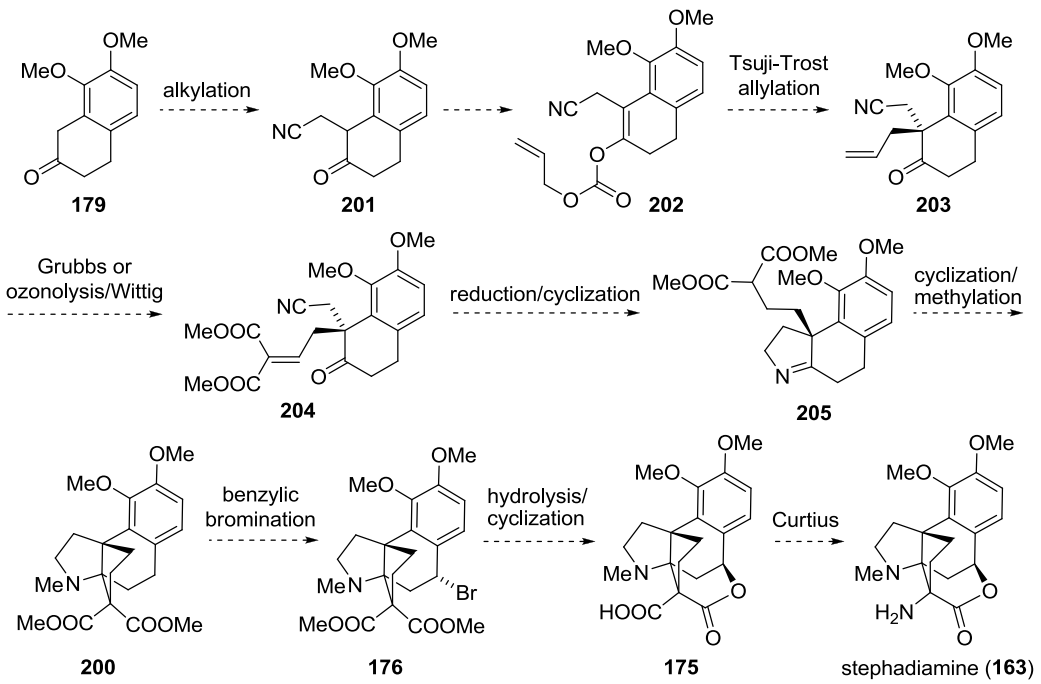
In the future, attempts toward the cyclopropane opening/aminoalkylation cascade could be made (Scheme 57). This key step of the synthesis would provide access to the propellane skeleton **200** featuring the first NTC center of stephadiamine (**163**). Intermolecular cyclopropane opening reactions are enhanced by activation of the adjacent carbonyl group with Lewis acids, such as ytterbium or scandium triflates.[80] This fact would also provide the potential to apply chiral Lewis acid catalysis to form the correspondent quaternary benzylic stereocenter in enantioselective manner, eventually leading to an asymmetric synthesis of stephadiamine (**163**).



Scheme 57. Envisioned synthetic route to stephadiamine (**163**) *via* cyclopropane opening/aminoalkylation strategy.

A subsequent selective bromination of diester **200** in the benzylic position should lead to bromide **176**, which in turn can be converted to lactone **175** by means of hydrolysis and lactone formation. The final step in the total synthesis of stephadiamine (**163**) is envisioned to be a Curtius rearrangement forming the second NTC center. This route is currently under investigation by N. Vrielink as a part of her Master's project in the Trauner laboratories.

In addition, we developed a second alternative synthetic strategy for the synthesis of stephadiamine (**163**) starting from β-tetralone **179** since the pursued synthetic route proved to be more challenging than expected (Scheme 58). This new route would start with an alkylation of tetralone **179** forming nitrile **201**. Alkylations of this type on similar systems are known in the literature and can be performed using enamine catalysis to avoid double alkylation processes.[90] Next, nitrile **201** could be converted to enol ether **202**, which in turn should smoothly undergo enantioselective Tsuji-Trost allylation forming the benzylic quaternary stereocenter in **203** even in an asymmetric way.[91] Enantioselective Tsuji-Trost allylation is a powerful method for installation of hindered stereocenters[92] and has been applied successfully in total synthesis.[93] The diester moiety present in compound **204** could be then introduced using either Grubbs' metathesis or an ozonolysis/Wittig olefination sequence. The propellane motif of diester **200** is likely to be incorporated into substrate **204** by means of a reduction of the Michael system and the nitrile portion,[90b] followed by an intramolecular imine formation to give imine **205**, which would then cyclize to propellane **200**. Most likely, these transformations could take place as a cascade reaction in a one pot process providing propellane **200** directly from nitrile **204**.



Scheme 58. Alternative synthetic route to stephadiamine (**163**).

Finally, after *N*-methylation, the same sequence as described in the first synthetic strategy toward stephadiamine (**163**) could be employed to accomplish the synthesis of the natural product. This sequence involves benzylic bromination of diester **200**, hydrolysis and intramolecular lactone formation (→**175**) as well as a closing Curtius rearrangement.[79c,94]

This second strategy includes the powerful enantioselective Tsuji-Trost allylation and the cascade reduction/double cyclization reaction as key steps, which forms the first NTC-center of stephadiamine (**163**). Thus, this strategy is a short efficient alternative representing a modern and interesting route for the first asymmetric synthesis to this natural product. Overall, the versatile β-tetralone **179** turned out to be a flexible key building block and could serve as starting material in additional alternative entries to stephadiamine (**163**) leaving room for further investigations.

Chapter III: Synthetic Studies Toward Divergolides C and D

12. Introduction

'Mir erschien jetzt alles so einfach, dass ich kaum glauben konnte, dass in der Zwischenzeit niemand die gleiche Idee gehabt haben könnte. – Everything now seemed so simple to me that I could hardly believe that nobody else (...) could have had the same idea (...).'

(Feodor Lynen)

Feodor Lynen was still surprised when he made this statement a few years after the publication of the groundbreaking results of the structural elucidation of acetyl coenzyme A (**206**) (acetyl-CoA, Figure 14).[95] The structural mystery of the 'activated acetic acid', one of the key building blocks in metabolism, was solved. Earlier in 1947, biochemist Fritz Lipmann discovered the new coenzyme named 'coenzyme A' from pigeon liver extracts, which was able to transfer acetyl groups.[96] The structure of this molecule featured pantothenate, adenosine, phosphate and sulfur units. However, the exact chemical constitution of compound **206**, and especially the nature of the bond between acetate and coenzyme were so complicated that they remained unclear. It was attributed to the genius of Lynen to reveal the 'activated acetate' as thioester[97] of coenzyme A.[98]

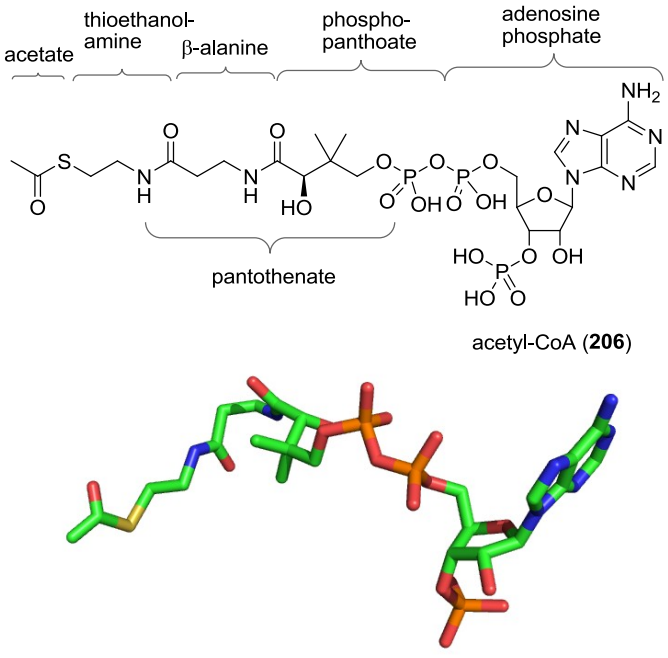
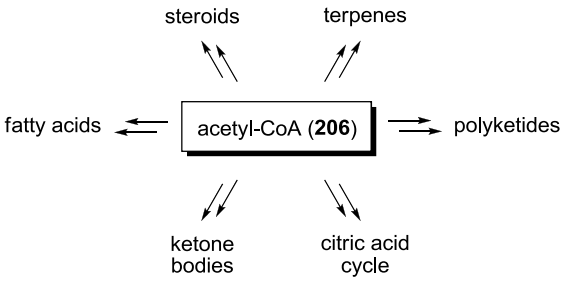


Figure 14. Structure and X-ray analysis[99] of acetyl coenzyme A (**206**).

The structural elucidation of acetyl-CoA (**206**) was the prerequisite for the exploration and understanding of many anabolic and catabolic pathways of the cell. Being the key building block of the acetate pathway, acetyl-CoA **206** is the central precursor for many natural metabolites like ketone bodies, fatty acids, steroids, terpenes, or polyketides. In addition to that, acetyl-CoA (**206**) enters the citric acid cycle to generate energy and several biosynthetic intermediates (Scheme 59).[49]



Scheme 59. Acetyl coenzyme A (**206**) as central precursor for many biological metabolites.

Among biological metabolites, the polyketides are a large and structurally diverse class of natural products, which is biosynthetically related to fatty acids. Depending on the genetic code of the producing enzyme complex, they are divided into three different types. Type I polyketide synthases (PKSs) are found in bacteria and fungi, and are often responsible for the formation of macrolide structures like erythromycin A (**207**) (Figure 15). These PKSs are very large, but single multifunctional proteins, containing several individual domains. Type I PKSs can be divided into 'iterative', i.e. repeating, and 'non-iterative' systems. Iterative systems use their functional domains repeatedly to produce a particular polyketide, while the more important non-iterative PKSs possess a distinct active site for every single enzyme-catalyzed step leading to more diverse polyketide chains. In contrast, type II PKSs are complexes, composed of numerous individual monofunctional proteins. The occurrence of these systems is restricted to bacteria and they usually produce aromatic polyketides, e.g. doxorubicin (**208**). Type II PKSs are known to be of the iterative type only. The third types of PKSs are responsible for the chain extension of cinnamoyl-CoA starter units, thus leading to flavonoids, e.g. naringenin (**209**) (Figure 15), and stilbenes. These type III PKSs differ from the other systems as they employ only one single active site to perform all synthetic transformations. They are usually found in plants, bacteria, and fungi.[58]

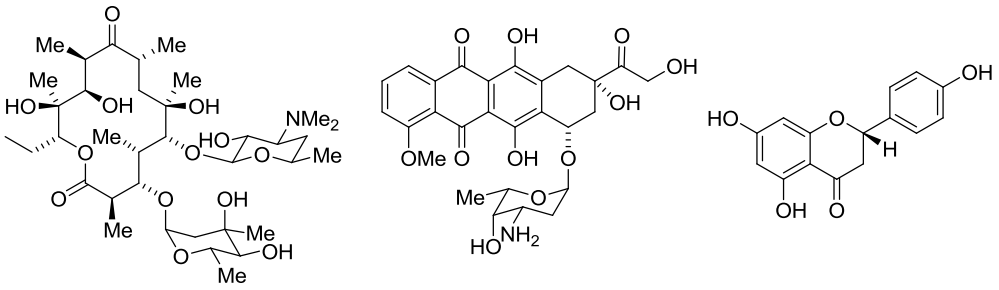


Figure 15. Structural examples of polyketides of the three different types: erythromycin A (**207**) (type I), doxorubicin (**208**) (type II), naringenin (**209**) (type III).

Within the type I polyketides, the ansa macrolides (or ansamycins) comprise a family of mostly bioactive natural products predominantly isolated from actinomycetes.[100] The name 'ansa macrolides', as initially introduced by A. Lüttringhaus[101] and later used by V. Prelog and W. Oppolzer,[102] was derived from the basket-like shape of these molecules possessing a 'handle' (Latin: *ansa* = 'handle'). This 'handle' is fused *via* an amide bond to a mono- or bicyclic aromatic ring as can be found for example in geldanamycin (**210**)[103] or rifamycin SV (**211**)[104] (Figure 16). Thus, these molecules are lactams in contrast to the previously mentioned macrolactone erythromycin A (**207**).

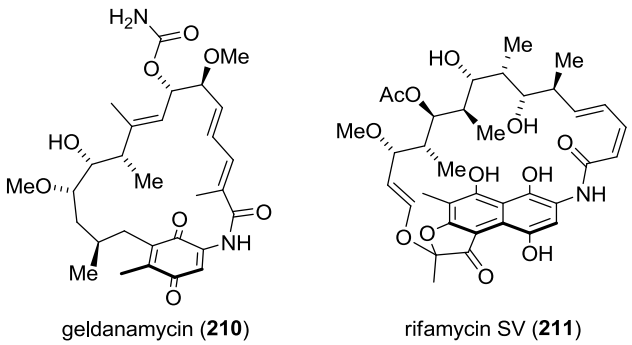


Figure 16. Structures of ansa macrolides geldanamycin (**210**) and rifamycin SV (**211**).

Among the ansa macrolide natural products, several molecules with biologically interesting activity were identified. Geldanamycin (**210**) is a prominent compound in anti-tumor research which inhibits the heat shock protein 90 (HSP90).[105] In contrast to that, rifamycin SV (**211**) is a highly active antibacterial agent and the first member of the rifamycin family that was used in clinical trials. Further synthetic modifications of this natural product led to more potent drugs.[58]

Structurally, ansa macrolides **210** and **211** can be subdivided into two different types. While geldanamycin (**210**) shows a benzenic quinone core, the ansa-polyketide 'handle' of rifamycin

SV (**211**) is connected to a naphtohydroquinone moiety. Despite the structural difference, the use of similar building blocks is often encountered in the biosynthesis of ansalactams. For instance, both type I polyketide natural products, **210** and **211**, are derived from the same starter unit 3-amino-5-hydroxy-benzoic acid (AHBA) (**212**) (*vide infra*, Scheme 60).[106]

Divergolides A–D (**213**–**216**)[14] are another family of the large class of 3,5-AHBA-derived natural products (Figure 17).[107] Like most ansamycins, they also show remarkable anti-infective and antitumoral activities.[14] Despite this fact, no total synthesis of a divergolide has yet been reported.

During the isolation process of **213**–**216**, the fermentation extract showed a complex metabolome. Due to little amounts, C. Hertweck and co-workers were only able to isolate and fully characterize the structures of divergolides A–D (**213**–**216**). It is very likely that more, presumably highly bioactive natural products and metabolites could be found in these extracts. Since our group is interested in the synthesis of naphthalenic ansa macrolactams,[108] we set out to support the search and structural elucidation of new compounds of the divergolide class by means of total synthesis.

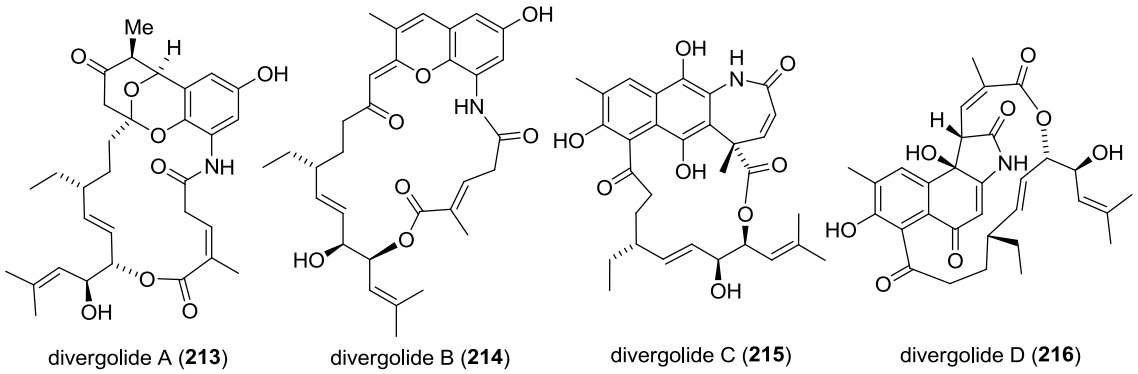


Figure 17. Structures of divergolides A–D (**213**–**216**).

Hence, this project was focused on the following aspects:

- total synthesis of divergolides C (**215**) and D (**216**) from a common precursor, which itself is more likely a metabolite of the divergolide biosynthesis;
- structural characterization of the intermediates which could correspond to the natural metabolites;
- providing the synthetic precursors to the Hertweck group to support the investigation of metabolites of the divergolide biogenesis.

13. Isolation, Biology and Structural Features of the Divergolide Family

Mangroves are trees that grow in saline sediments along the tropical and subtropical coast. The family consists of various species. Among them, the mangrove tree *Bruguiera gymnorrhiza* is predominant at the Chinese coast. Thus, it is not surprising that the bark and the roots of these trees are used in traditional Chinese folk medicine to treat diarrhea, throat inflammation and hemostasis for centuries.[14] While several chemical components of the plant itself were subject to various investigations,[109] the biological potential of the endophytes (bacteria or fungi that live within the plant) were insufficiently explored.[110] Therefore, the Hertweck group investigated the cultured endophyte strain *Streptomyces* sp. HKI0576 in detail, which was isolated from the stem of *B. gymnorrhiza* with several other strains of bacteria *Streptomyces spp*. The first extracts of this strain afforded a complex metabolome with a vast variety of different compounds. However, only trace amounts of the new structures could be isolated. After scale up of the fermentation process, four new ansamycins, namely divergolides A–D (**213**–**216**), were obtained and structurally elucidated by NMR spectroscopy and mass spectrometry techniques (*vide supra*, Figure 17). In addition to that, the structure of divergolide A was confirmed by X-ray crystallography (Figure 18).[14]

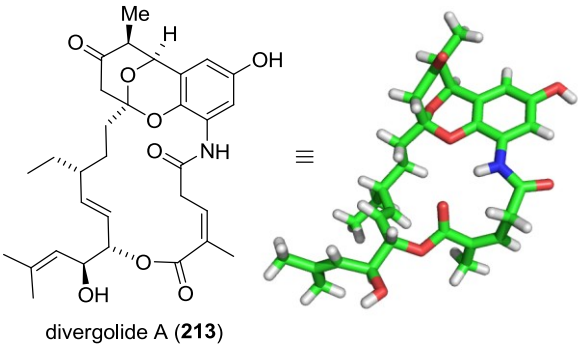


Figure 18. Structure and X-ray analysis of divergolide A (**213**).

Interestingly, although being structurally different, all four natural products **213**–**216** show useful biological activities. During an antibacterial screening[14] it was found that divergolide A (**213**) exhibits the strongest activity against *Mycobacterium vaccae*, whereas divergolide D (**216**) is more active against *Bacillus subtilis* and *Staphylococcus aureus*. In contrast to that, divergolide C (**215**) is the only of all four compounds that displays activity against *Enterococcus faecalis*, albeit just moderate. Further cytotoxicity screenings against 40 tumor cell lines revealed that only divergolide D (**216**) showed mentionable activity. In particular, cell lines corresponding to lung cancer (LXFA 629L), pancreatic cancer (PANC-1), renal cancer

(RXF 486L), and sarcoma (Saos-2) were most sensitive toward natural product **216**, with IC_{50} values ranging from 1.0 to 2.0 μM. Overall, it was noticed that among the ansamycins **213**–**216**, divergolide A (**213**) could be a promising compound for the development of anti-infectives, whereas divergolide D (**216**) might be a potent lead structure for antitumor drugs.[14]

Over the past years, our group got interested in the synthesis of naphthalenic ansa macrolactams.[108] Thus, this project is focused on the total synthesis of divergolides C (**215**) and D (**216**), since these natural products incorporate a naphthalene core. The structures of **215** and **216**, including the numbering of the carbon skeleton suggested by Hertweck and co-workers, are shown in Figure 19.[14] Both compounds show a tetracyclic scaffold in which a highly substituted naphthalenic moiety is connected with a polyketide ansa bridge. Whereas the aromatic nucleus of divergolide C (**215**) is a hydroquinone derivative, divergolide D (**216**) possesses a naphtoquinone as the central unit. The naphthalenic portions are extended by a 7-membered lactam ring in case of **215**, and a 5-membered lactam in **216**. The remaining polyketide ansa chains form macrolactones of different sizes: 15-membered in **215** and even 19-membered in compound **216**. Interestingly, two different allylic hydroxy groups at C-11 and C-12 are incorporated in the formation of the cyclic esters. In addition to that, divergolide C (**215**) shows four stereogenic centers at C-4", C-8, C-11, and C-12, one of which (C-4") is quaternary and benzylic. In contrast, divergolide D (**216**) possesses even five stereocenters at C-5', C-2", C-8, C-11, and C-12. A remarkable attribute of both compounds is the unprecedented isobutenyl side chain at C-12, which is an unusual extender unit in type I polyketide synthesis.[14] These outstanding structural features make the divergolides C (**215**) and D (**216**) interesting targets for total synthesis.

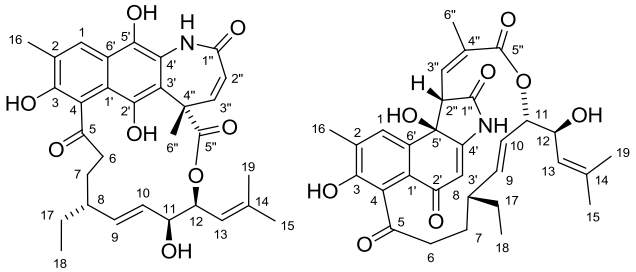
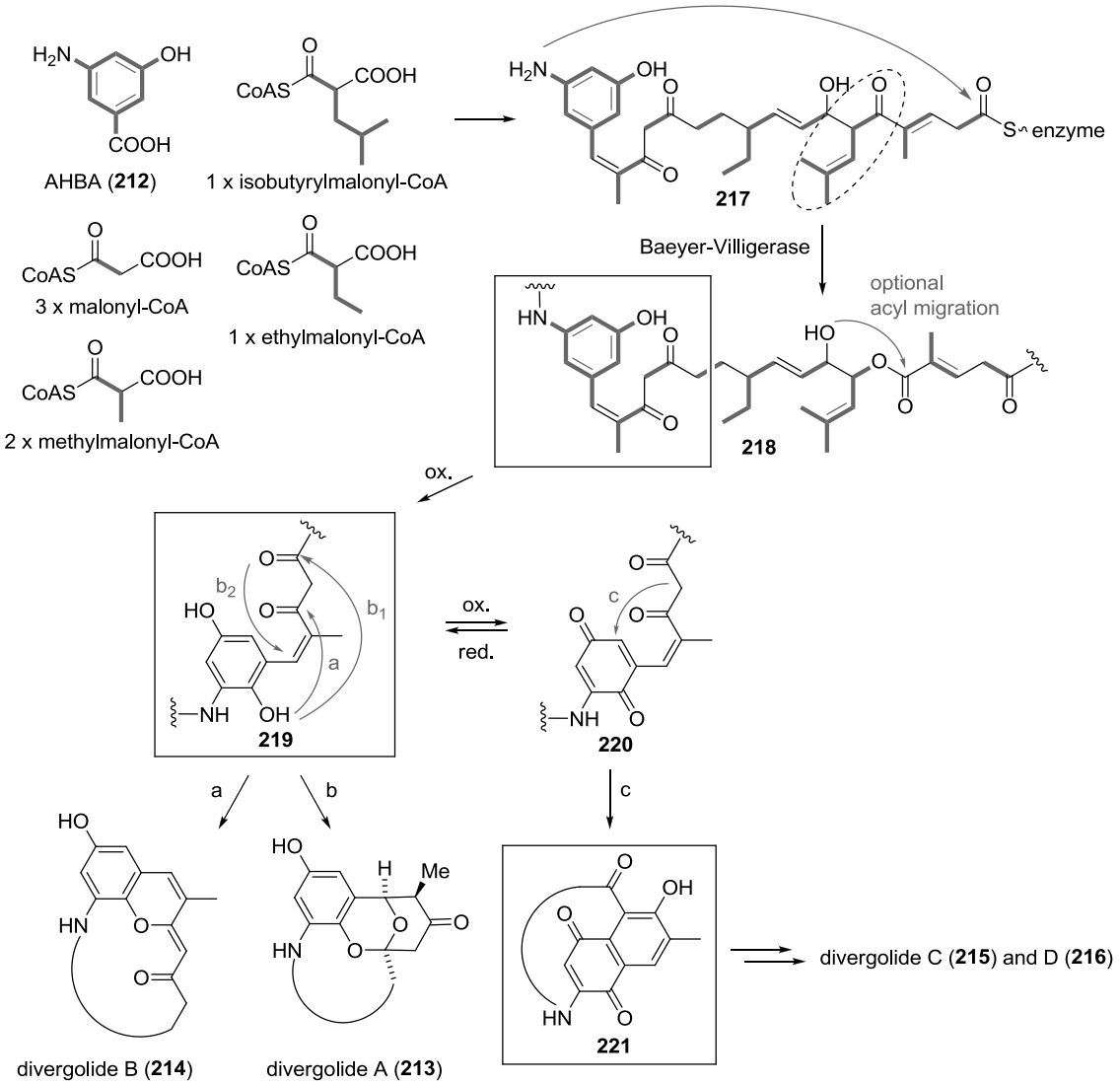


Figure 19. Structures of divergolides C (**215**) and D (**216**) with carbon skeleton numbering suggested by C. Hertweck and co-workers.[14]

Although the structures of divergolides A–D (**213**–**216**) differ from each other, it is anticipated that they stem from the same biosynthetic precursor (Scheme 60).[14] Unfortunately, all isotope labeling experiments performed by Hertweck and co-workers, which could support the proposed biosynthesis, failed because insufficient amounts of isolated metabolites were

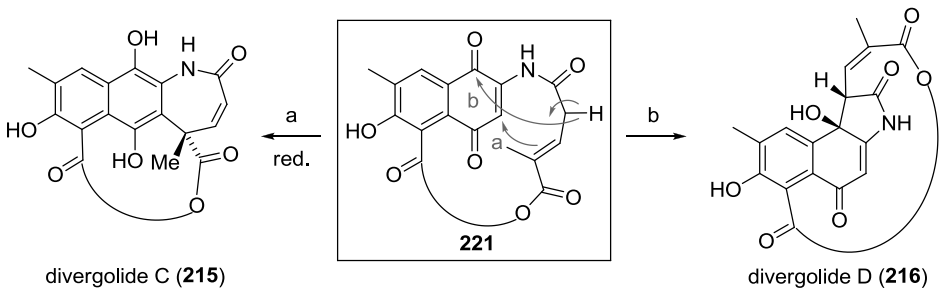
available. Nevertheless, Hertweck suggested that the starter unit AHBA (**212**), which itself is derived from the aminoshikimate pathway,[111] has been condensed by a type I PKS with two methylmalonyl-CoA, three malonyl-CoA, one ethylmalonyl-CoA, and one unprecedented isobutyrylmalonyl-CoA extender units (Scheme 60).[112] The unusual isobutyrylmalonyl-CoA unit[113] was observed in this class of natural products for the first time.[114] The resulting polyketide chain **217** is considered to have been intercepted by a Baeyer-Villigerase[115] to give ester **218** as a common precursor, which can undergo optional acyl migration to provide different ester pattern for the divergolide framework. After oxidation of the aromatic ring in intermediate **218**, the highly reactive polyketide side chain of **219** can undergo three different cyclization reactions to provide the diverse aromatic cores of the divergolides A–D (**213**–**219**) (Scheme 60).



Scheme 60. Proposed biosynthesis of divergolides A (**213**) and B (**214**) proposed by C. Hertweck and co-workers.[14]

In particular, the exomethylene-2*H*-benzopyran of divergolide B (**214**) could be formed after nucleophilic attack of the phenolic hydroxy group in **219** to the adjacent carbonyl group. Subsequent water elimination would result in chromene **214** (path a, Scheme 60). In the second scenario, the very same phenolic hydroxy group in **219** might attack the more distant carbonyl function (path b_1, Scheme 60), resulting in a hemiketal that could further cyclize by a Michael attack on the side chain double bond to the intriguing ring system of divergolide A (**213**) (path b_2, Scheme 60).[14]

On the other hand, the naphthalenic moieties of divergolides C (**215**) and D (**216**) might be formed after oxidation of hydroquinone **219** to the corresponding benzoquinone **220** and further cyclization to naphtoquinone **221** (path c, Scheme 60). As suggested by Hertweck and co-workers, this intermediate **221** could be a common biosynthetic precursor for the installment of the 5- and 7-membered lactams to give divergolides C (**215**) and D (**216**), respectively. Along these lines, divergolide C (**215**) is likely to result from an intramolecular attack of the carbonyl-activated methylene in compound **221** to the naphtoquinone in a vinylogous fashion (path a, Scheme 61). Alternatively, an aldol reaction could provide the pyrrolidone moiety of divergolide D (**216**) (path b, Scheme 61).[14] The specific stage of the biosynthesis at which the acyl migration step occurs to form the different scaffold of divergolides C (**215**) and D (**216**), is yet to be identified. This of course leads to further speculation if this event happens before, during, or after the cyclization processes.



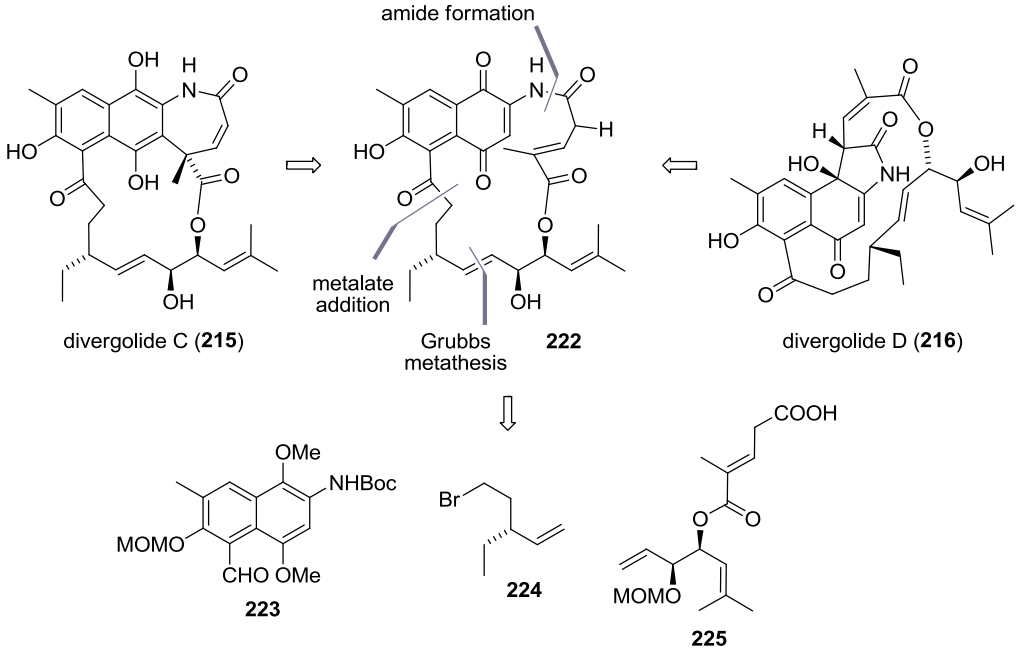
Scheme 61. Proposed biosynthesis of divergolides C (**215**) and D (**216**) by C. Hertweck and co-workers.[14]

The most remarkable feature of Hertweck's proposal is that all four divergolides A–D (**213**–**216**) fit into one biosynthetic scheme. Derived from one precursor **219**, flexible and diverse cyclization modes lead to different natural products of one family, thus called divergolides. This biosynthetic proposal is an inspiring basis for a divergent total synthesis approach to divergolides C (**215**) and D (**216**).

14. Results and Discussion of the Synthetic Studies Toward Divergolides C and D[ix]

14.1. Retrosynthetic Analysis for Divergolide C and D

According to Hertweck's proposed biosynthesis, divergolides C (**215**) and D (**216**) could be derived from one common precursor.[14] Inspired by this hypothesis, we designed a synthesis for both natural products relying on a biomimetic key step. This approach is based on the synthesis of macrocycle **222** as parent compound for **215** and **216**. Intermediate **222** is the equivalent to the proposed biosynthetic precursor **221**, although the esterification pattern in **222** fits only to divergolide C (**215**). For the synthesis of divergolide D (**216**), an acyl migration step has to take place in analogy to the biosynthetic ideal. Macrocycle **222** could be prepared from three different building blocks, such as naphthaldehyde **223**, western side chain **224**, and eastern side chain **225**. Naphthalene **223** should then be connected with **224** by means of a metallate addition. Further amide coupling with western side chain **225** and marcocyclization through Grubbs' metathesis could provide a protected derivative of precursor **222**.



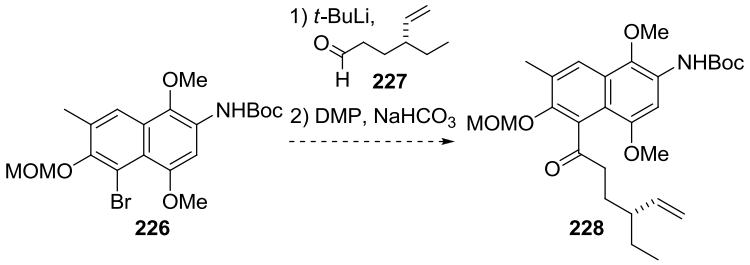
Scheme 62. Retrosynthesis of divergolides C (**215**) and D (**216**).

[ix] This project was performed in cooperation with A. Hager and C. A. Kuttruff, both PhD students of the Trauner research group.

14.2. Attachment of the Western Side Chain

14.2.1. First Strategy

The first stage of the synthetic work toward divergolides C (**215**) and D (**216**) was the preparation of naphthalene building block **222**. Thus, we envisioned the connection of bromonaphthalene **226**[x] with aldehyde **227** to provide ketone **228** after DMP oxidation (Scheme 63). For this coupling large amounts of aldehyde **227** in high enantiomeric purity were needed.

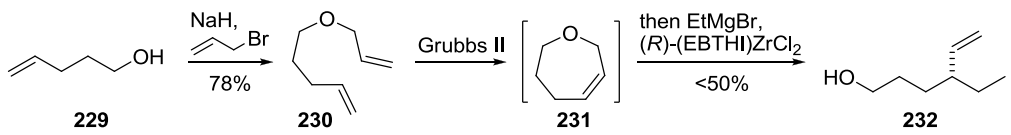


Scheme 63. Planned synthesis of naphthalene building block **228**.

The preparation of the respective alcohol **232** or its enantiomer has been described several times in the literature. For example, E.-i. Negishi and co-workers reported the synthesis of **232** through a tandem reaction of a zirconium-catalyzed asymmetric carboalumination of an alkene (ZACA)[117] and a lipase-catalyzed acetylation.[118] However, this route seemed not practicable for us to yield large amounts of alcohol **232**.

A. H. Hoveyda and co-workers published another synthesis of **232** by a zirconium-catalyzed ethylmagnesation of 7-membered heterocycles.[119] Thus, we were able to prepare ether **230** from 4-penten-1-ol (**229**) and allyl bromide (Scheme 64). Conversion of **230** into tetrahydrooxepine **231** by means of a ring closing metathesis (RCM) and subsequent treatment with EtMgBr and the zirconium catalyst gave alcohol **232**, however in unreliable and low yields (<50%). Furthermore, determination of the optical rotation indicated only small enantioselectivity of the reaction. This disappointing result might be caused by the low quality of the commercially available zirconium catalyst. As already mentioned by Hoveyda *et al.*, the freshly prepared and enantio-resolved catalyst gave the best results.[119] Another drawback of this method was the enormous costs of both catalysts which only allowed small scale reactions. Hence, the isolation of little amounts of volatile alcohol **232** was extremely difficult.

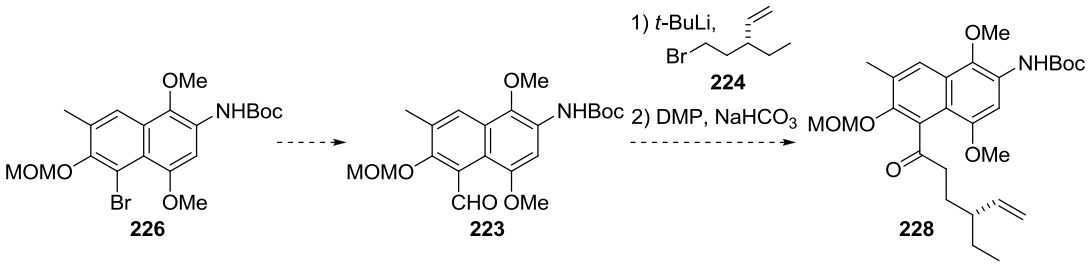
[x] The synthesis of **226** was performed by C. A. Kuttruff and was part of his PhD thesis.[116]



Scheme 64. Unsuccessful synthesis of alcohol **232**.

14.2.2. Second Strategy

Looking for alternatives, we finally focused on a slightly modified strategy for the synthesis of naphthalene building block **228** that required the preparation of naphthaldehyde **223** from bromonaphthalene **226** and its coupling to a C_1-shorter western side chain **224**. Bromide **224** should be transmetallated to serve as a nucleophile for the attack on naphthaldehyde **223** and, after oxidation, the earlier proposed naphthalene **228** would be obtained (Scheme 65).

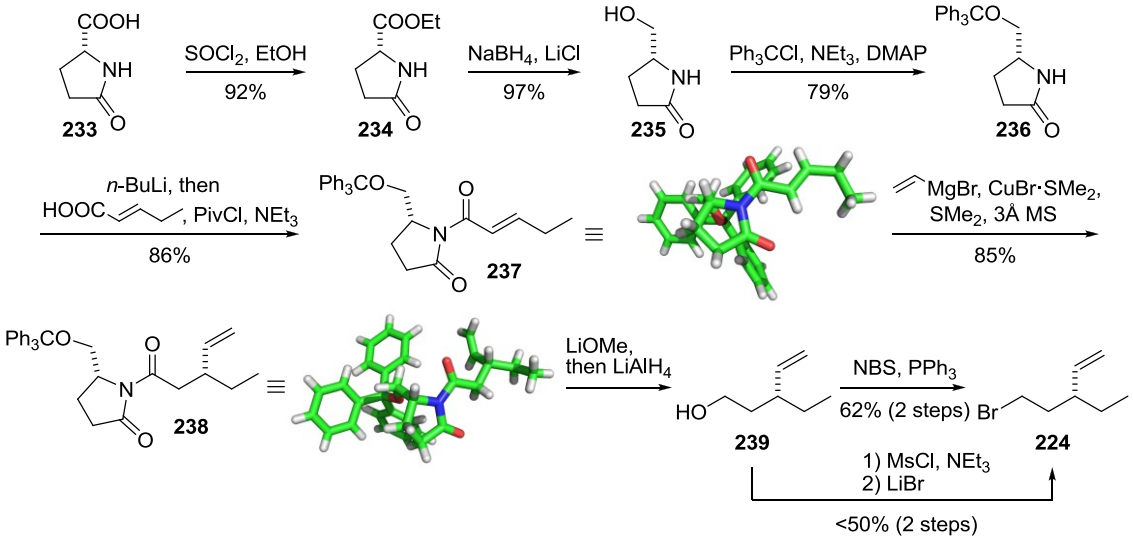


Scheme 65. Modified strategy for the synthesis of naphthalene building block **228**.

The enantioselective preparation of bromide **224** was envisioned through a 1,4-addition of a monoorganocopper reagent to auxiliary containing Michael system **237** (Scheme 66). Although this method was laid out earlier by Hoveyda and co-workers to establish the proposed absolute stereochemistry of their zirconium mediated transformations, no experimental details were reported in this publication.[120] For our purpose, we synthesized Koga's auxiliary **236**, which was known to control 1,4-additions in a highly selective manner.[121] Along these lines, we esterified D-pyroglutamic acid (**233**) to the corresponding ethyl ester **234** that was further reduced to alcohol **235** (Scheme 66). Reduction of **234** with $NaBH_4$ in the presence of LiCl provided alcohol **235** in high yields.[122] However, the success of this reaction was dependent on the purity of the starting material. Thus, when highly pure ester **234**, obtained after distillation, was used, this reaction could be driven to completion only by $LiBH_4$.[123] It was speculated that impurities or solvent residues might accelerate the reduction with $NaBH_4$ and LiCl on decagram scale. Protection of alcohol **235** then gave Koga's auxiliary **236**, which was acylated to provide Michael acceptor **237**. The highly stereoselective 1,4-addition of a monoorganocopper reagent afforded compound **238** as a single diastereomer in high yield. Its absolute stereochemistry was proven by X-ray analysis (Scheme 66). Neither the X-ray structure of the starting material **237**, nor the one of the product **238** show clear hints of a sterically unhindered trajectory for the

nucleophilic attack of the cuprate to explain the stereoselective outcome of the reaction. It was proposed that a different conformation and additional complexation of the substrate **237** with the reaction partners might be the reason for the stereoselective 1,4-addition.[124] The following cleavage of the auxiliary[xi] was more reluctant than anticipated, but combination of LiOMe and $LiAlH_4$ gave alcohol **239** that was directly converted into bromide **224** using Appel-type conditions. Another route from alcohol **239** to bromide **224** was a mesylation/substitution sequence. However, this way was lower yielding and less practicable. The side chain **224** turned out to be also extremely volatile so that unusual isolation methods were requested and the diminished yield was attributed to these isolation processes (see experimental section). Although this sequence is longer than the previously described catalytic ways (*vide supra*, Scheme 64), it allowed the preparation of decagram quantities of compound **238**,[xii] which was in turn converted into bromide **224**.

Overall, the enantiopure western side chain **224** was synthesized in sufficient quantity for full characterization and to proceed with the coupling to the naphthalene part.

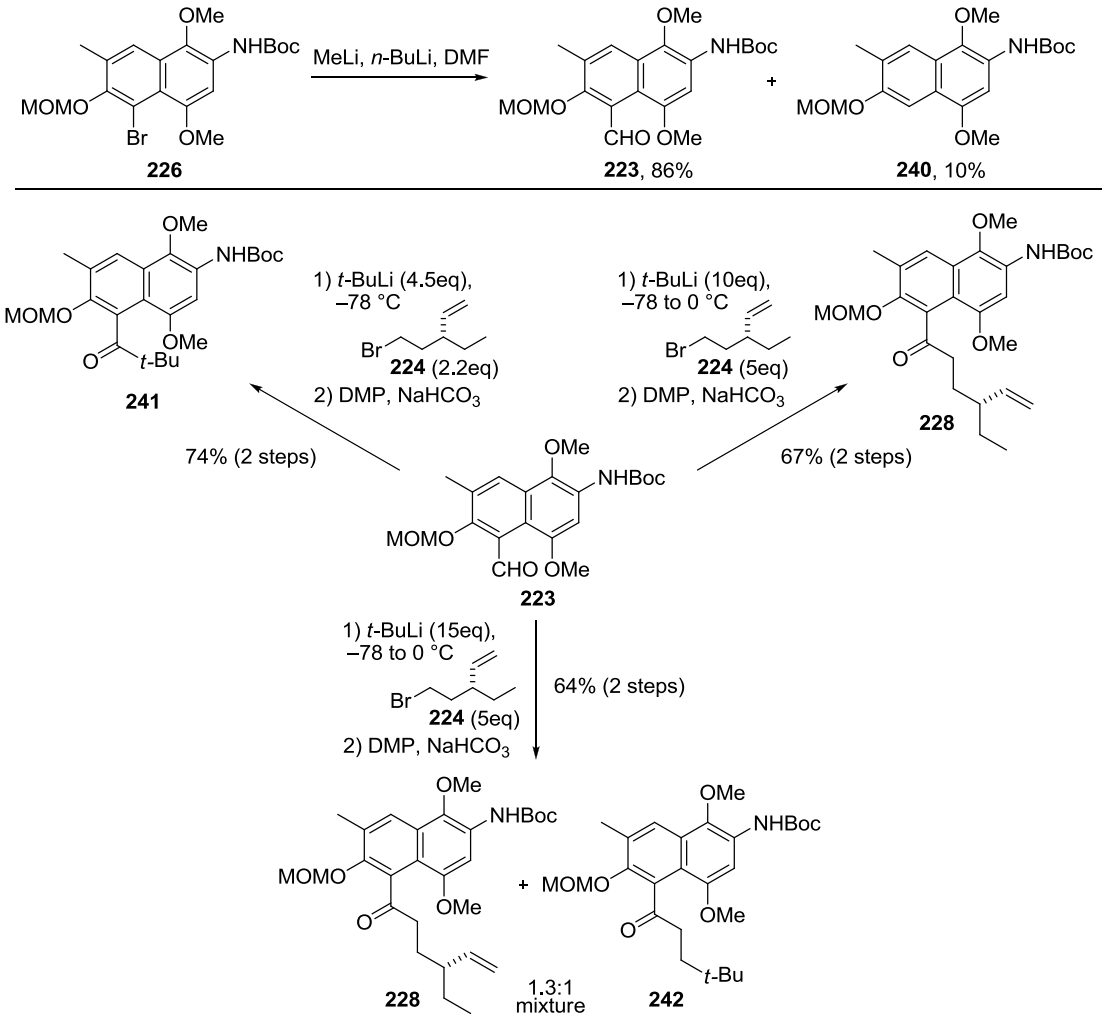


Scheme 66. Synthesis of western side chain **224**.

Since bromide side chain **224** was one carbon atom shorter than originally envisioned, we had to extend bromonaphthalene **226** by formation of naphthaldehyde **223**. Lithiation of **224** and quenching of the resulting anion with DMF provided compound **223** in good yield of 86% as well as protodemetallated byproduct **240** in 10% yield (Scheme 67, top). In order to attach the western side chain **224**, we had to optimize the reaction conditions carefully. Thus, conversion of naphthaldehyde **223** with 2.2 eq of bromide **224** and 4.5 eq of *t*-BuLi at −78 °C resulted in nucleophilic attack of the *t*-Bu anion into the aldehyde of naphthalene **223**. After

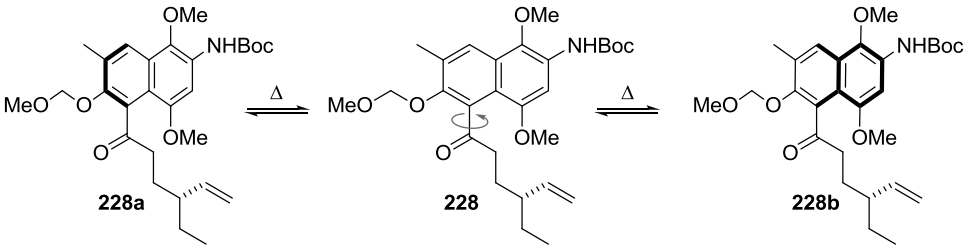
[xi] For the cleavage of the auxiliary see also PhD thesis of A. Hager.[54]
[xii] The synthesis of large amounts of compound **238** was performed together with A. Hager.

DMP oxidation we isolated ketone **241** in 74% yield over two steps (Scheme 67, bottom). This promising result showed that attack of large nucleophiles is possible in general, although aldehyde **223** is sterically crowded by the neighboring MOM and methoxy groups. On the other hand we realized that no transmetallation on **224** had taken place at −78 °C. Therefore, 5 eq of bromide **224** were treated with an excess (15 eq) of *t*-BuLi and the mixture was allowed to warm to 0 °C to form the lithiated side chain. After reaction with naphthaldehyde **223** and oxidation, the desired product **228** was isolated together with the co-polar side product **242** as a 1.3:1 mixture. Separation was only successful by HPLC. Compound **242** was presumably formed after *t*-BuLi had activated and cleaved THF[125] and the resulting anion had reacted with naphthaldehyde **223**. The best result of this alkylation reaction was obtained, when a mixture of bromide **224** (5 eq) and *t*-BuLi (10 eq) was stirred at 0 °C to undergo the transmetallation efficiently. The resulting lithiated side chain was attached to **223**, and after subsequent DMP oxidation, we finally observed naphthalene building block **228** in 67% over 2 steps. No byproduct was detected (Scheme 67, bottom).



Scheme 67. Preparation of naphthaldehyde **223** (top) and attachment of western side chain **228** (bottom).

Interestingly, NMR analysis revealed that the methylene groups in **228**, **241**, and **242** turned diastereotopic as soon as a side chain was attached to the carbonyl group. Since we did not observe any Boc-rotamers or NMR signal splitting in bromonaphthalene **226** and naphthaldehyde **223**, we attributed these findings to a hindered rotation around the axis between the carbonyl group and the naphthalene moiety (Scheme 68). Thus, in case of the desired product **228** the two diastereomers **228a** and **228b** could be seen in the NMR spectra as a 1:1 mixture.



Scheme 68. Rotation around the axis between the carbonyl group and the naphthalene moiety.

In order to show that the diastereomers **228a** and **228b** can be converted into each other by means of heating, we set out for high temperature ^{1}H-NMR experiments to follow the rotation around the axis. Indeed, at 60 °C the signals of the two diastereomers converged to one set of peaks in the NMR spectrum as it is illustrated for the methoxy protons of the MOM protecting group (Figure 20, box).

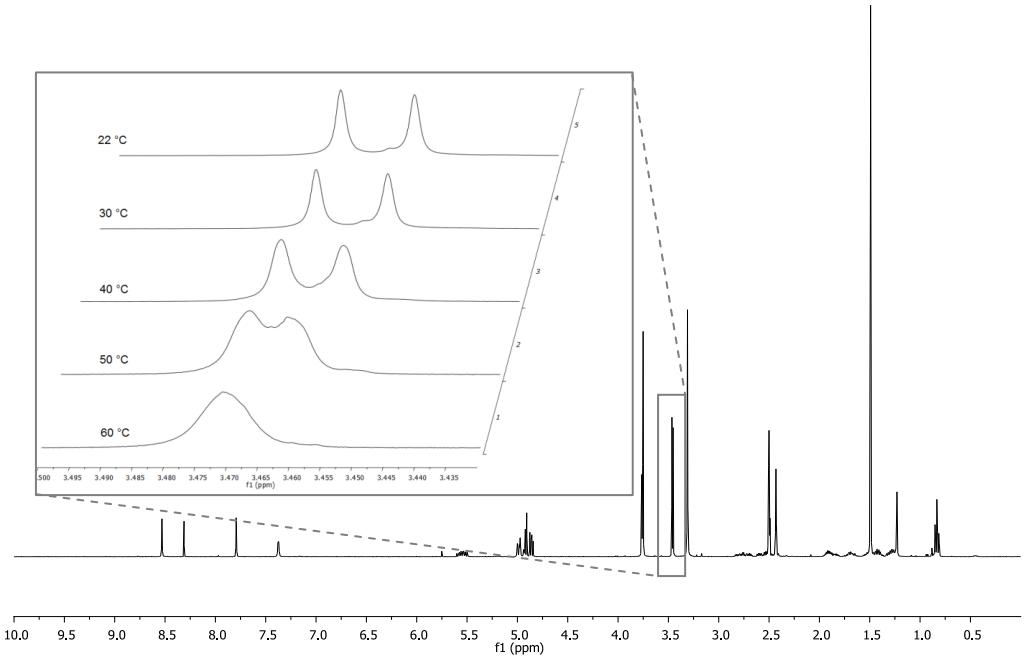
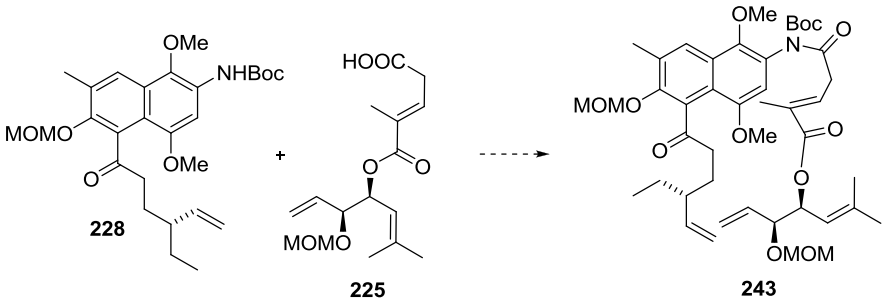


Figure 20. ^{1}H-NMR spectrum (400 MHz, dmso-d_6) of compound **228** at 22 °C and diastereomeric equilibration at elevated temperature (box).

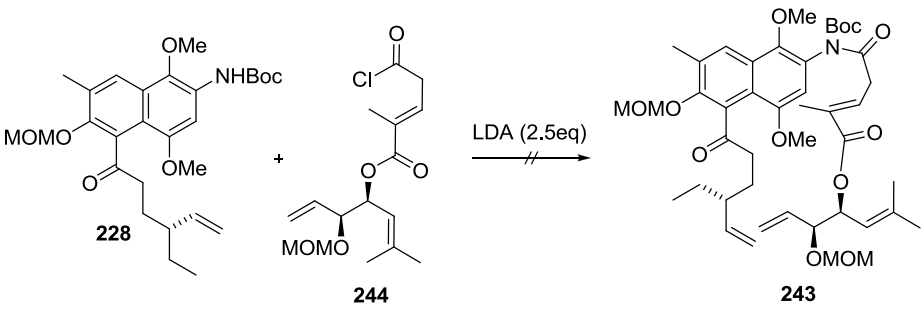
14.3. Attachment of the Eastern Side Chain[xiii]

The next stage of the synthesis was the coupling of the eastern side chain **225**[xiv] to the naphthalene building block **228** (Scheme 69). At the beginning of this investigation we decided to keep the Boc protecting group in **228** as it was reported that it can support the subsequent ring closing metathesis.[126] In addition, we envisioned a global deprotection of the MOM and Boc protecting groups under acidic conditions at the end of the synthesis to reduce the amount of steps.



Scheme 69. Envisioned coupling of the eastern side chain **225** to naphthalene building block **228**.

Along these lines, naphthalene building block **228** was deprotonated with LDA and the resulting anion was subjected to acid chloride **244**, which was prepared from carboxylic acid **225** and Ghosez's reagent or oxalyl chloride (Scheme 70). However, none of the desired product **243** was isolated and only staring material **228** was recovered.



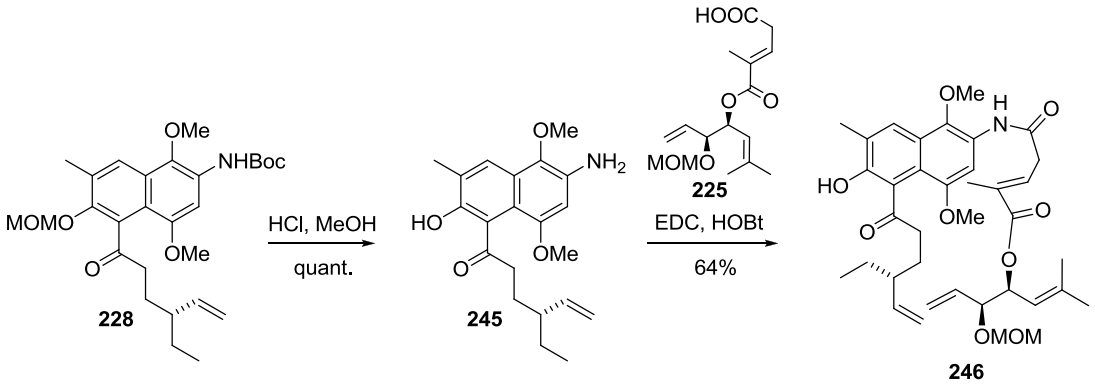
Scheme 70. Unsuccessful synthesis of compound **243**.

We realized soon that the direct acylation of Boc-protected naphthalene **228** with side chain **244** is more challenging than anticipated. The electronically withdrawing and sterically demanding effects of Boc protecting group might deactivate the nucleophilic nitrogen of naphthalene **228** in such a fashion that no reaction occurred. Therefore, we decided to remove

[xiii] The experimental work of this chapter was performed together with D. W. Terwilliger, an undergraduate researcher in the Trauner group.
[xiv] The synthesis of **225** was performed by A. Hager and was part of her PhD thesis.[54]

the protecting groups of **228** already at this stage prior to the side chain coupling. Acidic deprotection of both protecting groups with a freshly prepared solution of HCl in MeOH provided free aminonaphthalene **245** in quantitative yield (Scheme 71). It is worth noting that in compound **245** free rotation around the axis between the carbonyl group and the naphthalene moiety is enabled again. With aminonaphthalene **245** in hand, further studies regarding the coupling with side chain **225** could be made. Indeed, the successful amide coupling of free amine **245** with carboxylic acid **225** with EDC and HOBt was indicated by ^{1}H-NMR spectroscopy and high resolution mass spectrometry. The resulting naphthalene **246** incorporates both side chains and carbon atoms of the divergolides.

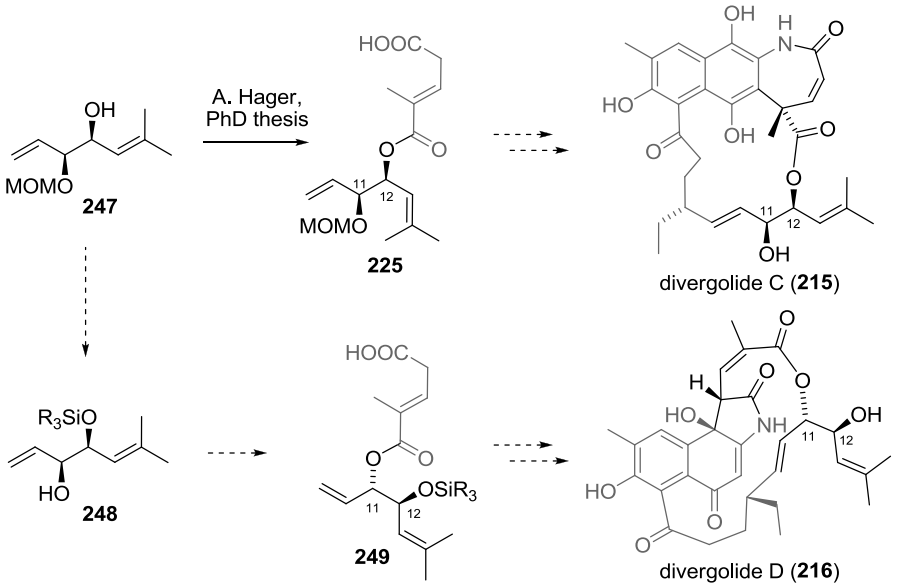
After the assembly of all three building blocks, the ring closing metathesis could be progressed to furnish the macrocycle. This is currently under investigation in the Trauner group by D. W. Terwilliger in course of his Master project.



Scheme 71. Attachment of western side chain **225** to building block **245**.

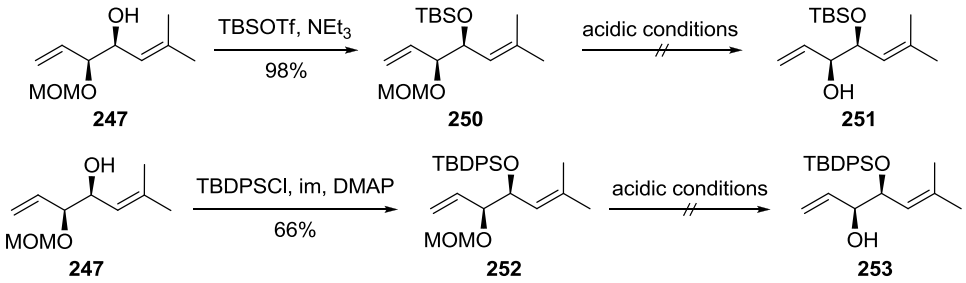
14.4. Targeting the Acyl Migration

In divergolides C (**215**) and D (**216**), the lactone moiety of the macrocycle is connected to different positions. Whereas in divergolide C (**215**), the cyclic ester is closed at the C-12 position, the C-11 position of divergolide D (**216**) serves as connection point. In the biosynthetic proposal (*vide supra*, Scheme 61) as well as in our biomimetic key step of our synthesis we hoped for a spontaneous acyl migration during the cyclization step. However, if no acyl migration took place, our eastern side chain **225** would only provide divergolide C (**215**) (Scheme 72). For the synthesis of divergolide D (**216**) a different substitution pattern of the side chain is necessary, as depicted in compound **249**.



Scheme 72. Different macrocyclic connections of divergolide C (**215**) and D (**216**).

In order to address the different substitution patterns, change of the protecting groups of **247** was envisioned to yield a silyl ether of type **248**. This compound would allow the preparation of side chain **249**, which should result in the formation of divergolide D (**216**). Along these lines, MOM ether **247**[xv] was converted into TBS ether **250** in excellent yields. Unfortunately, the MOM protective group could not be cleaved under acidic conditions (such as CSA, *B*-bromocatecholborane, $AlCl_3$, $Sc(OTf)_3$, $Bi(OTf)_3$, $MgBr_2$/EtSH), most of which gave intractable mixtures with little or no desired product **251**. Similar results were obtained with TBDPS ether **252** that was prepared from **247**. Again, deprotection conditions (such as PPTS, CSA, *B*-bromocatecholborane, HCl, $AlCl_3$, TFA) were not successful to yield **253**.



Scheme 73. Unsuccessful attempts to prepare silyl ethers **251** and **253**.

At this point, we decided to focus on the eastern side chain **225** as building block for the macrolide synthesis. No further experiments were carried out to synthesize the alternative side chain **249**.

[xv] Compound **247** was prepared by A. Hager.[54]

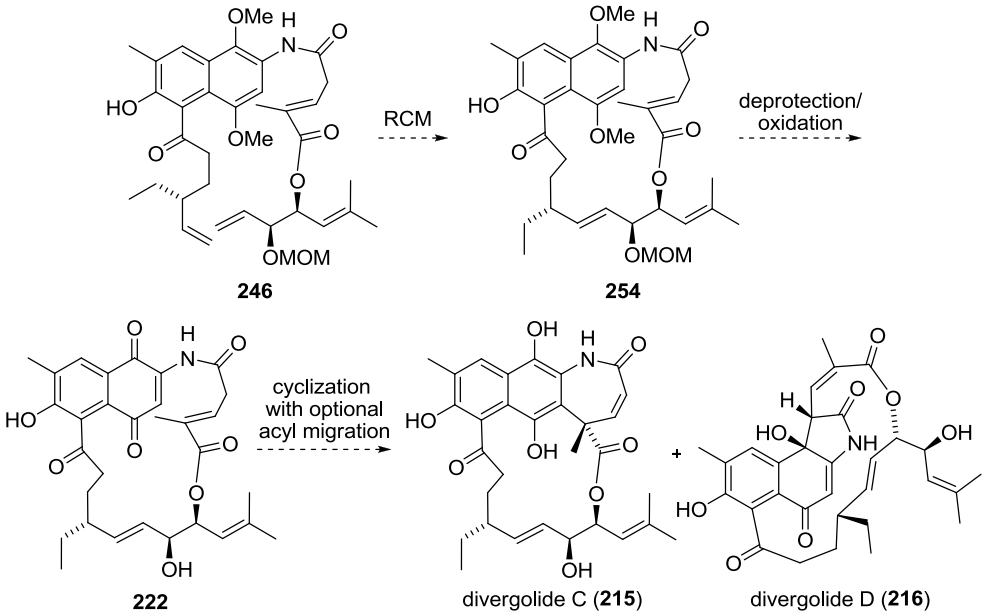
15. Conclusions and Further Work

In summary, progress toward the synthesis of divergolides C (**215**) and D (**216**) was achieved. Especially the installation of the side chains was investigated. In particular, we were attempting to prepare the longer western side chain **232** through enantioselective zirconium-catalyzed ring opening, following Hoveyda's methodology. However, only little amounts of desired alcohol **232** were observed and due to the high costs of the catalysts we changed the strategy for the side chain installation. In this context, we extended bromonaphthalene **226** by one carbon atom through forming the respective aldehyde **223**. The shorter side chain **224**, now needed for the attachment, was prepared by a diastereoselective monoorganocuprate addition to a Koga's auxiliary-derived Michael acceptor **237**. After removal of the auxiliary and conversion to the respective bromide **224**, we were able to prepare preparative amounts of enantiopure western side chain **224**, which was more challenging than initially expected. After some optimization, we were successful in the coupling of this side chain **224** to the naphthaldehyde **223** to yield naphthalene building block **228**. Since double acylation of the nitrogen of compound **228** failed, we removed the Boc and MOM protective groups to obtain the free aminonaphthalene **246**, which was ready for the attachment of the second side **225** chain through amide coupling to afford intermediate **246**. Finally, all three building blocks **223**, **224**, and **225** were assembled and investigations towards the closure of the macrocycle can be made. This is currently progressed by D. W. Terwilliger as a part of his Master project in the Trauner group.

In future, ring closing metathesis should provide macrocycle **254** and after a deprotection/oxidation sequence, general precursor **222** should be readily available (Scheme 74). This intermediate **222** would be more likely a metabolite in the divergolide biosynthesis. The final biomimetic cyclization and an optional acyl migration step should result in the first total synthesis of the divergolides C (**215**) and D (**216**). The natural products might be observed even during the oxidation step.

In order to address the acyl migration step, we tried to synthesize the alternative eastern side chain **249** that should directly give divergolide D (**216**) (Scheme 72). However, these attempts were not successful and no further experiments towards a different substitution pattern at the eastern side chain were carried out.

Overall, we advanced the synthesis of macrocycle **222**, which presumably is a natural product itself. This fact will be investigated together with the group of C. Hertweck.



Scheme 74. Overview of the remaining steps to divergolides C (**215**) and D (**216**).

Chapter IV: Synthesis of a Bacterial Signaling Molecule

16. Introduction

'It is time to close the book on infectious diseases (...).'

(William H. Stewart)

When the U.S. Surgeon General William H. Stewart made this infamous statement in the late 1960's,[127] it was believed that the fight against infectious diseases had been won. Unfortunately, this turned out to be a big mistake.[128] Infectious diseases are still one of the primary causes of death worldwide.[129] Although a wide range of antibiotics is available,[130] the increasing resistance of bacteria against existing drugs is a huge problem in the health care sector.[131] Thus, the search for new, antibiotic independent treatment options for bacterial transmitted diseases is gaining importance.

In this context, it is necessary to understand the complex biochemical processes that allow the communication of cells in bacterial strains.[132] For the cell-to-cell communication some bacteria use quorum sensing, a sophisticated molecular mechanism that is based on the production of small signaling molecules, the so-called autoinducers. When a specific cell density ('quorum') of a growing population is reached or the diffusion pathways of the signaling compounds through the cell membranes are limited, the amount of autoinducers increases. Upon passing a threshold concentration, the group responds with a population-wide alteration in specific gene expression. Quorum sensing is realized by bacteria to coordinate processes like bioluminescence, biofilm formation, or virulence factor production which would be ineffective if only individual cells undertook them. Thus, quorum sensing is a mechanism that allows bacterial strains to count their own cell numbers and determine the population density to function as multicellular organisms.[132-133]

A variety of different autoinducers have been identified,[132,134] but a novel class of signaling molecules, the α-hydroxyketones (AHKs), was found in different types of bacteria and attracted attention of the scientific community.[135] Over the past few years, AHK have been extensively investigated in the pathogens *Vibrio cholerae* and *Legionella pneumophila*.[133] Among them, the cholera autoinducer-1 (CAI-1) (**255**) and *Legionella* autoinducer-1 (LAI-1) (**256**) are the predominant and most efficient signaling molecules in their respective species (Figure 21).

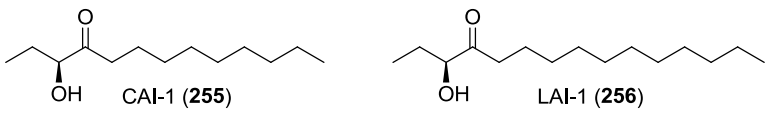


Figure 21. The structures of the signaling molecules cholera autoinducer-1 (CAI-1) (**255**) and *Legionella* autoinducer 1 (LAI-1) (**256**).

The bacteria strains *V. cholerae* and *L. pneumophila* are causative agent for fatal diseases. Whereas *V. cholerae* is responsible for the devastating diarrheal disease cholera,[136] the Legionnaires' disease or the milder form thereof, the Pontiac fever, is caused in more than 85% of all clinical cases by *L. pneumophila*.[137]

Given the effects of CAI-1 (**255**) and LAI-1 (**256**) on virulence, biofilm formation and extracellular filaments of *V. cholerae* or *L. pneumophila*, these signaling molecules or derivatives thereof have the potential for clinical or technical applications.

For a deeper understanding of the signaling circuit and in order to gain more insight in the mechanism of cell-cell communication, the research group of H. Hilbi investigates the gene regulation by α-hydroxyketone-mediated signaling in *L. pneumophila*. For this research, synthetic LAI-1 (**256**) is needed in pure form. Hence, this project aimed at providing the Hilbi group with pure *Legionella* autoinducer 1 (LAI-1) (**256**) for further investigation of the biochemical effects in signaling circuits of bacteria.

17. Autoinducer Regulatory Circuits in *V. Cholerae* and *L. Pneumophila*

V. cholerae and *L. pneumophila* colonize and grow in different ecological niches. According to changes in the environment the bacteria response with the respective gene expression to secure the survival of the species. The gene regulation proceeds through quorum sensing, which is dependent on the population density (as determined by the cell number per volume) or the growth phase (as determined by the growth rate).[133] The quorum sensing circuits of *V. cholerae* and *L. pneumophila* are detailed in the following sections.

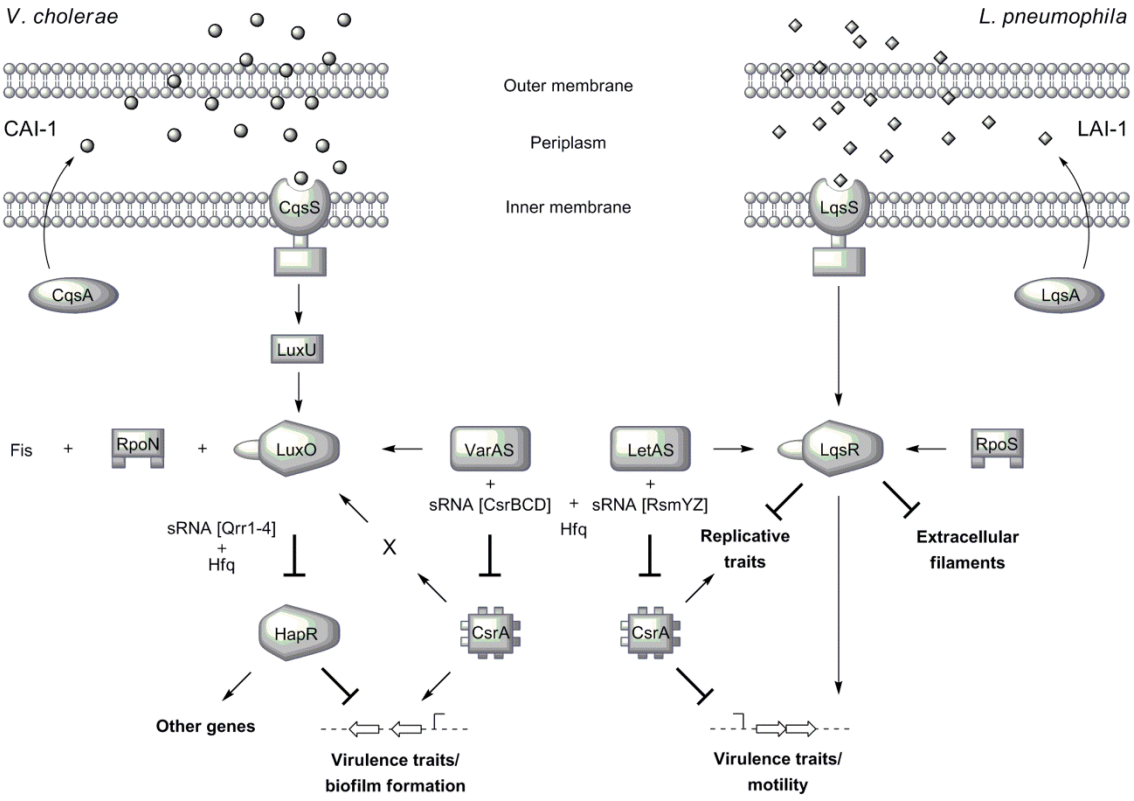
17.1. Quorum Sensing in *V. Cholerae*

The species *V. cholerae* are extracellular and pathogen bacteria, which are spread through contaminated water and food to provoke the infection disease cholera in humans. The facultative anaerobic organism regulates the gene expression through quorum sensing depending on the population density. In *V. cholerae* two parallel signaling circuits were identified, using different autoinducers.[133,135b] Here, only the α-hydroxyketone (AHK) mediated signaling is described.

Autoinducer CAI-1 (**255**) is produced by the enzyme CqsA (cholera quorum sensing autoinducer synthase) and recognized by the receptor CqsS (cholera quorum sensing sensor kinase) (Scheme 75, right). At low cell density, no or little amounts of autoinducers are present and the strain forms biofilm and expresses virulence factors. When the cell number is increased, the concentration of signaling molecules is raised and both processes are decelerated by quorum sensing.[133,135b]

In particular, in the absence of CAI-1 (**255**) (at a low cell density) the regulator protein LuxO is phosphorylated by the active phosphotransferase LuxU (Scheme 75, right). In combination with sigma factor RpoN and the small nucleotide protein Fis, phospho-LuxO induces the expression of the quorum regulatory sRNAs Qrr1−Qrr4. These sRNAs, together with the RNA chaperone Hfq, prevent the formation of the master regulating protein HapR by blocking the respective mRNA. The main regulator HapR would transcript several effector proteins, which could repress virulence traits and biofilm formation. On the other hand, in the presence of large amounts of CAI-1 (**255**) (at high bacterial density), the activity of LuxU is inhibited, regulator LuxO is dephosphorylated and inactive, the Qrr1−Qrr4 sRNAs are not formed, and HapR is produced. As a result, CAI-1 (**255**) represses the virulence and biofilm formation in *V. cholerae*. In addition, the two-component system VarAS promotes the formation of the sRNAs CsrBCD, which inhibit the activity of the global regulatory protein CsrA and regulate the expression of HapR. This phase of the life cycle allows the bacteria to leave the host cell and also further distribution in the environment to infect further hosts.[133,135b]

A complete understanding of the complex relationships of the AHK regulated signaling pathway in *V. cholerae* allows for a systematical treatment of infections in future. Thus, it could be clinically reasonable to apply AHK directly to the human body to repress virulence of the pathogen by manipulating the quorum sensing signaling circuit.



Scheme 75. AHK regulatory circuits in *L. pneumophila* (left) and *V. cholerae* (right).[xvi]

17.2. Quorum Sensing in *L. Pneumophila*

Legionellosis, including its two distinct forms Legionnaires' disease and the milder Pontiac fever, is an infection disease that exists worldwide.[137] The human disease is caused by different strains of the genus *Legionella*, among them the main elicitor *L. pneumophila*. Transmission of the pathogen typically happens through inhalation of contaminated aerosols. In contrast to *V. cholerae*, bacteria of the species *L. pneumophila* are intracellular pathogens that translocate their virulence factors directly into the host cell. Afterwards, the vacuoles of the cell are modified in such a fashion that the *Legionella* can reproduce there unlimitedly. Through interaction with the host, different cell functions like the formation of intracellular membrane are affected.[138] Subsequent lysis of the vacuoles and distribution of the bacteria cells enables new infection of further cells.

[xvi] Scheme adopted from the literature.[133]

Thus, two characteristic phases of a life circle of *L. pneumophila* are distinguished:[139] First, during the growing phase within the vacuole, the multiplication and growth of the cells is assisted by strong metabolic activity. Second, the stationary growth phase is reached, when the bacteria culture has reached a maximum regarding absolute cell numbers and the vacuole is destroyed. Then, virulence factors are produced and the stress resistance of the cells as well as motility by flagella formation is improved. As a result, the bacteria can reversibly switch between a stationary growth phase and a mobile infection state.

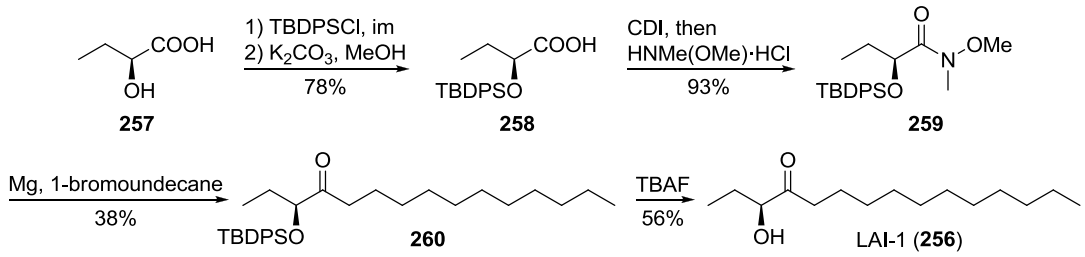
The signaling circuit in *L. pneumophila* that is regulated by AHK autoinducers is only linked to the stationary growth phase and is not dependent on the cell density as in *V. cholerae*. The underlying mechanisms of the pathway are investigated only to some extent, but it is known that the AHK LAI-1 (**256**) plays a major role in the signaling circuit.[133] In contrast to *V. cholerae*, no other autoinducer classes were found in *L. pneumophila*.[135a]

In analogy, LAI-1 (**256**) is produced by the enzyme LqsA (legionella quorum sensing autoinducer synthase) and detected by the receptor LqsS (legionella quorum sensing sensor kinase) (Scheme 75, left). The main regulator LqsR, which expresses virulence and motility of the bacteria, is controlled in combination with sigma factor RpoS and the two-component system LetAS. LetAS itself upregulates the production of small RNAs RsmYZ, which, together with the RNA chaperone Hfq, blocks the global repressor for traits CsrA. Although this signaling pathway is not fully understood, it was found that AHK signaling molecules promote the expression of virulence traits and increases motility. This part of the life cycle allows *L. pneumophila* to leave the growth and replication phase and enter the mobile infection state. Notably, while CAI-1 (**255**) represses virulence in *V. cholerae*, the opposite effect of LAI-1 (**256**) was observed in *L. pneumophila*.[133]

In order to complete the picture of the quorum sensing signaling circuit, the group of H. Hilbi investigates the effects autoinducer LAI-1 (**256**) on *L. pneumophila*. For this research, it could be possible to gain compound **256** from *Escherichia coli*, as described for CAI-1 (**255**),[135b] but the direct synthesis of LAI-1 (**256**) would provide pure material in large amounts. Thus, we decided to prepare and provide LAI-1 (**256**) to the Hilbi group to support further signaling research.

18. Synthesis of LAI-1[xvii]

The autoinducer LAI-1 (**256**) was prepared by following a similar procedure for the synthesis of CAI-1 (**255**).[135b] The commercially available (*S*)-2-hydroxybutyric acid (**257**) was protected as a TBDPS ether by a two step protocol to yield carboxylic acid **258**. Formation of Weinreb amide **259** followed by reaction with undecanemagnesium bromide provided ketone **260** in low, but unoptimized yield. Final deprotection with TBAF and HPLC purification gave LAI-1 (**256**) in pure form. Overall, more than 35 mg of the title compound was prepared and handed over to the group of H. Hilbi for further investigation of the signaling circuit.



Scheme 76. Synthesis of autoinducer LAI-1 (**256**).

19. Conclusions and Outlook

Overall, we were successful in the preparation of α-hydroxyketone autoinducer LAI-1 (**256**), which is regarded as the main signaling molecule of the quorum sensing circuit of *L. pneumophila*. Weinreb amide **259**, derived from (*S*)-2-hydroxybutyric acid (**257**), was converted into title compound **256** through attack of a Grignard reagent and subsequent deprotection with a total yield of 15% over 5 steps. The limiting step of that short sequence was the Grignard reaction that could potentially be optimized. Nevertheless, LAI-1 (**256**) was provided to the group of H. Hilbi to further investigate the AHK signaling pathways in *L. pneumophila*.

[xvii] The synthesis of LAI-1 (**256**) was performed with Felix Fahrnbauer, an undergraduate researcher in the Trauner group.

Chapter V: Experimental Procedures and Analytical Data

20. General Experimental Section

All reactions were performed under an atmosphere of argon and in oven-dried glassware (200 °C oven temperature) unless specified otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) was distilled prior to use from sodium and benzophenone, triethylamine (NEt_3) and *N*,*N*-Diisopropylethylamine (DIPEA) from calcium hydride. *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), dichloromethane (CH_2Cl_2), toluene, benzene, xylene, methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), and acetone were purchased from *Acros Organics* as 'extra dry' reagents under inert gas atmosphere and over molecular sieves. All other reagents were purchased from commercial sources and were used without further purification. Petroleum ether (PE) refers to fractions of isohexanes, which boil between 40 and 80 °C.

Analytical thin-layer chromatography (TLC) was carried out using pre-coated glass plates (silica gel 60 F_{254}) from *Merck*, and visualized by exposure to ultraviolet light (UV, 254 nm) and by staining with aqueous acidic ceric ammonium molybdate(IV) (CAM) solution. Flash column chromatography was performed using *Merck* silica gel 60 (40-63 μm particle size). For reversed phase (RP) TLC, pre-coated glass plates (silica gel C_{18} RP-18W/UV_{254}) from *Macherey-Nagel* were used, and preparative RP columns were performed on *Waters* silica gel (Preparative C_{18}, 125Å, 55-105 μm).

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian 300, Varian 400, Inova 400 or Varian 600 spectrometer. Chemical shifts (δ scale) are expressed in parts per million (ppm) and are calibrated using residual protic solvent as an internal reference ($CHCl_3$: δ = 7.26 ppm, MeOH-d_3: δ = 3.31 ppm, DMSO-d_5: δ = 2.50 ppm, acetic acid-d_3: δ = 2.04 ppm, $CHDCl_2$: δ = 5.32 ppm).[140] Data for ^{1}H-NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constants (Hz), integration). Couplings are expressed as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on the same spectrometers at 75, 100 and 150 Hz, respectively. Carbon chemical shifts (δ scale) are also expressed in parts per million (ppm) and are referenced to the central carbon resonances of the solvents ($CDCl_3$: δ = 77.16 ppm, MeOH-d_4: δ = 49.00 ppm, DMSO-d_5: δ = 39.52 ppm, acetic acid-d_3: δ = 179.00 ppm, $CHDCl_2$: δ = 53.84 ppm).[140] In order to assign the ^{1}H- and ^{13}C-NMR spectra, a range of 2D-NMR experiments (COSY, HSQC, HMBC, NOESY) were used as appropriate. The numbering of the proton and carbon atoms does not correspond to the IUPAC nomenclature.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System) equipped with an attenuated total reflection (ATR) measuring unit. IR data is reported in frequency of absorption (cm^{-1}). The IR bands are characterized as: w = weak, m = medium, s = strong, br = broad, or combinations thereof.

Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (electron ionization, EI) or on a Thermo Finnigan LTQ FT (electrospray ionization, ESI) instrument.

Melting points (mp) were measured on a Büchi Melting Point B-540 or SRS MPA120 EZ-Melt apparatus and are uncorrected.

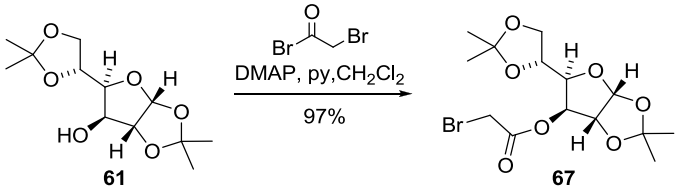
Optical rotations were measured at the given temperature (T in [°C]) on a Perkin-Elmer 241 or Krüss P8000-T polarimeter using a sodium lamp (λ = 589 nm, D-line). Measurements were carried out in a cell with a path length (l) of 0.5 dm. Concentrations (c) are expressed in g/(100 mL). Specific rotations ($[\alpha]_D^T$) were calculated using the equation $[\alpha]_D^T = 100 \cdot \alpha/(c \cdot l)$ and are reported in 10^{-1} deg cm^2 g^{-1}.

High performance liquid chromatography (HPLC) was performed with HPLC grade solvents and deionized water that was purified on a TKA MicroPure water purification system. All solvents were degassed with helium gas prior to use. Unless noticed otherwise, all experiments were carried out at room temperature; the column used is specified as appropriate. Analytical HPLC spectra were recorded on a ultra high performance liquid chromatography (UHPLC) system from the Agilent 1260 Infinity series (1260 degasser, 1260 Binary Pump VL, 1260 ALS auto sampler, 1260 TCC thermostatted column compartment, 1260 DAD diode array detector), which was computer-controlled through Agilent ChemStation software. Preparative HPLC was performed on a computer-operated Varian system (Galaxie Chromatography Software, two PrepStar pumps Model SD-1, manual injection, ProStar 335 Photo Diode Array Detector, 380-LC Evaporative Light Scattering Detector).

21. Experimental Procedures

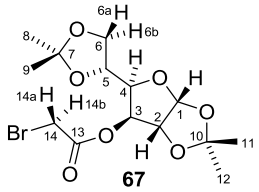
21.1. Experimental Data of Chapter I

(3a*R*,5*R*,6*S*,6a*R*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-tetrahydro-2*H*-furo[2,3-*d*][1,3]dioxol-6-yl 2-bromoacetate (67)[34]



A stirred solution of diacetone-D-glucose **61** (15.0 g, 57.6 mmol, 1.0 eq), DMAP (70.4 mg, 0.576 mmol, 10 mol%), and pyridine (6.96 mL, 86.4 mmol, 1.5 eq) in CH_2Cl_2 (125 mL) was cooled to 0 °C, and 2-bromoacetyl bromide was added dropwise. The reaction mixture was stirred for 40 min at 0 °C, then quenched at 0 °C with water (1.2 mL) and allowed to warm to room temperature. After stirring for an additional 15 min at room temperature, the resulting solution was diluted with EtOAc (200 mL). The organic phase was washed with water (2 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:acetone 99:1] provided bromo ester **67** (21.3 g, 56.0 mmol, 97%) as a white solid.

Bromo ester 67:



R_f = 0.39 [Petrol:EtOAc 4:1].

$[\alpha]_D^{21}$ = –39.6 (*c* = 0.93, MeOH).

mp: 51 – 53 °C.

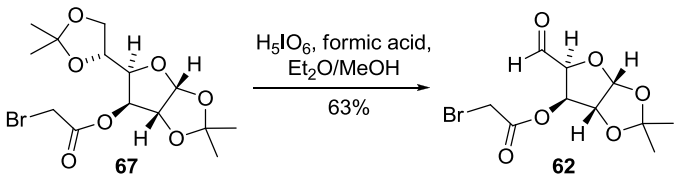
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.90 (d, *J* = 3.7 Hz, 1H, H-1), 5.32 (d, *J* = 2.8 Hz, 1H, H-3), 4.51 (d, *J* = 3.7 Hz, 1H, H-2), 4.27 – 4.19 (m, 2H, H-4, H-5), 4.11 (dd, *J* = 8.8, 5.6 Hz, 1H, H-6a), 4.01 (dd, *J* = 8.7, 4.5 Hz, 1H, H-6b), 3.87 (d, *J* = 12.3 Hz, 1H, H-14a or H-14b), 3.84 (d, *J* = 12.3 Hz, 1H, H-14a or H-14b), 1.52 (s, 3H, 3 x H-12), 1.41 (s, 3H, 3 x H-8), 1.32 (s, 3H, 3 x H-9 or 3 x H-11), 1.31 (s, 3H, 3 x H-9 or 3 x H-11) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.08 (C-13), 112.64 (C-10), 109.66 (C-7), 105.24 (C-1), 83.16 (C-2), 79.99 (C-4), 77.78 (C-3), 72.35 (C-5), 67.59 (C-6), 27.01 (C-8), 26.86 (C-12), 26.37 (C-11), 25.38 (C-9 or C-14), 25.35 (C-9 or C-14) ppm.

IR (ATR): $\tilde{\nu}$ = 2983 (m), 1769 (m), 1741 (m), 1383 (m), 1268 (m), 1205 (m), 1135 (m), 1069 (s), 1018 (s), 841 (m) cm^{-1}.

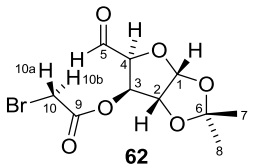
HRMS (ESI): calcd. for $C_{14}H_{25}BrNO_7^+$: 398.0809 $[M+NH_4]^+$
found: 398.0806 $[M+NH_4]^+$.

(3a*R*,5*S*,6*S*,6a*R*)-5-formyl-2,2-dimethyl-tetrahydro-2*H*-furo[2,3-*d*][1,3]dioxol-6-yl 2-bromoacetate (62)[34]



A solution of bromo ester **67** (6.71 g, 17.6 mmol, 1.0 eq) in Et_2O/MeOH (9:1, 50 mL) was cooled to 0 °C, and formic acid (25 mL) followed by periodic acid (4.81 g, 21.2 mmol, 1.2 eq) were added. The reaction mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for an additional 30 min until complete consumption of the starting material (as indicated by TLC analysis). The mixture was diluted with EtOAc (100 mL) and the organic phase was washed with water (2 x 20 mL), aq. $NaHCO_3$ (3 x 30 mL of a saturated solution), aq. $Na_2S_2O_3$ (3 x 10 mL of a saturated solution), dried ($MgSO_4$) and concentrated *in vacuo* to provide aldehyde **62** (3.44 g, 11.1 mmol, 63%) as a white solid.

Aldehyde 62:



R_f = 0.24 [PE:EtOAc 1:1] (streaking).

$[\alpha]_D^{21}$ = –17.3 (*c* = 1.0, MeOH).

mp: 66 – 67 °C.

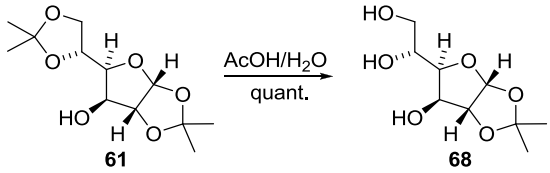
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1H, H-5), 6.09 (d, *J* = 3.5 Hz, 1H, H-1), 5.53 (dd, *J* = 3.4, 0.3 Hz, 1H, H-3), 4.74 (dd, *J* = 3.4, 0.8 Hz, 1H, H-4), 4.59 (d, *J* = 3.5 Hz, 1H, H-2), 3.78 (d, *J* = 12.5 Hz, 1H, H-10a or H-10b), 3.76 (d, *J* = 12.9 Hz, 1H, H-10a or H-10b), 1.51 (s, 3H, 3 x H-8), 1.33 (s, 3H, 3 x H-7) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.07 (C-5), 166.05 (C-9), 113.32 (C-6), 105.64 (C-1), 83.24 (C-4), 82.79 (C-2), 78.55 (C-3), 26.92 (C-8), 26.39 (C-7), 24.71 (C-10) ppm.

IR (ATR): $\tilde{\nu}$ = 3456 (w), 2987 (m), 1742 (s), 1376 (w), 1263 (m), 1160 (m), 1013 (s), 851 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{17}BrNO_6^+$: 326.0234 $[M+NH_4]^+$
found: 326.0234 $[M+NH_4]^+$.

1-[(3a*R*,5*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyl-tetrahydro-2*H*-furo[2,3-*d*][1,3]dioxol-5-yl] ethane-1,2-diol (68)[141]

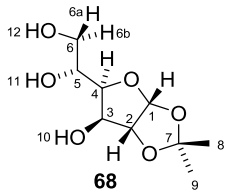


A solution of diacetone-D-glucose **61** (5.05 g, 19.4 mmol, 1.0 eq) in a mixture of acetic acid (90 mL) and water (60 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* to afford triol **68** (4.31 g, 19.6 mmol, quant.) as a white solid.

R_f = 0.21 [EtOAc].

$[\alpha]_D^{21}$ = –15.2 (*c* = 0.10, MeOH).

mp: 160 – 161 °C.



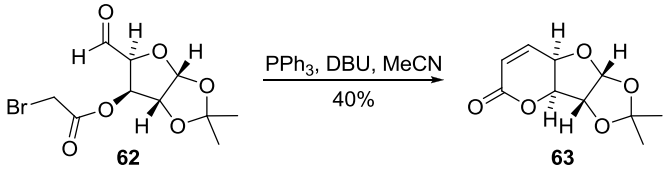
^{1}H-NMR (400 MHz, CD_3OD): δ = 5.87 (d, *J* = 3.7 Hz, 1H, H-1), 4.48 (d, *J* = 3.7 Hz, 1H, H-2), 4.20 (d, *J* = 2.7 Hz, 1H, H-3), 4.01 (dd, *J* = 8.4, 2.7 Hz, 1H, H-4), 3.91 – 3.85 (m, 1H, H-5), 3.76 (dd, *J* = 11.5, 3.1 Hz, 1H, H-6a or H-6b), 3.59 (dd, *J* = 11.5, 6.0 Hz, 1H, H-6a or H-6b), 1.45 (s, 3H, 3 x H-9), 1.29 (s, 3H, 3 x H-8) ppm.

^{13}C-NMR (100 MHz, CD_3OD): δ = 112.65 (C-7), 106.33 (C-1), 86.48 (C-2), 81.30 (C-4), 75.46 (C-3), 70.37 (C-5), 65.23 (C-6), 27.00 (C-9), 26.38 (C-8) ppm.

IR (ATR): $\tilde{\nu}$ = 3424 (s), 3317 (s), 2978 (m), 2927 (m), 1378 (m), 1263 (w), 1215 (m), 1037 (s), 1010 (s), 962 (m), 884 (m), 850 (m), 792 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_9H_{20}NO_6^+$: 238.1285 $[M+NH_4]^+$
found: 238.1285 $[M+NH_4]^+$.

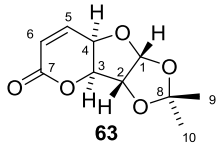
(1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodec-9-en-11-one (63)



A solution of aldehyde **62** (200 mg, 0.647 mmol, 1.0 eq) and PPh_3 (170 mg, 0.647 mmol, 1.0 eq) in MeCN (2 mL) was stirred at room temperature for 9 h. 1,8-Diazabicyclo[5.4.0]undec-7-ene (98.5 mg, 0.647 mmol, 1.0 eq) was added, and the mixture was stirred at room temperature for an additional 24 h, before it was diluted with Et_2O (30 mL). The organic phase

was washed with water (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:acetone 99:1] afforded unsaturated lactone **63** (55.5 mg, 0.262 mmol, 40%) as a white solid.

Unsaturated lactone 63:



63

R_f = 0.59 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = +28.9 (*c* = 0.56, MeOH).

mp: 70 °C.

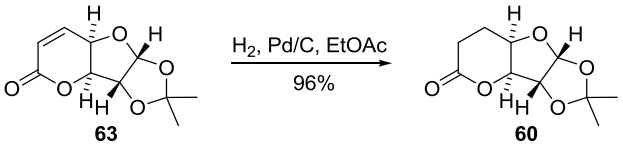
^{1}H-NMR (600 MHz, $CDCl_3$) δ = 6.96 (dd, *J* = 9.8, 5.7 Hz, 1H, H-5), 6.23 (d, *J* = 9.8 Hz, 1H, H-6), 6.02 (d, *J* = 3.7 Hz, 1H, H-1), 4.82 (d, *J* = 3.8 Hz, 1H, H-2), 4.81 (d, *J* = 3.2 Hz, 1H, H-3), 4.62 (dd, *J* = 5.7, 3.1 Hz, 1H, H-4), 1.53 (s, 3H, 3 x H-10), 1.35 (s, 3H, 3 x H-9) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 160.94 (C-7), 138.76 (C-5), 125.51 (C-6), 112.70 (C-8), 105.43 (C-1), 84.05 (C-2), 82.56 (C-3), 67.72 (C-4), 26.88 (C-10), 26.31 (C-9) ppm.

IR (ATR): $\tilde{\nu}$ = 2924 (w), 1729 (s), 1384 (w), 1212 (m), 1068 (s), 1017 (s), 888 (m), 826 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{16}NO_5^+$: 239.1023 $[M+NH_4]^+$
found: 239.1022 $[M+NH_4]^+$.

(1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecan-11-one (60)



63 **60**

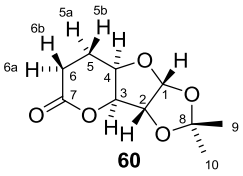
To a solution of unsaturated lactone **63** (246 mg, 1.16 mmol) in EtOAc (5 mL) was added palladium on charcoal (10 wt%, 47.0 mg), and the flask was purged with hydrogen gas five times. The mixture was then stirred under hydrogen atmosphere at room temperature for 15 h. The catalyst was removed by filtration through a pad of Celite, and the Celite was washed with EtOAc (20 mL). After concentrating the filtrate *in vacuo*, flash column chromatography [PE:EtOAc 4:1→3:1] afforded lactone **60** (238 mg, 1.11 mmol, 96%) as a white solid.

Lactone 60:

R_f = 0.46 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = +32.4 (*c* = 0.67, MeOH).

mp: 53 – 57 °C.



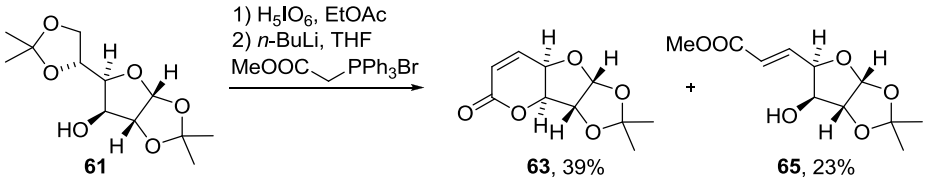
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.94 (d, *J* = 3.8 Hz, 1H, H-1)**,** 4.69 (m, 2H, H-2, H-3), 4.54 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1H, H-4), 2.65 (ddd, *J* = 17.6, 11.0, 6.6 Hz, 1H, H-6b), 2.45 (ddd, *J* = 17.5, 6.1, 4.4 Hz, 1H, H-6a), 2.27 – 2.06 (m, 2H, H-5a, H-5b), 1.50 (s, 3H, 3 x H-10), 1.32 (s, 3H, 3 x H-11) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.33 (C-7), 112.36 (C-8), 105.04 (C-1), 84.23 (C-2 or C-3), 83.85 (C-2 or C-3), 71.48 (C-4), 26.72 (C-9), 26.30 (C-10), 25.06 (C-6), 21.79 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 2982 (w), 2946 (w), 1738 (s), 1389 (w), 1183 (m), 1040 (s), 918 (m) cm^{-1}.

HRMS (EI): calcd. for $C_{10}H_{15}O_5^+$: 215.0914 $[M+H]^+$
found: 215.0927 $[M+H]^+$.

(1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodec-9-en-11-one (63) and methyl (2*E*)-3-[(3a*R*,5*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyl-tetrahydro-2*H*-furo[2,3-*d*][1,3] dioxol-5-yl]prop-2-enoate (65)[36]

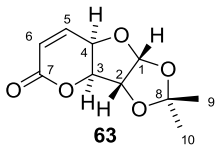


To a solution of diacetone-D-glucose **61** (3.00 g, 11.5 mmol, 1.0 eq) in EtOAc (215 mL) was added periodic acid (2.89 g, 12.7 mmol, 1.1 eq) and the resulting solution was stirred at room temperature for 2.5 h. During the reaction a white solid precipitated, which was removed by filtration through a pad of Celite. The Celite was washed with EtOAc (100 mL) and the filtrate was concentrated *in vacuo*. The crude sugar was then dried by azeotropic distillation with benzene (50 mL). A phosphonium ylide was prepared in a separate flask by adding dropwise a solution of *n*-BuLi in hexanes (2.5 M, 5.52 mL, 13.8 mmol, 1.2 eq) to a solution of (methoxycarbonylmethyl)triphenylphosphonium bromide (5.73 g, 13.8 mmol, 1.2 eq) in THF (180 mL) at 0 °C. This mixture was stirred at 0 °C for 30 min, and then a solution of the previously obtained crude sugar in THF (30 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 18 h. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 60 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 4:1→3:1→2:1→1:1] afforded unsaturated lactone **63** (959 mg, 4.52 mmol, 39%) as a white solid as well as *trans*-ester **65** (632 mg, 2.59 mmol, 23%) as colorless oil.

Unsaturated lactone 63:

Analytical data were identical with the material obtained earlier (*vide supra*).

R_f = 0.59 [PE:EtOAc 1:1].



$[\alpha]_D^{21}$ = +28.9 (*c* = 0.56, MeOH).

mp: 70 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ = 6.96 (dd, *J* = 9.8, 5.7 Hz, 1H, H-5), 6.23 (d, *J* = 9.8 Hz, 1H, H-6), 6.02 (d, *J* = 3.7 Hz, 1H, H-1), 4.82 (d, *J* = 3.8 Hz, 1H, H-2), 4.81 (d, *J* = 3.2 Hz, 1H, H-3), 4.62 (dd, *J* = 5.7, 3.1 Hz, 1H, H-4), 1.53 (s, 3H, 3 x H-10), 1.35 (s, 3H, 3 x H-9) ppm.

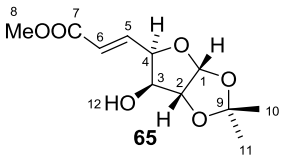
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 160.94 (C-7), 138.76 (C-5), 125.51 (C-6), 112.70 (C-8), 105.43 (C-1), 84.05 (C-2), 82.56 (C-3), 67.72 (C-4), 26.88 (C-10), 26.31 (C-9) ppm.

IR (ATR): $\tilde{\nu}$ = 2924 (w), 1729 (s), 1384 (w), 1212 (m), 1068 (s), 1017 (s), 888 (m), 826 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{16}NO_5^+$: 239.1023 $[M+NH_4]^+$

found: 239.1022 $[M+NH_4]^+$.

***Trans*-ester 65:**



R_f = 0.38 [PE:EtOAc 1:1].

$[\alpha]_D^{18}$ = –48.9° (*c* = 0.34, MeOH).

^{1}H-NMR (600 MHz, $CDCl_3$) δ = 6.92 (dd, *J* = 15.7, 4.3 Hz, 1H, H-5), 6.24 (d, *J* = 15.7 Hz, 1H, H-6), 5.97 (d, *J* = 3.7 Hz, 1H, H-1), 4.85 – 4.82 (m, 1H, H-4), 4.56 (d, *J* = 3.7 Hz, 1H, H-2), 4.23 (d, *J* = 2.8 Hz, 1H, H-3), 3.73 (s, 3H, 3 x H-8), 2.29 (br s, 1H, H-12), 1.49 (s, 3H, 3 x H-11), 1.31 (s, 3H, 3 x H-10) ppm.

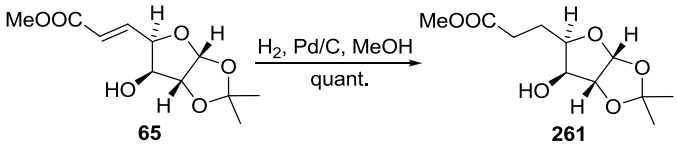
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 166.67 (C-7), 141.22 (C-5), 123.79 (C-6), 112.15 (C-9), 104.84 (C-1), 85.08 (C-2), 79.76 (C-4), 76.11 (C-3), 51.94 (C-8), 26.87 (C-11), 26.27 (C-10).

IR (ATR): $\tilde{\nu}$ = 3432 (m), 2957 (m), 1707 (s), 1311 (w), 1215 (m), 1072 (s), 1009 (s), 790 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{11}H_{20}NO_6^+$: 262.1285 $[M+NH_4]^+$

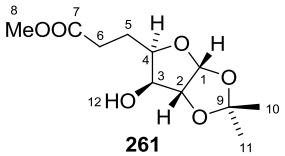
found: 262.1284 $[M+NH_4]^+$.

Methyl 3-[(3a*R*,5*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyl-tetrahydro-2*H*-furo[2,3-*d*][1,3]dioxol-5-yl]propanoate (261)



To a solution of unsaturated ester **65** (2.44 g, 10.0 mmol) in MeOH (40 mL) was added palladium on charcoal (10 wt%, 203 mg) and the flask was purged with hydrogen gas five times. The mixture was then stirred under hydrogen atmosphere at room temperature for 22 h. The catalyst was removed by filtration through a pad of Celite, and the Celite was washed with MeOH (60 mL). The filtrate was then concentrated *in vacuo* to afford ester **261** (2.47 g, 10.0 mmol, quant.) as a white solid.

Ester 261:



R_f = 0.31 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = –24.7 (*c* = 0.34, MeOH).

mp: 80 – 81 °C.

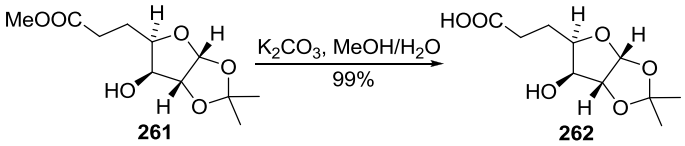
^{1}H-NMR (400 MHz, CD_3OD): δ = 5.83 (d, *J* = 3.8 Hz, 1H, H-1)**,** 4.46 (d, *J* = 3.8 Hz, 1H, H-2), 4.12 – 4.06 (m, 1H, H-4), 3.95 (d, *J* = 2.7 Hz, 1H, H-3), 3.67 (s, 3H, 3 x H-8), 2.49 – 2.42 (m, 2H, H-6a, H-6b), 1.99 – 1.88 (m, 2H, H-5a, H-5b), 1.43 (s, 3H, 3 x H-11), 1.29 (s, 3H, 3 x H-10) ppm.

^{13}C-NMR (100 MHz, CD_3OD): δ = 175.49 (C-7), 112.44 (C-9), 105.82 (C-1), 86.91 (C-2), 80.96 (C-4), 75.92 (C-3), 52.09 (C-8), 31.41 (C-6), 26.96 (C-11), 26.35 (C-10), 24.55 (C-5).

IR (ATR): $\tilde{\nu}$ = 3372 (s), 2991 (m), 1735 (s), 1372 (w), 1164 (m), 1082 (m), 788 (w) cm^{-1}.

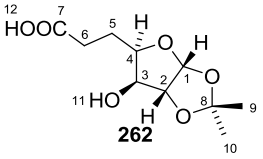
HRMS (ESI): calcd. for $C_{11}H_{18}NaO_6^+$: 269.0996 $[M+Na]^+$
found: 269.0994 $[M+Na]^+$.

3-[(3a*R*,5*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyl-tetrahydro-2*H*-furo[2,3-*d*][1,3]dioxol-5-yl] propanoic acid (262):



A solution of ester **261** (2.47 g, 10.0 mmol, 1.0 eq) and potassium carbonate (2.76 g, 20.0 mmol, 2.0 eq) in a mixture of MeOH and water (4:1, 50 mL) was stirred at room temperature for 22 h. The reaction mixture was concentrated under reduced pressure to a total volume of *ca.* 20 mL and then diluted with water (50 mL). After extracting the mixture with EtOAc (50 mL), the aqueous layer was acidified to pH 1 with aq. HCl (1 N, *ca.* 45 mL). The acidic aqueous layer was further extracted with EtOAc (6 x 100 mL). The combined organic fractions were then dried ($MgSO_4$) and concentrated *in vacuo* to afford carboxylic acid **262** (2.30 g, 9.90 mmol, 99%) as a white solid.

Carboxylic acid 262:



R_f = 0.71 [EtOAc:MeOH (0.5% formic acid) 9:1].

$[\alpha]_D^{21}$ = –22.9 (*c* = 0.44, MeOH).

mp: 96 – 97 °C.

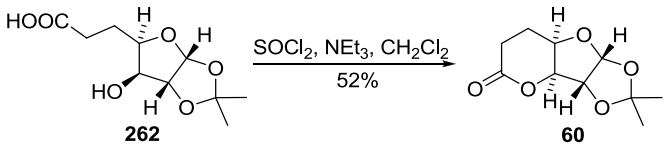
^{1}H-NMR (400 MHz, CD_3OD): δ = 5.83 (d, *J* = 3.8 Hz, 1H, H-1)**,** 4.47 (d, *J* = 3.8 Hz, 1H, H-2), 4.14 – 4.08 (m, 1H, H-4), 3.96 (d, *J* = 2.7 Hz, 1H, H-3), 2.46 – 2.39 (m, 2H, H-6a, H-6b), 1.98 – 1.86 (m, 2H, H-5a, H-5b), 1.43 (s, 3H, 3 x H-10), 1.29 (s, 3H, 3 x H-9) ppm.

^{13}C-NMR (100 MHz, CD_3OD): δ = 177.08 (C-7), 112.44 (C-8), 105.82 (C-1), 86.91 (C-2), 81.06 (C-4), 75.92 (C-3), 31.45 (C-6), 26.97 (C-10), 26.35 (C-9), 24.55 (C-5).

IR (ATR): $\tilde{\nu}$ = 3361 (m), 2988 (m), 1715 (s), 1382 (m), 1195 (s), 997 (s), 866 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{15}O_6^-$: 231.0874 $[M–H]^-$
found: 231.0872 $[M–H]^-$.

(1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecan-11-one (60)



A solution of carboxylic acid **262** (2.28 g, 9.82 mmol, 1.0 eq) and triethylamine (2.72 mL, 19.6 mmol, 2.0 eq) in CH_2Cl_2 (200 mL) was cooled to 0 °C and thionyl chloride (1.42 mL, 19.6 mmol, 2.0 eq) was added dropwise. The mixture was allowed to warm to room temperature and stirred at this temperature for 20 min. The mixture was then quenched with aq. NH_4Cl (100 mL of a saturated solution) and the mixture extracted with CH_2Cl_2 (3 x 150 mL). The combined organic fractions were washed with water (200 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 4:1→3:1→2:1] afforded lactone **60** (1.09 g, 5.09 mmol, 52%) as a white solid.

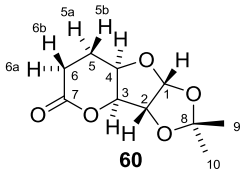
Lactone 60:

Analytical data were identical with the material obtained earlier (*vide supra*).

R_f = 0.46 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = +32.4 (*c* = 0.67, MeOH).

mp: 53 – 57 °C.



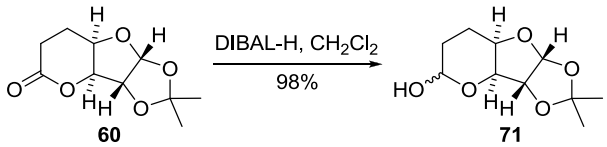
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.94 (d, *J* = 3.8 Hz, 1H, H-1)**,** 4.69 (m, 2H, H-2,H-3), 4.54 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1H, H-4), 2.65 (ddd, *J* = 17.6, 11.0, 6.6 Hz, 1H, H-6b), 2.45 (ddd, *J* = 17.5, 6.1, 4.4 Hz, 1H, H-6a), 2.27 – 2.06 (m, 2H, H-5a, H-5b), 1.50 (s, 3H, 3 x H-10), 1.32 (s, 3H, 3 x H-11) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.33 (C-7), 112.36 (C-8), 105.04 (C-1), 84.23 (C-2 or C-3), 83.85 (C-2 or C-3), 71.48 (C-4), 26.73 (C-9), 26.30 (C-10), 25.07 (C-6), 21.79 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 2982 (w), 2946 (w), 1738 (s), 1389 (w), 1183 (m), 1040 (s), 918 (m) cm^{-1}.

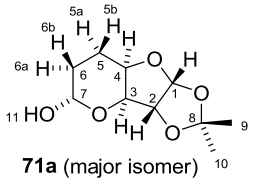
HRMS (EI): calcd. for $C_{10}H_{15}O_5^+$: 215.0914 $[M+H]^+$
found: 215.0927 $[M+H]^+$.

(1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecan-11-ol (71):



A solution of lactone **60** (380 mg, 1.77 mmol, 1.0 eq) in CH_2Cl_2 (6 mL) was cooled to –78 °C and a solution of diisobutylaluminium hydride in CH_2Cl_2 (1.0 M, 1.95 mL, 1.95 mmol, 1.1 eq) was added dropwise. After stirring the mixture at –78 °C for 20 min, the reaction was quenched at –78 °C by addition of aq. Rochelle salt (1.5 mL of a saturated solution) and water (1 mL). The mixture was allowed to warm to room temperature, stirred at this temperature for an additional 3 h and was then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford lactol **71** (374 mg, 1.73 mmol, 98%) as a white solid consisting of two diastereomers (d.r. 1.9:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Lactol 71:



R_f = 0.41 [PE:EtOAc 1:1].

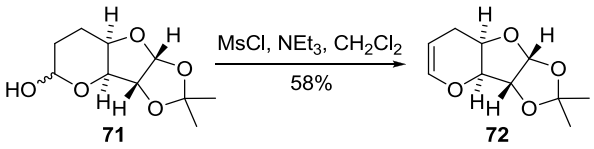
^{1}H-NMR (600 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 5.90 (d, *J* = 3.8 Hz, 1H, H-1), 5.23 – 5.21 (m, 1H, H-7), 4.47 (d, *J* = 3.8 Hz, 1H, H-2), 4.23 (br s, 2H, H-3, H-4), 2.88 (br s, 1H, H-11), 2.17 – 2.09 (m, 1H, H-5a or H-5b), 1.93 – 1.86 (m, 2H, H-5a or H-5b, H-6a or H-6b), 1.55 – 1.50 (m, 1H, H-6a or H-6b), 1.49 (s, 3H, 3 x H-10), 1.31 (s, 3H, 3 x H-9) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 111.51 (C-8), 105.32 (C-1), 91.29 (C-7), 84.85 (C-2), 73.37 (C-4), 72.58 (C-3), 26.78 (C-10), 26.30 (C-9), 23.66 (C-6), 17.95 (C-5).

IR (ATR): $\tilde{\nu}$ = 3429 (s), 2931 (s), 1374 (m), 1208 (m), 1079 (s), 820 (m) cm^{-1}.

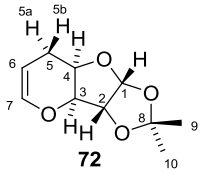
HRMS (EI): calcd. for $C_{10}H_{15}O_5^-$: 215.0925 $[M–H]^-$
found: 215.0931 $[M–H]^-$.

(1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodec-10-ene (72):



A solution of lactol **71** (79.5 mg, 0.368 mmol, 1.0 eq) and triethylamine (816 µL, 5.89 mmol, 16 eq) in CH_2Cl_2 (15 mL) was cooled to 0 °C and methanesulfonyl chloride (37.1 µL, 0.478 mmol, 1.3 eq) was added dropwise. The mixture was heated to 50 °C and stirred at this temperature for 2.5 h. After cooling to room temperature, volatile material was removed *in vacuo*, and the residue was subjected to gravity column chromatography [CH_2Cl_2] to afford dihydropyran **72** (42.2 mg, 0.213 mmol, 58%) as a white solid.

Dihydropyran 72:



R_f = 0.79 [PE:EtOAc 2:1].

$[\alpha]_D^{21}$ = +98.7 (*c* = 0.79, MeOH).

mp: 39 – 40 °C.

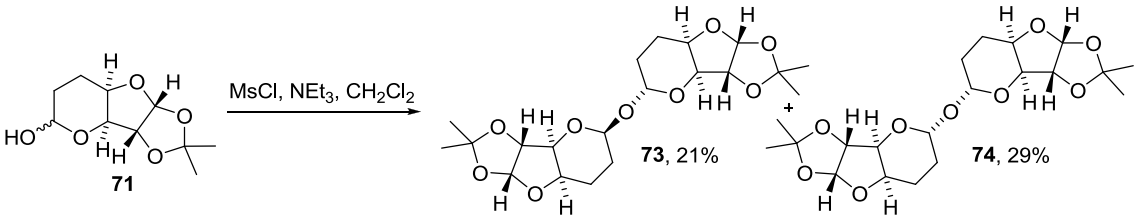
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.31 – 6.28 (m, 1H, H-7), 5.94 (d, *J* = 3.8 Hz, 1H, H-1), 4.69 – 4.65 (m, 1H, H-6), 4.60 (d, *J* = 3.8 Hz, 1H, H-2), 4.52 – 4.48 (m, 1H, H-4), 4.13 (br s, 1H, H-3), 2.40 – 2.33 (m, 1H, H-5a or H-5b), 4.60 (dd, *J* = 18.7, 4.4 Hz, 1H, H-5a or H-5b), 1.52 (s, 3H, 3 x H-10), 1.33 (s, 3H, 3 x H-9) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 141.94 (C-7), 111.94 (C-8), 105.00 (C-1), 97.24 (C-6), 84.25 (C-2), 75.92 (C-3), 72.50 (C-4), 26.66 (C-10), 26.27 (C-9), 20.72 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 2936 (m), 1662 (m), 1376 (w), 1208 (m), 1076 (s), 829 (m) cm^{-1}.

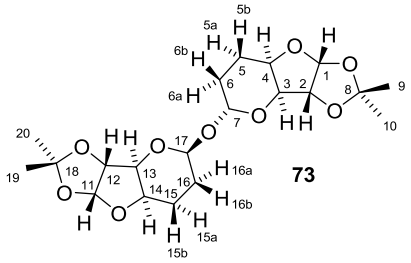
HRMS (EI): calcd. for $C_{10}H_{14}O_4^+$: 198.0887 $[M]^+$
found: 198.0886 $[M]^+$.

(2*R*,6*R*)-11-{[(2*R*,6*R*,11*S*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecan-11-yl]oxy}-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecane (73) and (2*R*,6*R*)-11-{[(2*R*,6*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecan-11-yl]oxy}-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodecane (74)



A solution of lactol **71** (333 mg, 1.54 mmol, 1.0 eq) and triethylamine (500 µL, 3.61 mmol, 2.3 eq) in CH_2Cl_2 (4 mL) was cooled to 0 °C and methanesulfonyl chloride (164 µL, 2.00 mmol, 1.3 eq) was added dropwise. The mixture was heated to 50 °C and stirred at this temperature for 20 h. After cooling to room temperature, volatile material was removed *in vacuo*, and the residue was subjected to gravity column chromatography [CH_2Cl_2] to afford dimer **73** (68.5 mg, 0.165 mmol, 21%) as a colorless oil and C_2-symmetric dimer **74** (91.9 mg, 0.222 mmol, 29%) as a white solid.

Dimer 73:



R_f = 0.40 [PE:EtOAc 2:1].

$[\alpha]_D^{21}$ = +15.4 (*c* = 0.36, MeOH).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.95 (d, *J* = 3.8 Hz, 1H, H-11), 5.89 (d, *J* = 3.8 Hz, 1H, H-1), 4.99 (br s, 1H, H-7), 4.59 – 4.56 (m, 1H, H-17), 4.55 (d, *J* = 3.8 Hz, 1H, H-12), 4.47 (d, *J* = 3.7 Hz, 1H, H-2), 4.33 (d, *J* = 2.1 Hz, 1H, H-3), 4.24 – 4.42 (m, 1H, H-4), 4.12 – 4.09 (m, 1H, H-14), 4.06 (d, *J* = 1.9 Hz, 1H, H-13), 2.23 – 2.19 (m, 1H, H-15a or H-15b), 2.14 – 2.06 (m, 1H, H-5a or H-5b), 1.93 – 1.85 (m, 2H, H-5a or H-5b, H-6a or H-6b), 1.83 – 1.73 (m, 2H, H-15a or H-15b, H-16a or H-16b), 1.62 – 1.55 (m, 1H, H-16a or H-16b), 1.55 – 1.48 (m, 1H, H-6a or H-6b), 1.50 (s, 3H, 3 x H-10 or 3 x H-20), 1.49 (s, 3H, 3 x H-10 or 3 x H-20), 1.33 (s, 3H, 3 x H-9 or 3 x H-19), 1.32 (s, 3H, 3 x H-9 or 3 x H-19) ppm.

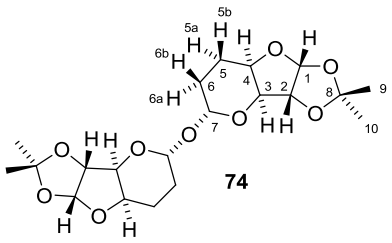
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 111.50 (C-8 or C-18), 111.49 (C-8 or C-18), 105.46 (C-11), 105.29 (C-1), 100.50 (C-17), 96.73 (C-7), 84.85 (C-2), 84.61 (C-12), 79.68 (C-13), 73.44 (C-4), 73.30 (C-3), 72.30 (C-14), 26.88 (C-10 or C-20), 26.82 (C-10 or C-20), 26.36 (C-9 or C-19), 26.32 (C-9 or C-19), 25.60 (C-16), 24.06 (C-15), 23.65 (C-6), 18.56 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 2934 (s), 1445 (w), 1372 (m), 1213 (m), 1164 (m), 1068 (s), 1010 (s), 947 (m), 902 (m), 825 (m), 756 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{20}H_{34}NO_9^+$: 432.2228 $[M+NH_4]^+$

found: 432.2227 $[M+NH_4]^+$.

C_2-symmetric dimer 74:



R_f = 0.34 [PE:EtOAc 4:1].

$[\alpha]_D^{20}$ = +208.2 (c = 1.0, MeOH).

mp: 149 – 153 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.91 (d, J = 3.8 Hz, 2H, 2 x H-1), 5.10 (br s, 2H, 2 x H-7), 4.48 (d, J = 3.8 Hz, 2H, 2 x H-2), 4.23 – 4.21 (m, 2H, 2 x H-4), 3.97 (d, J = 2.1 Hz, 2H, 2 x H-3), 2.10 – 2.04 (m, 2H, 2 x H-5a or 2 x H-5b), 1.99 – 1.89 (m, 4H, 2 x H-5a or 2 x H-5b, 2 x H-6a or 2 x H-6b), 1.49 (s, 6H, 6 x H-10), 1.52 – 1.44 (m, 2H, 2 x H-5a or 2 x H-5b), 1.31 (s, 6H, 6 x H-9) ppm.

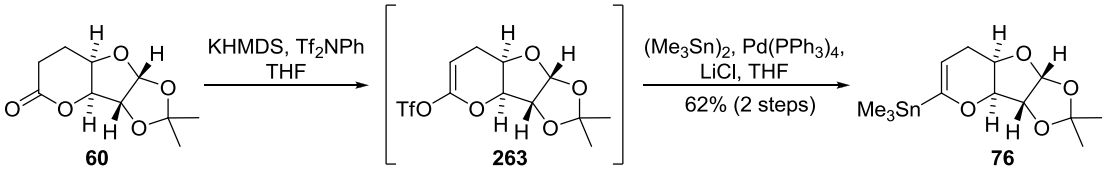
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 111.47 (2 x C-8), 105.31 (2 x C-1), 91.80 (2 x C-7), 84.68 (2 x C-2), 73.25 (2 x C-4), 72.97 (2 x C-3), 26.78 (2 x C-10), 26.27 (2 x C-9), 23.32 (2 x C-6), 18.47 (2 x C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 2936 (s), 1443 (w), 1376 (m), 1214 (m), 1134 (m), 1077 (s), 1016 (s), 982 (s), 902 (m), 827 (m), 745 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{20}H_{34}NO_9^+$: 432.2228 $[M+NH_4]^+$

found: 432.2228 $[M+NH_4]^+$.

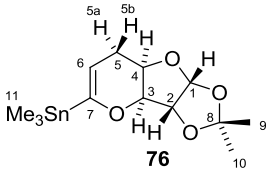
[(2*R*,6*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodec-10-en-11-yl]trimethyl-stannane (76):



A solution of lactone **60** (50.0 mg, 1.77 mmol, 1.0 eq) and *N*-phenyl-bis(trifluoromethanesulfonimide) (91.6 mg, 0.256 mmol, 1.1 eq) in THF (3 mL) was added slowly (over 45 min) with the aid of a syringe pump to a –78 °C cold solution of potassium hexamethyldisilazide (0.5 M in toluene, 606 µL, 0.303 mmol, 1.3 eq) in THF (1 mL). After

complete addition, the reaction mixture was stirred for an additional 10 min at –78 °C, and was then allowed to warm to room temperature. Volatile material was removed *in vacuo*, and the residue was subjected to flash column chromatography [PE:Et_2O 4:1 (+ 0.5% NEt_3)] to afford triflate **263**. The sensitive compound **263** was immediately dissolved in THF (6 mL) and hexamethyldistannane (72.5 µL, 0.350 mmol, 1.5 eq), lithium chloride (98.8 mg, 2.33 mmol, 10 eq) followed by tetrakis(triphenylphosphine)palladium(0) (13.5 mg, 11.7 µmol, 5 mol%) were added. The mixture was stirred at room temperature for 24 h, and then volatile material was removed *in vacuo*. The residue was subjected to column chromatography [PE:Et_2O 9:1] to afford stannane **76** (52.4 mg, 0.145 mmol, 62% over two steps) as a colorless oil.

Stannane 76:



76

R_f = 0.22 [PE:Et_2O 9:1].

$[\alpha]_D^{19}$ = +41.4 (c = 0.24, $CHCl_3$).

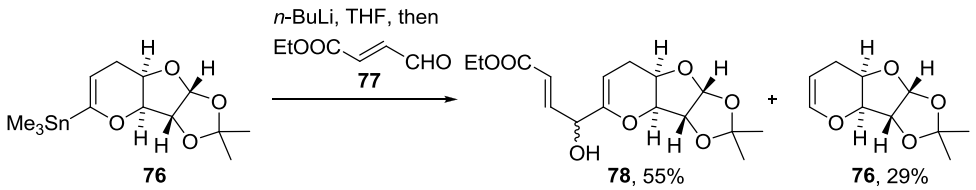
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.92 (d, J = 3.8, 1H, H-1), 4.79 – 4.71 (m, 1H, H-6), 4.58 (d, J = 3.8 Hz, 1H, H-2), 4.52 – 4.49 (m, 1H, H-4), 4.05 (br s, 1H, H-3), 2.40 – 2.32 (m, 1H, H-5a), 2.28 – 2.21 (m, 1H, H-5b), 1.52 (s, 3H, 3 x H-10), 1.33 (s, 3H, 3 x H-9), 0.15 (s, 9H, 3 x H-11) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.87 (C-7), 111.77 (C-8), 107.77 (C-6), 105.10 (C-1), 84.59 (C-2), 75.55 (C-3), 72.79 (C-4), 26.72 (C-10), 26.30 (C-9), 21.49 (C-5), –9.65 (C-11) ppm.

IR (ATR): $\tilde{\nu}$ = 2924 (s), 1623 (w), 1373 (w), 1077 (s), 1016 (m), 767 (m) cm^{-1}.

HRMS (EI): calcd. for $C_{13}H_{22}O_4Sn^+$: 362.0535 $[M]^+$
found: 362.0541 $[M]^+$.

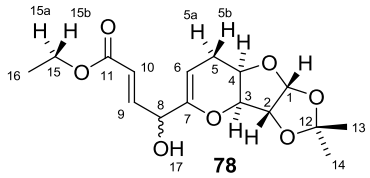
Ethyl (2*E*)-4-[(2*R*,6*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo[6.4.0.0^{2,6}]dodec-10-en-11-yl]-4-hydroxybut-2-enoate (78) and (1*S*,2*R*,6*R*,8*R*)-4,4-dimethyl-3,5,7,12-tetraoxatricyclo [6.4.0.0^{2,6}]dodec-10-ene (72):



A solution of stannane **76** (46.5 mg, 0.129 mmol, 1.0 eq) in THF (5 mL) was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (2.4 M, 64.6 µL, 0.155 mmol, 1.2 eq) was added

dropwise. The mixture was stirred at –78 °C for 15 min, then aldehyde **77** (18.7 µL, 0.155 mmol, 1.2 eq) was added and the resulting solution was stirred at –78 °C for an additional 15 min. The reaction was quenched with aq. NH_4Cl (4 mL of a saturated solution) and the mixture extracted with Et_2O (3 x 25 mL). The combined organic fractions were washed with brine (25 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→4:1→3:1] afforded alcohol **78** (23.1 mg, 70.8 µmol, 55%) as a colorless oil consisting of two diastereomers in a ratio of 1.2:1 (as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture, as well as protodemetallated product **72** (7.40 mg, 37.3 µmol, 29%) as a white solid.

Alcohol 78:



R_f = 0.52 [PE:EtOAc 1:1].

^{1}H-NMR (600 MHz, $CDCl_3$) (mixture of isomers, both isomers quoted, minor isomer primed): δ = 6.96 – 6.89 (m, 2H, H-9, H-9'), 6.14 – 6.06 (m, 2H, H-10, H-10'), 5.92 – 5.88 (m, 2H, H-1, H-1'), 4.86 – 4.83 (m, 1H, H-6), 4.81 – 4.78 (m, 1H, H-6'), 4.67 – 4.60 (m, 4H, H-2, H-2', H-8, H-8'), 4.50 – 4.47 (m, 2H, H-4, H-4'), 4.23 – 4.17 (m, 6H, H-3, H-3', H-15a, H-15b, H-15a', H-15b'), 2.43 – 2.33 (m, 4H, H-5a, H-5b, H-5a', H-5b'), 1.52 (br s, 6H, 3 x H-14, 3 x H-14'), 1.33 (br s, 6H, 3 x H-13, 3 x H-13'), 1.30 – 1.27 (m, 6H, 3 x H-16, 3 x H-16') ppm.

^{13}C-NMR (150 MHz, $CDCl_3$) (mixture of isomers, both isomers quoted, minor isomer primed): δ = 166.55 (C-11), 166.49 (C-11'), 150.61 (C-7), 150.47 (C-7'), 146.21 (C-9), 145.71 (C-9'), 121.97 (C-10'), 121.58 (C-10), 112.07 (C-12), 112.06 (C-12'), 104.87 (C-1'), 104.86 (C-1), 95.29 (C-6'), 94.69 (C-6), 84.08 (C-2'), 84.03 (C-2), 77.44 (C-3 or C-3'), 77.39 (C-3 or C-3'), 72.08 (C-4), 72.03 (C-4'), 71.44 (C-8), 71.30 (C-8'), 60.69 (C-15'), 60.67 (C-15), 26.58 (C-14 and C-14'), 26.21 (C-13), 26.20 (C-13'), 21.47 (C-5'), 21.46 (C-5), 14.34 (C-16 and C-16').

IR (ATR): $\tilde{\nu}$ = 3420 (m), 2962 (s), 1703 (m), 1374 (m), 1081 (s), 1016 (s), 865 (w) cm^{-1}.

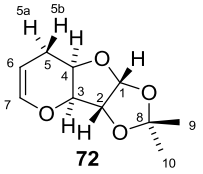
HRMS (EI): calcd. for $C_{16}H_{26}NO_7^+$: 344.1704 $[M+NH_4]^+$
found: 344.1704 $[M+NH_4]^+$.

Protodemetallated product 72:

Analytical data were identical with the material obtained earlier (*vide supra*).

R_f = 0.79 [PE:EtOAc 2:1].

$[\alpha]_D^{21}$ = +98.7 (*c* = 0.79, MeOH).



mp: 39 – 40 °C.

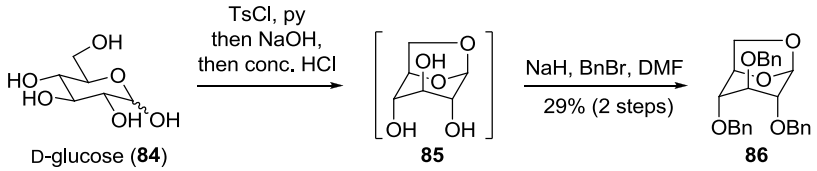
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.31 – 6.28 (m, 1H, H-7), 5.94 (d, *J* = 3.8 Hz, 1H, H-1), 4.69 – 4.65 (m, 1H, H-6), 4.60 (d, *J* = 3.8 Hz, 1H, H-2), 4.52 – 4.48 (m, 1H, H-4), 4.13 (br s, 1H, H-3), 2.40 – 2.33 (m, 1H, H-5a or H-5b), 4.60 (dd, *J* = 18.7, 4.4 Hz, 1H, H-5a or H-5b), 1.52 (s, 3H, 3 x H-10), 1.33 (s, 3H, 3 x H-9) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 141.94 (C-7), 111.94 (C-8), 105.00 (C-1), 97.24 (C-6), 84.25 (C-2), 75.92 (C-3), 72.50 (C-4), 26.66 (C-10), 26.27 (C-9), 20.72 (C-5).

IR (ATR): $\tilde{\nu}$ = 2936 (m), 1662 (m), 1376 (w), 1208 (m), 1076 (s), 829 (m) cm^{-1}.

HRMS (EI): calcd. for $C_{10}H_{14}O_4^+$: 198.0887 $[M]^+$
found: 198.0886 $[M]^+$.

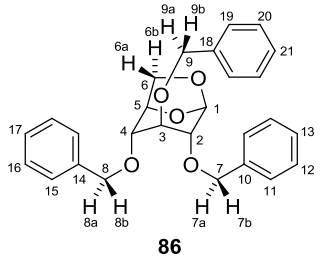
1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (86)[39-40]



A stirred solution of D-(+)-glucose monohydrate **84** (100 g, 505 mmol, 1.0 eq) in pyridine (1 L, dried over KOH pellets) was cooled to 16 °C (internal temperature) and a solution of *p*-toluenesulfonyl chloride (144 g, 757 mmol, 1.5 eq) in pyridine (300 mL, dried over KOH pellets) was added dropwise, keeping the internal temperature of the reaction mixture between 15 and 20 °C with the aid of a water-ice bath. After complete addition, stirring was continued for 90 additional min at 20 °C. The mixture was brought to pH 9 by addition of aq. NaOH (10 wt%, *ca.* 600 mL), then stirred for 60 min at room temperature. The pH was lowered to 7 by carefully adding conc. aq. HCl (*ca.* 20 mL), and the solvents were evaporated *in vacuo*. Azeotropic removal of pyridine and water residues with toluene (3 x 500 mL) gave a solid that was suspended in EtOH (500 mL) and filtered through a pad of florisil (14 x 5 cm, 100 – 200 mesh). Washing with ethanol (3.5 L) was continued until the filtrate was free of sugar derivatives (indicated by TLC) and subsequent removal of the solvent *in vacuo* (15 h rotary evaporator, 10 mbar; followed by 3 d high-vacuum, 10^{-2} mbar) provided a brown oil. The crude 1,6-anhydro-glucose **85** was dissolved in DMF (500 mL) and the solution was carefully added to a stirred, cooled suspension (water-ice bath) of sodium hydride (60 wt% in mineral oil, 202 g, 5.05 mol, 10 eq) in DMF (500 mL). After 25 min, benzyl bromide (360 mL, 3.03 mol, 6.0 eq) was added dropwise with the aid of a dropping funnel (caution: exothermic reaction!) and the reaction mixture was allowed to warm slowly to room temperature over 15 h. The reaction was then quenched carefully by dropwise addition of MeOH (300 mL) over a period of 3 h

(dropping funnel), followed by addition of water (500 mL). The mixture was divided into four aliquots and each aliquot was diluted with EtOAc (1 L) and water (500 mL), followed by separation of the phases. Each aqueous phase was extracted with EtOAc (2 x 500 mL) and all organic extracts were combined. The resulting organic fraction (*ca.* 8 L) was again divided into eight parts and every part (*ca.* 1 L) was washed successively with water (2 x 500 mL), aq. $NaHCO_3$ (2 x 500 mL of a saturated solution), aq. $KHSO_4$ (500 mL of a saturated solution) and brine (500 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a brown oil that was purified by flash column chromatography [PE:EtOAc 9:1→4:1], to provide the crude tribenzylated anhydro sugar **86**, which was crystallized from EtOH (150 mL), affording pure product **86** (56.3 g, 130 mmol, 26%) as white needles. Concentration of the mother liquors and flash column chromatography [PE:EtOAc 9:1→4:1] followed by recrystallization afforded additional material of **86** (7.15 g, 16.5 mmol), raising the total yield to 29%.

Anhydro sugar 86:



86

R_f = 0.46 [PE:EtOAc 3:1].

$[\alpha]_D^{21}$ = –30.4 (c = 1.0, $CHCl_3$).

mp: 89 °C.

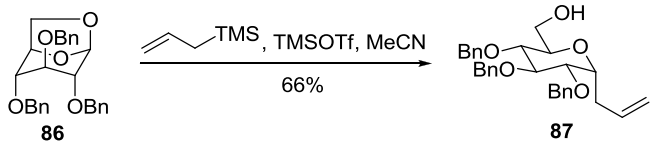
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.27 (m, 13H, 2 x H-11, 2 x H-12, H-13, 2 x H-15, 2 x H-16, H-17, 2 x H-20, H-21), 7.26 – 7.24 (m, 2H, 2 x H-19), 5.48 (s, 1H, H-1), 4.64 – 4.54 (m, 5H, H-5, H-7a, H-7b, H-8a, H-8b), 4.47 (d, J = 12.1 Hz, 1H, H-9a or H-9b), 4.42 (d, J = 12.1 Hz, 1H, H-9a or H-9b), 3.92 (dd, J = 7.2, 1.0 Hz, 1H, H-6a), 3.69 (dd, J = 7.1, 5.9 Hz, 1H, H-6b), 3.62 – 3.60 (m, 1H, H-3), 3.38 – 3.35 (m, 2H, H-2, H-4) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.06 (C-10 or C-14 or C-18), 138.02 (C-10 or C-14 or C-18), 137.98 (C-10 or C-14 or C-18), 128.59 (2 x C-11 or 2 x C-12 or 2 x C-15 or 2 x C-16 or 2 x C-19 or 2 x C-20), 128.56 (2 x C-11 or 2 x C-12 or 2 x C-15 or 2 x C-16 or 2 x C-19 or 2 x C-20), 128.56 (2 x C-11 or 2 x C-12 or 2 x C-15 or 2 x C-16 or 2 x C-19 or 2 x C-20), 128.08 (2 x C-11 or 2 x C-12 or 2 x C-15 or 2 x C-16 or 2 x C-19 or 2 x C-20), 127.96 (C-13 or C-17 or C-21), 127.96 (2 x C-11 or 2 x C-12 or 2 x C-15 or 2 x C-16 or 2 x C-19 or 2 x C-20), 127.95 (C-13 or C-17 or C-21), 127.95 (C-13 or C-17 or C-21), 127.86 (2 x C-11 or 2 x C-12 or 2 x C-15 or 2 x C-16 or 2 x C-19 or 2 x C-20), 100.75 (C-1), 76.99 (C-4), 76.33 (C-2), 76.24 (C-3), 74.53 (C-5), 72.16 (C-9), 71.91 (C-7 or C-8), 71.32 (C-7 or C-8), 65.56 (C-6) ppm.

IR (ATR): $\tilde{\nu}$ = 2961 (m), 2902 (m) 1454 (m), 1090 (s), 1022 (m), 748 (s) cm^{-1}.

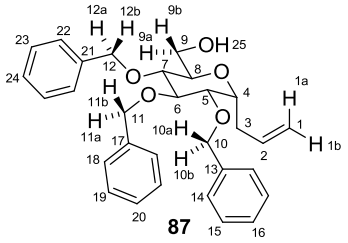
HRMS (ESI): calcd. for $C_{27}H_{28}NaO_5^+$: 455.1829 $[M+Na]^+$
found: 455.1825 $[M+Na]^+$.

[(2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-6-(prop-2-en-1-yl)oxan-2-yl]methanol (87)[40,42]



A solution of tribenzylated anhydro glucose **86** (50.1 g, 116 mmol, 1.0 eq) and allyltrimethylsilane (55.2 mL, 348 mmol, 3.0 eq) in MeCN (500 mL) was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (21.0 mL, 116 mmol, 1.0 eq) was added dropwise. The reaction mixture was stirred at room temperature for 22 h, then quenched with aq. $NaHCO_3$ (550 mL of a saturated solution) and diluted with water (300 mL). The mixture was extracted with CH_2Cl_2 (3 x 400 mL) and the combined organic fractions were washed with brine (1 L), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→6:1→5:1→4:1→3:1→1:1→1:2] afforded alkene **87** (36.4 g, 76.7 mmol, 66%) as a white solid.

Alkene 87:



R_f = 0.21 [PE:EtOAc 3:1].

$[\alpha]_D^{21}$ = +44.4 (c = 0.69, CH_2Cl_2).

mp: 78 – 79 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.27 (m, 15H, 2 x H-14, 2 x H-15, H-16, 2 x H-18, 2 x H-19, H-20, 2 x H-22, 2 x H-23, H-24), 5.77 (dddd, J = 17.3, 10.2, 6.9, 6.9 Hz, 1H, H-2), 5.14 – 5.07 (m, 2H, H-1a, H-1b), 4.94 (d, J = 10.9 Hz, 1H, H-11a or H-11b), 4.87 (d, J = 10.9 Hz, 1H, H-12a or H-12b), 4.83 (d, J = 10.9 Hz, 1H, H-11a or H-11b), 4.71 (d, J = 11.6 Hz, 1H, H-10a or H-10b), 4.63 (d, J = 11.6 Hz, 2H, H-10a or H-10b, H-12a or H-12b), 4.04 – 4.07 (m, 1H, H-4), 3.82 (dd, J = 9.1, 8.7 Hz, 1H, H-6), 3.78 – 3.75 (m, 1H, H-9a or H-9b), 3.71 (dd, J = 9.4, 5.8 Hz, 1H, H-5), 3.66 – 3.63 (m, 1H, H-9a or H-9b), 3.56 – 3.53 (m, 1H, H-8), 3.50 (dd, J = 9.8, 8.4 Hz, 1H, H-7), 2.55 – 2.46 (m, 2H, H-3a, H-3b), 1.79 (dd, J = 6.4, 6.4 Hz, 1H, H-25) ppm.

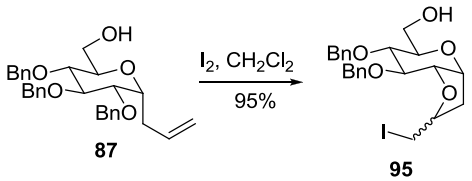
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.77 (C-17), 138.27 (C-13), 138.16 (C-21), 134.62 (C-2), 128.65 (2 x C-15 or 2 x C-19 or 2 x C-23), 128.60 (2 x C-15 or 2 x C-19 or 2 x C-23), 128.55 (2 x C-15 or 2 x C-19 or 2 x C-23), 128.23 (2 x C-22), 128.06 (C-16 or C-20 or C-24), 128.02 (2 x C-18), 127.99 (C-16 or C-20 or C-24), 127.95 (2 x C-14), 127.79 (C-16 or C-20 or C-24),

117.35 (C-1), 82.36 (C-6), 80.25 (C-5), 78.23 (C-7), 75.58 (C-11), 75.28 (C-12), 73.78 (C-4), 73.33 (C-10), 71.69 (C-8), 62.48 (C-9), 30.13 (C-3) ppm.

IR (ATR): $\tilde{\nu}$ = 3344 (br, m), 3032 (m), 2900 (m), 2336 (w), 1453 (m), 1094 (s), 1026 (s), 693 (s) cm^{-1}.

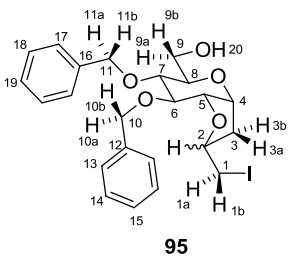
HRMS (ESI): calcd. for $C_{30}H_{38}NO_5^+$: 492.2744 $[M+NH_4]^+$
found: 492.2742 $[M+NH_4]^+$.

[(3a*R*,5*R*,6*R*,7*S*,7a*S*)-6,7-Bis(benzyloxy)-2-(iodomethyl)-hexahydro-2H-furo[3,2-*b*]pyran-5-yl]methanol (95):



A solution of **12** (23.7 g, 49.9 mmol, 1.0 eq) in CH_2Cl_2 (170 mL) was cooled to 0 °C and iodine (13.9 g, 54.9 mmol, 1.1 eq) was added in one portion. The mixture was stirred at 0 °C for 55 min until complete consumption of the starting material (as indicated by TLC analysis). The reaction was quenched with aq. $Na_2S_2O_3$ (150 mL of a saturated solution) and the biphasic system was stirred vigorously at room temperature for 30 min. The organic phase was separated and the aqueous layer was extracted further with CH_2Cl_2 (2 x 200 mL). The combined organic fractions were washed with water (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→4:1→2:1] afforded iodides **95** (20.6 g, 40.4 mmol, 81%) as a colorless oil consisting of two diastereomers in a ratio of 2.7:1 (as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Iodides 95:



95

R_f = 0.46 [PE:EtOAc 1:1].

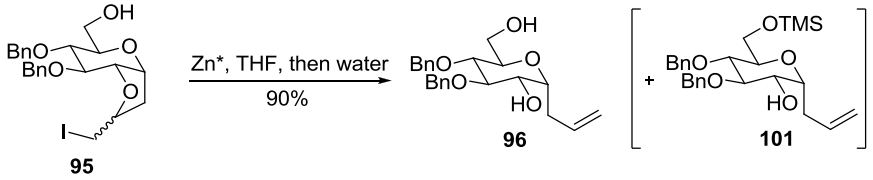
^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 7.44 – 7.27 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-17, 2 x H-18, H-19), 4.91 (d, *J* = 11.7 Hz, 1H, H-10a or H-10b), 4.88 (d, *J* = 11.3 Hz, 1H, H-11a or H-11b), 4.75 (d, *J* = 11.8 Hz, 1H, H-10a or H-10b), 4.60 (d, *J* = 11.1 Hz, 1H, H-11a or H-11b), 4.16 – 4.08 (m, 1H, H-2), 4.06 (dd, *J* = 5.6, 5.6 Hz, 1H, H-5), 3.88 (dd, *J* = 8.7, 5.5 Hz, 1H, H-6), 3.75 – 3.65 (m, 3H, H-9a, H-9b, H-8), 3.51 – 5.45 (m, 1H, H-7), 3.35 (dd, *J* = 9.9, 5.4 Hz, 1H, H-1a or H-1b), 3.31 – 3.26 (m, 1H, H-1a or H-1b), 2.31 – 2.23 (m, 1H, H-3a or H-3b), 2.01 – 1.93 (m, 1H, H-3a or H-3b), 1.92 (s, 1H, H-20) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 138.41 (C-12), 138.12 (C-16), 128.55 (2 x C-13 or 2 x C-14 or 2 x C-17 or 2 x C-18), 128.47 (2 x C-13 or 2 x C-14 or 2 x C-17 or 2 x C-18), 128.23 (2 x C-13 or 2 x C-14 or 2 x C-17 or 2 x C-18), 128.04 (2 x C-13 or 2 x C-14 or 2 x C-17 or 2 x C-18), 127.98 (C-15 or C-19), 127.76 (C-15 or C-19), 83.06 (C-5), 82.58 (C-6), 78.26 (C-2), 75.15 (C-8), 75.10 (C-7), 74.59 (C-4), 74.35 (C-11), 72.99 (C-10), 62.19 (C-9), 36.85 (C-3), 9.83 (C-1) ppm.

IR (ATR): $\tilde{\nu}$ = 3448 (br, m), 2874 (m), 1453 (m), 1363 (w), 1026 (s), 1094 (s), 695 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{23}H_{27}INaO_5^+$: 533.0795 $[M+Na]^+$
found: 533.0794 $[M+Na]^+$.

(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(hydroxymethyl)-2-(prop-2-en-1-yl)oxan-3-ol (96) and (2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-2-(prop-2-en-1-yl)-6-{[(trimethylsilyl)oxy] methyl} oxan-3-ol (101)

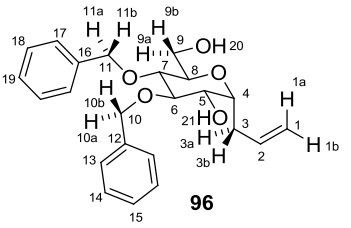


A suspension of zinc dust (26.4 g, 404 mmol, 10 eq) in THF (100 mL), containing 1,2-dibromoethane (348 µL, 4.04 mmol, 0.1 eq), was heated to 70 °C for one minute. After cooling to room temperature, chlorotrimethylsilane (516 µL, 4.04 mmol, 0.1 eq) was added and the suspension was stirred for 15 min until gas evolution had ceased.[46] A solution of the diastereomeric mixture of iodides **95** (20.6 g, 40.4 mmol, 1.0 eq) in THF (150 mL) was added, followed by water (50 mL), and the reaction mixture was stirred for 1 h at room temperature. The solid was removed by filtering the suspension through a pad of Celite and the residue was washed with Et_2O (300 mL). The filtrate was washed with aq. HCl (1 N, 200 mL) and the phases separated. The aqueous layer was extracted further with Et_2O (2 x 300 mL). The combined organic fractions were washed with aq. $NaHCO_3$ (500 mL of a saturated solution) and brine (500 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 4:1→3:1→2:1→1:1] afforded diol **96** (14.0 g, 36.4 mmol, 90%) as a white solid.

Diol 96:

R_f = 0.52 [PE:EtOAc 1:1].

$[\alpha]_D^{20}$ = +32.8 (*c* = 0.63, $CHCl_3$).



mp: 89 – 90 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.28 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-17, 2 x H-18, H-19), 5.82 (dddd, *J* = 17.1, 10.2, 7.0, 7.0 Hz, 1H, H-2), 5.17 – 5.12 (m, 1H, H-1a), 5.12 – 5.07 (m, 1H, H-1b), 4.74 (d, *J* = 11.6 Hz, 1H, H-10a or H-10b), 4.69 (d, *J* = 11.4 Hz, 1H, H-11a or H-11b), 4.65 (d, *J* = 11.6 Hz, 1H, H-10a or H-10b), 4.63 (d, *J* = 11.4 Hz, 1H, H-11a or H-11b), 4.00 (ddd, *J* = 9.0, 5.0, 3.7 Hz, 1H, H-4), 3.93 (dd, *J* = 11.4, 7.0 Hz, 1H, H-9a or H-9b), 3.89 – 3.84 (m, 1H, H-8), 3.75 (dd, *J* = 6.1, 6.1 Hz, 1H, H-6), 3.69 (dd, *J* = 6.3, 3.6 Hz, 1H, H-5), 3.63 (dd, *J* = 11.4, 3.3 Hz, 1H, H-9a or H-9b), 3.48 (dd, *J* = 5.6, 5.6 Hz, 1H, H-7), 2.50 – 2.34 (m, 2H, H-3a, H-3b) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.01 (C-12), 137.49 (C-16), 134.64 (C-2), 128.77 (2 x C-14 or 2 x C-18), 128.71 (2 x C-14 or 2 x C-18), 128.21 (C-15 or C-19), 128.18 (C-15 or C-19), 128.06 (2 x C-17), 127.84 (2 x C-13), 117.51 (C-1), 78.58 (C-6), 75.98 (C-7), 74.42 (C-8), 74.03 (C-10), 73.54 (C-11), 71.68 (C-4), 69.87 (C-5), 61.05 (C-9), 32.50 (C-3) ppm.

IR (ATR): $\tilde{\nu}$ = 3375 (br, m), 2915 (m), 2362 (w), 1453 (m), 1088 (s), 990 (s), 694 (s) cm^{-1}.

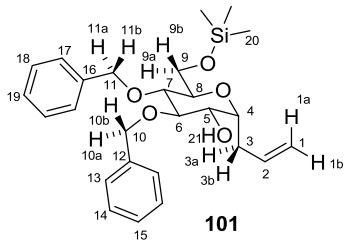
HRMS (ESI): calcd. for $C_{23}H_{28}NaO_5^+$: 407.1829 $[M+Na]^+$
found: 407.1832 $[M+Na]^+$.

TMS ether 101:

Trimethylsilylether **101** was obtained as a colorless oil in 9% yield when zinc was activated with 0.5 eq of 1,2-dibromoethane and 0.5 eq of chlorotrimethylsilane.[46]

R_f = 0.61 [PE:EtOAc 3:1].

$[\alpha]_D^{19}$ = +20.4 (*c* = 1.1, $CHCl_3$).



101

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.27 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-17, 2 x H-18, H-19), 5.84 (dddd, *J* = 17.1, 10.2, 6.9 Hz, 1H, H-2), 5.17 – 5.12 (m, 1H, H-1a), 5.08 – 5.05 (m, 1H, H-1b), 4.68 (d, *J* = 11.7 Hz, 1H, H-10a or H-10b), 4.65 (d, *J* = 11.7 Hz, 1H, H-11a or H-11b), 4.63 (d, *J* = 11.7 Hz, 1H, H-11a or H-11b), 4.59 (d, *J* = 11.7 Hz, 1H, H-10a or H-10b), 3.94 – 3.89 (m, 2H, H-4, H-8), 3.89 – 3.81 (m, 2H, H-9a, H-9b) 3.78 (dd, *J* = 5.1, 5.1 Hz, 1H, H-6), 3.66 – 3.62 (m, 2H, H-5, H-7), 2.98 – 2.95 (m, 1H, H-21), 2.47 – 2.34 (m, 2H, H-3a, H-3b), 0.10 (s, 9H, 9 x H-20) ppm.

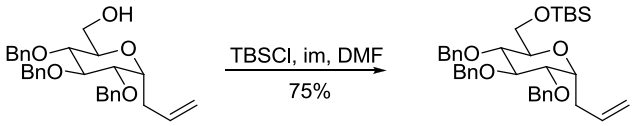
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.09 (C-12), 137.67 (C-16), 134.88 (C-2), 128.65 (2 x C-14 or 2 x C-18), 128.62 (2 x C-14 or 2 x C-18), 128.06 (2 x C-17 and C-15 or C-19), 128.04 (C-

15 or C-19), 127.79 (2 x C-13), 117.04 (C-1), 77.41 (C-6), 75.30 (C-8), 74.20 (C-7), 73.31 (C-10), 72.68 (C-11), 70.93 (C-4), 69.05 (C-5), 60.92 (C-9), 33.65 (C-3), –0.28 (3 x C-20) ppm.

IR (ATR): $\tilde{\nu}$ = 3467 (br, w), 2924 (m), 1454 (w), 1250 (m), 1074 (s), 838 (s), 696 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{26}H_{36}NaO_6Si^+$: 479.2224 $[M+Na]^+$
found: 479.2223 $[M+Na]^+$.

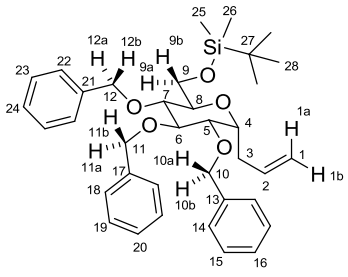
***Tert*-butyldimethyl{[(2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-(prop-2-en-1-yl)oxan-2-yl]methoxy}silane (98):**



87 **98**

To a solution of alcohol **87** (388 mg, 0.818 mmol, 1.0 eq) and imidazole (140 mg, 2.05 mmol, 2.5 eq) in DMF (1.5 mL) was added *tert*-butyldimethylsilyl chloride (148 mg, 0.982 mmol, 1.2 eq) and the resulting mixture was stirred at room temperature for 72 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic fractions were washed with aq. LiCl (10 wt%, 3 x 25 mL) and brine (25 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 99:1→49:1→19:1] afforded silyl ether **98** (360 mg, 0.611 mmol, 75%) as a colorless oil.

Silyl ether 98:



98

R_f = 0.52 [PE:EtOAc 9:1].

$[\alpha]_D^{20}$ = +33.9 (*c* = 1.2, $CHCl_3$).

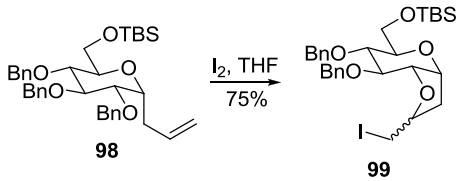
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.28 (m, 15H, 2 x H-14, 2 x H-15, H-16, 2 x H-18, 2 x H-19, H-20, 2 x H-22, 2 x H-23, H-24), 5.84 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H, H-2), 5.14 – 5.09 (m, 1H, H-1a), 5.09 – 5.05 (m, 1H, H-1b), 4.93 (d, *J* = 10.9 Hz, 1H, H-11a or H-11b), 4.88 (d, *J* = 10.9 Hz, 1H, H-12a or H-12b), 4.82 (d, *J* = 10.9 Hz, 1H, H-11a or H-11b), 4.71 (d, *J* = 11.6 Hz, 1H, H-10a or H-10b), 4.68 (d, *J* = 10.9 Hz, 1H, H-12a or H-12b), 4.65 (d, *J* = 11.6 Hz, 1H, H-10a or H-10b), 4.13 – 4.07 (m, 1H, H-4), 3.82 (dd, *J* = 8.9, 8.9 Hz, 1H, H-6), 3.82 – 3.78 (m, 2H, H-9a, H-9b), 3.71 (dd, *J* = 9.2, 5.7 Hz, 1H, H-5), 3.58 (dd, *J* = 9.6, 8.8 Hz, 1H, H-7), 3.53 – 3.50 (m, 1H, H-8), 2.56 – 2.48 (m, 1H, H-3a or H-3b), 2.48 – 2.42 (m, 1H, H-3a or H-3b), 0.91 (s, 9H, 9 x H-28), 0.06 (s, 6H, 3 x H-25, 3 x H-26) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 138.88 (C-17), 138.62 (C-13 or C-21), 138.47 (C-13 or C-21), 134.98 (C-2), 128.58 (2 x C-15 or 2 x C-19 or 2 x C-23), 128.55 (2 x C-15 or 2 x C-19 or 2 x C-23), 128.53 (2 x C-15 or 2 x C-19 or 2 x C-23), 128.13 (2 x C-14 or 2 x C-18 or 2 x C-22), 128.09 (2 x C-14 or 2 x C-18 or 2 x C-22), 127.89 (2 x C-14 or 2 x C-18 or 2 x C-22), 127.87 (C-16 or C-20 or C-24), 127.86 (C-16 or C-20 or C-24), 127.75 (C-16 or C-20 or C-24), 116.80 (C-1), 82.55 (C-6), 80.50 (C-5), 78.22 (C-7), 75.59 (C-11), 75.14 (C-12), 73.53 (C-4), 73.16 (C-10), 72.71 (C-8), 62.89 (C-9), 30.13 (C-3), 26.11 (3 x C-28), 18.49 (C-27), –4.94 (C-25 or C-26), –5.22 (C-25 or C-26) ppm.

IR (ATR): $\tilde{\nu}$ = 3066 (w), 3031 (w), 2927 (s), 2856 (s), 1454 (m), 1360 (w), 1252 (m), 1090 (s), 1028 (m), 912 (w), 836 (m), 697(m) cm^{-1}.

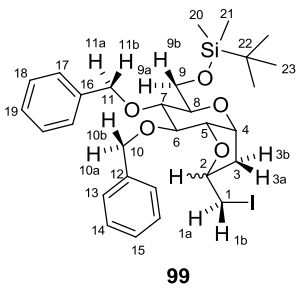
HRMS (ESI): calcd. for $C_{36}H_{52}NO_5Si^+$: 606.3609 $[M+NH_4]^+$
found: 606.3614 $[M+NH_4]^+$.

{[(3aR,5R,6R,7S,7aS)-6,7-bis(benzyloxy)-2-(iodomethyl)-hexahydro-2*H*-furo[3,2-*b*]pyran-5-yl]methoxy}(*tert*-butyl)dimethylsilane (99)



A solution of alkene **98** (188 mg, 0.319 mmol, 1.0 eq) in THF (1 mL) was cooled to 0 °C and iodine (502 mg, 1.98 mmol, 6.2 eq) was added in one portion. The mixture was stirred at 0 °C for 60 min until complete consumption of the starting material (as indicated by TLC analysis). The reaction was quenched with aq. $Na_2S_2O_3$ (2 mL of a saturated solution) and the biphasic system was stirred vigorously at room temperature for 30 min. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1] afforded iodides **99** (149 mg, 0.238 mmol, 75%) as a colorless oil consisting of two diastereomers (d.r. 4:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Iodides 99:



99

R_f = 0.34 [PE:EtOAc 9:1].

^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 7.43 – 7.28 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-

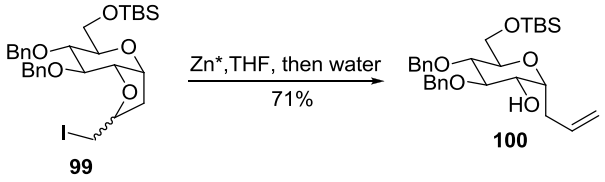
17, 2 x H-18, H-19), 4.96 – 4.87 (m, 2H, H-10a or H-10b, H-11a or H-11b), 4.78 – 4.74 (m, 1H, H-H-10a or H-10b), 4.71 – 4.66 (m, 1H, H-4), 4.60 (d, J = 11.2 Hz, 1H, H-11a or H-11b), 4.24 – 4.12 (m, 1H, H-2), 4.02 (dd, J = 5.1, 5.1 Hz, 1H, H-5), 3.86 (dd, J = 9.7, 5.3 Hz, 1H, H-6), 3.84 – 3.74 (m, 3H, H-7, H-9a, H-9b), 3.68 – 3.62 (m, 1H, H-8), 3.36 (dd, J = 9.7, 5.7 Hz, 1H, H-1a or H-1b), 3.32 – 3.26 (m, 1H, H-1a or H-1b), 2.31 – 2.22 (m, 1H, H-3a or H-3b), 1.95 (ddd, J = 13.7, 5.7, 3.7 Hz, 1H, H-3a or H-3b), 0.90 (s, 9H, 9 x H-23), 0.07 (s, 3H, 3 x H-20 or 3 x H-21), 0.05 (s, 3H, 3 x H-20 or 3 x H-21) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 138.68 (C-12 or C-16), 138.65 (C-12 or C-16), 128.49 (2 x C-14 or 2 x C-18), 128.45 (2 x C-14 or 2 x C-18), 128.10 (2 x C-13 or 2 x C17), 128.04 (2 x C-13 or 2 x C17), 127.79 (C-15 or C-19), 127.68 (C-15 or C-19), 85.51 (C-5), 83.69 (C-6), 79.00 (C-2), 77.02 (C-8), 75.49 (C-4), 74.68 (C-11), 74.37 (C-7), 73.01 (C-10), 63.64 (C-9), 37.62 (C-3), 26.07 (3 x C-23), 18.41 (C-22), 10.00 (C-1), –5.20 (C-20 or C-21), –5.26 (C-20 or C-21) ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (s), 2856 (s), 1454 (m), 1361 (m), 1252 (m), 1086 (s), 905 (w), 834 (s), 776 (m), 696 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{29}H_{45}INO_5Si^+$: 642.2106 $[M+NH_4]^+$
found: 642.2111 $[M+ NH_4]^+$.

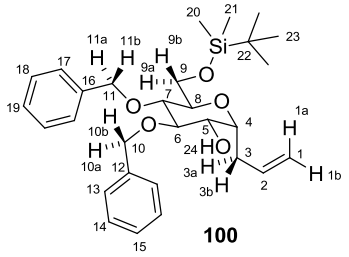
(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2-(prop-2-en-1-yl)oxan-3-ol (100):



A suspension of zinc dust (137 mg, 2.10 mmol, 10 eq) in THF (1 mL), containing 1,2-dibromoethane (9.05 µL, 0.105 mmol, 0.5 eq), was heated to 70 °C for one minute. After cooling to room temperature, chlorotrimethylsilane (13.4 µL, 0.105 mmol, 0.5 eq) was added and the suspension was stirred for 15 min until gas evolution had ceased. A solution of the diastereomeric mixture of iodides **99** (131 mg, 0.210 mmol, 1.0 eq) in THF (4 mL) was added followed by water (1 mL), and the reaction mixture was stirred for 1 h at room temperature. The solid was removed by filtering the suspension through a pad of Celite and the residue was washed with Et_2O (50 mL). The filtrate was diluted with water (10 mL) and the phases were separated. The aqueous layer was extracted further with Et_2O (2 x 20 mL). The combined organic fractions were washed with aq. $NaHCO_3$ (30 mL of a saturated solution) and brine

(30 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1] afforded alcohol **100** (74.0 mg, 0.148 mmol, 71%) as a colorless oil.

Alcohol 100:



100

R_f = 0.15 [PE:EtOAc 9:1].

$[\alpha]_D^{20}$ = +19.1 (c = 0.87, $CHCl_3$).

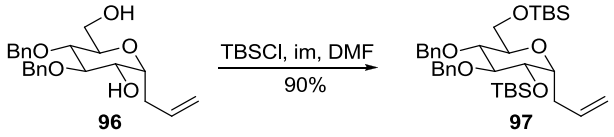
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.26 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-17, 2 x H-18, H-19), 5.84 (dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, 1H, H-2), 5.16 – 5.11 (m, 1H, H-1a), 5.08 – 5.04 (m, 1H, H-1b), 4.69 – 4.54 (m, 4H, H-10a, H-10b, H-11a, H-11b), 3.95 – 3.83 (m, 4H, H-4, H-5 or H-8, H-9a, H-9b), 3.79 (dd, J = 4.7, 4.7 Hz, 1H, H-6 or H-7), 3.71 – 3.68 (m, 1H, H-6 or H-7), 3.62 (br s, 1H, H-5 or H-8), 3.02 (br s, 1H, H-24), 2.47 – 2.33 (m, 2H, H-3a, H-3b), 0.88 (s, 9H, 9 x H-23), 0.04 (s, 3H, 3 x H-20 or 3 x H-21), 0.02 (s, 3H, 3 x H-20 or 3 x H-21) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.06 (C-12 or C-16), 137.69 (C-12 or C-16), 134.95 (C-2), 128.65 (2 x C-14 and 2 x C-18), 128.07 (C-15 or C-19), 128.04 (C-15 or C-19), 128.03 (2 x C-13 or 2 x C-17), 127.80 (2 x C-13 or 2 x C-17), 117.03 (C-1), 76.99 (C-6 or C-7), 75.56 (C-5 or C-8), 73.83 (C-6 or C-7), 73.11 (C-10 or C-11), 72.59 (C-10 or C-11), 70.76 (C-4), 68.98 (C-10 or C-11), 61.40 (C-9), 34.03 (C-3), 26.03 (3 x C-23), 18.36 (C-22), –5.17 (C-20 or C-21), –5.20 (C-20 or C-21) ppm.

IR (ATR): $\tilde{\nu}$ = 3490 (br w), 2928 (s), 2857 (m), 1455 (w), 1253 (m), 1081 (br, s), 834 (m), 778 (w), 698 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{29}H_{42}NaO_5Si^+$: 521.2694 $[M+Na]^+$
found: 521.2696 $[M+Na]^+$.

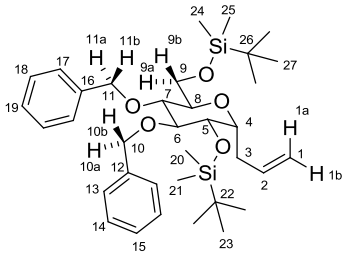
{[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-Bis(benzyloxy)-5-[(*tert*-butyldimethylsilyl)oxy]-6-(prop-2-en-1-yl)oxan-2-yl]methoxy}(*tert*-butyl)dimethylsilane (97):



To a solution of diol **96** (14.0 g, 36.4 mmol, 1.0 eq) and imidazole (12.4 g, 182 mmol, 5.0 eq) in DMF (30 mL) was added *tert*-butyldimethylsilyl chloride (16.5 g, 109 mmol, 3.0 eq) and the resulting mixture was stirred at room temperature for 42 h. Upon completion of the reaction, as monitored by TLC, the mixture was diluted with water (200 mL) and extracted with EtOAc

(3 x 300 mL). The combined organic fractions were washed with aq. LiCl (10 wt%, 3 x 300 mL) and brine (300 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 99:1→49:1→24:1] afforded bis-silyl ether **97** (20.0 g, 32.6 mmol, 90%) as a white solid.

Bis-silyl ether 97:



97

R_f = 0.62 [PE:EtOAc 9:1].

$[\alpha]_D^{18}$ = +31.3 (c = 1.3, $CHCl_3$).

mp: 55 – 57 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.21 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-17, 2 x H-18, H-19), 5.84 (dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, 1H, H-2), 5.15 – 5.02 (m, 2H, H-1a, H-1b), 4.91 (d, J = 11.3 Hz, 1H, H-10a or H-10b), 4.82 (d, J = 10.8 Hz, 1H, H-11a or H-11b), 4.81 (d, J = 11.3 Hz, 1H, H-10a or H-10b), 4.63 (d, J = 10.8 Hz, 1H, H-11a or H-11b), 3.96 – 3.89 (m, 1H, H-4), 3.84 (dd, J = 9.1, 5.9 Hz, 1H, H-5), 3.81 – 3.74 (m, 2H, H-9a, H-9b), 3.69 – 3.63 (m, 1H, H-6), 3.54 – 3.46 (m, 2H, H-7, H-8), 2.55 – 2.40 (m, 2H, H-3a, H-3b), 0.92 (s, 9H, 9 x H-23), 0.90 (s, 9H, 9 x H-27), 0.09 (s, 6H, 3 x H-20, 3 x H-21), 0.06 (s, 3H, 3 x H-24 or 3 x H-25), 0.05 (s, 3H, 3 x H-24 or 3 x H-25) ppm.

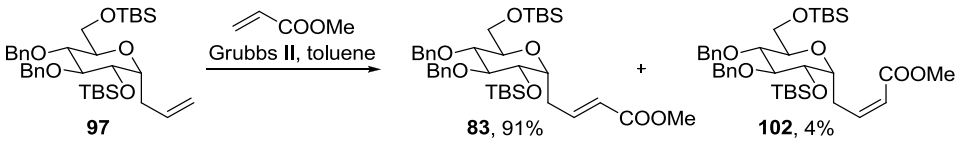
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.04 (C-12), 138.60 (C-16), 135.26 (C-2), 128.53 (2 x C-14 or 2 x C-18), 128.41 (2 x C-14 or 2 x C-18), 128.05 (2 x C-17), 127.80 (C-15 or C-19), 127.65 (2 x C-13), 127.49 (C-15 or C-19), 116.66 (C-1), 83.43 (C-6), 78.56 (C-7), 76.32 (C-4), 75.59 (C-10), 75.15 (C-11), 73.57 (C-5), 72.71 (C-8), 63.03 (C-9), 29.25 (C-3), 26.12 (3 x C-23 or 3 x C-27), 26.05 (3 x C-23 or 3 x C-27), 18.51 (C-26), 18.12 (C-22), –4.40 (C-20 or C-21), –4.50 (C-20 or C-21), –4.92 (C-24 or C-25), –5.20 (C-24 or C-25) ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (s), 1462 (w), 1252 (m), 1088 (s), 834 (s), 696 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{35}H_{60}NO_5Si_2^+$: 630.4005 $[M+NH_4]^+$

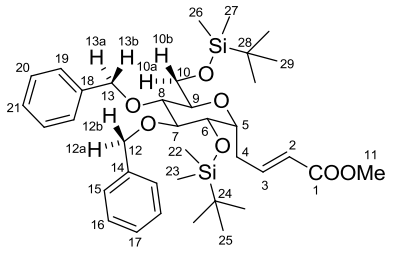
found: 630.4010 $[M+NH_4]^+$.

Methyl (2*E*)-4-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]but-2-enoate (83) and (2*Z*)-4-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]but-2-enoate (102)



Grubbs' catalyst, 2nd generation (172 mg, 0.203 mmol, 7 mol%) was added in one portion to a solution of alkene **97** (1.78 g, 2.90 mmol, 1.0 eq) and methyl acrylate (1.31 mL, 14.5 mmol, 5.0 eq) in toluene (15 mL), and the reaction mixture was stirred for 22 h at 60 °C. After cooling to room temperature, volatile material was removed *in vacuo*, and the residue was subjected to flash column chromatography [PE:EtOAc 100:0→49:1→19:1] to afford *trans*-ester **83** (1.77 g, 2.64 mmol, 91%) as a colorless oil, as well as *cis*-ester **102** (86.5 mg, 0.129 mmol, 4%) as colorless oil, in addition to recovered starting material **97** (78.5 mg, 0.128 mmol, 4%).

***Trans*-ester 83:**



R_f = 0.32 [PE:EtOAc 9:1].

$[\alpha]_D^{18}$ = +48.2 (*c* = 0.51, $CHCl_3$).

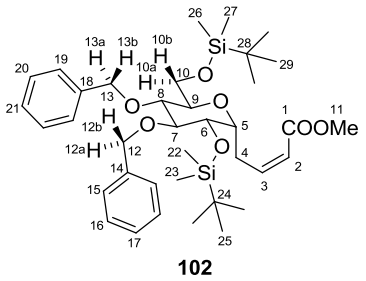
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.20 (m, 10H, 2 x H-15, 2 x H-16, H-17, 2 x H-19, 2 x H-20, H-21), 6.98 (ddd, *J* = 15.6, 7.5, 7.4 Hz, 1H, H-3) 5.92 (dd, *J* = 15.7, 0.7 Hz, 1H, H-2), 4.88 (d, *J* = 11.3 Hz, 1H, H-12a or H-12b), 4.80 (d, *J* = 11.3 Hz, 1H, H-12a or H-12b), 4.80 (d, *J* = 10.8 Hz, 1H, H-13a or H-13b), 4.62 (d, *J* = 10.8 Hz, 1H, H-13a or H-13b), 3.99 (ddd, *J* = 10.2, 5.2, 5.2 Hz, 1H, H-5), 3.83 (dd, *J* = 9.1, 5.9 Hz, 1H, H-6), 3.79 – 3.74 (m, 2H, H-10a, H-10b), 3.73 (s, 3H, 3 x H-11), 3.62 (dd, *J* = 8.9, 8.9 Hz, 1H, H-7), 3.52 – 3.44 (m, 2H, H-8, H-9), 2.67 – 2.56 (m, 2H, H-4a, H-4b), 0.90 (s, 9H, 9 x H-25), 0.89 (s, 9H, 9 x H-29), 0.08 (s, 6H, 3 x H-22, 3 x H-23), 0.05 (s, 3H, 3 x H-26 or 3 x H-27), 0.04 (s, 3H, 3 x H-26 or 3 x H-27) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 166.88 (C-1), 146.11 (C-3), 138.88 (C-14), 138.46 (C-18), 128.56 (2 x C-16 or 2 x C-20), 128.43 (2 x C-16 or 2 x C-20), 128.04 (2 x C-19), 127.86 (C-17 or C-21), 127.62 (2 x C-15), 127.55 (C-17 or C-21), 123.00 (C-2), 83.20 (C-7), 78.33 (C-8), 75.73 (C-5), 75.61 (C-12), 75.19 (C-13), 73.24 (C-6), 73.05 (C-9), 62.91 (C-10), 51.53 (C-11), 27.90 (C-4), 26.10 (3 x C-29), 26.02 (3 x C-25), 18.50 (C-28), 18.10 (C-24), –4.42 (C-22 or C-23), –4.50 (C-22 or C-23), –4.97 (C-26 or C-27), –5.23 (C-26 or C-27) ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (s), 1726 (s), 1471 (w), 1252 (m), 1089 (s), 835 (s), 697 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{37}H_{62}NO_7Si_2^+$: 688.4059 $[M+NH_4]^+$
found: 688.4065 $[M+NH_4]^+$.

***Cis*-ester 102:**



102

R_f = 0.54 [PE:EtOAc 9:1].

$[\alpha]_D^{18}$ = +19.8 (*c* = 0.74, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.20 (m, 10H, 2 x H-15, 2 x H-16, H-17, 2 x H-19, 2 x H-20, H-21), 6.34 (ddd, *J* = 11.6, 7.4, 6.5 Hz, 1H, H-3) 5.88 (ddd, *J* = 11.5, 1.9, 1,9 Hz, 1H, H-2), 4.90 (d, *J* = 11.3 Hz, 1H, H-12a or H-12b), 4.81 (d, *J* = 11.3 Hz, 1H, H-12a or H-12b), 4.81 (d, *J* = 11.0 Hz, 1H, H-13a or H-13b), 4.60 (d, *J* = 11.0 Hz, 1H, H-13a or H-13b), 3.99 (ddd, *J* = 12.0, 5.9, 3.5 Hz, 1H, H-5), 3.85 (dd, *J* = 9.2, 5.9 Hz, 1H, H-6), 3.76 – 3.68 (m, 3H, H-7, H-10a, H-10b), 3.71 (s, 3H, 3 x H-11), 3.49 (ddd, *J* = 9.6, 4.4, 1.8 Hz, 1H, H-9), 3.45 (dd, *J* = 9.8, 8.6 Hz, 1H, H-8), 3.31 – 3.24 (m, 1H, H-4a or H-4b), 3.01 – 2.95 (m, 1H, H-4a or H-4b), 0.91 (s, 9H, 9 x H-25), 0.88 (s, 9H, 9 x H-29), 0.08 (s, 3H, 3 x H-22 or 3 x H-23), 0.07 (s, 3H, 3 x H-22 or 3 x H-23), 0.03 (s, 3H, 3 x H-26 or 3 x H-27), 0.03 (s, 3H, 3 x H-26 or 3 x H-27) ppm.

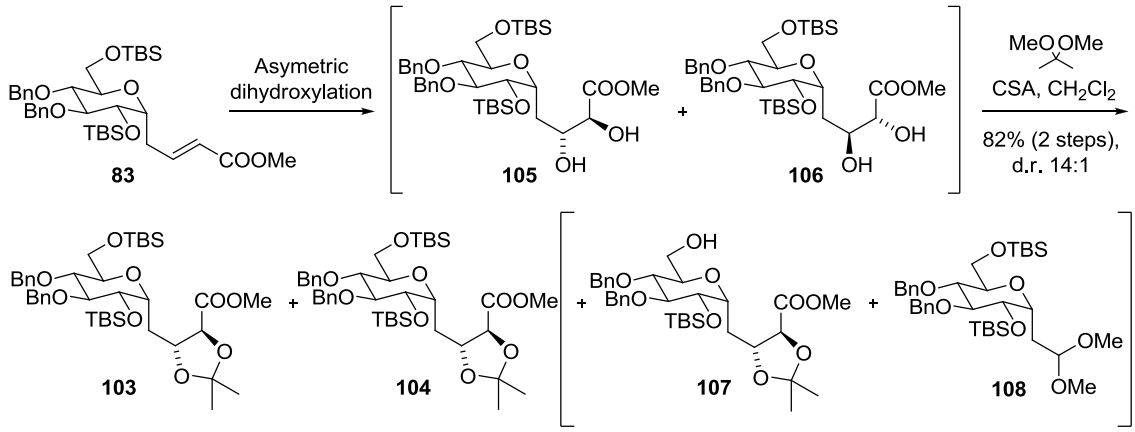
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 166.83 (C-1), 147.14 (C-3), 139.01 (C-14), 138.62 (C-18), 128.49 (2 x C-16 or 2 x C-20), 128.40 (2 x C-16 or 2 x C-20), 127.95 (2 x C-19), 127.74 (C-17 or C-21), 127.64 (2 x C-15), 127.47 (C-17 or C-21), 120.86 (C-2), 83.34 (C-7), 78.48 (C-8), 76.16 (C-5), 75.66 (C-12), 75.00 (C-13), 73.43 (C-6), 72.98 (C-9), 63.02 (C-10), 51.23 (C-11), 26.09 (3 x C-29), 26.03 (3 x C-25), 25.28 (C-4), 18.48 (C-28), 18.09 (C-24), –4.40 (C-22 or C-23), –4.53 (C-22 or C-23), –4.98 (C-26 or C-27), –5.24 (C-26 or C-27) ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (s), 1724 (s), 1462 (w), 1252 (m), 1087 (s), 834 (s), 696 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{37}H_{62}NO_7Si_2^+$: 688.4059 $[M+NH_4]^+$
found: 688.4058 $[M+NH_4]^+$.

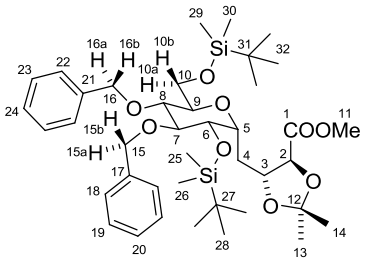
Methyl (4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolane-4-carboxylate (103), Methyl (4*R*,5*S*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolane-4-carboxylate (104), Methyl (2*S*,3*R*)-4-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl} oxan-2-yl]-2,3-dihydroxybutanoate (105), Methyl (2*R*,3*S*)-4-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}

oxan-2-yl]-2,3-dihydroxybutanoate (106), Methyl (4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-(hydroxymethyl)oxan-2-yl]methyl}2,2-dimethyl-1,3-dioxolane-4-carboxylate (107), and {[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-bis(benzyloxy)-5-[(*tert*-butyldimethylsilyl)oxy]-6-(2,2-dimethoxyethyl)oxan-2-yl]methoxy}(*tert*-butyl) dimethylsilane (108)



A solution of $K_3Fe(CN)_6$ (7.38 g, 22.4 mmol, 3.0 eq), K_2CO_3 (3.10 g, 22.4 mmol, 3.0 eq), $MeSO_2NH_2$ (709 mg, 7.45 mmol, 1.0 eq) and $(DHQD)_2PHAL$ (2.32 g, 2.98 mmol, 0.4 eq) in water (37 mL) was added to a solution of unsaturated ester **83** (5.00 g, 7.45 mmol, 1.0 eq) in *t*-BuOH (37 mL). To the biphasic system was added a solution of OsO_4 in *t*-BuOH (2.5 wt%, 1.49 mL, 0.119 mmol, 1.6 mol%) and the mixture was stirred vigorously at room temperature for 19 h. An excess of solid Na_2SO_3 (23 g) was added in one portion and the mixture was stirred for an additional 30 min. Water (100 mL) was added and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic fractions were washed successively with aq. HCl (1 N, 150 mL) and brine (150 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to afford crude diols **105** and **106** as a mixture of two diastereomers (d.r. 14:1, as determined by ^{1}H-NMR spectroscopy). The crude product was dissolved in CH_2Cl_2 (150 mL) and 2,2-dimethoxypropane (8.70 mL, 70.6 mmol, 10 eq), as well as (1*R*)-(−)-10-camphorsulfonic acid (164 mg, 0.706 mmol, 10 mol%) were added in succession. The reaction mixture was stirred at room temperature for 60 min, then quenched with aq. $NaHCO_3$ (150 mL of a saturated solution). The biphasic system was extracted with EtOAc (250 mL, 2 x 150 mL) and the combined organic fractions were washed with brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 49:1→19:1→9:1→4:1] afforded acetonides **103** and **104** (4.56 g, 6.12 mmol, 82% over two steps) as a colorless oil consisting of two diastereomers (d.r. 14:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture. An analytical sample of the mixture was purified by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), gradient, water (A)/MeOH (B); 0 min 85% B, 50 min 85% B, 70 min 90% B, 85 min 90% B, 100 min 92% B, 180 min 92% B; flow rate 21 mL/min; detection 205 nm: t_R(**103**) = 137.1 min, t_R(**104**) = 149.3 min] for full characterization of both isomers.

Major acetonide 103:



103

R_f = 0.25 [PE:EtOAc 9:1].

$[\alpha]_D^{21}$ = +36.9 (c = 1.0, $CHCl_3$).

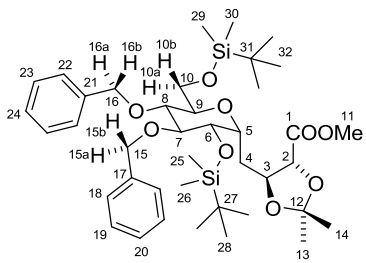
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.21 (m, 10H, 2 x H-18, 2 x H-19, H-20, 2 x H-22, 2 x H-23, H-24), 4.90 (d, J = 11.2 Hz, 1H, H-15a or H-15b), 4.81 (d, J = 10.8 Hz, 1H, H-16a or H-16b), 4.79 (d, J = 11.3 Hz, 1H, H-15a or H-15b), 4.58 (d, J = 10.8 Hz, 1H, H-16a or H-16b), 4.27 (ddd, J = 10.3, 7.9, 2.5 Hz, 1H, H-3), 4.21 – 4.15 (m, 1H, H-5), 4.19 (d, J = 7.9 Hz, 1H, H-2), 3.84 (dd, J = 9.3, 6.1 Hz, 1H, H-6), 3.81 – 3.77 (m, 1H, H-10a or H-10b), 3.77 (s, 3H, 3 x H-11), 3.70 (dd, J = 11.1, 4.8 Hz, 1H, H-10a or H-10b), 3.60 (dd, J = 8.9, 8.9 Hz, 1H, H-7), 3.50 – 3.45 (m, 1H, H-9), 3.42 (dd, J = 9.8, 8.5 Hz, 1H, H-8), 2.20 (ddd, J = 14.6, 12.2, 2.4 Hz, 1H, H-4a or H-4b), 1.97 (ddd, J = 14.7, 10.2, 2.1 Hz, 1H, H-4a or H-4b), 1.43 (s, 6H, 3 x H-13, 3 x H-14), 0.91 (s, 9H, 9 x H-28), 0.88 (s, 9H, 9 x H-32), 0.10 (s, 3H, 3 x H-25 or 3 x H-26), 0.08 (s, 3H, 3 x H-25 or 3 x H-26), 0.04 (s, 3H, 3 x H-29 or 3 x H-30), 0.03 (s, 3H, 3 x H-29 or 3 x H-30) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 171.05 (C-1), 138.99 (C-17), 138.44 (C-21), 128.57 (2 x C-19 or 2 x C-23), 128.43 (2 x C-19 or 2 x C-23), 128.14 (2 x C-22), 127.90 (C-20 or C-24), 127.62 (2 x C-18), 127.53 (C-20 or C-24), 111.05 (C-12), 83.33 (C-7), 79.29 (C-2), 78.63 (C-8), 75.61 (C-15), 75.27 (C-16), 75.21 (C-3), 73.18 (C-6 or C-9), 73.15 (C-6 or C-9), 73.06 (C-5), 63.18 (C-10), 52.53 (C-11), 28.71 (C-4), 27.28 (C-13 or C-14), 26.09 (3 x C-32), 26.07 (3 x C-28), 25.92 (C-13 or C-14), 18.46 (C-31), 18.17 (C-27), –4.48 (C-25 or C-26), –4.48 (C-25 or C-26), –4.98 (C-29 or C-30), –5.23 (C-29 or C-30) ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (s), 1765 (m), 1497 (w), 1252 (m), 1087 (s), 834 (s), 696 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{40}H_{68}NO_9Si_2^+$: 762.4427 $[M+NH_4]^+$
found: 762.4437 $[M+NH_4]^+$.

Minor acetonide 104:



104

R_f = 0.25 [PE:EtOAc 9:1].

$[\alpha]_D^{19}$ = +16.8 (c = 0.25, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.20 (m, 10H, 2 x H-18, 2 x H-19, H-20, 2 x H-22, 2 x H-23, H-24), 4.88 (d, J = 11.2 Hz, 1H, H-15a or H-15b), 4.81 (d, J = 10.7 Hz, 1H, H-16a or H-16b), 4.80 (d, J = 11.2 Hz, 1H, H-15a or H-15b), 4.63 (d, J = 10.8 Hz, 1H, H-16a or H-16b), 4.44 (d,

J = 8.0 Hz, 1H, H-2), 4.27 – 4.22 (m, 1H, H-3), 4.18 – 4.13 (m, 1H, H-5), 3.84 – 3.71 (m, 3H, H-6, H-10a, H-10b), 3.75 (s, 3H, 3 x H-11), 3.61 – 3.50 (m, 3H, H-7, H-8, H-9), 2.24 – 2.11 (m, 2H, H-4a, H-4b), 1.44 (s, 6H, 3 x H-13, 3 x H-14), 0.91 (s, 9H, 9 x H-28 or 9 x H-32), 0.89 (s, 9H, 9 x H-28 or 9 x H-32), 0.09 (s, 3H, 3 x H-25 or 3 x H-26 or 3 x H-29 or 3 x H-30), 0.08 (s, 3H, 3 x H-25 or 3 x H-26 or 3 x H-29 or 3 x H-30), 0.04 (s, 3H, 3 x H-25 or 3 x H-26 or 3 x H-29 or 3 x H-30), 0.04 (s, 3H, 3 x H-25 or 3 x H-26 or 3 x H-29 or 3 x H-30) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.30 (C-1), 138.95 (C-17), 138.58 (C-21), 128.54 (2 x C-19 or 2 x C-23), 128.42 (2 x C-19 or 2 x C-23), 128.06 (2 x C-22), 127.82 (C-20 or C-24), 127.69 (2 x C-18), 127.52 (C-20 or C-24), 110.66 (C-12), 83.26 (C-7), 78.39 (C-2 or C-8), 78.28 (C-2 or C-8), 77.09 (C-3), 75.64 (C-15), 75.17 (C-16), 73.23 (C-5 or C-6), 73.17 (C-5 or C-6), 72.81 (C-9), 62.71 (C-10), 52.43 (C-11), 27.14 (C-13 or C-14), 26.72 (C-4), 26.13 (3 x C-28 or 3 x C-32), 26.04 (3 x C-28 or 3 x C-32), 25.98 (C-13 or C-14), 18.55 (C-27 or C-31), 18.11 (C-27 or C-31), –4.45 (C-25 or C-26 or C-29 or C-30), –4.53 (C-25 or C-26 or C-29 or C-30), –4.94 (C-25 or C-26 or C-29 or C-30), –5.24 (C-25 or C-26 or C-29 or C-30) ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (s), 1763 (m), 1462 (w), 1252 (m), 1088 (s), 834 (s), 696 (m) cm^{-1}.

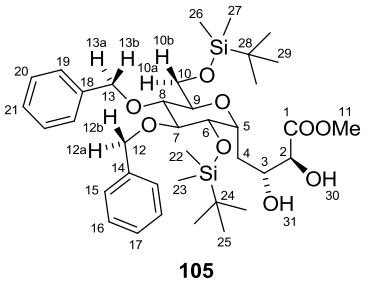
HRMS (ESI): calcd. for $C_{40}H_{68}NO_9Si_2^+$: 762.4427 $[M+NH_4]^+$
found: 762.4437 $[M+NH_4]^+$.

Major diol 105:

In order to characterize the diols **105** and **106**, an analytical sample of the crude mixture, obtained after asymmetric dihydroxylation, was purified by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), gradient, water (A)/MeOH (B); 0 min 80% B, 2 min 80% B, 40 min 90% B, 100 min 90% B; flow rate 19 mL/min; detection 205 nm: t_R(**105**) = 73.3 min, t_R(**106**) = 77.2 min] to yield both isomers as colorless oils.

R_f = 0.41 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +15.3 (*c* = 0.35, $CHCl_3$).



105

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.35 – 7.25 (m, 8H, 2 x H-15, 2 x H-16, H-17, 2 x H-20, H-21), 7.35 – 7.25 (m, 2H, 2 x H-19), 4.88 (d, *J* = 11.4 Hz, 1H, H-12a or H-12b), 4.79 (d, *J* = 10.9 Hz, 1H, H-13a or H-13b), 4.77 (d, *J* = 11.2 Hz, 1H, H-12a or H-12b), 4.54 (d, *J* = 11.1 Hz, 1H, H-13a or H-13b), 4.28 (br s, 1H, H-2), 4.13 – 4.06 (m, 2H, H-3, H-5), 3.82 (dd, *J* = 9.2, 5.9 Hz, 1H, H-6), 3.80 (s, 3H, 3 x H-11), 3.78 (dd, *J* = 10.5, 1.4 Hz, 1H, H-10a or H-10b), 3.68 – 3.58 (m, 3H, H-7, H-9, H-10a or H-10b), 3.38 (br s, 1H, H-30 or H-31), 3.33 (dd, *J* = 9.0, 9.0 Hz, 1H, H-8), 2.38 (br s, 1H, H-30 or H-31), 2.08 –

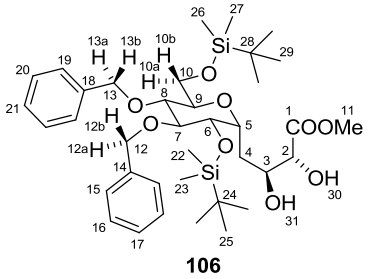
1.98 (m, 2H, H-4a, H4b), 0.91 (s, 9H, 9 x H-25), 0.88 (s, 9H, 9 x H-29), 0.09 (s, 3H, 3 x H-22 or 3 x H-23), 0.07 (s, 3H, 3 x H-22 or 3 x H-23), 0.05 (s, 3H, 3 x H-26 or 3 x H-27), 0.04 (s, 3H, 3 x H-26 or 3 x H-27) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 173.85 (C-1), 138.82 (C-14), 138.29 (C-18), 128.57 (2 x C-16 or 2 x C-20), 128.43 (2 x C-16 or 2 x C-20), 128.12 (2 x C-19), 127.92 (C-17 or C-21), 127.64 (2 x C-15), 127.57 (C-17 or C-21), 83.02 (C-7), 78.43 (C-8), 75.50 (C-12), 75.05 (C-13), 73.54 (C-5), 73.48 (C-2), 73.20 (C-6), 73.06 (C-9), 70.62 (C-3), 63.55 (C-10), 52.73 (C-11), 28.10 (C-4), 26.10 (3 x C-29), 26.02 (3 x C-25), 18.57 (C-28), 18.13 (C-24), –4.43 (C-22 or C-23), –4.49 (C-22 or C-23), –5.12 (C-26 or C-27), –5.30 (C-26 or C-27) ppm.

IR (ATR): $\tilde{\nu}$ = 3475 (m), 2928 (s), 1741 (m), 1462 (w), 1252 (m), 1084 (s), 834 (s), 776 (m), 697 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{37}H_{60}NaO_9Si_2^+$: 727.3668 $[M+Na]^+$
found: 727.3674 $[M+Na]^+$.

Minor diol 106:



106

R_f = 0.41 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +27.9 (c = 0.19, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.35 – 7.25 (m, 8H, 2 x H-15, 2 x H-16, H-17, 2 x H-20, H-21), 7.22 – 7.19 (m, 2H, 2 x H-19), 4.86 (d, J = 11.3 Hz, 1H, H-12a or H-12b), 4.78 (d, J = 11.1 Hz, 1H, H-13a or H-13b), 4.77 (d, J = 11.3 Hz, 1H, H-12a or H-12b), 4.52 (d, J = 11.1 Hz, 1H, H-13a or H-13b), 4.19 – 4.16 (m, 1H, H-3), 4.13 (ddd, J = 12.3, 6.1, 2.5 Hz, 1H, H-5), 4.10 – 4.08 (m, 1H, H-2), 3.83 – 3.80 (m, 1H, H-6), 3.80 (s, 3H, 3 x H-11), 3.78 – 3.74 (m, 2H, H-9, H-10a or H-10b), 3.63 (dd, J = 9.0, 9.0 Hz, 1H, H-7), 3.55 – 3.51 (m, 2H, H-10a or H-10b, H-31), 3.33 (dd, J = 9.0, 9.0 Hz, 1H, H-8), 3.09 (br d, J = 6.9 Hz, 1H, H-30), 2.22 (ddd, J = 15.2, 12.2, 9.2 Hz, 1H, H-4a or H-4b), 1.91 (ddd, J = 15.2, 2.8, 2.8 Hz, 1H, H-4a or H-4b), 0.90 (s, 9H, 9 x H-25), 0.86 (s, 9H, 9 x H-29), 0.08 (s, 3H, 3 x H-22 or 3 x H-23), 0.07 (s, 3H, 3 x H-22 or 3 x H-23), 0.01 (s, 3H, 3 x H-26 or 3 x H-27), 0.01 (s, 3H, 3 x H-26 or 3 x H-27) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 173.42 (C-1), 138.78 (C-14), 138.24 (C-18), 128.57 (2 x C-16 or 2 x C-20), 128.44 (2 x C-16 or 2 x C-20), 128.05 (2 x C-19), 127.94 (C-17 or C-21), 127.65 (2 x C-15), 127.58 (C-17 or C-21), 83.04 (C-7), 78.54 (C-8), 77.02 (C-5), 75.65 (C-12), 75.05 (C-13), 74.32 (C-2), 73.11 (C-6 and C-9), 73.00 (C-3), 63.35 (C-10), 52.64 (C-11), 27.46 (C-4), 26.04 (3 x C-25 or 3 x C-29), 26.00 (3 x C-25 or 3 x C-29), 18.50 (C-28), 18.09 (C-24), –4.43 (C-22 or C-23), –4.52 (C-22 or C-23), –5.21 (C-26 or C-27), –5.37 (C-26 or C-27) ppm.

IR (ATR): $\tilde{\nu}$ = 3474 (m), 2928 (s), 1744 (m), 1462 (w), 1252 (m), 1086 (s), 834 (s), 776 (m), 696 (w) cm^{-1}.

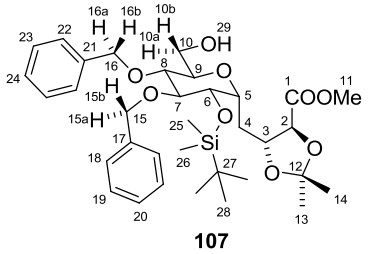
HRMS (ESI): calcd. for $C_{37}H_{60}NaO_9Si_2^+$: 727.3668 $[M+Na]^+$
found: 727.3673 $[M+Na]^+$.

Alcohol 107:

When diol **105** was transformed into acetonide **103** employing (1*R*)-(–)-10-camphorsulfonic acid, a side reaction was observed. Primary *tert*-butyldiphenylsilyl ether in compound **103** was cleaved during acetonide formation in acidic media when applied to extended reaction times. Alcohol **107** was then isolated as a colorless oil as a side product.

R_f = 0.17 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +40.5 (*c* = 0.95, $CHCl_3$).



107

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.34 (m, 2H, 2 x H-18), 7.34 – 7.26 (m, 6H, 2 x H-19, H-20, 2 x H-23, H-24), 7.25 – 7.22 (m, 2H, 2 x H-22), 4.90 (d, *J* = 11.4 Hz, 1H, H-15a or H-15b), 4.83 – 4.79 (m, 2H, H-15a or H-15b, H-16a or H-16b), 4.60 (d, *J* = 10.8 Hz, 1H, H-16a or H-16b), 4.29 – 4.24 (m, 1H, H-3), 4.20 (d, *J* = 7.8 Hz, 1H, H-2), 4.20 – 4.16 (m, 1H, H-5), 3.86 (dd, *J* = 9.0, 5.9 Hz, 1H, H-6), 3.79 (s, 3H, 3 x H-11), 3.79 – 3.76 (m, 1H, H-10a or H-10b), 3.70 (dd, *J* = 11.8, 4.2 Hz, 1H, H-10a or H-10b), 3.61 (dd, *J* = 8.8, 8.8 Hz, 1H, H-7), 3.57 – 3.53 (m, 1H, H-9), 3.53 – 3.48 (m, 1H, H-8), 2.23 – 2.17 (m, 1H, H-4a or H-4b), 2.07 – 2.00 (m, 1H, H-4a or H-4b), 1.45 (s, 6H, 3 x H-13, 3 x H-14), 0.92 (s, 9H, 9 x H-28), 0.11 (s, 3H, 3 x H-25 or 3 x H-26), 0.08 (s, 3H, 3 x H-25 or 3 x H-26) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.97 (C-1), 138.84 (C-17), 138.09 (C-21), 128.59 (2 x C-19 or 2 x C-23), 128.42 (2 x C-19 or 2 x C-23), 128.20 (2 x C-22), 128.01 (C-20 or C-24), 127.52 (C-20 or C-24), 127.44 (2 x C-18), 111.18 (C-12), 82.82 (C-7), 79.30 (C-2), 78.08 (C-8), 75.47 (C-3), 75.37 (C-15), 75.25 (C-16), 73.31 (C-5), 72.91 (C-6), 72.39 (C-9), 62.34 (C-10), 52.64 (C-11), 28.95 (C-4), 27.24 (C-13 or C-14), 26.01 (3 x C-28), 25.99 (C-13 or C-14), 18.13 (C-27), –4.52 (C-25 or C-26), –4.53 (C-25 or C-26) ppm.

IR (ATR): $\tilde{\nu}$ = 3492 (br w), 2930 (s), 1763 (m), 1454 (w), 1208 (br m), 1086 (br s), 836 (s), 778 (m), 696 (w) cm^{-1}.

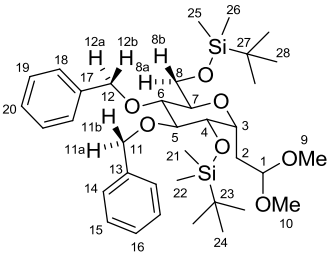
HRMS (ESI): calcd. for $C_{34}H_{50}NaO_9Si^+$: 653.3116 $[M+Na]^+$
found: 653.3113 $[M+Na]^+$.

Ketal 108:

When *trans*-ester **83** was transformed into acetonide **103** using OsO_4 (*vide supra*), a side reaction was observed. Diols **105** and/or **106** were cleaved when the amount of OsO_4 was increased to 3.2 mol%. Ketal **108** was isolated as colorless oil as a side product after the acidic protection step.

R_f = 0.37 [PE:EtOAc 9:1].

$[\alpha]_D^{21}$ = +35.2 (*c* = 0.60, $CHCl_3$).



108

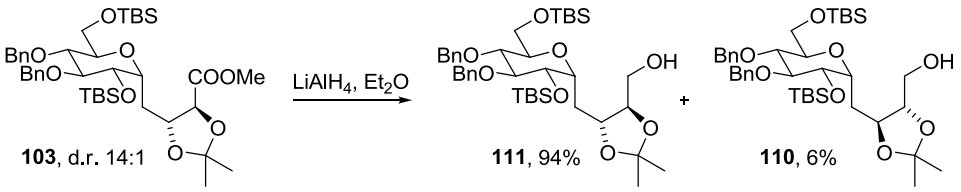
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.20 (m, 10H, 2 x H-14, 2 x H-15, H-16, 2 x H-18, 2 x H-19, H-20), 4.89 (d, *J* = 11.3 Hz, 1H, 11a or H-11b), 4.80 (d, *J* = 11.0 Hz, 1H, H-12a or H-12b), 4.78 (d, *J* = 11.2 Hz, 1H, H-11a or H-11b), 4.59 (d, *J* = 11.0 Hz, 1H, H-12a or H-12b), 4.54 (dd, *J* = 8.5, 3.1 Hz, 1H, H-1), 4.07 – 4.00 (m, 1H, H-3), 3.84 – 3.77 (m, 2H, H-4, H-8a or H-8b), 3.74 – 3.68 (m, 1H, H-8a or H-8b), 3.60 (dd, *J* = 9.0, 9.0 Hz, 1H, H-5), 3.56 – 3.50 (m, 1H, H-7), 3.45 – 3.39 (m, 1H, H-6), 3.37 (s, 3H, 3 x H-9 or 3 x H-10), 3.33 (s, 3H, 3 x H-9 or 3 x H-10), 2.07 – 1.89 (m, 2H, H-2a, H-2b), 0.91 (s, 9H, 9 x H-24), 0.90 (s, 9H, 9 x H-28), 0.09 (s, 3H, 3 x H-21 or 3 x H-22), 0.07 (s, 3H, 3 x H-21 or 3 x H-22), 0.05 (s, 3H, 3 x H-25 or 3 x H-26), 0.05 (s, 3H, 3 x H-25 or 3 x H-26) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.96 (C-13), 138.53 (C-17), 128.52 (2 x C-15 or 2 x C-19), 128.40 (2 x C-15 or 2 x C-19), 127.99 (2 x C-18), 127.80 (C-16 or C-20), 127.66 (2 x C-14), 127.49 (C-16 or C-20), 102.35 (C-1), 83.37 (C-5), 78.60 (C-6), 75.58 (C-11), 75.09 (C-12), 73.14 (C-3 or C-4 or C-7), 73.09 (C-3 or C-4 or C-7), 73.08 (C-3 or C-4 or C-7), 63.22 (C-10), 54.03 (C-9 or C-10), 53.05 (C-9 or C-10), 28.13 (C-2), 26.12 (3 x C-24 or 3 x C-28), 26.05 (3 x C-24 or 3 x C-28), 18.50 (C-27), 18.08 (C-23), –4.36 (C-21 or C-22), –4.56 (C-21 or C-22), –4.98 (C-25 or C-26), –5.19 (C-25 or C-26) ppm.

IR (ATR): $\tilde{\nu}$ = 2929 (s), 2857 (m), 1730 (br w), 1462 (w), 1360 (w), 1252 (m), 1093 (s), 833 (s), 776 (s), 696 (m) cm^{-1}.

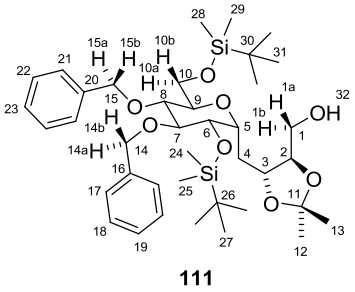
HRMS (ESI): calcd. for $C_{36}H_{60}NaO_7Si_2^+$: 683.3770 $[M+Na]^+$
found: 683.3771 $[M+Na]^+$.

[(4*R*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl] methanol (111) and [(4*S*,5*S*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-l]methanol (110):



A suspension of lithium aluminum hydride (167 mg, 4.39 mmol, 1.0 eq) in Et_2O (8 mL) was cooled to 0 °C and a solution of the diastereomeric mixture of ester **103** (188 mg, 0.319 mmol, 1.0 eq) in Et_2O (35 mL) was added *via* cannula. The resulting mixture was stirred at 0 °C for 10 min, then quenched carefully with aq. Rochelle salt (50 mL of a saturated solution). The mixture was allowed to warm to room temperature and stirred at this temperature for an additional 4 h. The resulting solution was then extracted with Et_2O (3 x 100 mL) and the combined organic fractions were washed with (brine), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 49:1→19:1→9:1→6:1→4:1→2:1] afforded major alcohol **111** (3.00 g, 4.18 mmol, 94%) and minor alcohol **110** (210 mg, 0.293 mmol, 6%), both as a colorless oils.

Major alcohol 111:



111

R_f = 0.47 [PE:EtOAc 3:1].

$[\alpha]_D^{19}$ = +35.4 (*c* = 0.98, $CHCl_3$).

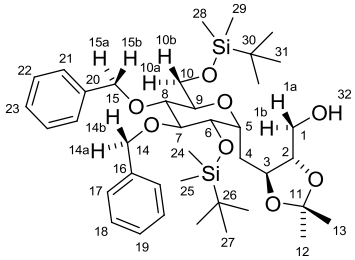
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.34 (m, 2H, 2 x H-17), 7.33 – 7.25 (m, 6H, 2 x H-18, H-19, 2 x H-22, H-23), 7.23 – 7.20 (m, 2H, 2 x H-21), 4.89 (d, *J* = 11.3 Hz, 1H, H-14a or H-14b), 4.80 (d, *J* = 11.0 Hz, 1H, H-15a or H-15b), 4.78 (d, *J* = 11.5, 1H, H-14a or H-14b), 4.57 (d, *J* = 10.8 Hz, 1H, H-15a or H-15b), 4.15 – 4.09 (m, 1H, H-5), 4.01 (ddd, *J* = 8.5, 8.5, 4.3 Hz, 1H, H-3), 3.85 – 3.81 (m, 2H, H-2, H-6), 3.79 (dd, *J* = 11.1, 1.7 Hz, 1H, H-10a or H-10b), 3.75 (br dd, *J* = 11.7, 3.5 Hz, 1H, H-1a or H-1b), 3.72 – 3.66 (m, 2H, H-1a or H-1b, H-10a or H-10b), 3.57 (dd, *J* = 9.0, 9.0 Hz, 1H, H-7), 3.50 – 3.46 (m, 1H, H-9), 3.44 – 3.39 (m, 1H, H-8), 2.05 – 1.90 (m, 3H, H-4a, H-4b, H-32), 1.40 (s, 3H, 3 x H-12 or 3 x H-13), 1.39 (s, 3H, 3 x H-12 or 3 x H-13), 0.91 (s, 9H, 9 x H-27), 0.89 (s, 9H, 9 x H-31), 0.10 (s, 3H, 3 x H-24 or 3 x H-25), 0.08 (s, 3H, 3 x H-24 or 3 x H-25), 0.06 (s, 3H, 3 x H-28 or 3 x H-29), 0.05 (s, 3H, 3 x H-28 or 3 x H-29) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.91 (C-16), 138.36 (C-20), 128.58 (2 x C-18 or 2 x C-22), 128.43 (2 x C-18 or 2 x C-22), 128.14 (2 x C-21), 127.92 (C-19 or C-23), 127.65 (2 x C-17), 127.55 (C-19 or C-23), 108.87 (C-11), 83.21 (C-7), 81.71 (C-2), 78.52 (C-8), 75.55 (C-14), 75.23 (C-15), 74.59 (C-3), 73.49 (C-5), 73.24 (C-9), 73.12 (C-6), 63.30 (C-10), 62.69 (C-1), 28.23 (C-4), 27.41 (C-12 or C-13), 27.21 (C-12 or C-13), 26.14 (3 x C-31), 26.06 (3 x C-27), 18.55 (C-30), 18.15 (C-26), –4.43 (C-24 or C-25), –4.48 (C-24 or C-25), –4.99 (C-28 or C-29), –5.21 (C-28 or C-29) ppm.

IR (ATR): $\tilde{\nu}$ = 3476 (br w), 2929 (s), 2857 (s), 1462 (w), 1379 (w), 1252 (m), 1081 (br s), 834 (s), 776 (m), 733 (w), 696 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{39}H_{68}NO_8Si_2^+$: 734.4478 $[M+NH_4]^+$
found: 734.4478 $[M+NH_4]^+$.

Minor alcohol 110:



110

R_f = 0.55 [PE:EtOAc 3:1].

$[\alpha]_D^{19}$ = +20.6 (c = 0.34, $CHCl_3$).

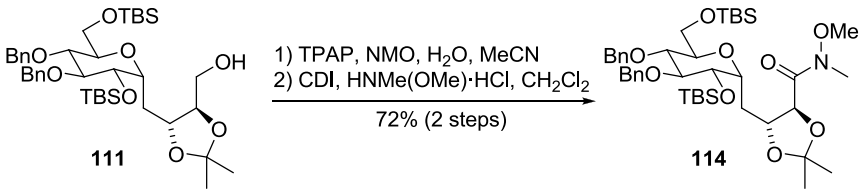
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.24 (m, 8H, 2 x H-17, 2 x H-18, H-19, 2 x H-22, H-23), 7.23 – 7.18 (m, 2H, 2 x H-21), 4.89 (d, J = 11.3 Hz, 1H, H-14a or H-14b), 4.79 (d, J = 11.1 Hz, 1H, H-15a or H-15b), 4.78 (d, J = 11.4 Hz, 1H, H-14a or H-14b), 4.54 (d, J = 11.1 Hz, 1H, H-15a or H-15b), 4.11 – 4.02 (m, 2H, H-3, H-5), 3.98 – 3.92 (m, 1H, H-2), 3.85 – 3.54 (m, 7H, H-1a, H-1b, H-6, H-7, H-9, H-10a, H-10b), 3.30 (dd, J = 9.2, 9.2 Hz, 1H, H-8), 2.72 – 2.64 (m, 1H, H-32), 2.25 (ddd, J = 16.1, 11.9, 4.2 Hz, 1H, H-4a or H-4b), 1.99 (ddd, J = 15.0, 7.3, 2.9 Hz, 1H, H-4a or H-4b), 1.39 (s, 3H, 3 x H-13), 1.38 (s, 3H, 3 x H-12), 0.91 (s, 9H, 9 x H-27), 0.88 (s, 9H, 9 x H-31), 0.09 (s, 3H, 3 x H-24 or 3 x H-25), 0.08 (s, 3H, 3 x H-24 or 3 x H-25), 0.05 (s, 3H, 3 x H-28 or 3 x H-29), 0.05 (s, 3H, 3 x H-28 or 3 x H-29) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.83 (C-16), 138.31 (C-20), 128.56 (2 x C-18 or 2 x C-22), 128.43 (2 x C-18 or 2 x C-22), 128.09 (2 x C-21), 127.91 (C-19 or C-23), 127.66 (2 x C-17), 127.56 (C-19 or C-23), 108.21 (C-11), 83.20 (C-7), 80.13 (C-2), 78.65 (C-8), 75.78 (C-3), 75.63 (C-14), 75.13 (C-15), 73.17 (C-6), 73.10 (C-9), 72.86 (C-5), 63.82 (C-9), 63.24 (C-1), 27.24 (C-13), 27.18 (C-4), 27.13 (C-12), 26.21 (3 x C-31), 26.04 (3 x C-27), 18.73 (C-30), 18.11 (C-26), –4.35 (C-24 or C-25), –4.51 (C-24 or C-25), –5.11 (C-28 or C-29), –5.25 (C-28 or C-29) ppm.

IR (ATR): $\tilde{\nu}$ = 3479 (br w), 2929 (s), 2857 (s), 1462 (w), 1379 (w), 1252 (m), 1089 (br s), 834 (s), 776 (m), 753 (w), 696 (w) cm^{-1}.

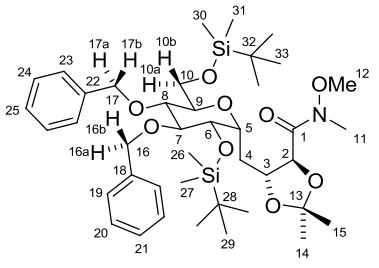
HRMS (ESI): calcd. for $C_{39}H_{68}NO_8Si_2^+$: 734.4478 $[M+NH_4]^+$
found: 734.4480 $[M+NH_4]^+$.

(4S,5R)-5-{[(2R,3S,4S,5R,6R)-4,5-Bis(benzyloxy)-3-[(tert-butyldimethylsilyl)oxy]-6-{[(tert-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-N-methoxy-N,2,2-trimethyl-1,3-dioxolane-4-carboxamide (114):



To a solution of alcohol **111** (2.06 g, 2.87 mmol, 1.0 eq), tetra-*n*-propylammonium perruthenate (202 mg, 0.574 mmol, 20 mol%), and *N*-methylmorpholine-*N*-oxide (1.35 g, 11.5 mmol, 4.0 eq) in MeCN (100 mL) was added water (1 mL), and the resulting solution was stirred at room temperature for 30 min. The solvent was evaporated *in vacuo* and azeotropic removal of water residues with toluene (1 x 20 mL) provided the crude product, which was subjected to flash column chromatography [PE:EtOAc 9:1→3:1→3:1 + 1% AcOH]. The obtained carboxylic acid was subsequently dissolved in CH_2Cl_2 (300 mL) and 1,1'-carbonyldiimidazole (1.16 g, 7.18 mmol, 2.5 eq) was added successively in ten equal portions and the mixture was stirred at room temperature for 10 min after each addition. Complete consumption of carboxylic acid was monitored by TLC analysis ('mini-workup' with MeOH), thereafter *N*,*O*-dimethylhydroxyl-amine hydrochloride (700 mg, 7.18 mmol, 2.5 eq) was added in one portion and the mixture was stirred for an additional 4 h. The reaction was quenched with water (100 mL) and the organic phase was separated. The aqueous layer was extracted further with EtOAc (3 x 250 mL). The combined organic fractions were washed with brine (250 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→4:1] afforded Weinreb amide **114** (1.61 g, 2.08 mmol, 72% over two steps) as a colorless oil.

Weinreb amide 114:



R_f = 0.47 [PE:EtOAc 3:1].

$[\alpha]_D^{19}$ = +27.2 (*c* = 0.92, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.22 (m, 10H, 2 x H-19, 2 x H-20, H-21, 2 x H-23, 2 x H-24, H-25), 4.88 (d, *J* = 11.3 Hz, 1H, H-16a or H-16b), 4.80 (d, *J* = 10.8 Hz, 1H, H-17a or H-17b), 4.78 (d, *J* = 11.3 Hz, 1H, H-16a or H-16b), 4.63 (d, *J* = 10.8 Hz, 1H, H-17a or H-17b), 4.54 – 4.40 (m, 2H, H-2, H-3), 4.15 (ddd, *J* = 11.7, 6.0, 2.3 Hz, 1H, H-5), 3.85 – 3.78 (m, 3H, H-6, H10a, H-

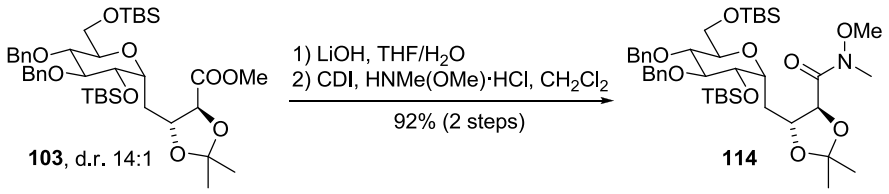
10b), 3.74 (s, 3H, 3 x H-12), 3.59 – 3.53 (m, 2H, H-7, H-8), 3.49 – 3.42 (m, 1H, H-9), 3.22 (br s, 3H, 3 x H-11), 2.08 – 2.01 (m, 1H, H-4a or H-4b), 1.99 – 1.93 (m, 1H, H-4a or H-4b), 1.45 (s, 3H, 3 x H-14 or 3 x H-15), 1.44 (s, 3H, 3 x H-14 or 3 x H-15), 0.92 (s, 9H, 9 x H-29), 0.90 (s, 9H, 9 x H-33), 0.11 (s, 3H, 3 x H-26 or 3 x H-27), 0.08 (s, 3H, 3 x H-26 or 3 x H-27), 0.06 (s, 3H, 3 x H-30 or 3 x H-31), 0.05 (s, 3H, 3 x H-30 or 3 x H-31) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.40 (C-1), 139.02 (C-18), 138.65 (C-22), 128.52 (2 x C-20 or 2 x C-24), 128.40 (2 x C-20 or 2 x C-24), 128.06 (2 x C-23), 127.78 (C-25), 127.65 (2 x C-19), 127.49 (C-21), 110.62 (C-13), 83.21 (C-7), 78.17 (C-8), 77.58 (C-2), 75.50 (C-16), 75.11 (C-17), 75.08 (C-3), 73.15 (C-5 or C-6), 73.12 (C-5 or C-6), 72.87 (C-9), 62.69 (C-10), 61.77 (C-12), 32.48 (C-11), 28.11 (C-4), 27.64 (C-14 or C-15), 26.38 (C-14 or C-15), 26.14 (3 x C-33), 26.10 (3 x C-29), 18.50 (C-32), 18.18 (C-28), –4.45 (C-26 or C-27), –4.48 (C-26 or C-27), –4.85 (C-30 or C-31), –5.26 (C-30 or C-31) ppm.

IR (ATR): $\tilde{\nu}$ = 2930 (s), 1669 (m), 1252 (m), 1086 (s), 833 (s), 697 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{41}H_{71}N_2O_9Si_2^+$: 791.4693 $[M+NH_4]^+$
found: 791.4694 $[M+NH_4]^+$.

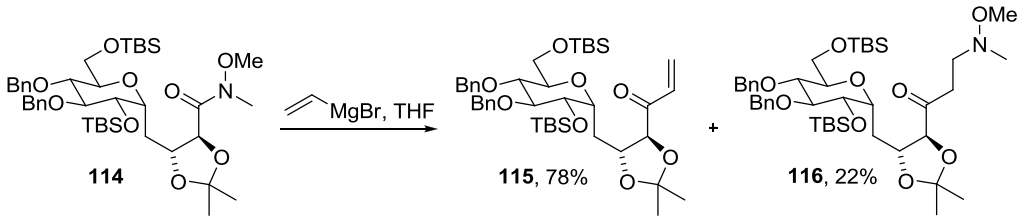
(4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-*N*-methoxy-N,2,2-trimethyl-1,3-dioxolane-4-carboxamide (114):



To a solution of the diastereomeric mixture of ester **103** (13.1 g, 17.5 mmol, 1.0 eq) in a mixture of THF and water (3:1, 300 mL) was added lithium hydroxide monohydrate (2.20 g, 52.5 mmol, 3.0 eq) and the resulting solution was stirred at room temperature for 35 min. The mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 300 mL). The combined organic fractions were washed with brine (300 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude carboxylic acid. Further azeotropic removal (toluene, 2 x 150 mL) of solvent residues provided dry acid, which was subsequently dissolved in CH_2Cl_2 (300 mL). 1,1'-Carbonyldiimidazole (8.52 g, 52.5 mmol, 3.0 eq) was added in six equal portions, and the mixture was stirred at room temperature for 10 min after each addition. Complete consumption of carboxylic acid was monitored by TLC analysis ('mini-workup' with MeOH), thereafter *N*,*O*-dimethylhydroxylamine hydrochloride (5.12 g, 52.5 mmol, 3.0 eq) was added in one

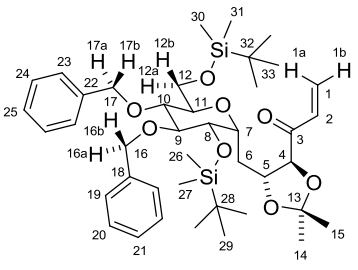
portion and the mixture was stirred for an additional 4 h. The reaction was quenched with water (200 mL) and the organic phase was separated. The aqueous layer was extracted further with Et_2O (3 x 300 mL). The combined organic fractions were washed with brine (300 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→4:1→1:1] afforded Weinreb amide **114** (12.5 g, 16.1 mmol, 92% over two steps) as a colorless oil. The ^{1}H-NMR spectrum indicated traces of the second diastereomer resulting from the Sharpless dihydroxylation.

1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-one (115) and 1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]-3-[methoxy(methyl)amino]propan-1-one (116)



A solution of Weinreb amide **114** (6.70 g, 8.65 mmol, 1.0 eq) in THF (300 mL) was cooled to –10 °C and a solution of vinylmagnesium bromide in THF (1.0 M, 7.80 mL, 7.75 mmol, 1.2 eq) was added dropwise. After stirring for 30 min at –10 °C, the mixture was allowed to warm to room temperature and stirred for an additional 10 min. The reaction was quenched with water (300 mL) and the aqueous layer was extracted with Et_2O (3 x 400 mL). The combined organic fractions were washed with brine (400 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1→4:1] afforded vinyl ketone **115** (3.72 g, 5.02 mmol, 78%) and ketone **116** (1.14 g, 1.42 mmol, 22%), both as colorless oils.

Vinyl ketone 115:



R_f = 0.39 [PE:EtOAc 9:1].

$[\alpha]_D^{19}$ = +26.9 (*c* = 1.2, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.23 (m, 10H, 2 x H-19, 2 x H-20, H-21, 2 x H-23, 2 x H-24, H-25), 6.88 (dd, *J* = 17.4, 10.6 Hz, 1H, H-2), 6.45 (dd, *J* = 17.4, 1.7 Hz, 1H, H-1a), 5.82 (dd, *J* = 10.6, 1.8 Hz, 1H, H-1b), 4.90 (d, *J* = 11.2 Hz, 1H, H-16a or H-16b), 4.82 (d, *J* = 11.1 Hz, 1H, H-17a or H-17b), 4.79 (d, *J* = 11.3 Hz, 1H, H-16a or H-16b), 4.59 (d, *J* = 11.0 Hz, 1H, H-17a or H-17b),

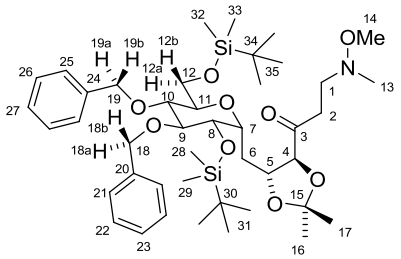
4.22 – 4.17 (m, 3H, H-4, H-5, H-7), 3.84 (dd, J = 9.4, 6.1 Hz, 1H, H-8), 3.77 (dd, J = 11.2, 1.8 Hz, 1H, H-12a or H-12b), 3.70 (dd, J = 11.1, 5.0 Hz, 1H, H-12a or H-12b), 3.61 (dd, J = 9.1, 9.1 Hz, 1H, H-9), 3.48 (ddd, J = 9.8, 5.0, 1.8 Hz, 1H, H-11), 3.42 (dd, J = 9.8, 8.9 Hz, 1H, H-10), 2.18 – 2.12 (m, 1H, H-6a or H-6b), 2.02 – 1.95 (m, 1H, H-6a or H-6b), 1.45 (s, 3H, 3 x H-14 or 3 x H-15), 1.42 (s, 3H, 3 x H-14 or 3 x H-15), 0.93 (s, 9H, 9 x H-29), 0.87 (s, 9H, 9 x H-33), 0.12 (s, 3H, 3 x H-26 or 3 x H-27), 0.09 (s, 3H, 3 x H-26 or 3 x H-27), 0.03 (s, 3H, 3 x H-30 or 3 x H-31), 0.02 (s, 3H, 3 x H-30 or 3 x H-31) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 198.10 (C-3), 138.98 (C-18), 138.54 (C-22), 131.16 (C-2), 130.64 (C-1), 128.49 (2 x C-20 or 2 x C-24), 128.39 (2 x C-20 or 2 x C-24), 127.97 (2 x C-23), 127.76 (C-25), 127.65 (2 x C-19), 127.48 (C-21), 110.61 (C-13), 84.70 (C-4), 83.28 (C-9), 78.60 (C-10), 75.62 (C-16), 75.11 (C-17), 74.51 (C-5), 73.14 (C-7 or C-8 or C-11), 73.08 (C-7 or C-8 or C-11), 73.04 (C-7 or C-8 or C-11), 63.16 (C-12), 28.56 (C-6), 27.34 (C-14 or C-15), 26.38 (C-14 or C-15), 26.13 (3 x C-33), 26.06 (3 x C-29), 18.47 (C-32), 18.15 (C-28), –4.48 (C-26 or C-27), –4.50 (C-26 or C-27), –4.97 (C-30 or C-31), –5.27 (C-30 or C-31) ppm.

IR (ATR): $\tilde{\nu}$ = 2929 (s), 1698 (w), 1252 (m), 1086 (s), 834 (s), 696 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{41}H_{68}NO_8Si_2^+$: 758.4478 $[M+NH_4]^+$
found: 758.4480 $[M+NH_4]^+$.

Keton 116:



116

R_f = 0.59 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +23.9 (c = 1.1, $CHCl_3$).

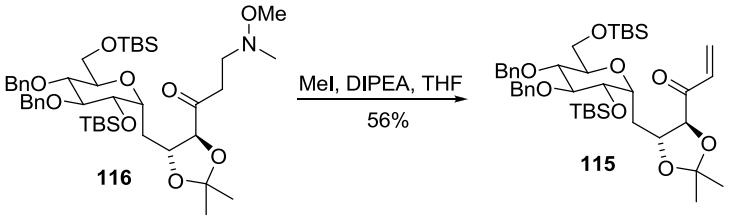
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.35 – 7.22 (m, 10H, 2 x H-21, 2 x H-22, H-23, 2 x H-25, 2 x H-26, H-27), 4.88 (d, J = 11.2 Hz, 1H, H-18a or H-18b), 4.81 (d, J = 11.0 Hz, 1H, H-19a or H-19b), 4.78 (d, J = 11.2 Hz, 1H, H-18a or H-18b), 4.60 (d, J = 11.0 Hz, 1H, H-19a or H-19b), 4.17 (ddd, J = 12.2, 6.1, 2.0 Hz, 1H, H-7), 4.12 (ddd, J = 10.5, 8.2, 2.2 Hz, 1H, H-5), 4.04 (d, J = 8.2 Hz, 1H, H-4), 3.83 (dd, J = 9.4, 6.1 Hz, 1H, H-8), 3.76 (dd, J = 11.2, 1.7 Hz, 1H, H-12a or H-12b), 3.73 (dd, J = 11.2, 4.1 Hz, 1H, H-12a or H-12b), 3.59 (dd, J = 8.8, 8.8 Hz, 1H, H-9), 3.51 (br s, 3H, 3 x H-14), 3.50 – 3.42 (m, 2H, H-10, H-11), 3.03 – 2.84 (m, 4H, 2 x H-1, 2 x H-2), 2.60 (s, 3H, 3 x H-13), 2.16 (ddd, J = 14.5, 12.3, 2.2 Hz, 1H, H-6a or H-6b), 1.93 (ddd, J = 14.8, 10.5, 2.1 Hz, 1H, H-6a or H-6b), 1.42 (s, 3H, 3 x H-16 or 3 x H-17), 1.42 (s, 3H, 3 x H-16 or 3 x H-17), 0.91 (s, 9H, 9 x H-31), 0.88 (s, 9H, 9 x H-35), 0.10 (s, 3H, 3 x H-28 or 3 x H-29), 0.08 (s, 3H, 3 x H-28 or 3 x H-29), 0.04 (s, 3H, 3 x H-32 or 3 x H-33), 0.03 (s, 3H, 3 x H-32 or 3 x H-33) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 208.92 (C-3), 139.01 (C-20), 138.64 (C-24), 128.47 (2 x C-22 or 2 x C-26), 128.39 (2 x C-22 or 2 x C-26), 127.90 (2 x C-25), 127.70 (C-27), 127.68 (2 x C-21), 127.47 (C-23), 110.40 (C-15), 85.31 (C-4), 83.30 (C-9), 78.49 (C-10), 75.63 (C-18), 75.05 (C-19), 74.17 (C-5), 73.14 (C-8), 73.08 (C-7), 72.91 (C-11), 63.06 (C-12), 60.10 (C-14), 54.51 (C-1), 45.10 (C-13), 36.75 (C-2), 28.81 (C-6), 27.31 (C-16 or C-17), 26.50 (C-16 or C-17), 26.12 (3 x C-31), 26.06 (3 x C-35), 18.47 (C-34), 18.15 (C-30), –4.48 (C-28 or C-29), –4.50 (C-28 or C-29), –4.94 (C-32 or C-33), –5.26 (C-32 or C33) ppm.

IR (ATR): $\tilde{\nu}$ = 2930 (s), 1715 (w), 1252 (m), 1086 (s), 834 (s), 696 (w) cm^{-1}.

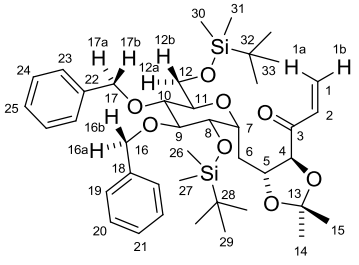
HRMS (ESI): calcd. for $C_{43}H_{72}NO_9Si_2^+$: 802.4740 $[M+H]^+$
found: 802.4743 $[M+H]^+$.

1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-one (115):



To a solution of ketone **116** (200 mg, 0.249 mmol, 1.0 eq) in THF (15 mL) was added *N*,*N*-diisopropylethylamine (84.7 µL, 0.498 mmol, 2.0 eq) followed methyl iodide (0.23 mL, 3.74 mmol, 15 eq), and the resulting mixture was heated to 50 °C for 7 d. The reaction was quenched with aq. $NaHCO_3$ (20 mL of a saturated solution) and the mixture was extracted with Et_2O (3 x 25 mL) and the combined organic fraction were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1] afforded vinyl ketone **115** (103 mg, 0.139 mmol, 56%) and starting material **116** (48.1 mg, 60.0 µmol, 24%), both as colorless oils.

Vinyl ketone 115:



115

Analytical data were identical with the material obtained earlier (*vide supra*).

R_f = 0.39 [PE:EtOAc 9:1].

$[\alpha]_D^{19}$ = +26.9 (*c* = 1.2, $CHCl_3$).

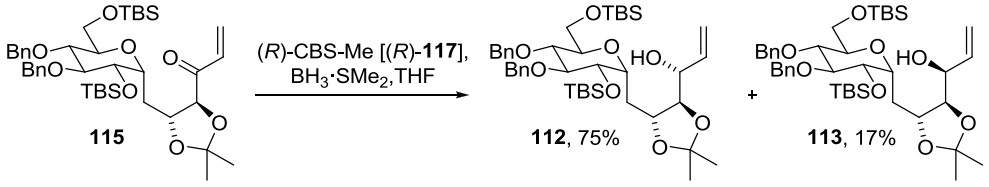
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.23 (m, 10H, 2 x H-19, 2 x H-20, H-21, 2 x H-23, 2 x H-24, H-25), 6.88 (dd, *J* = 17.4, 10.6 Hz, 1H, H-2), 6.45 (dd, *J* = 17.4, 1.7 Hz, 1H, H-1a), 5.82 (dd, *J* = 10.6, 1.8 Hz, 1H, H-1b), 4.90 (d, *J* = 11.2 Hz, 1H, H-16a or H-16b), 4.82 (d, *J* = 11.1 Hz, 1H, H-17a or H-17b), 4.79 (d, *J* = 11.3 Hz, 1H, H-16a or H-16b), 4.59 (d, *J* = 11.0 Hz, 1H, H-17a or H-17b), 4.22 – 4.17 (m, 3H, H-4, H-5, H-7), 3.84 (dd, *J* = 9.4, 6.1 Hz, 1H, H-8), 3.77 (dd, *J* = 11.2, 1.8 Hz, 1H, H-12a or H-12b), 3.70 (dd, *J* = 11.1, 5.0 Hz, 1H, H-12a or H-12b), 3.61 (dd, *J* = 9.1, 9.1 Hz, 1H, H-9), 3.48 (ddd, *J* = 9.8, 5.0, 1.8 Hz, 1H, H-11), 3.42 (dd, *J* = 9.8, 8.9 Hz, 1H, H-10), 2.18 – 2.12 (m, 1H, H-6a or H-6b), 2.02 – 1.95 (m, 1H, H-6a or H-6b), 1.45 (s, 3H, 3 x H-14 or 3 x H-15), 1.42 (s, 3H, 3 x H-14 or 3 x H-15), 0.93 (s, 9H, 9 x H-29), 0.87 (s, 9H, 9 x H-33), 0.12 (s, 3H, 3 x H-26 or 3 x H-27), 0.09 (s, 3H, 3 x H-26 or 3 x H-27), 0.03 (s, 3H, 3 x H-30 or 3 x H-31), 0.02 (s, 3H, 3 x H-30 or 3 x H-31) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 198.10 (C-3), 138.98 (C-18), 138.54 (C-22), 131.16 (C-2), 130.64 (C-1), 128.49 (2 x C-20 or 2 x C-24), 128.39 (2 x C-20 or 2 x C-24), 127.97 (2 x C-23), 127.76 (C-25), 127.65 (2 x C-19), 127.48 (C-21), 110.61 (C-13), 84.70 (C-4), 83.28 (C-9), 78.60 (C-10), 75.62 (C-16), 75.11 (C-17), 74.51 (C-5), 73.14 (C-7 or C-8 or C-11), 73.08 (C-7 or C-8 or C-11), 73.04 (C-7 or C-8 or C-11), 63.16 (C-12), 28.56 (C-6), 27.34 (C-14 or C-15), 26.38 (C-14 or C-15), 26.13 (3 x C-33), 26.06 (3 x C-29), 18.47 (C-32), 18.15 (C-28), –4.48 (C-26 or C-27), –4.50 (C-26 or C-27), –4.97 (C-30 or C-31), –5.27 (C-30 or C-31) ppm.

IR (ATR): $\tilde{\nu}$ = 2929 (s), 1698 (w), 1252 (m), 1086 (s), 834 (s), 696 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{41}H_{68}NO_8Si_2^+$: 758.4478 $[M+NH_4]^+$
found: 758.4480 $[M+NH_4]^+$.

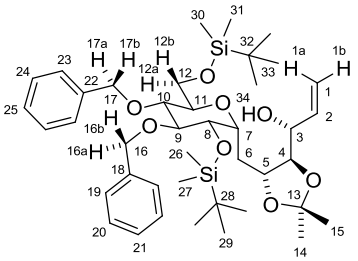
(1*R*)-1-[(4*R*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (112) and (1*S*)-1-[(4*R*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (113):



Toluene was removed from a solution of (*R*)-(–)-2-methyl-CBS-oxazaborolidine [(*R*)-**117**] in toluene (1.0 M, 4.24 mL, 4.24 mmol, 2.0 eq) and the residue was dried *in vacuo*. The CBS reagent was re-dissolved in THF (50 mL), and the resulting solution was added *via* cannula to a

stirred solution of vinyl ketone **115** (1.57 g, 2.12 mmol, 1.0 eq) in THF (110 mL), which had been pre-cooled to –30 °C. A solution of borane dimethyl sulfide complex in THF (2.0 M, 1.17 mL, 2.33 mmol, 1.1 eq) was then added dropwise, and the mixture was stirred at –30 °C for 1.5 h. The reaction was quenched at –30 °C with MeOH (10 mL) and allowed to warm to room temperature. A mixture (2:1, 120 mL) of aq. NaOH (10 wt%) and aq. $NaHCO_3$ (saturated solution) was added, and the resulting solution was extracted with Et_2O (3 x 200 mL). The combined organic fractions were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford crude alcohols **112** and **113** as a mixture of two diastereomers (d.r. 4.4:1, as determined by ^{1}H-NMR spectroscopy). Flash column chromatography [PE:EtOAc 19:1→9:1→4:1] afforded allylic alcohol **112** (1.19 g, 1.60 mmol, 75%) and the minor diastereomer **113** (267 mg, 0.359 mmol, 17%), both as colorless oils.

Allylic alcohol 112:



112

R_f = 0.73 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +32.2 (*c* = 1.1, $CHCl_3$).

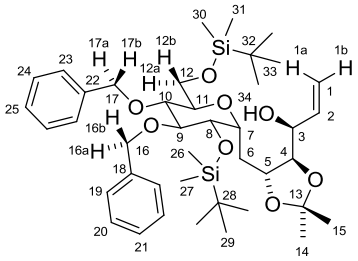
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.21 (m, 10H, 2 x H-19, 2 x H-20, H-21, 2 x H-23, 2 x H-24, H-25), 5.93 (ddd, *J* = 17.3, 10.6, 5.3 Hz, 1H, H-2), 5.39 (ddd, *J* = 17.3, 1.6, 1.6 Hz, 1H, H-1a), 5.25 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H, H-1b), 4.89 (d, *J* = 11.3 Hz, 1H, H-16a or H-16b), 4.79 (d, *J* = 10.7 Hz, 1H, H-17a or H-17b), 4.78 (d, *J* = 11.0 Hz, 1H, H-16a or H-16b), 4.60 (d, *J* = 10.9 Hz, 1H, H-17a or H-17b), 4.28 – 4.25 (m, 1H, H-3), 4.18 – 4.13 (m, 2H, H-5, H-7), 3.83 (dd, *J* = 9.3, 6.1 Hz, 1H, H-8), 3.80 – 3.75 (m, 1H, H-12a or H-12b), 3.75 – 3.69 (m, 2H, H-4, H-12a or H-12b), 3.55 (dd, *J* = 8.9, 8.9 Hz, 1H, H-9), 3.47 – 3.41 (m, 2H, H-10, H-11), 2.33 (br s, 1H, H-34), 1.99 (ddd, *J* = 14.7, 12.1, 2.6 Hz, 1H, H-6a or H-6b), 1.89 (ddd, *J* = 14.8, 10.0, 2.2 Hz, 1H, H-6a or H-6b), 1.40 (s, 3H, 3 x H-15), 1.38 (s, 3H, 3 x H-14), 0.91 (s, 9H, 9 x H-29), 0.90 (s, 9H, 9 x H-33), 0.10 (s, 3H, 3 x H-26 or 3 x H-27), 0.07 (s, 3H, 3 x H-26 or 3 x H-27), 0.07 (s, 3H, 3 x H-30 or 3 x H-31), 0.06 (s, 3H, 3 x H-30 or 3 x H-31) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 139.03 (C-18), 138.53 (C-22), 136.59 (C-2), 128.53 (2 x C-20 or 2 x C-24), 128.40 (2 x C-20 or 2 x C-24), 128.09 (2 x C-23), 127.84 (C-25), 127.61 (2 x C-19), 127.49 (C-21), 116.51 (C-1), 109.05 (C-13), 83.43 (C-9), 83.23 (C-4), 78.58 (C-10), 75.58 (C-16), 74.15 (C-17), 74.09 (C-7), 73.62 (C-5), 73.21 (C-8), 72.02 (C-11), 72.61 (C-3), 63.20 (C-12), 29.33 (C-6), 27.46 (C-14), 27.19 (C-15), 26.17 (3 x C-29 or 3 x C-33), 26.08 (3 x C-29 or 3 x C-33), 18.58 (C-32), 18.16 (C-28), –4.42 (C-26 or C-27), –4.50 (C-26 or C-27), –4.95 (C-30 or C-31), –5.20 (C-30 or C-31) ppm.

IR (ATR): $\tilde{\nu}$ = 3460 (br, w), 2929 (s), 1462 (w), 1252 (m), 1077 (s), 834 (s), 696 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{41}H_{70}NO_8Si_2^+$: 760.4634 $[M+NH_4]^+$
found: 760.4636 $[M+NH_4]^+$.

Alcohol 113:



113

R_f = 0.67 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +57.5 (c = 0.41, $CHCl_3$).

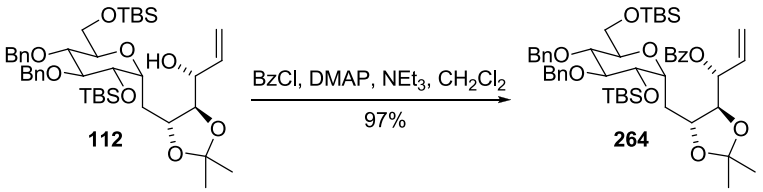
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.21 (m, 10H, 2 x H-19, 2 x H-20, H-21, 2 x H-23, 2 x H-24, H-25), 5.85 (ddd, J = 17.1, 10.5, 6.2 Hz, 1H, H-2), 5.40 (ddd, J = 17.2, 1.7, 1.7 Hz, 1H, H-1a), 5.27 (ddd, J = 10.5, 1.3, 1.3 Hz, 1H, H-1b), 4.89 (d, J = 11.3 Hz, 1H, H-16a or H-16b), 4.79 (d, J = 10.7 Hz, 1H, H-17a or H-17b), 4.78 (d, J = 11.1 Hz, 1H, H-16a or H-16b), 4.59 (d, J = 10.8 Hz, 1H, H-17a or H-17b), 4.17 – 4.13 (m, 1H, H-7), 4.13 – 4.09 (m, 1H, H-3), 4.09 – 4.04 (m, 1H, H-5), 3.82 (dd, J = 9.3, 6.1 Hz, 1H, H-8), 3.77 (dd, J = 11.1, 1.8 Hz, 1H, H-12a or H-12b), 3.73 (dd, J = 11.1, 4.6 Hz, 1H, H-12a or H-12b), 3.68 (dd, J = 7.8, 5.4 Hz, 1H, H-4), 3.54 (dd, J = 9.0, 9.0 Hz, 1H, H-9), 3.45 (dd, J = 9.3, 9.3 Hz, 1H, H-10), 3.39 (ddd, J = 9.8, 4.6, 1.8 Hz, 1H, H-11), 2.35 (br d, J = 4.8 Hz, 1H, H-34), 1.93 – 1.87 (m, 2H, H-6a, H-6b), 1.41 (s, 3H, 3 x H-15), 1.39 (s, 3H, 3 x H-14), 0.91 (s, 9H, 9 x H-29), 0.90 (s, 9H, 9 x H-33), 0.10 (s, 3H, 3 x H-26 or 3 x H-27), 0.07 (s, 3H, 3 x H-26 or 3 x H-27), 0.06 (s, 3H, 3 x H-30 or 3 x H-31), 0.05 (s, 3H, 3 x H-30 or 3 x H-31) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.99 (C-18), 138.46 (C-22), 136.83 (C-2), 128.56 (2 x C-20 or 2 x C-24), 128.42 (2 x C-20 or 2 x C-24), 128.11 (2 x C-23), 127.88 (C-25), 127.60 (2 x C-19), 127.51 (C-21), 117.68 (C-1), 109.29 (C-13), 83.89 (C-4), 83.33 (C-9), 78.49 (C-10), 75.57 (C-16), 75.21 (C-17), 73.99 (C-5), 73.50 (C-3), 73.40 (C-7), 73.18 (C-11), 73.13 (C-8), 63.10 (C-12), 28.57 (C-6), 27.59 (C-14), 27.30 (C-15), 26.15 (3 x C-29 or 3 x C-33), 26.07 (3 x C-29 or 3 x C-33), 18.54 (C-32), 18.16 (C-28), –4.44 (C-26 or C-27), –4.49 (C-26 or C-27), –4.95 (C-30 or C-31), –5.19 (C-30 or C-31) ppm.

IR (ATR): $\tilde{\nu}$ = 3458 (br, w), 2929 (s), 1462 (w), 1252 (m), 1083 (s), 834 (s), 696 (w) cm^{-1}.

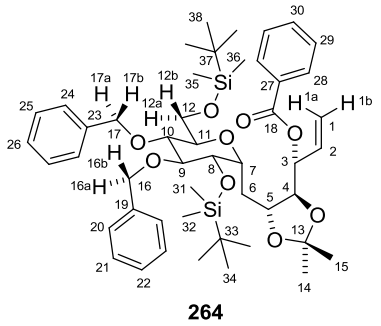
HRMS (ESI): calcd. for $C_{41}H_{70}NO_8Si_2^+$: 760.4634 $[M+NH_4]^+$
found: 760.4635 $[M+NH_4]^+$.

(1*R*)-1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-yl benzoate (264)



A solution of allylic alcohol **112** (120 mg, 0.161 mmol, 1.0 eq), 4-(dimethylamino)pyridine (2.00 mg, 16.1 µmol, 10 mol%) and triethylamine (134 µL, 0.966 mmol, 6.0 eq) in CH_2Cl_2 (3 mL) was cooled to 0 °C and benzoyl chloride (37.4 µL, 0.322 mmol, 2.0 eq) was added dropwise. The solution was stirred at 0 °C for 10 min, then at room temperature for a further 20 h. The reaction was quenched with aq. $NaHCO_3$ (5 mL of a saturated solution) and the mixture extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 49:1→29:1→9:1] afforded benzoate ester **264** (132 mg, 0.156 mmol, 97%) as a colorless oil.

Benzoate ester 264:



R_f = 0.47 [PE:EtOAc 9:1].

$[\alpha]_D^{20}$ = +42.9 (*c* = 0.63, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.08 – 8.05 (m, 2H, 2 x H-28), 7.44 – 7.40 (m, 1H, H-30), 7.37 – 7.24 (m, 10H, 2 x H-20, 2 x H-21, H-22, 2 x H-25, H-26, 2 x H-29), 7.19 – 7.16 (m, 2H, 2 x H-24), 6.00 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H, H-2), 5.64 – 5.60 (m, 1H, H-3), 5.40 (ddd, *J* = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.33 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.84 (d, *J* = 11.2 Hz, 1H, H-16a or H-16b), 4.74 (d, *J* = 10.9 Hz, 1H, H-17a or H-17b), 4.73 (d, *J* = 11.2 Hz, 1H, H-16a or H-16b), 4.54 (d, *J* = 10.9 Hz, 1H, H-17a or H-17b), 4.21 – 4.13 (m, 2H, H-5, H-7), 3.96 (dd, *J* = 7.7, 5.5 Hz, 1H, H-4), 3.81 – 3.77 (m, 1H, H-8), 3.59 – 3.54 (m, 2H, H-12a, H-12b), 3.46 – 3.40 (m, 2H, H-9, H-10), 3.17 – 3.13 (m, 1H, H-11), 2.03 – 1.89 (m, 2H, H-6a, H-6b), 1.40 (s, 3H, 3 x H-14), 1.36 (s, 3H, 3 x H-15), 0.91 (s, 9H, 9 x H-34), 0.87 (s, 9H, 9 x H-38), 0.08 (s, 3H, 3 x H-31 or 3 x H-32), 0.06 (s, 3H, 3 x H-31 or 3 x H-32), 0.03 (s, 3H, 3 x H-35 or 3 x H-36), 0.01 (s, 3H, 3 x H-35 or 3 x H-36) ppm.

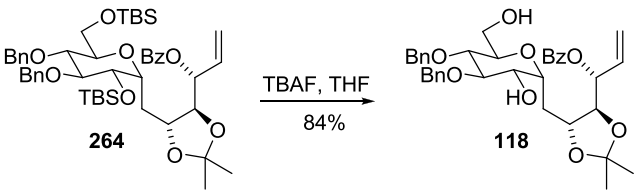
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 165.37 (C-18), 139.03 (C-19), 138.79 (C-23), 133.40 (C-30), 133.05 (C-2), 129.86 (C-27), 129.78 (2 x C-28), 128.67 (2 x C-29), 128.40 (2 x C-21 or 2 x C-25), 128.38 (2 x C-21 or 2 x C-25), 127.98 (2 x C-24), 127.66 (2 x C-20 and C-26), 127.49 (C-

22), 118.68 (C-1), 109.77 (C-13), 83.36 (C-9), 81.99 (C-4), 78.15 (C-10), 75.58 (C-16), 74.91 (C-17), 74.86 (C-3), 74.48 (C-5), 73.33 (C-7), 73.08 (C-8), 72.87 (C-11), 62.57 (C-12), 29.06 (C-6), 27.67 (C-14), 27.13 (C-15), 26.15 (3 x C-38), 26.09 (3 x C-34), 18.53 (C-37), 18.17 (C-33), –4.46 (C-31 or C-32), –4.51 (C-31 or C-32), –4.93 (C-35 or C-36), –5.28 (C-35 or C-36) ppm.

IR (ATR): $\tilde{\nu}$ = 2930 (m), 1726 (m), 1252 (m), 1085 (s), 834 (s), 697 (m) cm^{-1}.

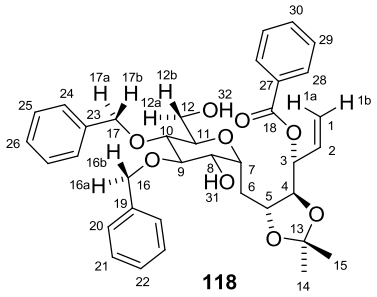
HRMS (ESI): calcd. for $C_{48}H_{74}NO_9Si_2^+$: 864.4897 $[M+NH_4]^+$
found: 864.4896 $[M+NH_4]^+$.

(1*R*)-1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-hydroxy-6-(hydroxymethyl) oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-yl benzoate (118)



To a solution of benzoyl-protected alcohol **264** (936 mg, 1.10 mmol, 1.0 eq) in THF (50 mL) was added a solution of tetrabutylammonium fluoride in THF (1.0 M, 3.30 mL, 3.30 mmol, 3.0 eq), and the resulting mixture was stirred at room temperature for 20 h. The reaction was quenched with aq. $NaHCO_3$ (70 mL of a saturated solution), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic fractions were washed with brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 3:1] afforded diol **118** (569 mg, 0.920 mmol, 84%) as a white sticky foam.

Diol 118:



R_f = 0.51 [PE:EtOAc 1:1].

$[\alpha]_D^{22}$ = +34.5 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.09 – 8.06 (m, 2H, 2 x H-28), 7.54 – 7.51 (m, 1H, H-30), 7.44 – 7.40 (m, 2H, 2 x H-29), 7.37 – 7.29 (m, 6H, 2 x H-21, H-22, 2 x H-25, H-26), 7.28 – 7.24 (m, 4H, 2 x H-20, 2 x H-24) 5.98 (ddd, *J* = 17.1, 10.6, 6.3 Hz, 1H, H-2), 5.69 – 5.65 (m, 1H, H-3), 5.43 (ddd, *J* = 17.3, 1.2, 1.2 Hz, 1H, H-1a), 5.35 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.61 – 4.52 (m, 4H, H-16a, H-16b, H-17a, H-17b), 4.32 (ddd, *J* = 10.9, 8.0, 3.3 Hz, 1H, H-5), 4.21 (ddd, *J* = 11.2, 2.9, 2.9 Hz, 1H, H-7), 4.17 (dd, *J* = 12.3, 9.4 Hz, 1H, H-12a or H-12b), 3.96 (dd, *J* = 8.0, 4.8 Hz, 1H, H-4), 3.95 – 3.90 (m, 1H, H-11), 3.73 – 3.70 (m, 1H, H-9), 3.59 – 3.55 (m, 1H, H-8), 3.38

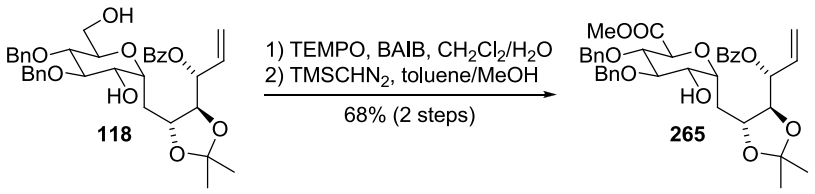
(dd, *J* = 12.3, 3.9 Hz, 1H, H-12a or H-12b), 3.35 – 3.31 (m, 1H, H-10), 2.95 (br s, 1H, H-31 or H-32), 2.24 (ddd, *J* = 14.3, 11.2, 3.3 Hz, 1H, H-6a or H-6b), 1.65 (ddd, *J* = 13.9, 10.5, 3.3 Hz, 1H, H-6a or H-6b), 1.43 (s, 3H, 3 x H-14), 1.37 (s, 3H, 3 x H-15) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 165.58 (C-18), 137.80 (C-19), 137.32 (C-23), 133.33 (C-30), 132.46 (C-2), 130.00 (C-27), 129.89 (2 x C-28), 128.75 (2 x C-21 or 2 x C-25), 128.67 (2 x C-21 or 2 x C-25), 128.60 (2 x C-29), 128.22 (C-22 or C-26), 128.21 (C-22 or C-26), 128.02 (2 x C-20 or 2 x C-24), 127.82 (2 x C-20 or 2 x C-24), 119.31 (C-1), 109.53 (C-13), 82.60 (C-4), 76.50 (C-9), 75.56 (C-11), 74.56 (C-5), 74.40 (C-3), 74.09 (C-10), 73.28 (C-16), 72.57 (C-17), 69.32 (C-8), 66.15 (C-7), 59.47 (C-12), 33.21 (C-6), 27.59 (C-14), 26.92 (C-15) ppm.

IR (ATR): $\tilde{\nu}$ = 3473 (s), 2880 (m), 1721 (m), 1267 (m), 1070 (s), 856 (w), 751 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{36}H_{46}NO_9^+$: 636.3167 $[M+NH_4]^+$
found: 636.3169 $[M+NH_4]^+$.

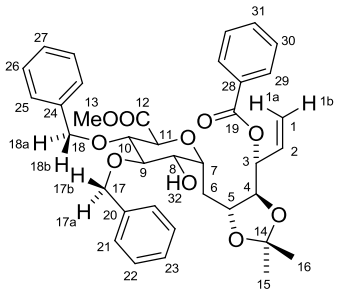
Methyl (2*S*,3*S*,4*R*,5*S*,6*R*)-6-{[(4*R*,5*S*)-5-[(1*R*)-1-(benzoyloxy)prop-2-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3,4-bis(benzyloxy)-5-hydroxyoxane-2-carboxylate (265):



To a solution of diol **118** (110 mg, 0.178 mmol, 1.0 eq) in a mixture of CH_2Cl_2 and water (2:1, 9 mL) was added 2,2,6,6-tetramethylpiperidine-1-oxyl (27.8 mg, 0.178 mmol, 1.0 eq) and (diacetoxyiodo)benzene (287 mg, 0.890 mmol, 5.0 eq), and the resulting biphasic system was stirred vigorously at room temperature for 5 h. A second equivalent of 2,2,6,6-tetramethylpiperidine-1-oxyl (27.8 mg, 0.178 mmol, 1.0 eq) was added and the mixture was stirred at room temperature for an additional 2 h. The reaction was quenched with aq. $Na_2S_2O_3$ (10 mL of a half-saturated solution) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude carboxylic acid, which was immediately re-dissolved in toluene/MeOH (7:1, 8 mL). To this mixture, a solution of (trimethylsilyl)diazomethane in hexanes (2.0 M, 107 µL, 0.214 mmol, 1.2 eq) was carefully added dropwise, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with acetic acid (100 µL) and diluted with water (15 mL). The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1→4:1] afforded ester **265** (78.4 mg, 0.121 mmol, 68% over two steps) as a colorless oil.

Ester 265:



265

R_f = 0.50 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +39.1 (c = 0.89, $CHCl_3$).

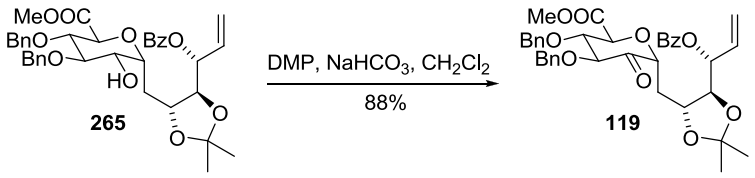
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.09 – 8.07 (m, 2H, 2 x H-29), 7.49 – 7.54 (m, 1H, H-31), 7.40 – 7.27 (m, 10H, 2 x H-22, H-23, 2 x H-25, 2 x H-26, H-27, 2 x H-30), 7.22 – 7.19 (m, 2H, 2 x H-21), 5.74 (ddd, J = 17.2, 10.6, 6.6 Hz, 1H, H-2), 5.76 – 5.72 (m, 1H, H-3), 5.46 (ddd, J = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.35 (ddd, J = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.62 (d, J = 11.7 Hz, 1H, H-18a or H-18b), 4.53 (d, J = 11.7 Hz, 1H, H-18a or H-18b), 4.50 – 4.50 (m, 3H, H-7, H-11, H-17a or H-17b), 4.40 (d, J = 11.8 Hz, 1H, H-17a or H-17b), 4.34 (ddd, J = 8.0, 8.0, 3.4 Hz, 1H, H-5), 4.17 – 4.14 (m, 1H, H-10), 4.00 (dd, J = 7.9, 4.5 Hz, 1H, H-4), 3.77 (dd, J = 3.2, 3.2 Hz, 1H, H-9), 3.60 (s, 3H, 3 x H-13), 3.54 – 3.50 (m, 1H, H-8), 3.28 (br d, J = 11.4, 1H, H-32), 2.23 (ddd, J = 14.5, 10.1, 3.4 Hz, 1H, H-6a or H-6b), 1.77 (ddd, J = 14.6, 8.1, 2.8 Hz, 1H, H-6a or H-6b), 1.44 (s, 3H, 3 x H-15), 1.41 (s, 3H, 3 x H-16) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.25 (C-12), 165.61 (C-19), 137.49 (C-20), 136.85 (C-24), 133.05 (C-31), 132.84 (C-2), 130.38 (C-28), 129.94 (2 x C-29), 128.76 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.54 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.39 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.37 (C-27), 128.04 (2 x C-25), 128.03 (C-23), 127.73 (2 x C-21), 119.35 (C-1), 109.39 (C-14), 82.50 (C-4), 75.77 (C-5), 75.11 (C-3), 74.15 (C-10), 73.29 (C-11), 72.90 (C-9), 72.27 (C-18), 71.91 (C-17), 69.27 (C-8), 69.13 (C-7), 52.03 (C-13), 36.39 (C-6), 27.65 (C-15), 27.00 (C-16) ppm.

IR (ATR): $\tilde{\nu}$ = 3513 (br, w), 2932 (w), 1754 (w), 1720 (s), 1453 (w), 1266 (m), 1095 (s), 920 (w), 711 (s) cm^{-1}.

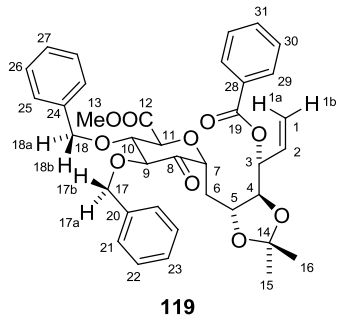
HRMS (ESI): calcd. for $C_{37}H_{42}ClO_{10}^-$: 681.2472 $[M+Cl]^-$
found: 681.2471 $[M+Cl]^-$.

Methyl (2*S*,3*S*,4*S*,6*R*)-6-{[(4*R*,5*S*)-5-[(1*R*)-1-(benzoyloxy)prop-2-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3,4-bis(benzyloxy)-5-oxooxane-2-carboxylate (119)



To a solution of alcohol **265** (78.4 mg, 0.121 mmol, 1.0 eq) in CH_2Cl_2 (7 mL) was added $NaHCO_3$ (153 mg, 1.82 mmol, 15 eq), followed by Dess-Martin periodinane (128 mg, 0.303 mmol, 2.5 eq) in one portion, and the resulting suspension was stirred at room temperature for 40 min. The reaction was quenched with a mixture (1:1, 14 mL) of aq. $NaHCO_3$ (saturated solution) and aq. $Na_2S_2O_3$ (saturated solution) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→4:1] afforded ketone **119** (68.5 mg, 0.106 mmol, 88%) as a colorless oil.

Ketone 119:



R_f = 0.53 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +54.6 (*c* = 0.95, $CHCl_3$).

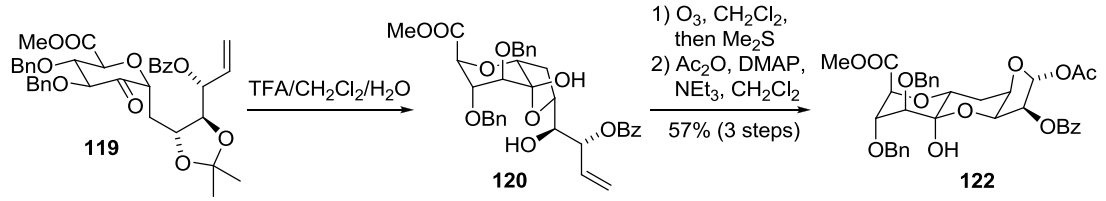
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.08 – 8.05 (m, 2H, 2 x H-29), 7.54 – 7.50 (m, 1H, H-31), 7.42 – 7.39 (m, 2H, 2 x H-30), 7.36 – 7.26 (m, 10H, 2 x H-21, 2 x H-22, H-23, 2 x H-25, 2 x H-26, H-27), 6.00 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H, H-2), 5.72 – 5.68 (m, 1H, H-3), 5.44 (ddd, *J* = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.34 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.75 – 4.68 (m, 3H, H-7, H-17a or H-17b, H-18a or H-18b), 4.64 (d, *J* = 10.4 Hz, 1H, H-18a or H-18b), 4.53 – 4.49 (m, 2H, H-11, H-17a or H-17b), 4.27 – 4.23 (m, 2H, H-5, H-10), 4.19 (d, *J* = 7.1 Hz, 1H, H-9), 3.98 (dd, *J* = 7.8, 4.5 Hz, 1H, H-4), 3.66 (s, 3H, 3 x H-13), 2.17 (ddd, *J* = 14.5, 8.8, 3.0 Hz, 1H, H-6a or H-6b), 1.97 (ddd, *J* = 14.4, 10.1, 3.3 Hz, 1H, H-6a or H-6b), 1.41 (s, 3H, 3 x H-15), 1.37 (s, 3H, 3 x H-16) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.34 (C-8), 170.13 (C-12), 165.51 (C-19), 137.47 (C-24), 137.11 (C-20), 133.24 (C-31), 132.53 (C-2), 130.16 (C-28), 129.87 (2 x C-29), 128.59 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.56 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.54 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.19 (C-23 or C-27), 128.12 (2 x C-21 or 2 x C-25), 128.10 (C-23 or C-27), 128.09 (2 x C-21 or 2 x C-25), 119.45 (C-1), 109.77 (C-14), 82.12 (C-4), 81.57 (C-9), 79.22 (C-10), 75.93 (C-7), 75.25 (C-11), 74.56 (C-3), 74.30 (C-5), 73.43 (C-17), 73.38 (C-18), 52.39 (C-13), 34.74 (C-6), 27.57 (C-15), 27.05 (C-16) ppm.

IR (ATR): $\tilde{\nu}$ = 2934 (w), 1722 (s), 1453 (w), 1268 (s), 1069 (s), 711 (s) cm^{-1}.

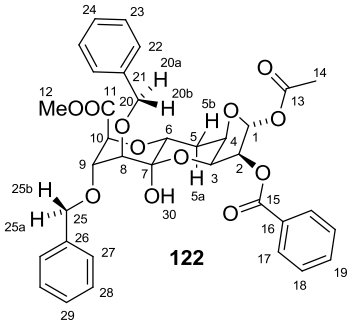
HRMS (ESI): calcd. for $C_{37}H_{44}NO_{10}^{+}$: 662.2960 $[M+NH_4]^+$
found: 662.2958 $[M+NH_4]^+$.

Methyl (1*R*,3*S*,4*S*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(acetyloxy)-4-(benzoyloxy)-12,13-bis(benzyloxy)-1-hydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (122) and Methyl (2*R*,3a*R*,5*S*,6*S*,7*S*,7a*S*)-2-[(1*S*,2*R*)-2-(benzoyloxy)-1-hydroxybut-3-en-1-yl]-6,7-bis(benzyloxy)-7a-hydroxy-hexahydro-2H-furo[3,2-*b*]pyran-5-carboxylate (120)



A solution of ketone **119** (64.0 mg, 99.3 µmol, 1.0 eq) in a TFA/CH_2Cl_2/H_2O (9:1:1, 4 mL) mixture was stirred at room temperature for 15 min. The solvent was removed by azeotropic distillation with toluene (3 x 8 mL), the resulting residue was taken up in EtOAc (20 mL) and aq. $NaHCO_3$ (15 mL of a saturated solution) was added. The organic phase was separated and the aqueous layer was extracted further with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (6 mL) and the resulting solution cooled to –78 °C. Ozone was bubbled through the reaction mixture until a slight blue color persisted. Excess ozone was discharged by bubbling argon through the mixture and dimethyl sulfide (0.29 mL, 3.97 mmol, 40 eq) was added at –78 °C. The solution was allowed to warm to room temperature and stirred at this temperature for 3 h. Water (15 mL) was added and the mixture extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude hemiacetal, which was subsequently dissolved in CH_2Cl_2 (5 mL). To this solution was added 4-(dimethylamino)pyridine (2.43 mg, 19.9 µmol, 20 mol%), triethylamine (20.7 µL, 0.149 mmol, 1.5 eq), and acetic anhydride (11.2 µL, 0.119 mmol, 1.2 eq), and the mixture was stirred at room temperature for 1 h. The reaction was quenched with aq. NH_4Cl (15 mL of a saturated solution) and the mixture extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 4:1→3:1→1:1] afforded the tricyclic compound **122** (36.5 mg, 56.3 µmol, 57% over three steps) as a colorless oil and as a single diastereomer.

Tricyclic compound 122:



R_f = 0.55 [PE:EtOAc 1:1].

$[\alpha]_D^{22}$ = +68.4 (c = 0.98, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.01 – 7.98 (m, 2H, 2 x H-17), 7.57 – 7.53 (m, 1H, H-19), 7.39 – 7.35 (m, 2H, 2 x H-18), 7.34 – 7.21 (m, 8H, 2 x H-23, H-24, 2 x H-27, 2 x H-28, H-29), 7.10 – 7.04 (m, 2H, 2 x H-22), 6.46 (d, J = 3.8 Hz, 1H, H-1), 5.45 (dd, J = 4.9, 3.8 Hz, 1H, H-2), 4.84 (dd, J = 4.9, 2.0 Hz, 1H, H-3), 4.80 (d, J = 11.8 Hz, 1H, H-20a or H-20b), 4.73 (dd, J = 11.6, 5.1 Hz, 1H, H-6), 4.60 – 4.51 (m, 4H, H-4, H-25a, H-25b, H-30), 4.47 (s, 1H, H-10), 4.35 (d, J = 11.8 Hz, 1H, H-20a or H-20b), 4.25 (dd, J = 3.4, 1.2 Hz, 1H, H-9), 3.59 (s, 3H, 3 x H-12), 3.50 (d, J = 3.4 Hz, 1H, H-8), 2.32 (ddd, J = 13.6, 5.1, 2.5 Hz, 1H, H-5a or H-5b), 2.19 – 2.12 (m, 1H, H-5a or H-5b), 2.12 (s, 3H, 3 x H-14) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.40 (C-13), 169.55 (C-11), 165.33 (C-15), 138.07 (C-21), 136.21 (C-26), 133.54 (C-19), 130.02 (2 x C-17), 129.24 (C-16), 128.77 (2 x C-23 or 2 x C-28), 128.57 (2 x C-18), 128.49 (C-29), 128.39 (2 x C-23 or 2 x C-28), 128.06 (2 x C-27), 127.71 (C-24), 127.33 (2 x C-22), 99.88 (C-1), 93.78 (C-7), 79.95 (C-2), 78.27 (C-9), 78.01 (C-4), 74.12 (C-10), 73.75 (C-8), 73.66 (C-20), 72.43 (C-25), 70.12 (C-3), 65.42 (C-6), 52.38 (C-12), 25.88 (C-5), 21.33 (C-14) ppm.

IR (ATR): $\tilde{\nu}$ = 3443 (br, w), 2952 (w), 1726 (s), 1453 (w), 1276 (m), 1096 (s), 1006 (s), 698 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{35}H_{40}O_{12}N^+$: 666.2545 $[M+NH_4]^+$
found: 666.2541 $[M+NH_4]^+$.

Intermediate 120:

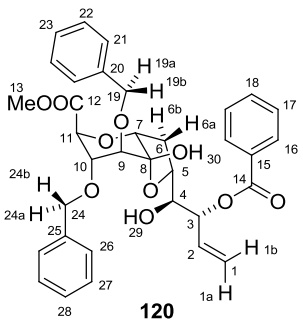
In order to characterize intermediate **120**, an analytical sample of the crude mixture obtained after acetonide deprotection was purified by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), isocratic elution, water (A)/MeOH (B); 80% B; flow rate 16 mL/min; detection 206 nm: t_R(**120**) = 13.6 min] to yield the major intermediate **120** as a white crystalline solid.

R_f = 0.17 [PE:EtOAc 3:1].

$[\alpha]_D^{21}$ = +32.1 (c = 0.79, $CHCl_3$).

mp: 71 – 73 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.10 – 8.05 (m, 2H, 2 x H-16), 7.60 – 7.52 (m, 1H, H-18), 7.46 – 7.39 (m, 2H, 2 x H-17), 7.39 – 7.28 (m, 8H, 2 x H-22, H-23, 2 x H-26, 2 x H-27, H-28), 7.25 – 7.19 (m, 2H, 2 x H-21), 5.94 (ddd, *J* = 17.3, 10.7, 5.7 Hz, 1H, H-2), 5.48 – 5.41 (m, 1H, H-3), 5.28 – 5.16 (m, 2H, H-1a, H-1b), 4.70 – 4.62 (m, 2H, H-24a, H-24b), 4.62 – 4.52 (m, 3H, H-5, H-7, H-19a or H-19b), 4.48 – 4.42 (m, 2H, H-11, H-19a or H-19b), 4.18 (dd, *J* = 5.4, 3.0 Hz, 1H, H-10), 3.80 (d, *J* = 4.5 Hz, 1H, H-9), 3.74 – 3.65 (m, 1H, H-4), 3.61 (s, 3H, 3 x H-13), 3.55 – 3.46 (m, 1H, H-29), 3.21 (s, 1H, H-30), 2.59 (ddd, *J* = 15.0, 9.3, 5.8 Hz, 1H, H-6a), 2.05 (dd, *J* = 13.9, 4.2 Hz, 1H, H-6b) ppm.



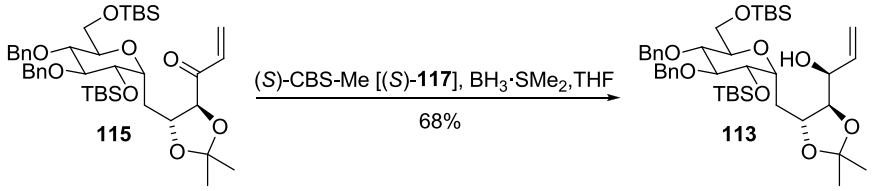
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.26 (C-12), 165.42 (C-14), 136.90 (C-25), 136.55 (C-20), 134.39 (C-2), 133.12 (C-18), 130.42 (C-15), 129.88 (2 x C-16), 128.80 (2 x C-22 or 2 x C-27), 128.78 (2 x C-22 or 2 x C-27), 128.57 (C-23 or C-28), 128.50 (2 x C-17), 128.37 (C-23 or C-28), 128.37 (2 x C-21 or 2 x C-26), 128.35 (2 x C-21 or 2 x C-26), 117.39 (C-1), 101.45 (C-8), 77.74 (C-5), 76.86 (C-7), 75.55 (C-3), 74.97 (C-9), 74.07 (C-4), 73.94 (C-10), 73.61 (C-11 or C-19), 73.60 (C-11 or C-19), 72.95 (C-24), 52.22 (C-13), 34.13 (C-6) ppm.

IR (ATR): $\tilde{\nu}$ = 3406 (br, w), 2937 (w), 1753 (w), 1714 (m), 1270 (s), 1093 (s), 714 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{34}H_{36}ClO_{10}^-$: 639.2002 $[M+Cl]^-$

found: 639.1998 $[M+Cl]^-$.

(1*S*)-1-[(4*R*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (113)

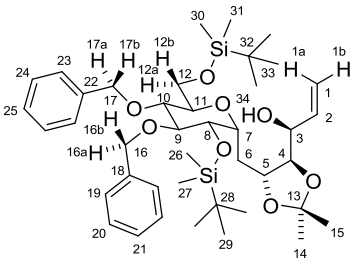


Toluene was removed from a solution of (*S*)-(–)-2-methyl-CBS-oxazaborolidine [(*S*)-**117**] in toluene (1.0 M, 675 µL, 0.675 mmol, 10 mol%) and the residue dried *in vacuo*. The CBS reagent was re-dissolved in THF (30 mL), and the resulting solution was added *via* cannula to a stirred solution of vinyl ketone **115** (5.00 g, 6.75 mmol, 1.0 eq) in THF (170 mL), pre-cooled to –25 °C. A solution of borane dimethyl sulfide complex in THF (2.0 M, 3.71 mL, 7.42 mmol, 1.1 eq) was added dropwise. The mixture was allowed to warm to 0 °C over 2 h and stirred at this temperature for an additional 30 min. The reaction was quenched with MeOH (10 mL) and

diluted with a mixture (2:1, 120 mL) of aq. NaOH (10 wt%) and aq. $NaHCO_3$ (saturated solution). The resulting solution was extracted with Et_2O (3 x 250 mL), and the combined organic fractions were washed with brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to provide crude alcohols **113** and **112** as a mixture of two diastereomers (d.r. 14:1, as determined by ^{1}H-NMR spectroscopy). Flash column chromatography [PE:EtOAc 19:1→9:1→4:1] afforded allylic alcohol **113** (3.43 g, 4.62 mmol, 68%) as colorless oil.

Allylic Alcohol 113:

Analytical data were identical with the material obtained earlier (*vide supra*).



113

R_f = 0.67 [PE:EtOAc 3:1].

$[\alpha]_D^{20}$ = +57.5 (*c* = 0.41, $CHCl_3$).

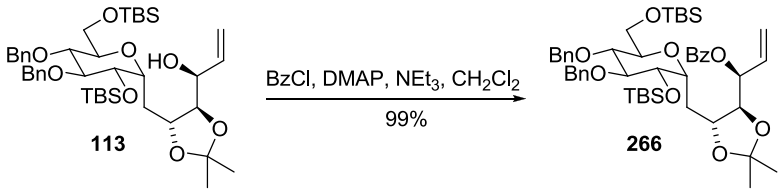
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.21 (m, 10H, 2 x H-19, 2 x H-20, H-21, 2 x H-23, 2 x H-24, H-25), 5.85 (ddd, *J* = 17.1, 10.5, 6.2 Hz, 1H, H-2), 5.40 (ddd, *J* = 17.2, 1.7, 1.7 Hz, 1H, H-1a), 5.27 (ddd, *J* = 10.5, 1.3, 1.3 Hz, 1H, H-1b), 4.89 (d, *J* = 11.3 Hz, 1H, H-16a or H-16b), 4.79 (d, *J* = 10.7 Hz, 1H, H-17a or H-17b), 4.78 (d, *J* = 11.1 Hz, 1H, H-16a or H-16b), 4.59 (d, *J* = 10.8 Hz, 1H, H-17a or H-17b), 4.17 – 4.13 (m, 1H, H-7), 4.13 – 4.09 (m, 1H, H-3), 4.09 – 4.04 (m, 1H, H-5), 3.82 (dd, *J* = 9.3, 6.1 Hz, 1H, H-8), 3.77 (dd, *J* = 11.1, 1.8 Hz, 1H, H-12a or H-12b), 3.73 (dd, *J* = 11.1, 4.6 Hz, 1H, H-12a or H-12b), 3.68 (dd, *J* = 7.8, 5.4 Hz, 1H, H-4), 3.54 (dd, *J* = 9.0, 9.0 Hz, 1H, H-9), 3.45 (dd, *J* = 9.3, 9.3 Hz, 1H, H-10), 3.39 (ddd, *J* = 9.8, 4.6, 1.8 Hz, 1H, H-11), 2.35 (br d, *J* = 4.8 Hz, 1H, H-34), 1.93 – 1.87 (m, 2H, H-6a, H-6b), 1.41 (s, 3H, 3 x H-15), 1.39 (s, 3H, 3 x H-14), 0.91 (s, 9H, 9 x H-29), 0.90 (s, 9H, 9 x H-33), 0.10 (s, 3H, 3 x H-26 or 3 x H-27), 0.07 (s, 3H, 3 x H-26 or 3 x H-27), 0.06 (s, 3H, 3 x H-30 or 3 x H-31), 0.05 (s, 3H, 3 x H-30 or 3 x H-31) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.99 (C-18), 138.46 (C-22), 136.83 (C-2), 128.56 (2 x C-20 or 2 x C-24), 128.42 (2 x C-20 or 2 x C-24), 128.11 (2 x C-23), 127.88 (C-25), 127.60 (2 x C-19), 127.51 (C-21), 117.68 (C-1), 109.29 (C-13), 83.89 (C-4), 83.33 (C-9), 78.49 (C-10), 75.57 (C-16), 75.21 (C-17), 73.99 (C-5), 73.50 (C-3), 73.40 (C-7), 73.18 (C-11), 73.13 (C-8), 63.10 (C-12), 28.57 (C-6), 27.59 (C-14), 27.30 (C-15), 26.15 (3 x C-29 or 3 x C-33), 26.07 (3 x C-29 or 3 x C-33), 18.54 (C-32), 18.16 (C-28), –4.44 (C-26 or C-27), –4.49 (C-26 or C-27), –4.95 (C-30 or C-31), –5.19 (C-30 or C-31) ppm.

IR (ATR): $\tilde{\nu}$ = 3458 (br, w), 2929 (s), 1462 (w), 1252 (m), 1083 (s), 834 (s), 696 (w) cm^{-1}.

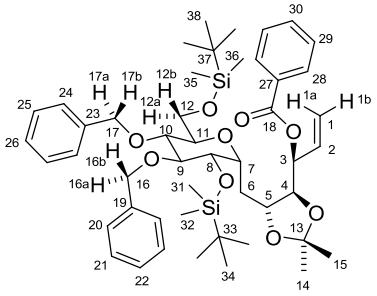
HRMS (ESI): calcd. for $C_{41}H_{70}NO_8Si_2^+$: 760.4634 $[M+NH_4]^+$
found: 760.4635 $[M+NH_4]^+$.

(1*S*)-1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-yl benzoate (266)



A solution of allylic alcohol **113** (3.43 g, 4.62 mmol, 1.0 eq), 4-(dimethylamino)pyridine (56.4 mg, 0.462 mmol, 10 mol%) and triethylamine (3.86 mL, 27.7 mmol, 6.0 eq) in CH_2Cl_2 (80 mL) was cooled to 0 °C, and benzoyl chloride (1.07 mL, 9.24 mmol, 2.0 eq) was added dropwise. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred at this temperature for 10 h. The reaction was quenched with aq. $NaHCO_3$ (150 mL of a saturated solution) and extracted with EtOAc (3 x 200 mL). The combined organic fractions were washed with brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 49:1→29:1→9:1] afforded benzoyl protected alcohol **266** (3.89 g, 4.59 mmol, 99%) as a colorless oil.

Benzoate ester 266:



R_f = 0.47 [PE:EtOAc 9:1].

$[\alpha]_D^{20}$ = +16.0 (*c* = 1.1, $CHCl_3$).

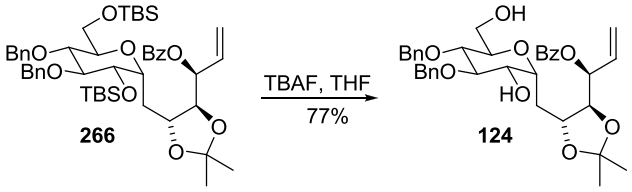
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.10 – 8.07 (m, 2H, 2 x H-28), 7.52 – 7.49 (m, 1H, H-30), 7.42 – 7.38 (m, 2H, 2 x H-29), 7.36 – 7.24 (m, 10H, 2 x H-20, 2 x H-21, H-22, 2 x H-24, 2 x H-25, H-26), 5.98 (ddd, *J* = 17.1, 10.6, 6.4 Hz, 1H, H-2), 5.73 – 5.70 (m, 1H, H-3), 5.45 (ddd, *J* = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.35 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.86 (d, *J* = 11.2 Hz, 1H, H-16a or H-16b), 4.82 (d, *J* = 10.8 Hz, 1H, H-17a or H-17b), 4.76 (d, *J* = 11.2 Hz, 1H, H-16a or H-16b), 4.65 (d, *J* = 10.8 Hz, 1H, H-17a or H-17b), 4.16 (ddd, *J* = 12.0, 6.1, 2.1 Hz, 1H, H-7), 4.09 (ddd, *J* = 10.4, 8.1, 2.2 Hz, 1H, H-5), 3.94 (dd, *J* = 8.1, 4.9 Hz, 1H, H-4), 3.84 – 3.79 (m, 2H, H-8, H-12a or H-12b), 3.68 (dd, *J* = 11.3, 1.7 Hz, 1H, H-12a or H-12b), 3.55 – 3.51 (m, 2H, H-9, H-10), 3.47 – 3.42 (m, 1H, H-11), 2.01 (ddd, *J* = 14.3, 12.1, 2.2 Hz, 1H, H-6a or H-6b), 1.91 (ddd, *J* = 14.7, 10.4, 2.1 Hz, 1H, H-6a or H-6b), 1.42 (s, 3H, 3 x H-15), 1.40 (s, 3H, 3 x H-14), 0.90 (s, 9H, 9 x H-34), 0.89 (s, 9H, 9 x H-38), 0.10 (s, 3H, 3 x H-31 or 3 x H-32), 0.07 (s, 3H, 3 x H-31 or 3 x H-32), 0.02 (s, 3H, 3 x H-35 or 3 x H-36), 0.01 (s, 3H, 3 x H-35 or 3 x H-36) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 165.55 (C-18), 139.02 (C-19), 138.71 (C-23), 133.27 (C-30), 132.77 (C-2), 130.06 (C-27), 129.85 (2 x C-28), 128.66 (2 x C-29), 128.48 (2 x C-21 or 2 x C-25), 128.41 (2 x C-21 or 2 x C-25), 128.05 (2 x C-24), 127.76 (C-26), 127.65 (2 x C-20), 127.49 (C-22), 119.16 (C-1), 109.46 (C-13), 83.46 (C-9), 81.81 (C-4), 78.24 (C-10), 75.62 (C-16), 75.11 (C-17), 74.07 (C-3), 73.28 (C-7), 73.24 (C-5), 73.14 (C-8), 72.95 (C-11), 62.79 (C-12), 28.25 (C-6), 27.57 (C-14), 27.03 (C-15), 26.15 (3 x C-38), 26.07 (3 x C-34), 18.54 (C-37), 18.16 (C-33), –4.47 (C-31 or C-32), –4.50 (C-31 or C-32), –4.96 (C-35 or C-36), –5.26 (C-35 or C-36) ppm.

IR (ATR): $\tilde{\nu}$ = 2929 (m), 1723 (m), 1251 (m), 1086 (s), 834 (s), 696 (m) cm^{-1}.

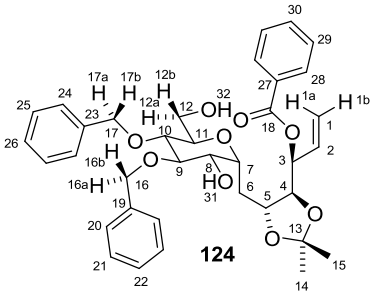
HRMS (ESI): calcd. for $C_{48}H_{74}NO_9Si_2^+$: 864.4897 $[M+NH_4]^+$
found: 864.4899 $[M+NH_4]^+$.

(1*S*)-1-[(4*S*,5*R*)-5-{[(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-hydroxy-6-(hydroxymethyl) oxan-2-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-yl benzoate (124)



To a solution of benzoyl protected alcohol **266** (254 mg, 0.300 mmol, 1.0 eq) in THF (12 mL) was added a solution of tetrabutylammonium fluoride in THF (1.0 M, 900 µL, 0.900 mmol, 3.0 eq), and the resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with aq. $NaHCO_3$ (20 mL of a saturated solution) and extracted with EtOAc (3 x 25 mL). The combined organic fractions were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 3:1] afforded diol **124** (143 mg, 0.231 mmol, 77%) as a white sticky foam.

Diol 124:



R_f = 0.51 [PE:EtOAc 1:1].

$[\alpha]_D^{22}$ = +8.1 (*c* = 1.0, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 – 8.07 (m, 2H, 2 x H-28), 7.58 – 7.53 (m, 1H, H-30), 7.46 – 7.41 (m, 2H, 2 x H-29), 7.38 – 7.26 (m, 10H, 2 x H-20, 2 x H-21, H-22, 2 x H-24, 2 x H-25, H-26), 5.97 (ddd, *J* = 17.2, 10.6, 6.3 Hz, 1H, H-2), 5.74 – 5.69 (m, 1H, H-3), 5.46 (ddd, *J* = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.36 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.66 – 4.56 (m, 4H, H-16a, H-16b, H-17a, H-17b),

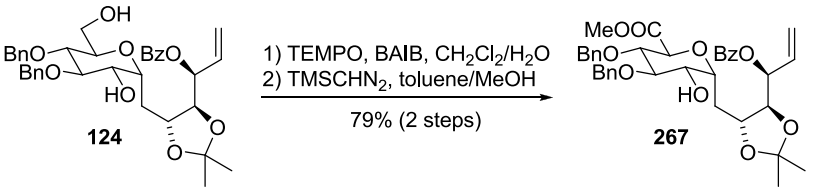
4.27 – 4.15 (m, 3H, H-5, H-7, H-12a or H-12b), 4.02 – 3.95 (m, 2H, H-4, H-11), 3.75 (dd, *J* = 4.5, 4.5 Hz, 1H, H-9), 3.61 – 3.55 (br m, 1H, H-8), 3.42 (dd, *J* = 12.3, 3.6 Hz, 1H, H-12a or H-12b), 3.38 (dd, *J* = 4.0, 4.0 Hz, 1H, H-10), 3.02 (br d, *J* = 8.4 Hz, 1H, H-31), 2.79 (br s, 1H, H-32), 2.24 (ddd, *J* = 14.5, 11.3, 3.5 Hz, 1H, H-6a or H-6b), 1.65 (ddd, *J* = 13.6, 10.1, 3.2 Hz, 1H, H-6a or H-6b), 1.45 (s, 3H, 3 x H-14 or 3 x H-15), 1.44 (s, 3H, 3 x H-14 or 3 x H-15) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.67 (C-18), 137.80 (C-19 or C-23), 137.32 (C-19 or C-23), 133.33 (C-30), 132.48 (C-2), 129.98 (C-27), 129.89 (2 x C-28), 128.72 (2 x C-21 or 2 x C-25), 128.69 (2 x C-21 or 2 x C-25), 128.59 (2 x C-29), 128.20 (C-22 or C-26), 128.16 (C-22 or C-26), 128.02 (2 x C-20 or 2 x C-24), 127.80 (2 x C-20 or 2 x C-24), 119.32 (C-1), 109.40 (C-13), 82.26 (C-4), 76.74 (C-9), 75.45 (C-11), 74.34 (C-10), 73.77 (C-3 and C-5), 73.35 (C-16), 72.72 (C-17), 69.43 (C-8), 66.51 (C-7), 59.62 (C-12), 32.58 (C-6), 27.58 (C-14 or C-15), 26.91 (C-14 or C-15) ppm.

IR (ATR): $\tilde{\nu}$ = 3449 (w), 2932 (w), 1719 (m), 1266 (m), 1068 (s), 851 (w), 696 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{36}H_{46}NO_9^+$: 636.3167 $[M+NH_4]^+$
found: 636.3164 $[M+NH_4]^+$.

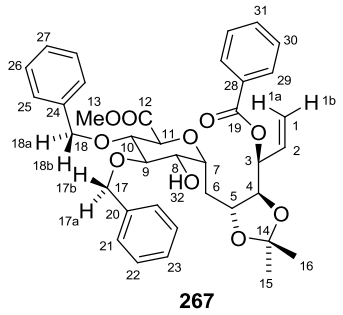
Methyl (2*S*,3*S*,4*R*,5*S*,6*R*)-6-{[(4*R*,5*S*)-5-[(1*S*)-1-(benzoyloxy)prop-2-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3,4-bis(benzyloxy)-5-hydroxyoxane-2-carboxylate (267)



To a solution of diol **124** (1.87 g, 3.02 mmol, 1.0 eq) in a mixture of CH_2Cl_2 and water (2:1, 135 mL) was added 2,2,6,6-tetramethylpiperidine-1-oxyl (472 mg, 3.02 mmol, 1.0 eq) and (diacetoxyiodo)benzene (4.86 g, 15.1 mmol, 5.0 eq), and the resulting biphasic system was stirred vigorously at room temperature for 2 h. A second equivalent of 2,2,6,6-tetramethylpiperidine-1-oxyl (472 mg, 3.02 mmol, 1.0 eq) was added, and the mixture was stirred for an additional 3.5 h. The reaction was quenched with aq. $Na_2S_2O_3$ (100 mL of a half-saturated solution) and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic fractions were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude carboxylic acid, which was immediately re-dissolved in toluene/MeOH (7:1, 120 mL). To this mixture, a solution of (trimethylsilyl)diazomethane in hexanes (2.0 M, 1.81 mL, 3.63 mmol, 1.2 eq) was added dropwise, and the resulting mixture stirred at room temperature for 1 h. The reaction was quenched with acetic acid (1.4 mL) and

diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 150 mL) and the combined organic fractions were washed with brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→4:1] afforded ester **267** (1.54 g, 2.38 mmol, 79% over two steps) as a white sticky foam.

Ester 267:



267

R_f = 0.28 [PE:EtOAc 3:1].

$[\alpha]_D^{23}$ = +5.4 (*c* = 1.1, $CHCl_3$).

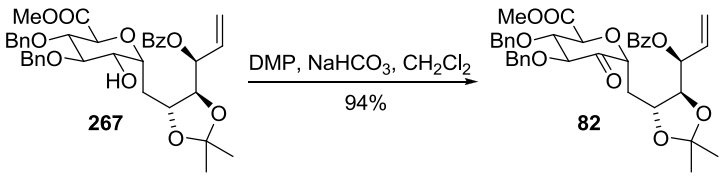
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.12 – 8.09 (m, 2H, 2 x H-29), 7.54 – 7.51 (m, 1H, H-31), 7.42 – 7.26 (m, 10H, 2 x H-22, H-23, 2 x H-25, 2 x H-26, H-27, 2 x H-30), 7.21 – 7.19 (m, 2H, 2 x H-21), 5.99 (ddd, *J* = 17.2, 8.4, 4.2 Hz, 1H, H-2), 5.75 – 5.72 (m, 1H, H-3), 5.42 (ddd, *J* = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.32 (ddd, *J* = 10.6, 1.3, 1.3 Hz, 1H, H-1b), 4.71 (d, *J* = 11.6 Hz, 1H, H-18a or H-18b), 4.61 (d, *J* = 11.6 Hz, 1H, H-18a or H-18b), 4.55 (s, 1H, H-11), 4.50 – 4.44 (m, 2H, H-7, H-17a or H-17b), 4.40 (d, *J* = 11.7 Hz, 1H, H-17a or H-17b), 4.37 (ddd, *J* = 7.7, 7.7, 3.7 Hz, 1H, H-5), 4.19 (ddd, *J* = 3.0, 1.4, 1.4 Hz, 1H, H-10), 3.96 (dd, *J* = 7.8, 4.3 Hz, 1H, H-4), 3.80 (dd, *J* = 3.3, 3.3 Hz, 1H, H-9), 3.55 – 3.51 (m, 1H, H-8), 3.48 (s, 3H, 3 x H-13), 3.38 (d, *J* = 11.6 Hz, 1H, H-32), 2.19 (ddd, *J* = 14.4, 10.0, 3.7 Hz, 1H, H-6a or H-6b), 1.77 (ddd, *J* = 14.4, 10.0, 3.7 Hz, 1H, H-6a or H-6b), 1.50 (s, 3H, 3 x H-16), 1.46 (s, 3H, 3 x H-15) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.12 (C-12), 165.60 (C-19), 137.43 (C-20), 136.82 (C-24), 133.16 (C-2), 133.04 (C-31), 130.40 (C-28), 129.85 (2 x C-29), 128.76 (2 x C-22 or 2 x C-26), 128.48 (2 x C-22 or 2 x C-26), 128.45 (2 x C-30), 128.38 (C-27), 128.08 (2 x C-25), 127.98 (C-23), 127.69 (2 x C-21), 118.60 (C-1), 109.08 (C-14), 82.48 (C-4), 74.66 (C-5), 74.27 (C-10), 73.77 (C-3), 73.31 (C-11), 72.85 (C-9), 72.37 (C-18), 71.88 (C-17), 69.31 (C-7), 69.15 (C-8), 51.90 (C-13), 35.70 (C-6), 27.69 (C-15), 27.03 (C-16) ppm.

IR (ATR): $\tilde{\nu}$ = 3507 (br, w), 2931 (w), 1755 (w), 1720 (s), 1452 (w), 1267 (m), 1069 (s), 921 (w), 711 (s) cm^{-1}.

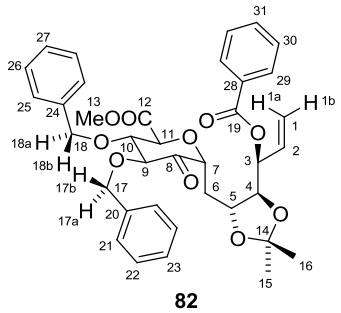
HRMS (ESI): calcd. for $C_{37}H_{46}NO_{10}^+$: 664.3116 $[M+NH_4]^+$
found: 664.3114 $[M+NH_4]^+$.

Methyl (2*S*,3*S*,4*S*,6*R*)-6-{[(4*R*,5*S*)-5-[(1*S*)-1-(benzoyloxy)prop-2-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3,4-bis(benzyloxy)-5-oxooxane-2-carboxylate (82)



To a solution of alcohol **267** (1.54 g, 2.38 mmol, 1.0 eq) in CH_2Cl_2 (120 mL) was added $NaHCO_3$ (3.00 g, 35.7 mmol, 15 eq) and Dess-Martin periodinane (2.52 g, 5.95 mmol, 2.5 eq) in one portion, and the resulting suspension was stirred at room temperature for 1 h. The reaction was quenched with a mixture (1:1, 100 mL) of aq. $NaHCO_3$ (saturated solution) and aq. $Na_2S_2O_3$ (saturated solution) and diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 150 mL) and the combined organic fractions were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 5:1] afforded ketone **82** (1.45 g, 2.25 mmol, 94%) as a colorless oil.

Ketone 82:



R_f = 0.40 [PE:EtOAc 3:1].

$[\alpha]_D^{22}$ = +25.2 (*c* = 1.0, $CHCl_3$).

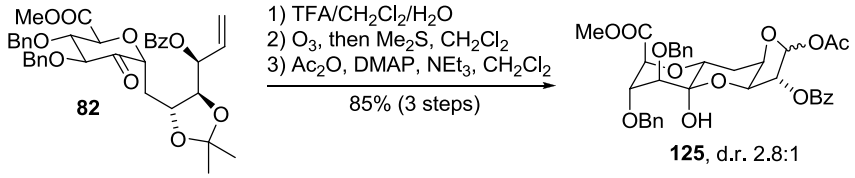
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.10 – 8.06 (m, 2H, 2 x H-29), 7.58 – 7.52 (m, 1H, H-31), 7.46 – 7.40 (m, 2H, 2 x H-30), 7.38 – 7.27 (m, 10H, 2 x H-21, 2 x H-22, H-23, 2 x H-25, 2 x H-26, H-27), 5.95 (ddd, *J* = 17.2, 10.6, 6.2 Hz, 1H, H-2), 5.72 – 5.65 (m, 1H, H-3), 5.43 (ddd, *J* = 17.3, 1.3, 1.3 Hz, 1H, H-1a), 5.33 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H-1b), 4.76 – 4.70 (m, 3H, H-7, H-17a or H-17b, H-18a or H-18b), 4.68 (d, *J* = 11.5 Hz, 1H, H-18a or H-18b), 4.57 (d, *J* = 4.2 Hz, 1H, H-11), 4.51 (d, *J* = 11.4 Hz, 1H, H-17a or H-17b), 4.28 (dd, *J* = 7.1, 4.2 Hz, 1H, H-10), 4.26 – 4.19 (m, 2H, H-5, H-9), 3.96 (dd, *J* = 7.7, 4.7 Hz, 1H, H-4), 3.60 (s, 3H, 3 x H-13), 2.14 (ddd, *J* = 14.5, 8.5, 2.9 Hz, 1H, H-6a or H-6b), 1.95 (ddd, *J* = 13.7, 10.0, 3.4 Hz, 1H, H-6a or H-6b), 1.45 (s, 3H, 3 x H-16), 1.42 (s, 3H, 3 x H-15) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.27 (C-8), 170.04 (C-12), 165.59 (C-19), 137.42 (C-24), 137.05 (C-20), 133.23 (C-31), 132.74 (C-2), 130.17 (C-28), 129.86 (2 x C-29), 128.58 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.57 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.56 (2 x C-22 or 2 x C-26 or 2 x C-30), 128.18 (C-23 or C-27), 128.13 (C-23 or C-27), 128.11 (2 x C-21, 2 x C-25), 119.12 (C-1), 109.57 (C-14), 81.93 (C-4), 81.52 (C-9), 79.28 (C-10), 75.91 (C-7), 75.23 (C-11), 73.84 (C-3), 73.43 (C-5 or C-17 or C-18), 73.40 (C-5 or C-17 or C-18), 73.37 (C-5 or C-17 or C-18), 52.37 (C-13), 34.14 (C-6), 27.62 (C-15), 27.06 (C-16) ppm.

IR (ATR): $\tilde{\nu}$ = 2934 (w), 1720 (s), 1452 (w), 1267 (s), 1066 (s), 711 (s) cm^{-1}.

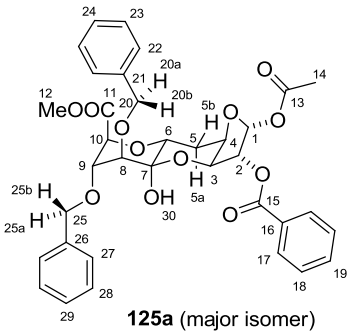
HRMS (ESI): calcd. for $C_{37}H_{44}NO_{10}^{+}$: 662.2960 $[M+NH_4]^+$
found: 662.2960 $[M+NH_4]^+$.

Methyl (1*R*,3*S*,4*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(acetyloxy)-4-(benzoyloxy)-12,13-bis(benzyloxy)-1-hydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (125)



A solution of ketone **82** (880 mg, 1.36 mmol, 1.0 eq) in a TFA/CH_2Cl_2/H_2O (9:1:1, 600 mL) mixture was stirred at room temperature for 15 min. The solvent was removed by azeotropic distillation with toluene (3 x 50 mL), the resulting residue was taken up in EtOAc (50 mL) and aq. $NaHCO_3$ (50 mL of a saturated solution) was added. The organic phase was separated and the aqueous layer extracted further with EtOAc (2 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (70 mL) and the resulting solution cooled to –78 °C. Ozone was bubbled through the reaction mixture until a slight blue color persisted. Excess ozone was discharged by bubbling argon through the mixture and dimethyl sulfide (4.02 mL, 54.4 mmol, 40 eq) was added at –78 °C. The solution was allowed to warm to room temperature and stirred at this temperature for 2.5 h. Water (80 mL) was added and the mixture extracted with EtOAc (3 x 150 mL). The combined organic fractions were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide the crude hemiacetal, which was subsequently dissolved in CH_2Cl_2 (60 mL). To this solution was added 4-(dimethylamino)pyridine (33.2 mg, 0.272 mmol, 20 mol%), triethylamine (377 µL, 2.72 mmol, 2.0 eq) and acetic anhydride (193 µL, 2.04 mmol, 1.5 eq), and the mixture was stirred at room temperature for 3 h. The reaction was quenched with aq. NH_4Cl (100 mL of a saturated solution) and the mixture extracted with EtOAc (3 x 150 mL). The combined organic fractions were washed with brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 4:1→3:1→2:1→1:1] afforded the tricyclic compound **125** (750 mg, 1.16 mmol, 85% over three steps) as a white solid consisting of two diastereomers (d.r. 2.8:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Tricyclic compound 125:



R_f = 0.15 [PE:EtOAc 3:1].

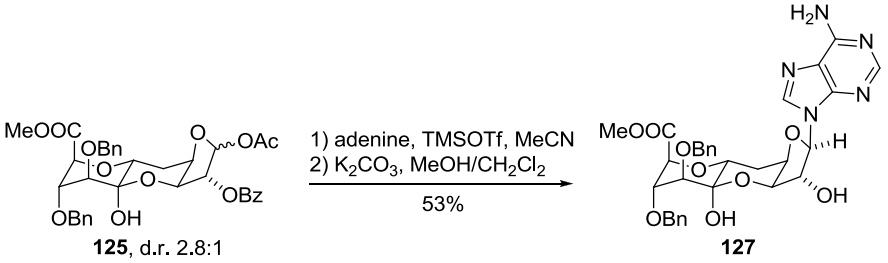
^{1}H-NMR (600 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 8.05 – 8.02 (m, 2H, 2 x H-17), 7.61 – 7.58 (m, 1H, H-19), 7.48 – 7.44 (m, 2H, 2 x H-18), 7.38 – 7.25 (m, 10H, 2 x H-22, 2 x H-23, H-24, 2 x H-27, 2 x H-28, H-29), 6.51 (d, *J* = 4.7 Hz, 1H, H-1), 5.47 (d, *J* = 4.7 Hz, 1H, H-2), 4.74 (d, *J* = 11.8 Hz, 1H, H-20a or H-20b), 4.68 – 4.62 (m, 4H, H-3, H-6, H-25a, H-25b), 4.62 – 4.58 (m, 1H, H-4), 4.55 – 4.53 (m, 1H, H-20a or H-20b), 4.49 (br s, 1H, H-10), 4.34 – 4.32 (m, 1H, H-9), 3.60 (d, *J* = 4.7 Hz, 1H, H-8), 3.59 (s, 3H, 3 x H-12), 2.40 – 2.32 (m, 1H, H-5a or H-5b), 2.21 – 2.13 (m, 1H, H-5a or H-5b), 1.91 (s, 3H, 3 x H-14) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 169.52 (C-11), 169.46 (C-13), 165.13 (C-15), 137.78 (C-21), 136.21 (C-26), 133.59 (C-19), 129.82 (2 x C-17), 129.28 (C-16), 128.85 (2 x C-23 or 2 x C-28), 128.65 (2 x C-18), 128.60 (C-29), 128.50 (2 x C-23 or 2 x C-28), 128.16 (2 x C-27), 127.91 (C-24), 127.64 (2 x C-22), 95.44 (C-1), 93.73 (C-7), 78.01 (C-2), 77.88 (C-9), 76.95 (C-4), 75.31 (C-3), 74.18 (C-10), 74.07 (C-8), 73.70 (C-20), 72.64 (C-25), 65.18 (C-6), 52.39 (C-12), 25.40 (C-5), 20.94 (C-14) ppm.

IR (ATR): $\tilde{\nu}$ = 3442 (br, w), 2948 (w), 1752 (m), 1726 (s), 1452 (w), 1270 (m), 1107 (s), 1011 (s), 713 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{35}H_{36}ClO_{12}^-$: 683.1901 $[M+Cl]^-$
found: 683.1894 $[M+Cl]^-$.

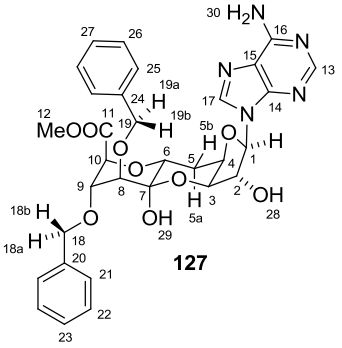
Methyl (1*R*,3*S*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(6-amino-9*H*-purin-9-yl)-4-(benzoyloxy)-12,13-bis(benzyloxy)-1-hydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (127)



To a suspension of acetate **125** (77.6 mg, 0.120 mmol, 1.0 eq) and adenine (24.2 mg, 0.179 mmol, 1.5 eq) in MeCN (5.5 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (130 µL, 0.720 mmol, 6.0 eq). The resulting solution was stirred at

room temperature for 15 min, then diluted with aq. $NaHCO_3$ (10 mL of a saturated solution). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was re-dissolved in a mixture of MeOH and CH_2Cl_2 (2:1, 6 mL) and K_2CO_3 (16.6 mg, 0.120 mmol, 1.0 eq) was added in one portion. The reaction mixture was stirred at room temperature for 50 min, then quenched with aq. $NaHCO_3$ (10 mL of a saturated solution). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic fraction were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 49:1→24:1] afforded glycoside **127** (39.1 mg, 63.1 μmol, 53% over two steps) as a white solid as a single diastereomer.

Glycoside 127



127

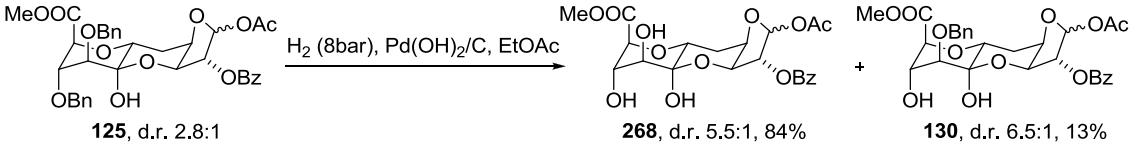
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.36 (s, 1H, H-17), 8.26 (s, 1H, H-13), 7.33 – 7.28 (m, 3H, 2 x H-22, H-23 or H-27), 7.21 – 7.14 (m, 5H, 2 x H-21, 2 x H-26, H-23 or H-27), 7.05 – 7.01 (m, 2H, 2 x H-25), 6.18 (s, 2H, 2 x H-30), 6.14 (s, 1H, H-1), 4.91 (s, 1H, H-29), 4.73 (dd, *J* = 11.6, 5.2 Hz, 1H, H-6), 4.60 (d, *J* = 2.3 Hz, 1H, H-4), 4.50 – 4.41 (m, 6H, H-2, H-3, H-10, H-18a, H-18b, H-19a or H-19b), 4.27 (d, *J* = 12.7, 1H, H-19a or H-19b), 4.12 – 4.09 (m, 1H, H-9), 3.73 (s, 3H, 3 x H-12), 3.46 (d, *J* = 3.1 Hz, 1H, H-8), 2.76 (br s, 1H, H-28), 2.46 – 2.38 (m, 1H, H-5a or H-5b), 2.26 – 2.19 (m, 1H, H-5a or H-5b) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 169.63 (C-11), 155.63 (C-16), 152.64 (C-13), 148.99 (C-14), 139.66 (C-17), 136.71 (C-24), 136.15 (C-20), 128.79 (2 x C-22), 128.55 (C-23 or C-27), 128.48 (2 x C-21 or 2 x C-25 or 2 x C-26), 128.44 (2 x C-21 or 2 x C-25 or 2 x C-26), 128.17 (2 x C-21 or 2 x C-26 and C-23 or C-27), 119.54 (C-15), 93.20 (C-7), 91.69 (C-1), 81.53 (C-2), 78.63 (C-4), 76.65 (C-9), 76.32 (C-3), 74.07 (C-10), 73.26 (C-8), 73.10 (C-19), 72.42 (C-18), 65.56 (C-6), 52.51 (C-12), 25.65 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 3338 (br w), 3130 (br w), 2941 (w), 1751 (br w), 1638 (m), 1598 (m), 1416 (w), 1291 (w), 1206 (m), 1053 (br s), 964 (m), 856 (w), 741 (m), 698 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{31}H_{34}O_9N_5^+$: 620.2351 $[M+H]^+$
found: 620.2352 $[M+H]^+$.

Methyl (1*S*,3*S*,4*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(acetyloxy)-4-(benzoyloxy)-1,12,13-trihydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (268) and Methyl (1*R*,3*S*,4*R*,5*S*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(acetyloxy)-4-(benzoyloxy)-13-(benzyloxy)-1,12-dihydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (130)

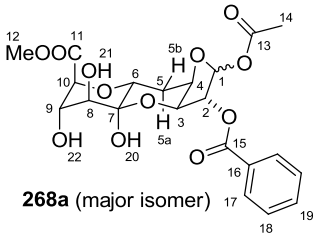


125, d.r. 2.8:1 → **268**, d.r. 5.5:1, 84% + **130**, d.r. 6.5:1, 13%

An autoclave apparatus was charged with a solution of tricyclic compound **125** (282 mg, 0.435 mmol, 1.0 eq) in EtOAc (28 mL) and $Pd(OH)_2/C$ (20 wt%, 196 mg) was added. The autoclave apparatus was purged with hydrogen gas five times and the resulting suspension was stirred under hydrogen atmosphere (8 bar) at room temperature for 20 h. The catalyst was removed by filtration through a pad of Celite, the Celite was washed with EtOAc (40 mL) and the filtrate concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 2:1→1:1] afforded the triol **268** (172 mg, 0.367 mmol, 84%) as a white solid representing a complex mixture of structurally unknown isomers (including two main diastereomers of **268** in a 5.5:1 ratio as determined by ^{1}H-NMR spectroscopy). The mixture was used immediately in the next step. Furthermore, monobenzylated product **130** (30.6 mg, 54.6 µmol, 13%) was isolated as a white solid consisting of two diastereomers (d.r. 6.5:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Triol 268:

For full NMR-characterization, an analytical sample of the major isomer **268a** was isolated, which was sufficiently clean to assign the NMR-signals conclusively. Configuration of **268a** at C-1 remained unclear.



268a (major isomer)

R_f = 0.15 [PE:EtOAc 1:2].

^{1}H-NMR (600 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 7.99 – 7.95 (m, 2H, 2 x H-17), 7.59 – 7.55 (m, 1H, H-19), 7.45 – 7.40 (m, 2H, 2 x H-18), 6.52 (d, *J* = 4.8 Hz, 1H, H-1), 5.47 (d, *J* = 4.8 Hz, 1H, H-2), 4.69 (br s, 1H, H-20 or H-21 or H-22), 4.62 – 4.58 (m, 1H, H-4), 4.57 (d, *J* = 2.5 Hz, 1H, H-3), 4.55 (dd, *J* = 12.5, 5.7 Hz, 1H, H-6), 4.51 – 4.47 (br m, 1H, H-9), 4.44 (s, 1H, H-10), 4.08 (br s, 1H, H-20 or H-21 or H-22), 3.79 (d, *J* = 3.2 Hz, 1H, H-8), 3.75 (s, 3H, 3 x H-12), 3.19 (br s, 1H, H-20, or H-21 or H-22), 2.38 – 2.32 (m, 1H, H-5a or H-5b), 2.24 – 2.18 (m, 1H, H-5a or H-5b), 1.93 (s, 3H, 3 x H-14) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 170.08 (C-11), 169.84 (C-13), 165.53 (C-15), 133.83 (C-19), 129.84 (2 x C-17), 128.97 (C-16), 128.71 (2 x C-

18), 95.65 (C-1), 93.38 (C-7), 77.84 (C-2), 77.02 (C-4), 76.73 (C-10), 75.39 (C-3), 71.24 (C-9), 70.69 (C-8), 63.89 (C-6), 52.47 (C-12), 25.17 (C-5), 20.95 (C-14) ppm.

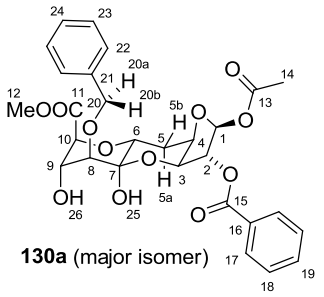
IR (ATR): $\tilde{\nu}$ = 3432 (br, m), 2951 (w), 1725 (s), 1222 (m), 1010 (s), 751 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{28}NO_{12}^{+}$: 486.1606 $[M+NH_4]^+$
found: 486.1613 $[M+NH_4]^+$.

Monobenzylated product 130:

For full characterization of the major isomer of monobenzylated product **130**, an analytical sample of the diastereomeric mixture was purified by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), gradient, water (A)/MeCN (B) +0.1% formic acid; 0 min 50% B, 2 min 50% B, 25 min 90% B; flow rate 15 mL/min; detection 231 nm: t_R(**130b**) = 15.4 min, t_R(**130a**) = 16.1 min].

Major isomer 130a:



R_f = 0.64 [PE:EtOAc 1:2].

$[\alpha]_D^{23}$ = +30.3 (*c* = 1.1, $CHCl_3$).

mp: 82 – 85 °C.

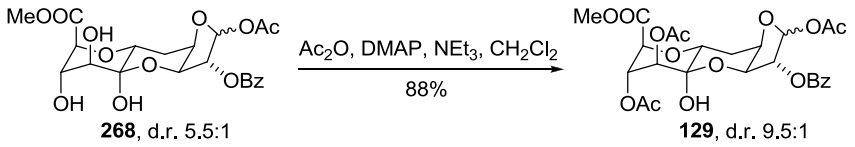
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.03 – 8.00 (m, 2H, 2 x H-17), 7.63 – 7.59 (m, 1H, H-19), 7.49 – 7.44 (m, 2H, 2 x H-18), 7.33 – 7.22 (m, 5H, 2 x H-22, 2 x H-23, H-24), 6.25 (s, 1H, H-1), 5.42 (s, 1H, H-2), 4.91 (d, *J* = 12.5 Hz, 1H, H-20a or H-20b), 4.71 – 4.65 (m, 1H, H-6), 4.60 – 4.56 (m, 2H, H-4, H-20a or H-20b), 4.52 – 4.49 (m, 1H, H-9), 4.44 (br s, 2H, H-3, H-10), 3.66 (s, 3H, 3 x H-12), 3.51 (d, *J* = 3.3 Hz, 1H, H-8), 2.42 – 2.36 (m, 1H, H-5a or H-5b), 2.23 – 2.16 (m, 1H, H-5a or H-5b), 1.71 (s, 3H, 3 x H-14) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.22 (C-13), 169.58 (C-11), 165.46 (C-15), 138.23 (C-21), 134.10 (C-19), 130.00 (2 x C-17), 128.79 (2 x C-18), 128.73 (C-16), 128.41 (2 x C-23), 127.74 (C-24), 127.15 (2 x C-22), 99.32 (C-1), 94.05 (C-7), 81.95 (C-2), 79.09 (C-4), 76.98 (C-8 and C-10), 73.54 (C-20), 73.05 (C-3), 70.95 (C-9), 64.73 (C-6), 52.07 (C-12), 25.93 (C-5), 20.64 (C-14) ppm.

IR (ATR): $\tilde{\nu}$ = 3387 (w), 2946 (w), 1725 (m), 1452 (w), 1221 (br m), 1107 (s), 1011 (s), 899 (w), 739 (m), 712 (s) cm^{-1}.

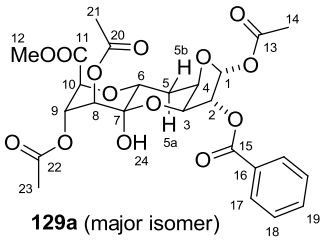
HRMS (ESI): calcd. for $C_{28}H_{34}NO_{12}^{+}$: 576.2076 $[M+NH_4]^+$
found: 576.2082 $[M+NH_4]^+$.

Methyl (1*R*,3*S*,4*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5,12,13-tris(acetyloxy)-4-(benzoyloxy)-1-hydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (129)



To a solution of triol **268** (127 mg, 0.271 mmol, 1.0 eq) in CH_2Cl_2 (7 mL) was added 4-(dimethylamino)pyridine (6.62 mg, 54.2 µmol, 20 mol%), triethylamine (94.0 µL, 0.678 mmol, 2.5 eq) and acetic anhydride (56.3 µL, 0.596 mmol, 2.2 eq), and the mixture was stirred at room temperature for 8 min. The reaction was quenched with aq. NH_4Cl (10 mL of a saturated solution), and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 3:1→1:1→1:2] afforded triacetate **129** (112 mg, 0.239 mmol, 88%) as a white solid consisting of two diastereomers (d.r. 9.5:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Triacetate 129:



R_f = 0.47 [PE:EtOAc 1:2].

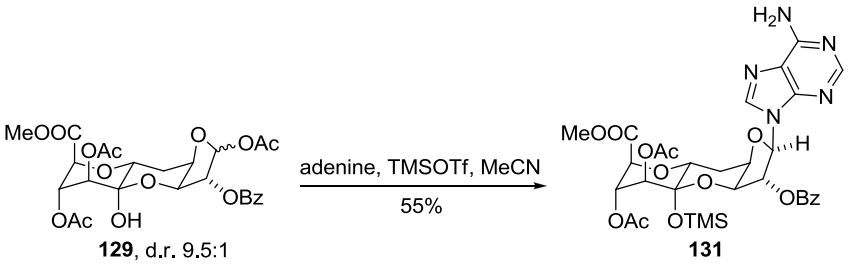
^{1}H-NMR (600 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 8.03 – 8.00 (m, 2H, 2 x H-17), 7.61 – 7.57 (m, 1H, H-19), 7.47 – 7.44 (m, 2H, 2 x H-18), 6.48 (d, *J* = 4.6 Hz, 1H, H-1), 5.53 – 5.52 (m, 1H, H-9), 5.39 (d, *J* = 4.6 Hz, 1H, H-2), 4.97 (d, *J* = 2.9 Hz, 1H, H-8), 4.62 – 4.58 (m, 2H, H-3, H-4), 4.49 (s, 1H, H-10), 4.40 (dd, *J* = 11.6, 5.3 Hz, 1H, H-6), 3.84 (s, 3H, 3 x H-12), 3.39 (s, 1H, H-24), 2.42 – 2.38 (m, 1H, H-5a or H-5b), 2.18 (s, 3H, 3 x H-23), 2.19 – 2.15 (m, 1H, H-5a or H-5b), 2.06 (s, 3H, 3 x H-21), 1.90 (s, 3H, 3 x H-14) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$) (mixture of isomers, major isomer quoted): δ = 169.53 (C-13), 168.86 (C-22), 168.52 (C-20), 168.43 (C-11), 165.13 (C-15), 133.68 (C-19), 129.84 (2 x C-17), 129.17 (C-16), 128.68 (2 x C-18), 95.18 (C-1), 91.33 (C-7), 77.72 (C-2), 76.54 (C-3), 75.33 (C-4), 74.67 (C-10), 70.36 (C-9), 68.37 (C-8), 65.40 (C-6), 52.89 (C-12), 25.22 (C-5), 21.15 (C-23), 20.95 (C-14), 20.82 (C-21) ppm.

IR (ATR): $\tilde{\nu}$ = 3446 (br, w), 2947 (w), 1730 (s), 1370 (w), 1222 (s), 1012 (s), 713 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{25}H_{28}ClO_{14}^-$: 587.1173 $[M+Cl]^-$
found: 587.1178 $[M+Cl]^-$.

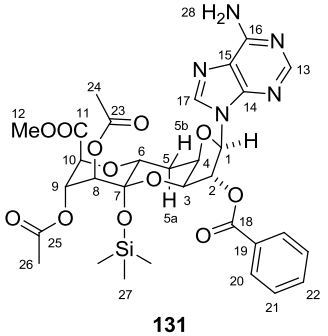
Methyl (1*S*,3*S*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-12,13-bis(acetyloxy)-5-(6-amino-9H-purin-9-yl)-4-(benzoyloxy)-1-[(trimethylsilyl)oxy]-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (131)



129, d.r. 9.5:1 **131**

To a suspension of triacetate **129** (112 mg, 0.239 mmol, 1.0 eq) and adenine (48.5 mg, 0.359 mmol, 1.5 eq) in MeCN (11 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (260 µL, 1.43 mmol, 6.0 eq). The resulting solution was stirred at room temperature for 5 min, then diluted with aq. $NaHCO_3$ (20 mL of a saturated solution). The mixture was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic fractions were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 99:1→49:1→29:1] afforded glycoside **131** (92.3 mg, 0.132 mmol, 55%) as a white solid as a single diastereomer.

Glycoside 131:



131

R_f = 0.39 [EtOAc].

$[\alpha]_D^{23}$ = –18.8 (*c* = 0.88, $CHCl_3$).

mp: 138 – 140 °C.

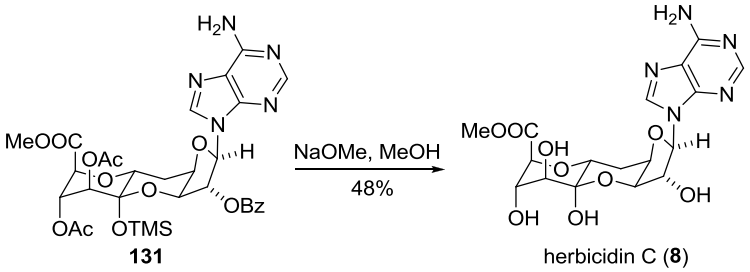
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1H, H-13), 8.28 (s, 1H, H-17), 8.07 – 8.02 (m, 2H, 2 x H-20), 7.65 – 7.59 (m, 1H, H-22), 7.50 – 7.45 (m, 2H, 2 x H-21), 6.45 (d, *J* = 1.5 Hz, 1H, H-1), 5.83 (s, 2H, 2 x H-28), 5.52 – 5.50 (m, 2H, H-9, H-2), 5.13 (d, *J* = 2.5 Hz, 1H, H-8), 4.58 – 4.55 (m, 1H, H-4), 4.51 (s, 1H, H-10), 4.44 – 4.37 (m, 2H, H-3, H-6), 3.78 (s, 3H, 3 x H-12), 2.42 – 2.35 (m, 1H, H-5a or H-5b), 2.30 (s, 3H, 3 x H-24), 2.29 – 2.21 (m, 1H, H-5a or H-5b), 2.19 (s, 3H, 3 x H-26), 0.35 (s, 9H, 9 x H-27) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.96 (C-25), 169.29 (C-23), 168.97 (C-11), 165.00 (C-18), 155.54 (C-16), 153.35 (C-13), 150.04 (C-14), 139.25 (C-17), 134.09 (C-22), 130.04 (2 x C-20), 128.78 (2 x C-21), 128.60 (C-19), 119.31 (C-15), 93.89 (C-7), 86.86 (C-1), 83.05 (C-2), 77.83 (C-4), 75.45 (C-3), 74.75 (C-10), 70.43 (C-9), 69.59 (C-8), 66.45 (C-6), 52.86 (C-12), 25.28 (C-5), 21.65 (C-26), 21.17 (C-24), 2.50 (3 x C-27) ppm.

IR (ATR): $\tilde{\nu}$ = 3374 (br, w), 2953 (w), 1733 (s), 1634 (m), 1594 (w), 1253 (s), 1045 (s), 843 (m) cm^{-1}.

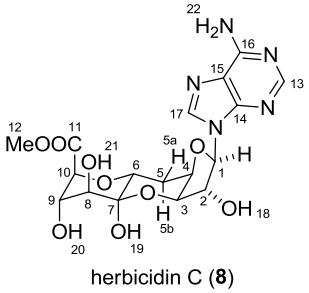
HRMS (ESI): calcd. for $C_{31}H_{38}O_{12}N_5Si^+$: 700.2281 $[M+H]^+$
found: 700.2287 $[M+H]^+$.

Methyl (1*S*,3*R*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(6-amino-9*H*-purin-9-yl)-1,4,12,13-tetrahydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (8)



To a solution of glycoside **131** (10.6 mg, 15.1 µmol, 1.0 eq) in MeOH (1 mL) was added sodium methoxide (3.27 mg, 60.6 µmol, 4.0 eq), and the resulting mixture was stirred at room temperature for 90 min. The reaction was quenched with aq. HCl (1 N, 1 mL) and the mixture concentrated *in vacuo*. RP-18 flash column chromatography [H_2O:MeOH 100:0→9:1→4:1→2:1→1:1] afforded herbicidin C (**8**) (3.10 mg, 7.06 µmol, 48%) as a white solid.

Herbicidin C (8):



R_f = 0.22 [CH_2Cl_2:MeOH 6:1].

$[\alpha]_D^{21}$ = +26.9 (*c* = 0.70, MeOH).

mp: 152 °C (decomposition).

^{1}H-NMR (600 MHz, CD_3OD): δ = 8.70 (s, 1H, H-17), 8.21 (s, 1H, H-13), 6.11 (d, *J* = 1.0 Hz, 1H, H-1), 4.66 (dd, *J* = 10.6, 6.3 Hz, 1H, H-6), 4.53 (ddd, *J* = 2.8, 2.8, 2.7 Hz, 1H, H-4), 4.36 (br s, 1H, H-10), 4.34 (dd, *J* = 3.5, 1.5 Hz, 1H, H-9), 4.32 (s, 1H, H-2), 4.31 (d, *J* = 2.3 Hz, 1H, H-3), 3.71 (s, 3H, 3 x H-12), 3.70 (d, *J* = 3.5 Hz, 1H, H-8), 2.25 – 2.21 (m, 2H, H-5a, H-5b) ppm.

^{13}C-NMR (150 MHz, CD_3OD): δ = 171.80 (C-11), 157.15 (C-16), 153.87 (C-13), 150.37 (C-14), 142.56 (C-17), 119.38 (C-15), 94.51 (C-7), 91.63 (C-1), 82.78 (C-2), 79.72 (C-4), 78.01 (C-10), 77.33 (C-3), 73.80 (C-9), 71.22 (C-8), 65.57 (C-6), 52.30 (C-12), 26.52 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 3212 (m), 2924 (m), 1732 (w), 1623 (s), 1220 (m), 1049 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{17}H_{22}N_5O_9^+$: 440.1412 $[M+H]^+$
found: 440.1418 $[M+H]^+$.

Table 5. NMR-data [including ^1H (600 MHz), ^{13}C (150 MHz), HSQC, COSY, HMBC and NOESY] of herbicidin C (**8**) in CD_3OD.

position	δ_C [ppm]	δ_H [ppm]	HSQC	COSY	HMBC	NOESY
1	91.63	6.11	C-1	H-2	C-2, C-3, C-4, C-14, C-17	H-2, H-4
2	82.78	4.33	C-2	H-1	C-3, C-4	H-1, H-17
3	77.33	4.31	C-3	H-4	C-1, C-2, C-4	H-4
4	79.72	4.55 – 4.52	C-4	H-3, H-$5_{a,b}$	C-6	H-1, H-3, H-$5_{a,b}$
$5_{a,b}$	26.52	2.25 – 2.21	C-5	H-4, H-6	C-3, C-4, C-6, C-7	H-4, H-6
6	65.57	4.66	C-6	H-$5_{a,b}$	C-5	H-$5_{a,b}$, H-17
7	94.51	-	-	-	-	-
8	71.22	3.71	C-8	H-9	C-6, C-7, C-9, C-10	H-9
9	73.80	4.35 – 4.34	C-9	H-8	C-7, C-8	H-8
10	78.01	4.36	C-10	-	C-6, C-8, C-9, C-11,	-
11	171.80	-	-	-	-	-
12	52.30	3.71	C-12	-	C-11	-
13	153.87	8.21	C-13	-	C-14, C-15, C-16	-
14	150.37	-	-	-	-	-
15	119.38	-	-	-	-	-
16	157.15	-	-	-	-	-
17	142.56	8.70	C-17	-	C-14, C-15, C-16	H-2, H-6
18	-	-	-	-	-	-
19	-	-	-	-	-	-
20	-	-	-	-	-	-
21	-	-	-	-	-	-
22	-	-	-	-	-	-

Structural Verification of Herbicidin C (8) by Comparison with an Authentic Sample

A solution of synthetic material **8** (2.22 mg) in MeOH-d_4 (0.6 mL) was added in four portions (0.15 mL each) to a solution of natural herbicidin C (nat-**8**)[xviii] (2.18 mg) in MeOH-d_4 (0.6 mL). After every addition, a ^1H-NMR spectrum (600 MHz) was recorded. Comparison of the data unambiguously verified that the synthetic herbicidin C (**8**) was identical to the authentic material nat-**8**, since a second set of signals was not detected. In addition to this, a presumably pH- or residual solvent-dependent chemical shift of the protons of **8** was observed, which was most distinctive for the adenine protons H-13 and H-17 (Figure 22).

[xviii] A sample of natural herbicidin C (nat-**8**) was provided by Bayer CropScience AG.

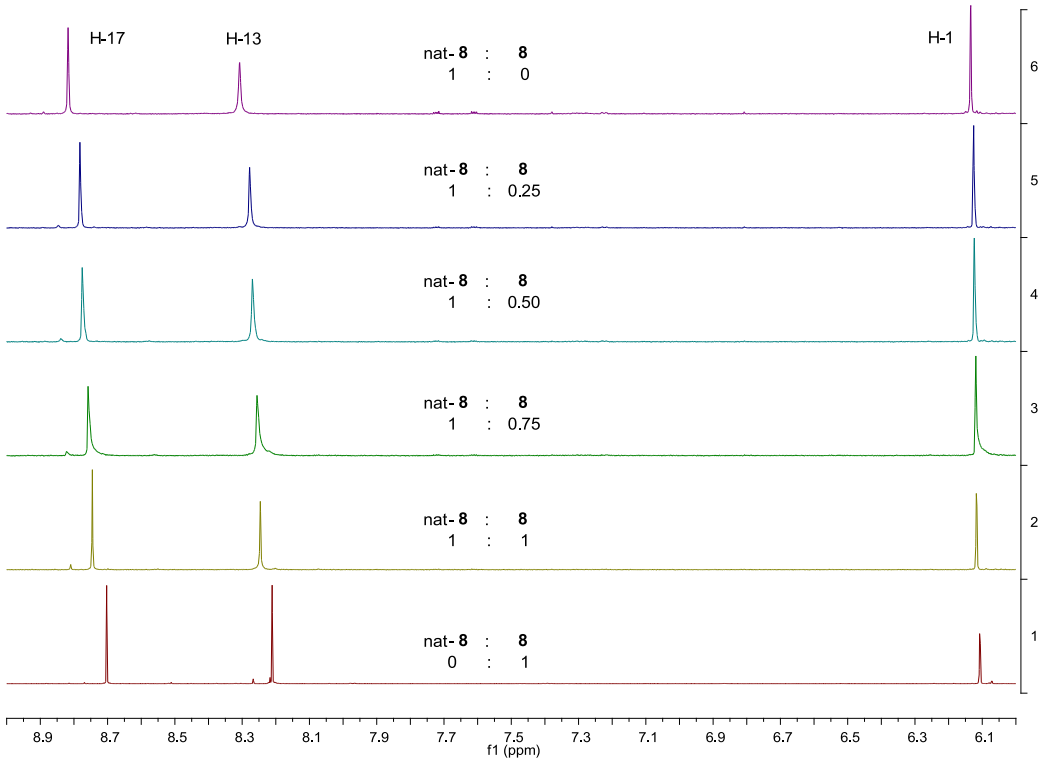
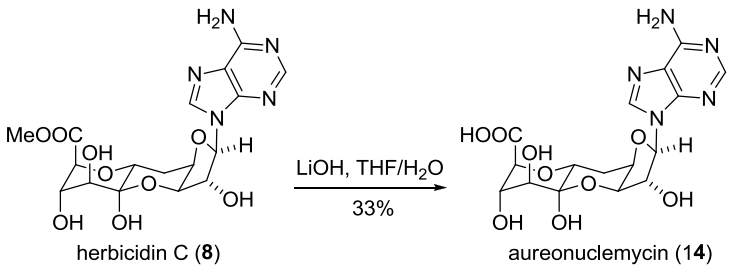


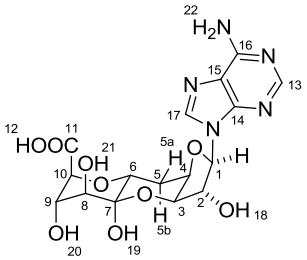
Figure 22. Comparison of ^{1}H-NMR data derived from the titration experiment with synthetic **3** and natural herbicidin C nat-**3**.

(1*S*,3*R*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(6-amino-9*H*-purin-9-yl)-1,4,12,13-tetrahydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylic acid (14)



A solution of herbicidin C (**8**) (4.70 mg, 10.7 µmol, 1.0 eq) and lithium hydroxide (0.38 mg, 16.0 µmol, 1.5 eq) in a mixture of THF and water (3:1, 1 mL) was stirred at room temperature for 15 min. The reaction was quenched with one drop of acetic acid and the mixture concentrated *in vacuo*. RP-18 flash column chromatography [H_2O:MeCN 100:0→99:1→9:1→4:1] afforded aureonuclemycin (**14**) (1.50 mg, 3.53 µmol, 33%) as a white solid.

Aureonuclemycin (14):



aureonuclemycin (**14**)

R_f = 0.52 [RP, H_2O].

$[\alpha]_D^{21}$ = +32.0 (c = 0.08, MeOH).

mp: 195 °C (decomposition).

^{1}H-NMR (600 MHz, CD_3OD): δ = 8.78 (s, 1H, H-17), 8.20 (s, 1H, H-13), 6.09 (d, J = 0.9 Hz, 1H, H-1), 4.60 (dd, J = 11.7, 5.2 Hz, 1H, H-6), 4.53 – 4.50 (m, 1H, H-4), 4.41 (d, J = 3.1 Hz, 1H, H-9), 4.32 (s, 1H, H-2), 4.30 (d, J = 2.2 Hz, 1H, H-3), 4.25 (br s, 1H, H-10), 3.70 (d, J = 3.2 Hz, 1H, H-8), 2.31 – 2.26 (m, 1H, H-5a), 2.22 – 2.16 (m, 1H, H-5b) ppm.

^{13}C-NMR (150 MHz, CD_3OD): δ = 175.17 (inferred from HMBC, C-11), 157.16 (C-16), 153.78 (C-13), 150.41 (C-14), 142.87 (C-17), 119.40 (C-15), 94.83 (C-7), 91.38 (C-1), 82.86 (C-2), 79.99 (br, C-10), 79.63 (C-4), 77.21 (C-3), 73.25 (C-9), 71.96 (C-8), 65.24 (C-6), 26.52 (C-5) ppm.

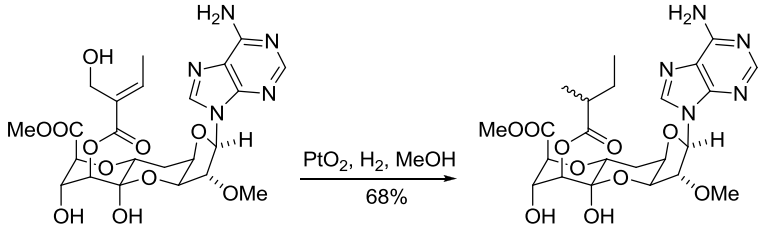
IR (ATR): $\tilde{\nu}$ = 3198 (m), 1603 (m), 1418 (m), 1080 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{20}N_5O_9^+$: 426.1256 $[M+H]^+$
found: 426.1257 $[M+H]^+$.

Table 6. NMR-data [including ^{1}H (600 MHz), ^{13}C (150 MHz), HSQC, COSY, HMBC and NOESY] of aureonuclemycin (**14**) in CD_3OD.

position	δ_C [ppm]	δ_H [ppm]	HSQC	COSY	HMBC	NOESY
1	91.38	6.09	C-1	H-2	C-2, C-14, C-17	H-2, H-4
2	82.86	4.32	C-2	H-1	C-3, C-4	H-1, H-17
3	77.21	4.30	C-3	H-4	C-1, C-2, C-4	H-4, H-5_b
4	79.63	4.53 – 4.50	C-4	H-3, H-5_a, H-5_b	C-6	H-1, H-3, H-5_a, H-5_b
5_a	26.52	2.31 – 2.26	C-5	H-4, H-6	C-6	H-4, H-6
5_b	26.52	2.22 – 2.16	C-5	H-4, H-6	-	H-4
6	65.24	4.60	C-6	H-5_a, H-5_b	-	H-5_a, H-17
7	94.83	-	-	-	-	-
8	71.96	3.70	C-8	H-9	C-7, C-10	H-9
9	73.25	4.41	C-9	H-8, H-10	C-7, C-8	H-8, H-10
10	79.99	4.25	C-10	H-9	C-6, C-8, C-9, C-11	H-9
11	175.17	-	-	-	-	-
12	-	-	-	-	-	-
13	153.78	8.20	C-13	-	C-14, C-16	-
14	150.41	-	-	-	-	-
15	119.40	-	-	-	-	-
16	157.16	-	-	-	-	-
17	142.87	8.78	C-17	-	C-14, C-15	H-2, H-6
18	-	-	-	-	-	-
19	-	-	-	-	-	-
20	-	-	-	-	-	-
21	-	-	-	-	-	-
22	-	-	-	-	-	-

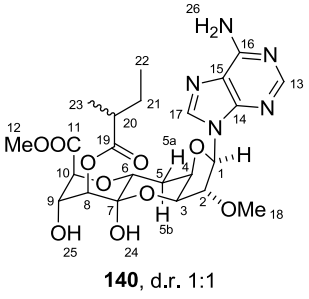
Methyl (1*R*,3*S*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(6-amino-9*H*-purin-9-yl)-1,12-dihydroxy-4-methoxy-13-[(2-methylbutanoyl)oxy]-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (140):



herbicidin A (**8**) → **140**, d.r. 1:1

To a solution of herbicidin A (**8**) (151 mg, 0.274 mmol, 1.0 eq) in MeOH (7.5 mL) was added platinum(IV) oxide (6.22 mg, 27.4 µmol, 10 mol%) and the flask was purged with hydrogen gas five times. The mixture was then stirred under hydrogen atmosphere at room temperature for 20 h. The catalyst was removed by filtration through a pad of Celite, and the Celite was washed with MeOH (20 mL). The filtrate was then concentrated *in vacuo*, and flash column chromatography [CH_2Cl_2:MeOH 49:1→24:1→19:1] afforded glycoside **140** (99.5 mg, 0.185 mmol, 68%) as a white solid consisting of two diastereomers of **140** and a third, structurally unknown, minor compound (4:4:1 ratio, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Glycoside 140:


140, d.r. 1:1

R_f = 0.51 [CH_2Cl_2:MeOH 9:1].

^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of isomers, both isomers quoted, one isomer primed): δ = 8.22 (s, 1H, H-13 or H-13'), 8.21 (s, 1H, H-13 or H-13'), 8.21 (s, 1H, H-17'), 8.17 (s, 1H, H-17), 6.09 (d, *J* = 1.4 Hz, 1H, H-1'), 6.07 (d, *J* = 1.3 Hz, 1H, H-1), 4.90 – 4.89 (m, 1H, H-8), 4.86 – 4.84 (m, 1H, H-8'), 4.54 – 4.46 (m, 8H, H-3, H-4, H-6, H-10, H-3', H-4', H-6', H-10'), 4.33 (dd, *J* = 3.0, 1.4 Hz, 1H, H-9'), 4.26 (dd, *J* = 3.0, 1.4 Hz, 1H, H-9), 4.08 (d, *J* = 1.4 Hz, 1H, H-2), 4.01 (d, *J* = 1.4 Hz, 1H, H-2'), 3.78 (s, 6H, 3 x H-12, 3 x H-12'), 3.52 (s, 3H, 3 x H-18), 3.51 (s, 3H, 3 x H-18'), 2.50 – 2.44 (m, 1H, H-20'), 2.42 – 2.36 (m, 1H, H-20), 2.33 – 2.28 (m, 4H, H-5a, H-5b, H-5a', H-5b'), 1.66 – 1.28 (m, 4H, H-21a, H-21b, H-21a', H-21b'), 1.13 (d, *J* = 7.0 Hz, 3H, 3 x H-23'), 0.93 (dd, *J* = 7.5, 7.5 Hz, 3H, 3 x H-22), 0.86 (d, *J* = 6.9 Hz, 3H, 3 x H-23), 0.65 (dd, *J* = 7.4, 7.4 Hz, 3H, 3 x H-22') ppm.

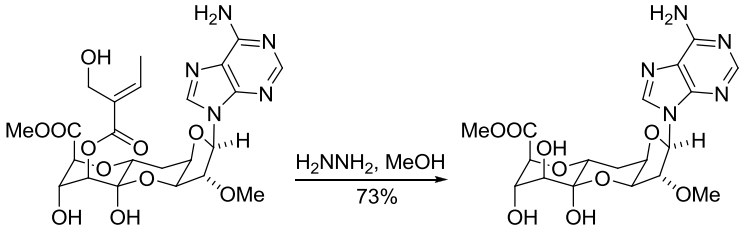
^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of isomers, both isomers quoted, one isomer primed): δ = 177.05 (C-19'), 176.96 (C-19), 171.47 (C-11 or C-11'), 171.45 (C-11 or C-11'), 157.32 (C-16 or C-16'), 157.30 (C-16 or C-16'), 154.04 (C-13 or C-13'), 154.01 (C-13 or C-13'), 150.36 (C-14 or C-14'), 150.29 (C-14 or C-14'), 140.11 (C-17'), 139.89 (C-17), 120.19 (C-15 and C-

15'), 92.61 (C-7 or C-7'), 92.57 (C-7 or C-7'), 91.98 (C-2'), 91.78 (C-2), 90.20 (C-1), 90.01 (C-1'), 79.62 (C-4 or C-4'), 79.57 (C-4 or C-4'), 78.28 (C-10 and C-10'), 74.88 (C-3 or C-3'), 74.82 (C-3 or C-3'), 72.44 (C-8'), 72.20 (C-8), 70.52 (C-9), 70.10 (C-9'), 66.88 (C-6 or C-6'), 66.77 (C-6 or C-6'), 58.56 (C-18 and C-18'), 52.87 (C-12 or C-12'), 52.82 (C-12 or C-12'), 41.50 (C-20), 41.33 (C-20'), 27.75 (C-21'), 27.50 (C-21), 26.96 (C-5 and C-5'), 17.24 (C-23'), 16.80 (C-23), 11.61 (C-22), 11.34 (C-22') ppm.

IR (ATR): $\tilde{\nu}$ = 3344 (w), 2939 (w), 1734 (m), 1637 (m), 1463 (w), 1299 (w), 1201 (m), 1139 (s), 1060 (s), 999 (m), 908 (w), 714 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{23}H_{32}N_5O_{10}^+$: 538.2144 $[M+H]^+$
found: 538.2141 $[M+H]^+$.

Methyl (1*S*,3*S*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-5-(6-amino-9*H*-purin-9-yl)-1,12,13-trihydroxy-4-methoxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (7):



A solution of herbicidin A (**6**) (50.6 mg, 91.7 µmol, 1.0 eq) in MeOH (5 mL) was cooled to 0 °C and hydrazine hydrate (51 wt% hydrazine, 11.4 µL, 187 µmol, 2.0 eq) was added. The mixture was allowed to warm to room temperature and stirred at this temperature for 22 h. The reaction was quenched with aq. HCl (1 M, 2 mL) and CH_2Cl_2 (5 mL) was added. The aqueous layer was separated and the organic phase was extracted further with aq. HCl (1 M, 2 x 2 mL). The combined aqueous fractions were concentrated *in vacuo*, and RP-18 flash column chromatography [H_2O:MeOH 100:0→49:1→24:1→14:1→9:1→6:1→4:1→3:1→2:1→1:1→1:2→1:3→1:4→1:5→0:100] afforded herbicidin B (**7**) (30.2 mg, 66.6 µmol, 73%) as a white solid.

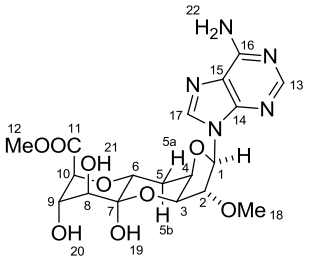
Herbicidin B (7):

R_f = 0.34 [CH_2Cl_2:MeOH 6:1].

$[\alpha]_D^{22}$ = +47.5 (*c* = 1.0, MeOH).

mp: 146 °C (decomposition).

^{1}H-NMR (600 MHz, CD_3OD): δ = 8.68 (s, 1H, H-17), 8.21 (s, 1H, H-13), 6.17 (d, *J* = 1.1 Hz, 1H, H-1), 4.67 (dd, *J* = 9.4, 7.6 Hz, 1H, H-6), 4.44 (d, *J* = 2.3 Hz, 1H, H-3), 4.44 – 4.41 (m, 1H, H-4), 4.37 (s, 1H, H-10), 4.37 – 4.34 (m, 1H, H-9), 4.00 (s, 1H, H-2), 3.73 – 3.71 (m, 1H, H-8), 3.71 (s, 3H, 3 x H-12), 3.46 (s, 3H, 3 x H-18), 2.25 – 2.21 (m, 2H, H-5a, H-5b) ppm.



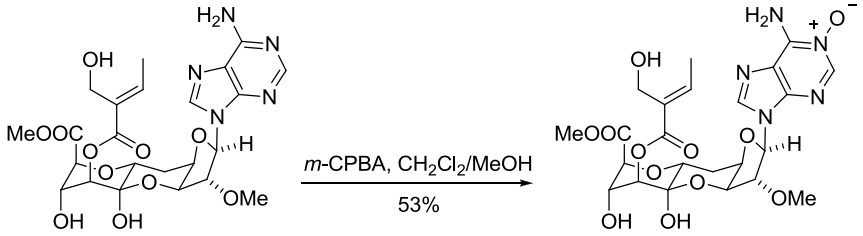
herbicidin B (**7**)

^{13}C-NMR (150 MHz, CD_3OD): δ = 171.78 (C-11), 157.14 (C-16), 153.96 (C-13), 150.27 (C-14), 142.42 (C-17), 119.35 (C-15), 94.64 (C-7), 92.15 (C-2), 89.10 (C-1), 79.71 (C-4), 78.01 (C-10), 74.34 (C-3), 73.79 (C-9), 71.24 (C-8), 65.47 (C-6), 58.39 (C-18), 52.32 (C-12), 26.41 (C-5) ppm.

IR (ATR): $\tilde{\nu}$ = 3328 (w), 2937 (w), 1734 (w), 1640 (m), 1599 (m), 1419 (w), 1298 (w), 1045 (s), 997 (s), 857 (w), 709 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{18}H_{24}N_5O_9^+$: 454.1569 $[M+H]^+$
found: 454.1571 $[M+H]^+$.

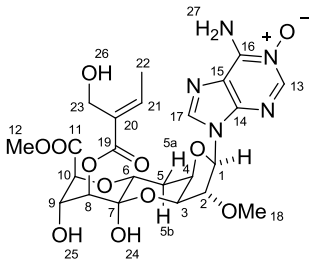
6-Amino-9-[(1*R*,3*S*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-1,12-dihydroxy-13-{[(2*E*)-2-(hydroxymethyl)but-2-enoyl]oxy}-4-methoxy-11-(methoxycarbonyl)-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecan-5-yl]-9*H*-purin-1-ium-1-olate (134):



herbicidin A (**6**) **134**

To a solution of herbicidin A (**6**) (51.3 mg, 93.0 µmol, 1.0 eq) in a mixture of CH_2Cl_2 and MeOH (4:1, 2.5 mL) was added 3-chloroperbenzoic acid (48.1 mg, 0.279 mmol, 3.0 eq) in one portion, and the resulting solution was stirred at room temperature for 21 h. The reaction mixture was concentrated *in vacuo*, and flash column chromatography [CH_2Cl_2:MeOH 6:1→4:1] provided the crude product, which was further purified by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), gradient, water (A)/MeCN (B) +0.1% formic acid; 0 min 5% B, 2 min 5% B, 25 min 95% B; flow rate 15 mL/min; detection 227 nm: t_R(**134**) = 12.6 min] to afford *N*-oxide **134** (28.1 mg, 49.5 µmol, 53%) as a white solid.

***N*-oxide 134:**



134

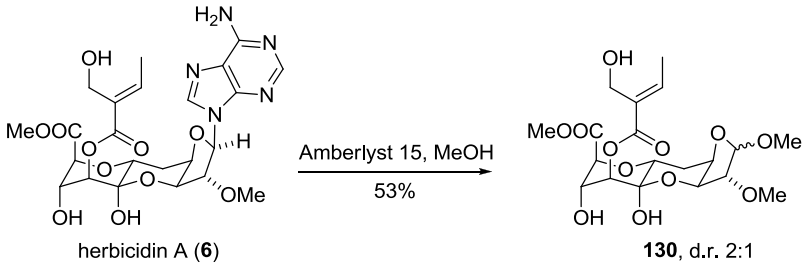
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1H, H-13), 8.10 (s, 1H, H-17), 6.80 (q, *J* = 7.2 Hz, 1H, H-21), 6.06 (d, *J* = 1.6 Hz, 1H, H-1), 5.07 (d, *J* = 3.2 Hz, 1H, H-8), 4.54 (dd, *J* = 10.9, 6.0 Hz, 1H, H-6), 4.49 (d, *J* = 2.2 Hz, 1H, H-3), 4.48 (s, 1H, H-10), 4.43 – 4.38 (m, 3H, H-4, H-23a, H-23b), 4.33 (dd, *J* = 3.3, 1.2 Hz, 1H, H-9), 4.06 (d, *J* = 1.5 Hz, 1H, H-2), 3.64 (s, 3H, 3 x H-12), 3.41 (s, 3H, 3 x H-18), 2.33 – 2.22 (m, 2H, H-5a, H-5b), 2.02 (d, *J* = 7.2 Hz, 3H, 3 x H-22) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.32 (C-11), 166.05 (C-19), 150.13 (C-16), 145.71 (C-13 or C-21), 145.62 (C-13 or C-21), 144.77 (C-14), 143.59 (C-17), 132.44 (C-20), 119.55 (C-15), 93.30 (C-7), 91.53 (C-2), 88.63 (C-1), 79.35 (C-4), 78.25 (C-10), 74.49 (C-3), 71.87 (C-8), 70.60 (C-9), 66.47 (C-6), 58.39 (C-18), 56.28 (C-23), 52.83 (C-12), 26.53 (C-5), 15.10 (C-22) ppm.

IR (ATR): $\tilde{\nu}$ = 3283 (w), 2949 (w), 1715 (m), 1665 (m), 1497 (w), 1214 (m), 1061 (s), 830 (w), 700 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{23}H_{30}N_5O_{12}^+$: 568.1885 $[M+H]^+$
found: 568.1882 $[M+H]^+$.

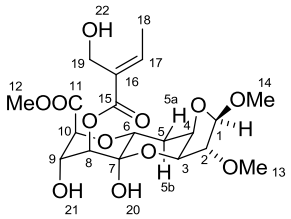
Methyl (1*R*,3*S*,4*R*,5*R*,7*R*,9*R*,11*S*,12*S*,13*S*)-1,12-dihydroxy-13-{[(2*E*)-2-(hydroxymethyl) but-2-enoyl]oxy}-4,5-dimethoxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (135a) and Methyl (1*R*,3*S*,4*R*,5*S*,7*R*,9*R*,11*S*,12*S*,13*S*)-1,12-dihydroxy-13-{[(2*E*)-2-(hydroxymethyl)but-2-enoyl]oxy}-4,5-dimethoxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane-11-carboxylate (135b):



herbicidin A (**6**) **130**, d.r. 2:1

To a solution of herbicidin A (**6**) (108 mg, 0.196 mmol, 1.0 eq) in MeOH (10 mL) was added amberlyst 15 resin (hydrogen form, dry, 50 mg). The resulting mixture was refluxed at 90 °C for 2 h until complete consumption of the starting material (as indicated by TLC analysis). The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and stirred for 48 h to remove absorbed material from the resin. The resin was then removed by filtration over cotton wool and the filtrate concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 99:1→20:1] afforded acetals **130** (47.9 mg, 0.104 mmol, 53%) as white solid consisting of two diastereomers (d.r. 2:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture. An analytical sample of the mixture was purified by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), gradient, water (A)/MeOH (B); 0 min 20% B, 2 min 20% B, 30 min 73% B; flow rate 15 mL/min; detection 222 nm: t_R(**135b**) = 17.9 min, t_R(**135a**) = 22.3 min] for full characterization of both isomers.

Major acetal 135a:



135a (Major isomer)

R_f = 0.53 [CH_2Cl_2:MeOH 9:1].

$[\alpha]_D^{21}$ = +54.4 (*c* = 0.58, MeOH).

mp: 51 – 52 °C.

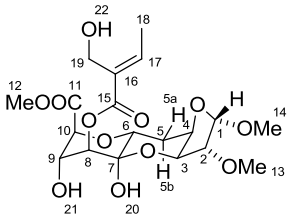
^{1}H-NMR (600 MHz, CD_3OD): δ = 6.94 (q, *J* = 7.2 Hz, 1H, H-17), 4.86 – 4.85 (m, 1H, H-8), 4.79 (s, 1H, H-1), 4.50 (dd, *J* = 11.1, 5.7 Hz, 1H, H-6), 4.43 (br s, 1H, H-10), 4.36 (dd, *J* = 3.3, 1.4 Hz, 1H, H-9), 4.30 (br s, 2H, H-19a, H-19b), 4.29 – 4.27 (m, 1H, H-4), 4.18 (d, *J* = 3.0 Hz, 1H, H-3), 3.65 (s, 3H, 3 x H-12), 3.55 (br s, 1H, H-2), 3.36 (s, 3H, 3 x H-13), 3.35 (s, 3H, 3 x H-14), 2.21 – 2.12 (m, 2H, H-5a, H-5b), 1.95 (d, *J* = 7.2 Hz, 3H, 3 x H-18) ppm.

^{13}C-NMR (150 MHz, CD_3OD): δ = 171.32 (C-11), 166.62 (C-15), 143.79 (C-17), 133.21 (C-16), 109.94 (C-1), 92.57 (C-7), 90.94 (C-2), 78.23 (C-4), 78.10 (C-10), 73.79 (C-3), 71.73 (C-8), 70.28 (C-9), 66.80 (C-6), 57.96 (C-13), 56.11 (C-19), 55.93 (C-14), 52.73 (C-12), 27.26 (C-5), 14.52 (C-18) ppm.

IR (ATR): $\tilde{\nu}$ = 3422 (m), 2940 (m), 1716 (s), 1438 (w), 1271 (m), 1114 (s), 1012 (s), 962 (m), 759 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{19}H_{28}NaO_{12}^+$: 471.1473 $[M+Na]^+$
found: 471.1471 $[M+Na]^+$.

Minor acetal 135b:



135b (Minor isomer)

R_f = 0.53 [CH_2Cl_2:MeOH 9:1].

$[\alpha]_D^{21}$ = +132.0 (c = 0.25, MeOH).

mp: 63 – 65 °C.

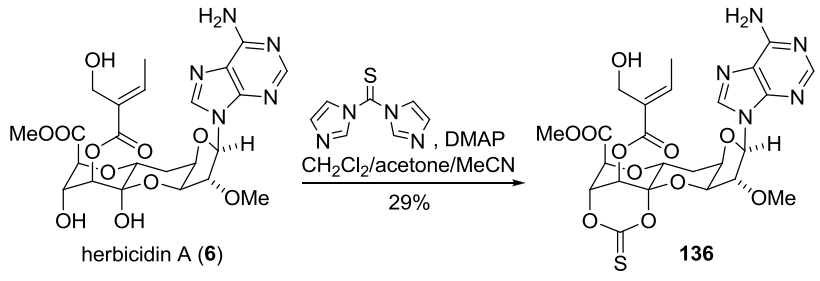
^{1}H-NMR (600 MHz, CD_3OD): δ = 6.88 (q, J = 7.2 Hz, 1H, H-17), 4.98 (d, J = 4.4 Hz, 1H, H-1), 4.90 (d, J = 3.3 Hz, 1H, H-8), 4.44 – 4.40 (m, 2H, H-6, H-10), 4.33 – 4.32 (m, 1H, H-9), 4.30 – 4.26 (m, 3H, H-4, H-19a, H-9b), 4.20 (d, J = 2.6 Hz, 1H, H-3), 3.65 (s, 3H, 3 x H-12), 3.65 – 3.63 (m, 1H, H-2), 3.42 (s, 3H, 3 x H-14), 3.36 (s, 3H, 3 x H-13), 2.13 – 2.10 (m, 2H, H-5a, H-5b), 1.94 (d, J = 7.2 Hz, 3H, 3 x H-18) ppm.

^{13}C-NMR (150 MHz, CD_3OD): δ = 171.34 (C-11), 166.33 (C-15), 143.73 (C-17), 133.44 (C-16), 105.10 (C-1), 92.66 (C-7), 87.21 (C-2), 78.27 (C-10), 75.91 (C-3), 75.78 (C-4), 71.66 (C-8), 70.47 (C-9), 66.59 (C-6), 59.31 (C-13), 56.60 (C-14), 56.05 (C-19), 52.73 (C-12), 26.62 (C-5), 14.51 (C-18) ppm.

IR (ATR): $\tilde{\nu}$ = 3407 (m), 2936 (m), 1718 (s), 1438 (w), 1269 (m), 1197 (m), 1137 (s), 1015 (s), 965 (m), 774 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{19}H_{28}NaO_{12}^+$: 471.1473 $[M+Na]^+$
found: 471.1471 $[M+Na]^+$.

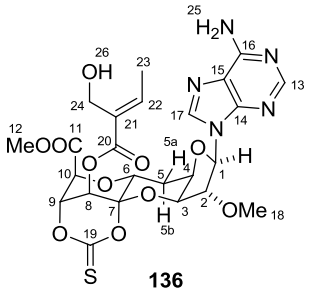
Methyl (1*S*,3*S*,4*R*,5*S*,7*R*,9*R*,11*S*,12*S*,16*S*)-5-(6-amino-9*H*-purin-9-yl)-16-{[(2*E*)-2-(hydroxymethyl)but-2-enoyl]oxy}-4-methoxy-14-oxo-2,6,10,13,15-pentaoxa-14λ^4-thiatetracyclo[10.3.1.0^{1,9}.0^{3,7}]hexadecane-11-carboxylate (136):



To a solution of herbicidin A (**6**) (46.3 mg, 84.0 µmol, 1.0 eq) and 4-(dimethylamino)pyridine (1.03 mg, 8.40 µmol, 10 mol%) in a CH_2Cl_2/acetone/MeCN (3:1:1, 5 mL) mixture was added 1,1'-thiocarbonyldiimidazole (90%, 18.3 mg, 92.3 µmol, 1.1 eq) in one portion, and the resulting mixture was stirred at room temperature for 72 h. The reaction was quenched with aq. NH_4Cl (5 mL of a saturated solution) and the mixture was extracted with CH_2Cl_2 (3 x 10 mL).

The combined organic fractions were washed with brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 14:1] afforded thiocarbonate **136** (14.3 mg, 24.1 µmol, 29%) as a white solid.

Thiocarbonate 136:



136

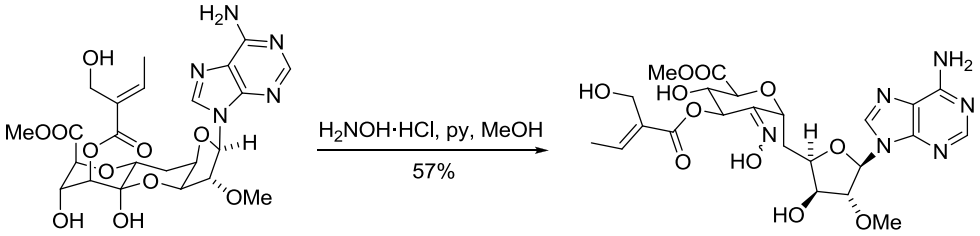
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.18 (s, 1H, H-13), 7.71 (s, 1H, H-17), 7.30 (s, 2H, 2 x H-25), 6.65 (q, *J* = 7.2 Hz, 1H, H-22), 5.95 (d, *J* = 2.4 Hz, 1H, H-1), 5.66 (d, *J* = 4.3 Hz, 1H, H-8), 5.35 (dd, *J* = 4.4, 2.2 Hz, 1H, H-9), 5.13 (d, *J* = 2.0 Hz, 1H, H-10), 4.84 (dd, *J* = 5.5, 5.5 Hz, 1H, H-26), 4.65 (d, *J* = 2.3 Hz, 1H, H-3), 4.57 (dd, *J* = 11.6, 5.5 Hz, 1H, H-6), 4.55 – 4.52 (m, 1H, H-4), 4.47 (d, *J* = 2.4 Hz, 1H, H-2), 4.25 – 4.20 (m, 2H, H-24a, H-24b), 3.55 (s, 3H, 3 x H-12), 3.38 (s, 3H, 3 x H-18), 2.41 – 2.34 (m, 1H, H-5a or H-5b), 2.08 – 1.98 (m, 1H, H-5a or H-5b), 1.95 (d, *J* = 7.2 Hz, 3H, 3 x H-23) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 185.54 (C-19), 166.73 (C-11), 163.45 (C-20), 156.00 (C-16), 153.19 (C-13), 149.23 (C-14), 145.39 (C-22), 137.76 (C-17), 130.26 (C-21), 118.03 (C-15), 100.76 (C-7), 88.21 (C-2), 86.55 (C-1), 75.60 (C-9), 75.08 (C-4), 74.98 (C-3), 72.85 (C-10), 64.77 (C-6), 62.33 (C-8), 57.65 (C-18), 54.25 (C-24), 52.79 (C-12), 24.70 (C-5), 14.73 (C-23) ppm.

IR (ATR): $\tilde{\nu}$ = 3546 (w), 3146 (w), 2328 (w), 1740 (m), 1728 (m), 1630 (w), 1438 (w), 1286 (s), 1210 (s), 1166 (s), 1002 (s), 957 (m), 850 (w), 699 (w) cm^{-1}.

HRMS (FAB): calcd. for $C_{24}H_{28}N_5O_{11}S^+$: 594.1501 $[M+H]^+$
found: 594.1501 $[M+H]^+$.

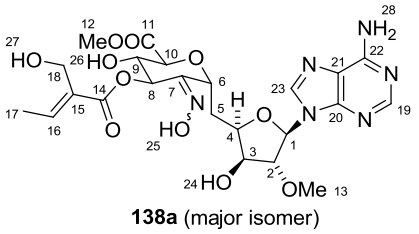
Methyl (2*S*,3*S*,4*R*,5*E*,6*R*)-6-{[(2*R*,3*S*,4*R*,5*S*)-5-(6-amino-9*H*-purin-9-yl)-3-hydroxy-4-methoxyoxolan-2-yl]methyl}-3-hydroxy-5-(hydroxyimino)-4-{[(2*E*)-2-(hydroxymethyl)but-2-enoyl]oxy}oxane-2-carboxylate (138)



herbicidin A (**6**) **138**

A solution of herbicidin A (**6**) (71.9 mg, 0.130 mmol, 1.0 eq), pyridine (210 µL, 2.60 mmol, 20 eq) and hydroxylamine hydrochloride (10.8 mg, 0.156 mmol, 1.2 eq) in MeOH (5 mL) was stirred at room temperature for 47 h. In order to drive the reaction to completion, hydroxylamine hydrochloride (10.8 mg, 0.156 mmol, 1.2 eq) was added, and the reaction mixture was stirred at room temperature for an additional 21 h. Volatile material was removed *in vacuo* and the residue subjected to flash column chromatography [CH_2Cl_2:MeOH 9:1] to afford major oxime **138a** (26.4 mg, 46.6 µmol, 36%) as a white solid and a mixture of minor oxime **138b** and major oxime **134a** (4:1, as determined by ^{1}H-NMR spectroscopy, 15.1 mg, 26.7 µmol, 21%), as well as recovered starting material **6** (6.60 mg, 12.0 µmol, 9%). The stereochemistry of major and minor oxime **138a** and **138b** remained unclear.

Major oxime 138:



138a (major isomer)

R_f = 0.55 [CH_2Cl_2:MeOH 4:1].

$[\alpha]_D^{21}$ = +36.5 (*c* = 0.46, MeOH).

mp: 130 °C (decomposition).

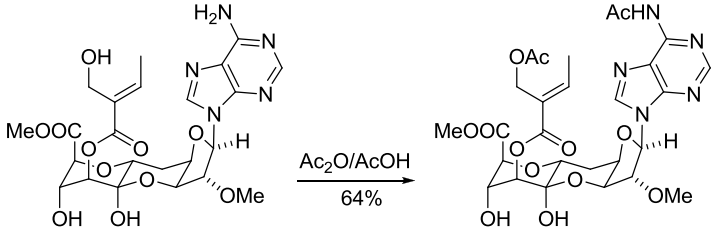
^{1}H-NMR (600 MHz, CD_3OD): δ = 8.30 (s, 1H, H-23), 8.21 (s, 1H, H-19), 7.09 (q, *J* = 7.2 Hz, 1H, H-16), 6.03 (d, *J* = 1.2 Hz, 1H, H-1), 5.65 (d, *J* = 9.1, 1H, H-8), 5.43 (dd, *J* = 10.4, 3.9 Hz, 1H, H-6), 4.47 (d, *J* = 7.7 Hz, 1H, H-10), 4.38 (d, *J* = 12.1 Hz, 1H, H-18a or H-18b), 4.35 (d, *J* = 12.1 Hz, 1H, H-18a or H-18b), 4.33 – 4.30 (m, 1H, H-4), 4.23 (d, *J* = 3.2 Hz, 1H, H-3), 4.11 – 4.06 (m, 2H, H-2, H-9), 3.79 (s, 3H, 3 x H-12), 3.52 (s, 3H, 3 x H-13), 2.45 – 2.39 (m, 1H, H-5a or H-5b), 2.28 – 2.22 (m, 1H, H-5a or H-5b), 1.94 (d, *J* = 7.3, 3H, 3 x H-17) ppm.

^{13}C-NMR (150 MHz, CD_3OD): δ = 171.42 (C-11), 167.63 (C-14), 157.33 (C-22), 153.58 (C-19), 153.09 (C-7), 149.65 (C-20), 143.69 (C-16), 141.81 (C-23), 133.29 (C-15), 120.35 (C-21), 92.69 (C-2), 89.92 (C-1), 81.52 (C-4), 76.32 (C-10), 74.89 (C-3), 73.33 (C-8), 72.51 (C-9), 69.83 (C-6), 58.32 (C-13), 56.31 (C-18), 52.94 (C-12), 29.11 (C-5), 14.40 (C-18) ppm.

IR (ATR): $\tilde{\nu}$ = 3202 (w), 2923 (w), 1716 (m), 1641 (m), 1476 (w), 1334 (w), 1273 (m), 1206 (m), 1082 (s), 989 (s), 831 (w) cm^{-1}.

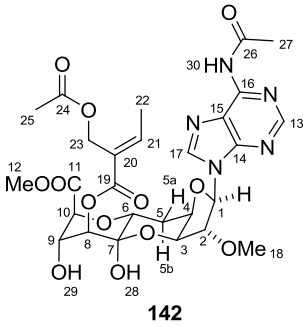
HRMS (ESI): calcd. for $C_{23}H_{31}N_6O_{11}^+$: 567.2045 $[M+H]^+$
found: 567.2044 $[M+H]^+$.

Methyl (1R,3*S*,4*R*,5*S*,7*R*,9*R*,11*S*,12*S*,13*S*)-13-{[(2*E*)-2-[(acetyloxy)methyl]but-2-enoyl]oxy}-5-(6-acetamido-9*H*-purin-9-yl)-1,12-dihydroxy-4-methoxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}] tridecane-11-carboxylate (142)



A solution of herbicidin A (**6**) (45.7 mg, 82.9 µmol, 1eq) in a mixture of acetic acid and acetic anhydride (1:1, 4 mL) was heated to 40 °C and stirred at this temperature for 50 h. The reaction was quenched with water (15 mL) and the mixture stirred at 40 °C for an additional 30 min, then allowed to cool to room temperature. The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic fractions were washed with aq. $NaHCO_3$ (20 mL of a saturated solution) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:acetone 5:1] afforded acetate **142** (33.8 mg, 53.1 µmol, 64%) as a white solid.

Acetate 142:



R_f = 0.51 [CH_2Cl_2:MeOH 9:1].

$[\alpha]_D^{21}$ = +34.0 (*c* = 0.10, acetone).

mp: 93 – 95 °C.

^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.55 (s, 1H, H-30), 8.69 (s, 1H, H-13), 8.07 (s, 1H, H-17), 6.96 (s, 1H, H-28), 6.89 (q, *J* = 7.2 Hz, 1H, H-21), 6.07 (d, *J* = 1.7 Hz, 1H, H-1), 5.66 (d, *J* = 7.8 Hz, 1H, H-29), 4.97 (d, *J* = 3.1 Hz, 1H, H-8), 4.84 (d, *J* = 12.0 Hz, 1H, H-23a or H-23b), 4.80 (d, *J* = 12.0 Hz, 1H, H-23a or H-23b), 4.48 (s, 1H, H-10), 4.42 (d, *J* = 2.3 Hz, 1H, H-3), 4.40 – 4.35 (m, 2H, H-4, H-6), 4.22 (d, *J* = 1.7 Hz, 1H, H-2), 4.17 (ddd, *J* = 7.8, 3.2, 1.3 Hz, 1H, H-9), 3.51 (s, 3H, 3 x H-12), 3.35 (s, 3H, 3 x H-18), 2.25 (s, 3H, 3 x H-27), 2.19 – 2.13 (m, 1H,

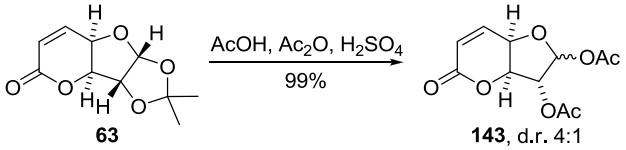
H-5a or H-5b), 2.11 – 2.06 (m, 1H, H-5a or H-5b), 2.04 (d, J = 7.2 Hz, 3H, 3 x H-22), 1.96 (s, 3H, 3 x H-25) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 170.65 (C-24), 169.94 (C-11), 169.26 (C-26), 164.27 (C-19), 152.57 (C-13), 151.99 (C-14), 150.14 (C-16), 147.93 (C-21), 141.78 (C-17), 126.54 (C-20), 123.76 (C-15), 91.90 (C-7), 89.62 (C-2), 86.92 (C-1), 77.72 (C-4), 76.57 (C-10), 73.01 (C-3), 71.00 (C-8), 69.11 (C-9), 65.17 (C-6), 57.84 (C-18), 57.71 (C-23), 52.30 (C-12), 25.85 (C-5), 24.45 (C-27), 21.02 (C-25), 15.30 (C-22) ppm.

IR (ATR): $\tilde{\nu}$ = 3249 (w), 2948 (w), 1719 (m), 1607 (m), 1586 (m), 1457 (m), 1371 (m), 1224 (s), 1134 (s), 1064 (s), 1001 (s), 964 (m), 856 (w), 747 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{27}H_{34}N_5O_{13}^+$: 636.2148 $[M+H]^+$
found: 636.2145 $[M+H]^+$.

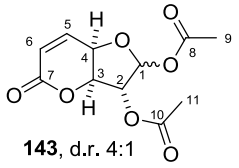
(3*R*,3a*R*,7a*R*)-2-(acetyloxy)-3a,7a-dimethyl-5-oxo-2*H*,3*H*,3a*H*,5*H*,7a*H*-furo[3,2-*b*]pyran-3-yl acetate (143)



63 **143**, d.r. 4:1

To a solution of unsaturated lactone **63** (402 mg, 1.89 mmol, 1.0 eq) in acetic acid (13.5 mL) was added conc. H_2SO_4 (15.0 µL), followed by acetic anhydride (448 µL, 4.74 mmol, 2.5 eq). The reaction mixture was stirred at room temperature for 20 h, then carefully quenched with $NaHCO_3$ (20 g) and diluted with water (20 mL). Aq. $NaHCO_3$ (40 mL of a saturated solution) was added and the mixture extracted with CH_2Cl_2 (4 x 50 mL). The combined organic fractions were washed with brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 4:1→3:1→2:1→1:1] afforded acetate **143** (481 mg, 1.88 mmol, 99%) as a colorless oil consisting of two diastereomers (d.r. 4:1, as determined by ^{1}H-NMR spectroscopy) as inseparable mixture.

Acetate 143:


143, d.r. 4:1

R_f = 0.57 [PE:EtOAc 1:1].

^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of isomer, both isomers quoted, minor isomer primed): 6.89 (dd, J = 10.0, 4.9 Hz, 1H, H-5), 6.80 (dd, J = 10.1, 4.1 Hz, 1H, H-5'), 6.42 (d, J = 4.6, 1H, H-1'), 6.18 – 6.13 (m, 3H, H-1, H-6, H-6'), 5.42 – 5.40 (m, 1H, H-2), 5.34 – 5.30 (m, 1H, H-2'), 5.18 (dd, J = 6.9, 5.3 Hz, 1H, H-3'), 5.03 (dd, J = 6.0, 1.3 Hz, 1H, H-3), 4.84 –

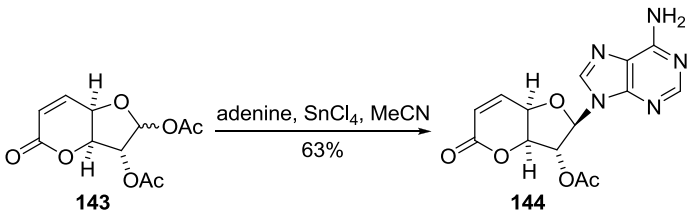
4.78 (m, 2H, H-4, H-4'), 2.12 (s, 3H, 3 x H-11), 2.10 (s, 3H, 3 x H-11'), 2.07 (s, 3H, 3 x H-9'), 2.00 (s, 3H, 3 x H-9) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) (mixture of isomer, both isomers quoted, minor isomer primed): δ = 169.48 (C-10'), 169.30 (C-10), 169.12 (C-8'), 169.11 (C-8), 159.47 (C-7), 159.42 (C-7'), 140.16 (C-5), 139.97 (C-5'), 122.96 (C-6), 122.90 (C-6'), 98.70 (C-1), 92.23 (C-1'), 80.99 (C-3), 80.52 (C-2), 79.93 (C-3'), 77.48 (C-2'), 70.26 (C-4), 66.58 (C-4'), 20.92 (C-9 and C-9'), 20.67 (C-11), 20.37 (C-11') ppm.

IR (ATR): $\tilde{\nu}$ = 3004 (w), 1732 (s), 1370 (m), 1208 (s), 1159 (w), 1110 (m), 1013 (m), 862 (w), 818 (w), 754 (w) cm^{-1}.

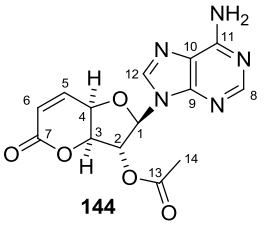
HRMS (ESI): calcd. for $C_{11}H_{12}NaO_7^+$: 279.0475 $[M+Na]^+$
found: 279.0475 $[M+Na]^+$.

(2*R*,3*R*,3a*R*,7a*R*)-2-(6-amino-9*H*-purin-9-yl)-3a,7a-dimethyl-5-oxo-2*H*,3*H*,3a*H*,5*H*,7a*H*-furo[3,2-*b*]pyran-3-yl acetate (144)



To a suspension of acetate **143** (53.7 mg, 0.210 mmol, 1.0 eq) and adenine (42.6 mg, 0.315 mmol, 1.5 eq) in MeCN (5 mL) was added tin(IV) chloride (49.1 µL, 0.420 mmol, 2.0 eq), and the resulting solution was heated to 60 °C and stirred at this temperature for 4.5 h. After cooling to room temperature, the reaction mixture was quenched with aq. $NaHCO_3$ (1.4 mL of a saturated solution) and the mixture extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:AcOH 19:1→1:1] afforded glycoside **144** (44.0 mg, 0.133 mmol, 63%) as a white solid.

Glycoside 144:



R_f = 0.57 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = –100.0 (*c* = 0.98, AcOH).

mp: 179 – 181 °C (decomposition).

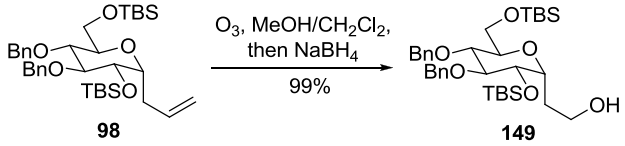
^{1}H-NMR (400 MHz, acetic acid-d_4): 8.38 (br s, 1H, H-8), 8.28 (s, 1H, H-12), 7.12 (dd, J = 9.8, 5.4 Hz, 1H, H-5), 6.45 (d, J = 2.1 Hz, 1H, H-1), 6.38 (d, J = 9.8 Hz, 1H, H-6), 5.81 (s, 1H, H-2), 5.26 (dd, J = 4.1, 1.1 Hz, 1H, H-3), 4.97 – 4.91 (m, 1H, H-4), 2.18 (s, 3H, 3 x H-14) ppm.

^{13}C-NMR (100 MHz, acetic acid-d_4): δ = 171.88 (C-13), 162.70 (C-7), 156.15 (C-11), 152.11 (C-8), 150.14 (C-9), 141.60 (C-12), 140.67 (C-5), 126.30 (C-6), 119.51 (C-10), 89.54 (C-1), 83.24 (C-3), 82.82 (C-2), 71.66 (C-4), 21.29 (C-14) ppm.

IR (ATR): $\tilde{\nu}$ = 3428 (s), 3276 (s), 3170 (s), 2924 (m), 1732 (m), 1550 (s), 1408 (s), 1300 (w), 1201 (s), 1100 (m), 1055 (m)m, 961 (w), 798 (w) cm^{-1}.

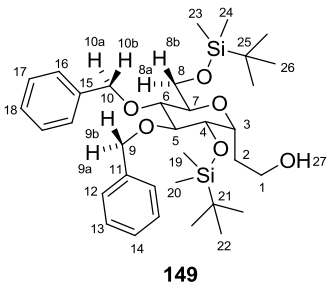
HRMS (ESI): calcd. for $C_{14}H_{14}N_5O_5^+$: 332.0989 $[M+H]^+$
found: 332.0990 $[M+H]^+$.

2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxan-2-yl]ethan-1-ol (149)



A solution of alkene **98** (100 mg, 0.163 mmol, 1.0 eq) in a mixture of CH_2Cl_2 and MeOH (1:1, 10 mL) was cooled to −78 °C and ozone was bubbled through the reaction mixture until a slight blue color persisted. Excess ozone was discharged by bubbling argon through the mixture, and then the solution was warmed to 0 °C. Sodium borohydride (34.0 mg, 0.978 mmol, 6.0 eq) was added in one portion, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 40 min, the reaction was quenched with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 49:1→19:1→9:1] afforded alcohol **149** (100 mg, 0.162 mmol, 99%) as a colorless oil.

Alcohol 149:



R_f = 0.28 [PE:EtOAc 9:1].

$[\alpha]_D^{19}$ = +4.48 (c = 0.71, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.25 (m, 8H, 2 x H-12, 2 x H-13, H-14, 2 x H-17, H-18), 7.23 – 7.20 (m, 2H, 2 x H-16), 4.89 (d, J = 11.3 Hz, 1H, H-9a or H-9b), 4.79 (d, J = 11.1 Hz, 2H, H-9a or H-9b, H-10a or H-

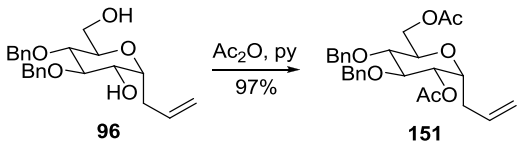
10b), 4.54 (d, J = 11.1 Hz, 1H, H-10a or H-10b), 4.07 (ddd, J = 11.9, 6.0, 3.0 Hz, 1H, H-3), 3.84 – 3.77 (m, 4H, H-1a, H-1b, H-4, H-8a or H-8b), 3.77 – 3.72 (m, 1H, H-7), 3.64 (dd, J = 9.0, 9.0 Hz, 1H, H-5), 3.54 (dd, J = 10.7, 6.9 Hz, 1H, H-8a or H-8b), 3.32 (dd, J = 9.8, 8.8 Hz, 1H, H-6), 2.11 – 2.03 (m, 1H, H-2a or H-2b), 1.87 – 1.81 (m, 1H, H-2a or H-2b), 0.90 (s, 9H, 9 x H-22), 0.89 (s, 9H, 9 x H-26), 0.07 (s, 3H, 3 x H-19 or 3 x H-20), 0.07 (s, 3H, 3 x H-19 or 3 x H-20), 0.04 (s, 3H, 3 x H-23 or 3 x H-24), 0.03 (s, 3H, 3 x H-23 or 3 x H-24) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 138.87 (C-11), 138.30 (C-15), 128.56 (2 x C-13 or 2 x C-17), 128.42 (2 x C-13 or 2 x C-17), 128.07 (2 x C-16), 127.92 (C-14 or C-18), 127.60 (2 x C-12), 127.54 (C-14 or C-18), 83.21 (C-5), 78.86 (C-6), 77.49 (C-3), 75.56 (C-9), 75.06 (C-10), 73.28 (C-4), 73.08 (C-7), 63.63 (C-8), 62.29 (C-1), 27.03 (C-2), 26.09 (3 x C-22 or 3 x C-26), 26.02 (3 x C-22 or 3 x C-26), 18.54 (C-25), 18.10 (C-21), –4.41 (C-19 or C-21), –4.52 (C-19 or C-21), −5.17 (C-23 or C-24), −5.31 (C-23 or C-24) ppm.

IR (ATR): $\tilde{\nu}$ = 3480 (w), 2929 (s), 1472 (w), 1252 (m), 1089 (s), 833 (s), 776 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{34}H_{56}NaO_6Si_2^+$: 639.3508 $[M+Na]^+$
found: 639.3504 $[M+Na]^+$.

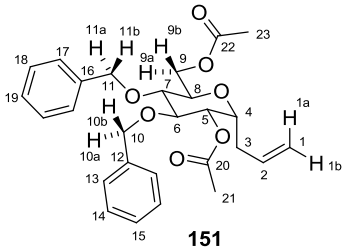
[(2*R*,3*R*,4*S*,5*S*,6*R*)-5-(acetyloxy)-3,4-bis(benzyloxy)-6-(prop-2-en-1-yl)oxan-2-yl]methyl acetate (151)



96 **151**

A solution of diol **96** (38.2 mg, 99.4 µmol, 1.0 eq) in pyridine (1.5 mL) was cooled to 0 °C and acetic anhydride (1.5 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2 h. The solvent was removed by azeotropic distillation with toluene (3 x 6 mL), and the residue was subjected to flash column chromatography [PE:EtOAc 9:1→5:1→3:1] to afford diacetate **151** (45.3 mg, 96.7 µmol, 97%) as a white solid.

Diacetate 151:


151

R_f = 0.57 [PE:EtOAc 2:1].

$[\alpha]_D^{21}$ = +36.0 (c = 1.1, $CHCl_3$).

mp: 91 – 93 °C.

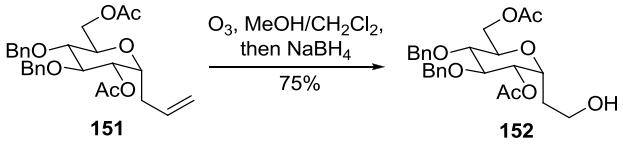
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.24 (m, 10H, 2 x H-13, 2 x H-14, H-15, 2 x H-17, 2 x H-18, H-19), 5.75 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H, H-2), 5.14 – 5.06 (m, 2H, H-1a, H-1b), 5.04 (dd, *J* = 8.3, 5.2 Hz, 1H, H-5), 4.81 – 4.72 (m, 3H, H-10a, H-10b, H-11a or H-11b), 4.55 (d, *J* = 11.0 Hz, 1H, H-11a or H-11b), 4.30 – 4.21 (m, 2H, H-9a, H-9b), 4.18 (ddd, *J* = 10.1, 5.0, 5.0 Hz, 1H, H-4), 3.86 (dd, *J* = 8.0, 8.0 Hz, 1H, H-6), 3.79 (ddd, *J* = 8.4, 4.9, 3.3 Hz, 1H, H-8), 3.52 (dd, *J* = 8.7, 7.7 Hz, 1H, H-7), 2.52 – 2.42 (m, 1H, H-3a or H-3b), 2.30 – 2.22 (m, 1H, H-3a or H-3b), 2.04 (s, 3H, 3 x H-23), 2.00 (s, 3H, 3 x H-21) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.86 (C-22), 170.15 (C-20), 138.21 (C-12), 137.68 (C-16), 133.68 (C-2), 128.64 (2 x C-14 or 2 x C-18), 128.62 (2 x C-14 or 2 x C-18), 128.26 (2 x C-17), 128.15 (C-15 or C-19), 127.96 (C-15 or C-19), 127.81 (2 x C-13), 117.57 (C-1), 79.58 (C-6), 77.07 (C-7), 74.78 (C-10), 74.62 (C-11), 72.43 (C-5), 71.49 (C-4), 70.65 (C-8), 63.12 (C-9), 31.53 (C-3), 21.06 (C-21), 20.97 (C-23) ppm.

IR (ATR): $\tilde{\nu}$ = 2910 (w), 1739 (s), 1454 (w), 1367 (m) 1227 (s), 1028 (s), 910 (w), 741 (m), 695 (s) cm^{-1}.

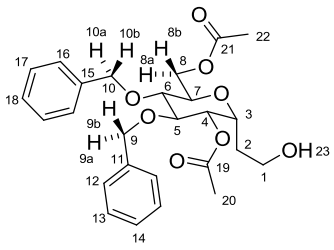
HRMS (ESI): calcd. for $C_{27}H_{36}NO_7^+$: 486.2486 $[M+NH_4]^+$
found: 486.2491 $[M+NH_4]^+$.

[(2*R*,3*R*,4*S*,5*S*,6*R*)-5-(acetyloxy)-3,4-bis(benzyloxy)-6-(2-hydroxyethyl)oxan-2-yl]methyl acetate (152):



A solution of alkene **151** (563 mg, 1.20 mmol, 1.0 eq) in a mixture of CH_2Cl_2 and MeOH (1:1, 48 mL) was cooled to –78 °C and ozone was bubbled through the reaction mixture until a slight blue color persisted. Excess ozone was discharged by bubbling argon through the mixture, and then the solution was warmed to 0 °C. Sodium borohydride (273 mg, 7.22 mmol, 6.0 eq) was added in one portion, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 1 h, the reaction was quenched with water (40 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→5:1→3:1→2:1→1:1→1:2→1:3] afforded alcohol **152** (423 mg, 0.895 mmol, 75%) as a white solid.

Alcohol 152:



152

R_f = 0.37 [PE:EtOAc 1:2].

$[\alpha]_D^{21}$ = +42.9 (c = 1.0, $CHCl_3$).

mp: 93 – 95 °C.

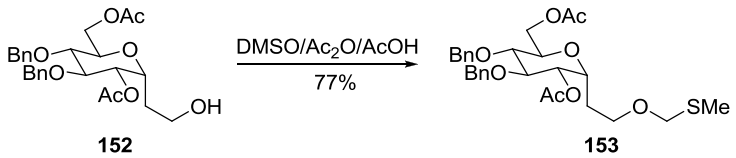
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38 – 7.27 (m, 8H, 2 x H-12, 2 x H-13, H-14, 2 x H-17, H-18), 7.26 – 7.23 (m, 2H, 2 x H-16), 4.98 (dd, J = 7.3, 4.6 Hz, 1H, H-4), 4.75 – 4.70 (m, 2H, H-9a, H-9b), 4.70 (d, J = 11.3 Hz, 1H, H-10a or H-10b), 4.52 (d, J = 11.3 Hz, 1H, H-10a or H-10b), 4.38 (dd, J = 11.9, 7.3 Hz, 1H, H-8a or H-8b), 4.32 (ddd, J = 11.4, 4.4, 3.0 Hz, 1H, H-3), 4.18 (dd, J = 11.9, 2.7 Hz, 1H, H-8a or H-8b), 3.96 (ddd, J = 7.4, 7.4, 2.7 Hz, 1H, H-7), 3.84 (dd, J = 7.0, 7.0 Hz, 1H, H-5), 3.78 – 3.72 (m, 2H, 2 x H-1), 3.43 (dd, J = 7.1, 7.1 Hz, 1H, H-6), 2.28 (br s, 1H, H-23), 2.06 (s, 3H, 3 x H-22), 2.01 (s, 3H, 3 x H-20), 2.04 – 1.97 (m, 1H, H-2a or H-2b), 1.65 – 1.58 (m, 1H, H-2a or H-2b) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 171.00 (C-21), 170.32 (C-19), 137.98 (C-11), 137.57 (C-15), 128.65 (2 x C-13 or 2 x C-17), 128.64 (2 x C-13 or 2 x C-17), 128.16 (C-14 or C-18), 128.14 (2 x C-16), 128.05 (C-14 or C-18), 127.87 (2 x C-12), 77.93 (C-5), 76.24 (C-6), 74.35 (C-9), 74.07 (C-10), 71.86 (C-4), 71.80 (C-7), 70.18 (C-3), 62.87 (C-8), 60.44 (C-1), 29.76 (C-2), 21.07 (C-20), 20.95 (C-22) ppm.

IR (ATR): $\tilde{\nu}$ = 3477 (w), 2897 (w), 1713 (s), 1369 (w), 1239 (s), 1119 (m), 1043 (s), 858 (w), 751 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{26}H_{36}NO_8^+$: 490.2241 $[M+NH_4]^+$
found: 490.2240 $[M+NH_4]^+$.

[(2*R*,3*R*,4*S*,5*S*,6*R*)-5-(acetyloxy)-3,4-bis(benzyloxy)-6-{2-[(methylsulfanyl)methoxy]ethyl} oxan-2-yl]methyl acetate (153)

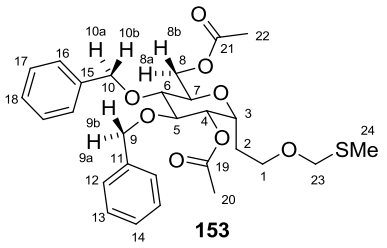


152 **153**

A solution of alcohol **152** (423 mg, 0.895 mmol, 1.0 eq) in a mixture of dimethyl sulfoxide, acetic anhydride and acetic acid (5:3:1, 10 mL) was stirred at room temperature for 19 h. The reaction mixture was diluted with EtOAc (25 mL) and water (10 mL), followed by separation of the phases. The aqueous layer was extracted further with EtOAc (2 x 15 mL). The combined organic fractions were washed with aq. $NaHCO_3$ (50 mL of a saturated solution), dried ($MgSO_4$)

and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→5:1→3:1] afforded methoxythiomethyl ether **153** (367 mg, 0.688 mmol, 77%) as a white solid.

Methoxythiomethyl ether 153:



153

R_f = 0.29 [PE:EtOAc 3:1].

$[\alpha]_D^{21}$ = +44.3 (c = 1.0, $CHCl_3$).

mp: 60 – 62 °C.

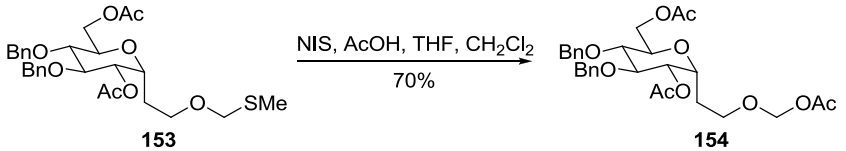
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36 – 7.27 (m, 8H, 2 x H-12, 2 x H-13, H-14, 2 x H-17, H-18), 7.27 – 7.24 (m, 2H, 2 x H-16), 5.04 (dd, J = 8.1, 5.1 Hz, 1H, H-4), 4.78 – 4.71 (m, 3H, H-9a, H-9b, H-10a or H-10b), 4.62 (d, J = 11.4 Hz, 1H, H-23a or H-23b), 4.59 (d, J = 11.4 Hz, 1H, H-23a or H-23b), 4.54 (d, J = 11.1 Hz, 1H, H-10a or H-10b), 4.31 – 4.22 (m, 3H, H-3, H-8a, H-8b), 3.83 (dd, J = 7.8, 7.8 Hz, 1H, H-5), 3.82 – 3.78 (m, 1H, H-7), 3.64 – 3.53 (m, 2H, H-1a, H-1b), 3.51 (dd, J = 8.4, 7.6 Hz, 1H, H-6), 2.13 (s, 3H, 3 x H-24), 2.05 (s, 3H, 3 x H-22), 2.00 (s, 3H, 3 x H-20), 2.00 – 1.93 (m, 1H, H-2a or H-2b), 1.80 – 1.74 (m, 1H, H-2a or H-2b) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.87 (C-21), 170.14 (C-19), 138.13 (C-11), 137.66 (C-15), 128.63 (2 x C-13 or 2 x C-17), 128.61 (2 x C-13 or 2 x C-17), 128.21 (2 x C-16), 128.14 (C-14 or C-18), 127.97 (C-14 or C-18), 127.83 (2 x C-12), 79.28 (C-5), 76.90 (C-6), 75.56 (C-23), 74.67 (C-9), 74.52 (C-10), 72.22 (C-4), 70.94 (C-7), 69.09 (C-3), 64.16 (C-1), 63.17 (C-8), 26.82 (C-2), 21.08 (C-20), 21.00 (C-22), 14.06 (C-24) ppm.

IR (ATR): $\tilde{\nu}$ = 2908 (m), 1739 (s), 1366 (m), 1280 (w), 1222 (s), 1044 (s), 864 (w), 695 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{28}H_{36}NaO_8S^+$: 555.2023 $[M+Na]^+$
found: 555.2027 $[M+Na]^+$.

{2-[(2*R*,3*S*,4*S*,5*R*,6*R*)-3-(acetyloxy)-6-[(acetyloxy)methyl]-4,5-bis(benzyloxy)oxan-2-yl]ethoxy}methyl acetate (154)

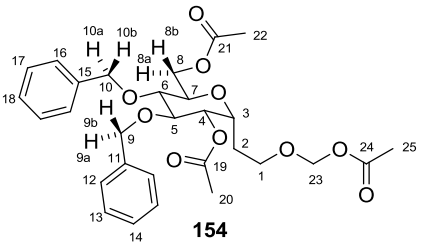


153 **154**

A mixture of acetic acid (13.5 µL, 0.236 mmol, 1.25 eq) and activated molecular sieve (30 mg, powdered, 3Å) in THF (1 mL) was stirred at room temperature for 2 h, then *N*-iodosuccinimide (53.3 mg, 0.236 mmol, 1.25 eq) was added. Separately, a suspension of methoxythiomethyl

ether **153** (101 mg, 0.189 mmol, 1.0 eq) and activated molecular sieve (100 mg, powdered, 3Å) in CH_2Cl_2 (12 mL) was stirred at room temperature for 1.5 h, then cooled to 0 °C. To this suspension, the previously prepared acetic acid/ *N*-iodosuccinimide mixture was added *via* cannula and the reaction mixture was stirred at 0 °C for 45 min. The suspension was diluted with CH_2Cl_2 (15 mL) and the molecular sieve was removed by suction filtration. The filtrate was washed with aq. $Na_2S_2O_3$ (30 mL of a saturated solution), aq. $NaHCO_3$ (30 mL of a saturated solution) and water (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→5:1→3:1→1:1] afforded acetate **154** (71.4 mg, 0.131 mmol, 70%) as a colorless oil.

Acetate 154:



154

R_f = 0.70 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = +42.3 (c = 1.0, $CHCl_3$).

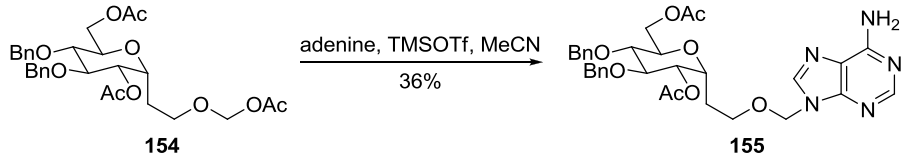
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37 – 7.27 (m, 8H, 2 x H-12, 2 x H-13, H-14, 2 x H-17, H-18), 7.27 – 7.23 (m, 2H, 2 xH-16), 5.28 (d, J = 6.2 Hz, 1H, H-23a or H-23b), 5.20 (d, J = 6.2 Hz, 1H, H-23a or H-23b), 5.03 (dd, J = 8.0, 5.1 Hz, 1H, H-4), 4.77 – 4.71 (m, 3H, H-9a, H-9b, H-10a or H-10b), 4.53 (d, J = 11.1 Hz, 1H, H-10a or H-10b), 4.29 – 4.20 (m, 3H, H-3, H-8a, H-8b), 3.82 (dd, J = 7.7, 7.7 Hz, 1H, H-5), 3.80 – 3.76 (m, 1H, H-7), 3.75 – 3.70 (m, 1H, H-1a or H-1b), 3.70 – 3.64 (m, 1H, H-1a or H-1b), 3.50 (dd, J = 8.2, 7.6 Hz, 1H, H-6), 2.08 (s, 3H, 3 x H-25), 2.05 (s, 3H, 3 x H-22), 2.00 (s, 3H, 3 x H-20), 1.99 – 1.92 (m, 1H, H-2a or H-2b), 1.80 – 1.73 (m, 1H, H-2a or H-2b) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 170.83 (C-21), 170.68 (C-24), 170.14 (C-19), 138.09 (C-11), 137.65 (C-15), 128.63 (2 x C-13 or 2 x C-17), 128.62 (2 x C-13 or 2 x C-17), 128.20 (2 x C-16), 128.14 (C-14 or C-18), 127.99 (C-14 or C-18), 127.84 (2 x C-12), 89.36 (C-23), 79.13 (C-5), 76.74 (C-6), 74.63 (C-9), 74.46 (C-10), 72.07 (C-4), 71.03 (C-7), 68.76 (C-3), 66.51 (C-1), 63.09 (C-8), 26.97 (C-2), 21.14 (C-25), 21.06 (C-20), 20.95 (C-22) ppm.

IR (ATR): $\tilde{\nu}$ = 2957 (w), 1738 (s), 1454 (w), 1366 (m), 1224 (s), 1099 (m), 1011 (s), 941 (m), 738 (m), 698 (m) cm^{-1}.

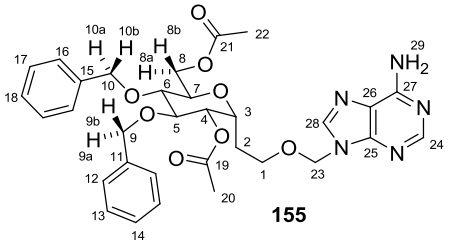
HRMS (ESI): calcd. for $C_{29}H_{36}NaO_{10}^+$: 567.2206 $[M+Na]^+$
found: 567.2204 $[M+Na]^+$.

[(2*R*,3*R*,4*S*,5*S*,6*R*)-5-(acetyloxy)-6-{2-[(6-amino-9*H*-purin-9-yl)methoxy]ethyl}-3,4-bis(benzyloxy)oxan-2-yl]methyl acetate (155):



To a suspension of triacetate **154** (38.6 mg, 70.9 µmol, 1.0 eq) and adenine (14.4 mg, 0.106 mmol, 1.5 eq) in MeCN (4 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (77.0 µL, 0.425 mmol, 6.0 eq). The resulting solution was stirred at room temperature for 5 min, then diluted with aq. $NaHCO_3$ (15 mL of a saturated solution). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 100:1→49:1→24:1→14:1] afforded glycoside **155** (15.7 mg, 25.3 mmol, 36%) as a white solid.

Glycoside 155:



R_f = 0.40 [CH_2Cl_2:MeOH 9:1].

$[\alpha]_D^{21}$ = +43.3 (*c* = 0.84, MeOH).

mp: 102 °C.

^{1}H-NMR (600 MHz, CD_3OD): δ = 8.23 (s, 1H, H-28), 8.22 (s, 1H, H-24), 7.33 – 7.23 (m, 10H, 2 x H-12, 2 x H-13, H-14, 2 x H-16, 2 x H-17, H-18), 5.63 – 5.58 (m, 2H, H-23a, H-23b), 4.87 – 4.84 (m, 1H, H-4), 4.72 – 4.68 (m, 2H, H-9a, 9b), 4.68 (d, *J* = 11.3 Hz, 1H, H-10a or H-10b), 4.53 (d, *J* = 11.3 Hz, 1H, H-10a or H-10b), 4.18 – 4.07 (m, 3H, H-3, H-8a, H-8b), 3.83 (dd, *J* = 7.6, 7.6 Hz, 1H, H-5), 3.74 – 3.70 (m, 1H, H-7), 3.61 – 3.58 (m, 2H, H-1a, H-1b), 3.43 (dd, *J* = 7.9, 7.7 Hz, 1H, H-6), 1.97 (s, 3H, 3 x H-22), 1.96 – 1.90 (m, 1H, H-2a or H-2b), 1.93 (s, 3H, 3 x H-20), 1.72 – 1.65 (m, 1H, H-2a or H-2b) ppm.

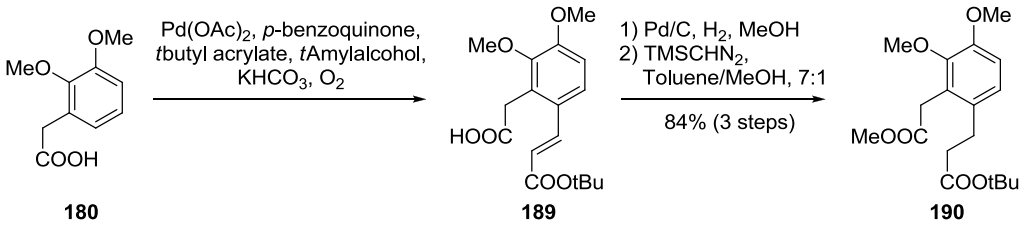
^{13}C-NMR (150 MHz, CD_3OD): δ = 172.49 (C-21), 171.73 (C-19), 157.40 (C-27), 154.19 (C-24), 150.99 (C-25), 142.90 (C-28), 139.63 (C-11), 139.31 (C-15), 129.44 (2 x C-13 or 2 x C-17), 129.40 (2 x C-13 or 2 x C-17), 129.14 (2 x C-16), 128.93 (2 x C-12), 128.87 (C-14 or C-18), 128.81 (C-14 or C-18), 119.96 (C-26), 79.82 (C-5), 77.92 (C-6), 75.40 (C-9), 75.07 (C-10), 74.07 (C-23), 73.33 (C-4), 72.26 (C-7), 69.69 (C-3), 66.46 (C-1), 64.07 (C-8), 27.64 (C-2), 20.83 (C-20), 20.74 (C-22) ppm.

IR (ATR): $\tilde{\nu}$ = 3320 (w), 3160 (w), 2940 (w), 1739 (s), 1643 (m), 1475 (w), 1368 (w), 1232 (s), 1100 (s), 1038 (m), 906 (w), 754 (w), 698 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{32}H_{38}N_5O_8^+$: 620.2715 $[M+H]^+$
found: 620.2713 $[M+H]^+$.

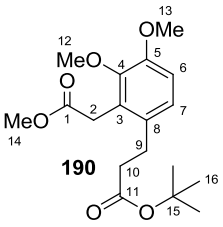
21.2. Experimental Data of Chapter II

***Tert*-butyl 3-[3,4-dimethoxy-2-(2-methoxy-2-oxoethyl)phenyl]propanoate (190) and 2-{6-[(1*E*)-3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-2,3-dimethoxyphenyl}acetic acid (189)**



An autoclave apparatus was charged with a suspension of 2,3-dimethoxyphenylacetic acid (**180**) (10.0 g, 51.0 mmol, 1.0 eq), *para*-benzoquinone (276 mg, 1.28 mmol, 5 mol%), $KHCO_3$ (10.2 g, 102 mmol, 2.0 eq), *tert*-butyl acrylate (22.4 mL, 153 mmol, 3.0 eq) and $Pd(OAc)_2$ (1.15 g, 5.10 mmol, 10 mol%) in *tert*-amylalcohol (100 mL). The autoclave apparatus was purged with oxygen gas five times and the reaction mixture was stirred under oxygen atmosphere (3 bar) at 85 °C for 96 h. After cooling to room temperature, aq. HCl (2 M, 150 mL) was added and the mixture extracted with Et_2O (3 x 200 mL). The combined organic fractions were dried ($MgSO_4$), and all solid material was removed by filtering the suspension through a pad of Celite. The Celite was washed with Et_2O (100 mL) and the filtrate was concentrated *in vacuo* to afford crude **189**, which was immediately re-dissolved in MeOH (300 mL). To this solution, palladium on charcoal (10 wt%, 2.00 g) was added and the flask was purged with hydrogen gas five times. The mixture was then stirred under hydrogen atmosphere at room temperature for 16 h. The catalyst was removed by filtration through a pad of Celite, and the Celite was washed with MeOH (200 mL). The filtrate was concentrated *in vacuo* to afford crude saturated ester, which was immediately re-dissolved in toluene/MeOH (7:1, 314 mL). This mixture was cooled to 0 °C and a solution of (trimethylsilyl)diazomethane in hexanes (2.0 M, 30.6 mL, 61.2 mmol, 1.2 eq) was added dropwise. After stirring for 15 min at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 40 min. The reaction was quenched with acetic acid (15 mL) and diluted with aq. $NaHCO_3$ (600 mL of a saturated solution). The mixture was extracted with EtOAc (3 x 400 mL) and the combined organic fractions were washed with brine (500 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1→6:1→4:1] afforded methyl ester **190** (14.5 g, 42.8 mmol, 84% over 3 steps) as a colorless oil.

Compound 190:



R_f = 0.27 [PE:EtOAc 9:1].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 8.5 Hz, 1H, H-7), 6.80 (d, *J* = 8.5 Hz, 1H, H-6), 3.84 (s, 3H, 3 x H-13), 3.81 (s, 3H, 3 x H-12), 3.75 (s, 2H, 2 x H-2), 3.69 (s, 3H, 3 x H-14), 2.86 – 2.79 (m, 2H, 2 x H-9), 2.48 – 2.41 (m, 2H, 2 x H-10), 1.43 (s, 9H, 9 x H-16) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 172.36 (C-1 and C-11), 151.08 (C-5), 147.76 (C-4), 132.50 (C-8), 127.21 (C-3), 124.20 (C-7), 111.60 (C-6), 80.53 (C-15), 60.61 (C-12), 55.85 (C-13), 52.12 (C-14), 36.64 (C-10), 32.12 (C-2), 28.25 (3 x C-16), 27.94 (C-9) ppm.

IR (ATR): $\tilde{\nu}$ = 2976 (w), 1726 (s), 1492 (m), 1366 (m), 1275 (s), 1145 (s), 1083 (s), 753 (s) cm^{-1}.

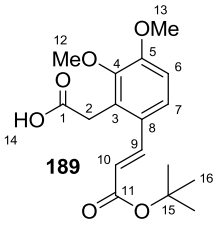
HRMS (EI): calcd. for $C_{18}H_{26}O_6^+$: 338.1724 $[M]^+$
found: 338.1718 $[M]^+$.

Carboxylic Acid 189:

In order to fully characterize carboxylic acid **189**, an analytical sample of the crude mixture, obtained after palladium-catalyzed C–H activation, was purified by flash column chromatography [PE:EtOAc 3:1 + 1% AcOH] to yield **189** as a white solid.

R_f = 0.20 [PE:EtOAc 3:1 + 1% AcOH].

mp: 115 – 117 °C.



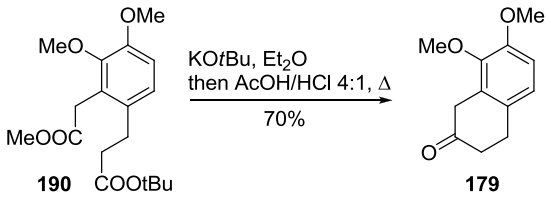
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.7 Hz, 1H, H-9), 7.34 (d, *J* = 8.7 Hz, 1H, H-7), 6.87 (d, *J* = 8.7 Hz, 1H, H-6), 6.20 (d, *J* = 15.6 Hz, 1H, H-10), 3.90 – 3.86 (m, 5H, 2 x H-2, 3 x H-13), 3.83 (s, 3H, 3 x H-12), 1.51 (s, 9H, 9 x H-16) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 176.71 (C-1), 166.45 (C-11), 153.83 (C-5), 147.65 (C-4), 140.32 (C-9), 127.82 (C-3), 127.64 (C-8), 122.88 (C-7), 120.96 (C-10), 111.85 (C-6), 80.65 (C-15), 60.81 (C-13), 55.88 (C-12), 31.80 (C-2), 28.34 (3 x C-16) ppm.

IR (ATR): $\tilde{\nu}$ = 2983 (w), 1734 (m), 1700 (s) 1494 (s), 1255 (m), 1145 (s), 1078 (s), 801 (m) cm^{-1}.

HRMS (EI): calcd. for $C_{17}H_{22}O_6^+$: 322.1411 $[M]^+$
found: 322.1400 $[M]^+$.

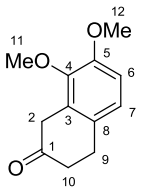
7,8-Dimethoxy-1,2,3,4-tetrahydronaphthalen-2-one (179)



190 **179**

To a solution of diester **190** (8.07 g, 23.8 mmol, 1.0 eq) in Et_2O (300 mL) was added potassium *tert*-butoxide (3.34 g, 29.8 mmol, 1.25 eq) in one portion, and the resulting mixture was stirred at room temperature for 35 min. The reaction mixture was cooled to 0 °C and aq. HCl (1 M, 300 mL) was carefully added. The mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 200 mL). The combined organic fractions were washed with brine (200 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was immediately re-dissolved in acetic acid (190 mL) and conc. aq. HCl (50 mL) was added. The mixture was heated to 110 °C for 3 h and then cooled to 0 °C. After the reaction was quenched carefully with solid $NaHCO_3$ (280 g), water (700 mL) was added and the mixture was extracted with Et_2O (3 x 300 mL). The combined organic fractions were washed with aq. $NaHCO_3$ (2 x 500 mL) and brine (500 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1→3:1] afforded β-tetralone **179** (3.45 g, 16.7 mmol, 70%) as a white solid.

β-Tetralone 179:



179

R_f = 0.43 [PE:EtOAc 3:1].

mp: 75 – 76 °C.

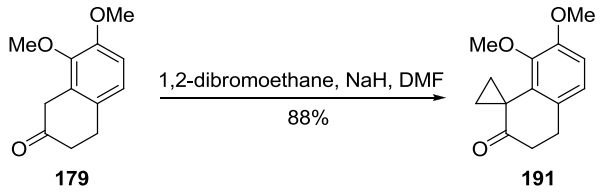
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 8.3 Hz, 1H, H-7), 6.79 (d, *J* = 8.3 Hz, 1H, H-6), 3.86 (s, 3H, 3 x H-12), 3.81 (s, 3H, 3 x H-11), 3.60 (s, 2H, 2 x H-2), 3.04 – 2.97 (m, 2H, 2 x H-9), 2.58 – 2.51 (m, 2H, H-10) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 210.58 (C-1), 151.41 (C-5), 146.48 (C-4), 129.66 (C-8), 127.47 (C-3), 122.96 (C-7), 110.89 (C-6), 60.58 (C-11), 56.05 (C-12), 38.91 (C-10), 38.71 (C-2), 28.25 (C-9) ppm.

IR (ATR): $\tilde{\nu}$ = 2998 (w), 2944 (w), 1702 (s), 1492 (s), 1350 (w), 1273 (s), 1155 (w), 1080 (s), 802 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{12}H_{14}O_3^+$: 206.0937 $[M]^+$
found: 206.0942 $[M]^+$.

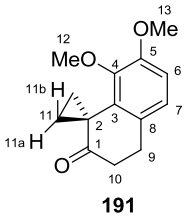
7',8'-Dimethoxy-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]-2'-one (191)



179 **191**

A solution of β-tetralone **179** (2.92 g, 14.2 mmol, 1.0 eq) and 1,2-dibromoethane (1.81 mL, 21.3 mmol, 1.5 eq) in DMF (50 mL) was cooled to 0 °C and sodium hydride (60 wt% in mineral oil, 1.25 g, 31.2 mmol, 2.2 eq) was added. The reaction mixture was stirred at 0 °C for 1.5 h, then quenched at 0 °C with MeOH (90 mL) and diluted with water (300 mL). The mixture was extracted with Et_2O (4 x 250 mL) and the combined organic layers dried (Na_2SO_4), then concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 3:1] afforded cyclopropane **191** (2.92 g, 12.5 mmol, 88%) as a white solid.

Cyclopropane 191:



191

R_f = 0.57 [PE:EtOAc 3:1].

mp: 59 – 61 °C.

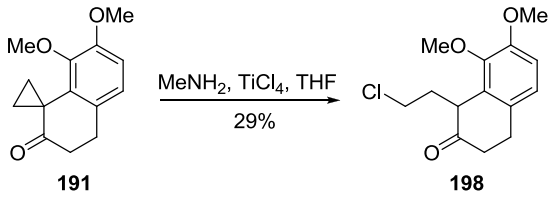
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.92 – 6.88 (m, 1H, H-7), 6.73 (d, *J* = 8.2 Hz, 1H, H-6), 3.84 (s, 3H, 3 x H-13), 3.73 (s, 3H, 3 x H-12), 3.03 – 2.96 (m, 2H, 2 x H-9), 2.66 – 2.59 (m, 2H, 2 x H-10), 1.90 – 1.85 (m, 2H, 2 x H-11b), 1.69 – 1.64 (m, 2H, 2 x H-11a) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 210.26 (C-1), 152.17 (C-5), 146.91 (C-4), 131.94 (C-8), 130.36 (C-3), 122.91 (C-7), 109.90 (C-6), 61.49 (C-12), 55.98 (C-13), 39.34 (C-10), 31.28 (C-2), 28.16 (C-9), 21.28 (2 x C-11) ppm.

IR (ATR): $\tilde{\nu}$ = 2936 (m), 1686 (m), 1575 (w), 1478 (m), 1263 (s), 1045 (s), 883 (w), 797 (m) cm^{-1}.

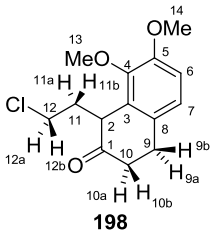
HRMS (EI): calcd. for $C_{14}H_{16}O_3^+$: 232.1094 $[M]^+$
found: 232.1097 $[M]^+$.

1-(2-Chloroethyl)-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-one (198)



To a solution of cyclopropane **191** (10.0 mg, 43.0 µmol, 1.0 eq) in THF (0.5 mL) was added a solution of methylamine in THF (2.0 M, 177 µL, 0.344 mmol, 8.0 eq), followed by a solution of titanium(IV) chloride in toluene (1.0 M, 21.5 µL, 21.5 µmol, 0.5 eq). The reaction mixture was stirred at room temperature for 5 d, then quenched with aq. $NaHCO_3$ (5 mL of a saturated solution). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic fractions were washed with brine (10 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 19:1→9:1→4:1] afforded chloride **198** (3.3 mg, 12.3 µmol, 29%) as a colorless oil.

Chloride 198:



R_f = 0.36 [PE:EtOAc 3:1].

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.92 (br d, *J* = 8.3 Hz, 1H, H-7), 6.81 (d, *J* = 8.3 Hz, 1H, H-6), 3.87 (s, 3H, 3 x H-14), 3.87 – 3.85 (m, 1H, H-2), 3.84 (s, 3H, 3 x H-13), 3.58 (ddd, *J* = 10.9, 8.5, 5.7 Hz, 1H, H-12a or H-12b), 3.48 (ddd, *J* = 10.9, 8.4, 7.1 Hz, 1H, H-12a or H-12b), 3.18 – 3.11 (m, 1H, H-9a or H-9b), 2.91 (ddd, *J* = 15.6, 6.4, 2.7 Hz, 1H, H-9a or H-9b), 2.74 (ddd, *J* = 17.3, 5.0, 2.7 Hz, 1H, H-10a or H-10b), 2.48 – 2.41 (m, 1H, H-10a or H-10b), 2.28 – 2.17 (m, 2H, H-11a, H-11b) ppm.

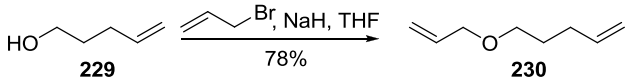
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.33 (C-1), 151.48 (C-5), 146.72 (C-4), 130.37 (C-3), 129.33 (C-8), 123.40 (C-7), 111.36 (C-6), 60.91 (C-13), 55.98 (C-14), 46.26 (C-2), 42.46 (C-12), 38.40 (C-10), 36.47 (C-11), 27.25 (C-9) ppm.

IR (ATR): $\tilde{\nu}$ = 2942 (w), 1706 (s), 1606 (w), 1491 (s), 1278 (s), 1087 (s), 807 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{14}H_{16}ClO_3^+$: 267.0782 $[M–H]^+$
found: 267.0781 $[M–H]^+$.

21.3. Experimental Data of Chapter III

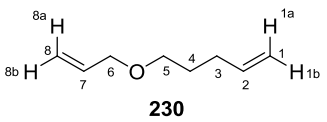
5-(Prop-2-en-1-yloxy)pent-1-ene (230)[142]



229 **230**

A suspension of sodium hydride (60 wt% in mineral oil, 4.36 g, 109 mmol, 2.0 eq) in THF (50 mL) was cooled to 0 °C and 4-penten-1-ol (**229**) (5.60 mL, 54.6 mmol, 1.0 eq) added dropwise. The mixture was stirred at 0 °C for 10 min until gas evolution had ceased, and then allyl bromide (9.43 mL, 109 mmol, 2.0 eq) was added. The reaction mixture was stirred at 0 °C for an additional 5 min, then allowed to warm to room temperature and stirred at this temperature for 15 h. The reaction mixture was carefully quenched with water (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Vacuum distillation (80 °C oil bath temperature, 30 mbar) of the residue afforded ether **230** (5.37 g, 42.6 mmol, 78%) as a colorless liquid.

Ether 230:



230

R_f = 0.59 [PE:EtOAc 9:1].

bp: 45 °C (30 mbar).

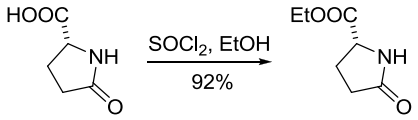
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.99 – 5.74 (m, 2H, H-2, H-7), 5.32 – 5.22 (m, 1H, H-8a), 5.19 – 5.14 (m, 1H, H-8b), 5.07 – 4.92 (m, 2H, H-1a, H-1b), 3.98 – 3.94 (m, 2H, 2 x H-6), 3.44 (t, *J* = 6.6 Hz, 2H, 2 x H-5), 2.18 – 2.08 (m, 2H, 2 x H-3), 1.74 – 1.63 (m, 2H, 2 x H-4) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 138.42 (C-2), 135.14 (C-7), 116.87 (C-8), 114.84 (C-1), 71.95 (C-6), 69.82 (C-5), 30.46 (C-3), 29.06 (C-4) ppm.

IR (ATR): $\tilde{\nu}$ = 3079 (w), 2938 (w), 2852 (m), 1642 (w), 1449 (w), 1345 (w), 1104 (br s), 992 (m), 912 (s) cm^{-1}.

HRMS (EI): calcd. for $C_8H_{13}O^+$: 125.0961 $[M–H]^+$
found: 125.0969 $[M–H]^+$.

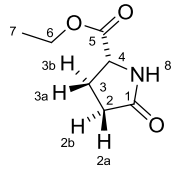
Ethyl (2*R*)-5-oxopyrrolidine-2-carboxylate (234)[122-123]



233 **234**

A solution of D-pyroglutamic acid **234** (39.1 g, 303 mmol, 1eq) in EtOH (560 mL) was cooled to 0 °C and thionyl chloride (33.0 mL, 454 mmol, 1.5 eq) was added dropwise. After complete addition, the reaction mixture was heated to 80 °C and refluxed for 1.5 h. The solution was cooled to room temperature and volatile material was removed *in vacuo*. Vacuum distillation (180 °C oil bath temperature, $7 \cdot 10^{-1}$ mbar) of the residue afforded D-pyroglutamic acid ethyl ester **234** (34.7 g, 221 mmol, 73%) as a colorless oil. Flash column chromatography [CH_2Cl_2:MeOH 24:1] of the distillation residue provided additional material of **234** (8.92 g, 56.8 mmol), raising the total yield to 92%.

D-pyroglutamic acid ethyl ester 234:



234

R_f = 0.40 [CH_2Cl_2:MeOH 9:1].

$[\alpha]_D^{21}$ = –5.6 (*c* = 0.99, EtOH), $[\alpha]_D^{21}$ = –1.4 (*c* = 0.99, $CHCl_3$).

bp: 144 °C ($7 \cdot 10^{-1}$ mbar).

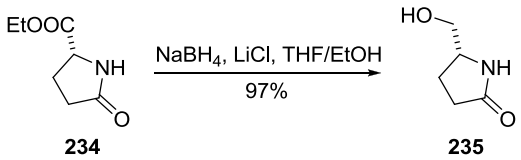
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.21 (br s, 1H, H-8), 4.20 – 4.09 (m, 3H, H-4, H-6a, H-6b), 2.45 – 2.20 (m, 3H, H-2a, H-2b, H-3a or H-3b), 2.19 – 2.05 (m, 1H, H-3a or H-3b), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, 3 x H-7) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 178.40 (C-1), 172.12 (C-5), 61.48 (C-6), 55.60 (C-4), 29.31 (C-2), 24.74 (C-3), 14.06 (C-7) ppm.

IR (ATR): $\tilde{\nu}$ = 3227 (br, w), 2980 (w), 1692 (s), 1420 (w), 1379 (w), 1192 (s), 1027 (m), 860 (w), 662 (br, w) cm^{-1}.

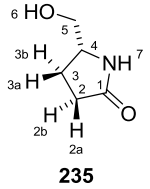
HRMS (EI): calcd. for $C_7H_{11}NO_3^+$: 157.0733 $[M]^+$
found: 157.0731 $[M]^+$.

(5*R*)-5-(hydroxymethyl)pyrrolidin-2-one (235)[122-123]



To a solution of D-pyroglutamic acid ethyl ester **234** (8.90 g, 56.6 mmol, 1eq) in THF (90 mL) was added sodium borohydride (4.28 g, 113 mmol, 2.0 eq), lithium chloride (4.80 g, 113 mmol, 2.0 eq) followed by EtOH (20 mL), and the resulting mixture was stirred at room temperature for 20 h. The reaction was quenched with aq. citric acid (5 wt%, 110 mL) and volatile material removed *in vacuo*. The remaining solid was suspended in a mixture of EtOAc and MeOH (3:1, *ca.* 200 mL) and filtered through a pad of Celite. The Celite was washed with a mixture of EtOAc and MeOH (3:1, *ca.* 100 mL) and the filtrate concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 9:1] afforded alcohol **235** (8.92 g, 54.9 mmol, 97%) as a white solid.

Alcohol 235:



235

R_f = 0.22 [CH_2Cl_2:MeOH 9:1].

$[\alpha]_D^{21}$ = –86.0 (*c* = 1.0, $CHCl_3$).

mp: 79 – 83 °C.

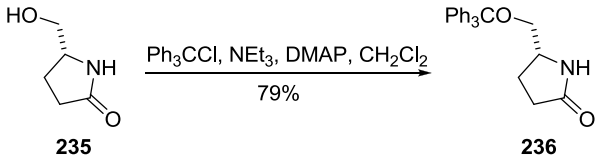
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35 (br s, 1H, H-7), 4.36 – 4.25 (m, 1H, H-6), 3.85 – 3.72 (m, 1H, H-4), 3.65 (ddd, *J* = 11.4, 5.8, 3.2 Hz, 1H, H-5a or H-5b), 3.50 – 3.37 (m, 1H, H-5a or H-5b), 2.44 – 2.23 (m, 2H, H-2a, H-2b), 2.22 – 2.08 (m, 1H, H-3a or H-3b), 1.85 – 1.70 (m, 1H, H-3a or H-3b) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 179.53 (C-1), 65.94 (C-5), 56.64 (C-4), 30.42 (C-2), 22.73 (C-3) ppm.

IR (ATR): $\tilde{\nu}$ = 3189 (br, m), 2827 (w), 1650 (br, s), 1422 (m), 1230 (w), 1080 (m), 1018 (m), 969 (m), 786 (s), 641 (s) cm^{-1}.

HRMS (EI): calcd. for $C_5H_9NO_2^+$: 115.0628 $[M]^+$
found: 115.0621 $[M]^+$.

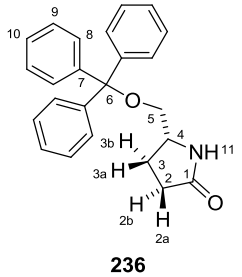
(5R)-5-[(triphenylmethoxy)methyl]pyrrolidin-2-one (236)[143]



235 **236**

To a solution of alcohol **235** (3.47 g, 30.1 mmol, 1eq), triethylamine (6.30 mL, 45.2 mmol, 1.5 eq) and 4-(dimethylamino)pyridine (368 mg, 3.01 mmol, 10 mol%) in CH_2Cl_2 (300 mL) was added triphenylmethyl chloride (10.1 g, 36.1 mmol, 1.2 eq) in three portions, and the mixture was stirred at room temperature for 5 min after each addition. The reaction mixture was stirred for an additional 6 h, then quenched with water (150 mL). The organic phase was separated, washed further with water (2 x 150 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [CH_2Cl_2:MeOH 100:1→19:1] afforded auxiliary **236** (8.56 g, 23.9 mmol, 79%) as a white solid.

Koga's auxiliary 236:



236

R_f = 0.56 [CH_2Cl_2:MeOH 6:1], 0.27 [PE:EtOAc 1:2]

$[\alpha]_D^{21}$ = –12.2 (*c* = 1.0, $CHCl_3$).

mp: 161 – 163 °C.

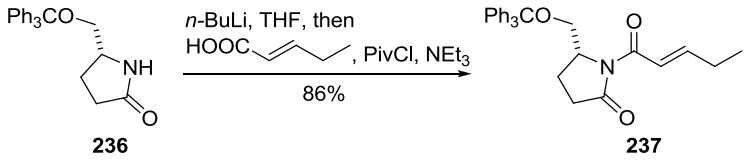
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 – 7.38 (m, 6H, 6 x H-8), 7.34 – 7.28 (m, 6H, 6 x H-9), 7.28 – 7.22 (m, 3H, 3 x H-10), 5.97 (br s, 1H, H-11), 3.90 – 3.82 (m, 1H, H-4), 3.20 (dd, *J* = 9.3, 4.0 Hz, 1H, H-5a or H-5b), 3.00 (dd, *J* = 9.3, 8.0 Hz, 1H, H-5a or H-5b), 2.33 – 2.27 (m, 2H, H-2a, H-2b), 2.19 – 2.08 (m, 1H, H-3a or H-3b), 1.72 – 1.61 (m, 1H, H-3a or H-3b) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 177.94 (C-1), 143.72 (C-7), 128.70 (6 x C-8), 128.05 (6 x C-9), 127.33 (3 x C-10), 86.99 (C-6), 67.32 (C-5), 54.15 (C-4), 29.74 (C-2), 23.44 (C-3) ppm.

IR (ATR): $\tilde{\nu}$ = 3189 (br, w), 3057 (w), 2911 (w), 1686 (s), 1489 (w), 1447 (m), 1284 (w), 1081 (m), 1002 (w), 899 (w), 760 (m), 692 (s), 631 (m) cm^{-1}.

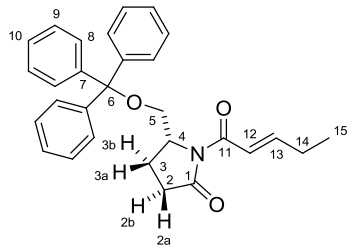
HRMS (EI): calcd. for $C_{24}H_{23}NO_2^+$: 357.1723 $[M]^+$
found: 357.1713 $[M]^+$.

(5*R*)-1-[(2*E*)-pent-2-enoyl]-5-[(triphenylmethoxy)methyl]pyrrolidin-2-one (237)



A solution of auxiliary **236** (16.7 g, 46.7 mmol, 1.0 eq) in THF (200 mL) was cooled to −78 °C and a solution of *n*-butyllithium in hexanes (2.5 M, 23.4 mL, 58.4 mmol, 1.25 eq) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min. In a separate flask, a solution of *trans*-2-pentenoic acid (5.90 mL, 58.4 mmol, 1.25 eq) and triethylamine (11.4 mL, 81.7 mmol, 1.75 eq) was cooled to 0 °C and pivaloyl chloride (7.90 mL, 64.1 mmol, 1.37 eq) was added dropwise. The solution was stirred at 0 °C for 30 min, then added slowly *via* cannula to the previously prepared amide anion solution at −78 °C. The reaction was allowed to warm to room temperature over a period of 2 h, then quenched with aq. NH_4Cl (500 mL of a saturated solution). The mixture was extracted with EtOAc (3 x 300 mL) and the combined organic fractions were washed with aq. $NaHCO_3$ (400 mL of a saturated solution), water (400 mL) and brine (400 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→6:1→4:1] afforded imide **237** (17.6 g, 40.0 mmol, 86%) as a white solid.

Imide 237:



237

R_f = 0.50 [PE:EtOAc 3:1]

$[\alpha]_D^{23}$ = +84.7 (*c* = 1.0, CH_2Cl_2).

mp: 107 – 108 °C.

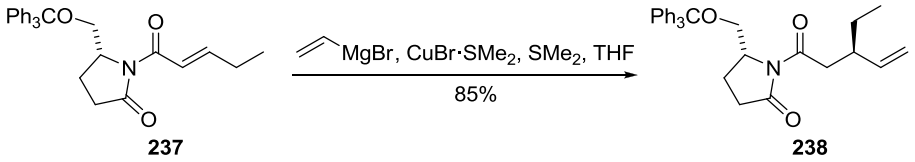
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 – 7.33 (m, 6H, 6 x H-8), 7.32 – 7.19 (m, 10H, 6 x H-9, 3 x H-10, H-12), 7.13 (ddd, *J* = 15.4, 6.4, 6.4 Hz, 1H, H-13), 4.60 – 4.50 (m, 1H, H-4), 3.57 (dd, *J* = 9.7, 4.0 Hz, 1H, H-5a or H-5b), 3.16 (dd, *J* = 9.7, 2.7 Hz, 1H, H-5a or H-5b), 2.97 (ddd, *J* = 17.9, 11.0, 10.0 Hz, 1H, H-2a or H-2b), 2.50 (ddd, *J* = 17.9, 9.7, 2.2 Hz, 1H, H-2a or H-2b), 2.39 – 2.27 (m, 2H, H-14a, H-14b), 2.17 – 1.91 (m, 2H, H-3a, H-3b), 1.14 (dd, *J* = 7.4, 7.4 Hz, 3H, 3 x H-15) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 176.54 (C-1), 166.16 (C-11), 152.00 (C-13), 143.84 (3 x C-7), 128.70 (6 x C-8), 128.00 (6 x C-9), 127.23 (3 x C-10), 121.89 (C-12), 87.16 (C-6), 64.28 (C-5), 56.91 (C-4), 33.53 (C-2), 25.99 (C-14), 21.24 (C-3), 12.60 (C-15) ppm.

IR (ATR): $\tilde{\nu}$ = 3100 (br, w), 2967 (w), 2929 (w), 1728 (s), 1675 (s), 1621 (m), 1490 (m), 1356 (m), 1291 (m), 1193 (s), 1151 (m), 1080 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{29}H_{29}NO_3Na^+$: 462.2040 $[M+Na]^+$
found: 462.2035 $[M+Na]^+$.

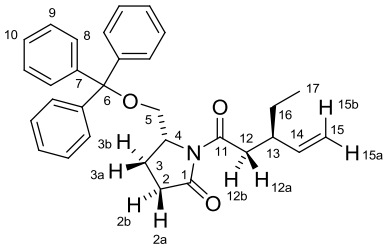
(5*R*)-1-[(3*R*)-3-ethylpent-4-enoyl]-5-[(triphenylmethoxy)methyl]pyrrolidin-2-one (238)



237 **238**

To a suspension of copper(I) bromide dimethyl sulfide complex (9.40 g, 45.7 mmol, 1.5 eq) and dimethyl sulfide (135 mL, 1.83 mol, 60 eq) in THF (770 mL) was added activated molecular sieve (12 g, pellets, 3Å), and the resulting mixture was cooled to –45 °C. A solution of vinylmagnesium bromide in THF (1.0 M, 91.5 mL, 91.5 mmol, 3.0 eq) was added dropwise and the solution stirred at –45 °C for 20 min. Then, a solution of imide **237** (13.4 g, 30.5 mmol, 1.0 eq) in THF (130 mL) was added *via* cannula, and the reaction mixture was stirred at –45 °C for an additional 60 min. The reaction was quenched with aq. NH_4Cl (300 mL of a saturated solution), warmed to room temperature and diluted with water (200 mL). The mixture was extracted with EtOAc (3 x 500 mL), and the combined organic fractions were divided into two parts. Each part (*ca.* 750 mL) was washed with water (2 x 500 mL) and brine (500 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 8:1] afforded alkene **238** (12.1 g, 25.9 mmol, 85%) as a white solid.

Alkene 238:



238

R_f = 0.31 [PE:EtOAc 5:1]

$[\alpha]_D^{24}$ = +64.7 (*c* = 1.0, CH_2Cl_2).

mp: 108 – 109 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.38 – 7.33 (m, 6H, 6 x H-8), 7.32 – 7.19 (m, 9H, 6 x H-9, 3 x H-10), 5.67 (ddd, *J* = 17.2, 10.2, 8.4 Hz, 1H, H-14), 5.05 – 4.93 (m, 2H, H-15a, H-15b), 4.51 – 4.42 (m, 1H, H-4), 3.52 (dd, *J* = 9.7, 4.1 Hz, 1H, H-5a or H-5b), 3.16 (dd, *J* = 9.7, 2.7 Hz, 1H, H-5a or H-5b), 3.08 – 2.83 (m, 3H, H-2a or H-2b, H-12a, H-12b), 2.57 – 2.39 (m, 2H, H-2a or H-2b, H-13), 2.14 – 1.85 (m, 2H, H-3a, H-3b), 1.57 – 1.23 (m, 2H, H-16a, H-16b), 0.87 (dd, *J* = 7.4, 7.4 Hz, 3H, 3 x H-17) ppm.

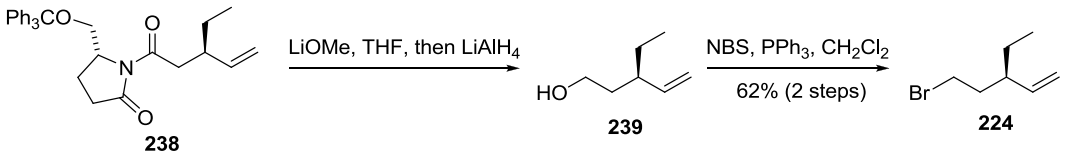
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 176.33 (C-1), 172.87 (C-11), 143.83 (3 x C-7), 141.50 (C-14), 128.71 (6 x C-8), 128.03 (6 x C-9), 127.28 (3 x C-10), 114.97 (C-15), 87.17 (C-6), 64.06 (C-5),

56.87 (C-4), 42.08 (C-12), 41.34 (C-13), 33.38 (C-2), 27.53 (C-16), 21.46 (C-3), 11.67 (C-17) ppm.

IR (ATR): $\tilde{\nu}$ = 2959 (w), 2876 (w), 1733 (s), 1691 (s), 1489 (m), 1370 (m), 1280 (m), 1219 (m), 1198 (m), 1074 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{31}H_{33}NO_3Na^+$: 490.2353 $[M+Na]^+$
found: 462.2348 $[M+Na]^+$.

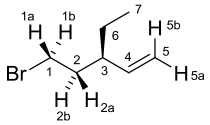
(3*R*)-5-bromo-3-ethylpent-1-ene (224) and (3*R*)-3-ethylpent-4-en-1-ol (239)



A solution of methanol (3.12 mL, 77.0 mmol, 9.0 eq) in THF (2 mL) was cooled to 0 °C and a solution of *n*-butyllithium in hexanes (2.35 M, 21.8 mL, 51.3 mmol, 6.0 eq) was added carefully. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 15 min. A solution of alkene **238** (4.00 g, 8.55 mmol, 1.0 eq) in THF (8 mL) was added *via* cannula, and the reaction mixture was stirred at room temperature for 20 h. Then, the solution was cooled to 0 °C and lithium aluminum hydride (973 mg, 25.7 mmol, 3.0 eq) was added. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred at this temperature for an additional 5.5 h. The reaction was quenched by adding carefully aq. Rochelle salt (30 mL of a saturated solution), diluted with water (30 mL) and stirred at room temperature for 1 h. The mixture was extracted with Et_2O (3 x 20 mL), and the combined organic fractions were washed with brine (20 mL), then dried ($MgSO_4$) and concentrated to a volume of *ca.* 20 mL by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 45→80 °C oil bath temperature). The distillation residue was subjected to flash column chromatography [*n*-pentane:Et_2O 7:1] and the resulting fraction were concentrated by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 50 °C oil bath temperature) to yield a mixture of volatile alcohol **239**, Et_2O and *n*-pentane (1.76 g, 1:2:0.4, as determined by ^{1}H-NMR spectroscopy, 7.71 mmol of **239**, 90%). The mixture was diluted with CH_2Cl_2 (10 mL), then triphenylphosphine (2.70 g, 10.3 mmol, 1.2 eq) was added and the solution cooled to 0 °C. *N*-bromosuccinimide (1.83 g, 10.3 mmol, 1.2 eq) was added in one portion and the resulting mixture stirred at 0 °C for 15 min. The reaction was quenched with water (20 mL) and the mixture extracted with Et_2O (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), then dried ($MgSO_4$) and concentrated to a volume of *ca.* 15 mL by removing the

solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 45 °C oil bath temperature). The distillation residue was subjected to flash column chromatography [*n*-pentane] and the product containing fractions were concentrated by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 50→80 °C oil bath temperature) to yield a mixture of volatile bromide **224** and *n*-pentane (1.13 g, 2:1, as determined by ^{1}H-NMR spectroscopy, 5.33 mmol of **224**, 62% over 2 steps) as a colorless liquid. A stock solution of bromide **224** in THF (0.36 M) was prepared and stored over molecular sieve (pellets, 3Å).

Bromide 224:



224

R_f = 0.80 [*n*-pentane].

$[\alpha]_D^{24}$ = –46.0 (*c* = 0.45, *n*-pentane).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.52 – 5.41 (m, 1H, H-4), 5.09 – 5.02 (m, 2H, H-5a, H-5b), 3.48 – 3.41 (m, 1H, H-1a or H-1b), 3.33 (ddd, *J* = 9.8, 8.3, 7.3 Hz, 1H, H-1a or H-1b), 2.16 – 2.05 (m, 1H, H-3), 1.99 – 1.89 (m, 1H, H-2a or H-2b), 1.82 – 1.71 (m, 1H, H-2a or H-2b), 1.48 – 1.37 (m, 1H, H-6a or H-6b), 1.36 – 1.23 (m, 1H, H-6a or H-6b), 0.88 (dd, *J* = 7.4, 7.4 Hz, 3H, 3 x H-7) ppm.

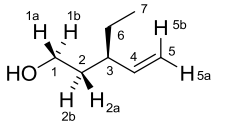
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.12 (C-4), 116.17 (C-5), 44.57 (C-3), 37.63 (C-2), 32.19 (C-1), 27.69 (C-6), 11.64 (C-7) ppm.

IR (ATR): $\tilde{\nu}$ = 3078 (w), 2964 (m), 1641 (w), 1461 (w), 1252 (m), 1100 (w), 996 (m), 915 (s), 756 (w), 676 (w) cm^{-1}.

HRMS (EI): calcd. for $C_7H_{13}Br^+$: 176.0195 $[M]^+$
found: 176.0189 $[M]^+$.

Alcohol 239:

For the purpose of full characterization of volatile alcohol **239**, an analytical sample was concentrated *in vacuo*.



239

R_f = 0.70 [PE: EtOAc 3:1].

$[\alpha]_D^{23}$ = –11.1 (*c* = 0.50, Et_2O).

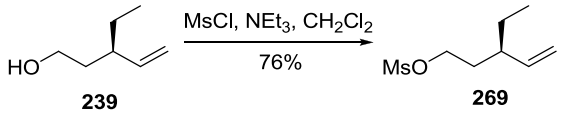
^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 5.63 – 5.52 (m, 1H, H-4), 5.04 – 4.96 (m, 2H, H-5a, H-5b), 3.67 – 3.53 (m, 2H, H-1a, H-1b), 2.08 – 1.97 (m, 1H, H-3), 1.70 – 1.60 (m, 1H, H-2a or H-2b), 1.52 – 1.39 (m, 2H, H-2a or H-2b, H-6a or H-6b), 1.32 – 1.23 (m, 1H, H-6a or H-6b), 0.86 (dd, *J* = 7.4, 7.4 Hz, 3H, 3 x H-7) ppm.

^{13}C-NMR (100 MHz, CD_2Cl_2): δ = 143.25 (C-4), 114.90 (C-5), 61.45 (C-1), 43.18 (C-3), 38.00 (C-2), 28.27 (C-6), 11.72 (C-7) ppm.

IR (ATR): $\tilde{\nu}$ = 3319 (m), 2960 (m), 2924 (m), 1640 (w), 1463 (w), 1420 (w), 1379 (w), 1057 (s), 994 (s) cm^{-1}.

HRMS (EI): calcd. for $C_7H_{14}O^+$: 114.1045 $[M]^+$
found: 114.1039 $[M]^+$.

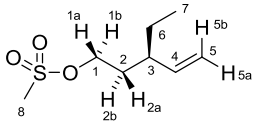
(3*R*)-3-ethylpent-4-en-1-yl methanesulfonate (269)



239 **269**

A solution of alcohol **239** (25.8 mg, 0.226 mmol, 1.0 eq) and triethylamine (62.7 µL, 0.452 mmol, 2.0 eq) in CH_2Cl_2 (1 mL) was cooled to 0 °C and methanesulfonyl chloride (19.2 µL, 0.249 mmol, 1.1 eq) was added dropwise. The resulting solution was stirred at 0 °C for 2 h. The reaction mixture was then quenched with aq. NH_4Cl (5 mL of a saturated solution) and extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [*n*-pentane:Et_2O 7:1] afforded mesylate **269** (33.0 mg, 0.172 mmol, 76%) as a colorless liquid.

Mesylate 269:



269

R_f = 0.39 [PE:EtOAc 3:1].

$[\alpha]_D^{22}$ = –12.4 (*c* = 0.88, *n*-pentane).

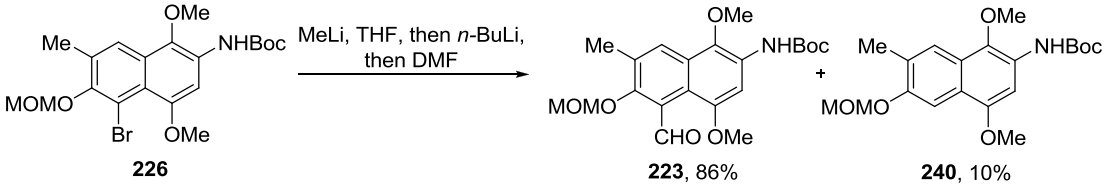
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.57 – 5.42 (m, 1H, H-4), 5.12 – 4.98 (m, 2H, H-5a, H-5b), 4.30 – 4.12 (m, 2H, H-1a, H-1b), 2.99 (s, 3H, 3 x H-8), 2.13 – 1.99 (m, 1H, H-3), 1.96 – 1.82 (m, 1H, H-2a or H-2b), 1.69 – 1.55 (m, 1H, H-2a or H-2b), 1.52 – 1.22 (m, 2H, H-6a, H-6b), 0.87 (ddd, *J* = 7.3, 7.3, 1.3 Hz, 3H, 3 x H-7) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.05 (C-4), 116.35 (C-5), 68.69 (C-1), 42.22 (C-3), 37.44 (C-8), 33.80 (C-2), 27.89 (C-6), 11.55 (C-7) ppm.

IR (ATR): $\tilde{\nu}$ = 2964 (w), 2934 (w), 1739 (w), 1464 (w), 1350 (s), 1171 (s), 956 (s), 916 (s), 828 (m), 677 (w) cm^{-1}.

HRMS: not detected with EI or ESI methods.

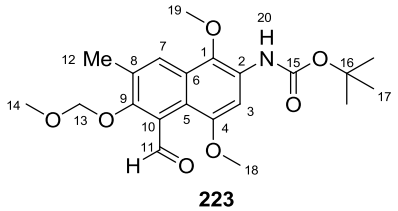
***Tert*-butyl *N*-[5-formyl-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-yl] carbamate (223) and *tert*-butyl *N*-[1,4-dimethoxy-6-(methoxymethoxy)-7-methyl-naphthalen-2-yl]carbamate (240)**



226 **223**, 86% **240**, 10%

A solution of bromide **226** (250 mg, 0.548 mmol, 1.0 eq) in THF (12 mL) was cooled to −78 °C, and a solution of methyllithium in Et_2O (1.6 M, 688 µL, 1.10 mmol, 2.0 eq) was added dropwise. The resulting mixture was stirred at −78 °C for 30 min, and then a solution of *n*-butyllithium in hexanes (2.35 M, 515 µL, 1.21 mmol, 2.2 eq) was added. After additional 30 min at −78 °C, dimethylformamide (424 µL, 5.48 mmol, 10 eq) was added and the reaction mixture stirred further at −78 °C for 30 min, then allowed to warm to room temperature within 10 min. The reaction was quenched with aq. NH_4Cl (10 mL of a saturated solution) and the mixture extracted with Et_2O (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→6:1] afforded aldehyde **223** (190 mg, 0.469 mmol, 86%) as a yellowish solid and protodemetallated naphthalene **240** (21.3 mg, 56.4 µmol, 10%) as a white solid.

Naphthaldehyde 223:



223

R_f = 0.40 [PE:EtOAc 3:1].

mp: 107 – 108 °C.

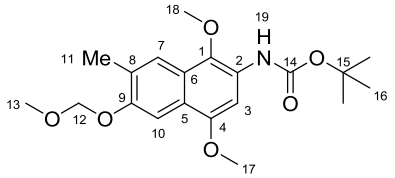
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 10.64 (s, 1H, H-11), 7.83 (br s, 1H, H-20), 7.80 (s, 1H, H-7), 7.14 (br s, 1H, H-3), 5.06 (s, 2H, 2 x H-13), 3.94 (s, 3H, 3 x H-18), 3.84 (s, 3H, 3 x H-19), 3.58 (s, 3H, 3 x H-14), 2.48 (s, 3H, 3 x H-12), 1.56 (s, 9H, 9 x H-17) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 194.34 (C-11), 152.93 (C-15), 151.95 (C-4), 151.14 (C-9), 135.64 (C-1), 133.18 (C-8), 128.74 (C-10), 128.43 (C-3), 125.52 (C-6), 124.79 (C-7), 119.08 (C-5), 102.22 (C-13), 99.27 (C-2), 81.07 (C-16), 61.65 (C-19), 57.72 (C-14), 56.34 (C-18), 28.54 (3 x C-17), 17.93 (C-12) ppm.

IR (ATR): $\tilde{\nu}$ = 3301 (w), 2941 (w), 1722 (m), 1694 (m), 1625 (w), 1364 (w), 1231 (m), 1149 (s), 966 (s), 876 (w), 706 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{27}NNaO_7^+$: 428.1680 $[M+Na]^+$
found: 428.1679 $[M+Na]^+$.

Naphthalene 240:



240

R_f = 0.62 [PE: EtOAc 3:1].

mp: 109 – 111 °C.

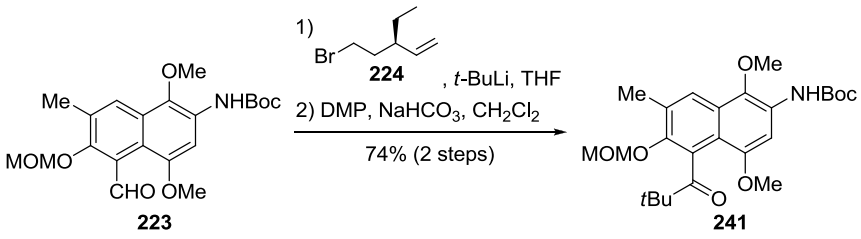
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.70 (br s, 1H, H-19), 7.67 (s, 1H, H-7), 7.64 (s, 1H, H-10), 7.10 (br s, 1H, H-3), 5.33 (s, 2H, 2 x H-12), 3.99 (s, 3H, 3 x H-17), 3.85 (s, 3H, 3 x H-18), 3.53 (s, 3H, 3 x H-13), 2.42 (s, 3H, 3 x H-11), 1.56 (s, 9H, 9 x H-16) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 152.99 (C-14), 152.87 (C-9), 151.27 (C-4), 135.37 (C-1), 129.59 (C-8), 126.27 (C-3), 123.31 (C-6), 121.99 (C-7), 121.83 (C-5), 103.51 (C-10), 97.30 (C-3), 94.41 (C-12), 80.44 (C-15), 61.39 (C-18), 56.19 (C-13), 55.68 (C-17), 28.41 (C-16), 17.25 (C-11) ppm.

IR (ATR): $\tilde{\nu}$ = 3299 (m), 2974 (m), 2924 (m), 1725 (m), 1613 (m), 1502 (m), 1461 (m), 1410 (w), 1331 (m), 1216 (m), 1151 (s), 1045 (m), 987 (s), 880 (w), 726 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_{20}H_{27}NNaO_6^+$: 400.1731 $[M+Na]^+$
found: 400.1730 $[M+Na]^+$.

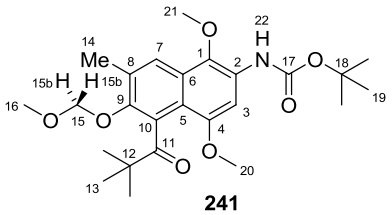
***Tert*-butyl *N*-[5-(2,2-dimethylpropanoyl)-1,4-dimethoxy-6-(methoxymethoxy)-7-methyl-naphthalen-2-yl]carbamate (241)**



A solution of bromide **224** in THF (0.36 M, 303 µL, 0.109 mmol, 2.2 eq) was diluted with THF (0.5 mL) and cooled to −78 °C. A solution of *t*-butyllithium in pentane (1.7 M, 131 µL, 0.222 mmol, 4.5 eq) was added dropwise and the resulting mixture stirred at −78 °C for 15 min. A solution of aldehyde **223** (20.0 mg, 49.3 µmol, 1.0 eq) in THF (1.5 mL) was added *via* cannula and the reaction mixture stirred at −78 °C for an additional 20 min. The reaction mixture was quenched with aq. NH_4Cl (5 mL of a saturated solution), allowed to warm to room temperature, and then extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was immediately dissolved in CH_2Cl_2 (2 mL) and the resulting solution cooled to 0 °C. Solid $NaHCO_3$ (62.1 mg, 0.740 mmol, 15 eq) was added followed by Dess-Martin periodinane

(41.8 mg, 98.6 µmol, 2.0 eq). The resulting suspension was stirred at 0 °C for 10 min, was then allowed to warm to room temperature and stirred at this temperature for an additional 70 min. The reaction was quenched with a mixture (1:1, 5 mL) of aq. $NaHCO_3$ (saturated solution) and aq. $Na_2S_2O_3$ (saturated solution) and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1→6:1] afforded ketone **241** (16.8 mg, 36.4 µmol, 74% over two steps) as a thick, yellow oil.

Naphthalene building block 241:



241

R_f = 0.37 [PE:EtOAc 3:1].

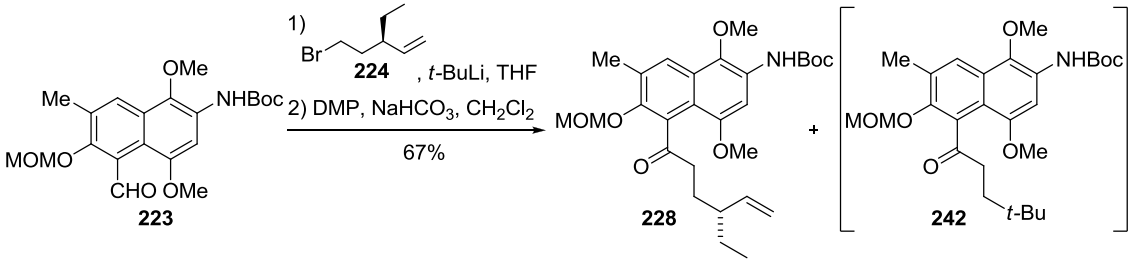
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.76 (br s, 1H, H-22), 7.72 (d, *J* = 1.0, 1H, H-7), 7.13 (br s, 1H, H-3), 4.92 – 4.89 (m, 2H, H-15a, H-15b), 3.86 (s, 3H, 3 x H-20), 3.84 (s, 3H, 3 x H-21), 3.56 (s, 3H, 3 x H-16), 2.51 (d, *J* = 0.9 Hz, 3H, 3 x H-14), 1.56 (s, 9H, 9 x H-19), 1.18 (s, 9H, 9 x H-13) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 214.06 (C-11), 152.97 (C-17), 151.25 (C-4), 149.36 (C-9), 135.58 (C-1), 133.17 (C-8), 129.80 (C-6 or C-10), 128.06 (C-3), 125.48 (C-6 or C-10), 122.94 (C-7), 119.11 (C-5), 101.80 (C-15), 98.88 (C-2), 80.97 (C-18), 61.56 (C-21), 57.91 (C-16), 56.26 (C-20), 46.03 (C-12), 28.55 (3 x C-19), 27.83 (3 x C-13), 17.98 (C-14) ppm.

IR (ATR): $\tilde{\nu}$ = 2976 (w), 1726 (m), 1626 (m), 1495 (m), 1367 (m), 1230 (m), 1153 (s), 1046 (m), 925 (m), 875 (w), 754 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{25}H_{36}NO_7^+$: 462.2486 $[M+H]^+$
found: 462.2486 $[M+H]^+$.

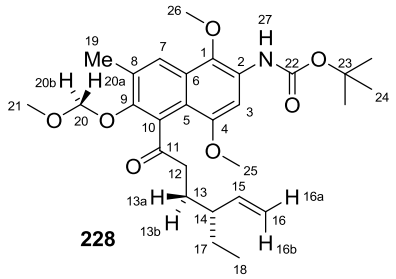
***Tert*-butyl *N*-{5-[(4*R*)-4-ethylhex-5-enoyl]-1,4-dimethoxy-6-(methoxymethoxy)-7-methyl-naphthalen-2-yl}carbamate (228) and *tert*-butyl *N*-[5-(4,4-dimethylpentanoyl)-1,4-dimethoxy-6-(methoxymethoxy)-7-methyl-naphthalen-2-yl]carbamate (242)**



A solution of bromide **224** in THF (0.36 M, 494 µL, 0.178 mmol, 5.0 eq) was diluted with THF (0.5 mL) and cooled to −78 °C. A solution of *t*-butyllithium in pentane (1.7 M, 209 µL,

0.355 mmol, 10 eq) was added dropwise and the resulting mixture stirred at −78 °C for 30 min. The reaction mixture was warmed to 0 °C and stirred at this temperature for an additional 30 min. After cooling to −78 °C, a solution of aldehyde **223** (14.4 mg, 35.5 µmol, 1.0 eq) in THF (1.5 mL) was added *via* cannula and the reaction mixture stirred at −78 °C for an additional 30 min. The reaction mixture was quenched with aq. NH_4Cl (5 mL of a saturated solution), allowed to warm to room temperature and then extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was immediately dissolved in CH_2Cl_2 (2 mL), and $NaHCO_3$ (44.7 mg, 0.533 mmol, 15 eq) was added followed by Dess-Martin periodinane (30.1 mg, 71.0 µmol, 2.0 eq). The resulting suspension was stirred at room temperature for 60 min. Then, the reaction was quenched with a mixture (1:1, 5 mL) of aq. $NaHCO_3$ (saturated solution) and aq. $Na_2S_2O_3$ (saturated solution), and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 9:1] afforded ketone **228** (11.7 mg, 23.3 µmol, 67% over two steps) as a white solid consisting of two atropisomers (d.r. 1:1, as determined by ^{1}H-NMR spectroscopy) as an inseparable mixture.

Naphthalene building block 228:



228

R_f = 0.44 [PE:EtOAc 3:1].

^{1}H-NMR (400 MHz, $CDCl_3$) (mixture of isomers, both isomers quoted, one isomer primed): δ = 7.76 (s, 2H, H-27, H-27'), 7.72 – 7.70 (m, 2H, H-7, H-7'), 7.13 (br s, 2H, H-3, H-3'), 5.58 – 5.44 (m, 2H, H-15, H-15'), 5.00 – 4.89 (m, 8H, H-16a, H-16b, H-16a', H-16b', H-20a, H-20b, H-20a', H-20b'), 3.87 (s, 3H, 3 x H-25 or 3 x H-25'), 3.86 (s, 3H, 3 x H-25 or 3 x H-25'), 3.83 (br s, 6H, 3 x H-26, 3 x H-26'), 3.57 (s, 3H, 3 x H-21 or 3 x H-21'), 3.56 (s, 3H, 3 x H-21 or 3 x H-21'), 2.97 – 2.86 (m, 1H, H-12a or H-12b), 2.84 – 2.74 (m, 1H, H-12a' or H-12b'), 2.72 – 2.62 (m, 1H, H-12a' or H-12b'), 2.61 – 2.51 (m, 1H, H-12a or H-12b), 2.50 – 2.47 (m, 6H, 3 x H-19, 3 x H-19'), 2.03 – 1.93 (m, 1H, H-13a or H-13b), 1.93 – 1.83 (m, 2H, H-14, H-14'), 1.83 – 1.73 (m, 2H, H-13a', H-13b'), 1.66 – 1.58 (m, 1H, H-13a or H-13b), 1.55 (br s, 18H, 9 x H-24, 9 x H-24'), 1.50 – 1.38 (m, 2H, H-17a or H-17b, H-17a' or H-17b'), 1.38 – 1.24 (m, 2H, H-17a or H-17b, H-17a' or H-17b'), 0.89 – 0.84 (m, 6H, 3 x H-18, 3 x H-18') ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of isomers, both isomers quoted, one isomer primed): δ = 207.03 (C-11 or C-11'), 206.97 (C-11 or C-11'), 152.95 (C-22 and C-22'), 151.29 (C-4 or C-4'), 151.28 (C-4 or C-4'), 149.09 (C-9 or C-9'), 149.01 (C-9 or C-9'), 142.60 (C-15 or C-15'), 142.56 (C-15 or C-15'), 135.62 (C-1 or C-1'), 135.58 (C-1 or C-1'), 132.93 (C-8 or C-8'), 132.91 (C-8 or C-8'), 131.63 (C-3 or C-6 or C-10 or C-3' or C-6' or C-10'), 131.58 (C-3 or C-6 or C-10

or C-3' or C-6' or C-10'), 128.19 (C-3 and C-3', or C-6 and C-6', or C-10 and C-10'), 125.72 (C-3 and C-3', or C-6 and C-6', or C-10 and C-10'), 123.05 (C-7 or C-7'), 123.02 (C-7 or C-7'), 118.19 (C-5 or C-5'), 118.15 (C-5 or C-5'), 115.11 (C-16 or C-16'), 114.99 (C-16 or C-16'), 101.68 (C-20 or C-20'), 101.59 (C-20 or C-20'), 98.97 (C-2 or C-2'), 98.85 (C-2 or C-2'), 80.98 (C-23 and C-23'), 61.56 (C-26 and C-26'), 57.75 (C-21 and C-21'), 56.44 (C-25 or C-25'), 56.38 (C-25 or C-25'), 45.45 (C-14 or C-14'), 45.42 (C-14 or C-14'), 43.24 (C-12 or C-12'), 43.16 (C-12 or C-12'), 28.52 (3 x C-24 and 3 x C-24'), 28.24 (C-13 or C-13'), 28.21 (C-13 or C-13'), 27.94 (C-17 or C-17'), 27.73 (C-17 or C-17'), 17.80 (C-19 or C-19'), 17.79 (C-19 or C-19'), 11.78 (C-18 or C-18'), 11.76 (C-18 or C-18') ppm.

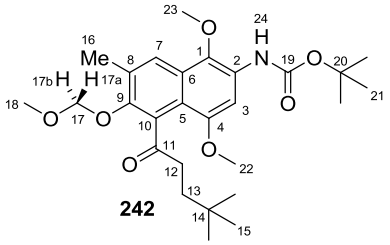
IR (ATR): $\tilde{\nu}$ = 3431 (w), 2955 (m), 1707 (m), 1626 (m), 1605 (w), 1495 (m), 1456 (m), 1366 (m), 1229 (m), 1146 (s), 1046 (m), 986 (m), 930 (m), 880 (w), 753 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{28}H_{40}NO_7^+$: 502.2799 $[M+H]^+$
found: 502.2796 $[M+H]^+$.

Ketone 242:

Side product **242** was obtained as a yellowish solid when 15 eq of *tert*-butyllithium and 5.0 eq of bromide **224** was used. Compound **242** could be separated from the product **224** by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), gradient, water (A)/MeCN (B); 0 min 80% B, 2 min 80% B, 40 min 100% B; flow rate 15 mL/min; detection 255 nm: t_R(**242**) = 27.0 min, t_R(**228**) = 28.5 min].

R_f = 0.44 [PE:EtOAc 3:1].



mp: 44 – 45 °C.

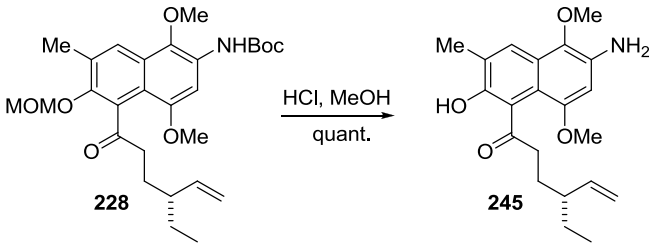
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (br s, 1H, H-24), 7.72 (d, *J* = 1.0 Hz, 1H, H-7), 7.14 (br s, 1H, H-3), 5.00 (d, *J* = 5.5 Hz, 1H, H-17a or H-17b), 4.93 (d, *J* = 5.5 Hz, 1H, H-17a or H-17b), 3.88 (s, 3H, 3 x H-22), 3.84 (s, 3H, 3 x H-23), 3.57 (s, 3H, 3 x H-18), 2.88 (ddd, *J* = 18.0, 12.3, 4.0 Hz, 1H, H-12a or H-12b), 2.67 – 2.56 (m, 1H, H-12a or H-12b), 2.49 (d, *J* = 0.9 Hz, 3H, 3 x H-16), 1.83 – 1.74 (m, 1H, H-13a or H-13b), 1.64 – 1.56 (m, 1H, H-13a or H-13b), 1.55 (s, 9H, 9 x H-21), 0.90 (s, 9H, 9 x H-15) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.18 (C-11), 152.95 (C-19), 151.26 (C-4), 148.94 (C-9), 135.60 (C-1), 132.91 (C-8), 131.75 (C-3 or C-6 or C-10), 128.21 (C-3 or C-6 or C-10), 125.74 (C-3 or C-6 or C-10), 123.05 (C-7), 118.15 (C-5), 101.58 (C-17), 98.83 (C-2), 80.98 (C-20), 61.56 (C-23), 57.76 (C-18), 56.41 (C-22), 40.98 (C-12), 37.13 (C-13), 29.86 (C-14), 29.40 (3 x C-15), 28.52 (3 x C-21), 17.79 (C-16) ppm.

IR (ATR): $\tilde{\nu}$ = 2954 (w), 1708 (br m), 1626 (m), 1495 (m), 1366 (m), 1229 (m), 1146 (s), 1046 (m), 985 (m), 930 (m), 880 (w), 759 (w) cm^{-1}.

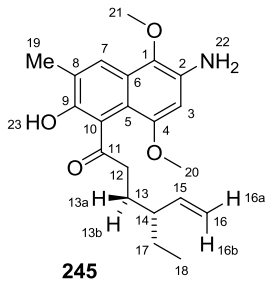
HRMS (ESI): calcd. for $C_{27}H_{39}NNaO_7^+$: 512.2619 $[M+Na]^+$
found: 512.2617 $[M+Na]^+$.

1-(6-Amino-2-hydroxy-5,8-dimethoxy-3-methylnaphthalen-1-yl)-4-ethylhex-5-en-1-one (245)



To a solution of protected aminonaphthalene **228** (21.7 mg, 43.3 µmol, 1.0 eq) in MeOH (1 mL) was added dropwise a solution of HCl in MeOH (1 mL), prepared by bubbling HCl gas (NaCl, conc. H_2SO_4) through MeOH for 30 min, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with aq. $NaHCO_3$ (10 mL of a saturated solution) and the mixture extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 3:1] afforded aminonaphthalene **245** (15.5 mg, 43.3 µmol, quant.) as a yellow oil.

Aminonaphthalene 245:



245

R_f = 0.59 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = +7.1 (c = 0.20, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.70 (d, J = 1.0 Hz, 1H, H-7), 6.39 (s, 1H, H-3), 5.42 (ddd, J = 17.2, 10.1, 8.8 Hz, 1H, H-15), 4.88 (dd, J = 10.2, 1.8 Hz, 1H, H-16a), 4.83 – 4.73 (m, 1H, H-16b), 3.84 (s, 3H, 3 x H-21), 3.80 (s, 3H, 3 x H-20), 3.52 – 2.43 (br m, 2H, H-12a, H-12b), 2.38 (d, J = 1.0 Hz, 3H, 3 x H-19), 1.76 (br s, 2H, H-13a or H-13b, H-14), 1.58 (br s, 1H, H-13a or H-13b), 1.40 – 1.32 (m, 1H, H-17a or 17b), 1.27 – 1.19 (m, 1H, H-17a or 17b), 0.81 (dd, J = 7.4, 7.4 Hz, 3H, 3 x H-18).

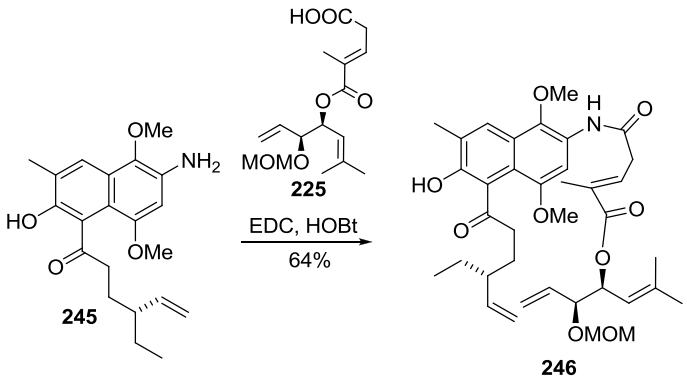
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 210.31 (C-11), 151.74 (C-9), 150.85 (C-4), 142.35 (C-15), 134.27 (C-1), 128.72 (C-8), 125.20 (C-7), 124.38 (C-2 or C-6 or C-10), 116.68 (C-2 or C-6 or C-10), 116.34 (C-5), 115.06 (C-16), 99.53 (C-3), 60.47 (C-21), 55.99 (C-22), 45.79 (C-14),

42.81 (C-12), 30.33 (C-13), 27.83 (C-17), 17.10 (C-19), 11.75 (C-18), one aromatic carbon (C-2 or C-6 or C-10) not observed.

IR (ATR): $\tilde{\nu}$ = 3362 (br w), 2927 (m), 1688 (w), 1626 (s), 1442 (w), 1391 (m), 1228 (s), 992 (m), 753 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{28}NO_4^+$: 358.2013 $[M+H]^+$
found: 358.2008 $[M+H]^+$.

(3*S*,4*S*)-3-(methoxymethoxy)-6-methylhepta-1,5-dien-4-yl (2*E*)-4-({5-[(4*R*)-4-ethylhex-5-enoyl]-6-hydroxy-1,4-dimethoxy-7-methylnaphthalen-2-yl}carbamoyl)-2-methylbut-2-enoate (246)



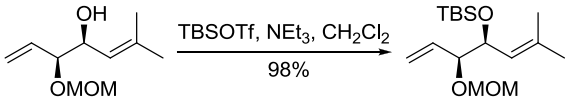
To a solution of carboxylic acid **225** (12.5 mg, 40.1 µmol, 1.2 eq) in DMF (0.35 mL) was added 1-hydroxybenzotriazole hydrate (86 wt%, 10.4 mg, 66.8 µmol, 2.0 eq), and the mixture was cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide (11.8 µL, 66.8 µmol, 2.0 eq) was added followed by a solution of aminonaphthalene **245** (11.9 mg, 33.4 µmol, 1.0 eq) in DMF (0.50 mL). The reaction mixture was stirred at 0 °C for 1h and was then allowed to warm to room temperature. After stirring at this temperature for an additional 19 h, the reaction was diluted with Et_2O (10 mL). The organic phase was washed with aq. LiCl (10 wt%, 3 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 3:1] afforded naphthalene **246** (14.0 mg, 21.5 µmol, 64%) as a yellow oil consisting of a mixture of isomers.

Aminonaphthalene 246:

R_f = 0.83 [PE:EtOAc 1:1].

HRMS (ESI): calcd. for $C_{37}H_{49}NNaO_9^+$: 674.3300 $[M+Na]^+$
found: 674.3293 $[M+Na]^+$.

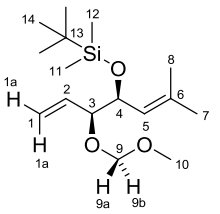
***Tert*-butyl[(2*S*,3*S*)-3-(methoxymethoxy)-2-(2-methylprop-1-en-1-yl)pent-4-en-1-yl]dimethylsilane (250)**



247 **250**

To a solution of alcohol **247** (184 mg, 0.988 mmol, 1.0 eq) in CH_2Cl_2 (8 mL) was added triethylamine (219 µL, 1.58 mmol, 1.6 eq), followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (340 µL, 1.48 mmol, 1.5 eq), and the resulting solution was stirred at room temperature for 5 min. The reaction mixture was quenched with aq. NH_4Cl (10 mL of a saturated solution) and extracted with Et_2O (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 49:1] afforded *tert*-butyldimethylsilyl ether **250** (291 mg, 0.968 mmol, 98%) as a colorless liquid.

TBS ether 250:



250

R_f = 0.46 [PE:EtOAc 9:1].

$[\alpha]_D^{21}$ = +25.0 (*c* = 1.1, $CHCl_3$).

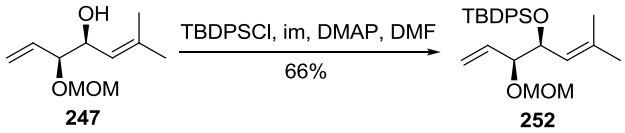
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.75 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H, H-2), 5.29 – 5.16 (m, 2H, H-1a, H-1b), 5.16 – 5.10 (m, 1H, H-5), 4.70 – 4.64 (m, 2H, H-9a, H-9b), 4.35 (dd, *J* = 9.2, 6.1 Hz, 1H, H-4), 3.99 – 3.92 (m, 1H, H-3), 3.36 (s, 3H, 3 x H-10), 1.70 (d, *J* = 1.4 Hz, 3H, 3 x H-7 or 3 x H-8), 1.63 (d, *J* = 1.3 Hz, 3H, 3 x H-7 or 3 x H-8), 0.87 (s, 9H, 9 x H-14), 0.04 (s, 3H, 3 x H-11 or 3 x H-12), 0.01 (s, 3H, 3 x H-11 or 3 x H-12) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 135.34 (C-2), 133.81 (C-6), 125.48 (C-5), 117.55 (C-1), 94.96 (C-9), 81.01 (C-3), 72.38 (C-4), 55.55 (C-10), 26.01 (3 x C-14), 25.84 (C-7 or C-8), 18.76 (C-7 or C-8), 18.38 (C-13), –4.24 (C-11 or C-12), –4.59 (C-11 or C-12) ppm.

IR (ATR): $\tilde{\nu}$ = 2927 (m), 2856 (m), 1677 (w), 1472 (w), 1249 (m), 1037 (br s), 921 (m), 831 (s), 774 (s), 667 (m) cm^{-1}.

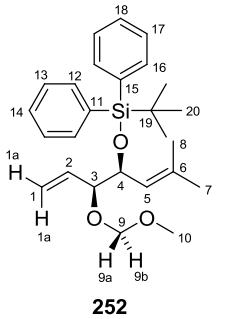
HRMS (ESI): calcd. for $C_{16}H_{32}NaO_3Si^+$: 323.2013 $[M+Na]^+$
found: 323.2015 $[M+Na]^+$.

***Tert*-butyl[(2*S*,3*S*)-3-(methoxymethoxy)-2-(2-methylprop-1-en-1-yl)pent-4-en-1-yl]diphenylsilane (252)**



To a solution of alcohol **247** (160 mg, 0.859 mmol, 1.0 eq), imidazole (93.3 mg, 1.37 mmol, 1.6 eq) and 4-(dimethylamino)pyridine (10.5 mg, 85.9 µmol, 10 mol%) in DMF (6 mL) was added *tert*-butyldiphenylsilyl chloride (335 µL, 1.29 mmol, 1.5 eq), and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (30 mL) and washed with aq. LiCl (10 wt%, 3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 99:1→49:1→19:1→4:1] afforded *tert*-butyldiphenylsilyl ether **252** (242 mg, 0.570 mmol, 66%) as a colorless oil, as well as remaining starting material **247** (20.1 mg, 0.108 mmol, 13%).

TBDPS ether 252:



R_f = 0.75 [PE:EtOAc 3:1].

$[\alpha]_D^{21}$ = +13.8 (*c* = 1.2, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.74 – 7.71 (m, 2H, 2 x H-12 or 2 x H-16), 7.68 – 7.66 (m, 2H, 2 x H-12 or 2 x H-16), 7.43 – 7.32 (m, 6H, 2 x H-13, H-14, 2 x H-17, H-18), 5.88 – 5.81 (m, 1H, H-2), 5.31 – 5.26 (m, 1H, H-1a), 5.25 – 5.22 (m, 1H, H-1b), 5.15 – 5.11 (m, 1H, H-5), 4.62 (dd, *J* = 6.6, 0.4 Hz, 1H, H-9a or H-9b), 4.56 (d, *J* = 6.6 Hz, 1H, H-9a or H-9b), 4.43 (dd, *J* = 9.4, 5.6 Hz, 1H, H-4), 4.07 (dd, *J* = 6.1, 6.1 Hz, 1H, H-3), 3.26 (s, 3H, 3 x H-10), 1.51 (d, *J* = 1.3 Hz, 3H, 3 x H-7 or 3 x H-8), 1.09 (d, *J* = 1.4 Hz, 3H, 3 x H-7 or 3 x H-8), 1.05 (s, 9H, 9 x H-20) ppm.

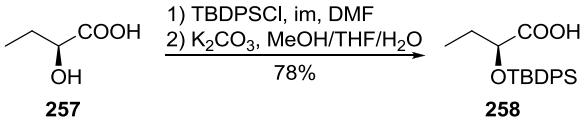
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 136.15 (2 x C-12 or 2 x C-16), 136.11 (2 x C-12 or 2 x C-16), 135.43 (C-6), 134.97 (C-2), 134.52 (C-11 or C-15), 134.31 (C-11 or C-15), 129.60 (C-14 or C-18), 129.42 (C-14 or C-18), 127.58 (2 x C-13 or 2 x C-17), 127.32 (2 x C-13 or 2 x C-17), 124.22 (C-5), 117.76 (C-1), 94.78 (C-9), 80.59 (C-3), 72.19 (C-4), 55.52 (C-10), 27.14 (3 x C-20), 25.87 (C-7 or C-8), 19.50 (C-19), 18.25 (C-7 or C-8) ppm.

IR (ATR): $\tilde{\nu}$ = 3072 (w), 2931 (m), 2858 (m), 1473 (w), 1428 (m), 1376 (w), 1150 (w), 1104 (m), 1034 (s), 920 (m), 822 (m), 798 (m), 739 (m), 700 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{26}H_{36}NaO_3Si^+$: 447.2326 $[M+Na]^+$
found: 447.2323 $[M+Na]^+$.

21.4. Experimental Data of Chapter IV

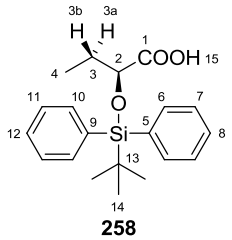
(2*S*)-2-(2,2-dimethyl-1,1-diphenylpropoxy)butanoic acid (258)



257 **258**

A solution of (*S*)-2-hydroxybutyric acid (**257**) (1.00 g, 9.61 mmol, 1.0 eq) in DMF (4 mL) was cooled to 0 °C and a solution of *tert*-butyldiphenylsilyl chloride (7.91 mL, 30.8 mmol, 3.2 eq) and imidazole (6.90 g, 101 mmol, 10.5 eq) in DMF (6 mL) was added dropwise. After complete addition, stirring was continued at room temperature for 21 h. The reaction was quenched with brine (100 mL) and the mixture extracted with PE:Et_2O (3:1, 5 x 50 mL). The combined organic fractions were washed with water (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in a mixture of MeOH and THF (3:2, 75 mL) and the solution cooled to 0 °C. A solution of K_2CO_3 (2.98 g, 21.6 mmol, 2.2 eq) in water (17 mL) was added dropwise. After complete addition, stirring was continued at room temperature for 17 h. The reaction was quenched with brine (100 mL), and the pH of the mixture was lowered to 1 by carefully adding conc. H_2SO_4. The mixture was extracted with PE:Et_2O (3:1, 4 x 100 mL) and the combined organic fractions were re-extracted with aq. NaOH (2 wt%, 4 x 100 mL). The combined basic aqueous fractions were cooled to 0 °C and the pH was lowered to 1 by carefully adding conc. H_2SO_4. The mixture was then extracted with CH_2Cl_2 (5 x 100 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford the protected alcohol **258** (2.56 g, 7.48 mmol, 78%) as white solid.

TBDPS ether 258:



258

R_f = 0.78 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = –14.0 (*c* = 1.8, $CHCl_3$).

mp: 56 °C.

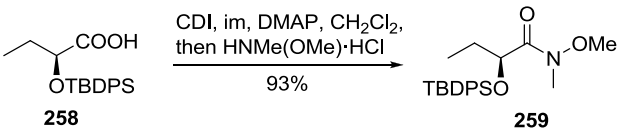
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68 – 7.60 (m, 4H, 2 x H-6, 2 x H-10), 7.49 – 7.43 (m, 2H, H-8, H-12), 7.43 – 7.36 (m, 4H, 2 x H-7, 2 x H-11), 4.31 (dd, *J* = 5.6, 4.2 Hz, 1H, H-2), 1.79 – 1.68 (m, 1H, H-3a or H-3b), 1.64 – 1.52 (m, 1H, H-3a or H-3b), 1.13 (s, 9H, 9 x H-14), 0.89 (t, *J* = 7.4, 3H, 3 x H-4) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.74 (C-1), 135.85 (2 x C-6 or 2 x C-10), 135.83 (2 x C-6 or 2 x C-10), 132.66 (C-5 or C-9), 132.12 (C-5 or C-9), 130.44 (C-8 or C-12), 130.43 (C-8 or C-12), 128.11 (2 x C-7 or 2 x C-11), 128.04 (2 x C-7 or 2 x C-11), 73.77 (C-2), 27.62 (C-3), 27.07 (3 x C-14), 19.45 (C-13), 8.24 (C-4).

IR (ATR): $\tilde{\nu}$ = 3226 (s), 2935 (s), 1760 (s), 1427 (m), 1092 (s), 1012 (m), 702 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{20}H_{25}O_3Si^+$: 341.1578 $[M–H]^–$
found: 341.1575 $[M–H]^–$.

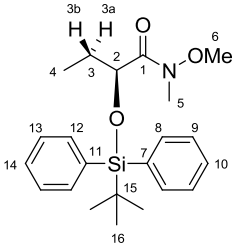
(2*S*)-2-(2,2-dimethyl-1,1-diphenylpropoxy)-*N*-methoxy-*N*-methylbutanamide (259)



258 **259**

A solution of acid **258** (2.46 g, 7.18 mmol, 1.0 eq) in CH_2Cl_2 (19 mL) was cooled to 0 °C and 1,1'-carbonyldiimidazole (2.33 g, 14.4 mmol, 2.0 eq) was added in one portion. The solution was allowed to warm to room temperature and stirred at this temperature for 25 h. The mixture was then cooled to 0 °C and *N*,*O*-dimethylhydroxylamine hydrochloride (1.40 g, 14.4 mmol, 2.0 eq), imidazole (980 mg, 14.4 mmol, 2.0 eq) and 4-(dimethylamino)pyridine (26.4 mg, 0.216 mmol, 3 mol%) were added. After warming to room temperature, the reaction mixture was stirred at this temperature for an additional 23 h. The mixture was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with aq. HCl (2 N, 2 x 100 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EA 19:1→9:1→5:1] afforded Weinreb amide **259** (2.57 g, 6.66 mmol, 93%) as a colorless solid.

Weinreb amide 259:



259

R_f = 0.83 [PE:EtOAc 1:1].

$[\alpha]_D^{21}$ = –0.7 (*c* = 1.7, $CHCl_3$).

mp: 69 °C.

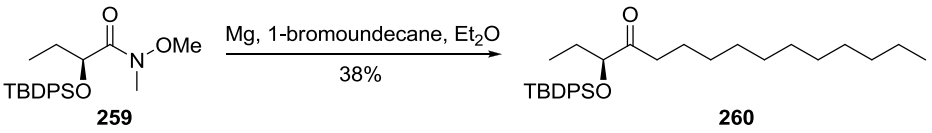
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.72 – 7.68 (m, 4H, 2 x H-8, 2 x H-12), 7.44 – 7.32 (m, 6H, 2 x H-9, H-10, 2 x H-13, H-14), 4.46 – 4.40 (m, 1H, H-2), 3.11 (br s, 3H, 3 x H-6), 2.99 (s, 3H, 3 x H-5), 1.79 – 1.69 (m, 2H, H-3a, H-3b), 1.09 (s, 9H, 9 x H-16), 0.91 (t, *J* = 7.5, 3H, 3 x H-4) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.52 (inferred from HMBC, C-1), 136.29 (2 x C-8 or 2 x C-12), 136.08 (2 x C-8 or 2 x C-12), 133.98 (H-7 or C-11), 133.67 (C-7 or C-11), 129.74 (C-10 or C-14), 129.69 (C-10 or C-14), 127.64 (2 x C-9 or 2 x C-13), 127.52 (2 x C-9 or 2 x C-13), 71.31 (inferred from HSQC, C-2), 60.69 (C-6), 32.35 (inferred from HSQC, C-5), 27.92 (C-3), 27.05 (C-16), 19.58 (C-15), 9.59 (C-4).

IR (ATR): $\tilde{\nu}$ = 2937 (m), 1668 (s), 1430 (w), 1111 (m), 704 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{22}H_{31}NNaO_3Si^+$: 408.1965 $[M+Na]^+$
found: 408.1964 $[M+Na]^+$.

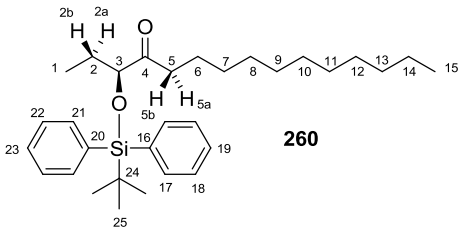
(3*S*)-3-(2,2-dimethyl-1,1-diphenylpropoxy)pentadecan-4-one (260)



259 **260**

Magnesium turnings (61.9 mg, 2.55 mmol, 4.9 eq) were dried at 650 °C (heat gun) *in vacuo* (10^{-3} mbar) for 10 min. After cooling to room temperature, Et_2O (0.5 mL) and 1,2-dibromoethane (6.79 µL, 78.8 µmol, 20 mol%) were added. A solution of 1-bromoundecane (470 µL, 2.11 mmol, 4.1 eq) in Et_2O (2 mL) was added dropwise over a period of 15 min, and the resulting mixture was stirred at room temperature for an additional 30 min. This freshly prepared Grignard solution was added dropwise to a 0 °C cold solution of Weinreb amide **259** (200 mg, 0.519 mmol, 1.0 eq) in Et_2O (5 mL). The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred at this temperature for an additional 21 h. The mixture was diluted with Et_2O (10 mL) and the reaction quenched at 0 °C with water (10 mL). The mixture was allowed to warm to room temperature, the organic phase was separated and washed with aq. $KHSO_4$ (10 wt%, 2 x 20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EA 100:0→49:1→19:1] afforded ketone **260** (94.2 mg, 0.200 mmol, 38%) as a colorless liquid.

Ketone 260:



260

R_f = 0.50 [PE:EtOAc 19:1].

$[\alpha]_D^{21}$ = –21.6 (*c* = 0.75, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.66 – 7.59 (m, 4H, 2 x H-17, 2 x H-21), 7.45 – 7.40 (m, 2H, H-19, H-23), 7.39 – 7.33 (m, 4H, 2 x H-18, 2 x H-22), 4.11 (dd, *J* = 6.2, 5.4 Hz, 1H, H-3), 2.44 (ddd, *J* = 17.8, 8.4, 6.3 Hz, 1H, H-5a or H-5b), 2.35 (ddd, *J* = 17.8, 8.4, 6.4 Hz, 1H, H-5a or H-5b), 1.68 – 1.56 (m, 2H, H-2a, H-2b), 1.45 – 1.34 (m, 2H, H-6a, H-6b), 1.33 – 1.14 (m, 16H, H-7a, H-7b, H-8a, H-8b, H-9a, H-9b, H-10a, H-10b, H-11a, H-11b, H-12a, H-12b, H-13a, H-13b, H-14a, H-14b), 1.11 (s, 9H, 9 x H-25), 0.88 (dd, *J* = 7.1, 7.1 Hz, 3H, 3 x H-15), 0.81 (dd, *J* = 7.5, 7.5 Hz, 3H, 3 x H-1) ppm.

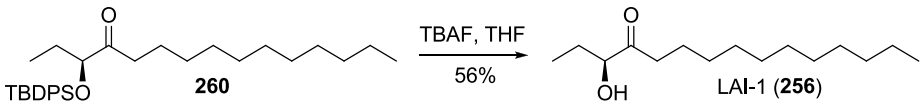
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 213.04 (C-4), 135.99 (2 x C-17 or 2 x C-21), 135.95 (2 x C-17 or 2 x C-21), 133.82 (C-16 or C-20), 133.36 (C-16 or C-20), 129.99 (C-19 or C-23), 129.96

(C-19 or C-23), 127.83 (2 x C-18 or 2 x C-22), 127.77 (2 x C-18 or 2 x C-22), 80.16 (C-3), 38.16 (C-5), 32.07 (C-13), 29.78 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.77 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.62 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.58 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.50 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.39 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 27.96 (C-2), 27.16 (3 x C-25), 23.10 (C-6), 22.85 (C-14), 19.54 (C-24), 14.28 (C-15), 8.96 (C-1) ppm.

IR (ATR): $\tilde{\nu}$ = 2925 (m), 2855 (m), 1716 (w), 1428 (w), 1106 (m), 700 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{30}H_{45}O_2Si^+$: 465.3183 $[M–CH_3]^+$
found: 465.3184 $[M–CH_3]^+$.

(3*S*)-3-hydroxypentadecan-4-one (256)



A solution of silyl ether **260** (128 mg, 0.266 mmol, 1.0 eq) in THF (4.5 mL) was cooled to 0 °C and a solution of tetrabutylammonium fluoride in THF (1.0 M, 772 µL, 0.772 mmol, 2.9 eq) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 3 h. The reaction was quenched with aq. $NaHCO_3$ (15 mL of a saturated solution) and the mixture extracted with Et_2O (2 x 20 mL). The combined organic fractions were washed with water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [PE:EtOAc 100:0→19:1] and further purification by HPLC [Dynamax Microsorb 60-8 C18 (250 x 21.4 mm), isocratic elution, water (A)/MeCN (B); 78% B; flow rate 16.8 mL/min; detection 200 nm: t_R (**256**) = 27.3 min] afforded LAI-1 (**256**) (36.2 mg, 0.149 mmol, 56%) as a colorless liquid.

LAI-1 (256):

R_f = 0.43 [PE:EtOAc 9:1].

$[\alpha]_D^{21}$ = –51.6 (*c* = 0.90, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (dd, *J* = 6.8, 4.0 Hz, 1H, H-3), 3.44 (br s, 1H, H-16), 2.50 – 2.38 (m, 2H, H-5a, H-5b), 1.96 – 1.83 (m, 1H, H-2a or H-2b), 1.66 – 1.52 (m, 3H, H-2a or H-2b, H-6a, H6b), 1.34 – 1.17 (m, 16H, H-7a, H-7b, H-8a, H-8b, H-9a, H-9b, H-10a, H-10b, H-11a, H-11b, H-12a, H-12b, H-13a, H-13b, H-14a, H-14b), 0.93 (dd, *J* = 7.4, 7.4 Hz, 3H, 3 x H-1), 0.87 (dd, *J* = 6.9, 6.9 Hz, 3H, 3 x H-15) ppm.

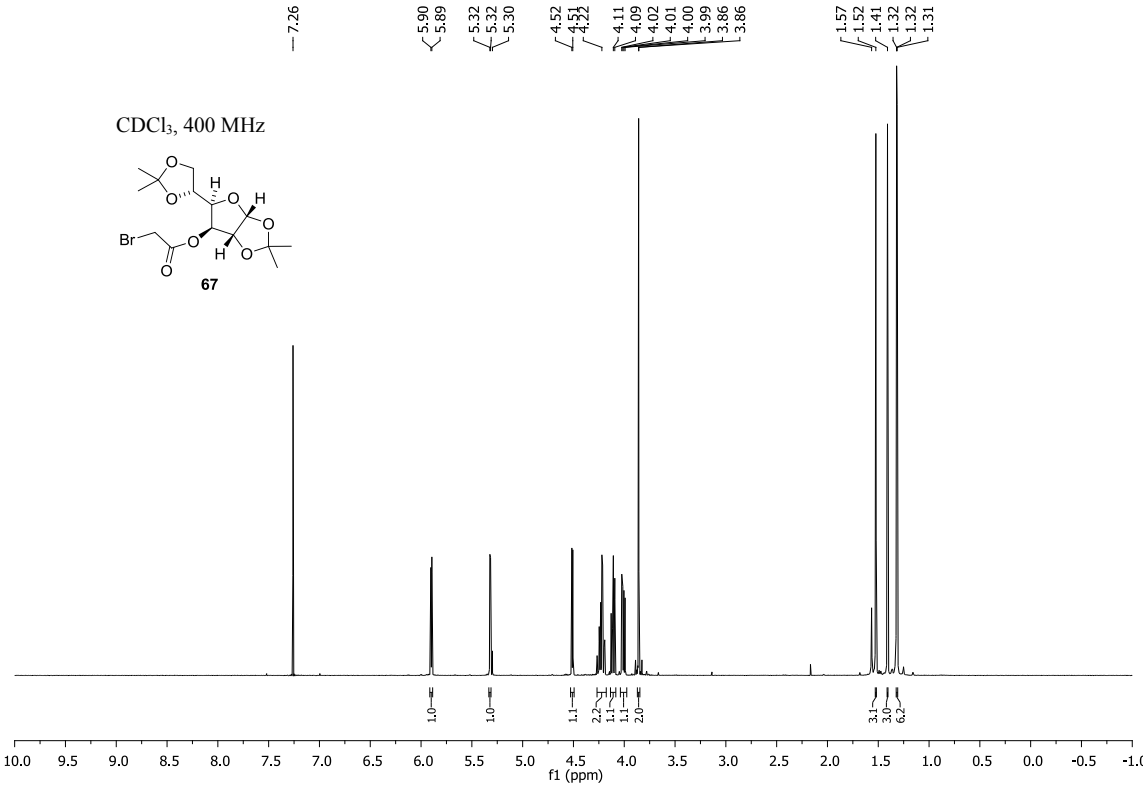
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.58 (C-4), 77.30 (C-3), 38.03 (C-5), 32.05 (C-13), 29.73 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.73 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.58 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.49 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.47 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 29.39 (C-7 or C-8 or C-9 or C-10 or C-11 or C-12), 26.90 (C-2), 23.76 (C-6), 22.83 (C-14), 14.26 (C-15), 9.02 (C-1) ppm.

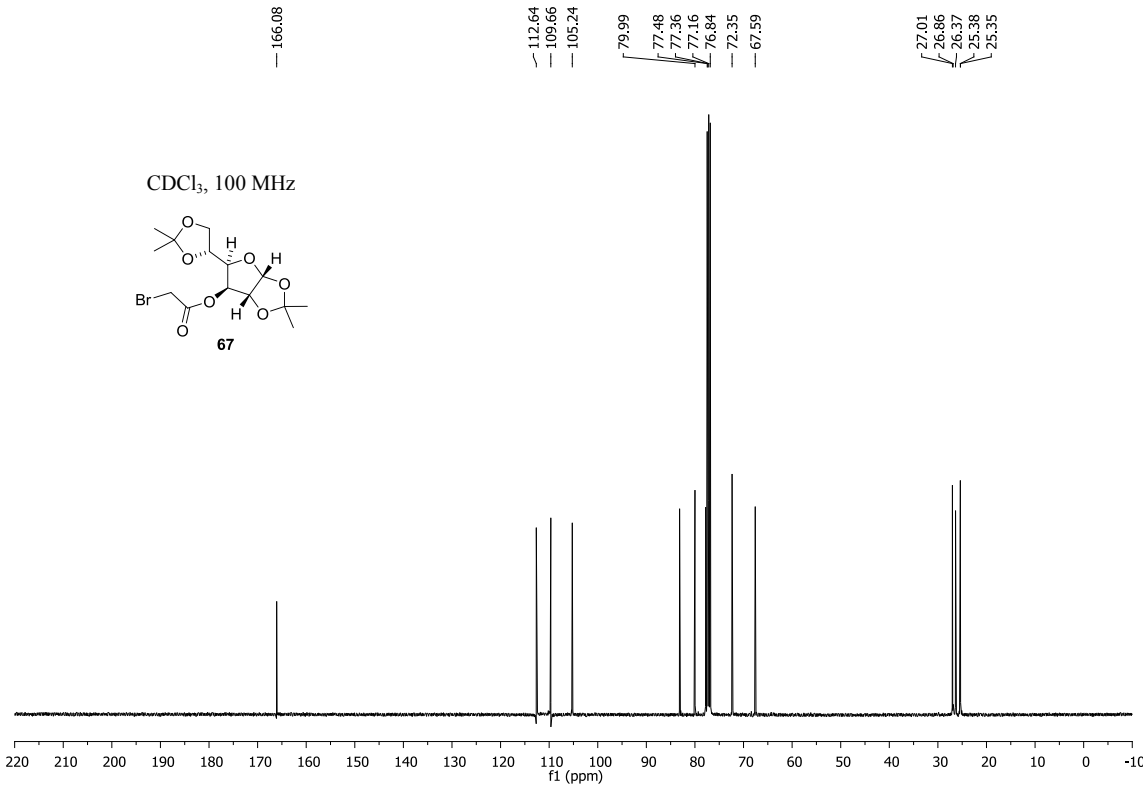
IR (ATR): $\tilde{\nu}$ = 3482 (br, w), 2923 (s), 2854 (m), 1710 (s), 1464 (m), 1075 (w), 981 (m), 722 (w) cm^{-1}.

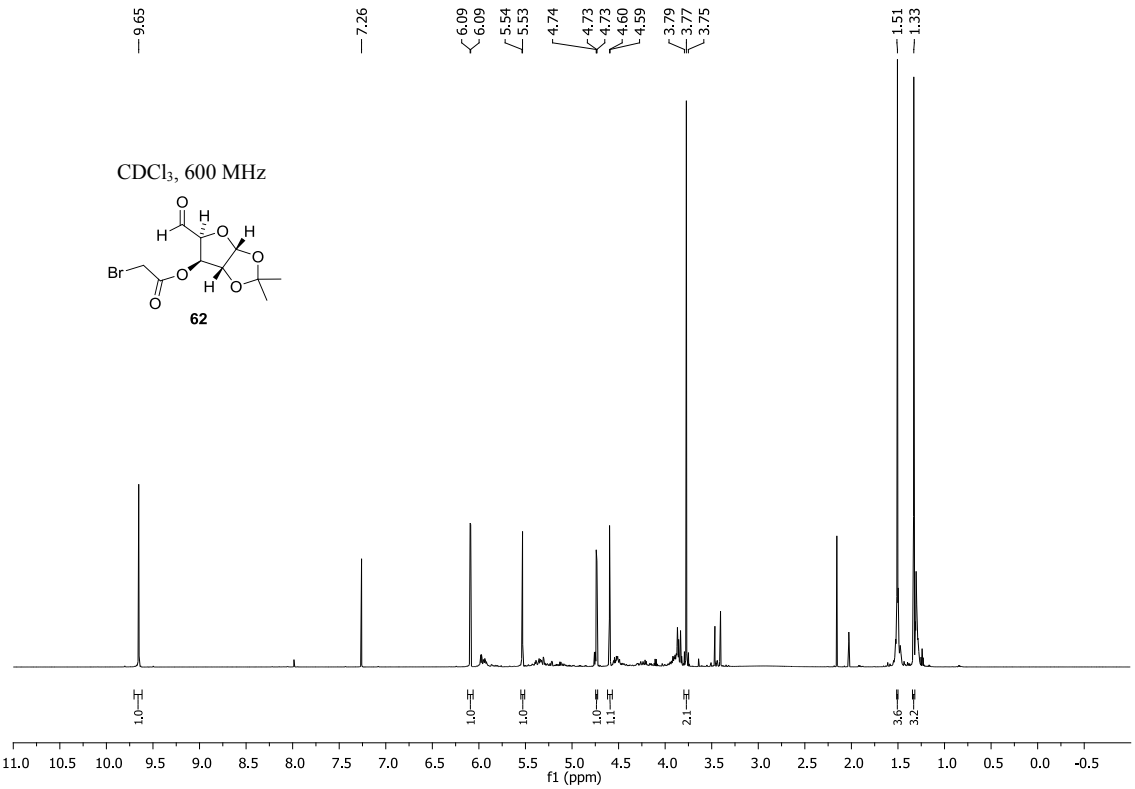
HRMS (EI): calcd. for $C_{15}H_{30}ClO_2^-$: 277.1940 $[M+Cl]^-$
found: 277.1936 $[M+Cl]^-$.

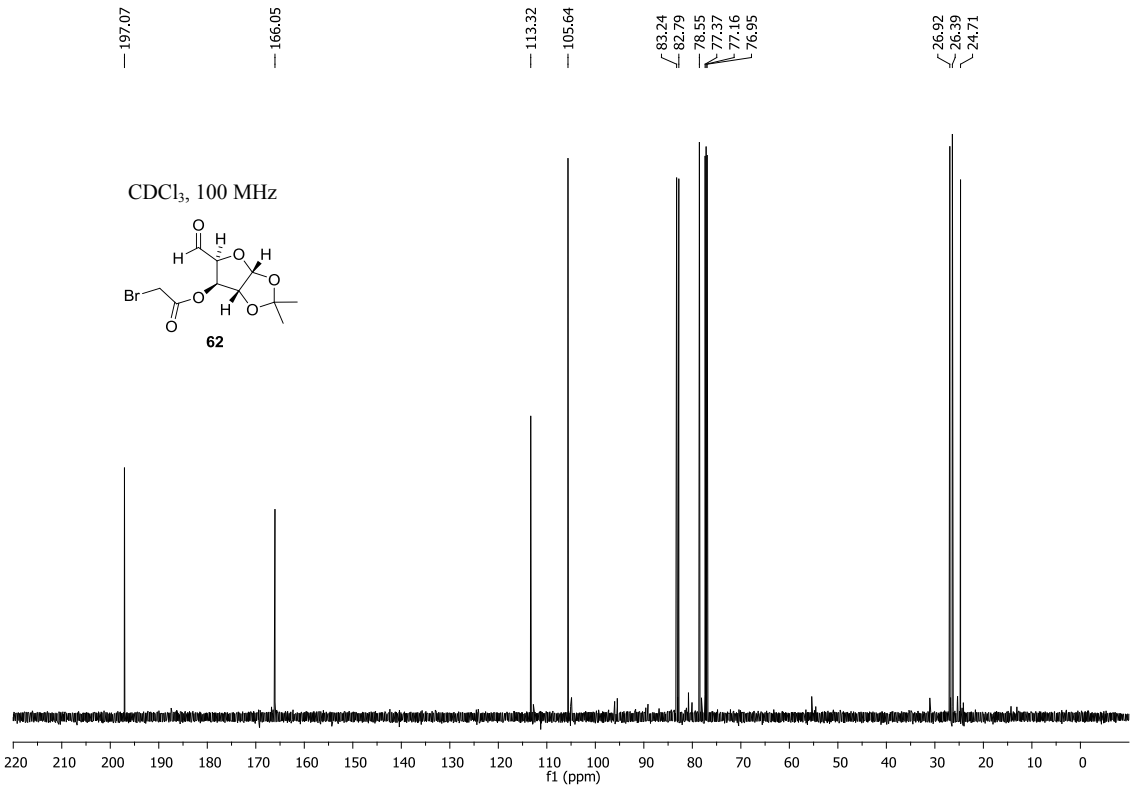
22. Appendices

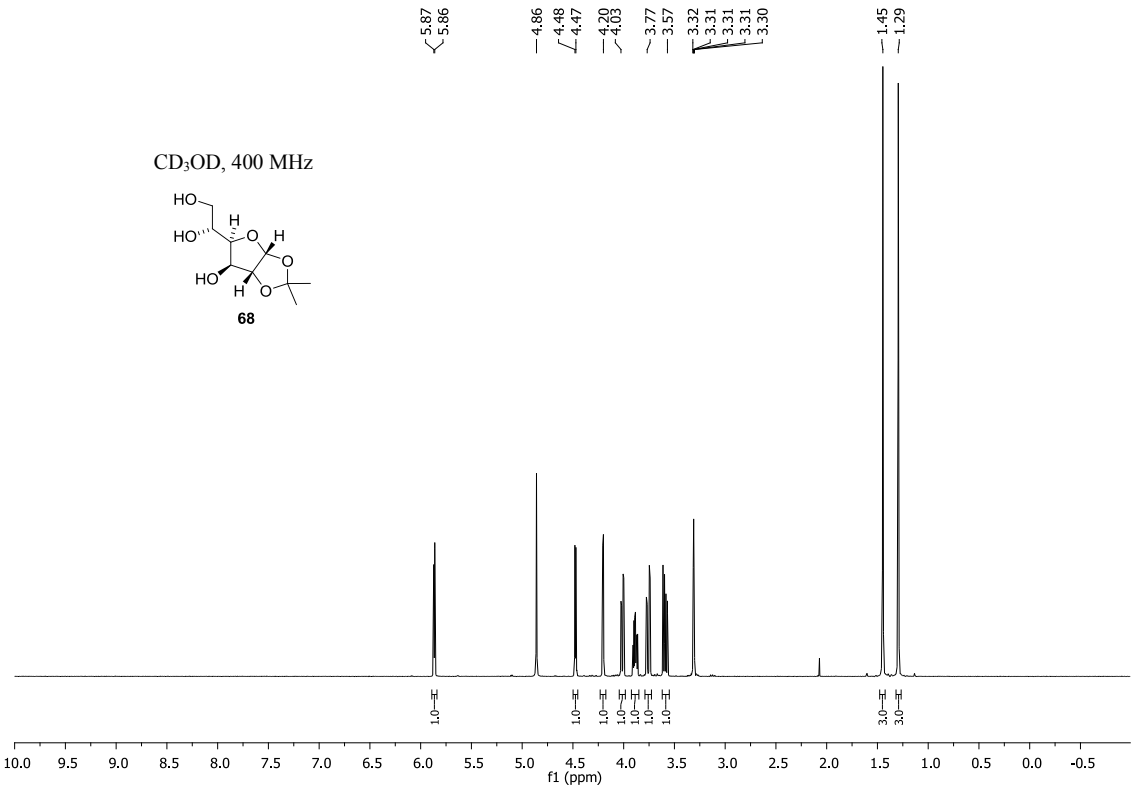
22.1. NMR Spectra of Chapter I

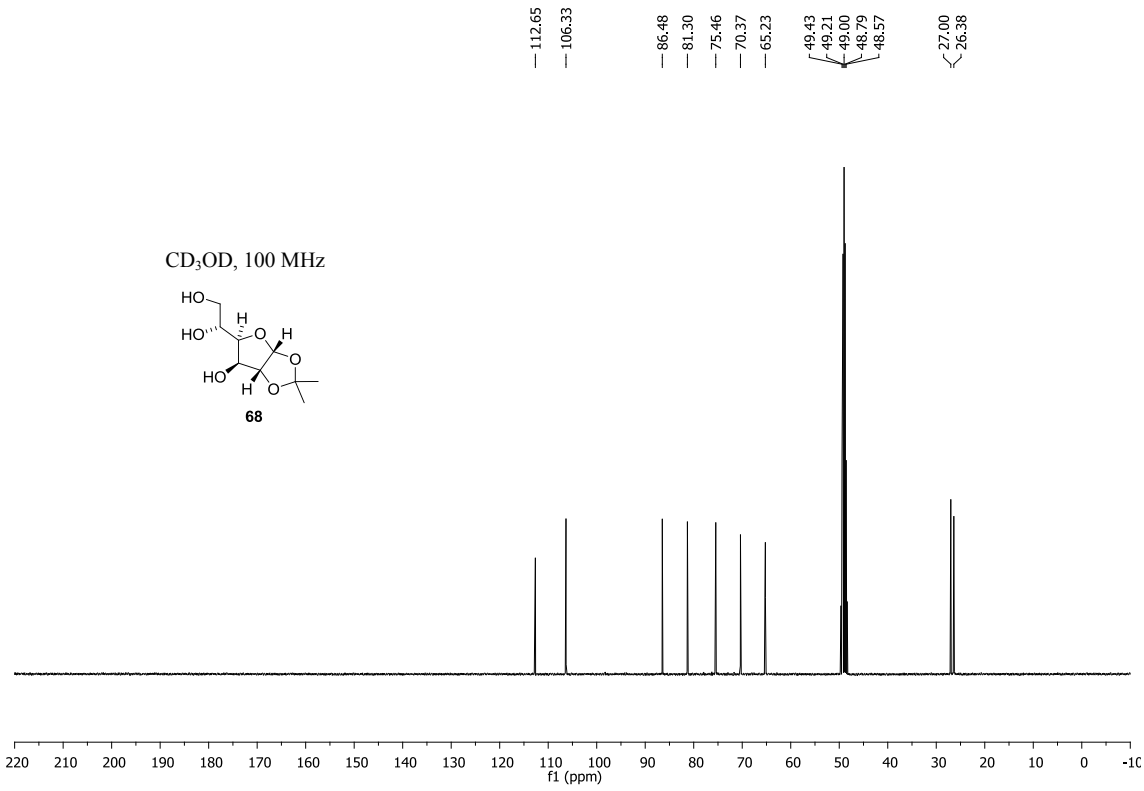


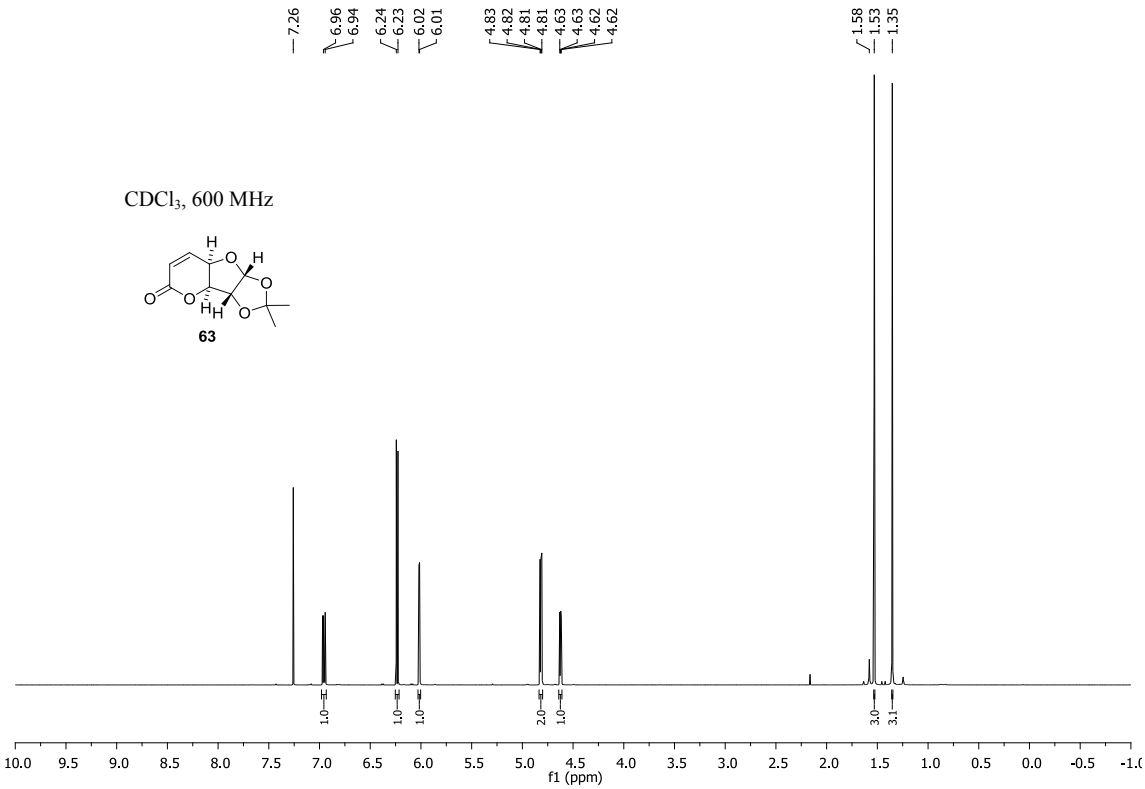


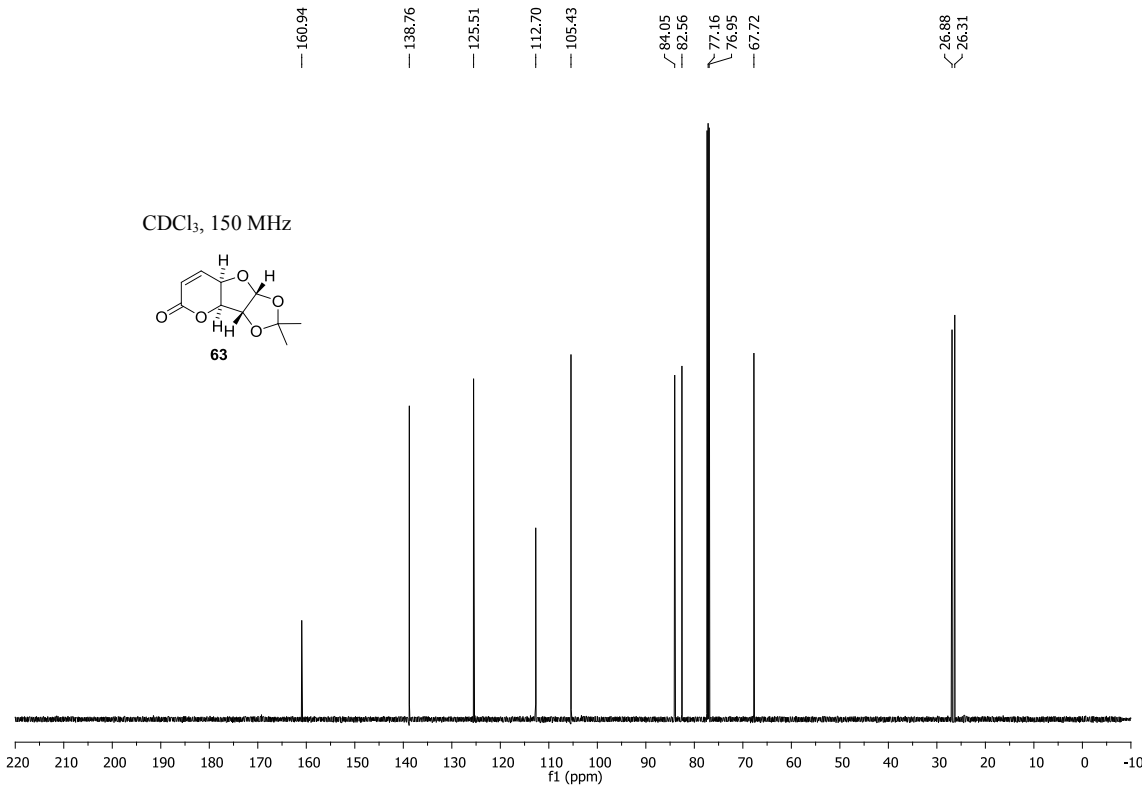

9.65
7.26
6.09
6.09
5.54
5.53
4.74
4.73
4.73
4.60
4.59
3.79
3.77
3.75
1.51
1.33
CDCl3, 600 MHz
Br
O
H
O
H
O
H
O
O
62
1.0
1.0
1.0
1.0
1.1
2.1
3.6
3.2
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


197.07
166.05
113.32
105.64
83.24
82.79
78.55
77.37
77.16
76.95
26.92
26.39
24.71
CDCl3, 100 MHz
Br
O
H
O
H
O
H
O
O
62
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


5.87
5.86
4.86
4.48
4.47
4.20
4.03
3.77
3.57
3.32
3.31
3.31
3.31
3.30
1.45
1.29
CD3OD, 400 MHz
HO
HO
HO
H
O
H
O
H
O
68
1.0
1.0
1.0
1.0
1.0
1.0
3.0
3.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


112.65
106.33
86.48
81.30
75.46
70.37
65.23
49.43
49.21
49.00
48.79
48.57
27.00
26.38
CD3OD, 100 MHz
HO
HO
HO
H
O
H
O
H
O
68
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26
6.96
6.94
6.24
6.23
6.02
6.01
4.83
4.82
4.81
4.81
4.63
4.63
4.62
4.62
1.58
1.53
1.35
CDCl3, 600 MHz
63
1.0
1.0
1.0
2.0
1.0
3.0
3.1
f1 (ppm)


160.94
138.76
125.51
112.70
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84.05
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77.16
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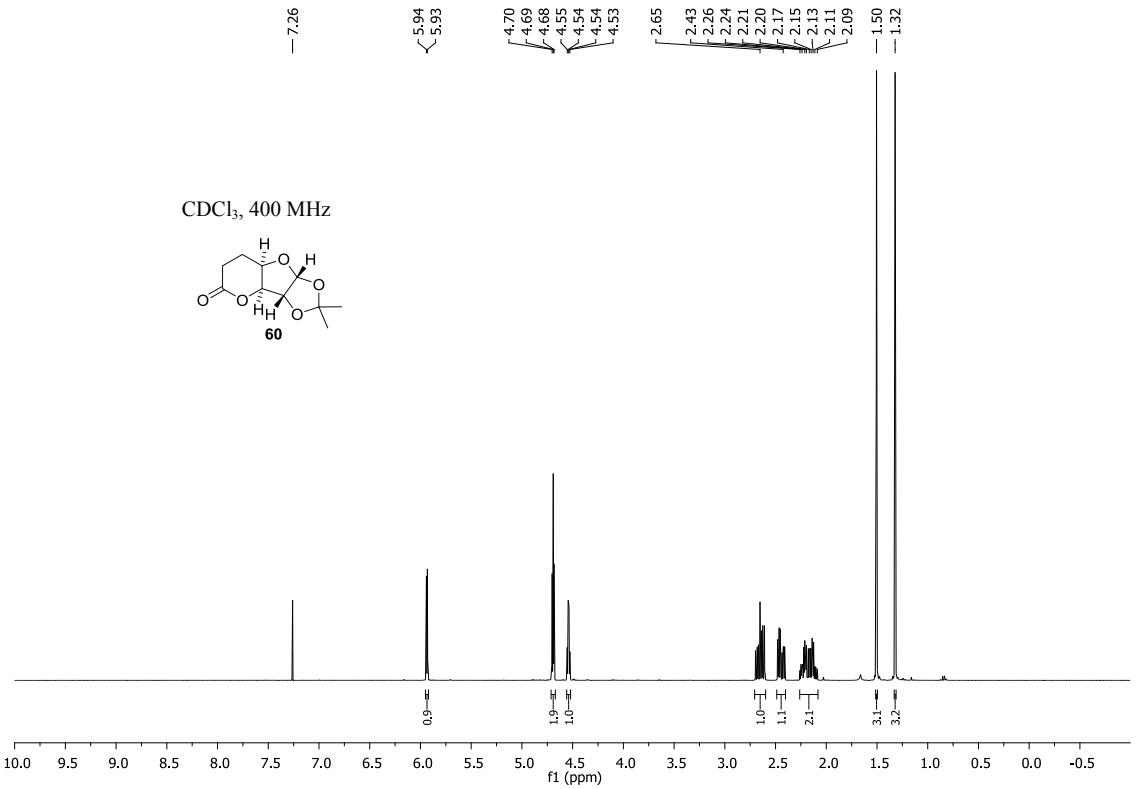
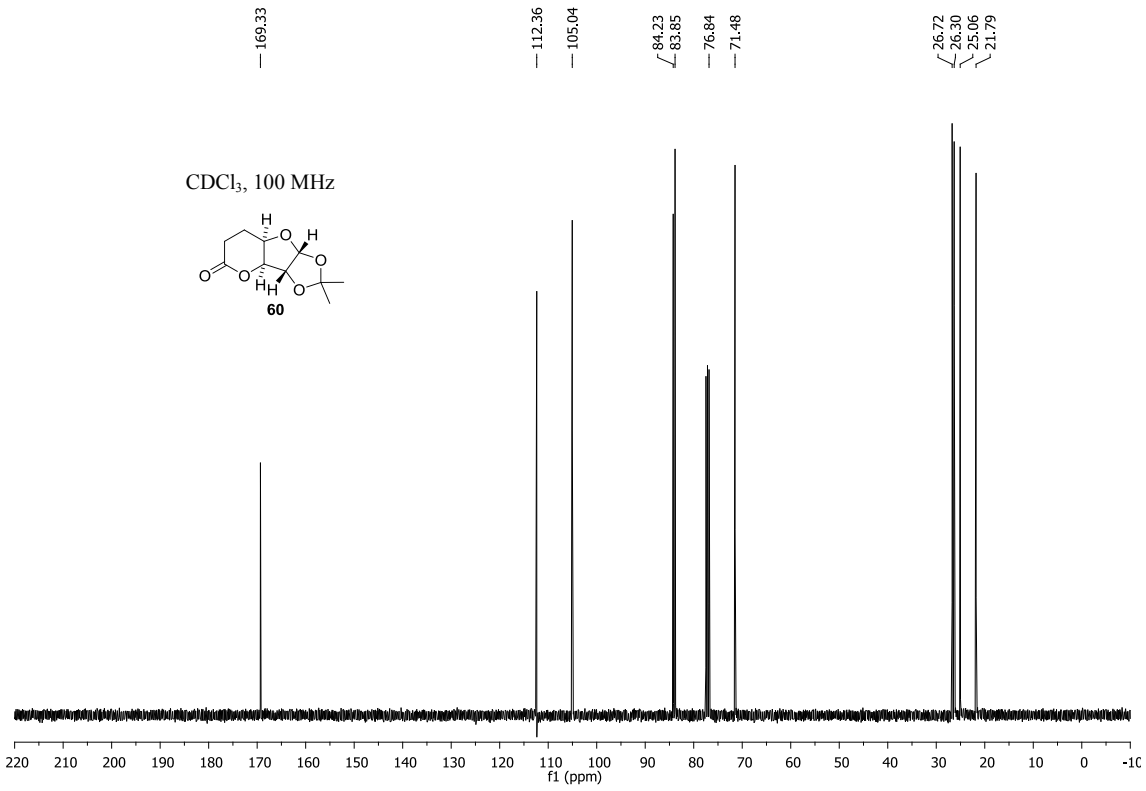
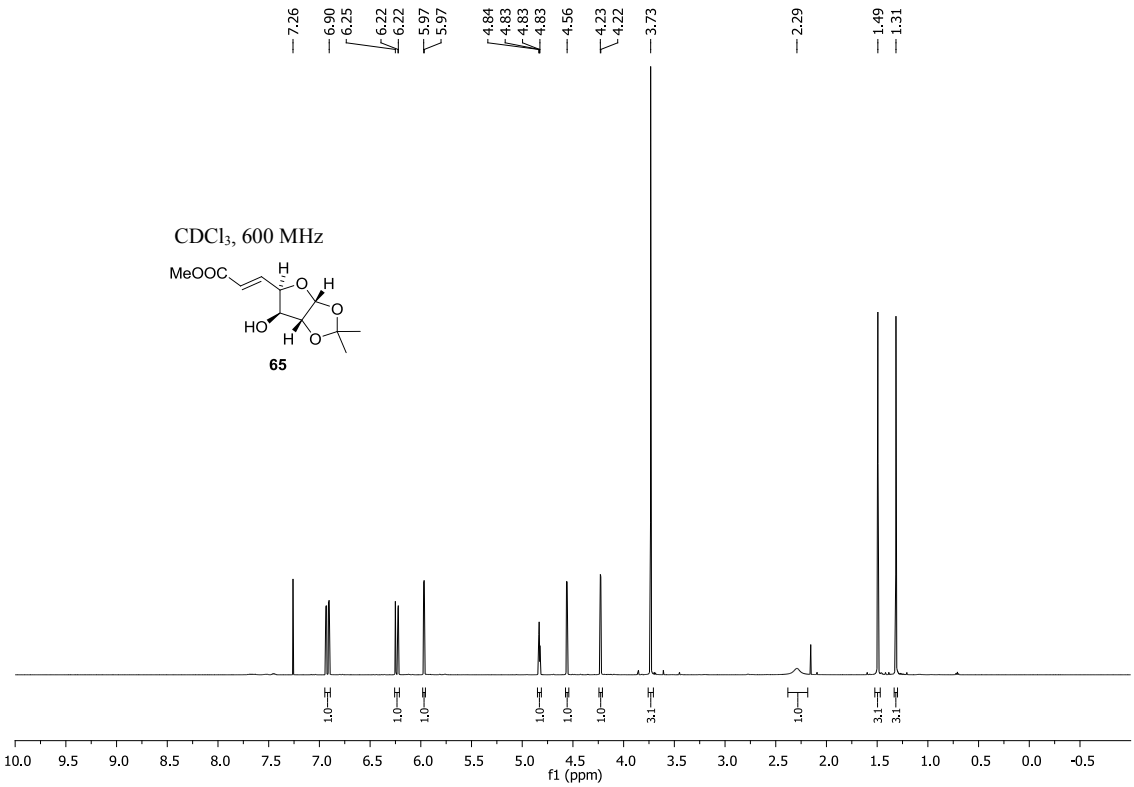
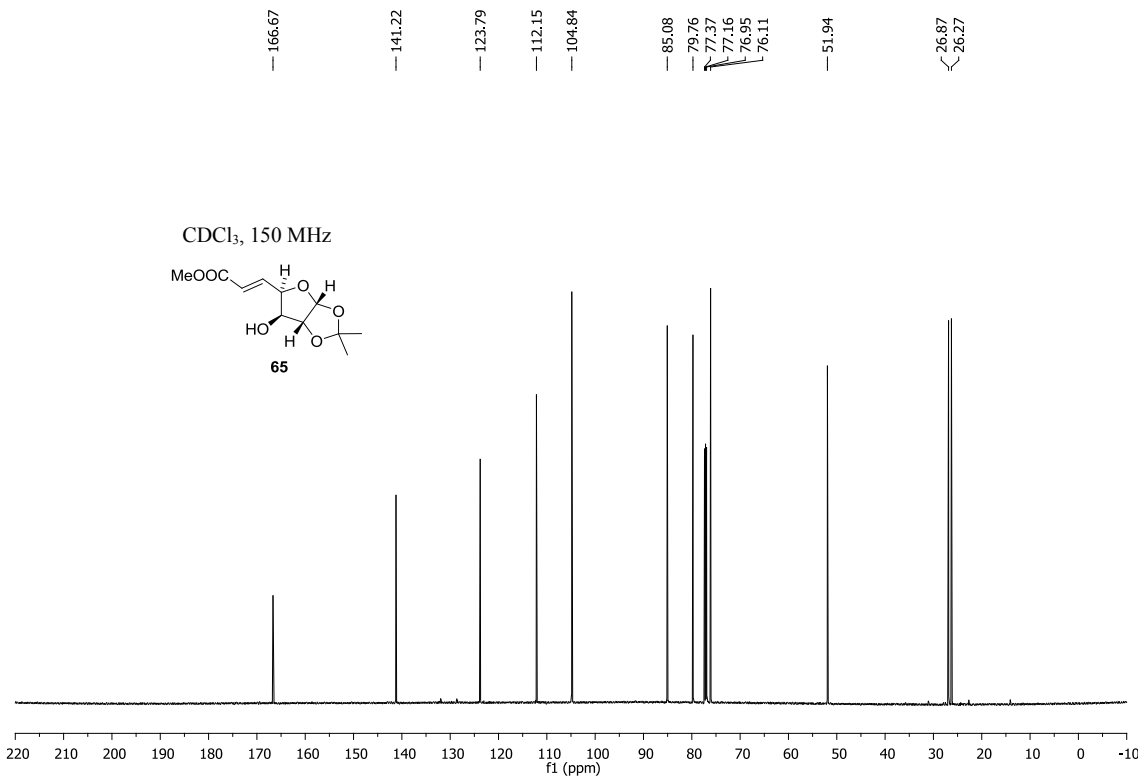
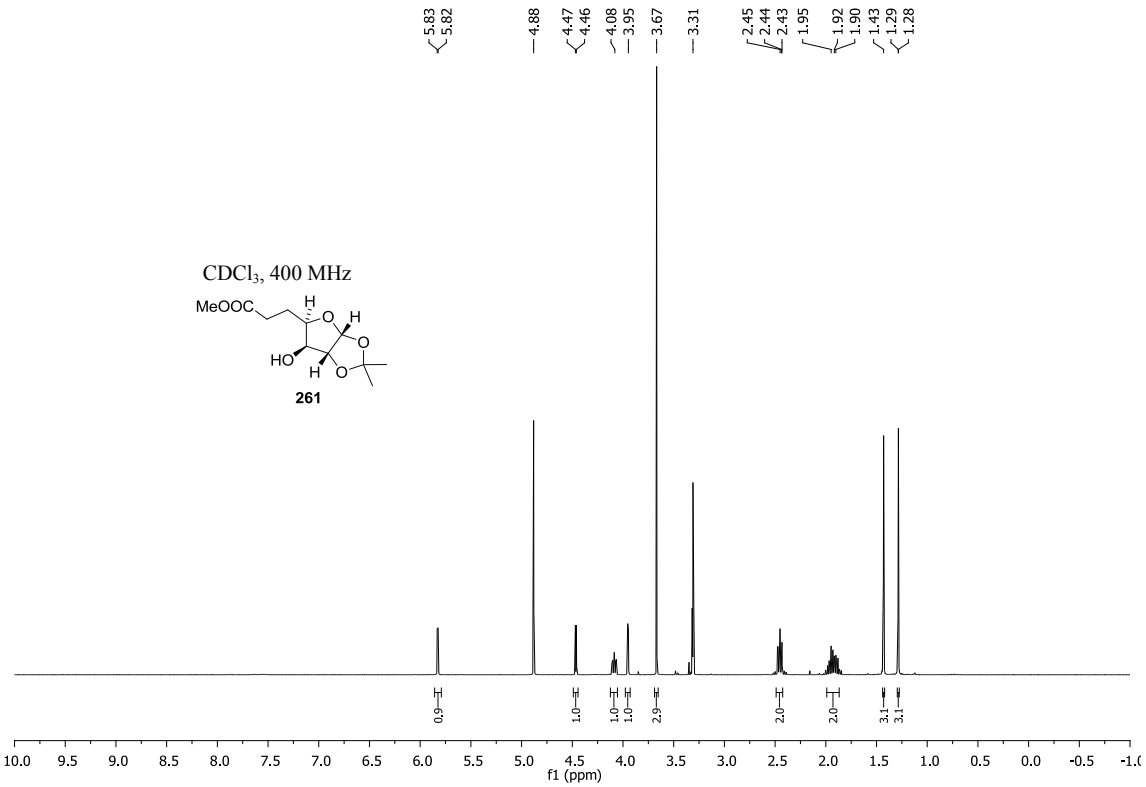
26.88
26.31
CDCl3, 150 MHz
63
f1 (ppm)

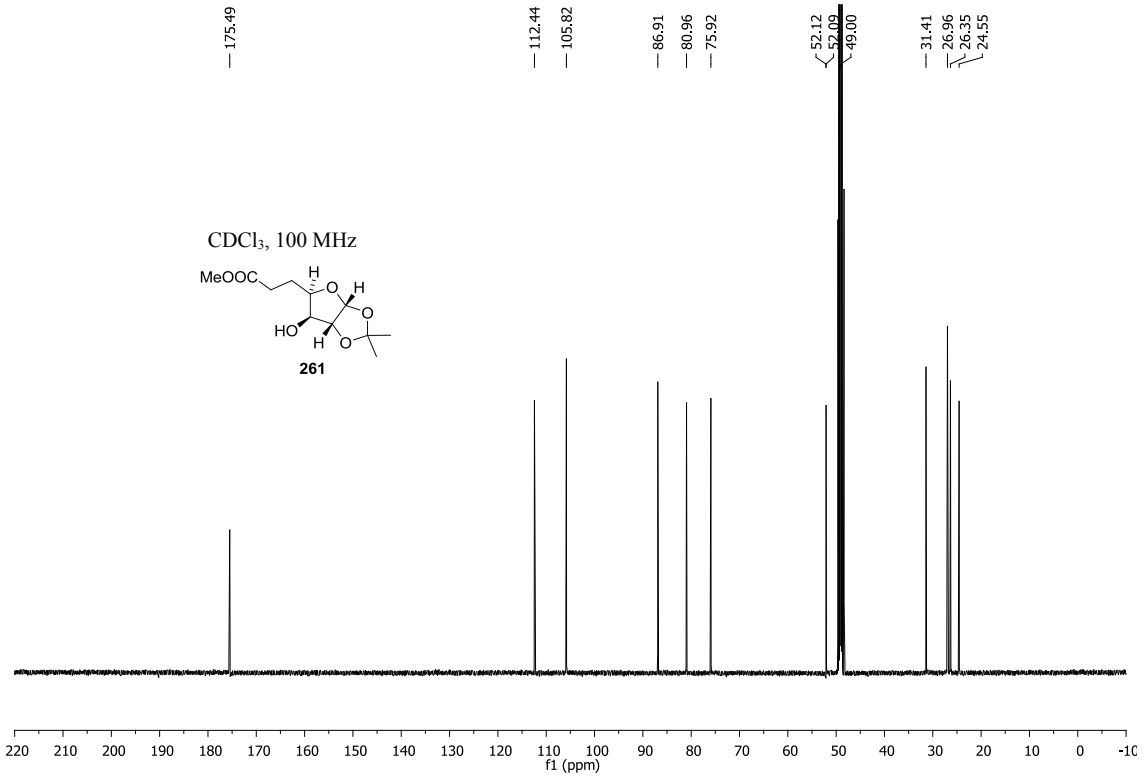

7.26
5.94
5.93
4.70
4.69
4.68
4.55
4.54
4.54
4.53
2.65
2.43
2.26
2.24
2.21
2.20
2.17
2.15
2.13
2.11
2.09
1.50
1.32
CDCl3, 400 MHz
60
0.9
1.9
1.0
1.0
1.1
2.1
3.1
3.2
f1 (ppm)

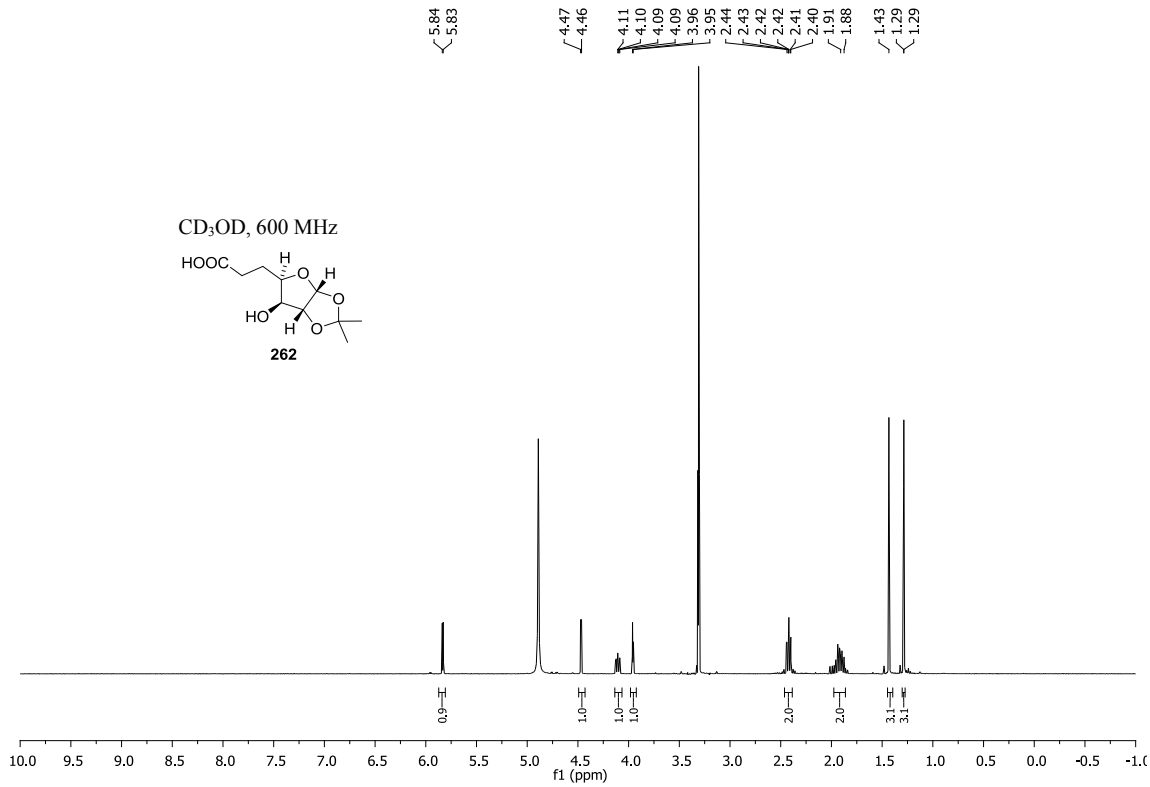

169.33
112.36
105.04
84.23
83.85
76.84
71.48
26.72
26.30
25.06
21.79
CDCl3, 100 MHz
60
f1 (ppm)

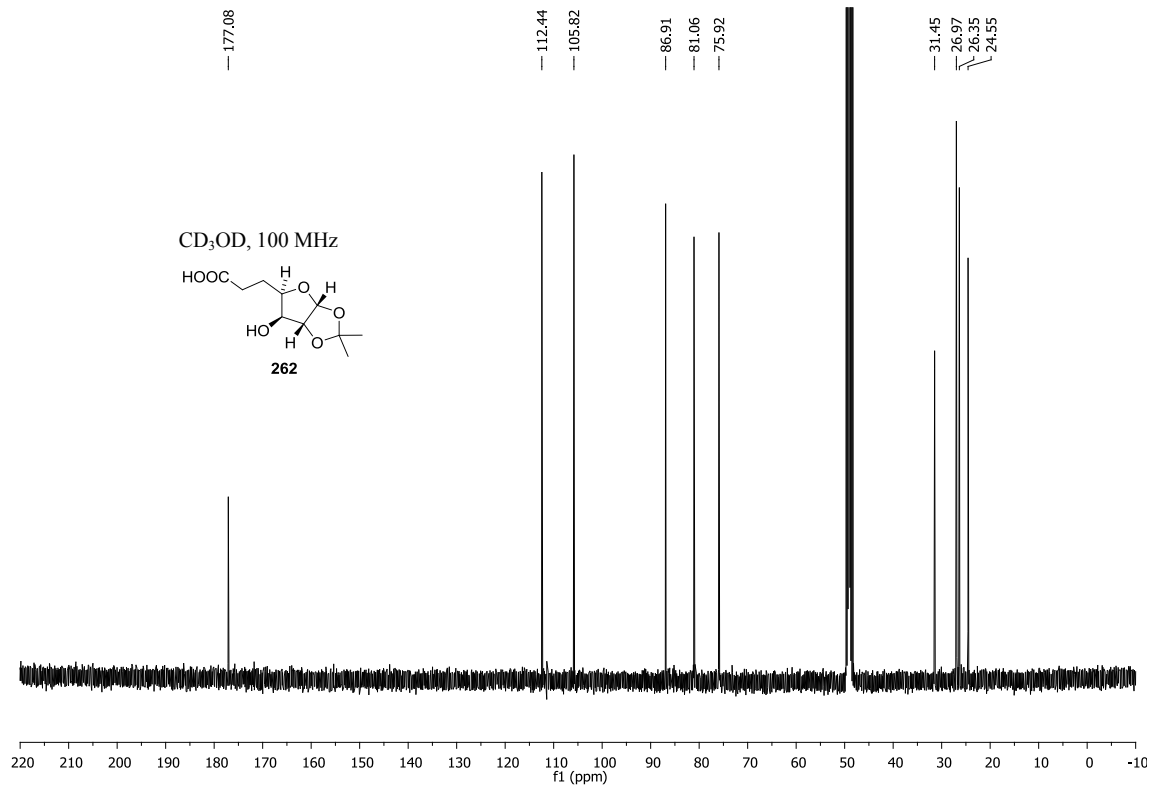

7.26
6.90
6.25
6.22
6.22
5.97
5.97
4.84
4.83
4.83
4.83
4.56
4.23
4.22
3.73
2.29
1.49
1.31
CDCl3, 600 MHz
MeOOC
HO
65
1.0
1.0
1.0
1.0
1.0
1.0
3.1
1.0
3.1
3.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

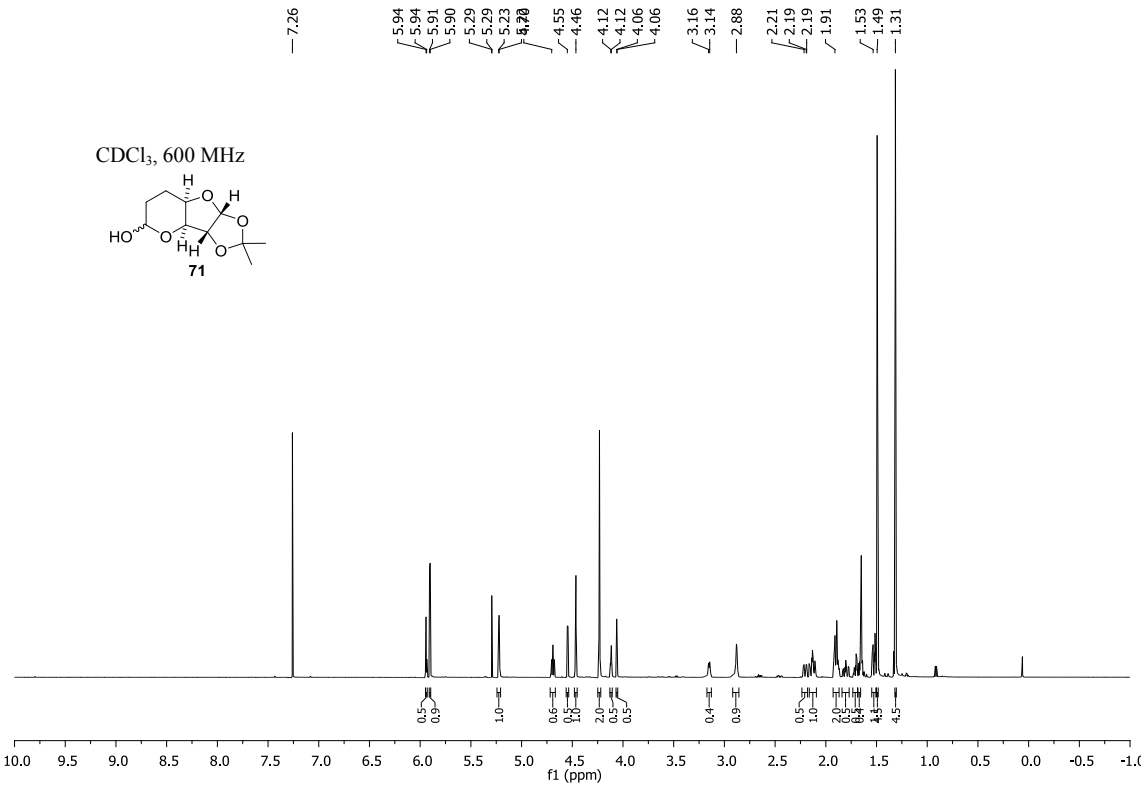

166.67
141.22
123.79
112.15
104.84
85.08
79.76
77.37
77.16
76.95
76.11
51.94
26.87
26.27
CDCl3, 150 MHz
MeOOC
HO
65
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

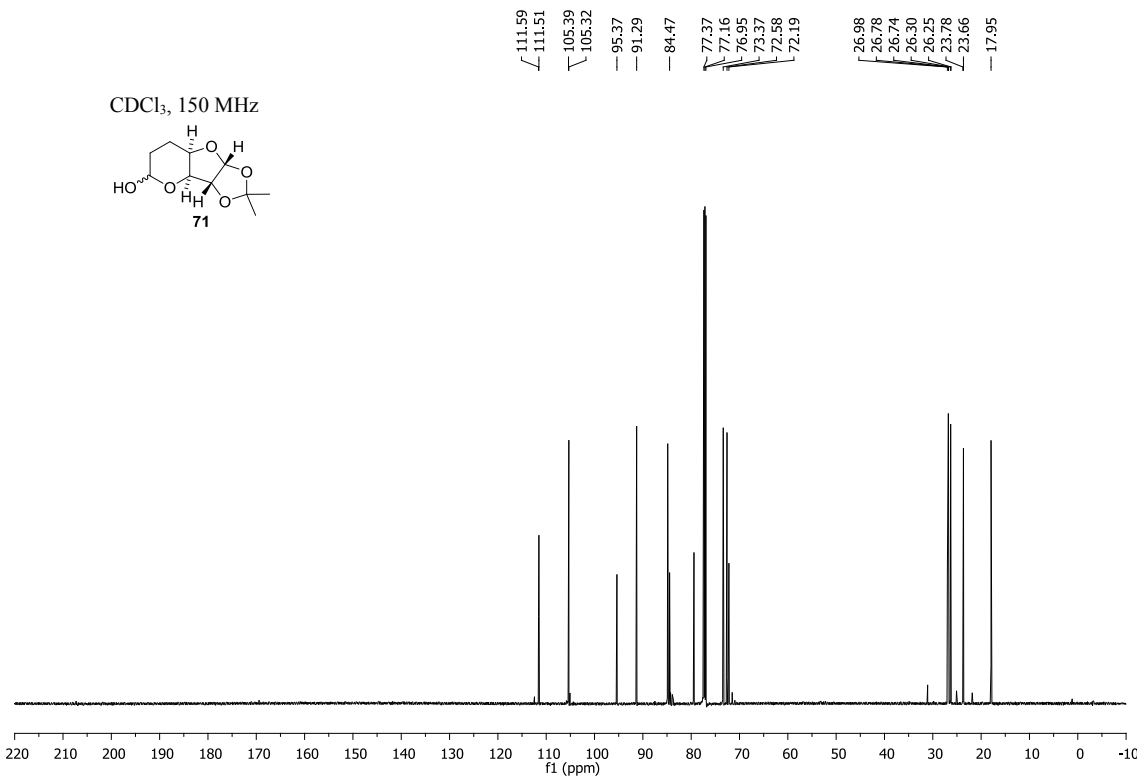

5.83
5.82
4.88
4.47
4.46
4.08
3.95
3.67
3.31
2.45
2.44
2.43
1.95
1.92
1.90
1.43
1.29
1.28
CDCl3, 400 MHz
MeOOC
HO
261
0.9
1.0
1.0
1.0
2.9
2.0
2.0
3.1
3.1
f1 (ppm)

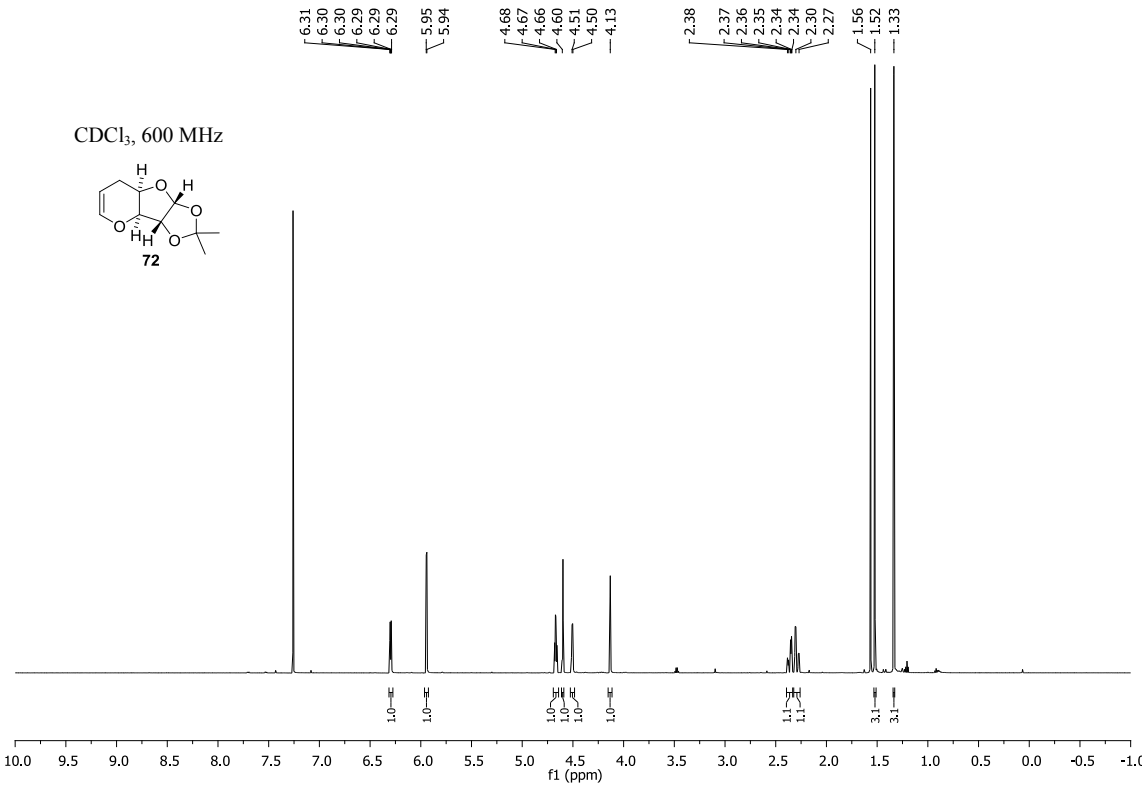

175.49
112.44
105.82
86.91
80.96
75.92
52.12
52.09
49.00
31.41
26.96
26.35
24.55
CDCl3, 100 MHz
MeOOC
HO
261
f1 (ppm)

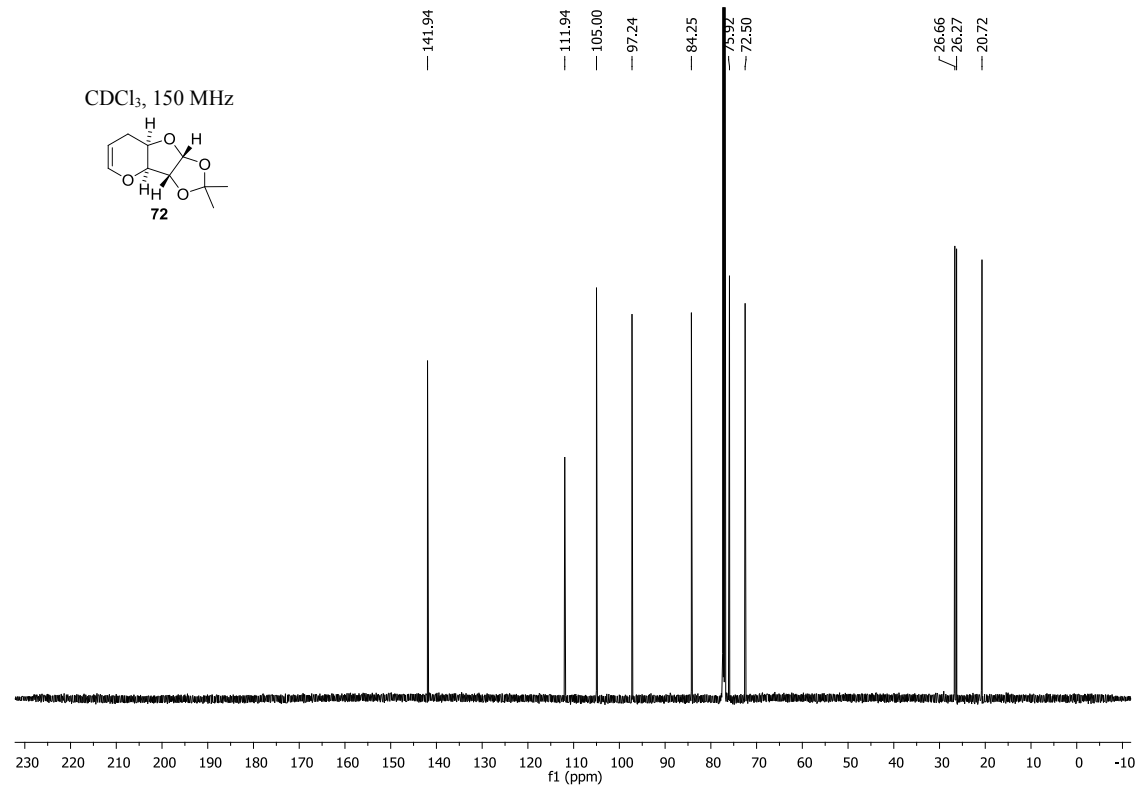

5.84
5.83
4.47
4.46
4.11
4.10
4.09
4.09
3.96
3.95
2.44
2.43
2.42
2.42
2.41
2.40
1.91
1.88
1.43
1.29
1.29
CD3OD, 600 MHz
HOOC
HO
262
0.9
1.0
1.0
1.0
2.0
2.0
3.1
3.1
f1 (ppm)

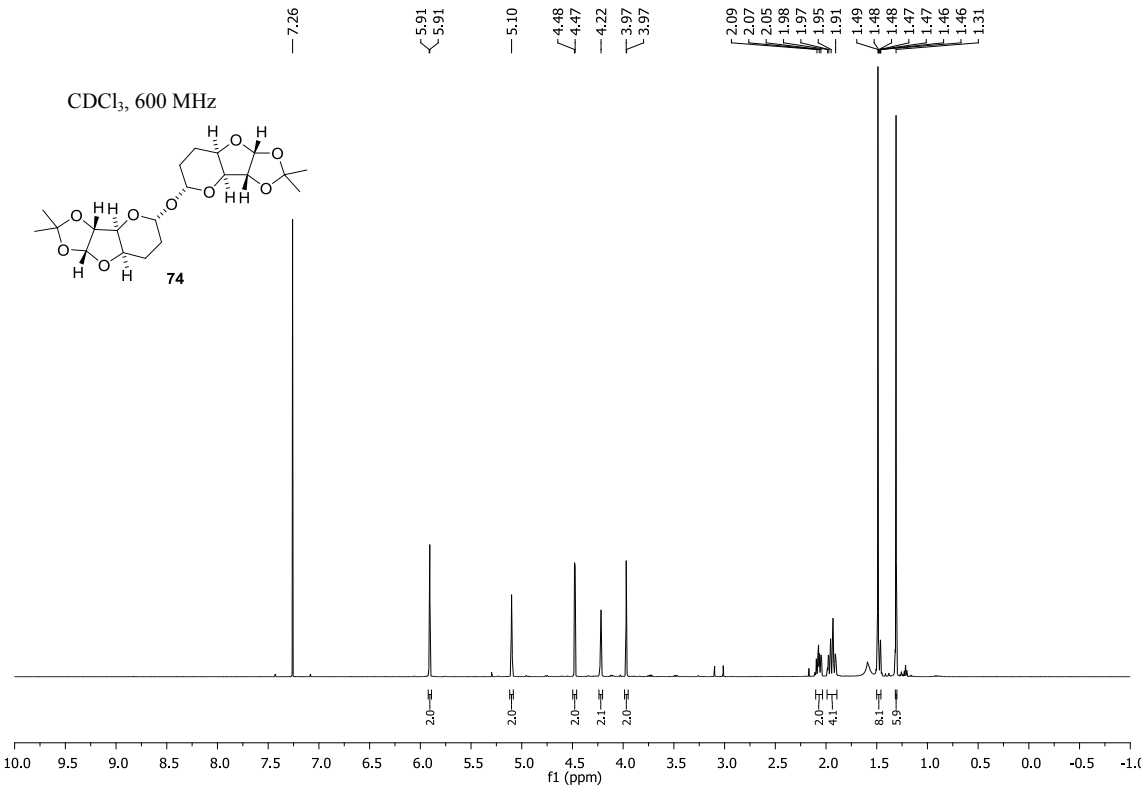

177.08
112.44
105.82
86.91
81.06
75.92
31.45
26.97
26.35
24.55
CD3OD, 100 MHz
HOOC
HO
262
f1 (ppm)

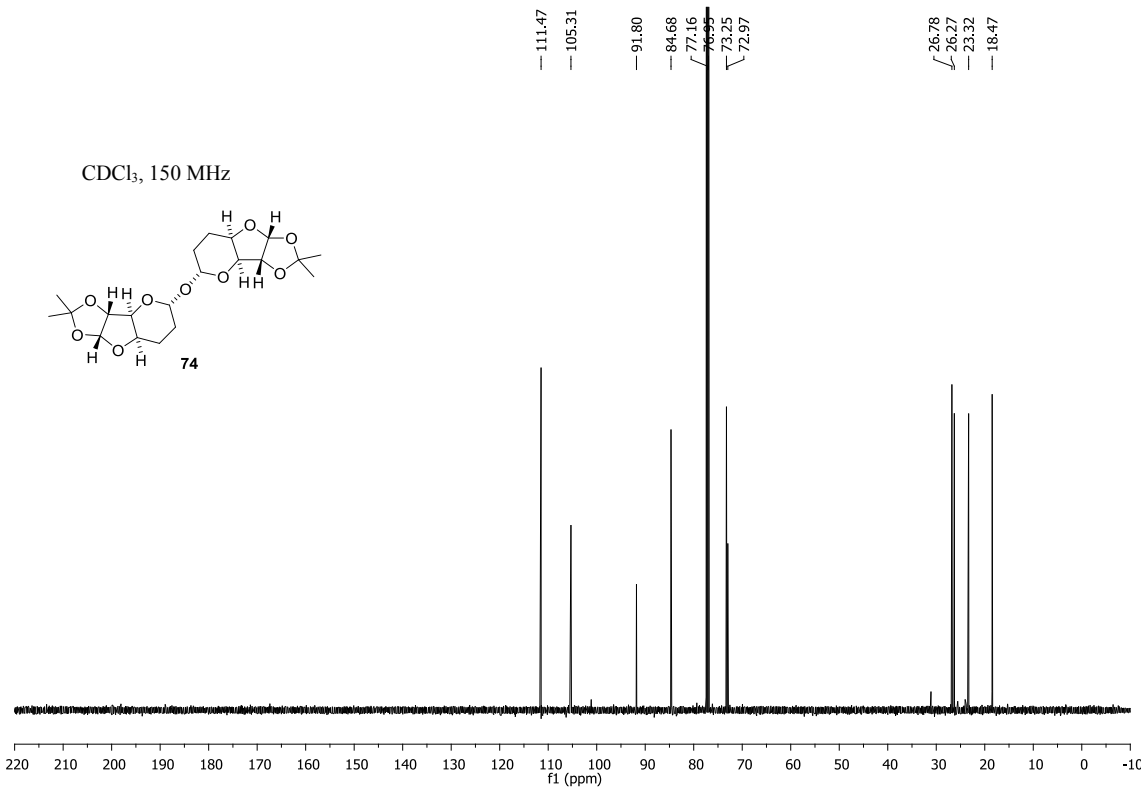

CDCl3, 600 MHz
71
7.26
5.94
5.91
5.90
5.29
5.23
4.55
4.46
4.12
4.06
3.16
3.14
2.88
2.21
2.19
1.91
1.53
1.49
1.31
f1 (ppm)

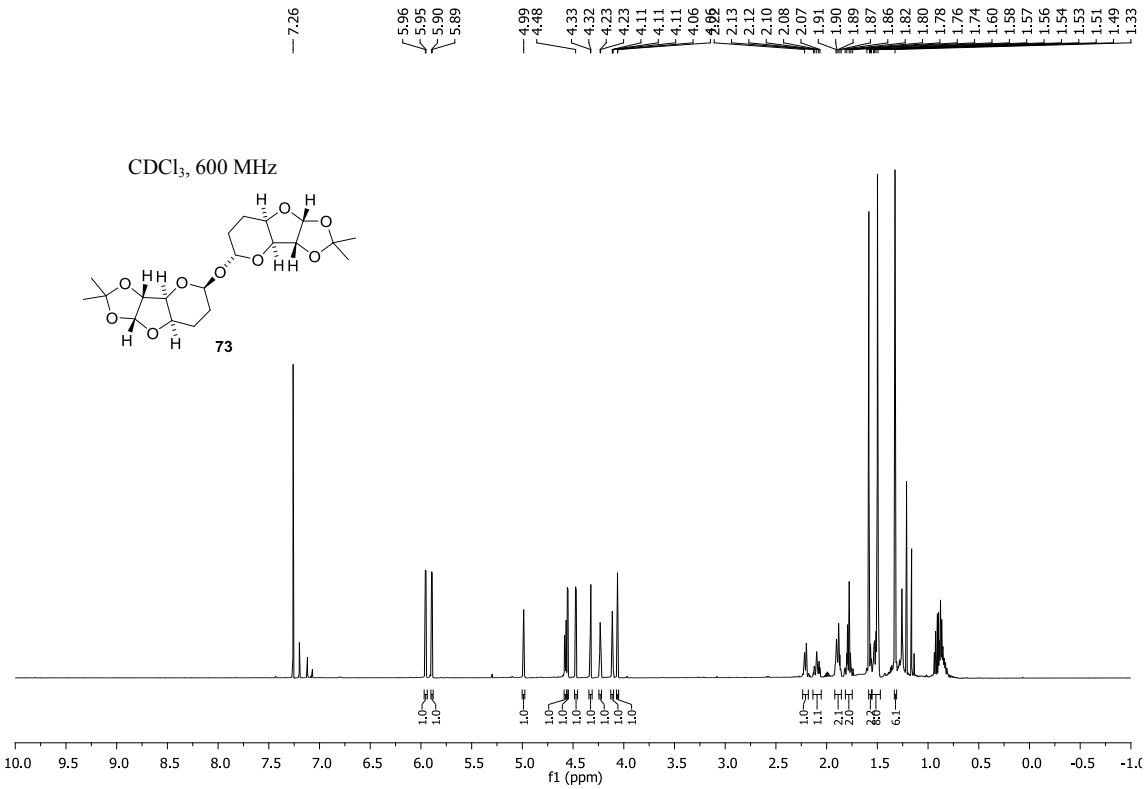

CDCl3, 150 MHz
71
111.59
111.51
105.39
105.32
95.37
91.29
84.47
77.37
77.16
76.95
73.37
72.58
72.19
26.98
26.78
26.74
26.30
26.25
23.78
23.66
17.95
f1 (ppm)

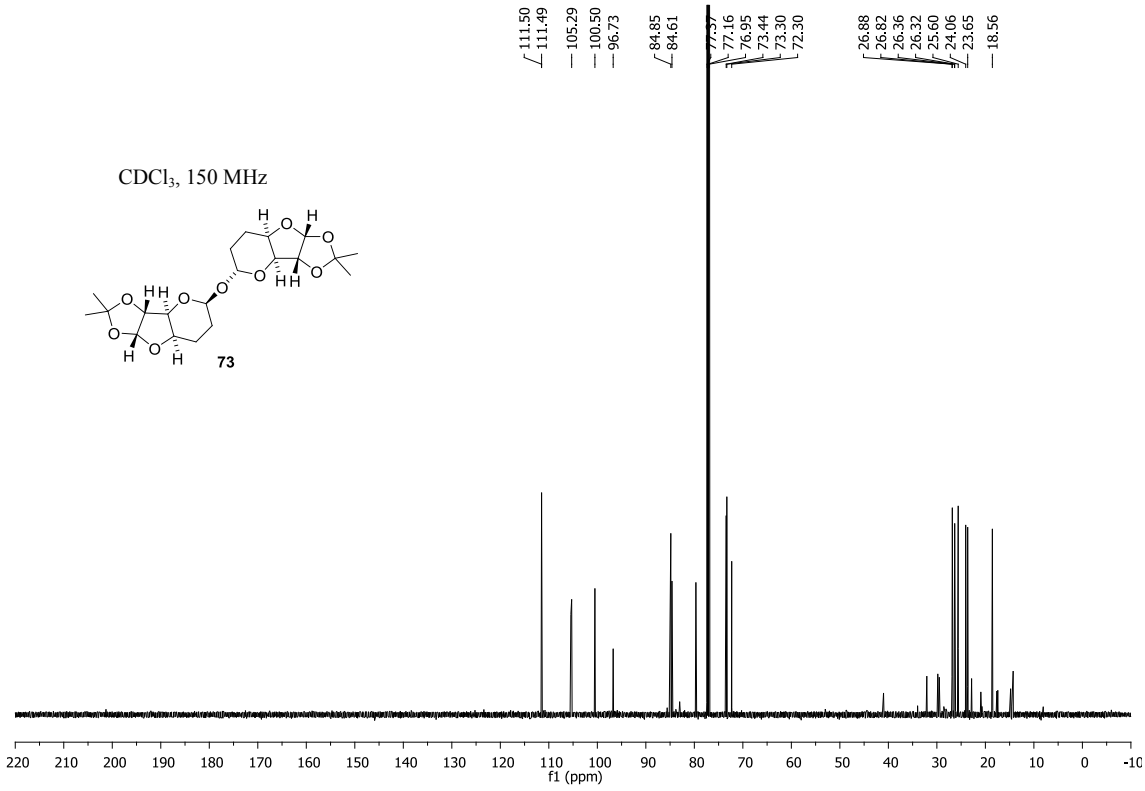

CDCl3, 600 MHz
72
6.31
6.30
6.30
6.29
6.29
6.29
5.95
5.94
4.68
4.67
4.66
4.60
4.51
4.50
4.13
2.38
2.37
2.36
2.35
2.34
2.34
2.30
2.27
1.56
1.52
1.33
1.0
1.0
1.0
1.0
1.0
1.1
1.1
3.1
3.1
f1 (ppm)

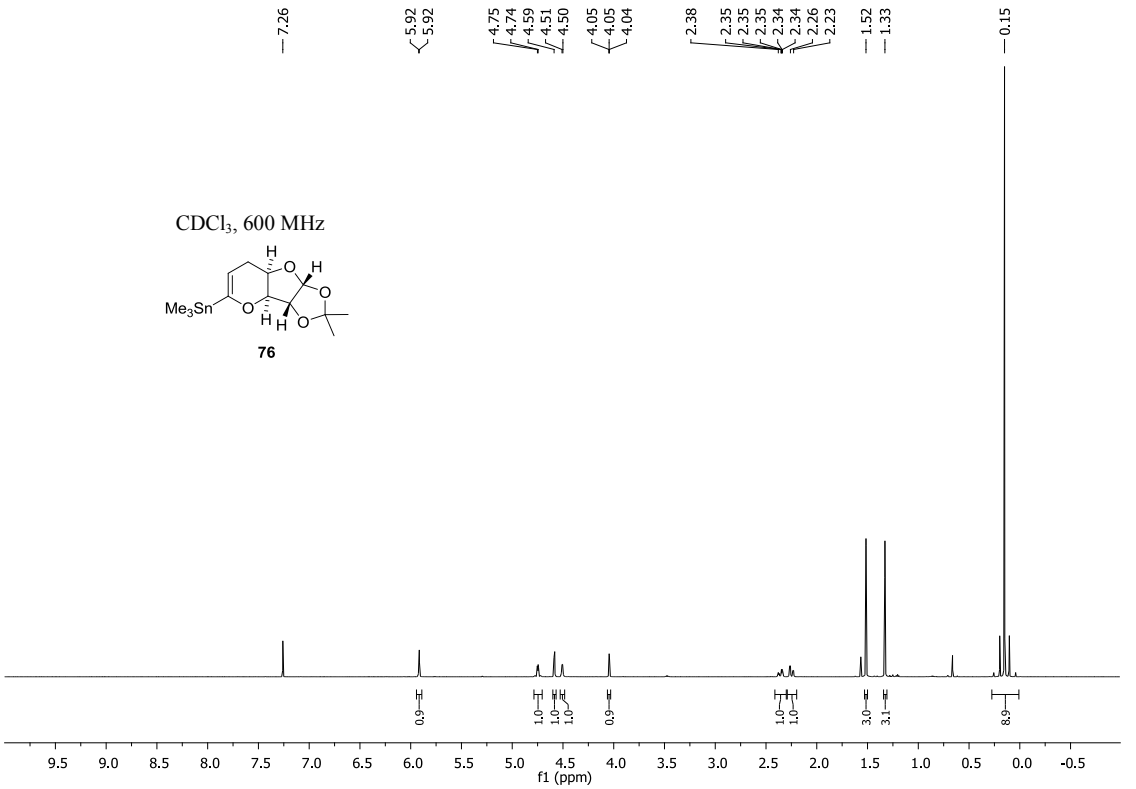

CDCl3, 150 MHz
72
141.94
111.94
105.00
97.24
84.25
75.92
72.50
26.66
26.27
20.72
f1 (ppm)

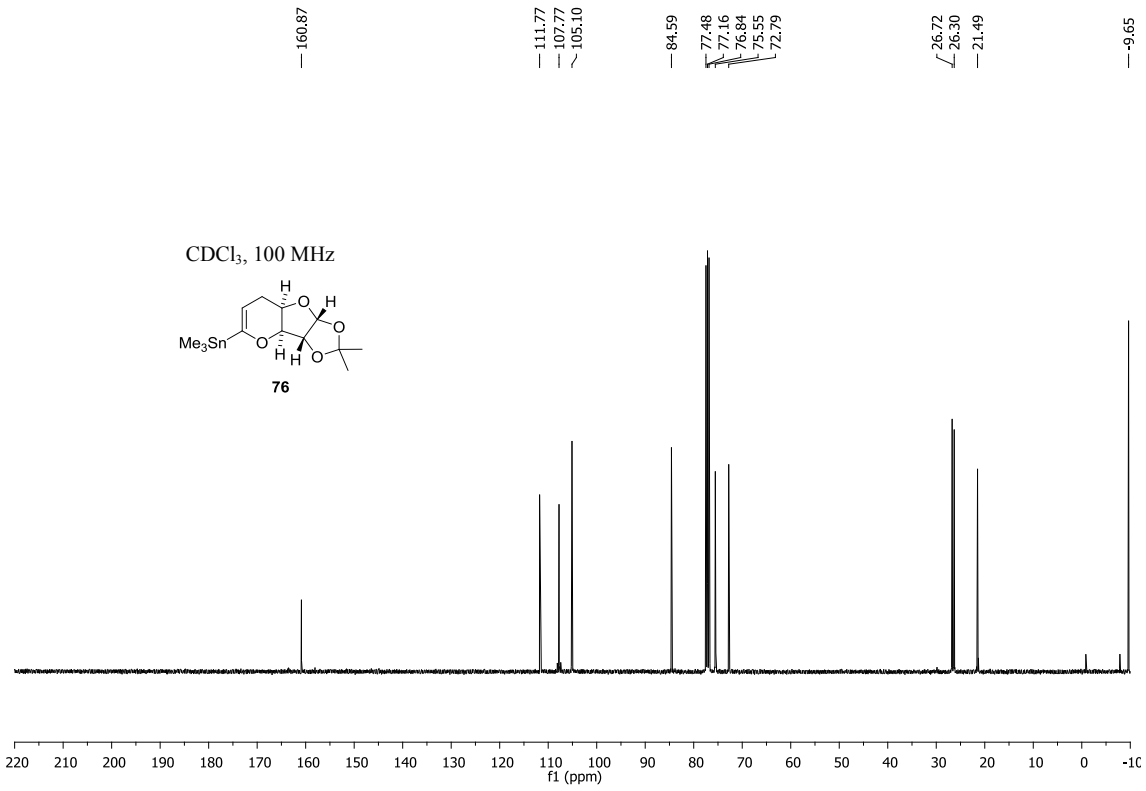

7.26
5.91
5.91
5.10
4.48
4.47
4.22
3.97
3.97
2.09
2.07
2.05
1.98
1.97
1.95
1.91
1.49
1.48
1.48
1.47
1.47
1.46
1.46
1.31
CDCl3, 600 MHz
74
2.0
2.0
2.0
2.1
2.0
2.0
4.1
8.1
5.9
f1 (ppm)

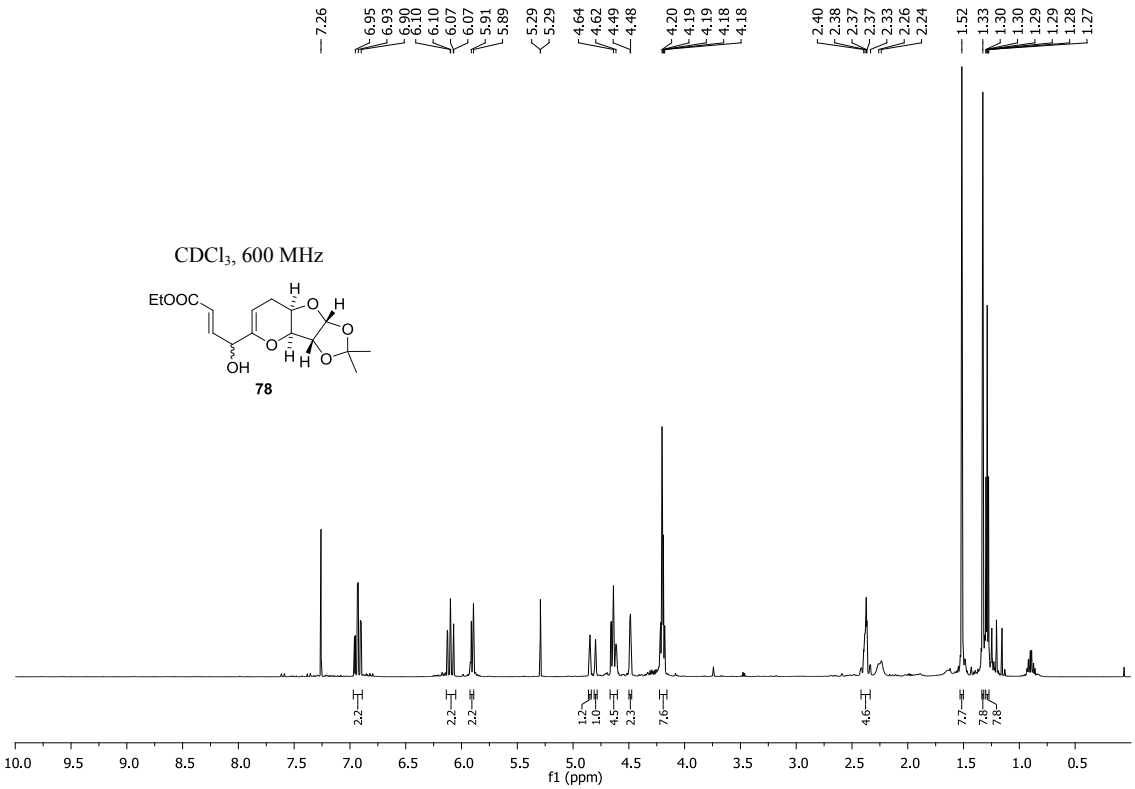

111.47
105.31
91.80
84.68
77.16
76.95
73.25
72.97
26.78
26.27
23.32
18.47
CDCl3, 150 MHz
74
f1 (ppm)

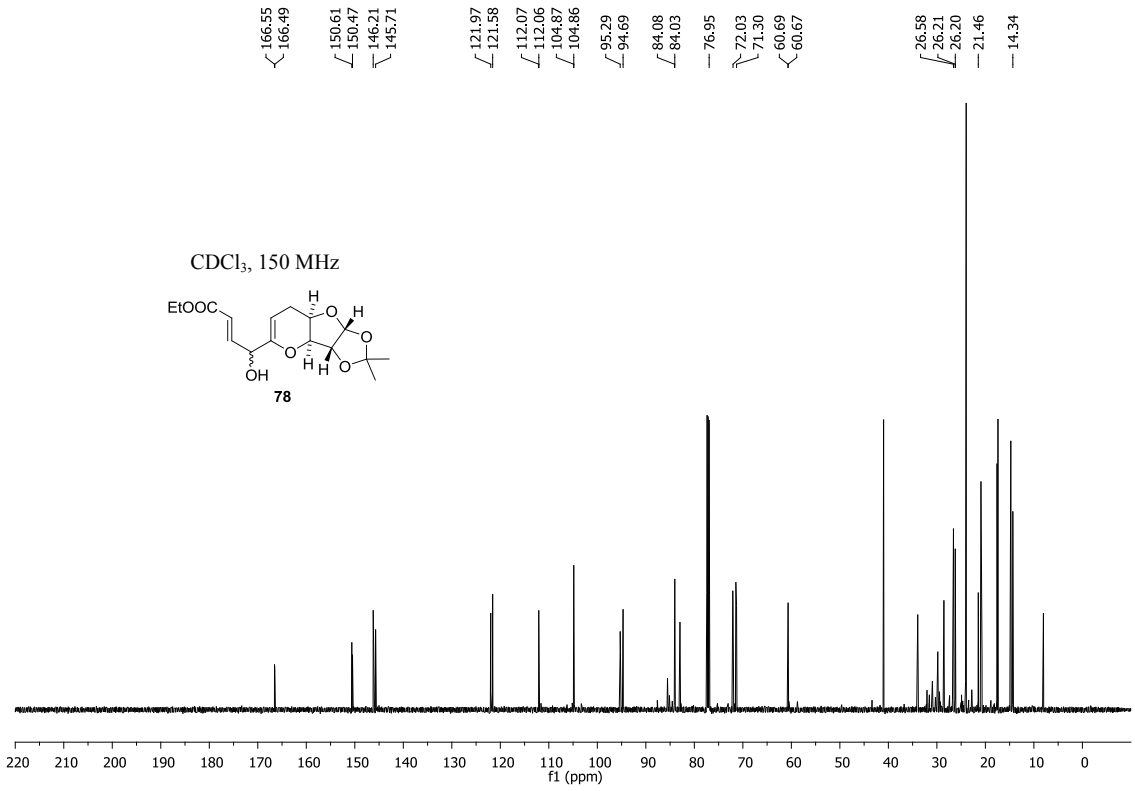

7.26
5.96
5.95
5.90
5.89
4.99
4.48
4.33
4.32
4.23
4.23
4.11
4.11
4.11
4.06
2.13
2.12
2.10
2.08
2.07
1.91
1.90
1.89
1.87
1.86
1.82
1.80
1.78
1.76
1.74
1.60
1.58
1.57
1.56
1.54
1.53
1.51
1.49
1.33
CDCl3, 600 MHz
73
f1 (ppm)

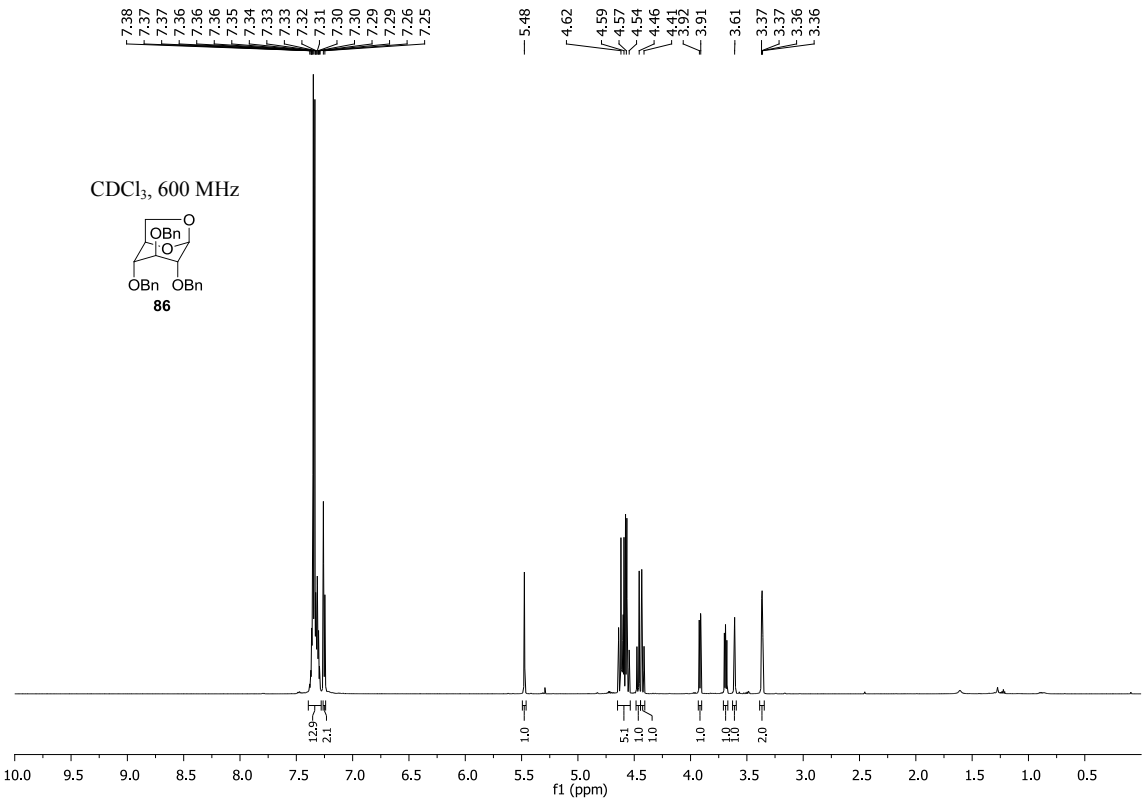

111.50
111.49
105.29
100.50
96.73
84.85
84.61
77.16
76.95
73.44
73.30
72.30
26.88
26.82
26.36
26.32
25.60
24.06
23.65
18.56
CDCl3, 150 MHz
73
f1 (ppm)

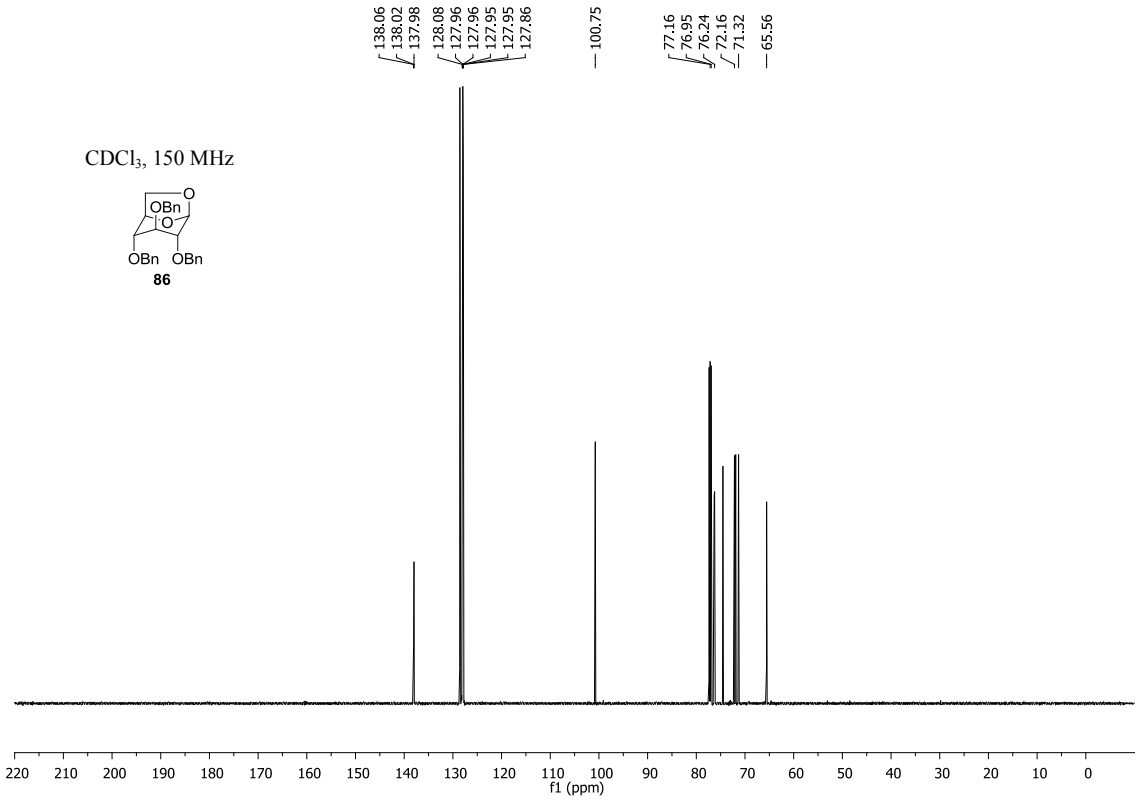

7.26
5.92
5.92
4.75
4.74
4.59
4.51
4.50
4.05
4.05
4.04
2.38
2.35
2.35
2.35
2.34
2.34
2.26
2.23
1.52
1.33
0.15
CDCl3, 600 MHz
Me3Sn
76
0.9
1.0
1.0
1.0
0.9
1.0
1.0
3.0
3.1
8.9
f1 (ppm)

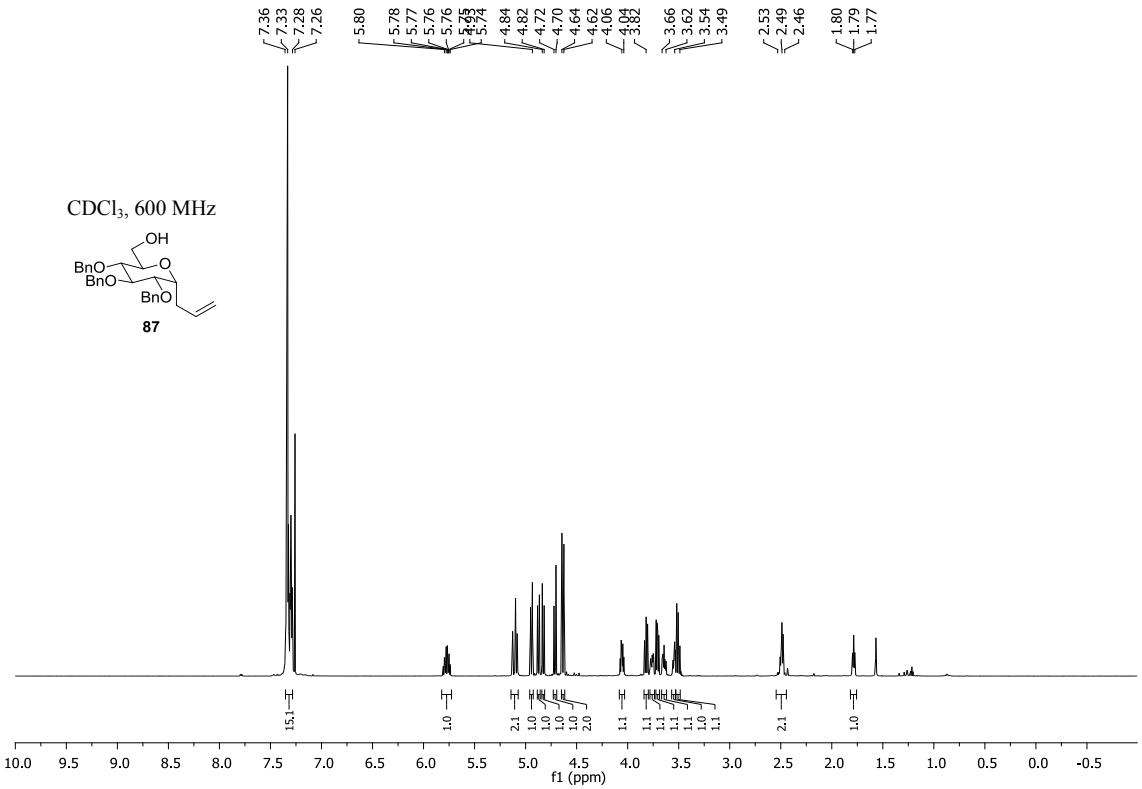

160.87
111.77
107.77
105.10
84.59
77.48
77.16
76.84
75.55
72.79
26.72
26.30
21.49
-9.65
CDCl3, 100 MHz
Me3Sn
76
f1 (ppm)

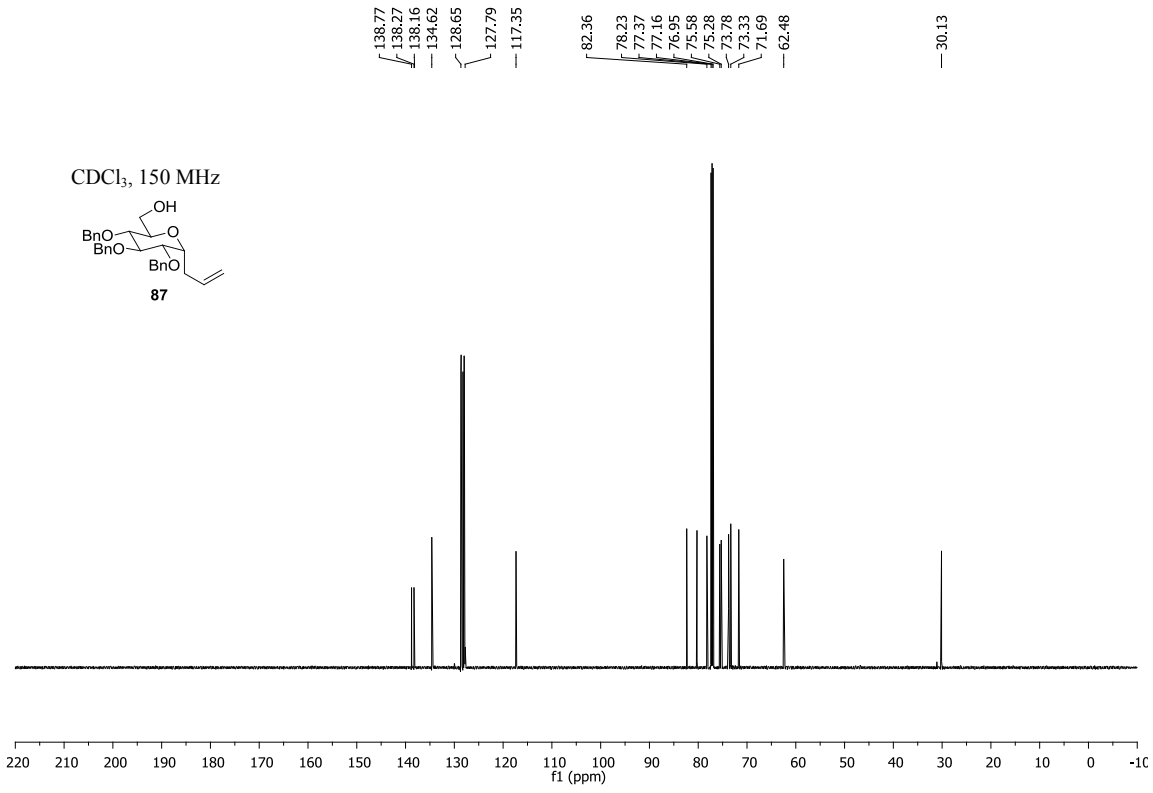

7.26
6.95
6.93
6.90
6.10
6.10
6.07
6.07
5.91
5.89
5.29
5.29
4.64
4.62
4.49
4.48
4.20
4.19
4.19
4.18
4.18
2.40
2.38
2.37
2.37
2.33
2.26
2.24
1.52
1.33
1.30
1.30
1.29
1.29
1.28
1.27
CDCl3, 600 MHz
EtOOC
OH
78
2.2
2.2
2.2
1.2
1.0
4.5
2.3
7.6
4.6
7.7
7.8
7.8
f1 (ppm)

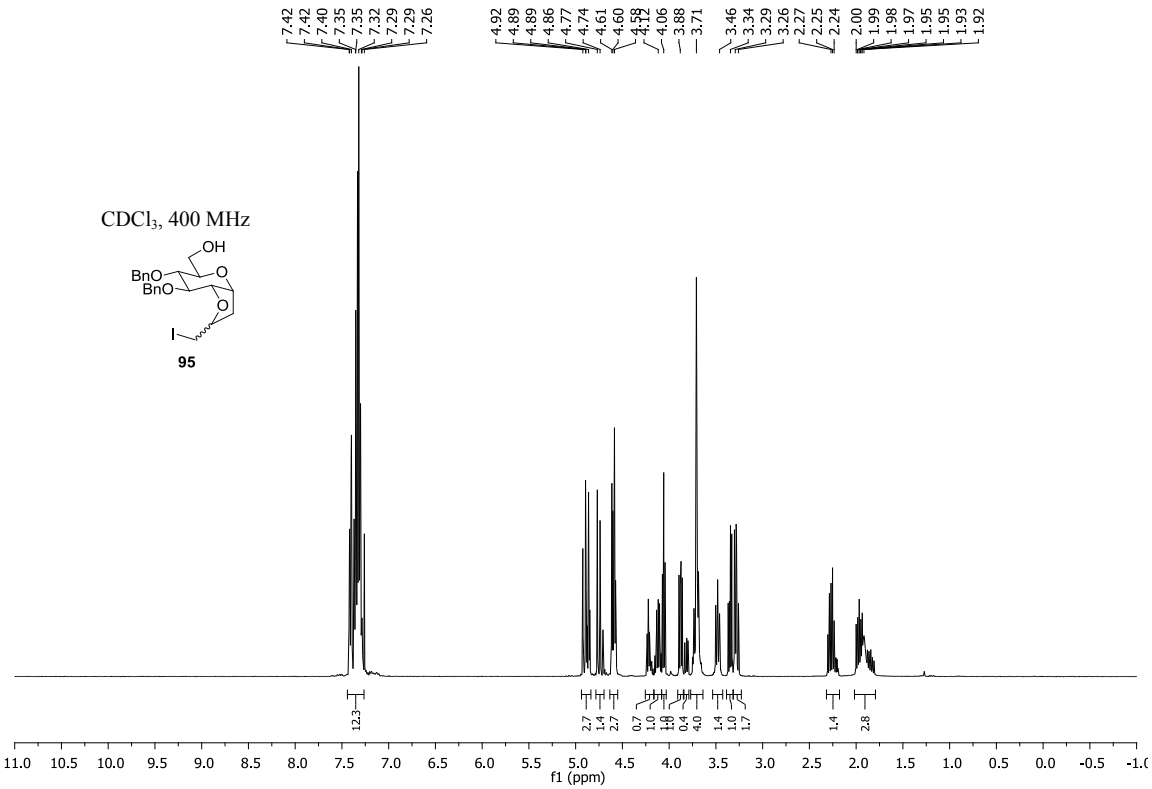

166.55
166.49
150.61
150.47
146.21
145.71
121.97
121.58
112.07
112.06
104.87
104.86
95.29
94.69
84.08
84.03
76.95
72.03
71.30
60.69
60.67
26.58
26.21
26.20
21.46
14.34
CDCl3, 150 MHz
EtOOC
OH
78
f1 (ppm)

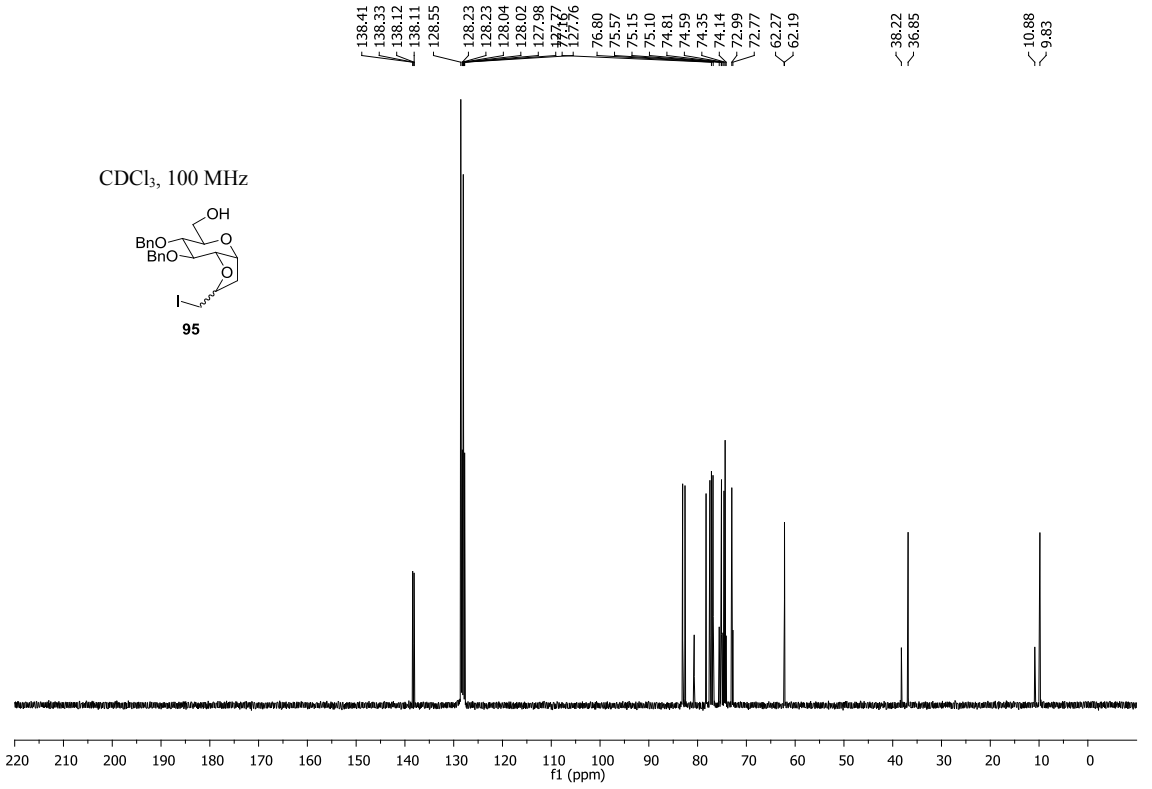

7.38
7.37
7.37
7.36
7.36
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.30
7.30
7.29
7.29
7.26
7.25
5.48
4.62
4.59
4.57
4.54
4.46
4.41
3.92
3.91
3.61
3.37
3.37
3.36
3.36
CDCl3, 600 MHz
O
OBn
O
OBn OBn
86
12.9
2.1
1.0
5.1
1.0
1.0
1.0
1.0
1.0
2.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

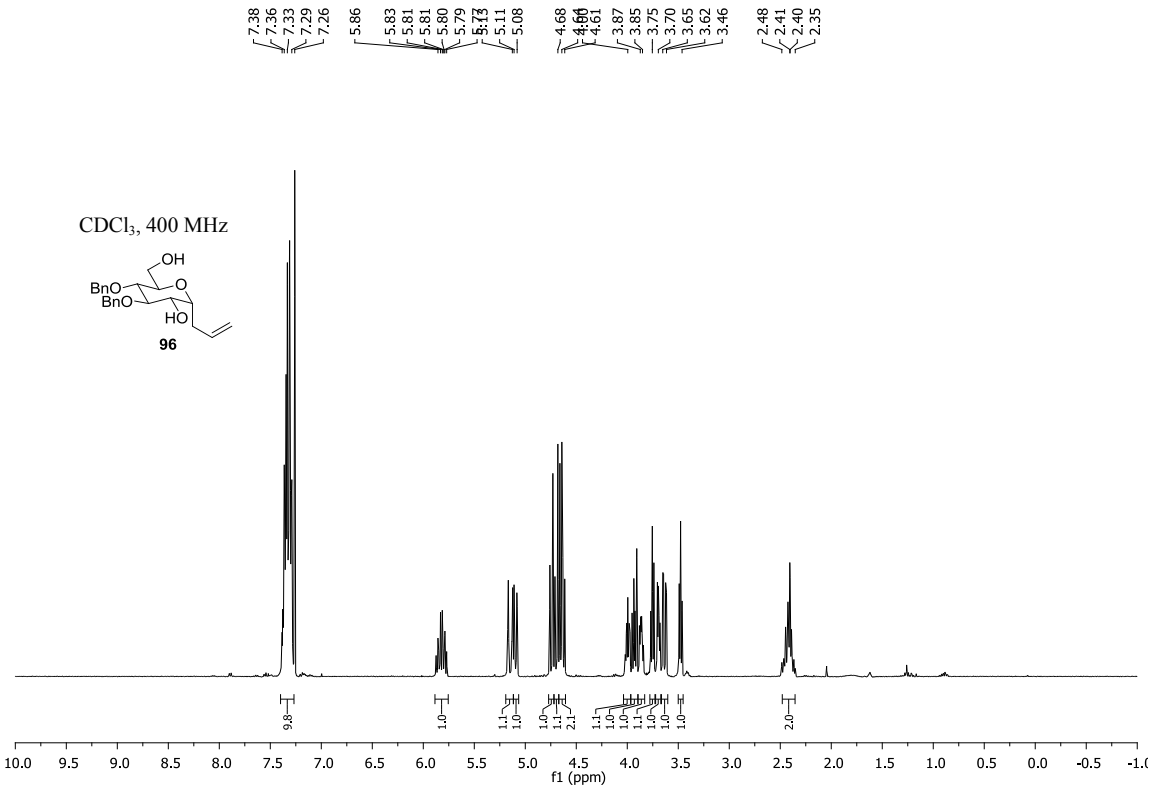

138.06
138.02
137.98
128.08
127.96
127.96
127.95
127.95
127.86
100.75
77.16
76.95
76.24
72.16
71.32
65.56
CDCl3, 150 MHz
O
OBn
O
OBn OBn
86
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

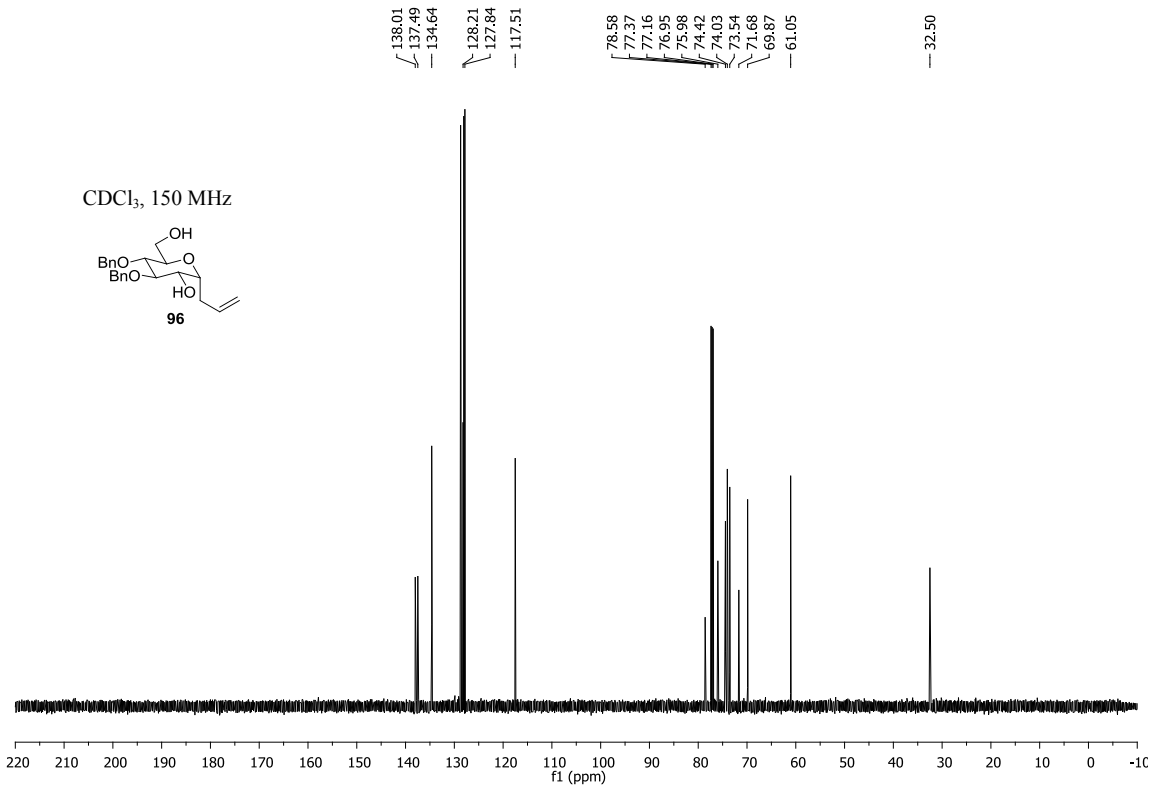

CDCl3, 600 MHz
OH
BnO
BnO
O
BnO
87
7.36
7.33
7.28
7.26
5.80
5.78
5.77
5.76
5.76
5.75
5.74
4.84
4.82
4.72
4.70
4.64
4.62
4.06
3.84
3.82
3.66
3.62
3.54
3.49
2.53
2.49
2.46
1.80
1.79
1.77
15.1
1.0
2.1
1.0
1.0
1.0
2.0
1.1
1.1
1.1
1.1
1.0
1.1
2.1
1.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

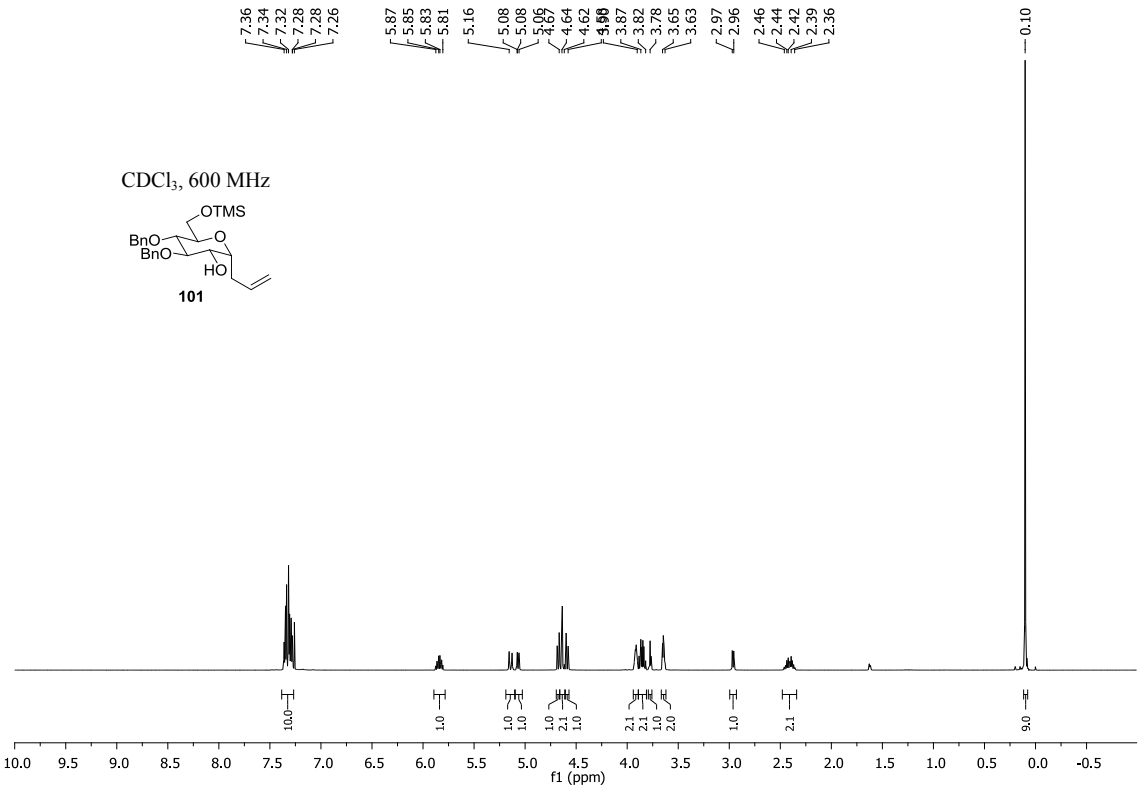

CDCl3, 150 MHz
OH
BnO
BnO
O
BnO
87
138.77
138.27
138.16
134.62
128.65
127.79
117.35
82.36
78.23
77.37
77.16
76.95
75.58
75.28
73.78
73.33
71.69
62.48
30.13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

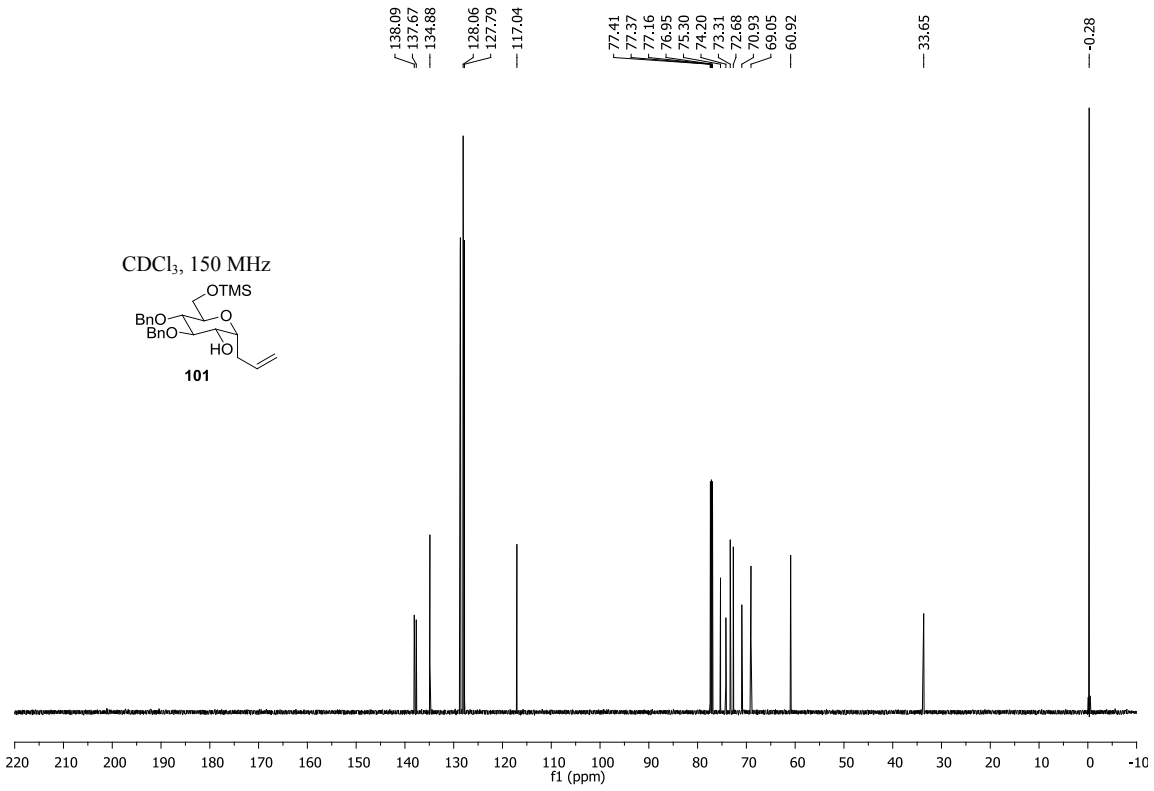

CDCl3, 400 MHz
OH
BnO
BnO
O
O
I
95
f1 (ppm)

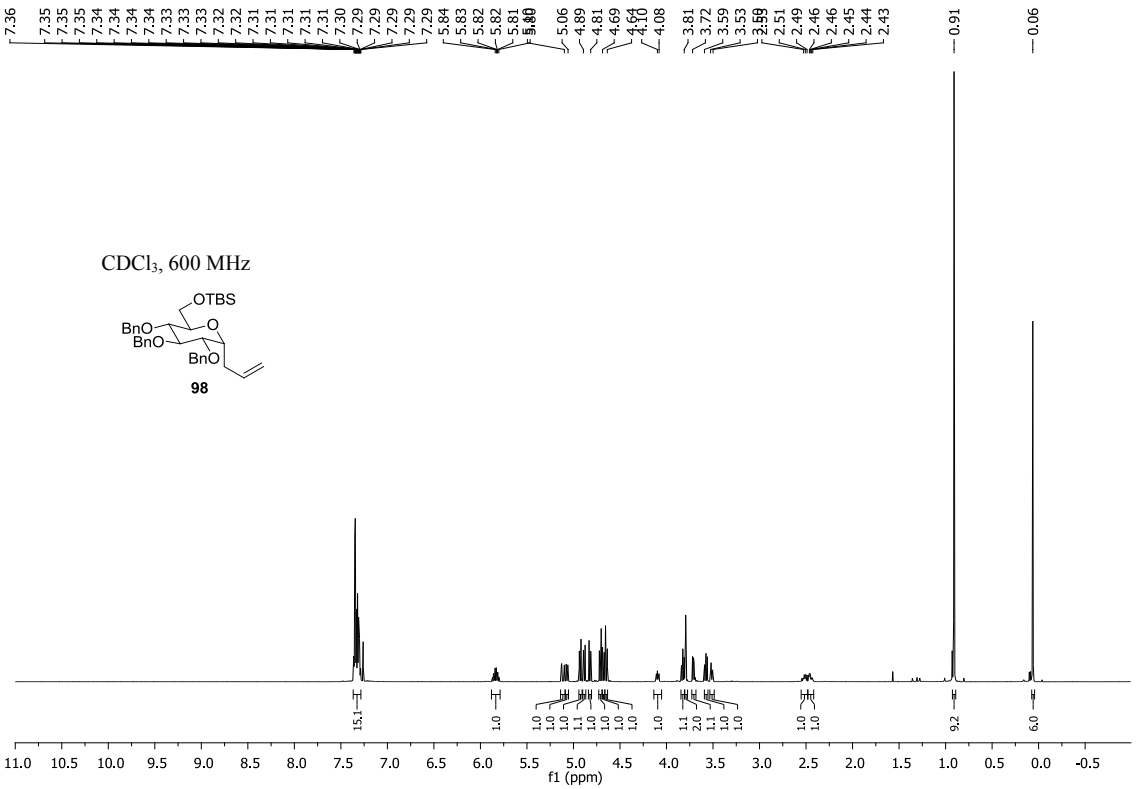

CDCl3, 100 MHz
OH
BnO
BnO
O
O
I
95
f1 (ppm)

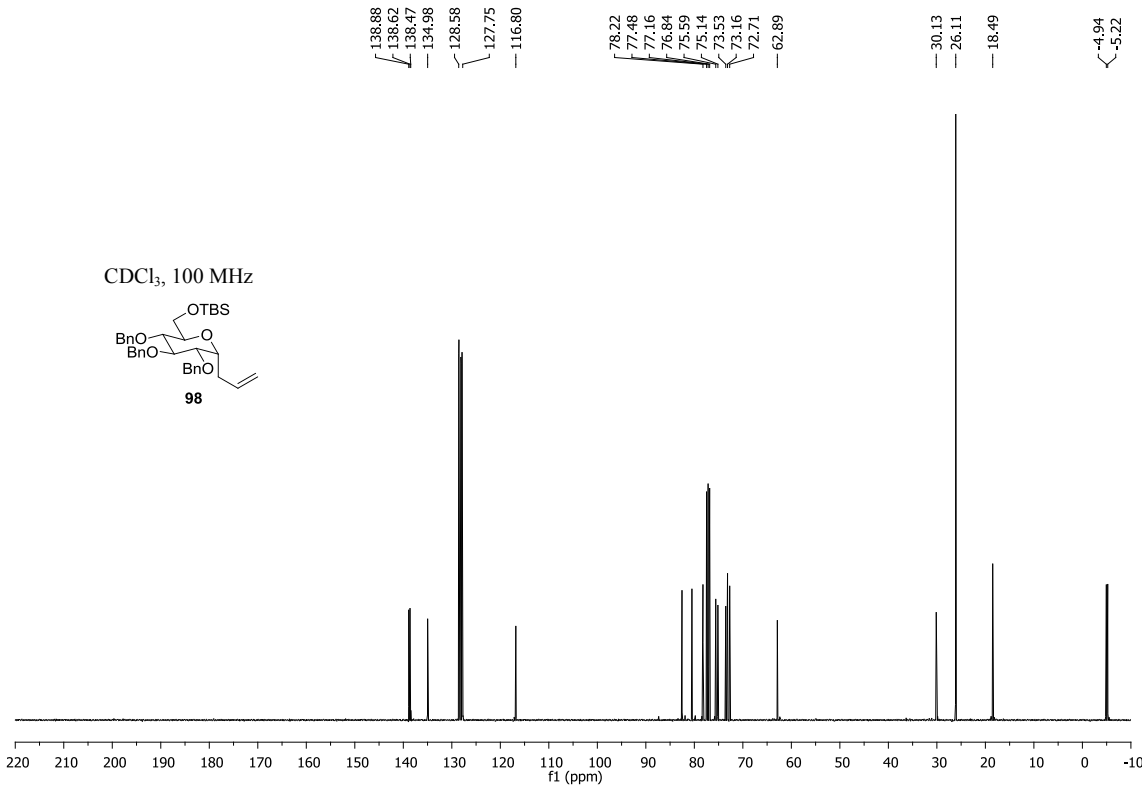

7.38
7.36
7.33
7.29
7.26
5.86
5.83
5.81
5.81
5.80
5.79
5.13
5.11
5.08
4.68
4.64
4.61
3.87
3.85
3.75
3.70
3.65
3.62
3.46
2.48
2.41
2.40
2.35
CDCl3, 400 MHz
OH
BnO
BnO
O
HO
96
9.8
1.0
1.1
1.0
1.0
1.1
2.1
1.1
1.0
1.0
1.1
1.0
1.0
1.0
2.0
f1 (ppm)

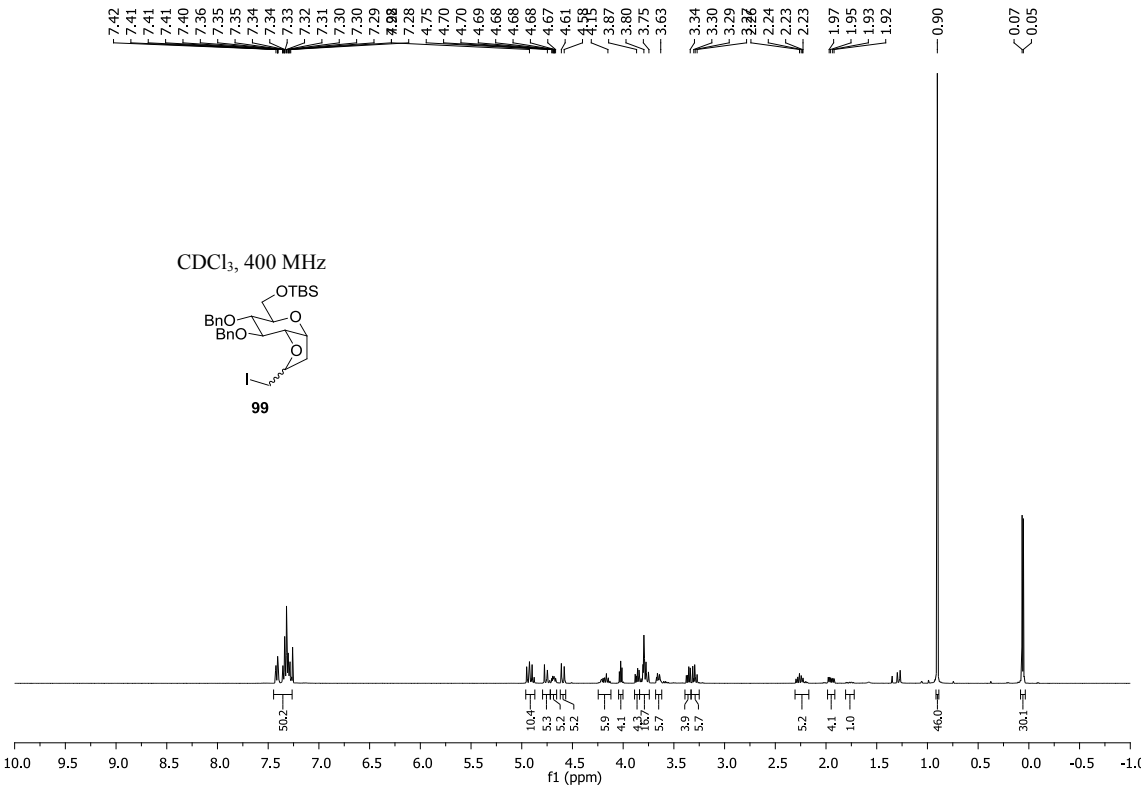

138.01
137.49
134.64
128.21
127.84
117.51
78.58
77.37
77.16
76.95
75.98
74.42
74.03
73.54
71.68
69.87
61.05
32.50
CDCl3, 150 MHz
OH
BnO
BnO
O
HO
96
f1 (ppm)

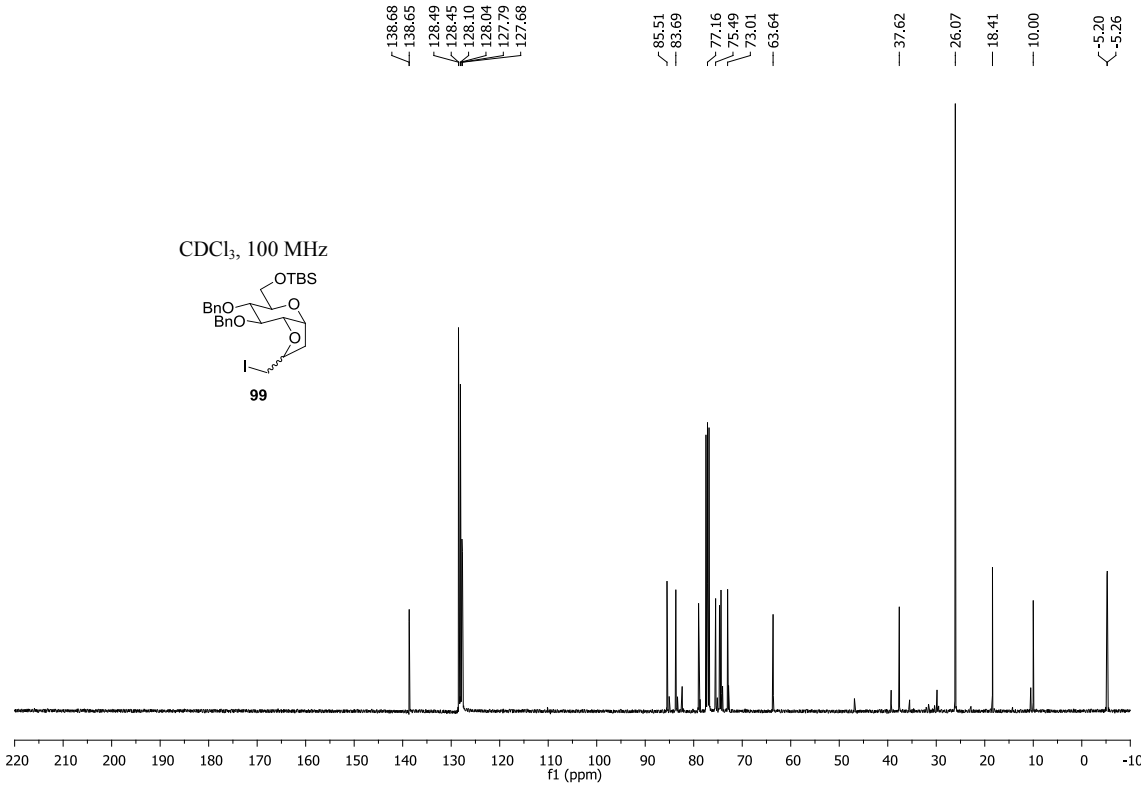

CDCl3, 600 MHz
OTMS
BnO
BnO
O
HO
101
f1 (ppm)

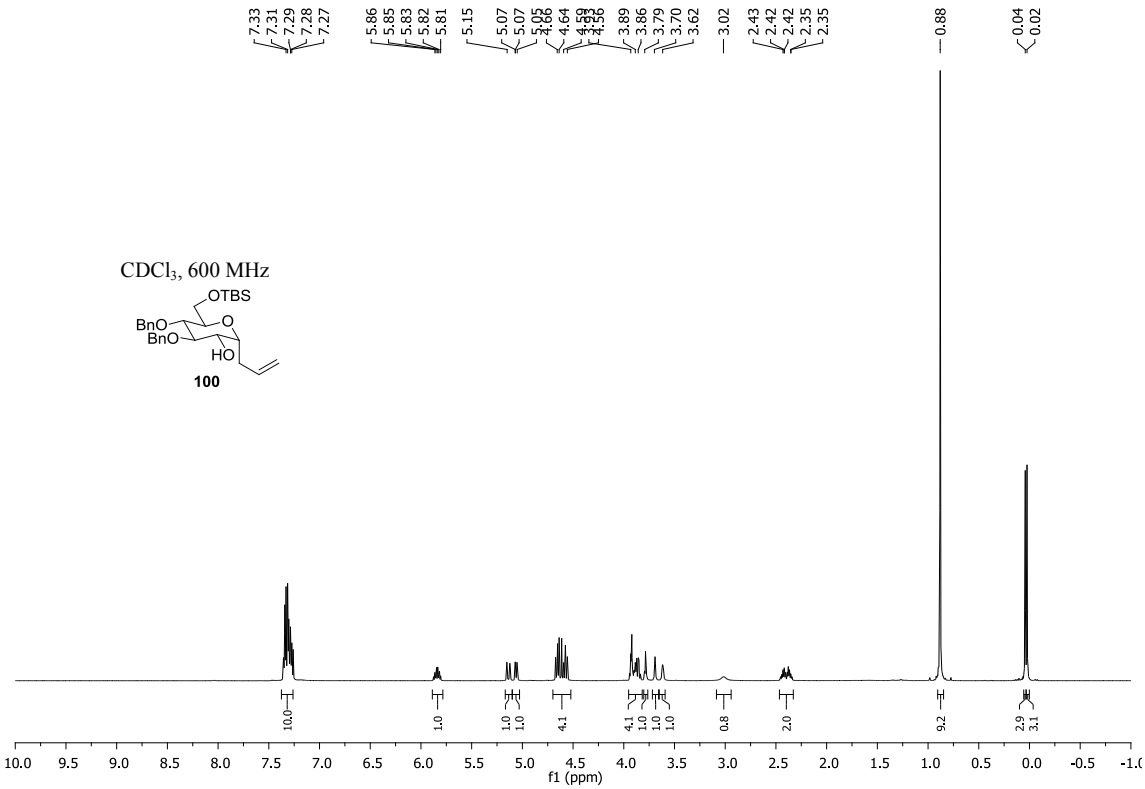

CDCl3, 150 MHz
OTMS
BnO
BnO
O
HO
101
f1 (ppm)

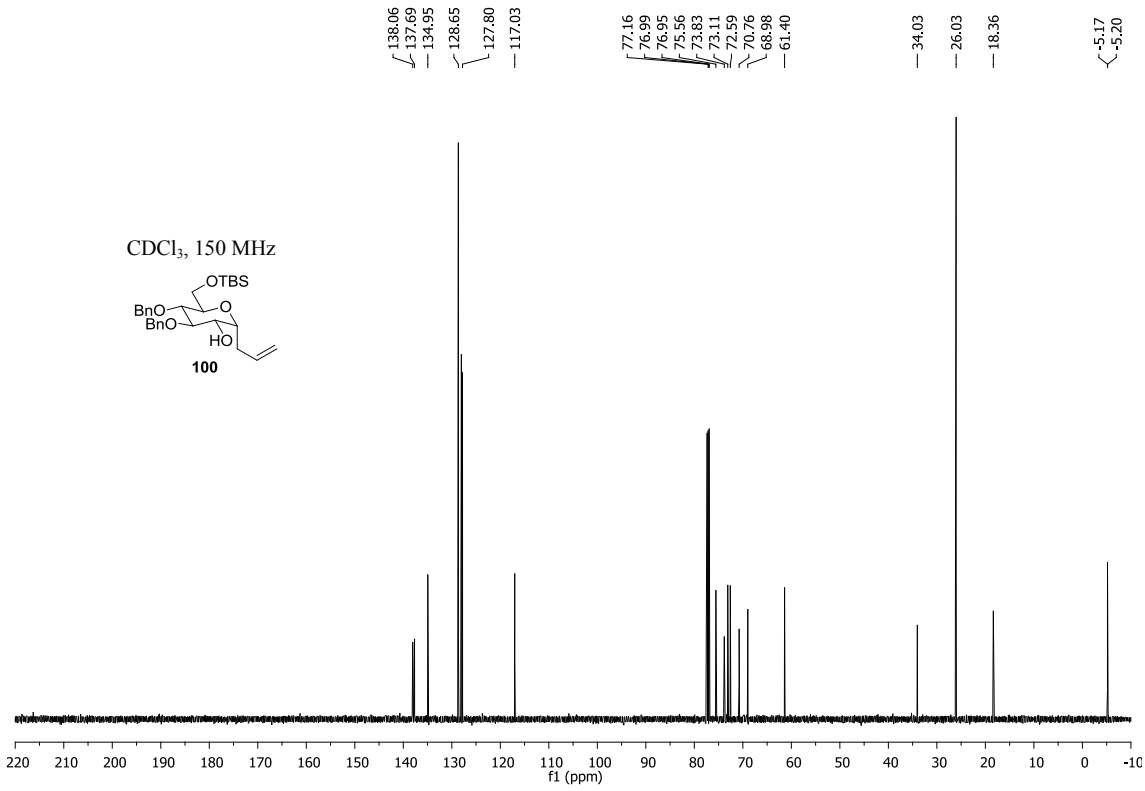

CDCl3, 600 MHz
OTBS
BnO
BnO
BnO
O
98
f1 (ppm)

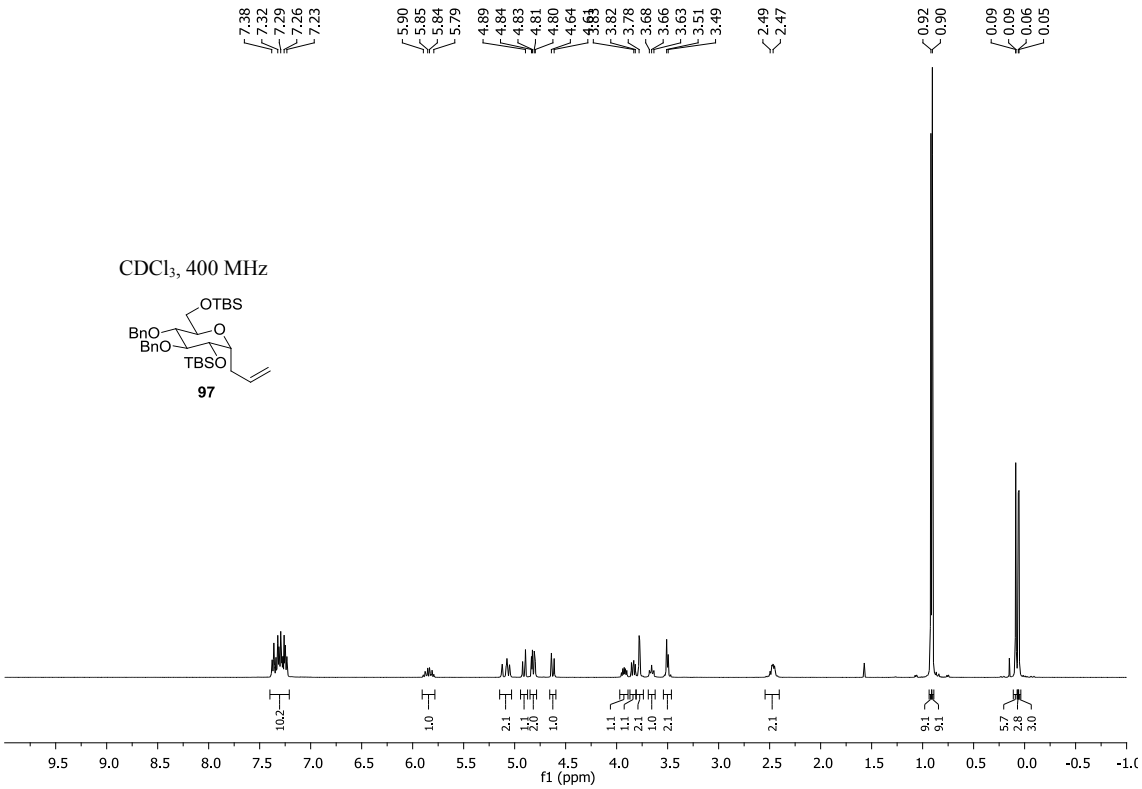

CDCl3, 100 MHz
OTBS
BnO
BnO
BnO
O
98
f1 (ppm)

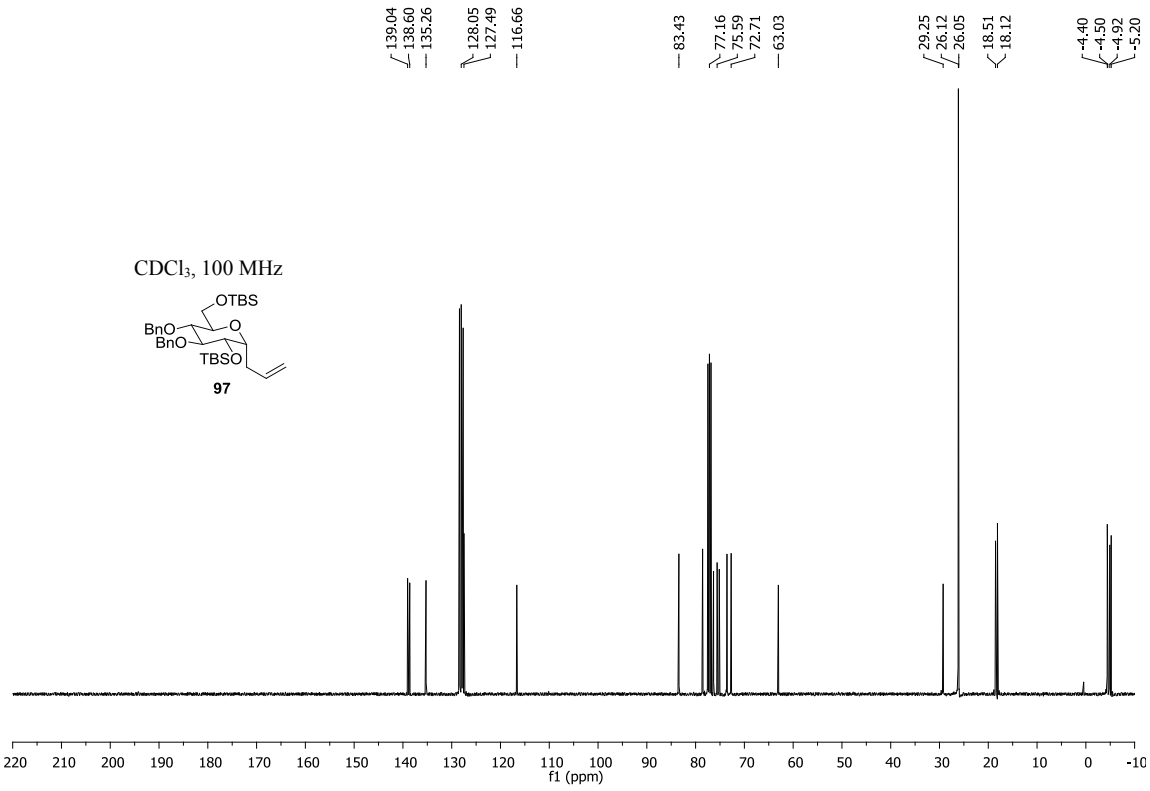

CDCl3, 400 MHz
OTBS
BnO
BnO
O
O
I
99
f1 (ppm)

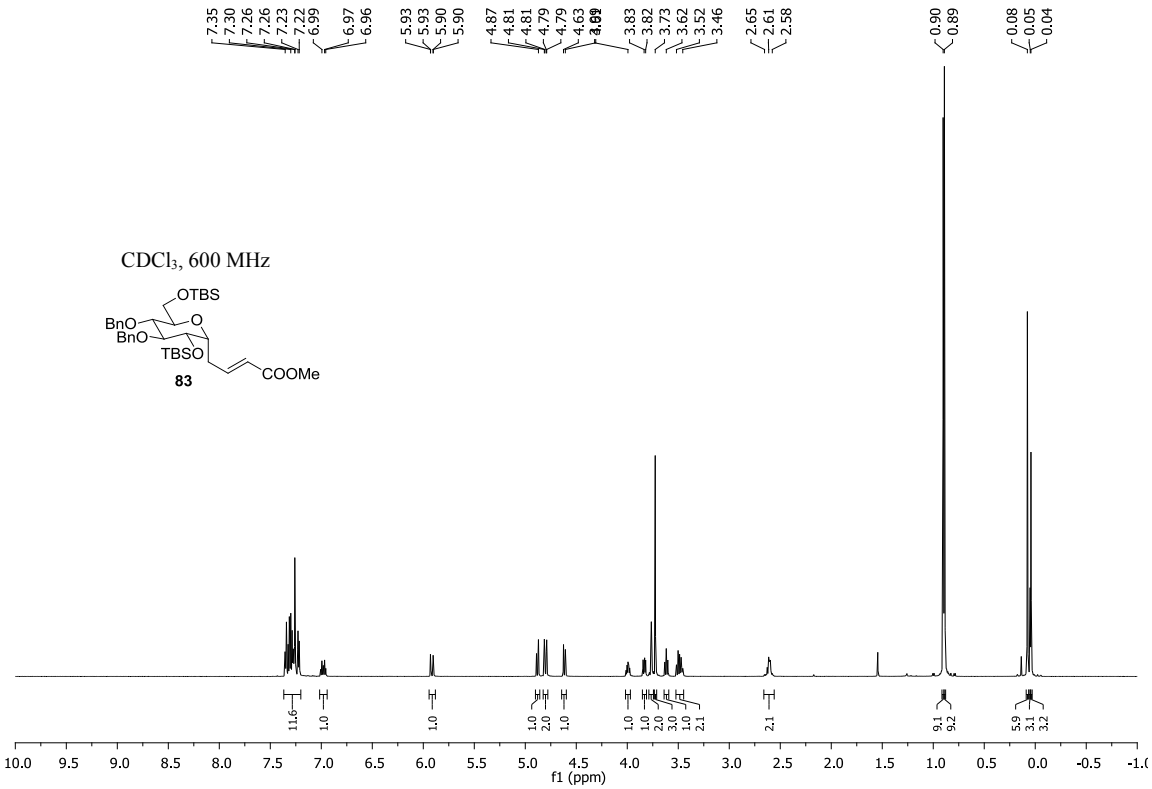

CDCl3, 100 MHz
OTBS
BnO
BnO
O
O
I
99
f1 (ppm)

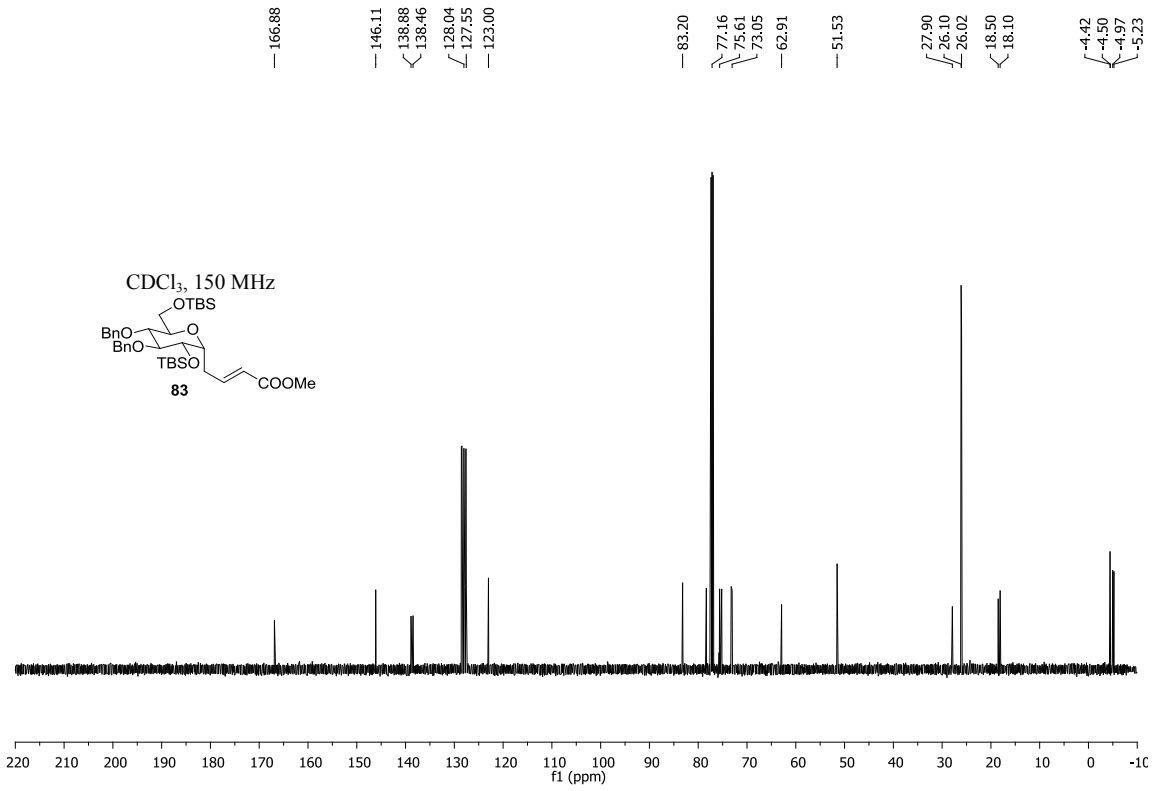

CDCl3, 600 MHz
OTBS
BnO
BnO
O
HO
100
f1 (ppm)

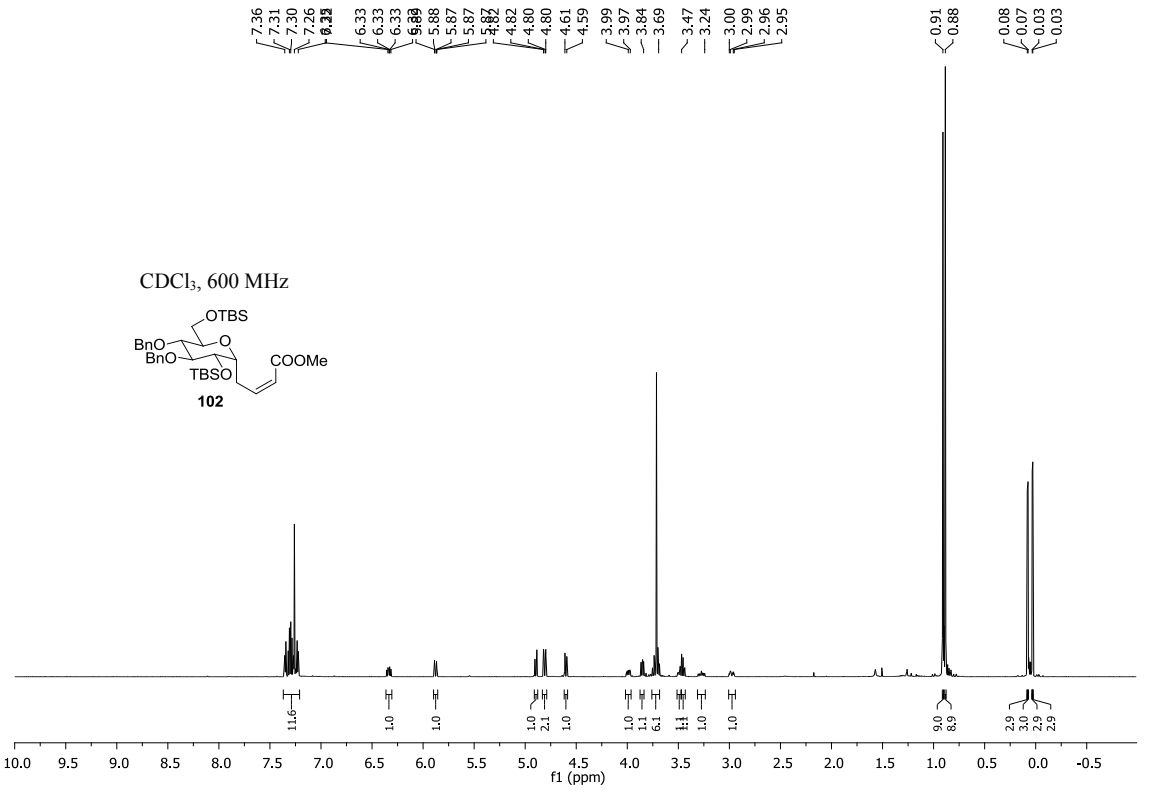

CDCl3, 150 MHz
OTBS
BnO
BnO
O
HO
100
f1 (ppm)

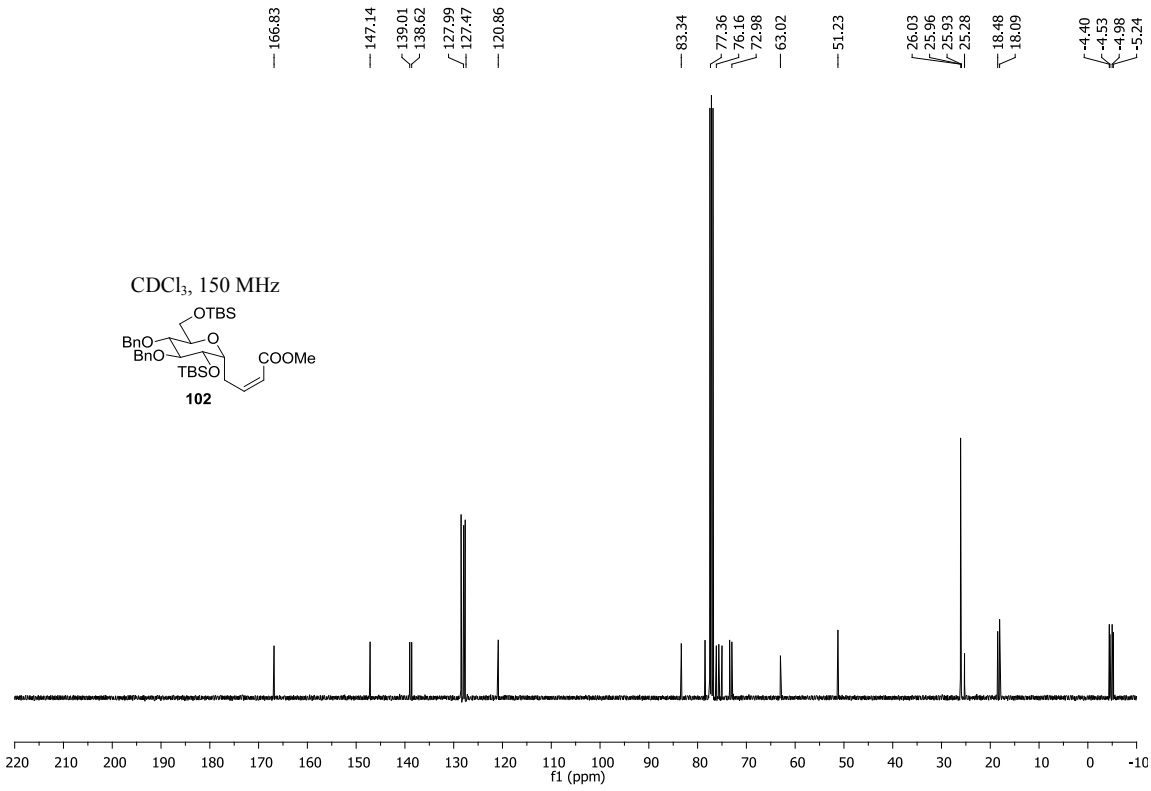

7.38
7.32
7.29
7.26
7.23
5.90
5.85
5.84
5.79
4.89
4.84
4.83
4.81
4.80
4.64
3.82
3.78
3.68
3.66
3.63
3.51
3.49
2.49
2.47
0.92
0.90
0.09
0.09
0.06
0.05
CDCl3, 400 MHz
OTBS
BnO
BnO
O
TBSO
97
10.2
1.0
2.1
2.1
2.0
1.0
1.1
1.1
2.1
1.0
2.1
2.1
9.1
9.1
5.7
2.8
3.0
f1 (ppm)

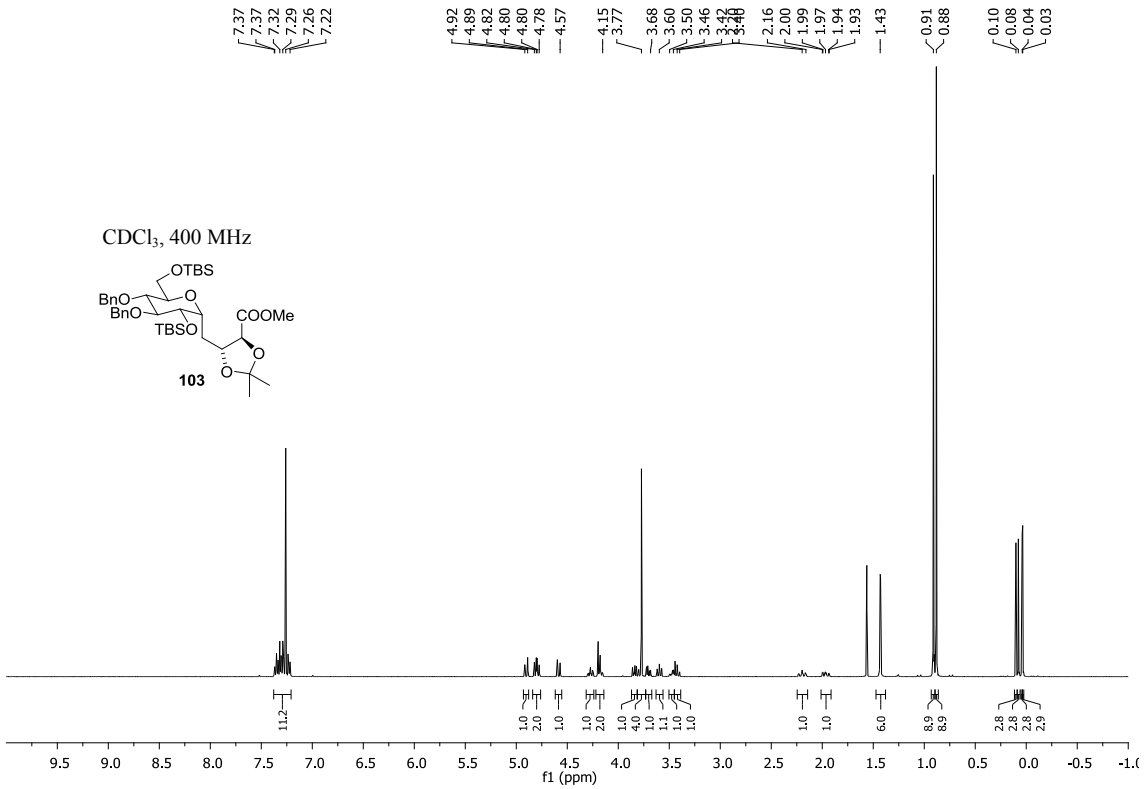

139.04
138.60
135.26
128.05
127.49
116.66
83.43
77.16
75.59
72.71
63.03
29.25
26.12
26.05
18.51
18.12
-4.40
-4.50
-4.92
-5.20
CDCl3, 100 MHz
OTBS
BnO
BnO
O
TBSO
97
f1 (ppm)

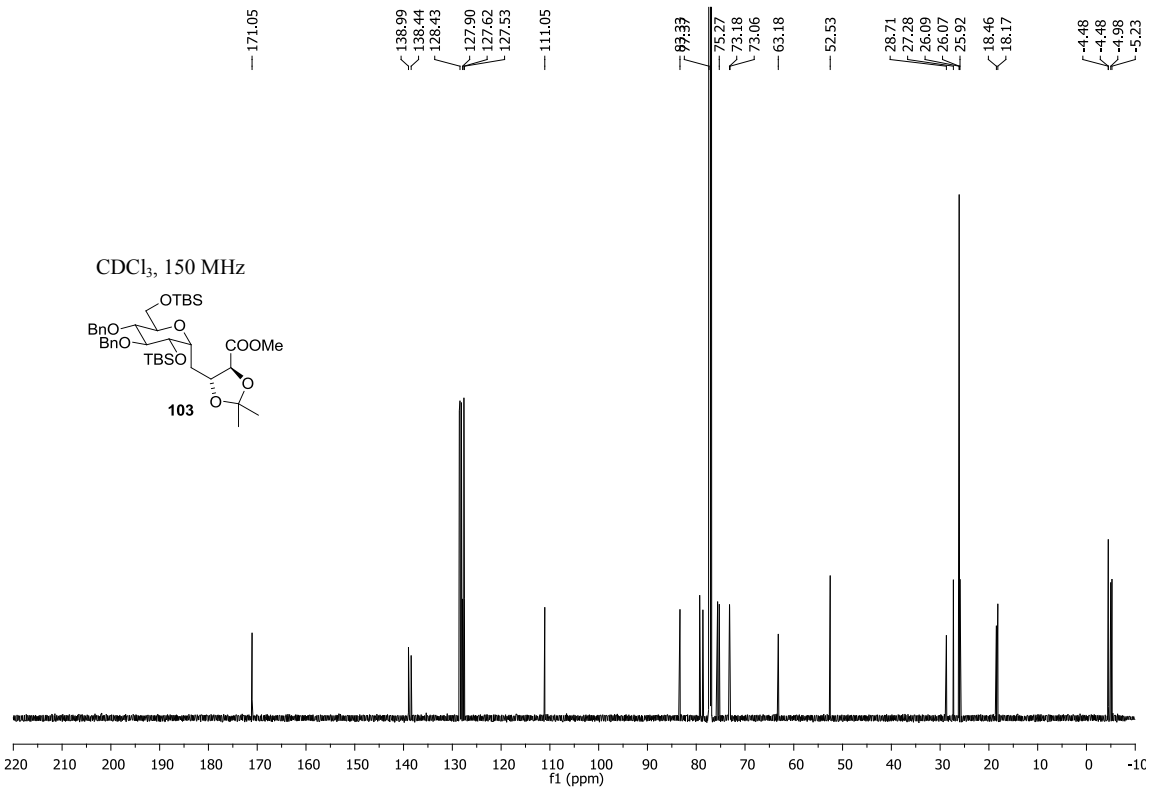

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
O
COOMe
83
f1 (ppm)

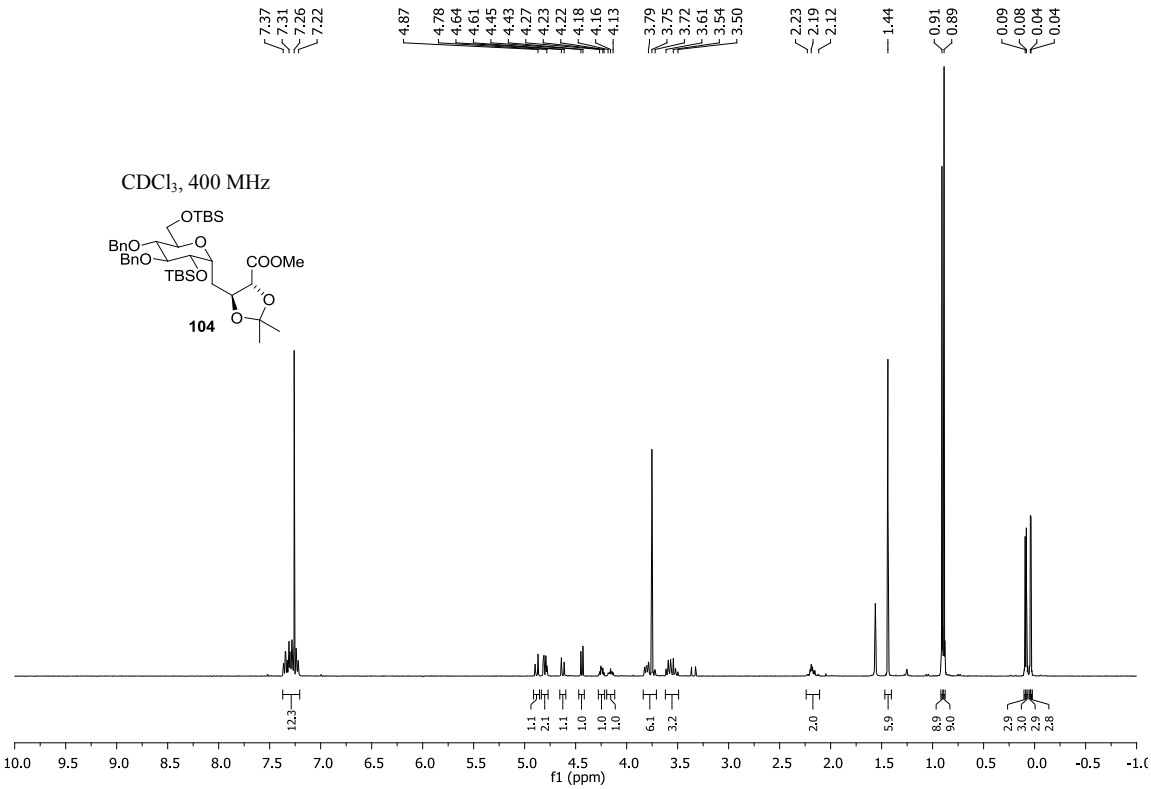

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
O
COOMe
83
f1 (ppm)

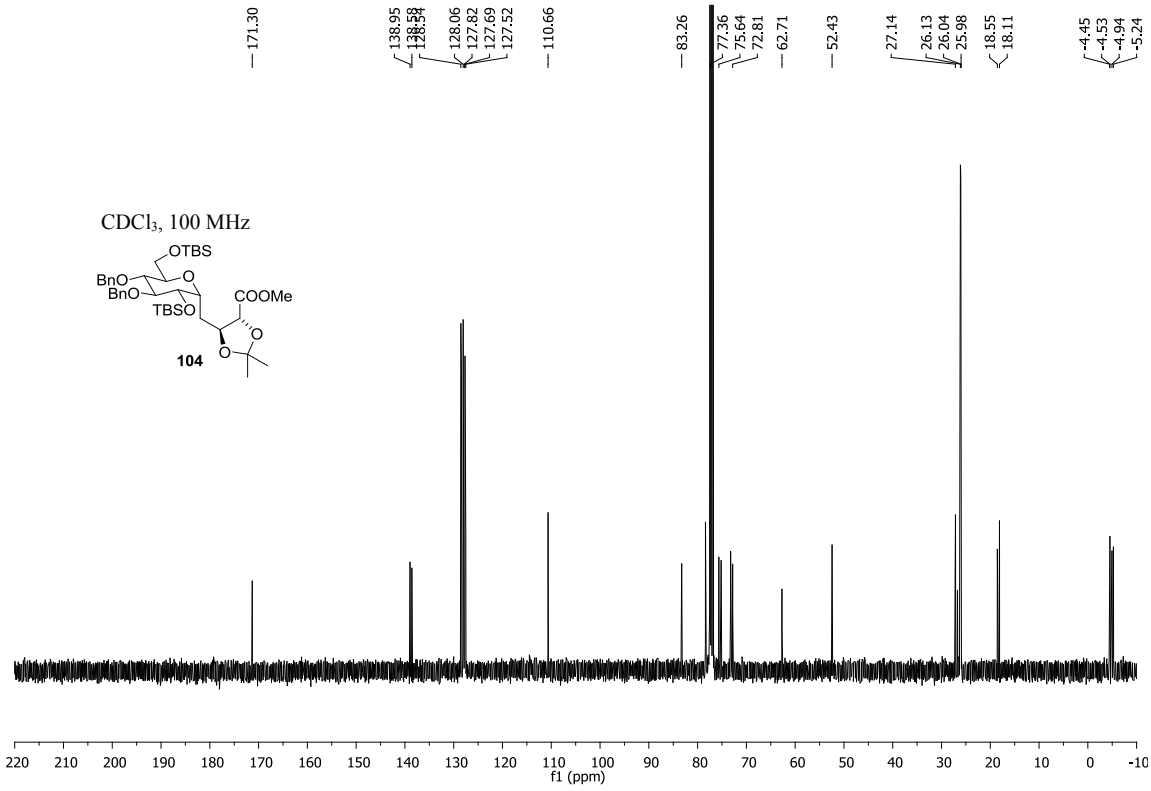

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
COOMe
102
f1 (ppm)

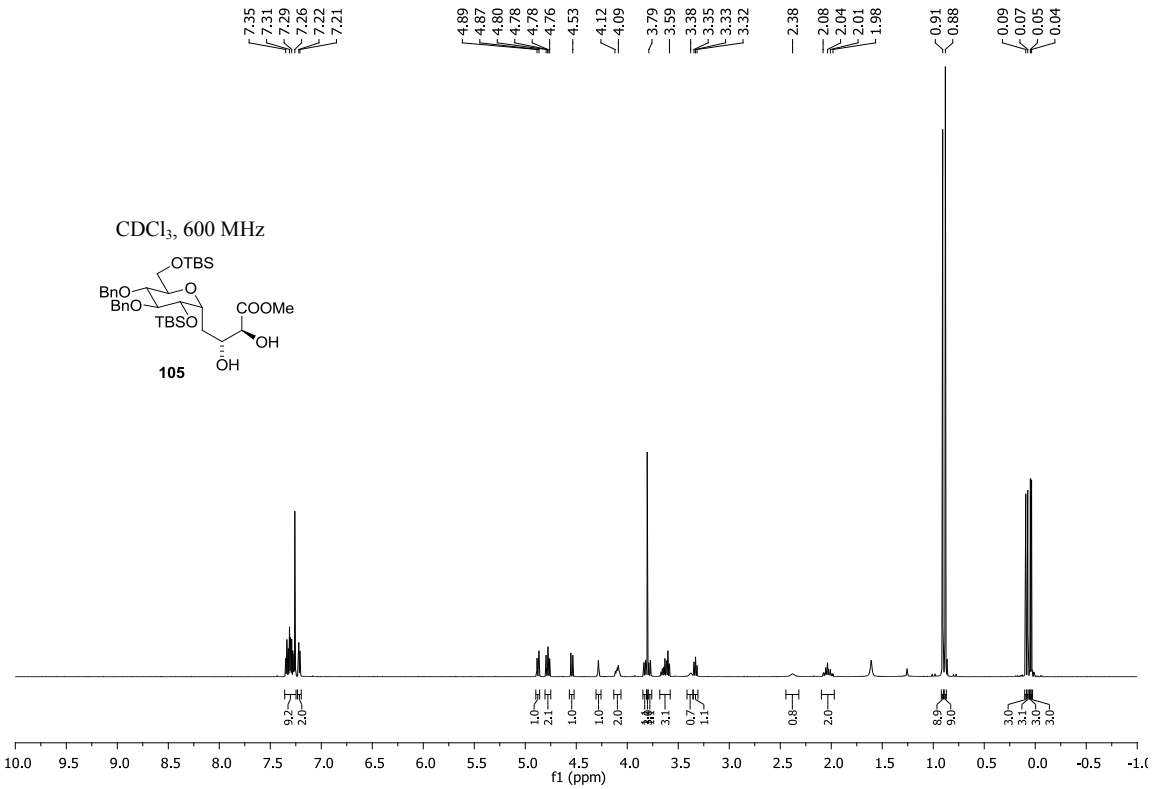

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
COOMe
102
f1 (ppm)

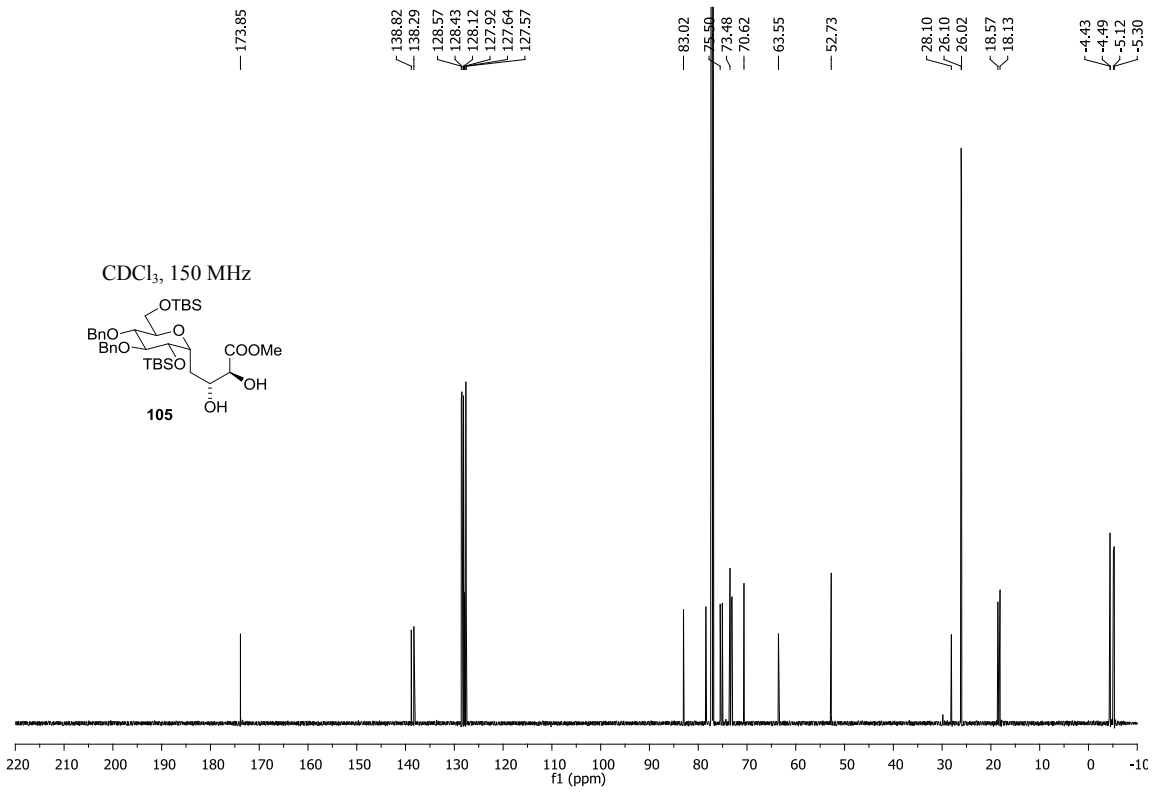

CDCl3, 400 MHz
OTBS
BnO
BnO
TBSO
COOMe
103
f1 (ppm)

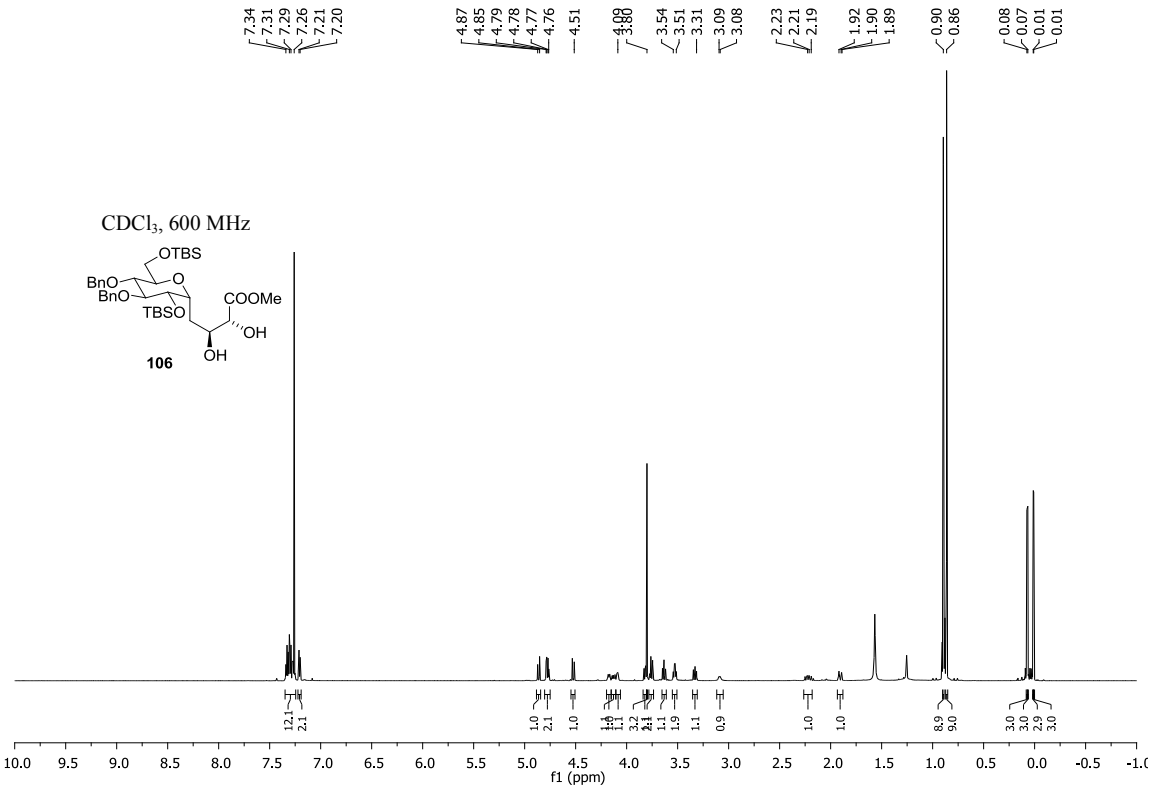

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
COOMe
103
f1 (ppm)

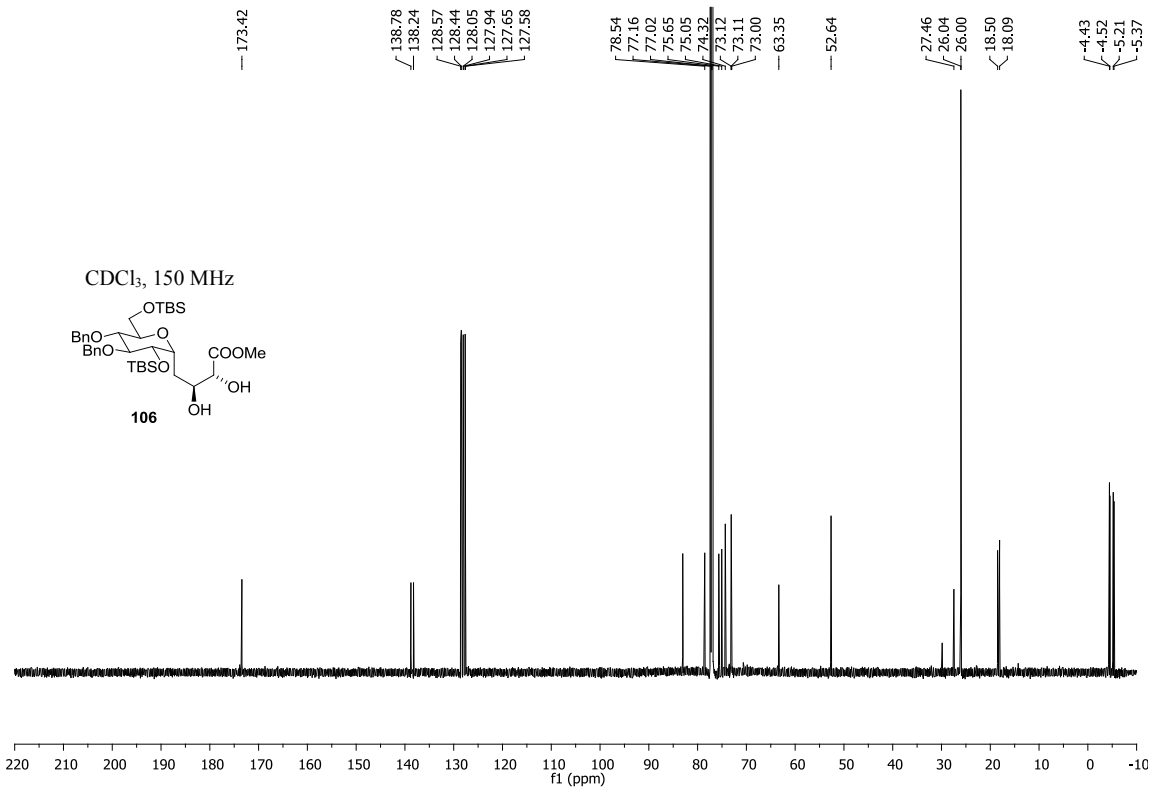

CDCl3, 400 MHz
OTBS
BnO
BnO
TBSO
COOMe
104
f1 (ppm)

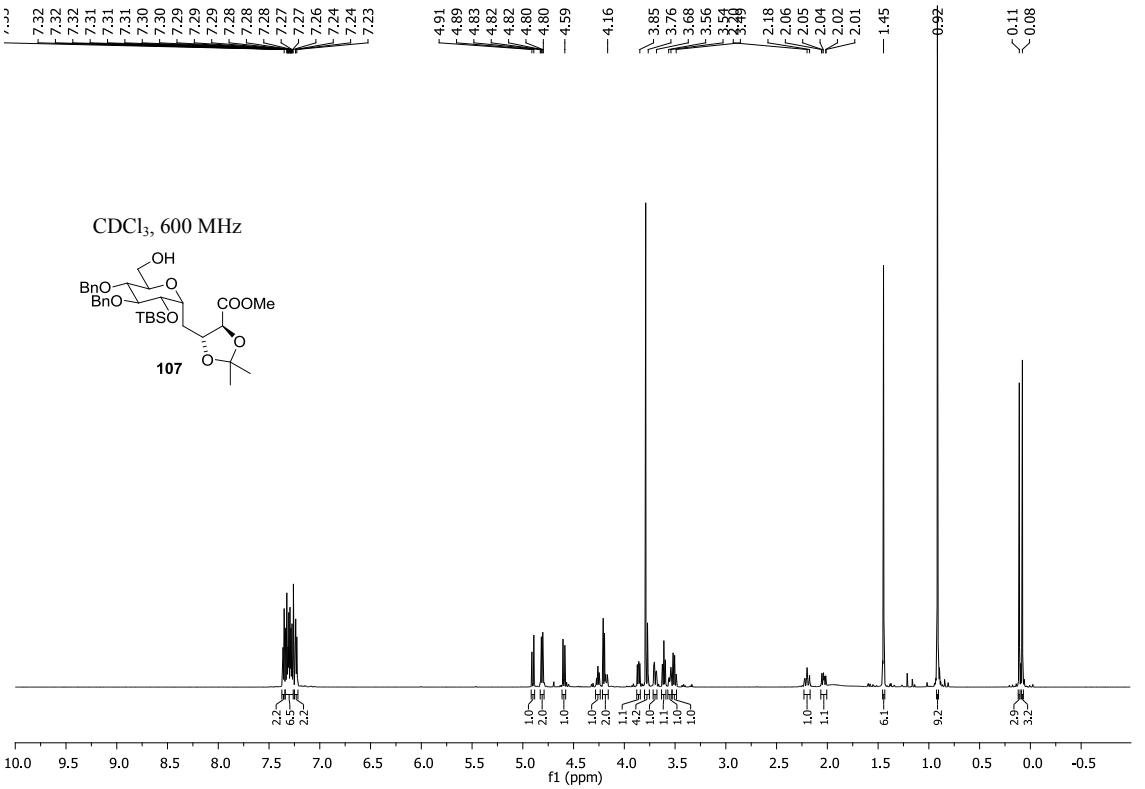

CDCl3, 100 MHz
OTBS
BnO
BnO
TBSO
COOMe
104
f1 (ppm)

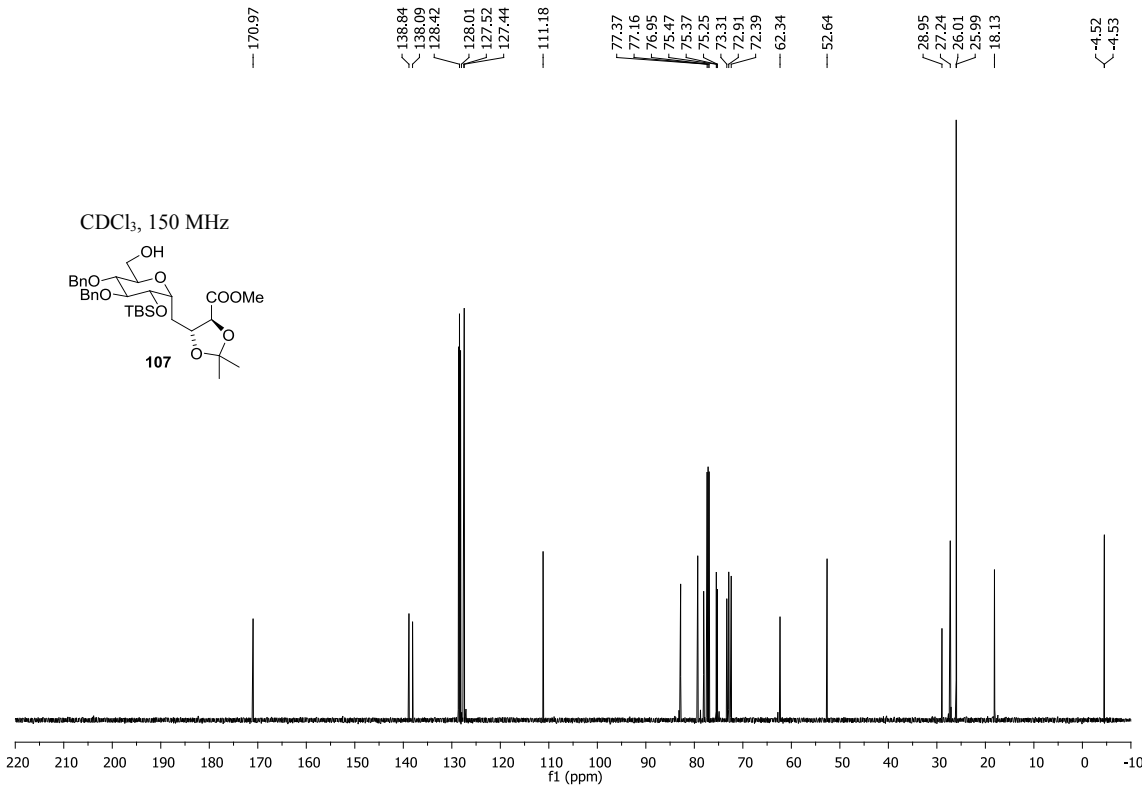

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
COOMe
OH
OH
105
f1 (ppm)

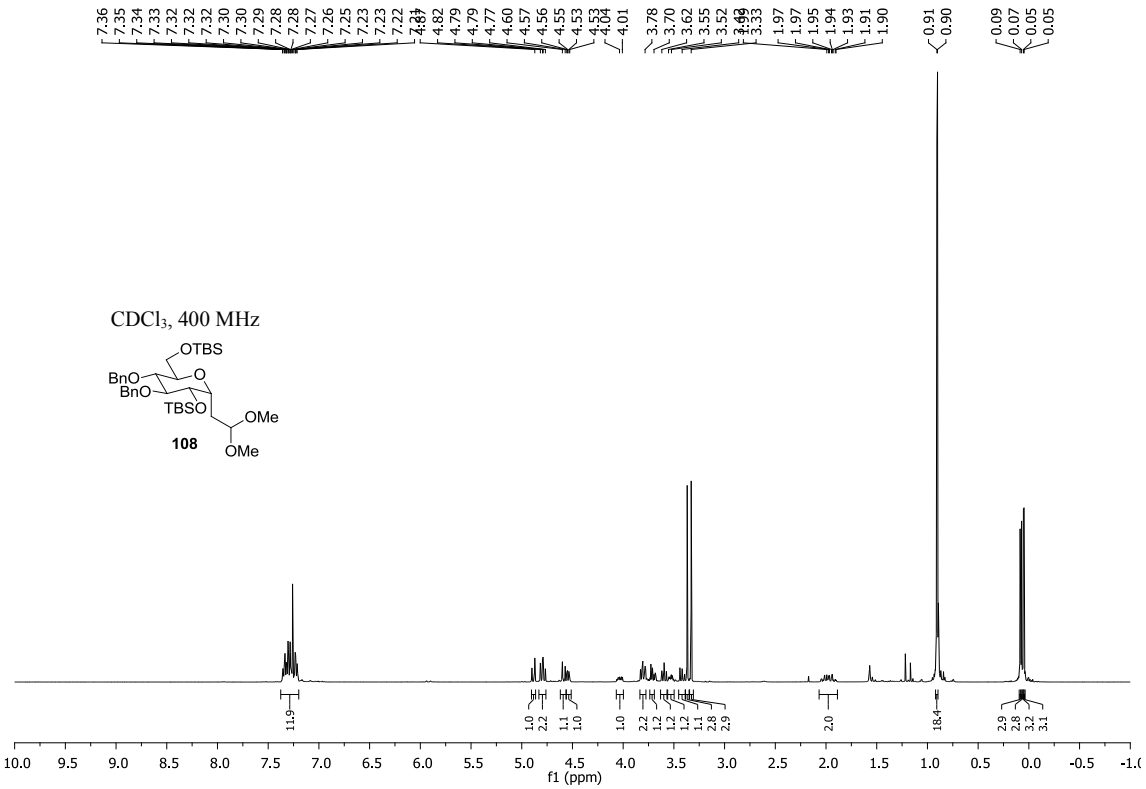

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
COOMe
OH
OH
105
f1 (ppm)

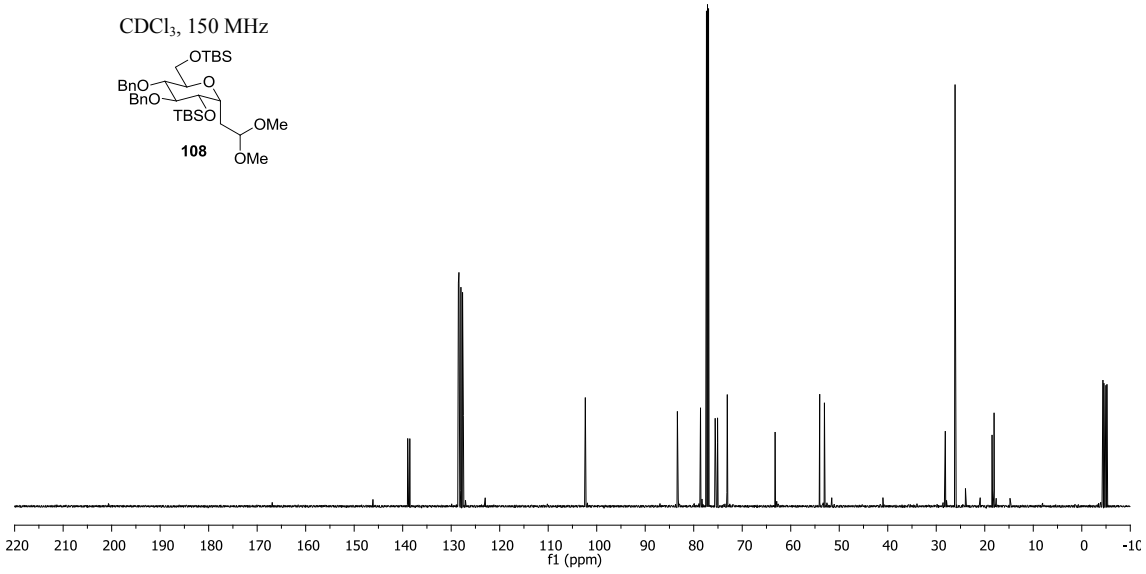

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
COOMe
OH
OH
106
f1 (ppm)

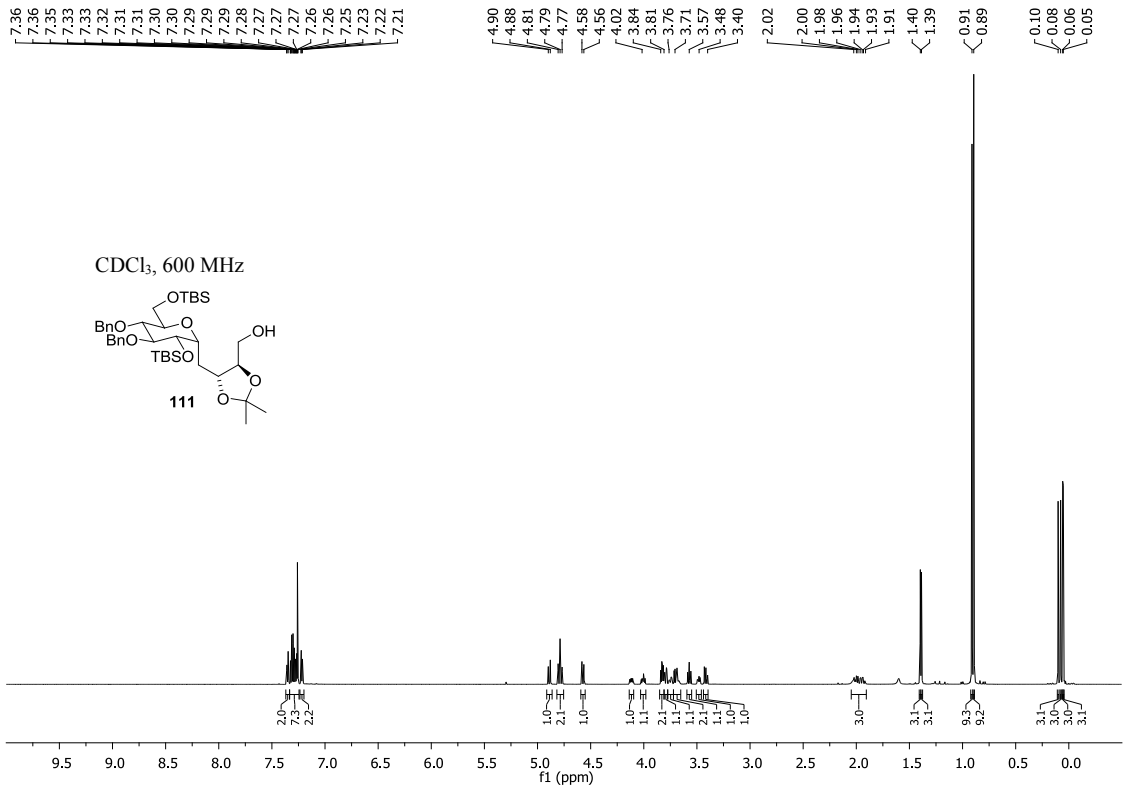

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
COOMe
OH
OH
106
f1 (ppm)

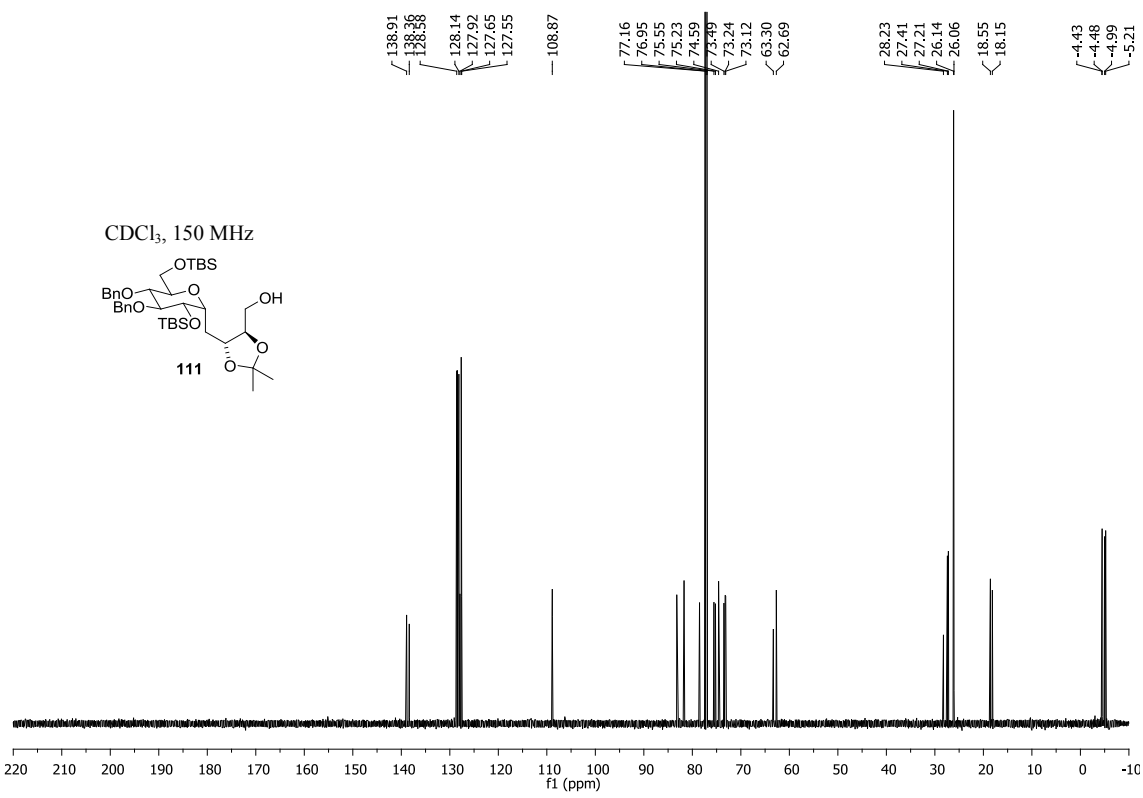

CDCl3, 600 MHz
OH
BnO
BnO
O
TBSO
COOMe
O
O
107
f1 (ppm)

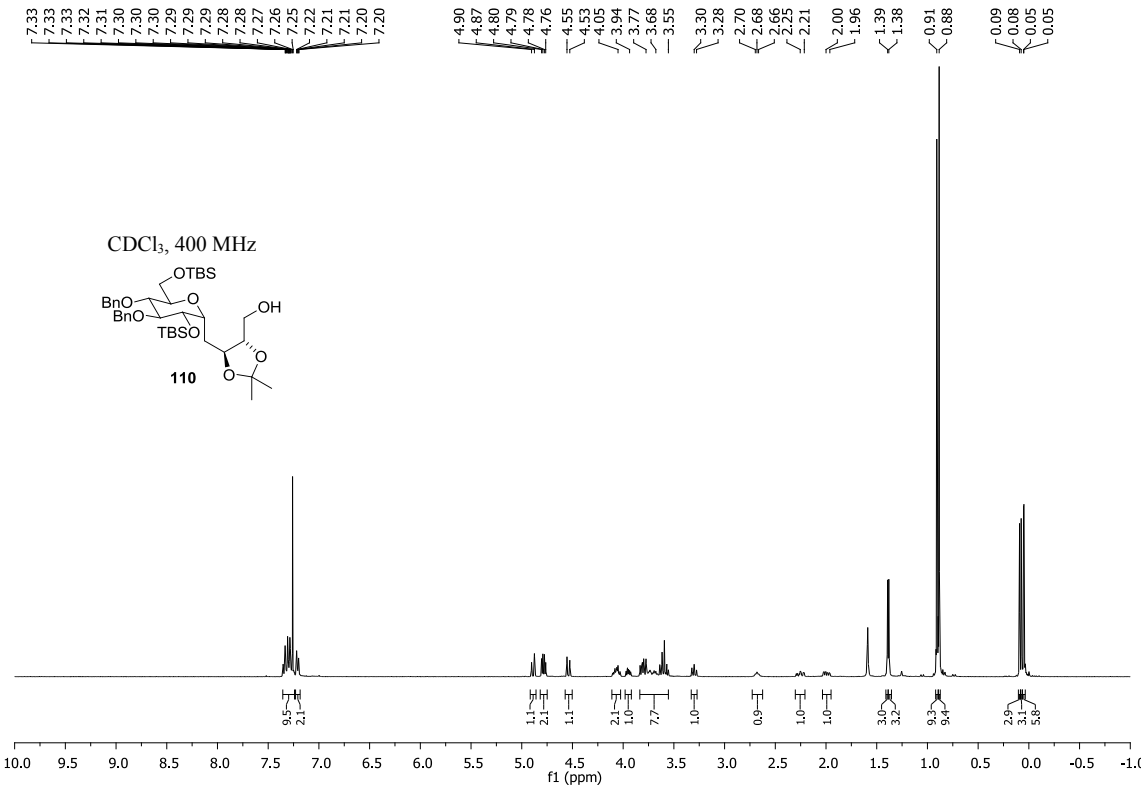

CDCl3, 150 MHz
OH
BnO
BnO
O
TBSO
COOMe
O
O
107
f1 (ppm)

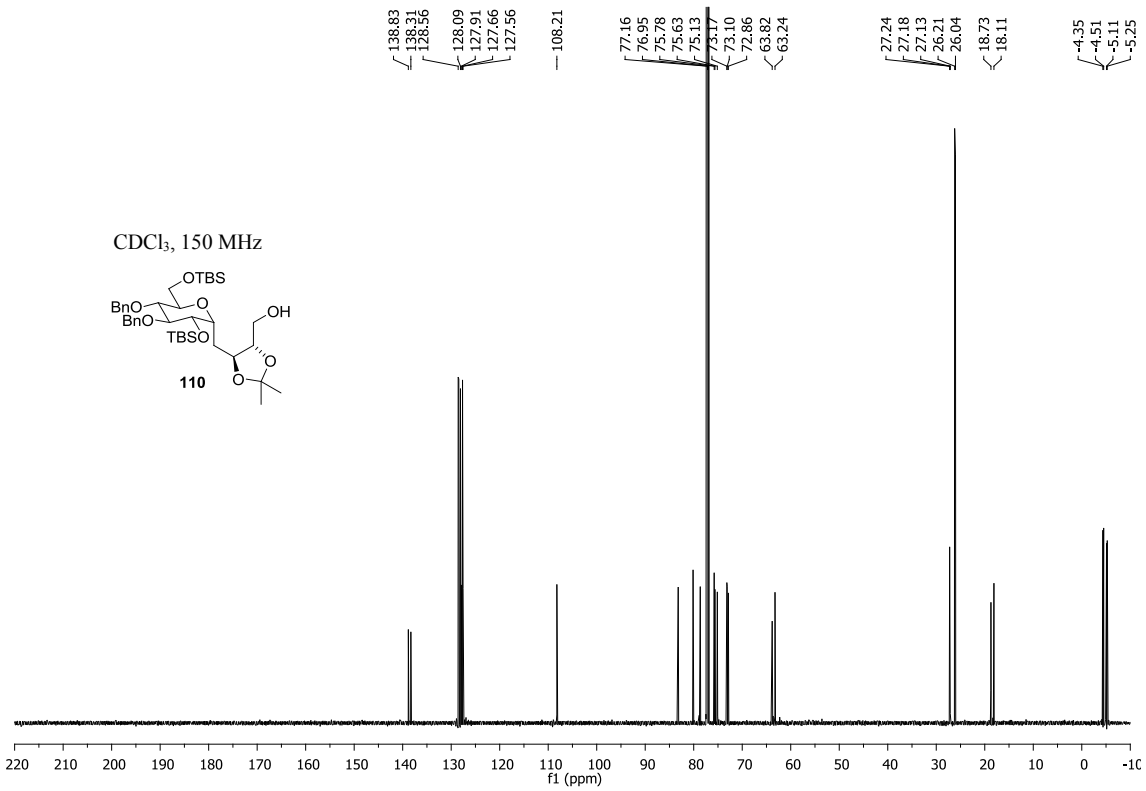

CDCl3, 400 MHz
OTBS
BnO
BnO
TBSO
OMe
OMe
108
f1 (ppm)

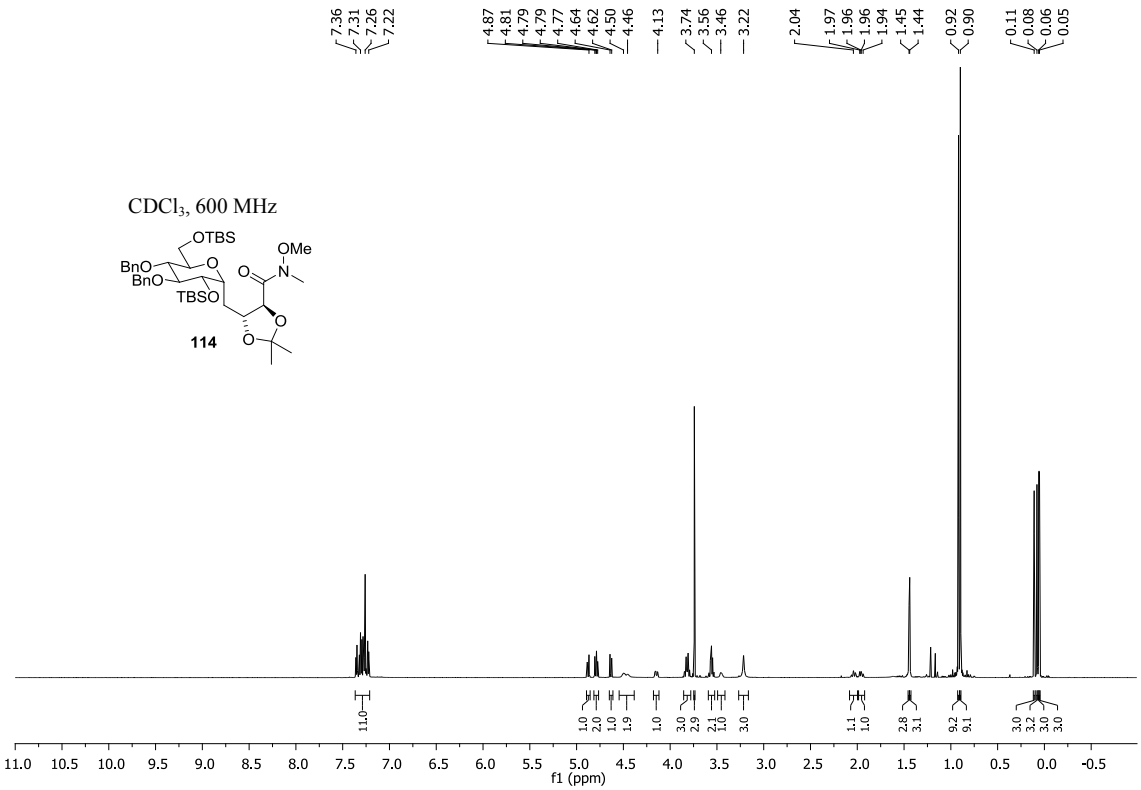

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
OMe
OMe
108
f1 (ppm)

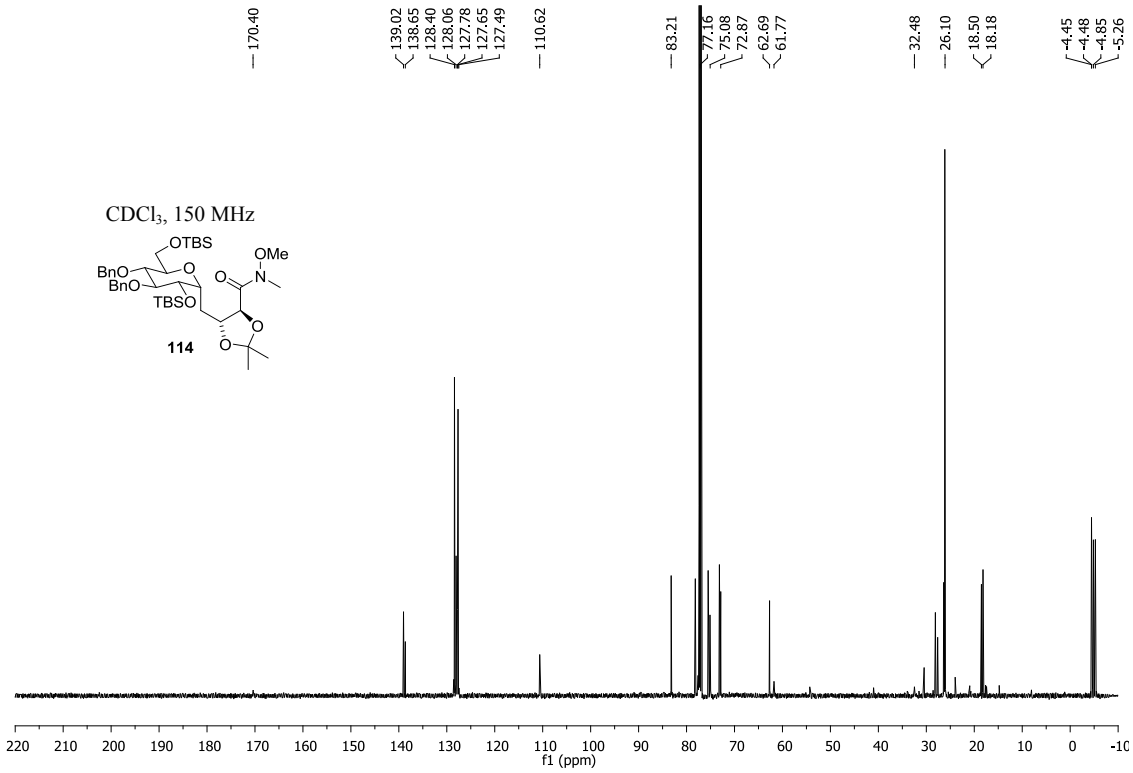

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
O
OH
O
O
111
f1 (ppm)

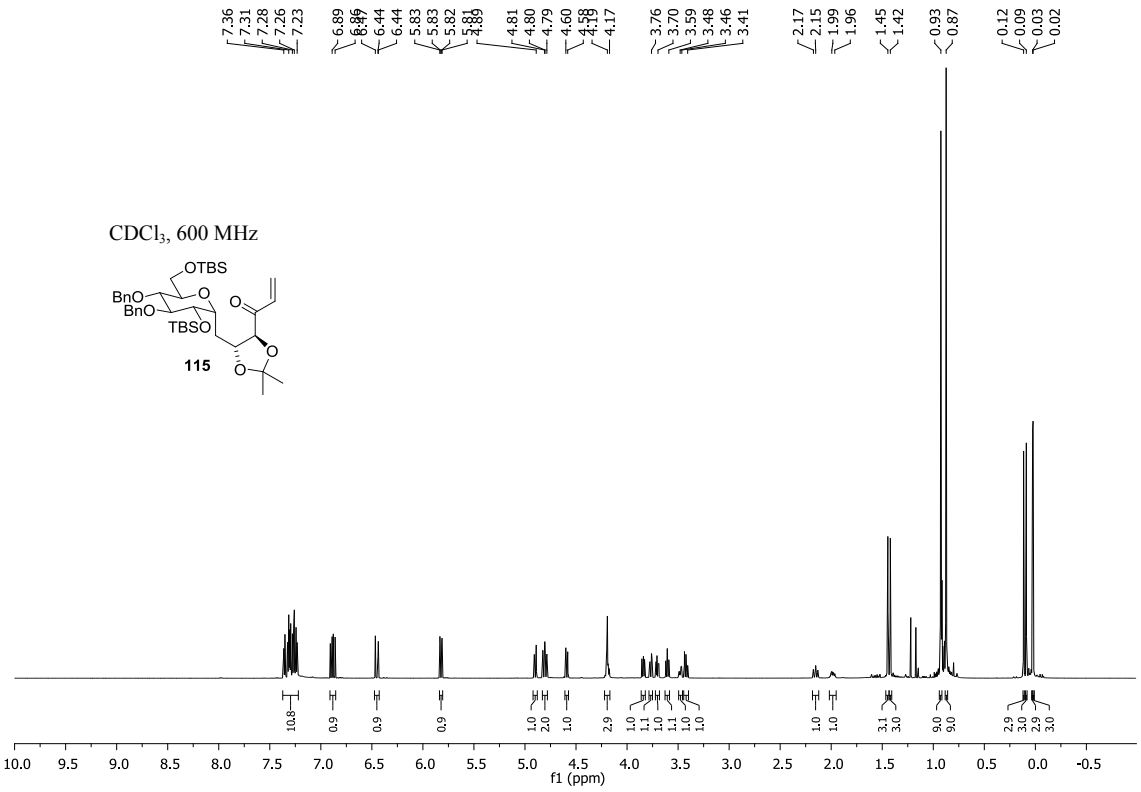

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
O
OH
O
O
111
f1 (ppm)

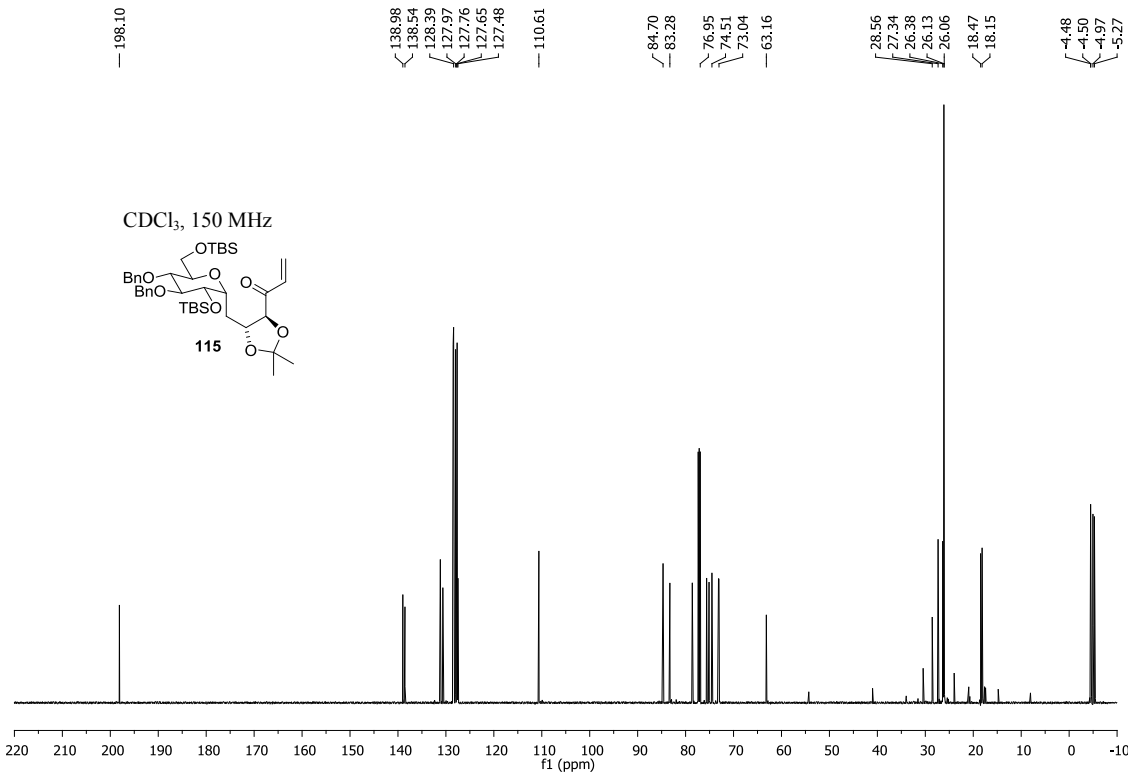

CDCl3, 400 MHz
OTBS
BnO
BnO
TBSO
OH
O
O
O
110
f1 (ppm)

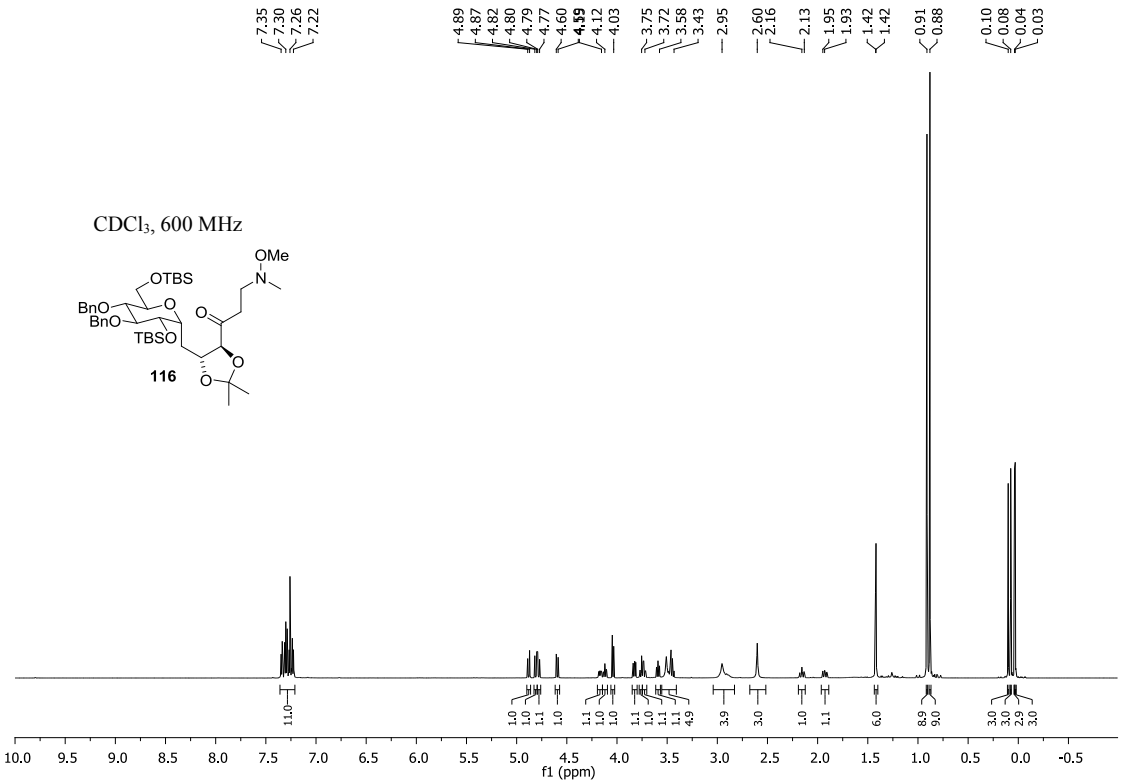

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
OH
O
O
O
110
f1 (ppm)

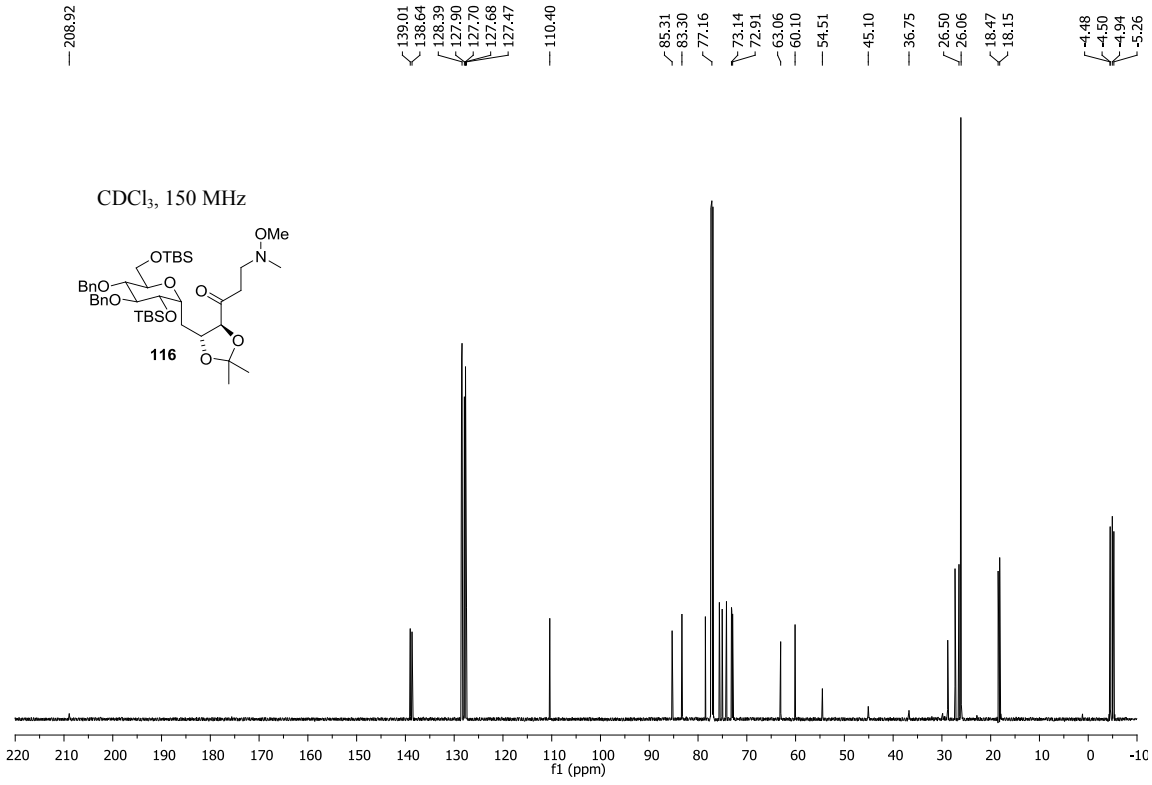

CDCl3, 600 MHz
OTBS
OMe
BnO
BnO
TBSO
114
f1 (ppm)

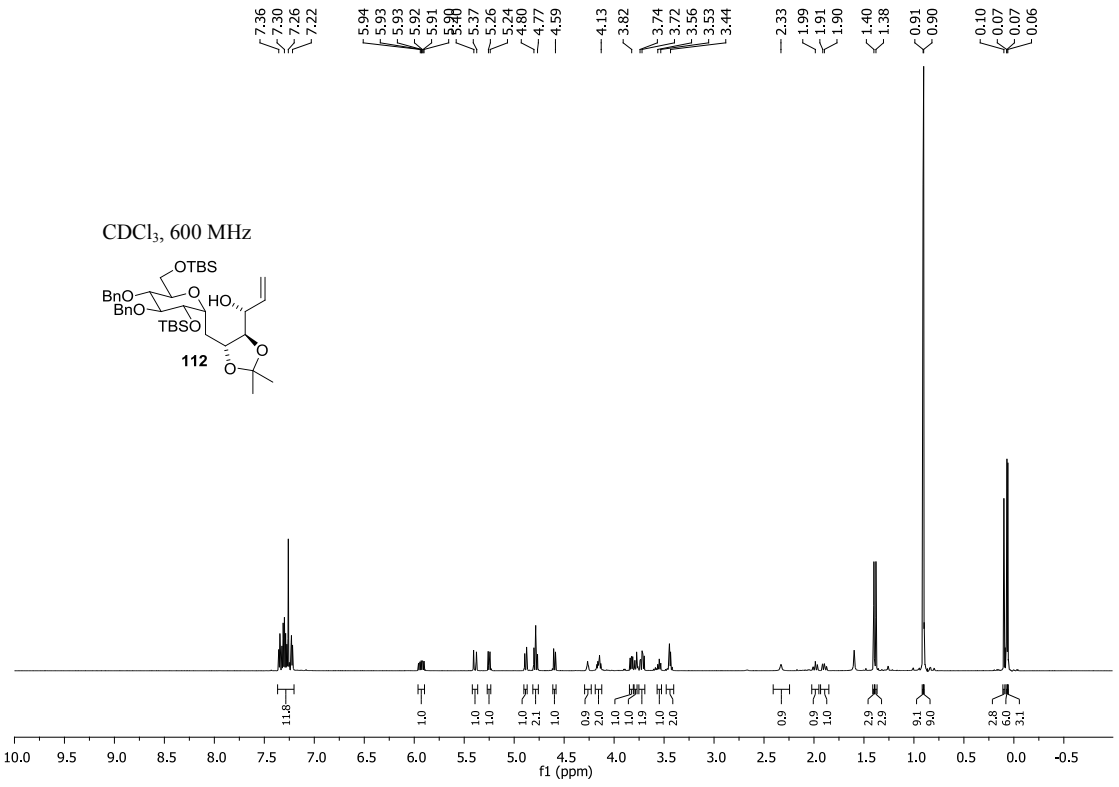

CDCl3, 150 MHz
OTBS
OMe
BnO
BnO
TBSO
114
f1 (ppm)

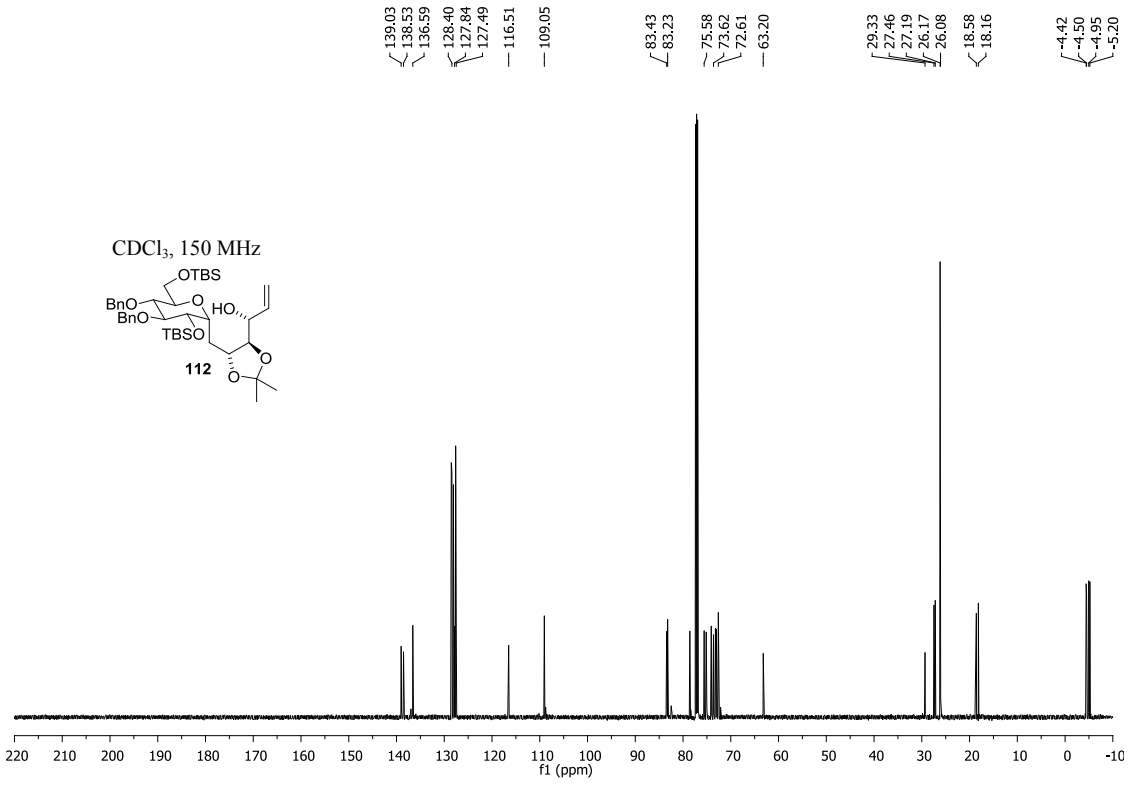

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
O
115
f1 (ppm)

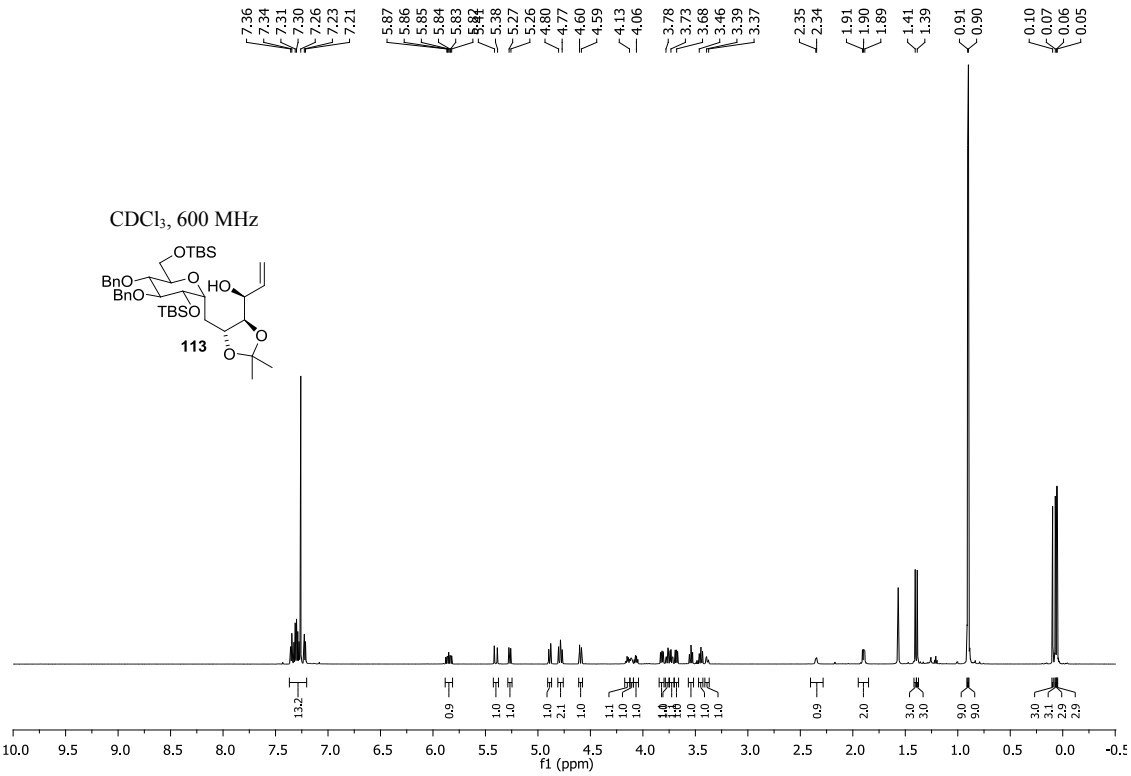

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
O
115
f1 (ppm)

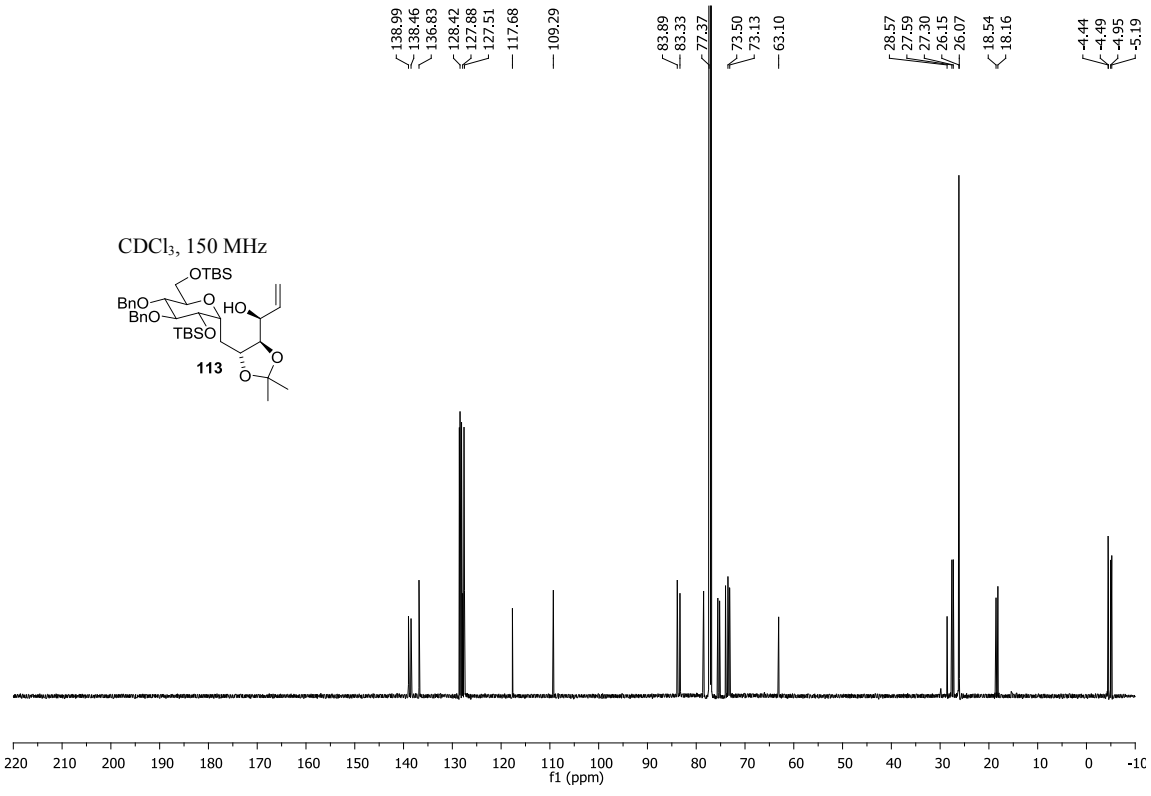

CDCl3, 600 MHz
OMe
N
OTBS
BnO
BnO
TBSO
O
O
O
O
116
f1 (ppm)

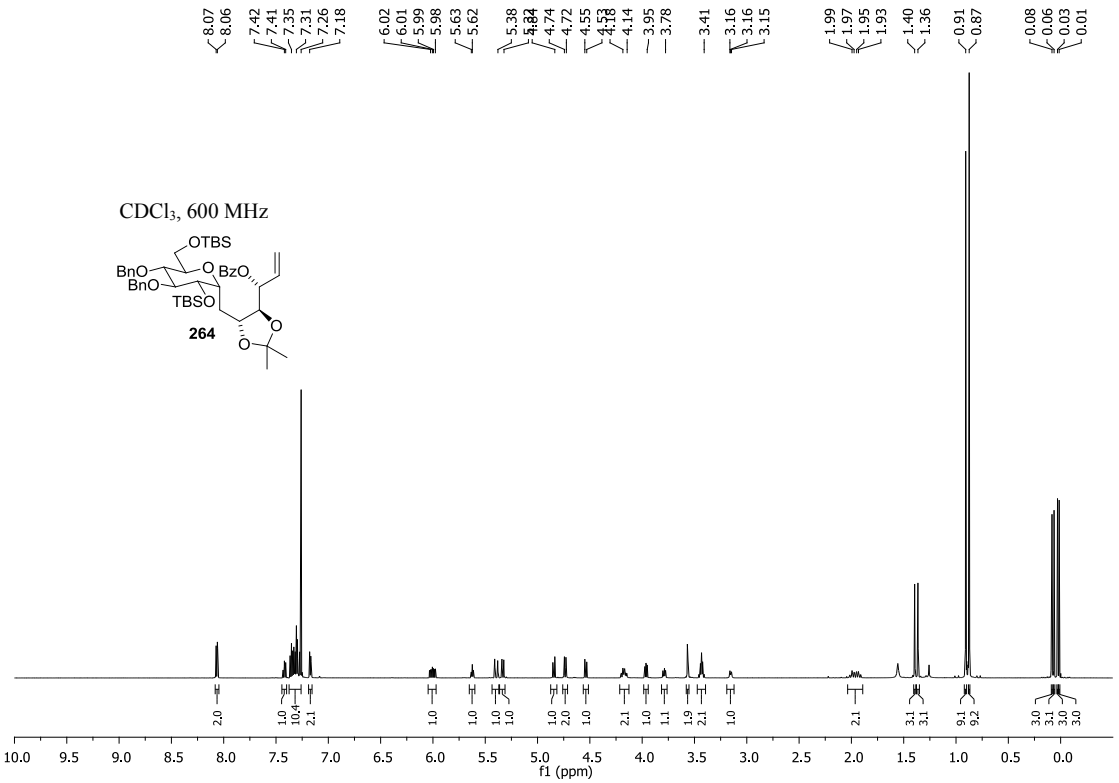

CDCl3, 150 MHz
OMe
N
OTBS
BnO
BnO
TBSO
O
O
O
O
116
f1 (ppm)

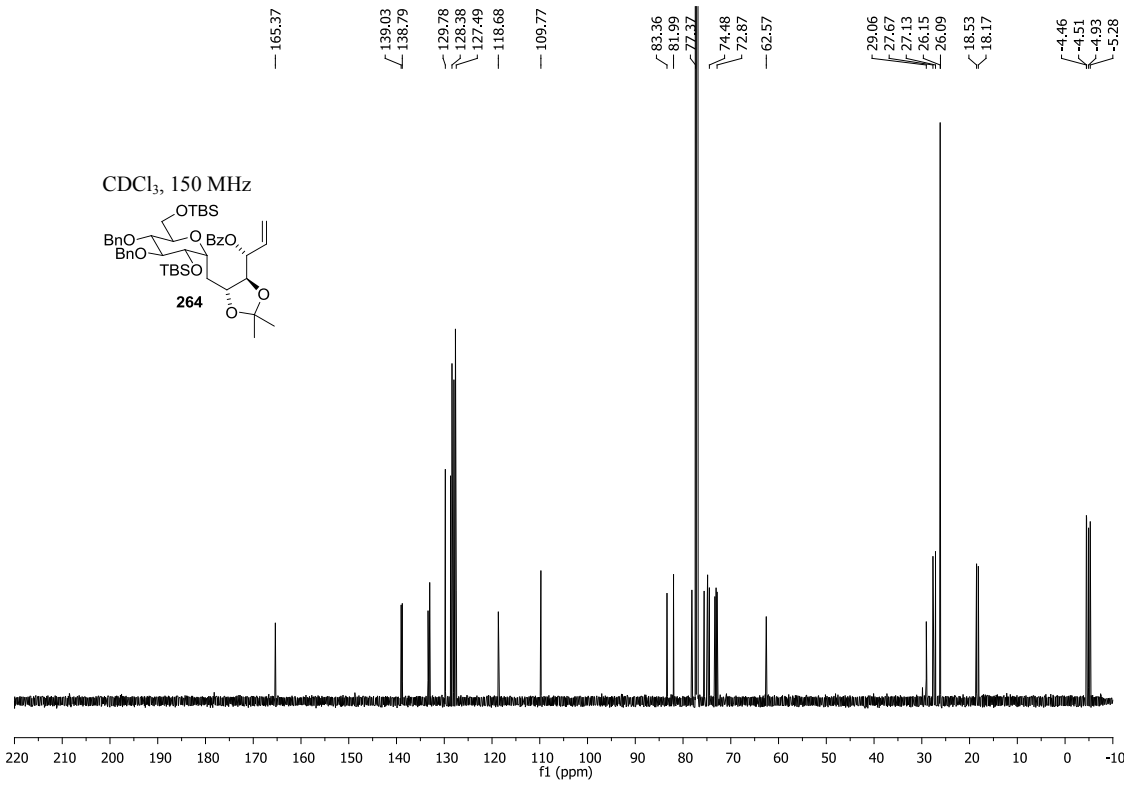

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
HO
O
O
112
f1 (ppm)

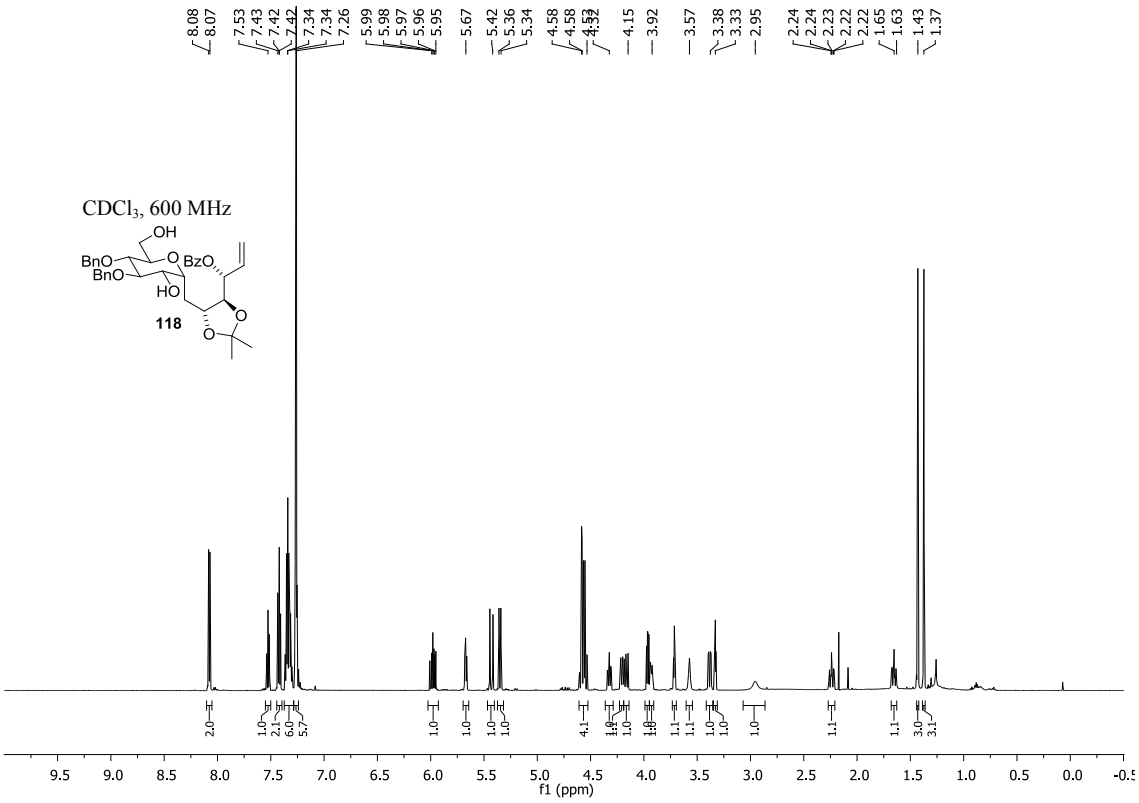

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
HO
O
O
112
f1 (ppm)

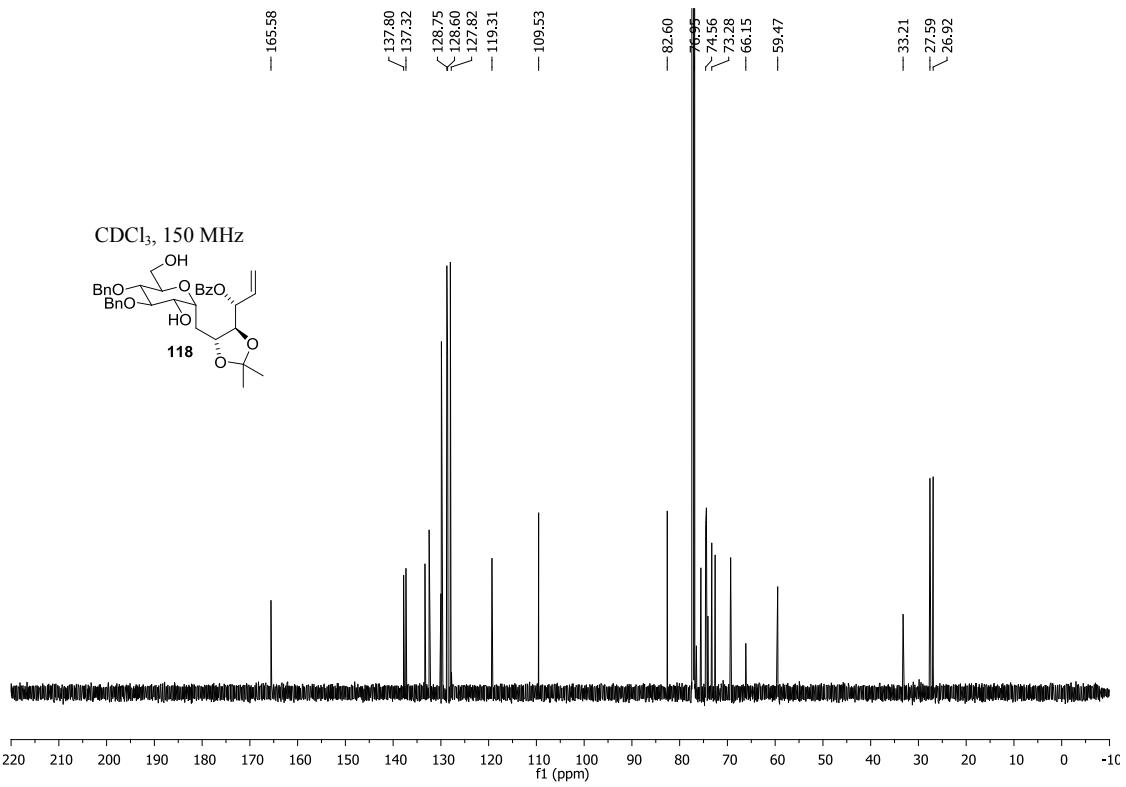

CDCl3, 600 MHz
OTBS
BnO
BnO
TBSO
HO
O
O
O
113
f1 (ppm)

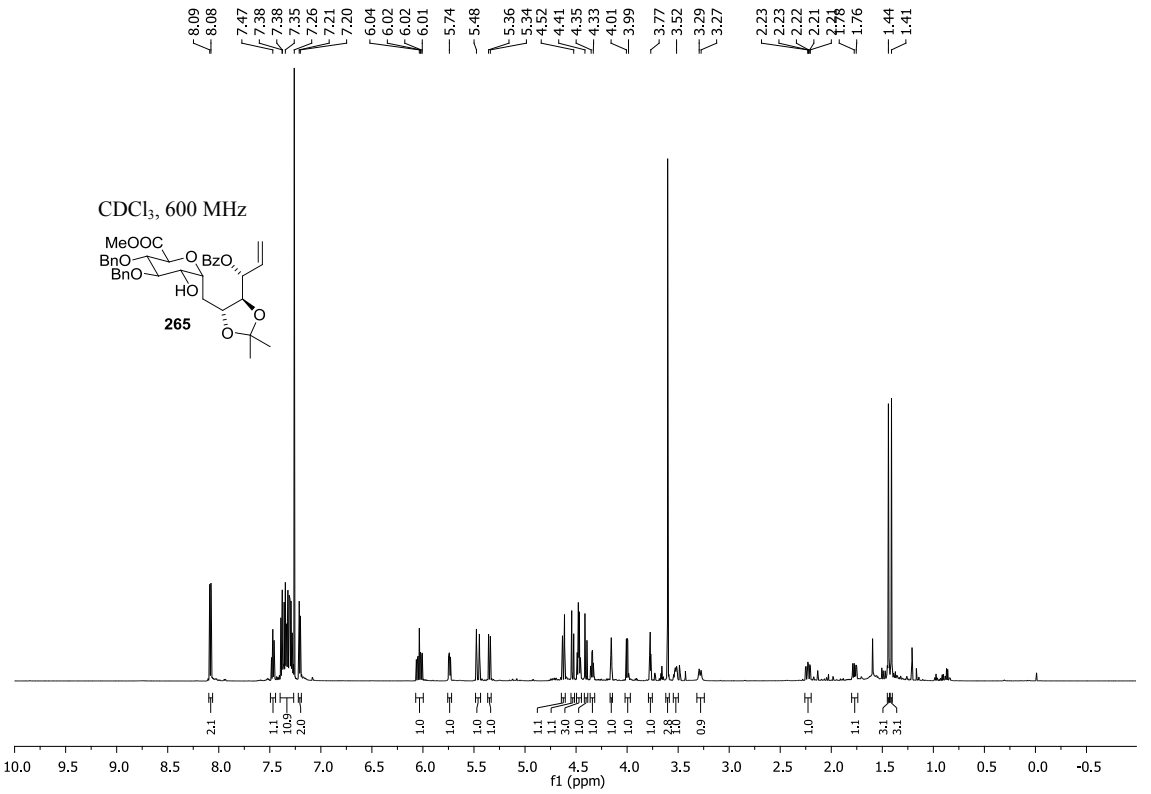

CDCl3, 150 MHz
OTBS
BnO
BnO
TBSO
HO
O
O
O
113
f1 (ppm)

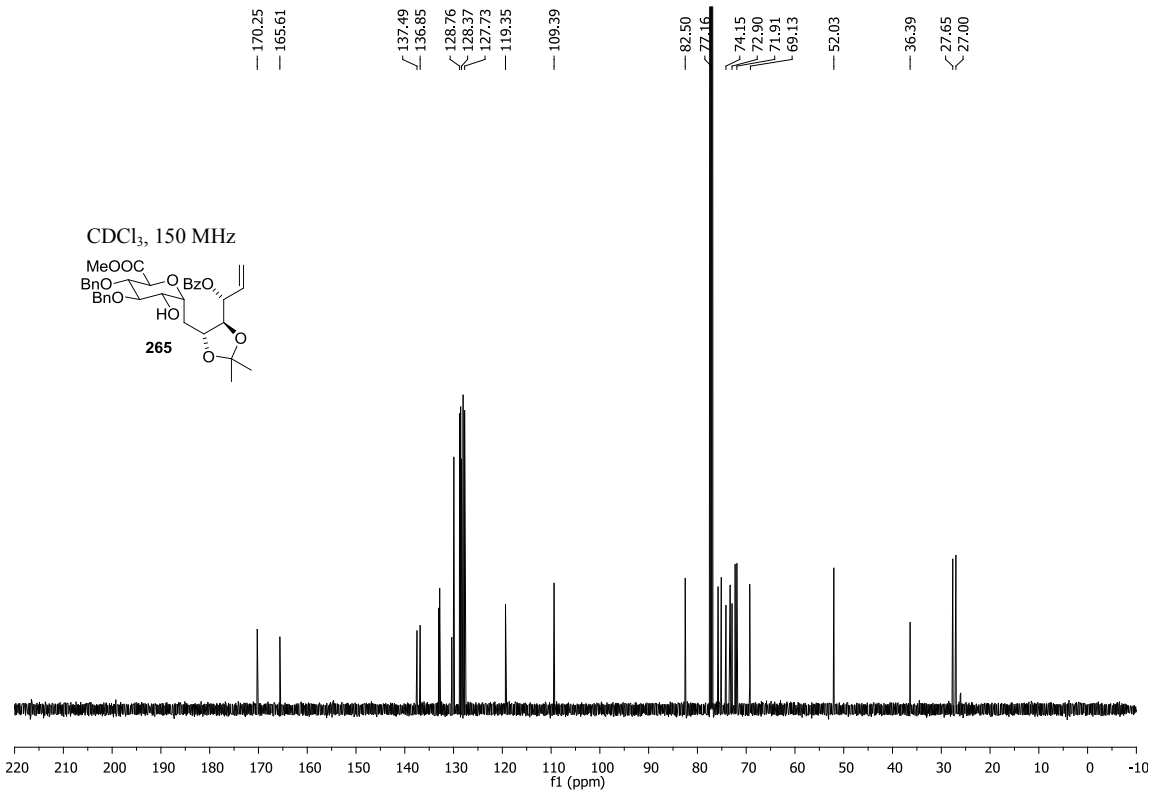

CDCl3, 600 MHz
OTBS
BnO
BnO
O
BzO
TBSO
O
O
264
f1 (ppm)

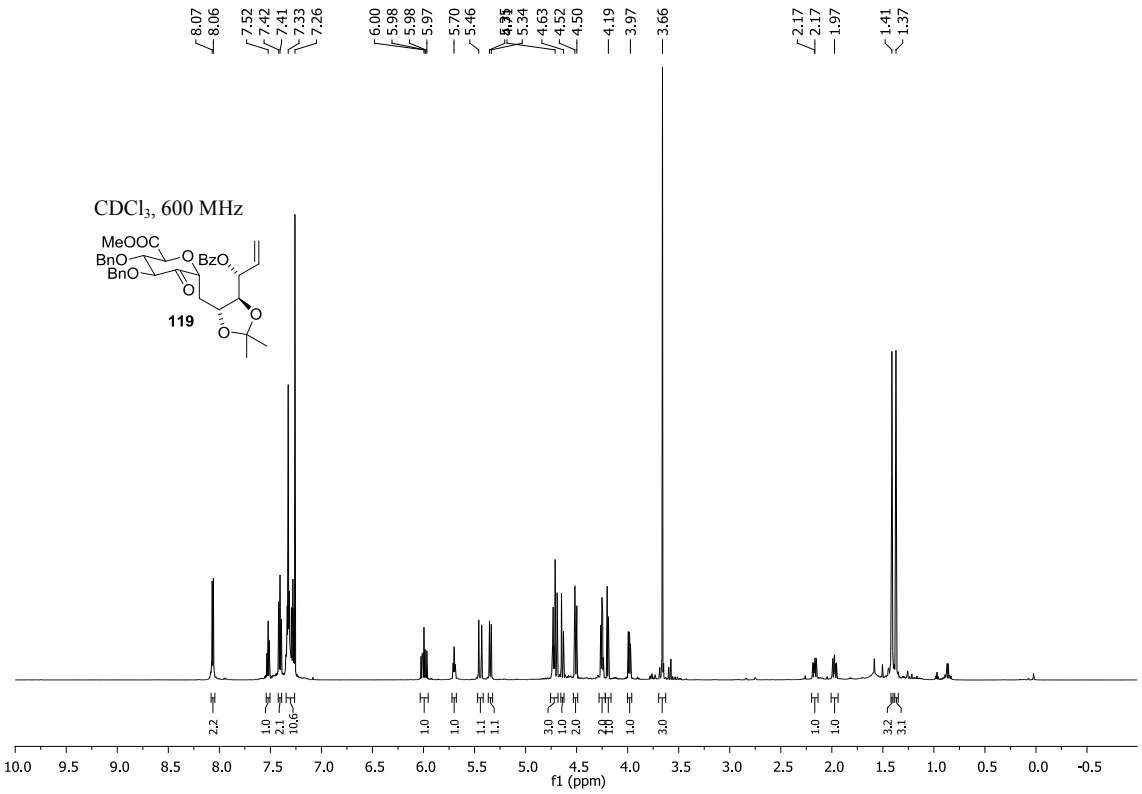

CDCl3, 150 MHz
OTBS
BnO
BnO
O
BzO
TBSO
O
O
264
f1 (ppm)

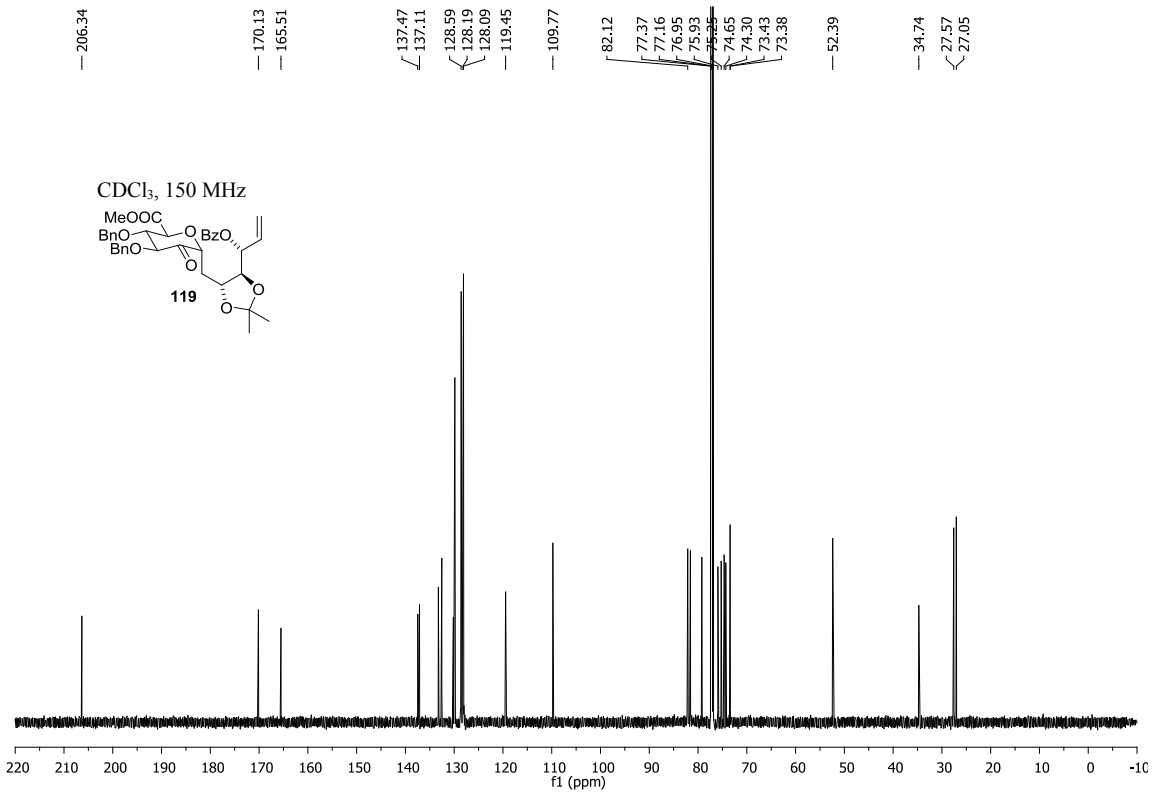

CDCl3, 600 MHz
OH
BnO
BnO
O
BzO
HO
O
O
118
f1 (ppm)

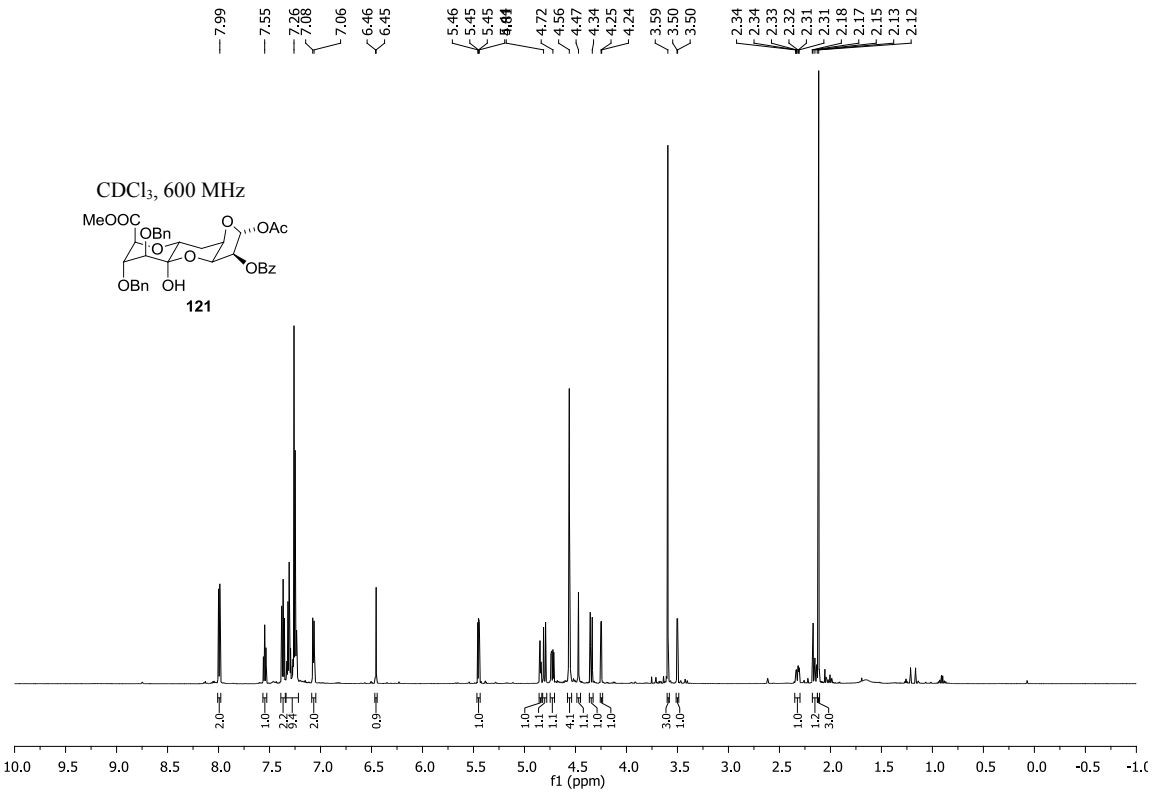

CDCl3, 150 MHz
OH
BnO
BnO
O
BzO
HO
O
O
118
f1 (ppm)

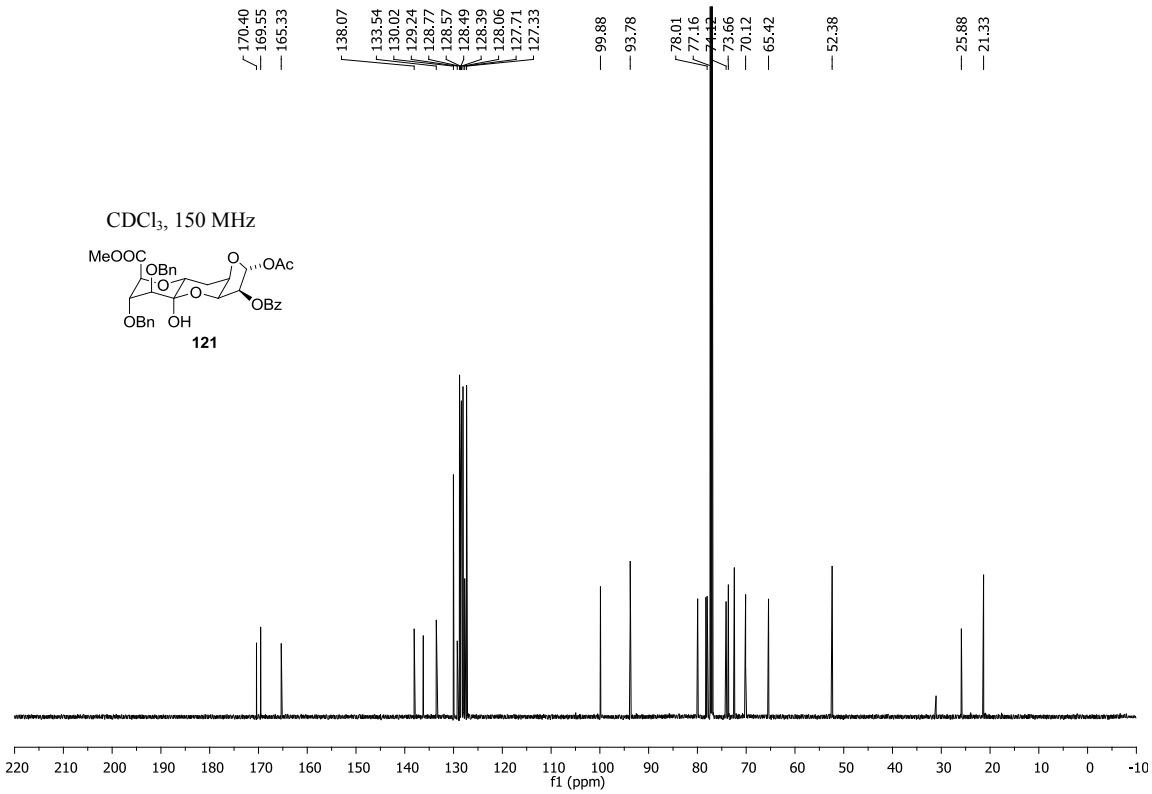

CDCl3, 600 MHz
MeOOC
BnO
BnO
O
BzO
HO
O
O
265
f1 (ppm)

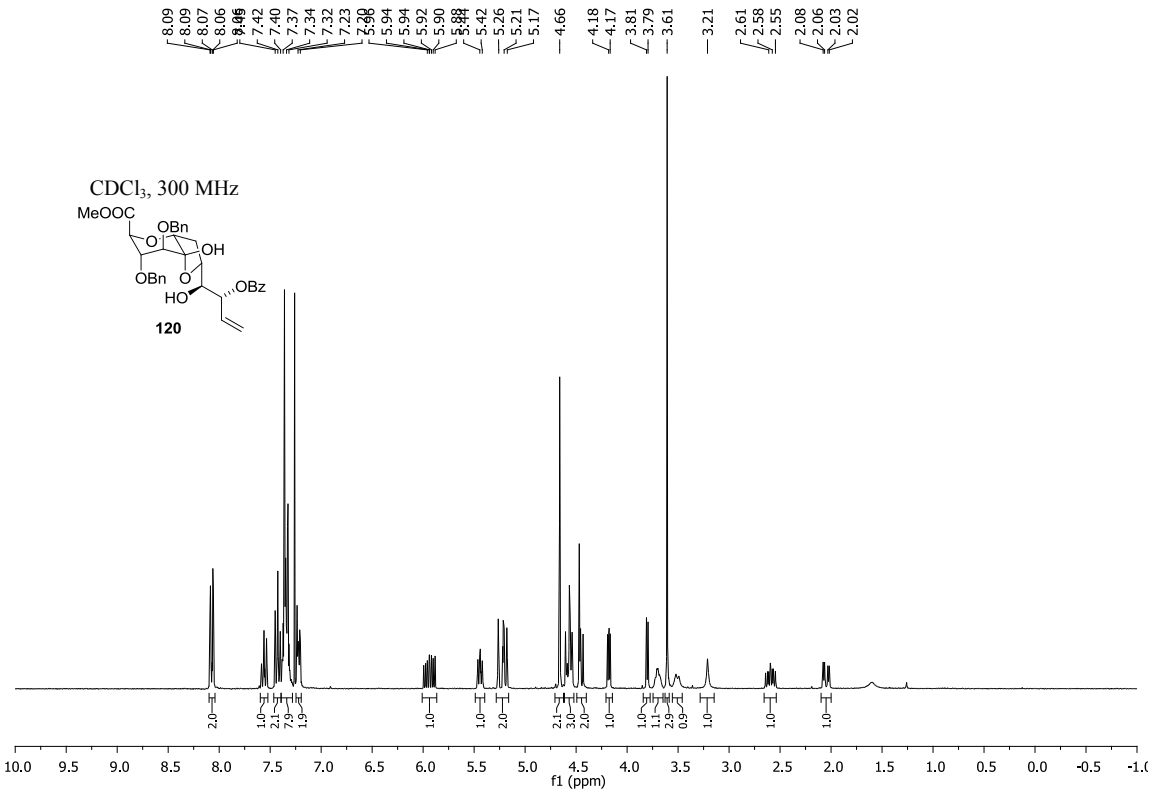

CDCl3, 150 MHz
MeOOC
BnO
BnO
O
BzO
HO
O
O
265
f1 (ppm)

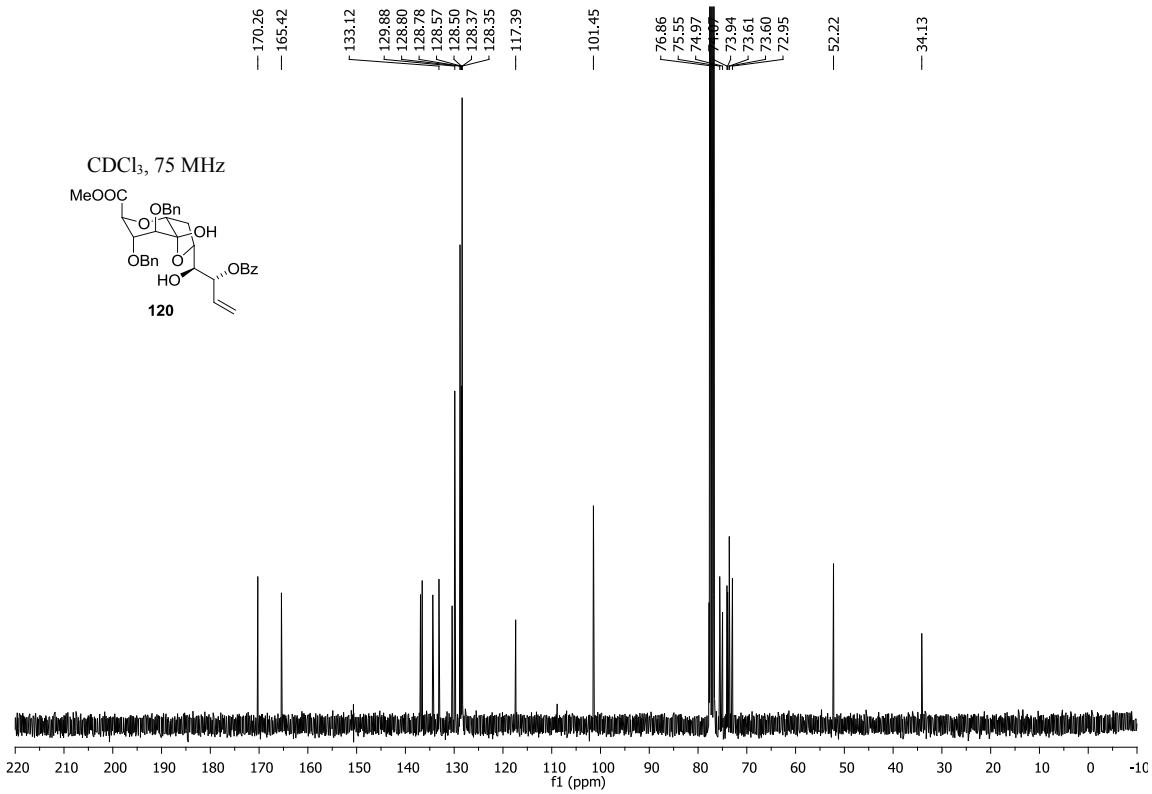

CDCl3, 600 MHz
MeOOC
BnO
BnO
O
BzO
O
O
O
119
f1 (ppm)

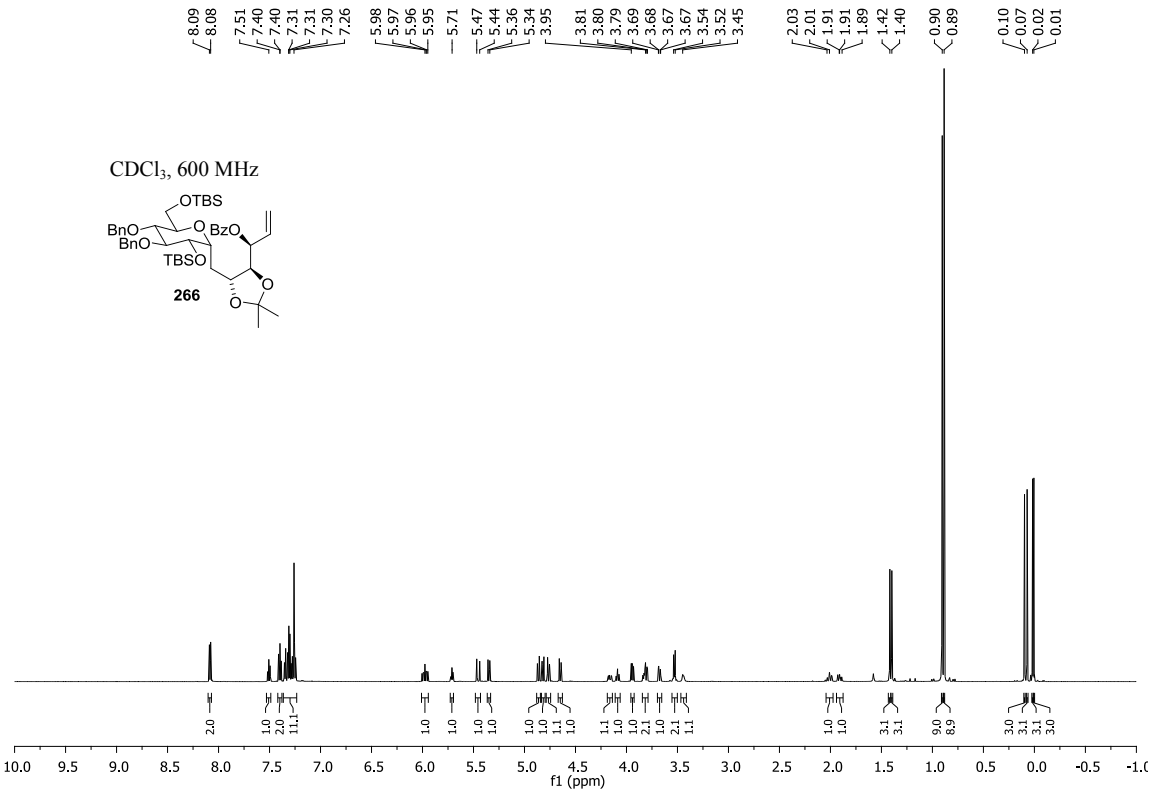

CDCl3, 150 MHz
MeOOC
BnO
BnO
O
BzO
O
O
O
119
f1 (ppm)

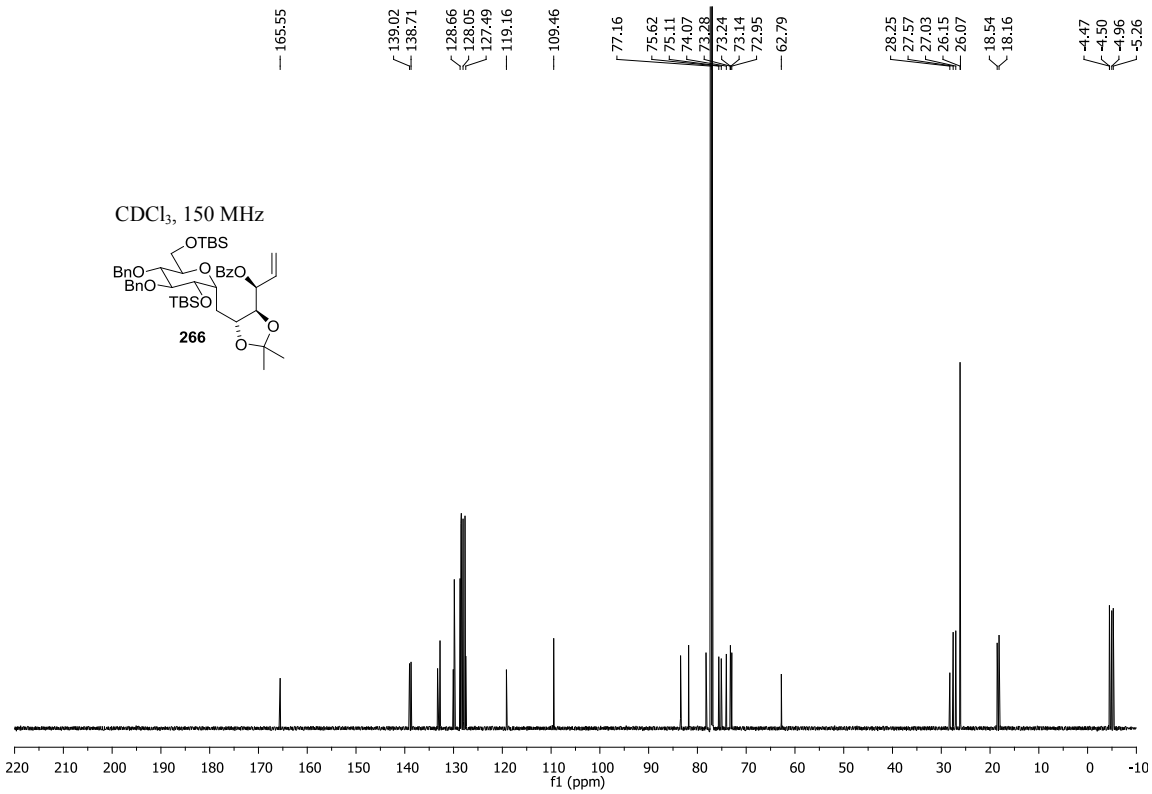

7.99
7.55
7.26
7.08
7.06
6.46
6.45
5.46
5.45
5.45
4.72
4.56
4.47
4.34
4.25
4.24
3.59
3.50
3.50
2.34
2.34
2.33
2.32
2.31
2.31
2.18
2.17
2.15
2.13
2.12
CDCl3, 600 MHz
MeOOC
OBn
O
OAc
OBz
OBn
OH
121
f1 (ppm)

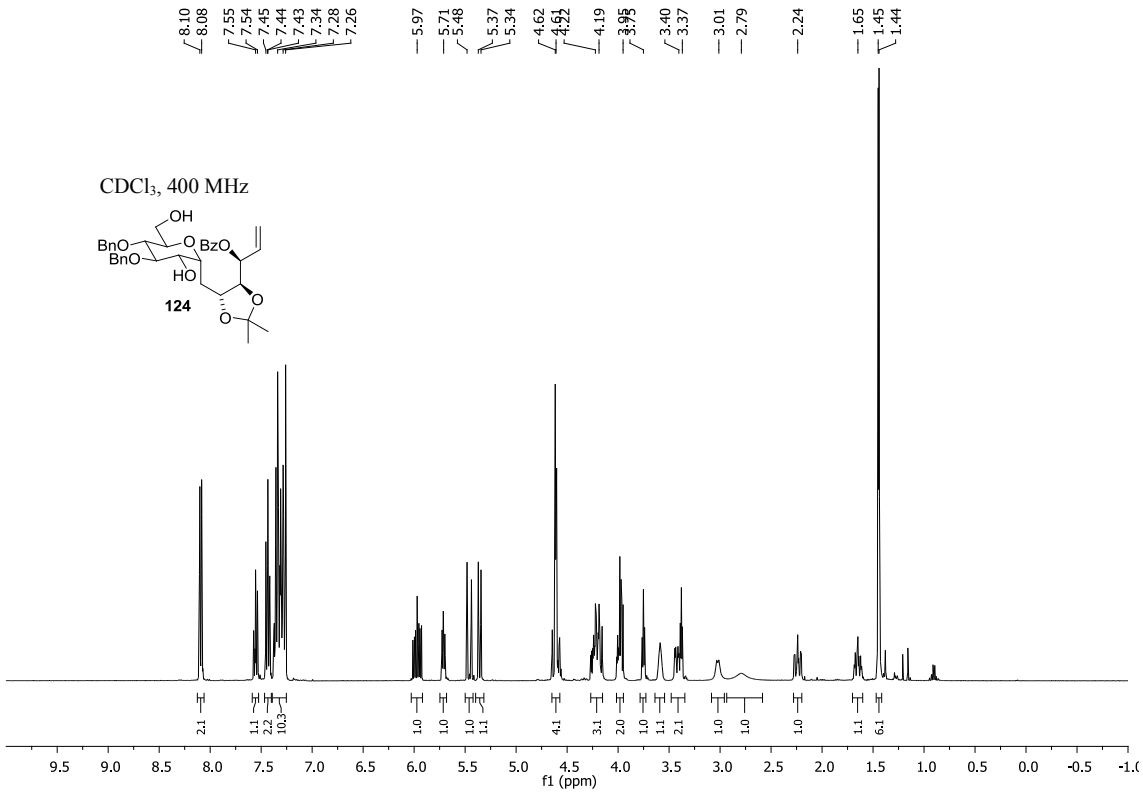

170.40
169.55
165.33
138.07
133.54
130.02
129.24
128.77
128.57
128.49
128.39
128.06
127.71
127.33
99.88
93.78
78.01
77.16
73.66
70.12
65.42
52.38
25.88
21.33
CDCl3, 150 MHz
MeOOC
OBn
O
OAc
OBz
OBn
OH
121
f1 (ppm)

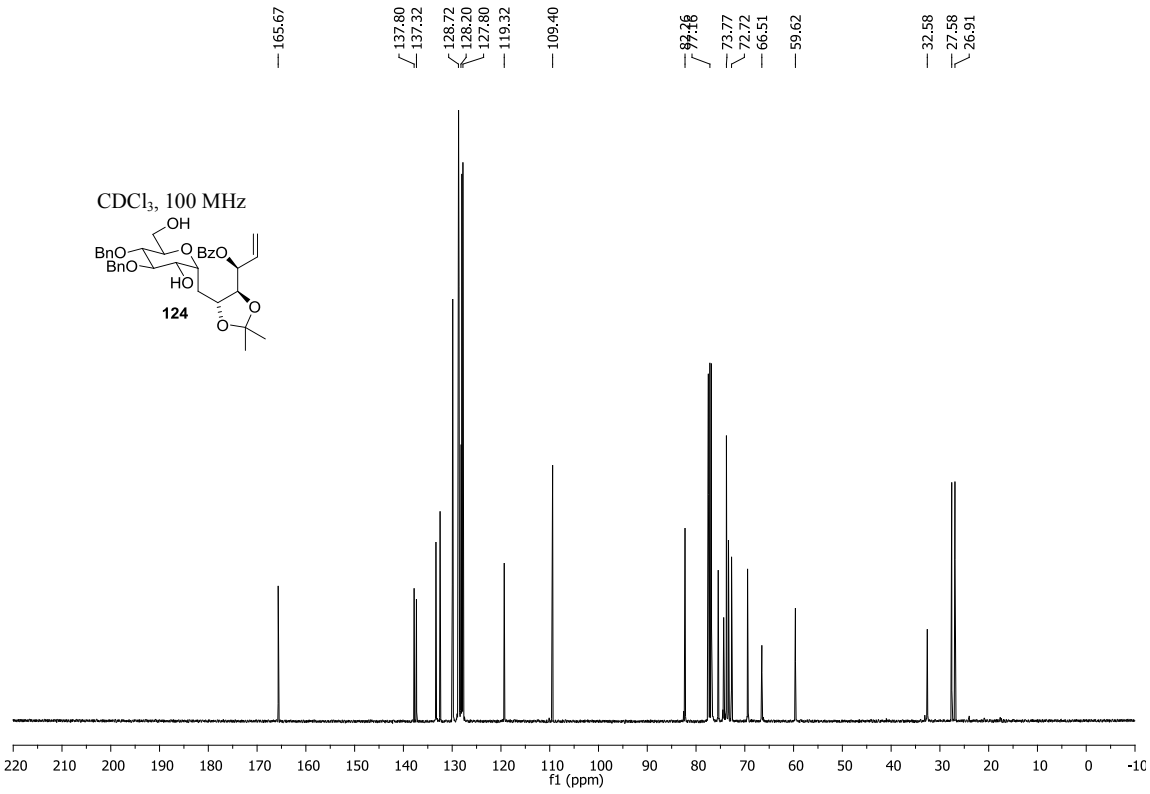

CDCl3, 300 MHz
MeOOC
OBn
OH
OBn
HO
OBz
120
f1 (ppm)

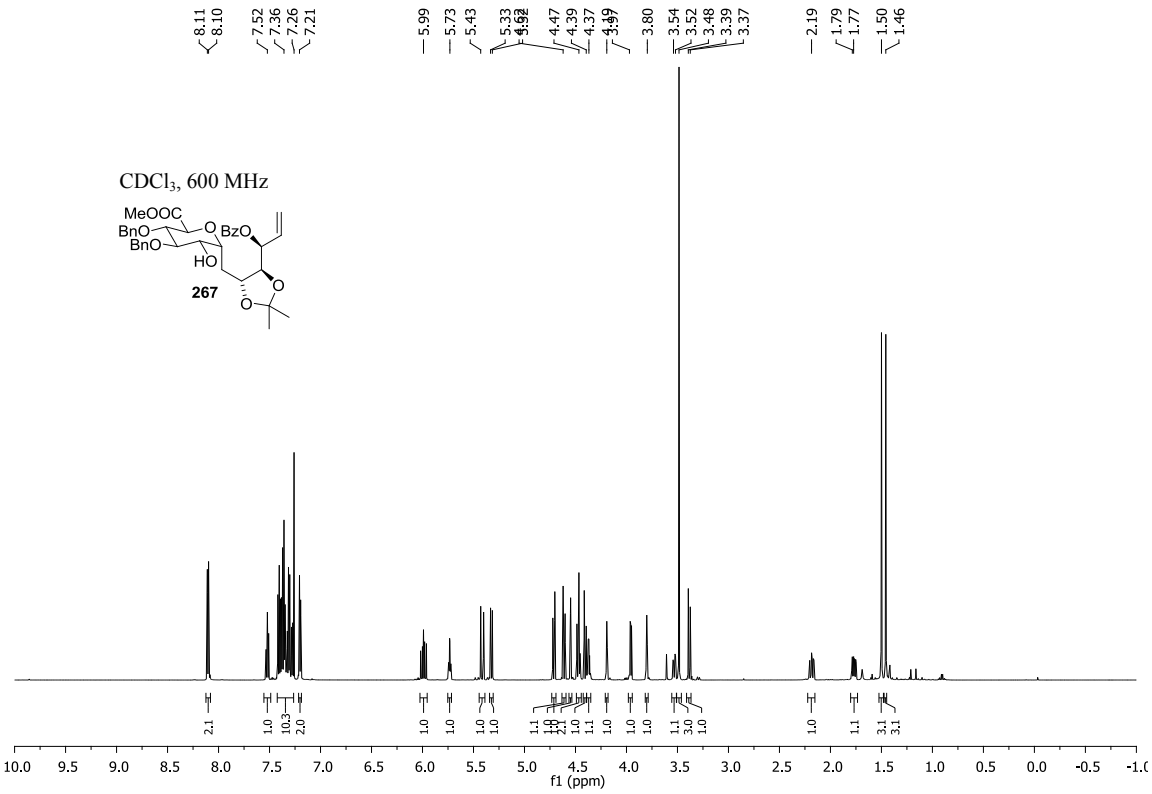

CDCl3, 75 MHz
MeOOC
OBn
OH
OBn
HO
OBz
120
f1 (ppm)

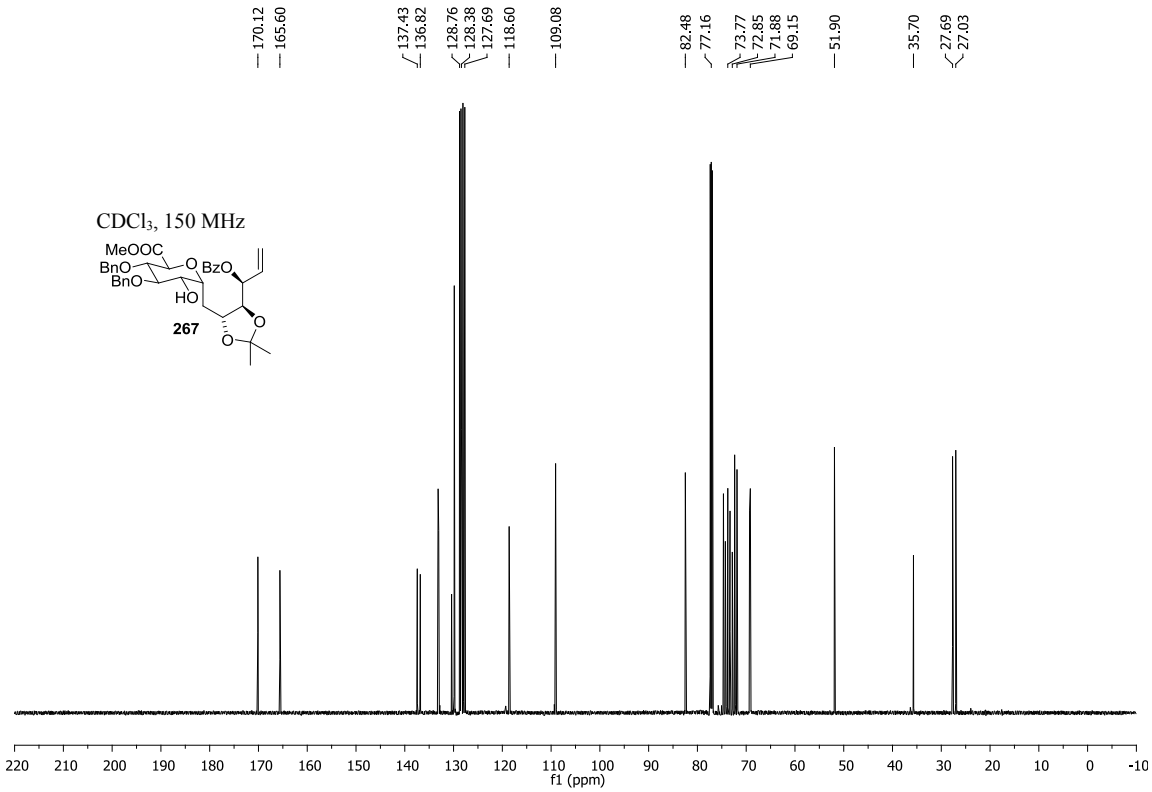

8.09
8.08
7.51
7.40
7.40
7.31
7.31
7.30
7.26
5.98
5.97
5.96
5.95
5.71
5.47
5.44
5.36
5.34
3.95
3.81
3.80
3.79
3.69
3.68
3.67
3.67
3.54
3.52
3.45
2.03
2.01
1.91
1.91
1.89
1.42
1.40
0.90
0.89
0.10
0.07
0.02
0.01
CDCl3, 600 MHz
OTBS
BnO
BnO
O
BzO
TBSO
O
O
266
f1 (ppm)

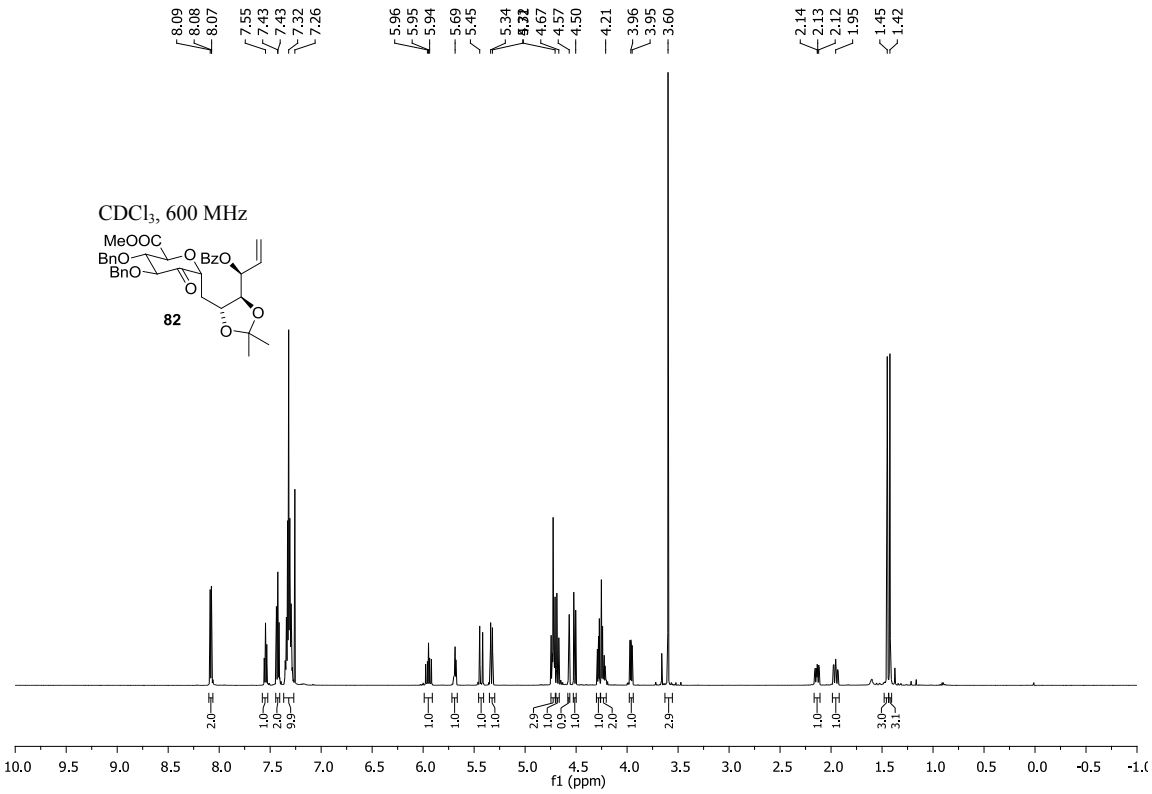

165.55
139.02
138.71
128.66
128.05
127.49
119.16
109.46
77.16
75.62
75.11
74.07
73.28
73.24
73.14
72.95
62.79
28.25
27.57
27.03
26.15
26.07
18.54
18.16
-4.47
-4.50
-4.96
-5.26
CDCl3, 150 MHz
OTBS
BnO
BnO
O
BzO
TBSO
O
O
266
f1 (ppm)

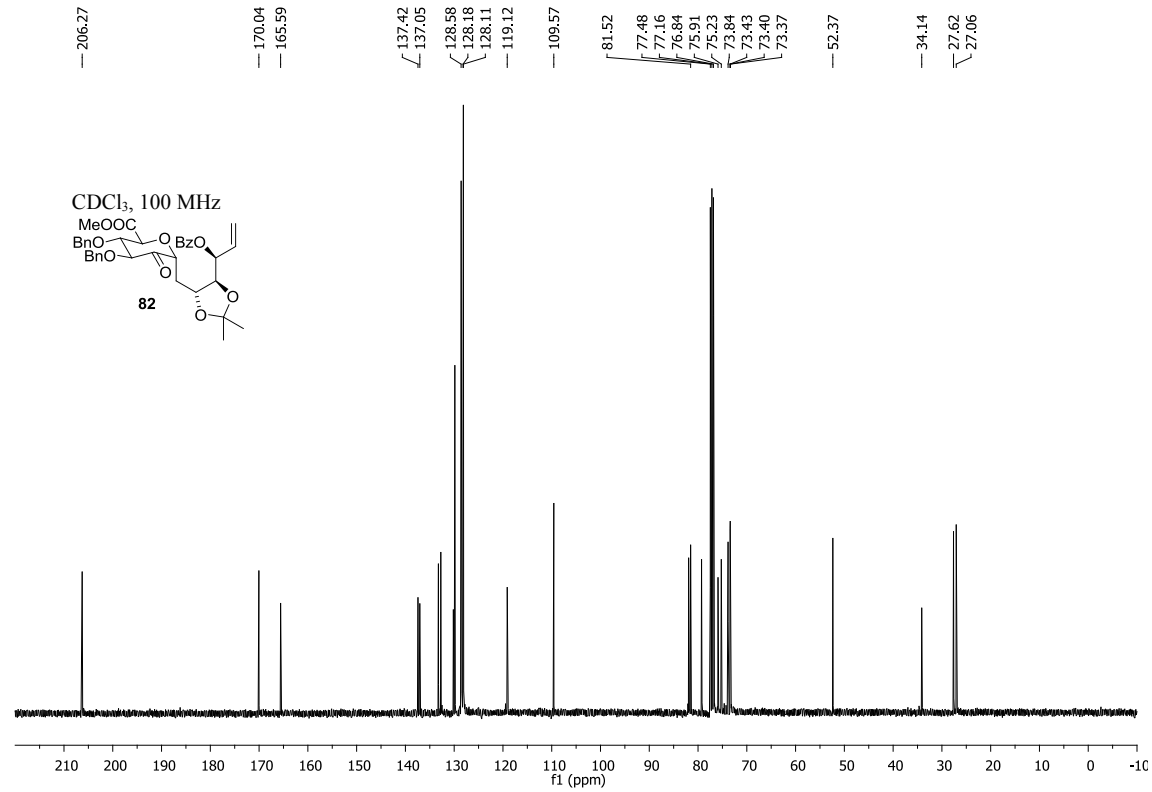

CDCl3, 400 MHz
OH
BnO
BnO
O
BzO
HO
O
O
124
8.10
8.08
7.55
7.54
7.45
7.44
7.43
7.34
7.28
7.26
5.97
5.71
5.48
5.37
5.34
4.62
4.51
4.42
4.19
3.95
3.75
3.40
3.37
3.01
2.79
2.24
1.65
1.45
1.44
2.1
1.1
2.2
10.3
1.0
1.0
1.0
1.1
4.1
3.1
2.0
1.0
1.1
2.1
1.0
1.0
1.0
1.1
6.1
f1 (ppm)

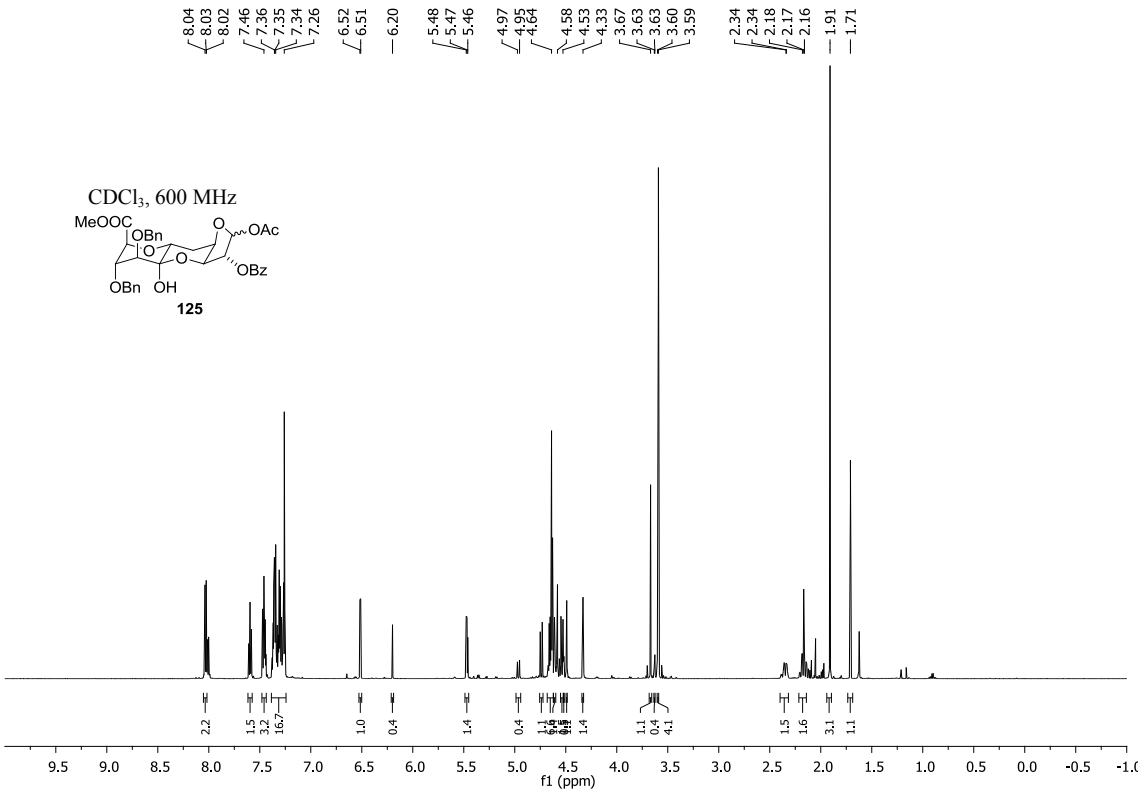

CDCl3, 100 MHz
OH
BnO
BnO
O
BzO
HO
O
O
124
165.67
137.80
137.32
128.72
128.20
127.80
119.32
109.40
82.26
77.16
73.77
72.72
66.51
59.62
32.58
27.58
26.91
f1 (ppm)

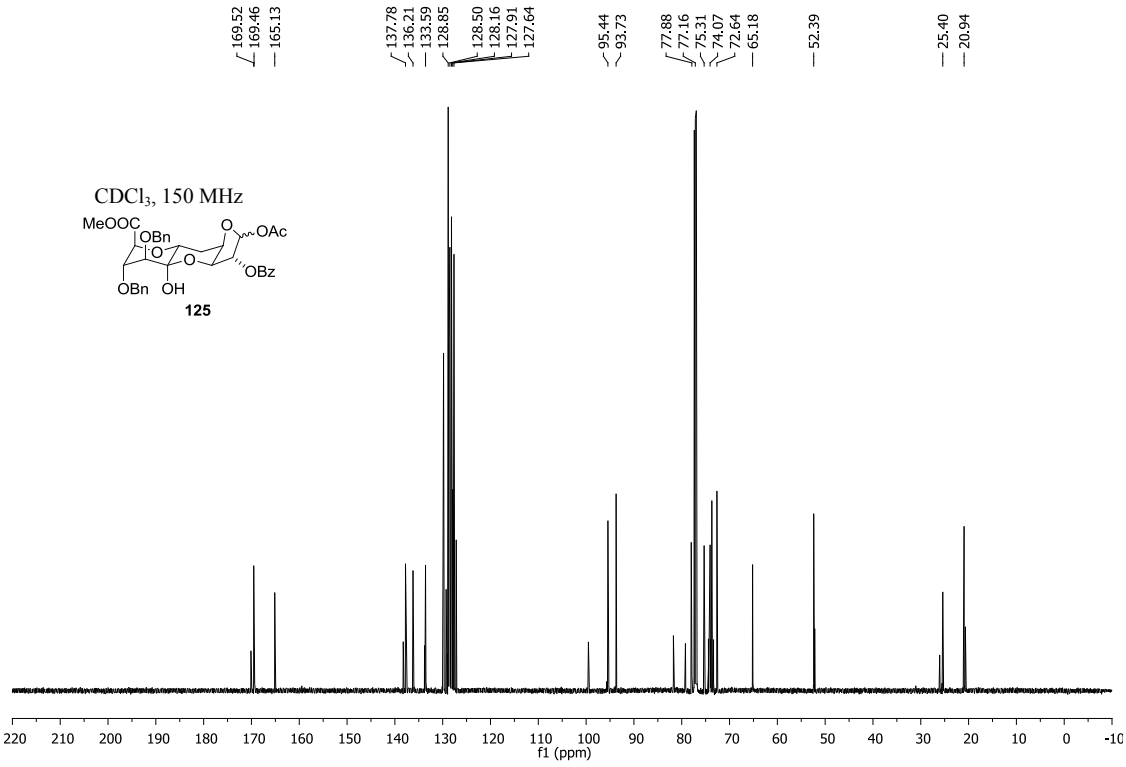

8.11
8.10
7.52
7.36
7.26
7.21
5.99
5.73
5.43
5.33
4.47
4.39
4.37
3.80
3.54
3.52
3.48
3.39
3.37
2.19
1.79
1.77
1.50
1.46
CDCl3, 600 MHz
MeOOC
BnO
BnO
O
BzO
HO
O
O
267
f1 (ppm)

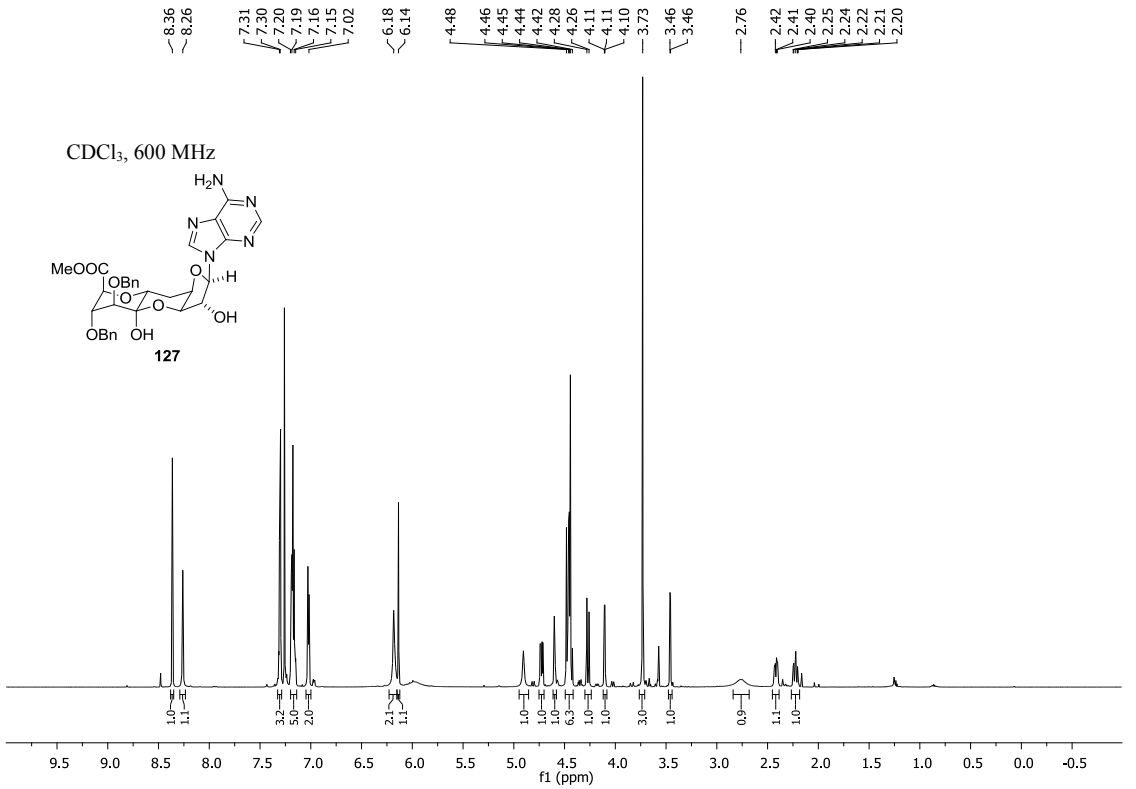

170.12
165.60
137.43
136.82
128.76
128.38
127.69
118.60
109.08
82.48
77.16
73.77
72.85
71.88
69.15
51.90
35.70
27.69
27.03
CDCl3, 150 MHz
MeOOC
BnO
BnO
O
BzO
HO
O
O
267
f1 (ppm)

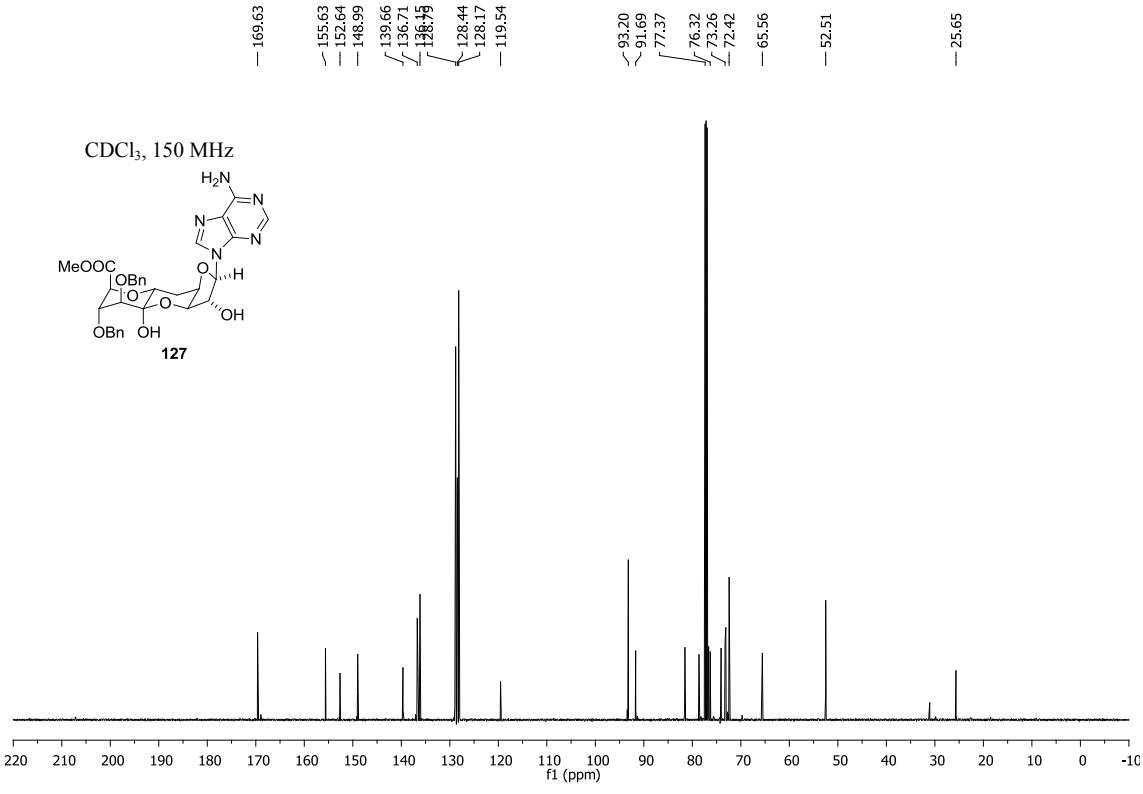

8.09
8.08
8.07
7.55
7.43
7.43
7.32
7.26
5.96
5.95
5.94
5.69
5.45
5.34
4.67
4.57
4.50
4.21
3.96
3.95
3.60
2.14
2.13
2.12
1.95
1.45
1.42
CDCl3, 600 MHz
MeOOC
BnO
BnO
O
BzO
O
O
O
82
f1 (ppm)

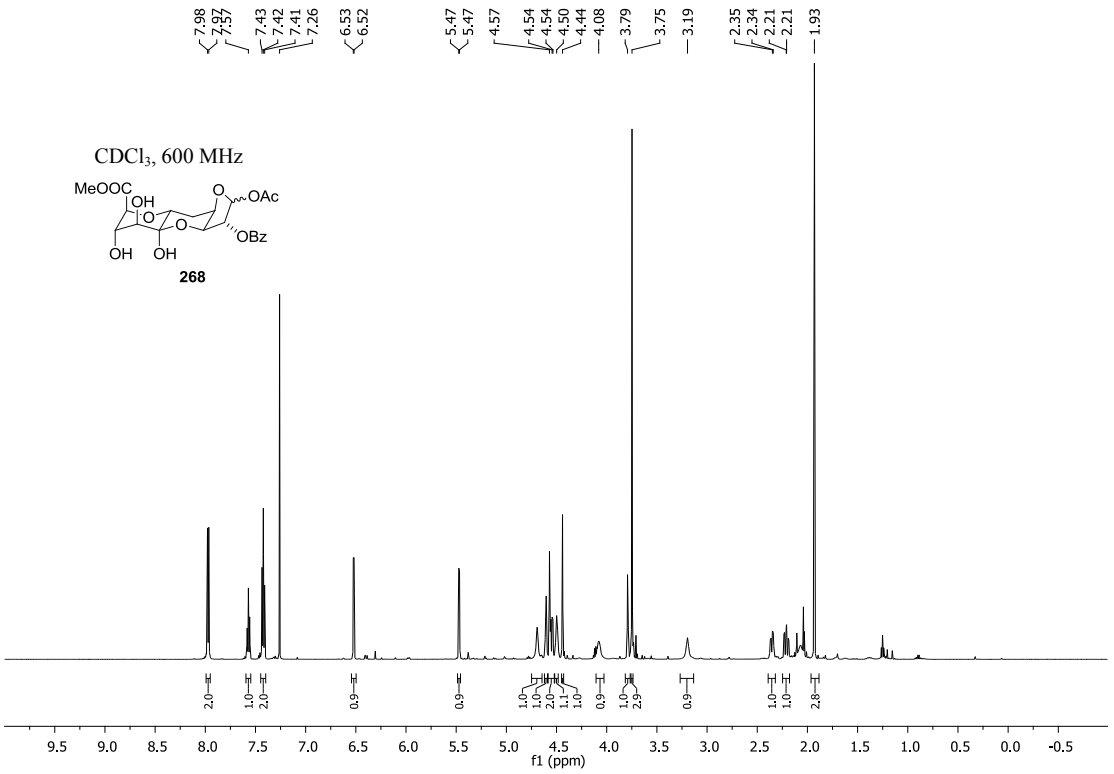

206.27
170.04
165.59
137.42
137.05
128.58
128.18
128.11
119.12
109.57
81.52
77.48
77.16
76.84
75.91
75.23
73.84
73.43
73.40
73.37
52.37
34.14
27.62
27.06
CDCl3, 100 MHz
MeOOC
BnO
BnO
O
BzO
O
O
O
82
f1 (ppm)

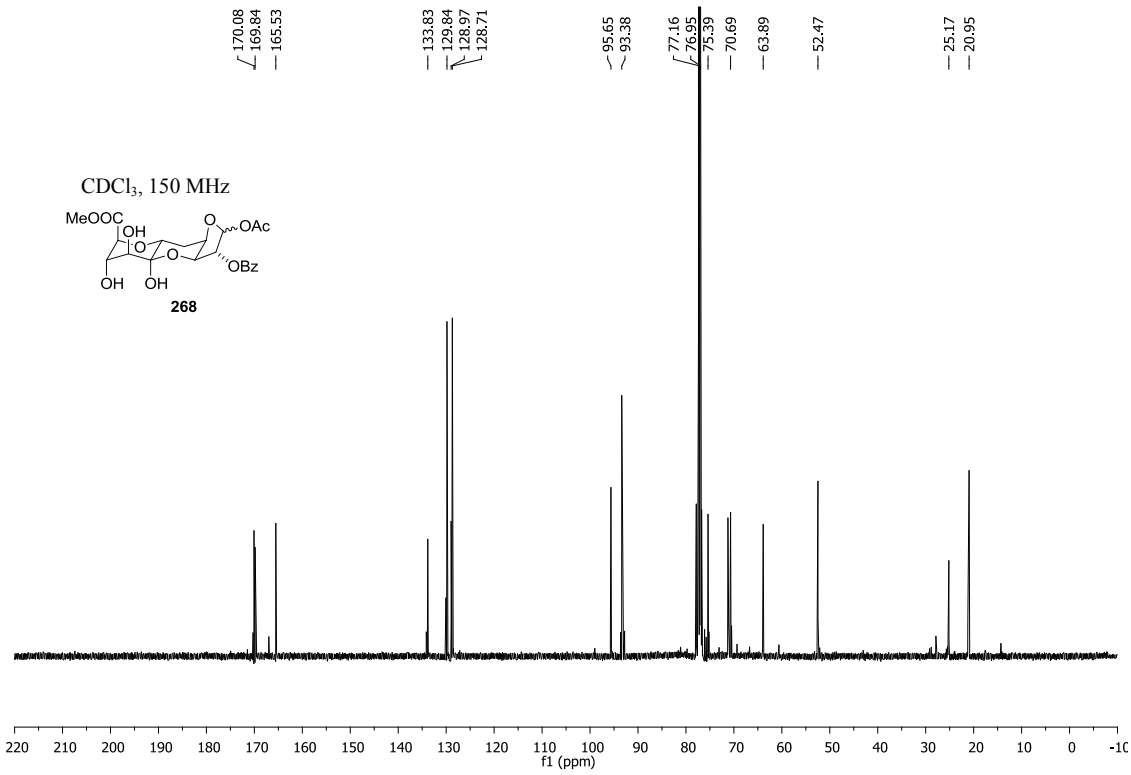

8.04
8.03
8.02
7.46
7.36
7.35
7.34
7.26
6.52
6.51
6.20
5.48
5.47
5.46
4.97
4.95
4.64
4.58
4.53
4.33
3.67
3.63
3.63
3.60
3.59
2.34
2.34
2.18
2.17
2.16
1.91
1.71
CDCl3, 600 MHz
MeOOC
OBn
O
OAc
O
O
OBz
OBn OH
125
f1 (ppm)

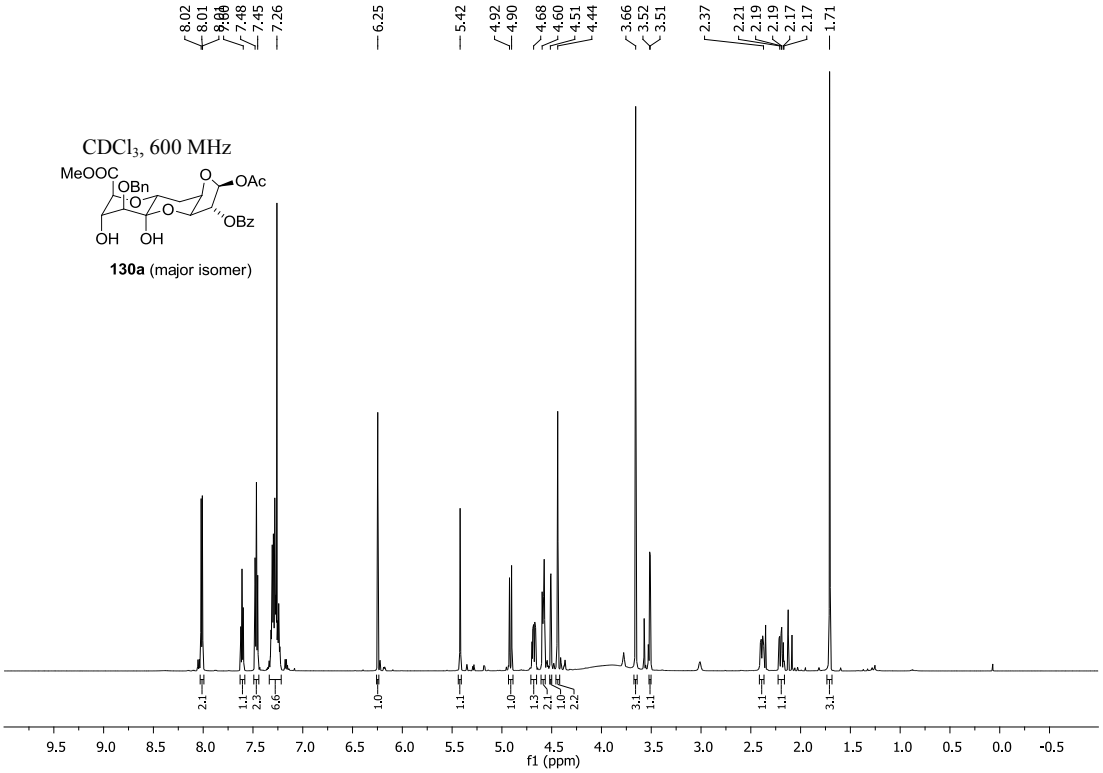

169.52
169.46
165.13
137.78
136.21
133.59
128.85
128.50
128.16
127.91
127.64
95.44
93.73
77.88
77.16
75.31
74.07
72.64
65.18
52.39
25.40
20.94
CDCl3, 150 MHz
MeOOC
OBn
O
OAc
O
O
OBz
OBn OH
125
f1 (ppm)

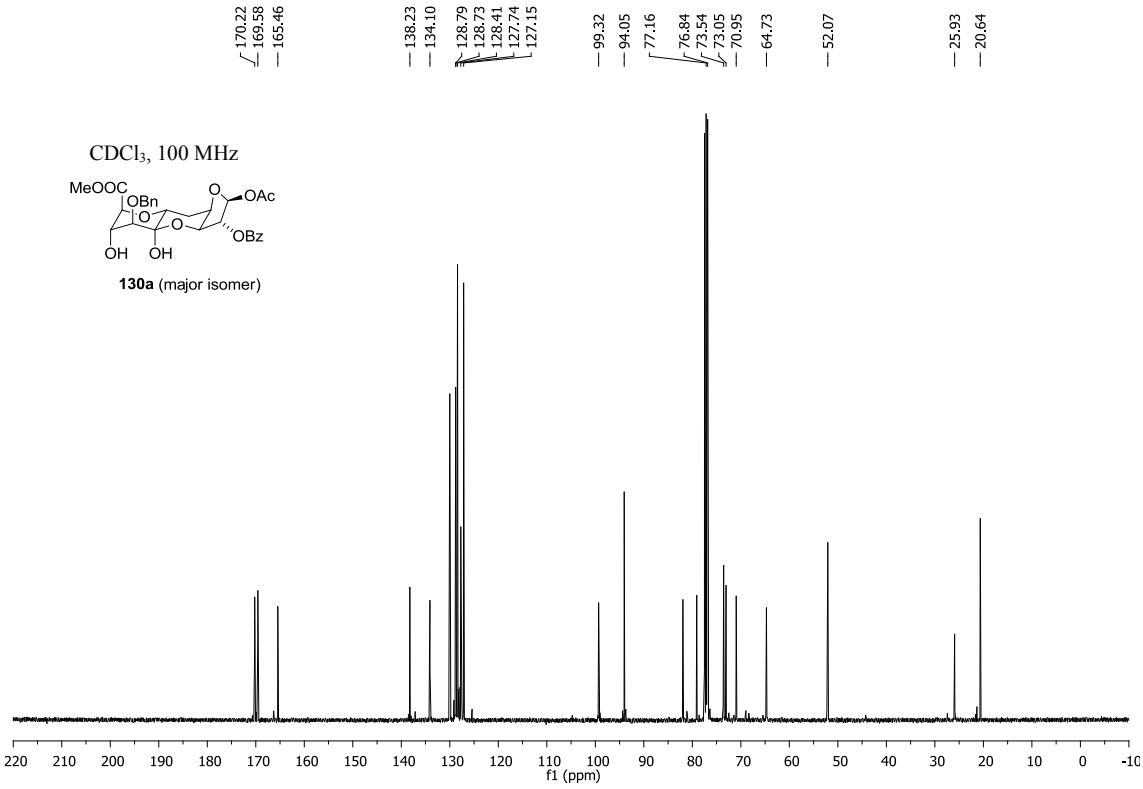

8.36
8.26
7.31
7.30
7.20
7.19
7.16
7.15
7.02
6.18
6.14
4.48
4.46
4.45
4.44
4.42
4.28
4.26
4.11
4.11
4.10
3.73
3.46
3.46
2.76
2.42
2.41
2.40
2.25
2.24
2.22
2.21
2.20
CDCl3, 600 MHz
MeOOC
OBn
OBn
OH
OH
127
f1 (ppm)

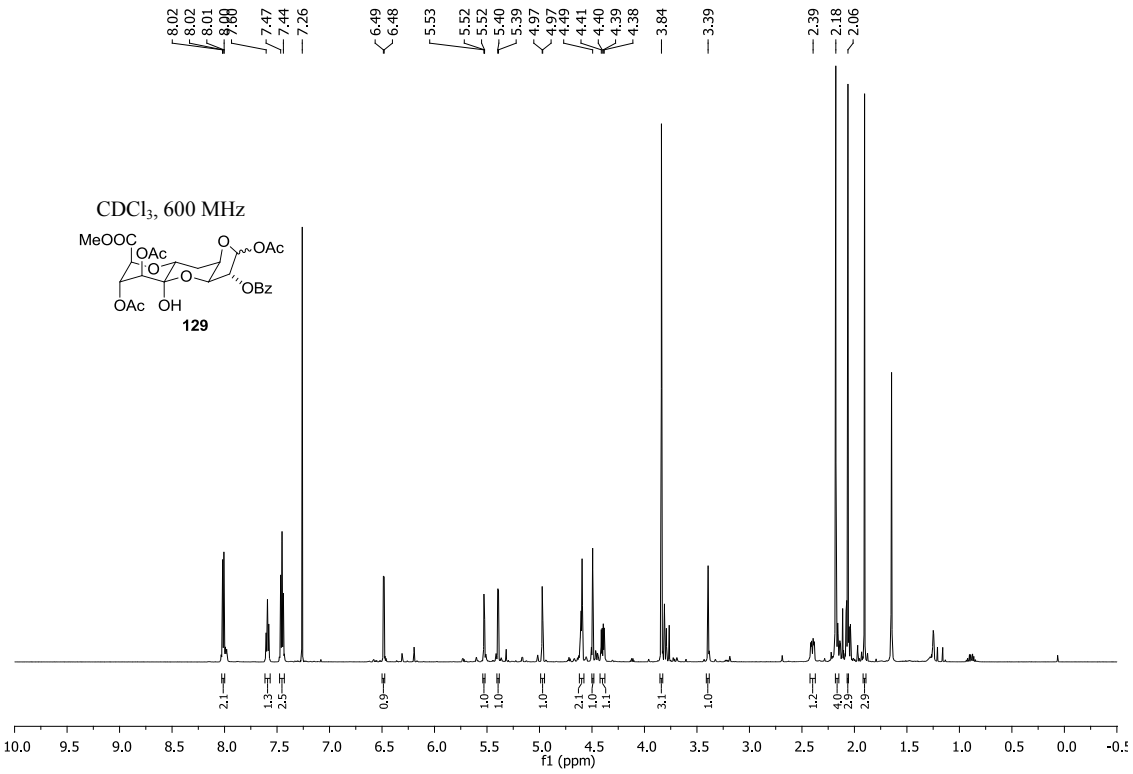

169.63
155.63
152.64
148.99
139.66
136.71
128.44
128.17
119.54
93.20
91.69
77.37
76.32
73.26
72.42
65.56
52.51
25.65
CDCl3, 150 MHz
MeOOC
OBn
OBn
OH
OH
127
f1 (ppm)

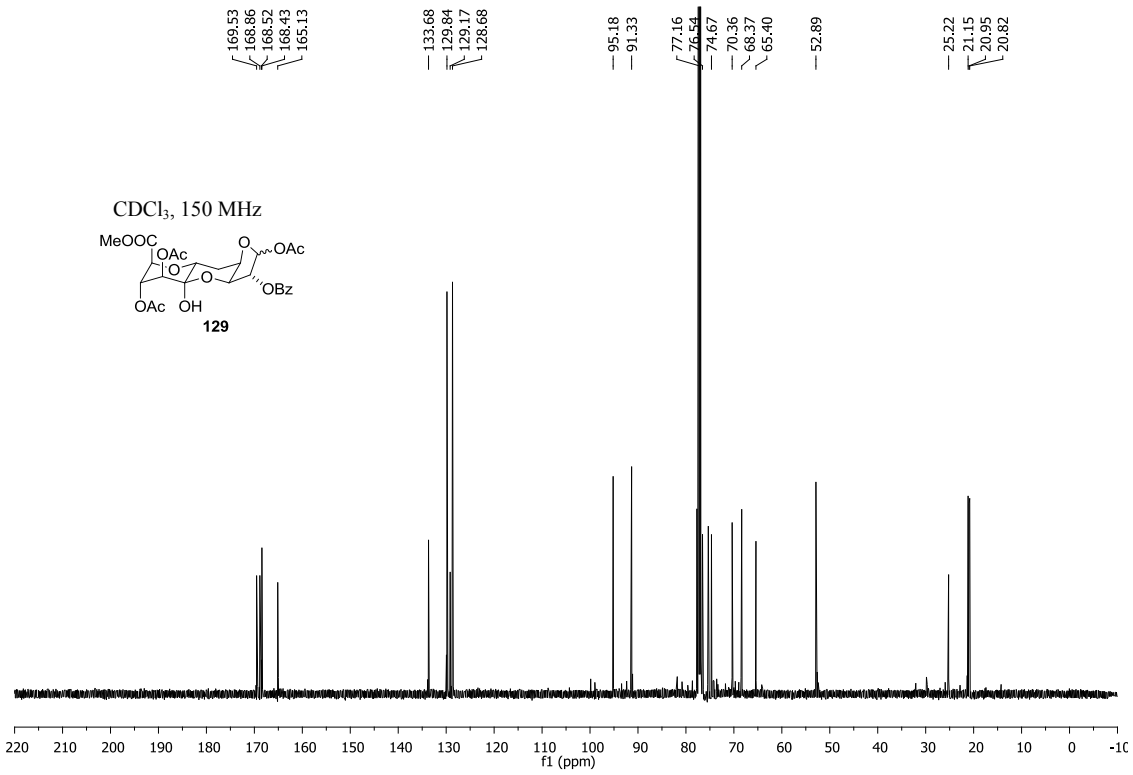

7.98
7.97
7.57
7.43
7.42
7.41
7.26
6.53
6.52
5.47
5.47
4.57
4.54
4.54
4.50
4.44
4.08
3.79
3.75
3.19
2.35
2.34
2.21
2.21
1.93
CDCl3, 600 MHz
MeOOC
OH
O
O
OAc
O
OBz
OH
OH
268
2.0
1.0
2.0
0.9
0.9
1.0
1.0
2.0
1.1
1.0
0.9
1.0
2.9
0.9
1.0
1.0
2.8
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

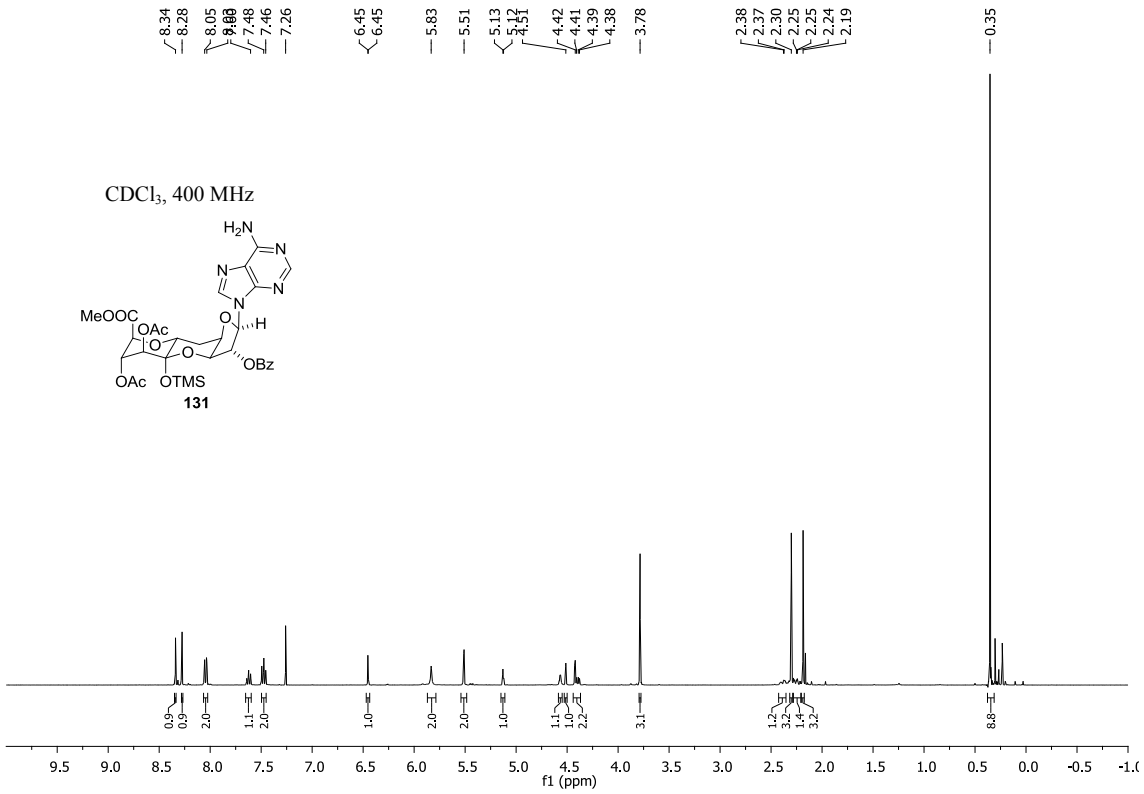

170.08
169.84
165.53
133.83
129.84
128.97
128.71
95.65
93.38
77.16
76.95
75.39
70.69
63.89
52.47
25.17
20.95
CDCl3, 150 MHz
MeOOC
OH
O
O
OAc
O
OBz
OH
OH
268
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

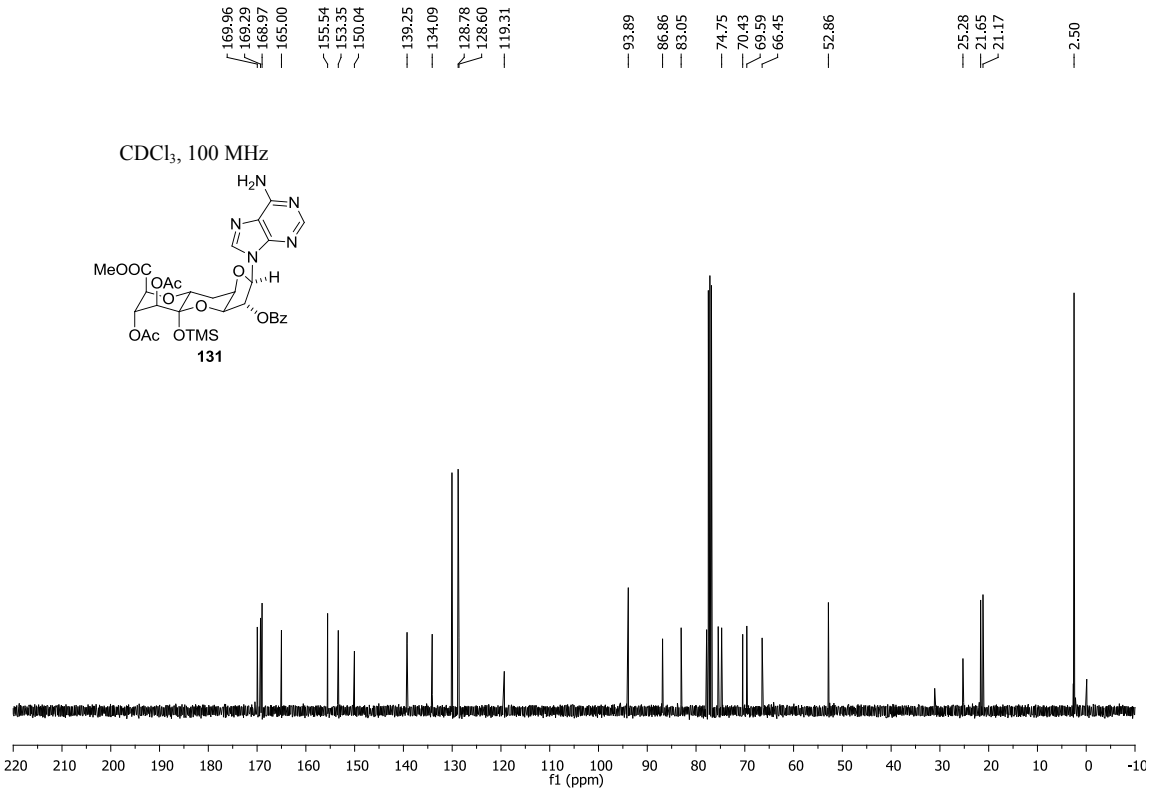

8.02
8.01
7.48
7.45
7.26
6.25
5.42
4.92
4.90
4.68
4.60
4.51
4.44
3.66
3.52
3.51
2.37
2.21
2.19
2.17
2.17
1.71
CDCl3, 600 MHz
MeOOC
OBn
O
OAc
O
OBz
OH
OH
130a (major isomer)
f1 (ppm)

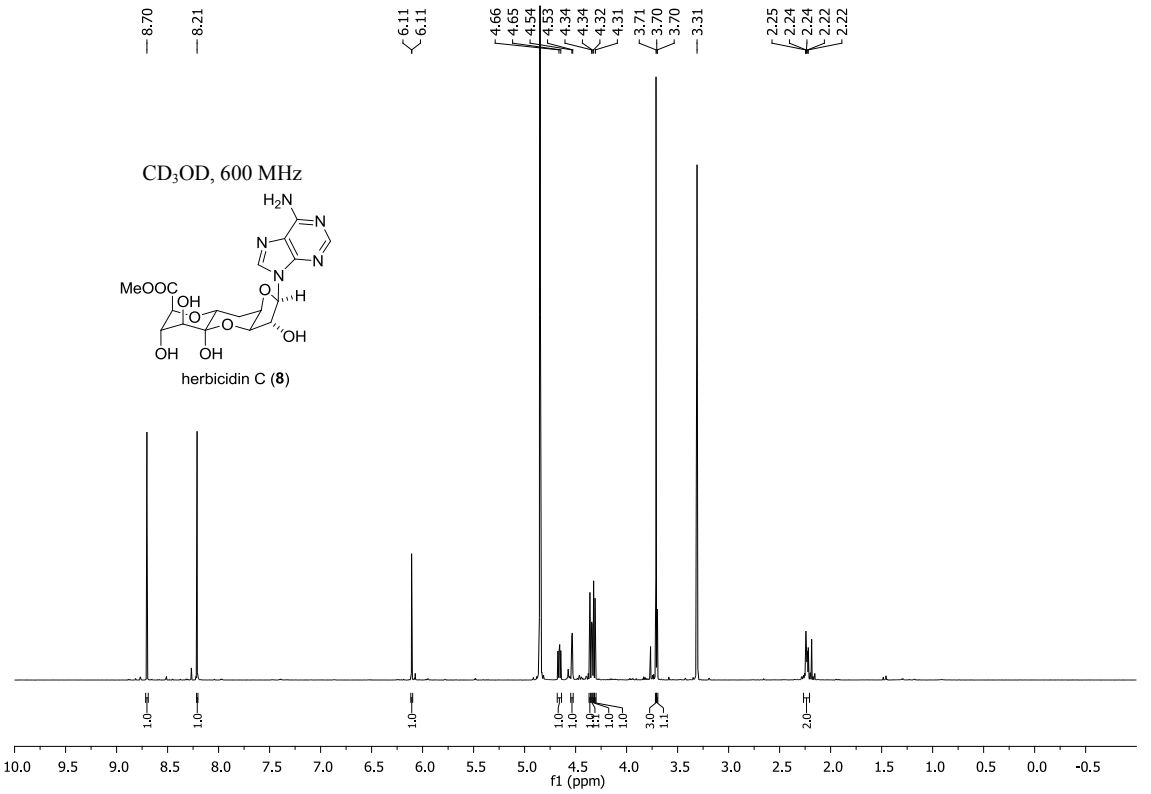

170.22
169.58
165.46
138.23
134.10
128.79
128.73
128.41
127.74
127.15
99.32
94.05
77.16
76.84
73.54
73.05
70.95
64.73
52.07
25.93
20.64
CDCl3, 100 MHz
MeOOC
OBn
O
OAc
O
OBz
OH
OH
130a (major isomer)
f1 (ppm)

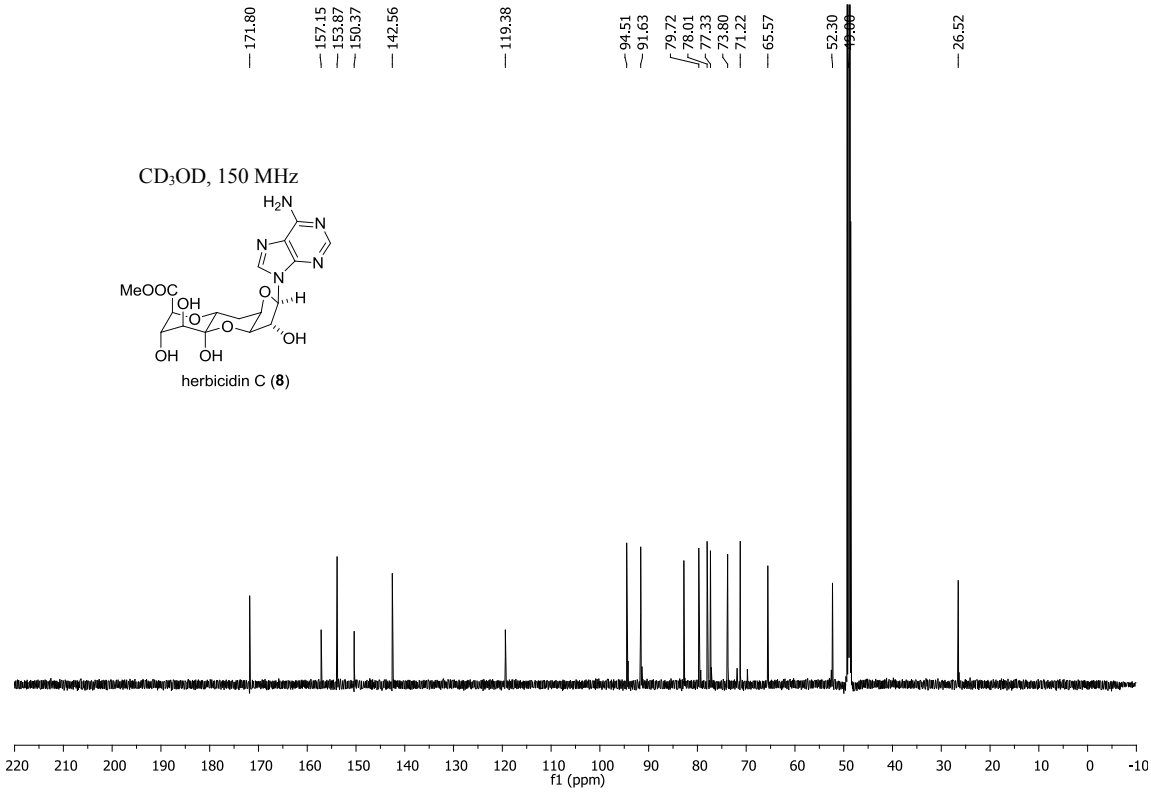

8.02
8.02
8.01
7.47
7.44
7.26
6.49
6.48
5.53
5.52
5.52
5.40
5.39
4.97
4.97
4.49
4.41
4.40
4.39
4.38
3.84
3.39
2.39
2.18
2.06
CDCl3, 600 MHz
MeOOC
OAc
OAc
OBz
OAc
OH
129
f1 (ppm)

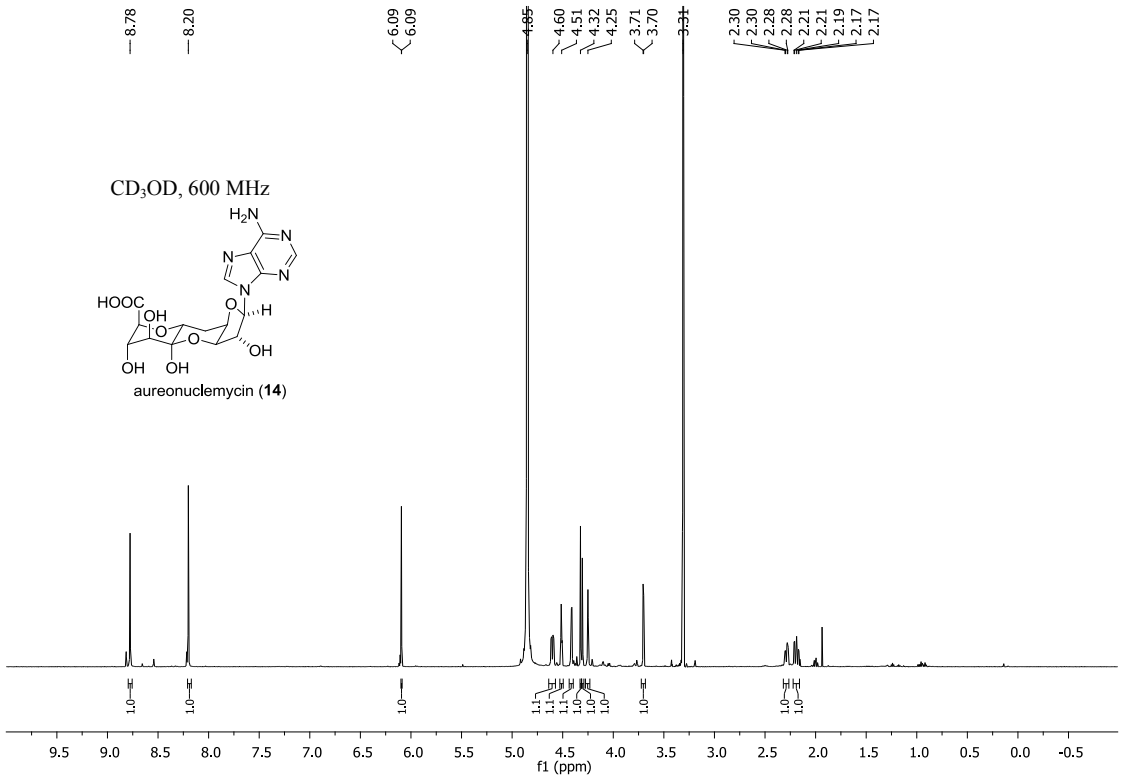

169.53
168.86
168.52
168.43
165.13
133.68
129.84
129.17
128.68
95.18
91.33
77.16
76.54
74.67
70.36
68.37
65.40
52.89
25.22
21.15
20.95
20.82
CDCl3, 150 MHz
MeOOC
OAc
OAc
OBz
OAc
OH
129
f1 (ppm)

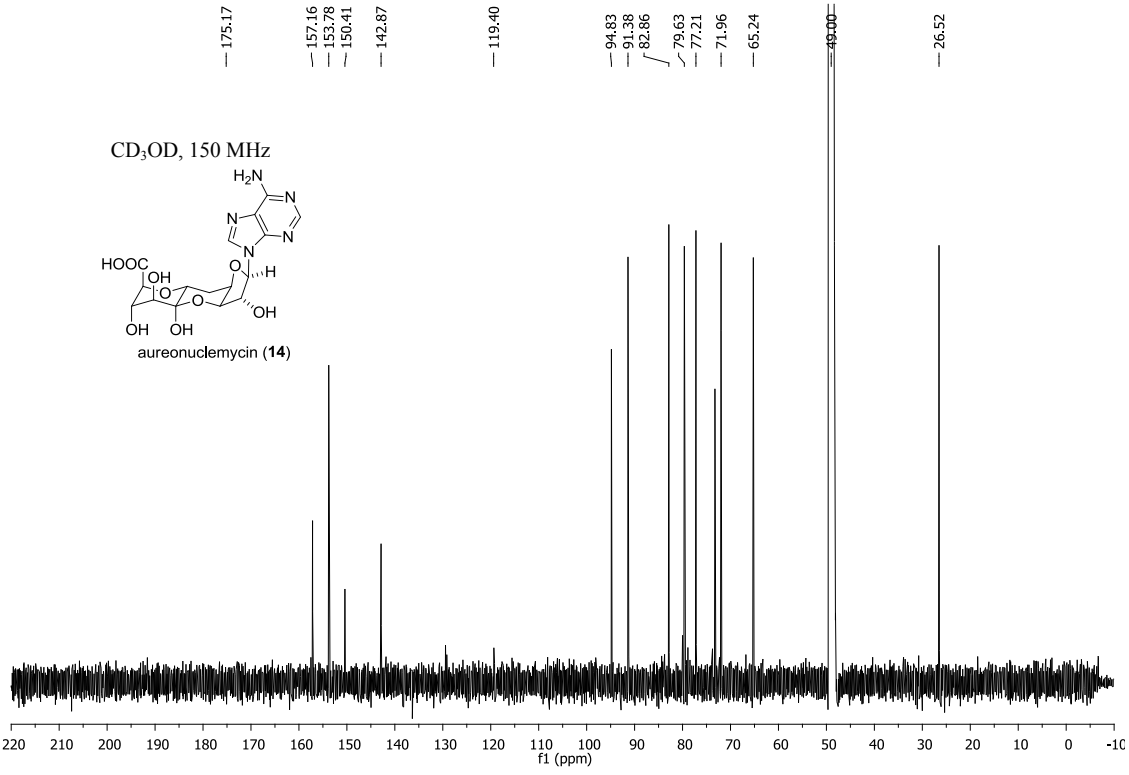

8.34
8.28
8.05
7.48
7.46
7.26
6.45
6.45
5.83
5.51
5.13
5.12
4.51
4.42
4.41
4.39
4.38
3.78
2.38
2.37
2.30
2.25
2.25
2.24
2.19
0.35
CDCl3, 400 MHz
H2N
MeOOC
OAc
O
H
OBz
OAc
OTMS
131
f1 (ppm)

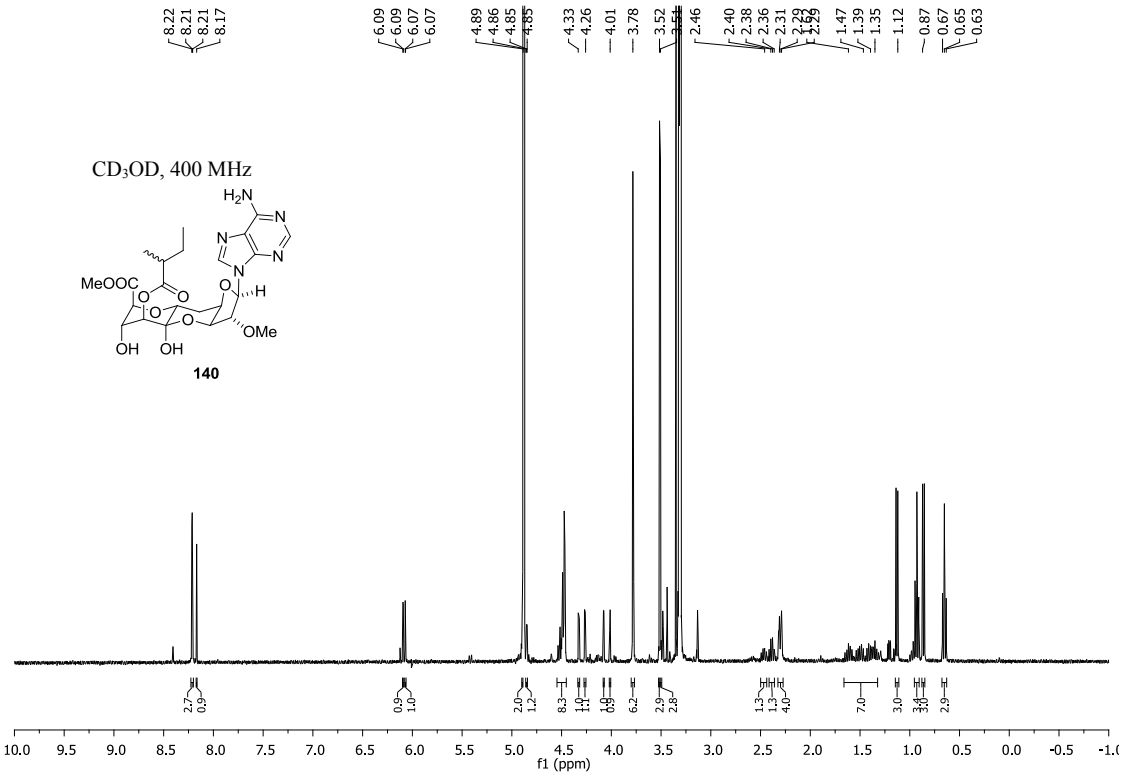

169.96
169.29
168.97
165.00
155.54
153.35
150.04
139.25
134.09
128.78
128.60
119.31
93.89
86.86
83.05
74.75
70.43
69.59
66.45
52.86
25.28
21.65
21.17
2.50
CDCl3, 100 MHz
H2N
MeOOC
OAc
O
H
OBz
OAc
OTMS
131
f1 (ppm)

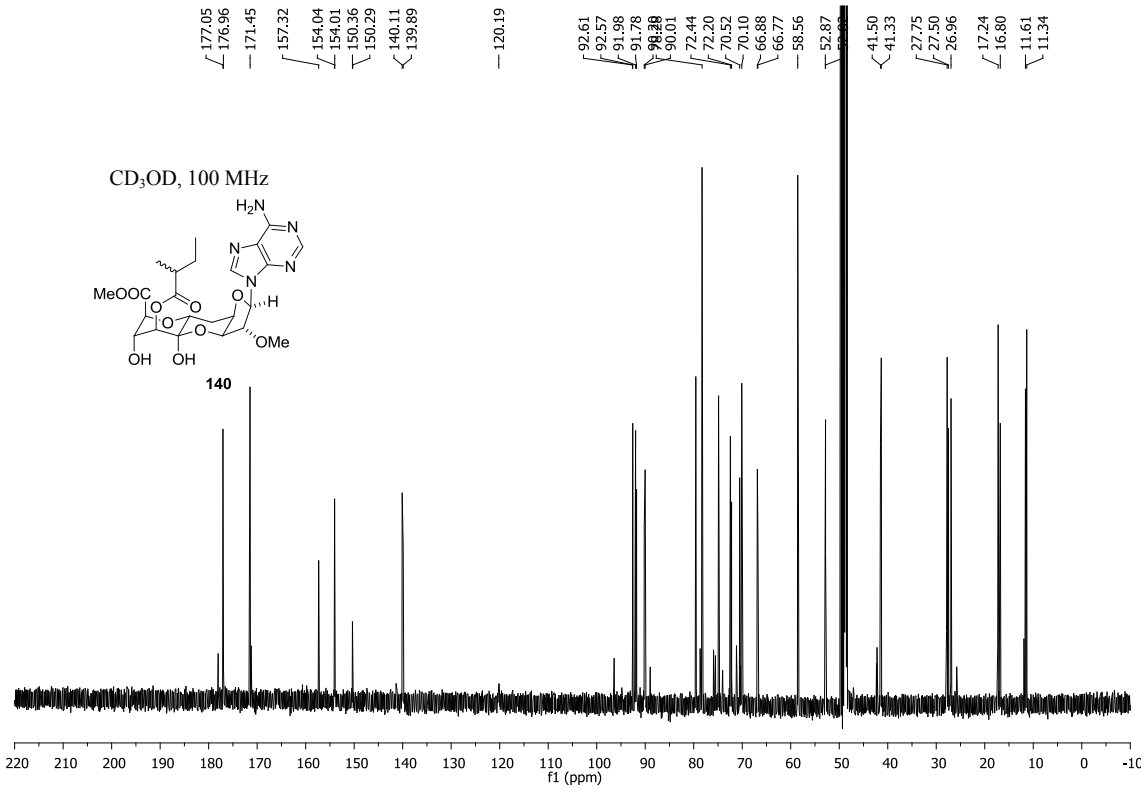

8.70
8.21
6.11
6.11
4.66
4.65
4.54
4.53
4.34
4.34
4.32
4.31
3.71
3.70
3.70
3.31
2.25
2.24
2.24
2.22
2.22
CD3OD, 600 MHz
herbicidin C (8)
f1 (ppm)

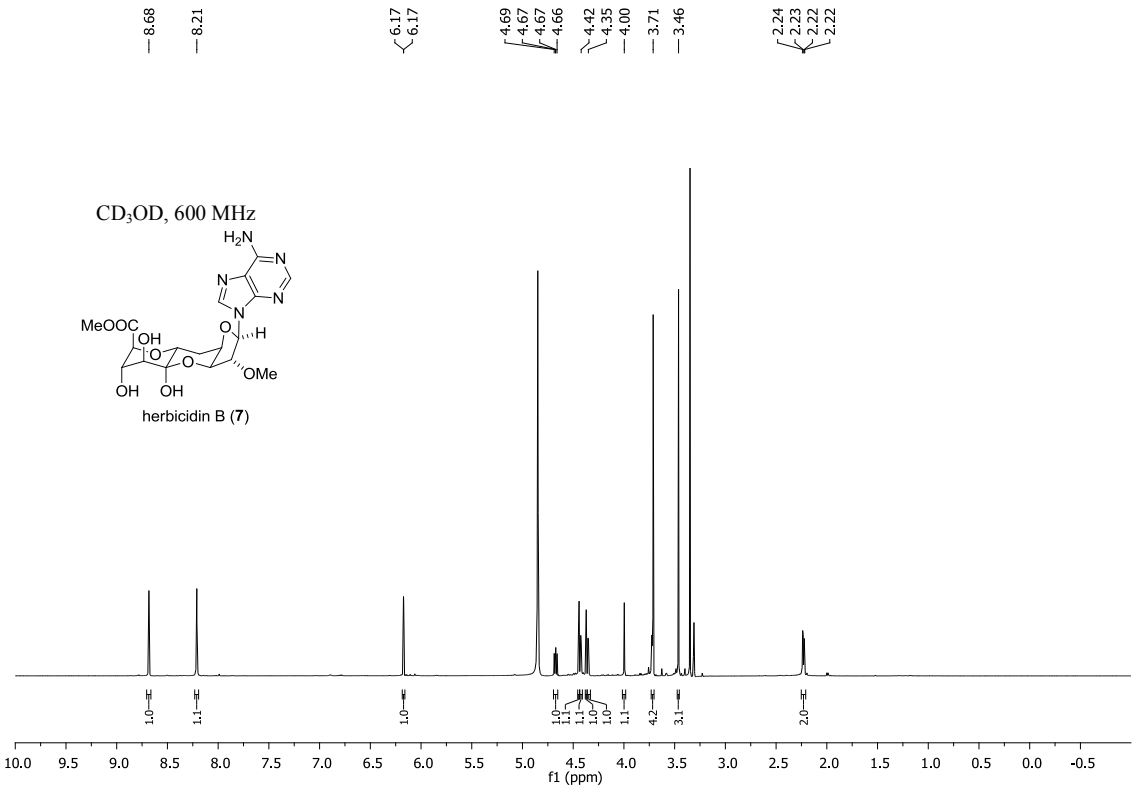

171.80
157.15
153.87
150.37
142.56
119.38
94.51
91.63
79.72
78.01
77.33
73.80
71.22
65.57
52.30
49.00
26.52
CD3OD, 150 MHz
herbicidin C (8)
f1 (ppm)

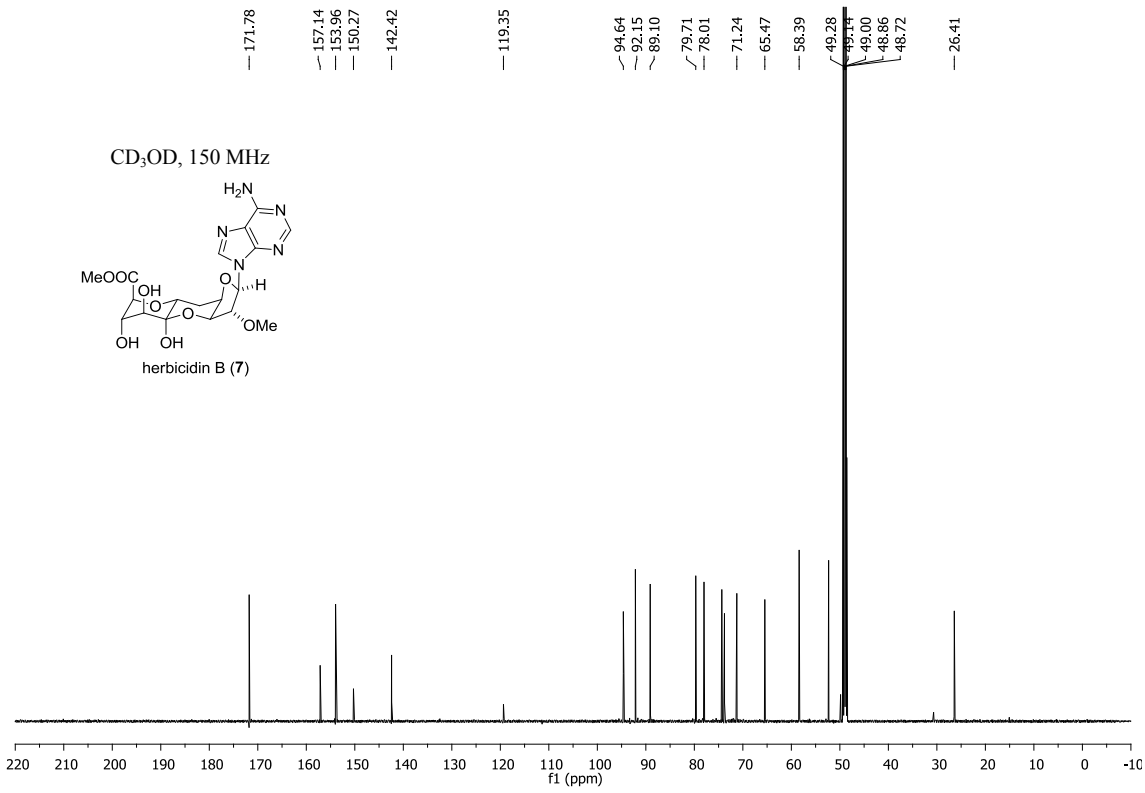

8.78
8.20
6.09
6.09
4.85
4.60
4.51
4.32
4.25
3.71
3.70
3.31
2.30
2.30
2.28
2.28
2.21
2.21
2.19
2.17
2.17
CD3OD, 600 MHz
aureonuclemycin (14)
f1 (ppm)

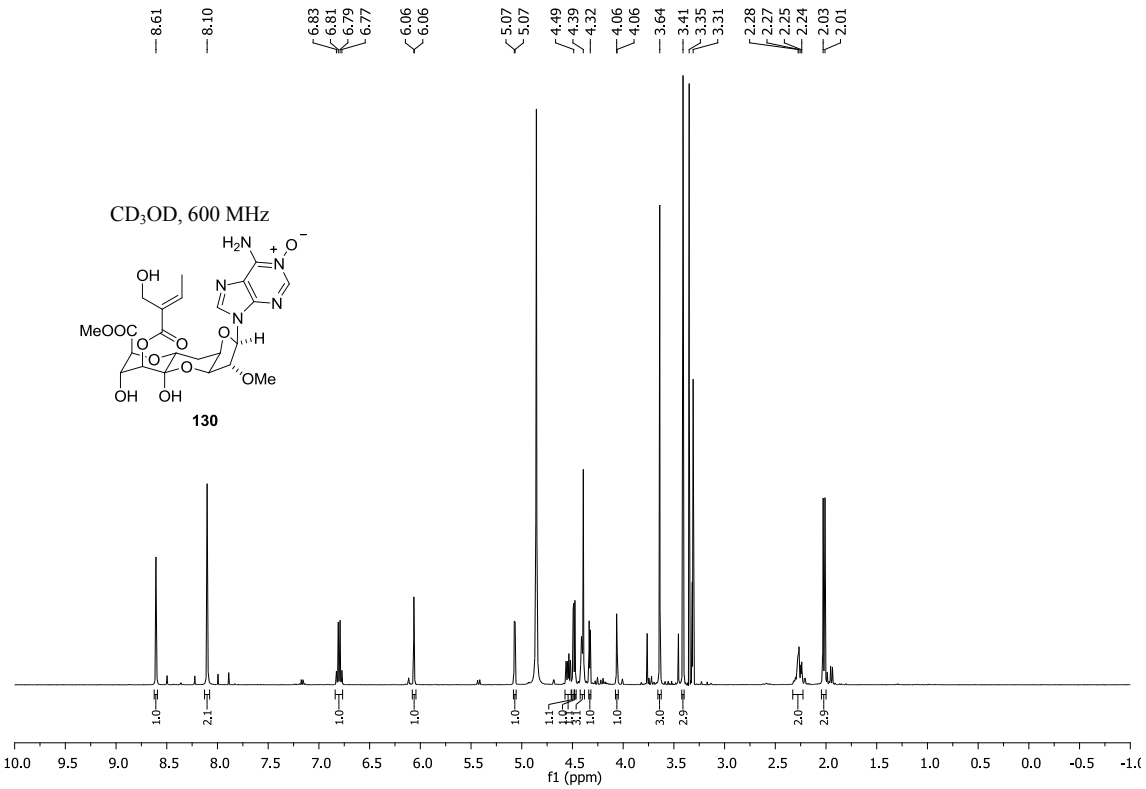

175.17
157.16
153.78
150.41
142.87
119.40
94.83
91.38
82.86
79.63
77.21
71.96
65.24
49.00
26.52
CD3OD, 150 MHz
aureonuclemycin (14)
f1 (ppm)

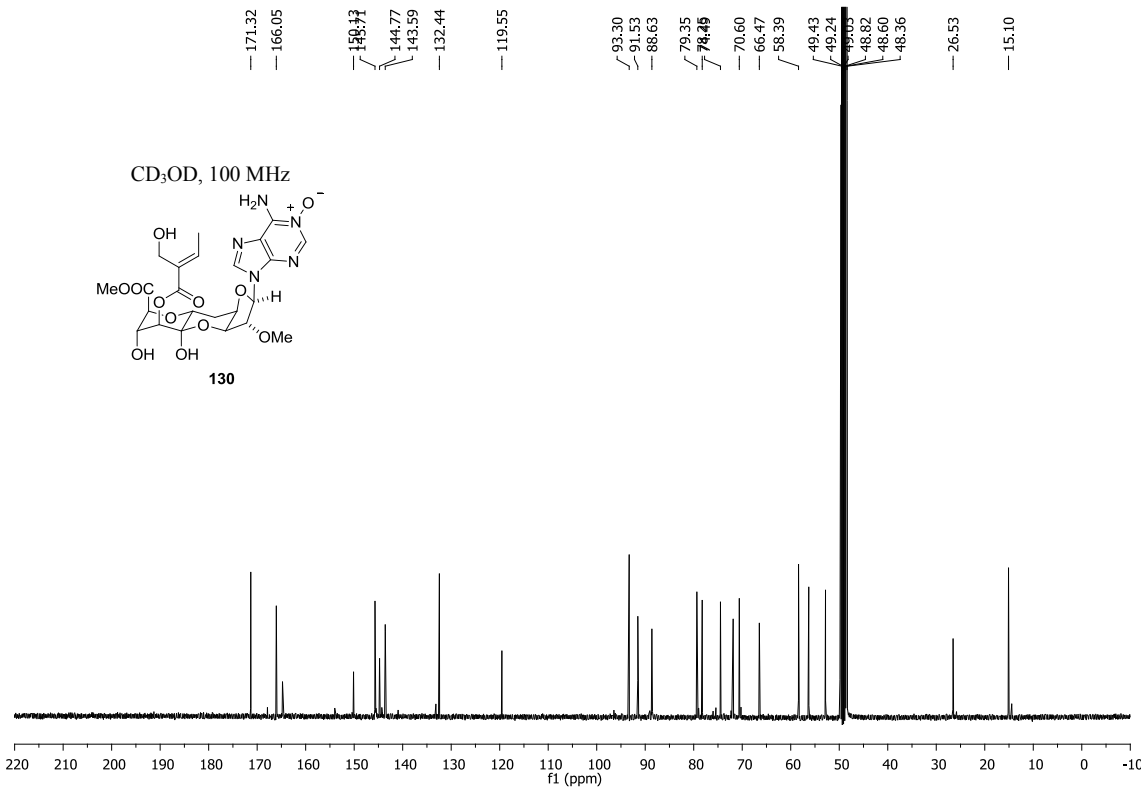

CD3OD, 400 MHz
140
f1 (ppm)

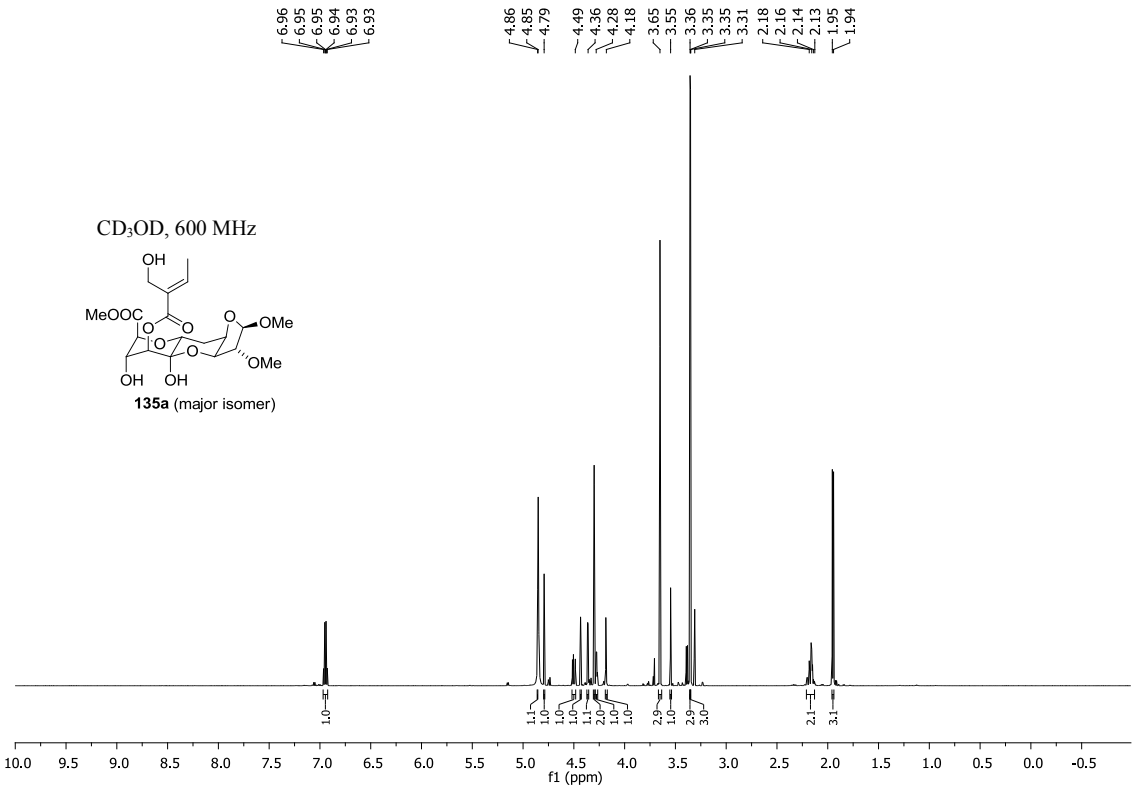

CD3OD, 100 MHz
140
f1 (ppm)

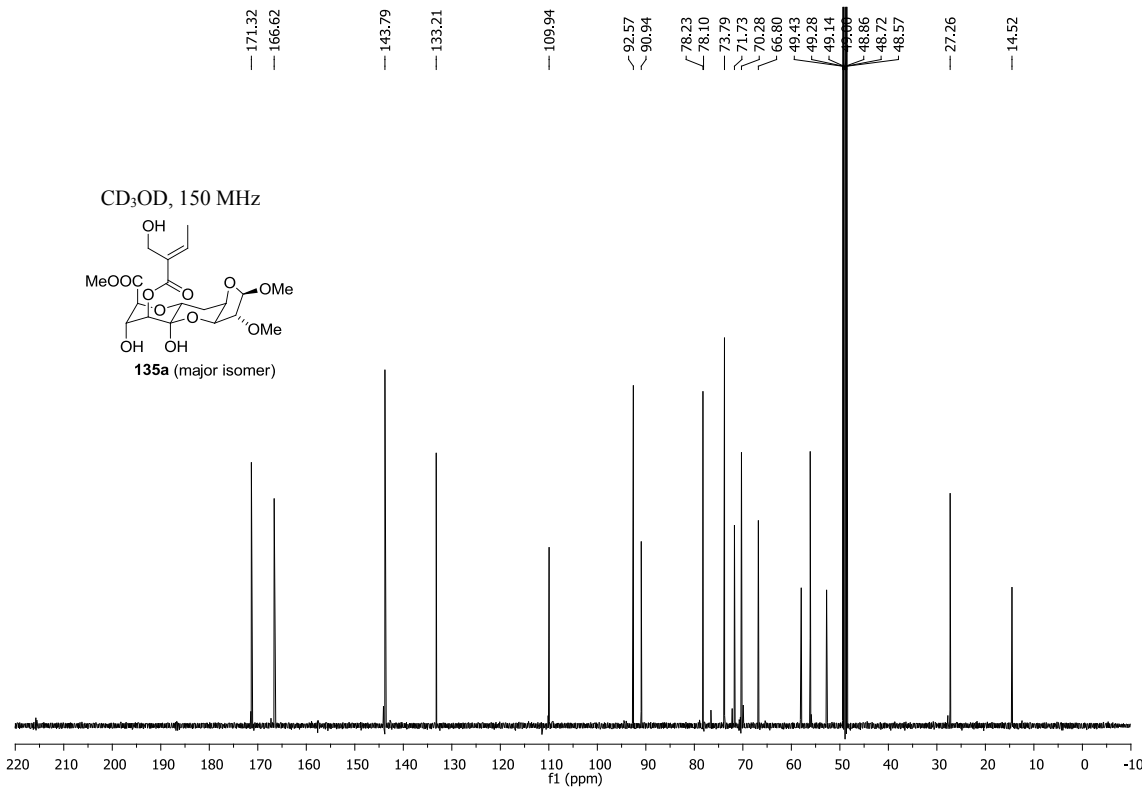

8.68
8.21
6.17
6.17
4.69
4.67
4.67
4.66
4.42
4.35
4.00
3.71
3.46
2.24
2.23
2.22
2.22
CD3OD, 600 MHz
herbicidin B (7)
f1 (ppm)

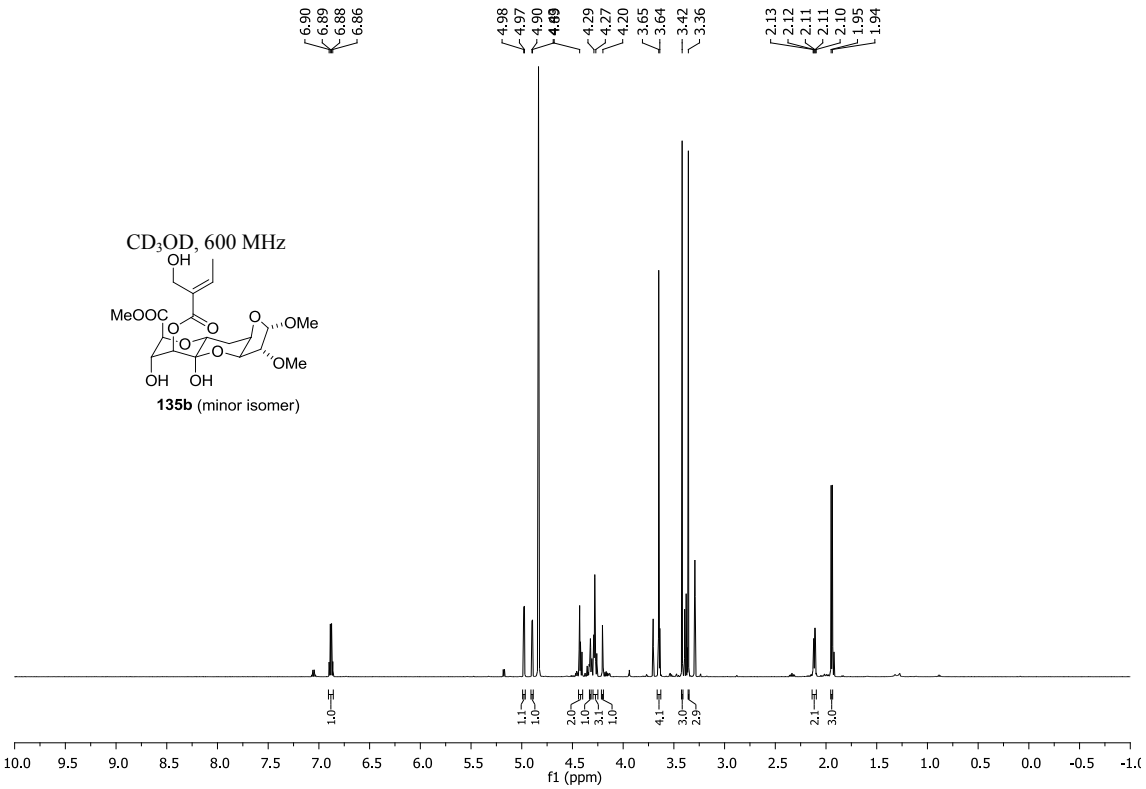

171.78
157.14
153.96
150.27
142.42
119.35
94.64
92.15
89.10
79.71
78.01
71.24
65.47
58.39
49.28
49.14
49.00
48.86
48.72
26.41
CD3OD, 150 MHz
herbicidin B (7)
f1 (ppm)

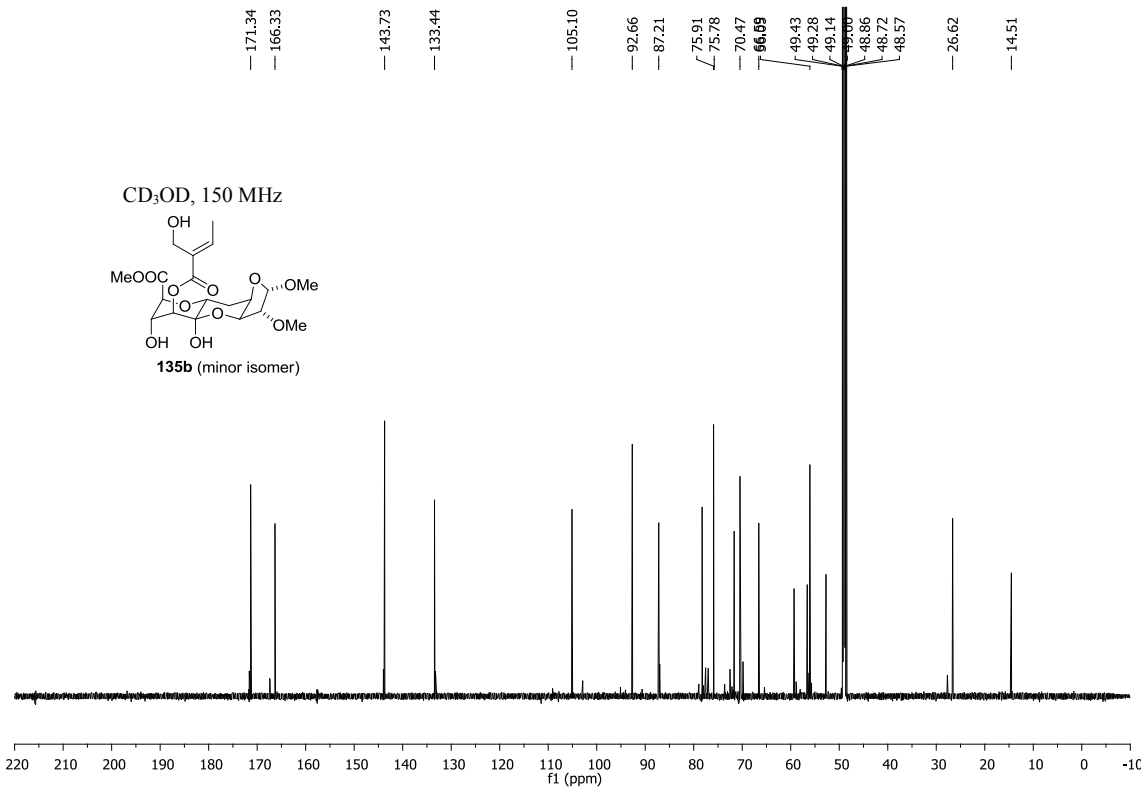

8.61
8.10
6.83
6.81
6.79
6.77
6.06
6.06
5.07
5.07
4.49
4.39
4.32
4.06
4.06
3.64
3.41
3.35
3.31
2.28
2.27
2.25
2.24
2.03
2.01
CD3OD, 600 MHz
130
f1 (ppm)

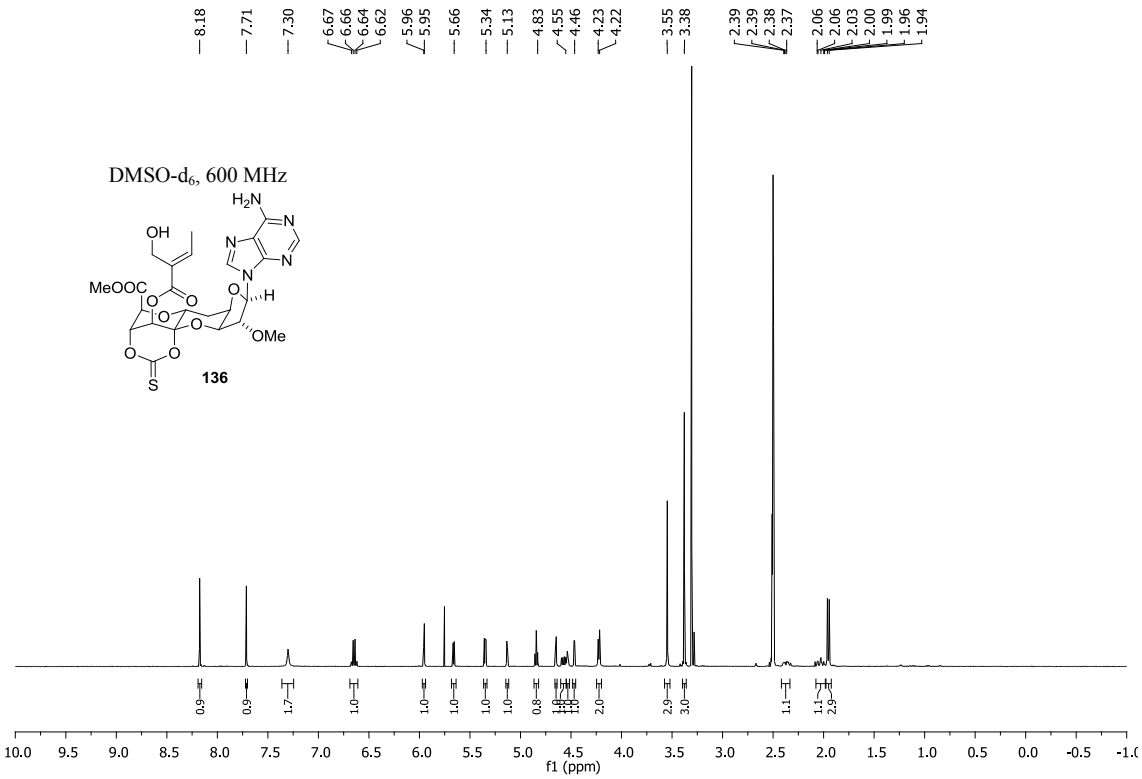

171.32
166.05
144.77
143.59
132.44
119.55
93.30
91.53
88.63
79.35
70.60
66.47
58.39
49.43
49.24
48.82
48.60
48.36
26.53
15.10
CD3OD, 100 MHz
130
f1 (ppm)

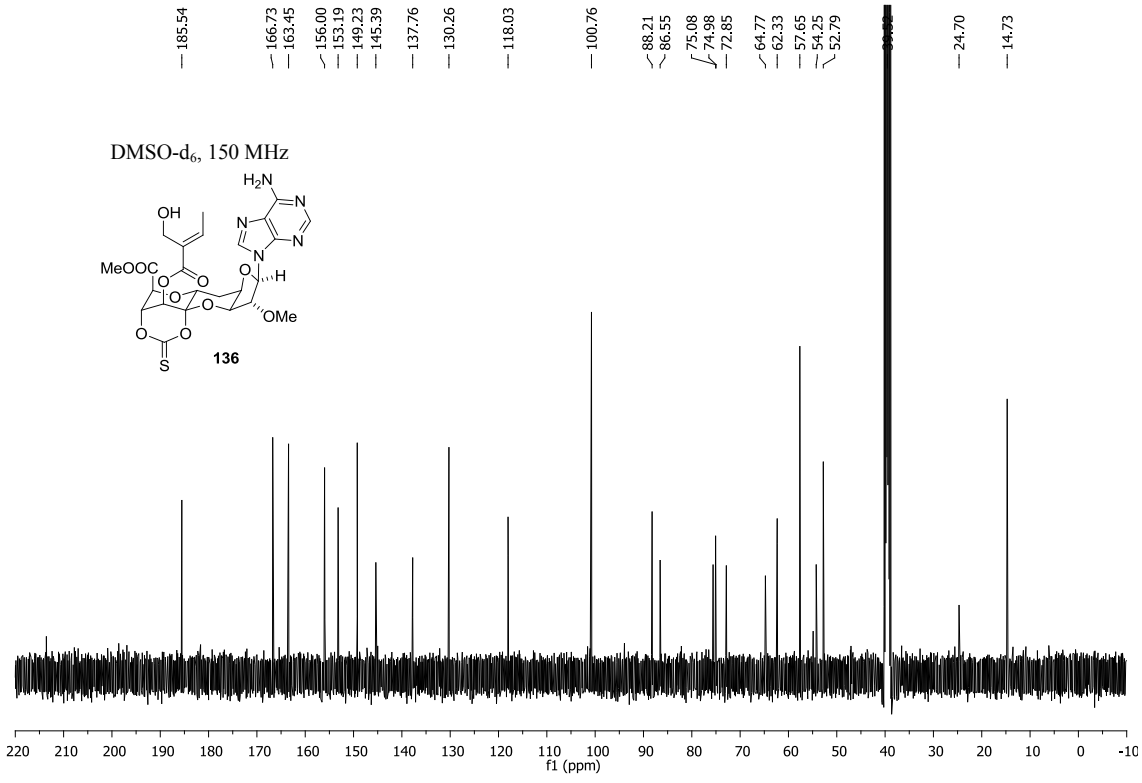

6.96
6.95
6.95
6.94
6.93
6.93
4.86
4.85
4.79
4.49
4.36
4.28
4.18
3.65
3.55
3.36
3.35
3.35
3.31
2.18
2.16
2.14
2.13
1.95
1.94
CD3OD, 600 MHz
OH
MeOOC
O
O
O
O
O
OMe
OMe
OH
OH
135a (major isomer)
1.0
1.1
1.0
1.0
1.1
2.0
1.0
1.0
2.9
1.0
2.9
3.0
2.1
3.1
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

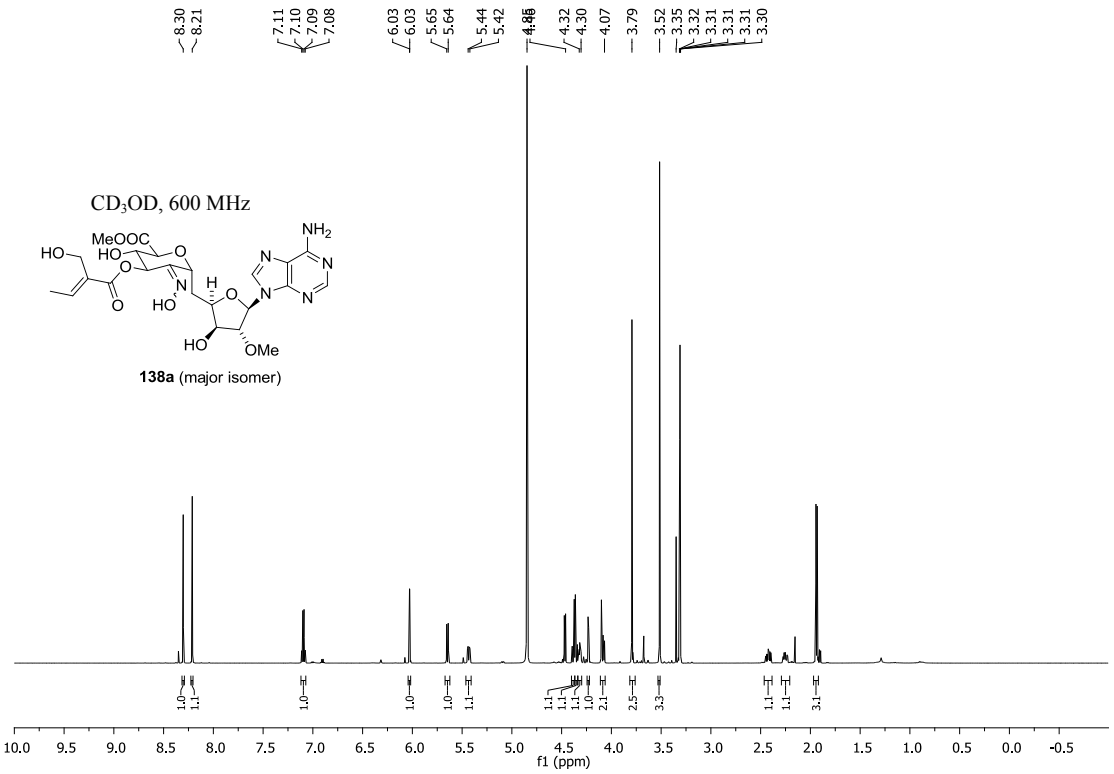

171.32
166.62
143.79
133.21
109.94
92.57
90.94
78.23
78.10
73.79
71.73
70.28
66.80
49.43
49.28
49.14
48.86
48.72
48.57
27.26
14.52
CD3OD, 150 MHz
OH
MeOOC
O
O
O
O
O
OMe
OMe
OH
OH
135a (major isomer)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

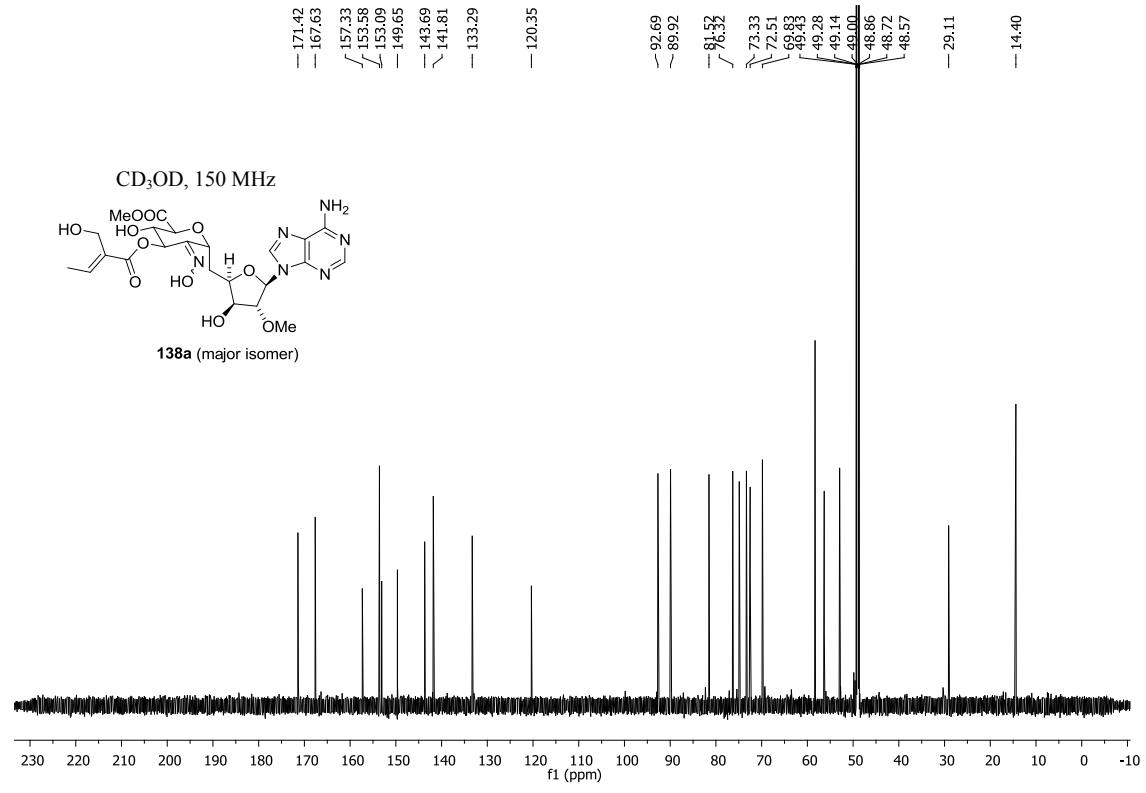

6.90
6.89
6.88
6.86
4.98
4.97
4.90
4.89
4.29
4.27
4.20
3.65
3.64
3.42
3.36
2.13
2.12
2.11
2.11
2.10
1.95
1.94
CD3OD, 600 MHz
OH
MeOOC
O
O
O
O
O
OMe
OMe
OH
OH
135b (minor isomer)
1.0
1.1
1.0
2.0
1.6
3.1
1.0
4.1
3.0
2.9
2.1
3.0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

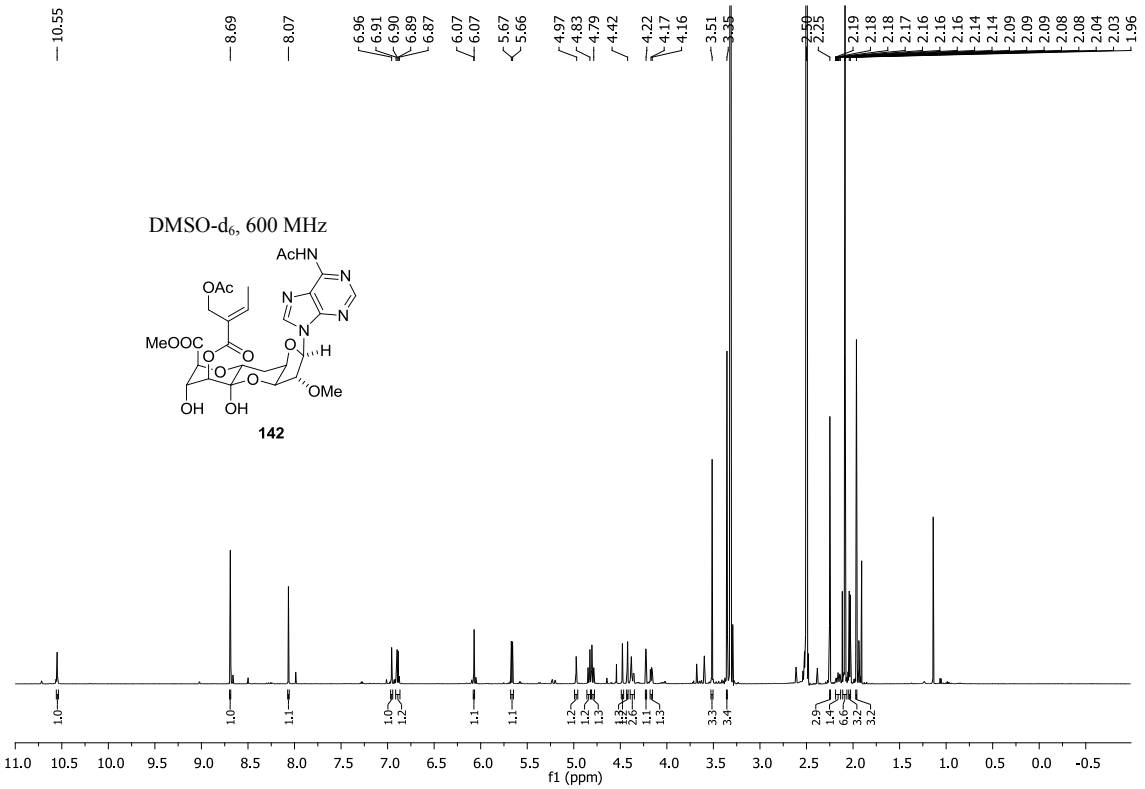

171.34
166.33
143.73
133.44
105.10
92.66
87.21
75.91
75.78
70.47
66.69
66.59
49.43
49.28
49.14
48.86
48.72
48.57
26.62
14.51
CD3OD, 150 MHz
OH
MeOOC
O
O
O
O
O
OMe
OMe
OH
OH
135b (minor isomer)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

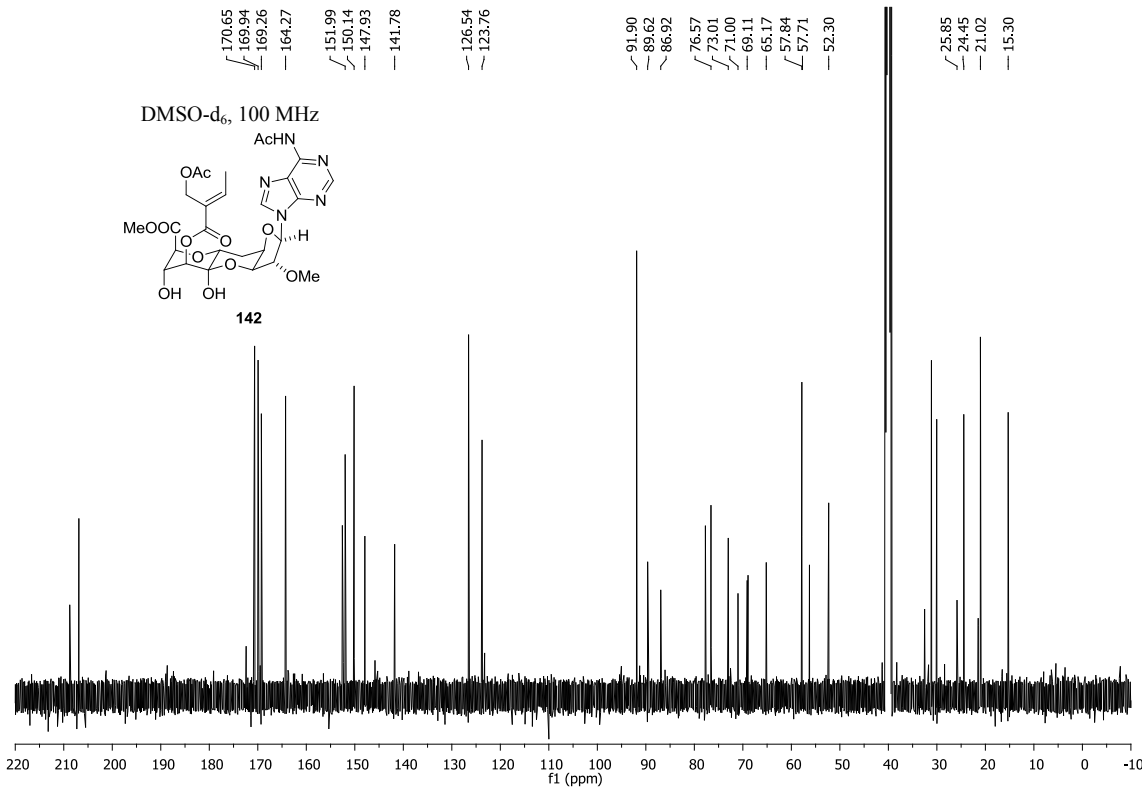

DMSO-d6, 600 MHz
136
f1 (ppm)

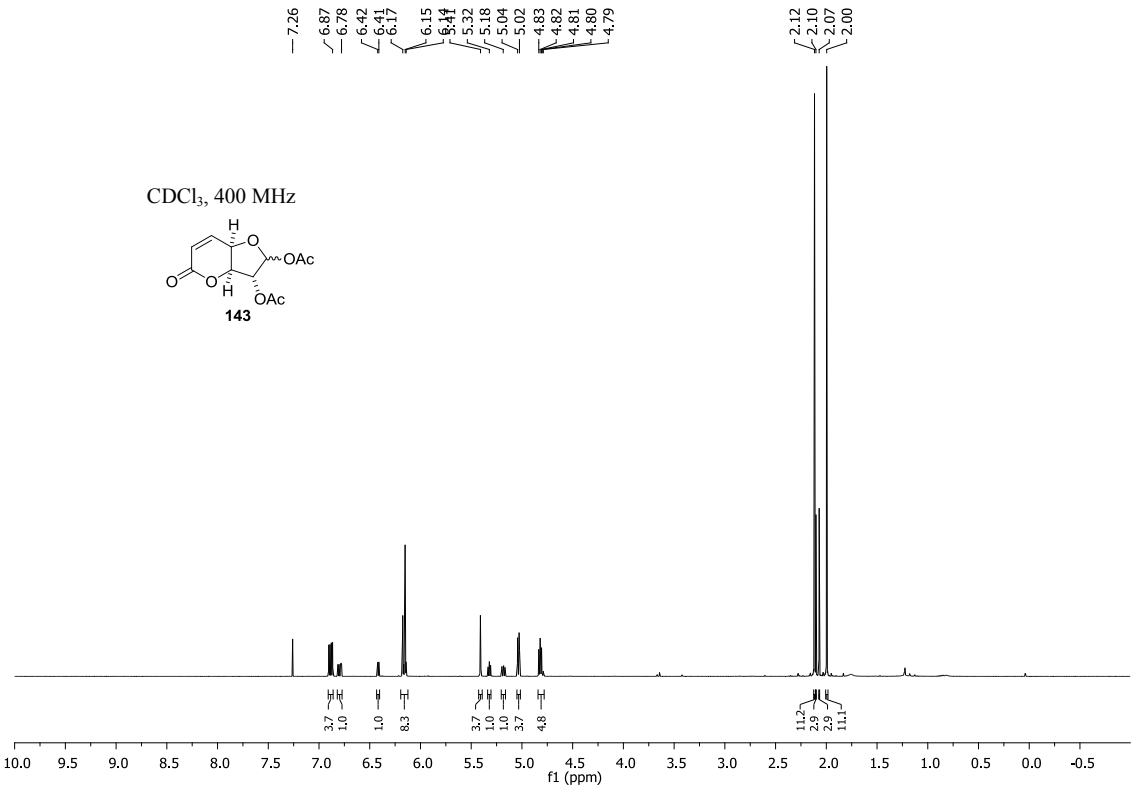

DMSO-d6, 150 MHz
136
f1 (ppm)

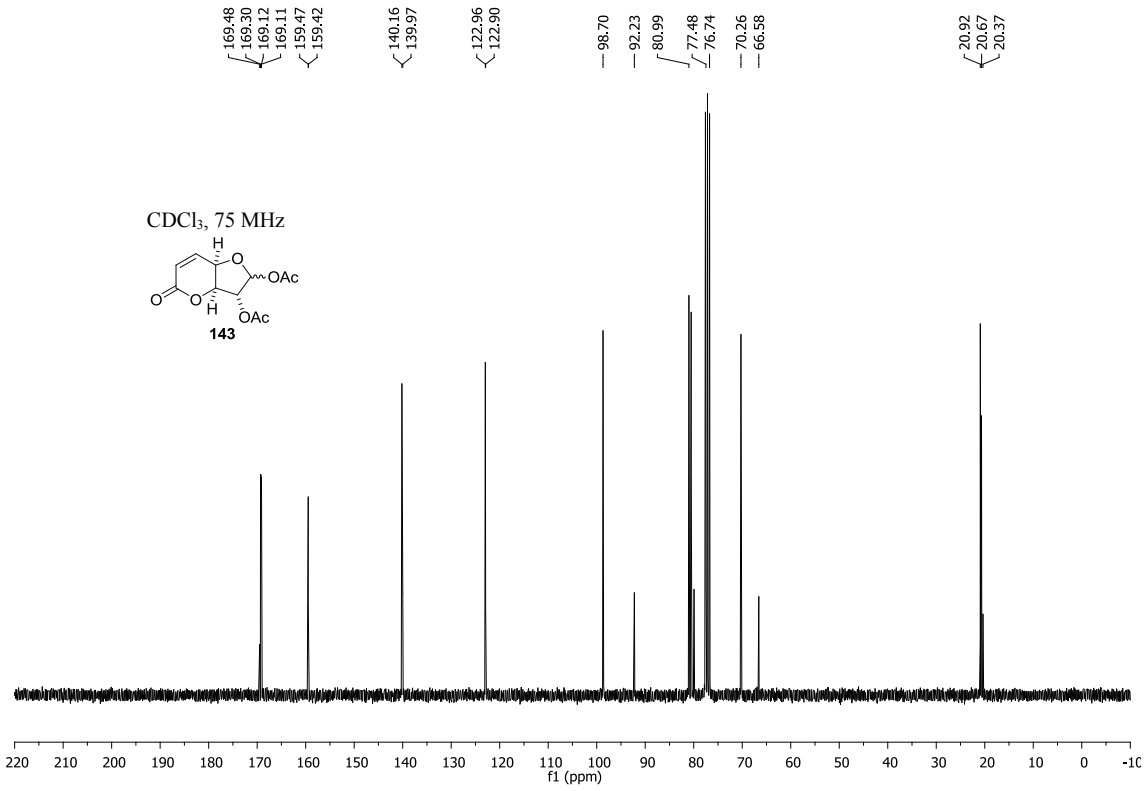

8.30
8.21
7.11
7.10
7.09
7.08
6.03
6.03
5.65
5.64
5.44
5.42
4.32
4.30
4.07
3.79
3.52
3.35
3.32
3.31
3.31
3.31
3.30
CD3OD, 600 MHz
MeOOC
HO
HO
O
O
N
HO
H
O
N
N
N
NH2
N
HO
HO
OMe
138a (major isomer)
f1 (ppm)

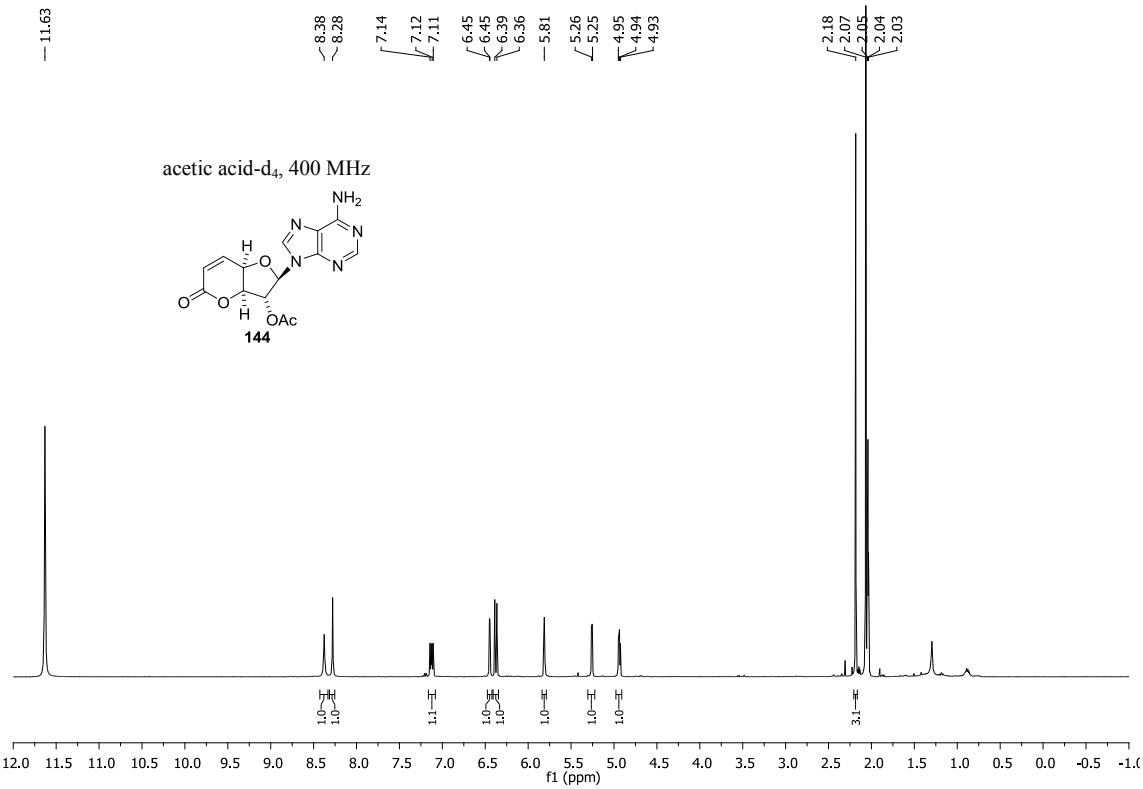

171.42
167.63
157.33
153.58
153.09
149.65
143.69
141.81
133.29
120.35
92.69
89.92
81.52
76.32
73.33
72.51
69.83
49.43
49.28
49.14
49.00
48.86
48.72
48.57
29.11
14.40
CD3OD, 150 MHz
MeOOC
HO
HO
O
O
N
HO
H
O
N
N
N
NH2
N
HO
HO
OMe
138a (major isomer)
f1 (ppm)

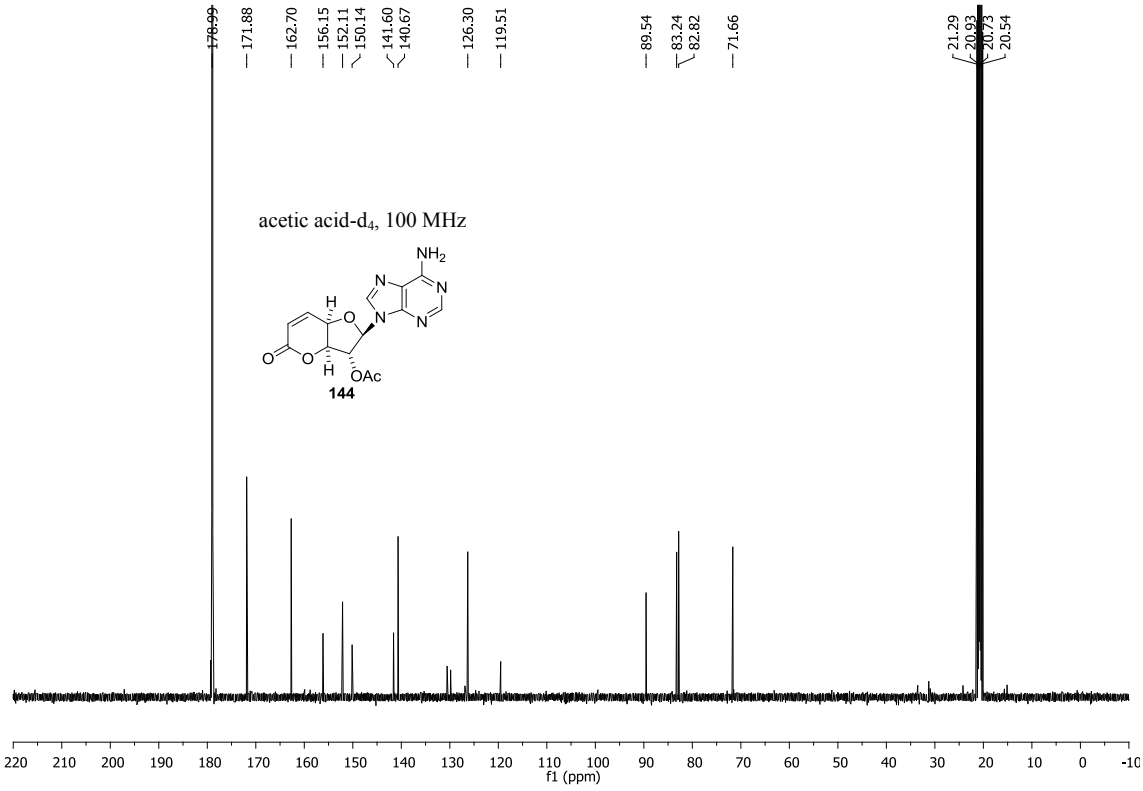

DMSO-d6, 600 MHz
AcHN
OAc
MeOOC
OMe
OH OH
142
f1 (ppm)

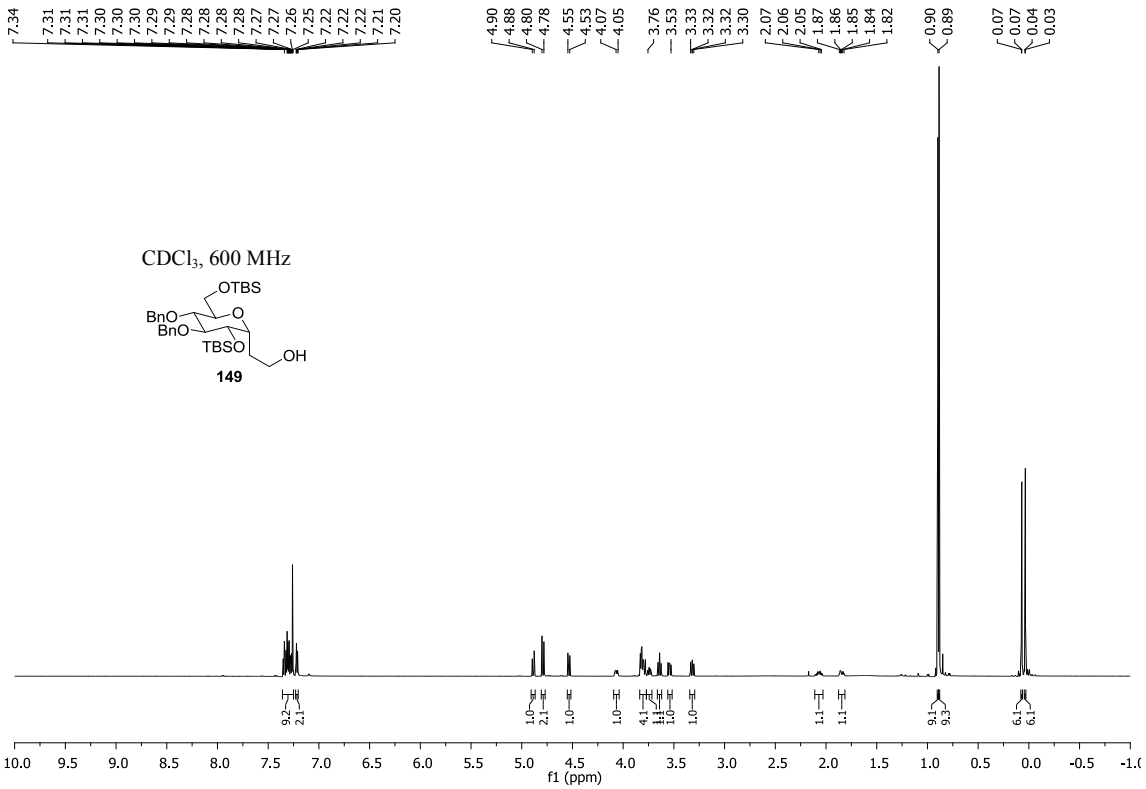

DMSO-d6, 100 MHz
AcHN
OAc
MeOOC
OMe
OH OH
142
f1 (ppm)

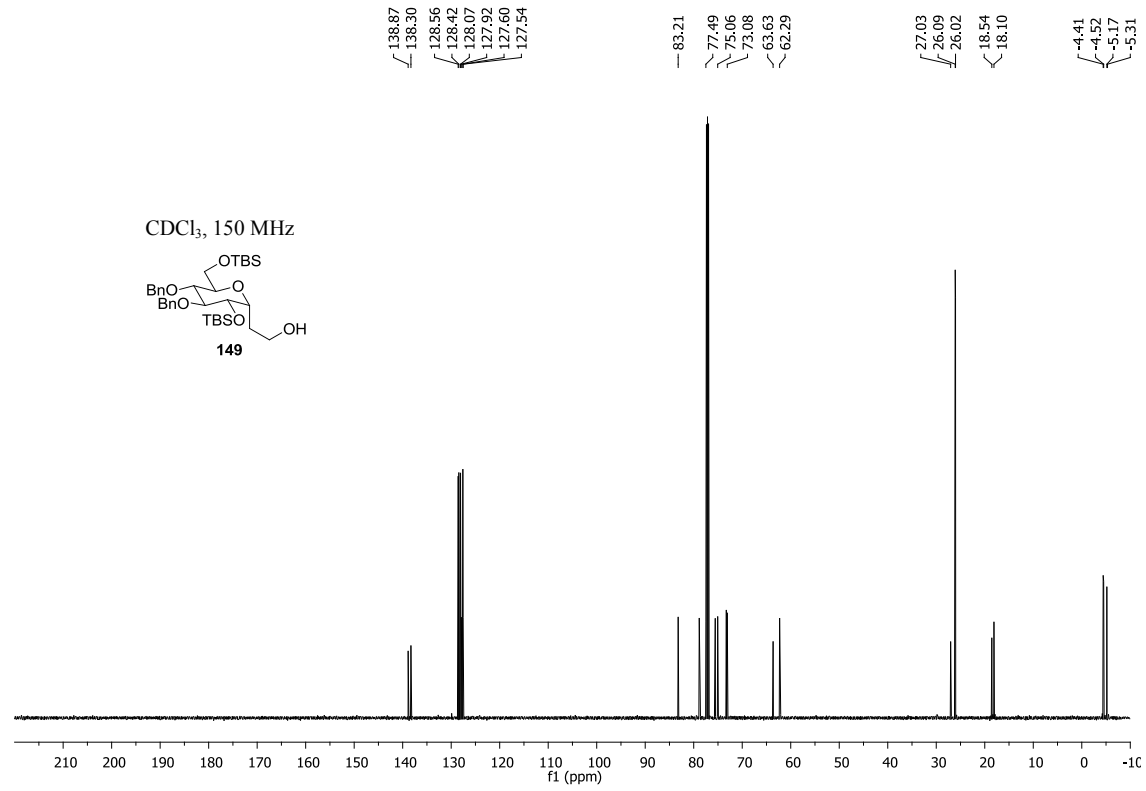

7.26
6.87
6.78
6.42
6.41
6.17
6.15
6.14
5.41
5.32
5.18
5.04
5.02
4.83
4.82
4.81
4.80
4.79
2.12
2.10
2.07
2.00
CDCl3, 400 MHz
H
O
OAc
O
O
H
OAc
143
3.7
1.0
1.0
8.3
3.7
1.0
1.0
3.7
4.8
11.2
2.9
2.9
11.1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

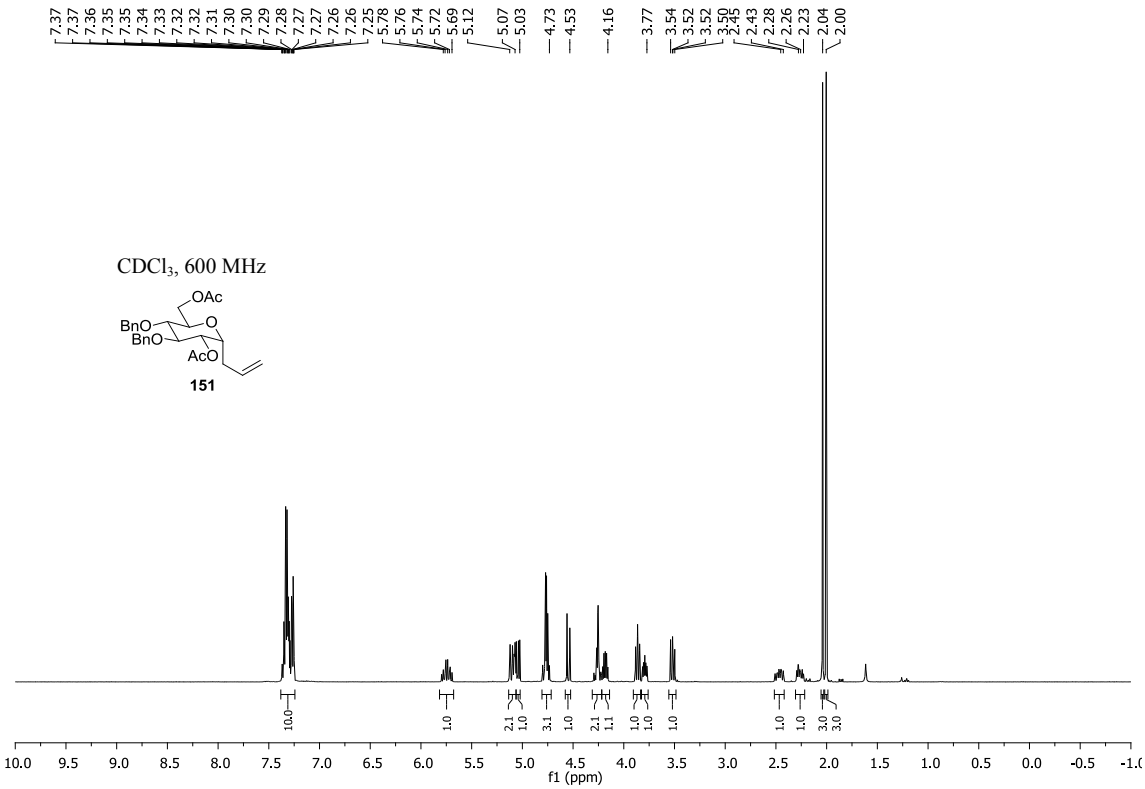

169.48
169.30
169.12
169.11
159.47
159.42
140.16
139.97
122.96
122.90
98.70
92.23
80.99
77.48
76.74
70.26
66.58
20.92
20.67
20.37
CDCl3, 75 MHz
H
O
OAc
O
O
H
OAc
143
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

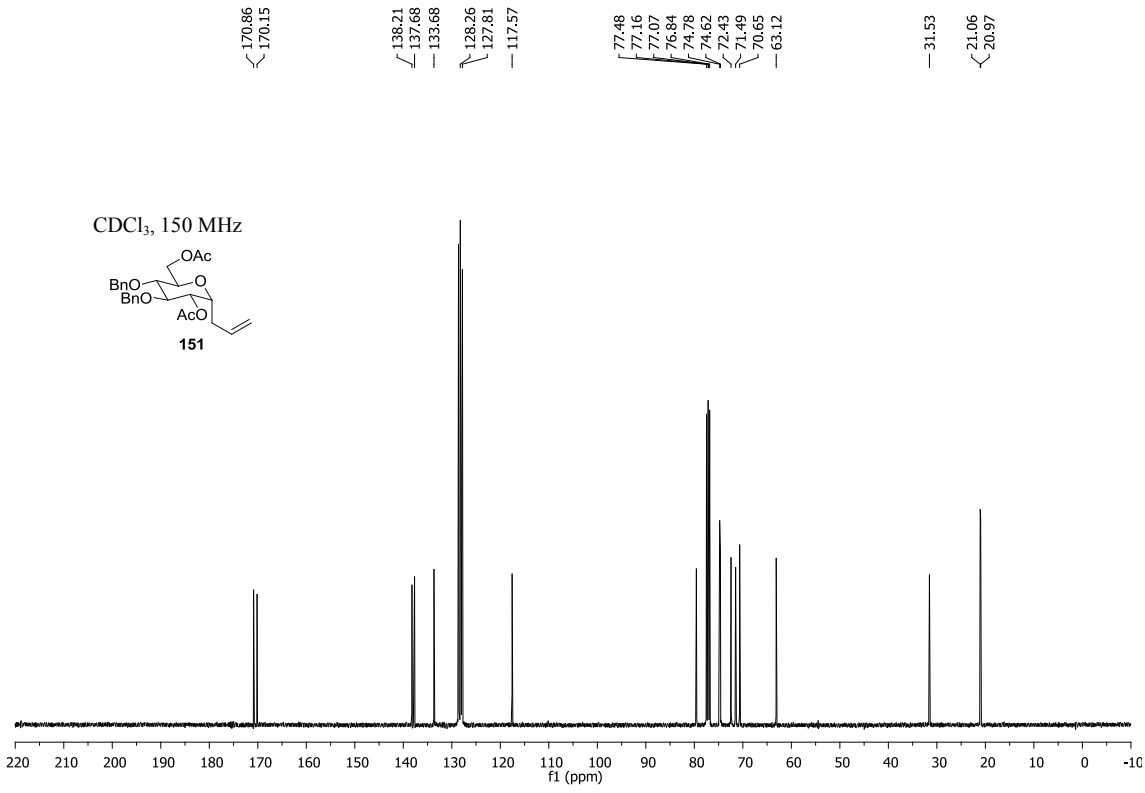

11.63
8.38
8.28
7.14
7.12
7.11
6.45
6.45
6.39
6.36
5.81
5.26
5.25
4.95
4.94
4.93
2.18
2.07
2.05
2.04
2.03
acetic acid-d4, 400 MHz
NH2
N
N
N
N
H
O
O
O
H
OAc
144
1.0
1.0
1.1
1.0
1.0
1.0
1.0
1.0
3.1
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

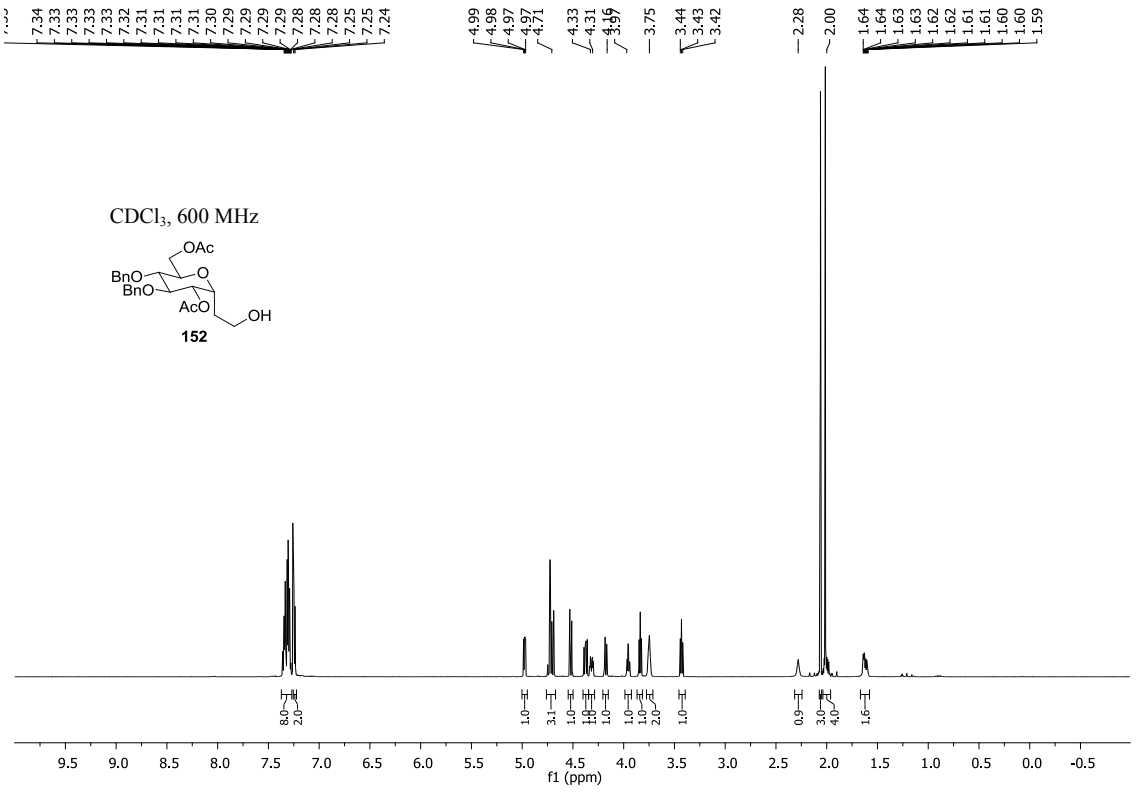

170.99
171.88
162.70
156.15
152.11
150.14
141.60
140.67
126.30
119.51
89.54
83.24
82.82
71.66
21.29
20.93
20.73
20.54
acetic acid-d4, 100 MHz
NH2
N
N
N
N
H
O
O
O
H
OAc
144
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

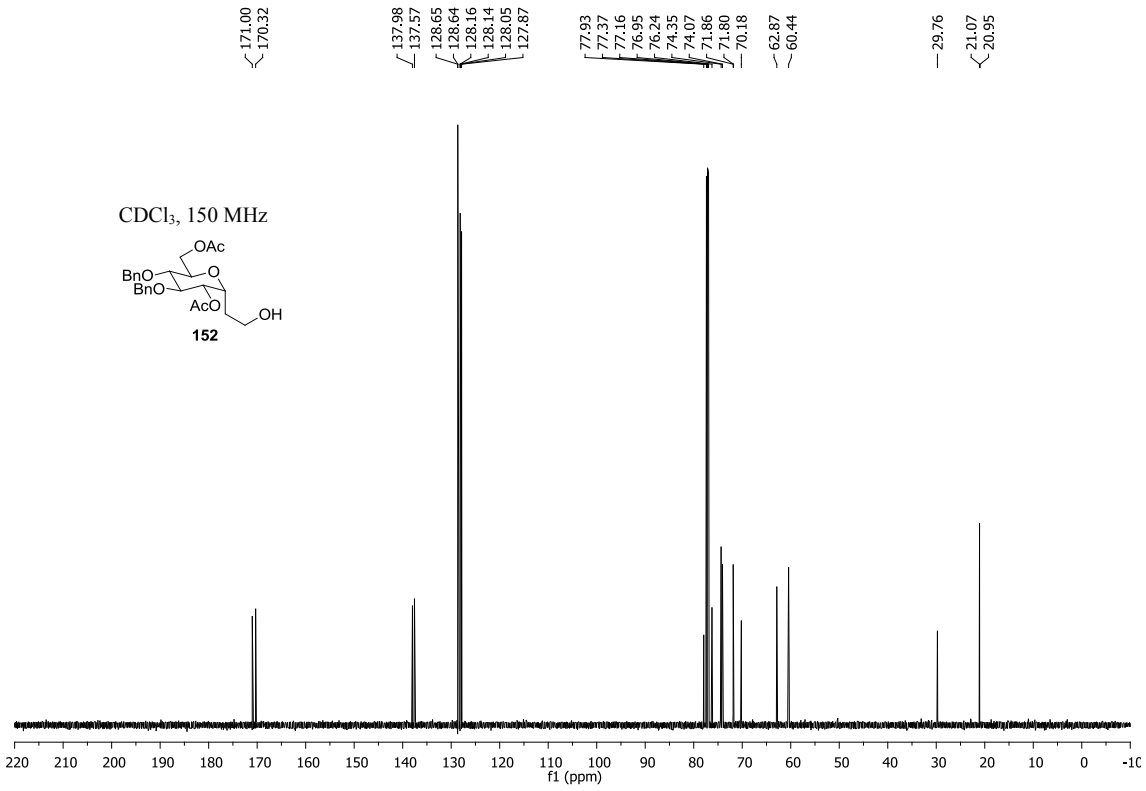

CDCl3, 600 MHz
OTBS
BnO
BnO
O
TBSO
OH
149
f1 (ppm)

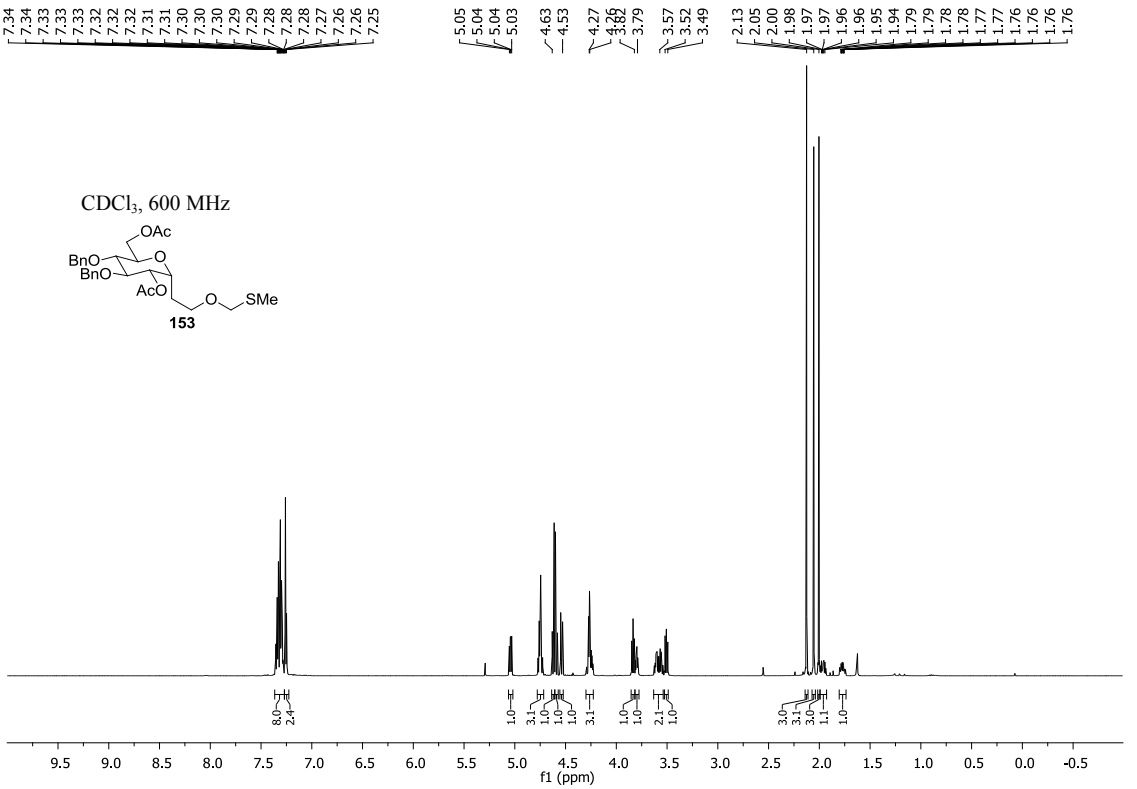

CDCl3, 150 MHz
OTBS
BnO
BnO
O
TBSO
OH
149
f1 (ppm)

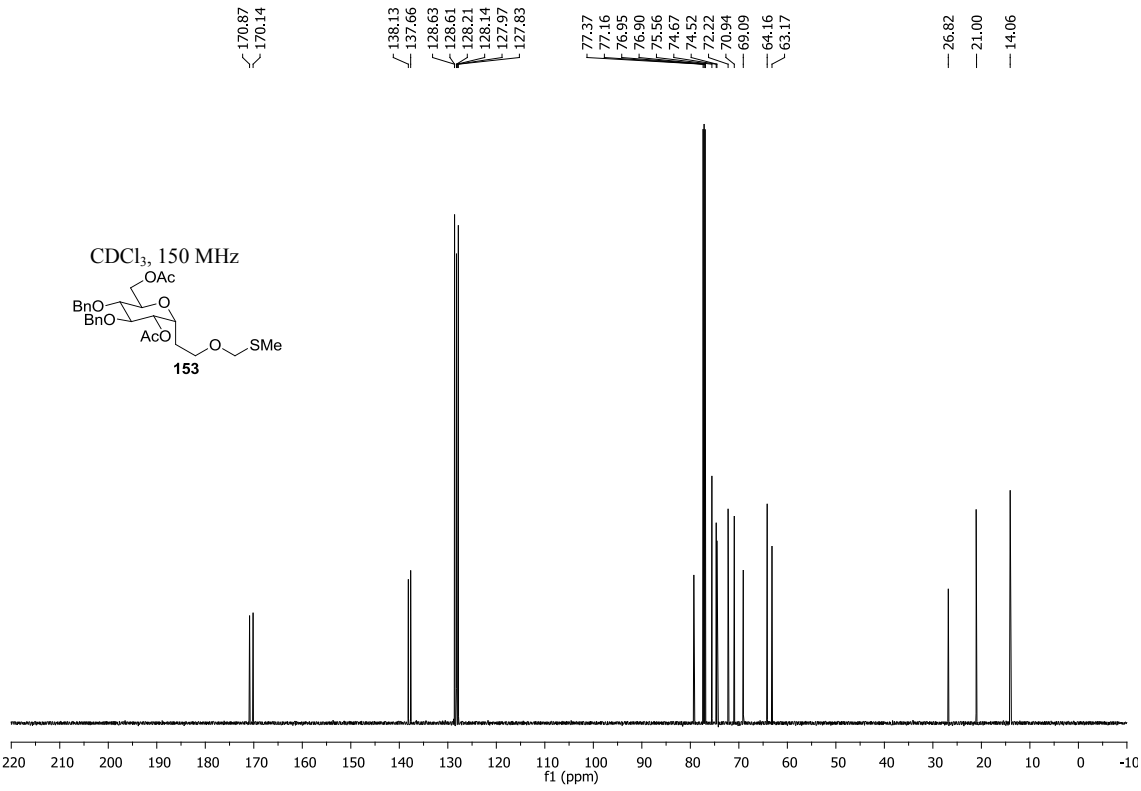

7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.26
7.26
7.25
5.78
5.76
5.74
5.72
5.69
5.12
5.07
5.03
4.73
4.53
4.16
3.77
3.54
3.52
3.52
3.50
2.45
2.43
2.28
2.26
2.23
2.04
2.00
CDCl3, 600 MHz
OAc
BnO
BnO
O
AcO
151
10.0
1.0
2.1
1.0
3.1
1.0
2.1
1.1
1.0
1.0
1.0
1.0
1.0
3.0
3.0
f1 (ppm)

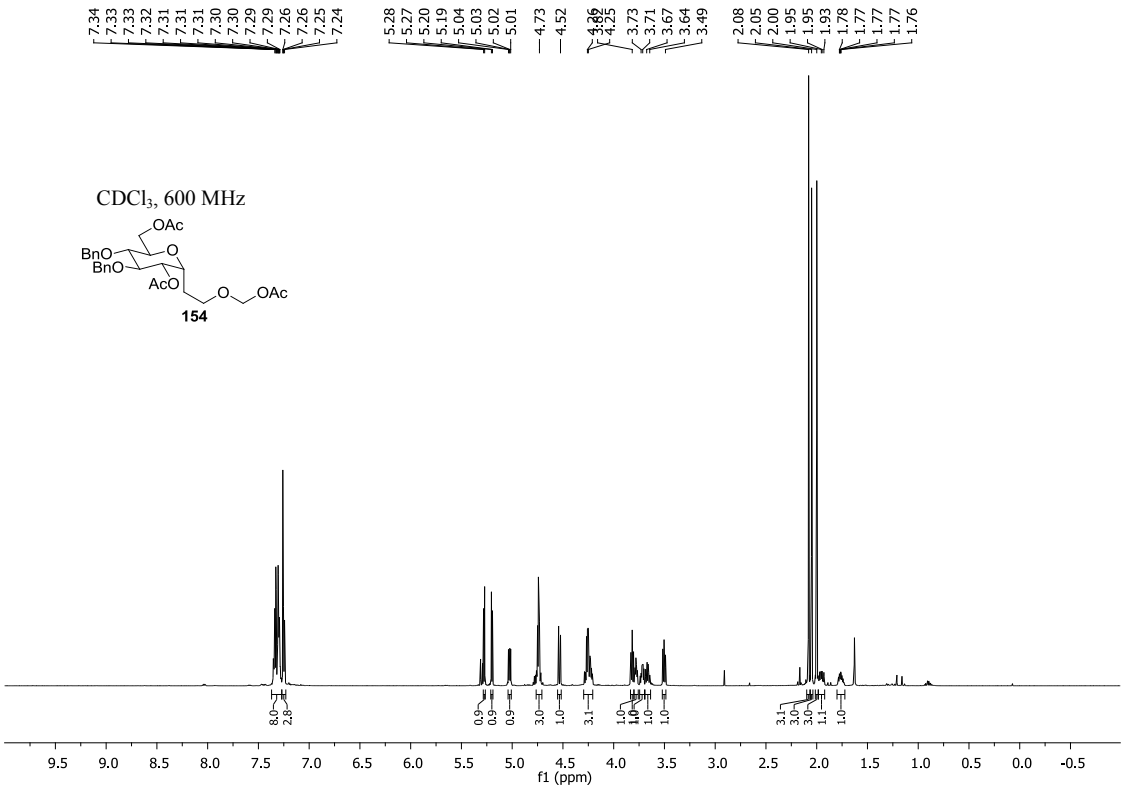

170.86
170.15
138.21
137.68
133.68
128.26
127.81
117.57
77.48
77.16
77.07
76.84
74.78
74.62
72.43
71.49
70.65
63.12
31.53
21.06
20.97
CDCl3, 150 MHz
OAc
BnO
BnO
O
AcO
151
f1 (ppm)

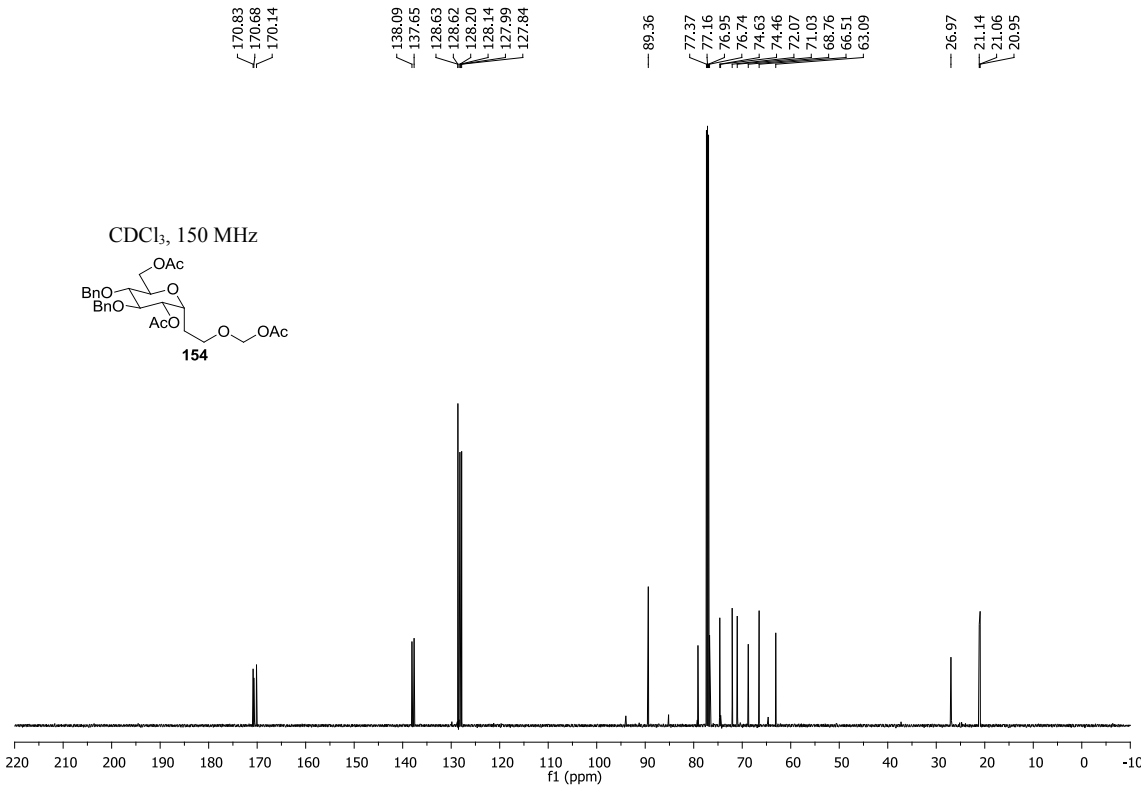

CDCl3, 600 MHz
OAc
BnO
BnO
O
AcO
OH
152
f1 (ppm)

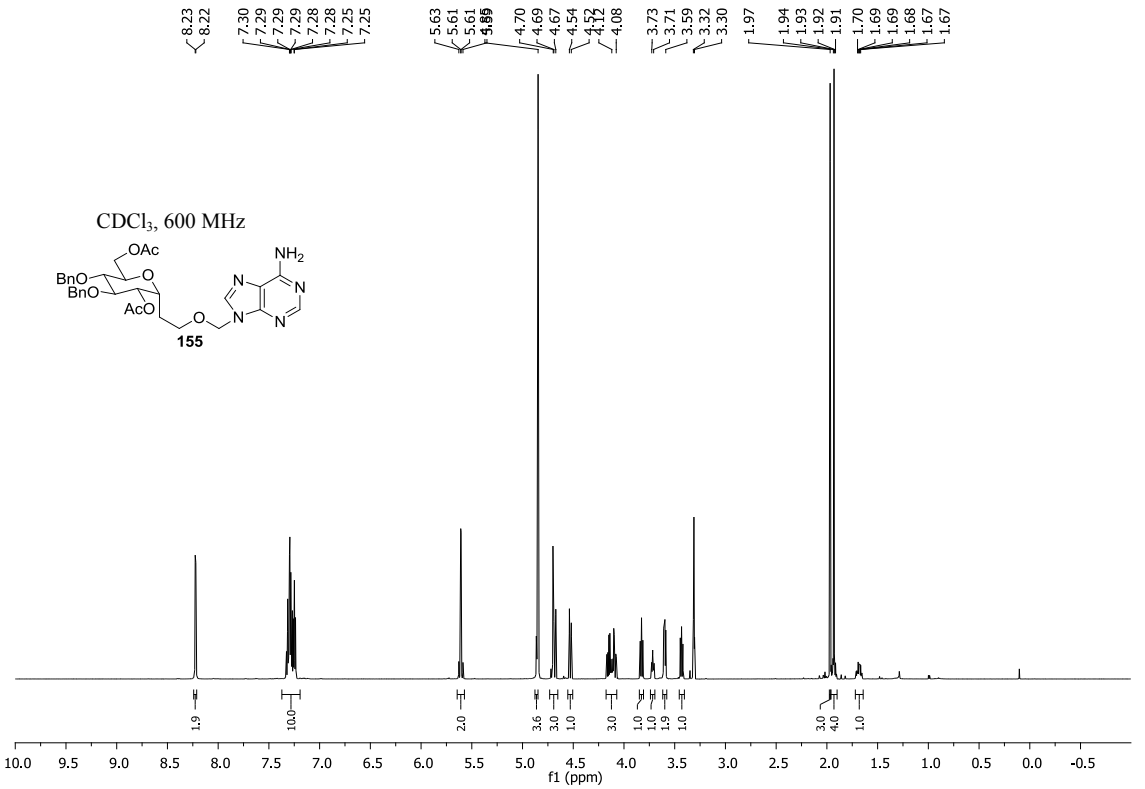

CDCl3, 150 MHz
OAc
BnO
BnO
O
AcO
OH
152
f1 (ppm)

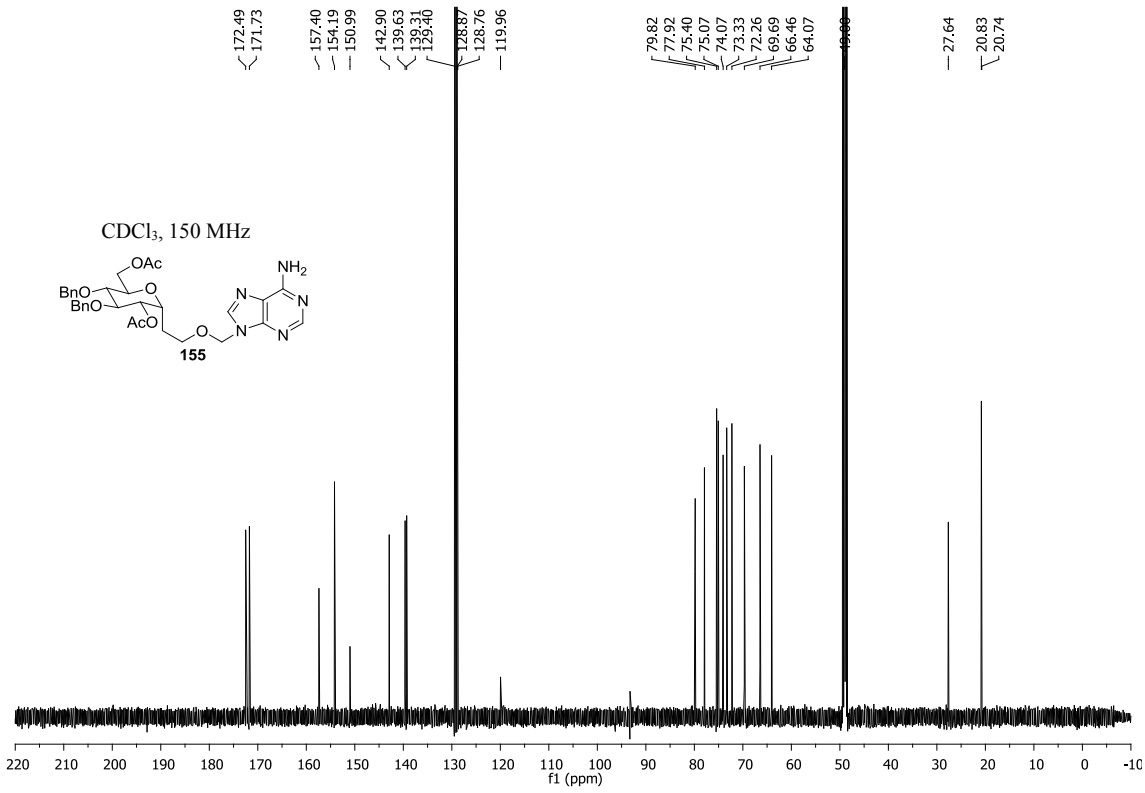

CDCl3, 600 MHz
OAc
BnO
BnO
O
AcO
O
SMe
153
f1 (ppm)


CDCl3, 150 MHz
OAc
BnO
BnO
O
AcO
O
SMe
153
f1 (ppm)

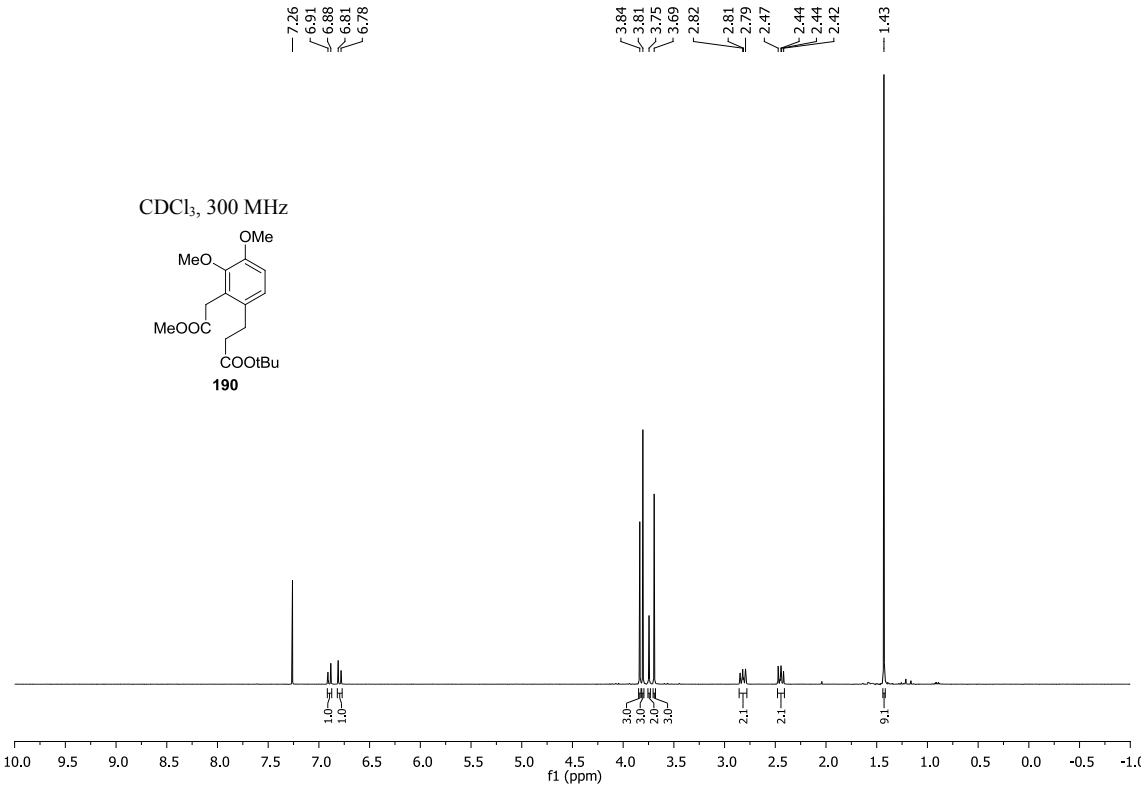

7.34
7.33
7.33
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.26
7.26
7.25
7.24
5.28
5.27
5.20
5.19
5.04
5.03
5.02
5.01
4.73
4.52
4.26
4.25
3.73
3.71
3.67
3.64
3.49
2.08
2.05
2.00
1.95
1.95
1.93
1.78
1.77
1.77
1.77
1.77
1.76
CDCl3, 600 MHz
OAc
BnO
BnO
AcO
O
OAc
154
8.0
2.8
0.9
0.9
0.9
3.0
1.0
3.1
1.0
1.0
1.0
1.0
3.1
3.0
3.0
1.1
1.0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

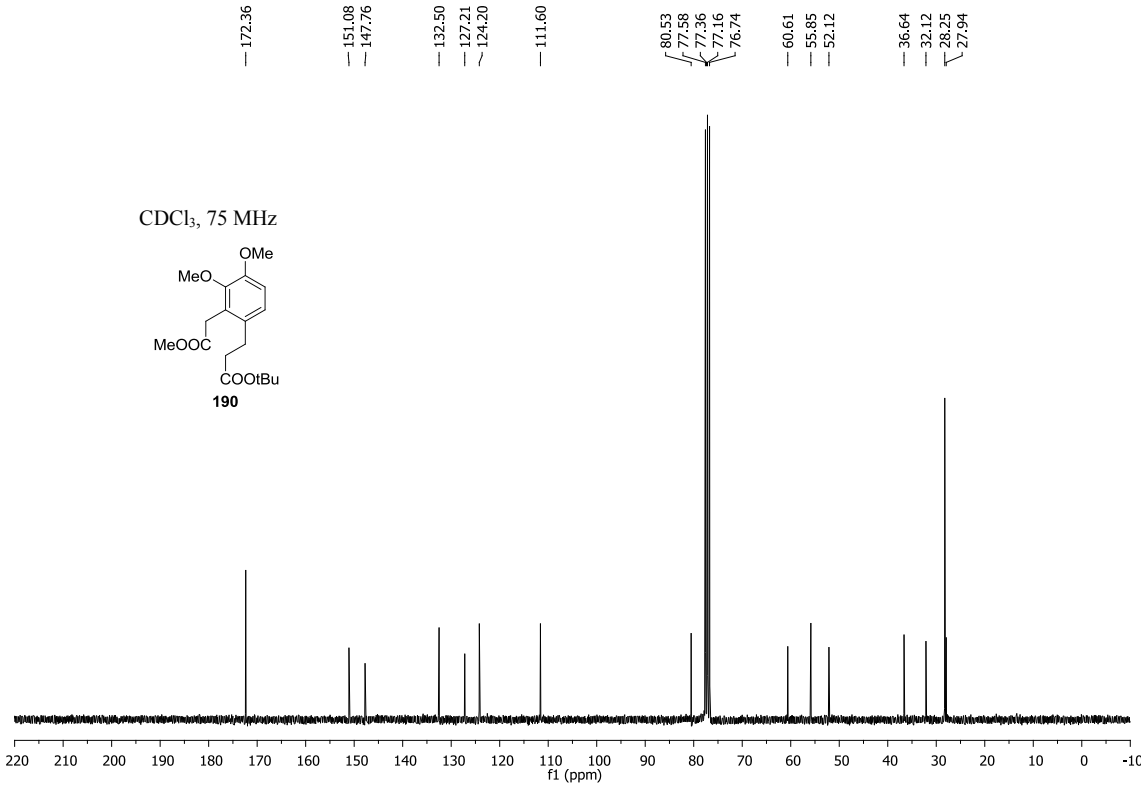

170.83
170.68
170.14
138.09
137.65
128.63
128.62
128.20
128.14
127.99
127.84
89.36
77.37
77.16
76.95
76.74
74.63
74.46
72.07
71.03
68.76
66.51
63.09
26.97
21.14
21.06
20.95
CDCl3, 150 MHz
OAc
BnO
BnO
AcO
O
OAc
154
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

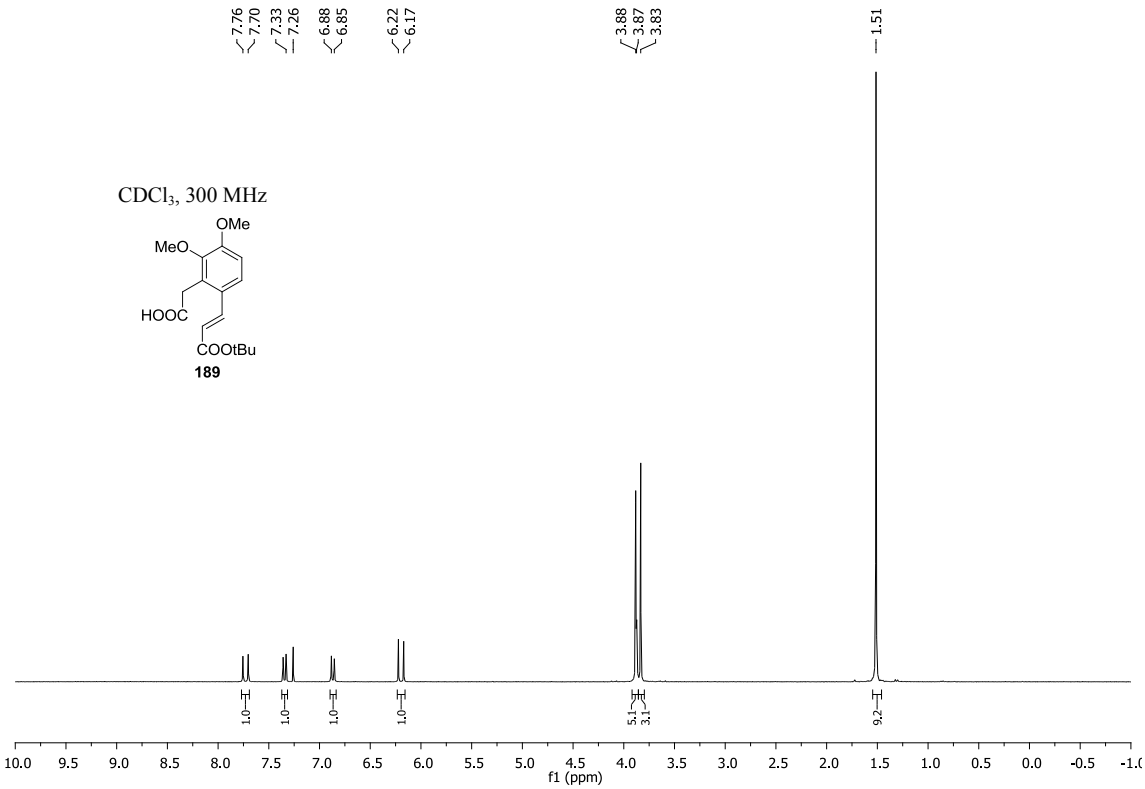

CDCl3, 600 MHz
OAc
BnO
BnO
AcO
O
NH2
N
N
N
N
O
155
8.23
8.22
7.30
7.29
7.29
7.29
7.28
7.28
7.25
7.25
5.63
5.61
4.70
4.69
4.67
4.54
4.52
4.12
4.08
3.73
3.71
3.59
3.32
3.30
1.97
1.94
1.93
1.92
1.91
1.70
1.69
1.69
1.68
1.67
1.67
1.9
10.0
2.0
3.6
3.0
1.0
3.0
1.0
1.0
1.9
1.0
3.0
4.0
1.0
f1 (ppm)

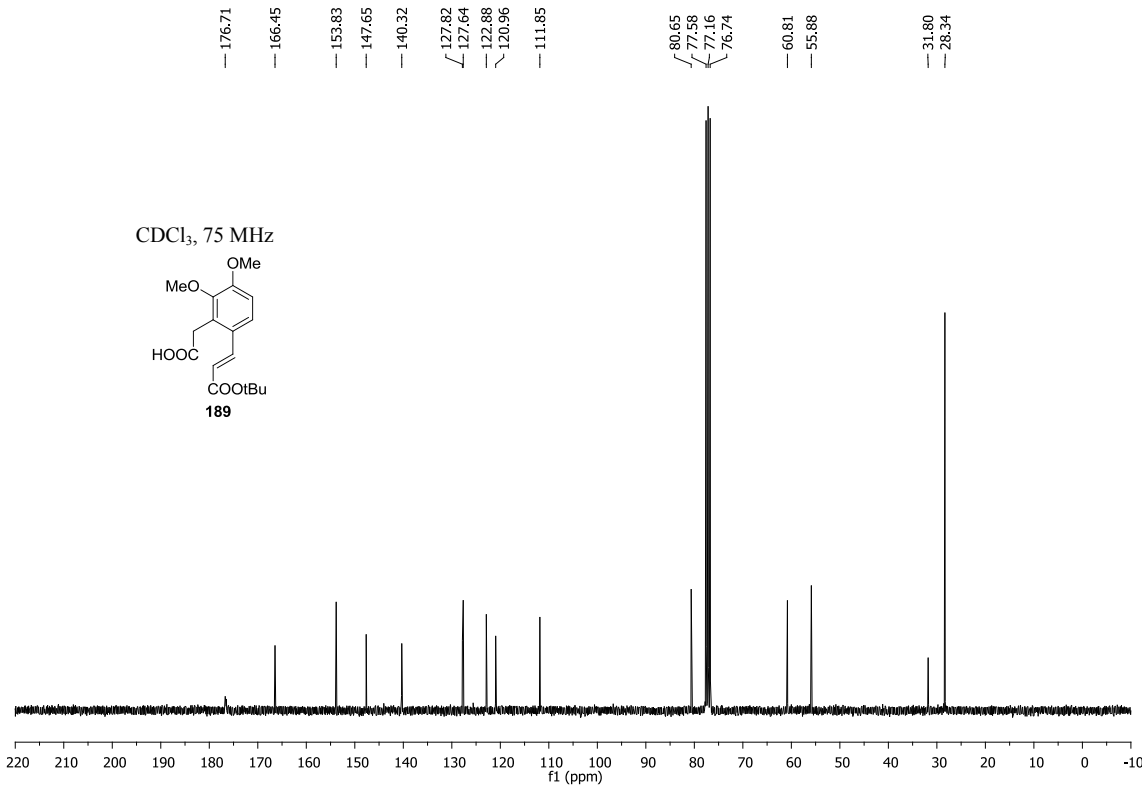

CDCl3, 150 MHz
OAc
BnO
BnO
AcO
O
NH2
N
N
N
N
O
155
172.49
171.73
157.40
154.19
150.99
142.90
139.63
139.31
129.40
128.87
128.76
119.96
79.82
77.92
75.40
75.07
74.07
73.33
72.26
69.69
66.46
64.07
27.64
20.83
20.74
f1 (ppm)

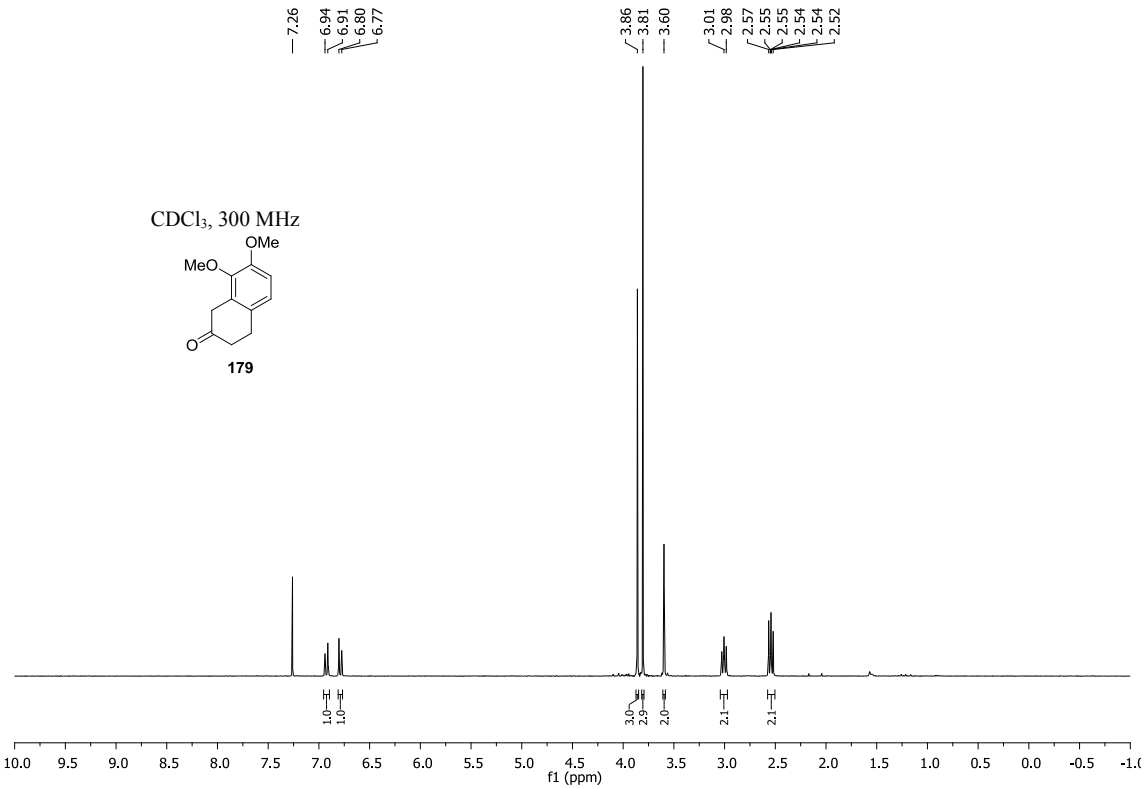
22.2. NMR Spectra of Chapter II

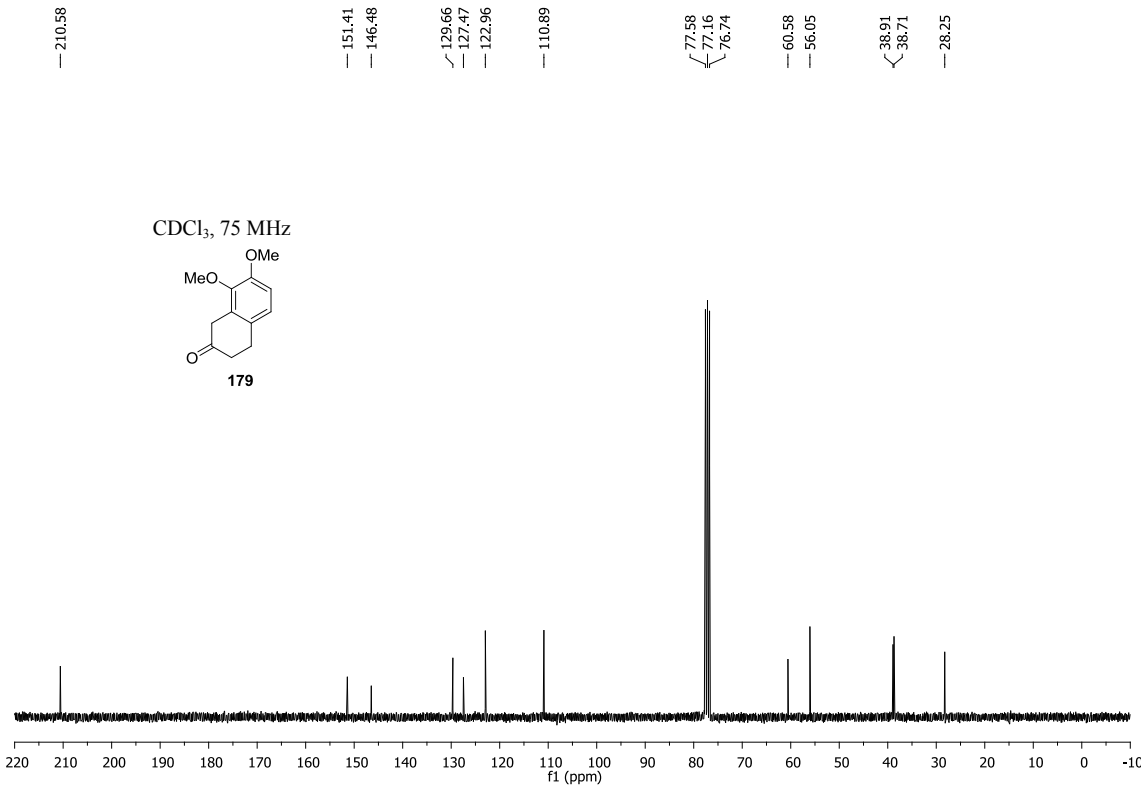


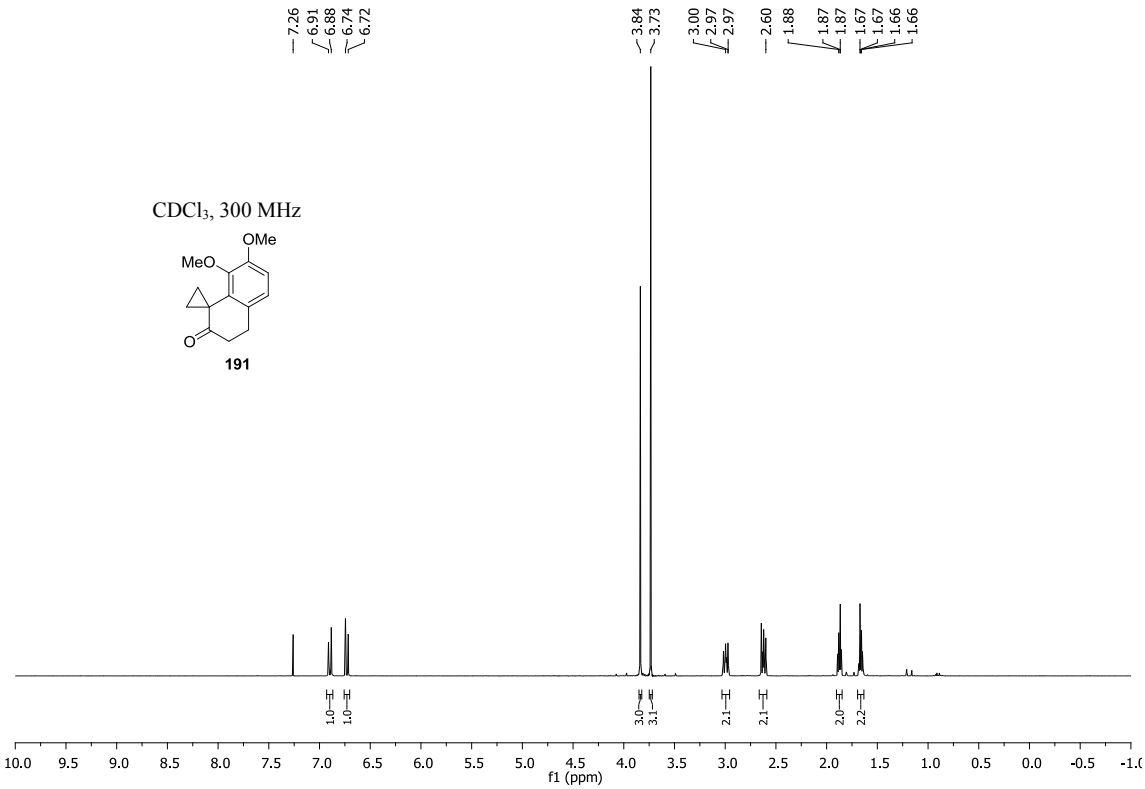


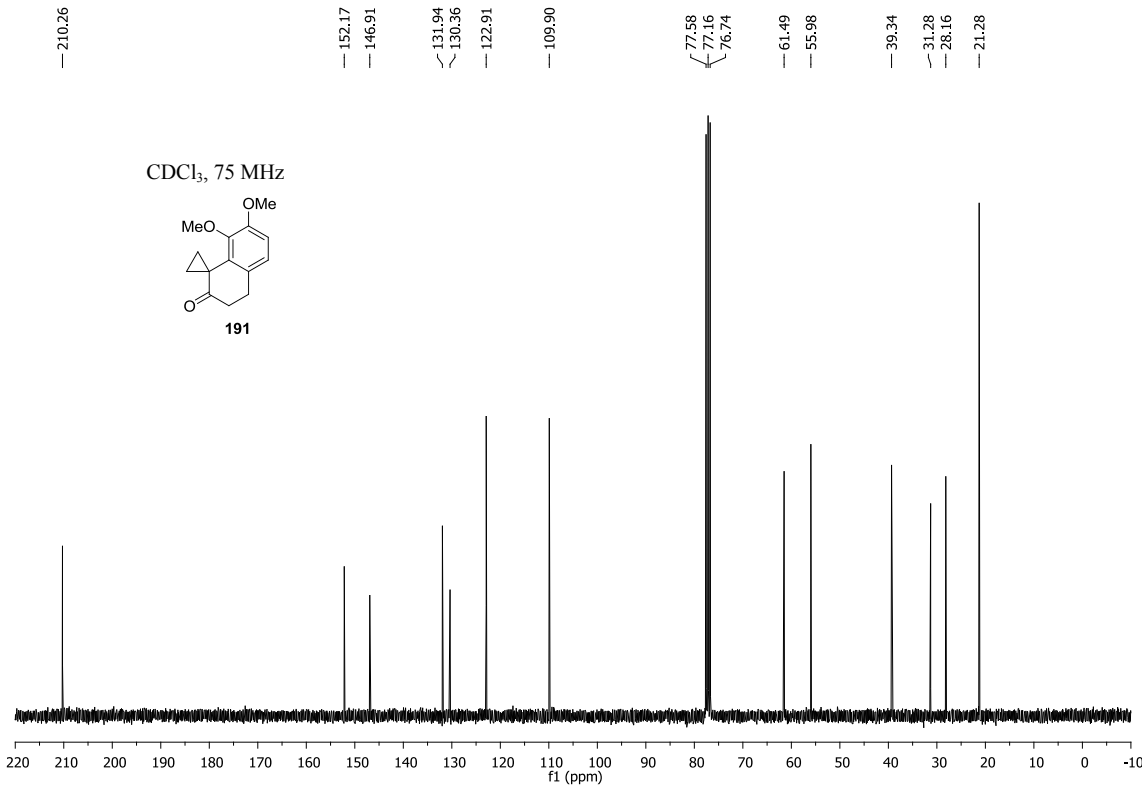

7.76
7.70
7.33
7.26
6.88
6.85
6.22
6.17
3.88
3.87
3.83
1.51
CDCl3, 300 MHz
OMe
MeO
HOOC
COOtBu
189
1.0
1.0
1.0
1.0
5.1
3.1
9.2
f1 (ppm)

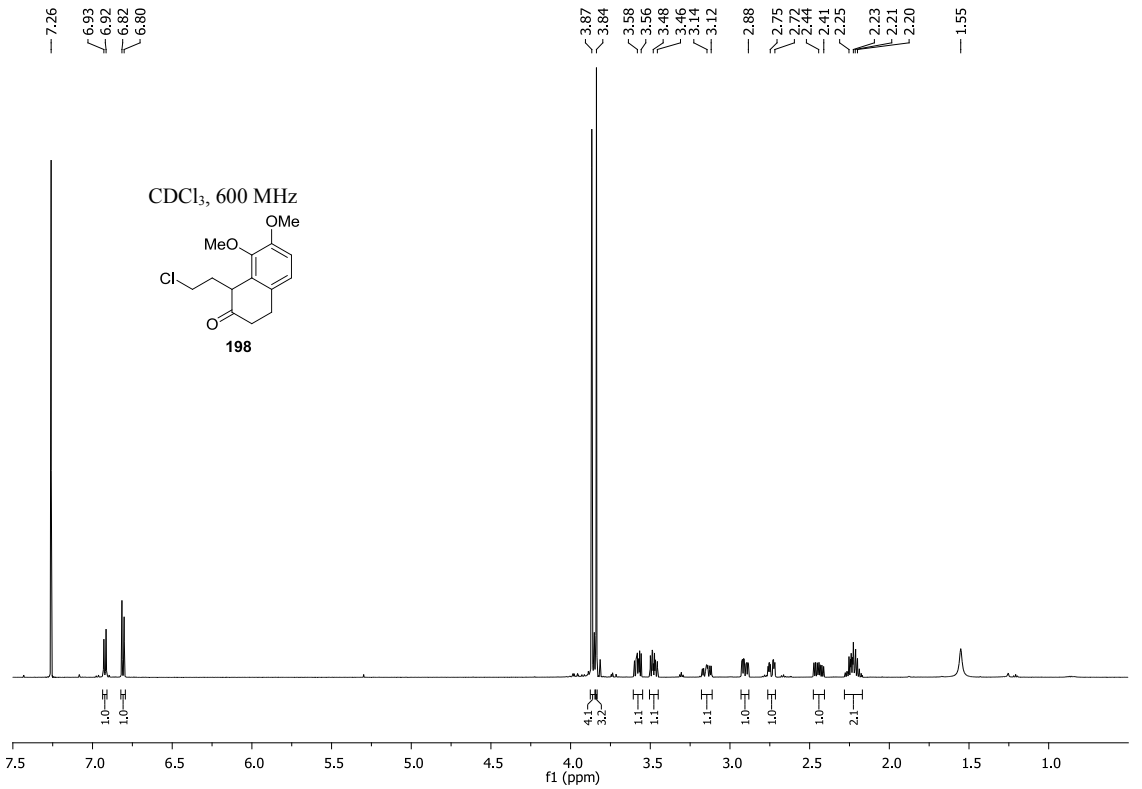

176.71
166.45
153.83
147.65
140.32
127.82
127.64
122.88
120.96
111.85
80.65
77.58
77.16
76.74
60.81
55.88
31.80
28.34
CDCl3, 75 MHz
OMe
MeO
HOOC
COOtBu
189
f1 (ppm)

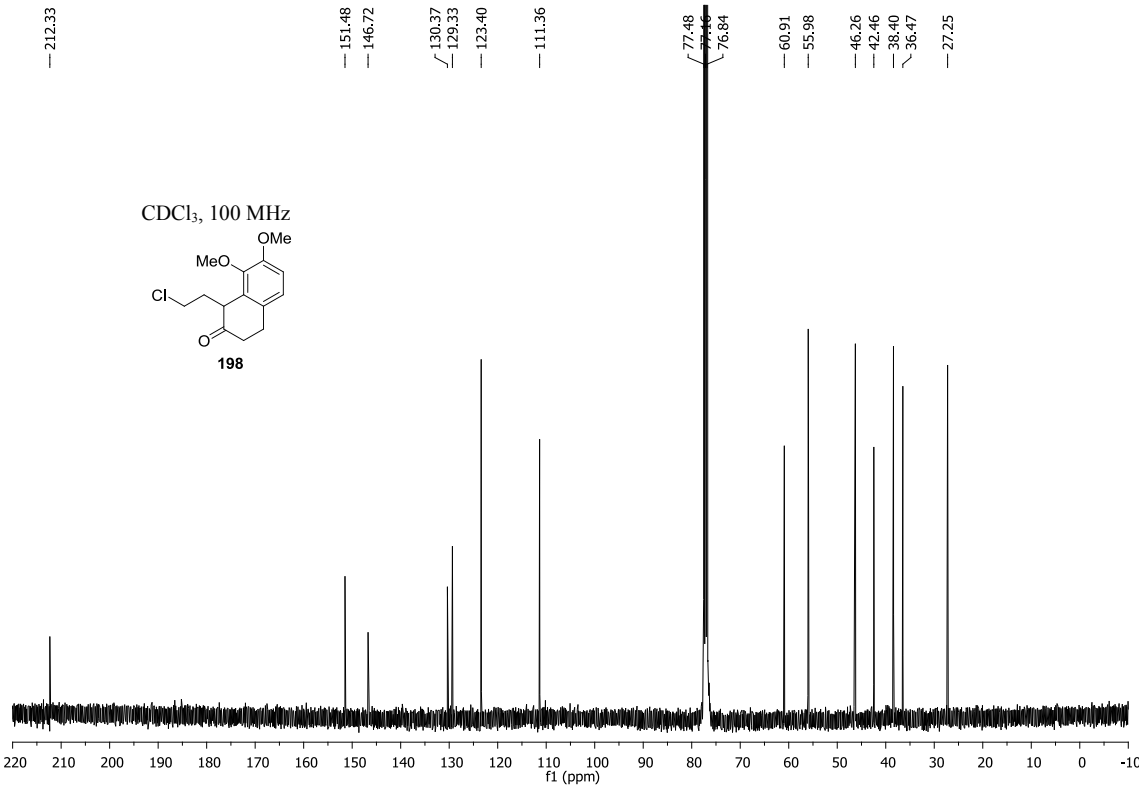

7.26
6.94
6.91
6.80
6.77
3.86
3.81
3.60
3.01
2.98
2.57
2.55
2.55
2.54
2.54
2.52
CDCl3, 300 MHz
OMe
MeO
O
179
1.0
1.0
3.0
2.9
2.0
2.1
2.1
f1 (ppm)


210.58
151.41
146.48
129.66
127.47
122.96
110.89
77.58
77.16
76.74
60.58
56.05
38.91
38.71
28.25
CDCl3, 75 MHz
OMe
MeO
O
179
f1 (ppm)

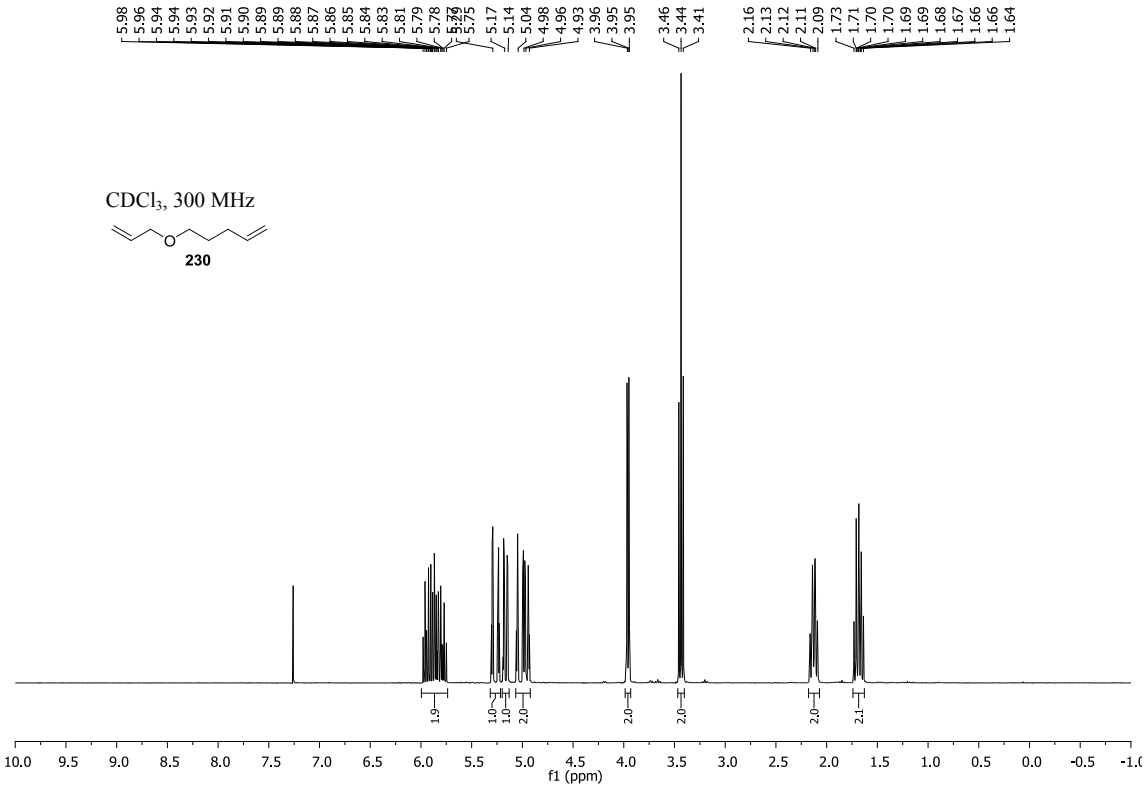

7.26
6.91
6.88
6.74
6.72
3.84
3.73
3.00
2.97
2.97
2.60
1.88
1.87
1.87
1.67
1.67
1.66
1.66
CDCl3, 300 MHz
OMe
MeO
O
191
1.0
1.0
3.0
3.1
2.1
2.1
2.0
2.2
f1 (ppm)

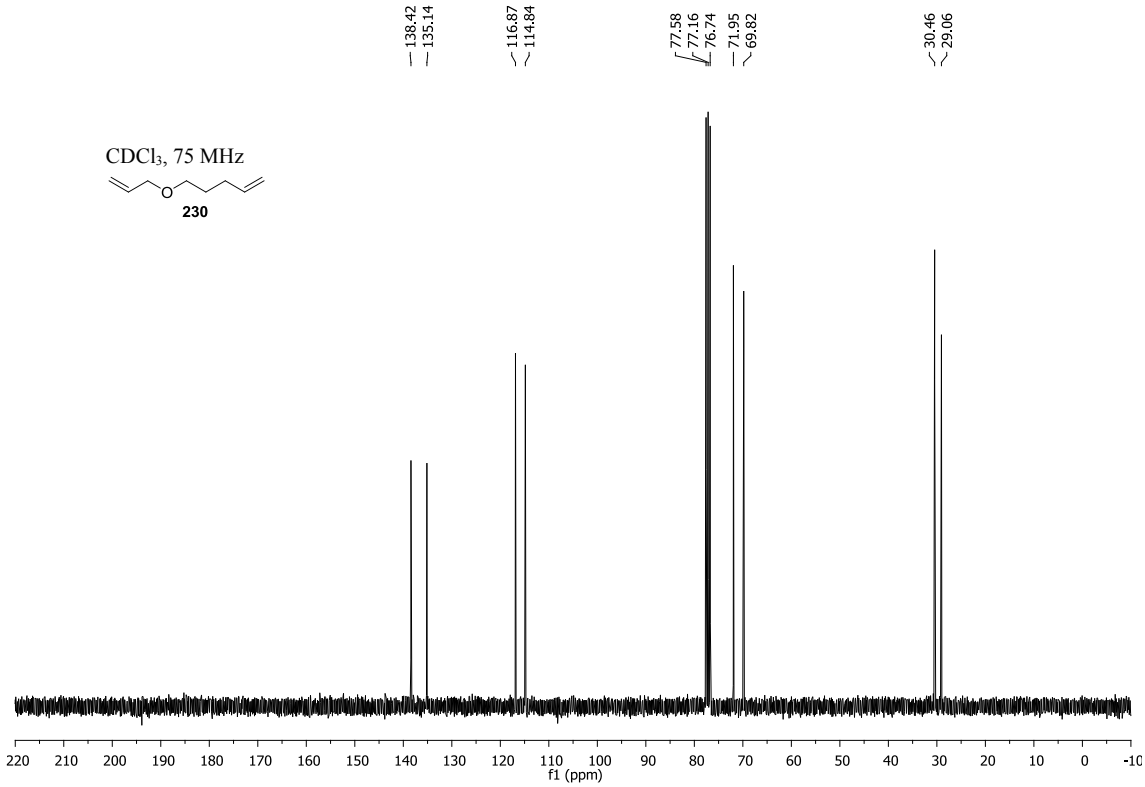

210.26
152.17
146.91
131.94
130.36
122.91
109.90
77.58
77.16
76.74
61.49
55.98
39.34
31.28
28.16
21.28
CDCl3, 75 MHz
OMe
MeO
O
191
f1 (ppm)

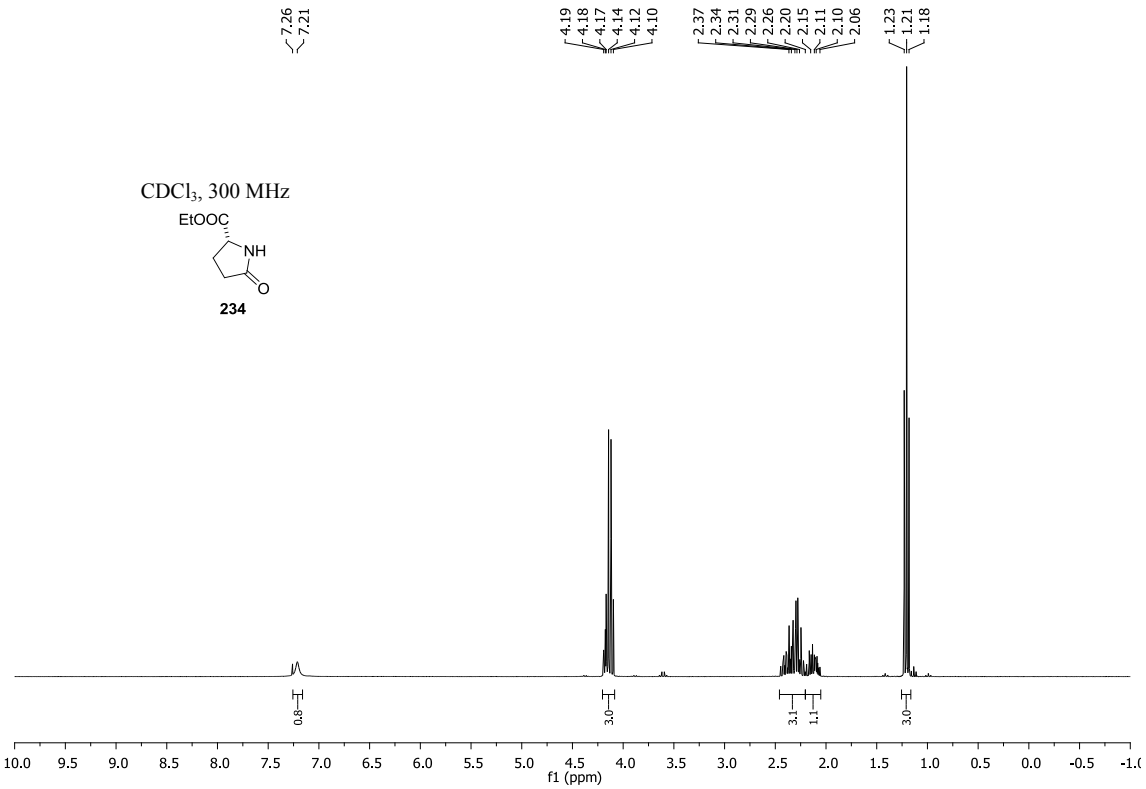

7.26
6.93
6.92
6.82
6.80
3.87
3.84
3.58
3.56
3.48
3.46
3.14
3.12
2.88
2.75
2.72
2.44
2.41
2.25
2.23
2.21
2.20
1.55
CDCl3, 600 MHz
OMe
MeO
Cl
O
198
1.0
1.0
4.1
3.2
1.1
1.1
1.1
1.0
1.0
1.0
2.1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

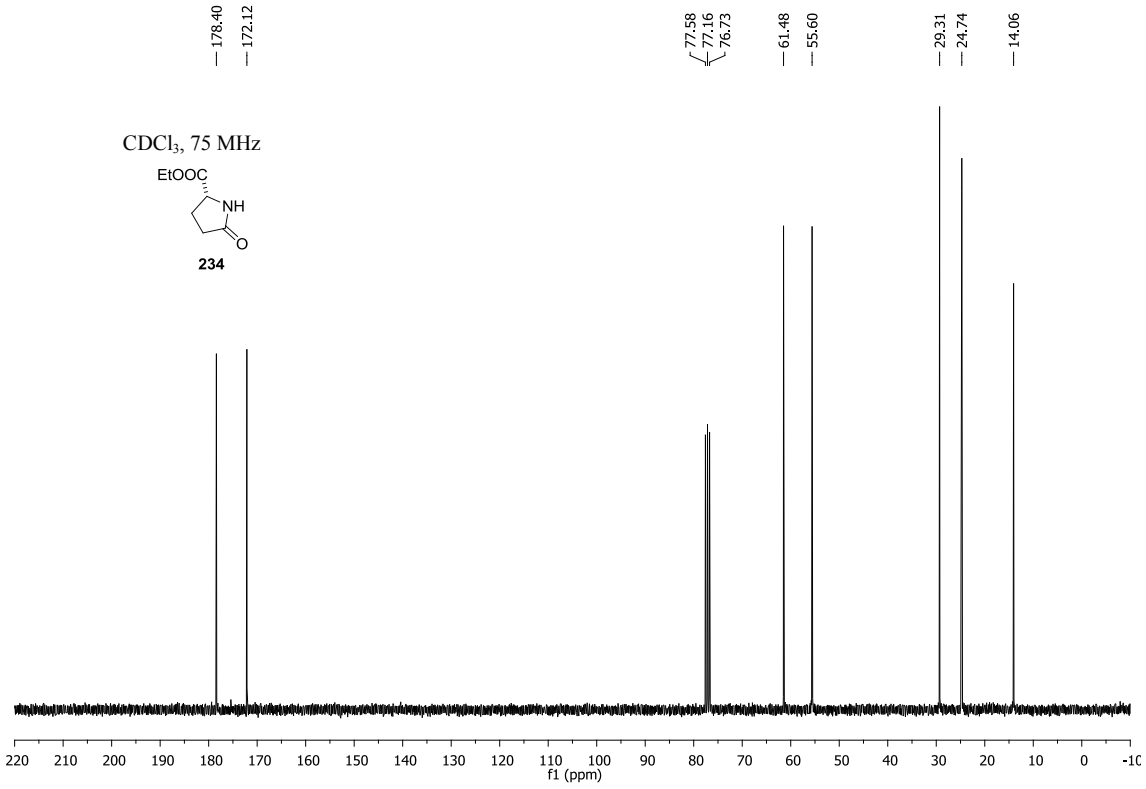

212.33
151.48
146.72
130.37
129.33
123.40
111.36
77.48
77.16
76.84
60.91
55.98
46.26
42.46
38.40
36.47
27.25
CDCl3, 100 MHz
OMe
MeO
Cl
O
198
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

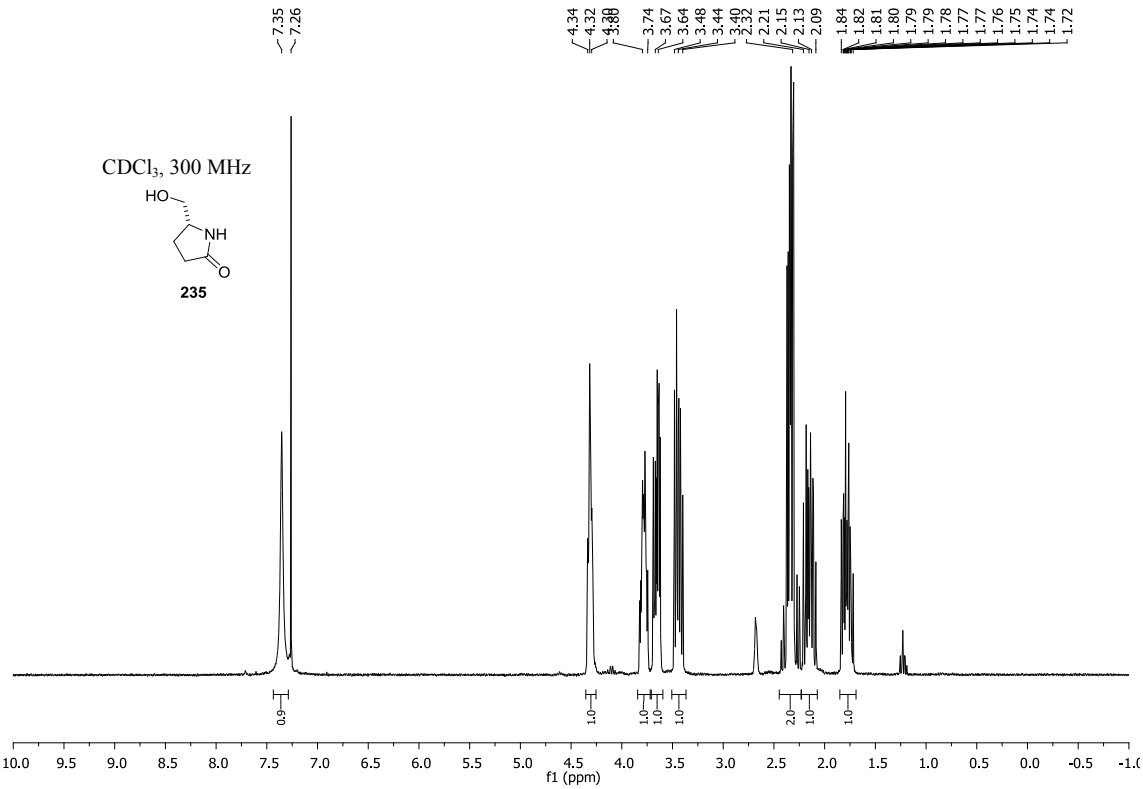
22.3. NMR Spectra of Chapter III

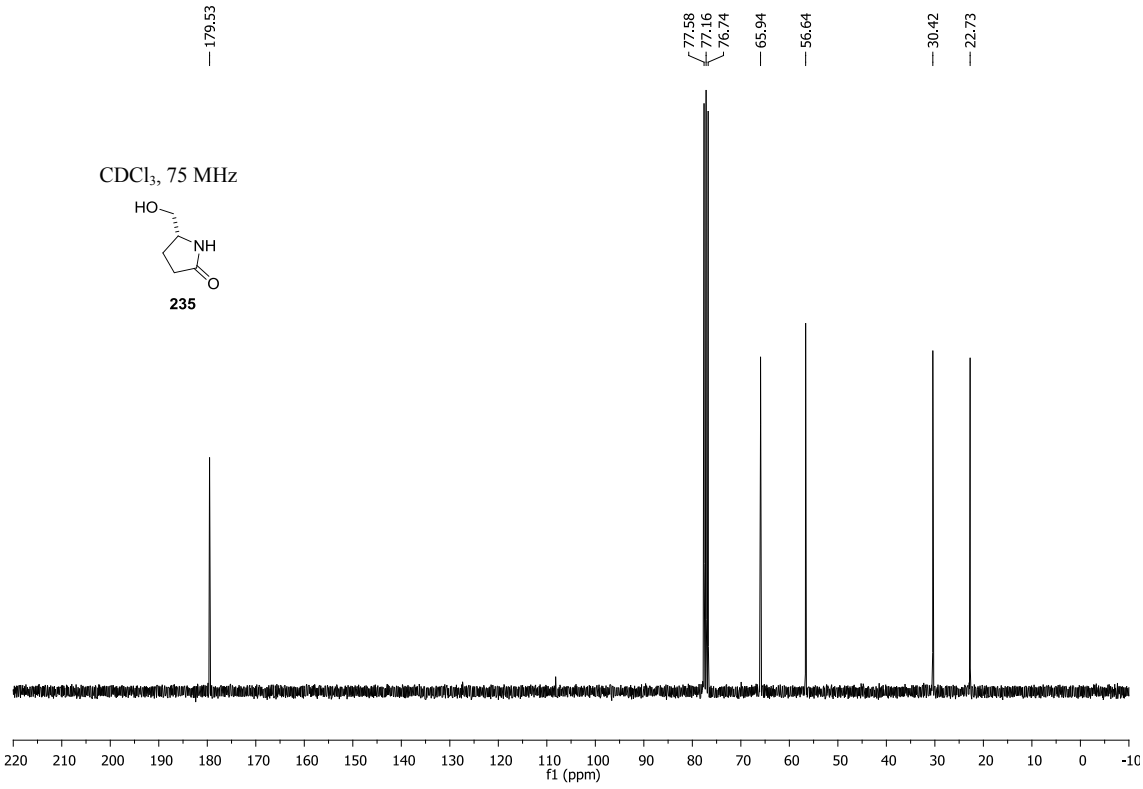


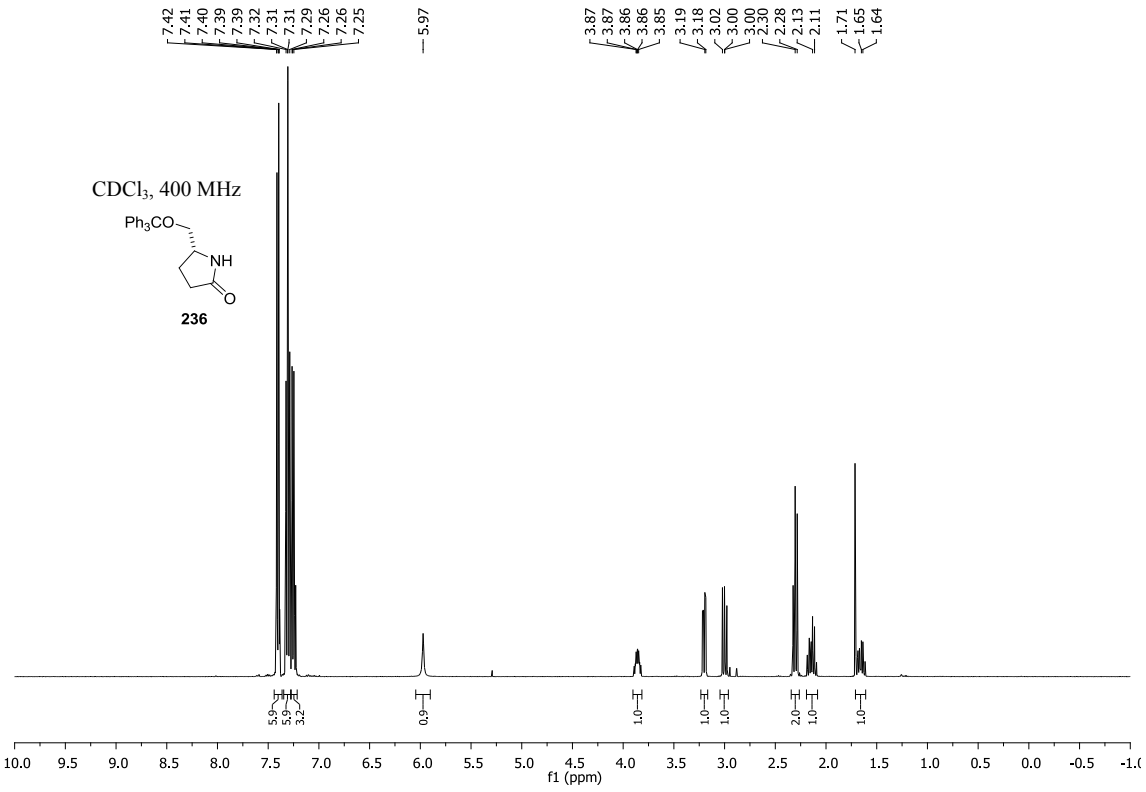


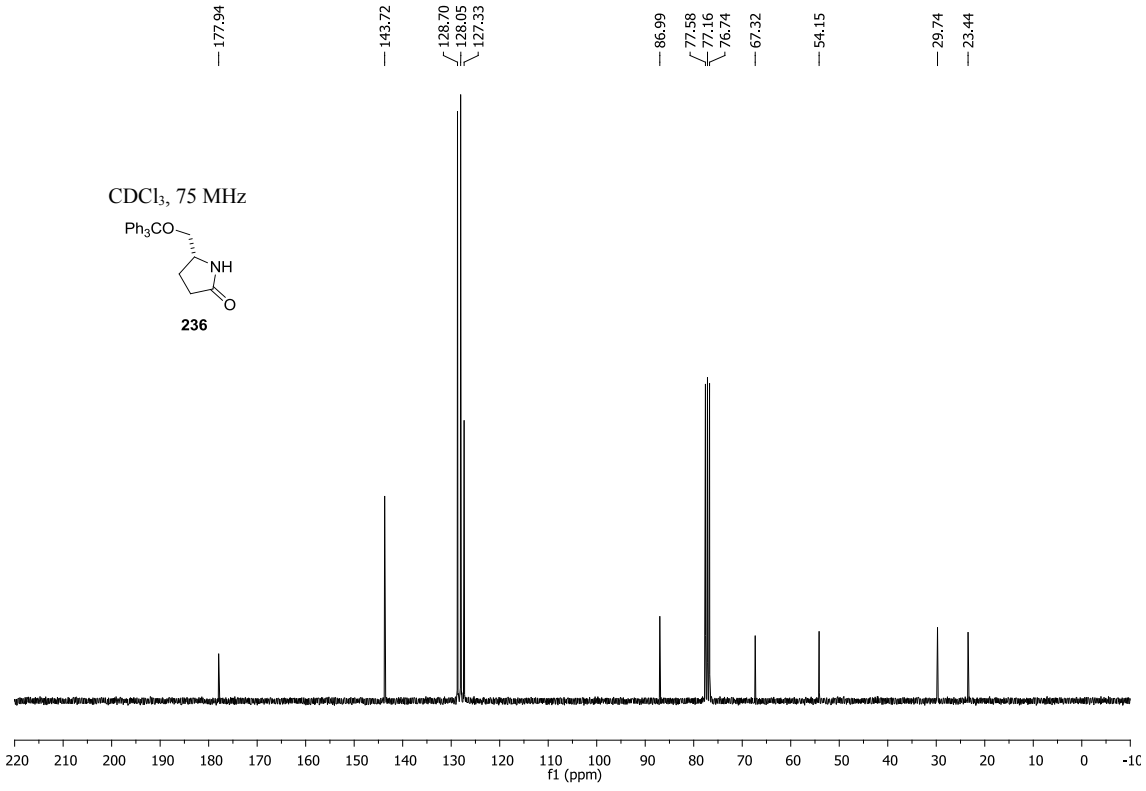

7.26
7.21
4.19
4.18
4.17
4.14
4.12
4.10
2.37
2.34
2.31
2.29
2.26
2.20
2.15
2.11
2.10
2.06
1.23
1.21
1.18
CDCl3, 300 MHz
EtOOC
NH
O
234
0.8
3.0
3.1
1.1
3.0
f1 (ppm)

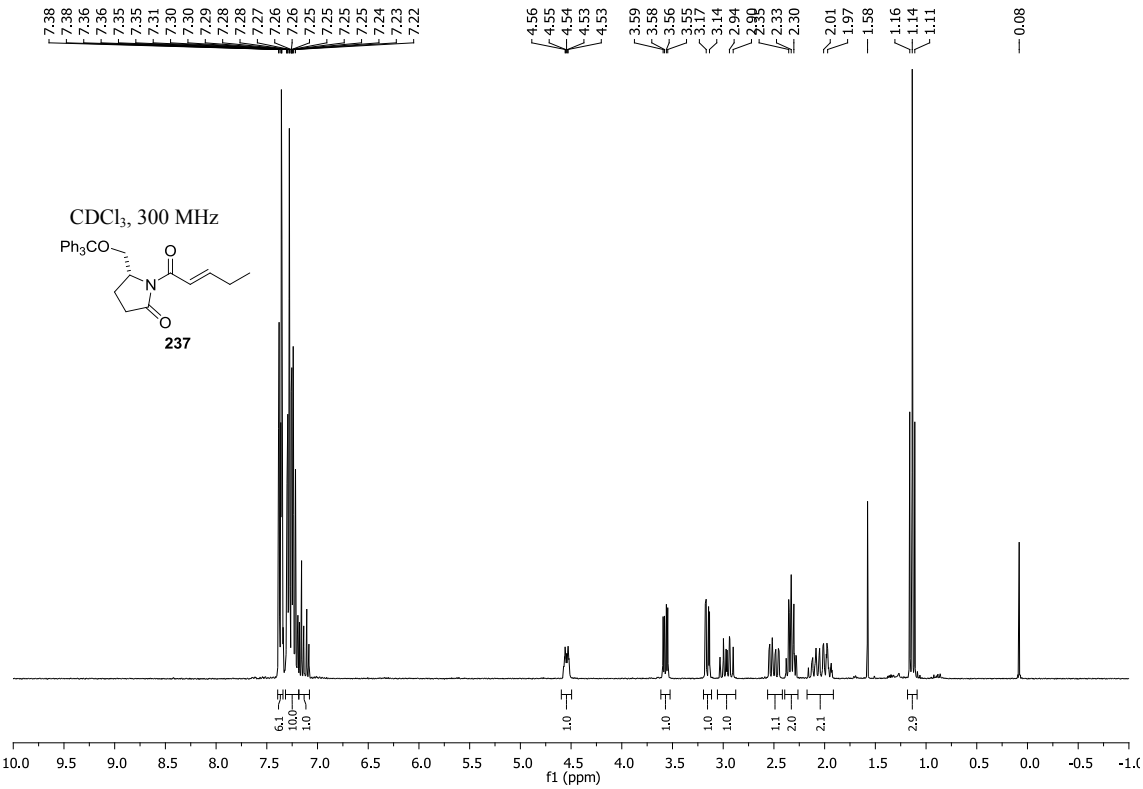

178.40
172.12
77.58
77.16
76.73
61.48
55.60
29.31
24.74
14.06
CDCl3, 75 MHz
EtOOC
NH
O
234
f1 (ppm)

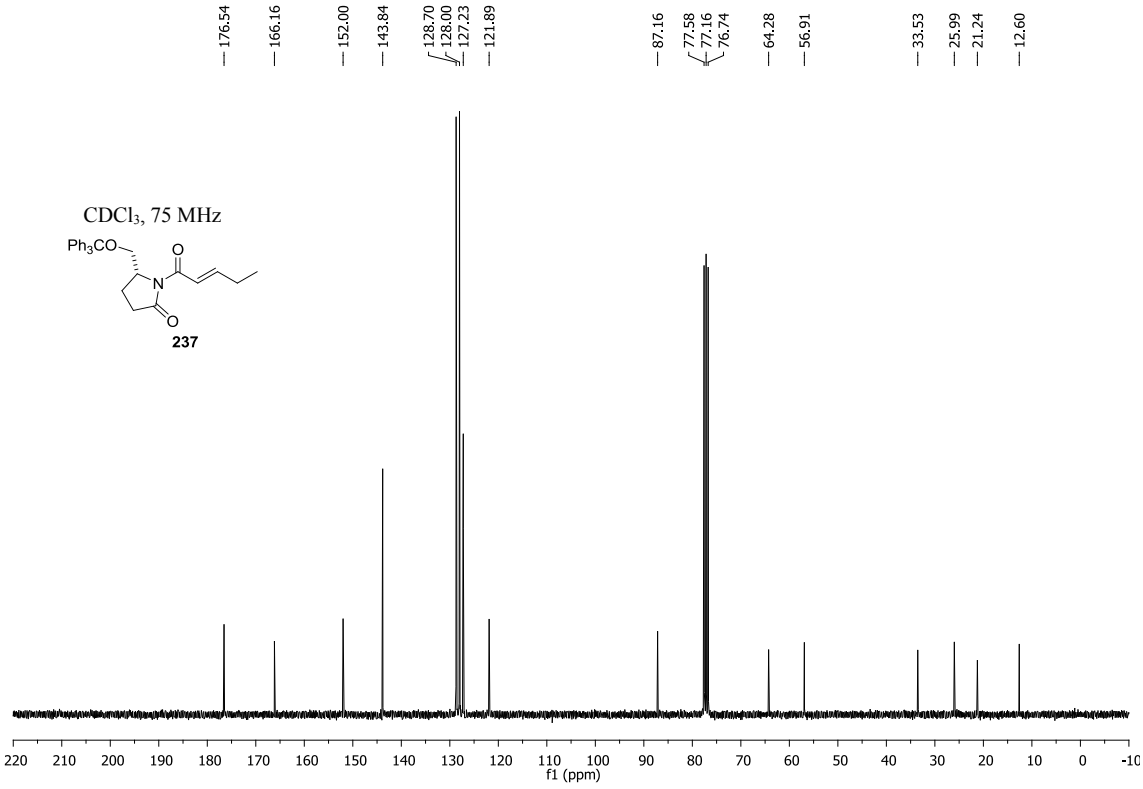

CDCl3, 300 MHz
HO
NH
O
235
7.35
7.26
4.34
4.32
4.30
3.74
3.67
3.64
3.48
3.44
3.40
2.32
2.21
2.15
2.13
2.09
1.84
1.82
1.81
1.80
1.79
1.79
1.78
1.77
1.77
1.76
1.75
1.74
1.74
1.72
0.9
1.0
1.0
1.0
1.0
2.0
1.0
1.0
f1 (ppm)

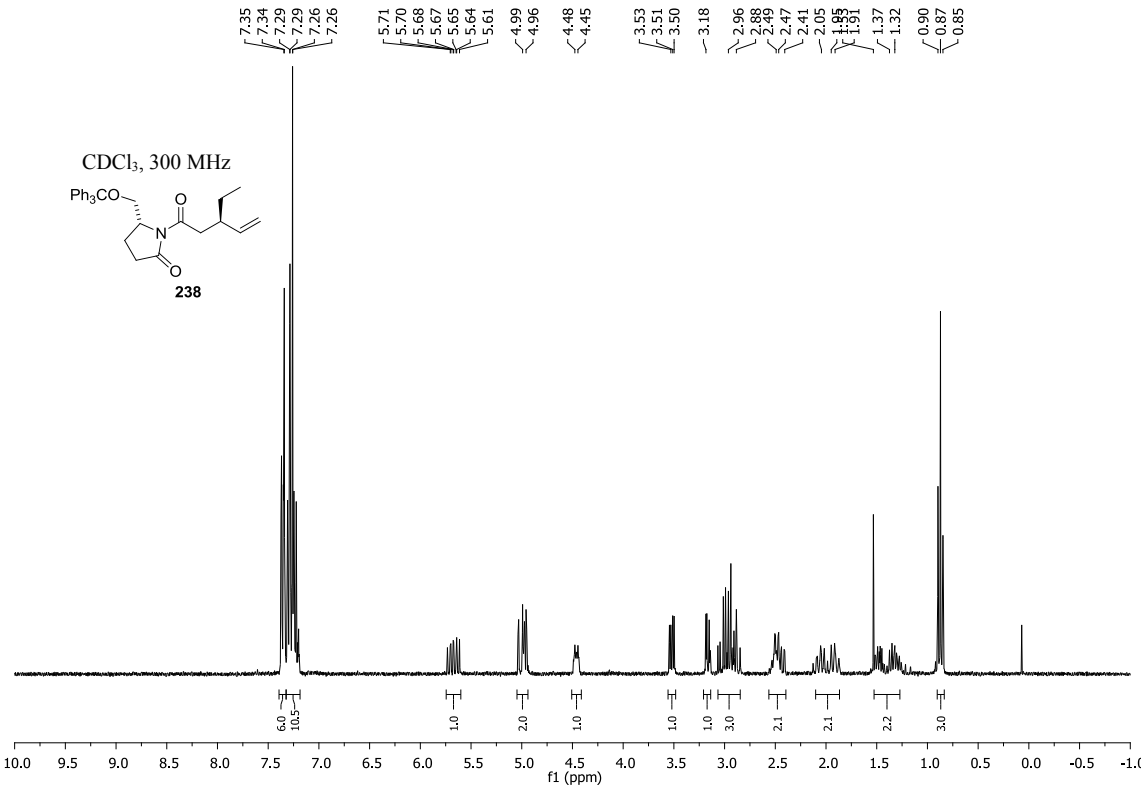

CDCl3, 75 MHz
HO
NH
O
235
179.53
77.58
77.16
76.74
65.94
56.64
30.42
22.73
f1 (ppm)

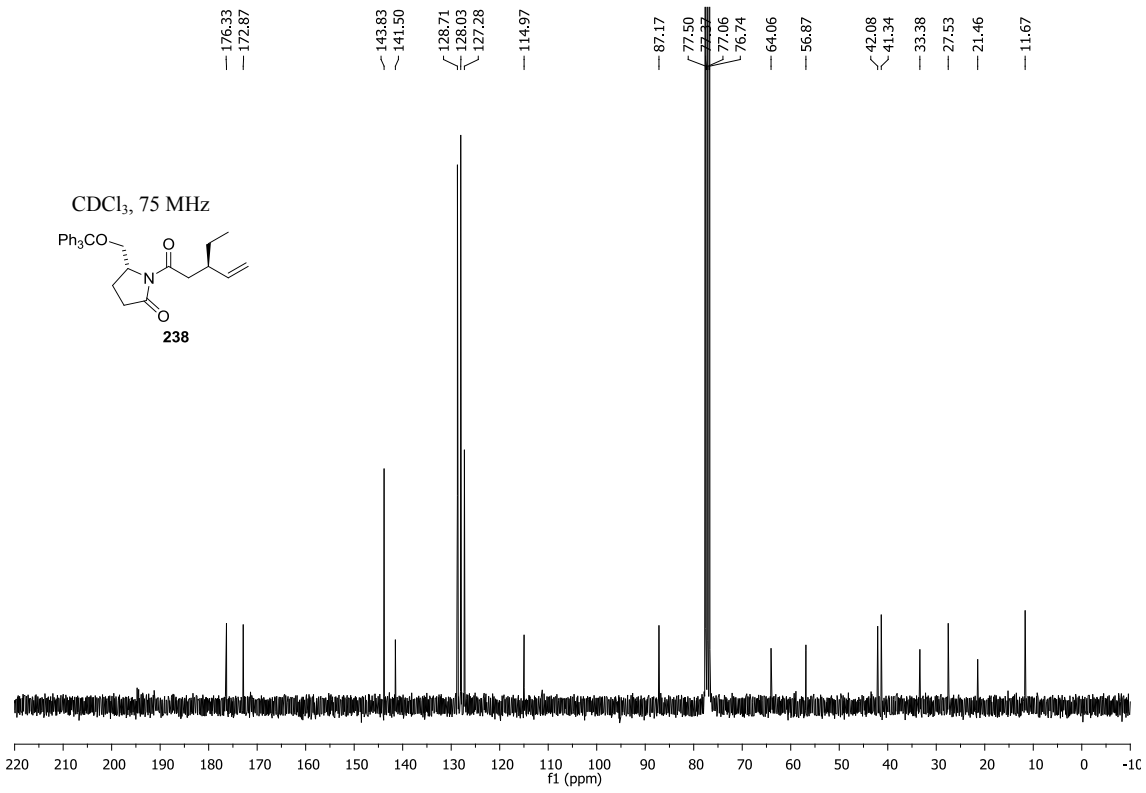

7.42
7.41
7.40
7.39
7.39
7.32
7.31
7.31
7.29
7.26
7.26
7.25
5.97
3.87
3.87
3.86
3.86
3.85
3.19
3.18
3.02
3.00
3.00
2.30
2.28
2.13
2.11
1.71
1.65
1.64
CDCl3, 400 MHz
Ph3CO
NH
O
236
5.9
5.9
3.2
0.9
1.0
1.0
1.0
2.0
1.0
1.0
f1 (ppm)

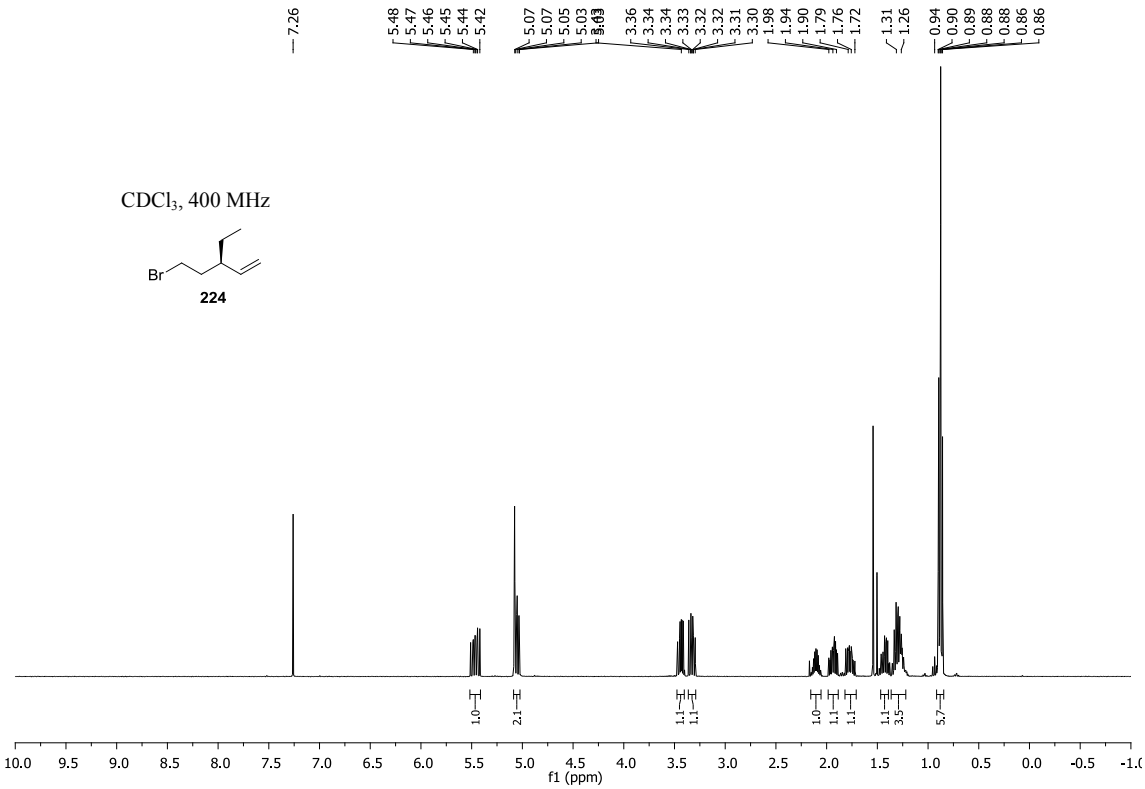

177.94
143.72
128.70
128.05
127.33
86.99
77.58
77.16
76.74
67.32
54.15
29.74
23.44
CDCl3, 75 MHz
Ph3CO
NH
O
236
f1 (ppm)


CDCl3, 300 MHz
Ph3CO
O
N
O
237
f1 (ppm)


CDCl3, 75 MHz
Ph3CO
O
N
O
237
f1 (ppm)

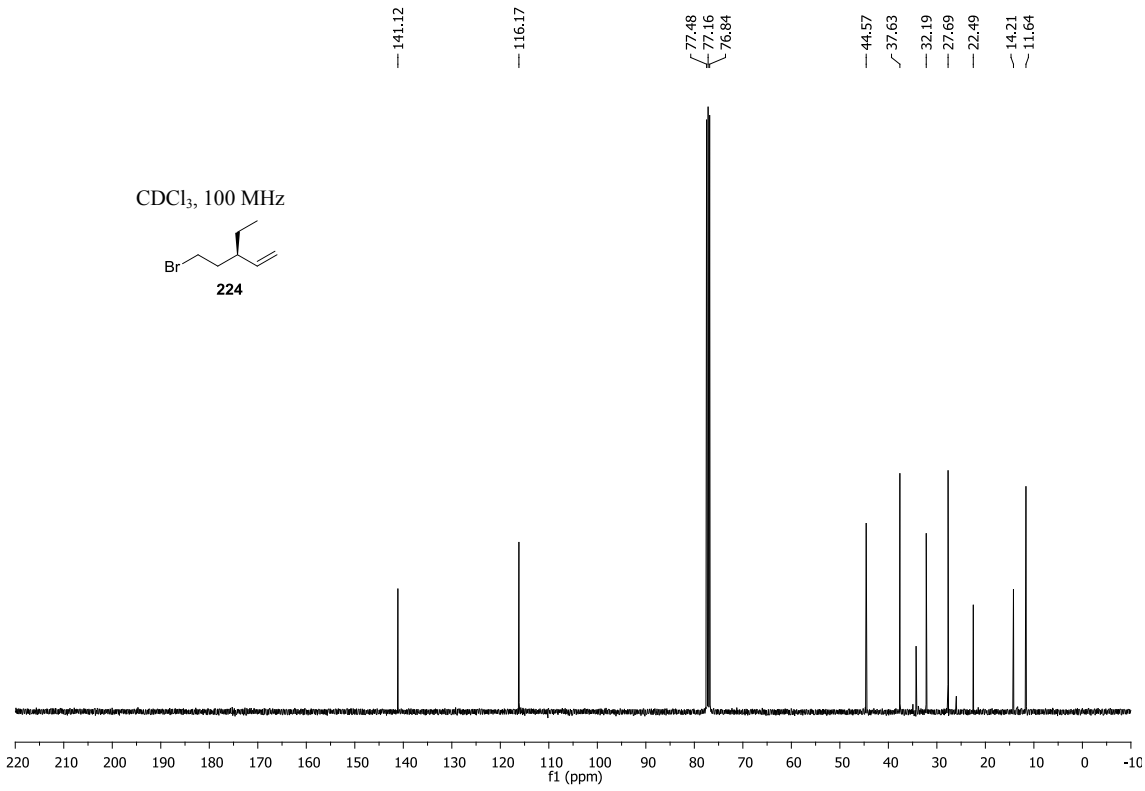

CDCl3, 300 MHz
Ph3CO
O
N
O
238
7.35
7.34
7.29
7.29
7.26
7.26
7.26
5.71
5.70
5.68
5.67
5.65
5.64
5.61
4.99
4.96
4.48
4.45
3.53
3.51
3.50
3.18
2.96
2.88
2.49
2.47
2.41
2.05
1.93
1.91
1.37
1.32
0.90
0.87
0.85
6.0
10.5
1.0
2.0
1.0
1.0
1.0
3.0
2.1
2.1
2.2
3.0
f1 (ppm)


CDCl3, 75 MHz
Ph3CO
O
N
O
238
176.33
172.87
143.83
141.50
128.71
128.03
127.28
114.97
87.17
77.50
77.06
76.74
64.06
56.87
42.08
41.34
33.38
27.53
21.46
11.67
f1 (ppm)



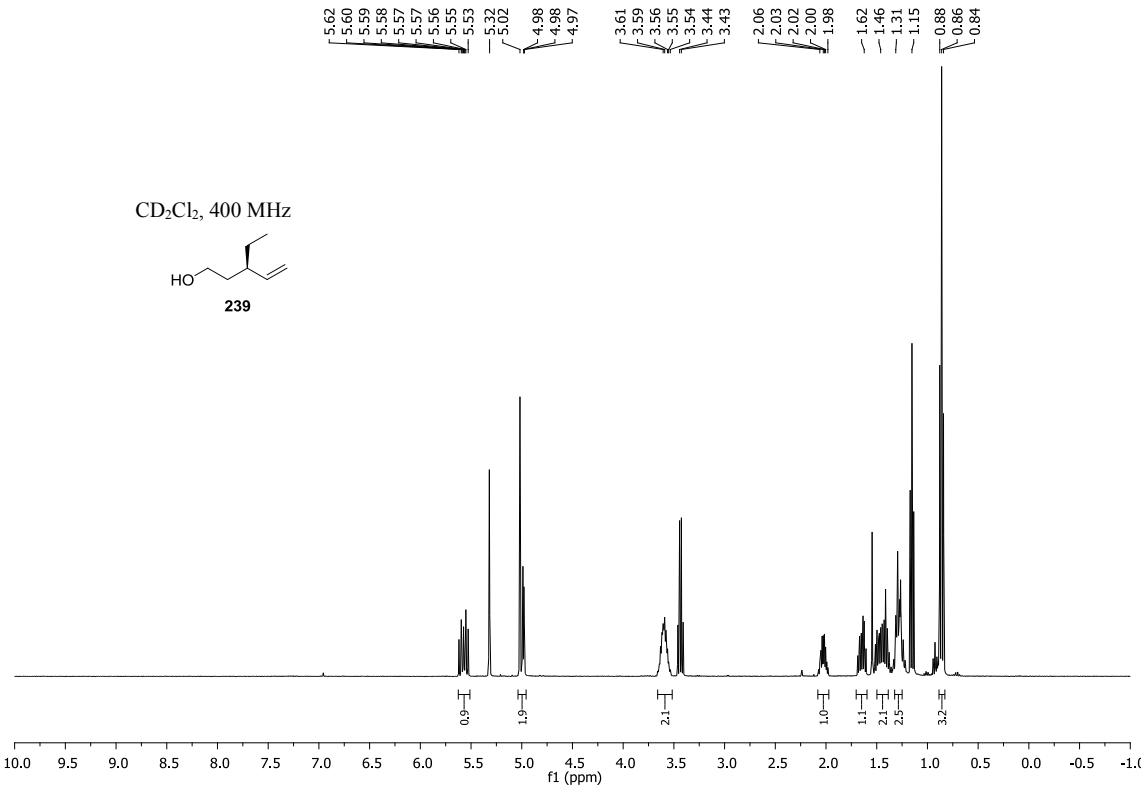
$CDCl_3$, 400 MHz

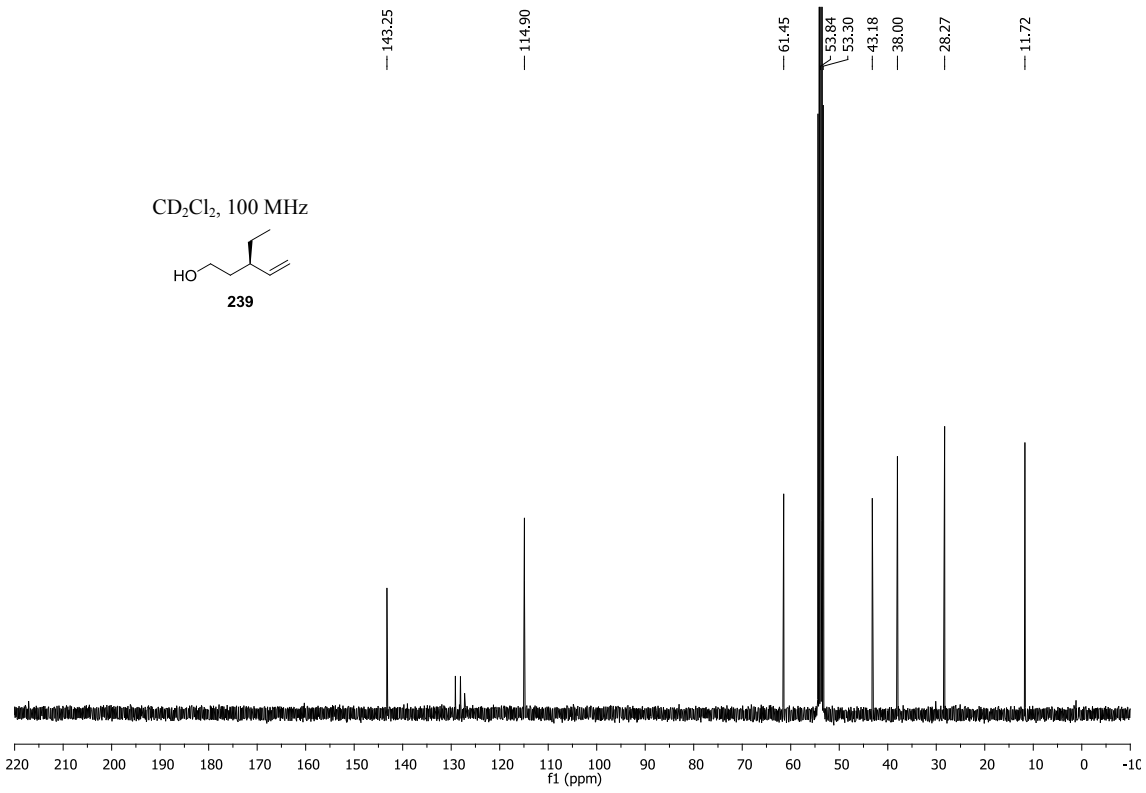
224

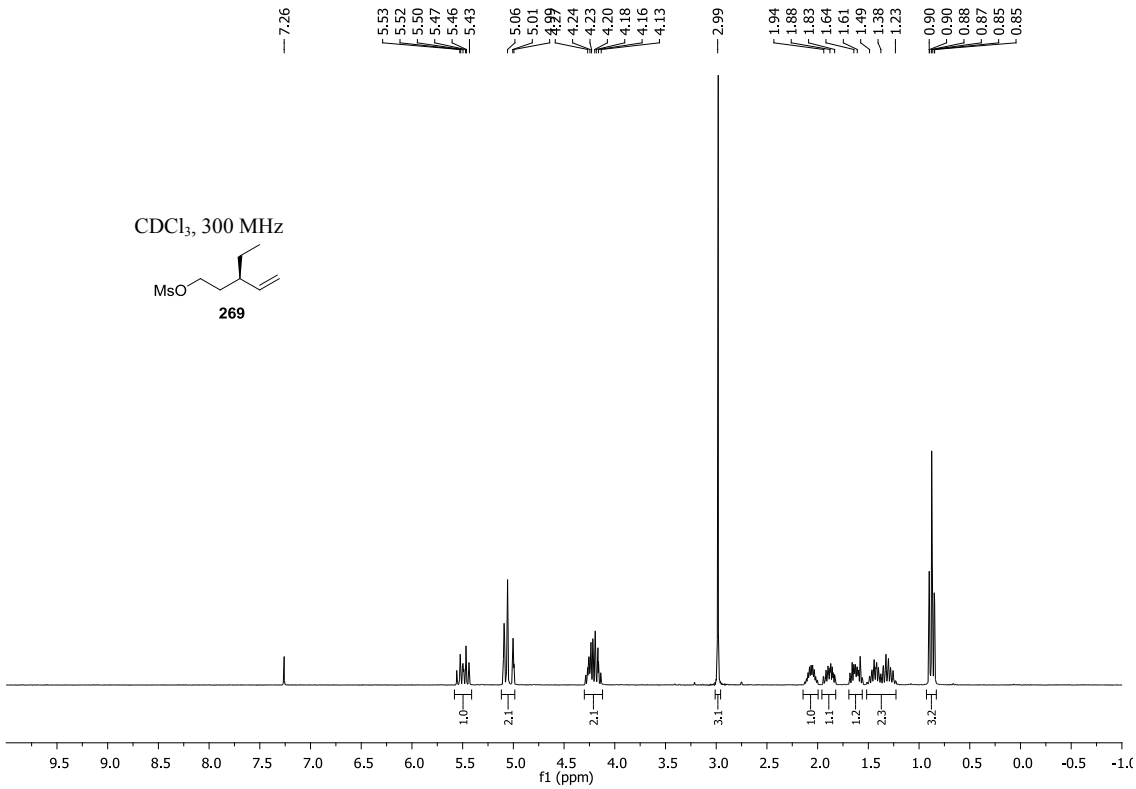


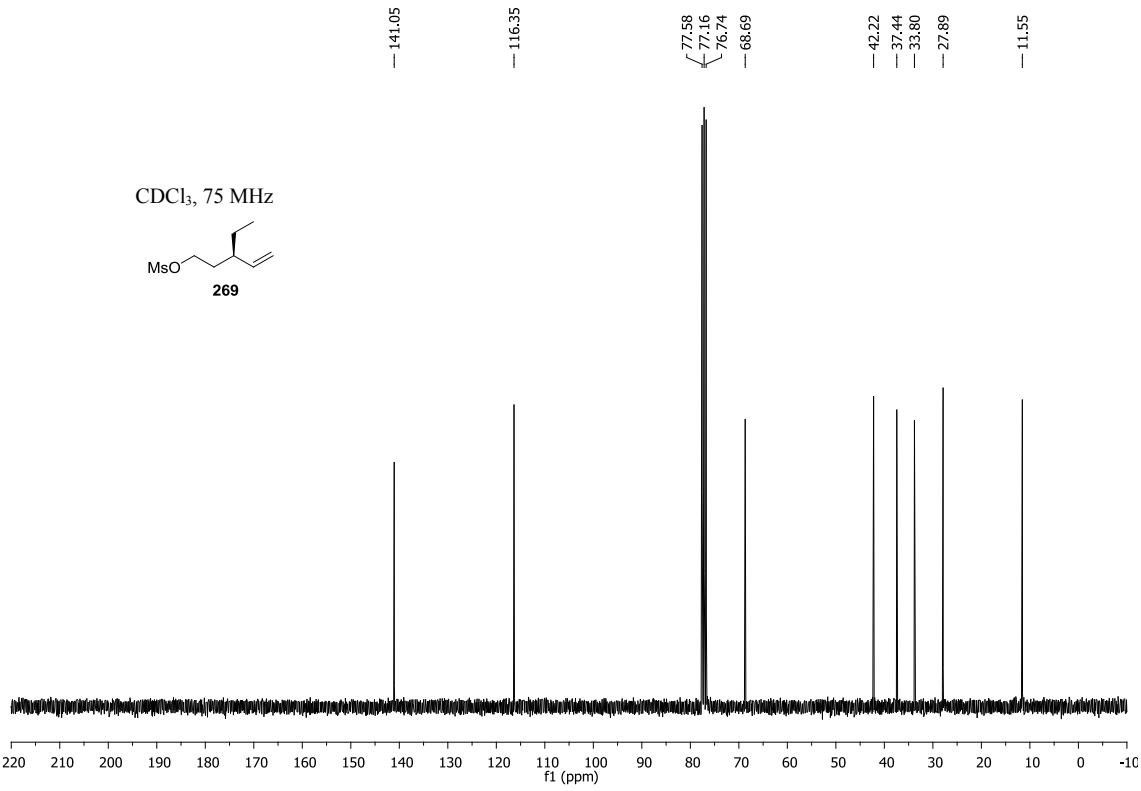
$CDCl_3$, 100 MHz

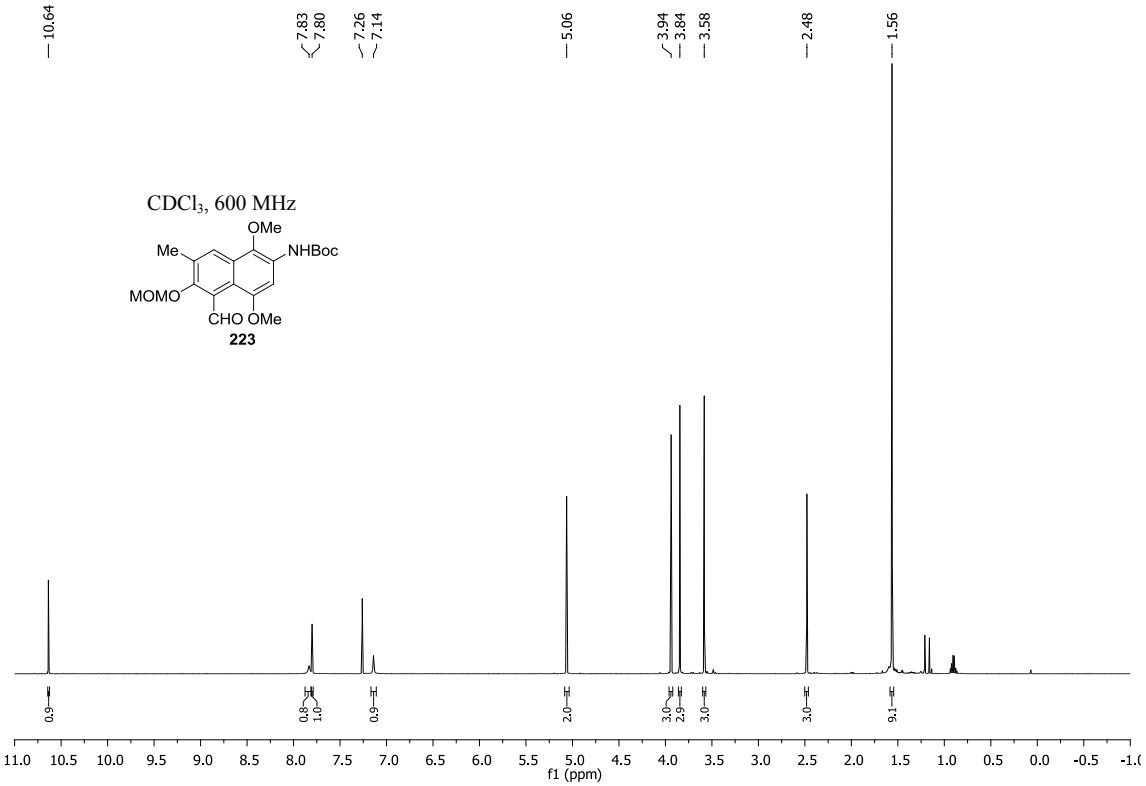
224

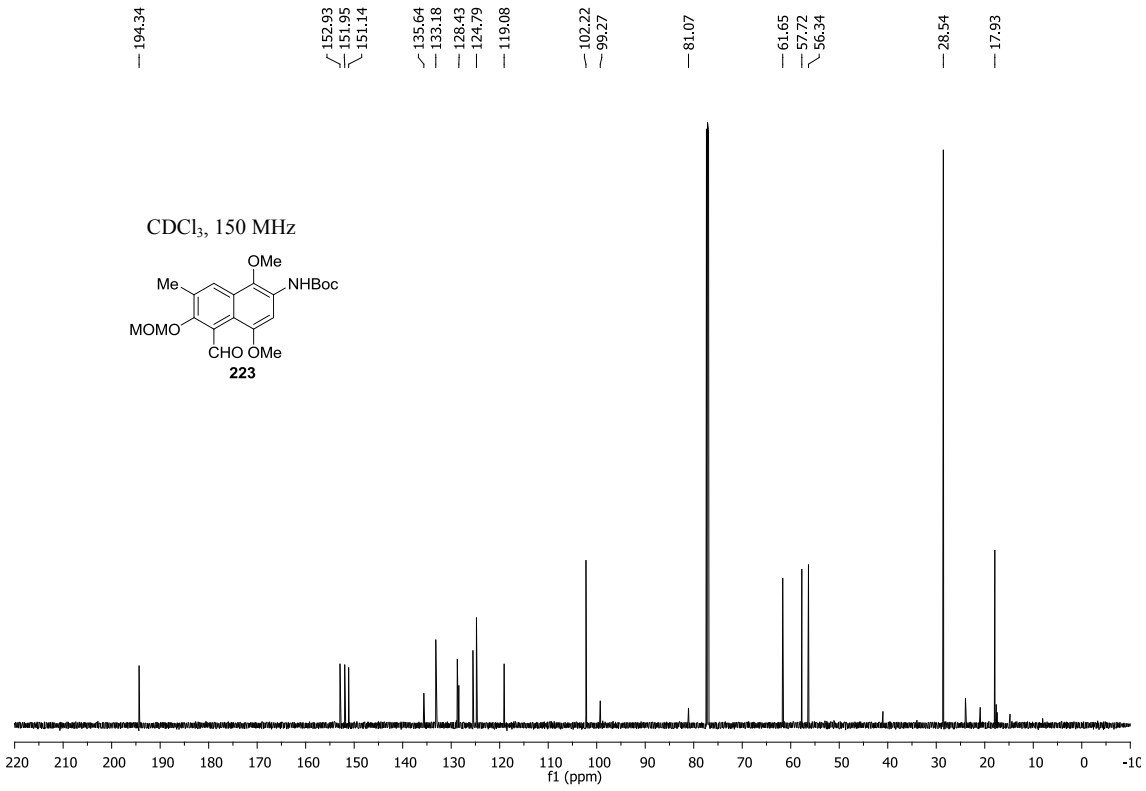

5.62
5.60
5.59
5.58
5.57
5.57
5.56
5.55
5.53
5.32
5.02
4.98
4.98
4.97
3.61
3.59
3.56
3.55
3.54
3.44
3.43
2.06
2.03
2.02
2.00
1.98
1.62
1.46
1.31
1.15
0.88
0.86
0.84
CD2Cl2, 400 MHz
HO
239
0.9
1.9
2.1
1.0
1.1
2.1
2.5
3.2
f1 (ppm)

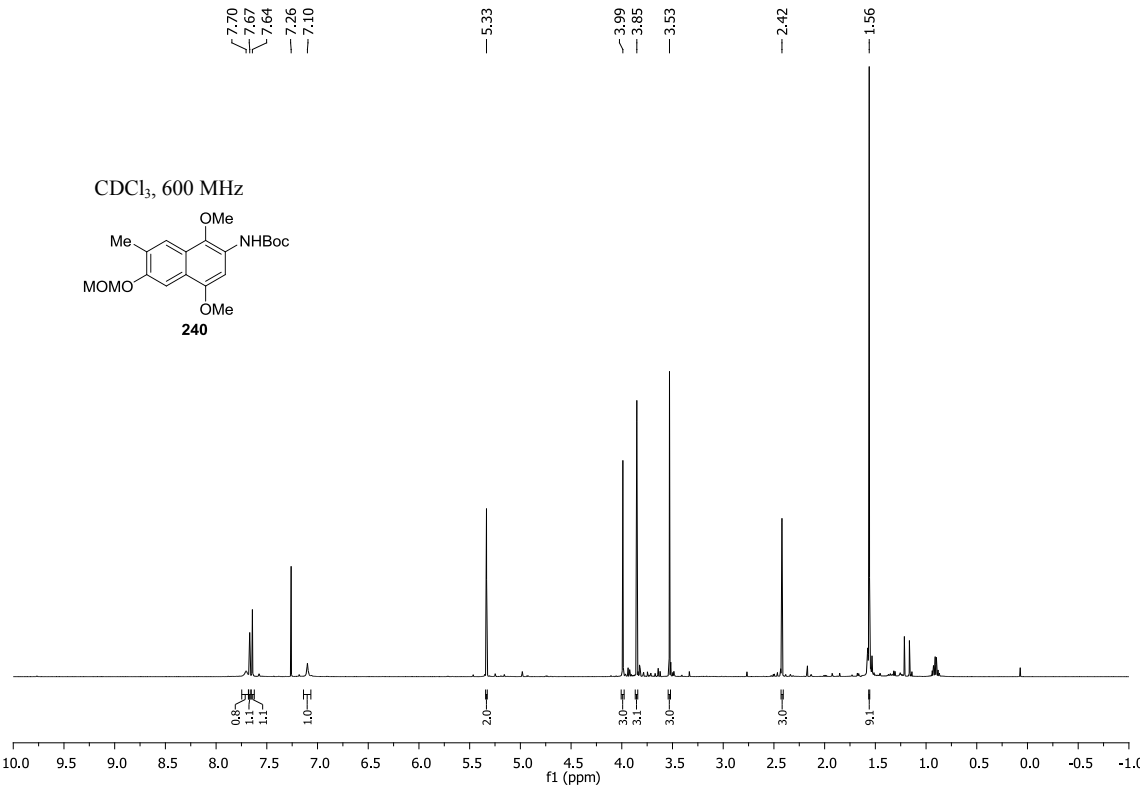

143.25
114.90
61.45
53.84
53.30
43.18
38.00
28.27
11.72
CD2Cl2, 100 MHz
HO
239
f1 (ppm)

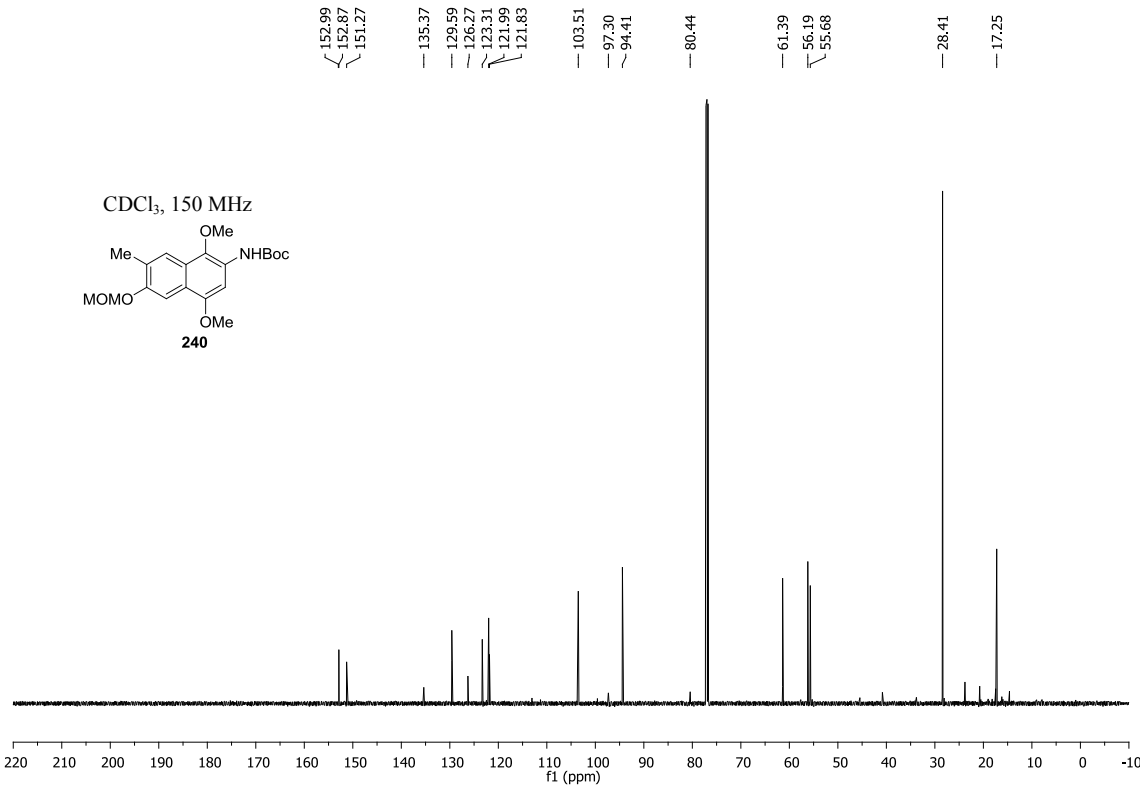

7.26
5.53
5.52
5.50
5.47
5.46
5.43
5.06
5.01
4.27
4.24
4.23
4.20
4.18
4.16
4.13
2.99
1.94
1.88
1.83
1.64
1.61
1.49
1.38
1.23
0.90
0.90
0.88
0.87
0.85
0.85
CDCl3, 300 MHz
MsO
269
1.0
2.1
2.1
3.1
1.0
1.1
1.2
2.3
3.2
f1 (ppm)

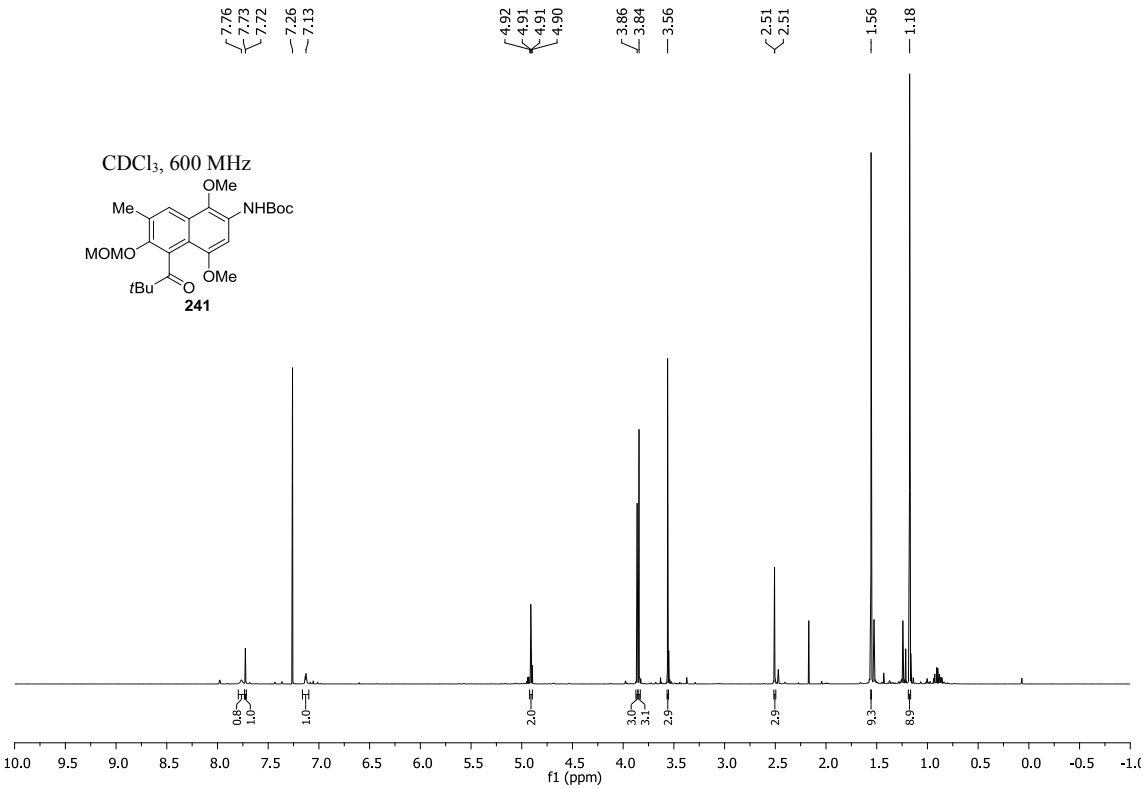

141.05
116.35
77.58
77.16
76.74
68.69
42.22
37.44
33.80
27.89
11.55
CDCl3, 75 MHz
MsO
269
f1 (ppm)

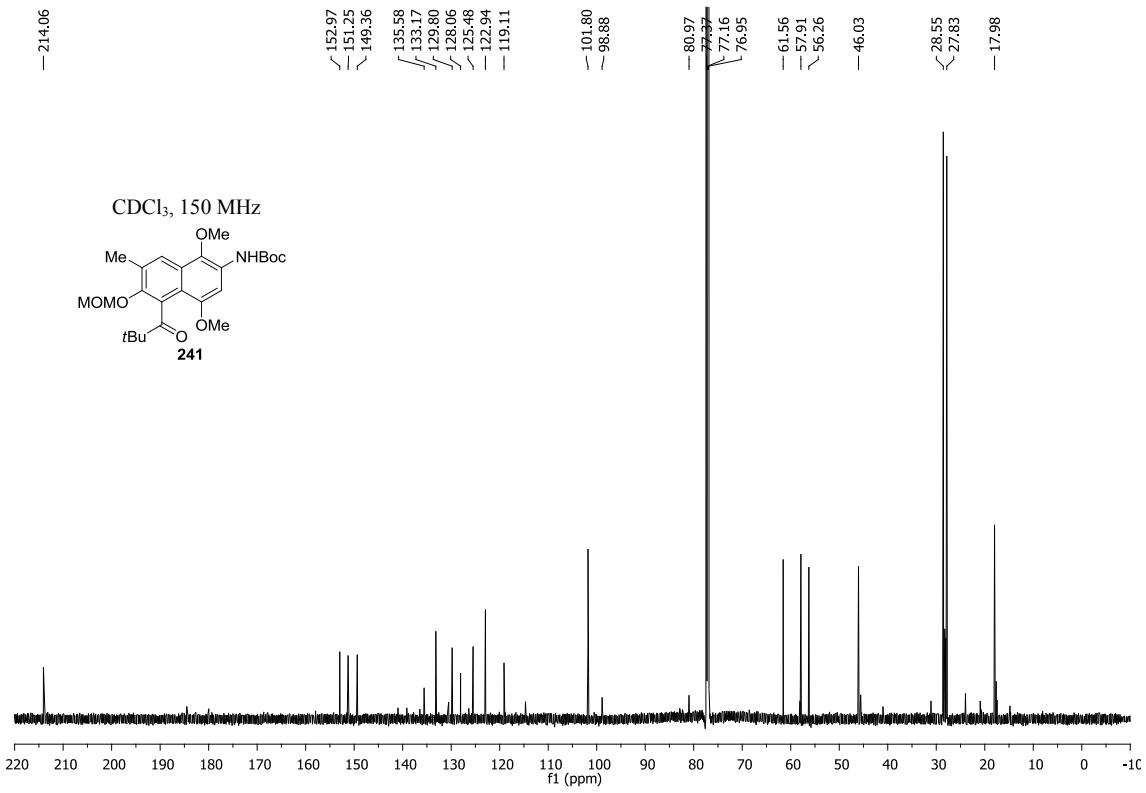

10.64
7.83
7.80
7.26
7.14
5.06
3.94
3.84
3.58
2.48
1.56
CDCl3, 600 MHz
OMe
Me
NHBoc
MOMO
CHO OMe
223
f1 (ppm)

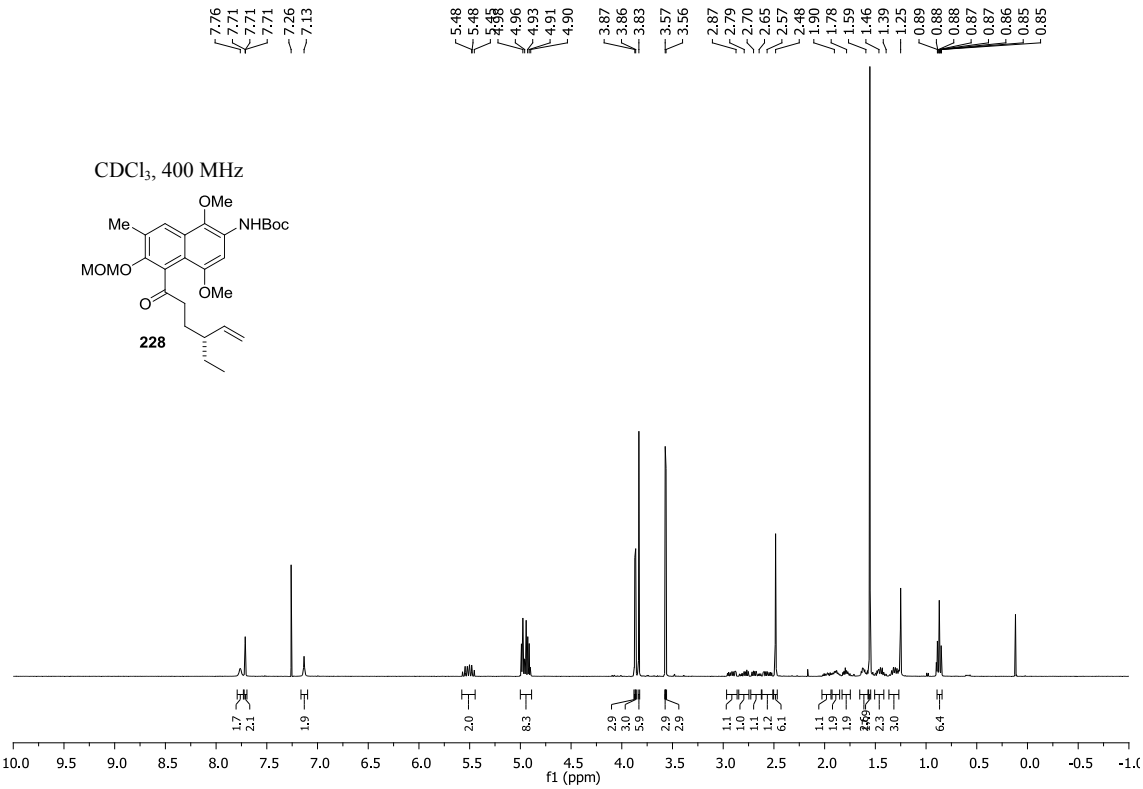

194.34
152.93
151.95
151.14
135.64
133.18
128.43
124.79
119.08
102.22
99.27
81.07
61.65
57.72
56.34
28.54
17.93
CDCl3, 150 MHz
OMe
Me
NHBoc
MOMO
CHO OMe
223
f1 (ppm)

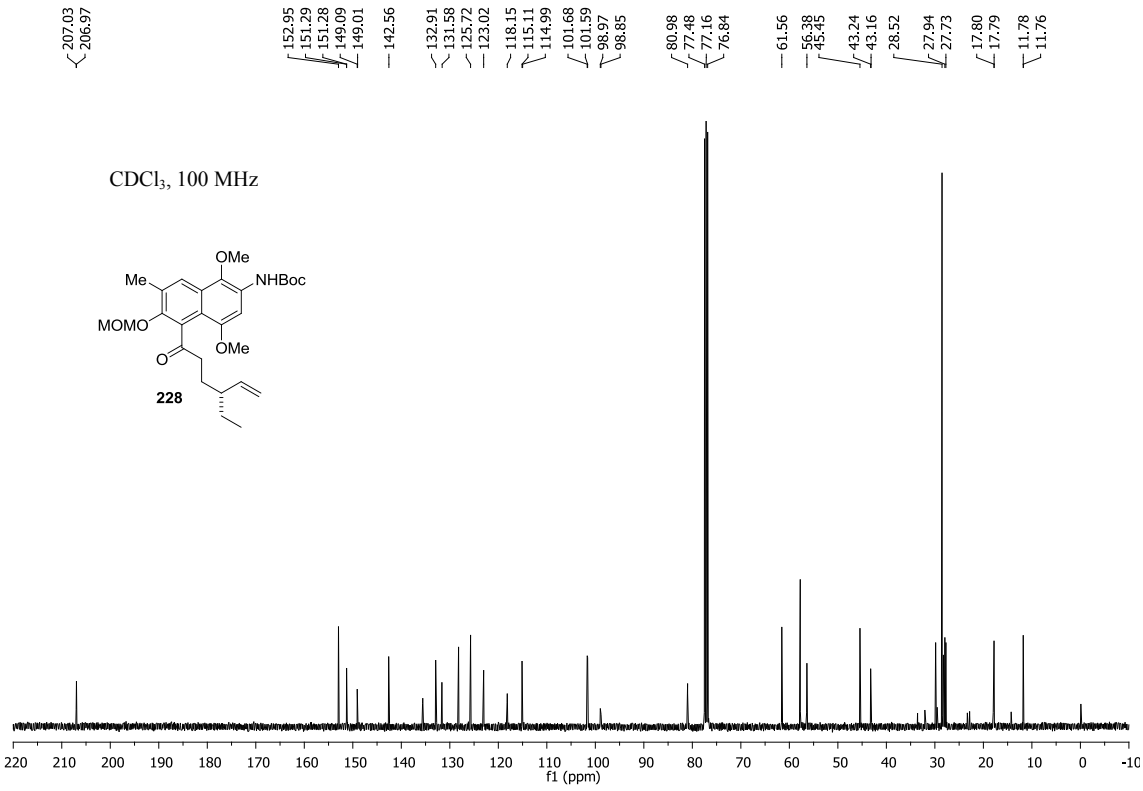

7.70
7.67
7.64
7.26
7.10
5.33
3.99
3.85
3.53
2.42
1.56
CDCl3, 600 MHz
OMe
Me
NHBoc
MOMO
OMe
240
0.8
1.1
1.1
1.0
2.0
3.0
3.1
3.0
3.0
9.1
f1 (ppm)

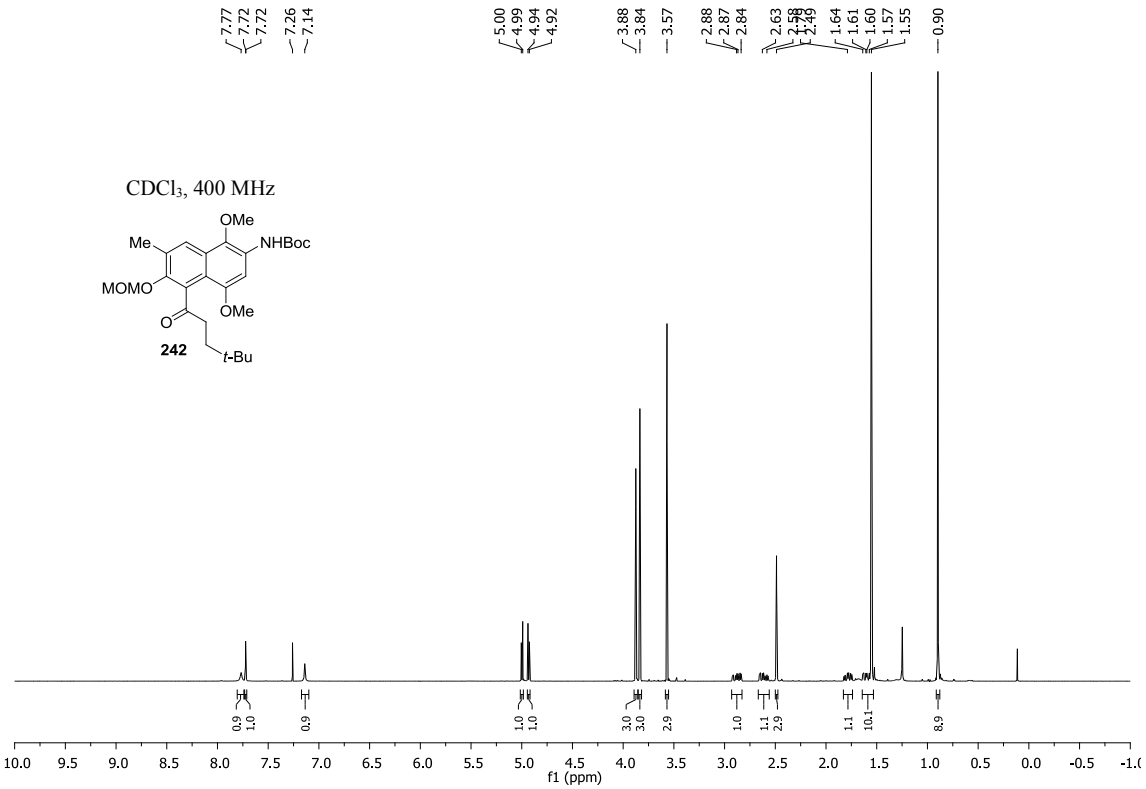

152.99
152.87
151.27
135.37
129.59
126.27
123.31
121.99
121.83
103.51
97.30
94.41
80.44
61.39
56.19
55.68
28.41
17.25
CDCl3, 150 MHz
OMe
Me
NHBoc
MOMO
OMe
240
f1 (ppm)

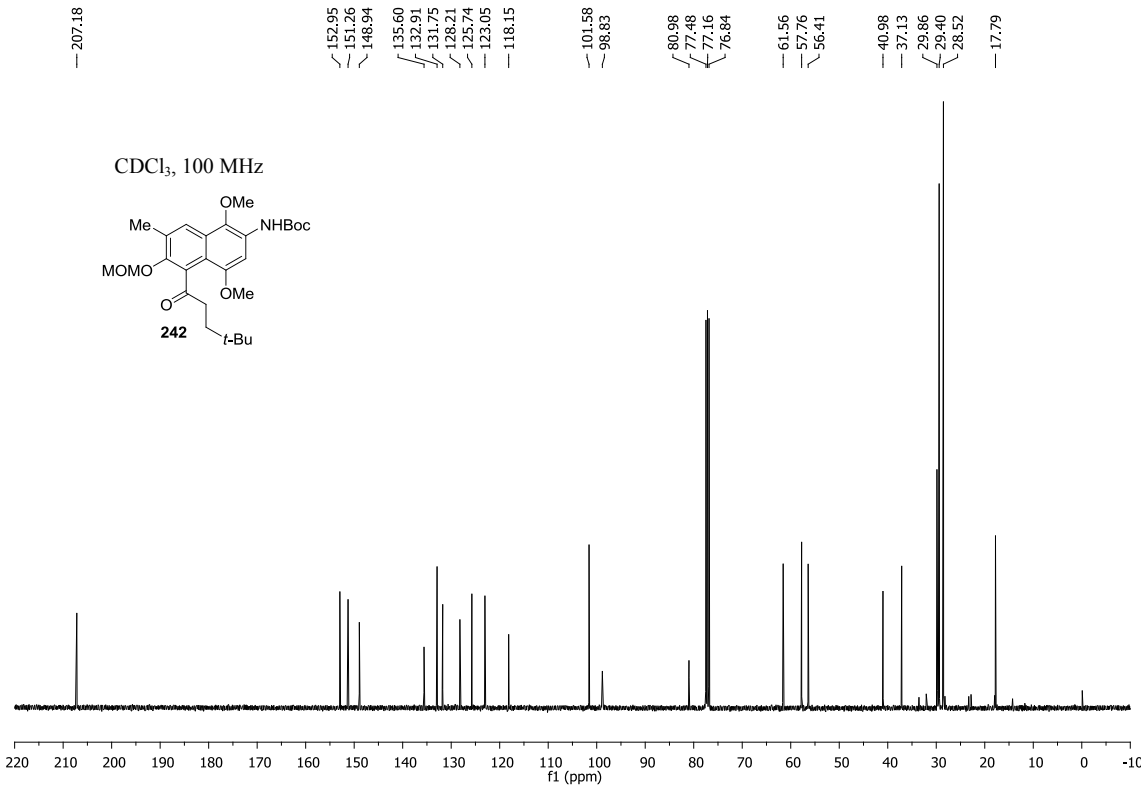

7.76
7.73
7.72
7.26
7.13
4.92
4.91
4.91
4.90
3.86
3.84
3.56
2.51
2.51
1.56
1.18
CDCl3, 600 MHz
OMe
NHBoc
Me
MOMO
OMe
tBu
O
241
0.8
1.0
1.0
2.0
3.0
3.1
2.9
2.9
9.3
8.9
f1 (ppm)

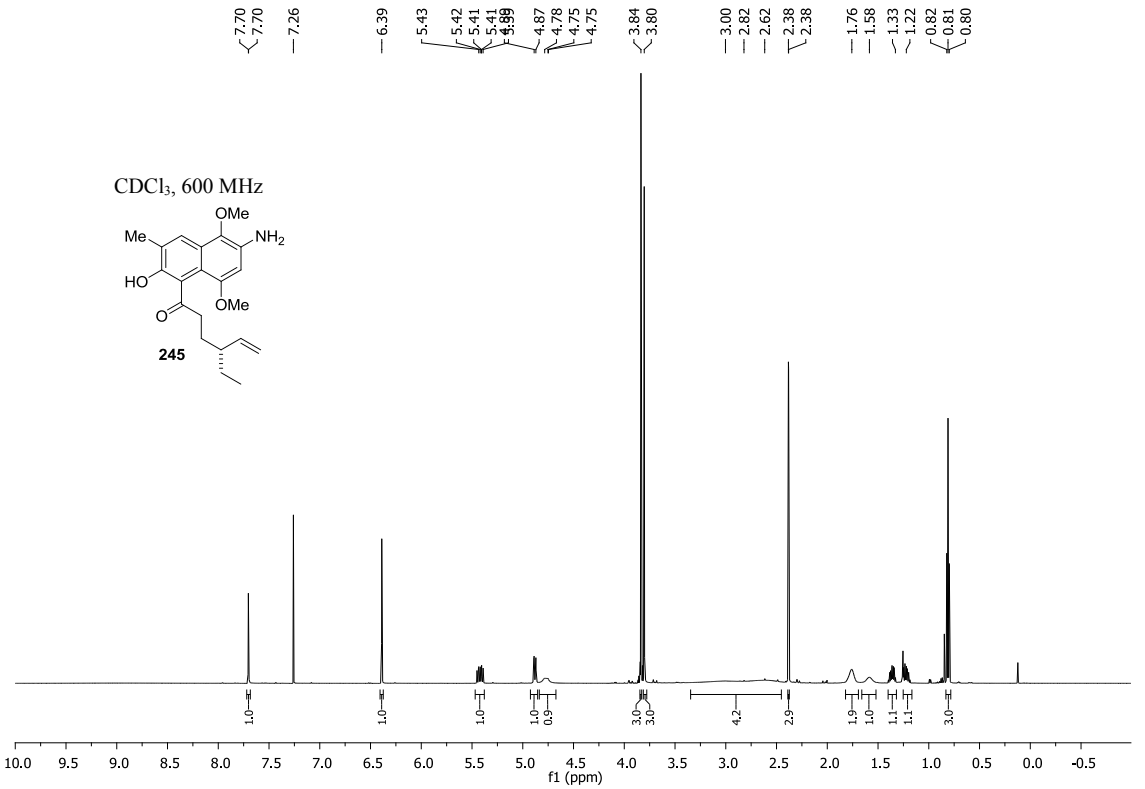

214.06
152.97
151.25
149.36
135.58
133.17
129.80
128.06
125.48
122.94
119.11
101.80
98.88
80.97
77.37
77.16
76.95
61.56
57.91
56.26
46.03
28.55
27.83
17.98
CDCl3, 150 MHz
OMe
NHBoc
Me
MOMO
OMe
tBu
O
241
f1 (ppm)

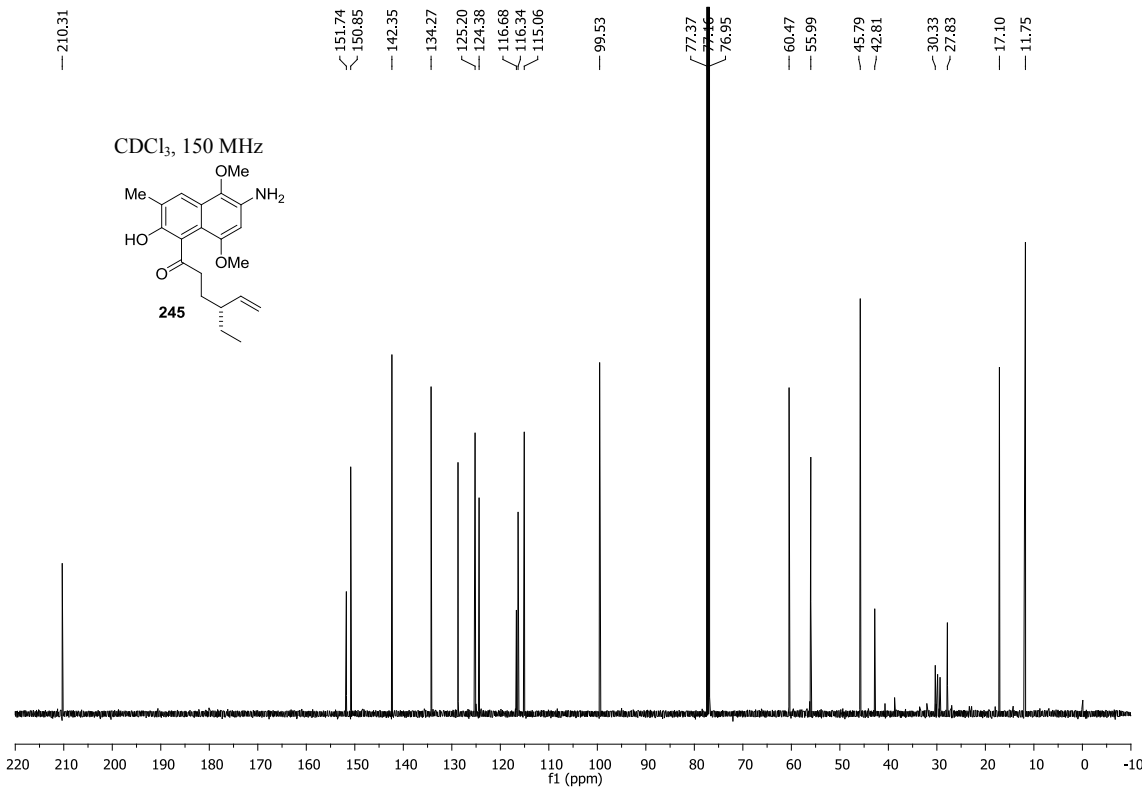

CDCl3, 400 MHz
OMe
NHBoc
Me
MOMO
OMe
O
228
f1 (ppm)

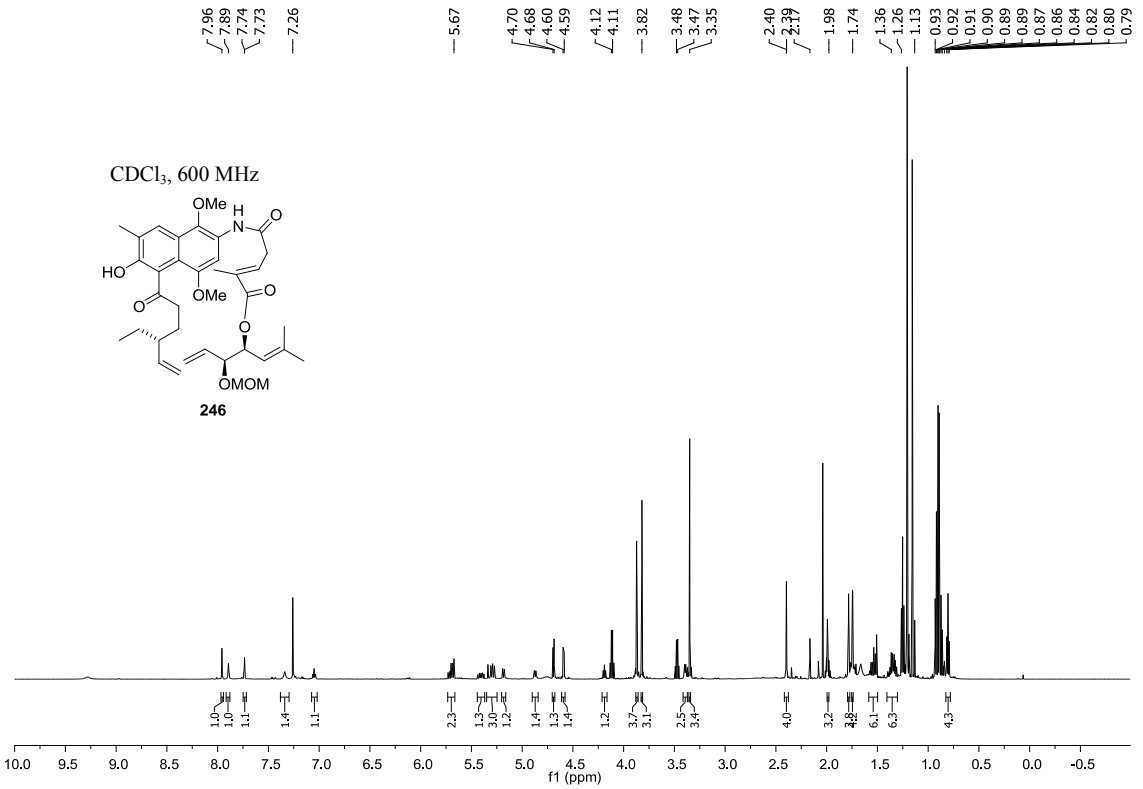

CDCl3, 100 MHz
OMe
NHBoc
Me
MOMO
OMe
O
228
f1 (ppm)

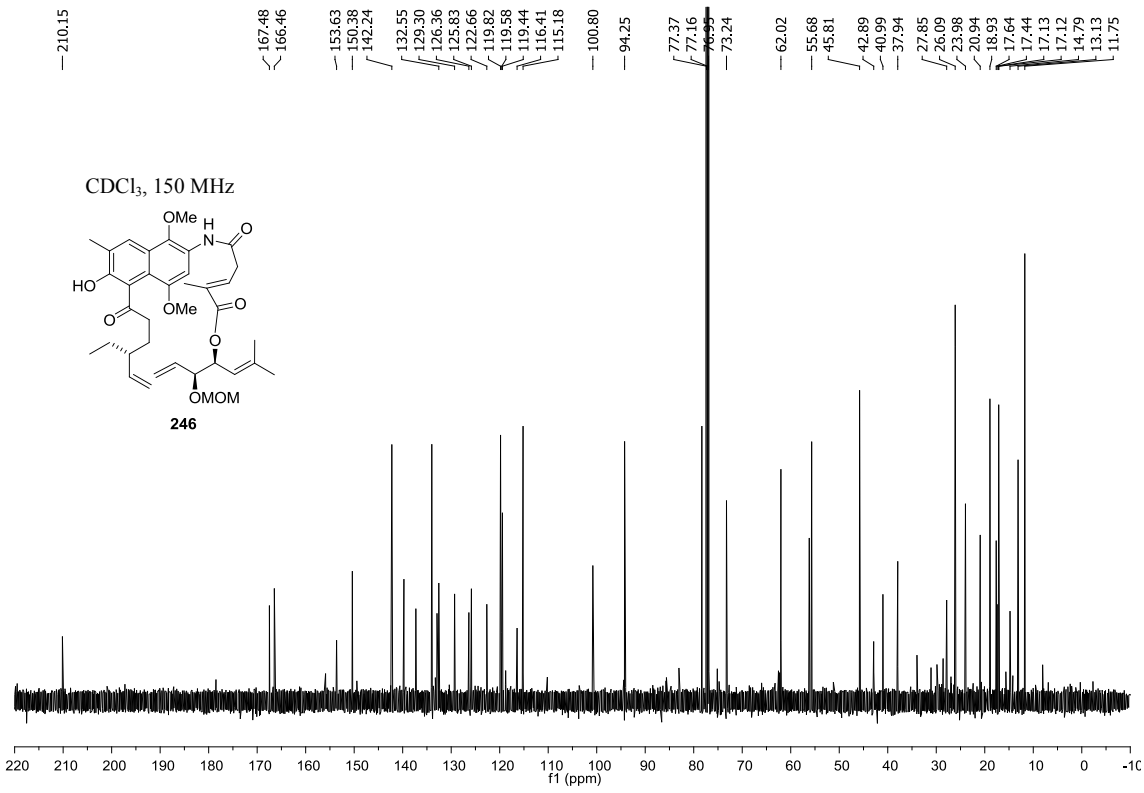

7.77
7.72
7.72
7.26
7.14
5.00
4.99
4.94
4.92
3.88
3.84
3.57
2.88
2.87
2.84
2.63
2.58
2.49
1.64
1.61
1.60
1.57
1.55
0.90
CDCl3, 400 MHz
OMe
Me
NHBoc
MOMO
OMe
O
242
t-Bu
f1 (ppm)

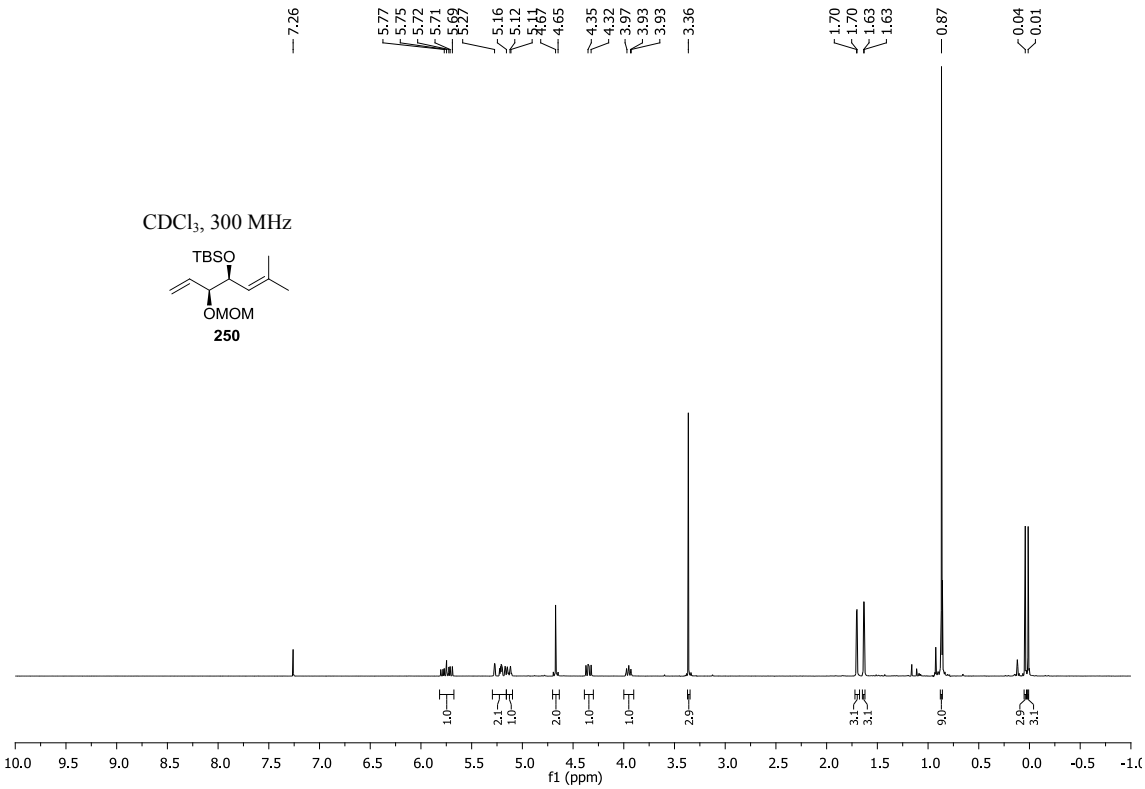

207.18
152.95
151.26
148.94
135.60
132.91
131.75
128.21
125.74
123.05
118.15
101.58
98.83
80.98
77.48
77.16
76.84
61.56
57.76
56.41
40.98
37.13
29.86
29.40
28.52
17.79
CDCl3, 100 MHz
OMe
Me
NHBoc
MOMO
OMe
O
242
t-Bu
f1 (ppm)


CDCl3, 600 MHz
OMe
Me
NH2
HO
OMe
O
245
f1 (ppm)


CDCl3, 150 MHz
OMe
Me
NH2
HO
OMe
O
245
f1 (ppm)

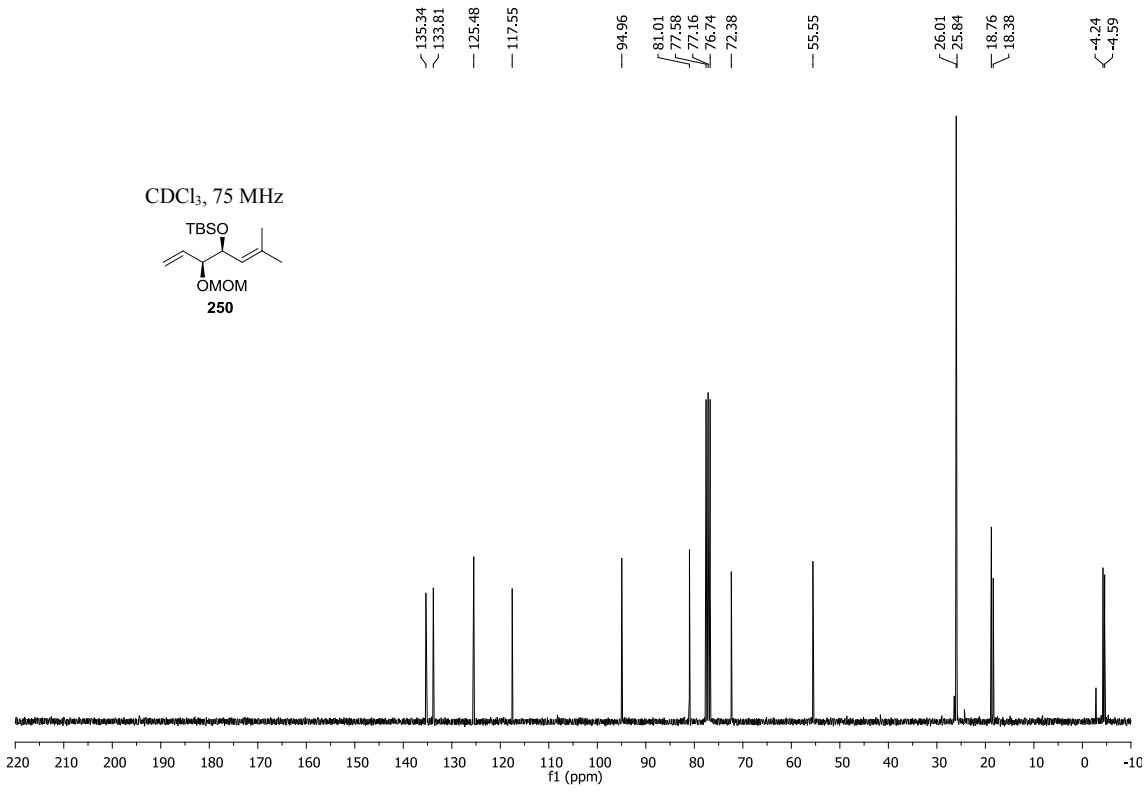

7.96
7.89
7.74
7.73
7.26
5.67
4.70
4.68
4.60
4.59
4.12
4.11
3.82
3.48
3.47
3.35
2.40
2.39
2.17
1.98
1.74
1.36
1.26
1.13
0.93
0.92
0.91
0.90
0.89
0.89
0.87
0.86
0.84
0.82
0.80
0.79
CDCl3, 600 MHz
OMe
H
N
O
HO
OMe
O
O
O
OMOM
246
f1 (ppm)


210.15
167.48
166.46
153.63
150.38
142.24
132.55
129.30
126.36
125.83
122.66
119.82
119.58
119.44
116.41
115.18
100.80
94.25
77.37
77.16
76.95
73.24
62.02
55.68
45.81
42.89
40.99
37.94
27.85
26.09
23.98
20.94
18.93
17.64
17.44
17.13
17.12
14.79
13.13
11.75
CDCl3, 150 MHz
OMe
H
N
O
HO
OMe
O
O
O
OMOM
246
f1 (ppm)



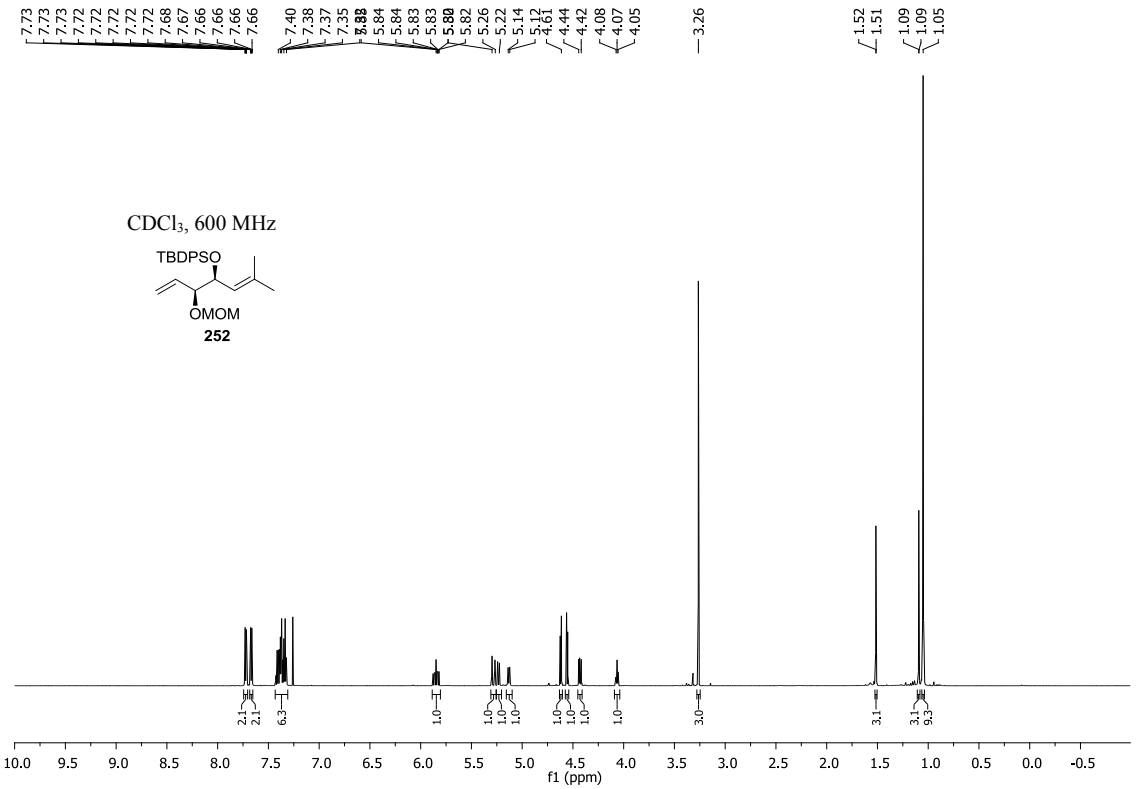
$CDCl_3$, 300 MHz

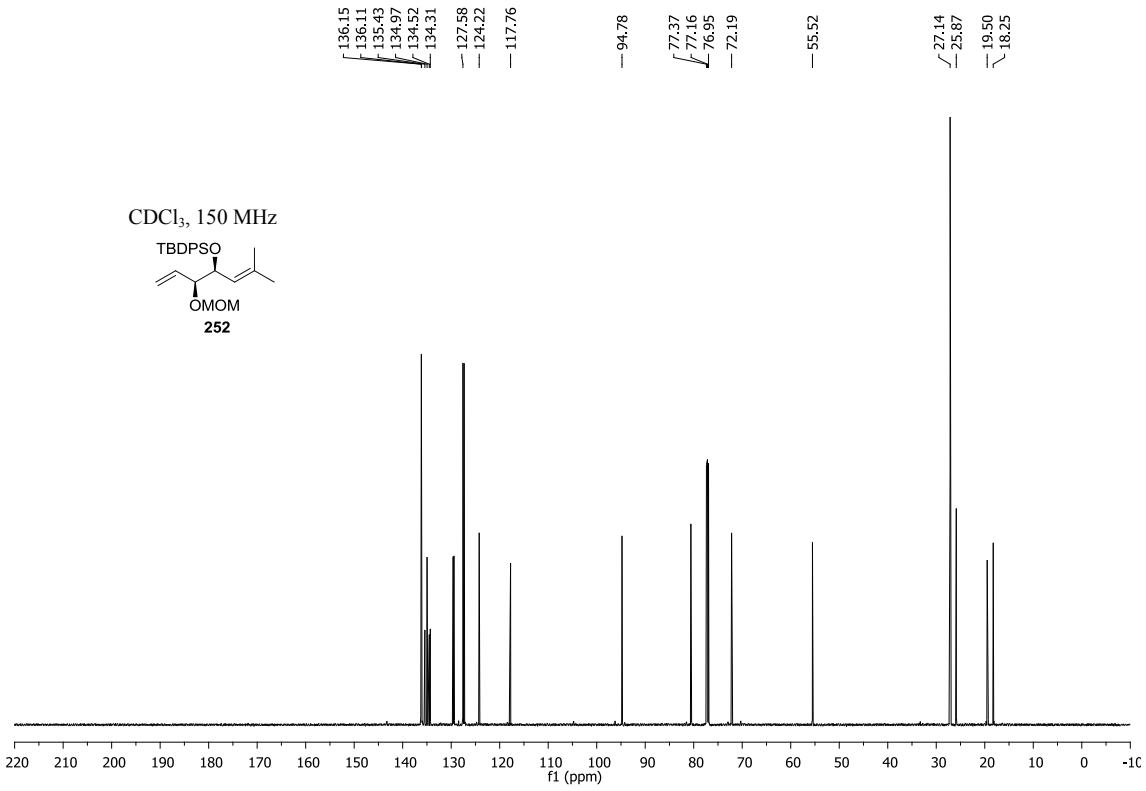
250



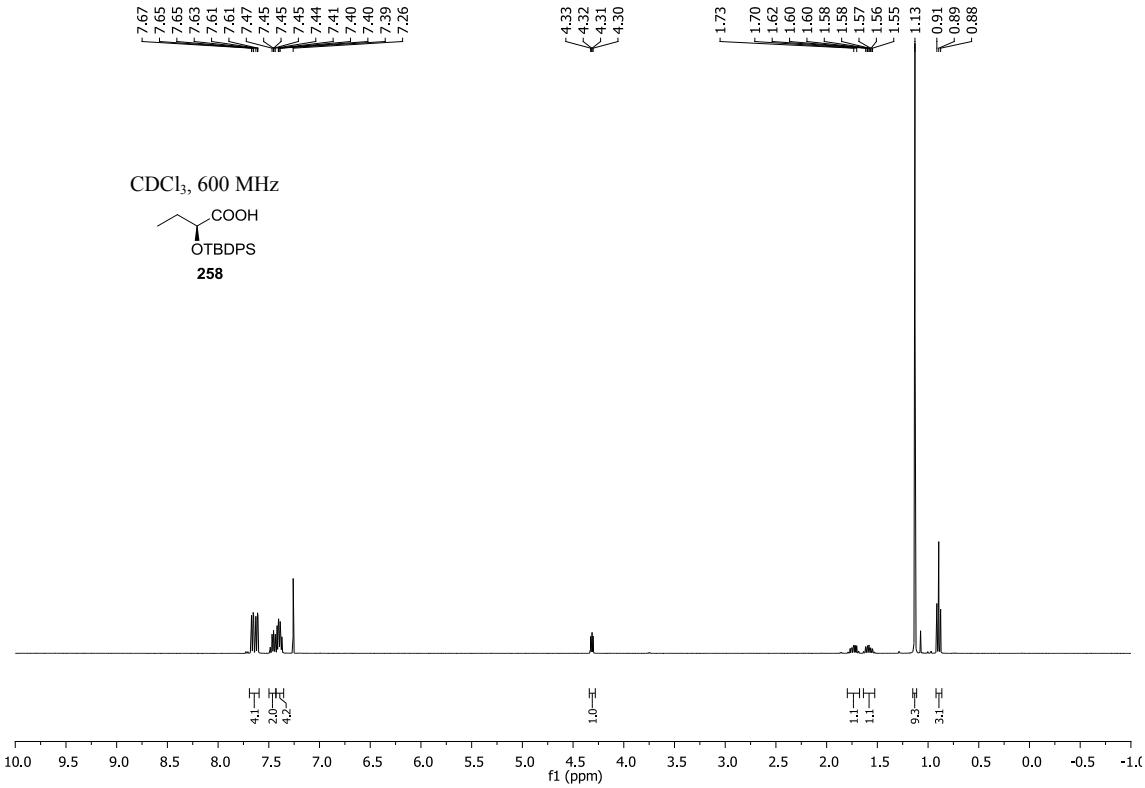
$CDCl_3$, 75 MHz

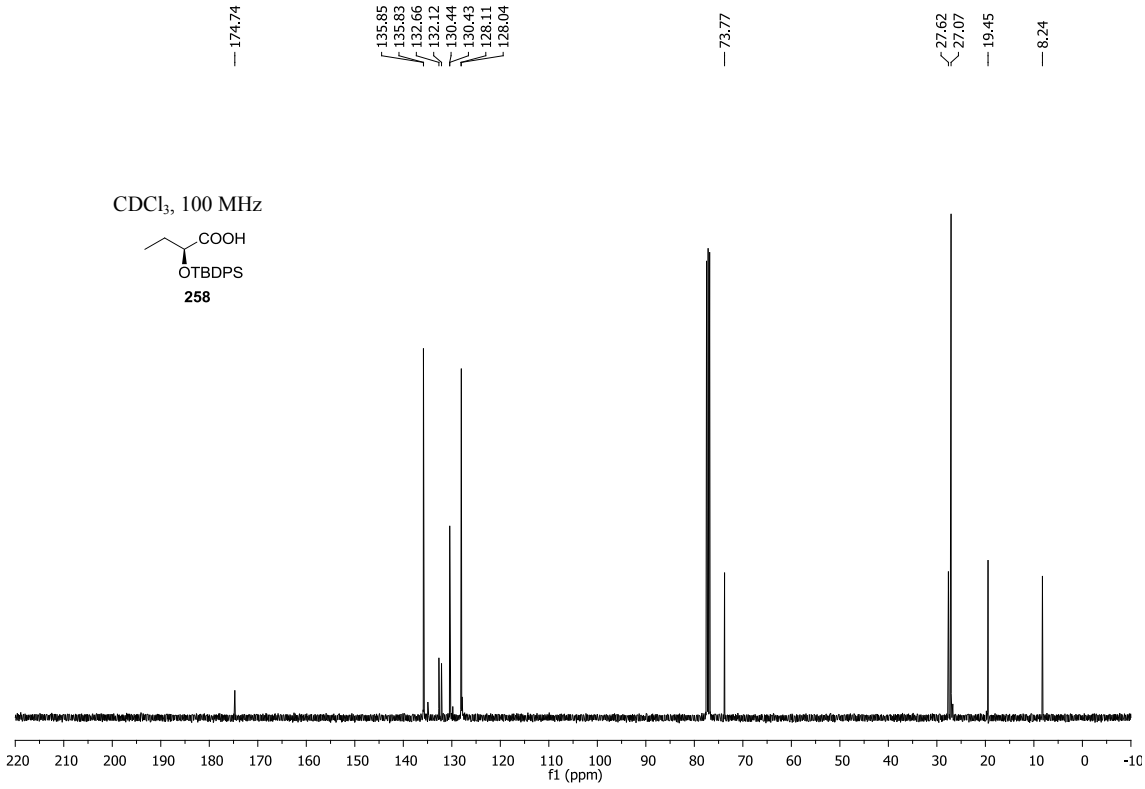
250

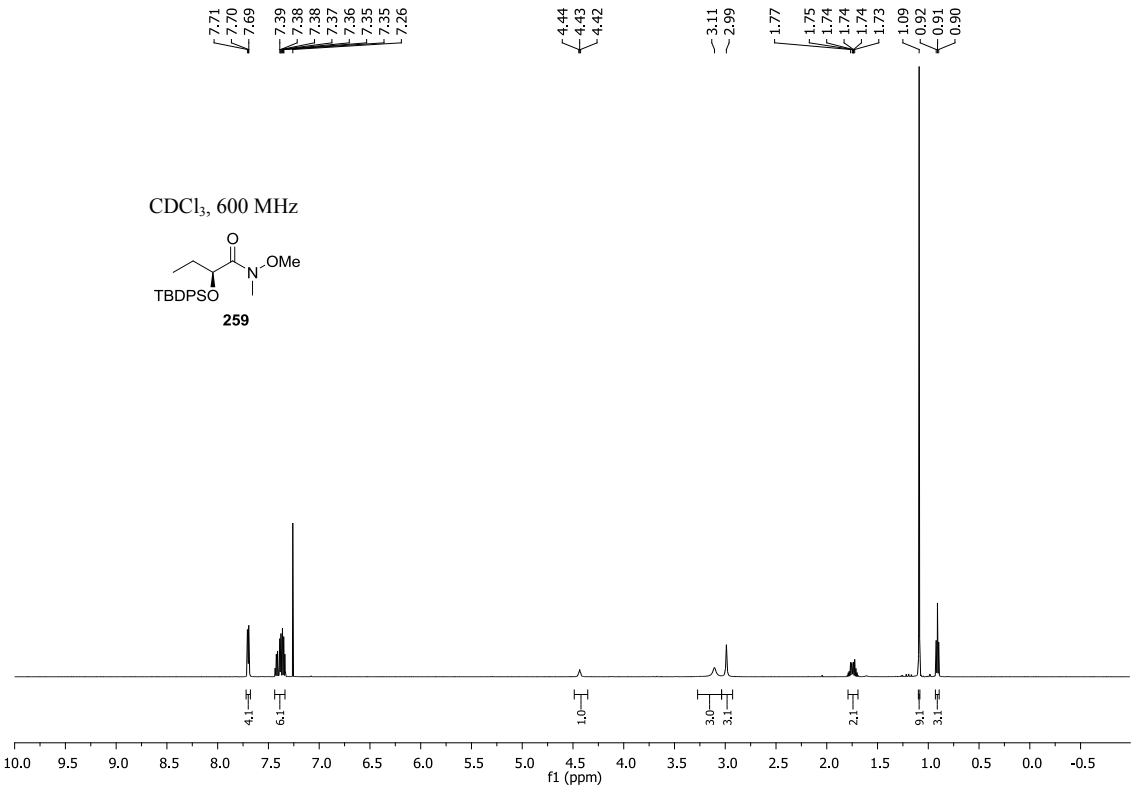

CDCl3, 600 MHz
TBDPSO
OMOM
252
f1 (ppm)

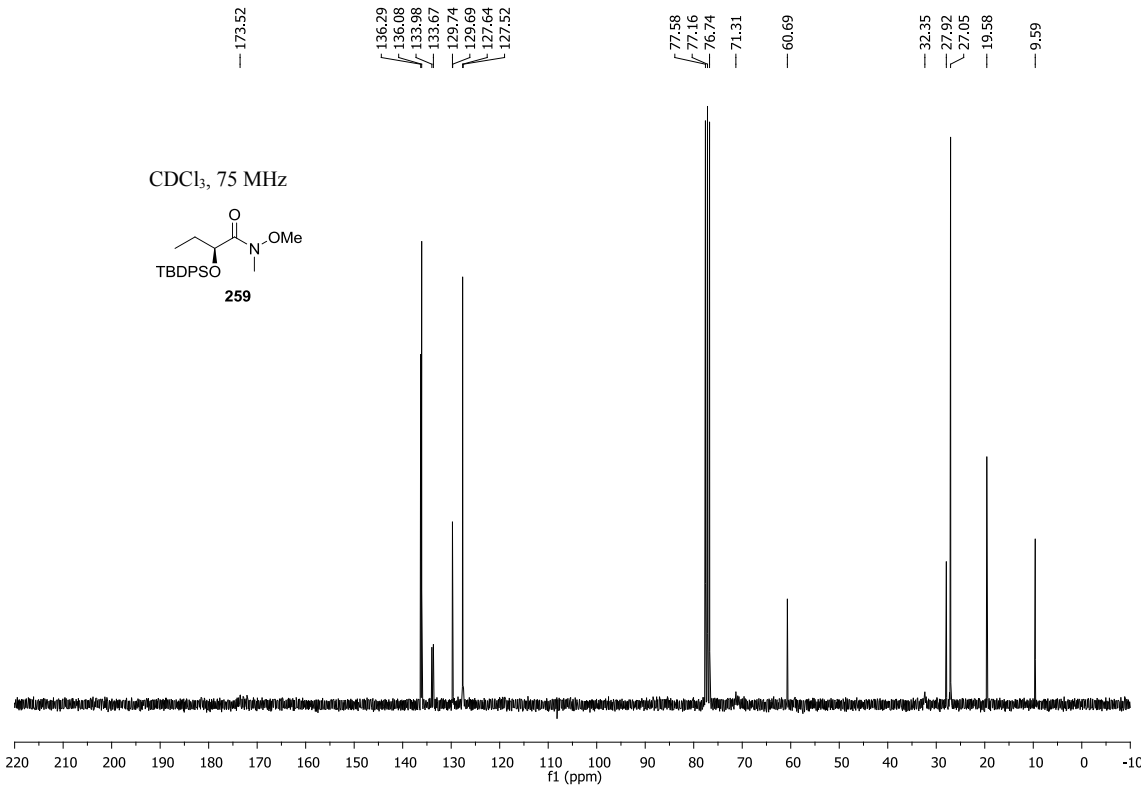

CDCl3, 150 MHz
TBDPSO
OMOM
252
f1 (ppm)

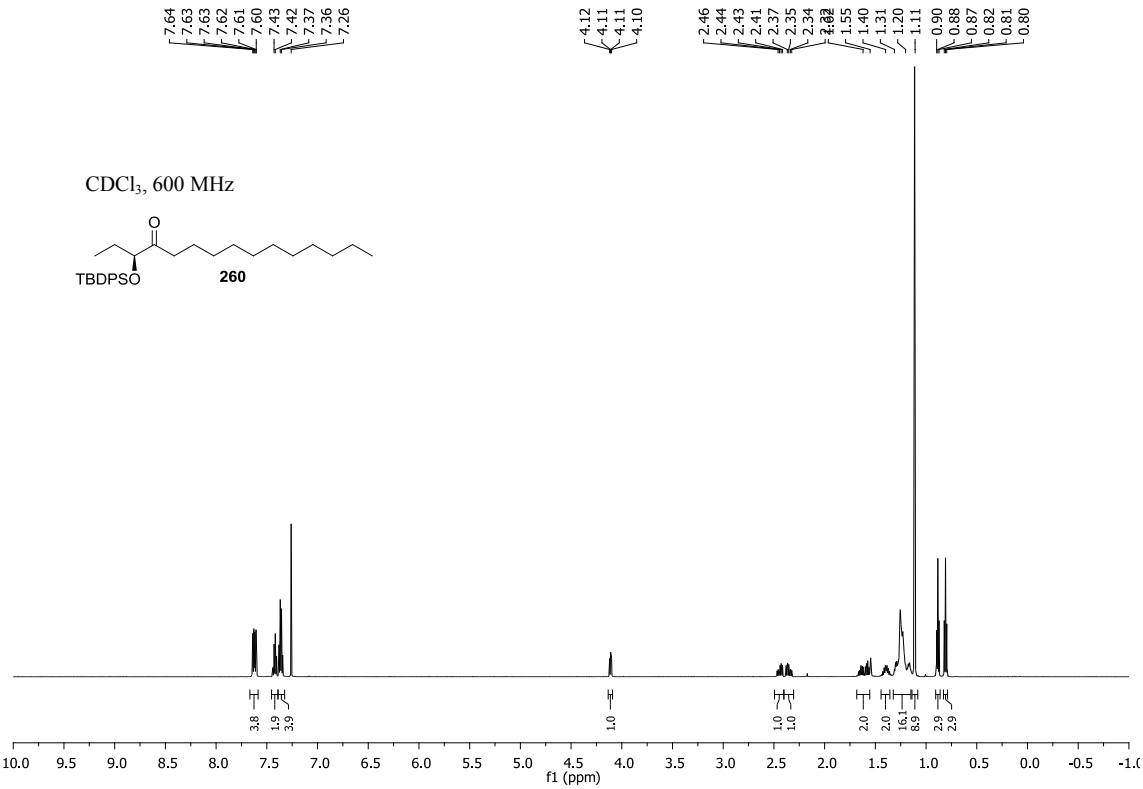
22.4. NMR Spectra of Chapter IV

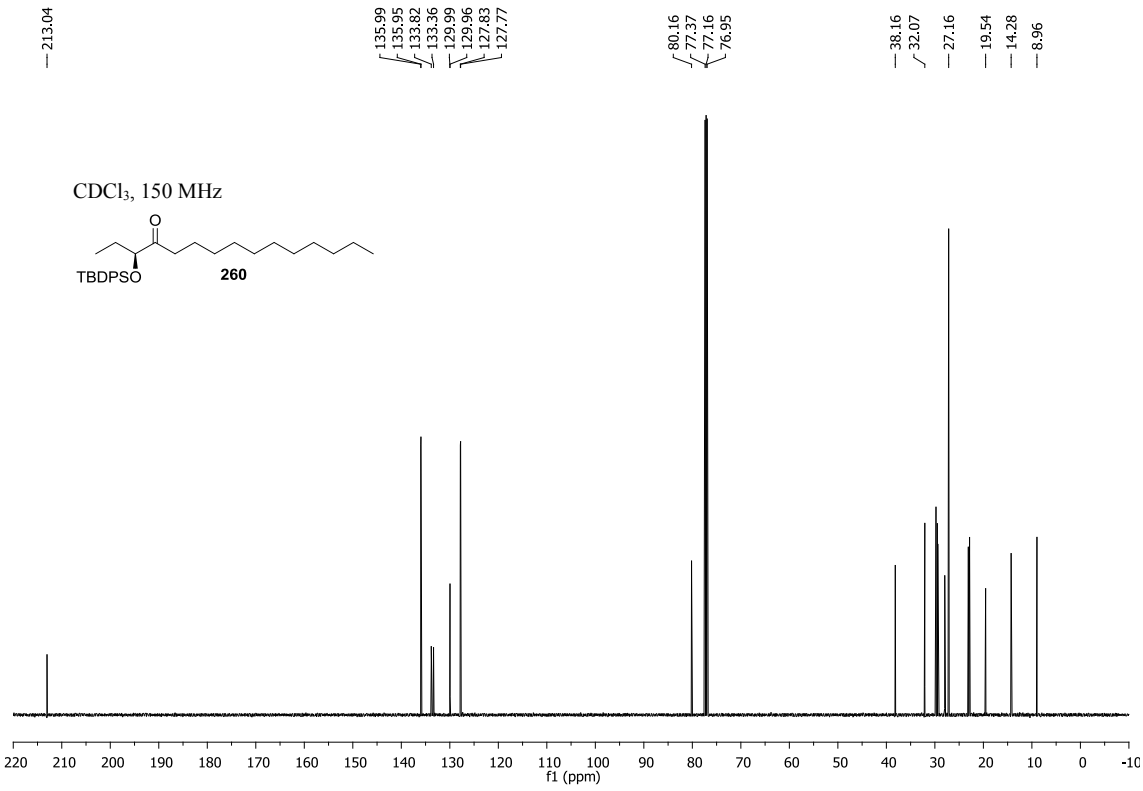


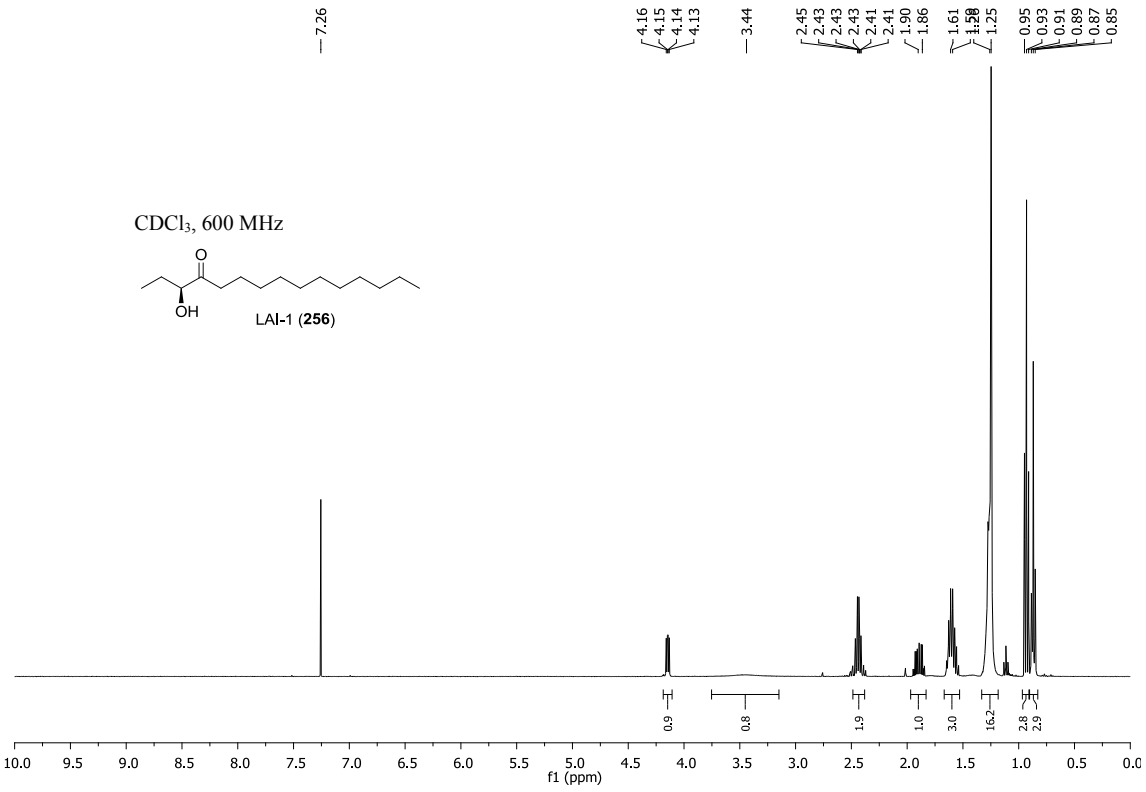


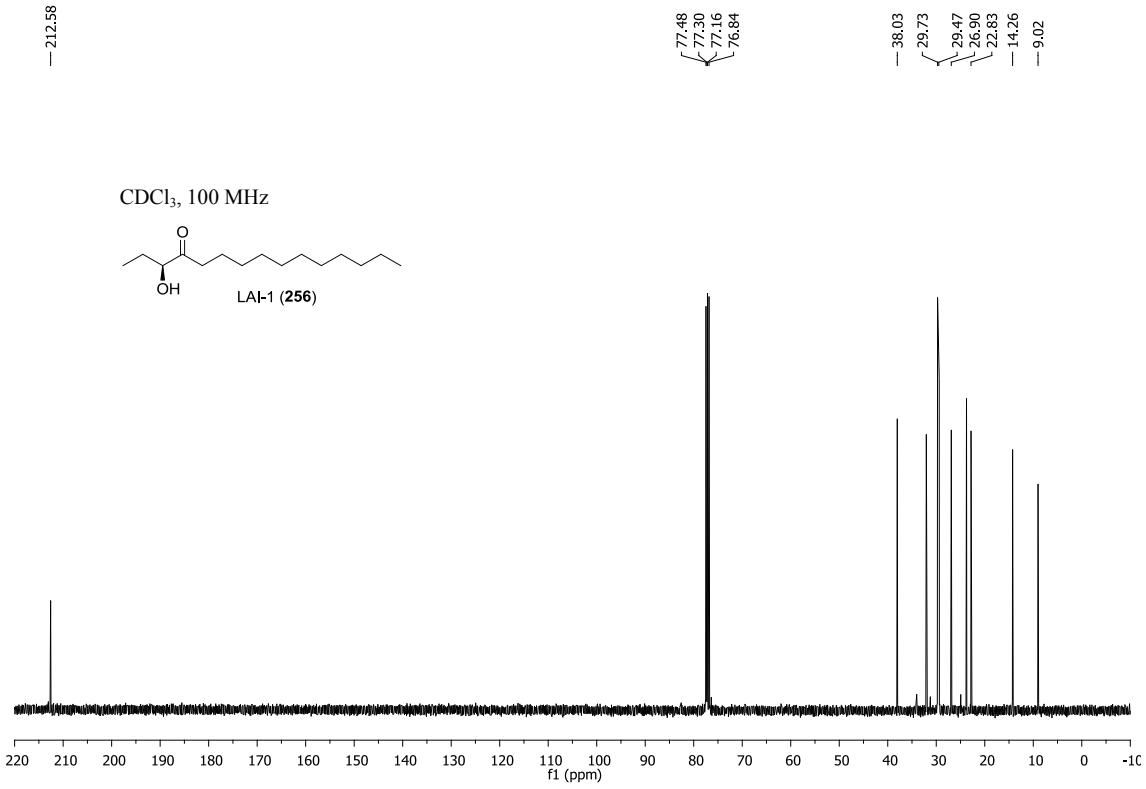

7.71
7.70
7.69
7.39
7.38
7.38
7.37
7.36
7.35
7.35
7.26
4.44
4.43
4.42
3.11
2.99
1.77
1.75
1.74
1.74
1.74
1.73
1.09
0.92
0.91
0.90
CDCl3, 600 MHz
O
N
OMe
TBDPSO
259
4.1
6.1
1.0
3.0
3.1
2.1
9.1
3.1
f1 (ppm)


173.52
136.29
136.08
133.98
133.67
129.74
129.69
127.64
127.52
77.58
77.16
76.74
71.31
60.69
32.35
27.92
27.05
19.58
9.59
CDCl3, 75 MHz
O
N
OMe
TBDPSO
259
f1 (ppm)


7.64
7.63
7.63
7.62
7.61
7.60
7.43
7.42
7.37
7.36
7.26
4.12
4.11
4.11
4.10
2.46
2.44
2.43
2.41
2.37
2.35
2.34
1.55
1.40
1.31
1.20
1.11
0.90
0.88
0.87
0.82
0.81
0.80
CDCl3, 600 MHz
O
TBDPSO
260
3.8
1.9
3.9
1.0
1.0
1.0
2.0
2.0
16.1
8.9
2.9
2.9
f1 (ppm)


213.04
135.99
135.95
133.82
133.36
129.99
129.96
127.83
127.77
80.16
77.37
77.16
76.95
38.16
32.07
27.16
19.54
14.28
8.96
CDCl3, 150 MHz
O
TBDPSO
260
f1 (ppm)


7.26
4.16
4.15
4.14
4.13
3.44
2.45
2.43
2.43
2.43
2.41
2.41
1.90
1.86
1.61
1.25
0.95
0.93
0.91
0.89
0.87
0.85
CDCl3, 600 MHz
O
OH
LAI-1 (256)
0.9
0.8
1.9
1.0
3.0
16.2
2.8
2.9
f1 (ppm)


212.58
77.48
77.30
77.16
76.84
38.03
29.73
29.47
26.90
22.83
14.26
9.02
CDCl3, 100 MHz
O
OH
LAI-1 (256)
f1 (ppm)

22.5. Single-Crystal X-Ray Analysis

All single-crystal X-ray analyses were carried out by P. Mayer and Prof. Karaghiosoff in the analytic department.

22.5.1. Single-Crystal X-Ray Analysis of Compound 67

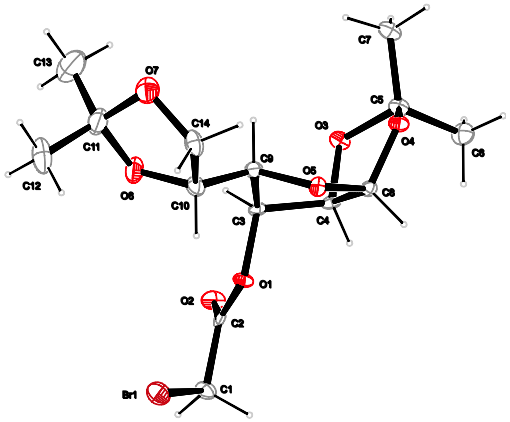


Figure 23. Molecular structure of **67** (one molecule out of the asymmetric unit).

Details are summarized in Table 7 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894249. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 7. Crystallographic data for **67**.

net formula	$C_{14}H_{21}BrO_7$
M_r/g mol^{-1}	381.216
crystal size/mm	0.30 × 0.23 × 0.10
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1$
a/Å	13.1405(5)
b/Å	9.1003(3)
c/Å	14.1366(4)
α/°	90
β/°	97.090(3)
γ/°	90
V/Å^3	1677.56(10)
Z	4
calc. density/g cm^{-3}	1.50942(9)
μ/mm^{-1}	2.480
absorption correction	'multi-scan'

transmission factor range	0.77095–1.00000
refls. measured	6923
R_{int}	0.0251
mean σ(*I*)/*I*	0.0887
θ range	4.24–26.33
observed refls.	3547
x, *y* (weighting scheme)	0.0373, 0
hydrogen refinement	constr
Flack parameter	0.016(9)
refls in refinement	5174
parameters	405
restraints	1
$R(F_{obs})$	0.0397
$R_w(F^2)$	0.0788
S	0.869
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	1.125
min electron density/e Å^{-3}	−0.393

22.5.2. Single-Crystal X-Ray Analysis for Compound 60

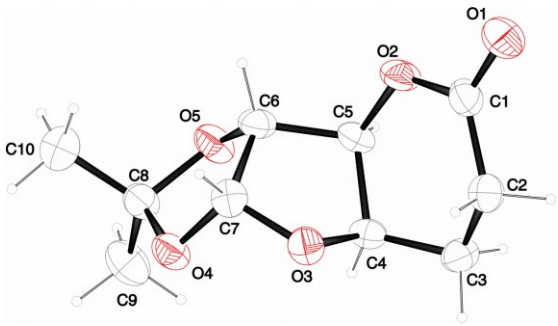


Figure 24. Molecular structure of **60**.

Correct structure derived from synthesis. 1484 Friedel pairs measured. Further details are summarized in Table 8 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894255. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 8. Crystallographic data for **60**.

net formula	$C_{10}H_{14}O_5$
M_r/g mol^{-1}	214.215
crystal size/mm	0.35 × 0.30 × 0.20
T/K	200(2)
radiation	MoKα

diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	7.1089(3)
b/Å	7.2805(3)
c/Å	20.2476(8)
α/°	90
β/°	90
γ/°	90
V/Å^3	1047.94(7)
Z	4
calc. density/g cm^{-3}	1.35778(9)
μ/mm^{-1}	0.109
absorption correction	'multi-scan'
transmission factor range	0.92429–1.00000
refls. measured	15607
R_{int}	0.0313
mean σ(*I*)/*I*	0.0413
θ range	4.13–32.73
observed refls.	2560
x, *y* (weighting scheme)	0.0381, 0
hydrogen refinement	constr
Flack parameter	0.0(7)
refls in refinement	3595
parameters	138
restraints	0
$R(F_{obs})$	0.0339
$R_w(F^2)$	0.0717
S	0.878
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.195
min electron density/e Å^{-3}	−0.156

22.5.3. Single-Crystal X-Ray Analysis for Compound 71

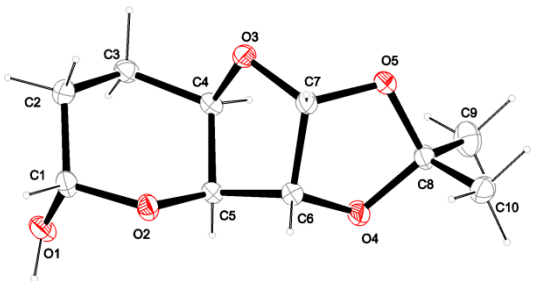


Figure 25. Molecular structure of **71**.

Flack parameter meaningless, absolute structure deduced from synthesis. Further details are summarized in Table 9 and are available from the Crystallographic Data Centre under the

depository numbers CCDC 894251. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 9. Crystallographic data for **71**.

net formula	$C_{10}H_{16}O_5$
M_r/g mol^{-1}	216.231
crystal size/mm	0.27 × 0.22 × 0.17
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	triclinic
space group	*P*1
a/Å	6.0447(3)
b/Å	6.9522(4)
c/Å	7.2801(5)
α/°	72.905(4)
β/°	71.641(3)
γ/°	69.728(4)
V/Å^3	266.45(3)
Z	1
calc. density/g cm^{-3}	1.34759(15)
μ/mm^{-1}	0.108
absorption correction	none
refls. measured	2259
R_{int}	0.0000
mean σ(*I*)/*I*	0.0381
θ range	3.70–27.42
observed refls.	2158
x, y (weighting scheme)	0.0661, 0.0301
hydrogen refinement	constr
Flack parameter	0.6(8)
refls in refinement	2259
parameters	139
restraints	3
$R(F_{obs})$	0.0387
$R_w(F^2)$	0.1066
S	1.059
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.288
min electron density/e Å^{-3}	−0.201

22.5.4. Single-Crystal X-Ray Analysis for Compound 72

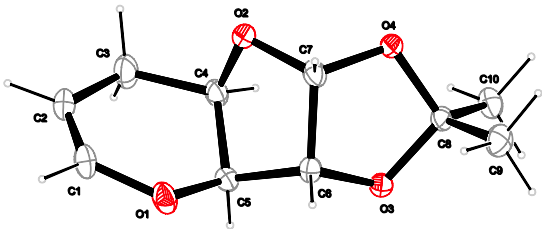


Figure 26. Molecular structure of **72**.

Flack parameter meaningless, absolute structure deduced from synthesis. Further details are summarized in Table 10 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894252. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 10. Crystallographic data for **72**.

net formula	$C_{10}H_{14}O_4$
M_r/g mol^{-1}	198.216
crystal size/mm	0.38 × 0.21 × 0.07
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1$
a/Å	8.4976(5)
b/Å	5.2988(3)
c/Å	11.0339(7)
α/°	90
β/°	93.476(5)
γ/°	90
V/Å^3	495.91(5)
Z	2
calc. density/g cm^{-3}	1.32746(13)
μ/mm^{-1}	0.102
absorption correction	'multi-scan'
transmission factor range	0.90715–1.00000
refls. measured	3177
R_{int}	0.0191
mean σ(*I*)/*I*	0.0456
θ range	4.27–26.33
observed refls.	1430
x, *y* (weighting scheme)	0.0261, 0
hydrogen refinement	constr
Flack parameter	−1.0(10)

refls in refinement	1841
parameters	129
restraints	1
$R(F_{obs})$	0.0330
$R_w(F^2)$	0.0620
S	0.957
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.125
min electron density/e Å^{-3}	−0.151

22.5.5. Single-Crystal X-Ray Analysis for Compound 74

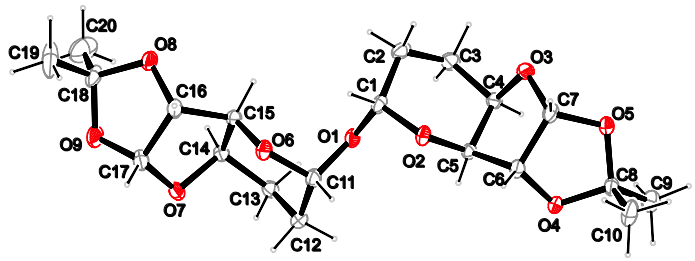


Figure 27. Molecular structure of **74**.

Flack parameter meaningless, absolute structure deduced from synthesis. 5956 Friedel pairs merged. Further details are summarized in Table 11 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894250. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 11. Crystallographic data for **74**.

net formula	$C_{20}H_{30}O_9$
M_r/g mol^{-1}	414.447
crystal size/mm	0.47 × 0.35 × 0.26
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1$
a/Å	10.7518(3)
b/Å	17.8960(6)
c/Å	16.0933(4)
α/°	90
β/°	90.165(2)
γ/°	90
V/Å^3	3096.57(16)
Z	6

calc. density/g cm^{-3}	1.33350(7)
μ/mm^{-1}	0.105
absorption correction	'multi-scan'
transmission factor range	0.99210–1.00000
refls. measured	23608
R_{int}	0.0301
mean σ(*I*)/*I*	0.0440
θ range	4.24–26.33
observed refls.	4858
x, y (weighting scheme)	0.0311, 0
hydrogen refinement	constr
Flack parameter	0.1(5)
refls in refinement	6461
parameters	796
restraints	1
$R(F_{obs})$	0.0289
$R_w(F^2)$	0.0554
S	0.878
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.148
min electron density/e Å^{-3}	−0.132

22.5.6. Single-Crystal X-Ray Analysis for Compound 86

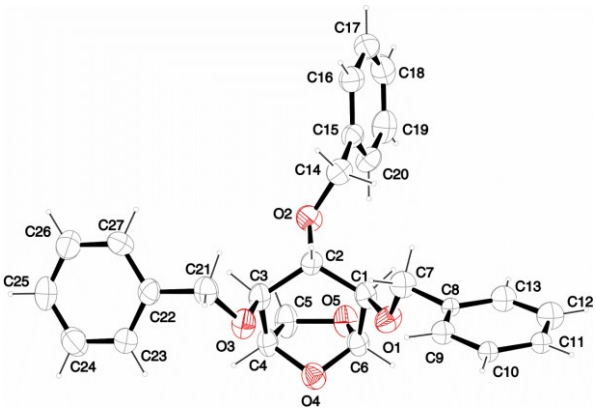


Figure 28. Molecular structure of **86**.

1908 Friedel pairs measured. Correct structure derived from synthesis. One benzyl group is disordered, split model applied, sof ratio 0.51/0.49. Only one of the disordered parts is shown in the figure. Further details are summarized in Table 12 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894257. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 12. Crystallographic data for **86**.

net formula	$C_{27}H_{28}O_5$
M_r/g mol^{-1}	432.508
crystal size/mm	0.40 × 0.10 × 0.05
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1$
a/Å	10.6997(6)
b/Å	9.6647(7)
c/Å	10.9106(6)
α/°	90
β/°	91.772(5)
γ/°	90
V/Å^3	1127.72(12)
Z	2
calc. density/g cm^{-3}	1.27373(14)
μ/mm^{-1}	0.087
absorption correction	'multi-scan'
transmission factor range	0.84473–1.00000
refls. measured	13363
R_{int}	0.0666
mean σ(*I*)/*I*	0.1042
θ range	4.19–25.25
observed refls.	2329
x, *y* (weighting scheme)	0.0238, 0
hydrogen refinement	constr
Flack parameter	−0.4(10)
refls in refinement	4072
parameters	283
restraints	1
$R(F_{obs})$	0.0400
$R_w(F^2)$	0.0700
S	0.782
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.160
min electron density/e Å^{-3}	−0.136

22.5.7. Single-Crystal X-Ray Analysis for Compound 98

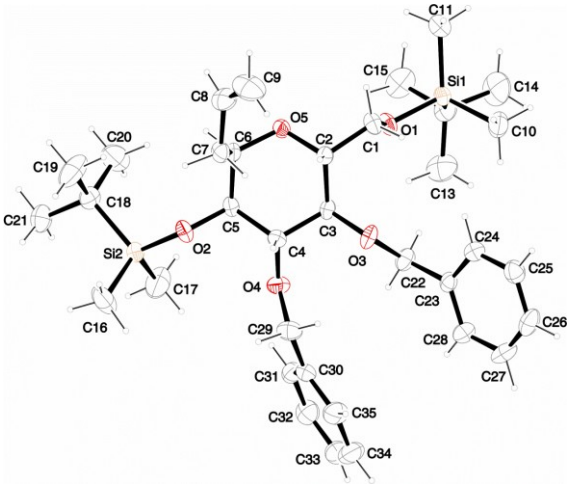


Figure 29. Molecular structure of **98**.

5111 Friedel pairs measured. Further details are summarized in Table 13 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894256. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 13. Crystallographic data for **98**.

net formula	$C_{35}H_{56}O_5Si_2$
M_r/g mol^{-1}	612.987
crystal size/mm	0.45 × 0.20 × 0.10
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	8.7850(3)
b/Å	10.6361(4)
c/Å	38.7310(19)
α/°	90
β/°	90
γ/°	90
V/Å^3	3619.0(3)
Z	4
calc. density/g cm^{-3}	1.12507(9)
μ/mm^{-1}	0.135
absorption correction	'multi-scan'
transmission factor range	0.86410–1.00000
refls. measured	43906
R_{int}	0.0651

mean σ(*I*)/*I*	0.0872
θ range	4.14–32.41
observed refls.	7653
x, *y* (weighting scheme)	0.0453, 0
hydrogen refinement	constr
Flack parameter	−0.05(8)
refls in refinement	11978
parameters	390
restraints	0
$R(F_{obs})$	0.0509
$R_w(F^2)$	0.1001
S	0.928
$shift/error_{max}$	0.001
max electron density/e $Å^{-3}$	0.328
min electron density/e $Å^{-3}$	−0.237

22.5.8. Single-Crystal X-Ray Analysis for Compound 123

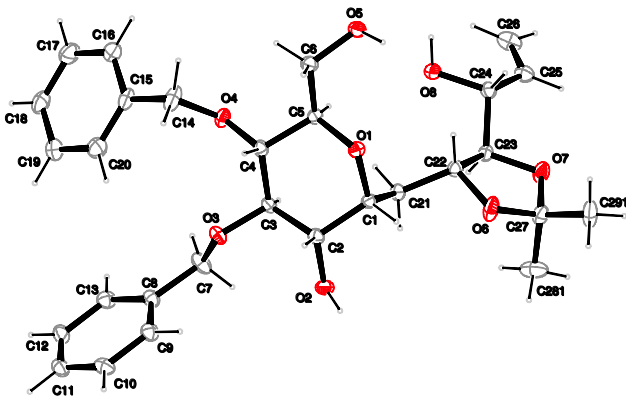


Figure 30. Molecular structure of **123**.

Methyl groups disordered, split model applied, sof ratio 0.25/0.75. Further details are summarized in Table 14 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894253. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 14. Crystallographic data for **123**.

net formula	$C_{29}H_{38}O_8$
M_r/g mol^{-1}	514.607
crystal size/mm	0.30 × 0.09 × 0.04
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'

crystal system	monoclinic
space group	$P2_1$
a/Å	14.6591(6)
b/Å	5.2307(2)
c/Å	18.5204(8)
α/°	90
β/°	105.576(2)
γ/°	90
V/Å^3	1367.94(10)
Z	2
calc. density/g cm^{-3}	1.24938(9)
μ/mm^{-1}	0.090
absorption correction	none
refls. measured	9302
R_{int}	0.0684
mean σ(*I*)/*I*	0.0858
θ range	3.16–25.33
observed refls.	3634
x, *y* (weighting scheme)	0.0356, 0.1295
hydrogen refinement	constr
Flack parameter	−0.1(11)
refls in refinement	4873
parameters	360
restraints	1
$R(F_{obs})$	0.0484
$R_w(F^2)$	0.1048
S	1.055
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.200
min electron density/e Å^{-3}	−0.206

22.5.9. Single-Crystal X-Ray Analysis for Compound 120

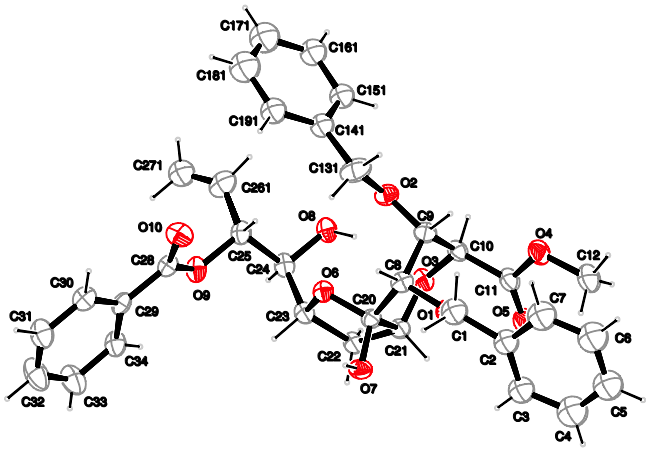


Figure 31. Molecular structure of **120** (of the disordered parts only the main components are shown).

The data collection was performed on a Nonius KappaCCD diffractometer equipped with a rotating anode generator at 173 K using MoKα-radiation (λ = 0.71073 Å, graded multilayer X-ray optics). The structure was solved by direct methods with SIR97[144] and refined by least-squares methods against F^2 with SHELXL-97.[145] The disorder of the benzyl group, a phenyl ring and the ethyl group has been handled by split models. All non-disordered non-hydrogen atoms were refined anisotropically, all disordered atoms have been refined isotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in Table 15 and are available from the Crystallographic Data Centre under the depository numbers CCDC 859056. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 15. Crystallographic data for **120**.

net formula	$C_{34}H_{36}O_{10}$
M_r/g mol^{-1}	604.644
crystal size/mm	0.38 × 0.14 × 0.12
crystal system	tetragonal
space group	$P4_3$
a/Å	13.3203(3)
b/Å	13.3203(3)
c/Å	18.4658(3)
α/°	90
β/°	90
γ/°	90
V/Å^3	3276.39(11)
Z	4
calc. density/g cm^{-3}	1.22580(4)
μ/mm^{-1}	0.090
absorption correction	none
refls. measured	20777
R_{int}	0.0395
mean σ(*I*)/*I*	0.0338
θ range	3.25–25.32
observed refls.	4680
x, *y* (weighting scheme)	0.0961, 1.1933
hydrogen refinement	constr
Flack parameter	0.5(13)
refls in refinement	5911
parameters	360
restraints	2
$R(F_{obs})$	0.0606
$R_w(F^2)$	0.1727
S	1.021
shift/error$_{max}$	0.004
max electron density/e Å^{-3}	0.309
min electron density/e Å^{-3}	−0.205

22.5.10. Single-Crystal X-Ray Analysis for Compound 142

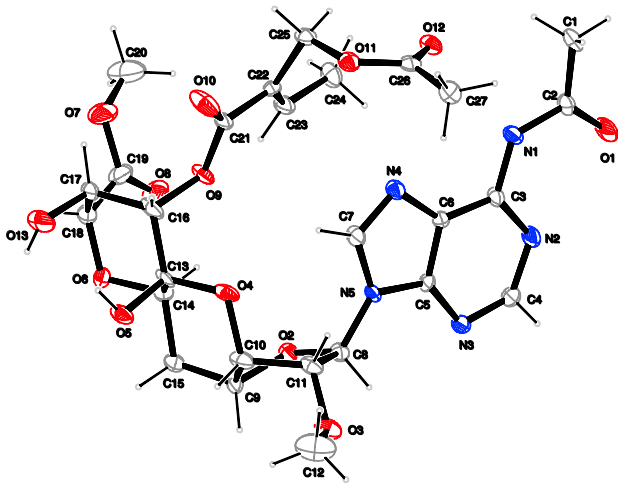


Figure 32. Molecular structure of **142**.

Disordered chloroform molecules have been fixed to a sof of 0.25 each. Further details are summarized in Table 16 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894254. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 16. Crystallographic data for **142**.

net formula	$C_{29.25}H_{34.25}Cl_{6.75}N_5O_{13}$
M_r/g mol^{-1}	903.167
crystal size/mm	0.28 × 0.051 × 0.048
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	triclinic
space group	*P*1
a/Å	9.0009(3)
b/Å	13.4703(5)
c/Å	18.7290(5)
α/°	105.394(2)
β/°	98.332(2)
γ/°	102.3890(10)
V/Å^3	2088.63(12)
Z	2
calc. density/g cm^{-3}	1.43612(8)
μ/mm^{-1}	0.522
absorption correction	none
refls. measured	14383
R_{int}	0.0000

mean σ(*I*)/*I*	0.0638
θ range	3.21–25.29
observed refls.	8947
x, *y* (weighting scheme)	0.1928, 2.7333
hydrogen refinement	constr
Flack parameter	0.07(12)
refls in refinement	14383
parameters	1000
restraints	9
$R(F_{obs})$	0.0987
$R_w(F^2)$	0.3140
S	1.029
$shift/error_{max}$	0.001
max electron density/e $Å^{-3}$	1.325
min electron density/e $Å^{-3}$	−0.567

22.5.11. Single-Crystal X-Ray Analysis for Compound 191

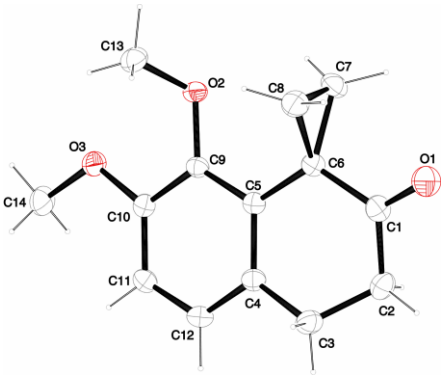


Figure 33. Molecular structure of **191**.

Details are summarized in Table 17 and are available from the Crystallographic Data Centre under the depository numbers CCDC 893995. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 17. Crystallographic data for **191**.

net formula	$C_{14}H_{16}O_3$
M_r/g mol^{-1}	232.275
crystal size/mm	0.38 × 0.20 × 0.17
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar

a/Å	8.2043(10)
b/Å	8.9981(11)
c/Å	9.7491(12)
α/°	64.913(12)
β/°	70.609(11)
γ/°	66.139(12)
V/Å^3	584.81(13)
Z	2
calc. density/g cm^{-3}	1.3191(3)
μ/mm^{-1}	0.092
absorption correction	'multi-scan'
transmission factor range	0.82941–1.00000
refls. measured	3141
R_{int}	0.0264
mean σ(*I*)/*I*	0.0429
θ range	4.34–26.37
observed refls.	1931
x, y (weighting scheme)	0.0613, 0.1358
hydrogen refinement	constr
refls in refinement	2345
parameters	156
restraints	0
$R(F_{obs})$	0.0496
$R_w(F^2)$	0.1369
S	1.062
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.248
min electron density/e Å^{-3}	−0.226

22.5.12. Single-Crystal X-Ray Analysis for Compound 237

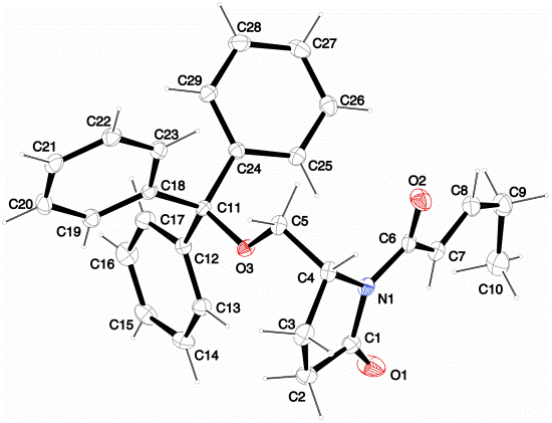


Figure 34. Molecular structure of **237**.

Flack parameter meaningless, correct structure deduced from synthesis. Further details are summarized in Table 18 and are available from the Crystallographic Data Centre under the

depository numbers CCDC 894000. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

Table 18. Crystallographic data for **237**.

net formula	$C_{29}H_{29}NO_3$
M_r/g mol^{-1}	439.546
crystal size/mm	0.28 × 0.19 × 0.12
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1
a/Å	6.9353(7)
b/Å	9.0952(19)
c/Å	10.104(2)
α/°	76.081(18)
β/°	77.509(13)
γ/°	71.231(15)
V/Å^3	579.00(18)
Z	1
calc. density/g cm^{-3}	1.2606(4)
μ/mm^{-1}	0.081
absorption correction	'multi-scan'
transmission factor range	0.92857–1.00000
refls. measured	3203
R_{int}	0.0369
mean σ(*I*)/*I*	0.0433
θ range	4.43–26.37
observed refls.	2617
x, y (weighting scheme)	0.0623, 0.0058
hydrogen refinement	constr
Flack parameter	1.0(12)
refls in refinement	2792
parameters	299
restraints	3
$R(F_{obs})$	0.0371
$R_w(F^2)$	0.1016
S	1.062
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.163
min electron density/e Å^{-3}	−0.177

22.5.13. Single-Crystal X-Ray Analysis for Compound 238

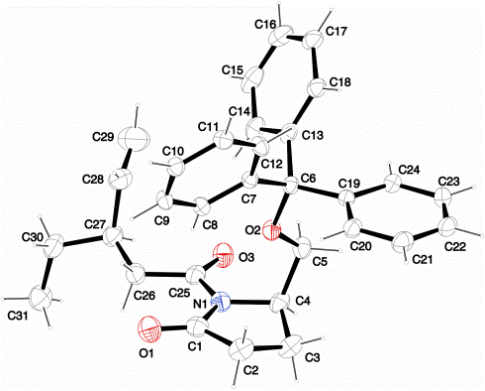


Figure 35. Molecular structure of **238**.

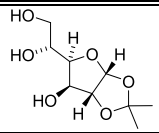
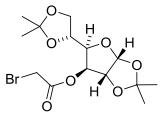
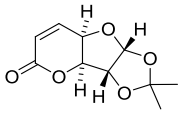
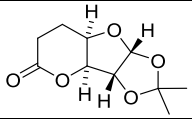
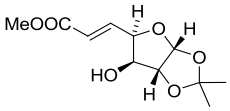
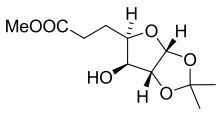
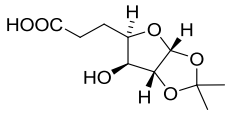
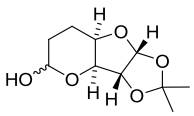
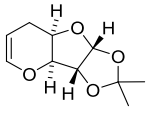
Absolute structure deduced from synthesis. Further details are summarized in Table 19 and are available from the Crystallographic Data Centre under the depository numbers CCDC 894001. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.

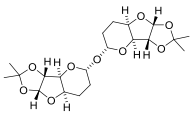
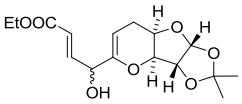
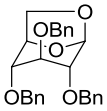
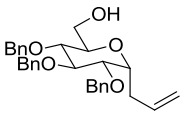
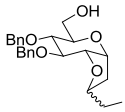
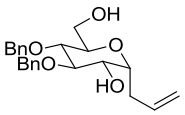
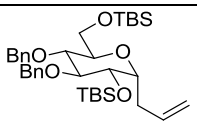
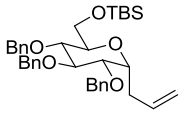
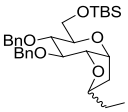
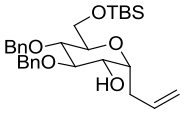
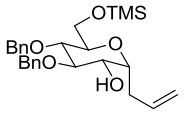
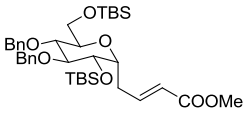
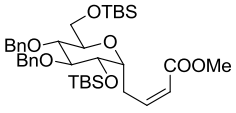
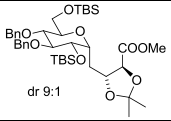
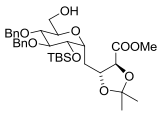
Table 19. Crystallographic data for **23**.

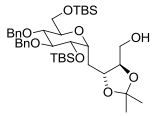
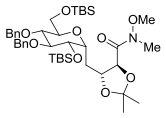
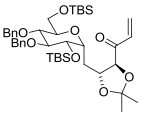
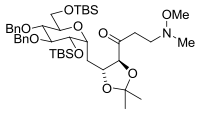
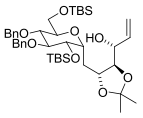
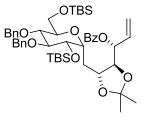
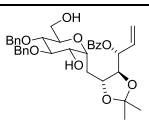
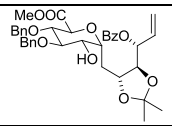
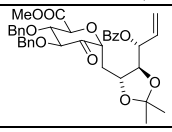
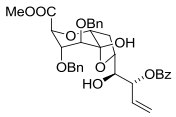
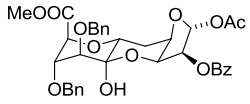
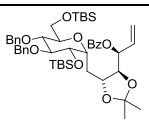
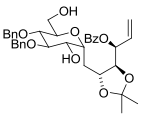
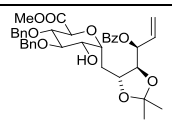
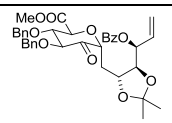
net formula	$C_{31}H_{33}NO_3$
M_r/g mol^{-1}	467.599
crystal size/mm	0.23 × 0.07 × 0.04
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1$
a/Å	9.1381(5)
b/Å	14.9979(5)
c/Å	9.6298(4)
α/°	90
β/°	106.100(2)
γ/°	90
V/Å^3	1268.02(10)
Z	2
calc. density/g cm^{-3}	1.22471(10)
μ/mm^{-1}	0.078
absorption correction	none
refls. measured	8252
R_{int}	0.0356
mean σ(I)/I	0.0545
θ range	3.50–25.37
observed refls.	3483
x, y (weighting scheme)	0.0614, 0.0936

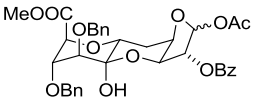
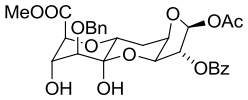
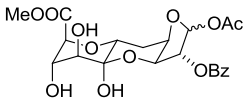
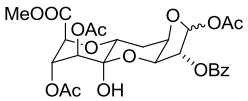
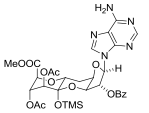
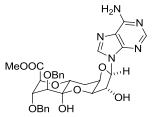
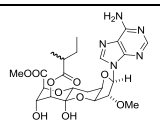
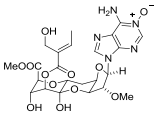
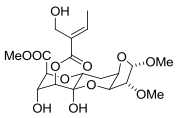
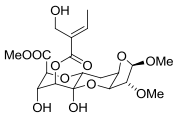
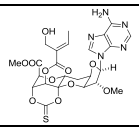
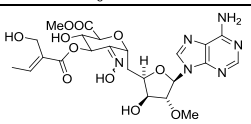
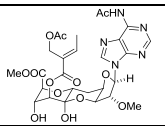
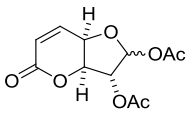
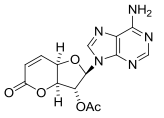
hydrogen refinement	constr
Flack parameter	2.3(14)
refls in refinement	4486
parameters	317
restraints	1
$R(F_{obs})$	0.0469
$R_w(F^2)$	0.1195
S	1.028
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.187
min electron density/e Å^{-3}	−0.217

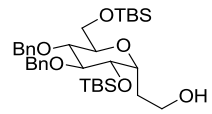
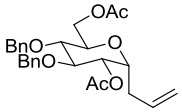
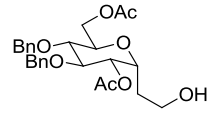
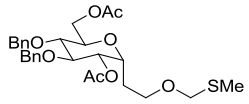
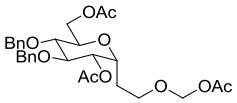
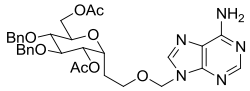
22.6. Compounds Sent to Bayer CropScience AG for SAR Study

Verbindung	Supplier ID:	Vial number:	Amount:	Purity:
	MR10	015001552076	16.11 mg	99% (by NMR)
	DH01	015001552063	11.80 mg	99% (by NMR)
	DH16	015001552039	10.34 mg	>99% (NMR clean)
	DH15	015001552040	10.15 mg	>99% (NMR clean)
	DH29C_B_C	015001552038	13.43 mg	>99% (NMR clean)
	MR26	015001552052	11.83 mg	>99% (NMR clean)
	DH136RP	015001552051	11.00 mg	99% (by NMR)
	DH65I	015001552050	10.48 mg	99% (by NMR)
	DH88A	015001552088	10.77 mg	99% (by NMR)

	DH65_2A	015001552050	11.53 mg	99% (by NMR)
	DH183A	015001552048	45.32 mg	95% (by NMR)
	DH167C_FS	015001552037	10.86 mg	99% (by NMR)
	DH175A_A_A	015001552062	8.90 mg	99% (by NMR)
	DH238_An	015001552100	13.70 mg	>99% (by NMR)
	DH191A_2	015001552074	8.70 mg	99% (by NMR)
	DH194A_2	015001552073	10.45 mg	98% (by NMR)
	DH177A	015001552075	12.61 mg	>99% (by NMR)
	DH186A	015001552049	12.20 mg	98% (by NMR)
	DH188B	015001552060	15.87 mg	99% (by NMR)
	DH239A_A	015001552098	17.60 mg	>99% (by NMR)
	DH198A	015001552086	19.58 mg	99% (by NMR)
	DH242B_A_A	015001552059	9.33 mg	99% (by NMR)
	DH253A	015001552034	7.92 mg	98% (by NMR)
	DH244B_A	015001552099	7.60 mg	98% (by NMR)

	DH264C	015001552047	10.20 mg	>99% (by NMR)
	DH357C	015001552084	9.36 mg	99% (by NMR)
	DH358A	015001552030	10.04 mg	99% (by NMR)
	DH401B_A	015001552029	13.65 mg	>99% (by NMR)
	DH290A-D	015001552033	7.27 mg	97% (by NMR)
	DH291A DH530B	015001552085 015001552044	7.12 mg 17.45 mg	99% (by NMR) >99% (by NMR)
	DH288AB_B	015001552072	5.70 mg	97% (by NMR)
	DH389A_A	015001552071	10.65 mg	99% (by NMR)
	DH388A	015001552058	9.76 mg	99% (by NMR)
	DH431A_F1	015001552042	13.77 mg	>99% (by NMR)
	DH444A	015001552054	8.92 mg	99% (by NMR)
	DH447A	015001552065	10.19 mg	>99% (by NMR)
	DH450B	015001552089	11.32 mg	>99% (by NMR)
	DH453A	015001552043	10.96 mg	99% (by NMR)
	DH454A	015001552101	9.67 mg	98% (by NMR)

	DH499B	015001552113	9.33 mg	99% (by NMR)
	monoBn MIX_F2	015001552045	9.92 mg	98% (by NMR)
	DH541B	015001552066	10.22 mg	95% (by NMR)
	DH542A	015001552114	10.45 mg	98% (by NMR)
	DH544A	015001552102	10.84 mg	99% (by NMR)
	DH554A_F1	015001552055	14.47 mg	99% (by NMR)
	GS28A_F1	015001552069	11.00 mg	98% (by NMR)
	GS37A_F1	015001552083	10.44 mg	98% (by NMR)
	DH152A_A1	015001552035	6.99 mg	99% (by NMR)
	DH152A_A2	015001552036	17.80 mg	99% (by NMR)
	DH573A GS02A DWT-19A_A	015001552070 015001552097 015001552068	9.00 mg 20.20 mg 10.53 mg	99% (by NMR) 99% (by NMR) 99% (by NMR)
	DH417B_F1	015001552041	9.69 mg	98% (by NMR)
	DH446A	015001552077	10.24 mg	97% (by NMR)
	MH06A	015001552046	7.17 mg	>99% (by NMR)
	MH19B	015001552032	7.30 mg	98% (by NMR)

	FF12B_A	015001552031	14.45 mg	>99% (by NMR)
	SL30B	015001552078	11.37 mg	>99% (by NMR)
	SL34B	015001552090	10.12 mg	>99% (by NMR)
	SL44	015001552056	10.33 mg	>99% (by NMR)
	SL49A	015001552057	10.35 mg	99% (by NMR)
	SL54	015001552067	15.13 mg	>99% (by NMR)

23. Literature

[1] S. Knapp, *Chem. Rev.* **1995**, *95*, 1859–1876.

[2] a) S. Ichikawa, *Chem. Pharm. Bull.* **2008**, *56*, 1059–1072; b) S. Ichikawa, A. Matsuda, *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 319–329.

[3] a) H. M. Binch, A. M. Griffin, T. Gallagher, *Pure Appl. Chem.* **1996**, *68*, 589–592; b) H. M. Binch, T. Gallagher, *J. Chem. Soc., Perkin Trans. 1* **1996**, 401–402; c) H. M. Binch, A. M. Griffin, S. Schwidetzky, M. V. J. Ramsay, T. Gallagher, F. W. Lichtenthaler, *J. Chem. Soc., Chem. Commun.* **1995**, 967–968; d) P. J. Cox, A. M. Griffin, N. J. Newcombe, S. Lister, M. V. J. Ramsay, D. Alker, T. Gallagher, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1443–1447; e) N. J. Newcombe, M. F. Mahon, K. C. Molloy, D. Alker, T. Gallagher, *J. Am. Chem. Soc.* **1993**, *115*, 6430–6431; f) P. Cox, M. F. Mahon, K. C. Molloy, S. Lister, T. Gallagher, *Tetrahedron Lett.* **1988**, *29*, 1993–1996.

[4] a) J. R. Bearder, M. L. Dewis, D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1* **1995**, 227–233; b) J. R. Bearder, M. L. Dewis, D. A. Whiting, *Synlett* **1993**, 805–806.

[5] A. H. Haines, A. J. Lamb, *Carbohydr. Res.* **1999**, *321*, 197–213.

[6] A. J. Fairbanks, E. Perrin, P. Sinaÿ, *Synlett* **1996**, 679–681.

[7] a) F. Emery, P. Vogel, *J. Org. Chem.* **1995**, *60*, 5843–5854; b) F. Emery, P. Vogel, *Tetrahedron Lett.* **1993**, *34*, 4209–4212.

[8] S. Ichikawa, S. Shuto, A. Matsuda, *J. Am. Chem. Soc.* **1999**, *121*, 10270–10280.

[9] R. B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, second ed., Elsevier Academic Press, Amsterdam, **2004**.

[10] D. Hager, P. Mayer, C. Paulitz, J. Tiebes, D. Trauner, *Angew. Chem. Int. Ed.* **2012**, *51*, 6525–6528.

[11] T. Taga, N. Akimoto, T. Ibuka, *Chem. Pharm. Bull.* **1984**, *32*, 4223–4225.

[12] D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319.

[13] a) D. A. Evans, C. Bryan, G. Wahl, *J. Org. Chem.* **1970**, *35*, 4122–4127; b) D. A. Evans, *J. Am. Chem. Soc.* **1970**, *92*, 7593–7595; c) S. L. Keely Jr, A. J. Martinez, F. C. Tahk, *Tetrahedron* **1970**, *26*, 4729–4742.

[14] L. Ding, A. Maier, H.-H. Fiebig, H. Görls, W.-H. Lin, G. Peschel, C. Hertweck, *Angew. Chem. Int. Ed.* **2011**, *50*, 1630–1634.

[15] a) F. Honcamp, *Handbuch der Pflanzenernährung und Düngerlehre, Vol. 1*, Springer, Berlin, **1931**; b) F. Honcamp, *Handbuch der Pflanzenernährung und Düngerlehre, Vol. 2*, Springer, Berlin, **1931**.

[16] a) J. H. Voss, *Homers Odysee*, fourth ed., J. G. Cotta'sche Buchhandlung, Stuttgart, **1814**; b) S. Butler, *The Odyssey*, Jonathan Cape, London, **1922**.

[17] a) A. Thaer, *Grundsätze der Rationellen Landwirtschaft*, Realschulbuchhandlung, Berlin, **1809**; b) A. Thaer, *Annalen der Fortschritte der Landwirtschaft in Theorie und Praxis*, Realschulbuchhandlung, Berlin, **1811**.

[18] a) J. Liebig, *Chemistry in its Application to Agriculture and Physiology*, T. B. Peterson, Philadelphia, **1847**; b) A. Vogel, *Zur Geschichte der Liebig'schen Mineraltheorie*, C. G. Lüderitz'sche Vertragsbuchhandlung Carl Habel, Berlin, **1883**.

[19] A. Finck, *Dünger und Düngung: Grundlagen und Anleitung zur Düngung der Kulturpflanzen*, second ed., Wiley-VCH, Weinheim, **1992**.

[20] a) F. Müller, A. P. Appleby, in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 39*, Wiley-VCH, Weinheim, **2000**, pp. 173–208; b) F. Müller, A. P. Appleby, in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 39*, Wiley-VCH, Weinheim, **2000**, pp. 209–385.

[21] G. E. Peterson, *Agricultural History* **1967**, *41*, 243–254.

[22] J. H. Quastel, in *Agricultural Control Chemicals, Vol. 1*, American Chemical Society, Washington, D.C., **1950**, pp. 244–249.

[23] a) IOM, *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, National Academic Press, Washington D.C., **1994**; b) A. L. Young, *The History, Use, Disposition and Enviromental Fate of Agent Orange*, Springer, New York, **2009**.
[24] a) S. O. Duke, *Environ. Health Perspect.* **1990**, *87*, 263–271; b) T. Seitz, M. G. Hoffmann, H. Krähmer, *Chem. unserer Zeit* **2003**, *37*, 112–126.
[25] G. Gunkel, B. Streit, *Water Res.* **1980**, *14*, 1573–1584.
[26] A. L. Cerdeira, S. O. Duke, *J. Environ. Qual.* **2006**, *35*, 1633–1658.
[27] J. M. Berg, J. L. Tymoczko, L. Stryer, *Biochemie*, fifth ed., Spektrum, Berlin, **2003**.
[28] a) S. O. Duke, S. B. Powles, *Pest Manag. Sci.* **2008**, *64*, 319–325; b) K.-H. König, *Chem. unserer Zeit* **1990**, *24*, 217–226; c) K.-H. König, *Chem. unserer Zeit* **1990**, *24*, 292–302.
[29] C. L. Cantrell, F. E. Dayan, S. O. Duke, *J. Nat. Prod.* **2012**, *75*, 1231–1242.
[30] a) M. Arai, T. Haneishi, N. Kitahara, R. Enokita, K. Kawakubo, Y. Kondo, *J. Antibiot.* **1976**, *29*, 863–869; b) T. Haneishi, A. Terahara, H. Kayamori, J. Yabe, M. Arai, *J. Antibiot.* **1976**, *29*, 870–875; c) Y. Takiguchi, H. Yoshikawa, A. Terahara, A. Torikata, M. Terao, *J. Antibiot.* **1979**, *32*, 857–861; d) Y. Takiguchi, H. Yoshikawa, A. Terahara, A. Torikata, M. Terao, *J. Antibiot.* **1979**, *32*, 862–867; e) A. Terahara, T. Haneishi, M. Arai, T. Hata, H. Kuwano, C. Tamura, *J. Antibiot.* **1982**, *35*, 1711–1714; f) H. Yoshikawa, Y. Takiguchi, M. Terao, *J. Antibiot.* **1983**, *36*, 30–35; g) M. Tsuzuki, G. Suzuki, *Chem. Abstr.* **1988**, *109*, 53206x; h) X. Dai, G. Li, Z. Wu, D. Lu, H. Wang, Z. Li, L. Zhou, X. Chen, W. Chen, *Chem. Abstr.* **1989**, *111*, 230661f; i) M. Kizuka, R. Enokita, K. Takahashi, Y. Okamoto, T. Otsuka, Y. Shigematsu, Y. Inoue, T. Okazaki, *Actinomycetol.* **1998**, *12*, 89–91.
[31] a) S. Shuto, S. Ichikawa, A. Matsuda, *Nucleic Acids Symp. Ser.* **1999**, 21–22; b) S. Ichikawa, *J. Pharm. Soc. Jpn.* **2006**, *126*, 579–595.
[32] S.-I. Nishimura, S. Nomura, K. Yamada, *Chem. Commun.* **1998**, 617–618.
[33] J. Yano, L.-S. Kan, P. O. P. Ts'o, *Biochim. Biophys. Acta* **1980**, *629*, 178–183.
[34] M. Bessodes, R. Benamghar, K. Antonakis, *Carbohydr. Res.* **1990**, *200*, 493–496.
[35] S. Jana, S. C. Roy, *Indian J. Chem., Sect B* **2007**, *46*, 707–709.
[36] F. Sartillo-Piscil, M. Vargas, C. Anaya de Parrodi, L. Quintero, *Tetrahedron Lett.* **2003**, *44*, 3919–3921.
[37] a) P. Lesimple, J.-M. Beau, G. Jaurand, P. Sinaÿ, *Tetrahedron Lett.* **1986**, *27*, 6201–6204; b) R. K. Boeckman, K. J. Bruza, *Tetrahedron Lett.* **1977**, 4187–4190; c) R. K. Boeckman, K. J. Bruza, *Tetrahedron* **1981**, *37*, 3997–4006.
[38] a) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965; b) H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99–103; c) G.-L. Zhao, I. Ibrahem, H. Sundén, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1210–1224.
[39] M. A. Zottola, R. Alonso, G. D. Vite, B. Fraser-Reid, *J. Org. Chem.* **1989**, *54*, 6123–6125.
[40] J. P. McDevitt, P. T. Lansbury, *J. Am. Chem. Soc.* **1996**, *118*, 3818–3828.
[41] a) A. Hosomi, Y. Sakata, H. Sakurai, *Tetrahedron Lett.* **1984**, *25*, 2383–2386; b) S. C. Hung, C. C. Lin, C. H. Wong, *Tetrahedron Lett.* **1997**, *38*, 5419–5422; c) J. Xie, *Eur. J. Org. Chem.* **2002**, 3411–3418.
[42] M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
[43] A. Hosomi, Y. Sakata, H. Sakurai, *Carbohydr. Res.* **1987**, *171*, 223–232.
[44] D. Nasipuri, *Stereochemistry of Organic Compunds: Principles and Applications*, first ed., Wiley-VCH, New York, **1991**.
[45] a) L. Cipolla, L. Lay, F. Nicotra, *J. Org. Chem.* **1997**, *62*, 6678–6681; b) F. Nicotra, L. Panza, G. Russo, *J. Org. Chem.* **1987**, *52*, 5627–5630; c) S. D. Rychnovsky, P. A. Bartlett, *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964.
[46] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390–2392.

[47] a) M. S. M. Timmer, M. V. Chumillas, W. E. Donker-Koopman, J. Alerts, G. A. van der Marel, H. S. Overkleeft, J. H. van Boom, *J. Carbohydr. Chem.* **2005**, *24*, 335–351; b) A. K. Chatterjee, T. L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
[48] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Amsterdam, **2005**.
[49] J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, **2001**.
[50] H. Vorbrüggen, C. Ruh-Pohlenz, *Handbook of Nucleoside Synthesis*, second ed., John Wiley & Sons, New York, **2001**.
[51] A. A. Koshkin, J. Fensholdt, H. M. Pfundheller, C. Lomholt, *J. Org. Chem.* **2001**, *66*, 8504-8512.
[52] S. Knapp, S. R. Nandan, *J. Org. Chem.* **1994**, *59*, 281–283.
[53] a) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, fourth ed., Blackwell Publishing Company, Oxford, **2000**; b) M. A. Stevens, D. I. Magrath, H. W. Smith, G. B. Brown, *J. Am. Chem. Soc.* **1958**, *80*, 2755–2758; c) A. Giner-Sorolla, C. Gryte, M. L. Cox, J. C. Parham, *J. Org. Chem.* **1971**, *36*, 1228–1232.
[54] A. Hager, PhD thesis, Department Chemie, LMU München, 2012
[55] G. A. Cordell, *The Alkaloids, Vol. 52*, Elsevier Academic Press, London, **1998**.
[56] M. Hesse, *Alkaloids: Nature's Curse or Blessing?*, first ed., Wiley-VCH, Weinheim, **2002**.
[57] a) A. W. Hofmann, *Ber. Chem.* **1881**, *14*, 659–669; b) A. W. Hofmann, *Ber. Chem.* **1885**, *18*, 5–23; c) A. Ladenburg, *Ber. Chem.* **1886**, *19*, 439–441.
[58] P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, third ed., Wiley-VCH, Chichester, **2009**.
[59] K. Roth, *Chem. unserer Zeit* **2011**, *45*, 202–218.
[60] B. Schaefer, *Chem. unserer Zeit* **2008**, *42*, 330–344.
[61] A. Hager, D. Hager, photo taken in the botanical garden of LMU München.
[62] P. S. Goltra, photo taken for the 'National Tropical Botanical Garden', www.ntbg.org.
[63] a) G. A. Cordell, M. L. Quinn-Beattie, N. R. Farnsworth, *Phytother. Res.* **2001**, *15*, 183–205; b) M. Wink, in *Studies in natural products chemistry, Vol. 21* (Ed.: A.-u. Rahman), Elsevier Science, Amsterdam, **2000**, pp. 3–122.
[64] J. Frackenpohl, *Chem. unserer Zeit* **2000**, *34*, 99–112.
[65] E. Paszthory, *Chem. unserer Zeit* **1996**, *30*, 96–102.
[66] F. Krömeke, *Friedrich Wil. Sertürner, der Entdecker des Morphiums: Lebensbild und Neudruck der Original-Morphiumarbeiten*, SEVERUS Verlag, Hamburg, **2010**.
[67] a) D. F. Taber, T. D. Neubert, M. F. Schlecht, *ChemInform* **2005**, *36*, 353–389; b) U. Rinner, T. Hudlicky, *Top. Curr. Chem.* **2012**, *309*, 33–66.
[68] J. Giere, this photo is in the public domain in those countries with a copyright term of life of the author plus 100 years or less, www.wikipedia.com.
[69] a) M. Matsui, in *The Alkaloids, Vol. 33* (Ed.: B. Arnold), Academic Press, London, **1988**, pp. 307–347; b) Y. Inubushi, T. Ibuka, in *The Alkaloids, Vol. 16* (Ed.: R. H. F. Manske), Academic Press, London, **1977**, pp. 393–430.
[70] M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui, *Tetrahedron Lett.* **1964**, *5*, 2937–2944.
[71] A. G. Schultz, A. Wang, *J. Am. Chem. Soc.* **1998**, *120*, 8259–8260.
[72] a) K. V. Chuang, R. Navarro, S. E. Reisman, *Angew. Chem. Int. Ed.* **2011**, *50*, 9447–9451; b) S. B. Herzon, N. A. Calandra, S. M. King, *Angew. Chem. Int. Ed.* **2011**, *50*, 8863–8866.
[73] L. He, Y.-H. Zhang, H.-Y. Guan, J.-X. Zhang, Q.-Y. Sun, X.-J. Hao, *J. Nat. Prod.* **2011**, *74*, 181–184.
[74] a) M. Tomita, T. Ibuka, Y. Inubuahi, K. Takeda, *Tetrahedron Lett.* **1964**, *5*, 3605–3616; b) T. Ibuka, K. Tanaka, Y. Inubushi, *Chem. Pharm. Bull.* **1974**, *22*, 907–921; c) T. Ibuka, K. Tanaka, Y. Inubushi, *Tetrahedron Lett.* **1972**, *13*, 1393–1396.

[75] P. Woodard, this photo was made available under the Creative Commons CC0 1.0 Universal Public Domain Dedication, www.wikipedia.com.
[76] K. W. Bentley, *Nat. Prod. Rep.* **2000**, *17*, 247–268.
[77] R. Lenz, M. H. Zenk, *Tetrahedron Lett.* **1994**, *35*, 3897–3900.
[78] a) A. R. Battersby, R. C. F. Jones, R. Kazlauskas, A. P. Ottridge, C. Poupat, J. Staunton, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2010–2015; b) A. R. Battersby, R. C. F. Jones, R. Kazlauskas, C. W. Thornber, S. Ruchirawat, J. Staunton, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2016–2029; c) A. R. Battersby, R. C. F. Jones, A. Minta, A. P. Ottridge, J. Staunton, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2030–2039.
[79] a) T. Curtius, *Ber. Chem.* **1890**, *23*, 3023–3033; b) T. Curtius, *J. Prakt. Chem.* **1894**, *50*, 275–294; c) A. P. Kozikowski, G. Campiani, P. Aagaard, M. McKinney, *J. Chem. Soc., Chem. Commun.* **1993**, 860–862.
[80] a) Q. Ding, Z. Wang, J. Wu, *Tetrahedron Lett.* **2009**, *50*, 198–200; b) T. P. Lebold, A. B. Leduc, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3770–3772; c) A. B. Leduc, T. P. Lebold, M. A. Kerr, *J. Org. Chem.* **2009**, *74*, 8414–8416.
[81] a) G. B. Diamond, M. D. Soffer, *J. Am. Chem. Soc.* **1952**, *74*, 4126–4127; b) M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson, E. A. Bowler, *J. Am. Chem. Soc.* **1950**, *72*, 3704–3709.
[82] M. A. McKervey, S. M. Tuladhar, M. F. Twohig, *J. Chem. Soc., Chem. Commun.* **1984**, 129–130.
[83] Á. Gorka, B. Czuczai, P. Szoleczky, L. Hazai, C. Szántay, V. Háda, *Synth. Commun.* **2005**, *35*, 2371–2378.
[84] E. V. Cabrera, J. L. Sanchez, A. K. Banerjee, *Org. Prep. Proced. Int.* **2011**, *43*, 364–367.
[85] D. Evans, C. Bryan, G. Wahl, *J. Org. Chem.* **1970**, *35*, 4122–4127.
[86] a) S. F. Cruse, J. Lear, C. L. Klein, P. H. Andersen, R. M. Dick, A. M. Crider, *J. Pharm. Sci.* **1993**, *82*, 334–339; b) G. Kavadias, S. Velkof, B. Belleau, *Can. J. Chem.* **1979**, *57*, 1852–1860.
[87] G. Argouarch, O. Samuel, H. B. Kagan, *Eur. J. Org. Chem.* **2000**, 2885–2891.
[88] A. R. Katritzky, A. Denisenko, S. N. Denisenko, M. Arend, *J. Heterocycl. Chem.* **2000**, *37*, 1309–1314.
[89] P. Yates, P. H. Helferty, P. Mahler, *Can. J. Chem.* **1983**, *61*, 78–85.
[90] a) J. J. McNally, M. A. Youngman, T. W. Lovenberg, D. H. Nepomuceno, S. J. Wilson, S. L. Dax, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 213–216; b) T. X. Nguyen, Y. Kobayashi, *J. Org. Chem.* **2008**, *73*, 5536–5541.
[91] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
[92] a) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323–332; b) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.
[93] J. A. Enquist, Jr., B. M. Stoltz, *Nature* **2008**, *453*, 1228–1231.
[94] A. P. Kozikowski, Y. Xia, E. R. Reddy, W. Tuckmantel, I. Hanin, X. C. Tang, *J. Org. Chem.* **1991**, *56*, 4636–4645.
[95] a) H. Will, *"Sei naiv und mach' ein Experiment": Feodor Lynen, Biographie des Münchner Biochemikers und Nobelpreisträgers*, Wiley-VCH, Weinheim, **2011**; b) H. Will, B. Hamprecht, *Angew. Chem. Int. Ed.* **2011**, *50*, 11580–11584.
[96] a) F. Lipmann, N. O. Kaplan, *J. Biol. Chem.* **1946**, *162*, 743–744; b) N. O. Kaplan, F. Lipmann, *J. Biol. Chem.* **1948**, *174*, 37–44.
[97] F. Lynen, E. Reichert, *Angew. Chem.* **1951**, *63*, 47–48.
[98] J. Baddiley, E. M. Thain, G. D. Novelli, F. Lipmann, *Nature* **1953**, *171*, 76–76.
[99] R. N. Dutnall, S. T. Tafrov, R. Sternglanz, V. Ramakrishnan, *Cell* **1998**, *94*, 427–438.
[100] D. O'Hagan, *The Polyketide Metabolites*, first ed., Ellis Horwood, Chichester, **1991**.
[101] a) A. Lüttringhaus, H. Gralheer, *Liebigs Ann. Chem.* **1945**, *557*, 108–112; b) A. Lüttringhaus, H. Gralheer, *Liebigs Ann. Chem.* **1945**, *557*, 112–120; c) A. Lüttringhaus, H. Gralheer, *Liebigs Ann. Chem.* **1942**, *550*, 67–98.

[102] a) V. Prelog, W. Oppolzer, *Helv. Chim. Acta* **1973**, *56*, 2279–2287; b) W. Oppolzer, V. Prelog, *Helv. Chim. Acta* **1973**, *56*, 2287–2314.
[103] Y. Fukuyo, C. R. Hunt, N. Horikoshi, *Cancer Lett.* **2010**, *290*, 24–35.
[104] H. G. Floss, T. W. Yu, *Chem. Rev.* **2005**, *105*, 621–632.
[105] C. E. Stebbins, A. A. Russo, C. Schneider, N. Rosen, F. U. Hartl, N. P. Pavletich, *Cell* **1997**, *89*, 239–250.
[106] B. S. Moore, C. Hertweck, *Nat. Prod. Rep.* **2002**, *19*, 70–99.
[107] Q. Kang, Y. Shen, L. Bai, *Nat. Prod. Rep.* **2012**, *29*, 243–263.
[108] C. A. Kuttruff, S. Geiger, M. Cakmak, P. Mayer, D. Trauner, *Org. Lett.* **2012**, *14*, 1070–1073.
[109] a) L. Han, X. S. Huang, I. Sattler, H. M. Dahse, H. Z. Fu, W. H. Lin, S. Grabley, *J. Nat. Prod.* **2004**, *67*, 1620–1623; b) C. Subrahmanyam, B. V. Rao, R. S. Ward, M. B. Hursthouse, D. E. Hibbs, *Phytochemistry* **1999**, *51*, 83–90; c) S. Misra, A. K. Datta, S. C. A. Choudhury, A. Ghosh, *Phytochemistry* **1987**, *26*, 3265–3268; d) S. Misra, A. Choudhury, A. K. Dutta, A. Ghosh, *Phytochemistry* **1984**, *23*, 2823–2827; e) A. Sarkar, S. N. Ganguly, *Indian J. Chem., Sect B* **1978**, *16*, 742–742.
[110] L. Ding, J. Münch, H. Goerls, A. Maier, H.-H. Fiebig, W.-H. Lin, C. Hertweck, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6685–6687.
[111] H. G. Floss, T.-W. Yu, K. Arakawa, *J. Antibiot.* **2011**, *64*, 35–44.
[112] Y. A. Chan, A. M. Podevels, B. M. Kevany, M. G. Thomas, *Nat. Prod. Rep.* **2009**, *26*, 90–114.
[113] Z. Xu, L. Ding, C. Hertweck, *Angew. Chem. Int. Ed.* **2011**, *50*, 4667–4670.
[114] M. C. Wilson, N. Sang-Jip, T. A. M. Gulder, C. A. Kauffman, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* **2011**, *133*, 1971–1977.
[115] M. Gibson, M. Nur-e-alam, F. Lipata, M. A. Oliveira, J. Rohr, *J. Am. Chem. Soc.* **2005**, *127*, 17594–17595.
[116] C. A. Kuttruff, PhD thesis, Department, LMU München, 2012
[117] E.-i. Negishi, *ARKIVOC* **2011**, *viii*, 34–53.
[118] B. Liang, E.-i. Negishi, *Org. Lett.* **2008**, *10*, 193–195.
[119] M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 4291–4298.
[120] J. P. Morken, M. T. Didiuk, A. H. Hoveyda, *J. Am. Chem. Soc.* **1993**, *115*, 6997–6998.
[121] K. Tomioka, T. Suenaga, K. Koga, *Tetrahedron Lett.* **1986**, *27*, 369–372.
[122] J. Zaminer, C. Brockmann, P. Huy, R. Opitz, C. Reuter, M. Beyermann, C. Freund, M. Müller, H. Oschkinat, R. Kühne, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2010**, *49*, 7111–7115.
[123] R. Amstutz, B. Ringdahl, B. Karlen, M. Roch, D. J. Jenden, *J. Med. Chem.* **1985**, *28*, 1760–1765.
[124] J. Dambacher, R. Anness, P. Pollock, M. Bergdahl, *Tetrahedron* **2004**, *60*, 2097–2110.
[125] a) J. Clayden, *Nat. Chem.* **2010**, *2*, 523–524; b) J. Clayden, S. A. Yasin, *New J. Chem.* **2002**, *26*, 191–192.
[126] C. Shu, X. Zeng, M.-H. Hao, X. Wei, N. K. Yee, C. A. Busacca, Z. Han, V. Farina, C. H. Senanayake, *Org. Lett.* **2008**, *10*, 1303–1306.
[127] B. Spellberg, *Clin. Infect. Dis.* **2008**, *47*, 294–294.
[128] a) B. Spellberg, R. Guidos, D. Gilbert, J. Bradley, H. W. Boucher, W. M. Scheld, J. G. Bartlett, J. Edwards, *Clin. Infect. Dis.* **2008**, *46*, 155–164; b) B. Spellberg, J. H. Powers, E. P. Brass, L. G. Miller, J. E. Edwards, *Clin. Infect. Dis.* **2004**, *38*, 1279–1286.
[129] WHO, www.who.int.
[130] E. J. Corey, B. Czakó, L. Kürti, *Molecules and Medicine*, John Wiley & Sons, New Jersey, **2007**.
[131] a) G. D. Wright, *Chem. Biol.* **2012**, *19*, 3–10; b) G. D. Wright, H. Poinar, *Trends Microbiol.* **2012**, *20*, 157–159; c) J. Davies, D. Davies, *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 417–433; d) D. A. Sack, R. B. Sack, G. B. Nair, A. K. Siddique, *Lancet* **2004**, *363*, 223–233.

[132] B. L. Bassler, R. Losick, *Cell* **2006**, *125*, 237–246.
[133] A. Tiaden, T. Spirig, H. Hilbi, *Trends Microbiol.* **2010**, *18*, 288–297.
[134] M. B. Miller, B. L. Bassler, *Annu. Rev. Microbiol.* **2001**, *55*, 165–199.
[135] a) T. Spirig, A. Tiaden, P. Kiefer, C. Buchrieser, J. A. Vorholt, H. Hilbi, *J. Biol. Chem.* **2008**, *283*, 18113–18123; b) D. A. Higgins, M. E. Pomianek, C. M. Kraml, R. K. Taylor, M. F. Semmelhack, B. L. Bassler, *Nature* **2007**, *450*, 883–886.
[136] E. J. Nelson, J. B. Harris, J. Glenn Morris, S. B. Calderwood, A. Camilli, *Nat. Rev. Microbiol.* **2009**, *7*, 693–702.
[137] B. S. Fields, R. F. Benson, R. E. Besser, *Clin. Microbiol. Rev.* **2002**, *15*, 506–526.
[138] R. R. Isberg, T. J. O'Connor, M. Heidtman, *Nat. Rev. Microbiol.* **2009**, *7*, 13–24.
[139] A. B. Molofsky, M. S. Swanson, *Mol. Microbiol.* **2004**, *53*, 29–40.
[140] a) H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512–7515; b) G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.
[141] D. Gautam, D. N. Kumar, B. V. Rao, *Tetrahedron: Asymmetry* **2006**, *17*, 819–821.
[142] H. Murakami, T. Minami, F. Ozawa, *J. Org. Chem.* **2004**, *69*, 4482–4486.
[143] W. Adam, A. Zhang, *Eur. J. Org. Chem.* **2004**, 147–152.
[144] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
[145] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122.