SYNTHETIC, CHEMICAL AND BIOLOGICAL STUDIES OF FR901464 ANALOGUES

by

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University of Pittsburgh, 2010

Since the total synthesis of FR901464 was achieved in our group, its structure-activity relationships were extensively studied through analogue syntheses. Here I described the syntheses and biological activities of two acetal and two cyclopropane analogues. Although the acetal analogues were less potent than their parental analogue meayamycin, they retained nanomolar activity against MCF-7 cells. Meanwhile, the methyl groups on the acetal ring slightly influenced the activities. Compared to analogue meayamycin C, these two cyclopropane analogues were equipotent towards MCF-7 cell lines, which implied that the cyclopropane moiety might not inhibit the binding to the targets.

I also developed an efficient strategy to synthesize the C1'-C5' side chain with Ando's reagent. Subsequently, a convergent strategy was used to prepare a new acetal analogue over 20 steps with 12 steps in the longest linear sequence.

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ABBREVIAITONS

[α]	specific rotation
Ac	acetyl
AIBN	2,2'-azo bisisobutyronitrile
appt	apparent
br	broad
Boc	*tert*-butoxycarbonyl
CBS	Corey-Bakshi-Shibata
CSA	camphorsulfonic acid
d	doublet
dr	diastereomeric ratio
DCE	1,2-dichloroethane
DIBALH	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
dr	diastereomeric ratio
EI	electron ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
g	gram

GI_{50}	concentration required to inhibit growth by 50%
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HRMS	high resolution mass spectrometry
Hz	Hertz
J	coupling constant
k	kilo-
L	liter
LAH	lithium aluminum hydride
m	milli; multiplet
M	molar
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
MHz	megahertz
mol	mole
MW	molecular weight
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
q	quartet
R_f	retention factor
s	second; singlet

SiO_2	silica gel
sp.	species
SAP	spliceosome-associated protein
t	*tert*
TFA	trifluoroacetic acid
THF	tetrahydrofuran

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SYNTHESIS AND BIOLOGICAL STUDIES OF FR901464 ANALOGUES

1.1 INTRODUCTION OF FR901464

1.1.1 Isolation and characterization of FR901464

The targets of current commercially available cancer drugs include DNA, nuclear hormone receptors, kinases, the proteasome, and microtubules.[1] Because the low specificity of these chemotherapeutic agents between cancer and normal cells leads to high toxicity, exploring new cancer therapy targets is of paramount importance.[2-6] The transcriptional pathway has emerged as a promising cancer target.[7-9] In order to search for new agents that regulate the transcriptional pathway of cancer cells, the Nakajima group at the Fujisawa Pharmaceutical Company employed a new screening system to select transcriptional regulators. In the screening system, a plasmid with the promoter of simian virus 40 (SV40) upstream of a chloramphenicol acetyltransferase (CAT) reporter gene was stably transfected into human breast adenocarcinoma MCF-7 cells.[10] Using this screening system, FR901463, FR901464 and FR901465 (Figure 1) were identified in the bacterium *Pseudomonas sp.* No. 2663. After isolation, the effects of these compounds were examined on different cancer cells.[10] The results showed that FR901464 was the most promising antiproliferative agent among these three compounds, with IC_{50} values of 0.31−1.69 ng/mL against HCT-116 (human colon carcinoma cells), SW480 (human colon adenocarcinoma cells), A549 (human lung carcinoma cells), MCF-7 (human breast adenocarcinoma cells), and P388

(murine leukemia cells) cancer cell lines. FR901464 also inhibited the growth of tumors from P388, A549, Colon 38 (murine colon adenocarcinoma cells) and Meth A (murine fibrosarcoma cells) cells in mice in a dose range of 0.056−1 mg/kg.[11-12]

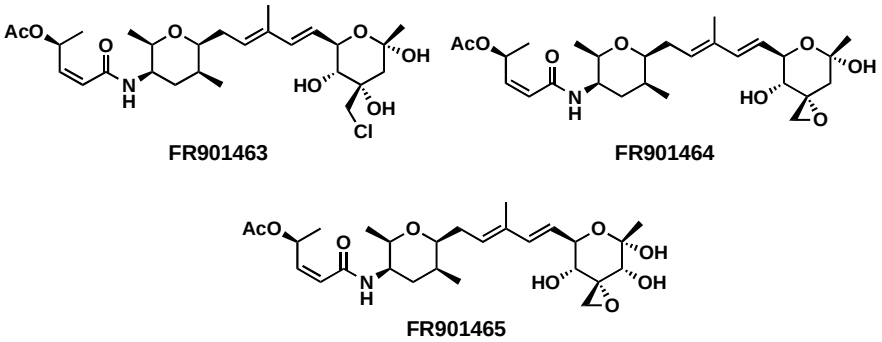


Figure 1. Structures of FR901463, FR901464, and FR901465

In order to study the mode of action of FR901464, its biological activities were examined by the Nakajima group. The accumulation of CAT protein in the aforementioned MCF-7 cell line was monitored upon treatment of these cells with FR901464. The CAT protein expression increase was detected at 6 h after drug treatment and continued for 18 h. In the FR901464-free control cells, no CAT protein accumulation was observed. The analysis of the cell cycle distribution of MCF-7 cells treated with FR901464 showed G_1 and G_2/M phase arrest.[13] In contrast, the known DNA synthesis inhibitors adriamycin and camptothecin induced S phase arrest, and the microtubule modulator taxol induced G_2/M phase arrest.[11] The differences in cell cycle distribution caused by FR901464 and these well-known anticancer agents indicated a unique mode of action of FR901464.

The unique biological activities of FR901464 intrigued the scientists to identify the targets. In the Kitahara group, a methylated FR901464 derivative named spliceostatin A (Figure 2) was synthesized and found to be more active than the parent compound. The better activity

was due to the higher chemical stability of the methyl acetal compared to the labile hemiacetal of FR901464.[14] Subsequently, they synthesized the biotinylated derivative of spliceostatin A (Figure 2). Although the biotinylated spliceostatin A was less potent than FR901464, the Yoshida group successfully used the compound as a probe to isolate the cellular target of FR90146. The results showed that the FR901464 and its derivatives inhibited *in vitro* splicing by binding to splicing factor 3b (SF3b),[15] a subcomplex of the U2 small nuclear ribonucleoprotein in the spliceosome.[16]

SF3b, with a mass of ~450 kD, is composed of seven proteins, SF3b155, SF3b145, SF3b130, SF3b49, p14, SF3b14b and SF3b10, and responsible for the recognition of the pre-messenger RNA's branch site. At the beginning of the splicing, several SF3b proteins bind to the vicinity of the branch point, and the protein p14 is directly cross-linked to the adenosine of the intron. SF3b plays a vital role for the accurate excision of introns from pre-messenger RNA to form mature RNA.[17]

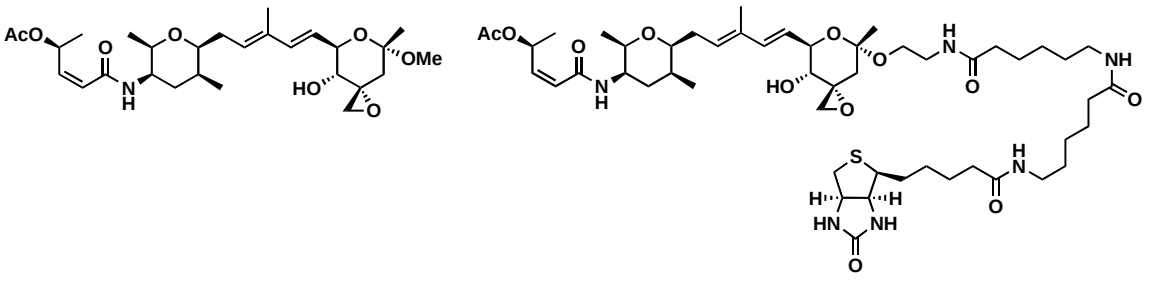


Figure 2. Structures of spliceostatin A and biotinylated spliceostatin A

Since SF3b was identified as the target of FR901464, other anticancer agents were also found to bind to the U2 subunit. In 2004, the Sakai group at Eisai Co., Ltd., using a placental alkaline phosphatase (PLAP) reporter gene controlled by a vascular endothelial growth factor (VEGF) promoter, screened seven unique 12-membered macrolides, named pladienolides, from the culture broth of *Streptomyces platensis* Mer-11107.[18-19] Of the seven compounds,

pladienolide B (Figure 3) was the most potent antiproliferative agent with GI_{50} values of 0.4−9.8 nM against 39 human cancer cell lines. Six drug-resistant cell lines, P388/CPT, P388/ETP, P388/CDDP, P388/VCR, HCT-116/5-FU and MES-SA/Dx5, were examined. Pladienolide B showed similar anticancer activity against these drug-resistant cell lines and the parental cell lines.[20] In 2007, the Mizui group in Eisai Co., Ltd. used biotin-tagged pladienolide B (Figure 3) as a probe to treat HeLa cells and revealed that spliceosome associated protein 130 in the SF3b complex was a target of pladienolide B. [21]

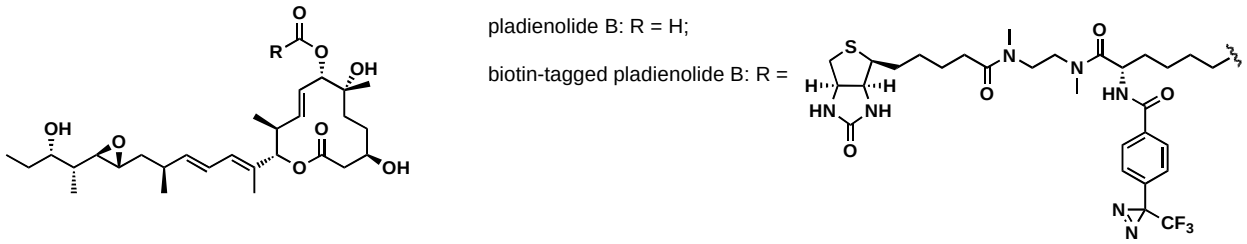


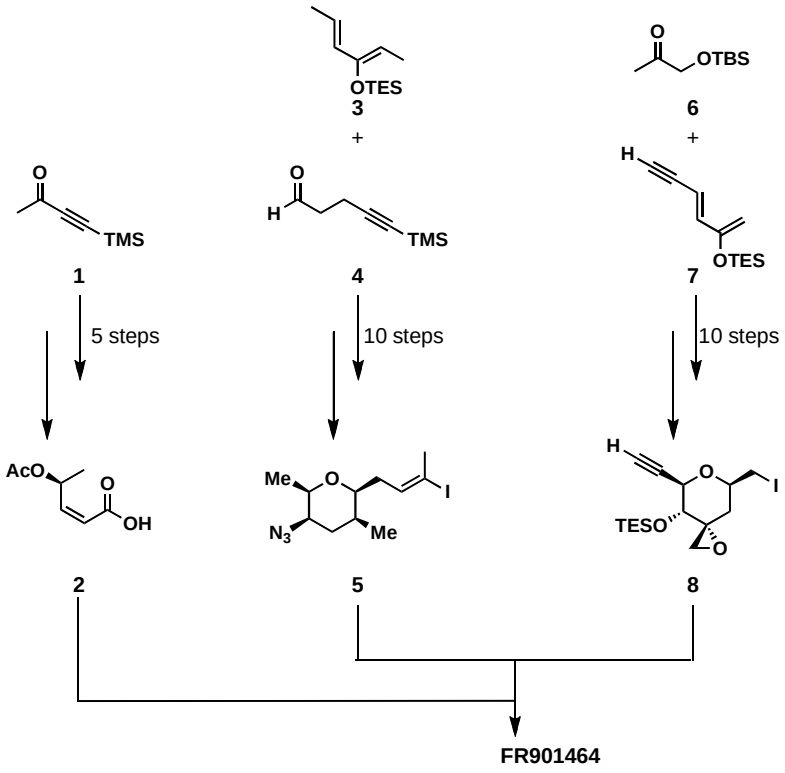
Figure 3. Structures of pladienolide B and biotin-tagged pladienolide B.

In summary, FR901464 and pladienolide B, screened with different methods, proved to target spliceosome subcomplex SF3b and inhibit pre-mRNA splicing and showed high antiproliferative potency in several cancer cell lines. The spliceosome may be a new target for cancer.

1.1.2 Total synthesis of FR901464

The total synthesis of FR901464 was first achieved by the Jacobsen group in 2000 (Scheme 1). The acid fragment **2** was prepared from commercially available 4-(trimethylsilyl)-3-butyn-2-one **1** with the stereocenter constructed by a Noyori asymmetric hydrogenation.[22] Fragment **5** was synthesized from diene **3** and aldehyde **4** via an asymmetric chromium-catalyzed hetero-Diels-

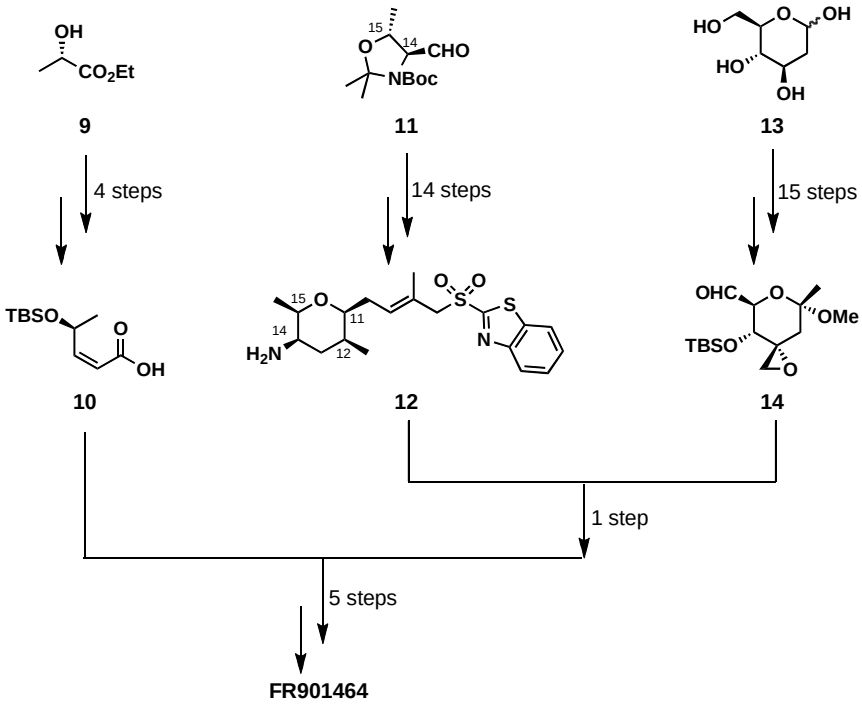
Alder reaction.[23] The synthesis of fragment **8** began from propanone **6** and dienyne **7** through cycloaddition,[23] Rubottom oxidation,[24] hydrozirconation and epoxidation. With fragment **5** and **8** in hand, a Negishi coupling[25] reaction was applied. After the installation of side chain **2**, the synthesis of FR901464 was achieved in a total of 37 steps, with 19 steps in the longest linear sequence.[26-27]



Scheme 1. Jacobsen's total synthesis of FR901464

The Kitahara group employed a chiral pool strategy to complete the second total synthesis of FR901464.[28] Because several problems were encountered in the synthesis, such as a low yield in the Julia olefination[29] and poor regioselectivity during the epoxidation, they revised the key steps in their second generation of total synthesis.[30] In Kitahara's second total synthesis of FR901464 (Scheme 2), the acid fragment **10** was prepared from (*S*)-lactate **9** in four steps. Garner's aldehyde **11**,[31] with set C14 and C15 two stereocenters of FR901464, was used to

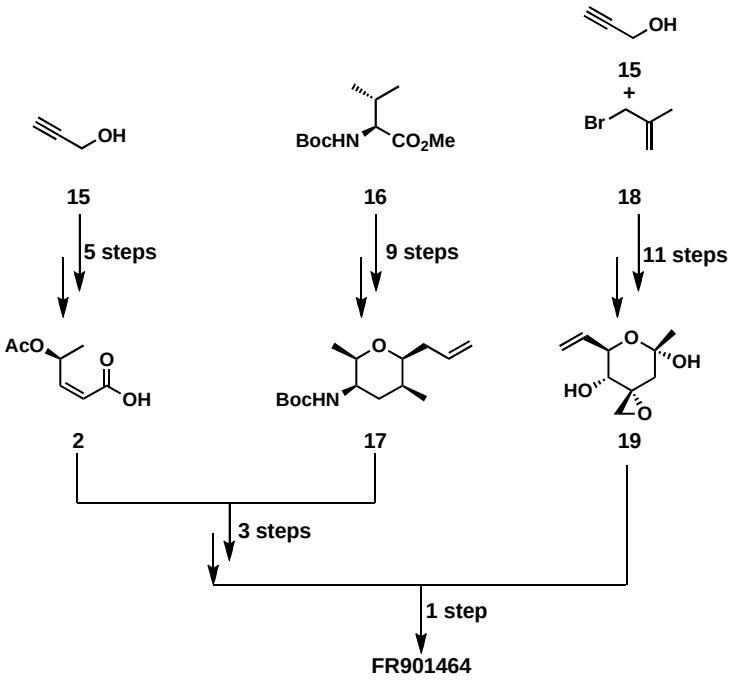
synthesize sulfone **12**, in which the stereocenters C11 and C12 were established with platinum-catalyzed hydrogenation. The synthesis of fragment **14** began with 2-deoxy-D-glucose **13** containing C4 and C5 stereocenters and was finished in 15 steps. After fragments **10** and **12** were coupled by amidation, the resulting product was subjected to modified Julia olefination followed by four additional steps to produce FR901464. The total synthesis was completed in 41 total steps, with 22 steps in the longest linear sequence.[30]



Scheme 2. Kitahara's total synthesis of FR90464

The Koide group developed a more concise way to accomplish the total synthesis of FR901464 (Scheme 3). The acid side chain **2** was synthesized from propargyl alcohol **15** with the C4' stereocenter established through CBS reduction.[32] The synthesis of the tetrahydropyran ring **17** began with the L-threonine derivative **16** and was completed in 9 steps. Intermediate **19** was prepared from propargyl alcohol **15** and methallyl bromide **18** in 11 steps. With the three fragments in hand, an amidation reaction assembled acid **2** and protected amine **17** to form an advanced intermediate, which was subjected to two more steps followed by cross olefin

metathesis to give FR901464. The total synthesis of FR901464 was achieved in 29 steps, with 13 steps in the longest linear sequence.[1,33]



Scheme 3. Koide's total synthesis of FR901464

1.1.3 Previous synthesis and biological activity of FR901464 analogues

The structure-reactivity relationship (SAR) of FR901464 has been partially elucidated through analogue synthesis (Figure 4). The Jacobsen group synthesized analogues **20**–**24** to study the side chain, the hemiacetal, and the epoxide, respectively. FR901464 and these analogues were tested for their anticancer effects against Tag Jurkat cells.[27] The GI_{50} value of compound **20** was 1700 nM, which was three orders of magnitude more than that of FR901464 (GI_{50} = 2.0 nM), meaning that the side chain plays a key role for the biological activity of FR901464.[27] Compound **21**, the C4' epimer of FR901464, was less potent than the parent compound by 15-fold.[27] The activity of **22** was the same as the natural product, demonstrating that equilibration to an open chain ketone was not essential for biological activity. The activity of compound **23**

bearing an inverted stereocenter at C3 dropped two orders of magnitude. Furthermore, after the epoxide was replaced by a cyclopropyl moiety, the resulting compound **24** completely lost biological activity, which suggested that epoxide moiety was vital to the biological activity of the compound.[27]

The Takahashi group synthesized two FR901464 derivatives, cyclopropane **25** and *ω*-amine ester **26**, by modifying the C4-hydroxy group and C4'-ester group of FR901464 with amino-alkyl group. The EL-4 mouse lymphoma T-cell line was used to test the biological activities of the two compounds and FR901464. The GI_{50} values of **25** and **26** were 500 nM and 83 nM, respectively, which were two orders and one order of magnitude higher than that of FR901464, respectively.[34]

The Kitahara group used a cytomegalovirus (CMV) promoter-driven transcription system to test two FR901464 analogues, spliceostatin A (Figure 2) and alkene **27**. Spliceostatin A was more potent than FR901464, but derivative **27** almost completely lost biological activity, which further supported the significant contribution of the epoxide moiety to the biological activity of FR901464.[14]

The lability of FR901464 prompted the Koide group to examine the stability of fragment **19**. The half-life of **19** is only 8 h and 4 h in pH 7.0 and 7.4 buffer, respectively.[1] The following mechanistic study implied that the hemiacetal functionality was unstable. The Koide group replaced the C1-hydroxy group with a methyl group and found the resulting analogue **28** (meayamycin) (GI_{50}, 10.2 pM) was 100-fold more active than FR901464 (GI_{50}, 1.1 nM) in MCF-7 cells.[1] After this discovery, the Koide group synthesized a series of analogues **29**, **30** and **31**. In alcohols **29**, **30** and methyl ether **31**, the epoxide moiety was substituted with oxygen-containing groups. These analogues showed no anticancer activity against MCF-7 cells even at 10 μM. This

result was consistent with that from the Jacobsen and Kitahara groups and suggested that the epoxide moiety played a vital role in the antiproliferative activity.

For the purpose of simplifying the left-hand ring and studying its SAR, the Koide group prepared gem-dimethyl analogues **32** and **33**, which exhibited GI_{50} values of 0.30 and 2.5 nM, respectively. Compared with meayamycin **28**, the decreased biological activities were attributed to the loss of hydrophobicity caused by removing the methyl group and replacing the methylene group with oxygen. [35]

Alcohols **34** and **35** were prepared to examine the importance of the C4' stereocenter and the acetyl group to the biological activity. The activity of **34** was 24 times (GI_{50} = 0.48 nM) lower than that of meayamycin, while the GI_{50} of analogue **35** dropped one order of magnitude in comparison with meayamycin. The results demonstrated that the acetyl group and the C4' stereocenter played a crucial role in the mode of action of FR901464. After deacetylation, the improved hydrophilicity might contribute to the loss of potency. In addition, the C4' free alcohol in these two compounds can form intramolecular hydrogen bonds with C1' carbonyl, which facilitates the change of the orientation 5'-methyl group and C4'-hydrogen. The change of conformation diminished the biological activity of the analogues. The degradation of meayamycin in human serum showed that the acetyl group could be hydrolyzed, with a half life of 2 h.[36] Compound **36** (meayamycin B) was then synthesized by replacing the acetyl group with morpholine-based carbamate to improve the stability.[37-39] The increased stability would extend the half-life. In turn, the actual concentration of the compound *in vivo* or *in vitro* was hypothesized to increase, and the potency of the compound would therefore be enhanced. As anticipated, the biological activity of compound **36** was improved in comparison to compound **28** against several cell lines.[35]

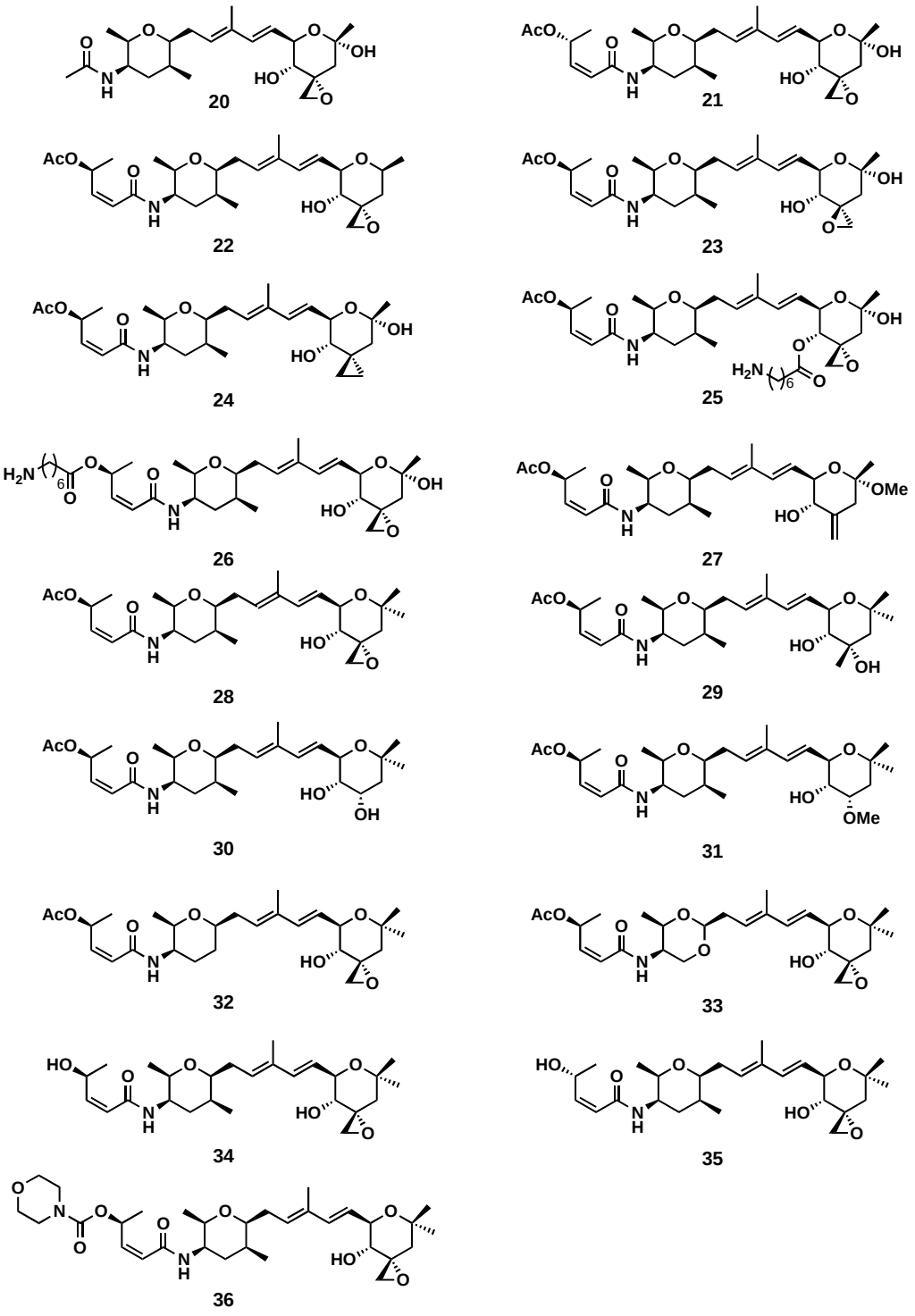


Figure 4. FR901464 analogues

Chemical biology studies uncovered that FR901464 and pladienolide B have a very similar mode of action.[15,21] Inspired by these findings, the Webb group used their model to

design a new compound **37**.[40] In the compound, the highly substituted left tetrhydropyran ring was replaced with a cis-1,4-substituted cyclohexyl group, eliminating the C4-hydroxy group.[40] Although compound **37**, with an IC_{50} of 2.29 μM against MCF-7 cell lines, was less potent than FR901464, it was very synthetically tractable. Compound **37** also showed a biological profile similar to that of FR901464, which suggested that it might have the same mode of action as FR901464.[40] Based on their discovery, the Webb group synthesized a series of compounds to further understand the SAR. Four carbamate derivatives containing a basic amine group were prepared (Figure 5), which were hypothesized to have enhanced solubility and esterase resistance.[41] The carbamate derivatives **38a-b** showed, however, less potency against JVM-2 cell lines in comparison to **37**.[41] They also synthesized a set of ester analogues **39a-i**, and studied the biological activity of **39a** in which the acetyl was replaced with a more hindered isobutyryl moiety to improve stability *in vivo*.[41] In addition, compound **39a** should preserve high chemical stability in phosphate buffered saline (pH 7.4, $t_{1/2}$ = 1200 h at 22 °C). Compound **39a** exhibited selective antitumor activity against certain adult and pediatric cancer types.[41] Due to limited solubility of compound **39a** in water or aqueous buffer,[41] a cyclic acetal analogue **40** was designed to improve the solubility. Compound **40** was more soluble than **39a** in phosphate buffered saline, and had biological activity similar to **39a** against JeKo-1 cell lines. Both **39a** and **40** displayed mRNA splicing inhibition activity, and presumably had similar molecular targets of FR901464 or pladienolide B.[41]

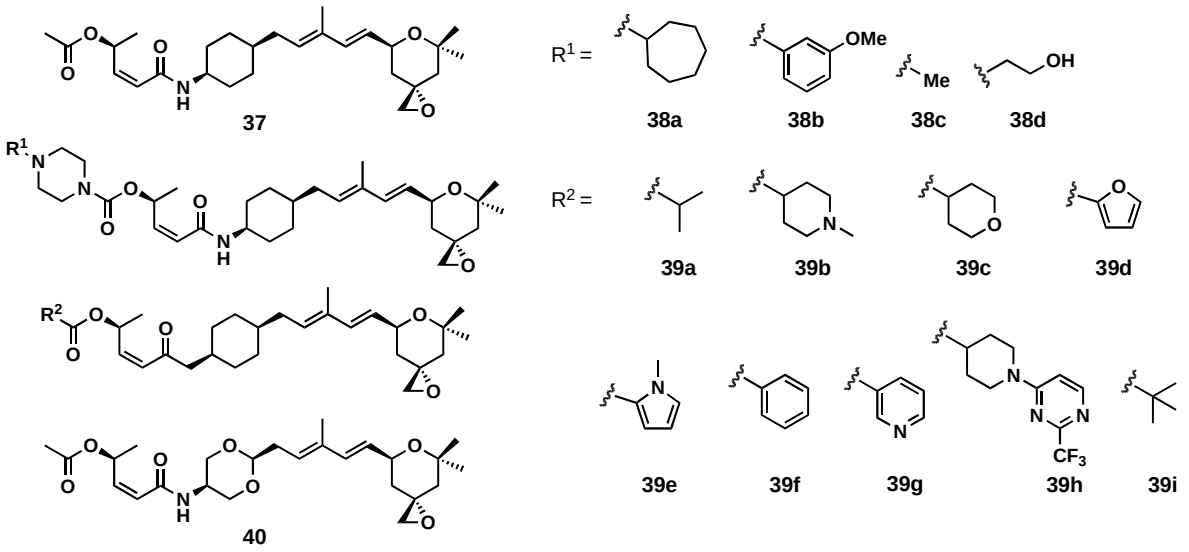


Figure 5. Structures of **37** and its analogues

In summary, the replacement of the C1-hydroxy group (Figure 6) with a methyl group improved the potency of analogues, which indicates that the open-chain ketone isomer is not responsible for the cytotoxicity of FR901464. The C3-expoide group is important for the biological activity of FR901464. Protection of the C4-hydroxy group with a methyl group diminished the biological activity. Cyclopropanation of the C8-C9 double bond induced loss of the anticancer potency. Modifying the left-hand pyran ring caused a decrease in the biological activity because of diminished hydrophobicity and alteration of conformations. Last but not least, the biologically labile C4'-acetate is important to the FR901464, but it can be substituted with a morpholine-based carbamate to enhance stability and potency.

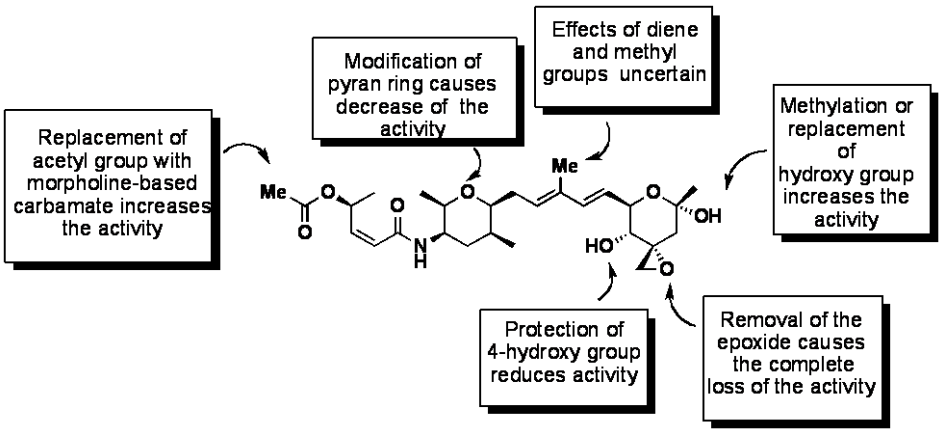


Figure 6. Structure-activity relationship of FR901464

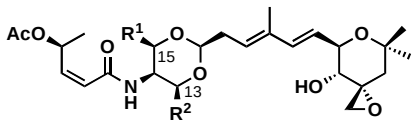
1.2 SYNTHESIS AND BIOLOGICAL ACTIVITY OF FR901464 ANALOGUES

1.2.1 The synthesis and biological activity of acetal analogues

1.2.1.1 Introduction of acetal analogues

In order to develop a more efficient synthesis, the Koide group has been engaged in the design and synthesis of simplified but potent analogues of FR901464. During this work, acetal analogue **33** (Figure 4) was synthesized in 21 steps by Dr. Miaosheng Li.[35] In analogue **33**, the left-hand pyran ring was replaced by an acetal ring that could be easily obtained. Although the replacement resulted in the loss of biological activity, in comparison with its parent analogue **28** (meayamycin), analogue **33** still has a nanomolar IC_{50} value (2.5 nM).[35]

The current study examines the influence of the acetal ring on the biological activity. I decided to synthesize acetal analogues **41** and **42** to probe the impact of substituents at positions 13 and 15 (Figure 7).

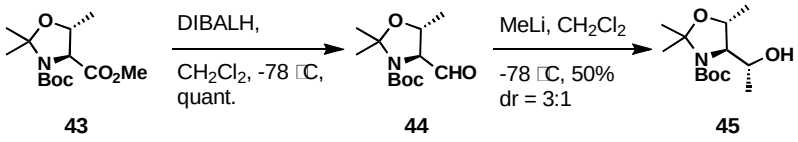


41 (R^1, R^2 = Me)
42 (R^1, R^2 = H)

Figure 7. Structures of acetal analogues **41** and **42**

1.2.1.2 Synthesis of acetal analogues

Initially, efforts toward the synthesis of analogue **41** begun by converting compound **45** from **43**[33] (Scheme 4). Oxazolidine **43** was treated with DIBALH to give Garner's aldehyde **44**,[31,42-43] which was subjected to nucleophilic addition with MeLi. The addition reaction gave the undesired diastereoisomer **45** as a major compound, however, via a non-chelation controlled Felkin-Anh model[44-46] (Figure 8), in which the methyl nucleophile attacked on the less hindered *re*-face to give the *trans* product.[47]



Scheme 4. Nucleophilic addition to Garner's aldehyde

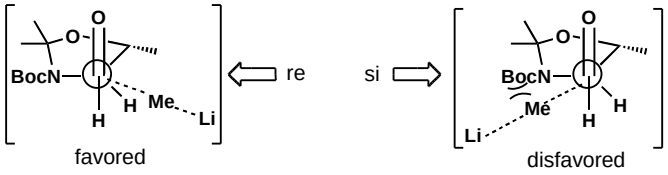
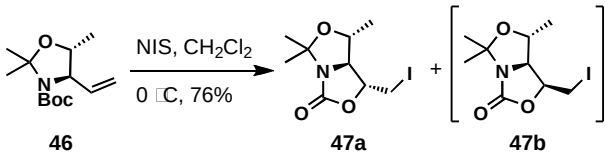


Figure 8. Model of methyl nucleophile addition to Garner's aldehyde

Due to the unsuccessful nucleophilic addition to Garner's aldehyde, I started to search for a new route. I discovered that olefin **46**[33] could be treated with NIS to afford desired iodide **47a** (Scheme 5) as the major compound via iodocyclization[48-50], and a minor compound was tentatively assigned as iodide **47b** (4.6-6:1 dr).



Scheme 5. Regio- and diastereoselective iodocyclization of **46**

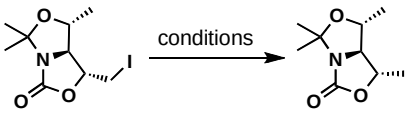
To explain the diastereoselectivity of the iodocyclization, two possible transition states were proposed (Figure 9). If iodine attacked the α-face of the olefin in **46**, intermediate iodiranium **48a** would be formed. The carbonyl oxygen of the carbamate attacked the C13-I bond backside to give compound **47a**. Intermediate iodiranium **48b**, formed by iodine attacking on the β-face of the olefin, had a higher activation energy because of the steric interaction between H_a and H_b in the transition state.

Figure 9. Iodonium transition states **48a** and **48b**

The subsequent reduction of the iodide compound **47** proved to be problematic (Table 1). The palladium-catalyzed dehalogenation reaction[51] was applied to reduce **47**, but no reaction happened at room temperature or elevated temperature. When Et_3SiH was used as a solvent at 80 °C, the thin layer chromatography showed an intractable result. Then, two conditions, $LiAlH_4$[52] and AIBN/Bu_3SnH,[53] were employed to remove the iodine; however, both of these conditions

gave intractable products. I therefore applied a Pd/C catalyzed-hydrogenation[54] condition to reduce the iodide. In order to neutralize the side product acid HI, bases NaOH and $NaHCO_3$ were first applied, but led to a low yield of oxazolidin **49**. Et_3N was then used, and the reaction proceeded smoothly to provide **49** in 86% yield.

Table 1. Reduction of iodide **47a**

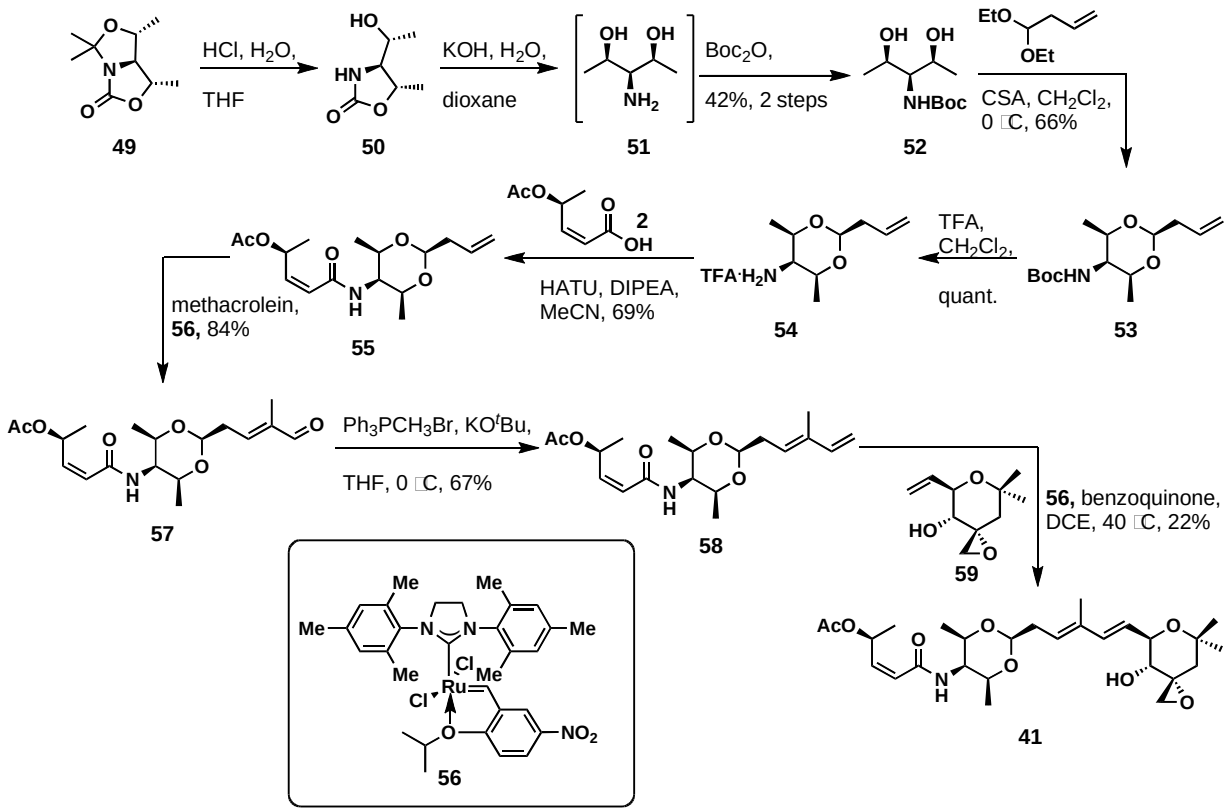


47a **49**

entry	catalyst (equiv)	reagent (equiv)	solvent	temperature	time	result
1	$PdCl_2$ (5 mol%)	Et_3SiH (1.5)	Et_2O	rt	2 h	no reaction
2	$PdCl_2$ (5 mol%)	Et_3SiH (1.5)	toluene	reflux	2 h	no reaction
3	$PdCl_2$ (5 mol%)	Et_3SiH (1.5)	none	80 °C	2 h	intractable products
4	none	LAH (2.0)	THF	rt	1 h	intractable products
5	none	AIBN(0.2) Bu_3SnH (3.0)	toluene	rt	12 h	intractable products
6	Pd/C (5 mol%)	NaOH (1.2), H_2 (1 atm)	EtOH	rt	6 h	15%
7	Pd/C (5 mol%)	$NaHCO_3$ (2.0), H_2 (1 atm)	EtOH	rt	1.2 h	46%
8	Pd/C (5 mol%)	Et_3N (6.0), H_2 (1 atm)	EtOH	rt	22 h	86%

Acidic hydrolysis of **49** gave alcohol **50** (Scheme 6),[44] which was further exposed to KOH to generate diol **51**. Due to the high water solubility of **50** and **51**, it was laborious to extract these two intermediates from the aqueous layer. Once the Boc-protected compound **52** was formed, purification became easier and more efficient. Subsequently, **52** was treated with 3-butenal diethyl acetal and a catalytic amount of CSA to furnish segment **53**.

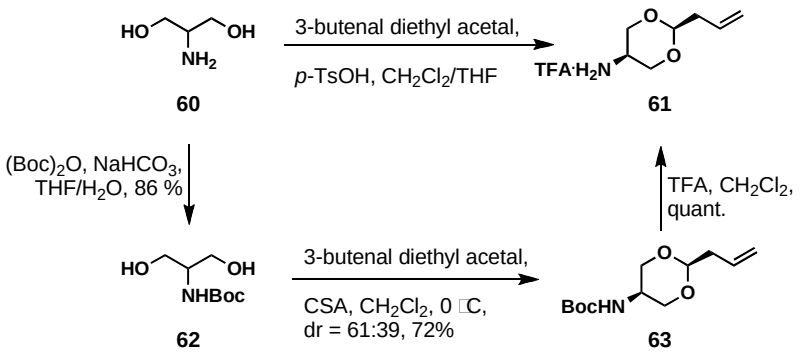
With **53** in hand, amine **54** was afforded after removal of Boc (Scheme 6), and subsequently subjected to a coupling reaction with fragment **2**. The resulting intermediate olefin **55** was exposed to methacrolein and ruthenium complex **56**[55-56] to furnish aldehyde **57** via a cross metathesis reaction. The Wittig reaction was then used to convert aldehyde **57** to diene **58**. The acetal analogue **41** was then completed by exposure of diene **58** to the right fragment **59** and pre-catalyst **56** in 22% yield.



Scheme 6. Synthesis of **41**

At this stage, two acetal analogues, **33** and **41**, were available containing one and two methyl groups on the cyclic acetal, respectively. The third acetal analogue **42** without a methyl group on the cyclic acetal (Figure 7) was also synthesized. Synthesis of analogue **42** began with the preparation of fragment **61** (Scheme 8). With commercially available amine **60**, 3-butenal

diethyl acetal and 0.1 equivalent of *p*-TsOH were used in attempts to form the acetal ring,[57] but no desired product was obtained. I envisioned that the free amine might influence the reaction by forming five member ring,[58] and could be protected *in situ* with excess acid. After the amount of *p*-TsOH was increased to 1.3 equivalents, **61** was produced with 13% yield. Because of the low yield of acetal formation with the free amine, **60** was protected by using Boc_2O. The resulting diol **62** was subjected to acetal formation with 3-butenal diethyl acetal to afford acetal **63** (*cis* : *trans* = 61 : 39). After recrystallization, the diastereoisomeric ratio increased from 61:39 to 83:17. The Boc group was then removed with TFA to afford **61** in 49% yield over three steps.



Scheme 7. Synthesis of **61**

The NMR spectra for *cis* and *trans*-**63** showed the existence of an intramolecular hydrogen bond (Figure 10) in *cis*-**63**, which accounts for the preference of the *cis* isomer.[59] The chemical shift of N-H in *cis*-**63** is 5.51 ppm (broad doublet); by contrast, *trans*-**63** presents a free N-H group with a broad peak at 4.15 ppm.

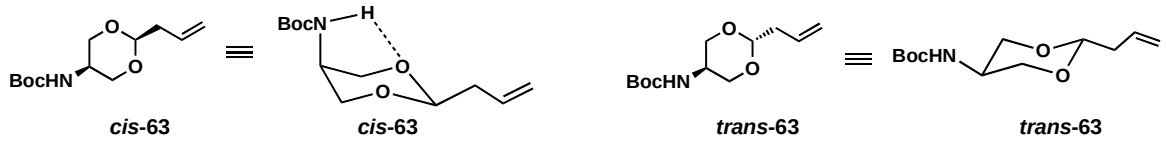
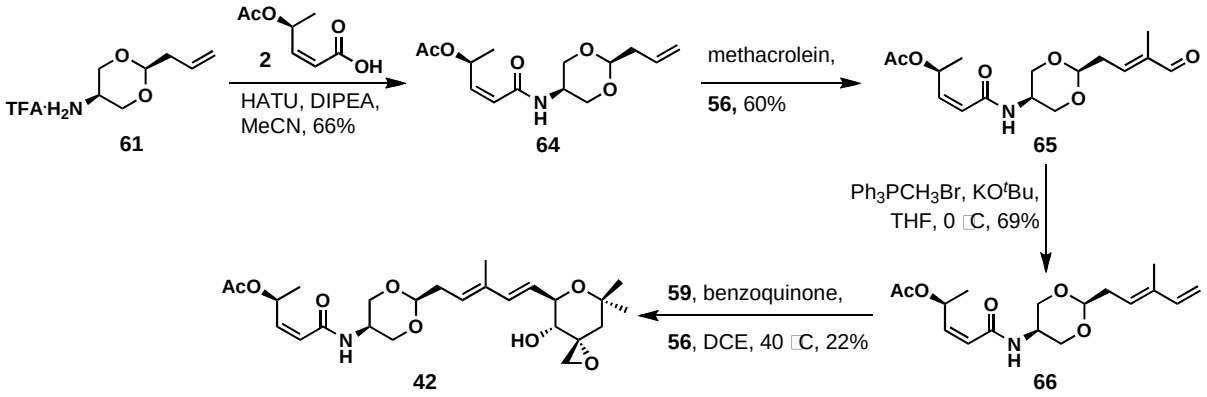


Figure 10. H-bonding potential for acetal **63**

Acetal analogue **42** was then completed as follows. Intermediate **61** was synthesized from **58** and acid **2** (Scheme 8) and further treated with methacrolein and **53** to afford aldehyde **62**. The diene fragment **63**, constructed via the Wittig reaction from **62**, was subjected to metathesis reaction with **56** and **53** to afford the acetal analogue **38**.

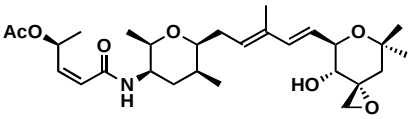
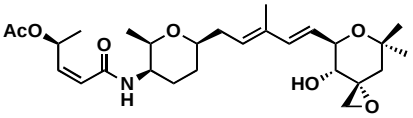
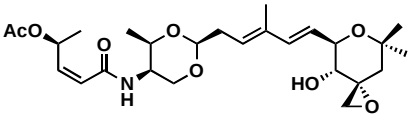
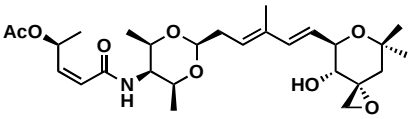
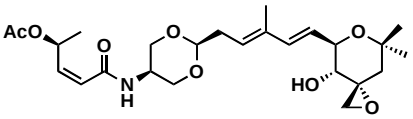


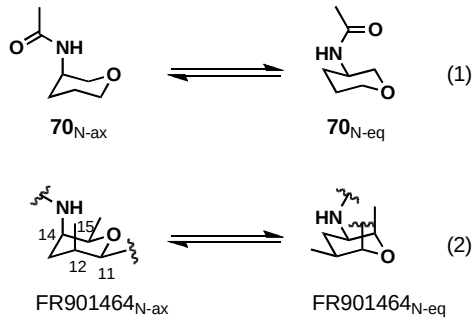
Scheme 8. Synthesis of **42**

1.2.1.3 The biological activity of acetal analogues

The anticancer activities of these two acetal analogues **41** and **42** against MCF-7 cells (Table 2) were examined by Sami Osman in the Koide group. The GI_{50} values for **41** and **42** were determined to be 85 and 19 nM, respectively. To account for their different biological activities, the conformation differences of the two compounds were studied. Previously, the Vasella group examined the conformations of compound **70** in water and found that the $\mathbf{70}_{N\text{-}ax}$ had an unexpectedly high ratio of 33% (Scheme 9). The hydrogen bonding between the amide hydrogen and the oxygen presumably stabilized the conformer $\mathbf{70}_{N\text{-}ax}$.[60]

Table 2. Antiproliferative activities of **28**, **32**, **33**, **41** and **42** against MCF-7 cells

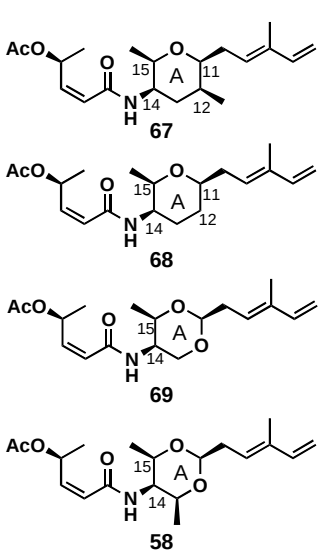
FR901464 analogues	GI_{50} (nM)
 **28**	0.020
 **32**	0.30
 **33**	2.5
 **41**	85
 **42**	19



Scheme 9. Conformations of compound **70** and FR901464

The conformer $FR901464_{N\text{-}ax}$ would be even more favored because the severe 1,3-interaction between substituents on C11 and C15 in $FR901464_{N\text{-}eq}$. $FR901464_{N\text{-}ax}$ was supposed to be the dominating conformer. With this hypothesis, the coupling constants of protons in the A rings in left side fragments of **67**, **68** and **69** of the corresponding analogues **28**, **32** and **33** were examined (Figure 11) (CD_3OD was used as solvent).[35] For **67**, $J_{11\text{-}12}$ was 2.8 Hz and $J_{14\text{-}15}$ was 2.1 Hz, indicating a chair-like structure. For **68**, $J_{11\text{-}12}$ was 3.5 Hz and $J_{14\text{-}15}$ was 1.6 Hz, and

$J_{14\text{-}15}$s in acetals **69** and **58** were 1.8 and 1.5 Hz, respectively, thus indicating that the bond angles are similar in all four structures.[35] Therefore, the variation in their biological activity is not due to the difference of conformation in the A-ring.



	$J_{11\text{-}12}$ in Hz	$J_{14\text{-}15}$ in Hz
67	2.8	2.1
68	3.5	1.6
69	-	1.8
58	-	1.5

Figure 11. Structures of **58**, **67**, **68** and **69** and couplings in the A rings

An additional reason behind the decrease in biological activity may be the diminished hydrophobicity of the A ring. The effect of this trend was demonstrated with compounds **28**, **32**, **33** and **42** (Figure 12). Hydrophobicity was reduced in comparison to **28** by eliminating C12-methyl group in **32**, replacing C12 with an oxygen atom in **33**, removing another methyl group at C15 position in analogue **42**. With a corresponding loss of hydrophobicity, these four analogues' GI_{50} values increased from 0.020 to 19 nM against MCF-7 cells. This indicated that the hydrophobicity of the compounds played a vital role for the anticancer activities. In addition, the roles of substituents at positions 13 and 15 were probed. Replacement of a hydrogen at C13 with a methyl group was detrimental to the biological activity. The deletion of the C15 methyl group

also caused a loss of the antiproliferative activity. The syntheses of these analogues investigated the significance of the substitutents at positions 12, 13 and 15.

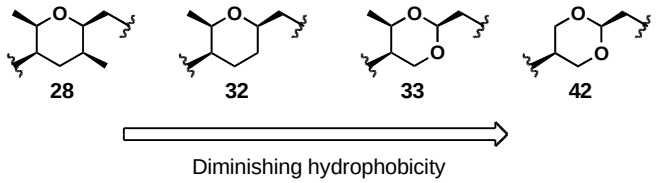
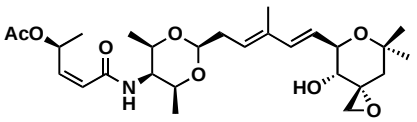


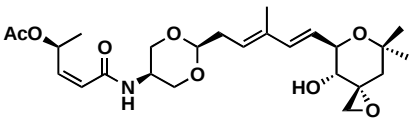
Figure 12. The hydrophobicity of the left-hand ring in analogues 28, 32, 33 and 42.

Compared to compound **40** synthesized by the Webb group, analogue **42** retained the C4-hydroxy group. Compound **40** showed nanomolar activity against JeKo-1 cell lines (GI_{50} = 150 nM), while the GI_{50} of **42** against MCF-7 cells was 19 nM. Unfortunately, because these two compounds had been tested in different cell lines, it was difficult to determine the importance of the C4-hydroxy group to the biological activity of FR901464. However, compound **40** showed activity against JeKo-1 cell lines very similar to that of compound **39a**, which was less potent than **42** against MCF-7 cells. It can thus be speculated that compound **40** is less active than analogue **42** in MCF-7 cell lines, and the C4-hydroxy group possibly benefits the biological activity of FR901464.

In conclusion, acetal analogues **41** and **42** were synthesized and tested in MCF-7 cells. The results suggested the methyl groups on the acetal ring moderately influence the biological activity of the acetal analogues.



41 (GI_{50} = 85 nM)



42 (GI_{50} = 19 nM)

1.2.2 The synthesis and biological activity of cyclopropane analogues

1.2.2.1 Introduction

Cyclopropyl groups occurring in natural products or in synthesized compounds can sometimes improve the biological activity of compounds.[61-62] Several cyclopropane-containing analogues of epothilone [63-64] and (+)-discodermolide[65] have been synthesized and proven to improve or maintain the biological activities as compound to the parent molecules. However, the cyclopropane moiety also induced the activity loss of compounds, such as *cis*- and *trans*-2-(aminomethyl) cyclopropane carboxylic acids[66] and several cyclopropane analogues of penciclovir.[67]

The diene moiety in FR901464 has two faces, which might have different preferences to the target. In addition, the 1,3-diene was found to be subject to facile isomerization under acidic conditions,[1] which might also occur in cells. I questioned whether the *trans*, *trans*-diene moiety was actually the biological active species. To address these hypothesis, cyclopropane analogues **71** and **72** (Figure 13) were designed in which either face of the diene was blocked and the cyclopropane moiety also maintained the *trans* arrangement afforded by the C8-C9 double bond.

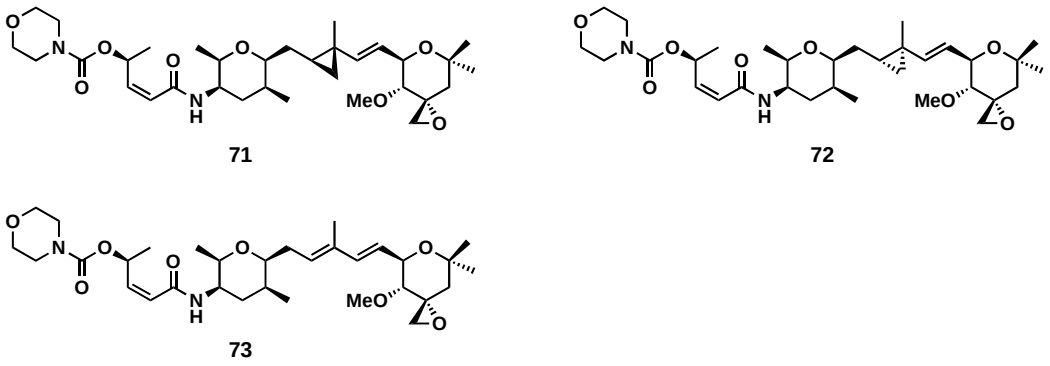
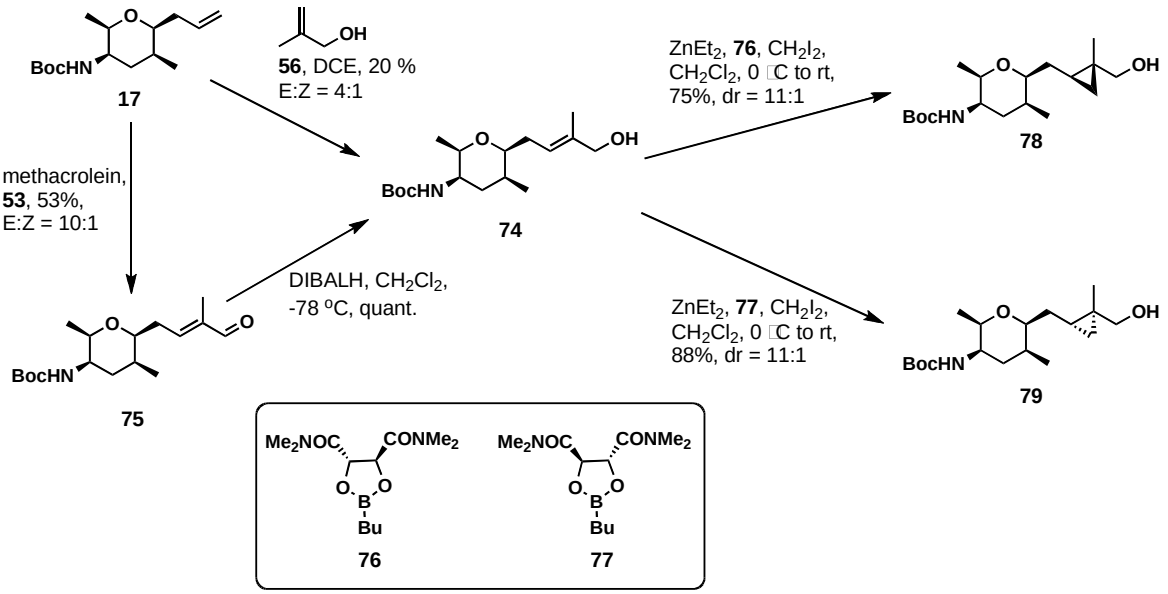


Figure 13. Structures of analogues **71**, **72** and **73**

1.2.2.2 The synthesis of cyclopropane analogues

Efforts towards these two analogues were focused on building the cyclopropane ring. I started from intermediate **17**[1] and 2-methyl-2-propen-1-ol (Scheme 10), which were treated with ruthenium complex **56** to give allylic alcohol **74**. Unfortunately, the reaction suffered from a slow rate and poor selectivity (E:Z = 4:1). Instead of 2-methyl-2-propen-1-ol, methacrolein was alternatively chosen for the metathesis reaction,[68] and enone **75** was made in 53% yield with an improved selectivity (E:Z = 10:1). Enone **75** was reduced with DIBALH to provide **74** in quantitative yield. A diastereoselective Simmons-Smith reaction[69] with chiral ligands **76** or **77** transferred **74** to **78** or **79**, respectively, with moderate selectivity. Two possible transition states for the diastereoselective cyclopropanation of **74** are presented as structures **80a** and **80b** in Figure 14. In conformation **80b**, the double bond is folded away from the amide carbonyl group that loosely connects with the zinc, while zinc carbenoid is brought in a closer proximity to the amide carbonyl group in conformation **80a**. Compared to **80b**, **80a** has lower energy and is therefore predicted to be the excess diastereomer.[69] The C8 methyl group has strong interaction with the zinc reagent in the transition state **80a**.[69]



Scheme 10. Synthesis of **75** and **76**

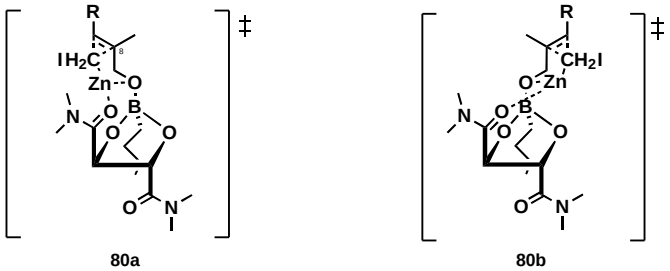
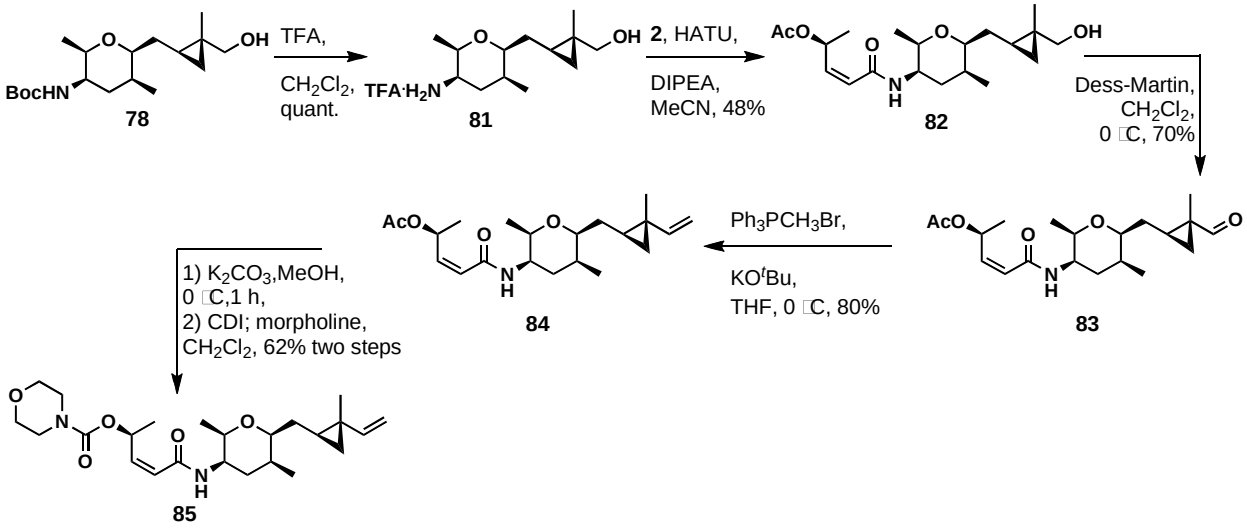


Figure 14. Transition-state model for the cyclopropanation

After **78** was deprotected with TFA, the resulting amine **81** was coupled with acid **2** to produce **82** (Scheme 11). Subsequent Dess-Martin[70] oxidation of **82** afforded **83**, and the aldehyde was then exposed to the Wittig reagent to give **84**. Transformation of **84** into carbamate **85** was accomplished through methanolysis of the acetate, activation of the resulting alcohol with CDI, and nucleophilic substitution with morpholine.

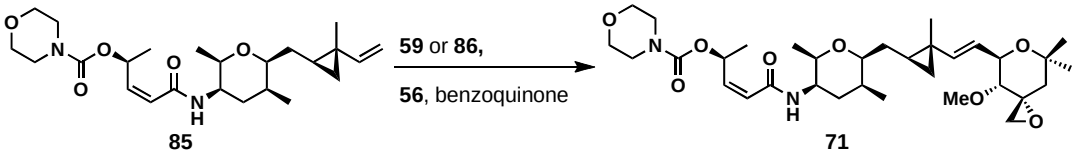


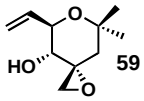
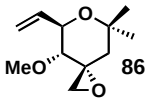
Scheme 11. Synthesis of **85**

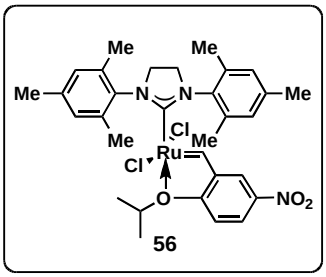
I encountered some difficulties in the last step metathesis reaction because of the highly substituted allylic position. Fragment **59** (Table 3) was first employed as a cross metathesis

partner at 40 °C, but no desired product was observed. Subsequently, the temperature was increased to 70 °C, giving the dimer of **59** as the major product. Due to the introduction of the cyclopropyl group, the left fragment **85** was sluggish in the metathesis reaction, but **59** was very reactive to the ruthenium complex. Reducing the reactivity of the right fragment was a practical way to solve the problem. Moreover, it was previously found that when **86** was applied in the metathesis reaction, the corresponding product was obtained smoothly without significant dimerization of **86**.[71] Inspired by this result, fragment **86** was then used to couple with **85** via a metathesis reaction in toluene at 70 °C, and analogue **71** was formed in 22% yield.

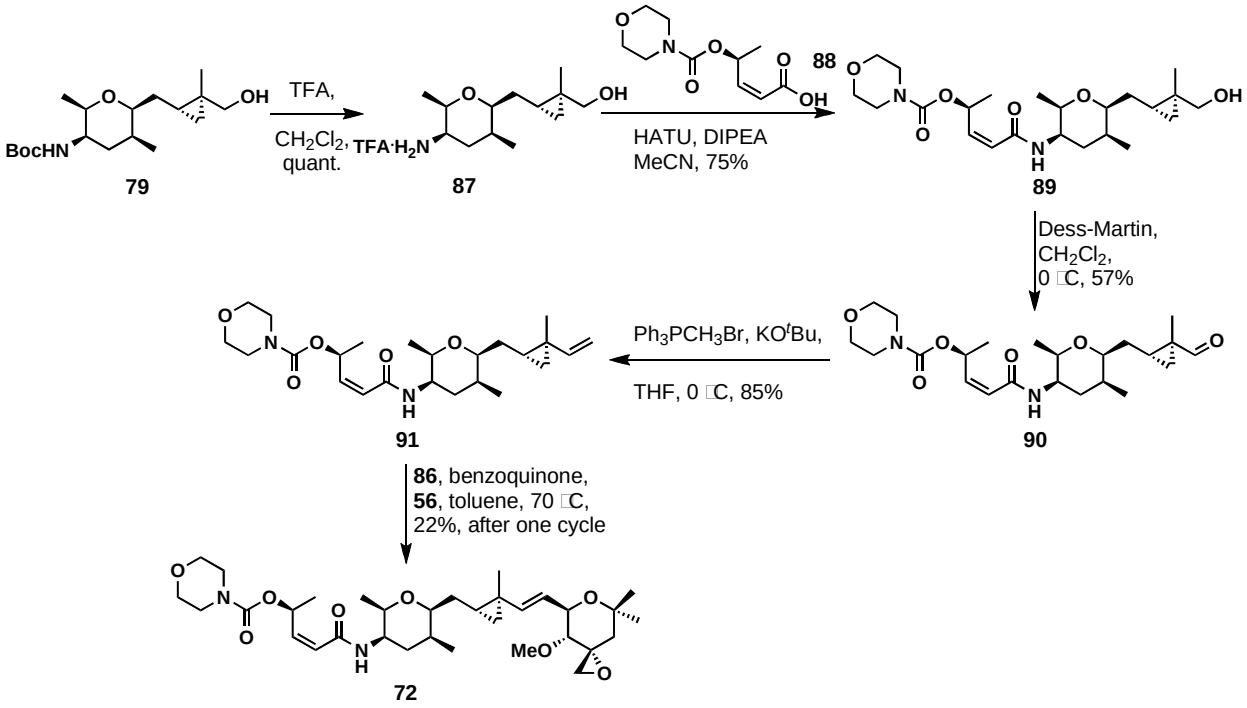
Table 3. Synthesis of cyclopropane analogue



right fragment	temperature	solvent	result
 **59**	40 to 70 □C	DCE	dimerization of right fragment
 **86**	70 □C	toluene	22% after one cycle


56

I applied a similar strategy to synthesize analogue **72** (Scheme 12). Amine **87,** produced from **79**, was assembled with acid **88** via a coupling reaction to afford alcohol **89**. Dess-Martin oxidation of compound **89** gave aldehyde **90** with a moderate yield. Compound **90** was subjected to the Wittig reaction to provide left fragment **91**, which was coupled with **86** under the same conditions as before to furnish analogue **72** in 22% yield.

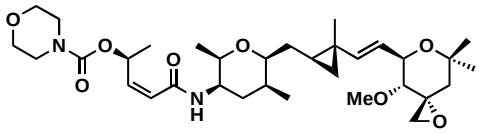
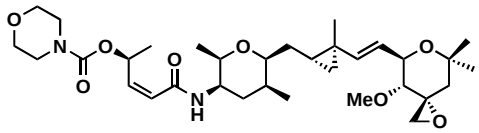
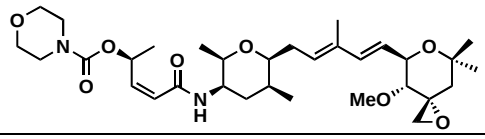


Scheme 12. Synthesis of **72**

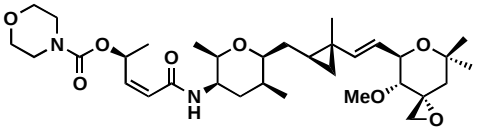
1.2.2.3 The biological activity of cyclopropane analogues

In antiproliferative experiments, MCF-7 cells were treated with cyclopropane analogues **71** and **72**. Analogue **73**, with a GI_{50} of 0.38 nM,[71] was used as a reference compound. The results showed that analogues **71** and **72** exhibited very similar GI_{50} values, 15 and 10 nM, respectively. Although they were less potent than **73** (Table 4), they were still quite active, and retained biological activities in the nanomolar range. The slightly reduced biological activities might be due to the conformational change after the introduction of the cyclopropane moiety, not the expected steric hindrance on the target binding caused by this moiety. Compared to analogue **73**, the similar activities of these two cyclopropane analogues **71** and **72** suggest that the *trans* isomer of the C8-C9 double bond of FR901464 is the active species.

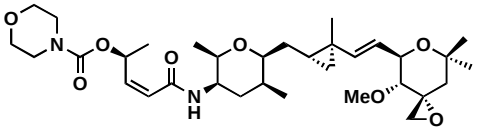
Table 4. Antiproliferative activities of **71**, **72** and **73** against MCF-7 cells

FR901464 analogues	GI_{50} (nM)
 **71**	15
 **72**	10
 **73**	0.38

In summary, two cyclopropane analogues, **71** and **72**, were synthesized with the cyclopropane moiety constructed via an asymmetric Simmons-Smith reaction. Compared to analogue **73**, these two analogues were equipotent towards MCF-7 cell lines, which implied that the cyclopropane moiety might not inhibit the binding to the targets. In addition, the cyclopropane ring also locked the compound into a *trans* configuration at the site of interest. The respectable biological activities of **71** and **72** in comparison to **73** suggest that the *trans* isomer is the active form of FR901464.



71 (GI_{50} = 15 nM)

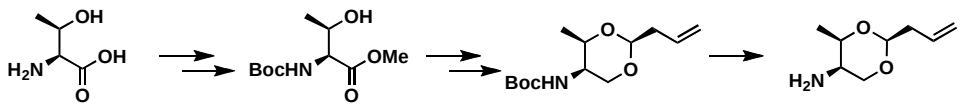


72 (GI_{50} = 10 nM)

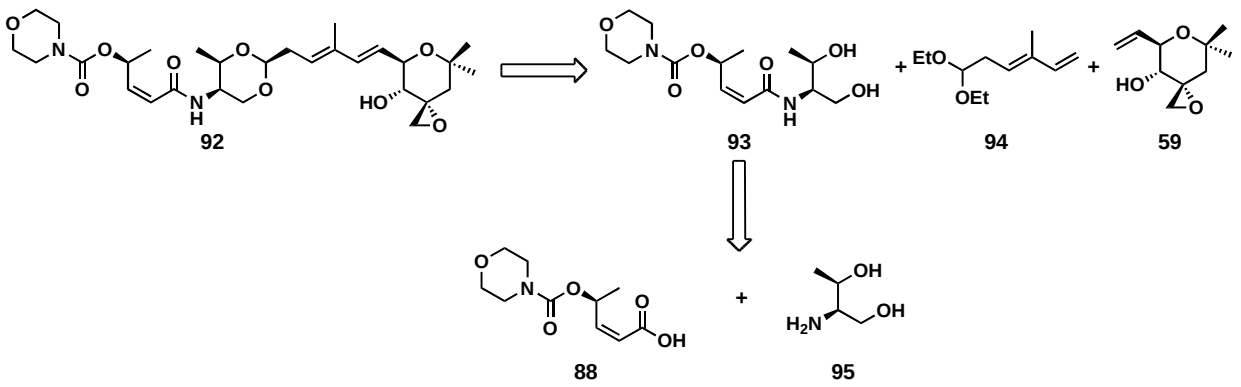
1.2.3 Development of a concise route to synthesize a new acetal analogue of FR901464

1.2.3.1 Introduction

The most efficient total synthesis of FR901464 has 29 steps in total with 13 steps in the longest linear sequence.[1,33] The long syntheses led to difficulties in obtaining sufficient material for biological testing. Following the completion of the total synthesis of FR901464 in the Koide group, its SAR was studied by preparing a series of analogues. Meanwhile, strategies were developed to synthesize simpler analogues with potent activity. During this course, acetal analogue **33** (Figure 4) was synthesized.[35] Although analogue **33** was moderately potent compared to other analogues, the simplified left-hand acetal ring was easily accessed. Concurrently, if the acetyl side chain was changed to a more biologically stable morpholine-based carbamate side chain,[35] the potency could be improved. In the first generation synthesis of acetal analogues, the free amine of the acetal ring was required to protection and deprotection (Scheme 13),[35] which influenced the synthetic efficacy. Therefore, I decided to synthesize acetal analogue **92** (Scheme 14) via a modified strategy by assembling **88**and diol amine **95** first.



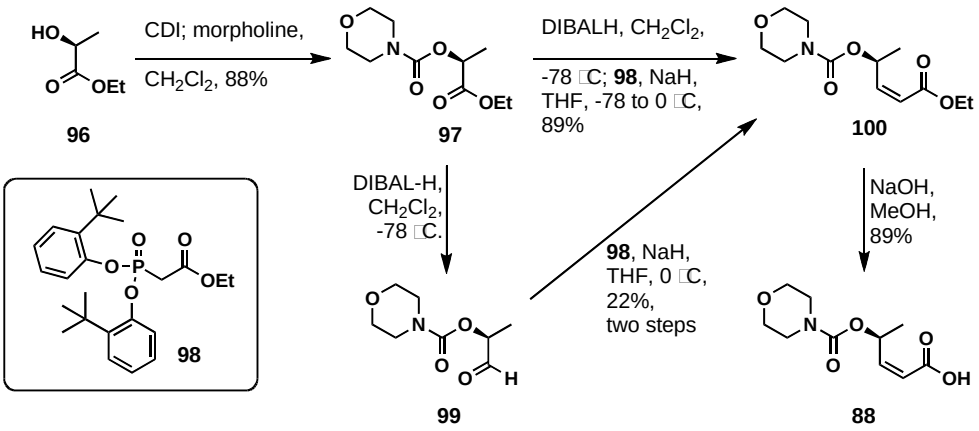
Scheme 13. The first generation synthesis of the acetal ring



Scheme 14. Retrosynthetic analysis of **92**

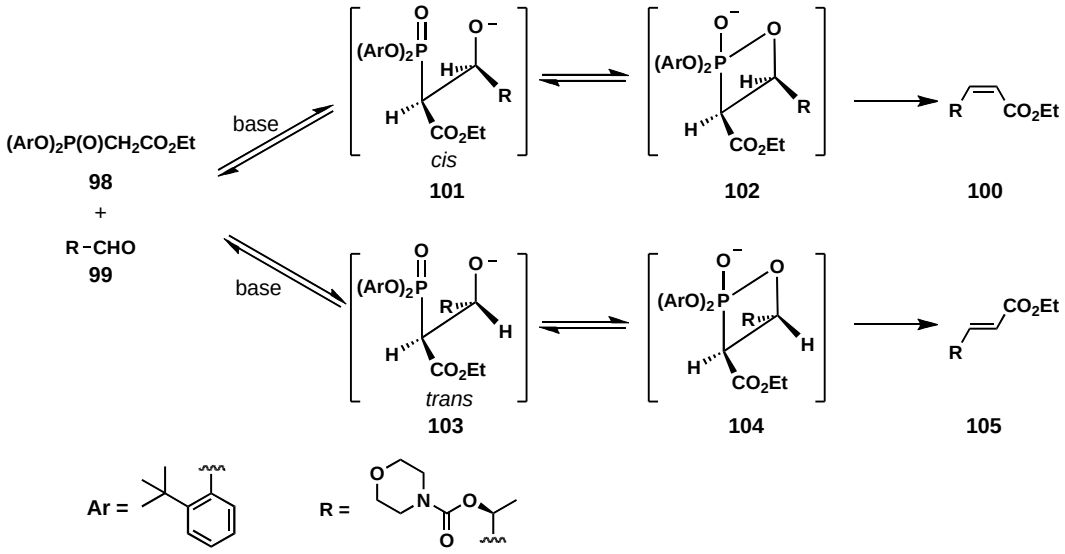
1.2.3.2 Concise synthesis of FR901464 acetal analogue

I started the synthesis of the acetal analogue **92** by developing a concise strategy to prepare acid **88**. Previously, side chain **88** (Scheme 15) was synthesized from propargylic alcohol **15** (Scheme 3) in 7 steps,[35] and the stereocenter was constructed by using a CBS reduction. I realized that it would be more convenient to construct the *cis* double bond with an aldehyde[28] (Scheme 15) and Ando's reagent **98**.[72-77] Therefore, carbamate **97** was assembled first by the treatment of **96** with CDI and morphoine. Then, **97** was treated with DIBALH to give crude **99**, followed by olefination with Ando's reagent **98** to afford **100** with 94% *Z*-selectivity. However, the yield was only 22% over two steps. The low yield was presumably due to the high water solubility of **99**. I was also concerned that aldehyde **99** might suffer from racemization during workup. Therefore, a one-pot procedure was developed, in which, without separation of aldehyde **99** from the reaction mixture, Ando's reagent **98** was added immediately after the ester **97** disappeared. Pleasingly, ester **100** was obtained in 89% yield. Subsequent hydrolysis of ester **100** with NaOH gave fragment **88** in 70% total yield over three steps.



Scheme 15. Synthesis of **88**

The mechanism of this Horner-Wadsworth-Emmons reaction[78-79] is shown in Scheme 16. Ando's reagent **98** and aldehyde **99** formed two intermediates **101** and **103** in the presence of base (Scheme 16). Intermediate **101** was kinetically favored over **103**, and irreversibly collapsed to *Z*-olefin **100** via **102**. The electron-withdrawing property of aryloxy group increased the reactivity of the adduct **101** to *Z*-olefin, which consequently lowered the ratio of decomposition to the starting materials. Therefore, the predominant formation of *Z*-olefin **100** was observed.[77] In addition, the *tert*-butyl group on the *ortho* position could enhance the *Z*-selectivity of the reaction.[77] The enhancement of selectivity is presumably caused by the bulkiness of the *tert*-butyl group destabilizing the intermediate **102**. As shown in Figure 15, the hydrogens on the *tert*-butyl group are in very close vicinity.



Scheme 16. The mechanism of Horner–Wadsworth–Emmons reaction with Ando reagents

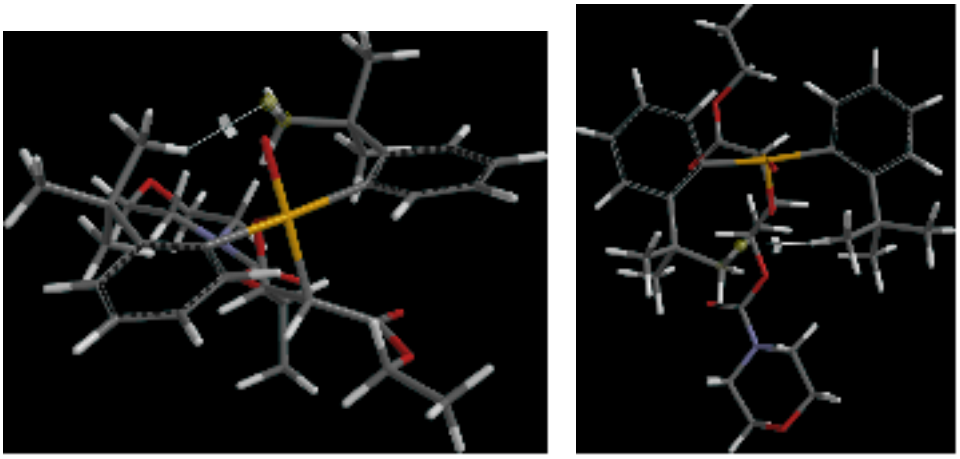
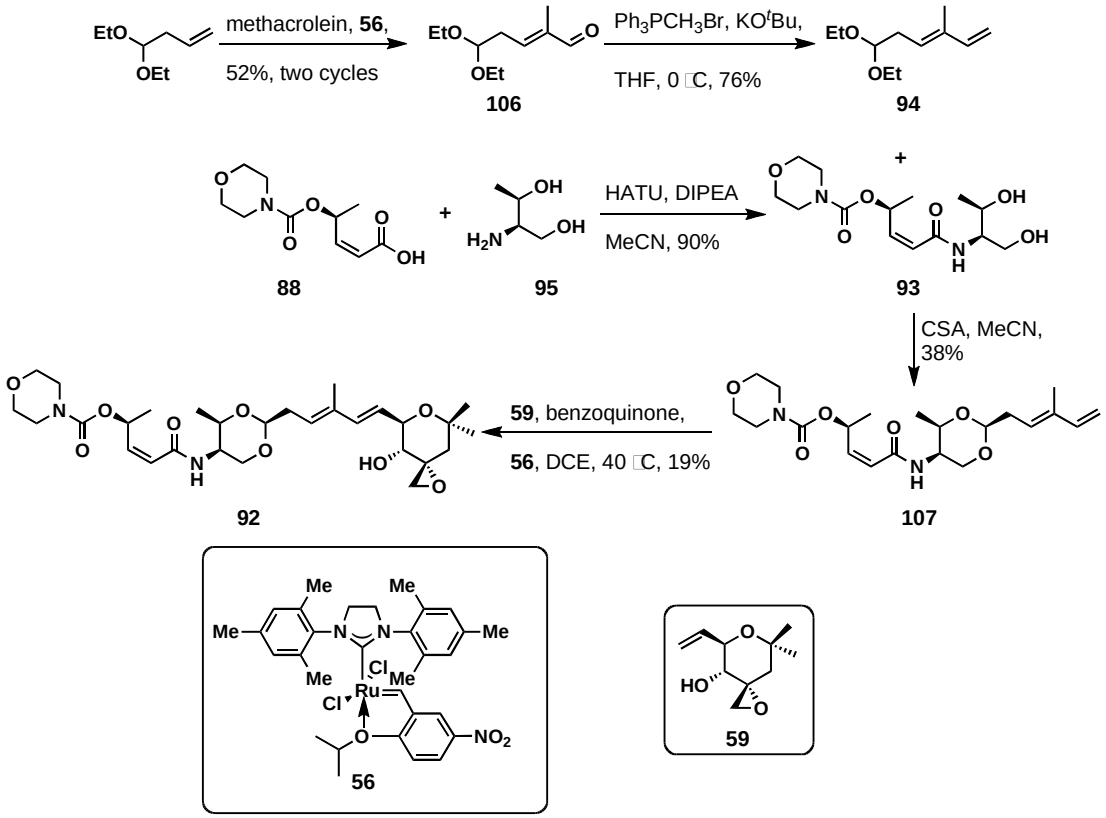


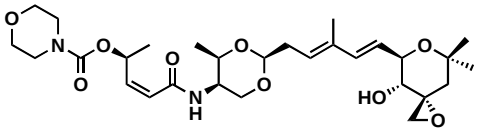
Figure 15. Two-dimensional views of intermediate **102**

Diene intermediate **94** was prepared from 3-butenal diethyl acetal and methacrolein (Scheme 17). These two compounds were coupled via a cross metathesis reaction to give enone **106**. Further treatment of **106** with the Wittig reagent resulted in fragment diene **94**. Subsequent acetal formation between **93** and **94** afforded fragment **107** as a single diastereoisomer. The synthesis of analogue **92** was then accomplished by coupling **107** and **59** by using a cross metathesis reaction.



Scheme 17. Synthesis of **92**

In summary, the side chain **88** was prepared from commercially available (−)-ethyl L-lactate in 3 steps. Moreover, the acetal ring was successfully formed at a late stage with protection and deprotection of the amino group. Acetal analogue **92** was synthesized with a new strategy containing a total of 20 steps, with 12 steps in the longest linear sequence. The antiproliferative profile of **92** is under study in the Koide laboratory. Simultaneously, a concise synthesis of the right fragment **59** is being developed in the laboratory.



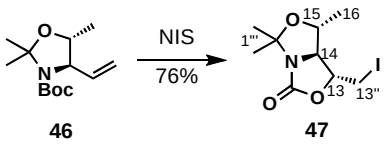
92

EXPERIMENTAL SECTION

General techniques. All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Acetonitrile was dried by passing through hot silica gel. Yields refer to spectroscopically (^1H NMR) homogenous materials, unless otherwise stated.

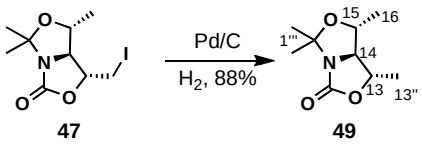
All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck (EMD) silica gel plates (60F-254) using UV light (254 nm), anisaldehyde in ethanol, 2.4% phosphomolybdic acid/1.4% phosphoric acid/5% sulfuric acid in H_2O, or 0.2% ninhydrin in ethanol and heat as developing agents. TSI silica gel (230-400 mesh) was used for flash column chromatography.

NMR spectra were recorded on AM300, AM500 or AM600 (Bruker) instruments and calibrated using a solvent peak as an internal reference. The following abbreviations are used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High-resolution mass spectra were obtained by using EBE geometry and electron impact ionization (EI) or a Q-TOF API-US with electrospray ionization (ESI) in the positive ion modes.



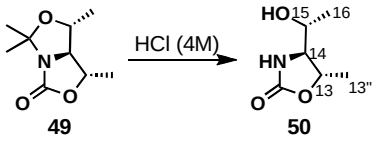
Preparation of 47. An oven-dried, 100-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **46** (2.05 g, 8.49 mmol) and CH_2Cl_2 (30 mL). The solution was cooled in an ice-water bath and NIS (2.87 g, 12.7 mmol) was added in one potion. The resulting mixture was warmed to 4 °C and stirred at the same temperature for 110 h. After additional NIS (0.96 g, 4.3 mmol) was added, the stirring was continued for 22 h at 4 °C, and saturated aqueous $Na_2S_2O_3$ (2 × 10 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5 to 20% EtOAc in hexanes) on silica gel (90 mL) to afford **47** (2.02 g, 76%, dr = 6:1) as a yellow oil.

Data for **47**: R_f = 0.33 (30% EtOAc in hexanes); IR (neat): 2982, 2933, 1764 (C=O), 1711, 1419, 1384, 1369, 1306, 1246, 1170, 1106, 1029 cm^{-1}; ^1H NMR (600 MHz, 293K, $CDCl_3$) δ 4.40 (dt, 1H, *J* = 10.2, 4.2 Hz), 3.85 (dq, 1H, *J* = 8.4, 6.0 Hz), 3.60 (dd, 1H, *J* = 8.4, 4.2 Hz), 3.46 (dd, 1H, *J* = 10.2, 4.2 Hz), 3.25 (t, 1H, *J* = 10.2 Hz), 1.71 (s, 3H), 1.50 (s, 3H), 1.39 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 293K) δ 156.0, 95.0, 76.2, 74.9, 70.3, 29.6, 24.1, 17.4, 6.2; HRMS (EI+) calcd. for $C_8H_{11}NO_3I$ $[M–CH_3]^+$ 295.9784, found 295.9779.



Preparation of 49. A 250-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar was charged with **47** (8.90 g, 28.6 mmol), followed by EtOH (120 mL) and Et_3N (24.1 mL, 0.172 mol). The flask was flushed with nitrogen, and charged with 10% Pd/C (0.45 g, 1.5 mol%). The flask was then fitted with a three-way connected with a hydrogen balloon, and flushed with hydrogen. The resulting mixture was stirred at 23 °C for 22 h under hydrogen atmosphere. The mixture was filtered through celite and washed with EtOAc (100 mL). The filtrate was concentrated *in vacuo*, and the crude residue was redissolved in EtOAc (100 mL). The resulting solution was washed with water (2 × 20 mL), saturated aqueous $CuSO_4$ (2 × 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10 to 40% EtOAc in hexanes) on silica gel (200 mL) to afford **49** (4.7 g, 88%) as a colorless oil.

Data for **49**: R_f = 0.49 (60% EtOAc in hexanes); IR (neat): 2983, 2934, 1759 (C=O), 1455, 1384, 1369, 1312, 1243, 1099, 1033 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 4.39 (dq, 1H, *J* = 6.0, 5.0 Hz, 13-H), 3.83 (dq, 1H, *J* = 10.5, 6.0 Hz, 15-H), 3.42 (dd, 1H, *J* = 10.5, 5.0 Hz, 14-H), 1.69 (s, 3H), 1.48 (s, 3H), 1.47 (d, 3H, *J* = 6.0 Hz), 1.28 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, 293K, $CDCl_3$) δ 156.5, 94.6, 76.2, 73.1, 71.8, 29.4, 24.1, 21.6, 17.2; HRMS (EI+) calcd. for $C_8H_{12}NO_3$ $[M–CH_3]^+$ 170.0817, found 170.0819.

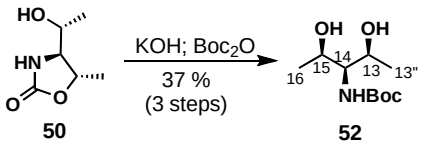


49 **50**

Preparation of 50. A 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a rubber septum was charged with **49** (1.73 g, 9.32 mmol), THF (20 mL) and aqueous HCl (4 M, 10 mL). The resulting mixture was stirred at 23 °C for 30

min and then quenched with aqueous $NaHCO_3$ (4 M, 10 mL). The organic solvent was removed *in vacuo*, and the residue was used for next step.

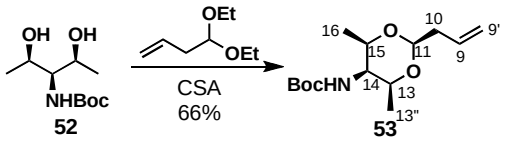
Data for **50**: R_f = 0.35 (10% MeOH in CH_2Cl_2); IR (neat): 3645, 3368, 2958, 2923, 1740 (C=O), 1431, 1389, 1312, 1233, 1157, 1120, 1078, 1052 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.73 (br s, 1H, NH), 4.45 (dq, 1H, *J* = 6.5, 6.0 Hz, 13-H), 3.69 (dq, 1H, *J* = 6.0, 6.0 Hz, 15-H), 3.27 (t, 1H, *J* = 6.0 Hz, 14-H), 1.44 (d, 1H, *J* = 6.5 Hz), 1.18 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, 293K, $CDCl_3$) δ 160.0, 76.0, 68.9, 65.6, 21.1, 19.3; HRMS (EI+) calcd. for $C_6H_{12}NO_3$ $[M]^+$ 146.0817, found 146.0816.



Preparation of 52 . A 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a condenser was charged with crude **50** (1.36g, 9.32 mmol) in water (10 mL), a solution of KOH (4 M, 10 mL) and dioxane (20 mL). The mixture was heated to reflux in an oil bath for 1h. After being cooled to 23 °C, Boc_2O (6.20 g, 28.4 mmol) was added. The mixture was then stirred at 23 °C for 20 h, and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (30 to 60% EtOAc in hexanes) on silica gel (100 mL) to afford **52** (0.76 g, 37% for 3 steps) as a colorless oil.

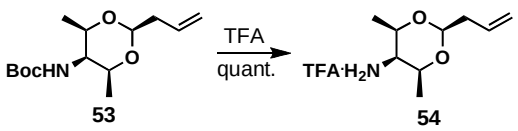
Data for **52**: R_f = 0.38 (10% MeOH in CH_2Cl_2); IR (neat): 3409, 2977, 2934, 1692 (C=O), 1505, 1465, 1393, 1367, 1250, 1169, 1121, 1069 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.29 (br d, 1H, *J* = 9.6 Hz, NH), 4.08 (qd, 2H, *J* = 6.3, 1.5 Hz, 13- or 15-H), 3.35 (d,

1H, J = 9.9 Hz, 14-H), 1.44 (s, 9H), 1.17 (d, 6H, J = 6.3 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 157.1, 79.3, 71.1, 57.8, 28.3, 20.3; HRMS (EI+) calcd. for $C_{10}H_{21}NO_4$ $[M]^+$ 219.1471, found 219.1470.

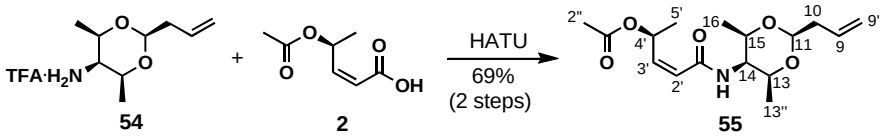


Preparation of 53. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **52** (0.670 g, 3.47 mmol) and CH_2Cl_2 (12 mL). The solution was cooled in an ice-water bath, and then 3-butenal diethyl acetal (0.71 mL, 4.1 mmol) and CSA (81 mg, 0.35 mmol) were added sequentially. The mixture was warmed to 4 °C and stirred at the same temperature for 64 h. Et_3N (0.10 mL) was added, and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (2 to 8% EtOAc in hexanes) on silica gel (25 mL) to afford the acetal **53** (616 mg, 66%) as a colorless oil.

Data for **53**: R_f = 0.58 (30% EtOAc in hexanes); IR (neat): 3454, 2981, 1644 (C=O), 1502, 1365, 1312, 1238, 1167, 1133, 1082, 1019 cm^{-1}; ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 5.89–5.75 (m, 1H, 9-H), 5.16–5.08 (m, 1H, 9'-H), 4.95 (br d, 1H, J = 10.2 Hz, NH), 3.84 (qd, 2H, J = 6.6, 1.5 Hz, 13- or 15-H), 3.39 (dt, 1H, J = 10.2, 1.5 Hz, 14-H), 2.40–2.36 (m, 2H, 10-H), 1.46 (s, 9H), 1.19 (d, 6H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293K) δ 156.5, 132.6, 117.6, 101.6, 79.2, 75.5, 51.6, 39.3, 28.3, 17.3; HRMS (EI+) calcd. for $C_{14}H_{25}NO_4$ $[M]^+$ 271.1784, found 271.1771.



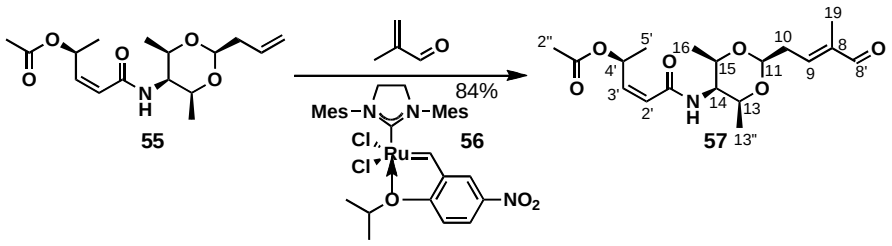
Preparation of 54. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a rubber septum was charged with **53** (0.23 g, 0.84 mmol) and CH_2Cl_2 (7.2 mL). The mixture was cooled in an ice-water bath, and TFA (0.8 mL) was added dropwise via a syringe. The resulting mixture was warmed to 23 °C and stirred at the same temperature for 3 h. After concentration of the mixture, heptanes (5 mL) was added and removed *in vacuo*. The residue was dissolved in MeCN (4 mL) and used in the next step.



Preparation of 55. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **2** (0.220 g, 1.39 mmol), MeCN (4 mL) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (0.528 g, 1.39 mmol) followed by *N, N′*-diisopropylethylamine (0.810 mL, 4.64 mmol). The resulting mixture was stirred at 23 °C for 5 min, and then cannulated to a solution of **54** in MeCN (4 mL). After 10 min at 23 °C, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (15 to 40% EtOAc in hexanes) on silica gel (12 mL) to afford **55** (180 mg, 69%) as a colorless oil.

Data for **55**: R_f = 0.41 (40% EtOAc in hexanes); IR (neat): 3324, 2981, 2933, 2859, 1736 (C=O), 1671 (C=O), 1641, 1512, 1439, 1371, 1341, 1307, 1242, 1177, 1123, 1046 cm^{-1}; $[\alpha]_D^{22}$ -

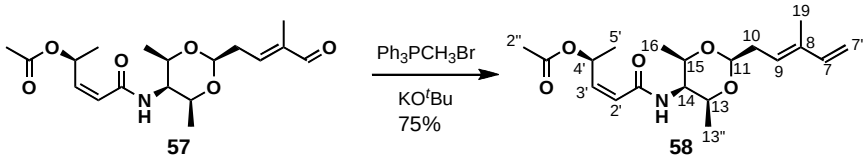
12.0 (*c* 0.94, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.58 (br d, 1H, *J* = 9.3 Hz, NH), 6.16 (dq, 1H, *J* = 6.6, 6.6 Hz, 4'-H), 5.93–5.75 (m, 3H, 9-, 2'- and 3'-H), 5.16–5.07 (m, 2H, 9'-H), 4.66 (t, 1H, *J* = 5.4 Hz, 11-H), 3.93–3.83 (m, 3H, 13-, 14- and 15-H), 2.41–2.37 (m, 2H, 10-H), 2.04 (s, 3H, 2"-H), 1.37 (d, 3H, *J* = 6.3 Hz), 1.19 (d, 3H, *J* = 6.3 Hz), 1.17 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.8, 166.0, 142.8, 132.8, 123.1, 117.9, 102.0, 75.6, 75.4, 69.1, 50.4, 39.5, 21.4, 20.2, 17.7, 17.6; HRMS (EI+) calcd. for $C_{16}H_{25}NO_5$ $[M]^+$ 311.1733, found 311.1736.



Preparation of 57. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **55** (0.14 g, 0.44 mmol) followed by methacrolein (1.10 mL, 13.6 mmol) and **56** (4.0 mg, 5.0 μmol). The resulting mixture was stirred at 23 °C for 23 h, and the excess methacrolein was removed *in vacuo*. The residue was purified by flash chromatography (30 to 50% EtOAc in hexanes) on silica gel (8 mL) to afford **57** (85 mg, 84%) as a white solid.

Data for **57**: R_f = 0.26 (60% EtOAc in hexanes); IR (neat): 3361, 2982, 2935, 2867, 1735 (C=O), 1674 (C=O), 1643 (C=O), 1519, 1417, 1372, 1340, 1308, 1243, 1175, 1124, 1047 cm^{-1}; $[\alpha]_D^{22}$ -11.9 (*c* 0.73, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 9.45 (s, 1H, 8'-H), 6.71 (br d, 1H, *J* = 9.6 Hz, NH), 6.61–6.56 (m, 1H, 9-H), 6.12–6.02 (m, 1H, 4'-H), 5.90–5.81 (m, 2H, 2'- and 3'-H), 4.81 (t, 1H, *J* = 5.4 Hz, 11-H), 3.98–3.09 (m, 3H, 13-, 14- and 15-H), 2.74–2.70 (m, 2H, 10-H), 2.06 (s, 3H, 2"-H), 1.76 (d, 3H, *J* = 1.2 Hz, 19-H), 1.38 (d, 3H, *J* = 6.6 Hz), 1.20 (d,

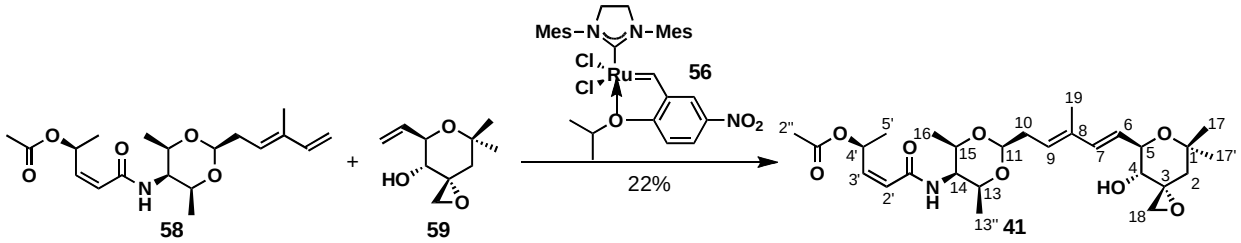
3H, J = 6.6 Hz), 1.18 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 195.2, 171.0, 166.2, 147.7, 141.6, 141.4, 123.5, 100.5, 75.8, 75.6, 69.1, 50.3, 34.8, 21.4, 20.2, 17.7, 17.6, 9.7; HRMS (ESI+) calcd. for $C_{18}H_{27}NO_6Na$ $[M+Na]^+$ 376.1736, found 376.1733.



Preparation of 58. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with methyltriphenylphosphonium bromide (0.35 g, 0.97 mmol) and THF (3 mL). The mixture was cooled in an ice-water bath and a solution of KO^{t}Bu in THF (0.85 mL, 1M, 0.85 mmol) was added via a syringe. After 30 min at 0 °C, aldehyde **57** (86 mg, 0.24 mmol) in THF (1 mL) was added via cannula and rinsed with additional THF (1 mL). The reaction mixture was stirred at 0 °C for 20 min, and saturated aqueous NH_4Cl (2 mL) was added. After removal of THF, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10 to 30% EtOAc in hexanes) on silica gel (8 mL) to afford **58** (57 mg, 67%) as a colorless oil.

Data for **58**: R_f = 0.60 (60% EtOAc in hexanes); IR (neat): 3331, 2981, 2933, 2864, 1737 (C=O), 1672 (C=O), 1642, 1512, 1443, 1371, 1340, 1307, 1242, 1175, 1125, 1047 cm^{-1}; $[\alpha]_D^{22}$ -13.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 6.53 (br d, 1H, J = 9.6 Hz, NH), 6.35 (dd, 1H, J = 17.4, 10.8 Hz, 7-H), 6.21–6.09 (m, 1H, 4'-H), 5.92–5.82 (m, 2H, 2' and 3'-H), 5.53 (t, 1H, J = 7.2 Hz, 9-H), 5.10 (d, 1H, J = 17.4 Hz, 7'-H), 4.96 (d, 1H, J = 10.8 Hz, 7'-H), 4.67 (t, 1H, J = 5.4 Hz, 11-H), 3.94–3.86 (m, 3H, 13-, 14- and 15-H), 2.50 (t, 2H, J = 6.3 Hz, 10-H),

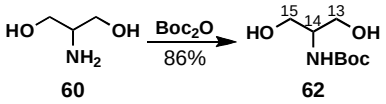
2.05 (s, 3H, 2"-H), 1.75 (d, 3H, J = 0.9 Hz, 19-H), 1.38 (d, 3H, J = 6.3 Hz), 1.18 (d, 3H, J = 5.4 Hz), 1.16 (d, 3H, J = 5.4 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.6, 165.8, 142.3, 141.2, 136.3, 126.0, 123.0, 111.4, 101.8, 75.4, 75.3, 68.9, 50.2, 34.0, 21.2, 20.0, 17.6, 17.4, 12.0; HRMS (EI+) calcd. for $C_{19}H_{29}NO_5$ $[M]^+$ 351.2046, found 351.2028.



Preparation of 41. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a rubber septum was charged with **58** (27 mg, 78 μmol), **59** (23 mg, 0.13 mmol), DCE (0.5 mL) and **56** (2.6 mg, 3.8 μmol). The mixture was heated to 40 °C and stirred for 4 h at the same temperature. Additional **56** (2.6 mg, 3.8 μmol) was added. After 10 total hours, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (5 mL) to afford **41** (6.5 mg, 16%) as a solid, and a mixture of **58** and **59** (23 mg).

An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a rubber septum was charged with recovered **58** and **59** (23 mg) followed by DCE (0.3 mL) and **56** (2.6 mg, 3.8 μmol). The reaction mixture was heated to 40 °C. After 23 h at the same temperature, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (4 mL) to afford **41** (2.5 mg, 6%). The combined yield of **41** after one cycle was 9.0 mg (22%). **41** was further purified by preparative TLC, and afforded as a white solid.

Data for **41**: R_f = 0.30 (70% EtOAc in hexanes); IR (neat): 3732, 3584, 2920, 2851, 1733 (C=O), 1670 (C=O), 1649, 1557, 1519, 1456, 1372, 1242, 1123, 1049 cm^{-1}; $[\alpha]_D^{22}$ +9.1 (*c* 0.10, $CHCl_3$); ^1H NMR (500 MHz, 293K, CD_2Cl_2) δ 6.35 (d, 1H, *J* = 15.5 Hz, 7-H), 6.31 (br d, 1H, *J* = 10.0 Hz, NH), 6.21–6.16 (m, 1H, 4'-H), 5.91 (dd, 1H, *J* = 11.5, 8.0 Hz, 3'-H), 5.84 (dd, 1H, *J* = 11.5, 1.0 Hz, 2'-H), 5.66 (dd, 1H, *J* = 15.5, 7.0 Hz, 6-H), 5.53 (t, 1H, *J* = 7.5 Hz, 9-H), 4.66 (t, 1H, *J* = 5.5 Hz, 11-H), 3.91–3.87 (m, 3H), 3.83 (m, 1H), 3.48 (t, 1H, *J* = 10.0 Hz, 4-H), 2.96 (d, 1H, *J* = 4.5 Hz, 18-H), 2.90–2.44 (m, 2H, 10-H), 2.46 (d, 1H, *J* = 4.5 Hz, 18-H), 2.16 (d, 1H, *J* = 14.0 Hz, 2-H), 2.02 (s, 3H, 2"-H), 1.77 (s, 3H, 19-H), 1.61 (d, 1H, *J* = 11.5 Hz, 4-OH), 1.40 (d, 1H, *J* = 14.0 Hz, 2-H), 1.36 (s, 3H), 1.34 (d, 3H, *J* = 6.5 Hz), 1.23 (s, 3H), 1.14 (d, 3H, *J* = 6.5 Hz), 1.12 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, 293K, CD_2Cl_2) δ 170.4, 165.5, 142.9, 137.2, 135.3, 126.5, 125.8, 122.6, 101.7, 75.3, 75.2, 74.5, 72.7, 68.6, 68.2, 57.4, 50.0, 47.4, 42.7, 34.0, 31.6, 30.7, 24.6, 22.7, 21.0, 19.8, 17.2; HRMS (EI+) calcd. for $C_{27}H_{41}NO_8$ $[M]^+$ 507.2832, found 507.2851.

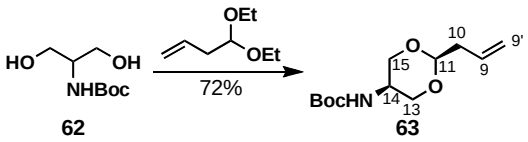


60 **62**

Preparation of 62. A 100-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar was charged with 2-amino-1,3-propanediol (0.94 g, 10 mmol), THF (18 mL) and water (12 mL). The mixture was cooled in an ice-water bath, and Boc_2O (2.36 g, 10.8 mmol) and $NaHCO_3$ (1.73 g, 20.6 mmol) were added to the mixture sequentially. The resulting mixture was warmed to 23 °C and stirred at the same temperature for 18 h. The mixture was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue

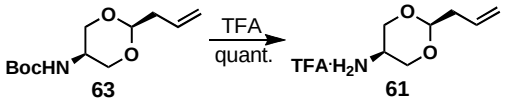
was purified by flash chromatography (2 to 10% MeOH in CH_2Cl_2) on silica gel (100 mL) to afford **62** (1.70 g, 86%) as a colorless oil.

Data for **62**. See Benoist, E.; Loussouarn, A.; Remaud, P.; Chatal, J. F.; Gestin, J. F. *Synthesis* **1998**, 1113-1118.



62 **63**

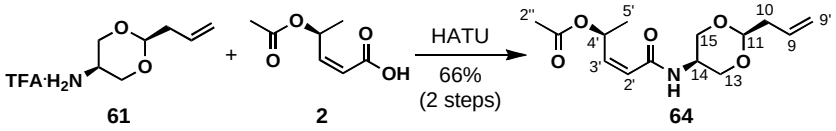
Preparation of 63. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **62** (0.737 g, 3.86 mmol), CH_2Cl_2 (15 mL) and THF (5 mL). The solution was cooled in an ice-water bath, and 3-butenal diethyl acetal (0.98 mL, 5.8 mmol) and CSA (91 mg, 0.39 mmol) were added. The mixture was stirred at 0 °C for 70 h and then warmed to 23 °C. After additional 20 h, Et_3N (0.10 mL) was added, and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (5 to 20% EtOAc in hexanes) on silica gel (50 mL) to afford **63** (647 mg, 72%, dr = 1.5:1.0) as a colorless oil. Its *trans* diastereoisomer was partially separated by recrystallization. After recrystallization, the diastereoisomer ratio was 5:1.



63 **61**

Preparation of 61. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a rubber septum was charged with **63** (345 mg, 1.42 mmol) and CH_2Cl_2 (9 mL). The solution was cooled in ice-water bath, and TFA (1 mL)

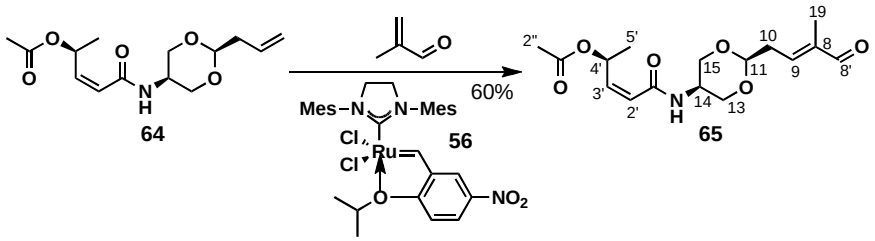
was added dropwise via a syringe. The resulting mixture was warmed to 23 °C and stirred for 6.5 h. After concentration of the mixture, heptane (7 mL) was added and removed *in vacuo*. The residue was dissolved in MeCN (6 mL) and used in the next step.



Preparation of 64. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **2** (0.270 g, 1.70 mmol), CH_3CN (6 mL) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (0.646 g, 1.70 mmol), followed by *N, N′*-diisopropylethylamine (0.990 mL, 5.68 mmol) via a syringe. The resulting mixture was stirred at 23 °C for 5 min and then added to the solution of **61** in MeCN prepared in last step. The resulting pale yellow solution was stirred 23 °C for 20 min. Water (7 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10 to 50% EtOAc in hexanes) on silica gel (30 mL) to afford **64** (265 mg, 66%) as a colorless oil.

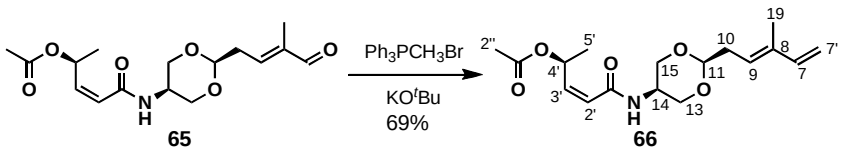
Data for **64**: R_f = 0.28 (50% EtOAc in hexanes); IR (neat): 3417, 2978, 2930, 2859, 1732 (C=O), 1667 (C=O), 1640, 1528, 1452, 1372, 1244, 1145, 1119, 1073, 1048, 1013 cm^{-1}; $[\alpha]_D^{22}$ +3.7 (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 7.20 (br d, 1H, *J* = 6.6 Hz, NH), 6.14 (dq, 1H, *J* = 6.6, 6.6 Hz, 4'-H), 5.91–5.75 (m, 3H, 9-, 2'- and 3'-H), 5.18–5.09 (m, 2H, 9'-H), 4.65 (t, 1H, *J* = 5.1 Hz, 11-H), 4.05–3.92 (m, 5H, 13-, 14- and 15-H), 2.45–2.40 (m, 2H, 10-H), 2.06 (s, 3H, 2''-H), 1.38 (d, 3H, *J* = 6.3 Hz, 5'-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 171.0, 165.1,

142.5, 132.4, 123.6, 118.3, 102.3, 70.5, 69.1, 44.1, 39.8, 21.5, 20.4; HRMS (EI+) calcd. for $C_{14}H_{21}NO_5$ $[M]^+$ 283.1420, found 283.1410.



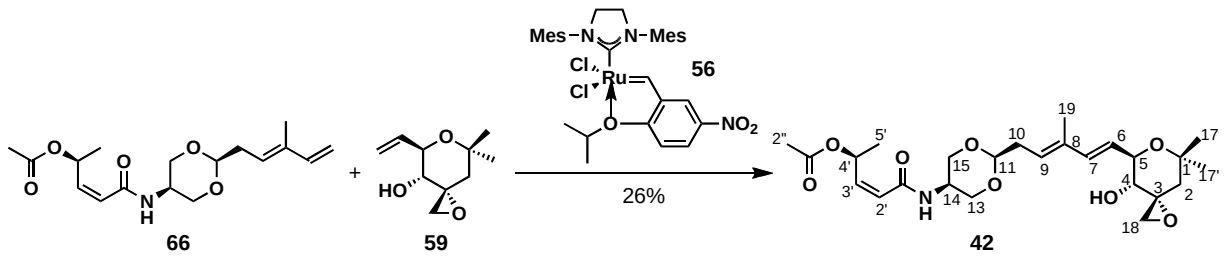
Preparation of 65. A 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a nitrogen inlet and a rubber septum was charged with **64** (0.27 g, 0.95 mmol), methacrolein (1.2 mL, 14 mmol) and **56** (6.3 mg, 9.4 μmol). The resulting mixture was stirred 23 °C for 22 h, and additional **56** (6.3 mg, 9.4 μmol) was added. The stirring was continued for 13 h and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (30 to 80% EtOAc in hexanes) on silica gel (15 mL) to afford **65** (185 mg, 60%) as a colorless oil.

Data for **65**: R_f = 0.25 (70% EtOAc in hexanes); IR (neat): 3425, 2977, 2929, 2858, 1730 (C=O), 1668 (C=O), 1641(C=O), 1529, 1373, 1246, 1129, 1048, 1020 cm^{-1}; $[\alpha]_D^{22}$ +2.7 (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 9.44 (s, 1H, 7-H), 7.42 (br d, 1H, *J* = 7.5 Hz, NH), 6.59 (dq, 1H, *J* = 6.9, 0.9 Hz, 9-H), 6.10–6.00 (m, 1H, 4'-H), 5.83 (d, 2H, *J* = 3.3 Hz, 2'- and 3'-H), 4.79 (t, 1H, *J* = 5.4 Hz, 11-H), 4.07–3.06 (m, 5H, 13-, 14- and 15-H), 2.71 (t, 2H, *J* = 5.4 Hz, 10-H), 2.06 (s, 3H, 2''-H), 1.76 (s, 3H, 19-H), 1.37 (d, 3H, *J* = 6.3 Hz, 5'-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 194.8, 170.9, 164.9, 146.9, 141.3, 141.1, 123.7, 100.7, 70.2, 68.8, 43.6, 34.6, 21.2, 20.1, 9.4; HRMS (ESI+) calcd. for $C_{16}H_{23}NO_6Na$ $[M+Na]^+$ 348.1423, found 348.1438.



Preparation of 66. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with methyltriphenylphosphonium bromide (0.803 g, 2.25 mmol) and THF (8 mL). The solution was cooled in an ice-water bath, and a solution of KO^{t}Bu in THF (1M, 1.90 mL, 1.90 mmol) was added via a syringe. The mixture was stirred for 10 min at the same temperature. A solution of **65** (0.183 g, 0.566 mmol) in THF (7 mL) was added to the mixture via cannula, and the stirring was continued for 10 min. H_2O (5 mL) was added. After removal of THF, the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10 to 50% EtOAc in hexanes) on silica gel (20 mL) to afford **66** (124 mg, 69%) as a colorless oil.

Data for **66**: R_f = 0.36 (50% EtOAc in hexanes); IR (neat): 3358, 2978, 2933, 2861, 1735 (C=O), 1668 (C=O), 1639, 1526, 1451, 1419, 1372, 1244, 1157, 1131, 1049, 1011 cm^{-1}; $[\alpha]_D^{23}$ -15.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 7.24 (br d, 1H, *J* = 8.1 Hz, NH), 6.39 (dd, 1H, *J* = 17.4, 10.8 Hz, 7-H), 6.13 (dq, 1H, *J* = 6.6, 6.6 Hz, 4'-H), 5.90–5.79 (m, 2H, 2'- and 3'-H_2), 5.52 (t, 1H, *J* = 7.2 Hz, 9-H), 5.13 (d, 1H, *J* = 17.4 Hz, 7'-H), 4.98 (d, 1H, *J* = 10.5 Hz, 7'-H), 4.64 (t, 1H, *J* = 5.1 Hz, 11-H), 4.04–3.93 (m, 5H, 13-, 14- and 15-H), 2.52 (t, 2H, *J* = 6.3 Hz, 10-H), 2.06 (s, 3H, 2"-H), 1.76 (s, 3H, 19-H), 1.38 (d, 3H, *J* = 6.6 Hz, 5'-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.7, 164.8, 141.9, 141.1, 136.5, 125.4, 123.4, 111.5, 102.1, 70.2, 68.8, 43.8, 34.1, 21.2, 20.1, 11.9; HRMS (ESI+) calcd. for $C_{17}H_{25}NO_5Na$ $[M+Na]^+$ 346.1630, found 346.1654.

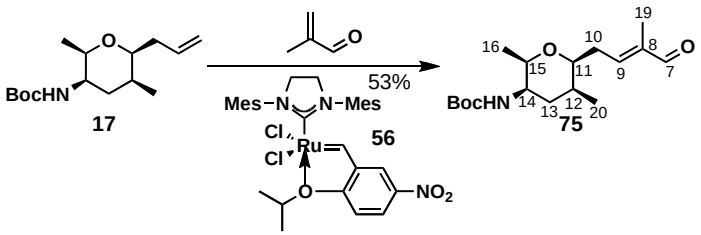


Preparation of 42. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **66** (55 mg, 0.17 mmol), **56** (25 mg, 0.14 mmol), DCE (0.5 mL), benzoquinone (3.7 mg, 34 μmol) and **56** (5.7 mg, 8.5 μmol). The mixture was heated to 40 ^{o}C and stirred at the same temperature for 4 h, and additional **56** (5.7 mg, 8.5 μmol) was added to the mixture. The stirring was continued at the same temperature for 18 h, and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (12 mL) to afford **42** (15 mg, 18%) as a solid, and a mixture of **66** and **59** (74 mg).

An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with recovered **66** and **59** (74 mg), DCE (0.3 mL) and **56** (6.2 mg, 9.2 μmol). The mixture was heated to 40 ^{o}C and stirred at the same temperature for 22 h. The mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (10 mL) to afford **42** (7 mg, 8%). The combined yield of **42** after one cycle is 22 mg (26%). **42** was further purified by preparative TLC, and afforded as a white solid.

Data for **42**: R_f = 0.15 (70% EtOAc in hexanes); IR (neat): 3341, 1973, 2923, 2856, 1734 (C=O), 1668 (C=O), 1638, 1526, 1372, 1243, 1129, 1049, 1012 cm^{-1}; $[\alpha]_D^{23}$ +13.9 (*c* 0.77, $CHCl_3$); ^{1}H NMR (600 MHz, 293K, CD_2Cl_2) δ 7.02 (br d, 1H, *J* = 9.1 Hz, NH), 6.34 (d, 1H, *J* = 15.6 Hz, 7-H), 6.17 (m, 1H, 4'-H), 5.89 (dd, 1H, *J* = 12.0, 9.8 Hz, 3'-H), 5.80 (dd, 1H, *J* = 12.0, 1.2 Hz, 2'-H), 5.65 (dd, 1H, *J* = 15.6, 6.6 Hz, 6-H), 5.52 (t, 1H, *J* = 7.2 Hz, 9-H), 4.62 (t, 1H, *J* =

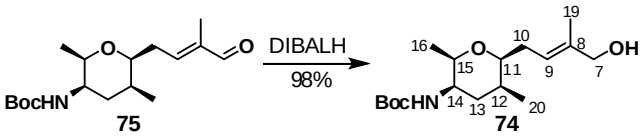
4.8 Hz, 11-H), 3.97–3.90 (m, 6H, 5-, 13-, 14- and 15-H), 3.48 (t, 1H, *J* = 10.2 Hz, 4-H), 2.96 (d, 1H, *J* = 4.2 Hz, 18-H), 2.47 (m, 2H, 10-H), 2.46 (d, 1H, *J* = 4.2 Hz, 18-H), 2.02 (s, 3H, 2"-Me), 1.76 (s, 3H, 19-Me), 1.61 (d, 1H, *J* = 10.2 Hz, 4-OH), 1.35 (s, 3H, 17-H), 1.34 (d, 3H, *J* = 6.6 Hz, 5'-H), 1.23 (s, 3H, 17'-H); ^{13}C NMR (150 MHz, 293K, CD_2Cl_2) δ 170.5, 164.5, 142.7, 137.1, 135.5, 126.1, 125.9, 122.9, 102.0, 74.5, 72.6, 70.1, 68.5, 68.2, 57.4, 47.4, 43.8, 42.7, 34.1, 30.7, 29.7, 23.3, 21.0, 19.8, 12.4; HRMS (ESI+) calcd. for $C_{25}H_{37}NO_8Na$ $[M+Na]^+$ 502.2417, found 502.2382.



Preparation of 75. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **17** (0.280 g, 1.04 mmol), methacrolein (1.70 mL, 20.8 mmol) and **56** (21 mg, 31 μmol). The resulting mixture was stirred at 23 °C for 43 h, and the excess methacrolein was removed *in vacuo*. The residue was purified by flash chromatography (5 to 30% EtOAc in hexanes) on silica gel (15 mL) to afford **75** (85 mg, 84%) as a pale yellow liquid.

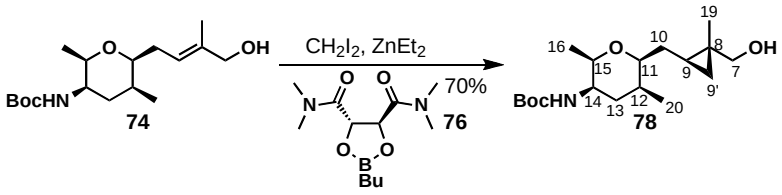
Data for **75**: R_f = 0.26 (30% EtOAc in hexanes); IR (neat): 3461, 2976, 2932, 1714 (C=O), 1689 (C=O), 1646, 1497, 1389, 1365, 1345, 1315, 1237, 1168, 1064 cm^{-1}; $[\alpha]_D^{21}$ -24.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, 293K, $CDCl_3$) δ 9.43 (s, 1H, 7-H), 6.58–6.53 (m, 1H, 9-H), 4.73 (br d, 1H, *J* = 9.3 Hz, NH), 3.66–3.59 (m, 3H, 11-, 14- and 16-H), 2.62–2.36 (m, 2H, 10-H), 2.02–1.92 (m, 2H, 13-H), 1.77 (s, 4H, 12- and 19-H), 1.45 (s, 9H), 1.17 (d, 3H, *J* = 6.3 Hz), 1.08 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 195.3, 156.0, 150.8, 140.8, 79.9, 79.4,

48.4, 36.2, 33.1, 29.8, 28.7, 17.9, 15.3, 9.7; HRMS (EI+) calcd. for $C_{17}H_{29}NO_4$ $[M]^+$ 311.2097, found 311.2100.



Preparation of 74. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **75** (65 mg, 0.21 mmol) and CH_2Cl_2 (2.0 mL). The solution was cooled in a dry ice-acetone bath and then DIBALH (0.25 mL, 1 M, 0.25 mmol) was added dropwise via a syringe. After 10 min at -78 °C, the reaction was quenched with a solution of potassium sodium tartrate (1 M, 4 mL) at the same temperature. The resulting mixture was warmed to 23 °C, stirred at the same temperature for 20 min, and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10 to 30% EtOAc in hexanes) on silica gel (12 mL) to afford **74** (64.0 mg, 98%) as a colorless oil.

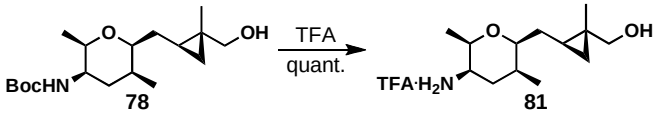
Data for **74**: R_f = 0.35 (60% EtOAc in hexanes); IR (neat): 3458, 2976, 2931, 1715 (C=O), 1499, 1390, 1366, 1238, 1169, 1060 cm^{-1}; $[\alpha]_D^{22}$ -4.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.42 (ddd, 1H, *J* = 7.2, 7.2, 0.9 Hz, 9-H), 4.76 (d, 1H, *J* = 9.3 Hz, NH), 4.02 (s, 2H, 7-H), 3.65–3.55 (m, 2H), 3.49 (ddd, 1H, *J* = 7.2, 7.2, 2.7 Hz), 2.34–2.10 (m, 2H, 10-H), 1.97–1.85 (m, 2H, 13-H), 1.80–1.75 (m, 1H, 12-H), 1.69 (s, 3H, 19-H), 1.45 (s, 9H), 1.16 (d, 3H, *J* = 6.3 Hz), 1.03 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 156.1, 136.8, 121.8, 81.0, 79.2, 69.0, 48.6, 36.3, 31.6, 29.2, 28.7, 18.0, 15.2, 14.2; HRMS (EI+) calcd. for $C_{17}H_{31}NO_4$ $[M]^+$ 313.2253, found 313.2242.



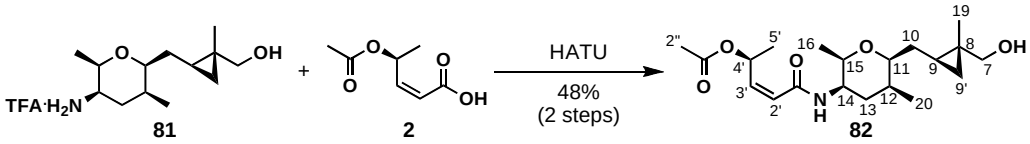
Preparation of 78. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with CH_2Cl_2 (5.0 mL) and diethylzinc (3.40 mL, 1.95 mmol). The mixture was cooled in ice-water bath and then diiodomethane (0.220 mL, 2.73 mmol) was added dropwise via a syringe. The resulting mixture was stirred at 0 °C for 10 min. A mixed solution of (*S*,*S*)-dioxaborolane **76** (0.212 g, 0.785 mmol) and **74** (0.123 g, 0.392 mmol) in CH_2Cl_2 (5.0 mL) was added via cannula. The resulting mixture was warmed to 23 °C and stirred at the same temperature for 1 h. Saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10 to 50% EtOAc in hexanes) on silica gel (15 mL) to afford **78** (91.2 mg, 70%, dr = 10.5:1) as a colorless oil.

Data for **78**: R_f = 0.35 (60% EtOAc in hexanes); IR (neat): 3458, 2975, 2931, 1716 (C=O), 1498, 1457, 1390, 1365, 1344, 1315, 1235, 1170, 1058 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 4.78 (br d, 1H, *J* = 9.5 Hz, NH), 3.63 (dq, 1H, *J* = 6.5, 2.0 Hz), 3.58–3.51 (m, 2H), 3.39 (d, 1H, *J* = 10.5 Hz, 7-H), 3.22 (d, 1H, *J* = 10.5 Hz, 7-H), 1.91 (t, 2H, *J* = 3.5 Hz), 1.78–1.75 (m, 1H), 1.65–1.59 (m, 1H), 1.43 (s, 9H); 1.29–1.24 (m, 1H), 1.15 (d, 3H, *J* = 6.0 Hz), 1.00 (d, 3H, *J* = 7.5 Hz), 0.70–0.65 (m, 1H), 0.56 (dd, 1H, *J* = 9.0, 4.5 Hz), 0.01 (dd, 1H, *J* = 5.0, 5.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 156.1, 81.7, 79.3, 76.6, 72.7, 48.6, 36.4, 32.4, 29.7,

28.6, 22.4, 18.9, 17.9, 16.8, 16.1, 15.6, 15.5; MS (ESI+) *m/z* 233 $[M - H_2NBoc + Na]^+$; HRMS (ESI+) calcd. for $C_{18}H_{23}NO_6Na$ $[M+Na]^+$ 350.2307, found 350.2276.



Preparation of 81. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **78** (73 mg, 0.22 mmol) and CH_2Cl_2 (1.5 mL). The solution was cooled in ice-water bath. A solution of TFA in CH_2Cl_2 (1:4 v/v, 1.5 mL) was added via a syringe. Then the reaction mixture was warmed to 23 °C and stirred for 2 h. After concentration of the mixture, heptanes (4 mL) was added and removed *in vacuo*. The residue was dissolved in MeCN (2 mL) and used in the next step.



Preparation of 82. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **2** (42 mg, 0.26 mmol), MeCN (2 mL) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (85 mg, 0.22 mmol), followed by *N, N′*-diisopropylethylamine (0.16 mL, 0.89 mmol). The resulting mixture was added to a solution of **81** in MeCN (2 mL) and rinsed with additional MeCN (1 mL). After 10 min at 23 °C, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The

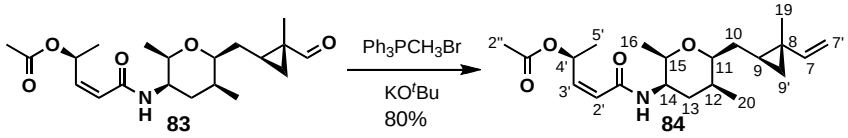
combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (30 to 60% EtOAc in hexanes) on silica gel (12 mL) to afford **82** (39.5 mg, 48%) as a colorless oil.

Data for **82**: R_f = 0.21 (70% EtOAc in hexanes); IR (neat): 3357, 2931, 1737 (C=O), 1667 (C=O), 1629, 1518, 1455, 1374, 1243, 1146, 1050 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.24 (dq, 1H, *J* = 6.5 Hz, 4'-H), 6.10 (br d, 1H, *J* = 9.0 Hz, NH), 5.86 (dd, 1H, *J* = 11.5, 7.5 Hz, 3'-H), 5.72 (dd, 1H, *J* = 11.5, 1.0 Hz, 2'-H), 3.95 (dddd, 1H, *J* = 9.0, 5.5, 2.5, 2.5 Hz), 3.70 (qd, 1H, *J* = 6.5, 2.5 Hz), 3.58 (ddd, 1H, *J* = 8.0, 5.0, 2.5 Hz), 3.41 (d, 1H, *J* = 10.5 Hz, 7-H), 3.24 (d, 1H, *J* = 10.5 Hz, 7-H), 2.04 (s, 3H, 2''-H), 1.98 (t, 2H, *J* = 3.5 Hz), 1.84–1.79 (m, 1H), 1.63 (ddd, 1H, *J* = 14.5, 8.6, 6.5 Hz), 1.39 (d, 3H, *J* = 6.5 Hz), 1.32–1.27 (m, 1H), 1.25 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz), 1.01 (d, 3H, *J* = 7.0 Hz), 0.73–0.67 (m, 1H), 0.57 (dd, 1H, *J* = 9.0, 4.5 Hz), 0.03 (dd, 1H, *J* = 4.5, 4.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.6, 164.3, 143.7, 122.8, 81.9, 76.2, 72.7, 69.2, 47.4, 36.2, 32.4, 29.9, 29.7, 22.4, 21.5, 20.2, 18.9, 18.1, 16.9, 16.1; HRMS (ESI+) calcd. for $C_{20}H_{33}NO_5Na$ $[M+Na]^+$ 390.2256, found 390.2233.

Preparation of 83. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with Dess-Martin periodinane (77 mg, 0.18 mol) and CH_2Cl_2 (3.0 mL). The resulting mixture was cooled in an ice-water bath, and **82** (33 mg, 90 μmol) was added. The mixture was stirred at 0 °C for 1.5 h. Saturated aqueous $NaHCO_3$ (3 mL) and Na_2SO_3 (220 mg) were added, and the stirring was continued for 30 min. The mixture was extracted with EtOAc (3 × 10 mL).

The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (20 to 50% EtOAc in hexanes) on silica gel (7 mL) to afford **83** (23 mg, 70%) as a colorless oil.

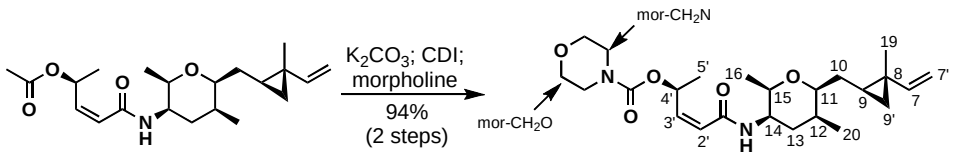
Data for **83**: R_f = 0.31 (60% EtOAc in hexanes); IR (neat): 3357, 2973, 2932, 1735 (C=O), 1702 (C=O), 1669 (C=O), 1637, 1519, 1456, 1371, 1317, 1245, 1123, 1049 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 8.68 (s, 1H, 7-H), 6.27–6.22 (m, 1H, *J* = 8.0, 6.5, 1.5 Hz, 4'-H), 6.02 (br d, 1H, *J* = 9.0 Hz, NH), 5.89 (dd, 1H, *J* = 11.5, 8.0 Hz, 3'-H), 5.72 (d, 1H, *J* = 11.5, 1.0 Hz, 2'-H), 3.98–3.96 (m, 1H), 3.69 (qd, 1H, *J* = 6.5, 2.5 Hz), 3.59 (ddd, 1H, *J* = 8.5, 5.5, 3.0 Hz), 2.05 (s, 3H, 2'-H), 2.00–1.98 (m, 2H), 1.82–1.77 (m, 2H), 1.52–1.46 (m, 1H), 1.40 (d, 3H, *J* = 6.5 Hz), 1.37–1.29 (m, 2H), 1.26 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz), 1.13 (d, 3H, *J* = 7.5 Hz), 0.66 (dd, 1H, *J* = 6.5, 4.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 202.7, 170.6, 165.1, 143.7, 122.8, 81.0, 76.3, 69.1, 47.3, 36.2, 32.1, 31.9, 29.8, 22.1, 21.5, 20.2, 20.1, 18.0, 15.5, 11.7; HRMS (EI+) calcd. for $C_{20}H_{31}NO_5$ $[M]^+$ 365.2202, found 365.2199.



Preparation of 84. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with methyltriphenylphosphonium bromide (0.18 g, 0.49 mmol) and THF (2 mL). The resulting mixture was cooled in an ice-water bath and then a solution of KO^{t}Bu in THF (0.41 mL, 1 M, 0.41 mmol) was added. The mixture was stirred at 0 °C for 20 min, aldehyde **83** (31 mg, 81 μmol) in THF (1 mL) was added via cannula and rinsed with THF (1 mL). After 10 min, H_2O (2 mL) was added. After removal of THF, the mixture was extracted with EtOAc (2 × 15

mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5 to 30% EtOAc in hexanes) on silica gel (5 mL) to afford **84** (23.6 mg, 80%) as a colorless oil.

Data for **84**: R_f = 0.47 (50% EtOAc in hexanes); IR (neat): 3362, 2925, 2853, 1738 (C=O), 1668 (C=O), 1634, 1521, 1457, 1370, 1244, 1050 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.27 (dqd, 1H, *J* = 8.0, 6.5, 1.0 Hz, 4'-H), 6.00 (br d, 1H, *J* = 9.0 Hz, NH), 5.90 (dd, 1H, *J* = 11.5, 8.0 Hz, 3'-H), 5.71 (dd, 1H, *J* = 11.5, 1.0 Hz, 2'-H), 5.40 (dd, 1H, *J* = 17.0, 10.5 Hz, 7-H), 4.91 (dd, 1H, *J* = 17.0, 1.0 Hz, 7'-H), 4.84 (dd, 1H, *J* = 10.5, 1.0 Hz, 7'-H), 3.96 (dddd, 1H, *J* = 9.0, 5.5, 2.5, 2.5 Hz), 3.69 (qd, 1H, *J* = 6.5, 2.5 Hz), 3.54 (dt, 1H, *J* = 7.0, 2.5 Hz), 2.05 (s, 3H, 2''-H), 1.99–1.97 (m, 2H), 1.86–1.81 (m, 1H), 1.77–1.72 (m, 1H), 1.40 (d, 3H, *J* = 6.5 Hz), 1.35–1.30 (m, 1H), 1.17 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.5 Hz), 0.83 (m, 1H), 0.77 (dd, 1H, *J* = 8.5, 4.0 Hz), 0.30 (dd, 1H, *J* = 5.5, 4.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.6, 165.1, 147.7, 143.8, 122.8, 109.2, 81.5, 76.2, 69.2, 47.4, 36.3, 32.9, 29.4, 22.6, 21.9, 21.5, 21.1, 20.2, 18.1, 16.0, 15.5; HRMS (EI+) calcd. for $C_{21}H_{33}NO_4$ $[M]^+$ 363.2410, found 363.2425.



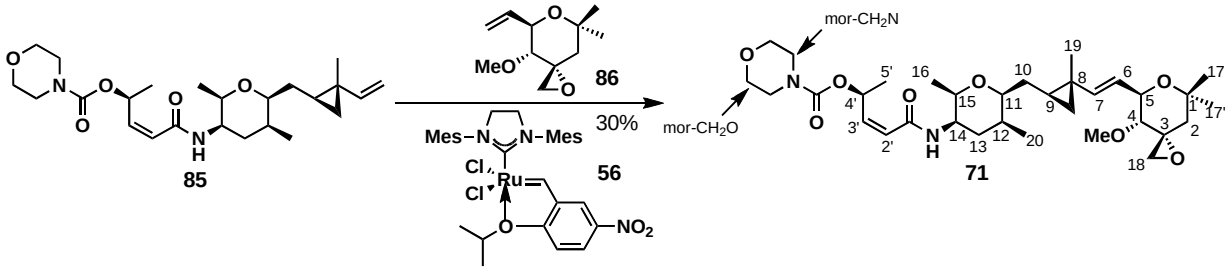
84 **85**

Preparation of 85. A 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a rubber septum was charged with **84** (23.6 mg, 65.8 μmol) and THF (1 mL). The mixture was cooled in an ice-water bath and then K_2CO_3 (22.4 mg, 162

μmol) was added. After 2 h at 0 °C, saturated aqueous NH_4Cl (60 μL) was added. The resulting mixture was stirred for 5 min, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was used in the next step without further purification.

An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with the crude residue (20.9 mg, 64.9 μmol), CH_2Cl_2 (1 mL) and 1,1'-carbonyldiimidazole (26.5 mg, 163 μmol). The resulting mixture was stirred at 23 °C for 13 h and then morpholine (28.5 μL, 327 μmol) was added. The stirring was continued for 7 h at 23 °C, and the solvent was removed. The reside was purified by flash chromatography (10 to 50% EtOAc in hexanes) on silica gel (6 mL) to afford **85** (26.7 mg, 94%) as a colorless oil.

Data for **85**: R_f = 0.37 (70% EtOAc in hexanes); IR (neat): 3356, 2961, 2927, 2854, 1702 (C=O), 1669 (C=O), 1634, 1519, 1457, 1423, 1365, 1316, 1279, 1241, 1117, 1063, 1018 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.19–6.13 (m, 2H), 5.92 (dd, 1H, *J* = 11.5, 8.0 Hz, 3'-H), 5.71 (dd, 1H, *J* = 11.5, 1.0 Hz, 2'-H), 5.40 (dd, 1H, *J* = 17.0, 10.5 Hz, 7-H), 4.91 (dd, 1H, *J* = 17.0, 1.5 Hz, 7'-H), 4.84 (dd, 1H, *J* = 10.5, 1.5 Hz, 7'-H), 3.96 (dq, 1H, *J* = 9.0, 3.0 Hz), 3.69 (dq, 1H, *J* = 6.0, 2.0 Hz), 3.66 (t, 4H, *J* = 4.5 Hz), 3.54 (dt, 1H, *J* = 7.0, 2.5 Hz), 3.47 (t, 4H, *J* = 4.5 Hz), 1.98–1.97 (m, 2H), 1.86–1.81 (m, 1H), 1.76–1.71 (m, 1H), 1.42 (d, 3H, *J* = 6.5 Hz), 1.37–1.30 (m, 1H), 1.17 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.5 Hz), 0.83 (m, 1H), 0.77 (dd, 1H, *J* = 9.0, 4.5 Hz), 0.29 (dd, 1H, *J* = 6.0, 4.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 164.9, 154.9, 147.5, 144.1, 122.3, 108.9, 81.2, 75.9, 70.1, 66.6, 64.6, 47.2, 36.0, 32.7, 29.7, 29.2, 22.4, 21.7, 20.9, 20.2, 17.9, 15.8, 15.2; MS (ESI+) *m/z* 435 $[M+H]^+$; HRMS (ES+) calcd. for $C_{24}H_{38}N_2O_5Na$ $[M+Na]^+$ 457.2678, found 457.2643.

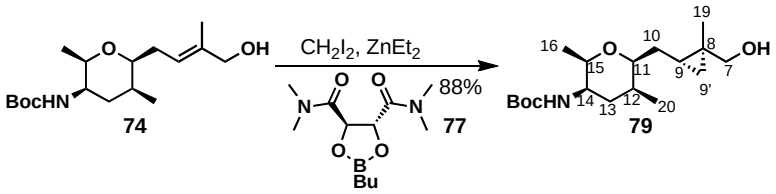


Preparation of 71. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **85** (22 mg, 51 μmol), **86** (17 mg, 86 μmol) and toluene (0.5 mL), followed by benzoquinone (1.1 mg, 10 μmol) and **56** (3.4 mg, 5.1 μmol). The resulting mixture was heated to 70 °C and stirred at the same temperature. After 14 h, the mixture was cooled to 23 °C and concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (5 mL) to afford **71** (7.2 mg, 23%) as a solid, and a mixture of **85** and **86** (24 mg).

An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with the mixture of **85** and **86** (24 mg) and toluene (0.3 mL), followed by benzoquinone (1.0 mg, 10 μmol) and **56** (3.0 mg, 4.5 μmol). The resulting mixture was heated to 70 °C. After 22 h at the same temperature, the mixture was cooled to 23 °C and concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (5 mL) to afford **71** (1.8 mg, 7%) as a solid. The combined yield of **71** after one cycle is 9.0 mg (30%). **71** was further purified by preparative TLC, and afforded as a white solid.

Data for **71**: R_f = 0.14 (70% EtOAc in hexanes); IR (neat): 3345, 2954, 2925, 2867, 1709 (C=O), 1672 (C=O), 1635, 1612, 1510, 1457, 1365, 1108, 1003 cm^{-1}; ^1H NMR (600 MHz, 293K, C_6D_6) δ 6.72 (dq, 1H, *J* = 6.6, 6.6 Hz, 4'-H), 6.06 (d, 1H, *J* = 9.0 Hz, NH), 5.76 (dd, 1H, *J* = 11.4, 7.8 Hz, 3'-H), 5.66 (dd, 1H, *J* = 15.6, 6.6 Hz, 6-H), 5.53 (d, 1H, *J* = 15.6 Hz, 7-H), 5.31 (dd, 1H,

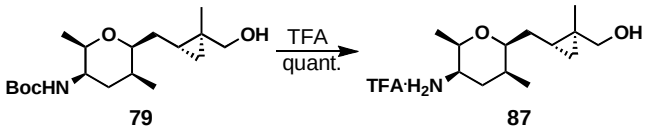
J = 11.4, 1.2 Hz, 2'-H), 4.46 (dd, 1H, *J* = 9.0, 6.6 Hz), 4.04–4.01 (m, 1H), 3.29–3.24 (m, 2H), 3.18 (br s, 6H), 3.15 (s, 3H, 4-OMe), 3.06 (br s, 2H), 2.93 (d, 1H, *J* = 9.6 Hz, 4-H), 2.74 (d, 1H, *J* = 5.4 Hz, 18-H), 2.07 (d, 1H, *J* = 5.4 Hz, 18-H), 1.79 (d, 1H, *J* = 14.4 Hz, 2-H), 1.59–1.54 (m, 2H), 1.49 (d, 3H, *J* = 6.6 Hz), 1.47 (s, 3H), 1.42–1.36 (m, 2H), 1.21 (s, 3H), 1.13 (d, 3H, *J* = 6.6 Hz), 1.12 (s, 3H), 1.05 (d, 1H, *J* = 13.8 Hz, 2-H), 0.93–0.88 (m, 1H), 0.91 (d, 3H, *J* = 7.2 Hz), 0.70 (dd, 1H, *J* = 8.4, 4.2 Hz), 0.20 (dd, 1H, *J* = 4.8, 4.8 Hz); ^{13}C NMR (150 MHz, 293K, C_6D_6) δ 164.6, 154.6, 143.0, 142.1, 124.3, 123.1, 81.0, 79.4, 75.8, 73.4, 72.8, 69.9, 60.0, 56.5, 47.1, 47.0, 43.6, 35.9, 32.9, 31.2, 29.3, 23.8, 22.7, 20.9, 20.7, 20.4, 17.9, 16.5, 15.0; HRMS (ESI+) calcd. for $C_{33}H_{52}N_2O_8Na$ $[M+Na]^+$ 627.3621, found 627.3658.



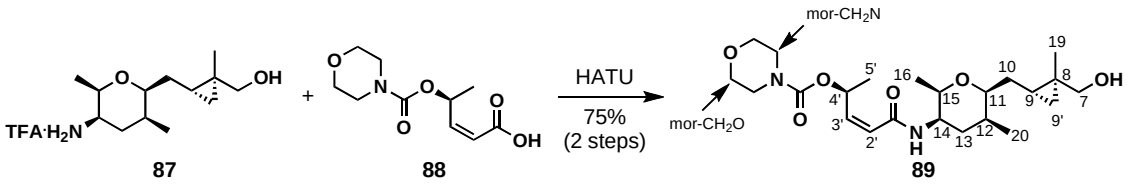
Preparation of 79. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with diethylzinc (2.57 mL, 1.47 mmol) and CH_2Cl_2 (3.0 mL). The solution was cooled in an ice-water bath and diiodomethane (0.170 mL, 2.05 mmol) was added slowly via a syringe. The resulting mixture was stirred at 0 °C for 10 min, and a mixed solution of (*R*,*R*)-dioxaborolane **77** (158 mg, 0.585 mmol) and **74** (92.0 mg, 0.294 mmol) in CH_2Cl_2 (3.0 mL) was added via cannula. After the addition, the reaction mixture was warmed to 23 °C and stirred at the same temperature for 30 min. Saturated aqueous NH_4Cl (3 mL) was added, and the mixtrue was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue

was purified by flash chromatography (10 to 40% EtOAc in hexanes) on silica gel (8 mL) to afford **79** (85.1 mg, 88%, dr = 11:1) as a colorless oil.

Data for **79**: R_f = 0.35 (60% EtOAc in hexanes); IR (neat): 3457, 2975, 2930, 1715 (C=O), 1499, 1391, 1366, 1345, 1237, 1171, 1080, 1058 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 4.80 (br d, 1H, *J* = 9.5 Hz, NH), 3.62 (dq, 1H, *J* = 6.5, 2.0 Hz), 3.57–3.55 (m, 1H), 3.49 (dt, 1H, *J* = 7.0, 2.0 Hz), 3.36 (d, 1H, *J* =11.0 Hz, 7-H), 3.27 (d, 1H, *J* = 11.0 Hz, 7-H), 1.95–1.88 (m, 1H), 1.92 (t, 2H, *J* = 4.0 Hz), 1.82–1.75 (m, 1H), 1.43 (s, 9H), 1.30–1.24 (m, 1H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.14 (s, 3H), 1.02 (d, 3H, *J* = 7.5 Hz), 0.71–0.66 (m, 1H), 0.56 (dd, 1H, *J* = 9.0, 4.5 Hz), 0.07 (dd, 1H, *J* = 5.0, 5.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 156.0, 81.5, 79.1, 76.3, 72.3, 48.4, 36.0, 31.9, 29.4, 28.4, 21.9, 17.9, 17.7, 16.5, 15.5, 15.0; MS (EI+) *m/z* 210 $[M - H_2NBoc]^+$; HRMS (EI+) calcd. for $C_{17}H_{30}NO_4$ $[M–CH_3]^+$ 312.2175, found 312.2168.



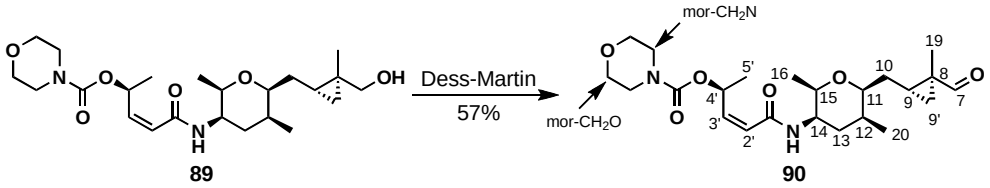
Preparation of 87. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **79** (115 mg, 0.351 mmol) and CH_2Cl_2 (2.5 mL). The mixture was cooled in an ice-water bath, and a solution of TFA in CH_2Cl_2 (1:4 v/v, 2.5 mL) was added slowly via a syringe. The reaction was warmed to 23 °C and stirred at the same temperature for 3 h. After concentration of the mixture, heptanes (4 mL) was added and removed *in vacuo*. The residue was dissolved in MeCN (4 mL) and used in the next step.



Preparation of 89. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **88** (121 mg, 0.528 mmol), MeCN (4 mL) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (201 mg, 0.529 mmol), followed by *N, N′*-diisopropylethylamine (0.240 mL, 1.40 mmol). The resulting mixture was added to a stirred solution of **87** in MeCN (3 mL) at 23 °C and rinsed with additional MeCN (1 mL). After 10 min at 23 °C, saturated aqueous NH_4Cl (3 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (70 to 100% EtOAc in hexanes) on silica gel (15 mL) to afford **89** (115 mg, 75%) as a white solid.

Data for **89**: R_f = 0.20 (EtOAc); IR (neat): 3585, 3420, 3207, 2921, 1668 (C=O), 1519, 1438, 1378, 1279, 1252, 1111, 1048 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.19 (br d, 1H, *J* = 9.5 Hz, NH), 6.17–6.12 (m, 1H, 4'-H), 5.93 (dd, 1H, *J* = 11.5, 8.0 Hz, 3'-H), 5.71 (dd, 1H, *J* = 11.5, 1.5 Hz, 2'-H), 3.97–3.93 (m, 1H), 3.69 (dq, 1H, *J* = 6.5, 2.5 Hz), 3.66 (t, 4H, *J* = 4.5 Hz), 3.52 (ddd, 1H, *J* = 7.0, 5.0, 3.0 Hz), 3.47 (t, 4H, *J* = 4.5 Hz), 3.38 (d, 1H, *J* = 11.0 Hz, 7-H), 3.29 (d, 1H, *J* = 11.0 Hz, 7-H), 1.98 (t, 2H, *J* = 3.5 Hz), 1.85–1.82 (m, 1H), 1.51–1.47 (m, 2H), 1.41 (d, 3H, *J* = 6.5 Hz), 1.16 (d, 3H, *J* = 6.0 Hz), 1.15 (s, 3H), 1.03 (d, 3H, *J* = 7.5 Hz), 0.73–0.67 (m, 1H), 0.57 (dd, 1H, *J* = 8.5, 4.5 Hz), 0.08 (dd, 1H, *J* = 5.0, 5.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 164.9, 154.9, 144.2, 122.2, 81.6, 75.9, 70.1, 66.6, 47.1, 35.9, 31.9, 29.2, 22.0, 20.5, 20.2, 17.9, 16.5, 15.5, 15.1; ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 170.6, 164.3, 143.7,

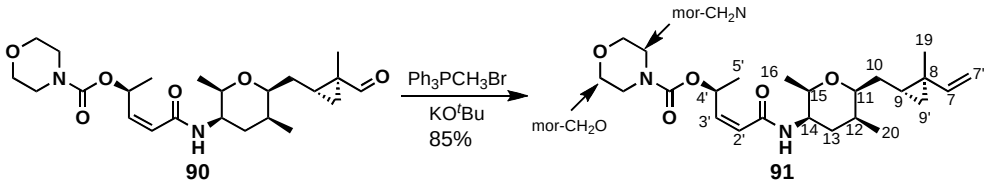
122.8, 81.9, 76.2, 72.7, 69.2, 47.4, 36.2, 32.4, 29.9, 29.7, 22.4, 21.5, 20.2, 18.9, 18.1, 16.9, 16.1; HRMS (EI+) calcd. for $C_{23}H_{38}N_2O_6$ $[M]^+$ 438.2730, found 438.2743.



Preparation of 90. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **89** (56.1 mg, 0.128 mmol) and CH_2Cl_2 (3.0 mL). The solution was cooled in an ice-water bath, and Dess-Martin periodinane (108 mg, 0.255 mmol) were added. The reaction was stirred at 0 °C for 5 h, and saturated aqueous $NaHCO_3$ (3 mL) and Na_2SO_3 (320 mg) were added. The stirring was continued for 30 min, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (30 to 90% EtOAc in hexanes) on silica gel (6 mL) to afford **90** (32.1 mg, 57%) as a white solid.

Data for **90**: R_f = 0.28 (80% EtOAc in hexanes); IR (neat): 2927, 1697 (C=O), 1520, 1434, 1385, 1278, 1247, 1118, 1073 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 8.67 (s, 1H, 7-H), 6.16–6.13 (m, 2H), 5.93 (dd, 1H, *J* = 12.0, 8.0 Hz, 3'-H), 5.71 (dd, 1H, *J* = 12.0, 1.0 Hz, 2'-H), 3.97 (dq, 1H, *J* = 9.0, 2.5 Hz), 3.68 (dq, 1H, *J* = 6.5, 2.5 Hz), 3.67 (t, 4H, *J* = 4.5 Hz), 3.52 (ddd, 1H, *J* = 8.0, 5.0, 3.0 Hz), 3.47 (t, 4H, *J* = 4.5 Hz), 1.99–1.98 (m, 2H), 1.85–1.78 (m, 1H), 1.65–1.59 (m, 1H), 1.54–1.45 (m, 2H), 1.42 (d, 3H, *J* = 6.5 Hz), 1.37–1.34 (m, 1H), 1.25 (s, 3H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.5 Hz), 0.73 (dd, 1H, *J* = 6.5, 5.0 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 202.5, 165.0, 154.9, 144.2, 122.3, 80.9, 76.0, 70.1, 66.6, 47.0, 35.9, 31.5,

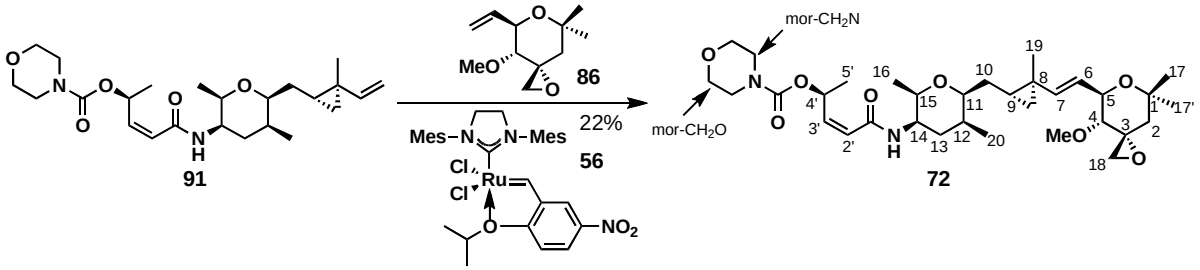
29.5, 21.6, 20.2, 19.8, 17.8, 15.1, 11.2; HRMS (ESI+) calcd. for $C_{23}H_{36}N_2O_6Na$ $[M+Na]^+$ 459.2471, found 459.2483.



Preparation of 91. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with methyltriphenylphosphonium bromide (0.11 g, 0.31 mmol) and THF (2.5 mL). The mixture was cooled in an ice-water bath and a solution of KO^{t}Bu in THF (0.25 mL, 1 M, 0.25 mmol) was added. The resulting mixture was stirred at 0 °C for 20 min, and aldehyde **90** (27 mg, 61 μmol) in THF (1 mL) was added via cannula and rinsed with additional THF (1 mL). After 10 min at 0 °C, H_2O (4 mL) was added. After removal of THF, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (20 to 50% EtOAc in hexanes) on silica gel (5 mL) to afford **91** (23.0 mg, 85%) as a colorless oil.

Data for **91**: R_f = 0.37 (70% EtOAc in hexanes); IR (neat): 3358, 2925, 2855, 1702 (C=O), 1669 (C=O), 1634, 1516, 1457, 1426, 1367, 1302, 1277, 1241, 1220, 1119, 1074, 1022 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.19–6.13 (m, 2H), 5.93 (dd, 1H, *J* = 11.5, 7.5 Hz, 3'-H), 5.71 (dd, 1H, *J* = 11.5, 1.0 Hz, 2'-H), 5.41 (dd, 1H, *J* = 17.0, 10.5 Hz, 7-H), 4.93 (dd, 1H, *J* = 17.0, 1.0 Hz, 7'-H), 4.85 (dd, 1H, *J* = 10.5, 1.0 Hz, 7'-H), 3.96 (dq, 1H, *J* = 9.0, 3.0 Hz), 3.69 (dq, 1H, *J* = 6.5, 2.0 Hz), 3.66 (t, 4H, *J* = 4.5 Hz), 3.52 (dt, 1H, *J* = 7.0, 2.5 Hz), 3.47 (t, 4H, *J* = 4.5

Hz), 1.98–1.97 (m, 2H), 1.87–1.81 (m, 1H), 1.67–1.61 (m, 1H), 1.51–1.45 (m, 1H), 1.42 (d, 3H, *J* = 6.5 Hz), 1.17 (s, 3H), 1.16 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 0.83 (m, 1H), 0.77 (dd, 1H, *J* = 8.5, 4.0 Hz), 0.34 (dd, 1H, *J* = 6.0, 4.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 165.1, 155.2, 147.8, 144.4, 122.5, 109.2, 81.8, 76.1, 70.4, 66.9, 47.4, 36.2, 32.3, 29.9, 29.3, 22.4, 21.8, 20.9, 20.4, 18.1, 15.9, 15.2; HRMS (ESI+) calcd. for $C_{24}H_{38}N_2O_5Na$ $[M+Na]^+$ 457.2678, found 457.2694.

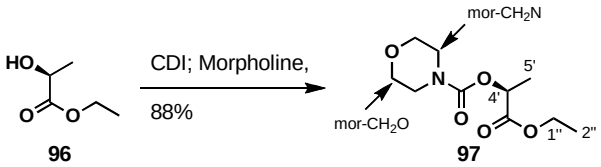


Preparation of 72. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **91** (30 mg, 68 μmol), **86** (18 mg, 95 μmol) and toluene (0.8 mL), followed by benzoquinone (1.5 mg, 14 μmol), and **56** (4.5 mg, 6.8 μmol). The resulting mixture was heated to 70 °C and stirred at the same temperature. After 27 h, the mixture was cooled to 23 °C and concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (15 mL) to afford **72** (6.6 mg, 16%) as a solid, and a mixture of **91** and **86** (27 mg).

An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with the mixture of **91** and **86** (27mg) and toluene (0.6 mL), followed by benzoquinone (1.0 mg, 10 μmol) and **56** (3.5 mg, 5.2 μmol). The resulting mixture was heated to 70 °C. After 22 h at the same temperature,

the mixture was cooled to 23 °C and concentrated *in vacuo*. The residue was purified by flash chromatography (10 to 80% EtOAc in hexanes) on silica gel (10 mL) to afford **72** (2.5 mg, 6%) as a solid. The combined yield of **72** after one cycle is 9.1 mg (22%). **72** was further purified by preparative TLC, and afforded as a white solid.

Data for **72**: R_f = 0.14 (70% EtOAc in hexanes); IR (neat): 3359, 2972, 2927, 2855, 1701 (C=O), 1669 (C=O), 1638, 1518, 1457, 1425, 1369, 1303, 1276, 1241, 1194, 1120, 1072, 1023, 1002 cm^{-1}; ^1H NMR (600 MHz, 293K, C_6D_6) δ 6.69 (dq, 1H, *J* = 6.6, 6.6 Hz, 4'-H), 6.09 (d, 1H, *J* = 9.0 Hz, NH), 5.74 (dd, 1H, *J* = 11.4, 7.8 Hz, 3'-H), 5.65 (dd, 1H, *J* = 15.6, 6.6 Hz, 6-H), 5.50 (d, 1H, *J* = 15.6 Hz, 7-H), 5.32 (dd, 1H, *J* = 11.4, 1.2 Hz, 2'-H), 4.44 (dd, 1H, *J* = 9.6, 6.6 Hz), 4.04–4.02 (m, 1H), 3.30–3.27 (m, 1H), 3.26–3.23 (m, 1H), 3.18 (br s, 6H), 3.15 (s, 3H, Me), 3.05 (br s, 2H), 2.92 (d, 1H, *J* = 9.6 Hz, 4-H), 2.72 (d, 1H, *J* = 5.4 Hz, 18-H), 2.06 (d, 1H, *J* = 5.4 Hz, 18-H), 1.77 (d, 1H, *J* = 13.8 Hz, 2-H), 1.73–1.69 (m, 1H), 1.58–1.52 (m, 2H), 1.41–1.38 (m, 2H), 1.48 (d, 3H, *J* = 6.6 Hz), 1.46 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.14 (d, 3H, *J* = 6.6 Hz), 1.04 (d, 1H, *J* = 13.8 Hz, 2-H), 0.92 (d, 3H, *J* = 7.8 Hz), 0.86–0.81 (m, 1H), 0.72 (dd, 1H, *J* = 9.0, 4.2 Hz), 0.13 (dd, 1H, *J* = 4.2, 4.2 Hz). ^{13}C NMR (150 MHz, 293K, C_6D_6) δ 165.1, 155.1, 143.8, 142.5, 124.8, 123.6, 82.0, 80.0, 76.4, 73.9, 73.4, 70.5, 60.6, 57.1, 47.7, 47.6, 44.2, 36.4, 32.9, 31.8, 29.9, 24.4, 22.7, 21.3, 21.2, 20.9, 18.4, 16.8, 15.4; HRMS (ESI+) calcd. for $C_{33}H_{52}N_2O_8Na$ $[M+Na]^+$ 627.3621, found 627.3627.

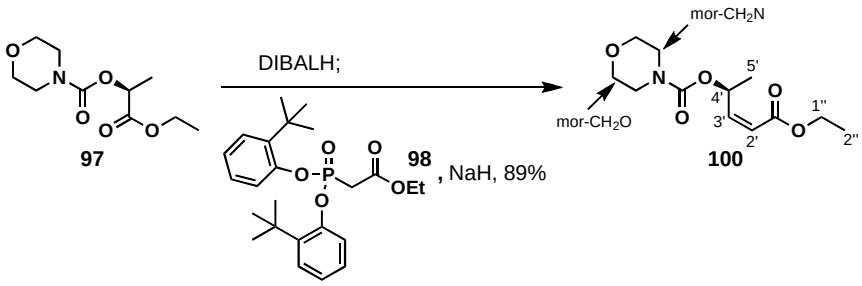


96 97

Preparation of 97. An oven-dried, 1000-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was

charged with **96** (33.8 g, 0.286 mol), CH_2Cl_2 (300 mL) and CDI (48.7 g, 0.300 mol). The resulting mixture was stirred at 23 °C for 20 h and then cooled to 0 °C. Morpholine (37.4 g, 0.429 mol) was added dropwise. After the addition, the mixture was warmed to 23 °C, stirred for an additional 2 h, and concentrated *in vacuo*. The residue was purified by dry column vacuum chromatography (10 to 70% EtOAc in hexanes) on silica gel (1000 mL) to afford **97** (58.1 mg, 88%) as colorless liquid.

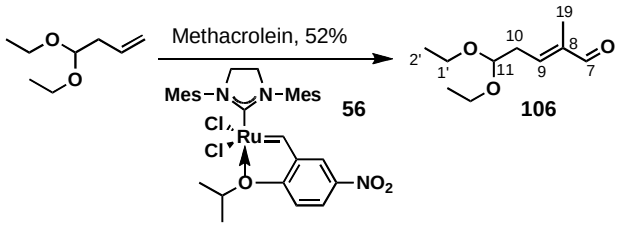
Data for **97**: R_f = 0.33 (40% EtOAc in hexanes); $[\alpha]_D^{22}$ +18.3 (*c* 1.00, $CHCl_3$); IR (neat): 3494, 2984, 2859, 1753 (C=O), 1710 (C=O), 1430, 1371, 1302, 1277, 1245, 1203, 1113, 1048, 1021 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 5.01 (q, 1H, *J* = 7.2 Hz, 4'-H), 4.17 (q, 2H, *J* = 7.2 Hz, 1"-H), 3.65 (t, 4H, *J* = 4.8 Hz, mor-CH_2O), 3.48 (br s, 4H, mor-CH_2N), 1.45 (d, 3H, *J* = 6.9 Hz, 5'-H), 1.25 (t, 3H, *J* = 7.2 Hz, 2"-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 171.4, 154.5, 69.5, 66.5, 61.2, 44.3, 17.1, 14.1; HRMS (EI+) calcd. for $C_{10}H_{17}NO_5$ $[M]^+$ 231.1107, found 231.1098.



Preparation of 100. An oven-dried, 1000-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **98** (128 g, 0.296 mol) and THF (300 mL). The solution was cooled in an ice-water bath, and NaH (11.4 g, 60%, 0.285 mol) was added in portions. The resulting mixture was stirred at 0 °C over 0.5 h before use.

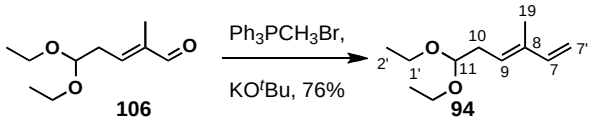
An oven-dried, 2000-mL, single-necked, round-bottomed flask equipped with a Teflon-coated Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **97** (45.6 g, 0.197 mol), and CH_2Cl_2 (450 mL). The solution was cooled in a dry ice-acetone bath, and DIBALH (207 mL, CH_2Cl_2, 0.207 mol) was added dropwise via a syringe over 50 min. After the addition, the ylide solution was added slowly via cannula over 20 min. The mixture was warmed to 23 °C slowly and stirred at the same temperature for 4.5 h. Then reaction was cooled to 0 °C, and EtOAc (500 mL) and HCl (1 M, 500 mL) were added. The mixture was separated, and the aqueous layer was extracted by EtOAc (3 × 250 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by dry column vacuum chromatography (10 to 50% EtOAc in hexanes) on silica gel (1000 mL) to afford **100** (45.1 g, 89%) as a colorless oil.

Data for **100**: R_f = 0.34 (40% EtOAc in hexanes); $[\alpha]_D^{22}$ +45.0 (*c* 1.12, $CHCl_3$); IR (neat): 2966, 2862, 1708 (C=O), 1487, 1426, 1367, 1300, 1278, 1242, 1195, 1118, 1088, 1053, 1025 cm^{-1}; ^1H NMR (300 MHz, 293K, $CDCl_3$) δ 6.20 (dq, 1H, *J* = 8.1, 6.3 Hz), 6.16 (dd, 1H, *J* = 10.5, 8.1 Hz), 5.77 (d, 1H, *J* = 10.5 Hz, 4'-H), 4.18 (q, 2H, *J* = 7.2 Hz, 1''-H), 3.65 (t, 4H, *J* = 4.5 Hz, mor-CH_2O), 3.45 (t, 4H, *J* = 4.5 Hz, mor-CH_2N), 1.38 (d, 3H, *J* = 6.3 Hz, 5'-H), 1.29 (t, 3H, *J* = 6.9 Hz, 2''-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 165.6, 155.0, 149.3, 119.6, 70.0, 66.8, 60.6, 20.0, 14.4, 14.3; HRMS (EI+) calcd. for $C_{12}H_{19}NO_5$ $[M]^+$ 257.1263, found 257.1257.



Preparation of 106. An oven-dried, 25-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with 3-butenal diethyl acetal (0.33 g, 2.3 mmol), methacrolein (2.90 mL, 34.6 mmol) and **56** (15 mg, 23 μmol). The resulting of mixture was stirred at 23 °C for 8 h and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 30% Et_2O in hexanes) on silica gel (25 mL) to afford **106** (0.22 mg, 52%) as colorless liquid.

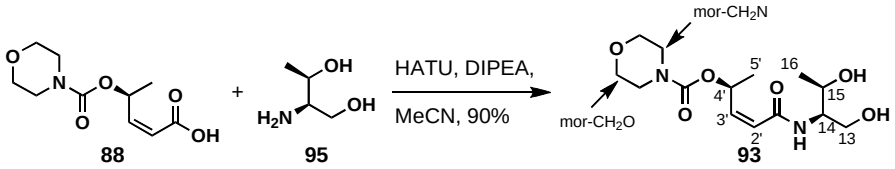
Data for **106**: R_f = 0.25 (10% EtOAc in hexanes); IR (neat): 2976, 2881, 2711, 1689 (C=O), 1647, 1444, 1374, 1344, 1201, 1124, 1062 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 9.44 (s, 1H, 7-H), 6.56 (td, 1H, *J* = 7.0, 1.5 Hz, 9-H), 4.66 (t, 1H, *J* = 5.5 Hz, 11-H), 3.69 (dq, 2H, *J* = 9.5, 7.0 Hz, 1'-H), 3.55 (dq, 2H, *J* = 9.5, 7.0 Hz, 7'-H), 2.70 (td, 2H, *J* = 7.0, 1.0 Hz, 10-H), 1.77 (d, 3H, *J* = 1.0 Hz, 19-H), 1.23 (t, 6H, *J* = 7.0 Hz, 2'-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 195.1, 148.5, 140.9, 101.2, 61.8, 34.0, 15.3, 9.4;



Preparation of 94. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with methyltriphenylphosphonium bromide (0.719 g, 2.14 mmol) and THF (6 mL). The solution was cooled in an ice-water bath, and a solution of KO^tBu (1M, 1.90 mL, 1.90 mmol) in THF was added via a syringe. The mixture was stirred for 10 min at 0 °C, and a solution of **106** (201 mg, 1.07 mmol) in THF (5 mL) was added via cannula. After 10 min, H_2O (5 mL) was added. After removal of THF, the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and

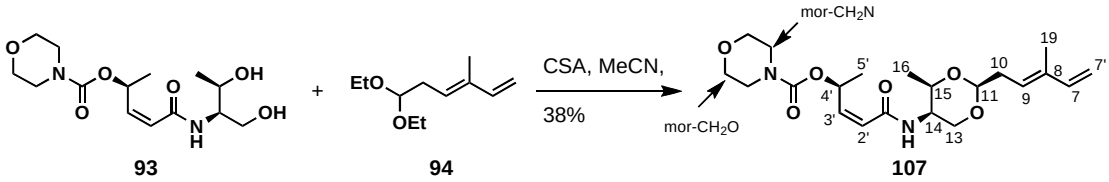
concentrated *in vacuo*. The crude residue was purified by flash chromatography (hexanes) on silica gel (20 mL) to afford **94** (137 mg, 63%) as a colorless oil.

Data for **94**: R_f = 0.25 (2% EtOAc in hexanes); IR (neat): 3433, 3090, 2976, 2880, 1644, 1608, 1443, 1373, 1343, 1205, 1128, 1063, 1015 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 6.40 (dd, 1H, *J* = 17.5, 10.5 Hz, 7-H), 5.51 (t, 1H, *J* = 7.0 Hz, 9-H), 5.12 (d, 1H, *J* = 17.5 Hz, 7'-H), 4.96 (d, 1H, *J* = 10.5 Hz, 7'-H), 4.53 (t, 1H, *J* = 6.0 Hz, 11-H), 3.66 (dq, 2H, *J* = 9.5, 7.0 Hz, 1'-H), 3.52 (dq, 2H, *J* = 9.5. 7.0 Hz, 1'-H), 2.50 (t, 2H, *J* = 6.5 Hz, 10-H), 1.76 (d, 3H, *J* = 1.0 Hz, 19-H), 1.22 (t, 6H, *J* = 7.0 Hz, 2'-H); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 141.7, 136.3, 127.3, 111.4, 102.7, 61.6, 33.5, 15.7, 12.3;



Preparation of 93. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **88** (0.535 mg, 2.33 mmol), **95** (0.270 mg, 2.59 mmol), MeCN (15 mL), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (0.629 mg, 2.33 mmol). And *N, N′*-diisopropylethylamine (0.810 mL, 4.66 mmol) was added to the mixture slowly via a syringe. The resulting mixture was stirred at 23 °C for 20 min and saturated aqueous NH_4Cl (0.5 mL) was added. The mixture was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (2 to 10 % MeOH in EtOAc) on silica gel (25 mL) to afford **93** (0.717 g, 97%) as a white solid.

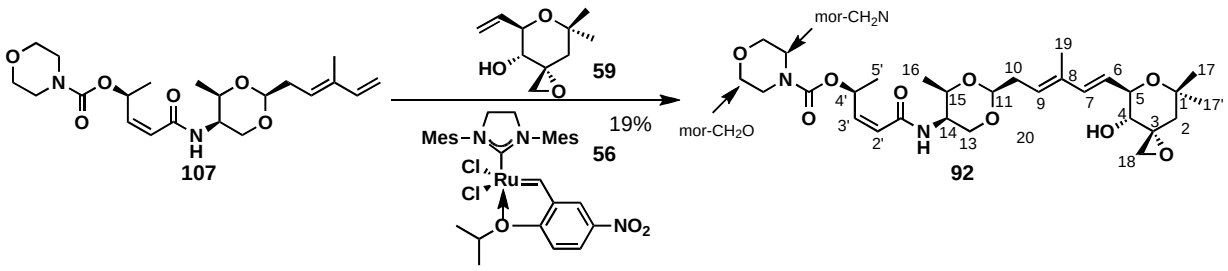
Data for **93**: R_f = 0.32 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ +22.4 (*c* 1.00, $CHCl_3$); IR (neat): 3405, 2972, 2930, 2863, 1671 (C=O), 1538, 1432, 1372, 1301, 1278, 1246, 1116, 1050, 1022 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 7.39 (br d, 1H, *J* = 9.0 Hz, NH), 6.00 (d, 1H, *J* = 11.0 Hz, 2'-H), 5.76 (dq, 1H, *J* = 10.0, 6.5 Hz, 4'-H), 5.72 (dd, 1H, *J* = 11.0, 10.0 Hz, 3'-H), 4.21 (qd, 1H, *J* = 6.5, 2.5 Hz), 4.03 (dd, 1H, *J* = 11.5, 2.5 Hz), 3.84–3.79 (m, 2H, mor-CH_2O), 3.66 (s, 4H, mor-CH_2N), 3.45 (d, 4H, *J* = 16.5 Hz), 1.39 (d, 3H, *J* = 6.0 Hz), 1.22 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 167.2, 155.7, 137.5, 126.8, 70.2, 70.1, 66.7, 65.8, 55.7, 20.8, 20.6; HRMS (ESI+) calcd. for $C_{14}H_{24}N_2O_6Na$ $[M+Na]^+$ 339.1532, found 339.1517.



Preparation of 107. An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **93** (0.250 mg, 0.790 mmol), **94** (0.146 mg, 0.790 mmol) and CH_2Cl_2 (6 mL), followed by CSA (36.7 mg, 0.158 mmol). Et_3N (50 μL) was added, and the solution was removed *in vacuo*. The crude residue was purified by flash chromatography (50 to 90% EtOAc in hexanes) on silica gel (30 mL) to afford **107** (121 mg, 38%) as a white solid.

Data for **107**: R_f = 0.20 (60% EtOAc in hexanes); $[\alpha]_D^{22}$ +4.5 (*c* 1.00, $CHCl_3$); IR (neat): 3322, 2978, 2930, 2860, 1695 (C=O), 1671 (C=O), 1525, 1428, 1365, 1278, 1243, 1120, 1052, 1022 cm^{-1}; ^1H NMR (500 MHz, 293K, $CDCl_3$) δ 7.36 (br d, 1H, *J* = 9.0 Hz, NH), 6.38 (dd, 1H, *J* = 17.0, 11.0 Hz, 7-H), 5.99 (dq, 1H, *J* = 6.5, 6.5 Hz, 4'-H), 5.89–5.83 (m, 2H), 5.52 (t, 1H, *J* = 6.5 Hz, 9-H), 5.13 (d, 1H, *J* = 17.0 Hz, 7'-H), 4.97 (d, 1H, *J* = 11.0 Hz, 7'-H), 4.65 (t, 1H, *J* = 5.0

Hz, 11-H), 4.03 (dd, 1H, *J* = 12.0, 1.5 Hz), 3.97–3.93 (m, 2H), 3.89 (dd, 1H, *J* = 12.0, 1.5 Hz), 3.65 (t, 4H, *J* = 4.5 Hz, mor-CH_2O), 3.47 (s, 4H, mor-CH_2N), 2.51 (t, 2H, *J* = 6.0 Hz, 10-H), 1.75 (d, 3H, *J* = 0.5 Hz, 19-H), 1.39 (d, 3H, *J* = 6.5 Hz), 1.18 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, 293K, $CDCl_3$) δ 165.8, 155.3, 142.2, 141.2, 136.7, 126.1, 123.7, 111.7, 102.2, 74.9, 71.4, 70.1, 66.9, 47.1, 44.4, 34.5, 20.7, 17.9, 12.3; HRMS (ESI +) calcd. for $C_{21}H_{32}N_2O_6Na$ $[M+Na]^+$ 431.2158, found 431.2142.



Preparation of 92. An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with **107** (57 mg, 0.14 mmol), **59** (35 mg, 0.19 mol) and DCE (2 mL), followed by benzoquinone (3.0 mg, 28 μmol), and **56** (9.3 mg, 14 μmol). The resulting mixture was heated to 43 °C, and stirred at the same temperature. After 27 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (20 to 90% EtOAc in hexanes) on silica gel (10 mL) to afford **92** (12 mg, 15%) as a solid, and a mixture of **107** and **59** (37 mg).

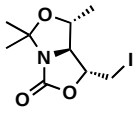
An oven-dried, 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with the mixture of **107** and **59** (37 mg) and DCE (1 mL), followed by benzoquinone (1.1 mg, 11 μmol) and **56** (3.5 mg, 5.2 μmol). The resulting mixture was heated to 45 °C, and stirred at the same temperature. After 20 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash

chromatography (20 to 90% EtOAc in hexanes) on silica gel (8 mL) to afford **92** (3.1 mg, 6%) as a solid. The combined yield of **92** after one cycle is 14.8 mg (19%). **92** was further purified by preparative TLC, and afforded as a white solid.

Data for **92**: R_f = 0.11 (80% EtOAc in hexanes); $[\alpha]_D^{22}$ +13.8 (*c* 0.40, $CHCl_3$); IR (neat): 3427, 2925, 1670 (C=O), 1530, 1429, 1366, 1277, 1244, 1122, 1051 cm^{-1}; ^1H NMR (600 MHz, 293K, CD_2Cl_2) δ 7.11 (br d, 1H, *J* = 9.6 Hz, NH), 6.34 (d, 1H, *J* = 15.6 Hz, 7-H), 6.01 (dq, 1H, *J* = 6.6, 6.6 Hz, 4'-H), 5.88 (dd, 1H, *J* = 12.0, 8.4 Hz, 3'-H), 5.81 (dd, 1H, *J* = 12.0, 0.6 Hz, 2'-H), 5.65 (dd, 1H, *J* = 15.6, 6.6 Hz, 6-H), 5.52 (t, 1H, *J* = 7.2 Hz, 9-H), 4.63 (t, 1H, *J* = 5.4 Hz, 11-H), 3.98–3.92 (m, 3H), 3.90–3.87 (m, 2H), 3.61 (s, 4H, mor-CH_2O), 3.48 (t, 1H, *J* = 10.2 Hz, 4-H), 3.43 (s, 4H, mor-CH_2N), 2.96 (d, 1H, *J* = 4.8 Hz, 18-H), 2.52–2.43 (m, 2H), 2.46 (d, 1H, *J* = 4.8 Hz, 18-H), 2.16 (d, 1H, *J* = 14.4 Hz, 2-H), 1.76 (s, 3H), 1.62 (d, 1H, *J* = 10.8 Hz, 4-OH), 1.39 (d, 1H, *J* = 14.4 Hz, 2-H), 1.35 (s, 3H), 1.34 (d, 3H, *J* = 6.6 Hz), 1.23 (s, 3H), 1.12 (d, 3H, *J* = 6.6 Hz); HRMS (EI+) calcd. for $C_{29}H_{44}N_2O_9$ $[M]^+$ 564.3047, found 564.3058.

1.3 ^{1}H AND ^{13}C SPECTRA

^{1}H NMR of 47: $CDCl_3$, 293 K, 600 MHz



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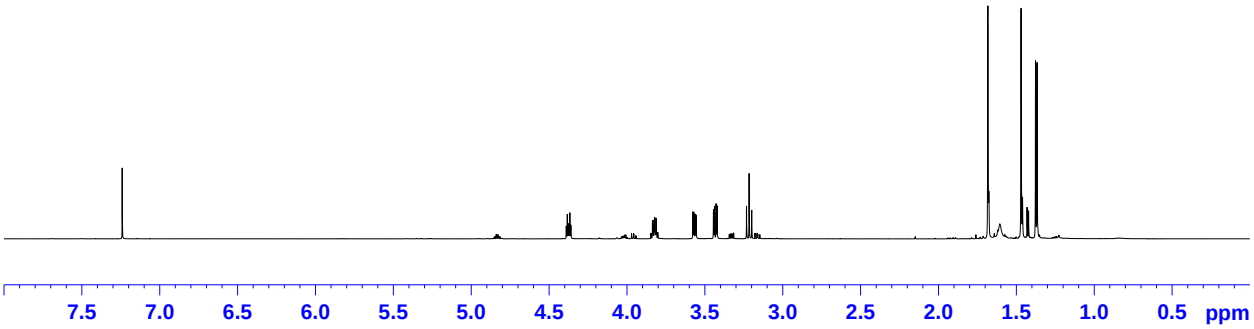
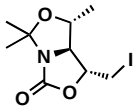


^{13}C NMR of 47: $CDCl_3$, 293 K, 125 MHz



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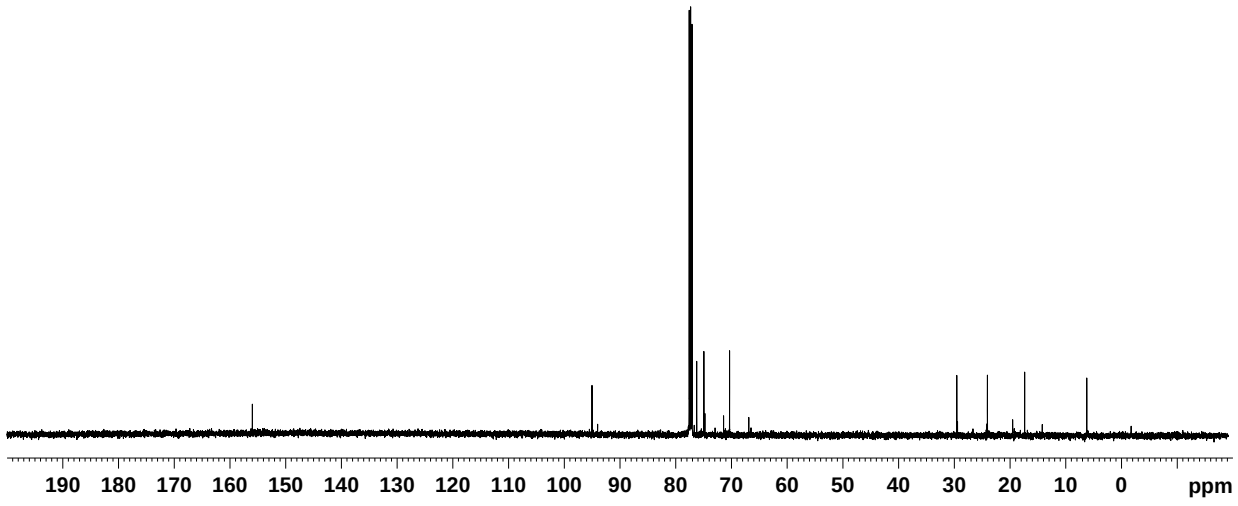
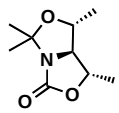


^{1}H NMR of 49: $CDCl_3$, 293 K, 500 MHz



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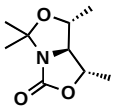
^{13}C NMR of 49: $CDCl_3$, 293 K, 125 MHz



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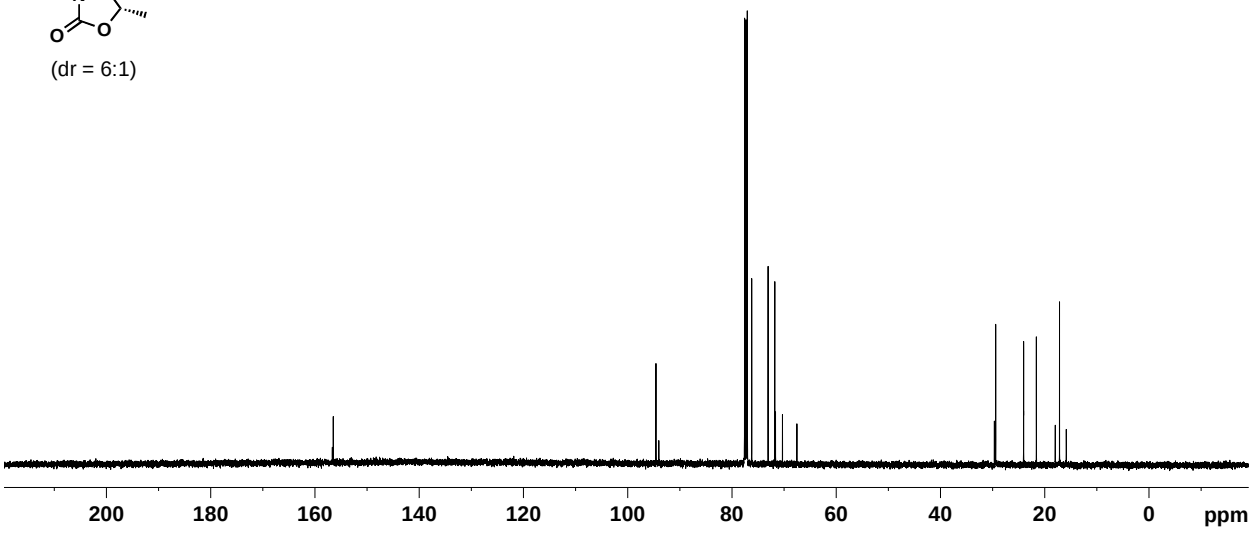
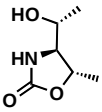


^{1}H NMR of 50: $CDCl_3$, 293 K, 500 MHz



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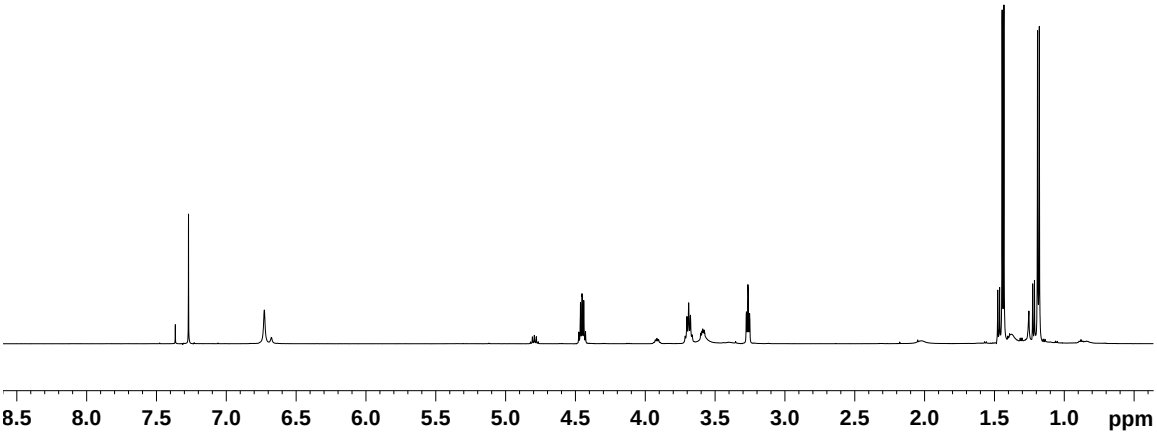
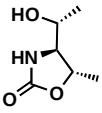


^{13}C NMR of 50: $CDCl_3$, 293 K, 75 MHz



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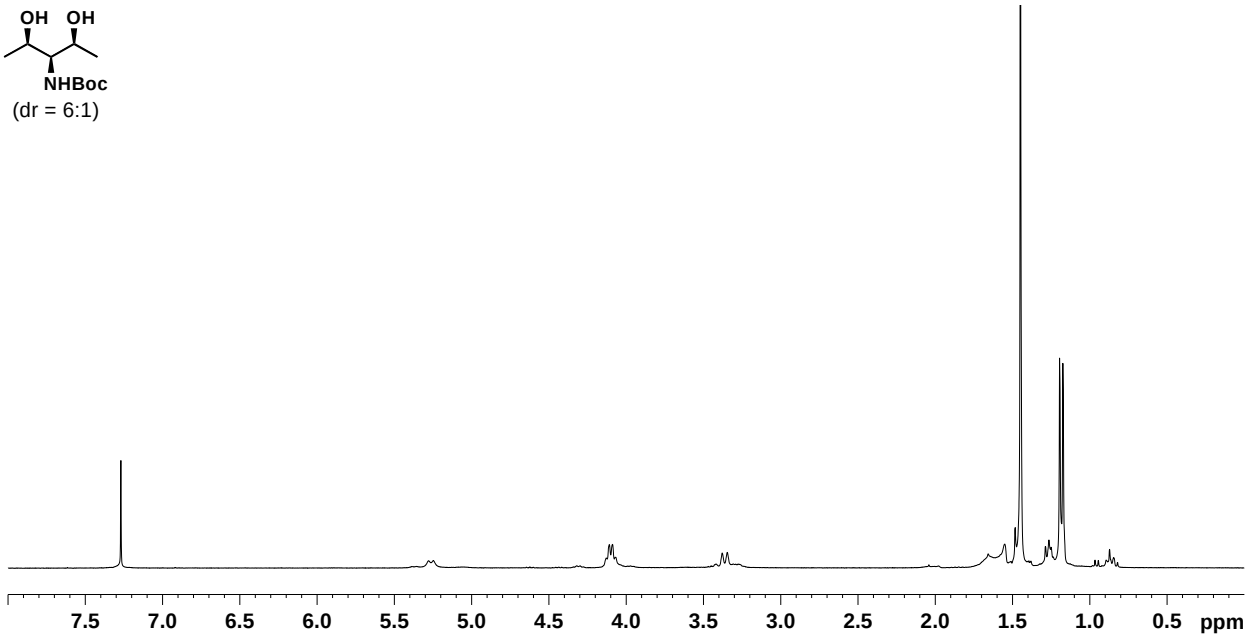
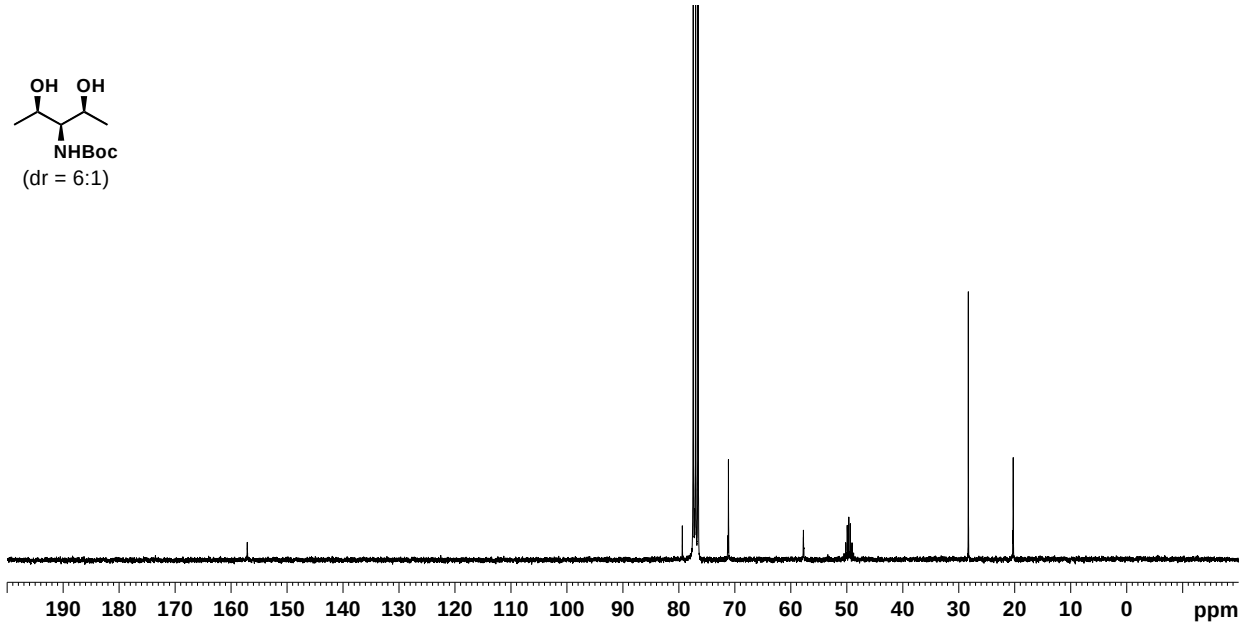
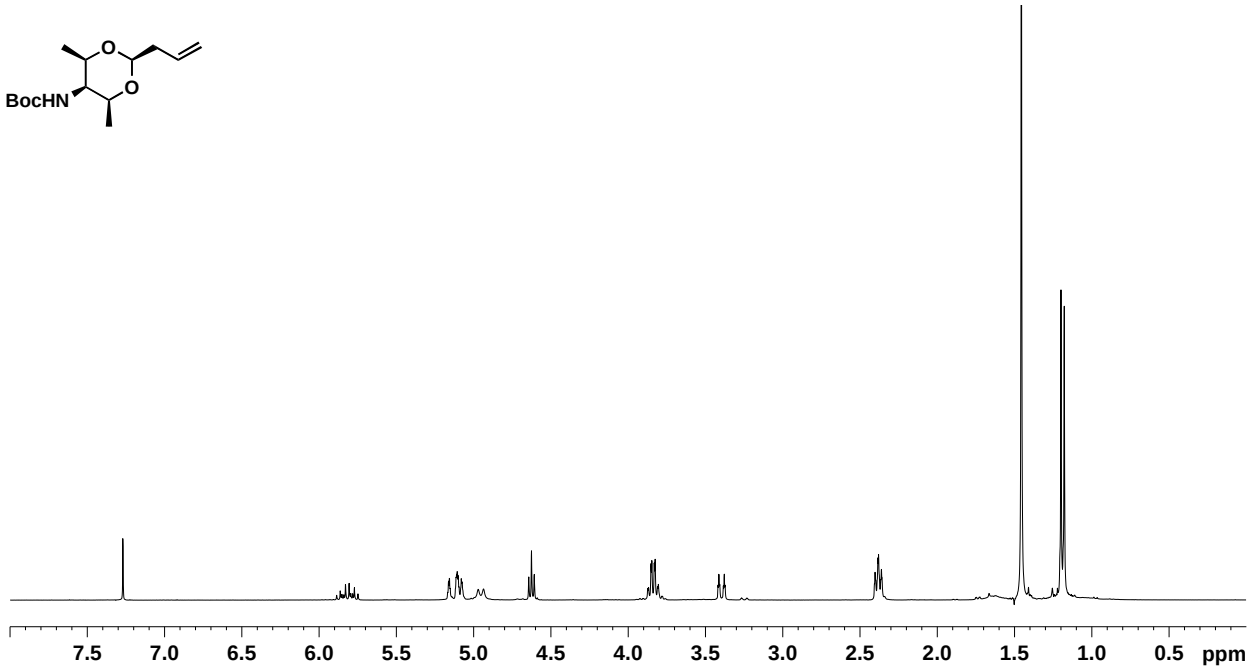
^{1}H NMR of 52: $CDCl_3$, 293 K, 300 MHz



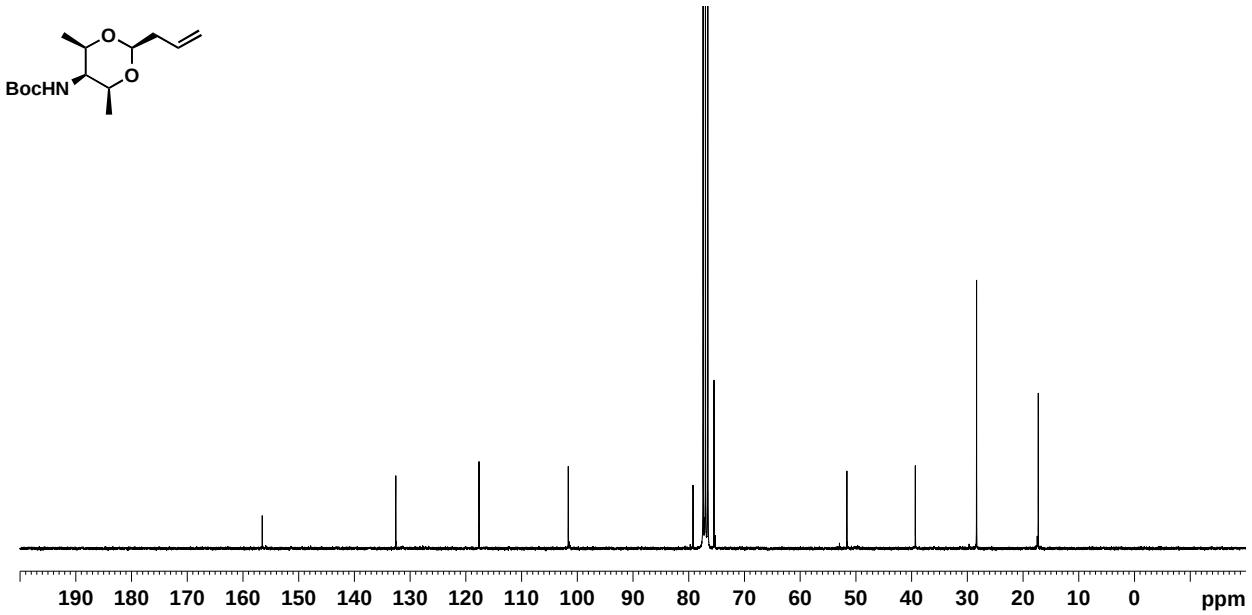
^{13}C NMR of 52: $CDCl_3$, 293 K, 75 MHz



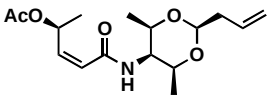
^{1}H NMR of 53: $CDCl_3$, 293 K, 300 MHz

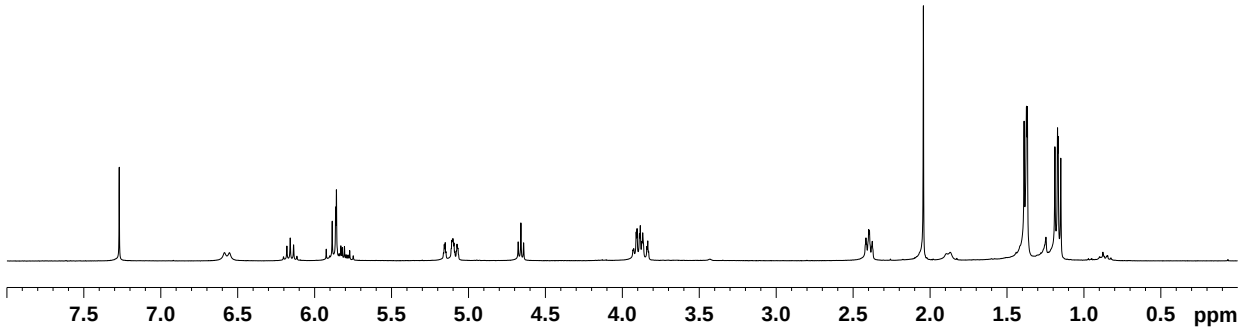


^{13}C NMR of 53: $CDCl_3$, 293 K, 75 MHz

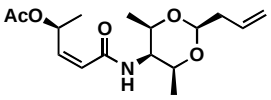


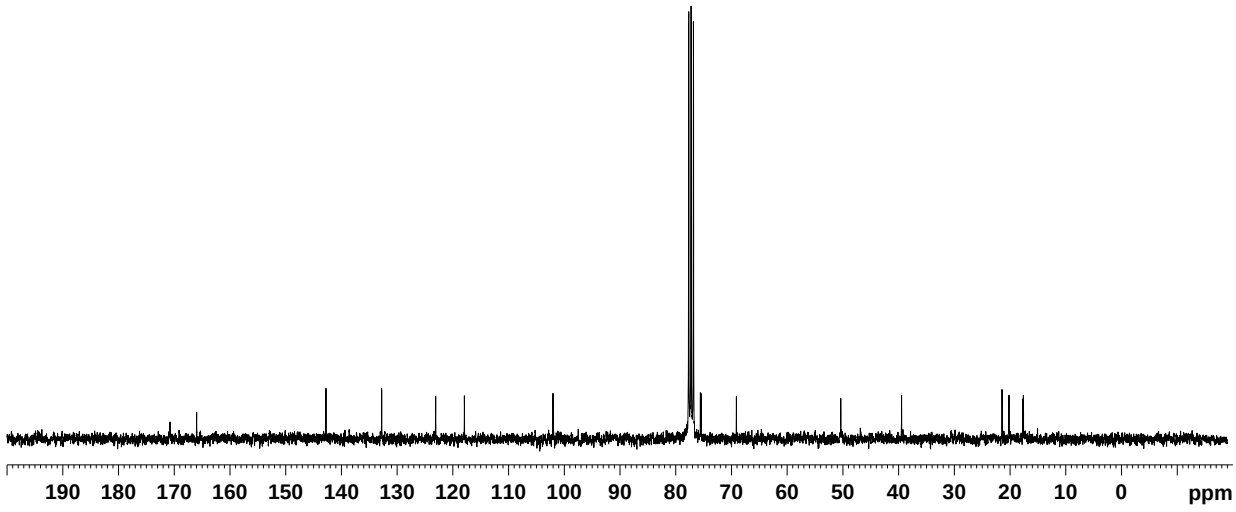
^{1}H NMR of 55: $CDCl_3$, 293 K, 300 MHz



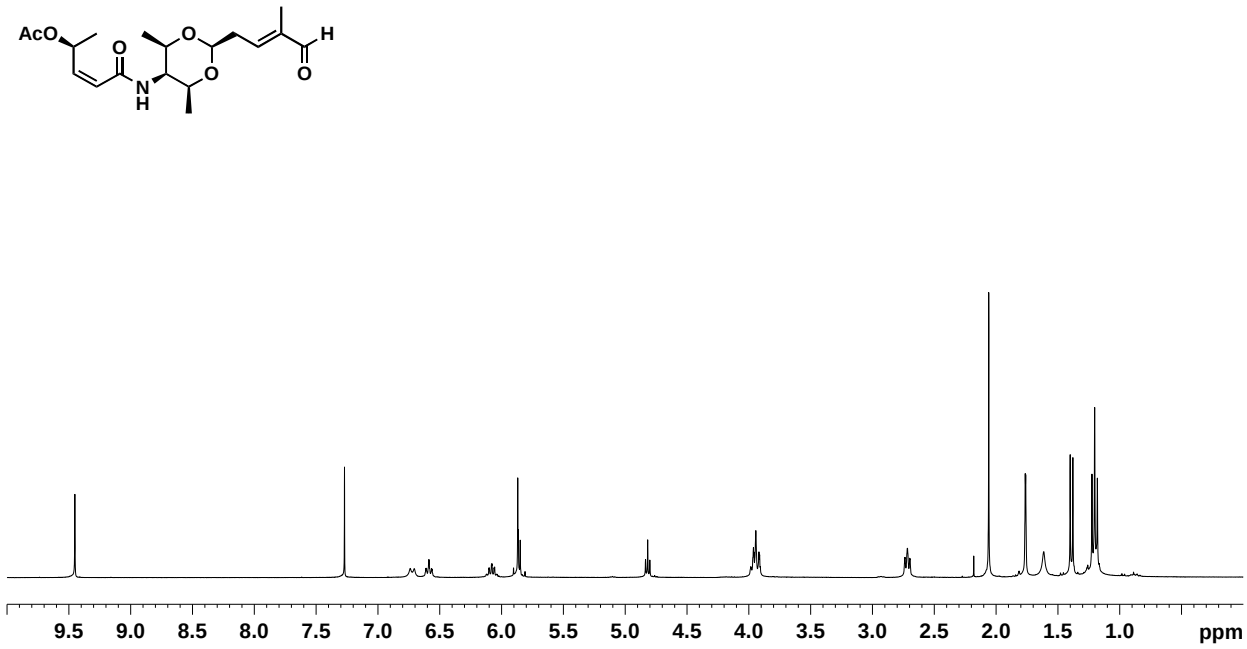


^{13}C NMR of 55: $CDCl_3$, 293 K, 75 MHz

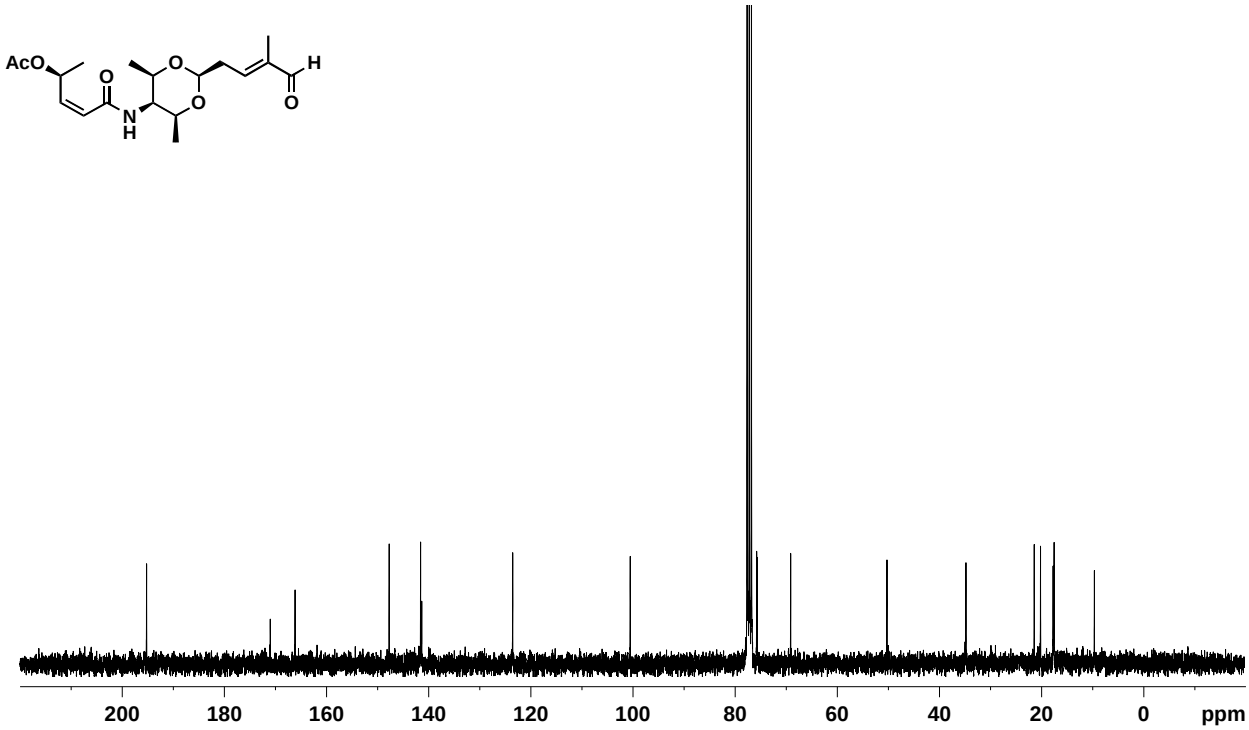




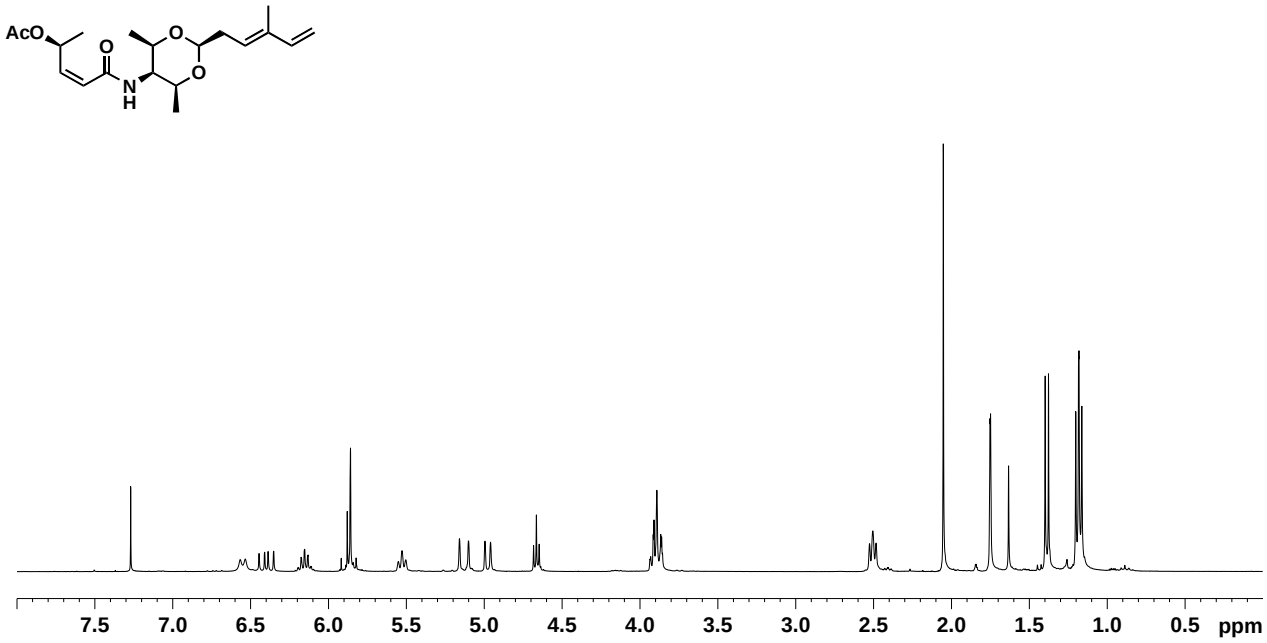
^{1}H NMR of 57: $CDCl_3$, 293 K, 300 MHz



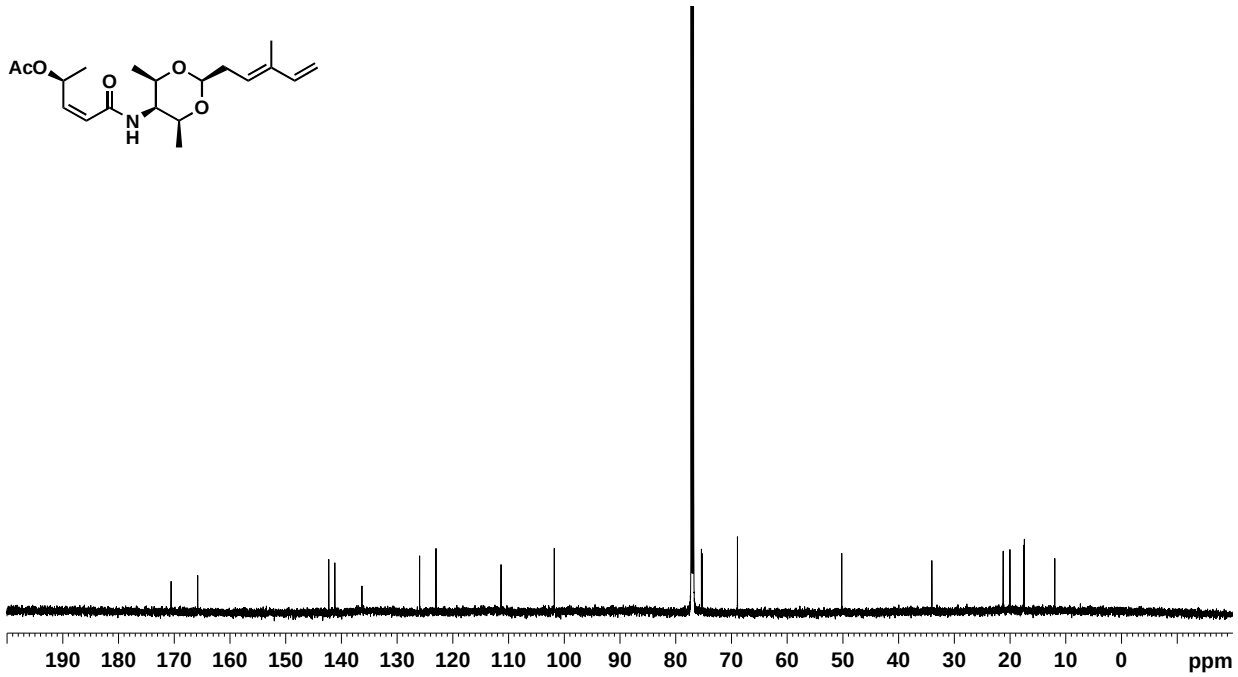
^{13}C NMR of 57: $CDCl_3$, 293 K, 75 MHz



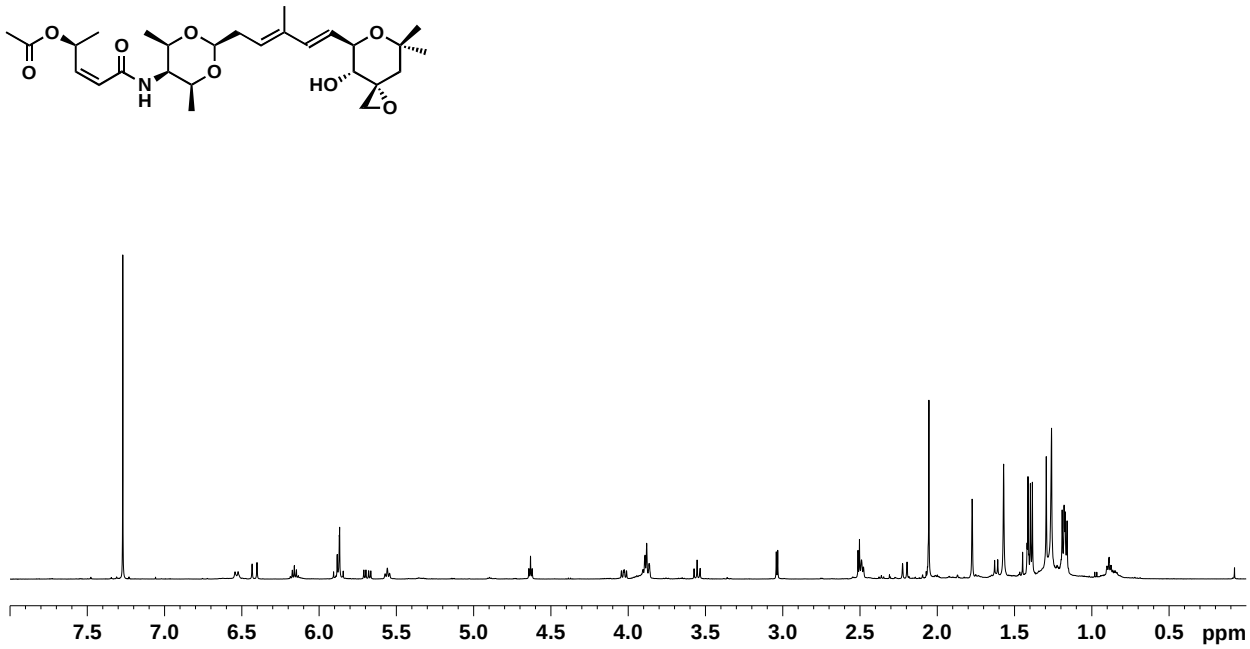
^{1}H NMR of 58: $CDCl_3$, 293 K, 300 MHz



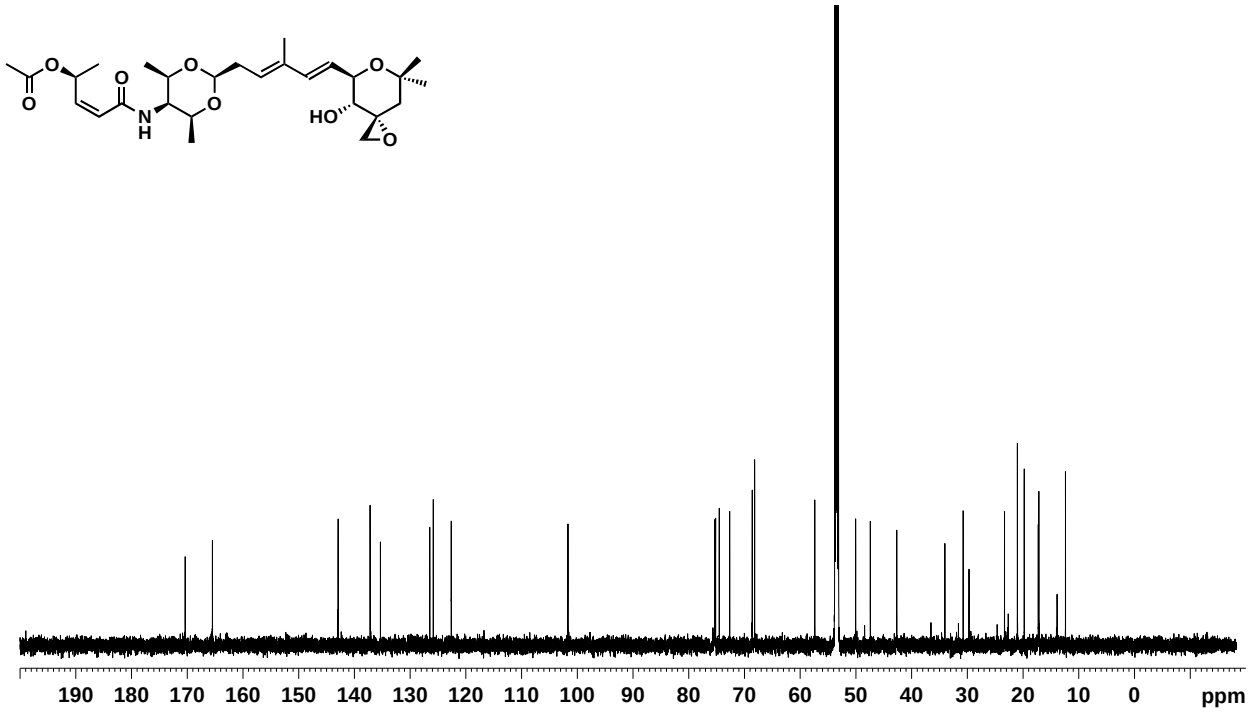
^{13}C NMR of 58: $CDCl_3$, 293 K, 75 MHz



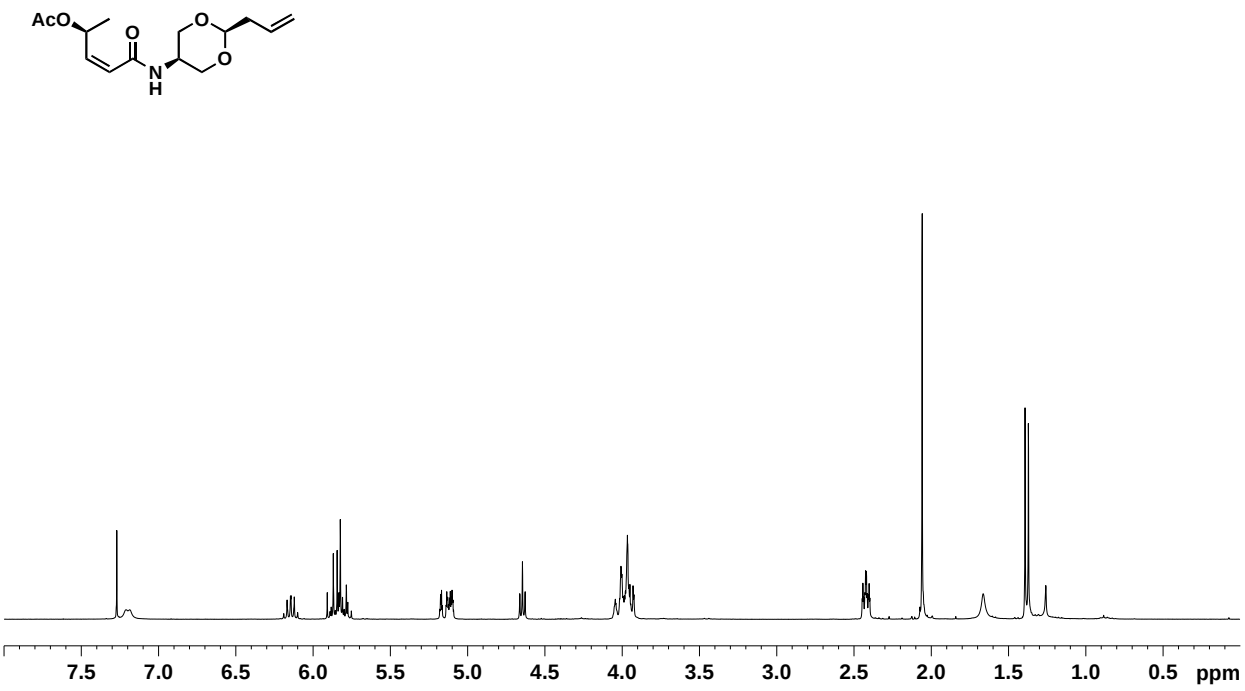
^{1}H NMR of 41: $CDCl_3$, 293 K, 500 MHz



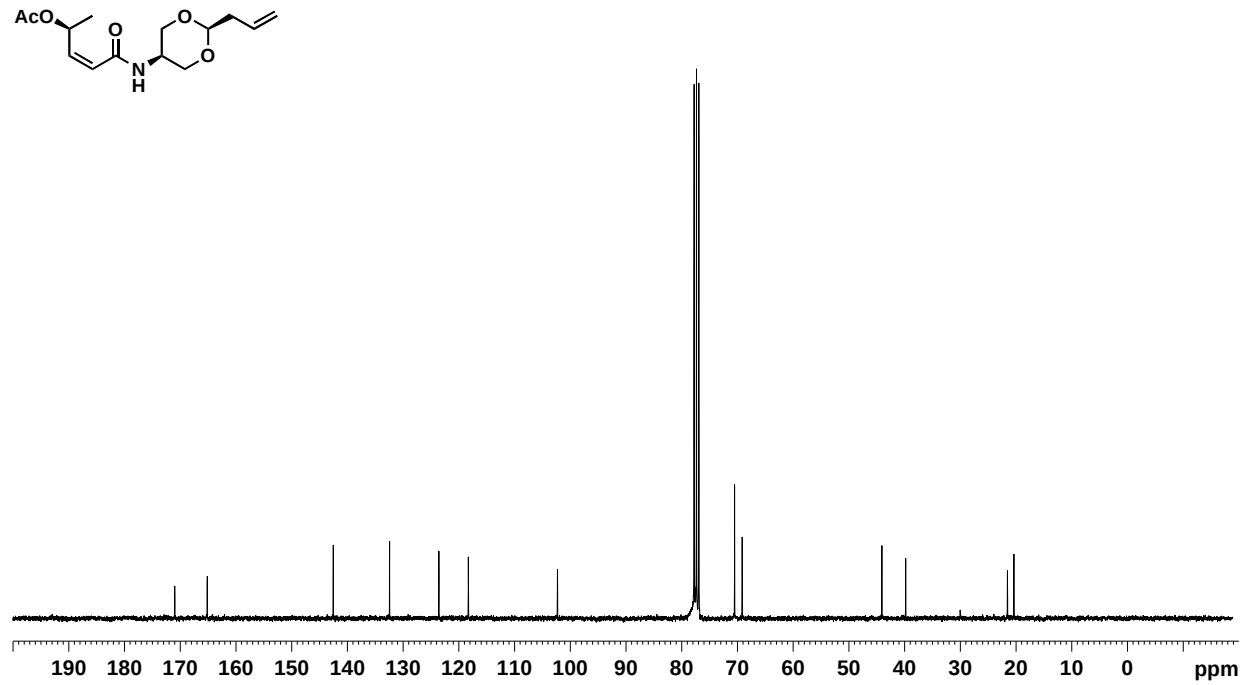
^{13}C NMR of 41: CDCl3, 293 K, 300 MHz



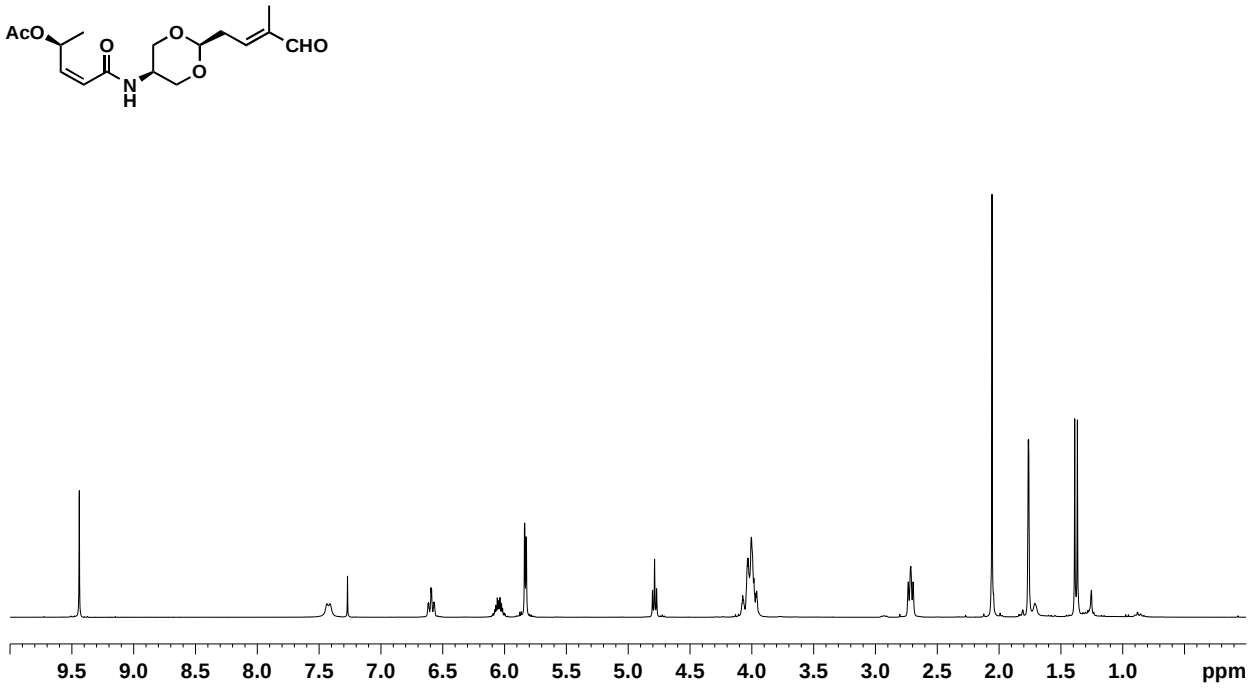
^{1}H NMR of 64: $CDCl_3$, 293 K, 300 MHz



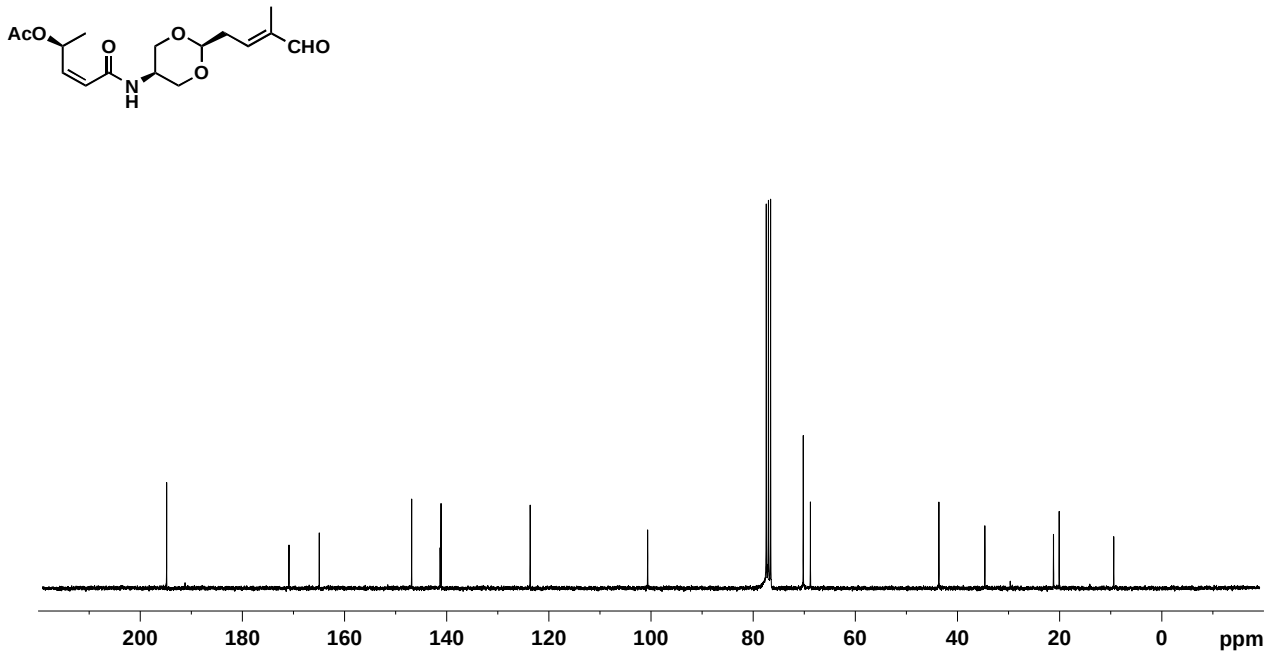
^{13}C NMR of 64: $CDCl_3$, 293 K, 75 MHz



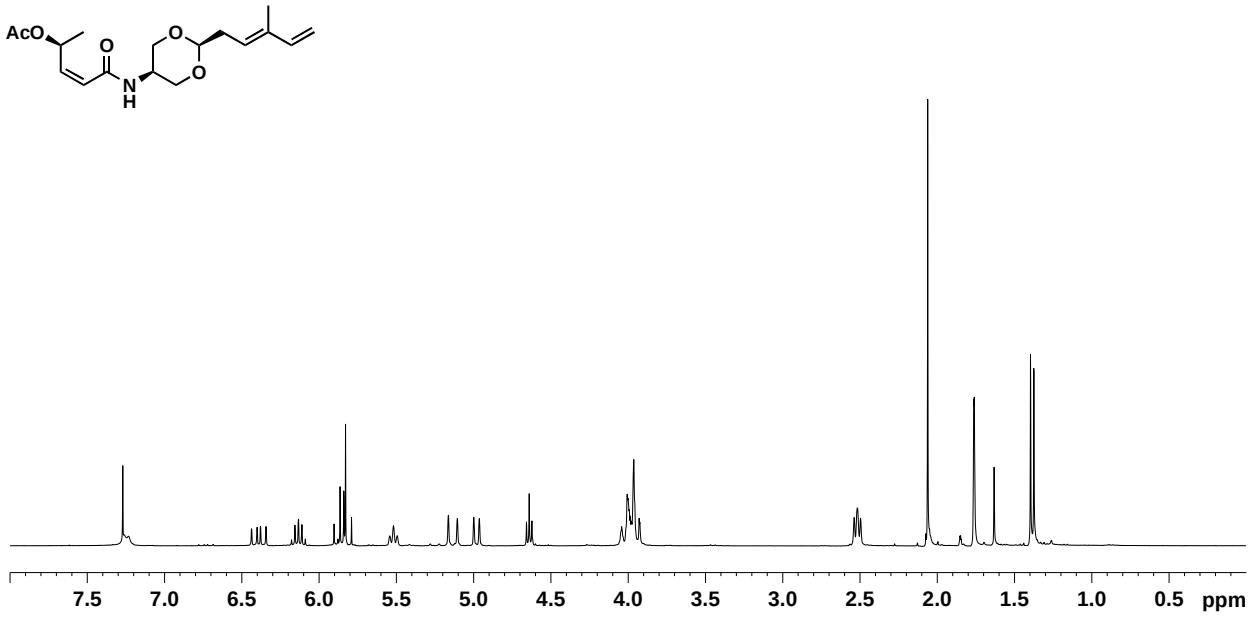
^{1}H NMR of 65: $CDCl_3$, 293 K, 300 MHz



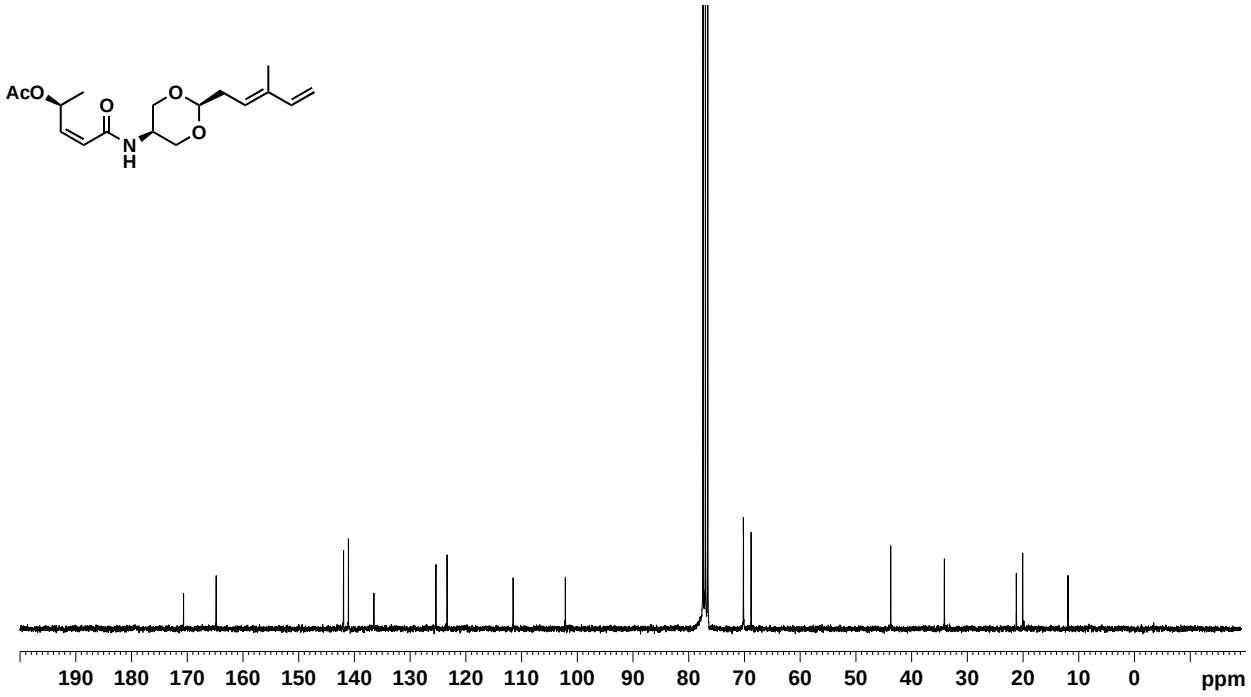
^{13}C NMR of 65: $CDCl_3$, 293 K, 75 MHz



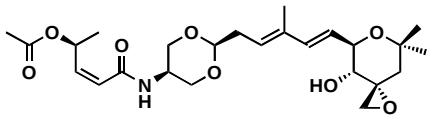
^{1}H NMR of 66: $CDCl_3$, 293 K, 300 MHz

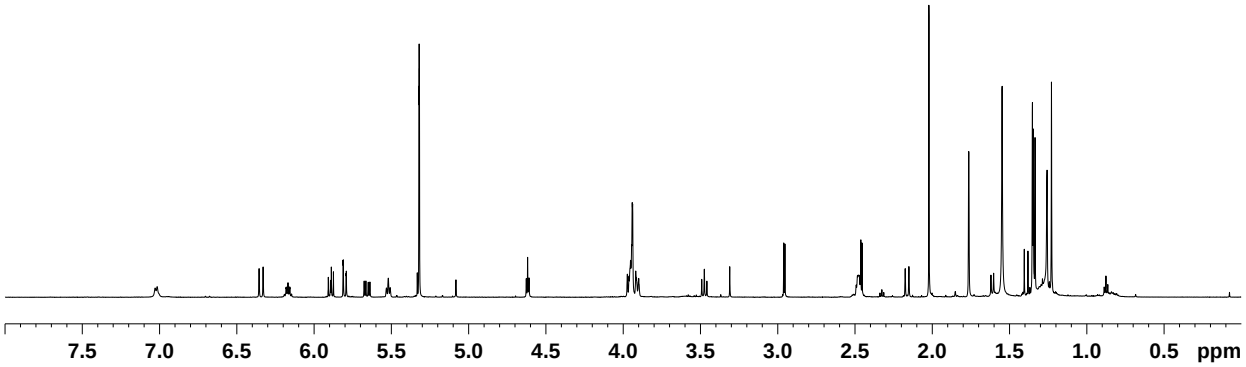


^{13}C NMR of 66: $CDCl_3$, 293 K, 75 MHz

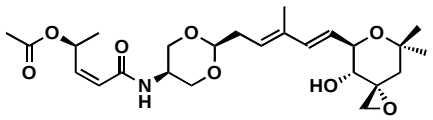


^{1}H NMR of 42: $CDCl_3$, 293 K, 600 MHz

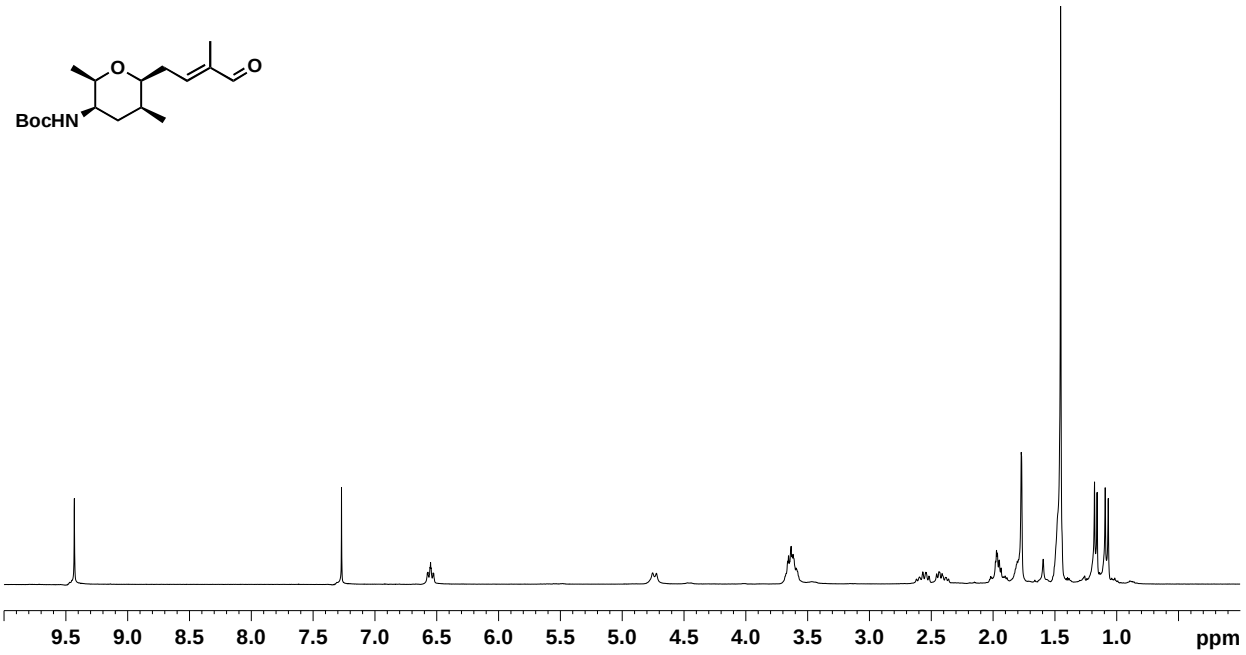




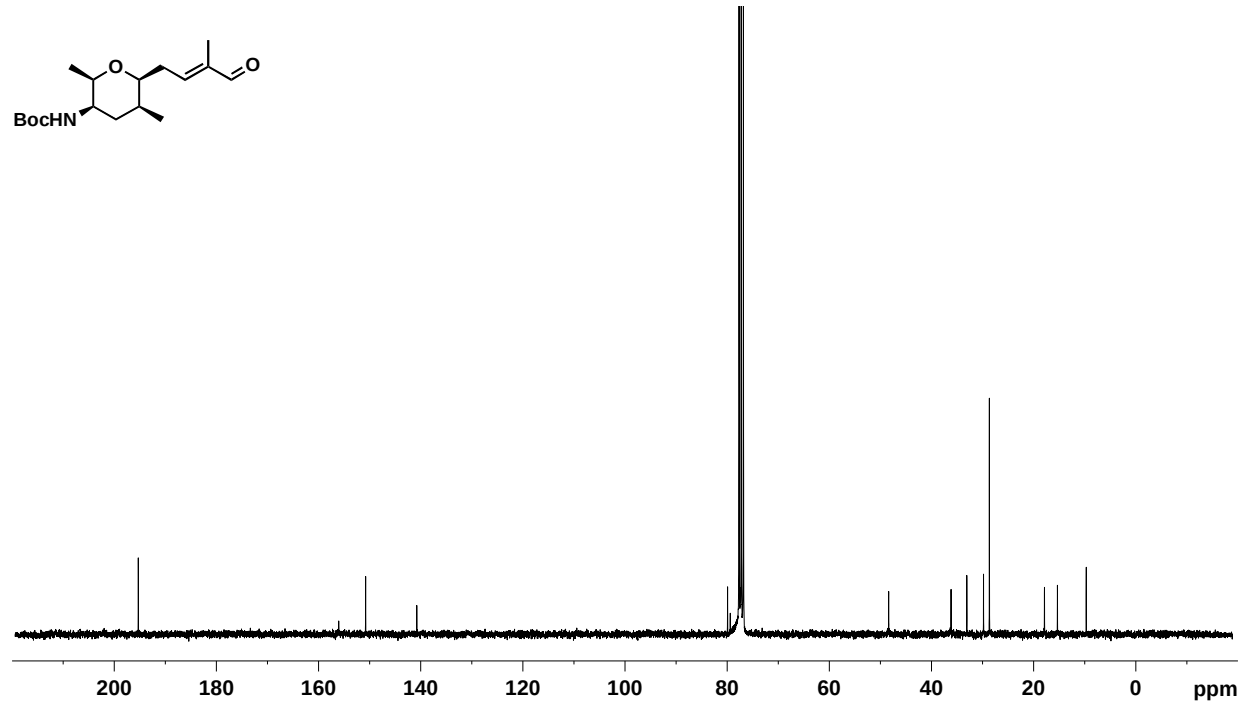
^{13}C NMR of 42: $CDCl_3$, 293 K, 150 MHz



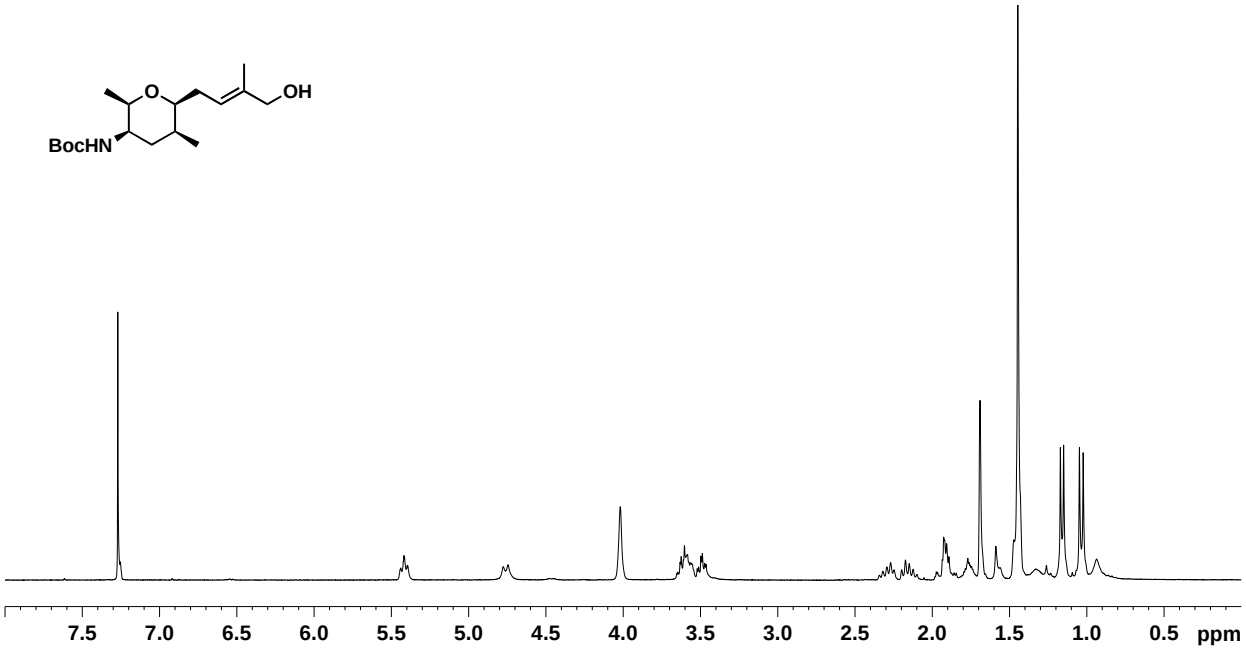
^{1}H NMR of 75: $CDCl_3$, 293 K, 300 MHz



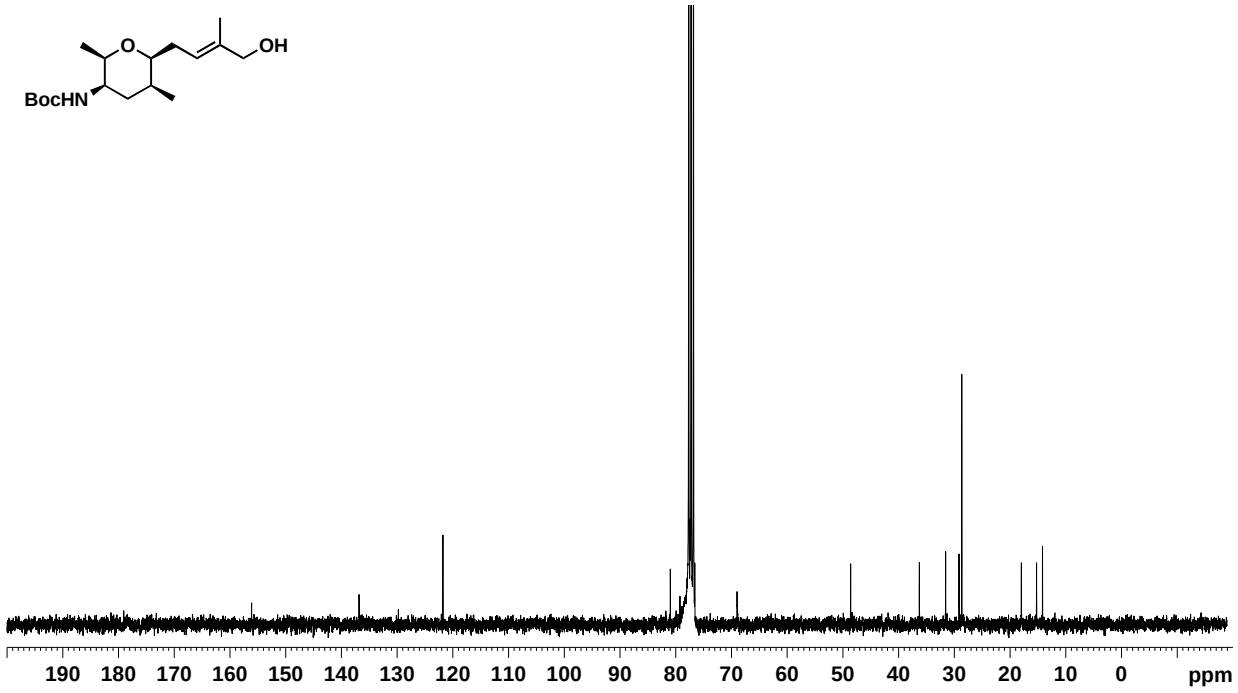
^{13}C NMR of 75: $CDCl_3$, 293 K, 75 MHz



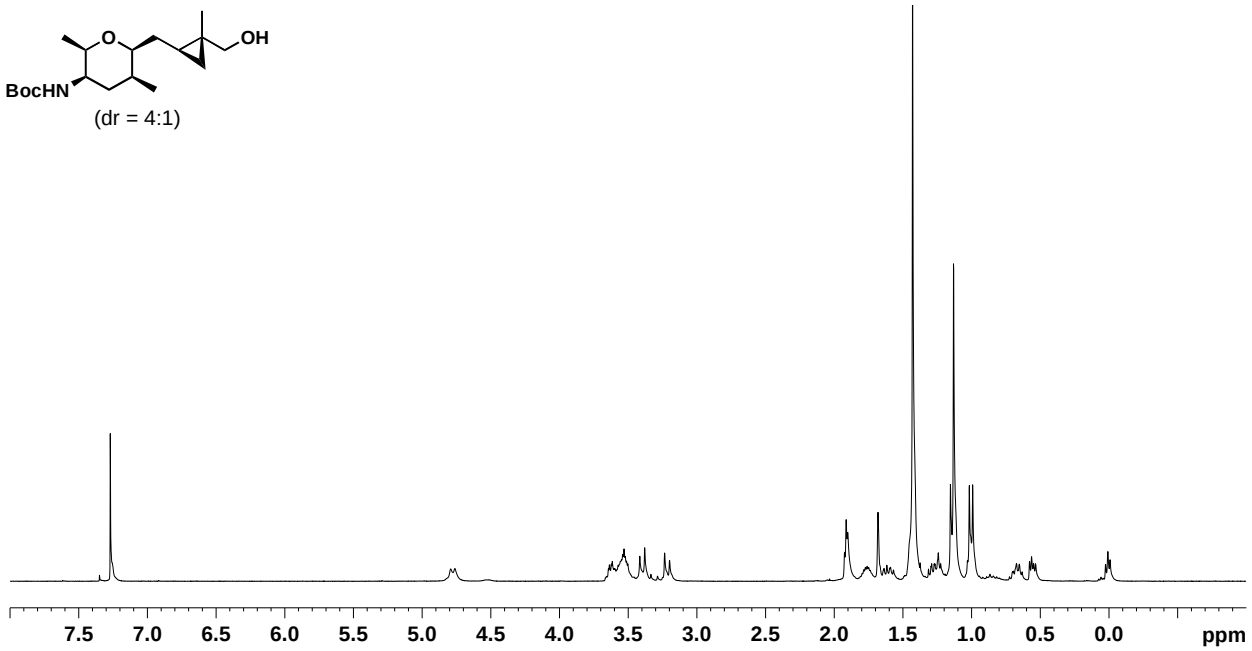
^{1}H NMR of 74: $CDCl_3$, 293 K, 500 MHz



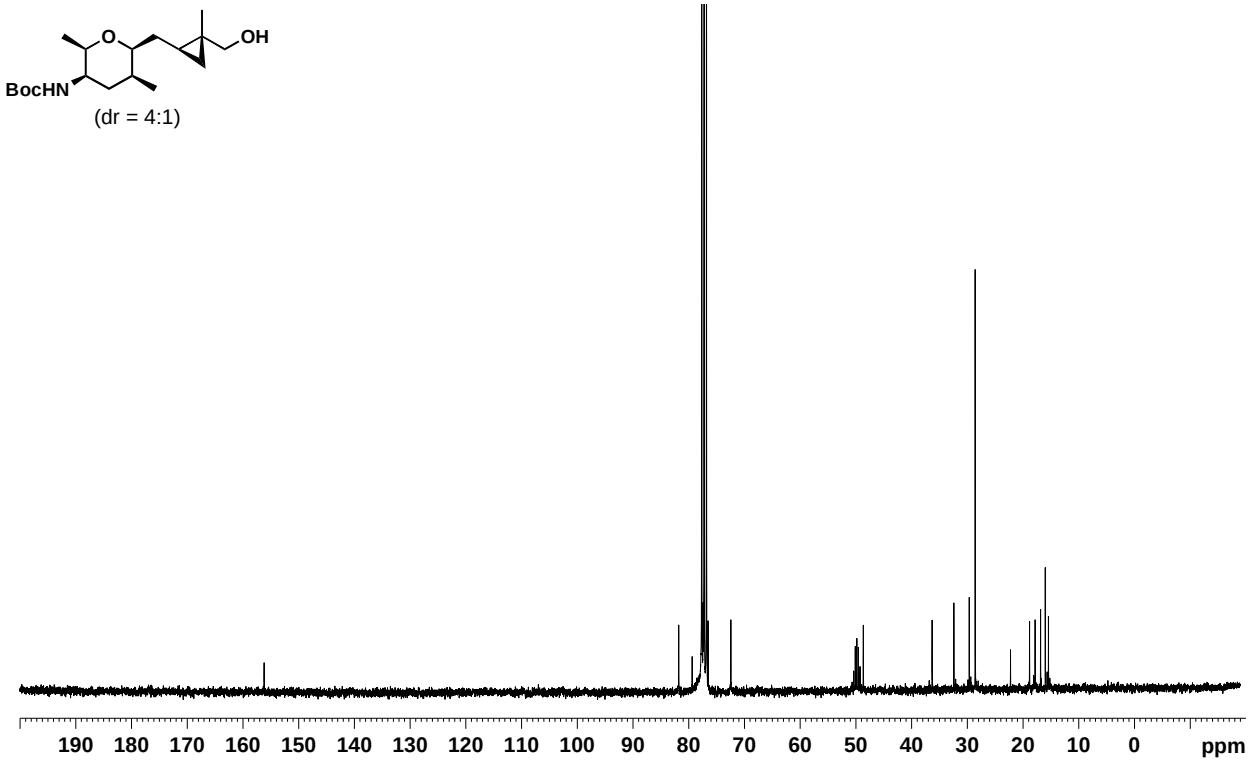
^{13}C NMR of 74: $CDCl_3$, 293 K, 75 MHz



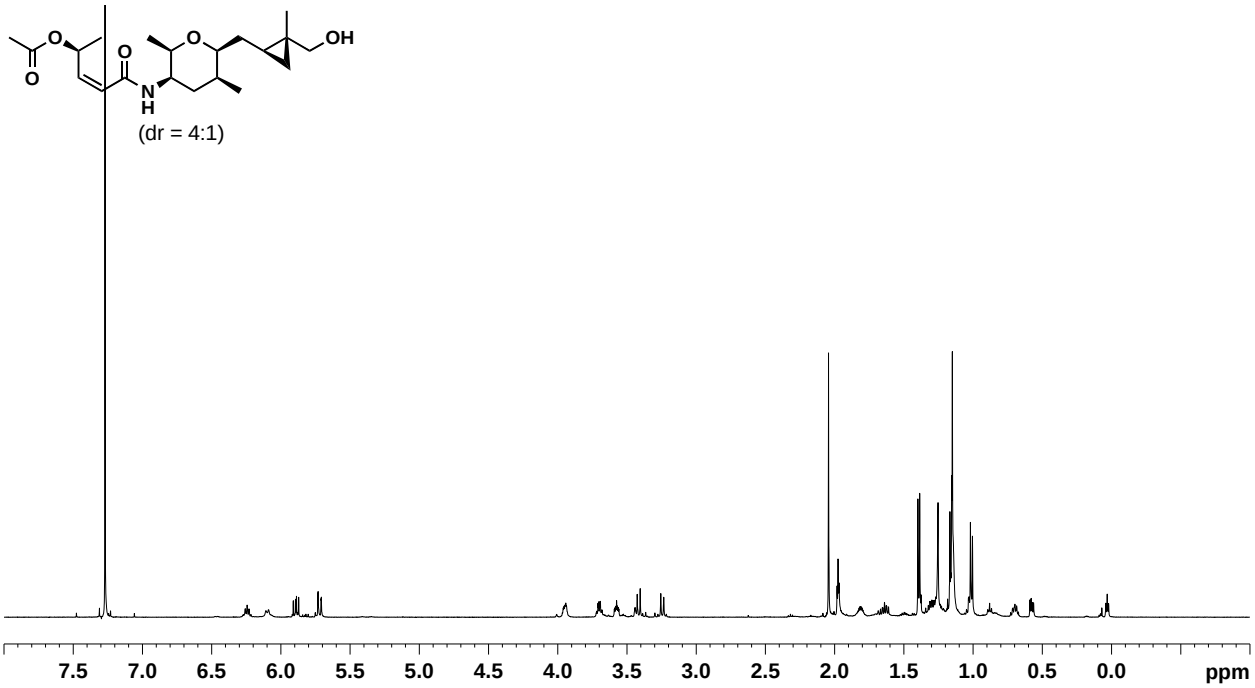
^{1}H NMR of 78: $CDCl_3$, 293 K, 500 MHz



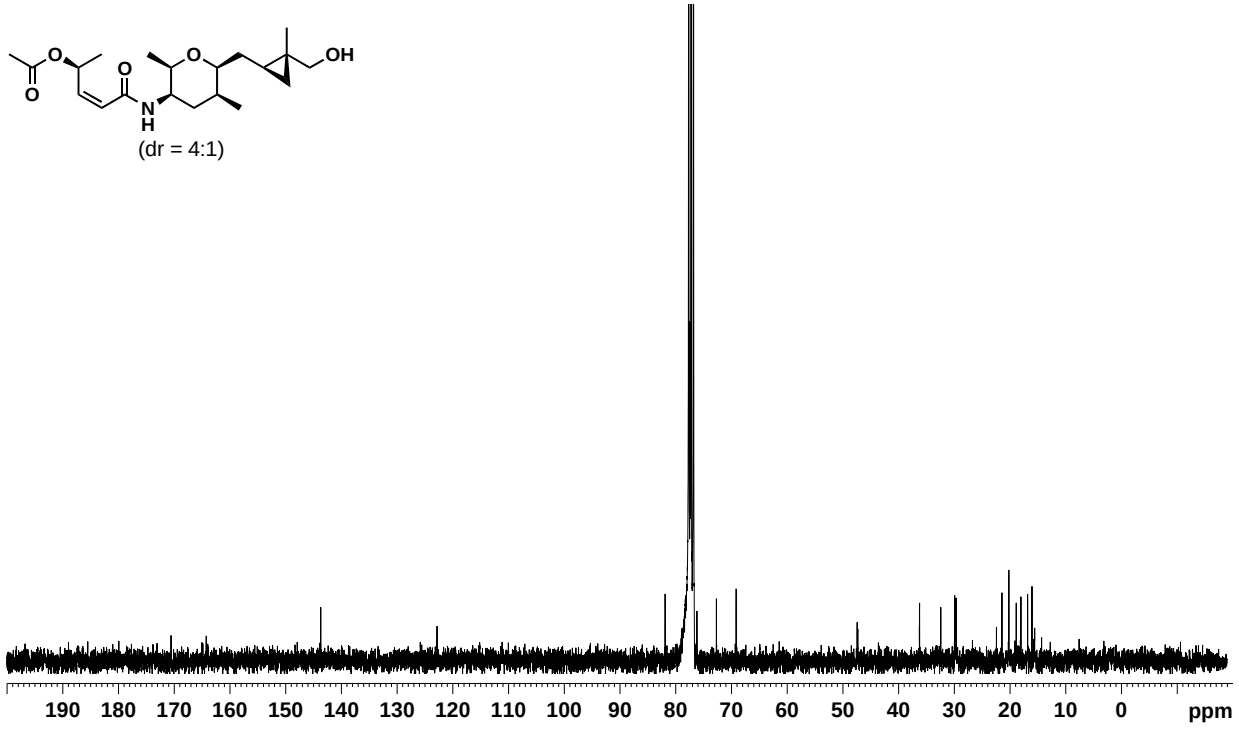
^{13}C NMR of 78: $CDCl_3$, 293 K, 75 MHz



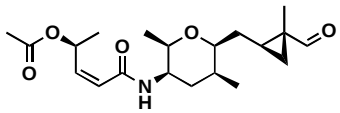
^{1}H NMR of 81: $CDCl_3$, 293 K, 500 MHz



^{13}C NMR of 81: $CDCl_3$, 293 K, 75 MHz



^{1}H NMR of 83: $CDCl_3$, 293 K, 500 MHz



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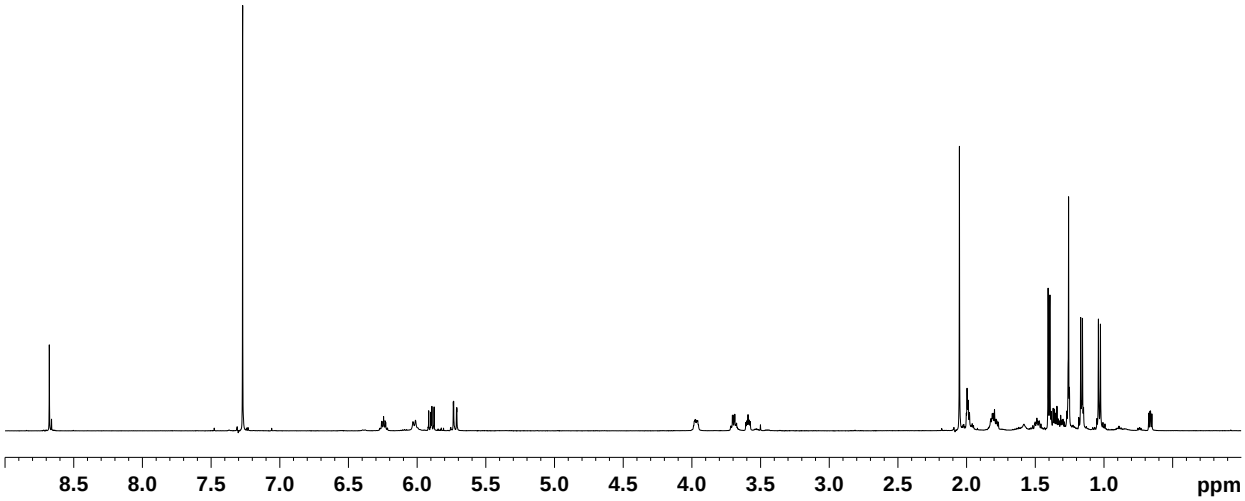
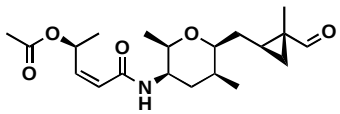


^{13}C NMR of 83: $CDCl_3$, 293 K, 75 MHz



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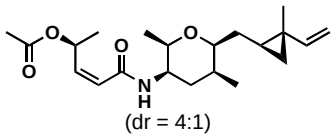
^{1}H NMR of 84: $CDCl_3$, 293 K, 500 MHz



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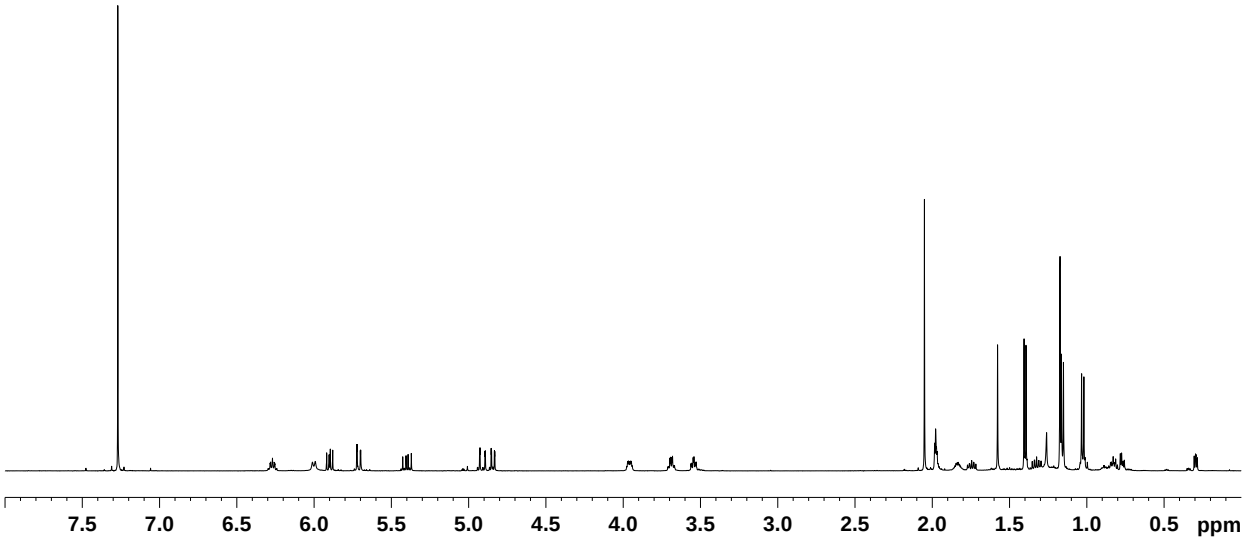
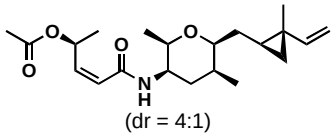


^{13}C NMR of 84: $CDCl_3$, 293 K, 75 MHz



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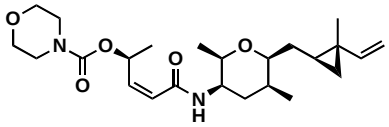
^{1}H NMR of 85: $CDCl_3$, 293 K, 500 MHz



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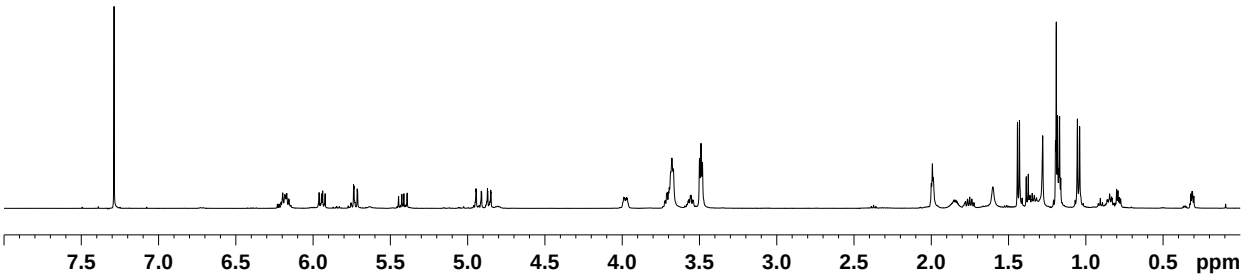
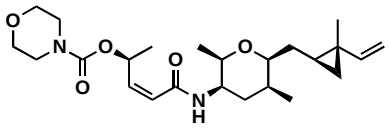


^{13}C NMR of 85: $CDCl_3$, 293 K, 75 MHz



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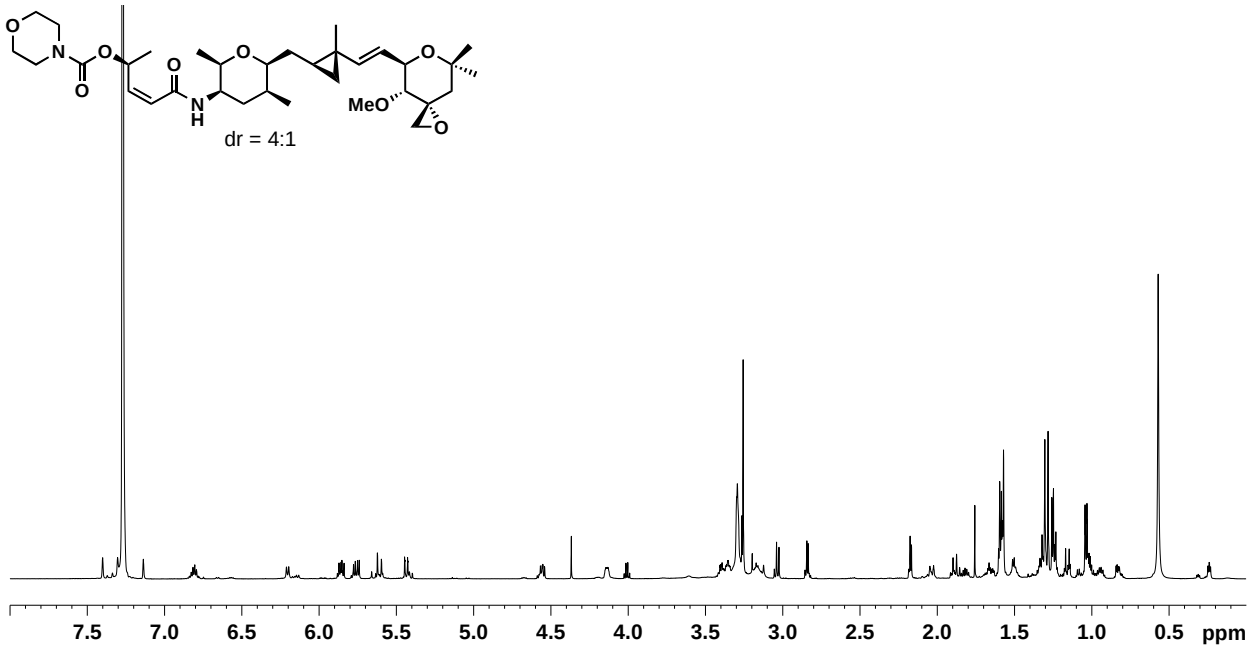
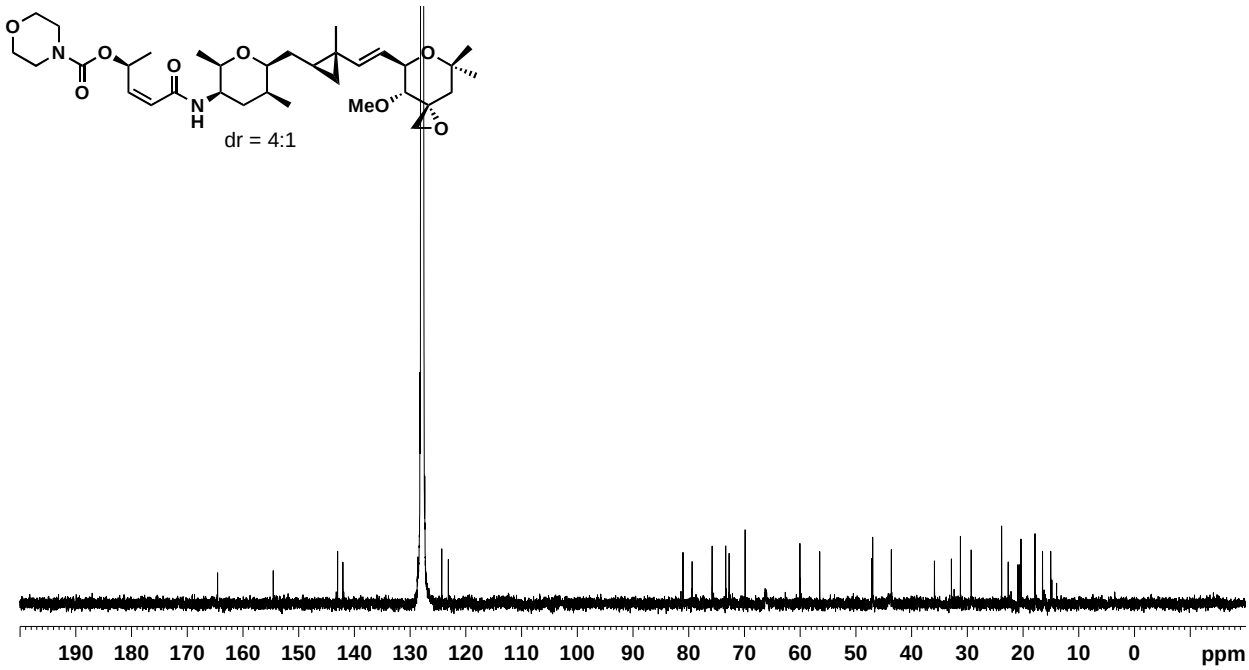
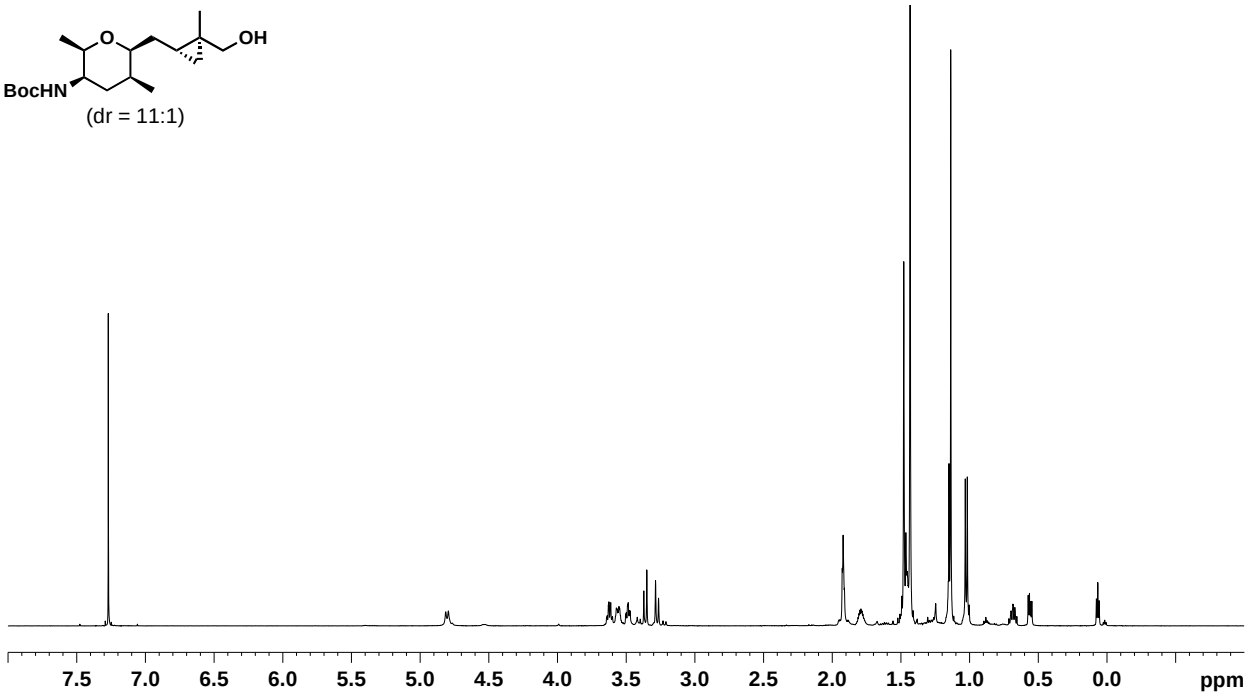
^{1}H NMR of 71: $CDCl_3$, 293 K, 600 MHz



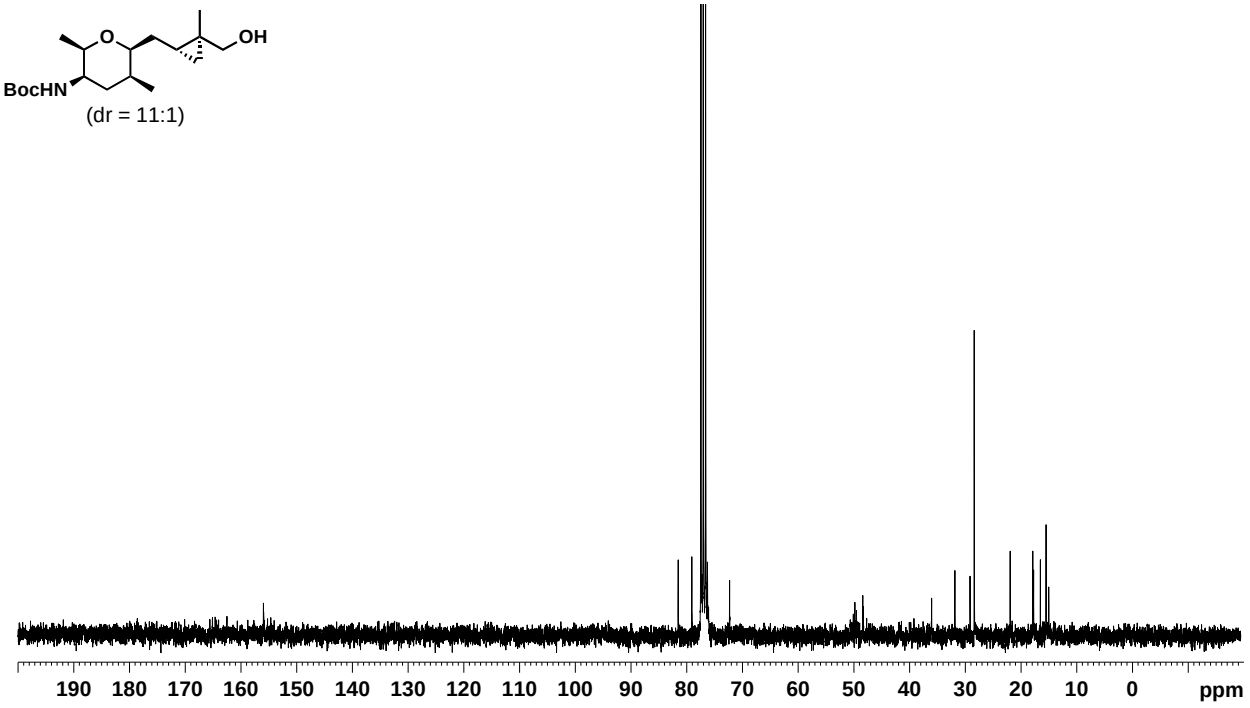
^{13}C NMR of 71: $CDCl_3$, 293 K, 150 MHz



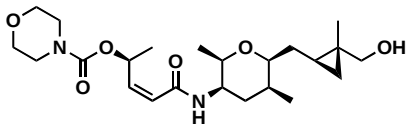
^{1}H NMR of 79: $CDCl_3$, 293 K, 500 MHz



^{13}C NMR of 79: $CDCl_3$, 293 K, 75 MHz



^{1}H NMR of 89: $CDCl_3$, 293 K, 500 MHz



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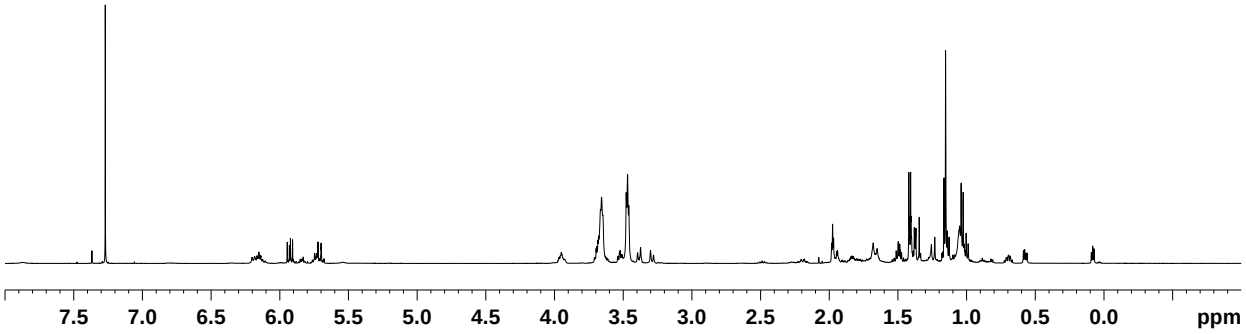
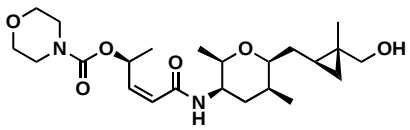


^{13}C NMR of 89: $CDCl_3$, 293 K, 75 MHz



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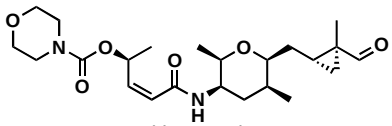
^{1}H NMR of 90: $CDCl_3$, 293 K, 500 MHz



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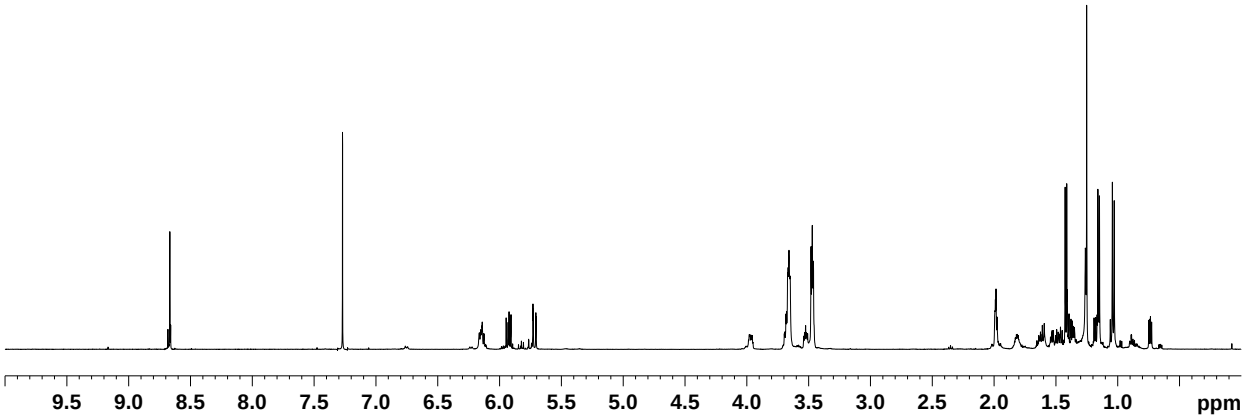
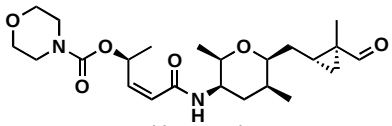


^{13}C NMR of 90: $CDCl_3$, 293 K, 75 MHz



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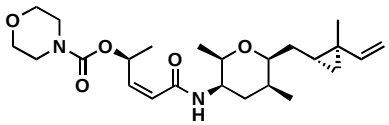
^{1}H NMR of 91: $CDCl_3$, 293 K, 500 MHz



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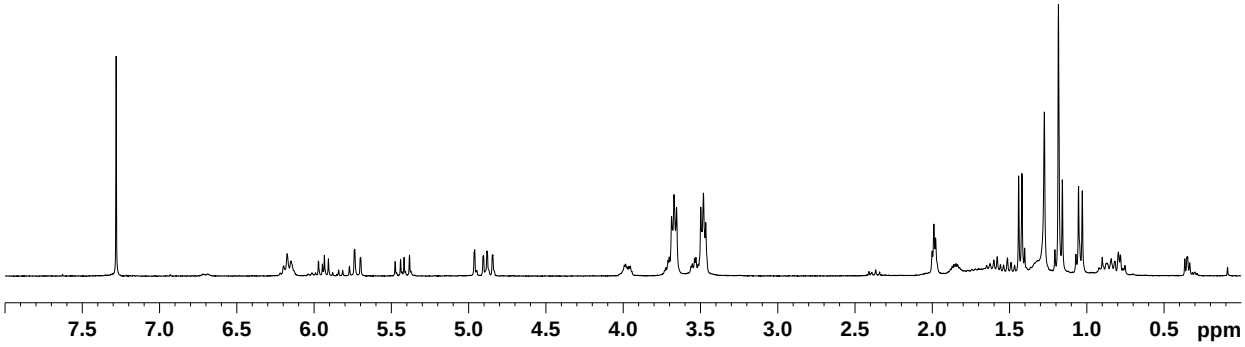
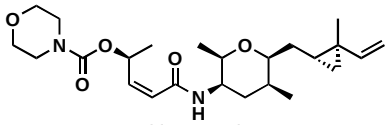


^{13}C NMR of 91: $CDCl_3$, 293 K, 75 MHz



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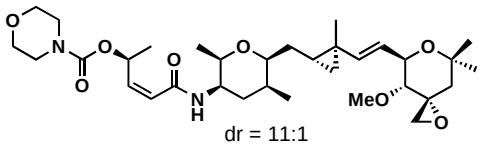
^{1}H NMR of 72: $CDCl_3$, 293 K, 600 MHz



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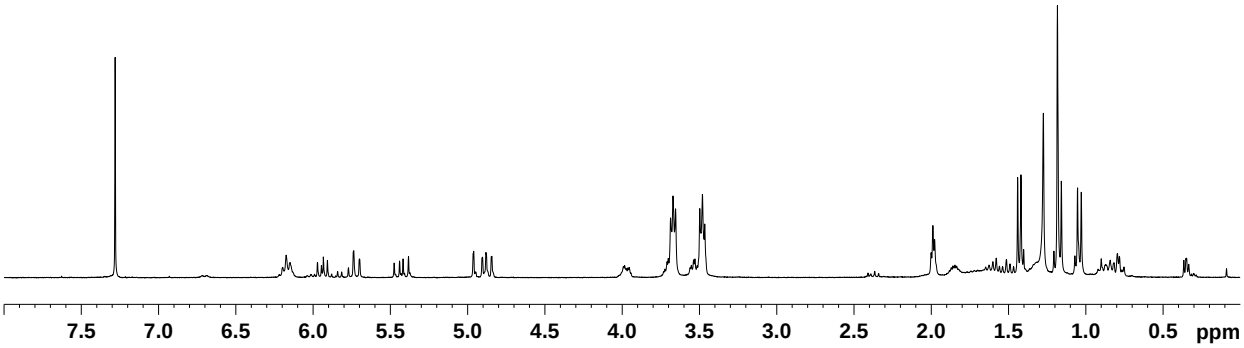
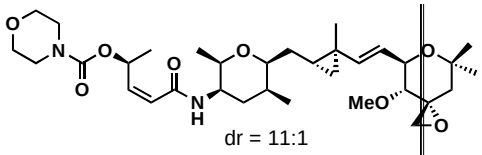
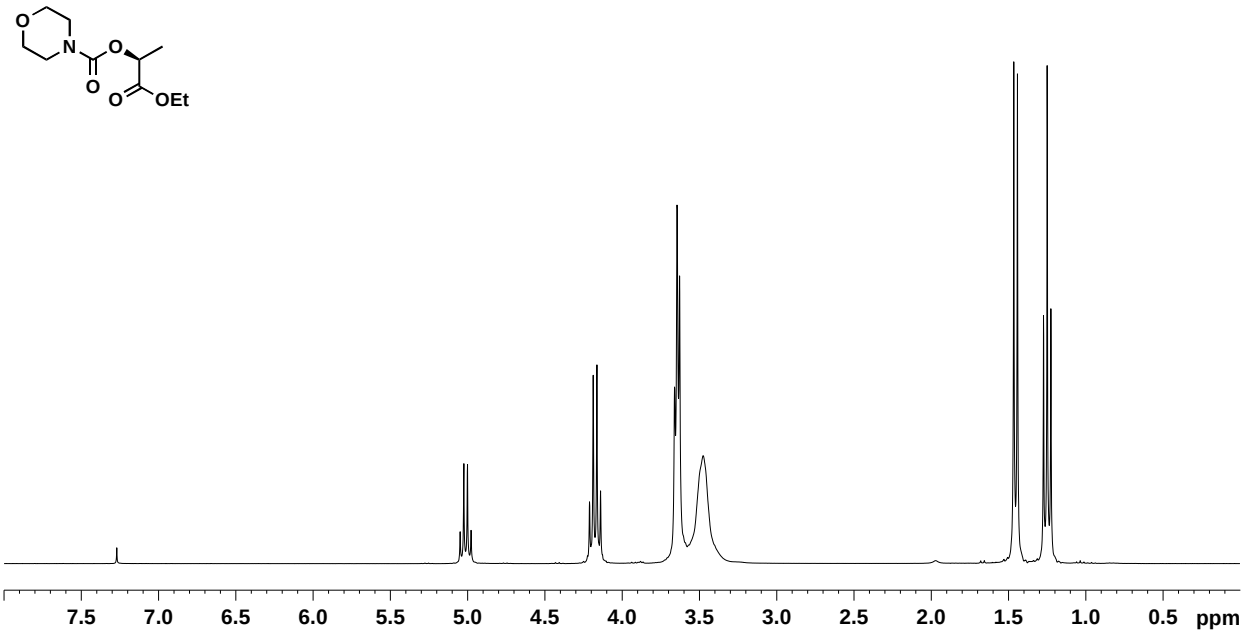


^{13}C NMR of 72: $CDCl_3$, 293 K, 150 MHz

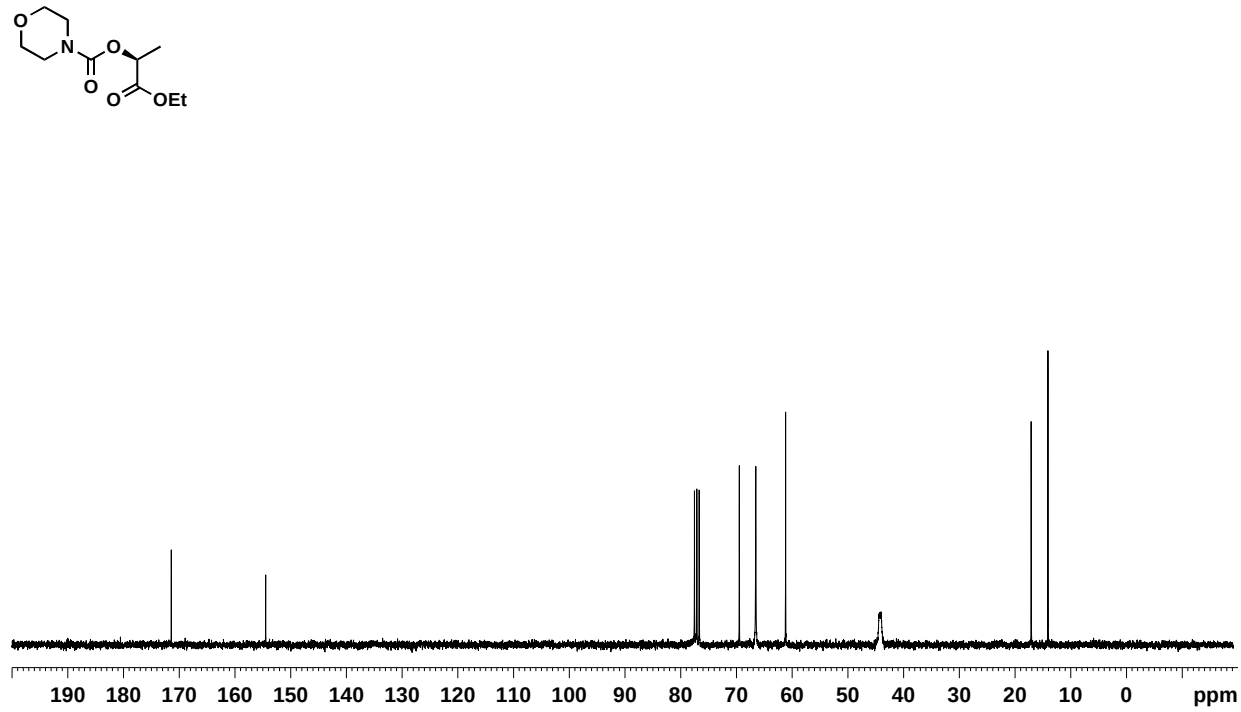


dr = 11:1

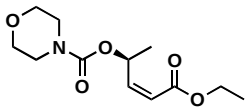
^{1}H NMR of 97: $CDCl_3$, 293 K, 300 MHz



^{13}C NMR of 97: $CDCl_3$, 293 K, 75 MHz



^{1}H NMR of 100: $CDCl_3$, 293 K, 300 MHz



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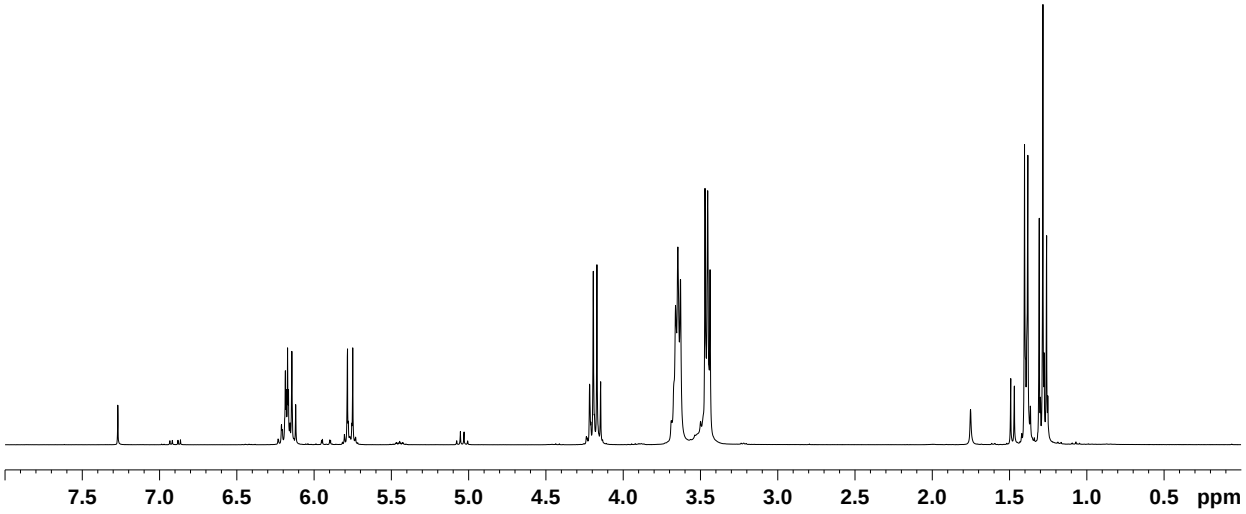
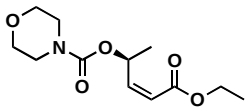


^{13}C NMR of 100: $CDCl_3$, 293 K, 75 MHz



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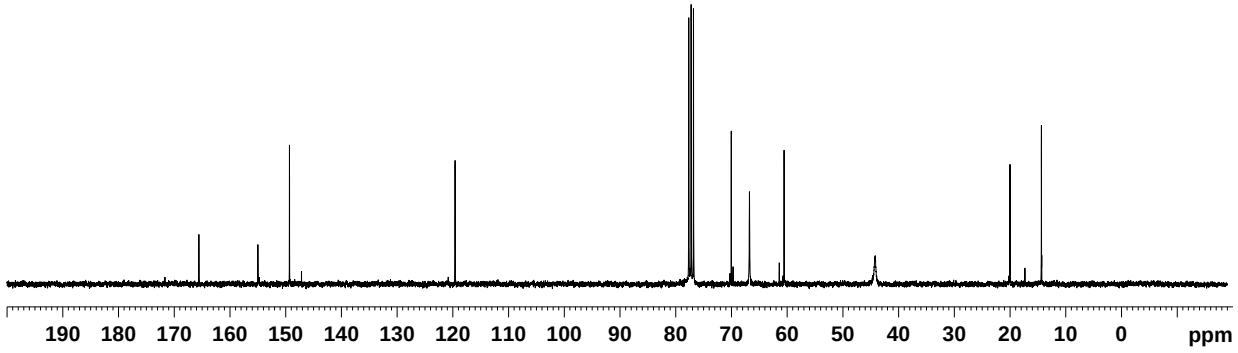
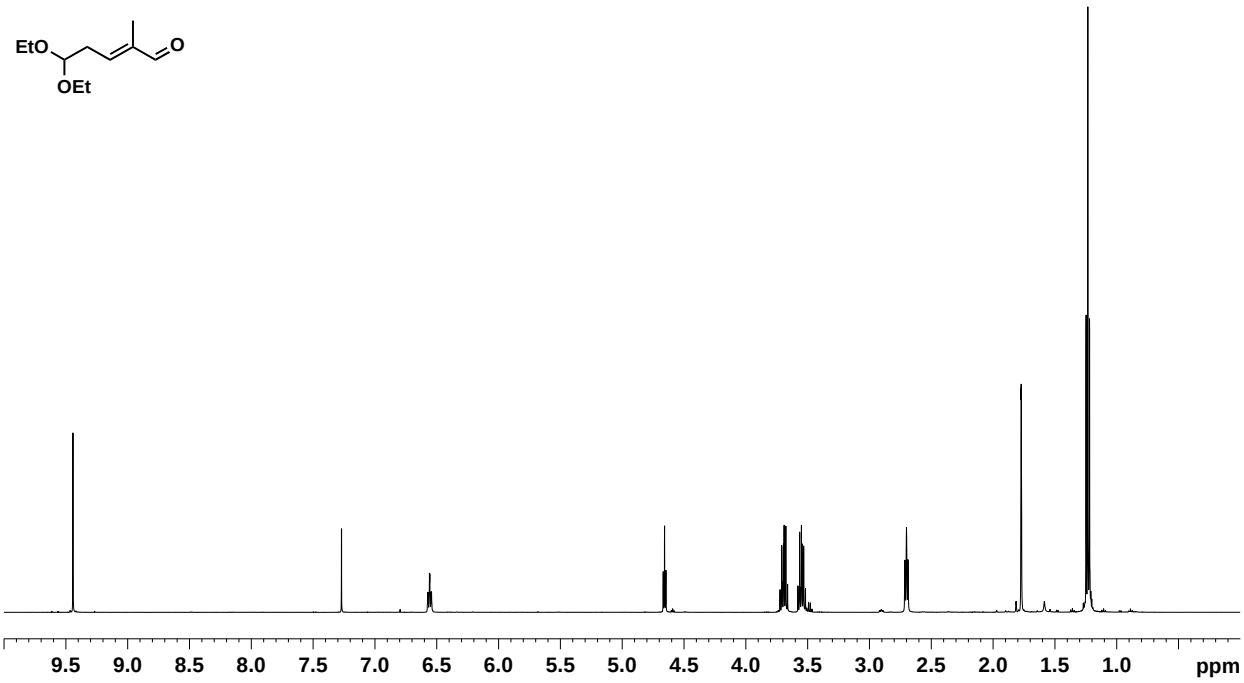
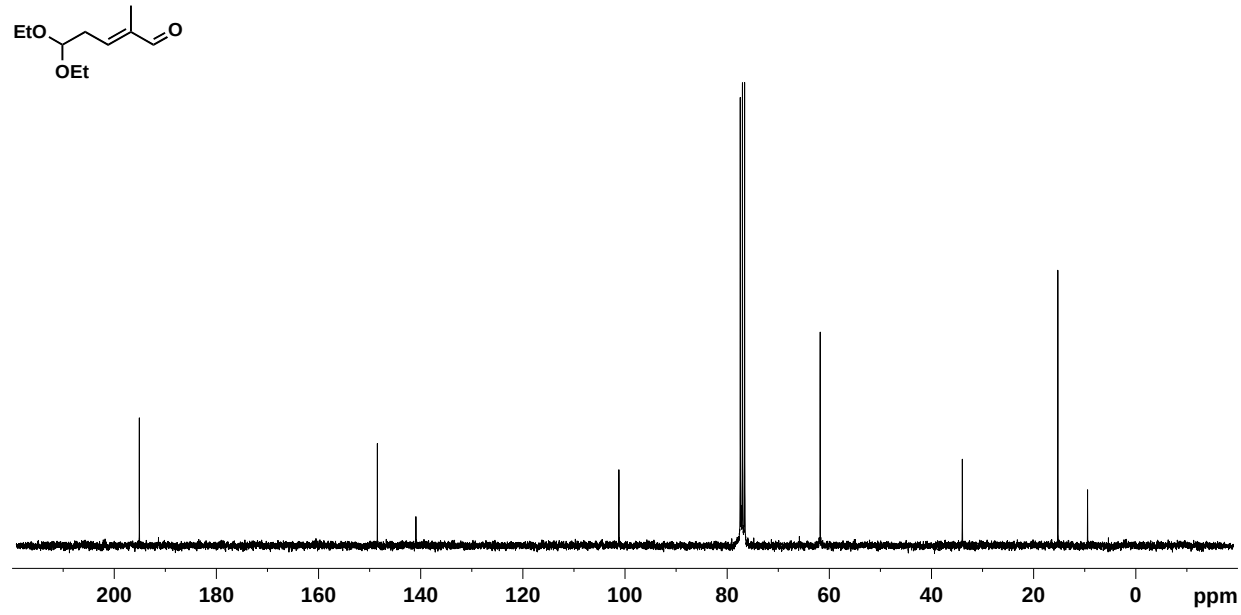


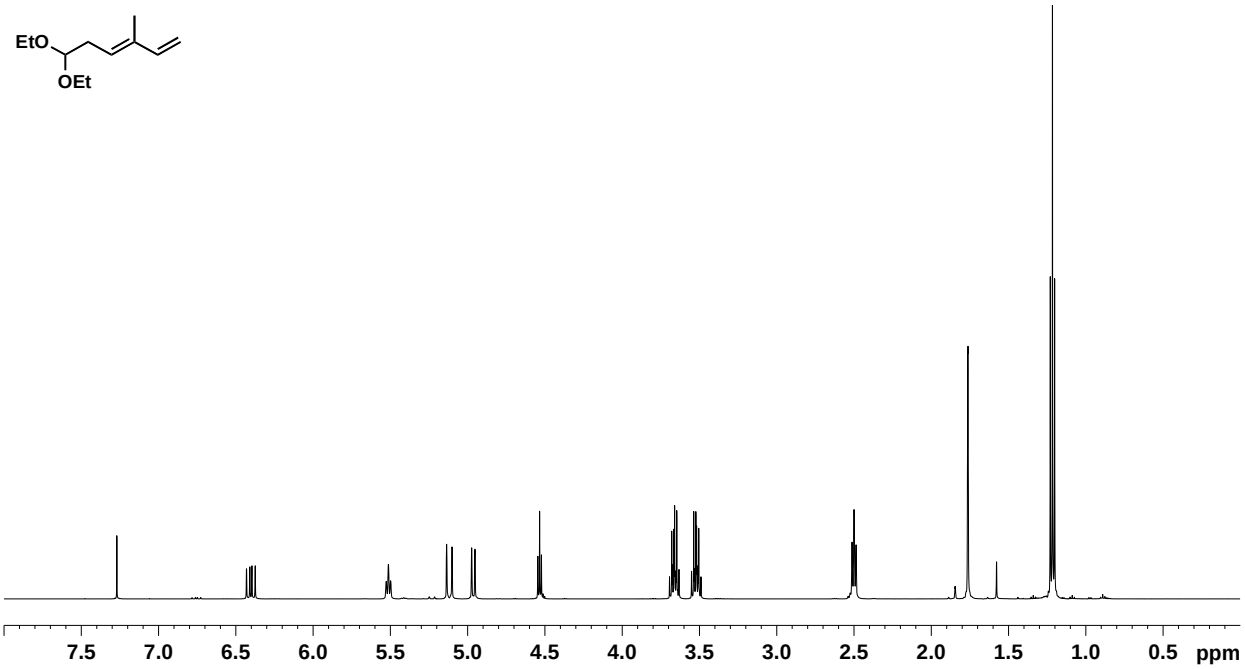
^{1}H NMR of 106: $CDCl_3$, 293 K, 500 MHz



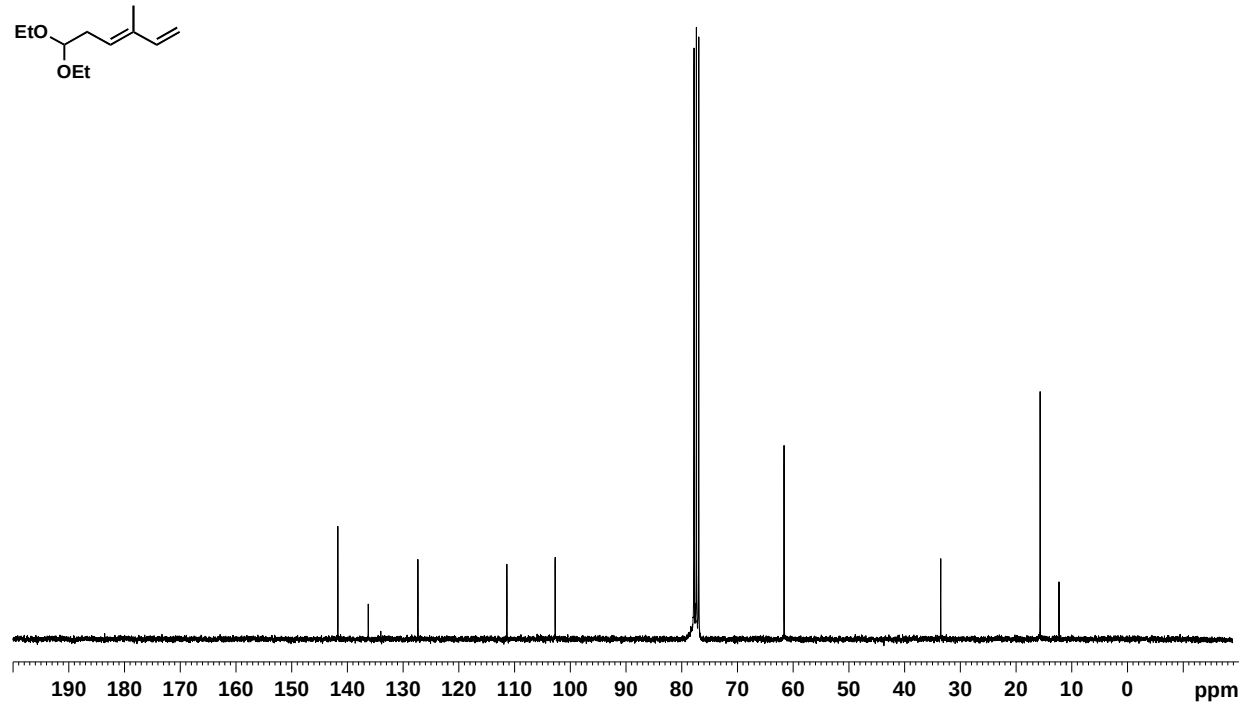
^{13}C NMR of 106: $CDCl_3$, 293 K, 75 MHz



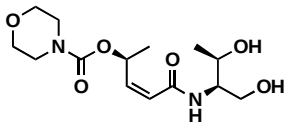
^{1}H NMR of 94: $CDCl_3$, 293 K, 300 MHz

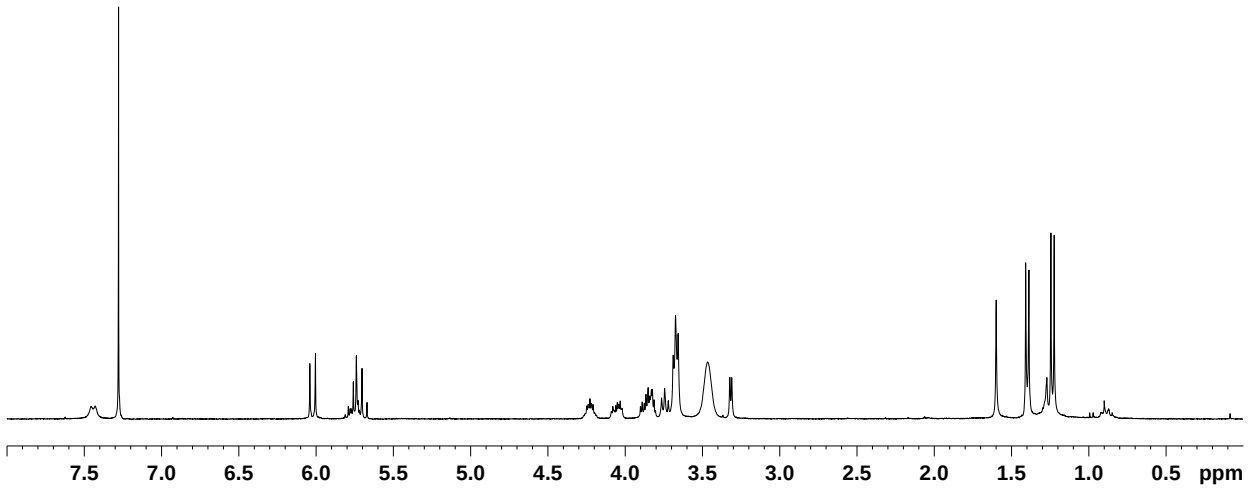


^{13}C NMR of 94: $CDCl_3$, 293 K, 75 MHz

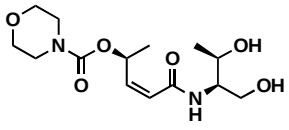


^{1}H NMR of 93: $CDCl_3$, 293 K, 500 MHz

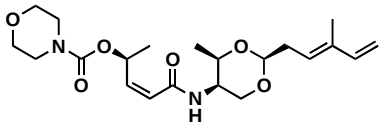


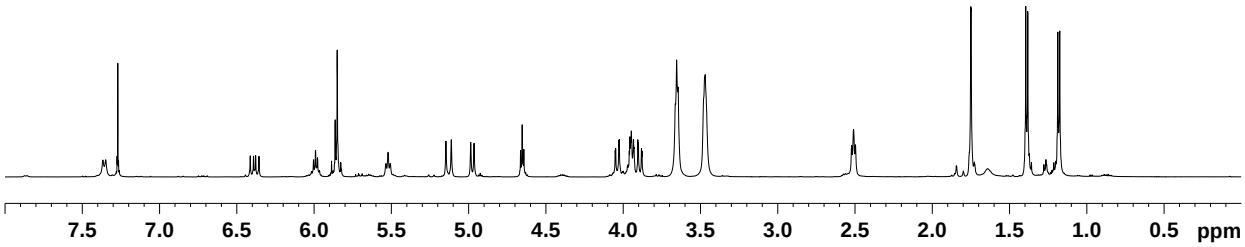


^{13}C NMR of 93: $CDCl_3$, 293 K, 75 MHz

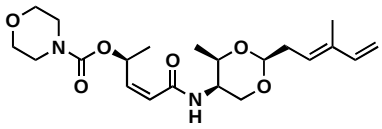


^{1}H NMR of 107: $CDCl_3$, 293 K, 500 MHz

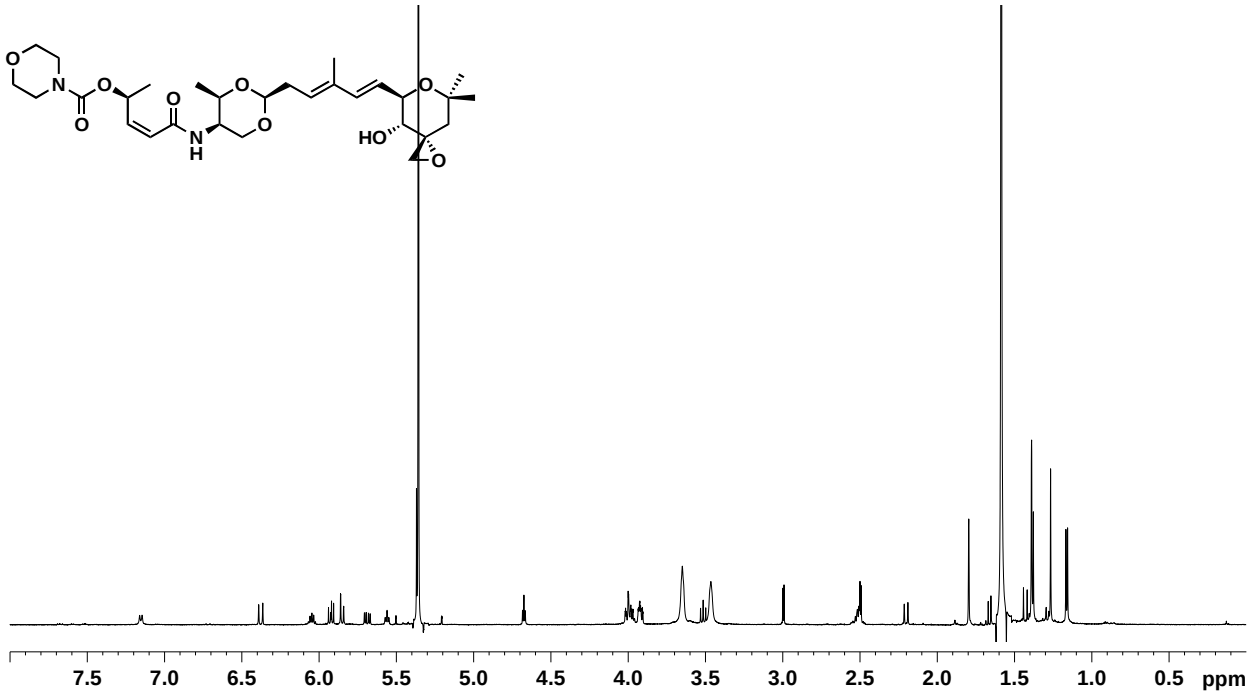




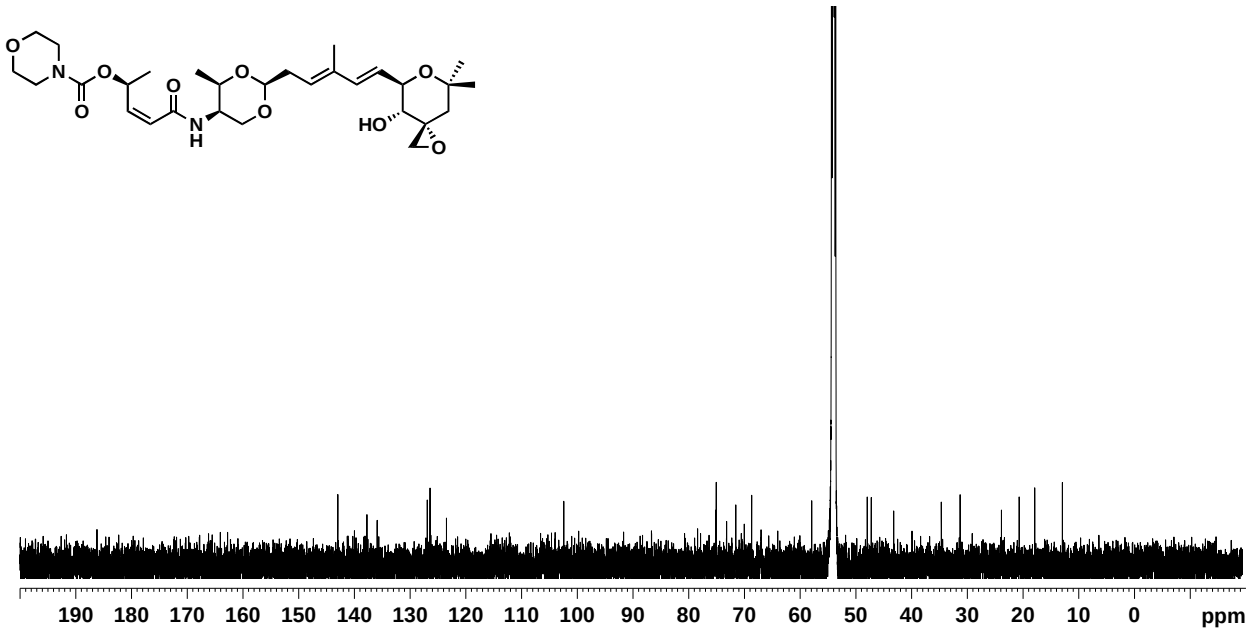
^{13}C NMR of 107: $CDCl_3$, 293 K, 75 MHz



^{1}H NMR of 92: $CDCl_3$, 293 K, 600 MHz



^{13}C NMR of 92: $CDCl_3$, 293 K, 150 MHz



Bibliography

(1) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Czaicki, N. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 2648.

(2) Gibbs, J. B. *Science* **2000**, *287*, 1969.

(3) Nanda, A.; St Croix, B. *Curr. Opin. Oncol.* **2004**, *16*, 44.

(4) Carvajal, R. D.; Tse, A.; Schwartz, G. K. *Clin. Cancer Res.* **2006**, *12*, 6869.

(5) Morin, P. J. *Cancer Res.* **2005**, *65*, 9603.

(6) Barton, J.; Blackledge, G.; Wakeling, A. *Urology* **2001**, *58*, 114.

(7) deConinck, E.; McPherson, L.; Weigel, R. *Mol. Cell. Biol.* **1995**, *15*, 2191.

(8) Thomson, J. M.; Newman, M.; Parker, J. S.; Morin-Kensicki, E. M.; Wright, T.; Hammond, S. M. *Genes Dev.* **2006**, *20*, 2202.

(9) Sunters, A.; de Mattos, S. F.; Stahl, M.; Brosens, J. J.; Zoumpoulidou, G.; Saunders, C. A.; Coffer, P. J.; Medema, R. H.; Coombes, R. C.; Lam, E. W. F. *J. Biol. Chem.* **2003**, *278*, 49795.

(10) Nakajima, H.; Sato, B.; Fujita, T.; Takase, S.; Terano, H.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 1196.

(11) Nakajima, H.; Hori, Y.; Terano, H.; Okuhara, M.; Manda, T.; Matsumoto, S.; Shimomura, K. *J. Antibiot.* **1996**, *49*, 1204.

(12) Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96.

(13) Dulic, V.; Kaufmann, W. K.; Wilson, S. J.; Tlsty, T. D.; Lees, E.; Harper, J. W.; Elledge, S. J.; Reed, S. I. *Cell* **1994**, *76*, 1013.

(14) Motoyoshi, H.; Horigome, M.; Ishigami, K.; Yoshida, T.; Horinouchi, S.; Yoshida, M.; Watanabe, H.; Kitahara, T. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 2178.

(15) Kaida, D.; Motoyoshi, H.; Tashiro, E.; Nojima, T.; Hagiwara, M.; Ishigami, K.; Watanabe, H.; Kitahara, T.; Yoshida, T.; Nakajima, H.; Tani, T.; Horinouchi, S.; Yoshida, M. *Nat. Chem. Biol.* **2007**, *3*, 576.

(16) Kramer, A. *Annu. Rev. Biochem.* **1996**, *65*, 367.

(17) Golas, M. M.; Sander, B.; Will, C. L.; Luhrmann, R.; Stark, H. *Science* **2003**, *300*, 980.

(18) Sakai, T.; Sameshima, T.; Matsufuji, M.; Kawamura, N.; Dobashi, K.; Mizui, Y. *J. Antibiot.* **2004**, *57*, 173.

(19) Sakai, T.; Asai, N.; Okuda, A.; Kawamura, N.; Mizui, Y. *J. Antibiot.* **2004**, *57*, 180.

(20) Mizui, Y.; Sakai, T.; Iwata, M.; Uenaka, T.; Okamoto, K.; Shimizu, H.; Yamori, T.; Yoshimatsu, K.; Asada, M. *J. Antibiot.* **2004**, *57*, 188.

(21) Kotake, Y.; Sagane, K.; Owa, T.; Mimori-Kiyosue, Y.; Shimizu, H.; Uesugi, M.; Ishihama, Y.; Iwata, M.; Mizui, Y. *Nat. Chem. Biol.* **2007**, *3*, 570.

(22) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(23) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.

(24) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

(25) Casares, J. A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Am. Chem. Soc.* **2007**, *129*, 3508.

(26) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482.

(27) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974.

(28) Horigome, M.; Motoyoshi, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2001**, *42*, 8207.

(29) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833.

(30) Motoyoshi, H.; Horigome, M.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2006**, *62*, 1378.

(31) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.

(32) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(33) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Koide, K. *J. Am. Chem. Soc.* **2006**, *128*, 2792.

(34) Imamura, Y.; Ohtsu, Y.; Tanaka, H.; Hatakeyama, M.; Manabe, T.; Kawaguchi, H.; Handa, H.; Takahashi, T. *Heterocycles* **2004**, *64*, 51.

(35) Albert, B. J.; Osman, S.; Wang, Y.; Li, M.; Koide, K., submitted.

(36) Albert, B. J.; McPherson, P. A.; O'Brien, K.; Czaicki, N. L.; DeStefino, V.; Osman, S.; Li, M. S.; Day, B. W.; Grabowski, P. J.; Moore, M. J.; Vogt, A.; Koide, K. *Mol. Cancer Ther.* **2009**, *8*, 2308.

(37) Huang, T. L.; Szekacs, A.; Uematsu, T.; Kuwano, E.; Parkinson, A.; Hammock, B. D. *Pharm. Res.* **1993**, *10*, 639.

(38) Yoon, K. J. P.; Morton, C. L.; Potter, P. M.; Danks, M. K.; Lee, R. E. *Bioorgan. Med. Chem.* **2003**, *11*, 3237.

(39) Slatter, J. G.; Su, P.; Sams, J. P.; Schaaf, L. J.; Wienkers, L. C. *Drug Metab. Dispos.* **1997**, *25*, 1157.

(40) Lagisetti, C.; Pourpak, A.; Jiang, Q.; Cui, X.; Goronga, T.; Morris, S. W.; Webb, T. R. *J. Med. Chem.* **2008**, *51*, 6220.

(41) Lagisetti, C.; Pourpak, A.; Goronga, T.; Jiang, Q.; Cui, X.; Hyle, J.; Lahti, J. M.; Morris, S. W.; Webb, T. R. *J. Med. Chem.* **2009**, *52*, 6979.

(42) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18.

(43) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395.

(44) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195.

(45) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199.

(46) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(47) This work was partialy done by Dr. Shin Ando.

(48) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 719.

(49) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *J. Org. Chem.* **1997**, *62*, 2106.

(50) Jorda-Gregori, J. M.; Gonzalez-Rosende, M. E.; Sepulveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1135.

(51) Boukherroub, R.; Chatgilialoglu, C.; Manuel, G. *Organometallics* **1996**, *15*, 1508.

(52) Welder, C. O.; Ashby, E. C. *J. Org. Chem.* **1997**, *62*, 4829.

(53) Kuivila, H. G. M., Lawrence W. *J. Org. Chem.* **1963**, *28*, 2165.

(54) Matulic-Adamic, J.; Pavela-Vrancic, M.; Skaric, V. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2681.

(55) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038.

(56) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.

(57) Gu, K. L.; Bi, L. R.; Zhao, M.; Wang, C.; Ju, J. F.; Peng, S. Q. *Bioorgan. Med. Chem.* **2007**, *15*, 4775.

(58) Chaouni-Benabdallah, A.; Subra, G.; Bonnet, P. A.; Fernandez, J. P.; Chapat, J. P.; Vallet, P.; Muller, R. N. *Tetrahedron* **1994**, *50*, 12923.

(59) Onda, M. Y., Yasuhiko; Inoue, Yoshio; Chujo, Riichiro. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4015.

(60) Bernet, B.; Piantini, U.; Vasella, A. *Carbohydr. Res.* **1990**, *204*, 11.

(61) Salaün, J. *Topics Curr. Chem.* **2000**, *207*, 67.

(62) Liu, C.; Tamm, M.; Nötzel, M. W.; de Meijere, A.; Schilling, J. K.; Kingston, D. G. I. *Tetrahedron Lett.* **2003**, *44*, 2049.

(63) Johnson, J.; Kim, S. H.; Bifano, M.; DiMarco, J.; Fairchild, C.; Gougoutas, J.; Lee, F.; Long, B.; Tokarski, J.; Vite, G. *Org. Lett.* **2000**, *2*, 1537.

(64) Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y. B.; Tong, W. P.; He, L. F.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825.

(65) Smith, A. B.; Xian, M.; Liu, F. H. *Org. Lett.* **2005**, *7*, 4613.

(66) Gardner, C. R.; Roberts, C. J.; Walker, R. J.; Chidley, L.; Clements-Jewery, S. *Neuropharmacology* **1982**, *21*, 197.

(67) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284.

(68) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(69) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

(70) Dess, D. B.; Martin, J. C. *The Journal of Organic Chemistry* **1983**, *48*, 4155.

(71) Osman, S.; Albert, B. J.; Wang, Y.; Li, M.; Czaicki, N. L.; Koide, K., Submitted.

(72) Ando, K. *Synlett* **2001**, 1272.

(73) Behnam, S. M.; Behnam, S. E.; Ando, K.; Green, N. S.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 8970.

(74) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745.

(75) Ando, K. *J. Org. Chem.* **1999**, *64*, 6815.

(76) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406.

(77) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411.

(78) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(79) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.