I. SPIRODIEPOXIDE APPLICATION: PSYMBERIN

II. DIRECT CARBINOLAMIDE SYNTHESIS

By

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ABSTRACT OF THE DISSERTATION

III.   SPIRODIEPOXIDE APPLICATION: PSYMBERIN

II. DIRECT CARBINOLAMIDE SYNTHESIS

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Dissertation Director:

Professor Lawrence J. Williams

The complete structure of Psymberin was determined with the application of the Universal NMR database approach. A formal synthesis of psymberin was completed with the application of spirodiepoxides. An assembly of a dihydroisocumarin ring was accomplished from a complex aldehyde and an anion derived from a pentasubstituted arene. A new condition to couple an aldehyde and an amide was achieved to reach a carbinolamide moiety. This condition was applied for the synthesis of analogs and hybrid structures. In a separate study, a metal and a ligand were investigated to promote the coupling between thioacids and azides.

ACKNOWLEDGEMENT

DEDICATION

This thesis is dedicated to my family.

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List of Abbreviations

^{o}C	degrees Celsius
2,6-lut.	2,6-lutidine
Ac	acetate
acac	acetylacetonate
Bn	benzyl
Boc	*t*-butyloxycarbonyl
Bu	butyl
δ	chemical shift (parts per million)
d	doublet
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
ee	enantiomeric excess
FCC	flash column chromatography
h	hour(s)
Hz	hertz
i	iso
imid.	imidazole
LC_{50}	concentration that will eliminate 50% of a given population when administered as a single dose
m	multiplet
M	molar (moles/liter)

m/z	mass to charge ratio
m-CBA	meta-chlorobenzoic acid
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
min	minutes
ml	milliliters
mol	moles
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
MTP	methoxytrifluoromethylphenyl
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidant
OTf	trifluoromethanesulfonyl
P	protecting group (generic)
p	para
Pd/C	palladium on carbon
Ph	phenyl
PMB	(4-methoxy)benzyl
PMP	4-methoxyphenyl
ppm	parts per million

Chapter I

Structure Elucidation of Psymberin

I. Introduction: Pederin Family

A potent insect toxin was isolated in 1949 from *Paederus fuscipes*, a Japanese beetle known for its severely irritating bite. This natural product was named pederin and its structure was determined by X-ray crystallography in 1968.[1] Over the years, a large family of natural products, named after pederin due to structural resemblance, has been discovered. The pederin family is now composed of more than 30 members, including myclamides A-B,[2] onnamides A-F[3] and theopederins A-L,[4] icadamides A-B,[5] pseudopederin and pederone[6], which were all isolated from marine sponges unlike the first member pederin (See Figure 1).

The members of the pederin family contain different tetrahydropyran rings on each side of an amide. The left segment (**F2.1**) is identical within the family, whereas there are slight structural differences in the right segment (**F2.3**) from member to member. The other striking similarity is that both segments are bridged by *O*-methyl carbinolamide (**F2.2**), which is a rare functional group in organic chemistry.

Figure 1 Representative Members of the Pederin Family
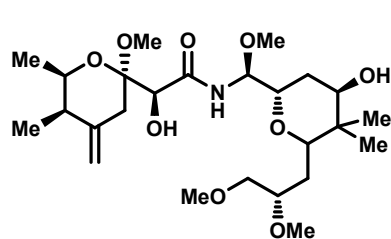
Pederin (F1.1)

Mycalamide A (F1.2)

R=arginyl
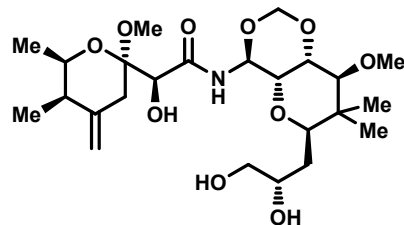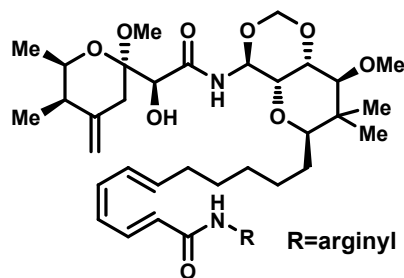
Onnamide A (F1.3)
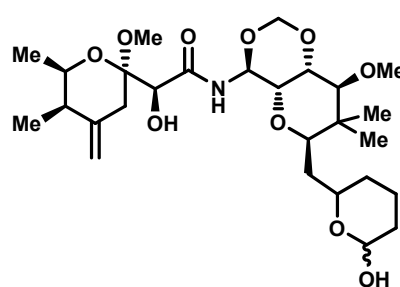
Theopederin A F(1.4)

Figure 2 Structural Similarities within the Pederin Family
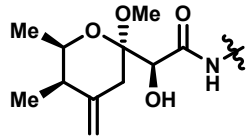
Left Segment (F2.1)
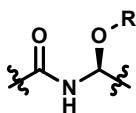
***O*-methyl carbinolamide (F2.2)**
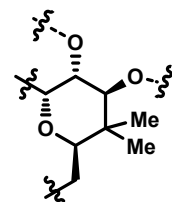
Right Segment (F2.3)

II. A new Member of the Pederin Family: Psymberin

The Pettit and Crews groups independently isolated a new member of the pederin family in 2004. It was isolated from the marine sponge *Ircinia ramose* and named irciniastatin A by the Pettit group.[7] Shortly thereafter, the Crews group reported the isolation of this natural product from the marine sponge *Psammocinia*, located in the waters of Papua New Guinea, and named it psymberin.[6] This natural product was considered a new member for the pederin family as it has a highly substituted tetrahydropyran ring "the right segment" like the pederin molecules and the *O*-methyl carbinolamide functional group. The dihydroisocoumarin ring moiety and lack of an exocyclic olefin containing tetrahydropyran ring constitute the structural differences of psymberin from the other pederin members.

Figure 3 Psymberin
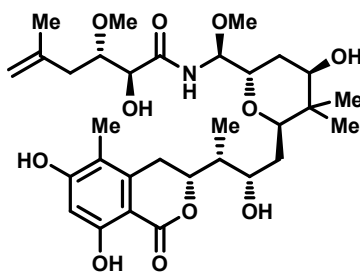
Psymberin (F3)

III. Biological Activity

Many members of the pederin family possess potent antiviral and antitumor properties apparently due to their ability to arrest protein synthesis. Pederin was shown to efficiently inhibit mitosis of HeLa cells and block protein and DNA synthesis.[8]

Mycalamides displayed inhibition toward marine leukemia P388, human promyelocytic (HL-60), human lung (A549) and colon (HT-29) carcinoma cells at nanomolar levels. Mycalamide A also exhibited remarkable immunosuppressant activity at the picomolar level, making it more potent than the clinical agents FK506 and cyclosporine.[9]

The biological activity of psymberin was interestingly different from the other members in the pederin family. Unlike all the other family members, which showed near equipotent cytotoxicity against different tumor cell lines, psymberin exhibited remarkably selective cytotoxicity. The Crews group reported that the difference in activity can be as much as 10,000-fold. As shown in the Table 1, LC_{50} values were found to be around 2.5 nM against several melanoma, colon and breast cancer cell lines whereas it was found to be around 2.5 μM against all leukemia cell lines investigated.[6]

Due to the biological activity and structural differences between psymberin and members of the pederin family, a structure-activity relationship study is expected to reveal significant information regarding the biological action of these natural products. It is believed that the *O*-alkyl carbinolamide (**F2.2**, pg. 2) is necessary for cytotoxicity within all of the pederins. The right segment (**F2.3**, pg. 3) may not be crucial for the selective cytotoxicity since psymberin doesn't possess the typical tetrahydropyran ring. The dihydroisocumarin moiety and vinylic methyl termini could also be reasons for the unprecedented selective cytotoxicity of psymberin.

Table 1 Differential Cell Line Sensitivities (LC$_{50}$) to Psymberin as Identified in the NCI Developmental Therapeutics in Vitro Screening Program

Cell line	LC$_{50}$ (M)	Cell line	LC50 (M)
leukemia		melanoma	
CCRF-CEM	>2.5×10^{-5}	LOX IMVI	>2.5×10^{-5}
HL-60(TB)	>2.5×10^{-5}	MALME-3M	<2.5×10^{-9}
K-563	>2.5×10^{-5}	SK-MEL-2	>2.5×10^{-5}
MOLT-4	>2.5×10^{-5}	SK-MEL-5	<2.5×10^{-9}
RPMI-8226	>2.5×10^{-5}	SK-MEL-28	1.41×10^{-5}
SR	>2.5×10^{-5}	UACC-257	>2.5×10^{-5}
		UACC-62	<2.5×10^{-9}
breast cancer		colon cancer	
MCF7	>2.5×10^{-5}	HCC-2998	3.76×10^{-7}
HS 578T	>2.5×10^{-5}	HCT-116	<2.5×10^{-9}
MDA-MB-435	<2.5×10^{-9}	HT29	>2.5×10^{-5}
NCI-ADR-RES	1.9×10^{-5}	SW-620	>2.5×10^{-5}
T-47D	1.36×10^{-5}		

IV. Structural Determination of Irciniastatin A and Psymberin

A. Pettit Group: Irciniastatin A

As shown in Figure 4, the Pettit group was able to assign the structure of irciniastatin A (F**4.1**) by the use of high resolution mass spectroscopy and 2D-NMR spectroscopy.[7] Even though they were not able to fully define the assignment of relative and absolute configuration of the molecule, they deciphered the simple connectivity by 2D NMR techniques (principally APT, HMQC, HMBC, and ROESY). HMBC experiments were used to identify the amide linkage and to correlate the amide proton to the C_6 carbonyl carbon. Furthermore, interpretation of NOE enhancements provided the assignment of the relative stereochemistry of the carbinolamide and the tetrahydropyran ring. 2D-NOESY and ROESY experiments along with NOE correlations were particularly useful in the deduction of the relative configuration of the four stereogenic centers. They assigned those stereocenters as 7*R*, 8*S*, 10*R* and 12*R*. In addition to this, they defined the molecular formula as $C_{31}H_{48}NO_{11}$ from the molecular ion peak at *m/z* 610.3228 [M + H]$^+$ with the high-resolution FAB mass spectrometry.

Figure 4 Reported Structure of Irciniastatin A by Pettit group

Irciniastatin A (F4.1)

NOE correlations around tetrahydropyran ring (F4.2)
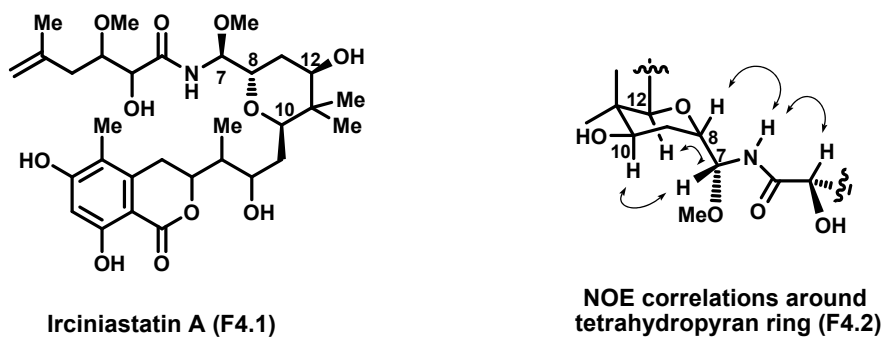
B. Crews Group: Psymberin

The Crews group employed similar NMR techniques and analyses to determine the structure of psymberin.[7] Unlike the Pettit group, they were able to assign the relative configuration of most of the stereocenters in the natural product by analyzing NOESY and COSY data as well as ^{1}H NMR coupling constants. Moreover, they used the spectral data obtained from the pederin family members as a reference to assign the absolute stereochemistry based on the following considerations; (a) a probable shared biogenetic origin, (b) analogous NMR data, (c) comparable cytotoxicity, and (d) similar [α] values.[10] They assigned 7 chiral centers as 5*S*, 8*S*, 9*S*, 11*R*, 13*R*, 15*S*, 16*R* and also determined the C17 chiral center to be *R* due to a positive Cotton effect generated by the chiral dihydroisocumarin moiety. Nevertheless, the Crews group was unable to define the configuration at the C4 stereocenter.

Figure 5 Reported Structure of Psymberin by the Crews group
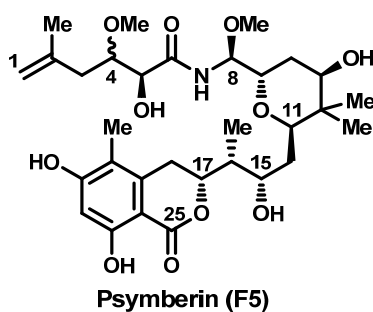
Psymberin (F5)

Both proposed structures shared similarities in the carbon skeleton and relative configuration of the core tetrahydropyran ring. The only difference was the Crews group assigned the chiral center at C8 in psymberin as S while the Pettit group assigned it as R.[11] Based on the similarities it was tempting to speculate that psymberin and irciniastatin

A were the same compounds. Matching NMRs of the two molecules was inconclusive since NMR spectrums were taken in different solvents ($CDCl_3$ by the Pettit group and CD_3OD by the Crews group).

V. Structural Elucidation of Psymberin: Universal NMR Database Approach

Structure elucidation of complex natural products represents a real challenge. Even modern NMR techniques may not generate adequate data for this task. For this reason Kishi and coworkers devised a novel approach to assign the relative and absolute configuration.[12] The concept and logic of this approach is to: (a) conceptually divide the molecules into small pieces (stereoclusters), (b) compare the NMR profile of a stereocluster to the NMR profile of a synthetic analog of each possible diastereomer, (c) predict the natural product based on the similarity of the NMR profile.

The hypotheses which were developed and later proved experimentally for the approach was (a) the spectroscopic signatures of these stereoclusters are inherent to the specific stereochemical arrangement of the substituents on the carbon chain, (b) the spectroscopic properties of these stereoclusters are independent of the rest of the molecule. On the basis of theses observations, the logic and guidelines were advanced to determine a stereocluster in a molecule. Kishi's group proved the efficiency, reliability and applicability of the approach on the complete structural assignment of several complex natural products.[13]

The complete structure of psymberin could not be determined because there was an ambiguity at one stereocenter of the amide side chain. The configuration of the C5 stereocenter was assigned based on analogy to the members of the pederin family but the

configuration of the C4 chiral center could not be assigned by multidimensional NMR spectroscopy. Our first task was to assign the relative stereochemistry of the amide side chain, since we were drawn to synthesize psymberin as well as its analogs. Therefore we applied the universal NMR database approach developed by Kishi and coworkers.[14] We easily identified the stereocluster based on this approach and built an anti (**F6.1**) and a syn (**F6.2**) model which were related to the corresponding stereocluster.

Figure 6 Anti and Syn Models
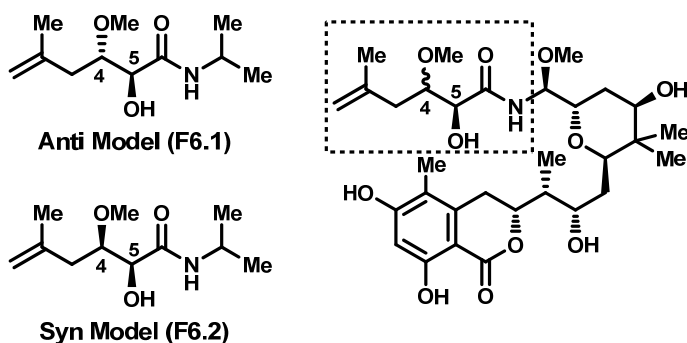
VI. *Synthesis of the Anti and Syn Models*

The synthesis of the anti (**F6.1**) and syn (**F6.2**) models commenced with the coupling of methallyl magnesium chloride[15] (**S1.2**) with acetonide-protected glyceraldehyde[16] (**S1.1**) derived from D-Mannitol (Scheme 1). This reaction afforded the product in 74% yield as an inseparable mixture of alcohols **S1.3** and **S1.4** (dr: 4:3). In order to obtain a single diastereomer of both **S1.3** and **S1.4** with high yield and diastereoselectivity, we tried the Keck reaction[17] conditions and treated the same aldehyde with methallyl stannate **S1.5** and chiral ligand R-BINOL. Although this reaction resulted in the formation of a single isomer **S1.3** with high selectivity, the yield was low

(~30%). As a result, we decided to pursue the Grignard addition reaction because it yielded both of the alcohols in high yield.

Scheme 1 Anti(S1.3) and Syn(S1.4) Products from Grignard and Keck reaction
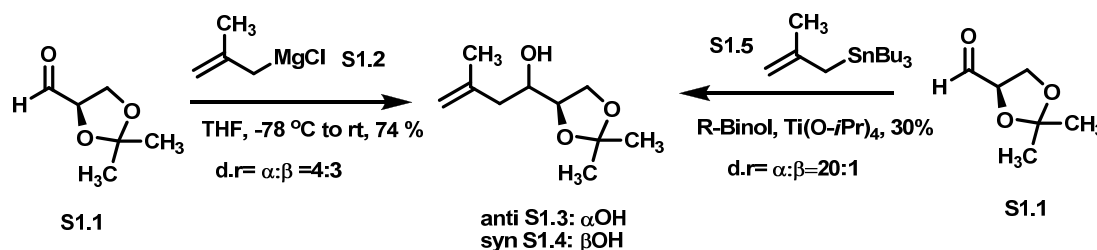
We treated the alcohol mixture with MeI under basic conditions and conveniently separated the anti (**S2.1**) and syn (**S2.2**) products by silica gel chromatography. We also obtained the anti product from methylation of the Keck reaction intermediate, which served as a reference for the structural assignment of the anti product.

From this point on both the anti and syn compounds were treated under the same conditions to synthesize the models (Scheme 2). Acetonide deprotection under acidic conditions afforded anti and syn diols.[18] Silylation of both hydroxyl groups followed by selective deprotection of the primary TBS group yielded the anti (**S2.3**) and syn (**S2.7**) alcohols. Oxidation of the alcohols, first to aldehyde under Swern oxidation conditions followed by oxidation of the resultant aldehydes, gave anti (**S2.4**) and syn (**S2.7**) hydroxyl carboxylic acids.[19] The cleavage of the secondary TBS group was affected under the Pinnick oxidation condition. The synthesis of the corresponding anti and syn amide models from hydroxyl carboxylic acid was accomplished in one pot by protection of the hydroxyl group with TMS followed by acyl chloride formation and subsequent amidation and finally deprotection of the TMS group.[20] The anti (**S2.5**) and syn (**S2.8**) models were obtained in 50% and 54% yields, respectively.

Scheme 2 Synthesis of Anti (S2.5) and Syn (S2.8) Models
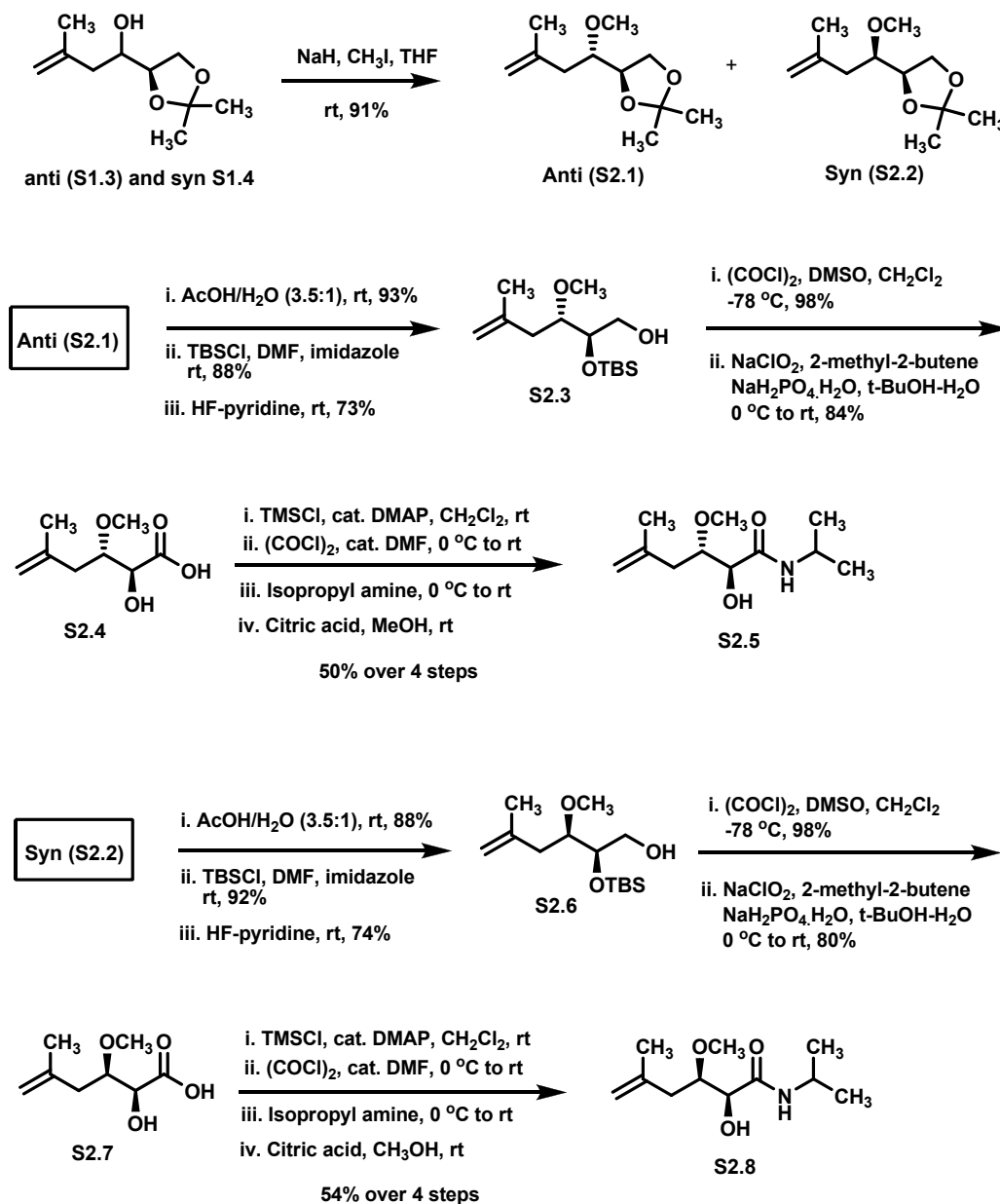
Surprisingly, the anti model was a white solid while the syn model was an oily compound. The structural proof of the anti model was unambiguously established by single-crystal X-ray crystallography, which revealed three closely related conformers (Figure 7).

Figure 7 Crystal structure: three conformers of the Anti model compound (F6.1).
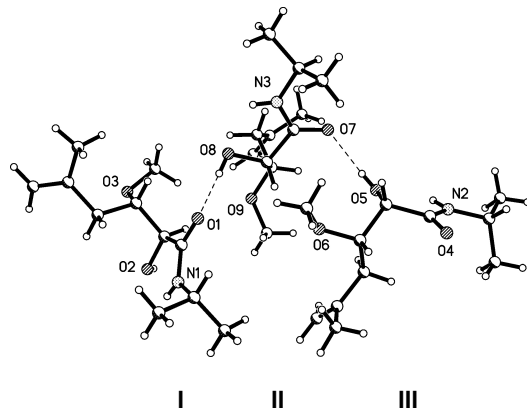
VII. Results and Discussions

The ^{1}H and ^{13}C NMR chemical shifts were determined for the model anti (**F6.1**) and syn (**F6.2**) compounds and compared to reported chemical shifts of psymberin. The data is represented in the histogram below where the difference ($\Delta\delta$) in chemical shifts for some key proton and carbon signals are calculated. As it is seen in Figure 8, the ^{1}H and ^{13}C NMR chemical shifts of the anti isomer and natural product show little differences, whereas corresponding chemical shifts for the syn isomer differ more with the chemical shifts of the natural product. This trend is especially apparent in the key signals of H3a, H3b, H4, H5, C3, C4, C4-OMe.

The Universal NMR Databases approach, where structural elucidation is achieved by spectral data comparison of complex structures to that of constructed simpler stereo-clusters, has been successfully applied to natural products like tetrafibricin, desertomycin, oasomycin.[16,17] This idea is based on that the chemical shift of a proton or carbon of a stereocluster is dependent on the relative stereochemistry resulting in different NMR signatures for the diastereoisomers. Provided the ^{1}H and ^{13}C chemical shifts of a short

model polyol differ from the mean chemical shifts of a set of polyols by ~0.10 ppm and ~1.0 ppm respectively, the difference is regarded as a significant.[21] The difference is assumed insignificant if the differential is smaller than 0.05 ppm and 0.50 ppm for ^{1}H and ^{13}C respectively. *Thus, there are two criteria that have to be met for NMR database approach to be valid: a) the difference in chemical shifts between the mismatched diastereomer and the unassigned complex structure must be significant and b) the difference between matched diastereomer and the unassigned complex structure must be insignificant.*

Figure 8 Differences in ^{1}H and ^{13}C chemical shifts between Models and Psymberin[22]
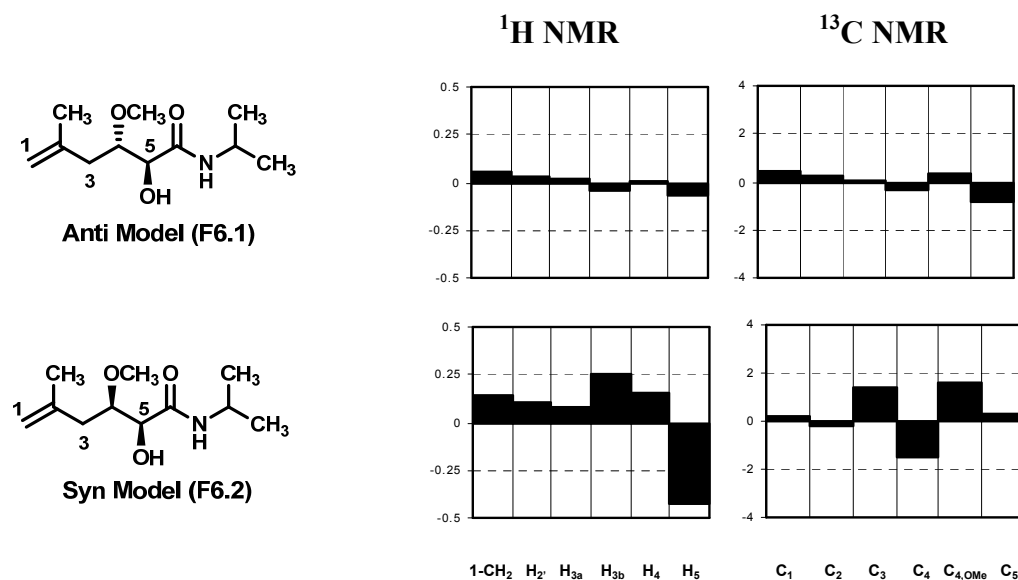
In the above study we showed that both criteria for NMR database approach are met, which led to the conclusion that the configuration of the amide side chain of psymberin is *anti*. This approach for structural assignment can not be applied for all stereoclusters. For instance, the ^{1}H and ^{13}C chemical shift differences of unfunctionalized 1,2-diols are very small such that one can not differentiate between diastereomers. For

such stereoclusters the $\Delta\delta$ of the ^{1}H signals are <0.04 ppm and $\Delta\delta$ is <0.4 ppm for ^{13}C signals so the application of this method for the structural assignment of complex natural products might be problematic.[5e,21] However, in such cases like that of amide side chain in psymberin, the 1,2-diol stereocluster is more functionalized and thus the diastereomers exhibit different NMR profiles.[23] The anti model (**F6.1**) and the natural product (**F5**) have a good correlation with a $\Delta\delta$ of <0.05 ppm for ^{1}H and <0.5 ppm for ^{13}C, whereas the syn model displays >0.15 ppm and >1.0 ppm differences for ^{1}H and ^{13}C, respectively.

VIII. *Coupling Constant Analysis*

For the structural proof of the natural product we also examined the homology of the coupling constants between the models and psymberin (Figure 9). The particular protons that were used for the analysis were vicinal protons H5-H4, H4-H3a and H4-H3b. For the anti model (**F6.1**) the coupling constant for the H5-H4 was 3.0 Hz whereas it was 1.8 Hz for the syn model (**F6.2**). The anti isomer also showed similar coupling constant values for the other two vicinal protons H4-H3a and H4-H3b, while it was inconclusive for the syn model because couplings appear as multiplets. Furthermore we calculated the estimated coupling constants from the crystal structure of three conformers for the anti model based on the average dihedral angles. The coupling constants that were obtained from the Karplus equation for the anti model (**F6.1**) were in good agreement with the natural product, as shown in figure 9. Even though the coupling constants for the natural product were taken in solution, they approximately matched what would be expected for the three conformers in the crystal.[24] The results support the *anti* assignment of the side chain of the natural product.

Figure 9 Coupling Constants Analysis for Psymberin[25]

$J_{4,3b}=9.3(9.5)$

$J_{5,4}=3.0(2.5)$

$J_{4,3a}=3.3(3.5)$
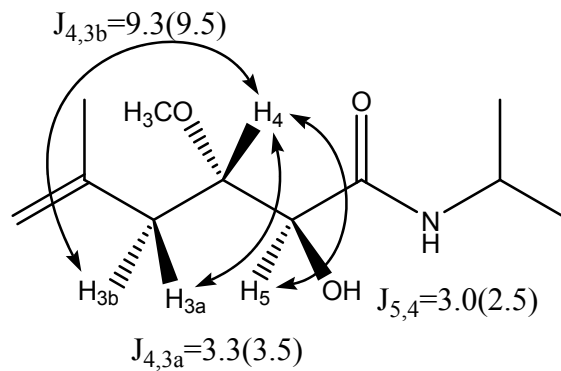
	Average Dihedral Angel for three conformers	H-H Coupling Constants		
		Estimated Average[a]	Anti Model (F**6.1**)	Psymberin
$\psi(H_5,H_4)$	-65.8	1-3	3.0	2.5
$\Phi(H_4,H_{3a})$	-66.1	1-3	3.0	3.5
$\theta(H_4,H_{3b})$	176.7	9-10	9.3	9.5

[a] Conformers in crystal structure

IX. Stereochemical Assignment of Amide Side Chain by Degradation Studies

Floreancig and coworkers used a different approach to assign the stereochemistry of the amide side chain.[26] They compared the products that were obtained from acid-mediated degradation of both models and psymberin. The models used for the studies were anti (**S3.3**), *ent*-anti (**S3.7**), syn (**S3.4**), *ent*-syn (**S3.8**) (Scheme 3). These molecules were readily accessed from methyl glycerate (**S3.1** and **S3.5**), which can be prepared in enantiomerically form from D-serine and L-serine. The esters (**S3.1** and **S3.5**) were reduced to the corresponding aldehydes (**S3.2** and **S3.6**) in 3 steps. Methallylation of the aldehydes (**S3.2** and **S3.6**) afforded the separable anti and syn products which were then carried on the corresponding carboxylic acids (anti; **S3.3** and **S3.7**, syn; **S3.4** and **S3.8**) in 3 steps. The last step transformation of the carboxylic acids into the *O*-methyl protected carbinolamides (anti; **S3.9** and **3.11**, syn; **3.13** and **3.15**) by the application of the Matsumoto protocol.[27] Exposure of these models to H_2SO_4 in MeOH at 60 $^{\circ}$C for 12 h afforded the corresponding cyclized products (anti **S3.10** and **S3.12**, syn **S3.14** and **S3.16**). These tetrahydrofurans were separable by GC and characterized by NOESY experiment to establish the spatial relation between the methoxy and carbomethoxy groups. Interestingly no epimerization was observed at the alpha position of the ester under the reaction conditions.

Similarly, they treated psymberin with H_2SO_4 in MeOH at 60 $^{\circ}$C for 12 h and obtained the cyclized tetrahydrofuran, which matched with the product produced from model **S3.11**, as determined by GC-MS. They concluded that the relative and absolute stereochemistry of the amide side chain should be anti 4*S*, 5*S* as in model **S3.11**, which is consistent with the NMR database approach applied by our group.[18]

Scheme 3 Degradation Studies

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22) (**A**) Difference between 1H-δ of psymberin (**F5**) and the anti and syn (**F6.2**) model. (**B**) Difference between ^{13}C-δ of **F5** and the anti (**F6.1**) and syn (**F6.2**) model. The x-axis identifies the signal (^{1}H or ^{13}C) and the y-axis corresponds to $\Delta\delta=\delta(\mathbf{F5})-\delta(\text{anti or syn})$. Data collected at 300MHz for ^{1}H and 75MHz for ^{13}C in CD_3OD. The chemical shift data for **F5** was taken from reference 6.

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Chapter II
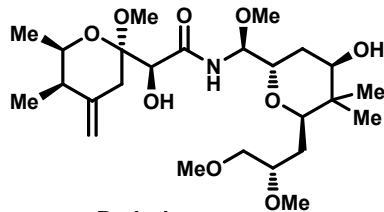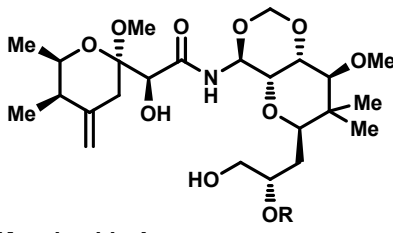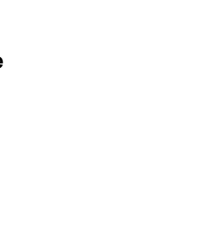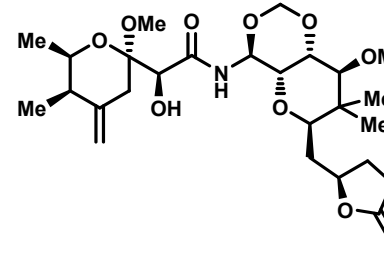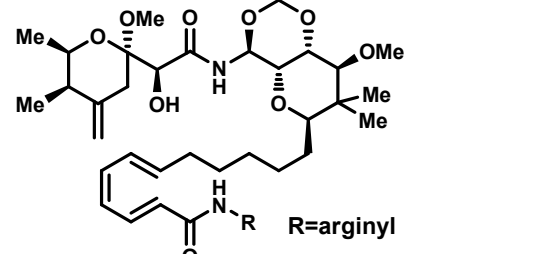
Synthetic Strategies for Pederin Family members

I. Introduction

Due to its high structural complexity and selective cytotoxicity we were drawn to develop a synthesis of the new member of the pederin family, psymberin. We sought to develop synthetic strategies to reach this molecule as well as analogous and hybrid structures, which may help in understanding the exceptional biological activity of the natural product. In order to achieve this difficult task we sought to take advantage of the tactics which were developed for the synthesis of the other members of the pederin family. In this chapter we deal with some examples of strategies developed by different groups in the past three decades. In light of these strategies we will focus on our two novel approaches to psymberin in the next two chapters.

As shown in Figure 10 many groups have spent a great deal of synthetic effort to finish total syntheses of the members of the pederin family,[1-5] as well as the partial and formal syntheses of these compounds.[6] Obviously, the challenges posed by these molecules stimulated many groups to execute creative synthetic tactics. Among these there is one common strategy that every group, without exception, applied: convergent construction of the molecules. This reasonable tactic has been very effective and applicable to all the members of the family.

Figure 10 Total Syntheses of Pederin Family Members by Different Groups

Pederin

	LLS
Matsumoto (1988)	30 steps
Nakata (2002)	24 steps
Kocienski (2000)	25 steps
Rawal (2007)	12 steps

LLS=Longest Linear Sequence

R=H, Mycalamide A

	LLS
Kishi (1990)	34 steps
Roush (2000)	31 steps
Trost (2003)	22 steps (Formal Synthesis)
Rawal (2005)	21 Steps
Toyota (2006)	34 steps

R=Me, Mycalamide B

	LLS
Kishi (1990)	35 steps
Kocienski (2000)	32 steps

Theopederin D

	LLS
Kocienski (2000)	34 steps

Onnamide A   R=arginyl

	LLS
Kishi (1991)	25 steps

We mentioned the similar structural units within the family members in Figure 2 (pg 2). In the case of the application of convergent synthesis, the left (**F2.1**) and right (**F2.3**) segments of the members constitute two simpler units to reach the target molecules (Figure 11). One unit is the pederic acid (**F11.1**). However, the other unit is either the core tetrahydropyran ring (**F11.2**) as seen in pederin or the trioxadecalin ring (**F11.3**) as seen in mycalamides, theopederins and onnamides. Even though highly efficient syntheses of these units have been published, the real challenge comes from

joining the units. Formation of the *O*-methyl carbinolamide (**F2.2**) from two units is a difficult task, since it is a very sensitive functional group. Nevertheless, there are several methods that can be applied to join these two units through the formation of *O*-methyl carbinolamide, which will be discussed in detail in chapter 4.

Figure 11 Disconnections for the Synthesis of Pederin and Mycalamide A
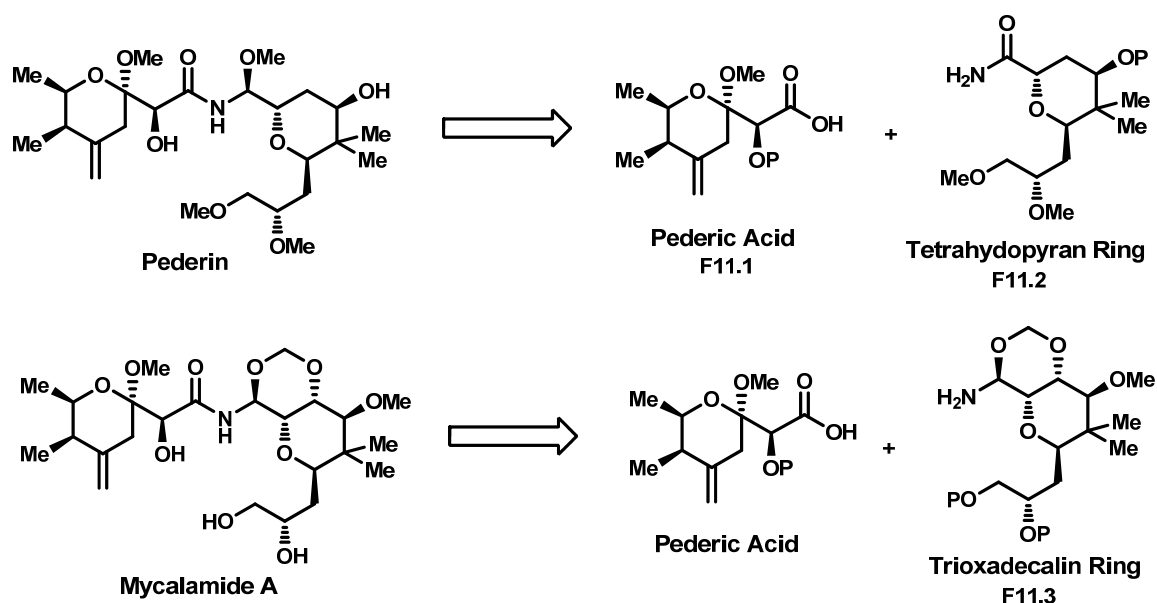
Similarly, the convergent synthesis of the psymberin can be done by joining two halves at the carbinolamide bond (Figure 12). The left segment, called psymberic acid (**F12.1**), is analogous to pederic acid (**F11.1**) in other members. The right segment, containing the core tetrahydropyran ring (**F11.2**) as in pederin, is additionally flanked by a dihydroisocumarin ring. The trioxodecalin ring (**F11.3**) looks similar since it bears a closely related core tetrahydropyran ring with an affixed six- membered ring.

Figure 12 Disconnection for Psymberin
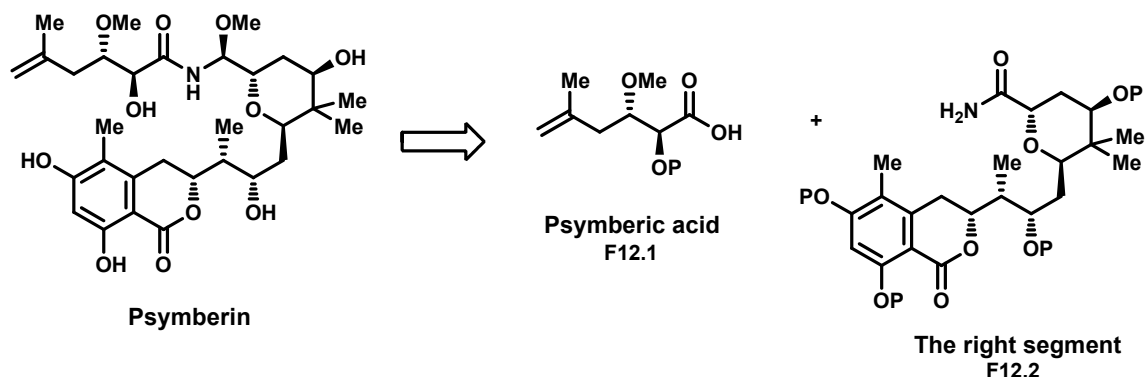
In 2005, the De Brabander group reported the first total synthesis of psymberin via the disconnection shown in Figure 12.[7] Later, the Floreancig group published a partial synthesis with the same strategy (**F12.2**).[8] Lastly, the Huang group came up with an interesting strategy by employing a linear synthetic strategy to finish the total synthesis.[9]

Our synthetic strategy also depended on the disconnection shown in Figure 12.[10] We accomplished the synthesis of the psymberic acid segment (**F12.1**), which was mentioned in Chapter 1 (Scheme 2). The construction of the right segment (**F12.2**) with a novel strategy and the formation of the O-methyl carbinolamide (**F2.2**) will be the focus of chapter 3 and 4, respectively. In this chapter, we will cover some elegant synthetic strategies for the synthesis of the tetrahydropyran ring and trioxadecalin ring systems from the literature. In addition to this, the syntheses of psymberic acid and the right segment of psymberin by the De Brabander and Floreancig groups are summarized. However, Huang's total synthesis of psymberin as well as completion of the total synthesis of pederin and the myclamides are addressed in Chapter 4.

II. Synthesis of the Tetrahydropyran Ring

A. The Matsumoto Strategy

   The early synthetic efforts to construct the tetrahydropyran ring were reported by

Matsumoto in 1982.[1a-e] The key step in their synthesis was the substrate directed

asymmetric reduction of the ketone of **S14.2** and, later, the ketone of **S14.4**. The core ring

formation was obtained from the epoxide under acidic conditions (**S14.6→S14.7**).

Regardless, the selectivity for the formation of the epoxide was low. The stereochemistry

of the ester group in **S14.8** was set by enolization and then kinetic protonation of **S14.9**,

which provided the desired product **S14.10** in low yield and selectivity. This route was

too lengthy, consisting of 23 steps.

Scheme 14 The Matsumoto Strategy
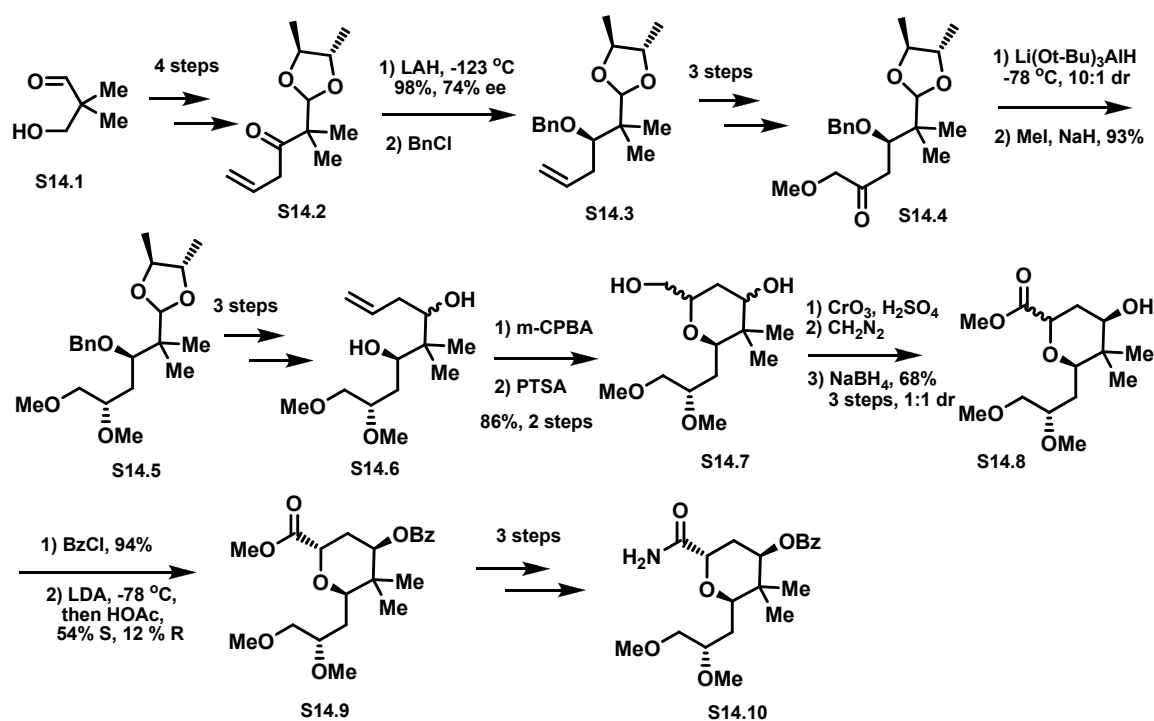
B. The Hoffmann Strategy;

A concise and highly efficient synthesis was accomplished by the Hoffman group.[6a-c] The first key step was asymmetric allylation of aldehyde **S15.2** with chiral borane reagent (**S15.9**), which gave good yield and moderate selectivity. The second key step was again asymmetric allylation of aldehyde **S15.4**, but this time with the different chiral borane reagent **S15.10**. Likewise, a fairly good yield and moderate selectivity was obtained from this reaction. Ozonolysis of the double bond in **S15.6** afforded the cyclic core structure in its hemiacetal form, which was subsequently protected with a benzoyl group (**S15.7**). They completed the synthesis of the ring by introducing a cyano group to **S15.7** followed by oxidation to the amide **S15.8**.

Scheme 15 The Hoffmann Strategy
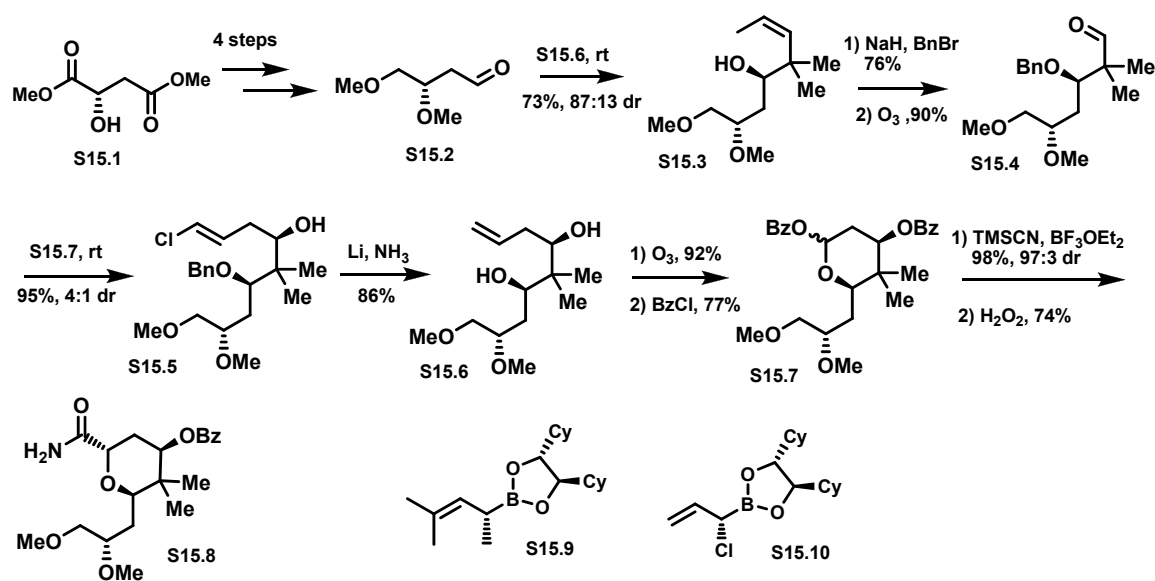
C. The Nakata Strategy

Another elegant synthesis of the tetrahydropyran was accomplished by the Nakata group.[1h] They applied a SmI$_2$-mediated intramolecular Reformatsky reaction to utilize the

core ring (**S16.1**→**S16.2**). This reaction took place smoothly, which afforded one single product in 85% yield. After introduction of an allyl group to **S16.3** with complete axial selectivity, the Sharpless asymmetric dihydroxylation of the double bond in **S16.3** furnished diol **S16.4** in good yield, albeit with low selectivity (3:1). The synthesis of **S16.5** was completed in 16 steps with a 35% overall yield.

Scheme 16 The Nakata Strategy
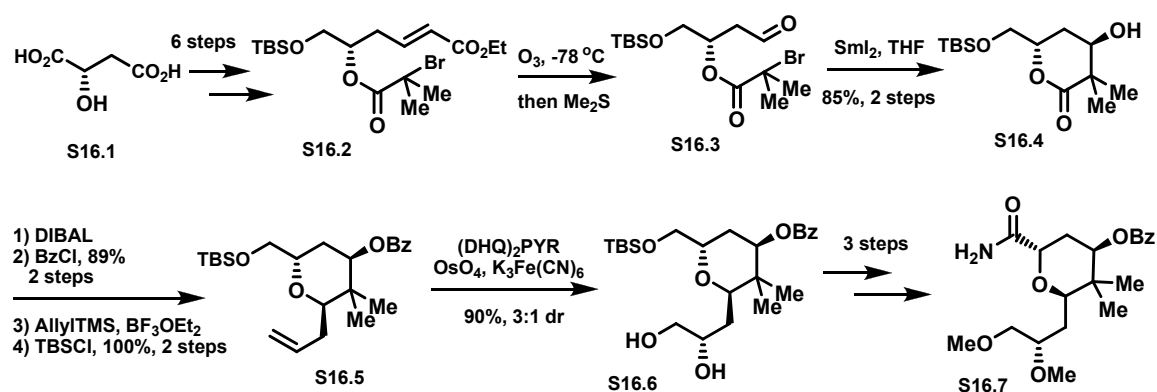
D. The Rawal Strategy

Recently, the Rawal group came up with an outstanding strategy for the synthesis of the core ring of pederin (Scheme 17).[1m] Assembly of the ring was convergently furnished by a three-step reaction sequence from aldehyde **S17.2**. Firstly, they applied a hetero-Diels-Alder reaction (or Mukaiyama Aldol cyclization) between aldehyde **S17.2** and diene **S17.3**, which took place with excellent diastereoselectivity. Secondly, they took advantage of a Mukaiyama-Micheal reaction to combine pyranone **S17.4** and silyl ketene **S17.5**, which also proceeded with excellent diastereoselectivity. Finally, the reduction of pyranone **S17.6** with L-Selectride predominantly afforded the desired product (**S17.7**) in 7 steps overall.

Scheme 17 The Rawal Strategy
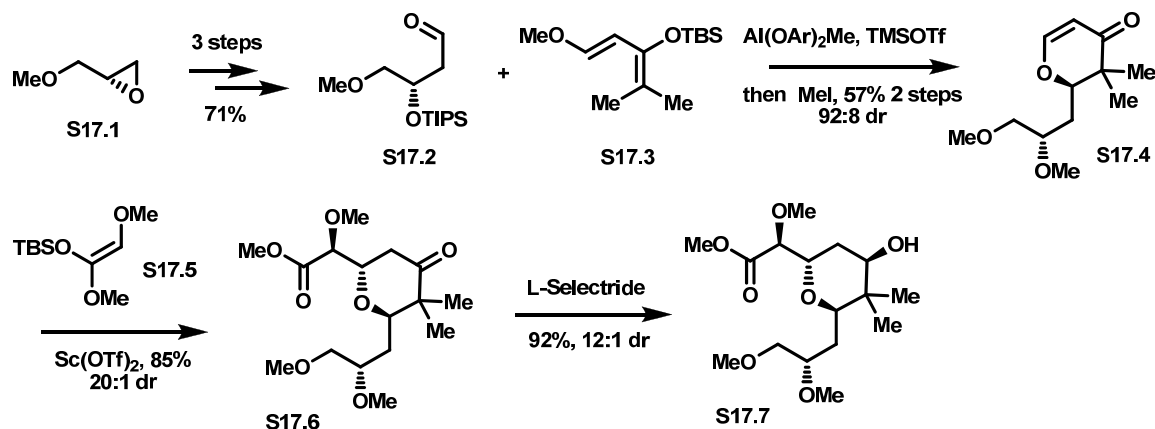
III. Synthesis of the Trioxadecalin Ring

The Rawal Strategy

The Rawal group has also recently published the total synthesis of mycalamide A.[1h] They applied effective and stereoselective methods for the preparation of the trioxadecalin ring (**F11.2**) and pederic acid (**F11.1**). Their synthesis started with methyl tartarate (**S18.1**), which was transformed into the aldehyde (**S18.2**) in 4 steps (Scheme 18). A chelation-controlled methallylation furnished alcohol **S18.3** as a single diastereomer. After protecting group manipulations, **S18.5** was treated with ozone and then acetic anhydride. The resulting lactol acetate was treated with allyltrimethylsilane and $BF_3.OEt_2$ to provide **S18.6** as a single diastereomer. Transformation of **S18.6** to **S18.7** was accomplished in three steps, which afforded the product in a ratio of 5.4:1. Asymmetric dihydroxylation resulted in the formation of the desired diol (**S18.8**), which was then protected as the corresponding acetate. The anomeric acetate was transformed to an azide with $TMSN_3$, which was reduced to a mixture of aminal diastereomers (**S18.9**). They completed the synthesis in 21 steps and 10.5% overall yield.

Scheme 18 The Rawal strategy
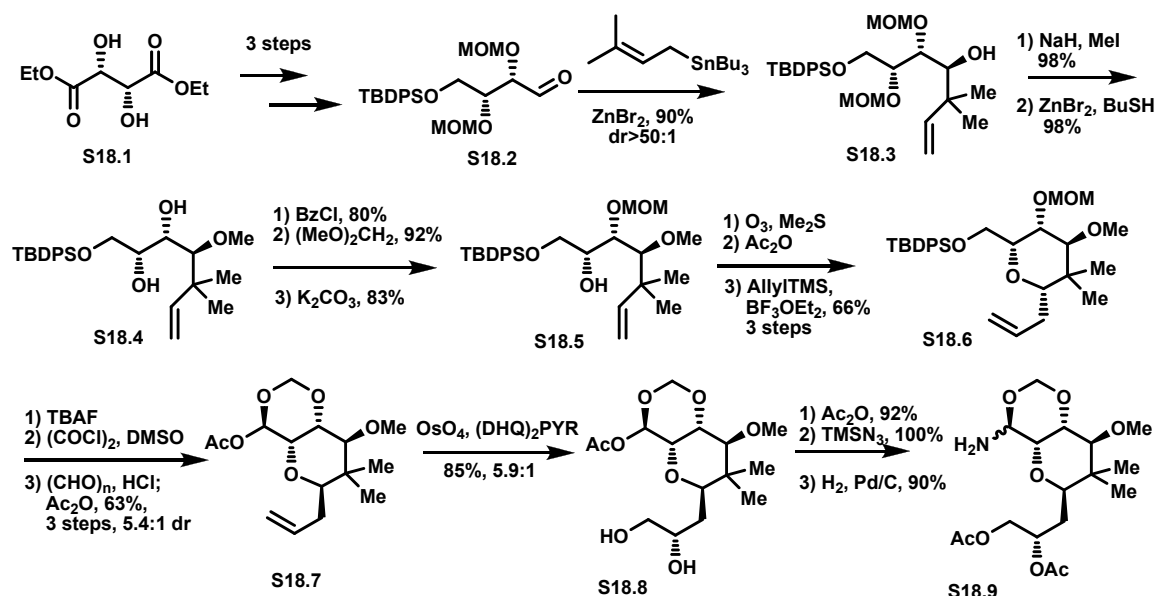
IV. Synthesis of the Psymberic Acid

The De Brabander Strategy

The De Brabander group started the synthesis of the target with the protected glyceraldehyde **S19.1** and treated it with a chiral borane reagent ((-)-Ipc$_2$BOMe) to afford an anti product which was methylated and deprotected to give the diol (**S19.2**).[7] The antipodal borane reagent ((+)-Ipc$_2$BOMe) was used to obtain the corresponding syn compound. Both anti and syn products were elaborated to their respective final carboxylic acids after a series of protecting group manipulation and oxidation reactions shown in Scheme 19.

Scheme 19 The De Brabander Strategy
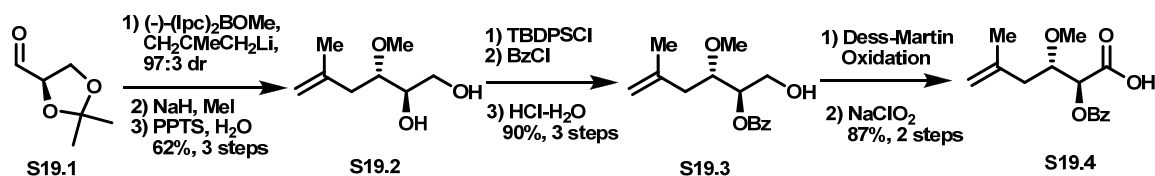
V. Synthesis of the Right Segment of Psymberin

A. The De Brabander Strategy

The synthesis of this segment stemmed from the coupling of two simpler units. The aryl fragment **S20.3** (Scheme 20) was finished in 7 steps from aryl aldehyde **S20.1** by employing such reaction conditions as: a) oxidation/amidation, (b) *ortho*-methalation/allylation, (c) methyl ether deprotection with BBr$_3$, (d) methyl ester formation, (e) protection with PMB group, (f) oxidative double bond cleavage.

The core pyran ring formation commenced with the application of asymmetric allylation of aldehydes **S20.4** and **S20.5** with Leighton's silane reagent (**S20.9**) to furnish a C_2-symmetrical diol, which was monosilylated to give **S20.6**. Ozonolysis followed by acetylation gave **S20.7**. The synthesis was completed by addition of an ethyl group to **S20.7**, displacement of acetate with TMSCN and then oxidation of a secondary alcohol to ketone **S20.8**.

Scheme 20 The De Brabander Strategy
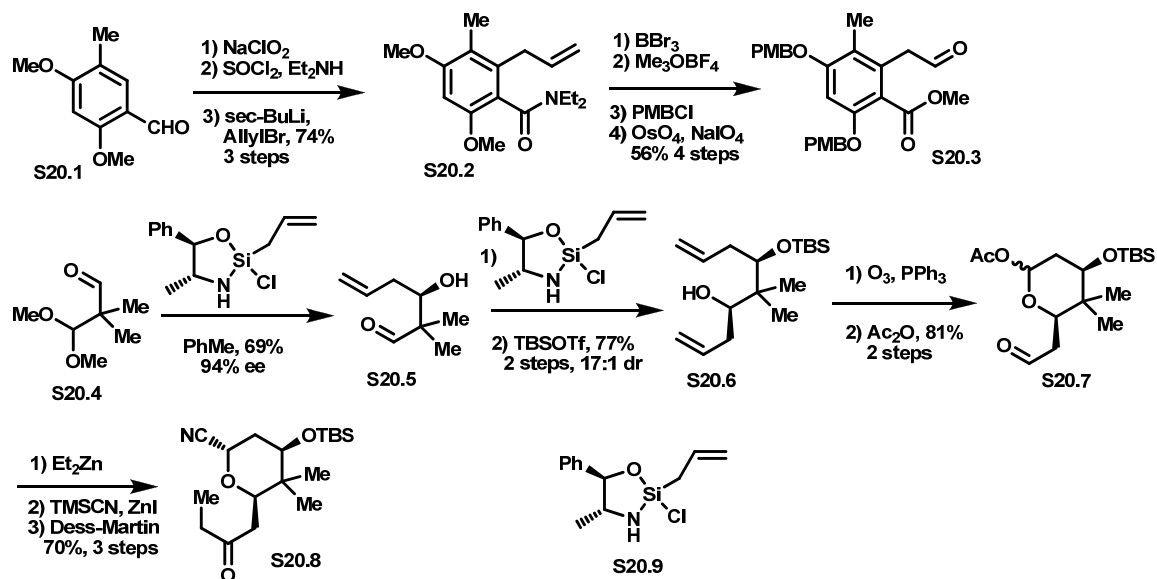
The coupling of the two units (**S20.2** and **S20.8**) was accomplished via an aldol reaction to afford the major syn product **S21.1**. 1,3 syn reduction of **S21.1** with catecholborane and then basic work-up gave a lactone, which was desilylated with TBAF to yield **S21.2**. The final steps to get the right segment **S21.3** were a hydrolysis of the nitrile group with the Parkins catalyst (**S21.4**), deprotection of the PMB group by hydrogenation and, lastly, acetylation of the hydroxyl groups with acetic anhydride.

Scheme 21 The De Brabander Strategy
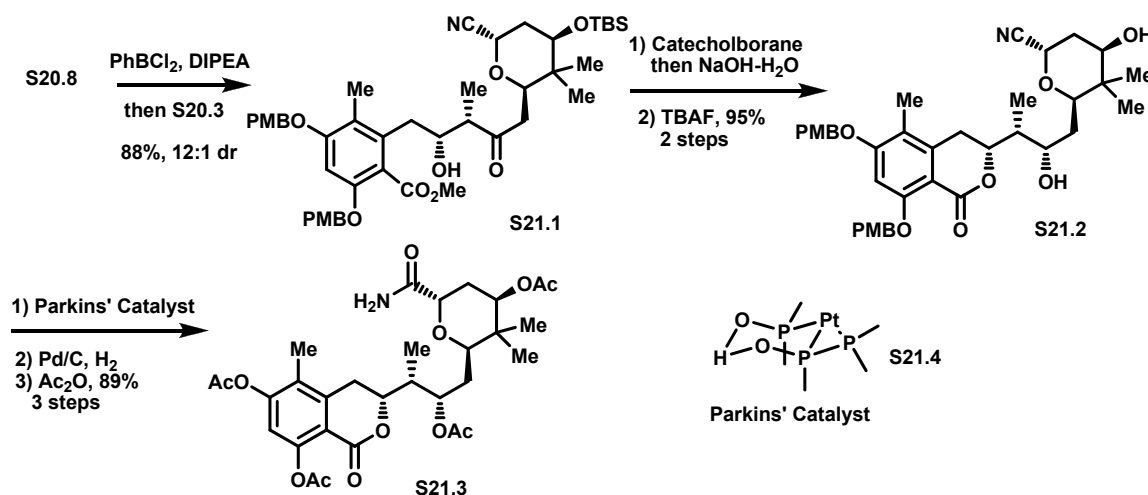
B. The Floreancig Strategy

This group accomplished the synthesis of the right segment from the coupling of **S22.6** and **S23.6**.[8] They used the Diels-Alder cycloaddition reaction between diene **S22.1** and allene **S22.2** as a key step in the preparation of the arene partner **S22.6**, which efficiently yielded 70% of the product. Protection of **S22.3** with TBS followed by reduction with DIBAL furnished aldehyde **S22.4**, which was exposed to the Brown crotylation conditions to produce **S22.5** as a single diastereomer. Protection with TBS followed by ozonolysis completed the synthesis of **S22.6**.

Scheme 22 The Floerancig Strategy
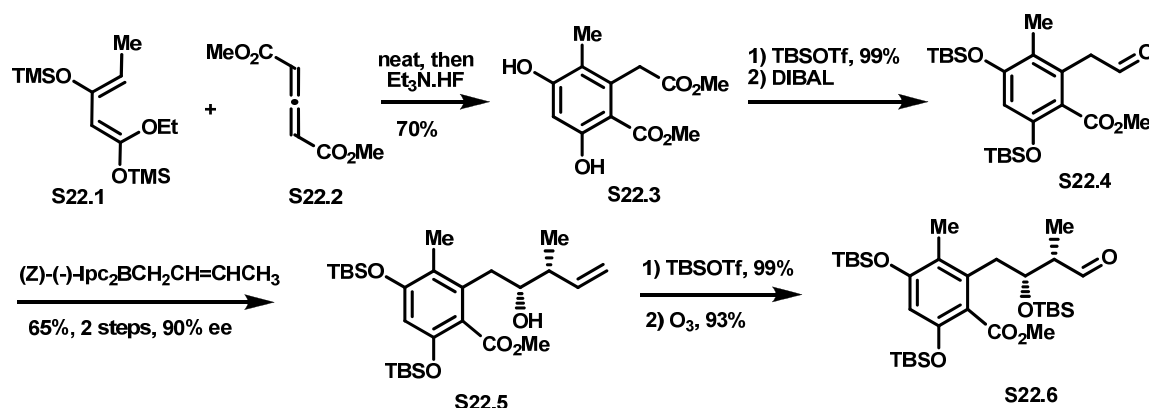
The preparation of the second coupling partner **S23.4** started from the reaction of aldehyde **S23.1** with Leighton's silane reagent **S23.2**, which gave the alcohol (**S23.3**) in high yield and selectivity. Protection with TES followed by TMS enol ether formation furnished **S23.4** quantitatively. **S22.6** and **S23.4** were coupled through a Mukaiyama aldol reaction in the presence of $BF_3 \cdot OEt_2$, which gave the desired product (**S23.5**) selectively in high yield. Substrate directed asymmetric reduction of **S23.5** afforded a single product (**S23.6**) in 74% yield. Ozonolysis followed by acetylation resulted in formation of tetrahydropyran **S23.7**. Exposure of **S23.7** to TMSCN replaced the anomeric acetyl group with a nitrile, which was then oxidized to amide **S23.8** with the Parkins catalyst (**S21.4**). They finished the synthesis of this segment in 12 steps from known materials in 15% overall yield. It should be noted, however, that this is a partial synthesis.

Scheme 23 The Floerancig Strategy

S23.1 + **S23.2** → PhMe, 90%, 94% ee → **S23.3**

1) TESCl
2) TMSOTf 100%, 2 steps → **S23.4**

S22.6, BF₃OEt₂, 95%, 6:1 dr →

S23.5 → Et₂BOMe, NaBH₄, 74% → **S23.6**

1) O₃, PPh₃ 76%
2) Ac₂O, 76% →

S23.7 → 1) TMSCN, BF₃OEt₂, 97% 2) Parkin Catalyst, 96% → **S23.8**
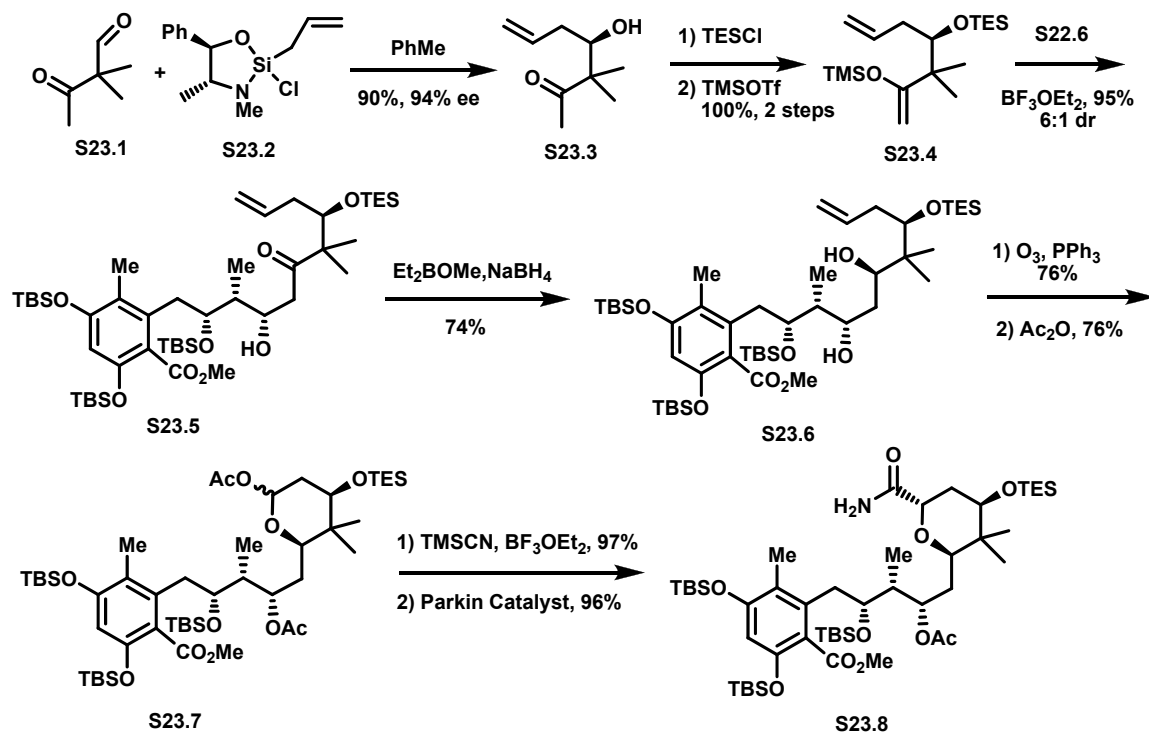
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Chapter III

Spirodiepoxide Application: Psymberin

I. Background Information for Spirodiepoxides

Spirodiepoxides (SDE) result from the double oxidation of an allene (Scheme 24, **S24.1**→**S24.2**). These molecules have an unusual structure bearing two affixed epoxides and represent a rare functional group. They are electrophilic compounds which would be expected to readily react with nucleophiles. Opening of SDEs with nucleophiles leads to a motif that has a ketone, alcohol and substitutent corresponding to the nucleophile (**S24.3**). It also generates two stereocenters at the alpha positions of the ketone. The major product is syn. As with other cascade reactions, allene oxidation to SDEs offers a new way to access densely functionalized structures.

Scheme 24 SDE Formation and Opening
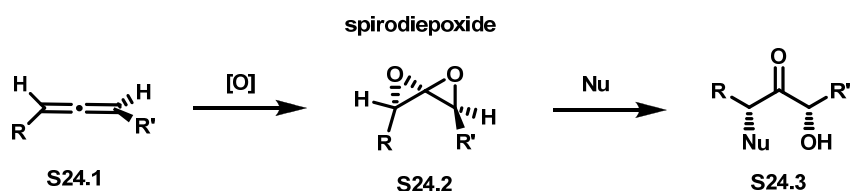
The oxidation of allenes can be accomplished by either a peracid oxidant or a neutral non-nucleophilic oxidant such as dimethyl dioxirane (DMDO). Decomposition of SDEs to various products can occur due to the acid by-product of oxidation by a peracid. However, DMDO affects a clean oxidation leading to isolable SDEs. The Crandall group performed initial studies of the formation and reactivity of SDEs after the discovery of

DMDO.[1] The SDEs studied were derived from unfunctionalized, achiral, symmetric allenes (Scheme 25, **S25.1→S25.3**). The addition of different types of nucleophiles to these SDEs, both intermolecularly and intramolecularly, was studied, which afforded modest product formation. The heteroatom nucleophiles for intermolecular opening of SDEs were water, alcohols, acetic acid, amines imidazole, thiophenol, fluoride and chloride.[1i] The addition of these nucleophiles was observed to attack at the less sterically hindered carbon atom of the SDE functionality in S_N2 fashion. Also, the addition of water to the cyclic SDE **S25.4** showed that both hydroxyl groups were oriented in the same direction (**S25.6**), which was the only example demonstrating that the syn product is the major product obtained from addition of a nucleophile to a SDE.[1i]

Scheme 25 SDEs by the Crandall Group
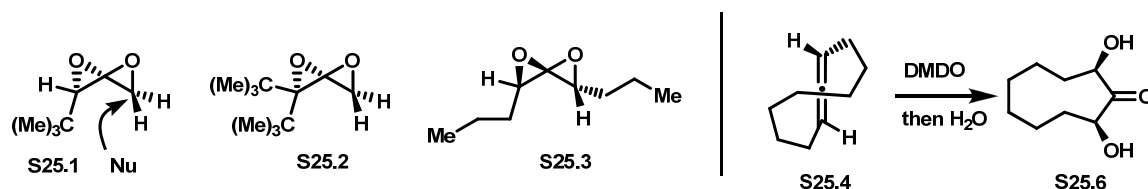
In the case of intramolecular nucleophilic addition to a SDE they reported formation of functionalized oxygen heterocycles from allenes tethered with three types of functional groups; (a) alcohols, (b) carboxylic acids, (c) aldehydes. The opening of α,δ-allenyl alcohols formed the furan products (**S26.1→S26.2** and **S26.5→S26.6**), while β,γ-allenyl alcohols gave the pyran products (**S26.3→S26.4** and **S26.7→S26.8**).[1g,1j] Relatively simple allenes, where R^1, R^2, R^3, R^4 were either H or CH$_3$ groups, were used for the investigation. The primary and tertiary alcohols were observed to efficiently open SDE intramolecularly, while no secondary alcohol openings were reported. The

regiochemistry of ring closure was dictated by the number of carbons in the tethered

chain in order to give favorable five or six-membered heterocycles by either exo or endo-

cyclization.[2]

Scheme 26 Cyclization of Allenic Alcohols
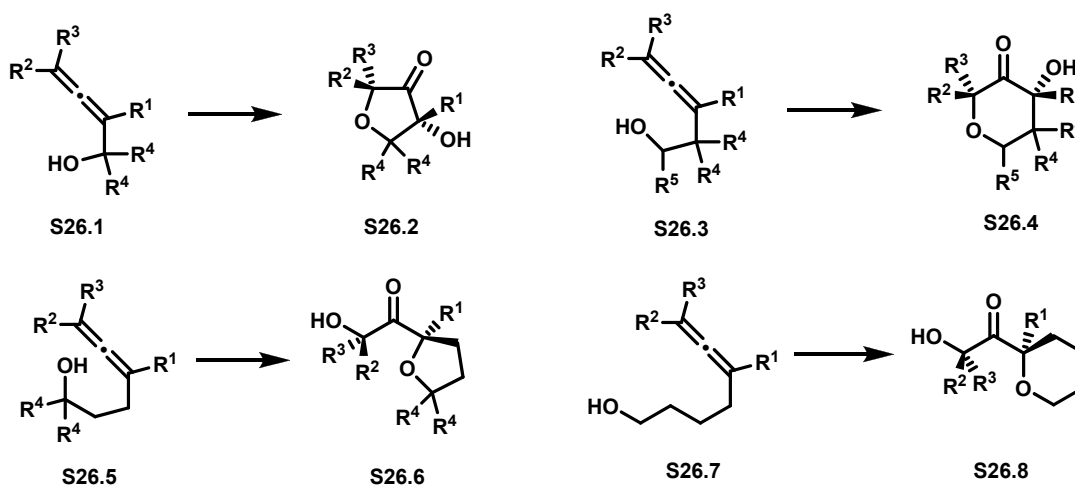
They also showed cyclization of several simple allenyl carboxylic acids to

provide five or six membered functionalized lactones.[1h,1j] Moreover, oxidation of allenyl

aldehydes and ketones led to the formation of corresponding cyclized products, which

were either hemiacetals or ketals depending on the solvent used.[1k] Interestingly, no

oxidation of aldehydes was observed since it is slower than that of an allene.

The Williams group has focused on developing new reactions and applying them

to the synthesis of biologically and chemically important molecules.[3] The first use of

SDE in total synthesis was elegantly demonstrated in the synthetic studies for the natural

product, epoximicin.[3f] In the course of these studies, it was also shown that SDEs can be

opened by different nucleophiles such as azides, the anion from of benzenesulfonamide,

lithium benzimidate and others. Additionally, the opening of SDEs with organocuprates

was developed and the efficiency of this methodology was demonstrated in the synthesis of a stereotetrad found in 9*S*-dihydroerythronolide A.[3e]

Our group also obtained the first crystal structure of the SDE derived from oxidation of tetramethyl allene (Scheme 27).[3c] Surprisingly, treatment of the allene (**S27.1**) with DMDO afforded the solid SDE (**S27.2**) which has a low melting point and thus purified by sublimation. The crystal structure data revealed significant information regarding key bond lengths, which were highlighted by the comparison to the data of a simple acetal (**S27.3**) and epoxide (**S27.4**). Significant structural features of SDE include; (a) shorter C2-O1/O2 bond lengths than simple acetals, (b) shorter C2-C1/C3 and C2-O1/O2 bonds than epoxides, (c) longer C1-O1 and C3-O2 bonds than epoxides. These data were also compared and matched to the data obtained computationally.

Scheme 27 Crystal Structure of SDE

Structure	C1-O1	C2-O1	C2-O2	C3-O2	C2-C1	C2-C3
SDE (S27.2)	1.517	1.393	1.393	1.517	1.446	1.446
Calculated (S27.2)	1.495	1.398	–	–	1.454	–
Acetal (S27.3)	–	1.429	–	–	–	–
Epoxide (S27.4	–	1.446	–	–	1.489	–
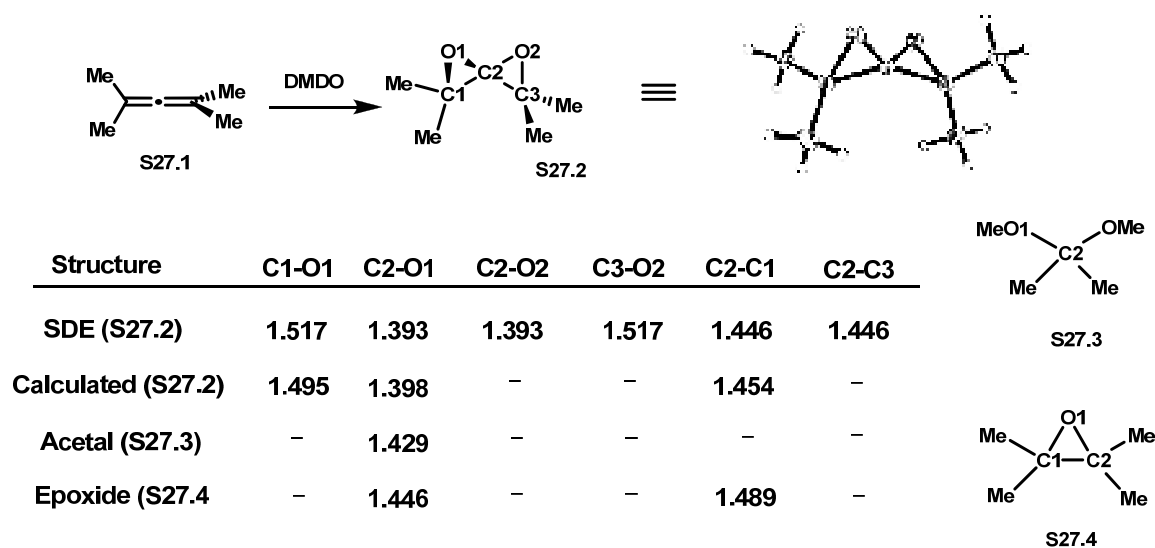
The mechanism of SDE opening is probably a one step process, even though there are some reported mechanistic models which involve charged intermediates (**S28.1** versus **S28.2**, **S28.3**, and **S28.4**). It is known that anionic nucleophiles open SDEs readily.

However, SDEs must be activated for neutral nucleophiles. These hydrogen-bonding activators are mostly hydroxylic reagents like water or methanol. A new type of nucleophiles which both activate and open SDEs was discovered by our group. We demonstrated an elegant way to form heterocycles from neutral nucleophiles such as benzamide, thiobenzamide and benzamidine.[3c] The transition model (**S28.8**) proposed for these transformation features similarly concerted opening of the activated SDE. This was also supported by computed transition models. It revealed that the C1-O1 bond lengthens, the O1-C2 bond shortens, and the C2-O2 bond lengthens when nucleophiles attack the SDE (Scheme 28).

Scheme 28 Transition Models for SDE Opening
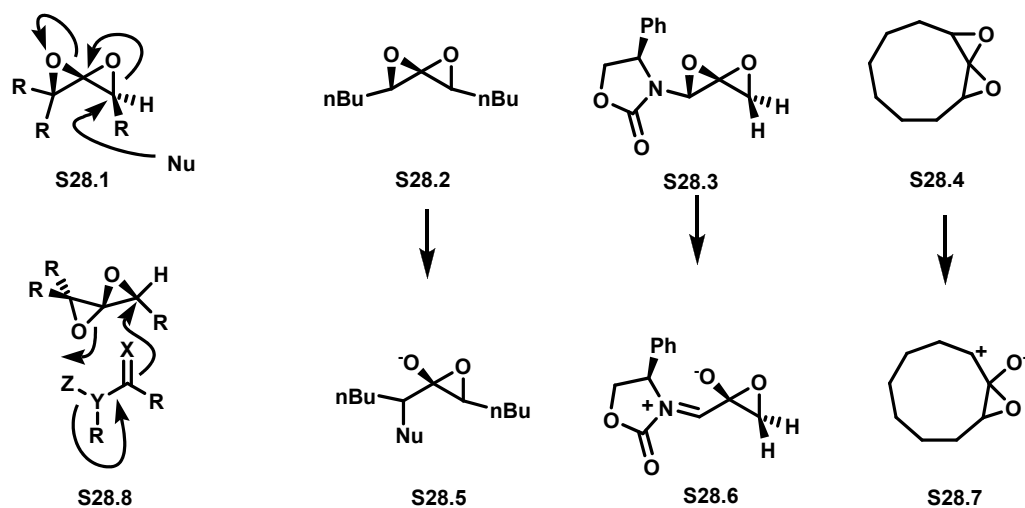
II. Spirodiepoxides in Psymberin Synthesis: 1ˢᵗ generation

As mentioned earlier, we wanted to synthesize psymberin and its analogs as well as hybrid structures. Therefore, we needed a novel and feasible strategy to reach this goal. As expected, the natural product **S29.1** was bisected into two segments; psymberic amide **S29.2** and the right segment **S29.3**. Preparation of **S29.3** of psymberin was a challenge as it contains a highly substituted core tetrahydropyran ring and an appended dihydroisocumarin ring. We envisioned the core tetrahydropyran ring **S29.4** could be accessed from SDE **S29.5**, which would be derived from oxidation of allene **S29.6**. This key step would give us both a highly oxygenated (X=O) and subsequently a simpler ring (X=H), which would enable us to prepare a range of psymberin analogs and hybrid structures. Addition of a propionate unit **S29.7** followed by dihydroisocumarin ring formation using **S29.8** would complete the synthesis of the right segment. Direct coupling of these two units will be discussed in chapter 4.

Scheme 29 Synthetic Plan: 1ˢᵗ generation
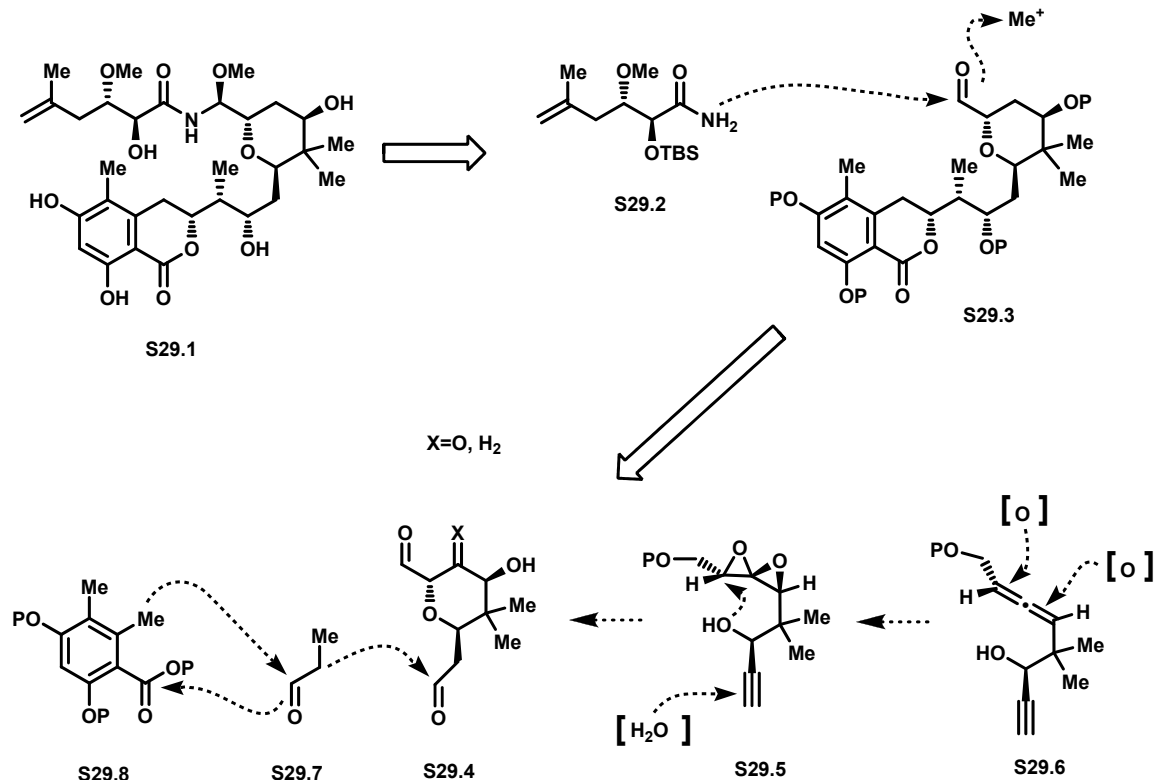
Unlike alkenes, oxidation of allenes includes a problem of regioselectivity. In general, the more substituted double bond will be more easily oxidized because it is more electron rich. In the case of mono- and tri-substituted allene the more substituted double bond will be oxidized first, but in case of di- and tetrasubstituted allenes regioselectivity may be governed by steric and electronic effects. The oxidation of trisubstituted and disubstituted allenes was demonstrated in Scheme 30. Another problem is stereoselectivity. The oxidation should take place on the face of the double bond which is most accessible.

Scheme 30 Stereoselectivity in Allene Oxidation
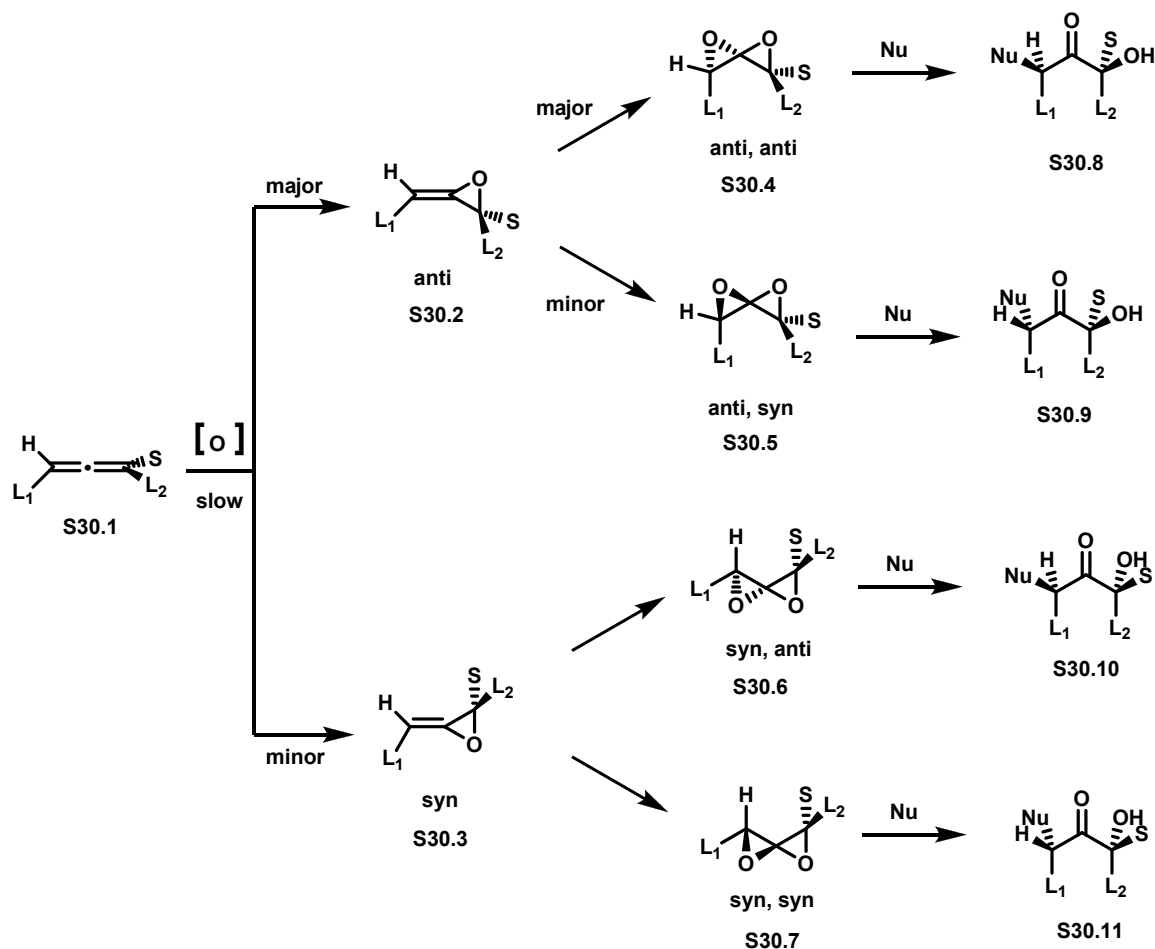
The first oxidation is comparatively slow and leads to the formation of major-anti (**S30.2**) and minor-syn (**S30.3**) allene oxides. The allene oxides which are very reactive because of their electron rich nature should oxidize rapidly and result in formation of SDEs.[4] The other problem is opening of a SDE regioselectively. The nucleophilic attack takes place on the carbon with less substituents for S_N2-like reactions and could give up to four different products (**S30.8**, **S30.9**, **S30.10**, **S30.11**). **S30.8** and **S30.11** as well as **S30.9** and **S30.10** are enantiomers. The major product should be **S30.8** resulting from the anti-anti SDE (**S30.4**), whereas the minor will be **S30.9**, formed from **S30.5**. The formation of the antipodal products (**S30.10** and **S30.11**) may not be observable if the

formation of the syn allene oxide (**S30.3**) is low. The ratio of the second oxidation will reflect the ratio of the major and minor products. For example, if the selectivity of the first oxidation is high (>20:1) and the second oxidation is low (2:1), the ratio of products will appear to be 2:1. Therefore, an enantiomerically pure product could be obtained from optically pure allene.

The initial work done by Crandall's group showed the formation of cyclic ethers from the oxidation of simples, unfunctionalized and achiral allenes (Scheme 26).[1g,1j] The major problem was that the selectivity of oxidation was not synthetically useful, for example, see Scheme 31. However, our group aimed to increase the streoselectivity of allene oxidation and to demonstrate the application in complex molecule synthesis. Dr. Shangguan, a former graduate student in our group, did some preliminary studies on the oxidation of allenes structurally similar to **S29.6**. Allene **S32.1** was prepared and treated with DMDO in acetone (Scheme 32). The corresponding SDE was cyclized immediately and afforded the isolable trans (**30.2**) and cis (**S30.3**) products in modest yield (60%) and in a ratio of 2.5 to 1, respectively.[3d]

Scheme 31 Simple Allene Cyclizations
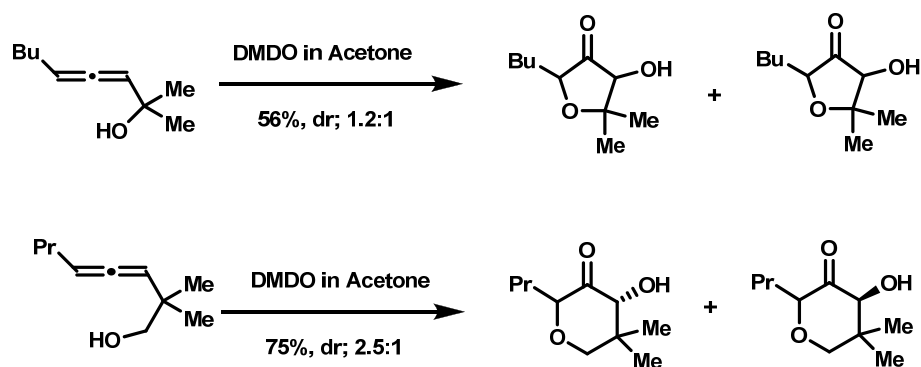
Scheme 32 Preliminary Results for Model Allenes

DMDO in acetone;   60%, dr; 2.5 : 1
DMDO in chloroform; 60%, dr; 6 : 1
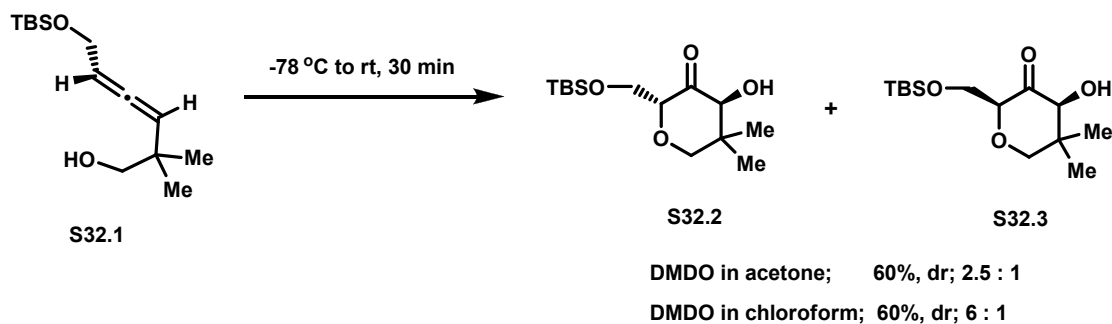
The Murray group developed a procedure to prepare DMDO in acetone.[5] Acetone is easily oxidized to DMDO upon treatment with potassium monopersulfate (Oxone®) at room temperature. The low-boiling solution of DMDO in acetone is then distilled and condensed with a cold trap. The resulting solution is a low concentration of DMDO (0.05-0.1M). However, Messeguer's group reported a modified procedure to increase the concentration of DMDO in different solvents such as chloroform, dicholormethane, ethyl acetate and toluene. The concentration of DMDO can approach 0.3 M after extraction with chloroform. This group also checked the reactivity of a DMDO solution in chloroform by epoxidation of cis-stilbene and found out that epoxidation takes place much faster than with DMDO in acetone solution.

When allene **S32.1** was treated with DMDO in chloroform, the trans **S32.2** and cis **S32.3** products were formed in a 6:1 ratio (Scheme 32). The improved stereoselectivity of the DMDO oxidation in chloroform could be a consequence hydrogen bonding formation between DMDO and chloroform, which would make it bulkier and more active than DMDO in acetone. This could result in an increase in the selectivity of the second oxidation of an allene. Our group demonstrated the improvement of stereoselectivity in SDE formation on simple and complex allenes by using DMDO in chloroform. In

addition to this, different solvent systems have also been studied to increase stereoselectivity on the oxidation of allenes.[6]

We aimed to synthesize the target allene (**S29.6)** asymmetrically. For this purpose, we pursued the Myers method to reach **S29.6** as it provides enantiomerically pure 1,3 disubstituted allenes in a single pot from propargyl alcohols.[7] In this procedure, optically pure propargyl alcohols (**S33.1**) are treated with *O*-nitrobenzenesulfonyl hydrazide under Mitsunobu conditions to afford the optically pure adduct **S33.2** with inversion at the stereocenter. Elimination followed by ene rearrangement in situ give rise to the formation of enantiopure allenes (Scheme 33).

Scheme 33 Myers Allene Synthesis
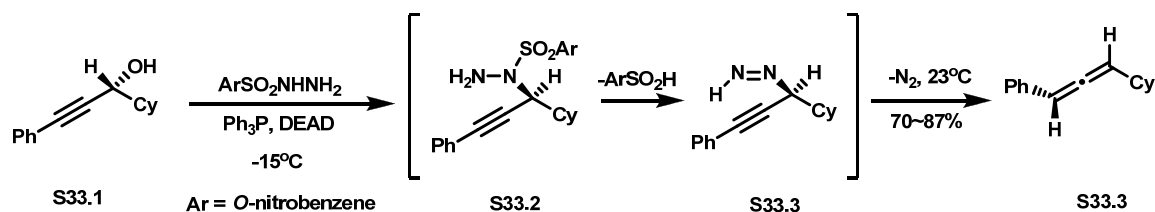
The strategy for the key allene **S29.6** leading to the core pyran ring is shown in Scheme 34. We reasoned that a simple allene (**S34.1**) could be accessed from propargyl alcohols **S34.2** and **S34.6** under the Myers conditions. Using alcohol **S34.2** would be a better choice since the first step, a Mitsunobu inversion reaction, would suffer from the presence of a neopentyl center in alcohol **S34.6**. The preparation of alkynone **S34.3** would be accomplished from the coupling of Weinreb amide (**S34.4**) and alkyne (**S34.5**).

Scheme 34 Synthetic Strategy for Allene S29.6
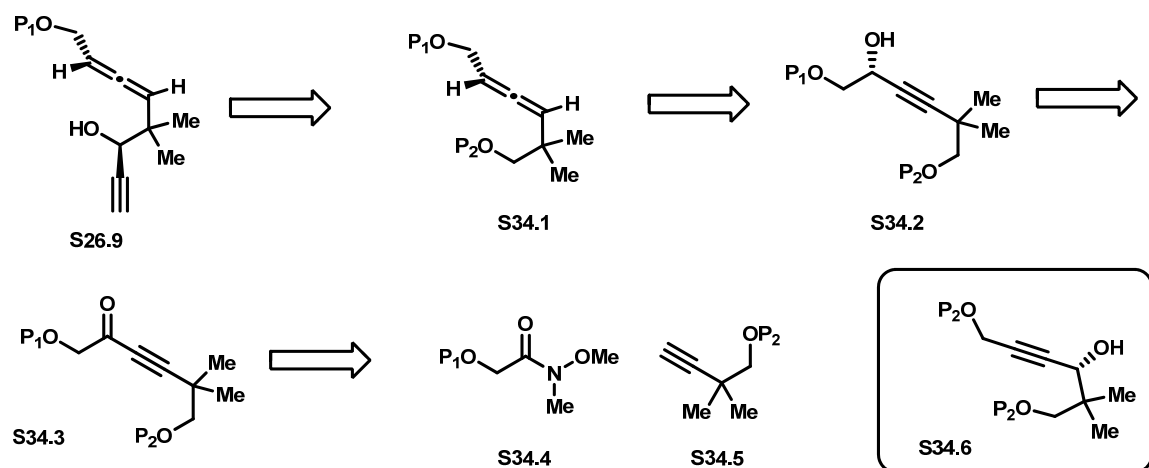
The synthesis is presented in Scheme 35. The alkyne (**S35.1**) was prepared using two different conditions from the same starting material. Under the Corey-Fuchs condition, aldehyde **S35.2** was reacted first with triphenylphospine and tetrabromomethane to yield a dibromoalkene compound, which on treatment with *n*-BuLi afforded the alkyne in 70% yield after two steps.[8] This reaction, when used in large scale, produced amounts of insoluble triphenylphosphine oxide solid as a by-product that were not easy to separate from the desired product. The Seyferth-Gilbert condition converted **S35.2** to **S35.1** in a higher yield 87% and provided an easier work-up to remove all the solids with a water wash.[9] For the Weinreb amide synthesis (**S35.5**), the methyl glycolate (**S35.3**) was first protected with TBDPS and was then added to a solution of *i*-PrMgCl and Me(OMe)NH.HCl to give **S35.5**.[10] To couple these two units, **S35.1** was first deprotonated with *n*-BuLi reagent and then treated with **S35.4** to give alkynone **S35.6** in 72% yield.

Scheme 35 Preparation of Alkyne and Weinreb amide
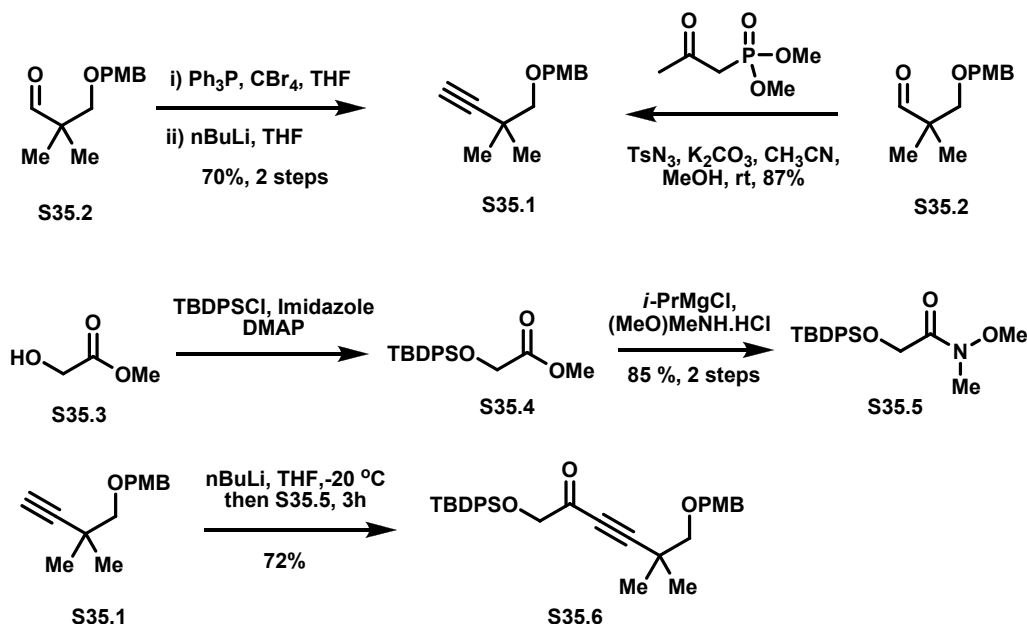
The asymmetric reduction of alkynone (**S35.6**) was achieved by using the Noyori condition (Scheme 36).[11] To a solution of Ru catalyst with chiral ligand (**S36.4**) in isopropanol was added a solution of (**S35.6**) in isopropanol at room temperature, which produced the product readily in 98% yield. The optical purity of the propargyl alcohol (**S36.1**) was measured by Mosher esters analysis and found to be 98% ee. It is known that a terminal alkyne can poison the Noyori catalyst. Therefore, using pure starting material is crucial for the reaction. The next step was the application of Myers' method to furnish the optically pure allene (**S36.2**) from **S36.1**, which gave the desired product in 70% yield. The side product of this reaction was found to be a product resulting from migration of the TBDPS group from primary alcohol to secondary alcohol. Also, the yield of the reaction was sensitive to the purity of the *O*-nitrobenzensulfonyl hydrizide, as reported by Myers.[6]

Scheme 36 Noyori Reduction
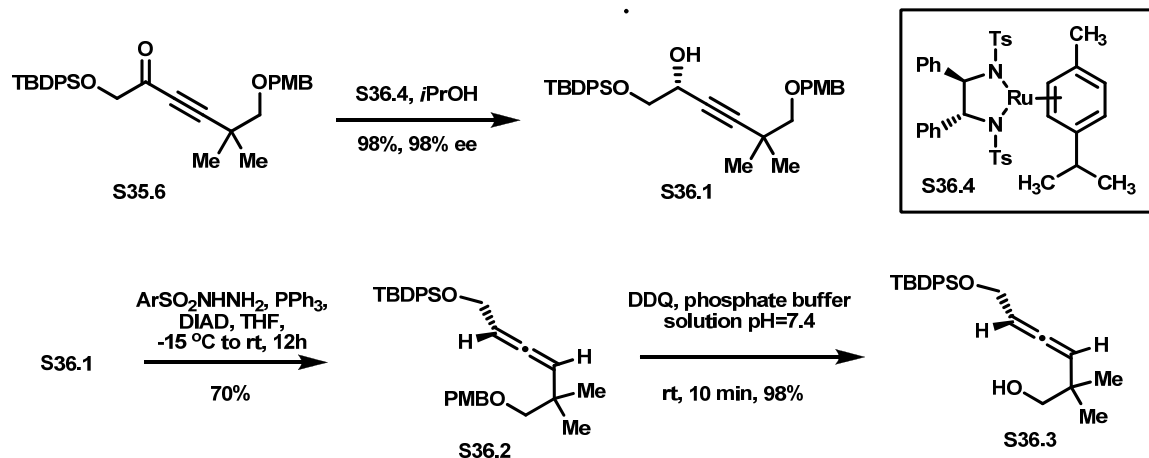
Treatment of **S36.2** with DDQ resulted in cleavage of the PMB group. The by-product anisaldehyde interestingly had the same Rf value with the original product and was hard to remove by FCC. However, reduction of it with $NaBH_4$ provided a clean separation of the allenyl alcohol (**S36.3**).

Oxidation of **S36.2** with Dess-Martin afforded the aldehyde (**S37.1**, Scheme 37), which was then treated with ethynylmagnesium bromide at low temperature to give rise to a mixture of **S37.3** and **S37.4** (dr; 1:1, determined by ^{1}H NMR). The diastereomeric mixture of alcohol products was exposed to the Dess-Martin reagent to afford the ketone **S37.2** in 80% yield over 3 steps. The asymmetric reduction of **S37.2** was accomplished by use of Corey-Bakshi-Shibata (*S*-isomer) reagent to give inseparable alcohols (**S37.3** and **S37.4**) in 90% yield.[12] The ratio of the reaction was 10:1, determined by ^{1}H NMR.

Scheme 37 Formation of the Key Allene
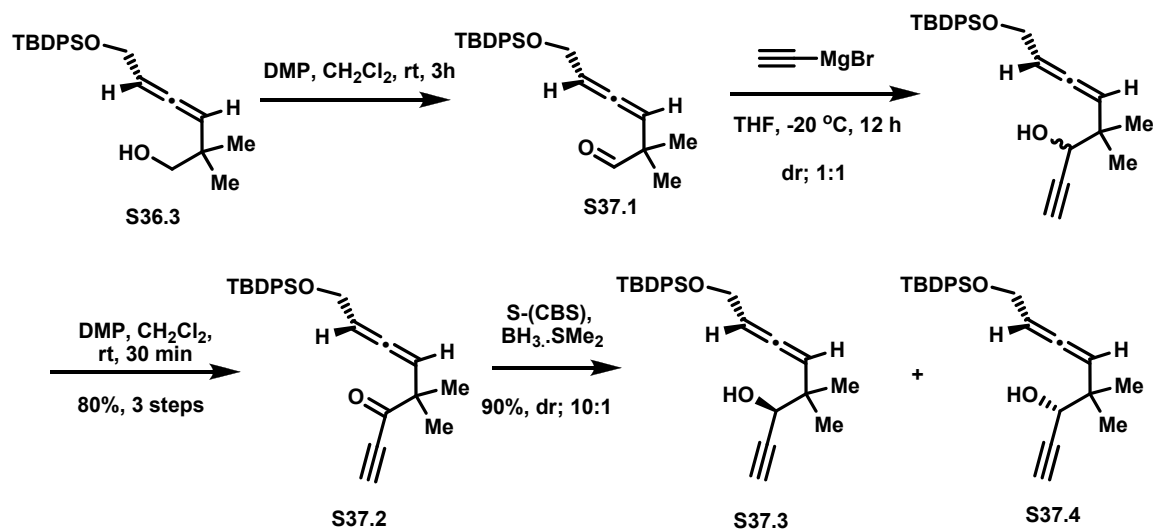
Dr. Shangguan prepared allenes **S38.1** and **S38.2** (Scheme 38). The general procedure applied for allene oxidation was: a solution of an allene in chloroform at low temperature was treated with a freshly prepared solution of DMDO. After 30 min, MeOH was added to the reaction mixture and stirred for 12h. Gratifyingly, cyclization of SDEs from all three allenes afforded 2,6 substituted trans and cis pyranones. In all cases, the 2,6 trans product was the major one. It was observed that the selectivity of the SDE formation changed with the size of the protecting groups. The bulkier they are the more selective product formation is. The smallest MOM protecting group gave a 4:1 ratio, TBS gave a 6:1 ratio. The bulkiest TBDPS group yielded 72% of the 2,6 trans disubstituted pyranone **S36.3**. With this reaction, the chemo-, regio- and stereo- selective oxidation of 1,3 disubtituted allenes was accomplished as planned. Consequently, the TBDPS group was found to be optimal for the synthesis of the target. Also, the terminal alkyne stayed intact since it is known that its oxidation with DMDO is slower than that of an allene.[13]

Scheme 38 Cyclization of Allenes

2,6 trans   2,6 cis

S38.1 P; MOM ⟶ 60%, dr; 4:1

S38.2 P; TBS ⟶ 70%, dr;6:1

S37.3 P: TBDPS ⟶ 72%, (2,6 trans, S38.3)
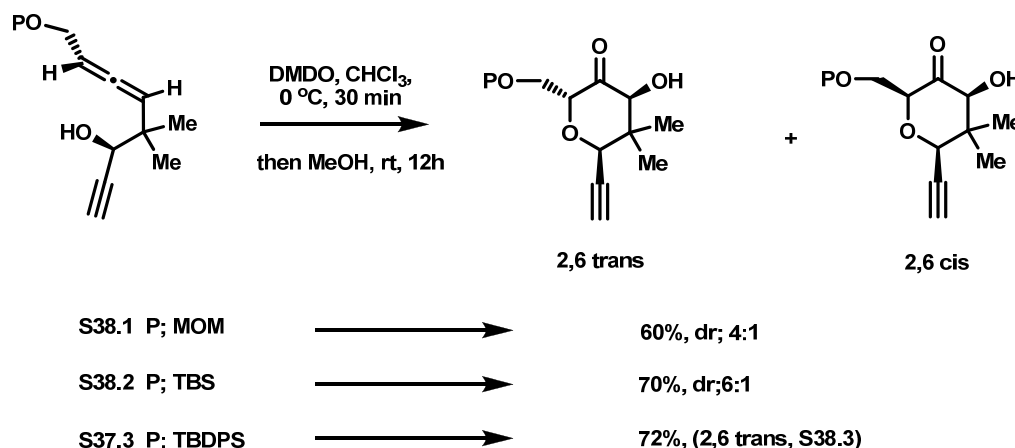
The DMDO oxidation of allenes in Scheme 38 gave only two isomers out of a possible four (check Scheme 30) and that the selectivity of oxidation changes with the size of protecting group were interesting observations. These results can be reasoned from stepwise oxidation of allene explained as followed. The first oxidation takes place regioselectively on the double bond distal to the oxygen substitutent which deactivates the proximal double bond. Moreover, this oxidation occurs slowly and highly stereoselectively, giving the anti allene oxide (**S39.1**) as the major intermediate and the syn allene oxide as minor intermediate (**S39.2**). Also, the size of the protecting groups appears to play a role in the selective formation of **S39.1** and **S39.2**. The second oxidation of **S39.1** should take place very fast and less stereoselectively, giving **S39.3** as the major SDE, since the sterically demanding *tert*-butyl group induces the delivery of oxygen from the opposite face. The minor SDE would be **S39.2**. **S39.3** and **S39.4** lead to the formation of the observed trans and cis products, respectively. The second of oxidation of the minor syn intermediate (**S39.2** could furnish the antipodal trans and cis products, but they could not be observed.

Scheme 39 SDE Formation from Allene
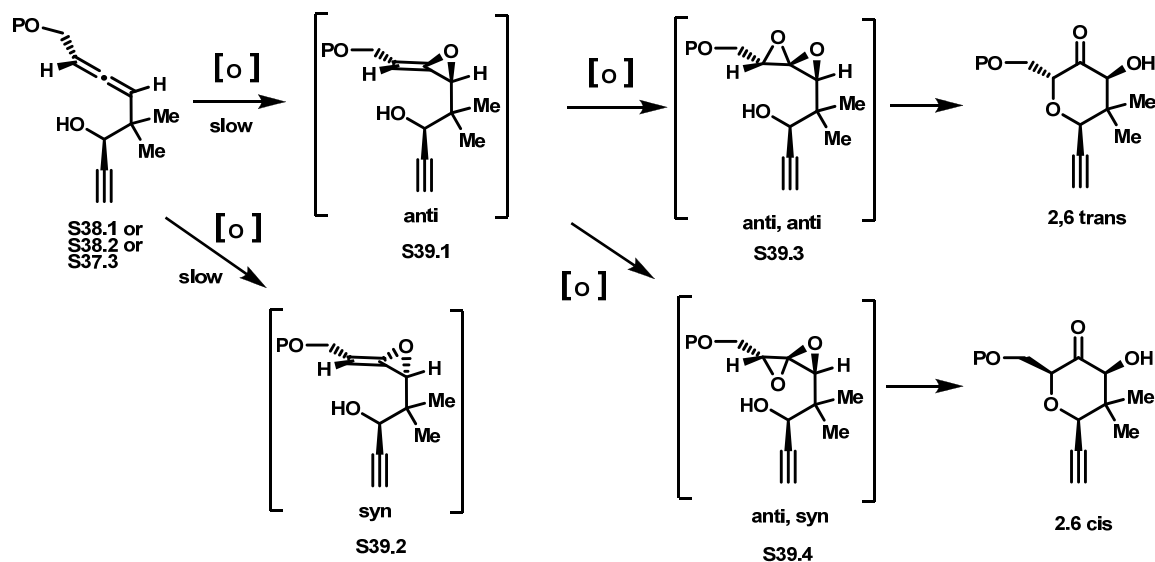
During the oxidation of allene **S37.3**, we needed to use MeOH whereas it was not necessary for the epimeric allene **S40.2** (also, P=MOM gave the same result) which cyclizes spontaneously to give the pyran ring (**S40.3**) without observing SDE (Scheme 38). These results led us to conclude that there is, surprisingly, a stable SDE (**S40.1**) formation upon oxidation of these types of allenes.

Scheme 40 Oxidation of Epimeric Allenes
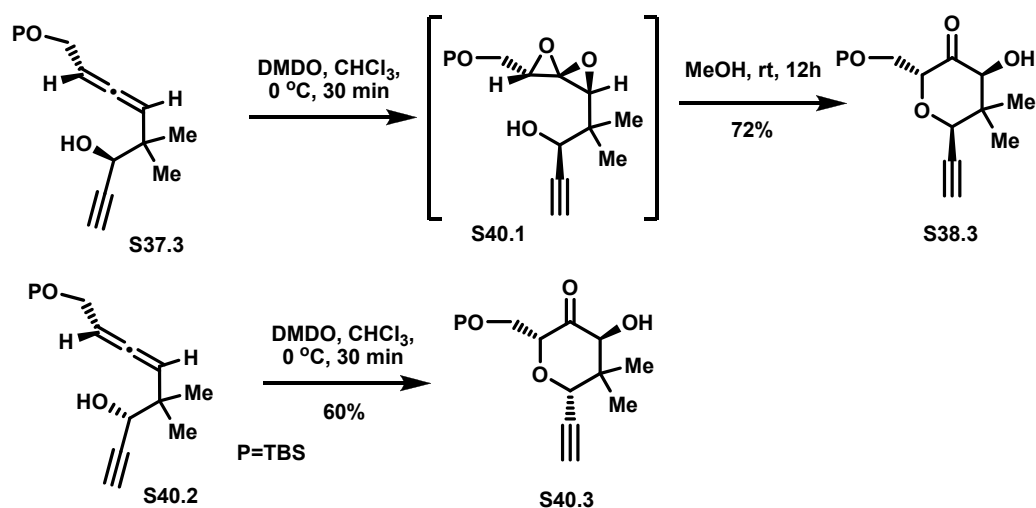
The different behavior of these allenes upon oxidation and the unusual stability of the resultant SDEs could be rationalized from the conformational preferences of the SDEs shown in Scheme 41. The resistance of SDE toward cyclization could be due to both stabilization of conformer **S41.1a** via favorable intramolecular hydrogen bonding and possible destabilization of reactive conformer **S41.1b** by steric interactions between alkyne and SDE. In the case of the epimeric allene (**S40.2**) oxidation, the reactive conformer **S41.2b**, which led directly to pyranone (**S.41.2**), would be favorable because the other conformer (**S41.2b**) suffers form severe steric interactions. Therefore, the cyclization of **S41.2b** would take place faster than **S41.1a**. MeOH may act to disrupt hydrogen bonding in **S41.1a** and promote cyclization. Additionally, the side products resulting from opening of **S41.1** with MeOH was observed in low yield (<10%).

Scheme 41 Stable SDEs
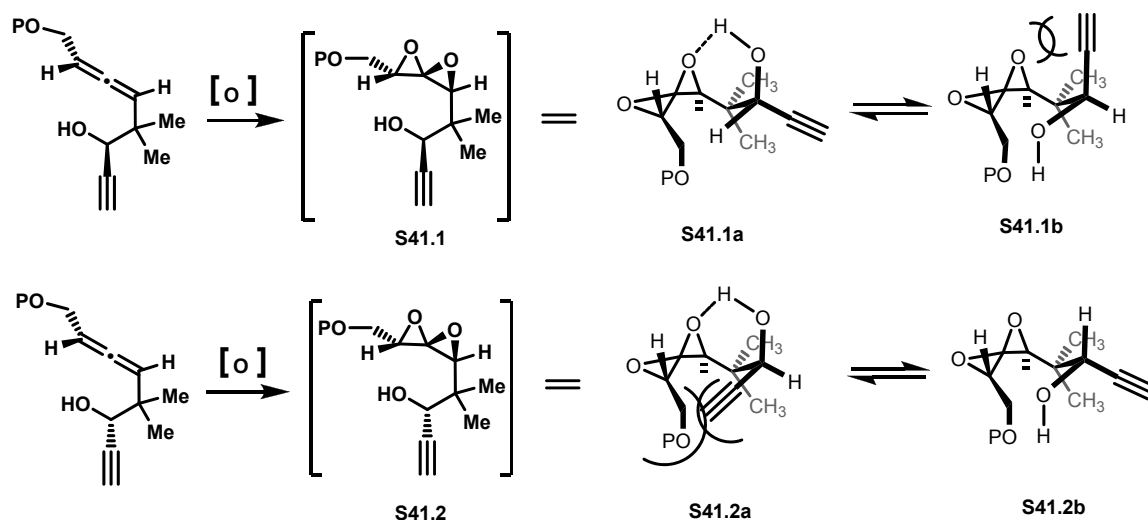
III. Synthesis of the Rawal Intermediate

We targeted compound **S18.5** (Scheme 18) in the Rawal mycalamide synthesis in order to show a novel approach to access the trioxadecalin ring systems in the pederins, which would also enable us to clarify the relative configuration of the product (**S38.3**) obtained from DMDO oxidation of the key allene (**S37.3**). The **S38.3** was selectively reduced with sodium triacetoxyborohydride to give the trans diol (**S42.1**) as the major product in 74%.[14] The hydroxyl group distal to the neopentyl center was selectively protected with a MOM group to give **S42.2** in 60% yield. The second protection furnished almost quantitatively **S42.3**. Hydroboration and then oxidation of **S42.3** gave rise to aldehyde **S42.4**, which was exposed to a Wittig ylide to give the alkene (**S18.5**). Based on ^{1}H NMR matching, the relative stereochemistry of the pyranone **S38.3** and the diol **S42.1** was proven to be correct.

Scheme 42 Synthesis of the Rawal Intermediate
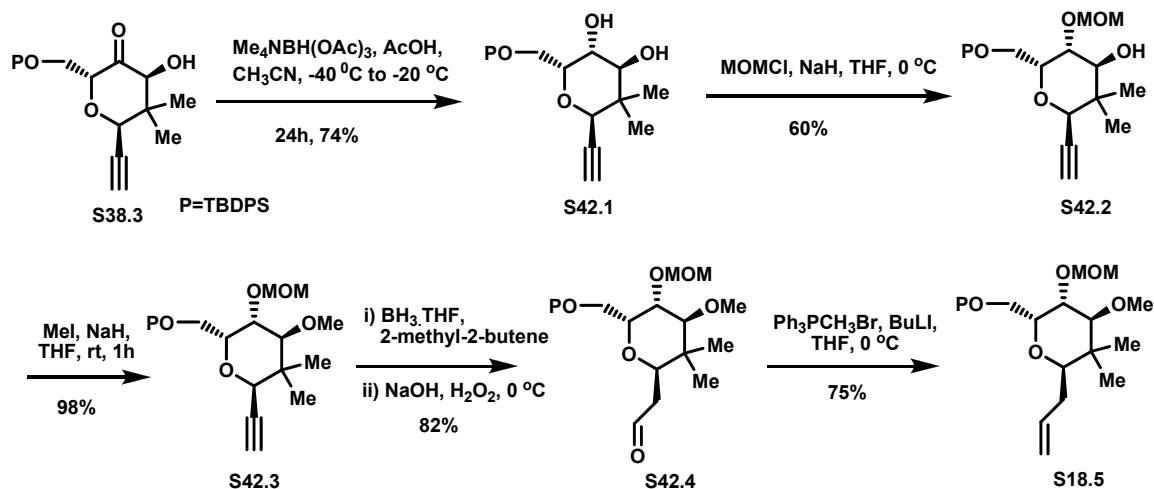
IV. Completion of the Formal Synthesis of Psymberin

In order to convert the carbonyl group in **S38.3** to a methylene, the known procedures such as hydrazine and dithiane formation were applied. But these conditions failed to give desired product formation. Nonetheless, removal of the ketone was accomplished from the pyranone (**S38.3**) in three steps. First, **S38.3** was selectively reduced to diol **S42.1** as shown in Scheme 42. Second, **S42.1** was converted to epoxide **S43.1** by treatment with tosyl chloride and NaH in wet THF (Scheme 43). For the direct epoxide formation, it is required to use wet THF, otherwise, the monotosylation of the alpha hydroxyl group in **S42.1** was observed, which could subsequently be converted to the epoxide upon treatment with NaH in wet THF. The different reactivity of both the hydroxyl groups in tosylation reaction may result from sterics. The S_N2 type displacement of tosylate with the β-hydroxyl anion is geometrically suitable to form epoxide **S43.1**. Finally, reductive opening of **S43.1** by DIBAL provided the alcohol (**S43.2**).[15] The yield of the DIBAL reaction depends on the reaction time (80%, in 1h). Longer reaction times could cause cleavage of the TBDPS group and reduction of the alkyne to an alkene at the same time. **S43.1** was protected with MOM to give **S43.3** in high yield. Hydroboration/oxidation of **S43.3** gave rise to aldehyde **S43.4**, which was exposed to aldol reaction conditions to afford the major syn product (**S43.5**) in 93% yield.[16] The formal synthesis of the psymberin was completed by Dr Shangguan. Briefly, conversion of **S43.5** to Weinreb amide **S43.6**, protection with a TES group and then reduction of the amide set the aldehyde (**S43.7**) for another crucial step, which was coupling with an arene partner to form the dihydroisocumarin ring.[17]

Scheme 43 Completion of Pyran Unit
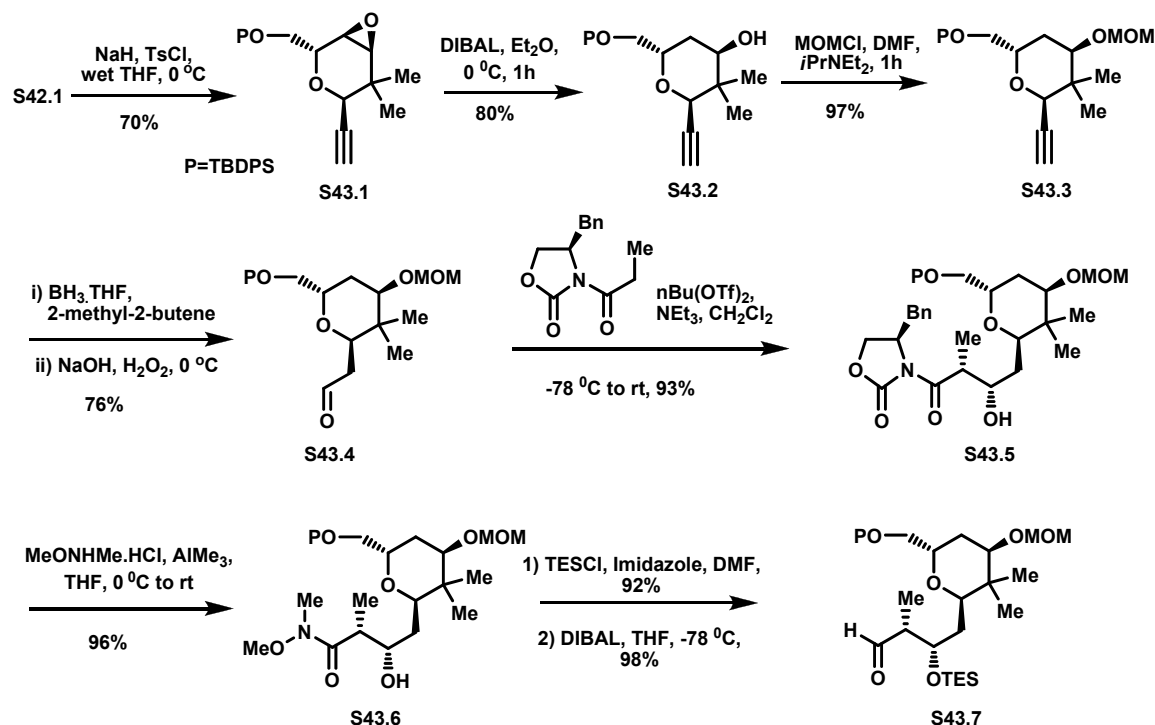
To construct the dihydroisocumarin ring, we envisioned a combination of the pentasubstituted arene (**S29.8**, Scheme 29) with an aldehyde in a single step. To do this, the ortho-toluate carbanion generated from **S29.8** with base reacts with an aldehyde to give rise to the lactone.[18] Generation of similar types of carbanions and reaction with different electrophiles such as Weinreb amides and esters are reported in the literature.[19] In particular, the Staunton group demonstrated formation of a lactone ring along with the side products from coupling of an aldehyde with a simple *O*-toluate carbanion.[17e]

The synthesis of the arene commenced with the transformation of dimedone (**S44.1**) to the aromatic product (**S44.2**, Scheme 44). Von Doering first reported the reaction by using acetic acid anhydride and sulfuric acid.[20] However, Nelson's group optimized it by using trifluoroactic anhydride.[21]

Scheme 44 Aromatization of Dimedone

S44.1   S44.2
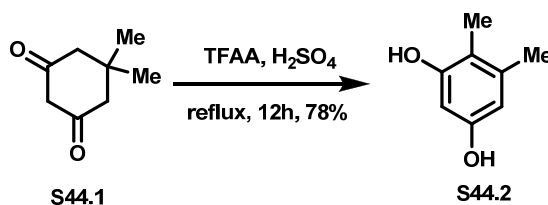
A reasonable mechanism of the interesting aromatization is given in Scheme 45. The key features of the mechanism are the addition of a sulfonium cation generated from sulfuric acid and trifluoroacetic anhydride to **S45.1** to generate cationic intermediate **S45.2**. After deprotonation, evolution of SO_2 from **S45.3** takes place to generate **S45.4**. 1,2 methyl migration followed by aromatization afforded **S45.6**, which gave the desired product after basic hydrolysis.

Scheme 45 Mechanism of Aromatization
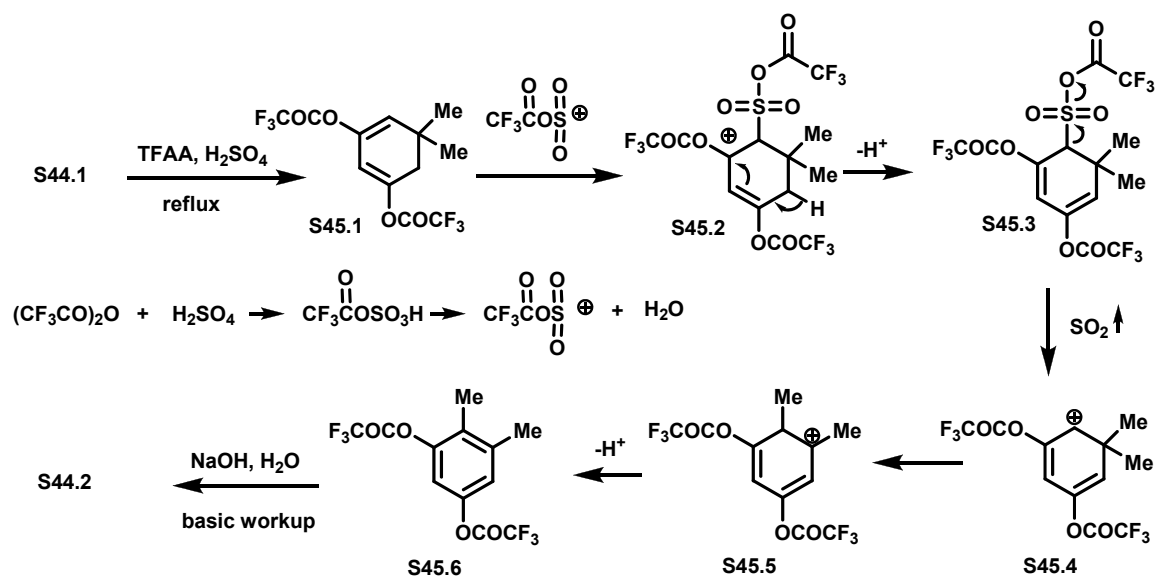
The next step was the formylation of **S44.2** by applying the Vilsmeier-Haack reaction.[22] The arene (**S44.2**) was exposed to phosphorous oxychloride and DMF in acetonitrile. Even though the yield of the reaction is 46%, this condition was safer than

the Gatterman reaction, in which hazardous reagents like zinc cyanide and hydrochloric acid are used.[23] The resulting hydroxyl aldehyde (**S46.1**) was masked as a MOM ether, oxidized to the carboxylic acid, and converted to the methyl ester (**S46.2**). The yield of the reaction sequence was 86% after three steps.

Scheme 46 Formation of Arene S44.2
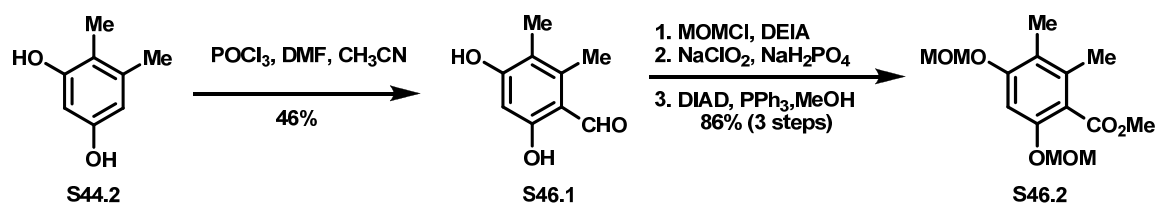
In order to see the formation of *O*-toluate carbanion formation, **S46.2** was treated with LDA at low temperature (Scheme 45). The deep red color indicated enolate formation (**S47.1**). Addition of TMSCl gave **S47.2**. In addition, the studies showed the MOM protection group was stable, while the silyl and Bn protecting groups did not survive under the reaction conditions.

Scheme 47 Anion Formation from Arene S42.2
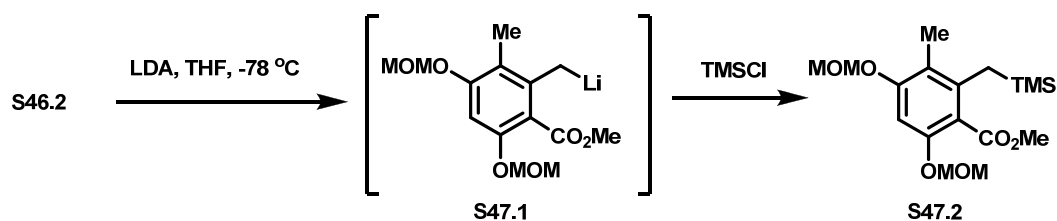
To couple **S47.2** and **S43.7** in the real system, the anion generated from **S44.2** by treatment with LDA at -78 °C was slowly added to the precooled aldehyde (**S43.7**) solution in THF. The inverse and slow addition of *O*-toulate carbanion was preferred to

diminish the side product, which formed from the addition of carbanion to the corresponding lactone product (**S48.1**). The coupling reaction gave **S48.1** as the major product predicted according to the Felkin-Ahn model in a ratio of 3.5 to 1 (64% yield, 94% brsm). Gratifyingly, the formation of the dihydroisocumarin ring from the coupling of the pentasubstituted arene **S47.2** and complex aldehyde **S43.7** represented the most sophisticated example to date. Removal of all MOM and TES protecting groups followed by acetylation furnished **S48.2** in 75% yield over 2 steps.[24] Cleavage of the TBDPS group and then oxidation gave the aldehyde (**S48.3**) in 74% yield after 2 steps. Oxidation of **S48.3** to a carboxylic acid and then amidation gave rise to amide **S48.4**, which has identical ^{1}H, ^{13}C NMR and optical rotation to the earlier data reported by De Brabander. The formal synthesis of psymberin was accomplished.[25]

Scheme 48 Completion of Formal Synthesis
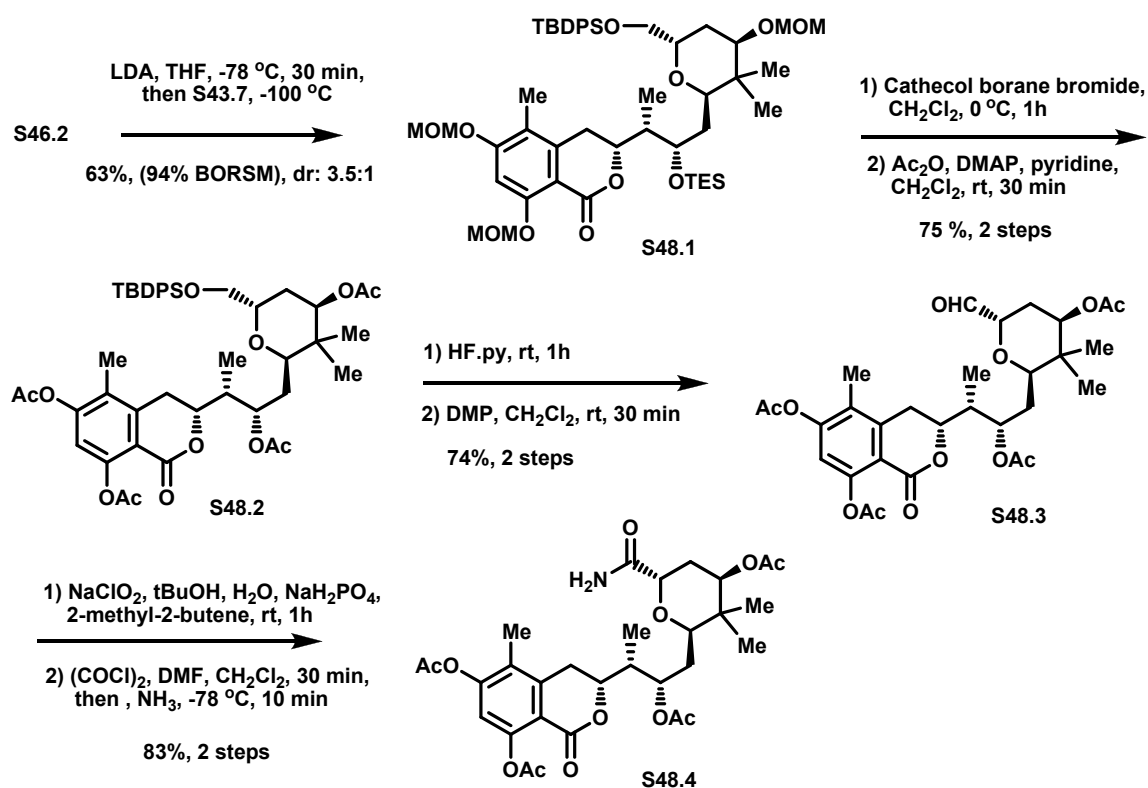
## IV. Spirodiepoxides in Psymberin Synthesis: 2nd generation

The synthesis of the right segment of psymberin was accomplished in 25 steps from known aldehyde (**S33.1**, Scheme 33). Our novel strategy demonstrated the oxidation of comparatively complex allene chemo-, regio-, and stereoselectively. The facile intramolecular opening of the resulting SDE to form six-membered cyclic ether represented the first application in the synthesis of complex molecules. Moreover, construction of a dihydroisocumarin ring from complex partners proved to be an elegant and efficient method. In light of these promising results, the synthesis of **S49.1** was envisioned from the SDE (**S49.2**) derived from oxidation of a more functionalized allene **S49.3** (Scheme 49). This would enable us to reach the target more directly and advance our understanding of the functional and protecting group compatibility of SDE chemistry. Moreover, the trend for the preference of epoxide opening has been studied in detail and found to be 5-exo>6-exo>6-endo. However, the trend for SDE cyclization has not been well established. Therefore, the oxidation of **S49.3** and exo vs endo opening in the presence of multiple hydroxyl groups is of interest. In the case of allene **S49.3**, it would be expected that 6-endo mode would be favorable over the neopentyl-like 6-exo cyclization despite the fact that 6-exo is more preferable in unbiased epoxide systems. The competition between the two modes, which could lead to complex mixtures of products, could be resolved if one of the hydroxyl groups was protected.

Scheme 49 Synthetic Strategy for 2nd Generation
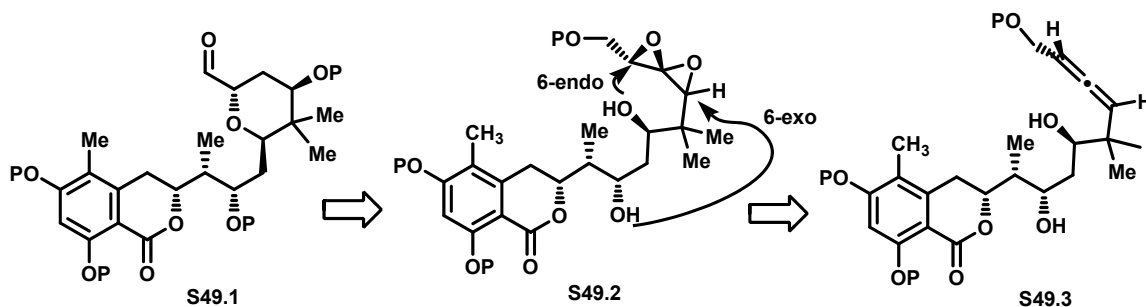
In related synthetic studies toward FR900482 mitomicinoids, the Williams group found that oxidation of the complex allene with DMDO gave several products, presumably due to deterioration of arene moiety.[3a]

Scheme 50 DMDO Oxidation of Allene in FR Synthesis
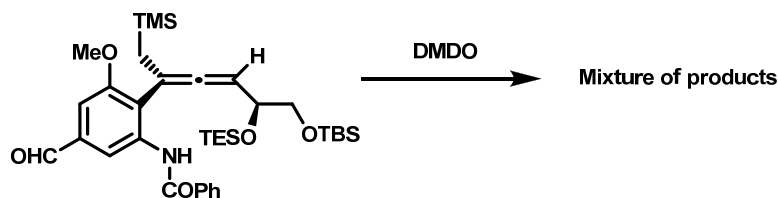
In order to prevent this problem for allene **S49.3**, the stability of arenes with MOM (**S51.1**) and acetate (**S51.2**) protecting groups under oxidation conditions were tested (Scheme 51). When **S51.1** was treated with DMDO, many products were observed within 10 min. However, **S51.2** was stable even after 24 hours. This different behavior could be reasoned from the nature of protecting groups, where an electron withdrawal acetate group could decrease the reactivity of an otherwise electron rich arene toward DMDO.[26]

Scheme 51 Stability of Arenes
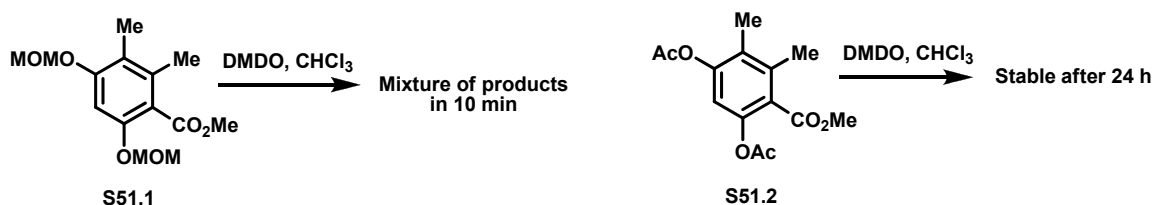
It was observed that PMB and Bn protecting groups may be cleaved under oxidation conditions. Therefore, this problem as well as protecting group compatibility prompted us to revise the second generation synthesis of psymberin. Our interest was to prepare an allene without an arene unit, which may not cause the above-mentioned problems. We envisioned that allene (**S49.3**) would be accessed from **S52.1**, which could be prepared from two simpler units; the allenyl aldehyde (**S52.3**) and a ketone (**S52.3**). Coupling of the two units could be achieved via the Paterson aldol condition.[27] The reagent controlled reduction of a ketone followed by selective protection of the hydroxyl group would generate the allene, ready for DMDO oxidation.

Scheme 52 Revised 2nd generation Strategy
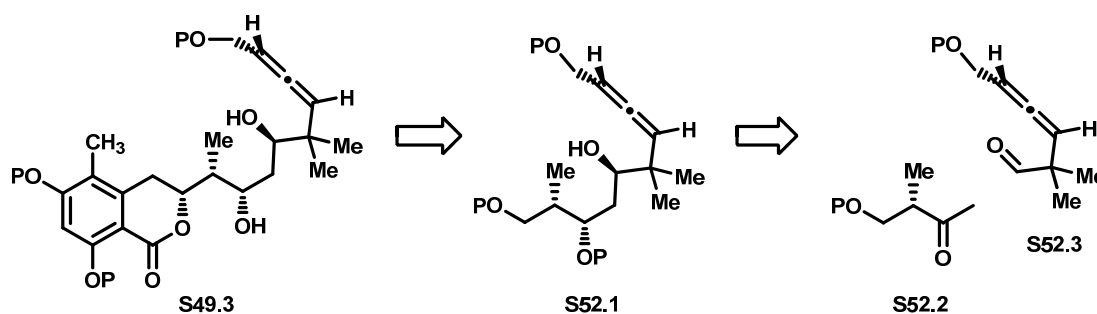
The known ketone (**S53.3**) was prepared in 3 steps from the chiral methyl ester (**S53.1**). TBS protection gave **S53.2**, which was converted to a Weinreb amide and then ketone (**S53.3**) in 82% yield after 2 steps (Scheme 53).

Scheme 53 Synthesis of Ketone S53.3
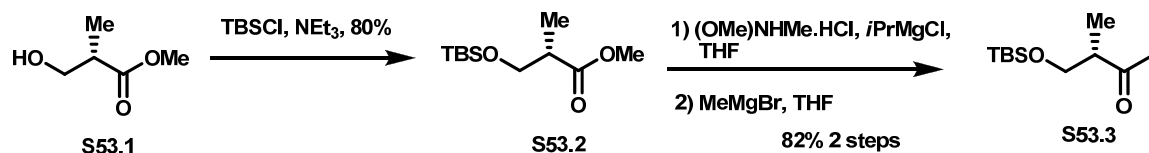
After a solution of **S53.3** in diethyl ether was treated with NEt₃ and Cy₂BCl at low temperature, a solution of allene aldehyde (**S37.1**, Scheme 37) in the same solvent was added to the reaction mixture at -78°C. The resultant alcohols were separated by FCC, providing the major product (**S54.1**) in 74% yield, and **S54.2** in 11% yield (dr; 7:1). The high selectivity of the substrate directed aldol reaction using an achiral borane reagent has been explained with a transition state model (**S54.3**) by the Paterson group. In the proposed chair-like transition state, the large R group of a ketone is positioned in such a way as to minimize destabilizing steric intereactions.[25] The efficiency and reliability of the reaction was shown in the synthesis of complex molecules by the same group.[25c] In order to ensure that the major product had desired configuration, the reaction was repeated with a chiral borane reagent providing **S54.1** as major product with a higher selectivity (<20:1), albeit in lower yield (30%).

Scheme 54 Paterson Aldol Reaction
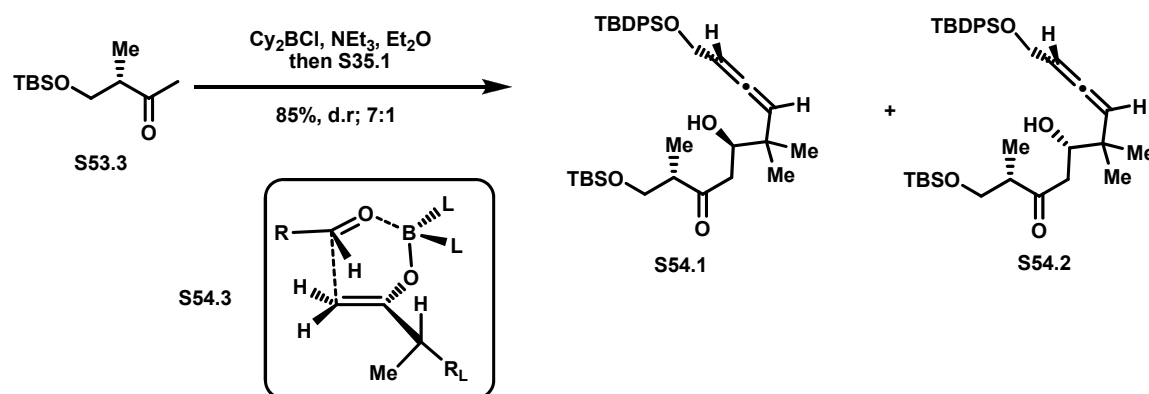
For the substrate directed asymmetric reduction of ketone **S54.1**, two different conditions were applied to provide 1,3 syn diol (Scheme 53). Treatment of **S54.1** with $(Et)_2BOMe$ and $NaBH_4$ gave **S55.1** in higher yield and ratio (95%, dr:20:1) than $ZnBH_4$ (84%, 10:1). The hydroxyl group distal to the neopentyl center in **S55.1** was selectively protected with either TBSOTf or alternatively with TBSCl to yield **S55.2**. Yields were not optimized.

Scheme 55 Asymmetric Reduction of Hydroxyl Ketone
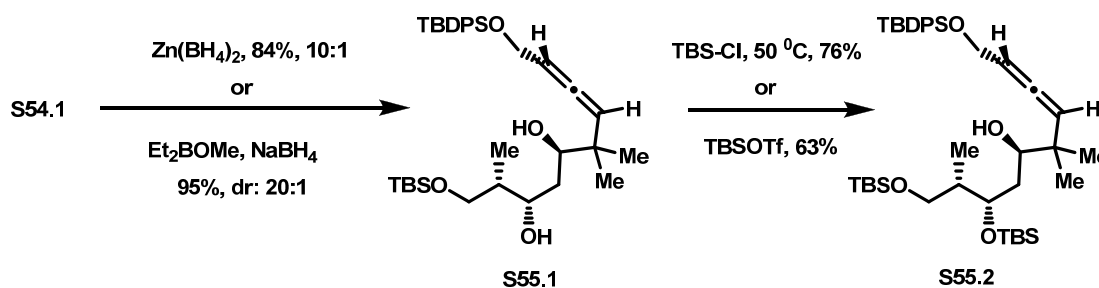
Unfortunately, the oxidation of **S55.2** with DMDO gave rise to a mixture of products. Even though the electron spray mass spectroscopy indicates the molecular ion peak corresponding to the desired product, it was very difficult to isolate out from the reaction mixture. Also, addition of MeOH and inverse addition did not work. Likewise, the oxidation of **S54.1,** structurally similar to **S55.2**, produced the same result. However, the oxidation of **S54.2**, epimeric to **S54.1**, furnished the cyclic ether ring (**S56.1**) in 40% yield. The product was fully characterized. Separation and characterization of products from DMDO oxidation of **S55.2** and **S54.1** would enable us to rationalize the behavior of the two similar allene **S54.1** and **S54.2**, but it was a very difficult process. This route was not further pursued because of these unexpected results.

Scheme 56 DMDO Oxidation of Allenes
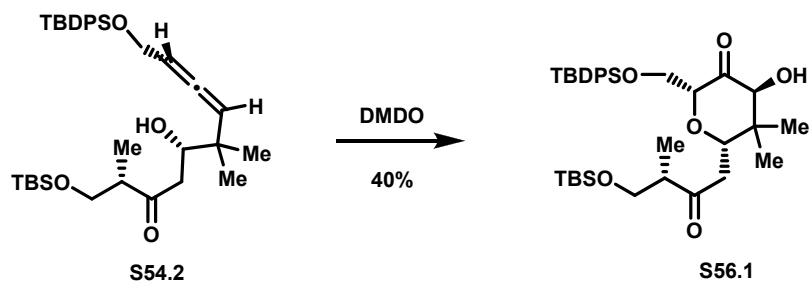
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Chapter IV

Direct Carbinolamide Synthesis

I. Introduction

The elegant synthesis of both the core ring with the application of SDE and the dihydroisocumarin ring were accomplished in order to reach the target molecule, psymberin. These novel and flexible strategies could also enable us to synthesize analogs and hybrid structures of psymberin. The last synthetic challenge posed by this complex molecule is to construct, efficiently and stereoselectively, the unique *O*-alkyl carbinolamide functional group (Figure 2, p2). Presumably, this group plays a significant role in the biological activity of the pederin family members. A probable mechanism for the biological action is eliminative cleavage of the C-O bond giving rise to an acylimine which could act as an alkylating agent.

In chapter 2 the synthetic strategies for the fragments of the pederin family members were discussed. These fragments are bridged by the *O*-alkyl carbinolamide. There are several creative methods reported for the construction of this motif. Among them, the Matsumoto and Roush methods, which are the most widely used, will be discussed in this chapter. In addition, the Huang group recently reported the total synthesis of psymberin and their approach will be mentioned here. Our group devised a different approach to build this highly sensitive motif and is applying it to the synthesis of analogs.

In the late 80's, the Matsumoto group developed an outstanding strategy to form

O-methyl carbinolamides, which was demonstrated in the first total synthesis of pederin. In this strategy, an amide (**S57.1**) is treated with trimethyloxonium tetrafluoroborate to give rise to an imidate (**S57.2**), which is subjected to an acyl chloride (**S57.3**) and a base to afford *N*-acyl imidate (**S57.4**). The resulting **S57.4** is readily reduced in situ with NaBH₄ in alcoholic solvents to the carbinolamide (**S57.5**). Although studies for the model and real systems afforded the motif in high yields, this approach suffered from poor stereoselectivity in product formation. For example, the pederin was obtained in a 1:3 ratio (desired:undesired) after the employment of this strategy in their total synthesis. Nevertheless, this synthetic method has been employed by several other groups to achieve both the synthesis of pederin and its analogs.

Scheme 57 The Matsumoto Strategy
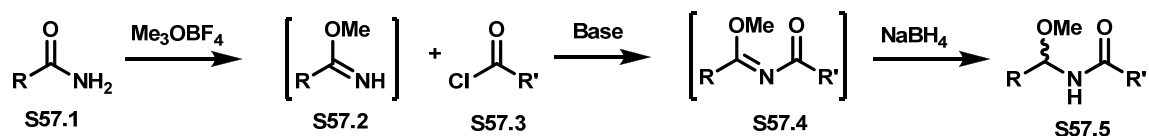
The De Brabander group recently applied the Matsumoto method in the total synthesis of psymberin. They prepared the amide (**S58.1**) and acyl chloride (**S58.2**) partners and combined them under the Matsumoto condition to get *O*-methyl protected carbinolamide. Albeit capricious, they found that polyvinyl pyridine base appeared to be uniquely effective among amine bases. After basic hydrolysis of the acetate and benzoate protecting groups, they obtained the natural product (**S58.3**) and its epimer in a 2.5 to 1 ratio. The yield was 56% based on recovered **S58.1**.

**Scheme 58 The De Brabander Synthesis of Psymberin**
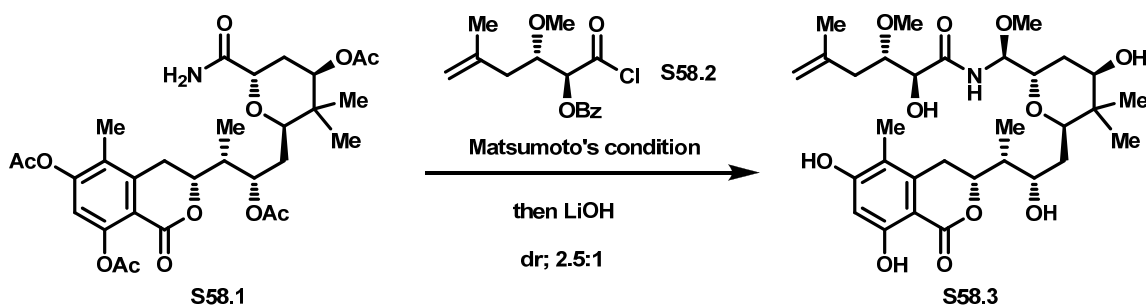
Another creative strategy was developed by the Roush group and employed in their total synthesis of mycalamide A. In this strategy, **S59.1** was converted to a carbamate (**S59.3**) through Curtius rearrangement of **S59.2** with diphenylphosphoryl azide in the presence of TMS ethanol. The resulting **S59.4** was then deprotonated with base and captured with an acyl chloride to give an *N*-acyl product (**S59.5**). Exposure of **S59.5** to the TBAF removed the trimethylsilylethoxy carbonyl (Teoc) group to readily afford the desired functionality (**S59.6**). The most striking feature of this method is complete stereocontrol. No epimerization is observed under the reaction conditions. Several other groups have applied this method successfully in the synthesis of the pederin family members.

Scheme 59 The Roush Strategy
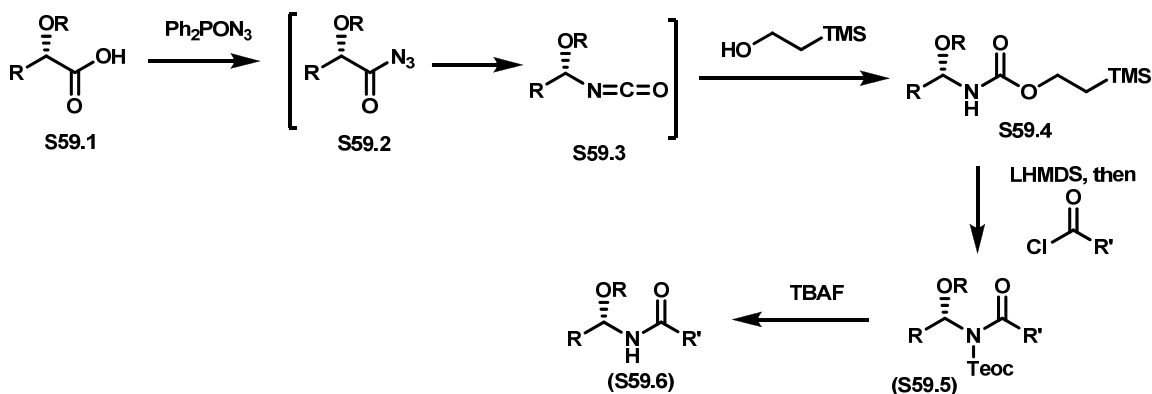
The Huang group developed an interesting method for the motif and applied it to the synthesis of psymberin. They converted an *N*-acyl enamine (**S60.1**) to the corresponding pyran (**S60.2**) using PhI(OAc)$_2$ as oxidant in a single step. They also investigated the likely mechanism of the reaction during the optimization and reported two possible pathways to product formation. For the synthesis of psymberin, they prepared precursor **S60.3** and treated it with the oxidant, which afforded a total yield of 72% of isolated products. The desired product (**S60.4**) was isolated in 30% yield among the four diastereomers. After protecting group manipulations and double bond formation in the acyclic side chain (5 steps), they completed the total synthesis of the natural product. Although this transformation leads to product formation very quickly, the selectivity is poor. Additionally, the reaction conditions may not be suitable for some functional groups, e.g. other C-C double bonds.

Scheme 60 The Huang Strategy
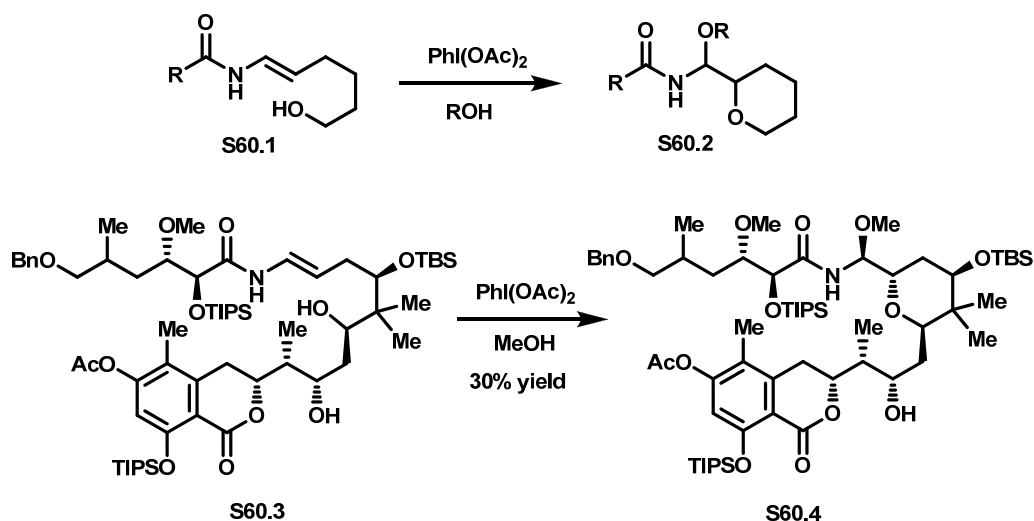
II. Direct Aldehyde-Amide Coupling

We completed a formal synthesis of psymberin. To complete total synthesis we could apply the Matsumoto coupling. However, the reported approaches to *O*-methyl carbinolamide formation require multi-step processes. We felt that a direct method that leads to formation of the motif stereoselectively is necessary. We envisioned that the desired motif would be accessible from methylation of a carbinolamide (**S61.3**), which would be in turn derived from a direct coupling of an amide (**S61.1**) and an aldehyde (**S61.2**). In the literature, direct coupling of two partners had been reported, but it was limited to only electron poor aldehydes and required relatively harsh conditions.[1] There are also indirect approaches reported for the motif formation.[2]

Scheme 61 Direct Aldehyde-Amide Coupling
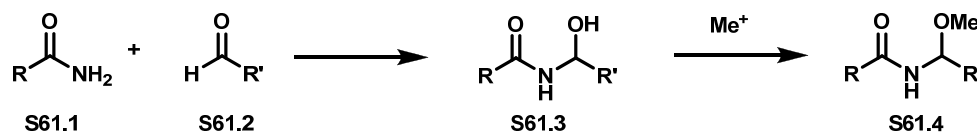
During the total synthesis of zampanolide, the Hoye group disclosed an approach that involved coupling an aldehyde (**S62.3**) with the metal imidate (**S62.2**) derived from an amide (**S62.1**) and DIBAL (Scheme 62).[3] This reaction was the first example of the direct coupling of two partners under mild conditions. However, they obtained a mixture of products (**S62.4**) in a ratio of 1: 1and no yield was reported.

Scheme 62 The Hoye Synthesis of Zampanolide
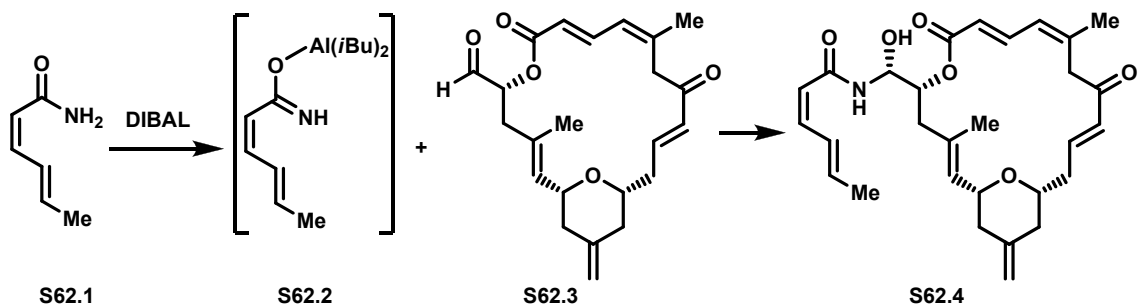
We anticipated that the complex aldehyde (**S63.2**) could be coupled with the complex amide (**S63.1**) under the same conditions to afford the corresponding carbinolamide. Unfortunately, the reaction failed to give the desired product. Consequently, we studied this reaction in more detail in terms of generality, reliability, and efficiency. In addition, the stereoselectivity issue must also be addressed.

**Scheme 63 Direct Coupling of Amide S63.1 and S63.3**
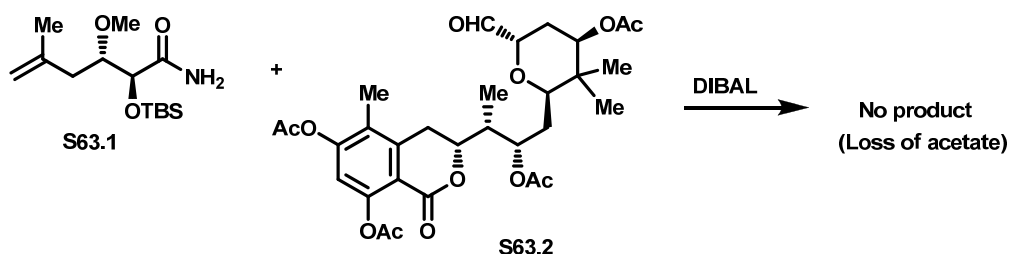
In principle, addition of an amide anion to an aldehyde represents a type of aldol reaction, which is one of the most studied reactions in organic chemistry. Aldol reactions have been efficiently and reliably applied in complex synthesis and provided stereoselective product formation under reagent or substrate controlled reaction conditions.[4] The enolates can be formed with different metals such as Li, B, Ti, Sn. Hence, we expected that different metal imidates could be generated from amides

coupled with aldehydes to provide carbinolamides. Boron imidates represent an alternative approach.

III. Results for Boron Imidates with Aldehydes

We applied the Paterson aldol reaction conditions to couple hexanamide (**S64.1**) and cyclohexanecarbaldehyde (**S64.2**).[5] Thus, **S64.1** (1.2 eq) was taken up in diethyl ether (0.2 M) and NEt$_3$ (2.0 eq) was then added. After cooling to 0 $^{\circ}$C, dicyclohexylboron chloride (1.3 eq, 1.0 M in hexane) was added. The heterogeneous mixture was stirred for 15 min and then **S64.2** (1.0 eq) was added. After 30 minutes the reaction was quenched with a mixture of MeOH/phosphate buffer (ph=7.40)/H$_2$O$_2$ (30%). Isolation and purification gave the carbinolamide (**S64.3**) in 88% yield.

Scheme 64 Simple Aldehyde and Amide Coupling
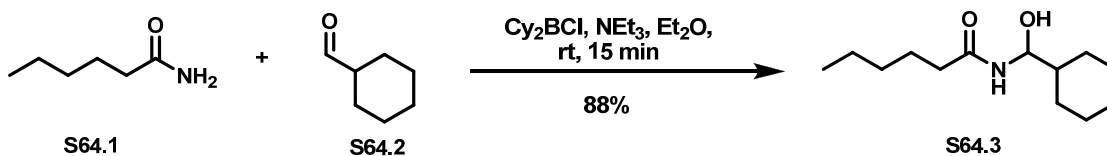
Presumably, boron imidate formation takes place under the reaction conditions and then couples the aldehyde. We then turned our attention to optimize product formation. In table 2, the yields were given with different equivalents of amide (**T2.1**), aldehyde (**T3.2**), Cy$_2$BCl, and NEt$_3$. Using either a slight excess of the imidate or aldehyde gave the same yield (entry 1-3 and 7). Finally, the yield did not change with excess imidate (entry 4, 5 and 6). As a result, entry 1 and 7 gave the optimal conditions. The solvent Et$_2$O was found to be a good choice since CH$_2$Cl$_2$, THF, and CH$_3$CN gave

the yields of 75%, 54%, 23%, respectively. Also, using the (nBu)$_2$BOTf for imidate formation did not improve the yield.

**Table 2 Optimization of Coupling Reaction**

Entry	T2.1	T2.2	Cy$_2$BCl	NEt$_3$	T2.3
1	1.2 eq	1.0 eq	1.2 eq	2.0 eq	84%
2	1.2 eq	1.0 eq	1.5 eq	2.0 eq	84%
3	1.4 eq	1.0 eq	1.1 eq	2.0 eq	78%
4	1.5 eq	1.0 eq	1.5 eq	2.0 eq	83%
5	2.0 eq	1.0 eq	2.0 eq	2.0 eq	82%
6	2.5 eq	1.0 eq	2.5 eq	3.0 eq	77%
7	1.0 eq	1.5 eq	1.05 eq	2.0 eq	84%

Several aldehydes and amides were coupled. The findings are tabulated in Scheme 65. The primary amides coupled readily with an aldehyde to give the carbinolamides (**S65.1**, **S65.2**, **S65.3**) in moderate yields. Interestingly, the cyclic amides (**S65.5**, **S65.6**) appeared to be unreactive, while the five-membered cyclic amide (**S65.4**) furnished the product in 87%. Also, carbamate (**S65.7**) and thioamide (**S65.9**) did not provide product. Unsaturated amides (**S65.9** and **S65.10**) were found to form the carbinolamide, albeit in low yields (less than 20%). Moreover, products formation was traceable on TLC for secondary amides (**S65.11** and **S65.12**), but the isolation was difficult since they reformed the starting materials during column separation.

Scheme 65 Examples of Aldehyde-Amide Coupling

S65.1, 65% S65.2, 71% S65.5 S65.7 S65.9, 20% S65.11

S65.3, 79%, 1:1 S65.4, 87% S65.6 S65.8 S65.10, 20% S65.12
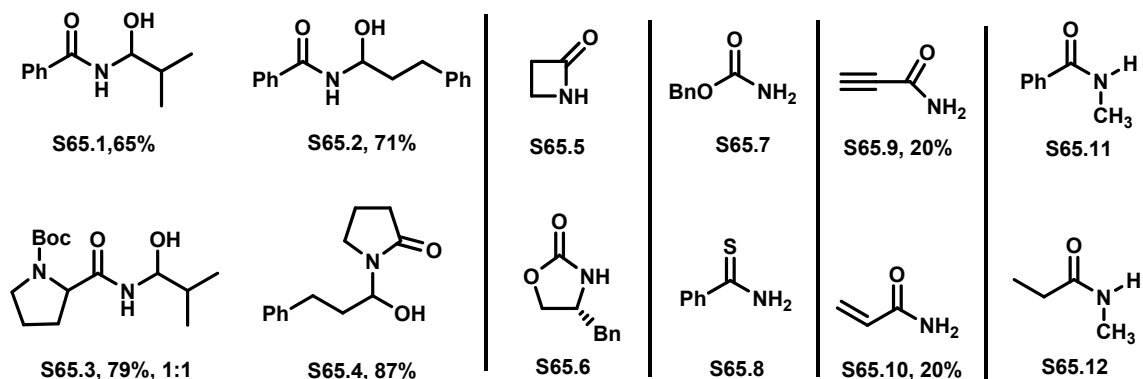
We also investigated stereoselective carbinolamide formation. For this matter, (-)-(Ipc)$_2$BCl was used for coupling of the amide (**T2.1**) and the aldehyde (**T2.2**).[6] The reaction yield of the coupling was 87% after isolation of product (**T2.3**). Chiral HPLC analysis indicated that the enantiomeric excess of the reaction was 18%. The product was column chromatographed a second time to determine if epimerization occurred during column purification, but the ee was the same as before. The reaction was carried out by using Cy$_2$BCl at low temperatures such as -78, -40 and -20°C. Unfortunately, no product formation was observed.

Much more research needs to be done to fully understand this reaction. In a reagent controlled aldol reactions, it is known that the selectivity results from the formation of a chair-like Zimmerman-Traxler transition state.[6] It is likely that this reaction follows the same mechanism.

IV. Complex Amide and Aldehyde Coupling: Analogs

We wanted to prepare analogs of psymberin to understand its mode of biological action. In addition, we wanted to investigate our new coupling reaction. The complex

amides (**S66.2** and **S66.3**) were prepared from the hydroxyl carboxylic acid (**S66.1**) in 2 steps.

Scheme 66 Preparation of Complex Amides
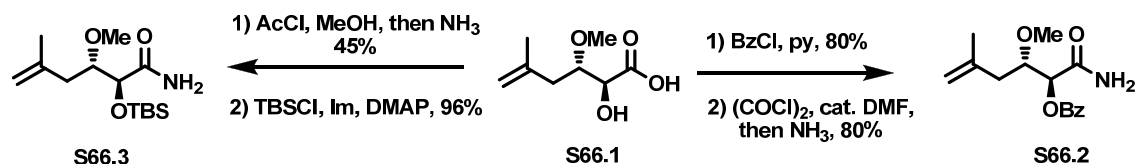
The preparation of complex aldehydes starts with the alcohol (**S43.2**), which was first protected as the acetate to afford **S67.1**. Then, deprotection of TBDPS followed by oxidation under Swern conditions gave rise to aldehyde **S67.2**. Similarly, reduction of the alkyne (**S67.1**), deprotection of TBDPS and then oxidation under Swern conditions yielded aldehyde **S67.4**. Interestingly, the coupling constant analysis indicated that the aldehyde group is positioned axially in **S67.2** and equatorially in **S67.4**, which may lead to differences in reactivity. In particular, the aldehyde (**S67.4**) would be useful as both it and **S63.2** contains a similar chain on the pyran ring.

For the preparation of aldehyde **S67.5**, the diol (**S42.1**) was first protected as the diaceate, deprotected with TBAF and then oxidized with DMP. The epoxide **S43.1** is deprotected with TBAF and oxidized to the aldehyde (**S67.6**). Both aldehydes were prone to β-elimination under oxidizing conditions. Therefore, they were used immidiatley after they were formed.

Scheme 67 Complex Aldehydes Preparation
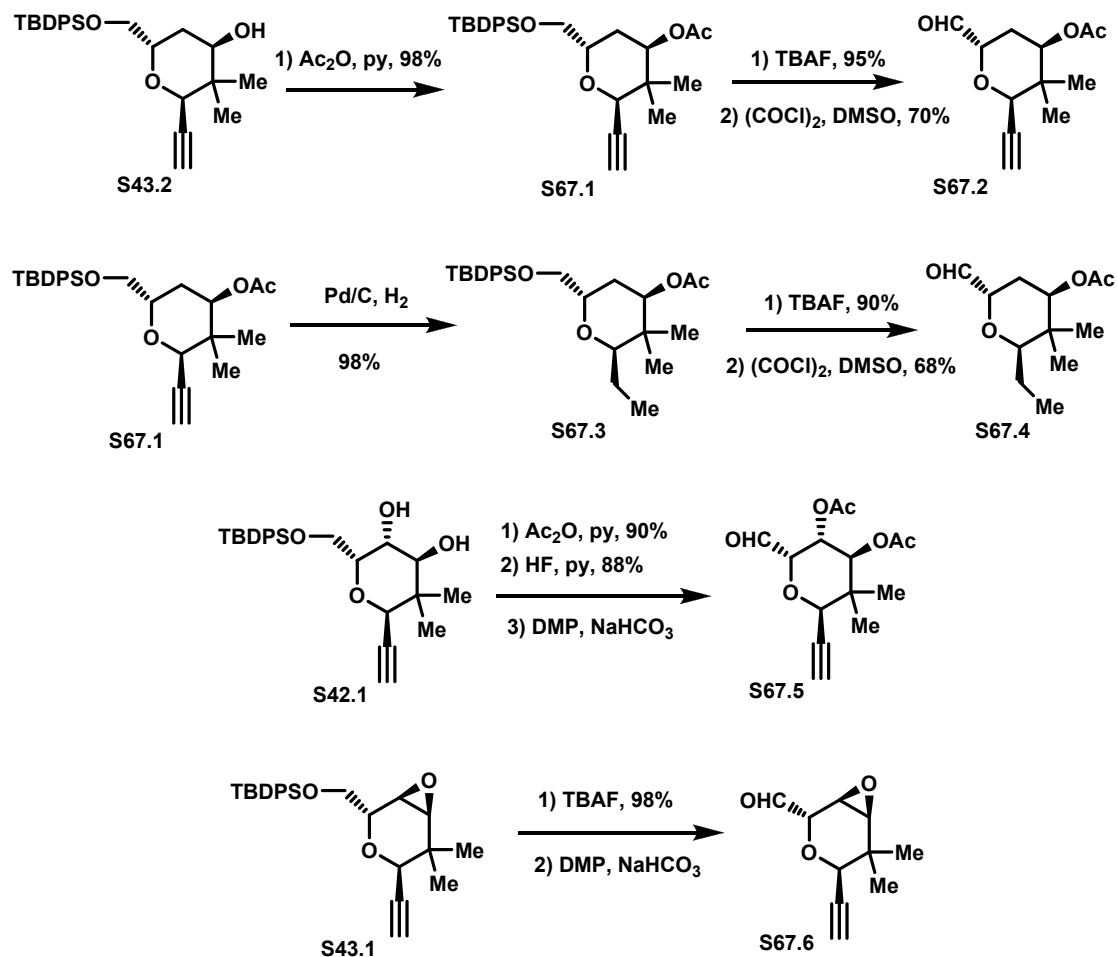
The findings from coupling of complex amides and aldehydes are given in Scheme 68. The union of the complex amide with cyclohexanecarbaldehyde efficiently took place under our conditions to give a mixture of separable carbinolamides (**S68.1**) in 66% yield (dr 1:1). Amides **S66.2** and **S66.3** coupled with the aldehyde **S67.2** with almost the same yield (**S68.2** and **S68.3**), indicating no effect from the protecting groups. Similarly no significant influence was observed from the pyran side chain (**S68.4**).

Scheme 68 Examples of Complex Amide and Aldehyde Coupling

(S68.1, 66%, dr 1:1)

(S68.2, 39%, dr 1:1)

(S68.3, 40%, dr 1:1)

(S68.4, 40%, dr; 2:1)
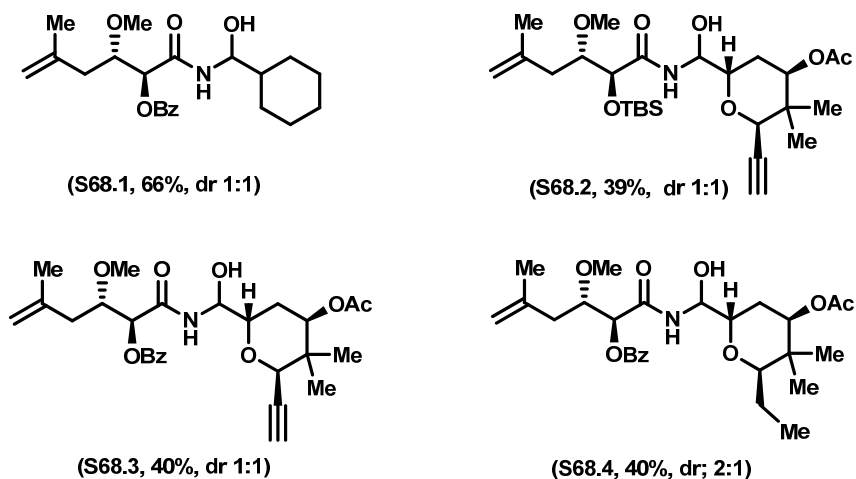
The pyran aldehydes (**S67.5** and **S67.6**) failed to give the corresponding carbinolamides under the coupling conditions. Instead of addition, β-elimination in the aldehydes took place to form compounds **S69.1** and **S69.2**. The Rawal group reported the same type of decomposition of similar aldehydes.[7] Compound **S69.1** was further treated with the imidate formed from the amide, but no product was observed.

**Scheme 69 Elimination Products**

S69.1

S69.2
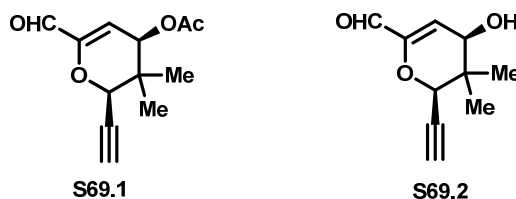
V. Stability of Carbinolamides

It is reported that the carbinolamides are inherently unstable functional groups and readily decompose to amide and aldehyde. However, the Porco and Bussolari groups

demonstrated that certain carbinolamides (**S70.1** and **S70.2**, Scheme 70) were unexpectedly stable, and even isolable by chromatography.[8] They proposed that the stability of these molecules resulted from extended hydrogen bonding, provided by a heteroatom positioned appropriately to act as a hydrogen bond acceptor. The Porco group showed experimentally that there was an interaction between the carbonyl group and the amide hydrogen, and they suggested that this is necessary for the stability.[10b] The presence of this interaction was supported by ^{1}H NMR since the peak exhibited by the hydrogen bonded NH appears at more downfield than that of the non-hydrogen bonded NH. Additionally, the stability of zampanolide (**S62.4**) was rationalized by invoking an intramolecular hydrogen-bond network, similar to **S70.2**.[9]

Scheme 70 Stable Carbinolamides
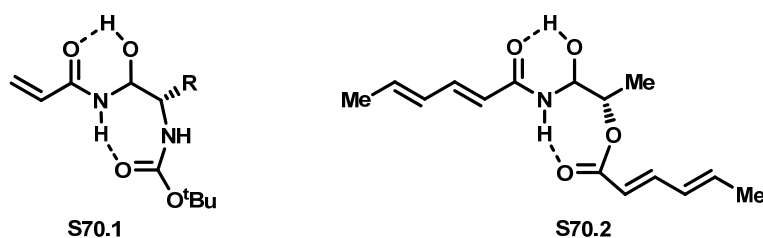
Although the hydrogen bond network is apparent in **S70.1** and **S70.2**, it has not been established as necessary. We believe this notion must be reevaluated based on the results we obtained during the application of our new condition for carbinolamide syntheses. We were able to isolate, characterize and manipulate the carbinolamides, which were devoid of hydrogen bonding interactions. Particularly, **S64.3**, **T2.3**, **S65.1**, **S65.2** and **S65.4** derived from simple aldehydes and amides exhibited unexpected stability under the reaction conditions, and accommodated aqueous work-up, flash column chromatography, routine handling, and storage. Moreover, the Smith group

demonstrated *O*-alkylation of the zamponilide carbinolamide did not any reduce the stability of the product.[11] Similarly, we methylated the carbinolamide **S64.3**, and not surprisingly isolated the stable **S71.1** (Scheme 71), which lacks of the stabilizing hydrogen bonding network. In light of these results, carbinolamides appear intrinsically stable, even in the absence of the intramolecular stabilizing interactions.

Scheme 71 Methylation of the Carbinolamide S64.3
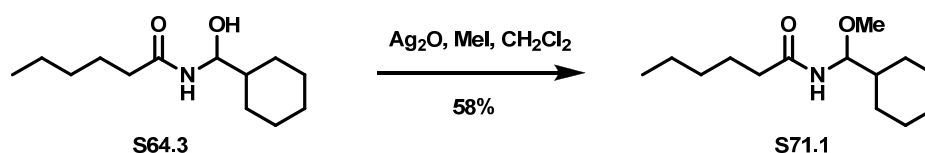
VI. Scope of the Boron Imidates

Normally, an amide could couple with an aldehyde either under harsh condition or when the aldehyde is electron poor. We demonstrated that the nucleophilicity of an amide increases when it is transformed to an imidate since the union with aldehydes took place smoothly under mild conditions. Likewise, we wanted to investigate the coupling of boron imidates with different electrophiles, which may lead to a variety of nitrogen containing functionality. For this purposes, the boron imidates were treated with such electrophiles as benzyl bromide, allyl tosylate, benzenesulfonyl chloride, benzoyl chloride, phenyl isocyanate, styrene as well as Micheal acceptors like cyclohexenone, 1-nitrocyclohexene and phenyl vinyl sulfone. Unfortunately, all were nonreactive to a boron imidate. Apparently, the nucleophilicity of a boron imdate too low to react with these electrophiles.

In order to increase of imidate nucleophilicity we tried borane reagents with

electron drawing groups like pinacol borane chloride and. But, the reactivity of the imidate was not improved. We turned our focus to the imidates of different metals. We tried $AlMe_2Cl$, $AgOTf$, $Sc(OTf)_3$, $SnCl_4$, $Zn(OTf)_2$, $MgBr_2 \cdot OEt_2$. Unfortunately, all of these attempts failed to increase the yield of the carbinolamide product.

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Chapter V

Metal Promoted Thioacid-Azide Coupling

I. Introduction

Our group investigated the reaction of thioacid-azide coupling, which gives an amide.[1] The amidation was shown to be effective in water and organic solvents. Moreover, the reaction was applied to a variety of thioacids and azides to obtain simple and complex amides, which were difficult to obtain by using conventional methods. [1a]

The reactivity of amidation depends on the electronic character of azides. The coupling of thioacids with electron poor azides approaches the ideal reaction profile, including short, room temperature reactions that give near quantitative yields, while electron rich azides require higher temperatures and longer reaction times. Some representative examples of both azides are given in Scheme 72.

Scheme 72 Examples of Electron Rich and Poor Azides
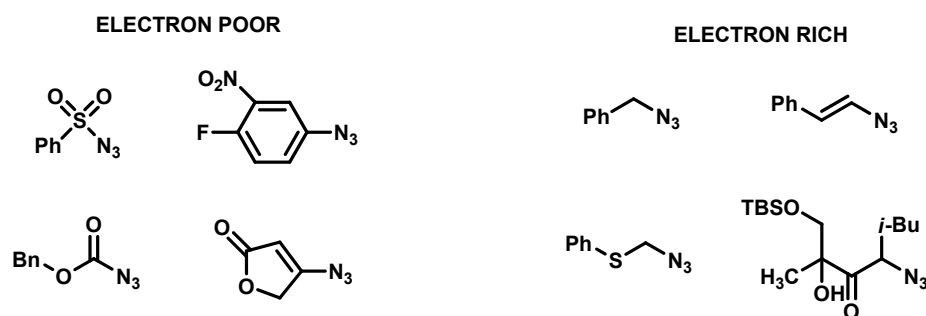
The experimental and computational data revealed two reaction pathways.[1d] For electron poor azides, it is a stepwise process, initially forming a nitrogen-sulfur bond, a

carbon-nitrogen bond forms in a separate step to give the thiatriazoline intermediate after protonation. The thiatriazoline intermediate decomposes to the amide product, nitrogen and sulfur via retro-[3+2] cycloaddition.

Scheme 73 Mechanism for Electron Withdrawing Azides
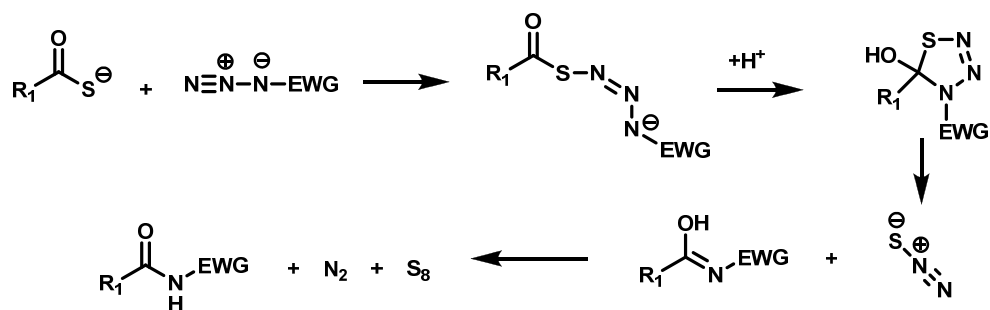
For electron rich substrates, it is a concerted process: carbon-nitrogen and sulfur-nitrogen bond formation takes place in a single step by anion-accelerated [3+2] cycloaddition. This give rise to the anion, after which protonation forms a thiatriazoline intermediate, which gives the amide product along with nitrogen and sulfur through the same mechanism.

Scheme 74 Mechanism for Electron Rich Azides
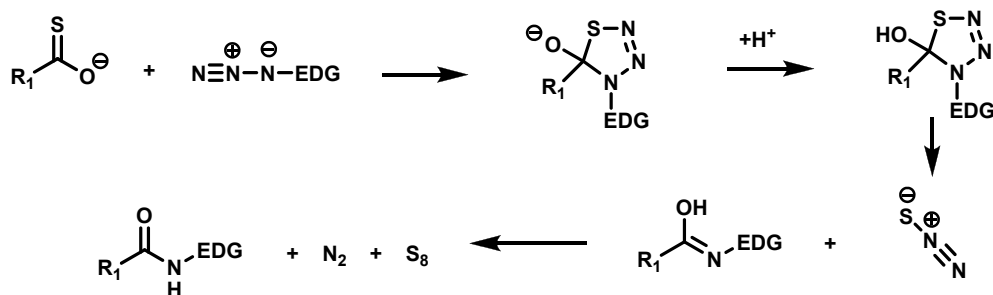
We hypothesized that a suitable metal would promote the reaction of electron rich azides with thioacids, as there is literature precedent that a metal can accelerate the [3+2]

cycloaddition.[2] Our goal was to facilitate the coupling of electron rich azides at room temperature in a conveniently short timeframe. We selected benzyl azide (**S75.2**) and thiobenzoic acid (**S75.1**) as our test substrates. Benzyl azide is a good model of electron rich primary azides and thiobenzoic acid is a good model of thioacids. Under the original conditions developed by our group, this reaction required 15 hours in refluxing chloroform to form the amide (**S75.3**) in 85% yield. Addition of trimethyl silyl triflate to thiobenzoic acid and triethyl amine or 2,6-lutidine effected complete conversion to trimethyl silyl thionobenzoate (**S75.4**). The silylation could be conveniently followed by ^{13}C-NMR. Thus, the 190 ppm signal apparent for thiobenzoic acid disappeared and a new signal at 213 ppm became evident within minutes. Subsequent treatment of thiobenzoic acid with benzyl azide failed to give rise to the corresponding amide (**S75.3**) product at room temperature with no measurable improvement at 60 °C (<4% after 20 hrs).

Scheme 75 Coupling of Thioacid and Thionoester with Azide
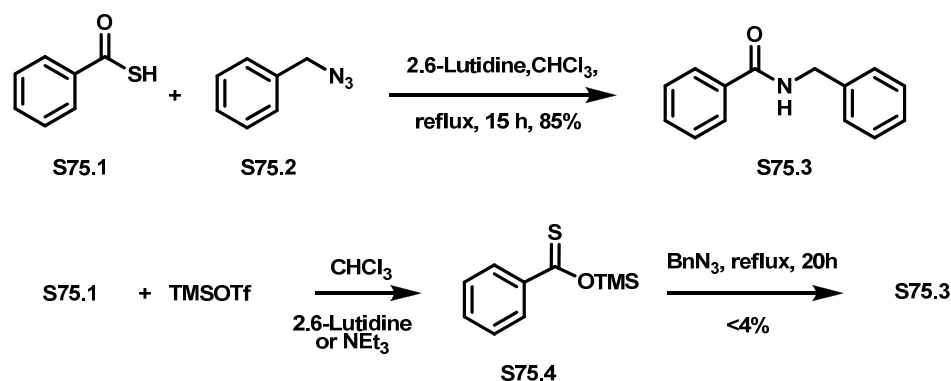
The Wong group found that the amidation reaction could be promoted in the presence of $RuCl_3$ and 2,6-Lutidine under mild conditions.[3] They showed the coupling of thioacetic acid with a limited set of electron rich azides to furnish acetamide products. We applied the same amidation conditions to our substrates; thiobenzoic acid and benzyl

azide. However, it provided the product in just 14% yield. Moreover, we examined RuCl$_3$ promoted coupling of thiobenzoic acid with **S75.1** and **S75.4** (thionoester) in the absence of base, but the yields were 27% and 14%, respectively. Therefore, we believe that RuCl$_3$ may not be the best choice for a metal promoter and also that these conditions are not general for thioacid and azide couplings. We thus screened Lewis acids in search of a promoter that would induce amidation within hours at room temperature.

During the initial investigations, the thionoester derived from thiobenzoic acid was used since the carbon sulfur double bond could function as a dipolarophile in [3+2] cycloaddition reaction. Our findings are tabulated in Table 3. We set out with the copper metals as they are known to facilitate the cycloaddition reaction of azides.[4] Unfortunately, they furnished the product in very low yields (entry 1 to 11), even in the presence of a ligand (entry 7 and 8). Similarly, most of the metals we tried did not provide the product (entry 12 to 24). In contrast, iron (II) chloride along with such bases as DMAP and 2,6 Lutidine gave **S75.3** in promising yields. However, the yields were not improved in the presence of different bases and with different stoichometric amounts of starting materials.

Table 3 Screening of Metal Promoter

Entry	Solvent	S75.4 (eq)	BnN₃ (eq)	Metal (1.0 eq)	Base	Yield (%)	Time (h)
1	CH₂Cl₂	1.0	1.0	CuSCN	no	8.3	20
2	CH₂Cl₂	1.0	1.0	CuCN	no	0	20
3	CH₃CN	1.0	0.5	CuI (0.5 eq)	no	10.2	20
4	CH₂Cl₂	1.0	1.0	CuBr	no	6.3	20
5	CH₂Cl₂	1.0	1.0	CuCl	no	9.5	20
6	CH₂Cl₂	1.0	1.0	CuOTf·Toluene	no	6.3	20
7	CH₂Cl₂	1.0	1.0	CuI	F₅-PhSH(1.0)	3.2	20
8	CH₂Cl₂	1.0	1.0	CuOTf	F₅-PhSH(1.0)	2.1	20
9	CH₂Cl₂	1.0	1.0	Cu(OTf)₂	no	0	20
10	CH₂Cl₂	1.0	1.0	Cu(di-Mebbik)₂·BF₄	no	10	20
11	CH₂Cl₂	1.0	1.0	Cu(CH₃CN)₄·PF₄	no	0	20
12	Et₂O	1.0	0.5	Zn(OTf)₂ (0.5 eq)	no	0	20
13	Et₂O	1.0	0.5	SnCl₂ (0.5 eq)	no	0	20
14	CH₂Cl₂	1.0	1.0	AgOTf	no	0	20
16	CH₂Cl₂	1.0	1.0	Ag(CH₃CN)₄·BF₄	no	0	20
17	CH₂Cl₂	1.0	1.0	Pd(OAc)₂	no	0	20
18	CH₂Cl₂	1.0	1.0	Pd(OAc)₂	Pyridine(1.0)	0	20
19	CH₂Cl₂	1.0	1.0	AlCl₃	no	0	20
20	CH₂Cl₂	1.0	1.0	BF₃OEt₂	no	0	20
21	CH₂Cl₂	1.0	1.0	NiCl₂	no	0	20
22	CH₂Cl₂	1.0	1.0	Cp₂Fe	no	0	20
23	CH₂Cl₂	1.0	1.0	Fe(acac)₃	no	0	20
24	CH₂Cl₂	1.0	1.0	Fe(acac)₃	Pyridine(1.0)	0	20
25	CH₂Cl₂	1.0	1.0	FeCl₂(1.0)	DMAP(1.0)	32	6
26	CH₂Cl₂	1.0	1.0	FeCl₂(1.0)	Lutidine(1.0)	41	6

The findings from the iron (III) chloride are given in Table 4. We obtained 35%
yield with 0.5 equivalent of the metal (entry 1), which was improved to 52% in the
presence of DMAP (0.5 eq) after screening many different bases (entry 2). This was the
highest yield up to this point. We proceeded to optimize the reaction by changing the
amount of the substrates. Doubling the amount of either the thionoester (**S75.4**) or the

benzyl azide did not affect the yield (entry 3 and 4). Using 1.0 equivalent of both metal and base increased the yield slightly (entry 4). The largest increase in yield occurred when using 2.0 equivalents of both $FeCl_3$ and DMAP (entry 6). Under these conditions, doubling the amount of the azide afforded the highest yield (82%) in the shortest time (entry 7). Methylene chloride was used as solvent for all presented data.

Table 4 Results from Iron (III) Chloride and Thionoester Coupling

Entry	S75.4 (eq)	BnN₃	Metal (eq)	Base (eq)	Yield (%)	Time (h)
1	1.0	1.0	FeCl₃(0.5)	no	35	7
2	1.0	1.0	FeCl₃(0.5)	DMAP (0.5)	52	7
3	2.0	1.0	FeCl₃(0.5)	DMAP (0.5)	50	7
4	1.0	2.0	FeCl₃(0.5)	DMAP (0.5)	42	7
5	1.0	1.0	FeCl₃(1.0)	DMAP (1.0)	56	6
6	1.0	1.0	FeCl₃(2.0)	DMAP (2.0)	71	3
7	1.0	2.0	FeCl₃(2.0)	DMAP (2.0)	82	3

All the attempts to further improve the yield of the optimized condition (Table 4 entry 7) such as using other solvents (THF, Et_2O, CH_3CN), changing the order of addition of substrates, and altering concentration were not satisfactory. In addition, longer reaction times did not provide higher yields. The best time of the reaction was found to be 3 h since the yields were 48% and 62% after 1h and 2h, respectively.

We also applied these conditions (Table 4, entry 7) to thiobenzoic acid in order to see the effect of thionoester on the reaction. Virtually the same yield was obtained when 2.0 equivalents of both $FeCl_3$ and DMAP were used for the coupling of the azide with thiobenzoic acid (Table 5, entry 1). The increased amount of metal and azide did not influence the yield significantly (entry 2 and 3). Interestingly, it was found that DMAP plays a critical role in the amidation, since almost no product formation was observed in
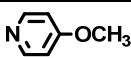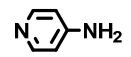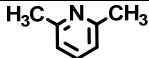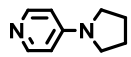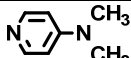
its absence. Therefore, we turned our attention to other bases to understand the role of a base in the coupling.

Table 5 Results from Iron (III) Chloride and Thioacid Coupling

Entry	S75.1 (eq)	BnN$_3$ (eq)	FeCl$_3$ (eq)	DMAP (eq)	Yield (%)	Time (h)
1	1.0	2.0	2.0	2.0	78	3
2	1.0	2.0	3.0	3.0	77	3
3	1.0	2.0	4.0	4.0	74	3
4	1.0	2.0	2.0	no	0	18
5	1.0	1.0	0.5	no	9	22

We focused on the pyridines bearing electron donating groups since they resemble DMAP in terms of electronic structure. The results are given in Table 6. The yields for each thiobenzoic acid (**S75.1**) and thionoester (**S75.4**) were obtained by using 2.0 equivalents of both FeCl$_3$ and base in 3 h. Interestingly, the methoxy (entry 1), amino (entry 2) and dimethyl (entry 3) substituents provided very low yields for the coupling of both **S75.1** and **S75.4**. However, the pyrrolidine group on pyridine (entry 4) gave rise to the amide in almost the same yield as DMAP.

Table 6 Results from Using Different Bases

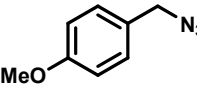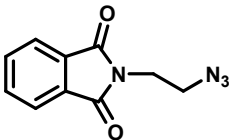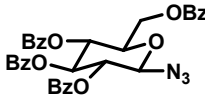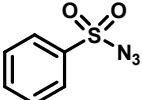| Entry	Bases	S75.1 (% yield)	S75.4 (% yield)
1	N⟨⟩-OCH$_3$	26	9
2	N⟨⟩-NH$_2$	27	trace
3	H$_3$C-N-CH$_3$	trace	trace
4	N⟨⟩-N⟨⟩	72	72
5	N⟨⟩-N(CH$_3$)$_2$	78	82
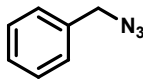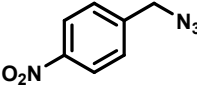
We also tested different iron halides under the reoptimized conditions (Scheme 76). For this purpose, FeCl$_2$, FeBr$_2$, and FeF$_3$ were applied to the model system in presence of DMAP. The iron (III) fluoride and iron (II) bromide furnished the product in low yields, while iron (II) chloride gave a modest yield (60%).

**Scheme 76 Results for Different Iron Halides**
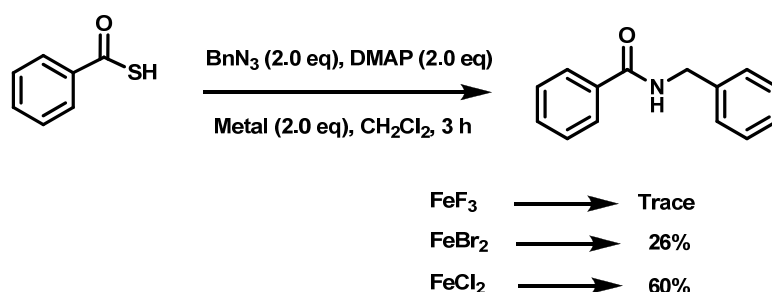
Iron (III) chloride and DMAP appear to be a good system for the amidation. Therefore, the optimized condition was applied to a variety of thioacids and azides. For this study, the azides were prepared form the corresponding halides (see table 7 and Scheme 77) and thiobenzoic acid and thioacetic acid were applied as the other coupling partner. The results for some azides are given in table 7. The coupling of the benzyl azide with thioacetic acid furnished the corresponding amide in 62% yield (entry 1). Likewise, substituted benzyl azides formed the products in moderate yields (entry 2 and 3). The imide substituted primary azide also provided the amides (entry 4). The thionoester (**S75.4**) gave rise to the amides with the electron rich and poor azides (entry 5 and 6), albeit in low yields.

Table 7 Results from Thioacid-Azide Coupling

Entry	R'-N$_3$	R=-Ph	R=-CH$_3$
1		81%	62%
2		66%	73%
3		67%	67%
4		80%	60%
		S75.4	
5		13%	-
6		25%	-

We prepared the azides shown in Scheme 77, since the corresponding amines could not easily lead to amides by conventional methods. Unfortunately, the optimized condition resulted in decomposition of azides **S77.1**, **S77.2**, **S77.3**, and **S77.4**. **S77.5** was not reactive even after longer reaction times. The azides **S77.6**, **S77.7**, and **S77.8** coupled to **S75.4**, but the yields were very low (<5%).

Scheme 77 The Azides Failed to Couple

S77.1   S77.2   S77.5   S77.6   S77.8   S77.3   S77.4   S77.7
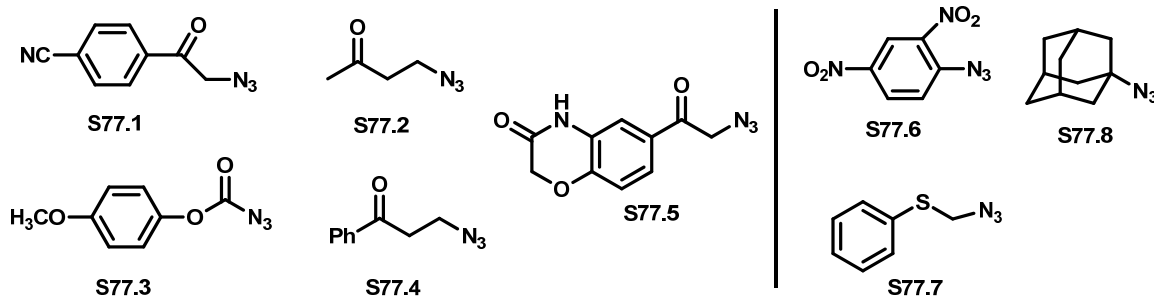
II. Discussions for the Mechanism of Thioacid-Azide Coupling

Although our findings were not generally applicable, we were still interested in the likely mechanism of the coupling reaction which gives a good yield for certain substrates. We carried out some control reactions. Benzyl amine was not observed. Although reduction of benzyl azide is possible, it is not observed when the benzyl azide is exposed to iron (III) chloride and DMAP (Scheme 78). If benzyl amine is formed, it must be rapidly converted into another substance.

We checked the stability of benzyl azide and thiobenzoic acid under the reaction conditions (Scheme 78). The benzyl azide decomposed upon treatment with iron (III) chloride, yet it survived in presence of $FeCl_3$ and DMAP. We also observed the same pattern for the azides in Scheme 76. Similarly, the thiobenzoic acid was observed to form the dimer (**S78.1**) slowly over time when treated with either $FeCl_3$ or $FeCl_3$ and DMAP.

**Scheme 78 Control Reactions for Azide and Thioacid**
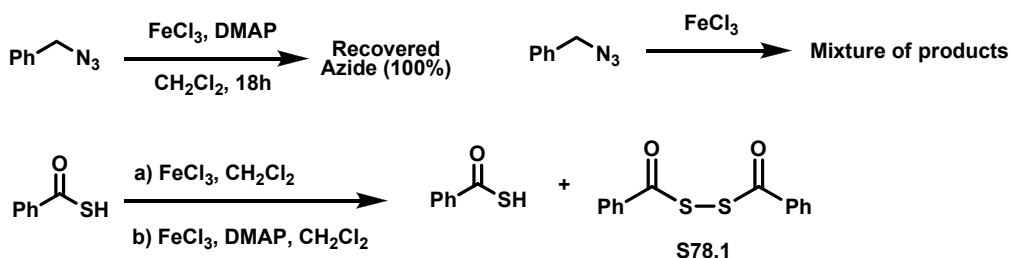
During the optimization studies, we observed by-product formation along with the major amide product. Interestingly, when the yield of the amide (**S75.3**) jumps from 35% (Table 4, entry 1) to 82% (Table 4, entry 7), the side product formation was significantly diminished. The yields for **S79.1**, **S79.2**, and **S79.3** were less then 5% when the highest yield for **S75.3** was obtained. The structure of these side products was identified in order to investigate their possible relevance to the mechanism of the coupling (Scheme 79). **S79.1** and **S79.2** were crystallized and structural proof was accomplished by X-ray crystallography. Sulfur (**S79.5**) was identified by melting point measurement, while the usual spectroscopic methods used for **S79.3**. In addition to these side products, dimer formation (**S78.1**) was detected for all data in Table 4 and 5.

Scheme 79 Side and by-Products from Amidation
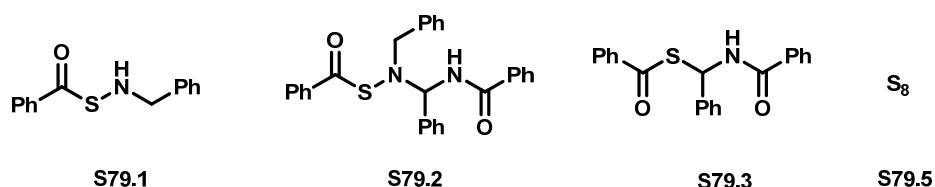
We checked the importance of the dimer (**S78.1**), since it forms immediately upon mixing the substrates (Scheme 78). **S78.1** and the benzyl azide were exposed to the metal and base. No amide formation was detected after 18 h (Scheme 80).

Scheme 80 Dimer and Benzyl Azide
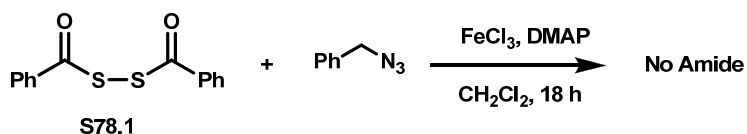
We noted that both **S79.1** and amide (**S75.3**) form almost simultaneously under

the amidation reaction conditions. Therefore, we next focused on **S79.1**. A literature search revealed interesting information about molecules of this sort (Scheme 81). The Alliger group obtained amide (**S81.4**, X=O) or thioamide (**S81.4**, X=S) and sulfur from oxidative coupling of thioacid (X=O) or dithioacid (X=S) salts with cyclohexylamine (**S81.2**).[5] They postulated that the reaction proceeded through the unstable *N*-cyclohexyl-*S*-aroylhydrosulfamine (**S81.3**). Moreover, the Bohme group reported amide (**S81.7**) and sulfur formation from the reaction of **S81.5** with diethylamine, which presumably resulted from immediate decomposition of unstable intermediate **S81.6**.[6] They also obtained similar results for piperidine and aniline. The Raasch group showed that stable *S*-aroylhydrosulfamines (**S81.10**) could be prepared by mixing sodium salts of both thioacids (**S81.8**) and hydroxylamine-*O*-sulfonate (**S81.9**).[7] Their conditions corroborate the reported instability of both *N*-alkyl-*S*-aroylhydrosulfamines (**S81.3**) and *S*-acylhydrosulfamines (**S81.6**) (see intermediates **S81.13** and **S81.16**). They speculated that the decomposition of *S*-aroylhydrosulfamines to an amide and sulfur could involve a bimolecular process, forming a cyclic intermediate or transition state (**S82.1**). The more basic *N*-alkyl derivatives could readily lead to similar transition states, causing the observed instability of *N*-alkyl-*S*-hydrosulfanamines (**S81.3**, **S81.6**, **and S81.16**). Furthermore, they rationalized the stability of *S*-aroylhydrosulfamines (**S81.8**), in contrast to their aliphatic analogs (**S81.5**, **S81.15**), due to the additional resonance conjugation (**S82.2**).

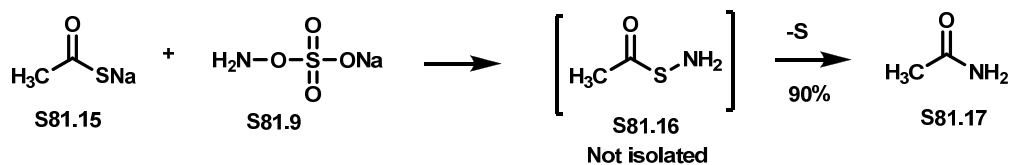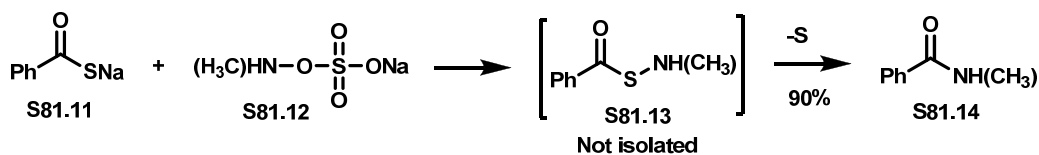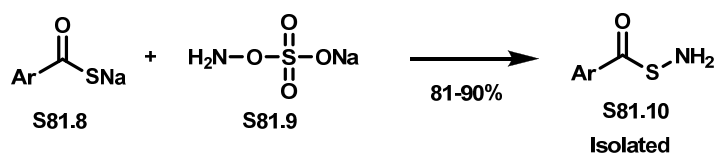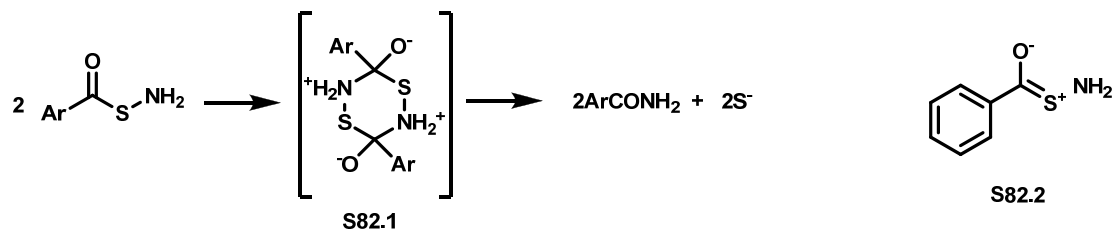## Scheme 81 Stable and Unstable Hydrosulfamines

Alliger, 1949
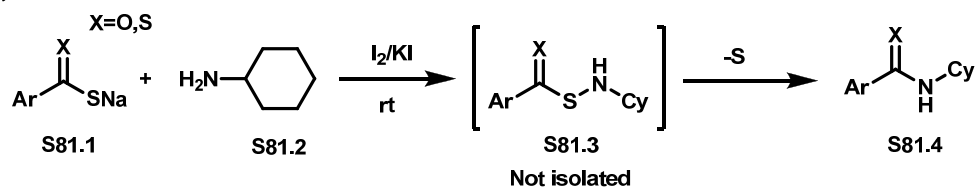
**Bohme, 1952**
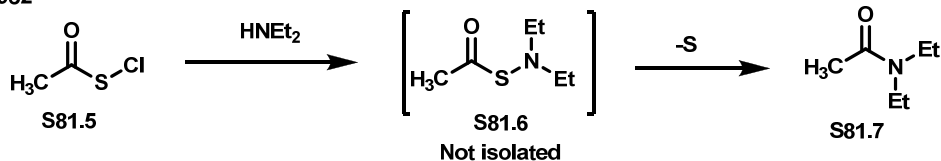
Raasch, 1972

Scheme 82 The Mechanism for Decomposition S-Aroylhydrosulfamines

Much of the work presented in Scheme 81 and 82 is speculative. Our work may

serve to clarify some of these notions. The side product **S79.1** is very closely related to the putatively unstable *N*-alkyl-*S*-aroylhydrosulfamines, but it was isolated without decomposition. Control reactions done on **S79.1** reveal other significant information. Exposure of **S79.1** to the metal and base gave no amide, while treatment with the thiobenzoic acid furnished quantitatively the amide product in five minutes. Sulfur formation was also observed as reported. Moreover, the rapid formation of the same amide and sulfur was detected on treatment with thioacetic acid. In addition, the **S79.1** was unexpectedly found to be stable to the triflouroacetic acid, in contrast to the thioacid derivatives.

Scheme 83 Control Reactions on Side Product S79.1
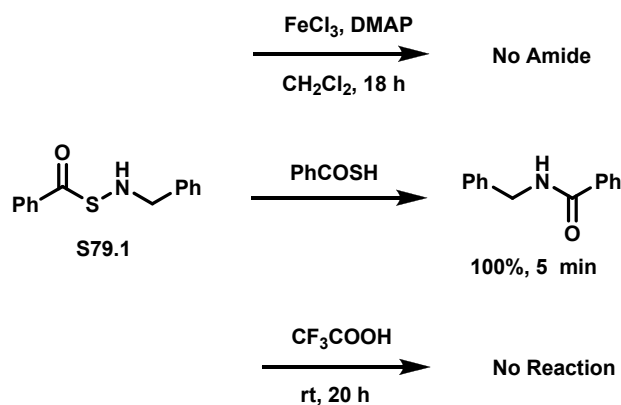
The cyclic intermediate (**S82.1**) was proposed by Raasch. However, performing a crossover experiment between two stable S-aroylhydrosulfamines, which decompose at about same rates would distinguish unimolecular and bimolecular process. As indicated in Scheme 84, a unimolecular process could also be speculated for decomposition of similar molecules. Both thiaocid and trifluoroacetic acid could protonate two basic sites on **S79.1**, which could lead to either **S84.1** or **S84.2**. In principle, both trifluoroacetic and

thiobenzoic acid could lead to **S84.3**. The opening of **S84.4** likely would not be facile for trifluoroacetic acid due to the low nucleophilicity of the trifluoroaceate anion. A thiocarboxylate could give **S84.4**, which could give rise to the amide and **S84.5**. **S84.5** decomposes to the observed the dimer (**S78.1**) and sulfur products. However, this mechanism is unnecessarily complex. Another alternative is that **S84.2** is attacked by thiobenzoic acid to give **S78.1** directly. This species is a very potent acylating agent, as is **S84.5**. Amines react almost instantaneously with such thioanhydrides. This accounts for very rapid conversion of **S79.1** to amide (Scheme 83), avoids unlikely events such as **S84.1→S84.3**, and most of the speculative notions of Alliger, Bohme and Raasch. Although we did not observe benzyl amine in our reaction, it would be expected to form only in trace quantity before rapidly reacting with **S78.1** to give the amide product.

Scheme 84 The Proposed Mechanism of Amide Formation from S79.1
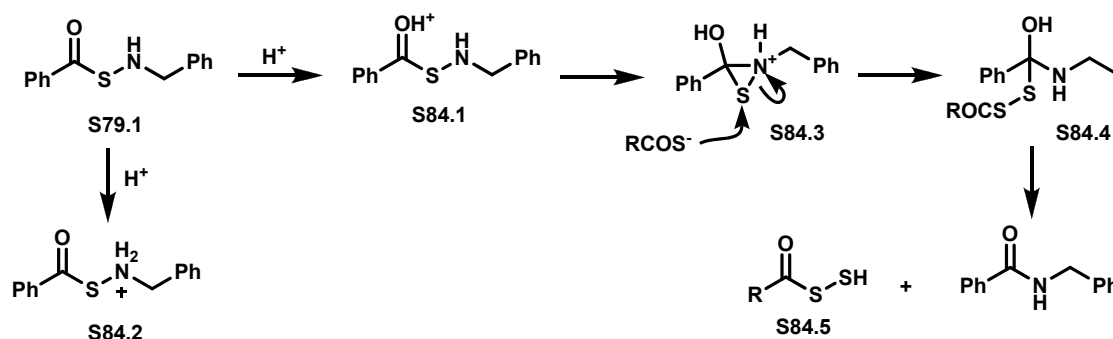
Although iron (III) chemistry is complex, and ascertaining the precise mechanism of amidation is beyond the scope of these studies, several observations are noteworthy. The iron (III) chloride and DMAP combination could have a substantial effect on the formation of **S79.1**, since all the metals in Table 3 and all bases in Table 6, except for entry 4, failed to couple. The promoter and base could give rise to complex structures

S85.1 and **S85.2**. An iron complex could coordinate to the internal or to the terminal azide nitrogen and form, for example, **S85.3**, either of which could facilitate attack of thiobenzoate. Sulfur-nitrogen bond formation could take place simultaneously with loss of nitrogen, which would lead to formation of the **S79.1**.

Scheme 85 The Mechanism for the Formation of S79.1
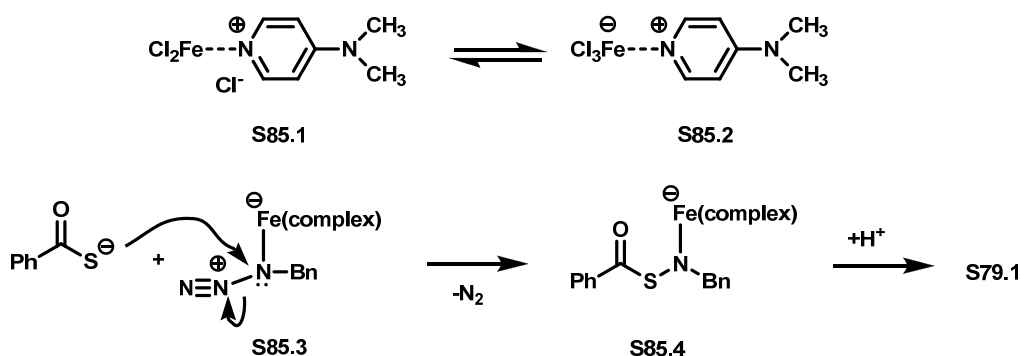
We were also curious about side products **S79.2** and **S79.3** since they diminish as formation of the major amide product increases. Based on their structure, it is reasonable to speculate that they are formed from a different pathway than **S79.1**, which could likely involve the highly reactive intermediate **S86.3** (Scheme 86). Nucleophiles readily add to the similar electrophiles.[8] In this case the nucleophiles are the **S79.1** and the thiobenzoate anion. A plausible mechanism for formation of **S86.3** is by rearrangement of the azide. The same type of intermediate as **S86.2** was also invoked by the Kerr group earlier.[9] Nucleophilic addition of **S79.1** to or thiobenzoic acid **S86.3** would provide **S79.2** and **S79.3**.

Scheme 86 The Formation of the Intermediate S86.3
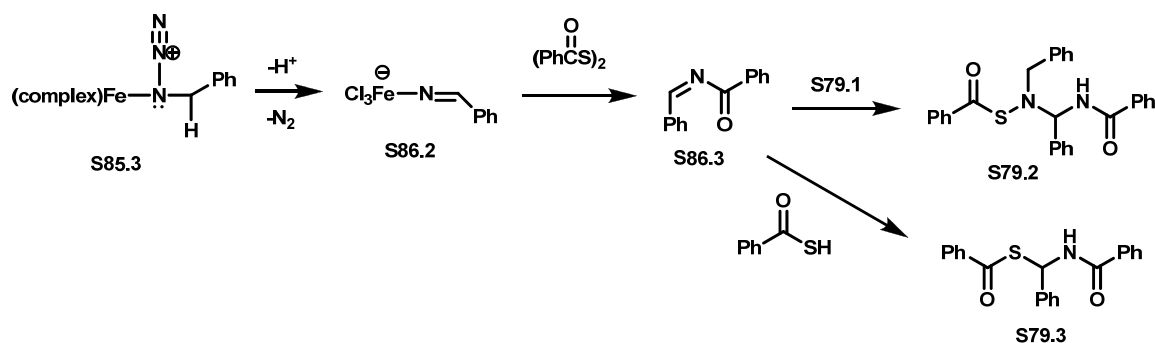
In contrast to the reported instability, the metal promoted amidation revealed a stable intermediate (**S79.1** and **S79.2**). Although amide product formation was unambiguously established from **S79.1** upon treatment with thiobenzoic acid, it has not been established as the major path by which the amide product is formed. Indeed, it is speculative to indicate that similar mechanism could take place for the thioacid-azide coupling, as opposed to the reported mechanisms.[1] Nevertheless, this mechanism could be considered as an alternative pathway for amide formation.

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5) Alliger, G.; Smith, G. E. P. Jr.; Carr, E. L.; Stevens, H. P. *J. Org. Chem*. **1949**, *42,* 7296.

6) Bohme, H.; Clement, M. *Justus Liebegs Ann. Chem*. **1952**, *61*, 576.

7) Raasch, M. S. *J. Org. Chem*. **1972**, *24*, 3820.

8) Gizecki, P.; Dhal, R.; Poulard, C.; Gosselin, P.; Dujardin, G. *J. Org. Chem*. **2003**, 68, 4338-4344.

9) Barrett, I. C.; Langille, J. D.; Kerr, M. A. *J. Org. Chem*. **2000**, *65*, 6268-6269.

EXPERIMENTAL

General: Starting materials, reagents and solvents were purchased from commercial suppliers (Aldrich, Fischer, Advanced ChemTech) and used without further purification unless otherwise stated. All reactions were conducted in oven-dried (135 ^{o}C) glassware under an inert atmosphere of argon. The progress of reactions was monitored by silica gel thin layer chromatography (tlc) plates (mesh size 60Å with fluorescent indicator, Sigma-Aldrich), visualized under UV and charred using cerium or anisaldehyde stain. Products were purified by flash column chromatography (FCC) on 120-400 mesh silica gel (Fisher). Infrared (FTIR) spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on either a Varian-300 instrument (300 MHz) or a Varian-400 instrument (400 MHz) unless otherwise stated. Chemical shifts are reported in ppm relative to residual CHCl$_3$ signal. Data is reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), and coupling constants (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on either a Varian-300 instrument (75 MHz) or a Varian-400 instrument (100 MHz) unless otherwise stated. Optical rotations were recorded at 25 ^{o}C using the sodium D line (589 nm), on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

CHAPTER 1
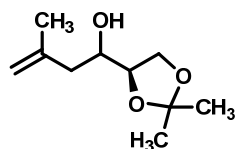
anti (S1.3): αOH
syn (S1.4): βOH

To a solution of methallylmagnesium chloride in THF (0.0375 mole, 0.8 M) at -78 °C was added slowly a solution of protected glyceraldeyhde **S1.1** (0.025 mole, 3.25g) in THF (62.5 ml) down the inside of the flask. The reaction mixture was allowed to warm to room temperature, and stirred for additional 4 h. The mixture was then cooled to -78 °C, quenched with saturated NH_4Cl solution, extracted with Et_2O, and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by FCC using hexane:acetone (15:1) as eluent to give **5** and **6** as a colorless oil (3.4g, 74%). The ratio anti:syn alcohol was 4:3, as determined by ^{1}H-NMR. R_F 0.22 (15:1-hexane:acetone); IR ν_{max}(neat)/cm^{-1} 3475, 3057, 2986, 1648, 1067; δ_H (400 MHz, CDCl$_3$) 4.86-4.85 (2H, brs), 4.79-4.78 (2H, brs), 4.04-3.65 (8H, m), 2.29-2.05 (6H, m), 1.75 (6H, brs) 1.42-1.40 (6H, s), 1.35-1.34 (6H, s); δ_C (100 MHz, CDCl$_3$) 141.9 (s), 141.7 (s) , 113.57 (t), 113.50 (t), 109.3 (s), 109.0 (s), 78.6 (d) , 78.3 (d), 69.8 (d), 68.8 (d), 65.9 (t), 65.3 (t), 42.0 (q), 41.7 (q), 26.5 (two signals, q), 25.27 (q), 25.25 (q), 22.4 (t), 22.3 (t); *m/z* (ESIMS) found: 187 (M+1)$^+$; calcd: 187.
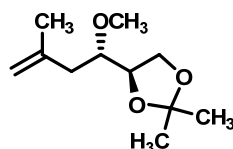

Anti (S2.1)
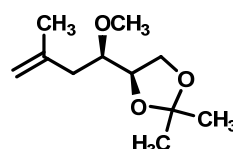
Syn (S2.2)

The mixture of **S1.3** and **S1.4** (1.25g, 6.7mmol) was dissolved in THF (12 ml), and cooled to 0 °C. NaH (484 mg, 12.1 mmol, 60% dispersion in mineral oil) was added and the mixture was stirred for 15 min. To this CH_3I (1.90 g, 0.84 ml, 13.4 mmol) was added and the mixture was allowed to warm to room temperature and stirred over 12 h. The reaction mixture was quenched with sat. NH_4Cl, extracted with Et_2O and dried over Na_2SO_4. After removing the solvent *in vacuo*, the residue was purified by FCC using with hexane:acetone (70:1) as eluent to give 657 mg (49%) *anti* isomer **S2.1** and 523 mg (39%) *syn* isomer **S2.2** as colorless oils (total yield 93%). **Anti isomer S2.1**; R_F 0.44 (40:1-hexane:acetone); $[\alpha]^{22}_D$ +19.0 (c 4.52, $CHCl_3$); IR v_{max}(neat)/cm^{-1} 3076, 2985, 1647, 1104; δ_H (400 MHz, $CDCl_3$) 4.82-4.79 (1H, brs), 4.789-4.786 (1H, brs) , 4.08-4.00 (2H, m), 3.90-3.87 (1H, m), 3.47-3.44 (1H, m), 3.44 (3H, s), 2.30-2.15 (2H, m), 1.79 (3H, s), 1.42 (3H,s), 1.34 (3H, s); δ_C (100 MHz, $CDCl_3$) 142.2 (s), 112.9 (t), 108.9 (s), 79.7 (q), 77.4 (d), 65.7 (t), 58.5 (d), 39.3 (q), 26.3 (q), 25.2 (q), 22.7 (t); *m/z* (ESIMS) found: 201 (M+1)$^+$; calcd: 201.

Syn isomer S2.2; R_F 0.27 (40:1-hexane:acetone); $[\alpha]^{22}_D$ +9.7 (c 0.72, $CHCl_3$); IR v_{max}(neat)/cm^{-1} 3076, 2985, 1647, 1107; δ_H (400 MHz, $CDCl_3$) 4.82 (1H, brs), 4.78 (1H, brs), 4.19-4.14 (1H, m), 3.992 (1H, dd, J=6.8, 8.4), 3.70-3.66 (1H, m), 3.46 (3H, m), 3.41-3.36 (1H, m), 2.73 (2H, d, J=5.6), 1.79 (3H, s), 1.43 (3H, s), 1.36 (3H, s); δ_C (100 MHz, $CDCl_3$) 142.1 (s), 112.9 (t), 109.1 (s), 80.3 (q), 77.6 (d), 65.7 (t), 58.3 (d), 38.5 (q), 26.4 (q), 25.2 (q), 22.8 (t); *m/z* (ESIMS) found: 201 (M+1)$^+$; calcd: 201.

CH₃ OCH₃ ... S2.1 → CH₃ OCH₃ ... OH, OTBS ... S2.3
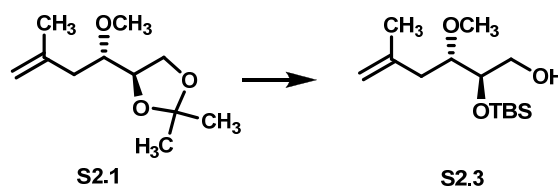
The protected diol **S2.1** (627 mg, 3.1 mmol) was stirred in 6.5 ml of AcOH:H_2O mixture (4:1) for 20 h at room temperature. The reaction mixture was concentrated and purified by FCC using with hexane:acetone (5:1) as eluent to afford 461 mg (93%) diol as a colorless oil. R_F 0.10 (5:1-hexane:acetone); $[\alpha]^{22}_D$ +22.5 (c 1.42, CHCl₃); IR v_{max}(neat)/cm^{-1} 3395, 3086, 2935, 1649, 1101; δ_H (400 MHz, CDCl₃) 4.83 (1H, brs), 4.79 (1H, brs), 3.57-3.68 (3H, m), 3.52-3.48 (1H, m), 3.41 (3H, s), 3.00 (2H, brs), 2.364-2.328 (1H, m), 2.203-2.206 (1H, m), 1.78 (3H, s); δ_C (100 MHz, CDCl₃) 142.2 (s), 113.2 (t), 81.7 (q), 72.4 (d), 63.1 (t), 58.3 (d), 38.7 (q), 22.7 (t); *m/z* (ESIMS) found: 183 (M+23)⁺; calcd: 183.

To a solution of diol (205 mg, 1.28 mmol) in DMF (4 ml) was added imidazole (262 mg, 3.84 mmol) and TBSCl (503 mg, 3.33 mmol). The reaction mixture was stirred overnight, and then diluted with H_2O. The solution was extracted with Et_2O, dried over Na_2SO_4. After removing the solvent in vacuo, the residue was purified by FCC using hexane:acetone (40:1) as eluent to give 437 mg (88%) bis-[TBS] ether as a colorless oil. R_F 0.93 (40:1-hexane:acetone); $[\alpha]^{22}_D$ -8.7 (c 6.06, CHCl₃); IR v_{max}(neat)/cm^{-1} 3076, 2955, 1650, 1183, 1082; δ_H (300 MHz, CDCl₃) 4.79 (1H, brs), 4.80 (1H, brs), 4.77 (1H, brs), 3.82-3.77 (1H, m), 3.56 (2H, d, J=5.7 Hz), 3.47-3.42 (1H, m), 3.38 (3H, s), 2.25 (2H, d, J=6.9 Hz), 1.77 (3H, s), 0.90 (9H, s), 0.89 (9H, s), 0.06 (6H, s), 0.07 (6H, s); δ_C (75 MHz, CDCl₃) 143.6 (s) , 112.1 (t), 81.3 (q), 74.5 (d), 64.6 (t), 58.3 (d), 38.7 (q), 26.3

(q), 26.2 (q), 23.1 (t), 18.6 (s), 18.5 (s), -4.1 (q), -4.3 (q), -4.9 (q), -5.0 (q); *m/z* (ESIMS) found: 411 (M+23)$^+$; calcd: 411.

To a solution of bis-[TBS] ether (440 mg, 1.13 mmol) in THF (3.6 ml) in a plastic vial was added pyridine (0.60 ml) and HF-pyridine (0.1 ml of a 65-70% solution of HF in pyridine). The mixture was stirred 22 h, then diluted with Et$_2$O and washed with 0.5 M HCl solution. The aqueous layer was re-extracted with Et$_2$O. The combined organic layers were washed with saturated CuSO$_4$.H$_2$O and dried over NaSO$_4$. After removing the solvent, the residue was purified by FCC using hexane:acetone (20:1) as eluent to give 226 mg (73%) mono-alcohol **S2.3** as a colorless oil. R$_F$ 0.24 (20:1-hexane:acetone); [α]^{22}$_D$ +5.4 (c 2.98, CHCl$_3$); IR v_{max}(neat)/cm^{-1} 3456, 3076, 2930, 1649, 1112; δ$_H$ (400 MHz, CDCl$_3$) 4.81 (1H, brs), 4.79 (1H, brs) 3.73-3.60 (3H, m), 3.43 (3H, s), 3.41-3.39 (1H, m), 2.29-2.15 (3H, m), 0.9 (9H, s), 0.09 (6H, s); δ$_C$ (100 MHz, CDCl$_3$) 142.9 (s), 112.9 (t), 82.1 (q), 74.5 (d), 64.1 (t), 59.3 (d), 40.4 (q), 26.1 (q), 23.1 (t), 18.4 (s), -4.0 (q), -4.1 (q); *m/z* (ESIMS) found: 275 (M+1)$^+$; calcd: 275.
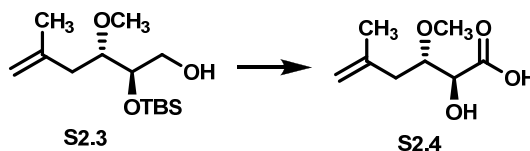
A solution of oxalyl chloride (0.19 ml, 2.18 mmol) in CH$_2$Cl$_2$ (7 ml) was cooled down to -78 °C. DMSO (0.340 ml, 4.79 mmol) was syringed in one portion and stirred for 15 min. Then the alcohol **S2.3** (396 mg, 1.45 mmol) dissolved in CH$_2$Cl$_2$ (7 ml) was added slowly. After 30 min Et$_3$N (1,026 ml, 7.4 mmol) was added after which the cooling bath was replaced by an ice bath. Stirring was continued for 20 min, and then diluted with

CH_2Cl_2 and H_2O. Extraction with CH_2Cl_2 and drying over Na_2SO_4 furnished 386 mg (98%) aldehyde. $[\alpha]^{22}_D$ -27.6 (c 0.98, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3069, 2955, 2858, 1733, 1647, 1109; δ_H (400 MHz, $CDCl_3$) 9.59 (1H, d, J=1.1 Hz) 4.82 (2H, brs), 4.13 (1H, dd, J=2.4, 1.1 Hz), 3.60 (1H, dt, J=7.0, 2.4 Hz), 3.61 (3H, s), 2.33-2.21 (2H, m), 0.93 (9H, s), 0.08 (6H, d, J=8.2 Hz); δ_C (75 MHz, $CDCl_3$) 203.4 (s), 141.4 (s), 114.8 (t), 83.0 (q), 78.7 (d), 58.1 (d), 38.8 (q), 26.0 (q), 22.9 (t), 18.5 (s), -4.4 (q), -4.5 (q); m/z (ESIMS) found: 273 (M+1)$^+$; calcd: 273.

A solution of aldehyde (150 mg, 0.55 mmol) in 12.5 ml tBuOH-H_2O (3.5:1) was cooled to 0 ^{o}C, to which was added NaH_2PO_4·H_2O (137 mg, 0.99 mmol), 2-methyl-2-butene (10 mmol, 5.2 ml from 2 M solution in THF) and $NaClO_2$ (122 mg, 1.35 mmol). The cooling bath was removed after 5 min and stirring was continued for 2 h. The mixture was concentrated, diluted with H_2O, acidified with 1 N HCl until pH 2-3 was reached, and then extracted with Et_2O (5×). The organic extract was washed with brine and dried over Na_2SO_4. After removing the solvent in vacuo, the residue was purified by FCC (50% hexane:acetone and 1% AcOH) to furnish 80 mg (84%) carboxylic acid **S2.4** as a colorless oil. R_F 0.34 (1:1:0.01-hexane:acetone:acetic acid); $[\alpha]^{22}_D$ +18.6 (c 0.86, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3600-2500, 3395, 3077, 2936, 1732, 1651,1105; δ_H (300 MHz, $CDCl_3$) 4.87 (1H, brs), 4.84 (1H, brs), 4.40 (1H, d, J=3.9 Hz), 3.76-3.71 (1H, m), 3.48 (3H, s), 2.46-2.29 (2H, m), 1.79 (3H, s); δ_C (75 MHz, $CDCl_3$) 175.1 (s) , 141.4 (s), 114.0 (t), 81.4 (q), 71.3 (d), 58.3 (d), 37.8 (q), 23.0 (t); m/z (ESIMS) found: 197 (M+23)$^+$; calcd: 197.

S2.4   S2.5
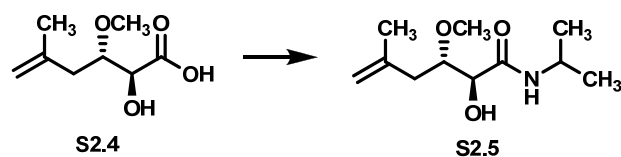
To a solution of 2-hydroxy-carboxylic acid **S2.4** (43.5 mg, 0.25 mmol), catalytic amount

of DMAP (~1 mg), and pyridine (43 μl, 0.53 mmol) was added TMSCl (68 μl, 0.53

mmol) dropwise. The reaction was stirred at room temperature for 3 h. The reaction was

cooled to 0 °C and catalytic DMF (1 drop) was added followed by oxalyl chloride (25 μl,

0.28 mmol). The reaction mixture was stirred for 30 min at 0 °C and then 30 min at room

temperature. After cooling the mixture to 0 °C, a solution of isopropyl amine (43 μl, 0.5

mmol) in pyridine (121 μl, 1.5 mmol) was added and the reaction was allowed to warm to

room temperature and stir for 2 h. Citric acid (111.3 mg, 0.53 mmol) was dissolved in

methanol (1 ml) and added to the reaction. After 45 min, the mixture was poured into o

separatory funnel and diluted with ethyl acetate. The organic phase was washed with 1 N

HCl and the aqueous wash was back extracted with ethyl acetate. The combined organic

layers were washed with a saturated bicarbonate solution followed by brine and dried

over Na_2SO_4. After removing the solvent, the residue was purified by FCC using

hexane:acetone (5:1) as eluent to furnish 27 mg (50%) amide **S2.5** as a white solid. For

crystallization, 1 mg of purified compound **S2.5** was dissolved in 1 ml of CH_2Cl_2, and

then almost 1 ml of hexane was added until turbidity appeared. Colorless crystals were

obtained in next day. R_F 0.36 (5:1-hexane:acetone); $[\alpha]^{22}_D$ -24.2 (c 0.99, $CHCl_3$); IR

(KBr) 3391, 3285, 3077, 2974, 1650, 1648, 1104; δ_H (300 MHz, CD_3OD) 4.76 (1H, s),

4.73 (1H, s), 4.26 (1H, d, J=3 Hz), 4.00 (1H, m, J=6.6 Hz), 3.66 (1H, dt, J=9.3, 3.0), 3.38

(3H, s), 2.27 (1H, ddd, J=14, 9.3, 0.6), 2.05 (1H, dd, J=14, 3.6), 1.73 (3H, s), 1.56 (6H,

dd, J=6.6, 4.5 Hz); (75 MHz, $CDCl_3$) 172.3 (s), 142.6 (s), 111.7 (t), 81.4 (q), 71.2 (d),

56.5 (d), 41.1 (d), 37.2 (q), 21.8 (t), 21.48 (q), 21.43 (q); *m/z* (ESIMS) found: 216 (M+1)$^+$; calcd: 216.


S2.2   S2.6
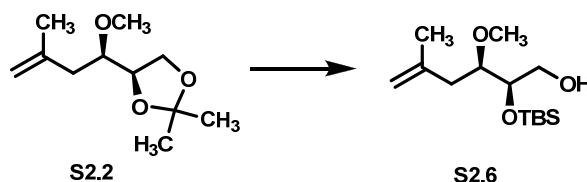
The protected diol **S2.2** (627 mg, 3.1 mmol) was stirred in 6.5 ml of AcOH:H$_2$O mixture (4:1) for 20 h at room temperature. The reaction mixture was concentrated and purified by FCC using hexane:acetone (5:1) as eluent to afford 436 mg (88%) diol as a colorless oil. R$_F$ 0.08 (5:1-hexane:acetone); [α]$^{22}_D$ -29.2 (c 0.24, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3076, 2985, 1647, 1107; δ$_H$ (400 MHz, CDCl$_3$) 4.82 (1H, brs), 4.78 (1H, brs), 4.19-4.14 (1H, m), 3.992 (1H, dd, J=6.8, 8.4), 3.70-3.66 (1H, m), 3.46 (3H, m), 3.41-3.36 (1H, m), 2.73 (2H, d, J=5.6), 1.79 (3H, s), 1.43 (3H, s), 1.36 (3H, s); δ$_C$ (100 MHz, CDCl$_3$) 142.0 (s), 113.4 (t), 79.9 (q), 72.7 (d), 64.0 (t), 57.9 (d), 38.1 (q), 22.8 (t); *m/z* (ESIMS) found: 201 (M+1)$^+$; calcd: 201.

To a solution of the above diol (205 mg, 1.28 mmol) in DMF (4 ml) was added imidazole (262 mg, 3.84 mmol) and TBSCl (503 mg, 3.33 mmol). The reaction mixture was stirred overnight and then diluted with H$_2$O, extracted with Et$_2$O, and dried over Na$_2$SO$_4$. After removing the solvent in vacuo, the residue was purified by FCC using hexane:acetone (40:1) as eluent to give 457 mg (92%) bis-TBS ether as a colorless oil. R$_F$ 0.93 (40:1-hexane:acetone); [α]$^{22}_D$ +5.6 (c 0.90, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3076, 2955, 1648, 1111; δ$_H$ (400 MHz, CDCl$_3$) 4.79 (1H, brs), 4.76 (1H, brs), 3.80-3.72 (2H, m), 3.53-3.49 (1H, m), 3.43-3.40 (1H, m), 3.40 (3H, s), 2.330 (1H, dd, J=14.4, 2.8), 2.10 (1H, dd, J=14.4,

9.2), 0.90 (18H, s), 0.09 (6H, s), 0.06 (6H, brs); δ_C (400 MHz, CDCl$_3$) 143.8 (s), 112.2 (t), 80.8 (q), 74.1 (d), 64.2 (t), 58.6 (d), 38.0 (q), 26.2 (q), 26.1 (q), 22.9 (t), 18.5 (s), 18.3 (s), -3.9 (q), -4.5 (q), -5.0 (q), -5.1 (q); *m/z* (ESIMS) found: 411 (M+23)$^+$; calcd: 411.

To a solution of bis-TBS ether (440 mg, 1.13 mmol) in THF (3.6 ml) in a plastic vial was added pyridine (0.60 ml) and HF-pyridine (0.1 ml of a 65-70% solution of HF in pyridine). The mixture was stirred 22 h, then diluted with Et$_2$O and washed with 0.5 M HCl solution. The aqueous layer was re-extracted with Et$_2$O. The combined organic layers were washed with saturated CuSO$_4$·H$_2$O and dried over NaSO$_4$. After removing the solvent, the residue was purified by FCC using hexane:acetone (20:1) as eluent to give 229 mg (74%) alcohol **12** as a colorless oil. R_F 0.24 (20:1-hexane:acetone); $[\alpha]^{22}_D$ +3.3 (c 1.80, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3461, 3076, 2930, 1647, 1107; (400 MHz, CDCl$_3$) 4.80 (1H, brs), 4.77 (1H, brs), 3.93-3.89 (1H, m), 3.72-3.68 (1H, m), 3.58-3.54 (1H, m), 3.43-3.418 (1H, m), 3.410 (3H, s), 2.36 (1H, d, J=14.4 Hz), 2.24 (1H, brs), 2.12 (1H, dd, J=14.4, 9.6 Hz), 1.77 (3H, s), 0.90 (9H, s), 0.11 (6H, s); δ_C (100 MHz, CDCl$_3$) 143.3 (s), 112.5 (t), 82.3 (q), 71.9 (d), 63.8 (t), 58.7 (d), 37.8 (q), 26.1 (q), 23.1 (t), 18.4 (s), -4.2 (q); *m/z* (ESIMS) found: 275 (M+1)$^+$; calcd: 275.
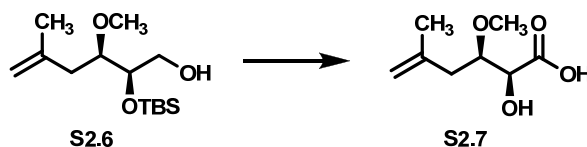
A solution of oxalyl chloride (0.19 ml, 2.18 mmol) in CH$_2$Cl$_2$ (7 ml) was cooled down to -78 °C. DMSO (0.340 ml, 4.79 mmol) was syringed in one portion and stirred for 15 min. Then the alcohol **S2.6** (396 mg, 1.45 mmol) dissolved in CH$_2$Cl$_2$ (7 ml) was added

slowly. After 30 min Et$_3$N (1,026 ml, 7.4 mmol) was added after which the cooling bath was replaced by an ice bath. Stirring was continued for 20 min, and then diluted with CH$_2$Cl$_2$ and H$_2$O. Extraction with CH$_2$Cl$_2$ and drying over Na$_2$SO$_4$ furnished 386 mg (98%) aldehyde. [α]$^{22}_D$ -5.9 (c 1.18, CHCl$_3$); IR ν$_{max}$(neat)/cm^{-1} 3078, 2932, 2858, 1736, 1648, 1099; δ$_H$ (400 MHz, CDCl$_3$) 9.69 (1H, d, J=1.2 Hz), 4.79 (1H, brs), 4.75 (1H, brs), 4.07 (1H, dd, J=3.9, 1.2 Hz), 3.66-3.61 (1H, m), 3.35 (3H, s), 2.34-2.29 (1H, m), 2,24-2.17 (1H, m), 0.91 (9H, s), 0.05 (6H, d, J=7.6 Hz); δ$_C$ (75 MHz, CDCl$_3$) 203.7 (s), 142.2 (s), 113.1 (t), 81.5 (q), 78.7 (d), 58.7 (d), 38.4 (q), 26.1 (q), 23.1 (t), 18.6 (s), -4.1 (q), -4.6 (q); m/z (ESIMS) found: 273 (M+1)$^+$; calcd: 273.

A solution of aldehyde (150 mg, 0.55 mmol) in 12.5 ml of tBuOH-H$_2$O (3.5:1) was cooled to 0 ^{o}C and added NaH$_2$PO$_4$·H$_2$O (137 mg, 0.99 mmol), 2-methyl-2-butene (10 mmol, 5.2 ml from 2 M solution in THF) and NaClO$_2$ (122 mg, 1.35 mmol). The cooling bath was removed after 5 min and stirring was continued for 2 h. The mixture was concentrated, diluted with H$_2$O, and then 1 N HCl was added until pH 2-3 was reached. The mixture was extracted with Et$_2$O (5×), and the combined organic extract was washed with brine and dried over Na$_2$SO$_4$. After removing the solvent in vacuo, the residue was purified by FCC (50% hexane:acetone and 1% AcOH) to furnish 77 mg (80%) carboxylic acid **S2.7** as a colorless oil. R$_F$ 0.34 (1:1:0.01-hexane:acetone:acetic acid); [α]$^{22}_D$ +6.0 (c 1.16, CHCl$_3$); IR ν$_{max}$(neat)/cm^{-1} 3600-2600, 3346, 3076, 2936, 1732, 1650, 1089; δ$_H$ (300 MHz, CDCl$_3$) 4.87 (1H, brs), 4.84 (1H, brs), 4.21 (1H, s), 3.83 (1H, t, J=7.2 Hz), 3.40 (3H, s), 2.38 (2H, d, J=7.2 Hz); (75 MHz, CDCl$_3$) 177.3 (s), 141.3 (s), 114.3 (t),

80.2 (q), 71.3 (d), 58.5 (d), 38.2 (q), 23.1 (t); *m/z* (ESIMS) found: 197 (M+23)⁺; calcd: 197.

S2.7   S2.8
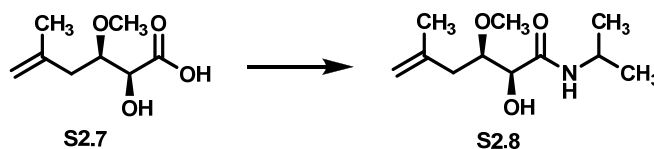
To a solution of 2-hydroxy-carboxylic acid **S2.7** (43.5 mg, 0.25 mmol), catalytic amount of DMAP, and pyridine (43 μl, 0.53 mmol) was added TMSCl (68 μl, 0.53 mmol) dropwise. The reaction was stirred at room temperature for 3 h. The reaction was cooled to 0 °C and catalytic amount of DMF (1 drop) was added followed by oxalyl chloride (25 μl, 0.28 mmol). The reaction mixture was stirred for 30 min at 0 °C and then 30 min at room temperature. After cooling the mixture to 0 °C , a solution of isopropyl amine (43 μl, 0.5 mmol) in pyridine (121 μl, 1.5 mmol) was added and the reaction was allowed to warm to room temperature and stir for 2 h. Citric acid (111.3 mg, 0.53 mmol) was dissolved in methanol (1 ml) and added to the reaction. After 45 min, the mixture was poured into a separatory funnel and diluted with ethyl acetate. The organic phase was washed with 1 N HCl and the aqueous wash was back extracted with ethyl acetate. The combined organic layers were washed with a saturated bicarbonate solution followed by brine and dried over Na_2SO_4. After removing the solvent, the residue was purified by FCC using hexane:acetone (5:1) as eluent to furnish 29 mg (54%) amide **S2.8** as a colorless oil. M.p. 62-63 °C; R_F 0.36 (5:1-hexane:acetone); $[\alpha]^{22}_D$ -26.7 (c 2.32, $CHCl_3$); IR ν_{max}(neat)/cm⁻¹ 3390, 3340, 3076, 2971, 1650, 1090; δ_H (300 MHz, CD_3OD) 4.84-4.83 (1H, brs), 4.81-4.80 (1H, brs), 4.02 (1H, m, J=6.6 Hz), 3.90 (1H, d, J=1.8 Hz), 3.83-3.77 (1H, m), 3.33 (3H, s), 2.40-2.26 (2H, m), 1.80 (3H, s), 1.17 (6H, dd, J=6.6, 2.4 Hz); (75

MHz, CDCl$_3$) 173.4 (s), 142.2 (s), 112.6 (s), 80.2 (q), 72.2 (d), 57.8 (d), 41.2 (d), 38.6

(q), 21.8 (t), 21.5 (q), 21.4 (q); *m/z* (ESIMS) found: 216 (M+1)$^+$; calcd: 216.

Crystal Structure: Three Conformers of **S2.5**.

I   II   III
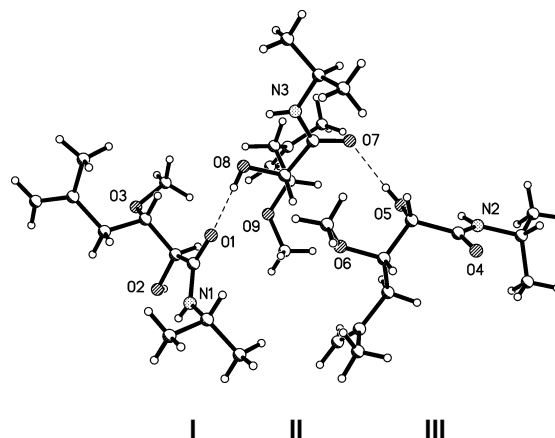
Empirical formula	C11 H21 N O3
Formula weight	215.29
Temperature 1	00(2) K
Wavelength	0.71073 Å
Crystal system	Hexagonal
Space group	P6(1)
Unit cell dimensions	a = 11.3849(3) Å $\square$= 90°.
	b = 11.3849(3) Å $\square$= 90°.
	c = 51.704(3) Å $\square$ = 120°.
Volume	5803.8(4) Å3
Z	18
Density (calculated)	1.109 Mg/m3
Absorption coefficient	0.080 mm-1
F(000)	2124

Crystal size	.22 x 0.20 x 0.10 mm3
Theta range for data collection	2.07 to 28.37°.
Index ranges	-15<=h<=15, -15<=k<=15, -68<=l<=68
Reflections collected	61964
Independent reflections	9635 [R(int) = 0.0454]
Completeness to theta = 28.37°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9999 and 0.8502
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	9635 / 1 / 440
Goodness-of-fit on	F21.036
Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.1110
R indices (all data)	R1 = 0.0561, wR2 = 0.1164
Absolute structure parameter	0.1(6)
Largest diff. peak and hole	0.580 and -0.202 e.Å-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **S2.5**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	2766(2)	-3690(2)	-649(1)	25(1)
O(1)	2163(1)	-4572(1)	-1051(1)	30(1)
O(2)	4219(1)	-1200(1)	-815(1)	26(1)
O(3)	5189(1)	-860(1)	-1356(1)	27(1)
C(1)	6842(2)	-2111(2)	-1273(1)	38(1)

C(2)	6368(3)	-3265(4)	-1454(1)	62(1)
C(3)	8190(3)	-1026(3)	-1259(1)	66(1)
C(4)	5799(2)	-2152(2)	-1084(1)	29(1)
C(5)	4621(2)	-2098(2)	-1216(1)	24(1)
C(6)	4321(2)	-891(2)	-1558(1)	32(1)
C(7)	3583(2)	-2158(2)	-1016(1)	23(1)
C(8)	2774(2)	-3585(2)	-905(1)	24(1)
C(9)	2033(2)	-4977(2)	-510(1)	30(1)
C(10)	3032(3)	-5254(2)	-368(1)	45(1)
C(11)	1004(2)	-4943(2)	-328(1)	44(1)
N(2)	-6455(2)	-7779(2)	-1251(1)	29(1)
O(4)	-6295(2)	-9292(1)	-993(1)	33(1)
O(5)	-3923(2)	-6477(2)	-1367(1)	36(1)
O(6)	-2013(1)	-6609(1)	-1017(1)	32(1)
C(12)	-2712(2)	-5598(2)	-573(1)	32(1)
C(13)	-1985(2)	-4274(2)	-527(1)	41(1)
C(14)	-2712(2)	-6623(2)	-390(1)	37(1)
C(15)	-3593(2)	-6131(2)	-808(1)	32(1)
C(16)	-3418(2)	-7193(2)	-958(1)	27(1)
C(17)	-1612(2)	-7571(2)	-1079(1)	40(1)
C(18)	-4263(2)	-7612(2)	-1207(1)	29(1)
C(19)	-5767(2)	-8312(2)	-1141(1)	27(1)
C(20)	-7907(2)	-8299(2)	-1209(1)	32(1)
C(21)	-8174(3)	-7971(3)	-937(1)	44(1)
C(22)	-8398(2)	-7685(2)	-1412(1)	40(1)
N(3)	-380(2)	-6569(2)	-1821(1)	26(1)
O(7)	-2138(1)	-6241(2)	-1735(1)	32(1)
O(8)	1325(1)	-4582(1)	-1535(1)	26(1)
O(9)	658(1)	-2516(1)	-1381(1)	30(1)
C(23)	205(2)	-1862(2)	-1926(1)	28(1)
C(24)	-986(2)	-2381(2)	-2105(1)	42(1)
C(25)	892(3)	-580(2)	-1847(1)	43(1)
C(26)	571(2)	-2895(2)	-1834(1)	26(1)
C(27)	-73(2)	-3521(2)	-1573(1)	24(1)
C(28)	12(2)	-2813(2)	-1135(1)	34(1)
C(29)	-15(2)	-4815(2)	-1517(1)	24(1)

C(30)	-939(2)	-5941(2)	-1703(1)	24(1)
C(31)	-1128(2)	-7738(2)	-1993(1)	30(1)
C(32)	-109(2)	-7844(2)	-2166(1)	40(1)
C(33)	-1970(3)	-9018(2)	-1838(1)	46(1)

Table 3.   Bond lengths [Å] and angles [°] for **S2.5**.

N(1)-C(8)	1.328(2)	C(11)-H(11A)	0.9800
N(1)-C(9)	1.463(2)	C(11)-H(11B)	0.9800
N(1)-H(1N)	0.76(2)	C(11)-H(11C)	0.9800
O(1)-C(8)	1.238(2)	N(2)-C(19)	1.332(2)
O(2)-C(7)	1.414(2)	N(2)-C(20)	1.468(3)
O(2)-H(2O)	0.78(3)	N(2)-H(2N)	0.84(2)
O(3)-C(5)	1.422(2)	O(4)-C(19)	1.235(2)
O(3)-C(6)	1.426(2)	O(5)-C(18)	1.416(2)
C(1)-C(3)	1.411(4)	O(5)-H(5O)	0.76(3)
C(1)-C(2)	1.480(4)	O(6)-C(17)	1.419(2)
C(1)-C(4)	1.519(3)	O(6)-C(16)	1.424(2)
C(2)-H(2A)	0.9800	C(12)-C(13)	1.329(3)
C(2)-H(2B)	0.9800	C(12)-C(15)	1.501(3)
C(2)-H(2C)	0.9800	C(12)-C(14)	1.501(3)
C(3)-H(3A)	0.9500	C(13)-H(13A)	0.9500
C(3)-H(3B)	0.9500	C(13)-H(13B)	0.9500
C(4)-C(5)	1.532(3)	C(14)-H(14A)	0.9800
C(4)-H(4A)	0.9900	C(14)-H(14B)	0.9800
C(4)-H(4B)	0.9900	C(14)-H(14C)	0.9800
C(5)-C(7)	1.545(2)	C(15)-C(16)	1.531(3)
C(5)-H(5)	1.0000	C(15)-H(15A)	0.9900
C(6)-H(6A)	0.9800	C(15)-H(15B)	0.9900
C(6)-H(6B)	0.9800	C(16)-C(18)	1.533(3)
C(6)-H(6C)	0.9800	C(16)-H(16)	1.0000
C(10)-H(10A)	0.9800	C(17)-H(17A)	0.9800
C(10)-H(10B)	0.9800	C(17)-H(17B)	0.9800
C(10)-H(10C)	0.9800	C(17)-H(17C)	0.9800

C(18)-C(19)	1.523(3)	C(29)-H(29)	1.0000
C(18)-H(18)	1.0000	C(31)-C(33)	1.514(3)
C(20)-C(22)	1.515(3)	C(31)-C(32)	1.518(3)
C(20)-C(21)	1.522(3)	C(31)-H(31)	1.0000
C(20)-H(20)	1.0000	C(32)-H(32A)	0.9800
C(21)-H(21A)	0.9800	C(32)-H(32B)	0.9800
C(21)-H(21B)	0.9800	C(32)-H(32C)	0.9800
C(21)-H(21C)	0.9800	C(33)-H(33A)	0.9800
C(22)-H(22A)	0.9800	C(33)-H(33B)	0.9800
C(22)-H(22B)	0.9800	C(33)-H(33C)	0.9800
C(22)-H(22C)	0.9800	C(8)-N(1)-C(9)	123.74(16)
N(3)-C(30)	1.322(2)	C(8)-N(1)-H(1N)	117.4(18)
N(3)-C(31)	1.466(2)	C(9)-N(1)-H(1N)	118.9(18)
N(3)-H(3N)	0.83(2)	C(7)-O(2)-H(2O)	105(2)
O(7)-C(30)	1.241(2)	C(5)-O(3)-C(6)	112.56(14)
O(8)-C(29)	1.414(2)	C(3)-C(1)-C(2)	124.2(2)
O(8)-H(8O)	0.80(3)	C(3)-C(1)-C(4)	119.1(2)
O(9)-C(28)	1.425(2)	C(2)-C(1)-C(4)	116.6(2)
O(9)-C(27)	1.426(2)	C(1)-C(2)-H(2A)	109.5
C(23)-C(25)	1.328(3)	C(1)-C(2)-H(2B)	109.5
C(23)-C(24)	1.498(3)	H(2A)-C(2)-H(2B)	109.5
C(23)-C(26)	1.507(3)	C(1)-C(2)-H(2C)	109.5
C(24)-H(24A)	0.9800	H(2A)-C(2)-H(2C)	109.5
C(24)-H(24B)	0.9800	H(2B)-C(2)-H(2C)	109.5
C(24)-H(24C)	0.9800	C(1)-C(3)-H(3A)	120.0
C(25)-H(25A)	0.9500	C(1)-C(3)-H(3B)	120.0
C(25)-H(25B)	0.9500	H(3A)-C(3)-H(3B)	120.0
C(26)-C(27)	1.531(2)	C(1)-C(4)-C(5)	113.65(15)
C(26)-H(26A)	0.9900	C(1)-C(4)-H(4A)	108.8
C(26)-H(26B)	0.9900	C(5)-C(4)-H(4A)	108.8
C(27)-C(29)	1.536(2)	C(1)-C(4)-H(4B)	108.8
C(27)-H(27)	1.0000	C(5)-C(4)-H(4B)	108.8
C(28)-H(28A)	0.9800	H(4A)-C(4)-H(4B)	107.7
C(28)-H(28B)	0.9800	O(3)-C(5)-C(4)	107.05(15)
C(28)-H(28C)	0.9800	O(3)-C(5)-C(7)	110.16(13)
C(29)-C(30)	1.525(2)	C(4)-C(5)-C(7)	111.49(14)

O(3)-C(5)-H(5)	109.4	C(19)-N(2)-C(20)	123.60(17)
C(4)-C(5)-H(5)	109.4	C(19)-N(2)-H(2N)	112.7(15)
C(7)-C(5)-H(5)	109.4	C(20)-N(2)-H(2N)	123.6(15)
O(3)-C(6)-H(6A)	109.5	C(18)-O(5)-H(5O)	113(2)
O(3)-C(6)-H(6B)	109.5	C(17)-O(6)-C(16)	114.05(15)
H(6A)-C(6)-H(6B)	109.5	C(13)-C(12)-C(15)	121.0(2)
O(3)-C(6)-H(6C)	109.5	C(13)-C(12)-C(14)	121.8(2)
H(6A)-C(6)-H(6C)	109.5	C(15)-C(12)-C(14)	117.17(18)
H(6B)-C(6)-H(6C)	109.5	C(12)-C(13)-H(13A)	120.0
O(2)-C(7)-C(8)	110.57(14)	C(12)-C(13)-H(13B)	120.0
O(2)-C(7)-C(5)	111.78(14)	H(13A)-C(13)-H(13B)	120.0
C(8)-C(7)-C(5)	109.85(14)	C(12)-C(14)-H(14A)	109.5
O(2)-C(7)-H(7)	108.2	C(12)-C(14)-H(14B)	109.5
C(8)-C(7)-H(7)	108.2	H(14A)-C(14)-H(14B)	109.5
C(5)-C(7)-H(7)	108.2	C(12)-C(14)-H(14C)	109.5
O(1)-C(8)-N(1)	123.40(16)	H(14A)-C(14)-H(14C)	109.5
O(1)-C(8)-C(7)	120.34(15)	H(14B)-C(14)-H(14C)	109.5
N(1)-C(8)-C(7)	116.26(15)	C(12)-C(15)-C(16)	113.95(16)
N(1)-C(9)-C(10)	109.68(17)	C(12)-C(15)-H(15A)	108.8
N(1)-C(9)-C(11)	109.91(17)	C(16)-C(15)-H(15A)	108.8
C(10)-C(9)-C(11)	111.98(18)	C(12)-C(15)-H(15B)	108.8
N(1)-C(9)-H(9)	108.4	C(16)-C(15)-H(15B)	108.8
C(10)-C(9)-H(9)	108.4	H(15A)-C(15)-H(15B)	107.7
C(11)-C(9)-H(9)	108.4	O(6)-C(16)-C(15)	107.36(15)
C(9)-C(10)-H(10A)	109.5	O(6)-C(16)-C(18)	110.51(15)
C(9)-C(10)-H(10B)	109.5	C(15)-C(16)-C(18)	111.20(15)
H(10A)-C(10)-H(10B)	109.5	O(6)-C(16)-H(16)	109.2
C(9)-C(10)-H(10C)	109.5	C(15)-C(16)-H(16)	109.2
H(10A)-C(10)-H(10C)	109.5	C(18)-C(16)-H(16)	109.2
H(10B)-C(10)-H(10C)	109.5	O(6)-C(17)-H(17A)	109.5
C(9)-C(11)-H(11A)	109.5	O(6)-C(17)-H(17B)	109.5
C(9)-C(11)-H(11B)	109.5	H(17A)-C(17)-H(17B)	109.5
H(11A)-C(11)-H(11B)	109.5	C(12)-C(17)-H(17C)	109.5
C(9)-C(11)-H(11C)	109.5	H(17A)-C(17)-H(17C)	109.5
H(11A)-C(11)-H(11C)	109.5	H(17B)-C(17)-H(17C)	109.5
H(11B)-C(11)-H(11C)	109.5	O(5)-C(18)-C(19)	109.30(15)

O(5)-C(18)-C(16)	111.34(16)	H(24A)-C(24)-H(24B)	109.5
C(19)-C(18)-C(16)	110.03(15)	C(23)-C(24)-H(24C)	109.5
O(5)-C(18)-H(18)	108.7	H(24A)-C(24)-H(24C)	109.5
C(19)-C(18)-H(18)	108.7	H(24B)-C(24)-H(24C)	109.5
C(16)-C(18)-H(18)	108.7	C(23)-C(25)-H(25A)	120.0
O(4)-C(19)-N(2)	122.99(18)	C(23)-C(25)-H(25B)	120.0
O(4)-C(19)-C(18)	121.53(16)	H(25A)-C(25)-H(25B)	120.0
N(2)-C(19)-C(18)	115.47(17)	C(23)-C(26)-C(27)	112.58(15)
N(2)-C(20)-C(22)	108.20(17)	C(23)-C(26)-H(26A)	109.1
N(2)-C(20)-C(21)	111.08(17)	C(27)-C(26)-H(26A)	109.1
C(22)-C(20)-C(21)	111.25(17)	C(23)-C(26)-H(26B)	109.1
N(2)-C(20)-H(20)	108.8	C(27)-C(26)-H(26B)	109.1
C(22)-C(20)-H(20)	108.7	H(26A)-C(26)-H(26B)	107.8
C(21)-C(20)-H(20)	108.8	O(9)-C(27)-C(26)	106.79(14)
C(20)-C(21)-H(21A)	109.5	O(9)-C(27)-C(29)	110.44(14)
C(20)-C(21)-H(21B)	109.5	C(26)-C(27)-C(29)	112.01(14)
H(21A)-C(21)-H(21B)	109.5	O(9)-C(27)-H(27)	109.2
C(20)-C(21)-H(21C)	109.5	C(26)-C(27)-H(27)	109.2
H(21A)-C(21)-H(21C)	109.5	C(29)-C(27)-H(27)	109.2
H(21B)-C(21)-H(21C)	109.5	O(9)-C(28)-H(28A)	109.5
C(20)-C(22)-H(22A)	109.5	O(9)-C(28)-H(28B)	109.5
C(20)-C(22)-H(22B)	109.5 H(22A)-C(22)-H(22B)	H(28A)-C(28)-H(28B)	109.5 O(9)-C(28)-H(28C)
	109.5		109.5
C(20)-C(22)-H(22C)	109.5	H(28A)-C(28)-H(28C)	109.5
H(22A)-C(22)-H(22C)	109.5	H(28B)-C(28)-H(28C)	109.5
H(22B)-C(22)-H(22C)	109.5	O(8)-C(29)-C(30)	110.03(14)
C(30)-N(3)-C(31)	123.65(16)	O(8)-C(29)-C(27)	111.52(15)
C(30)-N(3)-H(3N)	115.4(15)	C(30)-C(29)-C(27)	110.03(14)
C(31)-N(3)-H(3N)	120.9(15)	O(8)-C(29)-H(29)	108.4
C(29)-O(8)-H(8O)	105.6(18)	C(30)-C(29)-H(29)	108.4
C(28)-O(9)-C(27)	114.03(14)	C(27)-C(29)-H(29)	108.4
C(25)-C(23)-C(24)	122.81(19)	O(7)-C(30)-N(3)	123.28(17)
C(25)-C(23)-C(26)	121.40(19)	O(7)-C(30)-C(29)	121.19(16)
C(24)-C(23)-C(26)	115.78(17)	N(3)-C(30)-C(29)	115.53(15)
C(23)-C(24)-H(24A)	109.5	N(3)-C(31)-C(33)	110.66(16)
C(23)-C(24)-H(24B)	109.5	N(3)-C(31)-C(32)	108.06(17)

C(33)-C(31)-C(32)	112.22(18)	C(32)-C(31)-H(31)	108.6
N(3)-C(31)-H(31)	108.6	C(33)-C(31)-H(31)	108.6
H(32B)-C(32)-H(32C)	109.5	C(31)-C(32)-H(32A)	109.5
C(31)-C(33)-H(33A)	109.5	C(31)-C(32)-H(32B)	109.5
C(31)-C(33)-H(33B)	109.5	H(32A)-C(32)-H(32B)	109.5
H(33A)-C(33)-H(33B)	109.5	H(33B)-C(33)-H(33C)	109.5
C(31)-C(33)-H(33C)	109.5	C(31)-C(32)-H(32C)	109.5
H(33A)-C(33)-H(33C)	109.5	H(32A)-C(32)-H(32C)	109.5

Table 4. Anisotropic displacement parameters $(Å^2 x\ 10^3)$ for Sezgin's Amide. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	28(1)	18(1)	25(1)	-1(1)	-3(1)	8(1)
O(1)	38(1)	24(1)	25(1)	-2(1)	-10(1)	12(1)
O(2)	31(1)	20(1)	27(1)	-1(1)	-1(1)	13(1)
O(3)	27(1)	28(1)	25(1)	7(1)	-2(1)	12(1)
C(1)	50(1)	58(1)	29(1)	10(1)	6(1)	43(1)
C(2)	66(2)	103(2)	49(2)	-31(2)	-17(1)	66(2)
C(3)	77(2)	91(2)	70(2)	44(2)	49(2)	73(2)
C(4)	35(1)	39(1)	23(1)	1(1)	-2(1)	24(1)
C(5)	30(1)	24(1)	21(1)	0(1)	-2(1)	15(1)
C(6)	37(1)	33(1)	25(1)	7(1)	-3(1)	15(1)
C(7)	25(1)	23(1)	24(1)	2(1)	-3(1)	14(1)
C(8)	25(1)	25(1)	25(1)	1(1)	-5(1)	15(1)
C(9)	36(1)	22(1)	24(1)	2(1)	-7(1)	8(1)
C(10)	55(1)	33(1)	48(1)	2(1)	-13(1)	23(1)
C(11)	40(1)	45(1)	37(1)	7(1)	6(1)	13(1)
N(2)	34(1)	27(1)	32(1)	2(1)	1(1)	19(1)
O(4)	37(1)	27(1)	43(1)	5(1)	4(1)	21(1)
O(5)	41(1)	45(1)	33(1)	13(1)	11(1)	29(1)
O(6)	32(1)	34(1)	36(1)	4(1)	6(1)	22(1)

C(12)	28(1)	36(1)	33(1)	-4(1)	7(1)	17(1)
C(13)	43(1)	37(1)	45(1)	-7(1)	3(1)	21(1)
C(14)	34(1)	37(1)	31(1)	1(1)	1(1)	11(1)
C(15)	35(1)	36(1)	33(1)	-2(1)	3(1)	22(1)
C(16)	27(1)	27(1)	29(1)	2(1)	4(1)	15(1)
C(17)	48(1)	46(1)	41(1)	14(1)	14(1)	36(1)
C(18)	37(1)	33(1)	27(1)	2(1)	3(1)	24(1)
C(19)	34(1)	27(1)	26(1)	-4(1)	-1(1)	20(1)
C(20)	33(1)	31(1)	36(1)	-1(1)	-2(1)	20(1)
C(21)	47(1)	62(2)	39(1)	2(1)	4(1)	38(1)
C(22)	40(1)	45(1)	43(1)	-2(1)	-7(1)	28(1)
N(3)	26(1)	28(1)	23(1)	-3(1)	-4(1)	14(1)
O(7)	23(1)	40(1)	33(1)	-5(1)	-2(1)	15(1)
O(8)	26(1)	35(1)	21(1)	-1(1)	-5(1)	17(1)
O(9)	35(1)	31(1)	22(1)	-4(1)	-1(1)	15(1)
C(23)	35(1)	37(1)	21(1)	6(1)	7(1)	23(1)
C(24)	47(1)	51(1)	38(1)	-1(1)	-10(1)	32(1)
C(25)	49(1)	33(1)	49(1)	5(1)	0(1)	22(1)
C(26)	29(1)	31(1)	23(1)	0(1)	1(1)	19(1)
C(27)	26(1)	29(1)	21(1)	-1(1)	1(1)	17(1)
C(28)	44(1)	43(1)	24(1)	-3(1)	1(1)	29(1)
C(29)	26(1)	29(1)	17(1)	-1(1)	-1(1)	15(1)
C(30)	25(1)	27(1)	20(1)	2(1)	1(1)	13(1)
C(31)	35(1)	33(1)	25(1)	-6(1)	-6(1)	19(1)
C(32)	53(1)	44(1)	30(1)	-6(1)	-2(1)	31(1)
C(33)	49(1)	33(1)	40(1)	-7(1)	0(1)	8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) **for S2.5**.

	x	y	z	U(eq)
H(1N)	3180(20)	-3040(20)	-572(5)	26(6)

H(2O)	4120(30)	-590(30)	-854(5)	39
H(2A)	7134	-3161	-1558	94
H(2B)	5672	-3283	-1568	94
H(2C)	5983	-4115	-1356	94
H(3A)	8860	-1006	-1372	79
H(3B)	8427	-315	-1138	79
H(4A)	6255	-1375	-964	35
H(4B)	5430	-2994	-981	35
H(5)	4156	-2877	-1338	29
H(6A)	3478	-1008	-1483	49
H(6B)	4112	-1649	-1675	49
H(6C)	4776	-37	-1655	49
H(7)	2939	-1943	-1107	28
H(9)	1535	-5718	-639	36
H(10A)	3525	-4539	-239	67
H(10B)	3676	-5269	-492	67
H(10C)	2541	-6134	-280	67
H(11A)	389	-4745	-427	66
H(11B)	1478	-4237	-197	66
H(11C)	482	-5825	-243	66
H(2N)	-5960(20)	-7080(20)	-1338(5)	27(5)
H(5O)	-3400(30)	-6370(30)	-1469(6)	54
H(13A)	-2018	-3650	-644	50
H(13B)	-1432	-3953	-377	50
H(14A)	-2241	-6169	-230	55
H(14B)	-2246	-7056	-470	55
H(14C)	-3649	-7313	-350	55
H(15A)	-3385	-5362	-925	39
H(15B)	-4554	-6538	-755	39
H(16)	-3709	-8011	-847	32
H(17A)	-2076	-8057	-1237	59
H(17B)	-1854	-8219	-936	59
H(17C)	-629	-7103	-1106	59
H(18)	-4080	-8264	-1304	35
H(20)	-8403	-9306	-1231	38
H(21A)	-7745	-6986	-917	67

H(21B)	-7794	-8329	-810	67
H(21C)	-9153	-8388	-910	67
H(22A)	-8173	-7873	-1584	60
H(22B)	-7955	-6702	-1386	60
H(22C)	-9383	-8082	-1397	60
H(3N)	430(20)	-6280(20)	-1787(4)	23(5)
H(8O)	1590(30)	-4510(20)	-1389(6)	37(7)
H(24A)	-1198	-1660	-2138	63
H(24B)	-1772	-3157	-2025	63
H(24C)	-766	-2664	-2268	63
H(25A)	634	51	-1905	51
H(25B)	1641	-295	-1733	51
H(26A)	1570	-2456	-1819	31
H(26B)	270	-3625	-1965	31
H(27)	-1041	-3742	-1573	29
H(28A)	58	-3571	-1056	51
H(28B)	-940	-3059	-1156	51
H(28C)	473	-2013	-1023	51
H(29)	-349	-5116	-1336	28
H(31)	-1750	-7571	-2104	36
H(32A)	577	-7890	-2060	59
H(32B)	330	-7046	-2279	59
H(32C)	-578	-8665	-2273	59
H(33A)	-2583	-8890	-1723	69
H(33B)	-1369	-9215	-1734	69
H(33C)	-2502	-9776	-1955	69

Table 6. Torsion angles [°] for **S2.5**.

C(3)-C(1)-C(4)-C(5)	118.5(2)	O(3)-C(5)-C(7)-O(2)	-68.37(17)
C(2)-C(1)-C(4)-C(5)	-63.6(2)	C(4)-C(5)-C(7)-O(2)	50.33(19)
C(6)-O(3)-C(5)-C(4)	158.44(15)	O(3)-C(5)-C(7)-C(8)	168.50(13)
C(6)-O(3)-C(5)-C(7)	-80.17(18)	C(4)-C(5)-C(7)-C(8)	-72.80(18)
C(1)-C(4)-C(5)-O(3)	-60.1(2)	C(9)-N(1)-C(8)-O(1)	-0.3(3)
C(1)-C(4)-C(5)-C(7)	179.36(16)	C(9)-N(1)-C(8)-C(7)	179.42(16)

O(2)-C(7)-C(8)-O(1)	-178.54(16)	C(16)-C(18)-C(19)-N(2)	125.03(17)
C(5)-C(7)-C(8)-O(1)	-54.7(2)	C(19)-N(2)-C(20)-C(22)	-165.93(18)
O(2)-C(7)-C(8)-N(1)	1.8(2)	C(19)-N(2)-C(20)-C(21)	71.7(2)
C(5)-C(7)-C(8)-N(1)	125.62(17)	C(25)-C(23)-C(26)-C(27)	84.4(2)
C(8)-N(1)-C(9)-C(10)	116.0(2)	C(24)-C(23)-C(26)-C(27)	-94.6(2)
C(8)-N(1)-C(9)-C(11)	-120.5(2)	C(28)-O(9)-C(27)-C(26)	166.84(15)
C(13)-C(12)-C(15)-C(16)	132.0(2)	C(28)-O(9)-C(27)-C(29)	-71.14(19)
C(14)-C(12)-C(15)-C(16)	-49.3(2)	C(23)-C(26)-C(27)-O(9)	-74.13(19)
C(17)-O(6)-C(16)-C(15)	160.62(16)	C(23)-C(26)-C(27)-C(29)	164.85(15)
C(17)-O(6)-C(16)-C(18)	-77.95(19)	O(9)-C(27)-C(29)-O(8)	-64.58(18)
C(12)-C(15)-C(16)-O(6)	-54.6(2)	C(26)-C(27)-C(29)-O(8)	54.30(19)
C(12)-C(15)-C(16)-C(18)	-175.62(16)	O(9)-C(27)-C(29)-C(30)	173.03(13)
O(6)-C(16)-C(18)-O(5)	-62.05(19)	C(26)-C(27)-C(29)-C(30)	-68.09(19)
C(15)-C(16)-C(18)-O(5)	57.1(2)	C(31)-N(3)-C(30)-O(7)	-3.5(3)
O(6)-C(16)-C(18)-C(19)	176.61(14)	C(31)-N(3)-C(30)-C(29)	175.57(16)
C(15)-C(16)-C(18)-C(19)	-64.3(2)	O(8)-C(29)-C(30)-O(7)	-174.06(16)
C(20)-N(2)-C(19)-O(4)	-0.5(3)	C(27)-C(29)-C(30)-O(7)	-50.8(2)
C(20)-N(2)-C(19)-C(18)	-179.27(17)	O(8)-C(29)-C(30)-N(3)	6.8(2)
O(5)-C(18)-C(19)-O(4)	-176.30(17)	C(27)-C(29)-C(30)-N(3)	130.08(16)
C(16)-C(18)-C(19)-O(4)	-53.7(2)	C(30)-N(3)-C(31)-C(33)	-77.7(2)
O(5)-C(18)-C(19)-N(2)	2.5(2)	C(30)-N(3)-C(31)-C(32)	159.02(17)

Table 7. Hydrogen bonds for **S2.5** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2O)...O(4)#1	0.78(3)	1.91(3)	2.6795(18)	171(3)
O(5)-H(5O)...O(7)	0.76(3)	1.94(3)	2.696(2)	175(3)
O(8)-H(8O)...O(1)	0.80(3)	1.88(3)	2.6726(18)	172(2)

Symmetry transformations used to generate equivalent atoms: #1 x+1,y+1,z

CHAPTER 3

S35.2 → S35.1
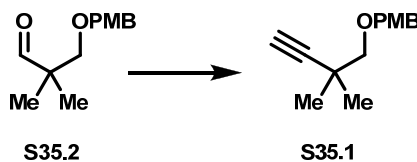
To a solution of K_2CO_3 (24.8 g, 180 mmol), TsN_3 (15.3 g, 78 mmol) in 400 mL was syringed dimethyl-(2-oxapropyl) phosphonate (10.6 mL, 78 mmol) at rt. After stirring for 2 h, a solution of aldehyde **S35.2** (13.3 g, 60 mmol) in 80 mL of MeOH was added. Stirring continued for 20 h, the mixture was concentrated under reduced pressure and then diluted with distilled water. The mixture was extracted with Et_2O and dried over Na_2SO_4. Purification by FCC using ethyl acetate / hexane (1:20) afforded 11.4 g (85%) alkyne **S35.1** as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3290, 2970, 2934, 2100, 1612, 1586, 1513; ^{1}H NMR (400 MHz, CDCl$_3$) 7.28 (2H, d, J= 8.4 Hz), 6.88 (2H, d, J= 8.4 Hz), 4.54 (2H, s), 3.80 (3H, s), 3.29 (2H, s), 2.12 (1H, s), 1.23 (3H, s); ^{13}C NMR (75 MHz, CDCl$_3$) 161.8, 159.1, 130.5, 129.1, 113.7, 90.3, 73.0, 68.1, 55.2, 32.2, 26.0. *m/z* (ESIMS) calculated for $C_{14}H_{18}O_2Na$ [MNa]$^+$ 241.12, found: 241.1.

S35.1 → S35.6
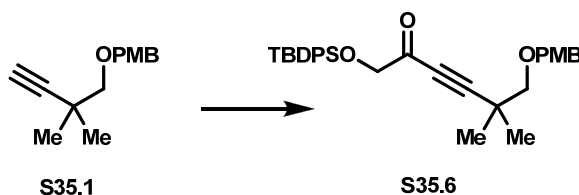
To a solution of alkyne **S35.1** (200 mg, 0.9 mmol) in THF was added 0.4 mL n-BuLi (2.5M) at -78 ^{o}C. After warming to 0 ^{o}C and stirring for 30 min, the reaction mixture was cooled to -78 ^{o}C and a solution of weinreb amide **S35.5** in THF was added slowly.

Stirring continued for 2h at -20 °C and the mixture was quenched with NH$_4$Cl solution. The mixture was extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:10) to give 400 mg product **S35.6** (85%) as a colorless oil. IR v_{max}(neat)/cm^{-1} 3068, 2950, 2925, 2200, 1696, 1673, 1612, 1513, 1427, 1110, 702; ^{1}H NMR (300 MHz, CDCl$_3$) 7.70-7.67 (4H, m), 7.44-7.35 (6H, m), 7.23 (2H, d, J= 5.4 Hz), 6.85 (2H, d, J= 5.4 Hz), 4.48 (2H, s), 4.29 (2H, s), 3.80 (3H, s), 3.3 (2H, s), 1.25 (6H, s), 1.09 (9H, s); m/z (ESIMS) calculated for C$_{32}$H$_{38}$O$_4$SiNa [MNa]$^+$ 537.24, found: 537.3.

S35.6 → S36.1
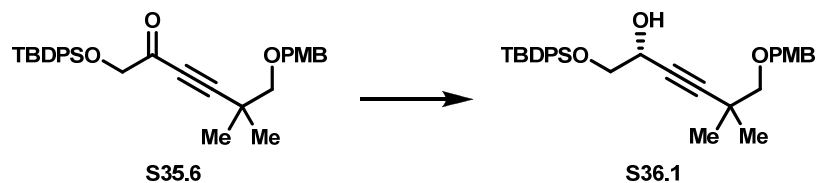
To a solution of Noyori catalyst in 3 mL iPrOH was added a solution of ketone **S35.6** (372 mg, 1.00 mmol) in 3 mL iPrOH. The mixture was stirred for 30 min, then was concentrated in vacuo. Purification of the residue by FCC using hexane/ethyl acetate (1:10) furnished 362 mg (97%) alcohol **S36.1** as a colorless oil. [α]$^{25}_D$ = -9.6 (c = 0.83, CHCl$_3$); IR v_{max}(neat)/cm^{-1} 3448, 3070, 2955, 2930, 2238, 1612, 1513, 1427, 1247, 1112, 702; ^{1}H NMR (300 MHz, CDCl$_3$) 7.71-7.65 (4H, m), 7.45-7.35 (6H, m), 7.24 (2H, d, J= 5.4 Hz), 6.84 (2H, d, J= 5.4 Hz), 4.49-4.45 (3H, m), 3.80-3.66 (4H, m), 1.20 (6H, s), 1.06 (9H, s); m/z (ESIMS) calculated for C$_{32}$H$_{40}$O$_4$SiNa [MNa]$^+$ 539.26, found: 539.4..

S36.1   S36.2
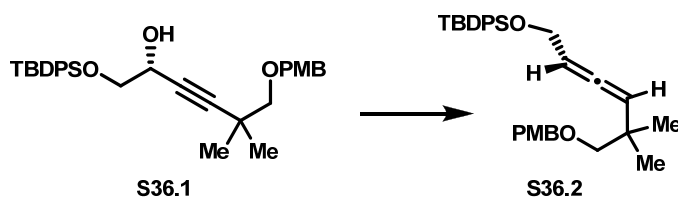
A solution of PPh$_3$ (249 mg, 0.95 mmol) in 2 mL THF was cooled to -15 $^\circ$C and was added DIAD (192 mg, 0.95 mmol). The mixture was stirred for 10 min then a solution of alcohol **S36.1** (300 mg, 0.63 mmol) in 2 mL THF was added. After 10 min, NBSH (206 mg, 0.95 mmol) in 1 mL THF was added at -15 $^\circ$C. Stirring continued after warming to rt for 12 h. The solvent was removed under vacuum and the crude was directly purified by FCC (silica gel, hexane/ethyl acetate 1:15) to afford allene **S36.2** (201 mg, 61%) as a colorless oil. $[\alpha]^{25}_D$ = -35.7 (c = 1.82, CHCl$_3$); IR v_{max}(neat)/cm^{-1} 3070, 2958, 2930, 1962, 1612, 1513, 1112, 702; ^{1}H NMR (300 MHz, CDCl$_3$) 7.73-7.67 (4H, m), 7.42-7.26 (6H, m), 7.23 (2H, d, J= 5.7 Hz), 6.86 (2H, d, J= 5.7 Hz), 5.35-5.22 (2H, m), 4.43(2H, s), 4.20 (2H, dd, J= 2.7, 6.0), 3.80 (3H, s), 3.15 (2H, s) 1.04 (9H, s), 1.02 (3H, s), 1.01 (3H, s); m/z (ESIMS) calculated for C$_{32}$H$_{40}$O$_3$SiNa [MNa]$^+$ 523.26, found: 523.3.

S36.2   S36.3
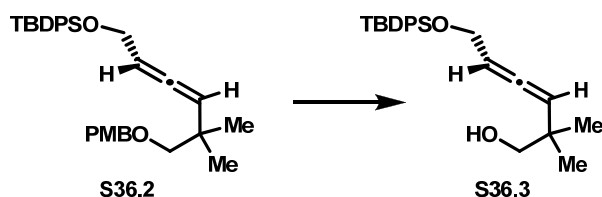
To a solution of allene **S36.2** (6.25 g, 12.4) in CH$_2$Cl$_2$ (80 mL) was added buffer (8 mL, pH= 7.40) and cooled to 0 $^\circ$C. DDQ was added to the mixture and stirred for 30 min. The reaction mixture was quenched with NaHCO$_3$, diluted with H$_2$O, extracted with CH$_2$Cl$_2$ and dried over Na$_2$SO$_4$. Solvent was evaporated and the residue was treated with excess amount of NaBH$_4$ in MeOH to remove the resulting anisaldeyhde. The mixture was

quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 and purified by FCC using hexane/ethyl acetate (20:1) as eluent to furnish alcohol **S36.3** (4.65 g, 98%) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3419, 3071, 2959, 2930, 2858, 1962, 1471, 1427, 1112, 702; ^{1}H NMR (400 MHz, CDCl$_3$) 7.70-7.68 (4H, m), 7.45-7.36 (6H, m), 5.36-5.31 (1H, m), 5.17-5.14 (1H, m), 4.20-4.17 (2H, m), 3.42 (1H, d, J=10.8 Hz), 3.31 (1H, d, J=10.8 Hz), 1.05 (9H, s), 1.01 (6H, s); ^{13}C NMR (100 MHz) 201.9, 135.7, 133.6, 129.9, 127.9, 100.9, 93.7, 71.5, 62.0, 37.7, 26.9, 25.1, 24.9, 19.4; *m/z* (ESIMS) calculated for $C_{24}H_{32}O_3$2iNa [MNa]$^+$ 403.2, found: 403.3.

S36.3 → S37.1
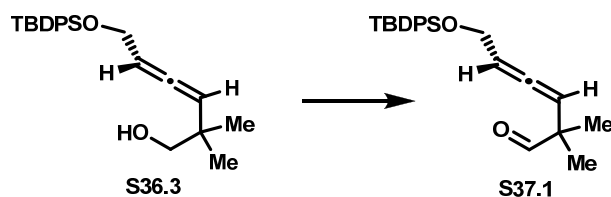
A solution of alcohol **S36.3**(6.4 g, 16.8 mmol) in CH_2Cl_2 (100 mL) was treated with Dess-Martin periodinone at room temperature, After stirring for 2 h, the mixture was quenched with a 2:1 (v/v) mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and solvent was removed in vacuo. Purification by FCC using hexane/ethyl acetate as eluent furnished aldehyde **S37.1** (5.4 g, 85%) as a colorless oil.

S37.1 → S37.2
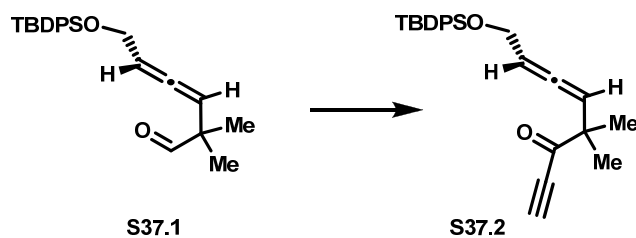
To the solution of aldehyde **S37.1** (5.2 g, 13.7 mmol) in THF (80 mL) at -78 °C was

added the ethynyl magnesium bromide solution slowly. After stirring for 5 min, the reaction mixture was placed in refrigerator for 12 h. The mixture was quenched with saturated NH_4Cl at cold temperature, extracted with CH_2Cl_2 and then dried over Na_2SO_4. The crude alcohol was dissolved in CH_2Cl_2 (100 mL) and treated with Dess-Martin periodinone (8.2 g, 19.3 mmol) at room temperature. The mixture was stirred for 30 min and then quenched with a 2:1 (v/v) mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$. The aqueous phase was extracted with CH_2Cl_2 and dried over Na_2SO_4. Evaporation of the solvent and then purification by FCC using hexane/ethyl aceate (20:1) as eluent afforded ketone **S37.2** (4.9 g, 89% over two steps) as a colorless oil. IR v_{max}(neat)/cm^{-1} 3269, 3071, 2961, 2931, 2091, 1964, 1680, 1464, 1427, 1112, 702; ^{1}H NMR (400 MHz, CDCl$_3$) 7.68-7.66 (4H, m), 7.42-7.35 (6H, m), 5.48-5.43 (1H, m), 5.35-5.32 (1H, m), 4.24-4.22 (2H, m), 3.13 (1H, s), 1.27 (6H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz) 203.3, 190.3, 135.7, 133.7, 129.9, 127.9, 97.6, 95.2, 80.8, 79.8, 61.9, 48.5, 27.0, 24.1, 23.8, 19.4; *m/z* (ESIMS) calculated for $C_{26}H_{30}O_2SiNa$ [MNa]$^+$ 425.19, found: 425.2.
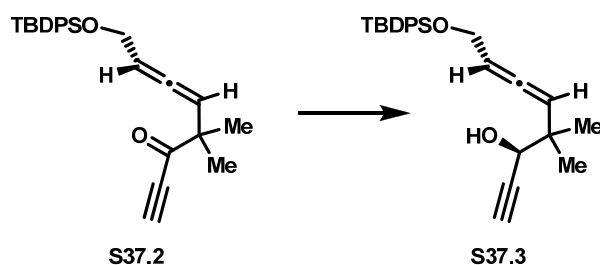
A solution of S-(CBS) (2.6 g, 9.32 mmol) in THF (40 mL) at -30 ^{o}C was treated with BH$_3$•SMe$_2$ (4.66 mL, 9.32mmol). After stirring for 15 min, a solution of allene **S37.2** (3.57 g, 8.80 mmol) in THF was added over the course of 10 min. The reaction mixture was stirred for 1 h and quenched with MeOH. The mixture was concentrated down and purified by FCC using hexane/ethyl acetate (1:30) as eluent to furnish alcohol **S37.3**

(3.20 g, 90%, dr: 10;1) as a colorless oil. $[\alpha]^{25}_D$ = -83.5 (c = 1.70, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3303, 3071, 2961, 2930, 1953, 1472, 1427, 1112, 701; ^{1}H NMR (400 MHz, CDCl$_3$) 7.69(m, 4H), 7.40 (m, 6H), 5.38 (dd, 1H, J= 6.0, 12.0Hz), 5.27 (m, 1H), 4.21 (m, 2H), 4.06 (dd, 1H, J= 2.4, 6.4 Hz), 2.41 (d, 1H, J= 2.0 Hz), 2.16 (d, 1H, J= 6.8 Hz), 1.11 (s, 3H), 1.11 (s, 3H), 1.05 (s, 9H) ; ^{1}H NMR (400 MHz, CDCl$_3$) 202.8, 135.6, 133.6, 133.5, 129.7, 127.7, 98.9, 93.9, 74.1, 70.2, 62.1, 40.3, 26.8, 24.1, 23.3, 19.2; m/z (ESIMS) calculated for C$_{26}$H$_{32}$O$_2$SiNa [MNa]$^+$ 427.21, found: 427.2.

S37.3   S38.3

To a solution of allene **S37.3** (3.0 g, 7.42 mmol) in CHCl$_3$ (100 mL) was added DMDO in CHCl$_3$ (115 mL, 22 mmol) slowly at 0 ^{o}C. The mixture was stirred for 40 min at 0 ^{o}C, followed by addition of MeOH. After stirring for 12 h at room temperature the mixture was concentrated down in vacuo. Purification by FCC using hexane/ethyl acetate (25:1) as eluent provided ketone **S38.3** (2.27 g, 70 %) as a colorless oil. The ratio was 8:1, as determined by NMR. $[\alpha]^{25}_D$ = +6.76 (c = 1.05, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3500, 3285, 3071, 2962, 2931, 1732, 1471, 1428, 1113, 701; ^{1}H NMR (400 MHz, CDCl$_3$) 7.70-7.56 (4H, m), 7.48-7.36 (6H, m), 5.16 (1H, d, J= 2.4 Hz), 4.26 (2H, s), 4.05 (1H, dd, J= 11.6, 3.6 Hz), 3.90 (1H, dd, J= 11.6, 3.6 Hz), 3.5 (1H, brs), 2.57 (1H, d, J= 2.4 Hz), 1.05 (9H, s), 1.04 (3H, s), 1.01 (3H, s); ^{13}C NMR (100 MHz) 208.6, 161.9, 135.7, 135.6, 135.0, 132.0, 130.1, 129.6, 128.0, 127.7, 81.5, 81.1, 79.1, 75.2, 73.1, 66.0, 44.4, 26.8, 26.6, 23.2, 19.1, 14.9; m/z (ESIMS) calculated for C$_{26}$H$_{34}$O$_4$SiNa [MNa]$^+$ 459.20, found: 459.2.

To a solution of ketone **S38.3** (2.03 g, 4.6 mmol) and $Me_4NBH(OAc)_3$ (6.12 g, 23.3 mmol) , in CH_3CN (40 mL) at -40 ^{o}C was added acetic acid (10.0 mL). After 5 min, the reaction mixture was warmed to -20 ^{o}C and kept at -20 ^{o}C for 48 h. The mixture was quenched with saturated $NaHCO_3$ at cold temperature, extracted with CH_2Cl_2 and dried over Na_2SO_4. Solvent was removed in vacuo and then the crude was purified by FCC using hexane/ethyl acetate (1:2) as eluent to give diol **S42.1** (1.50 g, 74 %) as a white foam. $[\alpha]^{25}_D$= +25.0 (c = 1.00, $CHCl_3$); IR v_{max}(neat)/cm^{-1} 3436, 3304, 3071, 2960, 2931, 1723, 1471, 1427, 1113, 702; ^{1}H NMR (400 MHz, $CDCl_3$) 7.72-7.69 (4H, m), 7.44-7.39 (6H, m), 4.30 (1H, d, J= 2.4 Hz), 4.2 (1H, q, J= 5.2 Hz), 4.07 (1H, dd, J= 11.2, 4.8 Hz) , 4.00-3.92 (2H, m), 3.55 (1H, d, J= 8 Hz), 2.48 (1H, d, J= 2.4 Hz), 1.10 (6H, s), 1.07 (9H, s); ^{13}C NMR (75 MHz) 135.8, 132.6, 130.1, 128.0, 80.5, 76.7, 75.2, 73.7, 71.4, 70.7, 63.2, 56.8, 39.9, 27.2, 24.3, 19.5; m/z (ESIMS) calculated for $C_{32}H_{40}O_3SiNa$ [MNa]$^+$ 461.21, found: 461.3.
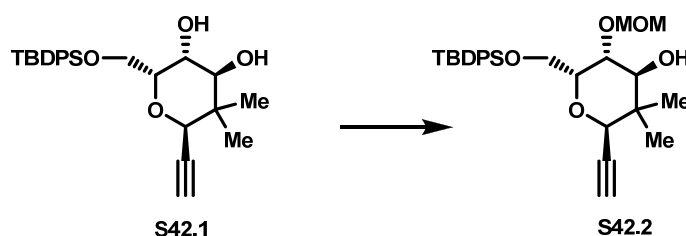
To a solution of diol **S42.1** (94 mg, 0.215 mmol) in 5.0 mL THF (containing trace water) at 0 °C was added NaH (60% of suspension in mineral oil, 45 mg, 1.125 mmol). After stirring for 5 min, MOMCl (52 mg, 0.65 mmol) was added dropwise. The reaction flask was kept in an ice bath for 10 min and then the ice bath was removed. After stirring for another 30 min, the reaction was quenched with NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:4) to give 62 mg compound **S42.2** (60%) as a colorless oil. $[\alpha]^{25}_D = +39.8$ (c = 1.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.22(4H, m), 7.41 (6H, m), 4.66 (1H, d, J= 6.8 Hz), 4.63 (1H, d, J= 6.8 Hz), 4.43 (1H, d, J = 2.0 Hz), 4.17 (1H, m), 3.94 (2H, m), 3.71 (1H, dd, J= 6.4, 8.8 Hz), 3.60 (1H, dd, J= 2.8, 8.8 Hz), 3.35 (3H, s), 3.14 (1H, br), 2.47 (1H, d, J= 2.0 Hz), 1.11 (3H, s), 1.07 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 136.0, 135.9, 133.4, 133.3, 130.0, 130.0, 128.0, 127.9, 98.2, 80.6, 78.9, 75.5, 74.7, 74.5, 70.7, 62.0, 56.3, 40.4, 27.1, 27.0, 23.8, 19.3, 15.4; IR v max (neat) /cm^{-1} 3464, 3293, 3068, 3040, 1471, 1428, 1111. m/z (ESIMS) calculated for $C_{28}H_{38}O_5SiNa$ [MNa]$^+$ 505.24, found: 505.4.

S42.2 → S42.3
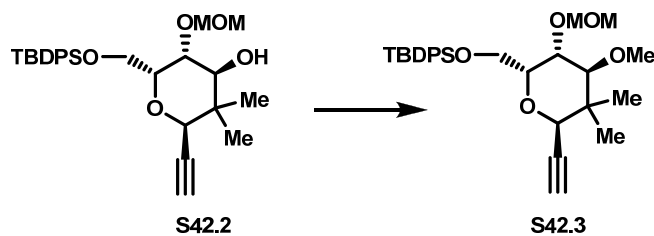
To a solution of compound **S42.2** (48 mg, 0.100 mmol) in 1.0 mL THF at 0 °C was added NaH (60% of suspension in mineral oil, 20 mg, 0.500 mmol). After stirring for 5 min, MeI (284 mg, 2.00 mmol) was added. The reaction flask was kept in an ice bath for 5 min and then the ice bath was removed. After stirring for another 1 h, the reaction was

quenched with NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:10) to give 49 mg compound **S42.3** (99%) as a colorless oil. $[\alpha]^{25}_D$ = +16.2 (c = 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 7.73 (m, 4H), 7.40 (m, 6H), 4.71 (d, 1H, J = 6.6 Hz) 4.61 (d, 1H, J = 6.6 Hz), 4.51 (d, 1H, J = 1.5 Hz), 4.11 (dd, 1H, J= 4.8, 10.5 Hz), 3.95 (dd, 2H, J= 3.9, 4.5 Hz), 3.85 (dd, 1H, J= 6.0, 8.4 Hz), 3.50 (s, 3H), 3.28 (m, 4H), 2.43 (d, 1H, J= 2.1 Hz) 1.07 (s, 9H), 1.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 136.0, 135.9, 133.3, 133.2, 130.0, 129.9, 128.0, 127.9, 97.5, 85.2, 80.7, 75.1, 74.2, 71.3, 63.0, 61.6, 56.0, 40.9, 27.05, 24.2, 19.3, 16.6; IR v max (neat) / cm^{-1} 3289, 3072, 3048, 1471, 1428, 1112. m/z (ESIMS) calculated for $C_{29}H_{40}O_5SiNa$ $[MNa]^+$ 519.25, found: 519.4.
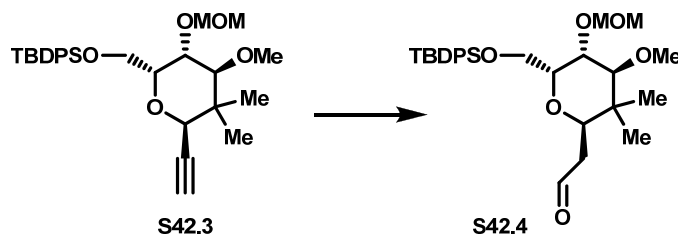
To a solution of BH_3/THF (0.3 mL, 1.0 M) at 0^oC was added 2-methyl-2-butene in THF (0.25 mL, 2.0 M). After stirring for 20 min, alkyne **S42.3** (33 mg, 0.066 mmol) in 1 mL THF was added. The reaction was kept at 0^oC for 30 min and then 0.2 mL 3 M NaOH solution and 0.2 mL H_2O_2 was added. After stirring for another 15 min at 0 ^oC, the reaction mixture was diluted with distilled water and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:8) to give 28 mg compound **S42.4** (82%) as a colorless oil. $[\alpha]^{25}_D$ = +16.7 (c = 0.30, $CHCl_3$); ^1H

NMR (400 MHz, CDCl$_3$) 9.78 (dd, 1H, J= 1.6, 2.4 Hz), 7.73 (m, 4H), 7.41 (m, 6H) 4.66

(d, 1H, J= 6.8 Hz), 4.53 (d, 1H, J= 6.8 Hz), 4.27 (dd, 1H, J= 2.8, 10.4 Hz), 4.08 (dd, 1H,

J=6.4, 11.2 Hz), 3.99 (td, 1H, J= 2.8, 6.8 Hz), 3.84 (m, 1H), 3.51 (s, 3H), 3.29 (d, 1H, J=

9.6 Hz), 3.17 (s, 3H), 2.46 (ddd, 1H, J= 2.8, 10.8, 16.0 Hz) 2.35 (m, 1H), 1.07 (s, 9H),

0.96 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) 202.4, 136.0, 135.9, 133.3,

133.2, 130.0, 129.9, 128.0, 127.9, 97.2, 85.5, 80.7, 75.6, 73.9, 62.4, 62.0, 55.8, 43.5, 31.8,

27.0, 23.5, 19.3, 14.7; IR v max (neat)/cm^{-1} 3068, 3043, 1728, 1471, 1427, 1112; m/z

(ESIMS) calculated for C$_{30}$H$_{45}$O$_7$SiNa [MNaMeOH]$^+$ 569.29, found: 569.4.
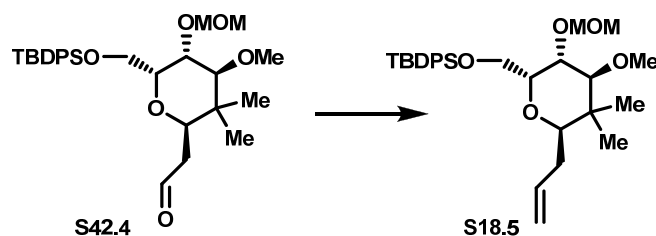
To a solution of Ph$_3$PCH$_3$Br (54 mg, 0.151 mmol) in 0.3 mL THF at 0 ^{o}C was added BuLi

in THF (0.05 mL, 2.5 M) dropwise. After stirring for 30 min, aldehyde **S42.4** (20 mg,

0.04 mmol) in 0.3 mL THF was added. The reaction was allowed to warm to room

temperature and stirred for 1.5 h, then it was quenched with NH4Cl solution and

extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and

concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl

acetate/hexane 1:8) to give 15 mg compound **S18.5** (75%) as colorless oil. [α]^{25}$_D$ = +16.7

(c = 0.38, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) 7.75 (m, 4H), 7.38 (m, 6H) 5.98 (m,1H),

5.11 (dd, 1H, J= 1.6, 17.2 Hz), 5.03 (d, 1H, J= 10.4 Hz), 4.60 (dd, 2H, J= 6.4, 50 Hz),

4.04 (dd, 1H, J= 6.4, 13.2 Hz), 3.84 (m, 1H), 3.71 (m, 1H), 3.50 (s, 3H), 3.18 (m, 4H),

2.18 (m, 2H), 1.06 (s, 9H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$)

137.3, 136.0, 136.0, 133.5, 133.4, 129.9, 129.8, 127.9, 127.8, 115.8, 97.2, 86.0, 78.1, 75.9, 62.2, 62.0, 55.7, 41.3, 33.8, 27.0, 23.6, 19.3, 14.3; IR v max (neat)/cm^{-1} 3072, 3048, 2888, 2855, 1638, 1471, 1427, 1389, 1360, 1147, 1112, 1037, 1021, 915, 825; m/z (ESIMS) calculated for $C_{30}H_{44}O_5SiNa$ [MNa]$^+$ 535.29, found: 535.4.
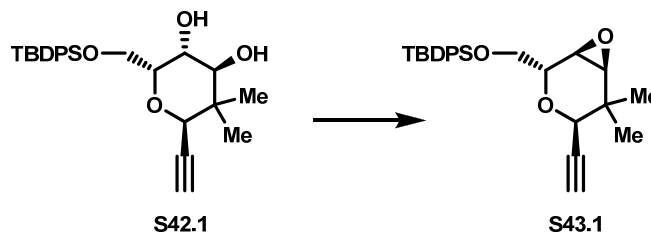
To a solution of diol **S42.1** (1.14 g, 2.6 mmol) in THF (20 mL, containing trace amount of water) at 0 $^{\circ}$C was added NaH (832 mg, 10.4 mmol, 60% dispersion in mineral oil) and the mixture was stirred for 10 min. To this was added a solution of TsCl in 6mL THF and 200 μl H_2O. After stirring for 30 min, the mixture was quenched with saturated NH_4Cl, extracted with CH_2Cl_2 and dried over Na_2SO_4. Solvent was removed and then the crude was purified by FCC using hexane/ethyl acetate (20:1) as eluent to furnish epoxide **S43.1** (760 mg, 70%) as a colorless oil. $[\alpha]^{25}_D$ = -8.9 (c = 1.23, CHCl$_3$); IR v_{max}(neat)/cm^{-1} 3285, 3071, 2960, 2930, 1471, 1427, 1113, 702; ^{1}H NMR (400 MHz, CDCl$_3$) 7.71-7.68 (4H, m), 7.50-7.40 (6H, m), 4.26 (1H, t, J= 4.4 Hz), 4.20 (1H, 2.4 Hz), 3.95-3.87 (1H, m), 3.38 (1H, d, J= 4.0 Hz), 3.00 (1H, d, J= 4.0 Hz), 2.51 (1H, d, J= 2.4 Hz), 1.24 (3H, s), 1.18 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz) 135.6, 133.1, 129.9, 127.8, 80.1, 75.7, 70.7, 70.2, 64.9, 58.4, 53.1, 33.4, 26.8, 24.2, 21.6, 19.2; m/z (ESIMS) calculated for $C_{26}H_{32}O_3Si$ Na [MNa]$^+$ 443.20, found: 443.3.

S43.1 → S43.2
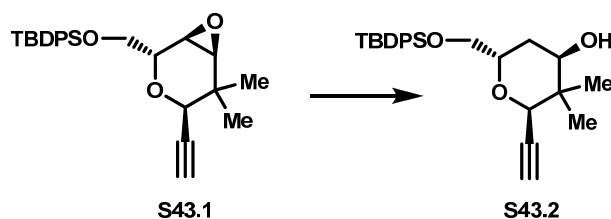
To a solution of epoxide **S43.1** (0.61 mg, 1.45 mmol) in Et$_2$O (10 mL) at 0 $^{\circ}$C was added

DIBAL (4.35 mL, 4.35 mmol) at one portion. After 10 min, the reaction mixture was

quenched with saturated Rochelle's salt and diluted with Et$_2$O. The resulting biphasic

solution was stirred for 1 h. The layers were separated, and then the aqueous layer was

extracted with Et$_2$O and dried over Na$_2$SO$_4$. Solvent was concentrated in vacuo and the

crude was purified by FCC using hexane/ethyl acetate (10:1) as eluent to afford alcohol

S43.2 (489 mg, 80%) as a colorless oil. $[\alpha]^{25}_D$ = +2.44 (c = 0.41, CHCl$_3$); IR

ν_{max}(neat)/cm^{-1} 3454, 3285, 3070, 2957, 2930, 1472, 1427, 1112, 702; ^{1}H NMR (400

MHz, CDCl$_3$) 7.69-7.67 (4H, m), 7.41-7.38 (6H, m), 4.40-4.20 (2H, m), 3.75 (2H, d, J=

4.8 Hz), 2.60-2.59 (1H, m), 2.38 (1H, d, J= 8.4 Hz), 2.04-1.97 (1H, m), 1.71-1.66 (1H,

m); m/z (ESIMS) calculated for C$_{26}$H$_{34}$O$_3$SiNa [MNa]$^+$ 445.22, found: 445.3.

S43.2 → S43.3
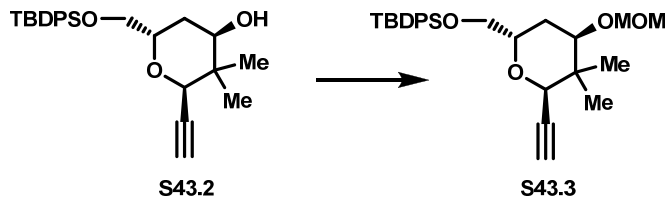
To a solution of alcohol **S43.2** (360 mg, 0.85 mmol) in DMF (10 mL) at 0 $^{\circ}$C was added

Hunig's base (1.5 mL, 8.53 mmol) followed by MOMCl (0.65 mL, 8.53 mmol). The

reaction mixture was stirred for 24 h at room temperature, and then quenched with

saturated NH$_4$Cl solution. The resulting mixture was extracted with CH$_2$Cl$_2$. The organic

layers were washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated under reduced

pressure under reduced pressure in vacuo. The crude was purified by FCC using ethyl acetate/hexane (1:20) to give product **S43.3** as a colorless oil (390 mg, 97%). $[\alpha]^{25}_D$ = +0.91 (c = 1.10, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3288, 3071, 2949, 2930, 1472, 1428, 1042, 702; ^{1}H NMR (400 MHz, CDCl$_3$) 7.70-7.67 (4H, m), 7.41-7.39 (6H, m), 4.70 (1H, d, J= 6.8 Hz), 4.60 (1H, d, J= 7.2 Hz), 4.22-4.18 (2H, m), 3.74 (2H, J= 9.2 Hz), 3.55-3.52 (1H, m), 3.38 (3H, s), 1.94-1.89 (2H, m), 1.10 (3H, s), 1.07 (9H, s), 1.06 (3H, s); ^{13}C NMR (100 MHz) 135.7, 133.4, 129.7, 127.7, 95.9, 81.3, 77.8, 74.0, 71.7, 70.4, 65.9, 55.5, 37.9, 28.3, 26.8, 24.7, 19.2, 18.8; m/z (ESIMS) calculated for C$_{28}$H$_{38}$O$_4$SiNa [MNa]$^+$ 489.24, found: 489.3.

To the 2-methyl-2-butene (2.30 mL of 2 M solution in THF, 4.60 mmol) cooled to 0 °C was added BH$_3$•SMe$_2$ (1.15 mL of 1M solution in THF, 2.30 mmol) dropwise. The ice-bath was removed and the mixture was stirred for 1 h. The reaction mixture was cooled to 0 °C, to which was added a solution of alkyne **S43.3** (356 mg, 0.76 mmol) in THF slowly. The mixture was stirred for 30 min at room temperature and cooled back to 0 °C. The reaction mixture was quenched with a precooled solution of 4 mL of 3N NaOH and 1.4 mL of 30% H$_2$O$_2$ dropwise. The resulting mixture was stirred for 30 min at room temperature, then and extracted with CH$_2$Cl$_2$. The organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure under reduced pressure in vacuo. The crude was purified by FCC using hexane/ethyl acetate (15:1) to furnish aldehyde **S43.4** (282 mg,

76%) as a colorless oil. $[\alpha]^{25}_D$ = +7.14 (c = 0.84, CHCl$_3$); IR ν_{max}(neat)/cm^{-1} 3071, 2949,

2931, 2888, 2857, 1728, 1472, 1428, 1112, 702; ^{1}H NMR (400 MHz, CDCl$_3$) 9.72 (1H,

dd, J= 1.6, 3.6 Hz), 4.68 (1H, d, J= 5.2 Hz), 4.59 (1H, d, J= 5.2 Hz), 4.04-3.96 (2H, m),

3.78-3.67 (2H, m), 2.85-2.77 (1H, m), 2.44 (1H, qd, J= 1, 17.6 Hz), 1.94-1.88 (1H, m),

1.81-1.74 (1H, m); ^{13}C NMR (100 MHz) 202.5, 135.6, 133.3, 129.7, 127.7, 95.9, 78.2,

75.0, 70.0, 65.5, 55.6, 43.4, 37.4, 28.2, 26.8, 24.4, 19.1, 17.0; *m/z* (ESIMS) calculated for

C$_{28}$H$_{40}$O$_5$SiNa [MNa]$^+$ 507.25, found: 507.3.
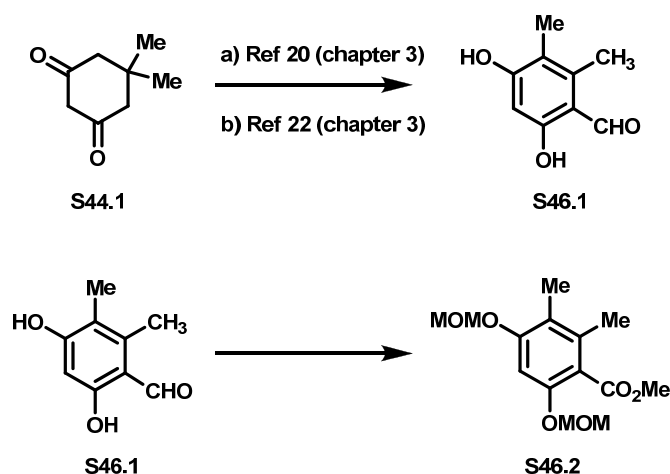
To a solution of aldehyde **S46.1** (1.65g, 9.96 mmol) in DMF (12 ml) at 0 ^{o}C was added

Hunig's base (5.2 ml, 29.9 mmol) and MOMCl (2.27 ml, 29.9 mmol). After stirring for

20 h at room temperature, the reaction mixture was quenched with saturated NH$_4$Cl and

then extracted with CH$_2$Cl$_2$. The extracts were dried over Na$_2$SO$_4$ and concentrated in

vacuo. The crude was passed through a pad of silica gel and used for next step without

further purification.

A solution of aldehyde (2.4 mg, 9.4 mmol) in 120 ml tBuOH-H$_2$O (1:1) was cooled to 0

^{o}C, to which was added NaH$_2$PO$_4$·H$_2$O (3.38 g, 28.2 mmol), 2-methyl-2-butene (12.1 ml

from 2 M solution in THF, 28.2 mmol) and NaClO$_2$ (3.18 g, 28.2 mmol). After stirring for 4 h, the mixture was concentrated down, extracted with EtOAc and dried over Na$_2$SO$_4$. The crude was passed through a pad of silica gel and used for next step without further purification.

A solution of acid (2.48 g, 9.2 mmol) in THF (25 ml) was treated with PPh$_3$ (4.82 g, 18.4 mmol) and MeOH (1.8 ml, 46 mmol) which was then cooled to 0 $^{\circ}$C. DIAD (3.72 g, 18.4 mmol) was added to reaction mixture. After stirring for 12 h, the mixture was diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The organic extracts were dried over Na$_2$SO$_4$ and concentrated down under reduced pressure. The crude was purified by FCC using hexane:ethyl acetate (10:1) as eluent to furnish ester **S46.2** (2.43 g, 86% over 3 steps) as yellowish oil. IR ν_{max}(neat)/cm^{-1} 2952, 2913, 2827, 1731, 1597, 1481, 1436, 1271, 1153, 923; ^{1}H NMR (400 MHz, CDCl$_3$) 6.77 (1H, s), 5.17 (2H, s), 5.13 (2H, s), 3.89 (3H, s), 3.46 (6H, s), 2.18 (3H, s), 2.11 (3H, s); ^{13}C NMR (100 MHz) 169.4, 156.5, 152.6, 135.6, 120.1, 119.5, 100.2, 95.3, 94.9, 56.4, 56.3, 52.3, 17.2, 11.6; *m/z* (ESIMS) calculated for C$_{14}$H$_{20}$O$_6$Na [MNa]$^+$ 307.2, found: 307.2.

Crystal structure of Spirodiepoxide
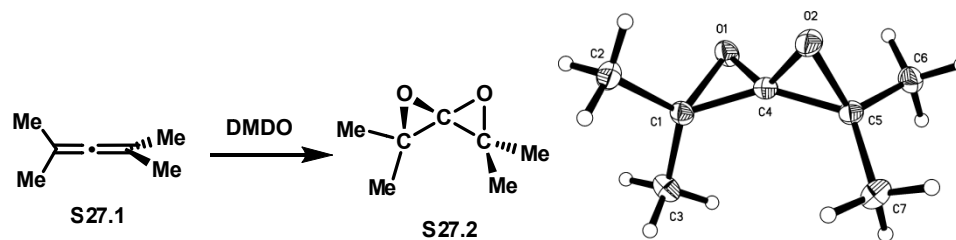
Empirical formula	C7 H12 O2	
Formula weight	128.17	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I4(1)/a	
Unit cell dimensions	a = 10.7367(6) Å	□ = 90°.
	b = 10.7367(6) Å	□ = 90°.
	c = 25.6705(15) Å	□ = 90°.
Volume	2959.2(8) Å^3	
Z	16	
Density (calculated)	1.151 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	1120	
Crystal size	.60 x .51 x .10 mm^3	
Theta range for data collection	2.06 to 30.50°.	

Index ranges	-15<=h<=14, -15<=k<=15, -36<=l<=36
Reflections collected	17976
Independent reflections	2270 [R(int) = 0.0280]
Completeness to theta = 30.50°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9999 and 0.8614
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2270 / 0 / 130
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1058
R indices (all data)	R1 = 0.0520, wR2 = 0.1128
Largest diff. peak and hole	0.503 and -0.150 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for spirodiepoxide. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6904(1)	5028(1)	806(1)	20(1)
O(2)	7527(1)	4403(1)	1695(1)	20(1)
C(1)	8314(1)	4994(1)	767(1)	16(1)
C(2)	8816(1)	3740(1)	621(1)	22(1)
C(3)	8875(1)	6102(1)	501(1)	22(1)
C(4)	7640(1)	5140(1)	1250(1)	15(1)
C(5)	7494(1)	5814(1)	1733(1)	16(1)
C(6)	6240(1)	6316(1)	1879(1)	22(1)
C(7)	8602(1)	6375(1)	1999(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for spirodiepoxide.

O(1)-C(4)	1.3934(10)	C(3)-H(3B)	0.962(16)
O(1)-C(1)	1.5168(10)	C(3)-H(3C)	0.946(14)
O(2)-C(4)	1.3932(10)	C(4)-C(5)	1.4440(12)
O(2)-C(5)	1.5177(10)	C(5)-C(7)	1.4975(12)
C(1)-C(4)	1.4455(12)	C(5)-C(6)	1.4986(12)
C(1)-C(3)	1.4978(12)	C(6)-H(6A)	0.959(14)
C(1)-C(2)	1.4981(12)	C(6)-H(6B)	0.944(16)
C(2)-H(2A)	0.961(14)	C(6)-H(6C)	0.974(14)
C(2)-H(2B)	0.959(17)	C(7)-H(7A)	0.960(15)
C(2)-H(2C)	0.976(14)	C(7)-H(7B)	0.960(17)
C(3)-H(3A)	0.952(14)	C(7)-H(7C)	0.963(13)
C(4)-O(1)-C(1)	59.38(5)	O(1)-C(4)-C(5)	133.29(7)
C(4)-O(2)-C(5)	59.30(5)	O(2)-C(4)-C(1)	133.25(7)
C(4)-C(1)-C(3)	120.41(8)	O(1)-C(4)-C(1)	64.56(6)
C(4)-C(1)-C(2)	119.46(8)	C(5)-C(4)-C(1)	147.79(7)
C(3)-C(1)-C(2)	117.10(8)	C(4)-C(5)-C(7)	120.46(8)
C(4)-C(1)-O(1)	56.05(5)	C(4)-C(5)-C(6)	119.47(8)
C(3)-C(1)-O(1)	114.37(7)	C(7)-C(5)-C(6)	117.06(8)
C(2)-C(1)-O(1)	113.42(7)	C(4)-C(5)-O(2)	56.05(5)
C(1)-C(2)-H(2A)	108.6(8)	C(7)-C(5)-O(2)	114.41(7)
C(1)-C(2)-H(2B)	110.0(8)	C(6)-C(5)-O(2)	113.37(7)
H(2A)-C(2)-H(2B)	107.2(12)	C(5)-C(6)-H(6A)	108.9(8)
C(1)-C(2)-H(2C)	111.3(8)	C(5)-C(6)-H(6B)	110.5(8)
H(2A)-C(2)-H(2C)	109.5(11)	H(6A)-C(6)-H(6B)	106.5(12)
H(2B)-C(2)-H(2C)	110.1(12)	C(5)-C(6)-H(6C)	110.9(8)
C(1)-C(3)-H(3A)	110.0(8)	H(6A)-C(6)-H(6C)	110.3(11)
C(1)-C(3)-H(3B)	110.0(9)	H(6B)-C(6)-H(6C)	109.6(11)
H(3A)-C(3)-H(3B)	110.7(12)	C(5)-C(7)-H(7A)	109.8(8)
C(1)-C(3)-H(3C)	108.5(9)	C(5)-C(7)-H(7B)	110.0(9)
H(3A)-C(3)-H(3C)	109.6(12)	H(7A)-C(7)-H(7B)	111.4(13)
H(3B)-C(3)-H(3C)	108.0(12)	C(5)-C(7)-H(7C)	108.2(8)
O(2)-C(4)-O(1)	124.93(7)	H(7A)-C(7)-H(7C)	109.6(12)
O(2)-C(4)-C(5)	64.65(6)	H(7B)-C(7)-H(7C)	107.8(12)

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for spirodiepoxide. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\,h^2\,a^{*2}U^{11} + \dots + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	12(1)	30(1)	18(1)	-3(1)	-1(1)	-1(1)
O(2)	29(1)	12(1)	18(1)	1(1)	2(1)	-1(1)
C(1)	12(1)	19(1)	17(1)	-1(1)	-1(1)	0(1)
C(2)	21(1)	21(1)	24(1)	-7(1)	2(1)	1(1)
C(3)	18(1)	24(1)	24(1)	5(1)	4(1)	1(1)
C(4)	14(1)	14(1)	17(1)	1(1)	-1(1)	-1(1)
C(5)	19(1)	12(1)	17(1)	1(1)	1(1)	0(1)
C(6)	21(1)	21(1)	24(1)	-2(1)	6(1)	0(1)
C(7)	23(1)	19(1)	24(1)	-4(1)	-5(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for spirodiepoxide.

	x	y	z	U(eq)
H(2A)	9702(13)	3741(13)	676(6)	30(3)
H(2B)	8678(13)	3586(13)	258(7)	32(3)
H(2C)	8436(13)	3081(13)	829(6)	31(3)
H(3A)	8498(13)	6847(13)	626(6)	31(3)
H(3B)	8775(13)	6031(13)	130(6)	30(3)
H(3C)	9738(13)	6118(13)	575(6)	29(3)
H(6A)	6238(13)	7201(13)	1827(5)	27(3)
H(6B)	6081(13)	6184(13)	2237(6)	30(3)
H(6C)	5586(12)	5928(13)	1672(5)	29(3)
H(7A)	9352(13)	5997(13)	1871(6)	33(4)
H(7B)	8527(14)	6279(14)	2370(7)	34(4)
H(7C)	8612(12)	7254(13)	1924(5)	26(3)

Table 6. Torsion angles [°] for spirodiepoxide.

C(4)-O(1)-C(1)-C(3)	-111.40(8)
C(4)-O(1)-C(1)-C(2)	110.76(8)
C(5)-O(2)-C(4)-O(1)	-126.48(9)
C(5)-O(2)-C(4)-C(1)	147.10(10)
C(1)-O(1)-C(4)-O(2)	-126.39(9)
C(1)-O(1)-C(4)-C(5)	147.04(10)
C(3)-C(1)-C(4)-O(2)	-144.50(9)
C(2)-C(1)-C(4)-O(2)	15.23(13)
O(1)-C(1)-C(4)-O(2)	115.03(10)
C(3)-C(1)-C(4)-O(1)	100.47(8)
C(2)-C(1)-C(4)-O(1)	-99.80(8)
C(3)-C(1)-C(4)-C(5)	-31.55(18)
C(2)-C(1)-C(4)-C(5)	128.19(13)
O(1)-C(1)-C(4)-C(5)	-132.02(15)
O(2)-C(4)-C(5)-C(7)	100.49(8)
O(1)-C(4)-C(5)-C(7)	-144.42(9)
C(1)-C(4)-C(5)-C(7)	-31.59(18)
O(2)-C(4)-C(5)-C(6)	-99.72(8)
O(1)-C(4)-C(5)-C(6)	15.37(13)
C(1)-C(4)-C(5)-C(6)	128.20(13)
O(1)-C(4)-C(5)-O(2)	115.09(10)
C(1)-C(4)-C(5)-O(2)	-132.08(15)
C(4)-O(2)-C(5)-C(7)	-111.44(8)
C(4)-O(2)-C(5)-C(6)	110.80(8)

CHAPTER 4
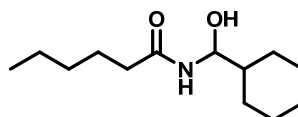
S64.3

To a solution of hexanamide (75mg, 0.65 mmol) in 3 mL Et$_2$O was added NEt$_3$ (101 mg, 1.0 mmol) and the mixture was cooled to 0 °C. To this was added Cy$_2$BCl in hexane (0.75 mmol, 1.0 M) in one portion. After stirring at this temperature for 30 min, aldehyde (56 mg, 0.5 mmol) was added dropwise to the reaction mixture. The mixture was stirred for 30 min and quenched with MeOH, phosphate buffer (pH=7.4) and 30% H$_2$O$_2$. The resulting mixture was stirred for 30 min and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3) to give **S64.3** (100.6 mg, 88%) as white solid. IR v max (neat)/cm^{-1} 3246, 3068, 1645, 1553, 1026; ^{1}H NMR (300MHz, CDCl$_3$) 6.28 (d, 1H, J= 7.8 Hz), 5.06 (dd, 1H, J=7.8, 7.5Hz), 4.27 (br, 1H) 2.16 (t, 1H, J= 7.5Hz), 0.98-1.89 (m, 17H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75MHz, CDCl$_3$) 174.5, 77.7, 42.5, 37.1, 31.8, 28.5, 28.4, 26.6, 26.1, 26.0, 25.6, 22.7, 14.3; m/z (ESIMS) calculated for C$_{13}$H$_{25}$NO$_2$Na [MNa]$^+$ 250.18, found: 250.2.
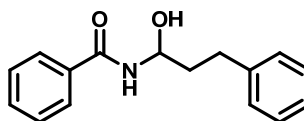
S65.2

A solution of benzamide (73 mg, 0.6 mmol) was treated with NEt$_3$ (0.140 ml, 1.0 mmol) and cooled to 0 °C. To this was added Cy$_2$BCl (0.65 mmol, 1M in Hexane), and then the

mixture was stirred for 30 min at room temperature. Then aldehyde (0.074 ml, 0.5 mmol) was added to reaction mixture. After the mixture was stirred for 30 min, the regular workup was applied. The crude product was purified by FCC (silica gel, hexane/ethyl acetate 2/1) to yield 90 mg (71%) of **S65.2** as a white solid. IR v max (neat)/cm^{-1} 3415, 3328, 3313, 3055, 3029, 2963, 2946, 1643, 1527, 1029; ^{1}H NMR (400MHz, CDCl$_3$) 7.61-7.59 (2H, m), 7.53-7.48 (1H, m), 7.42-7.39 (2H, m), 7.34-7.30 (2H, m), 7.27-7.22 (3H, m), 6.57-6.55 (1H, d, J=6.4), 5.55-5.50 (1H, m), 3.88 (1H, d, J=2.8), 2.97-2.90 (1H, m), 2.83-2.76 (1H, m), 2.20-2.01 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) 168.5, 141.2, 133.6, 132.2, 128.9, 128.8, 128.7, 127.1, 126.4, 75.0, 36.4, 31.1; m/z (ESIMS) calculated for C$_{16}$H$_{17}$NO$_2$Na [MNa]$^{+}$ 278.12, found: 278.0.

S65.4
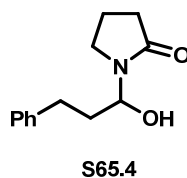
A solution of amide (204 mg, 2.4 mmol) was treated with NEt$_3$ (0.42 ml, 3.0 mmol) and cooled to 0 ^{o}C. To this was added Cy$_2$BCl (2.4 mmol, 1M in Hexane), and then the mixture was stirred for 30 min at room temperature. Then aldehyde (0.293 ml, 2.0 mmol) was added to reaction mixture. After the mixture was stirred for 30 min, the regular workup was applied. The crude product was purified by FCC (silica gel, hexane/ethyl acetate 2/1) to yield 381 mg (87 %) of **S65.4** as colorless oil. IR v max (neat)/cm^{-1} 3348, 3026, 2951, 2917, 1667, 1494, 1422. 1289; ^{1}H NMR (400MHz, CDCl$_3$) 7.29-7.26 (2H, m), 7.21-7.16 (3H, m), 5.52-5.48 (1H, m), 4.04 (1H, d, J=4.4), 3.58-3.52 (1H, m), 3.32-3.26 (1H, m), 2.80-2.73 (1H, m), 2.63-2.55 (1H, m), 2.42-2.28 (2H, m), 2.11-1.18 (4H, m); ^{13}C NMR (100 MHz, CDCl$_3$) 176.4, 141.3, 128.68, 128.61, 126.2, 75.19, 42.01, 35.2,

32.0, 31.8, 18.3; *m/z* (ESIMS) calculated for $C_{13}H_{17}NO_2Na$ [MNa]$^+$ 242.12, found: 242.0.
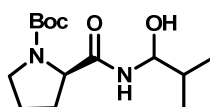
S65.3

A solution of amide (170 mg, 0.79 mmol) was treated with NEt₃ (0.180 ml, 0.158 mmol)
and cooled to 0 °C. To this was added Cy₂BCl (0.85 mmol, 1M in Hexane), and then the
mixture was stirred for 30 min at room temperature. Then aldehyde (170 mg, 0.66 mmol)
was added to reaction mixture. After the mixture was stirred for 30 min, the regular
workup was applied. The crude product was purified by FCC (silica gel, hexane/ethyl
acetate 2/1) to yield 150 mg (79%) of **S65.3** as a white solid. IR *v* max (neat)/cm^{-1} 3426,
3301, 2973, 2931, 2880, 1670, 1547, 1415, 1165; ^{1}H NMR (500MHz, CDCl₃) 7.83-7.71
(1H, m), 5.08-5.05 (2H, m), 4.30-4.20 (2H, m), 3.46-3.25 (6H, m), 2.50- 1.80 (10H, m),
1.47 (18H, s), 1.00-0.94 (12H, m); ^{13}C NMR (125 MHz, CDCl₃) 173.337, 173.336,
156.359, 156.351, 80.889, 80.876, 78.728, 78.728, 59.975, 59.945, 47.384, 47.295,
32.665, 32.665, 28.567, 28.567, 27.906, 27.251, 24.774, 23.979, 17.724, 17.612; *m/z*
(ESIMS) calculated for $C_{14}H_{26}N2O_4Na$ [MNa]$^+$ 309.18, found: 309.1.
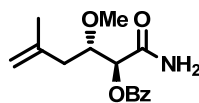
S66.2

A solution of α-hydroxycarboxylic acid (275 mg, 1.58 mmol) in CH₂Cl₂ (10 ml) was
cooled to 0 °C and treated with BzCl (0.37 ml, 3.16 mmol) and pyridine (0.32 ml, 3.95
mmol). After stirring for 1 h, the reaction was quenched with saturated NH₄Cl solution

and acidified with 3N HCl until pH 2-3. The mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. After removing the solvent in vacuo, the residue was purified by FCC (50% hexane:ethyl acetate and 1% AcOH) to furnish 350 mg (80%) a benzoyl protected carboxylic acid as a colorless oil.

To a solution of benzoyl protected carboxylic acid (290 mg, 1.04 mmol) in toluene (10 ml) was added oxallyl chloride (0.272 ml, 3.12 mmol) and catalytic amount DMF. After stirring for 20 min at room temperature, the mixture was cooled to -78 ^{o}C and exposed to NH_3 gas for 2 min. Stirring continued for 10 min and then the reaction was quenched with 3N HCl until pH 2-3. The mixture was extracted with CH_2Cl_2 (5×), and the combined organic extract was washed with brine and dried over Na_2SO_4. After removing the solvent in vacuo, the residue was purified by FCC using hexane:ethyl aceate (3:1) as eluate to furnish 220 mg (80%) S66.2 as a colorless oil. IR v max (neat)/cm^{-1} 3448, 3334, 3182, 3074, 2978, 2936, 1727, 1692, 1600, 1451, 1267, 1111; ^{1}H NMR (500MHz, CDCl$_3$) 8.09-8.07 (2H, m), 7.63-7.60 (1H, m), 7.50-7.47 (2H, m), 6.22 (1H, brs), 5.98 (1H, brs), 5.74 (1H, d, J=3.5), 4.86 (1H, s), 4.83 (1H, s), 3.46 (3H, s), 2.47-2.36 (2H, m), 1.80 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) 170.7, 165.2, 141.9, 133.9, 130.0, 129.3, 128.9, 113.9, 79.9, 73.4, 58.3, 38.6, 22.8; m/z (ESIMS) calculated for $C_{14}H_{26}N2O_4Na$ [MNa]$^+$ 309.18, found: 309.1. m/z (ESIMS) calculated for $C_{15}H_{19}NO_4Na$ [MNa]$^+$ 300.12, found: 299.4.
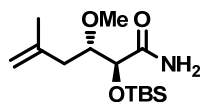
S66.3

To a solution of α-hydroxylamide (60 mg, 0.34 mmol) in DMF (4 ml) was added TBSCl

(102.6 mg, 0.68 mmol) and DMAP (83 mg, 0.68 mg). After stirring for 1 h, the reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. After removing the solvent in vacuo, the residue was purified by FCC using hexane:ethyl aceate (1:1) as eluate to furnish 94 mg (96%) **S66.2** as a colorless oil. IR v max (neat)/cm^{-1} 3467, 3264, 3141, 2953, 2932, 1694, 1657, 1252, 1109; ^{1}H NMR (400MHz, CDCl$_3$) 6.53 (1H, brs), 6.11 (1H, brs), 4.69 (1H, s), 4.65 (1H, s), 3.57-3.56 (1H, m), 3.29 (3H, s), 2.23-2.17 (1H, m), 2.01- 1.96 (1H, m), 1.64 (3H, s), 0.83 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) 175.3, 142.6, 112.7, 81.9, 74.1, 58.0, 37.6, 26.0, 22.8, 18.3, -4.3, -5.3; m/z (ESIMS) calculated for $C_{14}H_{29}NO_3NaSi$ [MNa]$^+$ 310.18, found: 310.2.
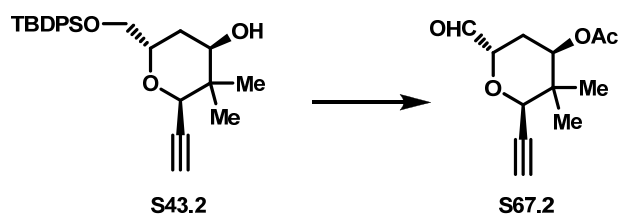
To a solution of alcohol (110 mg, 0.26 mmol) in pyridine (5 ml) was added Ac$_2$O (0.5 ml, 5.2 mmol) at rt. After 12 h, the mixture was quenched with saturated NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined organic extracts were washed with 1 N HCl solution and dried over Na$_2$SO$_4$. The crude was passed through a pad of silica gel and used for next step without further purification.

A solution of acetate protected alcohol (118 mg, 0.25 mmol) in THF (3 ml) was treated with TBAF (1.00 mmol, 1.0 M in THF) at rt. The reaction mixture was quenched with H$_2$O after 3 h, and extracted with CH$_2$Cl$_2$. The organic extracts were dried over Na$_2$SO$_4$ and concentrated down under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3) to give **S67.2** (53 mg, 90%, over 2 steps) as colorless oil.

To a solution of oxallyl chloride (33 ml, 0.37mmol) in CH_2Cl_2 (1 ml) at -78 °C was added

DMSO (53.0 ml, 0.75 mmol) slowly. After stirring for 15 min at that temperature, a

solution of alcohol (56.0 mg, 0.25 mmol) in CH_2Cl_2 was injected to the mixture. After 20

min, NEt_3 (173 ml, 1.25 mmol) was added to reaction mixture. Stirring continued at -78

°C for 5 min, and then ice-bath was removed. After stirring at rt for 20 min, the mixture

was quenched with sat NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 and

dried over Na_2SO_4. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3)

to give **S67.2** (40 mg, 70%) as colorless oil. IR v max (neat)/cm^{-1} 3283, 2925, 2854,

2103, 1736, 1456, 1243.6; ^1H NMR (500 MHz, CDCl$_3$) 9.74 (1H, s), 4.76 (1H, dd, J=6.5,

3.5 Hz), 4.53 (1H, dd, J=8.5, 4.5 Hz), 4.28 (1H, d, J=2.5 Hz), 4.28 (3H, s), 2.55 (1H, d,

J=2.5 Hz), 2.09 (3H, s), 2.08-2.05 (1H, m), 1.94-1.90 (1H, m), 1.08 (6H, s); ^{13}C NMR

(125 MHz, CDCl$_3$) 201.5, 170.3, 79.6, 75.8, 74.8, 72.8, 72.8, 37.4, 26.5, 24.3, 21.1, 19.2;

m/z (ESIMS) calculated for $C_{12}H_{16}O_4Na$ [MNa]$^+$ 247.2, found: 247.1.

A solution of **S67.1** (70 mg, 0.17 mmol) in EtOAc (2 ml) was treated with catalytic

amount of Pd-C and then stirred for 10 min under hydrogen gas. The mixture was filtered

through celite. The crude was passed through a pad of silica gel and used for next step

without further purification.

A solution of TBDPS protected pyran ring in THF (3 ml) was treated with TBAF and

stirred for 3 h. The reaction was diluted with water and extracted with CH_2Cl_2. The

extracts were dried over Na_2SO_4. After removal of solvent, the residue was purified by FCC (silica gel, ethyl acetate/hexane 1:4) to give 35 mg compound (88%, over 2 steps) as colorless oil.

To a solution of oxallyl chloride (0.021 ml, 0.23 mmol) in CH_2Cl_2 (1 ml) at -78 °C was added DMSO (0.033 ml, 0.47 mmol) slowly. After stirring for 15 min at that temperature, a solution of alcohol (35.0 mg, 0.15 mmol) in CH_2Cl_2 was injected to the mixture. After 20 min, NEt_3 (0.173 ml, 1.25 mmol) was added to reaction mixture. Stirring continued at -78 °C for 5 min, and then ice-bath was removed. After stirring at rt for 20 min, the mixture was quenched with sat NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3) to give **S67.4** (23.5 mg , 68%) as colorless oil. IR v max (neat)/cm^{-1} 2969, 2929, 2876, 1745, 1728, 470, 1368, 1235, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) 9.80 (1H, s), 4.53 (1H, dd, J=11.4, 4.8), 4.26 (1H, dd, J=6.9, 2.4), 3.10, (1H, dd, J=9.6, 2.7), 2.28 (1H, dd, J=13.2, 2.4), 2.06 (3H, s), 1.91-1.81 (1H, m), 1.40-1.50 (2H, m), 1.06 (3H. t, J=9.6), 0.93 (3H, s), 0.81 (3H, s); 203.7, 170.4, 83.6, 74.1, 37.9, 25.9, 23.0, 22.0, 21.2, 13.9, 11.7; m/z (ESIMS) calculated for $C_{12}H_{20}O_4Na$ [MNa]$^+$ 251.1, found: 251.1
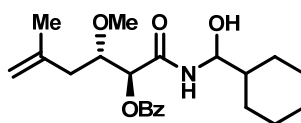
S68.1

To a solution of amide (100.0 mg, 0.35 mmol), in 3 ml of Et_2O was added NEt_3 (100 ml, 0.70 mmol) and the mixture was cooled to 0 °C. To this was added Cy_2BCl in hexane (0.52 mmol, 1.0 M) in one portion. After stirring at 0 °C for 30 min, aldehyde (32.5 mg, 0.29 mmol) was added to the reaction mixture. The mixture was stirred for 30 min and

quenched with MeOH, phosphate buffer (pH=7.4) and 30% H_2O_2. The resulting mixture was stirred for 30 min and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3) to give product (74 mg, 66%, dr=1:1 determined by HNMR).

Isomer A; IR v max (neat)/cm^{-1} 3433, 3358, 3073, 2927, 2853, 1728, 1671, 1520, 1451, 1263, 1111, 711; ^{1}H NMR (500MHz, CDCl$_3$) 8.08 (2H, d, J=7.5 Hz), 7.63 (1H, t, J=7.5 Hz), 7.50 (2H, t, J=7.5 Hz), 6.76 (1H, d, J=7.5 Hz), 5.66 (1H, d, J=4.0 Hz), 5.12 (1H, t, J=7.5 Hz), 4.86 (1H, s), 4.83 (1H, s), 3.97-3.94 (1H, m), 3.46 (3H, s), 3.45 (1H, bs), 2.44-2.38 (2H , m), 1.82-1.63 (7H, m), 1.25-0.96 (7H, m); ^{13}C NMR (125 MHz, CDCl$_3$) 169.4, 165.2, 141.8, 134.0, 130.0, 129.2, 128.9, 113.7, 79.9, 77.8, 73.8, 58.3, 42.1, 38.7, 28.09, 28.02, 26.4, 25.84, 25.78, 22.9; m/z (ESIMS) calculated for $C_{13}H_{25}NO_2Na$ [MNa]$^+$ 412.1, found: 412.1.

Isomer B; IR v max (neat)/cm^{-1} 3427, 3369, 3073, 2928, 2853, 1727.6, 1673, 1527, 1451, 1265, 1114, 710; ^{1}H NMR (500MHz, CDCl$_3$) 8.07 (2H, d, J=7.5 Hz), 7.63 (1H, t, J=7.5 Hz), 7.50 (2H, t, J=7.5 Hz), 6.79 (1H, d, 8 Hz), 5.66 (1H, d, J=4 Hz), 5.15 (1H, t, J=7.5 Hz), 4.85 (1H, s), 4.82(1H, s), 3.95-3.92 (1H, m), 3.46 (3H, s), 3.36 (1H, bs), 2.43-2.32 (2H, m), 1.86-1.66 (7 H, m), 1.28-1.04 (7H, m); ^{13}C NMR (125 MHz, CDCl$_3$) 169.2, 165.1, 141.8, 133.9, 130.0, 129.2, 128.9, 113.7, 79.9, 77.8, 73.7, 58.4, 42.2, 38.8, 28.16, 28.11, 26.4, 25.92, 25.82, 22.9; m/z (ESIMS) calculated for $C_{13}H_{25}NO_2Na$ [MNa]$^+$ 412.1, found: 412.1.

S68.2
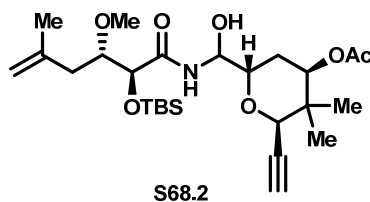
To a solution of **S66.3** (17.5 mg, 0.06 mmol) in 1 ml of Et$_2$O was added NEt$_3$ (14 ml, 0.10 mmol) the mixture was cooled to 0 ^{o}C. To this was added Cy$_2$BCl in hexane (0.075 ml, 1.0 M) in one portion. After stirring at 0 ^{o}C for 30 min, a solution of **S67.2** (10 mg, 0.04 mmol) in 0.4 ml of Et$_2$O was added to the reaction mixture. The mixture was stirred for 30 min at room temperature and quenched with MeOH, phosphate buffer (pH=7.4) and 30% H$_2$O$_2$. The resulting mixture was stirred for 30 min and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:5) to give product (8 mg, 40%, dr; 1:1 by HNMR).

Isomer A; ^{1}H NMR (500MHz, CDCl$_3$) 7.60 (1H, brs), 5.27-5.23 (1H, m), 4.90-4.89 (1H, m), 4.80 (1H, s), 4.77 (1H, s), 4.39 (1H, d, J=2.0 Hz), 4.24-4.20 (2H, m), 3.77 (1H, d, J=4.5 Hz), 3.71-3.68 (1H, m), 3.41 (3H, s), 2.50 (1H, d, J=2.0 Hz), 2.32-2.28 (2H, m), 2.09 (3H, s), 1.87-1.85 (2H, m), 1.75 (3H, s), 1.14 (3H, s), 1.04 (3H, s), 0.96 (9H, s), 0.16 (3H, s), 0.11 (3H, s).

Isomer B; ^{1}H NMR (500MHz, CDCl$_3$) 7.81(1H, brs), 5.28-5.25 (1H, m), 4.95-4.94 (1H, m), 4.79 (1H, s), 4.76 (1H, s), 4.40 (1H, d, J=2.0 Hz), 4.40 (1H, d, J=1.5 Hz), 4.33 (1H, d, J= 2.0 Hz), 4.15 (1H, d, J=11 Hz), 3.72-3.69 (1H, m), 3.41(3H, s), 3.09 (1H, d, J=6.0 Hz), 2.46 (1H, d, J=2.0 Hz), 2.33-2.28 (1H, m), 2.24-2.18 (1H, m), 2.09 (3H, s), 1.74 (3H, s), 1.68 (3H, s), 1.04 (3H ,s), 0.98 (3H, s), 0.16 (3H, s), 0.12 (3H, s).

(S68.3)
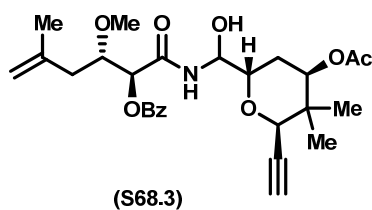
To a solution of **S66.2** (36.5 mg, 0.13 mmol) in 1 ml of Et$_2$O was added NEt$_3$ (14 ml, 0.10 mmol) the mixture was cooled to 0 ^{o}C. To this was added Cy$_2$BCl in hexane (0.075 ml, 1.0 M) in one portion. After stirring at 0 ^{o}C for 30 min, a solution of **S67.2** (20 mg, 0.09 mmol) in 0.4 ml of Et$_2$O was added to the reaction mixture. The mixture was stirred for 30 min at room temperature and quenched with MeOH, phosphate buffer (pH=7.4) and 30% H$_2$O$_2$. The resulting mixture was stirred for 30 min and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:5) to give a mixture of inseparable products (18 mg, 40%, dr; 1:1 by HNMR).

(S68.4)
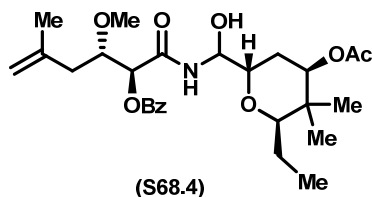
To a solution of **S66.2** (11.0 mg, 0.063 mmol) in 1 ml of Et$_2$O was added NEt$_3$ (14 ml, 0.10 mmol) the mixture was cooled to 0 ^{o}C. To this was added Cy$_2$BCl in hexane (0.075 ml, 1.0 M) in one portion. After stirring at 0 ^{o}C for 30 min, a solution of **S67.4** (20 mg, 0.09 mmol) in 0.4 ml of Et$_2$O was added to the reaction mixture. The mixture was stirred for 30 min at room temperature and quenched with MeOH, phosphate buffer (pH=7.4) and 30% H$_2$O$_2$. The resulting mixture was stirred for 30 min and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced

pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:5) to give a mixture of inseparable products (9 mg, 40%, dr; 2:1 by HNMR).

CHAPTER 5

General procedure for thionoesters:

A solution of thiobenzoic acid in CH_2Cl_2 (~0.2 M) was treated with NEt_3 and then cooled to 0 °C. This mixture was charged with TMSOTf and stirred for 10 min in ice bath. Then, $FeCl_3$, a base (if necessary) and an azide was added. The mixture was stirred for indicated time at room temperature, quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The extractions were dried over Na_2SO_4 and evaporate under vacuum. The crude was purified by FCC using Hex to give the corresponding amide product.

Genereal procedure for thioacids:

A solution of thioacid in CH_2Cl_2 (~0.2 M) was exposed to $FeCl_3$, a base (if necessary) and an azide and the mixture was stirred for indicated time at room temperature. The reaction quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The extractions were dried over Na_2SO_4 and evaporate under vacuum. The crude was purified by FCC to give the corresponding amide products.

Characterization of Side Products:

S79.1: m.p.= 41-42 °C. ^{1}H NMR (400 MHz, DMSO) 7.82-7.79 (2H, m), 7.70-7.66 (1H, m), 7.56-7.52 (2H, m), 7.37-7.23 (5H, m), 5.27 (1H, t, J= 4.8 Hz), 4.11 (2H, d, J=4.8 Hz). ^{13}C NMR (100 MHz, DMSO) 198.0, 139.8, 135.3, 134.4, 129.7, 128.7, 128.6, 127.6, 126.5, 55.1. IR v_{max} (KBr pellet, cm^{-1}) 3304, 3023, 2923, 2864, 2804, 1651, 1442.5, 1199, 1042, 907. *m/z* (ESIMS) calculated for $C_{14}H_{13}NOS$ [MH]$^+$ 244.07, found: 244.1.]

S79.2: m.p.= 108-109 °C. ^{1}H NMR (400 MHz, DMSO) 9.20 (1H, d, J=8.4 Hz), 7.98 (2H, d, J=7.2 Hz), 7.67-7.24 (18H, m), 6.57-6.55 (1H, d, J=8.4 Hz), 4.46 (2H, dd, J=70, 14 Hz). ^{13}C NMR (125 MHz, CHCl$_3$) 202.3, 166.9, 138.6, 137.6, 134.8, 134.3, 134.1, 131.9, 129.08, 129.04, 128.93, 128.91, 128.6, 128.5, 128.2, 127.7, 127.5, 127.2, 73.3, 60.0. IR ν_{max} (KBr pellet, cm^{-1}) 3328, 3056, 3025, 2917, 2857, 1658, 1595, 1575, 1511, 1479, 1203, 900. m/z (ESIMS) calculated for C$_{28}$H$_{24}$N$_2$O$_2$S [MNa]$^+$ 475.16, found: 475.2].

S79.3: m.p.= 158-160 °C. ^{1}H NMR (400 MHz, DMSO) 9.68 (1H, d, J=9.2 Hz), 7.94-7.89 (4H, m), 7.72-7.68 (1H, m), 7.58-7.32 (10H, m), 7.12 (1H, d, J=9.2 Hz). ^{13}C NMR (100 MHz, DMSO) 191.9, 166.3, 139.1, 136.7, 134.1, 132.2, 129.0, 128.9, 128.4, 127.70, 127.5, 127.52, 127.50, 127.0, 57.07. IR ν_{max} (KBr pellet, cm^{-1}) 3283, 3054, 2920, 1671, 1626, 1509, 1480, 1201, 903. m/z (ESIMS) calculated for C$_{21}$H$_{17}$NO$_2$S [MNa]$^+$ 370.1, found: 370.0].

All the azides in table 7 and Scheme 77 as well as the corresponding amides in table 7 are known compounds. The characterization data for the dimer **S78.1** were also reported in literature.

Crystal Structure: **S79.1**
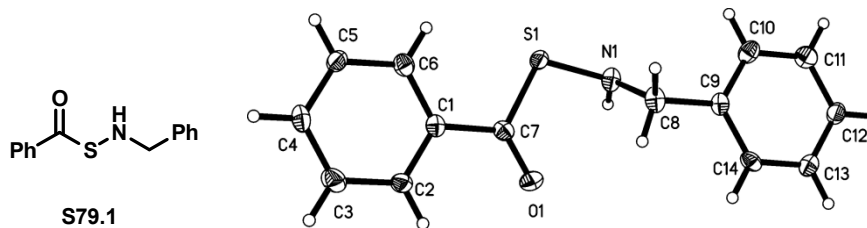
Empirical formula	C14 H13 N O S
Formula weight	243.31
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 8.0082(10) Å α = 90°.
	b = 5.3274(7) Å β = 96.577(2)°.
	c = 28.679(4) Å γ = 90°.
Volume	1215.5(3) Å^3
Z	4
Density (calculated)	1.330 Mg/m^3
Absorption coefficient	0.248 mm^{-1}
F(000)	512
Crystal size	0.41 x 0.27 x 0.03 mm^3
Theta range for data collection	2.56 to 30.54°.
Index ranges	-11<=h<=11, -7<=k<=7, -41<=l<=40

Reflections collected	13118
Independent reflections	3667 [R(int) = 0.0468]
Completeness to theta = 30.54°	98.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9999 and 0.6353
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3667 / 0 / 171
Goodness-of-fit on F^2	1.138
Final R indices [I>2sigma(I)]	R1 = 0.1508, wR2 = 0.3544
R indices (all data)	R1 = 0.1556, wR2 = 0.3564
Extinction coefficient	0.005(2)
Largest diff. peak and hole	1.270 and -1.695 e.Å^{-3}

Table. Preliminary bond lengths [Å] and angles [°] for **S79.1**.

S(1)-N(1)	1.664(5)	C(4)-H(4)	0.9300
S(1)-C(7)	1.770(6)	C(5)-C(6)	1.386(8)
N(1)-C(8)	1.469(8)	C(5)-H(5)	0.9300
N(1)-H(1)	0.87(7)	C(6)-H(6)	0.9300
O(1)-C(7)	1.210(7)	C(8)-C(9)	1.507(8)
C(1)-C(2)	1.391(8)	C(8)-H(8A)	0.9700
C(1)-C(6)	1.403(8)	C(8)-H(8B)	0.9700
C(1)-C(7)	1.492(8)	C(9)-C(14)	1.387(8)
C(2)-C(3)	1.388(8)	C(9)-C(10)	1.393(9)
C(2)-H(2)	0.9300	C(10)-C(11)	1.393(8)
C(3)-C(4)	1.381(9)	C(10)-H(10)	0.9300
C(3)-H(3)	0.9300	C(11)-C(12)	1.399(9)
C(4)-C(5)	1.382(9)	C(11)-H(11)	0.9300

C(12)-C(13)	1.389(9)	C(13)-H(13)	0.9300
C(12)-H(12)	0.9300	C(14)-H(14)	0.9300
C(13)-C(14)	1.395(8)		

N(1)-S(1)-C(7)	105.0(3)	N(1)-C(8)-H(8B)	109.7
C(8)-N(1)-S(1)	116.8(4)	C(9)-C(8)-H(8B)	109.7
C(8)-N(1)-H(1)	116(5)	H(8A)-C(8)-H(8B)	108.2
S(1)-N(1)-H(1)	107(4)	C(14)-C(9)-C(10)	119.1(5)
C(2)-C(1)-C(6)	119.9(5)	C(14)-C(9)-C(8)	119.7(5)
C(2)-C(1)-C(7)	119.0(5)	C(10)-C(9)-C(8)	121.2(6)
C(6)-C(1)-C(7)	121.1(5)	C(9)-C(10)-C(11)	120.6(6)
C(3)-C(2)-C(1)	119.8(6)	C(9)-C(10)-H(10)	119.7
C(3)-C(2)-H(2)	120.1	C(11)-C(10)-H(10)	119.7
C(1)-C(2)-H(2)	120.1	C(10)-C(11)-C(12)	120.1(6)
C(4)-C(3)-C(2)	120.4(6)	C(10)-C(11)-H(11)	120.0
C(4)-C(3)-H(3)	119.8	C(12)-C(11)-H(11)	120.0
C(2)-C(3)-H(3)	119.8	C(13)-C(12)-C(11)	119.2(6)
C(3)-C(4)-C(5)	120.0(6)	C(13)-C(12)-H(12)	120.4
C(3)-C(4)-H(4)	120.0	C(11)-C(12)-H(12)	120.4
C(5)-C(4)-H(4)	120.0	C(12)-C(13)-C(14)	120.4(6)
C(4)-C(5)-C(6)	120.7(6)	C(12)-C(13)-H(13)	119.8
C(4)-C(5)-H(5)	119.7	C(14)-C(13)-H(13)	119.8
C(6)-C(5)-H(5)	119.7	C(9)-C(14)-C(13)	120.6(5)
C(5)-C(6)-C(1)	119.3(6)	C(9)-C(14)-H(14)	119.7
C(5)-C(6)-H(6)	120.4	C(13)-C(14)-H(14)	119.7
C(1)-C(6)-H(6)	120.4	N(1)-C(8)-C(9)	109.8(5)
O(1)-C(7)-C(1)	122.4(6)	N(1)-C(8)-H(8A)	109.7
O(1)-C(7)-S(1)	121.2(5)	C(9)-C(8)-H(8A)	109.7
C(1)-C(7)-S(1)	116.3(4)		

Crystal Structure: **S79.2**
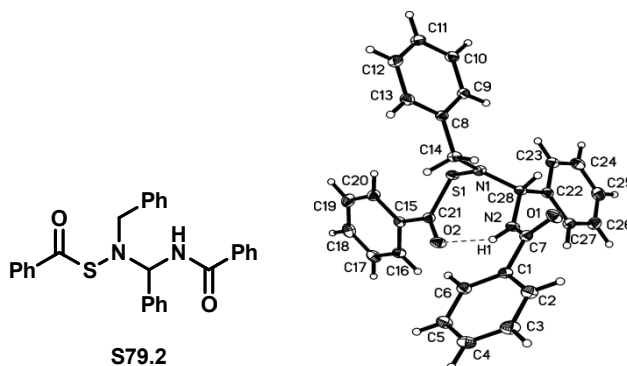
S79.2

Table 1. Crystal data and structure refinement for **S79.2**.

Empirical formula	C14 H12 N O S0.50
Formula weight	226.28
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.3486(7) Å $\square$ = 96.380(1)°.
	b = 10.9537(7) Å $\square$ = 114.609(1)°.
	c = 11.2778(7) Å $\square$ = 99.450(1)°.
Volume	1123.31(13) Å^3
Z	4
Density (calculated)	1.338 Mg/m^3
Absorption coefficient	0.173 mm^{-1}
F(000)	476
Crystal size	0.35 x 0.25 x 0.16 mm^3

Theta range for data collection	2.03 to 30.55°.
Index ranges	-14<=h<=14, -15<=k<=15, -16<=l<=15
Reflections collected	13384
Independent reflections	6761 [R(int) = 0.0170]
Completeness to theta = 30.55°	98.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9999 and 0.8445
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6761 / 0 / 394
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R1 = 0.0431, wR2 = 0.1067
R indices (all data)	R1 = 0.0487, wR2 = 0.1106
Largest diff. peak and hole	0.629 and -0.327 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Sezgin Side Product B. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4245(1)	6744(1)	2733(1)	15(1)
N(1)	4792(1)	7694(1)	4198(1)	14(1)
O(1)	7888(1)	9502(1)	7614(1)	22(1)
N(2)	7371(1)	8183(1)	5693(1)	15(1)
O(2)	6558(1)	5813(1)	3968(1)	21(1)
C(1)	9026(1)	7763(1)	7797(1)	15(1)
C(2)	10082(1)	8315(1)	9093(1)	20(1)
C(3)	10968(2)	7611(1)	9879(1)	24(1)

C(4)	10803(1)	6348(1)	9380(1)	23(1)
C(5)	9771(1)	5795(1)	8086(1)	21(1)
C(6)	8885(1)	6502(1)	7297(1)	17(1)
C(7)	8046(1)	8564(1)	7038(1)	15(1)
C(8)	2564(1)	7238(1)	4556(1)	14(1)
C(9)	1903(1)	7944(1)	3618(1)	16(1)
C(10)	434(1)	7945(1)	3177(1)	19(1)
C(11)	-400(1)	7238(1)	3667(1)	21(1)
C(12)	254(1)	6548(1)	4620(1)	22(1)
C(13)	1724(1)	6544(1)	5060(1)	18(1)
C(14)	4171(1)	7240(1)	5070(1)	16(1)
C(15)	4888(1)	4625(1)	1811(1)	15(1)
C(16)	5921(1)	4212(1)	1470(1)	17(1)
C(17)	5459(2)	3238(1)	384(1)	21(1)
C(18)	3981(2)	2664(1)	-354(1)	24(1)
C(19)	2958(2)	3059(1)	-6(1)	24(1)
C(20)	3403(1)	4048(1)	1070(1)	19(1)
C(21)	5407(1)	5673(1)	2977(1)	15(1)
C(22)	6459(1)	9329(1)	3824(1)	14(1)
C(23)	5330(1)	9713(1)	2839(1)	17(1)
C(24)	5604(1)	10405(1)	1976(1)	21(1)
C(25)	7013(2)	10726(1)	2085(1)	23(1)
C(26)	8136(1)	10348(1)	3059(1)	22(1)
C(27)	7863(1)	9655(1)	3926(1)	18(1)
C(28)	6155(1)	8672(1)	4830(1)	14(1)

Table 3.   Bond lengths [Å] and angles [°] for **S79.2**.

S(1)-N(1)	1.6670(10)	N(2)-C(28)	1.4603(14)
S(1)-C(21)	1.7774(12)	N(2)-H(1)	0.833(18)
N(1)-C(28)	1.4641(14)	O(2)-C(21)	1.2188(14)
N(1)-C(14)	1.4690(15)	C(1)-C(6)	1.3929(16)
O(1)-C(7)	1.2250(14)	C(1)-C(2)	1.3973(16)
N(2)-C(7)	1.3579(14)	C(1)-C(7)	1.5057(16)

C(2)-C(3)	1.3887(17)	C(15)-C(16)	1.3992(16)
C(2)-H(2)	0.966(19)	C(15)-C(21)	1.4865(15)
C(3)-C(4)	1.390(2)	C(16)-C(17)	1.3862(17)
C(3)-H(3)	0.98(2)	C(16)-H(16)	0.974(18)
C(4)-C(5)	1.3894(18)	C(17)-C(18)	1.3909(19)
C(4)-H(4)	0.964(17)	C(17)-H(17)	0.962(19)
C(5)-C(6)	1.3927(16)	C(18)-C(19)	1.387(2)
C(5)-H(5)	0.933(19)	C(18)-H(18)	0.936(18)
C(6)-H(6)	0.952(17)	C(19)-C(20)	1.3918(17)
C(8)-C(9)	1.3920(16)	C(19)-H(19)	0.985(19)
C(8)-C(13)	1.3956(16)	C(20)-H(20)	0.961(18)
C(8)-C(14)	1.5153(15)	C(22)-C(27)	1.3898(16)
C(9)-C(10)	1.3898(16)	C(22)-C(23)	1.4001(15)
C(9)-H(9)	0.927(18)	C(22)-C(28)	1.5193(16)
C(10)-C(11)	1.3865(18)	C(23)-C(24)	1.3880(17)
C(10)-H(10)	0.979(17)	C(23)-H(23)	0.969(17)
C(11)-C(12)	1.3873(19)	C(24)-C(25)	1.3921(19)
C(11)-H(11)	0.964(17)	C(24)-H(24)	0.939(18)
C(12)-C(13)	1.3909(17)	C(25)-C(26)	1.3867(19)
C(12)-H(12)	0.966(19)	C(25)-H(25)	0.947(19)
C(13)-H(13)	0.966(18)	C(26)-C(27)	1.3920(17)
C(14)-H(14A)	0.982(16)	C(26)-H(26)	0.966(18)
C(14)-H(14B)	0.983(17)	C(27)-H(27)	0.961(17)
C(15)-C(20)	1.3970(16)	C(28)-H(28)	0.991(15)
N(1)-S(1)-C(21)	107.46(5)	C(3)-C(2)-H(2)	120.6(11)
C(28)-N(1)-C(14)	116.96(9)	C(1)-C(2)-H(2)	118.9(11)
C(28)-N(1)-S(1)	123.10(8)	C(2)-C(3)-C(4)	119.98(12)
C(14)-N(1)-S(1)	116.40(8)	C(2)-C(3)-H(3)	121.9(11)
C(7)-N(2)-C(28)	122.78(10)	C(4)-C(3)-H(3)	118.1(11)
C(7)-N(2)-H(1)	118.4(12)	C(5)-C(4)-C(3)	120.02(12)
C(28)-N(2)-H(1)	115.9(12)	C(5)-C(4)-H(4)	119.8(10)
C(6)-C(1)-C(2)	119.22(11)	C(3)-C(4)-H(4)	120.1(10)
C(6)-C(1)-C(7)	123.45(10)	C(4)-C(5)-C(6)	119.97(12)
C(2)-C(1)-C(7)	117.27(10)	C(4)-C(5)-H(5)	120.9(11)
C(3)-C(2)-C(1)	120.43(12)	C(6)-C(5)-H(5)	119.1(11)

C(5)-C(6)-C(1)	120.37(11)	C(16)-C(17)-C(18)	120.35(12)
C(5)-C(6)-H(6)	118.8(10)	C(16)-C(17)-H(17)	120.6(11)
C(1)-C(6)-H(6)	120.7(10)	C(18)-C(17)-H(17)	119.0(11)
O(1)-C(7)-N(2)	122.92(11)	C(19)-C(18)-C(17)	120.22(12)
O(1)-C(7)-C(1)	121.21(10)	C(19)-C(18)-H(18)	119.3(11)
N(2)-C(7)-C(1)	115.86(10)	C(17)-C(18)-H(18)	120.4(11)
C(9)-C(8)-C(13)	118.58(11)	C(18)-C(19)-C(20)	120.06(12)
C(9)-C(8)-C(14)	121.80(10)	C(18)-C(19)-H(19)	122.4(11)
C(13)-C(8)-C(14)	119.59(10)	C(20)-C(19)-H(19)	117.5(11)
C(10)-C(9)-C(8)	120.82(11)	C(19)-C(20)-C(15)	119.69(11)
C(10)-C(9)-H(9)	118.6(11)	C(19)-C(20)-H(20)	121.7(11)
C(8)-C(9)-H(9)	120.6(11)	C(15)-C(20)-H(20)	118.6(11)
C(11)-C(10)-C(9)	120.29(11)	O(2)-C(21)-C(15)	122.78(10)
C(11)-C(10)-H(10)	120.8(10)	O(2)-C(21)-S(1)	123.80(9)
C(9)-C(10)-H(10)	118.9(10)	C(15)-C(21)-S(1)	113.30(8)
C(10)-C(11)-C(12)	119.34(11)	C(27)-C(22)-C(23)	118.85(11)
C(10)-C(11)-H(11)	119.9(10)	C(27)-C(22)-C(28)	121.41(10)
C(12)-C(11)-H(11)	120.8(10)	C(23)-C(22)-C(28)	119.50(10)
C(11)-C(12)-C(13)	120.46(12)	C(24)-C(23)-C(22)	120.69(11)
C(11)-C(12)-H(12)	120.3(11)	C(24)-C(23)-H(23)	119.1(10)
C(13)-C(12)-H(12)	119.2(11)	C(22)-C(23)-H(23)	120.2(10)
C(12)-C(13)-C(8)	120.49(11)	C(23)-C(24)-C(25)	120.04(12)
C(12)-C(13)-H(13)	119.0(11)	C(23)-C(24)-H(24)	121.9(11)
C(8)-C(13)-H(13)	120.5(11)	C(25)-C(24)-H(24)	118.0(11)
N(1)-C(14)-C(8)	112.67(9)	C(26)-C(25)-C(24)	119.51(12)
N(1)-C(14)-H(14A)	105.8(9)	C(26)-C(25)-H(25)	119.8(12)
C(8)-C(14)-H(14A)	110.5(9)	C(24)-C(25)-H(25)	120.6(12)
N(1)-C(14)-H(14B)	110.5(10)	C(25)-C(26)-C(27)	120.51(12)
C(8)-C(14)-H(14B)	109.6(10)	C(25)-C(26)-H(26)	120.5(10)
H(14A)-C(14)-H(14B)	107.6(13)	C(27)-C(26)-H(26)	119.0(10)
C(20)-C(15)-C(16)	120.16(11)	C(22)-C(27)-C(26)	120.40(11)
C(20)-C(15)-C(21)	121.24(10)	C(22)-C(27)-H(27)	120.7(10)
C(16)-C(15)-C(21)	118.60(10)	C(26)-C(27)-H(27)	118.9(10)
C(17)-C(16)-C(15)	119.52(11)	N(2)-C(28)-N(1)	111.35(9)
C(17)-C(16)-H(16)	121.0(11)	N(2)-C(28)-C(22)	113.72(9)
C(15)-C(16)-H(16)	119.5(11)	N(1)-C(28)-C(22)	112.04(9)

| N(2)-C(28)-H(28) | 105.7(9) | C(22)-C(28)-H(28) | 107.6(9) |
| N(1)-C(28)-H(28) | 105.9(9) | | |

Table 4.　Anisotropic displacement parameters　$(\text{Å}^2\text{x } 10^3)$ for **S79.2**.　The anisotropic displacement factor exponent takes the form: $-2\square^2[\ h^2\ a^{*2}U^{11} + ... \ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	13(1)	16(1)	12(1)	0(1)	3(1)	5(1)
N(1)	13(1)	16(1)	12(1)	0(1)	6(1)	3(1)
O(1)	26(1)	18(1)	16(1)	0(1)	5(1)	10(1)
N(2)	14(1)	17(1)	13(1)	2(1)	4(1)	7(1)
O(2)	18(1)	22(1)	17(1)	-1(1)	2(1)	9(1)
C(1)	14(1)	18(1)	12(1)	3(1)	5(1)	5(1)
C(2)	20(1)	22(1)	14(1)	1(1)	4(1)	6(1)
C(3)	21(1)	32(1)	14(1)	3(1)	2(1)	9(1)
C(4)	21(1)	28(1)	20(1)	9(1)	6(1)	11(1)
C(5)	21(1)	20(1)	21(1)	6(1)	8(1)	9(1)
C(6)	17(1)	18(1)	15(1)	3(1)	5(1)	5(1)
C(7)	13(1)	16(1)	14(1)	3(1)	5(1)	2(1)
C(8)	14(1)	14(1)	15(1)	1(1)	7(1)	4(1)
C(9)	15(1)	15(1)	17(1)	2(1)	7(1)	3(1)
C(10)	16(1)	18(1)	21(1)	2(1)	5(1)	5(1)
C(11)	14(1)	20(1)	27(1)	0(1)	9(1)	4(1)
C(12)	20(1)	21(1)	29(1)	4(1)	15(1)	4(1)
C(13)	19(1)	18(1)	21(1)	5(1)	11(1)	6(1)
C(14)	14(1)	19(1)	15(1)	5(1)	7(1)	6(1)
C(15)	17(1)	14(1)	13(1)	2(1)	6(1)	4(1)
C(16)	18(1)	19(1)	16(1)	3(1)	8(1)	7(1)
C(17)	29(1)	20(1)	18(1)	4(1)	12(1)	11(1)
C(18)	32(1)	18(1)	18(1)	-1(1)	11(1)	4(1)
C(19)	22(1)	21(1)	21(1)	-3(1)	7(1)	-1(1)
C(20)	17(1)	19(1)	19(1)	1(1)	8(1)	2(1)
C(21)	15(1)	15(1)	15(1)	2(1)	7(1)	4(1)

C(22)	15(1)	13(1)	14(1)	1(1)	6(1)	4(1)
C(23)	17(1)	18(1)	17(1)	4(1)	7(1)	6(1)
C(24)	25(1)	21(1)	20(1)	8(1)	9(1)	10(1)
C(25)	30(1)	20(1)	24(1)	8(1)	15(1)	7(1)
C(26)	20(1)	21(1)	26(1)	4(1)	13(1)	3(1)
C(27)	16(1)	17(1)	19(1)	2(1)	7(1)	3(1)
C(28)	12(1)	15(1)	13(1)	2(1)	4(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **S79.2**.

	x	y	z	U(eq)
H(1)	7457(19)	7499(17)	5364(17)	24(4)
H(2)	10200(20)	9197(18)	9427(19)	33(5)
H(3)	11720(20)	7978(18)	10790(20)	35(5)
H(4)	11385(19)	5847(16)	9937(17)	23(4)
H(5)	9650(20)	4948(18)	7736(18)	30(5)
H(6)	8145(19)	6095(16)	6431(17)	23(4)
H(9)	2443(19)	8445(17)	3295(17)	26(4)
H(10)	5(18)	8464(16)	2530(17)	23(4)
H(11)	-1428(19)	7217(16)	3333(17)	24(4)
H(12)	-310(20)	6050(17)	4970(18)	30(5)
H(13)	2160(20)	6055(17)	5722(18)	29(4)
H(14A)	4743(17)	7813(15)	5940(16)	17(4)
H(14B)	4309(18)	6388(16)	5191(16)	19(4)
H(16)	6952(19)	4630(16)	1985(17)	27(4)
H(17)	6153(19)	2955(17)	124(18)	28(4)
H(18)	3669(19)	1999(17)	-1082(18)	29(4)
H(19)	1900(20)	2678(18)	-510(19)	35(5)
H(20)	2716(19)	4344(17)	1328(18)	27(4)
H(23)	4345(19)	9500(16)	2755(17)	22(4)
H(24)	4870(20)	10683(17)	1318(18)	28(4)

H(25)	7210(20)	11196(18)	1499(19)	33(5)
H(26)	9122(19)	10580(16)	3159(17)	25(4)
H(27)	8661(18)	9412(16)	4599(17)	23(4)
H(28)	6012(16)	9311(14)	5430(15)	13(3)

Table 6. Torsion angles [°] for **S79.2**.

C(21)-S(1)-N(1)-C(28)	71.41(10)	C(20)-C(15)-C(16)-C(17)	0.80(18)
C(21)-S(1)-N(1)-C(14)	-86.70(9)	C(21)-C(15)-C(16)-C(17)	-179.83(11)
C(6)-C(1)-C(2)-C(3)	-0.80(19)	C(15)-C(16)-C(17)-C(18)	-0.76(18)
C(7)-C(1)-C(2)-C(3)	176.31(12)	C(16)-C(17)-C(18)-C(19)	-0.2(2)
C(1)-C(2)-C(3)-C(4)	-0.3(2)	C(17)-C(18)-C(19)-C(20)	1.2(2)
C(2)-C(3)-C(4)-C(5)	1.2(2)	C(18)-C(19)-C(20)-C(15)	-1.1(2)
C(3)-C(4)-C(5)-C(6)	-1.1(2)	C(16)-C(15)-C(20)-C(19)	0.13(18)
C(4)-C(5)-C(6)-C(1)	0.02(19)	C(21)-C(15)-C(20)-C(19)	-179.22(11)
C(2)-C(1)-C(6)-C(5)	0.92(18)	C(20)-C(15)-C(21)-O(2)	144.65(12)
C(7)-C(1)-C(6)-C(5)	-176.00(11)	C(16)-C(15)-C(21)-O(2)	-34.71(17)
C(28)-N(2)-C(7)-O(1)	-14.21(18)	C(20)-C(15)-C(21)-S(1)	-39.16(14)
C(28)-N(2)-C(7)-C(1)	166.22(10)	C(16)-C(15)-C(21)-S(1)	141.48(10)
C(6)-C(1)-C(7)-O(1)	157.20(12)	N(1)-S(1)-C(21)-O(2)	-14.09(12)
C(2)-C(1)-C(7)-O(1)	-19.78(17)	N(1)-S(1)-C(21)-C(15)	169.76(8)
C(6)-C(1)-C(7)-N(2)	-23.23(16)	C(27)-C(22)-C(23)-C(24)	0.19(17)
C(2)-C(1)-C(7)-N(2)	159.79(11)	C(28)-C(22)-C(23)-C(24)	174.70(11)
C(13)-C(8)-C(9)-C(10)	-0.91(17)	C(22)-C(23)-C(24)-C(25)	-0.10(19)
C(14)-C(8)-C(9)-C(10)	-178.89(11)	C(23)-C(24)-C(25)-C(26)	0.1(2)
C(8)-C(9)-C(10)-C(11)	-0.06(18)	C(24)-C(25)-C(26)-C(27)	-0.2(2)
C(9)-C(10)-C(11)-C(12)	1.20(19)	C(23)-C(22)-C(27)-C(26)	-0.28(17)
C(10)-C(11)-C(12)-C(13)	-1.36(19)	C(28)-C(22)-C(27)-C(26)	-174.68(11)
C(11)-C(12)-C(13)-C(8)	0.38(19)	C(25)-C(26)-C(27)-C(22)	0.29(19)
C(9)-C(8)-C(13)-C(12)	0.76(18)	C(7)-N(2)-C(28)-N(1)	-112.29(12)
C(14)-C(8)-C(13)-C(12)	178.78(11)	C(7)-N(2)-C(28)-C(22)	119.99(11)
C(28)-N(1)-C(14)-C(8)	130.18(10)	C(14)-N(1)-C(28)-N(2)	67.85(12)
S(1)-N(1)-C(14)-C(8)	-70.33(11)	S(1)-N(1)-C(28)-N(2)	-90.14(10)
C(9)-C(8)-C(14)-N(1)	-18.53(15)	C(14)-N(1)-C(28)-C(22)	-163.52(9)
C(13)-C(8)-C(14)-N(1)	163.52(10)	S(1)-N(1)-C(28)-C(22)	38.48(12)

| C(27)-C(22)-C(28)-N(2) | -12.87(15) | C(27)-C(22)-C(28)-N(1) | -140.24(11) |
| C(23)-C(22)-C(28)-N(2) | 172.76(10) | C(23)-C(22)-C(28)-N(1) | 45.40(14) |

Table 7. Hydrogen bonds for **S79.2** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(1)...O(2)	0.833(18)	2.080(18)	2.8339(13)	150.3(16)

NMR DATA

Anti (S2.1)

Anti (S2.1)

ppm

S2.4

S2.4

S2.5

S2.5

Syn (S2.2)

Syn (S2.2)

S2.6

ppm

S2.6

S2.7

ppm

185

S2.7

S2.8

ppm

187

S2.8

ppm

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
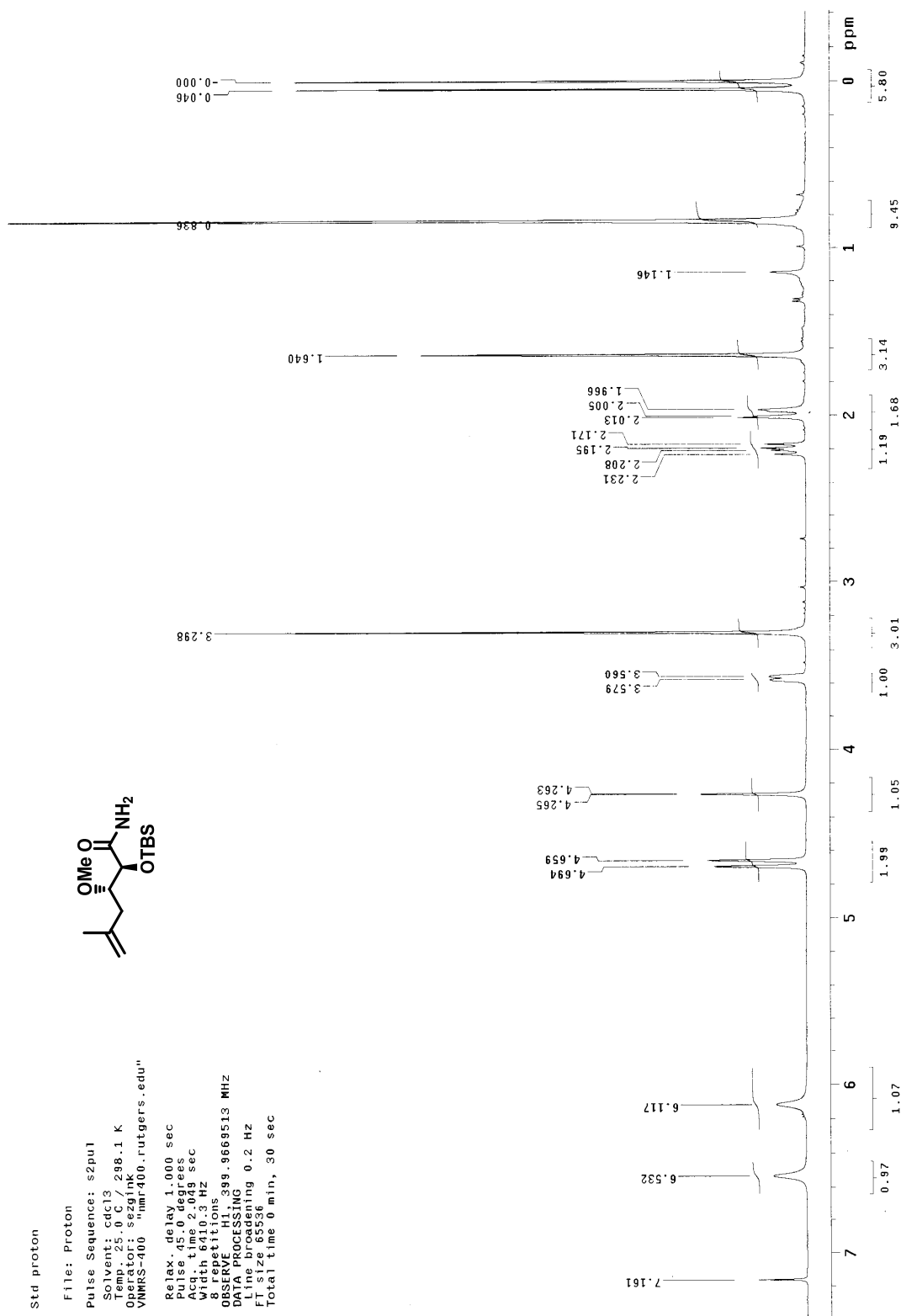Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
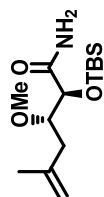OBSERVE H1, 399.9669188 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr-400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
832 repetitions
OBSERVE C13, 100.5717377 MHz
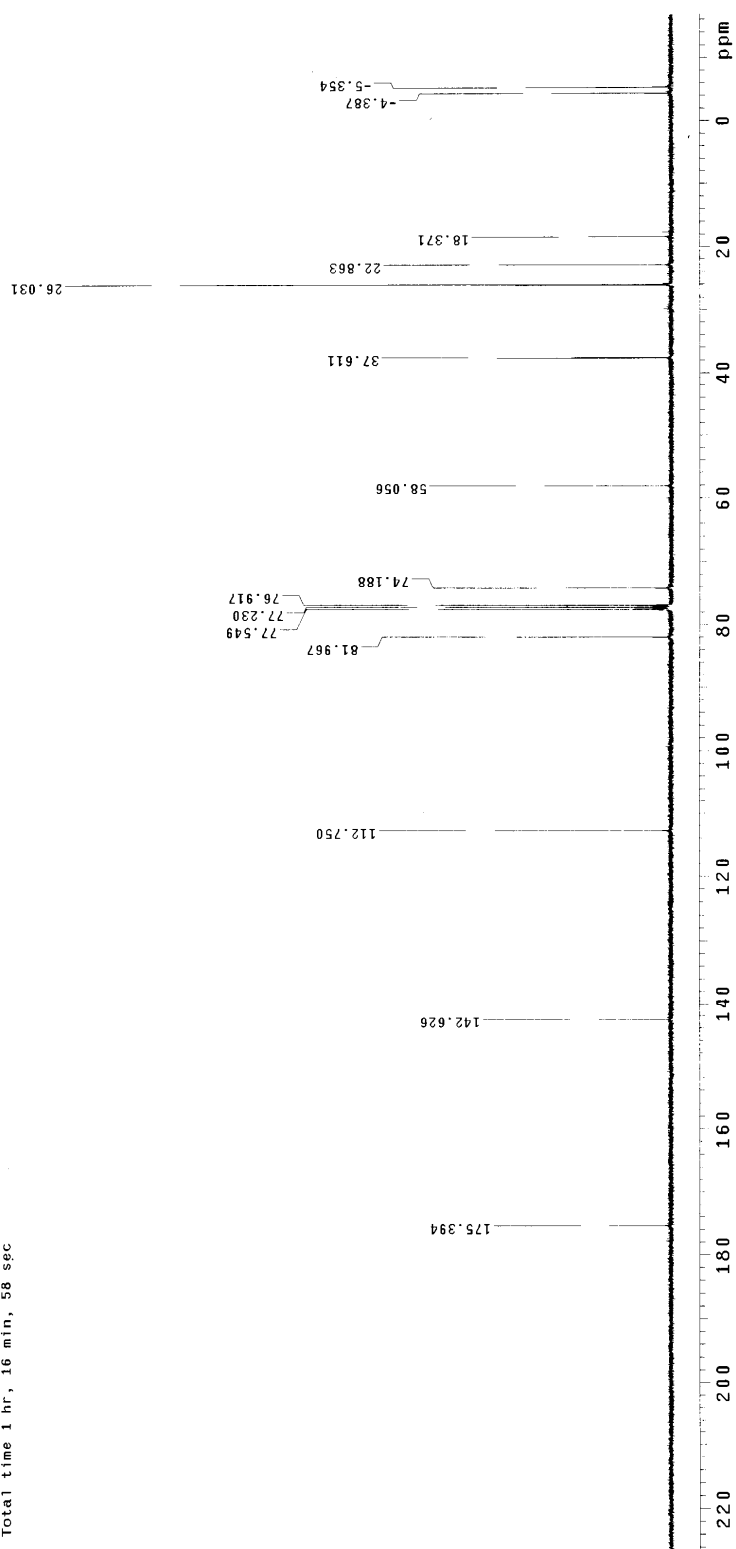DECOUPLE H1, 399.9689190 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min, 29 sec

203.358
190.306
135.791
133.783
133.768
129.915
127.915
97.593
95.265
80.792
79.833
77.557
77.244
76.925
61.983
48.574
27.006
24.127
23.882
19.434

ppm

Me
Me

TBDPSO

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9669114 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec

ppm

ppm

169.407
156.585
152.629
135.612
120.135
119.577
100.255
95.362
94.967
77.542
77.230
76.910
56.390
56.323
52.322
17.211
11.625

std proton

File: Proton

Pulse Sequence: s2pul

Relax. delay 1.000 sec
Pulse 45.0 degrees

ppm

Std proton

Pulse Sequence: s2pul

ppm

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Duration: s2gpul
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
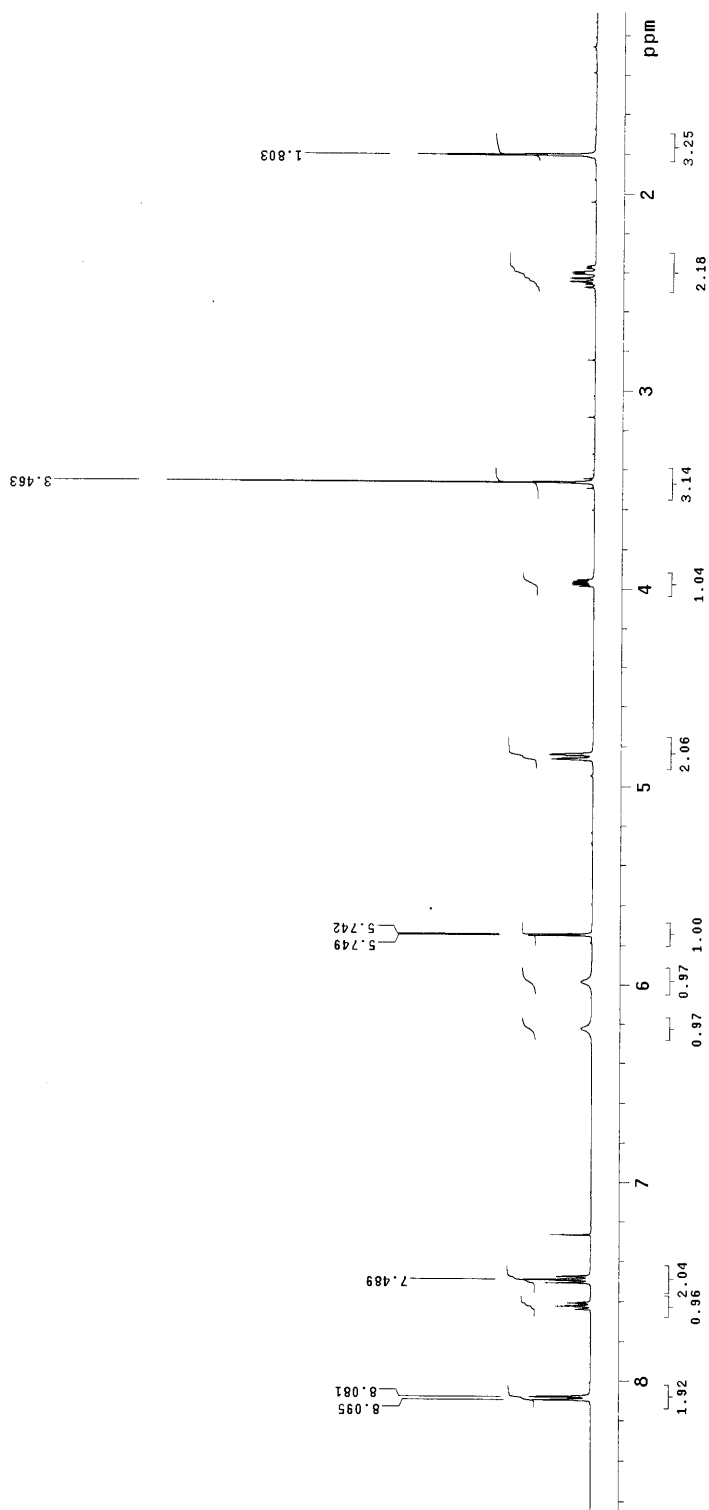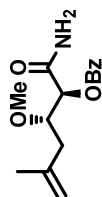Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9889124 MHz
DATA PROCESSING
line broadening 1.5 Hz
FT size 65536
Total time 0 min, 30 sec

ppm

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
736 repetitions
OBSERVE C13, 100.5717377 MHz
DECOUPLE H1, 399.9689190 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 16 min, 58 sec

168.574

141.272
133.619
132.258
128.941
128.822
128.733
127.178
126.464

77.542
77.430
77.222
76.910
75.058

36.414
31.118

ppm

0

20

40

60

80

100

120

140

160

180

200

220
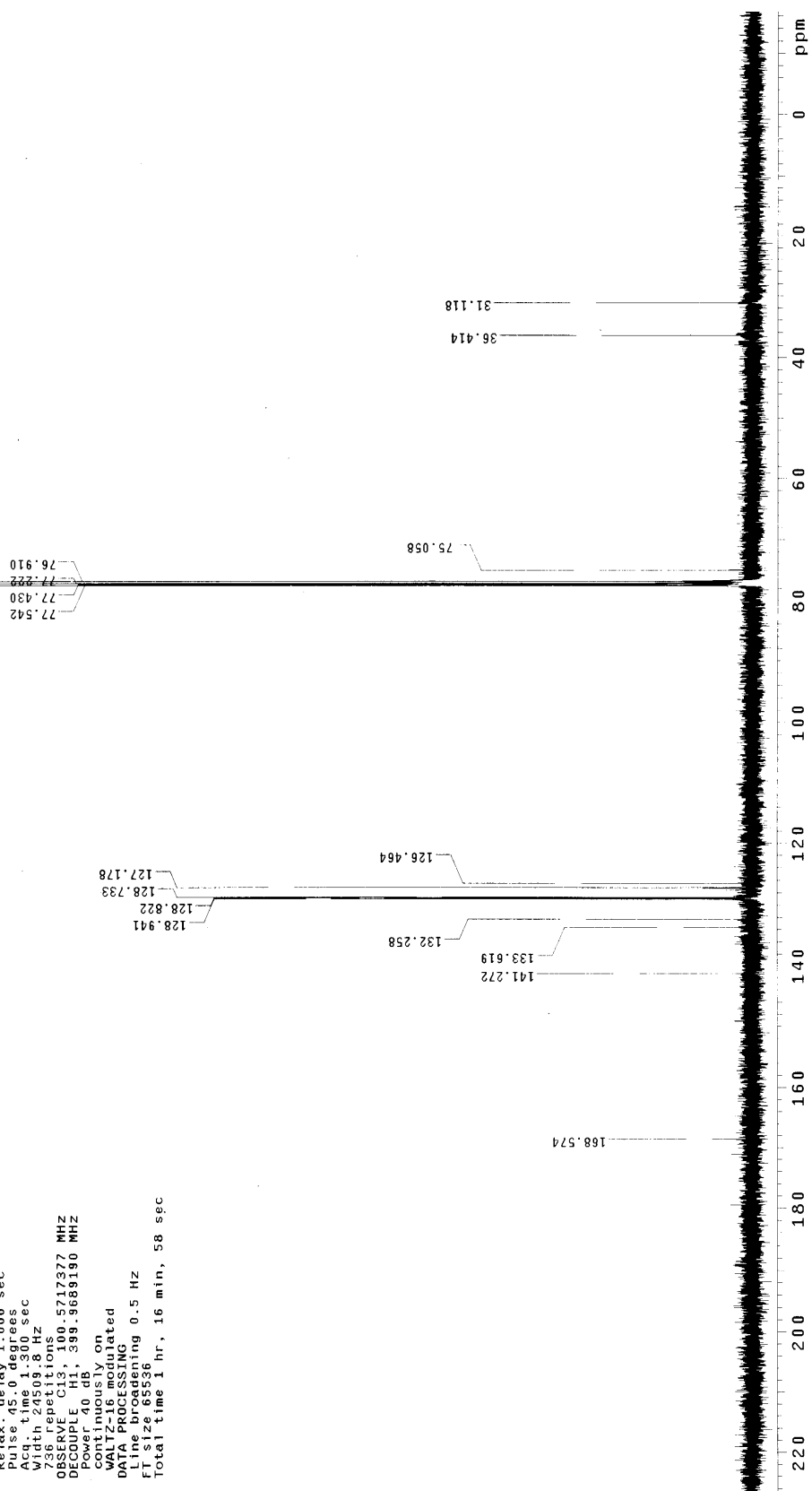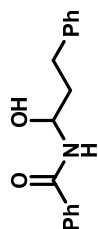
Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
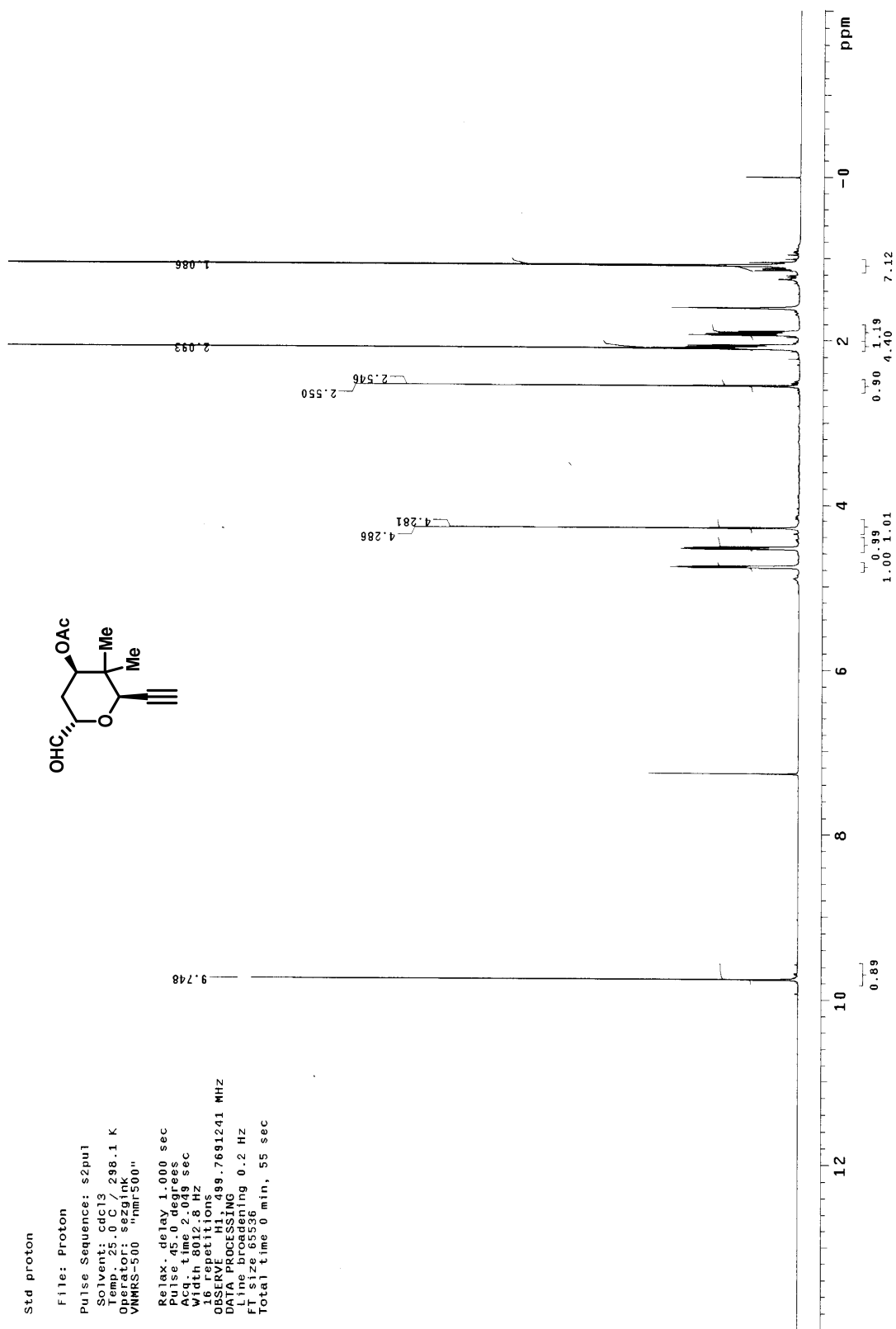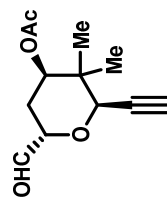Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9669120 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec

ppm

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
RS-506 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.800 sec
Width 30487.8 Hz
656 repetitions
OBSERVE C13, 125.6670162 MHz
DECOUPLE H1, 499.7716228 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
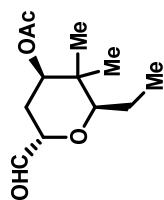Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 12 min, 26 sec

176.447
141.345
128.681
128.618
126.282
77.528
77.273
77.021
75.192
42.012
35.234
32.058
31.873
18.301

ppm
220 200 180 160 140 120 100 80 60 40 20 0

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.7691248 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec

0.962
0.976
0.986
0.947
1.000
1.472
1.616
1.887
2.265

13.23
20.11
3.15
11.03
6.23
2.02
2.00
1.09

ppm

8 7 6 5 4 3 2 1

ppm

17.612
17.724

28.562

32.665

47.295
47.384

76.925
77.244
77.445
77.557
78.224

Std proton

File: sezkinkiren

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
File: sezkinkiren
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
4880 repetitions
OBSERVE C13, 100.5717377 MHz
DECOUPLE H1, 399.9683190 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 12 min, 27 sec
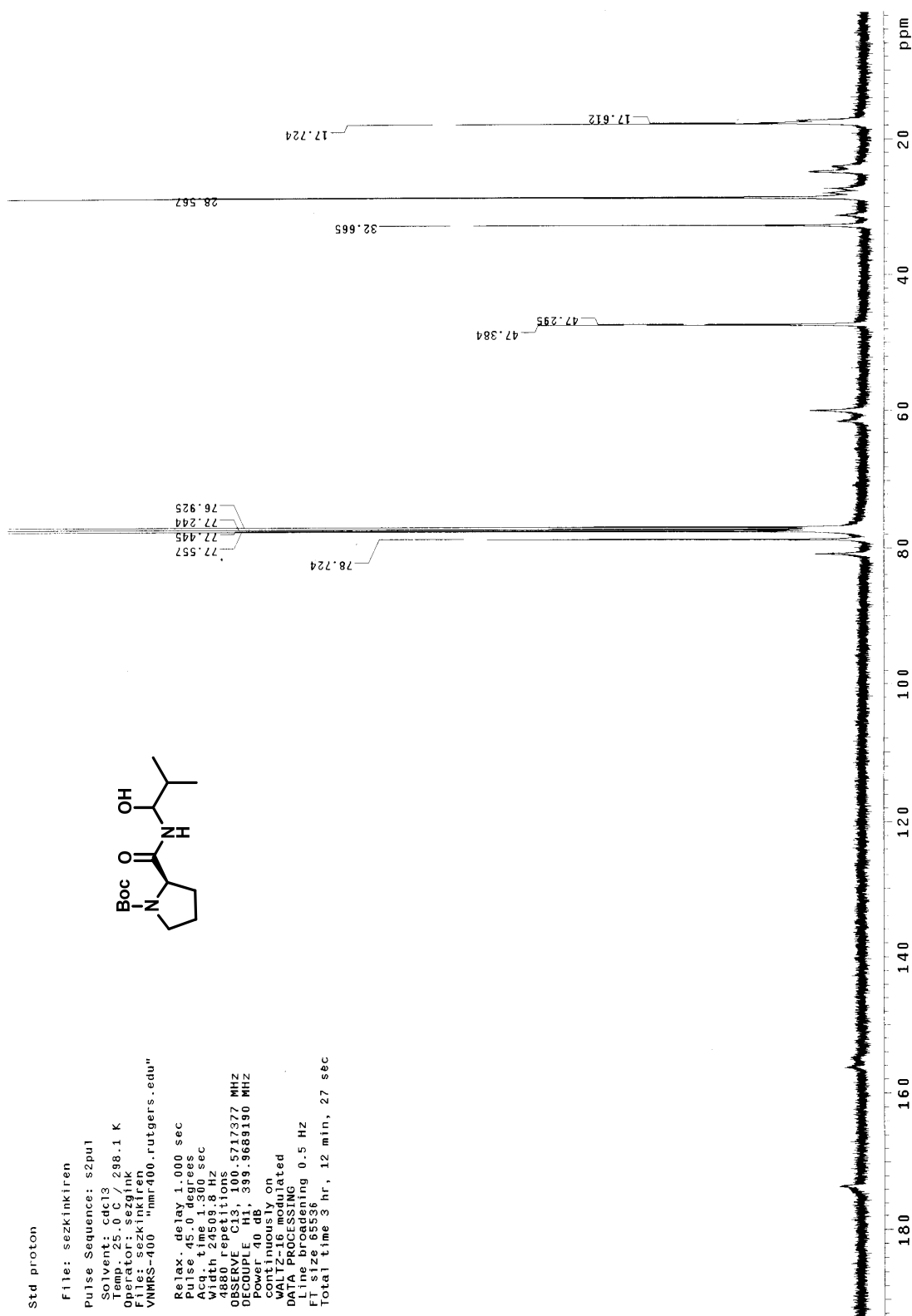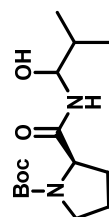
Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9669513 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec

ppm
0.000
0.046
0.836
1.146
1.640
1.966
2.005
2.013
2.171
2.195
2.208
2.231
3.298
3.560
3.579
4.263
4.265
4.659
4.694
6.117
6.532
7.161

5.80
9.45
3.14
1.68
1.19
3.01
1.00
1.05
1.99
1.07
0.97

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-400 "nmr400.rutgers.edu"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
704 repetitions
OBSERVE C13, 100.5717377 MHz
DECOUPLE H1, 399.9689190 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 16 min, 58 sec

-5.354
-4.387
18.371
22.863
26.031
37.611
58.056
74.188
76.917
77.230
77.549
81.967
112.750
142.626
175.394

ppm
0
20
40
60
80
100
120
140
160
180
200
220
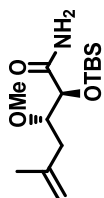
Std proton

File: SK-IV-76c13

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
File: SK-IV-76c13
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
1088 repetitions
OBSERVE C13, 125.6670162 MHz
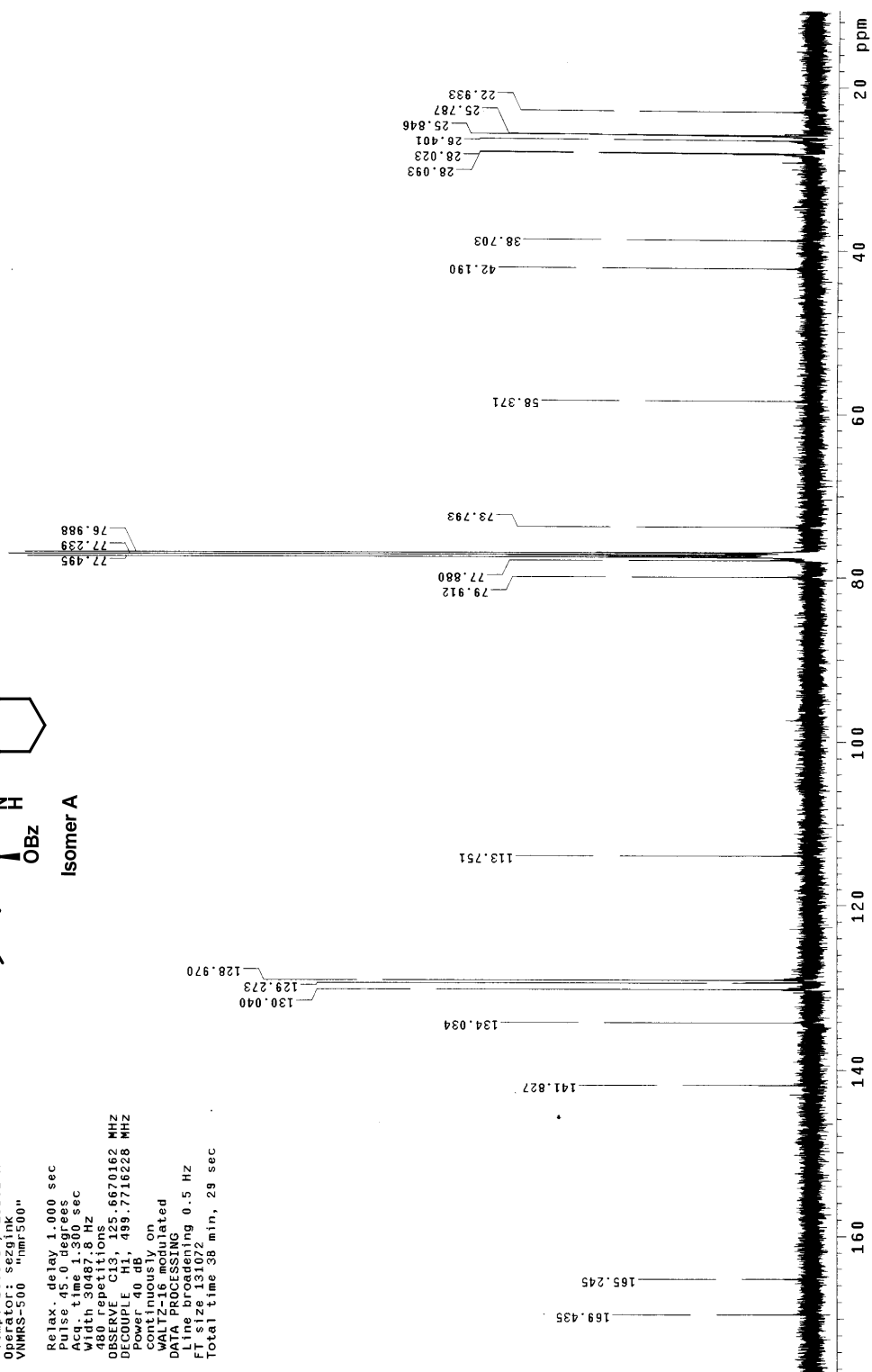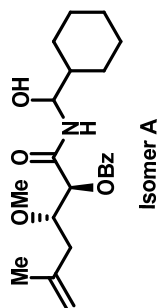DECOUPLE H1, 499.7716228 MHz
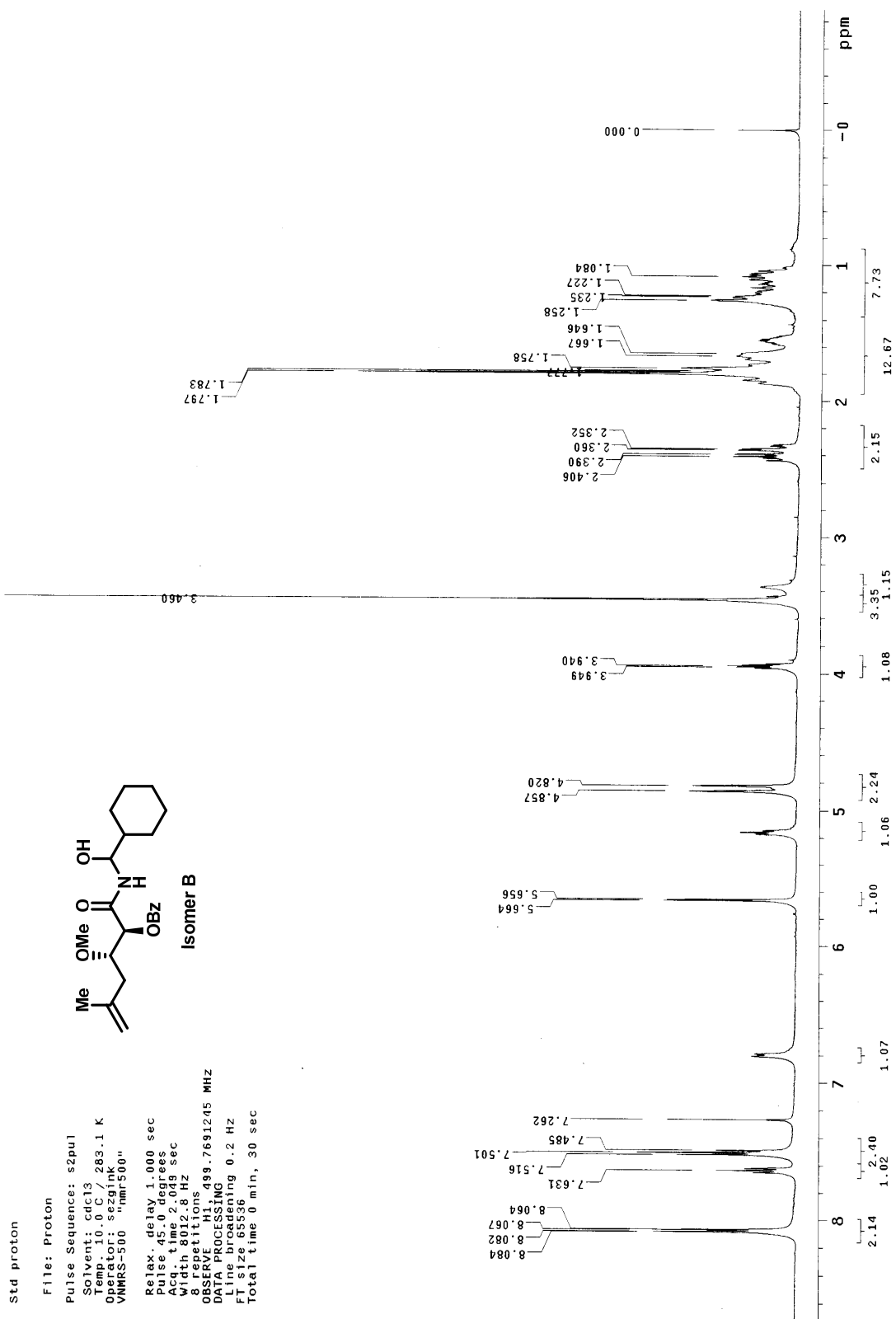Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 16 min, 58 sec
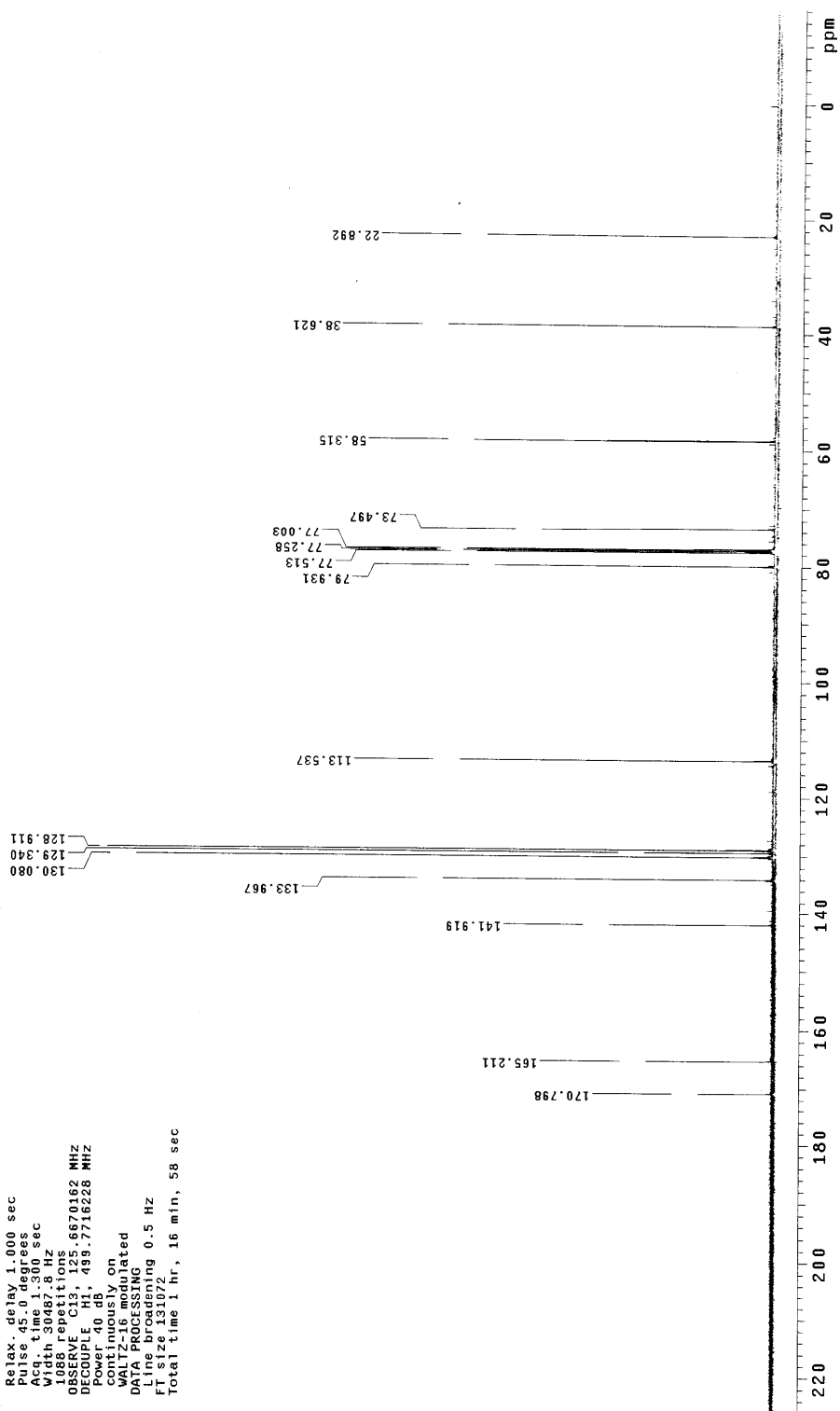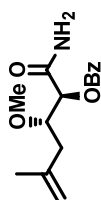
22.892
38.621
58.315
73.497
77.003
77.258
77.513
79.931
113.537
128.911
129.340
130.080
133.967
141.919
165.211
170.798

ppm
0
20
40
60
80
100
120
140
160
180
200
220

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
16 repetitions
OBSERVE H1, 499.7691241 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 55 sec

9.748

4.286
4.281

2.550
2.546

2.093

1.086

0.89

0.99 1.01
1.00 1.01

0.90
4.40

1.19
7.12

ppm
-0
2
4
6
8
10
12

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
128 repetitions
OBSERVE C13, 125.6670162 MHz
DECOUPLE H1, 499.7716228 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 38 min, 29 sec

201.594
170.339
79.638
76.995
77.247
77.502
75.859
74.815
72.856
72.823
37.433
26.579
24.399
21.182
19.297

Std proton

File: Carbon

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
2016 repetitions
OBSERVE C13, 125.6670162 MHz
DECOUPLE H1, 499.7716228 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 12 min, 26 sec

203.785
170.472
83.692
77.810
77.502
77.450
77.247
76.991
74.134
37.951
25.909
23.010
22.014
21.282
13.955
11.734

ppm
0
20
40
60
80
100
120
140
160
180
200
220
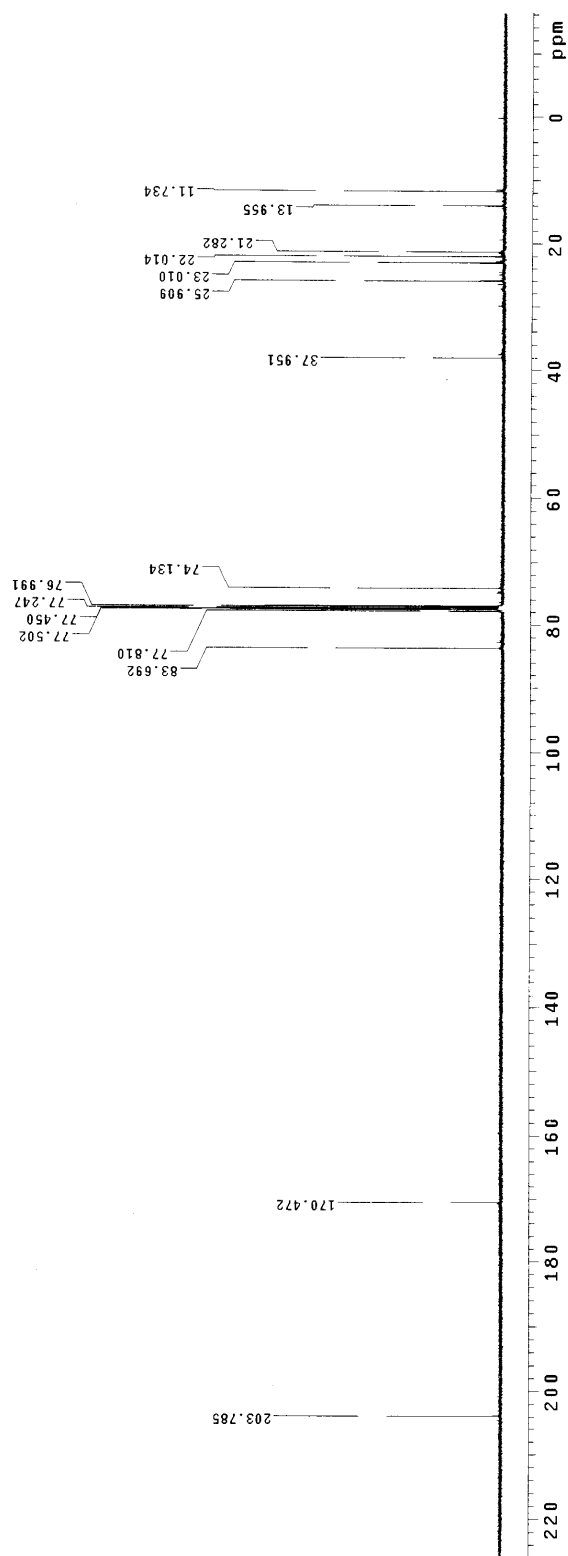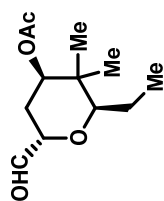
Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp: 10.0 C / 283.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
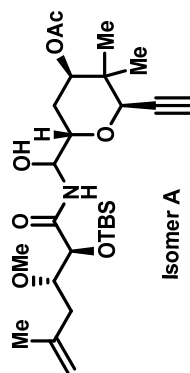Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.7691253 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec

Isomer A

ppm

7.77
12.61
2.25
4.02
1.01
2.25
0.98
1.00
1.08
2.21
1.01
2.04

1.711
1.801
1.634
3.458
4.838
4.862
5.654
5.662
7.262
7.490
7.506
7.521
8.076
8.079
8.093
8.095

Isomer A

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 10.0 C / 283.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.7691245 MHz
DATA PROCESSING
Line broadening 0.2 Hz
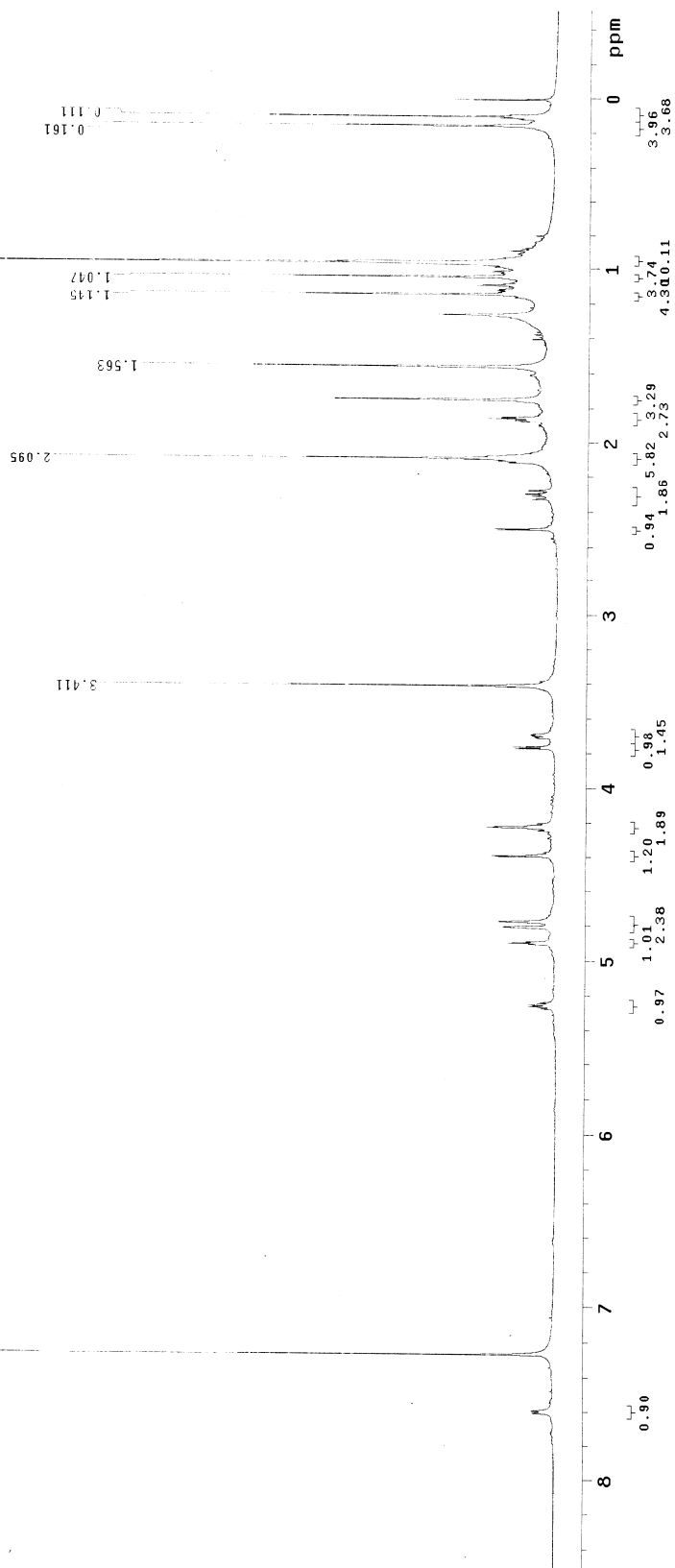FT size 65536
Total time 0 min, 30 sec

Isomer B

ppm

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 10.0 C / 283.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
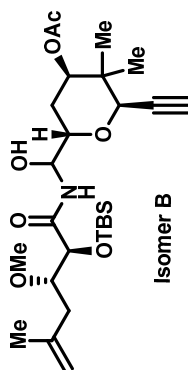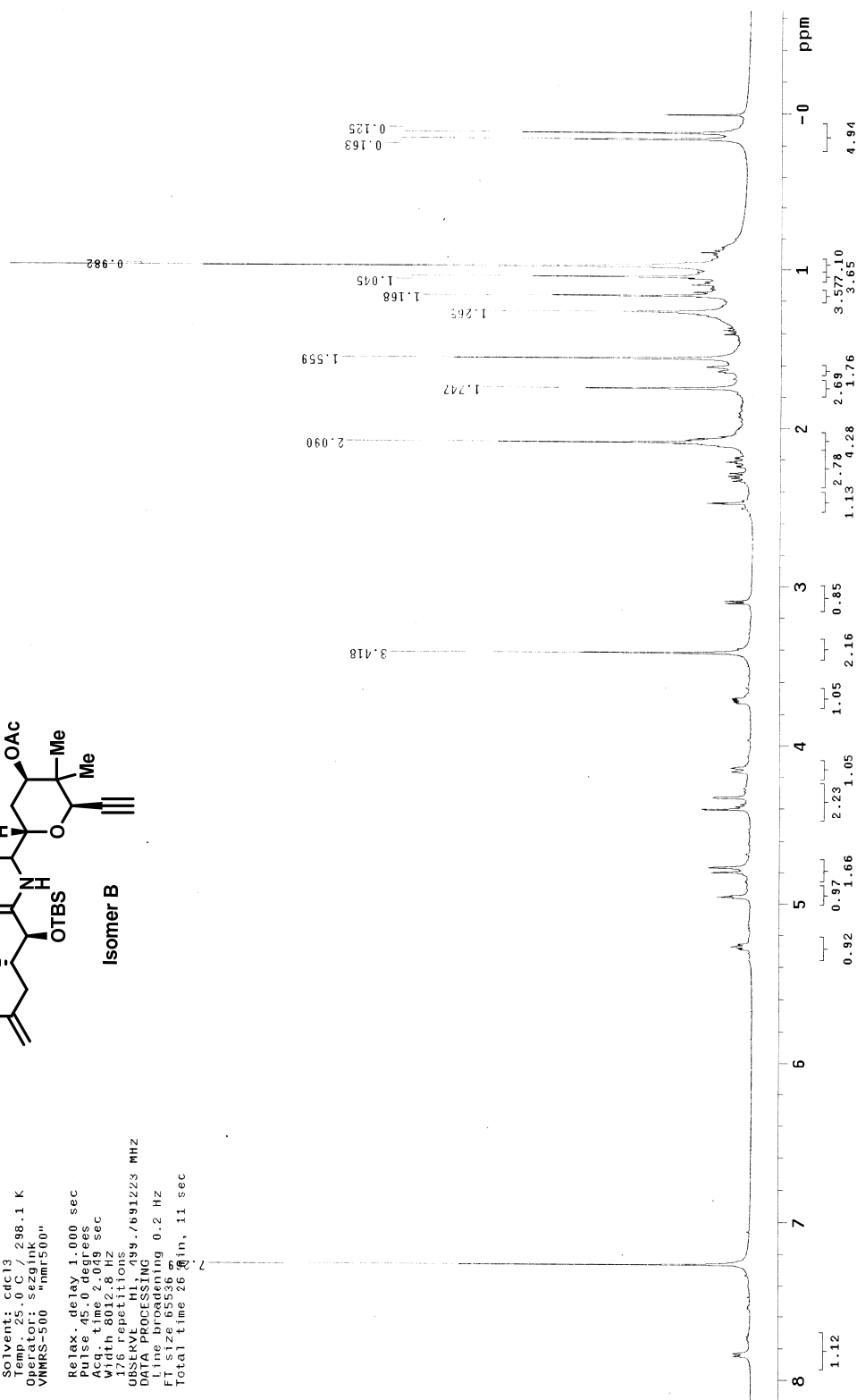Acq. time 1.300 sec
Width 30487.8 Hz
1000 repetitions
OBSERVE C13, 125.6670162 MHz
DECOUPLE H1, 499.7716228 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 38 min, 29 sec

Isomer B

22.940
25.827
25.920
26.464
28.119
28.160
38.814
42.253
58.438
76.988
77.243
77.499
73.782
77.847
79.931
113.703
128.951
129.347
130.036
133.986
141.827
165.145
169.228

ppm
0
20
40
60
80
100
120
140
160
180
200
220

Std proton

File: Proton

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
272 repetitions
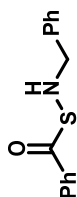OBSERVE H1, 499.7691223 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 26 min, 12 sec

Isomer A

ppm

Isomer B

3.338

4.105
4.117

7.351
7.546
7.567
7.685
7.799
7.802
7.820
7.823
7.334

1.00

0.02

0.90 0.98 0.43
0.47 1.80

ppm

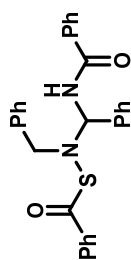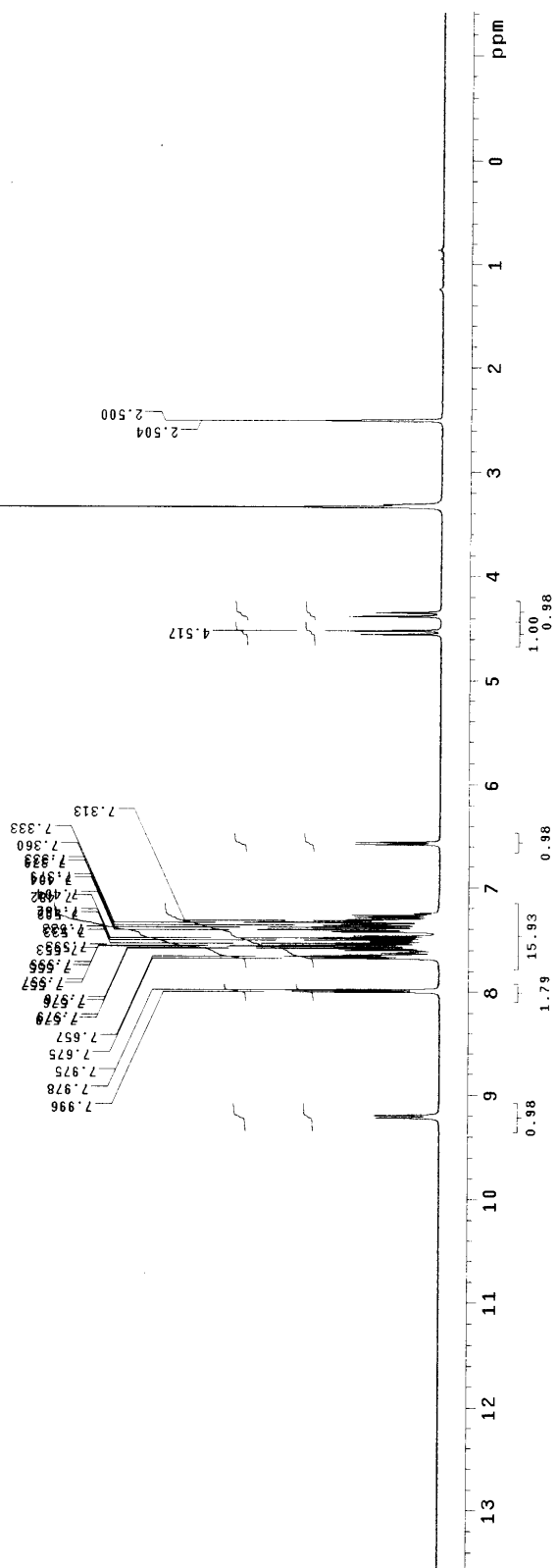Sk-I-297A-c13
Solvent: DMSO
Ambient temperature
UNITY-400 "cheme"
PULSE SEQUENCE
  Pulse 97.5 degrees
  Acq. time 1.199 sec
  Width 25000.0 Hz
  3500 repetitions
OBSERVE C13, 100.5725636 MHz
DECOUPLE H1, 399.9725471 MHz
  Power 38 dB
  continuously on
  WALTZ-16 modulated
Single precision data
DATA PROCESSING
  Line broadening 1.0 Hz
FT size 65536
Total time 69 minutes

ppm

39.784
39.996
40.201
39.579
39.366
40.413
40.618
55.115

126.589
127.598
128.660
128.690
129.737
134.418
135.358
139.887

198.063

Side B
Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
896 repetitions
OBSERVE C13, 125.6670162 MHz
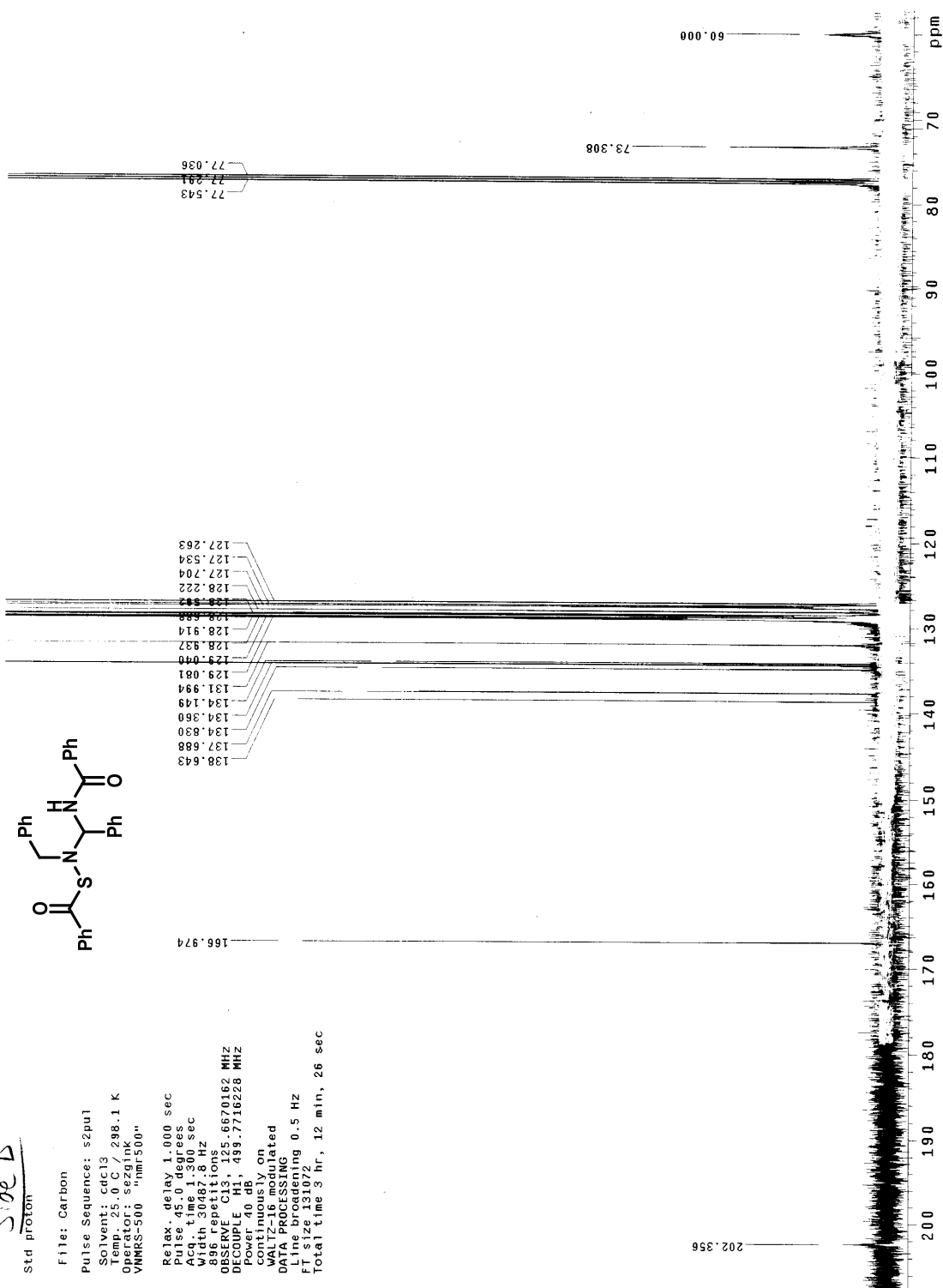DECOUPLE H1, 499.7716228 MHz
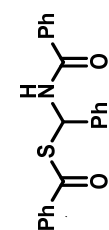Power 40 dB
continuously on
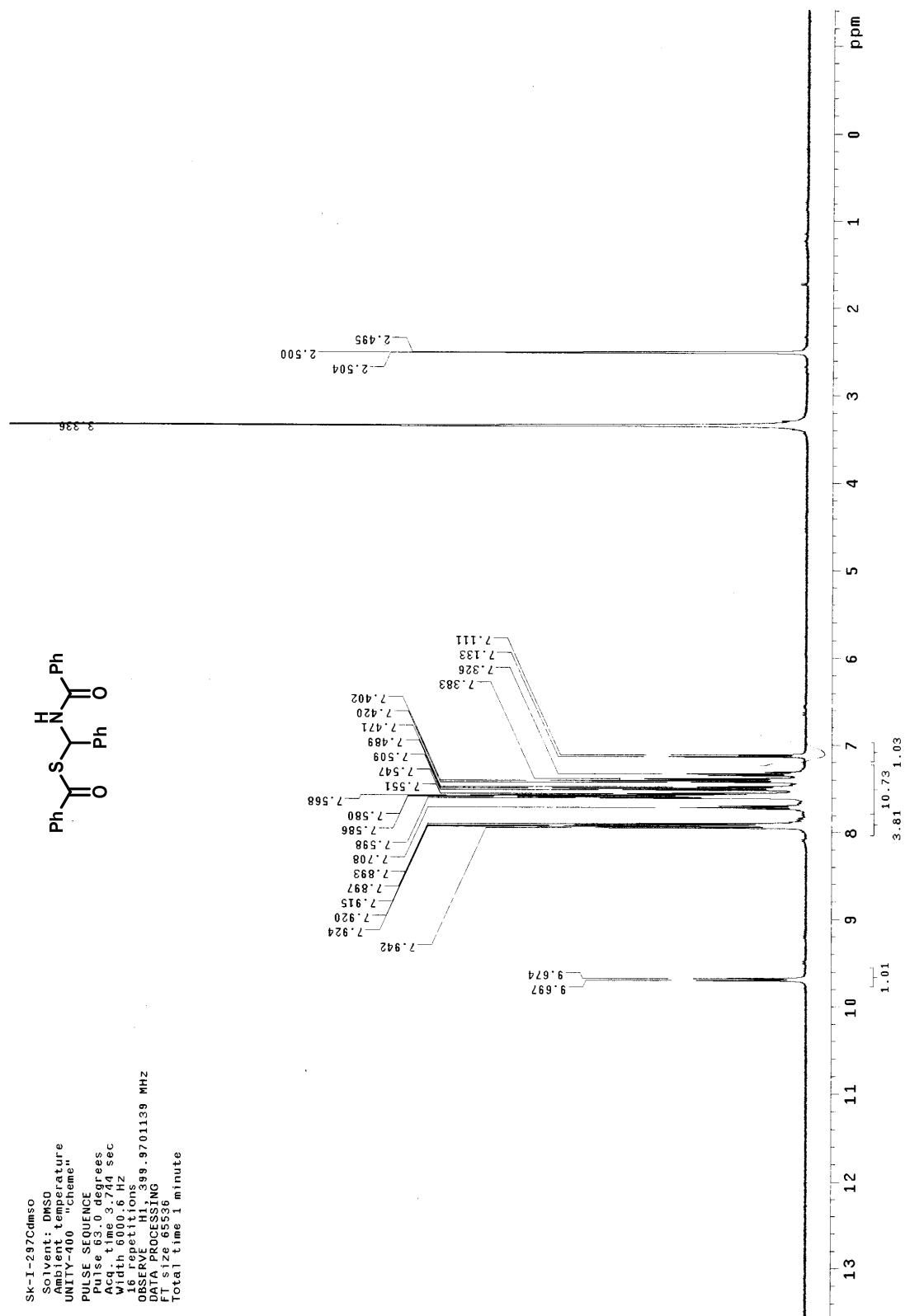WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 12 min, 26 sec

202.356

166.974

138.643
137.688
134.830
134.360
134.149
131.994
131.081
129.040
128.932
128.914
128.689
128.582
128.222
127.704
127.534
127.263

77.543
77.291
77.036

73.308

60.000

ppm

257

Std proton

File: Carbon

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: sezgink
VNMRS-500 "nmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
1072 repetitions
OBSERVE C13, 125.6670162 MHz
DECOUPLE H1, 499.7716228 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
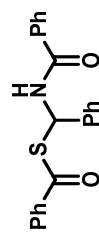DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 12 min, 26 sec

191.939

166.344

139.161
136.796
134.356
134.134
133.819
132.272
131.994
129.073
129.029
126.509
128.415
127.700
127.678
127.522
127.504
127.252
127.041

128.933
128.903
128.677

77.543
77.288
77.036

57.079

ppm
40
60
80
100
120
140
160
180
200
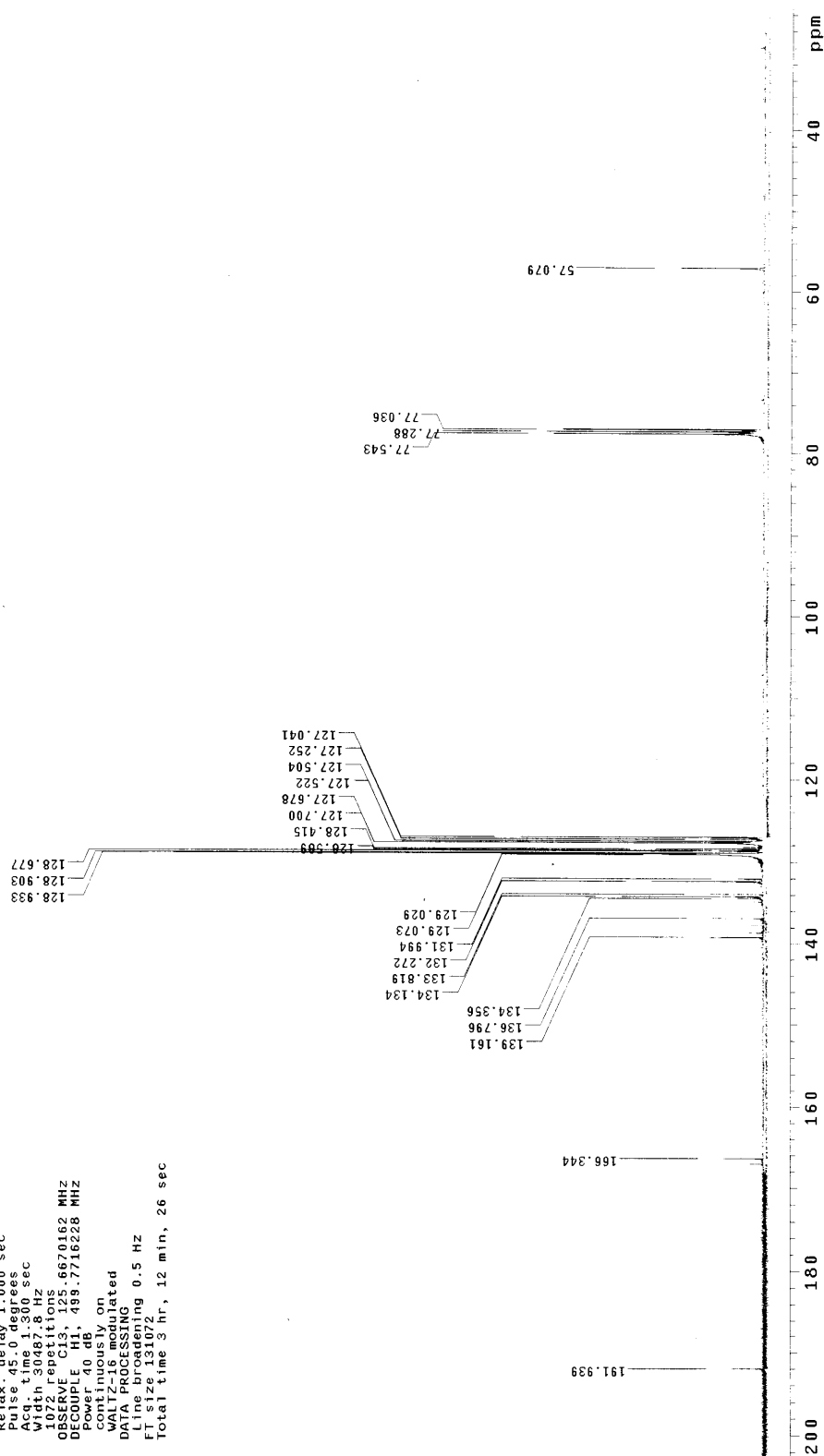
Vita

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Education

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1999   **BS in Chemistry**
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Academic & Teaching Activities

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Rutgers University, Piscataway, NJ

Publications

Journal Papers:

- Kiren, S.; Shangguan, N.; Williams, L. J. Direct Carbinolamide Synthesis. *Tetrahedron Lett*. **2007**, *48*, 7456-7459.
- Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. Spirodiepoxides: Heterocycle Synthesis and Mechanistic insight *Angew. Chem. Int. Ed*. **2007**, *46*, 7108-7111.
- Shangguan, N.; Kiren, S.; Williams, L. J. A Formal Synthesis of Psymberin. *Org. Lett*. **2007**, *9*, 1093-1096.
- Kiren, S.; Williams, L. J. Configuration of the Psymberin Side Chain. *Org. Lett*. **2005**, *7*, 2905-2908.
- Kiren, S.; Wang, Z.; Williams, L. J. Iron (III) Chloride and DMAP promoted Thioacid-azide coupling. (Manuscript in preparation).

Books:

- Concise Organic Chemistry for the Students of Chemistry, Biology and Medicine with Study Guide, Salih Yaslak, Sezgin Kiren, **2001**, Beta Basim Yayim Dagitim A. S. Istanbul/Turkey.