DISSERTATION

SYNTHETIC STUDIES ON (-) LEMONOMYCIN:

CONSTRUCTION OF THE TETRACYCLIC CORE

Submitted by

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ABSTRACT

SYNTHETIC STUDIES ON (-)-LEMONOMYCIN:

CONSTRUCTION OF THE TETRACYCLIC CORE

Documented herein are efforts towards the asymmetric total synthesis of (-)-lemonomycin, a member of the tetrahydroisoquinoline antitumor antibiotics family of natural products. We describe a concise route for the assembly of the tetracyclic core of this molecule, which involves a Pictet-Spengler reaction for the construction of the tetrahydroisoquinoline fragment and an azomethine ylide [3+2] dipolar cycloaddition for the construction of the diazabicyclo[3.2.1]octane ring system. The above-described synthetic efforts, while not totally successful, provide the basis for the future completion of the total synthesis of this natural product and other related compounds.

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DEDICATION

To Yorleny, Daniel, Gabriel and Sebastián

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CHAPTER 1

The tetrahydroisoquinoline family of antitumor antibiotics

1.1 Introduction

The tetrahydroisoquinoline antitumor antibiotics are family of natural products and their synthetic analogs.[1] Starting with the isolation of naphthyridinomycin (**1.1**) in 1974,[2] more than 70 natural products have been described in the literature. Structurally, their polycyclic skeleton contains tetrahydroisoquinoline moieties and 3,8-diazabicyclo[3.2.1]octane or 3,9-diazabicyclo[3.3.8]nonane ring systems. They are classified into the naphthyridinomycin (**1.1**), saframycin (**1.2**) and quinocarcin (**1.3**) sub-families.

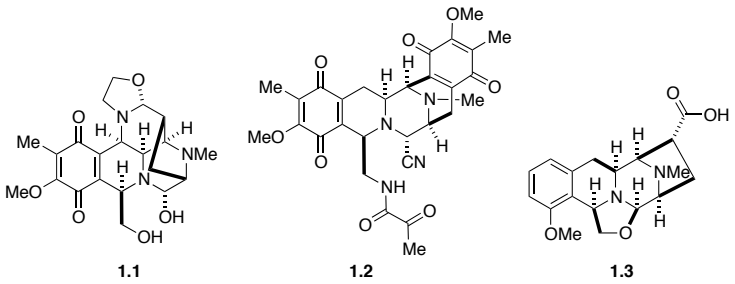
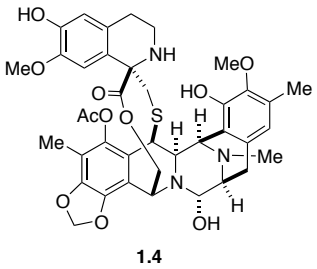


Figure 1.1. Representative members of the tetrahydroisoquinoline antitumor antibiotics

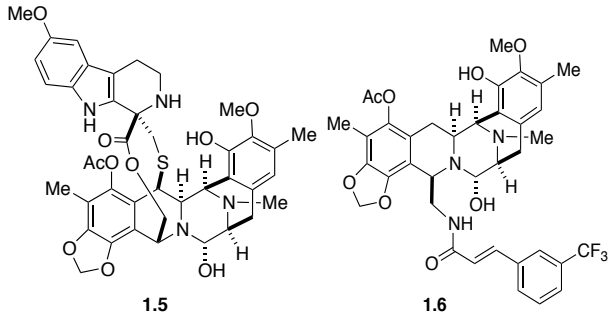
Several members of this family possess potent cytotoxic activities against tumor cells and bacteria. For instance, Ecteinascidin 743 (Et-743) (**1.4**), a compound isolated from the Caribbean tunicate *Ecteinascidia turbinata,* has been approved in Europe for the treatment of some types of advanced soft tissue sarcomas and platinum-resistant ovarian cancers.[3] In addition, it is undergoing phase II clinical trials for the treatment of translocation related sarcomas[4] and has shown antitumor activity against other malignancies, such as advanced breast cancer[5] and

prostate cancer.[6] PM-01183 (**1.5**), a synthetic analog of Et-743 (**1.4**), is currently in clinical development for the treatment of solid tumors.[7] Furthermore, the synthetic compound PM-00104 (**1.6)** is currently in phase II clinical trials for the treatment of multiple myeloma[8] and advanced solid tumors.[9]



1.4

Figure 1.2. Structure of ecteinascidin 743 (**1.4**)



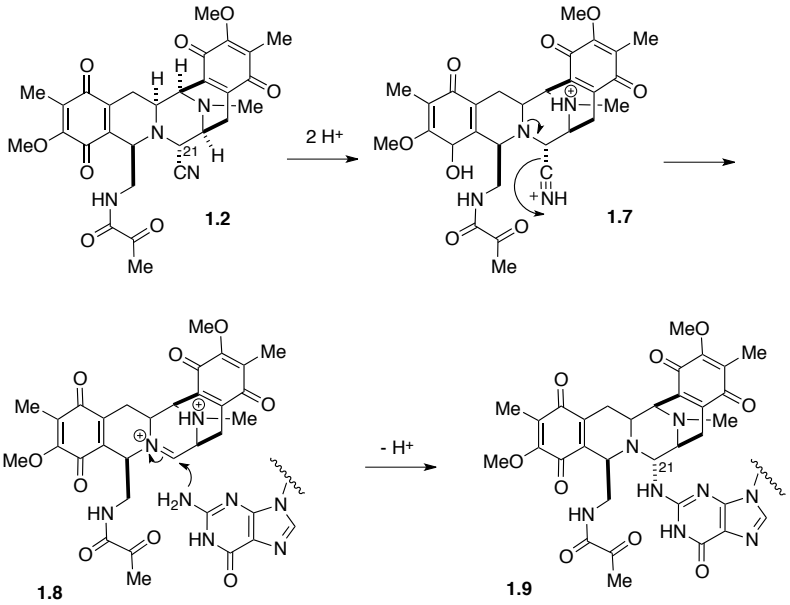
1.5 1.6

Figure 1.3. Structures of PM-01183 and PM-00104

1.2 Mechanisms of action

It has been shown that the tetrahydroisoquinoline antitumor antibiotics biological activities are the result of their interactions with cellular nucleic acids. The proposed mechanisms of action include DNA alkylation, DNA cross-linking and oxygen mediated DNA damage.[1] In 1982, Lown and coworkers proposed a mechanism of covalent bonding between saframycin A (**1.2**) and DNA (Scheme 1.1).[10] Upon protonation of the nitrile group connected to C-21, the lone pair of the adjacent nitrogen of intermediate **1.7** promotes the release of HCN and leads to the

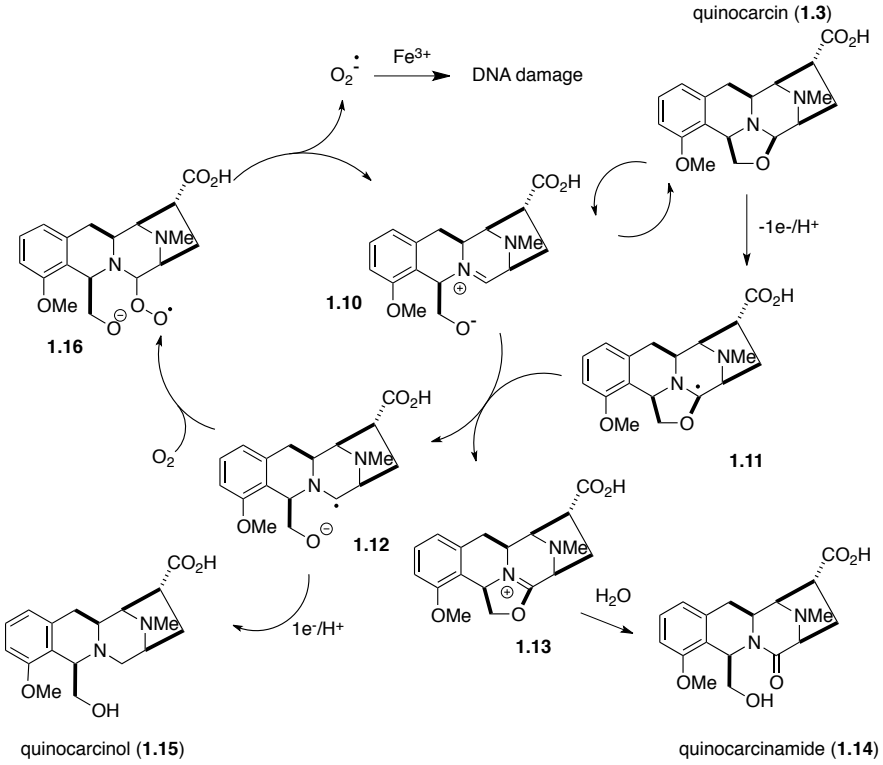
formation of iminium ion **1.8**. This highly electrophilic species is attacked by the N-2 atom of guanine in the minor grooves of G+C containing sequences, to generate covalently linked adducts such as **1.9**. An analogous mechanism has been proposed for similar compounds bearing hydroxyl or alkoxy leaving groups connected to C-21.



Scheme 1.1. Proposed mechanism of DNA alkylation by saframycin A

An additional DNA damaging mechanism was proposed for oxazolidine-containing members of the family. After an initial report of superoxide production by quinocarcin (**1.3**) made by Tomita and coworkers,[11] a series of experiments conducted by Williams and coworkers led to the proposal that the oxygen-dependent DNA scission events are associated with the disproportionation reactions experienced by the oxazolidine-containing tetrahydroisoquinoline antitumor antibiotics.[12,13] As outlined in Scheme 1.2, a single-electron transfer from **1.3** to the ring-opened tautomer **1.10**, followed by the concomitant deprotonation event, would produce oxazolidinyl radical **1.11** and radical anion **1.12**. Through a second single-electron oxidation, radical **1.11** generates oxazolidinium ion **1.13**, which is converted to quinocarcinamide **1.14** by

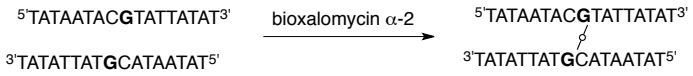
the addition of water. Radical anion **1.12** is the acceptor in a single electron transfer process that, with the concomitant protonation, leads to quinocarcinol **1.15**. In addition, radical anion **1.12** can trap an oxygen molecule to produce peroxy radical anion **1.16**. With the involvement of the lone electron pair of the adjacent nitrogen, **1.16** expels superoxide and regenerates **1.10**. Through Haber-Weiss/Fenton cycling, superoxide gives rise to hydroxyl radicals and triggers to DNA damaging events.[14,15,16]



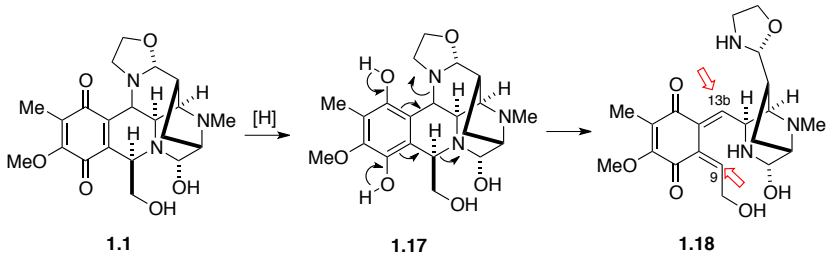
Scheme 1.2. Proposed mechanism of superoxide formation by quinocarcin

According to a series of experiments described by Williams, it was demonstrated that bioxalomycin α-2 (**1.17**) is capable of cross-linking duplex DNA strands.[17] The incubation at 37 °C of a buffered solution containing a 5'-^{32}P-labelled oligonucleotide and bioxalomycin α-2 led to the isolation of a cross-linked adduct (Scheme 1.3). It has been shown that the alkylation occurs in the exocyclic nitrogen of guanine and that the hydroquinone oxidation state is essential

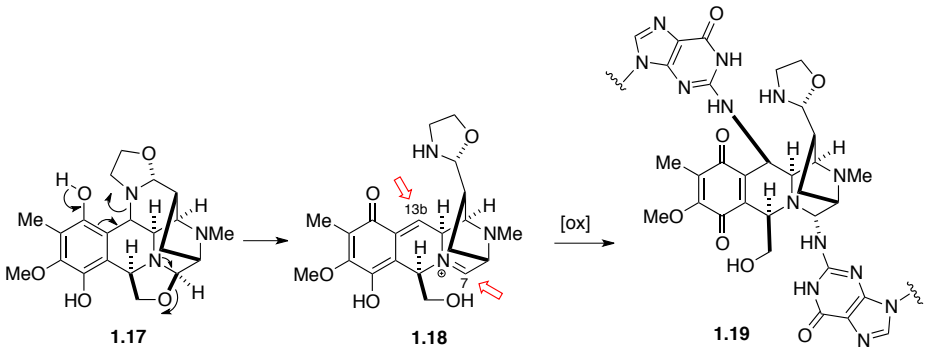
for this process. In spite of this, the exact structure of the DNA-bioxalomycin adduct remains unknown. In 1977, Moore suggested C-13b and C-9 as possible alkylation sites resulting from the formation of the *o*-quinone methide groups of **1.18**, which could be derived from bioxalomycin α-2 (**1.17**) (Scheme 1.4). Williams supported Moore's proposal for C-13b alkylation, and proposed a second alkylation site at C-7 instead of C-9 (Scheme 1.5). This assertion was based in the previous knowledge about the role of the α-aminonitrile/hemiaminal functionality in the biological activity of other members of the tetrahydroisoquinoline family of antitumor antibiotics.



Scheme 1.3. Bioxalomycin α-2 cross-linking adduct

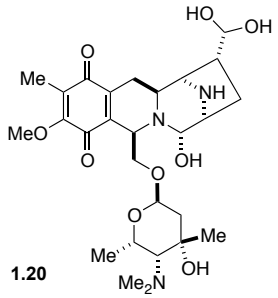


Scheme 1.4. Naphthyridinomycin-derived alkylating intermediate proposed by Moore



Scheme 1.5. Bioxalomycin α-2 cross-linking mechanism proposed by Williams

1.3 Lemonomycin



1.20

Figure 1.4. Structure of lemonomycin

Lemonomycin (**1.20**) is a member of the quinocarcin sub-family tetrahydroisoquinoline antitumor antibiotics. Its isolation from the fermentation broth of *Streptomyces candidus* (LL-AP191) was described by Whaley and coworkers in 1964.[18] The compound showed significant *in vitro* antimicrobial activities against both gram-negative and gram-positive bacteria (Table 1.1). In addition, in a series of assays it inhibited the bacterial growth *in vitro* at lower or similar concentrations, when compared to tetracycline, penicillin G and erythromycin (Table 1.2).

Table 1.1. In vitro antibacterial activities of lemonomycin

Organism	MIC (μg/mL)
Mycobacterium smegmatis ATCC 607	6.2
Staphylococcus aureus A TCC 6548P	0.2
Streptococcus faecalis ATCC 8043	0.4
Bacillus subtilis ATCC 6633	0.05
Pseudomonas fluorescens ATCC 12633	1.6
Proteus vulgaris ATCC 9484	0.4
Escherichia coli ATCC 9637	1.6
Salmonella gallinarum (Lederle 604)	0.8
Clostridium sporogenes ATCC 7955	>100

Table 1.2. Comparison of antibacterial activities of lemonomycin (**1.20**), tetracycline (A), penicillin G (B) and erythromycin (C), against various staphylococci and streptococci

Organism	MIC (μg/mL)			
	1.20	A	B	C
Staphylococcus aureus (Lederle 4050B-122-7)	0.08	10	>100	1.5
S. aureus (Lederle 4050B-122-10)	0.15	>100	>100	3
S. aureus (Lederle 4050B-122-13)	0.15	2.5	0.08	3
S. aureus (Lederle 4050B-122-14)	0.15	>100	0.04	3
S. aureus Rose ATCC 14154	0.15	>100	> 100	12.5
S. aureus Smith	0.04	2.5	0.8	1.5
Streptococcus faecalis ATCC 8043	0.4	2.5	2.5	0.4
S. pyogenes C203	<0.005	1.2	0.001	0.2
S. pyogenes (Lederle 8053B-40-2)	0.01	25	0.01	0.4
S. pyogenes (Lederle 8053B-40-3)	0.01	100	0.01	0.4
S. pyogenes NY5	<0.005	2.5	0.01	0.2
Streptococcus sp λ-Strep11	5.0	>100	2.5	1.5
Streptococcus sp. β-Strep 80	2.5	>100	2.5	1.5

The structure of lemonomycin was reported by He and coworkers in 2000,[19] which also confirmed the *in vitro* activity against susceptible strains of *S. aureus* and *B. subtilis* (MICs of 0.2 and 0.05 μg/mL, respectively) and performed *in vitro* assays with methicillin resistant *S. aureus* and vancomycin resistant *Enterococcus faecium* (MICs of 0.4 and 0.2 μg/mL,

respectively). In addition to the antibacterial activity, **1.20** also showed *in vitro* activity against the human colon tumor cell line HCT116 (IC_{50} = 0.36 μg/mL).

Structurally, the compound contains the tetracyclic core found in quinocarcin[20] which includes a 3,8-diazabicyclo ring system and a rare bis-desoxy aminosugar portion, which has only been found in a few natural products.[21]

1.4 Proposed biosyntheses for the tetrahydroisoquinoline antitumor antibiotics

The biosynthetic gene clusters of members of the three sub-families have been identified and the bioinformatics analyses revealed the polycyclic backbones are constructed by homologous nonribosomal peptide synthetases (NRPSs) (Figure 1.5).[22,23] According to Oikawa and coworkers, the four systems share a unique *N*-*t*erminal acyl ligase (AL) domain, which has been found in lipopeptide NRPSs. They proposed that the AL domain is involved in the activation of a fatty acid chain, which is incorporated into an *N*-acyl dipeptidyl moiety with the involvement of the two condensation-adenylation-peptidyl carrier protein (C-A-PCP) tri-domains. In addition, they suggested that a single module (SfmC and its homologs) is responsible for the incorporation of a tyrosine derivative into its PCP domain and the assembly of the tetrahydroisoquinoline rings, with the involvement of the reductase (R) and Pictet-Spenglerase (PS) domains. The NRPSs of quinocarcin (**1.3**) and cyanocycline (**1.27**) include an additional module (Qcn19 and Cya17, respectively), which is proposed to be involved in the formation of the pyrrolidine rings found in these natural products.[22] The detailed function of the NRPS modules will be discussed later. Finally, it has been proposed that a peptidase domain (SfmE and its homologs) removes the fatty acid chain at a late stage of the biosynthesis.[23]

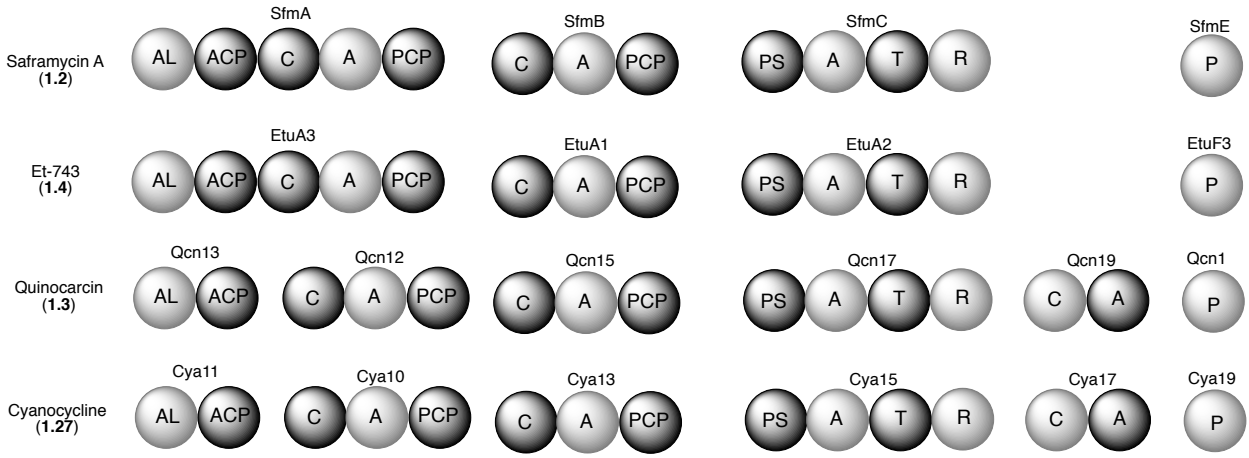
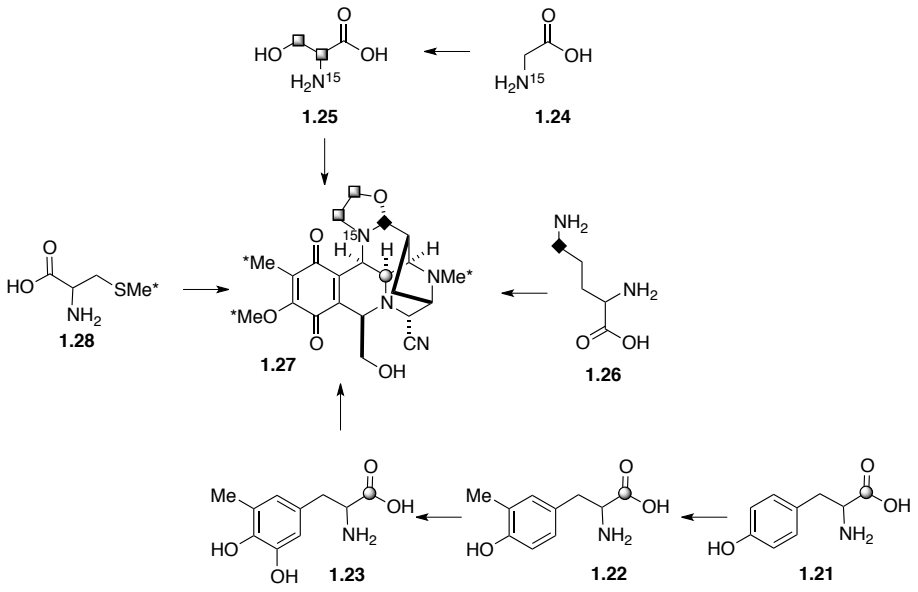
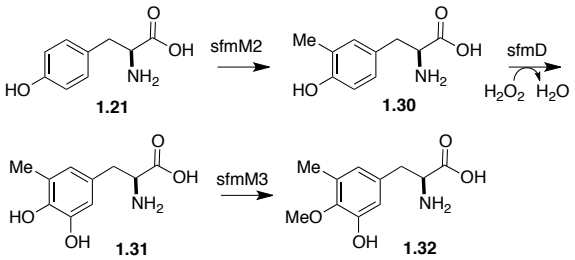


Figure 1.5. Domain organization of NRPSs for tetrahydroisoquinoline antitumor antibiotics biosynthesis. Abbreviations: A, adenylation domain; AL, acyl-CoA ligase domain; ACP, acyl carrier protein; C, condensation domain; PCP, peptidyl carrier protein; R, reductase domain; PS, Pictet-Spenglerase domain; P, peptidase domain



Scheme 1.6. Biosynthetic precursors to cyanocycline A (**1.27**)

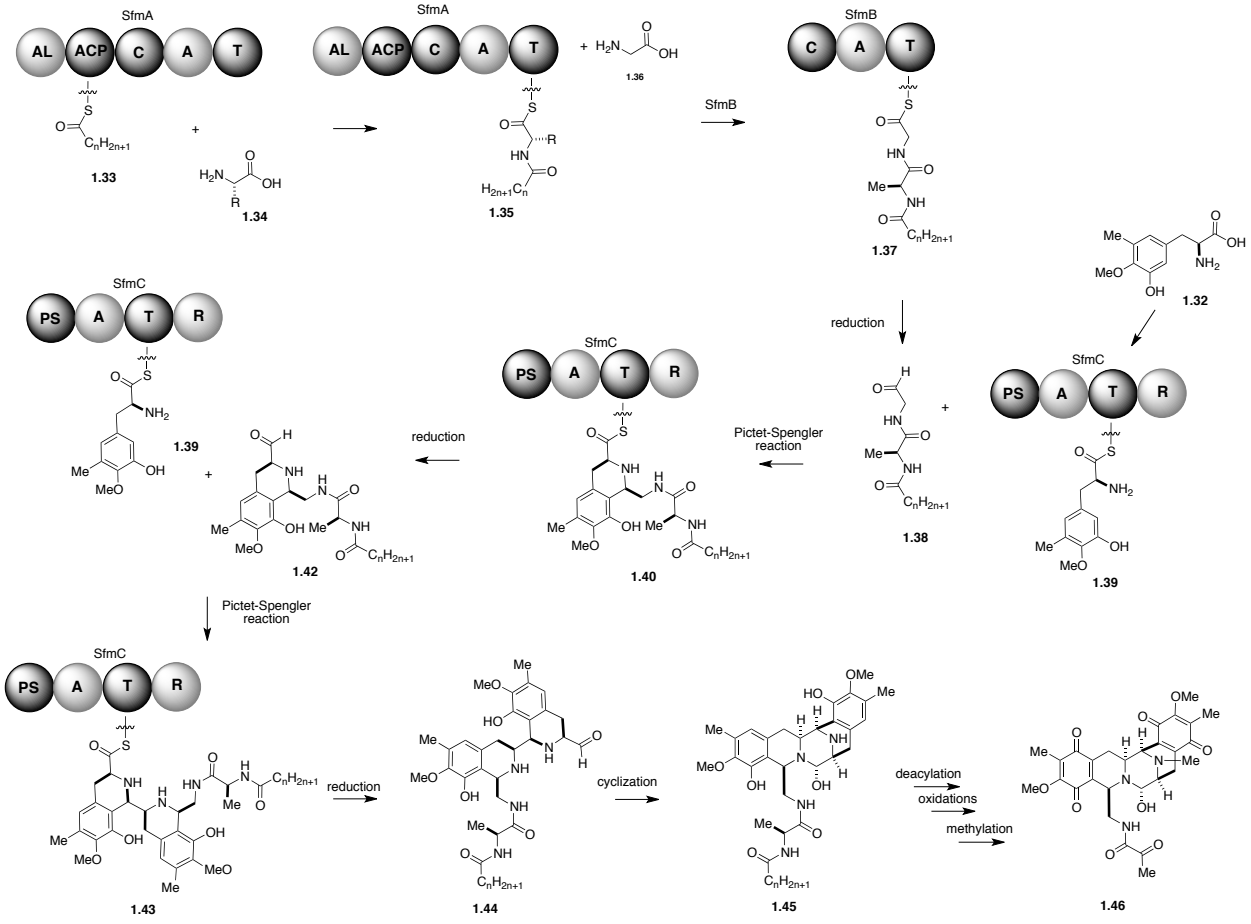


Scheme 1.7. Biosynthesis of 3-hydroxy-5-methyl-*O*-methyl-L-tyrosine (**1.32**)

The feeding studies conducted by Zmijewsky and coworkers demonstrated that tyrosine (**1.21**), glycine (**1.24**), serine (**1.25**) and ornithine (**1.26**) are incorporated into the polycyclic skeleton of cyanocycline A (**1.27**), and that methionine (**1.28**) is the source of the methyl groups (Scheme 1.6).[24] In their studies on the biosynthesis of saframycin A from *Streptomyces lavendulae,* Tang and coworkers identified a gene cassette that encodes the proteins responsible for the conversion of L-tyrosine (**1.21**) into 3-hydroxy-5-methyl-*O*-methyl-L-tyrosine (**1.32**) (Scheme 1.7).[25] SfmM2 and SfmM3 were identified as a *C*-methyl and *O*-methyl transferases, respectively,[25] and SfmD was characterized as a HEME-containing peroxidase that utilizes H_2O_2 as the oxidizing agent.[26]

A series of studies conducted by Oikawa and coworkers unveiled the role of the NRPS in the transformations that lead to the assembly of the pentacyclic core of saframycin A.[22,23,27] As shown in Scheme 1.8, they proposed that the starter module of the NRPS (SfmA) includes an acyl ligase (AL) - thiolation (T) didomain, which loads a fatty acid unit into the SfmA module (**1.33)**. The condensation-adenylation-thiolation (C-A-T) tridomain utilizes alanine (**1.34**) to build an *N*-acylalanine (**1.35**) unit. SfmB loads and activates a glycine fragment (**1.36**), which reacts with **1.35** to form an *N*-acylalanyl glycine unit (**1.37**). The thioester group is reduced by the reductase (R) module of SfmC, to release the *N*-acyl dipeptide aldehyde (**1.38**) from SfmB. The aldehyde reacts with SfmC loaded with the tyrosine derivative **1.39** in reaction catalyzed by

the Pictet-Spenglerase (PS) domain to form tetrahydroisoquinoline **1.40**. Then, aldehyde **1.42** is reductively released from the T domain, which is loaded with another unit of the tyrosine derivative. A second Pictet-Spengler reaction occurs between **1.42** and **1.39** to form intermediate **1.43**, which is reductively released as aldehyde **1.44.** The nitrogen of the southern tetrahydroisoquinoline ring attacks the aldehyde group to form the hemiaminal and complete the assembly of the pentacyclic core of saframycin A. Intermediate **1.45** is converted into pre-saframycin (**1.46**) through a series of transformations that include oxidations of the aromatic rings to *p*-quinones, an *N*-methylation, the hydrolysis of the *N*-acyl fragment by the peptidase module (SfmE) and the transamination of the alanine residue to form the pyruvyl fragment.

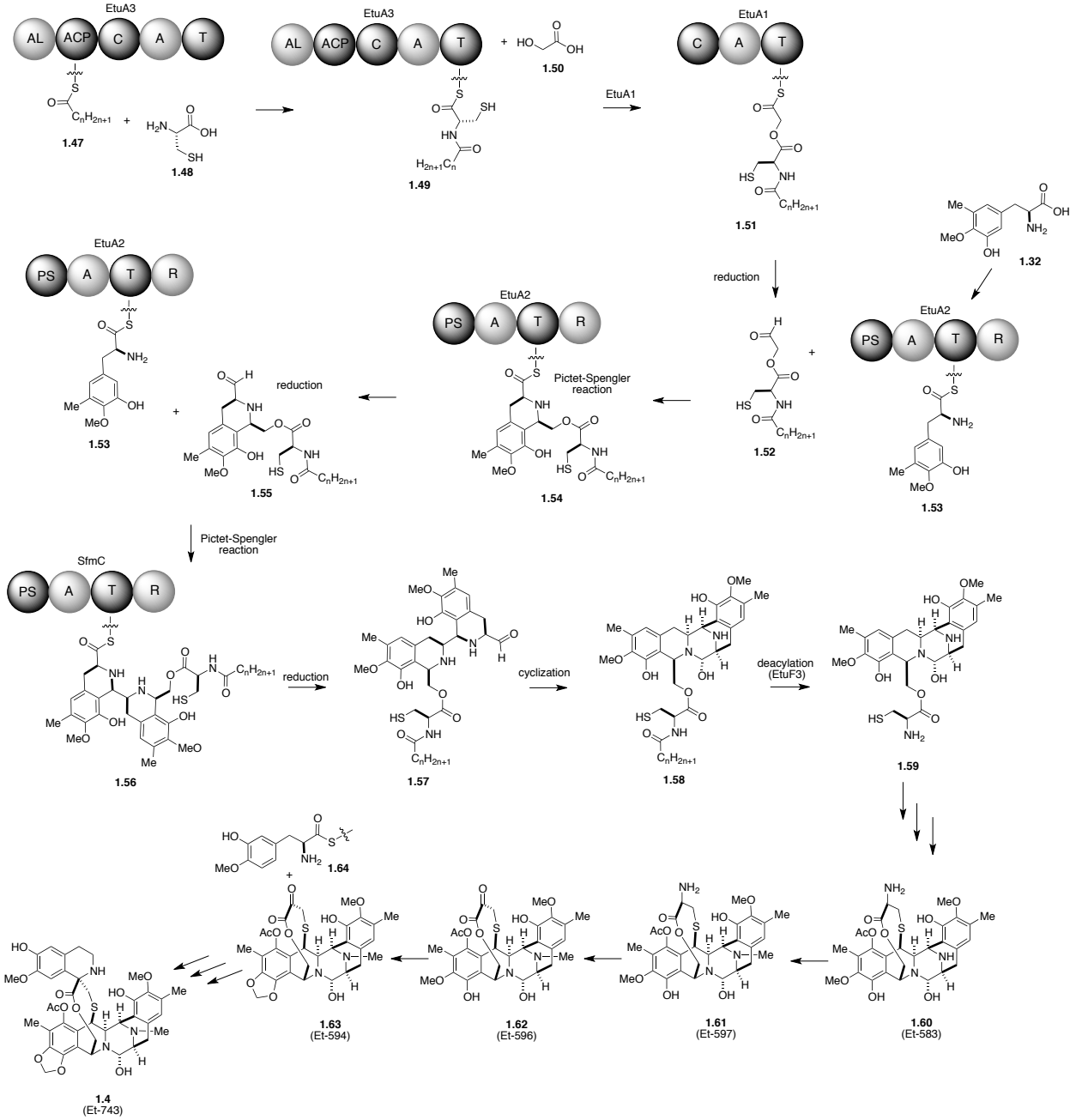


Scheme 1.8. Biosynthesis of pre-saframycin (**1.46**)

Sherman and coworkers identified the γ-protobacterium *Candidatus Endoecteinascidia frumentensis* as the bacterial symbiont of *E. turbinata* that produces Et-743 **(1.4)**[28] and proposed a biosynthetic pathway for this compound. They identified the genes encoding the enzymes EtuM1, EtuH and EtuM2, as homologues of SfmM2, SfmD and SfmM3, respectively, which are involved in the formation of 3-hydroxy-5-methyl-*O*-methyl-L-tyrosine (**1.32**) (*vide supra*). In addition, they identified the main modules of the NRPS as EtuA1, EtuA2 and EtuA3 and proposed the sequence outlined in Scheme 1.9. EtuA3 forms an *N*-acylcysteine fragment (**1.49**), which is combined by EtuA1 with a glycolic acid fragment (**1.50**) to build the T-loaded acylated depsipeptide **1**.**51**.

In accordance with Oikawa's proposed sequence (*vide supra*), intermediate **1.51** is reductively released by the R module of EtuA2 to form aldehyde **1.52**. The tyrosine derivative **1.32** is loaded into EtuA2, to initiate the iterative Pictet-Spengler/reduction sequence that leads to the formation of intermediate **1.57**, which cyclizes to produce pentacyclic intermediate **1.58**. It has been proposed that EtuF3 is the peptidase involved the removal of the acyl chain and that a subsequent multi-step process, including the oxidation of the left hand side aromatic ring, the addition of the sulfhydryl group into a putative *ortho*-quinone methide intermediate and an acetylation, leads to the formation of **1.60**. The compounds Et-583 (**1.60**), Et-597 (**1.61**), Et-596 (**1.62**) and Et-594 (**1.63**) have been isolated from *E. turbinata.* However, none of the enzymes involved in the transformation of **1.59** into Et-743 (**1.4**) have been identified. The proposed final steps of sequence involve the *N*-methylation of **1.60**, a transamination step that gives rise to the *S*-substituted pyruvyl fragment of **1.62** and an oxidation that forms the methylenedioxy moiety of **1.63**. Lastly, it was proposed that tyrosine derivative **1.64** is incorporated *via* a Pictet-Spengler

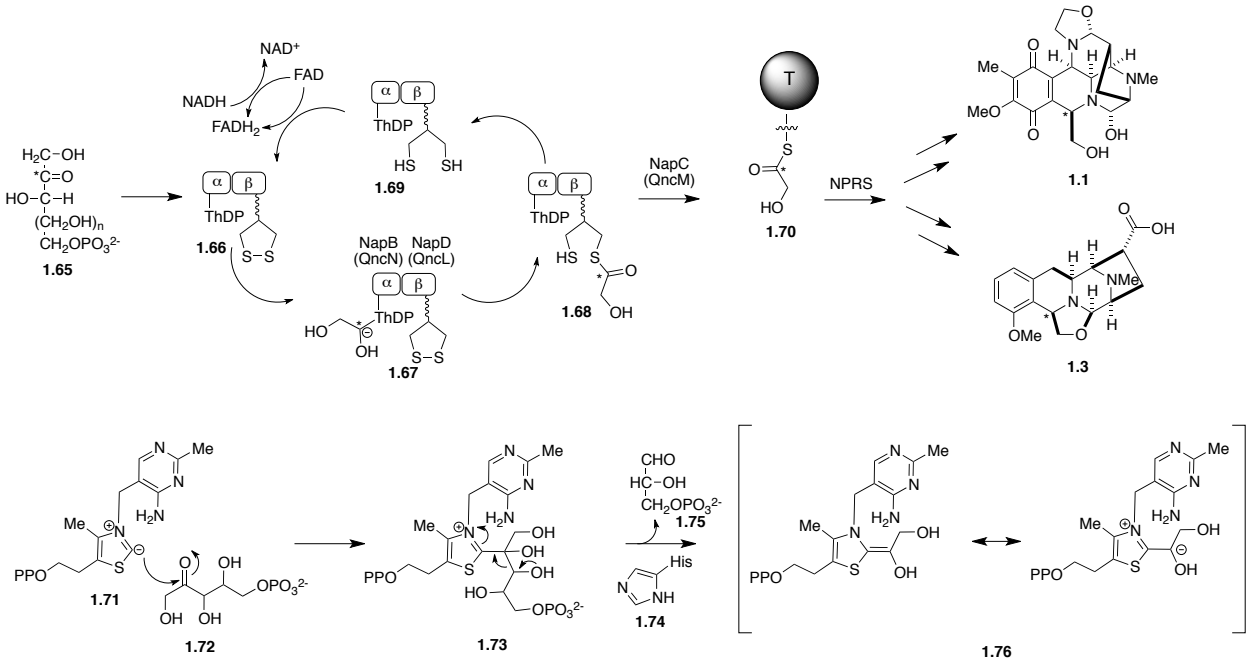
reaction to form the northern tetrahydroisoquinoline ring and that the resulting enzyme bound intermediate is converted into Et-743 through an unknown mechanism.



Scheme 1.9. Biosynthesis of Et-743 (**1.3**)

A report from Tang and coworkers revealed the biosynthetic origin of the glycolyl unit that is loaded into the starting modules of the NRPSs for naphthyridinomycin (**1.1**), from *Streptomyces lusitanus,* and quinocarcin (**1.3**), *Streptomyces melanovinaceus*. In both cases, they identified two-component transketolase (Tkase)/acyl carrier protein (ACP) systems that utilize ketoses as substrates for the preparation of the glycolyl fragments.[29] As shown in Scheme 1.10, the NapB/QncN modules utilize a ketose phosphate (**1.65**) to form a glycoaldehyde-ThDP unit (**1.67**). The C-2 fragment is transferred to a lipoyl fragment attached to NapD/QncL to form glycolyl lipoic acid intermediate **1.68**. Then, the NapC/QcnM modules catalyze the transfer of the glycolyl unit to an acyl carrier protein (ACP), to form **1.70**, which is utilized by the NRPSs for the incorporation of the C-2 fragment into the tetrahydroisoquinoline ring system of naphthyridinomycin (**1.1**) and quinocarcin (**1.3**). The mechanism of the ThDP-dependent incorporation of the C-2 unit into NapB/QncN starts with the attack of thiazolium ylide of thiamine diphosphate (ThDP) (**1.71**) into the carbonyl carbon of a ketose unit (**1.72**), to form intermediate **1.73**. Then, the bond between C-2 and C-3 breaks in a process assisted by the imidazole moiety of a histidine residue (**1.74**), leading to the formation of the glycoaldehyde intermediate **1.76** and an aldose, such as D-gliceralehyde-3-phosphate (**1.75**).

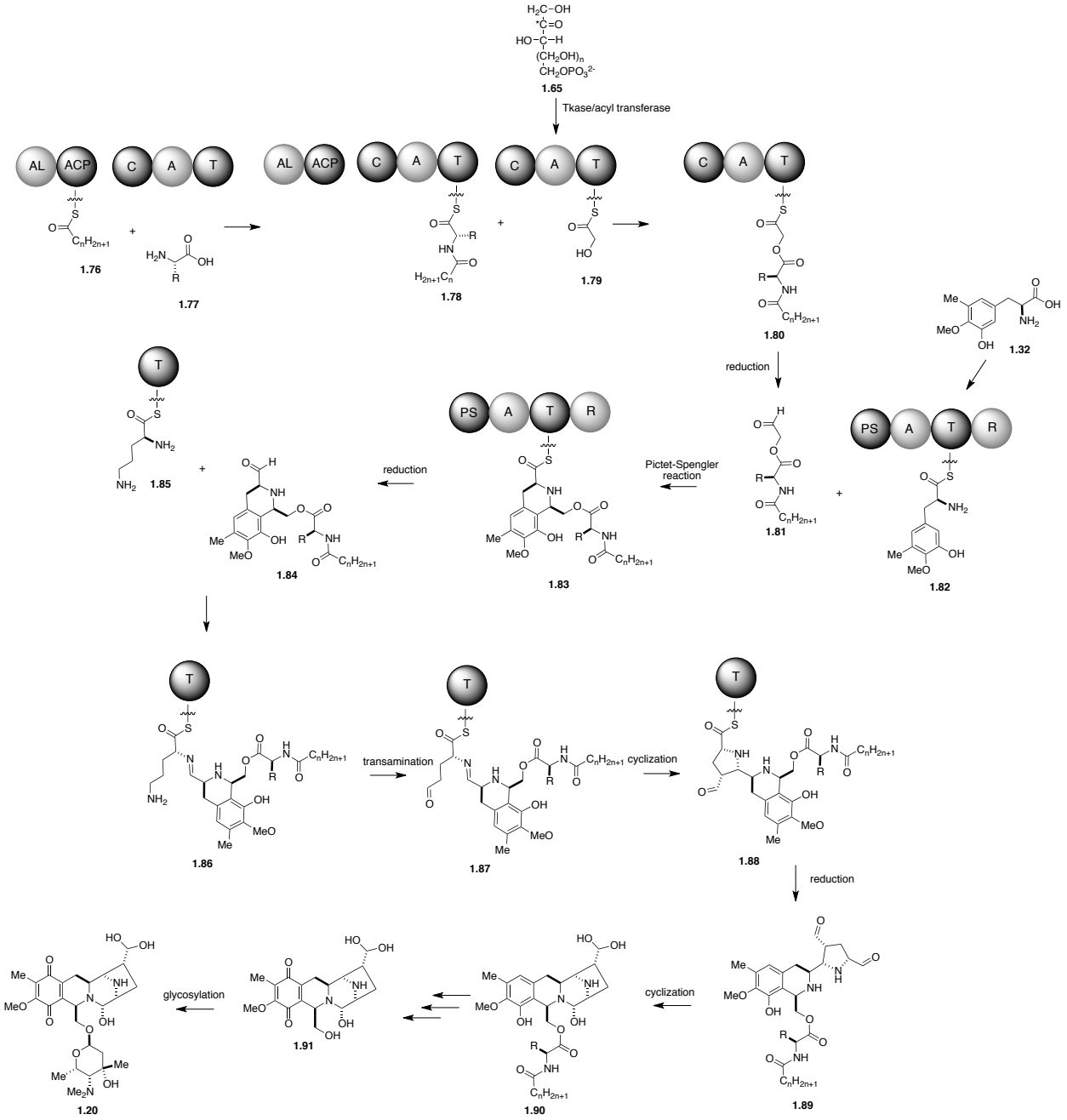
In their study of the Et-743 producing organism, Sherman and coworkers reported several genes with unknown roles in the biosynthetic pathway,[28] including two components of a possible pyruvate dehydrogenase complex (EtuP1 and EtuP2).[28] Tang and coworkers identified these two proteins as homologs of the NapB/QcnN and NapD/QcnL systems and proposed that the biosynthetic origin of the glycolyl unit is the same for the three pathways.[29]



Scheme 1.10. Biosynthetic origin of the C-2 unit of naphthyridinomycin and quinocarcin

1.5 Biosynthesis proposal for lemonomycin

The biosynthesis of lemonomycin has not been studied. However, we expect that it would occur analogously to the biosynthesis of the other members of the tetrahydroisoquinoline family of antitumor antibiotics. Based on the information discussed in the previous section, we propose that the tetracyclic ring system of lemonomycin is constructed by a NRPS homologous to the NRPSs of quinocarcin (**1.3**) and naphtryridomycin (**1.1**). As shown in Scheme 1.11, our proposed sequence involves the assembly of a T-loaded *N*-acyldepsipeptide **1.80** utilizing a an acyl fragment loaded into the ACP of the first module **1.76**, an unidentified amino acid **1.77** and a ketose-derived glycolyl unit **1.79** loaded into the third module.



Scheme 1.11. Proposed biosynthesis of lemonomycin

The *N*-acyldepsipeptide **1.80** is reductively released to afford aldehyde **1.81,** which reacts with the tyrosine derivative unit loaded into the T domain of the fourth module (**1.82**) to give intermediate **1.83**, in a reaction catalyzed by the Pictet-Spenglerase domain (PS). The reductase domain (R) reduces the thioester group to release aldehyde **1.84**, which reacts with the α-amino group of an D-ornithine unit loaded into the T-domain of an different module (**1.85**), to form imine intermediate **1.86**. The transamination of γ-amino group forms the aldehyde group of **1.87**, which could react *via* an enol intermediate addition into the imine group, to form the pyrrolidine group of **1.88**. In accordance with Oikawa's proposal, we submit that the formation of the pyrrolidine ring involves the participation of a module that is homologous to Qcn19 and Cya17. Then, the reduction of the thioester group would form dialdehyde **1.89**, which could cyclize to form the hemiaminal moiety of **1.90**. The hydrolyses of the peptide and ester groups and the oxidation of the aromatic ring would afford lemonomycin aglycon (**1.91**), which could be transformed into lemonomycin (**1.20**) *via* a glycosylation event.

CHAPTER 2

Previous synthetic work on lemonomycin

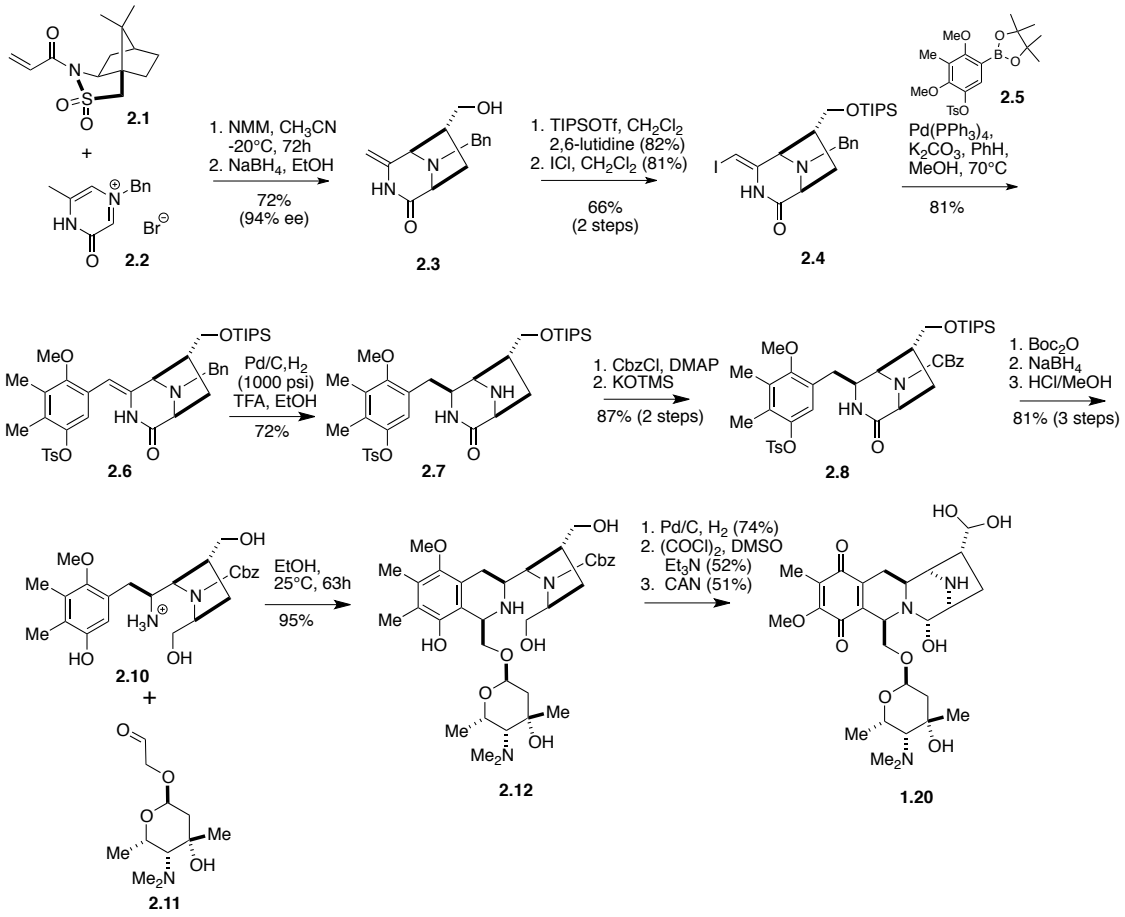
2.1 Introduction

The structural complexity and biological activities of the tetrahydroisoquinoline antitumor antibiotics have made them attractive targets for the synthetic community. In this chapter we will discuss the synthetic work related to lemonomycin. To date, there are two total syntheses of lemonomycin by Stoltz[30] and Fukuyama[31,32] and synthetic studies by Magnus,[33,34] Zhu,[35,36] Mulzer[37] and our laboratory.[38]

2.2 Stoltz's total synthesis

In 2003, Stoltz and coworkers made the first report of the total synthesis of lemonomycin.[30] Their concise and convergent approach involved a longest linear sequence of 15 steps. The synthetic sequence starts with a [3+2] dipolar cycloaddition between an Oppolzer's sultam-derived acrylamide (**2.1**) and oxidopyrazinium salt **2.2** (Scheme 2.1). The chiral auxiliary was removed under reductive conditions to afford primary alcohol **2.3**. Protection of the hydroxyl with TIPSOTf, followed by a stereospecific iodination gave *Z*-iodoenamide **2.4**, which was utilized in a Suzuki coupling with boronic ester **2.5** to form aryl enamide **2.6**. The reduction of the double bond and the hydrogenolysis of the benzyl group provided **2.7** stereospecifically. The secondary amine was converted into the Cbz carbamate and the phenolic tosylate was cleaved with KOTMS to give **2.8**. Then, the amide was converted into the Boc carbamate to facilitate the reduction of the carbonyl, and the acid-labile protecting groups were removed with methanolic HCl to give aminotriol **2.10**. This compound was combined in a Pictet-Spengler reaction with aldehyde **2.11** (*vide infra*) to afford substituted tetrahydroisoquinoline **2.12**. After

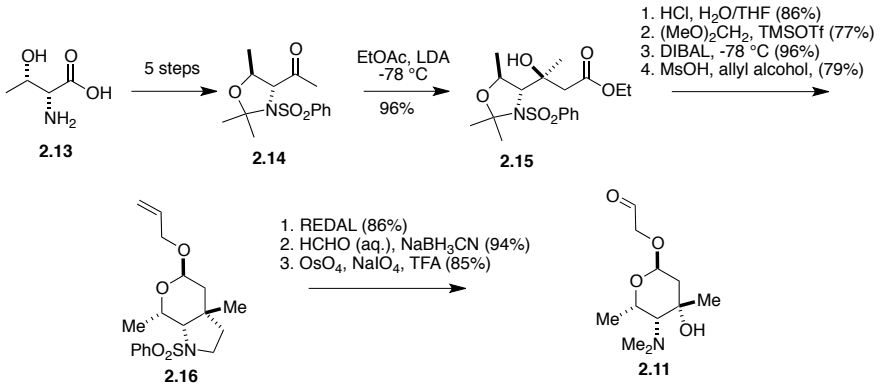
removing the Cbz carbamate under hydrogenolysis conditions, an oxidation under Swern conditions[39] was used to transform the two primary hydroxyls into the hemiaminal and aldehyde hydrate groups. Finally, an oxidation with ceric ammonium nitrate gave (-)-lemonomycin (**1.20**).



Scheme 2.1. Stoltz's total synthesis of lemonomycin (**1.20**)

The sequence for the preparation of aldehyde **2.11** started with the synthesis of ketone **2.14** from D-threonine (**2.13**) (Scheme 2.2). Felkin-controlled aldol addition of the lithium enolate of ethyl acetate into **2.14** gave **2.15** stereospecifically.[40] Then, formation of a lactone through the acid-mediated cleavage of the oxazolidine ring, followed by reaction with dimethoxymethane and TMSOTf to form the fused oxazolidine ring, reduction to the lactol with DIBAL and protection with allyl bromide provided **2.16**. Treatment with REDAL, which

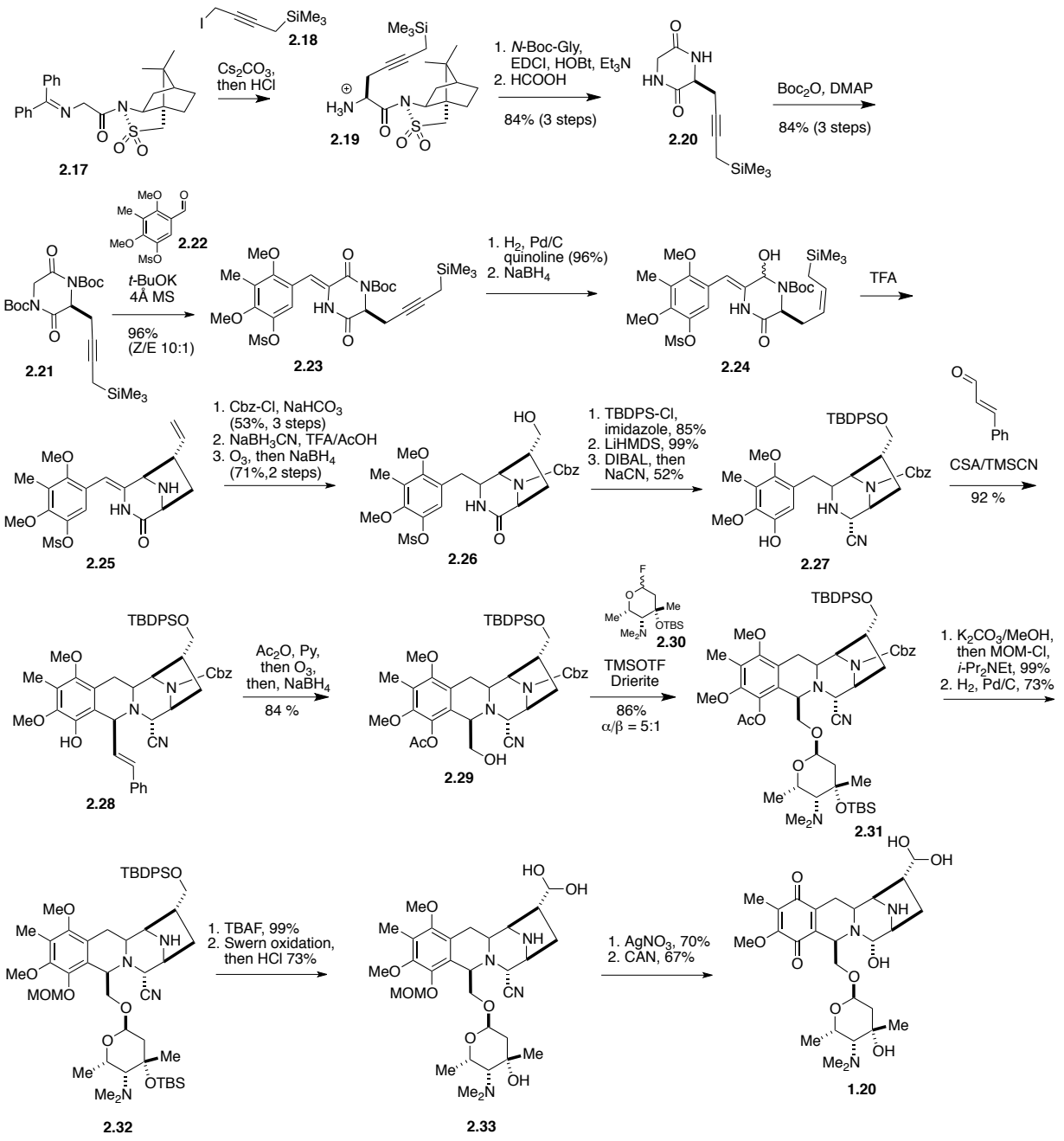
induced both the reduction of the hemiaminal ether and the cleavage of the benzenesulfonyl group, followed by a methylation under reductive amination conditions, and a Lemieux-Johnson oxidation,[41] gave **2.11**.



Scheme 2.2. Stoltz's synthesis of aldehyde **2.11**

2.2 Fukuyama's total synthesis

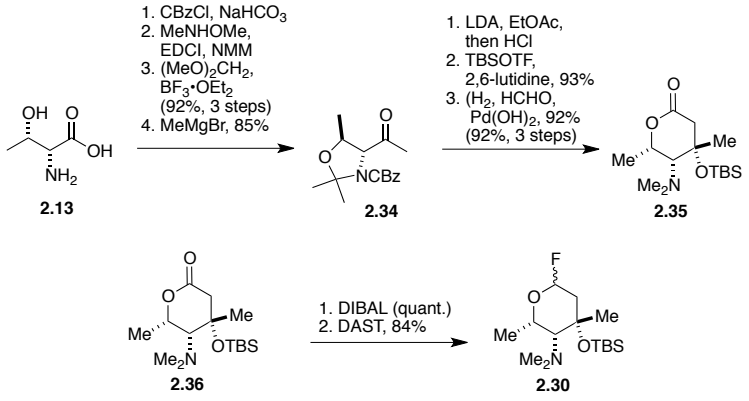
In 2012, Fukuyama and coworkers published their total synthesis of lemonomycin.[31] The first step in the sequence is the alkylation of Oppolzer's sultam derived glycinate **2.17** with iodopropargylsilane **2.18**, followed by acid hydrolysis of the imine to provide **2.19** as a single diastereomer (Scheme 2.3). Coupling with *N*-Boc glycine, followed by reflux with formic acid and protection with Boc anhydride gave diketopiperazine **2.21**. This compound was combined with aldehyde **2.22** in a Perkin-type condensation,[42] to form *Z*-enamide **2.23** with high stereoselectivity. Partial reduction of the triple bond, followed by sodium borohydride reduction of the activated carbonyl gave **2.24**. Then, a TFA-induced Hosomi-Sakurai reaction was employed to form the diazabicyclo[3.2.1]octane ring system of **2.25**. The secondary amine was



Scheme 2.3. Fukuyamas's total synthesis of lemonomycin (**1.20**)

converted into the Cbz carbamate and the enamide double bond was reduced with sodium cyanoborohydride under acidic conditions. Then, the resulting compound was treated with ozone followed by sodium borohydride, to afford **2.26**. The primary hydroxyl was converted into the

TBDPS silyl ether, the phenolic mesylate was removed with LiHMDS and the amide was treated with sodium cyanoborohydride and sodium cyanide to give aminonitrile **2.27**. This compound was combined with cinnamaldehyde in a Pictet-Spengler reaction that provided tetracycle **2.28** stereospecifically. Acetylation of the phenolic hydroxyl, followed by ozonolysis and treatment with sodium borohydride, gave **2.29**. A glycosylation reaction with fluoroglycoside **2.30** (*vide infra*) was employed to form **2.31**. A one-pot approach was used to cleave the phenolic acetate and install the methoxymethyl ether, and the Cbz group was removed under hydrogenolysis conditions to provide **2.32**. Then, removal of the silyl protecting groups with TBAF and oxidation of the primary alcohol under Swern conditions[39] with an acidic workup provided compound **2.33**. The completion of the synthesis was achieved by the conversion of the aminonitrile into the hemiaminal with $AgNO_3$ and the oxidation of the aromatic ring to the *p*-quinone using ceric ammonium nitrate.



Scheme 2.4. Fukuyama's synthesis of fluoroglycoside **2.30**

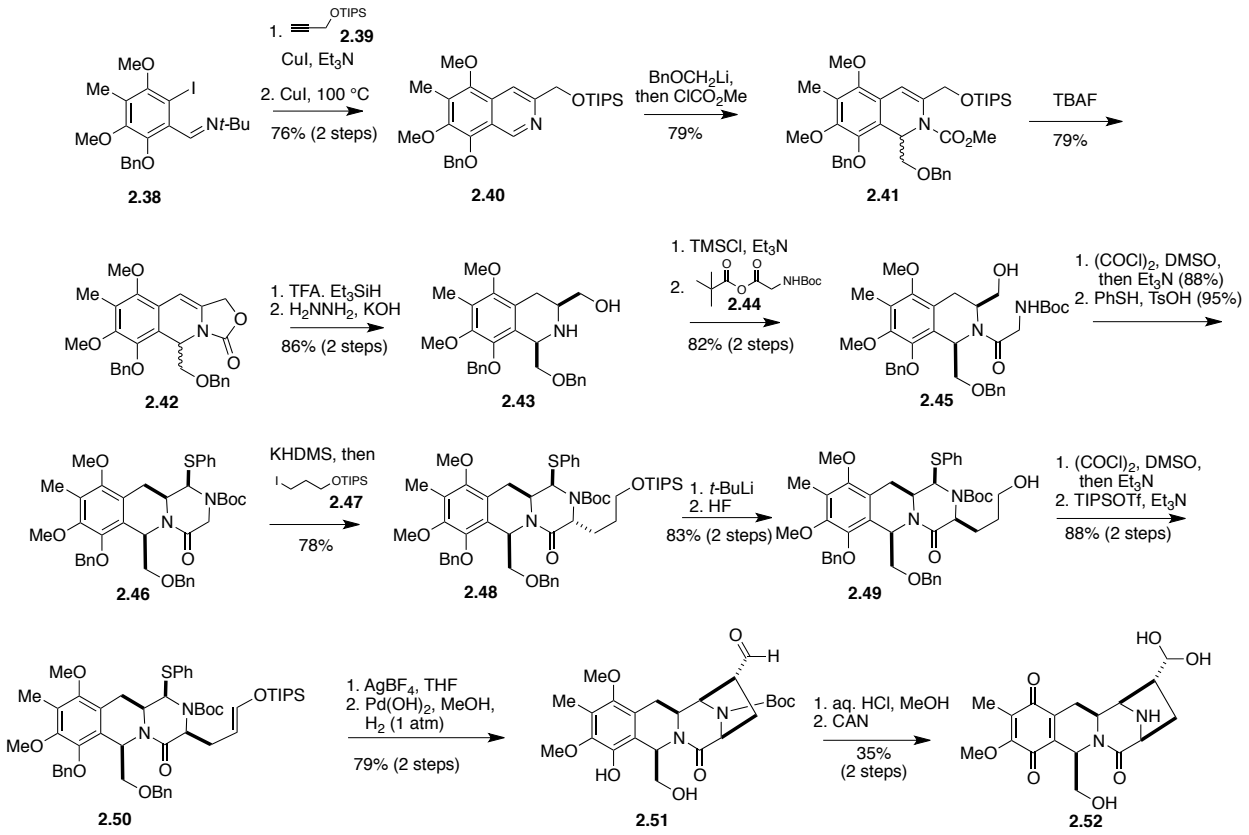
The synthesis of the glycosylation reagent **2.30** involves the preparation of ketone **2.34** from D-threonine (**2.13**), with a sequence comprising Cbz protection, conversion of the carboxylic acid into a Weinreb amide, formation of the oxazolidine ring and transformation into the methyl ketone with MeMgBr (Scheme 2.4). Then, Felkin controlled addition of the lithium

enolate of EtOAc,[40] followed by protection of the resulting tertiary alcohol as TBS ether and hydrogenolysis of the Cbz under reductive amination conditions gave lactone **2.35**. The sequence was completed with a DIBAL reduction and the conversion of the resulting lactol into the fluoroglycoside with DAST.[43]

2.3 Magnus's racemic synthesis of lemonomycinone amide

In 2005, Magnus and Matthews reported a racemic synthesis of lemonomycinone amide (**2.52**),[33] a putative natural product that is structurally related to lemonomycin aglycon. They built a quinoline system *via* a modification of the Larock isoquinoline synthesis[44] that involved the sequential coupling of *o*-iodoimine **2.38** with alkyne **2.39** under Castro conditions[45] and a copper-catalyzed ring closure (Scheme 2.5). The addition of benzyloxymethyllithium[46] to **2.40**, followed by treatment with methyl chloroformate gave isoquinoline **2.41**. The deprotection of the primary alcohol with TBAF induced the formation of the oxazolidinone ring, and the stereoselective reduction of the double bond, followed by treatment with hydrazine and KOH provided *cis*-substituted tetrahydroisoquinoline **2.43**. Then, conversion of the amino and hydroxyl groups into their silyl derivatives, followed by treatment with glycine derived mixed anhydride **2.44** provided amide **2.45**. Hemiaminal thioeter **2.46** was obtained by oxidizing the primary alcohol and treating the resulting hemiaminal ether with tiophenol under acidic conditions. The alkylation of **2.46** with iodide **2.47**, followed by inversion of the stereocenter with *tert*-BuLi and removal of the TIPS protecting group gave **2.49**. Then, oxidation under Swern conditions[39] and conversion of the resulting aldehyde into the silyl enol ether provided **2.50**. The formation of the diazabicyclo[3.2.1]octane ring system was achieved by treatment with $AgBF_4$, which triggers an *N*-acyliminium ion cyclization. The final three steps of the sequence

involve hydrogenolysis of the benzyl groups with Pearlman's catalyst, the removal of the *N*-Boc carbamate under acidic and the oxidation of the aromatic ring with ceric ammonium nitrate.

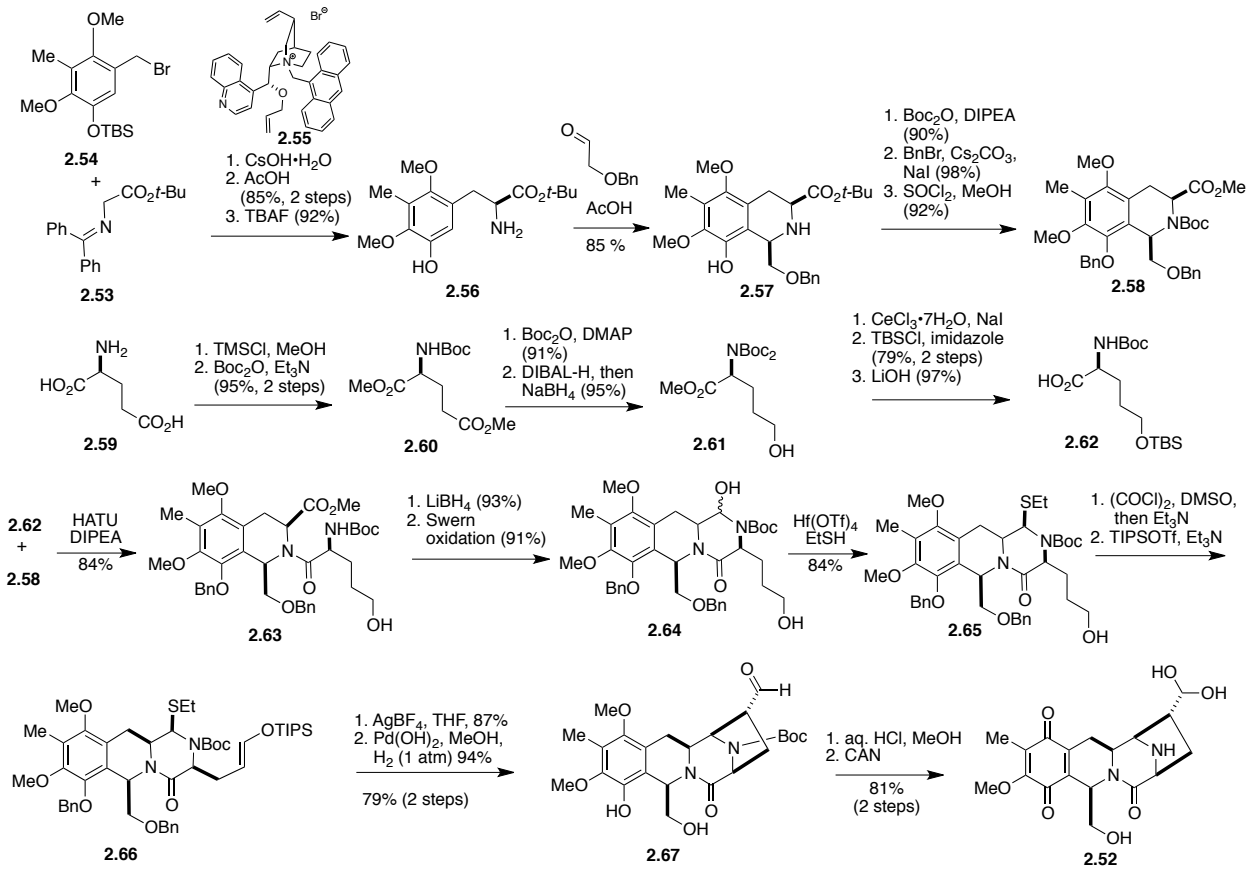


Scheme 2.5. Magnus' synthesis of lemonomycinone amide (**2.52**)

2.4 Zhu's asymmetric synthesis of lemonomycinone amide

In 2009, Zhu and coworkers published an asymmetric synthesis of lemonomycinone amide, which involved an overall strategy that replicated Magnus' approach for the construction of the diazabicyclo[3.2.1]octane ring system *via* a Lewis acid induced *N*-acyl iminium ion cyclization (*vide supra)*.[35b] The synthesis of the *cis*-tetrahydroisoquinoline fragment started with the enantioselective alkylation of *tert*-butyl glycinate **2.53** with benzyl bromide **2.54** in the presence of Corey-Lygo's phase transfer catalyst (**2.55**),[47,48] followed by hydrolysis of the imine and removal of the phenolic TBS ether to give tyrosine derivative **2.56** (Scheme 2.6). Then, a

Pictet-Spengler reaction between **2.56** and benzyloxyacetaldehyde provided *cis*-substituted tetrahydroisoquinoline **2.57**. Protection of the secondary amino group as the Boc carbamate, followed by benzylation of the phenol and methanolic acidolysis of the *tert*-butyl ester furnished compound **2.58**.

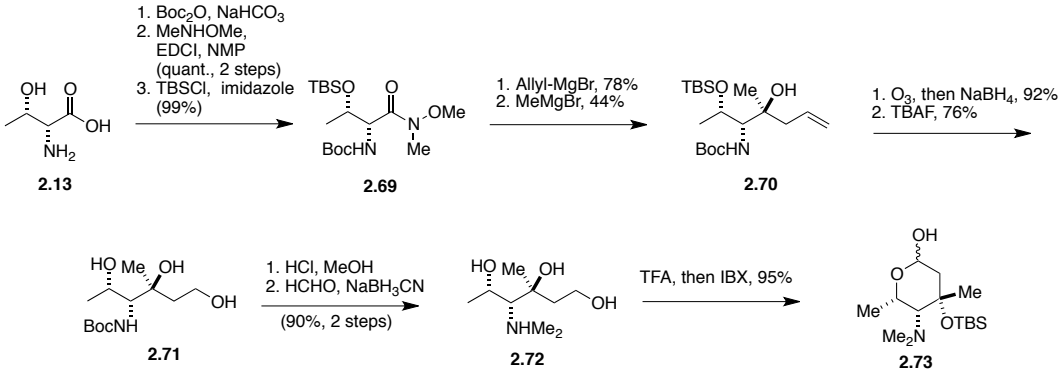


Scheme 2.6. Zhu's asymmetric synthesis of lemonomycinone amide (**2.52**)

The sequence used for the conversion of L-glutamic acid (**2.59**) into **2.61** comprises an esterification, two consecutive Boc protection steps, a regiospecific reduction of the less sterically hindered ester with DIBAL-H and a reduction with $NaBH_4$ to form the primary alcohol. Then, removal of one of the *N*-Boc groups with cerium chloride, followed by TBS protection of the primary alcohol and hydrolysis of the ester with LiOH provided compound **2.62**. Tetrahydroisoquinoline **2.58** and amino acid **2.62** were combined under peptide coupling

conditions to provide amide **2.63**. After the reduction of the methyl ester with lithium borohydride, the resulting primary alcohol was oxidized under Swern conditions[39] to afford hemiaminal **2.64**. Then, treatment with ethanothiol and hafnium triflate provided hemiaminal thioether **2.65**. This compound was converted into (-)-lemonomycinone amide using the same 5-step sequence employed by Magnus for the conversion of hemiaminal thioether **2.49** into (±)-lemonomycinone amide (*vide supra*).

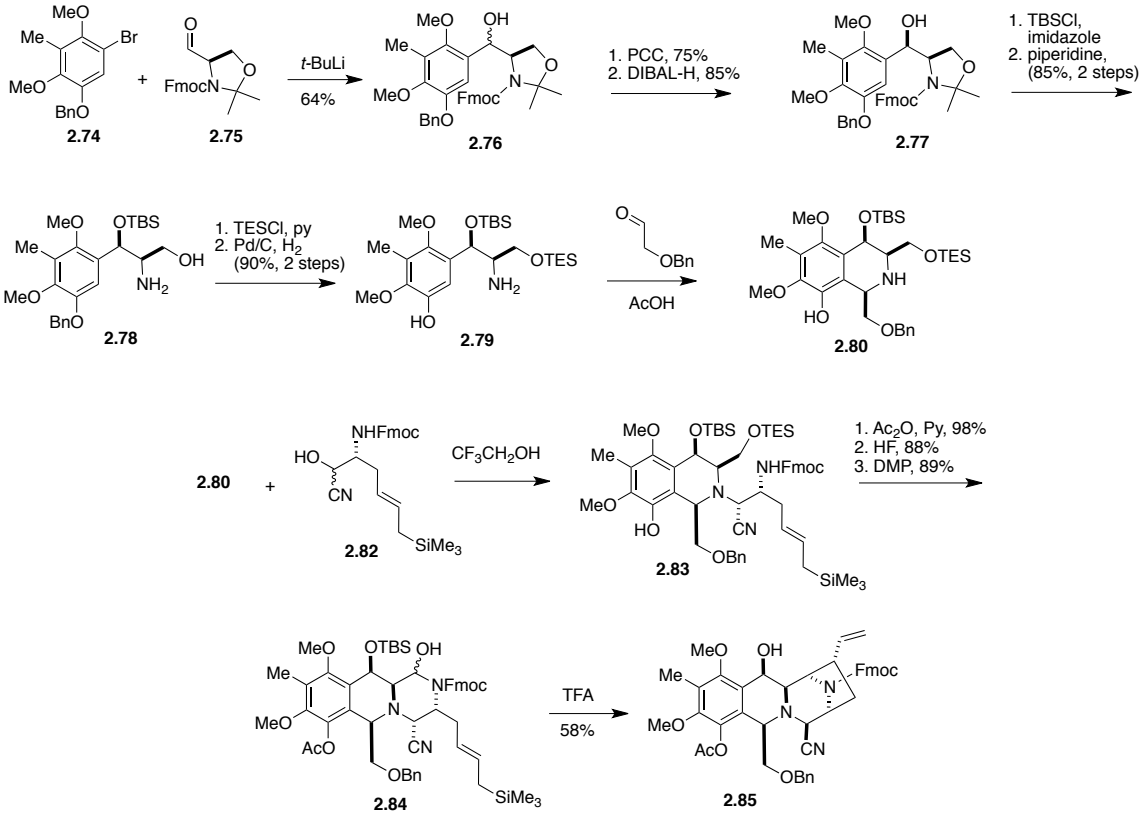
2.5 Zhu's asymmetric synthesis of lemonose



Scheme 2.7. Zhu's asymmetric synthesis of lemonose

In 2011, Zhu and coworkers published a synthesis of lemonose (**2.73**), the deoxyaminosugar found in lemonomycin.[36] Their sequence starts with the conversion of D-threonine (**2.13**) into Weinreb amide **2.69** (Scheme 2.7). Then, the treatment of allylmagnesium bromide, followed by a diastereoselective addition of methylmagnesium bromide provided tertiary alcohol **2.70**. Ozonolysis of the double bond with sodium borohydride as reducing agent, followed by treatment with TBAF furnished compound **2.71**. After removal of the Boc carbamate with methanolic HCl, the resulting amine was bis-methylated under reductive amination conditions. The final step involved the regioselective oxidation of the primary alcohol, which was accomplished with the treatment of **2.72** with IBX under acidic conditions**,** to give lemonose (**2.73**).

2.6 Mulzer's asymmetric construction of the tetracyclic core

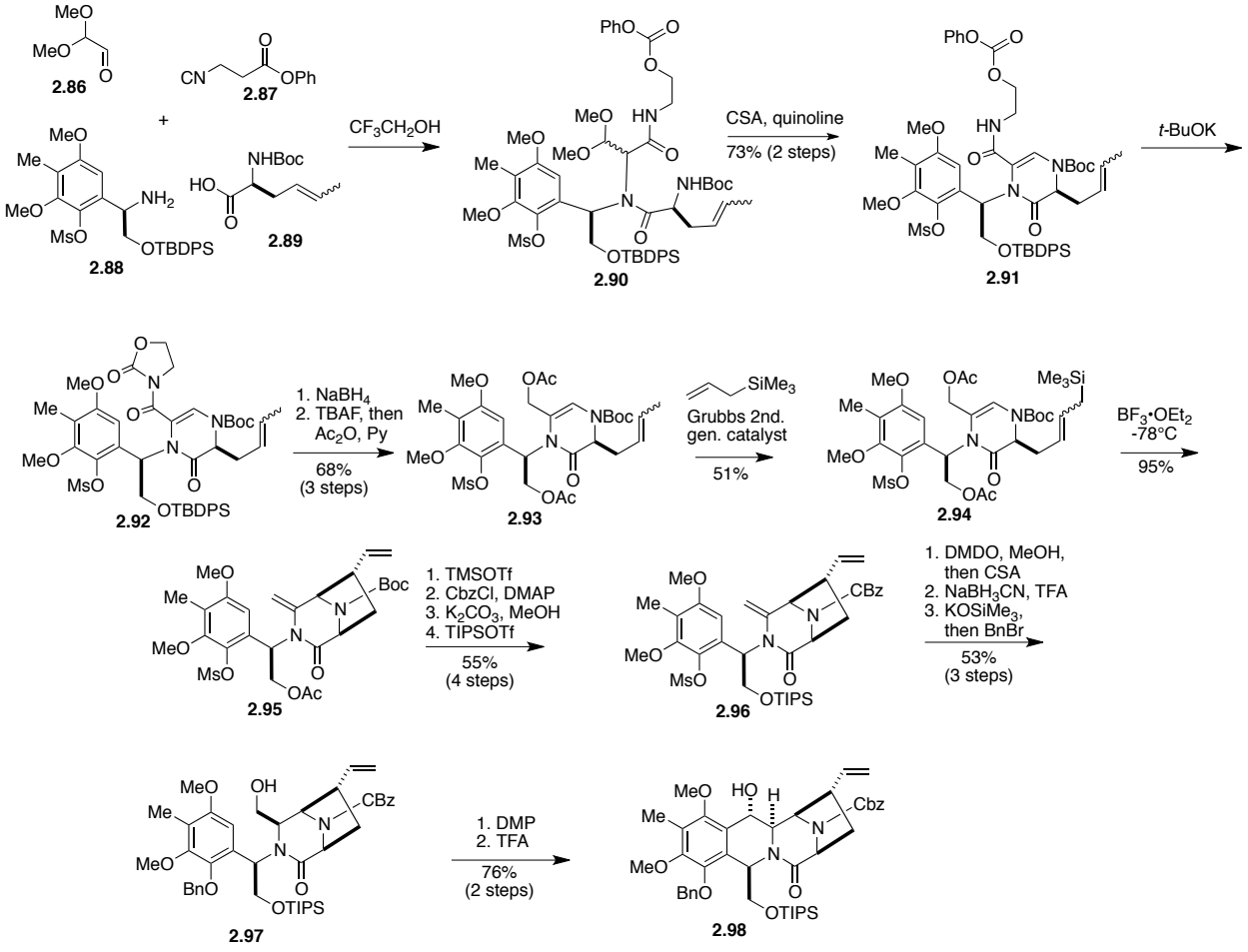


Scheme 2.8. Mulzer's synthesis of tetracycle **2.85**

In 2008, Mulzer and co-workers published a report of the asymmetric construction of the tetracyclic core of lemonomycin.[37] As shown in Scheme 2.8, their synthetic sequence started with the addition of the organolithium derivative of **2.74** into the Fmoc variant of *(R)*-Garner's aldehyde (**2.75**)[49] to afford alcohol **2.76** as a mixture of diastereomers, which was subjected to an oxidation-reduction sequence to provide **2.77** stereoselectively. Then, protection of the secondary alcohol as the TBS ether, followed by treatment with piperidine to cleave the Fmoc carbamate and the oxazolidine ring furnished aminoalcohol **2.78**. After protection of the primary alcohol as the TES ether and deprotection of the phenolic hydroxyl, the resulting aminophenol **2.79** was combined with benzyloxyacetaldehyde in a Pictet-Spengler reaction to form tetrahydroisoquinoline **2.80**. This compound was combined with cyanohydrin **2.82**[50] in

trifluoroethanol to give compound **2.83** as a mixture of diastereomers, which were separable *via* column chromatography. Then, acetylation of the phenol of the major diastereomer, followed by selective deprotection of the primary hydroxyl with HF and oxidation with Dess-Martin periodinane[51] provided hemiaminal **2.84**. The completion of the sequence was achieved by treating **2.84** with TFA to induce the formation of an *N*-acyl iminium ion that triggers the intramolecular Hosomi-Sakurai reaction, which leads to tetracycle **2.85**.

2.7 Fukuyama's asymmetric construction of the tetracyclic core



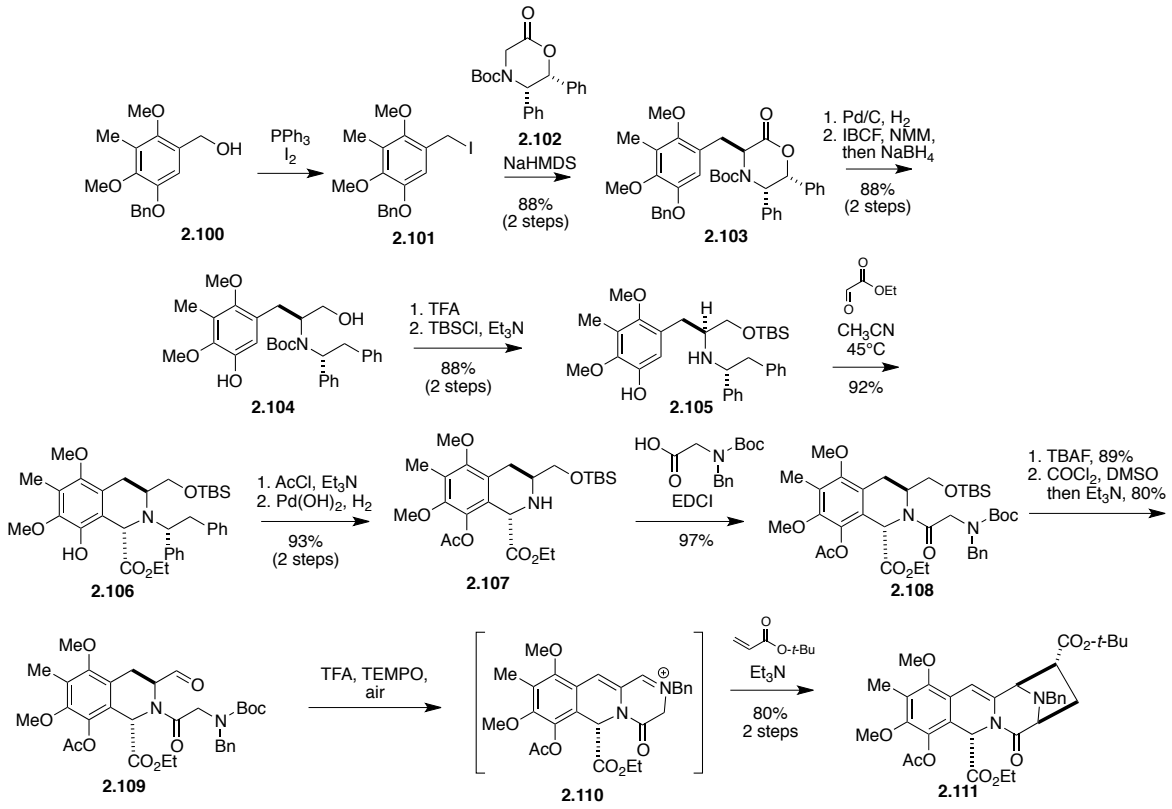
Scheme 2.9. Fukuyama's synthesis of tetracycle **2.98**

In 2005, a report from Fukuyama and coworkers described the assembly of the tetracyclic core of lemonomycin.[32] Their sequence starts with an Ugi four-component reaction[52] that forms peptide **2.90** (Scheme 2.9). Acid-promoted formation of the piperazinone, followed by treatment with potassium *tert*-butoxide provided compound **2.92**. Then, reduction of the exocyclic amide with $NaBH_4$, removal of the TBDPS protecting group and acetylation provided compound **2.93**. This compound was combined with allyltrimethylsilane in a cross metathesis reaction using Grubbs second-generation catalyst, to furnish compound **2.94**. Treatment with BF_3 etherate induced the formation of a conjugated *N*-acyl iminium ion, which underwent an intramolecular Hosomi-Sakurai reaction that formed the diazabicyclo[3.2.1]octane ring system of **2.95**. A four-step sequence was used to exchange the *N*-Boc and acetate groups for *N*-Cbz and TIPS groups, respectively, and form **2.96**. Then, the sequential treatment of this compound with DMDO and camphorsulfonic acid, followed by a stereospecific reduction with $NaBH_3CN$ under acidic conditions and exchange of the mesylate group for a benzyl group provided compound **2.97**. The sequence was completed with the oxidation of the primary alcohol with Dess-Martin periodinane[51] and the cyclization of the resulting aldehyde in a Friedel-Crafts hydroxyalkylation reaction, to form the tetrahydroisoquinoline fragment and provide tetracycle **2.98**.

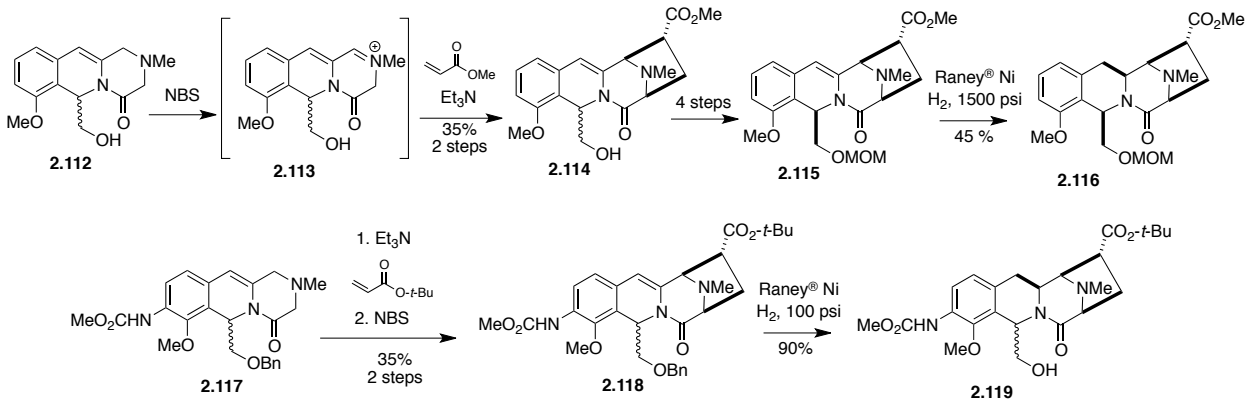
2.8 Williams' synthesis of the tetracyclic core

In 2007, Williams and coworkers published an asymmetric approach for the construction of the tetracyclic core of lemonomycin.[38,53] As shown in Scheme 2.10, the sequence starts with the conversion of alcohol **2.100**[54] into iodide **2.101**, which was coupled with *N*-Boc oxazinone **2.102**[55] to provide intermediate **2.103**. Then, selective hydrogenolysis of the lactone fragment, followed by conversion into a mixed anhydride and reduction with sodium borohydride furnished alcohol **2.104**. The *N*-Boc group was cleaved with TFA and the primary alcohol was

converted into the TBS ether to afford aminophenol **2.105**, which was converted into tetrahydroisoquinoline **2.106** in a Pictet-Spengler reaction with ethyl glyoxalate. After conversion of the phenolic hydroxyl into an acetate and removal of the 1,2-diphenylethyl fragment, the resulting tetrahydroisoquinoline **2.107** was combined with *N*-Bn-*N*-Boc-Gly under peptide coupling conditions. Removal of the TBS ether and oxidation under Swern conditions[39] provided aldehyde **2.109**, which was treated with TFA and TEMPO under air to form conjugated iminium ion **2.110**. Treatment with triethylamine formed an azomethine ylide, which underwent a [3+2] dipolar cycloaddition with *tert*-butyl acrylate to form tetracycle **2.111**.



Scheme 2.10. Williams' synthesis of tetracycle **2.111**



Scheme 2.11. Construction of the tetracyclic cores of quinocarcinamide and tetrazomine

A similar [3+2] dipolar cycloaddition strategy was used by Williams for the construction of the [3,8]-diazabicyclo ring system in the total syntheses of (-)-tetrazomine[56] and (±)-quinocarcinamide.[57] As shown in Scheme 2.11, the sequences involve the generation of an iminium ion *via* a NBS oxidation of a tricyclic allylic amine, followed by formation an azomethine ylide and its reaction with an acrylate ester. Both sequences required the reduction of the enamide double bond to complete the formation of the tetrahydroisoquinoline fragment found in the natural products. Treatment of **2.115** and **2.118** with H_2 and Raney® Nickel provided compounds **2.116** and **2.119**, respectively. However, in the synthetic sequence towards lemonomycin the attempts to effect a similar transformation were unsuccessful.[58] Compound **2.111** proved to be unreactive under a number of hydrogenation conditions, which included multiple catalysts and elevated pressures. These findings prompted the preparation of several derivatives of **2.111**, but all of the attempts to reduce the enamide double bond failed. The substrates and conditions of the attempted hydrogenation conditions are listed in Appendix 1.

CHAPTER 3

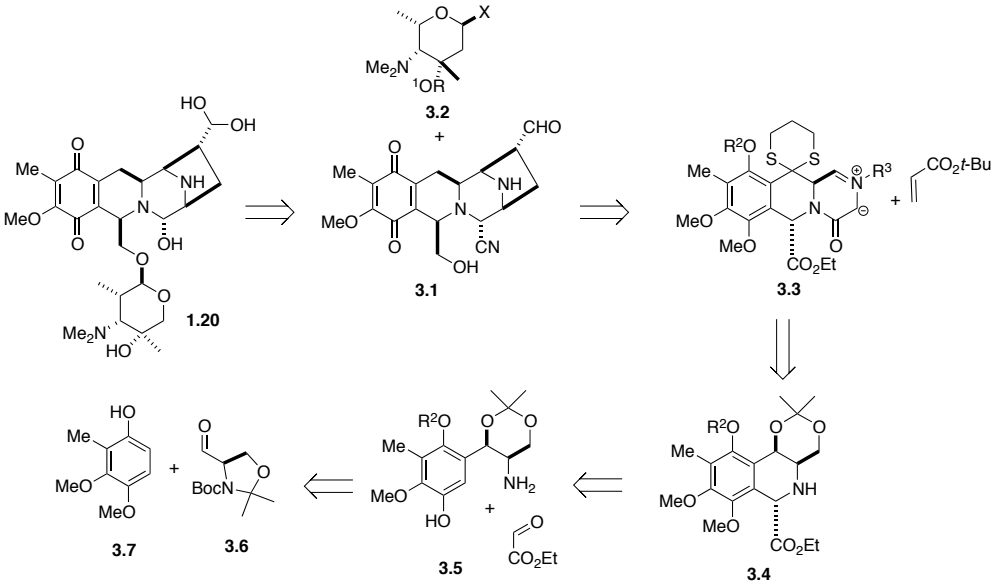
Studies towards the synthesis of lemonomycin

3.1 Synthetic goals

The primary goal of the project was the development of a concise, novel and high yield route for the asymmetric synthesis of (-)-lemonomycin (**1.20**). In our initial strategy, we intended to explore the use of Williams' [3+2] dipolar cycloaddition approach, which was described in Section 2.8. Our plan involved the preparation of substrates that would prevent the formation of the enamide double bond, in an attempt to circumvent the problems encountered with its lack of reactivity under catalytic hydrogenation conditions.

3.2 Dithiane approach

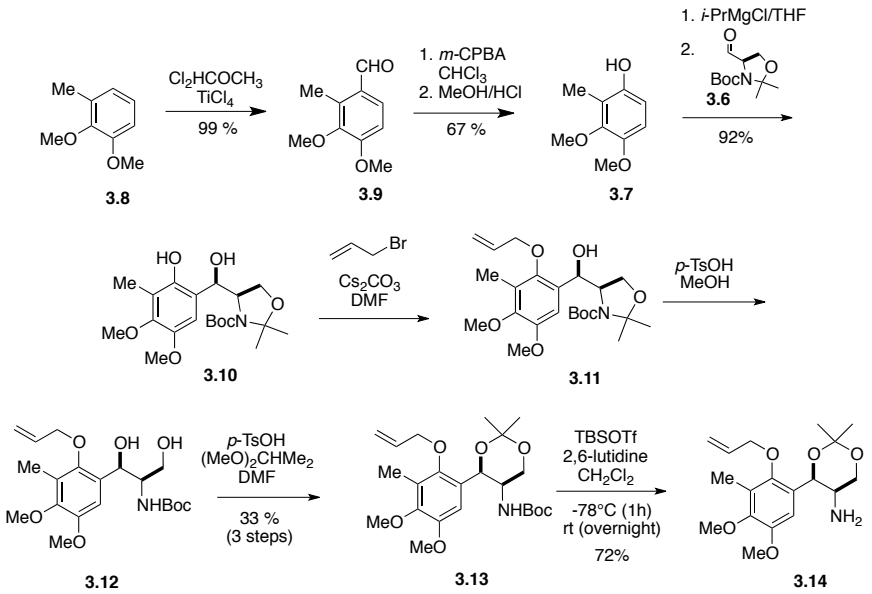
3.2.1 Retrosynthetic analysis



Scheme 3.1. Initial retrosynthetic analysis

We envisioned lemonomycin as the result of a late stage glycosylation of tetracycle **3.1** using lemonose derivative **3.2** (Scheme 3.1). Compound **3.1** could be derived from the cycloadduct of *tert*-butyl acrylate and azomethine ylide **3.3**. We expected that the presence of the dithiane moiety at the benzylic position of **3.3** would prevent the tautomerization process that leads to the formation of the enamide double bond. This intermediate could be prepared in several steps from tetrahydroisoquinoline **3.4**, which in turn would be the product of a Pictet-Spengler reaction between aminophenol **3.5** and ethyl glyoxalate. Finally, **3.5** could be prepared form the coupling product of phenol **3.7** and *(R)*-Garner's aldehyde **3.6**[59] under modified Casiraghi conditions.[60,61]

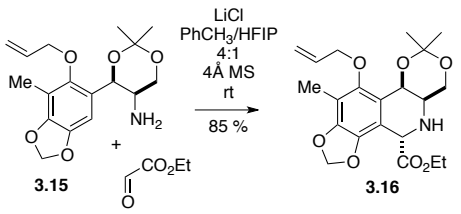
3.2.2 Synthesis of the first Pictet-Spengler substrate



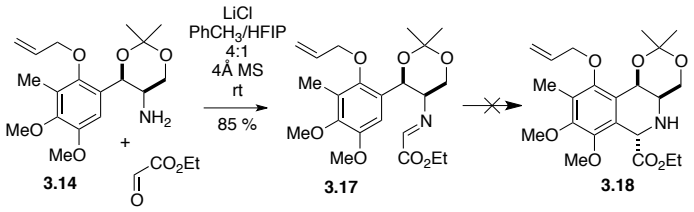
Scheme 3.2. Synthesis of compound **3.14**

Commercially available 2,3-dimethoxytoluene (**3.8**) was formylated under Rieche-Gross conditions and the resulting aldehyde (**3.9**) was treated with *m*-CPBA to provide phenol **3.7** (Scheme 3.2). This compound was sequentially treated with *i*-PrMgCl and *(R)*-Garner's aldehyde

3.6 to provide **3.10** in 92% yield. Allylation of the phenol, followed by acid-mediated methanolysis of the oxazolidine and conversion of the resulting diol into an acetonide afforded **3.13** in 33% yield. Then, the *N*-Boc carbamate was removed under Ohfune conditions[62] to furnish compound **3.14** in 72% yield. The compound was treated with the conditions described by Zhu and coworkers for the conversion of amine **3.15** into tetrahydroisoquinoline **3.16** (Scheme 3.3).[61] Intriguingly, despite the structural similarity between both compounds, **3.14** was not converted into the corresponding tetrahydroisoquinoline **3.18**, and only imine **3.17** was observed in the reaction mixture (Scheme 3.4). The use of higher temperatures (i.e. 40, 80 and 120 °C) led to the decomposition the imine, and the use of an alternate Brønsted acid (i.e. BHT) gave similar results.



Scheme 3.3. Zhu's Pictet-Spengler reaction

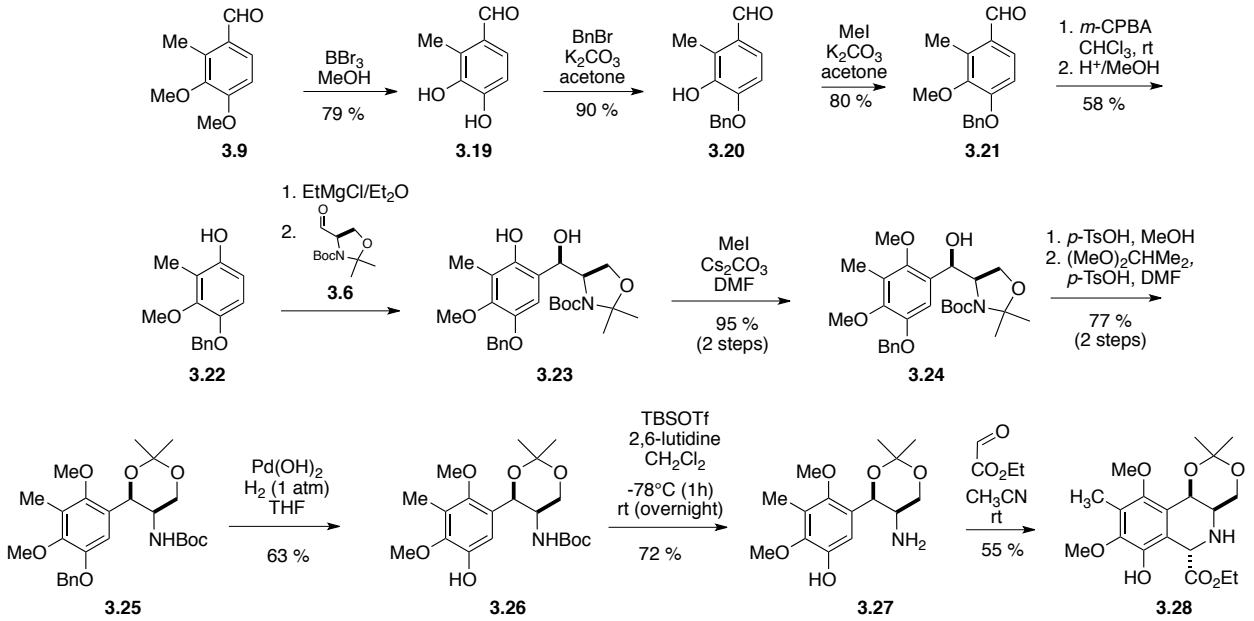


Scheme 3.4. Attempted synthesis of tetrahydroisoquinoline **3.18**

3.2.3 Formation of the tetrahydroisoquinoline system

We decided to abandon the initial route in favor of a synthetic sequence involving a Pictet-Spengler substrate with a free hydroxyl *ortho* to the unsubstituted aromatic position. This required the preparation of phenol **3.22**, which was accomplished in four steps from

benzaldehyde **3.9** (Scheme 3.5). The sequence involved bis-demethylation, selective protection of the hydroxyl *para* to the formyl group, methylation and a Dakin oxidation. The treatment of **3.22** with EtMgBr and *(R)*-Garner's aldehyde, followed by selective methylation of the phenolic hydroxyl gave compound **3.24** in 95% yield. The oxazolidine was cleaved under acidic conditions and the resulting diol was transformed into the acetonide to give **3.25** in 77% yield. Then, hydrogenolysis of the benzyl group with Pearlman's catalyst and removal of the Boc group under Ohfune conditions[62] gave aminophenol **3.27**. A Pictet-Spengler reaction between **3.27** and ethyl glyoxalate provided tetrahydroisoquinoline **3.28**.

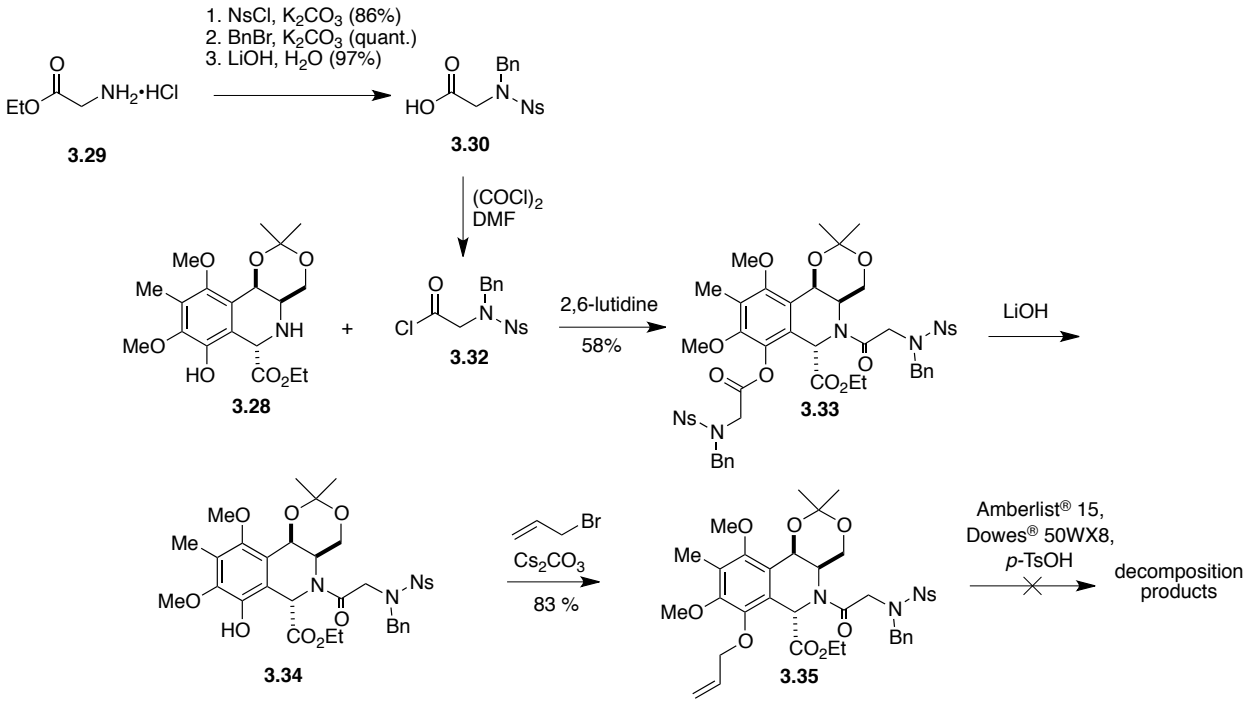


Scheme 3.5. Synthesis of tetrahydroisoquinoline **3.28**

3.2.4 Incorporation of the of the glycine fragment

A three-step sequence was used to transform glycine ethyl ester (**3.29)** into *N*-Bn-*N*-Ns-Gly (**3.30**) (Scheme 3.6). Then, treatment with oxalyl chloride provided acyl chloride **3.32**, which was reacted with tetrahydroisoquinoline **3.28** to provide compound **3.33**. Selective hydrolysis of the ester with lithium hydroxide, followed by conversion of the phenol into an allyl

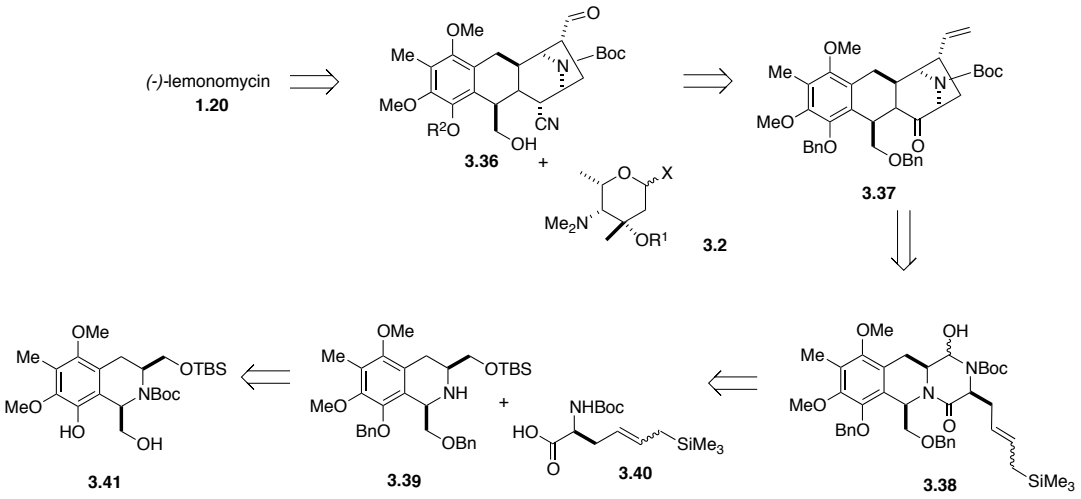
ether gave compound **3.35**. Our original plan for this compound involved the removal the acetonide, the selective protection of the primary alcohol and the oxidation of the secondary alcohol to form a ketone, which eventually would have allowed the installation of a 1,3-dithiane protecting group. However, the conditions tested for the hydrolysis of the acetonide led to decomposition of the starting material. These results prompted the re-evaluation of the synthetic approach that revealed that the planned number of steps for the construction of the tetracyclic core was close to 40 and we decided to abandon this route in favor of a more concise and convergent approach.



Scheme 3.6. Synthesis of amide **3.35**

3.3 Hosomi-Sakurai approach

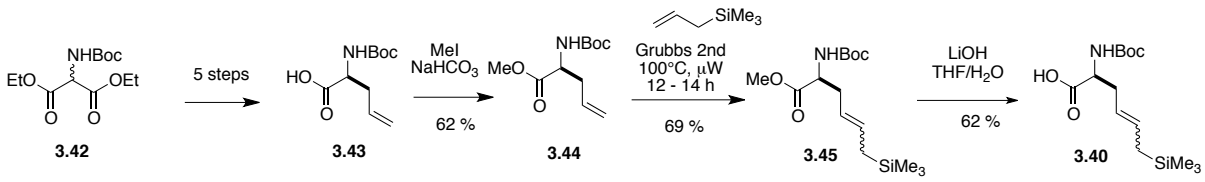
3.3.1 Retrosynthetic analysis



Scheme 3.7. Retrosynthetic analysis

As shown in Scheme 3.7, we envisioned lemonomycin as the result of the late stage glycosylation of tetracycle **3.36**, which could be derived form compound **3.37**. This compound could be obtained through an acid-catalyzed Hosomi-Sakurai reaction involving intermediate **3.38**, which could be accessed through the coupling of *(S)-N*-Boc-allylglycine **3.40** and tetrahydroisoquinoline **3.39**. This intermediate could be prepared from **3.41**, which is a known compound.[53]

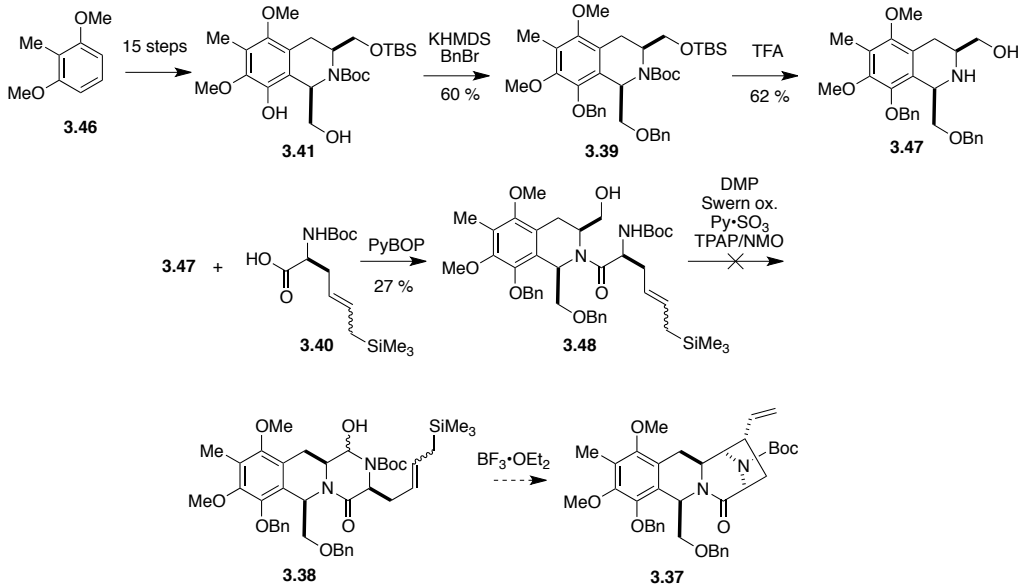
3.3.2 Synthesis of the allyltrimethylsilane glycine derivative



Scheme 3.8. Synthesis of carboxylic acid **3.40**

The preparation of the first coupling partner started with the synthesis of *(S)-N*-Boc-allylglycine (**3.43**) from diethylaminomalonate (**3.42**), using the 5-step sequence described by Berner and coworkers (Scheme 3.8).[63] Acid **3.43** was esterified with methyl iodide and sodium bicarbonate to give compound **3.44**. Treatment with allyltrimethylsilane and Grubbs second-generation catalyst under microwave irradiation gave **3.45**, which was converted into the desired acid **3.40** through LiOH-mediated hydrolysis and acidification.

3.3.3 Attempted formation of the cyclization precursor



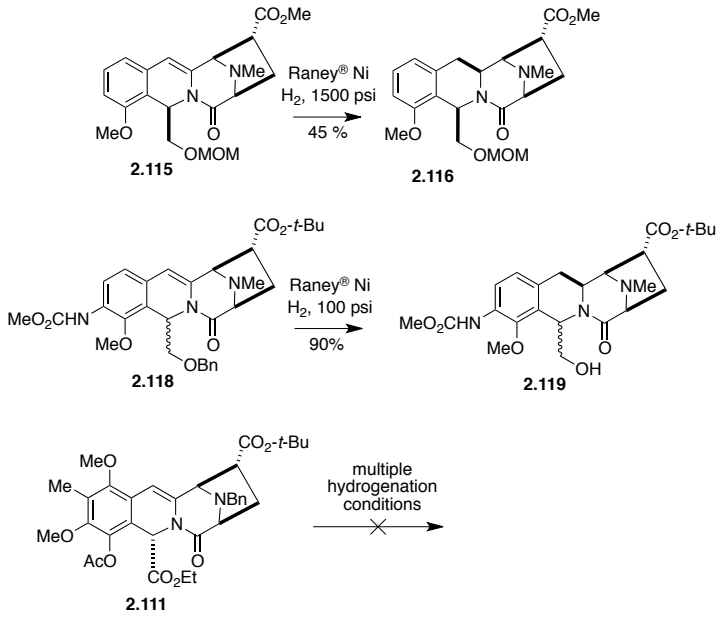
Scheme 3.9. Attempted formation of hemiaminal **3.38**

As shown in Scheme 3.9, the preparation of the tetrahydroisoquinoline fragment started with the synthesis of compound **3.41**, using a 15-step sequence from 2,6-dimethoxytoluene, which was described in a previous report from the Williams group.[53] The synthesis of **3.47** was achieved by bis-benzylation of **3.41**, followed by removal of the TBS and *N*-Boc protecting groups with trifluoroacetic acid. With compounds **3.47** and **3.40** in hand, we converted them in low yield into amide **3.48,** using PyBOP as the coupling reagent. We made several unsuccessful attempts to transform **3.48** into **3.38** using multiple oxidation conditions, including Swern oxidation,[39] TPAP/NMO,[64] Py•SO_3[65] and Dess-Martin periodinane.[51] These results prompted a new evaluation of the synthetic strategy in light of the publication of Mulzer's synthetic approach (*vide supra*),[37] which involved a very similar overall strategy that comprised the initial formation of the tetrahydroisoquinoline ring system and a homologous Hosomi-Sakurai reaction for the construction of the diazabicyclo[3.2.1]octane ring system. At that point in time we decided to abandon this route and to explore alternate synthetic approaches.

3.4 Redefinition of the synthetic strategy

An evaluation of the results discussed in the previous section prompted a reconsideration of the [3+2] dipolar cycloaddition strategy for the construction of the tetracyclic core. However, such endeavor required the implementation of a plan for addressing the issue of the reduction of the enamide double bond, which was discussed in Section 2.8. As shown in Scheme 3.10, there is a clear reactivity difference between compounds **2.115** and **2.118,** and compound **2.111** (Scheme 3.10) and its derivatives (Appendix 1). Our initial interpretation of these results was based on the apparent electronic differences between the aromatic rings of the two groups of compounds. We attributed the lack of reactivity of the enamide double bond to the higher number of electron donating aromatic substituents found in **2.111** and its derivatives. Therefore,

we decided to implement a synthetic plan aimed at the generation of hydrogenation substrates with less electron-rich aromatic moieties than the ones found in the unreactive compounds.

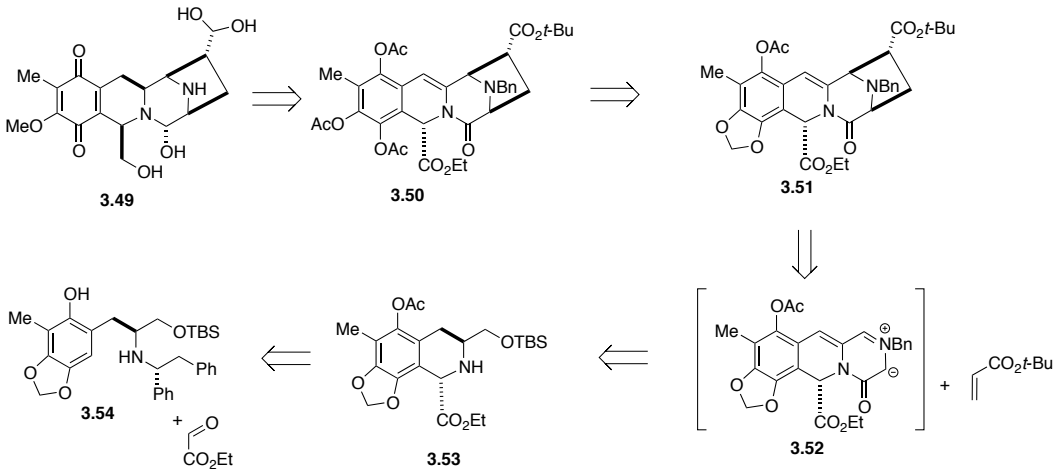


Scheme 3.10. Comparison of the hydrogenation substrates

3.5 Attempted formation of alternate cycloaddition precursors

3.5.1 Retrosynthetic analysis

In our updated synthetic plan, we envisioned that lemonomycin aglycon **3.49** could be derived from compound **3.50** through reduction of the double bond with three acetoxy susbstituents attached to the aromatic ring (Scheme 3.11). Compound **3.50** could be prepared with a sequence involving deacetylation, oxidation/cleavage of the methylenedioxy fragment,[66] reduction and acetylation, starting from compound **3.51**. This compound could be obtained as the product of a [3+2] dipolar cycloaddition involving *tert*-butyl acrylate and azomethine ylide **3.52**. This intermediate could be prepared from tetrahydroisoquinoline **3.53,** which could be formed with a Pictet-Spengler reaction between aminophenol **3.54** and ethyl glyoxalate.

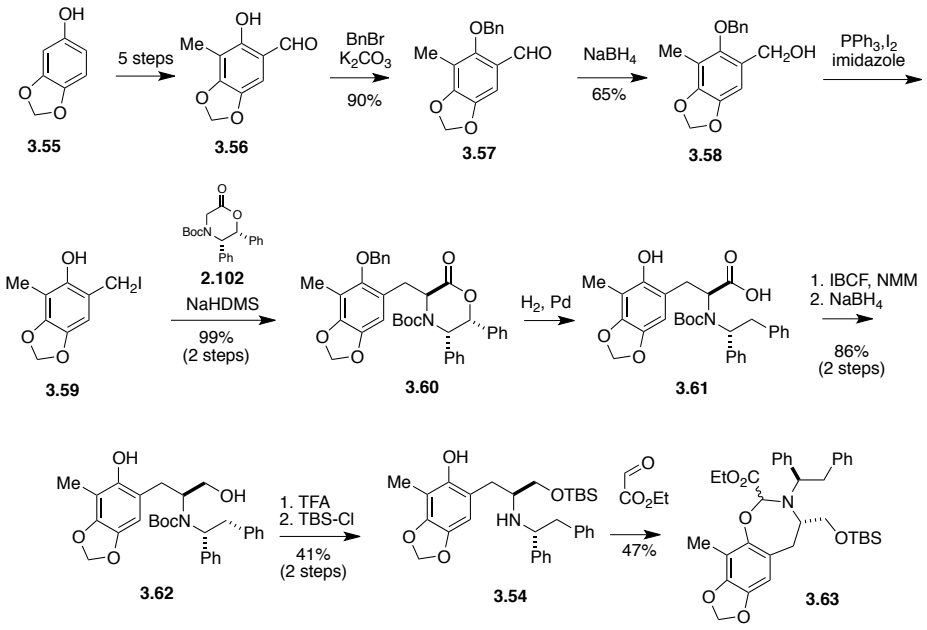


Scheme 3.11. Retrosynthetic analysis

3.5.2 Attempted formation of the tetrahydroisoquinoline system

We prepared aldehyde **3.56** using the 5-step sequence from sesamol (**3.55**) described by Saito and coworkers (Scheme 3.12).[67] Benzylation of the phenol, followed by reduction with sodium borohydride provided alcohol **3.58**. Then, we adapted the chemistry developed in the Williams group for the conversion of alcohol **2.100** into tetrahydroisoquinoline **2.106** (Scheme 2.10)[38, 53] to attempt the preparation of our desired tetrahydroisoquinoline system. Thus, alcohol **3.58** was transformed into the corresponding benzylic iodide (**3.59**), which was coupled with *N*-Boc oxazinone **2.102** to provide compound **3.60** in 99% yield. Selective hydrogenolysis of the lactone, followed by mixed anhydride formation and reduction with $NaBH_4$ afforded compound **3.62**, which was then converted into compound **3.54** after treatment with TFA to remove the *N*-Boc group and protection of the primary alcohol as the TBS ether. Aminophenol **3.54** was reacted with ethyl glyoxalate to provide a single diastereomer of a compound that was tentatively identified as oxazepane **3.63**. We submit that this result was caused by the nucleophilic attack of the phenolic oxygen onto the incipient imine. The obvious turnaround for this problem would involve the protection of the phenol and the use of Lewis or Brønsted acids to promote the

Pictet-Spengler reaction. However, we decided to focus on other concurrent approaches and no further experimental work was done with this route.

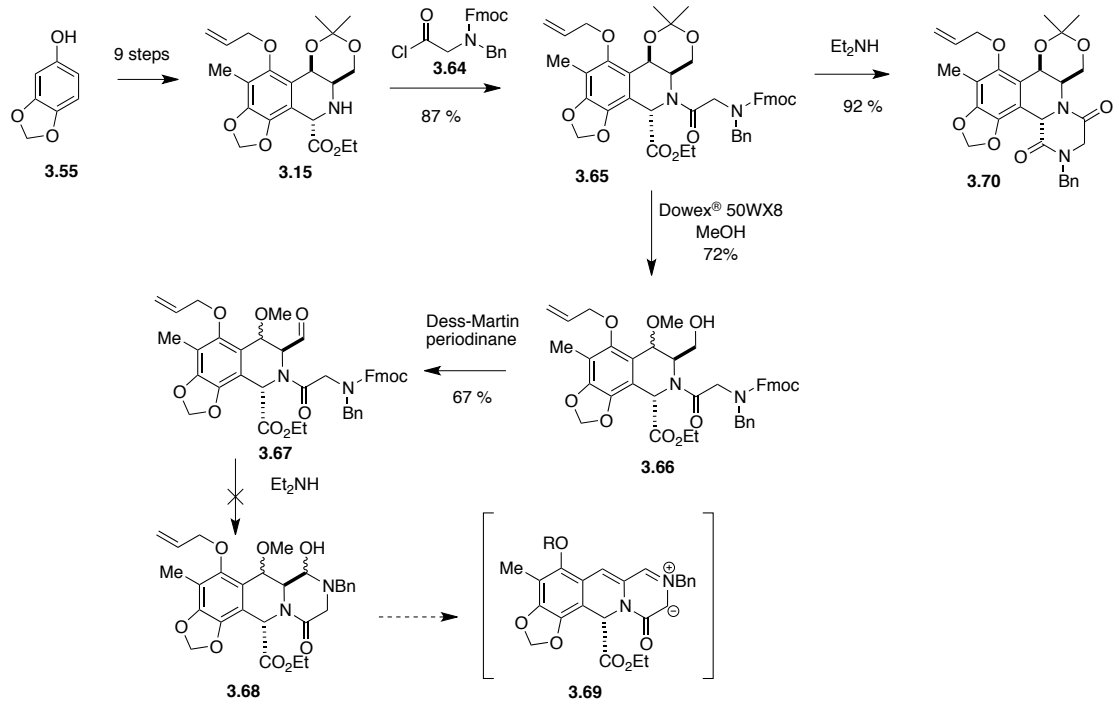


Scheme 3.12. Synthesis of oxazepane **3.63**

3.5.3 Attempted formation of a tricyclic hemiaminal

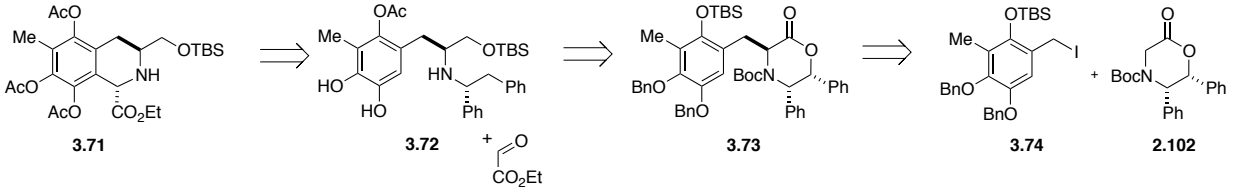
In an attempt to gain rapid access to our desired cycloaddition precursors, we decided to prepare known methylendioxy-substituted tetrahydroisoquinoline compounds, which can be accessed using concise routes. Consequently, we used the 9-step sequence described by Zhu and coworkers[61] to prepare compound **3.15** (Scheme 3.13). The reaction of **3.15** with acyl chloride **3.64** provided amide **3.65** in 64% yield. Treatment with Dowex® 50WX8 in methanol,[68] effected both the removal of the acetonide and the formation of the methyl ether to give compound **3.66**. Oxidation of primary alcohol with Dess-Martin periodinane[51] provided aldehyde **3.67**. The removal of the *N*-Fmoc group with diethylamine formed a single compound that could not be

identified as hemiaminal **3.68**, thus precluding the preparation of the desired azomethine ylide intermediate (**3.69**). This result prompted the modification of the sequence to attempt the removal of the *N*-Fmoc group in an earlier stage of the sequence. However, the treatment of compound **3.65** with diethylamine induced the formation of diketopiperazine **3.70**. At this stage we realized that the use of Fmoc as the protecting group in the glycine fragment was not compatible with our synthetic plan. However, our attempts to generate an analog of **3.65** with an *N*-Boc-*N*-Bn-glycyl fragment were unsuccessful. Therefore, we decided to focus on the other concurrent approaches that we were pursuing at that point in time and no further experimental work was done with this route.



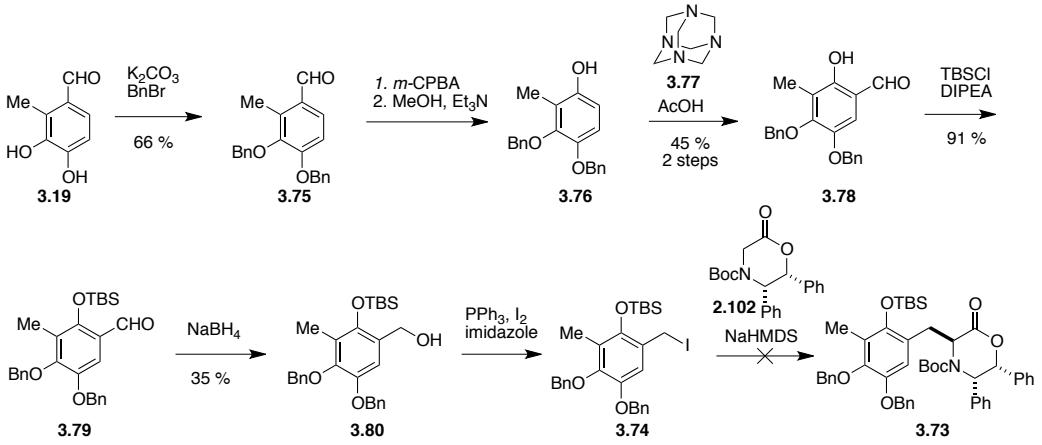
Scheme 3.13. Attempted formation of hemiaminal **3.68**

3.5.4 Orthogonally protected aromatic fragment approach.



Scheme 3.14. Updated rethrosynthetic analysis

We decided to modify the synthetic strategy outlined in Scheme 3.11, to attempt the formation of the tetrahydroisoquinoline using a Pictet-Spengler substrate that would include a hydroxyl group *ortho* to the unsubstituted aromatic position. As shown in Scheme 3.14, we envisioned that compound **3.71** could be accessed from aminocatechol **3.72** and ethyl glyoxalate. This compound could be derived from orthogonally protected oxazinone **3.73**, which in turn could be the product of the alkylation of *N*-Boc oxazinone **2.102** with benzylic iodide **3.74**. This plan mimics the strategy used for the preparation of compound **2.106** (Scheme 2.10) and the attempted formation of tetrahydroisoquinoline **3.53** (Schemes 3.11 and 3.12, *vide supra*).



Scheme 3.15. Attempted formation of oxazinone **3.73**

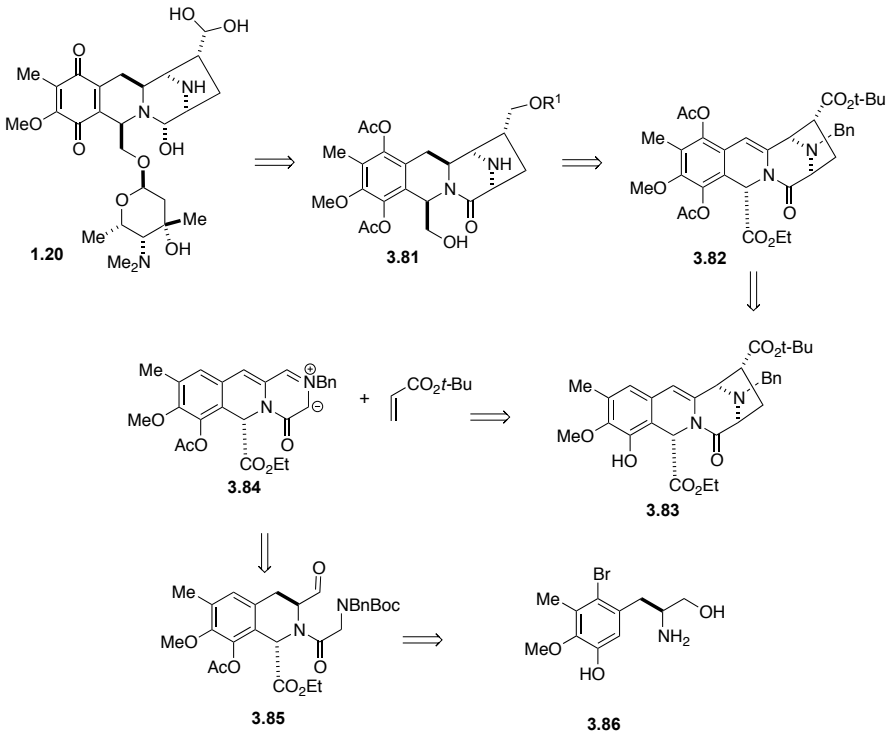
As shown in Scheme 3.15, the sequence that gave access to the orthogonally protected benzyl alcohol started with the bis-benzylation of aldehyde **3.19** to give **3.75.** A Dakin oxidation, followed by an *ortho*-formylation with hexamethylenetetramine in glacial acetic acid gave compound **3.78** in modest yield. Then, protection of the free phenol with TBSCl and DIPEA provided aldehyde **3.79**, which was reduced with $NaBH_4$ to give benzyl alcohol **3.80** in low yield. With this compound in hand, we unsuccessfully attempted its conversion into benzylic iodide **3.74** and the coupling with oxazinone **2.102**. The separation of the reaction mixture allowed the recovery of intact **2.102,** which was likely re-protonated during the aqueous quench, along with several unidentified products derived from **3.74**. We suspect that this result was caused by the low solubility of **3.74** in the reaction mixture, thus preventing the alkylation from happening. We submit that the solubility issues are caused by the large size of the benzyl, TBS and iodo substituents. Once again, we decided to focus on the other concurrent approach that we were pursuing at that point in time and no further experimental work was done with this route.

3.6 Construction of the tetracyclic core

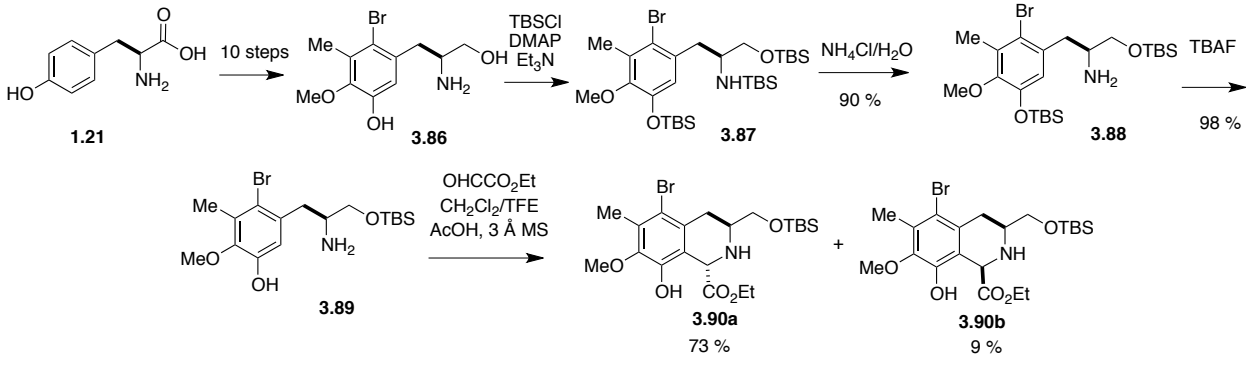
3.6.1 Retrosynthetic analysis

The unsatisfactory results discussed in previous sections forced a re-evaluation of the synthetic strategy and the exploration of alternative routes for the construction of the tetrahydroisoquinoline ring system. In our updated plan, we envisioned that lemonomycin could be accessed from compound **3.81**, which could be prepared from bis-acetoxy-substituted tetracycle **3.82** through reduction of the enamide double bond and epimerization of the southern benzylic position and reduction of the ester (Scheme 3.16). Compound **3.82** could be formed from tetracycle **3.83** through oxidation of the aromatic ring to the *para*-quinone, followed by reduction to the hydroquinone and acetylation. The preparation of **3.83** would involve the use of

the [3+2] dipolar cycloaddition involving azomethine ylide **3.84**, which could be obtained from aldehyde **3.85**. The tetrahydroisoquinoline system of **3.85** could be formed through a Pictet-Spengler reaction involving a derivative of bromotyrosinol **3.86**, which is a known compound.[69]



Scheme 3.16. Retrosynthetic analysis



Scheme 3.17. Synthesis of tetrahydroisoquinolined **3.90a** and **3.90b**

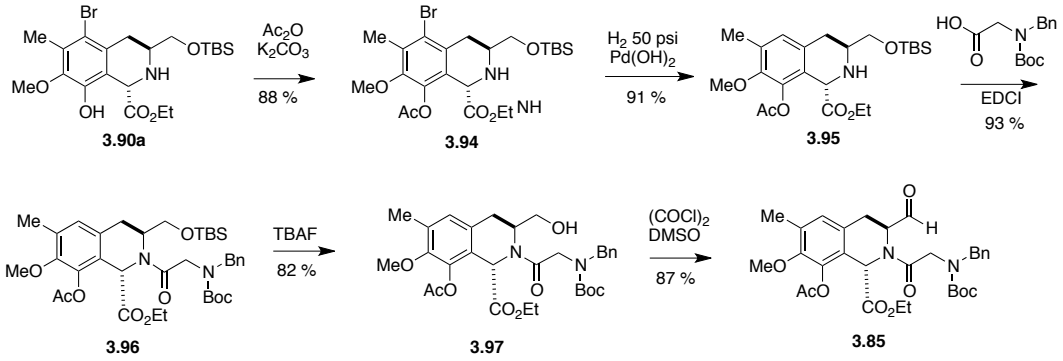
3.6.2 Synthesis of the tetrahydroisoquinoline fragment

The preparation of bromotyrosinol **3.86** (Scheme 3.17) was accomplished in 10 steps from L-tyrosine (**1.21)**, using the method described by Liao.[69] We initially attempted to perform the direct conversion of **3.86** into bis-silyl ether **3.88** using two equivalents of TBSCl, but the yields were inconsistent and low (<30%). The lack of reactivity of the primary hydroxyl of **3.86** is consistent with the regioselectivity observed in the reactions between TBSCl and diols bearing a β-aminoalcohol motif.[70] We concur with the explanation provided by the authors, which stated that the nucleophilicity of the primary hydroxyl is reduced by internal hydrogen bonding to the neighboring amino group. By increasing the relative amount of TBSCl to six equivalents, compound **3.86** was converted into the tris-silylated compound **3.87**. Unexpectedly, the hydrolysis of the silylamine function required a prolonged vigorous stirring with aqueous NH_4Cl at room temperature (~ 2h) to form the bis-silyl ether **3.88** in 90% yield. The phenolic silyl ether was selectively cleaved with one equivalent of TBAF at 0 °C,[71] to afford compound **3.89** in 98% yield.

The next step entailed the formation of the *trans*-tetrahydroisoquinoline ring *via* a Pictet-Spengler reaction between **3.89** and ethyl glyoxalate. Previously, our group reported a similar transformation, which was performed by stirring a solution of the starting materials in acetonitrile for 3.5 days at 50 °C, which afforded the *trans*- product stereospecifically.[53] A similar report by Zhu and coworkers involved the use of LiCl, hexafluorisopropanol and molecular sieves, and stirring the suspension in toluene at room temperature for 48 h.[61] Since none of these mild conditions led to the formation of the desired tetrahydroisoquinoline ring system, we decided to adapt the reaction conditions that were originally described by Zhu[72] to our substrate. The amount of acetic acid was reduced from 2.5 equivalents to 0.2 equivalents to

prevent cleavage of the *O*-TBS ether due to the prolonged exposure to the acid. In the present system, treatment of a solution of compound **3.89** and ethyl glyoxalate with CF_3CH_2OH, AcOH (0.2 eq.) and 4 Å MS afforded an 8:1 mixture of **3.90a** and **3.90b** in 82% yield. These two diastereomers were separated *via* flash chromatography

3.6.3 Formation of the tetracyclic ring system

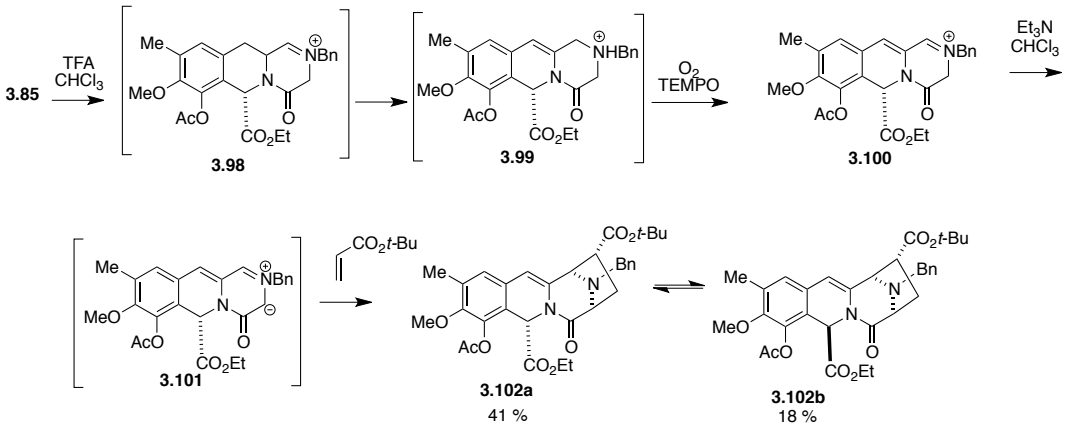


Scheme 3.18. Preparation of aldehyde **3.85**

As shown in Scheme 3.18, selective acetylation of compound **3.90a**,[73] followed by hydrogenolysis of the C-Br bond[69] provided tetrahydroisoquinoline **3.95** (Scheme 3.18). Following the conditions described in the previous report form the Williams group,[38] we converted compound **3.95** into aldehyde **3.85**, which is the substrate required for the [3+2] dipolar cycloaddition. Thus, tetrahydroisoquinoline **3.95** and *N*-Boc-*N*-Bn-Gly were coupled using EDCI, and the resulting amide was treated with TBAF to cleave the *O*-TBS ether and then oxidized under Swern conditions[39] to afford aldehyde **3.85**.

As illustrated in Scheme 3.19, aldehyde **3.85** was dissolved in $CHCl_3$ and treated under aerobic conditions with TFA[74,75,76] (50 eq.) and TEMPO (0.1 eq.), to generate iminium ion **3.98**, which tautomerizes to form ammonium ion **3.99**. This intermediate is autoxidized *in situ* to

afford conjugated iminium ion **3.100**, which was concentrated to dryness and taken up in $CHCl_3$. Addition of triethylamine induces the formation of azomethine ylide **3.101**, which is trapped *in situ* by *tert*-butyl acrylate to give a 2.4:1 mixture of tetracycles **3.102a** and **3.102b** in a combined 59% yield. We propose that the dipolarophile adds from the *Re* face of the iminium ion carbon to form **3.102a**, which epimerizes under the reaction conditions to form **3.102b.**



Scheme 3.19. Formation of cycloadducts **3.102a** and **3.102b**

3.6.4 Redefinition of the synthetic strategy

With compounds **3.102a** and **3.102b** in hand, we conducted a thorough examination of the previous related work, with the intention of choosing an optimal strategy for the reduction of the double bond. As part of such process, we built molecular models of the compounds that were successfully hydrogenated in the total syntheses of (-)-tetrazomine[56] and (±)-quinocarcinamide,[57] the newly synthesized tetracycles and some of the substrates that failed to undergo hydrogenation in the previous synthetic approach.[58] As shown in Figure 3.1, compounds **2.115** and **2.118a** have relatively small groups attached to the side of the tetracyclic structures that binds to the surface of the heterogeneous catalyst during the hydrogenation event. Moreover, we expect that an inversion of the configuration of the secondary amine nitrogen, which would

allow the formation of a coordinate bond, might improve the binding of the molecule to the catalyst and facilitate the reaction. The evaluation of the structure of **2.111** revealed several key facts that were overlooked during our previous assessments. First, we concluded that the formation of a bonding interaction between the enamide double bond carbons and the metal surface is not possible with a benzyl group attached to the amino nitrogen.

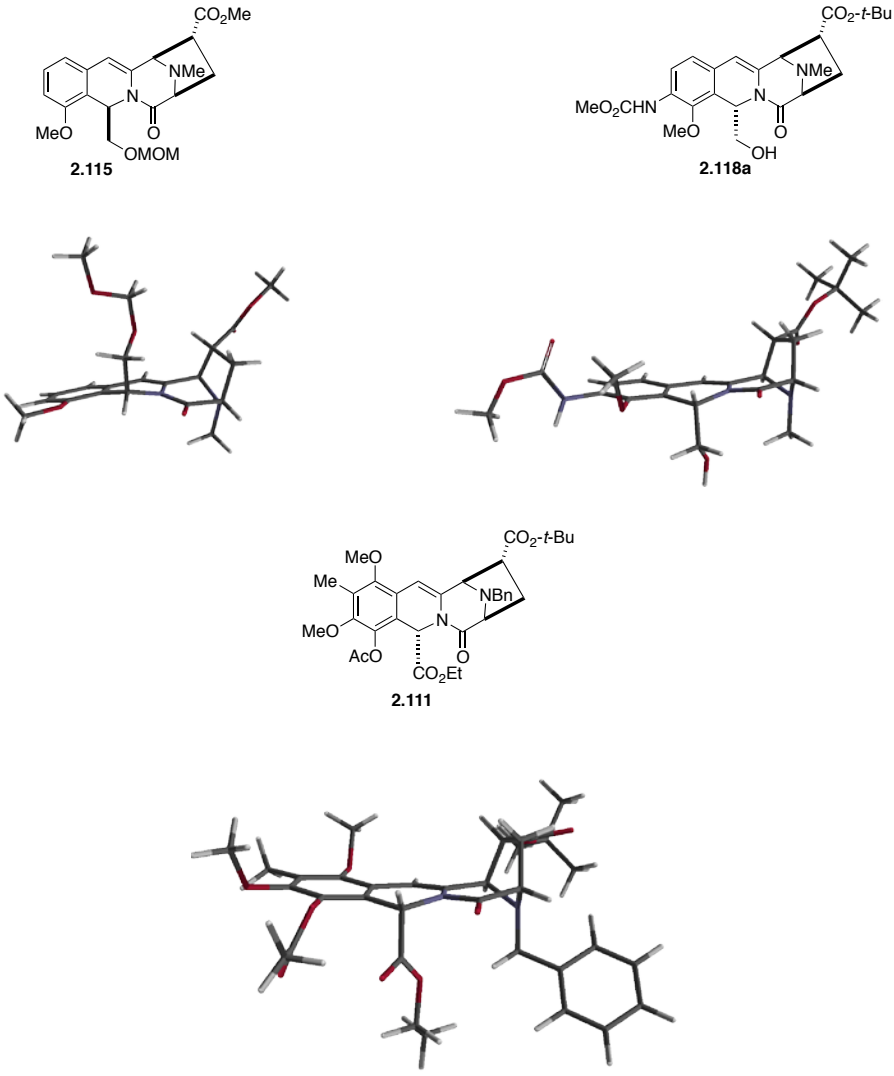
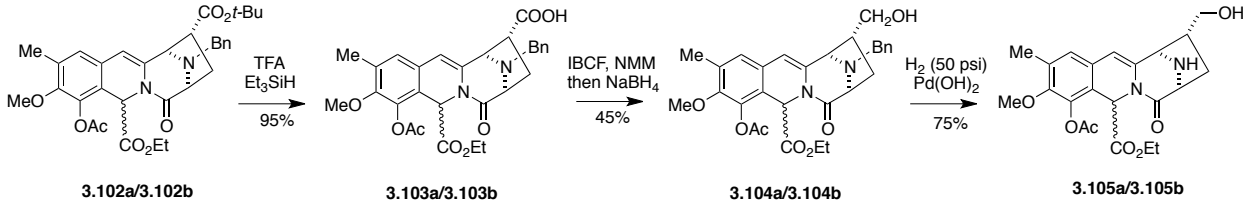


Figure 3.1. Representation of the calculated equilibrium geometry conformations[77] of compounds **2.115**, **2.118a** and **2.111**

Furthermore, we submit that inversion of the nitrogen configuration is not possible, because it would require the benzyl and *tert*-butyl ester substituents to be in close proximity. We also concluded that the ester groups of **2.111** prevent the formation of bonding interactions between the catalyst and the reactive centers, which would be required for a successful hydrogenolysis of the benzyl group. Therefore, we concluded that the removal of the benzyl group in our system would require the conversion of at least one of the ester groups into a smaller substituent (e.g., hydroxymethyl) or the inversion of the configuration at the southern benzylic position of the tetrahydroisoquinoline moiety. Lastly, we concluded that the reduction of the enamide double bound would require the removal of the benzyl group, and the conversion of the ethyl ester into a hydroxymethyl group or the inversion of the southern benzylic stereocenter.

3.6.5 Initial modification of the tetracyclic core

With the mixture of compounds **3.102a** and **3.102b** in hand, we attempted the use of basic conditions to modify the diastereomeric ratio. However, were unable to detect a change in the ratio using DBN, DBU, Cs_2CO_3 and Et_3N. The previous experiments conducted in the Williams group with similar systems indicated that reduction to the aldehyde is required for successful epimerization of the benzylic position.[56-58]



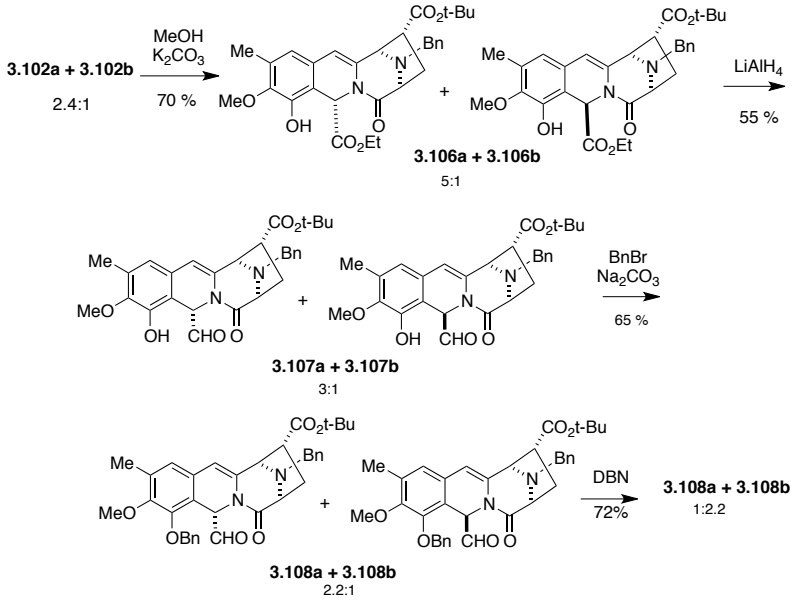
Scheme 3.20. Synthesis of compounds **3.105a** and **3.105b**

Then, we turned our attention to the conversion of the *tert*-butyl ester into a hydroxymethyl group to attempt the debenzylation of the piperazinone amine. Thus, following Williams group precedent,[58] treatment of **3.102a** and **3.102b** with TFA, followed by conversion into a mixed anhydride and reduction with sodium borohydride gave the desired mixture of epimeric alcohols **3.104a** and **3.104b** in moderate yield (Scheme 3.20). The use of standard conditions for the deprotection of tertiary benzylamines (Pearlman's catalyst, H_2 at 50 psi, EtOH) effected the conversion into **3.105a** and **3.105b** in 75% yield. This result confirmed one of the predictions discussed in the previous section, in relation to the influence of the *tert*-butyl ester group on the reactivity towards debenzylation of our tetracyclic compounds. At this stage, we decided to adopt a strategy aimed at the initial epimerization of the southern benzylic position, which involved attempting the debenzylation and transformation of the *tert*-butyl ester at later stages of the sequence. With this decision we intended to reduce the total number of steps in our planned sequence, because the use of a route utilizing compounds **3.105a** and **3.105b** would have required the installation of additional protecting groups on both the primary alcohol and the secondary amine.

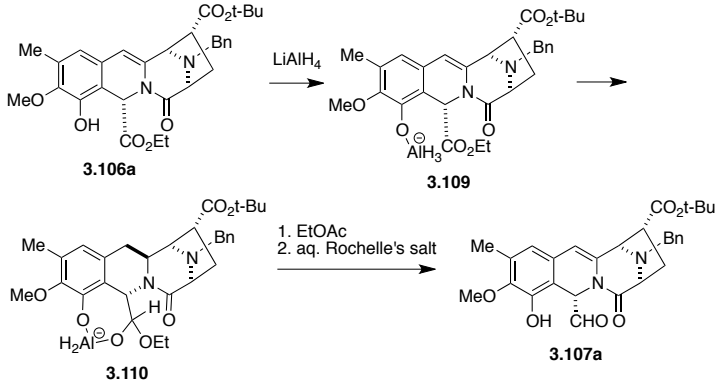
3.6.6 Epimerization of the southern benzylic stereocenter

Deacetylation of the **3.102a**/**3.102b** mixture under standard methanolysis conditions provided a 5:1 mixture of **3.106a** and **3.106b** in 70% yield (Scheme 3.21). We suggest that **3.106b** decomposes under the reaction conditions at a higher rate than **3.106a**, which provides an explanation for both the moderate yield and the change in the diastereomeric ratio. The chemoselective reduction of the ethyl esters with one equivalent of $LiAlH_4$ at -10 °C, afforded a 3:1 mixture of aldehydes **3.107a** and **3.107b** in 55% yield. As shown in Scheme 3.22, we propose that the observed chemoselectivity can be explained by the initial formation of a

phenoxyaluminum hydride species (**3.109**), which upon delivery one hydride to the ester, forms a stable 7-membered ring alkoxy(phenoxy)aluminum hydride species (**3.110**) that does not undergo a second hydride addition. We submit that the partial epimerization seen in this step is promoted by the slightly basic workup conditions.



Scheme 3.21. Synthesis of aldehydes **3.108a** and **3.108b**



Scheme 3.22. Proposed rationale for the chemoselective reduction of **3.106a/3.106b**

Then, treatment of **3.107a** and **3.107b** with BnBr and Na_2CO_3 formed the phenolic benzyl ethers and induced additional epimerization of the aldehyde's α carbon, to provide a 2.2:1

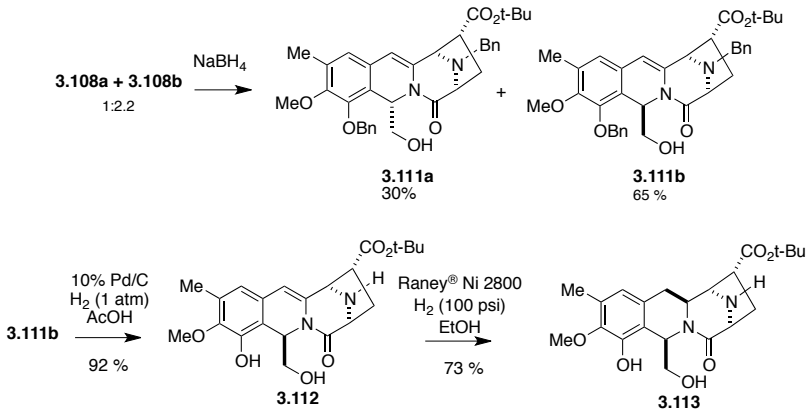
mixture of **3.108a** and **3.108b** which was then reacted with DBN in THF to invert the epimeric ratio (Scheme 3.21).[56-57,58] Since, these two compounds are very unstable to silica gel, we did not attempt their separation for the purpose of recycling of **3.108a**.

3.6.7 Hydrogenation of the enamide double bond

As shown in Scheme 3.23, the 1:2.2 mixture of aldehydes **3.108a** and **3.108b** was then treated with sodium borohydride to afford a mixture of alcohols **3.111a** and **3.111b**, which were separated *via* flash chromatography to give **3.111b** in 65% yield. The sequence used to transform the **3.102a/3.102b** mixture into **3.111b** not only provided the desired configuration in the benzylic position but also furnished an unhindered substrate for the *N*-debenzylation of the piperazinone amine. With compound **3.111b** in hand, we attempted the debenzylation reaction with the conditions used for the transformation of **3.104a**/**3.104b** into **3.105a**/**3.105b** (Pearlman's catalyst, H_2 at 50 psi, EtOH, Scheme 3.20). Unfortunately, the desired product was formed only the first attempted reaction and all the subsequent attempts to reproduce this result were unsuccessful. We tentatively identified the unstable product formed in the subsequent attempts as the corresponding bis-debenzylated hemiaminal ether, which could result from the reduction of the amide and the incorporation of EtOH. We also made several attempts using $Pd(OH)_2$ and aprotic solvents (e.g. THF, EtOAc), but only the *O*-debenzylation product was formed.

To our delight, the hydrogenolysis in glacial acetic acid (10% Pd/C, 1 atm) effected the bis-debenzylation of **3.111b** to afford **3.112** in 92% yield. The removal of the *N*-benzyl group provided the desired unhindered substrate for the hydrogenation of the enamide double bond. Gratifyingly, the treatment of **3.112** with Raney® nickel and H_2 100 psi[56] provided compound **3.113** in 73% yield. These two results confirmed our hypotheses about the role of the steric

factors in the outcome of both the debenzylation of the tertiary benzylamine and hydrogenation of the enamide double bond.



Scheme 3.23. Reduction of the enamide double bond

3.7 Concluding remarks

In summary, we have accomplished the asymmetric construction of the tetracyclic core of (-)-lemonomycin. An advanced tetracyclic intermediate was prepared from known bromotyrosinol **3.86** in sixteen steps. Efforts to gain access to (-)-lemonomycin through this advanced intermediate are currently under investigation.

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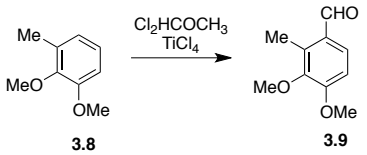
77. The equilibrium geometry conformations were calculated with Spartan'10, using the Hartree-Fock/3-21G model. Spartan'10, Wavefunction Inc. Irvine, CA.

CHAPTER 4

Experimental procedures

4.1 General conditions

Unless otherwise noted, all materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using flame-dried glassware. Organic solvents were degassed with argon and dried through a solvent purification system (Pure Process Technology). Flash chromatography was performed on silica gel grade 60 (230×400 mesh) from Sorbent Technologies. Thin layer chromatography was performed on glass plates coated with silica gel grade 60, from Merck. Melting points were measured in open-end capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers as indicated. Proton spectra in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm. Carbon spectra in $CDCl_3$ were referenced to 77.16 ppm. Proton spectra in CD_3OD were referenced to residual CHD_2OD at 3.34 ppm. Proton spectra in DMSO-d_6 were referenced to residual CD_3SOCD_2H at 2.50 ppm. Infrared spectra were recorded on a Bruker Tensor FT-IR spectrometer. High-resolution mass spectra were obtained using a TOF spectrometer using simultaneous electrospray (ESI) and atmospheric pressure chemical ionization (APCI). Optical rotations were recorded on a Rudolph Research Autopol polarimeter, at a wavelength of 589 nm.



3.8 **3.9**

4.2 3,4-dimethoxy-2-methylbenzaldehyde (3.9)

To a stirred solution of 2,3-dimethoxytoluene (**3.8**) (40.7g, 0.27 mol, 1 eq.) in CH_2Cl_2 (250 mL), at 0°C under Ar, was added $TiCl_4$ (47 mL, 0.43 mol, 1.6 eq.) followed by a dropwise addition of a solution of Cl_2HCOCH_3 (25 mL, 0.28 mol, 1.05 eq.) in CH_2Cl_2 (125 mL). The mixture was stirred at 0°C for 15 min and then at RT for 2h. The reaction was poured over crushed ice, stirred overnight, the phases separated and the organic layer was rinsed with 5% $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting oil was seeded with crystals from a previous batch to afford the title compound as a crystalline solid (47.0 g, 99%). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.11 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H).

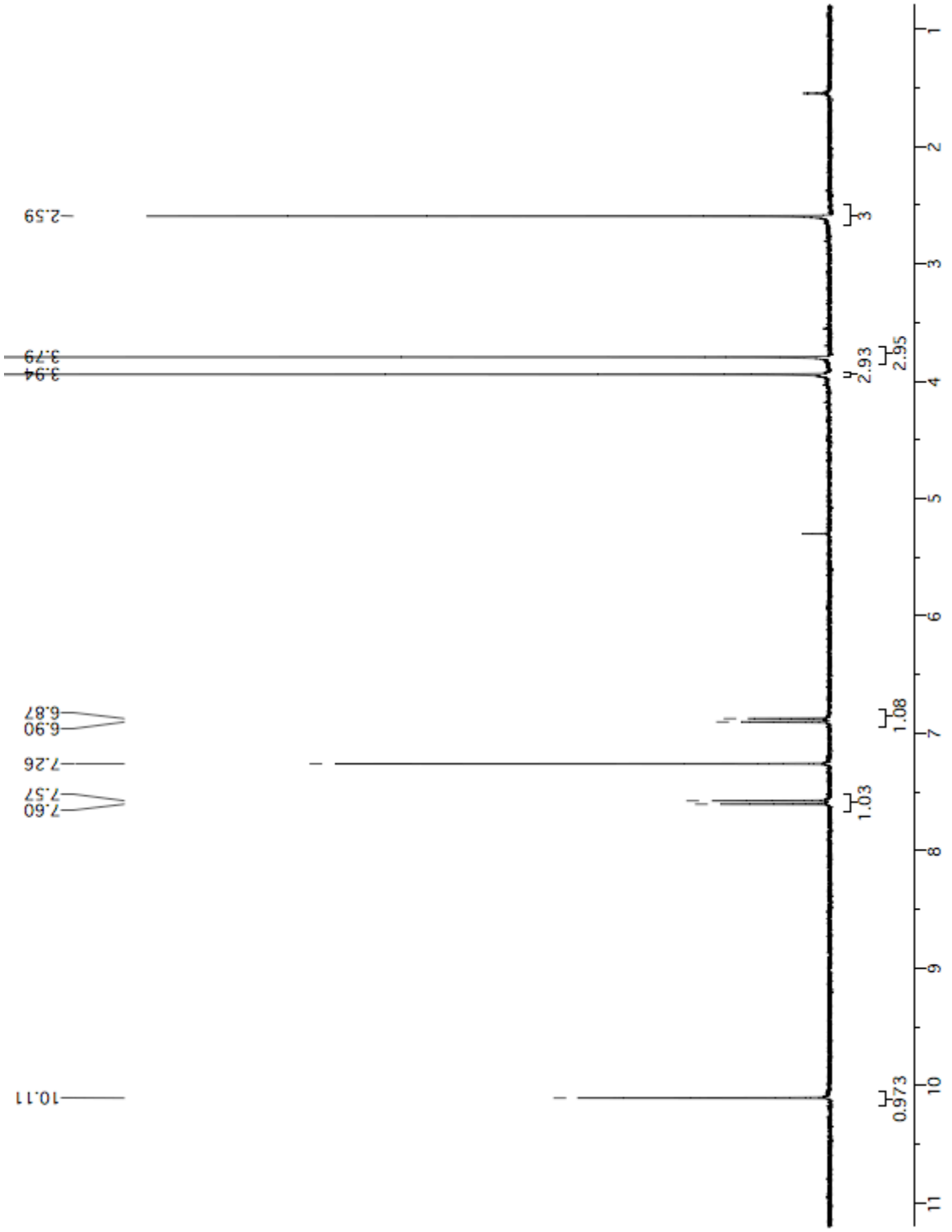
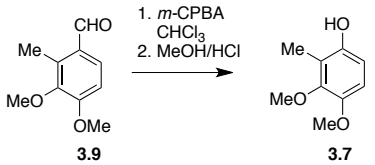


Figure 4.1. ^{1}H NMR spectrum of compound **3.9** (300 MHz, $CDCl_3$)



3.9 **3.7**

4.3 3,4-dimethoxy-2-methylphenol (3.7)

To a stirred solution of 3,4-dimethoxy-2-methylbenzaldehyde (**3.9**) (7.81 g, 43.4 mmol, 1 eq.) in $CHCl_3$ (200 mL) at 0°C was added *m*-CPBA (20.38 g, 130 mmol, 3.0 eq.). The solution was warmed to RT, stirred for 10 min. and then refluxed for 3h. The resulting mixture was washed with 10% NaS_2O_3 (2 × 100 mL), $NaHCO_3$ (3 × 50 mL) and brine (2 × 50 mL). The organic phase was concentrated under reduced pressure, diluted with MeOH (50 mL), cooled to 0°C, acidified with conc. HCl (1 mL, 12 mmol) and stirred at RT for 12h and then concentrated under reduced pressure. The residue was purified by flash chromatography with 5:1 hexanes/EtOAc to provide the title compound as a yellow solid (4.88 g., 67%). R_f = 0.4 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.64 (d, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 1H), 4.44 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.18 (s, 3H).

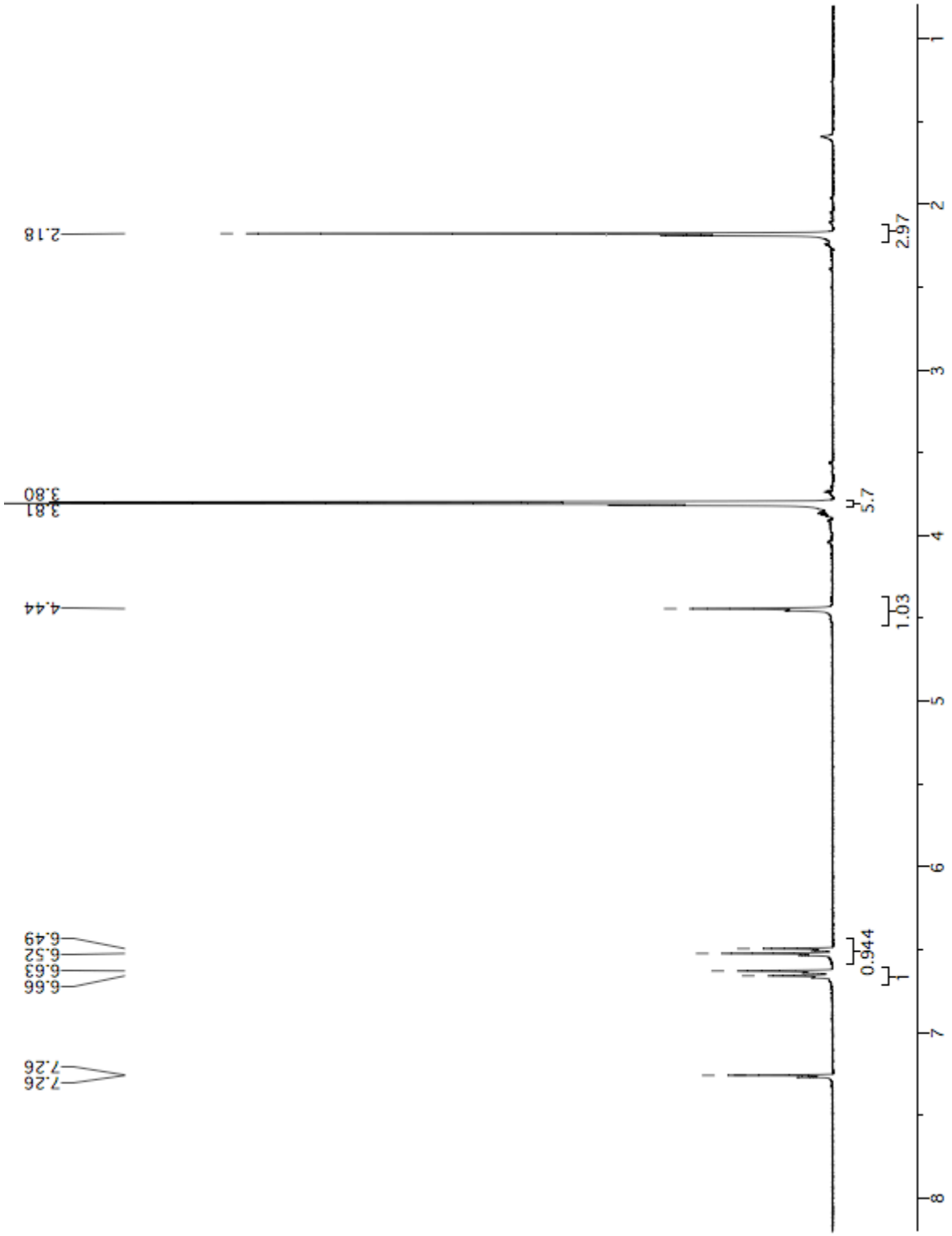
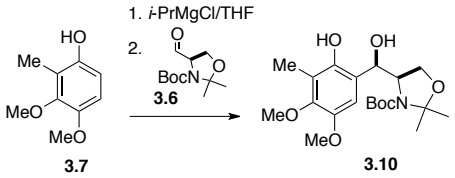


Figure 4.2. ^{1}H NMR spectrum of compound **3.7** (300 MHz, $CDCl_3$)



4.4 (*R*)-*tert*-butyl 4-((*R*)-hydroxy(2-hydroxy-4,5-dimethoxy-3-methylphenyl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (3.10)

To a solution of 3,4-dimethoxy-2-methylphenol (**3.7**) (0.22 g, 1.3 mmol, 1.0 eq.) in dry THF (3.0 mL), under Ar atmosphere, was added *i*-PrMgCl (2.0 M in THF, 700 µL, 1.4 mmol, 1.08 eq.) at RT. After 5 min. of stirring, a solution of *(R)-tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (*R*-Garner's aldehyde) (320 mg, 1.4 mmol, 1.8 eq.) in CH_2Cl_2 (3 mL) was added dropwise and the resulting mixture was stirred overnight. The reaction was quenched with sat. aq. NH_4Cl (10 mL), the phases were separated, the organic layer was rinsed with brine (10 mL), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography with 5:1 hexanes/EtOAc to afford the title compound (0.34g, 66%); R_f = 0.3 (4:1 hexanes/EtOAc) ^{1}H-NMR (300 MHz; CD_3OD): mixture of rotamers, δ 6.56 (s, 1H), 4.29-4.22 (m, 1H), 4.09-4.00 (m, 1H), 3.89 (dd, *J* = 9.4, 6.3 Hz, 1H), 3.77 (s, 3H), 3.73 (br s, 3H), 2.10 (s, 3H), 1.52 (br s, 9H), 1.44 (br s, 3H), 1.29 (br s, 3H). HRMS (FAB+) calcd. for $C_{20}H_{31}NO_7$ (M^+): (m/z) 397.2101; found (m/z) 397.2095.

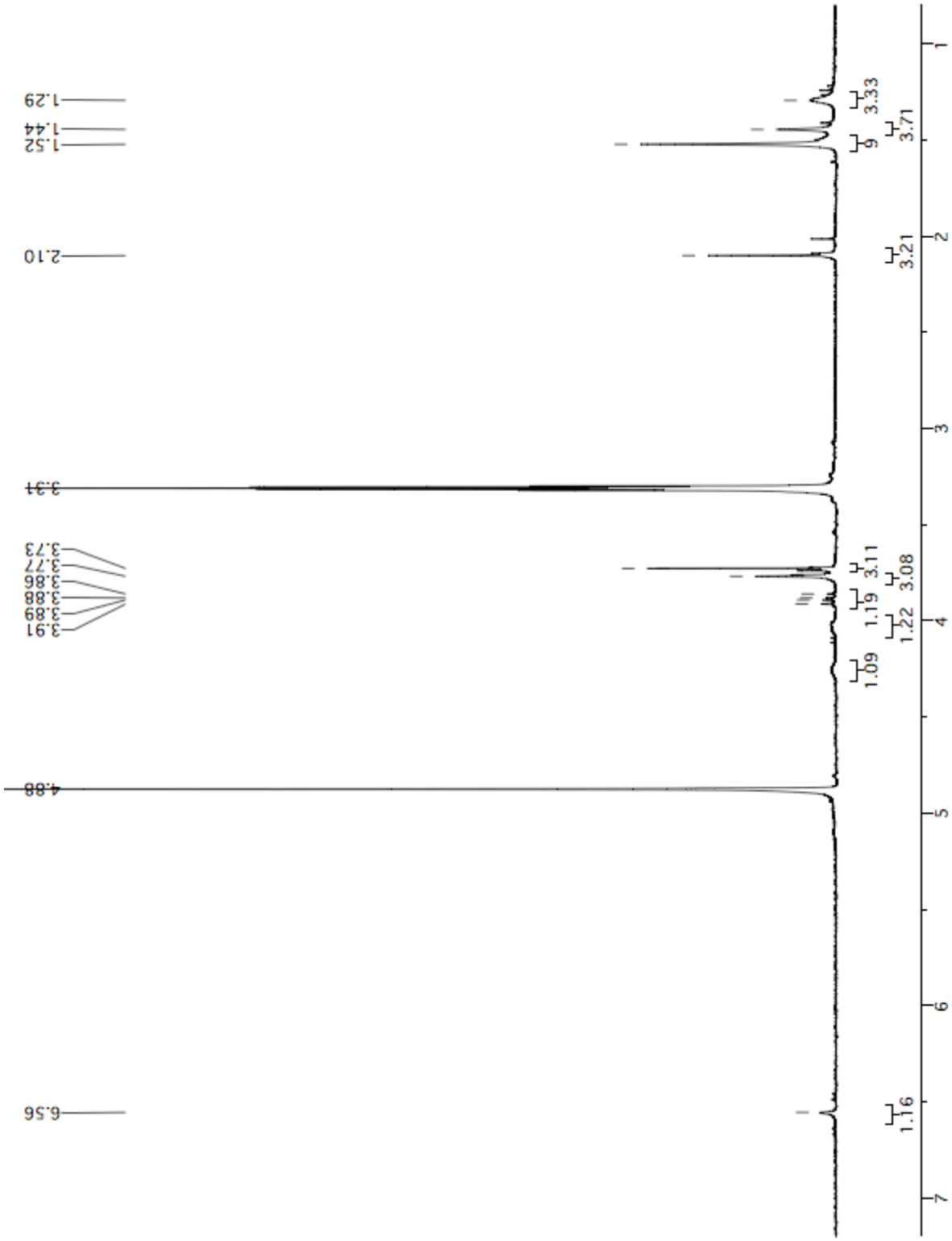
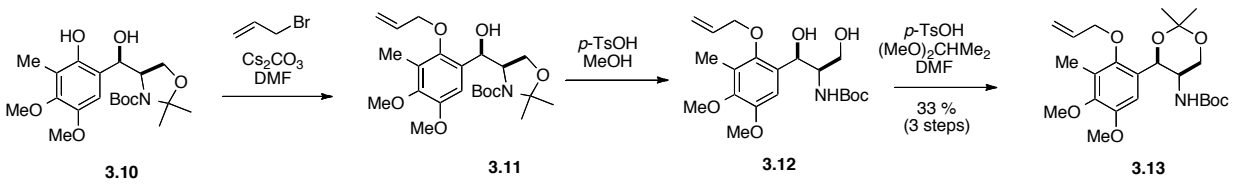


Figure 4.3. ^{1}H NMR spectrum of compound **3.10** (300 MHz, CD_3OD)



4.5 *Tert*-butyl ((4*R*,5*R*)-4-(2-(allyloxy)-4,5-dimethoxy-3-methylphenyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (3.13)

(*R*)-*tert*-butyl 4-((*R*)-(2-(allyloxy)-4,5-dimethoxy-3-methylphenyl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (3.11)

A solution of compound **3.10** (0.34 g, 0.86 mmol, 1.0 eq.) in dry DMF (8.0 mL) was added Cs_2CO_3 (0.56 g, 1.7 mmol, 2.0 eq.) followed by allyl bromide (450 mL, 5.2 mmol, 6.0 eq.). The solution was stirred under Ar atmosphere for 2h and NMR analysis revealed the consumption of the starting material. The reaction was diluted with H_2O (15 mL), extracted with diethyl ether (3 × 10 mL) and the organic layer was rinsed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the title compound as a yellow oil. This material was used in the following step without further purification. HRMS (FAB+) calcd. for $C_{23}H_{35}NO_7$: (M^+): (m/z) 437.2414; found (m/z) 437.2414.

Tert-butyl ((1*R*,2*R*)-1-(2-(allyloxy)-4,5-dimethoxy-3-methylphenyl)-1,3-dihydroxypropan-2-yl)carbamate (3.12)

To a solution of crude **3.11** (0.86 mmol, 1.0 eq.) in MeOH (15 mL) at 0°C was added *p*-TsOH (15 mg, 0.09 mmol, 0.1 eq.). The reaction was warmed to RT and stirred for 2h until TLC analysis revealed absence of starting material and a new strong spot at $R_f = 0$. The reaction was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers

were rinsed with 5% $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the title compound of a yellow oil. This material was used in the following step without further purification. MS (FAB+) calcd. for $C_{20}H_{32}NO_7$: (MH^+): (m/z) 398.2; found (m/z) 398.2.

***Tert*-butyl ((4R,5R)-4-(2-(allyloxy)-4,5-dimethoxy-3-methylphenyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (3.13)**

To a solution of crude **3.12** (261 mg, 0.66 mmol, 1.0 eq.) in dry DMF (5 mL) under Ar atmosphere were added *p*-TsOH (10 mg, 0.05 mmol.) and 2,2-dimethoxypropane (300 mL, 3.4 mmol, 2.0 eq.). The reaction stirred for 48 h, quenched with 5% $NaHCO_3$ (10 mL), diluted with H_2O (15 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were rinsed with 5% $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography with 5:1 hexanes/EtOAc to afford the title compound (125 mg, 33%, 3 steps). R_f = 0.30; ^{1}H-NMR (300 MHz; CD_3OD): mixture of rotamers, δ 6.89 (br s, 1H), 6.21-6.06 (m, 1H), 5.55-5.39 (m, 2H), 5.37-5.23 (m, 1H), 4.49-4.25 (m, 3H), 4.09 (q, *J* = 7.1 Hz, 1H), 3.88-3.80 (m, 3H), 3.77-3.68 (m, 5H), 2.16 (s, 3H), 1.55 (br s, 3H), 1.49 (br s, 3H), 1.24 (s, 9H). HRMS (FAB+) calcd. for $C_{23}H_{35}NO_7$: (MH^+): (m/z) 437.2414; found (m/z) 437.2414.

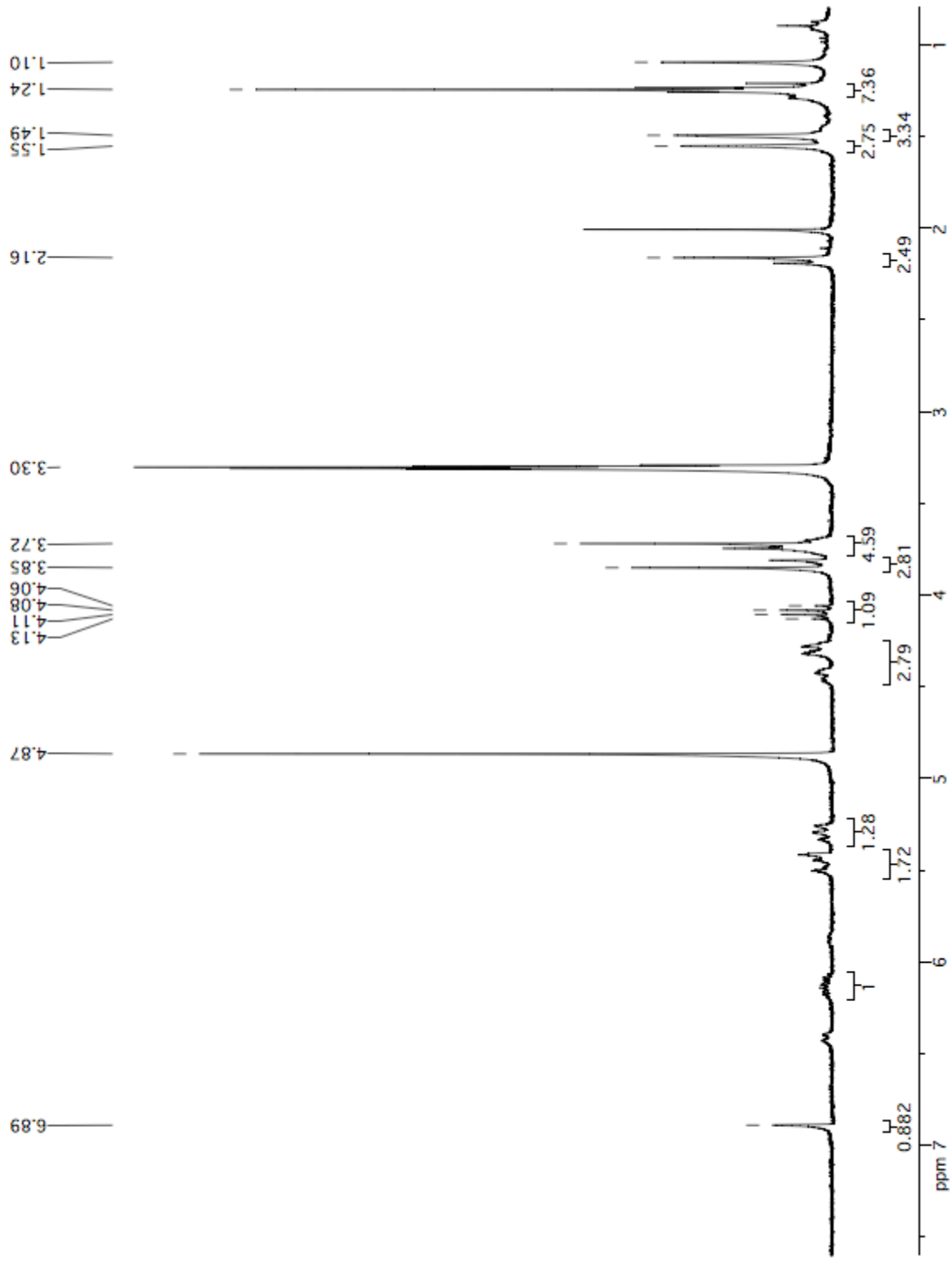
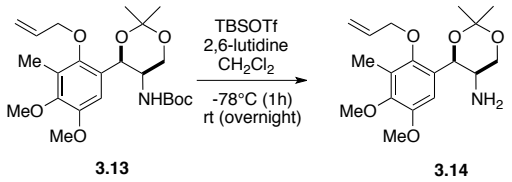


Figure 4.4. 1H NMR spectrum of compound **3.13** (300 MHz, CD_3OD)



4.6 (4*R*,5*R*)-4-(2-(allyloxy)-4,5-dimethoxy-3-methylphenyl)-2,2-dimethyl-1,3-dioxan-5-amine (3.14)

To a solution of **3.13** (90 mg, 0.21 mmol, 1.0 eq.) in dry CH_2Cl_2 (5 mL) was added 2,6-lutidine (150 µL, 1.3 mmol, 6.2 eq.). The solution was cooled to -78°C and TBSOTf (160 µL, 0.70 mmol, 3.4 eq.) was added dropwise. The reaction was stirred at this temperature for 1 h, warmed to RT and stirred for 12h. The reaction was quenched with MeOH (5 mL) and KF•$2H_2O$ (75 mg, 1.2 mmol, 6.0 eq.) was added with vigorous stirring. After 15 min. the solution was diluted with CH_2Cl_2 (5 mL), rinsed with 5% $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography with 4:1:0.1 EtOAc/hexanes/Et_3N to afford the title compound (51mg, 72%). R_f = 0.22 (4:1:0.1 EtOAc/hexanes/Et_3N); ^{1}H-NMR (300 MHz; CD_3OD): δ 7.09-6.85 (m, 1H), 6.18-6.11 (m, 1H), 5.64-5.22 (m, 1H), 4.56-4.16 (m, 1H), 3.92-3.82 (m, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.19 (s, 3H), 1.55 (s, 3H), 1.51 (s, 3H). HRMS (FAB+) calcd. for $C_{18}H_{28}NO_5$: (MH^+): (m/z) 338.1923; found (m/z) 338.1967.

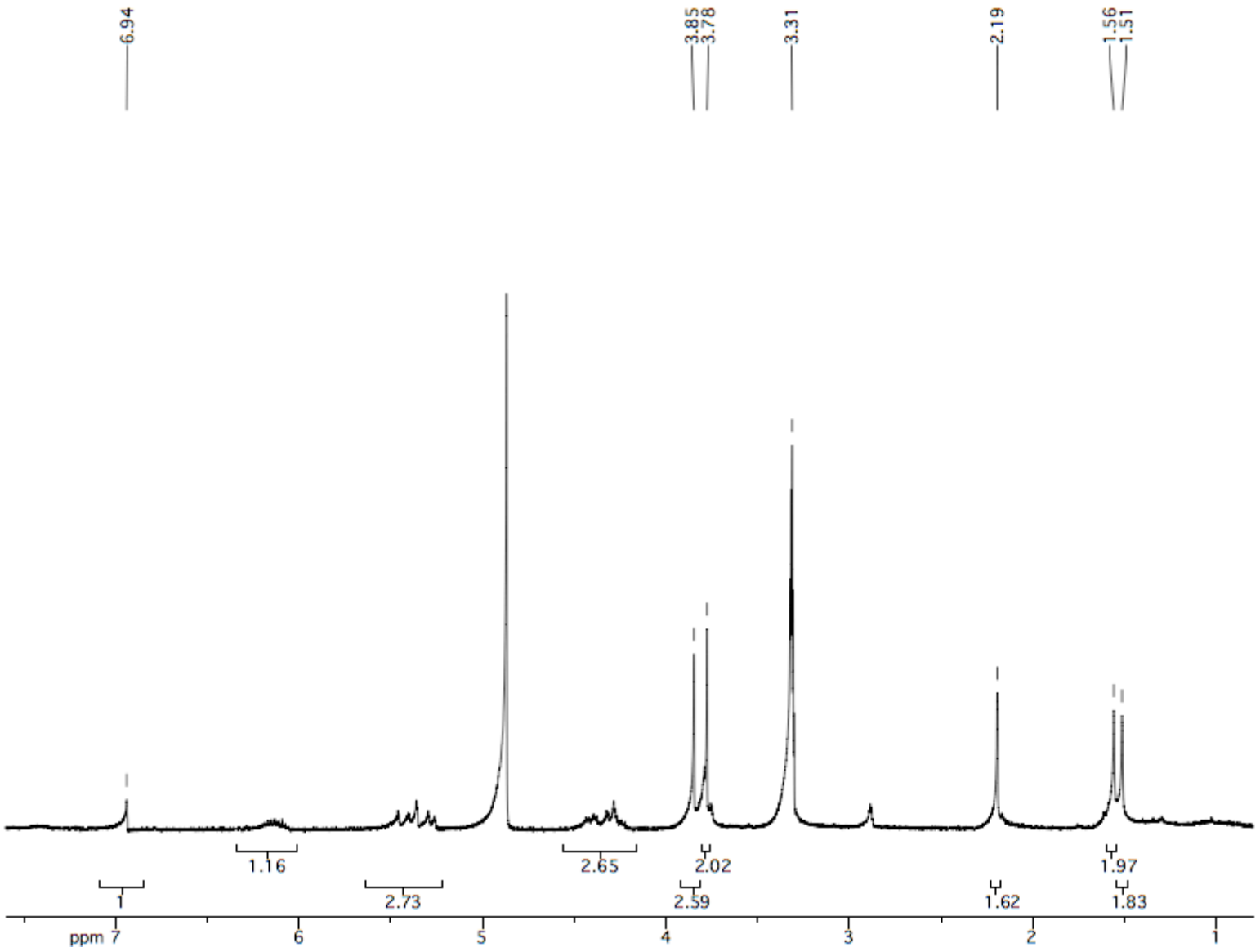
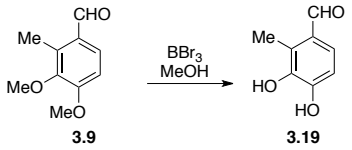


Figure 4.5. ^{1}H NMR spectrum of compound **3.14** (300 MHz, CD_3OD)



4.7 3,4-dihydroxy-2-methylbenzaldehyde (3.19)

To a stirred solution of 3,4-dimethoxy-2-methylbenzaldehyde (**3.9**) in (8.5 g, 47 mmol, 1 eq.) in $CHCl_3$ (100 mL) at -78°C was added dropwise BBr_3 (10 mL, 100 mmol, 2.0 eq.). The solution was stirred at this temperature for 15 min and then at RT for 1.5 h, cooled to -78°C and quenched with MeOH (40mL). The purple solution was diluted with brine (40 mL) and H_2O (40 mL). The aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were rinsed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a dark purple solid. This material was eluted through a silica plug and the solvent evaporated to afford the title compound as a brown solid (5.65 g, 79 %). This material was used in the next step without further purification. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.11(m, 1H), 7.35 (1/2 AB, J = 8.4 Hz, 1H), 6.86 (1/2 AB, J = 8.4 Hz, 1H), 6.00 (s, 1H), 2.59 (s, 3H).

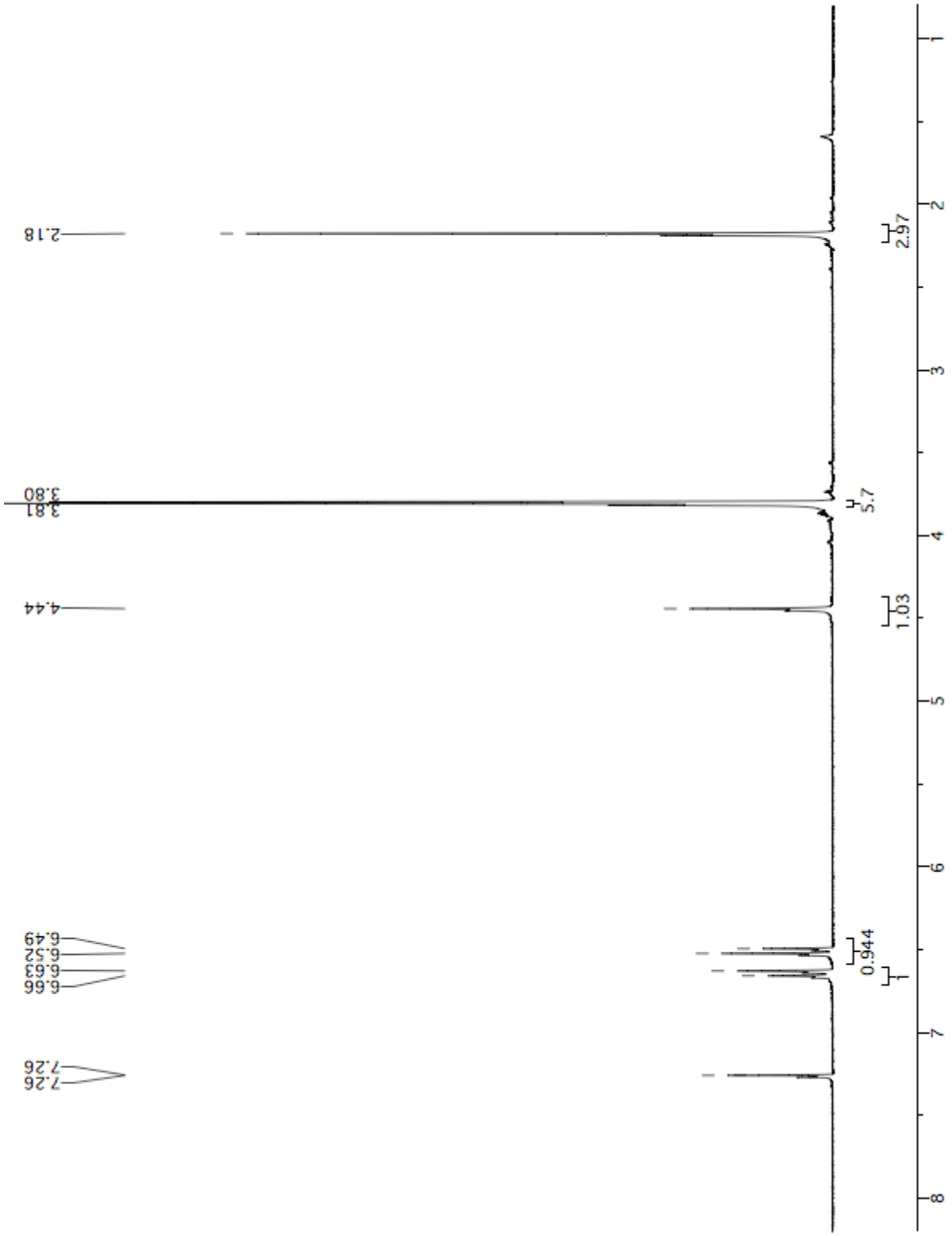
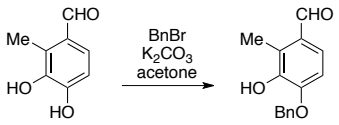


Figure 4.6. ^{1}H NMR spectrum of compound **3.19** (300 MHz, $CDCl_3$)



3.19 **3.20**

4.8 4-benzyloxy-3-hydroxy-2-methylbenzaldehyde (3.20)

To a solution of 3,4-dihydroxy-2-methylbenzaldehyde (**3.19**) (10.00 g, 65 mmol, 1 eq.) in acetone (100 mL) was added K_2CO_3 (8.97 g, 65 mmol, 1 eq.) and benzyl bromide (7.7 mL, 65 mmol, 1 eq.). The mixture was stirred under reflux for 48 h, concentrated under reduced pressure, suspended in $CHCl_3$, cooled to 0°C, filtered and concentrated to afford the title compound as a brown solid (11.95 g, 76%). This material was used without further purification. R_f = 0.45 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.11 (s, 1H), 7.42-7.35 (m, 7H), 6.91 (1/2 AB, *J* = 8.4 Hz, 1H), 5.86 (s, 1H), 5.20 (s, 2H), 2.58 (s, 3H).

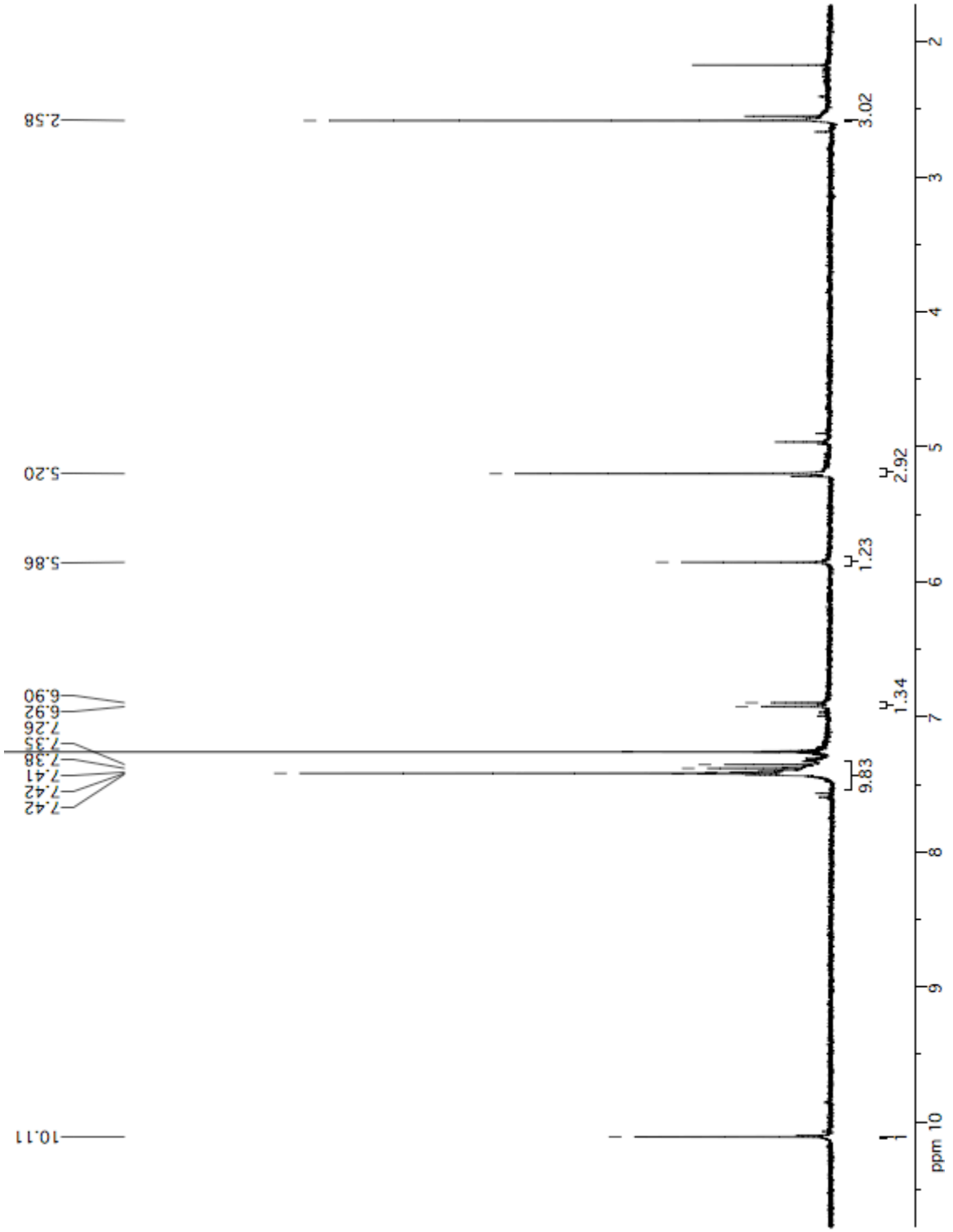
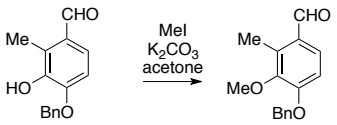


Figure 4.7. ^{1}H NMR spectrum of compound **3.20** (300 MHz, $CDCl_3$)



3.20 **3.21**

4.9 4-benzyloxy-3-methoxy-2-methylbenzaldehyde (3.21)

To a solution of 4-benzyloxy-3-hydroxy-2-methylbenzaldehyde (**3.20**) (11.95 g, 49 mmol, 1 eq.) in acetone (125 mL) was added K_2CO_3 (20.7 g, 150 mmol, 3 eq.) and methyl iodide (9.3 mL, 150 mmol, 3 eq.). The mixture was stirred at RT for 24 h, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography with 8:1 hexanes/EtOAc to afford the title compound as a yellow solid (10.0 g, 80%). R_f = 0.50 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.10 (s, 1H), 7.54 (1/2 AB, *J* = 8.6 Hz, 1H), 7.46-7.34 (m, 7H), 6.93 (1/2 AB, *J* = 8.6 Hz, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 2.60 (s, 3H).

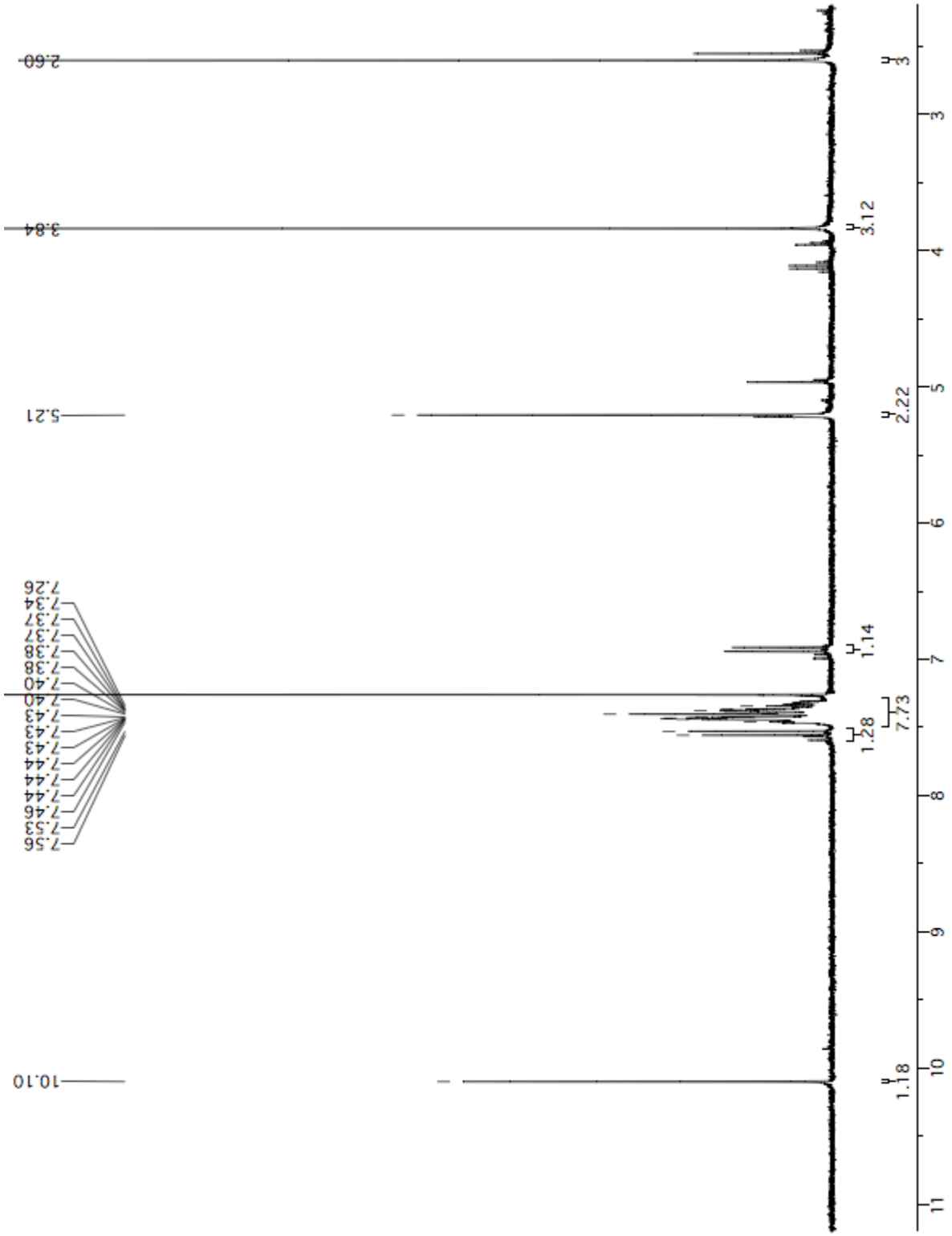
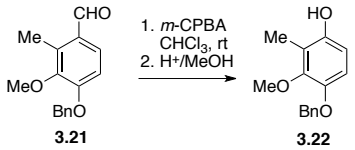


Figure 4.8. ^{1}H NMR spectrum of compound **3.21** (300 MHz, $CDCl_3$)



3.21 3.22

4.10 4-benzyloxy-3-methoxy-2-methylphenol (3.22)

To a stirred solution of 4-benzyloxy-3-methoxy-2-methylbenzaldehyde (**3.21**) (10.00 g, 39 mmol, 1 eq.) in $CHCl_3$ (300 mL) at 0°C was added *m*-CPBA (13.40 g, 78 mmol, 2.0 eq.). The solution was warmed to RT and stirred for 8h. The resulting mixture was washed with 10% NaS_2O_3 (2 × 100 mL), $NaHCO_3$ (3 × 50 mL) and brine (2 × 50 mL). The organic phase was concentrated under reduced pressure, diluted with MeOH (50 mL), cooled to 0°C, acidified with conc. HCl (1 mL, 12 mmol) and stirred at RT for 12h and then concentrated under reduced pressure. The residue was purified by flash chromatography with 5:1 hexanes/EtOAc to provide the title compound as a yellow solid (4.88g, 58 %). R_f = 0.50 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.45-7.33 (m, 8H), 6.68 (1/2 AB, J = 8.7 Hz, 1H), 6.47 (d, J = 8.8 Hz, 1H), 5.05 (s, 2H), 3.85 (s, 3H), 2.19 (s, 3H).

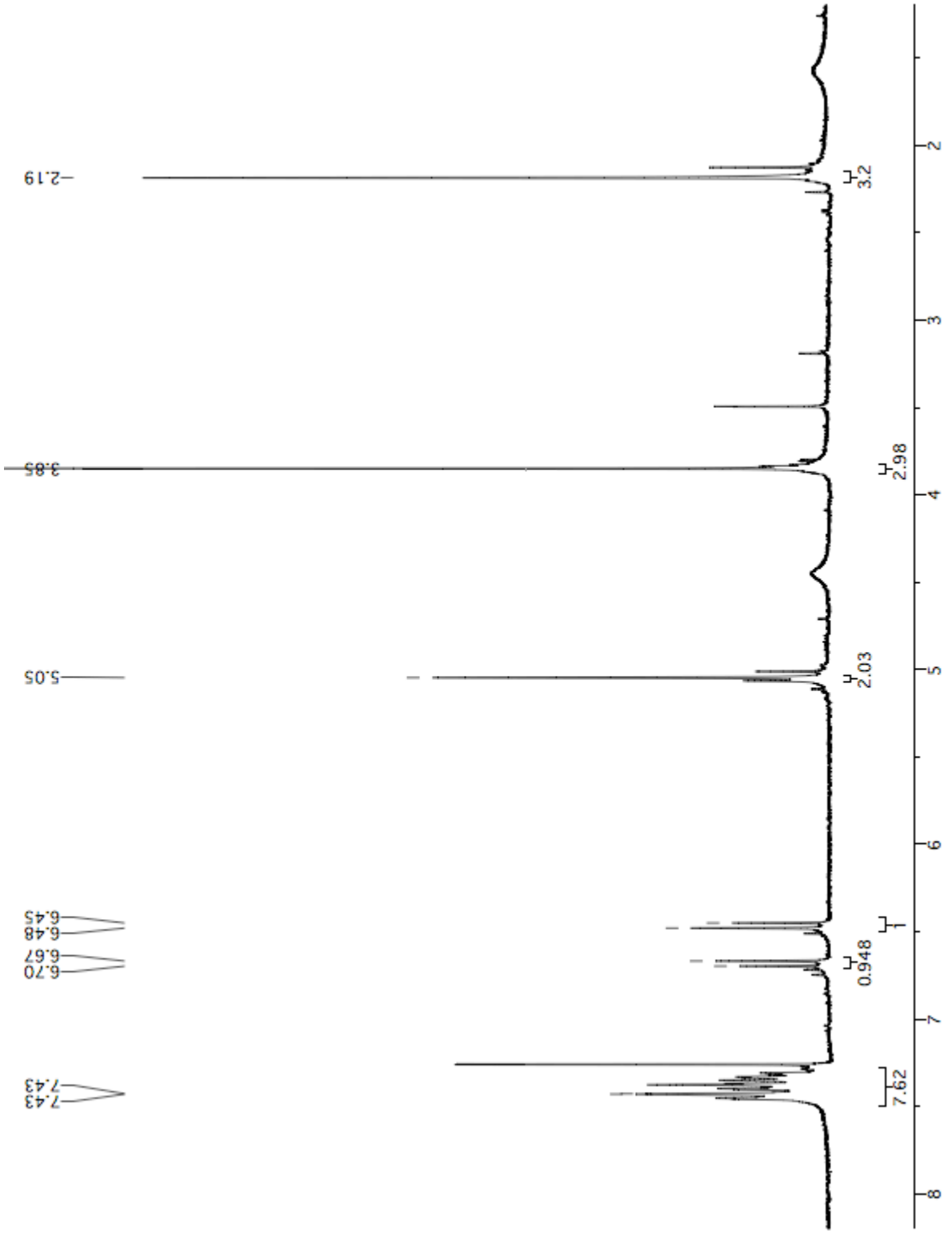
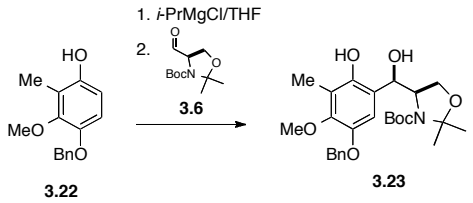


Figure 4.9. ^{1}H NMR spectrum of compound **3.22** (300 MHz, $CDCl_3$)



4.11 (*R*)-*tert*-butyl 4-((*R*)-(5-(benzyloxy)-2-hydroxy-4-methoxy-3-methylphenyl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (3.23)

To a solution of 4-benzyloxy-3-methoxy-2-methylphenol (**3.22**) (231 mg, 0.95 mmol, 1.0 eq.) in dry THF (2.0 mL), under Ar atmosphere, was added EtMgBr (3.0 M in Et_2O, 330 μL, 1.0 mmol, 1.05 eq.) at rt. After 5 min. of stirring, a solution of *(R)-tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (*R*-Garner's aldehyde) (300 mg, 1.0 mmol, 1.05 eq.) in CH_2Cl_2 (2 mL) was added dropwise and the resulting mixture was stirred overnight. The reaction was quenched with sat. aq. NH_4Cl (10 mL), the phases were separated, the organic layer was rinsed with brine, filtered and concentrated under reduced pressure to afford the title compound (292 mg, 66%), which was used without further purification. ^{1}H-NMR (300 MHz; $CDCl_3$): mixture of rotamers, δ 7.41-7.34 (m, 5H), 6.45 (s, 1H), 5.02 (s, *J* = 4.1 Hz, 2H), 4.69-4.65 (m, 1H), 4.36-4.34 (m, 1H), 3.84 (s, 3H), 2.16 (s, 3H), 1.60 (s, *3*H), 1.53 (s, 9H), 1.50 (s, 3H).HRMS (FAB+) calcd. for $C_{26}H_{35}NO_7$: (M^+): (m/z) 473.2414; found (m/z) 473.2414.

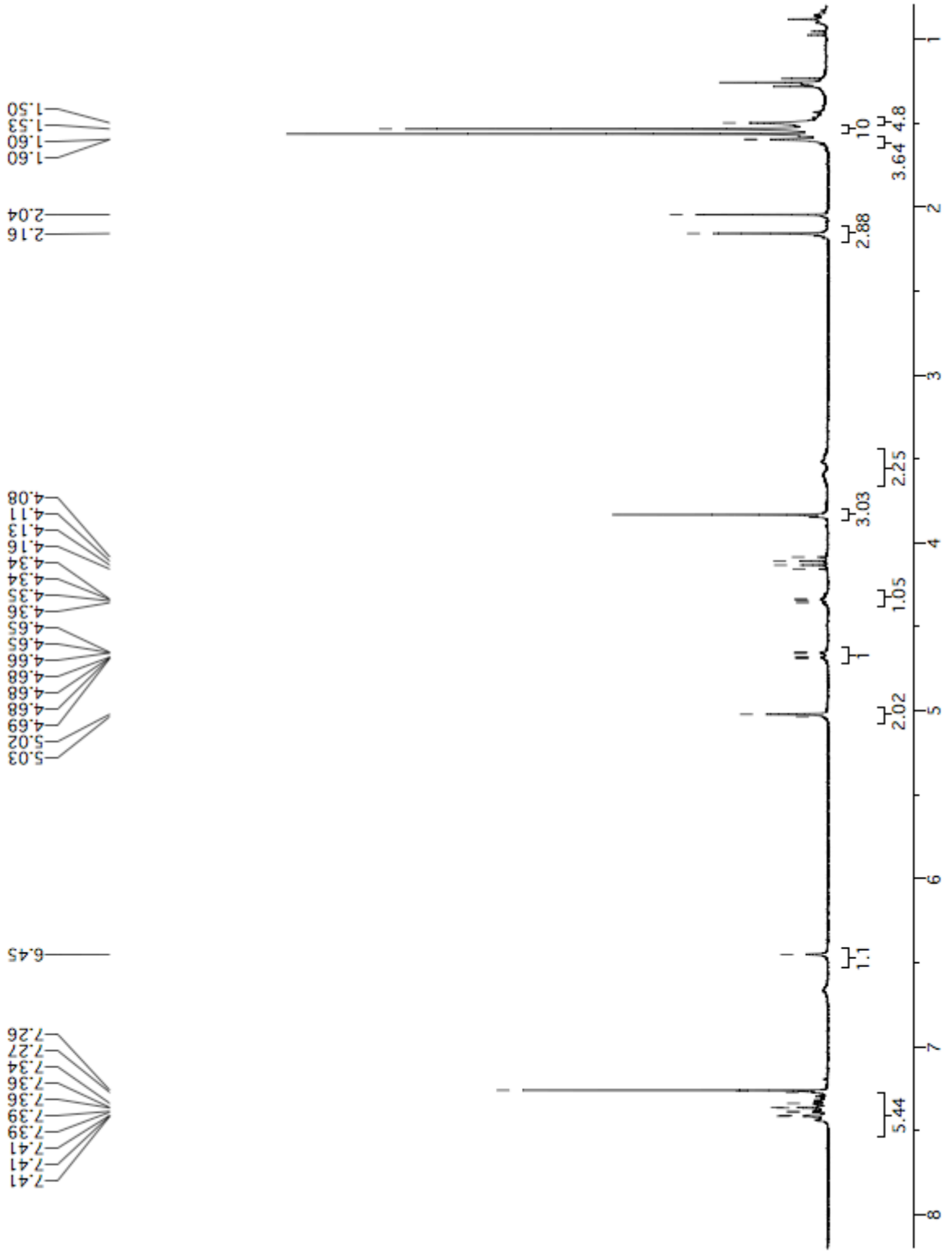
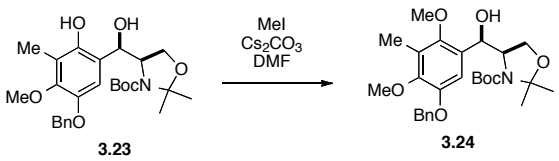


Figure 4.10. ^{1}H NMR spectrum of compound **3.23** (300 MHz, $CDCl_3$)



3.23 3.24

4.12 (*R*)-*tert*-butyl 4-((*R*)-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-(hydroxy)-methyl)-2,2-dimethyloxazolidine-3-carboxylate (3.24)

A solution of **3.23** (9.2 g, 19 mmol, 1.0 eq.) in acetone (100 mL) was added Cs_2CO_3 (5.24 g, 38 mmol, 2.0 eq.) followed by methyl iodide (3.53 mL, 56 mmol, 3.0 eq.). The solution was stirred under Ar atmosphere for 16h. The suspension was concentrated to dryness, diluted with H_2O (40 mL), extracted with diethyl ether (3 × 150 mL) and the organic layer was rinsed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography with 5:1 hexanes/EtOAc to afford of the title compound (8.33g, 89%). R_f = 0.1 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): mixture of carbamate rotamers, δ 7.46-7.31 (m, 3H), 6.89 (s, 1H), 5.47 (s, 1H), 5.07 (AB, *J* = 9.1 Hz, 2H), 4.25 (t, *J* = 11.3 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.64-3.55 (m, 3H), 2.22 (s, 3H), 1.65 (s, 3H), 1.56 (s, 9H), 1.50 (s, 3H).HRMS (FAB+) calcd. for $C_{27}H_{37}NO_7$: (M^+): (m/z) 487.2570; found (m/z) 487.2570.

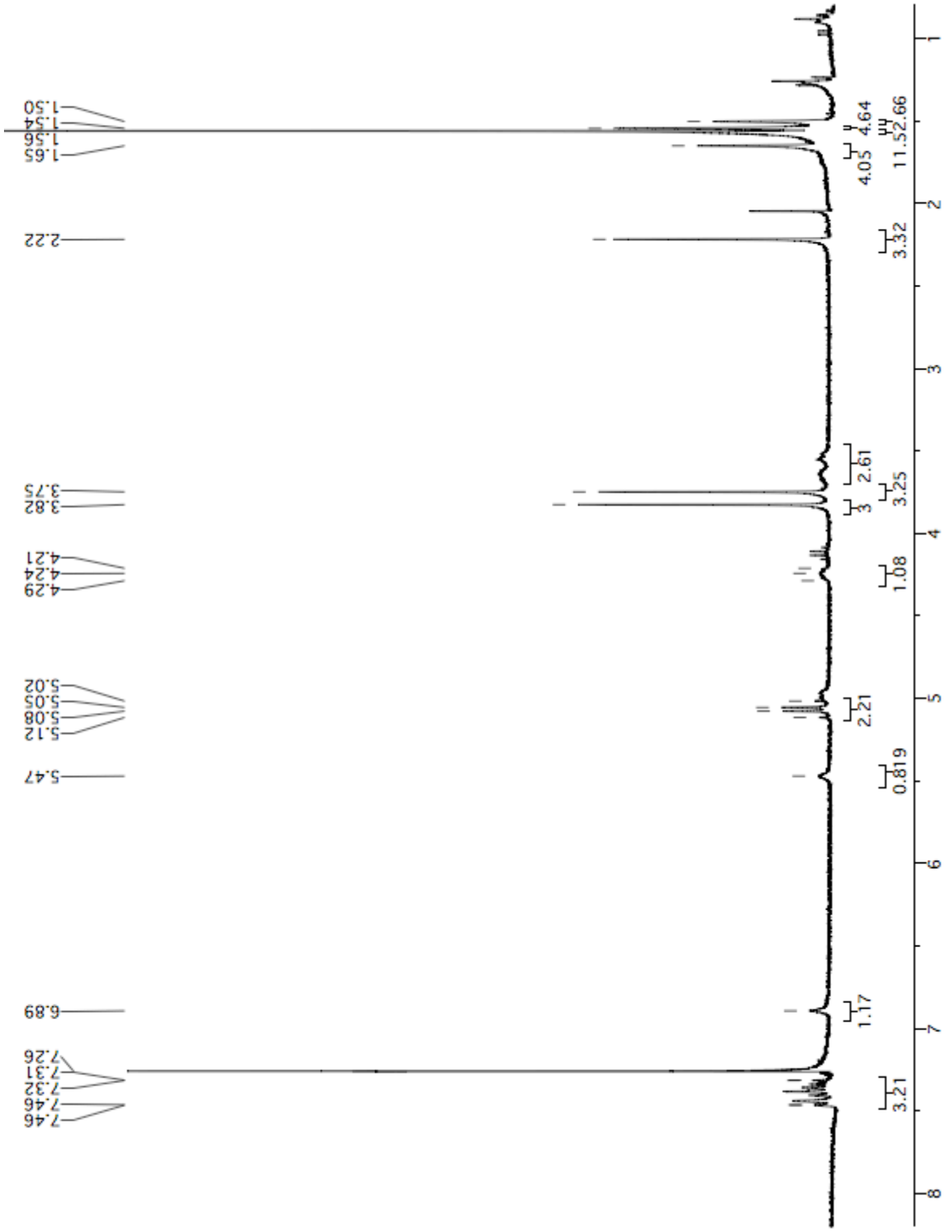
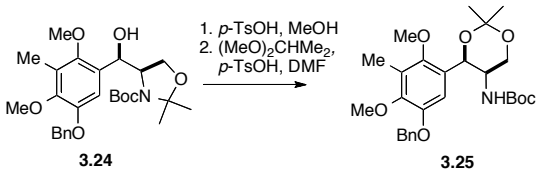


Figure 4.11. ^{1}H NMR spectrum of compound **3.24** (300 MHz, $CDCl_3$)



3.24 **3.25**

4.13 *tert*-butyl ((4*R*,5*R*)-4-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (3.25)

To a solution of compound **3.24** (130 mg, 0.26 mmol, 1.0 eq.) in MeOH (5 mL) at 0°C was added *p*-TsOH (5 mg, 0.03 mmol, ~ 0.1 eq.). The reaction was warmed to RT and stirred for 2h until TLC analysis revealed absence of starting material and a new strong spot at $R_f = 0$. The reaction was concentrated and the residue was dissolved in DMF (5 mL) under Ar atmosphere. To the solution was added 2,2-dimethoxypropane (300 μL, 3.4 mmol, 13eq.) and the reaction was stirred for 24 h, quenched with 5% $NaHCO_3$ (10 mL) and diluted with H_2O (15 mL), extracted with EtOAc (3 × 5 mL). The combined organic layers were rinsed with 5% $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography with 5:1 hexanes/EtOAc to afford the title compound (100 mg, 77%). R_f = 0.2 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): mixture of carbamate rotamers, δ 7.50-7.33 (m, 6H), 6.89 (s, 1H), 5.37-5.25 (m, 2H), 5.09 (s, 2H), 4.33-4.25 (m, 1H), 3.85-3.80 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 2.21 (s, 3H), 1.58 (s, 3H), 1.51 (s, 3H), 1.26 (s, 9H). HRMS (FAB+) calcd. for $C_{27}H_{37}NO_7$: (M^+): (m/z) 487.2570; found (m/z) 487.2570.

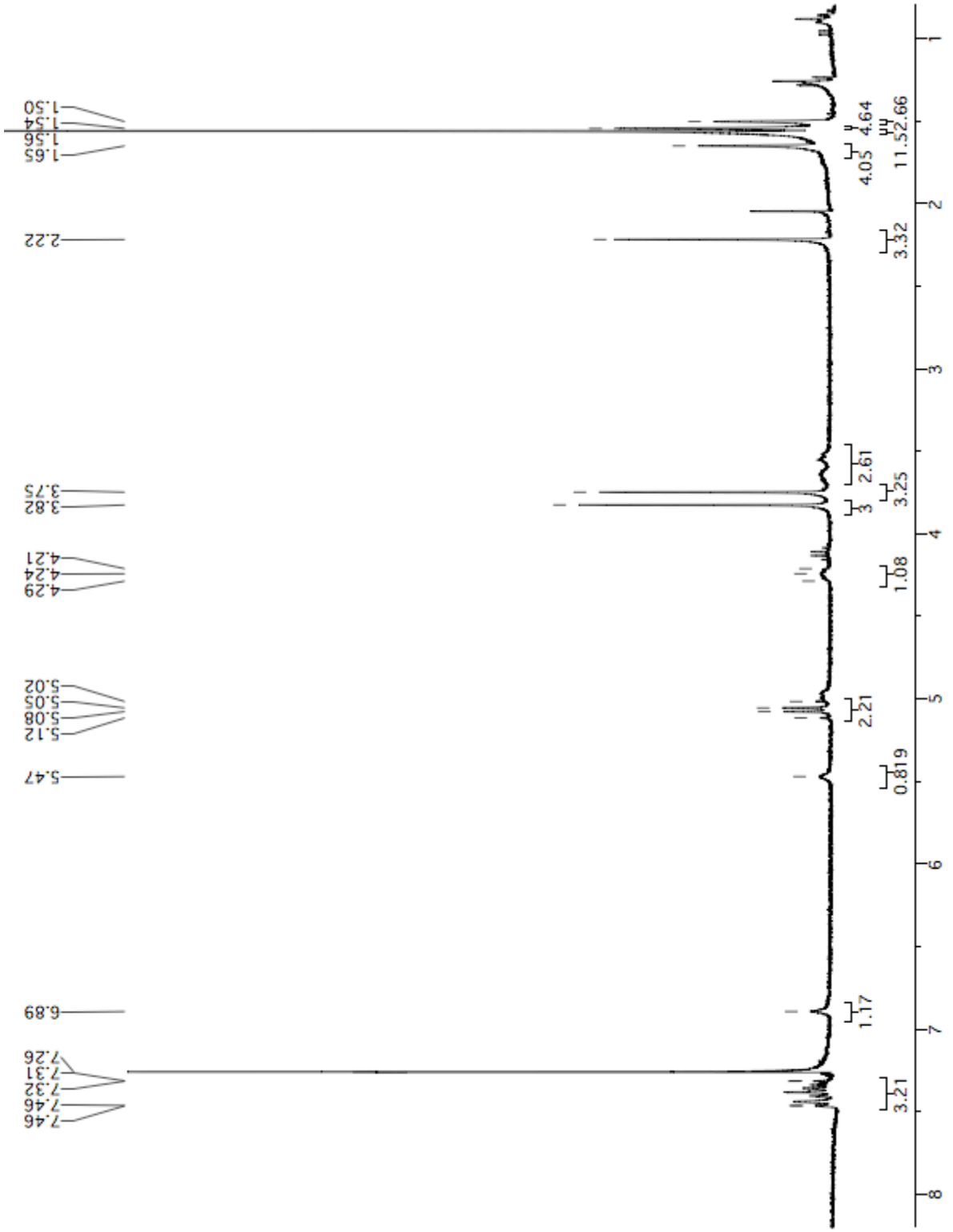
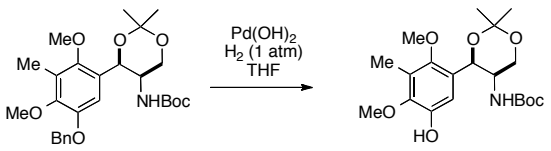


Figure 4.12. ^{1}H NMR spectrum of compound **3.25** (300 MHz, $CDCl_3$)



3.25 3.26

4.14 *tert*-butyl ((4*R*,5*R*)-4-(5-hydroxy-2,4-dimethoxy-3-methylphenyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (3.26)

To a solution of compound **3.25** (100 mg, 0.20 mmol, 1.0 eq.) in THF (15 mL) at 0°C was added $Pd(OH)_2$ (20 mg, 0.14 mmol, ~0.6 eq.). The reaction was evacuated and filled with H_2 (1 atm) three times and resulting suspension was stirred under H_2 for 4h, filtered through Celite® using EtOAc, concentrated under reduced pressure, and purified by flash chromatography (5:1, then 4:1 hexanes/EtOAc) to afford the title compound (52 mg, 63%). R_f = 0.2 (4:1 hexanes/EtOAc); ^{1}H NMR $CDCl_3$ (δ, ppm): ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.89 (s, 1H), 5.34 (s, 3H), 4.32-4.27 (m, 2H), 3.85-3.78 (m, 3H), 2.23 (s, 3H), 1.51 (s, 3H), 1.26 (s, 9H). HRMS (FAB+) calcd. for $C_{20}H_{31}NO_7$: (M^+): (m/z) 397.2101; found (m/z) 397.2101.

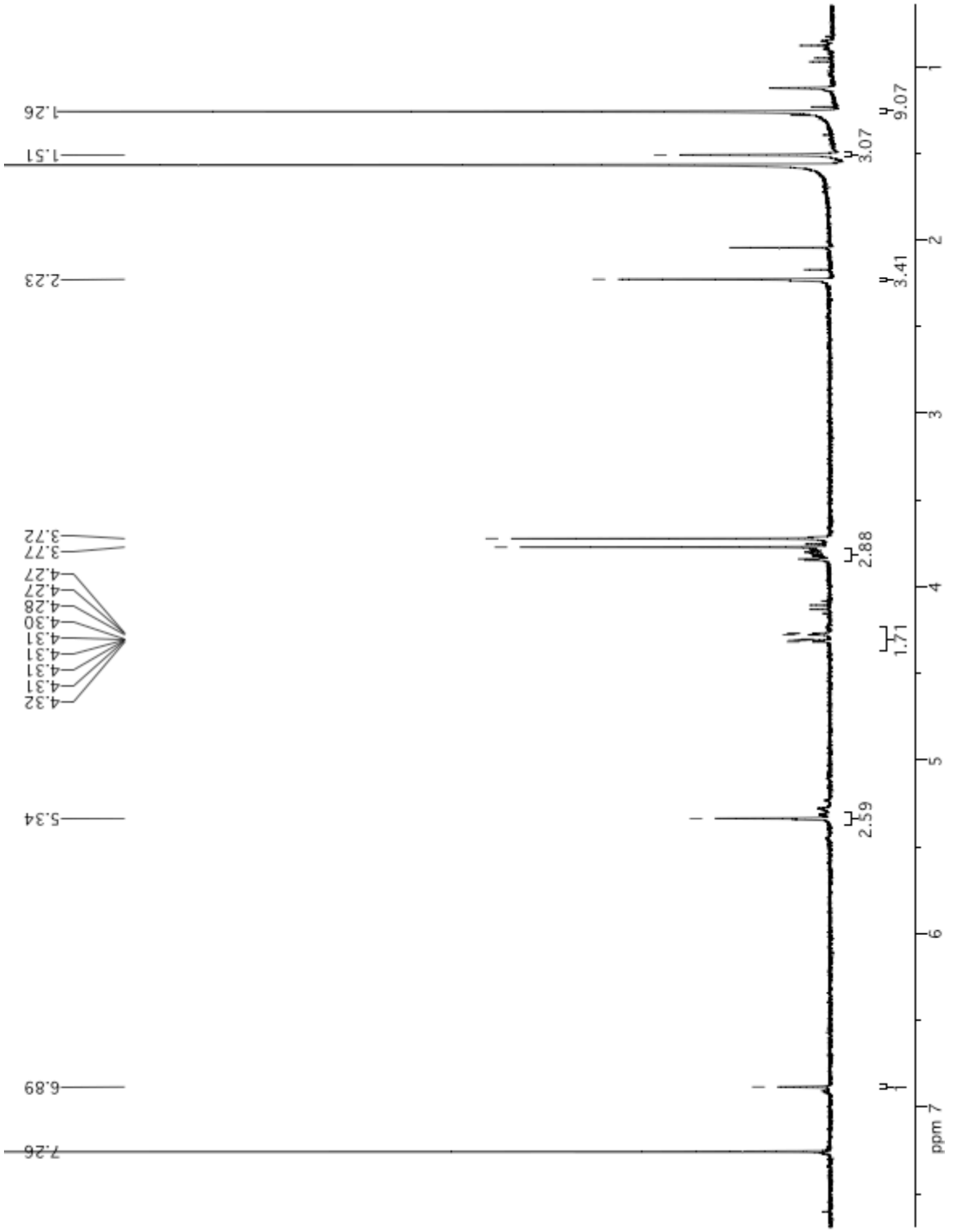
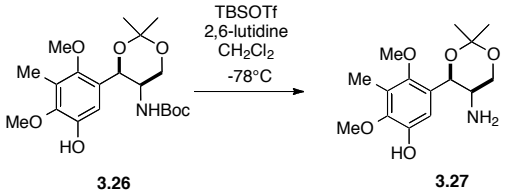


Figure 4.13. ^{1}H NMR spectrum of compound **3.26** (300 MHz, $CDCl_3$)



3.26 **3.27**

4.15 5-((4*R*,5*R*)-5-amino-2,2-dimethyl-1,3-dioxan-4-yl)-2,4-dimethoxy-3-methylphenol (3.27)

To a solution of compound **3.26** (1.55 mg, 3.9 mmol, 1.0 eq.) in dry CH_2Cl_2 (40 mL) was added 2,6-lutidine (1.55 mL, 13.3 mmol, 3.4 eq.). The solution was cooled to -78°C and TBSOTf (2.9 mL, 12.5 mmol, 3.2 eq.) was added dropwise. The reaction was stirred at this temperature for 1 h, warmed to RT and stirred for 12h. The reaction was quenched with MeOH (1 mL) and $KF•2H_2O$ (4 eq.) was added with vigorous stirring. After 15 min. the solution was diluted with CH_2Cl_2 (50 mL), rinsed with 5% $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography with 4:1:0.1 EtOAc/hexanes/Et_3N to afford the title compound (820 mg, 72 %). R_f = 0.1 4:1:0.1 EtOAc/hexanes/Et_3N; ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.94 (s, 1H), 5.27 (s, 1H), 4.30 (1/2 ABX, *J* = 11.7, 2.3 Hz, 1H), 3.86 (1/2 ABX, *J* = 11.7, 1.8 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 2.81 (q, *J* = 1.9 Hz, 1H), 2.24 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H). MS (FAB+) calcd. for $C_{15}H_{23}NO_5$: (MH^+): (m/z) 298.2; found (m/z) 298.2.

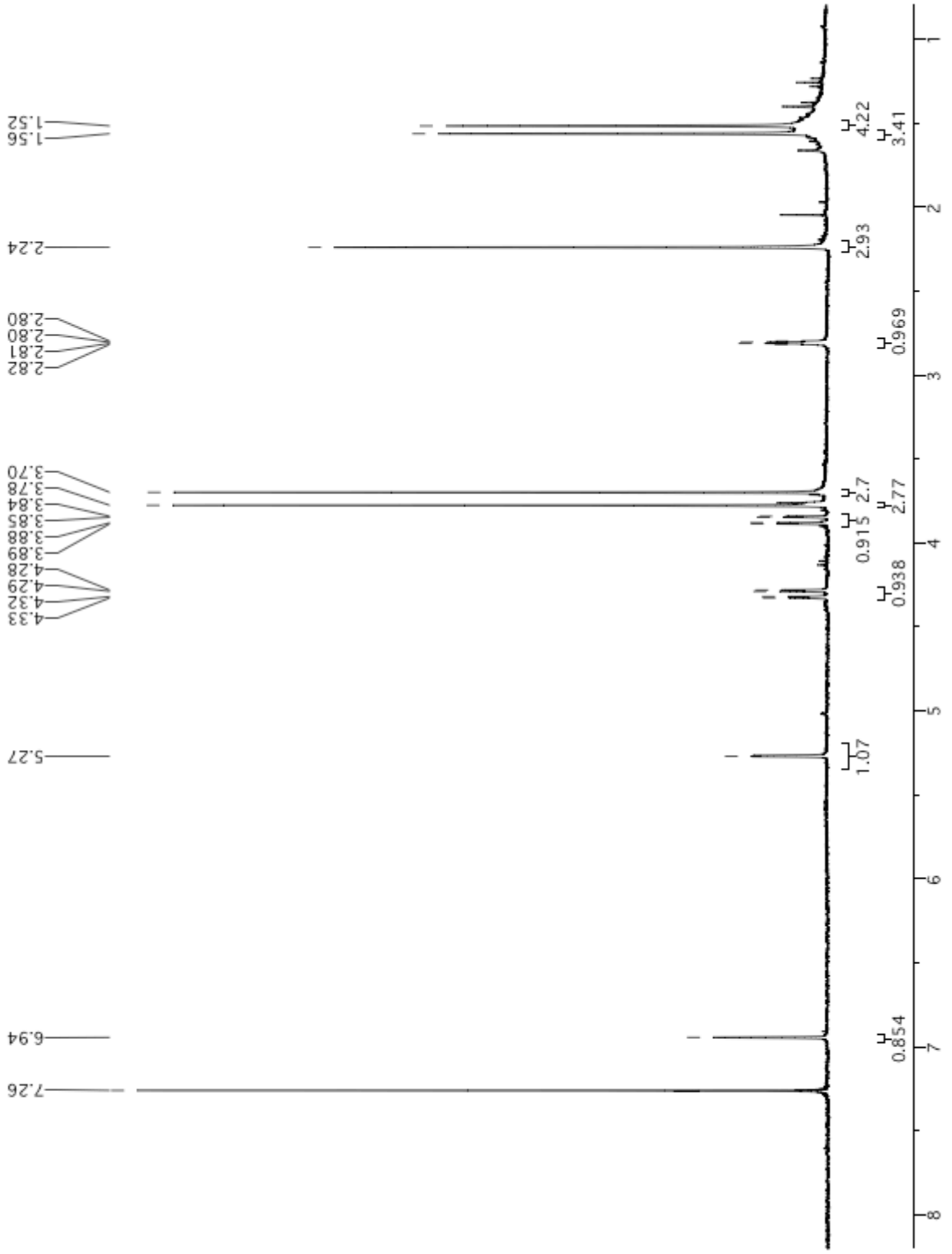
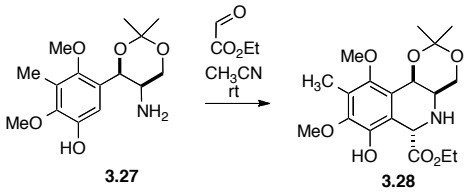


Figure 4.14. ^{1}H NMR spectrum of compound **3.27** (300 MHz, $CDCl_3$)



3.27 3.28

4.16 (4a*R*,6*S*,10b*R*)-ethyl 7-hydroxy-8,10-dimethoxy-2,2,9-trimethyl-4a,5,6,10b-tetrahydro-4*H*-[1,3]dioxino[5,4-*c*]isoquinoline-6-carboxylate (3.28)

A solution of compound **3.27** (1.00 g, 3.36 mmol, 1.0 eq.) and ethyl glyoxalate (734 μL of a 50% solution in toluene, 0.04 mmol, 4 eq.) in dry CH_3CN (70 mL) was prepared in a vial containing 4Å MS (1.00 g). The solution was stirred under Ar atmosphere for 24 h, filtered through Celite® and concentrated under reduced pressure. The crude material was purified by flash chromatography with 19:1 CH_2Cl_2/MeOH to afford the title compound (704 mg, 55 %). R_f = 0.5 19:1 CH_2Cl_2/MeOH); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.28 (s, 1H), 5.11 (d, *J* = 1.4 Hz, 1H), 4.80 (br s, 1H), 4.36-4.30, (m, 4H), 3.98-3.93 (m, 1H), 3.80 (d, s, 3H), 3.77 (s, 3H), 2.95-2.82 (m, 1H), 2.51 (br s, 1H), 2.22 (s, 3H), 1.65 (m, 3H), 1.43 (m, 3H), 1.34 (t, 7.1 Hz, 3H), 6. MS (FAB+) calcd. for $C_{19}H_{27}NO_7$: (MH^+): (m/z) 382.2; found (m/z) 382.2.

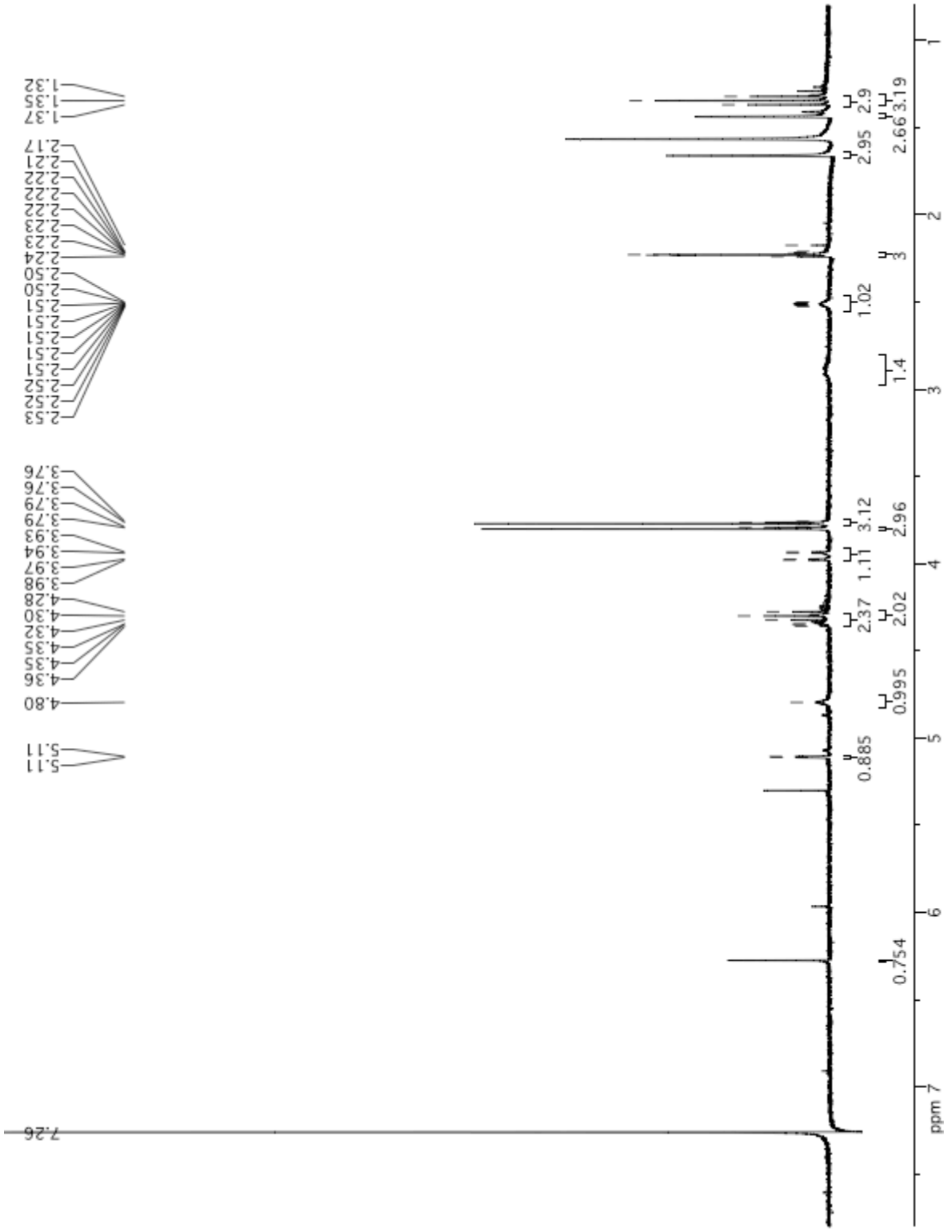
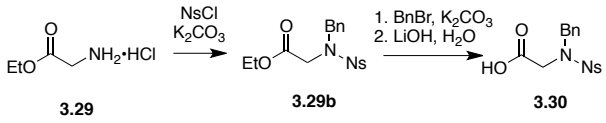


Figure 4.15. ^{1}H NMR spectrum of compound **3.28** (300 MHz, $CDCl_3$)



4.17 2-(*N*-benzyl-4-nitrophenylsulfonamido)acetic acid (3.30)

Ethyl 2-(4-nitrophenylsulfonamido)acetate (3.29b)

To a stirred suspension of GlyOEt•HCl (7.00 g, 50 mmol, 1.0 eq.) and K_2CO_3 (14.50 g, 100 mmol, 1.0 eq.) in water (40 mL) and dioxane (40 mL) at 0°C was added NsCl (11.08 g, 50 mmol, 1.0 eq.) in one portion. The reaction was stirred at RT for 48h, the dioxane evaporated, the residue partitioned between water and ethyl acetate/dichlorometane 4:1 (125mL), and the organic phase rinsed with sat. aq. $NaHCO_3$ (3×25 mL), water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure to afford the title compound as yellow oil (12.38 g, 86%), which was used in the next step without further purification. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.11-8.08 (m, 1H), 7.96-7.92 (m, 1H), 7.76-7.73 (m, 2H), 4.05 (q, J = 7.2 Hz, 2H), 4.00 (s, 2H), 1.16 (t, J = 7.2 Hz, 3H).

2-(*N*-benzyl-4-nitrophenylsulfonamido)acetic acid (3.30)

A suspension of N-Ns-Gly-OEt (12.38g 43 mmol, 1.0 eq.), BnBr (5.28 mL, 44 mmol, 1.0 eq) and K_2CO_3 (18.3 g, 133 mmol, 3.1 eq.) in CH_3CN (450 mL) was stirred under argon for 16h. The reaction was concentrated under reduced pressure, partitioned between water (200 mL) and ethyl acetate (200mL), the aqueous phase was rinsed with ethyl acetate (2×50 mL) and the combined organic layers were rinsed with brine, dried (Na_2SO_4), filtered and concentrated to afford the title compound as a yellow oil (16.5 g, quant.). The material was used in the next step without further purification.

To a stirred solution of N-Ns-Gly-OEt (2.06 g, 5.0 mmol) in THF/H_2O/MeOH 3:2:1 (18 mL) was added LiOH•2H_2O (630 mg, 15 mmol). The reaction was stirred for 3h, quenched with 1M HCl (30 mL), extracted with EtOAc (2×30 mL), rinsed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated to afford the title compound as a yellow solid (1.70 g, 97%). The solid was dried under vacuum overnight and used in the next step without further purification. ^{1}H-NMR (300 MHz; DMSO-d_6): δ 8.15-7.80 (m, 5H), 7.33-7.19 (m, 5H), 4.58 (s, 2H), 3.92 (d, J = 0.5 Hz, 2H).

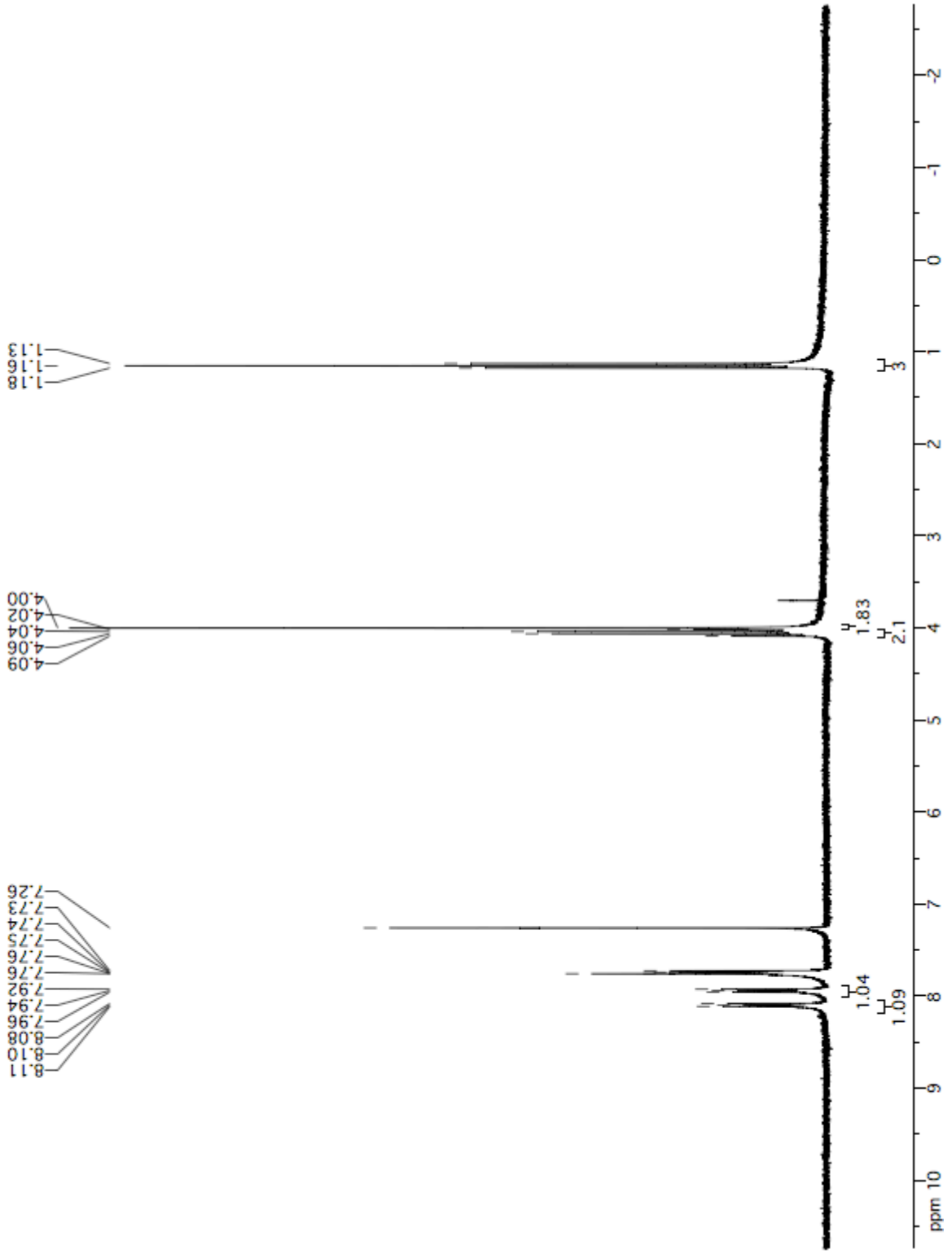


Figure 4.16. ^{1}H NMR spectrum of compound **3.29b** (300 MHz, $CDCl_3$)

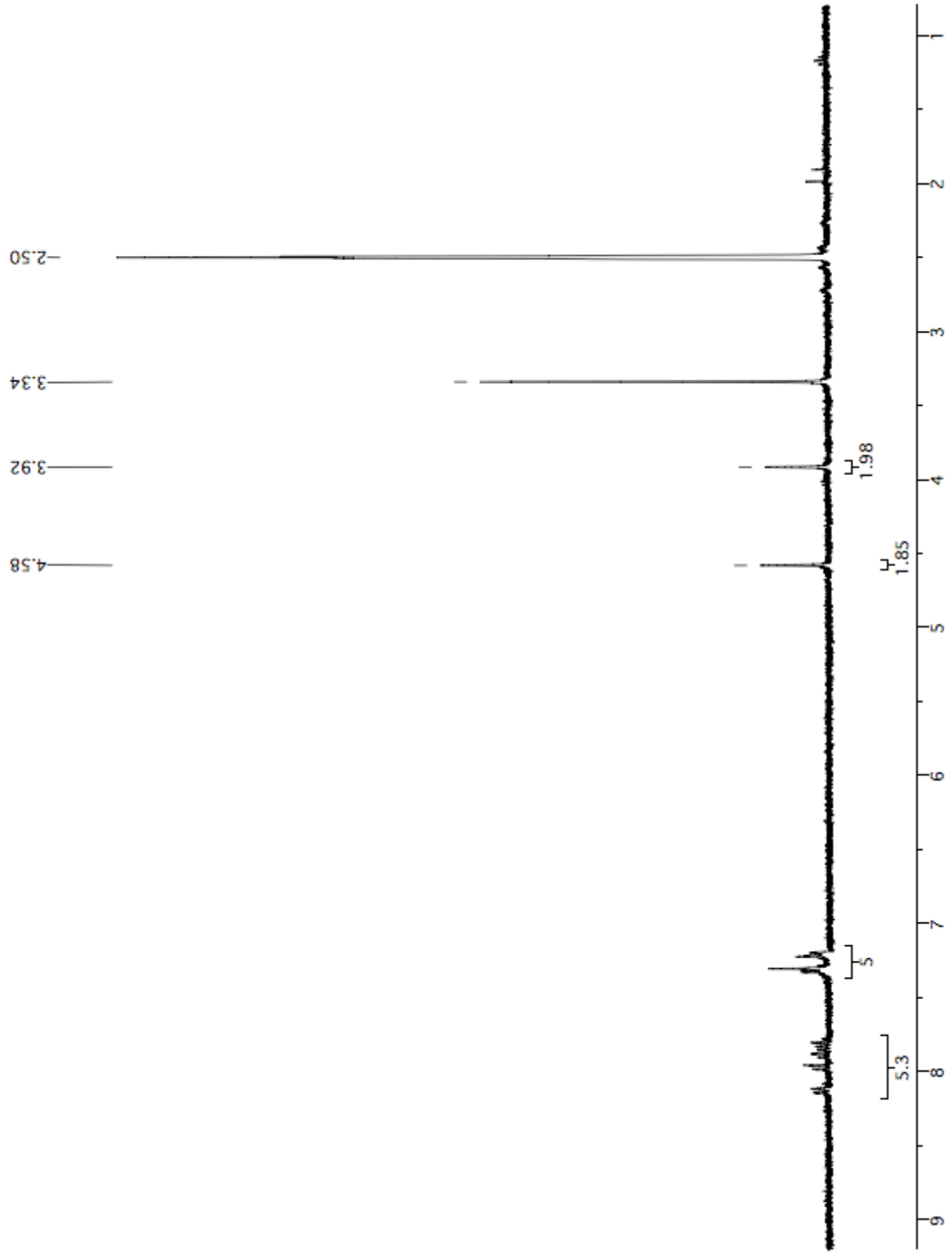
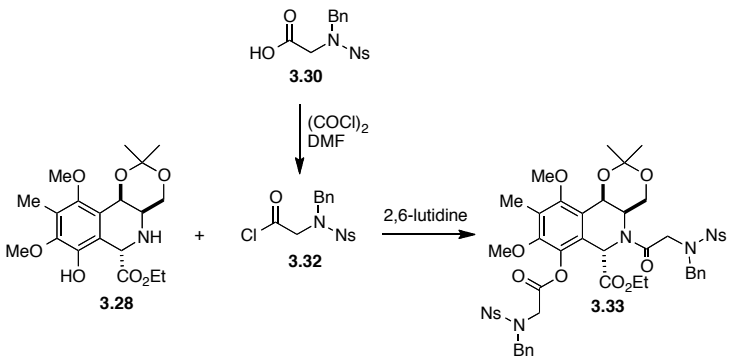


Figure 4.17. ^{1}H NMR spectrum of compound **3.30** (300 MHz, DMSO-d_6)



4.18 (4a*R*,6*S*,10b*R*)-ethyl 7-(2-(*N*-benzyl-4-nitrophenylsulfonamido)acetoxy)-5-(2-(*N*-benzyl-4-nitrophenylsulfonamido)acetyl)-8,10-dimethoxy-2,2,9-trimethyl-4a,5,6,10b-tetrahydro-4*H*-[1,3]dioxino[5,4-*c*]isoquinoline-6-carboxylate (3.33)

Compounds **3.28** and **3.30** were azeotropically dried with toluene prior to use. To a solution of **3.30** (203 mg, 0.580 mmol) in 3 mL of CH_2Cl_2 at RT under argon atmosphere was added 3.6 mL of oxalyl chloride, after which DMF (6.6 μL) was added to the stirring solution. The reaction was stirred for 20 min, after which the mixture was concentrated using the rotary evaporator to afford the corresponding crude acid chloride. The acid chloride was azeotropically dried with toluene to remove residual oxalyl chloride, and was then re-dissolved in 3 mL of CH_2Cl_2 at RT under argon atmosphere and cooled to 0 °C. A solution comprised of compound **3.28** (110 mg, 0.29 mmol) and 2,6-lutidine (37 μL, 0.318 mmol) in 3 mL of CH_2Cl_2 was added via cannula. The reaction was stirred at 0 °C for 45 min, after which the mixture was quenched with sat. aq. NH_4Cl (20 mL). The mixture was diluted with CH_2Cl_2 (50 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes 4:1) to afford the title compound as a colorless oil (120 mg, 58%). The ^{1}H NMR

spectrum revealed the presence of a complex mixture of carbamate rotamers. (See Figure 4.18)

HRMS(ESI/APCI+) for $C_{49}H_{52}N_5O_{17}S_2$: (MH^+): calc. (m/z) 1046.2800; found (m/z) 1046.2784

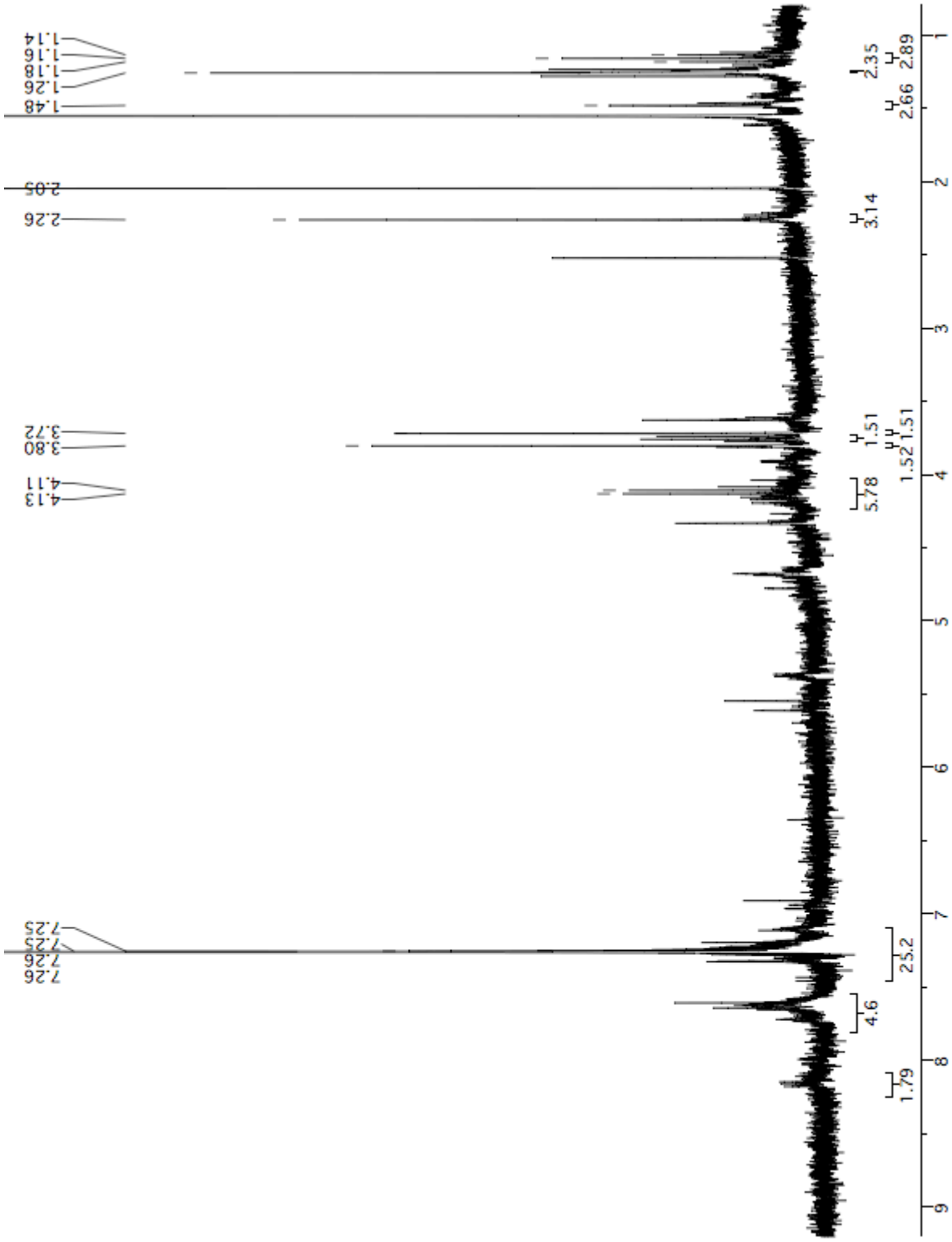
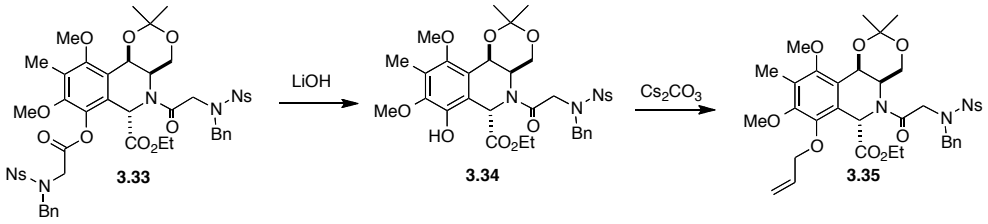


Figure 4.18. ^{1}H NMR spectrum of compound **3.33** (300 MHz, $CDCl_3$)



4.19 (4a*R*,6*S*,10b*R*)-ethyl 7-(allyloxy)-5-(2-(*N*-benzyl-4-nitrophenylsulfonamido)acetyl)-8,10-dimethoxy-2,2,9-trimethyl-4a,5,6,10b-tetrahydro-4*H*-[1,3]dioxino[5,4-*c*]isoquinoline-6-carboxylate (3.35)

(4a*R*,6*S*,10b*R*)-ethyl 5-(2-(*N*-benzyl-4-nitrophenylsulfonamido)acetyl)-7-hydroxy-8,10-dimethoxy-2,2,9-trimethyl-4a,5,6,10b-tetrahydro-4*H*-[1,3]dioxino[5,4-*c*]isoquinoline-6-carboxylate (3.34)

To a solution of Compound **3.33** (5 mg, 0.005 mmol) in H_2O/EtOH/THF (2:2:1, 500 μL) was added LiOH•$2H_2O$ (0.3 mg, 0.007 mmol) and the reaction was stirred for 10 minutes. The mixture was acidified with NH_4Cl (1 mL), concentrated under reduced pressure and extracted with EtOAc (3×2 mL), rinsed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated to give the title compound. The material was used in the next step without further purification. HRMS(ESI/APCI+) for $C_{34}H_{39}N_3O_{12}SNa$: (MNa^+): calc (m/z) 736.2147; found (m/z) 736.2146

(4a*R*,6*S*,10b*R*)-ethyl 7-(allyloxy)-5-(2-(*N*-benzyl-4-nitrophenylsulfonamido)acetyl)-8,10-dimethoxy-2,2,9-trimethyl-4a,5,6,10b-tetrahydro-4*H*-[1,3]dioxino[5,4-*c*]isoquinoline-6-carboxylate (3.35)

A suspension of compound **3.34** (crude from previous step, 0.05 mmol), allyl bromide (3 μL, 0.1 mmol) and Cs_2CO_3 (5 mg, 0.015 mmol) in (500 μL) was stirred under Ar for 12 h. The solvent was evaporated and the residue was partitioned between water (5 mL) and EtOAc (5 mL). The organic phase was rinsed with brine (2 mL), dried (Na_2SO_4), filtered and concentrated by flash

chromatography (EtOAc/hex 1:1) to give the title compound as a colorless oil (3 mg, 83%). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 8.17 (dt, *J* = 4.7, 2.3 Hz, 1H), 7.65-7.61 (m, 3H), 7.29-7.27 (m, 5H), 5.94-5.85 (m, 1H), 5.57 (s, 1H), 5.37 (d, *J* = 4.2 Hz, 1H), 5.26-5.19 (m, 1H), 5.10-5.05 (m, 1H), 4.82 (s, 1H), 4.68 (s, 1H), 4.55-4.42 (m, 3H), 4.37 (s, 1H), 4.26 (s, 1H), 4.21-4.11 (m, 2H), 3.93-3.87 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H), 1.48 (s, 3H), 1.25 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

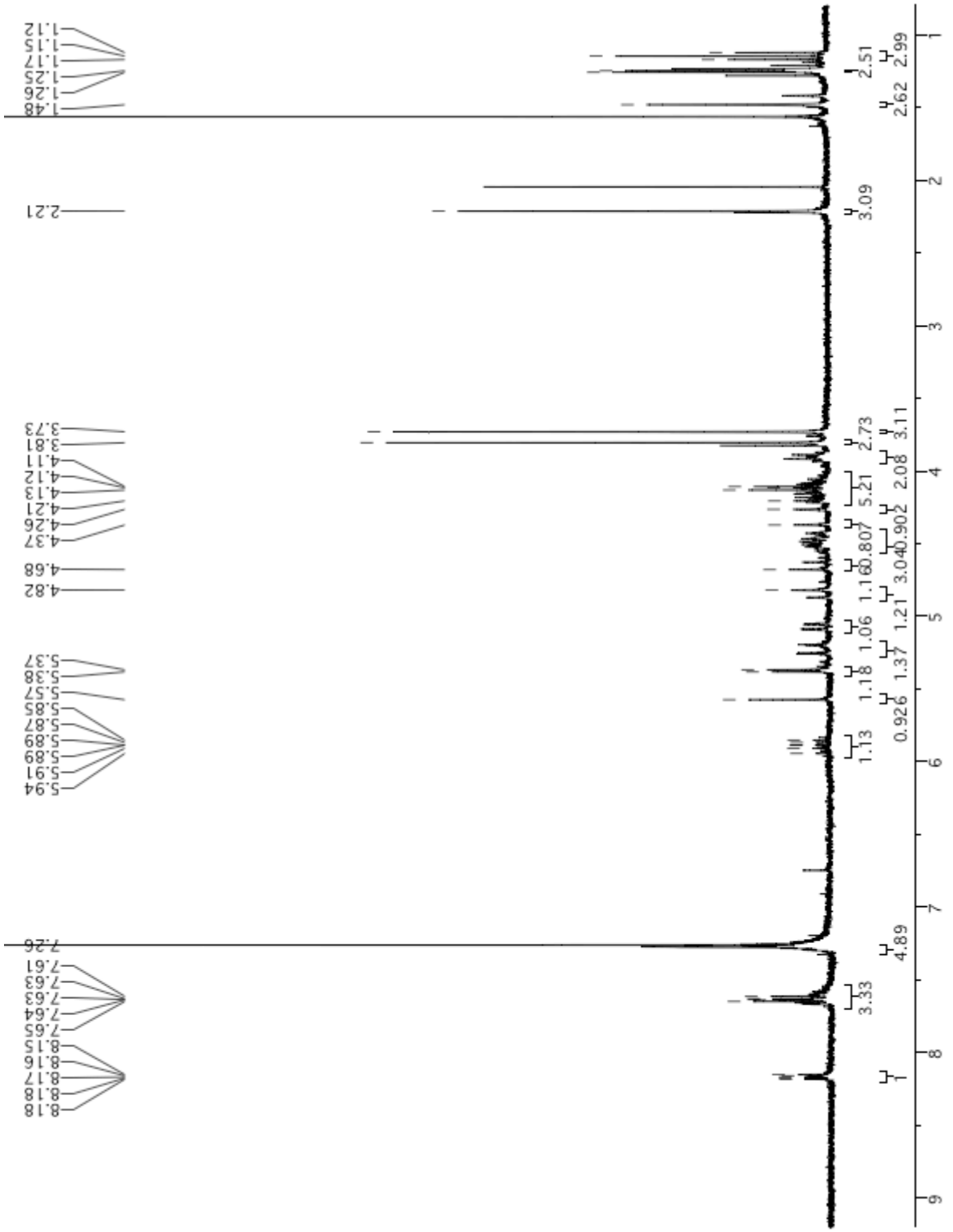
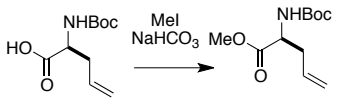


Figure 4.19. ^{1}H NMR spectrum of compound **3.35** (300 MHz, $CDCl_3$)



3.43 3.44

4.20 (*S*)-methyl 2-((*tert*-butoxycarbonyl)amino)pent-4-enoate (3.44)

(*S*)-Boc-allylglycine (**3.43**) (302 mg, 1 mmol) and $NaHCO_3$ (252 mg, 2 mmol) were suspended in DMF (6 mL) under Ar atmosphere. Iodomethane (286 μL, 3 mmol) was added and the reaction was stirred for 24h, poured over 25 mL of water, the phases separated, the aqueous phase extracted with EtOAc (2×25 mL) and the combined organic phases rinsed with water (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated. The resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc) to give the title compound as a clear colorless oil (199 mg, 62 %). R_f = 0.2 (6:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.71-5.57 (m, 1H), 5.10-5.05 (m, 3H), 4.35-4.29 (m, 1H), 3.65 (s, 3H), 2.54-2.37 (m, 2H), 1.35 (s, 9H).

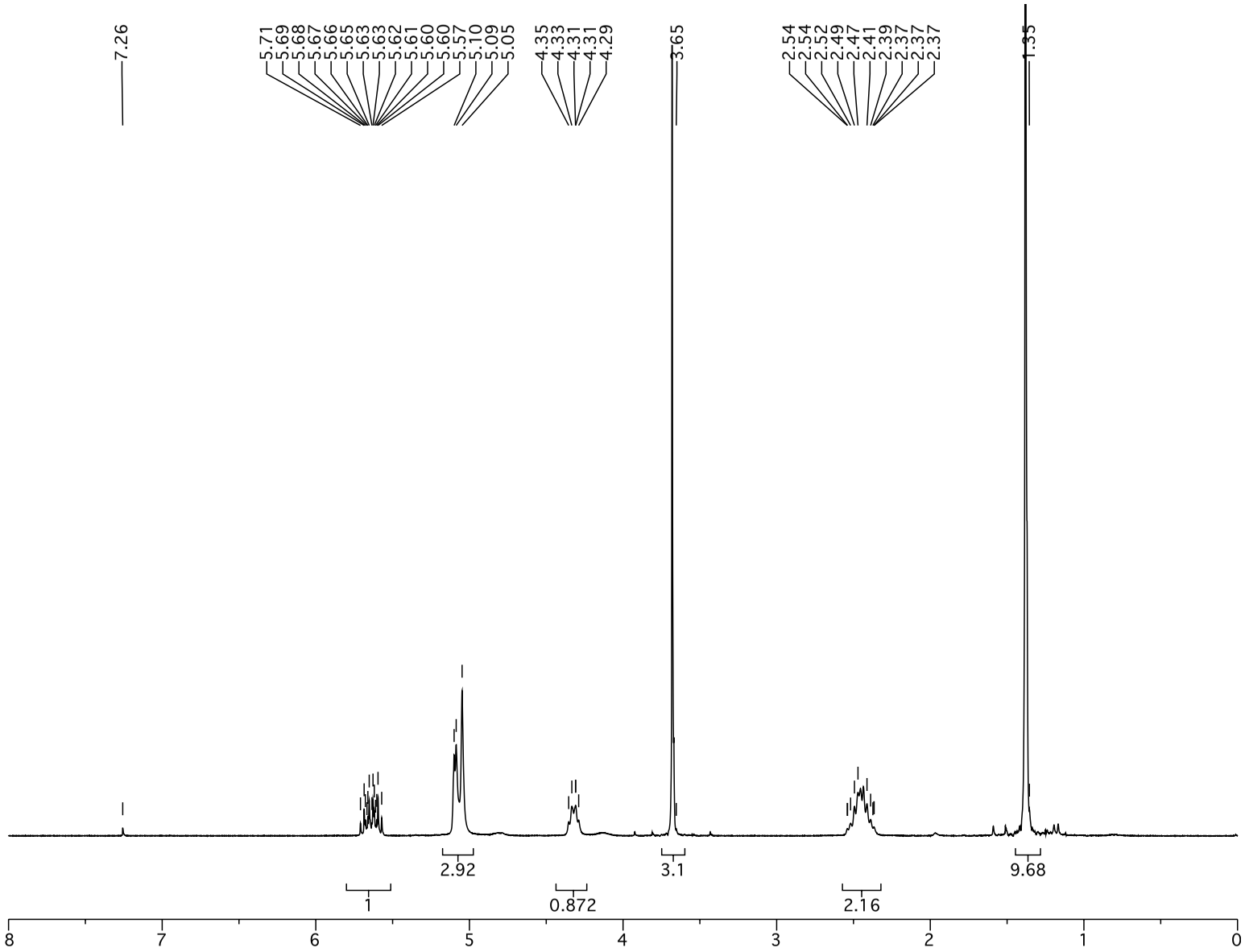
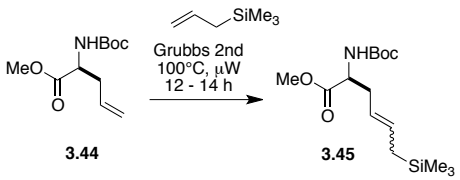


Figure 4.20. ^{1}H NMR spectrum of compound **3.44** (300 MHz, $CDCl_3$)



3.44 3.45

4.21 (*S*)-methyl 2-((*tert*-butoxycarbonyl)amino)-6-(trimethylsilyl)hex-4-enoate (3.45)

Compound (**3.44**) (199 mg, 0.86 mmol) and Grubbs 2nd generation catalyst (40 mg, 0.047 mmol, 5.5 mol %) were dissolved in DCM (8 mL) in a microwave reaction vessel and the resulting solution was degassed with Ar for 5 min. and placed in a microwave reactor (maximum power = 100 W, 100°C for 12h). The reaction mixture was concentrated under vacuum and the resulting solid was purified by flash chromatography (9:1 hexanes/EtOAc) to afford the title compound as a colorless oil (188 mg, 69%). R_f = 0.5 (6:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.56-5.45 (m, 1H), 5.14-4.96 (m, 1H), 3.73 (s, 3H), 2.53-2.38 (m, 2H), 1.43 (s, 9H), 1.43 (s, 9H), -0.01 (s, 6H).

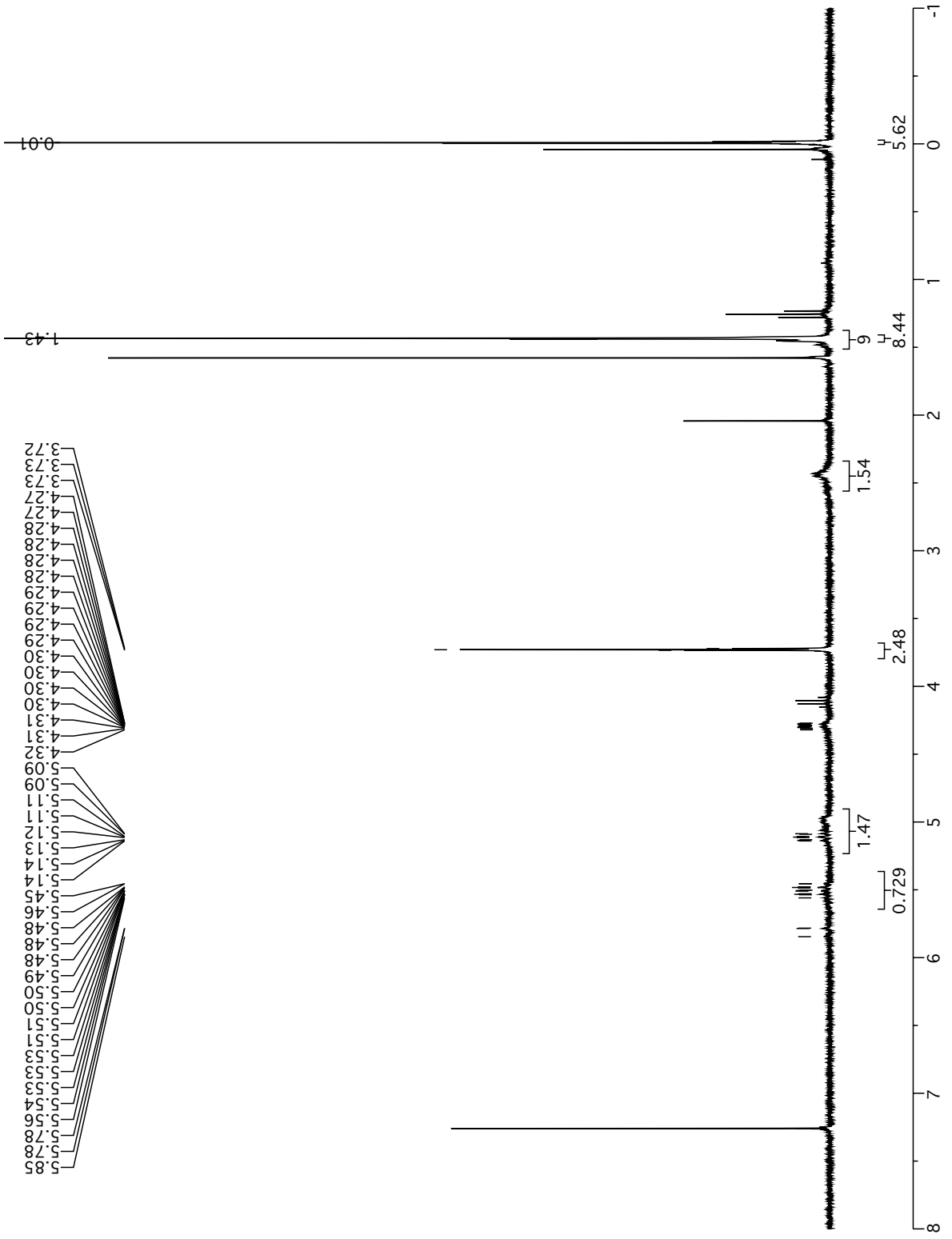
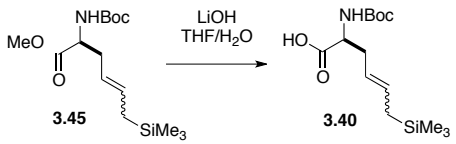


Figure 4.21. ^{1}H NMR spectrum of compound **3.45** (300 MHz, $CDCl_3$)



4.22 (*S*)-2-((*tert*-butoxycarbonyl)amino)-6-(trimethylsilyl)hex-4-enoic acid (3.40)

To a solution of compound **3.45** (188 mg, 0.60 mmol) in THF (8 mL) were added water (1.6 mL) and LiOH•H_2O (100 mg, 2.4 mmol) and the resulting suspension was stirred for 2h, diluted with water (20mL), acidified to pH=4 with 1N HCl and diluted with EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×20 mL) and the combined organic phases were rinsed with brine (20 mL) dried (Na_2SO_4), filtered and concentrated. The resulting oil was purified by flash chromatography (1:1 hexanes/EtOAc) to afford the title compound as a clear colorless oil (120 mg, 62 %). R_f = 0.1 (1:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.55-5.50 (m, 1H), 5.19-5.05 (m, 2H), 4.15 (s, 1H), 2.51-2.44 (m, 2H), 1.46-1.39 (m, 9H).

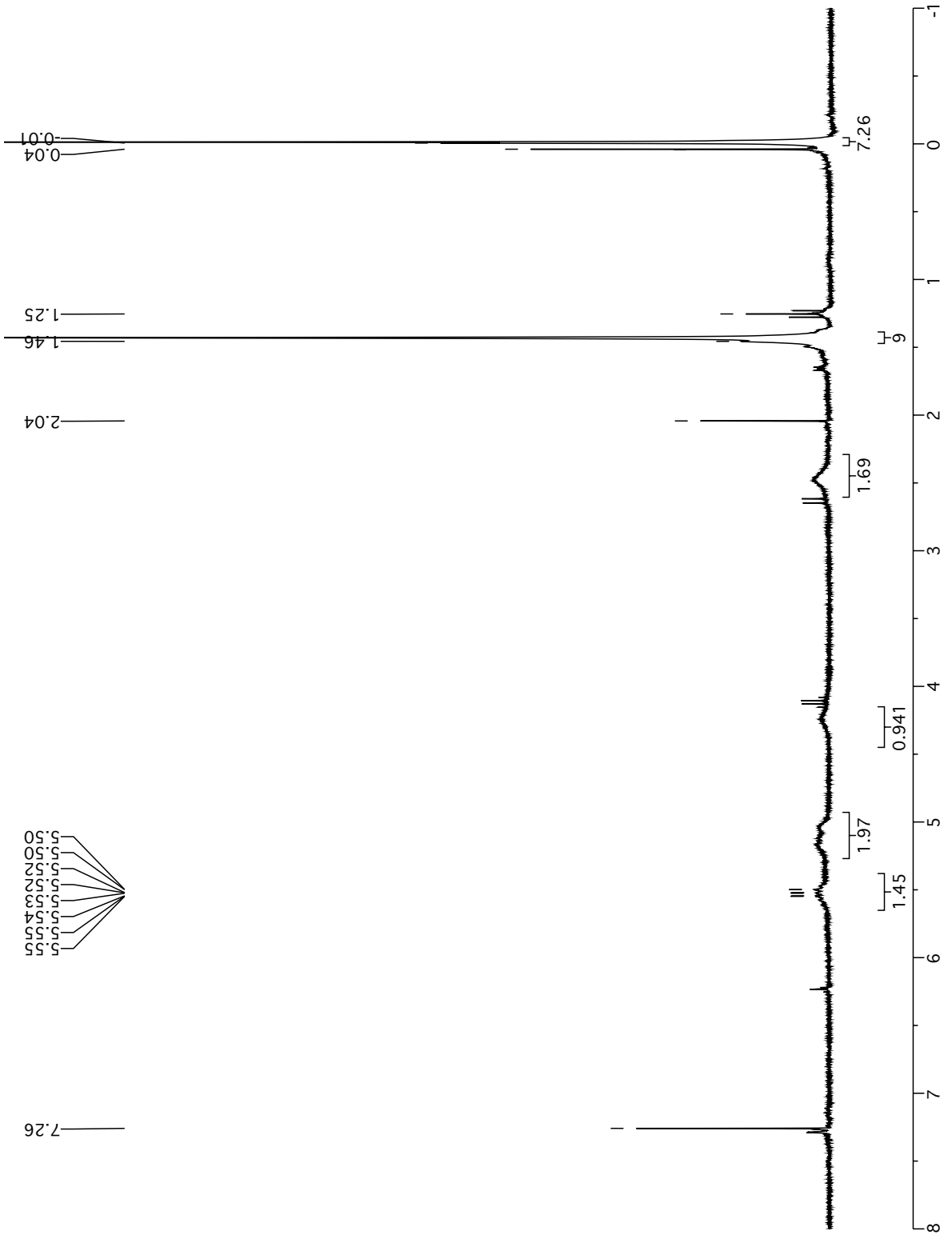
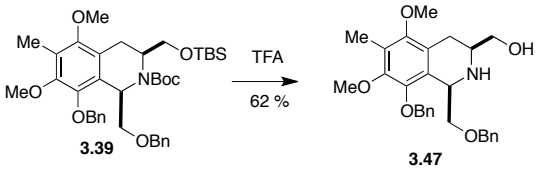


Figure 4.22. ^{1}H NMR spectrum of compound **3.40** (300 MHz, $CDCl_3$)



4.23 ((1*R*,3*S*)-8-(benzyloxy)-1-((benzyloxy)methyl)-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (3.47)

To a solution of compound **3.39** (220 mg) in CH_2Cl_2 (3.25 mL) was added TFA (0.964 mL, 40 eq) and the resulting mixture was stirred for 2h (until TLC revealed absence of SM). The reaction was diluted with water (20 mL), the TFA quenched with $NaHCO_3$ sat., the phases separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL) and the combined organic phases were rinsed with brine (20 mL) dried (Na_2SO_4), filtered and concentrated. The resulting oil was purified by flash chromatography (1:1 hexanes/EtOAc followed by EtOAc) to afford the title compound as a clear colorless oil (120 mg, 62 %). R_f = 0.1 (EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.43-7.17 (m, 5H), 5.03 (d, *J* = 5.7 Hz, 2H), 4.40 (d, *J* = 2.9 Hz, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.56-3.53 (m, 3H), 3.30-3.23 (m, 3H), 2.96-2.90 (m, 3H), 2.24 (s, 3H).

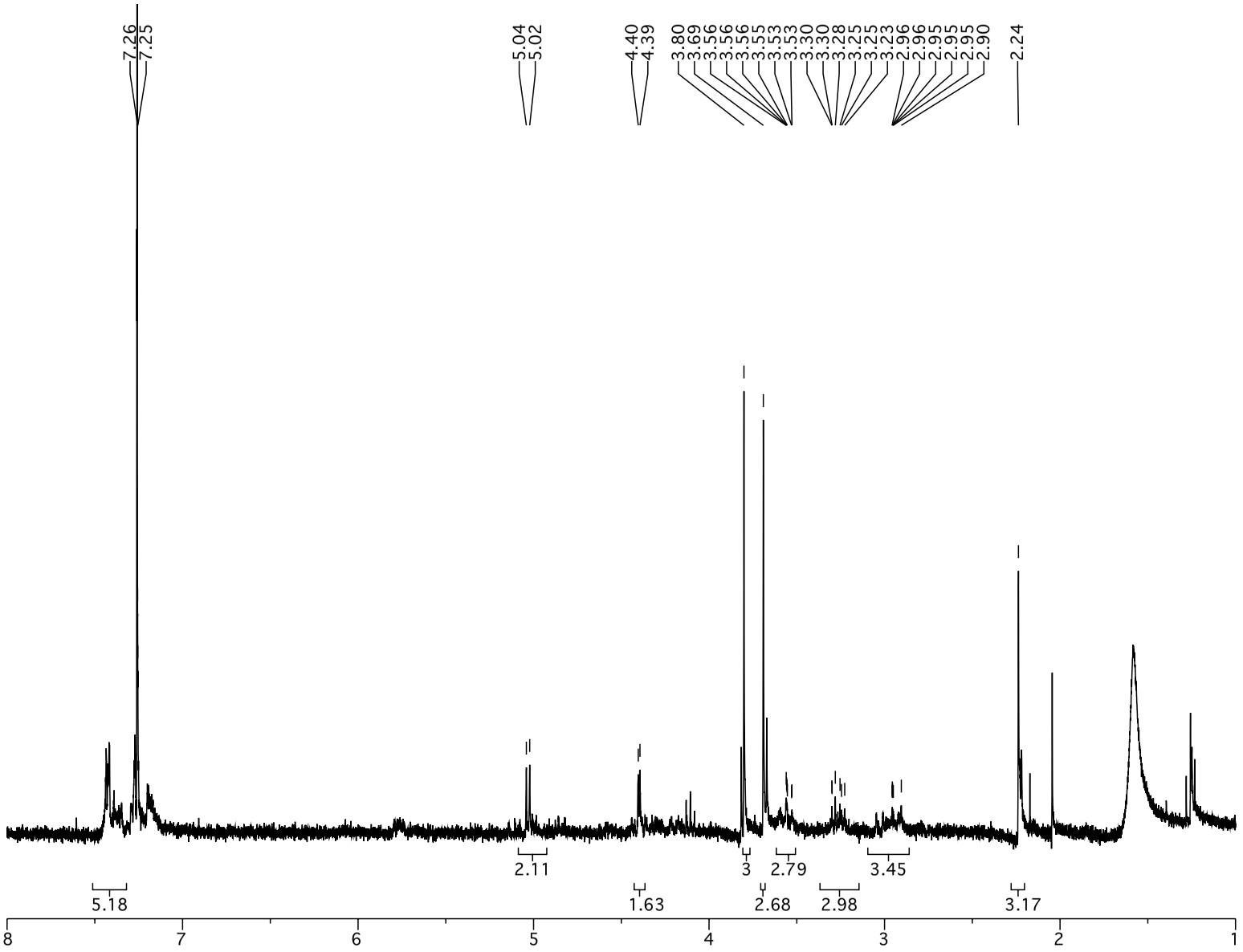
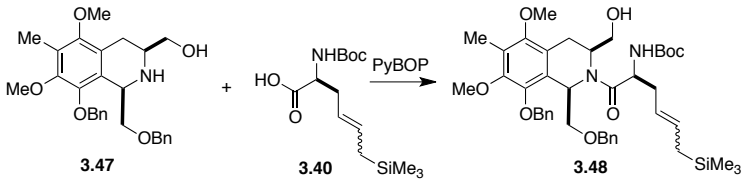


Figure 4.23. ^{1}H NMR spectrum of compound **3.47** (300 MHz, $CDCl_3$)



4.24 *Tert*-butyl ((*S*)-1-((1*R*,3*S*)-8-(benzyloxy)-1-((benzyloxy)methyl)-3-(hydroxymethyl)-5,7-dimethoxy-6-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-1-oxo-6-(trimethylsilyl)hex-4-en-2-yl)carbamate (3.48)

A solution of compound **3.47** (70 mg, 0.15 mmol), PyBOP (84 mg, 0.16 mmol) and compound **3.40** (45 mg, 0.15 mmol) in CH_2Cl_2 (700 μL) was stirred for 24 h and diluted with CH_2Cl_2 (5 mL) and sat. aq. NH_4Cl (5 mL). The phases were separated and the aqueous phase was rinsed with CH_2Cl_2 (2×5 mL). The combined organic phases were rinsed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated. The resulting oil was purified by flash chromatography (3:1 hexanes/EtOAc) to afford the title compound (30 mg, 27%) as a clear colorless oil. R_f = 0.15 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.38-7.23 (m, 5H), 5.04 (d, *J* = 11.0 Hz, 2H), 4.83 (d, *J* = 10.9 Hz, 1H), 4.30 (d, *J* = 4.6 Hz, 1H), 4.20-4.13 (m, 2H), 3.81-3.78 (m, 2H), 3.68 (s, 3H), 3.54 (s, 1H), 2.91-2.85 (m, 2H), 2.45-2.42 (m, 2H), 2.21 (s, 3H), 1.43 (s, 9H), -0.02 (s, 6H).

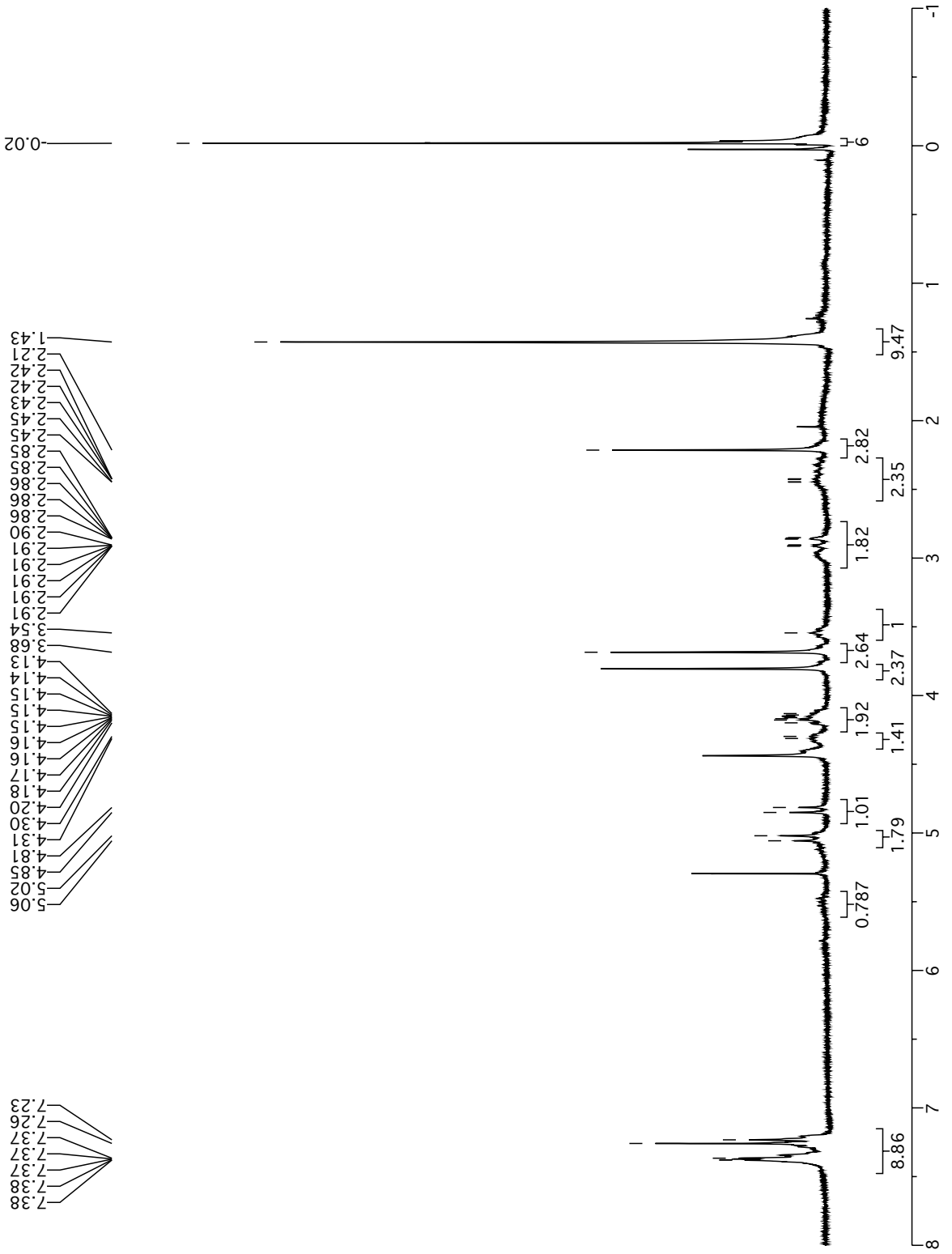
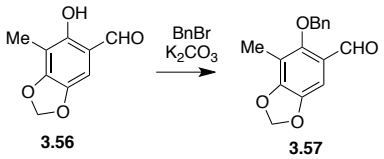


Figure 4.24. ^{1}H NMR spectrum of compound **3.48** (300 MHz, $CDCl_3$)



4.25 6-(benzyloxy)-7-methylbenzo[*d*][1,3]dioxole-5-carbaldehyde (3.57)

To a suspension of aldehyde **3.56** (500 mg, 2.78 mmol) and K_2CO_3 (1.5 g, 8.33 mmol) in acetone (30 mL) was added BnBr (400 µL, 3.36 mmol). The reaction was stirred for 24h, diluted with water (30 mL), concentrated under vacuum and the aqueous phase extracted with EtOAc (2×25 mL). The combined organic phases were concentrated, dried (Na_2SO_4), filtered and evaporated under vacuum. The resulting solid was purified by flash chromatography (3:1 hexanes/EtOAc) to afford the title compound as yellow solid (680 mg, 90%). R_f = 0.4 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.07 (s, 1H), 7.40 (s, 5H), 7.12 (s, 1H), 6.05 (s, 2H), 4.93 (s, 1H), 2.21 (s, 3H).

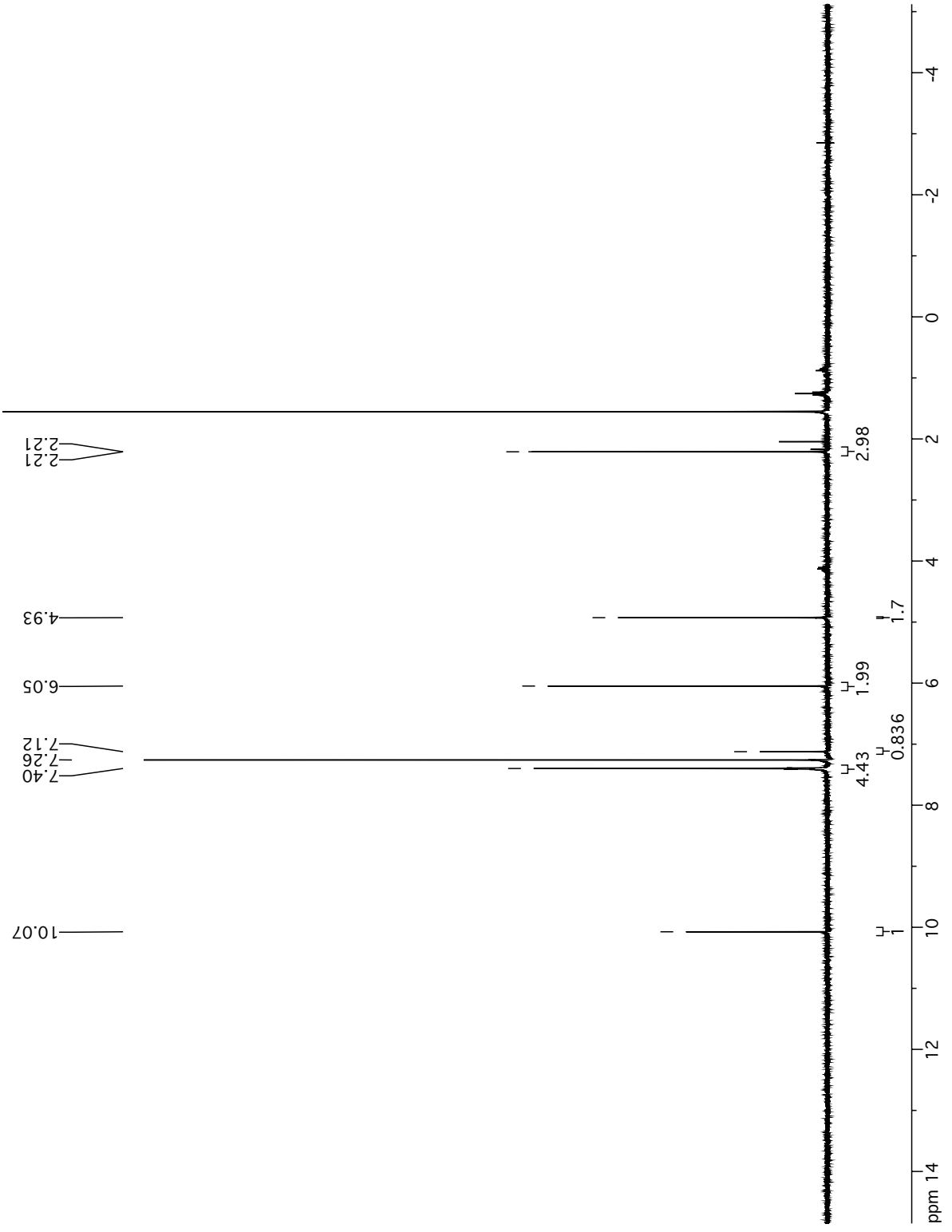
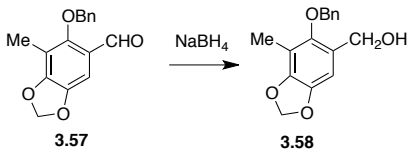


Figure 4.25. ^{1}H NMR spectrum of compound **3.57** (300 MHz, $CDCl_3$)



3.57 3.58

4.26 6-(hydroxymethyl)-4-methylbenzo[*d*][1,3]dioxol-5-ol (3.58)

To a solution of aldehyde **3.57** (680 mg, 2.5 mmol) in EtOH (15 mL) was added $NaBH_4$ (38 mg, 1 mmol). The reaction was stirred for 3h, quenched with 1N HCl (15 mL) and concentrated under vacuum. The aqueous phase extracted with EtOAc (2×25 mL). The combined organic phases were concentrated under, dried (Na_2SO_4), filtered and evaporated. The resulting solid was purified by flash chromatography (3:1 hexanes/EtOAc) to afford the title compound as a white solid (450 mg, 65 %). R_f = 0.2 (3:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.39-7.33 (m, 6H), 6.73 (s, 1H), 5.92 (s, 2H), 4.76 (s, 2H), 4.48 (s, 2H), 2.17 (s, 3H).

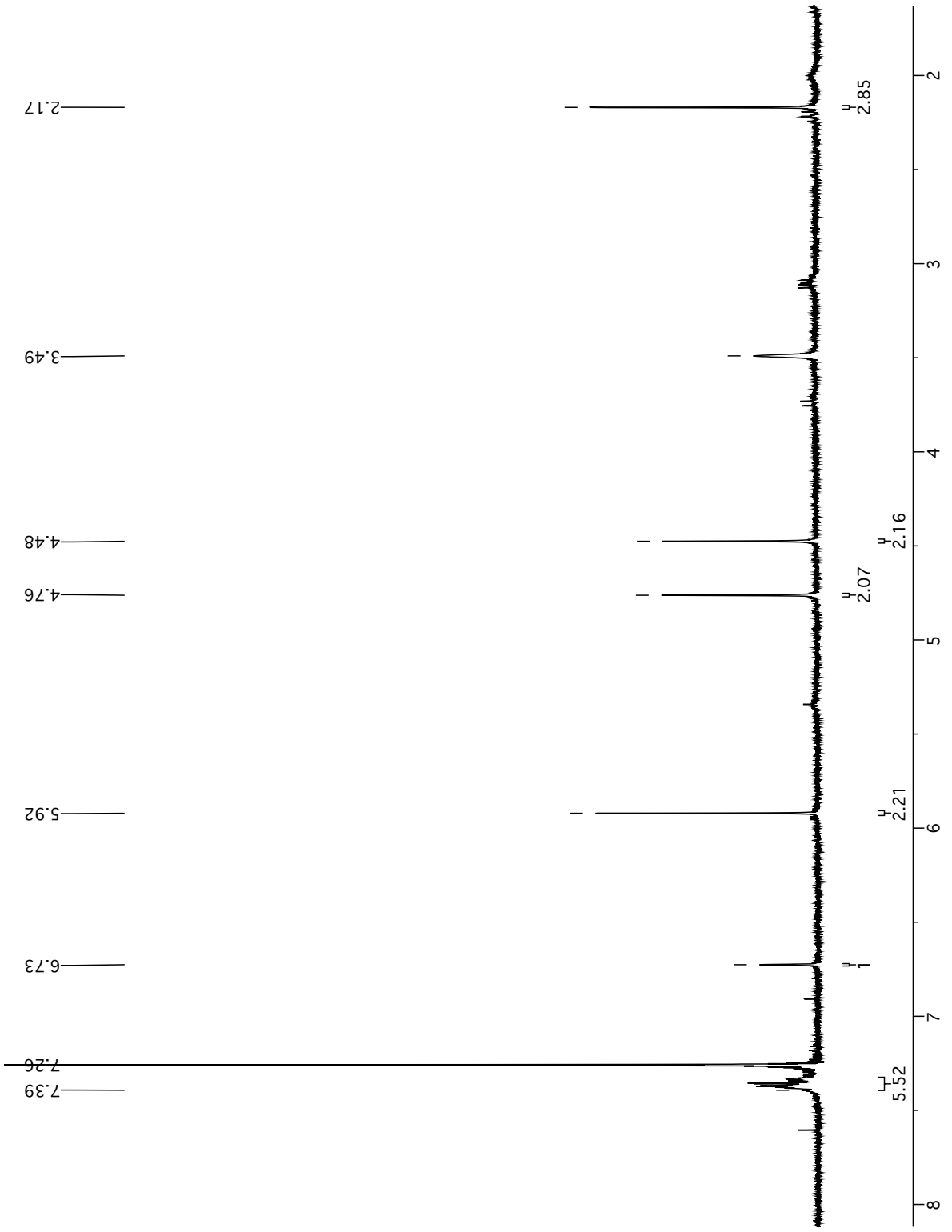
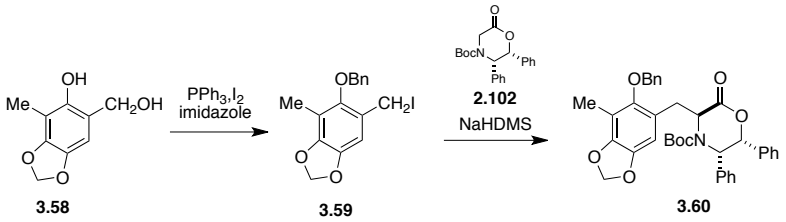


Figure 4.26. ^{1}H NMR spectrum of compound **3.58** (300 MHz, $CDCl_3$)



4.27 (3*S*,5*S*,6*R*)-*tert*-butyl 3-((6-(benzyloxy)-7-methylbenzo[*d*][1,3]dioxol-5-yl)methyl)-2-oxo-5,6-diphenylmorpholine-4-carboxylate (3.60)

To a solution of PPh_3 (5.51 g, 21 mmol) in 100 mL of dry CH_2Cl_2 at 0°C under Ar atmosphere, was added I_2 (5.32 g, 21 mmol) in several small portions over 1 min. The mixture was stirred for 5 min, after which a solution consisting of benzyl alchohol **3.58** (3.812 g, 14 mmol) and imidazole (2.85 mg, 42 mmol) in 150 mL of dry CH_2Cl_2 was added dropwise over 5 min by cannula. The mixture was stirred at 0°C for 45 minutes and quenched with 100 mL of 5% $NaHSO_3$. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 75 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a pale-yellow solid. The crude material was kept under vacuum and covered with aluminum foil for 12 h (to avoid exposure to light) and used in the following step without further purification.

Tert-butyl (*2R,3S*)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (**3.102**) (4.94 mg, 14 mmol, 1.0 eq.) was dissolved in 140 mL of anhydrous THF under Ar atmosphere and the mixture was cooled to -78°C. NaHDMS (1.0 M in THF, 16 mL, 16 mmol, 1.15 eq.) was added dropwise over 5 minutes and the mixture was stirred for 45 min, after which a solution of crude benzyl iodide (12) in 140 mL of dry THF was added over 5 minutes by cannula. The reaction was stirred for 4h at -78°C, quenched with 10 mL of sat. aq. NH_4Cl, allowed to warm to RT, and diluted with 250 mL of EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (3×100mL). The combined organic phases were rinsed with brine (100 mL and dried (Na_2SO_4),

filtered and concentrated under reduced pressure and the crude material was purified with flash chromatography (hexanes/EtOAc 4:1) to give the title compound as a white crystalline solid (8.45 mg, 99%). R_f = 0.3 (hexanes/EtOAc 4:1); ^{1}H NMR: mixture of rotamers, ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.42-7.34 (m, 2H), 7.23-7.01 (s, 10H), 6.74 (s, 1H), 6.69-6.64 (m, 2H), 6.51 (t, *J* = 6.6 Hz, 2H), 5.97 - 5.92 (d, m, 2H), 5.57 (d, *J* = 3.1 Hz, 1H), 5.35 (d, *J* = 3.0 Hz, 1H), 5.24-5.19 (m, 1H), 5.06-5.00 (m, 1H), 3.39 (dd, *J* = 13.4, 8.5 Hz, 1H), 3.28-3.20 (m, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 1.57 (s, 9H).

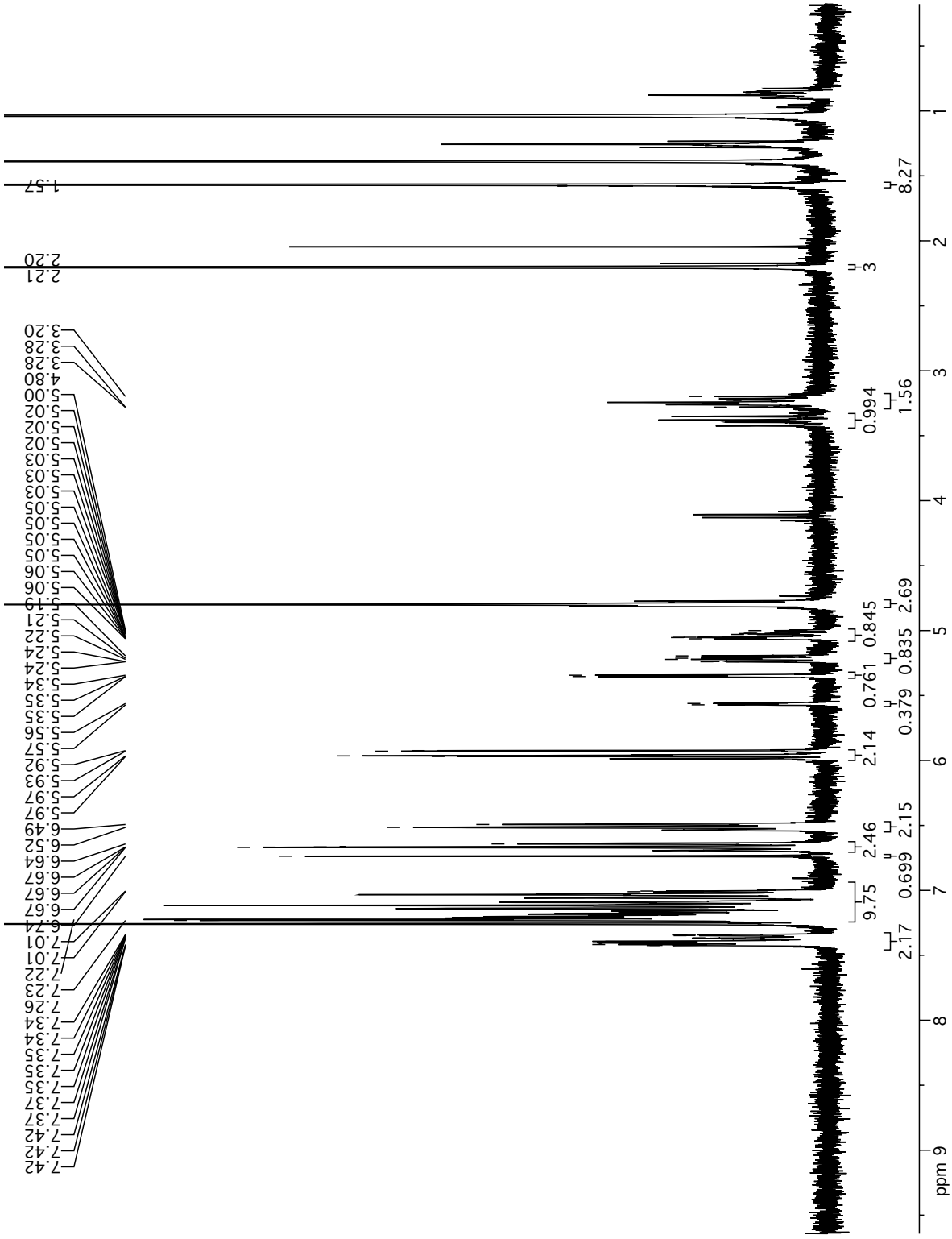
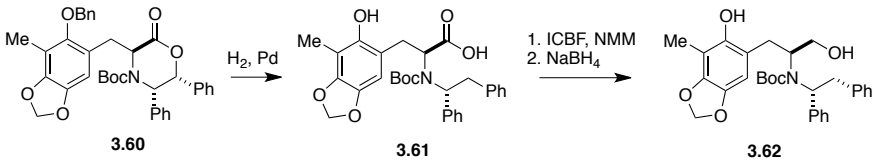


Figure 4.27. ^{1}H NMR spectrum of compound **3.60** (300 MHz, $CDCl_3$)



4.28 *Tert*-butyl ((*R*)-1,2-diphenylethyl)((*S*)-1-hydroxy-3-(6-hydroxy-7-methylbenzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate (3.62)

Compound **3.60** (300 mg, 0.5 mmol) was dissolved in MeOH (8mL) and THF (8 mL). 80 mg of 10% Pd/C were added and the resulting suspension was evacuated three times and filled with H_2 (1 atm), and stirred under H_2 (1 atm) for 24 h. The reaction was filtered through Celite® using EtOAc to transfer the material and the filtrate was evaporated to give an oil. The crude material was dissolved in 10 mL of dry THF under Ar atmosphere and NMM (76 μL, 0.69 mmol, 1.2 eq) was added dropwise over 30 s., followed by isobutyl chloroformate (91 μL, 0.69 mmol, 1.2 eq). The reaction was stirred at RT for 30 min and the resulting suspension was loaded into a short column of Celite® (previously rinsed with anhydrous THF). Using vacuum, the solution was transferred to a flask containing $NaBH_4$ (380 mg, 7 mmol, 10 eq.) dissolved in H_2O (10 mL) at 0°C, using 6 mL of THF to rinse the flask. The reaction was stirred at 0°C for 2h and quenched by adding AcOH/H_2O (1:1) (500 μL) dropwise over 1 minute. The reaction was immediately diluted with EtOAc (10 mL) and H_2O (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried, filtered and concentrated. The resulting crude was purified by flash chromatography (hexanes/EtOAc 4:1) to afford the title compound a as a colorless oil (235 mg, 86%). R_f = 0.38 (hexanes/EtOAc 4:1); ^{1}H-NMR (300 MHz; $CDCl_3$): mixture of carbamate rotamers, low solubility, δ 7.51-7.48 (m, 5H), 7.28-7.20 (m, 10H), 5.80-5.76 (m, 2H), 3.44-3.22 (m, 3H), 3.17-3.00 (m, 2H), 2.06 (s, 3H), 1.35 (s, 9H).

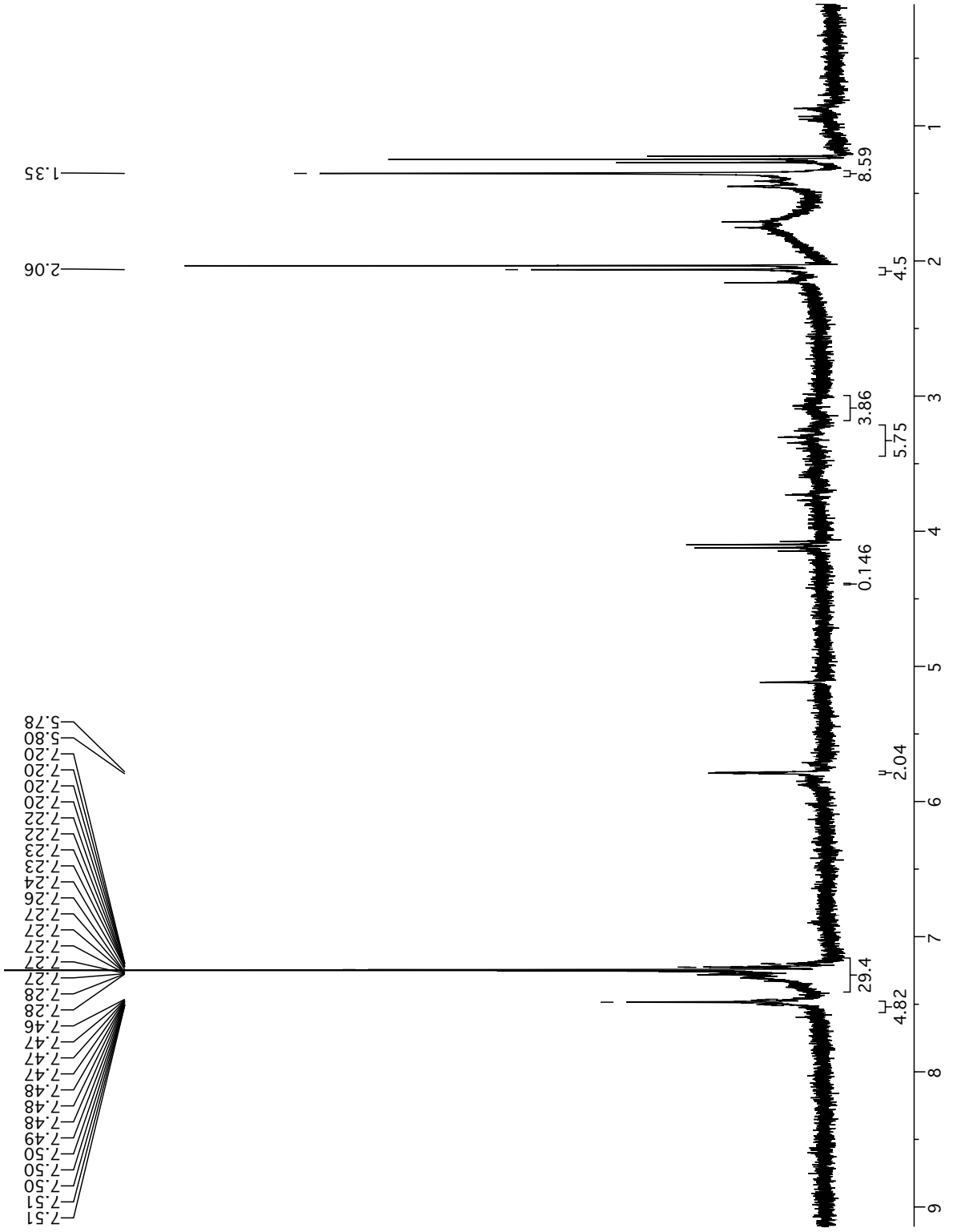
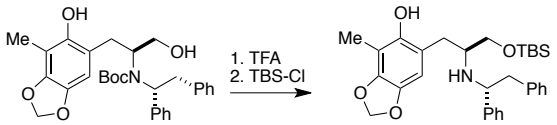


Figure 4.28. ^{1}H NMR spectrum of compound **3.62** (300 MHz, $CDCl_3$)



3.62 3.54

4.29 *Tert*-butyl ((*R*)-1,2-diphenylethyl)((*S*)-1-hydroxy-3-(6-hydroxy-7-methyl-benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)carbamate (3.54)

To a solution of compound **3.62** (235 mg, 0.47 mmol, 1.0 eq.) in dry CH_2Cl_2 (20 mL) under Ar atmosphere, were added 600 μL of TFA (8 mmol). The solution was stirred at RT for 2h, diluted with 5mL of CH_2Cl_2 and 5 mL of aq. $NaHCO_3$. The phases were separated and the organic phase was rinsed with 5% aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude aminoalcohol (177 mg, 0.44 mmol). The crude material was dissolved in dry CH_2Cl_2 (43 mL) under Ar atmosphere and then TBS-Cl (131 mg, 0.88, 2 eq.) was added. The reaction mixture was stirred for 16 h, poured over 10 mL of water and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were rinsed with brine and dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified with flash chromatography (hexanes/EtOAc 6:1) to afford the title compound as a colorless oil (100 mg, 41%). R_f = 0.5 (hexanes/EtOAc 6:1); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.23-7.05 (m, 8H), 6.86-6.83 (m, 2H), 6.25 (s, 1H), 5.87 (AB, *J* = 1.5 Hz, 2H), 4.07-4.01 (m, 2H), 3.45-2.77 (m, 5H), 2.20 (s, 3H), 0.81 (s, 9H), -0.07 (d, *J* = 5.5 Hz, 6H).

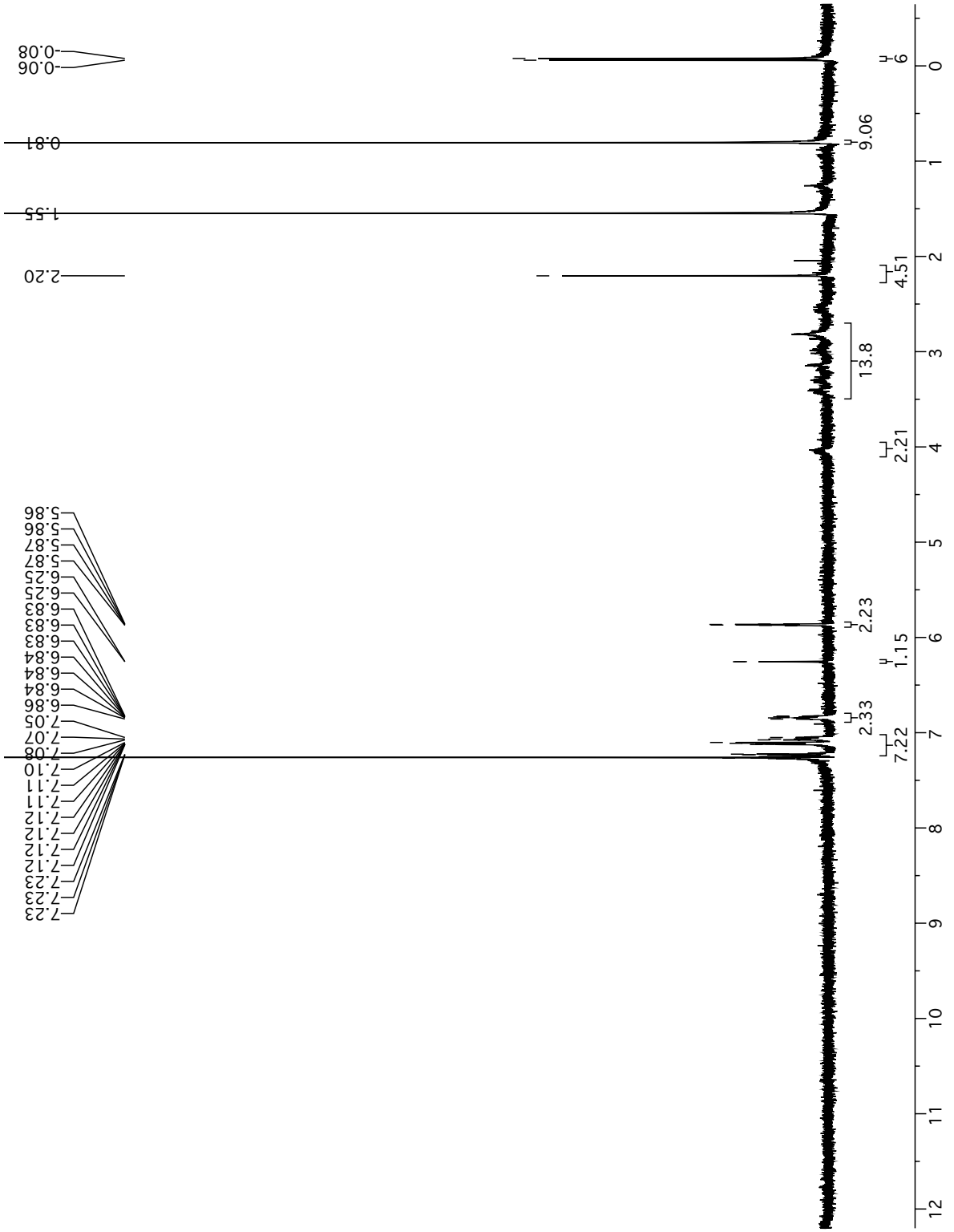
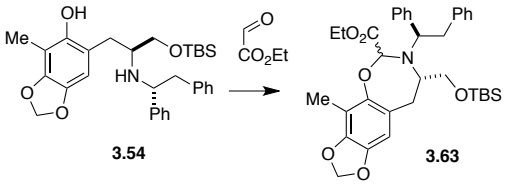


Figure 4.29. ^{1}H NMR spectrum of compound **3.54** (300 MHz, $CDCl_3$)



4.30 (8*S*)-ethyl 8-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-((*R*)-1,2-diphenylethyl)-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-*f*][1,3]oxazepine-6-carboxylate (3.63)

To a solution of compound **3.54** (100 mg, 0.19 mmol, 1.0 eq.) in 2.00 mL of acetonitrile under Ar atmosphere, was added of 50% ethyl glyoxalate in toluene (56 µL, 0.26 mmol, 1.4 eq.). The reaction was stirred at 45°C for 3 days. After cooling to RT, the mixture was filtered through Celite® using EtOAc to transfer the material. The solvents were evaporated and the resulting crude was purified by flash chromatography (hexanes/EtOAc 6:1) to afford the title compound as pale yellow solid (55 mg, 47%); R_f = 0.25 (hexanes/EtOAc 6:1); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.22-6.94 (m, 10H), 5.78 (d, *J* = 4.3 Hz, 2H), 5.77 (s, 1H), 4.15-4.05 (m, 2H), 3.96-3.85 (m, 1H), 3.44-3.33 (m, 3H), 3.24 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.12-3.04 (m, 1H), 2.33-2.26 (m, 1H), 1.96-1.91 (m, 1H), 1.87 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.79 (s, 9H), -0.10 (d, *J* = 5.0 Hz, 6H).

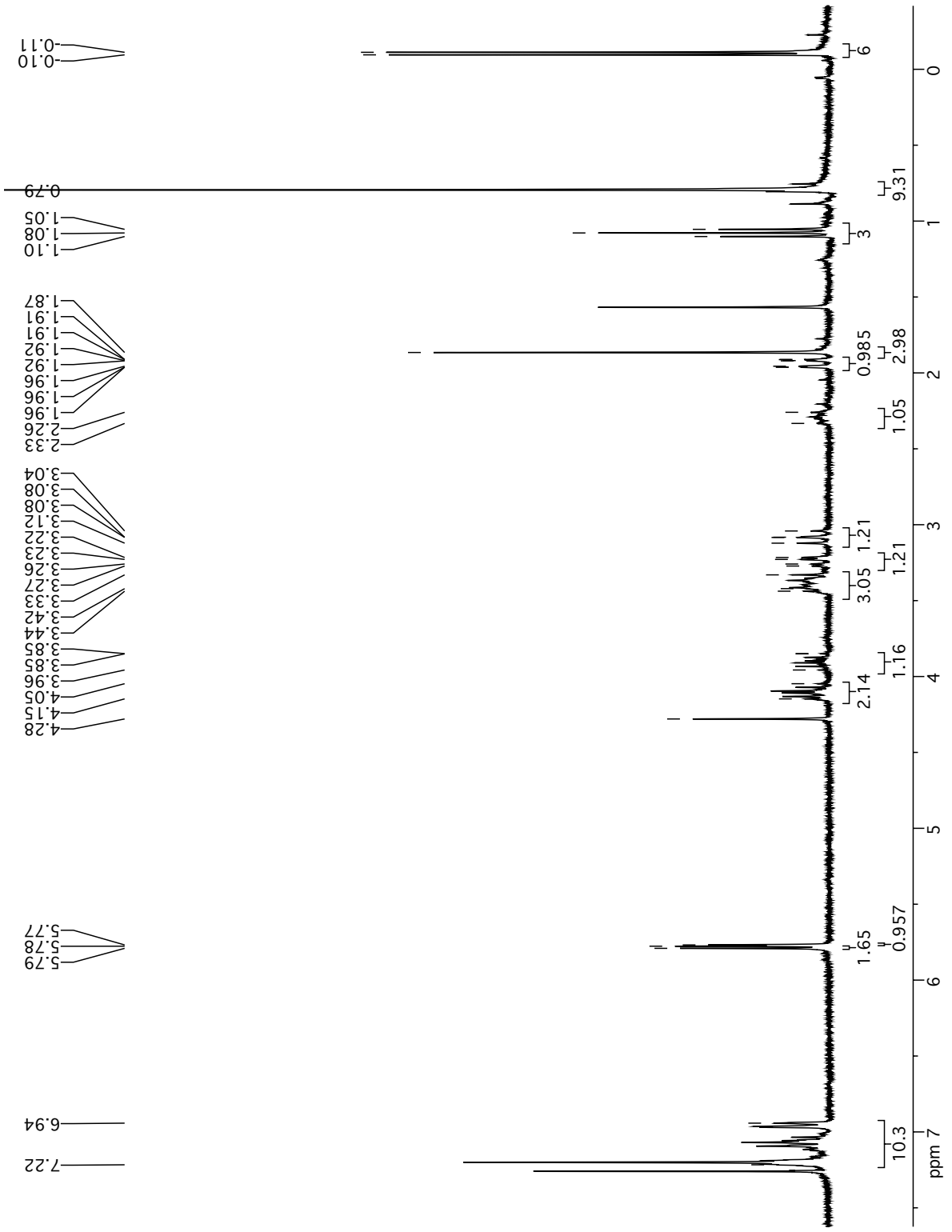
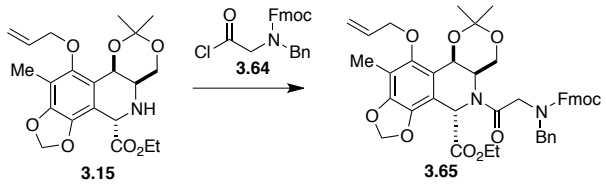


Figure 4.30. ^{1}H NMR spectrum of compound **3.63** (300 MHz, $CDCl_3$)



4.31 (4*S*,5a*R*,9a*R*)-ethyl 5-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)acetyl)-10-(allyloxy)-8,8,11-trimethyl-5,5a,6,9a-tetrahydro-4*H*-[1,3]dioxino[5,4-*c*][1,3]dioxolo[4,5-*h*]isoquinoline-4-carboxylate (3.65)

To a solution of *N*-Bn-*N*-Fmoc-Gly (347 mg, 0.900 mmol, 1.2 eq) in CH_2Cl_2 (8 mL) was added oxalyl chloride (2.0 mL, ~30 eq) at RT under Ar, to which was added dry DMF (6 μL) dropwise. After stirring for 1 h, the solution was concentrated, and then concentrated from dry toluene and dried under vacuum. The acid chloride was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. To this was added a solution compound **3.15** (303 mg, 0.748 mmol) and 2,6-lutidine (95 μL, 1.1 eq) in CH_2Cl_2 (5 mL) dropwise. The reaction was stirred 20 h, and then quenched with aq. NH_4Cl (25 mL). The aqueous phase was extracted with CH_2Cl_2 (4×25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Flash chromatography (3:1 hexanes:EtOAc) provided the title compound (507 mg, 64%). R_f = 0.30 (2:1 hexanes:EtOAc) ^{1}H-NMR (300 MHz; $CDCl_3$): mixture of rotamers δ 7.72-7.13 (m, 12H), 6.04-6.01 (m, 1H), 6.01-5.82 (m, 4H), 5.38-5.22 (m, 3H), 5.10-5.08 (m, 1H), 4.66-4.02 (m, 9H), 3.70-3.66 (m, 2H), 2.13 (s, 3H), 1.57 (s, 6H), 1.21 (t, *J* = 7.7 Hz, 3H), 1.10 (t, *J* = 6.8 Hz, 3H).

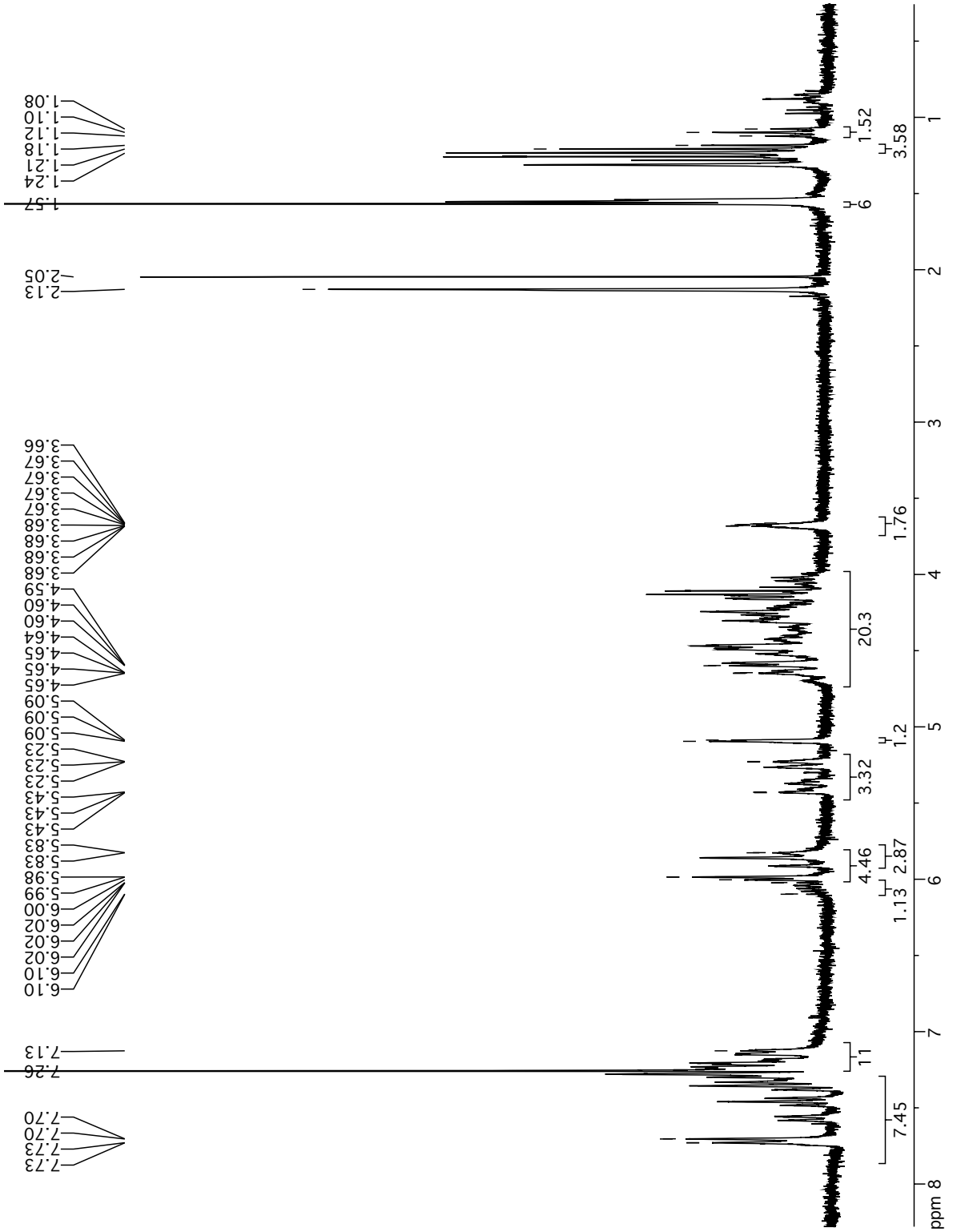
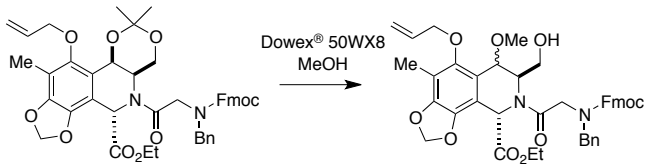


Figure 4.31. ^{1}H NMR spectrum of compound **3.65** (300 MHz, $CDCl_3$)



3.65 3.66

4.32 (7*R*,9*S*)-ethyl 8-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)acetyl)-5-(allyloxy)-7-(hydroxymethyl)-6-methoxy-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-*h*]isoquinoline-9-carboxylate (3.66)

Compound **3.65** (50 mg, 0.65 mmol) was dissolved in dry MeOH (2.5 mL), and Dowex® 50WX8 cationic resin (50 mg) was added (the resin was rinsed with dry MeOH and dried under a steam of Ar). The reaction was stirred under Ar for 72h, filtered through a pad of Celite® using MeOH and CH_2Cl_2 to transfer the material. The filtrate was evaporated and the residue was purified with flash chromatography (1:1 hexanes:EtOAc) to give the title compound (35 mg 72%). R_f = 0.15 (1:1 hexanes:EtOAc). ^{1}H-NMR (300 MHz; $CDCl_3$): mixture of rotamers δ 7.75-7.73 (m, 2H), 7.60-7.11 (m, 11H), 6.16-5.77 (m, 4H), 5.50-5.18 (m, 3H), 5.06-4.64 (m, 3H), 3.10 (s, 3H), 1.19 (t, 3H, 7.2 Hz), 1.13-1.08 (t, 3H, 7.2 Hz).

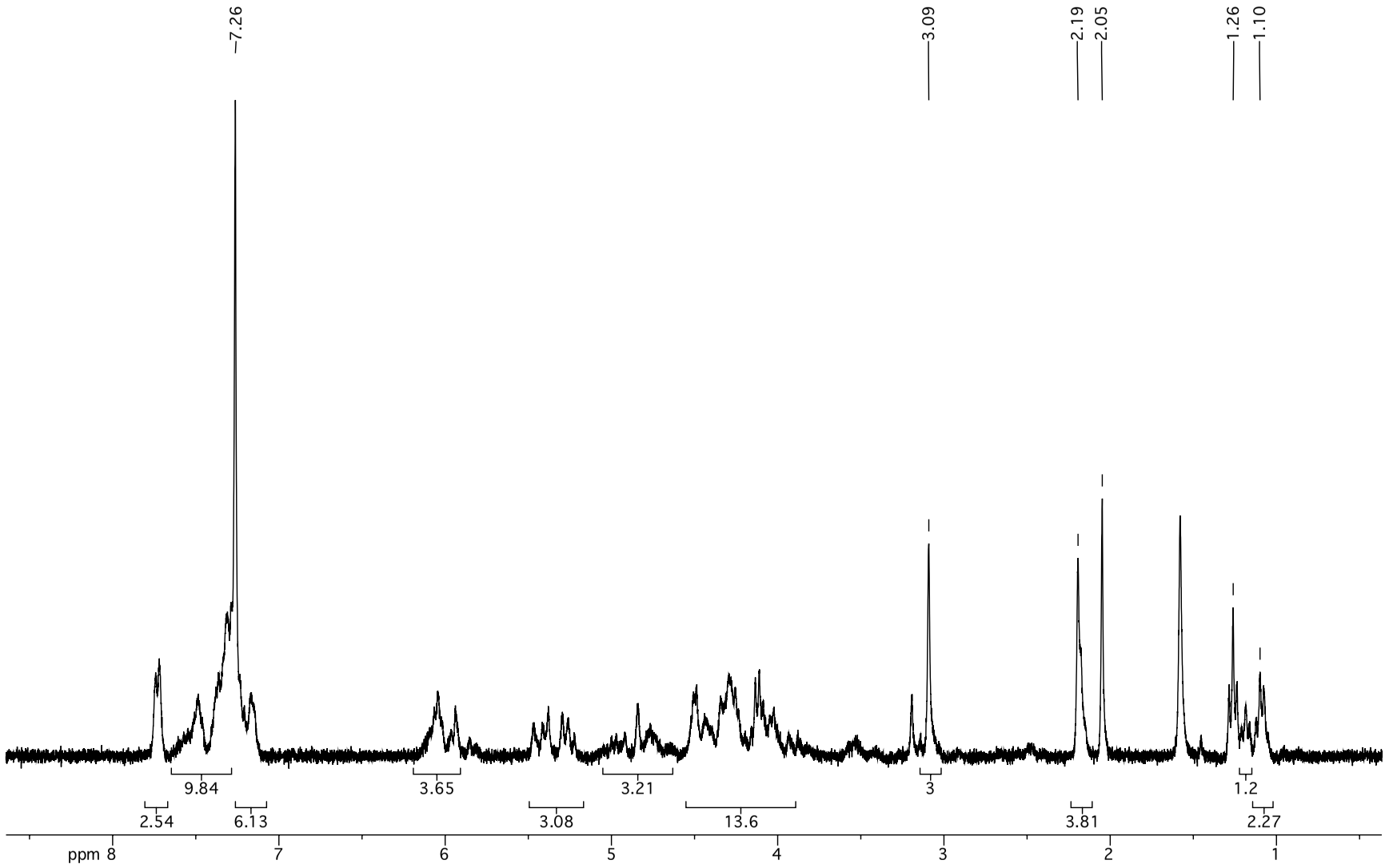
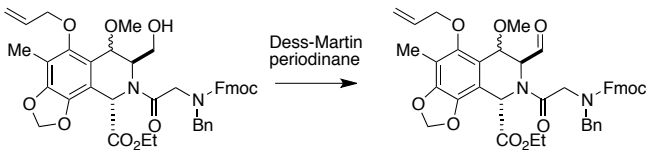


Figure 4.32. ^{1}H NMR spectrum of compound **3.66** (300 MHz, $CDCl_3$)



3.66 3.67

4.33 (7*S*,9*S*)-ethyl 8-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)acetyl)-5-(allyloxy)-7-formyl-6-methoxy-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-*h*]isoquinoline-9-carboxylate (3.67)

To suspension of compound **3.66** (90mg, 0.12 mmol) and $NaHCO_3$ (141 mg, 1.68 mmol, 14 eq.) in CH_2Cl_2 (9 mL), was added Dess-Martin periodinane (77 mg, 0.18 mmol, 1.5 eq.). The mixture was stirred at RT for 2h and the reaction was quenched with sat. aq. $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2, and the organic phase was rinsed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting oil was purified with flash chromatography (4:1 hexanes:EtOAc) to give the title compound (60 mg, 72%); R_f = 0.15 (1:1 Hexanes:EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 9.01 (s, 1H), 8.96-8.93 (m,), 7.80-7.67 (m, 3H), 7.55-7.29 (m, 8H), 7.22-7.08 (m, 3H), 6.11-5.86 (m, 4H), 5.65-5.57 (m, 1H), 5.52-5.22 (m, 4H), 5.10-4.83 (m, 4H), 3.07 (s, 3H), 2.15 (s, 3H), 1.11 (t, *J* = 9.2 Hz, 3H).

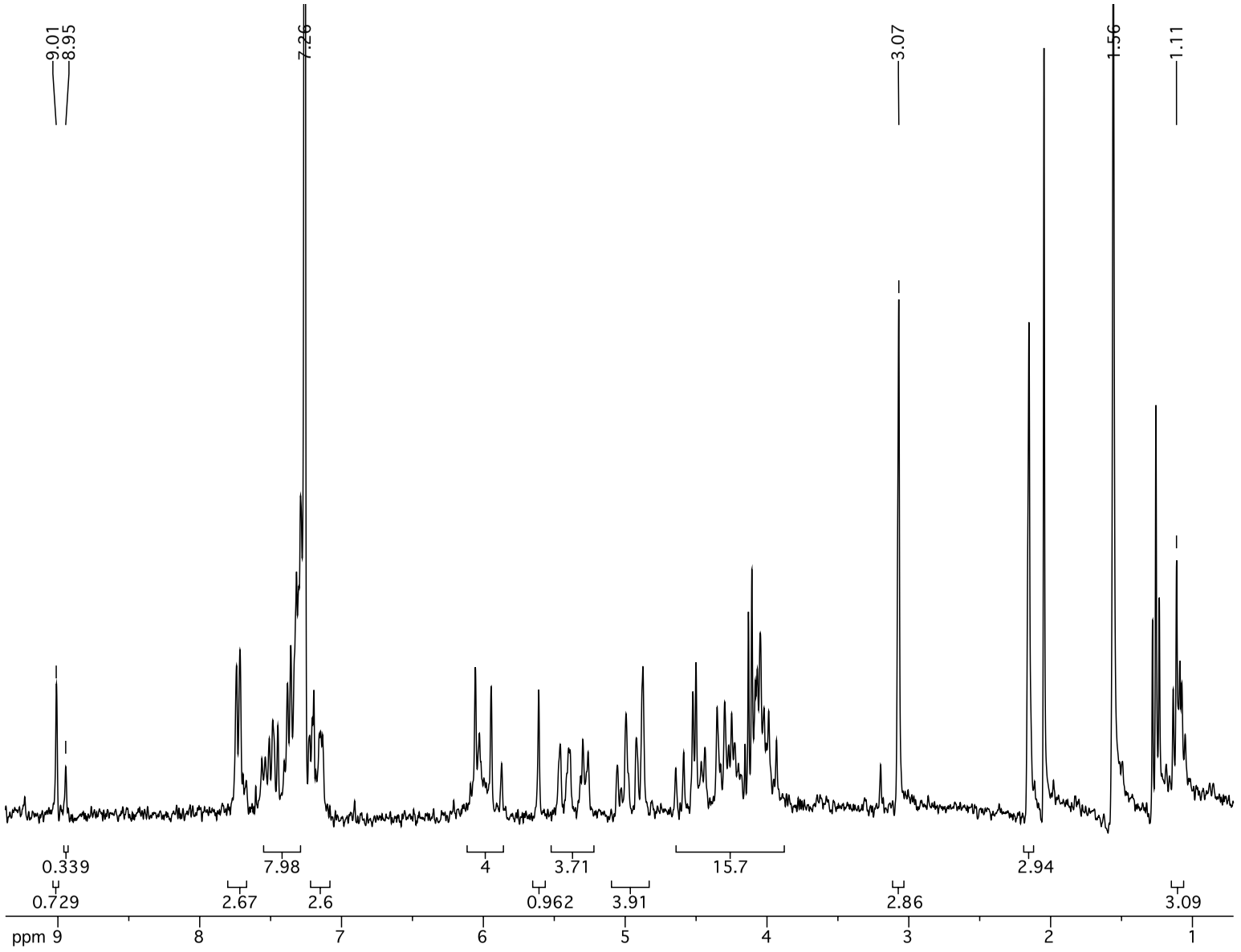
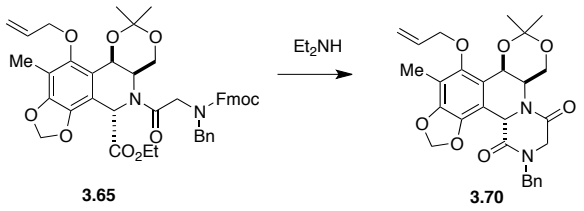


Figure 4.33. ^{1}H NMR spectrum of compound **3.67** (300 MHz, $CDCl_3$)



4.34 (4a*R*,9c*S*,14a*R*)-5-(allyloxy)-11-benzyl-3,3,6-trimethyl-1,11,12,14a-tetrahydro-[1,3]dioxino[5,4-*c*][1,3]dioxolo[4,5-*h*]pyrazino[2,1-*a*]isoquinoline-10,13(4a*H*,9c*H*)-dione (3.70)

A solution of compound **3.65** (in 10 mg 0.13 mmol) in CH_2Cl_2 (1 mL) and Et_2NH (1 mL) was stirred under Ar for 1h. The reaction was concentrated and the residue was purified by flash chromatography (3:1 hexanes:EtOAc) to give the title compound as a yellow solid (6 mg, 92%). R_f = 0.50 (2:1 hexanes:EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.40-7.31 (m, 5H), 6.12-6.03 (m, 1H), 6.01-6.00 (m, 1H), 5.92 (s, 1H), 5.83 (d, *J* = 1.4 Hz, 1H), 5.54-5.53 (m, 1H), 5.41 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.31-5.26 (m, 1H), 5.06 (d, *J* = 14.4 Hz, 1H), 4.37 (d, *J* = 14.4 Hz, 2H), 4.33-4.22 (m, 2H), 4.20-4.11 (m, 2H), 4.06-3.98 (m, 2H), 3.90-3.75 (m, 3H), 2.13 (s, 3H), 1.57 (s, 3H), 1.43 (s, 3H).

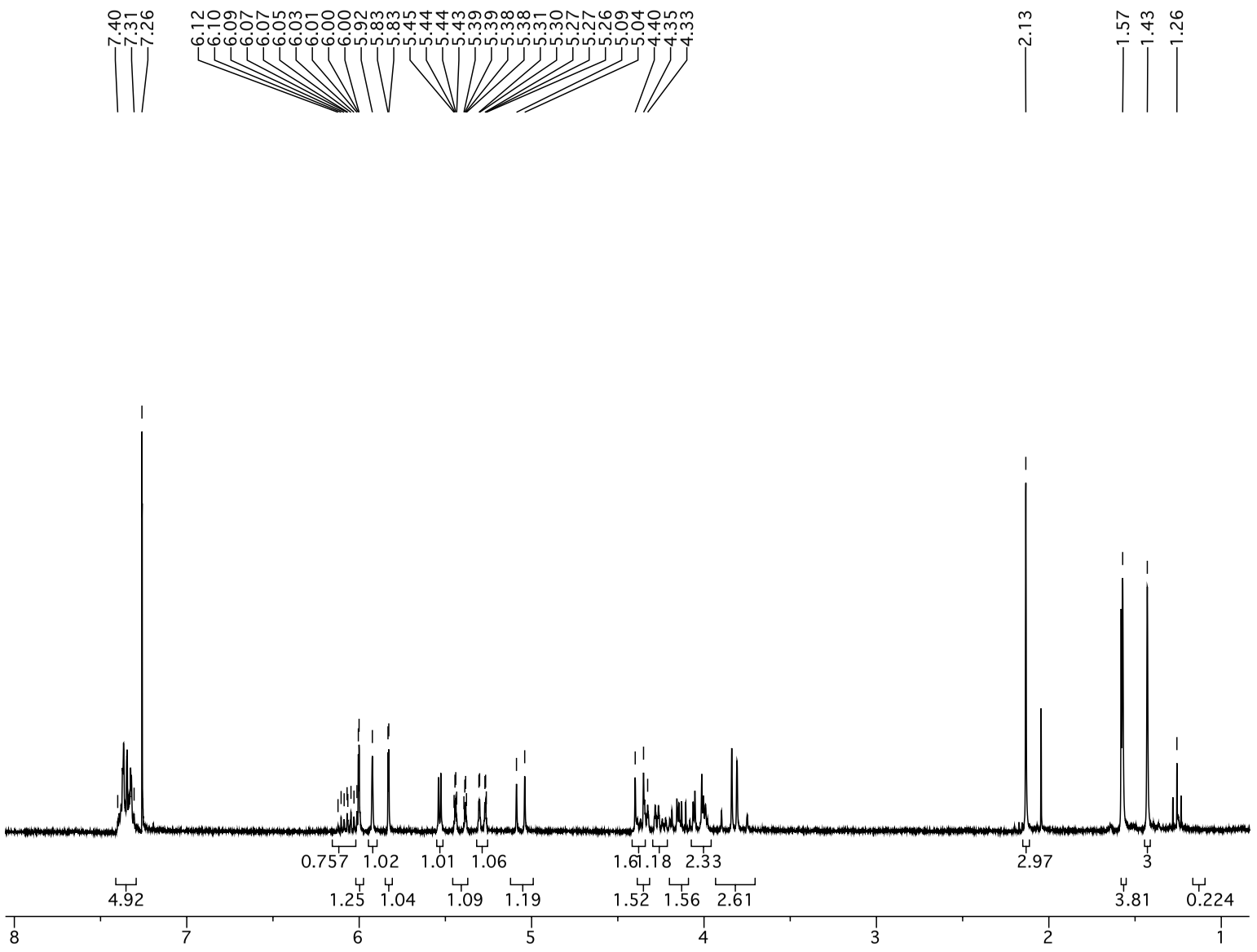
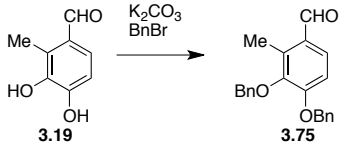


Figure 4.34. ^{1}H NMR spectrum of compound **3.70** (300 MHz, $CDCl_3$)



3.19 **3.75**

4.35 3,4-bis(benzyloxy)-2-methylbenzaldehyde (3.75)

To a solution of 3,4-dihydroxy-2-methylbenzaldehyde (**3.19**) (1.25 g, 8.26 mmol, 1 eq.) in DMF (14 mL) was added K_2CO_3 (2.28 g, 16.5 mmol, 2 eq.) and BnBr (2.5 mL, 2. mmol, 1 eq.). The mixture was stirred under argon for 48 h, filtered, concentrated under reduced pressure, and purified by flash chromatography (4:1 hexanes/EtOAc) to afford (1.80 g, 66%) of the title compound as a white solid. R_f = 0.40 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.10 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.48-7.31 (m, 10H), 6.99-6.97 (d, 1H, *J* = 8.5 Hz, 1H), 5.22 (s, 2H), 4.96 (s, 2H), 2.55 (s, 3H)

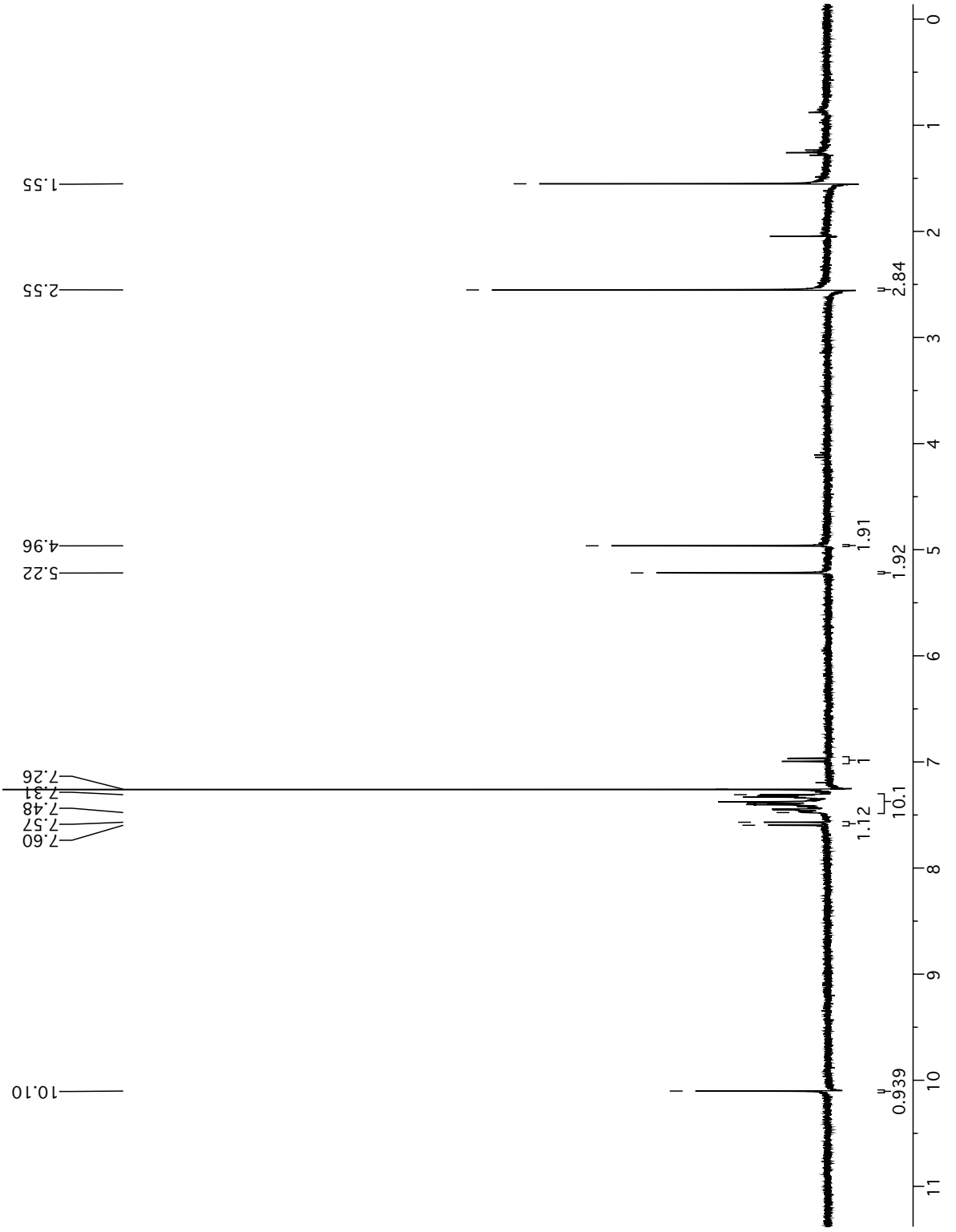
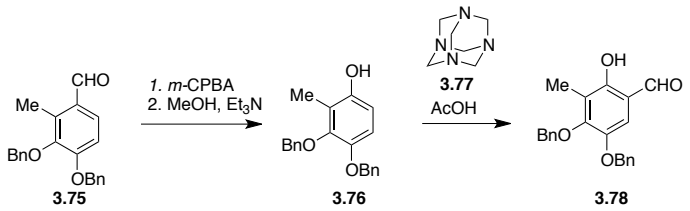


Figure 4.35. ^{1}H NMR spectrum of compound **3.75** (300 MHz, $CDCl_3$)



4.36 4,5-bis(benzyloxy)-2-hydroxy-3-methylbenzaldehyde (3.78)

To a stirred solution of 3,4-benzyloxy-2-methylbenzaldehyde (**3.75**) (3.50 g, 10.5 mmol, 1 eq.) in $CHCl_3$ (105 mL) was added *m*-CPBA (3.62 g, 21.0 mmol, 2.0 eq.). The solution was stirred at RT for 12 h. The resulting mixture was washed with 10% NaS_2O_3 (2 × 50 mL), $NaHCO_3$ (3 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. To a solution of the resulting oil in CH_2Cl_2/MeOH 1:1 (105 mL) was added triethylamine (1.40 mL, 10.1 mmol, 1.25 eq) and the reaction was stirred under Ar for 4h, concentrated under vacuum to give 3,4-bis(benzyloxy)-2-methylphenol **(3.76)** as a brown solid (3.02 g, 90%), which was used without further purification. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.46-7.30 (m, 11H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 5.06 (s, 2H), 5.01 (s, 2H), 2.12 (s, 3H).

A solution of 3,4-bis(benzyloxy)-2-methylphenol (**3.76**) (0.92 g, 2.87 mmol) and hexamethylenetetramine (2.40 g, 17.2 mmol, 6 eq) in AcOH (30 mL) was heated under reflux for 3h. The reaction was allowed to cool to RT, quenched with H_2O (60 mL), the aqueous phase was rinsed extracted with EtOAc (3×25 mL) and the combined organic phases were rinsed with H_2O (25 mL) brine (25 mL), dried (Na_2SO_4), filtered, concentrated under vacuum and purified by flash chromatography (hexanes/EtOAc 6:1) to give 4,5-bis(benzyloxy)-2-hydroxy-3-methylbenzaldehyde (**3.78**) as a light yellow solid (0.50 g, 50%). R_f = 0.3 (hexanes/EtOAc 6:1); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 11.29 (s, 1H), 9.71 (s, 1H), 7.46-7.32 (m, 11H), 6.95 (s, 1H), 5.14 (s, 2H), 5.10 (s, 2H), 2.11 (s, 3H).

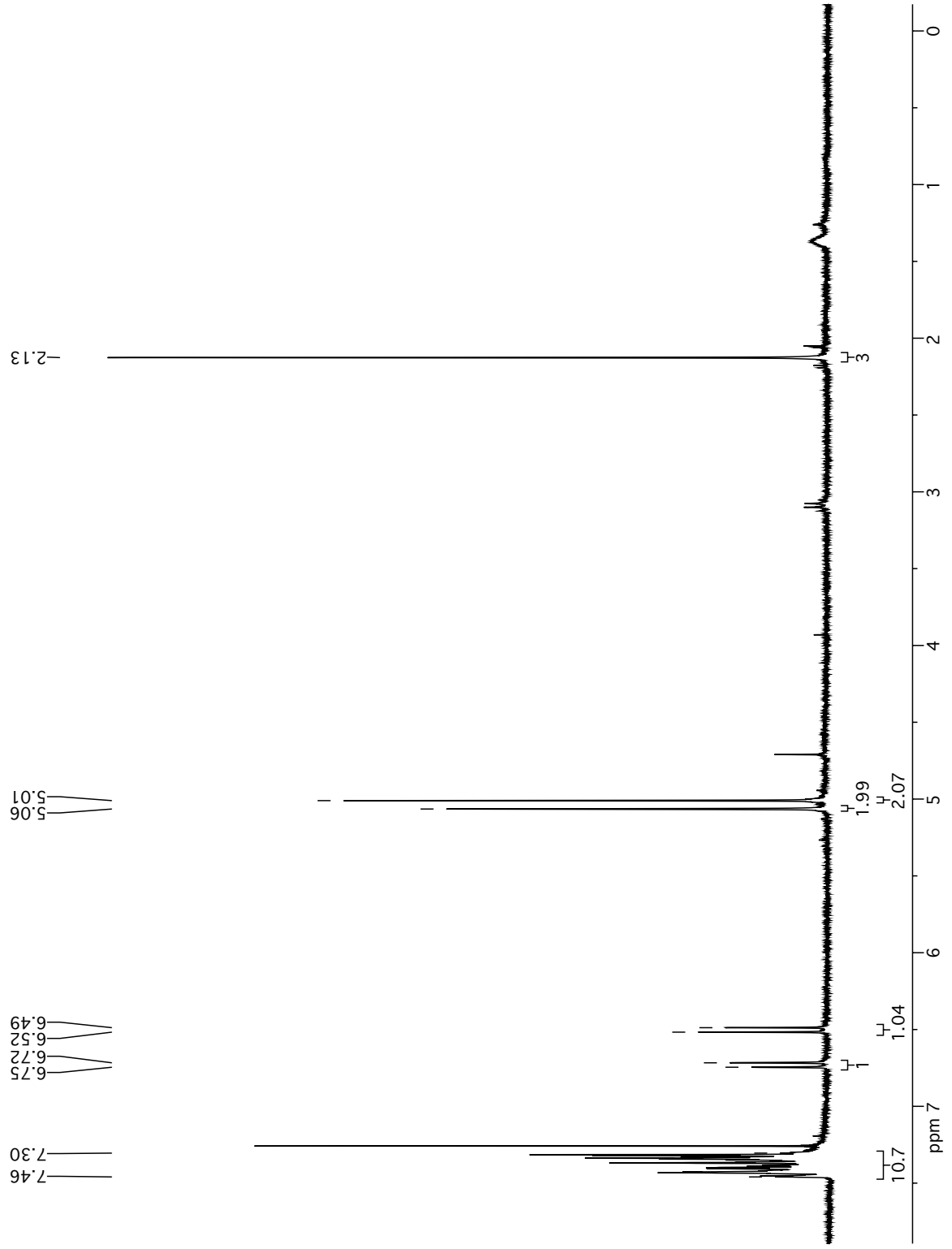


Figure 4.36. ^{1}H NMR spectrum of compound **3.76** (300 MHz, $CDCl_3$)

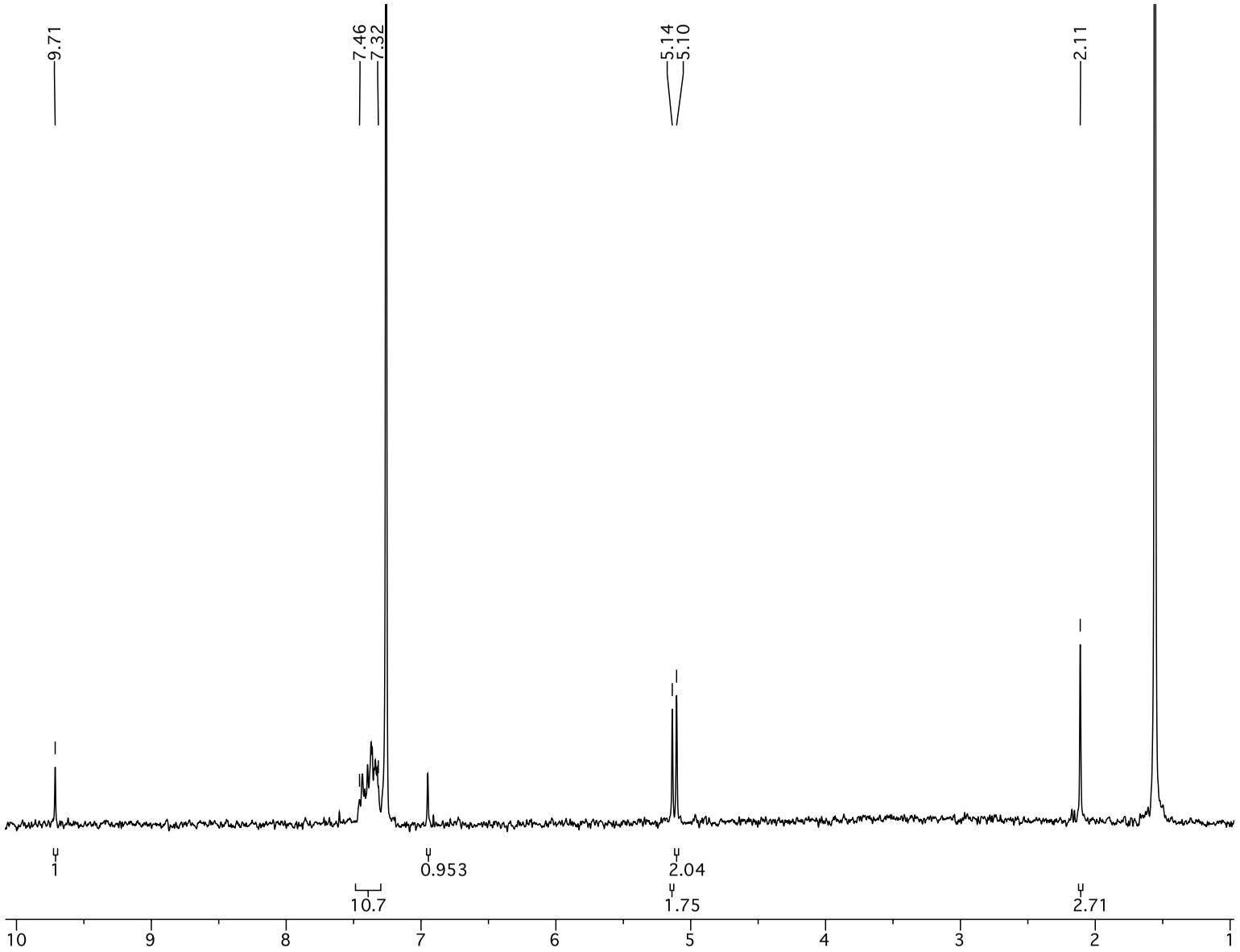
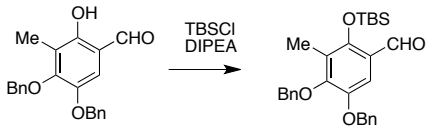


Figure 4.37. ^{1}H NMR spectrum of compound **3.78** (300 MHz, $CDCl_3$)



3.78 **3.79**

4.37 4,5-bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-3-methylbenzaldehyde (3.79)

To a solution of compound **3.78** (1.438 g, 4.13 mmol, 1 eq.) and TBS-Cl (1.247 g, 8.26 mmol, 2.0 eq.) in DMF (16 mL) was added DIPEA (2.16 mL, 12.4 mmol, 3.0 eq). The reaction was stirred under Ar for 2h, quenched with 1N HCl (50 mL) and the resulting aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, concentrated under vacuum and purified by flash chromatography (hexanes/EtOAc 9:1) to afford the title compound as a light yellow solid (1.75 g, 92%). R_f = 0.5 (hexanes/EtOAc 6:1); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.20 (s, 1H), 7.48-7.29 (m, 10H), 5.12 (s, 2H), 5.11 (s, 2H), 2.04 (s, 3H), 1.04 (s, 9H), 0.10 (s, 6H).

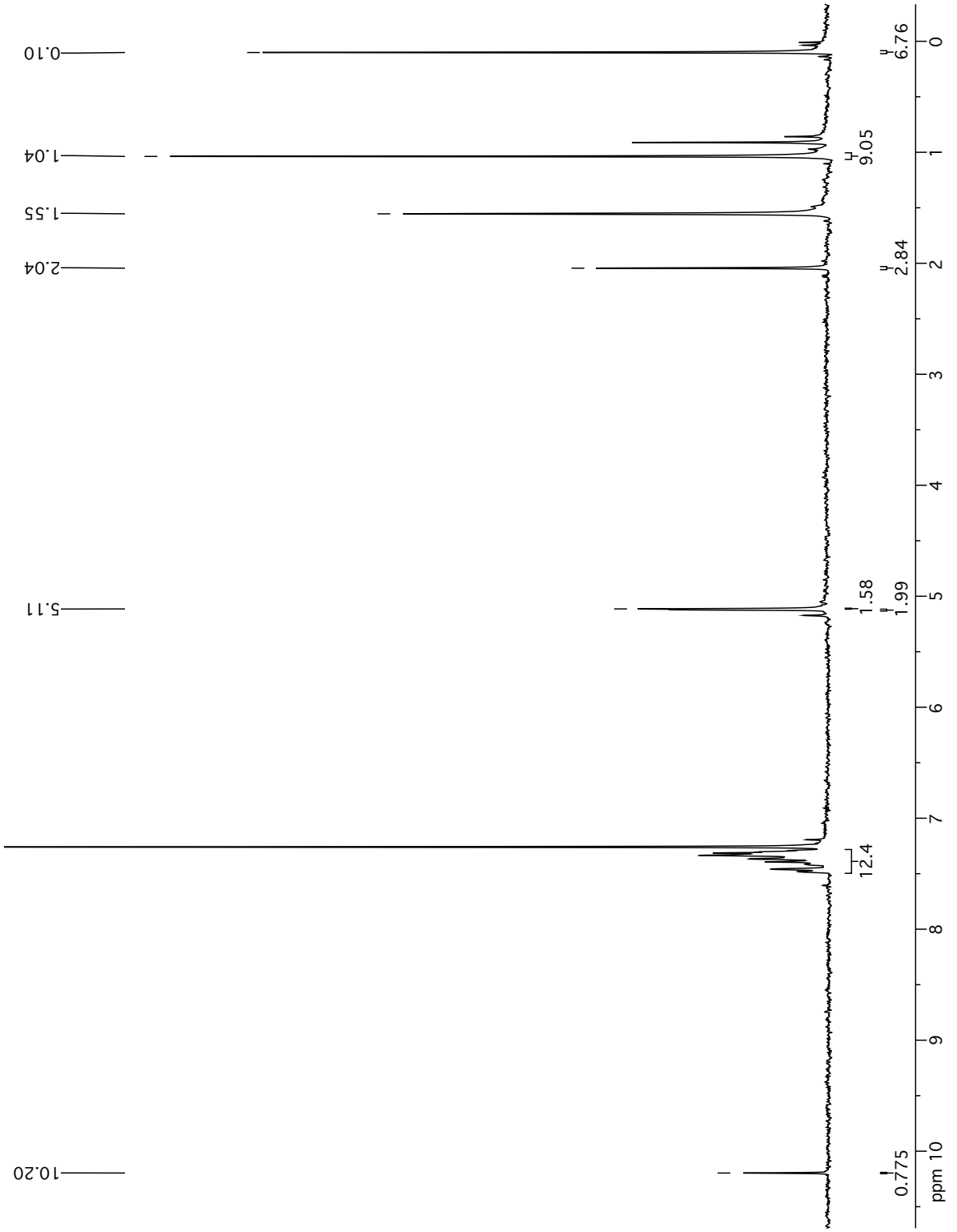
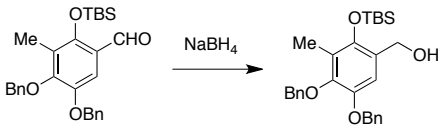


Figure 4.38. ^{1}H NMR spectrum of compound **3.79** (300 MHz, $CDCl_3$)



3.79 **3.80**

4.38 (4,5-bis(benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-3-methylphenyl)methanol (3.80)

To a solution of compound **3.79** (1.75 g, 3.79 mmol, 1 eq.) in CH_2Cl_2/MeOH 1:1 (38 mL) was added $NaBH_4$ (720 mg, 19 mmol, 5.0 eq). The reaction was stirred under Ar for 2h, quenched with sat. aq. NH_4Cl (50 mL) and the resulting aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, concentrated under vacuum and purified by flash chromatography (hexanes/EtOAc, 9:1 to 6:1) to afford the title compound as a colorless oil (625 mg, 35 %). R_f = 0.1 (hexanes/EtOAc 6:1); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.46-7.30 (m, 10H), 6.91 (s, 1H), 5.10 (s, 2H), 5.00 (s, 2H), 4.62 (s, 2H), 2.07 (s, 3H), 1.02 (s, 9H), 0.14 (s, 6H).

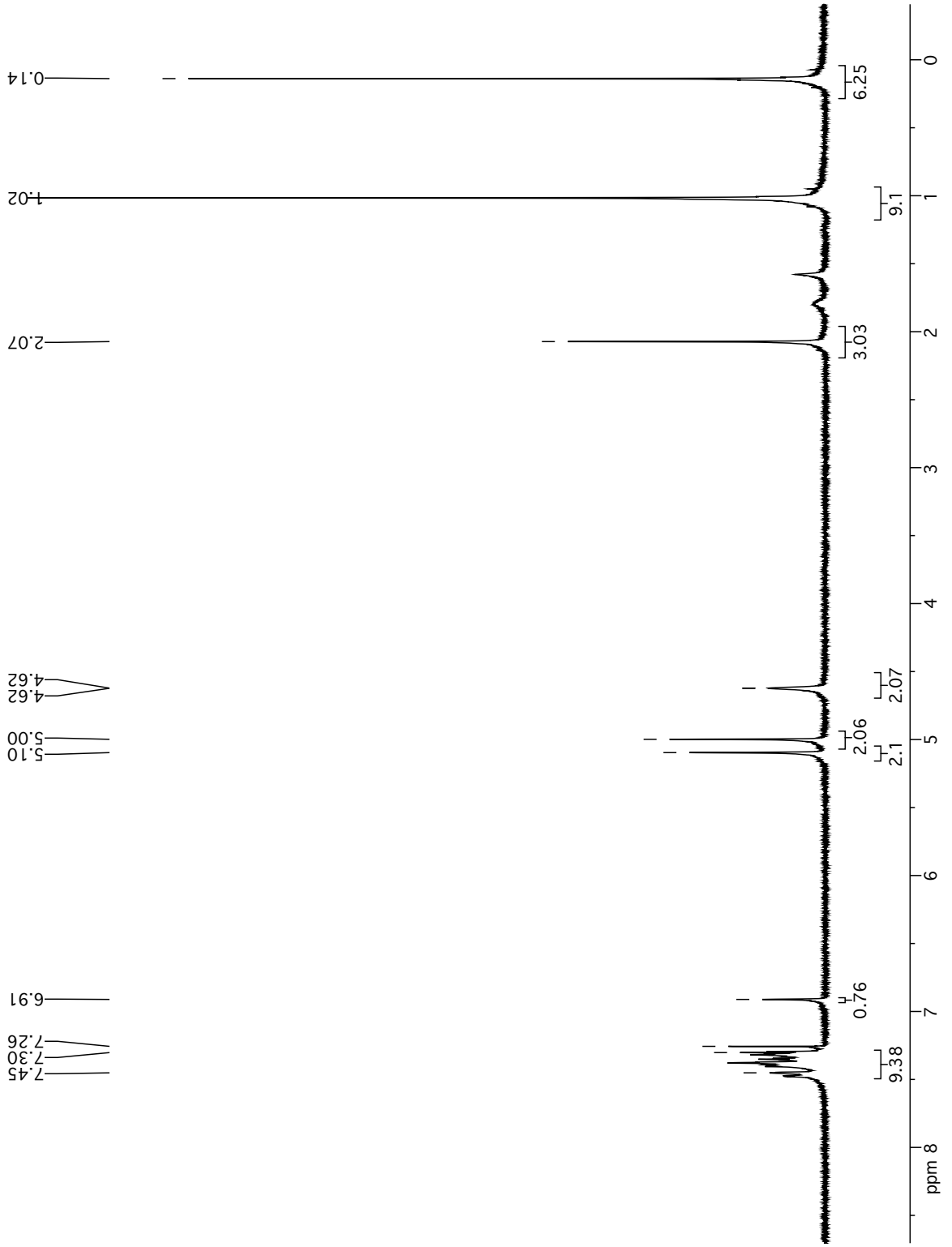
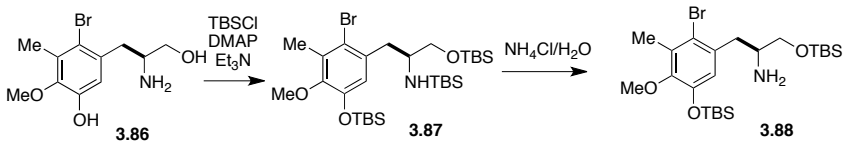


Figure 4.39. ^{1}H NMR spectrum of compound **3.80** (300 MHz, $CDCl_3$)



4.39 (*S*)-1-(2-bromo-5-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-3-methylphenyl)-3-((*tert*-butyldimethylsilyl)oxy)propan-2-amine (3.88)

To a stirred solution of compound **3.86** (1.55 g, 5.36 mmol, 1 eq.) in CH_2Cl_2 (90 mL, 0.06 M), were added DMAP (327 mg, 2.68 mmol, 0.5 eq.), Et_3N (4.48 mL, 32.2 mmol, 6.00 eq.) and TBS-Cl (4.86 g, 32.2 mmol, 6 eq.). The reaction was stirred under Ar for 3 h at RT, and then sat. aq. NH_4Cl (50 mL) was added and the mixture was stirred for 2h. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexane/EtOAc 5:1) to give the title compound **3.88** (2.50 g, 90%) as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.65 (s, 1H), 3.72 (s, 3H), 3.61 (1/2 ABX, *J* = 9.7, 4.1 Hz, 1H), 3.47 (1/2 ABX, *J* = 9.7, 6.5 Hz, 1H), 3.20-3.14 (m, 1H), 2.87 (1/2 ABX, *J* = 13.4, 5.4 Hz, 1H), 2.57 (1/2 ABX, *J* = 13.4, 8.0 Hz, 1H), 2.35 (s, 3H), 1.00 (s, 9H), 0.91 (s, 9H), 0.17 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 148.8, 147.6, 134.6, 133.1, 121.3, 119.4, 67.6, 60.2, 52.9, 41.3, 26.1, 25.8, 18.4, 18.4, 17.2, -4.4, -5.2; R_f (SiO_2, 2:1 hexanes/EtOAc) 0.35; $[\alpha]_D^{25}$ = + 0.9 ° (c=0.35, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2996, 2930, 2858, 2471, 839 cm^{-1}; HRMS (MH^+), found 520.2103. $C_{23}H_{45}BrNO_3Si_2$ requires 520.2101.

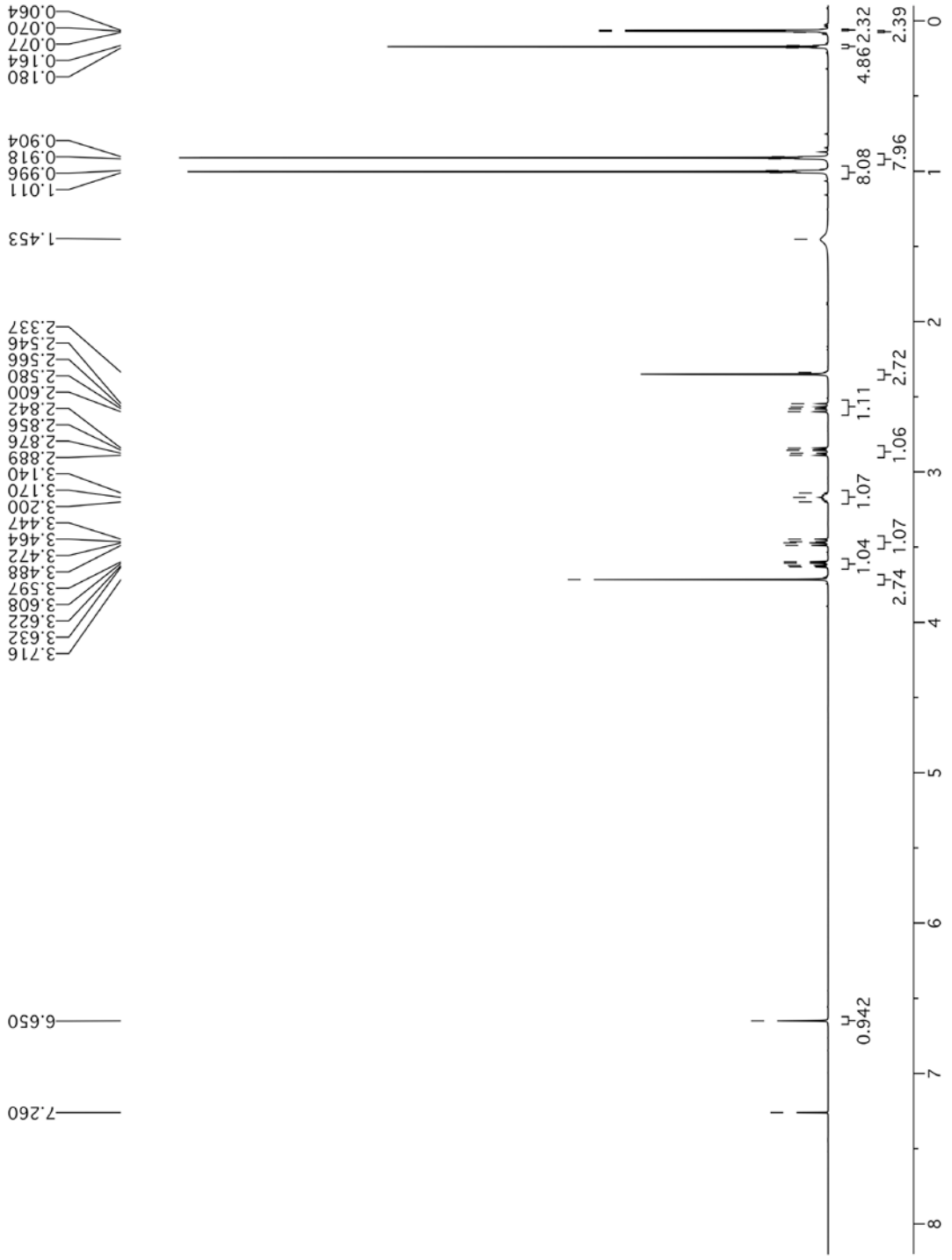


Figure 4.40. ^{1}H NMR spectrum of compound **3.88** (400 MHz, $CDCl_3$)

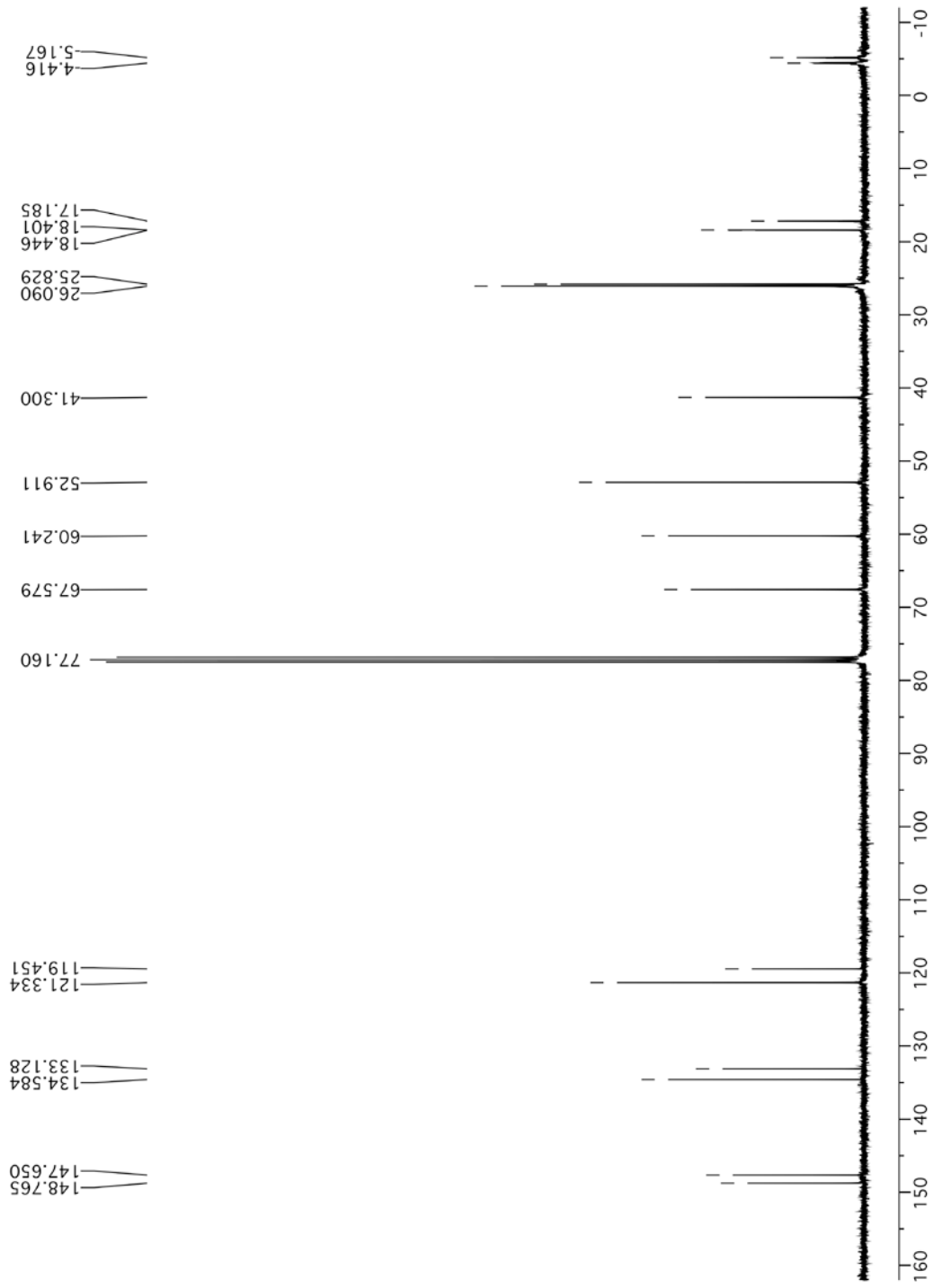
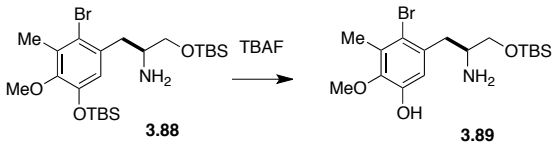


Figure 4.41. ^{13}C NMR spectrum of compound **3.88** (101 MHz, $CDCl_3$)



4.40 (S)-5-(2-amino-3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-bromo-2-methoxy-3-methylphenol (3.89)

To a stirred solution of compound **3.88** (1.59 g, 3.05 mmol, 1 eq.) in THF (100 mL, 0.03 M), under Ar, at 0 °C, was added a 1.0 solution M of TBAF in THF (3.05 mL, 3.05 mmol,, 1 eq.). The reaction was stirred for 25 minutes and quenched with sat. aq. NH_4Cl (50 mL). The phases were allowed to warm to RT, the aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 10:1) to give the title compound **3.89** (1.23 g, 98%) as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.77 (s, 1H), 3.73 (s, 3H), 3.71-3.66 (m, 1H), 3.56-3.50 (m, 1H), 3.27-3.24 (m, 1H), 2.92 (1/2 ABX, *J* = 13.5, 4.6 Hz, 1H), 2.62 (1/2 ABX, *J* = 13.5, 9.0 Hz, 1H), 2.34 (s, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 148.4, 145.0, 134.6, 132.2, 117.2, 116.1, 67.1, 60.8, 52.9, 52.7, 40.5, 26.1, 18.4, 17.2, -5.2, -5.2. R_f (SiO_2, CH_2Cl_2/MeOH 10:1) 0.4; $[\alpha]_D^{25}$ = + 8.3 ° (c=0.41, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3263 (br), 2954, 2928, 2856, 1578, 1471, 1092 cm^{-1}; HRMS (MH^+), found 406.1233. $C_{17}H_{31}BrNO_3Si$ requires 406.1236

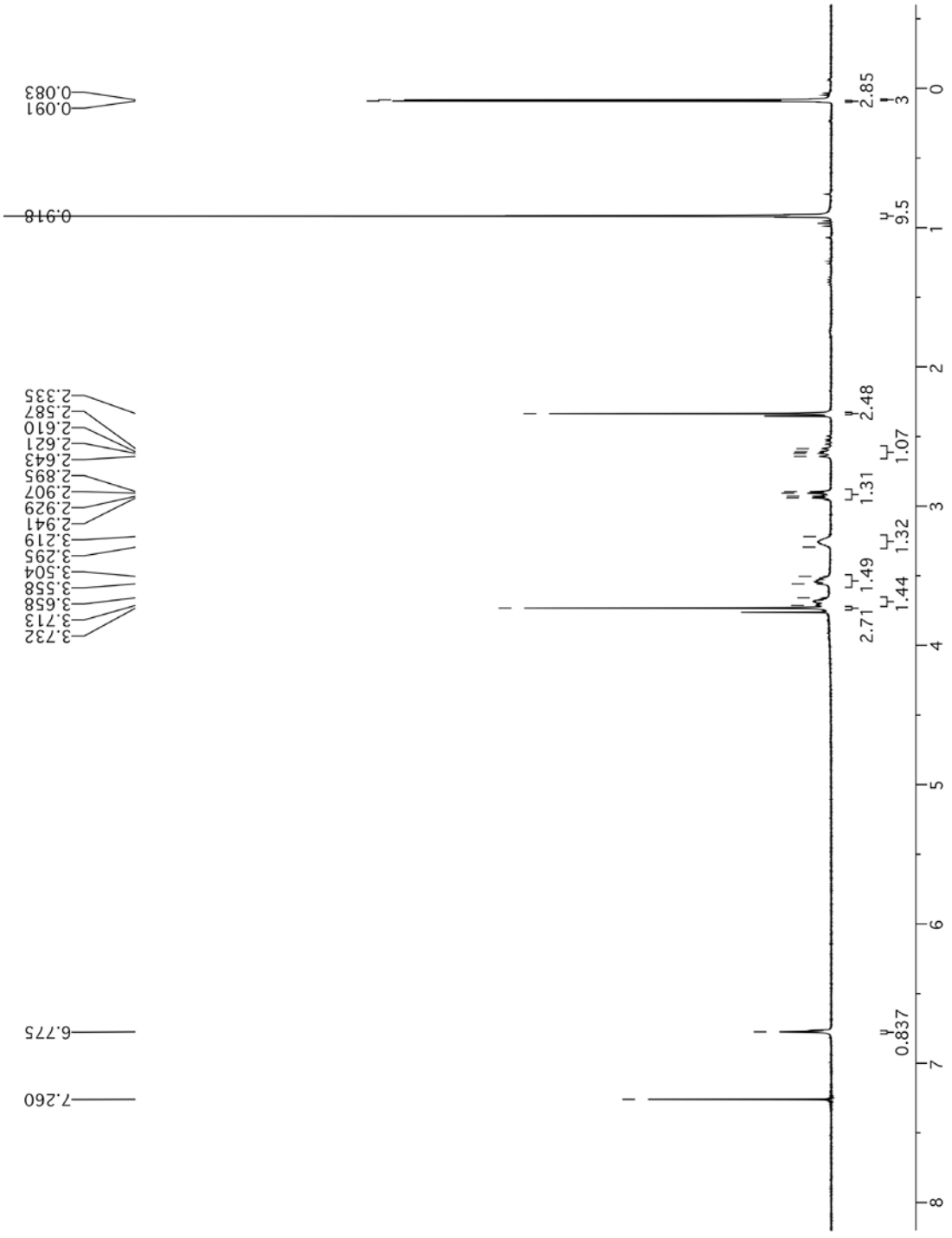


Figure 4.42. ^{1}H NMR spectrum of compound **3.89** (400 MHz, $CDCl_3$)

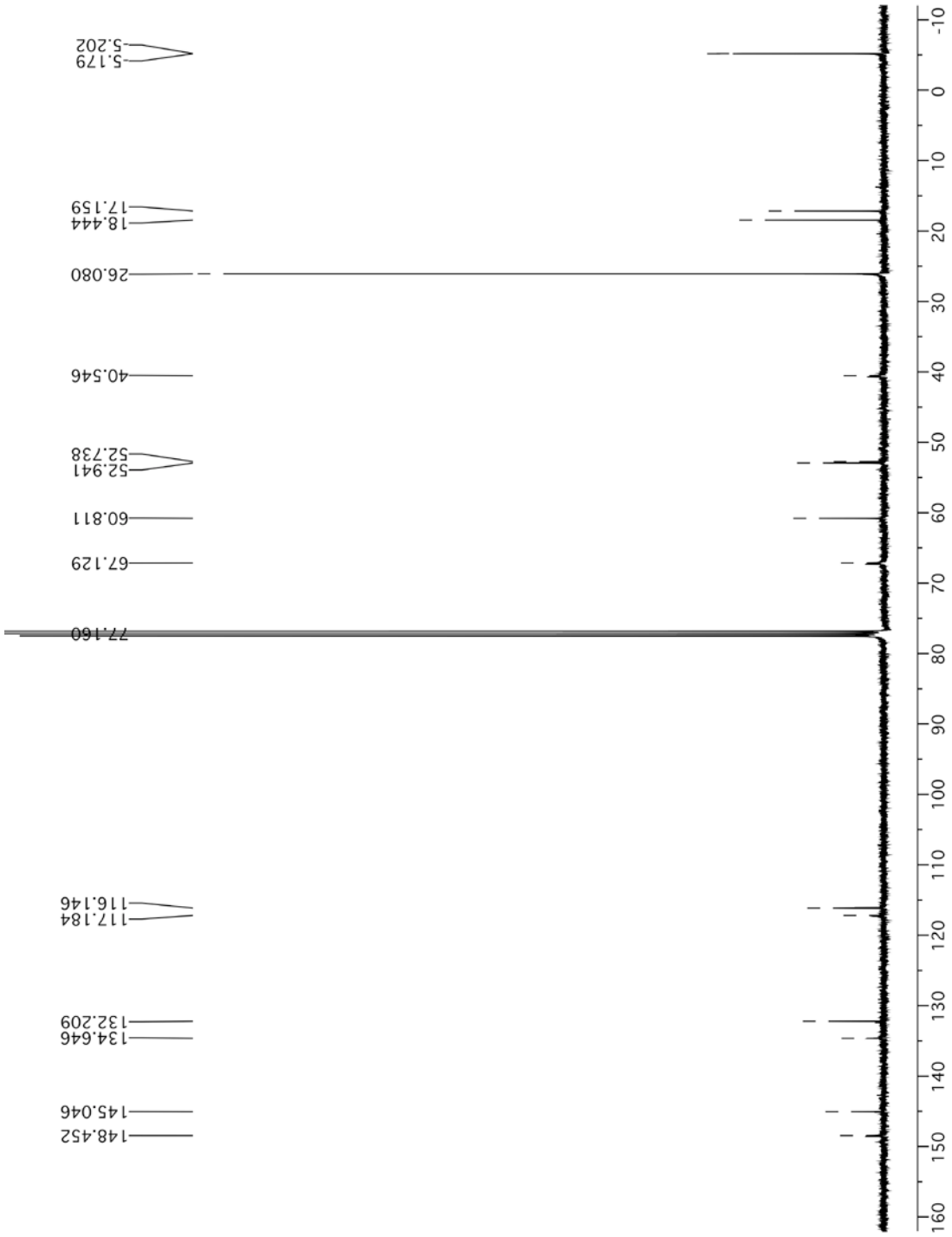
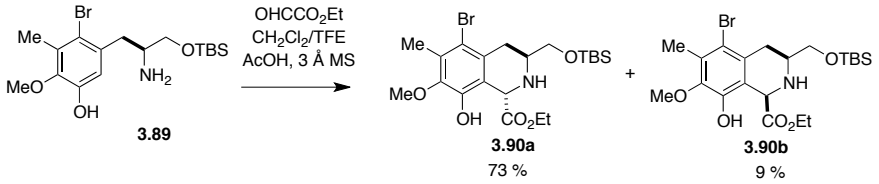


Figure 4.43. ^{13}C NMR spectrum of compound **3.89** (101 MHz, $CDCl_3$)



4.42 *(1S,3S)*-ethyl 5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate (3.90a) and *(1R,3S)*-ethyl 5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3.90b)

To a stirred solution of compound **3.89** (5.43 g, 13.4 mmol, 1.0 eq.) in CH_2Cl_2 (134 mL, 0.10 M), under Ar, were added, 4Å molecular sieves (2.72 g), CF_3CH_2OH (13.4 mL), AcOH (153 µL, 2.68 mmol, 0.20 eq.) and ethyl glyoxalate (50% solution in $PhCH_3$, 2.93 mL, 14.8 mmol, 1.1 eq.). The reaction was stirred overnight, diluted with CH_2Cl_2 (50 mL), filtered through Celite® and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1) to give compound **3.90a** (4.78g, 73%) as a white solid and compound **3.90b** (610 mg, 9%) as a white solid. Compound **3.90a**: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.25 (br s, 1H), 4.89 (s, 1H), 4.26-4.18 (m, 2H), 3.82 (1/2 ABX, J = 9.8, 3.5 Hz, 1H), 3.76 (s, 3H), 3.54 (1/2 ABX, J = 9.8, 8.5 Hz, 1H), 3.13-3.07 (m, 1H), 2.71 (1/2 ABX, J = 16.9, 4.1 Hz, 1H), 2.35 (s, 3H), 2.27 (1/2 ABX, J = 16.9, 11.3 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.9, 145.6, 144.3, 130.8, 130.7, 120.0, 118.4, 66.9, 61.7, 61.2, 55.6, 51.6, 32.7, 26.0, 18.4, 17.0, 16.9, 14.4, 14.4, -5.1, -5.2, -5.2, -5.3; m.p. = 47 °C; R_f (SiO_2, hexanes/EtOAc 4:1) 0.40; $[\alpha]_D^{25}$ = -24.3 ° (c = 0.885, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3284 (br), 2955, 2931, 2857, 1739, 1462, 1178 cm^{-1}; HRMS (MH^+), found 490.1446. $C_{21}H_{35}BrNO_5Si$ requires 490.1447. Compound **3.90b**: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.86 (br s, 1H), 4.78 (s, 1H), 4.30-4.15 (m, 2H), 3.80 (1/2 ABX, J = 9.9, 4.1 Hz, 1H), 3.74 (s,

3H), 3.68 (1/2 ABX, J = 9.9, 6.6 Hz, 1H), 2.95 -2.89 (m, 1H), 2.77 (1/2 ABX, J = 16.6, 3.1 Hz, 1H), 2.44 (1/2 ABX, J = 16.6, 8.5 Hz, 2H), 2.36 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H).; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.8, 145.1, 143.9, 132.0, 130.4, 120.3, 118.4, 66.7, 61.5, 61.4, 58.4, 54.5, 33.0, 26.1, 26.0, 18.5, 17.0, 14.2, -5.1, -5.2; m.p. = 95 °C; R_f (SiO_2, hexanes/EtOAc 4:1) 0.37; $[\alpha]_D^{25}$ = -36.7 ° (c = 0.600, $CHCl_3$); IR (film, CH2Cl2), ν_{max} 3314 (br), 2955, 2931, 2858, 1738, 1463, 1257 cm^{-1}; HRMS (MH^+), found 490.1456. $C_{21}H_{35}BrNO_5Si$ requires 490.1447.

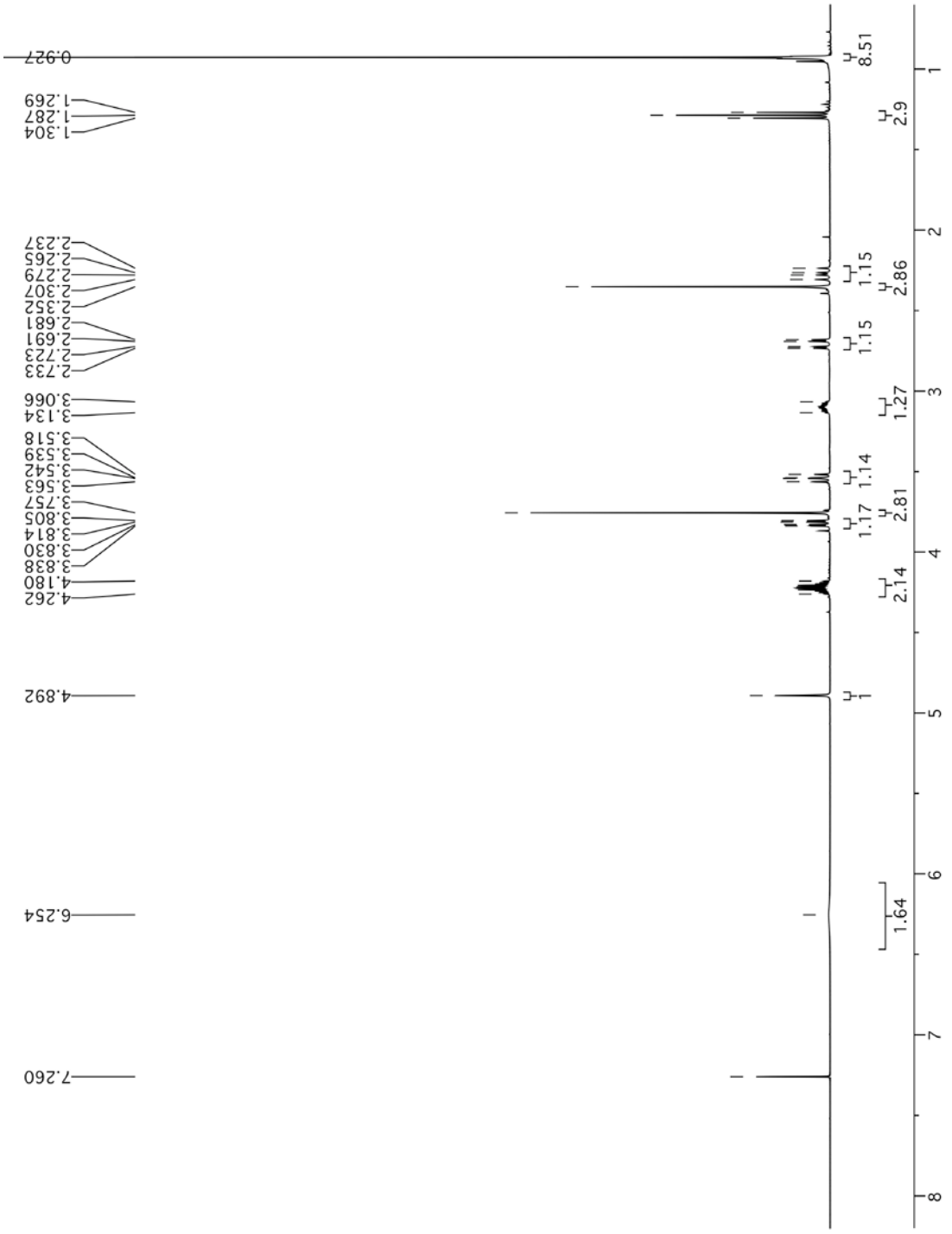


Figure 4.44. ^{1}H NMR spectrum of compound **3.90a** (400 MHz, $CDCl_3$)

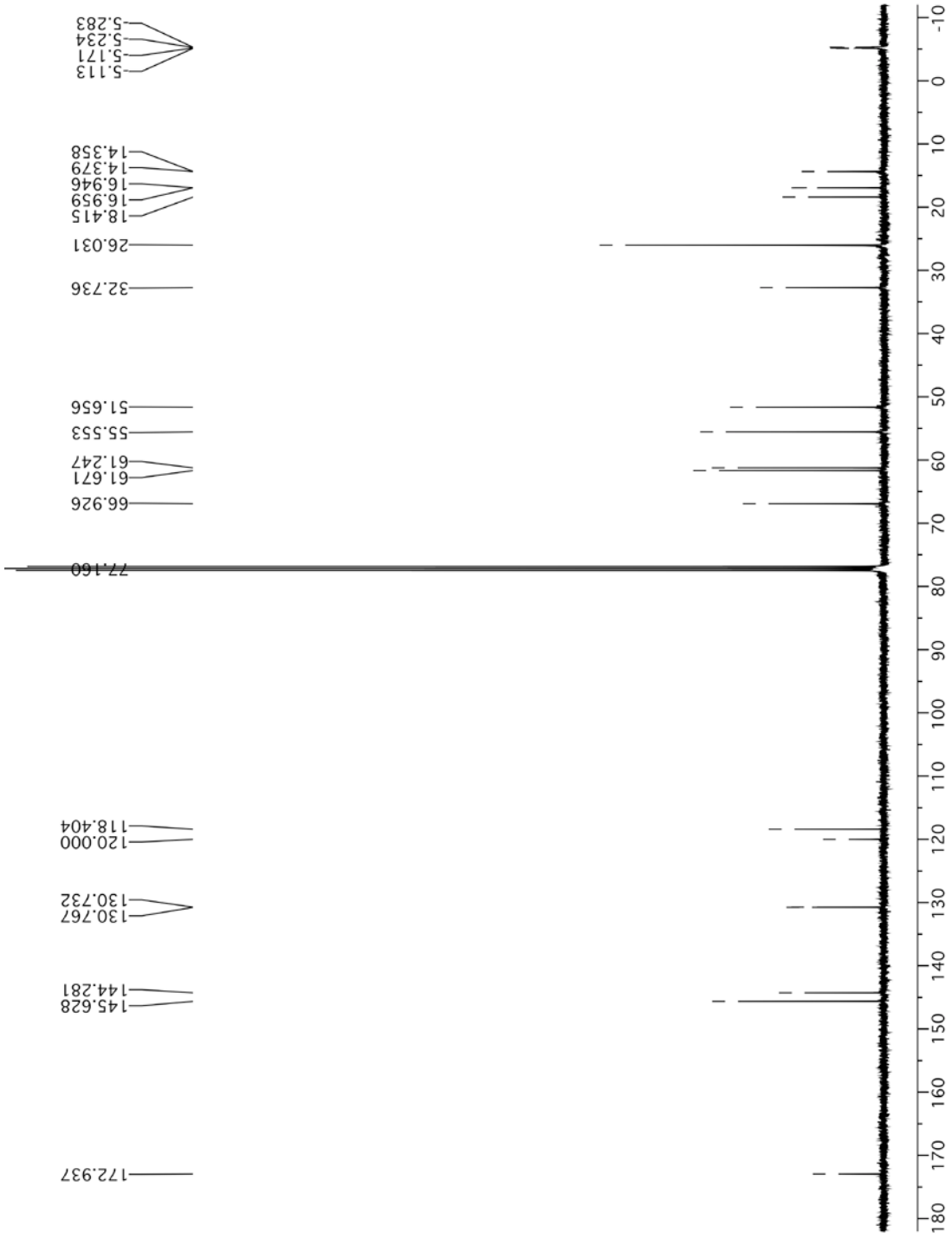


Figure 4.45. ^{13}C NMR spectrum of compound **3.90a** (101 MHz, $CDCl_3$)

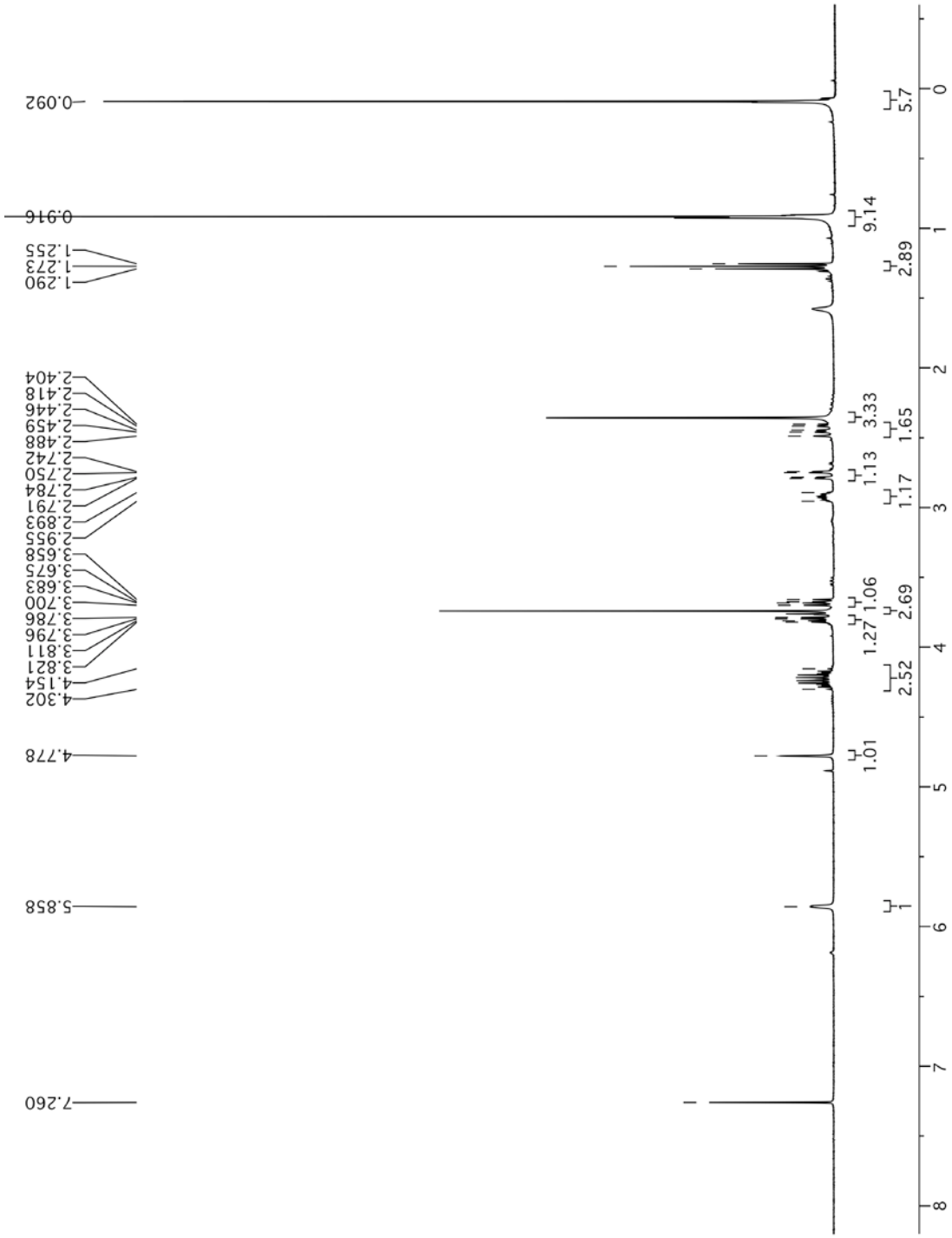


Figure 4.46. ^{1}H NMR spectrum of compound **3.90b** (400 MHz, $CDCl_3$)

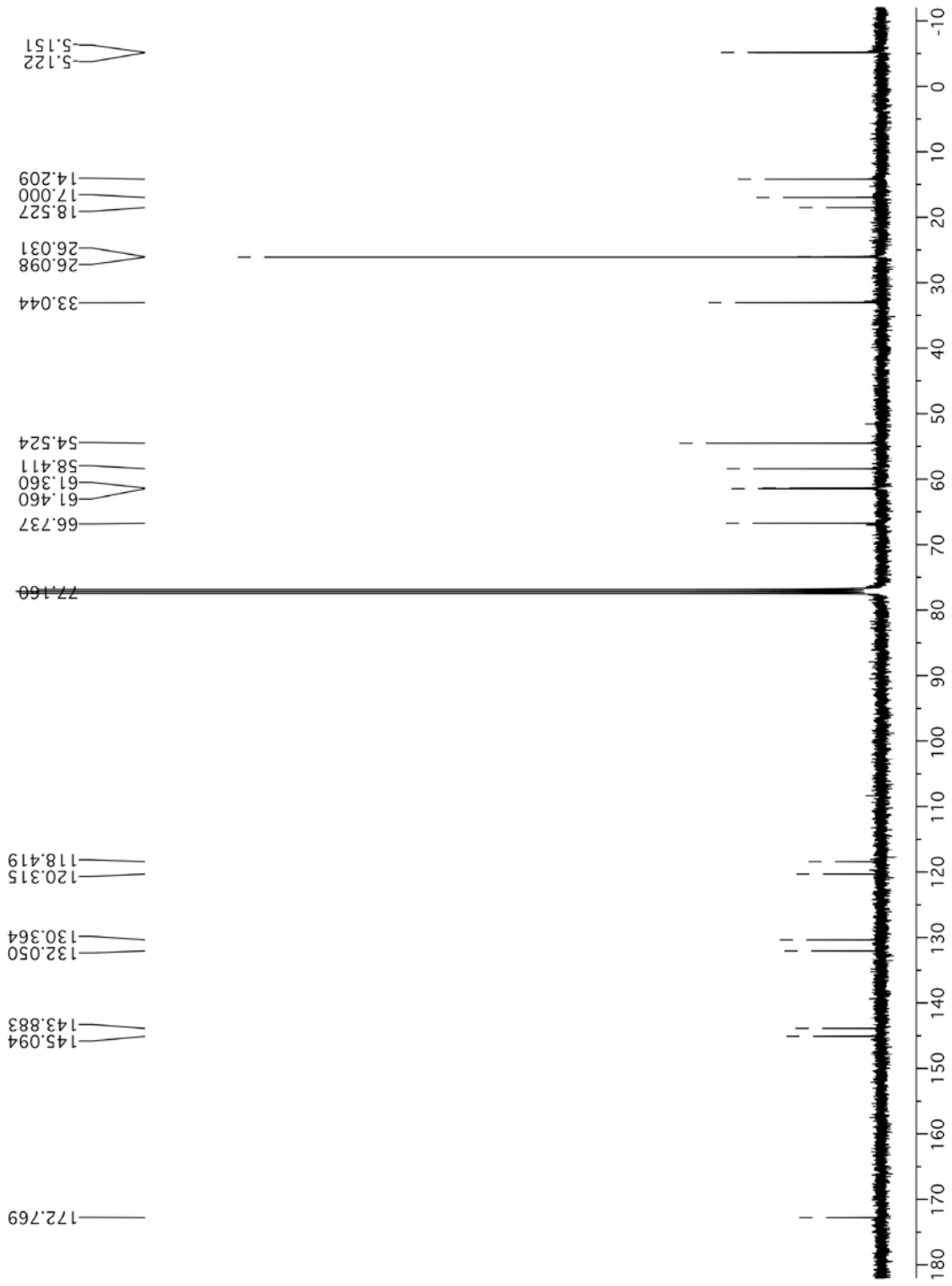
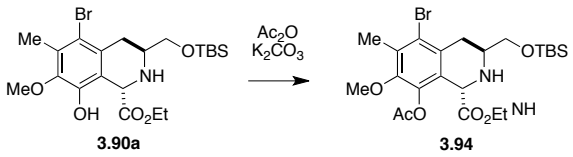


Figure 4.47. ^{13}C NMR spectrum of compound **3.90b** (101 MHz, $CDCl_3$)



3.90a **3.94**

4.43 *(1S,3S)*-ethyl 8-acetoxy-5-bromo-3-(((*tert*-butyldimethyl-silyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate (3.94)

To a stirred solution of compound **3.90a** (840 mg, 1.72 mmol, 1.0 eq.) in acetone (34 mL, 0.05 M), under Ar, were added K_2CO_3 (1.20 g, 8.64 mmol, 5.0 eq.) and acetic anhydride (162 µL, 1.72 mmol, 1.0 eq.). The suspension was stirred overnight, the solvent was evaporated and the residue was partitioned between water (25 mL) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2×25 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1) to give the title compound **3.94** (800 mg, 88%) as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 4.66 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.81 (1/2 ABX, *J* = 9.8, 3.5 Hz, 1H), 3.70 (s, 3H), 3.55 (1/2 ABX, *J* = 9.8, 7.6 Hz, 1H), 3.22-3.16 (m, 1H), 2.74 (1/2 ABX, *J* = 16.9, 4.1 Hz, 2H), 2.38 (s, 3H), 2.37-2.33 (m, 1H), 2.29 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.921 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 171.8, 167.9, 148.6, 141.0, 132.5, 131.5, 125.9, 125.8, 66.7, 61.5, 61.1, 55.8, 51.0, 32.6, 26.0, 20.6, 18.4, 17.1, 14.4, -5.2, -5.3. R_f (SiO_2, hexanes/EtOAc 4:1) 0.45; $[\alpha]_D^{25}$ = -21.1 ° (c = 1.10, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2956, 2932, 2856, 1780, 1737, 1462, 1192 cm^{-1}; HRMS (MH^+), found 532.1561. $C_{23}H_{37}BrNO_6Si$ requires 530.1574

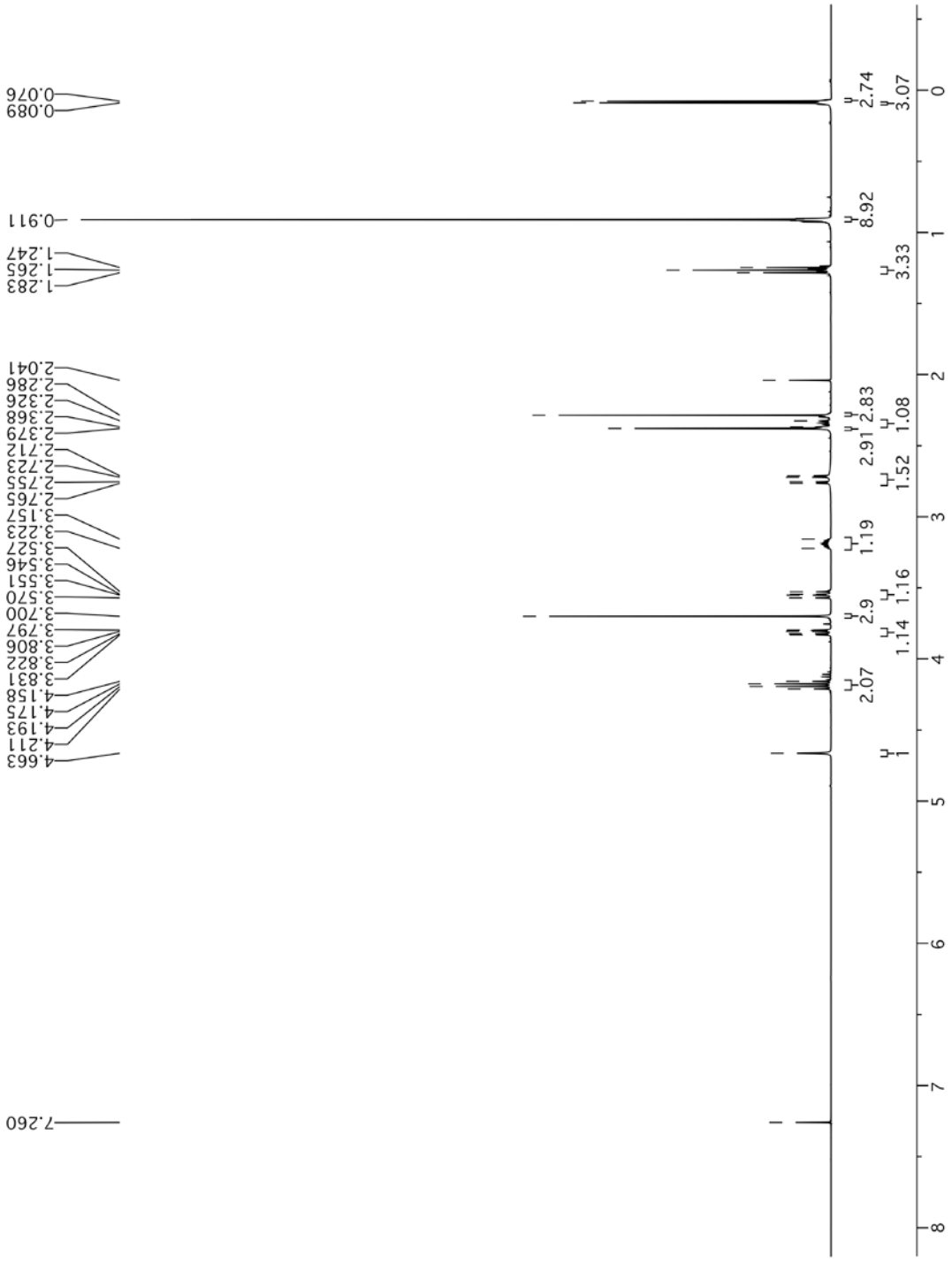


Figure 4.48. ^{1}H NMR spectrum of compound **3.94** (400 MHz, $CDCl_3$)

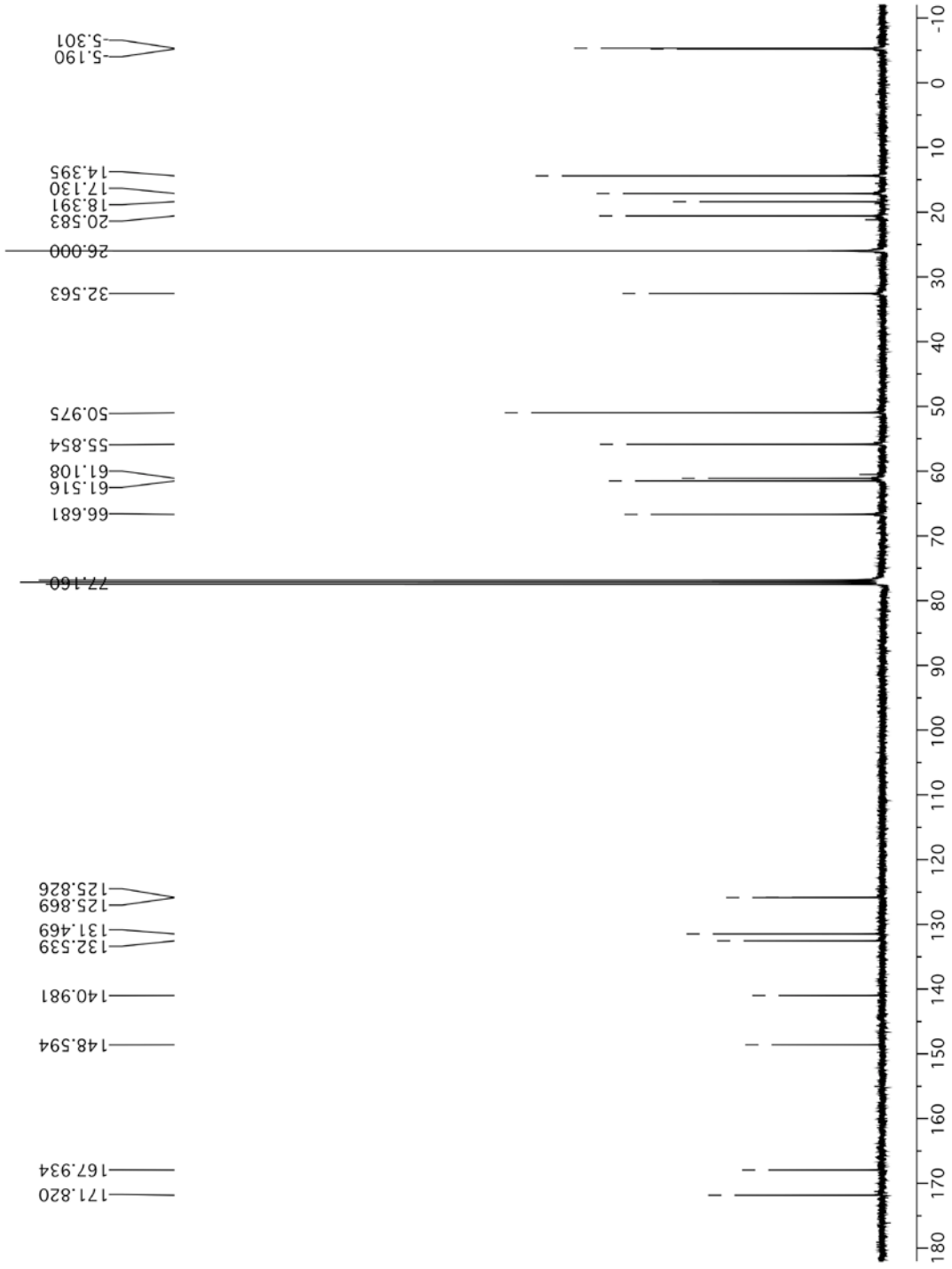
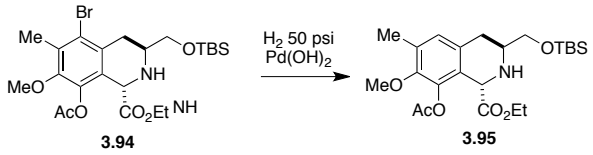


Figure 4.49. ^{13}C NMR spectrum of compound **3.94** (101 MHz, $CDCl_3$)



4.44 *(1S,3S)*-ethyl 8-acetoxy-3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3.95)

A solution of compound **3.94** (2.90 g, 5.46 mmol) in MeOH (110 mL, 0.05 M), and Pearlman's catalyst (20% $Pd(OH)_2/C$, 580 mg) were placed in a Fisher-Porter bottle, under Ar. The mixture was sparged with Ar for 5 minutes and the vessel was filled with hydrogen gas at 50 psi. The reaction was vigorously stirred overnight and then filtered through Celite® and the vessel was rinsed with MeOH (50 mL) and EtOAc (50 mL). The solution was concentrated under vacuum to dryness and partitioned between sat. aq. $NaHCO_3$ (75 mL) and EtOAc (75 mL). The aqueous phase was extracted with EtOAc (2×75 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1, 4:1 and 3:1) to give the title compound **3.95** (2.25 g, 91%) as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.85 (s, 1H), 4.65 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.73 (1/2 ABX, *J* = 9.8, 3.7 Hz, 1H), 3.70 (s, 3H), 3.52 (1/2 ABX, *J* = 9.8, 7.2 Hz, 1H), 3.28-3.22 (m, 1H), 2.59 (1/2 ABX, *J* = 16.1, 4.2 Hz, 1H), 2.50 (1/2 ABX, *J* = 16.1, 10.7 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.2, 168.3, 148.2, 141.6, 131.5, 131.1, 129.2, 124.0, 66.7, 61.3, 60.6, 55.6, 50.7, 30.2, 26.0, 20.6, 18.4, 16.0, 14.4, -5.2, -5.3. R_f (SiO_2, hexanes/EtOAc 4:1) 0.42; $[\alpha]_D^{25}$ = -17 ° (c = 0.42, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2954, 2929, 2857, 1775, 1737, 1197 cm^{-1}; HRMS (MH^+), found 452.244. $C_{23}H_{38}NO_6Si$ requires 452.2468.

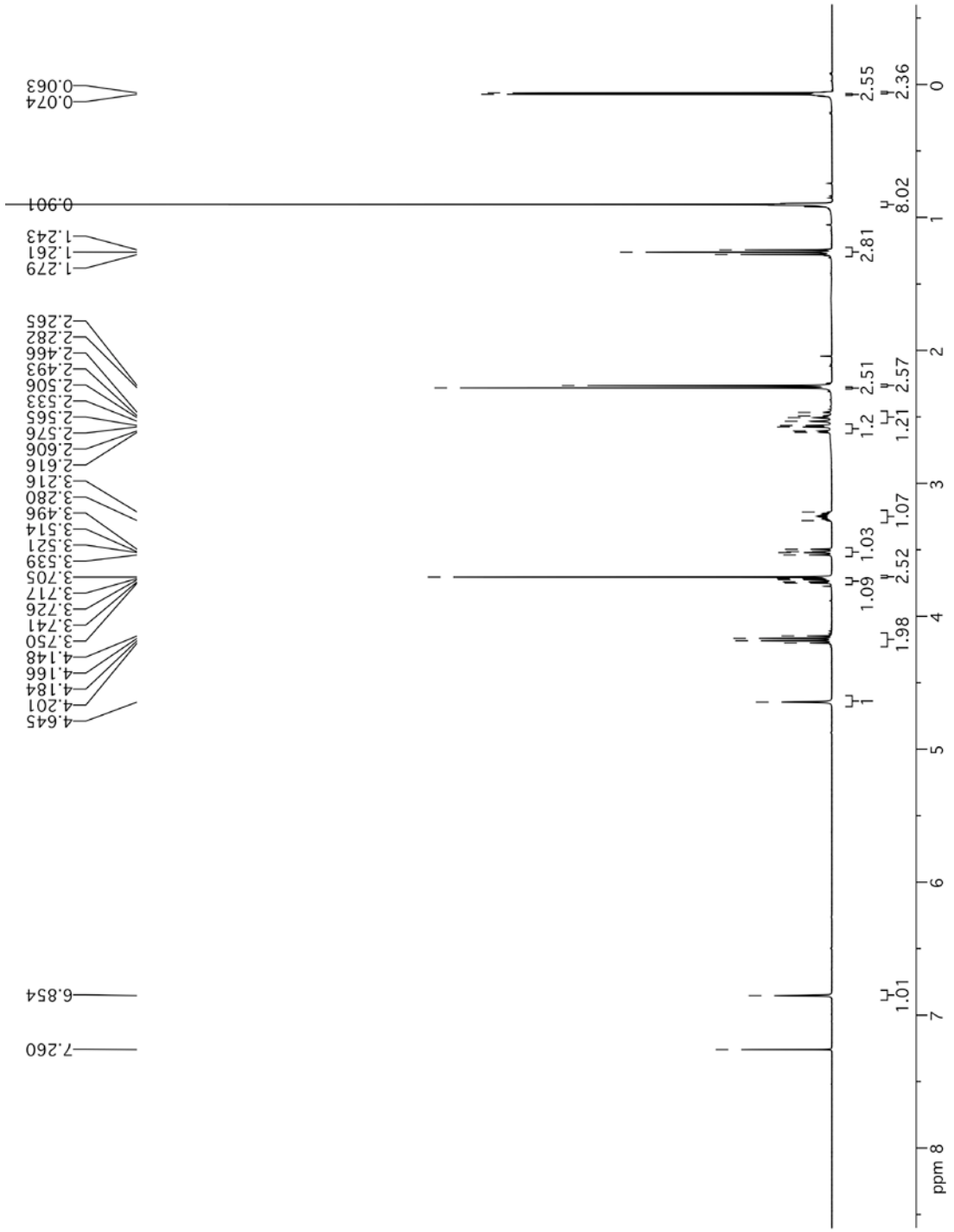


Figure 4.50. ^{1}H NMR spectrum of compound **3.95** (400 MHz, $CDCl_3$)

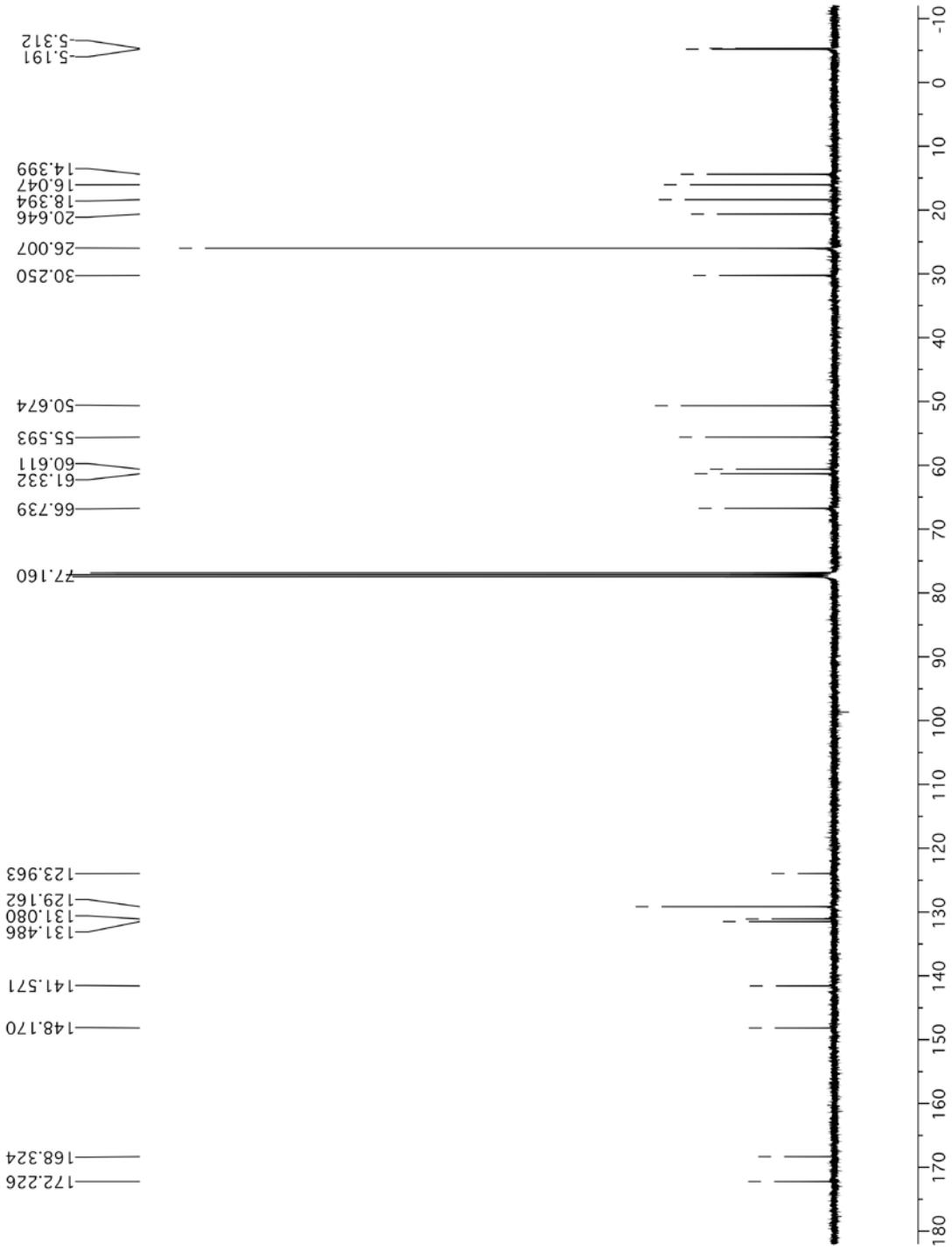
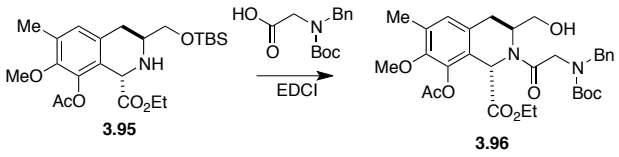


Figure 4.51. ^{13}C NMR spectrum of compound **3.95** (101 MHz, $CDCl_3$)



4.45 *(1S,3S)*-ethyl 8-acetoxy-2-(2-(benzyl(*tert*-butoxycarbonyl)-amino)acetyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3.96)

A solution of compound **3.95** (2.20 g, 4.87 mmol, 1.0 eq.), *N*-Bn-*N*-Boc-glycine (2.58 g, 9.74 mmol, 2.0 eq.) and EDCI (1.40 g, 7.31 mmol, 1.5 eq.) in CH_2Cl_2 (2.5 mL, 2 M), under Ar, was stirred for 2.5 days. The reaction was diluted with EtOAc (200 mL), and the solution was extracted with water (100 mL), sat. aq. $NaHCO_3$ (2×100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1, 3:1 and 2:1) to give the title compound **3.96** (3.15 g, 93%) as a colorless oil. ^{1}H-NMR (300 MHz; DMSO-d_6, 393 K, mixture of rotamers): δ 7.36-7.24 (m, 5H), 6.94 (s, 1H), 6.88 (s, 1H, minor rotamer), 5.48 (s, 1H), 4.49 (1/2 AB, J = 15.6 Hz, 1H), 4.39 (1/2 AB, J = 15.6.0 Hz, 1H), 4.33-4.27 (m, 2H), 4.13-3.87 (m, 3H), 3.69 (s, 3H), 3.66 (s, 1H, minor rotamer), 3.34-3.10 (br m, 2H), 3.07-2.91 (br m, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H, minor rotamer), 2.23 (s, 1H, minor rotamer), 1.41 (s, 9H), 1.21 (t, J = 7.0 Hz, 3H, minor rotamer), 1.12 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 0.6 Hz, 2H), 0.79 (s, 9H), 0.08 (s, 3H, minor rotamer), 0.04 (s, 3H, minor rotamer), 0.03 (m, 3H, minor rotamer), -0.11 (s, 3H), -0.14 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 170.1, 169.7, 168.1, 168.0, 156.1, 149.6, 129.2, 129.1, 128.7, 128.4, 127.8, 127.5, 127.5, 127.4, 121.6, 80.5, 80.4, 71.6, 61.9, 61.3, 60.7, 53.6, 53.6, 53.5, 53.0, 53.0, 52.9, 52.9, 50.9, 47.7, 29.5, 28.5, 28.4, 26.0, 26.0, 25.9, 20.9, 18.3, 16.1, 16.0, 14.0, 13.9, -5.3, -5.4, -5.4, -5.7. R_f (SiO_2, hexanes/EtOAc 3:1) 0.30; $[\alpha]_D^{25}$ =

+26.8 ° (c = 0.995, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2956, 2931, 2857, 1781, 1743, 1703, 1668, 1199 cm^{-1}; HRMS (MH^+), found 699.3666. $C_{37}H_{55}N_2O_9Si$ requires 699.3677.

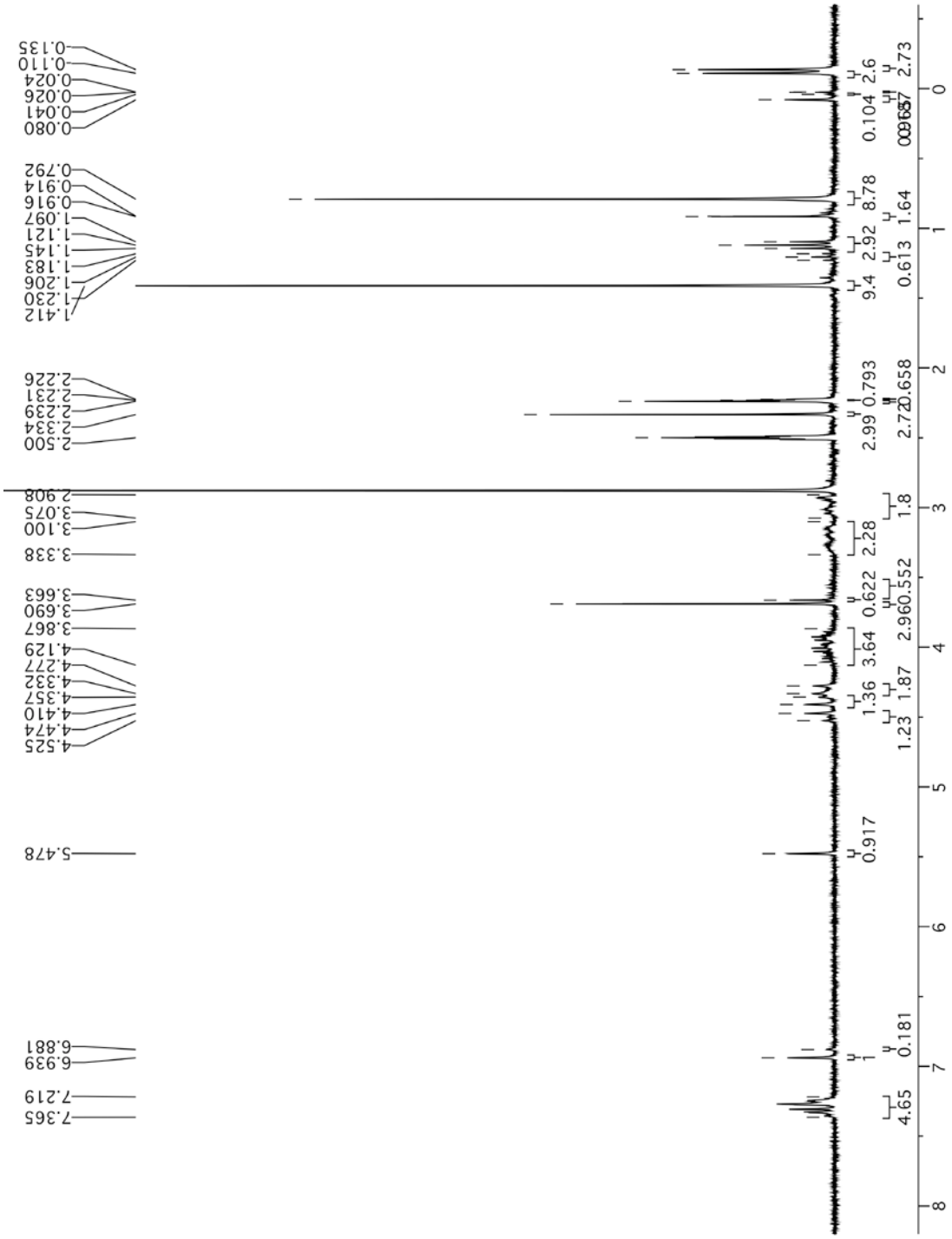


Figure 4.52. ^{1}H NMR spectrum of compound **3.96** (300 MHz, DMSO-d_6, 393K)

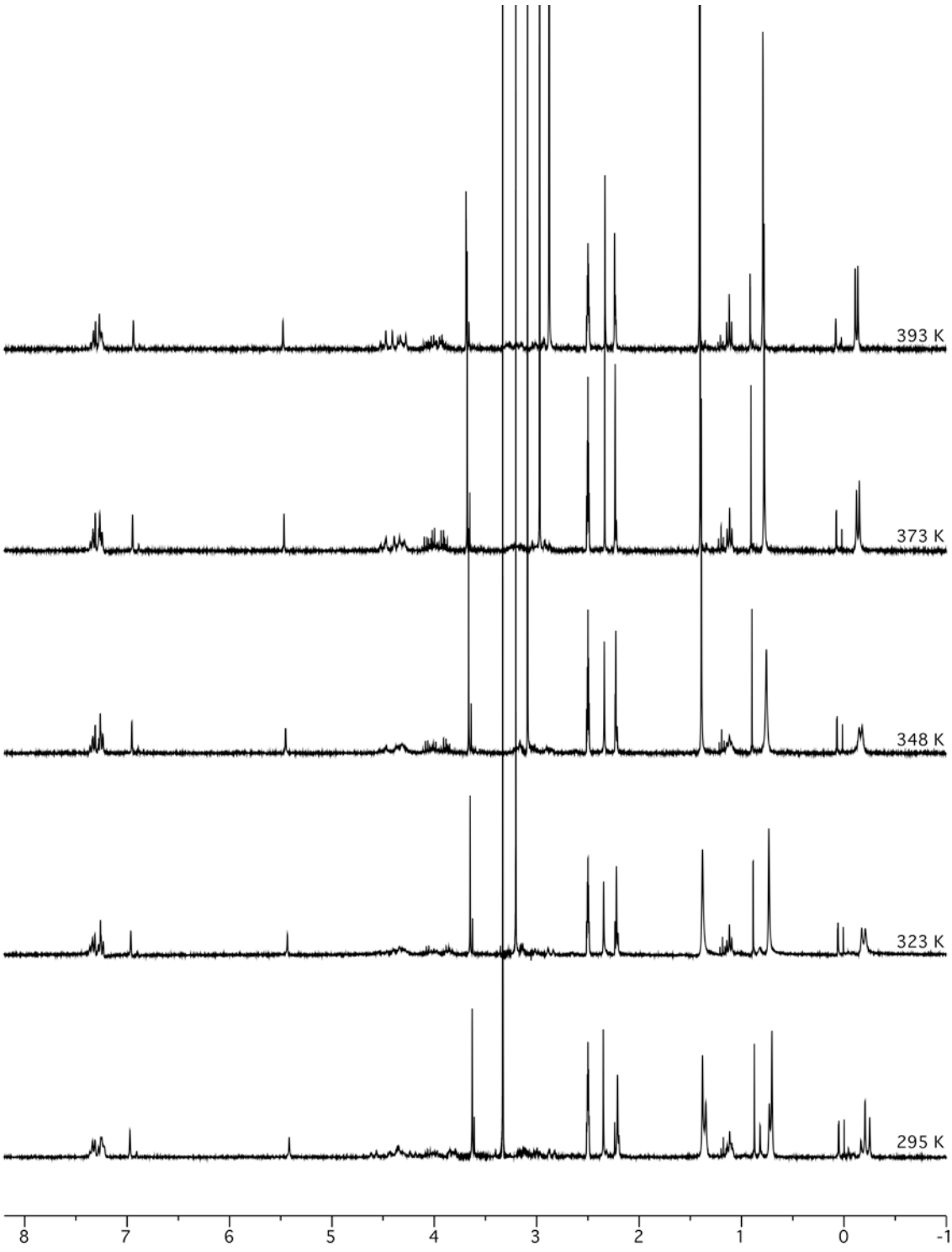


Figure 4.53. ^{1}H-NMR spectra of compound **3.96**

(300 MHz, DMSO-d_6, 295, 323, 348, 373 and 393K)

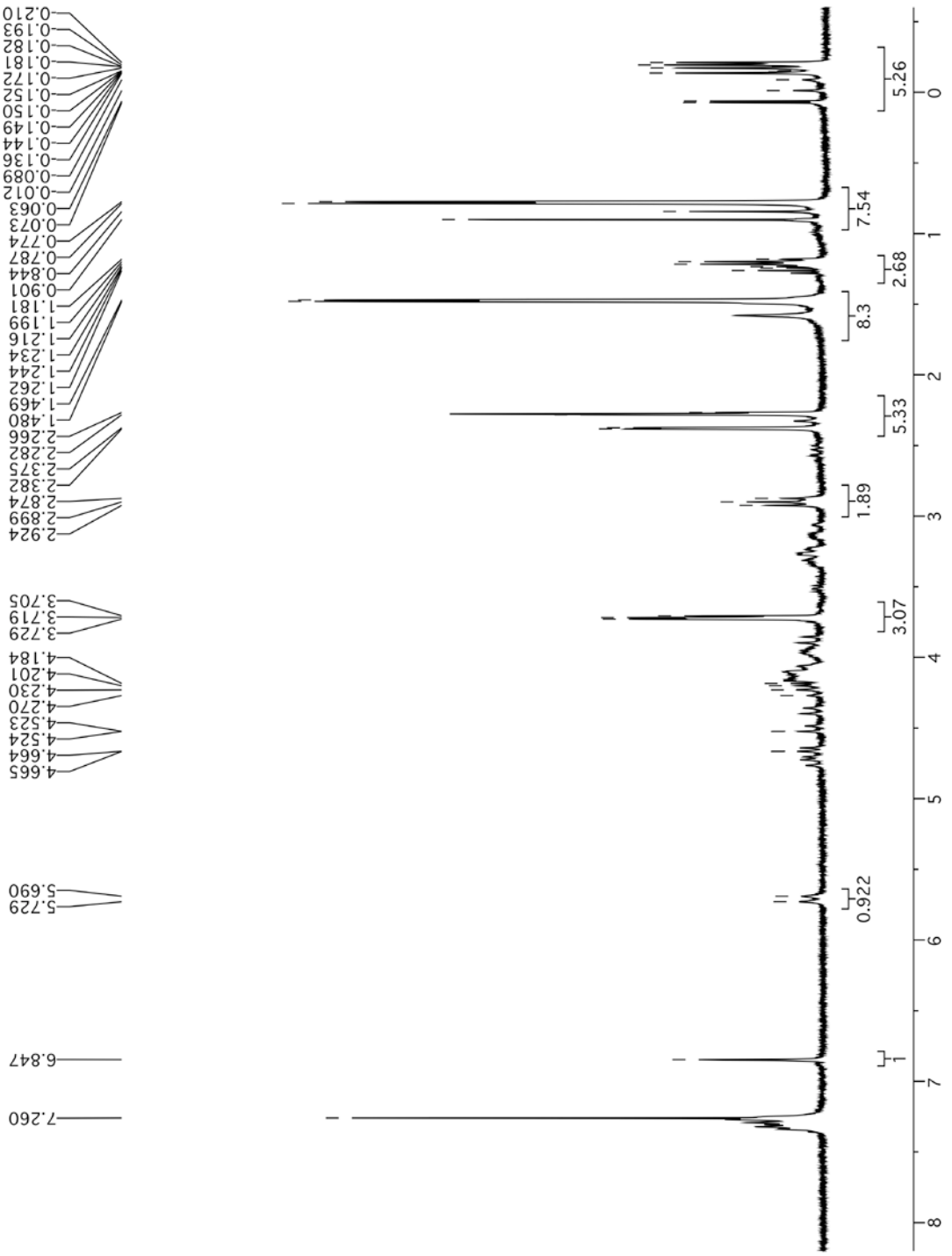


Figure 4.54. ^{1}H NMR spectrum of compound **3.96** (400 MHz, $CDCl_3$)

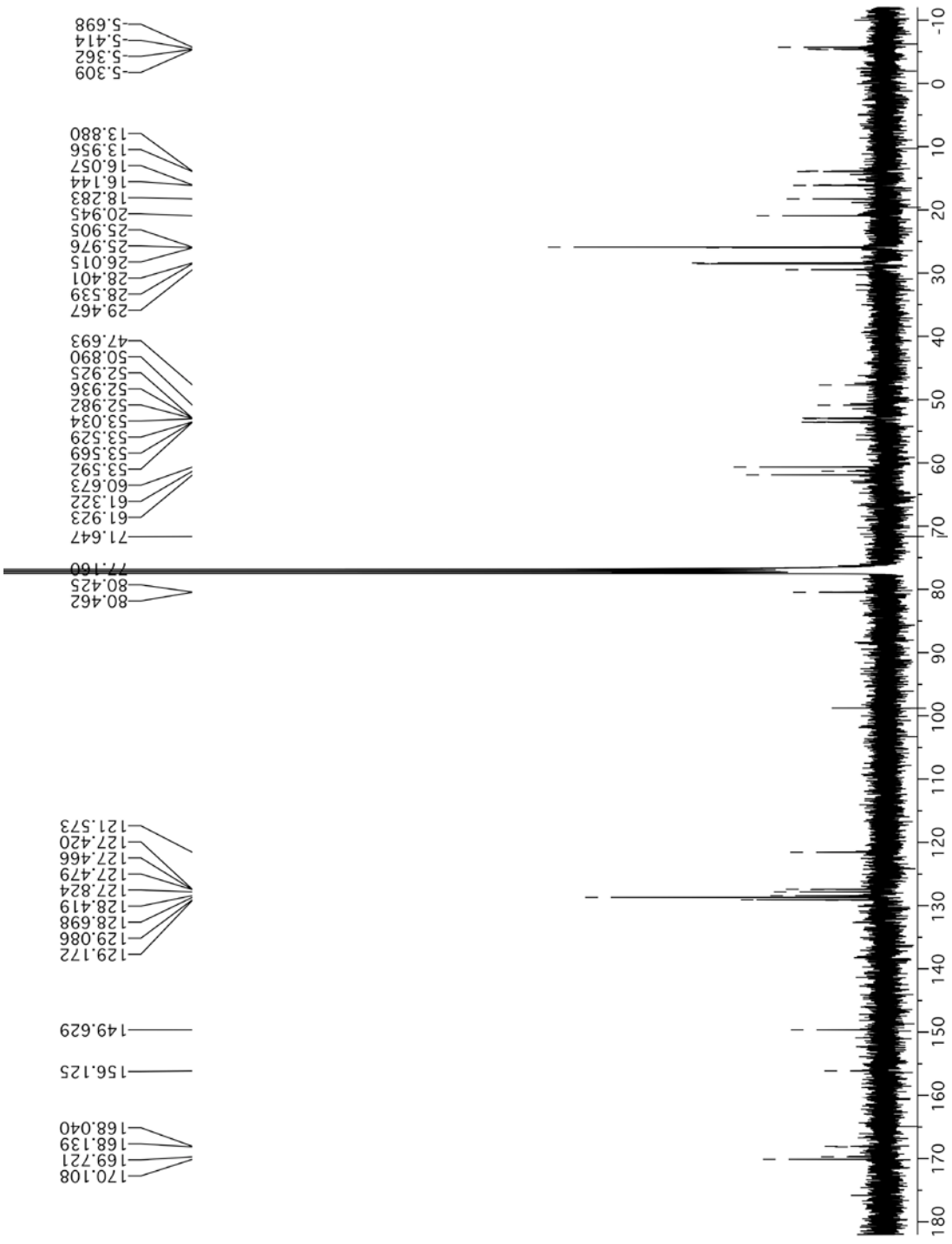


Figure 4.55. ^{13}C NMR spectrum of compound **3.96** (101 MHz, $CDCl_3$)

4.46 (1*S*,3*S*)-ethyl 2-(2-(benzyl(*tert*-butoxycarbonyl)amino)acetyl)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3.97)

To a solution of compound **3.96** (765 mg, 1.09 mmol, 1.0 eq.) in THF (10 mL, 0.11 M), under Ar, were added MeOH (625 μL) and TBAF (1.0 M solution in THF, 2.18 mL, 2.0 eq.). The reaction was stirred overnight and quenched with sat. aq. NH_4Cl (50 mL) and then diluted with EtOAc (100 mL). The phases were separated, the aqueous phase was extracted with EtOAc (2×25 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was dissolved in the minimal amount of CH_2Cl_2 and purified by flash chromatography (silica gel, hexanes/EtOAc 2:1, then 1:1) to give the title compound **3.97** as a white amorphous solid (525 mg, 82%). ^{1}H-NMR (300 MHz; DMSO-d_6, 393 K): δ 7.36-7.26 (m, 5H), 6.96 (s, 1H), 5.50 (s, 1H), 4.49-4.40 (br m, 2H), 4.27-4.17 (br m, 2H), 4.07-3.89 (m, 3H), 3.70 (s, 3H), 3.19-3.03 (br m, 2H), 2.94-2.81 (m, 2H, overlapped with H_2O signal), 2.34 (s, 3H), 2.25 (s, 3H), 1.41 (s, 9H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 170.2, 170.1, 168.0, 168.0, 156.4, 154.8, 152.8, 149.7, 145.0, 141.7, 141.5, 138.1, 138.1, 138.0, 132.9, 132.8, 130.2, 130.0, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 127.8, 127.7, 127.5, 127.5, 127.1, 124.2, 121.2, 80.9, 80.4, 65.1, 63.8, 62.0, 60.6, 53.7, 53.5, 52.7, 52.0, 51.0, 47.9, 30.6, 30.0, 29.5, 28.5, 28.4, 20.9, 16.2, 13.8; m.p. 80 °C; R_f (SiO_2, hexanes/EtOAc 1:1) 0.35; $[\alpha]_D^{25}$ = +78 ° (c = 0.44, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3455 (br), 2977, 2935, 1780, 1742, 1698, 1663, 1200 cm^{-1}; HRMS (MH^+), found 585.2816. $C_{31}H_{41}N_2O_9$ requires 585.2812.

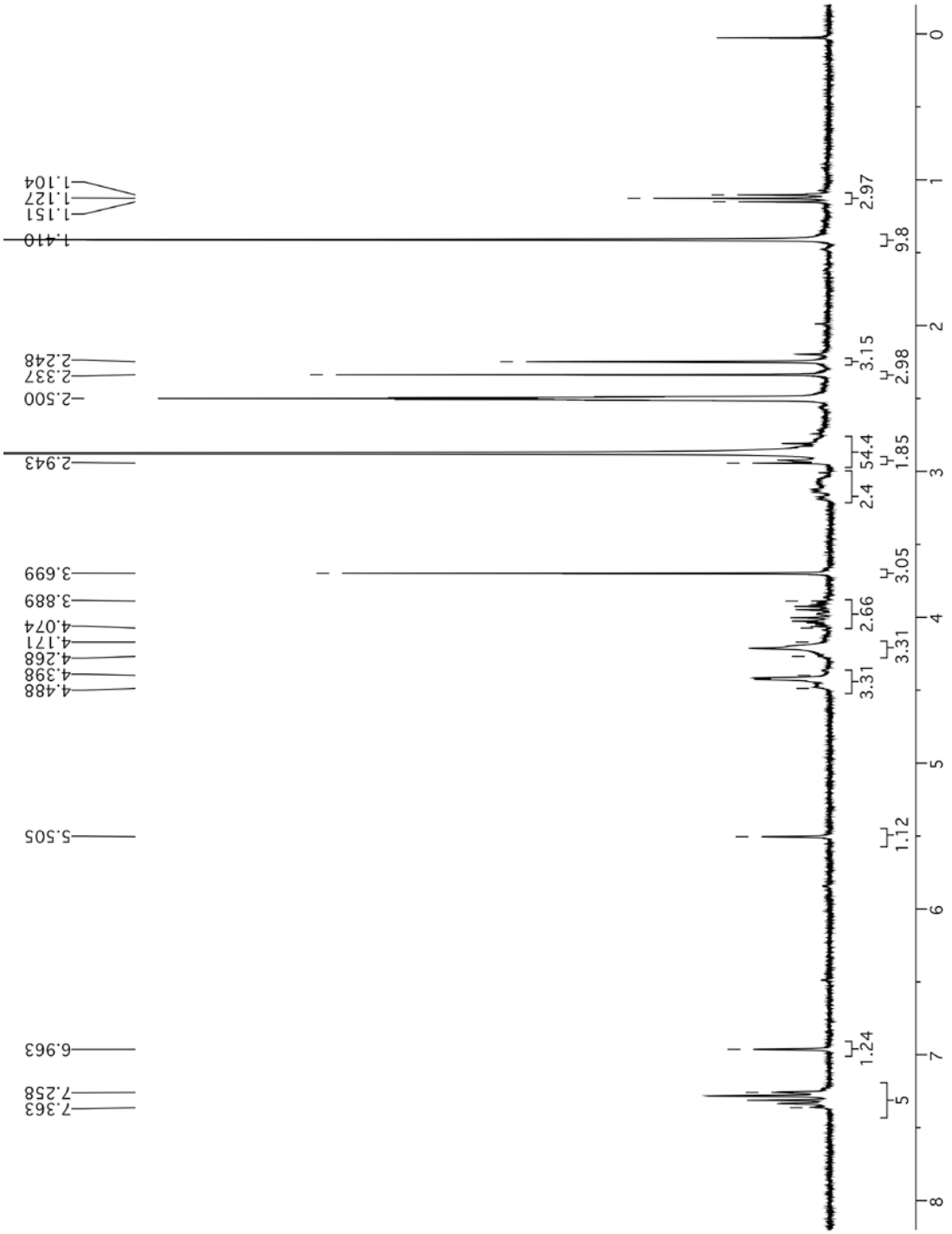


Figure 4.56. ^{1}H NMR spectrum of compound **3.97** (300 MHz, DMSO-d_6, 393K)

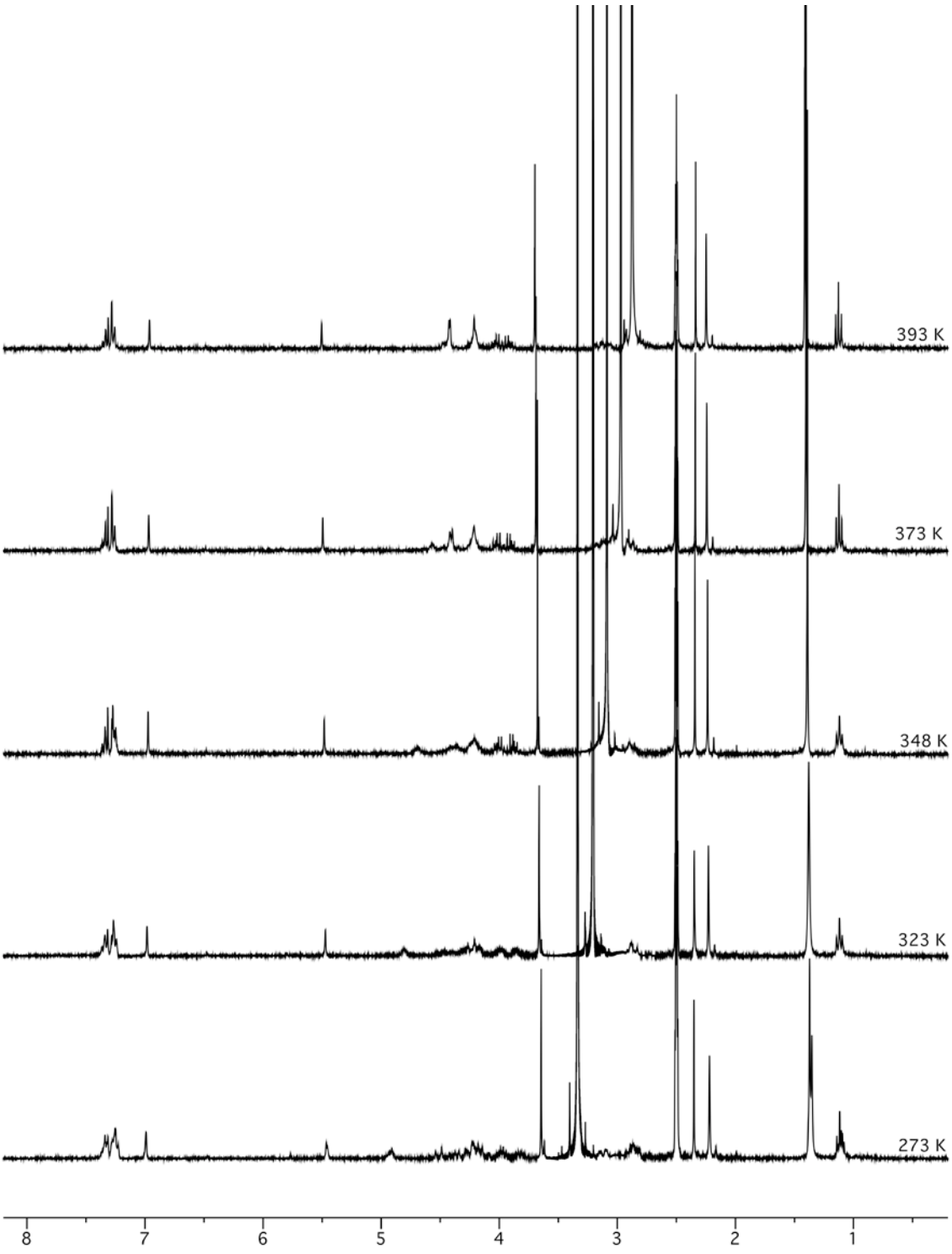


Figure 4.57. ^{1}H-NMR spectra of compound **3.97** (300 MHz, DMSO-d_6, 295, 323, 348, 373 and 393K)

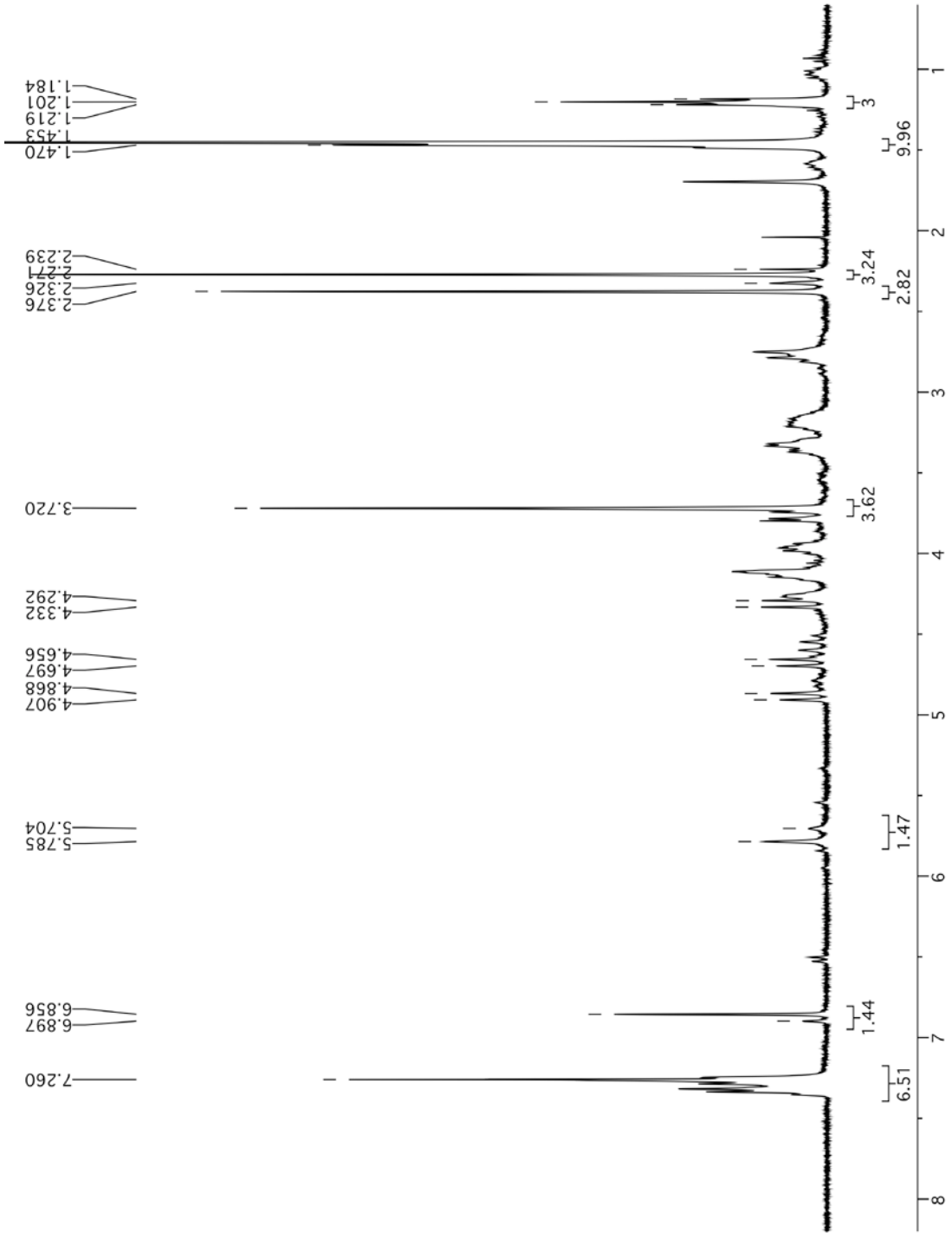


Figure 4.58. ^{1}H NMR spectrum of compound **3.97** (400 MHz, $CDCl_3$)

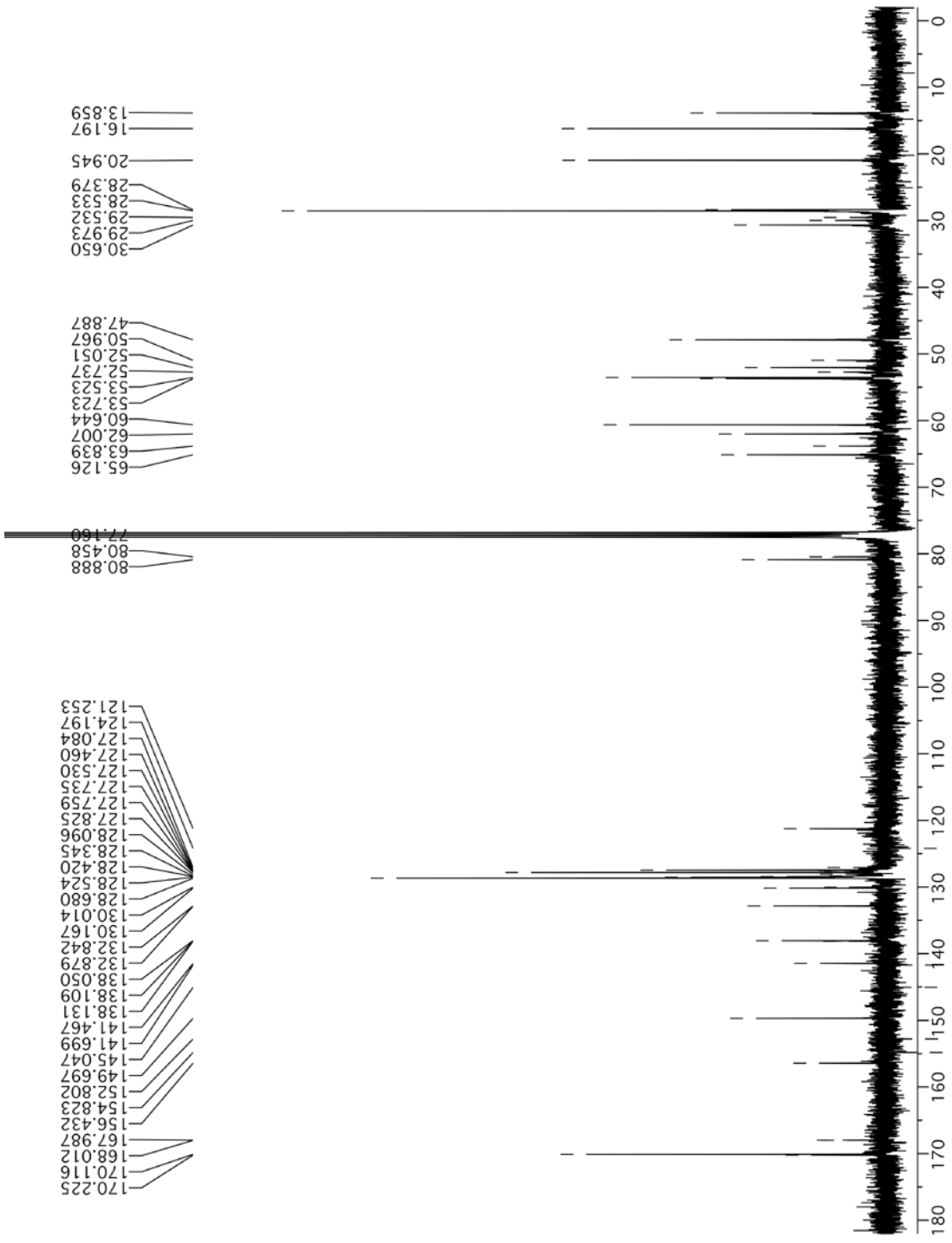
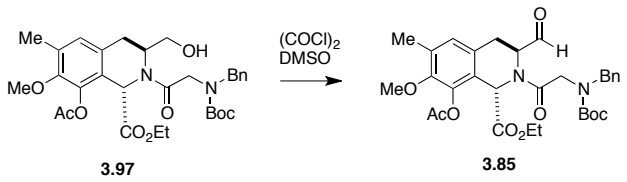


Figure 4.59. ^{13}C NMR spectrum of compound **3.97** (101 MHz, $CDCl_3$)



4.47 (1*S*,3*S*)-ethyl 2-(2-(benzyl(*tert*-butoxycarbonyl)amino)-acetyl)-3-formyl-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3.85)

A solution of oxalyl chloride (825 μL, 9.75 mmol, 3.0 eq.) in CH_2Cl_2 (22.5 mL), under Ar, was cooled to -78 C, and DMSO (921 μL, 13.0 mmol, 4.0 eq.) was added dropwise. The resulting mixture was stirred an additional 30 min at -78 °C. A solution of compound **3.97** (1.90 mg, 3.25 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) at RT was then added slowly by cannula, and the mixture continued to stir at -78 °C for 30 min. Triethylamine (4.50 mL, 32.5 mmol, 10 eq.) was then added dropwise, and the solution was stirred for 15 min at -78 °C and an additional 30 min at 0 °C. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and allowed to warm to RT. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 2:1, then 1:1) to give the title compound **3.85** (1.65 g, 87%) as a colorless oil, which solidifies upon standing to afford a colorless amorphous solid. ^{1}H-NMR (300 MHz; DMSO-d_6, 373 K, mixture of rotamers): δ 9.54 (s, 1H, minor rotamer), 9.28 (s, 1H), 7.35-7.23 (m, 5H), 7.08 (s, 1H, minor rotamer), 7.01 (s, 1H), 6.94 (s, 1H, minor rotamer), 6.91 (s, 1H, minor rotamer), 5.70 (s, 1H), 5.10-4.88 (m, 1H), 4.52-4.28 (m, 3H), 4.26-4.14 (m, 1H), 4.13-3.98 (m, 2H), 3.97-3.86 (m, 1H), 3.69 (s, 3H, minor rotamer), 3.68 (s, 3H, minor rotamer), 3.67 (s, 3H), 3.38-3.27 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H, minor rotamer), 2.25 (s, 3H, minor rotamer), 2.24 (s, 3H, minor rotamer), 2.22 (s, 3H), 1.41 (s, 9H, minor rotamer), 1.40 (s, 9H), 1.36 (s, 9H,

minor rotamer), 1.34 (s, 9H, minor rotamer), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 201.2, 199.6, 199.2, 169.9, 167.8, 155.9, 155.8, 150.2, 149.7, 141.5, 141.0, 137.6, 137.5, 137.5, 133.6, 133.3, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 122.6, 122.1, 81.0, 80.8, 62.7, 62.2, 60.9, 60.6, 60.6, 60.2, 53.7, 53.5, 53.3, 50.9, 47.8, 47.6, 47.1, 29.6, 28.5, 28.5, 28.4, 28.2, 20.9, 16.2, 13.8; m.p. 78 °C; R_f (SiO_2, hexanes/EtOAc 1:1) 0.40; $[\alpha]_D^{25}$ = +35 ° (c = 0.23, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2978, 2937, 1780, 1742, 1699, 1673, 1200 cm^{-1}; HRMS (MH^+), found 583.2654. $C_{31}H_{39}N_2O_9$ requires 583.2656.

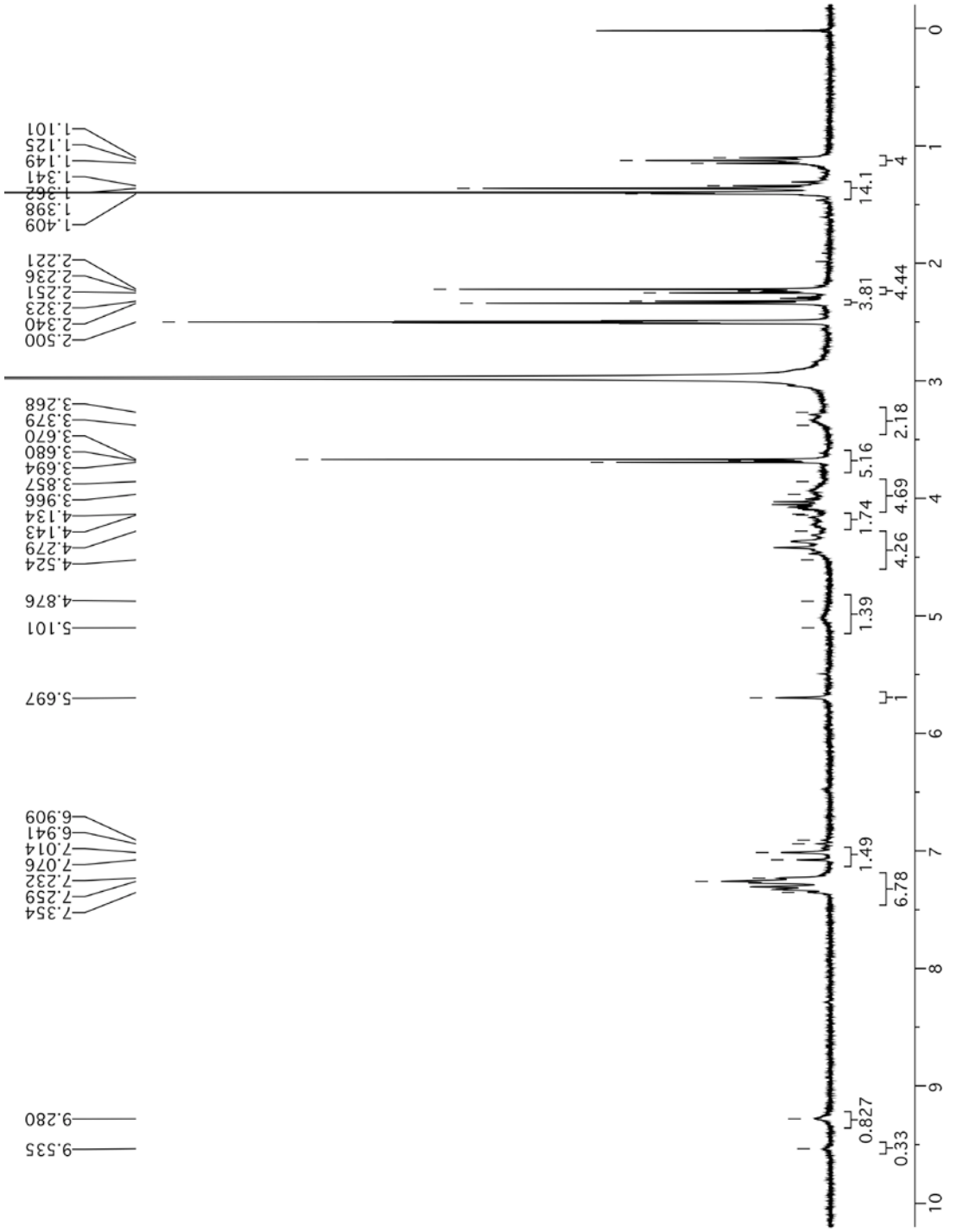


Figure 4.60. ^{1}H NMR spectrum of compound **3.85** (300 MHz, DMSO-d_6, 373K)

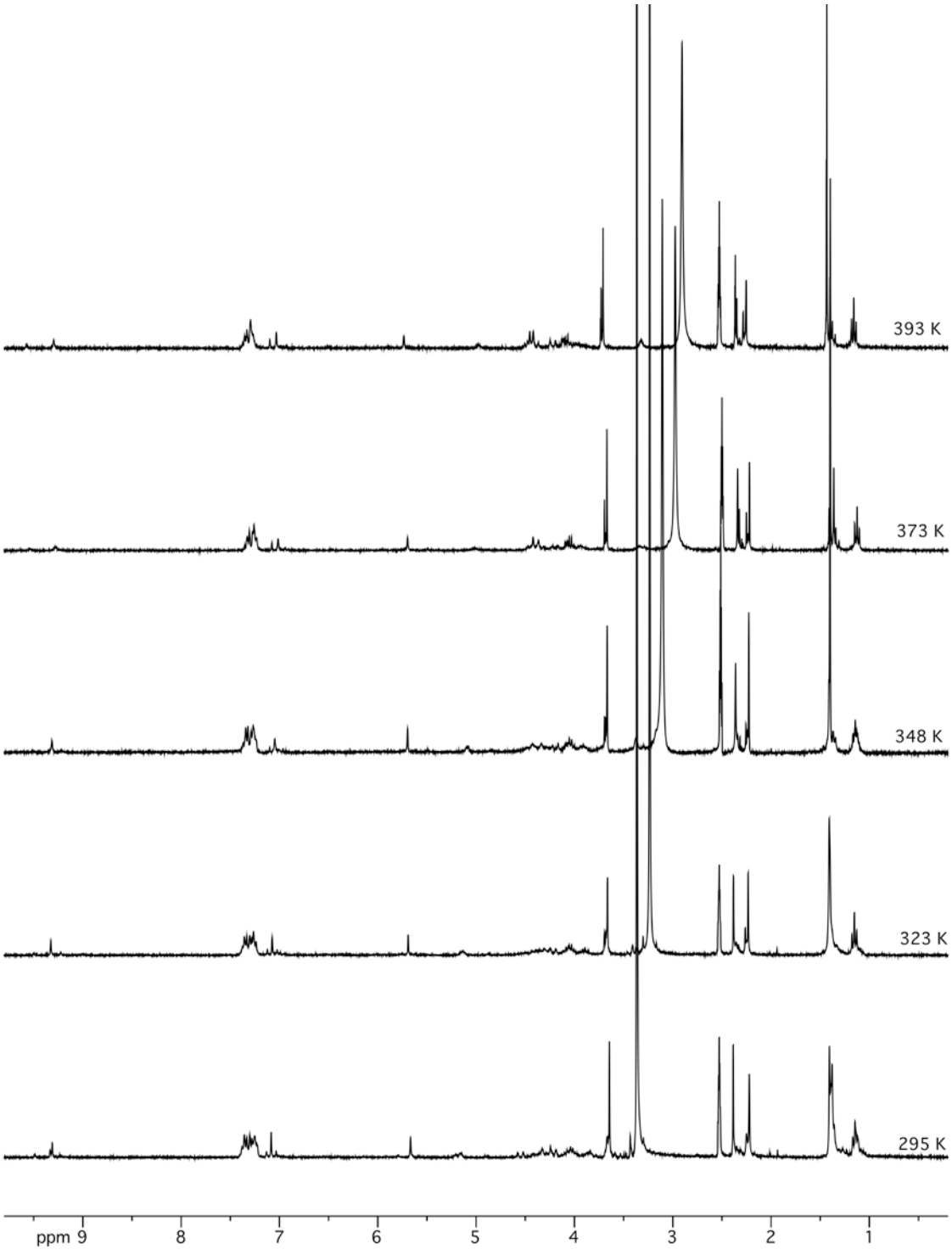


Figure 4.61. ^{1}H-NMR spectra of compound **3.85**

(300 MHz, DMSO-d_6, 295, 323, 348, 373 and 393K)

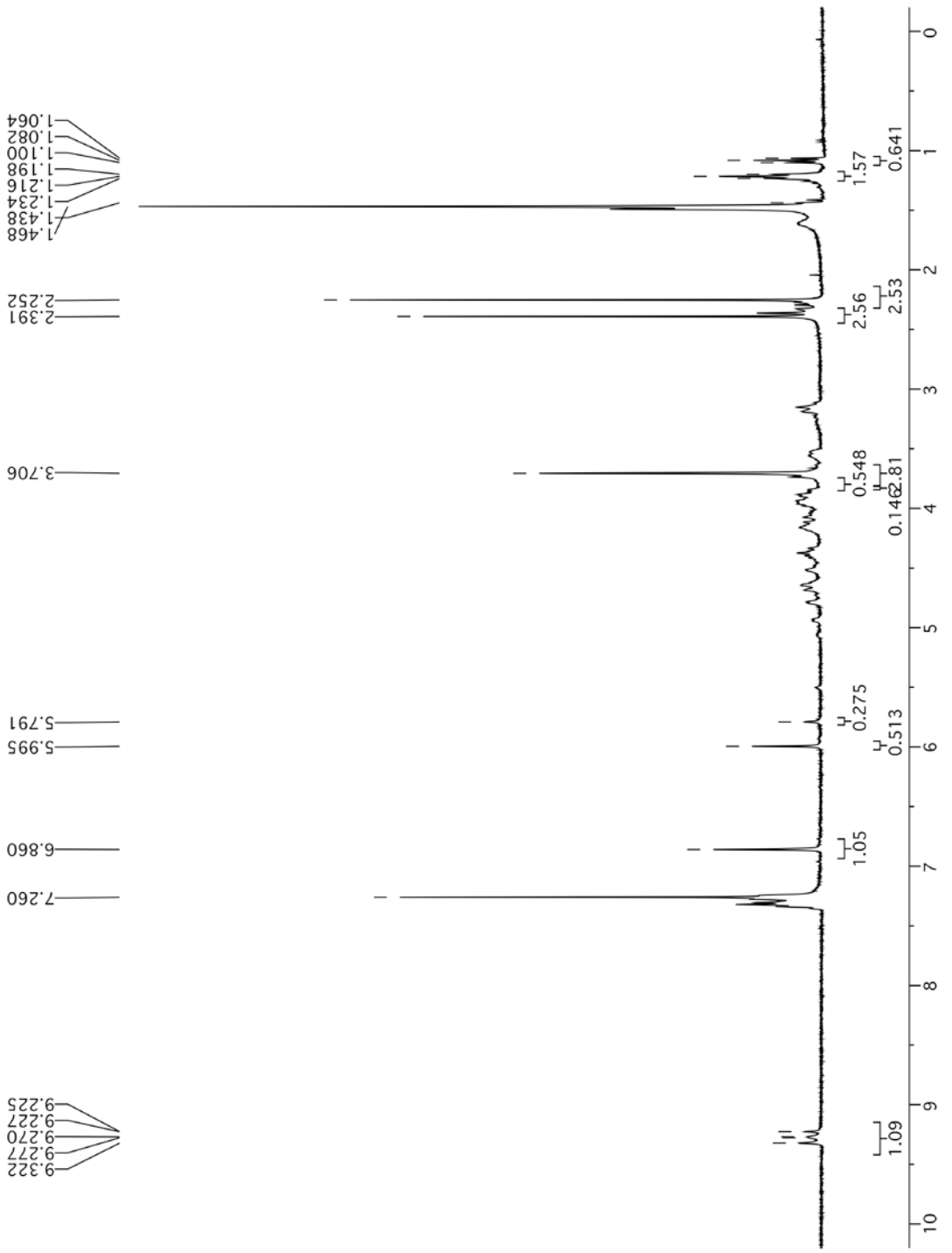


Figure 4.62. ^{1}H NMR spectrum of compound **3.85** (400 MHz, $CDCl_3$)

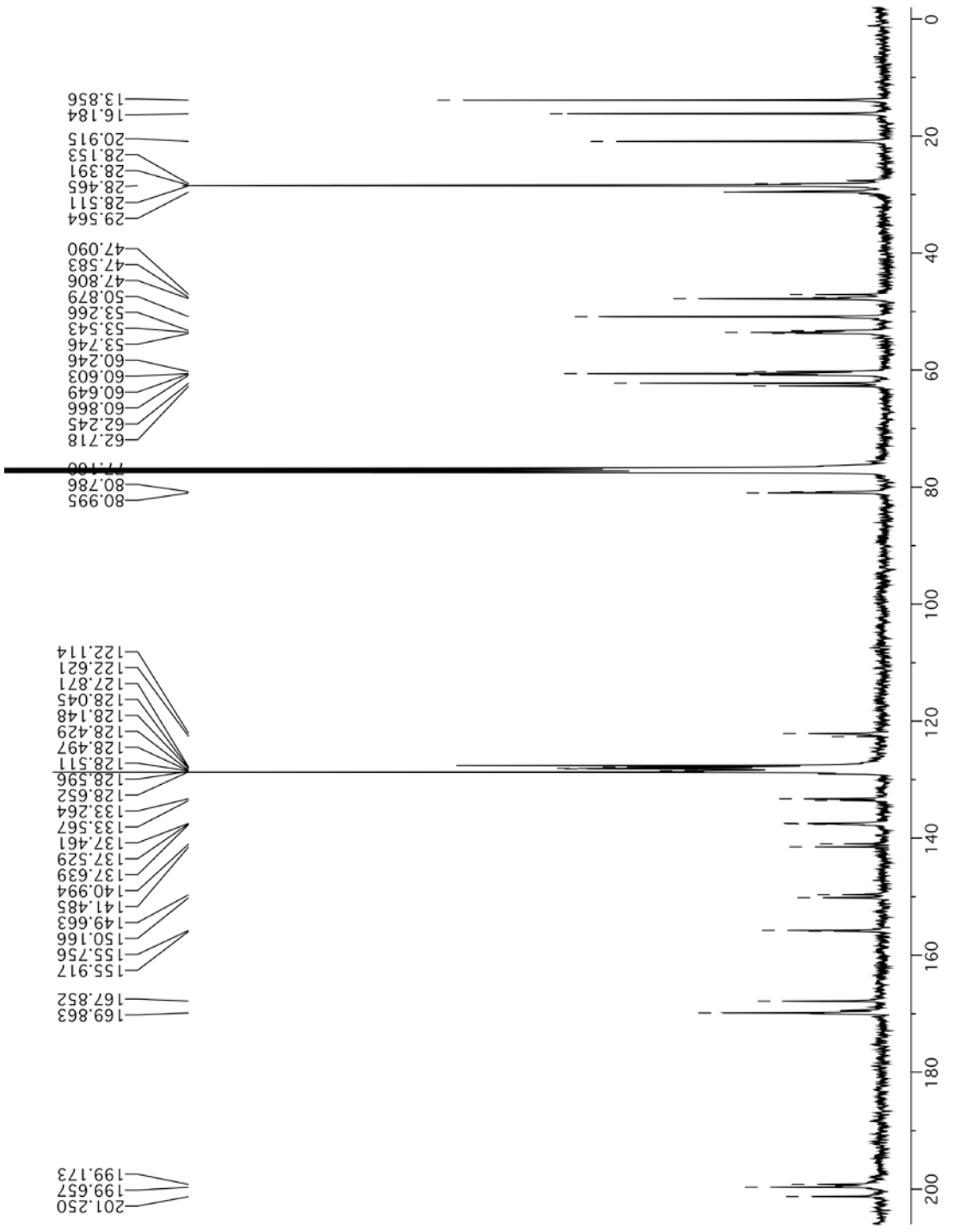
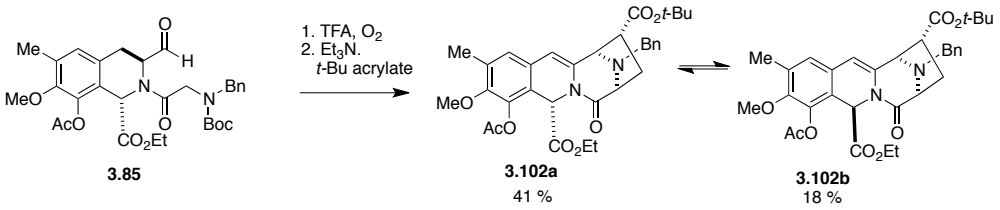


Figure 4.63. ^{13}C NMR spectrum of compound **3.85** (101 MHz, $CDCl_3$)



4.48 (5*S*,8*S*,10*R*,11*S*)-10-*tert*-butyl 5-ethyl 4-acetoxy-13-benzyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (3.102a) and (5*R*,8*S*,10*R*,11*S*)-10-*tert*-butyl 5-ethyl 4-acetoxy-13-benzyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (3.102b)

To solution of compound **3.85** (1.65 g, 2.83 mmol, 1.0 eq.) in $CHCl_3$ (28 mL, 0.1 M), under air, were added TEMPO (44 mg, 0.28 mmol, 0.10 eq.), and trifluoroacetic acid (10.8 mL, 142 mmol, 50 eq.) and the flask was loosely capped with a Teflon® stopper. The solution was stirred for 4h, the solvent was evaporated to dryness under vacuum and the residue was taken up in $CHCl_3$. The solution was cooled to 0 °C and then *tert*-butyl acrylate (8.20 mL, 56.6 mmol, 20 eq.) and triethylamine (3.95 mL, 28.3 mmol, 10 eq.) were added. The reaction was allowed to warm to RT and stirred overnight. The solution was diluted with EtOAc (200 mL), rinsed with sat. aq. NH_4Cl (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1, 3:1) to afford a 2.4:1 mixture of the title compounds **3.102a** and **3.102b** (985 mg, 59%) as a yellow oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.41-7.22 (m, 5H), 6.74 (s, 1H, minor diastereomer), 6.73 (s, 1H), 6.36 (s, 1H, minor diastereomer), 6.27 (s, 1H), 5.51 (s, 1H, minor diastereomer), 5.50 (s, 1H), 4.28-3.96 (m, 6H), 3.89-3.71 (m, 2H), 3.75 (s, 3H, minor diastereomer), 3.72 (s, 3H), 2.80-2.67 (m, 2H), 2.45 (dd, *J* = 13.0, 9.8 Hz, 1H, minor diastereomer), 2.40 (s, 3H), 2.39 (s, 3H, minor diastereomer), 2.28 (s,

3H, minor diastereomer), 2.26 (s, 3H), 2.13 (dd, J = 13.3, 9.5 Hz, 1H), 1.46 (s, 9H, minor diastereomer), 1.42 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H, minor diastereomer); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.4, 171.7, 168.7, 167.9, 149.9, 141.6, 133.1, 129.0, 128.6, 128.4, 128.4, 127.4, 127.3, 126.6, 125.0, 124.8, 117.3, 116.7, 104.6, 103.1, 81.4, 81.3, 65.1, 64.1, 63.1, 62.6, 62.4, 62.3, 60.7, 60.6, 52.7, 51.8, 51.3, 50.7, 50.0, 48.0, 34.3, 31.9, 31.7, 28.2, 22.8, 21.0, 16.1, 14.2, 14.0; R_f (SiO_2, hexanes/EtOAc 3:1) 0.5; $[\alpha]_D^{25}$ = -65.0 ° (c = 0.320, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 2980, 2936, 1781, 1741, 1693, 1651 cm^{-1}; HRMS (MH^+), found 591.2712. $C_{33}H_{39}N_2O_8$ requires 591.2706.

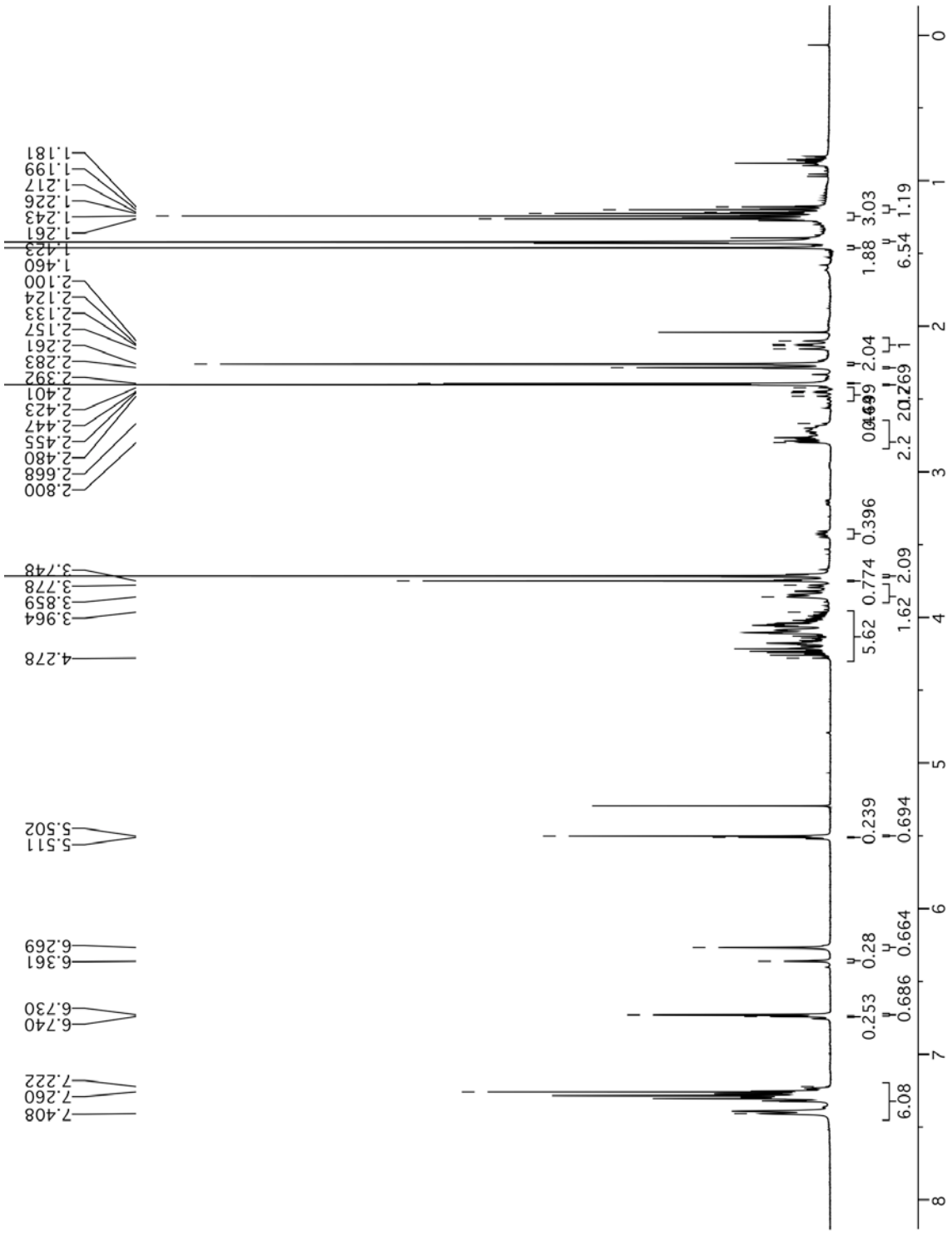


Figure 4.64. ^{1}H NMR spectrum of compounds **3.102a** and **3.102b** (400 MHz, $CDCl_3$)

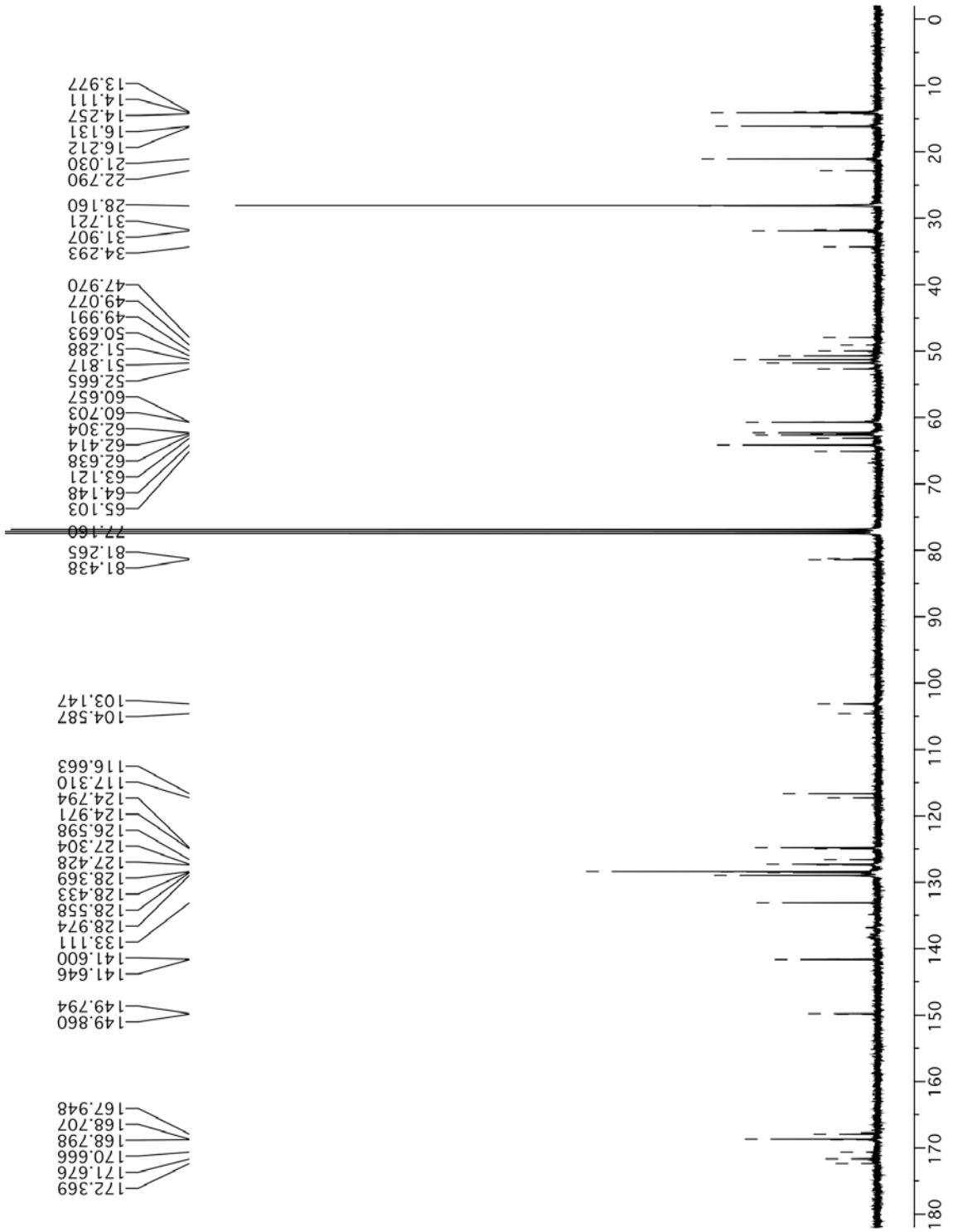
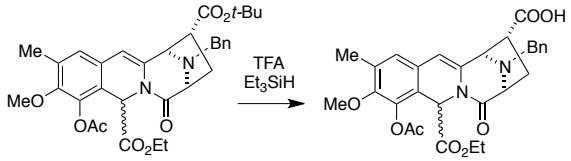


Figure 4.65. ^{13}C NMR spectrum of compounds **3.102a** and **3.102b** (101 MHz, $CDCl_3$)



3.102a/3.102b **3.103a/3.103b**

4.49 (8*S*,10*R*,11*S*)-4-acetoxy-13-benzyl-5-(ethoxycarbonyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylic acid (3.103a/3.103b)

To a solution of a mixture of compounds **3.102a** and **3.102b** (110 mg, 0.186 mmol) in CH_2Cl_2 (600 µL) at 0°C, was added Et_xSiH (240 µL, 1.5 mmol, 8 eq.), followed by TFA (600 µL, 7.84 mmol, 42 eq.). The resulting mixture was cooled to 5°C. After 24 h, the reaction concentrated to dryness and partitioned between H_2O (10 mL) and CH_2Cl_2 (25 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under vacuum. The resulting residue was purified by flash chromatography (hexanes:EtOAc 1:1 to 1:2) to provide a mixture of compounds **3.103a/3.103b** as a colorless oil (0.38 g, 95% yield). R_f = 0.1 (hexanes:EtOAc 1:2); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.41-7.32 (m, 5H), 6.83-6.81 (s, 1H), 6.78 (s, 1H), 6.38 (s, 1H), 6.30 (s, 1H), 5.66 (m, 1H), 4.42-3.88 (m, 13H), 3.76 (s, 1H), 3.74 (s, 3H), 2.41 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H).

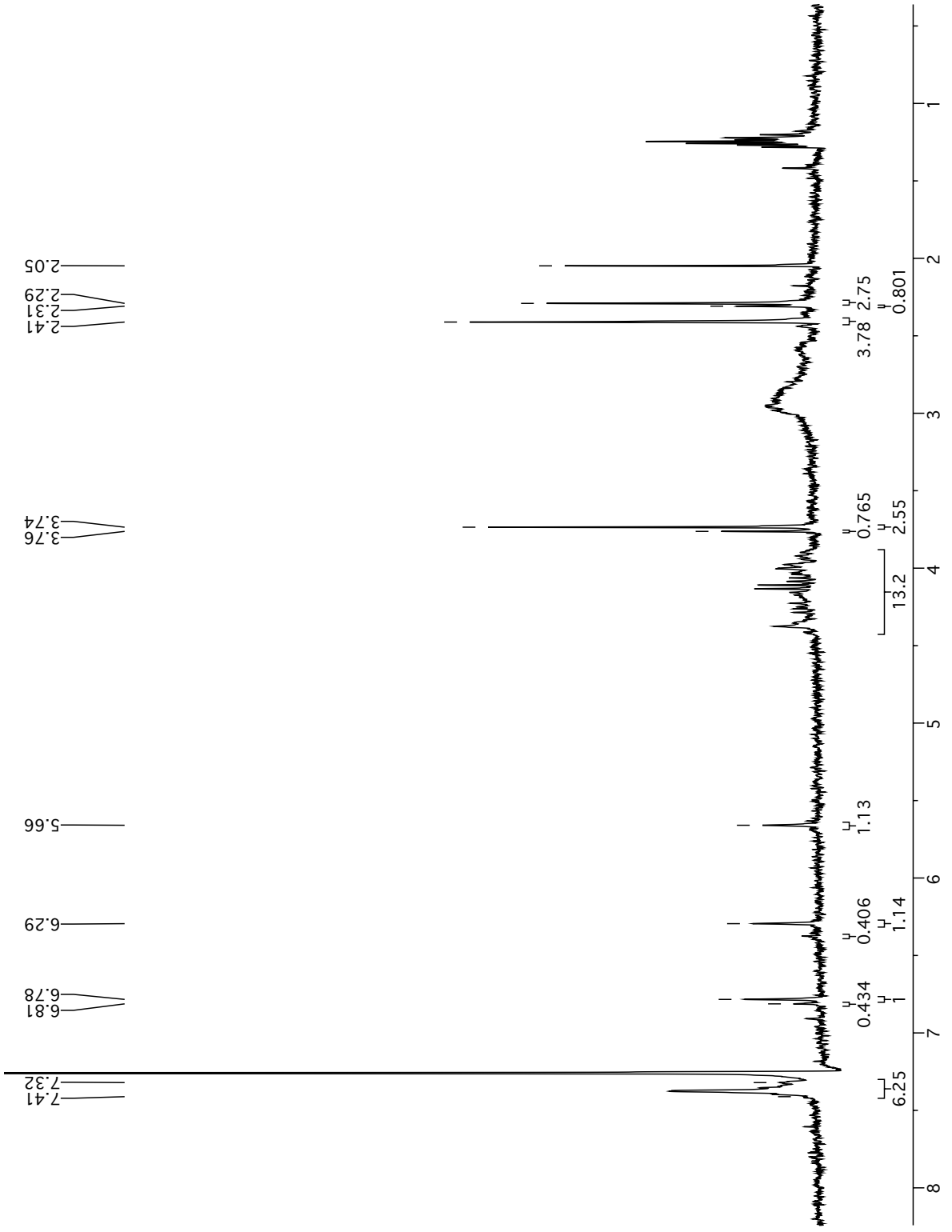
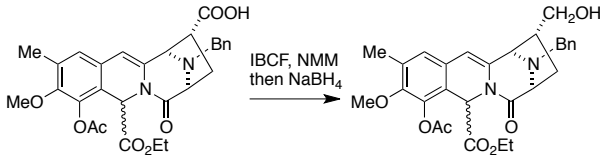


Figure 4.66. ^{1}H NMR spectrum of compounds **3.103a** and **3.103b** (300 MHz, $CDCl_3$)



3.103a/3.103b **3.104a/3.104b**

4.50 (8*S*,10*R*,11*S*)-ethyl 4-acetoxy-13-benzyl-10-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5-carboxylate (3.104a/3.104b)

To a solution of a mixture of compounds **3.103a** and **3.103b** (96 mg, 0.18 mmol) in THF (4 mL) at 0 °C was added NMM (27 μL, 0.22 mmol, 1.2 eq.), followed by isobutyl chloroformate (29 μL, 0.25 mmol, 1.4 eq.). The reaction was then warmed to room temperature and after 20 min was filtered through Celite® and added to an ice-cold suspension of $NaBH_4$ (68 mg, 1.8 mmol, 10 eq.) in water (4 mL). The reaction mixture was stirred at 0 °C for 20 minutes and then quenched with 2N HCl (2 mL). The resulting mixture was stirred for another 30 minutes at 0 °C and then diluted with water (25 mL), extracted with EtOAc (3×10 mL), washed with brine (25 mL), dried (Na_2SO_4) and concentrated under vacuum. The resulting residue was purified by flash chromatography (hexanes:EtOAc 1:1) to give a mixture of compounds **3.104a** and **3.104b** as a colorless oil (42 mg, 45%). R_f = 0.3 (hexanes:EtOAc 1:1); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.37-7.29 (m, 5H), 6.76 (s, 1H), 6.72 (s, 1H), 6.28 (s, 1H), 5.50 (s, 1H), 4.29-3.98 (m, 6H), 3.83-3.74 (m, 5H), 3.73 (s, 3H), 3.57 (dd, *J* = 10.2, 5.3 Hz, 1H), 2.41 (s, 3H), 2.27 (s, 3H), 1.24 (d, *J* = 7.1 Hz, 3H), (d, *J* = 7.1 Hz, 3H).

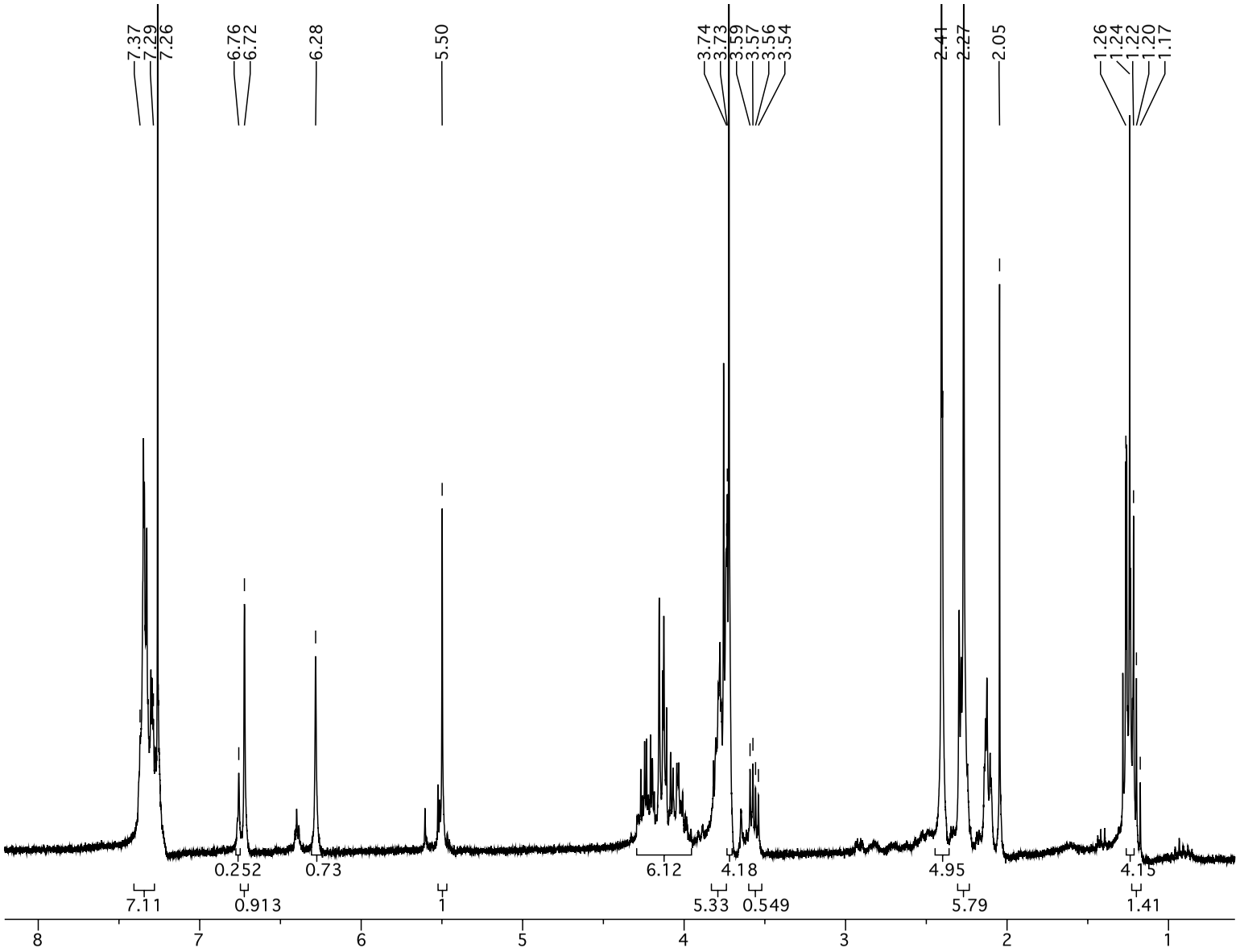
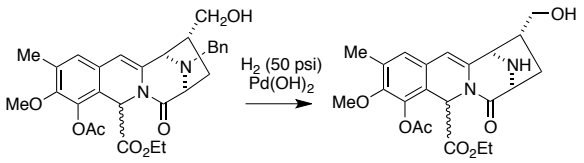


Figure 4.67. ^{1}H NMR spectrum of compounds **3.104a** and **3.104b** (300 MHz, $CDCl_3$)



3.104a/3.104b 3.105a/3.105b

4.51 (8*S*,10*R*,11*R*)-ethyl 4-acetoxy-10-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5-carboxylate (3.105a/3.105b)

To a solution of a mixture of compounds **3.104a** and **3.104b** (10 mg, 0.019 mmol) in MeOH (1 mL) in a 5 mL vial, was added Pearlman's catalyst (20% $Pd(OH)_2/C$). The vial was placed in a Fisher-Porter bottle, under Ar, the suspension was sparged with Ar for 5 minutes and the vessel was filled with hydrogen gas at 50 psi. The reaction was vigorously stirred overnight and then suspension was filtered through Celite®, using MeOH and EtOAc to transfer the material. The filtrate was concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 98:2) to afford a mixture of compounds **3.105a** and **3.105b** (6 mg, 75%) as a colorless oil. R_f = 0.2 ($CHCl_3$/MeOH 95:5); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.72 (s, 1H), 6.21 (s, 1H), 5.57 (s, 1H), 5.55 (s, 1H), 4.18-3.83 (m, 5H), 3.71 (s, 3H), 3.61-3.56 (m, 1H), 3.09-2.92 (m, 2H), 2.39 (s, 3H), 2.26 (s, 4H), 1.22-1.14 (m, 3H).

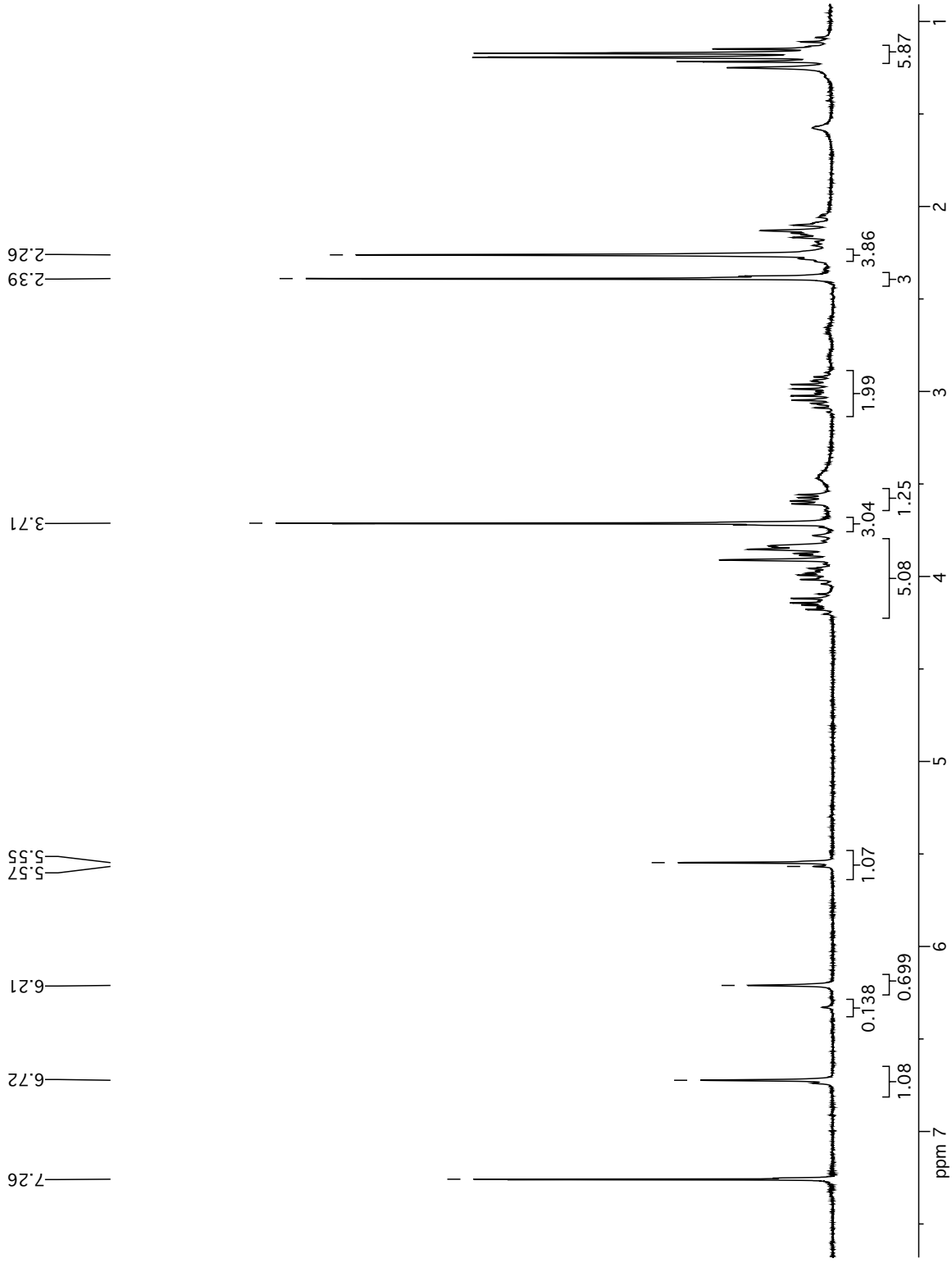
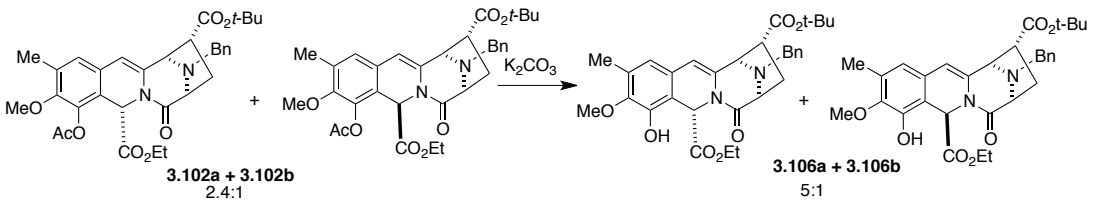


Figure 4.68. ^{1}H NMR spectrum of compounds **3.105a** and **3.105b** (300 MHz, $CDCl_3$)



4.52 (5*S*,8*S*,10*R*,11*S*)-10-*tert*-butyl 5-ethyl 13-benzyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (3.106a) and (5*R*,8*S*,10*R*,11*S*)-10-*tert*-butyl 5-ethyl 13-benzyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (3.106b)

To a stirred solution of a 2.6:1 mixture of compounds **3.102a** and **3.102b** (410 mg, 0.695 mmol, 1.0 eq.) in THF/MeOH 1:1 (14 mL, 0.05 M), under Ar, was added K_2CO_3 (192 mg, 1.39 mmol, 2.0 eq.). The suspension was stirred for 2.5 h, the solvent was evaporated and the residue was partitioned between phosphate buffer (0.1 M, pH = 7.5, 50 mL) and EtOAc (33 mL). The aqueous phase was extracted with EtOAc (2×33 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 5:1 mixture of the title compounds **3.106a** and **3.106b** (255 mg, 67%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.24 (m, 5H), 6.76 (s, 1H), 6.63 (s, 1H, minor diastereomer), 6.49 (s, 1H, minor diastereomer), 6.43 (s, 1H, minor diastereomer), 6.42 (s, 1H), 6.39 (s, 5H), 5.46 (s, 1H, minor diastereomer), 5.45 (s, 1H. minor diastereomer), 4.24 (q, *J* = 7.1 Hz, 2H), 4.19-3.9 (m, 5H), 4.07 (s, 1H), 3.86 (d, *J* = 7.5 Hz, 1H), 3.84 (s, 1H, minor diastereomer), 3.82 (s, 3H), 3.31 (dd, *J* = 9.8, 6.0 Hz, 1H, minor diastereomer), 2.79 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.74-2.66 (m, 1H), 2.46 (dd, *J* = 13.0, 9.9 Hz, 1H,

minor diastereomer), 2.26 (s, 3H, minor diastereomer), 2.24 (s, 3H), 2.13 (dd, J = 13.4, 9.6 Hz, 6H), 1.46 (s, 9H, minor diastereomer), 1.42 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H, minor diastereomer); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.4, 171.9, 170.7, 170.6, 170.4, 168.9, 146.9, 146.8, 146.2, 138.5, 138.0, 136.1, 134.2, 131.9, 131.7, 128.5, 127.4, 127.3, 126.6, 126.0, 119.1, 119.1, 110.8, 103.4, 81.3, 64.3, 62.7, 62.6, 60.8, 60.8, 52.2, 52.2, 52.1, 51.5, 50.8, 48.2, 32.1, 28.2, 28.1, 22.8, 15.9, 14.3; R_f (SiO_2, hexanes/EtOAc 2:1) 0.45; $[\alpha]_D^{25}$ = -73.6 ° (c = 0.282, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3374 (br), 2980, 2938, 1736, 1689, 1647, 1154 cm^{-1}; HRMS (MH^+), found 549.2606. $C_{31}H_{37}N_2O_7$ requires 549.2601.

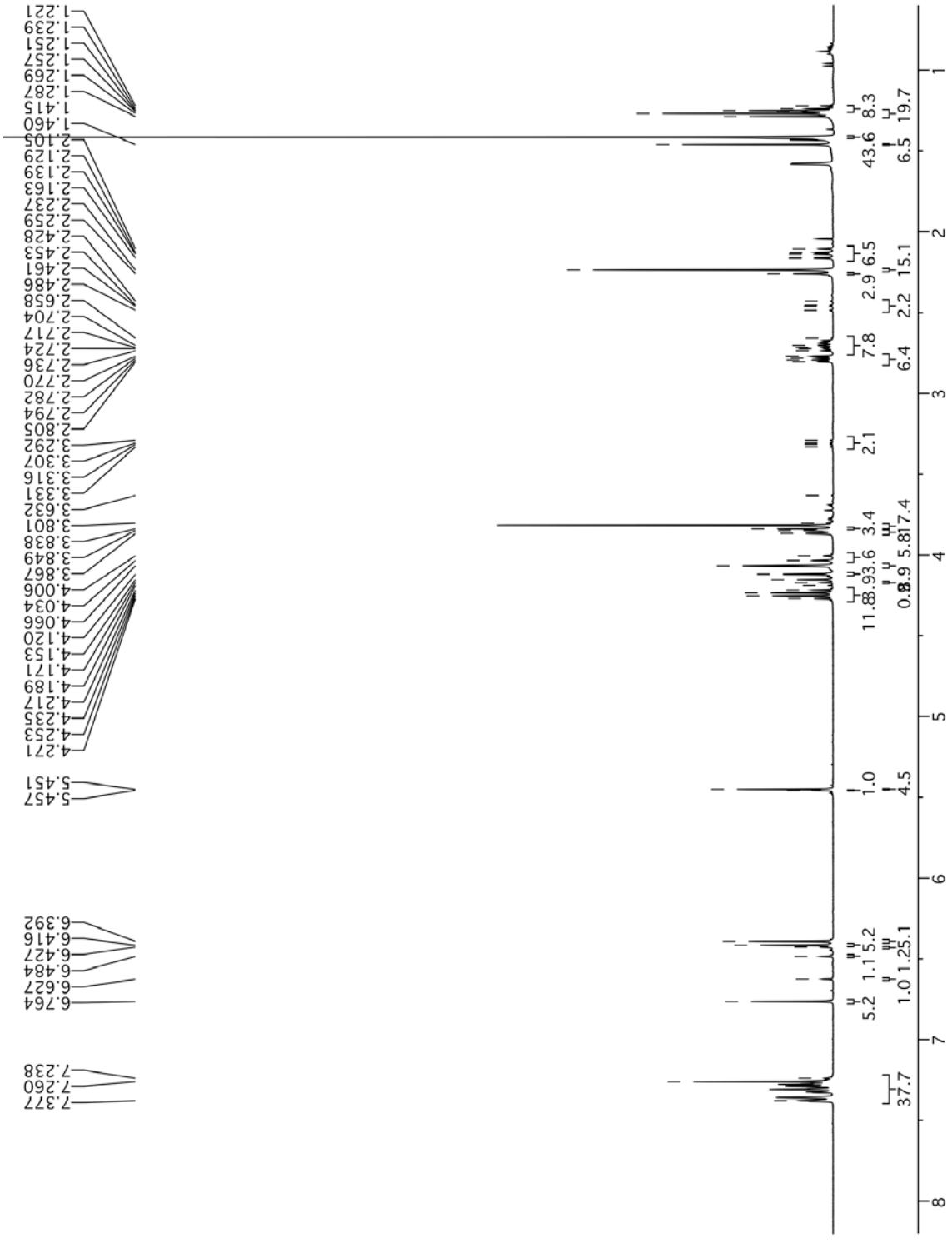


Figure 4.69. ^{1}H NMR spectrum of compounds **3.106a** and **3.106b** (400 MHz, $CDCl_3$)

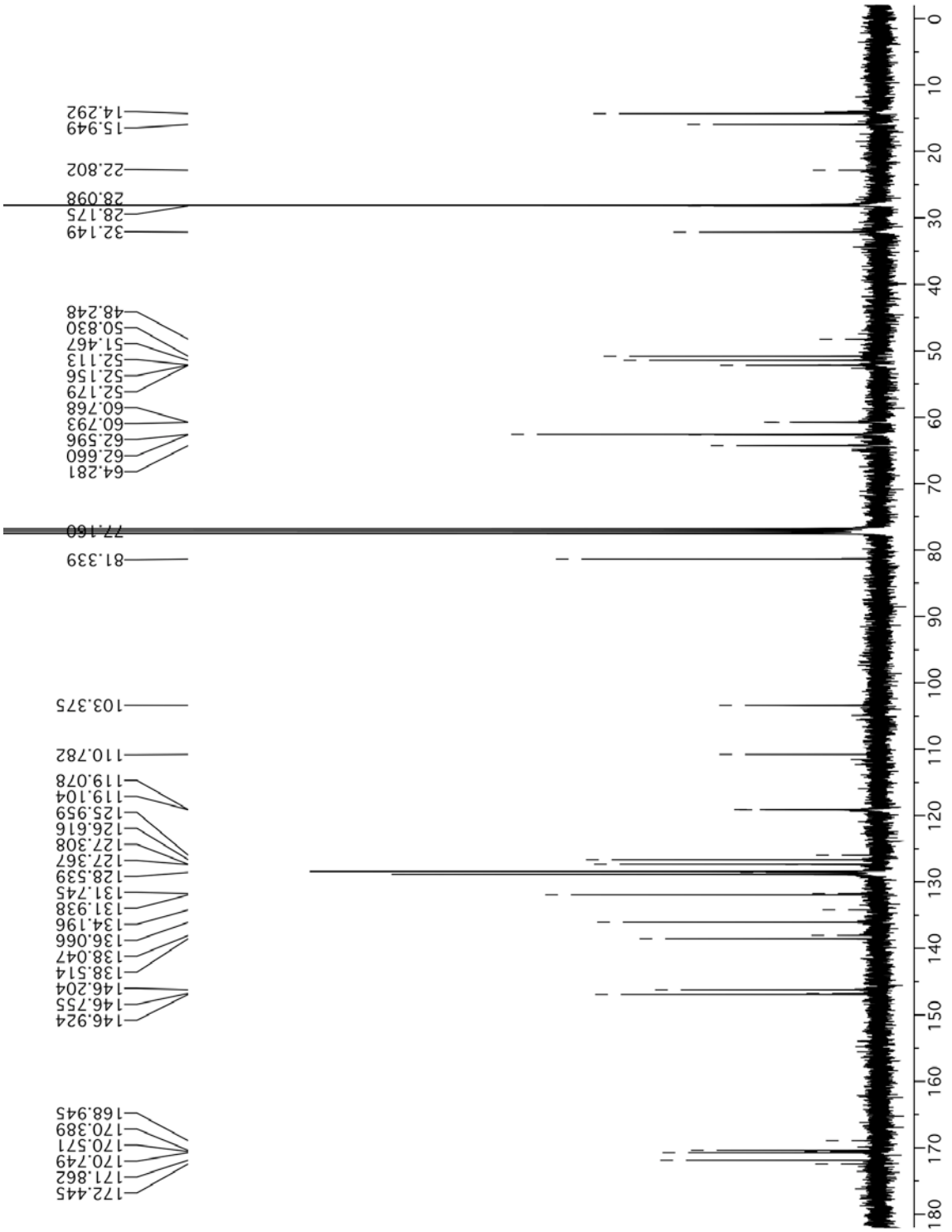
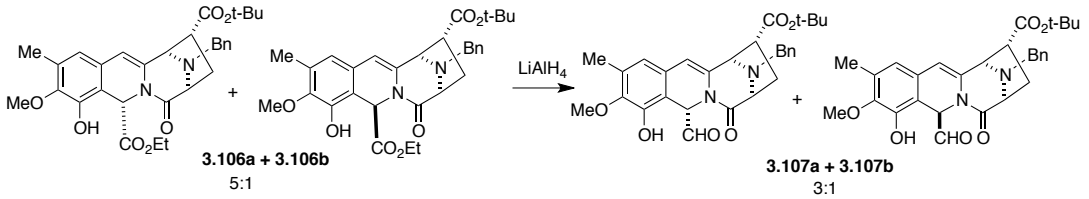


Figure 4.70. ^{13}C NMR spectrum of compounds **3.106a** and **3.106b** (101 MHz, $CDCl_3$)



4.53 (5S,8S,10R,11S)-*tert*-butyl 13-benzyl-5-formyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epimino-azepino[1,2-b]isoquinoline-10-carboxylate (3.107a) and *(5R,8S,10R,11S)-tert*-butyl 13-benzyl-5-formyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (3.107b)

A solution of $LiAlH_4$ in THF (1.0 M, 447 μL, 0.447 mmol, 1.0 eq.) was added dropwise to a solution of a 5:1 mixture of compounds **3.106a** and **3.106b** (245 mg, 0.447 mmol, 1.0 eq.) in THF (9 mL, 0.05 M), under Ar, at -10 °C. The solution was stirred for 10 minutes at this temperature, quenched with EtOAc (12 mL) and sat. aq. Rochelle's salt (12 mL) and allowed to warm to RT. The flask was covered with aluminum foil and stirred overnight under a stream of Ar. The solution was diluted with phosphate buffer (0.1 M, pH = 7.5, 50 mL), the phases were separated and aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 3:1 mixture of the title compounds **3.107a** and **3.107b** (124 mg, 55%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.48 (s, 1H), 9.38 (s, 1H, minor diastereomer), 7.41-7.23 (m, 5H), 6.58 (s, 1H), 6.57 (s, 1H, minor diastereomer), 6.43 (s, 1H, minor diastereomer), 6.41 (s, 1H), 6.18 (s, 1H, minor diastereomer), 6.17 (s, 1H, minor diastereomer), 4.25 (1/2 AB, *J* = 13.5 Hz, 1H), 4.18 (1/2 AB, *J* = 13.5 Hz, 1H), 4.07 (s, 1H), 4.00 (s, 1H, minor diastereomer), 3.83 (s, 3H, minor diastereomer),

3.81 (s, 3H, minor diastereomer), 3.40 (dd, J = 9.7, 6.0 Hz, 1H, minor diastereomer), 2.81 (dd, J = 9.5, 4.7 Hz, 1H), 2.73-2.67 (m, 1H), 2.59 (dd, J = 13.0, 9.8 Hz, 1H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.15 (dd, J = 13.4, 9.6 Hz, 1H), 1.48 (s, 9H, minor diastereomer), 1.46 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.1, 191.3, 172.5, 171.9, 170.1, 145.7, 144.6, 138.6, 138.0, 136.6, 135.3, 131.5, 128.8, 128.4, 127.5, 127.2, 119.4, 119.2, 107.3, 104.0, 102.7, 102.6, 81.4, 64.1, 64.0, 62.9, 62.8, 61.2, 61.1, 58.6, 58.5, 51.6, 50.8, 48.8, 34.7, 32.4, 31.7, 29.8, 28.1, 22.8, 16.0, 14.3; Rf (SiO_2, hexanes/EtOAc 2:1) 0.42; $[\alpha]_D^{25}$ = -64.8 ° (c = 0.250, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3331 (br), 2977, 2935, 1733, 1679, 1642, 1154 cm^{-1}; HRMS (MH^+), found 505.2345. $C_{29}H_{33}N_2O_6$ requires 505.2339.

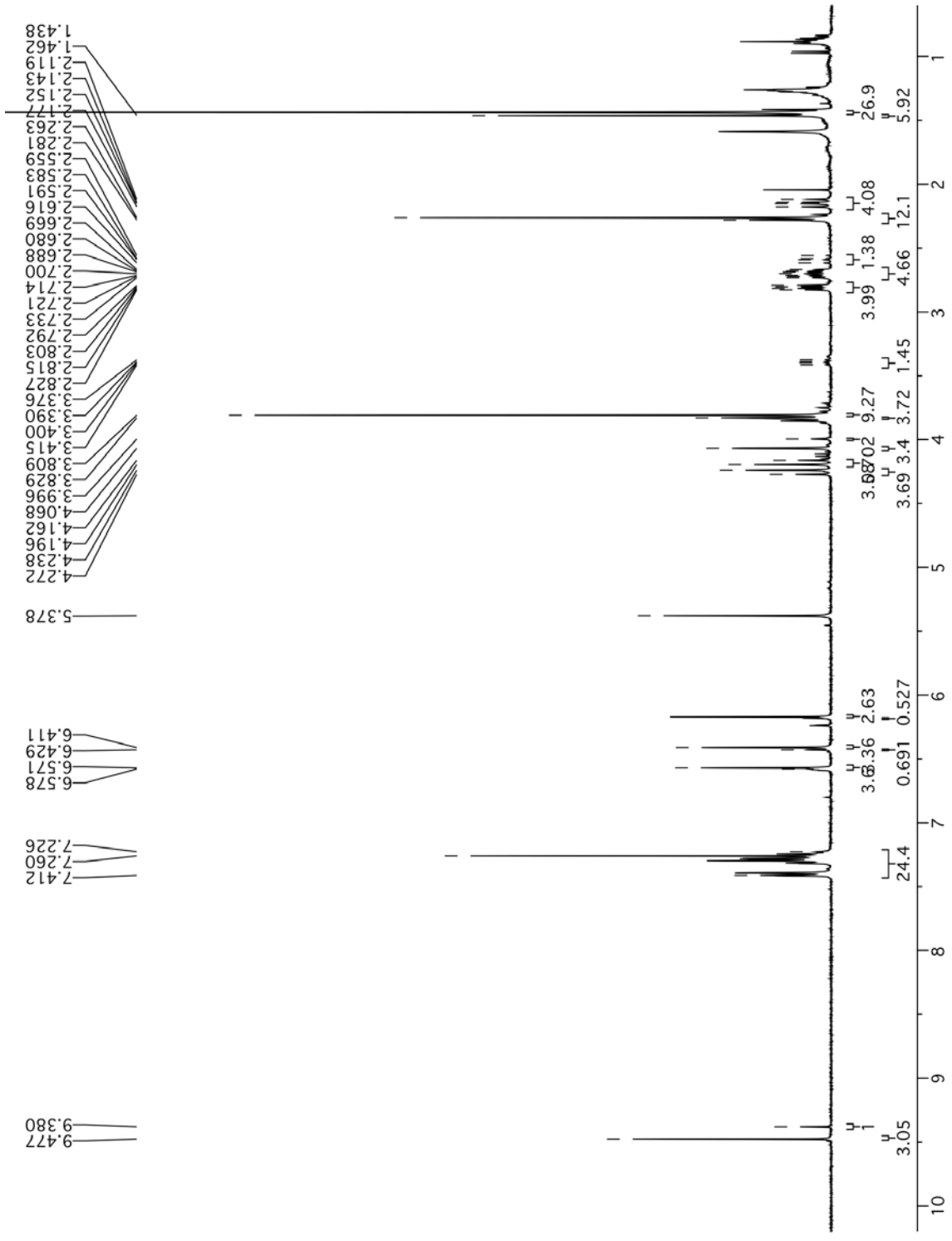


Figure 4.71. ^{1}H NMR spectrum of compound **3.107a** and **3.107b** (400 MHz, $CDCl_3$)

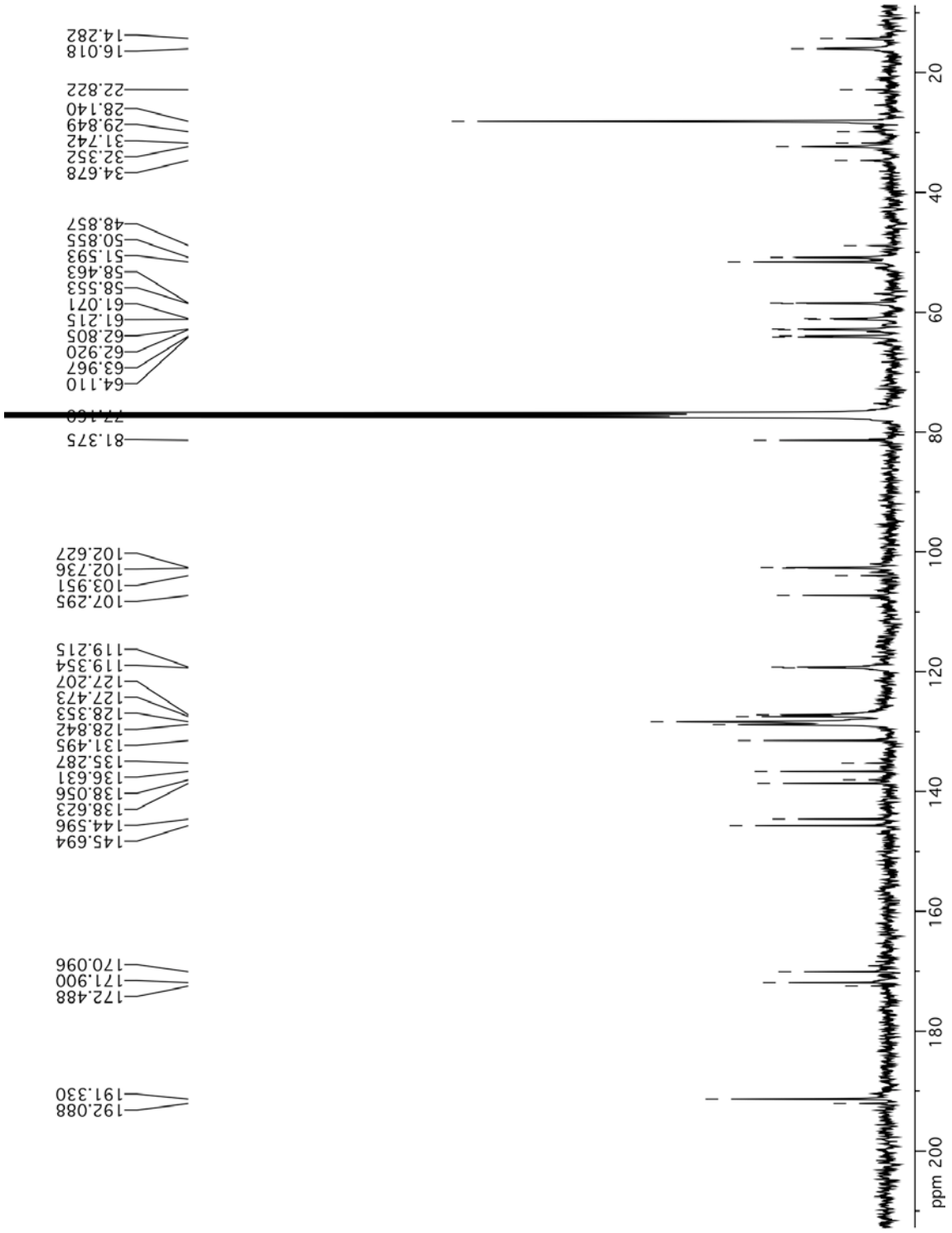
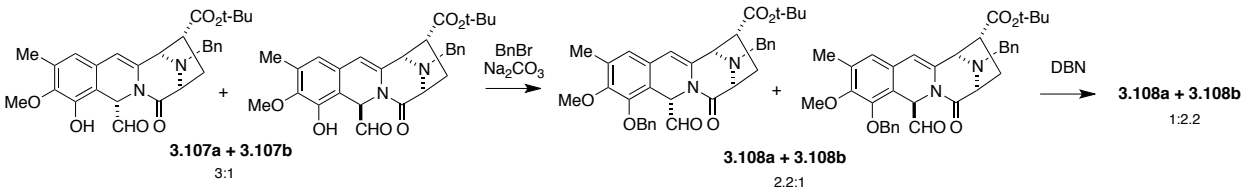


Figure 4.72. ^{13}C NMR spectrum of compound **3.107a** and **3.107b** (101 MHz, $CDCl_3$)



4.54 (5*S*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (3.108a) and (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (5R,8S,10R,11S)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (3.108b)

To a stirred solution of a 3:1 mixture of compounds **3.107a** and **3.107b** (115 mg, 0.228 mmol, 1.0 eq.) and benzyl bromide (108 μL, 0.912 mmol, 4.0 eq.) in DMF (7.6 mL, 0.03 M), under Ar, were added tetrabutylammonium iodide (9.0 mg, 0.023 mmol, 0.10 eq.) and finely ground anhydrous Na_2CO_3 (241 mg, 2.28 mmol, 10 eq.). The mixture was vigorously stirred for 2h and diluted with water (25 mL) and phosphate buffer (0.1 M, pH = 7.5, 25 mL). The aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 6:1, 4:1) to afford a 2.2:1 mixture of compounds **3.108a** and **3.108b** (88 mg, 65%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.32 (s, 1H), 9.19 (s, 1H minor diastereomer), 7.48-7.22 (m, 10H), 6.63 (s, 1H, minor diastereomer), 6.62 (s, 1H), 6.38 (s, 1H, minor diastereomer), 6.36 (s, 1H), 5.37 (s, 1H), 5.36 (s, minor diastereomer), 5.28 (1/2 AB, *J* =

11.1 Hz, 1H, minor diastereomer), 5.26 (1/2 AB, *J* = 11.1 Hz, 2H), 5.20 (1/2 AB, *J* = 11.1 Hz, 1H, minor diastereomer), 5.14 (1/2 AB, *J* = 11.1 Hz, 1H), 4.20 (1/2 AB, *J* = 13.5 Hz, 1H), 4.14 (1/2 AB, *J* = 13.5 Hz, 1H), 4.05 (s, 1H), 3.97 (s, 1H, minor diastereomer), 3.86 (s, 3H, minor diastereomer), 3.84 (s, 3H), 3.80 (1/2 AB, *J* = 13.5 Hz, 1H) 3.79 (d, *J* = 7.4 Hz, 1H), 3.75 (d, *J* = 6.9 Hz, minor diastereomer), 3.68 (1/2 AB, *J* = 13.5 Hz, 1H, minor diastereomer), 3.37 (dd, *J* = 9.7, 6.1 Hz, 1H, minor diastereomer), 2.78 (dd, *J* = 9.6, 4.7 Hz, 1H), 2.71-2.64 (m, 2H), 2.53 (1/2 ABX, *J* = 13.1, 9.9 Hz, 1H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.10 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.45 (s, 9H minor diastereomer), 1.44 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.5, 191.7, 171.9, 169.8, 168.8, 150.4, 150.3, 148.3, 148.1, 138.6, 138.1, 136.9, 136.9, 136.6, 135.3, 133.7, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 127.4, 127.2, 126.9, 123.1, 122.8, 115.0, 114.6, 103.9, 102.5, 81.4, 81.2, 75.0, 75.0, 65.0, 63.9, 63.1, 62.8, 60.5, 58.8, 57.3, 52.8, 51.6, 48.8, 34.7, 32.2, 28.2, 16.0, 16.0; R_f (SiO_2, hexanes/EtOAc 4:1) 0.45; $[\alpha]_D^{25}$ = -64 ° (c = 0.32, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3030, 2976, 2934, 1733, 1688, 1646, 1154 cm^{-1}; HRMS (MH^+), found 595.2801. $C_{36}H_{39}N_2O_6$ requires 595.2808.

To a stirred solution of a 2.2:1 mixture of compounds **3.108a** and **3.108b** (88 mg, 0.15 mmol, 1.0 eq.) in THF (2 mL, 0.08 M), under Ar, was added DBN (19 μL, 0.15 mmol, 1.0 eq.). The mixture was stirred for 30 minutes and then diluted with phosphate buffer (0.1 M, pH = 7.5, 50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was dissolved in the minimal amount of EtOAc purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 1:2.2 mixture of compounds **3.108a** and **3.108b** (64 mg, 72%) as a pale yellow oil, which was used in the next

step without further purification. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.32 (s, 1H, minor diastereomer), 9.19 (s, 1H), 7.48-7.24 (m, 10H), 6.63 (s, 1H), 6.62 (s, 1H, minor diastereomer), 6.38 (s, 1H), 6.36 (s, 1H, minor diastereomer), 5.37 (s, 1H, minor diastereomer), 5.36 (s, 1H), 5.28 (1/2 AB, *J* = 11.1 Hz, 1H), 5.26 (1/2 AB, *J* = 11.1 Hz, 1H, minor diastereomer), 5.19 (1/2 AB, *J* = 11.1 Hz, 1H), 5.13 (1/2 AB, *J* = 11.2 Hz, 2H, minor diastereomer), 4.20 (1/2 AB, *J* = 13.4 Hz, 1H, minor diastereomer), 4.14 (1/2 AB, *J* = 13.5 Hz, 1H minor diastereomer), 4.05 (s, 1H, minor diastereomer), 3.97 (s, 1H), 3.86 (s, 3H, minor diastereomer), 3.84 (s, 3H, minor diastereomer), 3.81 (1/2 AB, *J* = 13.6 Hz, 1H), 3.79 (d, *J* = 6.2 Hz, 4H), 3.75 (d, *J* = 6.6 Hz, 3H), 3.68 (1/2 AB, *J* = 13.4 Hz, 3H), 3.37 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.78 (dd, *J* = 9.5, 4.7 Hz, 1H, minor diastereomer), 2.71-2.65 (m, 2H), 2.53 (1/2 ABX, *J* = 13.0, 9.9 Hz, 3H), 2.28 (s, 3H), 2.26 (s, 3H, minor diastereomer), 2.10 (dd, *J* = 13.4, 9.5 Hz, 1H, minor diastereomer), 1.45 (s, 9H), 1.44 (s, 9H, minor diastereomer); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.5, 191.7, 172.5, 171.9, 168.8, 150.4, 148.1, 138.0, 136.9, 135.3, 133.7, 128.9, 128.8, 128.8, 128.6, 128.5, 128.4, 128.3, 127.4, 127.2, 126.9, 123.1, 122.8, 115.0, 114.6, 103.9, 102.5, 81.4, 81.2, 75.0, 75.0, 65.0, 63.9, 63.1, 62.7, 60.4, 58.8, 57.3, 52.7, 51.6, 50.9, 48.8, 34.7, 32.2, 28.2, 28.1, 16.0, 16.0; R_f (SiO_2, hexanes/EtOAc); $[\alpha]_D^{25}$ = +27 ° (c = 0.22, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3029, 2969, 2935, 1732, 1688, 1647, 1154 cm^{-1}; HRMS (MH^+), 595.2789. $C_{36}H_{39}N_2O_6$ requires 595.2808.

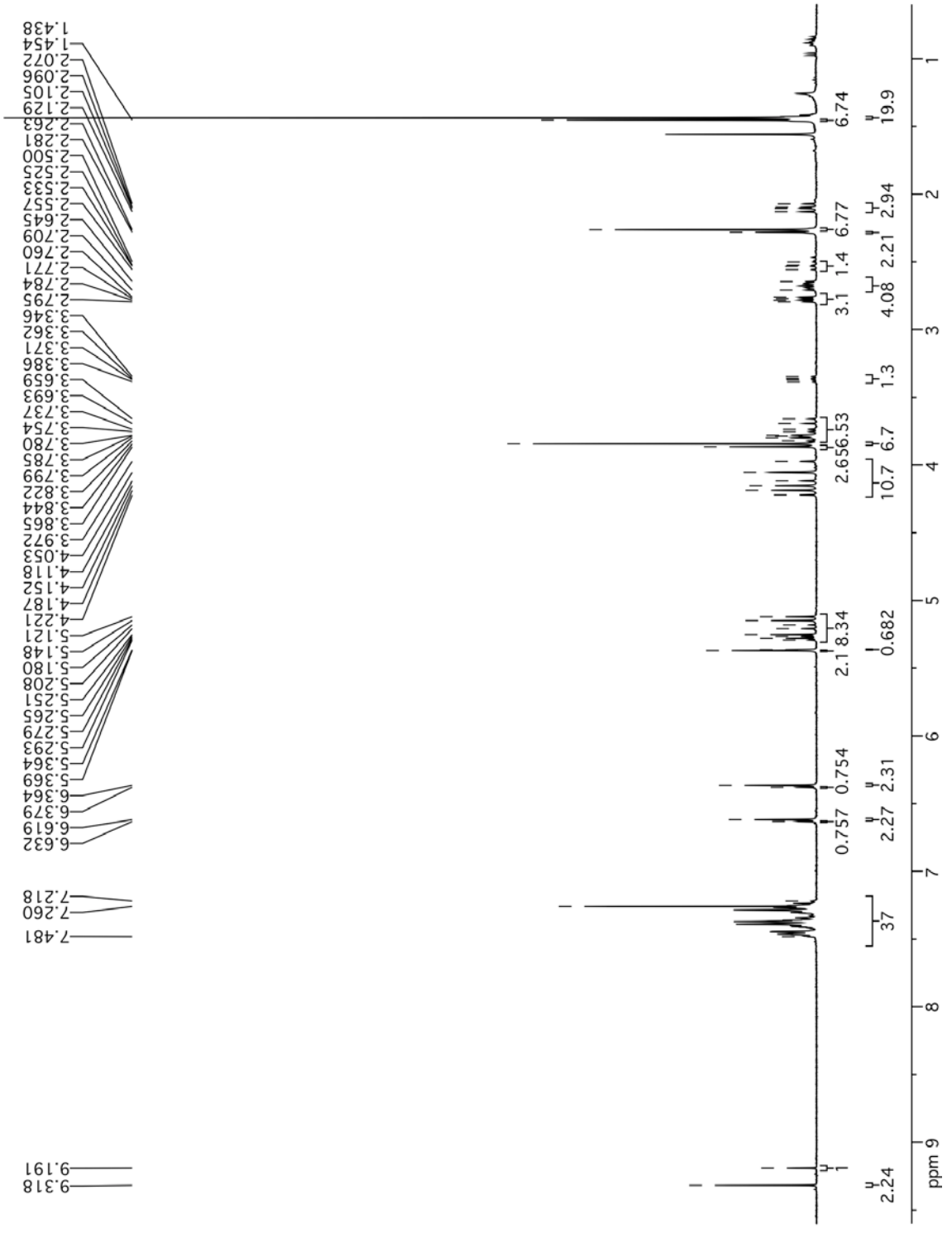


Figure 4.73. ^{1}H NMR spectrum of a 2.2:1 mixture of compounds **3.108a** and **3.108b** (400 MHz, $CDCl_3$)

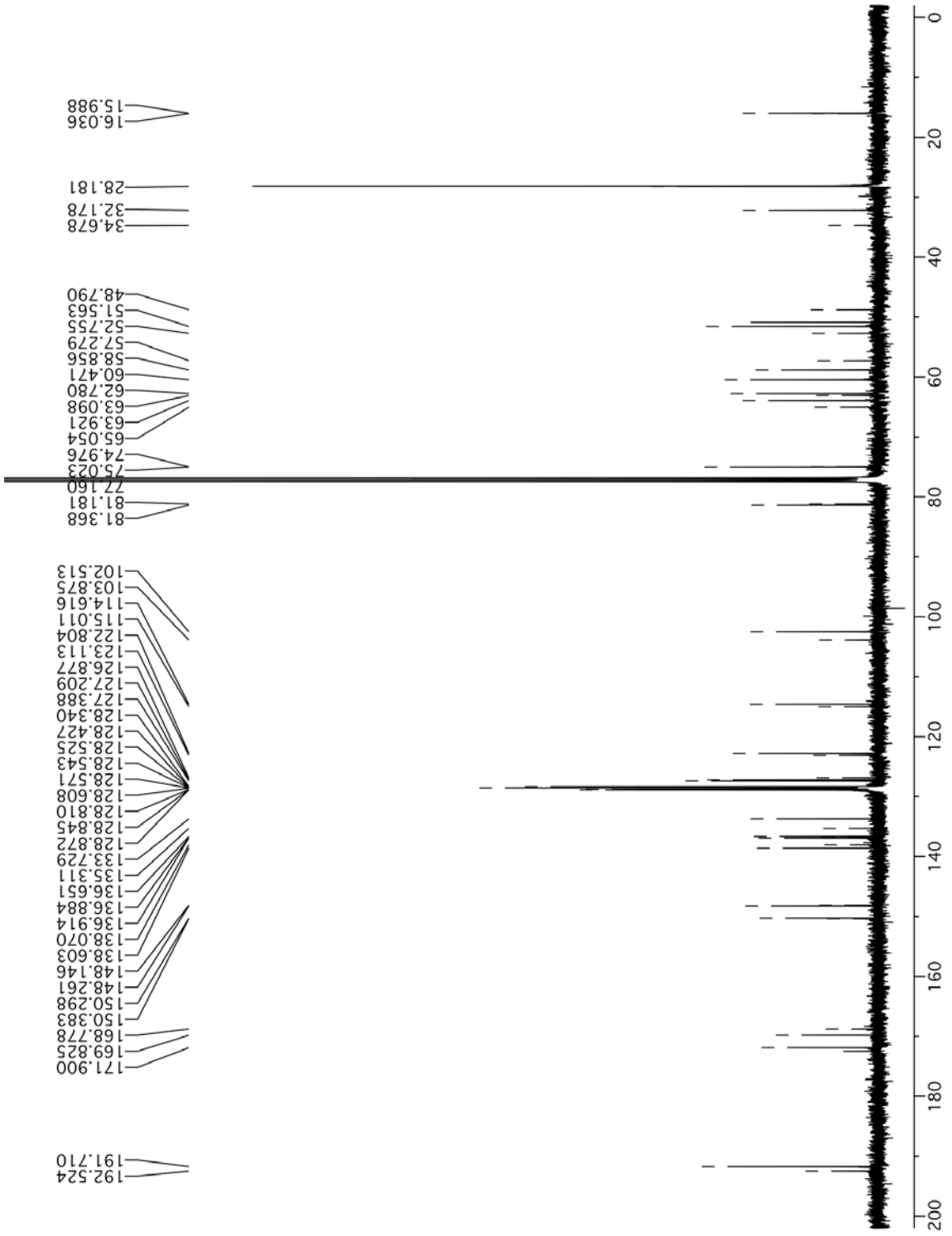


Figure 4.74. ^{13}C NMR spectrum of a 2.2:1 mixture of compounds **3.108a** and **3.108b** (101 MHz, $CDCl_3$)

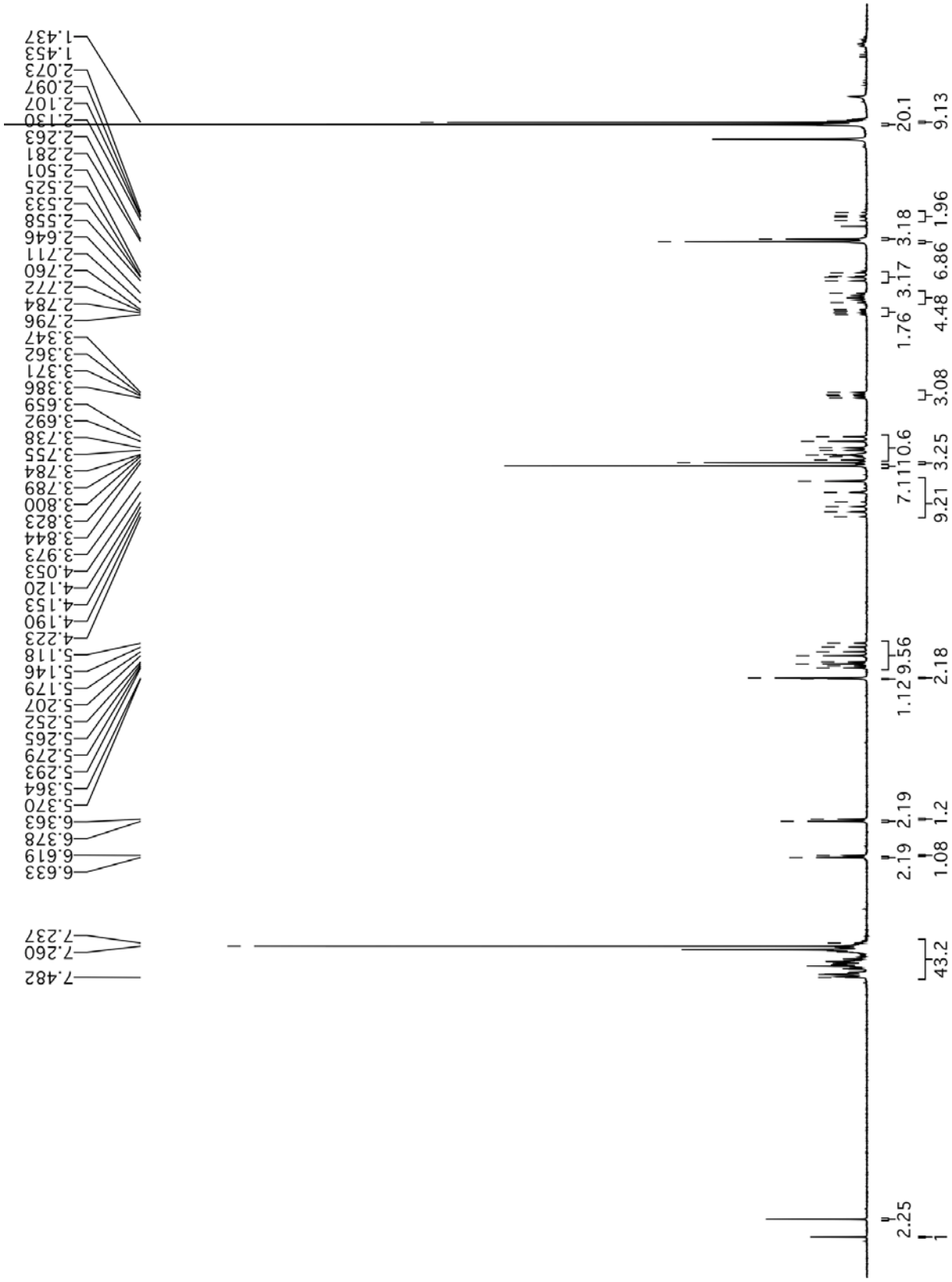


Figure 4.75. ^{1}H NMR spectrum of a 1:2.2 mixture of compounds **3.108a** and **3.108b** (400 MHz, $CDCl_3$)

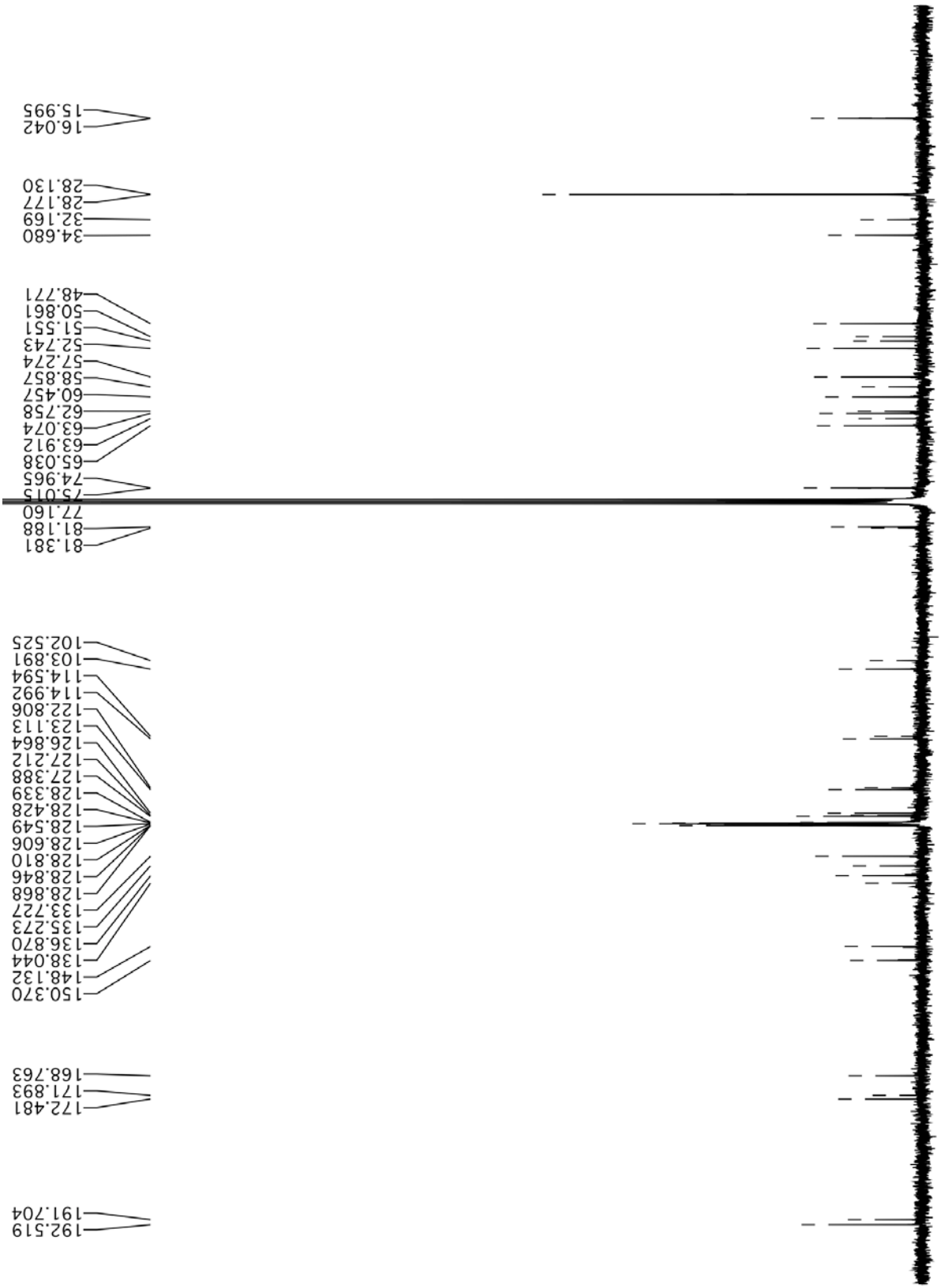
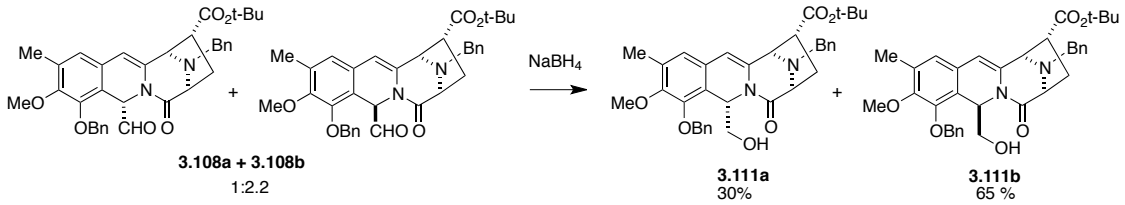


Figure 4.76. ^{13}C NMR spectrum of a 1:2.2 mixture of compounds **3.108a** and **3.108b** (101 MHz, $CDCl_3$)



4.55 (5*S*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (3.111a) and (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-b]isoquinoline-10-carboxylate (3.111b)

To a stirred solution of a mixture of compounds **3.108a** and **3.108b** (60 mg, 0.10 mmol) in EtOH (5 mL, 0.20 M), at 0 °C, under Ar, was added $NaBH_4$ (30 mg, 0.80 mmol 8.0 eq.). The reaction was stirred at RT for 2 hours, quenched with 1N HCl (2.4 mL, 2.40 mmol, 24 eq.) and diluted with phosphate buffer (0.1 M, pH = 7.5, 50 mL). The aqueous phase was extracted with EtOAc (3×25 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford the title compounds **3.111a** (18 mg, 30%) as a colorless oil and compound **3.111b** (38 mg, 65%) as a colorless oil. Compound **3.111a**: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.50-7.22 (m, 10H), 6.62 (s, 1H), 6.14 (t, *J* = 6.1 Hz, 1H), 5.48 (s, 1H), 5.18 (1/2 AB, *J* = 11.1 Hz, 1H), 5.09 (1/2 AB, *J* = 11.1 Hz, 1H), 4.10 (s, 1H), 3.97 (1/2 AB, *J* = 13.3 Hz, 1H), 3.87 (1/2 AB, *J* = 13.3 Hz, 1H), 3.79 (d, *J* = 7.7 Hz, 1H), 3.73 (s, 1H), 2.69 (ddt, *J* = 27.0, 9.0, 4.6 Hz, 2H), 2.25 (s, 3H), 2.06 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.90 (br t, 6.0 Hz, 1H), 1.44 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 171.9, 171.7, 150.5, 148.2, 138.3, 137.2, 135.6, 132.6, 128.7, 128.5, 128.4, 128.4, 127.6, 127.3, 122.1, 120.1, 103.7, 81.3, 75.1,

65.4, 64.2, 62.7, 60.4, 51.7, 51.3, 50.7, 31.6, 28.1, 28.1, 15.9, 14.3; R_f (SiO_2, hexanes/EtOAc 4:1) 0.12; $[\alpha]_D^{25}$ = -60.0 ° (c = 0.895, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3447 (br), 3063, 3030, 2934, 2870, 1730, 1676, 1636, 1154 cm^{-1}; HRMS (MH^+), found 597.2971. $C_{36}H_{41}N_2O_6$ requires 597.2965. Compound **3.111b**: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.62 (s, 1H), 6.09 (dd, *J* = 8.4, 4.4 Hz, 1H), 5.45 (s, 1H), 5.17 (1/2 AB, *J* = 11.1 Hz, 1H), 5.14 (1/2 AB, *J* = 11.1 Hz, 1H), 3.95 (s, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 13.5 Hz, 1H), 3.73 (d, *J* = 6.6 Hz, 1H), 3.63 (d, *J* = 13.4 Hz, 1H), 3.63-3.50 (m, 1H), 3.15 (dd, *J* = 9.8, 6.1 Hz, 1H), 2.63 (dt, *J* = 12.8, 6.5 Hz, 1H), 2.45 (dd, *J* = 13.0, 9.8 Hz, 1H), 1.77-1.74 (br m, 1H), 1.45 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.3, 170.4, 150.6, 147.9, 138.1, 137.2, 134.0, 132.5, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 127.3, 126.5, 122.8, 122.7, 120.6, 105.3, 105.3, 81.3, 75.0, 65.5, 65.5, 63.1, 63.0, 60.4, 52.7, 49.4, 49.4, 48.4, 34.8, 28.2, 16.0, 16.0; R_f (SiO_2, hexanes/EtOAc 4:1) 0.10; $[\alpha]_D^{25}$ = +64 ° (c = 0.31, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3444 (br), 3062, 3029, 2970, 2927, 1729, 1682, 1639, 1154 cm^{-1}; HRMS (MH^+), found 597.2974. $C_{36}H_{41}N_2O_6$ requires 597.2965.

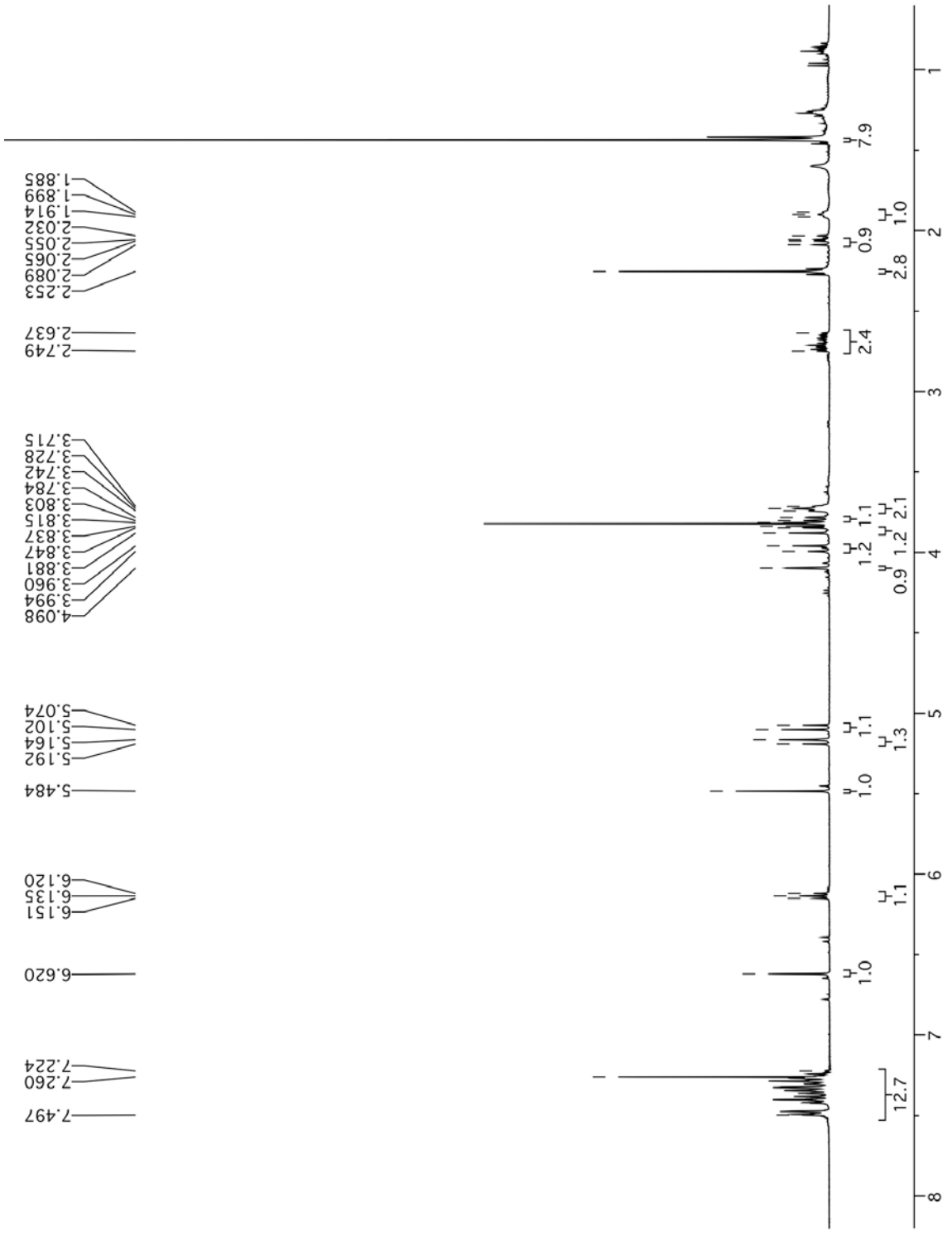


Figure 4.77. ^{1}H NMR spectrum of compound **3.111a** (400 MHz, $CDCl_3$)

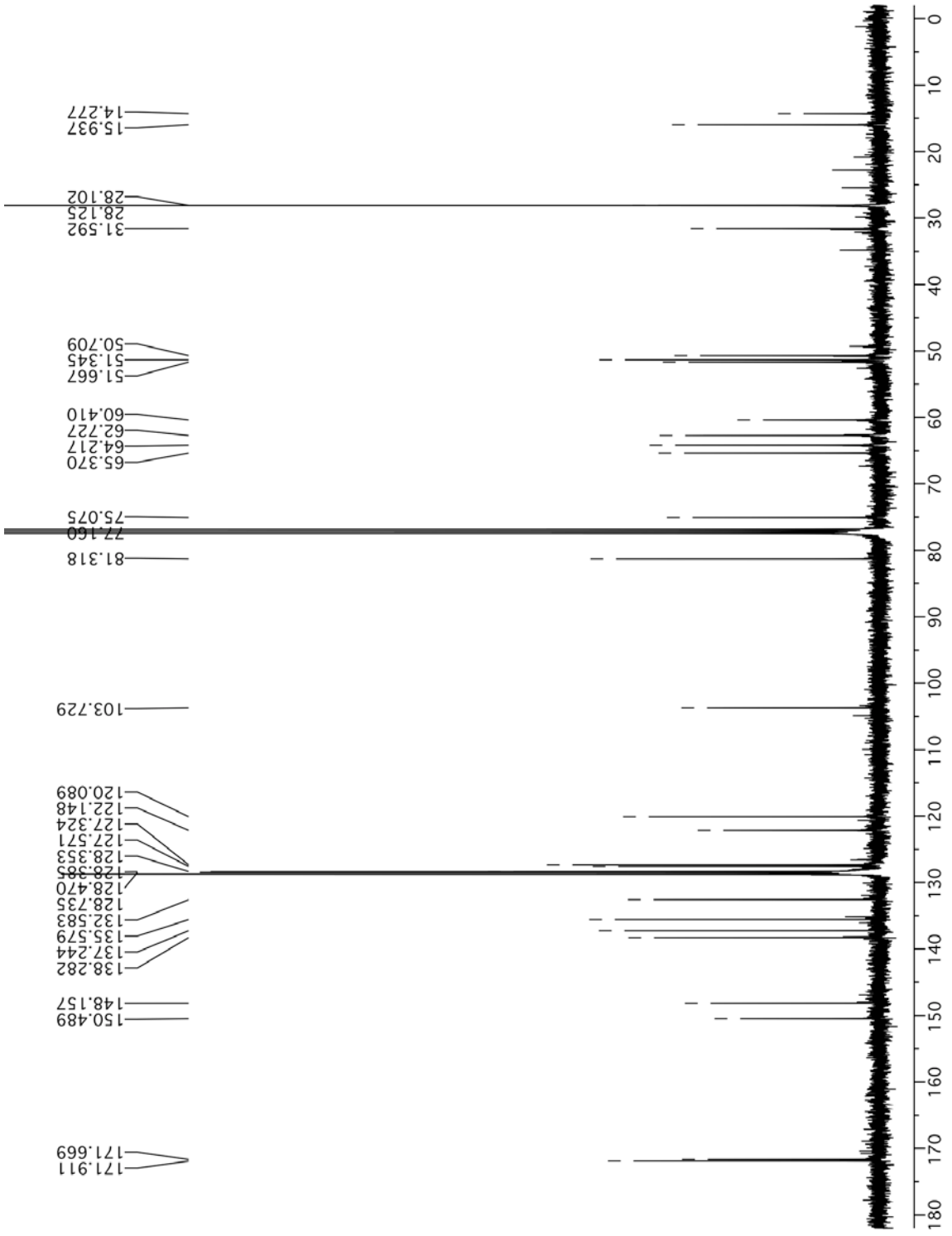


Figure 4.78. ^{13}C NMR spectrum of compound **3.111a** (101 MHz, $CDCl_3$)

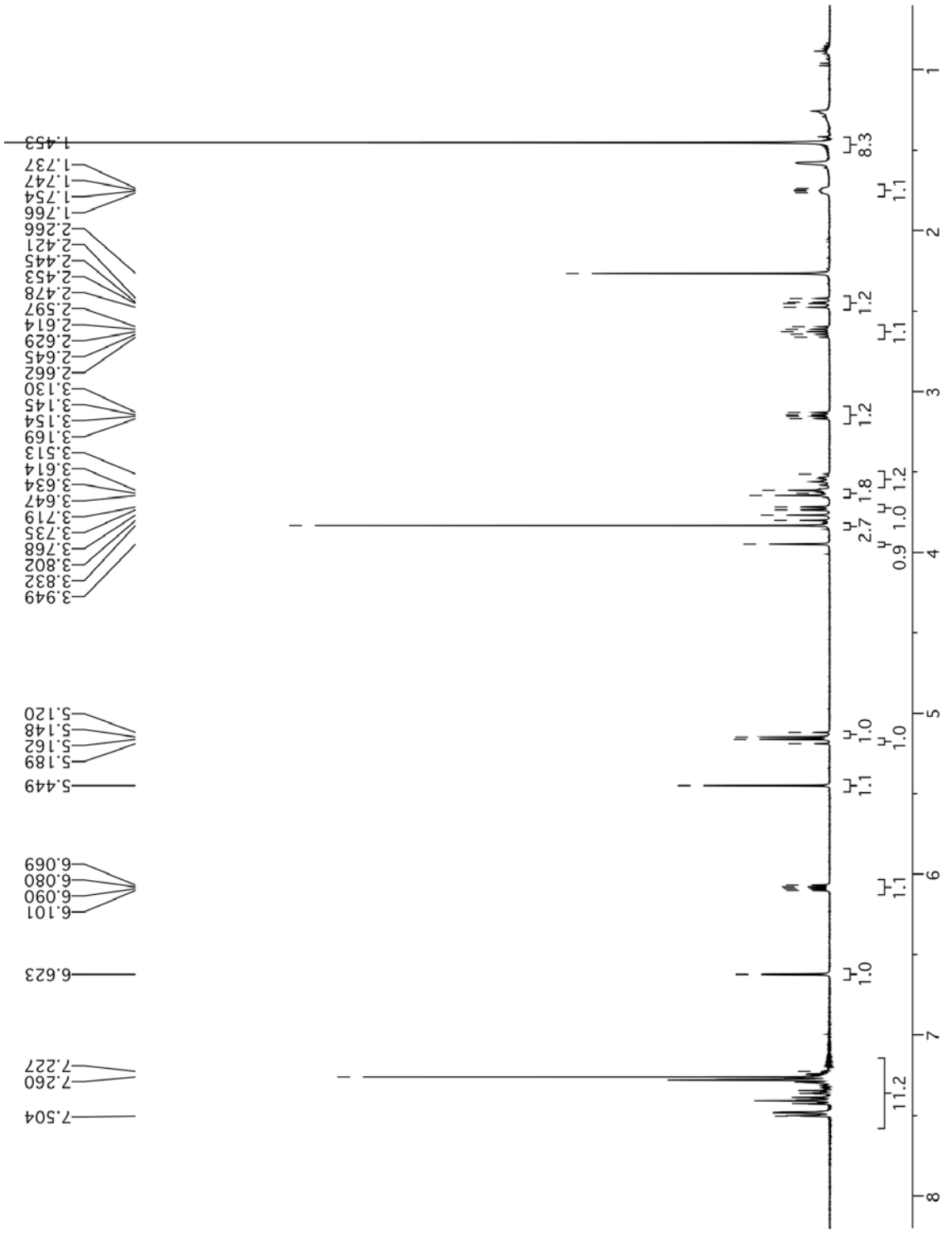


Figure 4.79. ^{1}H NMR spectrum of compound **3.111b** (400 MHz, $CDCl_3$)

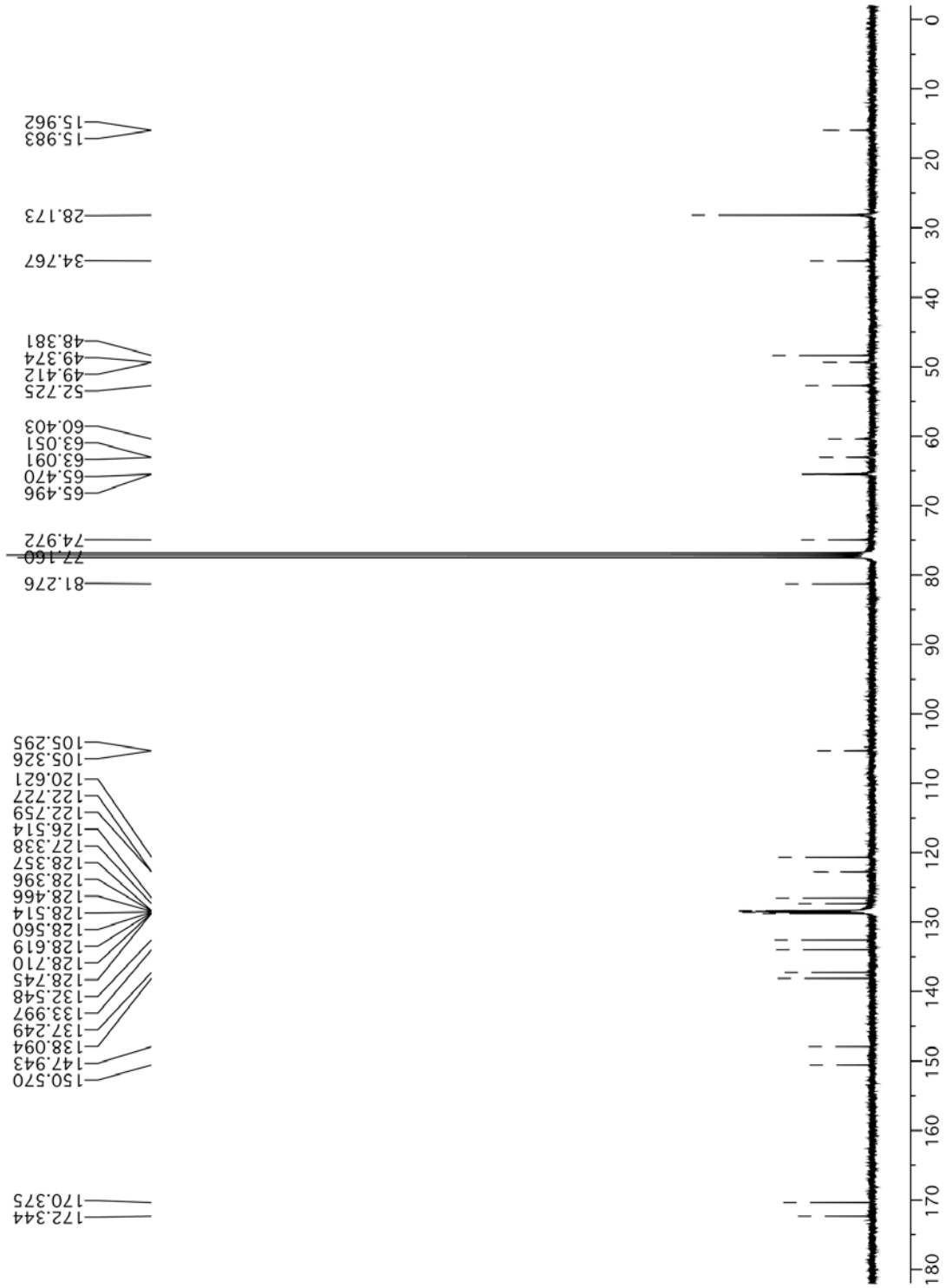
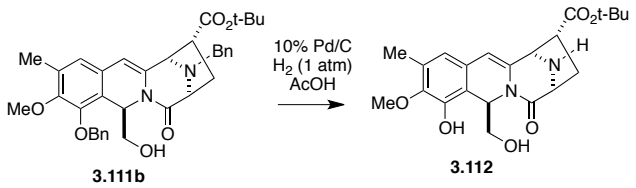


Figure 4.80. ^{13}C NMR spectrum of compound **3.111b** (101 MHz, $CDCl_3$)



4.56 (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epimino-azepino[1,2-*b*]isoquinoline-10-carboxylate (3.112)

A solution of compound **3.111b** (7.0 mg, 0.012 mmol) in glacial acetic acid (1 mL) and 10% Pd/C (7 mg) were placed in round bottom flask and sparged with Ar for 5 minutes. The vessel was evacuated and filled with hydrogen three times. The reaction was vigorously stirred overnight under hydrogen (1 atm). The suspension was diluted with CH_2Cl_2 (25 mL) and then filtered through Celite® and the flask was rinsed with CH_2Cl_2 (3×5 mL). The solution was extracted with sat. aq. $NaHCO_3$ (3×15 mL). The combined aqueous layers were diluted with phosphate buffer (0.1 M, pH = 7.5, 25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 97:3) to afford compound **3.112** (4.6 mg, 92%) as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.40 (s, 1H), 6.05 (dd, *J* = 7.9, 4.1 Hz, 1H), 5.53 (s, 1H), 4.30 (s, 1H), 4.09 (d, *J* = 6.7 Hz, 1H), 3.78-3.74 (m, 2H), 3.76 (s, 3H), 3.65-3.60 (m, 1H), 3.17 (dd, *J* = 9.3, 6.2 Hz, 1H), 2.61 (dd, *J* = 13.1, 9.4 Hz, 1H), 2.32 (dt, *J* = 13.2, 6.6 Hz, 1H) 2.24 (s, 3H), 1.47 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.4, 171.1, 145.2, 144.7, 144.7, 136.9, 136.8, 130.3, 127.1, 119.1, 112.9, 112.9, 102.7, 81.6, 65.1, 62.4, 61.8, 61.0, 49.5, 48.1, 37.0, 29.8, 29.8, 28.2, 15.9; R_f (SiO_2, $CHCl_3$/MeOH 95:5) 0.17; $[\alpha]_D^{25}$ = +4.3 ° (c = 0.23, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3262 (br),

2969, 2925, 2854, 1719, 1683, 1646, 1154 cm^{-1}; HRMS (MH^+), found 417.2033. $C_{22}H_{29}N_2O_6$ requires 417.2026.

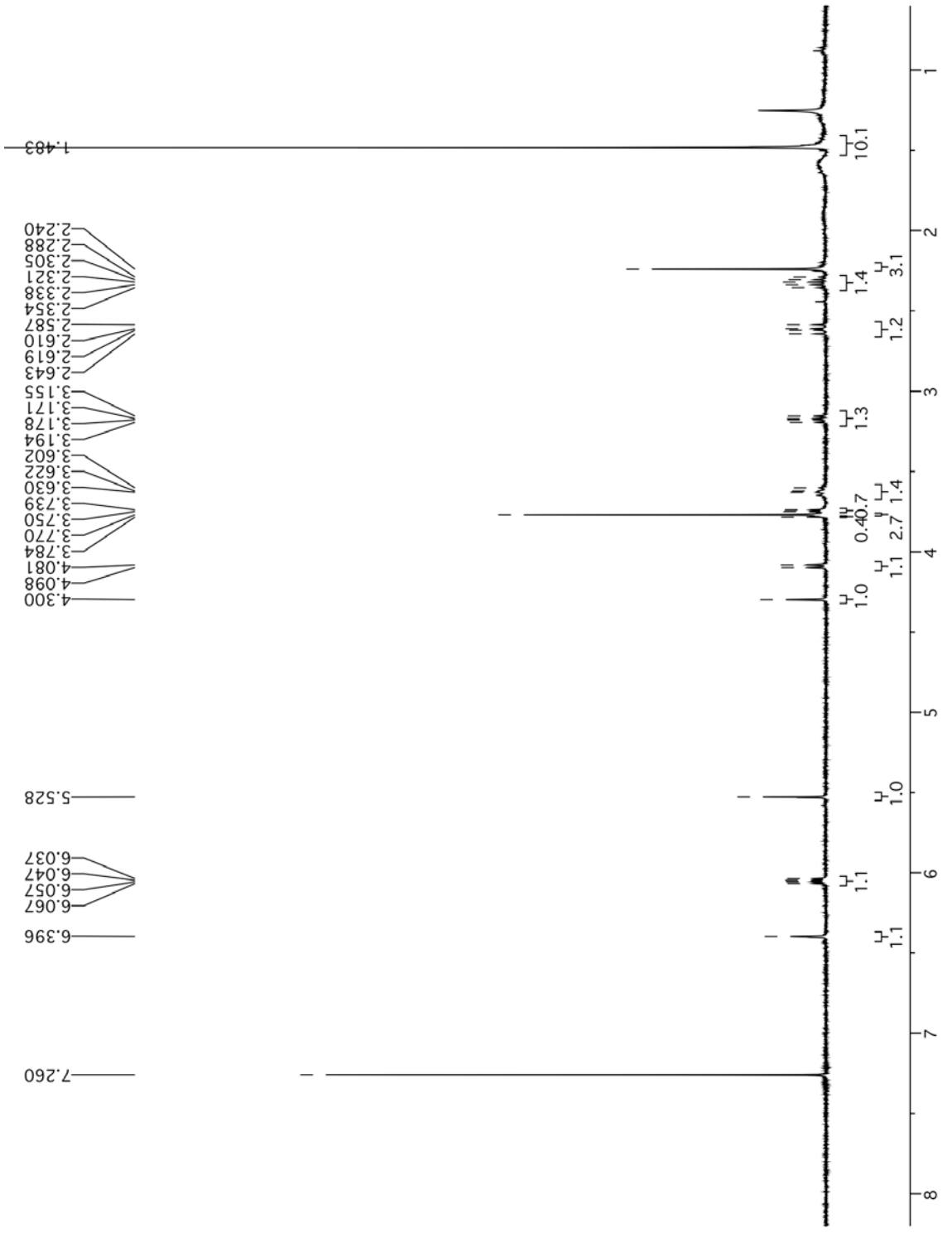


Figure 4.81. ^{1}H NMR spectrum of compound **3.112** (400 MHz, $CDCl_3$)

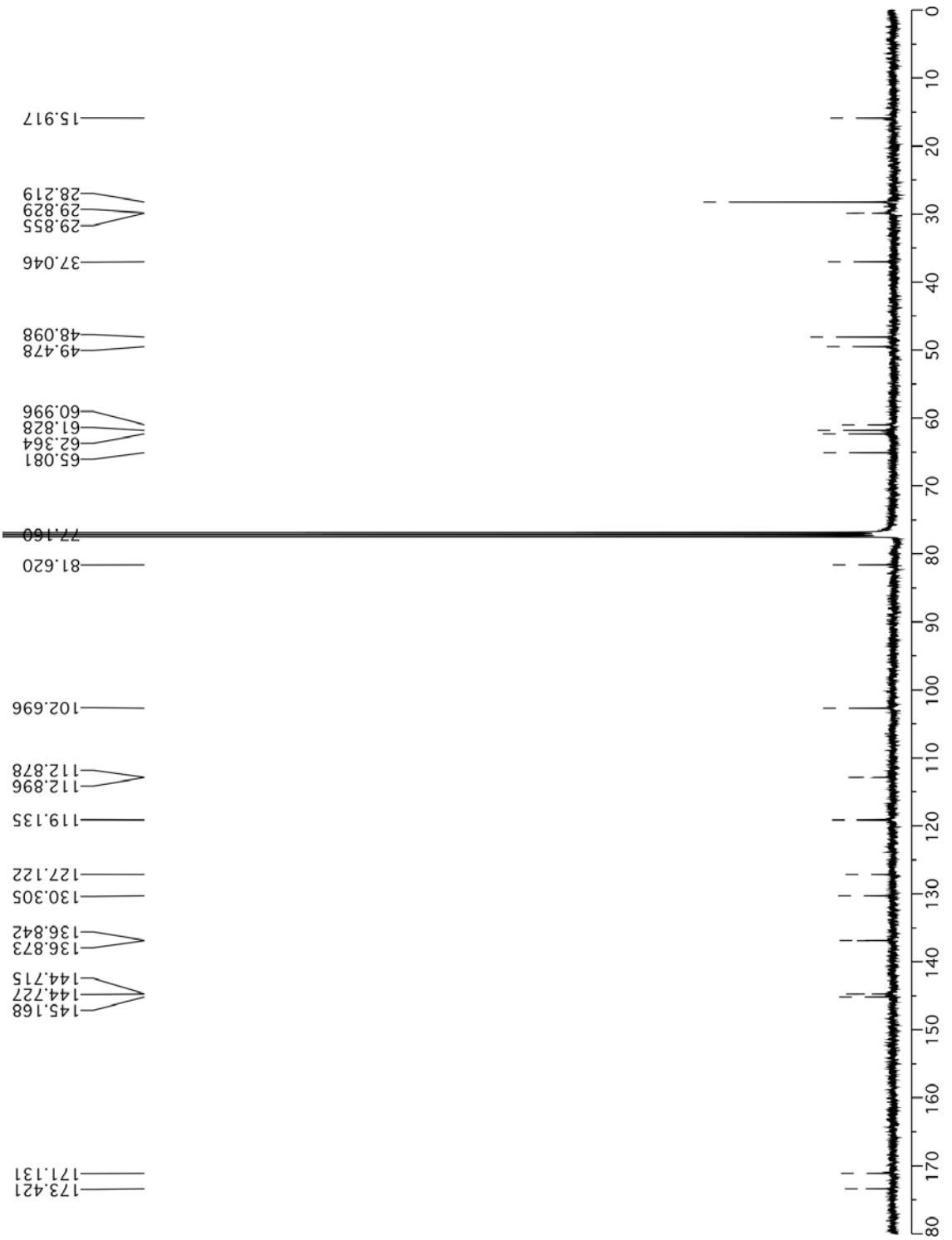
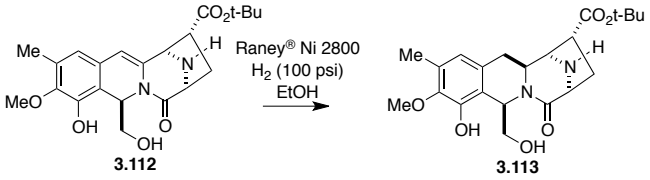


Figure 4.82. ^{13}C NMR spectrum of compound **3.112** (101 MHz, $CDCl_3$)



4.57 (5*R*,8S,10*R*,11*S*,11a*S*)-*tert*-butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11,11a, 12- octahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (3.113)

To a solution of compound **3.112** (4.6 mg, 0.011 mmol) in EtOH (1 mL) in a 5 mL vial, was added a slurry of Raney® nickel 2800 (500 μL of commercially available water slurry, washed with EtOH (3×1 mL) and suspended in EtOH (1 mL)). The vial was placed in a Fisher-Porter bottle, under Ar, the suspension was sparged with Ar for 5 minutes and the vessel was filled with hydrogen gas at 100 psi. The reaction was vigorously stirred overnight, diluted with EtOAc (10 mL) and sat. aq. Rochelle's salt (10 mL), and stirred vigorously for 2 h. The biphasic suspension was filtered through Celite®, the phases separated and the aqueous phase extracted with EtOAc (3×10 mL). The combined organic phases were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 97:3) to afford compound **3.113** (3.4 mg, 74%) as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.51 (s, 1H), 5.59 (dd, *J* = 5.6, 3.4 Hz, 1H), 3.96 (d, *J* = 6.1 Hz, 1H), 3.88 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.78 (s, 3H), 3.77-3.76 (m, 1H), 3.67 (dt, *J* = 12.4, 2.6 Hz, 1H), 3.61 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.16 (dd, *J* = 9.0, 6.4 Hz, 1H), 2.84 (t, *J* = 13.5 Hz, 1H), 2.54 (dd, *J* = 14.7, 2.2 Hz, 1H), 2.50 (dd, *J* = 13.2, 9.0 Hz, 1H), 2.27 (s, 3H), 2.18 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.53-1.45 (m, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 174.4, 172.4, 145.7, 132.0, 129.7, 121.2, 120.2, 118.0, 81.5, 67.8, 63.0, 62.2, 61.0, 60.8, 52.6, 42.8, 38.8, 32.1, 29.9, 28.2, 15.9; R_f (SiO_2, $CHCl_3$/MeOH 95:5) 0.20; $[\alpha]_D^{25}$ = -36 ° (c = 0.080, $CHCl_3$); IR (film,

CH_2Cl_2), ν_{max} 3286 (br), 2958, 2925, 2855, 1729, 1652, 1456 cm^{-1}; HRMS (MH^+), found 419.2174. $C_{22}H_{31}N_2O_6$ requires 419.2182.

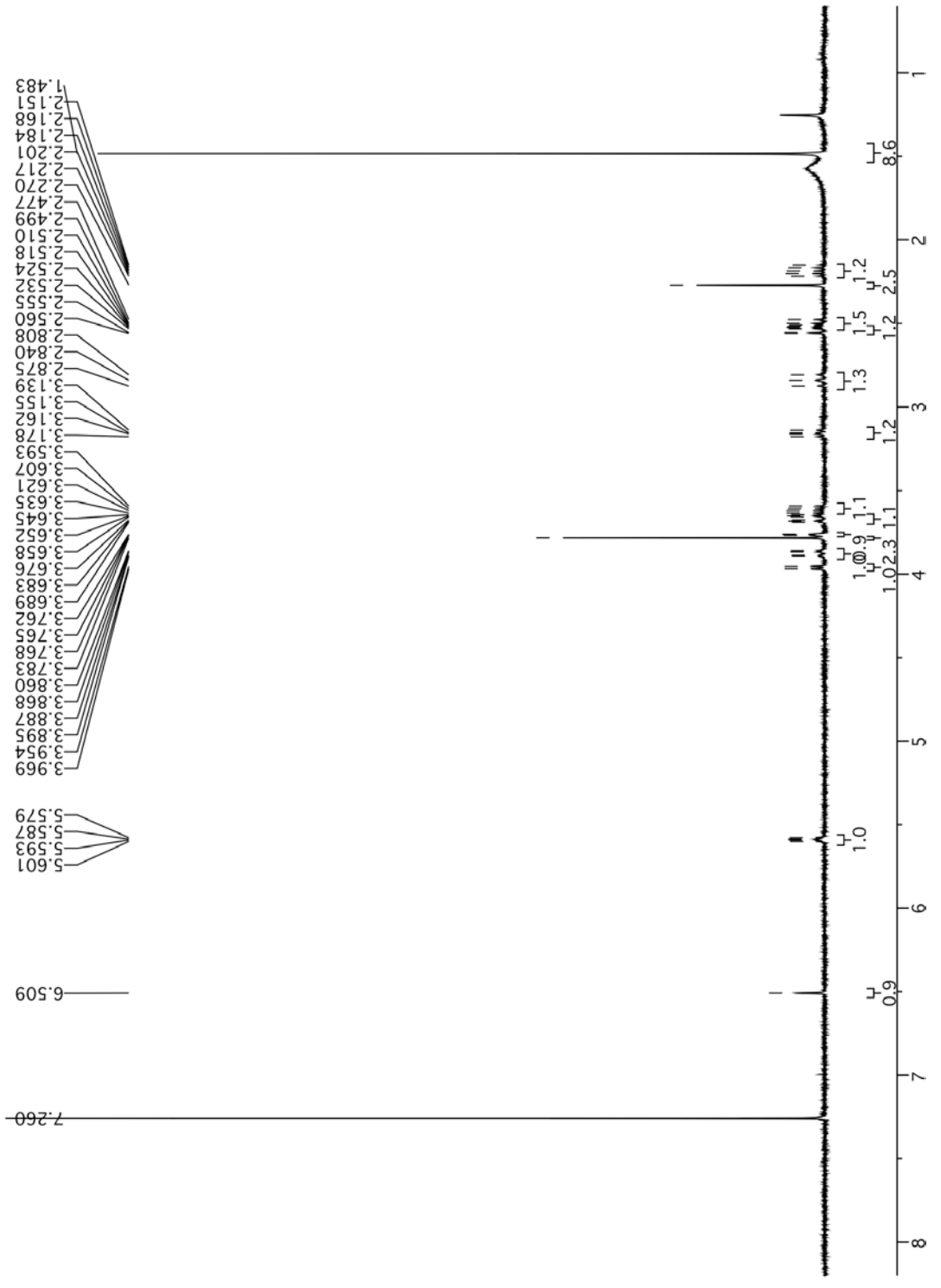


Figure 4.83. ^{1}H NMR spectrum of compound **3.113** (400 MHz, $CDCl_3$)

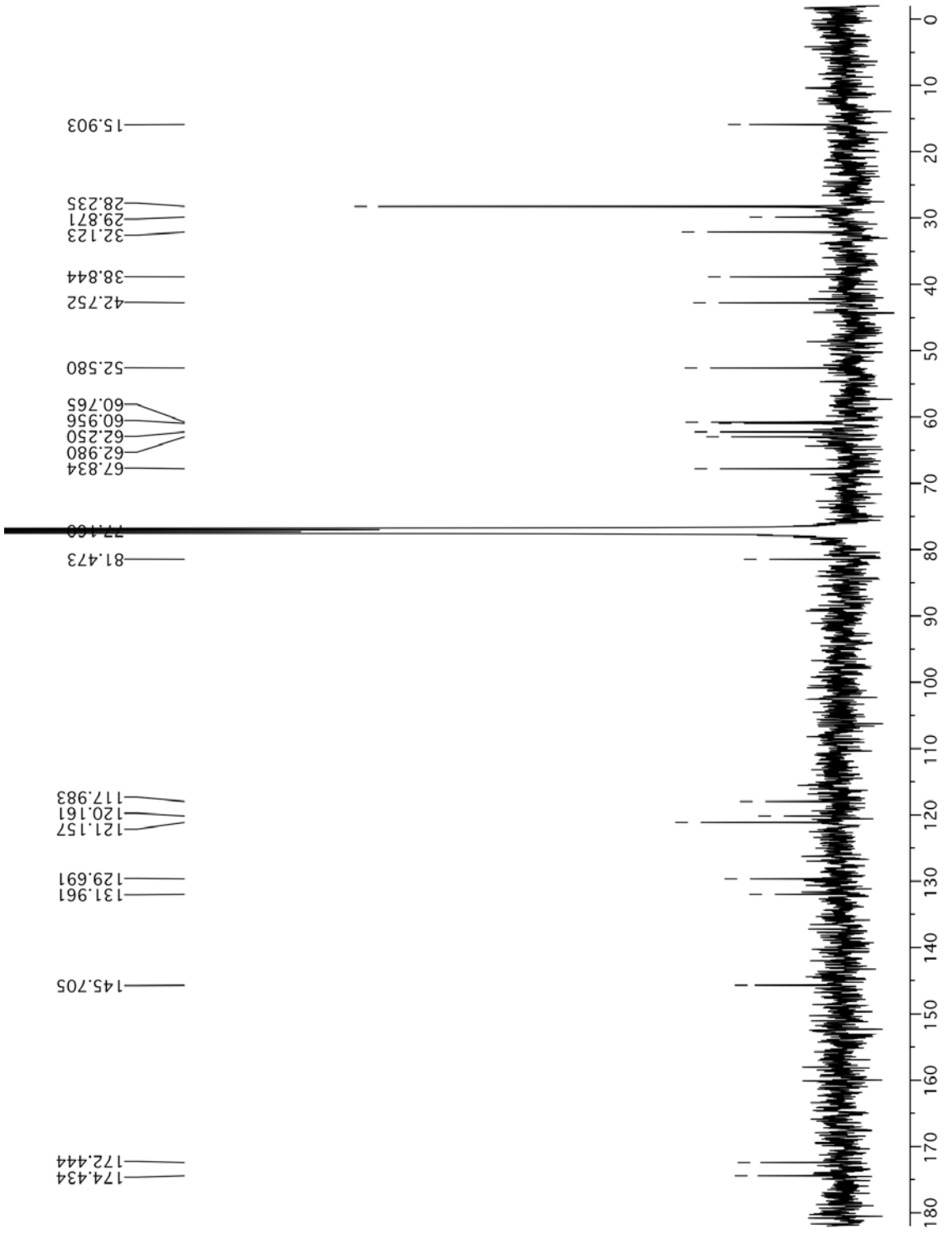
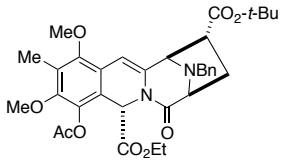


Figure 4.84. ^{13}C NMR spectrum of compound **3.113** (101 MHz, $CDCl_3$)

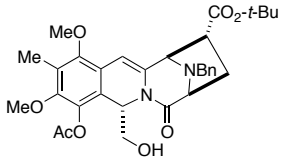
APPENDIX 1

Substrates and conditions of the enamide hydrogenation attempts listed in reference 58



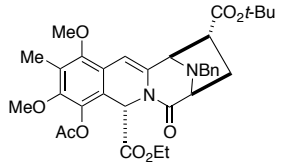
2.111

Catalyst	H_2 pressure /psi	Temperature	Result
Raney Ni	1500	r.t.	S.M.
Rh/C	1300	r.t.	S.M.
Rh/Alumina	1300	r.t.	S.M.
$Rh(OAc)_2$	1500	r.t.	S.M.
$RhCl_3$	1500	r.t.	S.M.
Wilkinson's cat.	1500	r.t.	S.M.
Ir/C	1300	r.t.	S.M.
Crabtree's cat.	1500	r.t.	S.M.
Pd/C	1300	r.t.	S.M.
$PdCl_2$	1300	r.t.	S.M.
$Pd(OH)_2$	1300	r.t.	S.M.
Raney Ni	2000	r.t.	de-Bn + S.M.
Rh/Alumina	2000	65 °C	de-Bn + S.M.
Raney Ni	1500	65 °C	Unidentified product



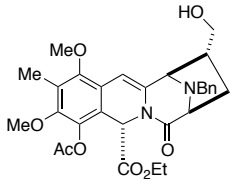
A1-335

Catalyst	H_2 pressure /psi	Temperature	Result
Raney Ni	1300	r.t.	S.M.
Rh/C	1500	65 °C	S.M.
$RhCl_3$	1500	65 °C	S.M.
$Pd(OH)_2$	1500	65 °C	S.M.
Ir/C	1300	r.t/	S.M.



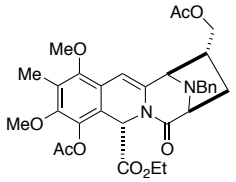
A1-336

Catalyst	H_2 pressure /psi	Temperature	Result
Wilkinson's cat.	1500	r.t.	Show vinyl proton



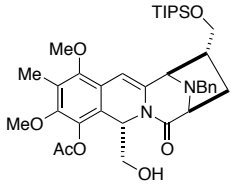
A1-337

Catalyst	H_2 pressure /psi	Temperature	Result
Rh/C	1500	65 °C	S.M.
$RhCl_3$	1500	65 °C	S.M.
$Pd(OH)_2$	1500	65 °C	S.M.
Pd/C, TFA	1300	r.t.	Removal of *N*-Bn



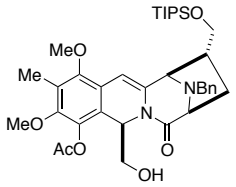
A1-338

Catalyst	H_2 pressure /psi	Temperature	Result
Pd/C, TFA	1300	r.t.	Removal of *N*-Bn



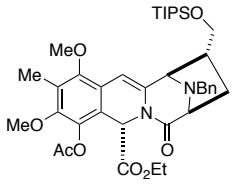
A1-325

Catalyst	H_2 pressure /psi	Temperature	Result
Pd/C, TFA	1300	r.t.	Removal of *N*-Bn
Wilkinson's cat.	2000	65 °C	SM
Ru black	2000	65 °C	SM
Raney Ni	2000	65 °C	Unidentified product



A1-328

Catalyst	H_2 pressure /psi	Temperature	Result
Pd/C, TFA	1300	r.t.	Removal of *N*-Bn
Raney Ni	2000	r.t.	Removal of *N*-Bn, S.M.
Raney Ni	2000	65 °C	Unidentified product



A1-322

Catalyst	H_2 pressure /psi	Temperature	Result
$PdCl_2$	1800	65 °C	Removal of *N*-Bn

APPENDIX 2

Publications

Tetrahedron xxx (2013) 1–8

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Synthetic studies on lemonomycin: construction of the tetracyclic core

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[3+2] Dipolar cycloaddition

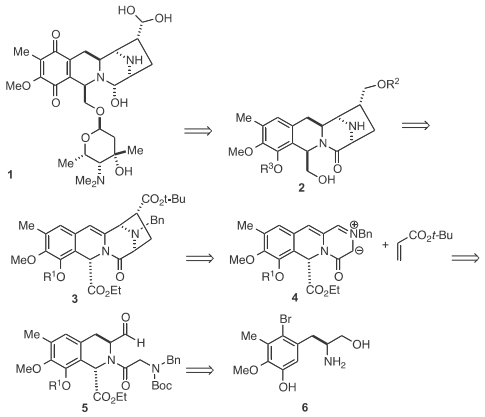
ABSTRACT

A substrate-induced stereocontrol strategy was used to gain access to the tetracyclic core of (−)-lemonomycin. An advanced intermediate was prepared from a known substituted tyrosinol through a 16-step sequence, which involved a Pictet–Spengler reaction, a [3+2] dipolar cycloaddition and an enamide hydrogenation.

1. Introduction

Lemonomycin (**1**) is a member of the tetrahydroisoquinoline (THIQ) family of antitumor antibiotics.[1] It was isolated from the fermentation broth of *Streptomyces candidus* (LL-AP191) in 1964,[2,3] and its structure was reported by He and co-workers in 2000.[4] This compound showed significant in vitro antimicrobial activities against both gram-negative and gram-positive bacteria, including antibiotic-resistant strains, as well as against the human colon tumor cell line HCT116.[2–4] Structurally, the compound contains the tetracyclic core found in quinocarcin[5] and tetrazomine,[6] which includes a 3,8-diazabicyclo ring system and a rare bis-desoxy aminosugar portion, which has only been found in a few natural products.[7–11] The structural complexity and biological activities of this substance have made lemonomycin an attractive target for the synthetic community. To date, there are two total syntheses by Stoltz[12] and Fukuyama[13] and synthetic studies by Magnus,[14,15] Zhu,[16–18] Mulzer,[19] and our laboratory.[20]

As shown in Scheme 1, we envisioned that the final steps in the synthesis of lemonomycin (**1**) would involve a late-stage glycosylation reaction, and the formation of the quinone, hemiaminal, and aldehyde hydrate functional groups. Compound **2** could be accessed through the epimerization of the southern benzylic position and the reduction of the enamide double bond found in tetracycle **3**. This key intermediate could be prepared from aldehyde **5** via azomethine ylide **4**, using a [3+2] dipolar cycloaddition approach previously developed by our group.[20] This key reaction was also used for the construction of the [3,8]-diazabicyclo ring system in our total syntheses of (−)-tetrazomine[21] and (±)-quinocarcinamide.[22] The tetrahydroisoquinoline system of **5** could be formed through a Pictet–Spengler reaction involving a derivative of compound **6**, which is a known compound.[23]



Scheme 1. Retrosynthetic analysis.

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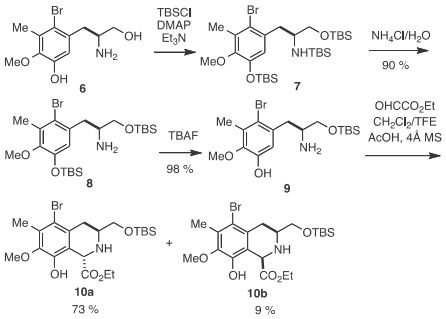
2. Results and discussion

Our synthetic sequence starts with substituted tyrosinol **6**, which can be prepared from commercially available L-tyrosine methyl ester according to the procedure described by Liao.[23] We initially attempted to perform the direct conversion of **6** into bis-silyl ether **8** using 2 equiv of TBS-Cl, but the yields were inconsistent and low (<30%).[24,25] By increasing the relative amount of TBS-Cl to 6 equiv, compound **6** was converted into the tris-silylated compound **7**. Unexpectedly, the hydrolysis of the silyl-amine function required a prolonged vigorous stirring with aq NH_4Cl at rt (~2 h) to form the bis-silyl ether **8** in 90% yield. The phenolic silyl ether was selectively cleaved with 1 equiv of TBAF at 0 °C,[26] to afford compound **9** in 98% yield (Scheme 2).

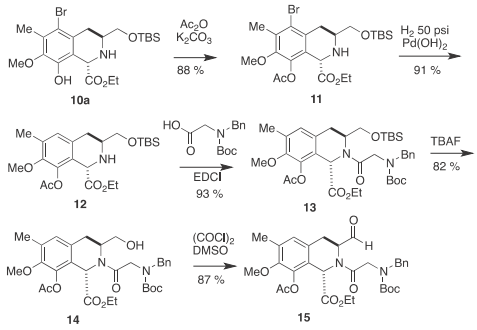


Scheme 2. Tetrahydroisoquinoline ring formation.

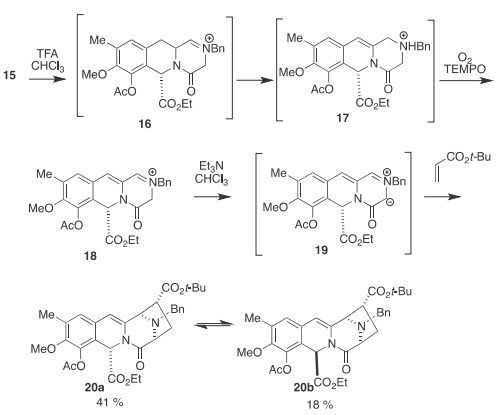
The next step entailed the formation of the *trans*-tetrahydroisoquinoline ring via a Pictet–Spengler reaction between **9** and ethyl glyoxalate. Previously, our group reported a similar transformation, which was performed by stirring a solution of the starting materials in acetonitrile for 3.5 days at 50 °C, which afforded the trans-product stereospecifically.[27] A similar report by Zhu and co-workers involved the use of LiCl, hexafluoroisopropanol and molecular sieves, and stirring the suspension in toluene at rt for 48 h. Since none of these mild conditions led to the formation of the desired tetrahydroisoquinoline ring system, we decided to adapt the reaction conditions that were originally described by Zhu[28,29] to our substrate. The amount of acetic acid was reduced from 2.5 equiv to 0.2 equiv to prevent cleavage of the *O*-TBS ether due to the prolonged exposure to the acid. In the present system, treatment of a solution of compound **9** and ethyl glyoxylate with CF_3CH_2OH, AcOH (0.2 equiv), and 4 Å MS afforded an 8:1 mixture of **10a** and **10b** in 82% yield. These two diastereomers were separated via flash chromatography and **10a** was subjected to selective acetylation,[30] followed by hydrogenolysis of the C–Br bond[23] to afford compound **12** (Scheme 3).

Following the conditions described in our previous report,[20] we converted THIQ **12** into the [3+2] dipolar cycloaddition adducts **20a** and **20b**. Thus, THIQ **12** and *N*-Boc-*N*-Bn-Gly were coupled using EDCI, and the resulting amide was treated with TBAF to cleave the *O*-TBS ether, followed by a Swern oxidation[31] to afford aldehyde **15** (Scheme 3).

As illustrated in Scheme 4, aldehyde **15** was dissolved in $CHCl_3$ and treated under aerobic conditions with TFA[32–34] (50 equiv) and TEMPO (0.1 equiv), to generate iminium ion **16**, which tautomerizes to form ammonium ion **17**. This intermediate is autoxidized in situ to afford conjugated iminium ion **18**, which was concentrated to dryness and taken up in $CHCl_3$. Addition of triethylamine induces the formation of azomethine ylide **19**, which is trapped in situ by *tert*-butyl acrylate to give a 2.4:1 mixture of tetracycles **20a** and **20b** in a combined 59% yield.[35]

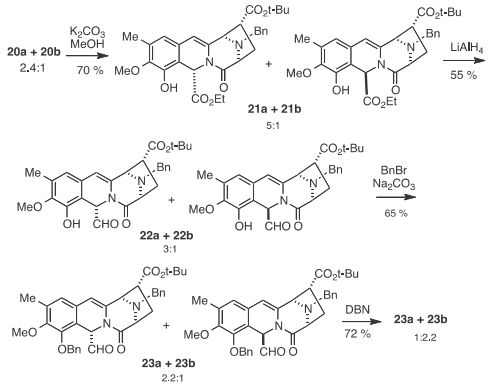


Scheme 3. Preparation of aldehyde **15**.



Scheme 4. Formation of cycloadducts **20a** and **20b**.

The deacetylation of the **20a**/**20b** mixture under standard methanolysis conditions provided a 5:1 mixture of **21a** and **21b** in 70% yield (Scheme 5). We suggest that **21b** decomposes under the reaction conditions at a higher rate than **21a**, which provides an explanation for both the moderate yield and the change in the diastereomeric ratio. The chemoselective reduction of the ethyl esters with 1 equiv of $LiAlH_4$ at −10 °C, afforded a 3:1 mixture of aldehydes **22a** and **22b** in 55% yield.[36] We submit that the partial



Scheme 5. Synthesis of aldehydes **23a** and **23b**.

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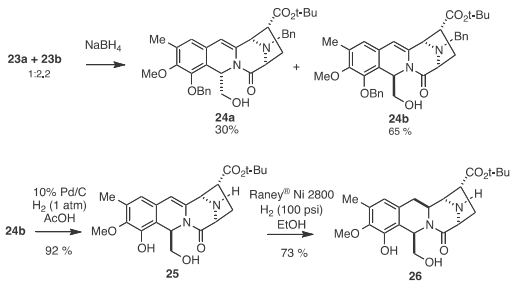
epimerization seen in this step is promoted by the slightly basic workup conditions. Treatment with BnBr and Na_2CO_3 formed the phenolic benzyl ethers and induced additional epimerization of the aldehyde's α carbon, to provide a 2.2:1 mixture of **23a** and **23b**,[37] which was then reacted with DBN in THF to invert the epimeric ratio.[21,22]

The 1:2.2 mixture of aldehydes **23a** and **23b** was then treated with sodium borohydride to afford a mixture of alcohols **24a** and **24b**, which were separated via flash chromatography to afford **24b** in 65% yield (Scheme 6). The sequence used to transform the **20a**/**20b** mixture into **24b** not only provided the desired configuration in the benzylic position but also furnished an unhindered substrate for the *N*-debenzylation of the piperazinone amine. Thus, hydrogenolysis of **24b** in glacial acetic acid (10% Pd/C, 1 atm) effected the bis-debenzylation to afford **25** in 92% yield. Similarly, the removal of the *N*-benzyl group also provided an unhindered substrate for the hydrogenation of the enamide double bond from the *Re* face of C-3 (lemonomycin numbering). Gratifyingly, the hydrogenation of **25** with Raney® nickel at 100 psi[21] provided compound **26** in 73% yield.



Scheme 6. Synthesis of compound **26**.

3. Conclusion

In summary, we have accomplished the construction of the tetracyclic core of (−)-lemonomycin. Compound **26** was prepared from known bromotyrosinol **6** in 16 steps. Efforts to gain access to (−)-lemonomycin through this advanced intermediate are currently under investigation.

4. Experimental section

4.1. General methods

Unless otherwise noted, all materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using flame-dried glassware. Organic solvents were degassed with argon and dried through a solvent purification system (Pure Process Technology). Flash chromatography was performed on silica gel grade 60 (230×400 mesh) from Sorbent Technologies. Thin layer chromatography was performed on glass plates coated with silica gel grade 60, from Merck. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers as indicated. Proton spectra in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm. Carbon spectra in $CDCl_3$ were referenced to 77.16 ppm. Proton spectra in DMSO-d_6 were referenced to residual CD_3SOCD_2H at 2.50 ppm. Infrared spectra were recorded on a Bruker Tensor FT-IR spectrometer. High-resolution mass spectra were obtained using a TOF spectrometer using simultaneous electrospray (ESI) and atmospheric pressure chemical ionization (APCI). Optical rotations were recorded on a Rudolph Research Autopol polarimeter, at a wavelength of 589 nm.

4.2. (*S*)-1-(2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-3-methylphenyl)-3-((*tert*-butyldimethylsilyl)oxy) propan-2-amine (8)

To a stirred solution of compound **6** (1.55 g, 5.36 mmol, 1 equiv) (**6**) in CH_2Cl_2 (90 mL, 0.06 M), were added DMAP (327 mg, 2.68 mmol, 0.5 equiv), Et_3N (4.48 mL, 32.2 mmol, 6.00 equiv), and TBS-Cl (4.86 g, 32.2 mmol, 6 equiv). The reaction was stirred under Ar for 3 h at rt, and then satd aq NH_4Cl (50 mL) was added and the mixture was stirred for 2 h. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexane/EtOAc 5:1) to give the title compound **8** (2.50 g, 90%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.65 (s, 1H), 3.72 (s, 3H), 3.61 (1/2 ABX, *J*=9.7, 4.1 Hz, 1H), 3.47 (1/2 ABX, *J*=9.7, 6.5 Hz, 1H), 3.20–3.14 (m, 1H), 2.87 (1/2 ABX, *J*=13.4, 5.4 Hz, 1H), 2.57 (1/2 ABX, *J*=13.4, 8.0 Hz, 1H), 2.35 (s, 3H), 1.00 (s, 9H), 0.91 (s, 9H), 0.17 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 147.6, 134.6, 133.1, 121.3, 119.4, 67.6, 60.2, 52.9, 41.3, 26.1, 25.8, 18.4, 18.4, 17.2, −4.4, −5.2; R_f (SiO_2, 2:1 hexanes/EtOAc) 0.35; $[\alpha]_D^{25}$ +0.9 (*c* 0.35, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2996, 2930, 2858, 2471, 839 cm^{-1}; HRMS (MH^+), found 520.2103. $C_{23}H_{45}BrNO_3Si_2$ requires 520.2101.

4.3. (*S*)-5-(2-Amino-3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-bromo-2-methoxy-3-methylphenol (9)

To a stirred solution of compound **8** (1.59 g, 3.05 mmol, 1 equiv) in THF (100 mL, 0.03 M), under Ar, at 0 °C, was added a 1.0 solution M of TBAF in THF (3.05 mL, 3.05 mmol, 1 equiv). The reaction was stirred for 25 min and quenched with satd aq NH_4Cl (50 mL). The phases were allowed to warm to rt, the aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 10:1) to give the title compound **9** (1.23 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.77 (s, 1H), 3.73 (s, 3H), 3.71–3.66 (m, 1H), 3.56–3.50 (m, 1H), 3.27–3.24 (m, 1H), 2.92 (1/2 ABX, *J*=13.5, 4.6 Hz, 1H), 2.62 (1/2 ABX, *J*=13.5, 9.0 Hz, 1H), 2.34 (s, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.4, 145.0, 134.6, 132.2, 117.2, 116.1, 67.1, 60.8, 52.9, 52.7, 40.5, 26.1, 18.4, 17.2, −5.2, −5.2. R_f (SiO_2, CH_2Cl_2/MeOH 10:1) 0.4; $[\alpha]_D^{25}$ +8.3 (*c* 0.41, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3263 (br), 2954, 2928, 2856, 1578, 1471, 1092 cm^{-1}; HRMS (MH^+), found 406.1233. $C_{17}H_{31}BrNO_3Si$ requires 406.1236.

4.4. (1*S*,3*S*)-Ethyl 5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (10a) and (1*R*,3*S*)-ethyl 5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (10b)

To a stirred solution of compound **9** (5.43 g, 13.4 mmol, 1.0 equiv) in CH_2Cl_2 (134 mL, 0.10 M), under Ar, were added, 4 Å molecular sieves (2.72 g), CF_3CH_2OH (13.4 mL), AcOH (153 μL, 2.68 mmol, 0.20 equiv), and ethyl glyoxalate (50% solution in $PhCH_3$, 2.93 mL, 14.8 mmol, 1.1 equiv). The reaction was stirred overnight, diluted with CH_2Cl_2 (50 mL), filtered through Celite®, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1) to give

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compound **10a** (4.78 g, 73%) as a white solid and compound **10b** (610 mg, 9%) as a white solid. Compound **10a**: ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.25 (br s, 1H), 4.89 (s, 1H), 4.26–4.18 (m, 2H), 3.82 (1/2 ABX, J=9.8, 3.5 Hz, 1H), 3.76 (s, 3H), 3.54 (1/2 ABX, J=9.8, 8.5 Hz, 1H), 3.13–3.07 (m, 1H), 2.71 (1/2 ABX, J=16.9, 4.1 Hz, 1H), 2.35 (s, 3H), 2.27 (1/2 ABX, J=16.9, 11.3 Hz, 1H), 1.29 (t, J=7.1 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 145.6, 144.3, 130.8, 130.7, 120.0, 118.4, 66.9, 61.7, 61.2, 55.6, 51.6, 32.7, 26.0, 18.4, 17.0, 16.9, 14.4, 14.4, −5.1, −5.2, −5.2, −5.3; mp=47 °C; R_f (SiO_2, hexanes/EtOAc 4:1) 0.40; $[\alpha]_D^{25}$ −24.3 (c 0.885, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3284 (br), 2955, 2931, 2857, 1739, 1462, 1178 cm^{-1}; HRMS (MH^+), found 490.1446. $C_{21}H_{35}BrNO_5Si$ requires 490.1447. Compound **10b**: ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.86 (br s, 1H), 4.78 (s, 1H), 4.30–4.15 (m, 2H), 3.80 (1/2 ABX, J=9.9, 4.1 Hz, 1H), 3.74 (s, 3H), 3.68 (1/2 ABX, J=9.9, 6.6 Hz, 1H), 2.95–2.89 (m, 1H), 2.77 (1/2 ABX, J=16.6, 3.1 Hz, 1H), 2.44 (1/2 ABX, J=16.6, 8.5 Hz, 2H), 2.36 (s, 3H), 1.27 (t, J=7.1 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 145.1, 143.9, 132.0, 130.4, 120.3, 118.4, 66.7, 61.5, 61.4, 58.4, 54.5, 33.0, 26.1, 26.0, 18.5, 17.0, 14.2, −5.1, −5.2; mp=95 °C; R_f (SiO_2, hexanes/EtOAc 4:1) 0.37; $[\alpha]_D^{25}$ −36.7 (c 0.600, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3314 (br), 2955, 2931, 2858, 1738, 1463, 1257 cm^{-1}; HRMS (MH^+), found 490.1456. $C_{21}H_{35}BrNO_5Si$ requires 490.1447.

4.5. (1*S*,3*S*)-Ethyl 8-acetoxy-5-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (11)

To a stirred solution of compound **10a** (840 mg, 1.72 mmol, 1.0 equiv) in acetone (34 mL, 0.05 M), under Ar, were added K_2CO_3 (1.20 g, 8.64 mmol, 5.0 equiv) and acetic anhydride (162 μL, 1.72 mmol, 1.0 equiv). The suspension was stirred overnight, the solvent was evaporated, and the residue was partitioned between water (25 mL) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2×25 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1) to give the title compound **11** (800 mg, 88%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.66 (s, 1H), 4.18 (q, J=7.1 Hz, 2H), 3.81 (1/2 ABX, J=9.8, 3.5 Hz, 1H), 3.70 (s, 3H), 3.55 (1/2 ABX, J=9.8, 7.6 Hz, 1H), 3.22–3.16 (m, 1H), 2.74 (1/2 ABX, J=16.9, 4.1 Hz, 2H), 2.38 (s, 3H), 2.37–2.33 (m, 1H), 2.29 (s, 3H), 1.27 (t, J=7.1 Hz, 3H), 0.921 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 167.9, 148.6, 141.0, 132.5, 131.5, 125.9, 125.8, 66.7, 61.5, 61.1, 55.8, 51.0, 32.6, 26.0, 20.6, 18.4, 17.1, 14.4, −5.2, −5.3. R_f (SiO_2, hexanes/EtOAc 4:1) 0.45; $[\alpha]_D^{25}$ −21.1 (c 1.10, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2956, 2932, 2856, 1780, 1737, 1462, 1192 cm^{-1}; HRMS (MH^+), found 532.1561. $C_{23}H_{37}BrNO_6Si$ requires 530.1574.

4.6. (1*S*,3*S*)-Ethyl 8-acetoxy-3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (12)

A solution of compound **11** (2.90 g, 5.46 mmol) in MeOH (110 mL, 0.05 M), and Pearlman's catalyst (20% $Pd(OH)_2$/C, 580 mg) were placed in a Fisher–Porter bottle, under Ar. The mixture was sparged with Ar for 5 min and the vessel was filled with hydrogen gas at 50 psi. The reaction was vigorously stirred overnight and then filtered through Celite® and the vessel was rinsed with MeOH (50 mL) and EtOAc (50 mL). The solution was concentrated under vacuum to dryness and partitioned between satd aq $NaHCO_3$ (75 mL) and EtOAc (75 mL). The aqueous phase was extracted with EtOAc (2×75 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 5:1, 4:1 and 3:1) to give the title compound **12** (2.25 g, 91%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.85 (s, 1H), 4.65 (s, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.73 (1/2 ABX, J=9.8, 3.7 Hz, 1H), 3.70 (s, 3H), 3.52 (1/2 ABX, J=9.8, 7.2 Hz, 1H), 3.28–3.22 (m, 1H), 2.59 (1/2 ABX, J=16.1, 4.2 Hz, 1H), 2.50 (1/2 ABX, J=16.1, 10.7 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 1.26 (t, J=7.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 168.3, 148.2, 141.6, 131.5, 131.1, 129.2, 124.0, 66.7, 61.3, 60.6, 55.6, 50.7, 30.2, 26.0, 20.6, 18.4, 16.0, 14.4, −5.2, −5.3. R_f (SiO_2, hexanes/EtOAc 4:1) 0.42; $[\alpha]_D^{25}$ −17 (c 0.42, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2954, 2929, 2857, 1775, 1737, 1197 cm^{-1}; HRMS (MH^+), found 452.244. $C_{23}H_{38}NO_6Si$ requires 452.2468.

4.7. (1*S*,3*S*)-Ethyl 8-acetoxy-2-(2-(benzyl(*tert*-butoxycarbonyl)-amino)acetyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (13)

A solution of compound **12** (2.20 g, 4.87 mmol, 1.0 equiv), *N*-Bn-*N*-Boc-glycine (2.58 g, 9.74 mmol, 2.0 equiv), and EDCI (1.40 g, 7.31 mmol, 1.5 equiv) in CH_2Cl_2 (2.5 mL, 2 M), under Ar, was stirred for 2.5 days. The reaction was diluted with EtOAc (200 mL), and the solution was extracted with water (100 mL), satd aq $NaHCO_3$ (2×100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1, 3:1 and 2:1) to give the title compound **13** (3.15 g, 93%) as a colorless oil. ^{1}H NMR (300 MHz; DMSO-d_6, 393 K, mixture of rotamers): δ 7.36–7.24 (m, 5H), 6.94 (s, 1H), 6.88 (s, 1H, minor rotamer), 5.48 (s, 1H), 4.49 (1/2 AB, J=15.6 Hz, 1H), 4.39 (1/2 AB, J=15.6.0 Hz, 1H), 4.33–4.27 (m, 2H), 4.13–3.87 (m, 3H), 3.69 (s, 3H), 3.66 (s, 1H, minor rotamer), 3.34–3.10 (br m, 2H), 3.07–2.91 (br m, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H, minor rotamer), 2.23 (s, 1H, minor rotamer), 1.41 (s, 9H), 1.21 (t, J=7.0 Hz, 3H, minor rotamer), 1.12 (t, J=7.1 Hz, 3H), 0.92 (d, J=0.6 Hz, 2H), 0.79 (s, 9H), 0.08 (s, 3H, minor rotamer), 0.04 (s, 3H, minor rotamer), 0.03 (m, 3H, minor rotamer), −0.11 (s, 3H), −0.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 170.1, 169.7, 168.1, 168.0, 156.1, 149.6, 129.2, 129.1, 128.7, 128.4, 127.8, 127.5, 127.5, 127.4, 121.6, 80.5, 80.4, 71.6, 61.9, 61.3, 60.7, 53.6, 53.6, 53.5, 53.0, 53.0, 52.9, 52.9, 50.9, 47.7, 29.5, 28.5, 28.4, 26.0, 26.0, 25.9, 20.9, 18.3, 16.1, 16.0, 14.0, 13.9, −5.3, −5.4, −5.4, −5.7. R_f (SiO_2, hexanes/EtOAc 3:1) 0.30; $[\alpha]_D^{25}$ +26.8 (c 0.995, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2956, 2931, 2857, 1781, 1743, 1703, 1668, 1199 cm^{-1}; HRMS (MH^+), found 699.3666. $C_{37}H_{55}N_2O_9Si$ requires 699.3677.

4.8. (1*S*,3*S*)-Ethyl 2-(2-(benzyl(*tert*-butoxycarbonyl)amino)acetyl)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (14)

To a solution of compound **13** (765 mg, 1.09 mmol, 1.0 equiv) in THF (10 mL, 0.11 M), under Ar, were added MeOH (625 μL) and TBAF (1.0 M solution in THF, 2.18 mL, 2.0 equiv). The reaction was stirred overnight and quenched with satd aq NH_4Cl (50 mL) and then diluted with EtOAc (100 mL). The phases were separated, the aqueous phase was extracted with EtOAc (2×25 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was dissolved in the minimal amount of CH_2Cl_2 and purified by flash chromatography (silica gel, hexanes/EtOAc 2:1, then 1:1) to give the title compound **14** (525 mg, 82%) as a white amorphous solid. ^{1}H NMR (300 MHz; DMSO-d_6, 393 K): δ 7.36–7.26 (m, 5H), 6.96 (s, 1H), 5.50 (s, 1H), 4.49–4.40 (br m, 2H), 4.27–4.17 (br m, 2H), 4.07–3.89 (m, 3H), 3.70 (s, 3H), 3.19–3.03 (br m, 2H), 2.94–2.81 (m, 2H, overlapped with H_2O signal), 2.34 (s, 3H), 2.25 (s, 3H), 1.41 (s, 9H),

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1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 170.2, 170.1, 168.0, 168.0, 156.4, 154.8, 152.8, 149.7, 145.0, 141.7, 141.5, 138.1, 138.1, 138.0, 132.9, 132.8, 130.2, 130.0, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 127.8, 127.7, 127.5, 127.5, 127.1, 124.2, 121.2, 80.9, 80.4, 65.1, 63.8, 62.0, 60.6, 53.7, 53.5, 52.7, 52.0, 51.0, 47.9, 30.6, 30.0, 29.5, 28.5, 28.4, 20.9, 16.2, 13.8; mp 80 °C; R_f (SiO_2, hexanes/EtOAc 1:1) 0.35; $[\alpha]_D^{25}$ +78 (c 0.44, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3455 (br), 2977, 2935, 1780, 1742, 1698, 1663, 1200 cm^{-1}; HRMS (MH^+), found 585.2816. $C_{31}H_{41}N_2O_9$ requires 585.2812.

4.9. (1*S*,3*S*)-Ethyl 2-(2-(benzyl(*tert*-butoxycarbonyl)amino)-acetyl)-3-formyl-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (15)

A solution of oxalyl chloride (825 μL, 9.75 mmol, 3.0 equiv) in CH_2Cl_2 (22.5 mL), under Ar, was cooled to −78 °C, and DMSO (921 μL, 13.0 mmol, 4.0 equiv) was added dropwise. The resulting mixture was stirred an additional 30 min at −78 °C. A solution of compound **14** (1.90 mg, 3.25 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at rt was then added slowly by cannula, and the mixture continued to stir at −78 °C for 30 min. Triethylamine (4.50 mL, 32.5 mmol, 10 equiv) was then added dropwise, and the solution was stirred for 15 min at −78 °C and an additional 30 min at 0 °C. The reaction was quenched with satd aq NH_4Cl (50 mL) and allowed to warm to rt. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 2:1, then 1:1) to give the title compound **15** (1.65 g, 87%) as a colorless oil, which solidifies upon standing to afford a colorless amorphous solid. ^{1}H NMR (300 MHz; DMSO-d_6, 373 K, mixture of rotamers): δ 9.54 (s, 1H, minor rotamer), 9.28 (s, 1H), 7.35−7.23 (m, 5H), 7.08 (s, 1H, minor rotamer), 7.01 (s, 1H), 6.94 (s, 1H, minor rotamer), 6.91 (s, 1H, minor rotamer), 5.70 (s, 1H), 5.10−4.88 (m, 1H), 4.52−4.28 (m, 3H), 4.26−4.14 (m, 1H), 4.13−3.98 (m, 2H), 3.97−3.86 (m, 1H), 3.69 (s, 3H, minor rotamer), 3.68 (s, 3H, minor rotamer), 3.67 (s, 3H), 3.38−3.27 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H, minor rotamer), 2.25 (s, 3H, minor rotamer), 2.24 (s, 3H, minor rotamer), 2.22 (s, 3H), 1.41 (s, 9H, minor rotamer), 1.40 (s, 9H), 1.36 (s, 9H, minor rotamer), 1.34 (s, 9H, minor rotamer), 1.12 (t, J=7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 201.2, 199.6, 199.2, 169.9, 167.8, 155.9, 155.8, 150.2, 149.7, 141.5, 141.0, 137.6, 137.5, 137.5, 133.6, 133.3, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 122.6, 122.1, 81.0, 80.8, 62.7, 62.2, 60.9, 60.6, 60.6, 60.2, 53.7, 53.5, 53.3, 50.9, 47.8, 47.6, 47.1, 29.6, 28.5, 28.5, 28.4, 28.2, 20.9, 16.2, 13.8; mp 78 °C; R_f (SiO_2, hexanes/EtOAc 1:1) 0.40; $[\alpha]_D^{25}$ +35 (c 0.23, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 2978, 2937, 1780, 1742, 1699, 1673, 1200 cm^{-1}; HRMS (MH^+), found 583.2654. $C_{31}H_{39}N_2O_9$ requires 583.2656.

4.10. (5*S*,8*S*,10*R*,11*S*)-10-*tert*-Butyl 5-ethyl 4-acetoxy-13-benzyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (20a) and (5*R*,8*S*,10*R*,11*S*)-10-*tert*-butyl 5-ethyl 4-acetoxy-13-benzyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (20b)

To solution of compound **15** (1.65 g, 2.83 mmol, 1.0 equiv) in $CHCl_3$ (28 mL, 0.1 M), under air, were added TEMPO (44 mg, 0.28 mmol, 0.10 equiv), and trifluoroacetic acid (10.8 mL, 142 mmol, 50 equiv) and the flask was loosely capped with a Teflon® stopper. The solution was stirred for 4 h, the solvent was evaporated to dryness under vacuum and the residue was taken up in $CHCl_3$. The solution was cooled to 0 °C and then *tert*-butyl acrylate (8.20 mL, 56.6 mmol, 20 equiv) and triethylamine (3.95 mL, 28.3 mmol, 10 equiv) were added. The reaction was allowed to warm to rt and stirred overnight. The solution was diluted with EtOAc (200 mL), rinsed with satd aq NH_4Cl (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1, 3:1) to afford a 2.4:1 mixture of the title compounds **20a** and **20b** (985 mg, 59%) as a yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41−7.22 (m, 5H), 6.74 (s, 1H, minor diastereomer), 6.73 (s, 1H), 6.36 (s, 1H, minor diastereomer), 6.27 (s, 1H), 5.51 (s, 1H, minor diastereomer), 5.50 (s, 1H), 4.28−3.96 (m, 6H), 3.89−3.71 (m, 2H), 3.75 (s, 3H, minor diastereomer), 3.72 (s, 3H), 2.80−2.67 (m, 2H), 2.45 (dd, J=13.0, 9.8 Hz, 1H, minor diastereomer), 2.40 (s, 3H), 2.39 (s, 3H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.13 (dd, J=13.3, 9.5 Hz, 1H), 1.46 (s, 9H, minor diastereomer), 1.42 (s, 9H), 1.24 (t, J=7.1 Hz, 3H), 1.20 (t, J=7.2 Hz, 3H, minor diastereomer); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 171.7, 168.7, 167.9, 149.9, 141.6, 133.1, 129.0, 128.6, 128.4, 128.4, 127.4, 127.3, 126.6, 125.0, 124.8, 117.3, 116.7, 104.6, 103.1, 81.4, 81.3, 65.1, 64.1, 63.1, 62.6, 62.4, 62.3, 60.7, 60.6, 52.7, 51.8, 51.3, 50.7, 50.0, 48.0, 34.3, 31.9, 31.7, 28.2, 22.8, 21.0, 16.1, 14.2, 14.0; R_f (SiO_2, hexanes/EtOAc 3:1) 0.5; $[\alpha]_D^{25}$ −65.0 (c 0.320, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 2980, 2936, 1781, 1741, 1693, 1651 cm^{-1}; HRMS (MH^+), found 591.2712. $C_{33}H_{39}N_2O_8$ requires 591.2706.

4.11. (5*S*,8*S*,10*R*,11*S*)-10-*tert*-Butyl 5-ethyl 13-benzyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (21a) and (5*R*,8*S*,10*R*,11*S*)-10-*tert*-butyl 5-ethyl 13-benzyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-5,10-dicarboxylate (21b)

To a stirred solution of a 2.6:1 mixture of compounds **20a** and **20b** (410 mg, 0.695 mmol, 1.0 equiv) in THF/MeOH 1:1 (14 mL, 0.05 M), under Ar, was added K_2CO_3 (192 mg, 1.39 mmol, 2.0 equiv). The suspension was stirred for 2.5 h, the solvent was evaporated and the residue was partitioned between phosphate buffer (0.1 M, pH=7.5, 50 mL) and EtOAc (33 mL). The aqueous phase was extracted with EtOAc (2×33 mL) and the combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 5:1 mixture of the title compounds **21a** and **21b** (255 mg, 67%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.38−7.24 (m, 5H), 6.76 (s, 1H), 6.63 (s, 1H, minor diastereomer), 6.49 (s, 1H, minor diastereomer), 6.43 (s, 1H, minor diastereomer), 6.42 (s, 1H), 6.39 (s, 5H), 5.46 (s, 1H, minor diastereomer), 5.45 (s, 1H. minor diastereomer), 4.24 (q, J=7.1 Hz, 2H), 4.19−3.9 (m, 5H), 4.07 (s, 1H), 3.86 (d, J=7.5 Hz, 1H), 3.84 (s, 1H, minor diastereomer), 3.82 (s, 3H), 3.31 (dd, J=9.8, 6.0 Hz, 1H, minor diastereomer), 2.79 (dd, J=9.5, 4.6 Hz, 1H), 2.74−2.66 (m, 1H), 2.46 (dd, J=13.0, 9.9 Hz, 1H, minor diastereomer), 2.26 (s, 3H, minor diastereomer), 2.24 (s, 3H), 2.13 (dd, J=13.4, 9.6 Hz, 6H), 1.46 (s, 9H, minor diastereomer), 1.42 (s, 9H), 1.27 (t, J=7.1 Hz, 3H), 1.24 (t, J=7.2 Hz, 3H, minor diastereomer); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 171.9, 170.7, 170.6, 170.4, 168.9, 146.9, 146.8, 146.2, 138.5, 138.0, 136.1, 134.2, 131.9, 131.7, 128.5, 127.4, 127.3, 126.6, 126.0, 119.1, 119.1, 110.8, 103.4, 81.3, 64.3, 62.7, 62.6, 60.8, 60.8, 52.2, 52.2, 52.1, 51.5, 50.8, 48.2, 32.1, 28.2, 28.1, 22.8, 15.9, 14.3; R_f (SiO_2, hexanes/EtOAc 2:1) 0.45; $[\alpha]_D^{25}$ −73.6 (c 0.282, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3374 (br), 2980, 2938, 1736, 1689, 1647, 1154 cm^{-1}; HRMS (MH^+), found 549.2606. $C_{31}H_{37}N_2O_7$ requires 549.2601.

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4.12. (5*S*,8*S*,10*R*,11*S*)-*tert*-Butyl 13-benzyl-5-formyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (22a) and (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-5-formyl-4-hydroxy-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (22b)

A solution of $LiAlH_4$ in THF (1.0 M, 447 μL, 0.447 mmol, 1.0 equiv) was added dropwise to a solution of a 5:1 mixture of compounds **21a** and **21b** (245 mg, 0.447 mmol, 1.0 equiv) in THF (9 mL, 0.05 M), under Ar, at −10 °C. The solution was stirred for 10 min at this temperature, quenched with EtOAc (12 mL) and satd aq Rochelle's salt (12 mL) and allowed to warm to rt. The flask was covered with aluminum foil and stirred overnight under a stream of Ar. The solution was diluted with phosphate buffer (0.1 M, pH=7.5, 50 mL), the phases were separated and aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 3:1 mixture of the title compounds **22a** and **22b** (124 mg, 55%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.48 (s, 1H), 9.38 (s, 1H, minor diastereomer), 7.41–7.23 (m, 5H), 6.58 (s, 1H), 6.57 (s, 1H, minor diastereomer), 6.43 (s, 1H, minor diastereomer), 6.41 (s, 1H), 6.18 (s, 1H, minor diastereomer), 6.17 (s, 1H, minor diastereomer), 4.25 (1/2 AB, *J*=13.5 Hz, 1H), 4.18 (1/2 AB, *J*=13.5 Hz, 1H), 4.07 (s, 1H), 4.00 (s, 1H, minor diastereomer), 3.83 (s, 3H, minor diastereomer), 3.81 (s, 3H, minor diastereomer), 3.40 (dd, *J*=9.7, 6.0 Hz, 1H, minor diastereomer), 2.81 (dd, *J*=9.5, 4.7 Hz, 1H), 2.73–2.67 (m, 1H), 2.59 (dd, *J*=13.0, 9.8 Hz, 1H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.15 (dd, *J*=13.4, 9.6 Hz, 1H), 1.48 (s, 9H, minor diastereomer), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.1, 191.3, 172.5, 171.9, 170.1, 145.7, 144.6, 138.6, 138.0, 136.6, 135.3, 131.5, 128.8, 128.4, 127.5, 127.2, 119.4, 119.2, 107.3, 104.0, 102.7, 102.6, 81.4, 64.1, 64.0, 62.9, 62.8, 61.2, 61.1, 58.6, 58.5, 51.6, 50.8, 48.8, 34.7, 32.4, 31.7, 29.8, 28.1, 22.8, 16.0, 14.3; R_f (SiO_2, hexanes/EtOAc 2:1) 0.42; $[\alpha]_D^{25}$ −64.8 (*c* 0.250, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3331 (br), 2977, 2935, 1733, 1679, 1642, 1154 cm^{-1}; HRMS (MH^+), found 505.2345. $C_{29}H_{33}N_2O_6$ requires 505.2339.

4.13. (5*S*,8*S*,10*R*,11*S*)-*tert*-Butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (23a) and (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-formyl-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (23b)

To a stirred solution of a 3:1 mixture of compounds **22a** and **22b** (115 mg, 0.228 mmol, 1.0 equiv) and benzyl bromide (108 μL, 0.912 mmol, 4.0 equiv) in DMF (7.6 mL, 0.03 M), under Ar, were added tetrabutylammonium iodide (9.0 mg, 0.023 mmol, 0.10 equiv) and finely ground anhydrous Na_2CO_3 (241 mg, 2.28 mmol, 10 equiv). The mixture was vigorously stirred for 2 h and diluted with water (25 mL) and phosphate buffer (0.1 M, pH=7.5, 25 mL). The aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 6:1, 4:1) to afford a 2.2:1 mixture of compounds **23a** and **23b** (88 mg, 65%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.32 (s, 1H), 9.19 (s, 1H minor diastereomer), 7.48–7.22 (m, 10H), 6.63 (s, 1H, minor diastereomer), 6.62 (s, 1H), 6.38 (s, 1H, minor diastereomer), 6.36 (s, 1H), 5.37 (s, 1H), 5.36 (s, minor diastereomer), 5.28 (1/2 AB, *J*=11.1 Hz, 1H, minor diastereomer), 5.26 (1/2 AB, *J*=11.1 Hz, 2H), 5.20 (1/2 AB, *J*=11.1 Hz, 1H, minor diastereomer), 5.14 (1/2 AB, *J*=11.1 Hz, 1H), 4.20 (1/2 AB, *J*=13.5 Hz, 1H), 4.14 (1/2 AB, *J*=13.5 Hz, 1H), 4.05 (s, 1H), 3.97 (s, 1H, minor diastereomer), 3.86 (s, 3H, minor diastereomer), 3.84 (s, 3H), 3.80 (1/2 AB, *J*=13.5 Hz, 1H) 3.79 (d, *J*=7.4 Hz, 1H), 3.75 (d, *J*=6.9 Hz, minor diastereomer), 3.68 (1/2 AB, *J*=13.5 Hz, 1H, minor diastereomer), 3.37 (dd, *J*=9.7, 6.1 Hz, 1H, minor diastereomer), 2.78 (dd, *J*=9.6, 4.7 Hz, 1H), 2.71–2.64 (m, 2H), 2.53 (1/2 ABX, *J*=13.1, 9.9 Hz, 1H, minor diastereomer), 2.28 (s, 3H, minor diastereomer), 2.26 (s, 3H), 2.10 (dd, *J*=13.3, 9.7 Hz, 1H), 1.45 (s, 9H minor diastereomer), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.5, 191.7, 171.9, 169.8, 168.8, 150.4, 150.3, 148.3, 148.1, 138.6, 138.1, 136.9, 136.9, 136.6, 135.3, 133.7, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 127.4, 127.2, 126.9, 123.1, 122.8, 115.0, 114.6, 103.9, 102.5, 81.4, 81.2, 75.0, 75.0, 65.0, 63.9, 63.1, 62.8, 60.5, 58.8, 57.3, 52.8, 51.6, 48.8, 34.7, 32.2, 28.2, 16.0, 16.0; R_f (SiO_2, hexanes/EtOAc 4:1) 0.45; $[\alpha]_D^{25}$ −64 (*c* 0.32, CH_2Cl_2); IR (film, CH_2Cl_2), ν_{max} 3030, 2976, 2934, 1733, 1688, 1646, 1154 cm^{-1}; HRMS (MH^+), found 595.2801. $C_{36}H_{39}N_2O_6$ requires 595.2808.

To a stirred solution of a 2.2:1 mixture of compounds **23a** and **23b** (88 mg, 0.15 mmol, 1.0 equiv) in THF (2 mL, 0.08 M), under Ar, was added DBN (19 μL, 0.15 mmol, 1.0 equiv). The mixture was stirred for 30 min and then diluted with phosphate buffer (0.1 M, pH=7.5, 50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (3×33 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was dissolved in the minimal amount of EtOAc purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford a 1:2.2 mixture of compounds **23a** and **23b** (64 mg, 72%) as a pale yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.32 (s, 1H, minor diastereomer), 9.19 (s, 1H), 7.48–7.24 (m, 10H), 6.63 (s, 1H), 6.62 (s, 1H, minor diastereomer), 6.38 (s, 1H), 6.36 (s, 1H, minor diastereomer), 5.37 (s, 1H, minor diastereomer), 5.36 (s, 1H), 5.28 (1/2 AB, *J*=11.1 Hz, 1H), 5.26 (1/2 AB, *J*=11.1 Hz, 1H, minor diastereomer), 5.19 (1/2 AB, *J*=11.1 Hz, 1H), 5.13 (1/2 AB, *J*=11.2 Hz, 2H, minor diastereomer), 4.20 (1/2 AB, *J*=13.4 Hz, 1H, minor diastereomer), 4.14 (1/2 AB, *J*=13.5 Hz, 1H minor diastereomer), 4.05 (s, 1H, minor diastereomer), 3.97 (s, 1H), 3.86 (s, 3H, minor diastereomer), 3.84 (s, 3H, minor diastereomer), 3.81 (1/2 AB, *J*=13.6 Hz, 1H), 3.79 (d, *J*=6.2 Hz, 4H), 3.75 (d, *J*=6.6 Hz, 3H), 3.68 (1/2 AB, *J*=13.4 Hz, 3H), 3.37 (dd, *J*=9.8, 6.0 Hz, 1H), 2.78 (dd, *J*=9.5, 4.7 Hz, 1H, minor diastereomer), 2.71–2.65 (m, 2H), 2.53 (1/2 ABX, *J*=13.0, 9.9 Hz, 3H), 2.28 (s, 3H), 2.26 (s, 3H, minor diastereomer), 2.10 (dd, *J*=13.4, 9.5 Hz, 1H, minor diastereomer), 1.45 (s, 9H), 1.44 (s, 9H, minor diastereomer); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.5, 191.7, 172.5, 171.9, 168.8, 150.4, 148.1, 138.0, 136.9, 135.3, 133.7, 128.9, 128.8, 128.8, 128.6, 128.5, 128.4, 128.3, 127.4, 127.2, 126.9, 123.1, 122.8, 115.0, 114.6, 103.9, 102.5, 81.4, 81.2, 75.0, 75.0, 65.0, 63.9, 63.1, 62.7, 60.4, 58.8, 57.3, 52.7, 51.6, 50.9, 48.8, 34.7, 32.2, 28.2, 28.1, 16.0, 16.0; R_f (SiO_2, hexanes/EtOAc); $[\alpha]_D^{25}$ +27 (*c* 0.22, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3029, 2969, 2935, 1732, 1688, 1647, 1154 cm^{-1}; HRMS (MH^+), 595.2789. $C_{36}H_{39}N_2O_6$ requires 595.2808.

4.14. (5*S*,8*S*,10*R*,11*S*)-*tert*-Butyl 13-benzyl-4-(benzyloxy)-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (24a) and (5*R*,8*S*,10*R*,11*S*)-*tert*-butyl 13-benzyl-4-(benzyloxy)-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (24b)

To a stirred solution of a mixture of compounds **23a** and **23b** (60 mg, 0.10 mmol) in EtOH (5 mL, 0.20 M), at 0 °C, under Ar, was

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added $NaBH_4$ (30 mg, 0.80 mmol 8.0 equiv). The reaction was stirred at rt for 2 h, quenched with 1 N HCl (2.4 mL, 2.40 mmol, 24 equiv) and diluted with phosphate buffer (0.1 M, pH=7.5, 50 mL). The aqueous phase was extracted with EtOAc (3×25 mL) and the combined organic layers were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to afford compounds **23a** (18 mg, 30%) as a colorless oil and compound **23b** (38 mg, 65%) as a colorless oil. Compound **23a**: ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.50–7.22 (m, 10H), 6.62 (s, 1H), 6.14 (t, J=6.1 Hz, 1H), 5.48 (s, 1H), 5.18 (1/2 AB, J=11.1 Hz, 1H), 5.09 (1/2 AB, J=11.1 Hz, 1H), 4.10 (s, 1H), 3.97 (1/2 AB, J=13.3 Hz, 1H), 3.87 (1/2 AB, J=13.3 Hz, 1H), 3.79 (d, J=7.7 Hz, 1H), 3.73 (s, 1H), 2.69 (ddt, J=27.0, 9.0, 4.6 Hz, 2H), 2.25 (s, 3H), 2.06 (dd, J=13.3, 9.5 Hz, 1H), 1.90 (br t, 6.0 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 171.7, 150.5, 148.2, 138.3, 137.2, 135.6, 132.6, 128.7, 128.5, 128.4, 128.4, 127.6, 127.3, 122.1, 120.1, 103.7, 81.3, 75.1, 65.4, 64.2, 62.7, 60.4, 51.7, 51.3, 50.7, 31.6, 28.1, 28.1, 15.9, 14.3; R_f (SiO_2, hexanes/EtOAc 4:1) 0.12; $[\alpha]_D^{25}$ −60.0 (c 0.895, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3447 (br), 3063, 3030, 2934, 2870, 1730, 1676, 1636, 1154 cm^{-1}; HRMS (MH^+), found 597.2971. $C_{36}H_{41}N_2O_6$ requires 597.2965. Compound **24b**: ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.62 (s, 1H), 6.09 (dd, J=8.4, 4.4 Hz, 1H), 5.45 (s, 1H), 5.17 (1/2 AB, J=11.1 Hz, 1H), 5.14 (1/2 AB, J=11.1 Hz, 1H), 3.95 (s, 1H), 3.83 (s, 3H), 3.78 (d, J=13.5 Hz, 1H), 3.73 (d, J=6.6 Hz, 1H), 3.63 (d, J=13.4 Hz, 1H), 3.63–3.50 (m, 1H), 3.15 (dd, J=9.8, 6.1 Hz, 1H), 2.63 (dt, J=12.8, 6.5 Hz, 1H), 2.45 (dd, J=13.0, 9.8 Hz, 1H), 1.77–1.74 (br m, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 170.4, 150.6, 147.9, 138.1, 137.2, 134.0, 132.5, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 127.3, 126.5, 122.8, 122.7, 120.6, 105.3, 105.3, 81.3, 75.0, 65.5, 65.5, 63.1, 63.0, 60.4, 52.7, 49.4, 49.4, 48.4, 34.8, 28.2, 16.0, 16.0; R_f (SiO_2, hexanes/EtOAc 4:1) 0.10; $[\alpha]_D^{25}$ +64 (c 0.31, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3444 (br), 3062, 3029, 2970, 2927, 1729, 1682, 1639, 1154 cm^{-1}; HRMS (MH^+), found 597.2974. $C_{36}H_{41}N_2O_6$ requires 597.2965.

4.15. (5*R*,8*S*,10*R*,11*S*)-*tert*-Butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11-hexahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (25)

A solution of compound **24b** (7.0 mg, 0.012 mmol) in glacial acetic acid (1 mL) and 10% Pd/C (7 mg) were placed in round bottom flask and sparged with Ar for 5 min. The vessel was evacuated and filled with hydrogen three times. The reaction was vigorously stirred overnight under hydrogen (1 atm). The suspension was diluted with CH_2Cl_2 (25 mL) and then filtered through Celite® and the flask was rinsed with CH_2Cl_2 (3×5 mL). The solution was extracted with satd aq $NaHCO_3$ (3×15 mL). The combined aqueous layers were diluted with phosphate buffer (0.1 M, pH=7.5, 25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were rinsed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 97:3) to afford compound **25** (4.6 mg, 92%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.40 (s, 1H), 6.05 (dd, J=7.9, 4.1 Hz, 1H), 5.53 (s, 1H), 4.30 (s, 1H), 4.09 (d, J=6.7 Hz, 1H), 3.78–3.74 (m, 2H), 3.76 (s, 3H), 3.65–3.60 (m, 1H), 3.17 (dd, J=9.3, 6.2 Hz, 1H), 2.61 (dd, J=13.1, 9.4 Hz, 1H), 2.32 (dt, J=13.2, 6.6 Hz, 1H) 2.24 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 171.1, 145.2, 144.7, 144.7, 136.9, 136.8, 130.3, 127.1, 119.1, 112.9, 112.9, 102.7, 81.6, 65.1, 62.4, 61.8, 61.0, 49.5, 48.1, 37.0, 29.8, 29.8, 28.2, 15.9; R_f (SiO_2, $CHCl_3$/MeOH 95:5) 0.17; $[\alpha]_D^{25}$ +4.3 (c 0.23, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3262 (br), 2969, 2925, 2854, 1719, 1683, 1646, 1154 cm^{-1}; HRMS (MH^+), found 417.2033. $C_{22}H_{29}N_2O_6$ requires 417.2026.

4.16. (5*R*,8*S*,10*R*,11*S*,11a*S*)-*tert*-Butyl 4-hydroxy-5-(hydroxymethyl)-3-methoxy-2-methyl-7-oxo-5,7,8,9,10,11,11a,12-octahydro-8,11-epiminoazepino[1,2-*b*]isoquinoline-10-carboxylate (26)

To a solution of compound **25** (4.6 mg, 0.011 mmol) in EtOH (1 mL) in a 5 mL vial, was added a slurry of Raney® nickel 2800 (500 μL of commercially available water slurry, washed with EtOH (3×1 mL) and suspended in EtOH (1 mL)). The vial was placed in a Fisher–Porter bottle, under Ar, the suspension was sparged with Ar for 5 min and the vessel was filled with hydrogen gas at 100 psi. The reaction was vigorously stirred overnight, diluted with EtOAc (10 mL) and satd aq Rochelle's salt (10 mL), and stirred vigorously for 2 h. The biphasic suspension was filtered through Celite®, the phases separated and the aqueous phase extracted with EtOAc (3×10 mL). The combined organic phases were rinsed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH 97:3) to afford compound **26** (3.4 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.51 (s, 1H), 5.59 (dd, J=5.6, 3.4 Hz, 1H), 3.96 (d, J=6.1 Hz, 1H), 3.88 (dd, J=10.9, 3.2 Hz, 1H), 3.78 (s, 3H), 3.77–3.76 (m, 1H), 3.67 (dt, J=12.4, 2.6 Hz, 1H), 3.61 (dd, J=11.1, 5.8 Hz, 1H), 3.16 (dd, J=9.0, 6.4 Hz, 1H), 2.84 (t, J=13.5 Hz, 1H), 2.54 (dd, J=14.7, 2.2 Hz, 1H), 2.50 (dd, J=13.2, 9.0 Hz, 1H), 2.27 (s, 3H), 2.18 (dt, J=13.2, 6.6 Hz, 1H), 1.53–1.45 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 172.4, 145.7, 132.0, 129.7, 121.2, 120.2, 118.0, 81.5, 67.8, 63.0, 62.2, 61.0, 60.8, 52.6, 42.8, 38.8, 32.1, 29.9, 28.2, 15.9; R_f (SiO_2, $CHCl_3$/MeOH 95:5) 0.20; $[\alpha]_D^{25}$ −36 (c 0.080, $CHCl_3$); IR (film, CH_2Cl_2), ν_{max} 3286 (br), 2958, 2925, 2855, 1729, 1652, 1456 cm^{-1}; HRMS (MH^+), found 419.2174. $C_{22}H_{31}N_2O_6$ requires 419.2182.

Acknowledgements

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Supplementary data

^{1}H and ^{13}C NMR spectra of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.009.

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24. The lack of reactivity of the primary hydroxyl of **7** is consistent with the regioselectivity observed in the reaction between TBS-Cl and diols bearing a β-aminoalcohol motif (Ref. 24). We concur with the explanation provided by the authors, which stated that the nucleophilicity of the primary hydroxyl is reduced by internal hydrogen bonding to the neighboring amino group.
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35. As illustrated in Scheme 4, we propose that the dipolarophile adds from the Re face of the iminium ion carbon to form **20a**, which epimerizes under the reaction conditions to form **20b**.
36. We propose that the observed chemoselectivity can be explained by the initial formation of a phenoxyaluminum hydride species, which upon delivery of one hydride to the ester, forms a stable seven-membered ring alkoxy(phenoxy) aluminum hydride species.
37. Compounds **23a** and **23b** are unstable to silica gel. Consequently, we did not attempt their separation for the purpose of recycling of **23a**.

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APPENDIX 3

Research proposal

Synthesis of Lagunamide C
Research Proposal

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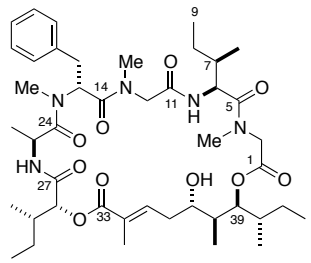
Department of Chemistry

Abstract

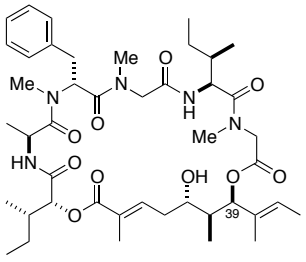
A stereodivergent strategy for the structural revision of lagunamide C has been proposed. This cyclodepsipeptide is a member of the aurilide class of natural products and was isolated from the marine cyanobacterium *Lyngbya majuscula.* It showed potent cytotoxic activities against a panel of cancer cell lines, including P388, A549, PC3, HCT8, and SK-OV3. Its polyketide fragment is synthetically challenging due to the presence of a 1,4-dihydroxy-2,5-dimethyl structural motif. To set the configuration of the key stereocenters, I proposed a tunable route involving an acetate aldol reaction, a Charrette cyclopropanation, and a Corey-Bakshi-Shibata (CBS) reduction.

I. Introduction

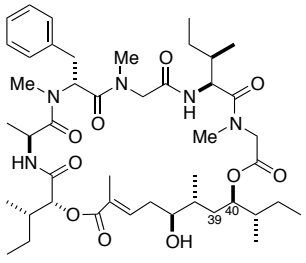
The lagunamides are a family of cytotoxic cyclodepsipeptides isolated by Tan and coworkers.[1,2] These compounds belong to the aurilide class of natural products,[3,4,5,6] which are the product of mixed NRPS-PKS systems. A sample of the marine cyanobacterium *Lyngbya majuscula* was collected at Pulau Hantu Besar, Singapore, in 2007. The chromatographic separation of the organic extracts afforded lagunamides A, B and C, which showed potent cytotoxic activities against a panel of cancer cell lines, including P388, A549, PC3, HCT8, and SK-OV3 cells, with IC_{50} values ranging from 1.6 nM to 24 nM.[2,7]



1
Lagunamide A (published structure)



2
Lagunamide B (published structure)

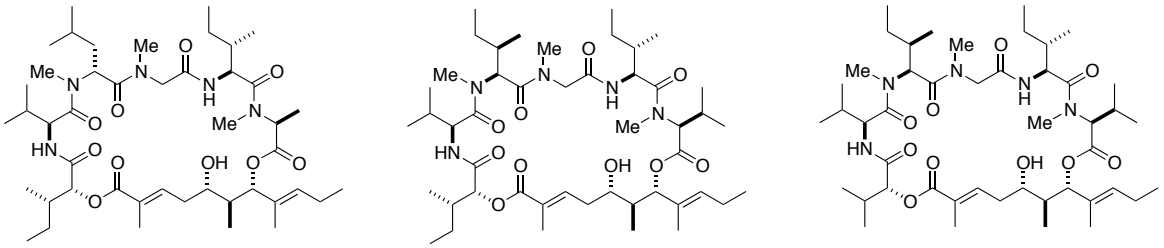


3
Lagunamide C (published structure)

Figure 1. Structures reported in the isolation articles

According to Tan and co-workers, the lagunamides comprise a polypeptide portion featuring a D-*allo*-2-hydroxyisoleucic acid fragment connected to L-Ala, *N*-Me-D-Phe, Gly, L-*allo*-

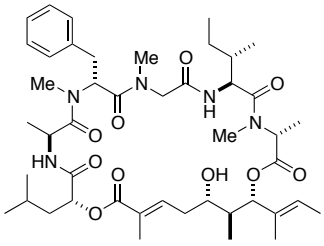
isoleucine and *N*-Me-L-Ala residues. The reported polyketide fragment for lagunamide B is structurally related to the one found in kulokekahilide-2,[2,5] which has identical C-33 - C-38 and C-40 - C42 segments (lagunamide A numbering) and opposite stereochemistry at C-39 (see Figure 2). Both the reduction of the exocyclic double bond seen in lagunimides A and C, and the presence of an extra methylene group in the polyketide fragment of lagunamide C (C-39) are unprecedented features in the aurilide class of natural products.



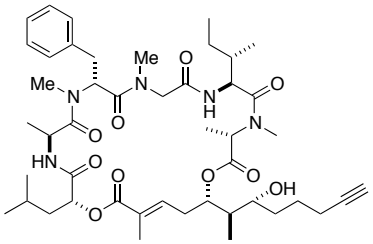
4
aurilide

5
aurilide B

6
aurilide B



7
kulokekahilide-2

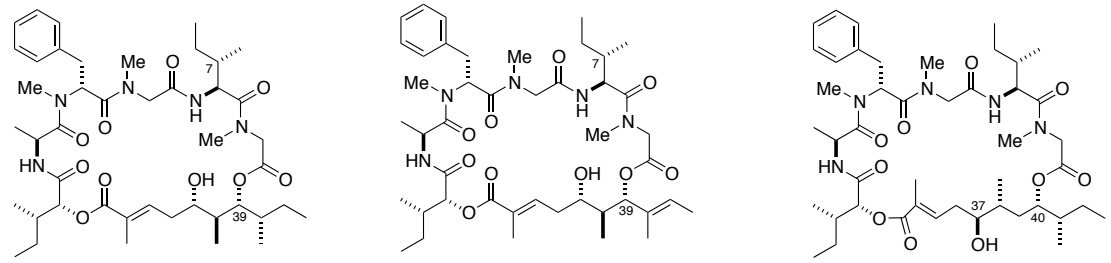


8
palau'amide

Figure 2. Aurilide Class of Natural products

In a recent communication, Ye and coworkers published the total synthesis and structural revision of lagunamide A.[8] In the revised structure (9), the L-*allo*-isoleucine residue was replaced with a L-isoleucine residue and the absolute configuration at C-39 was inverted. Both structural features are consistent with all of the previously isolated members of the aurilide class. Consequently, I expect that the structures of lagunamide B (10) and C (11) must include a L-isoleucine residue in the northern part of the structure. In addition, I expect the polyketide found in lagunamide B to be the same fragment found in kulokekahilide-2. Given the unprecedented nature of lagunamide C's polyketide fragment, I can only assume that the configurations at C-37, C-38 and C-41 must be identical to the ones found in the corresponding carbons in all of the other members of the aurilide class. This structural assignment is based on the assumption that similar enzymes are involved in the reduction events that form these stereocenters. Since the biosynthetic process that leads to the insertion of the extra methylene C-39 unit is unknown, the only information available to predict the stereochemistry at C-40 is the

incorrect NMR analysis discussed in the original isolation paper, which was similar to the one employed to assign the stereochemistry of C-39 in lagunamides A and B.[1,2] Consequently, I also expect the configuration at C-40 in the natural product to be consistent with all of the members of the aurilide class.



9
Lagunamide A (revised structure)

10
Lagunamide B (proposed structure)

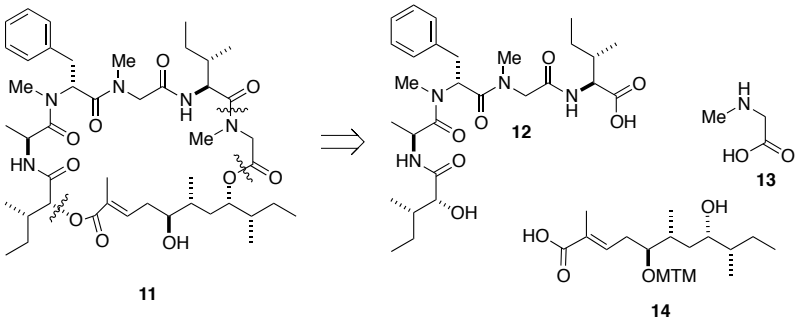
11
Lagunamide C (proposed structure)

Figure 3. Revised and proposed structures for lagunamides A-C

II. Proposed Area of Research

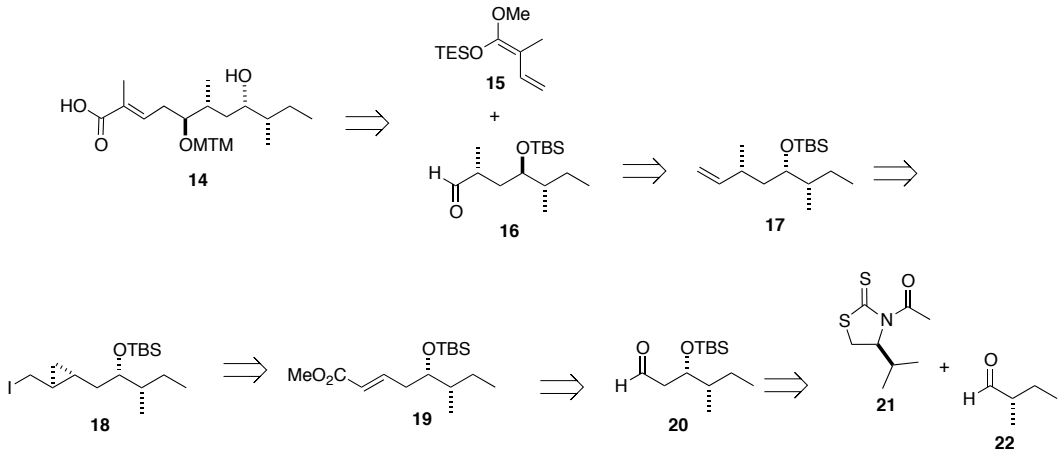
To date, no synthesis of lagunamide C has been reported and its structure has not been confirmed. Given its potent cytotoxic activities, effort should be directed towards establishing or confirming the correct structure of the compound, and using the synthetic routes to prepare analogs that could be used for structure-activity relationship (SAR) studies. This proposal will delineate efforts towards a) developing a stereodivergent synthetic route to access multiple possible diastereomers of the polyketide fragment, b) gaining access to lagunamide C, and c) gaining access to lagunamide C analogs.

III. Retrosynthetic Analysis



Scheme 1. Retrosynthetic Analysis for Lagunamide C (11) access

Retrosynthetically, I envision the disconnection of the macrocycle to the three key units illustrated in Scheme 1. Given the ready availability of sarcosine (**13**) and the building blocks required to prepare compound **12**, I expect that the main synthetic challenge will be the preparation of acid **14**. As shown in Scheme 2, this key intermediate could be accessed via a Mukaiyama vinylogous aldol reaction[9] of silyl ketene acetal **15** and aldehyde **16**, which in turn could be obtained from alkene **17** through the reductive opening of iodomethylcyclopropane **18**. The latter could be prepared from ester **19**, through reduction to the allylic alcohol, followed by an asymmetric cyclopropanation and substitution with iodide. Compound **19** could be obtained through a Wittig reaction with aldehyde **20**, which in turn could be prepared using an acetate aldol reaction of thiazolidinethione **21** and *(S)*-2-methylbutanal (**22**).

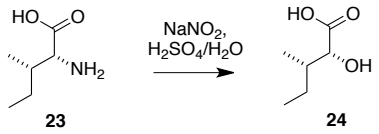


Scheme 2. Retrosynthetic Analysis for polyketide (14) access

IV. Proposed Synthesis of Lagunamide C

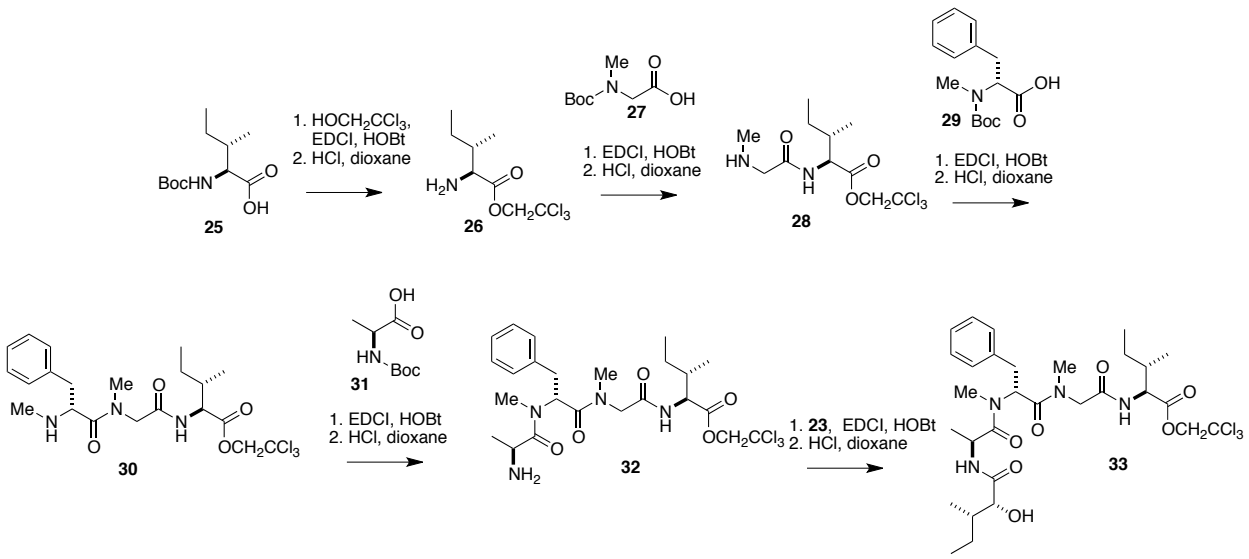
Herein is the proposed convergent synthesis of Lagunamide C.

a) Synthesis of polypeptide 33



Scheme 3. Synthesis of D-*allo*-2-hydroxyisoleucic acid

Commercially available D-*allo*-isoleucine (**23**) will be diazotized and hydrolyzed with configuration retention, to provide D-*allo*-2-hydroxyisoleucic acid (**24**) (Scheme 3).[10]



Scheme 4. Proposed Synthesis of polypeptide 33

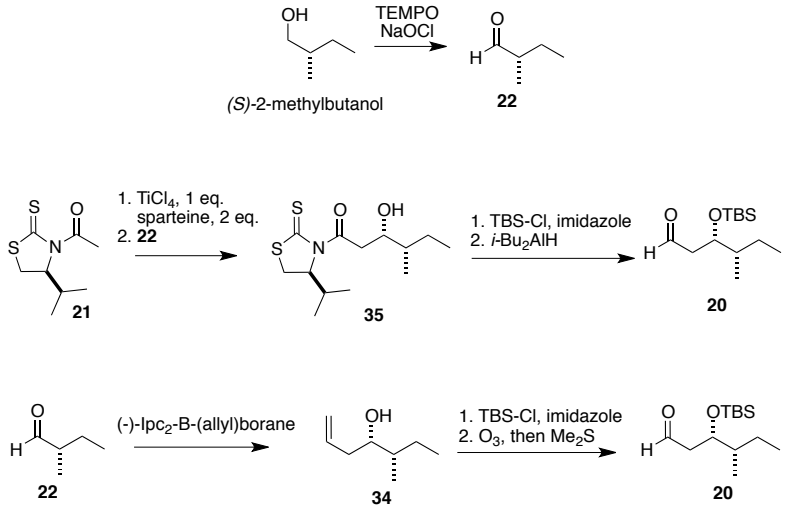
For all of the peptide-coupling and esterification reactions, the choices of the acid activating reagent and the conditions will be based on factors such as price, convenience, product optical purity and yield, and will depend on the outcome of each particular reaction. The peptide couplings of Scheme 6 are shown using the EDCI/HOBt combination. If problems arise, any other standard carboxylic acid activating agents, such as DCC, HATU, PyBOP, BOP-Cl, DMAP, or the like, may be used.[11,12]

Commercially available *N*-Boc-L-isoleucine will be converted into the corresponding trichloroethyl ester, followed by *N*-Boc removal,[13] to provide compound **26,** which in turn will be coupled with *N*-Boc sarcosine (**27**) to give dipeptide **28** (Scheme 4). Tetrapeptide **32** will be prepared with two similar coupling/deprotection cycles involving *N*-Me-D-phenylalanine **29** and *N*-Me-L-Ala **31.** The esterification of D-*allo*-2-hydroxyisoleucic acid (**24**) with **32** will afford compound **33**.

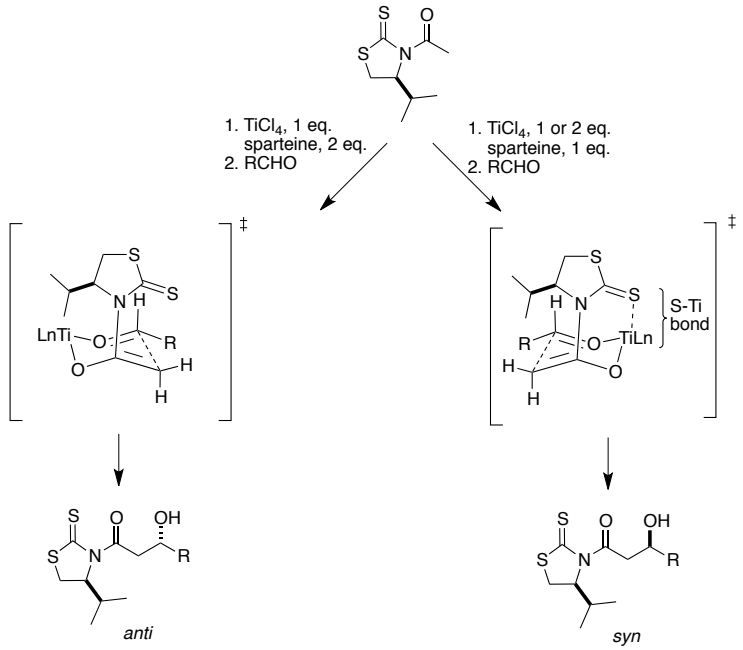
b) Synthesis of aldehyde 45

Commercially available *(S)*-2-methylbutanol will be oxidized with TEMPO/NaOCl to give aldehyde *(S)*-methylbutanal (**22**).[14] I intend to use an acetate aldol reaction between *N*-acetyl thiazolidine-2-thione **21** and compound **22** to gain access to compound **35** (Scheme 5). According to Hodge and Olivo,[15] the use of 2 equivalents of base generates an open transition state where the chiral auxiliary is not coordinated to the titanium atom, and leads to the desired *anti* product (Scheme 6). Presumably, the bidentate amine coordinates to the titanium atom and

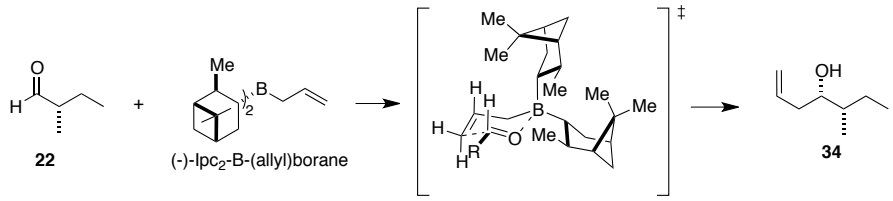
disfavors the coordination of the thiocarbonyl sulfur to the metal center.[16] If problems arise, and the stereochemical outcome of the acetate aldol reactions are not optimal, I will explore the use of alternate thiazolidine-2-thiones,[16, 17, 18, 19] oxazolidine-2-thiones[19] or oxazolidinones[20, 21] to obtain the desired *anti* products with acceptable diastereomeric excesses. With compound **35** in hand, I will convert its secondary hydroxyl into the corresponding *tert*-butyldimethylsilyl ether, followed by direct reduction of the *N*-acetyl thiazolidine-2-thione with DIBAL-H[18] to provide aldehyde **20**.



Scheme 5. Proposed syntheses of aldehyde 20



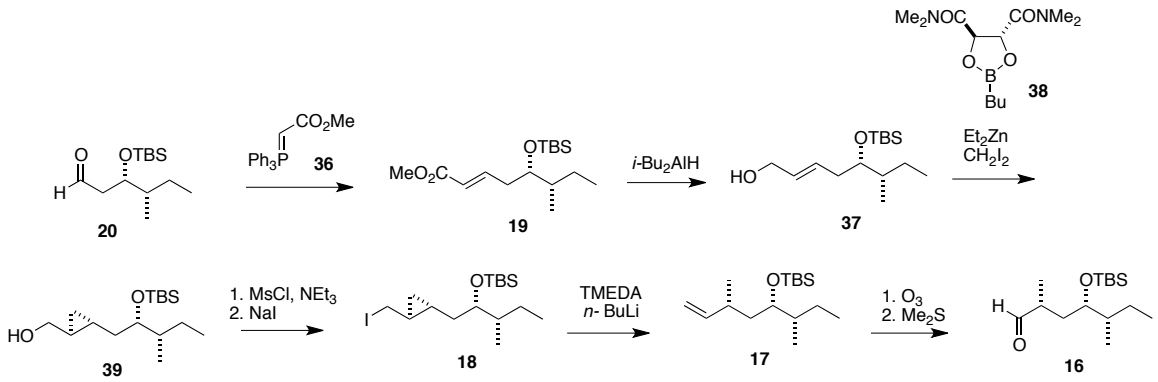
Scheme 6. Proposed transition states for the Ti-mediated acetate aldol reactions



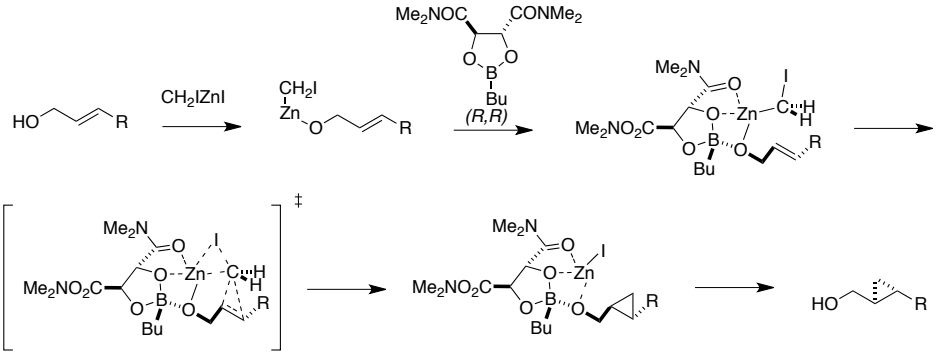
Scheme 7. Proposed transition state for the allylboration reaction

Alternatively, following the procedure reported by Brown,[22] the allylboration of aldehyde **22** with (-)-Ipc_2-B-(allyl)borane will provide alcohol **34** (Scheme 5). The selectivity of this reaction can be explained by the chair-like transition state shown in Scheme 7, where the aldehyde carbon chain occupies an equatorial position and the facial selectivity is governed by the minimization of steric interactions between the axial Ipc ligand and the allyl side chain.[23] TBS protection of **34**, followed by reductive ozonolysis conditions would afford aldehyde **20**.

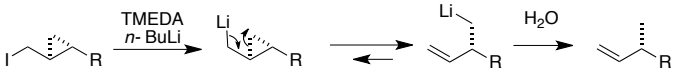
As shown in Scheme 8, aldehyde **20** will be reacted with stabilized Wittig reagent **36** to give ester **19**. Reduction with two equivalents of DIBAL-H will provide allylic alcohol **37**, which in turn will be submitted to Charette's cyclopropanation conditions [24] with diiodomethane, diethylzinc and *(R,R)*-dioxaborolane **38** to give compound **39**. It has been proposed that the stereochemical outcome of the cyclopropanation reaction is governed by the formation of a zinc complex that includes the allylic alcohol-derived alkoxide and the dioxaborolane chiral catalyst (Scheme 9).[25] Mesylation of primary alcohol **39**, followed by substitution with iodide will afford substituted iodomethylcyclopropane **18**. Following Charette's protocol, formation of a cyclopropylmethyllithium species via lithium-halogen exchange will trigger the formation of a homoallylic lithium species, which upon quenching with H_2O, will afford alkene **17** (Scheme 10)**.**[26] The low stability of the (cyclopropylmethyl)lithium species, which rearrange to homoallyl lithium species in the presence of lithium coordinating agents or solvents, was originally described by Lansbury.[27] The process is thought to be driven by the gain in stability produced by the energy that is released when the strained cyclopropyl ring opens and forms the more stable homoallylic species. Compound **17** will be subjected to reductive ozonolysis conditions to provide aldehyde **16**. Alternatively, the aldehyde could be prepared by treating alkene **17** with OsO_4 and $NaIO_4$. Precedent for the approach for the proposed conversion of aldehyde **20** into aldehyde **16** can be found in a similar sequence described by Maier.[28]



Scheme 8. Proposed synthesis of aldehyde 16



Scheme 9. Proposed rationale for the asymmetric cyclopropanation reaction

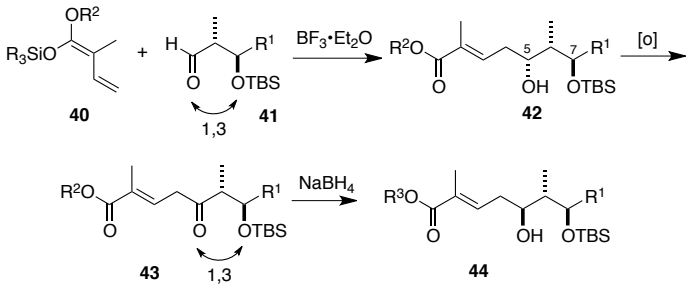


Scheme 10. Lithium-mediated cyclopropyl ring opening

c) Synthesis of acid 50

For the elongation of the polyketide chain, I intend to use a Mukaiyama vinylogous aldol reaction (MVAR)[9] between aldehyde **16** and silyl ketene acetal **15**. Analog transformations were used for the synthesis of the polyketide fragments found in several members of the aurilide class, including aurilide (**4**),[3] kulokekahilide-2[29] (**7**) and palau'amide (**8**).[30] According to the authors, all of these reactions produced single diastereomers, which had the undesired configuration at C-5 (Scheme 11). According to Evans, the high selectivity can be explained by a transition state that combines the mutually reinforcing effects of the α-methyl and β-OTBS groups.[31] The stereochemistry at C-5 was inverted by oxidizing the secondary alcohol and

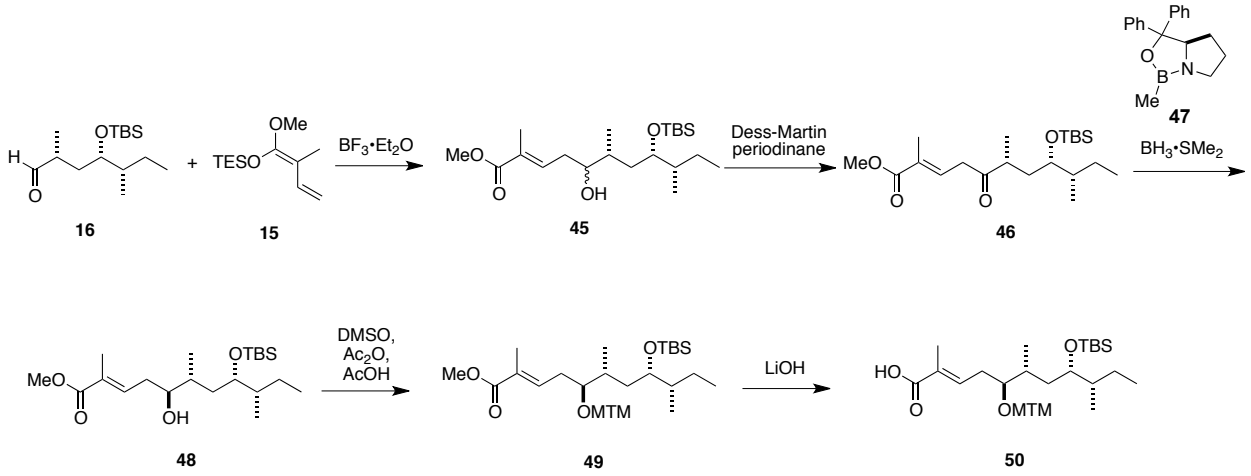
performing a sodium borohydride reduction, which provided the desired diastereomer stereoselectively. Several authors have reported similar stereoselectivity in other reactions involving α-methyl-β-OTBS ketones.[32,33,34] Based on both the above discussed influence of the α and β groups in the outcome of the MVARs, and Evans' work on 1,3-asymmetric induction in hydride reductions of β-substituted ketones,[35] I propose that the OTBS group also plays a significant role in the asymmetric induction of these reductions.



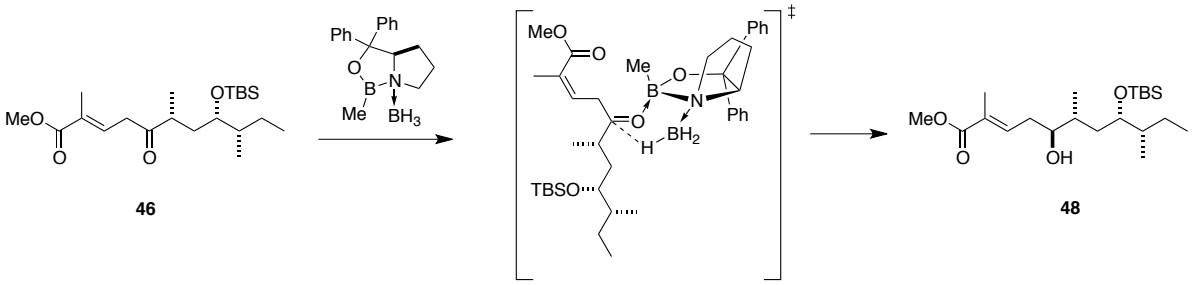
Scheme 11. Asymmetric vinyloguos Mukaiyama aldol reaction/C-4 inversion sequence

As shown in Scheme 12, the proposed aldehyde intermediate **16** is unsubstituted in the β position and the OTBS group is in the γ position. Based on the rationale provided for the asymmetric induction seen in Scheme 11, I do not foresee a high degree of selectivity with the proposed MVAR. In addition, I only found two loosely related examples, which used a $ZnCl_2$ as the Lewis acid and gave a 3:1 mixture of diastereomers,[36] or used a chiral catalyst for the asymmetric induction.[37] In both cases, the aldehydes were structurally simpler than the proposed substrate. Consequently, attempting an asymmetric implementation of this particular MVAR could be a difficult endeavor and therefore I decided to propose a conservative approach for the elongation of the polyketide intermediate. This route involves the isolation of **45** as a diastereomeric mixture, the oxidation of the secondary hydroxyl using Dess-Martin periodane to give compound **46** and a Corey-Bakshi-Shibata (CBS) reduction[38] of the ketone to afford hydroxyester **48**. I chose a reaction involving an asymmetric catalyst because the keto substrate **46** does not have a protected hydroxyl in the β position, and I do not expect that it will be stereoselectively reduced by an achiral reducing agent such as $NaBH_4$. Based on a preliminary conformational analysis, I expect that the use of the *(S)*-(-)-2-methyl-CBS-oxazaborolidine **47** will lead to the preferential formation of transition state shown in Scheme 13, where the interactions between the bulkier ketone substituent and the methyl group attached to the boron atom are minimized.[39] Accordingly, I expect that the hydride would add to the carbonyl's *si* face

to afford compound **48**. Protection of the free hydroxyl as the methylthiomethyl ether,[40] followed by alkaline hydrolysis of the methyl ester with LiOH will afford carboxylic acid **50**.



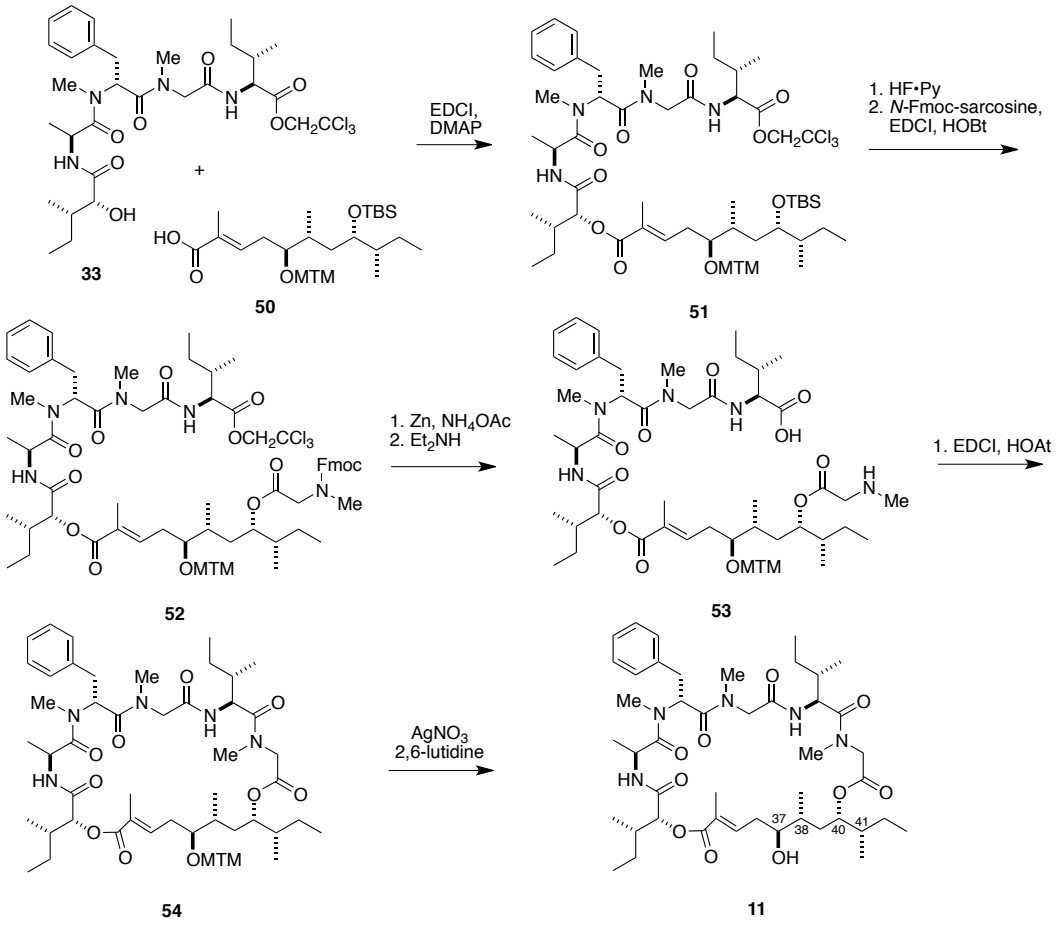
Scheme 12. Proposed synthesis of the protected polyketide fragment



Scheme 13. Proposed transition state for the CBS reduction

d) Synthesis of lagunamide C (11)

As shown in Scheme 14, formation of the ester of protected acid **50** and polypeptide **33** using EDCI and DMAP will provide compound **51**. Removal of the TBS group with HF/pyridine, followed by esterification with *N*-Fmoc-sarcosine will afford compound **52**. After removing the TCE ester and the Fmoc group, the resulting compound will be reacted with EDCI/HOAt to form the macrocycle. The removal of the MTM protecting group with $AgNO_3$ will afford lagunamide C (**11**). Precedent for the conversion of polypeptide **33** into the unprotected macrocycle can be found in a similar sequence described by Yamada for the synthesis of aurilide.[3]



Scheme 14. Proposed completion of the synthesis of lagunamide C (11)

e) Synthesis of alternate diastereomers of the polyketide fragment

The NMR spectrum of the synthetic macrocylcle will be compared with the reported NMR data for lagunamide C. If the NMR spectra do not match, I will adapt the sequence to synthesize diastereomers of acid **50**, which will be used to build diastereomeric macrocycles in an attempt to synthesize the natural product**.** The choice of the chiral center(s) to be inverted will be based on the discrepancies of the corresponding ^{13}C and/or ^{1}H NMR signals.[8] The synthesis of C-41 epimers of **11** could be performed by starting the sequence with *(R)*-2-butanol. This compound is not commercially available and can be obtained in 5 steps from *(S)*-3-hydroxy-2-methylproprionate.[41] The proposed reactions for setting the three remaining chiral centers involve the use of chiral catalysts that were chosen in order to minimize the effect of the previously installed stereocenters on the stereochemical outcome of each reaction. Thus, I expect that by using the enantiomers of thiazolidine-2-thione **21**, dioxaborolane **38** and oxazaborolidine **47**, under the conditions described above, I will be able to selectively access

the diastereomers with opposite stereochemistry at C-40, C-38 and C-37, respectively. Alternatively, the stereochemistry of C-40 could be inverted by using thiazolidine-2-thione **21** with equimolar amounts of $TiCl_4$ and sparteine. As shown in Scheme 6, these conditions would promote the formation of a closed transition state, which lead to the *syn* product.[15] As mentioned above, if stereoselectivy problems arise, alternate thiazolidine-2-thiones,[17,18,19,19] oxazolidine-2-thiones[19] or oxazolidinones[21,21] could be used to obtain the desired *syn* products. Furthermore, the use of (+)-Ipc_2B(allyl)borane instead of (-)-Ipc_2B(allyl)borane in the allyboration reaction could also provide compounds with inverted stereochemistry at C-40.

V. Biological evaluation

The total synthesis of lagunamide C would allow the production of quantities appropriate for the confirmation of the reported biological activities and for conducting further studies that could provide information about its mode of action. In addition, the above described stereodivergent routes would allow the syntheses of lagunamide C analogs that could be used for SAR studies. The information obtained from these preliminary biological studies could lay the groundwork for a broader program aimed at the generation of rationally designed lagunamide C analogs.

VI. Conclusion

A stereodivergent synthetic route has been proposed for the structural revision of lagunamide C and the preparation of analogs thereof. The key reactions are a) an asymmetric acetate aldol reaction, b) a Charette asymmetric cyclopropanation, and c) Corey-Bakshi-Shibata (CBS) reduction. Upon confirmation of lagunamide C's structure, the biological activity of the synthetic material will be confirmed and its analogs will be evaluated.

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LIST OF ABBREVIATIONS

A	Adenylation domain
ACP	Acyl carrier protein
AcCl	Acetyl chloride
AL	Acyl-CoA ligase domain
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyldicarbonate
C	Condensation domain
CAN	Ceric ammonium nitrate
Cbz	Benzyl chloroformate
CSA	Camphorsulfonic acid
DAST	Diethylaminosulfur trifluoride
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL	Diisobutyl aluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)-pyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane

DMDO	Dimethyldioxirane
DMSO	Dimethylsulfoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et_3N	Triethylamine
EtOAc	Ethyl Acetate
Fmoc	(9H-fluoren-9-ylmethoxy)carbonyl
HFIP	Hexafluoroisopropanol
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroybenzotriazole
IBCF	Isobutyl chlorformate
IBX	*o*-Iodoxybenzoic acid
KHDMS	Potassium bis(trimethylsilyl)amide
KOTMS	Potassium trimethylsilanolate
LDA	Lithium *N,N*-diisopropylamide
MIC	Minimal inhibitory concentration
MS	Molecular sieves
Ms	Methanesulfonyl
m-CPBA	*m*-Chloroperbenzoic acid
MeI	Methyl iodide
MOM	Methoxymethyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NMM	*N*-Methylmorpholine

NMO	*N*-Methylmorpholine-*N*-Oxide
NMP	*N*-Methyl pyrrolidine
NRPS	Nonribosomal peptide synthetase
Ns	2-Nitrobenzenesulfonyl
P	Peptidase domain
PCC	Pyridinium chlorochromate
PCP	Peptidyl carrier protein
Pd/C	Palladium on carbon
PS	Pictet-Spenglerase domain
Py	Pyridine
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
R	Reductase domain
REDAL	Sodium bis(2-methoxyethoxy)aluminum hydride
T	Thiolation domain
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenlsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TES	Triethylsilyl
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol

TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl trifluoromethylsulfonate
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethylsulfonate
TPAP	Tetrapropylammonium perruthenate
Ts	*p*-Toluenesulfonyl
p-TsOH	*p*-Toluenesulfonic acid