A Synthetic Approach to Quinocarcin and Cyanocycline A: The Ugi Reaction of Complex Aminoacids

by

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Abstract

This dissertation describes synthetic efforts towards the natural products quinocarcin and cyanocycline A. Our approach capitalizes on the Ugi reaction of a complex pyroglutamol-derived aminoacid. This ambitious strategy first required the synthesis of the aminoacid, which required considerable development; ultimately the route was optimized to become practical and consistently high-yielding. Ugi condensation reactions using this material were successful, providing advanced precursors of the target molecules.

Preface

A portion of the research described in Chapter 2 appeared in Turner, C. D. and Ciufolini, M. A. Useful building blocks for the stereocontrolled assembly of 2,3,5-trisubstituted pyrrolidines. *Heterocycles* **2012**, *85*, 85-94.

C.D.T. is responsible for: the performance of each of the experiments reported herein; much of the tactical synthetic planning; and the writing of a complete draft of this dissertation. M.A.C. provided: the overall synthetic strategy; many helpful tactical and technical suggestions; and a thorough editing of this document.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

[α]	specific rotation
Ac	acetyl
add'n	addition
Am	amyl
anh	anhydrous
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
BRSM	based on recovered starting material
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
C	cytosine (DNA residue)
CAN	ceric ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CC	column chromatography
CDI	1,1´-carbonyldiimidazole
cf.	*confer*
cm^{-1}	wavenumber(s)
CSA	camphorsulfonic acid
δ	chemical shift (ppm downfield from tetramethylsilane)
Cyh	cyclohexyl
d	doublet
D	dextrorotatory
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	*N*,*N*´-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIB	(diacetoxyiodo)benzene
Dibal	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DOPA	3,4-dihydroxyphenylalanine
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
E	carboxymethyl
E	entgegen (of an alkene)
ee	enantiomeric excess
ent	enantiomeric
epi	epimeric
ESI	electrospray ionization
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine (DNA residue)
h	hour(s)
[H]	reduction
HMPA	hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HOBt	1-hydroxybenzotriazole

HRMS	high resolution mass spectrometry
Hz	Hertz (s^{-1})
i	iso (as an alkyl group)
imid	1,3-imidazole
i.p.	intraperitoneal
IR	infrared
J	coupling constant
L	levorotatory
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
HMDS	hexamethyldisilizide
LN2	liquid nitrogen
m	meta (as a benzene substituent)
m	multiplet
M	molarity
Me	methyl
MIC	minimum inhibitory concentration
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
m.p.	melting point
Ms	methanesulfonyl
MS	mass spectrometry or molecular sieves
n	normal (as an alkyl group)
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
N-PSP	*N*-phenylselenophthalimide

NR	no reaction
[O]	oxidation
p	para (as a benzene substituent)
P	unspecified protecting group
Ph	phenyl
Phth	phthalimido
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
psi	pounds per square inch (lbs in^{-2})
PyBrOP	bromo-tris(pyrrolidino)phosphonium hexafluorophosphate
py	pyridine
q	quartet
quant.	quantitative
R	*rectus*
R_f	retention factor
rt	room temperature
rxn	reaction
s	singlet
S	*sinister*
SAM	*S*-adenosyl methionine
sat.	saturated
SEM	[2-(trimethylsilyl)ethoxy]methyl
SET	single electron transfer
SN2	bimolecular nucleophilic substitution
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl

t	tertiary (as an alkyl group)
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Thr	threonine
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium
Ts	*p*-toluenesulfonyl
U-4CR	Ugi four-component reaction
U-5C-4CR	Ugi five center, four-component reaction
UV	ultraviolet
VT	variable temperature
xs	excess
Z	zusammen (as an alkene)

Acknowledgements

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A special gesture of gratitude is reserved for my mentor and colleague, Prof. Ciufolini, whose innumerable observations involving chemical reactivity and life in general have made my time in graduate school infinitely more insightful.

I would also like to thank the members of the Ciufolini group for moral support, and for entertainment in many unexpected forms. Special mention is warranted for the crew in A312: Steven, David, Jaclyn, Jimmy, Josh, Taka, Gloria, Mendelsohn, Patrick, and Leanne.

Lastly, thanks to my family. You're always there when it counts.

1 Introduction

1.1 Tetrahydroisoquinoline natural products

In 1975, Canadian researchers at the University of Montreal reported the isolation of a new broad-spectrum antibiotic.[1] The material, which was named naphthyridinomycin, **1**, was recovered from the culture broth of a bacterium which was identified to be *Streptomyces*

Bacterium	MIC (μg/mL)
Staphylococcus aureus	<0.025
Streptococcus faecalis	<0.025
Escherichia coli	0.8
Salmonella pullorum	0.2
Klebsiella pneumoniae	0.05
Proteus vulgaris	0.4

Table 1. Minimum Inhibitory Concentrations (MICs) of **1** against selected bacteria

lusitanus, grown from a soil sample taken on Easter Island in the Polynesian Archipelago. The new alkaloid, a ruby-red, crystalline solid, ultimately yielded to structural assignment by X-ray crystallography. The material, while a potent antibiotic against both Gram-positive and Gram-negative bacteria (Table **1**), was also quite toxic. For instance, the intravenous LD_{50} in mice was equal to 3.1 mg/kg, death occurring 48 hours after injection. The newly discovered compound would become the lead member of a family of tetrahydroisoquinoline-containing antibiotics (Figure **1**),[2] all of which display an intricate hexa- or heptacyclic structure. The presence of sensitive functionality, such as oxazolidine, quinone, hydroquinone, and hemiaminal motifs, is apparent in all such compounds.

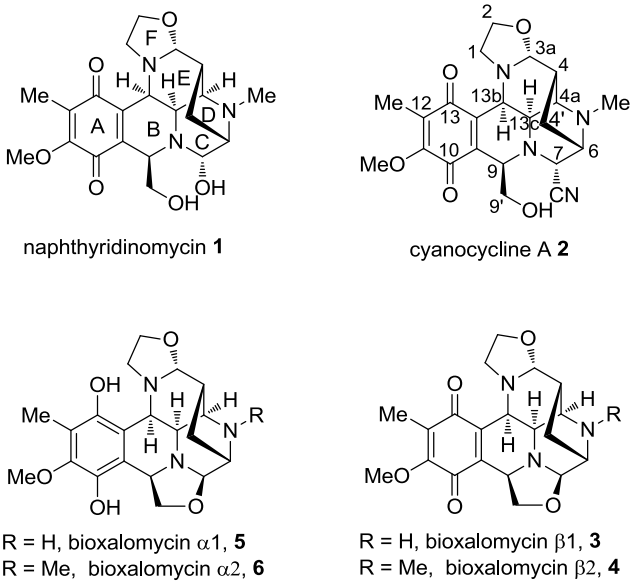


Figure 1. Naphthyridinomycin **1** and its congeners

Several years after the discovery of **1**, a closely related congener called cyanocycline A, **2**, was described. This substance, an orange-red crystalline solid, was isolated from a culture broth of *Streptomyces actinomycetes*, a bacterium found in a soil sample collected in Tama City, Tokyo, Japan.[3] X-ray analysis revealed its structure to be nearly identical to that of **1**. Indeed, the conversion of the latter into **2** was demonstrated almost simultaneously with the isolation of **2** as a discrete natural product.[4] Given the greatly enhanced stability **2** relative to **1**, many synthetic and structural studies have utilized the cyano form of the natural product, which may be readily obtained by treatment of culture broths with sodium cyanide. In fact, it has been suggested that **1** may be an artifact of isolation.[5]

A third group of cytotoxic substances belonging to the same family are the bioxalomycins, **3-6**. These natural products were isolated by Bernan and coworkers at the American Cyanamid Company from the bacterium *Streptomyces viridostaticus*,[6] primarily in the form of hydroquinone bioxalomycin α2, **6**. In a later paper,[5] the authors mention that, in an

attempt to isolate naphthyridinomycin **1** from the culture broth of *S. lusitanus*, the only compound recovered corresponded to bioxalomycin β2, **4**. This observation led to the surmise that the actual "natural products" may be the bioxalomycins, which, depending on the precise biochemical conditions and isolation method, may advance to naphthyridinomycin **1** or

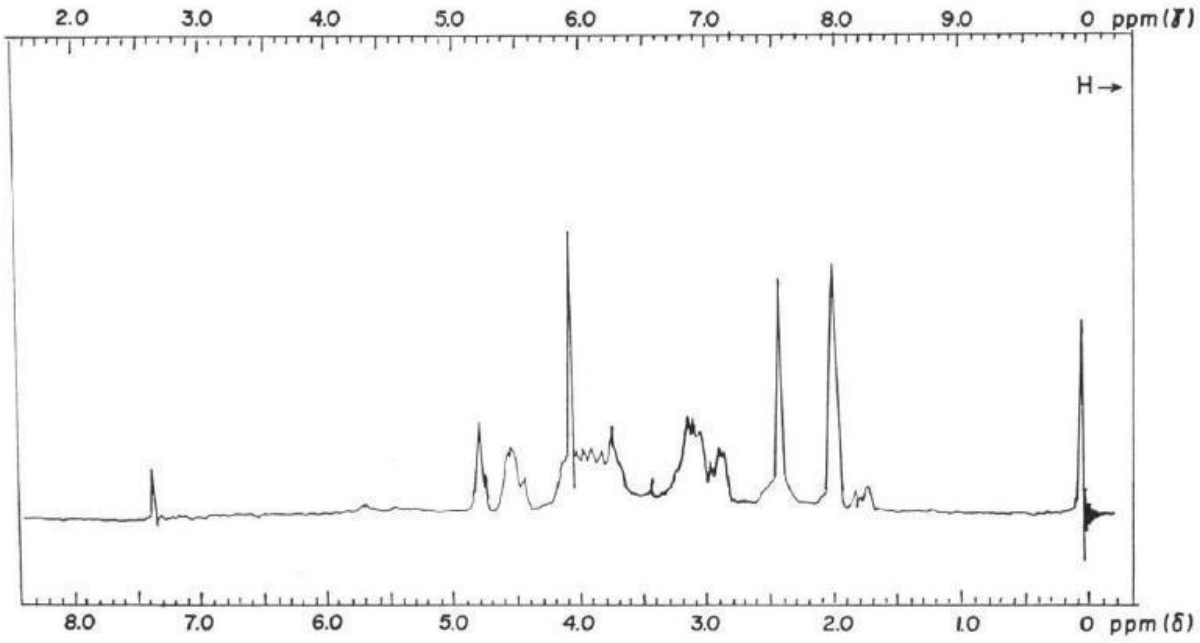


Figure 2. ^{1}H NMR spectrum of **1** as originally published[1]

cyanocycline **2**. The authors speculate that since **1** is more highly crystalline than **5**, fortuitous crystallization of **1** occurred in the course of the original X-ray structural work. As seen in Figure **2**, the NMR spectrum of the originally isolated material could not have provided definitive evidence of structure.

A structurally related tetrahydroisoquinoline natural product, quinocarcin, **7** (Figure **3**), was described in 1983 by Tomita *et al.*[7] The new substance, originally termed DC-52, was

isolated from a culture broth of *Streptomyces melanovinaceus*, an organism first collected from a soil sample taken at Machida-shi, a town near Tokyo, and so dubbed for the mauve color of its colonies growing on an agar medium. An 18-liter culture broth afforded 90 mg of **7** along with 30 mg of DC-52-d, **9**, also called quinocarcinol. Though complete structural elucidation using the NMR methods of the time proved impossible, the authors obtained crystals of **9**, thus allowing X-ray analysis to prove its structure. Given the similarity between the two molecules, the structure of **7** could be ascertained on the basis of spectral comparison, and confidently assigned when sodium borohydride reduction gave **9**.[8] Interestingly, the correct absolute configuration of **7** would be predicted by an early computational study based on its binding affinity for DNA.[9]

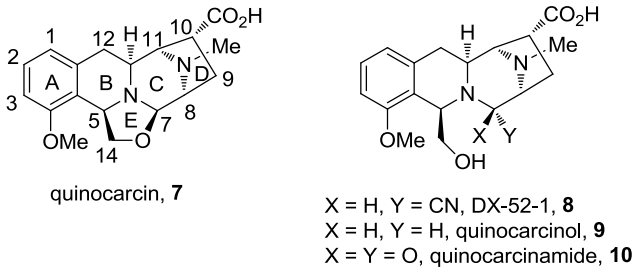


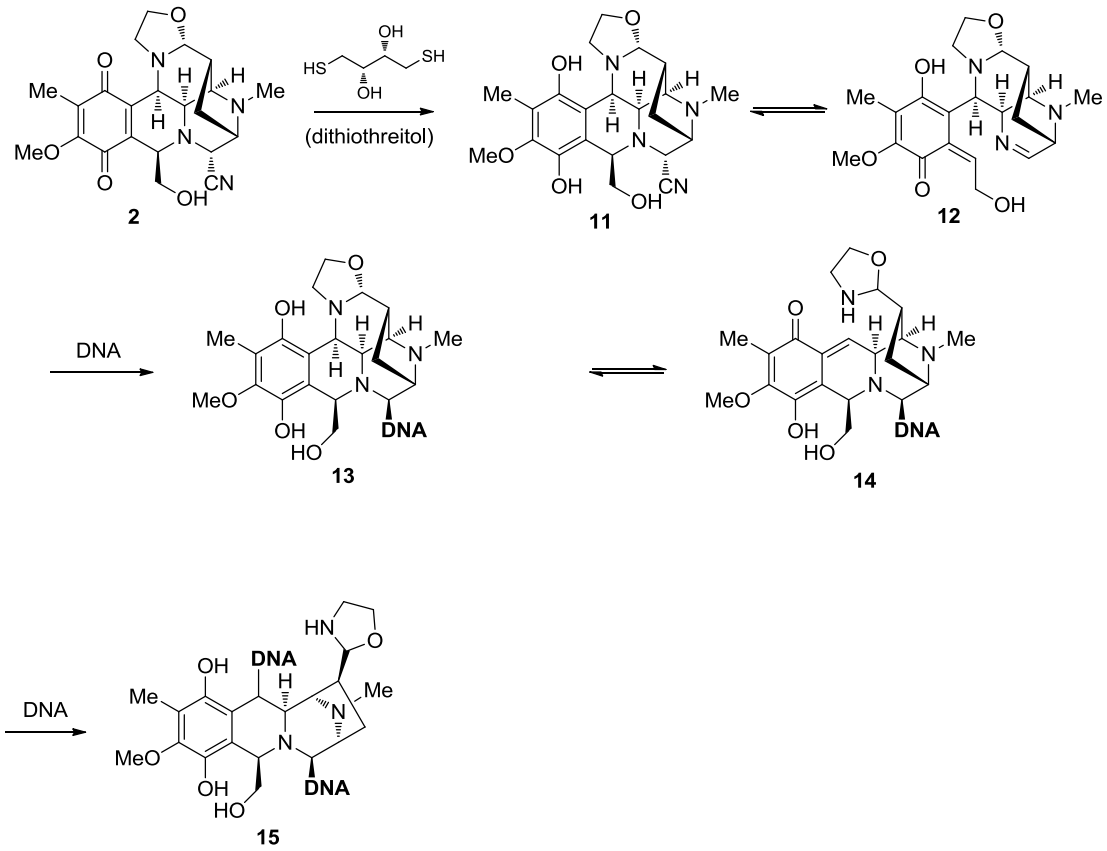
Figure 3. Quinocarcin **7** and its congeners

The newly discovered material **7** was found to have a minimum inhibitory concentration (MIC) of just under 100 μg/mL against *Staphylococcus aureus* and a few other bacteria, showing its limited antibacterial capability. However, it was effective against mouse lymphocytic leukemia P388 *via* intraperitoneal injection, giving a 47% increase of life span at doses of 12.5 mg/kg. More interestingly, it demonstrated growth inhibitory activity comparable to mitomycin C and cisplatin in human tumor cell xenografts in mice.[10] A more detailed study using KW2152, the citrate salt of **7**, on melanoma xenografts showed significant anti-tumor activity.[11] Specifically, with three i.p. dosings of 40 mg/kg, a partial tumor reduction was observed in 6 of

10 models, and a complete tumor reduction was observed in 1 of 10 models after 19 days. A nitrile-containing analog of **7**, DX-52-1, **8**, was entered into Phase I human trials, which were ultimately halted due to safety and toxicity concerns.[12]

1.2 Mechanisms of action

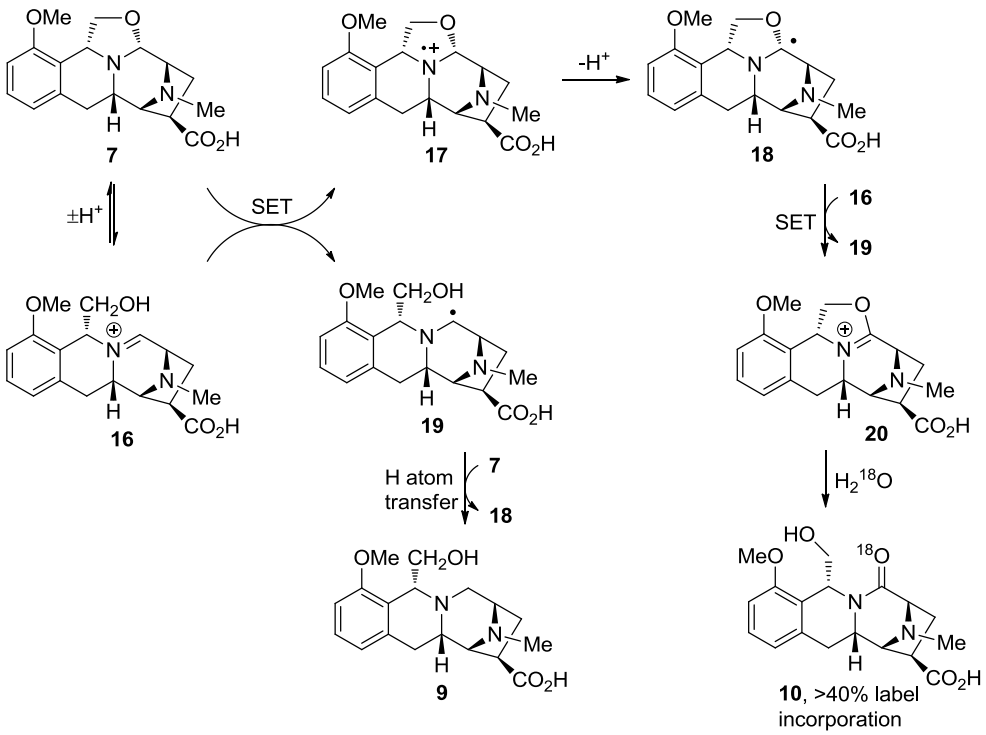
The mechanism of action of compounds **2-6** has been studied to some extent. Research has shown that cyanocycline A has the ability to cross-link DNA, although the expression of such an activity requires prior reduction of the quinone with dithiothreitol.[13] The compound may thus be classified as a bioreductive agent.[14] It is likely that the hydroquinone form of the molecule, **11**, expels a cyanide ion while opening the B-ring, creating an electrophilic site at C7 (Scheme **1**). A second alkylation can then proceed by opening of the E-ring, again assisted by electronic donation from the hydroquinone, to present a second electrophilic site at C13b. Indeed, bioxalomycin α2, **6**, which already incorporates a hydroquinone, does not require reductive activation, selectively cross-linking DNA at $^{5'}CG^{3'}$ sites. Molecular Mechanics calculations support the assertion that **2** intercalated at the aromatic nucleus might cross-link DNA in the manner suggested.[13]



Scheme 1. Possible DNA cross-linking mechanism of **2**

The mechanism of action of quinocarcin **7** was investigated by the discoverers themselves,[15] who determined that it damages DNA through the generation of oxygen radicals, as if it were a quinoid compound. The absence of a quinone moiety in **7** suggested that a novel mechanism might be responsible for the observed effects. Williams carried out extensive investigations in this area.[16] A key observation was that pure **7** dissolved in deoxygenated water was slowly converted into an equimolar mixture of two new materials: quinocarcinol **9** and quinocarcinamide **10**. This transformation, details of which are outlined in Scheme **2**, occurred at

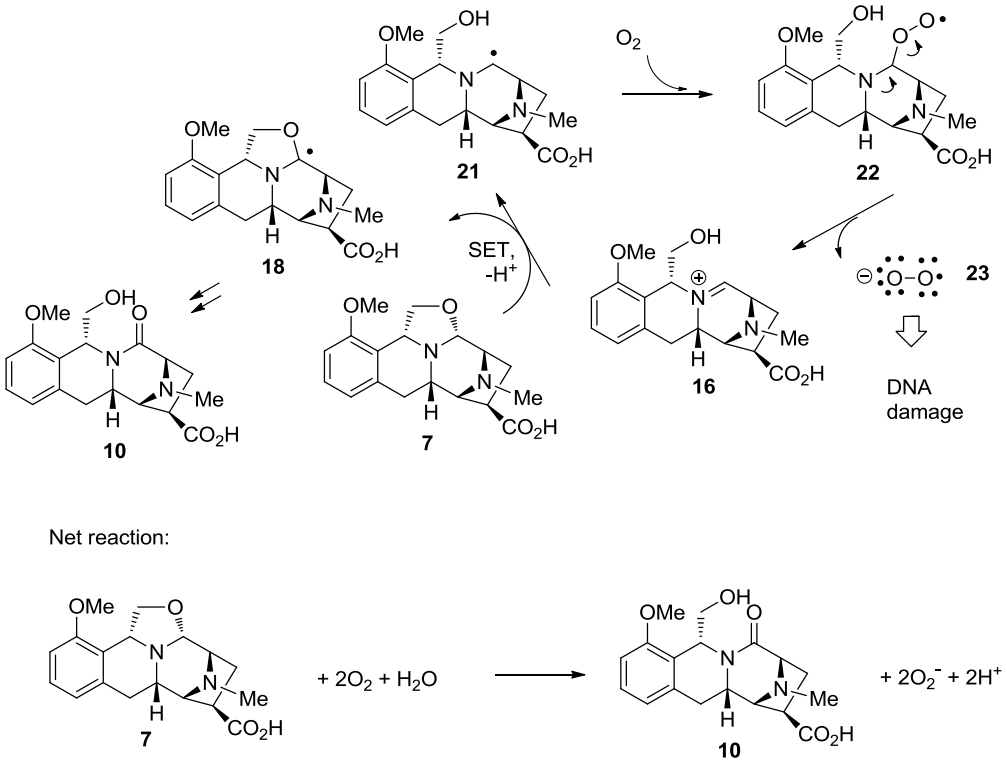
room temperature and it was postulated to involve a Cannizzaro-like disproportionation of iminium ion **16**. Available evidence suggests that the process involves single electron transfer from intact **7** to ring-opened isomer **16**, leading to radical **19** and radical cation **17**. The radical species **19**, upon undergoing a further one-electron reduction, is converted to **9**. Radical cation **17** will lose a proton, giving electron-rich radical **18**, which acts to donate another electron, perhaps to iminium **16**, to form oxazolidinium ion **21**, which is hydrolyzed to quinocarcinamide **10**. When **7** was dissolved in deoxygenated $H_2{}^{18}O$, it was noted that recovered **10**, when submitted to mass-spectrometric analysis, showed more than 40% label incorporation.



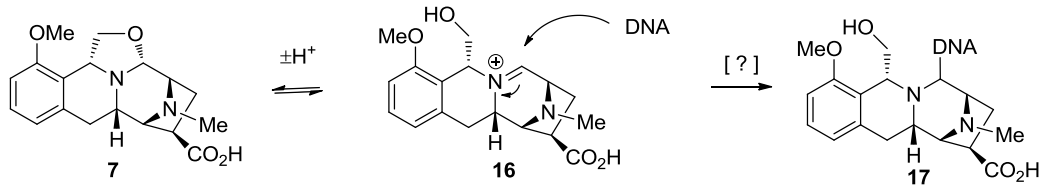
Scheme 2. Possible disproportionation mechanism of **7**

The generation of such radical species in the presence of oxygen could produce superoxide ion. Specifically, trapping of **21** by a molecule of oxygen may provide **22**. Ionization of the latter assisted by the nitrogen atom would release superoxide ion, **23**, and ring-opened quinocarcin **16**. The superoxide produced by this process might then go on to cause DNA damage through known mechanisms, for example, by dismutation to form hydrogen peroxide and subsequent reduction by adventitious Fe(II) to produce hydroxyl radical (Fenton reaction) (Scheme **3**).[17]

It is conceivable that a parallel mechanism of action may involve DNA alkylation, a possibility which was suggested by Remers and collaborators during a computational study.[9] This may occur through addition of a nucleophilic component of DNA—perhaps a guanine C-7 amino group—to iminium ion **16** (Scheme **4**).



Scheme 3. Possible mechanism for the formation of superoxide ion by **7**



Scheme 4. Possible DNA alkylation by **7**

However, the aforementioned study revealed that the preferred conformation of **7** was not favorable for oxazolidine ring-opening, meaning that a DNA-alkylation mechanism through an iminium ion at C7 would require the higher-energy conformer **25**. However, a stereoelectronic effect of chair-chair conformer **24** (proper alignment of the electronic lone pair overlap of the oxazolidine nitrogen with the antibonding orbital of the C7 hydrogen) would enhance the rate of the disproportionation reaction and facilitate the formation of radical **18**.

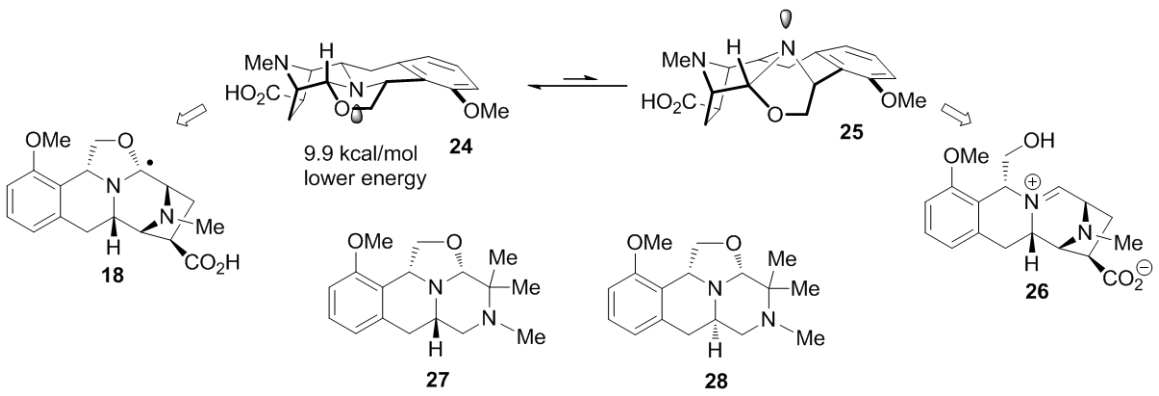


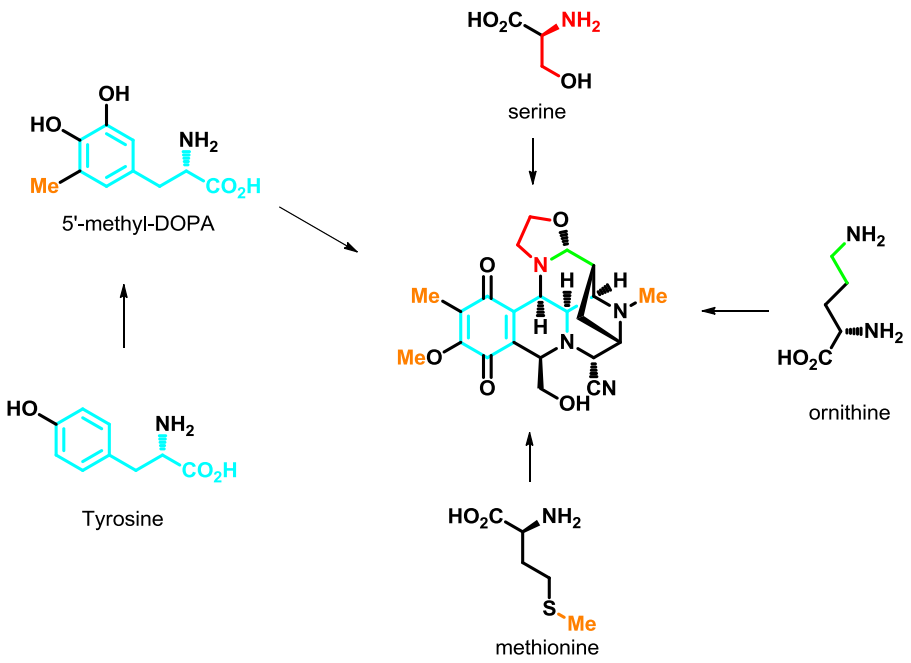
Figure 4. A predicted conformational effect in the DNA-cleaving ability of 7

On such a basis, Williams endeavored to synthesize two analogs of **7** which differed in configuration at C11a (**7** numbering), namely **27** (C11a hydrogen *anti* to oxazolidine) and **28**

(C11a hydrogen *syn* to oxazolidine).[16a] *Anti* compound **27** was found to exist as a chair-chair conformer by X-ray crystallography, thus mimicking the stereoelectronic activation of the C7 hydrogen as in **24** (Figure **4**). The citrate salts of these two materials were tested for DNA cleavage ability, and it was discovered that **27** was approximately six times more active than its isomer **28,** exhibiting superior DNA cleavage yield, based on single strand scissions of covalently closed circular DNA per molecule of **27/28**. These observations were taken to support the mechanism of action of Scheme **3**.

1.3 Biosynthesis

A few papers have appeared in the literature investigating the biosynthetic origins of naphthyridinomycin, and given the close similarity between its structure and that of cyanocycline, one supposes that the biosynthetic pathways must be closely related. The bacterium *S. lusitanus* was cultured in the presence of radiolabeled (^{14}C) amino acids and it was discovered that carbon atoms from tyrosine, methionine, glycine, and ornithine were all incorporated into the natural product. An NMR study demonstrated that uniformly labeled ^{13}C tyrosine was incorporated; later, it was found that tyrosine is first modified to 5´-methyl-DOPA before being incorporated.[18] The *N*-, *O*-, and aromatic methyl groups were shown to derive from the *S*-methyl group of methionine, presumably after conversion of the latter to *S*-adenosyl methionine (SAM).[19] It has also been reported that glycine is converted to serine before incorporation.[20] The origins of C9 and C9´ are still unknown. A pictorial summary of results in this area is found in Scheme **5**.



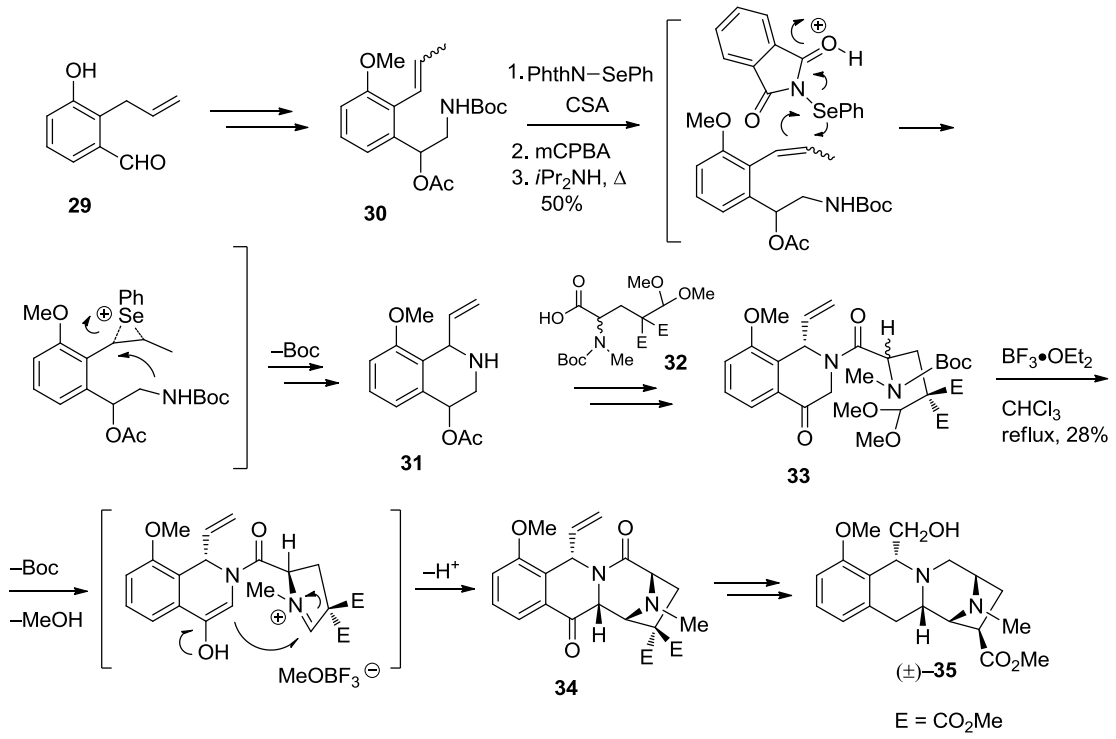
Scheme 5. Proposed biosynthetic origins of **2**

1.4 Prior syntheses

An excellent, detailed review of synthetic work targeting both **2** and **7** up to 2002, was published by Williams.[2] More recently, developments in the synthesis of **2** have also been reviewed.[21] In the interests of providing a new perspective on the great body of work in this area, the current document will focus on the overall synthetic strategies used in each case, along with highlights of key steps and/or difficulties encountered in each synthesis. Only total syntheses of **2**, **7**, and their direct congeners will be included.

1.4.1 Total syntheses of quinocarcin: Danishefsky

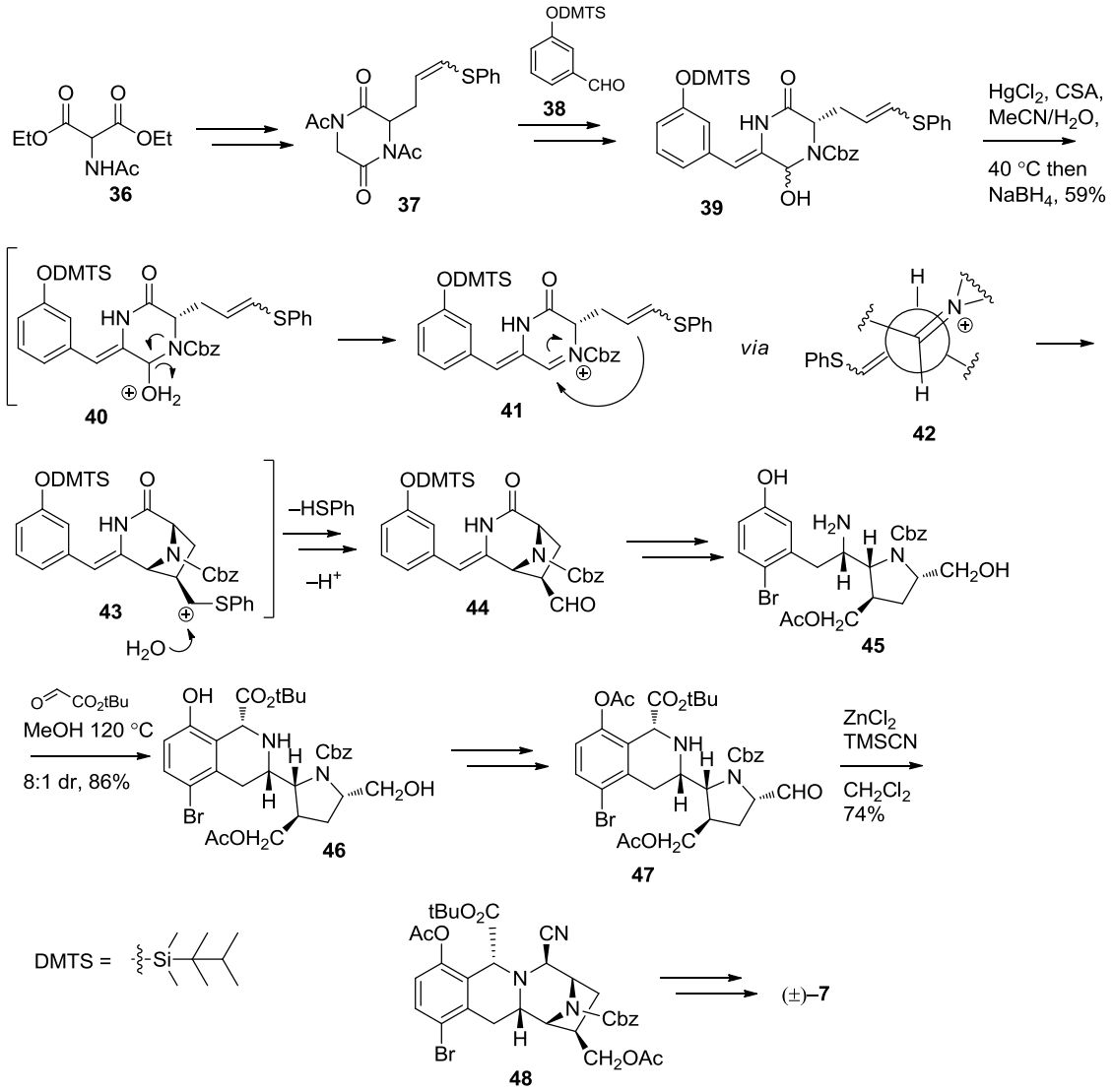
Danishefsky completed a landmark synthesis of a close congener of quinocarcin in 1985, in the form of quinocarcinol methyl ester **35**.[22] The synthesis began with allylated phenol **29**, the product of a Claisen rearrangement, which was elaborated to **30** through a cyanohydrin intermediate and double-bond isomerization. A key bond-forming sequence furnished tetrahydroisoquinoline **31** through an *N*-phenylselenophthalimide (*N*-PSP; the Nicolaou reagent)-mediated cyclization of carbamate **30** in the presence of CSA.[23] Further elaboration yielded acetal **33** as a 1:1 mixture of diastereomers. Subsequent release of the Boc and acetal units with BF_3•OEt_2 triggered formation of an iminium ion, followed by a Mannich cyclization in to give **34**. Relative to later syntheses, the formation of the C11-C11a bond (**7** numbering) as a key step would prove to be unique. The authors note that the diastereomer of **33** corresponding to the undesired isomer of **34** did not undergo cyclization, which helps explain the moderate yield of this step. The resulting tetracyclic intermediate **34** was carried through deoxygenation of the amide and ketone carbonyl groups, diastereoselective Krapcho decarboxylation, and conversion of the vinyl substituent to a hydroxymethyl group, to give (±)-**35**. The longest linear sequence in this synthesis was 25 steps starting from *m*-hydroxybenzaldehyde (Scheme **6**). The conciseness of this route is impressive given the synthetic technology available at the time.



Scheme 6. Danishefsky's synthesis of racemic **35**

1.4.2 Total syntheses of quinocarcin: Fukuyama

The first total synthesis of racemic **7** was completed by Fukuyama in 1988.[24] The synthesis began with the condensation of piperazinedione **37** with aromatic aldehyde **38** under catalysis by *t*BuOK (Scheme **7**). A subsequent adjustment of protecting groups gave **39**. The key formation of the pyrrolidine core was completed by an amidoalkylation reaction wherein a pendant vinylsulfide added to *N*-acyliminium ion **41**. This gave an aldehyde **44** that was immediately reduced to the corresponding alcohol. The C10 configuration is imagined to arise through a Yamamoto-type transition state[25] in the attack of the vinyl sulfide (*cf.* **42**). Although



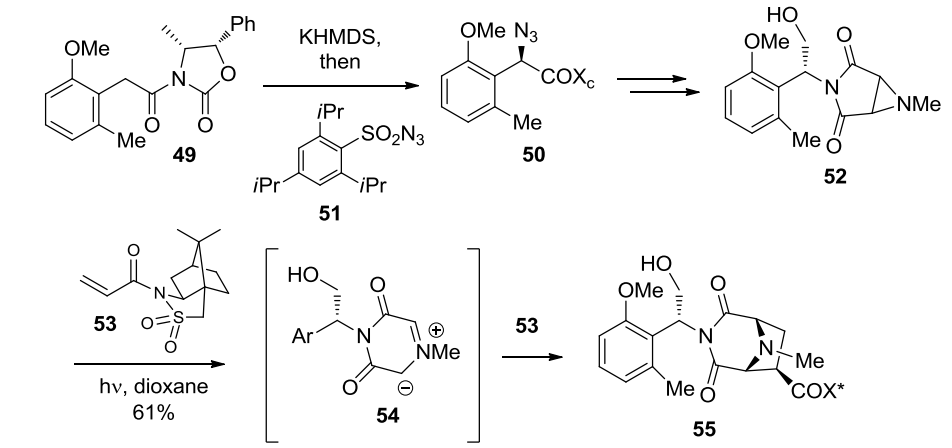
Scheme 7. Fukuyama's total synthesis of racemic **7**

later syntheses used modified conditions, the formation of the C10-C11 bond by attack of an olefin on an *N*-acyl iminium ion would be repeated by multiple research groups. The enamide system in **44** underwent diastereoselective hydrogenation under vigorous conditions (100 °C, 2000 psi H_2) in the presence of Raney Ni. The resultant was then advanced to **45** through a protection-deprotection sequence, which allowed facile opening of the piperazinone ring.

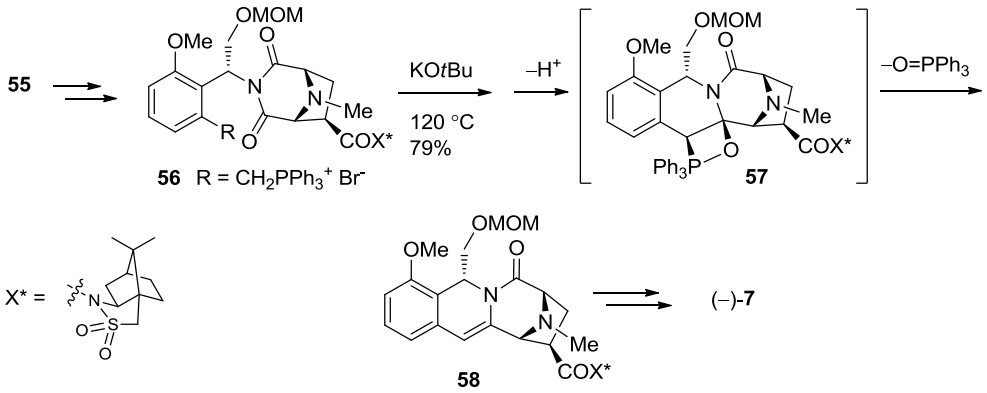
Reaction of **45** with *tert*-butyl glyoxylate in hot methanol resulted in the diastereoselective formation of tetrahydroisoquinoline **46** through a Pictet-Spengler cyclization. Compound **46** was then advanced to **47**, which upon exposure to TMSCN and $ZnCl_2$ was transformed into bridged intermediate **48**. Evidently, the intramolecular condensation of the free amine and the aldehyde produced a transient iminium ion, which was trapped by cyanide ion. The use of cyanide as trapping agent was inspired by the work of Hirata, who had previously used it to form the stable quinocarcin derivative DX-52-1.[26] Completion of (±)-**7** required a relatively high total of 37 steps from commercial diethyl acetamidomalonate, although the methods introduced were often adopted in later syntheses.

1.4.3 Total syntheses of quinocarcin: Garner

Five years after Fukuyama's effort, Garner completed the first asymmetric synthesis of **7**.[27] The correct configuration of key stereogenic centers was secured through reactions that employed suitable chiral auxiliaries. Indeed, the opening moves of the synthesis saw the enolate of Evans imide **49** undergoing auxiliary-directed azidation,[28] as a prelude to the elaboration of the product **50** into key intermediate **52**. It is worthy of note that the latter operation involved the cycloaddition of azidomethane to a maleimide as a means of installing the *N*-methylaziridine unit. It is also well established that CH_3N_3 is an exceedingly hazardous material, which may detonate for no apparent reason.[29] The above notwithstanding, no safety alerts are present in the paper, contrary to contemporary practice. Upon photochemical irradiation, the aziridine ring



Scheme 8. Chiral auxiliaries in Garner's total synthesis of **7**



Scheme 9. The completion of Garner's total synthesis of **7**

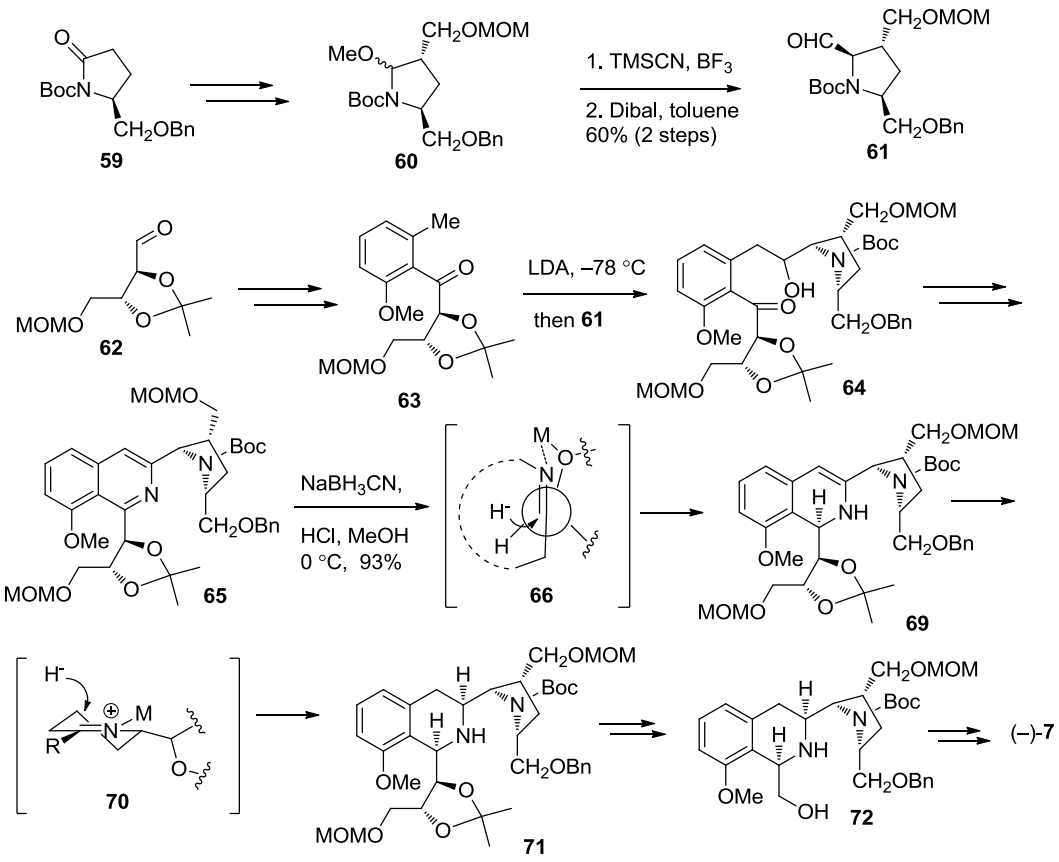
in **52** underwent electrocyclic opening to a presumed dipolar species **54**, which was intercepted *in situ* with Oppolzer complex[30] **53**. The product **55** of this noteworthy dipolar cycloaddition reaction was obtained as a stereochemically homogeneous material.

The total synthesis of **7** was rapidly completed from **55** as delineated in Scheme **9**. A straightforward sequence advanced **55** to phosphonium salt **56**. This material, upon deprotonation (*t*-BuOK) and heating to 120 °C, underwent a highly regioselective Wittig reaction through the intermediacy of strained oxaphosphetane **57** to furnish **58**. The latter could be

advanced to (−)-**7** through six additional steps, for a total of 24 steps from commercially available 2-methoxy-6-methylbenzaldehyde.

1.4.4 Total syntheses of quinocarcin: Terashima

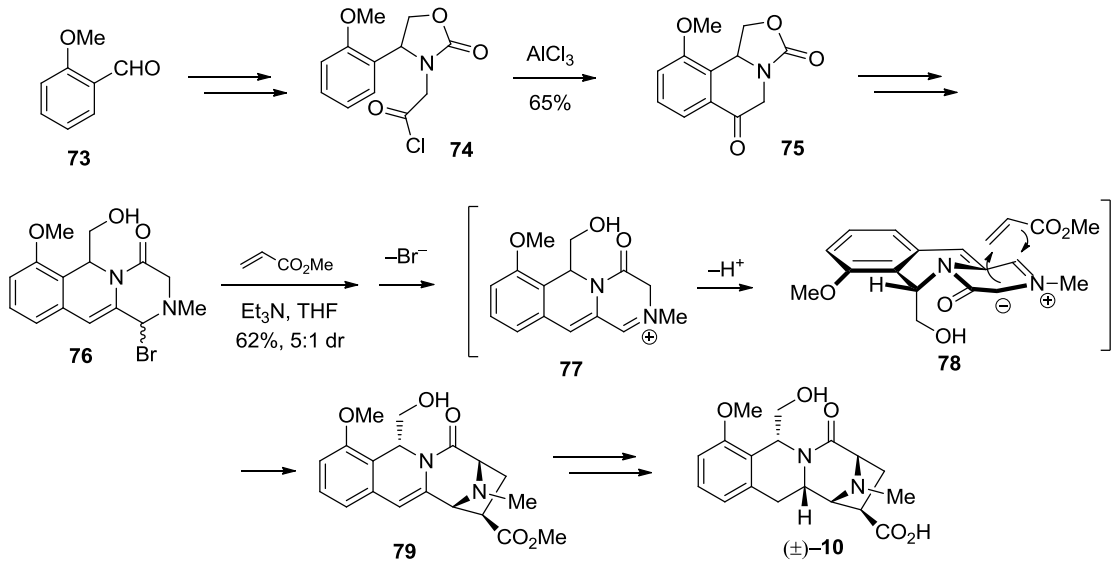
A subsequent asymmetric total synthesis of **7** by Terashima utilized pyroglutamic acid and threose derivatives as the source of chirality.[31] In the early stages, protected pyroglutamol **59** was elaborated into **61**, while protected D-threose **62** was reacted with 2-methoxy-6-methyl-phenyllithium and the product of such a reaction was re-oxidized to give **63** (Scheme **10**). Fragments **61** and **63** were then united through a noteworthy reaction, which entailed the selective deprotonation of **63** at the benzylic methyl group (LDA) and the addition of the corresponding anion to **61**. The emerging **64** was oxidized to a diketone, condensation of which with ammonia yielded quinoline **65**. This heterocycle was reduced diastereoselectively to the tetrahydroisoquinoline **71** using sodium cyanoborohydride in acidic methanol. The authors report that the reaction proceeded in 93% yield and with "complete diastereoselectivity." They furthermore indicate that the stereochemical course of the transformation is consistent with a Cram-chelation model[32] of nucleophilic attack at C-5, and with an axial attack of hydride at C-11a on cyclohexenyl-like iminium ion **70**.[33] Release of the acetonide in **71**, oxidative cleavage of the resulting diol using $NaIO_4$, and reduction of the transient aldehyde afforded **72**, setting the stage for closure of the C-ring using Fukuyama's conditions ($ZnCl_2$, TMSCN, CH_2Cl_2). Several additional steps provided (−)-**7**. This synthesis required a total of 37 linear steps beginning with L-glutamic acid.



Scheme 10. Terashima's total synthesis of **7**

1.4.5 Total syntheses of quinocarcin: Williams

In 1995, Williams completed his own synthesis of racemic quinocarcinamide **10**.[34] The key aspect of Williams' strategy was the execution of a dipolar cycloaddition of substance **76** with methyl acrylate (Scheme **11**), in a manner reminiscent of the earlier Garner approach. The assembly of acid chloride **74** proceeded in a conventional fashion, when Friedel-Crafts acylation provided a key bond formation to the aromatic moiety (**74** to **75**).[35] Further elaboration yielded allylic bromide **76**. With the addition of triethylamine and methyl acrylate, the cycloaddition of this material proceeded in 62% yield with a 5:1 dr. The authors rationalize the observed stereochemical outcome by the approach of the dipolarophile from the less-hindered β-side of the



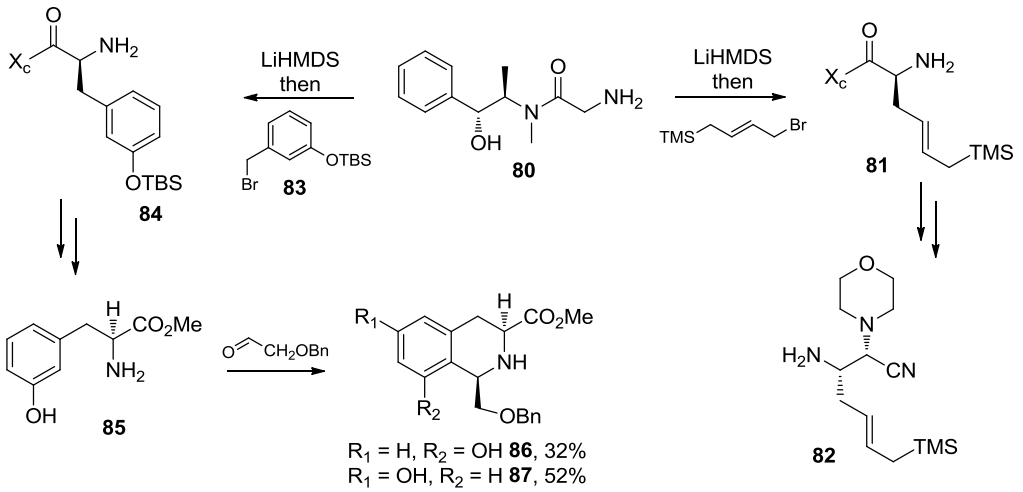
Scheme 11. Williams' synthesis of racemic **10**

molecule (*cf.* **78**). Cycloaddition product **79** was converted over a few steps into (±)-**10**. In total, 25 steps were needed starting from 2-methoxybenzaldehyde **73**.

1.4.6 Total syntheses of quinocarcin: Myers

Following a ten-year period of inactivity in this area, Andrew Myers announced an unusually concise enantioselective synthesis of quinocarcin.[36] This work showcased the application of aminoacid-derived, masked α-aminoaldehydes—the chemistry of which has been extensively studied in the author's laboratory[37]—to complex problems in synthesis. Furthermore, it demonstrated the use of new chiral auxiliaries for the stereocontrolled alkylation of glycine enolates.[38]

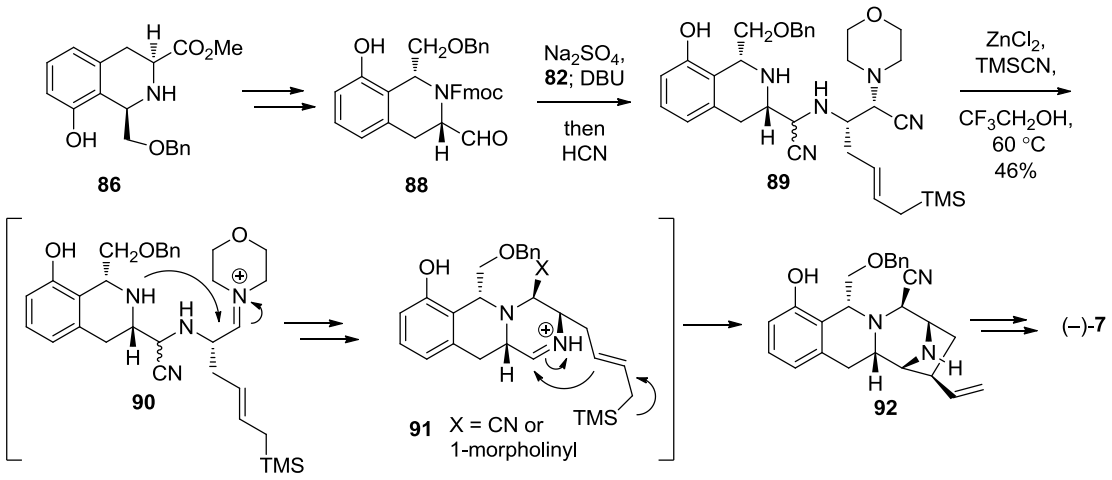
The Myers strategy rested on the merger of fragments **82** and **86**, which were prepared as outlined in Scheme **12**. In either case, the starting point was glycine amide **80**: the resultant of



Scheme 12. Pseudoephedrine auxiliaries in Myers' total synthesis of **7**

the union of a molecule of glycine with one of pseudoephedrine (the so-called Myers auxiliary). Alkylation product **81** was carried through several steps to provide masked aminoaldehyde **82**, while **84** was converted into **86**. The latter operation suffered from an annoying (but—unfortunately—predictable[39]) issue of regioselectivity. Specifically, the Pictet-Spengler reaction of **85** with 2-benzyloxyacetaldehyde furnished primarily the undesired *para*- type isomer **87** (5:3 ratio with respect to the desired **86**). Fortunately, the two isomers were separable.

The correct diastereomer **86** was transformed into Fmoc-protected aminoaldehyde **88**, which was condensed with **82** in the presence of Na_2SO_4 to afford an imine (Scheme **13**). Release of the Fmoc protection (DBU) and reaction with HCN resulted in formation of the Strecker product **89**. A remarkable cascade of reactions ensued upon exposure of the latter to the action of $ZnCl_2$ and TMSCN in 2,2,2-trifluoroethanol. Expulsion of cyanide generated presumed morpholinium ion **90**, cyclization and further decyanation gave transient iminium ion **91**. This

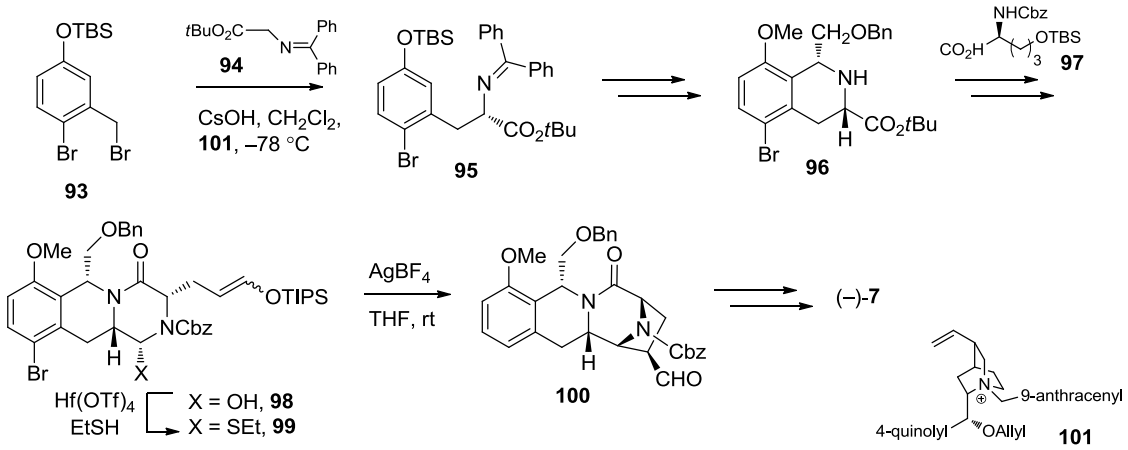


Scheme 13. The completion of Myers' total synthesis of **7**

intermediate then underwent Sakurai-type cyclization to generate **92**. The authors conclusively determined that formation of the piperazine preceded Sakurai-type D-ring closure. Finally, compound **92** was elaborated in a straightforward manner to (−)-**7**. Myers' convergent synthesis of this challenging molecule proceeded in only 17 steps from glycine methyl ester.

1.4.7 Total syntheses of quinocarcin: Zhu

In 2008, J. Zhu, then at the Institut de la Chimie des Substances Naturelles, at Gif-sur-Yvette, France described yet another synthesis[40] that began with a phase-transfer alkylation of glycine imine **94** under conditions developed by Corey (Scheme **14**).[41] This provided *meta*-tyrosine derivative **95**, which was elaborated to tetrahydroisoquinoline **96** using the well-proven Pictet-Spengler methodology. The resultant **96** was coupled with glutamic acid derivative **97** and carried through several manipulations to give **98**. One noteworthy aspect of the synthesis was the use of the unusual Lewis acid $Hf(OTf)_4$ to form the thioamidal **99** by reaction of **98** with ethanethiol. In another reaction that finds close analogy in the work of Fukuyama (Scheme **7**),

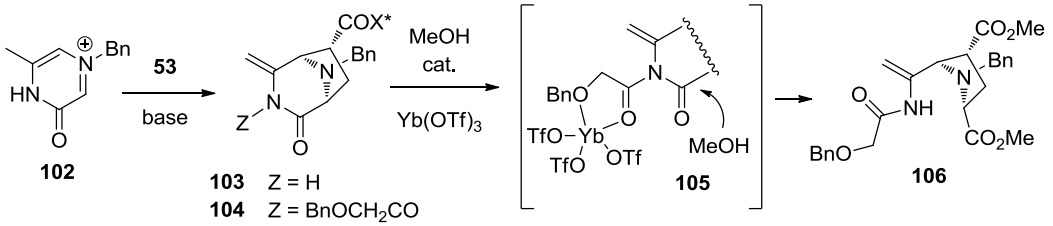


Scheme 14. Zhu's total synthesis of **7**

material **99** was treated with $AgBF_4$ to trigger closure of the D-ring of quinocarcin by an amidoalkylation process. The resulting aldehyde **100** was advanced through a few uneventful steps to produce (−)-**7**. In total, the synthesis comprised 23 steps from *m*-hydroxybenzaldehyde.

1.4.8 Total syntheses of quinocarcin: Stoltz

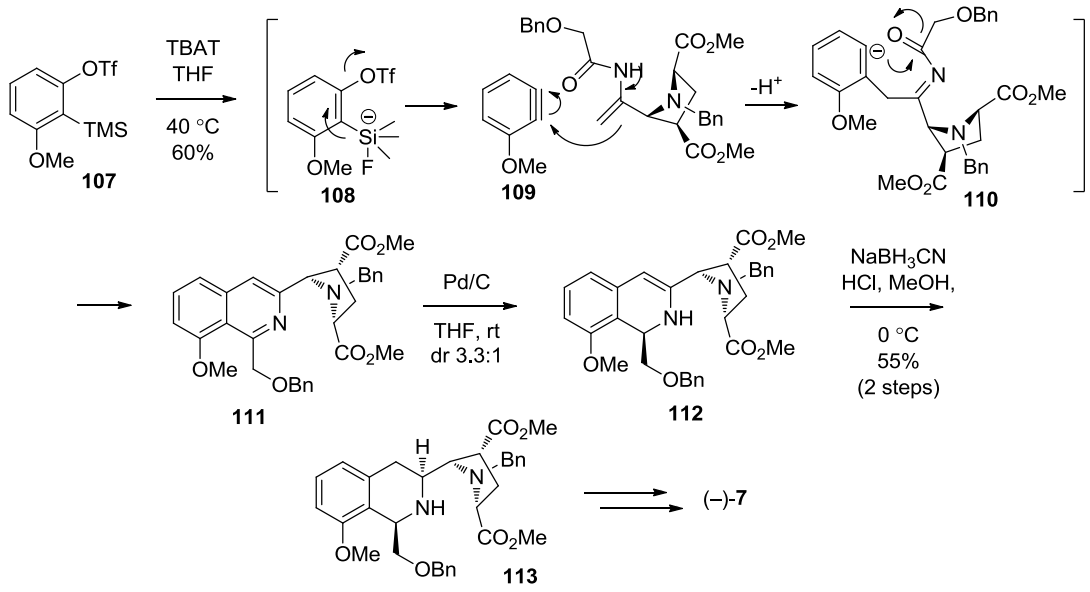
Later in the same year, Stoltz published what corresponds to the most recent synthesis of quinocarcin at time of this writing.[42] A key strategic principle here was the use of an annulation technique, devised earlier by the authors,[43] to secure an advanced intermediate through the reaction of a benzyne with compound **106**. As seen in Scheme **15**, the preparation of the latter began with the dipolar cycloaddition of **102** to Oppolzer acrylamide **53**: a step that is reminiscent of the Garner approach. The bicyclic material **103** that resulted was converted to the *N*-(benzyloxy)acetyl derivative in preparation for a regioselective methanolysis that gave compound **106**. Such a step was carried out in the presence $Yb(OTf)_3$, which presumably



Scheme 15. The early steps of Stoltz's total synthesis of **7**

combined with the substrate to form chelate complex **105**. The benzyloxyacetamide unit in **105** possesses enhanced nucleofugal character, resulting in preferential formation of the desired **106**. It should be mentioned that the methanolysis reaction was found to be quite problematic in terms of regioselectivity, and that numerous alternatives had to be explored before the above solution materialized.

A crucial phase of the synthesis involved the condensation of **106** with a benzyne generated by treatment of arene **107** with tetrabutylammonium triphenyldifluorosilicate (TBAT, Scheme **16**), resulting in formation of isoquinoline **111** in 60% isolated yield. A presumed mechanism for this noteworthy transformation envisions an initial regioselective addition of the enamide to the aryne. Subsequently, reactive intermediate **110** undergoes cyclization and ultimate dehydration to **111**. The authors provide no rationale for the regioselectivity observed in this key reaction, which afforded a product similar to the Terashima quinocarcin intermediate (Scheme **10**). Hydrogenation of **111** gave a 3.3 : 1 mixture of **112** (desired, major) plus the corresponding α-diastereomer (undesired, minor). Again, no explanation was provided for the



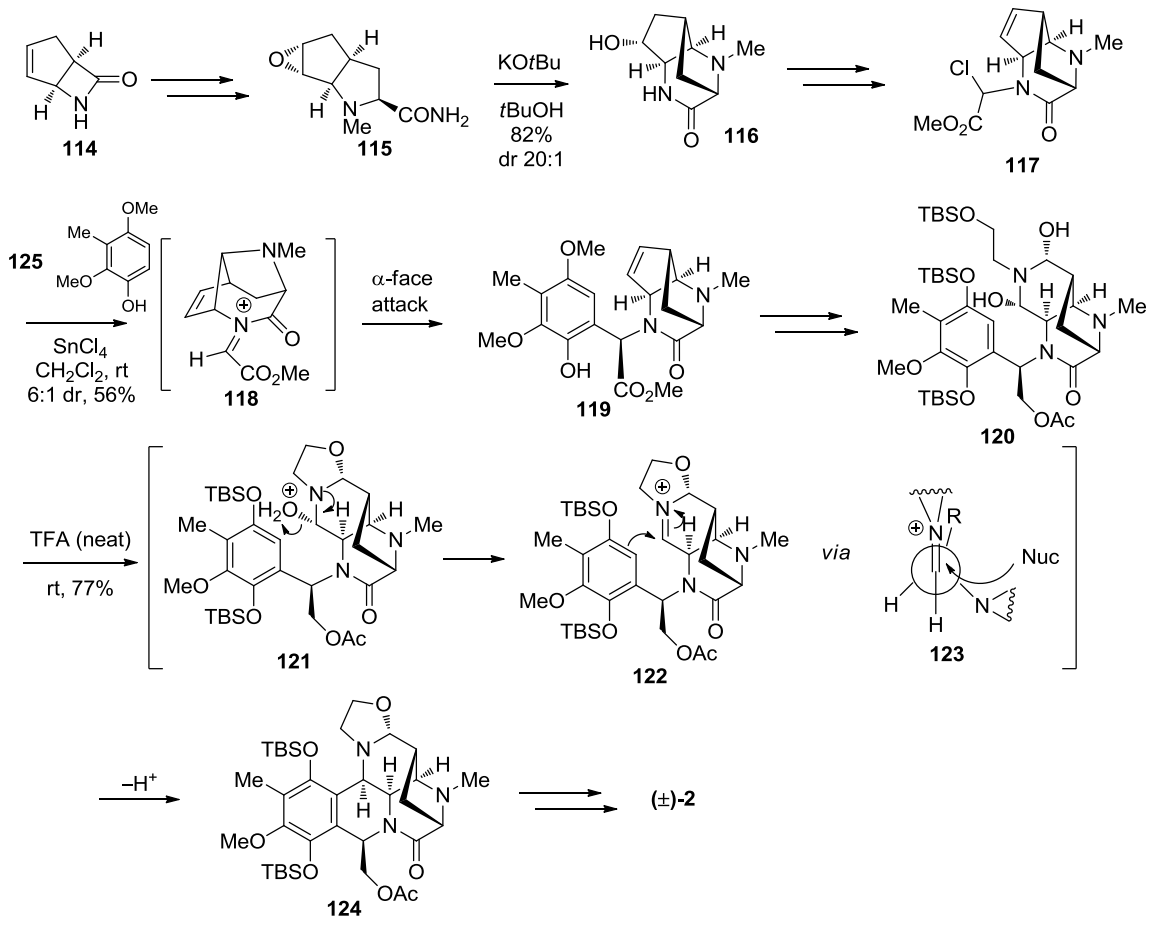
Scheme 16. The completion of Stoltz's total synthesis of **7**

observed selectivity. Further reduction of **112** with $NaBH_3CN$ furnished **113**, which was readily advanced to (−)-**7**. The synthesis was finished in an admirably concise manner, needing only 13 steps from commercial entities.

1.4.9 Total syntheses of cyanocycline: Evans

Turning now to a review of published work on **2** and congeners, we note that contrary to the case of **7**, only 3 total syntheses of this exceedingly challenging target have been accomplished. The first one of these was completed by Evans in 1986, and it afforded a racemic end product.[44] The synthesis began with β-lactam **114** (Scheme **17**), readily available through the reaction of cyclopentadiene with chlorosulfonyl isocyanate. This material was advanced to epoxide **115**, which cyclized regioselectively to alcohol **116** upon treatment with potassium *tert*-butoxide. The alcohol was converted into **117**, setting the stage for the first key step of the

synthesis. This entailed the amidoalkylation of phenol **125** with **117** under catalysis by $SnCl_4$. This reaction was found to proceed with good diastereoselectivity, which the authors rationalize based on attack of **125** on the *Z*-iminium ion, with approach of the nucleophile from the less-hindered α face. The product, **119**, was elaborated to hemiaminal **120**, dissolution of which in TFA induced a cascade of events leading directly to compound **124**. By way of mechanism, one may envision reversible cyclization of **120** to oxazolidine **121** and subsequent dehydration to a presumed iminium ion **122**. The latter may engage the nearby aromatic ring in a Pictet-Spengler mode. The overall reaction proceeded in good yield. While the authors do not provide a rationale for the stereoselectivity of this final step, one may surmise that the conformation of the bowl-

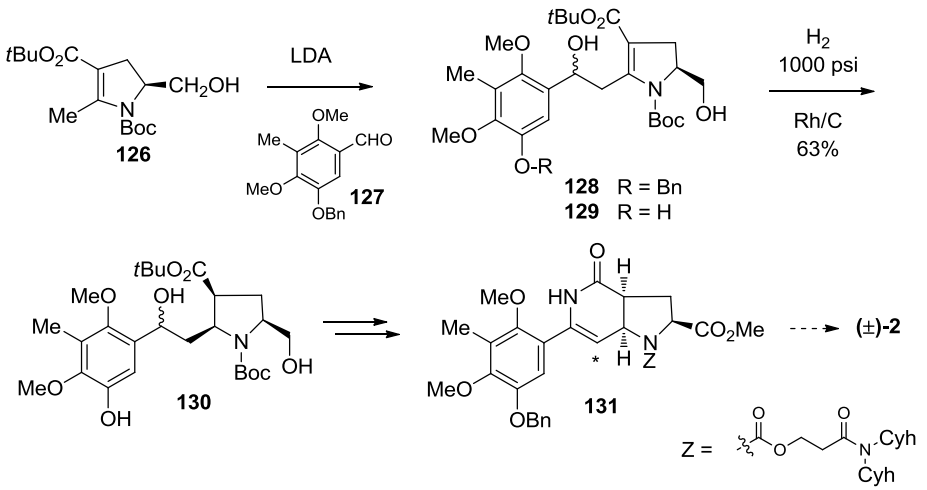


Scheme 17. Evans' total synthesis of racemic **2**

shaped heterocyclic moiety of **122** only permits cyclization from the *Re**-face of the iminium ion. Also of note, the TBS-protected hydroquinone survived the extended acid treatment. The total synthesis of **2** was completed rapidly from **124** and it required 35 steps from commercial materials.

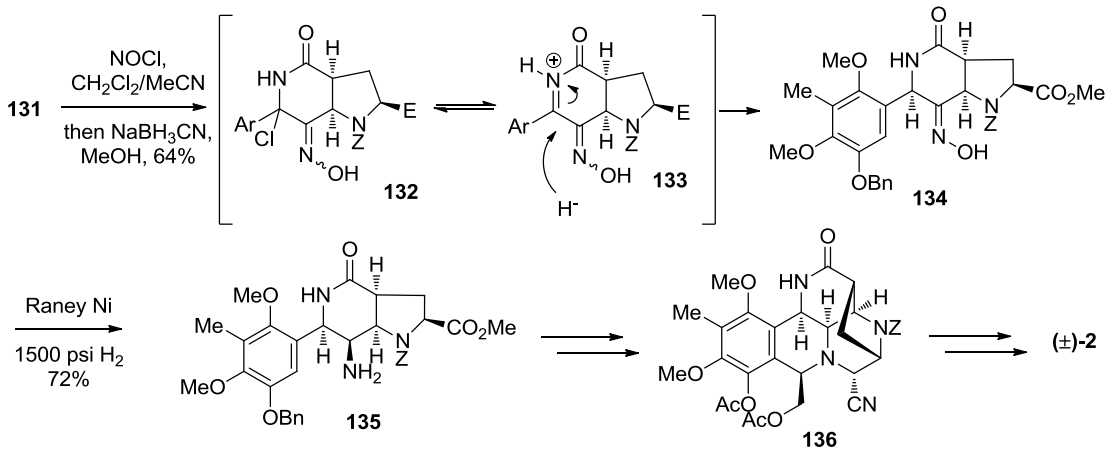
1.4.10 Total syntheses of cyanocycline: Fukuyama

Shortly after Evans's pioneering report, Fukuyama announced a second total synthesis of racemic **2**.[45] Strategically, the effort envisioned the union of fragments **126** and **127**, followed by appropriate manipulations of the resultant **128** (Scheme **18**). It will be seen that the advancement of **131** to **2** proved to be problematic, and it required a highly original solution. In any event, compound **126**, readily prepared in 3 steps through the condensation of the *tert*-butyl ester of *N*-Boc-dehydroalanine with *tert*-butyl acetoacetate, was deprotonated (LDA) and the resulting anion was converted into a presumed Zn enolate (addition of $ZnCl_2$). The latter added to aldehyde **127** to yield **128**. The next step of the sequence required a diastereoselective reduction of the double bond in **128**. Such an operation was best conducted using the free phenol **129** in lieu of **128**. Accordingly, hydrogenation of **129** over Rh/C under 1000 psi of H_2 provided **130**, which was advanced to the key intermediate **131**. One unusual element here is the use of the protecting group, *N*,*N*-dicyclohexyl-3-carboxypropanamide, rendered in Scheme **18** as substituent Z. This sturdy protecting group, which nonetheless may be released under gently basic conditions (retro-Michael elimination of the carbamate) proved to instrumental for the success of subsequent operations.



Scheme 18. The opening moves of Fukuyama's total synthesis of **2**

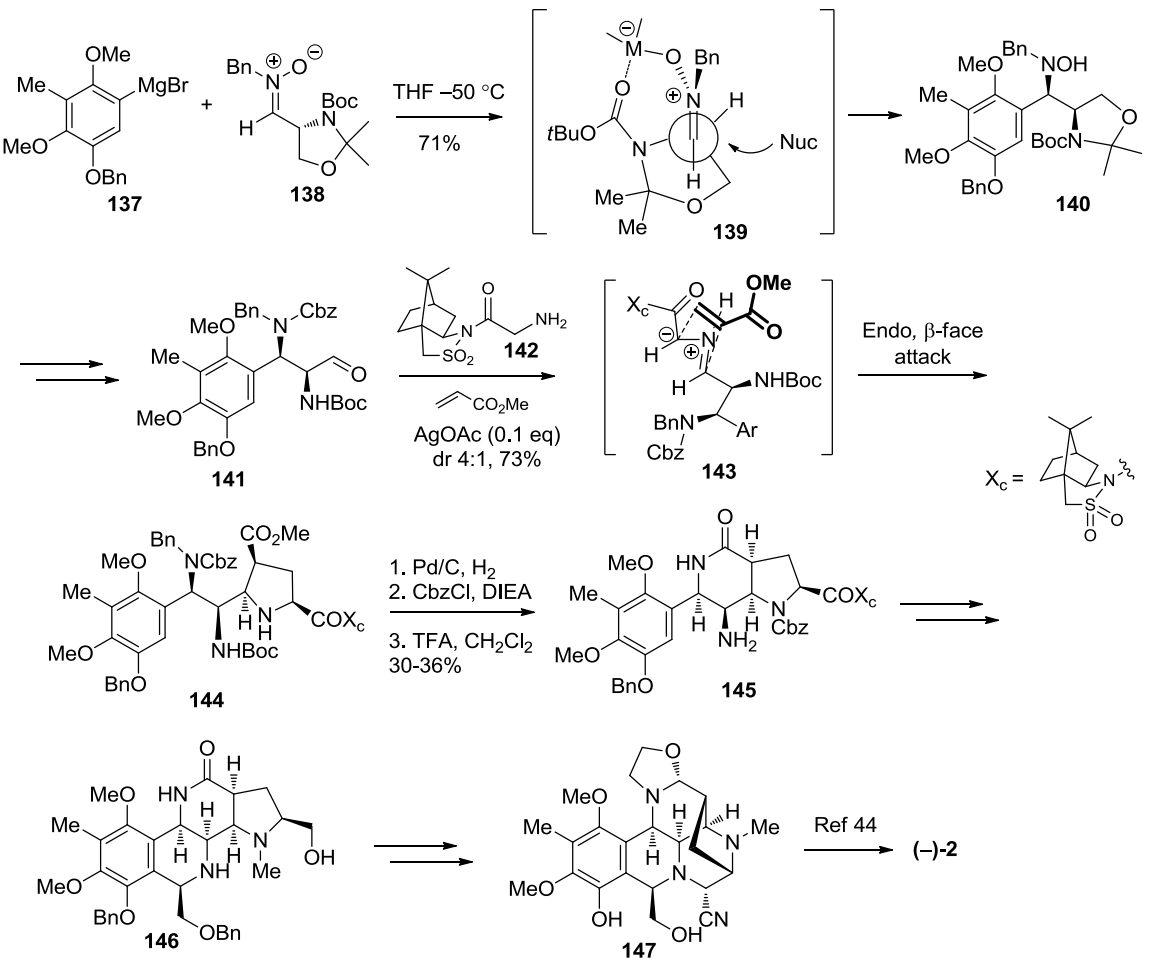
Innumerable attempts to elaborate **131** into a more advanced precursor of **2**, in particular, the introduction of heteroatomic functionality at the starred carbon atom, produced a stream of disappointing results. Success was finally achieved by reaction of the substrate with nitrosyl chloride. The primary product of such a treatment, presumably compound **132** (Scheme **19**) was stereoselectively reduced *in situ* with $NaBH_3CN$, leading to oxime **134**. The authors identify the preparation of **134** as "undoubtedly, the most important step" of the synthesis. Raney nickel reduction of the oxime proceeded diastereoselectively to form **135**, from which the synthesis was completed in a straightforward manner. Overall, the synthesis required 32 steps.



Scheme 19. The completion of Fukuyama's total synthesis of **2**

1.4.10 Total syntheses of cyanocycline: Garner

A formal total synthesis of **2** was described 20 years later by Garner.[46] A key early step was the preparation of 1,2-diamino segment **140** through a Merino-type[47] addition of aryl Grignard reagent **137** to nitrone **138** (Scheme **20**). The addition took place stereoselectively to the *Re*-face of the nitrone, presumably through chelate complex **139**, leading to hydroxylamine **140** as a single diastereomer. This product was advanced to aldehyde **141**: the precursor for a crucial dipolar cycloaddition of the type demonstrated earlier in Scheme **8**.[48] In the event, Oppolzer glycine derivative **142** condensed with **141** to give an imine, which upon deprotonation, generated a 1,3-dipolar entity that underwent cycloaddition to methyl acrylate. Product **144** was thus obtained in a moderately diastereoselective fashion (dr = 4:1). The authors invoke an *endo* chelation-controlled cycloaddition (*cf.* **143**) to account for the stereochemical outcome of the reaction. In any case, substance **144** was advanced to **145**, which resembles Fukuyama's intermediate **135** (Scheme **19**). This material was elaborated to known compound



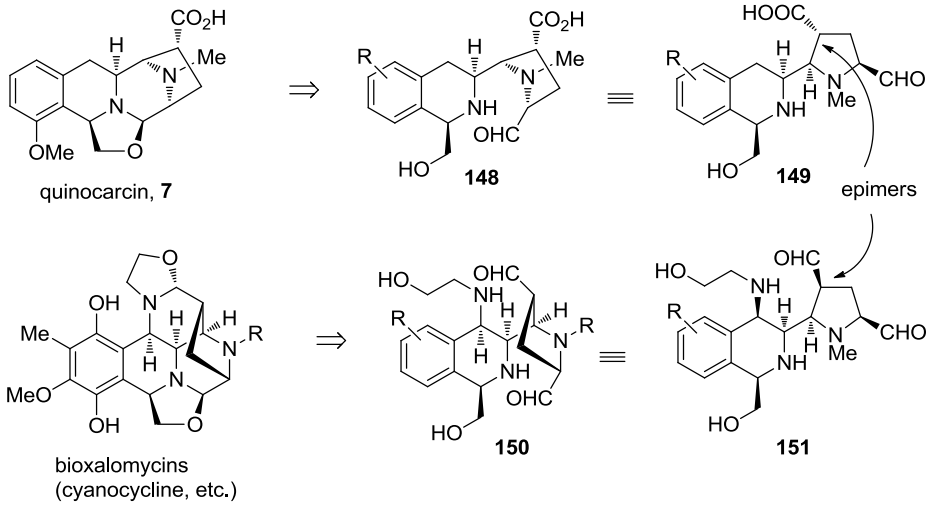
Scheme 20. Garner's total synthesis of **2**

147[45] by a sequence similar to that used earlier by Fukuyama, thereby completing the formal synthesis of (−)-**2** in a brief 22 steps.

It is clear from the discussion above that, with the exception of the Stoltz synthesis, known routes to the natural products rely on an early introduction of aromatic subunits. It was perceived that a late installation of such segments may lead to improvements in conciseness and overall efficiency, as well as enabling a unified approach to the entire class of molecules, as detailed in the next section.

1.5 Retrosynthetic considerations

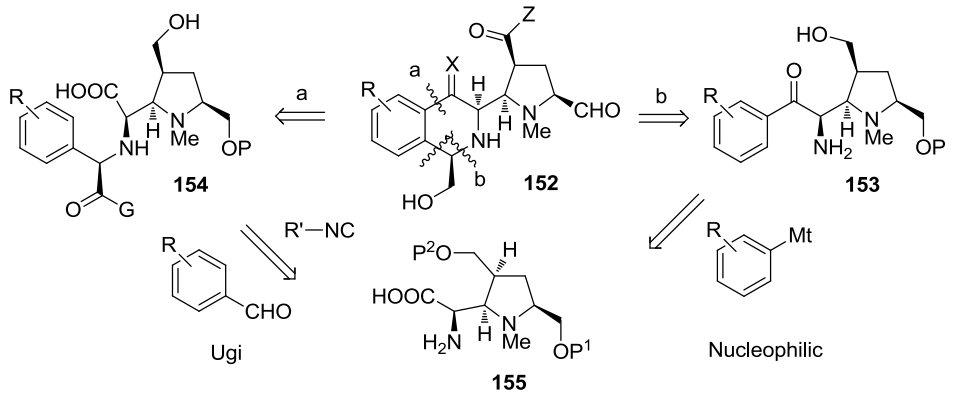
Our approach imagines the construction of a nitrogenous entity corresponding to the common "aliphatic" core of quinocarcin and the bioxalomycins. Said core would combine with various aromatic fragments to give advanced intermediates suitable for further elaboration into any member of the family or congener thereof. To illustrate (Scheme **21**), release of the oxazolidine rings in the natural products furnishes retrons **149** and **151**, which are epimeric at the indicated positions.



Scheme 21. Retrosynthetic analysis of **7** and **2**-**6**

Further analysis of **149** and **151** suggests that either could derive from precursor **152**, wherein X represents either a pair of H's, or a carbonyl, or an H and an OH group. Compound **152** could be dissected at the level of bond *a* to reveal acid **154**, which could advance to **152** by an intramolecular aromatic ring acylation process. Prior work in our group had determined that substance **154** should be available through an Ugi-type reaction between amino acid **155**, an isonitrile and an aromatic aldehyde (*vide infra*). Alternatively, retro-Pictet-Spengler dissection of

bonds *b* produces **153**, which could emerge upon reaction of a suitably activated form of **155** with an aryl organometallic agent (Scheme **22**). Amino acid **155**, or an appropriate analog, thus became the primary objective of this investigation.



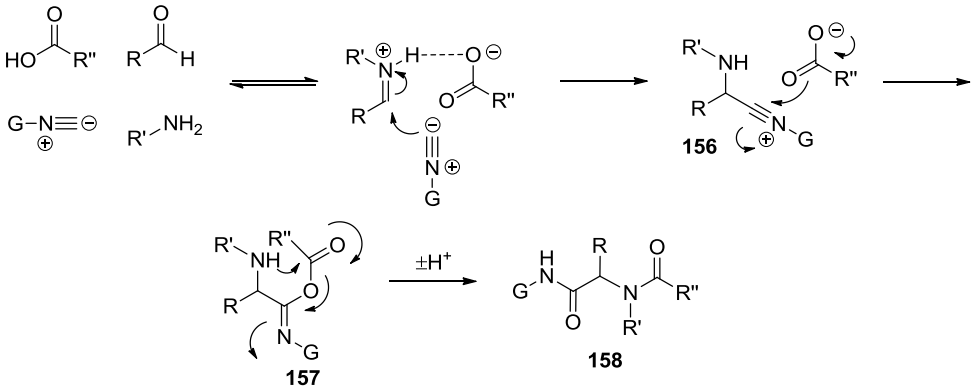
Scheme 22. Retrosynthetic analysis of **152**

Before delving into the details of how **155** was prepared, it seems appropriate to review the Ugi reaction, particularly the variant of the process of interest in the present case. A brief summary of key aspects of this chemistry appears in the following section.

1.6 The Ugi reaction

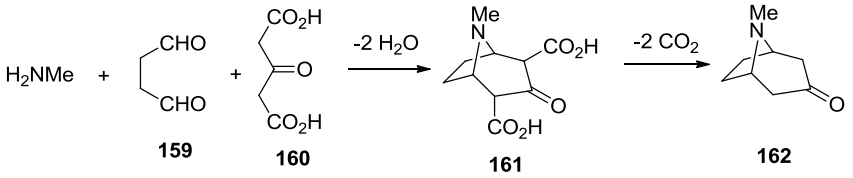
The Ugi reaction involves the condensation of an aldehyde (sometimes, a ketone), an amine, a carboxylic acid, and an isonitrile, to yield α-amido amides. The four components of the Ugi reaction are simply admixed and allowed to combine to furnish the ultimate product. A process so constituted is described as a multicomponent reaction (MCR). Thus, the Ugi condensation is commonly described as a 4-component reaction ("U-4CR" in contemporary parlance), and since its development, it has found wide use, e.g., in divergent (library) synthesis,[49] in target-oriented synthesis,[50] and in drug discovery.[51]

A likely mechanism for the U-4CR is shown in Scheme **23**. The reaction begins with the reversible condensation of an amine with an aldehyde, or, alternatively, with a pre-formed imine. This species then reacts with the isocyanide to form a putative nitrilium **156**, which is trapped by the acid component. A so-called Mumm rearrangement[52] follows, irreversibly transferring an acyl group to nitrogen to form product **158**. Computational studies on the course of the Ugi reaction have recently been performed, suggesting that the isocyanide addition is an irreversible, rate-limiting step.[53]



Scheme 23. Mechanism of the Ugi four-component condensation

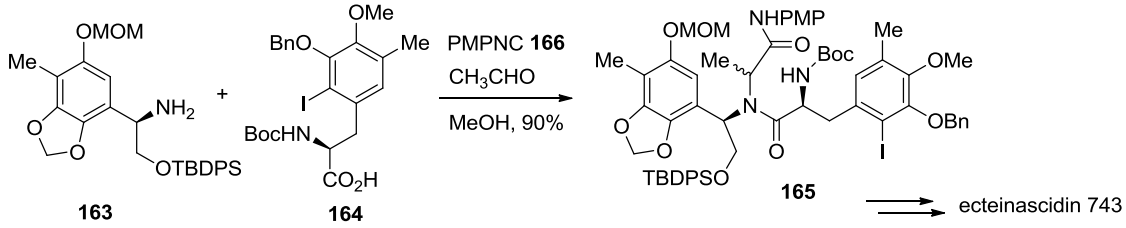
A brief parenthesis is in order at this juncture. It may be argued that Sir Robert Robinson's celebrated synthesis of tropinone **162** (*cf.* Scheme **24**)[54] marked the first use of a multi-component reaction in natural product synthesis. However, the modern era of MCRs began in 1921 with a report by Mario Passerini[55] on the reaction of isocyanides with aldehydes and carboxylic acids. These seminal reports languished in the literature for decades, until the work of Ivar Ugi[56] brought to the forefront the role of isocyanides in MCRs.[57] Isocyanides have remarkable properties, including the incorporation of a stable carbenoid carbon atom that engenders predictable and selective reactivity. These noteworthy agents had been known since



Scheme 24. Historical application of an MCR by Robinson

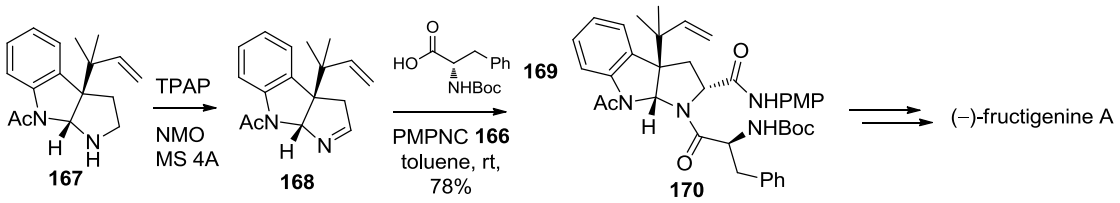
the 1800's,[58] but they had been unjustly neglected for too long, possibly due to their famously noisome odors.

The U-4CR has seen some prominent use in total synthesis, for example, in Fukuyama's synthesis of Ecteinascidin 743 (Scheme **25**).[59] The key reaction involved the condensation of amine **163** with acetaldehyde, in the presence of protected amino acid **164** and *p*-methoxyphenylisocyanide **166**. In this case, the Ugi reaction acts as a surrogate peptide coupling with concomitant alkylation of the amine component. Further elaboration to was able to yield the natural product.



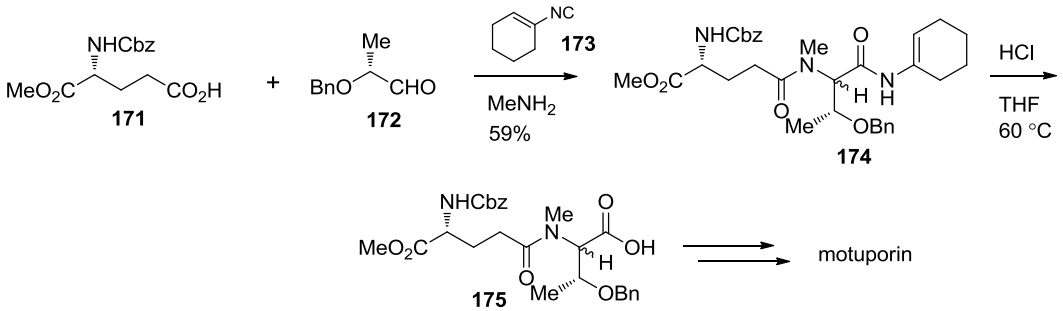
Scheme 25. The Ugi reaction in Fukuyama's synthesis of ecteinascidin 743

A clever use of a modification of the Ugi reaction was demonstrated by Kawasaki.[60] Ugi precursor imine **168**, which was generated by oxidation of the corresponding secondary amine **167** under anhydrous conditions using TPAP/NMO, reacted stereoselectively with *p*-methoxyphenyl isocyanide **166** and Boc-protected L-phenylalanine **169** to give key intermediate **170**. This material was advanced to the alkaloid (−)-fructigenine A (Scheme **26**).



Scheme 26. The Ugi reaction in Kawasaki's synthesis of fructigenine A

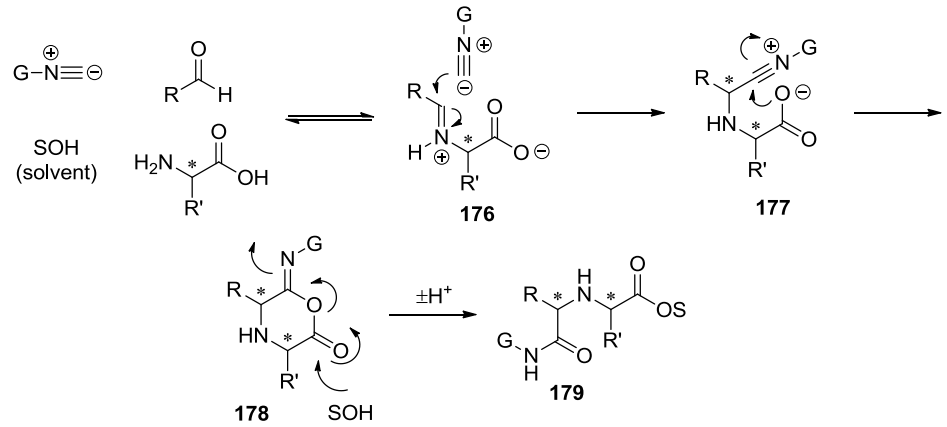
A recurring theme in the Ugi reaction is the need to cleave the amide resulting from the isocyanide component. One solution, first described by Ugi,[61] is to employ a cyclohexenyl isonitrile. The product thus obtained is an enamide, which can be selectively cleaved under gentle acidic conditions. An early step in the total synthesis of motuporin by Armstrong relies upon this chemistry to produce dipeptide **175** as shown in Scheme **27**.[62]



Scheme 27. A convertible isocyanide was used in Armstrong's synthesis of motuporin

Our particular interest lies in a special form of the Ugi condensation, introduced by Ugi himself,[63] in which the carboxylic acid and amine components are part of the same α-amino acid molecule. The reaction is normally carried out in alcohol solvents, leading to products **179** (Scheme **28**). Accordingly, it is often referred to as an Ugi five-center, four-component (amino acid, aldehyde, isonitrile, alcohol) reaction, or U-5C-4CR. By way of mechanism, it is likely that

amino acid and aldehyde initially condense to form an imine **176**. This is followed by isocyanide attack. The resultant nitrilium **177** is then trapped intramolecularly, followed by ring-opening of imidate **178**, often by the alcohol solvent, though trapping by a tethered alcohol to give a lactone is also common.

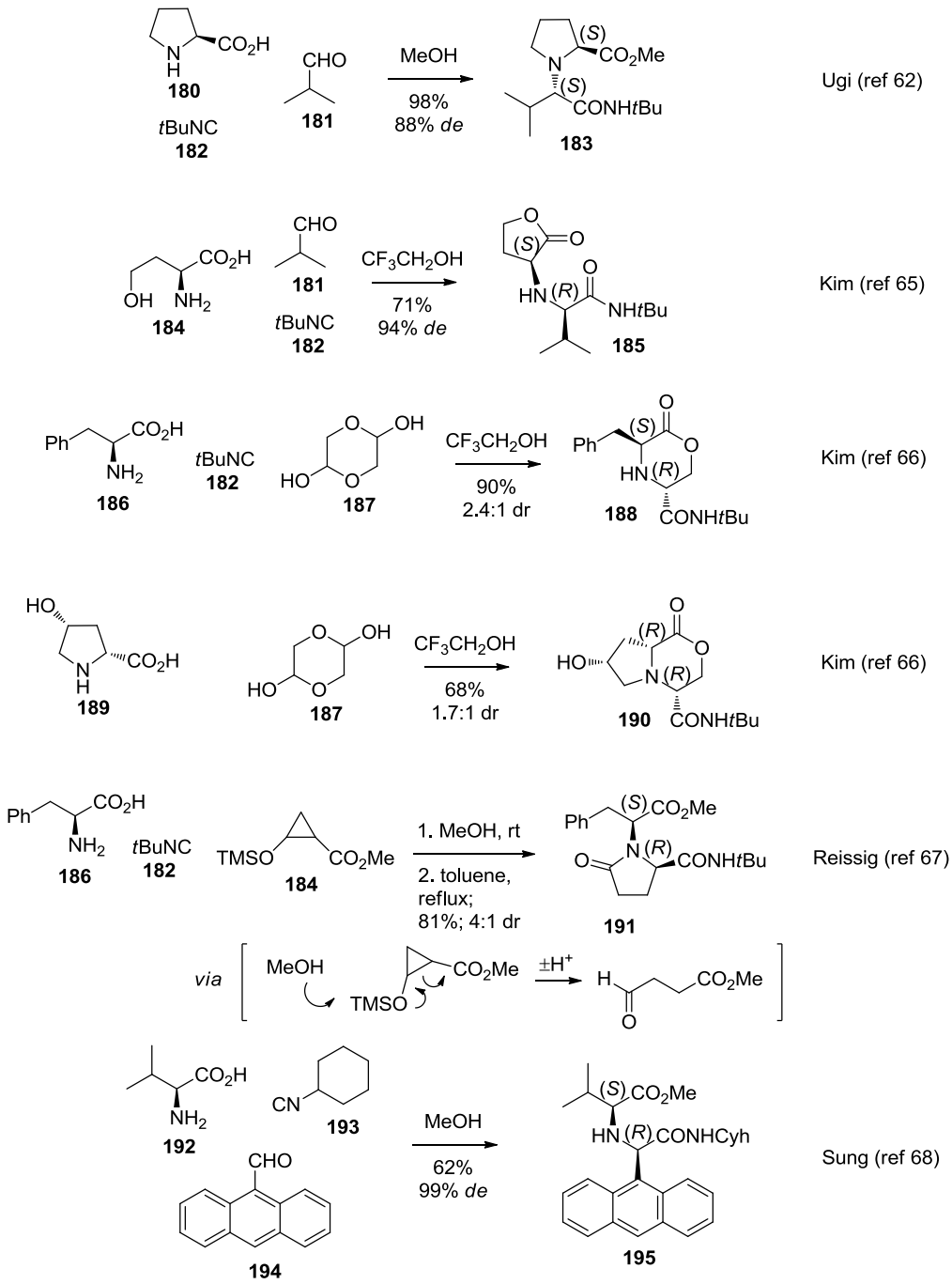


Scheme 28. Mechanism for the Ugi reaction of amino acids

It is recognized that the foregoing reactions possess inherent potential to proceed diastereoselectively, in that the stereogenic center that is present near the reaction site could direct the attack of the isocyanide to one particular face of the transient iminium ion (*cf.* **176** => **177**). Indeed, chiral auxiliaries have been utilized in ordinary Ugi reactions in order achieve diastereoinduction.[64] A (chiral) α-amino acid might well eliminate the need for chiral auxiliaries and elaborate catalysts.

The above notwithstanding, the Ugi reaction of α-aminoacids has received only sporadic attention since its initial report. One possible reason is that a key aspect of the chemistry, the question of diastereoselectivity, is poorly understood. Indeed, both the magnitude and the sense of stereochemical induction varies with the precise nature of the amino acid substrate. A sample of reactions for which the configuration of the product has been ascertained by X-ray

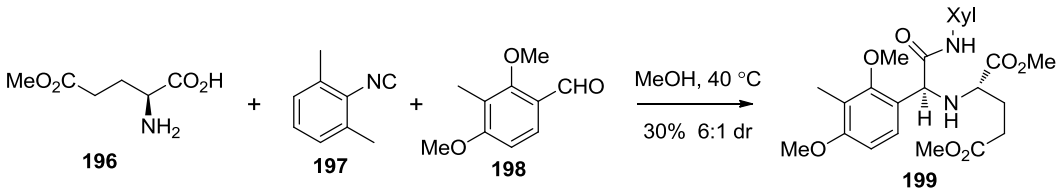
crystallography can be found in Scheme **29**. In Ugi's initial report,[63] the reaction of L-proline **180** with *tert*-butylisocyanide **182** and isobutyraldehyde **181**, gave **183**, which was found to have the



Scheme 29. Examples of the Ugi reaction of alpha amino acids with known product configuration

(*S*)- configuration at the newly formed center. In Seebach's parlance, **183** is thus the product of like (*l*) stereoinduction.[65] Later reports by Kim gave conflicting stereochemical results.[66,67] For example, the condensation of homoserine **184** with **181** and **182** proceeded with elevated levels of *unlike* (*u*) diastereoinduction to furnish **185**. On the other hand, the reaction of **186** with **187** and **182** gave **188** with a weak *l*-induction (dr = 2.4:1), and that of **188** with **182** and **187** occurred with a modest unlike (*u*) stereoselectivity (dr = 1.7:1). An interesting reaction described by Reissig uses silyloxycyclopropanes as masked aldehydes, and in one case, it also proceeded with *u* stereoselectivity (dr = 4:1).[68] Finally, an example from Sung using L-valine **192** occurred with very high *u* selectivity.[69]

As outlined earlier in Scheme **22**, our interest lies in the specific variant of the Ugi reaction in which an α-amino acid combines with an isonitrile and an aromatic aldehyde. A survey of the literature prior to 2004 reveals that although examples of efficient Ugi condensation of amino acids with aromatic aldehydes had been recorded, these reactions tend to proceed at slow rates and in variable yields, especially if the aldehyde is electron-rich. Indeed,



Scheme 30. Uncatalyzed Ugi reaction of **196** with **197** and **198**

preliminary experiments in our lab centering on the condensation of glutamic acid monomethyl ester, **196**, with aromatic aldehyde **198**, under standard Ugi conditions (MeOH, rt) revealed that the reaction rate was exceedingly slow.[70] The reaction proceeded faster at 40 °C, but some starting material (5-10%) remained even after a contact time of 4 days, whereupon the desired **199** was obtained in a modest 30% yield and as a 6:1 mixture of diastereomers (Scheme **30**).

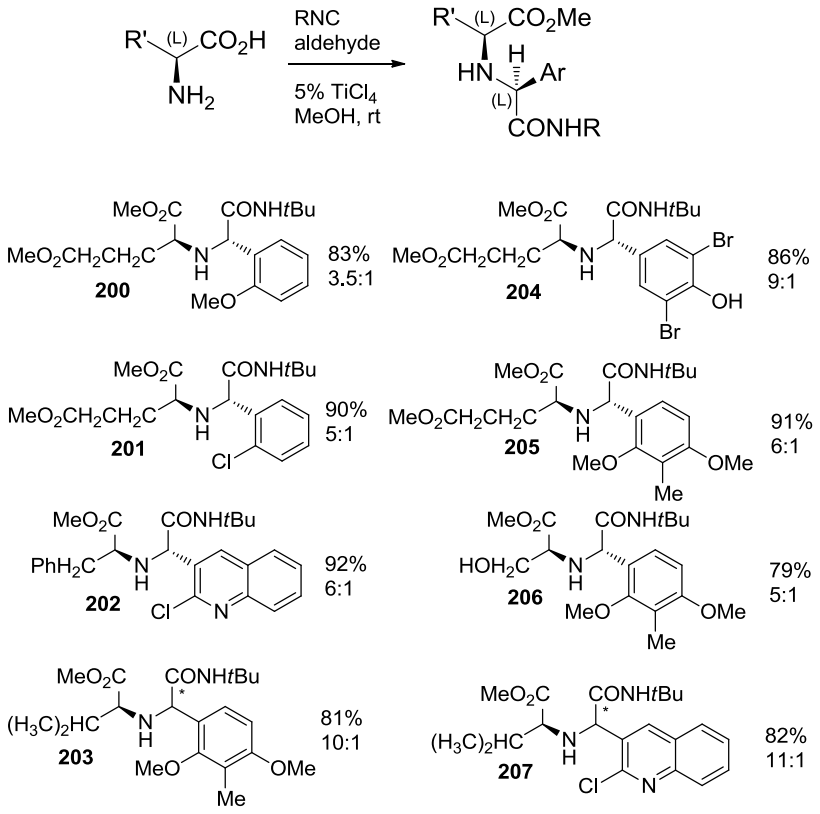
Suspecting that these difficulties were due to the slow rate of formation of iminium ions such as **176,** we sought an artifice that might accelerate the process, such as an appropriate Lewis acid promoter. We thus undertook a study examining the effect of various acid additives.[70] Our investigations revealed that a catalytic amount of $TiCl_4$ (5 mol%) in MeOH constituted a superior reaction system. The yield of **199** tripled compared to the uncatalyzed process, and the reaction proceeded much faster. However, the Lewis acid had virtually no effect on the diastereoselectivity, indicating that in all likelihood it was involved only in imine formation.

It may be argued that $TiCl_4$ and MeOH are likely to react, giving rise to titanium methoxides and HCl, which could itself promote the reaction. However, it was determined that HCl is not a competent replacement for $TiCl_4$, while $Ti(O\textit{i}Pr)_4$ is essentially as effective. This clearly demonstrated the requirement for a Lewis acid. We presume that Ti(IV) coordinates to the carbonyl group of the aldehyde, thereby accelerating the rate of nucleophilic addition of the amino component. It seems less likely that $TiCl_4$ reacts with water to form TiO_2, thus driving the equilibrium toward the imine through a LeChatelier effect. Only 5 mol% Ti(IV) are present, so that this stoichiometric process would make a negligible contribution to the overall reaction.

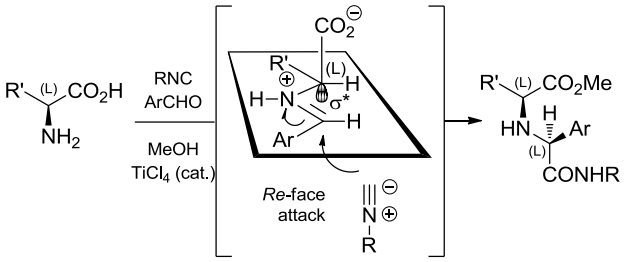
The new conditions proved to effect the Ugi reaction of a broad spectrum of aldehydes and amino acids. For example, phenylalanine, serine, tryptophan, valine, and glutamic acid 5-methyl ester are compatible; as are 3-pyridinylcarbaldehyde, *o*-anisaldehyde, 2-chloroquinolyl-3-carbaldehyde, 2-chlorobenzaldehyde, and others. Electron-rich aldehydes are quite competent, which is of particular interest due to their low electrophilicity, and for their compatibility with our synthetic goals.

Except for **200**, all products were recovered with satisfactory levels of diastereoinduction (> 4:1, in several cases > 10:1). Representative examples appear in Scheme **31**. The

configurations of compounds **199** and **205** were ascertained by X-ray diffractometry, whereupon it was established that the process had occurred with "like" stereoinduction. On such grounds, we extrapolated that all products tabulated in Scheme **31** had the (*S*) configuration of the newly formed stereogenic carbon, although—rigorously speaking—this hypothesis remains to be confirmed. In particular, the results of Sung (*cf.* Scheme **29**) indicate that caution is warranted in assigning the stereochemistry of valine-derived Ugi products **203** and **207**.



Scheme 31. Products of the Ugi reaction of amino acids with aromatic aldehydes



Scheme 32. Model for the stereochemical course of the Ugi reaction of amino acids

A rationale for the stereochemical course of the reaction is offered in Scheme **32**. It is presumed that the isocyanide attacks the *Re*-face of a planar zwitterionic iminium, opposite the adjacent C-C=O bond, which activates the iminium through a stereoelectronic effect. The orientation shown limits $A^{1,3}$ strain around an iminium with *E*- geometry. However, in light of the variability of the stereochemical outcomes of products of the Ugi reaction of α-aminoacids, as verified by X-ray analyses, we must stress the uncertainty inherent in such models.

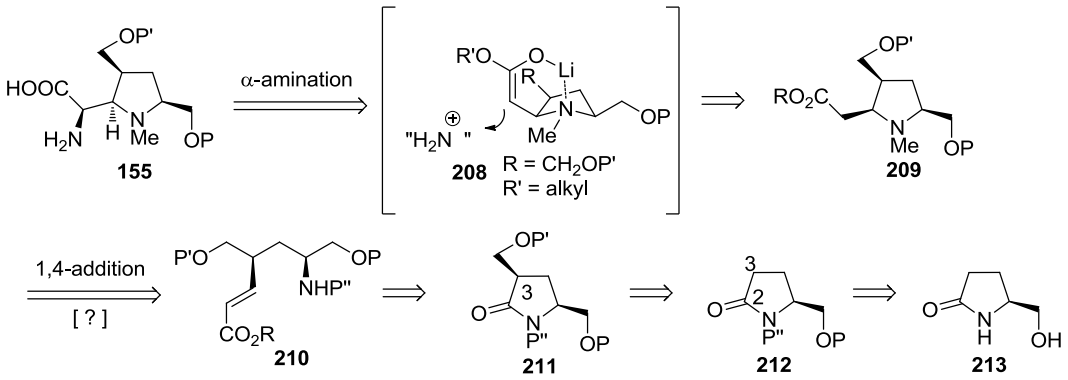
2 Synthetic Work

2.1 Synthesis of the aminoacid

Having laid out the synthetic plans and provided the necessary background, we will now describe the synthetic endeavors embarked upon in the course of this research. As stated previously, the first goal was the synthesis of a material corresponding to aminoacid **155** (Scheme **22**). Our initial retrosynthetic analysis of **155** was imagined to involve diastereoselective amination (this could occur under Evans azidation conditions[71] or through a Gennari-Evans-Vederas hydrazination[72]) of the enolate of **209**. It was surmised that the enolate of this material would exist as chelate **208**, wherein only the *Re* face of the nucleophile is readily accessible. Reaction with a suitable electrophilic amination agent should thus produce the desired (D)-aminoacid.

The requisite **209** could arise through diastereoselective cyclization of aminoester **210**. The selective formation of an *all cis* pyrrolidine product in a related reaction is documented in the work of Bonjoch.[73] In turn, substance **210** appeared to be readily available from pyroglutamol derivative **211**, which could be advanced to **210** *via* nucleophilic addition of a suitable two-carbon segment to the pyrrolidine carbonyl, followed by appropriate manipulations.

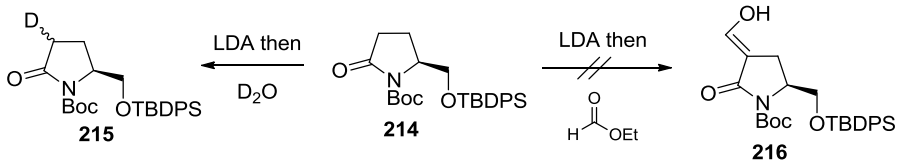
Finally, substrate **211** could derive from protected pyroglutamol **212** through Claisen-type condensation and facially selective hydrogenation of the resultant. The latter step was anticipated to take place selectively from the face of the molecule *anti* to the bulky CH_2OP side chain.[74] Such a stereochemical outcome would produce a material possessing a 3-position configuration that correlates with that at C4 of **2** and cognate natural products, but is opposite that required for the C10 stereocenter of **7**. However, it seemed likely that, based on



Scheme 33. Initial retrosynthetic analysis of **155**

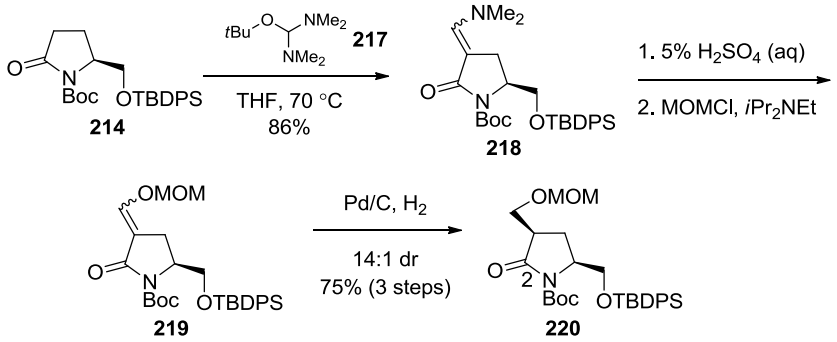
Danishefsky's synthesis of **35**, C10 *epi*-quinocarcin might be isomerized to the correct diastereomer,[22] rendering the above stereochemical issue essentially immaterial.

To test the foregoing hypotheses, commercially available pyroglutamol **213** was converted into the *N*-Boc, *O*-TBDPS derivative **214** by a literature procedure.[75] Deprotonation of **214** with LDA proceeded uneventfully, as apparent from the efficient incorporation of deuterium upon quenching with D_2O (*cf.* **215** – not fully characterized). However, attempts to induce formylation of the enolate with ethyl formate uniformly returned intractable mixtures. In a like vein, attempts to intercept the desired formyl derivative *in situ* with benzyloxymethyl chloride also failed (Scheme **34**).



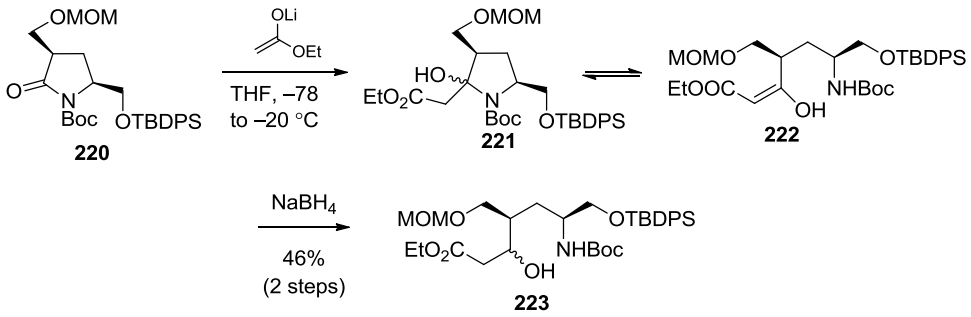
Scheme 34. Reaction of the enolate of **214** with ethyl formate failed

However, a one-carbon unit could be installed at the 3-position of **214** by treating it with Bredereck's reagent **217**,[76] a reaction which finds close analogy in the work of Danishefsky,[77] Weinreb[78] and Terashima.[31] In accord with the latter author, the resulting vinylogous urea could be hydrolyzed without loss of the *N*-*tert*-butoxycarbonyl by sonication of a suspension of **218** in aqueous H_2SO_4, and the emerging enol tautomer of the expected aldehyde was protected as a methoxymethyl (MOM) ether. The resulting **219** (not fully characterized) tended to polymerize upon standing. Accordingly, it was immediately subjected to hydrogenation over Pd/C without extensive purification. This reaction proceeded at atmospheric hydrogen pressure (albeit at high catalyst loading) and with good stereoselectivity, giving a 14:1 mixture in which was desired *cis*-isomer **220** was dominant. This was consonant with our expectations that **219** would be adsorbed onto the catalyst from the face opposite the bulky TBDPS ether.



Scheme 35. Synthesis of **220** from **214**

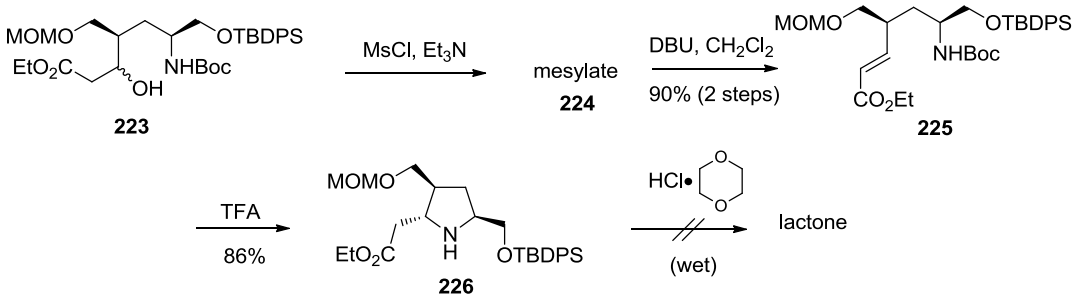
Our next synthetic goal was the two-carbon homologation of **220** at the 2-position. To this end, a Claisen-type condensation was performed. Addition of a solution of **220** to 1.5 equiv. of the lithium enolate of ethyl acetate was found to produce a mixture of enol and hemiaminal isomers **221** and **222** of the addition product (not characterized) (Scheme **36**). Use of additional



Scheme 36. Claisen-type condensation of **220**

base did not improve the yield of the enolate addition, rather leading to material which was more difficult to purify. The crude mixture was reduced with $NaBH_4$ in EtOH, so providing a modest yield of a 1:1 mixture of diastereomers of alcohol **223**, which were not separated.

Alcohols **223**, after mesylation under standard conditions, underwent elimination (DBU in CH_2Cl_2) to provide unsaturated ester **225** in excellent yield (the mesylate **224** was not thoroughly characterized). As expected, the Boc-protected nitrogen showed no proclivity to engage the unsaturated lactone in a 1,4-addition. However, release of the Boc group (TFA) occasioned immediate cyclization to **226**, which emerged as a single diastereomer. Unfortunately, this material was determined to be the undesired 2,5-*trans* isomer, in that it failed to lactonize after removal of the MOM protecting group (4M HCl in wet dioxane). Details of these discoveries are presented in Scheme **37**. A rationale for the formation of **226** invokes reaction from a conformer in which $A^{1,3}$ strain is minimized (*cf*. **227** in Figure **5**).



Scheme 37. Synthesis of **225** and its cyclization to undesired isomer **226**

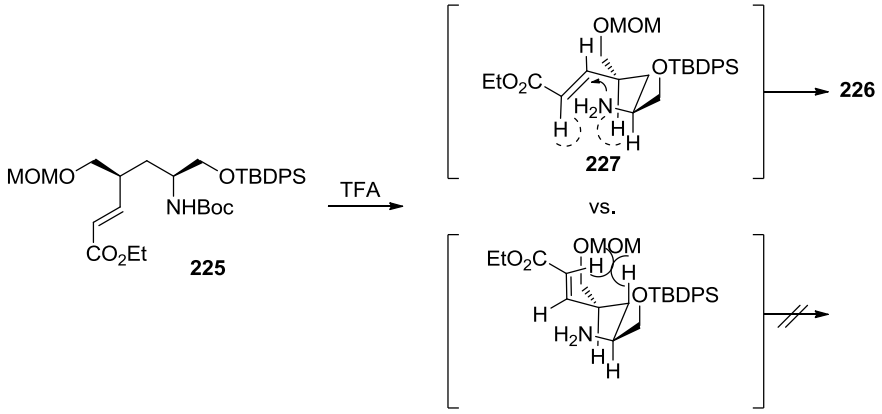
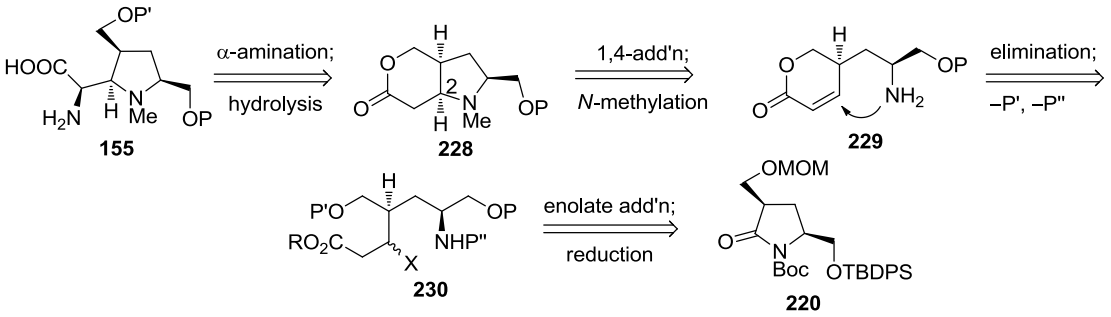


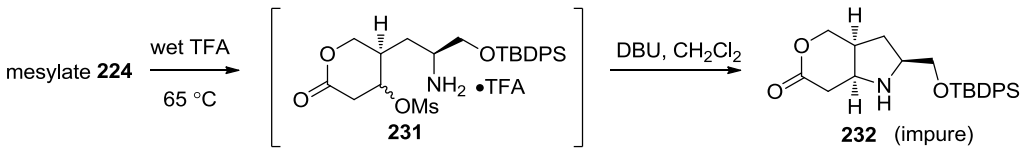
Figure 5. Rationale for the formation of **226** from **225**

The above setback notwithstanding, it appeared that the requisite *all cis* diastereomer could still be obtained from a variant of **225**, in which the carboxylic group and the MOM-protected oxygen are joined to form a lactone (*cf.* **229**, Scheme **38**). The Michael-type cyclization of **229** would now take place in a reliably *syn* mode, giving the desired configuration. Furthermore, a rigid bicyclic system could also provide superior stereocontrol in the subsequent installation of a nitrogen atom adjacent to the lactone carbonyl.



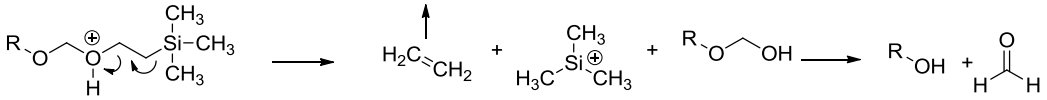
Scheme 38. Alternate retrosynthetic analysis of **155**

In the interest of forming an unsaturated lactone such as **229**, we attempted the MOM-deprotection of **224**, which proved challenging. Under standard aqueous conditions (aq. HCl in THF), loss of the TBDPS protection preceded lactone formation (Scheme **39**). It was soon discovered, however, that treatment with wet TFA in the absence of other solvents gave a compound with characteristic lactone peaks in its proton NMR spectrum, and an accompanying loss of the Boc group. This material, **231**, which was not fully characterized, emerged as a mixture of diastereomers. The TFA deprotection required overnight at rt; however, it was complete in about 1 hour if heated to 65 °C. Lactone **231** could be advanced to bicyclic compound **232** by treatment of the crude reaction mixture with DBU. Although the desired lactone was produced (as verified by later experiments which produced analytically pure material), the yield was low and the resulting material could not be fully purified, rendering the procedure unsatisfactory (Scheme **39**). Clearly, a more acid-labile protecting group was needed.



Scheme 39. Formation of **232** from **224**

It rapidly transpired that silyl ethers were inappropriate blocking groups, because analogs of **219** in which an SiR_3 unit replaced the MOM segment resisted heterogeneous hydrogenation. We thus opted for a 2-(trimethylsilyl)ethoxymethyl (SEM) protecting group in place of MOM. While the original report by Lipshutz suggests the use of TBAF in hot THF or HMPA to effect deprotection,[79] the use of basic conditions with our substrate might lead to problems, given that TBDPS deprotection is expected to proceed very rapidly under the suggested conditions, and that β-elimination of the alcohol derivative (i.e., X in **230**) could occur prior to lactonization. However, the literature indicates that such a protecting group may be cleaved easily under acidic conditions, even in the absence of a strong nucleophile (see Scheme **40**).[80] The TMS cation released during the reaction might be trapped by trifluoroacetate, adventitious water, or the alcohol freed during the course of the deprotection. In the latter case, a standard aqueous workup is expected to reveal the unprotected OH.



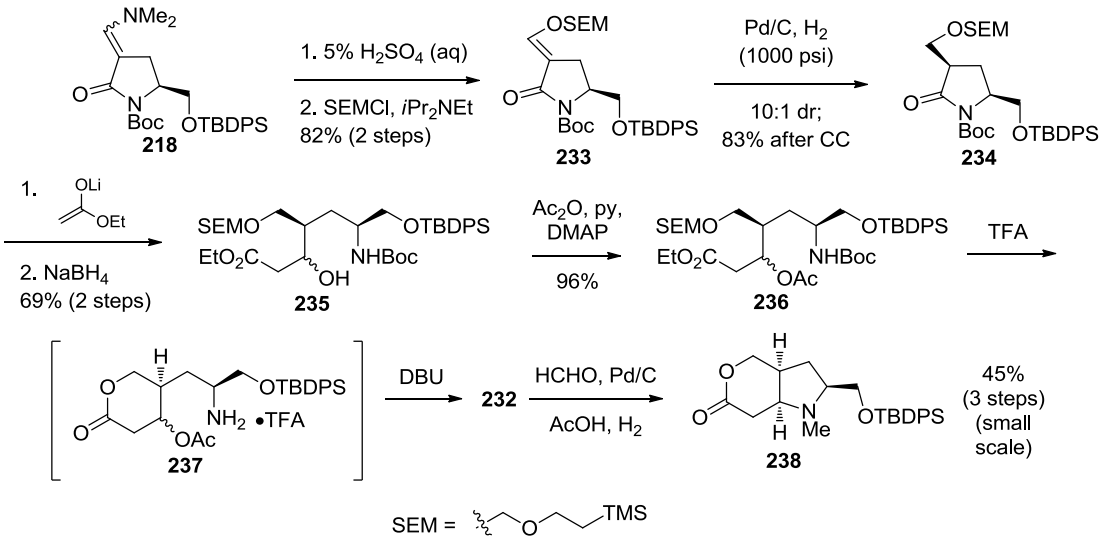
Scheme 40. Hypothesized mechanism of the decomposition of an SEM ether by protic acid

The synthesis of an SEM analog of **220**, compound **234** (Scheme **41**), was achieved by the same route employed earlier to make **220**. However, the catalytic hydrogenation of **233** was slow compared to the MOM congener, requiring about 12 hours at 1000 psi. Fortunately, the resulting product **234** was still a 10:1 mixture of separable diastereomers, just as in the case of **220**. This correct diasteromer (major product) was reacted with the lithium enolate of ethyl acetate, and the crude product reduced with $NaBH_4$ to give a diastereomeric mixture of alcohols **235** in satisfactory yield. The acetate **236** was formed in high yield using standard conditions.

The acid lability of SEM ether **236** was then tested by dissolution in neat TFA. It was found that, with no additional water in the reaction mixture, SEM deprotection (and accompanying removal of Boc) occurred within one hour at room temperature. The reaction was performed by simply stirring **236** in TFA at rt before evaporation under reduced pressure, resulting in smooth conversion into lactone **232.** Acetate elimination and cyclization also proceeded smoothly in the presence of DBU, and after reductive methylation (HCHO (aq), Pd/C, H_2, AcOH), the desired **238** could be obtained in 58% overall yield after chromatography (Scheme **41**; **238** is compatible with column chromatography in the free base form).

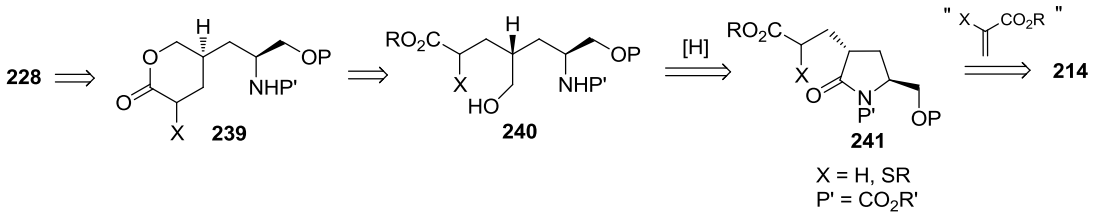
It should be noted that the above procedure, which had performed well on scales up to 100 mg of **236**, became problematic upon scale-up. In certain batches, acid treatment of **236** caused formation of byproducts of an unknown nature, and these were inseparable from the desired **232**. That these side products were not desilylated forms of **232** is clear from the fact that they could not be converted back to known materials by treatment with TBDPSCl and imidazole.

In these cases, all standard purification methods that were examined (alumina or silica gel chromatography with various solvent mixtures, crystallization) failed to surrender pure **232**. Attempts to elaborate the crude, impure lactone into **238** was of no avail, in that the impurities coeluted with the target amine as well. Interestingly, it was found that small amounts of pure **232** could be secured by C18 reverse-phase chromatography, but this method was entirely inappropriate for the preparation of significant quantities of lactone.



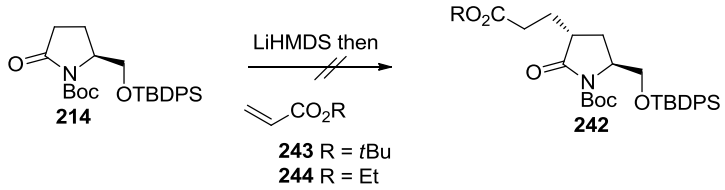
Scheme 41. Synthesis of **238** using the SEM protecting group

The route to **238** was clearly unsatisfactory: it lacked conciseness; the high-pressure hydrogenation limited material throughput; the use of expensive or cumbersome to prepare Bredereck's reagent was less than ideal; and, most importantly, TFA deprotection did not provide a reliable procedure upon scale-up, even when SEM protection was used. In search of a more reliable, flexible, concise, and scalable synthesis, we imagined an approach that entails the Michael addition of the enolate of a protected pyroglutamol to an acrylate (Scheme **42**). This addition should, in theory, occur preferentially from the less-hindered face of the molecule, giving the desired stereoisomer. Selective reduction of the imide to an alcohol and attack of this alcohol on the ester would give a lactone such as **239**. Introduction of unsaturation and cyclization would return the desired **228**. An acrylate ester in which group X were, e.g., PhS, would permit an especially direct access to **228** upon the oxidation to the sulfoxide and thermal elimination.



Scheme 42. Retrosynthesis of lactone **228** by Michael addition

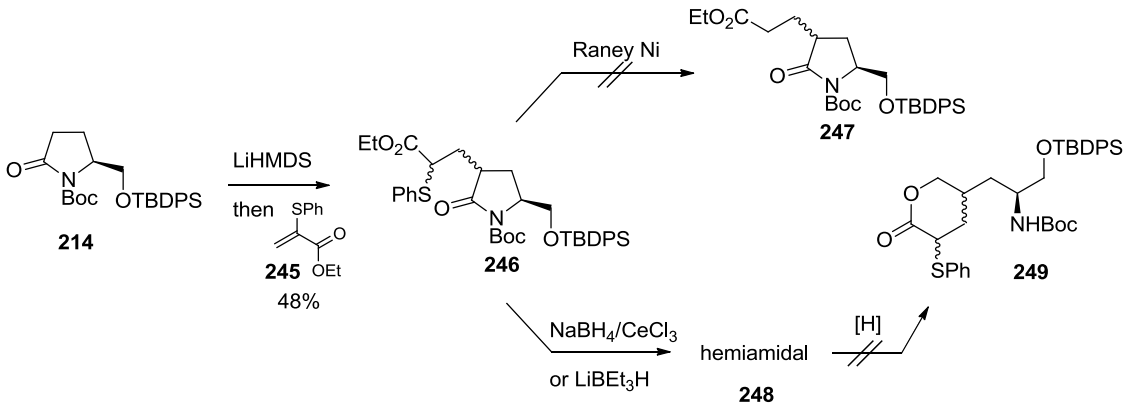
The enolate of **214** appeared to be a rather poor Michael donor toward ethyl or *tert*-butyl acrylate. Attempted reactions of this sort returned largely starting **214**, along with small amounts of what appeared to be a dimer (possibly resulting from the attack of enolate upon an intact molecule of **214**), which was a persistent side product whenever we formed the enolate of **214**. Similar difficulties have been recorded in the literature.[81] Attempted Michael addition of the enolate of **214** to *tert*-butyl acrylate **243** or ethyl acrylate **244** in the presence of BF_3•OEt_2 afforded an intractable mixture of numerous products (Scheme **43**).



Scheme 43. The enolate of **214** did not add to **243** or **244**

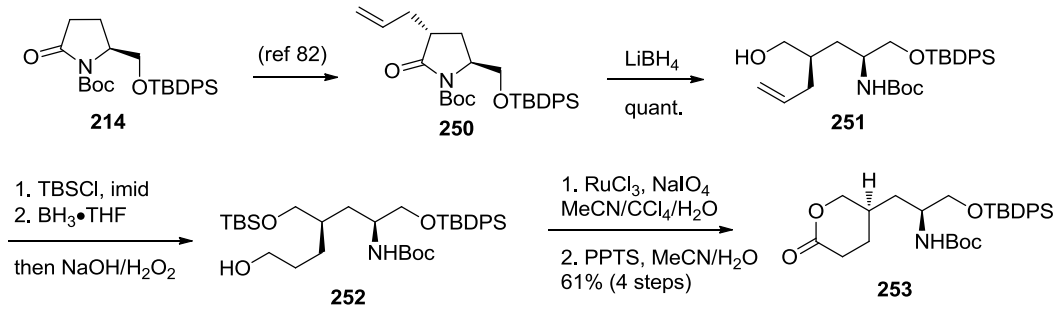
A more electrophilic Michael acceptor, in the form of ethyl 2-(phenylthio)acrylate, **245**,[82] combined with the enolate of **214** to give a mixture of diastereomeric products in modest yield. It was not clear at this juncture whether such products were epimeric solely (or largely) at the PhS-bearing carbon, or also at the ring carbon; i.e., whether the addition had occurred with acceptable or poor facial selectivity with respect to the enolate. To address the issue of facial selectivity,

product **246** was subjected to Raney Ni desulfurization in an attempt to reach **247**. However, this treatment caused decomposition. Endeavoring then to elaborate **246** to **248** (not fully characterized), the imide was partially reduced using $NaBH_4/CeCl_3$ or $LiBEt_3H$. The resultant hemiamidal **248** could be advanced no further: attempted formation of lactone **249** with gentle reductants [$NaBH(OAc)_3$] gave no reaction, while more active reducing agents ($LiBH_4$; $NaBH_4$ alone or in the presence of Et_3N) promoted overreduction. Finally, reduction of **246** with Dibal was not regioselective. Details of these finding are found in Scheme **44**.



Scheme 44. Attempted Michael-addition route to **228**

A surrogate for the Michael addition was available in the reaction of **214** with allyl bromide.[83] Contrary to other enolate reactions of pyroglutamols, this process is high-yielding; additionally, it results exclusively in the *trans*- product. We found that known allylation product **250** could easily be advanced through the several steps necessary to create key lactone **253**. To this end, **250** was reduced with $LiBH_4$ to give **251** in quantitative yield. The emerging alcohol was protected as a TBS ether before being subjected to hydroboration with BH_3•THF, followed by oxidative cleavage under standard aqueous conditions to give **252**. This new primary alcohol

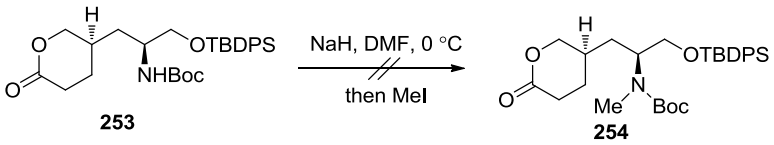


Scheme 45. Advancement of allylation product **250** to lactone **253**

was oxidized to the carboxylic acid with RuO_4 in biphasic medium,[84] which was superior to oxidation with TEMPO/DIB, provided that the reaction time was carefully controlled. The crude acid was freed of TBS protection using PPTS to provide lactone **253** (Scheme **45**).

A brief digression is appropriate at this stage. Experiment indicated that the *N*-methylation of **253**, e.g. with NaH/MeI in DMF, was troublesome, affording mixtures of various products (Scheme **46**). Given these results, it was decided to postpone *N*-methylation until after the selenation / selenoxide elimination[85] sequence. The latter would thus be carried out with the dianion of **253**.

Treatment of **253** with two equivalents of LDA at −78 °C in THF, trapping with PhSeBr and oxidation with H_2O_2, afforded conjugated lactone **255** in only 18-25% yield, signaling that optimization of the reaction conditions would be necessary. After considerable experimentation, it was found that a 54-58% yield of **255** could be realized if a solution of the enolate of **253** was

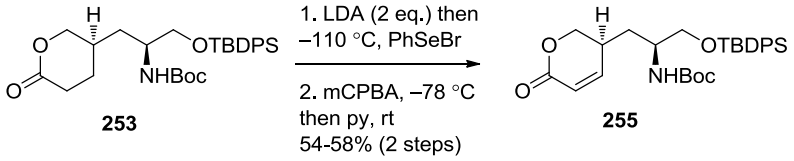


Scheme 46. *N*-methylation of **253** was unsuccessful

cooled to about −110 °C (LN2/EtOH bath) before rapid addition of a pre-cooled (−78 °C) solution of PhSeBr, and prompt quenching (5 minutes) with acetic acid. In particular, a very pure product could be obtained when good stirring was maintained and a slight deficit of PhSeBr was used, as indicated by the disappearance of red-brown color of the reagent immediately following its addition to the enolate. The subsequent oxidation of the selenide was best performed with mCPBA, as oxidation with H_2O_2 led to small amounts of byproducts. The results of these experiments, giving isolated yields following column chromatography, are presented in Table **2**.

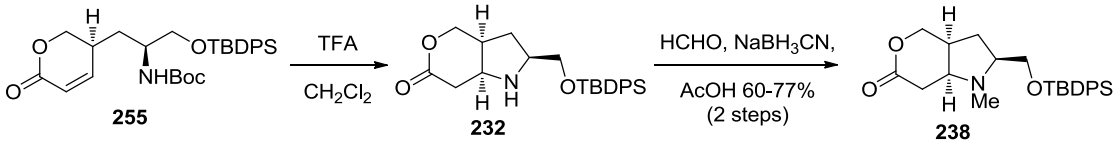
Entry	Enolate temp.	Equiv PhSeBr	PhSeBr soln. T	Rate of add'n	Rxn time (min)	Oxidation reagent	Scale	Yield
1	−78 °C	1.1	rt	dropwise	10	H_2O_2	36 mg	21%
2	−78 °C	2.8	rt	dropwise	10	H_2O_2	74 mg	18%
3	−78 °C	2.0	rt	dropwise	10	H_2O_2	61 mg	25%
4	−78 °C	2.0	rt	dropwise	5	mCPBA	54 mg	30%
5	−78 °C	1.3	rt	dropwise	5	mCPBA	52 mg	28%
6	−110 °C	1.5	rt	dropwise	10	mCPBA	79 mg	33%
7	−110 °C	2.0	rt	dropwise	5	mCPBA	55 mg	63%
8	−110 °C	2.0	rt	dropwise	10	mCPBA	745 mg	18%
9	−110 °C	2.0	0 °C	at once	5	mCPBA	1.5 g	52%
10	−110 °C	2.0	−78 °C	at once	5	mCPBA	2.6 g	54%
11	−110 °C	2.0	−78 °C	at once	5	mCPBA	4.1 g	58%

Table 2. Optimization of conditions for the selenation / oxidation of **253**



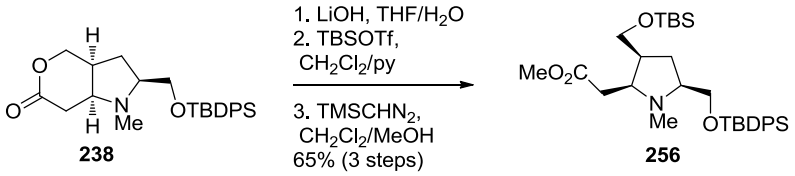
Scheme 47. Synthesis of **255** from **253**

The *N*-deprotection / cyclization of unsaturated lactone **255** with TFA proved quite sluggish, requiring overnight stirring. When off-the-shelf TFA was used, a significant loss of TBDPS was observed, therefore 1% TFAA (v/v, vs. TFA) was included to remove adventitious water. This made for a much cleaner reaction. Commercial 4N HCl•dioxane proved to be inferior to TFA as a Boc-releasing agent, in that it promoted the formation of numerous byproducts (TLC). Methylation of the amine then occurred under standard reductive amination conditions (HCHO, $NaBH_3CN$, AcOH, MeCN) to give **238** (Scheme **48**) in 60-77% overall yield from **255**.



Scheme 48. Synthesis of **238** from **255**

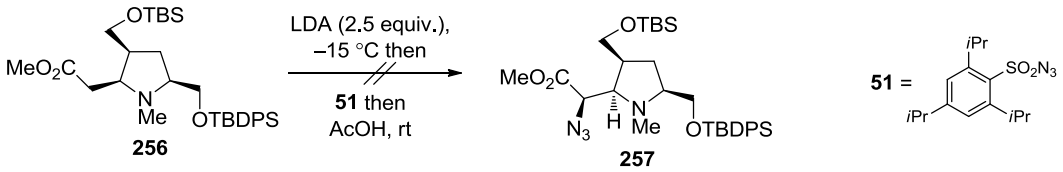
With a reliable gram-scale route to **238** available, we sought to create a suitable trisubstituted pyrrolidine precursor for nitrogen addition in accordance with Scheme **33**. This was accomplished in a straightforward manner. To wit, lactone **238** was hydrolyzed under standard conditions (LiOH, THF/H_2O, rt), and the reaction mixture evaporated to give the putative lithium carboxylate. This crude material was then protected at the alcohol by treatment with TBSOTf in CH_2Cl_2/pyridine. Finally, esterification was performed with $TMSCHN_2$ in CH_2Cl_2/MeOH, to give **256** in 65% yield over three steps (Scheme **49**).



Scheme 49. Synthesis of **256** in 3 steps from **238**

Ester **256** resisted deprotonation upon exposure to 1.1 equiv. of LDA at −78 °C for several hours (no deuterium incorporation upon quenching with D_2O), but enolate formation was achieved by reaction with 2.5 equivalents of LDA at −15 °C for 3.5 hours. The enolate, however, failed to undergo azidation upon reaction with **51**. Even after extended reaction times, such attempts returned largely recovered **256** (Scheme **50**). Some decomposition of the substrate was also evident from the ^{1}H NMR spectra of crude reaction mixtures.

Given the difficulties in functionalization of the enolate of **256**, we opted to attempt to functionalize lactone **238** directly. Initially, it was thought that reduction of an oxime might give the correct stereochemistry of the emerging aminolactone, but treatment of **238** with isoamyl nitrite and *t*-BuOK resulted in decomposition (Scheme **51**).

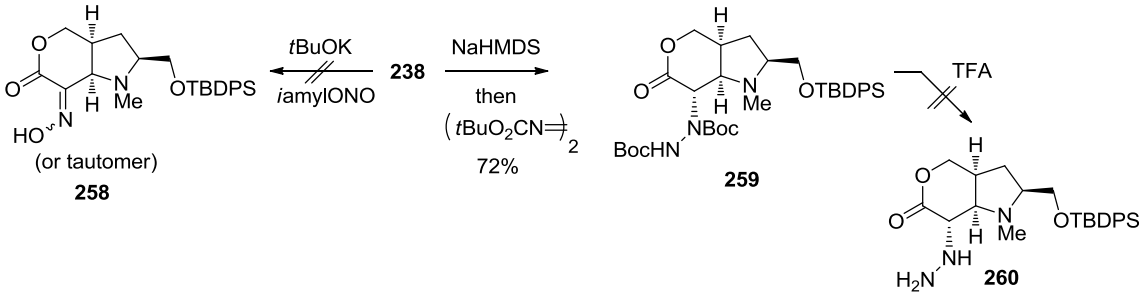


Scheme 50. The enolate of **256** failed to react with sulfonyl azide **51**

Contrary to **256**, lactone **238** did undergo enolization upon reaction with 1.1 equiv. of LDA at −78 °C for 2.5 hours. A Gennari-Evans-Vederas[71] hydrazination of the enolate produced the expected **259** in about 10% yield. Interestingly, the yield of **259** soared to 72% when the sodium enolate (from **238** and NaHMDS) was employed in the reaction. It also became apparent

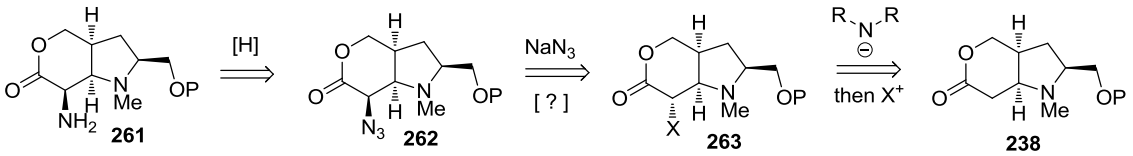
that deprotonation of the lactone with NaHMDS at −78 °C was complete within 1 h (D_2O quenching). We suspect that the lack of reactivity of the lithium enolate was due to the formation of kinetically stable Li aggregates. Rather than complicating the experimental protocol by the addition of cosolvents (DMPU; hazardous HMPA,[86] etc.) or LiCl,[86] we opted to employ the Na enolate of **238** in all subsequent reactions.

Not unexpectedly, compound **259** produced broad NMR spectra as a consequence of slow internal rotation of the tertiary Boc segment. No variable-temperature spectra were



Scheme 51. Initial attempts to react the enolate of **238** with electrophilic nitrogen sources

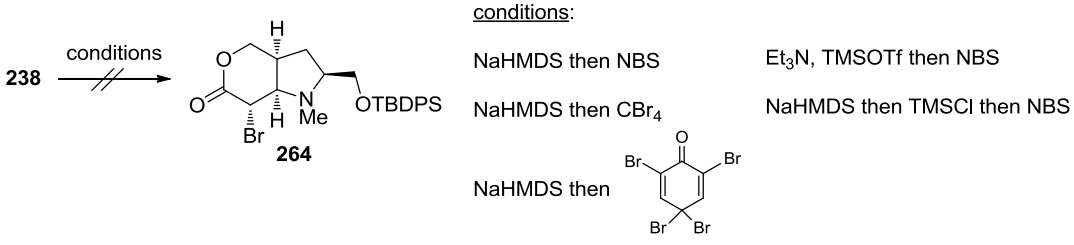
obtained, because it became obvious that **259** was a synthetic dead end. Indeed, numerous attempts to deprotect this hydrazine under acidic conditions gave only intractable mixtures (Scheme **51**). However, rt ^{1}H NMR indicated it to be essentially diastereomerically pure. In light of subsequent results (*vide infra*), it may be surmised that the azodicarboxylate reagent had indeed reacted from the convex face to the enolate; i.e., an L-α-hydrazinoacid had been created, instead of the required D-type material. Given the difficulty of further advancement of **259**, no definite stereochemical proof was sought.



Scheme 52. Possible method for the introduction of an amine to lactone **238**

An alternate route to introduce the desired amine would involve the S_N2 displacement of a suitably situated halide by azide ion (see Scheme **52**). Since an electrophile would be expected to approach from the convex face of the molecule, this sequence might produce the desired diastereomer after inversion of configuration during the subsequent S_N2 reaction.

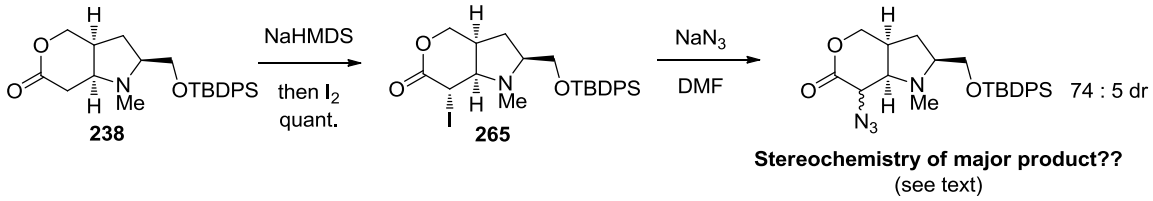
In pursuit of this plan, the sodium enolate of **238** was quenched with NBS. Though the reaction consistently gave a small amount of the desired bromide (not thoroughly characterized), the yield was too low to be synthetically useful. The enolate failed altogether to react with 2,4,4,6-tetrabromo-2,5-cyclohexadienone or carbon tetrabromide. Alternative α-bromination methods proved unsatisfactory, including treatment of **238** with TMSOTf and Et_3N followed by NBS, or quenching of the sodium enolate with TMSCl followed by in-situ reaction with NBS (Scheme **53**).



Scheme 53. Attempts to brominate **238** were unsatisfactory

We were gratified to find that the reaction of the sodium enolate of **238** with I_2 proceeded very cleanly, in high yield, and nearly instantaneously. In fact, the enolate solution could be titrated with a THF solution of I_2 until the persistence of the brown iodine color, giving a quantitative yield of **265** as a single diastereomer. The incoming electrophile was presumed to have approached from the convex face of the molecule, corresponding to the enolate *Si*- face, resulting in the configuration depicted in Scheme **54**.

Iodide **265** darkened upon standing; therefore, it was immediately subjected to an S_N2 reaction with azide ion (suspension of NaN_3 in DMF). The starting material was consumed rapidly, and the ^1H NMR spectra of the crude reaction mixture indicated the presence of predominantly a single isomer of the expected azide. During a larger-scale run of the substitution reaction, a second, more-polar product was observed to form. Mass spectrometry revealed this material to have the same mass as the initial product. We inferred that the new material must



Scheme 54. Synthesis of iodide **265** and its reaction with sodium azide

have been an epimer of the original. The two isomeric azides were readily separable by silica gel chromatography, given their widely differing polarities (R_f 0.43 for the original product, and 0.20 for the new one in 25/75 EtOAc/Hexanes). This permitted a thorough stereochemical investigation, which led to the assignment of their relative configurations as indicated in Figure **6** (indicated yields from reaction of **265** with sodium azide) on account of the following observations.

An MM+ study revealed that the least energetic conformations of the two diastereomeric azides are as illustrated in Figure **6**. The calculated dihedral angle between the protons rendered in blue in the α-isomer **268** (θ = 180 °C) and in the β-isomer **269** (θ = 0 °C) translate into a similar vicinal coupling constant. Indeed, assuming an approximate Karplus relationship[87] of the type

$$J = 8.5 \cos^2 \theta - 0.28 \quad (0 \leq \theta \leq 90)$$

$$J = 9.5 \cos^2 \theta - 0.28 \quad (90 \leq \theta \leq 180)$$

one may anticipate a difference of ca. 1 Hz between the two coupling constants, rendering a stereochemical assignment on such a basis rather untrustworthy. In fact, the measured *J* values for the protons in question were 6.3 Hz for **266** and 5.1 Hz for **267** in $CDCl_3$. Fortunately, a 1D NOE study furnished reliable stereochemical evidence in the form of strong dipolar couplings between H_x and the *N*-methyl H's, as well as H_x and the bridging lactone H, for the major isomer (see Figure **6**). In the minor (desired) isomer, the only notable NOE interaction was between H_y

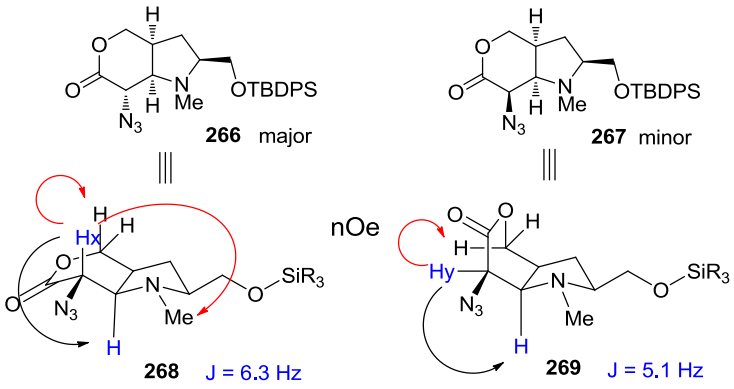
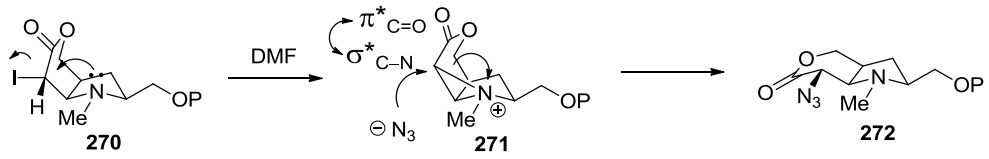


Figure 6. Scalar and dipolar couplings observed in the NOE spectra of **266** and **267**

and the bridging lactone H. Thus it was ascertained that the major product of substitution was in fact **266,** having the α-configuration at the azide-bearing carbon.

These findings demonstrated that the substitution reaction had occurred with *retention* of configuration, giving the undesired **266**. Such an outcome would result from a double inversion of configuration. One possible mechanism for this process envisions the intermediacy of aziridinium ion **271**[88] (Scheme **55**). Selective azide attack at the carbon atom adjacent to the carbonyl system (instead of, e.g., at the Me group) may be rationalized by invoking a lowering of the LUMO at this position as a consequence of mixing of the C-N σ* with the C=O π* orbitals. Elongation of the highlighted C-N bond as a result of strain[89] would contribute to LUMO lowering, further promoting regioselectivity in the observed sense. However, it must be stressed that mechanistic studies have not been performed at the present time. Alternate double inversion mechanisms, proceeding, e.g., through intermediate displacement by iodide released in the course of the reaction, cannot be eliminated from possibility.



Scheme 55. Hypothesized mechanisms for the formation of **266** from **265**

It was tempting to speculate about the at the origin of the minor, desired, isomer **267**. Although a true S_N2 reaction could certainly have been competing with the two-step substitution process, it was also possible that epimerization might be occurring in the course of the reaction, through reversible deprotonation of the azido lactone and reprotonation of the enolate from the

convex face of the molecule. In consideration of this latter possibility, **266** was treated with DBU in CH_2Cl_2 and the reaction allowed to reach equilibrium. The result was a 1 : 2 mixture of **267** to **266**. When the epimerization was attempted in MeCN, it was our pleasure to find that **267** was the major isomer in a ratio of 1.2 : 1 (based on isolated yield). When powerful polar aprotic solvents such as DMF and DMSO were used in the epimerization, a similar product ratio to that observed in MeCN was noted in each case (^{1}H NMR), but partial decomposition was apparent (

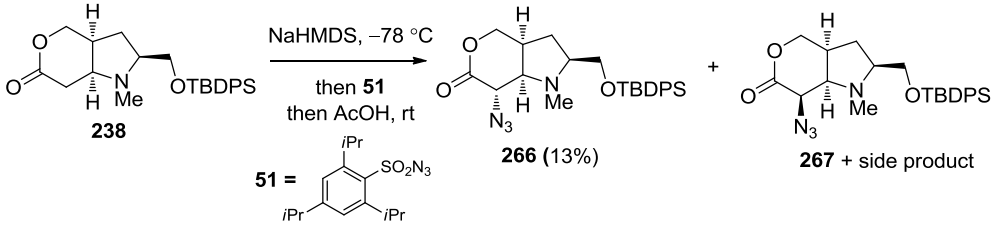
Table 3). An attempt to achieve higher conversion of **266** to **267**, through complete enolate formation followed by kinetic trapping, also resulted in decomposition. The strong solvent dependence of the equilibration was consistent with the observation that **267** is significantly more polar than **266**; therefore, it should accumulate to a greater extent in a more polar solvent.

Entry	Solvent	Ratio **267** : **266**
1	CH_2Cl_2	1 : 2
2	MeCN	1.2 : 1
3	DMF	~1.2 : 1
4	1:1 MeCN : DMSO	~1.2 : 1

Table 3. Product ratios in the epimerization of **266** to **267** in various solvents

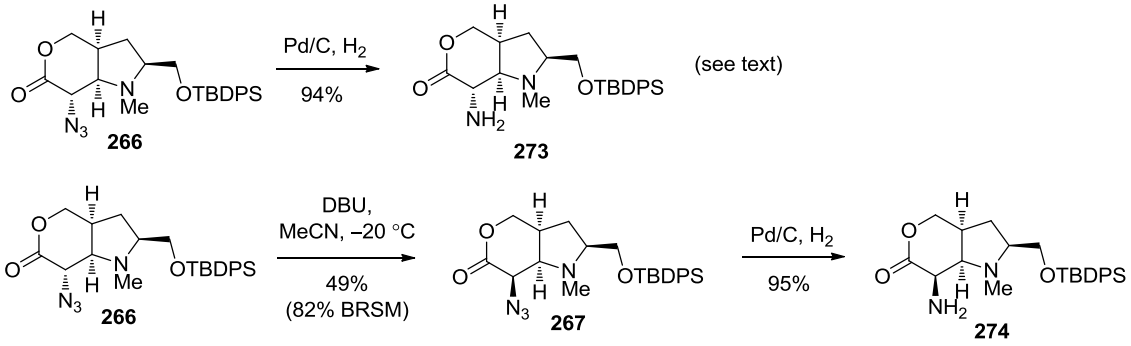
Given the successful isomerization of azide **266**, it is clear that a successful direct azidation of lactone **238** would save one or two synthetic steps. Unfortunately, the sodium enolate of **238**, when reacted with 2,4,6-triisopropylbenzenesulfonyl azide **51** followed by acetic acid, gave a mixture of products (Scheme **56**). Although a small amount of each azide isomer, i.e. **266** and **267**, could be identified in the reaction mixture, a third product was also present. Though we suspected this to be the product of diazo transfer (see Evans[28]) a method for its

separation from **267** was not immediately available. Given the difficulty of purification and the fact that the yield of the desired materials seemed quite low, the azidation by nucleophilic displacement of iodide (see Scheme **54**) was deemed the method of choice.



Scheme 56. Direct azidation of the sodium enolate of **238** was unsatisfactory

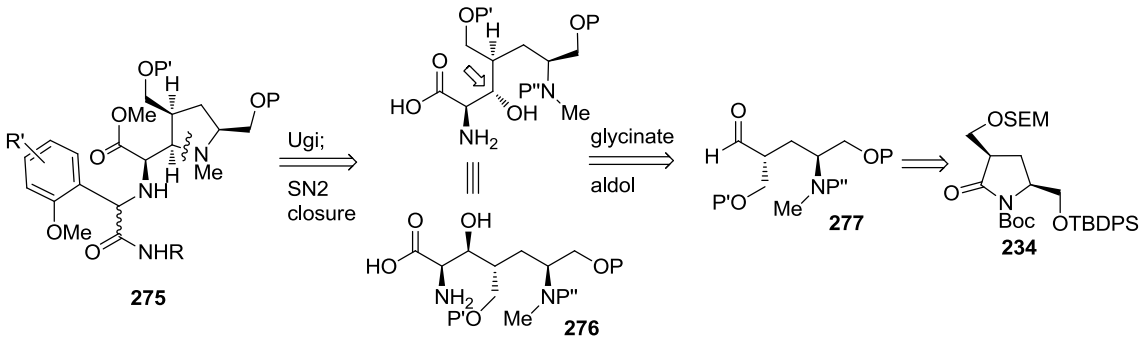
Reduction of azides **266** and **267** to their respective amines could be accomplished by hydrogenation (Pd/C) (Scheme **57**). Unfortunately, both reactions encountered occasional difficulty; the reduction of azide **266** in particular was capricious. For reasons that remain unclear, some batches of **266** reacted cleanly, while others were rapidly converted into a



Scheme 57. Advancement of **266** to amines **273** and **274**

multitude of undesired products. Such a variability cannot be attributed to the Pd catalyst, in that in all cases the latter was drawn from the same jar. At this time, one can only speculate about the source of the problem. Reduction of the azide using PPh_3 was even less satisfactory.

Throughout the project, we considered alternate synthetic schemes. Interesting possibilities for the synthesis of amino acid **155** arise from hypothetical S_N2 closure to form its pyrrolidine ring. Given a fixed configuration of the secondary alcohol (indicated by an arrow in Scheme **58**) e.g., in **276**, its activation in the presence of the free pyroglutamol-derived amine would lead to stereospecific closure of the five-membered ring, resulting in the necessary stereochemistry. An additional factor which made this route attractive was the possibility of performing a subsequent Ugi reaction on a less-hindered, linear form of the amino acid.



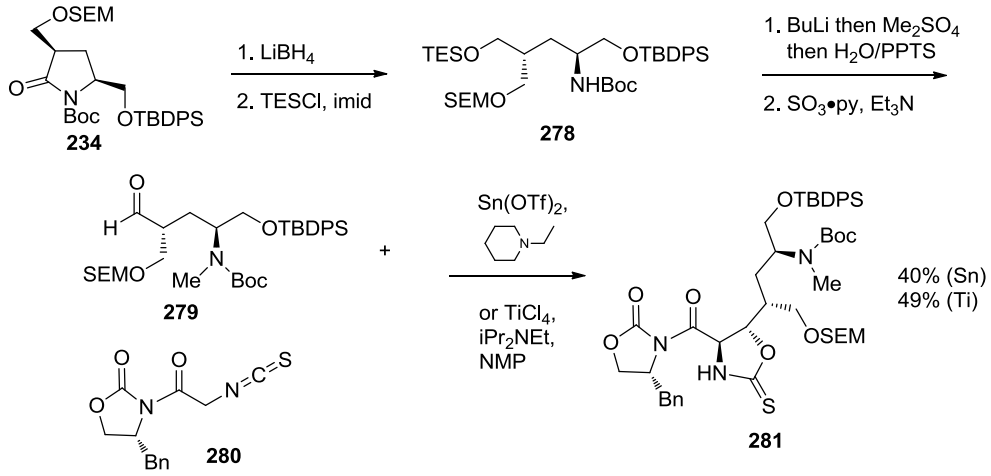
Scheme 58. Alternate retrosynthesis *via* glycinate aldol

One method to create the desired precursor would be a glycinate aldol proceeding with *syn* stereochemistry. Evans himself demonstrated that such a process is possible by protection of the gycine nitrogen as an isothiocyanate.[90] Such a derivative, functionalized with an appropriate chiral auxiliary, would add to aldehyde **277** to give **276**. The necessary glycine derivative is embodied in known imide **280.**[90] Aldehyde **277**, it seemed, could be readily prepared from pyroglutamol derivative **234**, a material of which we were in possession.

To this end, **234** was reduced with $LiBH_4$, and protected as the TES ether to give protected triol **278**. This material was *N*-methylated by deprotonation using BuLi and subsequent trapping with Me_2SO_4. The TES ether could be removed in the same pot after PPTS/water

treatment. The free alcohol was oxidized to the aldehyde under Parikh-Doering conditions[91] to give aldehyde **279**. Yields were not determined for this sequence.

Under catalysis by $Sn(OTf)_2$/*N*-ethylpiperidine[92] or $TiCl_4$/*i*Pr_2NEt/NMP,[93] **279** reacted with **280** to give the glycinate aldol product **281** in fair yield as seen in Scheme **59**. Upon initial inspection of the ^1H NMR, this material appeared to be a 1:1 mixture of diastereomers. A lack of selectivity in this seemingly-reliable variant of the aldol reaction has been observed by Zhu.[94] However, it was later discovered by variable temperature (VT) NMR (DMSO-*d6*, 80 °C) that the alleged diastereomers were in fact rotamers, and that the compound was a single isomer. Time constraints have permitted no further work on this route.

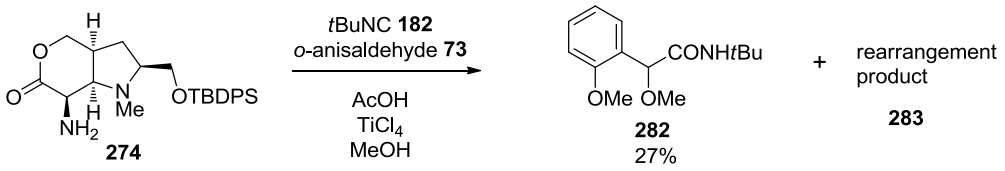


Scheme 59. Synthesis and glycinate aldol reaction of aldehyde **279**

2.2 Ugi reactions of complex aminoacids

It will be recalled that the Ti(IV)-promoted Ugi reaction devised in our group entailed the use of free aminoacids. This implied that lactones **273** and **274** would have to be hydrolytically cleaved to their corresponding aminoacids. On the other hand, the possibility that a successful Ugi condensation could be achieved with the aminolactones themselves was intriguing.

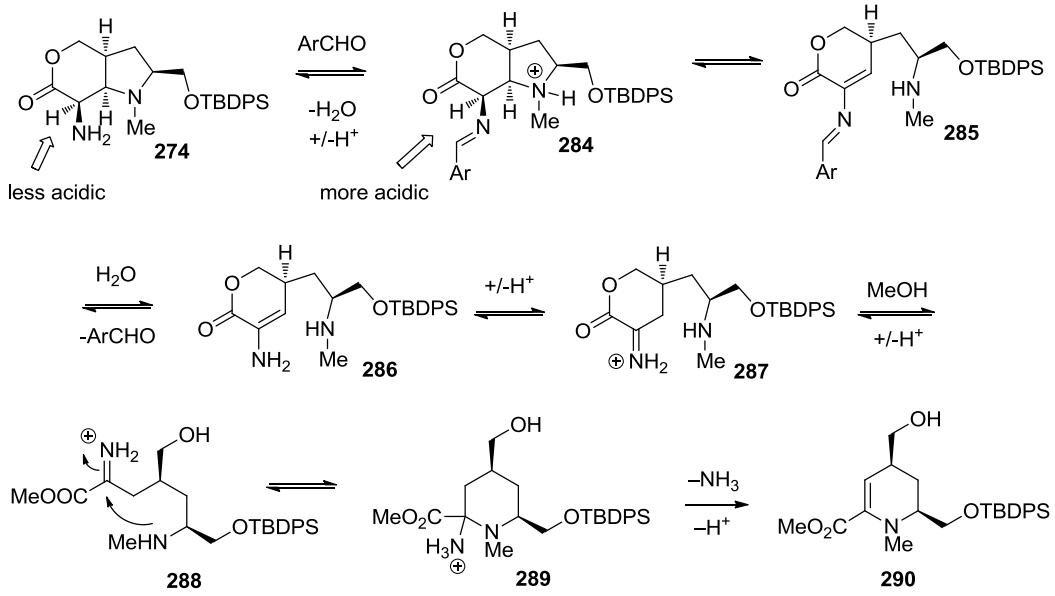
An interesting development unfolded when **274** was submitted to Ugi (U-4CR; acetic acid as the acid component) conditions. Instead of the expected Ugi condensation product, two compounds were isolated. One was the Passerini adduct **282**, and the other was a rearranged material with a characteristic ^{1}H NMR signal at 5.90 ppm (Scheme **60**). This product displayed



Scheme 60. Unexpected rearrangement in the attempted Ugi reaction of **274**

an M/Z of 453, which indicated that a nitrogen atom had been lost relative to the starting aminolactone. Mechanistic considerations and a preliminary COSY NMR study led to the conclusion that the unexpected product must be tetrahydropyridine **290** (Scheme **61**; not fully characterized). Some attempts were made to optimize the rearrangement of **274**. To our disbelief, changes to the reaction conditions, in particular omission of the aldehyde, inhibited the production of **283**. Treatment of **274** with HCl in methanol in the absence of an aldehyde also failed to provoke the rearrangement. On the basis of these observations, we believe that **290** could form through the mechanism depicted in Scheme **61**. Preliminary condensation of the

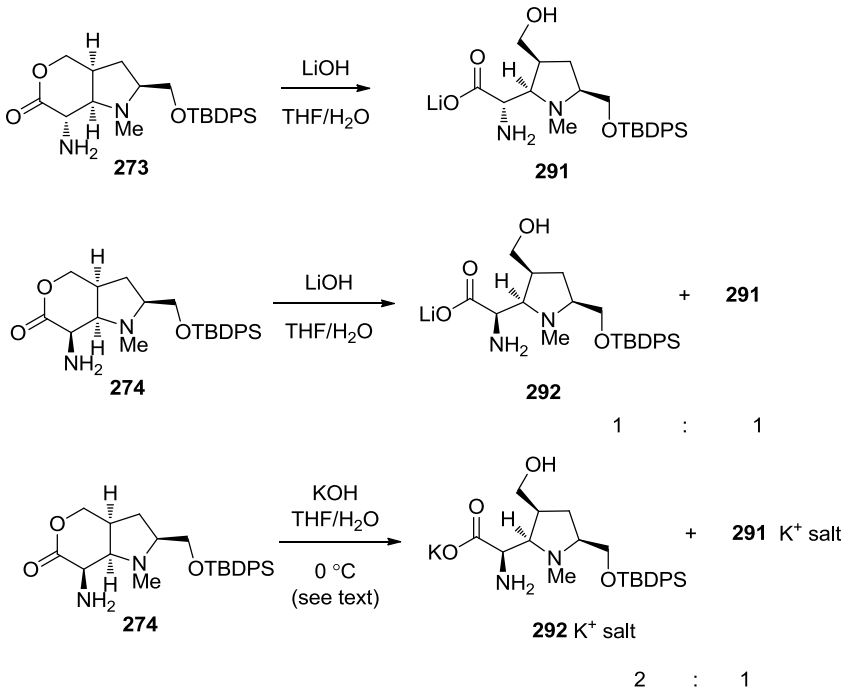
aminolactone with the aldehyde would give **284**. Previous investigations[95] indicate that coordination of the acetic acid additive to Ti(IV) produces a species with enhanced proton acidity, which might catalyze β-elimination of the pyrrolidine nitrogen (i.e., **284** to **285**) thanks also to the enhanced mobility of the carbonyl α-proton in imine **284**. This might explain why the aldehyde is required. Protonation of the enamine functionality in **286** leads to cation **287,** wherein the C=O group displays an unusually high degree of electrophilicity. Methanolysis could then occur, and the resultant **288** would cyclize to give **290**.



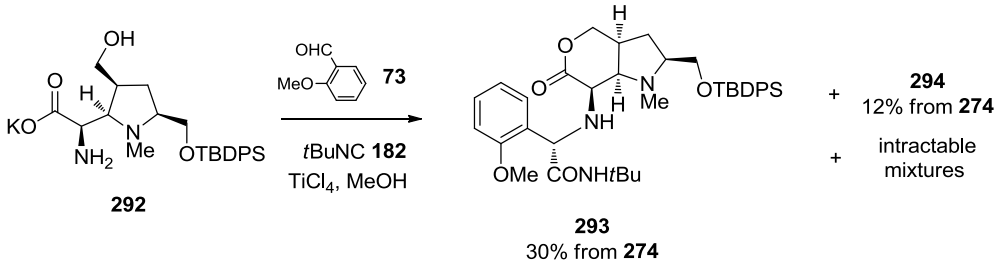
Scheme 61. Possible mechanism for the rearrangement of **274**

Our attention thus refocused on the conduct of an Ugi condensation with the free aminoacid form of **273**/**274**, which materials were available by lactone hydrolysis. While the undesired diastereomer **273** could be hydrolyzed cleanly and rapidly to carboxylate **291** (not fully characterized) under basic conditions (LiOH, THF/H_2O, rt), a major obstacle was encountered when a similar reaction was attempted using **274**. This process resulted in the

formation of a 1:1 mixture of the desired **292** plus **291**, signaling that epimerization of the substrate had occurred during the reaction. Over time we tested various methods of hydrolysis, and became quite distressed to discover that this epimerization could not be completely avoided. A number of standard conditions were examined ($MgBr_2$•OEt_2 in MeOH, K_2CO_3 in MeOH, LiOOH, MeN(OMe)MgCl), along with some unusual ones (heating in NaOAc (aq), treatment with $Yb(OTf)_3$ (aq), Bu_4NOH with and without metal ions). Ultimately, it was found that saponification with KOH in THF/H_2O at 0 °C gave carboxylate **292** (not fully characterized) as the dominant component of a 2:1 (^{1}H NMR) mixture of products (Scheme **62**). Attempted retrieval of the free acid forms of **291**-**292** by protonation of the carboxylate (TFA) triggered an immediate re-closure of the lactone. Subsequent Ugi reactions were thus carried out with salts **291** and **292,** because we had already determined that lactones are incompetent substrates.



Scheme 62. Hydrolysis of lactones **273** and **274**



Scheme 63. Ugi reaction of **292**

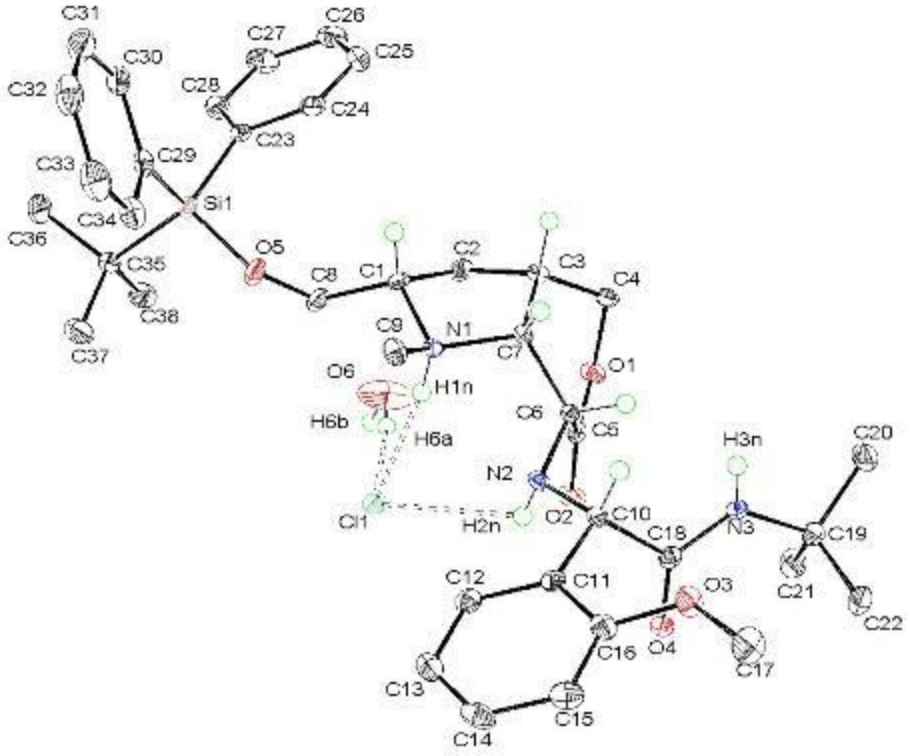
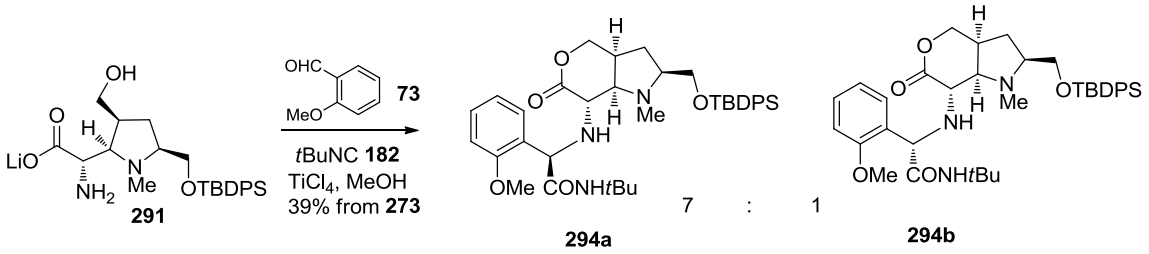


Figure 7. Solid-state structure of **293**

The reaction of the mixture of **292** and its epimer **291** with *o*-anisaldehyde **73** and *tert*-butylisocyanide **182** under our documented conditions was quite sluggish. This difficulty could be alleviated by the use of additional $TiCl_4$ (50 mol%; used for all subsequent reactions), which led to the isolation of a mixture of lactones **293** (major) and **294** (minor), obviously arising from **292** and **291**, respectively (Scheme **62**), and not from the corresponding lactones (*cf.* Scheme

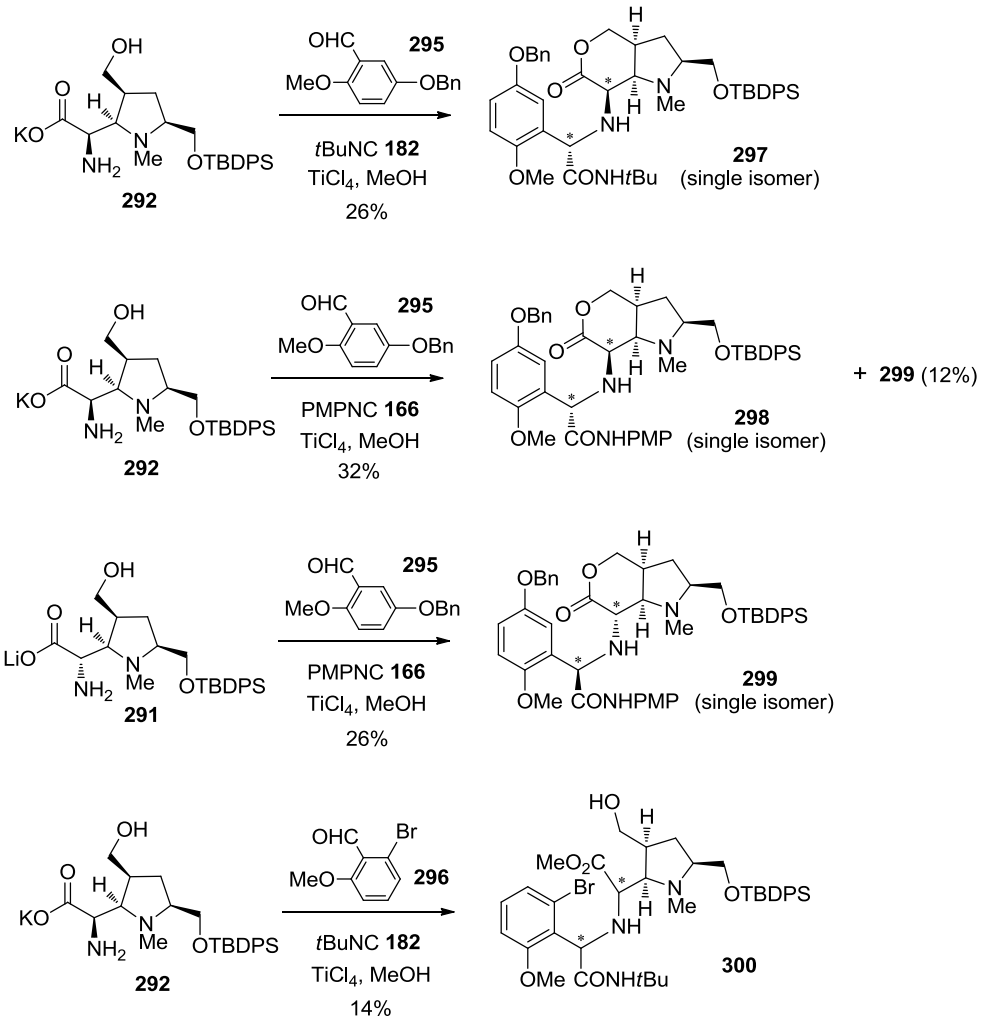
60). The major product, the more polar of the two, was obtained as a single diastereomer (NMR). Whereas in the free base form the substance was a thick gum, the corresponding hydrochloride eventually crystallized, permitting a structural elucidation by X-ray analysis. An ORTREP representation of **293** is found in Figure **7**. It is recognized that while this material arose from reaction of the D-amino acid **292**, the stereocenter produced by the Ugi reaction had the L-configuration. This is opposite to what was anticipated based on our previous work. A rationale for this will be presented below (*vide infra*).

The reaction of stereochemically homogeneous **291** with **73** and **182** in the presence of 50 mol% $TiCl_4$ furnished an inseparable 7:1 mixture of stereoisomeric lactones, which on the basis of the foregoing result we assign as diastereomers **294a** (major) and **294b** (minor; Scheme **64**). We stress that a conclusive stereochemical elucidation would require an X-ray crystal structure. Unfortunately, we were unable to obtain crystals of either the free base (thick oil) or the HCl salt of **294**.



Scheme 64. Ugi reaction of **291** and presumed configuration of the products

The Ugi reaction, though not high-yielding, appears to be fairly general. Several Ugi products could be isolated from the reactions of **291** and **292** with either **182** or *p*-methoxyphenylisocyanide **166** and 2-methoxy-5-benzyloxybenzaldehyde **295** or 2-bromo-6-



Scheme 65. Ugi products arising from reaction of **291** and **292**

methoxybenzaldehyde **296**. Interestingly, each Ugi product emerged as the lactone, with the exception of **300**, which was recovered as the methyl ester.

A rigorous stereochemical assignment of these products (starred centers) is only possible by X-ray crystallography. We do not possess such crystallographic data at the present time. Consequently, the (tentative) configurations shown in Scheme **65** were assigned on the basis—first of all—of the results obtained with D-aminoacid **292** (*ul*-selectivity). As far as the configuration of the C=O α-center of the lactone is concerned, a comparison of the ^{1}H NMR

spectra of epimeric pairs **266**/**267** and **273**/**274** with those of Ugi products reveals that the resonances of the lactonic methylene protons are crowded together in materials arising from D-aminoacid **292**, while they are well separated in those ensuing from L-aminoacid **291** (Figure **8**). This aided in the assignment of **297**. Finally, lactones possessing the α-D-configuration are consistently the more polar (smaller R_f value) isomers. In part because **298** is more polar than **299**, it was assigned to the D-aminolactone series.

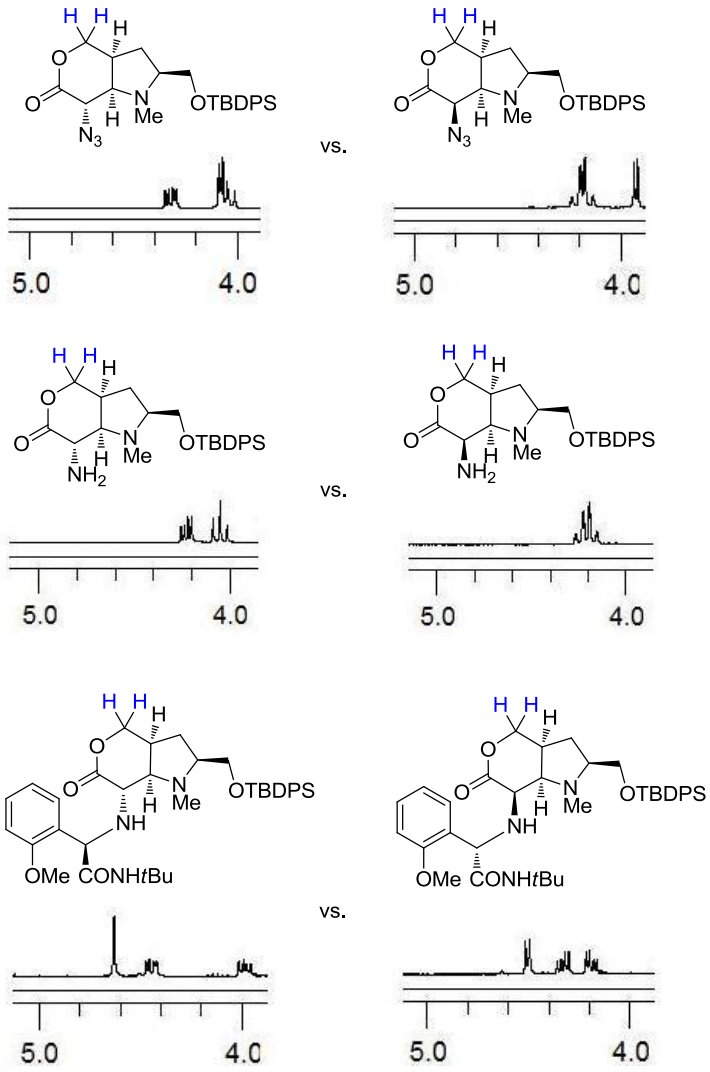
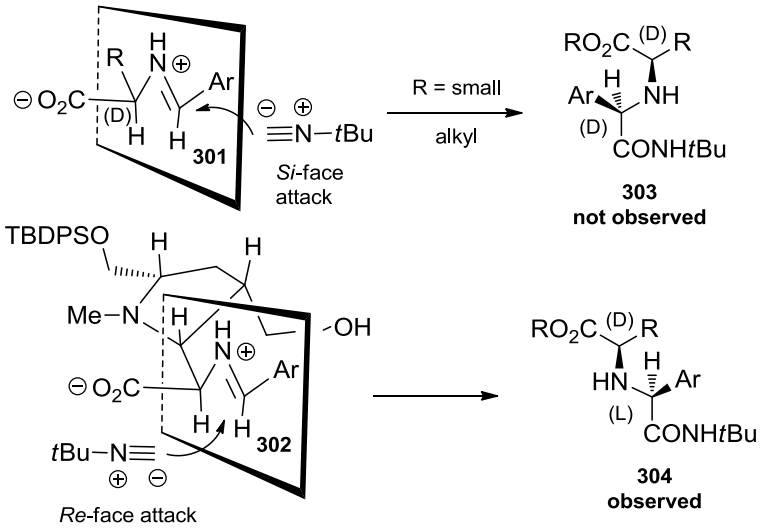


Figure 8. Lactone resonances and Ugi product stereochemistry

A rationale for the reversal of diastereoselectivity observed with aminoacid **292** emerges from an analysis of molecular models of zwitterions **301** and **302** (Scheme **66**). Transposition of the reactivity model of Scheme **32** to the (D)-aminoacid series produces structure **301**. For R = small alkyl, nucleophilic attack from the *Si*-face of the imine would be expected on stereoelectronic grounds (*cf.* Scheme **32** and accompanying discussion). But in the imine derived from **292**, access to the *Si*-face of **302** is blocked by one of the substituents on the pyrrolidine ring. As a result, nucleophilic attack occurs from the *Re*-face of the imine, leading to the observed **304**.



Scheme 66. Rationale for the stereochemical outcome of the Ugi condensation of **292**

An MM+ study of simplified iminium ion **305** (Figure **9**) provided pictorially appealing support for the foregoing. A computer-generated space-filling model of **305** optimized in the MM+ force field reveals that the *Si*-face of the imino linkage is blocked by the methyl group at the pyrrolidine C-4 position. This substituent occupies the same general region of space as the hydroxymethyl group in **302**. Attack of the isocyanide from the *Re*-face is therefore favored.

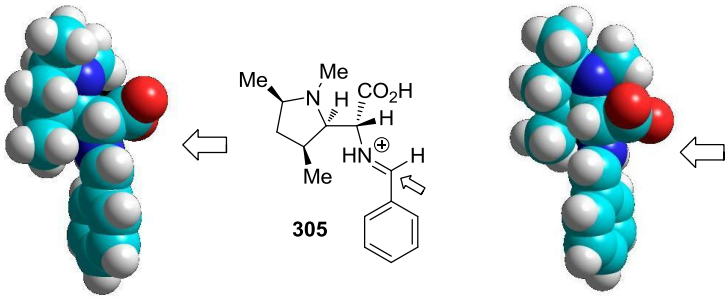
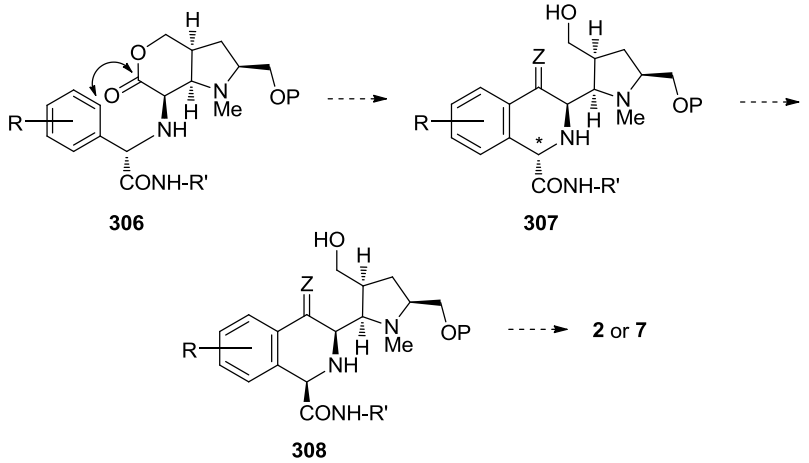


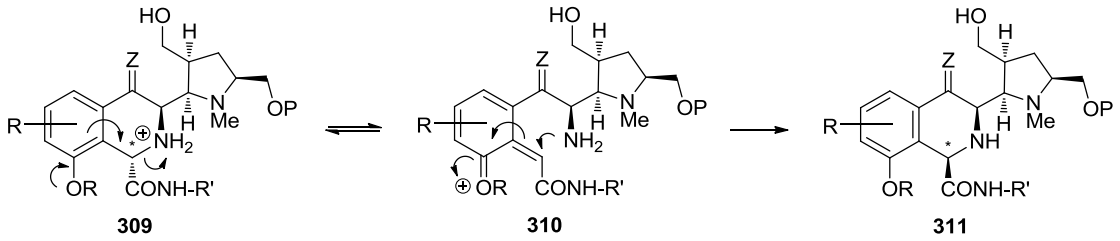
Figure 9. Space-filling model of iminium ion **305**

2.3 Synthetic efforts towards quinocarcin and cyanocycline A

The present section details exploratory work aiming to convert the Ugi lactones described above into more advanced precursors to quinocarcin and cyanocycline. Such an objective requires the formation of the C-C bond indicated in Scheme **67** (double-headed arrow), leading to **306**. The nature of substituent Z in the latter would be determined by the precise mode of ring closure (*vide infra*). In all cases, the configuration of the stereocenter arising from the Ugi reaction of **292** (C10 in Figure **7**; starred center in Scheme **68**) must be inverted to match the configuration of the corresponding carbon in **7** (C5 in Figure **3**) and **2** (C9 in Figure **1**). Previous studies[96] indicate that isoquinolines such as **307** tend to epimerize to the desired 1,3-*cis* stereoisomer under equilibrating conditions. Thus, it is likely that the desired isomer is the thermodynamically favorable one, and that epimerization can be readily achieved. Furthermore, equilibration could occur not only through reversible deprotonation of the pendant carbonyl functionality, but also *via* an acid-catalyzed ring opening according to the mechanism of Scheme **68**.

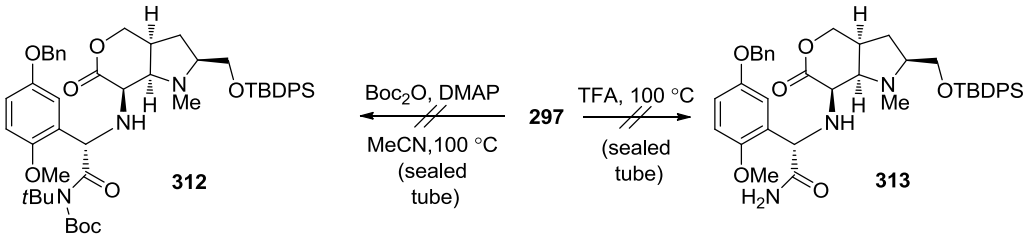


Scheme 67. Ugi condensation product ring closure and epimerization



Scheme 68. Acid-catalyzed epimerization of **309**

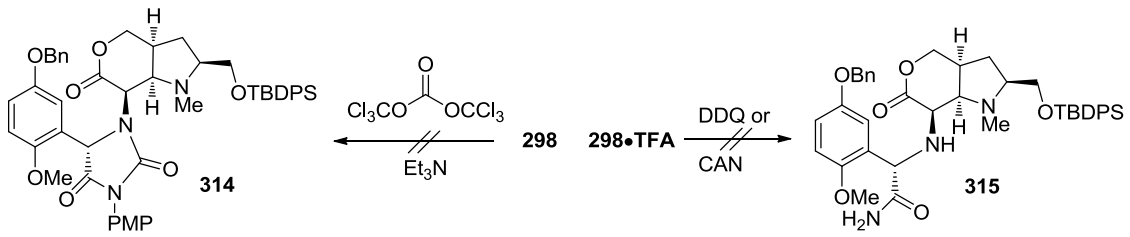
An ancillary issue that was briefly explored at this juncture focused on the removal of the *tert*-butyl amide in order to suppress possible side reactions. A plausible solution might be to activate the secondary amide with, e.g., a Boc group prior to hydrolysis or alcoholysis, or to release the *t*-Bu group under acidic conditions (Scheme **69**). However, treatment of compound **297** with Boc_2O and DMAP in MeCN at 100°C (sealed tube) for 12 h returned only starting material, indicating that neither the amide nor the amine were reactive enough to undergo acylation with Boc anhydride. In a like fashion, heating of **297** in neat TFA at 100°C (sealed tube) returned largely the starting material (some decomposition was evident, though).



Scheme 69. Attempts to cleave the secondary amide of **297**

The reluctance of the nitrogen atoms of Ugi products to undergo acylation manifested itself anew when **298**, in which a less sterically demanding 4-methoxyphenyl (PMP) replaces the *tert*-butyl group, was treated with an excess of triphosgene in the presence of Et_3N. No reaction

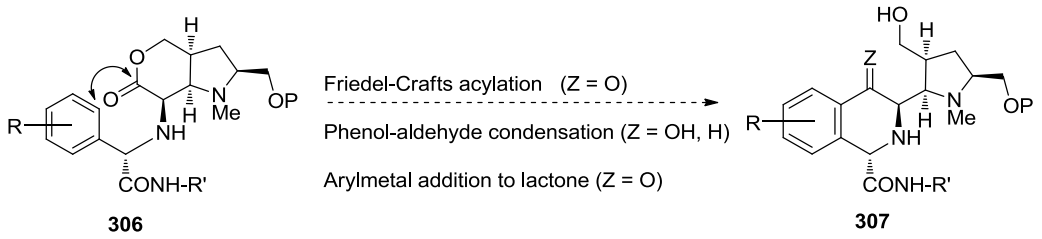
occurred (Scheme **70**). Attempted oxidative cleavage of the PMP group in the TFA salt of **298** (DDQ in MeCN/H_2O) also returned unchanged starting material. Conversely, ceric ammonium nitrate (CAN), under similar conditions, gave an intractable mixture.



Scheme 70. Attempts to cleave the secondary amide of **298**

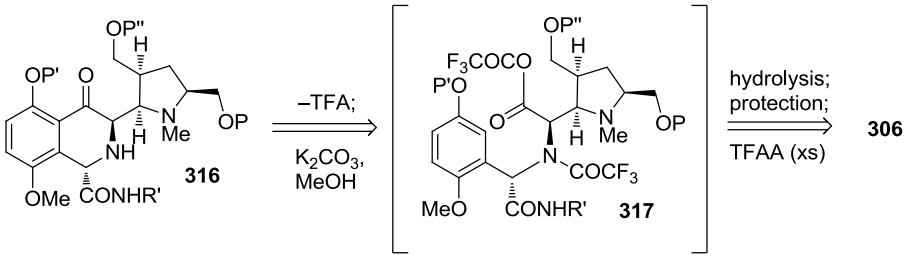
The above observations suggested that the nitrogen functionalities present in the Ugi condensation products are rather sturdy, and that they might well survive unscathed in the course of various reactions aiming to effect the desired cyclization. Accordingly, subsequent studies were carried out with unprotected substrates.

Three modes of cyclization of **306** were considered (Scheme **71**). Acid treatment of **306** could promote a Friedel-Crafts acylation leading to a ketone form of **307**. Second, a suitably positioned phenolic OH might permit the conduct of a phenol-aldehyde condensation, after reduction of the lactone to a lactol. Finally, the same end product would result upon appropriately regioselective metallation of the aromatic unit and nucleophilic attack into the lactone C=O group.



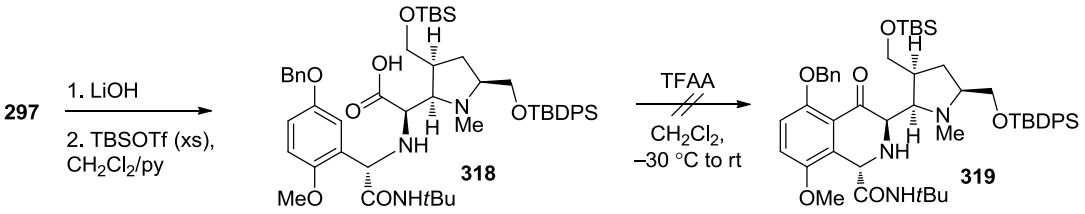
Scheme 71. Possible methods for the closure of quinocarcin's B-ring

One approach to the Friedel-Crafts cyclization of **306** rests on the long-recognized ability of mixed trifluoroacetic anhydrides to acylate aromatic rings.[97] In systems containing a free secondary amine such as **306**, TFAA provides the unique capability of concurrently protecting the amino group and activating the carboxylic functionality. Scheme **72** illustrates the aforementioned hypothesis, exploration of which requires a free carboxylic acid form of **306**.



Scheme 72. Method for the Friedel-Crafts closure of quinocarcin's B-ring

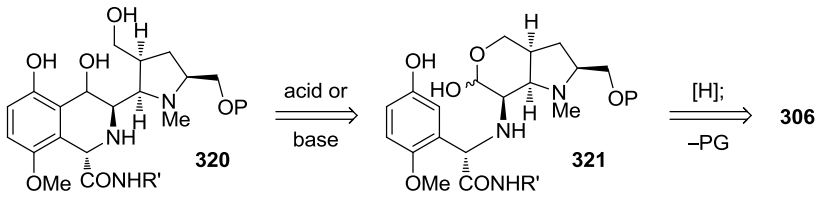
Basic hydrolysis of **297** under standard conditions (LiOH, THF/H_2O, rt) and evaporation of volatiles gave the putative carboxylate salt of **297**. This crude material was then dissolved in CH_2Cl_2/pyridine and treated with TBSOTf (−30 °C to rt). The product thus obtained, carboxylic acid **318** (^{1}H NMR, MS) was not fully characterized, but it was immediately subjected to excess TFAA in cold CH_2Cl_2. A series of color changes ensued, and when the reaction was finally



Scheme 73. Friedel-Crafts acylation of **318** was not successful

worked up, it was found to have occasioned the formation of a complex mixture of products, which could not be identified (Scheme **73**).

The second approach to the cyclization of Scheme **71** would proceed through the attack of a phenol on a tethered aldehyde (possibly masked as the lactol). A reaction of this sort could proceed under acidic or basic conditions. Such cyclization has been demonstrated in related systems, for example, by Fukuyama,[98] and was observed to occur spontaneously in some simpler substrates.[99] A suitable precursor for this cyclization is compound **321**, which could result upon Dibal reduction of **306** (Scheme **74**).

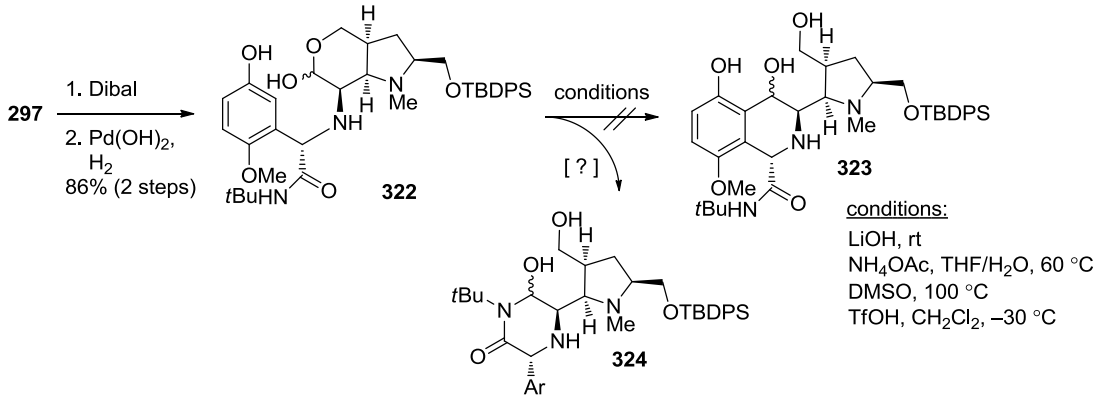


Scheme 74. Closure of quinocarcin's B-ring by the addition of a phenol to an aldehyde

To test this hypothesis, a mixture of diastereomers of lactol **322** was prepared by hemireduction of the lactone moiety of **297** (excess Dibal, CH_2Cl_2, −78 to −30 °C) and subsequent debenzylation (Pearlman's catalyst, 1 atm H_2) (Scheme **75**). Interestingly, hydrogenolysis of the benzyl group occurred smoothly at the stage of the lactol, but it proceeded

in an unsatisfactory manner with lactone **297**. With this substrate, the reaction tended to stall, resulting in incomplete deprotection. The reasons for this remain unclear.

When lactol **322** was subjected to LiOH at rt, a new material was formed, which was not the desired **323**. While the new product remains unidentified, the presence of a single aromatic resonance in its ^{1}H NMR spectrum signifies that no C-C bond formation had occurred at the level of the aromatic nucleus. We speculated that the compound may be hemiamidal **324**, and that reaction with a mild base at higher temperatures might promote reversible ring opening and

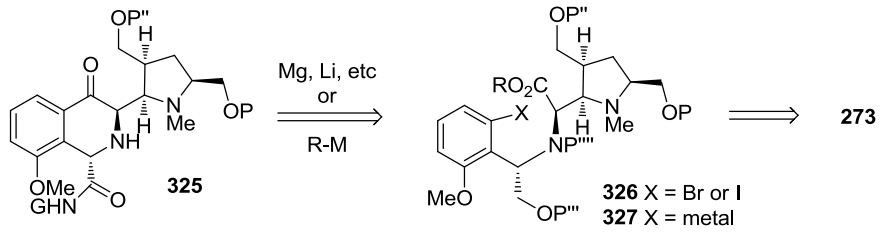


Scheme 75. Synthesis and reaction of lactol **322**

exposure of the free aldehyde, which could then react with the phenol to furnish the requisite **323**. To explore this possibility, **322** was treated with NH_4OAc in hot THF (ammonium acetate, THF/H_2O, 60 °C), and to DMSO at 100 °C. No evidence of the desired cyclization was observed under these conditions. Treatment of **322** with TfOH in cold CH_2Cl_2 gave a precipitate which did not undergo further reaction.

The third mode of cyclization (Scheme **71**) envisioned the intramolecular addition of an aryl organometallic agent to, e.g., the ester carbonyl of **300**. The exploration of this avenue required a prior optimization of the Ugi reaction of 2-halo-6-methoxybenzaldehydes with **292**. It

will be recalled (Scheme **65**) that this transformation afforded **300** in only 14% yield. Due to time constraints, this optimization has not been performed.



Scheme 76. Method for carbanionic closure of quinocarcin's B-ring

3 Conclusion

In the preceding pages, we have demonstrated a robust synthesis of key lactone **238**, and have outlined a number of methods by which it might be advanced to the natural products quinocarcin and cyanocycline A. The elaboration of **238** to **274** allowed examination of a previously-unknown molecular framework with remarkable properties. Furthermore, we have performed the Ugi condensation reaction of an aminoacid in a very challenging context. To our knowledge, this constitutes the first such example in natural product synthesis. We believe the work disclosed herein will prove useful to future research efforts exploring the chemistry of the Ugi reaction, and to chemical synthesis in general.

From the efforts described in the preceding pages, it is clear that the Ugi reaction of α-aminoacids has great potential as a key step in the synthesis of highly functionalized molecules. Due to its high diastereoselectivity, mild reaction conditions, and functional-group tolerance, this transformation warrants further investigation in the context of total synthesis. The diastereoselectivity of this process remains unpredictable.

Our own work towards the total synthesis of quinocarcin and cyanocycline using the Ugi technology has been hampered by numerous obstacles, which have conspired to render the route untenable, given the limited resources available. Ongoing work according to the Nucleophilic addition route of Scheme **22** is sure to meet with more success.

References

[1] Kluepfel, D.; Baker, H. A.; Piattoni, G.; Sehgal, S. N.; Sidorowicz, A.; Singh, K.; Vezina, C. *J. Antibiot.* **1975**, *28*, 497-502.

[2] Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.

[3] Takahashi, K.; Tomita, F. *J. Antibiot.* **1982**, *35*, 771-777.

[4] Zmijewski, M. J.; Goebel, M. *J. Antibiot.* **1982**, *35*, 524-526.

[5] Zaccardi, J.; Alluri, M.; Ashcroft, J.; Bernan, V.; Korshalla, J. D.; Morton, G. O.; Siegel, M.; Tsao, R.; Williams, D. R. *J. Org. Chem.* **1994**, *59*, 4045-4047.

[6] a. Bernan, V. S.; Montenegro D. A.; Korshalla, J. D.; Maiese, W. M.; Steinberg, D. A.; Greenstein, M. *J. Antibiot.* **1994**, *47*, 1417-1424. b. Singh, M. P.; Petersen, P. J.; Jacobus, N. V.; Maiese, W. M.; Greenstein, M.; Steinberg, D. A. *Antimicrob. Agents Chemother.* **1994**, *38*, 1808-1812.

[7] Tomita F.; Takahashi, K.; Shimizu, K-i. *J. Antibiot.* **1983**, *36*, 463-467.

[8] Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, *36*, 468-470.

[9] Hill, G. C.; Wunz, T. P.; Remers, W. A. *J. Comput. Aided Mol. Des.* **1988**, *2*, 91-106.

[10] Fujimoto, K.; Oka, T.; Morimoto, M. *Cancer Res.* **1987**, *47*, 1516-1522.

[11] Plowman, J.; Dykes, D. J.; Narayanan, V. L.; Abbott, B. J.; Saito, H.; Hirata, T.; Grever, M. R. *Cancer Res.* **1995**, *55*, 862-867.

[12] Bunnell, C.; Supko, J.; Eder, J.; Clark, J.; Lynch, T.; Kufe, D.; Shulman, L. *Cancer Chemother. Pharmacol.* **2001**, *48*, 347-355.

[13] Williams, R. M.; Herberich, B. *J. Am. Chem. Soc.* **1998**, *120*, 10272-10273.

[14] Moore, H. W. *Science* **1977**, *197*, 527-532.

[15] Takahashi, K.; Tomita, F.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268-1272.

[16] a.Williams, R. M.; Glinka, T.; Gallegos, R.; Ehrlich, P. P.; Flanagan, M. E.; Coffman, H.; Park, G. *Tetrahedron* **1991**, *47*, 2629-2642. b. Williams, R. M.; Glinka, T.; Flanagan, M. E.; Gallegos, R.; Coffman, H.; Pei, D. *J. Am. Chem. Soc.* **1992**, *114*, 733-740.

[17] Breen, A. P.; Murphy, J. A. *Free Radical Biol. Med.* **1995**, *18*, 1033-1077.

[18] Palaniswamy, V. A.; Gould, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 5651-5652.

[19] Zmijewski, M. J.; Mikolajczak, M.; Viswanatha, V.; Hruby, V. J. *J. Am. Chem. Soc.* **1982**, *104*, 4969-4971.

[20] Zmijewski, M. J. *J. Antibiot.* **1985**, *38*, 819-820.

[21] Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676-2690.

[22] Danishefsky, S. J.; Harrison, P. J.; Webb, R. R.; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421-1423.

[23] Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704-3706.

[24] Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196-5198.

[25] Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243-249.

[26] Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065-4068.

[27] Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742-10753.

[28] Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.

[29] Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240.

[30] Vandewalle, M.; Van, d. E.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035-4043.

[31] a. Saito, S.; Tamura, O.; Kobayashi, Y.; Matsuda, F.; Katoh, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 6193-6208. b. Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima,

S. *Tetrahedron* **1994**, *50*, 6221-6238. c. Katoh, T.; Kirihara, M.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6239-6258. d. Katoh, T.; Kirihara, M.; Yoshino, T.; Tamura, O.; Ikeuchi, F.; Nakatani, K.; Matsuda, F.; Yamada, K.; Gomi, K.; Ashizawa, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 6259-6270.

[32] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828-5835.

[33] Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289-296.

[34] Flanagan, M. E.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 6791-6797.

[35] Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615-2617.

[36] Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796-16797.

[37] Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401-8402.

[38] Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322-3327.

[39] A. Hom, R. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1997**, *62*, 6290-6297. b. Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; John Wiley: New York, 1951; Vol. 6, p 151.

[40] Wu, Y.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148-7152.

[41] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.

[42] Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270-17271.

[43] Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558-1559.

[44] a. Evans, D. A.; Biller, S. A. *Tetrahedron Lett.* **1985**, *26*, 1907-1910. b. Evans, D. A.; Biller, S. A. *Tetrahedron Lett.* **1985**, *26*, 1911-1914. c. Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478-2479.

[45] Fukuyama, T.; Li, L.; Laird, A. A.; Frank, R. K. *J. Am. Chem. Soc.* **1987**, *109*, 1587-1589.

[46] a. Kaniskan, H. Ü.; Garner, P. *J. Am. Chem. Soc.* **2007**, *129*, 15460-15461. b. Garner, P.; Kaniskan, H. Ü.; Keyari, C. M.; Weerasinghe, L. *J. Org. Chem.* **2011**, *76*, 5283-5294.

[47] Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629-646.

[48] Garner, P.; Kaniskan, H. Ü. *Tetrahedron Lett.* **2005**, *46*, 5181-5185.

[49] Ugi, I., Ed. *Isonitrile Chemistry*; Academic: New York, 1971.

[50] Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439-4486.

[51] Irini, A. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324-331.

[52] Mumm, O. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886-893.

[53] Chéron, N.; Ramozzi, R.; Kaïm, L. E.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1361-1366.

[54] Robinson, R. *J. Chem. Soc. , Trans.* **1917**, *111*, 876-899.

[55] a. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126-129. b. Passerini, M.; Ragni, G. *Gazz. Chim. Ital.* **1931**, *61*, 964-969.

[56] a. Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267-268. b. Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 8-21.

[57] Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89.

[58] Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316-321.

[59] Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552-6554.

[60] Takiguchi, S.; Iizuka, T.; Kumakura, Y.; Murasaki, K.; Ban, N.; Higuchi, K.; Kawasaki, T. *J. Org. Chem.* **2010**, *75*, 1126-1131.

[61] Ugi, I.; Rosendahl, F. K. *Justus Liebigs Ann. Chem.* **1963**, *666*, 65-67.

[62] Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355-6366.

[63] Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 173-175.

[64] Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651-652.

[65] Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* **1982**, *21*, 654-660.

[66] Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. K.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109-7112.

[67] Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149-4152.

[68] Zimmer, R.; Ziemer, A.; Gruner, M.; Brudgam, I.; Hartl, H.; Reissig, H.-U. *Synthesis* **2001**, 1649-1655.

[69] Sung, K.; Chen, F.; Chung, M. *Mol. Divers.* **2003**, *6*, 213-221.

[70] Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M. A. *Org. Lett.* **2004**, *6*, 3281-3284.

[71] Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.

[72] Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397-6399.

[73] a. Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem. Eur. J.* **2001**, *7*, 3446-3460. b. Bycroft, B. W.; Chhabra, S. R.; Kellam, B.; Smith, P. *Tetrahedron Lett.* **2003**, *44*, 973-976.

[74] Hernández, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314-323.

[75] Arndt, H.; Welz, R.; Müller, S.; Ziemer, B.; Koert, U. *Chem. Eur. J.* **2004**, *10*, 3945-3962.

[76] Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41-50.

[77] Danishefsky, S.; Berman, E.; Clizbe, L. A.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 4385-4386.

[78] Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1990**, *31*, 2105-2108.

[79] Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343-3346.

[80] Nicolaou, K. C.; Yue, E. W.; la Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; de Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467-494.

[81] a. Konas, D. W.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 8831-8842. b. Baldwin, J. E.; Moloney, M. G.; Bo Shim, S. *Tetrahedron Lett.* **1991**, *32*, 1379-1380.

[82] Leyendecker, F.; Comte, M. *Tetrahedron Lett.* **1982**, *23*, 5031-5034.

[83] Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1881-1884.

[84] Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.

[85] Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137-6139.

[86] Seebach, D. *Angew. Chem. Int. Ed Engl.* **1988**, *27*, 1624-1654.

[87] Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.

[88] Deyrup, J. A. Aziridines. In *Small Ring Heterocycles*; Hassner, A., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 42, Part 1; John Wiley & Sons: New York, NY, 1983; pp 168-177.

[89] Structure of Small and Large Rings. In *Comprhensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Elsevier: London, 1997; Vol. 7, Ch. 5.

[90] Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.

[91] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

[92] Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381-1390.

[93] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.

[94] Zhu, J.; Bouillon, J.; Singh, G. P.; Chastanet, J.; Bengelmans, R. *Tetrahedron Lett.* **1995**, *36*, 7081-7084.

[95] Ciufolini, M. A.; Deaton, M. V.; Zhu, S.; Chen, M. *Tetrahedron* **1997**, *53*, 16299-16312.

[96] Scott, J. D.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2951–2956.

[97] Ferrier, R. J.; Tedder, J. M. *J. Chem. Soc.* **1957**, 1435-1437.

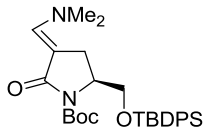
[97] Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095-3097.

[98] Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1992**, *33*, 3919-3922.

Appendix A: Experimental Protocols

Melting points were measured on a Mel-Temp apparatus and are uncorrected. Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at room temperature on a Bruker Avance II 300 instrument. Chemical shifts are reported in parts per million (ppm) on the δ scale using the solvent residual peak as internal standard, and coupling constants *J* are in Hz. Multiplicities are reported as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), "dd" (doublet of doublets), "ddd" (doublet of doublet of doublets), "m" (multiplet), "app" (apparent), and "br" (broad). High-resolution mass spectra (m/z) were obtained in the electrospray ionization (ESI) mode on a Micromass LCT instrument by the UBC Mass Spectrometry laboratory. Single crystal X-ray measurement was performed by Dr. Brian Patrick (UBC X-ray service) on a Bruker X8 APEX II diffractometer, with refinements made using the SHELXTL crystallographic software package of Bruker-AXS. Optical rotation was measured on a Jasco P-2000 polarimeter. IR spectroscopy was performed on a Perkin-Elmer Frontier instrument. THF was freshly distilled from Na/benzophenone ketyl under N_2, and CH_2Cl_2 was freshly distilled from CaH_2 under N_2. Commercial *n*-BuLi was titrated against diphenylacetic acid until a yellow color persisted. Where indicated, "pH 7 phosphate buffer" refers to Fisher Scientific SB109, which was used as received. Flash chromatography was performed on 230-400 mesh silica gel. Analytical TLC was carried out on aluminum-backed Merck silica gel 60 plates with fluorescent indicator, with spots being visualized by I_2 vapor deposition and alkaline aqueous $KMnO_4$. All reactions were performed under dry argon in oven–dried flasks equipped with Teflon™ stirbars. Flasks were fitted with rubber septa for the introduction of substrates, reagents and solvents *via* syringe.

A.1 Preparation of 218



Neat *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent; 3.8 mL, 18.0 mmol) was added to a warm (50 °C) solution of **214** (5.5 g, 12.0 mmol) in THF (4 mL) and the mixture was heated to 70 °C. Stirring at this temperature was continued overnight, during which time the solvent had partially evaporated and the reaction mixture had acquired a red color. The mixture was cooled, diluted with THF while still warm and applied directly to a silica gel column. Flash chromatography (elution with a 30/70 to 60/40 EtOAc/hexanes gradient) gave **218** (5.3 g, 10.3 mmol, 86% yield) as a faintly yellow, viscous oil that solidified on long standing to form pale yellow crystals, m.p. 88-89 °C; $[\alpha]_D^{20}$ –19.2 (c 1.9, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.44 (s, 9H), 3.01 (s, 6H), 3.06-2.90 (m, 2H), 3.69 (dd, *J* = 9.8, 6.4, 1H), 3.77 (dd, *J* = 9.8, 3.3, 1H), 4.13-4.19 (m, 1H), 7.11 (brs, 1H), 7.33-7.46 (m, 6H), 7.57-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 25.4, 26.8, 28.1, 41.9, 55.5, 64.8, 81.4, 93.8, 127.7, 127.7, 129.7, 133.3, 133.6, 135.5, 135.5, 145.9, 150.9, 170.6; IR (film, cm^{-1}): ν 1748, 1621; HRMS: calc. for $C_{29}H_{40}N_2O_4Na^{28}Si$ $[M + Na]^+$ 531.2655; found 531.2648.

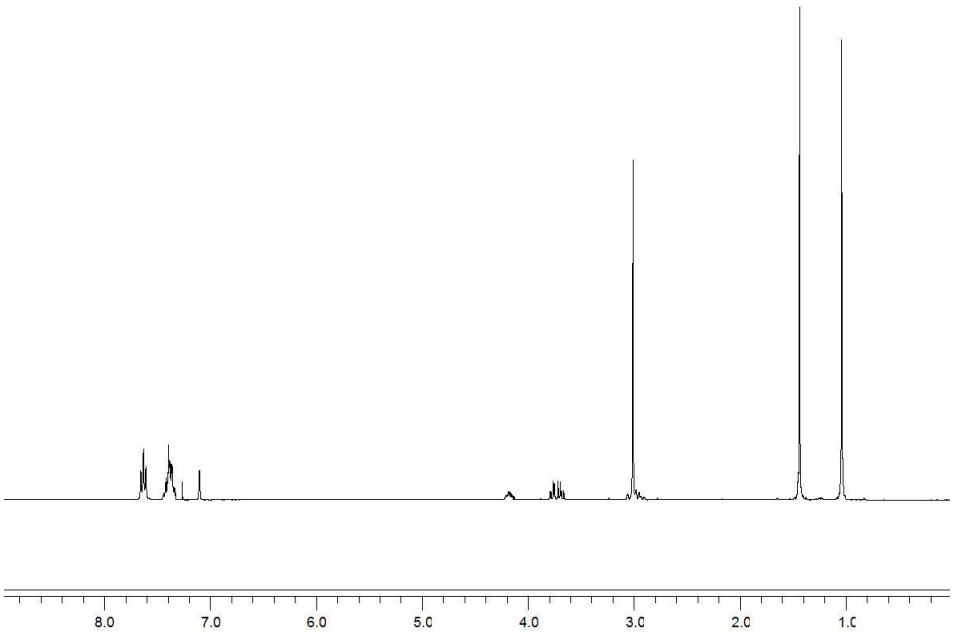


Figure 10. ^{1}H NMR spectrum of **218**

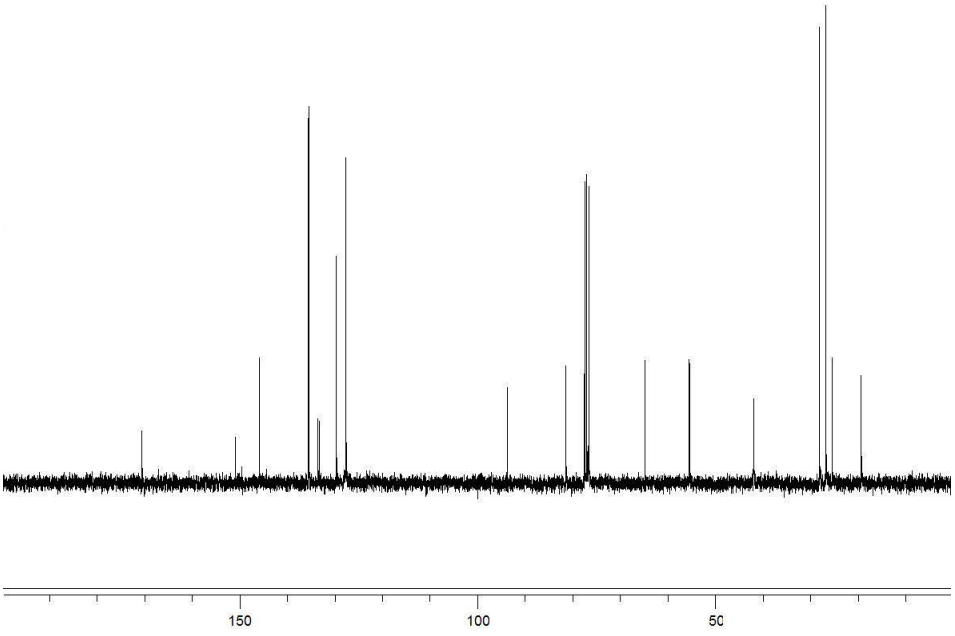
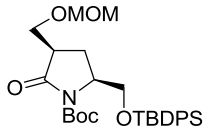


Figure 11. ^{13}C NMR spectrum of **218**

A.2 Preparation of **220**



A solution of **218** (4.3 g, 8.4 mmol) in THF (17 mL) was added to rapidly stirred H_2SO_4 (aq) (78 mL of 5% v/v solution) at rt, and the resulting milky suspension was sonicated for 40 min. Solid $NaHCO_3$ was then added in portions (GAS EVOLUTION) until gas evolution ceased. The residue was partitioned between H_2O and CH_2Cl_2, and the organic extract was dried (Na_2SO_4), filtered, and concentrated under vacuum. To a solution of the residue in CH_2Cl_2 (20 mL) at rt was added diisopropylethylamine (1.0 mL, 12.6 mmol), followed by the dropwise addition of chloromethyl methyl ether (2.2 mL, 12.6 mmol). The reaction was stirred for 1 hour at rt before being diluted with CH_2Cl_2 and poured into sat. NH_4Cl (aq). The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated under vacuum. To a solution of the residue in EtOAc (150 mL) was added Pd/C (10%, 2.0 g) and the reaction vessel was flushed with H_2. Stirring was continued overnight, when the mixture was filtered through Celite and evaporated to give **220** (3.32 g, 6.31 mmol, 75% yield over three steps) as a colorless oil, which was a 14:1 mixture of *cis* (**220**, major) and *trans* diastereomers. $[\alpha]_D^{20}$ –18.1 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H); 1.41 (s, 9H); 2.17-2.40 (m, 2H); 2.77-2.89 (m, 1H); 3.32 (s, 3H); 3.72-3.95 (m, 4H); 4.10-4.21 (m, 1H); 4.54-4.59 (m, 2H); 7.34-7.48 (m, 6H); 7.60-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 23.5, 26.8, 27.9, 43.2, 55.3, 56.9, 64.2, 67.0, 82.9, 96.5, 127.7, 129.8, 133.1, 133.3, 135.5, 135.6, 149.9, 174.3; IR (film, cm^{-1}): ν 1784, 1715; HRMS: calc. for $C_{29}H_{41}NO_6{}^{28}Si$ $[M + Na]^+$ 550.2601; found 550.2598.

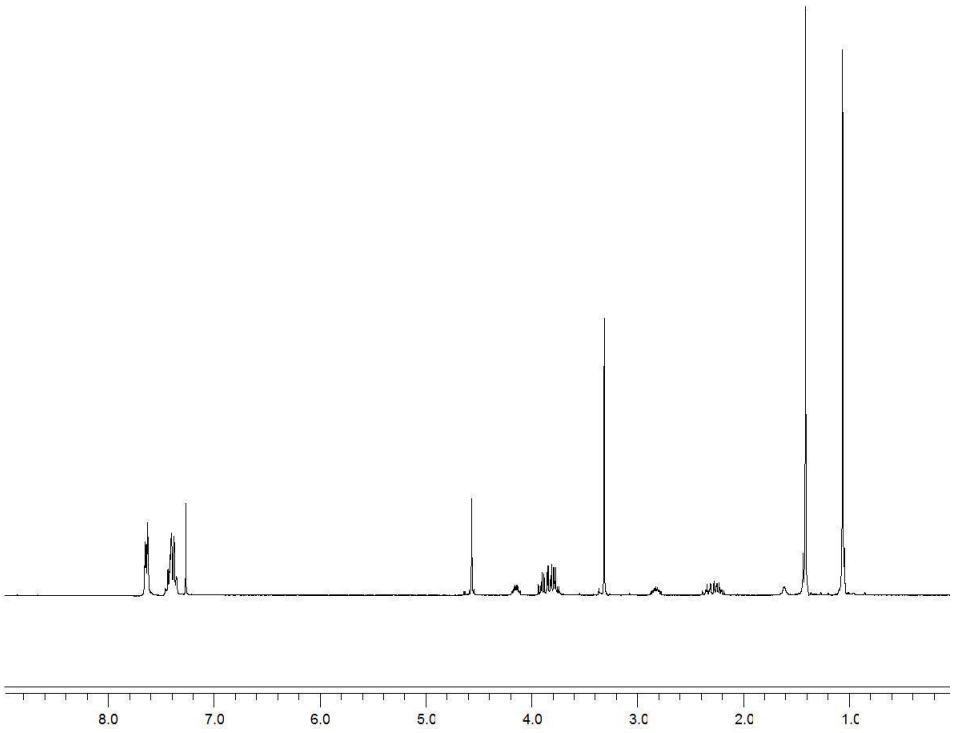


Figure 12. ^{1}H NMR spectrum of **220**

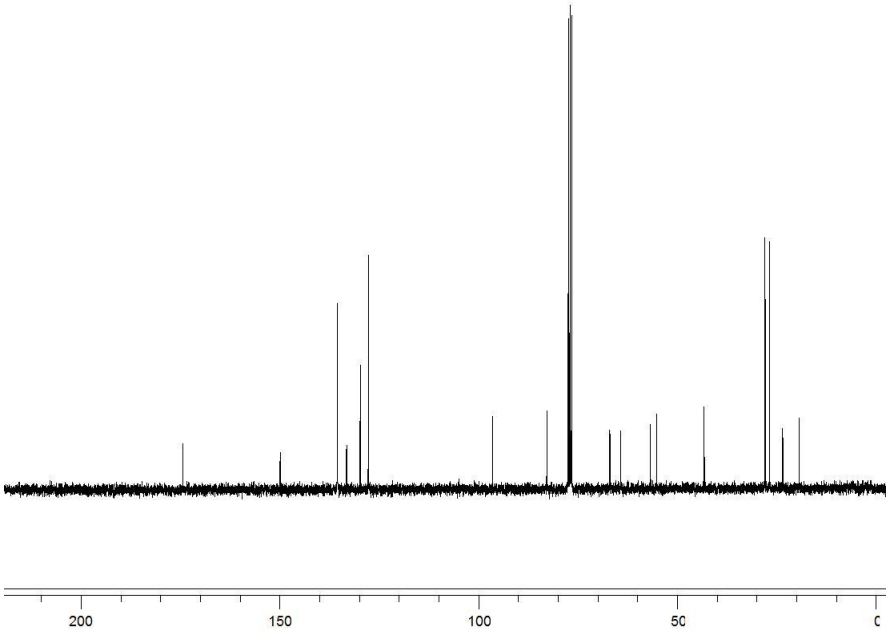
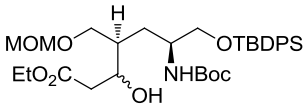


Figure 13. ^{13}C NMR spectrum of **220**

A.3 Preparation of 223



To a solution of diisopropylamine (82 μL, 0.58 mmol) in THF (3 mL) at –78 °C was added commercial butyllithium (2.5 M in hexanes, 0.25 mL, 0.64 mmol), and the solution was stirred for 15 min. Anhydrous ethyl acetate (57 μL, 0.58 mmol) was then added (syringe), and stirring was continued at the same temperature for 1.5 hours. Dropwise addition of a solution of **220** (252 mg, 0.48 mmol) in THF (1.5 mL) was performed, and the reaction mixture was warmed to –15 °C. Stirring was continued at this temperature until starting material was consumed (TLC, 2 hours). The mixture was poured into sat. NH_4Cl (aq), and the aqueous layer was extracted with two portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and stripped of volatiles under vacuum to give a colorless oil, which was carried on without purification. To the crude residue as an EtOH (1.5 mL) solution at rt was added $NaBH_4$ (22 mg, 0.58 mmol). The mixture was stirred at rt for 1 hour, when TLC monitoring indicated convergence to a single spot. The mixture was quenched by careful addition of sat. NH_4Cl (aq) (GAS EVOLUTION). The mixture was partitioned between water and CH_2Cl_2, the layers were separated, and the organic extract was dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (30/70 EtOAc/hexanes) to give **223** (135 mg, 0.22 mmol, 46% over two steps), a 1:1 mixture of diastereomers, as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.24-1.33 (m, 3H); 1.43 (s, 9H); 1.55-1.70 (m, 1H); 1.73-1.85 (m, 1H); 2.44-2.62 (m, 2H); 3.24-3.43 (m, 4H); 3.54-3.88 (m, 5H); 4.08-4.27 (m, 3H); 4.55-4.74 (m, 3H); 7.33-7.49 (m, 6H); 7.58-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.3, 26.9, 28.4, 28.5, 30.2, 39.1, 39.5, 39.6, 49.9, 55.5, 60.7, 66.4, 66.6, 67.0, 68.1, 70.1, 79.2, 96.7, 127.7,

129.8, 133.2, 133.3, 135.6, 155.7, 172.8; HRMS: calc. for $C_{33}H_{52}NO_8{}^{28}Si$ $[M + H]^+$ 618.3462; found 618.3467.

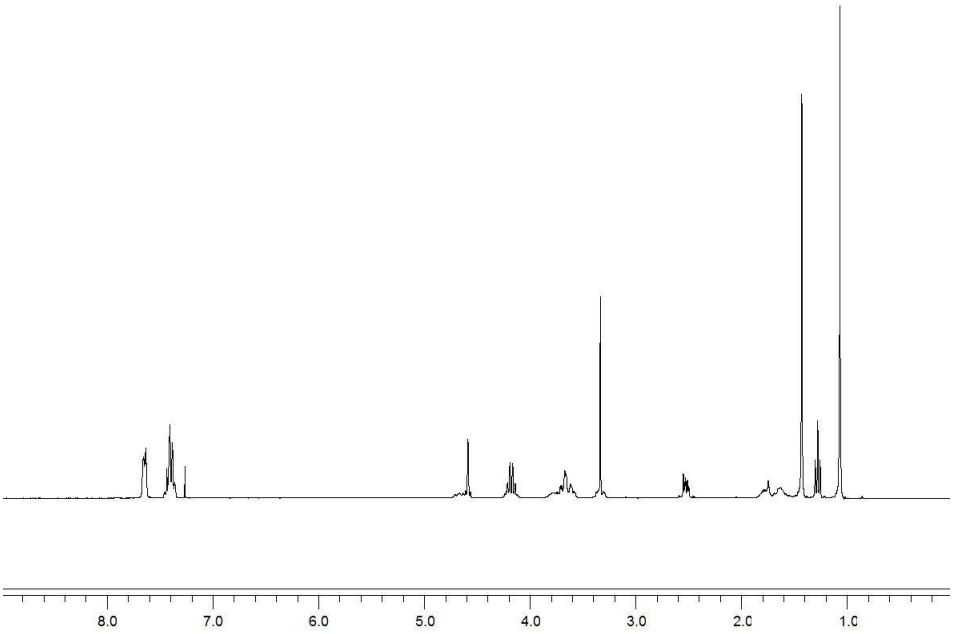


Figure 14. ^{1}H NMR spectrum of **223**

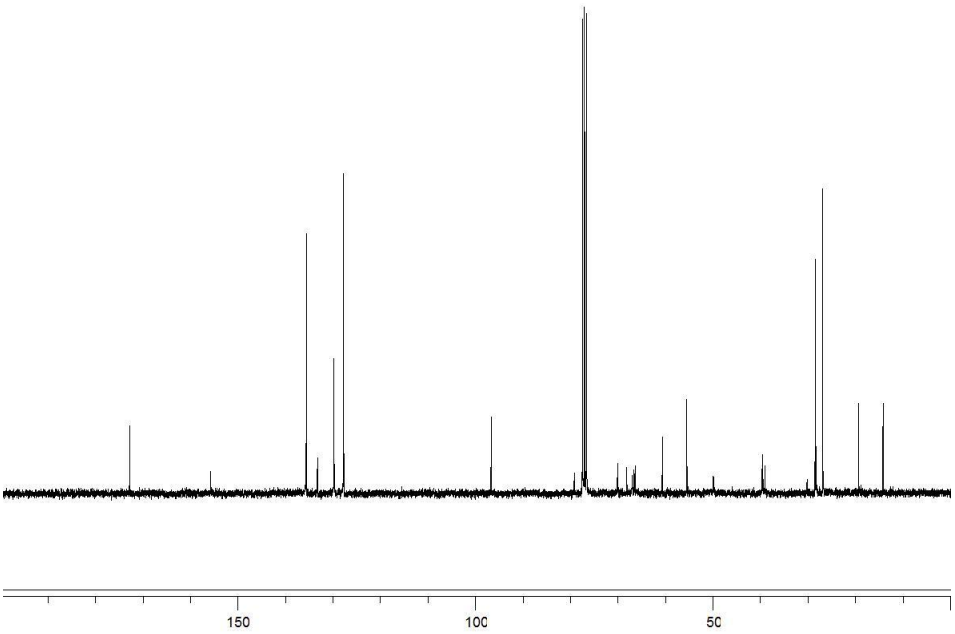
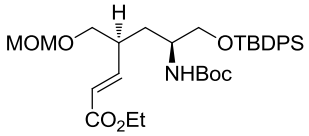


Figure 15. ^{13}C NMR spectrum of **223**

A.4 Preparation of 225



A CH_2Cl_2 (2 mL) solution of **223** (215 mg, 0.35 mmol), Et_3N (0.07 mL, 0.54 mmol), and MsCl (0.04 mL, 0.53 mmol) was stirred overnight at rt, before being poured into sat. NH_4Cl (aq) and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered, and evaporated under vacuum to give a colorless oil, which was re-dissolved in CH_2Cl_2 (3 mL). Addition of DBU (0.06 mL, 0.4 mmol) and stirring at rt for 2 hours caused complete conversion to **225** (TLC). The mixture was diluted with CH_2Cl_2 and poured into sat. NH_4Cl (aq). The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated under vacuum. Flash column chromatography (25/75 EtOAc/hexanes eluent) gave **225** (192 mg, 0.32 mmol, 90% over two steps) as a colorless oil. $[\alpha]_D^{20}$ +5.8 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H); 1.29 (t, *J* = 7.1, 3H); 1.44 (s, 9H); 1.52-1.67 (m, 2H); 1.76-1.93 (m, 1H); 2.40-2.60 (m, 1H); 3.33 (s, 3H); 3.49-3.63 (m, 3H); 3.63-3.81 (m, 2H); 4.18 (q, *J* = 7.1, 2H); 4.59 (s, 2H); 4.67 (brd, *J* = 9.0, 1H); 5.81 (d, *J* = 15.8, 1H); 6.88 (dd, *J* = 15.8, 8.5, 1H); 7.34-7.50 (m, 6H); 7.59-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.3, 26.9, 28.4, 32.9, 39.6, 50.0, 55.3, 60.2, 65.6, 69.6, 79.2, 96.5, 122.2, 127.8, 129.9, 133.1, 135.6, 149.7, 155.3, 166.3; IR (film, cm^{-1}): ν 1713; HRMS: calc. for $C_{33}H_{50}NO_7{}^{28}Si$ $[M + H]^+$ 600.3357; found 600.3365.

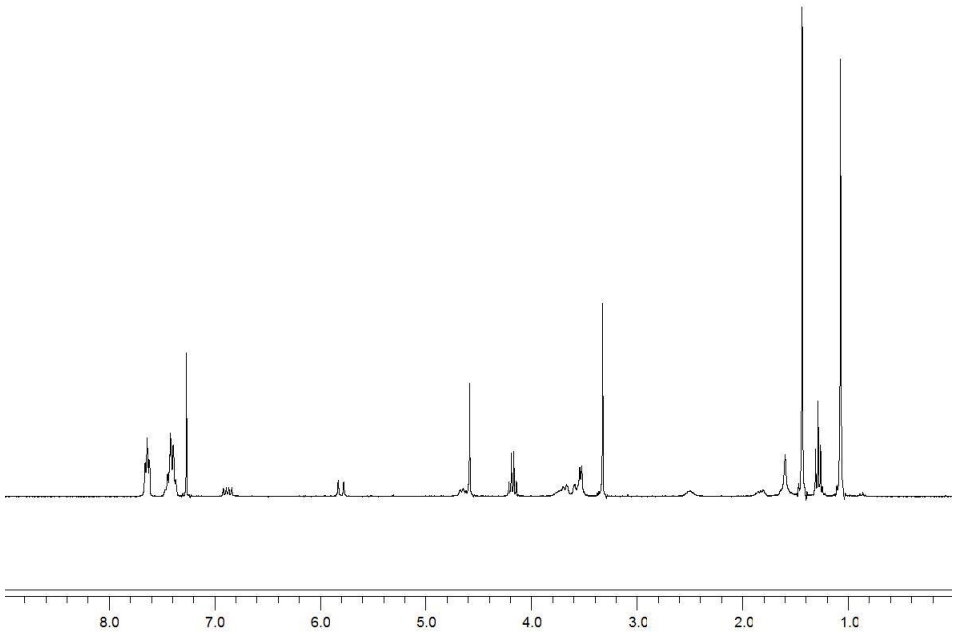


Figure 16. ^{1}H NMR spectrum of **225**

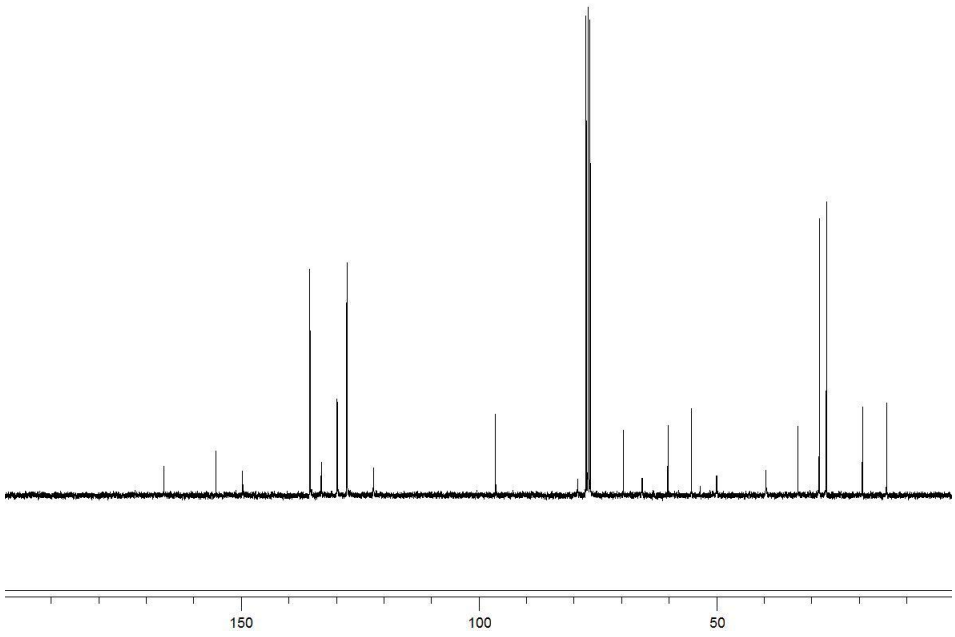
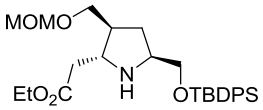


Figure 17. ^{13}C NMR spectrum of **225**

A.5 Preparation of 226



To a CH_2Cl_2 (3 mL) solution of **225** (112 mg, 0.19 mmol) was added TFA (0.15 mL), and the solution was stirred at rt for 6 hours. At this time, TLC monitoring indicated consumption of starting material. The mixture was neutralized by careful addition of sat. $NaHCO_3$ (aq) (GAS EVOLUTION) and dilution with CH_2Cl_2 and the organic layer was separated, dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue was dissolved in Et_2O, treated with activated charcoal (Norit®), filtered through Celite, and evaporated, giving **226** (80 mg, 0.16 mmol, 86% yield) as a faintly yellow oil. $[\alpha]_D^{20}$ +15.5 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.27 (m, 5H); 1.98-2.16 (m, 2H); 2.46 (dd, *J* = 15.9, 9.4, 1H); 2.69 (dd, *J* = 15.9, 3.7, 1H); 3.33 (s, 3H); 3.37-3.46 (m, 2H); 3.48 (d, *J* = 5.7, 1H); 3.56-3.61 (m, 2H); 4.16 (q, *J* = 7.1, 2H); 4.58 (s, 2H); 7.33-7.49 (m, 6H); 7.63-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.2, 26.8, 31.2, 40.4, 44.5, 55.2, 57.1, 58.1, 60.4, 66.1, 69.7, 96.5, 127.7, 129.7, 133.4, 135.6, 172.4; IR (film, cm^{-1}): ν 1729; HRMS: calc. for $C_{28}H_{42}NO_5{}^{28}Si$ $[M + H]^+$ 500.2832; found 500.2838.

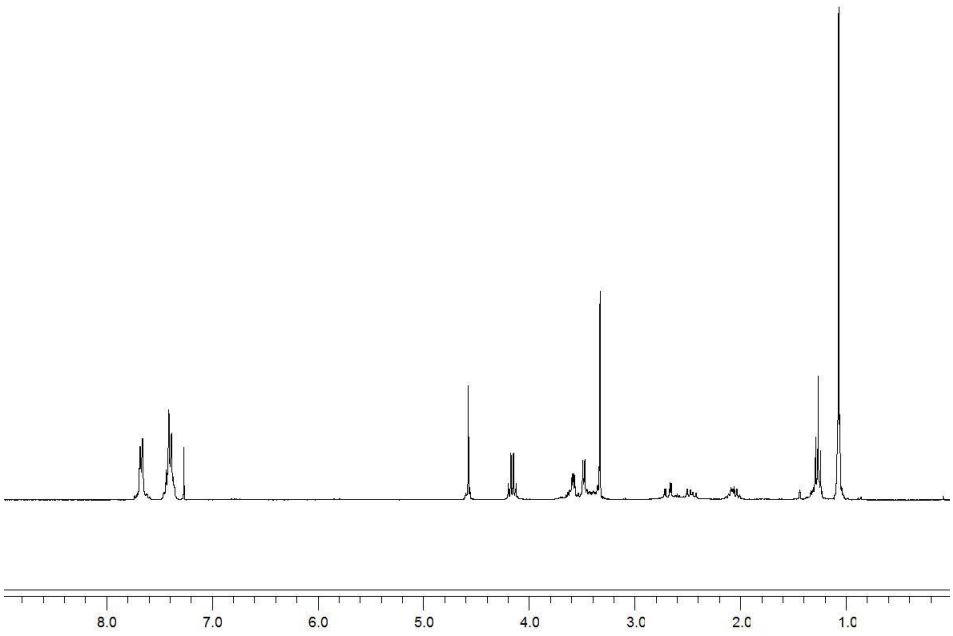


Figure 18. ^{1}H NMR spectrum of **226**

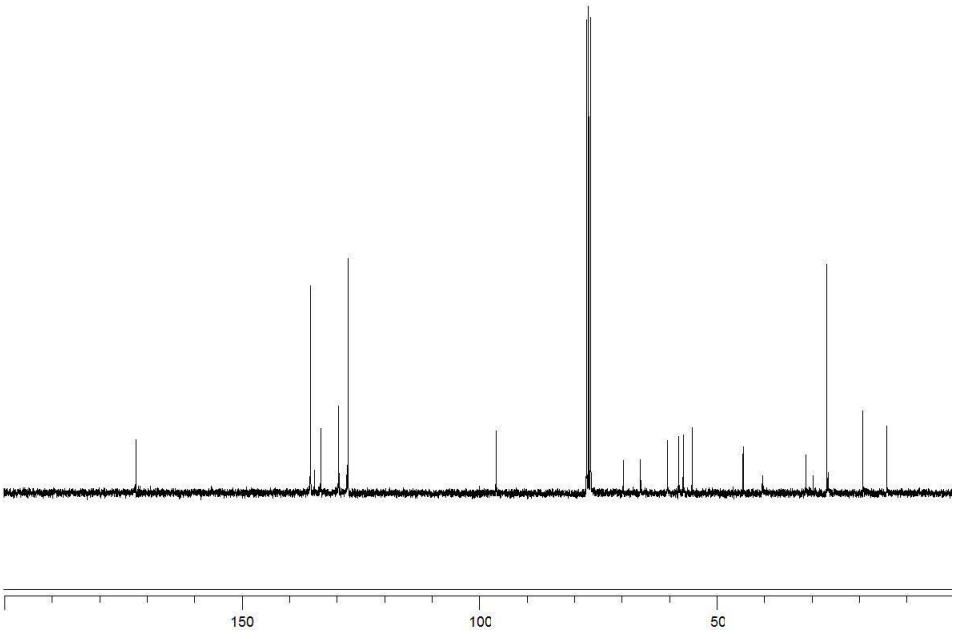
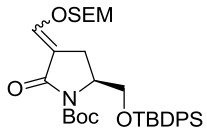


Figure 19. ^{13}C NMR spectrum of **226**

A.6 Preparation of 233



A solution of **218** (3.0 g, 5.9 mmol) in THF (12 mL) was added to rapidly stirred H_2SO_4 (aq) (55 mL of 5% v/v solution) at rt, and the resulting milky suspension was sonicated for 40 min. Solid $NaHCO_3$ was then added in portions (GAS EVOLUTION) until gas evolution ceased. The residue was partitioned between H_2O and CH_2Cl_2, and the organic extract was dried (Na_2SO_4), filtered, and concentrated under vacuum. To a CH_2Cl_2 (11 mL) solution of the residue and Hunig's base (2.1 mL, 12.0 mmol) at 0 °C was added SEMCl (1.6 mL, 9.0 mmol) over several minutes. The reaction was stirred until starting material had been consumed (TLC, about 30 min). Following dilution with CH_2Cl_2, the mixture was poured into sat. NH_4Cl (aq), the layers were separated, and the aqueous layer was extracted with one additional portion of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. Silica gel chromatography of the residue (20/80 EtOAc/hexanes eluent) gave **233** (3.0 g, 4.8 mmol, 82% yield over two steps), a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H), 0.95 (t, *J* = 8.3, 2H), 1.01 (s, 9H), 1.45 (s, 9H), 2,71 (ddd, *J* = 16.5, 8.9, 2.9, 1H), 2.82 (brd, *J* = 16.5, 1H), 3.65-3.71 (m, 3H), 3.83 (dd, *J* = 10.1, 4.6, 1H), 4.21-4.28 (m, 1H), 5.02-5.06 (m, 2H), 7.33-7.48 (m, 7H), 7.57-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.4, 17.9, 19.2, 23.5, 26.7, 28.0, 56.1, 64.8, 66.9, 82.3, 96.5, 110.6, 127.7, 127.7, 129.7, 132.9, 133.3, 135.5, 150.3, 150.6, 168.5; HRMS: calc. for $C_{33}H_{49}NO_6Na^{28}Si_2$ $[M + Na]^+$ 634.2996; found 634.3007.

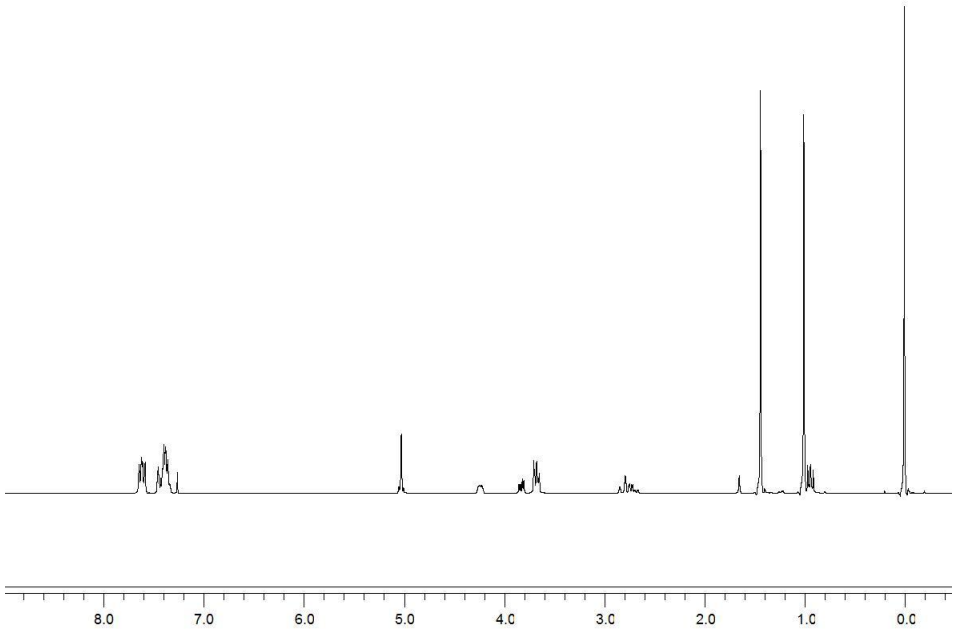


Figure 20. ^{1}H NMR spectrum of **233**

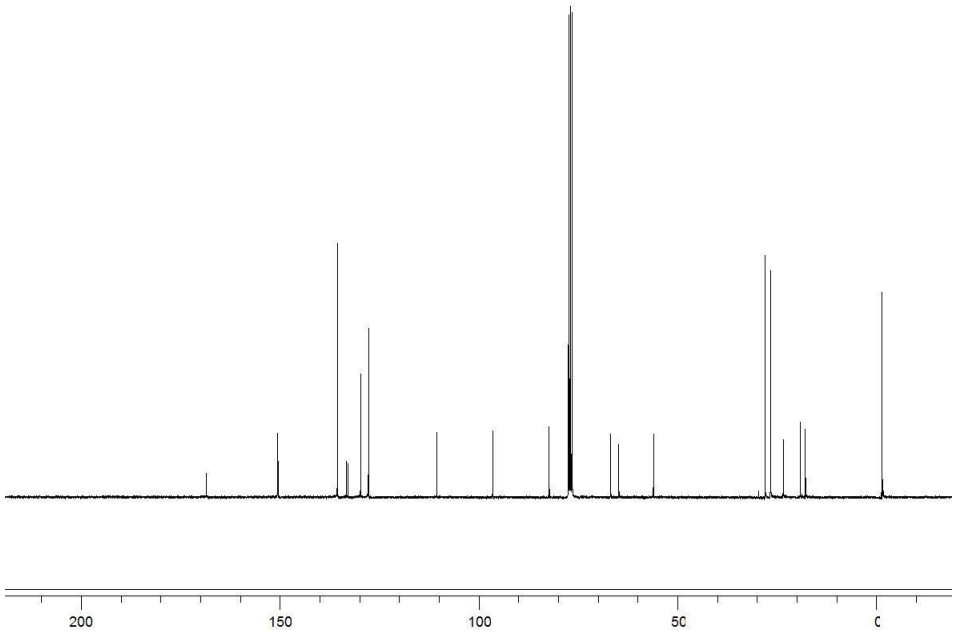
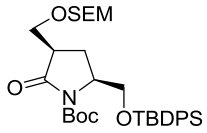


Figure 21. ^{13}C NMR spectrum of **233**

A.7 Preparation of **234**



A solution of **233** (3.0 g, 4.8 mmol) in EtOAc (60 mL) containing suspended Pd/C (10%, 1.3 g) was placed in a Parr reactor, which was pressurized to 1000 psi of H_2. After 24 hours of rapid stirring at rt, the catalyst was removed by filtration over a pad of Celite. Evaporation of solvent under vacuum gave the crude hydrogenated product as a 10:1 mixture of *cis* (**234**, major) and *trans* diastereomers. Pure **234** (2.5 g, 4.0 mmol, 83%), $[\alpha]_D^{20}$ –16.9 (c 1.1, EtOH), was readily isolated by flash chromatography (20/80 EtOAc/hexanes eluent). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H), 0.92 (t, *J* = 8.3, 2H), 1.06 (s, 9H), 1.41 (s, 9H), 2.16-2.38 (m, 2H), 2.77-2.88 (m, 1H), 3.52-3.65 (m, 2H), 3.75-3.85 (m, 3H), 3.91 (dd, *J* = 9.9, 5.9, 1H), 4.10-4.18 (m, 1H), 4.60-4.65 (m, 2H), 7.34-7.46 (m, 6H), 7.61-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.4, 18.0, 19.3, 23.6, 26.8, 27.9, 43.3, 56.9, 64.2, 65.1, 67.21, 82.8, 95.0, 127.7, 129.8, 133.1, 133.3, 135.5, 135.6, 150.0, 174.3; IR (film, cm^{-1}): ν 1785, 1713; HRMS: calc. for $C_{33}H_{51}NO_6Na^{28}Si_2$ $[M + Na]^+$ 636.5153; found 636.3143.

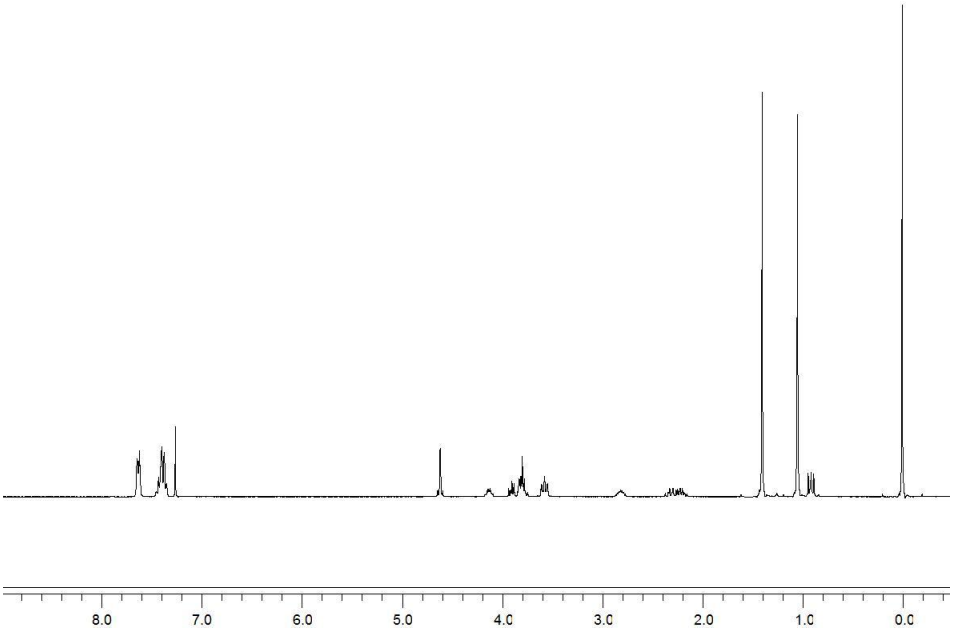


Figure 22. ^{1}H NMR spectrum of **234**

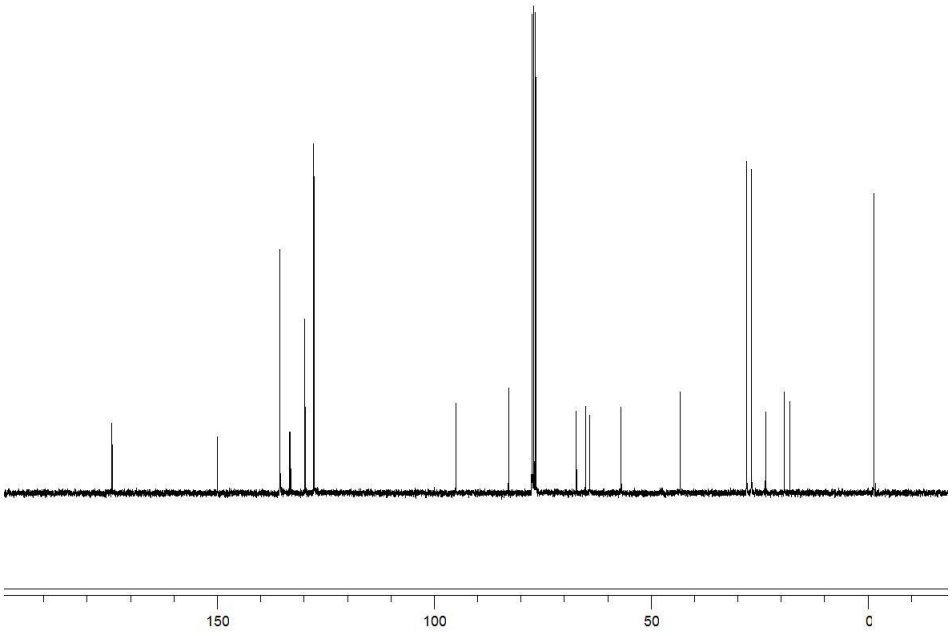
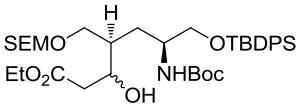


Figure 23. ^{13}C NMR spectrum of **234**

A.8 Preparation of 235



Commercial BuLi solution (1.6 M/ hexanes, 13.4 mL, 21.4 mmol) was added to a solution of diisopropylamine (2.9 mL, 20.0 mmol) in THF (43 mL) at –78 °C, and the mixture was stirred for 15 min. Anhydrous EtOAc (2.0 mL, 20.4 mmol) was added (syringe), and stirring was continued for 1.5 hrs at the same temperature. A solution of **234** (6.1 g, 9.9 mmol) in THF (11 mL) was added over several minutes, resulting in a lemon-yellow solution. The mixture was warmed to –25 °C and stirring was continued for 1.5 hrs, at which time TLC indicated that starting material had been consumed. The reaction was quenched with sat. NH_4Cl (aq) and stirring was continued as the mixture warmed to rt. The mixture was diluted with CH_2Cl_2, the layers were separated, and the aqueous phase was extracted with additional CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent removed under vacuum to give a clear oil that, being a mixture of isomers, was used in the next reaction without further purification. To a solution of the residue in EtOH (62 mL) at 0 °C was added $NaBH_4$ (430 mg, 11.4 mmol). The solution was stirred until TLC monitoring indicated convergence to a single spot, about 40 min. Sat. NH_4Cl (aq) was added (GAS EVOLUTION) and stirring continued for 15 min as the mixture was warmed to rt. The mixture was diluted with CH_2Cl_2, and washed with NH_4Cl. The aqueous phase was extracted with more CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under vacuum. Silica gel chromatography (20/80 to 25/75 EtOAc/hexanes gradient elution) gave **235** (4.8 g, 6.8 mmol, 69% yield over two steps), a colorless oil, as a 1:1 mixture of diastereomers. ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 9H), 0.93 (brt, 2H), 1.07 (s, 9H), 1.27 (brt, 3H), 1.43 (s, 9H), 1.55-1.71

(m, 2H), 1.71-1.84 (m, 1H), 2.43-2.59 (m, 2H), 3.54-3.82 (m, 8H), 4.17 (brq, 3H), 4.63 (m, 3H), 7.34-7.47 (m, 6H), 7.61-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.4, 14.2, 18.0, 19.3, 26.9, 28.4, 28.6, 39.0, 39.5, 39.7, 49.9, 60.6, 65.4, 66.3, 66.6, 68.3, 70.2, 79.1, 95.1, 127.7, 129.8, 133.3, 135.6, 135.6, 155.7, 172.8 HRMS: calc. for $C_{37}H_{61}NO_8Na^{28}Si_2$ $[M + Na]^+$ 726.3833; found 726.3815.

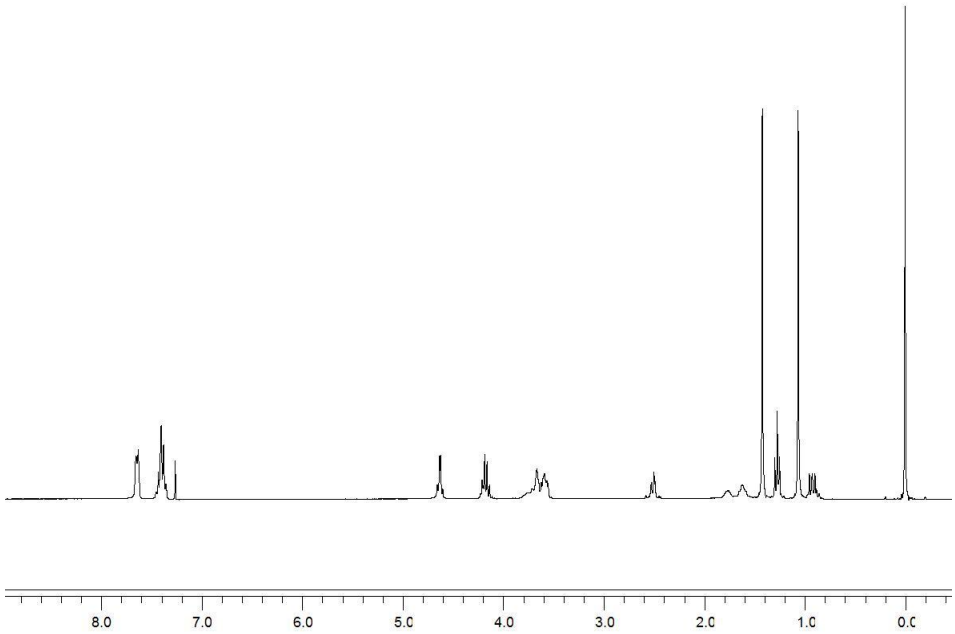


Figure 24. ^{1}H NMR spectrum of **235**

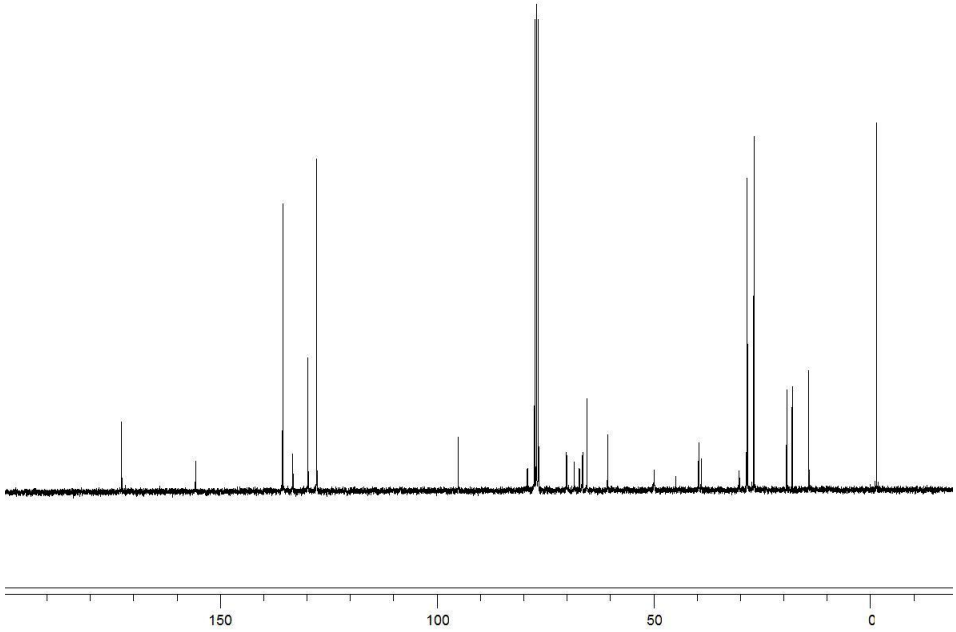
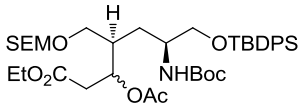


Figure 25. ^{13}C NMR spectrum of **235**

A.9 Preparation of 236



A CH_2Cl_2 (26 mL) solution of **235** (2.5 g, 3.6 mmol), pyridine (3.3 mL, 42.1 mmol), Ac_2O (3.9 mL, 44.0 mmol), and DMAP (53 mg, 0.4 mmol), was stirred overnight at rt, before being evaporated under vacuum. The residue was taken up in CH_2Cl_2, washed with 0.1 M HCl, dried (Na_2SO_4), filtered, and evaporated under vacuum. Flash chromatography (20/80 EtOAc/hexanes) of the residue gave **236** (2.60 g, 3.48 mmol, 96% yield), a 1:1 mixture of diastereomers, as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H), 0.92 (brt, 2H), 1.07 (s, 9H), 1.24 (brt, 3H), 1.43 (s, 9H), 1.51-1.66 (m, 3H), 2.03 (brs, 3H), 1.93-2.12 (m, 1H), 2.53-2.74 (m, 2H), 3.49-3.84 (m, 7H), 4.13 (brq, 2H), 4.61 (m, 2H), 5.34-5.44 (m, 1H), 7.35-7.47 (m, 6H), 7.60-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.4, 14.2, 18.0, 19.3, 21.0, 26.9, 28.4, 29.2, 36.6, 37.1, 38.2, 38.3, 49.6, 49.8, 60.6, 65.3, 66.2, 66.3, 66.5, 66.6, 71.3, 71.7, 79.2, 95.0, 95.1, 127.7, 129.8, 129.8, 133.2, 133.30, 135.56, 135.6, 155.5, 155.6, 169.9, 170.1, 170.6, 170.7; HRMS: calc. for $C_{39}H_{63}NO_9Na^{28}Si_2$ $[M + Na]^+$ 768.3939; found 768.3938.

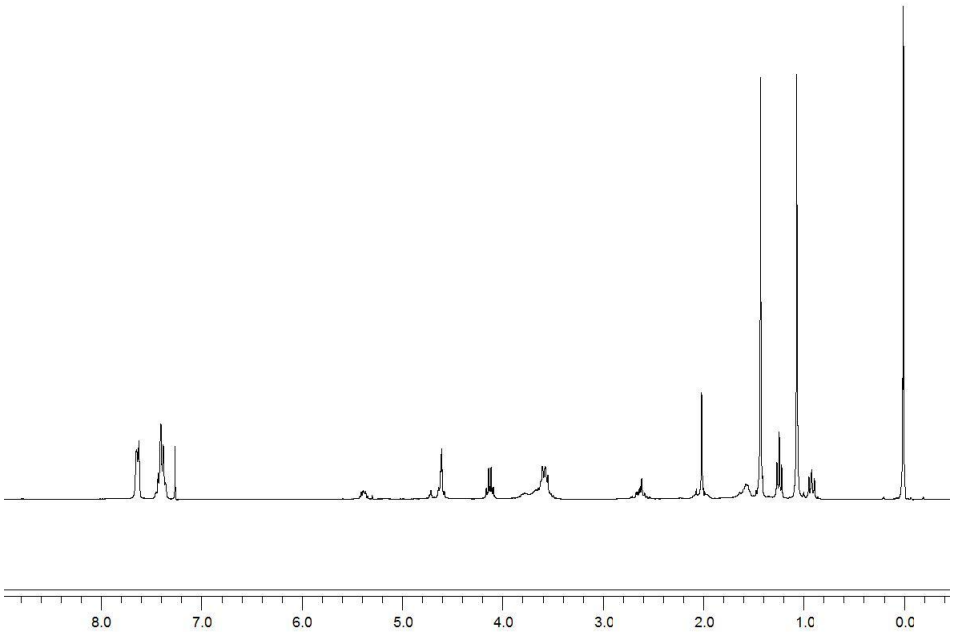


Figure 26. ^{1}H NMR spectrum of **236**

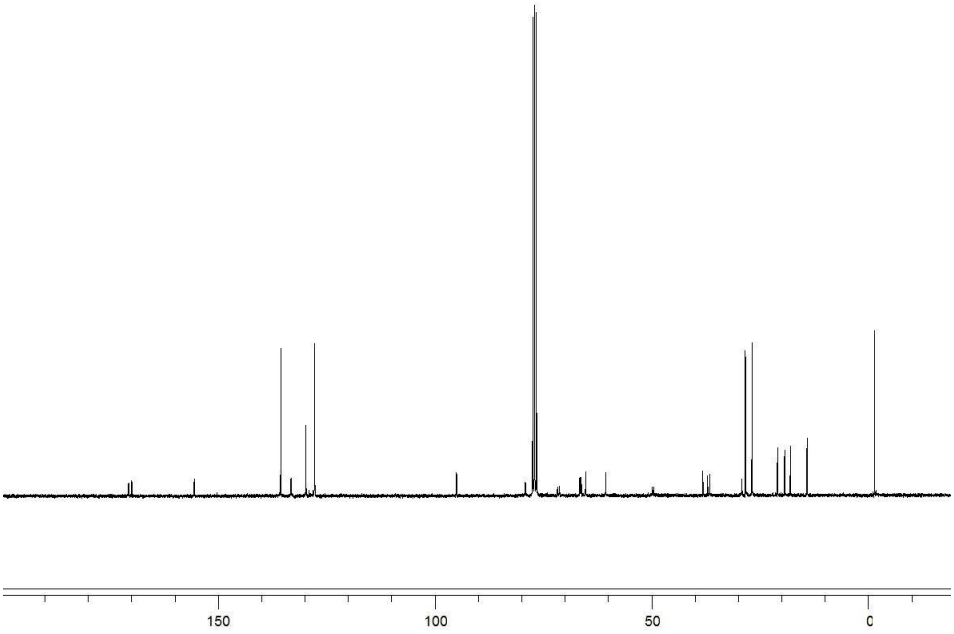
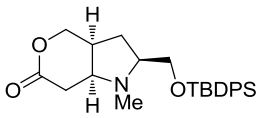


Figure 27. ^{13}C NMR spectrum of **236**

A.10 Preparation of 238



To rapidly stirred TFA (3.9 mL) at rt was added a solution of **236** (166 mg, 0.22 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at rt for 45 min before being diluted with CH_2Cl_2 and evaporated at ambient temperature. Periodic addition of CH_2Cl_2 during evaporation ensured removal of most of the TFA. The residue was taken up in more CH_2Cl_2 and washed with sat. $NaHCO_3$ (aq). The organic layer was dried (Na_2SO_4), filtered, and stripped of volatiles under vacuum to leave a yellow-brown oil. The residue was dissolved in CH_2Cl_2 (5 mL) at rt with stirring and DBU (0.08 mL, 0.49 mmol) was added. The solution was stirred for 30 min before being evaporated under reduced pressure. The residue was loaded on reverse phase (C18) silica gel, washed with water, and eluted with EtOH to give a brownish oil. To a CH_3CN (6.5 mL) solution of the residue at 0 °C was added formaldehyde (37% in water, 0.2 mL, 2.7 mmol). After 10 min stirring, $NaBH_3CN$ (181 mg, 2.87 mmol) was added, followed by the dropwise addition of AcOH (0.3 mL), and the mixture was stirred for 1 hour at rt. The reaction mixture was poured into sat. $NaHCO_3$ (aq), and the pH was brought to 9 by the addition of sat. Na_2CO_3 (aq). Extraction with CH_2Cl_2 and drying (Na_2SO_4), filtration, concentration under vacuum, and column chromatography (35/65 EtOAc/Hexanes eluent) gave **238** (43 mg, 0.10 mmol, 45% yield over 3 steps) as a colorless oil. $[\alpha]_D^{20}$ −33.2 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.40-1.51 (m, 1H), 2.08-2.17 (m, 1H), 2.25 (s, 3H), 2.42-2.65 (m, 4H), 2.81-2.88 (m, 1H), 3.55 (dd, *J* = 10.2, 5.6, 1H), 3.77 (dd, *J* = 10.2, 5.0, 1H), 4.07 (dd, *J* = 11.4, 5.4, 1H), 4.18 (dd, *J* = 11.4, 4.4, 1H), 7.35-7.47 (m, 6H), 7.62-7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 31.4, 34.6, 34.7, 39.1, 62.9, 66.5, 67.0, 69.3, 127.7, 129.7, 133.5, 133.6, 135.53,

135.6, 172.2; IR (film, cm^{-1}): ν 1748; HRMS: calc. for $C_{25}H_{34}NO_3{}^{28}Si$ $[M + H]^+$ 424.2308; found 424.2316.

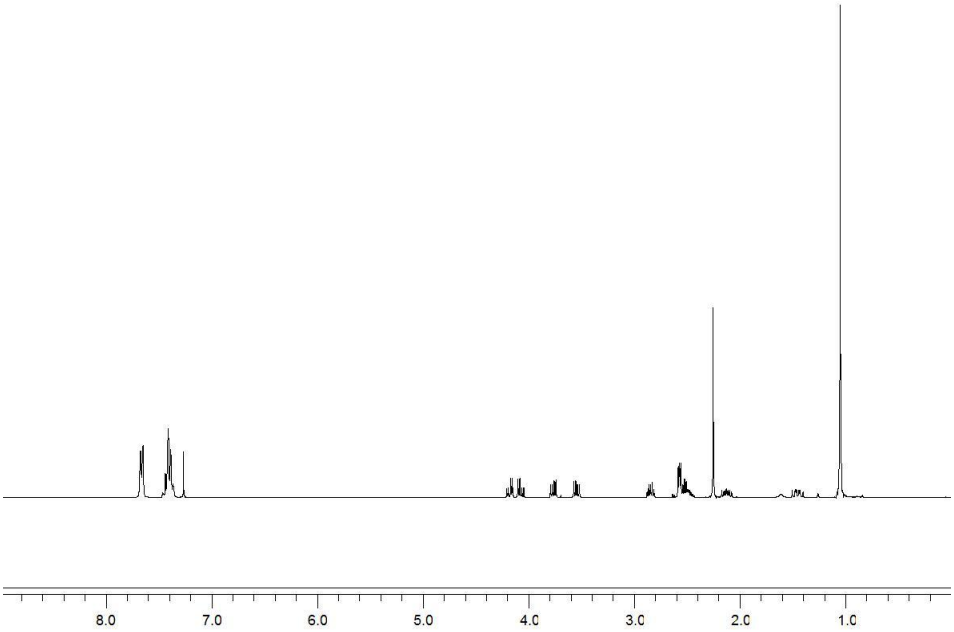


Figure 28. ^{1}H NMR spectrum of **238**

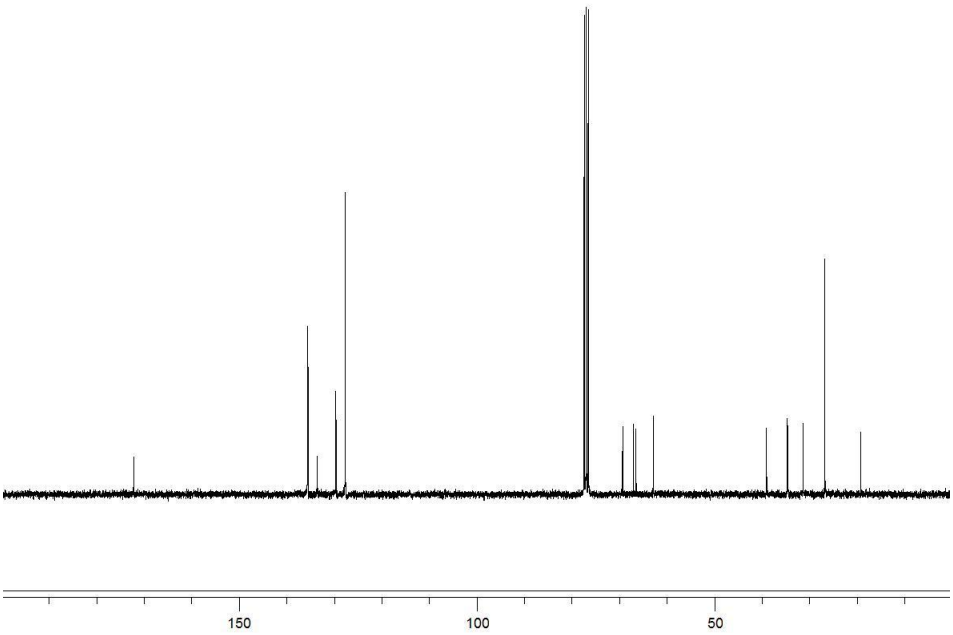
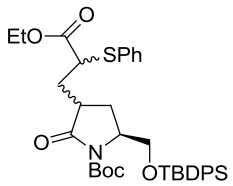


Figure 29. ^{13}C NMR spectrum of **238**

A.11 Preparation of 246



To a solution of hexamethyldisilazane (75 μL, 0.35 mmol) in THF (0.8 mL) at −78 °C was added *n*-BuLi (1.6 M/ hexanes, 0.23 mL, 0.37 mmol) and the solution was stirred for 15 minutes, when **214** (146 mg, 0.32 mmol) was added as a solution in THF (0.5 mL), and stirring was continued for 40 minutes. Finally, ethyl 2-(phenylthio)acrylate **245**[76] (78 mg, 0.37 mmol) was added as a solution in THF (0.3 mL), and the temperature was maintained for 1.5 hours. The mixture was diluted with CH_2Cl_2 and poured into sat. NH_4Cl (aq). The organic layer was separated, dried (Na_2SO_4), filtered, and stripped of solvent under vacuum. The residue was purified by column chromatography (25/75 EtOAc/Hexanes eluent) to give **246** (102 mg, 0.15 mmol, 48% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 9H); 1.11-1.19 (m, 3H); 1.45 (s, 9H); 1.73-1.95 (m, 2H); 2.26-2.46 (m, 2H); 3.11-3.29 (m, 1H); 3.63-3.72 (m, 1H); 3.82-4.19 (m, 5H); 7.26-7.33 (m, 3H); 7.35-7.49 (m, 8H); 7.57-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.0, 19.1, 26.8, 28.0, 28.9, 29.2, 33.3, 33.5, 39.6, 40.5, 48.5, 48.6, 56.9, 61.2, 61.2, 64.7, 64.8, 82.9, 127.8, 127.9, 128.0, 128.2, 128.9, 128.9, 129.9, 132.5, 132.6, 132.9, 133.2, 133.4, 133.7, 135.5, 135.5, 149.8, 171.8, 171.9, 175.8, 176.0; HRMS: calc. for $C_{37}H_{47}NO_6S^{28}SiNa$ $[M + Na]^+$ 684.2791; found 684.2786.

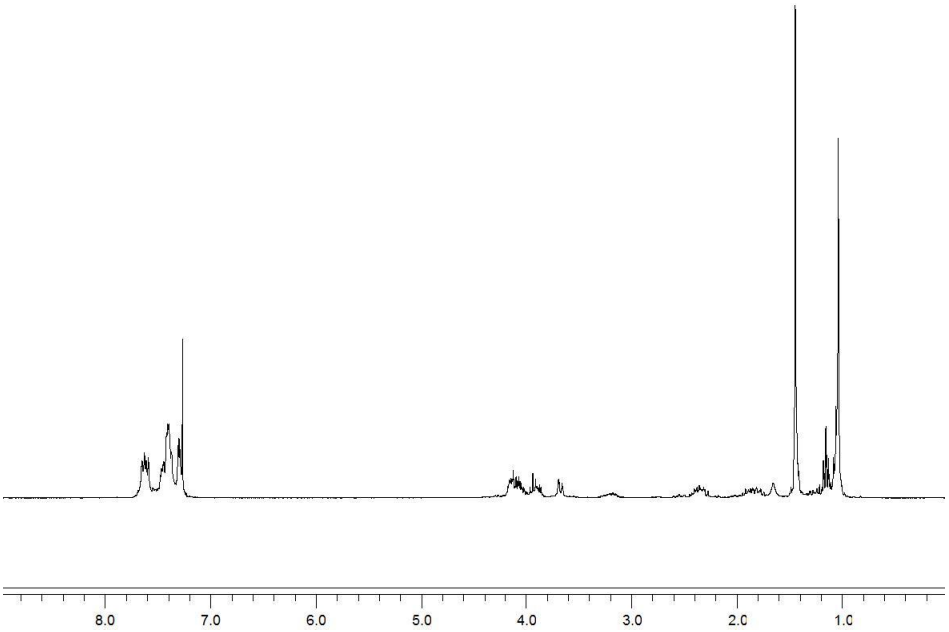


Figure 30. ^{1}H NMR spectrum of **246**

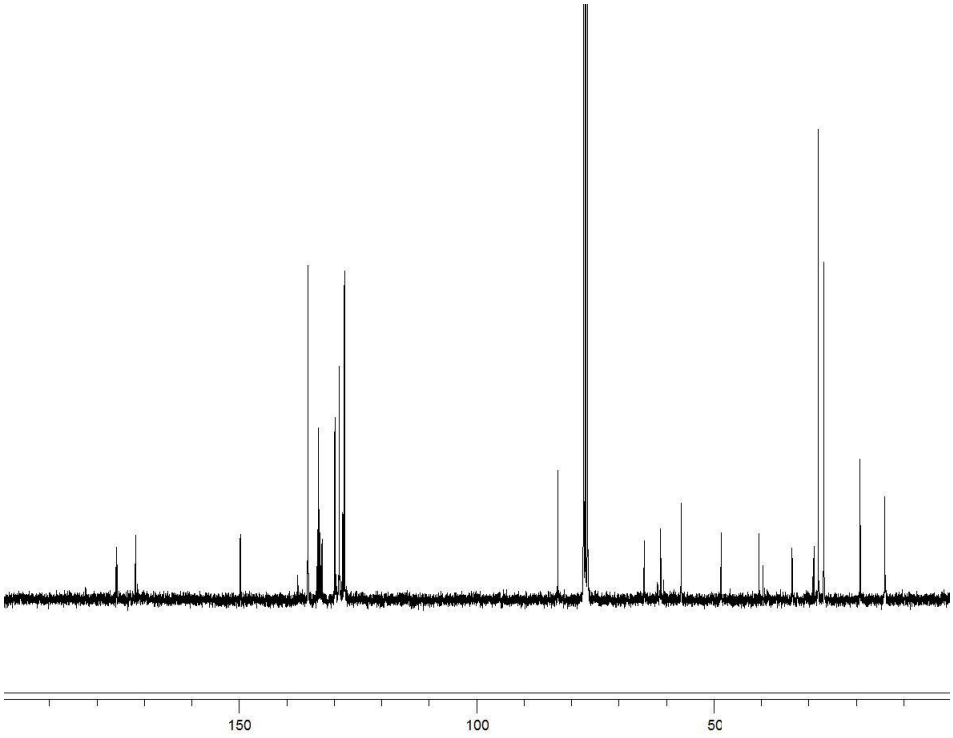
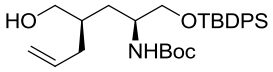


Figure 31. ^{13}C NMR spectrum of **246**

A.12 Preparation of 251



To a solution of **250**[83] (4.91 g, 9.95 mmol) in THF (48 mL) and EtOH (0.9 mL) at rt was added $LiBH_4$ (325 mg, 14.9 mmol). The mixture was stirred overnight, at which time a careful NH_4Cl (aq) quench was performed (GAS EVOLUTION). The mixture was diluted with CH_2Cl_2 and washed with more NH_4Cl (aq), and the organic extract was dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was pure **251** (4.85 g, 9.74 mmol, quant.), a colorless oil. $[\alpha]_D^{20}$ −20.5 (c 1.1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H); 1.43-1.50 (m, 10H); 1.52-1.78 (m, 2H); 1.93-2.07 (m, 1H); 2.07-2.22 (m, 1H); 3.47-3.67 (m, 3H); 3.67-3.77 (m, 1H); 3.90 (brs, 1H); 4.75 (brd, *J* = 8.5, 1H); 4.99-5.14 (m, 2H); 5.68-5.86 (m, 1H); 7.34-7.50 (m, 6H); 7.60-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 26.9, 28.4, 34.4, 36.8, 50.1, 66.0, 66.5, 79.4, 116.5, 127.7, 129.8, 133.3, 135.6, 136.8, 156.2; IR (film, cm^{-1}): ν 1499, 1693; HRMS: calc. for $C_{29}H_{44}NO_4{}^{28}Si$ $[M + H]^+$ 498.3040; found 498.3044.

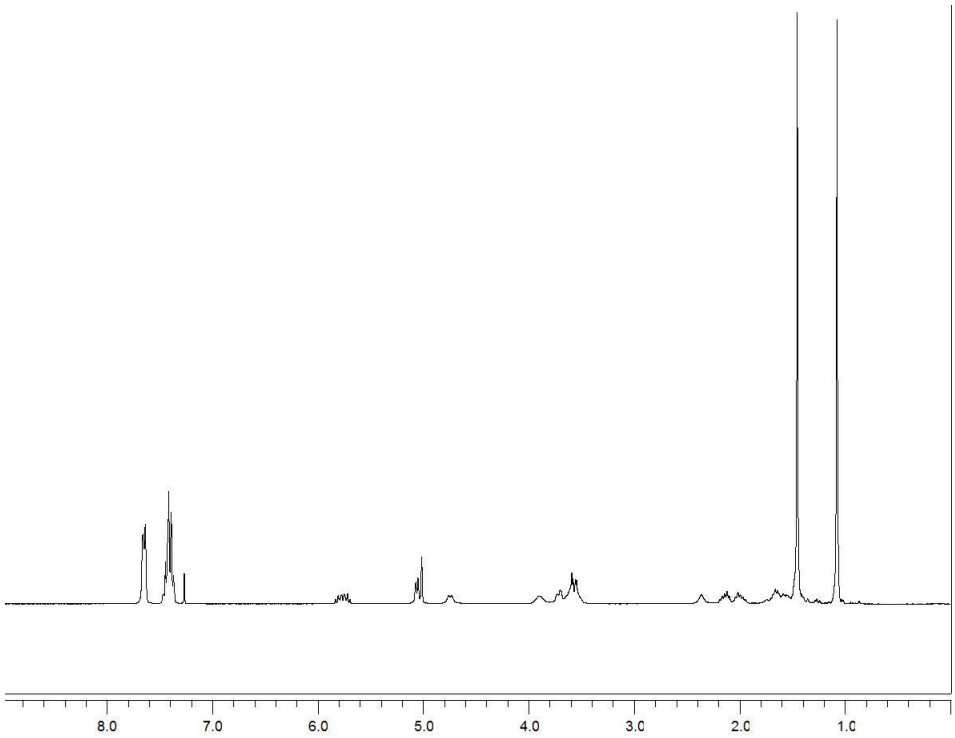


Figure 32. ^{1}H NMR spectrum of **251**

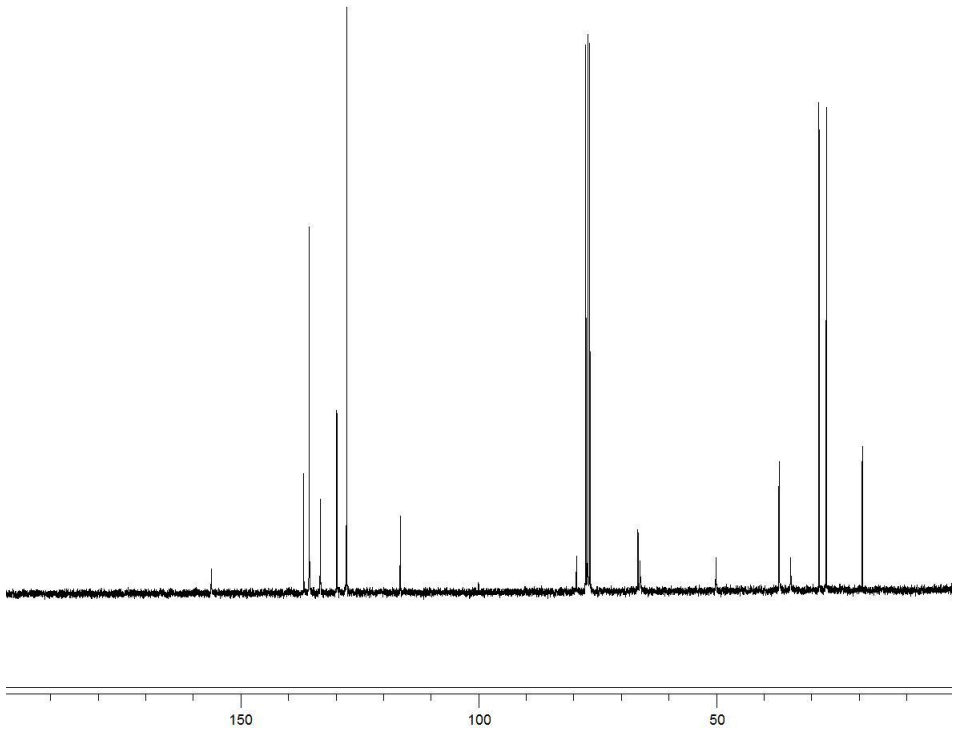
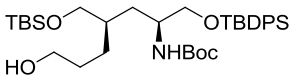


Figure 33. ^{13}C NMR spectrum of **251**

A.13 Preparation of 252



To a solution of **251** (6.89 g, 13.8 mmol) in CH_2Cl_2 (60 mL) at rt was added TBSCl (2.29 g, 15.2 mmol) and imidazole (1.12 g, 16.5 mmol), which generated a white precipitate. The mixture was stirred for 3 hours, at which time it was diluted with CH_2Cl_2 and washed with 0.1 M HCl (aq). The organic extract was dried (Na_2SO_4) filtered, and evaporated to give a colorless oil. To a solution of the residue in THF (67 mL) at rt was added BH_3•THF (1 M/THF, 15.2 mL, 15.2 mmol). The resulting solution was stirred for 4.5 hours, when water was carefully added (GAS EVOLUTION) until gas evolution had ceased. Then a 1:1 solution of 1 M NaOH and 30% H_2O_2 (20 mL) was added, and the mixture was rapidly stirred overnight. After quenching with sat. NH_4Cl (aq), partial evaporation was performed. The residue was diluted with CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated. An analytical sample could be obtained by flash column chromatography (25/75 EtOAc/hexanes eluent), giving **252** as a colorless oil. $[\alpha]_D^{20}$ −22.3 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H); 0.04 (s, 3H); 0.88 (s, 9H); 1.07 (s, 9H); 1.25-1.38 (m, 1H); 1.39-1.51 (m, 11H); 1.50-1.64 (m, 4H); 3.49-3.83 (m, 7H); 4.78 (brd, *J* = 7.9, 1H); 7.34-7.49 (m, 6H); 7.61-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4, 18.3, 19.3, 25.9, 26.9, 27.3, 28.4, 29.9, 33.1, 36.8, 49.8, 63.1, 64.7, 66.2, 79.0, 127.7, 129.7, 133.4, 135.6, 155.6; IR (film, cm^{-1}): ν 1698; HRMS: calc. for $C_{35}H_{60}NO_5{}^{28}Si_2$ $[M + H]^+$ 630.4010; found 630.4020.

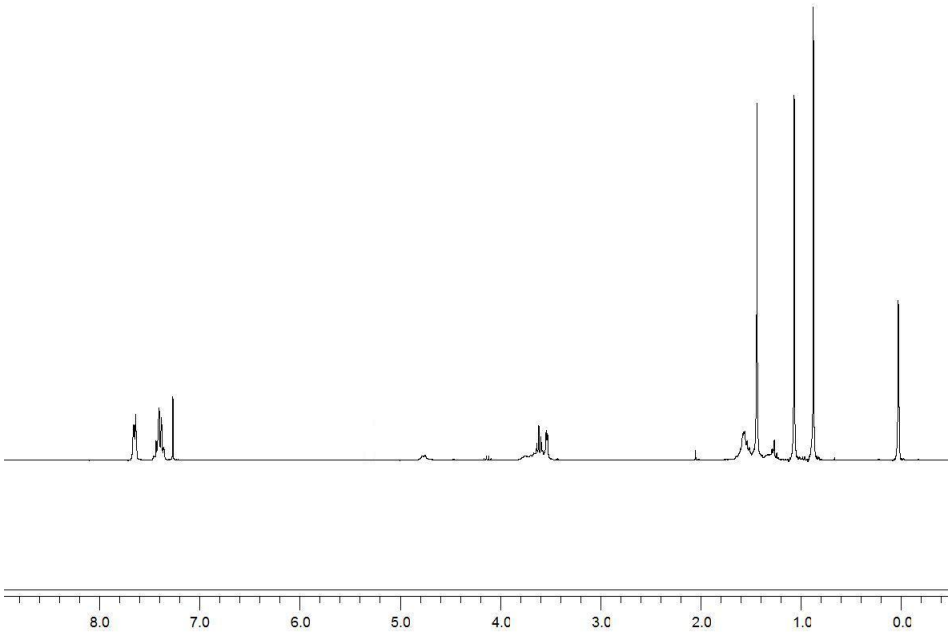


Figure 34. ^{1}H NMR spectrum of **252**

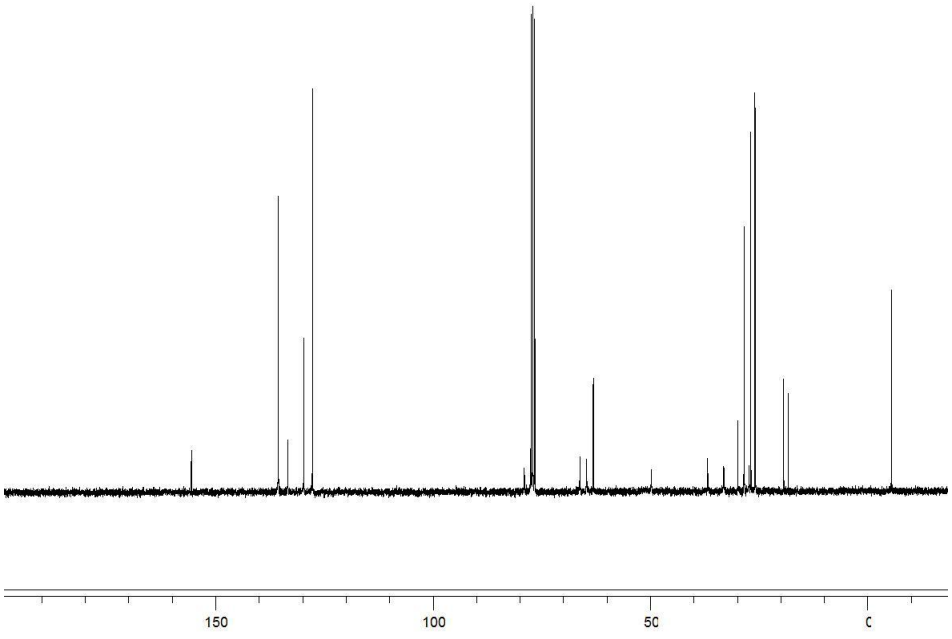
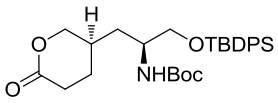


Figure 35. ^{13}C NMR spectrum of **252**

A.14 Preparation of 253



To a solution of the residual **252** (13.8 mmol) in a mixture of CCl_4 (28 mL), MeCN (28 mL) and H_2O (39 mL) was added $NaIO_4$ (11.7 g, 54.9 mmol) and $RuCl_3 \bullet xH_2O$ (58 mg, ~0.28 mmol). The resultant darkly-colored suspension was subjected to rapid stirring for 1.5 hours, when CH_2Cl_2 and water were added, and the layers separated. The organic layer was dried (Na_2SO_4), decanted, and stripped of volatiles under vacuum. The residue was dissolved in Et_2O, filtered through celite, and evaporated. Finally, the residue was filtered through a cake of silica gel (elution with 50/50 EtOAc/hexanes) to give a darkly-colored oil. The crude carboxylic acid was dissolved in MeCN (68 mL) and H_2O (6.8 mL), to which was added PPTS (1.35 g, 5.37 mmol). The solution was stirred overnight before being partially evaporated, diluted with CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography of the residue (40/60 EtOAc/hexanes eluent) gave **253** (4.30 g, 8.40 mmol, 61% over four steps) as a colorless oil. $[\alpha]_D^{20}$ −15.3 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (s, 9H); 1.45 (m, 12H); 1.76-2.01 (m, 2H); 2.35-2.49 (m, 1H); 2.52-2.65 (m, 1H); 3.50-3.63 (m, 1H); 3.64-3.80 (m, 2H); 3.89-4.02 (m, 1H); 4.28-4.29 (m, 1H); 4.74 (brd, *J* = 8.1, 1H); 7.35-7.50 (m, 6H); 7.60-7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 25.6, 26.9, 28.4, 28.9, 29.6, 33.9, 49.4, 65.6, 73.0, 79.6, 127.9, 130.0, 132.9, 135.6, 155.5, 171.3; IR (film, cm^{-1}): ν 1708, 1740; HRMS: calc. for $C_{29}H_{41}NO_5Na^{28}Si$ $[M + Na]^+$ 534.2652; found 534.2646.

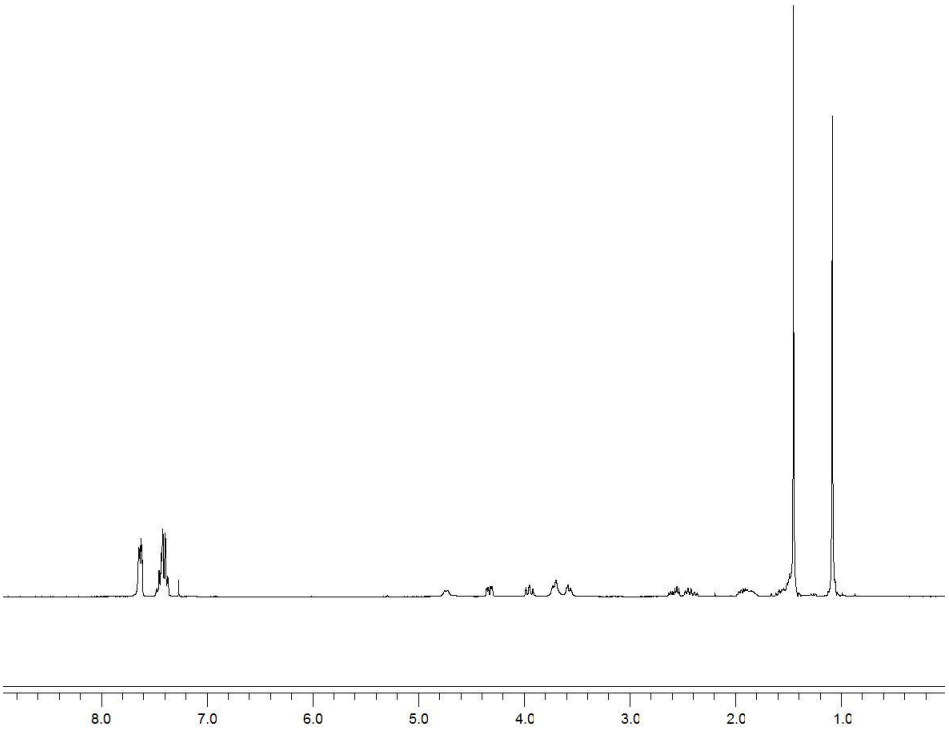


Figure 36. ^{1}H NMR spectrum of **253**

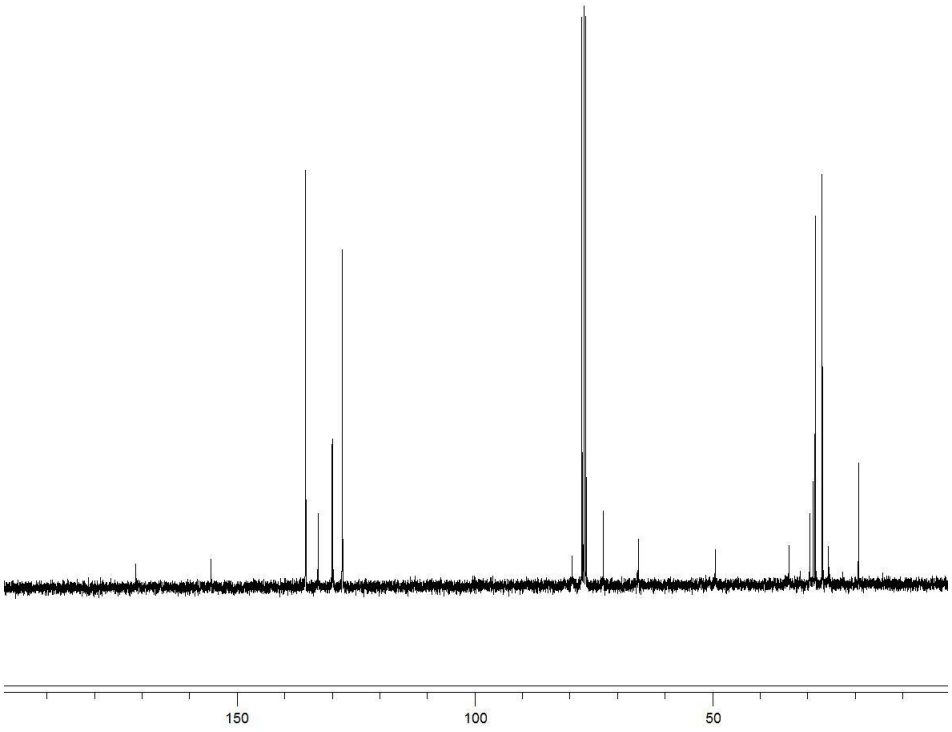
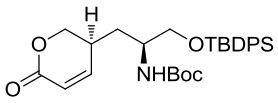


Figure 37. ^{13}C NMR spectrum of **253**

A.15 Preparation of 255



To a solution of diisopropylamine (2.26 mL, 16.1 mmol) in THF (80 mL) at −78 °C was added butyllithium (1.6 M/ hexanes, 10.6 mL, 16.9 mmol). The solution was stirred for 15 min at this temperature, when **253** (4.12 g, 8.05 mmol) was added as a solution in THF (12 mL), and stirring was continued for 1 hour at the same temperature. The solution was then cooled on an EtOH/LN2 bath (about −110 °C), before a solution of phenylselenyl bromide (3.80 g, 16.1 mmol) in THF (15 mL) pre-cooled to saturation (about −78 °C) was added as rapidly as possible. The resulting solution was stirred for an additional 5 min while the cold bath was maintained, at which time a solution of acetic acid (3.6 mL) in THF (3.6 mL) was added. The mixture was allowed to warm to room temperature with stirring. The resulting yellow mass was dissolved in sat. NH_4Cl (aq) and CH_2Cl_2. After separation, the organic layer was washed successively with sat. $NaHCO_3$ (aq) and sat. $Na_2S_2O_3$ (aq) before drying (Na_2SO_4), filtration, and evaporation under vacuum gave a yellow oil. To a suspension of mCPBA (4.20 g, 77% maximum) in CH_2Cl_2 (68 mL) at −78 °C was added a solution of the residue in CH_2Cl_2 (21 mL). The mixture was stirred for 1.5 hours at −78 °C, when pyridine (3.5 mL) was added, and the resulting solution was allowed to warm to room temperature. The reaction mixture was poured into sat. $NaHCO_3$ (aq) which had been previously brought to pH 9.5 with 1 M NaOH, and the layers were separated. The organic extract was washed with an additional portion of pH 9.5 $NaHCO_3$ (aq), dried (Na_2SO_4), filtered through Celite, and evaporated. Flash column chromatography (30/70 EtOAc/hexanes eluent) of the residue gave **255** (2.40 g, 4.71 mmol, 58% yield) as an amorphous white solid, m.p. 121-122 °C. $[\alpha]_D^{20}$ +10.9 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H); 1.45 (s, 9H); 1.57-1.67 (m, 2H); 2.43-2.56 (m, 1H); 3.54-3.64 (m, 1H); 3.68-3.84 (m, 2H);

4.23 (dd, *J* = 11.3,5.8, 1H); 4.43 (dd, *J* = 11.3, 4.6, 1H); 4.72 (brd, *J* = 9.0, 1H); 5.98 (dd, *J* = 9.8, 1.5, 1H); 6.83 (dd, *J* = 9.8, 4.3, 1H); 7.35-7.49 (m, 6H); 7.59-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 26.9, 28.4, 31.0, 33.0, 49.5, 66.0, 70.0, 79.7, 120.7, 127.9, 130.0, 132.9, 135.5, 150.2, 155.6, 163.8; IR (cm^{-1}): 1510, 1699, 1720; HRMS: calc. for $C_{29}H_{39}NO_5Na^{28}Si$ $[M + Na]^+$ 532.2495; found 532.2499.

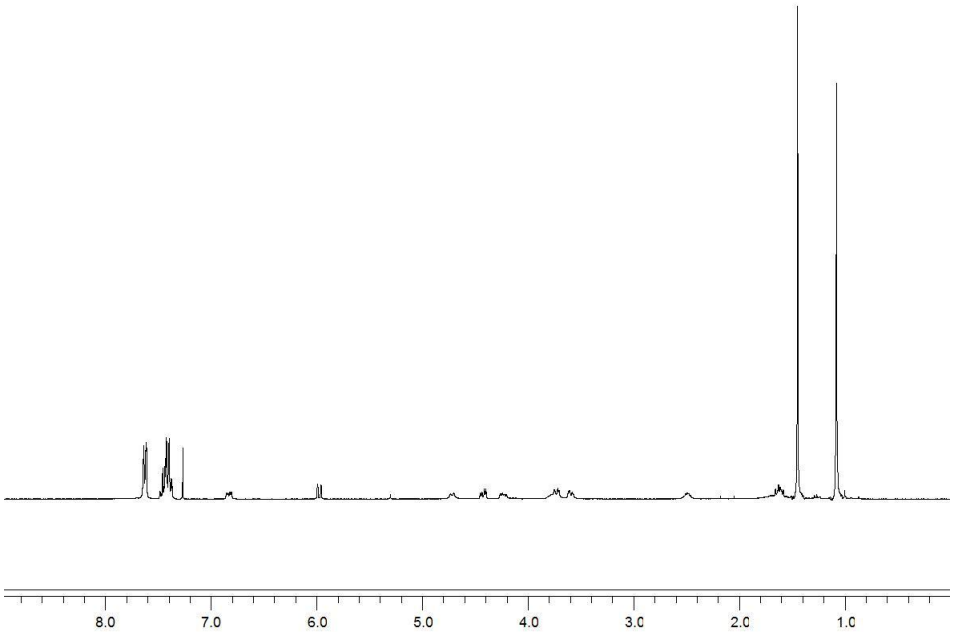


Figure 38. ^{1}H NMR spectrum of **255**

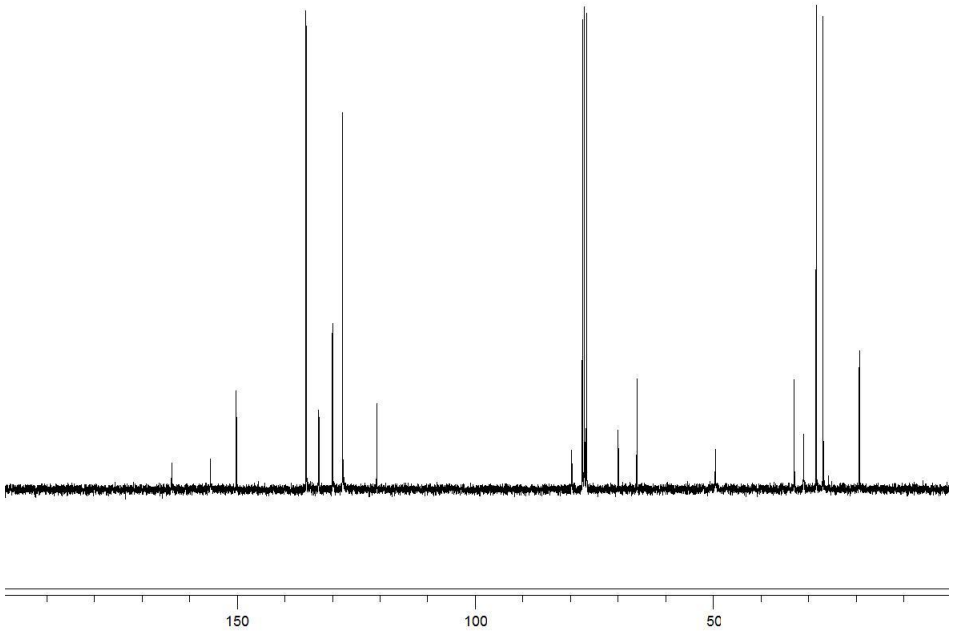
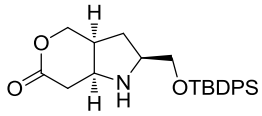


Figure 39. ^{13}C NMR spectrum of **255**

A.16 Preparation of 232 from 255



To a solution of **255** (1.16 g, 2.27 mmol) in CH_2Cl_2 (12 mL) at rt was added TFA (1.2 mL, containing 1% v/v TFAA) and the solution was stirred overnight at rt. Na_2CO_3 (s) (500 mg, 4.7 mmol) was added followed by the careful dropwise addition of water (5 mL) (GAS EVOLUTION). The mixture was diluted with water and CH_2Cl_2, and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give **232**, a faintly-colored oil. $[\alpha]_D^{20}$ –30.1 (c 1.1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.25-1.38 (m, 1H), 1.90-1.99 (m, 1H), 2.51-2.60 (m, 2H), 2.68 (dd, *J* = 15.3, 5.4, 1H), 3.19-3.28 (m, 1H), 3.61 (dd, *J* = 10.1, 6.5, 1H), 3.69-3.77 (m, 2H), 4.08 (dd, *J* = 11.7, 5.2, 1H), 4.22 (dd, *J* = 11.6, 4.4, 1H), 7.35-7.47 (m, 6H), 7.61-7.70 (m, 4H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 30.8, 36.4, 36.5, 53.3, 59.9, 67.0, 69.2, 127.7, 129.7, 133.4, 133.5, 135.5, 135.6, 172.2; IR (film, cm^{-1}): ν 1747; HRMS: calc. for $C_{24}H_{32}NO_3{}^{28}Si$ $[M + H]^+$ 410.2151; found 410.2148.

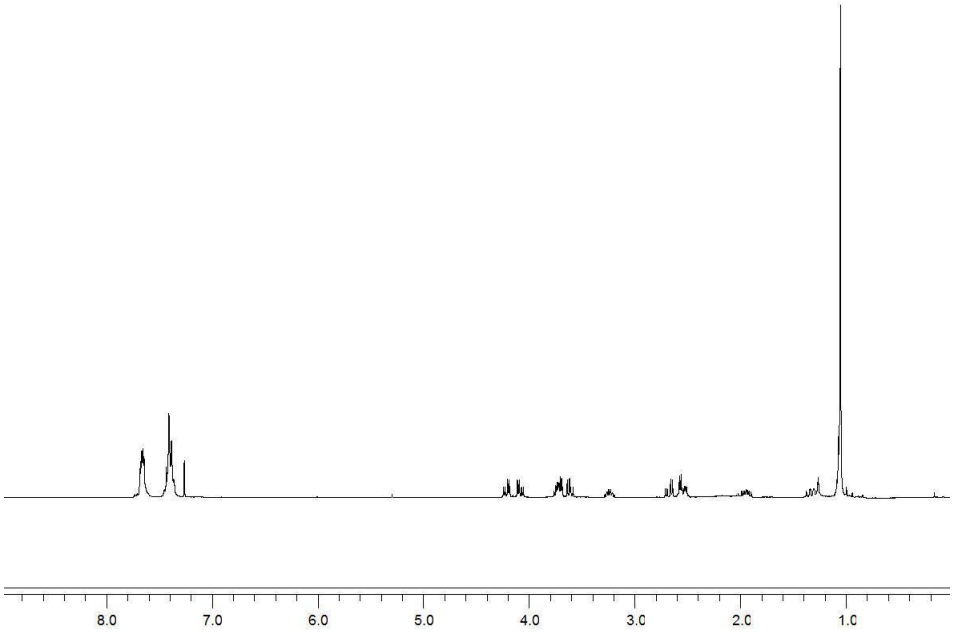


Figure 40. ^{1}H NMR spectrum of **232**

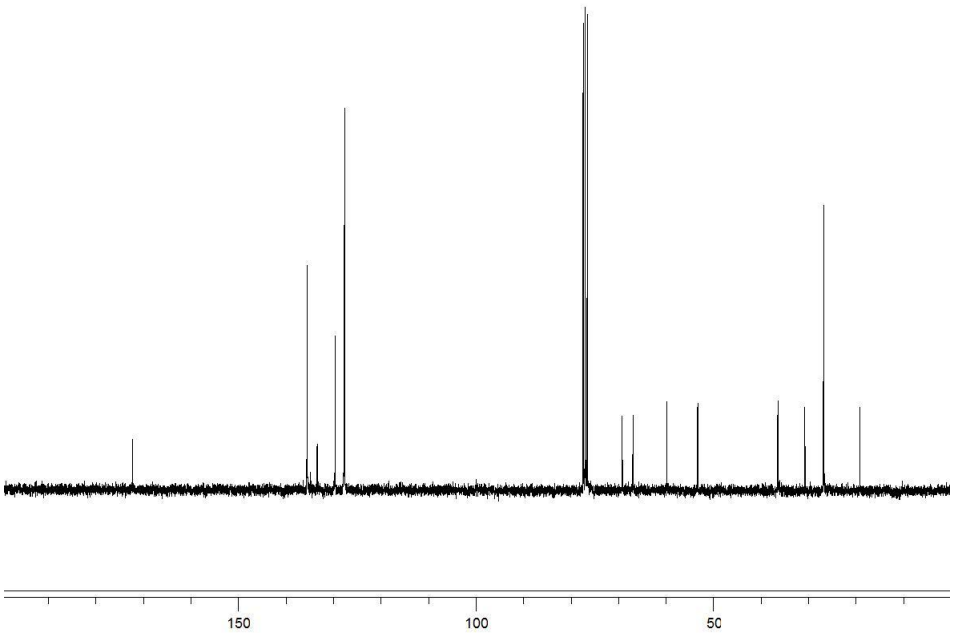
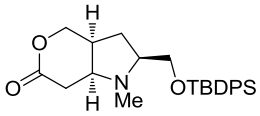


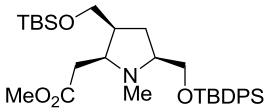
Figure 41. ^{13}C NMR spectrum of **232**

A.17 Preparation of 238 from 232



To a solution of residual **232** (2.27 mmol) in MeCN (10 mL) was added formaldehyde (37% aq., 1.1 mL, 12.2 mmol) and $NaBH_3CN$ (830 mg, 13.2 mmol). After the mixture was cooled to 10 °C, AcOH (2.0 mL) was added dropwise over several minutes. Stirring was continued at rt for forty minutes, when the mixture was diluted with sat. $NaHCO_3$ (aq) and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with a second portion of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography (35/65 EtOAc/hexanes eluent) gave **238** (651 mg, 1.54 mmol, 68% yield over two steps) as a colorless oil. Analytical data was identical to the material produced by the procedure reported above.

A.18 Preparation of 256



To a solution of **238** (32 mg, 0.076 mmol) in THF (1 mL) at rt was added H_2O (0.2 mL) and LiOH•H_2O (5 mg, 0.1 mmol). The mixture was stirred for 3 hours before being evaporated under reduced pressure, and co-evaporated once with toluene, to give a white foam. The residue was dissolved in 1:1 CH_2Cl_2:pyridine (1 mL) at −30 °C, to which was added TBSOTf (0.06 mL, 0.3 mmol). The solution was brought to rt, and stirring continued for 1.5 hours. The reaction mixture was poured into pH 7 phosphate buffer and extracted thrice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and stripped of solvent under vacuum. The residue, a colorless oil, was dissolved in 1:1 CH_2Cl_2:MeOH (1 mL) at rt, to which was cautiously added $TMSCHN_2$ (2.0 M/hexanes, 0.15 mL, 0.30 mmol) (GAS EVOLUTION). After the addition was complete the yellow solution was stirred for 25 minutes, before the reaction was stripped of volatiles under reduced pressure. The residue was purified by column chromatography (15/85 EtOAc/hexanes eluent) to give **256** (28 mg, 0.049 mmol, 65% yield over three steps) as a colorless oil. $[\alpha]_D^{20}$ +5.2 (c 0.7, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 6H); 0.87 (s, 9H); 1.06 (s, 9H); 1.25-1.39 (m, 1H); 1.97-2.10 (m, 1H); 2.27 (s, 3H); 2.29-2.63 (m, 4H); 2.88-2.98 (m, 1H); 3.38 (dd, *J* = 10.2, 6.6, 1H); 3.48 (dd, *J* = 10.2, 6.1, 1H); 3.60-3.74 (m, 5H); 7.34-7.46 (m, 6H); 7.66-7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4, −5.4, 18.3, 19.2, 25.9, 26.8, 30.7, 35.0, 41.0, 41.5, 51.4, 63.9, 65.2, 67.1, 67.8, 127.6, 129.5, 133.8, 133.8, 135.6, 135.7, 173.2; IR (film, cm^{-1}): ν 1740; HRMS: calc. for $C_{32}H_{52}NO_4{}^{28}Si_2$ $[M + H]^+$ 570.3435; found 570.3423.

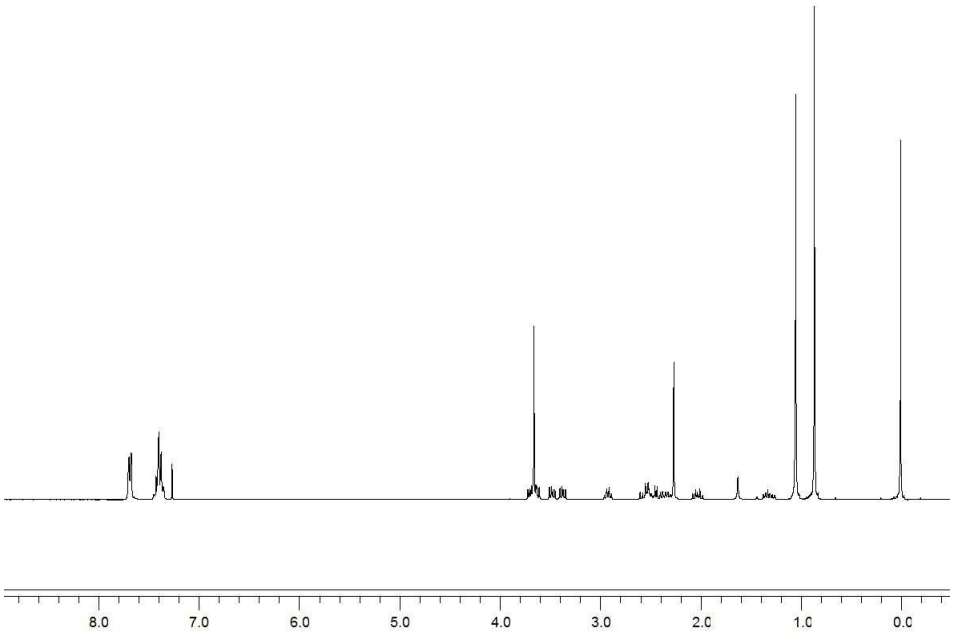


Figure 42. ^{1}H NMR spectrum of **256**

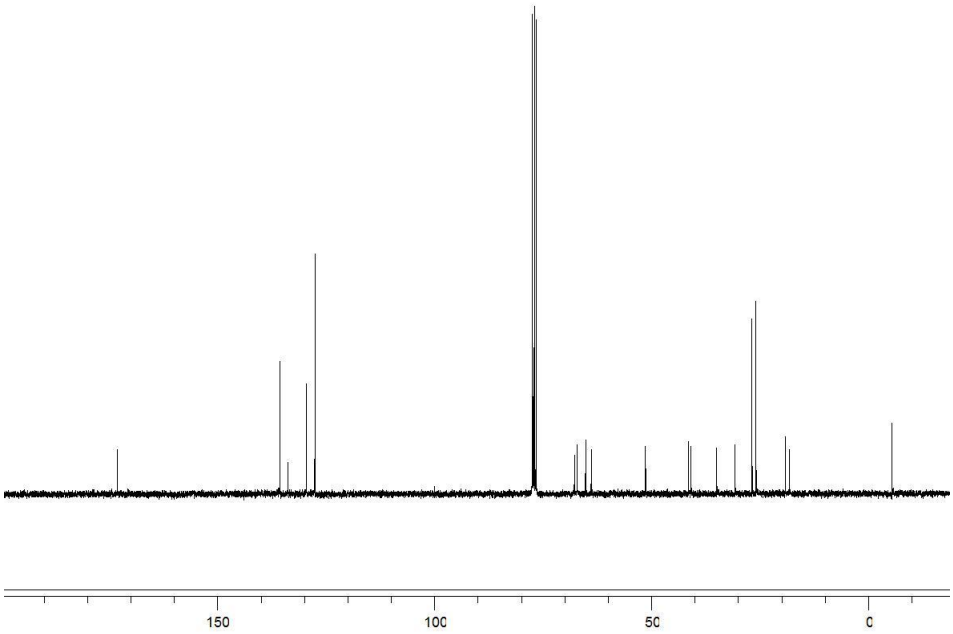
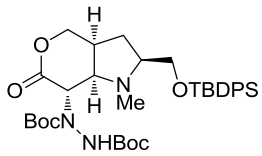


Figure 43. ^{13}C NMR spectrum of **256**

A.19 Preparation of 259



To a solution of **238** (39 mg, 0.092 mmol) in THF (1.2 mL) at −78 °C was added NaHMDS (1 M/THF, 0.14 mL, 0.14 mmol), and the solution was stirred for 2 hours at the same temperature. A solution of di-*tert*-butyl azodicarboxylate (32 mg, 0.14 mmol) in THF (0.3 mL) was then added. Upon consumption of starting material (35 min, TLC), the reaction mixture was poured into sat. $NaHCO_3$ (aq), when extraction proceeded with two portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The crude material was purified by column chromatography (15/85 EtOAc/hexanes eluent) to give **259** (43 mg, 0.066 mmol, 72% yield), a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H); 1.21-1.33 (m, 1H); 1.48 (apps, 18H); 2.04-2.21 (m, 1H); 2.33-2.49 (m, 4H); 2.50-2.63 (m, 1H); 2.81-2.96 (m, 1H); 3.54 (dd, *J* = 11.7, 5.1, 1H); 3.73 (dd, *J* = 11.7, 4.2, 1H); 4.04 (dd, *J* = 11.1, 4.5, 1H); 4.16 (appt, *J* = 11.4, 1H); 5.01 (brs, 1H); 6.67 (brs, 1H); 7.35-7.49 (m, 6H); 7.62-7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 26.8, 28.1, 28.2, 36.4, 39.0, 64.9, 65.7, 67.0, 69.7, 77.2, 80.9, 82.5, 127.7, 129.7, 133.5, 133.6, 135.6, 135.7, 155.0, 155.6, 155.7, 171.3; HRMS: calc. for $C_{35}H_{52}N_3O_7{}^{28}Si$ $[M + H]^+$ 654.3575; found 654.3585.

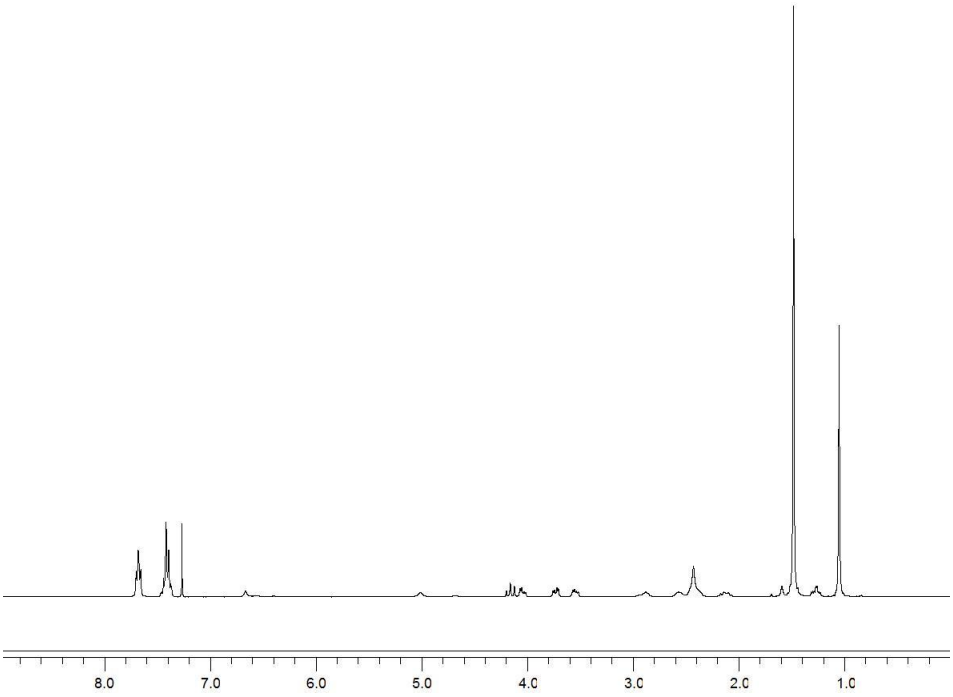


Figure 44. ^{1}H NMR spectrum of **259**

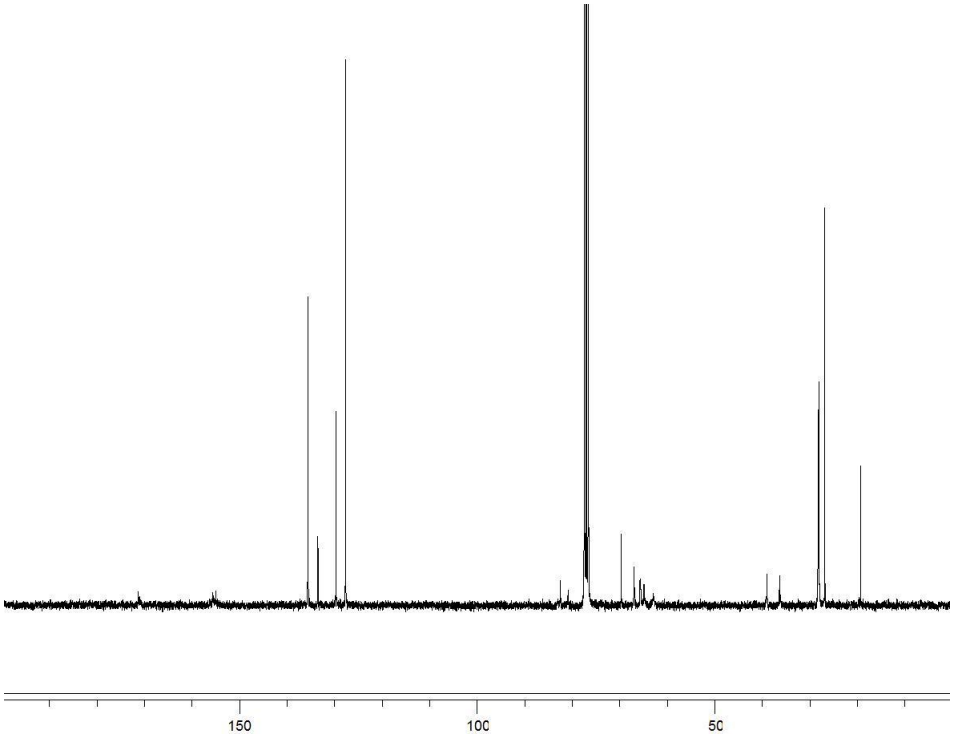
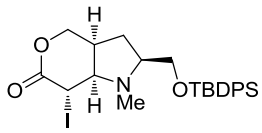


Figure 45. ^{13}C NMR spectrum of **259**

A.20 Preparation of 265



To a solution of **238** (628 mg, 1.48 mmol) in THF (12 mL) at −78 °C was added NaHMDS (0.6 M/ toluene, 3.0 mL, 1.8 mmol), and the solution was stirred for one hour at the same temperature. A solution of I_2 in THF (100 mg/mL) was then added dropwise until the yellow-brown iodine color persisted (4.0 mL was needed). Stirring continued for 10 minutes, with additional iodine solution added as necessary to maintain the yellow/brown color, when the reaction was quenched by the sequential addition of sat. NH_4Cl (aq) (6 mL) and sat. $Na_2S_2O_3$ (aq) (4 mL). After warming to rt with continued stirring, the resulting white suspension was diluted with pH 7 phosphate buffer and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and stripped of volatiles under vacuum to give a colorless oil which was pure **265** (808 mg, 1.47 mmol, quantitative). $[\alpha]_D^{20}$ −16.3 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H); 1.61-1.74 (m, 1H); 2.10-2.22 (m, 1H); 2.31 (s, 3H); 2.45-2.56 (m, 1H); 2.56-2.70 (m, 1H); 3.32 (dd, *J* = 9.9, 1.5, 1H); 3.53 (dd, *J* = 10.3, 5.5, 1H); 3.72 (dd, *J* = 10.3, 5.0, 1H); 4.27 (d, *J* = 11.8, 1H); 4.31 (d, *J* = 1.4, 1H); 4.84 (dd, *J* = 11.8, 3.8, 1H); 7.35-7.49 (m, 6H); 7.62-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 19.2, 26.8, 32.7, 32.9, 39.8, 66.0, 66.4, 69.9, 71.2, 127.7, 129.7, 133.4, 133.5, 135.5, 135.6, 167.8; IR (film, cm^{-1}): ν 1739; HRMS: calc. for $C_{25}H_{32}NO_3Na^{28}SiI$ $[M + Na]^+$ 572.1094; found 572.1083.

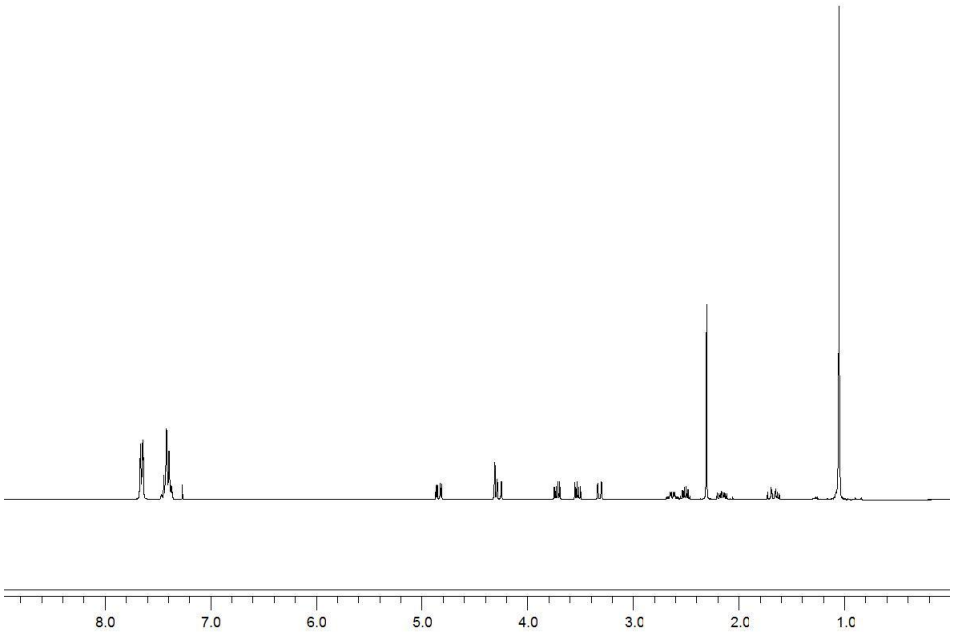


Figure 46. ^{1}H NMR spectrum of **265**

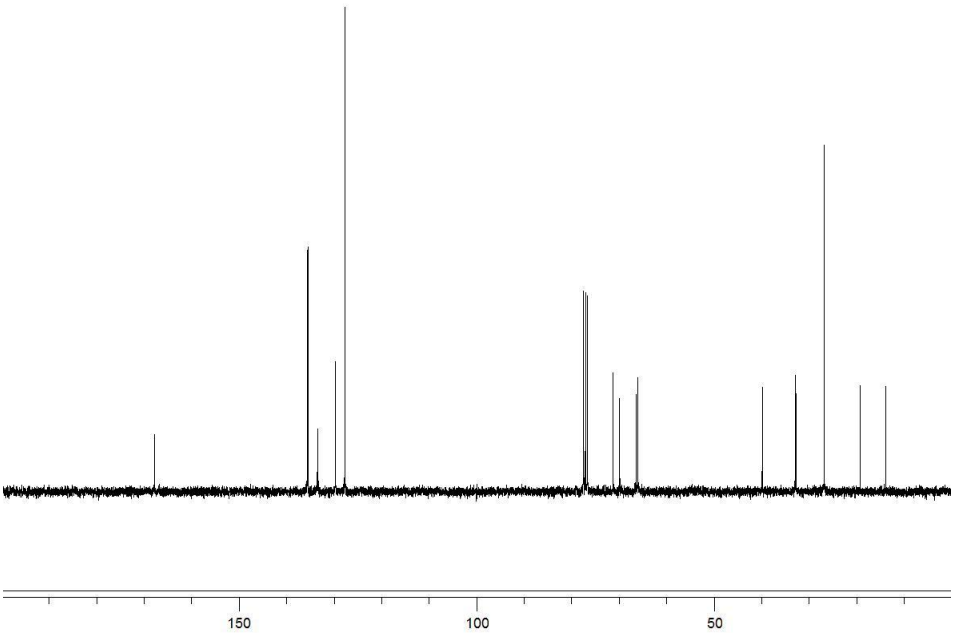
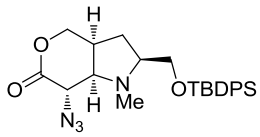


Figure 47. ^{13}C NMR spectrum of **265**

A.21 Preparation of 266



To **265** (808 mg, 1.47 mmol) and NaN_3 (350 mg, 5.4 mmol) was added DMF (8.0 mL), and the resulting suspension was stirred vigorously at rt for 35 minutes. The mixture was diluted with ethyl acetate and half-saturated brine and poured into pH 7 phosphate buffer. The layers were separated, and the aqueous layer was extracted several times with ethyl acetate. The combined organic layers were washed four times with brine, dried (Na_2SO_4), filtered, and evaporated under vacuum. Flash column chromatography (20/80 to 30/70 EtOAc/hexanes gradient elution) of the residue gave **266** (506 mg, 1.09 mmol, 74% yield) as a colorless oil. In addition, some **267** (33 mg, 0.07 mmol, 5% yield) was isolated. Analytical data for **266**: $[\alpha]_D^{20}$ −29.9 (c 0.5, EtOH); ^{1}H NMR (300 MHz, acetone-*d*6): δ 1.07 (s, 9H); 1.39-1.51 (m, 1H); 2.13-2.24 (m, 1H); 2.44 (s, 3H); 2.65-2.81 (m, 3H); 3.63 (dd, *J* = 10.3, 5.3, 1H); 3.83 (dd, *J* = 10.3, 4.5, 1H); 4.13-4.22 (m, 1H); 4.34 (dd *J* = 11.3, 5.5, 1H); 4.48 (d, *J* = 7.0, 1H); 7.42-7.53 (m, 6H); 7.70-7.78 (m, 4H); ^{13}C NMR (75 MHz, acetone-*d*6): δ 18.9, 26.4, 29.9, 35.4, 39.8, 63.5, 66.0, 67.6, 68.0, 68.9, 127.8, 129.8, 133.4, 135.5, 169.1; IR (film, cm^{-1}): ν 1754, 2107; HRMS: calc. for $C_{25}H_{32}N_4O_3Na^{28}Si$ $[M + Na]^+$ 487.2141; found 487.2136.

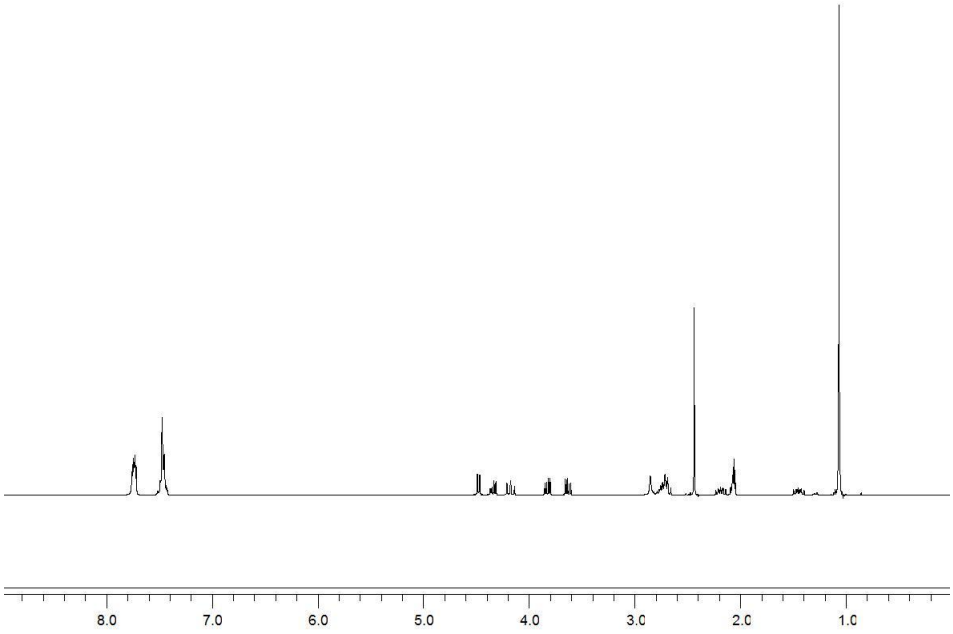


Figure 48. ^{1}H NMR spectrum of **266**

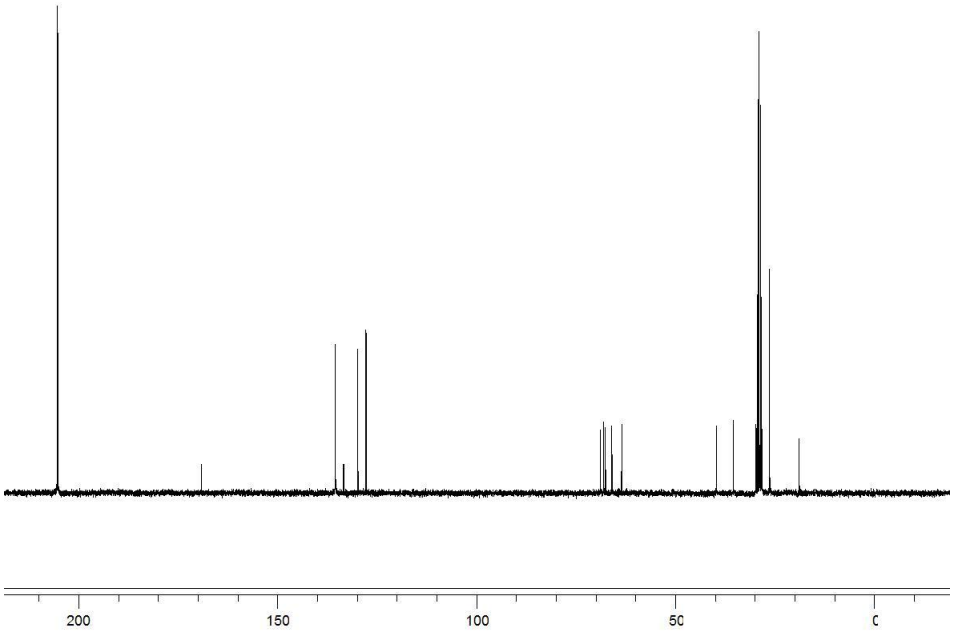


Figure 49. ^{13}C NMR spectrum of **266**

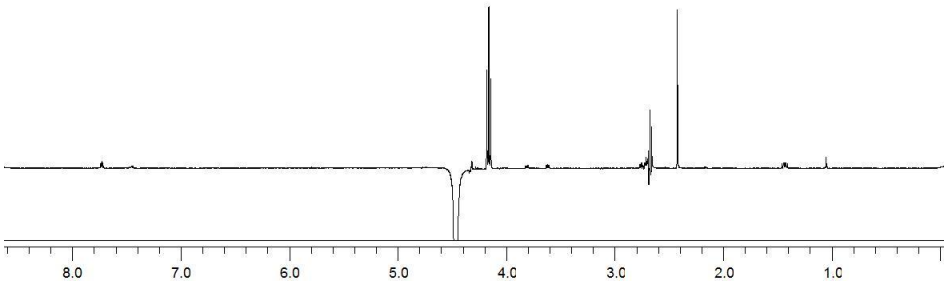
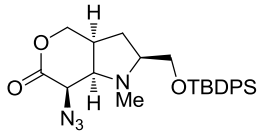


Figure 50. NOE spectrum of **266**, irradiation at 4.47 ppm

A.22 Preparation of 267



To a solution of **266** (365 mg, 0.79 mmol) in MeCN (8 mL) at −20 °C was added DBU (12 μL, 0.078 mmol) as a solution in CH_2Cl_2 (0.12 mL). The mixture was stirred for 2 hours at the same temperature before being diluted with CH_2Cl_2 and poured into sat. $NaHCO_3$ (aq), the layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2. After drying (Na_2SO_4), filtration, and removal of solvent under vacuum, the residue was purified by column chromatography (20/80 to 30/70 EtOAc/Hexanes gradient elution). The desired diastereomer **267** was isolated (178 mg, 0.38 mmol, 49% yield, 81% BRSM), along with some recovered **266** (145 mg, 0.31 mmol). Analytical data for **267**: $[\alpha]_D^{20}$ −54.9 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H); 1.66-1.79 (m, 1H); 2.11-2.22 (m, 1H); 2.51 (s, 3H); 2.57-2.79 (m, 2H); 3.31 (dd, *J* = 10.3, 5.2, 1H); 3.51 (dd, *J* = 10.4, 6.0, 1H); 3.74 (dd, *J* = 10.4, 4.9, 1H); 3.93 (d, *J* = 5.1, 1H); 4.10-4.25 (m, 2H); 7.35-7.48 (m, 6H); 7.61-7.70 (m 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 32.1, 36.1, 42.7, 61.0, 66.8, 67.3, 67.7, 127.7, 129.6, 129.7, 133.4, 133.6, 135.5, 135.6, 168.6; IR (film, cm^{-1}): ν 1755, 2111; HRMS: calc. for $C_{25}H_{32}N_4O_3Na^{28}Si$ $[M + Na]^+$ 487.2141; found 487.2130.

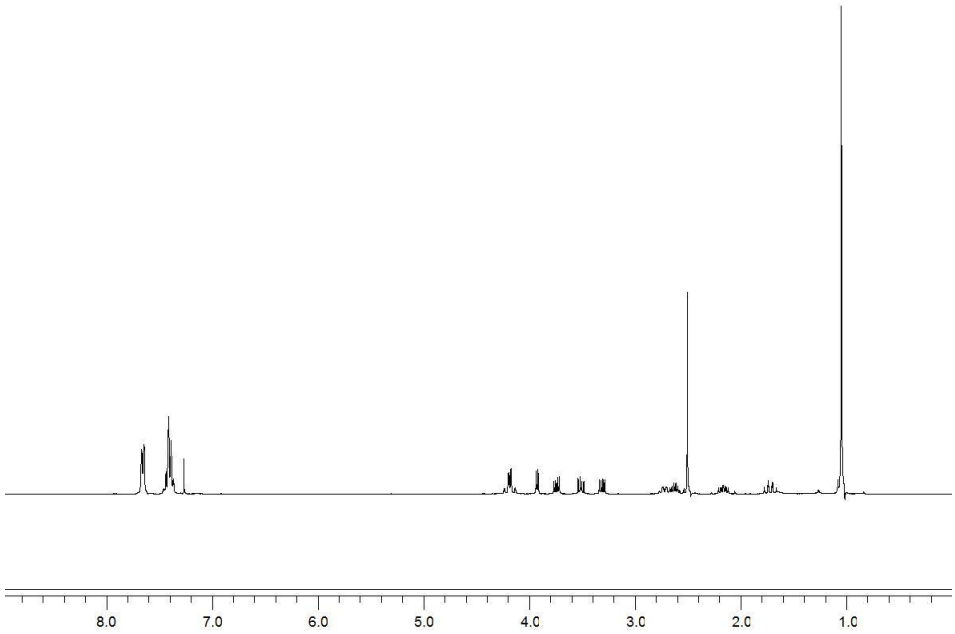


Figure 51. ^{1}H NMR spectrum of **267**

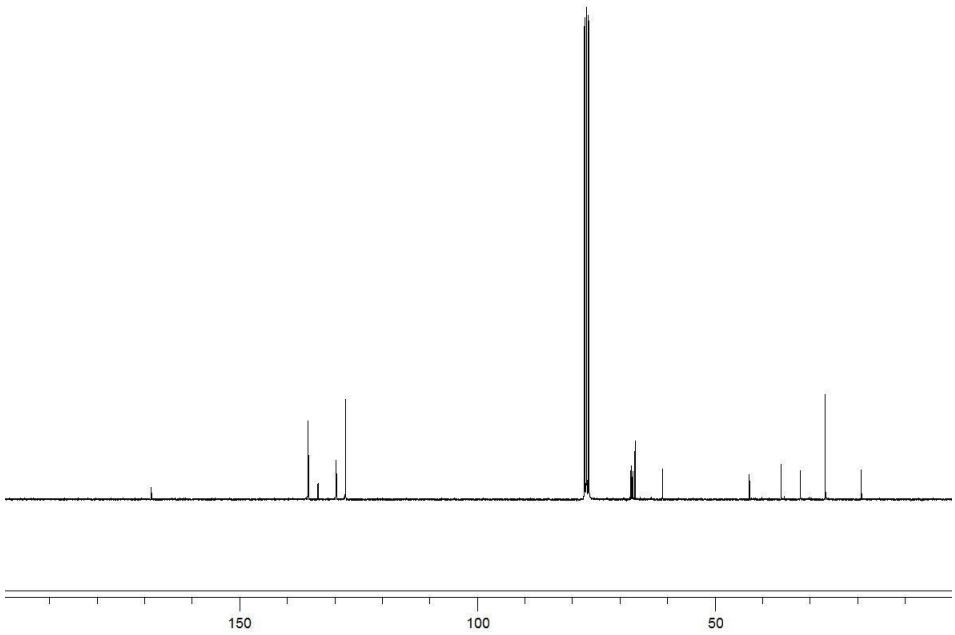


Figure 52. ^{13}C NMR spectrum of **267**

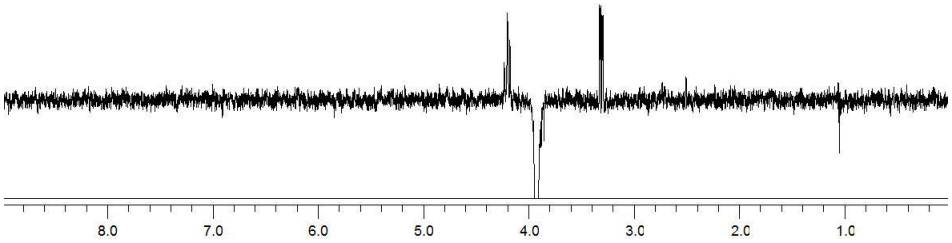
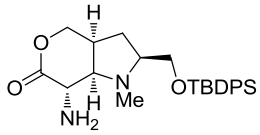


Figure 53. NOE spectrum of **267**, irradiation at 3.92 ppm

A.23 Preparation of 273



A solution of **266** (45 mg, 0.097 mmol) in EtOAc (1 mL) was flushed with argon before Pd/C (10%, 30 mg) was added, and the system was flushed with H_2 gas. The mixture was stirred for 5 hours, then filtered through Celite and concentrated under vacuum. The residue was pure **273** (40 mg, 0.091 mmol, 94% yield), a colorless oil. $[\alpha]_D^{20}$ −31.3 (c 0.3, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H); 1.22-1.34 (m, 1H); 1.67 (brs, 2H); 2.07-2.19 (m, 1H); 2.41-2.48 (m, 1H); 2.49 (s, 3H); 2.53-2.67 (m, 2H); 3.52-3.60 (m, 2H); 3.79 (dd, *J* = 10.5, 4.5, 1H); 4.05 (appt, *J* = 11.2, 1H); 4.23 (dd, *J* = 11.2, 5.6, 1H); 7.33-7.48 (m, 6H); 7.61-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 30.1, 36.0, 41.1, 56.6, 66.2, 68.3, 69.2, 70.9, 127.7, 129.6, 133.5, 135.6, 176.0; IR (film, cm^{-1}): ν 1749; HRMS: calc. for $C_{25}H_{35}N_2O_3{}^{28}Si$ $[M + H]^+$ 439.2417; found 439.2425.

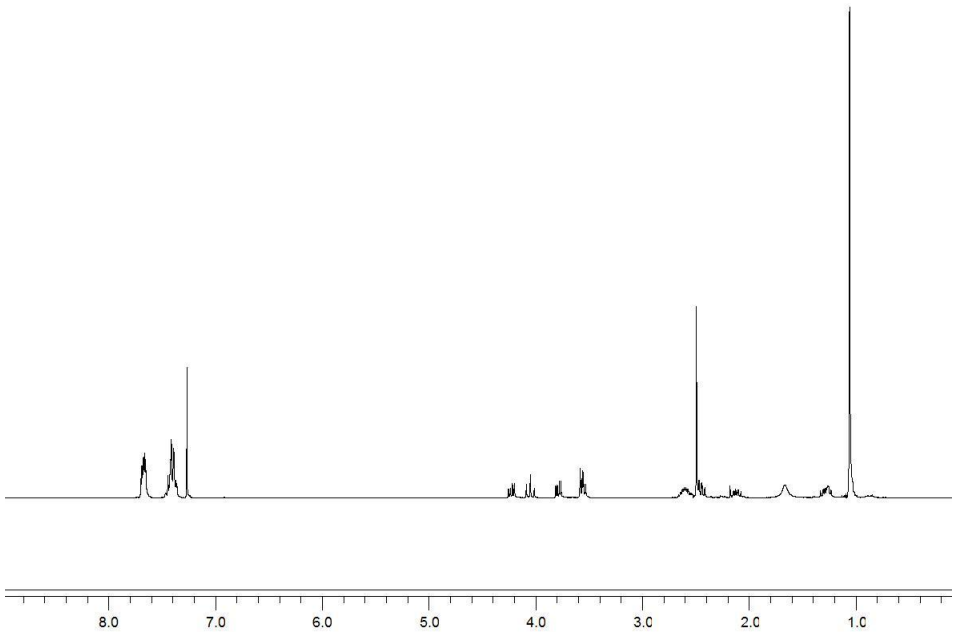


Figure 54. ^{1}H NMR spectrum of **273**

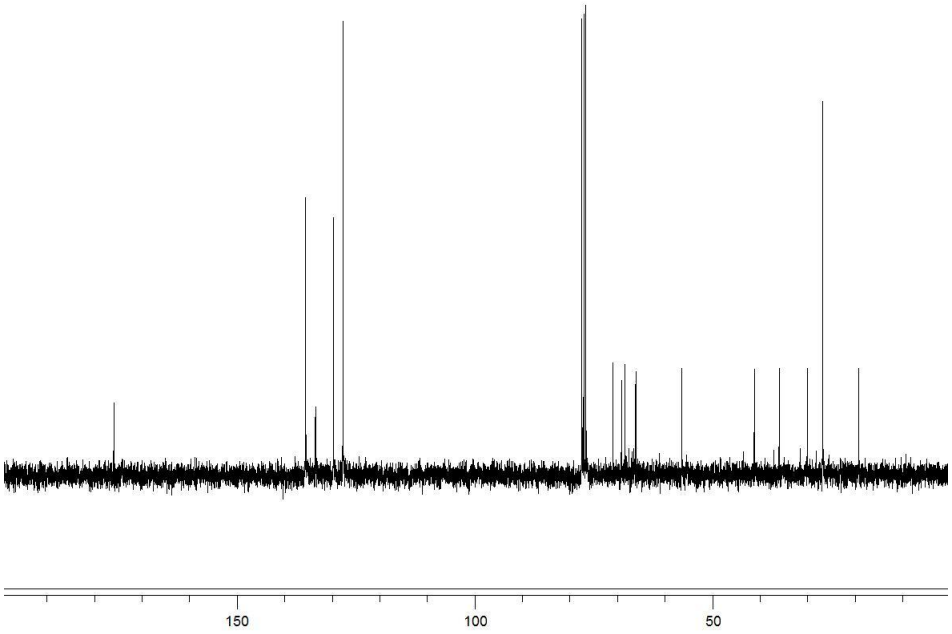
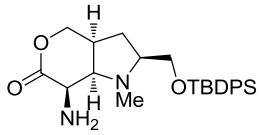


Figure 55. ^{13}C NMR spectrum of **273**

A.24 Preparation of 274



To a solution of **267** (249 mg, 0.54 mmol) in EtOAc (7 mL) was added Pd/C (10%, 80 mg), and the system was flushed with H_2 gas. The mixture was stirred for 3.5 hours, filtered through Celite, and concentrated under vacuum. The residue was pure **274** (223 mg, 0.51 mmol, 95% yield), a colorless oil. $[\alpha]_D^{20}$ −66.1 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H); 1.60-1.74 (m, 1H); 1.89 (brs, 2H); 2.03-2.17 (s, 1H); 2.44 (s, 3H); 2.56-2.79 (m, 2H); 3.30 (dd, *J* = 10.4, 6.0, 1H); 3.43-3.52 (m, 2H); 3.72 (dd, *J* = 10.4, 4.9, 1H); 4.14-4.28 (m, 2H); 7.34-7.48 (m, 6H); 7.61-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 31.7, 36.4, 44.1, 55.0, 66.6, 66.8, 67.2, 67.9, 127.7, 129.7, 133.5, 133.7, 135.5, 175.6; IR (film, cm^{-1}): ν 1748; HRMS: calc. for $C_{25}H_{35}N_2O_3{}^{28}Si$ $[M + H]^+$ 439.2417; found 439.2413.

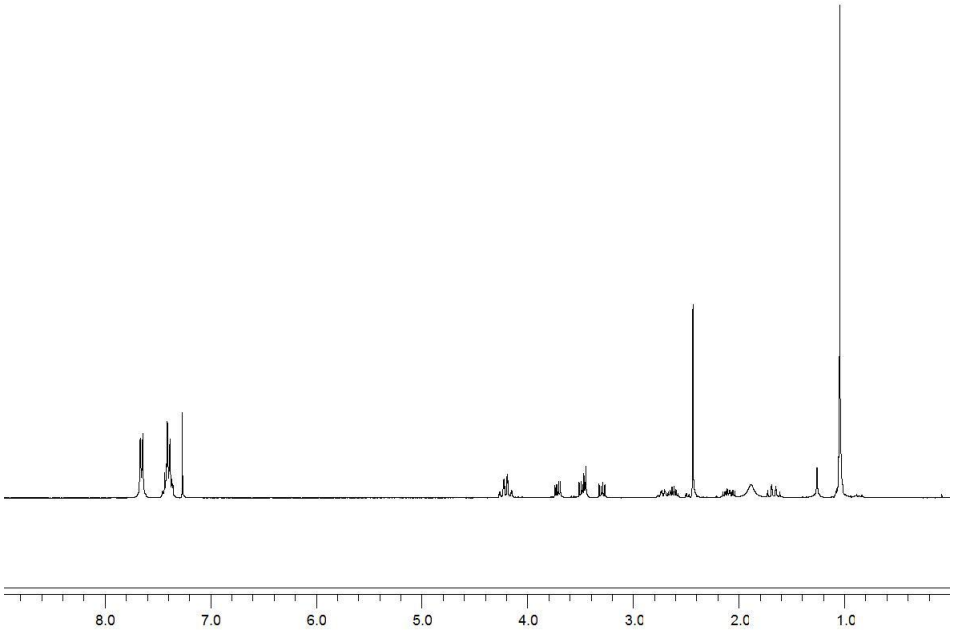


Figure 56. ^{1}H NMR spectrum of **274**

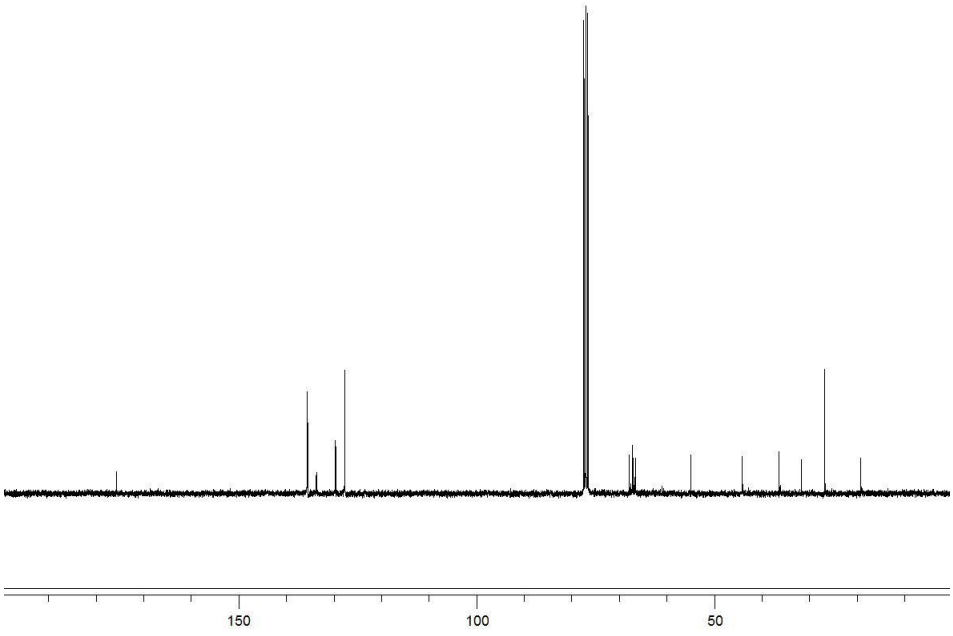
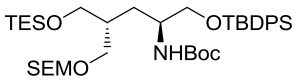


Figure 57. ^{13}C NMR spectrum of **274**

A.25 Preparation of 278



To a solution of **234** (1.21 g, 1.97 mmol) in THF (10 mL) and EtOH (0.2 mL) was added $LiBH_4$ (86 mg, 3.94 mmol). The resulting suspension was stirred overnight at rt, when TLC monitoring indicated consumption of starting material. The mixture was quenched with sat. NH_4Cl (aq) (GAS EVOLUTION!) and poured into additional sat. NH_4Cl (aq). Extraction proceeded with two portions of CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and stripped of solvent under vacuum to give a colorless oil, which was carried on without further purification. To a solution of 800 mg of the residue in CH_2Cl_2 (16 mL) was added TESCl (0.23 mL, 1.4 mmol) and imidazole (95 mg, 1.4 mmol). The solution was stirred for 1 hour at rt before being diluted with CH_2Cl_2 and washed with 0.05 M HCl (aq). The organic extract was dried (Na_2SO_4) and stripped of solvent under vacuum to give pure **278** (885 mg, 1.95 mmol), a colorless oil. $[\alpha]_D^{20}$ −16.0 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H); 0.60 (q, *J* = 7.8, 6H); 0.91-1.00 (m, 12H); 1.06 (s, 9H); 1.43 (s, 9H); 1.56-1.67 (m, 2H); 1.80-1.91 (m, 1H); 3.50-3.82 (m, 9H); 4.64 (s, 2H); 4.79-4.88 (m, 1H); 7.33-7.48 (m, 6H); 7.61-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.4, 4.3, 6.8, 18.1, 19.3, 26.9, 28.4, 30.4, 38.5, 50.3, 63.7, 65.0, 66.3, 67.9, 78.8, 95.1, 127.7, 127.8, 129.7, 129.8, 133.4, 135.6, 135.6, 155.5; IR (film, cm^{-1}): ν 1715; HRMS: calc. for $C_{33}H_{56}NO_6{}^{28}Si_2$ $[M - SiEt_3 + 2H]^+$ 618.3646; found 618.3661.

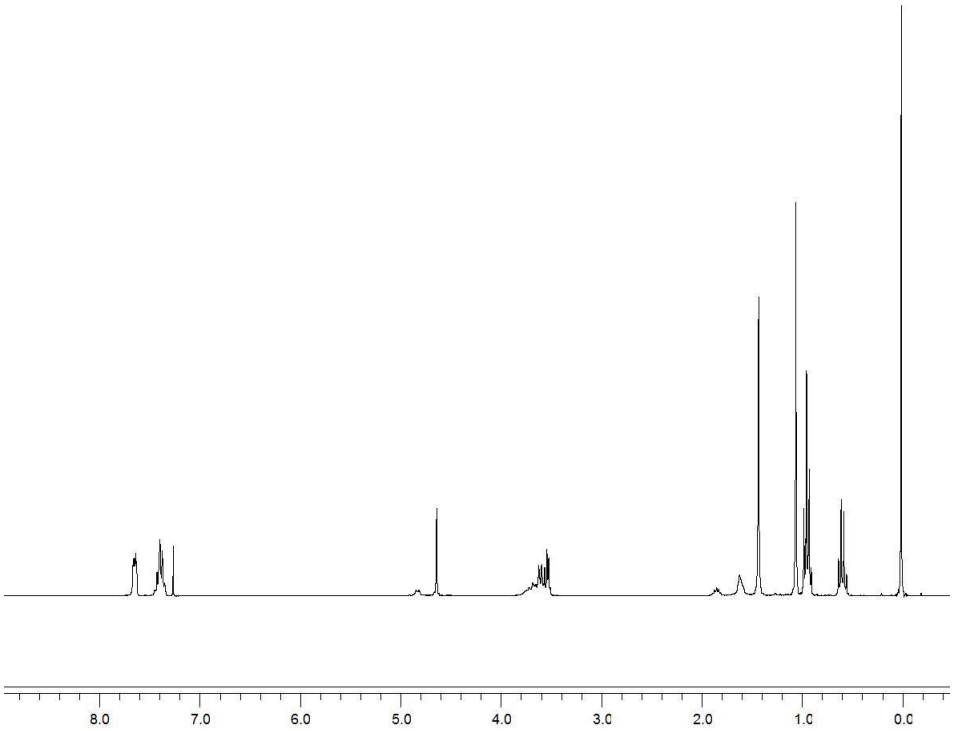


Figure 58. ^{1}H NMR spectrum of **278**

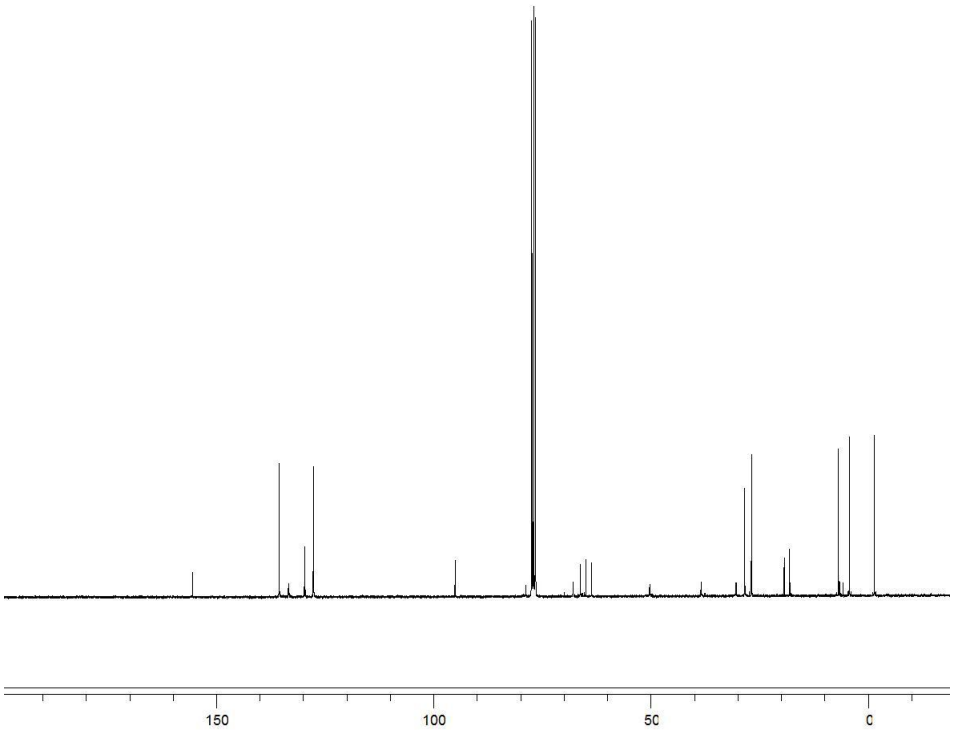
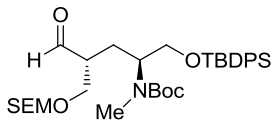


Figure 59. ^{13}C NMR spectrum of **278**

A.26 Preparation of 279



To a solution of **278** (833 mg, 1.14 mmol) in THF (14 mL) at −40 °C was added BuLi (0.78 mL, 1.6 M/ hexanes, 1.25 mmol), and stirring was continued for 30 min as the solution warmed to −10 °C. Dimethyl sulfate (TOXIC) was then added and stirring continued until starting material was consumed (TLC, 1 hour). Water (2 mL) and PPTS (315 mg, 1.25 mmol) were then added and the solution was warmed to rt and left for 3 hours. The mixture was poured into sat. $NaHCO_3$ (aq) and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered, and stripped of solvent under vacuum to give a colorless oil. To a solution of a portion of this material (65 mg, 0.1 mmol) in CH_2Cl_2 (1.4 mL) and DMSO (0.7 mL) was added triethylamine (0.07 mL, 0.50 mmol) and sulfur trioxide pyridine complex (64 mg, 0.40 mmol). The solution was stirred at rt for 1.5 hours, when TLC monitoring indicated consumption of starting material. The mixture was poured into 0.05 M HCl (aq) and extracted with additional CH_2Cl_2. The organic extract was dried (Na_2SO_4) and stripped of solvent under vacuum, and the residue was purified by column chromatography (20/80 EtOAc/Hexanes eluent) to give pure **279** (57 mg, 0.090 mmol), a colorless oil which existed as a rotameric mixture at rt. $[\alpha]_D^{20}$ −7.7 (c 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.04-0.05 (m, 9H); 0.87-0.98 (m, 2H), 0.98-1.10 (m, 9H); 1.21-1.54 (m, 10H); 1.82-1.96 (m, 1H); 2.38-2.57 (m, 1H); 2.59-2.81 (m, 3H); 3.49-3.68 (m, 4H); 3.71-3.81 (m, 1H); 3.84-3.93 (m, 1H); 4.15-4.49 (m, 1H); 4.55-4.72 (m, 2H); 7.32-7.48 (m, 6H); 7.59-7.70 (m, 4H); 9.69-9.72 (m, 1H); ^{1}H NMR (300 MHz, DMSO-*d6*, 80 °C): δ 0.00 (s, 9H); 0.84-0.90 (m, 2H); 1.02 (s, 9H); 1.40 (s, 9H); 1.45-1.54 (m, 1H); 1.79-1.89 (m, 1H); 2.38-2.45 (m, 1H); 2.64 (s, 3H); 3.51-3.81 (m, 6H); 4.22 (m, 1H); 4.57 (s, 2H); 7.37-7.49 (m,

6H); 7.58-7.66 (m, 4H); 9.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.4, 18.0, 19.2, 24.2, 26.8, 28.4, 49.0, 49.3, 64.2, 65.2, 65.3, 65.7, 79.4, 79.9, 95.0, 127.7, 128.4, 128.6, 129.7, 132.0, 132.0, 132.2, 133.3, 135.6, 156.0, 156.3, 202.7, 203.4; IR (film, cm^{-1}): ν 1692, 1737; HRMS: calc. for $C_{34}H_{55}NO_6Na^{28}Si_2$ $[M + H]^+$ 652.3466; found 652.3464.

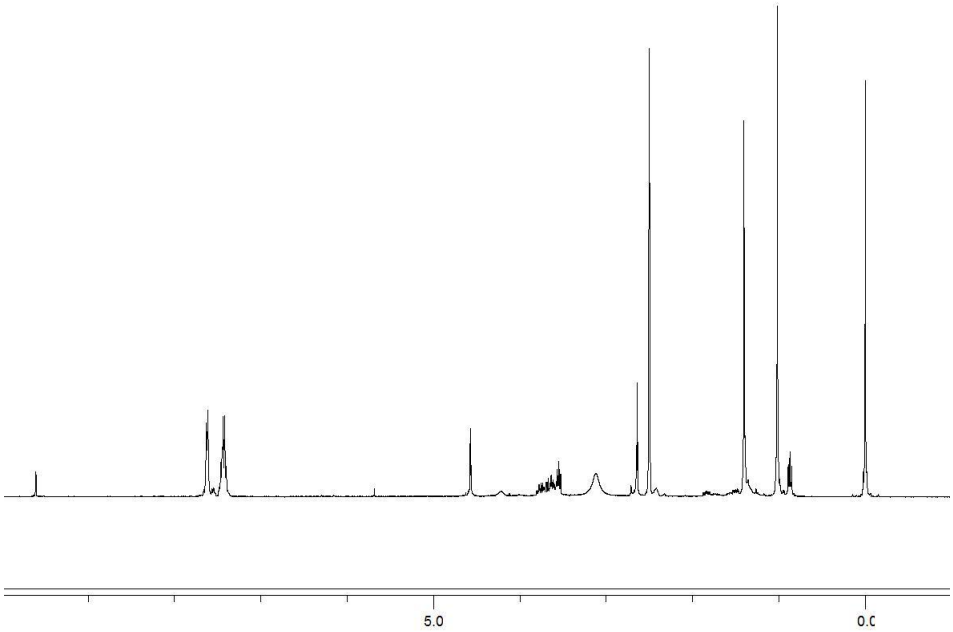


Figure 60. ^{1}H NMR spectrum of **279** at 80 °C in DMSO-*d*6

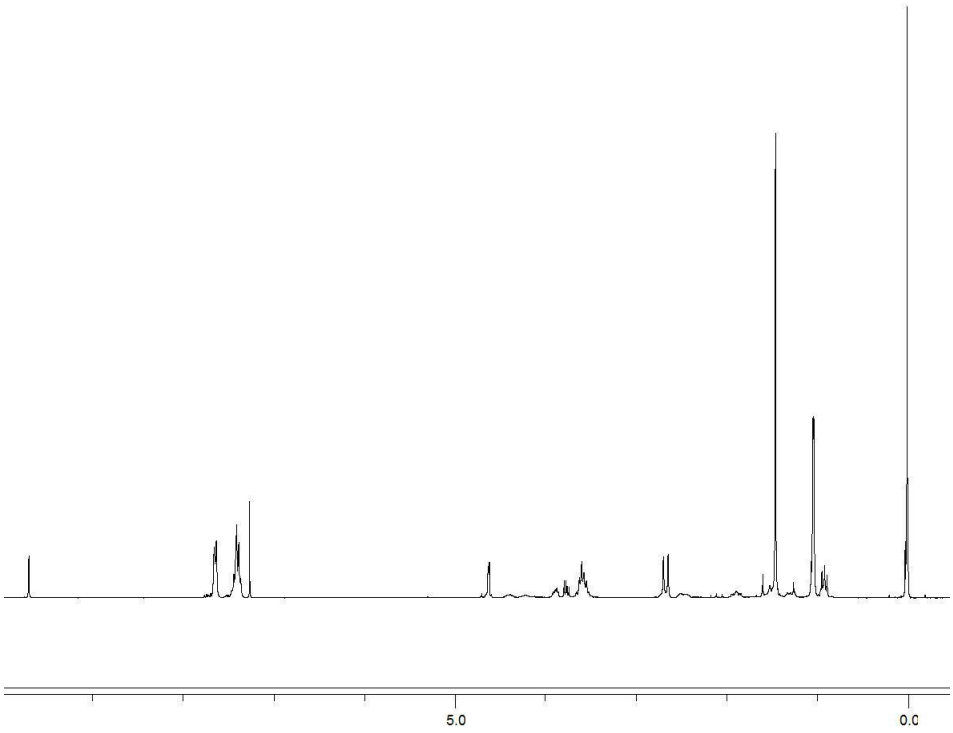


Figure 61. ^{1}H NMR spectrum of **279** ($CDCl_3$, rt)

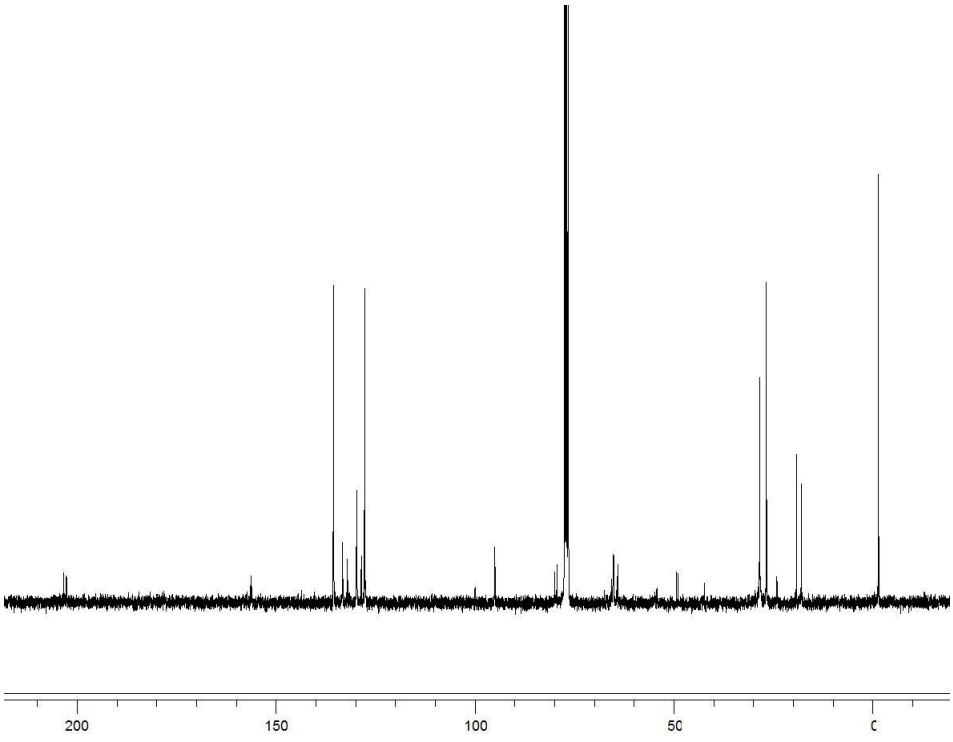
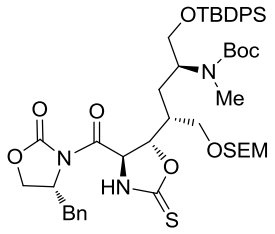


Figure 62. ^{13}C NMR spectrum of **279**

A.27 Preparation of 281

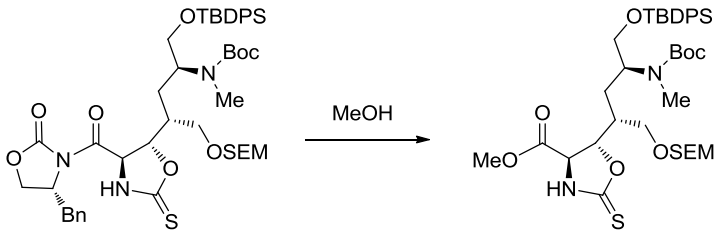


$Sn(OTf)_2$ method:

To a solution of $Sn(OTf)_2$ (260 mg, 0.62 mmol) in THF (2.4 mL) at −78 °C was added 1-ethylpiperidine (0.10 mL, 0.75 mmol) and a solution of **280**[90] (138 mg, 0.50 mmol) in THF (1 mL). The solution was stirred for 1.5 hours before **279** (313 mg, 0.50 mmol) was added as a solution in THF (0.8 mL). The solution was kept at −78 °C for three hours before being slowly warmed to −30 °C over two more hours. Finally, the mixture was diluted with CH_2Cl_2 and poured into sat. NH_4Cl (aq). The organic layer was separated, dried (Na_2SO_4) and stripped of solvent under vacuum. The residue was purified by column chromatography (30/70 EtOAc/Hexanes eluent) to give **281** (182 mg, 0.20 mmol, 40% yield), a colorless oil which existed as a rotameric mixture at rt. $[\alpha]_D^{20}$ −36.8 (c 1.6, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-*d6*, 80 °C): δ 0.00 (s, 9H); 0.85-0.92 (m, 2H); 1.03 (s, 9H); 1.25-1.35 (m, 1H); 1.39 (s, 9H); 1.62-1.70 (m, 1H); 2.00-2.09 (m, 1H); 2.67 (s, 3H); 2.94 (dd, *J* = 10.2, 6.0, 1H); 3.05 (s, 2H); 3.11 (dd, *J* = 10.2, 2.4, 1H); 3.45-3.54 (m, 1H); 3.54-3.71 (m, 5H); 4.19-4.27 (m, 2H); 4.40 (m, 1H); 4.57 (s, 2H); 4.66-4.73 (m, 1H); 5.14-5.19 (m, 1H); 5.35 (d, *J* = 3.3, 1H); 7.21-7.36 (m, 5H); 7.39-7.48 (m, 6H); 7.59-7.66 (m, 4H); 9.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ −1.4, 18.1, 19.2, 25.0, 26.8, 28.4, 28.5, 37.6, 38.8, 38.9, 55.3, 61.2, 64.1, 65.9, 66.1, 67.5, 79.4, 80.0, 84.0, 85.0, 95.3, 127.8, 129.2, 129.4, 129.8, 129.9, 133.1, 133.3, 134.0, 134.1, 135.5, 135.6, 153.7,

156.2, 156.4, 165.9, 166.1, 188.3, 188.4; IR (film, cm^{-1}): ν 1689, 1782; HRMS: calc. for $C_{38}H_{60}N_2O_8S^{28}Si_2Na$ $[M + Na]^+$ 783.3507; found 783.3508.

NOTE: The molecular ion calculated for this material was the product of methanolysis of the imide according to the following scheme:



$TiCl_4$ method:

To a solution of **280**[90] (27 mg, 0.10 mmol) in CH_2Cl_2 (0.6 mL) at −78 °C was added $TiCl_4$ (1 M/CH_2Cl_2, 0.10 mL, 0.1 mmol), followed 15 minutes later by *i*Pr_2NEt (19 μL, 0.11 mmol) (a deep purple color appeared) and after an additional 25 minutes, NMP (10 μL, 0.10 mmol). The mixture was stirred for 30 minutes before **279** (61 mg, 0.10 mmol) was added as a solution in CH_2Cl_2 (0.5 mL). The reaction mixture was warmed to −35 °C, which was maintained for 1.5 hours. The mixture was diluted with CH_2Cl_2 and poured into water. The organic layer was separated, dried (Na_2SO_4), filtered, and stripped of solvent under vacuum. The residue was purified by column chromatography (30/70 EtOAc/Hexanes eluent) to give **281** (43 mg, 0.05 mmol, 49% yield), a colorless oil. This material was identical to that obtained using the $Sn(OTf)_2$ method described above.

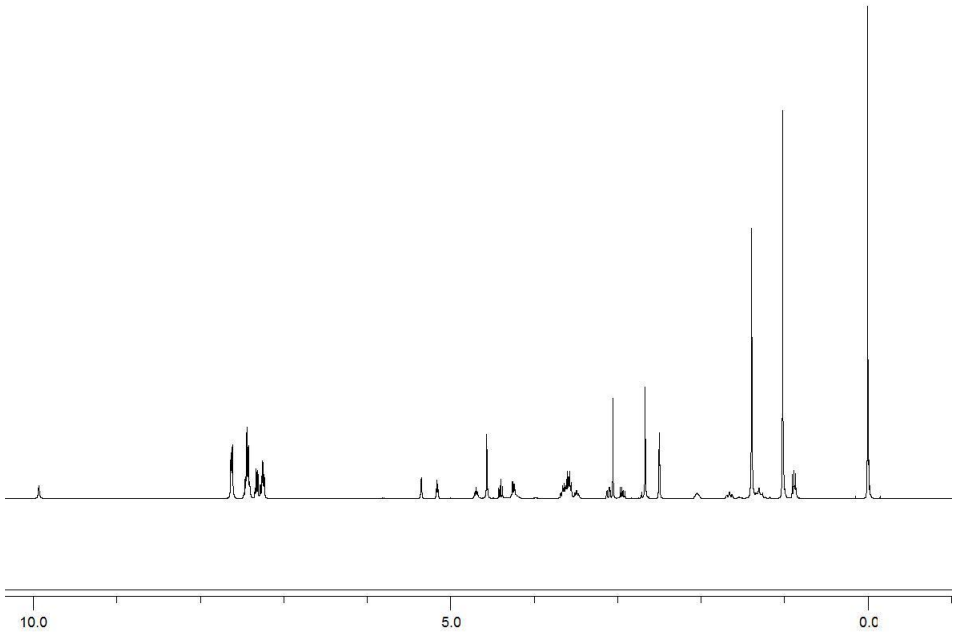


Figure 63. ^{1}H NMR spectrum of **281** at 80 °C in DMSO-*d*6

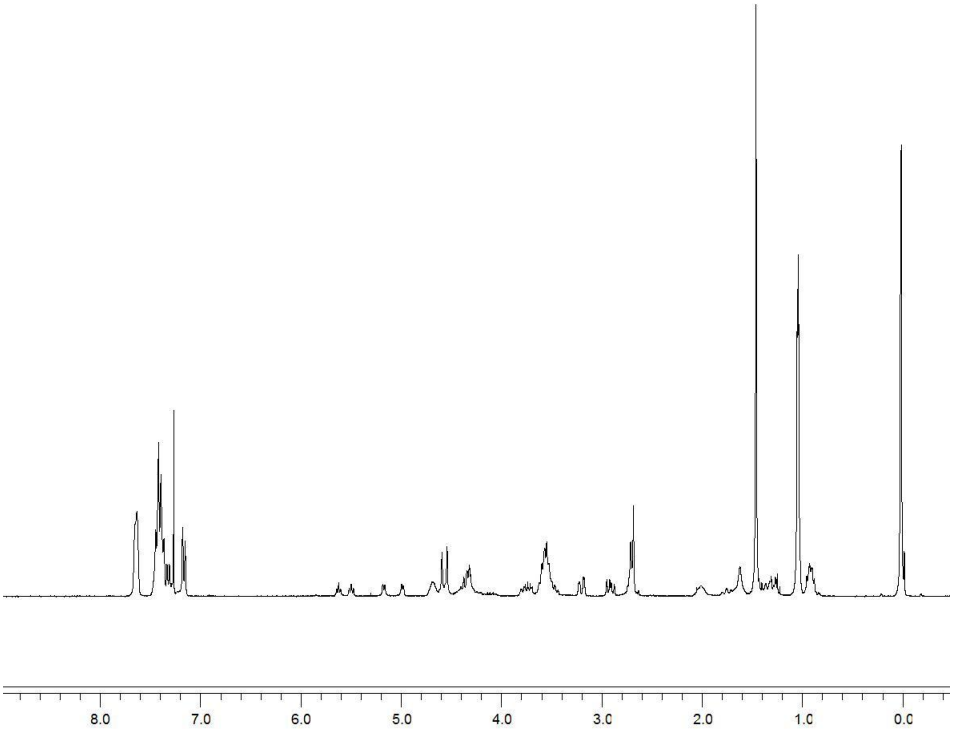


Figure 64. ^{1}H NMR spectrum of **281** ($CDCl_3$, rt)

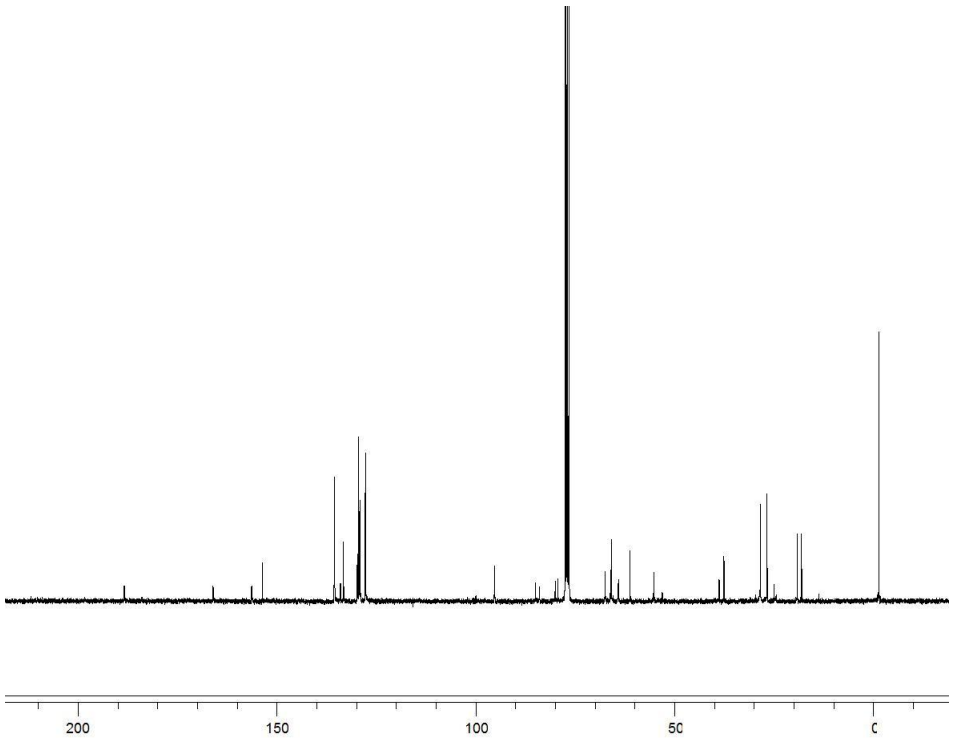
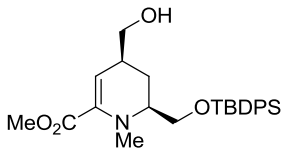


Figure 65. ^{13}C NMR spectrum of **281**

A.28 Preparation of 283



To a solution of **274** (49 mg, 0.11 mmol) in MeOH (1 mL) was added *o*-anisaldehyde (15 µL, 0.12 mmol), acetic acid (13 µL, 0.12 mmol), $TiCl_4$ (1 M/ CH_2Cl_2, 0.11 mL, 0.11 mmol), and *tert*-butyl isocyanide (13 µL, 0.12 mmol), and the solution was stirred overnight at rt. After quenching with pH 7 phosphate buffer, the mixture was diluted with EtOAc, poured into water, and the layers separated. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography (25/75 to 30/70 EtOAc/hexanes gradient elution) to give **283** (11 mg), a faintly yellow oil. Compound **282** (7 mg, 0.03 mmol, 27%), a colorless oil, was also recovered. Analytical data for **283**: $[\alpha]_D^{20}$ −15.1 (c 0.4, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.49-1.57 (m, 1H)*; 2.05-2.15 (m, 1H); 2.50-2.55 (m, 4H); 2.93-3.05 (s, 1H); 3.48-3.63 (m, 3H); 3.76 (s, 3H); 3.89 (dd, *J* = 9.9, 4.9, 1H); 5.90 (d, *J* = 2.6, 1H); 7.35-7.48 (m, 6H); 7.63-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.0, 26.9, 36.1, 39.0, 52.0, 60.7, 65.0, 66.5, 117.6, 127.7, 129.7, 133.5, 135.6, 141.2, 166.0; IR (film, cm^{-1}): ν 1724; HRMS: calc. for $C_{26}H_{35}NO_4Na^{28}Si$ $[M + Na]^+$ 476.2233; found 476.2234.

* Approximate value

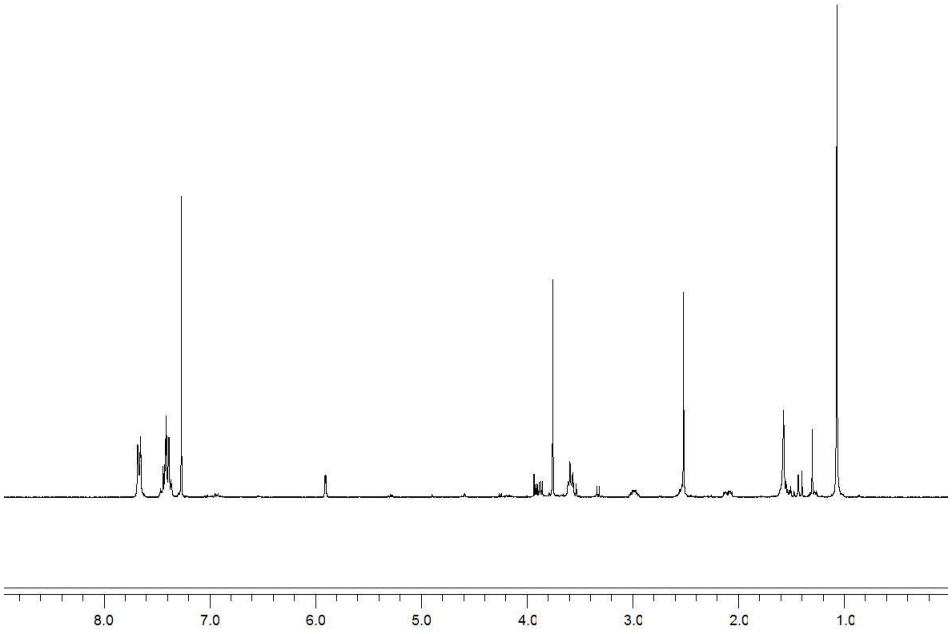


Figure 66. ^{1}H NMR spectrum of **283**

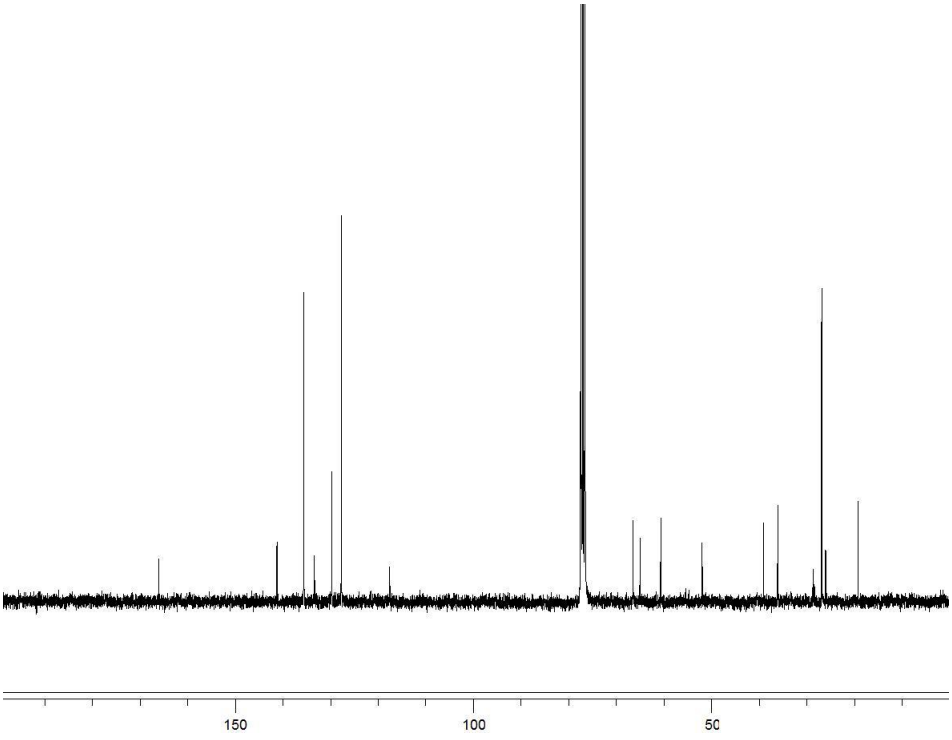
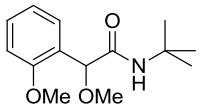


Figure 67. ^{13}C NMR spectrum of **283**

A.29 Data for 282



Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H); 3.32 (s, 3H); 3.85 (s, 3H); 4.90 (s, 1H); 6.71 (brs, 1H); 6.88-7.00 (m, 2H); 7.20-7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.8, 50.8, 55.7, 57.0, 78.9, 111.2, 120.7, 126.0, 128.9, 129.7, 158.0, 170.0; IR (film, cm^{-1}): ν 1678; HRMS: calc. for $C_{14}H_{22}NO_3$ $[M + H]^+$ 252.1600; found 252.1601.

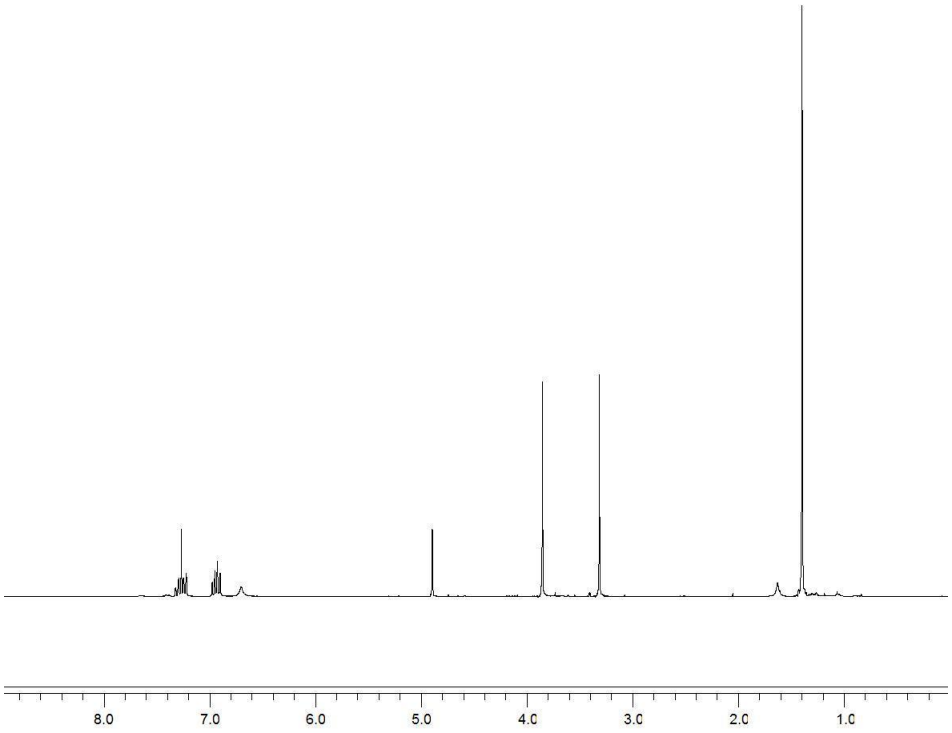


Figure 68. ^{1}H NMR spectrum of **282**

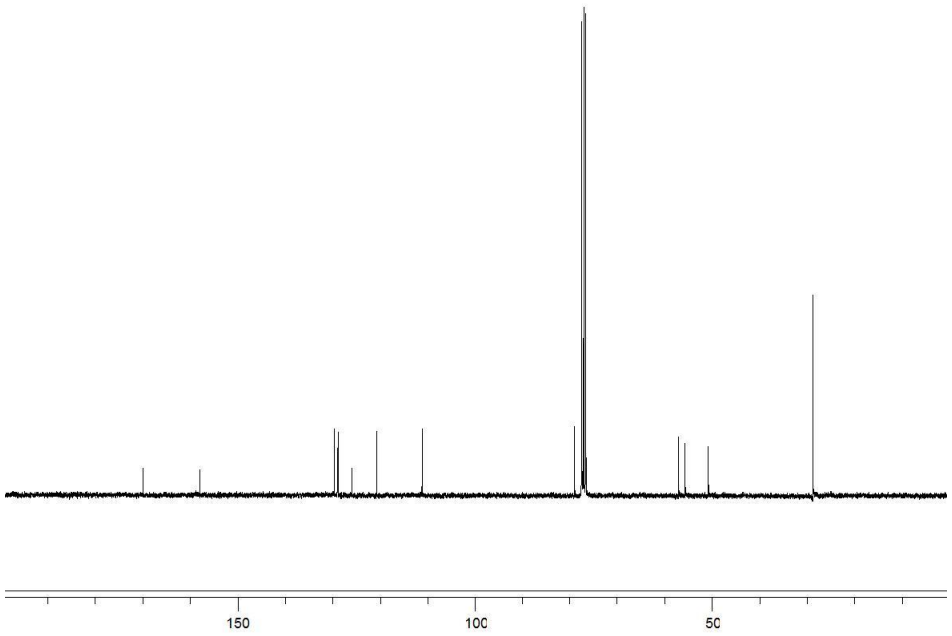
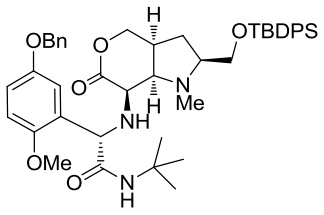


Figure 69. ^{13}C NMR spectrum of **282**

A.30 Procedure for hydrolysis of 274 and Ugi condensation: preparation of 297



To a solution of **274** (545 mg, 1.24 mmol) in THF (14.5 mL) at −5 °C was added KOH (aq) (0.5 M, 3.0 mL, 1.5 mmol) and water (3.0 mL). The resulting suspension was stirred, keeping the temperature between −5 and 0 °C, for 5 hours, when starting material was consumed (TLC). The mixture was evaporated to dryness under vacuum, giving crude **292** as a foamy, off-white solid. To a solution of the residue in MeOH (7.8 mL) at rt were added 2-methoxy-5-benzyloxybenzaldehyde (330 mg, 1.36 mmol) and $TiCl_4$ (neat, 0.09 mL, 0.8 mmol). The solution was stirred for 5 min, when *tert*-butylisocyanide (0.17 mL, 1.49 mmol) was added. Stirring was continued for 24 hours, at which time the reaction was quenched by the dropwise addition of a pH 7 phosphate buffer solution (5 mL). The reaction mixture was diluted with EtOAc and water, the layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered through celite, and evaporated. Flash column chromatography of the residue (30/70 to 45/55 EtOAc/hexanes gradient elution) gave **297**, a faintly yellow foam (247 mg, 0.32 mmol, 26% yield over two steps). $[\alpha]_D^{20}$ +6.7 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H); 1.31 (s, 9H); 1.39-1.55 (m, 1H); 2.04-2.17 (m, 1H); 2.24 (s, 3H); 2.50-2.68 (m, 2H); 2.90-3.00 (m, 1H); 3.06-3.22 (m, 2H); 3.49 (dd, *J* = 10.2, 6.3, 1H); 3.72-3.82 (m, 4H); 4.13 (dd, *J* = 11.4, 4.2, 1H); 4.25 (dd, *J* = 11.4, 4.7, 1H); 4.54 (brs, 1H); 5.04 (s, 2H); 6.76-6.83 (m, 2H); 6.83-6.89 (m, 1H); 7.13-7.18 (m, 1H); 7.28-7.49 (m, 10H); 7.63-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 28.7,

32.3, 35.6, 41.8, 50.6, 55.7, 58.2, 60.2, 66.8, 67.2, 67.9, 68.2, 70.4, 111.9, 114.9, 115.8, 127.4, 127.7, 127.8, 128.5, 128.9, 129.7, 133.5, 135.5, 137.3, 151.3, 153.0, 170.7, 172.8; IR (film, cm^{-1}): ν 1679, 1748; HRMS: calc. for $C_{45}H_{58}N_3O_6{}^{28}Si$ $[M + H]^+$ 764.4095; found 764.4089.

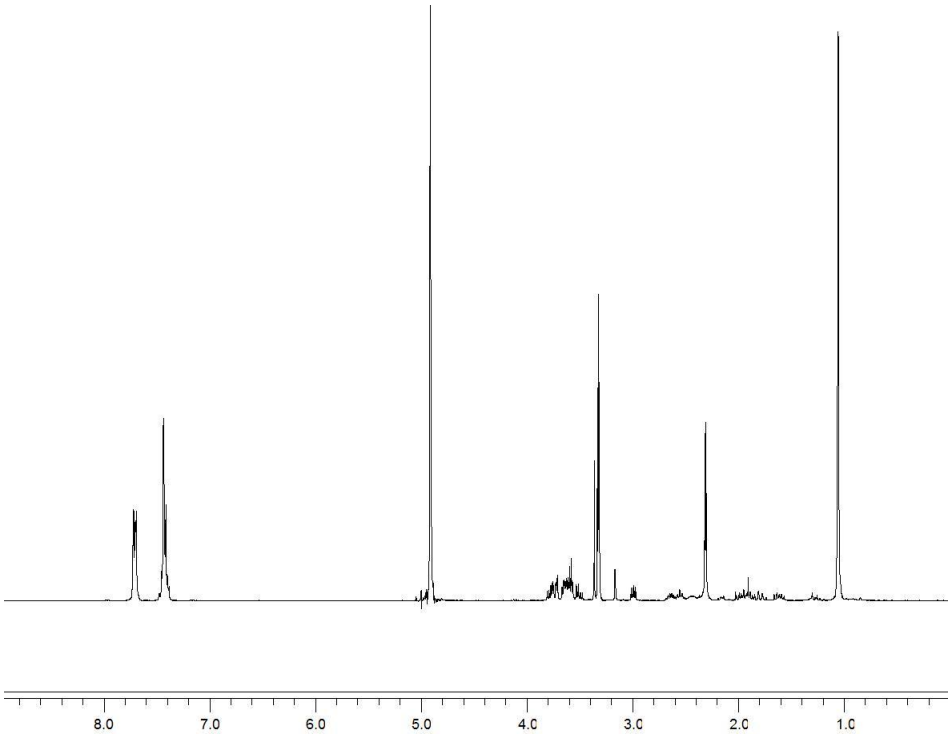


Figure 70. ^{1}H NMR spectrum of **292** (methanol-*d*4)

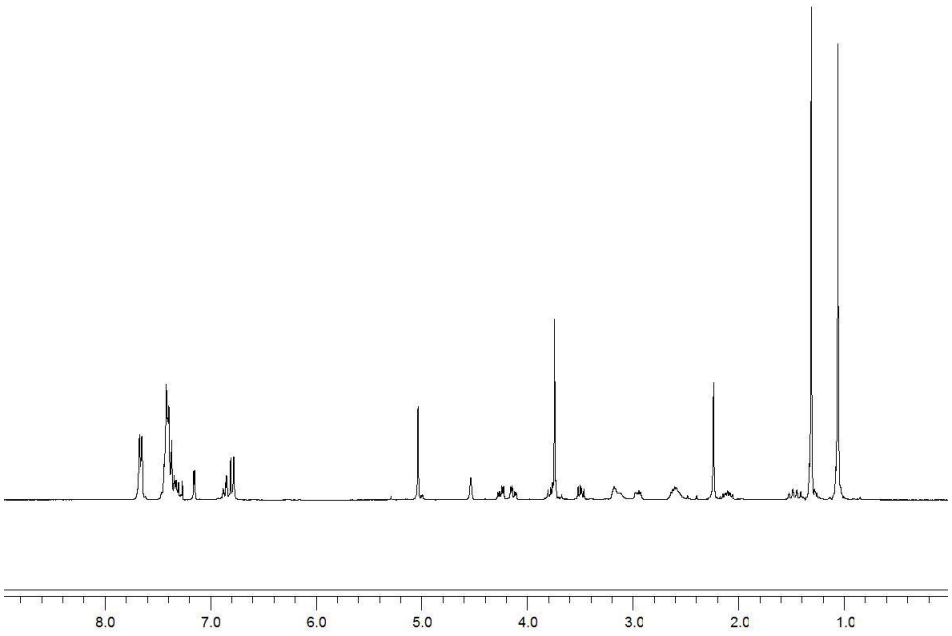


Figure 71. ^{1}H NMR spectrum of **297**

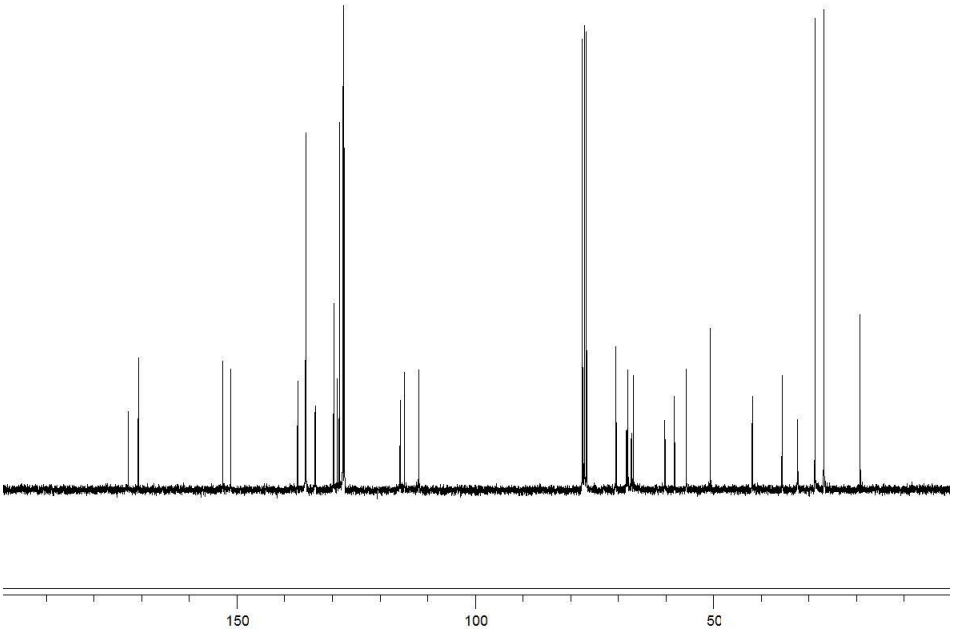
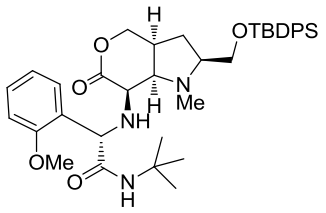


Figure 72. ^{13}C NMR spectrum of **297**

A.31 Data for 293



Prepared according to the procedure of **297**. 30% yield of a colorless oil. $[\alpha]_D^{20}$ +10.1 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H); 1.31 (s, 9H); 1.35-1.53 (m, 1H); 2.04-2.18 (m, 4H); 2.51-2.69 (m, 2H); 3.02 (dd, *J* = 10.5, 5.3, 1H); 3.11-3.19 (m, 1H); 3.21-3.29 (m, 1H); 3.49 (dd, *J* = 10.2, 6.3, 1H); 3.70-3.78 (m, 4H); 4.19 (dd, *J* = 11.2, 4.7, 1H); 4.33 (dd, *J* = 11.2, 6.0, 1H); 4.50 (d, *J* = 6.2, 1H); 6.76-7.00 (m, 3H); 7.20-7.29 (m, 1H); 7.32-7.48 (m, 7H); 7.59-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 28.7, 32.4, 35.3, 41.2, 50.6, 55.1, 58.0, 60.6, 66.6, 67.2, 67.9, 68.6, 110.6, 120.9, 127.6, 128.8, 129.5, 129.7, 133.4, 133.5, 135.5, 156.9, 170.9, 172.7; IR (film, cm^{-1}): ν 1679, 1747; HRMS: calc. for $C_{38}H_{52}N_3O_5{}^{28}Si$ $[M + H]^+$ 658.3676; found 658.3680.

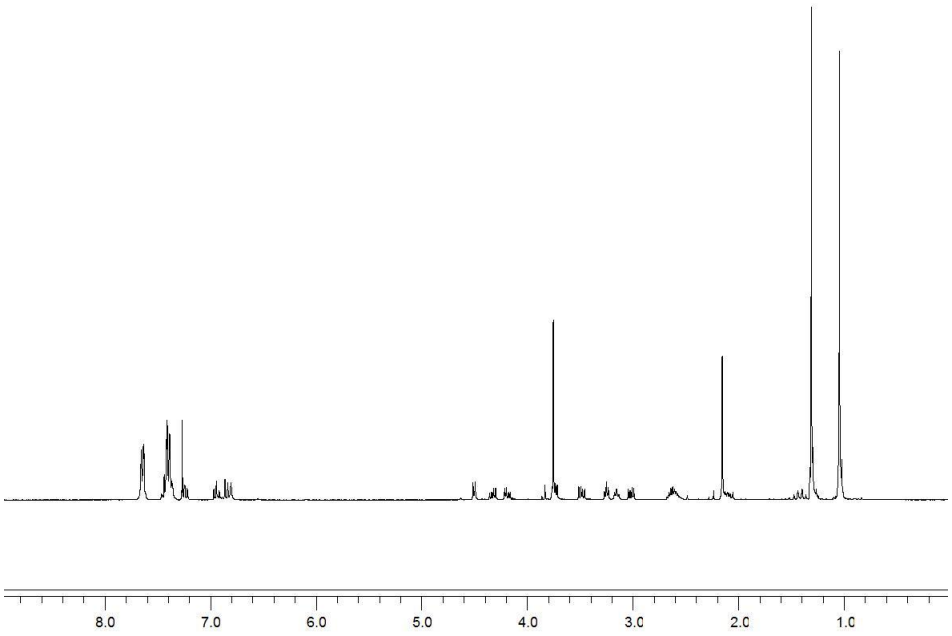


Figure 73. ^{1}H NMR spectrum of **293**

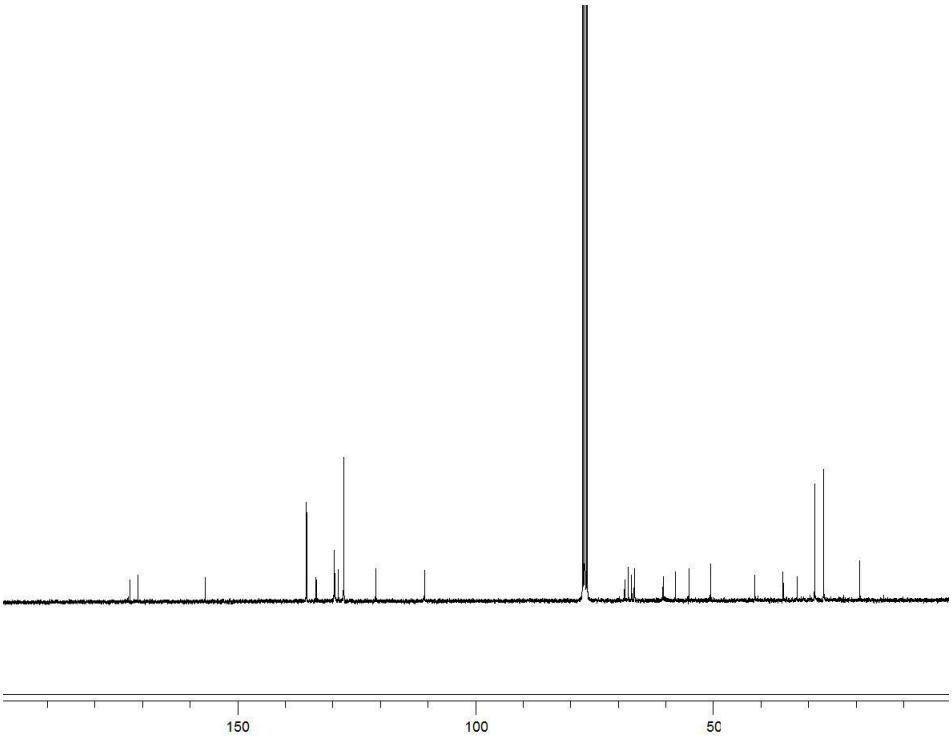
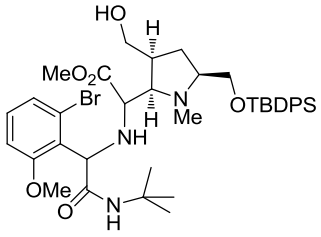


Figure 74. ^{13}C NMR spectrum of **293**

A.32 Data for 300



Prepared according to the procedure of **297**. 14% yield of a white foam. $[\alpha]_D^{20}$ +10.5 (c 0.9, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H); 1.38 (m, 11H); 1.62-1.73 (m, 2H); 1.95-2.08 (m, 1H); 2.11-2.26 (m, 1H); 2.43-2.55 (m, 1H); 2.79-2.86 (m, 1H); 3.29-3.45 (m, 3H); 3.50-3.64 (m, 5H); 3.74-3.82 (m, 4H); 4.91 (s, 1H); 6.70-6.77 (m, 1H); 6.80-6.89 (m, 1H); 7.03-7.18 (m, 2H); 7.35-7.49 (m, 6H); 7.62-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 28.6, 28.7, 30.6, 39.0, 41.9, 50.8, 52.3, 55.4, 57.5, 62.5, 62.8, 65.8, 67.6, 68.8, 110.4, 124.8, 127.1, 127.7, 127.8, 129.7, 129.8, 133.4, 133.5, 135.5, 135.6, 158.3, 170.1, 173.1; IR (film, cm^{-1}): ν 1677, 1740; HRMS: calc. for $C_{39}H_{55}{}^{79}BrN_3O_6Si$ $[M + H]^+$ 768.3044; found 768.3026.

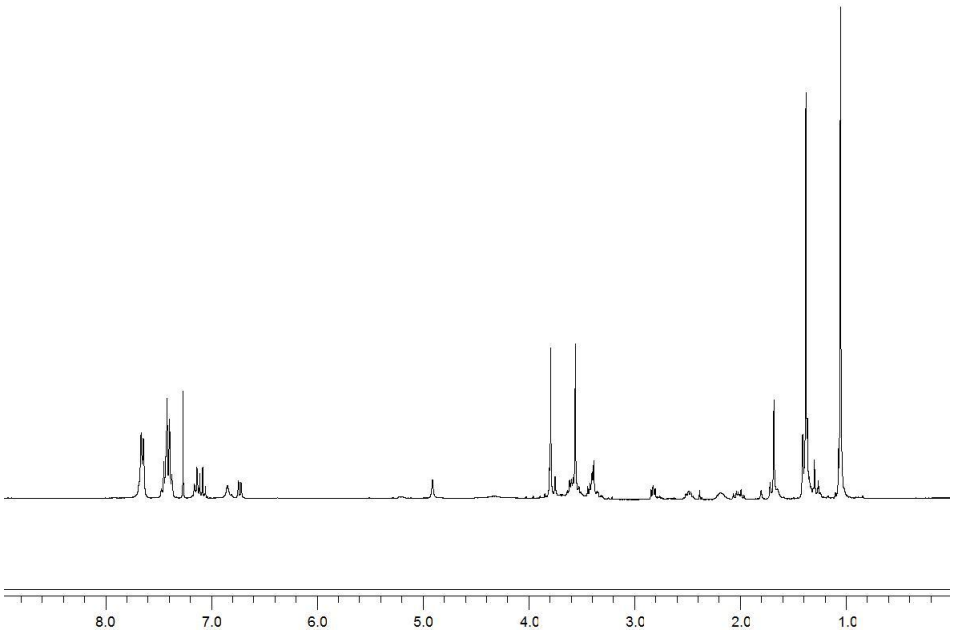


Figure 75. ^{1}H NMR spectrum of **300**

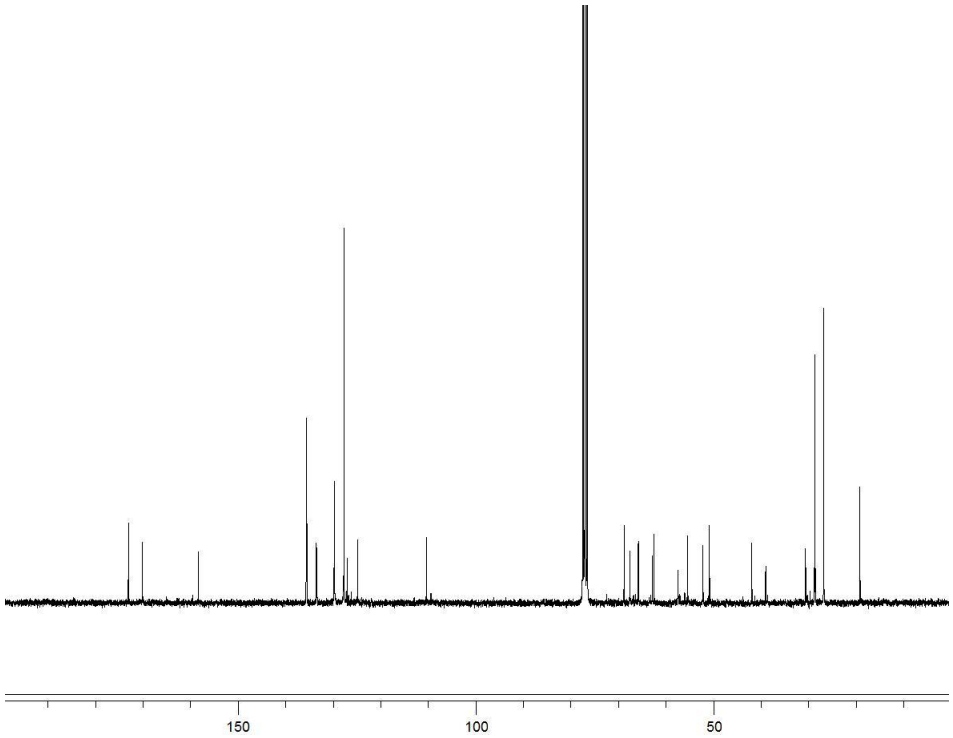
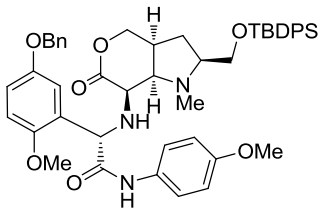


Figure 76. ^{13}C NMR spectrum of **300**

A.33 Data for 298



Prepared according to the procedure of **297**. 32% yield of a faintly yellow oil. $[\alpha]_D^{20}$ −9.8 (c 0.3, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 9H); 1.50-1.66 (m, 1H); 2.05-2.17 (m, 1H); 2.24 (s, 3H); 2.55-2.68 (m, 2H); 3.03 (dd, *J* = 10.3, 5.2, 1H); 3.15-3.27 (m, 2H); 3.49 (dd, *J* = 10.1, 6.2, 1H); 3.70-3.83 (m, 8H); 4.17 (dd, *J* = 11.4, 3.9, 1H); 4.27 (dd, *J* = 11.4, 4.1, 1H); 4.75 (d, *J* = 4.7, 1H); 5.03 (brs, 2H); 6.80-6.91 (m, 4H); 7.16-7.21 (m, 1H); 7.29-7.48 (m, 14H); 7.61-7.68 (m, 4H); 8.92 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 29.7, 32.1, 35.8, 42.3, 55.5, 56.1, 58.4, 60.3, 66.8, 67.1, 68.0, 70.4, 112.1, 114.0, 115.1, 115.9, 121.0, 127.5, 127.7, 127.8, 128.2, 128.5, 129.7, 131.4, 133.4, 133.6, 135.5, 135.6, 137.1, 151.2, 153.1, 156.0, 169.4, 173.1; IR (film, cm^{-1}): ν 1682, 1745; HRMS: calc. for $C_{48}H_{56}N_3O_7{}^{28}Si$ $[M + H]^+$ 814.3888; found 814.3881.

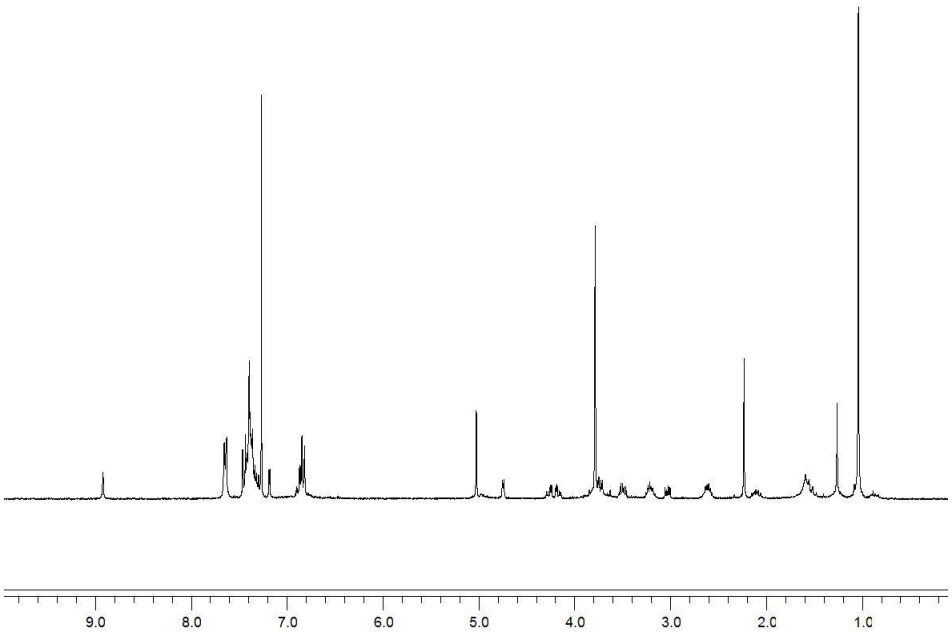


Figure 77. ^{1}H NMR spectrum of **298**

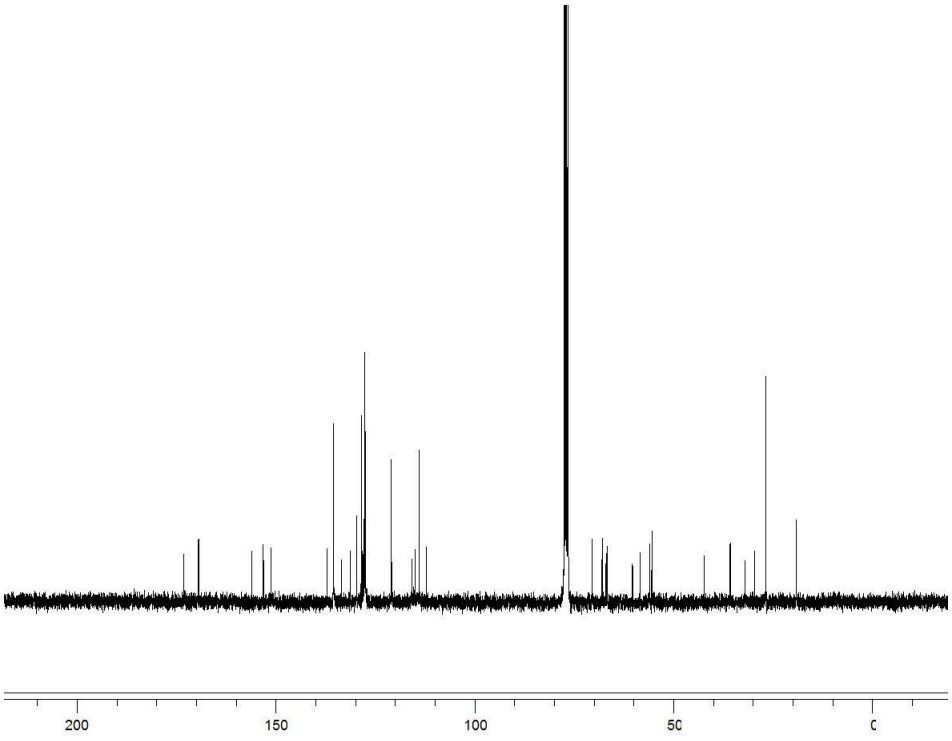
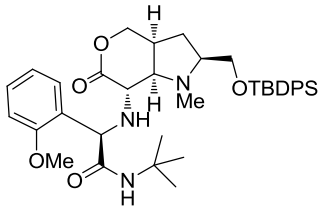


Figure 78. ^{13}C NMR spectrum of **298**

A.34 Procedure for hydrolysis of 273 and Ugi condensation: preparation of 294



To a solution of **273** (57 mg, 0.13 mmol) in THF (1.0 mL) and H_2O (0.2 mL) was added LiOH•H_2O (7 mg, 0.2 mmol), and the resulting suspension was stirred at rt. Following consumption of starting material (TLC, 4 hours), volatiles were removed under vacuum, and co-evaporation with MeOH was performed, giving crude **291** as a foamy white solid. To a solution of the residue in MeOH (0.8 mL) at rt was added *o*-anisaldehyde (17 µL, 0.14 mmol), $TiCl_4$ (1 M/CH_2Cl_2, 0.08 mL, 0.08 mmol), and *tert*-butylisocyanide (17 µL, 0.15 mmol). The yellow-colored solution was stirred overnight, when dropwise addition of pH 7 phosphate buffer was performed. The mixture was poured into more pH 7 phosphate buffer, and extraction proceeded with three portions of EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered through celite, and evaporated. Flash column chromatography of the residue (40/60 to 50/50 EtOAc/hexanes gradient elution) gave **294** (33 mg, 0.051 mmol, 39% yield), a colorless oil. $[\alpha]_D^{20}$ −36.3 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H); 1.30 (s, 9H); 2.03-2.16 (m, 1H); 2.24 (s, 3H); 2.49-2.63 (m, 2H); 3.23-3.29 (d, *J* = 4.9, 1H); 3.43 (dd, *J* = 9.5, 5.8, 1H); 3.68 (dd, *J* = 10.0, 4.6, 1H); 3.83 (s, 3H); 3.98 (dd, *J* = 11.5, 7.1, 1H); 4.63 (s, 1H); 4.45 (dd, *J* = 11.1, 4.5, 1H); 6.55 (s, 1H); 6.85-6.97 (m, 2H); 7.21-7.26 (m, 2H); 7.31-7.46 (m, 6H); 7.56-7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 28.7; 30.9; 31.1, 35.4, 40.7, 50.8, 55.4, 60.1, 60.3, 66.5, 67.9, 68.7, 69.7, 110.9, 121.1, 127.6, 128.8, 129.3, 129.7, 133.5, 135.5, 156.8, 171.0,

173.0; IR (film, cm^{-1}): ν 1679, 1748; HRMS: calc. for $C_{38}H_{52}N_3O_5{}^{28}Si$ $[M + H]^+$ 658.3676; found 658.3683.

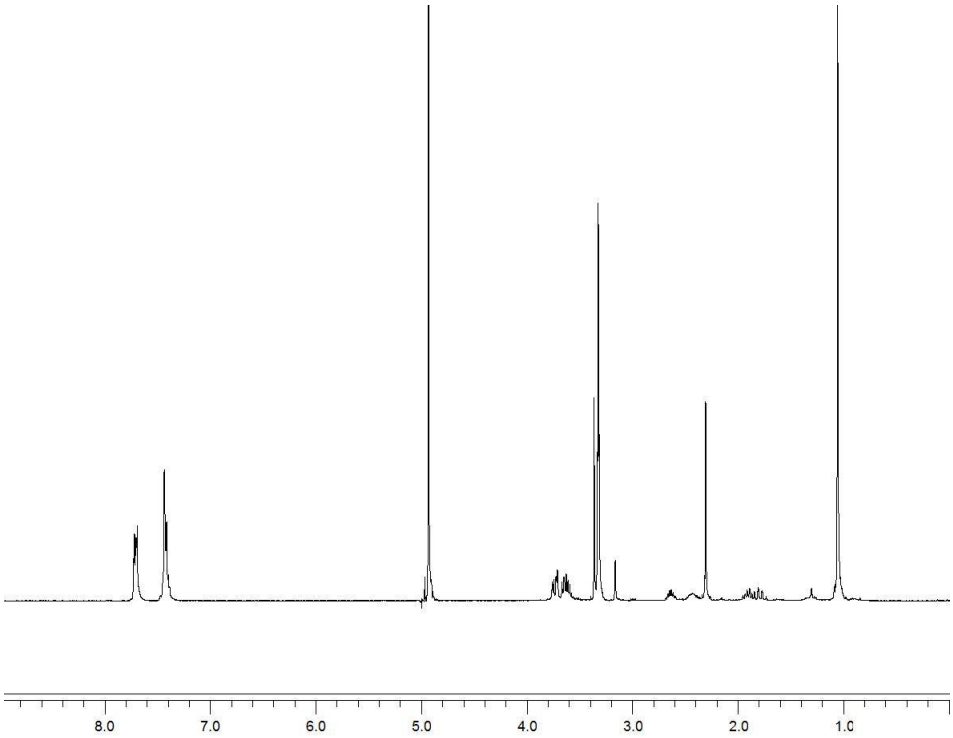


Figure 79. ^{1}H NMR spectrum of **291** (methanol-*d*4)

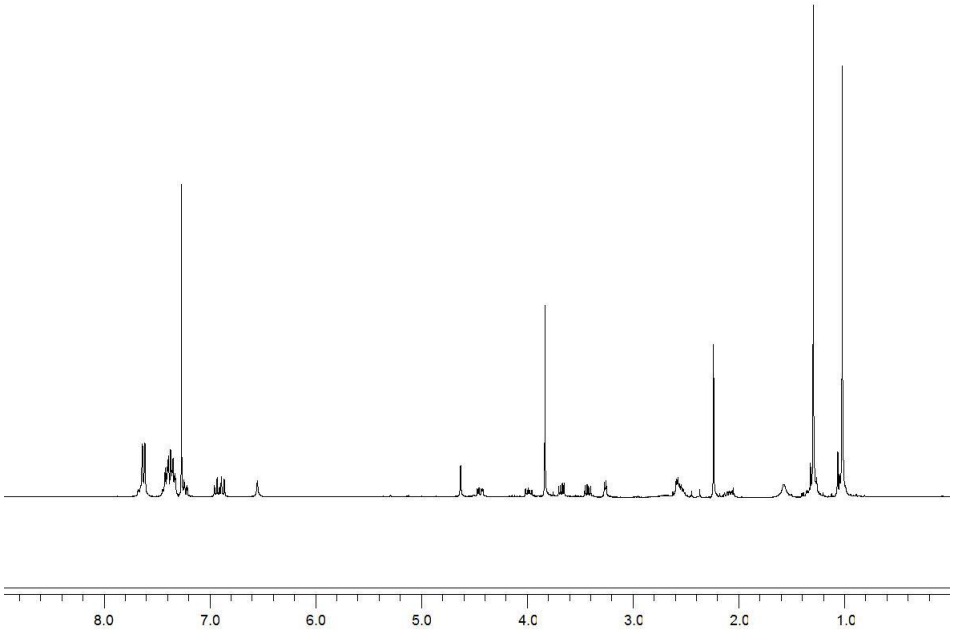


Figure 80. ^{1}H NMR spectrum of **294**

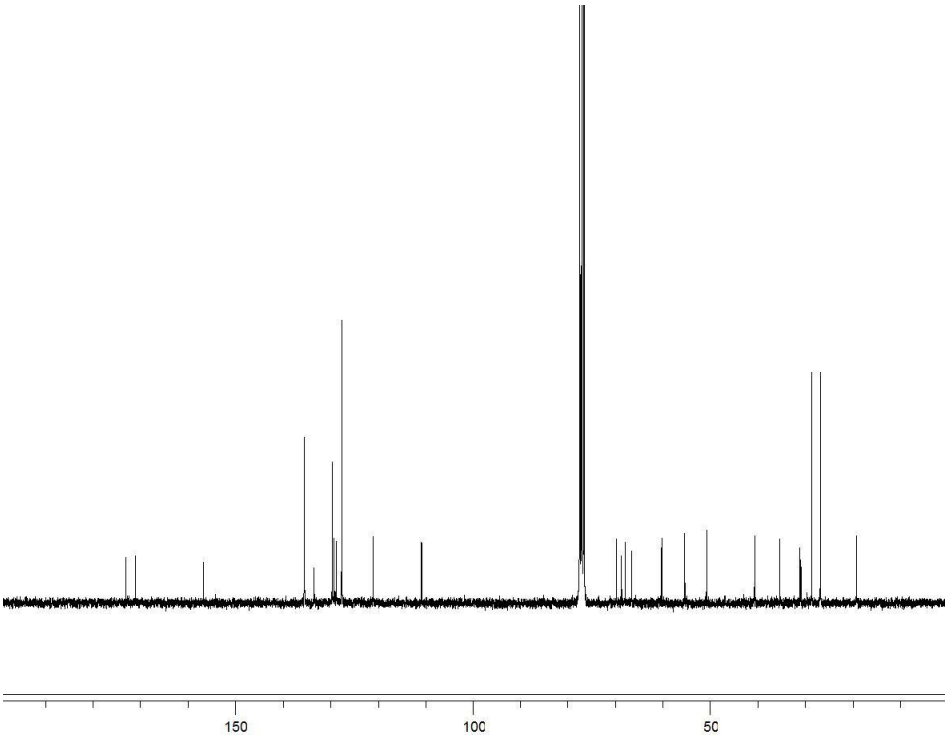
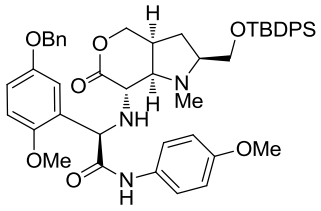


Figure 81. ^{13}C NMR spectrum of **294**

A.35 Data for 299



Prepared according to the procedure of **294**. 26% yield of a faintly yellow oil. $[\alpha]_D^{20}$ −45.5 (c 0.2, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 9H); 1.23-1.35 (m, 1H); 2.05-2.17 (m, 1H); 2.27 (s, 3H); 2.54-2.65 (m, 3H); 3.36 (brd, *J* = 4.4, 1H); 3.42 (dd, *J* = 10.2, 6.1, 1H); 3.69 (dd, *J* = 10.6, 4.8, 1H); 3.78 (s, 3H); 3.82 (s, 3H); 3.96-4.05 (m, 1H); 4.35 (m, 1H); 4.78 (brs, 1H); 4.93-5.02 (m, 2H); 6.79-6.89 (m, 4H); 7.10 (brd, *J* = 2.6, 1H); 7.27-7.49 (m, 14H); 7.59-7.68 (m, 4H); 8.88 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 30.8, 35.9, 40.9, 55.5, 56.2, 60.5, 61.3, 66.5, 68.1, 68.9, 69.8, 70.5, 112.3, 114.0, 115.0, 116.4, 121.1, 127.5, 127.7, 127.9, 128.1, 128.5, 129.7, 131.4, 133.4, 133.5, 135.5, 137.0, 151.1, 153.2, 156.0, 169.7, 173.7; IR (film, cm^{-1}): ν 1684, 1746; HRMS: calc. for $C_{48}H_{56}N_3O_7{}^{28}Si$ $[M + H]^+$ 814.3888; found 814.3906.

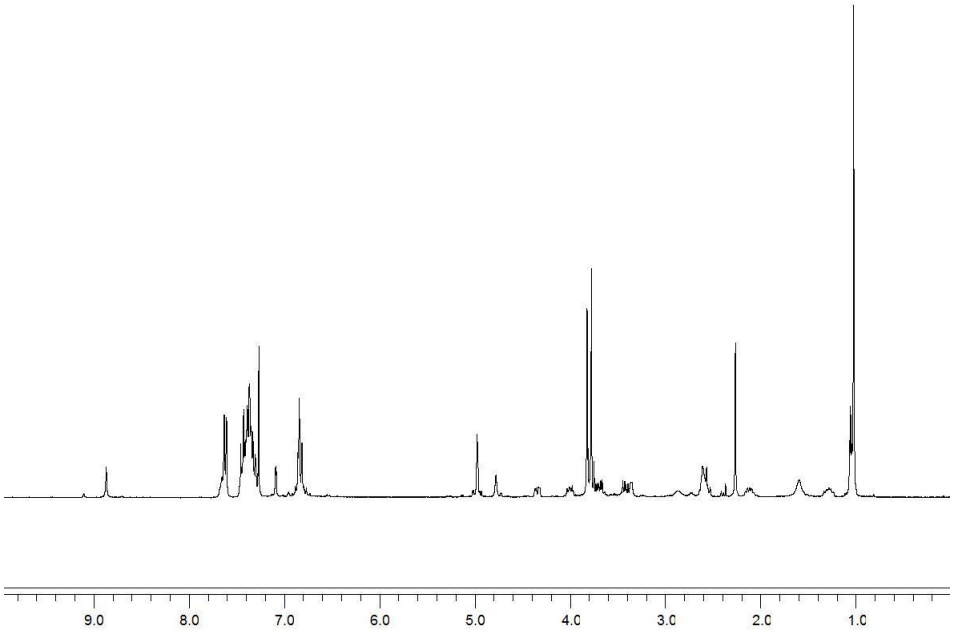


Figure 82. ^{1}H NMR spectrum of **299**

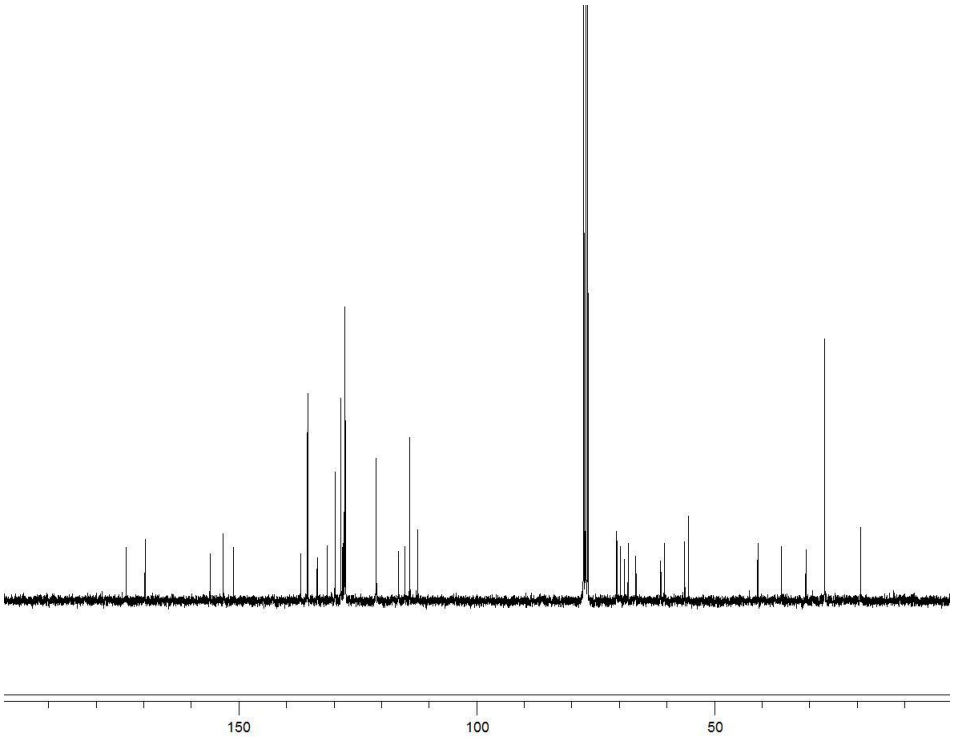
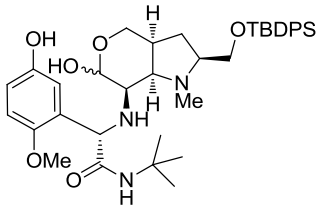


Figure 83. ^{13}C NMR spectrum of **299**

A.36 Preparation of 322



To a solution of **297** (17 mg, 0.022 mmol) in CH_2Cl_2 at −78 °C was added Dibal (1 M/ hexanes, 0.05 mL, 0.05 mmol), and the solution was stirred for 1 hour. Additional Dibal solution (0.02 mL) was added, and the reaction was slowly warmed to −50 °C over 1 hour, when starting material was found to be consumed (TLC). Ethyl acetate (0.05 mL) was added, and after 5 minutes, sat. Rochelle's salt (aq) was added, whereupon stirring continued as the mixture warmed to rt. The mixture was diluted with CH_2Cl_2, poured into sat. $NaHCO_3$ (aq), and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and stripped of solvent under vacuum. To a solution of the residue in EtOH (1 mL) was added $Pd(OH)_2/C$ (5%, 50-70% H_2O, 12 mg), and the reaction vessel was flushed with H_2. The suspension was stirred overnight at rt, when it was filtered over a pad of Celite. After volatiles were removed under vacuum, pure **322** (13 mg, 0.019 mmol, 86% yield), was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H); 1.21-1.31 (m, 1H); 1.38 (s, 9H); 1.86-2.02 (m, 2H); 2.25-2.36 (m, 1H); 2.44 (s, 3H); 2.48-2.59 (m, 1H); 2.73-2.80 (m, 1H); 2.91-2.97 (m, 1H); 3.41-3.81 (m, 6H); 4.26 (brd, J = 5.7, 1H); 5.09 (brs, 1H); 6.50-6.69 (m, 3H); 7.33-7.48 (m, 6H); 7.59-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 28.4, 28.6, 37.7, 42.8, 50.9, 56.2, 57.6, 59.8, 61.4, 66.5, 68.0, 69.0, 77.2, 93.9, 112.4, 115.5, 116.8, 127.8, 128.9, 129.8, 133.2, 135.6, 150.5, 172.3; HRMS: calc. for $C_{38}H_{54}N_3O_6{}^{28}Si$ $[M + H]^+$ 676.3782; found 676.3777.

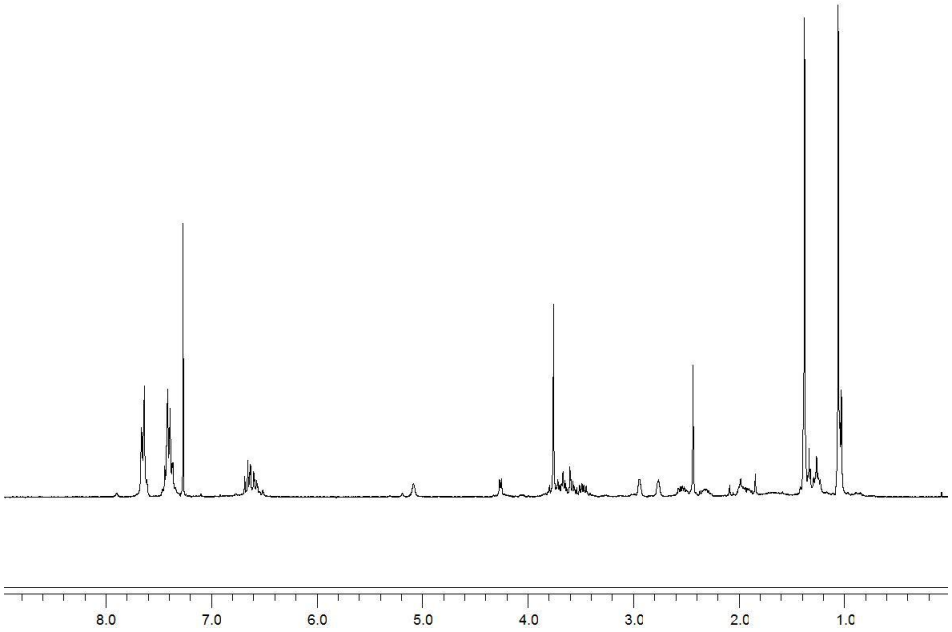


Figure 84. ^{1}H NMR spectrum of **322**

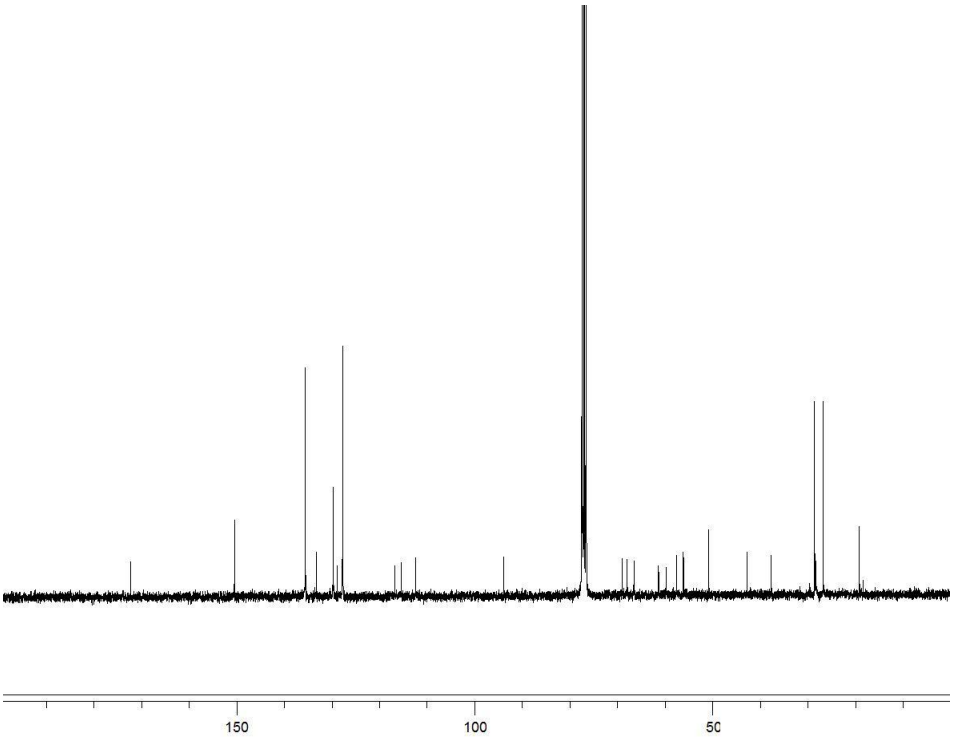


Figure 85. ^{13}C NMR spectrum of **322**

A.37 X-ray Crystallography Data for 293

Empirical Formula	$C_{38}H_{53}N_3O_{5.5}SiCl$
Formula Weight	703.37
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.06 X 0.08 X 0.30 mm
Crystal System	orthorhombic
Lattice Type	primitive
Lattice Parameters	a = 11.6026(4) Å b = 12.6325(4) Å c = 26.3107(9) Å $\alpha = 90^o$ $\beta = 90^o$ $\gamma = 90^o$ V = 3856.4(2) $Å^3$
Space Group	*P* $2_12_12_1$ (#19)
Z value	4
D_{calc}	1.211 g/cm^3
F_{000}	1508.00
μ(Mo-Kα)	1.76 cm^{-1}
Data Images	1980 exposures @ 30.0 seconds
Detector Position	40.10 mm
$2\theta_{max}$	52.1^o
No. of Reflections Measured	Total: 134603
Residuals (refined on F^2, all data): R1; wR2	0.040; 0.080
Goodness of Fit Indicator	1.08
No. Observations (I>2.00σ(I))	7036
Residuals (refined on F): R1; wR2	0.035; 0.079

URL: https://www2.chem.ubc.ca/local/resource/xrdb/member.php; Data set mc048