DISSERTATION

STUDIES TOWARD THE TOTAL SYNTHESIS OF MICROSCLERODERMIN G

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY CAMERON MOELLER BURNETT ENTITLED STUDIES TOWARD THE TOTAL SYNTHESIS OF MICROSCLERODERMIN G BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

STUDIES TOWARD THE SYNTHESIS OF MICROSCLERODERMIN G

We report our studies toward the synthesis of microsclerdermin G, a cyclic hexapeptide with antifungal and antitumor activity. The dehydrotryptophan amino acid was synthesized according to literature precedents. (3*R*)-γ-amino-β-hydroxybutyric acid (GABOB) was synthesized according to previous methodology from our research group. An aspartate-based precursor to the pyrrolidinone moiety of microsclerodermin G was prepared in four steps from known materials. 3-amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid (AMPTD) was prepared in seven steps from known materials; the synthesis utilized Evans' chiral oxazolidinone glycolate aldol reaction and the sulfinimine-based Mannich reaction developed by Ellman. Syntheses of two dipeptides are reported, as are other attempts at coupling of the various amino acids.

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ACKNOWLEDGEMENTS

First and foremost, I thank the Lord Jesus Christ for his work in me during this project. While my work did not reach the status of a total synthesis, the foundations laid during this time will shape the rest of my days. For His loving discipline I am grateful.

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Erika tolerated the vagaries of the laboratory life and of my personal development for too long, and her willingness to sacrifice herself to hold our family together allowed me to complete this dissertation. She has played more than an equal role in our partnership, and her love helped me to endure to the finish line of this decade-long race. Her willingness to speak the truth boldly and lovingly has sharpened me beyond measure, and I eagerly await the future with her by my side.

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List of abbreviations

AETD: 3-amino-10-(*p*-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid

AMMTD: (2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(*p*-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid

AMPTD: (2*S*,3*R*,4*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-3-amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid

APTO: (2*S*,3*R*,4*S*,5*S*,7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid

Boc: *tert*-butoxycarbonyl

Boc_2O: *tert*-butyl pyrocarbonate

Cbz: benzyloxycarbonyl

CDI: 1,1-carbonyldiimidazole

ΔTrp: dehydrotryptophan

DCC: *N*,*N*-dicyclohexylcarbodiimide

DEPC: diethylphosphoryl cyanide

DIBAL: diisobutylaluminum hydride

DKP: diketopiperazine

DMAP: *N,N*-dimethylaminopyridine

DMF: *N*,*N*-dimethylformamide

DPPA: diphenylphosphoryl azide

EDCI: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

Fm: fluorenylmethyl

Fmoc: fluorenylmethoxycarbonyl

GABOB: (3*R*)-γ-amino-β-hydroxybutyric acid

HOAt: 7-aza-*N*-hydroxybenzotriazole

HOBt: *N*-hydroxybenzotriazole

HRMS: high-resolution mass spectrometry

IBX: 2-iodoxybenzoic acid

KHMDS: potassium hexamethyldisilazane

KOTMS: potassium trimethylsilanolate

LAH: lithium aluminum hydride

MOM: methoxymethyl

NMR: nuclear magnetic resonance

oNB: *o*-nitrobenzyl

Pfp: pentafluorophenyl

PMB: *p*-methoxybenzyl

PMP: *p*-methoxyphenyl

TBAF: tetrabutylammonium fluoride

TBS: *t*-butyldimethylsilyl

TBDPS: *t*-butyldiphenylsilyl

Tce: 2,2,2-trichloroethyl

TES: triethylsilyl

THF: tetrahydrofuran

THP: tetrahydropyranyl

TFA: trifluoroacetic acid

TLC: thin-layer chromatography

TMS: trimethylsilyl

TMSE: 2-(trimethylsilyl)ethyl

CONTENTS

Chapter 1: Introduction

The microsclerodermins (**1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, Figure 1) are cyclic hexapeptides isolated from deep-water lithistid sponges by the late D. John Faulkner and coworkers at the Scripps Institution of Oceanography.[1,2,3] **1**, **2**, and **4**-**9** were isolated from *Microscleroderma* specimens collected in the Philippines and Palau, while **3** and **4** came from a *Theonella* specimen from the Philippines. This dissertation will detail our efforts toward synthesis of microsclerodermin G (**7**).

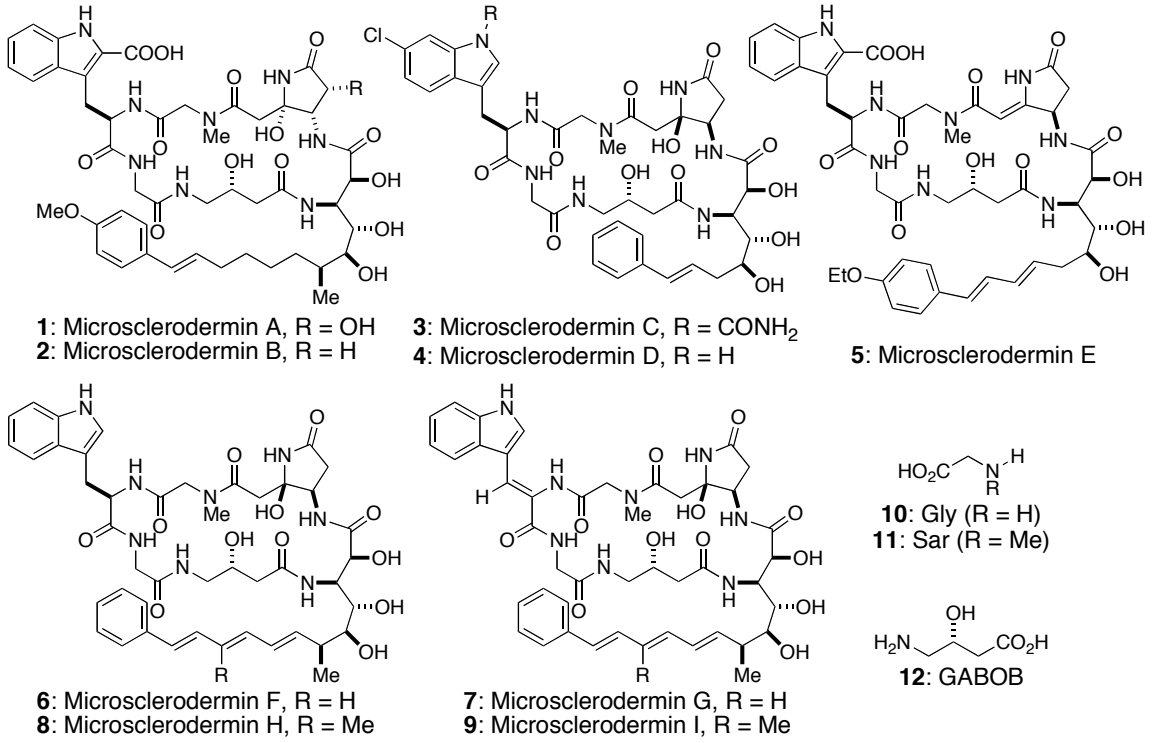


Figure 1

[1] *Microsclerodermins A and B. Antifungal Cyclic Peptides from the Lithistid Sponge* Microscleroderma *sp*. Bewley, C. A.; Debitus, C.; Faulkner, D. J. *J. Am. Chem. Soc*. **1994**, *116*, 7631-7636.
[2] *Microsclerodermins C-E, Antifungal Cyclic Peptides from the Lithistid Marine Sponges* Theonella *sp. and* Microscleroderma *sp*. Schmidt, E. W.; Faulkner, D. J. *Tetrahedron* **1998**, *54*, 3043-3046.
[3] *Microsclerodermins F-I, Antitumor and Antifungal Cyclic Peptides from the Lithistid Sponge* Microscleroderma sp. Qureshi, A.; Colin, P. L.; Faulkner, D. J. *Tetrahedron* **2000**, *56*, 3679-3685.

1.1: Structure and biological activity

The microsclerodermins have a 23-atom cyclic peptide core; common constituents include the α-amino acids glycine (**10**) and sarcosine (*N*-methylglycine, **11**) and the β-hydroxy-γ-amino acid GABOB (**12**). Variations are found in the modified D-tryptophan residue, the ω-aromatic 3-amino-2,4,5-trihydroxyacid, and the pyrrolidinone.

All microsclerodermins exhibit antifungal activity against *Candida albicans* (Table 1); Faulkner attributed the antifungal activity to the β-amino-ω-phenyl amino acid, though he presented no supporting evidence.[1]

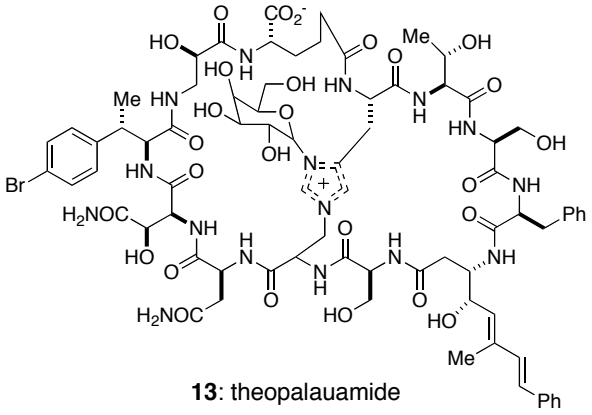
Table 1

Compound	MIC (mg/disk) vs. *C. albicans*	IC_{50} (μg/mL) vs. HCT-116
1	2.5	-
2	2.5	-
3	5	-
4	100	-
5	10	-
6	1.5	1.8
7	3	2.4
8	12	1.0
9	25	1.1

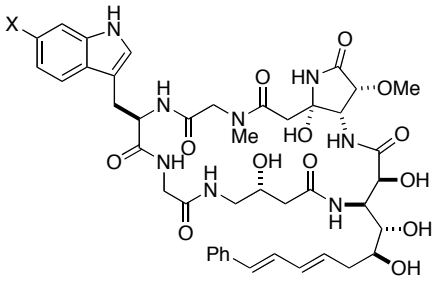
Microsclerodermins F-I exhibit antitumor activity against the HCT-116 colon carcinoma cell line; microsclerodermin mixtures showed activity against the P388 murine leukemia (IC_{50} = 1 μM) and A549 human lung adenocarcinoma (IC_{50} = 0.32 μM) cell lines.[3] Microsclerodermin F caused microtubule disruption in A549 cells, ranging from "subtle rearrangement" to "fibroblast-like morphology" to complete microtububle matrix disassembly, with α-tubulin globules uniformly distributed through the cytoplasm.[4]

[4] Wright, A. E.; Pomponi, S. A.; Longley, R. E.; Isbrucker, R. A. *Antiproliferative activity of microsclerodermins*. US Patent 6,384,187 B1 (2002).

Faulkner speculated that the microsclerodermins (and other β-amino acid-containing isolates) may be produced by symbiotic bacteria within the sponges, and used the presence of filamentous bacteria to guide selection of *Theonella* sponges that yielded **3** and **4**. However, **5** was isolated from an apparently bacterium-free *Microscleroderma* sponge.[1,2] Faulkner isolated theopalauamide (**13**, Figure 2) from symbiotic bacteria in *Theonella* sponges, lending some support to his theory.[5]



13: theopalauamide



14: pedein A (X = Cl)
15: pedein B (X = H)

Figure 2

Though it came after his death, further support was given to Faulkner's speculation by the 2008 isolation and structural determination of pedein A and B (**14** and **15**, Figure 2) from Myxobacteria.[6] These compounds exhibited broad-spectrum activity against yeast and fungi via interference with membrane integrity, but were inactive against tumor cells. The structural similarities of the pedeins and the microsclerodermins suggest a common bacterial origin, while the differing biological activity of **14** and **15** offers a lead for structure-activity relationship targets.

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[5] *Theopalauamide, a Cyclic Glycopeptide from Filamentous Bacterial Symbionts of the Lithistid Sponge* Theonella swinhoei *from Palau and Mozambique.* Schmidt, E. W.; Bewley, C. A.; Faulkner, J. D. *J. Org. Chem.* **1998**, *63*, 1254-1258.

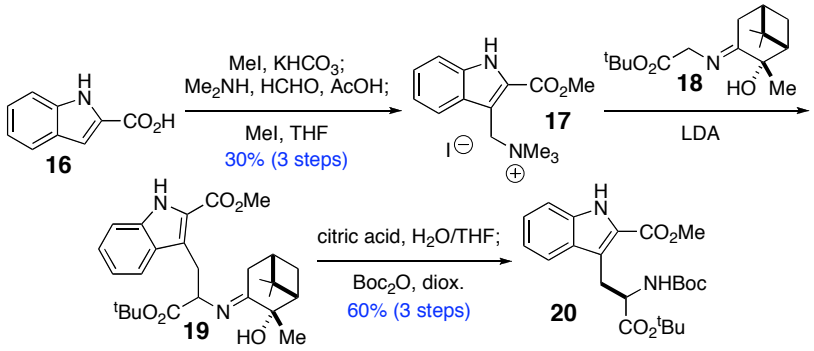
[6] *Pedein A and B: Production, Isolation, Structure Elucidation and Biological Properties of New Antifungal Cyclopeptides from* Chondromyces pediculatus *(Myxobacteria).* Kunze, B.; Böhlendorf, B.; Reichenbach, H.; Höfle, G. *J. Antibiot.* **2008**, *61*, 18-26.

1.2: Synthetic work by other groups

The microsclerodermins offer a challenging synthetic target, with four to five consecutive sp^3 stereocenters (and seven to nine total) and one to three alkenes conjugated with a phenyl ring in the polyhydroxy amino acid alone. Other interesting structural feaures include the extremely dehydration-prone pyrrolidinone hemiaminal and the adjacent β-keto amide; the γ-amino-β-hydroxy acid **13**; and the D-tryptophan and dehydrotryptophan residues with modifications around the indole ring. These structural features, along with the biological activity, have inspired a number of synthetic approaches to the microsclerodermin family, along with a single total synthesis (of **5**).

1.2.1: Shioiri's studies toward microsclerodermin B

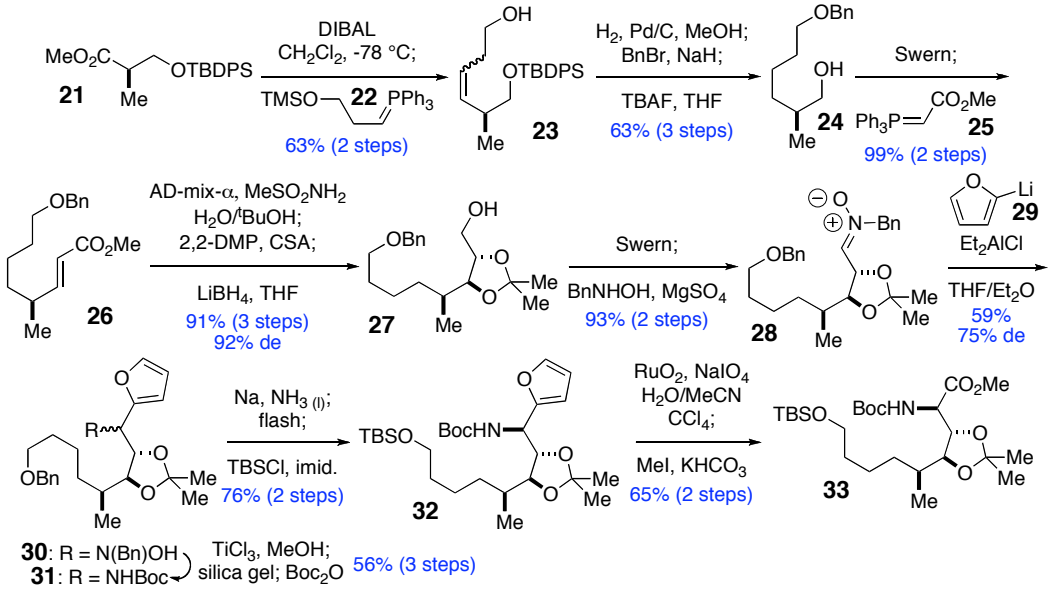
Takayuki Shioiri and co-workers at Nagoya City University reported studies toward **2**.[7,8] Synthesis of the tryptophan piece began with indole-2-carboxylate **16** (Scheme 1). Methyl esterification allowed two-step conversion to the gramine derivative **17**, and alkylation with imine **18** (derived from (-)-2-hydroxy-3-pinanone) gave adduct **19**. Cleavage of the auxiliary and Boc protection gave **20** in 18% yield over six steps.



Scheme 1

[7] *Construction of Three Building Blocks for the Total Synthesis of Microsclerodermins.* Sasaki, S.; Hamada, Y.; Shioiri, T. *Synlett* **1999**, *4*, 453-455.
[8] *Synthetic approach to microsclerodermins: construction of three building blocks.* Shioiri, T.; Sasaki, S.; Hamada, Y. *ARKIVOC* **2003**, *2*, 103-122.

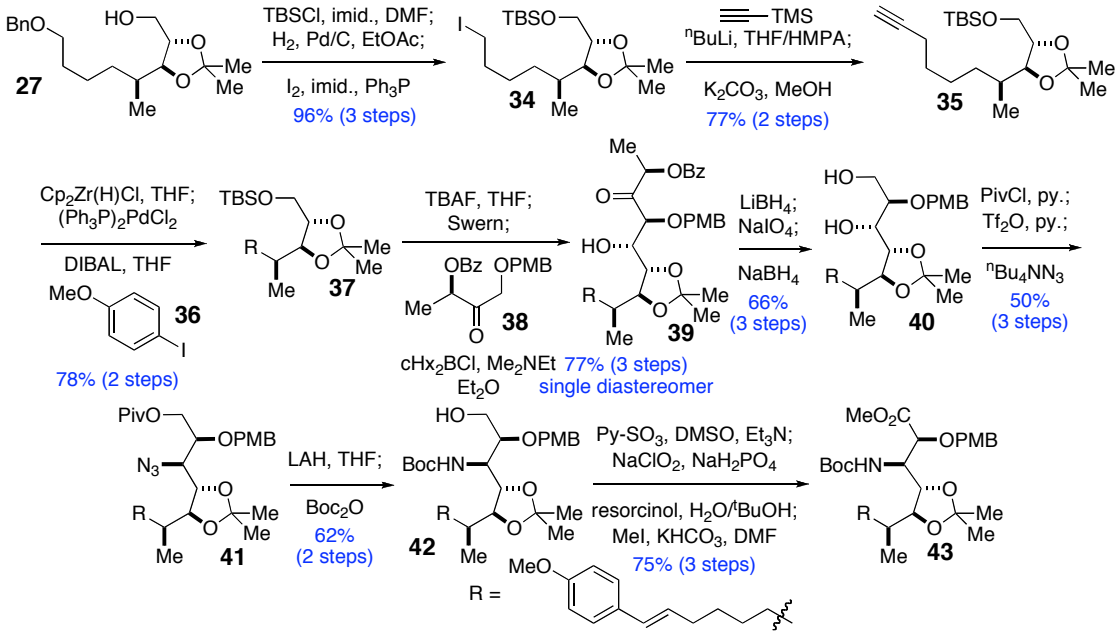
Shioiri originally reported a synthesis of an AMMTD fragment lacking one stereocenter and the phenylalkene side chain.[9] Half-reduction of TBDPS-Roche ester **21** gave the aldehyde, whose Wittig reaction with TMS ether **22** and workup with $KHSO_4$ gave alcohol **23** (Scheme 2); direct reaction with unprotected **21** gave racemization. Hydrogenation and benzylation were followed by TBDPS removal to give **24**. Oxidation to the aldehyde and Wittig reaction with **25** gave α,β-unsaturated ester **26**; Sharpless asymmetric dihydroxylation and diol protection as the acetonide allowed ester reduction to alcohol **27**. Oxidation to the aldehyde and condensation with *N*-benzylhydroxylamine gave nitrone **28**, to which 2-furyllithium **29** was added to give a mixture of diastereomeric adducts **30**. Treatment with titanium trichloride and silica freed the amine, whose Boc protection gave **31**. Birch removal of the *O*-benzyl group, separation of diastereomers via chromatography, and TBS protection allowed cleavage of the furan **32** to give the acid; esterification completed the fragment **33** in 4.7% yield over 23 steps.



Scheme 2

[9] *Synthetic Studies of Microsclerodermins. A Stereoselective Synthesis of a Core Building Block for (2S,3R,4S,5S,6S,11E)-3-Amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic Acid (AMMTD)*. Sasaki, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 3013-3016.

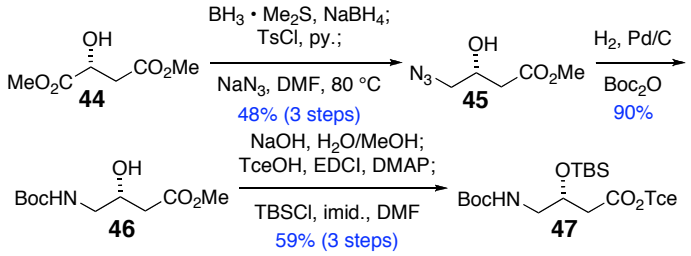
Synthesis of AMMTD proper began with TBS protection of **27** (Scheme 3).[10] The benzyl ether was converted to iodide **34** and displaced with lithium TMS-acetylide. Treatment with potassium carbonate gave alkyne **35**, whose hydrozirconation and Negishi coupling with *p*-iodoanisole (**36**) gave **37**. The TBS ether was removed and the alcohol oxidized to the aldehyde; *anti*-aldol addition of **38** under Paterson's conditions gave a single diastereomer of aldol product **39**, with the incorrect stereochemistry at the β carbon. Lithium borohydride reduced the ketone and removed the benzoate to allow periodate oxidation; the resultant aldehyde was reduced to diol **40**. Selective protection of the primary alcohol as its pivaloate allowed conversion of the secondary alcohol to the corresponding triflate and displacement with azide to give **41**. Treatment with LAH removed the pivaloate and reduced the azide; Boc-protection of the amine gave **42**. A two-step oxidation to the acid and esterification yielded **43** in 2.4% yield over 34 steps.



Scheme 3

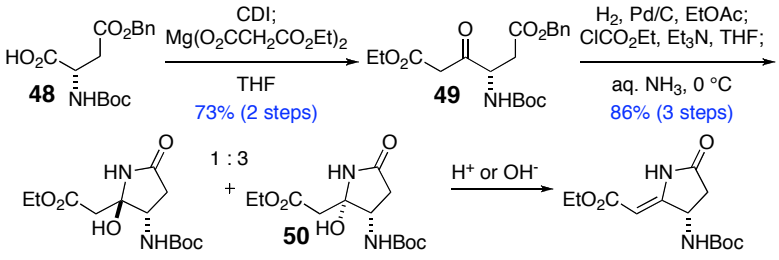
[10] *The Efficient Stereoselective Synthesis of (2S,3R,4S,5S,6S,11E)-3-Amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic Acid (AMMTD), a Component of Microsclerodermins of Marine Sponge Origin, as Its Protected Form*. Sasaki, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 3187-3190.

Directed reduction of the ester α to the alcohol of dimethyl (*R*)-malate (**44**), selective tosylation at the primary alcohol, and displacement with azide gave **45**; hydrogenation in the presence of Boc_2O gave **46** (Scheme 4). The methyl ester was replaced with the trichloroethyl ester by a hydrolysis/coupling sequence, and TBS protection of the alcohol gave **47** in 24% yield over seven steps.



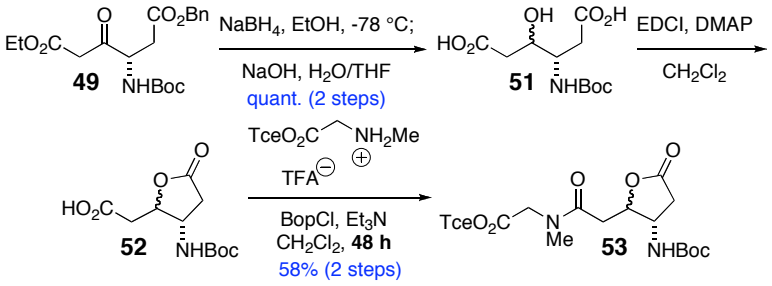
Scheme 4

β-benzyl-*N*-Boc-L-aspartate (**48**) was homologated to the β-keto ester **49** using the Brooks-Masamune protocol (Scheme 5). After hydrogenation of the benzyl ester allowed mixed anhydride formation, treatment with ammonia formed the amide, which closed onto the ketone functionality to yield a mixture of **50** and its carbinol diastereomer. Unfortunately, the β-ester hemiaminal dehydrated under both acidic and basic conditions.



Scheme 5

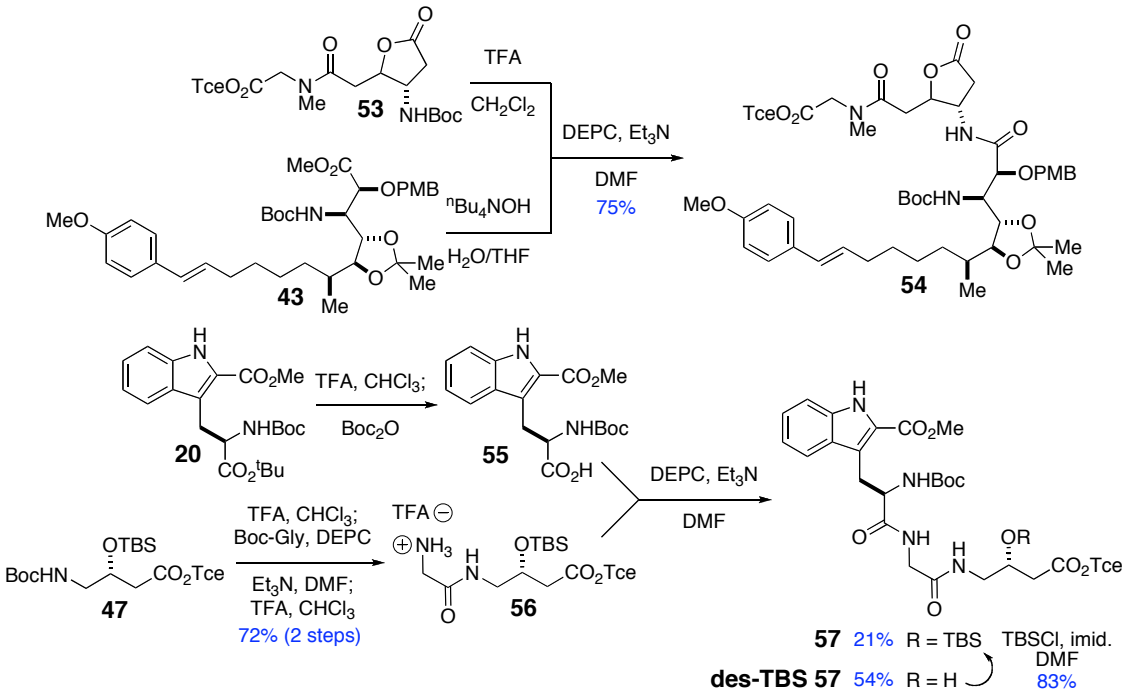
In light of the elimination, a masked pyrrolidinone precursor was synthesized. Reduction of the ketone of **49** and hydrolysis of both esters to give **51** allowed synthesis of five-membered lactone **52** under peptide coupling conditions (Scheme 6); the remaining acid underwent peptide coupling with the TFA salt of sarcosine trichloroethyl (Tce) ester to give the dipeptide **53** in 42% yield over six steps. Interestingly, the peptide coupling required two days to reach a moderate yield.



Scheme 6

Finally, Shioiri prepared a pair of tripeptides.[11] Dipeptide **53** was deprotected with TFA and ester **43** hydrolyzed to the acid; peptide coupling afforded tripeptide **54** in 75% yield from protected materials (Scheme 7). Meanwhile, D-tryptophan derivative **20** was treated with TFA to remove the Boc and *t*-butyl groups; reprotection yielded Boc-amine **55**. GABOB derivative **47** was deprotected with TFA and coupled with Boc-glycine in good yield; treatment of the dipeptide with TFA to give amine **56** allowed DEPC-mediated coupling to the tryptophan acid, giving tripeptide **57** in poor yield. The bulk of recovered mass consisted of des-TBS **57**; reprotection occurred smoothly to give an overall 66% yield.

[11] *Synthetic Approach to Microsclerodermins.* Sasaki, S.; Hamada, Y.; Shioiri, T. *Peptide Science* **1998** 17-20.

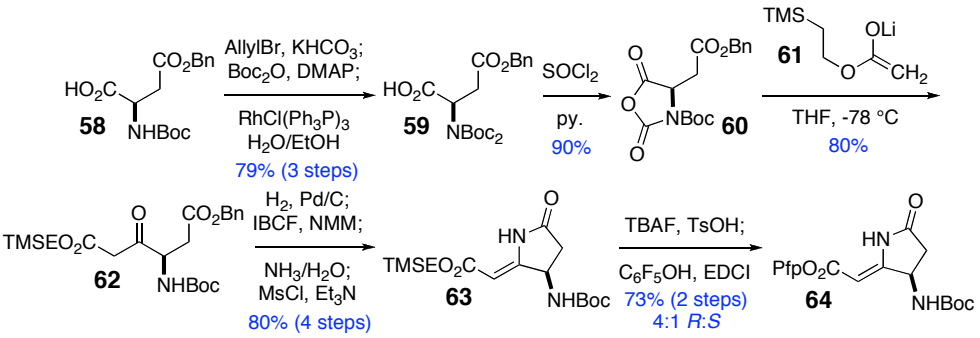


Scheme 7

No attempts at coupling the tripeptides have been reported, probably due to protecting-group problems; while the Tce ester should be easily removed, Boc removal in the presence of the acetonide (for **54**) and indole (for **57**) functionalities could be problematic.

1.2.2: Ma's total synthesis of microsclerodermin E

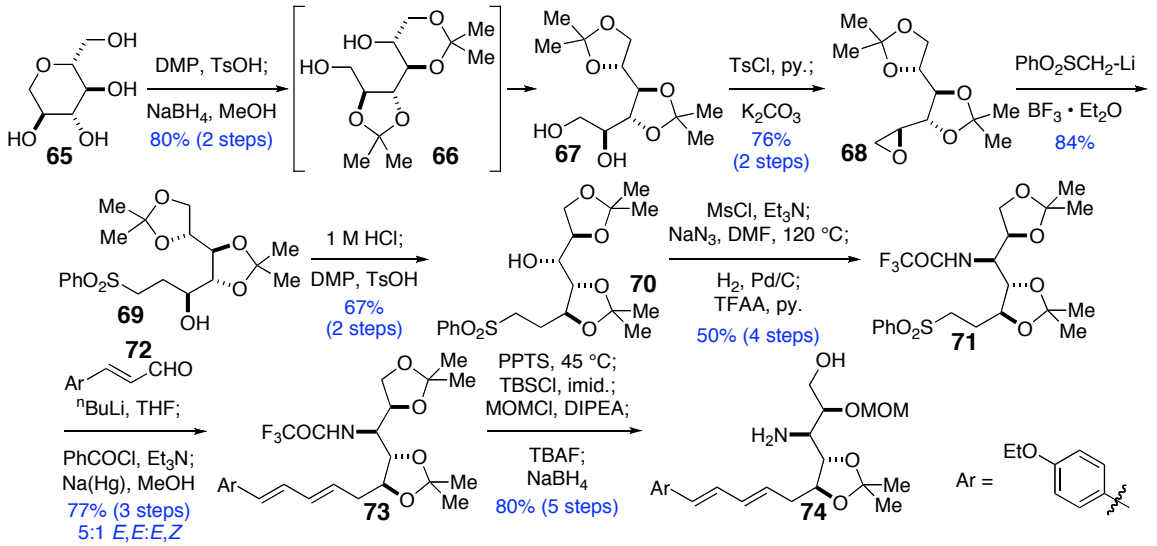
Dawei Ma and co-worker reported in 2003 an asymmetric total synthesis of microsclerodermin E, the simplest member of the family, lacking the hemiaminal and the methyl group in the β-amino acid AETD.[12] Synthesis of the dehydrated pyrrolidinone began with allylation of β-benzyl-*N*-Boc-D-aspartate **58** and installation of a second Boc group on the nitrogen (Scheme 8). Removal of the allyl group under rhodium catalysis to give acid **59** allowed formation of Leuchs anhydride **60**, which was opened with the lithium enolate **61** of 2-(trimethylsilyl)ethyl acetate to give β-keto ester **62**. The benzyl ester was cleaved by hydrogenation and the acid activated as a mixed anhydride and condensed with ammonia to give the amide, which closed upon the ketone to give a hemiaminal; treatment with mesyl chloride and triethylamine led to elimination, forming enamine **63**. Removal of the trimethylsilylethanol group with TBAF proceeded in good yield, but partial racemization was observed even in the presence of tosic acid; since the anion at the stereocenter would be conjugated with the α,β-unsaturated acid, it seems more likely than usual to be formed. Coupling with pentafluorophenyl alcohol gave activated ester **64** as an inseparable mixture of diastereomers in 33% yield over 11 steps.



Scheme 8

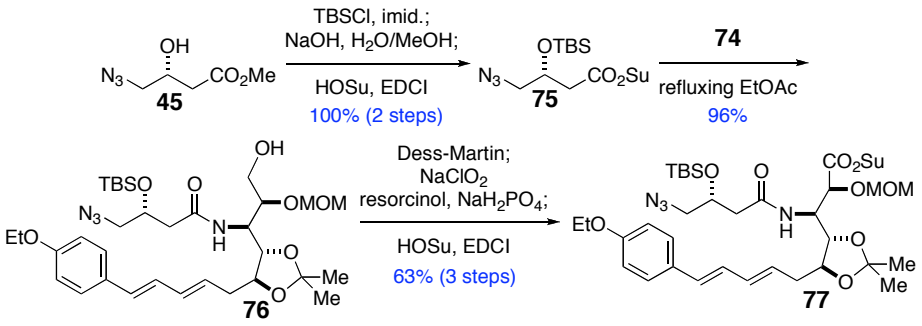
[12] *Total Synthesis of Microsclerodermin E.* Zhu, J.; Ma, D. *Angewandte Chem. Int. Ed.* **2003**, *42*, 5348-5351.

Ma began synthesis of AETD with a chiral molecule containing all four stereocenters. Protection of δ-gluconolactone (**65**) as its bis-acetonide allowed reduction of the lactone to the diol, which rearranged from the six-membered acetonide **66** to the terminal five-membered acetonide and from one internal acetonide to the other to give diol **67**. Tosylation of the primary alcohol and treatment with base gave epoxide **68**, which was opened with the lithium salt of methylphenyl sulfone to provide **69**. The acetonides were removed, then reinstalled to give **70**; formation of the less hindered internal acetonide unmasked the nitrogen position. Alcohol mesylation and displacement with azide were followed by azide reduction and treatment with trifluoroacetic anhydride to yield protected amine **71**. With the stereocenters completed, Julia olefination with aldehyde **72** installed the diene side chain to give **73** as a separable mixture of alkene isomers. Selective removal of the terminal acetonide and TBS protection of the primary alcohol allowed MOM protection of the secondary diol; removal of the TBS group and reductive cleavage of the trifluoroacetate gave amino alcohol **74**.



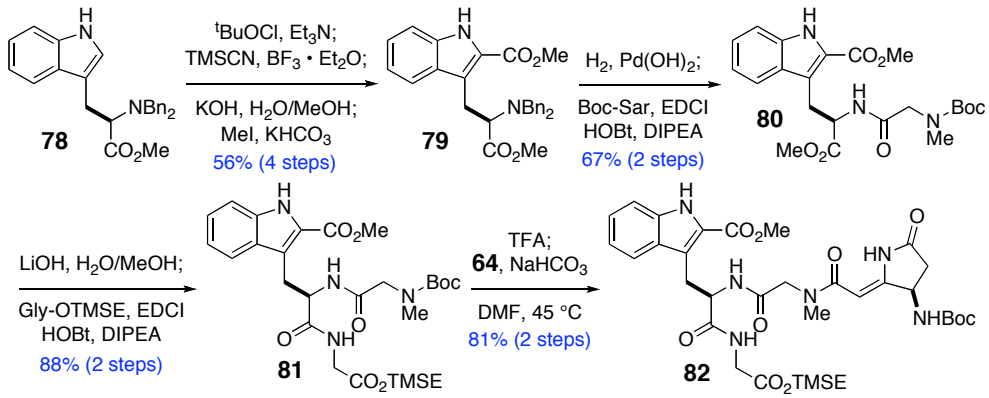
Scheme 9

After TBS protection of alcohol **45**, hydrolysis and coupling to succinimide gave activated ester **75** (Scheme 10), whose coupling with amine **74** gave dipeptide **76**. Two-step oxidation of the alcohol to the acid and coupling to succinimide gave activated ester **77**.



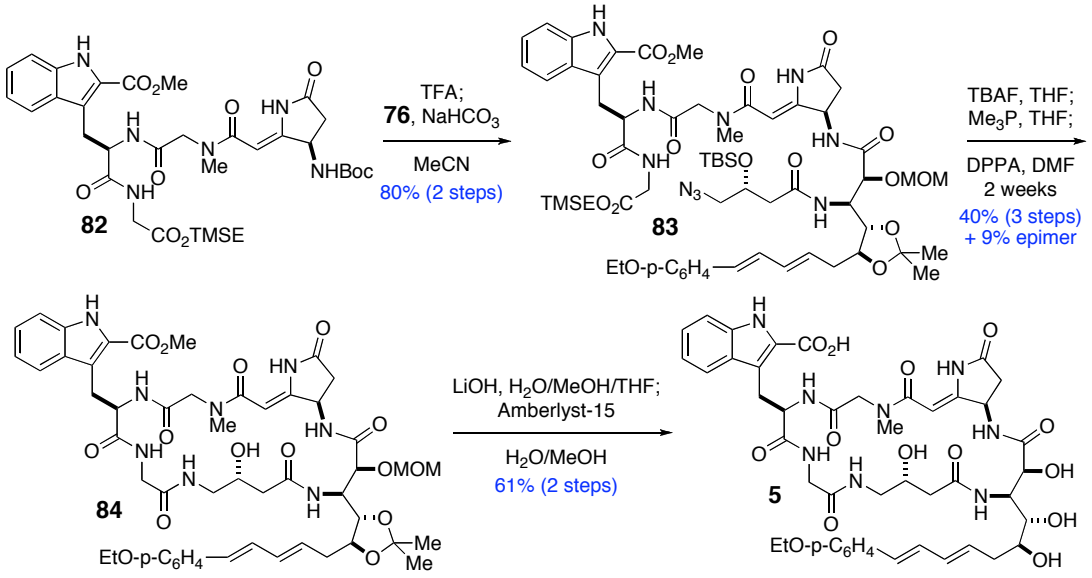
Scheme 10

After chlorination of protected D-tryptophan **78** at the 2' position and displacement with cyanide, nitrile hydrolysis and esterification gave diester **79** (Scheme 11). Removal of both *N*-benzyl groups allowed peptide coupling with Boc-sarcosine to give dipeptide **80**. Selective hydrolysis of the aliphatic methyl ester allowed peptide coupling with glycine TMS ethyl ester to give tripeptide **81**, and TFA removal of the Boc group allowed another coupling with activated ester **64** to give tetrapeptide **82**.



Scheme 11

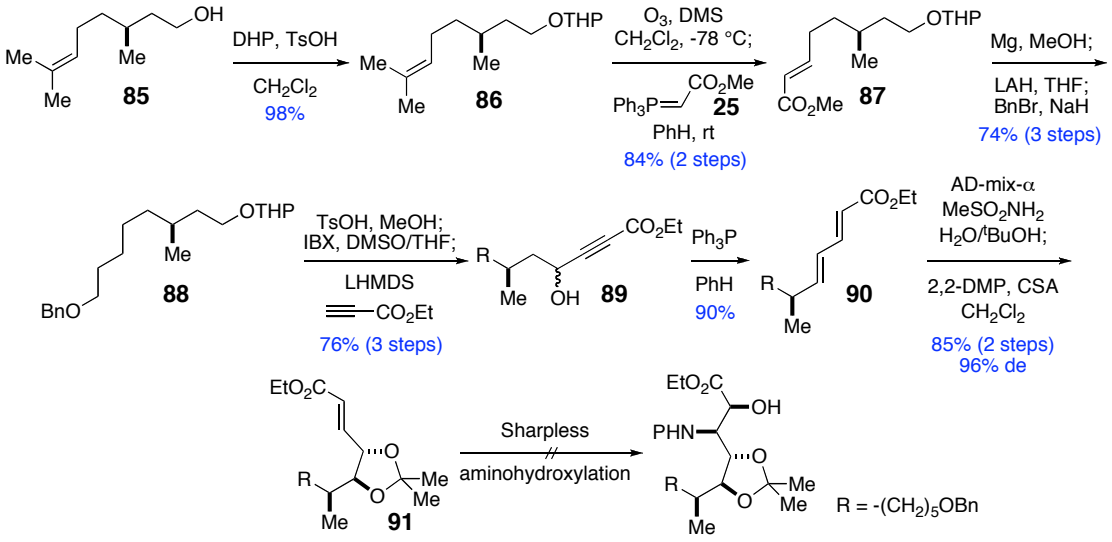
Removal of the Boc group of **82** and treatment with activated dipeptide **76** gave the linear hexapeptide precursor **83** (Scheme 12). Treatment with TBAF removed both the TMSE ester and the TBS group, and Staudinger reduction of the azide gave an amino acid. Macrocyclization with DPPA in DMF required two weeks to achieve a moderate yield of **84**; chromatographic separation of diastereomers (in the pyrrolidinone) was finally possible after the macrocyclization. Finally, hydrolysis of the indole ester and removal of the acid-sensitive protecting groups with mildly acidic resin gave microsclerodermin E (**5**) in 1.2% yield over 29 linear steps.



Scheme 12

1.2.3: Chandrasekhar's studies toward AMMTD

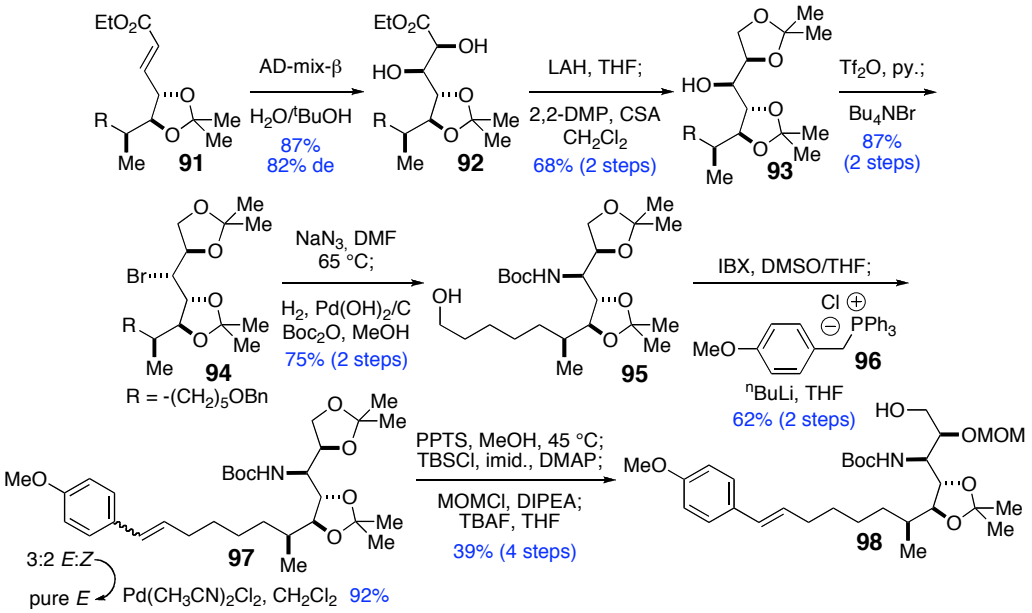
Srivari Chandrasekhar and co-worker at the Indian Institute of Chemical Technology synthesized a protected precursor of AMMTD.[13] THP protection of *S*-citronellol (**85**), which contains the necessary methyl stereocenter, allowed ozonolysis of alkene **86** and extension to **87** by Wittig reaction with **25** (Scheme 13). Treatment with magnesium in methanol effected conjugate reduction of the alkene, and LAH reduction of the ester was followed by conversion of the alcohol to benzyl ether **88**. The THP protection was removed and IBX oxidation allowed attack with lithiated ethylpropiolate to give alkyne alcohol **89** as an inconsequential mixture of diastereomers. Treatment with triphenylphosphine effected alcohol elimination via an allene, which rearranged to the desired conjugated diene **90**. Sharpless asymmetric dihydroxylation installed the vicinal diol as a separable mixture of diastereomers; the desired diastereomer was quickly protected as its acetonide **91**. At this stage Sharpless asymmetric aminohydroxylation was attempted, but failed.



Scheme 13

[13] *Stereoselective synthesis of the C1-C20 segment of the microsclerodermins A and B.* Chandrasekhar, S.; Sultana, S. S. *Tetrahedron Lett.* **2006**, *47*, 7255-7258.

With the failure to directly install the nitrogen, an indirect approach was taken. Dihydroxylation of the alkene **91** proceeded in good yield with modest diastereoselectivity to diol **92**, and reduction of the ester allowed selective formation of the less hindered acetonide **93** (Scheme 14). The remaining alcohol, which possessed the desired stereochemistry, was triflated, then brominated with inversion to give **94**; displacement with azide re-inverted the stereocenter, and hydrogenation in the presence of Boc anhydride removed the *O*-benzyl and converted the azide to the Boc-protected amine **95**, completing the five stereocenters. The freed alcohol was oxidized with IBX and subjected to Wittig olefination with **96** to give a 3:2 mixture of alkene isomers **97**; treament with bis(acetonitrile)palladium(II) chloride gave the pure *E* alkene in excellent yield. Selective removal of the terminal acetonide and TBS masking of the primary alcohol allowed MOM protection of the secondary alcohol, and TBAF removal of the TBS group gave alcohol **98** in 3.0% overall yield and 26 steps; oxidation to the acid would give a protected form of AMMTD.

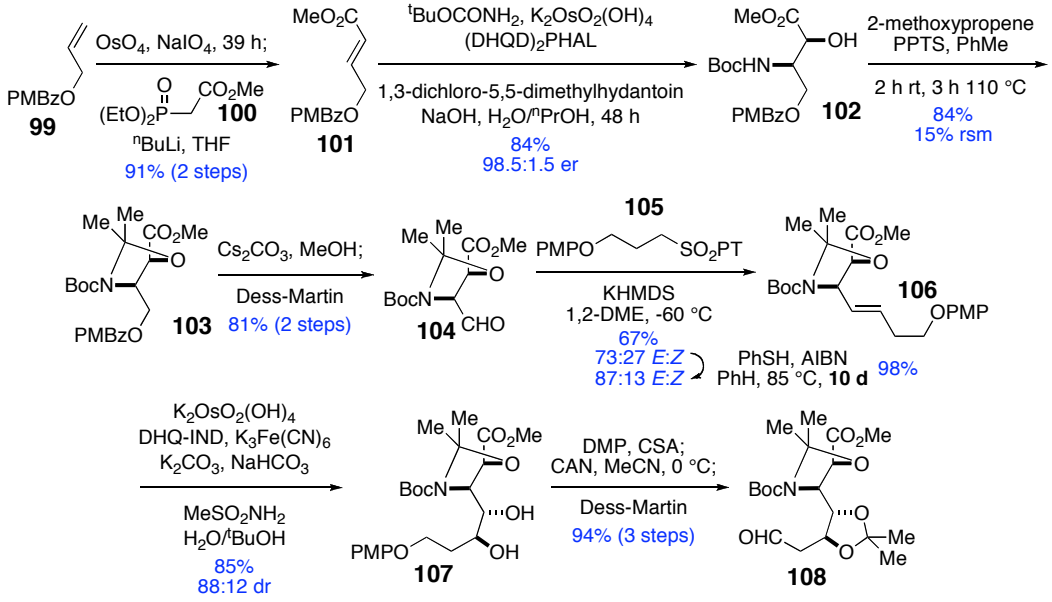


Scheme 14

1.2.4: McLeod's synthesis of APTO and AETD

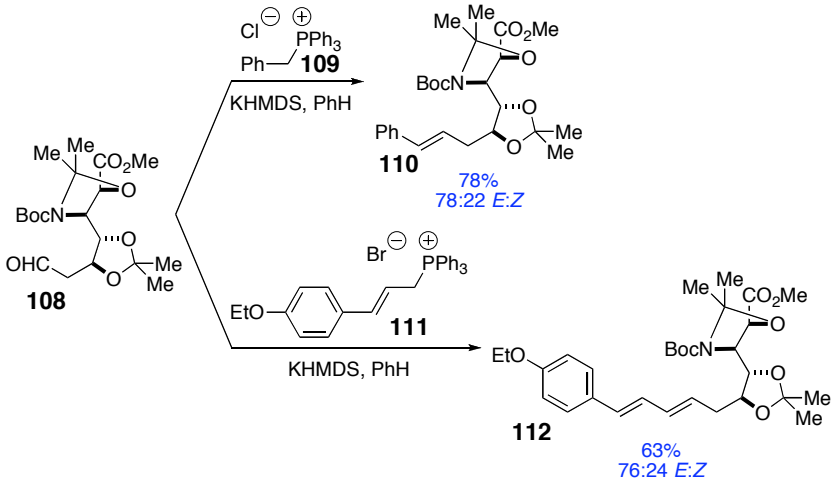
Malcolm McLeod and co-workers completed asymmetric syntheses of the β-amino acids APTO (from **3** and **4**) and AETD (from **5**).[14] One-pot dihydroxylation and periodate cleavage of allyl 4-methoxybenzoate **99** and Horner-Wadsworth-Emmons reaction of the resultant aldehyde with phosphonate **100** gave α,β-unsaturated ester **101** as a separable mixture of diastereomers (Scheme 15). Sharpless asymmetric aminohydroxylation of the alkene, using the aromatic benzoate as a directing group, gave the β-amino alcohol **102** in good yield and enantioselectivity. Formation of the *N*,*O*-acetonide **103**, accomplished stepwise on the oxygen at ambient temperature and the nitrogen at elevated temperature, allowed benzoate removal and oxidation to aldehyde **104**. Modified Julia olefination with **105** gave the alkene **106** as a mixture of isomers, with the majority being *E* alkene; treatment with phenylthiol radical isomerized about half of the undesired *Z* alkene to the desired *E* isomer over 10 days. Sharpless asymmetric dihydroxylation gave diol **107** as an inseparable mixture of diastereomers; acetonide formation and oxidative PMP removal allowed oxidation to key aldehyde **108**.

[14] *The enantioselective synthesis of APTO and AETD: polyhydroxylated β-amino acid constituents of the microsclerodermin cyclic peptides.* Shuter, E. C.; Duong, H.; Hutton, C. A.; McLeod, M. D. *Org. Biomol. Chem*. **2007**, *5*, 3183-3189.



Scheme 15

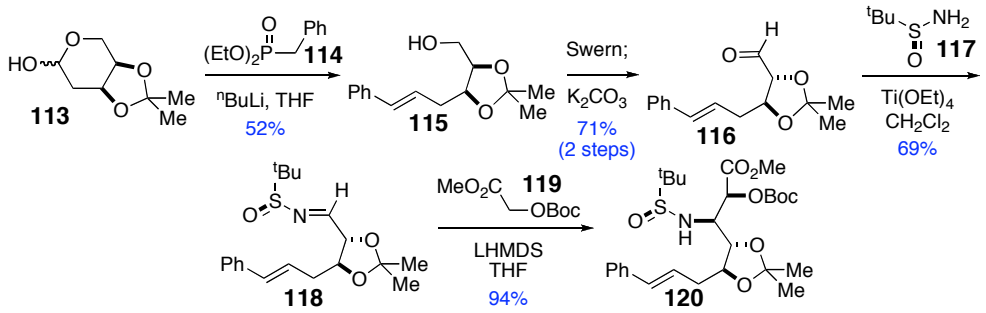
Aldehyde **108** provided a common intermediate for the completion of AETD and APTO derivatives. Wittig reaction with benzyltriphenylphosphonium chloride **109** and KHMDS gave APTO derivative **110**, while the conjugated phosphonium salt **111** gave AETD derivative **112** (Scheme 16).



Scheme 16

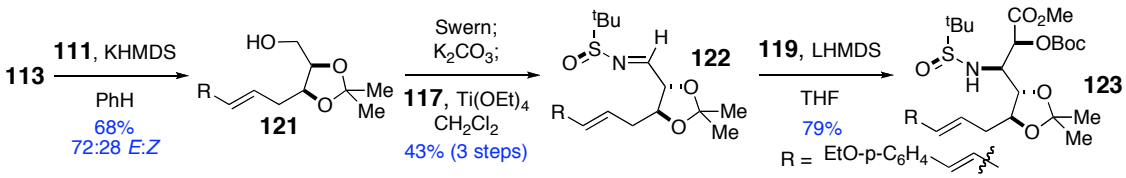
1.2.5: Aitken's synthesis of APTO and AETD

Aitken and co-workers developed concise syntheses of protected APTO and AETD.[15] Homologation of 2-deoxy-D-ribose acetonide (**113**) with benzyl diethyl-phosphonate (**114**) gave pure *E* alkene **115** (Scheme 17). Swern oxidation allowed epimerization of the adjacent carbinol, and condensation of aldehyde **116** with (*S*)-*t*-butylsulfinamide (**117**) gave sulfinimine **118**. Reaction with the enolate of *O*-Boc methyl glycolate (**119**) gave protected APTO **120** in high yield as a single diastereomer.



Scheme 17

After attempts at optimization, Aitken was forced to use Hutton's conditions for installation of the AETD diene side chain: reaction of **113** with phosphonium salt **111** gave the diene **121** as a separable mixture of diastereomers; after separation, the alcohol was oxidized and epimerized as before, and condensation with **117** gave sulfinimine **122** (Scheme 18). Reaction with the enolate of **119** gave a somewhat lower yield of **123**, albeit still as a single diastereomer.



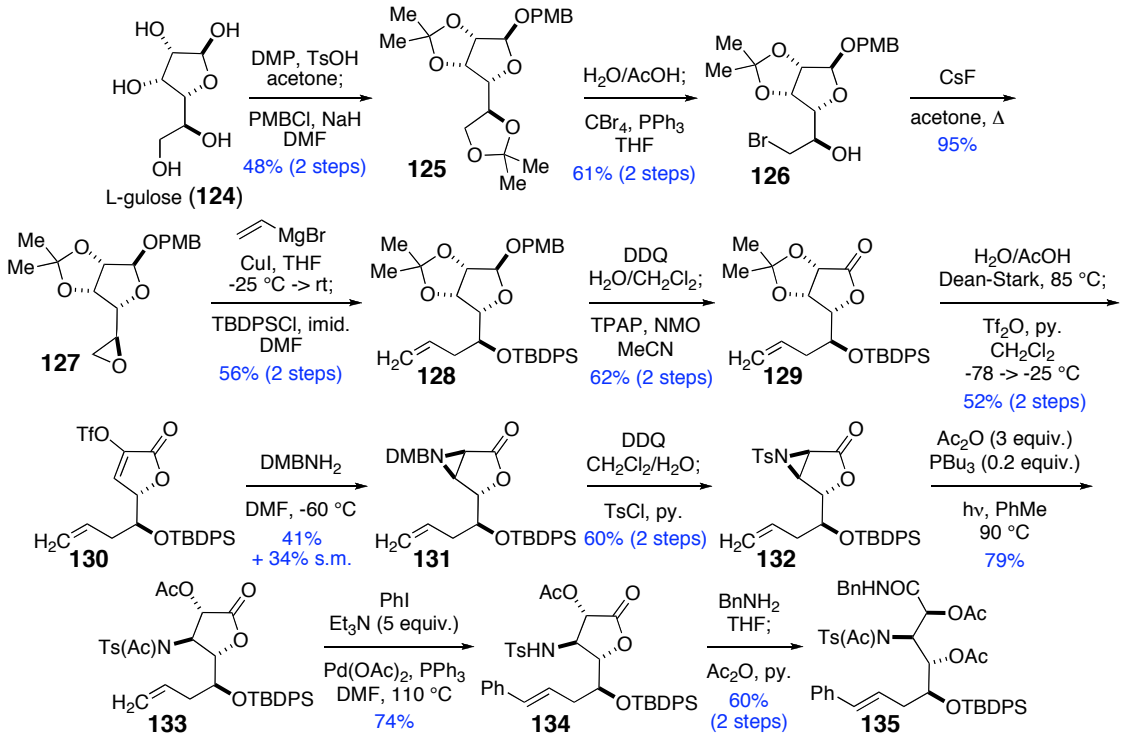
Scheme 18

[15] *Rapid Assembly of the Polyhydroxylated β-Amino Acid Constituents of Microsclerodermins C, D, and E.* Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841-844.

1.2.6: Dauban and Dodd's synthesis of APTO

The group of Dauban and Dodd reported a synthesis of protected APTO in 2009 via their aziridino-γ-lactone methodology.[16] Conversion of L-gulose (**124**) to its diacetonide and protection of the remaining free alcohol as PMB ether **125** was followed by selective removal of one acetonide to give a diol, which was converted to the terminal bromide **126** (Scheme 19); treatment with base converted the bromohydrin to epoxide **127**. Epoxide opening with vinyl cuprate and alcohol protection gave TBDPS ether **128**; removal of the PMB group and oxidation of the free alcohol gave lactone **129**. Treatment with triflic anhydride and pyridine gave the monotriflate **130** resulting from elimination of the triflate β to the carbonyl; treatment with dimethoxybenzylamine gave protected aziridine **131**, which was deprotected with DDQ and reprotected with an electron-withdrawing tosyl group to give **132**. Opening of the aziridine with tri-*n*-butylphosphine and acetic anhydride under microwave conditions gave the fully protected lactone **133** containing all chiral centers of APTO. Heck coupling with iodobenzene gave the conjugated aromatic **134**; excess triethylamine effected removal of the *N*-acetyl group. Treatment with benzylamine opened the lactone to give the secondary amide as a mixture of monoacetates, and acetylation of the mixture gave the diacetate **135** in 0.43% yield over 16 steps.

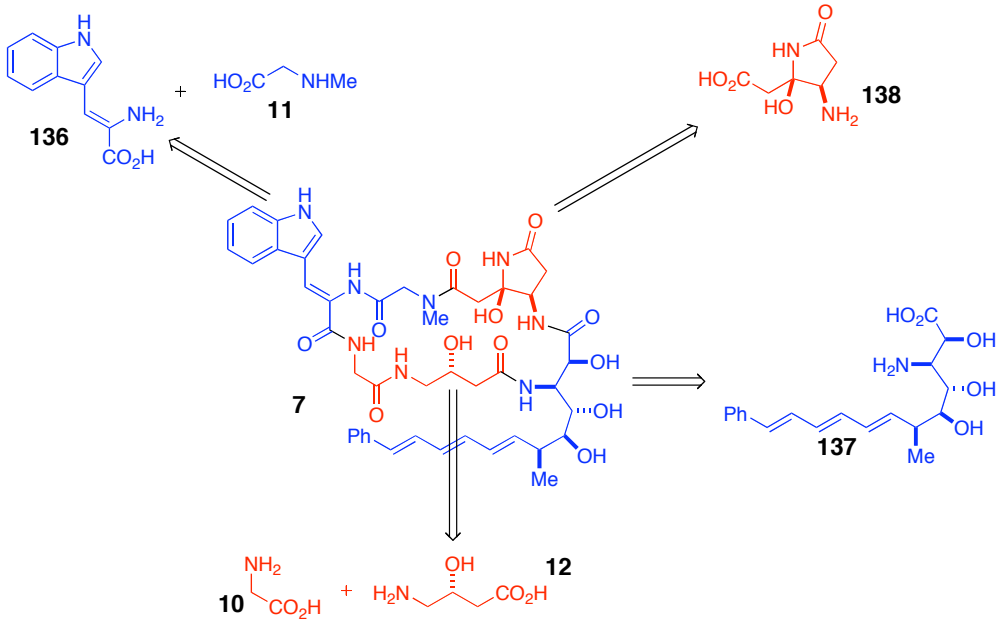
[16] *Enantiospecific Synthesis of a Protected Equivalent of APTO, the β-Amino Acid Fragment of Microsclerodermins C and D, by Aziridino-γ-lactone Methodology*. Tarrade-Matha, A.; Valle, M. S.; Tercinier, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2009**, 673-686.


L-gulose (124)
DMP, TsOH
acetone;
PMBCl, NaH
DMF
48% (2 steps)
125
H2O/AcOH;
CBr4, PPh3
THF
61% (2 steps)
126
CsF
acetone, Δ
95%
127
MgBr
CuI, THF
-25 °C -> rt;
TBDPSCl, imid.
DMF
56% (2 steps)
128
DDQ
H2O/CH2Cl2;
TPAP, NMO
MeCN
62% (2 steps)
129
H2O/AcOH
Dean-Stark, 85 °C;
Tf2O, py.
CH2Cl2
-78 -> -25 °C
52% (2 steps)
130
DMBNH2
DMF, -60 °C
41%
+ 34% s.m.
131
DDQ
CH2Cl2/H2O;
TsCl, py.
60% (2 steps)
132
Ac2O (3 equiv.)
PBu3 (0.2 equiv.)
hν, PhMe
90 °C
79%
133
PhI
Et3N (5 equiv.)
Pd(OAc)2, PPh3
DMF, 110 °C
74%
134
BnNH2
THF;
Ac2O, py.
60%
(2 steps)
135

Scheme 19

1.3: Our plans

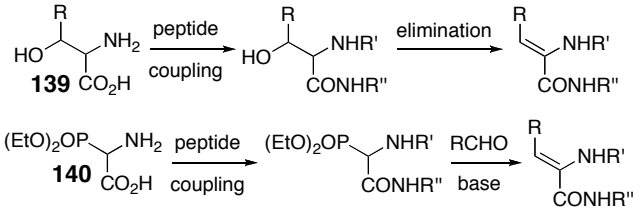
This thesis details our efforts toward the synthesis of microsclerodermin G (**7**). Microsclerodermins F-I are of interest to this group because of their antifungal and antitumor activity and because of the considerable synthetic challenge they present; we undertook a synthetic program in this area to conquer these challenging synthetic targets and to allow exploration of the biological activity of the microsclerodermins. Disconnection of the peptide bonds gave six amino acids (Scheme 20); as **10** and **11** were commercially available, we set the remaining amino acids as synthetic targets. The synthetic challenges we are addressing include the dehydrotryptophan residue **136**; GABOB (**12**); the polyhydroxylated β-amino acid AMPTD (**137**), which also contains a phenyltriene side chain; and the pyrrolidinone **138**, which includes a highly labile β-keto hemiaminal. We planned to address installation of the phenyltriene side chain of **137** and the pyrrolidinone hemiaminal of **138** at the end of the synthesis; thus we required only installation of an alcohol handle and protected nitrogen at the respective sites.



Scheme 20

Chapter 2: Synthesis and coupling of the tryptophan piece

Dehydrotryptophan, incorporated in microsclerodermins G and I, is uniquely able among the 20 proteinogenic amino acids to exist as the free dehydroamino acid, due to its extended conjugated system; even phenylalanine decomposes via imine tautomerization and hydrolysis to the α-ketoacid. Despite their instability in the free form, dehydroamino acids have been found in several natural products. Standard methods for synthetic incorporation of a dehydroamino acid include installation of a β-hydroxy functionality (e.g. **139**, Scheme 21),[17] which can be eliminated to the double bond after coupling, or an α-phosphonate (e.g. **140**),[18] allowing Horner-Emmons-Wadsworth alkene installation.



Scheme 21

We planned to incorporate the dehydrotryptophan residue directly into the peptide backbone, eliminating the extra steps and possible isomeric mixtures obtained via the above methods. Unfortunately, the conjugation that stabilizes the free amine also makes it less reactive than standard amines for peptide coupling, and we would have to find a suitably reactive coupling partner to realize this approach. The D-tryptophan residue found in microsclerodermins F and H is unmodified; the only synthetic challenge we anticipated for this piece was preventing racemization.

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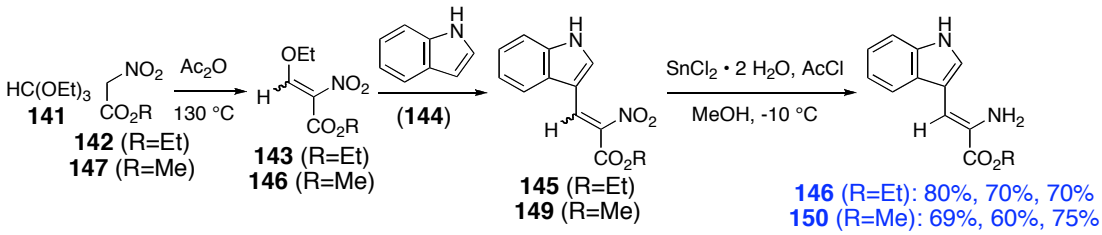
[17] *High yielding synthesis of dehydroamino acid and dehydropeptide derivatives*. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 3697-3703.
[18] *Synthesis of barretin*. Johnson, A.-L.; Bergman, J.; Sjögren, M.; Bohlin, L. *Tetrahedron* **2004**, *60*, 961-965.

2.1. Synthesis of the dehydrotryptophan residue

Commercially available triethyl orthoformate (**141**) and ethyl nitroacetate (**142**) underwent Knoevenagel reaction in acetic anhydride to give α,β-unsaturated ester **143** as a 3:1 *Z*:*E* mixture,[19] which underwent ethoxy-displacing Michael addition with indole (**144**) to yield nitro ester **145** as a 1:1 mixture of geometrical isomers (Scheme 22). Reduction of the nitro group with tin (II) chloride and concentrated hydrochloric acid at low temperature yielded the dehydrotryptophan ethyl ester **146** as a single geometrical isomer, as judged by ^{1}H NMR. This alkene had previously been reported as a mixture of geometrical isomers[20] or as the 6-methyl analogue.[21] We eventually switched to methyl nitroacetate (**147**), proceeding through alkene **148** and indole species **149** to give the methyl ester **150**; this simplified the NMR spectrum and allowed large-scale preparation.[22] This procedure gave a poor overall yield of the desired product (30-35%), we experienced inconsistency in the indole addition step, and the nitro reduction was poorly suited for scaling up due to the low temperature and large solvent volumes; we thus continued to explore alternate conditions.



Scheme 22

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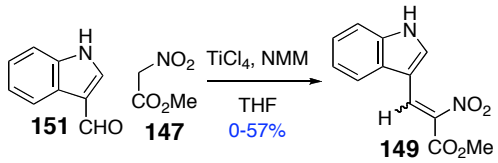
[19] *Methyl 2-Nitro-3-ethoxyacrylate and Related Compounds.* Kamlet, M. J. *J. Org. Chem.* **1959**, *24*, 714-715.

[20] E/Z-*Configurational Assignment of* N-*Acetyl-α,β-Dehydrotryptophan Ethyl Ester Produced by* L-*Tryptophan 2',3'-Oxidase from* Chromobacterium violaceum. Hammadi, A.; Ménez, A.; Genet, R. *Tetrahedron Lett.* **1996**, *37*, 3309-3312.

[21] *Synthesis of (*R*)-6-Methyltryptophan via Enantioselective Catalytic Hydrogenation.* Hengartner, U.; Valentine, D.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741-3747.

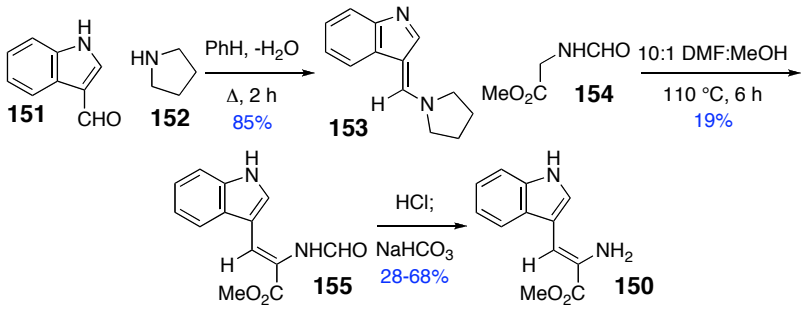
[22] *Methyl nitroacetate.* Zen, S.; Koyama, M.; Koto, S. *Org. Syn.* CV6, 797.

We synthesized the nitro ester **149** directly from **147** and indole-3-carboxaldehyde (**151**) under titanium tetrachloride promotion, though with variable yield (Scheme 23).[23] This procedure required a long reaction time and syringe-pump addition of reagents, so we attempted a simpler activation by heating the reactants in piperidine; unfortunately, no product was seen.[24] The relative ease of operation for the original procedure outweighed the somewhat improved yield of the titanium procedure.



Scheme 23

We explored another literature procedure toward the end of our studies.[25] **151** was reacted with pyrrolidine **152** to give enamine **153**, whose condensation with *N*-formylglycine methyl ester (**154**) gave the protected dehydrotryptophan **155** (Scheme 24). While deacylation with HCl and free-basing gave **150**, the pyrrolidine displacement gave a poor yield and removal of the *N*-formyl was inconsistent.



Scheme 24

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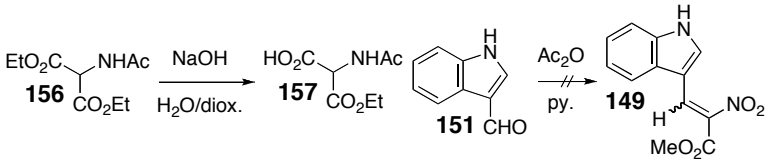
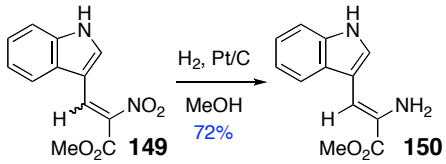
[23] *New preparative route to hetaryldienes and azadienes*. Nagy, I.; Hajós, G.; Riedl, Z. *Heterocycles* **2004**, *63*, 2287-2307.
[24] *Improved Syntheses of Indole-3-aldehyde*. Shabica, A. C.; Howe, E. E.; Ziegler, J. B.; Tishler, M. *J. Am. Chem. Soc.* **1946**, *68*, 1156-1157.
[25] *Useful Synthesis of α,β-Dehydrotryptophan Derivatives*. Moriya, T.; Yoneda, N.; Miyoshi, M.; Matsumoto, M. *J. Org. Chem.* **1982**, *47*, 94-98.

Our next route began with diethyl 2-acetamidomalonate (**156**), whose hydrolysis gave the acid **157** (Scheme 25); attempted condensation with **151** failed to yield **149**.[26]



Scheme 25

Attempts at reduction of **150** with iron or zinc in acetic acid failed; in a final effort to address the problems of our original route, we attempted reduction of the nitro compound **149** via hydrogenation (Scheme 26). While the reaction failed under a hydrogen balloon, we increased the pressure to 20 psi and were gratified to receive a good yield of the desired enamine **150** as a single diastereomer! We therefore see that acidic reduction conditions are not necessary for isomerization of the alkene geometry. One possible explanation is that the electron-rich indole could donate into the conjugated ester to give the zwitterionic resonance form; collapse to the neutral compound would allow isomerization to the more stable *Z* alkene. Conjugate addition of methanol to the α,β-unsaturated ester could also account for the isomerization; we would have to run the experiment in an aprotic solvent such as THF to distinguish between the two possibilities.



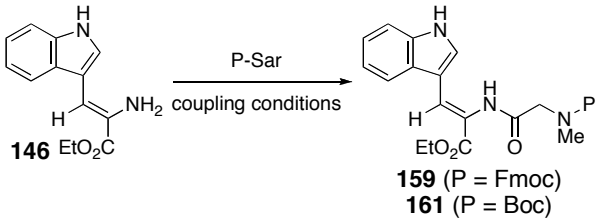
Scheme 26

[26] *Synthesis of BILN 2061, an HCV NS3 Protease Inhibitor with Proven Antiviral Effect in Humans.* Faucher, A.-M.; Bailey, M. D.; Beaulieu, P. L.; Brochu, C.; Duceppe, J.-S.; Ferland, J.-M.; Ghiro, E.; Gorys, V.; Halmos, T.; Kawai, S. H.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S.; Llinàs-Brunet, M. *Org. Lett.* **2004**, *6*, 2901-2904.

2.2: Synthesis of the sarcosine-dehydrotryptophan dipeptide

With the dehydrotryptophan methyl ester **150** in hand, we began to explore coupling of the free amine to give the sarcosine-dehydrotryptophan dipeptide. Only one instance of such a peptide coupling had been reported, between amine **146** and the acid chloride of Cbz-alanine.[25] We attempted to repeat the procedure by converting Fmoc-sarcosine (**158**) to the acid chloride, but its coupling with **146** consistently failed. The sole successful run gave only a 25% yield of the dipeptide **159**, and it seems likely that failure to produce the acid chloride would explain the failed reaction: we used oxalyl chloride instead of phosgene to produce the acid chloride and neglected to take an IR spectrum to confirm that the acid chloride had been produced. We also explored various other coupling conditions with Boc-sarcosine (**160**) to give dipeptide **161** (Table 2).

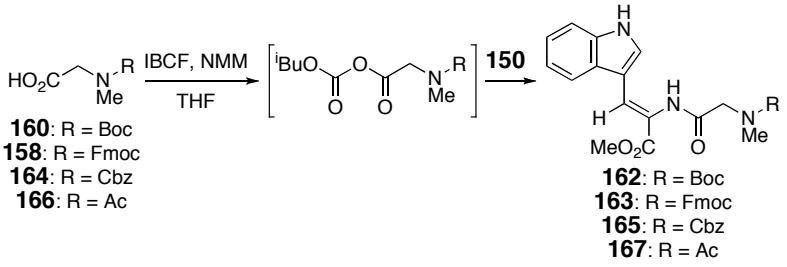
Table 2



P	Coupling conditions	% yield
Fmoc	Fmoc-Sar-Cl	0 - 25
Boc	DCC / DMAP	0
Boc	EDCI	6
Boc	IBCF / NMM	21

Around this time we found a literature example showing that the free amine of 6-methyldehydrotryptophan was amenable to acylation with simple anhydrides.[21] Given our preliminary result above, we hoped that this reactivity would remain without the extra electron density given by the methyl group, and that we could then extend this method to peptide coupling. We coupled **150** to various protected sarcosines with good results (Table 3): Boc-sarcosine **160** gave dipeptide **162**, Fmoc-sarcosine **158** gave dipeptide **163**, and Cbz-sarcosine **164** gave dipeptide **165**. (The failure of *N*-acetyl sarcosine **166** to give dipeptide **167** is most likely due to improper production of the protected sarcosine on our part.) Thus, this seems a general method; since acid chlorides and anhydrides are roughly equal in reactivity, it makes sense that the mixed anhydride method would also work for the deactivated dehydrotryptophan system.

Table 3



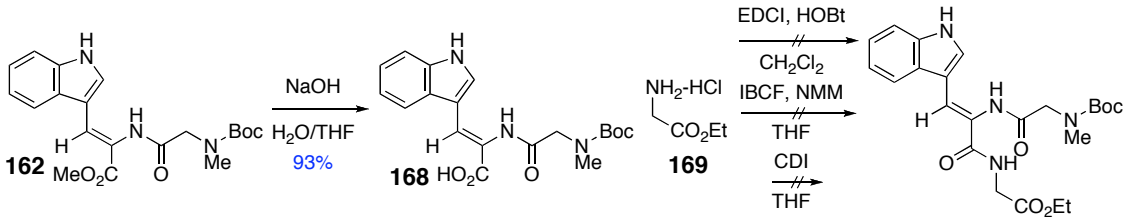
160: R = Boc
158: R = Fmoc
164: R = Cbz
166: R = Ac

162: R = Boc
163: R = Fmoc
165: R = Cbz
167: R = Ac

R	Yield
Boc	70
Fmoc	32
Cbz	52
Ac	0

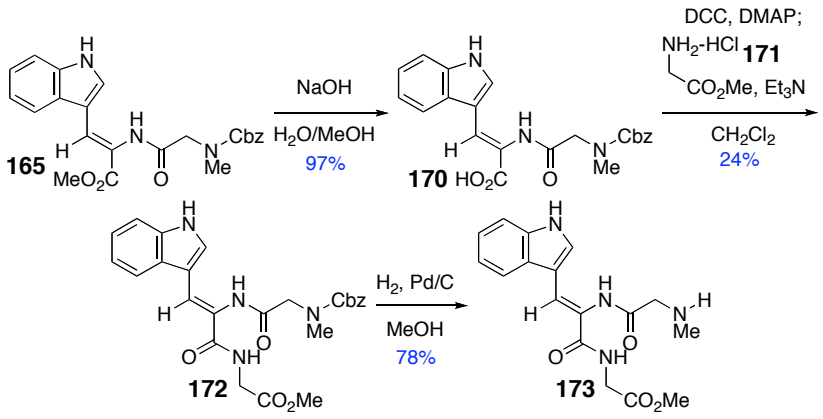
2.3: Coupling of the Sar-ΔTrp dipeptide at the *C* terminus

Hydrolysis of the methyl ester of **162** with NaOH gave reproducible high yields of acid **168** (Scheme 27). Repeated attempts to couple **168** with glycine ethyl ester hydrochloride (**169**) using EDCI/HOBt appeared unsuccessful, as did attempted coupling under mixed anhydride conditions or with carbonyldiimidazole. We did confirm the structure of **168**: reaction with diazomethane regenerated **162**, though we didn't isolate it.



Scheme 27

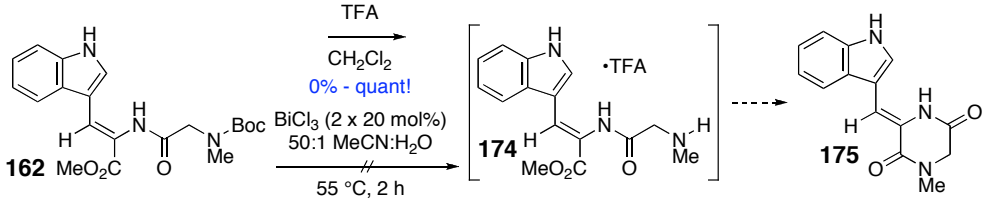
The analogous hydrolysis of Cbz-dipeptide **165** to the free acid **170** also proceeded in near-quantitative yield (Scheme 28). Activation with DCC and DMAP and coupling with glycine methyl ester hydrochloride (**171**) gave the desired tripeptide **172**, albeit in poor yield; it appears that the product was simply more polar than we expected, and thus we probably failed to recover the tripeptide from the earlier couplings. Hydrogenation of **172** gave the free amine **173** in good yield.



Scheme 28

2.4: Attempted coupling of the Sar-ΔTrp dipeptide at the *N* terminus

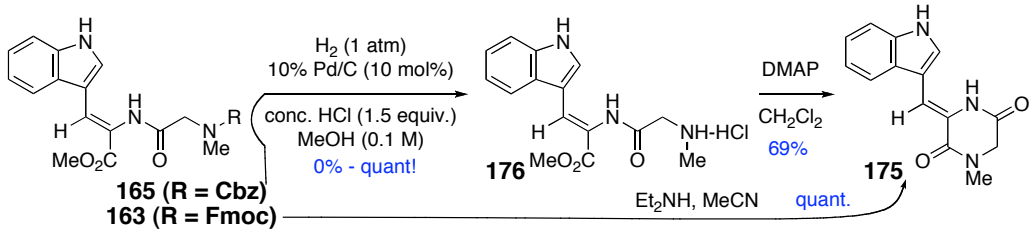
We also attempted extension of the dipeptide at the *N*-terminus. We originally deprotected the Boc group of **162** with TFA, but were not able to consistently obtain the amine **174** (Scheme 29). Worried about *tert*-butylation of the indole group of **162** during TFA-mediated deprotection, we attempted an alternative deprotection with bismuth trichloride;[27] however, **162** was recovered unchanged under these conditions. Returning to TFA use, we found that treatment of **174** with saturated aqueous $NaHCO_3$ led to decomposition. However, reducing to 10 equivalents of TFA appeared to successfully produce the desired amine. Later attempts at this deprotection failed to produce **174**; presumably the electron-rich sarcosine nitrogen could close to the diketopiperazine **175**, which would also explain the decomposition under basic conditions.



Scheme 29

Similar results were obtained from the Fmoc dipeptide **163** and Cbz dipeptide **165**. Attempted deprotection of the Fmoc dipeptide **163** led directly to the DKP **175** (Scheme 30). Hydrogenation of the Cbz dipeptide under acidic conditions only occasionally led to the salt **176**, and attempts to freebase the salt with DMAP led to the diketopiperazine **175**. With these results in hand, we abandoned our efforts at peptide coupling of the sarcosine nitrogen.

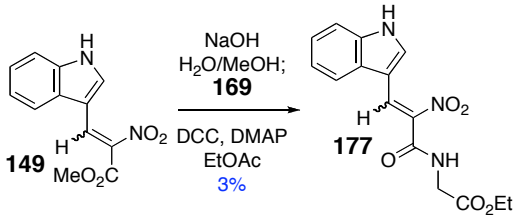
[27] *Chemoselective deprotetction of* N-*Boc group in amino acids and peptides by bismuth(III) trichloride.* Navath, R. S.; Pabbisetty, K. B.; Hu, L. *Tetrahedron Lett.* **2006**, *47*, 389~393.



Scheme 30

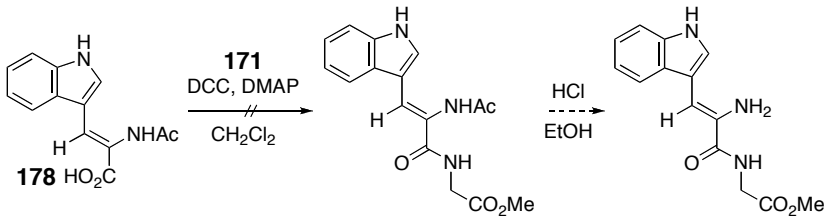
2.5: Coupling of the dehydrotryptophan carboxylate

We also attempted to synthesize the dehydrotryptophan-glycine dipeptide. We attempted hydrolysis of ester **149** but were unable to isolate the highly polar product; hydrolysis followed immediately by coupling with **169** appeared to give a small amount of the nitro-dipeptide **177** (Scheme 31), but the route was impractical to continue.



Scheme 31

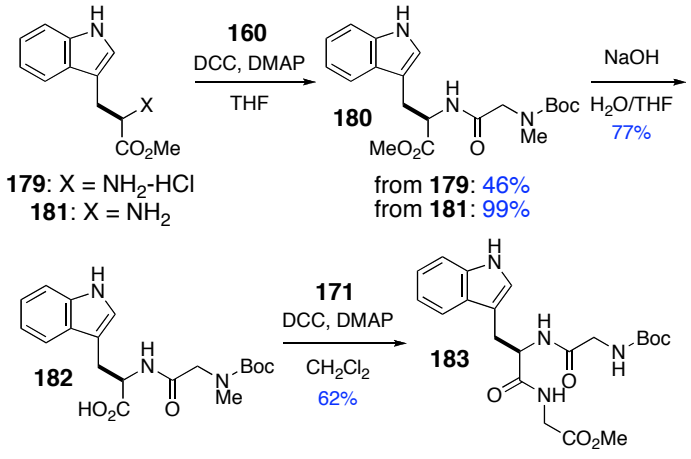
We also prepared *N*-acetyldehydrotryptophan **178** (Scheme 32) and attempted to couple it with **171**, but the product obtained did not possess a methyl ester signal in the NMR. In any event, removal of the *N*-acetyl group with HCl would likely have decomposed the dipeptide, and we abandoned this approach as well.



Scheme 32

2.6: Synthesis of the sarcosine-D-tryptophan dipeptide

Having largely failed in our attempts to extend our dehydrotryptophan methodology beyond a dipeptide, we decided to pursue d-tryptophan coupling to possibly allow synthesis of **6** or **8**. Coupling of commercially available D-tryptophan methyl ester hydrochloride (**179**) with **160** to give dipeptide **180** (Scheme 33); however, yields were low due to solubility problems. Esterification of commercial D-tryptophan and neutralization with sodium bicarbonate yielded free amine **181**, whose coupling proceeded essentially quantitatively. Hydrolysis of **180** yielded free acid **182**, and coupling with **171** gave the tripeptide **183**. We did not attempt to determine if epimerization had occurred at the tryptophan α carbon during the second coupling, and would need to do so before carrying on the tripeptide obtained. Alternatively, coupling glycine ethyl ester with *N*-Boc-D-tryptophan should minimize epimerization, and subsequent coupling of the tryptophan amine would allow elaboration of a stereochemically intact molecule.



Scheme 33

Chapter 3: Synthesis of GABOB

Numerous methods for the synthesis of the γ-amino-β-hydroxy amino acid GABOB (**12**) have been reported.[28] This chapter will not recap these events but rather focus on our efforts to find suitable peptide couplings for masked forms of **12**.

3.1: Direct synthesis of GABOB

We began our studies by repeating a synthesis of GABOB developed in the Williams group.[29] Ethyl acetate (**184**) was converted to TBS enol ether **185**, which underwent Mukaiyama aldol reaction with (+)-Cbz-Williams lactone **186** to give adduct **187**; treatment with boron trifluoride etherate yielded elimination product **188** (Scheme 34). Catalytic hydrogenation with palladium (II) chloride reduced the alkene and removed the Cbz group to give ester **189** quantitatively with a 95:5 diastereomeric ratio. Hydrolysis was followed by high-temperature hydrogenation to remove the chiral auxiliary; purification on an ion-exchange column gave the γ-amino acid **12** in 26% overall yield for six steps. We experienced a decreased yield from the reported procedure, primarily in the aldol reaction with the lactone and removal of the chiral auxiliary. The silyl enol ether could be moisture-sensitive, and failure to immediately purify and use it could lead to decomposition. We have also had repeated trouble conducting purification on an ion-exchange column; in light of these difficulties, we chose to explore direct synthesis of a protected GABOB.

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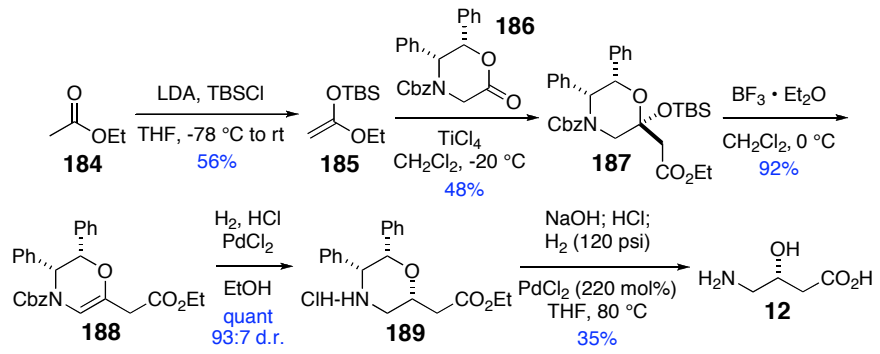
[28] *Short Synthesis of (*R*)- and (*S*)-4-Amino-3-Hydroxybutytic Acid (GABOB)*. Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Synthesis* **2005**, *4*, 579-582.

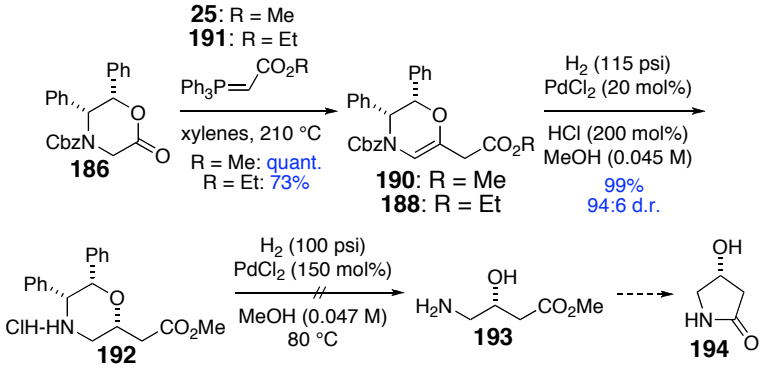
[29] *Asymmetric synthesis of (*R*)-(-)-carnitine*. Jain, R. P.; Williams, R. M. *Tetrahedron Lett.* **2001**, *27*, 4437-4440.



Scheme 34

3.2: Modifications of the original procedure

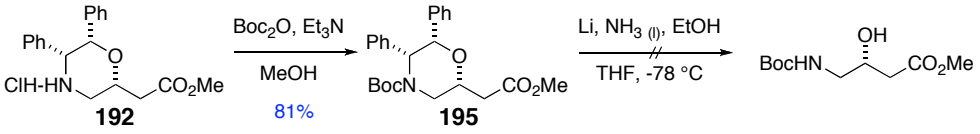
We first improved this procedure by adopting our co-workers' Wittig reaction of **186** with **25** to give methyl ester **190** directly (Scheme 35), greatly improving the yield while eliminating one step.[30] We also conducted the reaction with the ethyl reagent **191** to reproduce **188** in good yield, but preferred the simpler NMR spectrum of **190**. After alkene hydrogenation to give ester **192**, we attempted hydrogenation to directly remove the chiral auxiliary, but saw only incomplete cleavage. In light of the possibility that the free primary amine of the desired product **193** could close to the γ-lactam **194**, we chose to explore different routes.



Scheme 35

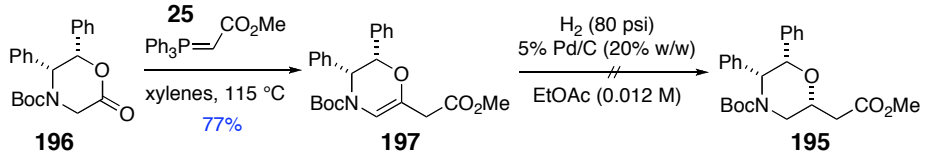
[30] *Asymmetric Synthesis of (+)-Negamycin*. Jain, R. P.; Williams, R. M. *J. Org. Chem*. **2002**, *67*, 6361-6365.

We reprotected the liberated amine of **192** as the Boc amine **195** (Scheme 36). Attempts at removal of the chiral template via Birch reduction were unsuccessful with varying times and temperatures; we later learned that ester will undergo Birch reduction to the corresponding alcohol, providing a likely decomposition pathway for this reaction.



Scheme 36

We next attempted a two-step Wittig-hydrogenation protocol for the synthesis of **195**, eliminating the need for consecutive hydrogenation steps. The previous procedure for the Wittig reactions involved reflux in xylenes at 220 °C, so less forcing conditions were explored. Although ethanol proved to be an unsuitable solvent, Wittig reaction of (+)-Boc-lactone **196** with **25** proceeded in good yield in refluxing toluene to give alkene **197** (Scheme 37). Unfortunately, the decreased temperature required a corresponding increase in time. Attempts to reduce the double bond under both neutral and acidic conditions with palladium on carbon were fruitless, suggesting that the bulky Boc group makes the alkene sterically inaccesible.

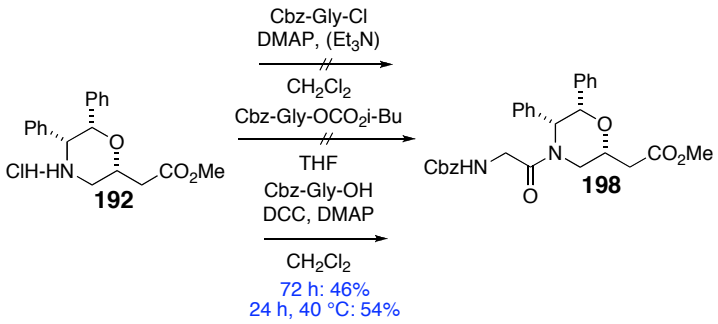


Scheme 37

3.3: Attempted synthesis of a glycine-GABOB dipeptide

We next decided to take advantage of the free amine produced by hydrogenation of the lactone Wittig product to introduce the glycine residue. We anticipated that high-temperature hydrogenation of the resultant masked dipeptide would allow auxiliary removal and concomitant deprotection. Coupling at the *N*-terminus with the four remaining amino acids would allow macrocyclization of the AMPTD amine onto the GABOB carboxyl, completely avoiding the possibility of racemization. Ma's synthesis of microsclerodermin E featured a macrocyclization at the Gly-GABOB linkage that required 14 days to reach 40% yield; we hoped that the phenyltriene and acetonide would reduce the flexibility of the AMPTD amine, leading to a quicker macrocyclization.

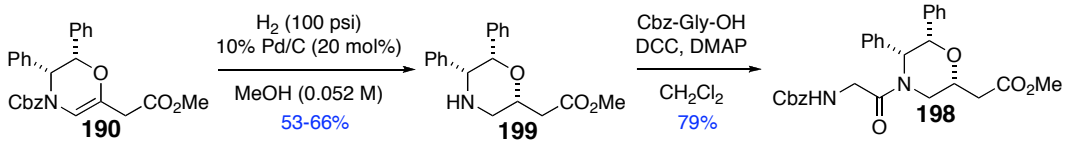
Peptide coupling of **192** with Cbz-glycine failed with the acid chloride or mixed anhydride, but coupling with DCC/DMAP yielded the acylated morpholine **198** in moderate yield as a white crystalline solid (Scheme 38).



Scheme 38

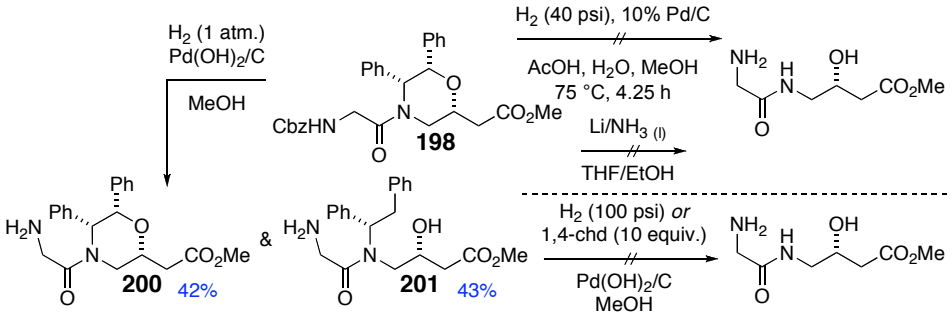
At this point, the hydrogen pressure required for reaction with $PdCl_2$ was limiting throughput, and the coupling yield of the resultant amine salt was modest. We thus attempted alkene reduction with palladium on carbon, and discovered that the pressure could be reduced to 100 psi, allowing the use of larger hydrogenation vessels.

Additionally, we obtained the reduced product as a single diastereomer, presumably due to the increased steric bulk of carbon-adsorbed palladium over palladium chloride. Previous attempts to free-base the HCl salt **192** failed, but the neutral reduction of enamine **190** yielded directly the free amine **199**, a much better coupling partner; the yield of **198** increased from 54% to 79%, even without heating (Scheme 39).



Scheme 39

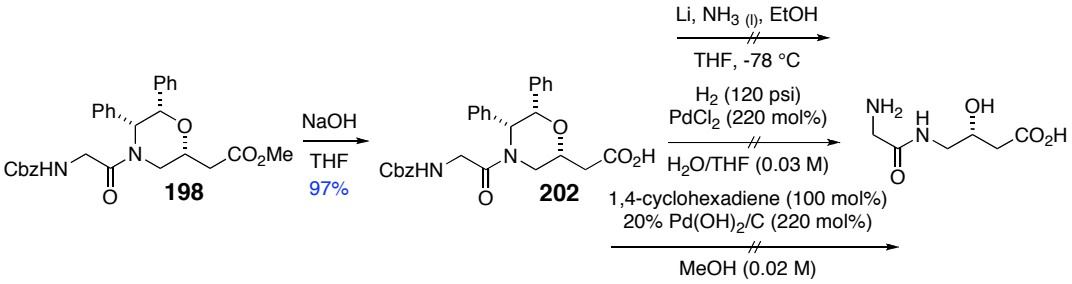
Attempts at removal of the chiral auxiliary from **198** showed that treatment with Pd/C under a hydrogen balloon cleaved first the Cbz group and then the benzylic oxygen bond, yielding products **200** and **201** (Scheme 40). The amide benzylic bond, though, was untouched even by 100 psi of hydrogen and Pearlman's catalyst, recently shown an effective catalyst for cleavage of the chiral auxiliary from sterically demanding substrates.[31] Hydrogenation of the Boc analogue under similar conditions also failed, as did transfer hydrogenation with 1,4-cyclohexadiene. Finally, Birch reduction of **198** gave bibenzyl but no desired product, presumably due to the same undesired ester reduction.



Scheme 40

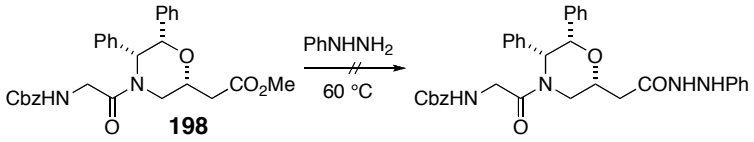
[31] *A Concise Asymmetric Synthesis of the ADE Fragment of Nakadomarin A*. Ahrendt, K. A.; Williams, R. M. *Org. Lett*. **2004**, *6*, 4539-4541.

In light of these results, we decided to hydrolyze methyl ester **198** to free acid **202** (Scheme 41). We first attempted hydrogenation of the auxiliary, hoping to precipitate the amino acid product from ether, but failed to cleave the template. Birch reduction and purification by ion-exchange chromatography also failed to yield the desired amino acid.



Scheme 41

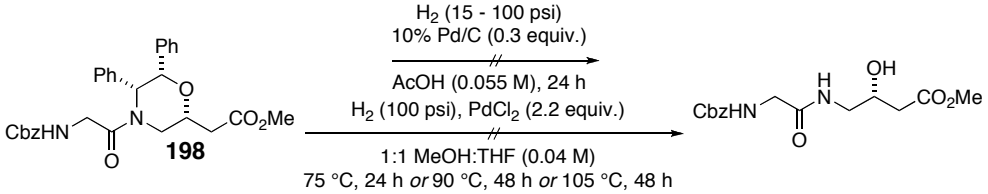
We attempted to replace the methyl ester of **198** with a phenylhydrazine group, which is reported to be stable to Birch reduction (Scheme 42).[32] We hoped that this would allow us to conduct the Birch reduction without freeing the acid terminus, aiding purification; however, we were unable to isolate the desired product.



Scheme 42

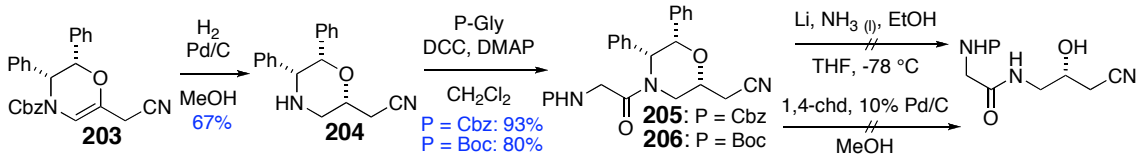
[32] *Phenylhydrazide as a Protective Group in Peptide Synthesis. The Oxidation of γ-Phenylhydrazides of* N-*Carbobenzoxy-α*-L-*glutamylamino Acid Esters with Manganese Dioxide*. Kelly, R. B. *J. Org. Chem*. **1963**, *28*, 453-456.

Using literature conditions for the palladium-catalyzed hydrogenolysis of a benzyl amide in acetic acid,[33] we found that the aromatic portion of **198** remained even at 100 psi of hydrogen (Scheme 43); palladium chloride in a THF/methanol mixture also failed to cleave the template even after 48 h at 105 °C. Worried about possible dehydration of the β-hydroxy ester with such long reaction times, we decided to abandon this route.



Scheme 43

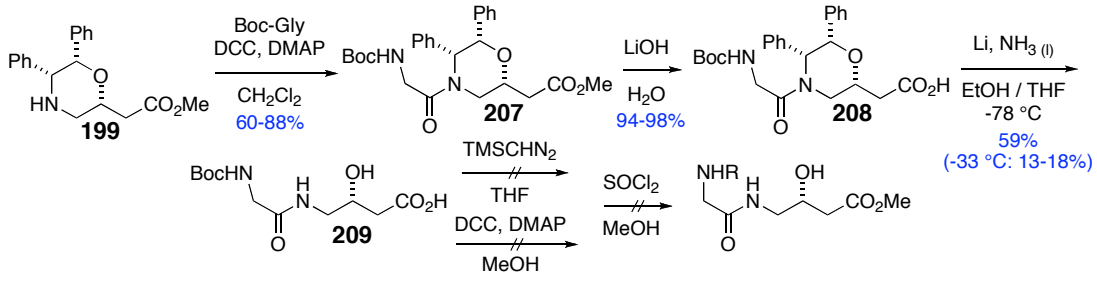
In light of our failure to obtain the desired dipeptide with either the ester or free acid, we decided to explore alternative carboxylic acid synthons. We settled upon the nitrile group as an acid equivalent that could be hydrolyzed after removal of the chiral template. Enamine **203**[34] was hydrogenated to give amine **204**, whose coupling with either Cbz- or Boc-protected glycine gave the Birch templates **205** or **206** in good yield over three steps (Scheme 44). Nitrile **205** was subjected to reduction with lithium (18 equivalents) and ammonia at -43 °C, yielding a product in which the nitrile was reduced to the amine; all other reducing-metal reactions on these substrates, including those performed with sodium or at various temperatures, yielded the same result.



Scheme 44

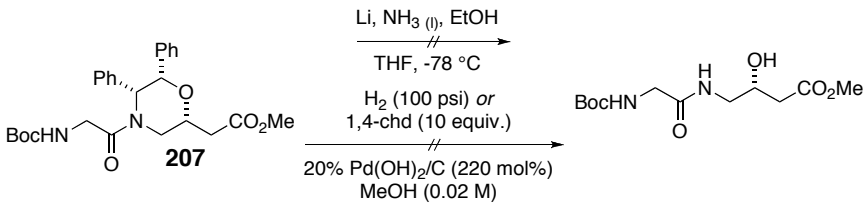
[33] *Ring Opening Reactions of* N-*Alkyl Oxazolidinones with Organolithium Reagents*. Jones, S.; Norton, H. C. *Synlett* **2004**, 338-340.
[34] *Asymmetric Synthesis of (+)-Hypusine*. Jain, R. P.; Albrecht, B. K.; DeMong, D. E.; Williams, R. M. *Org. Lett.* **2001**, *3*, 4287-4289.

Finally, we coupled amine **199** with Boc-glycine to give **207** in good yield and cleaved the ester to give Boc-acid **208** (Scheme 45). Birch reduction yielded the desired free acid **209**; we found that running the reaction at -78 °C instead of -33 °C resulted in a much higher yield of dipeptide, presumably due to elimination of overreduction. **209** quickly turns to brown oil after exposure to deuterated methanol; details of this possible decomposition are unclear. Unfortunately, attempts to install a methyl ester under either acidic or neutral conditions failed; we suspect that the acid is again decomposing.



Scheme 45

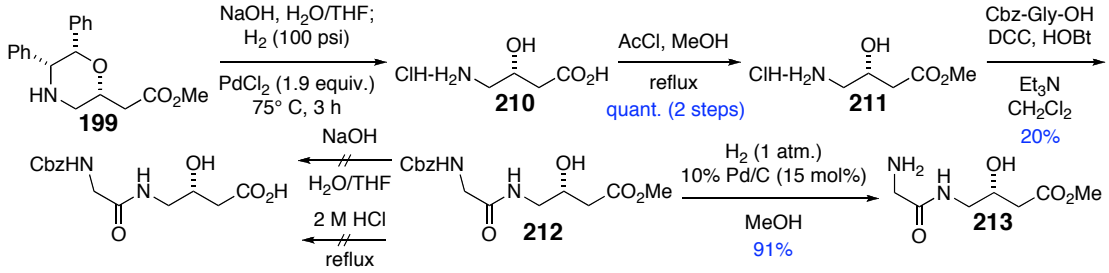
We also attempted hydrogenation and Birch reduction of the Boc-protected ester **207** in a last-ditch effort to save the masked dipeptide strategy (Scheme 46); as expected based on our previous results, though, both reactions failed.



Scheme 46

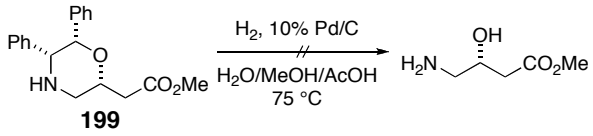
3.4: Peptide couplings of GABOB

After all attempts to produce a coupled GABOB via the diphenyloxazinone amine route proved unsuccessful, we returned to the couplings of free GABOB. We hydrolyzed the ester **199**, then removed the biphenyl with slightly lower palladium loading than previously reported to give GABOB hydrochloride **210**, which was isolated by dissolving the residue in methanol and filtration through Celite (Scheme 47). Treatment with thionyl chloride in refluxing methanol gave hydrochloride **211**, whose coupling with Cbz-glycine gave the Gly-GABOB dipeptide **212** in poor yield.[35] The Cbz group was easily removed by hydrogenation to give the dipeptide free amine **213**. Unfortunately, attempts to deprotect the ester after coupling resulted in decomposition under both acidic and basic conditions; we believe that either decarboxylation of the free or acid or, less likely, retro-aldol reaction is responsible.



Scheme 47

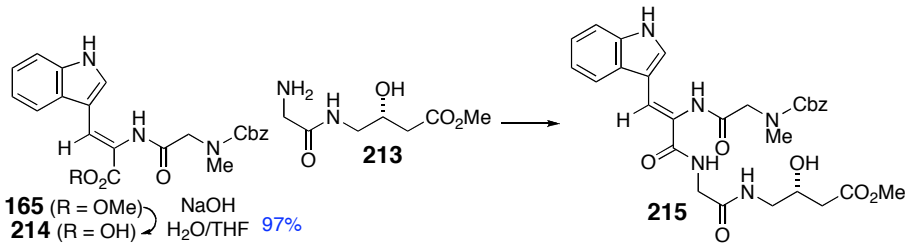
While conducting these experiments, we attempted to hydrogenate **199** directly to the free amine, but were unable to obtain the desired product (Scheme 48).



Scheme 48

[35] Ienaga, K.; Higashiura, K. *Peptide compound and a pharmaceutically acceptable salt thereof.* US Patent 5,110,797 A (1992).

Hydrolysis of the dipeptide ester **165** gave acid **214**, and we attempted coupling with the free amine **213** (Scheme 49); unfortunately, we never were able to purify the desired product **215**. This tetrapeptide would have provided an alternate route toward the previously discussed favorable macrocyclization at the GABOB-AMPTD linkage.



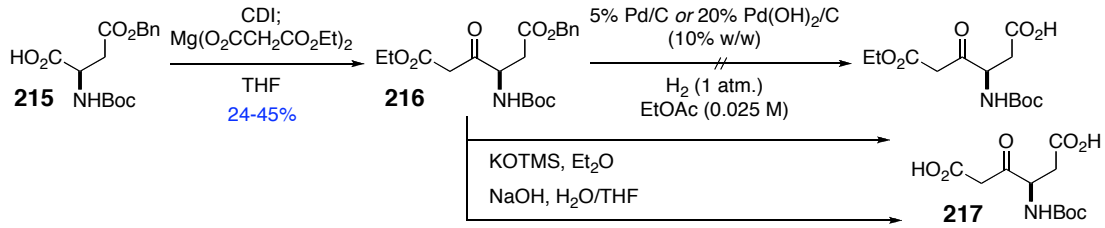
Scheme 49

Chapter 4: Pyrrolidinone fragment

Due to the reported high susceptibility of the β-amidohemiaminal moiety of the pyrrolidinone to elimination, we planned to introduce this functionality at the end of the synthesis. We thus required either a protected aspartate to which a nitrogen could be introduced in the last steps, or an asparagine derivative with an easily removed side-chain nitrogen protecting group. Our planned synthesis involved three steps: introduction of protecting groups at the α nitrogen and β acid or amide of a protected D-aspartate or asparagine, respectively; homologation of the α acid to a β-ketoester; and hydrolysis of the β-keto ester to the corresponding acid to allow peptide coupling. Our studies toward the pyrrolidinone have focused mainly on finding a compatible set of protecting groups for these three steps and have included both aspartate and asparagine derivatives.

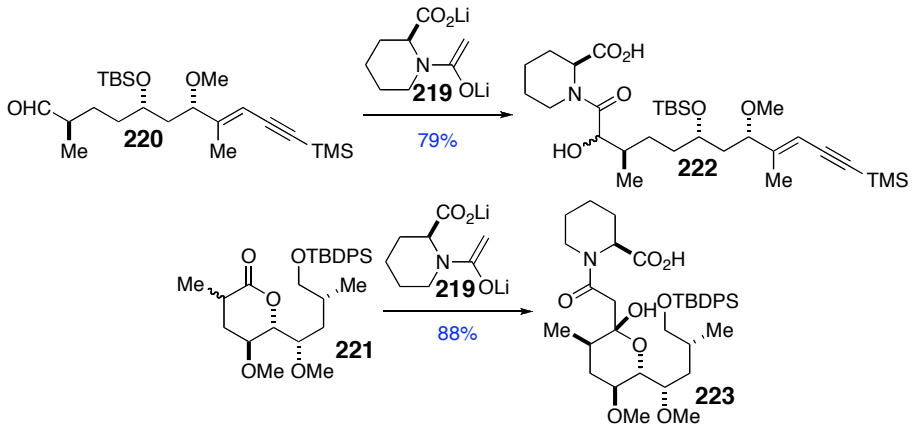
4.1: Studies with aspartate derivatives

We began our studies in this area by following Shioiri's precedent with the Brooks-Masamune conditions, in which a neutral magnesium salt of a malonate was used to extend a carboxylic acid to the corresponding β-keto ester without racemization. Commercially available β-benzyl-*N*-Boc-D-aspartate (**216**) was homologated to give β-keto ester **217**, albeit in lower yields than reported (Scheme 50); we attribute our difficulties to poor lab technique in our early days and consequent decomposition of the highly water-sensitive activating agent carbonyldiimidazole. Surprisingly, hydrogenation failed to remove the benzyl ester; potassium trimethylsilanolate and sodium hydroxide were too reactive to be selective, instead removing both esters to give diacid **218**.



Scheme 50

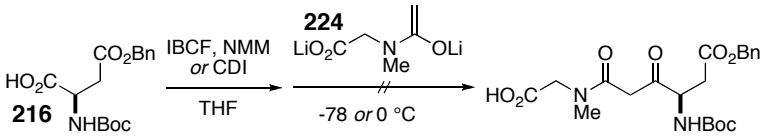
We turned to the addition of lithium enolates to install the β-keto linkage. Literature reports showed that the dilithio salt **219** of *N*-acetylpipecolinic acid added to aldehyde **220** as well as lactone **221** to give **222** and **223** (Scheme 51).[36,37] In light of these reports, we hoped that treatment of an activated form of **216** with the lithium dienolate **224** of *N*-acetylsarcosine would provide a β-keto amide (Scheme 52); such a reaction would convert the *N*-acetyl from a protecting group to an integral part of the synthesis and obviate the need for peptide coupling of the β-keto acid. This protocol would also allow direct coupling of the product with dehydrotryptophan methyl ester; selective removal of the benzyl ester and nitrogen installation would then be possible.



Scheme 51

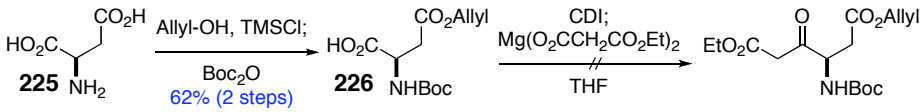
[36] *Total Synthesis of Rapamycin and Demethoxyrapamycin.* Smith III, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, Jr., J. L.; Leahy, J. W.; Maleczka, Jr., R. E. *J. Am. Chem. Soc.* **1995**, *117*, 5407-5408.
[37] *Synthetic studies on the immunosuppressive agent FK-506: construction of the polycarbonyl region.* Rupprecht, K. M.; Baker, R. K.; Boger, J.; Davis, A. A.; Hodges, P. J.; Kinneary, J. F. *Tetrahedron Lett.* **1998**, *39*, 233-236.

Unfortunately, the reaction failed to yield any of the desired dipeptide free acid. As we did not attempt to reproduce the literature reactions nor attempt the reaction on a simpler substrate, we cannot ascertain whether our failure was due to incorrect activation of the acid or an inability to correctly produce the dianion.



Scheme 52

At this point we began searching for a protecting-group strategy that would obviate the selectivity problem. We hoped that either the allyl[38] or fluorenylmethyl[39] ester of the β carboxylate would allow removal of the ethyl ester after homologation, allowing coupling to other fragments. (We were unable to reproduce the literature preparation of the *tert*-butyl[40] β ester.) Reaction of D-aspartatic acid (**225**) with allyl alcohol in the presence of trimethylsilyl chloride gave the β-allyl ester, and amine protection gave *N*-Boc-β-allyl-D-aspartate **226** in moderate yield (Scheme 53).[41] Initial attempts with the Brooks-Masamune reagent failed to yield the desired β-keto ester.



Scheme 53

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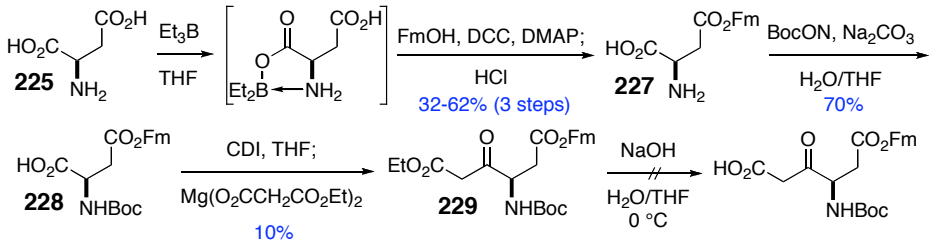
[38] *Chlorotrimethylsilane mediated formation of ω-allyl esters of aspartic and glutamic acids.* Belshaw, P. J.; Mzengeza, S.; Lajoie, G. A. *Synth. Comm.* **1990**, *20*, 3157-3160.
[39] *Convenient Syntheses of Fluorenylmethyl-Based Side Chain Derivatives of Glutamic and Aspartic acids, Lysine, and Cysteine.* Albericio, F.; Nicolás, E.; Rizo, J.; Ruiz-Gayo, M.; Pedroso, E.; Giralt, E. *Synthesis* **1990** 119-122.
[40] *Facile Synthesis of Tert-Butyl Ester of* N*-Protected Amino Acids with Tert-Butyl Bromide.* Chevallet, P.; Garrouste, P.; Malawska, B.; Martinez, J. *Tetrahedron Lett.* **1993**, *34*, 7409-7412.
[41] *Design and preparation of serine-threonine protein phosphatase inhibitors based upon the nodularin and microcystin toxin structures. Part 3.* Webster, K. L.; Maude, A. B.; O'Donnell, M. E.; Mehrotra, A. P.; Gani, D. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1673-1695.

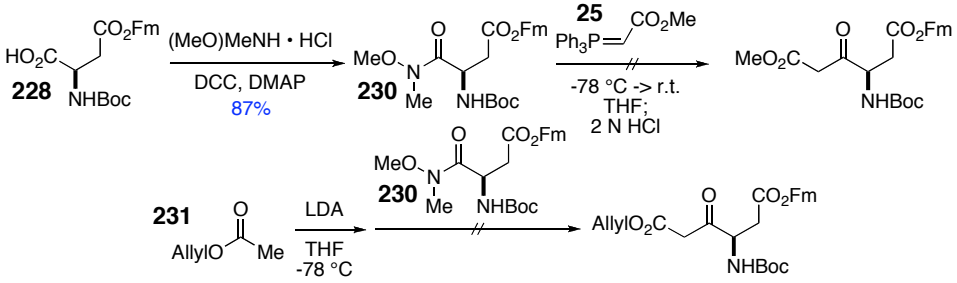
We soon realized that deprotection of the allyl ester, performed after macrocyclization, might corrupt the indole of the tryptophan moiety. In this light, we synthesized *N*-Boc-β-Fm-D-aspartate, as the fluorenylmethyl ester should be removed without effect to the rest of the molecule. Treatment of **225** with neat triethylborane led to formation of the N,O-complex (Scheme 54), which without isolation was coupled at the β-acid to FmOH in good yield; decomplexation with gaseous HCl gave the free amine **227**, which was Boc-protected to yield **228**. The first batch of product was used crude due to problems with recrystallization; unfortunately, yields of homologation product **229** were low, and attempted selective hydrolysis of the ethyl ester at low temperature was unsuccessful. The next batch of protected aspartate was successfully recrystallized under different conditions;[42] we were, however, unable to increase the homologation yield, and hydrolysis again failed. It is likely that the hydrolysis was nonselective and produced the diacid, in line with our earlier results; we were still fairly naïve in our chemistry knowledge and expected that the fluorenylmethyl ester would be sensitive only to the standard conditions, such as secondary bases. Even if the reaction had been selective, the fluorenylmethyl group would probably have been preferentially removed, an outcome we would later come to appreciate but would have seen as an obstacle at the time.



Scheme 54

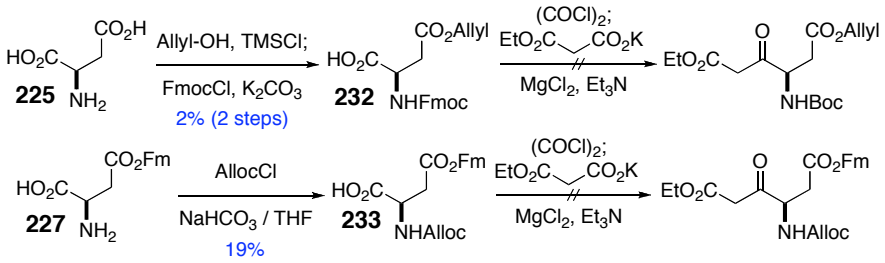
[42] *Potent and Prolonged Acting Cyclic Lactam Analogues of α-Melanotropin: Design Based on Molecular Dynamics*. Al-Obeidi, F.; Castrucci, A. M. de L.; Hadley, M. E.; Hruby, V. J. *J. Med. Chem.* **1989**, *32*, 2555-2561.

We then converted *N*-Boc-β-Fm aspartate **228** to the Weinreb amide **230**. We attempted to extend a recent protocol for homologation of Weinreb amides with Wittig reagents to the more basic ester ylide **25** (Scheme 55);[43] we saw no reaction at ambient temperature, and heating to reflux removed the fluorenylmethyl group, as did attempted acylation of the lithium enolate of allyl acetate (**231**) with **230**.[44]



Scheme 55

We next synthesized the Fmoc/allyl-protected aspartate **232**[41] and attempted its homologation via a different procedure (Scheme 56),[45] but this sequence also failed. We protected the nitrogen of **227** with an Alloc group to give aspartate **233** with "reversed" protecting groups, but again homologation failed; we failed to appreciate that the malonate potassium salt was likely basic enough to remove the Fmoc protecting group.



Scheme 56

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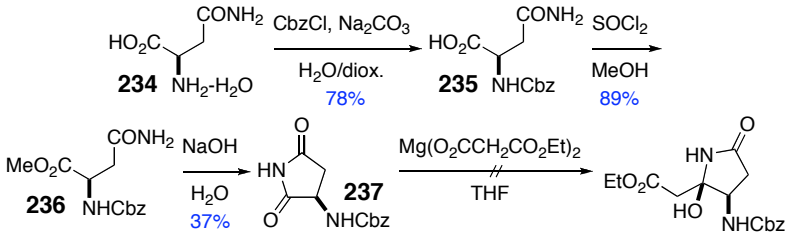
[43] *Direct Conversion of* N-*Methoxy*-N-*methylamides (Weinreb Amides) to Ketones via a Nonclassical Wittig Reaction*. Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427-1429.

[44] *Acylation of Ester Enolates by* N-*Methoxy*-N-*methylamides: An Effective Synthesis of β-Keto Esters*. Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229-4231.

[45] *A Safe, Economical Method for the Preparation of β-Oxo Esters*. Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290-292.

4.2. Asparagine-based approaches

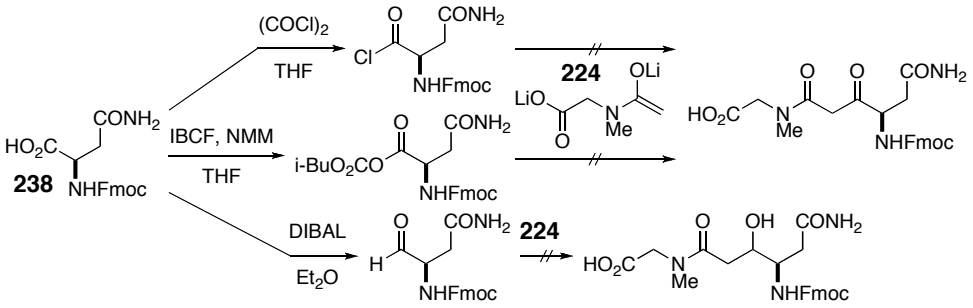
Our first attempt at synthesizing the pyrrolidinone from an asparagine derivative involved production of an asparagine succinimide. D-asparagine monohydrate (**234**) was selectively Cbz-protected at the α nitrogen to give acid **235**, which was converted to methyl ester **236** and treated with base to give pyrrolidinedione **237** (Scheme 57).[46] The usual neutral magnesium salt was introduced as a nucleophile but failed to effect the desired addition. We hoped that the increased electron density of the carbamate oxygens would attract magnesium, possibly directing nucleophilic attack to the desired carbon, while the steric bulk would prevent *syn* attack on the amide carbonyl. However, it seems likely that the magnesium salt was simply not a strong enough nucleophile to overcome the reduced electrophilicity of the carbamate as compared to the previous activated esters.



Scheme 57

We next attempted addition of the lithium dienolate **224** of *N*-acetylsarcosine (Scheme 58). Given that this reaction had previously failed with aspartate derivatives, we wanted to explore whether Fmoc-D-asparagine **238** would succeed; unfortunately, the reaction failed again. In addition to the reasons previously given for failure of this reaction, any enolate that was not simply quenched by the unprotected amide would most likely remove the Fmoc group.

[46] *Handy Access to Chiral* N,N'-*Disubstituted 3-Aminopyrrolidines*. Maddaluno, J.; Corruble, A.; Leroux, V.; Plé, G.; Duhamel, P. *Tetrahedron: Asymm*. **1992**, *3*, 1239-1242.



Scheme 58

In retrospect, at this point we should have seen if the lithium enolate in Scheme 58 was nucleophilic enough to react with the carbamate in Scheme 57; we unfortunately failed to appreciate this strategy at the time. Instead, we found in the literature a report of conversion of asparagine to β-cyanoalanine; this strategy appealed to us because of the lack of oxygenation in the side chain, which should speed the homologation reaction by eliminating unwanted attraction to the magnesium salt. Additionally, we hoped that a then-recent platinum-catalyzed method for mild nitrile hydration[47] would allow us to, as the last step of the synthesis, unmask the amide and directly form the hemiaminal with the β-ketoamide. Boc-D-asparagine **239** was dehydrated with pyridine and DCC to nitrile **240** (Scheme 59).[48] We obtained the product as a pale yellow foam after acid/base workup; we later applied a pyridine-free protocol for dehydration, but still received a foam.[49] CDI activation of the acid and homologation as usual gave β-keto ester **241** in low yield. Hydrolysis with sodium hydroxide appeared to give the desired acid **242**, though the NMR was messy; as a result we never carried out a coupling reaction.

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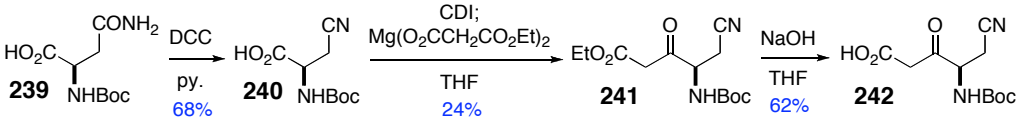
[47] *Platinum-Catalyzed Selective Hydration of Hindered Nitriles and Nitriles with Acid- or Base-Sensitive Groups.* Jiang, X.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327-2331.

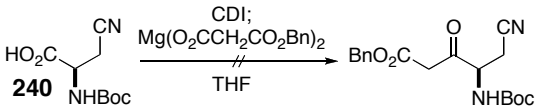
[48] *Synthesis, biological testing, and stereochemical assignment of an end group modified retro-inverso bombesin C-terminal nonapeptide.* Cushman, M.; Jurayj, J.; Moyer, J. D. *J. Org. Chem.* **1990**, *55*, 3186-3194.

[49] *Synthesis of a novel histidine analogue and its efficient incorporation into a protein* in vivo. Ikeda, Y.; Kawahara, S.; Taki, M.; Kuno, A.; Hasegawa, T.; Taira, K. *Protein Engineering* **2003**, *16*, 699-706.



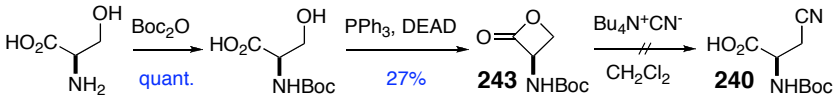
Scheme 59

Given Ma's observed racemization of the aspartate residue by TBAF, we desired a β-keto protecting group that could removed under non-basic conditions; the benzyl group seemed an appropriate choice for cleavage under neutral conditions. Monobenzyl malonate[50] was subjected to the usual Brooks-Masamune protocol with **240**; surprisingly, we received none of the desired β-keto benzyl ester (Scheme 60).



Scheme 60

We also tried to adapt some of Vederas' work.[51] The β-lactone **243** is reported to undergo ring opening after removal of the Boc group,[52] but we wished to explore direct opening of protected lactone **243** to give **240** (Scheme 61). The ring opening failed with both self-prepared and commercial samples of the cyanide salt; given the impracticality of protecting, deprotecting, and reprotecting the amine, we abandoned this route.



Scheme 61

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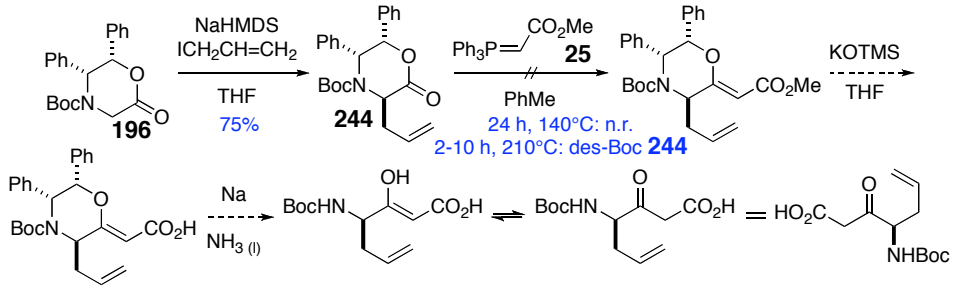
[50] *Orally Effective Acid Prodrugs of the β-Lactamase Inhibitor Sulbactam.* English, A. R.; Girard, D.; Jasys, V. J.; Martingano, R. J.; Kellogg, M. S. *J. Med. Chem.* **1990**, *33*, 344-347.

[51] N-tert-*Butoxycarbonyl-L-Serine β-Lactone and (S)-3-amino-2-oxetanone p-Toluenesulfonic Acid SALT.* Pansare, S. V.; Arnold, L. D.; Vederas, J. C. *Org. Synth., Coll. Vol. IX*, 24.

[52] *Synthesis of Optically Pure α-Amino Acids via Salts of α-Amino-β-propiolactone.* Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237~2241.

4.3: Approaches from Williams' lactone

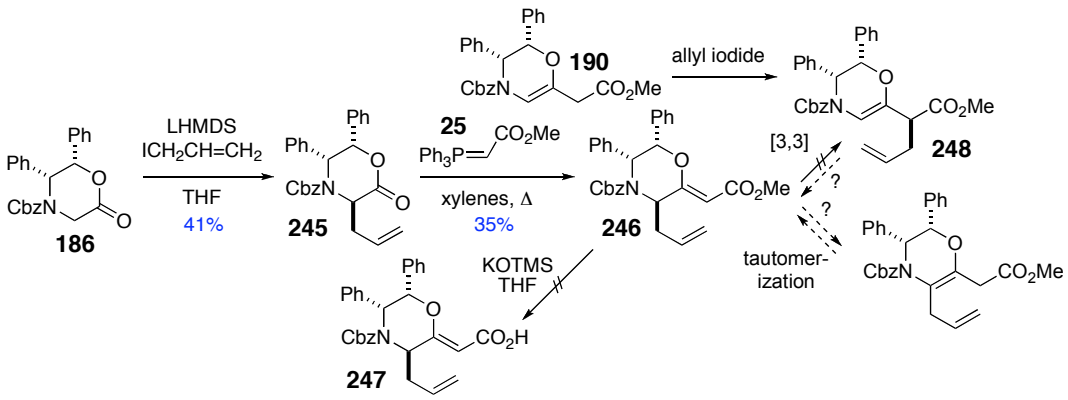
We tried to adapt the Williams' lactone methodology used in our GABOB work to the synthesis of the pyrrolidinone precursor. We envisioned that the known allylation of Boc-lactone **196** to give **244**[53] could be followed by Wittig homologation to yield the β-ketoester; deprotection of the ester, Birch reduction, and tautomerization would then unveil the β-ketoacid (Scheme 62). We were able to repeat the reported allylation in good yield; however, thermal Wittig reaction with **25** yielded only des-Boc-**244**.



Scheme 62

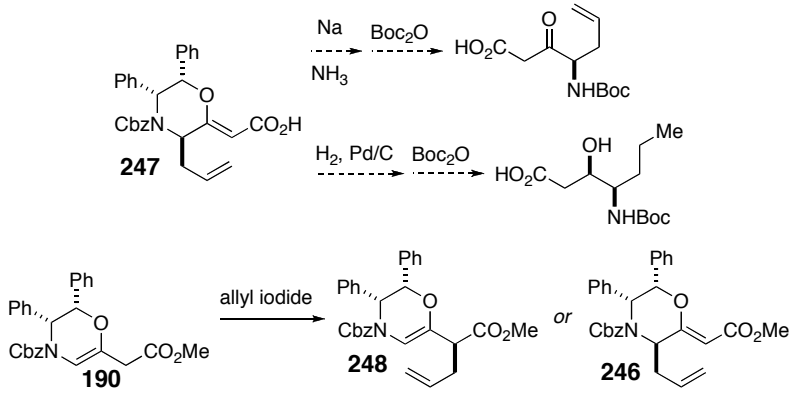
Extension of the allylation protocol to Cbz-lactone **186** gave **245** in moderate yield; Wittig reaction gave what appeared to be desired product **246** (Scheme 63), but removal of the methyl ester with KOTMS did not cleanly give putative acid **247**. We were unable to rule out the possibility of migration of the double bond to the endocyclic position during the synthesis of **246**. This should require only a ^{13}C NMR experiment to count the number of methlyene carbons, but we did not realize this at the time. We did, however, synthesize the putative Cope rearrangement product **248** via allylation of **190** and show that the two are distinct products. Another interesting experiment would be to heat **248** in refluxing xylenes to see whether the reverse Cope rearrangement takes place.

[53] *Efficient Asymmetric Synthesis of* N-tert-*Butoxycarbonyl α-Amino Acids using 4*-tert-*Butoxycarbonyl-5,6-Diphenylmorpholin-2-one: (*R*)-(*N-tert-*butoxycarbonyl)allylglycine.* Williams, R. M.; Sinclair, P. J.; DeMong, D. E. *Org. Synth.* **2004**, *80*, 31.



Scheme 63

This conversion of **245** to **246** is the first Wittig reaction of an α-substituted Williams' lactone. This route could provide a general route from **186** through **247** to β-keto-γ-substituted-γ-amino acids (via Birch reduction, Scheme 64) or β-hydroxy-γ-substituted-γ-amino acids (via hydrogenation); these statine analogues are potential disease therapies.[54] The use of metals to direct allylation of **190** at the α or γ positions (to **246** or **248**) could open further avenues for asymmetric synthesis of γ-amino acids.[55]



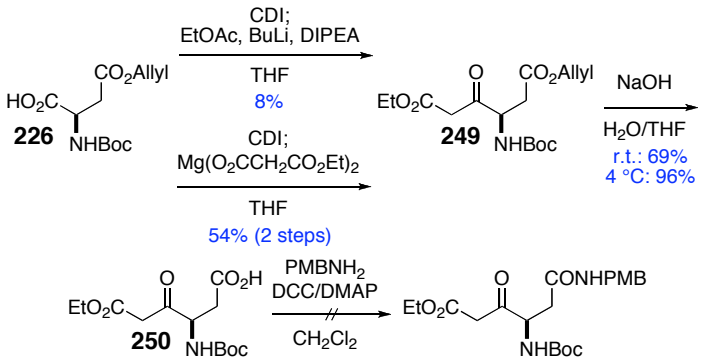
Scheme 64

[54] a) *Aspartic Protease Inhibitors: Expedient Synthesis of 2-Substituted Statines.* Travins, J. M.; Bursavich, M. G.; Veber, D. F.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2725-2728. b) *Ketoreductases in the synthesis of valuable chiral intermediates: application in the synthesis of α-hydroxy β-amino and β-hydroxy γ-amino acids*. Kambourakis, S.; Rozzell, J. D. *Tetrahedron* **2004**, *60*, 663-669.

[55] *Selective γ Alkylation of Dienolate Anions Derived from α,β-Unsaturated Acids. Applications to the Synthesis of Isoprenoid Olefins.* Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925-4935.

4.4: Favored approaches to the aspartate core

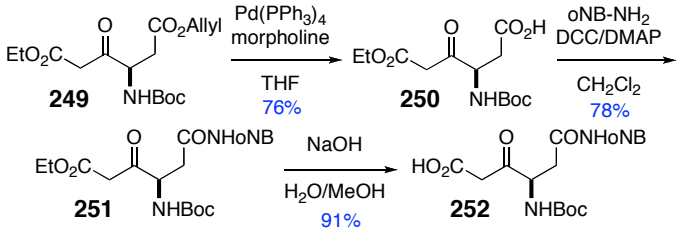
We have found two successful approaches to our desired framework, one from aspartate and one from asparagine. After exploring the various methodology discussed above, we returned to *N*-Boc-β-allyl D-aspartate **226**. While preparing a fresh batch to allow formation of the Weinreb amide, we attempted Brooks-Masamune homologation, and were gratified to receive a good yield of the desired product **249** (Scheme 65). Treatment of the imidazolide with the enolate of ethyl acetate also gave some product. Hydrolysis with sodium hydroxide appeared to cleave selectively the allyl ester, giving acid **250**. We initially saw this selective hydrolysis at the side-chain ester as problematic; however, we quickly realized that this would allow installation of a protected nitrogen for later conversion to the pyrrolidinone moiety. We then found that hydrolysis of **249** at 4 °C instead of ambient temperature gave near-quantitative yield of **250**. (We later carried out the allyl deprotection under $Pd(PPh_3)_4$-mediated conditions to give a good yield of **250** (Scheme 66),[56] and preferred the palladium conditions for the ease of workup.) We first attempted to couple with PMB amine, assuming that a mild oxidation could later remove the protecting group, but this coupling failed.



Scheme 65

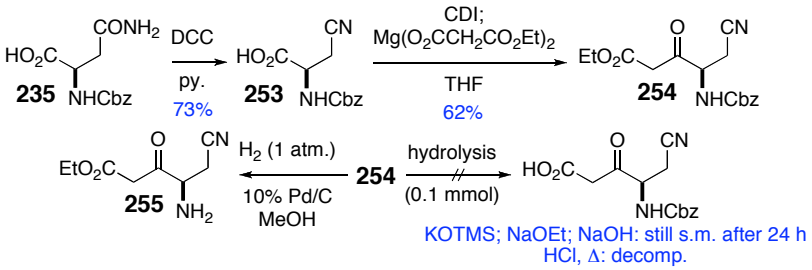
[56] *Selective Palladium-catalyzed deprotection of the allyl and allyloxycarbonyl groups in phosphate chemistry and in the presence of propargyl and propargyloxycarbonyl groups.* Zhang, H. X.; Guibé, F.; Balavoine, G. *Tetrahedron Lett*. **1988**, *29*, 623-626.

The free acid **250** was then coupled with *o*-nitrobenzylamine (oNB-NH_2) to give protected amide **251** (Scheme 66). The photolabile oNB protecting group was previously used in our group's synthesis of racemic aspirochlorine;[57] we anticipated that the mild removal of this group would prove advantageous for hemiaminal installation. Hydrolysis of the β-keto ester of **251** proceeded in good yield to give the free acid **252**. Thus we have completed synthesis of this fragment in four steps and good overall yield from **226**.



Scheme 66

After our above-mentioned efforts to produce Boc-β-cyano-D-alanine, we enlisted an alternative procedure. Dehydration of **235**[58] with acetic anhydride gave crystalline acid **253**, and homologation gave a moderate yield of β-keto ester **254** (Scheme 67). We were unable, though, to obtain the free β-ketoacid, a failure that stands in contrast to the hydrolysis of the Boc analogue **251**. Late in our studies, we were able to remove the Cbz group of **254** by hydrogenation to give amine **255** without affecting the nitrile.

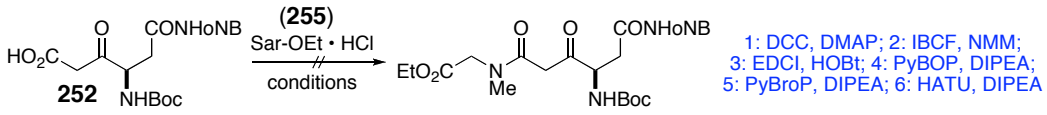


Scheme 67

[57] *Total Synthesis of (±)-Aspirochlorine*. Miknis, G. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 536-547.
[58] *Process for the production of 4-aminobutyric acid or its derivatives*. U.S. Patent 4,290,972, 1981.

4.5: Attempted synthesis of the aspartate-sarcosine dipeptide

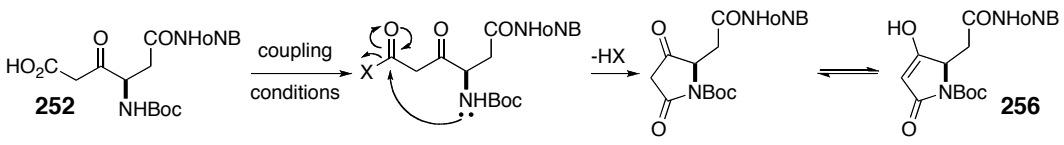
The brief mention above of a presumed β-keto acid hints at what has become the main problem with this project: we have been consistently, maddeningly unable to couple a β-keto acid. We sometimes observe decomposition, as with the hydrolysis of **254** (Scheme 66). Normally, though, hydrolysis gives a product in the appropriate layer, with a good NMR; however, upon attempted coupling (e.g. of **252**) with sarcosine ethyl ester hydrochloride (**256**), we are unable to obtain the desired dipeptides (Scheme 68). This is puzzling given that the sarcosine nitrogen should be activated (though sterically hindered) by its *N*-methyl, and that coupling of this nitrogen is known in the literature.[59] Hydrolysis of β-keto esters and subsequent couplings of the acids are also known.[60]



252

Scheme 68

We came to believe that the urethane-protected nitrogen (e.g. of **252**) could attack the activated ester intramolecularly to give the five-membered ring (Scheme 69); the ketone could then enolize to give the tetramic acid (e.g. **257**). This would explain why the acid appears to be produced, but no dipeptide is isolated from the coupling reaction.



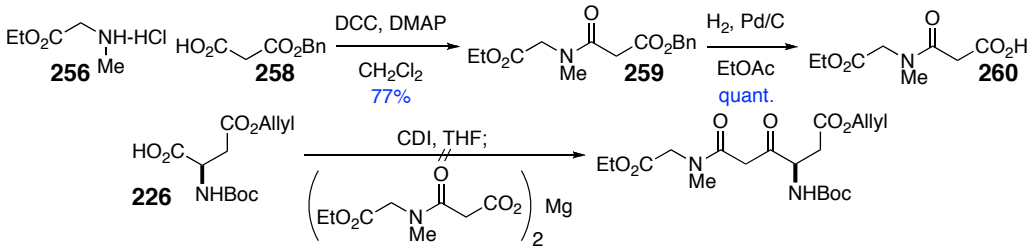
252 **256**

Scheme 69

[59] *Lyngbyastatin 1 and Ibu-epilyngbyastatin 1: Synthesis, Stereochemistry, and NMR Line Broadening.* Bai, R.; Bates, R. B.; Hamel, E.; Moore, R. E.; Nakkiew, P.; Pettit, G. R.; Sufi, B. A. *J. Nat. Prod.* **2002**, *65*, 1824-1829.

[60] *Approaches to the synthesis of arisugacin A.* Jung, M. E.; Min, S.-J. *Tetrahedron* **2007**, *63*, 3682-3701.

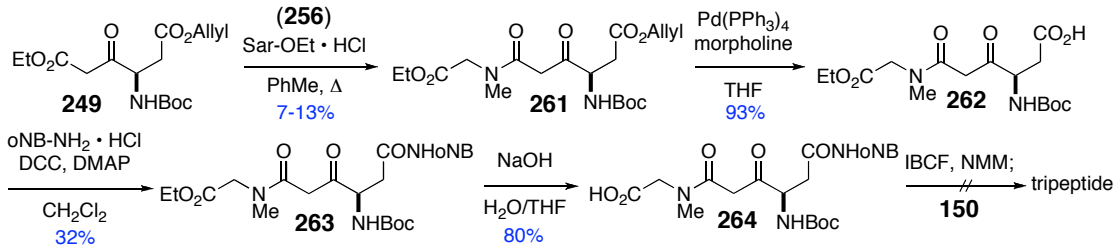
We came to this explanation too late in our career to isolate a tetramic acid. We have long sought, though, a way to synthesize the aspartate-sarcosine dipeptide while bypassing the free β-ketoacid. Our initial attempts involved the coupling of **256** with mono-benzyl malonate **258** to give the diester **259** in good yield (Scheme 70); hydrogenation of the benzyl ester gave the acid **260**. While we hoped that Brooks-Masamune homologation of **226** with this species would provide the corresponding dipeptide, in the event we were unable to isolate it.



Scheme 70

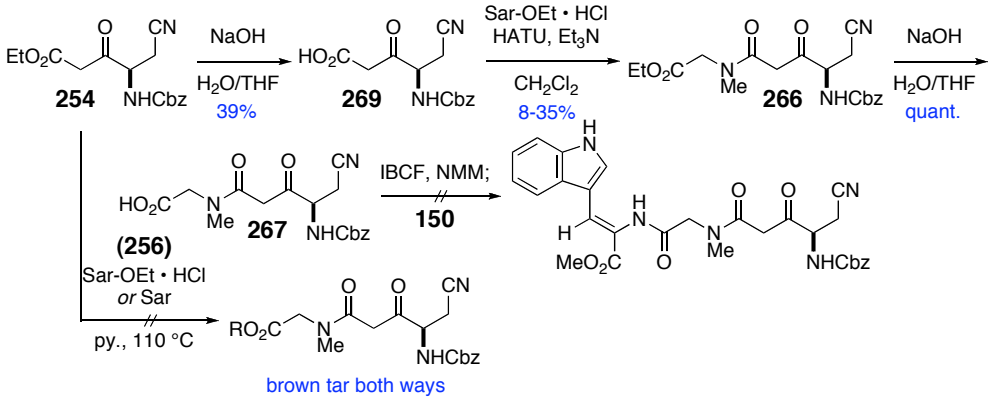
We next attempted to adapt the unique ability of β-keto esters to undergo transesterification via a ketene intermediate simply by heating in the appropriate alcohol to instead incorporate an amino acid.[61] Heating of β-keto ester **249** with **11** in toluene gave a poor yield of the desired dipeptide **261** (Scheme 71). The reaction was run with or without base, with the hydrochloride **256** or free sarcosine, with or without molecular sieves, even in pyridine, but gave product only occasionally and never above 15% yield. The small amount of **261** we were able to get was treated with palladium (tetrakis)tri-phenylphosphine and morpholine to give the side-chain acid **262**, which was promptly coupled with *o*-nitrobenzylamine to introduce the protected nitrogen. Hydrolysis of **263** gave the free acid **264**, as confirmed by HRMS; however, coupling with **150** failed.

[61] *Preparation of β-Keto Esters by 4-DMAP-Catalyzed Ester Exchange.* Taber, D. F.; Amedio Jr., J. C.; Patel, Y. K. *J. Org. Chem*. **1985**, *50*, 3618-3619.



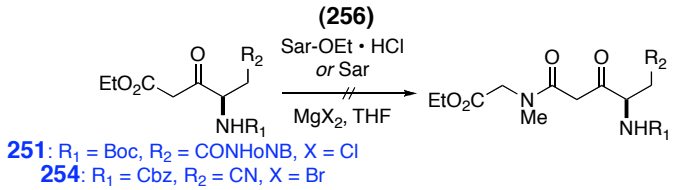
Scheme 71

The hydrolysis of β-ketoester **254** appeared to give the acid **265**, and attempted coupling with **256** seemed to give a small amount of dipeptide **266** (Scheme 72). Hydrolysis of this ester gave acid **267**, but coupling with **150** again failed. Direct thermal coupling of sarcosine to **254** also failed, yielding only a brown tar.



Scheme 72

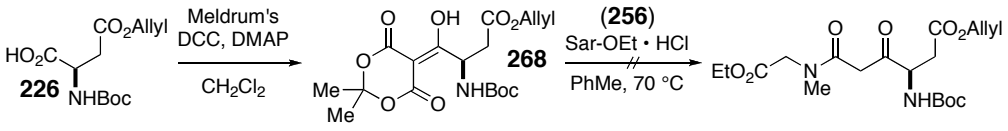
We next attempted to perform the same transamidation, but with magnesium chloride, known to work as a promoter for transesterification.[62] These attempts again gave no desired product (Scheme 73).



Scheme 73

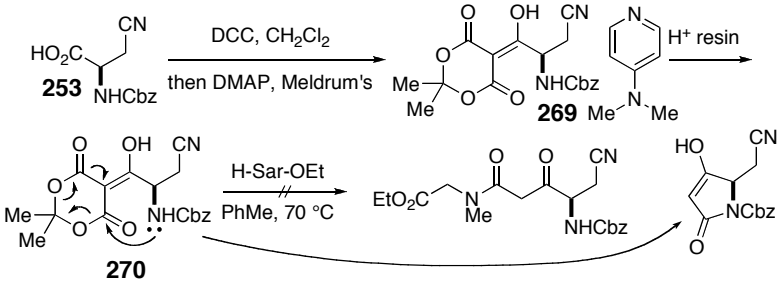
[62] *A novel method for the mild and selective amidation of diesters and the amidation of monoesters*. Guo, Z.; Dowdy, E. D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett*. **2001**, *42*, 1843-1845.

Acylation of Meldrum's acid with acid **226** gave the reactive species **268**,[63] but attempted introduction of **256** under thermal conditions failed (Scheme 74).



Scheme 74

We next adapted a literature procedure to acylate **253**, yielding the DMAP salt **269** (Scheme 75).[64] This salt was reported to be unreactive to attack with amines, requiring treatment with acidic ion-exchange resin to remove the DMAP and give free acid **270**. The published procedure used benzylamine for the ring opening; we attempted to extend this protocol to sarcosine ethyl ester, either as the hydrochloride or preneutralized to avoid the presence of base in the reaction mixture, but failed to receive the desired dipeptide. This publication reported that the amino acid nitrogen often interfered to form the tetramic acid, and we suspect we saw this decomposition.

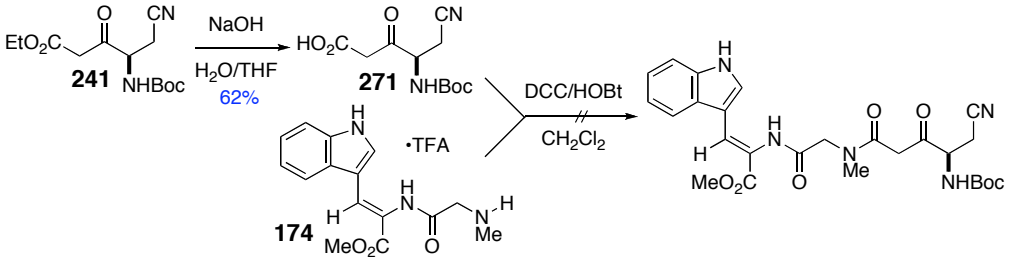


Scheme 75

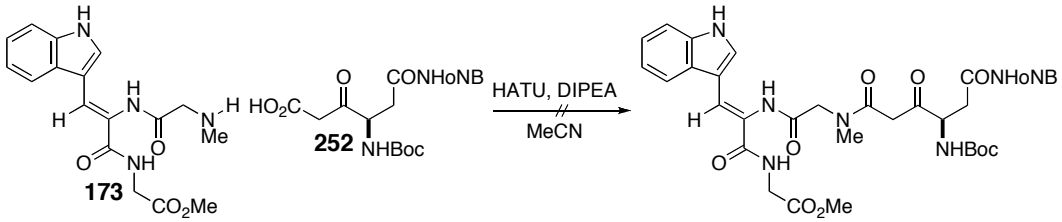
[63] *Mechanistic Evidence for an α-Oxoketene Pathway in the Formation of β-Ketoamides/Esters via Meldrum's Acid Adducts*. Xu, F.; Armstrong III, J. D.; Zhou, G. X.; Simmons, B.; Hughes, D.; Ge, Z.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **2004**, *126*, 13002-13009.

[64] *Preparation and Improved Stability of* N*-Boc-α-amino-5-acyl Meldrum's Acids, a Versatile Class of Building Blocks for Combinatorial Chemistry*. Raillard, S. P.; Chen, W.; Sullivan, E.; Bajjalieh, W.; Bhandari, A.; Baer, T. A. *J. Comb. Chem.* **2002**, *4*, 470-474.

Finally, with the sarcosine-dehydrotryptophan dipeptide apparently in hand, we attempted synthesis of the northern tripeptide. The β-keto ester **241** was subjected to hydrolysis to give what appeared to be β-keto acid **271**, which was subjected to coupling with putative **174** with DCC and HOBt (Scheme 76). Unfortunately, the reaction gave a brown solid that was too polar to be purified by flash chromatography under the conditions we tried; the color and polarity of the product suggests to us that DKP **175** was probably obtained from **174**. We attempted an analogous reaction of acid **252** with the tripeptide **173**, but again failed to obtain the coupling product (Scheme 77).



Scheme 76



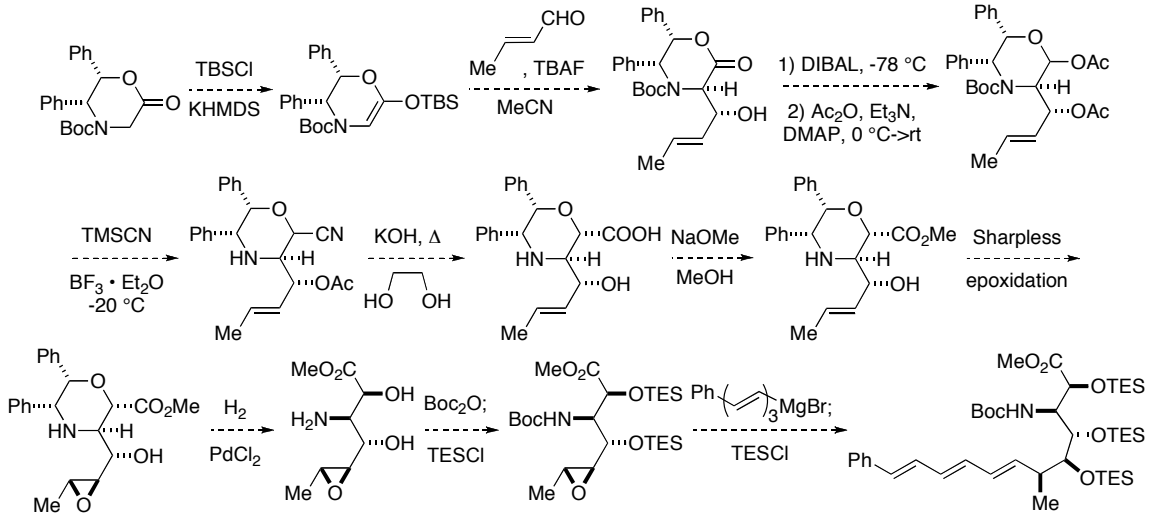
Scheme 77

Chapter 5: Synthesis of AMPTD

AMPTD is the most complex of the four amino acids we targeted, with five consecutive sp^3 stereocenters (comprising three alcohols, one amine, and one methyl) adjacent to an isomerization-prone all-*trans* phenyltriene.

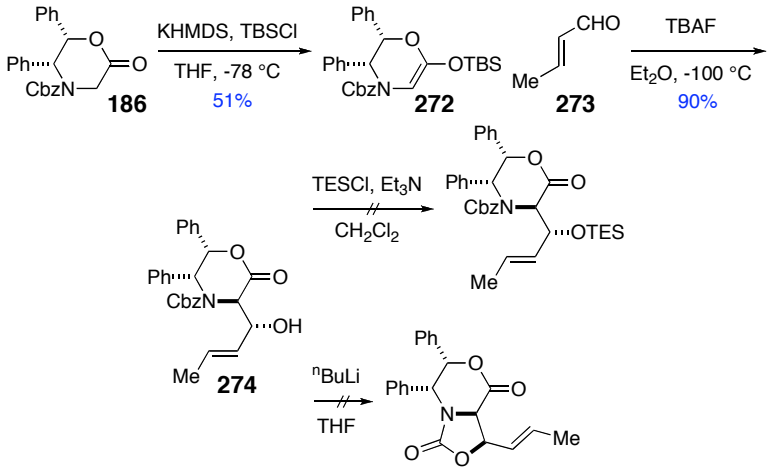
5.1: Studies from Williams' lactone

Our initial synthetic plan began with Williams' lactone, whose nitrogen we planned to use as the masked β-amino functionality of AMPTD. An aldol reaction of the lactone with crotonaldehyde would introduce the γ alcohol and set the β and γ stereocenters (Scheme 78). After conversion of the lactone into an α-hydroxyester, the alkene would provide a handle for incorporation of the remaining chiral centers, and the methyl group is located at the appropriate position for AMPTD. We hoped that an all-*trans*-α-halo-ω-phenyltriene could be coupled oxidatively to the alkene or Grignard-style to the epoxide (shown), setting the remaining chiral centers.



Scheme 78

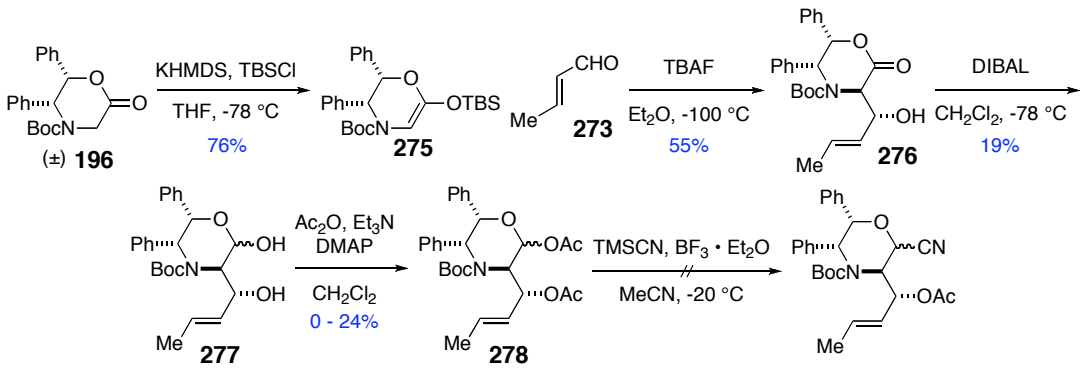
Treatment of **186** with KHMDS and TBSCl gave silyl enol ether **272** (Scheme 79), which was treated with TBAF in the presence of crotonaldehyde (**273**) to give aldol adduct **274** in high yield. Unfortunately, attempted silylation of the alcohol failed. Attempted closure onto the carbamate carbonyl to give the oxazolidinone also failed, preventing us from measuring the aldol diastereoselectivity. We then switched to the Boc analogue, as even were these problems surmounted, hydrogenation of the Cbz group would also saturate the alkene, preventing us from installing additional chiral centers.



Scheme 79

Racemic **196** gave silyl enol ether **275**, and aldol reaction with **273** gave **276** (Scheme 80). Reduction to lactol **277** and acetylation yielded **278**, which was treated with BF_3 and TMS cyanide to introduce a carboxylate equivalent.[65] Unfortunately, these reactions were low-yielding, and mass spectrometry showed no nitrile; we later realized that both DIBAL and triethylamine could have deprotonated the alcohol to produce retro-aldol reaction.

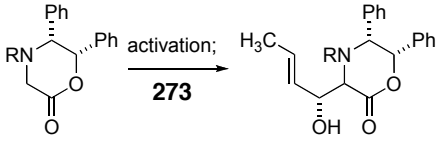
[65] *Stereocontrolled Asymmetric Synthesis of α-Hydroxy-β-amino Acids. A Stereodivergent Approach.* Aoyagi, Y.; Jain, R. P.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3472-3477.



Scheme 80

In the course of these studies we also explored various activation methods for the aldol reaction (Table 4). The boron enolate methodology previously developed in this group gave a one-time 14% yield of product, but the reaction could not be reproduced in several attempts.[66] Activation with titanium tetrachloride was also attempted, but failed to yield the desired product. The TBS-TBAF activation was the highest-yielding method, especially since the intermediate silyl enol ether can be obtained in near-quantitative yield.

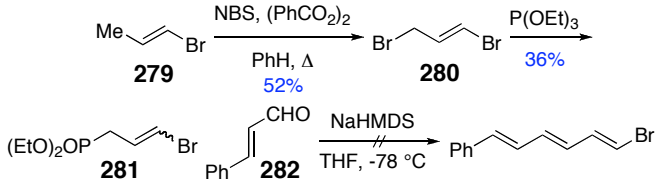
Table 4



Activation method	Boc-lactone yield	Cbz-lactone yield
Bu_2BOTf, Et_3N	0%	14% **274**
$TiCl_4$, Et_3N	N/A	0%
TBSCl, LDA; TBAF	66; 55%	71%; 90%

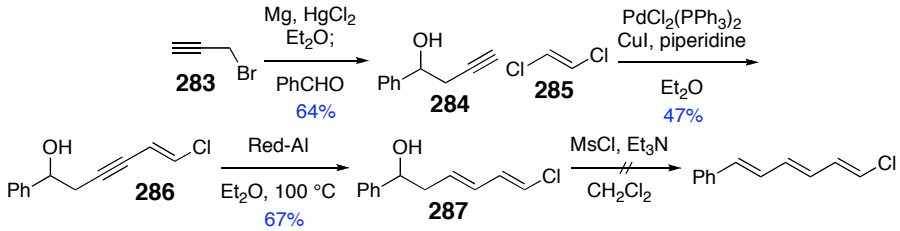
[66] *An efficient asymmetric synthesis of (2S,3S)- and (2R,3R)-β-hydroxyornithine.* DeMong, D. E.; Williams, R. M. *Tetrahedron Letters* **2001**, *42*, 183-185.

Finally, we attempted to prepare a suitable partner for incorporation of the triene side chain. We attempted to repeat a literature preparation of the appropriate bromo compound: radical bromination of *trans*-1-bromopropene **279** gave dibromo species **280**, which underwent Arbuzov reaction with triethyl phosphite to yield phosphonate **281** (Scheme 81).[67] Attempted Horner-Emmons-Wadsworth reaction of **281** with *trans*-cinnamaldehyde **282** was unsuccessful.



Scheme 81

Another literature route was used in an attempt to obtain the chloro derivative.[68] Activation and Grignard reaction of propargyl bromide (**283**) with benzaldehyde yielded homopropargylic alcohol **284** (Scheme 82). This alkyne underwent Sonogashira-type coupling with *trans*-1,2-dichloroethylene (**285**) to give chloroenyne **286**, and the triple bond was reduced with Red-Al to give *trans*,*trans*-chlorodiene **287**. The published procedure of alcohol mesylation followed by elimination failed to yield the desired triene.



Scheme 82

[67] *Reaction of nucleophilic reagents with several γ-halo-β-ethylenic phosphonates*. Lavielle, G.; Sturtz, G.; Normant, H. *Bull. Chim. Soc. Fr.* **1967**, *11*, 4186-4194.
[68] *Stereoselective approaches to (*E,E,E*) and (Z,*E,E*)-α-chloro-ω-substituted hexatrienes: Synthesis of all* E *polyenes*. Crousse, B.; Mladenova, M.; Ducept, P.; Alami, M.; Linstrumelle, G. *Tetrahedron* **1999**, *55*, 4353-4368.

At this point we abandoned the Williams' lactone template for this portion of the molecule. Even had we been able to synthesize the side chain, our route would have required an excessive number of linear steps to introduce the correct functionality, along with several protection and deprotection steps. Attempting to fix the observed problems with retro-aldol reaction would only have added to the lengthiness, and we resolved to seek a strategy in which the various chiral centers were introduced with not only the correct stereochemistry, but the correct substitution as well.

5.2: Studies from Williams' *O*-lactone

After exploring synthetic plans on paper for over a year, we struck upon a highly convergent route that was shorter than the original (Figure 3). An aldehyde derived from the Roche ester would undergo *syn*-selective aldol reaction with a chiral, α-oxygenated (glycolate) template. Alcohol protection and template removal would allow conversion of the carbonyl to an imine, and a *syn*-selective aldol reaction with another chiral glycolate would introduce the remaining chiral centers. Deprotection of the terminal alcohol, oxidation to the aldehyde, and condensation with a diene phosphonate would complete the molecule. This route allows synthesis of a wide variety of analogues if so desired.

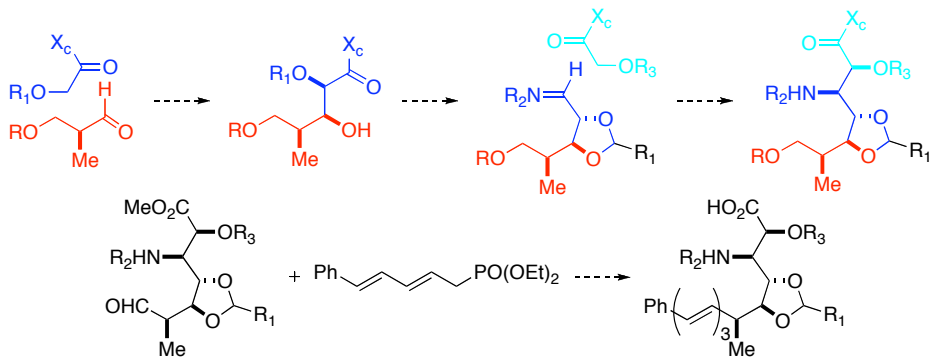
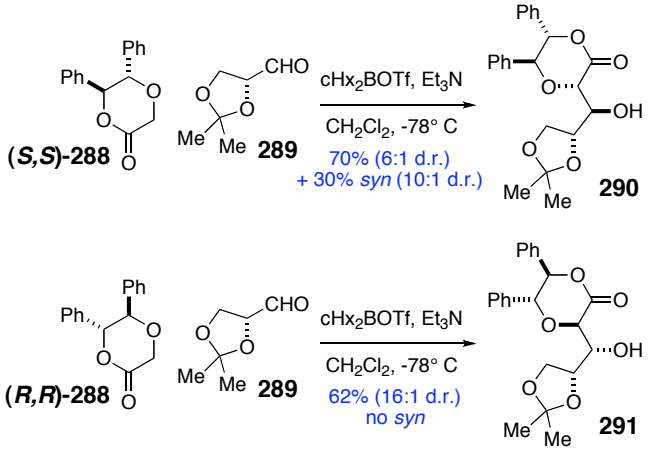


Figure 3

We first attempted to carry out this aldol strategy with an oxygenated Williams' lactone analog. We were inspired by the work of Merrit Andrus's group at BYU, who found that the *trans O*-lactone **288** could be enolized to perform aldol reactions,[69] with dicyclohexylboron triflate[70] giving the highest yields of aldol products. The template showed matched and mismatched cases with D-glyceraldehyde (**289**): while the (*R*,*R*) version gave **290** with decent diastereoselectivity, the (*S*,*S*) version gave a mixture of *syn* and *anti* products **291** with poorer diastereoselectivity (Scheme 83). Our studies in this area began with the synthesis of the *cis* lactone.

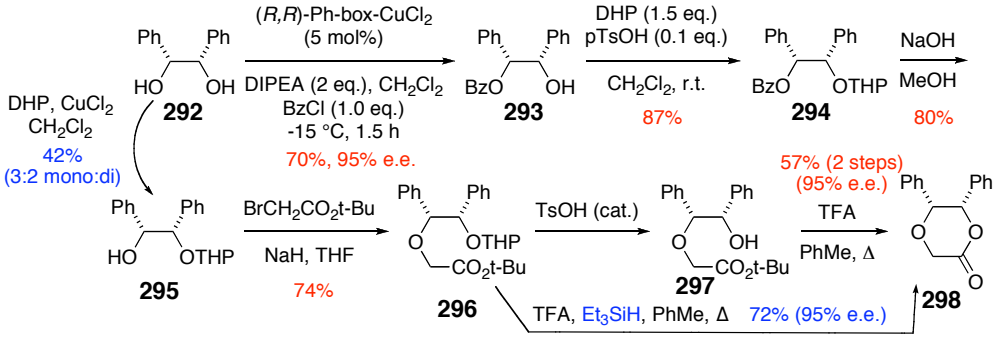


Scheme 83

[69] Anti-*Selective Glycolate Aldol Additions with an Oxapyrone Boron Enolate.* Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035-3037.
[70] *Dicyclohexylboron trifluoromethanesulfonate.* Abiko, A. *Org. Synth.* **2004**, *Coll. Vol. 10*, 273.

5.2.1: Synthesis of Williams' *O*-lactone

Tom Onishi, a postdoc in these labs, had independently prepared the appropriate substrate in a bid to synthesize α,β-dihydroxycarboxylic acids.[71] Copper-catalzyed desymmetrization of *meso*-hydrobenzoin (**292**) gave benzoate **293**,[72] whose free alcohol was protected with the THP group to give **294**. Benzoate removal gave alcohol **295**, and acylation with *tert*-butylbromoacetate gave cyclization precursor **296**. The initial patent reported treatment with tosic acid to remove the THP group, giving alcohol **297**, followed by cyclization with TFA to give the lactone **298**. We discovered that we could effect cyclization in a single step by adding triethylsilane to the TFA reaction, allowing us to avoid the tosic acid deprotection while receiving a higher yield of product (Scheme 84).



Scheme 84

Direct conversion of **292** to **295** in the presence of copper (II) chloride[73] was unsuccessful. Reaction at room temperature gave a 3:2 mixture of **295** and the bis-THP ether in 42% combined yield (Scheme 84); lower temperatures gave very low conversion. Addition of Hünig's base speeded the reaction, in accordance with results for the benzoylation, but no selectivity was observed.

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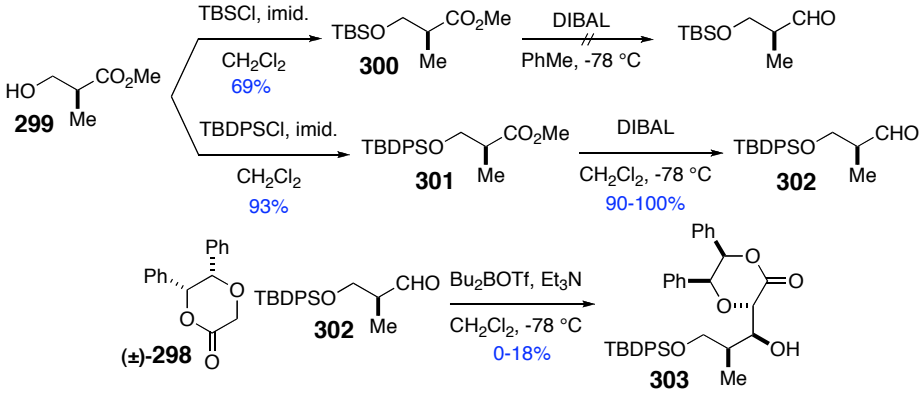
[71] *Chiral Lactones*. Onishi, T.; Williams, R. M. US Patent 7,173,141, February 6, 2007.
[72] *Copper Ion-Induced Activation and Asymmetric Benzoylation of 1,2-Diols: Kinetic Chiral Molecular Recognition.* Matsumura, Y.; Maki, T.; Muramaki, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052-2053.
[73] *Copper(II)chloride catalyzed tetrahydropyranylation of alcohols*. Bhalerao, U. T.; Davis, K. J.; Rao, B. V. *Synth. Comm*. **1996**, *26*, 3081-3085.

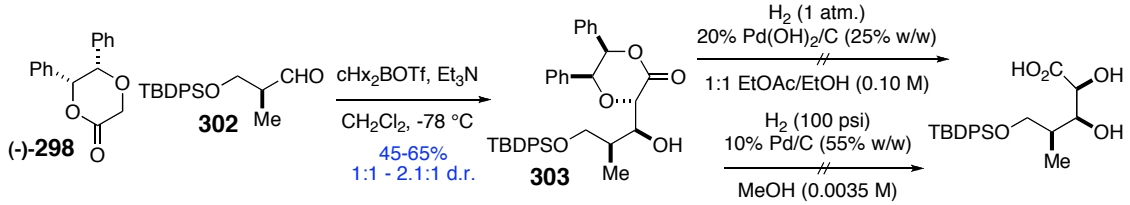
5.2.2: Reactions of Williams' *O*-lactone

The Roche ester **299** was TBS-protected to give **300** (Scheme 85), but we found that DIBAL removed the TBS group. Protection as TBDPS ester **301** allowed reduction to aldehyde **302**,[74] performed immediately before aldol reaction to avoid racemization. Enolization of racemic *O*-lactone **298** with dibutylboron triflate and triethylamine and reaction with **302** gave **303** in poor yield.



Scheme 85

The use of dicyclohexylboron triflate[75] and enantiomerically pure *cis* *O*-lactone gave **303** in good yield, but with little diastereoselectivity (Scheme 86). We then required removal of the biphenyl to allow stereochemical assignment, but our attempts failed! The published work requires 200 psi of hydrogen for removal, while our best equipment at the time could hold only 100 psi, and so this substrate was abandoned as well.



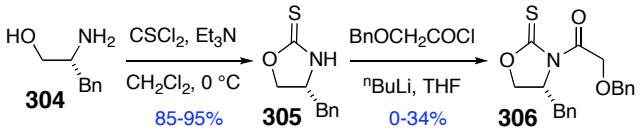
Scheme 86

[74] *Total Synthesis of the Antiviral Marine Natural Product (-)-Hennoxazole A*. Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169-4172.
[75] *Dicyclohexylboron trifluoromethanesulfonate*. Abiko, A. *Org. Synth. CV10* 273.

The main question for this auxiliary is the sense of diastereoinduction: the *trans*-dioxanone gives a predominantly *anti* relationship between the new chiral centers, but we were unable to discover whether the *cis*-dioxanone gives an *anti* or *syn* relationship. The synthesis of microsclerodermins requires a *syn* relationship; given that the synthesis of the *cis* form is much more involved, it would not be worth making if the addition still yields an *anti* product. We also would like to explore the use of titanium or aluminum enolates to influence the diastereoselectivity, as well as Birch reduction of **303** to remove the chiral template.

5.3: Studies from Crimmins' oxazolidinethione

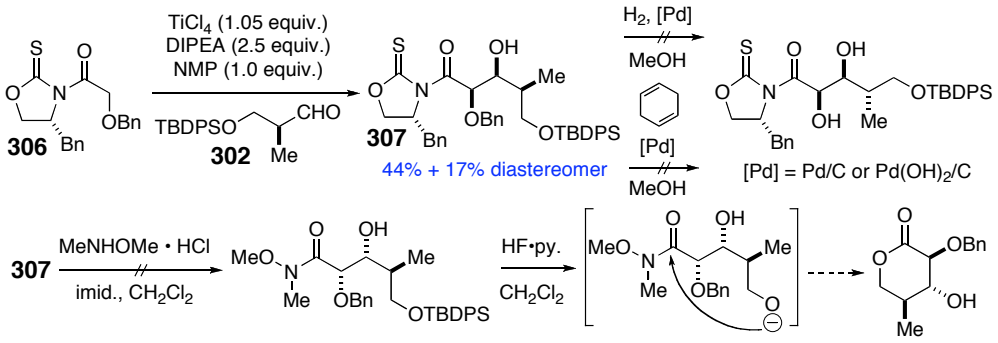
We next turned to the oxazolidinethione developed by Michael Crimmins at North Carolina for *syn*-selective glycolate aldol reactions. Phenylalaninol[76] (**304**) was reacted with thiophosgene to give oxazolidinethione **305** (Scheme 87),[77] and alkylation with benzyloxyacetyl chloride[78] yielded template **306**.[79]



Scheme 87

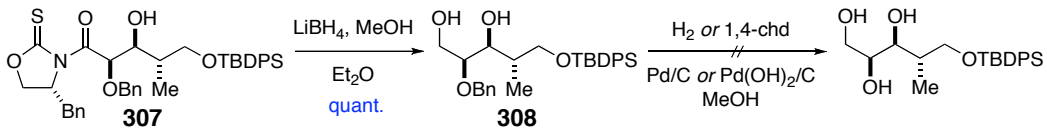
[76] *A Convenient Reduction of Amino Acids and Their Derivatives*. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571.
[77] *Asymmetric Aldol Additions: Use of Titanium Tetrachloride and (-)-Sparteine for the Soft Enolization of* N-*Acyl Oxazolidinones, Oxazolidinethiones, and Thiazolidinethiones*. Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem*. **2001**, *66*, 894-902.
[78] *Chiral Hetero Diels-Alder Products by Enantioselective and Diastereoselective Zirconium Catalysis. Scope, Limitation, Mechanism, and Application to the Concise Synthesis of (+)-Prelactone C and (+)-9-Deoxygoniopypyrone*. Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793-3798.
[79] Anti-*Selective Aldol Reactions with Titanium Enolates of* N-*Glycolyloxazolidinethiones*. Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591-594.

Aldol reaction of **306** with aldehyde **302** yielded a 2.6 : 1 mixture of **307** and its diastereomer, both with the correct mass (Scheme 88).[80] We anticipated that conversion to the Weinreb amide and TBDPS removal would lead to a lactone, whose coupling constants should reveal the stereochemistry. However, we were unable to introduce the methoxymethylamine under known conditions. Additionally, both transfer and gaseous hydrogenation conditions failed to yield the desired diol even after repeated attempts.



Scheme 88

We thought that the thione sulfur might be poisoning the Pd catalysts and thus preventing removal of the benzyl protecting group. In this light, the oxazolidinethione auxiliary was reductively removed with lithium borohydride to give diol **308** in quantitative yield (Scheme 89) with no evidence of auxiliary contaminantion. However, removal of the benzyl group under hydrogenation conditions again failed; it is unclear why the reaction did not proceed. Due to our complete inability to deprotect the aldol adducts, the oxazolidinethione route was abandoned.

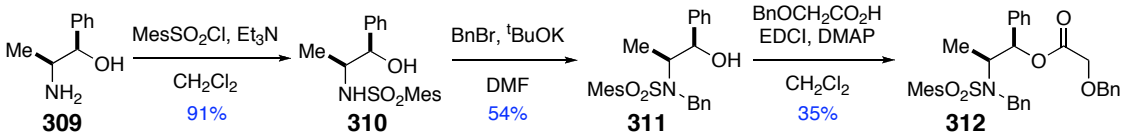


Scheme 89

[80] *An Improved Procedure for Asymmetric Aldol Additions with* N*-Acyl Oxazolidinones, Oxazolidinethiones and Thiazolidinethiones.* Crimmins, M. T.; She, J. *Synlett* **2004**, *8*, 1371-1374.

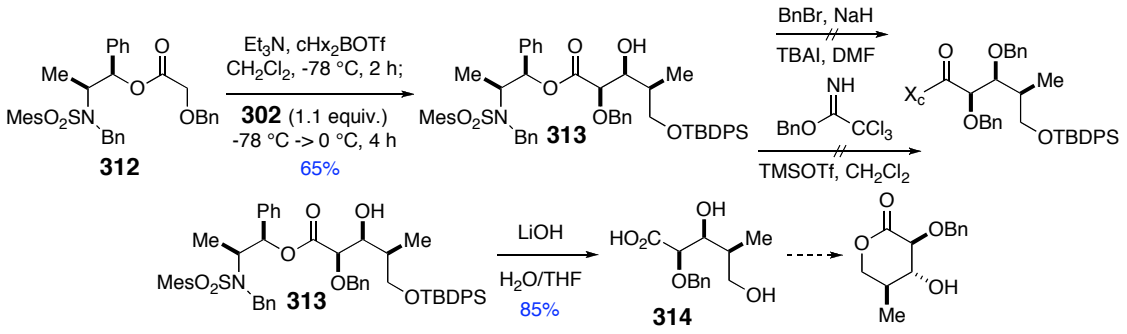
5.4: Studies from Andrus' norephedrine template

After our previous investigation into the *O*-lactone pioneered by Merritt Andrus and group of BYU, we found another method of his for the *syn* glycolate aldol, this one a modification of Masamune's norephedrine auxiliary for asymmetric propionate aldol reactions. After amine **309** was sulfonated to **310** and benzylated,[81] alcohol **311** was acylated with benzyloxyacetic acid to yield template **312** (Scheme 90).[82]



Scheme 90

Reaction of **312** with aldehyde **302** gave a 56% yield of **313** as a single diastereomer (Scheme 91); alcohol benzylation failed, and auxiliary hydrolysis also removed the TBDPS ether to give acid **314**. Lactonization could allow confirmation of stereochemistry via NMR analysis of coupling constants about the six-membered ring. However, there appeared to be no way to remove the auxiliary without also removing the TBDPS group, and so we turned to another chiral auxiliary.



Scheme 91

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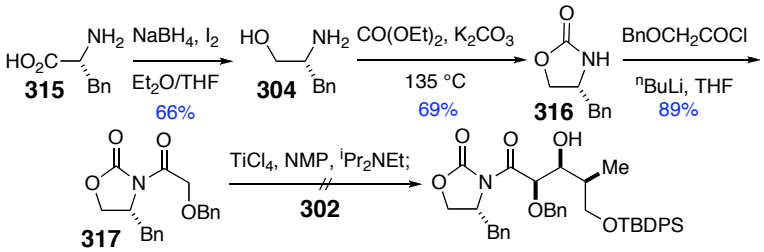
[81] *The* Anti-*Selective Boron-Mediated Asymmetric Aldol Reaction of Carboxylic Esters.* Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587.

[82] *Highly selective* syn *glycolate aldol reactions with boron enolates of Masamune norephedrine esters.* Andrus, M. B.; Sekhar, B. B. V. S.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett.* **2001**, *42*, 7197-7201.

5.5: Studies from Evans' oxazolidinone

At this point we turned to Evans' chiral oxazolidinone, which looked to be free of functional groups that could interfere with removal of the chiral auxiliary. Reduction of phenylalanine (**315**) to **304** and cyclization gave oxazolidinone **316** (Scheme 92); acylation with benzyloxyacetyl chloride gave **317**,[83,84] whose aldol reaction with **302** using Crimmins' titanium enolate failed consistently in our six attempts.[80]



Scheme 92

Reaction of **302** with the boron enolate of **317** for one hour at -78 °C to allow precomplexation, followed by one hour at ambient temperature, gave **318** in 20% yield (Scheme 93).[85] We increased the yield to 45% by running the reaction with no precomplexation and quenching at 0 °C, and later found that running at 0 °C gave purer **318**. Reductive removal of the oxazolidinone and conversion of the resultant diol to the 1,3-acetonide **319**[86] revealed a ^{1}H-^{1}H *J* value consistent with *syn* stereochemistry.[87]

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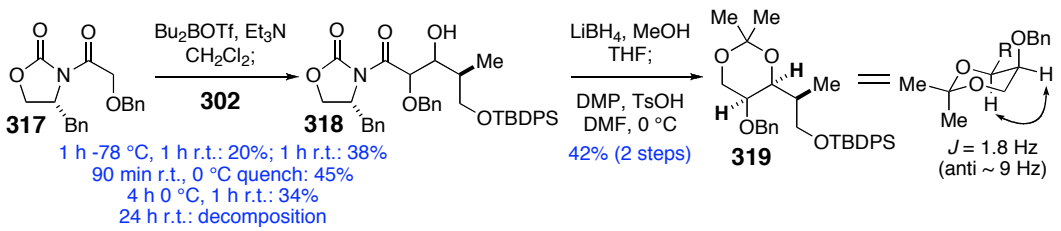
[83] a) *A Convenient Reduction of Amino Acids and Their Derivatives*. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571. b) *Approach toward the Total Synthesis of Orevactaene. 2. Convergent and Stereoselective Synthesis of the C18-C31 Domain of Orevactaene. Evidence for the Relative Configuration of the Side Chain.* Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem*. **2002**, *67*, 5176-5183.

[84] a) *An Improved, Convenient Procedure for Reduction of Amino Acids to Aminoalcohols: Use of $NaBH_4$-H_2SO_4*. Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517-5518. b) *(*S*)-4-(Phenylmethyl)-2-oxazolidinone*. Gage, J. R.; Evans, D. A. *Org. Synth. CV8* 528.

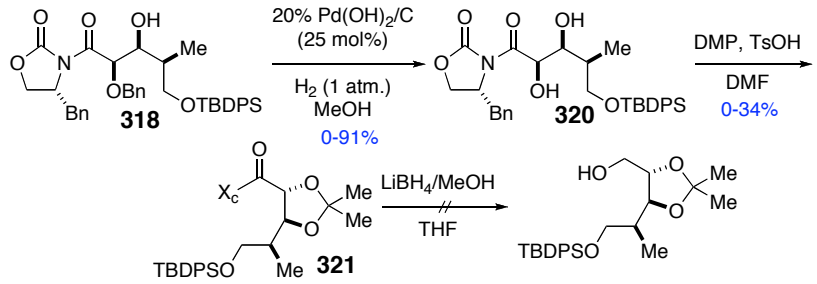
[85] *Enantioselective Synthesis of a (+)-(2*R*, 3*R*)-1,4-Benzodioxane-7-carbaldehyde Derivative, a Key Intermediate in the Total Synthesis of Haedoxan Analogs*. Nakamura, Y.; Hirata, M.; Kuwano, E.; Taniguchi, E. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1550-1554.

[86] *Complex Aldol Reactions for the Construction of Dense Polyol Stereoarrays: Synthesis of the C_{33}-C_{36} Region of Aflastatin A*. Evans, D. A.; Glorius, F.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3331-3333.



Scheme 93

We next wished to obtain a substrate for introduction of the two additional stereocenters. Hydrogenation of the benzyl ether to diol **320** gave a high yield on the first run but fared poorly in later attempts (Scheme 94). Conversion to acetonide **321** went badly on the first attempt, and subsequent attempts gave no desired product.[88] Finally, reductive removal of the oxazolidinone with lithium borohydride failed.



Scheme 94

We suspected that steric congestion of the nascent alcohol by the TBDPS group and oxazolidinone was blocking our attempts to elaborate the aldol adduct. In this light, we attempted to prepare the less bulky TES glycolate **322** via two distinct routes,[89] but were unsuccessful in both attempts (Scheme 95).

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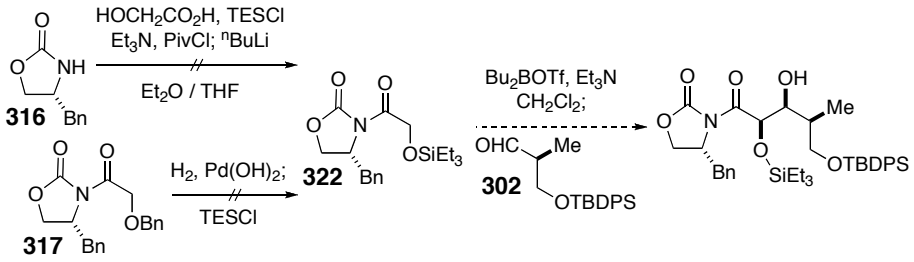
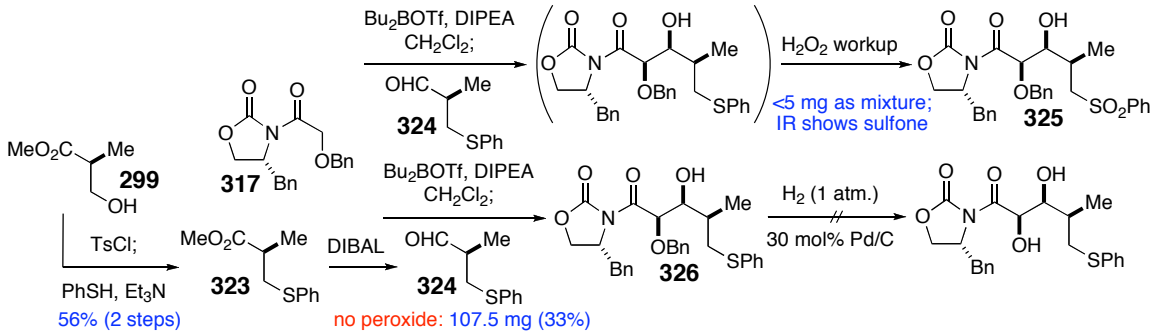
[87] *Acyclic Stereoselection. 32. Synthesis and Characterization of the Diastereomeric (4S)-Pentane-1,2,3,4,-tetrols*. Takai, K.; Heathcock, C. H. *J. Org. Chem*. **1985**, *50*, 3247-3251.
[88] *Absolute stereochemistry of amphidinolide C: synthesis of C-1-C-10 and C-17-C-29 segments*. Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613-1625.
[89] *Insights into Long-Range Structural Effects on the Stereochemistry of Aldol Condensations: A Practical Total Synthesis of Desoxyepothilone F*. Lee, C. B.; Wu, Z.; Zhang, F.; Chappell, M. D.; Stachel, S. J.; Chou, T.-C.; Guan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 5249-5259.



Scheme 95

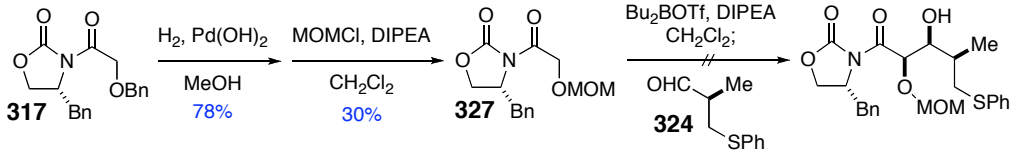
Upon further consideration, we targeted the phenylmercaptan analogue as a suitable aldehyde. The phenylmercaptan group would be less bulky than the TBDPS, and introduction of the sulfur moiety at the first stage of the synthesis would allow for a quick oxidation to the sulfone. This would allow Julia reaction to introduce the phenyltriene side chain and shorten the synthesis by eliminating alcohol protecting-group steps. Roche ester **299** was converted to its tosylate,[90] then treated with phenylthiol and triethylamine to give the ester **323** (Scheme 96); reduction to aldehyde **324** allowed aldol reaction with **317**. In our first attempt, the oxidative workup used converted the desired product to the sulfone **325**, but led to decomposition as well; oxidation to the sulfone at this stage would be counterproductive, as we wished to protect the nascent alcohol before introducing the side chain. Another reaction performed with non-oxidative workup yielded the desired aldol adduct **326** in moderate yield. Attempted hydrogenation of **326** returned virtually no mass; we suspect that the mercaptan moiety was lost by complexation to the palladium, as we thought we had seen earlier in the hydrogenation of sulfur-containing auxiliaries. As the benzyl ether was a poor combination with the sulfur analogue, we sought to vary the oxazolidinone alcohol protecting group.

[90] *Asymmetric Syntheses of Potent Antitumor Macrolides Cryptophycin B and Arenastatin A*. Ghosh, A. K.; Bischoff, A. *Eur. J. Org. Chem.* **2005**, 2131-2141.



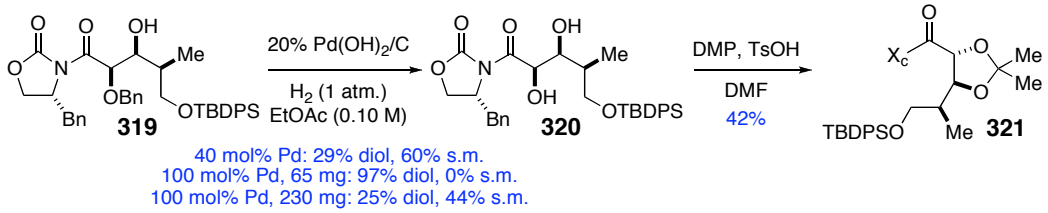
Scheme 96

We next prepared the MOM glycolate **327**,[91] hoping that acidic removal of the protecting group would be easier; however, aldol reaction with **324** failed (Scheme 97).



Scheme 97

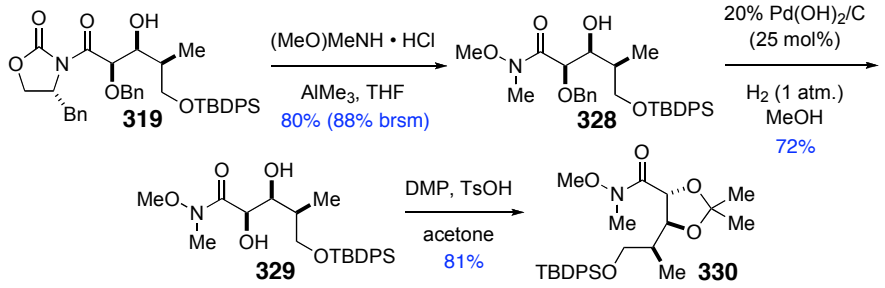
At this point we returned to our original benzyl / TBDPS protecting group combination. After a brief survey of solvent and palladium reagents, we found that 40 mol% of Pearlman's catalyst in ethyl acetate returned 60% starting material and about 30% of the desired diol; use of 100 mol% gave a 97% yield of diol **320** on a 65-mg scale (Scheme 98). We were then able to produce the desired acetonide **321** in 42% yield. Infuriatingly, scaleup to 230 mg reduced the yield of diol to 25%.



Scheme 98

[91] *Stereoselective Synthesis of the C(1)-C(11) Fragment of Peloruside A*. Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941-3944.

Believing that the steric bulk of the oxazolidinone was preventing removal of the benzyl ether and hindering formation of the acetonide, we sought to transaminate to the Weinreb amide,[92] which would reduce steric bulk and provide a facile handle for aldehyde production. Happily, our first attempt proceeded in 80% yield (88% brsm), giving product **328** cleanly and with a much-simplified NMR (Scheme 99). Hydrogenation proceeded with 25 mol% of Pearlman's catalyst to give the diol **329** in 72% yield, and formation of the acetonide **330** proceeded in 81% yield.



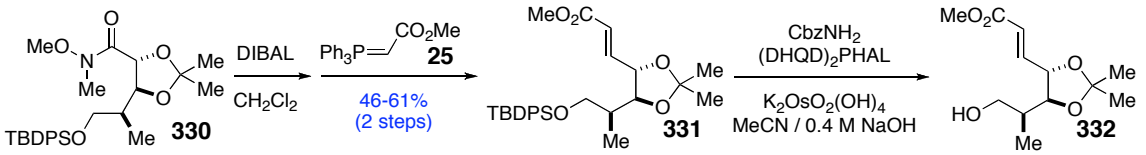
Scheme 99

These results seemed to support our theory of steric hindrance by the oxazolidinone as the main impediment to reduction of the benzyl ether. However, during an industrial interview our interviewer mentioned that he had experienced similar trouble, and reaction analysis had indicated that the variable yields were due to varying amounts of boron impurities carried through purification. Similarly, we could suppose that a single column purification was insufficient to remove all the boron from our aldol reaction, and variation in the amount of boron remaining was affecting hydrogenation yields. In addition to decreasing steric hindrance, the Weinreb amide product required another purification, allowing removal of any remaining boron impurities before hydrogenation.

[92] *Stereoselective synthesis of the α-glucosidase inhibitor nectrisine.* Hulme, A. N.; Montgomery, C. H. *Tetrahedron Lett.* **2003**, *44*, 7649-7653.

5.6: Introduction of the remaining chiral centers

We next reduced **330** to the corresponding aldehyde[93] and conducted a Wittig reaction[94] to give α,β-unsaturated ester **331** (Scheme 100). We then attempted the Sharpless asymmetric dihydroxylation reported by Janda[95] and used in these labs,[96] but in multiple attempts we observed only TBDPS loss to give **332** under the basic conditions.



Scheme 100

We then attempted to synthesize an ester analogue with protecting groups that would resist basic conditions. Bromoacetic acid **333** was converted to the PMB-glycolic acid **334** (Scheme 101), whose reported recrystallization failed in our hands. NMR revealed a 2:1 mixture of acid and DMF that was used as such after extended pumping failed to remove the DMF. Oxazolidinone **316** was acylated with the mixed pivalic anhydride obtained from **334** to give **335** in excellent yield.[97] Finally, the Roche ester **299** was protected to give benzyl ether **336**, albeit in much lower yield than reported.[98]

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[93] *General Strategies toward the Syntheses of Macrolide Antibiotics. The Total Syntheses of 6-Deoxyerythronolide B and Oleandolide*. Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921-5942.

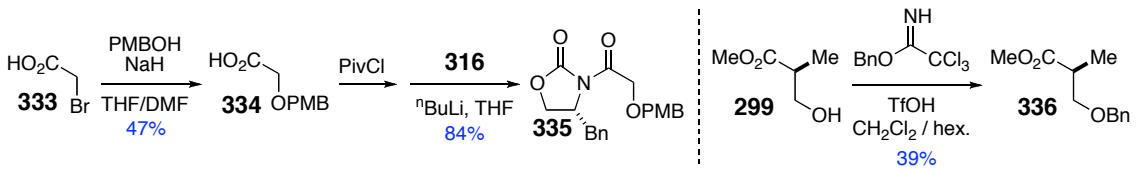
[94] *Enantioselective Synthesis of 10*-epi-*Anamarine via an Iterative Dihydroxylation Sequence*. Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 1069-1072.

[95] *An Efficient Asymmetric Route to 2,3-Diaminobutanoic Acids*. Han, H.; Yoon, J.; Janda, K. J. *J. Org. Chem.* **1998**, *63*, 2045-2048.

[96] *Synthesis of (*S,S)- *and* (R,R)-*2-Amino-3-methylaminobutanoic acid (AMBA)*. Hennings, D. D.; Williams, R. M. *Synthesis* **2000**, 1310-1314.

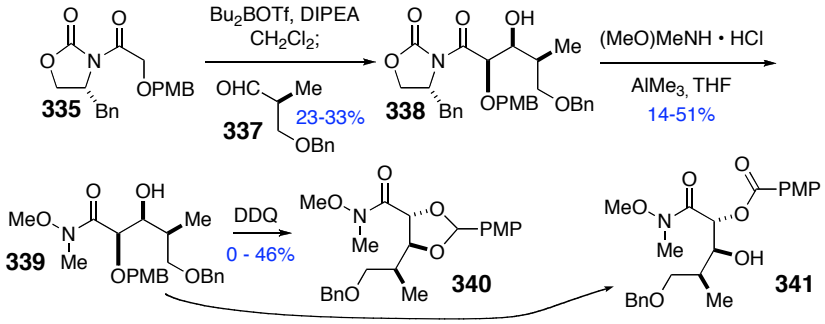
[97] *Synthesis, Crystal Structure Determination, and Biological Properties of the DNA-dependent Protein Kinase (DNA-PK) Inhibitor 3-Cyano-6-hydrazonomethyl-5-(4-pyridyl)pyrid-[1H]-2-one (OK-1035)*. Stockley, M.; Clegg, W.; Fontana, G.; Golding, B. T.; Martin, N.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2837-2841.

[98] *Convergent Enantioselective Synthesis of Vinigrol, an Architecturally Novel Diterpenoid with Potent Platelet Aggregation Inhibitory and Antihypertensive Properties. 1. Application of Anionic Sigmatropy to Construction of the Octalin Substructure*. Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096-6107.



Scheme 101

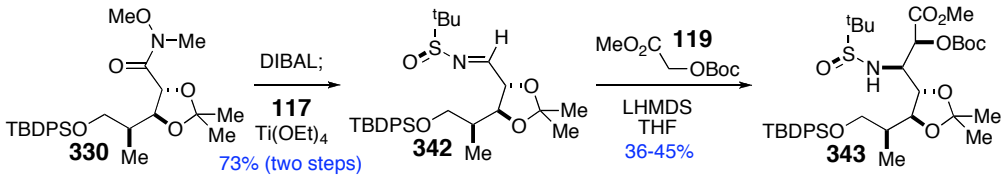
Reduction of **336** to aldehyde **337** and reaction with the boron enolate of **335** gave aldol adduct **338** (Scheme 102); while the reaction proceeded decently on small scale, attempted scale-up resulted in a poor yield of aldehyde and a correspondingly reduced amount of **338**. Conversion to Weinreb amide **339** proceeded in poor yield; oxidation of the PMB ether to PMP acetal **340** worked once in 46% yield, and in all other cases failed. We were even able to observe overoxidation to the PMP carbonate **341**.[99]



Scheme 102

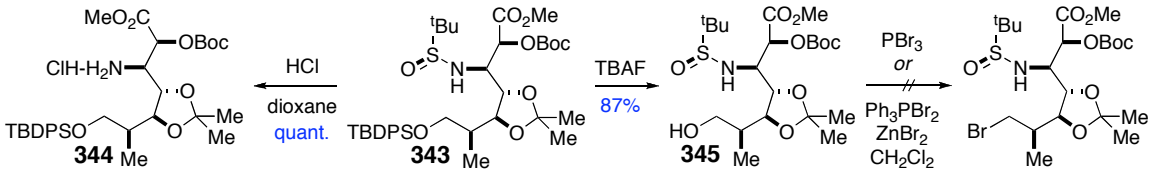
Around this time, Aitken published his application of Ellman sulfinimine methodology to the synthesis of the α and β stereocenters of the β-amino acids of **3**-**5**. Hoping to apply this methodology, we converted acetonide **330** via reduction and condensation with amine **117** to the chiral sulfimine **342** (Scheme 103).[9] Addition of Boc-protected methyl glycolate **119** gave ester **343**, bearing all chiral centers of AMPTD; stereochemistry is assumed, as we could not obtain a crystal suitable for X-ray analysis.

[99] *Protection of hydroxy groups by intramolecular oxidative formation of methoxybenzylidene acetals with DDQ*. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889-892.



Scheme 103

While Aitken did not discuss deprotection of the adduct, we discovered that treatment of **343** with a dry solution of HCl in dioxane allowed selective removal of the *tert*-butyl sulfinimine group in the presence of the acetonide and *O*-Boc groups to yield amine salt **344** (Scheme 104). (We later discovered that Hruby had carried out similar work on the selective removal of *N*-Boc groups in the presence of *tert*-butyl ethers.[100]) Additionally, TBAF-mediated removal of the TBDPS group from **343** proceeded smoothly to give **345**. We attempted replacement of the resultant alcohol with bromide with carbon tetrabromide, triphenylphosphine, and acetone in acetonitrile,[101] as well as triphenylphosphine dibromide in dichloromethane with catalytic zinc bromide.[102] However, these attempts were unsuccessful, presumably due to deprotection of the acetonide by the HBr formed. A successful hydrolysis of the ester of **343** would complete an orthogonal deprotection set, allowing elaboration of the core in any direction desired.



Scheme 104

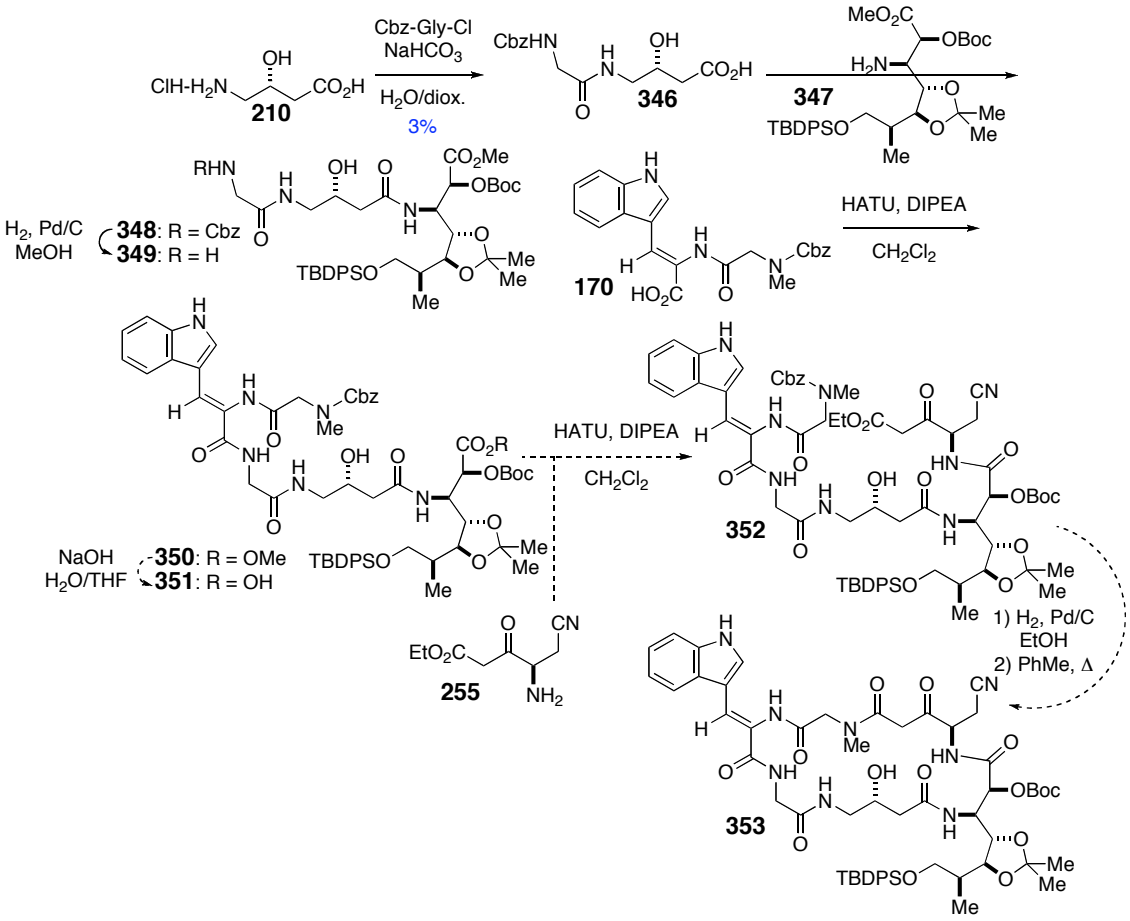
[100] *Fast, efficient and selective deprotection of the* tert*-butoxycarbonyl (Boc) group using HCl/dioxane (4 M)*. Han, G.; Tamaki, M.; Hruby, V. J. *J. Peptide Res.* **2001**, *58*, 338-341.
[101] *Reactivity of* t*-butyldimethylsilyl ethers : a facile conversion into bromides.* Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1987**, *28*, 1697-1698.
[102] *Reaction of Hindered Trialkylsilyl Esters and Trialkylsilyl Ethers with Triphenylphosphine Dibromide: Preparation of Carboxylic Acid Bromides and Alkyl Bromides under Mild Neutral Conditions.* Aizpurua, J. M.; Cossío, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941-4943.

Chapter 6: Conclusions and future work

We conducted brief efforts toward a macrocycle, which will be described here along with suggestions for future work on this molecule.

6.1: Studies toward macrocyclization

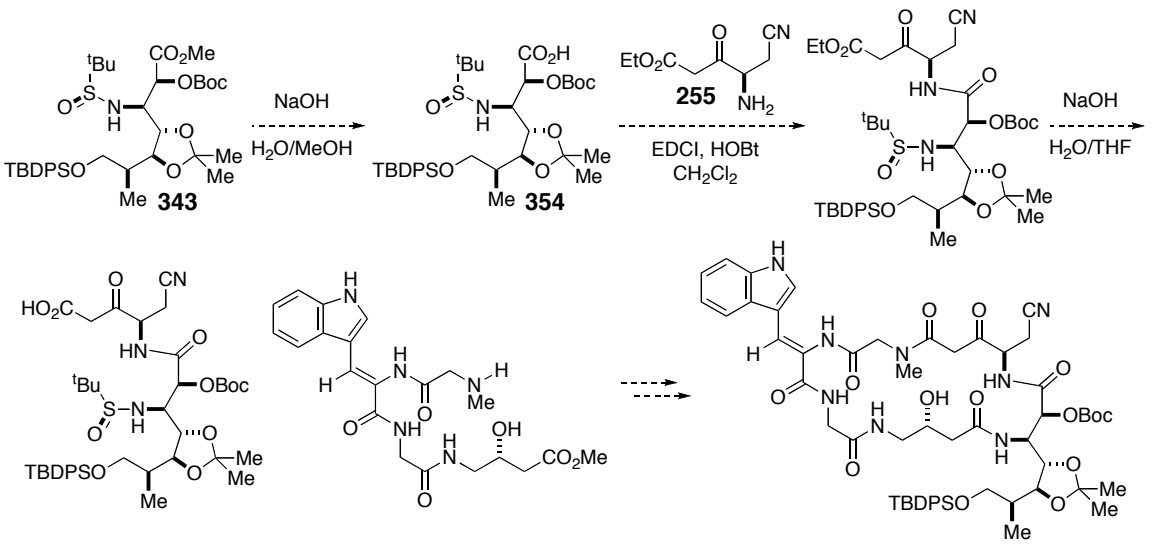
As our time in lab was running short, we decided to attempt coupling of GABOB hydrochloride (**210**) with the acid chloride of Cbz-glycine; this procedure appeared to give the desired dipeptide **346** (Scheme 105). We attempted coupling of the free acid with the free amine **347** of our AMPTD core (obtained by neutralization of hydrochloride **344** with sodium bicarbonate), which again appeared to give the desired tripeptide **348**. We hydrogenated this material and attempted coupling of the putative free amine **349** with the Sar-ΔTrp free acid **170**; the NMR spectrum was unclear, but we obtained material in the organic layer and assumed it to be pentapeptide **350**. We subjected this residue to hydrolysis to give the corresponding free acid **351**, which we attempted to couple with the free amine **255**; obtaining material in the organic layer, we assumed it to be hexapeptide **352**. As we had only a few milligrams at this point, we decided not to risk hydrolysis of the β-keto ester, and instead subjected the residue to hydrogenation to remove the final Cbz group, then attempted to effect macrocyclization via heating in toluene and closure of the free amine onto the resultant ketene. After four hours, we evaporated the solution and sent the residue for HRMS; unfortunately, grease peaks were seen directly over the area for the mass of cyclic peptide **353**. Given our previous problems with the ketene procedure, we suspect that the compound was not obtained.



Scheme 105

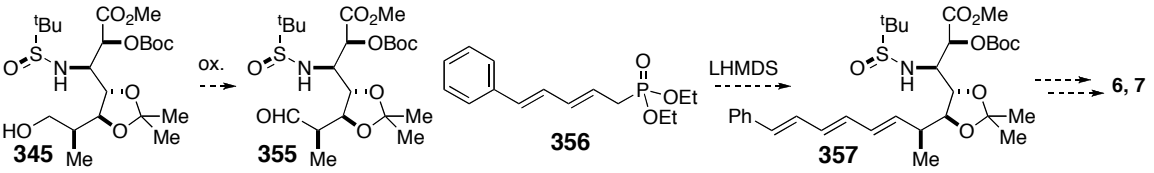
6.2: Other possibilities toward macrocyclization

Alternatively, we could hydrolyze the ester of the AMPTD core **343**; if TBDPS protection were maintained, we would couple the acid **354** with the free amine **255** to give a dipeptide (Scheme 106). We are extremely interested to see if the increased electron-sink effect of the amide, as opposed to the carbamate, would suppress formation of the tetramic acid derivative and allow peptide coupling at the β-keto acid. If this were the case, we should be able couple with the western tetrapeptide and conduct macrocycle synthesis as mentioned above; this route has the advantage that both potential macrocyclizations would not risk epimerization.



Scheme 106

Reaction of the aldehyde **355** derived from **345** with the known phosphonate **356** under Horner-Wadsworth-Emmons conditions should give the complete AMPTD molecule **357**, prepared for synthesis toward **6** and **7** (Scheme 107).[103] However, we are unclear at which juncture to bring in the phenyltriene side chain: if done too early, we risk the possibility of isomerization during subsequent steps due to ambient light, while installation after the AMPTD core is coupled to other amino acids could cause problems with the various sensitive functional groups in the molecule.

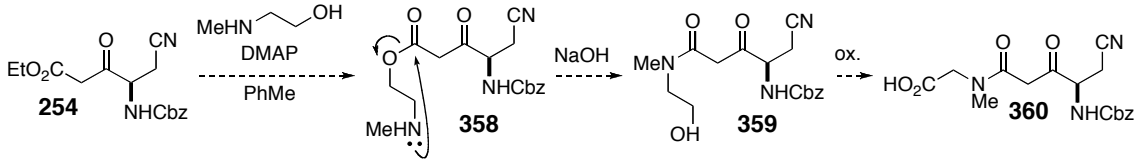


Scheme 107

[103] a) *Synthesis of fluorescent probes for localized membrane fluidity measurements*. Beck, A.; Heissler, D.; Duportail, G. *Tetrahedron* **1991**, *47*, 1459-1472. b) *A Practical Synthesis of the Ansa Chain of Benzenic Ansamycin Antibiotics: Total Synthesis of an Ansatrienol Derivative.* Kashin, D.; Meyer, A.; Wittenberg, R.; Schöning, K.-U.; Kamlage, S.; Kirschning, A. *Synthesis* **2006** 304-319.

6.3: Other possibilities for β-ketoamide synthesis

We have also attempted to imagine ways to get around the pesky β-ketoacid intermediate, in case our hypothesis of tetramic acid formation is incorrect and some other mechanism is causing decomposition. We begin one such idea with transesterification of β-ketoester **254** with *N*-methylethanolamine to give ester **358**. Treatment of this species with strong base could cause *O*- to *N*-acyl migration, giving the β-ketoamide **359**. Oxidation of the resultant alcohol would give the acid **360**, well positioned for coupling to dehydrotryptophan methyl ester **150** or a dehydrotryptophan-containing multipeptide. We would have to watch for decomposition of **254** via the previously postulated tetramic acid formation, but acyl transfer and oxidation should be fairly straightforward in this system. It may even be possible to combine the first two reactions into one by conducting the transesterification under more basic conditions than those provided by DMAP alone.



Scheme 108

6.4: Conclusions

We have completed the synthesis of the individual amino acids of **6-9**, excepting the triene side chain of AMPTD. Below we review our accomplishments in roughly increasing order of complexity, and close with thoughts on the overall synthesis.

The dehydrotryptophan residue was synthesized based on literature procedures, but we have developed new mixed anhydride methodology for its peptide coupling. We have also synthesized a tripeptide containing the D-tryptophan moiety required for the synthesis of **6** and **8**, though more work is needed to ensure the stereochemical integrity of this piece.

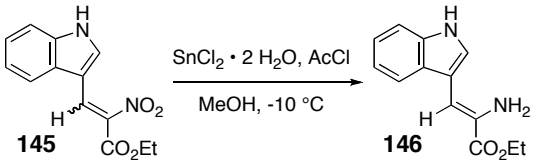
GABOB, previously synthesized many times in the literature, was synthesized using a procedure from this group based on Williams' lactone. We attempted to extend the methodology to the direct synthesis of dipeptides, but were unable to do so owing to problems with removal of the amide *N*-benzyl or decomposition of the deprotected dipeptides. We presume that the decomposition could be minized through optimization of the appropriate reactions. Synthesis of dipeptides via free GABOB was moderately successful in our hands, though, and this would be the preferred route for a quick attack on the microsclerodermins.

Direct synthesis of the β-amidohemiaminal found in the microsclerodermins was shown by Shioiri's work to be impractical. Synthesis of a pyrrolidinone precursor suitable for coupling to the other amino acids was achieved after many protecting group troubles. Unfortunately, we were consistently unable to achieve the coupling of β-ketoacids to the sarcosine moiety. Future work in this area must include development of a reproducible procedure for coupling of the β-ketoacid; we propose that acylation of the nitrogen moiety will prevent intramolecular decomposition to tetramic acid products. Alternatively, efforts to bypass the β-ketoacid were moderately successful in our hands. Optimization in this area could provide an easier way to get to the microsclerodermins.

Finally, the five-consecutive-sp^3-stereocenter core of AMPTD was synthesized in a concise route using Evans' oxazolidinone glycolate aldol reaction and Ellman's sulfinimine addition chemistry. While we drew the Ellman chemistry from Aitken's work on constituents of the microsclerodermins, we believe the brevity of our route makes it superior to those previously published for AMPTD, and our deprotection of the adduct goes beyond Aitken's work to provide a molecule that can be applied synthetically to the microsclerodermins. The protecting groups on our AMPTD core should be fully orthogonal, allowing elaboration at the amine or acid, as well as on the side chain. The ability to quickly install a variety of side chains would prove useful in medicinal chemistry efforts or efforts to probe the structure-activity relationship of the microsclerodermins. The ω-phenyltriene is proposed as a biologically active moiety, and installation of a triene capped with a methyl group would provide a simple test for this.

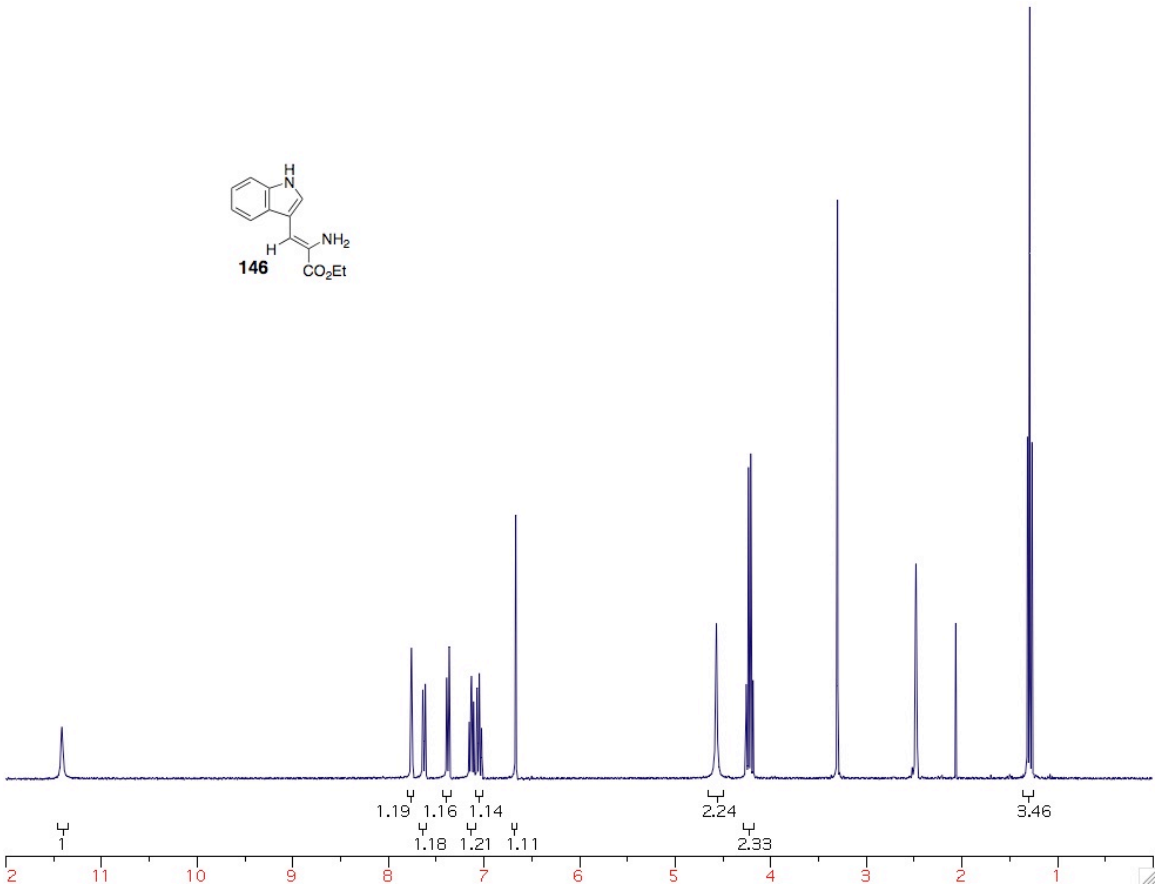
Coupling of the various amino acids has been problematic. Attempts to produce the aspartate-sarcosine dipeptide were unsuccessful, as were attempts at direct synthesis of the glycine-GABOB dipeptide with the chiral auxiliary in place. We were able to achieve the sarcosine-dehydrotryptophan and glycine-GABOB dipeptides, but were unable to obtain the AMPTD-aspartate dipeptide; we had planned to couple the three dipeptides to give the macrocyclic product, and did in fact attempt the sarcosine-dehydrotryptophan-glycine-GABOB coupling, though the results were unclear. We have also prepared the glycine-GABOB-AMPTD tripeptide and attempted coupling with the sarcosine-dehydrotryptophan dipeptide; while our results were again unclear, repeating this work and incorporating the aspartate could give an alternate path to the macrocycle. Careful studies would be needed to ascertain the proper stage for installation of the triene side chain, as well as the best way to join the constituent amino acids and close the microsclerodermin macrocycle. We believe that our work has laid a solid foundation for future efforts toward the microsclerodermins.

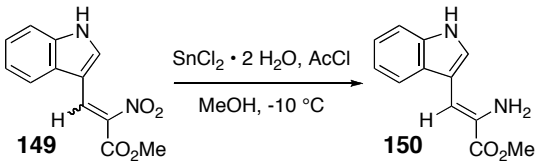
All non-aqueous reactions were run in flame-dried glassware under an Ar atmosphere. Reagents were obtained from Aldrich Chemical Co. and used without further purification. NMR spectra were taken on a Varian 300 MHz spectrometer.



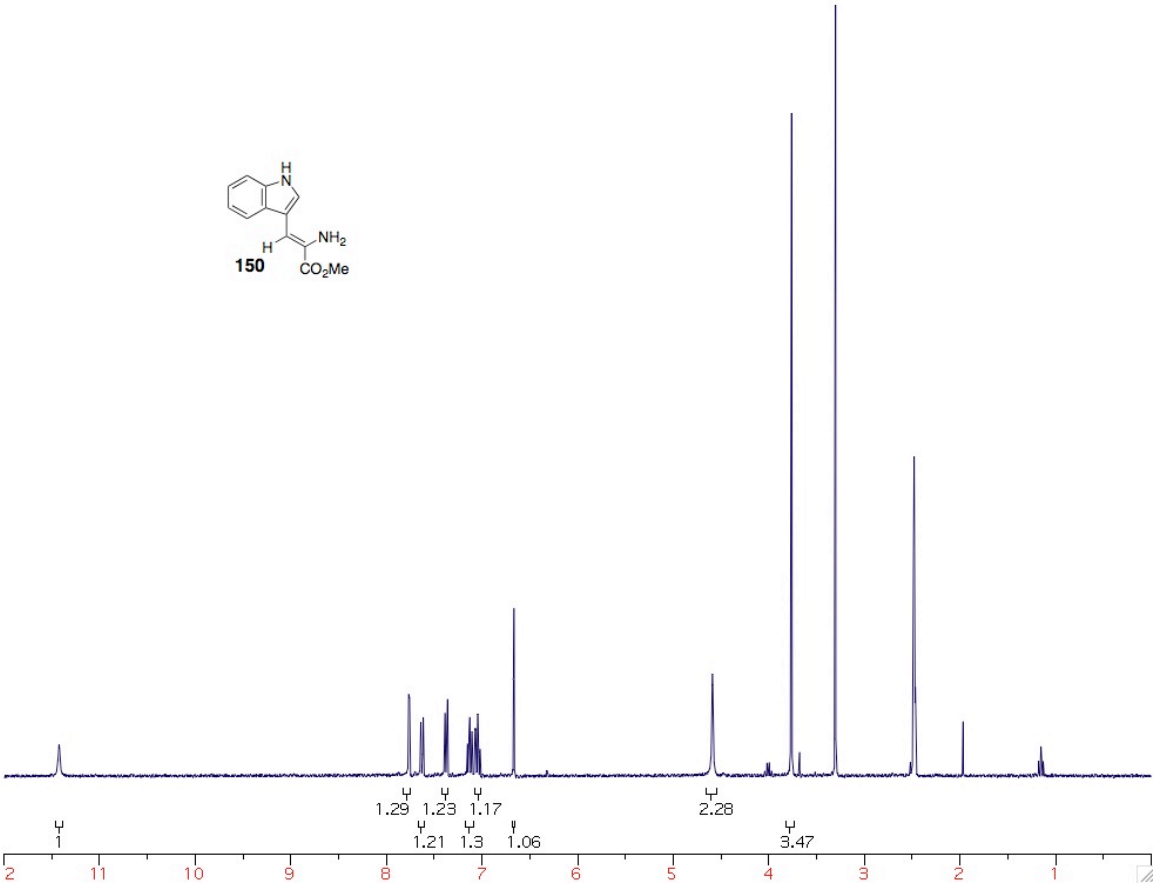
145 **146**

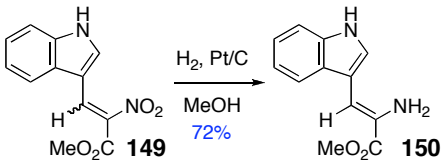
Tin chloride dihydrate (1.08 g, 4.79 mmol), acetyl chloride (0.78 mL, 11.0 mmol), and MeOH (5 mL) were mixed at -30 °C and added to a flask containing **145** and a stir bar at -10 °C. The resultant pale orange solution was stirred 90 min at -10 °C, gradually acquiring a salmon color. Concentrated HCl, Et_2O, and MeOH (5 mL each) were added and the resultant solution stirred 30 min at 0 °C. The solution was filtered and the filter cake washed with 1:1 9 M HCl : MeOH and Et_2O (20 mL each). The filter cake was partitioned between saturated aqueous $NaHCO_3$ and EtOAc (10 mL each) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated in vacuo to yield 221 mg (70%) **146** as a pale yellow solid. ^{1}H NMR δ (300 MHz, DMSO-d_6): 11.43 (br s, 1H), 7.74 (d, 1H, J = 2.4 Hz), 7.65 (d, 1H, J = 7.8 Hz), 7.39 (dt, 1H, J = 7.8, 0.8 Hz), 7.15 (m, 1H), 7.07 (m, 1H), 6.89 (s, 1H), 4.59 (br s, 2H), 4.24 (q, 2H, J = 7.2 Hz), 1.31 (t, 3H, J = 7.1 Hz).



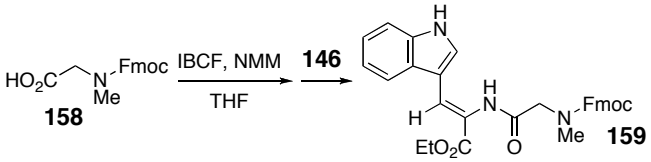


A mixture of tin chloride dihydrate (19.23 g, 85.2 mmol) and acetyl chloride (13.9 mL, 195 mmol) in MeOH (108 mL) in a 300-mL round-bottom flask was cooled to -25 °C and **149** added in portions over 8 min. The mixture was stirred 2.5 h at -5 °C, then treated with Et_2O and concentrated HCl (9 mL each) and stirred 30 min at 0 °C. The precipitate was filtered off and washed with 1:1 Et_2O : 9 M HCl (80 mL), then dried in vacuo. The resultant solid was partitioned between EtOAc and saturated aqueous $NaHCO_3$ (400 mL each); the organic layer was dried (Na_2SO_4) and evaporated in vacuo to yield 3.94 g (75%) **150** as a red oil that crystallized upon standing. ^{1}H NMR δ (300 MHz, DMSO-d_6): 11.44 (br s, 1H), 7.78 (d, 1H, J = 2.4 Hz), 7.65 (d, 1H, J = 7.8 Hz), 7.39 (d, 1H, J = 8.1 Hz), 7.15 (m, 1H), 7.07 (m, 1H), 6.69 (s, 1H), 4.61 (br s, 2H), 3.78 (s, 3H).

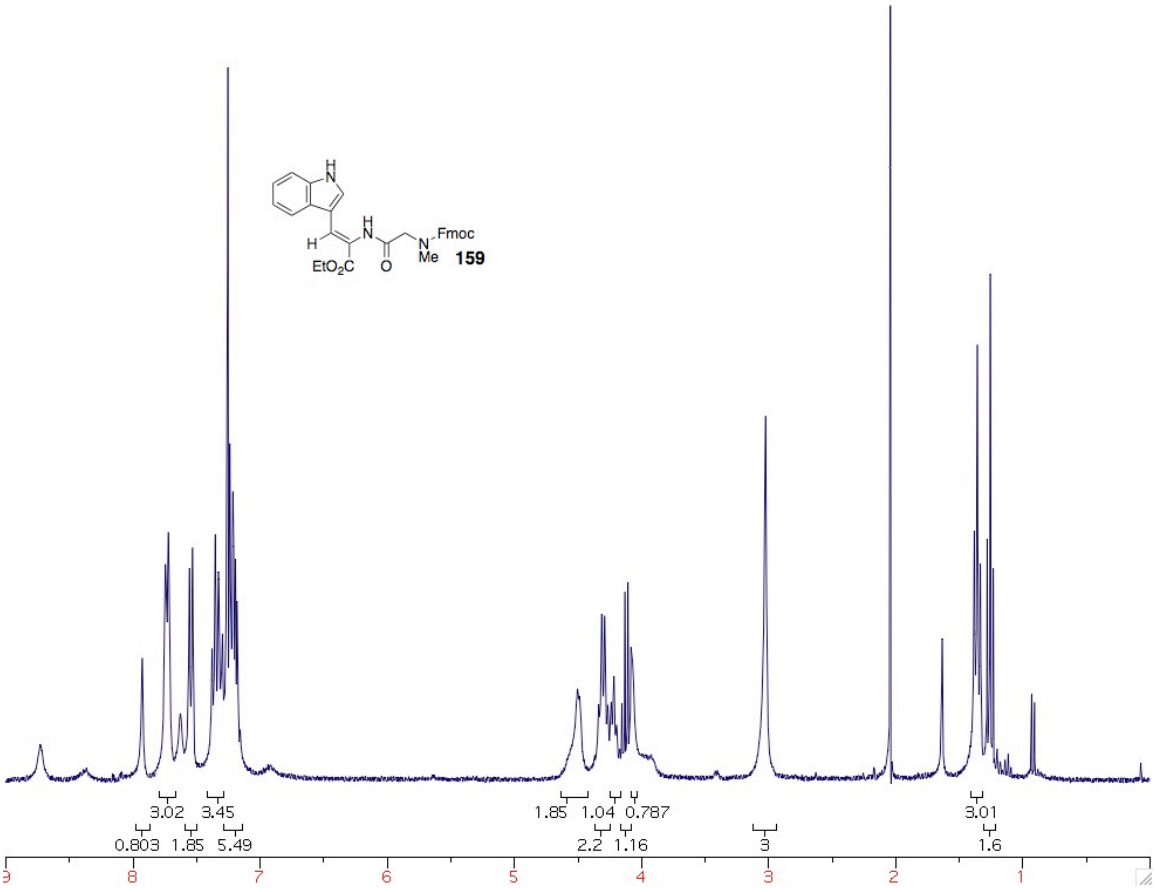


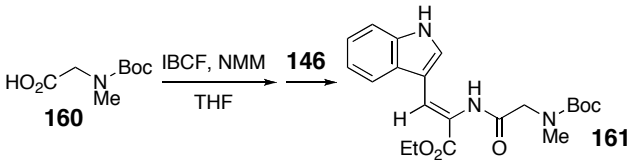


A mixture of **149** (91.1 mg, 0.37 mmol) and 5% platinum on carbon (9.1 mg, 0.0023 mmol) in EtOAc (25 mL) in a 3-oz pressure vessel was charged with H_2 (20 psi) and stirred 4.5 h, then filtered through a pad of Celite and evaporated in vacuo to give 90 mg yellow oil. Flash chromatography (98:2 CH_2Cl_2 : MeOH) yielded 57.4 mg (72%) **150**. R_f (98:2 CH_2Cl_2 : MeOH) = 0.26. NMR as above.

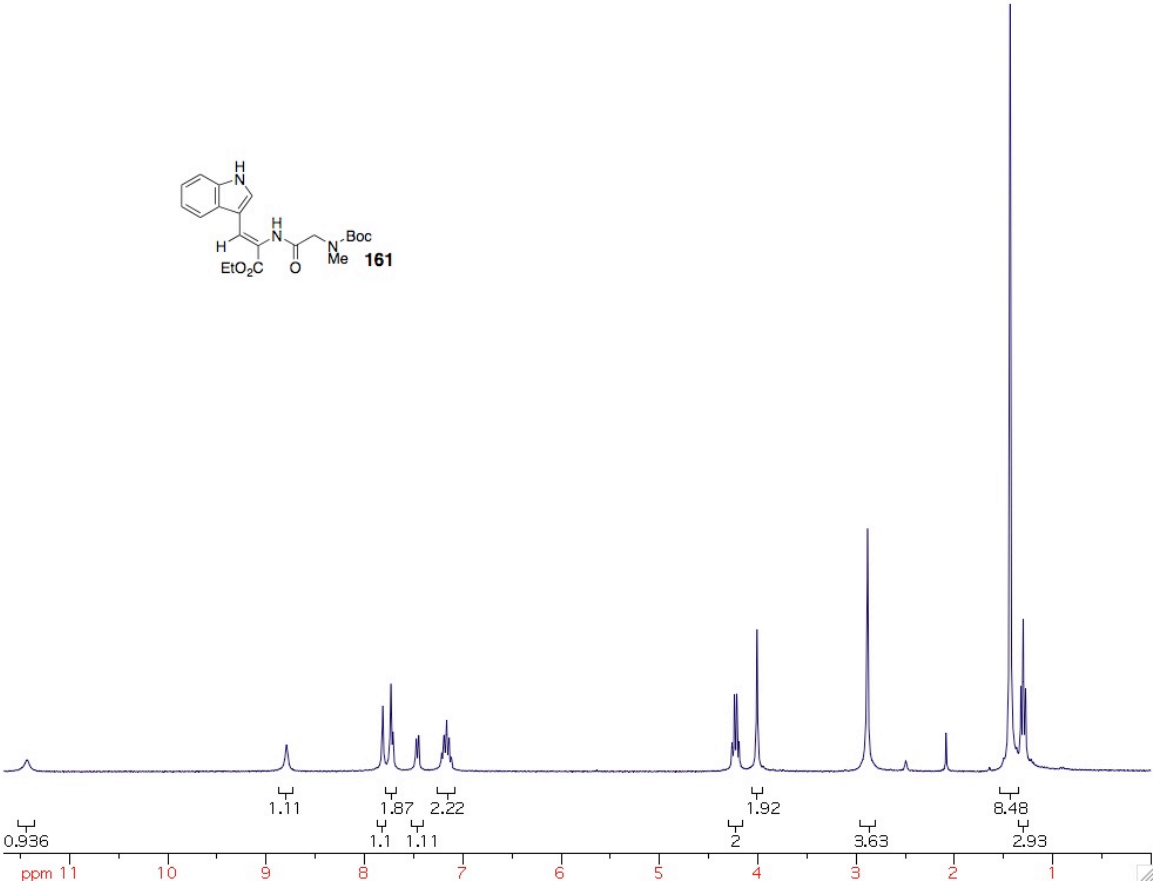


A solution of **158** (39 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was treated with oxalyl chloride (12 μL, 0.14 mmol) and DMF (1.1 μL, 0.014 mmol), causing bubbling. The solution was stirred 30 min and hexanes (2 mL) added. The mixture was vacuum filtered and concentrated in vacuo; the resultant acid chloride was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0 °C. A solution of **146** (27 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added, followed by DMAP (13 mg, 0.11 mmol), and the reaction stirred 1 h at ambient temperature. Water was added and the mixture extracted with Et_2O; the combined organic layers were dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography (1:1 hexanes : ethyl acetate) gave 16 mg of recovered **146** along with **159** (15 mg, 25%, 60% brsm). R_f (1:1 hexanes : ethyl acetate) = 0.45 (**146**), 0.17 (**159**). ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.0-7.0 (m, 14 H), 4.50 (m, 2 H), 4.30 (q, 2 H, J = 6.9 Hz), 4.22 (t, 1 H, J = 6.3 Hz), 4.12 (q, 1 H, J = 7.2 Hz), 4.07 (m, 1 H), 3.02 (br s, 3 H), 1.36 (t, 3 H, J = 7.2 Hz).

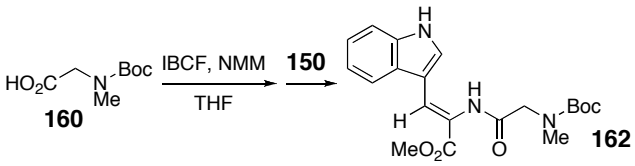




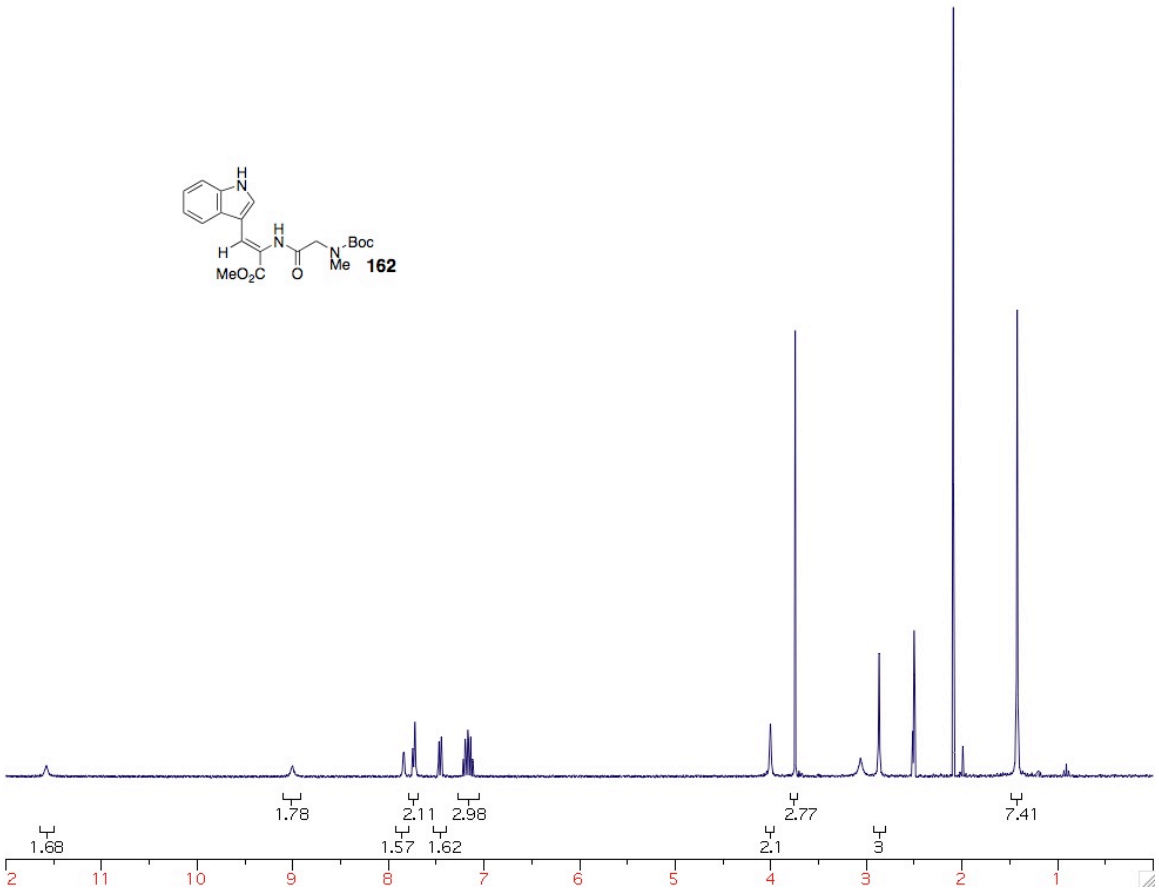
A solution of **160** (149 mg, 0.78 mmol) in THF (2.6 mL) at -5 °C was treated with *N*-methylmorpholine (102.5 μL, 0.93 mmol) and isobutyl chloroformate (87.5 μL, 0.67 mmol), producing a white precipitate. The mixture was stirred 10 min at -5 °C and a solution of **146** (180 mg, 0.78 mmol) in a small amount of THF was added via canula; the resultant yellowish mixture was stirred 45 min at 0 °C and 44 h at ambient temperature. The reaction mixture was washed with 10% citric acid, 5% $NaHCO_3$, and brine (10 mL each) and evaporated in vacuo; addition of CH_2Cl_2 produced a precipitate after 1 h. The precipitate was separated by vacuum filtration and dried to yield 56 mg (21%) **161**. ^1H NMR δ (300 MHz, $CDCl_3$, 383 K): 11.43 (br s, 1H), 8.79 (br s, 1 H), 7.81 (br s, 1 H), 7.73 (m, 2 H), 7.46 (d, 1 H, J = 7.2 Hz), 7.17 (m, 2 H), 4.23 (q, 2 H, J = 7.2 Hz), 4.01 (br s, 2 H), 2.88 (br s, 3 H), 1.44 (br s, 9 H), 1.30 (t, 3 H, J = 7.2 Hz).



CMB162 (1H, 13C, IR, MS, mp = 204-206 °C)



A solution of **160** (378 mg, 2.0 mmol) in THF (2 mL) at -5 °C was treated with *N*-methylmorpholine (223 μL, 2.0 mmol) and isobutyl chloroformate (263 μL, 2.0 mmol), producing a white precipitate, and the solution stirred 15 min at -5 °C. A solution of **150** (433 mg, 2.0 mmol) in THF (2 mL) was added via canula and the resultant yellowish mixture stirred 75 min at -5 °C and 18 h at ambient temperature. The mixture was diluted with EtOAc and water (10 mL each) and the organic layer washed with H_2O and brine (10 mL each). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Column chromatography (3:7 hexanes : ethyl acetate) yielded 589 mg (76%) **162**. ^{1}H NMR δ (300 MHz, DMSO-d_6, 353 K): 11.58 (br s, 1H), 9.00 (br s, 1H), 7.84 (m, 1H), 7.73 (m, 2H), 7.46 (m, 1H), 7.17 (m, 3H), 4.00 (s, 2H), 3.75 (s, 3H), 2.87 (s, 3H), 1.42 (s, 9H); ^{13}C NMR δ (100 MHz, DMSO-d_6): 169.08, 168.88, 166.13, 156.10, 155.78, 136.29, 129.51, 128.98, 127.65, 127.58, 127.29, 126.63, 122.95, 122.89, 121.06, 120.83, 120.43, 118.72, 112.68, 109.41, 79.60, 79.40, 67.67, 52.45, 52.13, 51.78, 36.26, 35.95, 31.34, 28.73, 28.66, 25.79; IR ($CHCl_3$): 3269, 2978, 2928, 1674, 1633, 1519, 1492, 1459, 1432, 1392, 1330, 1244, 1148, 1113, 742 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{25}N_3O_5$ (*m*/*z*): 387.1794, found (*m*/*z*): 387.1792.


H
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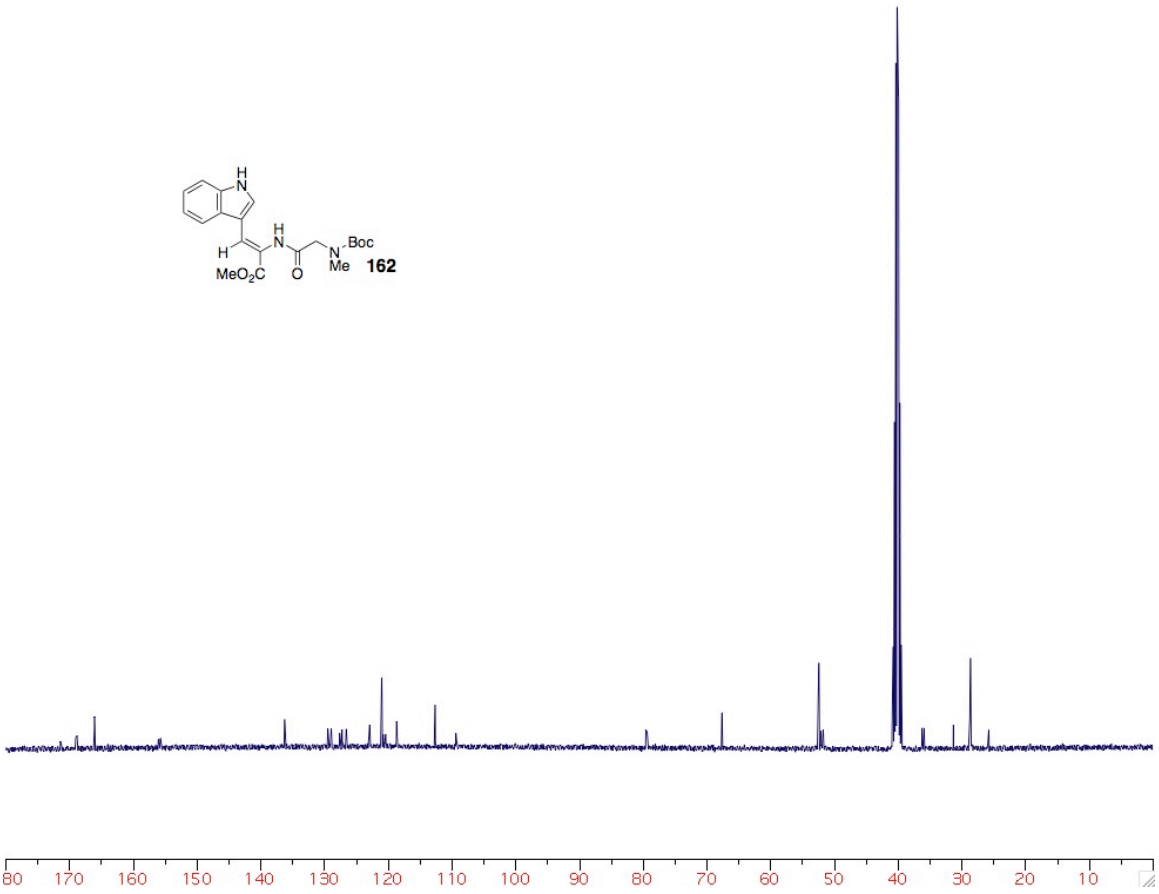
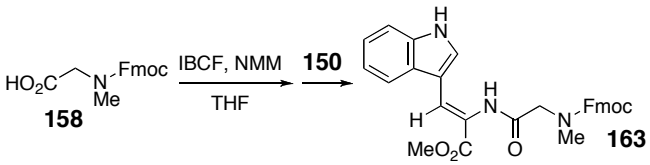
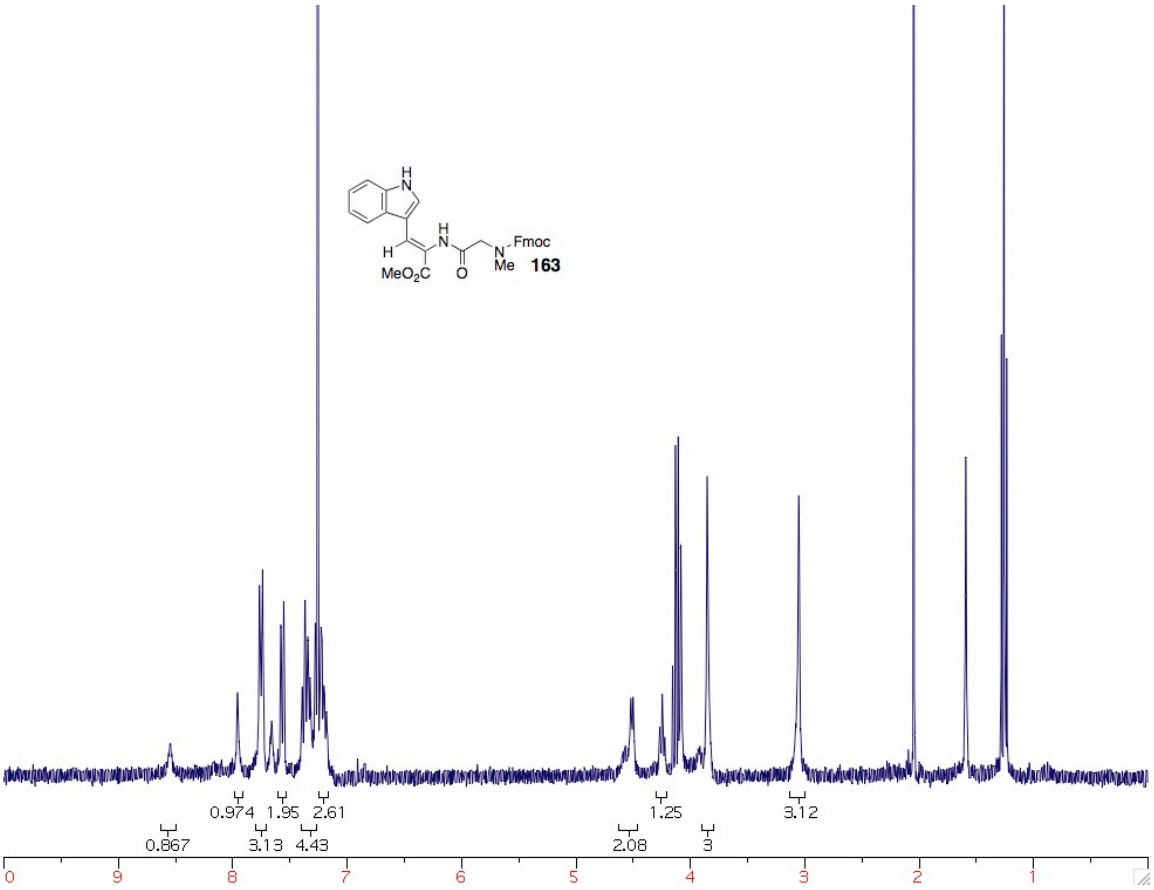
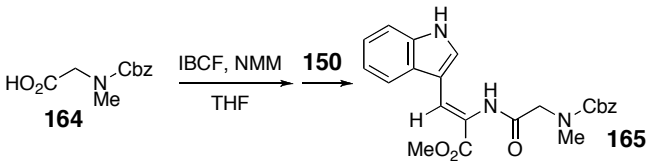




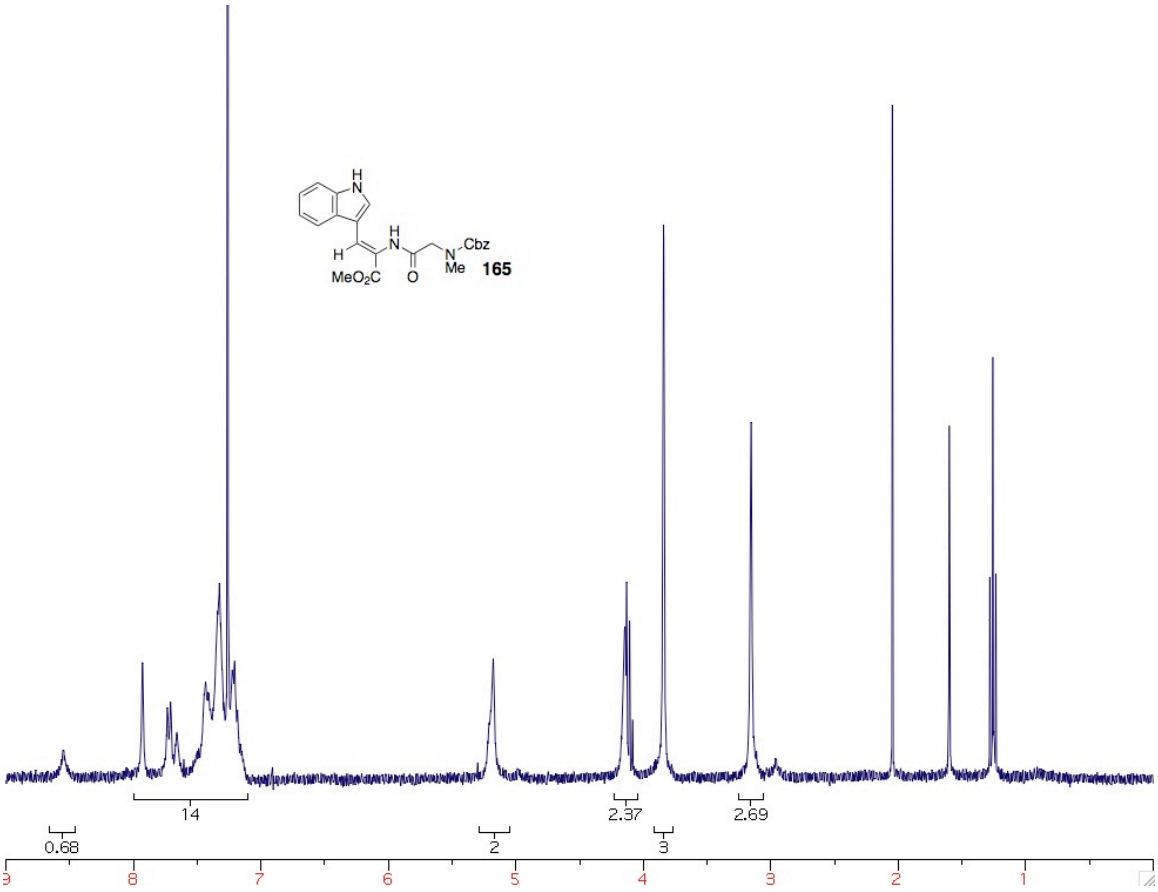
To a stirred solution of **158** (538.9 mg, 1.73 mmol) in THF (1.7 mL) at 3 °C were added isobutyl chloroformate (0.245 mL, 1.89 mmol) and *N*-methylmorpholine (0.21 mL, 1.91 mmol) and the solution was stirred 15 min at 0 °C. A solution of **150** (340.3 mg, 1.57 mmol) in THF (1.8 + 0.7 mL) was added via canula) and the combined solution was stirred 1 h at 0 °C and 20 h at ambient temperature, then quenched with 10% citric acid (9 mL) and diluted with EtOAc (12 mL). The organic layer is washed with H_2O, saturated aqueous $NaHCO_3$, and brine (12 mL each), dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (3:7 hexanes : ethyl acetate) yielded 256 mg (32%) **163**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.54 (br s, 1 H), 7.96 (br s, 1 H), 7.76 (d, 3 H, J = 7.8 Hz), 7.57 (d, 2 H, J = 7.5 Hz), 7.40-7.16 (m, 7 H), 4.64-4.44 (m, 2 H), 4.25 (t, 1 H, J = 6.0 Hz), 3.85 (br s, 3 H), 3.05 (br s, 3 H).

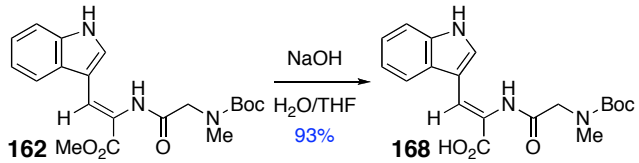




To a stirred solution of **164** (760.1 mg, 3.405 mmol) in THF (3.4 mL) at 0 °C were added isobutyl chloroformate (0.46 mL, 3.55 mmol) and *N*-methylmorpholine (0.39 mL, 3.55 mmol) and the mixture stirred 15 min at 0 °C, turning a cloudy white. A solution of **150** (699.8 mg, 3.24 mmol) in THF (3.4 mL) was added via canula and the combined solution stirred 25 h at ambient temperature, turning slowly from pale yellow to light chocolate brown. The reaction was quenched with 10% citric acid (15 mL) and diluted with EtOAc (25 mL); the organic layer was washed with H_2O, saturated aqueous $NaHCO_3$, and brine (25 mL each), then dried and evaporated to give 1.4626 g of crude product. Flash chromatography (3:7 hexanes : ethyl acetate) yielded 712.7 mg (52%) **165** as a yellowish foam. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.55 (br s, 1 H, indole NH), 7.9-7.1 (m, aromatic H), 5.18 (m, 2 H, benzyl CH_2), 4.14 (m, 2 H, amino acid CH_2), 3.84 (s, 3 H, OMe), 3.15

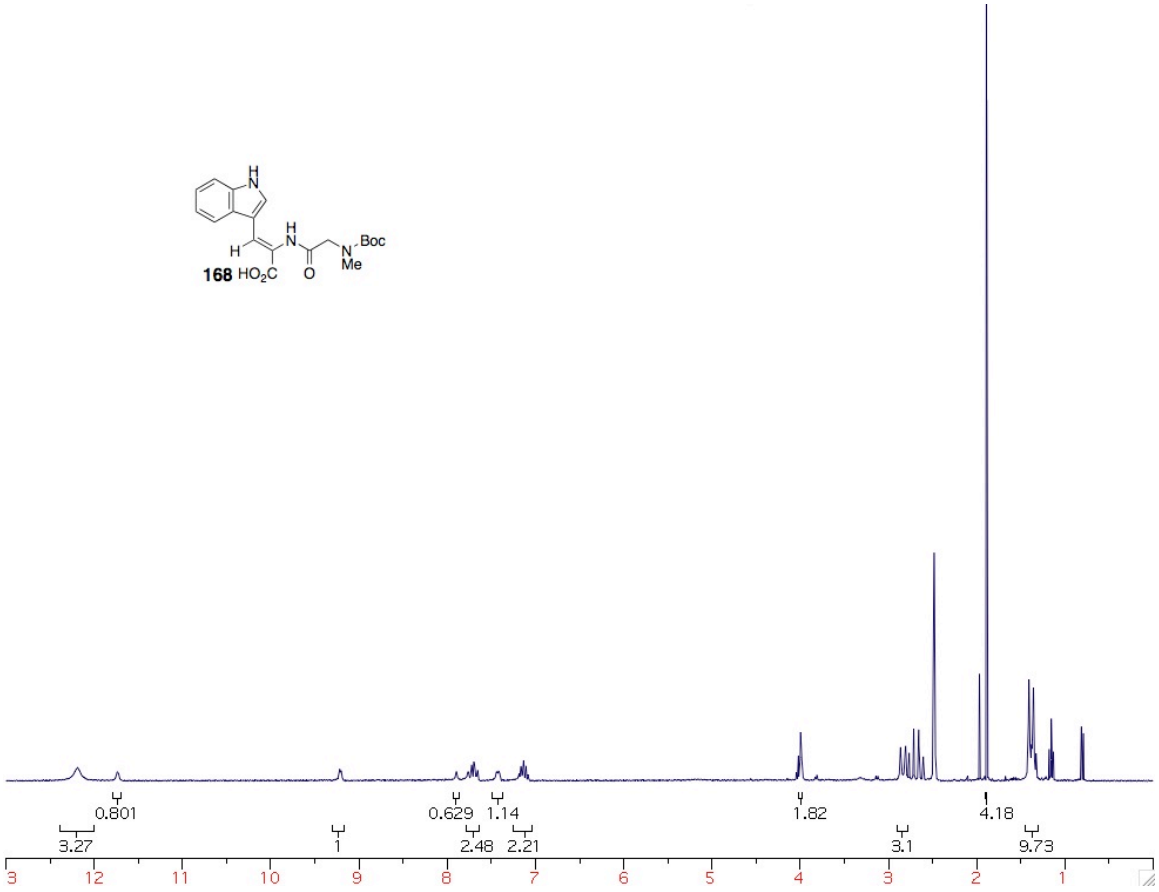
(s, 3 H, NMe). HRMS (TOF ES/APCI+) calc'd for $C_{23}H_{24}N_3O_5$ ($M+H^+$) 422.1710, found 422.1699.

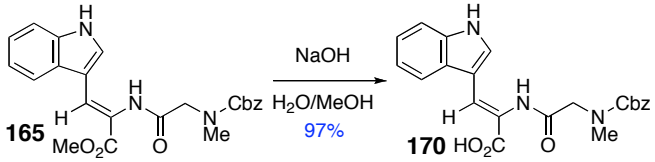




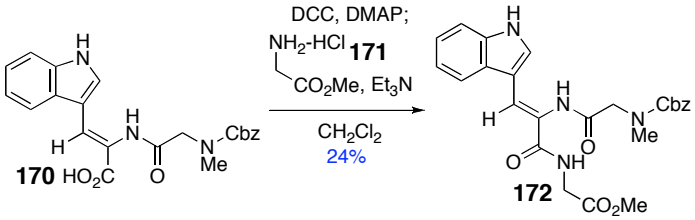
A solution of **162** (100 mg, 0.26 mmol) in 1:1 MeOH : H_2O (1 mL) was treated with NaOH (139 mg, 3.48 mmol) with stirring. The mixture was heated 20 min at 70 °C under a reflux condenser, then treated with ice (300 mg) and 10% citric acid (220 μL). The still-basic solution was diluted with H_2O (5 mL) and washed with EtOAc (10 mL), then adjusted to pH 3 (10% citric acid), producing a white precipitate. The solution was extracted with EtOAc (2 x 10 mL) and the combined organic extracts washed with brine (10 mL) and water (2 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give 95 mg pale yellow foam. The foam was dissolved in $CDCl_3$ and reconcentrated to remove remaining EtOAc, giving 91 mg (95%) of **168** as pale yellow

fine crystals. ^{1}H NMR δ (300 MHz, DMSO-d_6): 12.16 (br s, 1H), 11.74 (br s, 1H), 9.21 (br s, 1H), 7.89 (s, 1H), 7.70 (m, 3H), 7.42 (m, 1H), 7.13 (m, 2H), 3.99 (s, 2H), 2.83 (d, 3H, J = 16.8 Hz), 1.89 (s, 2H), 1.37 (m, 9H); HRMS (FAB+) calcd for $C_{19}H_{23}N_3O_5$ (*m*/*z*): 373.1638, found (*m*/*z*): 373.1638.

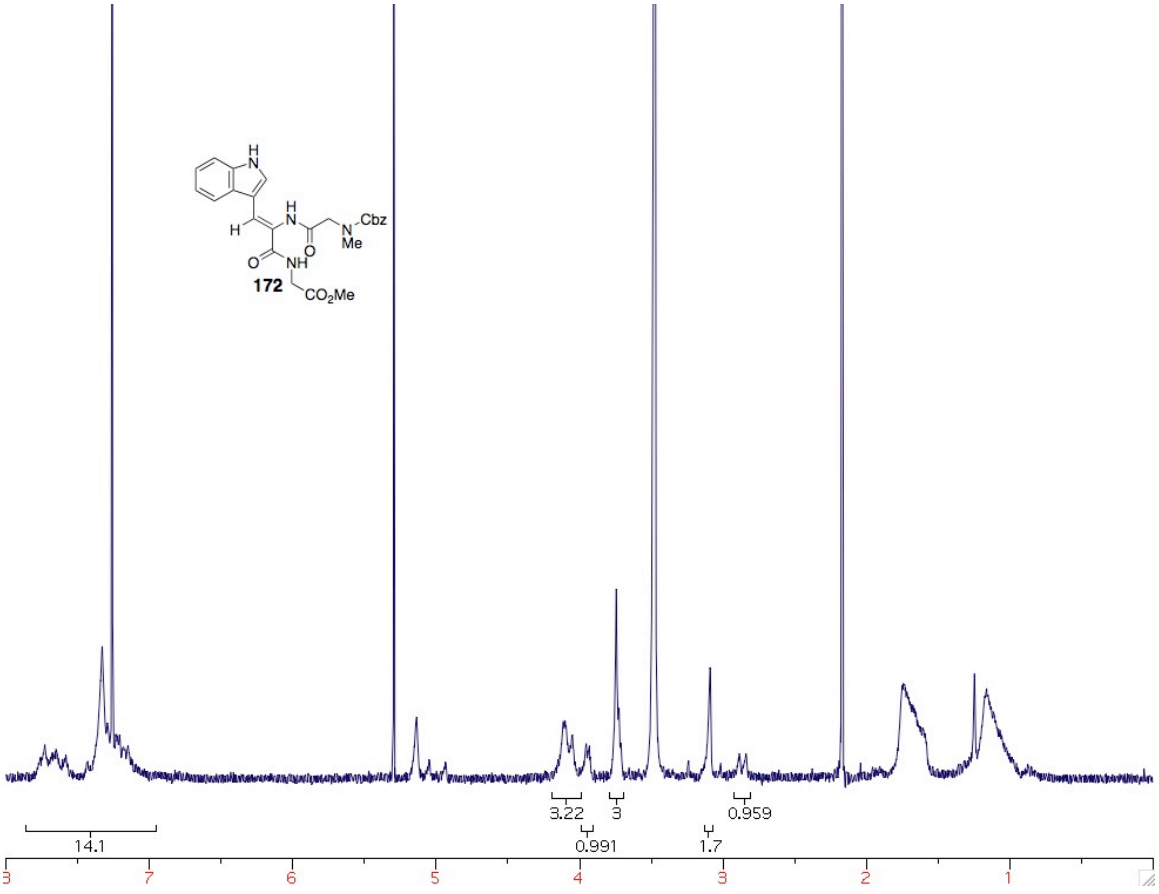


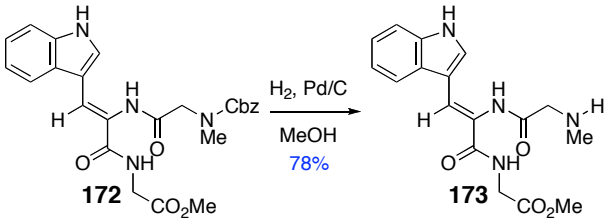


A solution of **165** (56.5 mg, 0.134 mmol) in THF (0.30 mL) was treated with 0.5 M NaOH (0.30 mL) and stirred overnight. The mixture was diluted with EtOAc and H_2O (5 mL each) and the aqueous layer adjusted to pH 3 (10% citric acid). Extraction of the acidified aqueous layer with EtOAc (2 x 5 mL) and evaporation of the acidic organic extracts gave 47.8 mg (88%) of **170** that was used without further purification.

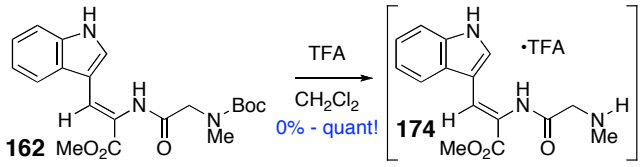


A mixture of **170** (41.2 mg, 0.101 mmol), **171** (15.3 mg, 0.122 mmol), DCC (24.1 mg, 0.117 mmol), and DMAP (1.8 mg, 0.015 mmol) in CH_2Cl_2 (0.5 mL) in a small vial was treated with Et_3N (0.02 mL, 0.14 mmol) and stirred 47 h, then filtered through cotton in a pipet and evaporated in vacuo to give 100 mg crude material. Flash chromatography (19:1 CH_2Cl_2 : MeOH) yielded 11.4 mg (24%) **172** as a colorless oil, possibly mixed with DCU. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.86-6.94 (m, 14 H), 4.20-3.90 (m, 4 H), 3.73 (m, 3 H), 3.09 (m, 2 H), 2.86 (d, 1 H, J = 7.8 Hz).

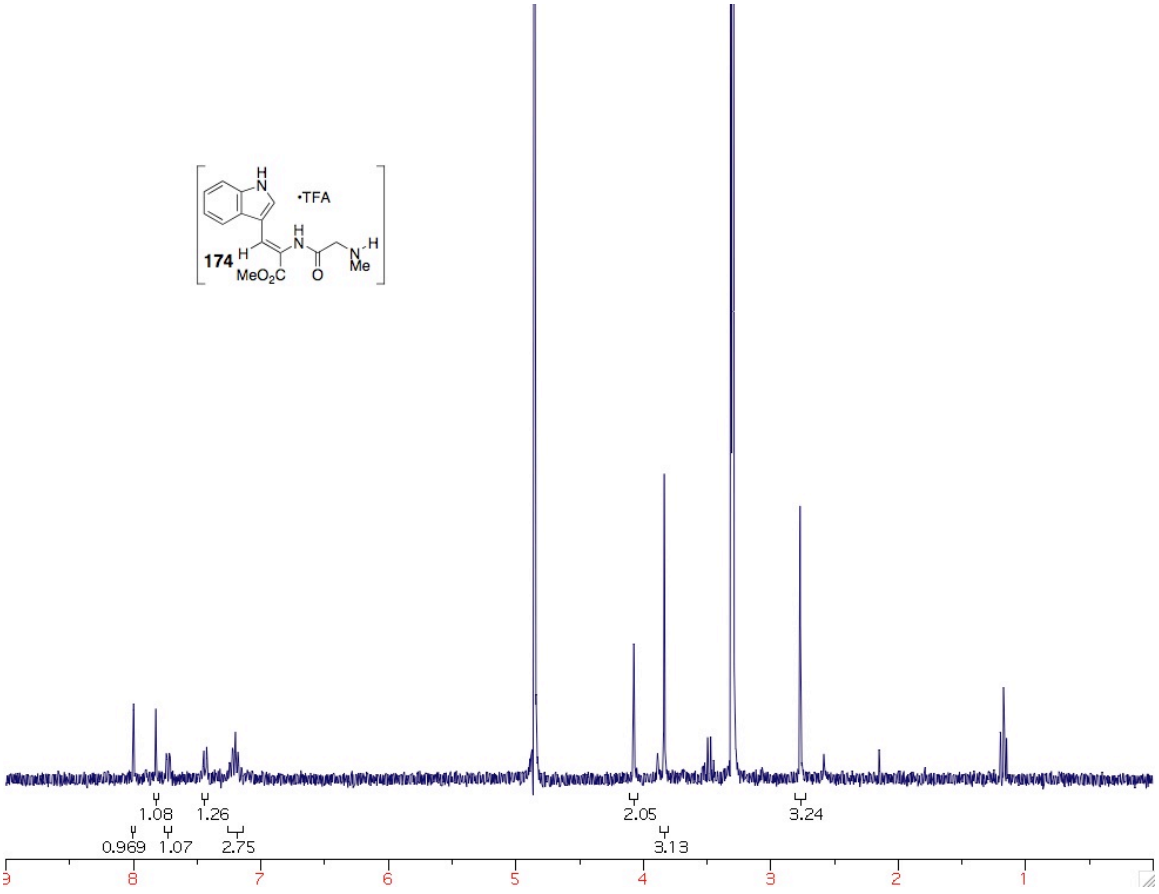


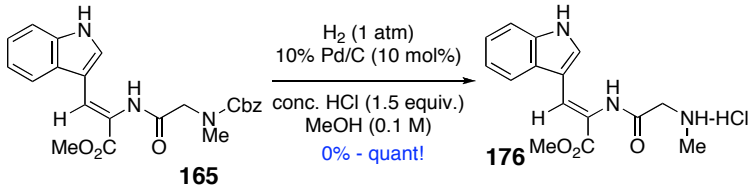


A solution of **172** (24.2 mg, 0.051 mmol) in EtOAc (1.53 mL) was treated with 5% platinum on carbon (9.9 mg, 0.0025 mmol) and fitted with a hydrogen balloon. The mixture was stirred 6 h, but TLC showed no progress. 10% palladium on carbon (5.9 mg, 0.0055 mmol) was added, the balloon was recharged, and the mixture was stirred 2.5 h, again making no progress. EtOH (1.53 mL) was added and the mixture stirred 2 h 15 min; at this point EtOAc (1.30 mL) and 10% palladium on carbon (23.6 mg, 0.022 mmol) were added and the mixture stirred 2 d 13 h. The mixture was filtered through a pad of Celite and evaporated in vacuo to give 13.6 mg (78%) **173** used without further purification.

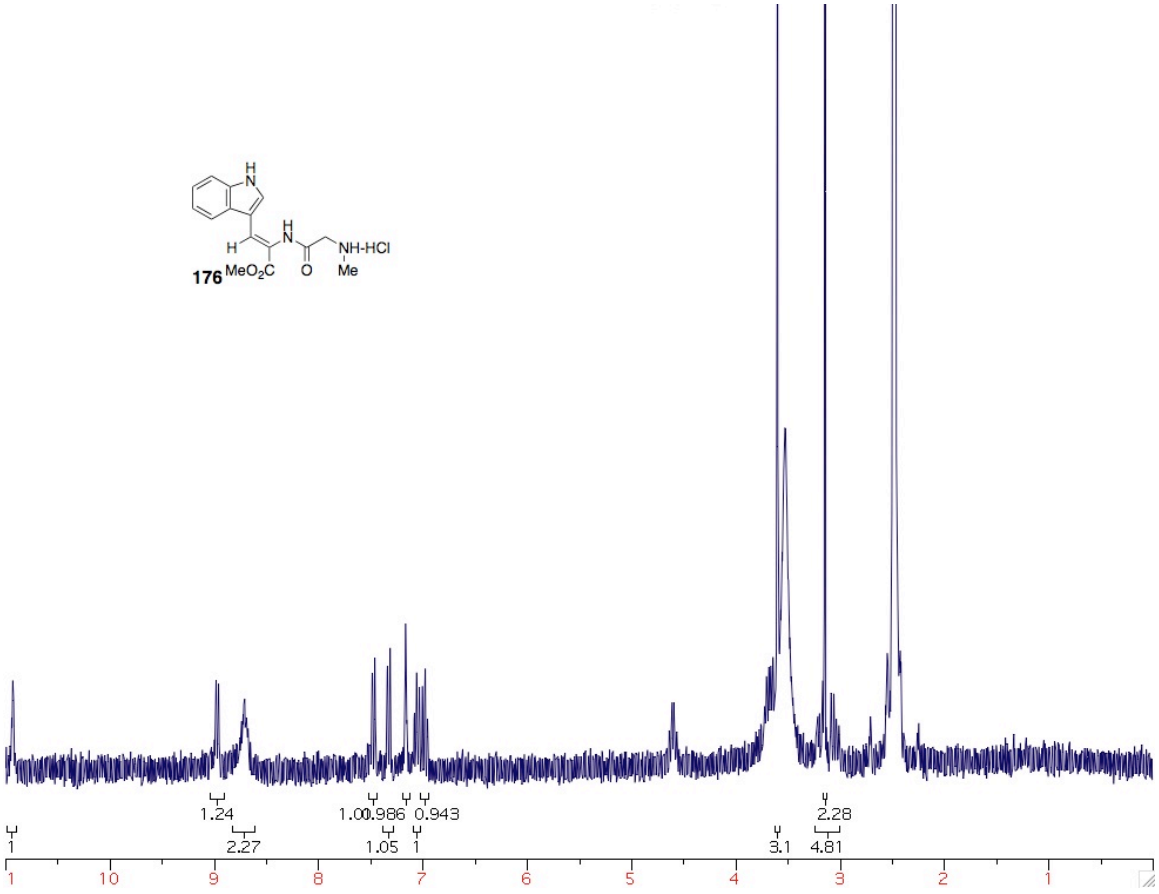


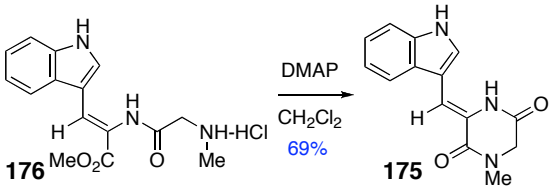
To a stirred solution of **162** (102.5 mg, 0.265 mmol) in CH_2Cl_2 (5.0 mL) in a 10-mL flame-dried round-bottom flask was added TFA (0.90 mL, 12.1 mmol) via syringe and the solution stirred 1 h, turning from brown to red. The solution was evaporated in vacuo and on hi-vac to yield 72.9 mg (96%) **174** as a red oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.00 (s, 1 H), 7.83 (s, 1 H), 7.73 (m, 1 H), 7.44 (m, 1 H), 7.2 (m, 3 H), 4.08 (s, 2 H), 3.84 (s, 3 H), 2.77 (s, 3 H).



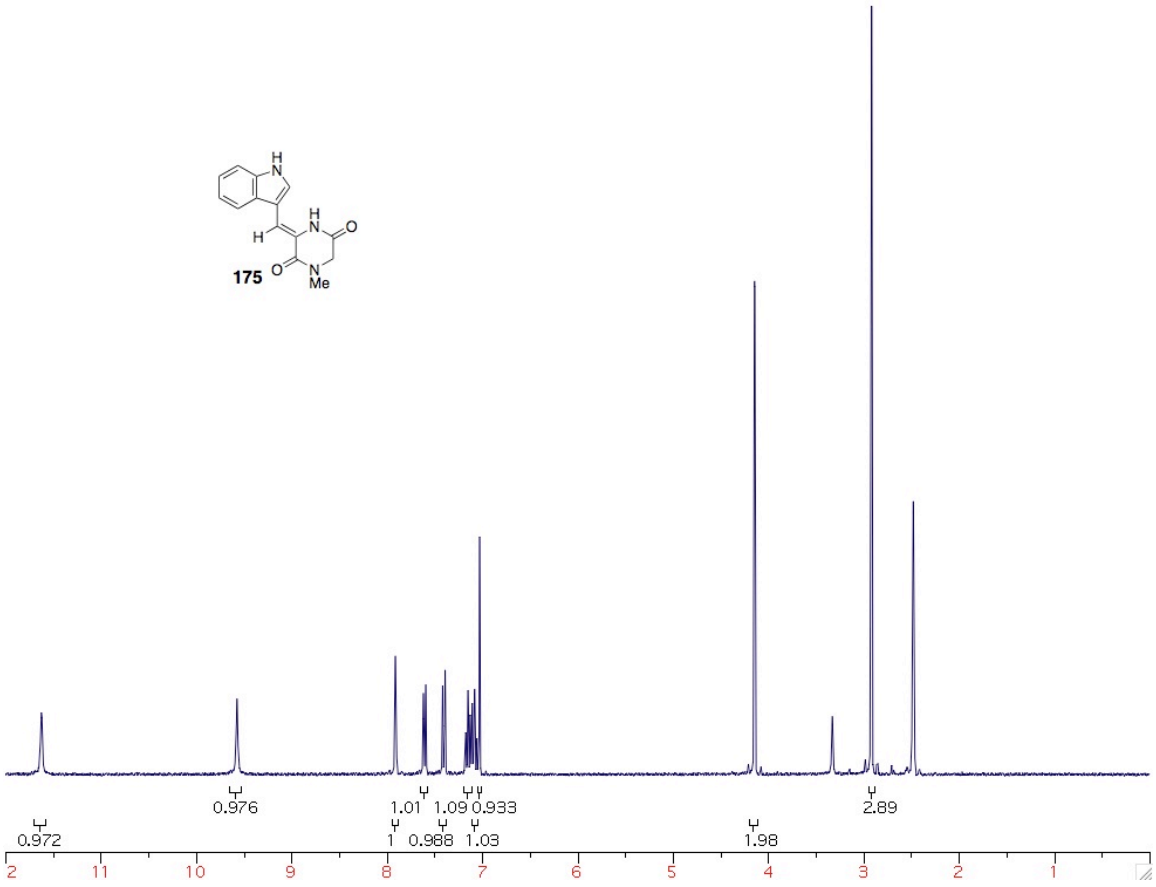


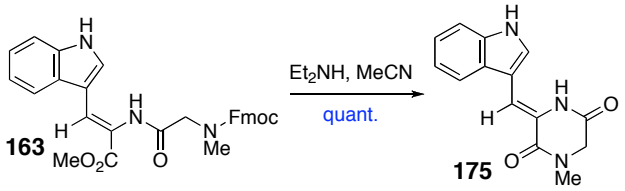
To a stirred solution of **165** (97.5 mg, 0.234 mmol) in concentrated HCl (0.03 mL) and MeOH (13 mL) was added 10% Pd/C (24.6 mg, 0.023 mmol) and the flask fitted with an H_2 balloon. The mixture was stirred 3.5 h (incomplete at 1 h), then filtered through a pad of Celite; evaporation of the filtrate yielded 84.3 mg (quant.) **176** as a sticky red foam. ^{1}H NMR δ (300 MHz, DMSO): 10.95 (s, 1 H, ind. NH), 8.97 (d, 1 H, 7.4 Hz, C-2 H), 8.71 (br s, 2 H, NH_2^+), 7.48 (d, 1 H, 7.3 Hz), 7.33 (d, 1 H, 7.8 Hz), 7.16 (m, 1 H, C=CH), 7.06 (m, 1 H, C-6 H), 6.98 (m, 1 H, C-5 H), 3.60 (s, 3 H, OMe), 3.24-3.00 (m, 2 H, CH_2), 3.15 (s, 3 H, NMe).



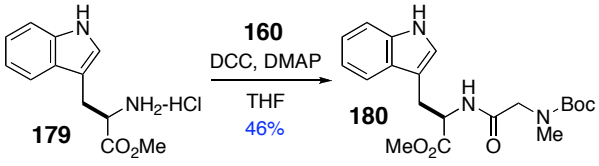


To a suspension of **176** (38.7 mg, 0.120 mmol) in CH_2Cl_2 (1.2 mL) in a small vial was added DMF (1.2 mL); once the solid dissolved, DMAP (15.0 mg, 0.123 mmol) was added and the mixture stirred 5.5 h. The solution was diluted with EtOAc (10 mL), yielding a white precipitate; shaking with saturated aqueous $NaHCO_3$ (10 mL) restored a clear solution. The aqueous layer was extracted with EtOAc (10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give a liquid; a yellow solid separated overnight from the liquid. Subjection of the mixture to hi-vac gave 21 mg (69%) **175** as a yellow solid. ^{1}H NMR δ (300 MHz, DMSO): 11.63 (s, 1 H, ind. NH), 9.58 (s, 1 H), 7.91 (d, 1 H, J = 2.7 Hz), 7.61 (d, 1 H, J = 7.5 Hz), 7.41 (d, 1 H, J = 8.1 Hz), 7.15 (m, 1 H), 7.08 (m, 1 H), 7.03 (s, 1 H), 4.15 (s, 2 H), 2.92 (s, 3 H). **HRMS**

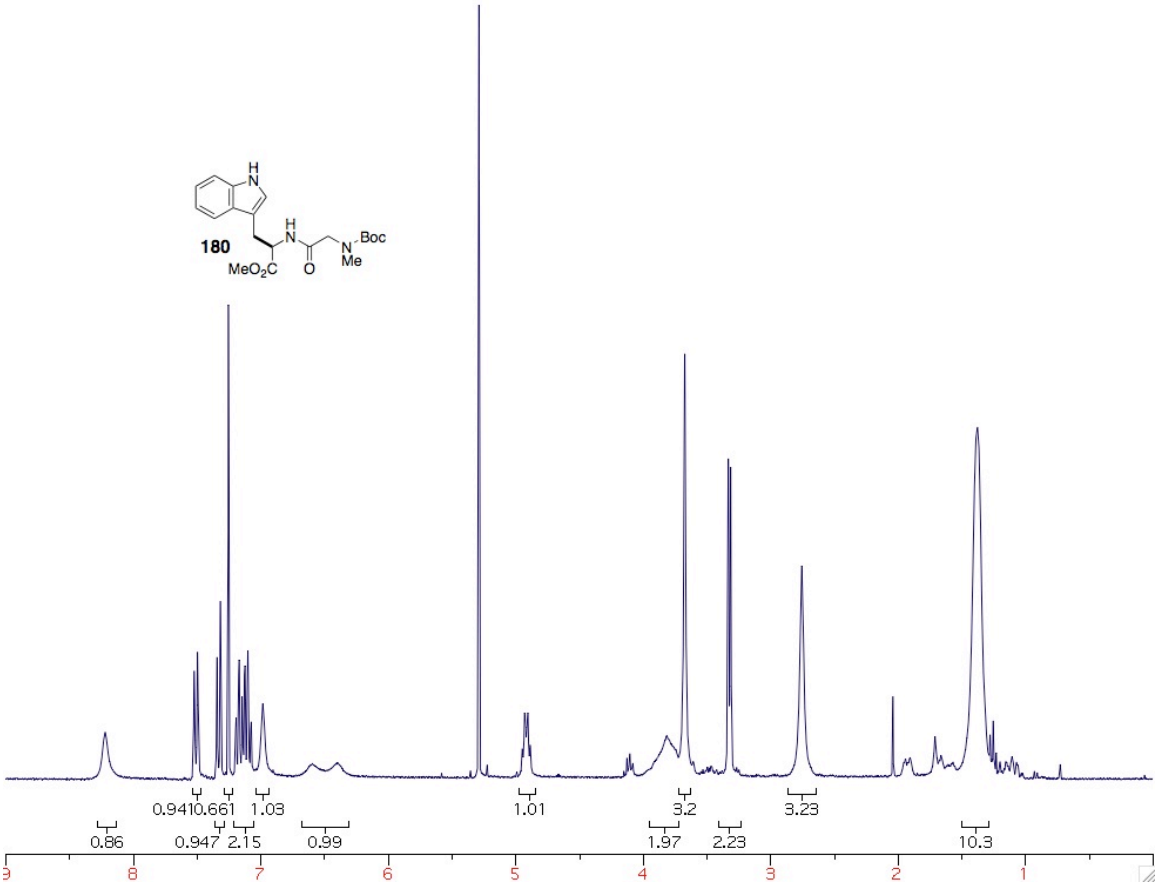


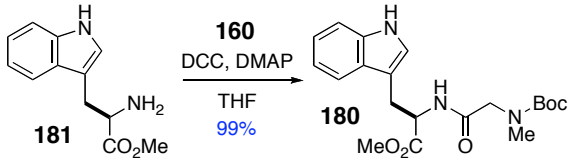


A mixture of **163** (127.9 mg, 0.251 mmol) in MeCN (5 mL) and CH_2Cl_2 (5 mL) was treated with diethylamine (0.26 mL, 2.51 mmol) and stirred 1 h, then transferred to a 25-mL round-bottom flask and evaporated in vacuo to give 115.5 mg (99%) **175** as a white powder.

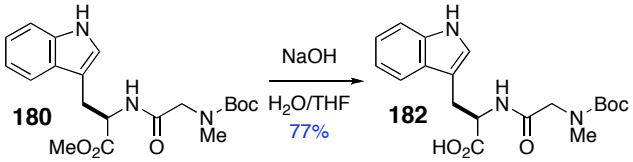


A solution of **179** (1.043 mmol, 4.1 mmol), **160** (775 mg, 4.1 mmol), DCC (930 mg, 4.5 mmol), and DMAP (50 mg, 0.41 mmol) in THF (20 mL) was stirred 18 h and diluted with CH_2Cl_2 and H_2O (30 mL each). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, 0.2 M HCl, brine, and H_2O (30 mL each), then dried (Na_2SO_4) and evaporated in vacuo to give 1.218 g of white solid. Flash chromatography (3:7 hexanes : ethyl acetate) yielded 735 mg (46%) **180** as an off-white foam mixed with needle-like crystals. R_f (3:7 hexanes : ethyl acetate) = 0.60. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.22 (br s, 1 H), 7.51 (d, 1 H, J = 7.5 Hz), 7.33 (d, 1 H, J = 7.8 Hz), 7.26 (s, 1 H), 7.20-7.08 (m, 2 H), 6.99 (br s, 1 H), 6.50 (br d, 1 H, J = 58.2 Hz), 4.92 (ABq, 1 H, J = 13.2, 5.7 Hz), 3.82 (m, 2 H), 3.68 (br s, 3 H), 3.32 (d, 2 H, J = 5.4 Hz), 2.76 (br s, 3 H), 1.37 (br s, 9 H).

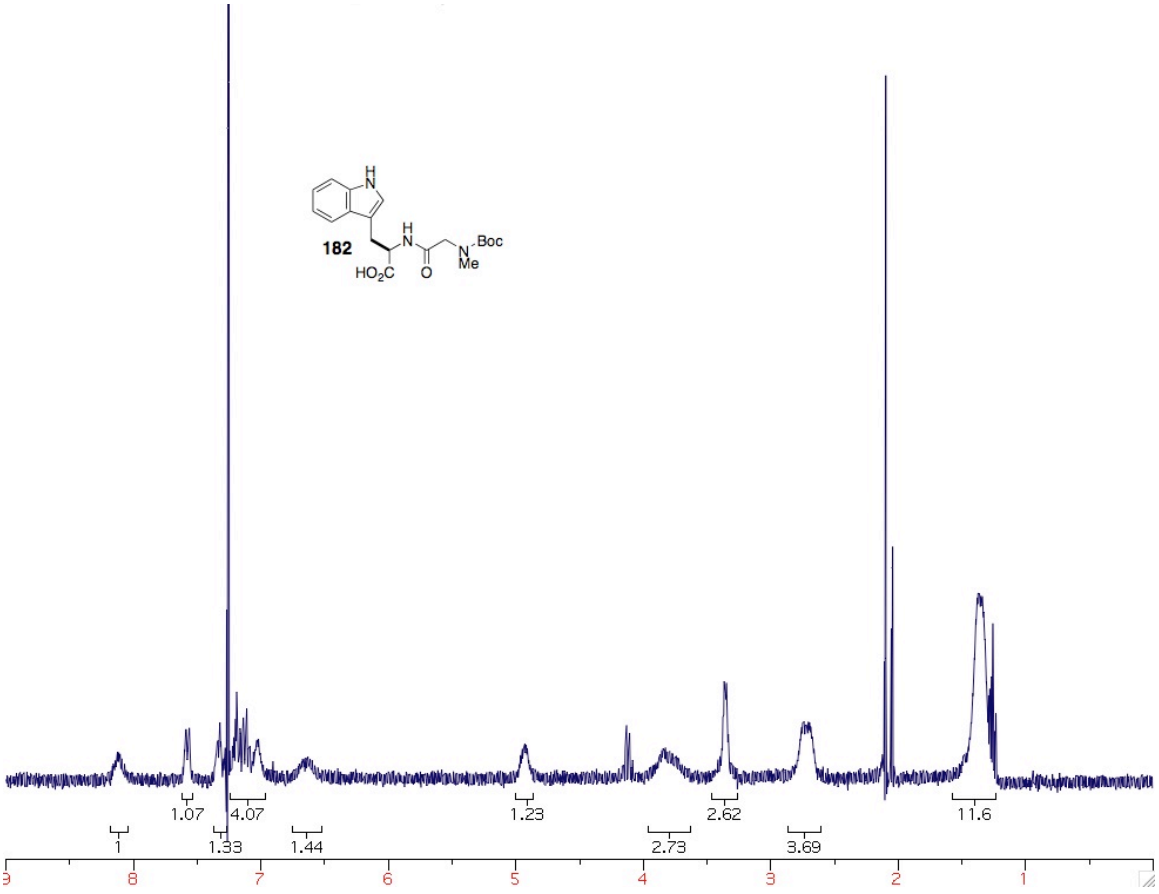


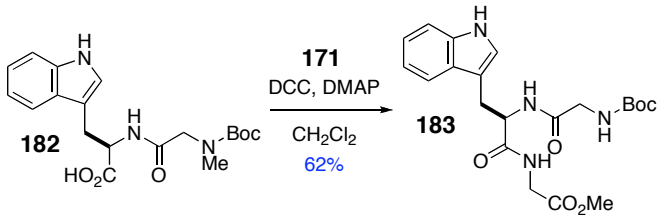


A solution of **181** (2.50 g, 11.5 mmol), **160** (2.17 g, 11.5 mmol), DCC (2.60 g, 12.6 mmol), and DMAP (140 mg, 1.15 mmol) in CH_2Cl_2 (50 mL) was stirred 15 h, then filtered in vacuo and the filter cake rinsed with CH_2Cl_2 (20 mL) to remove DCU. The organic layer was washed with 10% citric acid, H_2O, saturated aqueous $NaHCO_3$, brine, and H_2O, then dried (Na_2SO_4) and evaporated in vacuo to give 5.719 g of yellow foam. Flash chromatography (1:1 hexanes : ethyl acetate) yielded 4.4213 g (99%) of **180** as a white foam. R_f (1:1 hexanes : ethyl acetate) = 0.24.



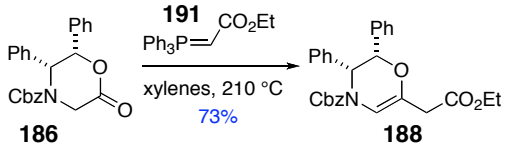
To a stirred solution of **180** (525.8 mg, 1.35 mmol) in THF (8 mL) was added a solution of NaOH (64 mg, 1.6 mmol) in H_2O (4 mL) and the combined solution stirred 2 h 10 min at ambient temperature, then poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was washed with Et_2O (3 x 10 mL) and adjusted to pH 3 (10% citric acid), then extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give 389 mg (77%) **182** as a white solid. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.13 (br s, 1 H), 7.57 (d, 1 H, J = 8.1 Hz), 7.32 (m, 1 H), 7.24-6.97 (m, 3 H), 6.63 (br s, 1 H), 4.93 (m, 1 H), 3.84 (m, 2 H), 3.35 (m, 2 H), 2.72 (br s, 3 H), 1.36 (br s, 9 H).



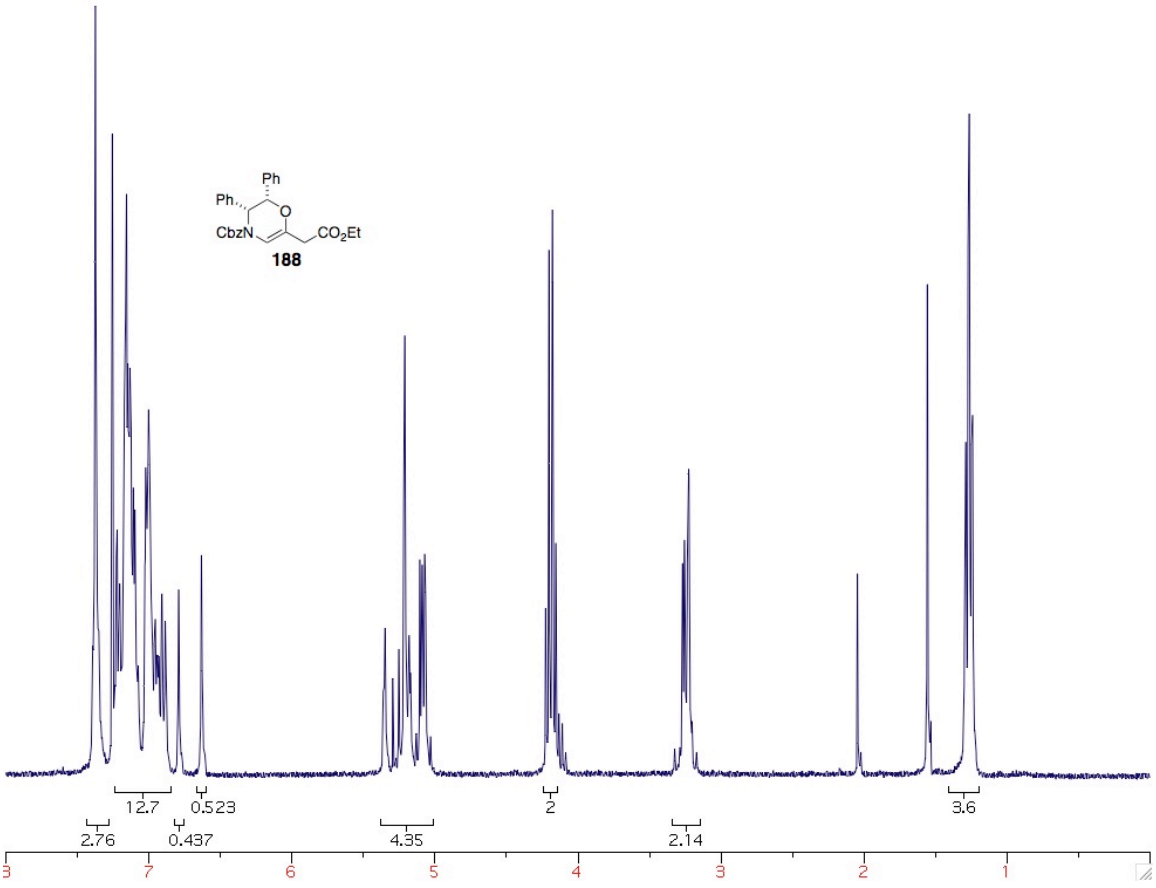


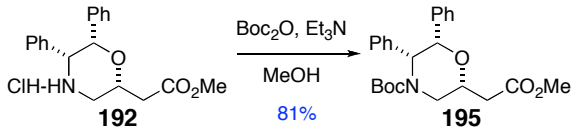
A solution of **182** (206.5 mg, 0.55 mmol), **171** (69.0 mg, 0.55 mmol), DCC (124.8 mg, 0.60 mmol), and DMAP (79.2 mg, 0.61 mmol) in CH_2Cl_2 (5.0 mL) was stirred 13 h and filtered in vacuo; the filtrate was evaporated in vacuo to give 306 mg of pale yellow foam. Flash chromatography (3:7 hexanes : ethyl acetate) yielded 151.5 mg (62%) **183** as an off-white foam.

CMB537 (HRMS?)



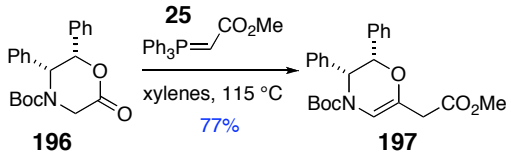
A mixture of **186** (1.90 g, 4.90 mmol) and **191** (4.30 g, 12.3 mmol) in xylenes (15 mL) was refluxed 3 h at 210 °C. The resultant solution was evaporated in vacuo and dissolved in CH_2Cl_2 (40 mL); the organic solution was washed with H_2O (40 mL), dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 1.64 g (73%) **188** as a viscous yellow oil. R_f (7:3 hexanes : ethyl acetate) = 0.58. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.43-6.59 (m, 17 H), 5.41-4.99 (m, 4 H), 4.19 (q, 2 H, J = 7.2 Hz), 3.29-3.17 (m, 2 H), 1.27 (dt, 3 H, J = 7.2, 2.4 Hz).



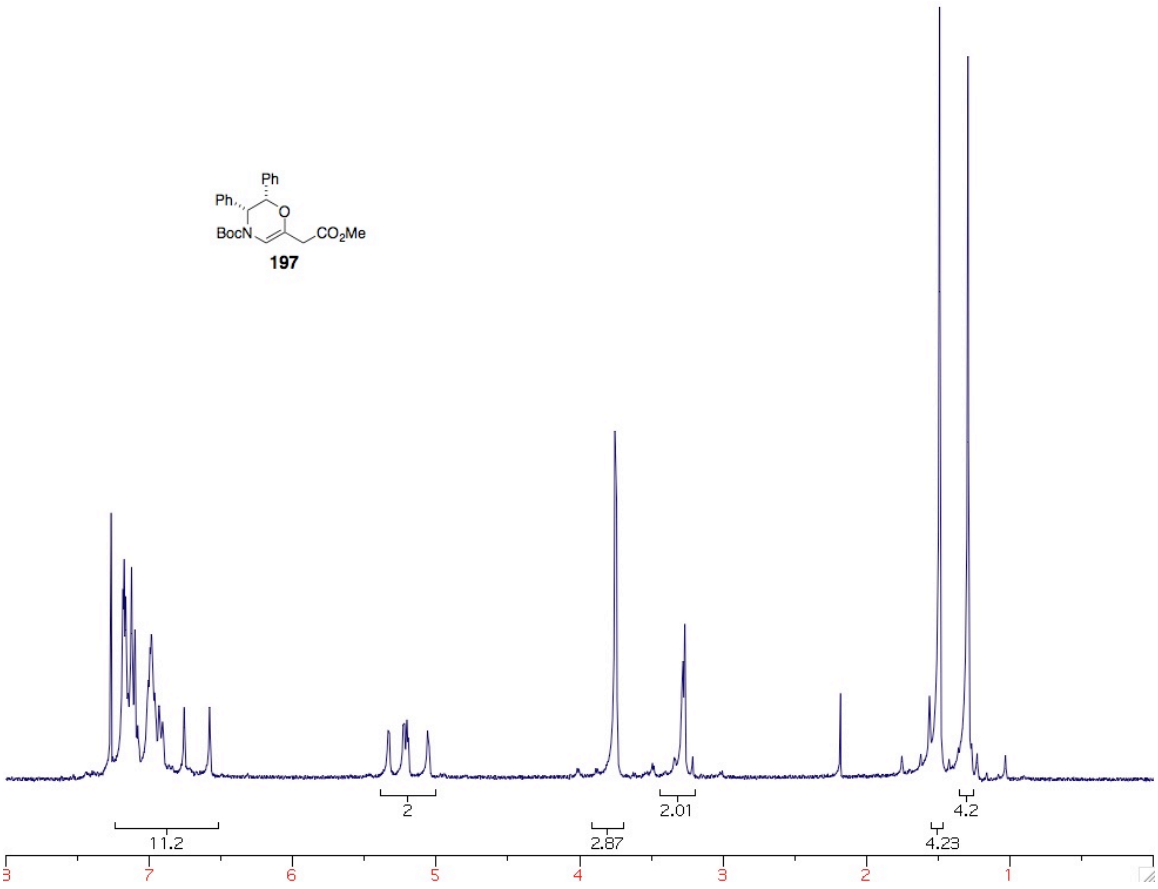


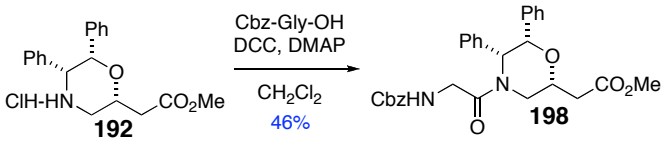
A solution of **192** (1.172 g, 3.24 mmol) and Et_3N (0.5 mL, 3.59 mmol) in MeOH (4.5 mL) was treated with Boc_2O (1.43 g, 6.55 mL) under vigorous stirring. The mixture solidified after 10 min, so MeOH and H_2O (5 mL each) were added and the solution stirred 30 min at 55 °C and 30 min at ambient temperature. The solution was evaporated in vacuo at 40 °C to give 2.065 g of whitish powder that was partitioned between EtOAc (300 mL) and H_2O (100 mL); the organic layer was dried (Na_2SO_4), filtered, and evaporated in vacuo to yield 1.123 g (81%) **195** as a whitish solid.

CMB193 (HRMS?)

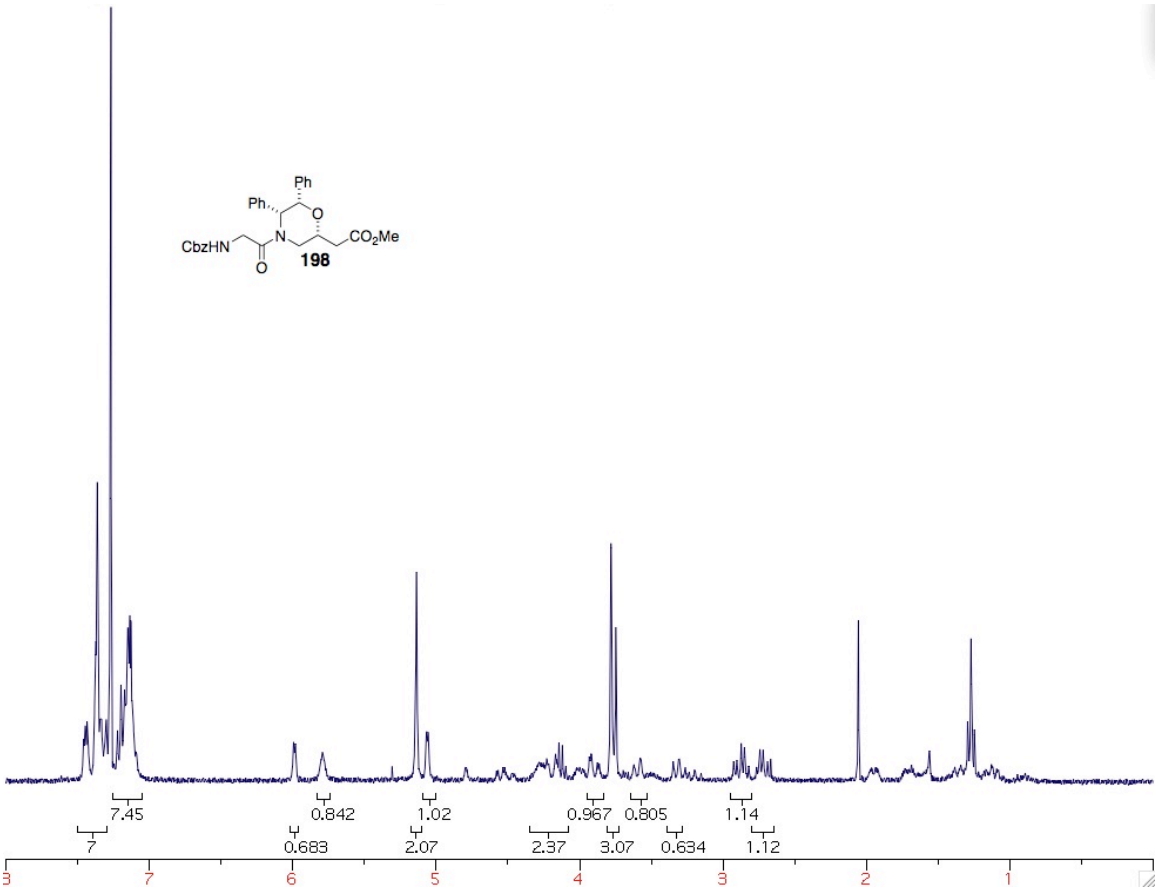


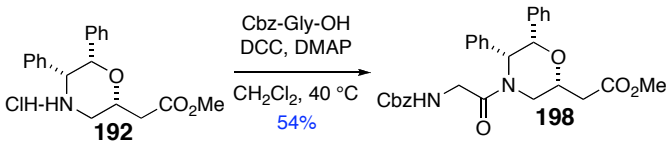
A solution of **196** (200.6 mg, 0.57 mmol) and **25** (378.5 mg, 1.13 mmol) in PhMe (2 mL) was heated 48 h at 115 °C. The resultant solution was evaporated in vacuo, dissolved in CH_2Cl_2, and washed with H_2O, then dried (Na_2SO_4) and evaporated in vacuo. Flash chromatography yielded 178 mg (77%) **197** as a pale yellow oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.32-6.55 (m, 11 H), 5.38-5.01 (m, 2 H), 3.75 (s, 3 H), 3.35-3.20 (m, 2 H), 1.49 + 1.29 (Boc rotamers, 9 H).



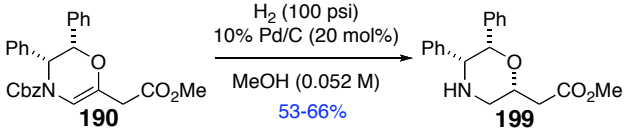


A mixture of **192** (87.0 mg, 0.25 mmol), Cbz-glycine (52.3 mg, 0.25 mmol), DCC (51.6 mg, 0.25 mmol), and DMAP (61.1 mg, 0.50 mmol) in CH_2Cl_2 (1.0 mL) was stirred 60 h and filtered in vacuo. Flash chromatography (1:1 hexanes : ethyl acetate) yielded 58 mg (46%) **198** as a white powder with tiny crystals. R_f (1:1 hexanes : ethyl acetate) = 0.49. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.47-7.06 (m, 15 H), 5.99 (d, 1 H, J = 3.6 Hz), 5.79 (br s, 1 H), 5.14 (s, 2 H), 5.06 (d, 1 H, J = 3.0 Hz), 4.37-4.08 (m, 2 H), 3.91 (m, 1 H), 3.78 + 3.75 (rotameric OMe), 3.60 (m, 1 H), 3.32 (m, 1 H), 2.88 (1/2ABqd, 1 H, J = 15.9, 6.6 Hz), 2.71 (1/2ABqd, 1 H, J = 15.9, 6.6 Hz). HRMS (FAB+) calcd. for $C_{29}H_{31}N_2O_6$ ($M+H^+$) (*m*/*z*): 503.2182, found (*m*/*z*): 503.2184.



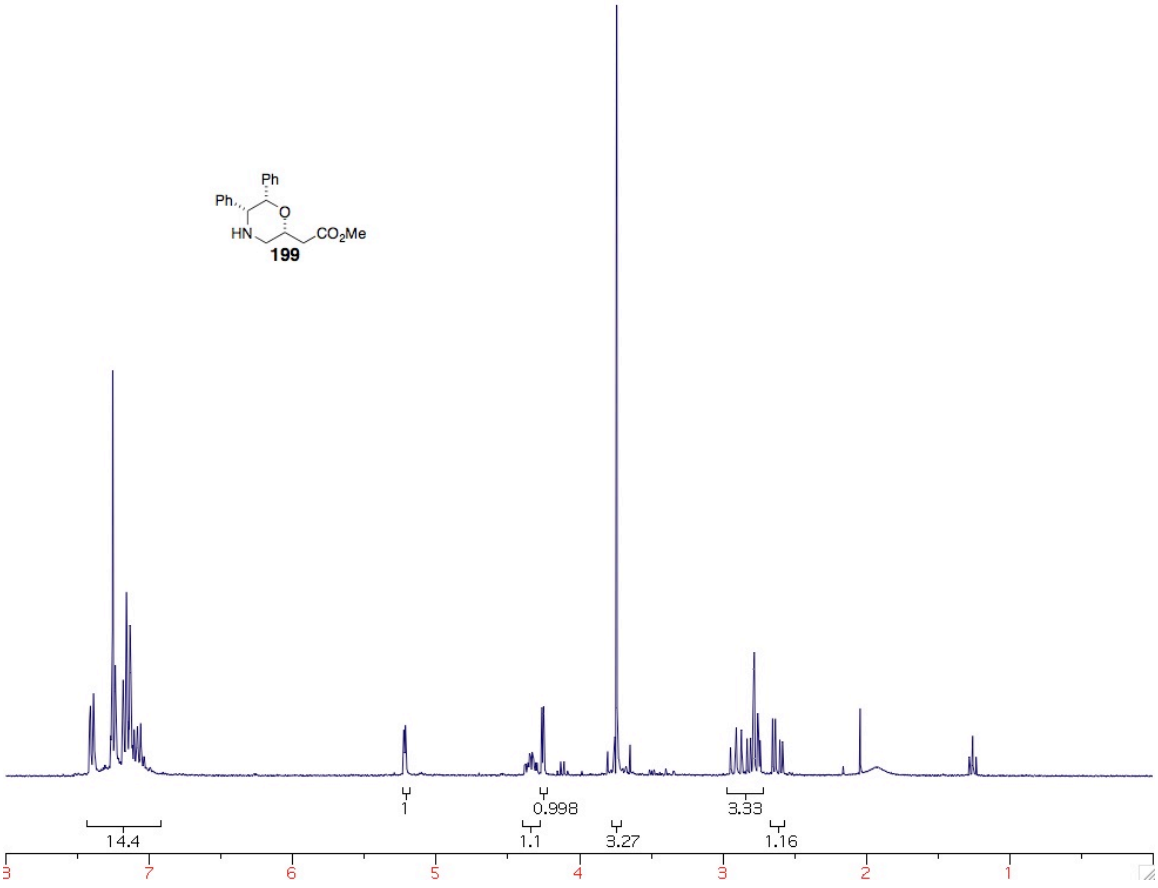


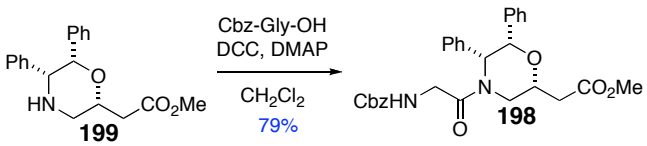
A mixture of **192** (173.9 mg, 0.5 mmol), Cbz-glycine (104.6 mg, 0.5 mmol), DCC (111.3 mg, 0.54 mmol), and DMAP (123.5 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was stirred 24 h at 40 °C under a reflux condenser. The mixture was filtered in vacuo and the filtrate evaporated. Flash chromatography (1:1 hexanes : ethyl acetate) yielded 138 mg (55%) **198** as white crystals.



A 3-oz. hydrogenation vessel was charged with a solution of **190** (10.43 g, 23.5 mmol) in MeOH (108 mL) and flushed 5 minutes with Ar. 10% Pd/C (3.7544 g, 3.52 mmol) was

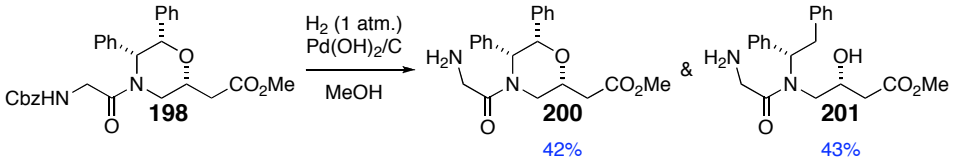
added portionwise and the pressure head fitted. The vessel was charged to 100 psi H_2 and stirred 24 h at ambient temperature, filtered through a pad of Celite, and evaporated under reducted pressure to give 7.34 g of yellow oil. Flash chromatography (19:1 CH_2Cl_2 / MeOH) yielded 5.90 g (81%) **199** as a reddish-orange oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.43-7.01 (m, 10 H), 5.22 (d, 1 H, J = 3.0 Hz), 4.34 (m, 1 H), 4.26 (d, 1 H, J = 3.3 Hz), 3.74 (s, 3 H), 2.96-2.74 (m, 3 H), 2.62 (1/2ABqd, 1 H, J = 15.3, 5.7 Hz). HRMS (FAB+) calcd. for $C_{19}H_{22}NO_3$ ($M+H^+$) (*m*/*z*): 312.1600, found (*m*/*z*): 312.1590.





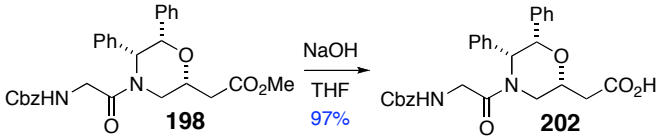
To a solution of Cbz-glycine (3.1180 g, 14.9 mmol) and **199** (4.73 g, 15.2 mmol) in CH_2Cl_2 (77 mL) were added DCC (3.4479 g, 16.7 mmol) and DMAP (188.6 mg, 1.54 mmol). The resultant solution was stirred 7 d and filtered; the filtrate was evaporated in

vacuo to give 8.78 g of yellow-orange oil. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 5.909 g (79%) **198** as a yellowish foam.

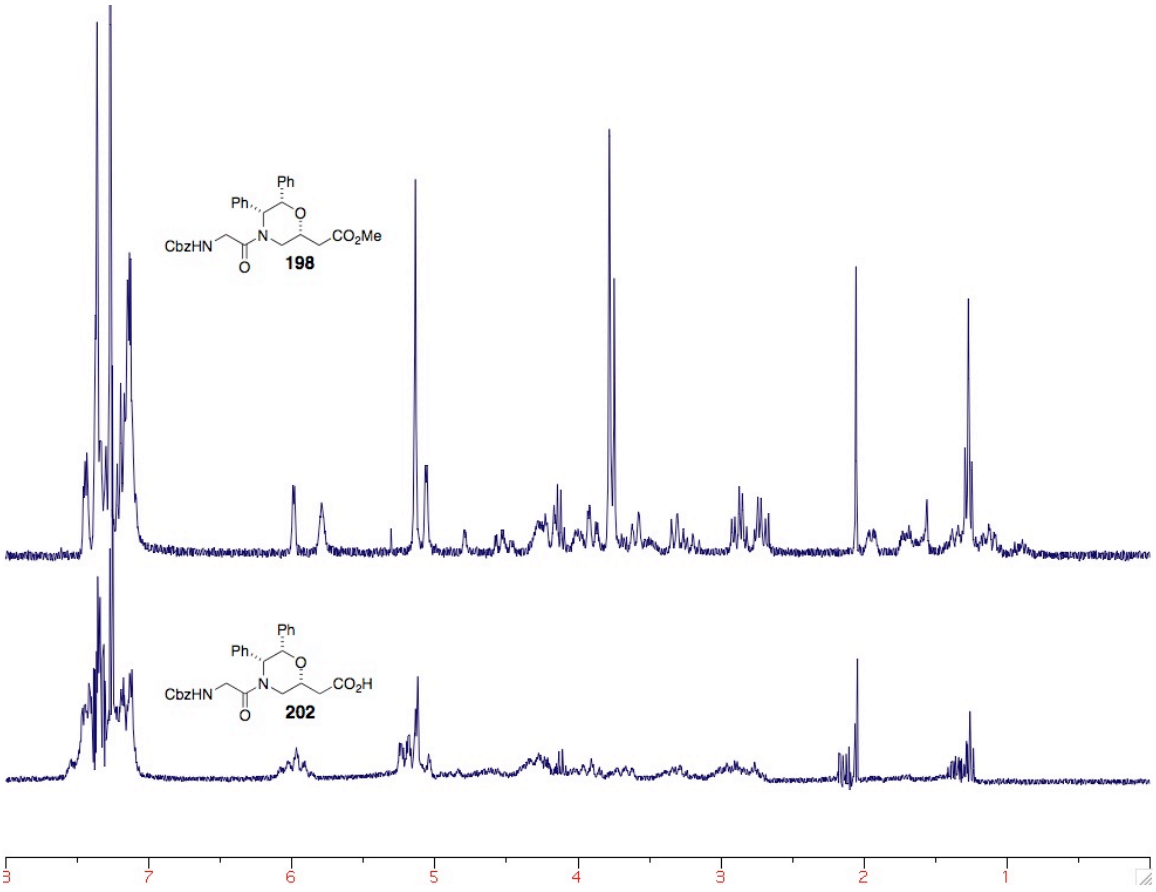


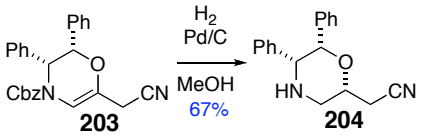
To a solution of **198** (248 mg, 0.49 mmol) in MeOH (3.5 mL) was added 20% $Pd(OH)_2/C$ (68.2 mg, 0.13 mmol) and H_2 bubbled through for 5 min. The solution was stirred under an H_2 balloon for 20 h (with the needle extending into the solution), then filtered through a pad of Celite that was rinsed with MeOH (10 mL). The filtrate was evaporated in vacuo, redissolved in PhMe, and re-evaporated in vacuo to give 178.7 mg of colorless crystals. Flash chromatography (9:1 CH_2Cl_2 : MeOH) yielded 75 mg (42%) of **200** and 78 mg (43%) of **201**, both showing contamination with $Ph_3P=O$. R_f (9:1 CH_2Cl_2 : MeOH) = 0.62 (**200**), 0.43 (**201**).

CMB482A (200), B (201) v. CMB266 (198)

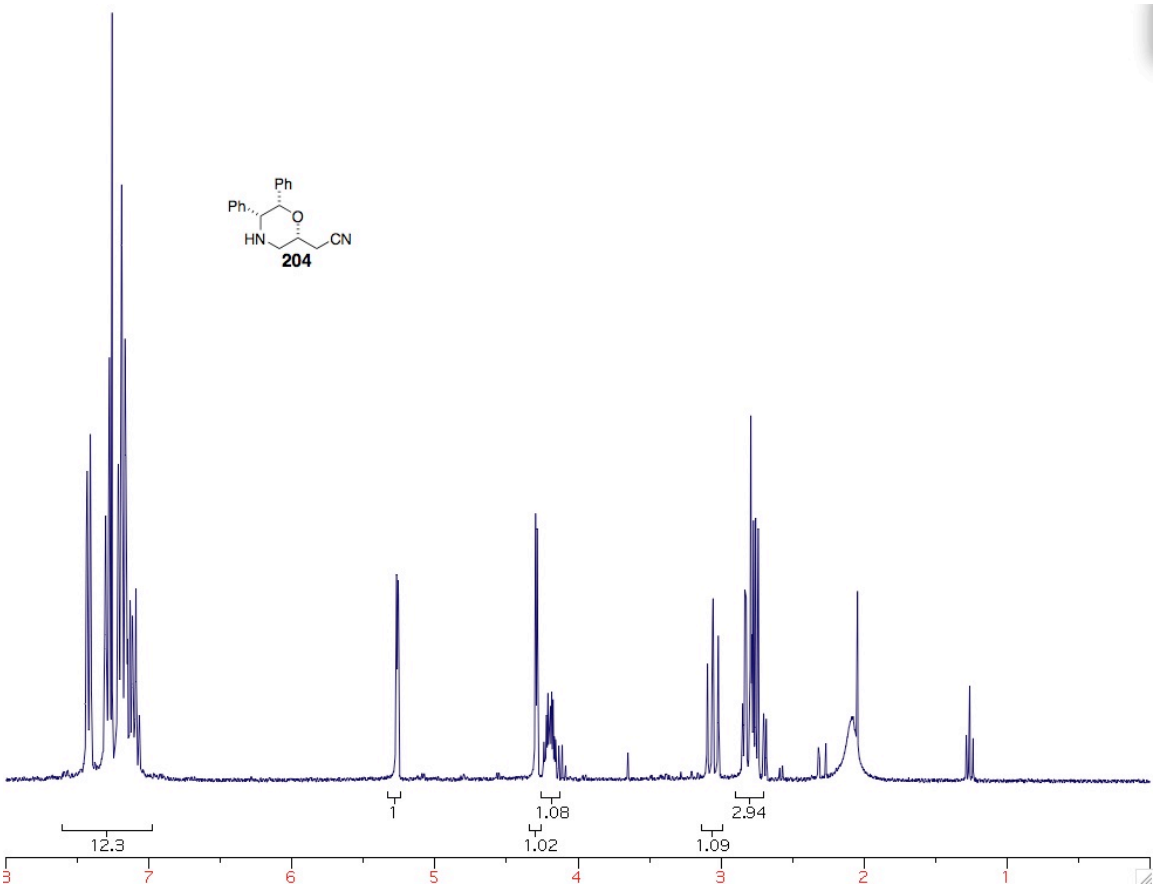


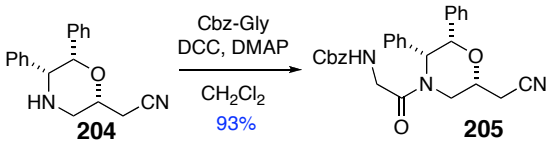
To a stirred solution of **198** (2.2948 g, 4.57 mmol) in THF (27.5 mL) in a 100-mL round-bottom flask was added 0.5 M NaOH (14.0 mL, 7.0 mmol). The resultant solution was stirred 16 h and diluted with H_2O (50 mL), then washed with Et_2O (50 mL). The aqueous portion was adjusted to pH 3 (10% citric acid) and extracted with EtOAc (2 x 50 mL); the combined EtOAc extracts were dried (Na_2SO_4) and evaporated to yield 1.683 g (75%) **202** as a yellow foam used without further purification.



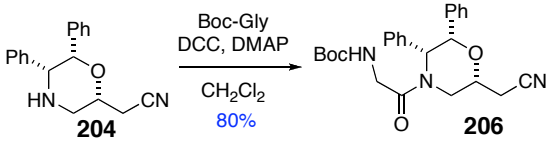


A solution of **203** (1.2119 g, 2.95 mmol) in MeOH (15 mL) was added to a 3-oz hydrogenation tube containing a stir bar; 10% Pd/C (0.47 g, 0.44 mmol) was added and Ar bubbled through the mixture for 10 min. A leak caused burns on hand during initial H_2 fill, so the seals were replaced and the flask charged with H_2 (100 psi). The mixture was stirred 24 h, then vented, and Ar was bubbled through the mixture for 10 min; the mixture was then filtered through a pad of Celite and evaporated in vacuo to give a red oil. Flash chromatography (99:1 CH_2Cl_2 : MeOH) yielded 548.5 mg (67%) **204** as a dark yellow foam. R_f (99:1 CH_2Cl_2 : MeOH) = 0.33. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.49-7.03 (m, 10 H), 5.26 (d, 1 H, J = 3.3 Hz), 4.29 (d, 1 H, J = 3.3 Hz), 4.20 (m, 1 H), 3.06 (m, 1 H), 2.87-2.71 (m, 3 H). **IR?**

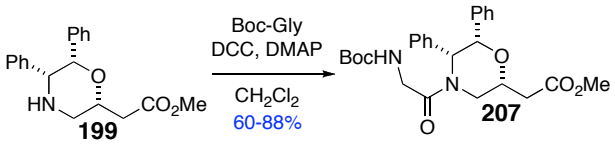




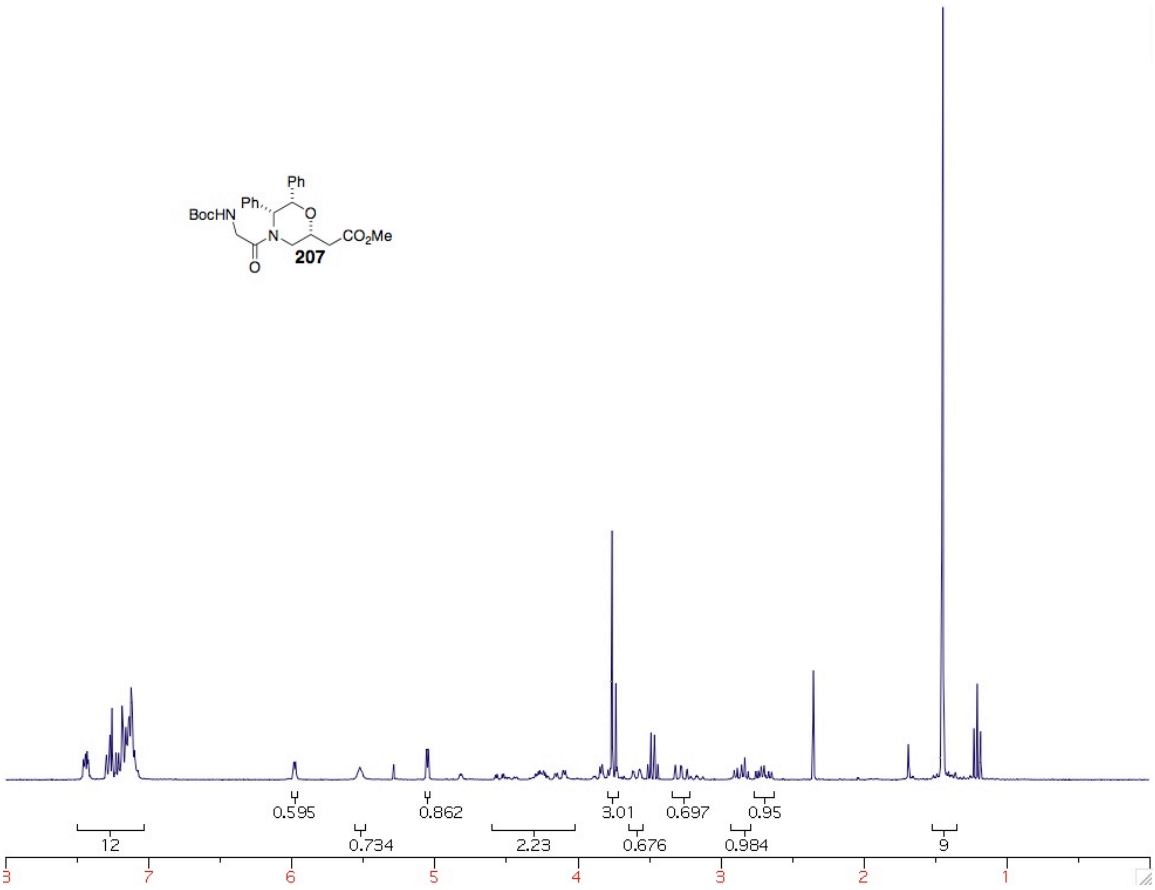
A 25-mL flame-dried round-bottom flask was charged with Cbz-glycine (412.2 mg, 1.97 mmol), DCC (447.2 mg, 2.17 mmol), DMAP (24.7 mg, 0.20 mmol), and a stir bar; a solution of **204** (548.5 mg, 1.97 mmol) in CH_2Cl_2 (8.0 mL) was added via canula and the solution stirred 3.5 h, then filtered in vacuo. The filtrate was evaporated in vacuo to give 1.0436 g of crude material; flash chromatography (1:1 hexanes : ethyl acetate) yielded 858.3 mg (93%) **205** as a pale yellow foam. R_f (1:1 hexanes : ethyl acetate) = 0.38.

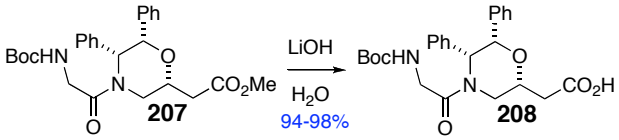


A solution of Boc-glycine (76.3 mg, 0.436 mmol), **204** (121.2 mg, 0.435 mmol), DCC (99.0 mg, 0.48 mmol), and DMAP (5.4 mg, 0.044 mmol) in CH_2Cl_2 (3.5 mL) was stirred 3 h 50 min and filtered in vacuo; the filtrate was evaporated in vacuo to give 230.4 mg of colorless solid. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 151.6 mg (80%) **206** as colorless crystals. R_f (7:3 hexanes : ethyl acetate) = 0.44.

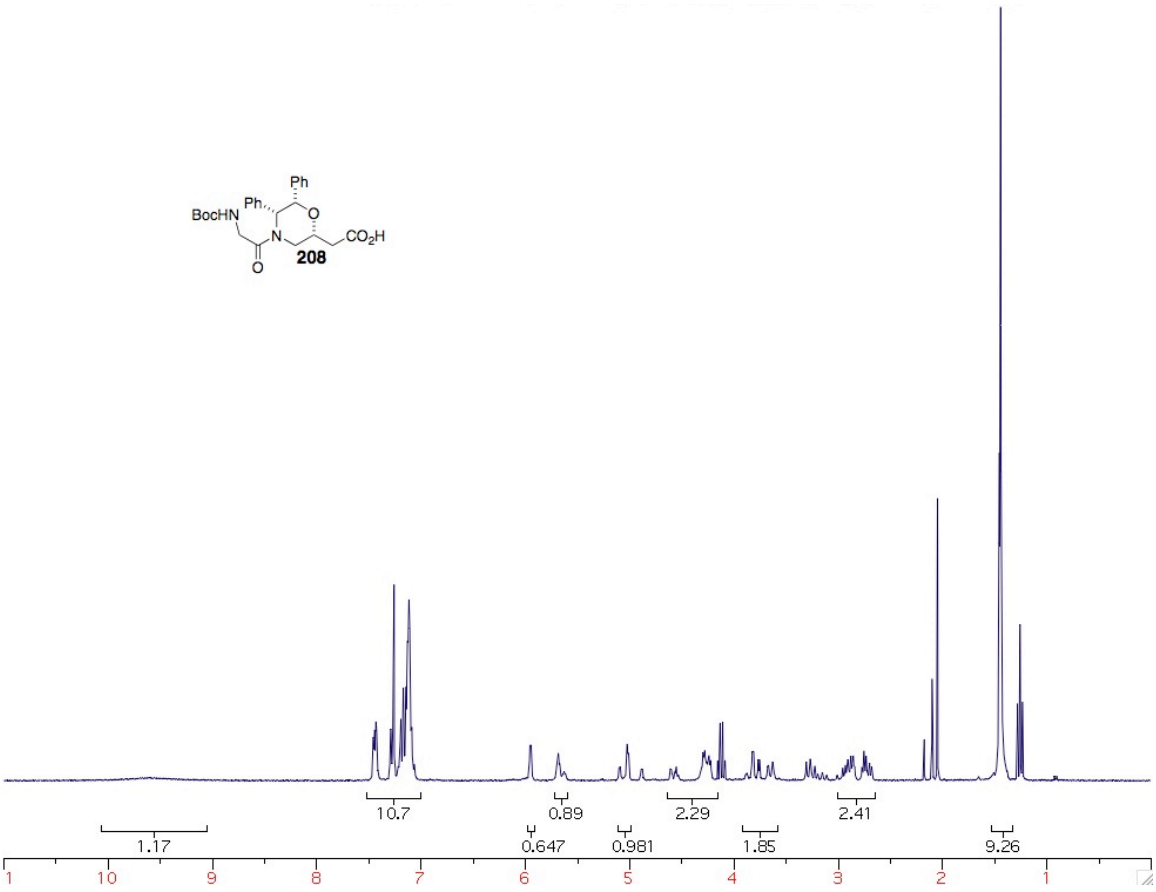


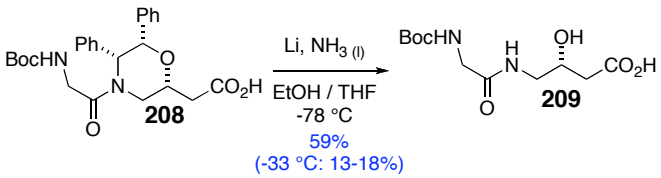
A solution of Boc-glycine (1.8611 g, 10.6 mmol), **199** (2.9550 g, 9.49 mmol), DCC (2.41 g, 11.7 mmol), and DMAP (129.9 mg, 1.00 mmol) in CH_2Cl_2 (53 mL) in a 100-mL round-bottom flask was stirred 20 h at ambient temperature and filtered; the filtrate was evaporated to give 5.5 g of yellow oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 3.924 g (88%) **207** as a white foam. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.48-7.07 (m, "18 H"), 5.98 (d, 1 H, 3.5 Hz), 5.56-5.48 (m, 1 H), 5.05 (d, 1 H, 3.6 Hz), 4.59-4.06 (m, 2 H), 3.76-3.73 (m, 3 H), 3.62-3.56 (m, 1 H), 3.32-3.24 (m, 1 H), 2.93-2.79 (m, 1 H), 2.77-2.63 (m, 1 H), 1.45 (m, 9 H).





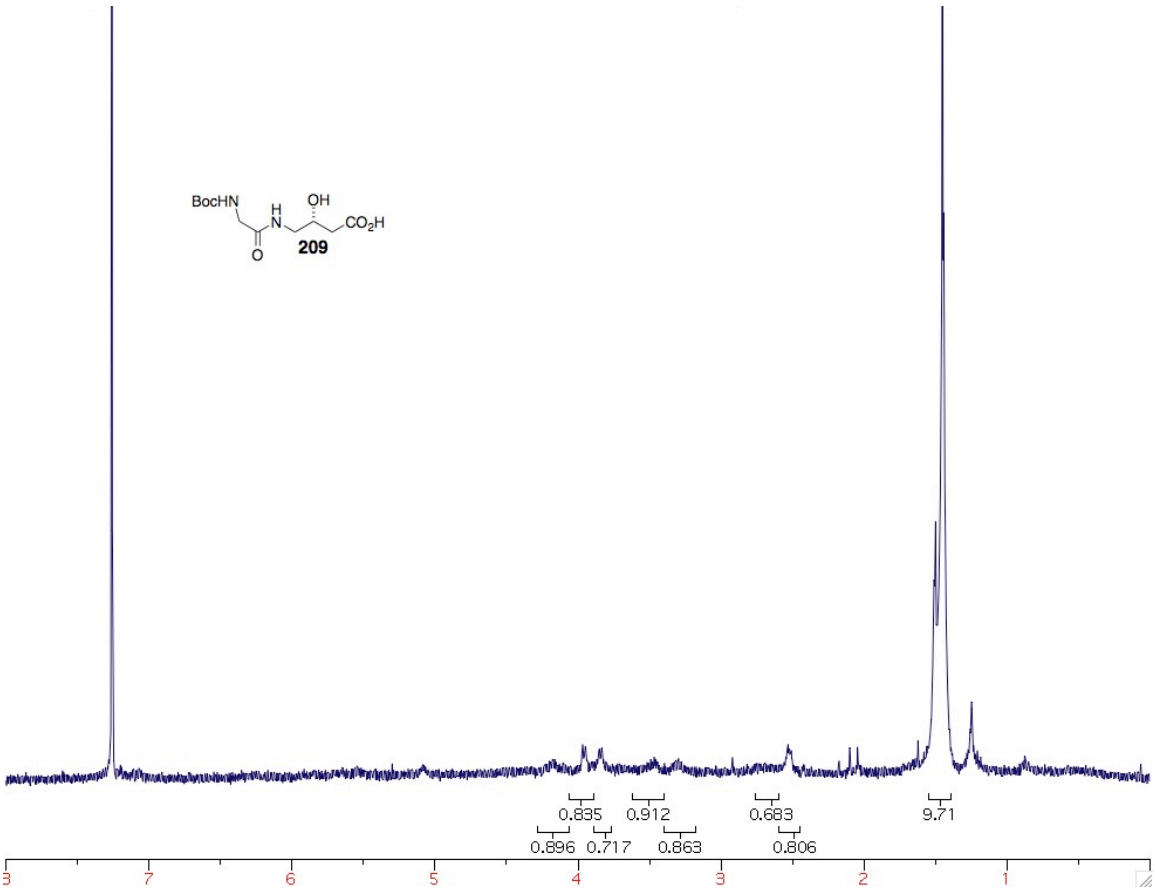
A solution of **207** (3.924 g, 8.37 mmol) in 0.5 M aqueous NaOH (26 mL) and THF (52 mL) was stirred 16 h at ambient temperature and diluted with CH_2Cl_2 and H_2O (100 mL each); the aqueous layer was adjusted to pH 3 (10% citric acid) and extracted with EtOAc (3 x 75 mL). The combined acidic organic extracts were dried (Na_2SO_4) and evaporated to yield 2.3347 g (61%) **208** as a white foam. ^{1}H NMR δ (300 MHz, $CDCl_3$): 9.63 (br s, 1 H), 7.50-7.05 (m, 10 H), 5.96 (d, 1 H, 3.5 Hz), 5.73-5.59 (m, 1 H), 5.02 (d, 1 H, 3.3 Hz), 4.63-4.19 (m, 2 H), 3.91-3.60 (m, 2 H), 3.10-2.66 (m, 2 H), 1.49-1.44 (m, 9 H).

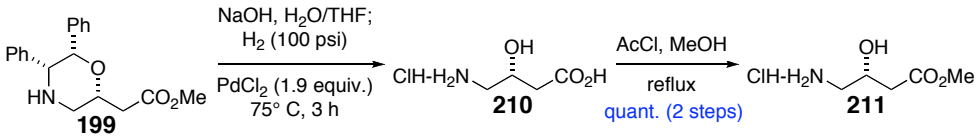




A 50-mL two-necked round-bottom flask was charged with Li (92 mg, 6.0 mmol), cooled to -78 °C and fitted with a -78 °C condenser, and charged with liquid NH_3 (25 mL) condensed directly from a cylinder. To this stirred solution was added a solution of **208** (227.3 mg, 0.500 mmol) and EtOH (0.35 mL) in THF (2.4 mL) via canula; the solution was stirred 45 min, with the blue color disappearing after 20 min. The reaction was quenched (solid NH_4Cl) and allowed to warm to ambient temperature; the flask was allowed to stir open to air for NH_3 evaporation and the residue dissolved in H_2O and EtOAc (25 mL each). The aqueous layer was washed with Et_2O (25 mL), adjusted to pH 3 (10% citric acid), and extracted with EtOAc (3 x 25 mL); the combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to yield 82 mg (59%) **209** as a colorless oil.

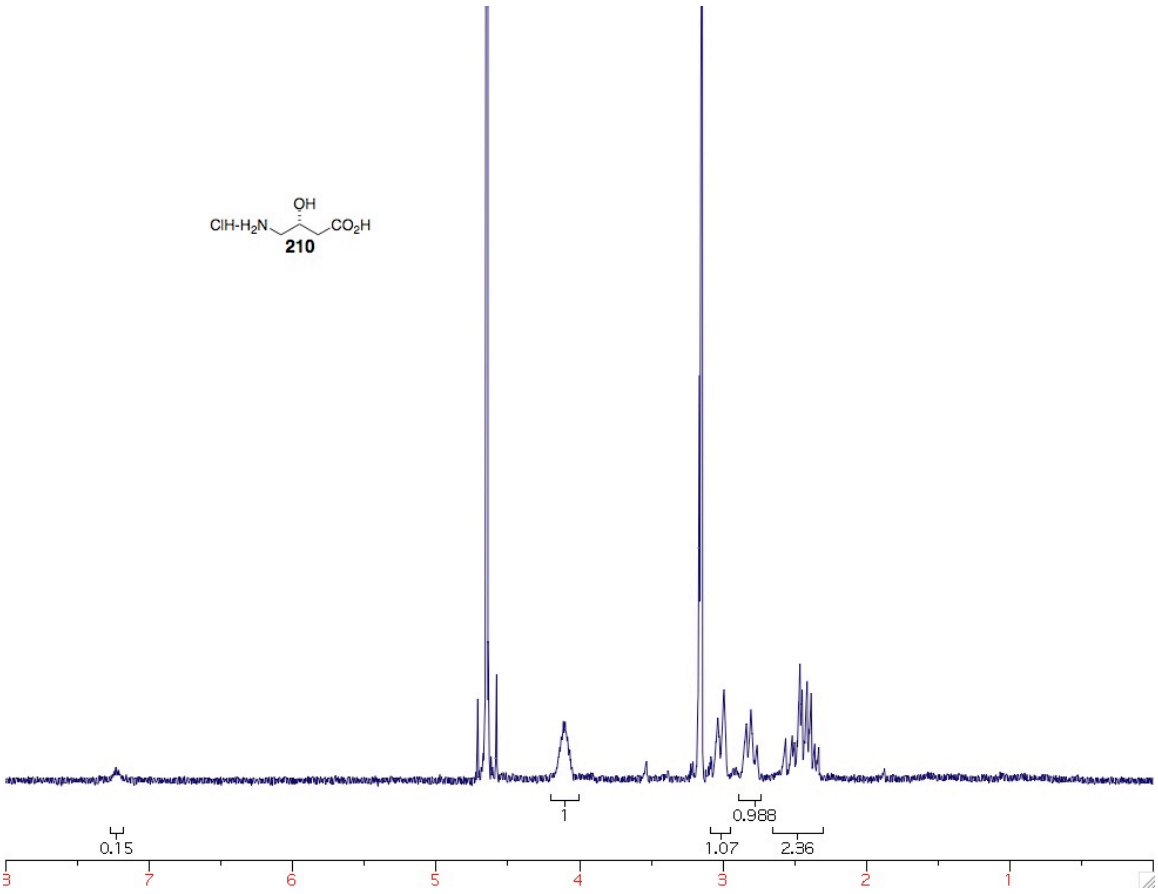
^{1}H NMR δ (300 MHz, $CDCl_3$): 4.19 (m, 1 H, CH-OH), 3.96 & 3.85 (m, 2 H, Boc-Gly α), 3.48 & 3.30 (m, 2 H, γ to acid), 2.82-2.55 (m, 2 H, α to acid), 1.46 (s, 9 H). HRMS (FAB+) calcd. for $C_{11}H_{21}N_2O_6$ ($M+H^+$) (*m*/*z*): 277.1400, found (*m*/*z*): 277.1396.





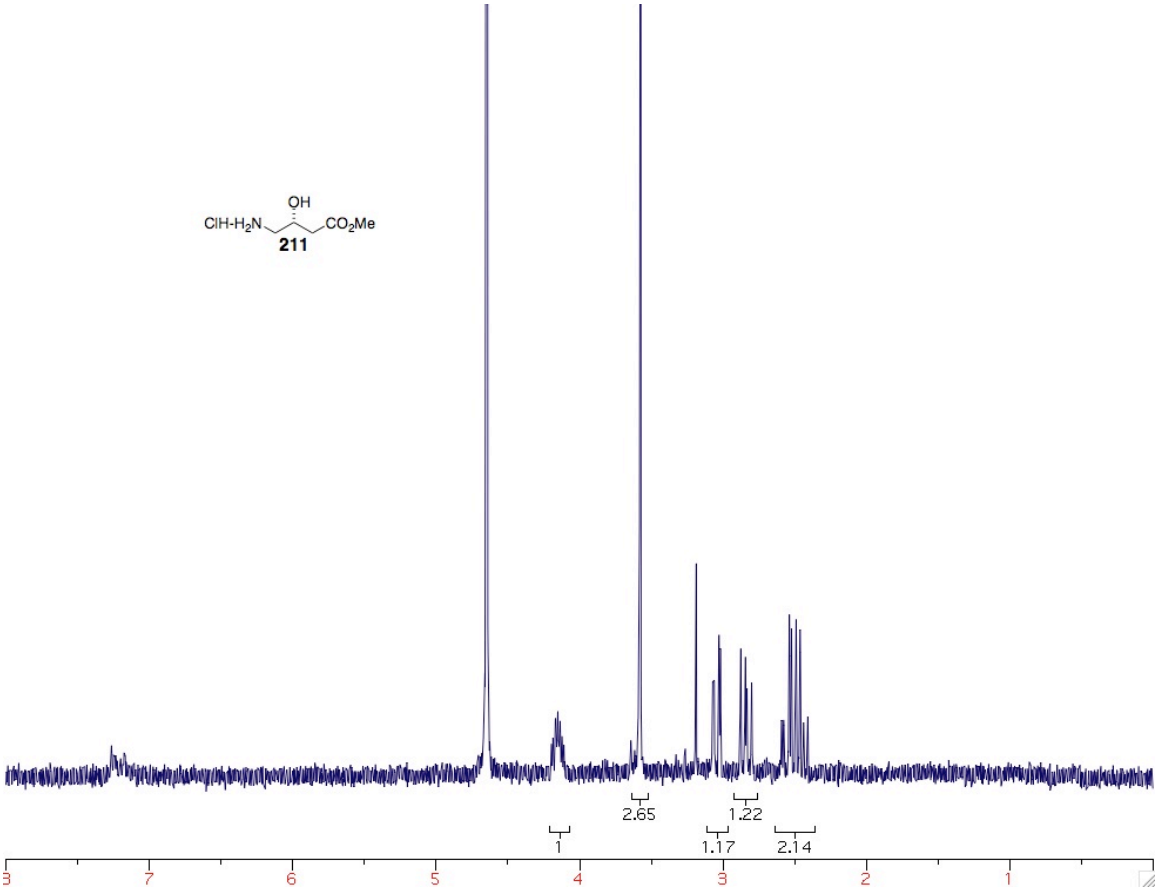
A solution of **199** (964.6 mg, 3.10 mmol) in 1 M NaOH (15.5 mL) and THF (56 mL) was stirred 10 h, then adjusted to pH 7 (1 M HCl) and diluted with H_2O (27 mL). The solution was transferred to a pressure vessel and flushed with Ar for 5 minutes, then charged with $PdCl_2$ (1.05 g, 5.92 mmol) and pressurized to 100 psi H_2. The mixture was stirred 3 h at 75-80 °C, producing a sparkling precipitate in the top layer, then cooled and filtered through a pad of Celite. The filtrate was concentrated at 60 °C and the residue evaporated from toluene, then triturated from Et_2O to give ~1.4 g of sticky white solid consisting of

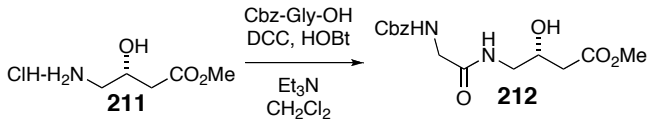
210 admixed with salts. ^{1}H NMR δ (300 MHz, D_2O): 4.10 (m, 1 H), 3.02 (m, 1 H), 2.81 (m, 1 H), 2.6-2.3 (m, 2 H).



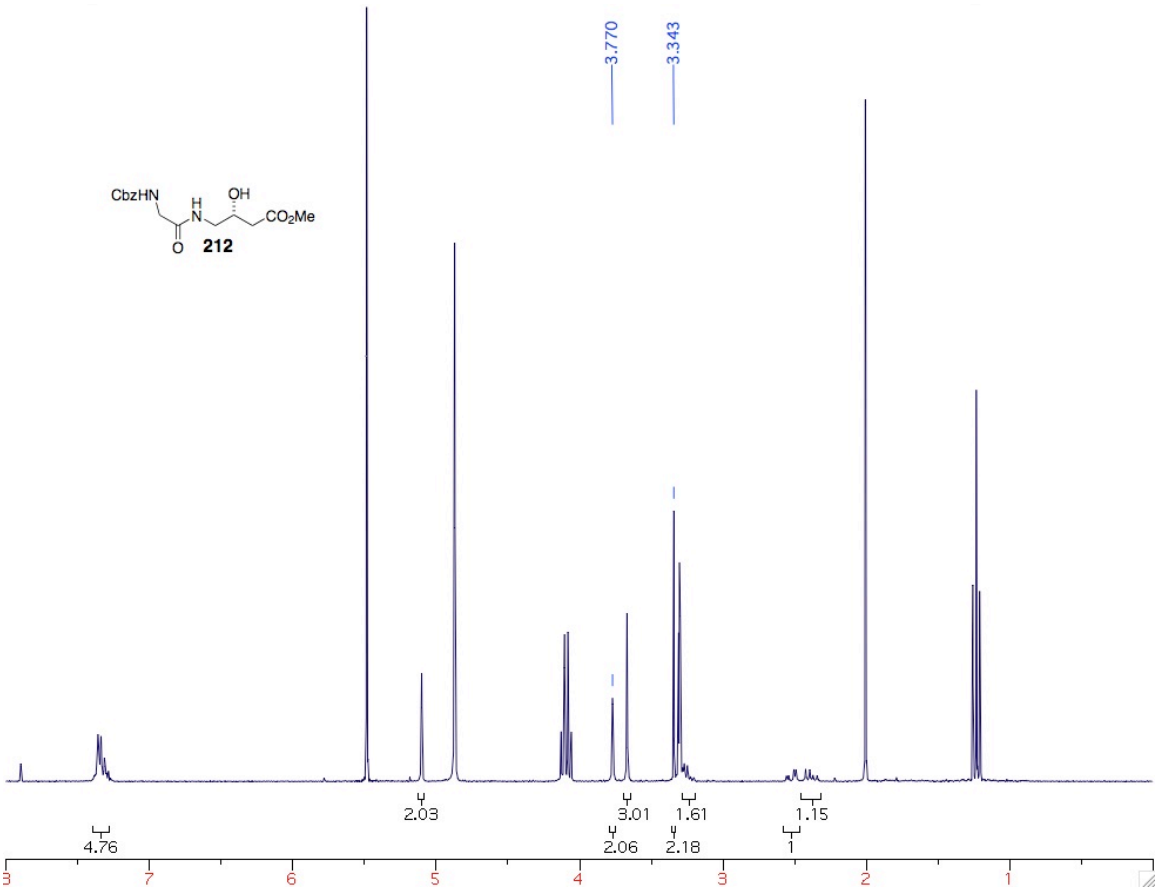
A solution of **210** (70.3 mg, 0.59 mmol) in a minimum of MeOH in a 10-mL pear-shaped flask was treated dropwise with a premixed solution of AcCl (0.4 mL, 5.6 mmol) in MeOH (4 mL). The resultant solution was stirred 18 h at 70 °C, then evaporated to give 80.4 mg (80%) **211** as a white solid after hi-vac. ^{1}H NMR crude δ (300 MHz, D_2O): 4.16 (m, 1 H), 3.58 (m, 3 H), 3.04 (m, 1 H), 2.86 (m, 1 H), 2.66-2.40 (m, 2 H).

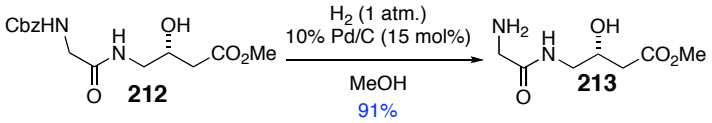
CMB1166/1194, **1240**, 1362/1368.



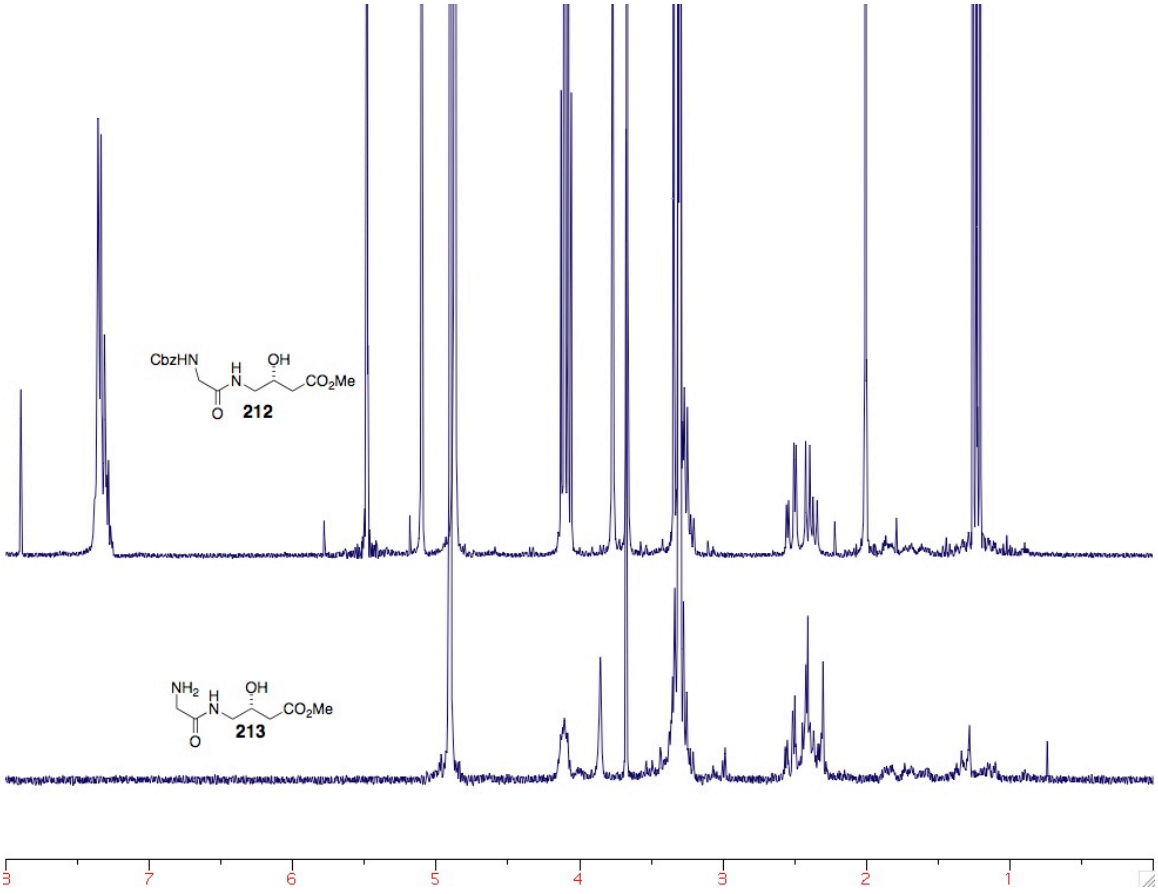


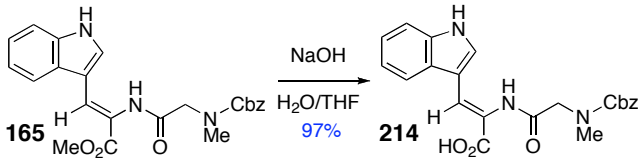
To a solution of **211** (170.1 mg, 1.00 mmol) and Cbz-glycine (230.8 mg, 1.10 mmol) in CH_2Cl_2 (4 mL) at 0 °C were added Et_3N (0.14 mL, 1.00 mmol) and DCC (228.2 mg, 1.11 mmol) and the mixture stirred 18 h while allowed to warm to ambient temperature. The mixture was filtered and evaporated, then diluted with EtOAc (10 mL) and washed with 10% citric acid, H_2O, saturated aqueous $NaHCO_3$, and brine (10 mL each); the organic layer was dried (Na_2SO_4) and evaporated to give 473 mg crude product. Flash chromatography (19:1 CH_2Cl_2 : MeOH) yielded 64.7 mg (20%) **212**. ^{1}H NMR δ (300 MHz, CD_3OD): 7.38-7.27 (m, 5 H), 5.10 (s, 2 H), 3.77 (s, 2 H), 3.67 (s, 3 H), 3.34 (s, 2 H), 3.29-3.18 (m, 1 H), 2.51 (1/2ABqd, J = 15.5, 4.4 Hz), 2.40 (1/2ABqd, J = 15.5, 8.6 Hz). HRMS calc'd for $C_{15}H_{20}N_2O_6$ (m/z): 324.1321, found (m/z): 324.1324.



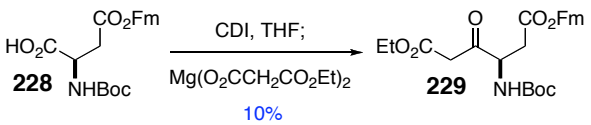


A solution of **212** (14.0 mg, 0.043 mmol) in MeOH (0.43 mL) in a 5-mL flame-dried round-bottom flask was treated with 10% Pd/C (6.9 mg, 0.0065 mmol) and fitted with an H_2 balloon, then stirred 5 h and filtered through Celite. The filtrate was evaporated to give 7.5 mg (91%) **213**. HRMS calc'd for $C_7H_{14}N_2O_4$ (*m*/*z*): 190.0954, found (*m*/*z*): 190.0954.

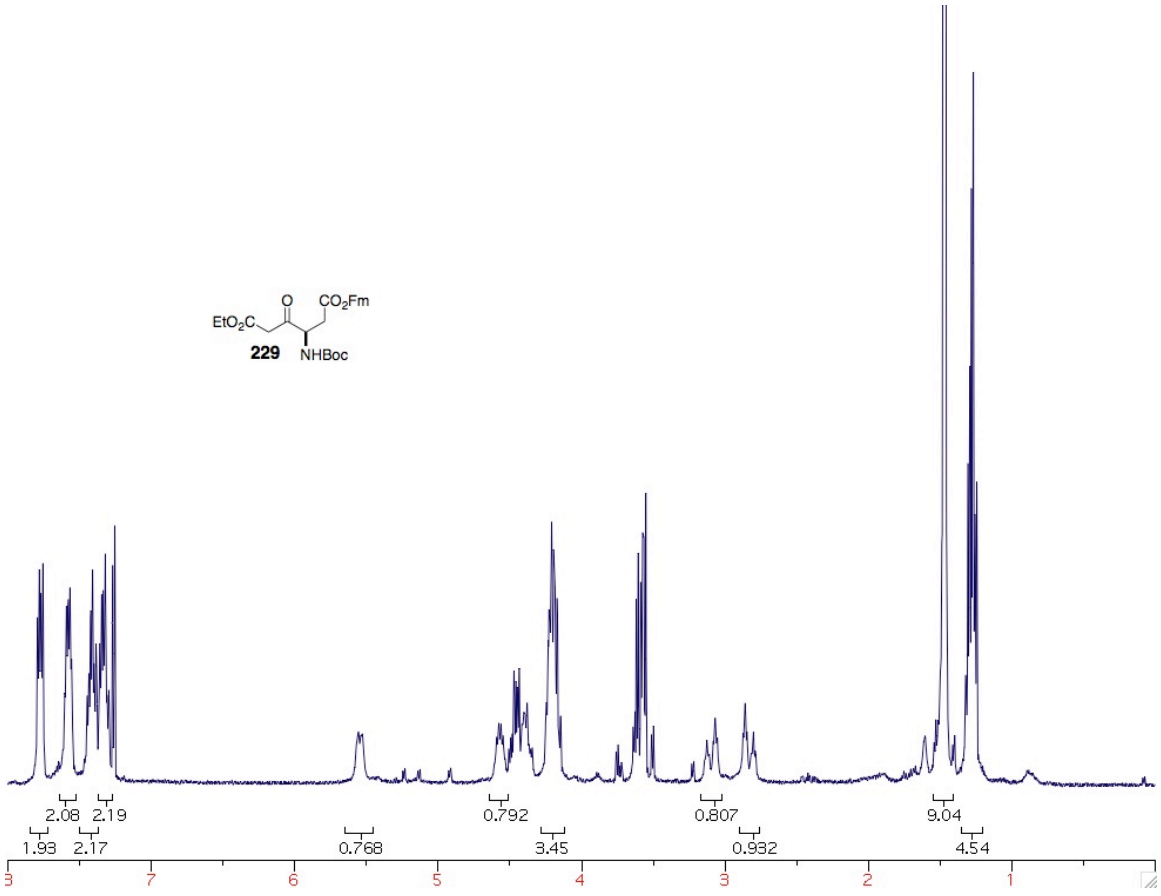


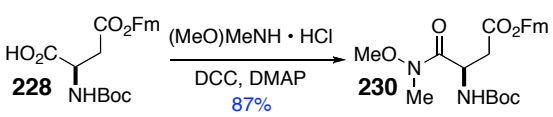


A mixture of **165** in 2 M NaOH (0.50 mL, 1.0 mmol) and MeOH (1.0 mL) was stirred 15 min, then solidified; CH_2Cl_2 (1 mL) was added to redissolve and the solution stirred 24 h, then diluted with H_2O and EtOAc (5 mL each). The aqueous layer was separated and adjusted to pH 3 (10% citric acid), then extracted with EtOAc (5 mL); the acidic organic extract was dried (Na_2SO_4) and evaporated in vacuo to yield 79.0 mg (97%) **214** used without further purification.

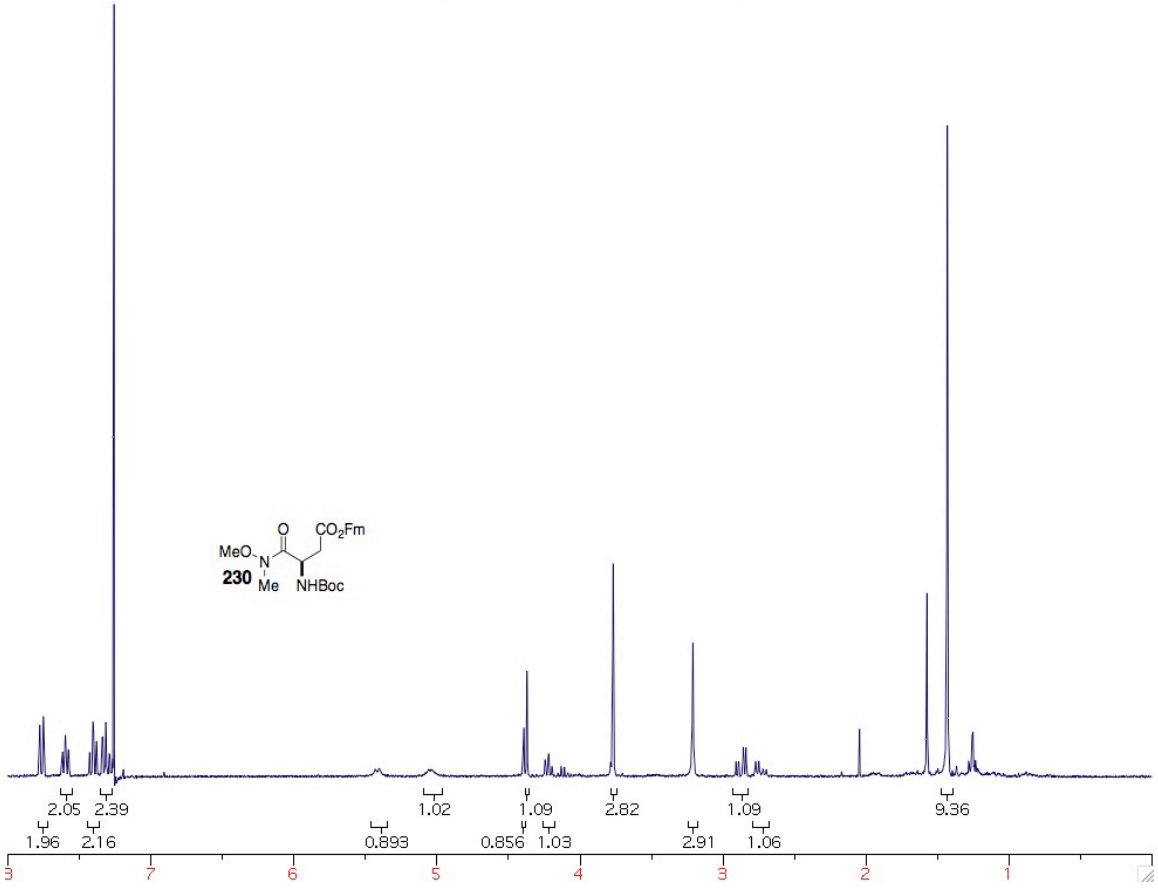


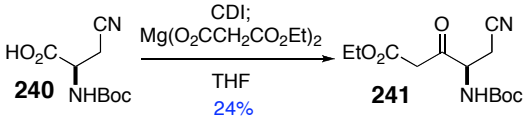
To a solution of **228** (411.5 mg, 1.0 mmol) in THF (4 mL) at 0 °C was added CDI (163.3 mg, 1.01 mmol) and the solution stirred 45 h at ambient temperature. In a separate flask a solution of *mono*-ethyl malonate (0.17 mL, 1.44 mmol) and magnesium ethoxide (84.0 mg, 0.73 mmol) in THF (4 mL) were stirred 1 h, then evaporated in vacuo; the residue was triturated from Et_2O and filtered to give 184.2 mg of light tan powder. The powder was dissolved in THF (4 mL + 4 mL rinse) and transferred via canula to the imidazolide solution, producing a yellow solution that was stirred 24 h and diluted with EtOAc (100 mL). The organic layer was washed with 1 M $KHSO_4$ and brine (30 mL each), dried (Na_2SO_4), and evaporated in vacuo to give 588 mg of yellow oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 50.0 mg (10%) **229**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.77 (m, 2 H), 7.58 (m, 2 H), 7.42 (m, 2 H), 7.32 (m, 2 H), 5.54 (m, 1 H), 4.57 (m, 1 H), 4.21 (m, 2 H), 3.08 (m, 1 H), 2.83 (m, 1 H), 1.47 (Boc rotamers, 9 H), 1.27 (m, 3 H).



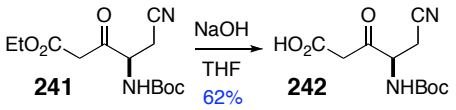


A solution of **228** (199.3 mg, 0.484 mmol), Weinreb salt (47.9 mg, 0.491 mmol), DCC (113.0 mg, 0.548 mmol), and DMAP (67.6 mg, 0.553 mmol) in CH_2Cl_2 (5.0 mL) was stirred 10.5 h and filtered. The filter cake was washed with CH_2Cl_2 (5 mL) and the combined filtrate washed with 10% citric acid and brine (10 mL each), dried (Na_2SO_4), and evaporated in vacuo to give 239 mg crude compound. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 190.5 mg (87%) **230** as a white solid. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.77 (m, 2 H), 7.58 (m, 2 H), 7.42 (m, 2 H), 7.32 (m, 2 H), 5.42 (br d, 1 H), 5.05 (m, 1 H), 4.39 (d, 1 H, J = 1.2 Hz), 4.37 (s, 1 H), 4.22 (m, 1 H), 3.77 (s, 3 H), 3.21 (s, 3 H), 2.87 (1/2ABqd, 1 H, J = 15.3, 5.7 Hz), 2.74 (1/2ABqd, 1 H, J = 15.3, 6.9 Hz), 1.43 (s, 9 H).

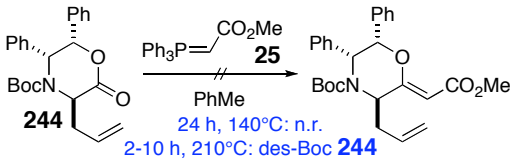




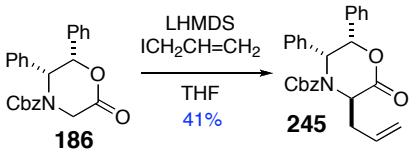
To a stirred solution of **240** (602 mg, 2.81 mmol) in THF (12 mL) at 0 °C was added CDI (478.2 mg, 2.95 mmol) and the solution stirred 6.5 h at ambient temperature. In a separate flask a mixture of magnesium ethoxide (241.2 mg, 2.11 mmol) and *mono*-ethyl malonate (0.50 mL, 4.2 mmol) in THF (10 mL) was stirred 1 h, then evaporated in vacuo; the residue was triturated from Et_2O and filtered in vacuo to give 523.2 mg reagent. The reagent was dissolved in THF (4 mL + 2 mL rinse) and transferred via canula to the imidazolide solution; the combined solution was stirred 41 h and diluted with EtOAc (280 mL). The organic layer was washed with 1 M aqueous $KHSO_4$ and brine (80 mL each), dried (Na_2SO_4), and evaporated in vacuo to give 934 mg of reddish-orange oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 191.6 mg (24%) **241**. R_f (7:3 hexanes : ethyl acetate) = 0.39.



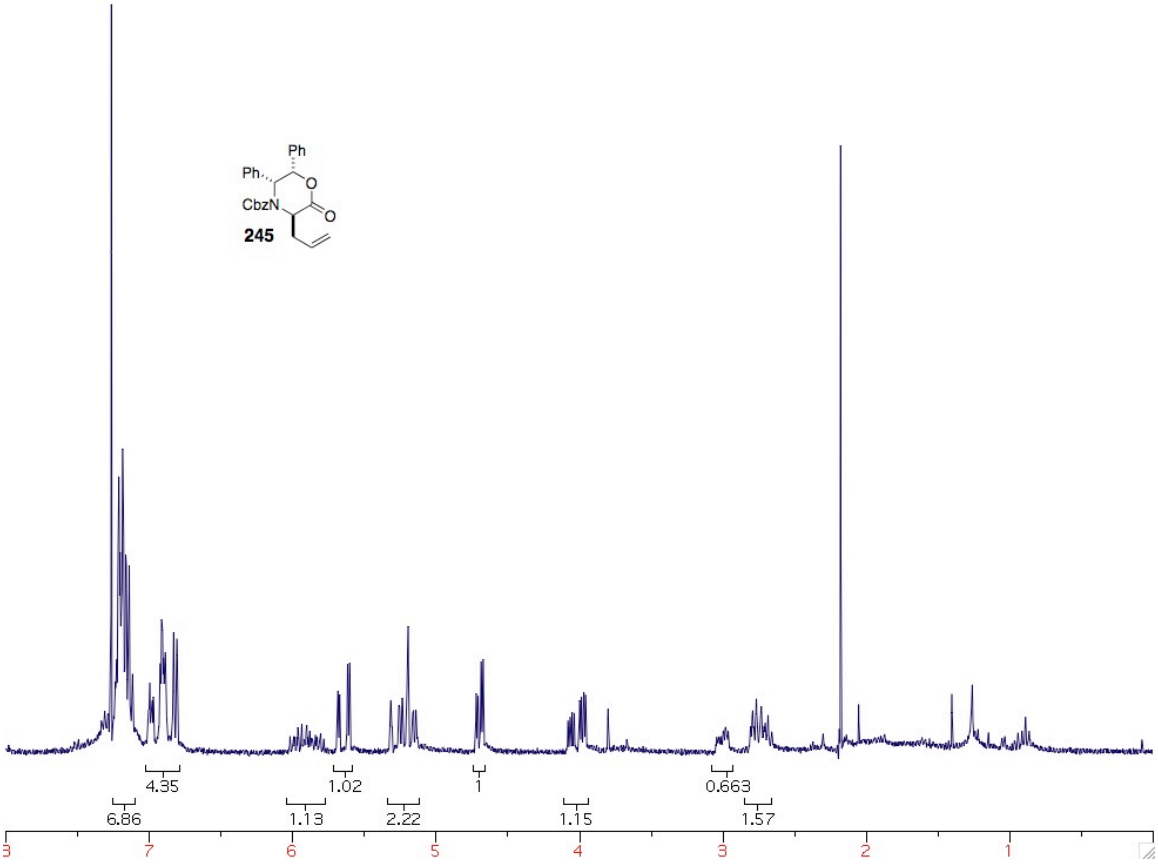
A solution of **241** (191.6 mg, 0.67 mmol) in THF (0.70 mL) was treated with 1 M aqueous NaOH (0.69 mL, 0.69 mmol) and stirred 88 h, then diluted with H_2O and EtOAc (5 mL each). The aqueous layer was adjusted to pH 3 (10% citric acid) and extracted with EtOAc (2 x 10 mL); the combined acidic organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give 107.8 mg (62%) **242** as a pale yellow oil.

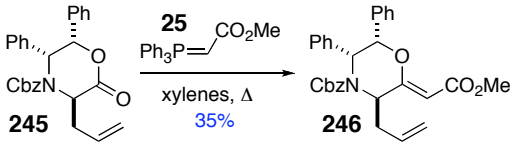


A solution of **244** (390.7 mg, 0.993 mmol) and **25** (665.0 mg, 1.99 mmol) in xylenes (10 mL) in a sealed tube was heated 10 h at 205 °C, then cooled to ambient temperature and evaporated in vacuo. Flash chromatography (9:1 hexanes : ethyl acetate) yielded 55 mg (16%) des-Boc **244**.

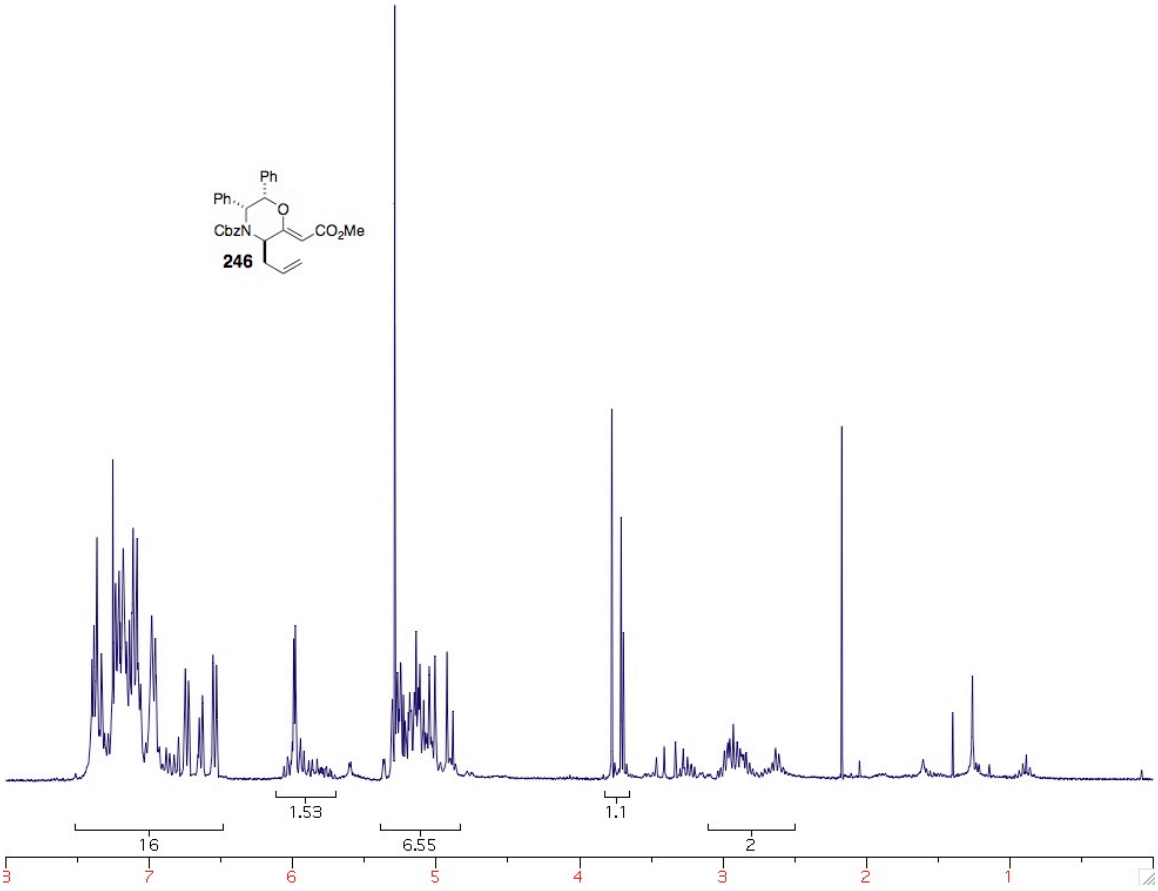


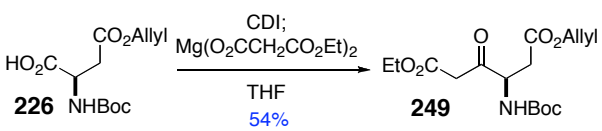
To a stirred solution of **186** (1.1004 g, 2.84 mmol) in THF (50 mL) was added allyl iodide (2.00 mL, 21.9 mmol) and the solution cooled to -78 °C. LHMDS (2.83 mL, 2.83 mmol, 1 M in THF) was added slowly via syringe and the solution stirred 1 h at -78 °C, then poured into H_2O (100 mL). The mixture was diluted with EtOAc (250 mL) and the organic layer washed with brine (100 mL), dried (Na_2SO_4), and evaporated in vacuo to give 1.1129 g crude material. Flash chromatography (9:1 hexanes : ethyl acetate) yielded 493.2 mg (41%) **245**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.40-6.79 (m, 15 H), 5.90 (m, 1 H), 5.64 (1/2ABqd, 1 H, J = 20.4, 3.9 Hz), 5.33-5.12 (m, 2 H), 4.69 (1/2ABqd, 1 H, J = 10.5, 4.2 Hz), 4.01 (m, 1 H), 3.00 (m, 1 H), 2.74 (m, 2 H).





A mixture of **245** (204.0 mg, 0.477 mmol) and **25** (398.8 mg, 1.19 mmol) in xylenes (1.5 mL) was heated 2 h at 210 °C in a sealed tube; the solution was cooled to ambient temperature and evaporated in vacuo to give crude material. Flash chromatography (9:1 hexanes : ethyl acetate) yielded 80 mg (35%) **246**. R_f (7:3 hexanes : ethyl acetate) = 0.65. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.45-6.51 (m, 15 H), 6.07-5.72 (m, 2 H), 5.39-4.86 (m, 6 H), 3.74 (m, 1 H), 3.08-2.52 (m, 2H).

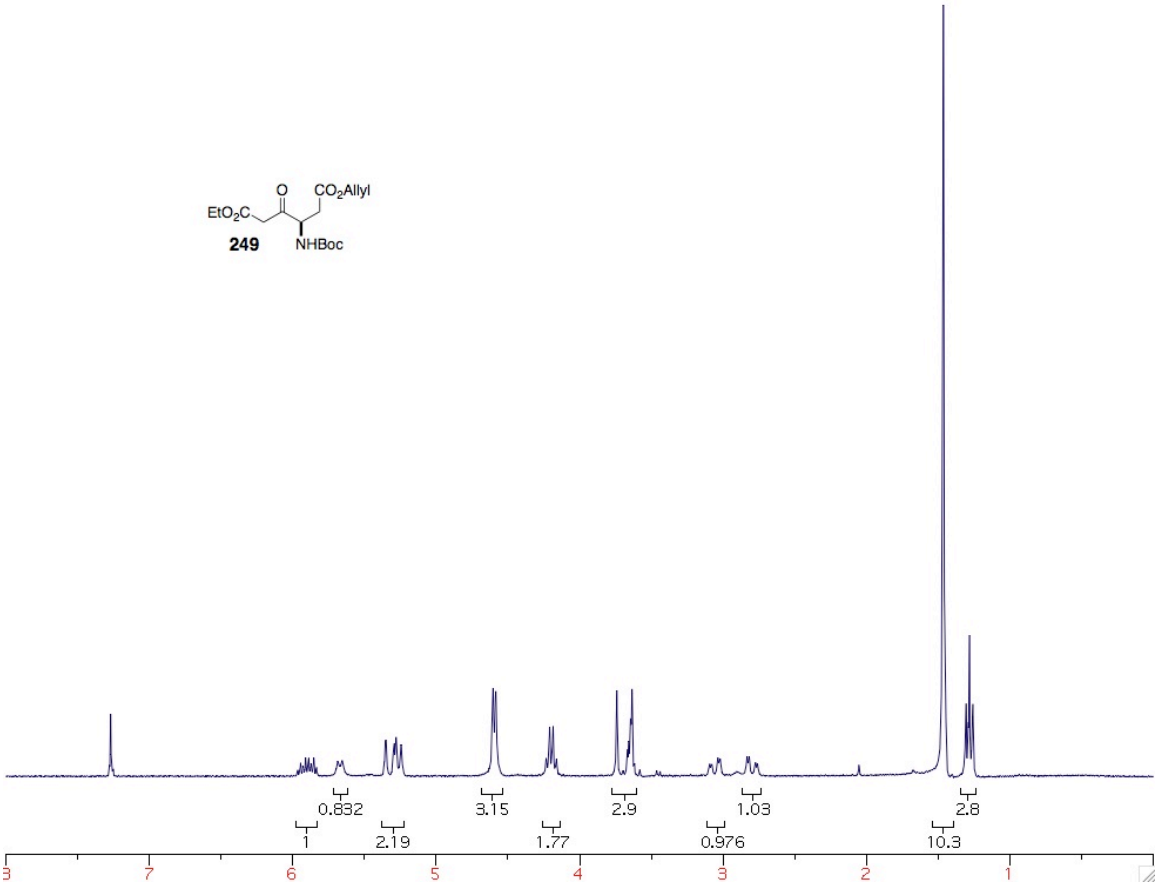


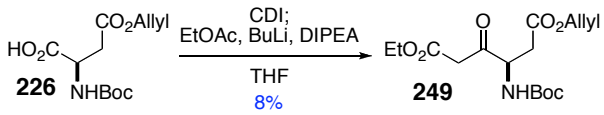


To a stirred solution of **226** (983.2 mg, 3.60 mmol) in THF (18 mL) in a 25-mL round-bottom flask at 0 °C was added CDI (612.5 mg, 3.77 mmol) and the solution stirred 6.5 h

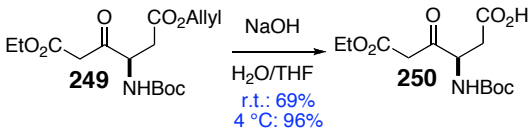
at ambient temperature. A 50-mL round-bottom flask was charged with a mixture of $Mg(O_2CCH_2CO_2Et)_2$ in THF (6 mL) and a stir bar; the imidazolide solution (+ 1 mL THF rinse) was added via canula and the combined solution stirred 20 h at ambient temperature, then poured into EtOAc (355 mL). The organic layer was washed with 1 M $KHSO_4$ and brine (110 mL), dried (Na_2SO_4), and evaporated to give 1.523 g of yellow oil. Flash chromatography (8:2 to 7:3 hexanes : ethyl acetate) yielded 661.2 mg (54%) **249** as a pale yellow oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 5.90 (m, 1 H, allyl CH), 5.65 (ABX, 1 H, NHBoc α), 5.37 - 5.22 (m, 2 H, allyl CH_2), 4.59 (d, 2 H, J = 5.80 Hz, allyl α), 4.20 (q, 2 H, J = 7.18 Hz, Et), 3.64 (m, 2 H, β-keto CH_2), 3.03 (ABXq, 1 H, J = 17.29 Hz, 4.83 Hz, Asp β), 2.81 (ABXq, 1 H, J = 17.30 Hz, 4.40 Hz, Asp β), 1.47 (s, 9 H, Boc), 1.28 (t, 3 H, J = 7.14 Hz, Et). HRMS (FAB+) calcd. for $C_{16}H_{26}N_1O_7$ ($M+H^+$) (m/z): 344.1709, found (m/z): 344.1709.

$Mg(O_2CCH_2CO_2Et)_2$: A solution of magnesium ethoxide (308.0 mg) and mono-ethyl malonate (0.64 mL) in THF (12 mL) in a 25-mL round-bottom flask was stirred 1 h at ambient temperature, then evaporated in vacuo. The residue was triturated in Et_2O and filtered to yield, after 30 seconds on hi-vac, the magnesium enolate (661.8 mg, 86%).

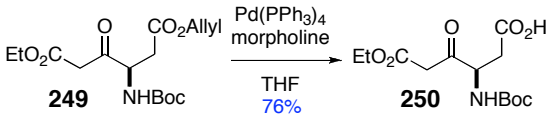




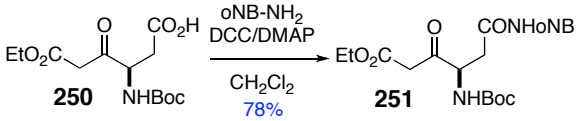
A mixture of DIPEA (0.98 mL, 7.0 mmol) and THF (17.5 mL) at -78 °C was treated dropwise with BuLi (2.8 mL, 7.0 mmol) and the mixture stirred 40 min at -78 °C. EtOAc (0.69 mL, 7.0 mmol) was added dropwise and the mixture stirred 52 min at -78 °C. In a separate flask a solution of **226** (547.0 mg, 2.00 mmol) in THF (4 mL) was treated with CDI (340.6 mg, 2.10 mmol) and stirred 1 h, then added dropwise via canula to the enolate solution. The combined solution was stirred 45 min at -78 °C, then quenched with 10% citric acid (25 mL) and warmed to ambient temperature. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), then dried (Na_2SO_4) and evaporated in vacuo to give 181.0 mg of yellow oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 55.3 mg (8%) **249** as a colorless oil.



To a stirred solution of CMB942 (578.8 mg, 1.685 mmol) in THF (3.37 mL) at 0 °C was added 0.5 M NaOH (3.37 mL) and the solution stirred 8 h at 0 °C and 67 h at 3 °C. The solution was diluted with H_2O and EtOAc (10 mL each) and the aqueous layer adjusted to pH 3 (10% citric acid), then extracted with EtOAc (2 x 25 mL). The combined acidic organic extracts were dried (Na_2SO_4) and evaporated to give 488.9 mg (96%) of yellow oil used without further purification.

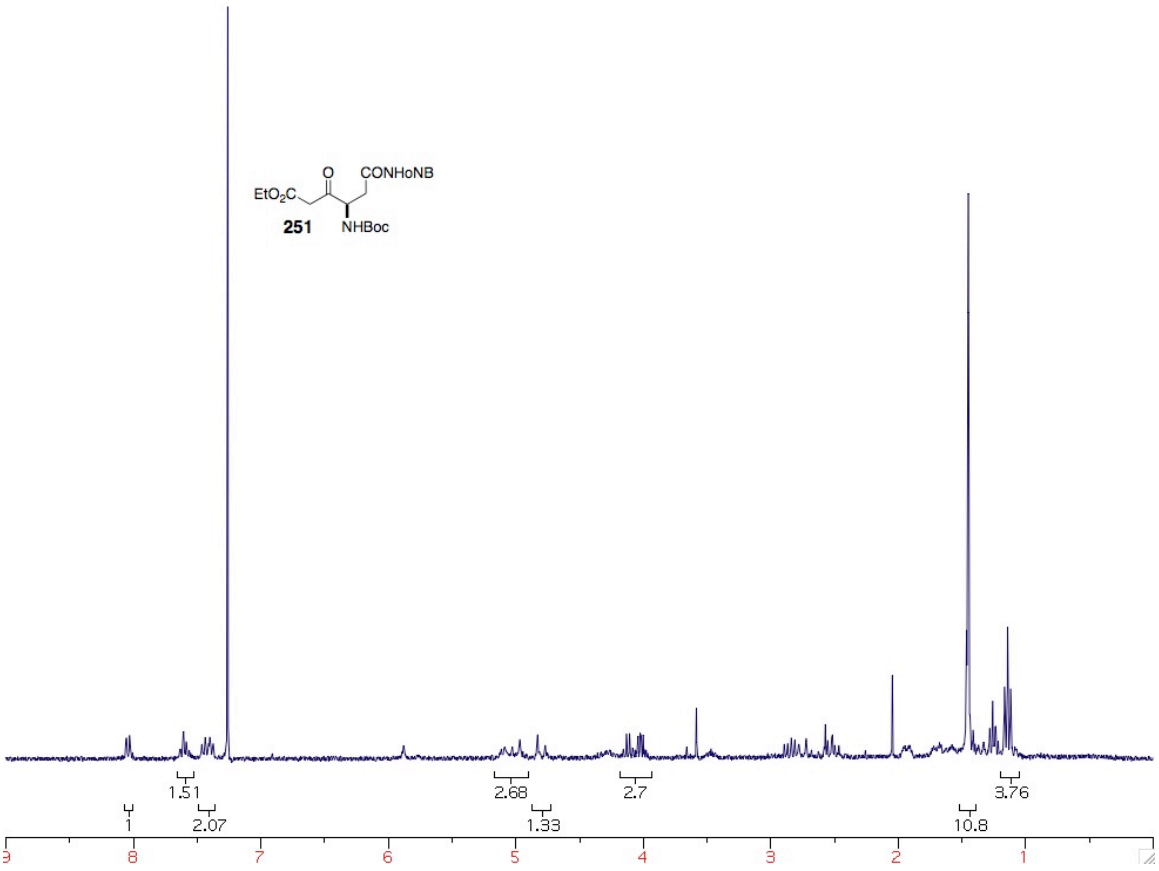


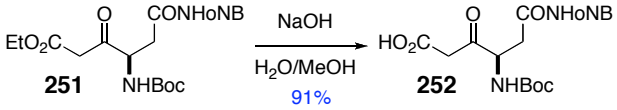
A stirred solution of **249** (225.9 mg, 0.658 mmol) in THF (5 mL) was treated with $Pd(PPh_3)_4$ (76.0 mg, 0.066 mmol) and morpholine (0.575 mL, 6.6 mmol) and the solution stirred 45 min, though the TLC showed completion at 15 min. The mixture was diluted with THF to 10 mL total volume, then extracted with saturated aqueous $NaHCO_3$ (2 x 10 mL). The combined aqueous extracts (containing some precipitated $NaHCO_3$, suggesting need for 5% solution in future runs) were adjusted to pH 3 (10% citric acid), bubbling and spilling in the process. The aqueous layer (~75 mL total volume) was extracted with EtOAc (2 x 50 mL); the combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give 152.4 mg (76%) **250** as a light yellow oil used without further purification, though NMR shows some Ph_3P contamination. R_f (19:1 CH_2Cl_2 : MeOH) = 0.29.



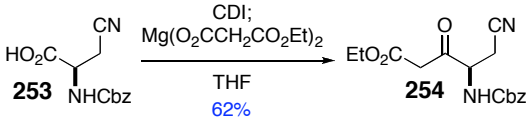
A mixture of **250** (387.8 mg, 1.278 mmol), oNB-NH_2-HCl (241.4 mg, 1.28 mmol), DCC (290.8 mg, 1.41 mmol), and DMAP (172.0 mg, 1.41 mmol) in CH_2Cl_2 (13 mL) was stirred overnight; workup gave 838 mg of off-white foam. Flash chromatography (7:3 to

1:1 hexanes : ethyl acetate) yielded 439.0 mg (78%) **251** as white crystals. [α] +6.8° (c=1, CH_2Cl_2). ^1H NMR δ (300 MHz, $CDCl_3$): 8.02-8.07 (m, 1 H), 7.64-7.55 (m, 1 H), 7.47-7.37 (m, 2 H), 5.16-4.95 (m, 2 H), 4.86-4.76 (m, 1 H), 4.08-3.96 (m, 2 H), 1.48-1.42 (m, 9 H), 1.18-1.10 (m, 3 H). HRMS (FAB+) calcd. for $C_{20}H_{27}N_3O_8Na$ ($M+Na^+$) (*m*/*z*): 460.1696, found (*m*/*z*): 460.1693.

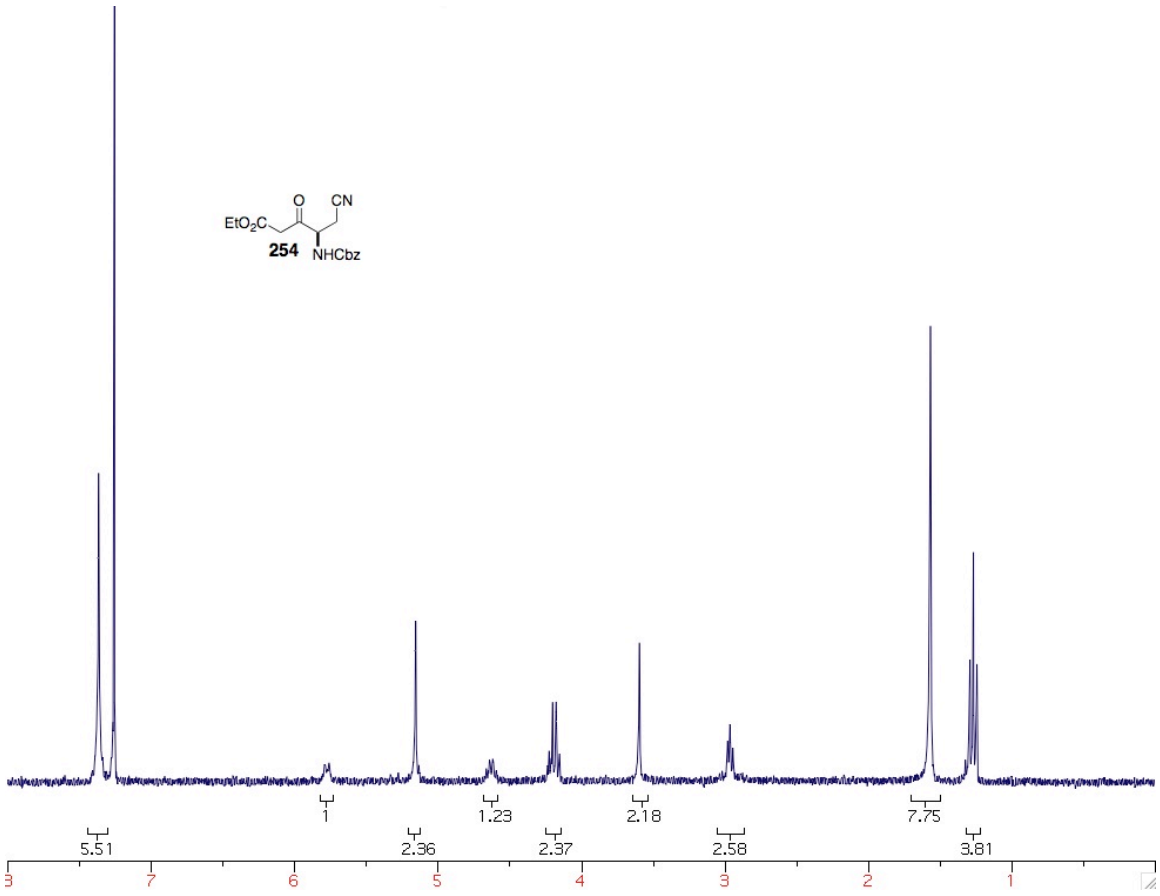


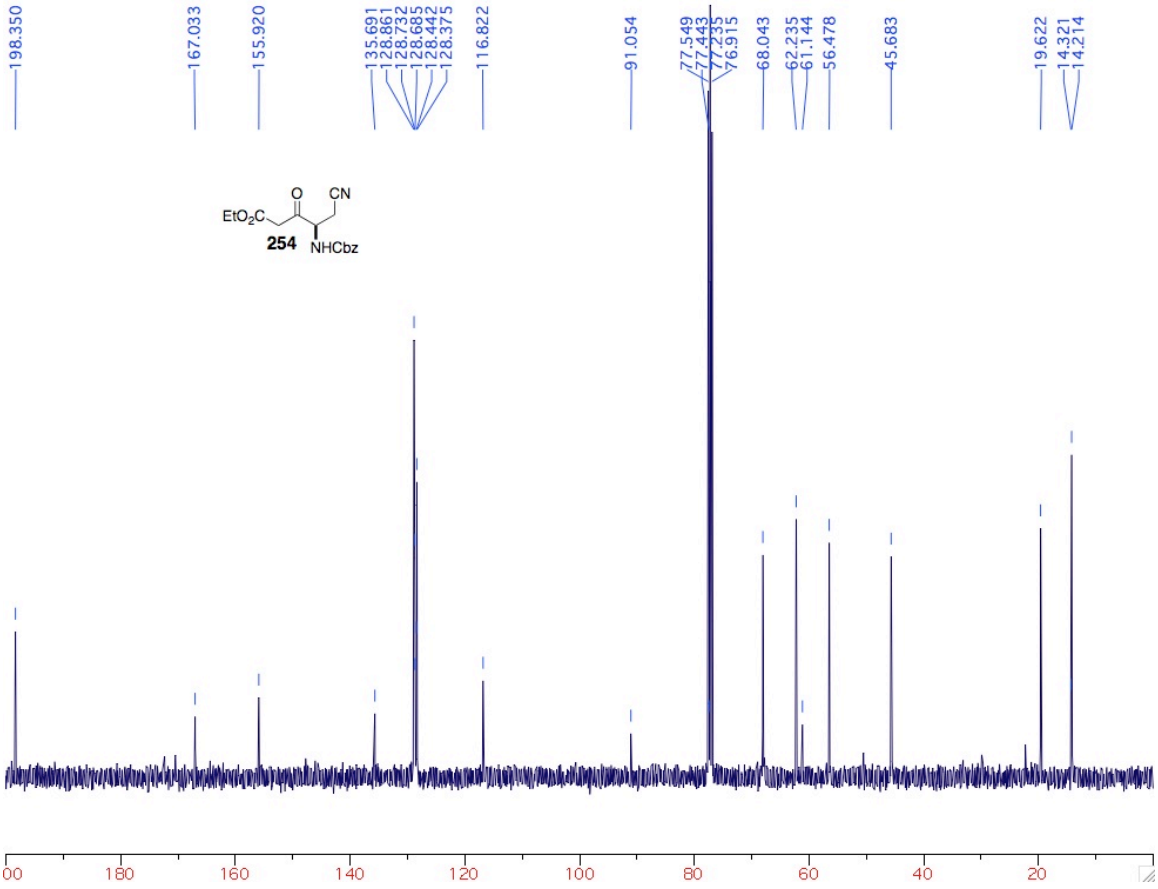


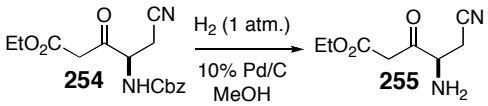
To a solution of **251** (101.0 mg, 0.231 mmol) in THF (2.3 mL) was added 0.5 M NaOH (0.485 mL, 0.243 mmol) and the mixture stirred 30 h at 3 °C. The solution was diluted with H_2O and EtOAc (15 mL each) and the aqueous layer adjusted to pH 3 (10% citric acid), then extracted with EtOAc (2 x 15 mL). The combined acidic organic extracts were dried (Na_2SO_4) and evaporated to yield 160 mg (quant.) **252** as a colorless oil used without futher purification.



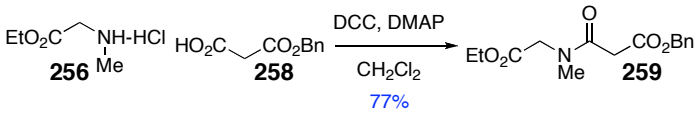
To a stirred solution of **253** (835.3 mg, 3.365 mmol) in THF (17 mL) at 0 °C was added CDI (545.7 mg, 3.365 mmol) and the solution stirred 1 h at ambient temperature. A 25-mL round-bottom flask was charged with a mixture of $Mg(O_2CCH_2CO_2Et)_2$ (706 mg) in THF (17 mL) and a stir bar; the imidazolide solution (+ 1 mL THF rinse) was added via canula over 10 min and the combined solution stirred 22 h, then poured into EtOAc (25 mL). The organic layer was washed with 1 M $KHSO_4$ and brine (25 mL each), dried (Na_2SO_4), and evaporated to give crude product. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 662.6 mg (62%) **254** as a pale yellow oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.40-7.33 (s, 5 H, Cbz), 5.88-5.81 (ABX, 1 H, NHCbz α), 5.16 (s, 2 H, Cbz), 4.26 (q, 2 H, J = 7.1 Hz, Et), 3.60 (s, 2 H, β-keto CH_2), 2.96 (m, 2 H, Asp β), 1.31 (t, 3 H, J = 7.1 Hz, Et). ^{13}C NMR δ (400 MHz, $CDCl_3$): 198.4, 167.0, 155.9, 128.9, 128.7, 128.7, 128.4, 128.4, 116.8, 91.1, 68.0, 62.2, 61.1, 56.5, 45.7, 19.6, 14.3, 14.2. HRMS (FAB+) calcd. for $C_{16}H_{26}N_1O_7$ ($M+H^+$) (m/z): 344.1709, found (m/z): 344.1709.


O
CN
EtO2C
254
NHCbz
1
1.23
2.18
7.75
5.51
2.36
2.37
2.58
3.81
8
7
6
5
4
3
2
1



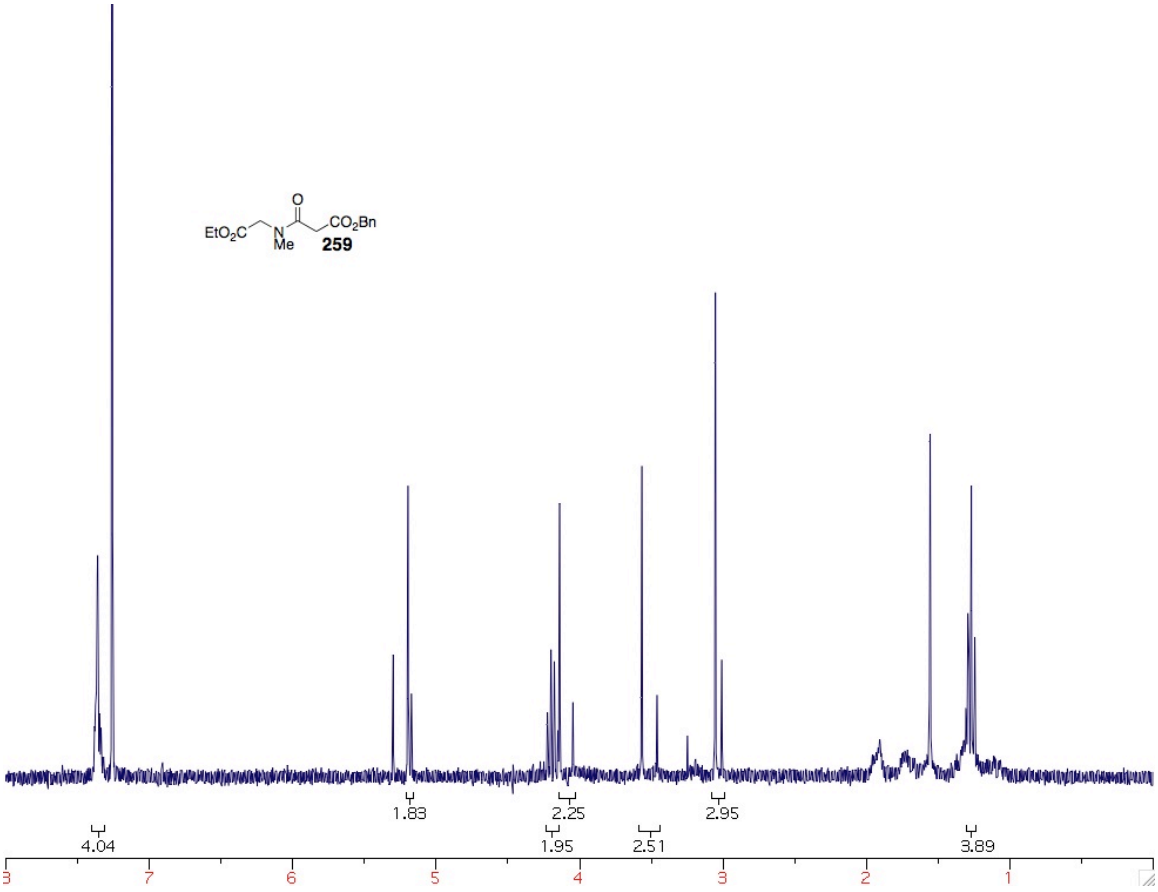


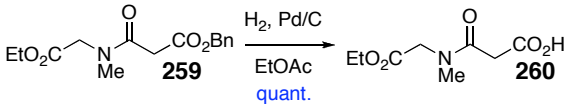
A solution of **254** (15.5 mg, 0.049 mmol) in THF (0.97 mL) was flushed with Ar, then treated with 5% Pd/C (15.5 mg, 0.007 mmol) and stirred 33 h. The mixture was filtered through a pad of Celite and evaporated to give 9.3 mg (quant.) **255** as a yellow oil used without further purification.



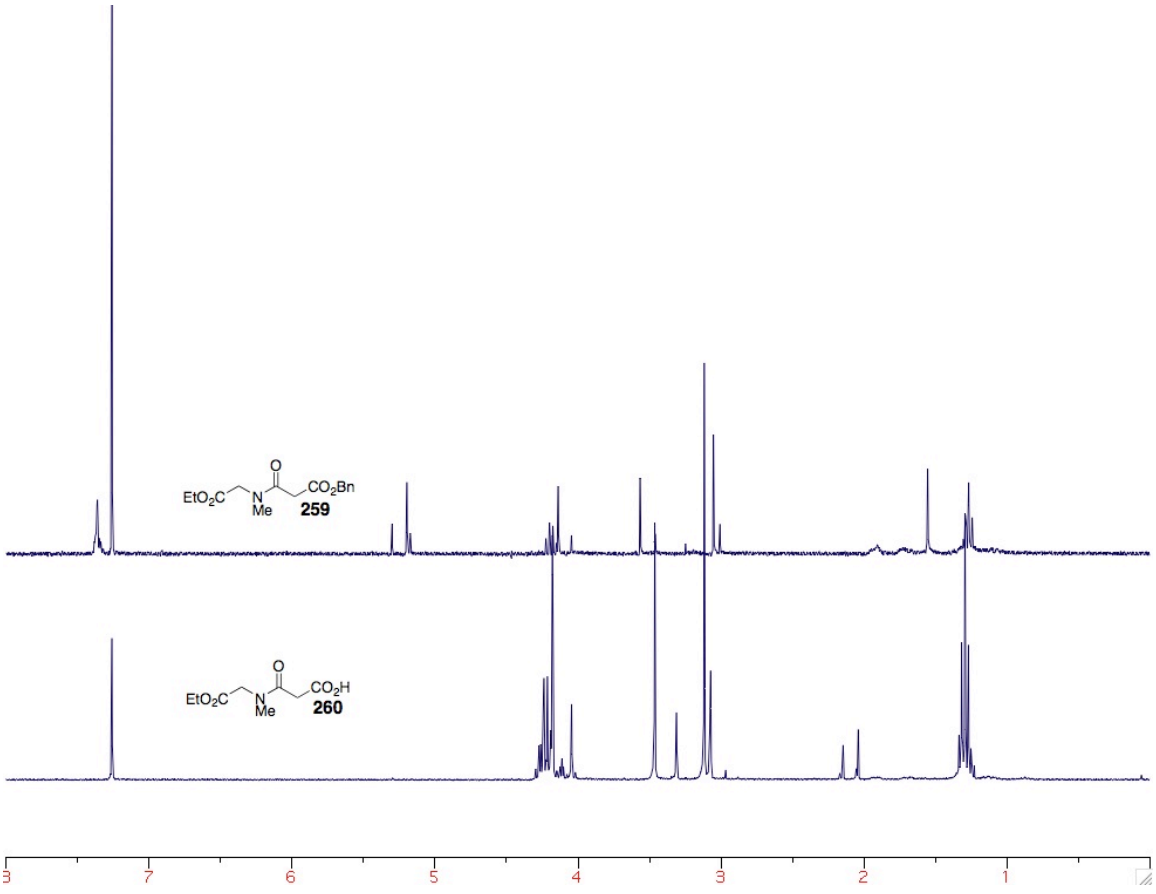
A mixture of **256** (79.4 mg, 0.517 mmol), **258** (100.4 mg, 0.517 mmol), DCC (117.4 mg, 0.569 mmol), and DMAP (70.0 mg, 0.573 mmol) in CH_2Cl_2 (2.6 mL) was stirred 6 h, then filtered and rinsed with CH_2Cl_2 (5 mL). The filtrate was washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine (10 mL each); the organic layer was dried

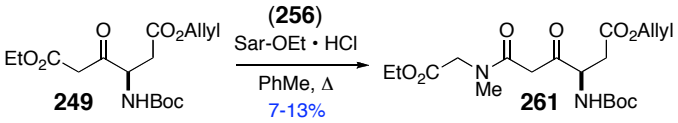
(Na_2SO_4) and evaporated in vacuo to yield 148.1 mg (98%) **259** as a yellow oily solid used without further purification. R_f (1:1 hexanes : ethyl acetate) = 0.43. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.36 (m, 5 H), 5.19 (rotamers, 2 H), 4.19 (q, 2 H, J = 7.2 Hz), 4.09 (rotamers, 2 H), 3.52 (rotamers, 2 H), 3.03 (rotamers, 3 H), 1.27 (t, 2 H, J = 7.2 Hz).



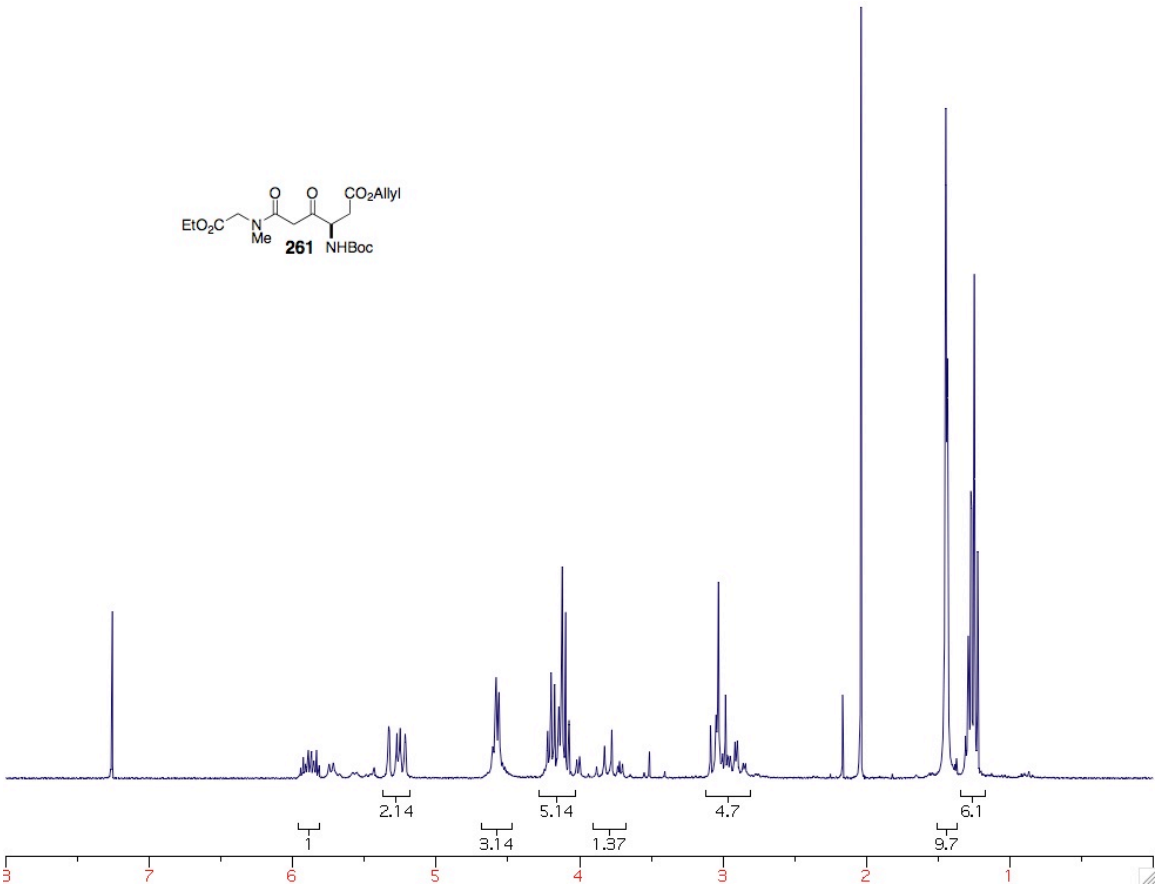


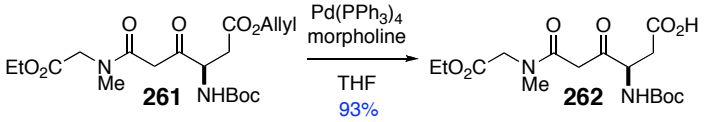
A 250-mL Ar-flushed round-bottom flask containing a mixture of **259** (3.30 g, 11.3 mmol) and 10% palladium on carbon (1.2045 g, 1.13 mmol) in EtOAc (75 mL) was fitted with an H_2 balloon and the mixture stirred 17 h, then filtered through a pad of Celite. The filtrate was evaporated in vacuo to yield 2.54 g (quant.) **260** as a thick oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 4.25 (m, 2 H), 4.12 (rotamers, 2 H), 3.40 (rotamers, 2 H), 3.10 (rotamers, 3 H), 1.29 (t, 2 H, J = 7.2 Hz).



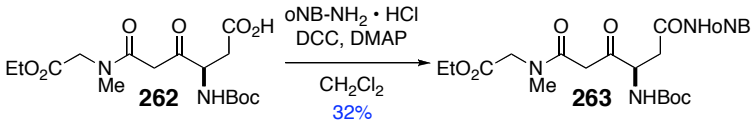


A mixture of **249** (171.9 mg, 0.50 mmol) and **256** (84.7 mg, 0.55 mmol) in PhMe (2.0 mL) in a 10-mL round-bottom flask was treated with Et_3N (0.10 mL, 0.72 mmol); a Dean-Stark trap containing PhMe was fitted to the flask and the mixture heated 3.5 h at 75 °C and 19 h at 80 °C, reaching dryness. TLC shows some product so the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL); the organic layer was dried (Na_2SO_4) and evaporated in vacuo to give 157.6 mg of crude product. Flash chromatography (6:4 hexanes : ethyl acetate) yielded 27.1 mg (13%) **261**. R_f (1:1 hexanes : ethyl acetate) = 0.26. ^{1}H NMR δ (300 MHz, $CDCl_3$): 5.98-5.80 (m, 1 H), 5.38-5.19 (m, 2 H), 4.58 (m, 2 H), 4.25-4.08 (m, 2 H), 3.84 (m, 1 H), 3.11-2.82 (m, 3 H), 1.44 (m, 9 H), 1.27 (m, 3 H).

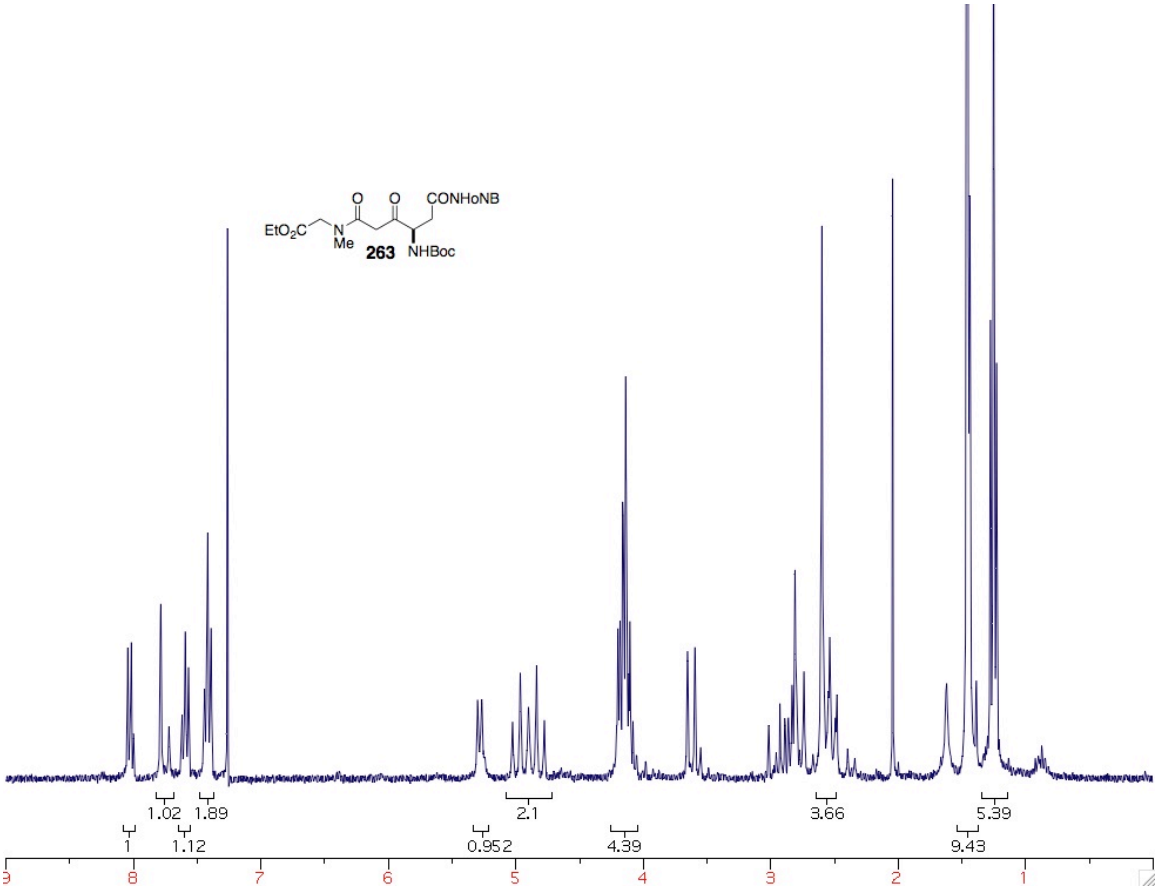


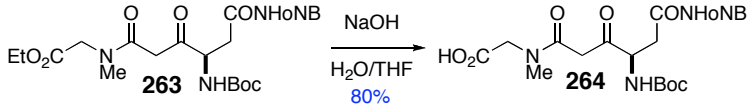


A solution of **261** (41.8 mg, 0.10 mmol) in THF (1.0 mL) was treated with $Pd(PPh_3)_4$ (0.4 mg, 0.00035 mmol) and stirred 5 minutes, then treated with morpholine (0.01 mL, 0.115 mmol). The solution was stirred 30 min and more $Pd(PPh_3)_4$ (5.8 mg, 0.0051 mmol) added; stirring for 75 minutes and evaporation gave 114.6 mg crude product. The mixture was taken up in 2.5% aqueous $NaHCO_3$ (4 mL) and washed with Et_2O (2 x 4 mL); the aqueous layer was adjusted to pH 2 (1 M HCl) and extracted with EtOAc (3 x 4 mL). The combined acidic organic extracts were dried (Na_2SO_4) and evaporated to give 27.3 mg (73%) **262** used without further purification.



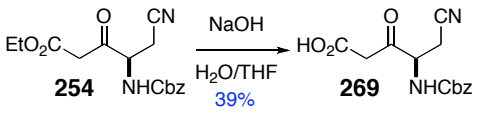
A mixture of **262** (27.3 mg, 0.0729 mmol), oNB-NH_2 • HCl (15.1 mg, 0.08 mmol), DCC (18.1 mg, 0.09 mmol), and DMAP (10.7 mg, 0.09 mmol) in CH_2Cl_2 (0.73 mL) was stirred 20.5 h, then filtered; the filtrate was evaporated in vacuo. Flash chromatography (3:7 hexanes : ethyl acetate) yielded 12.0 mg (32%) **263**. R_f (3:7 hexanes : ethyl acetate) = 0.31, R_f (1:1 hexanes : ethyl acetate) = 0.11. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.02 (m, 1 H), 7.76 (m, 1 H), 7.59 (m, 1 H), 7.42 (m, 2 H), 5.27 (m, 1 H), 4.90 (m, 2 H), 4.14 (m, 4 H), 2.55 (m, 3 H), 1.46 (m, 9 H), 1.25 (m, 5 H). HRMS (pos. TOF) calc'd for $C_{23}H_{32}N_4O_9Na$ ($M+Na^+$) (*m/z*): 531.2062; found (*m/z*): 531.2069.



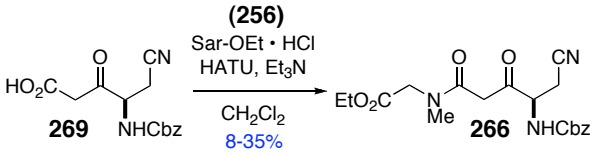


A solution of **263** (1.6 mg, 0.0031 mmol) in 0.5 M NaOH and THF (0.01 mL each) in a 1.5-dram vial was stirred 2 h and diluted with 50% aqueous $NaHCO_3$ and EtOAc (2 mL each); the vial was shaken and the organic layer removed. The aqueous layer was

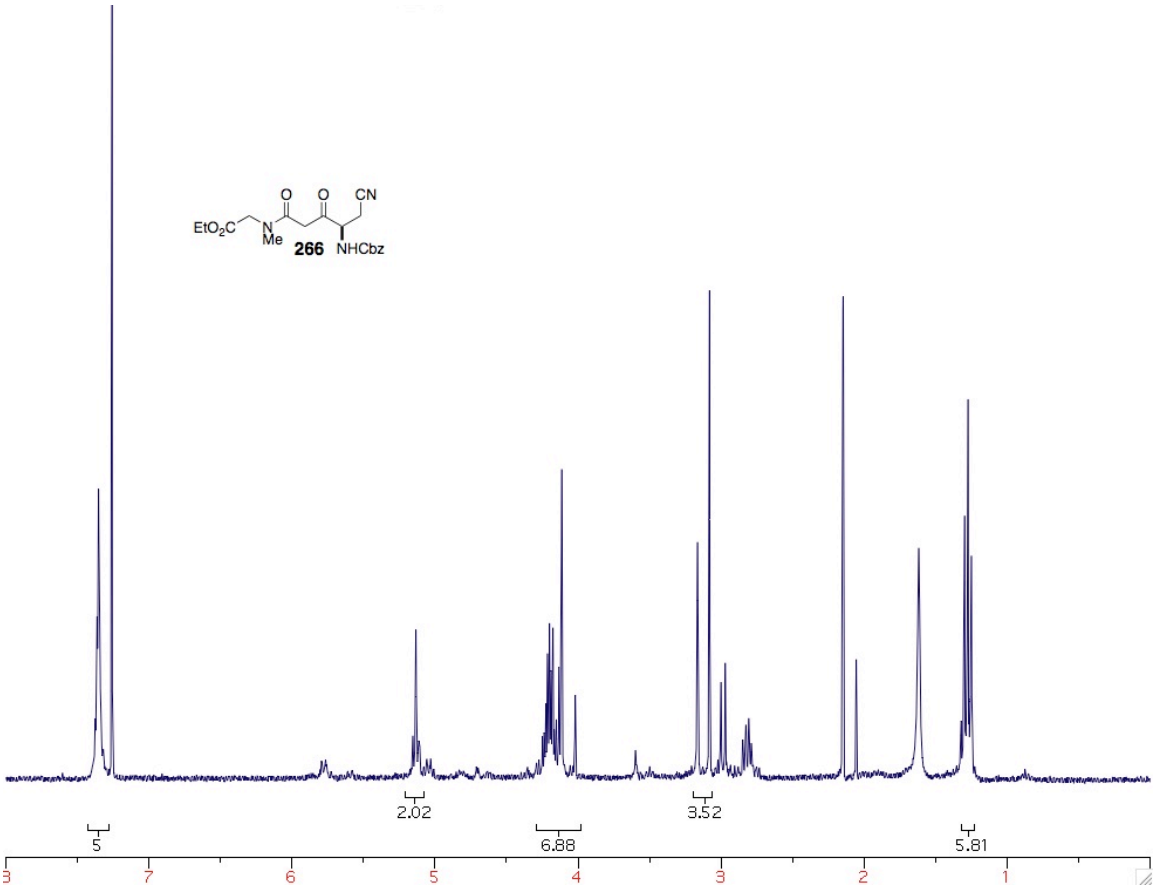
adjusted to pH 2 (1 M $KHSO_4$, ~1.6 mL) and extracted with EtOAc (2 x 2.5 mL). The combined acidic organic extracts were dried (Na_2SO_4) and evaporated to yield 1.2 mg (80%) **264** as a colorless oil. HRMS (neg. TOF) calc'd for $C_{21}H_{27}N_4O_9$ ($M\text{-}H^+$) (*m/z*): 479.1784; found (*m/z*): 479.1778.

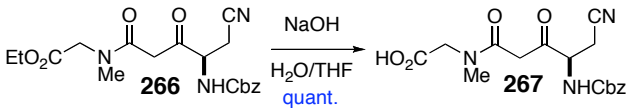


A solution of **254** (31.9 mg, 0.100 mmol) in 0.5 M aqueous NaOH (0.22 mL, 0.11 mmol) and THF (0.22 mL) was stirred 21 h and diluted with EtOAc (0.44 mL), then stirred 22 h and diluted with EtOAc (0.44 mL). The mixture was stirred 7 h and treated with 2 M NaOH (0.27 mL), then stirred 72 h more; acid/base workup gave 11.4 mg (39%) **269**.

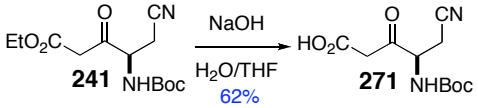


A mixture of **269** (57.3 mg, 0.197 mmol), **256** (31.8 mg, 0.207 mmol), and PyBroP (108.8 mg, 0.23 mmol) in CH_2Cl_2 (0.99 mL) was treated with Et_3N (0.06 mL, 0.43 mmol) and stirred 24 h, then diluted with CH_2Cl_2 (5 mL) and washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine (5 mL each). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to give 68.3 mg crude product. Flash chromatography (19:1 CH_2Cl_2 : MeOH) yielded 6.5 mg (8%) **266**. R_f (3:7 hexanes : ethyl acetate) = 0.74. R_f (1:1 hexanes : ethyl acetate) = 0.49. R_f (19:1 CH_2Cl_2 : MeOH) = 0.70. ^1H NMR δ (300 MHz, $CDCl_3$): 7.35 (m, 5 H), 5.13 (m, 2 H), 4.29-4.00 (m, 7 H), 3.12 (rotamers, 3 H), 1.27 (m, 6 H).

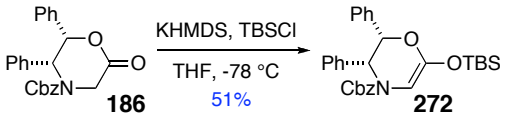




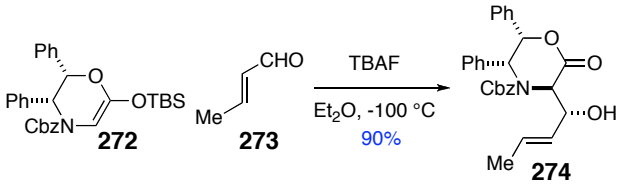
A solution of **266** (5.4 mg, 0.0139 mmol) in 0.5 M aqueous NaOH (0.055 mL, 0.028 mmol) and THF (0.055 mL) was stirred 9.5 h; acid/base workup gave >5 mg **267**.



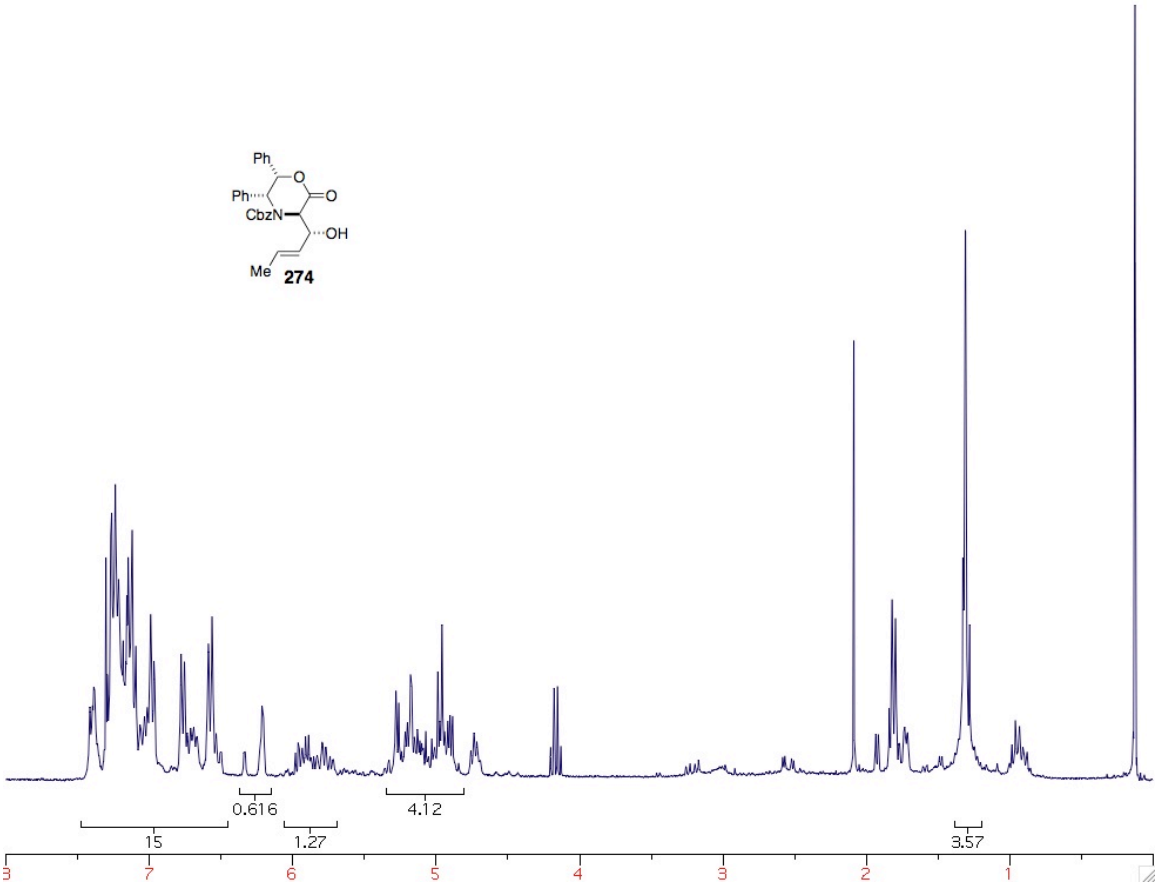
A solution of **241** (191.6 mg, 0.67 mmol) in THF (0.70 mL) was treated with 1 M aqueous NaOH (0.69 mL, 0.69 mmol) and stirred 88 h, then diluted with H_2O and EtOAc (5 mL each). The aqueous layer was adjusted to pH 3 (10% citric acid) and extracted with EtOAc (2 x 10 mL), then dried (Na_2SO_4) and evaporated in vacuo to give 107.8 mg (62%) **271** as a pale yellow oil.

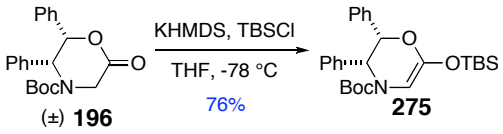


A 25-mL round-bottom flask was charged with **186** (186 mg, 0.48 mmol) and flame-dried; TBSCl (88.2 mg, 0.59 mmol), THF (10 mL), and a stir bar were added and the mixture stirred until the solid dissolved. The mixture was cooled to -78 °C and KHMDS (1.15 mL, 0.58 mmol, 0.5 M in PhMe) added; the combined mixture was stirred 15 min at -78 °C and allowed to warm to ambient temperature. The resultant yellow solution with white chunks was adsorbed onto Florisil (2.2 g) that was loaded onto a column and eluted with 9:1 hexanes : ethyl acetate to yield 122 mg (51%) **272**.

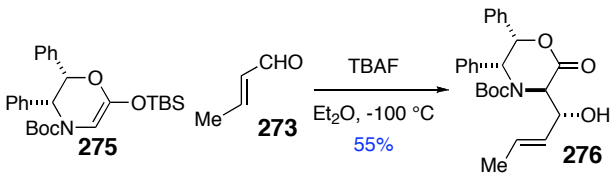


A solution of **272** (90.0 mg, 0.18 mmol) and **273** (0.15 mL, 1.8 mmol) in Et_2O (2.0 mL) at -95 °C was treated with TBAF (0.54 mL, 0.54 mmol, 1 M in THF). The reaction was complete after 25 min and was quenched with H_2O (6 mL) and warmed to ambient temperature, then diluted with EtOAc and extracted three times with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give 109.4 mg crude material. Flash chromatography (6 : 4 hexanes : ethyl acetate) yielded 74 mg (90%) **274** as a clear white solid. R_f (6 : 4 hexanes : ethyl acetate) = 0.8. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.48-6.47 (m, 15 H), 6.27 (m, 1 H), 6.02-5.70 (m, 2 H), 5.35-4.82 (m, 4 H), 1.31 (m, 3 H).



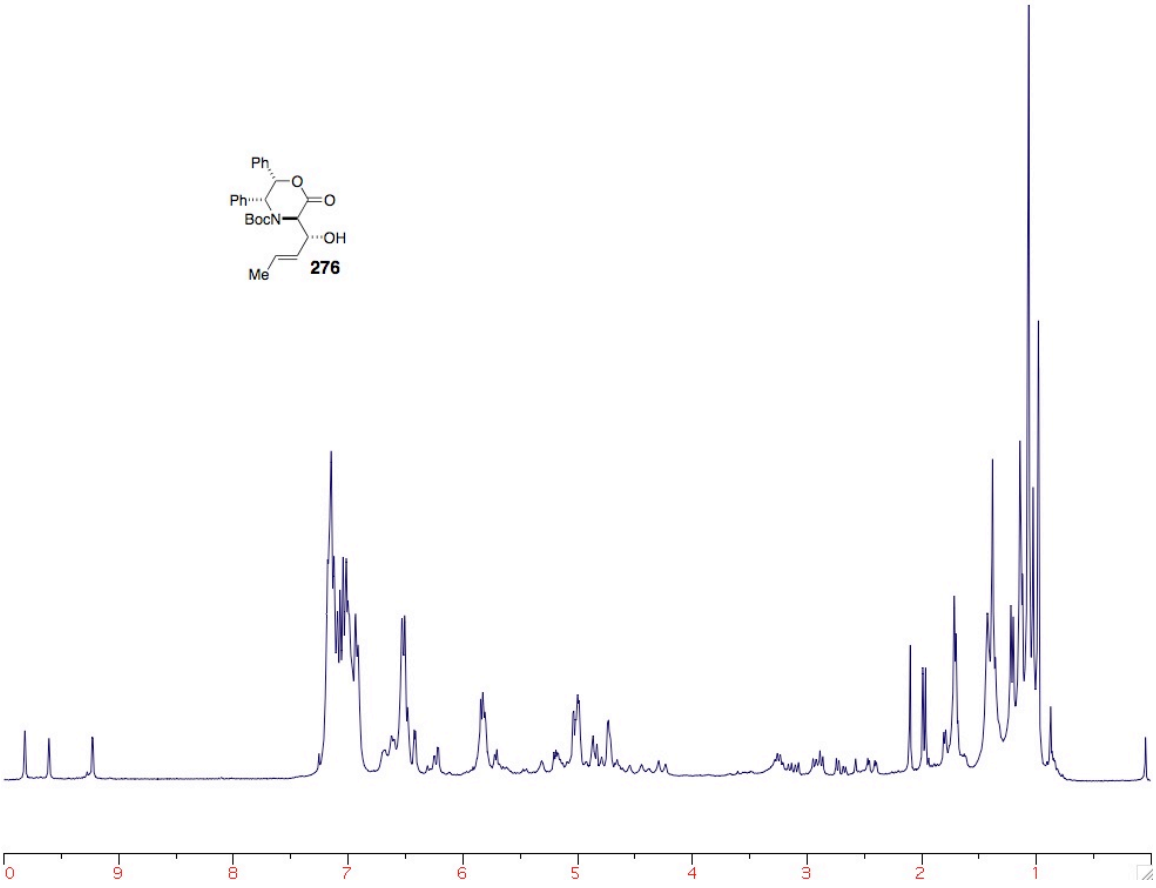


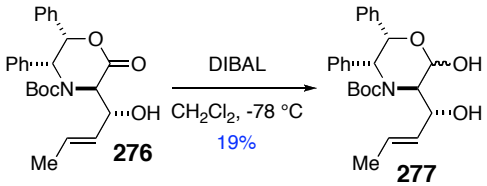
A solution of **196** (520 mg, 1.47 mmol) in THF (25 mL) at -78 °C was treated with TBSCl (230 mg, 1.53 mmol) and KHMDS (4.0 mL, 2.0 mmol); the combined solution was stirred 30 min at -78 °C and allowed to warm to ambient temperature. The mixture was evaporated and flushed through a base-washed silica plug to yield 521 mg (76%) **275** as a clear oil.



A solution of **275** (437 mg, 0.93 mmol) and **273** (0.78 mL, 9.4 mmol) in Et_2O (10 mL) at -95 °C was treated with TBAF (2.8 mL) and stirred 15 min at that temperature, then

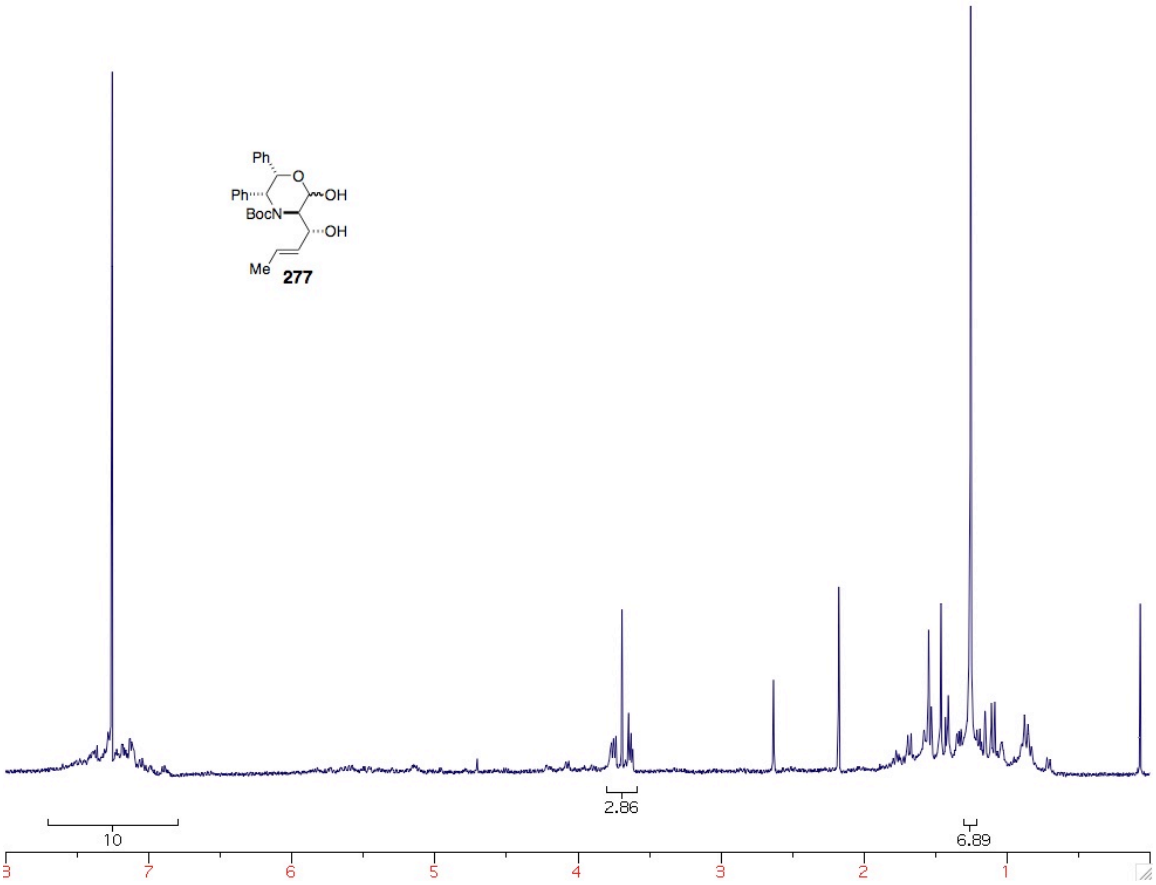
quenched with H_2O (10 mL) and allowed to warm to ambient temperature overnight. The mixture was diluted with EtOAc and H_2O (40 mL each) and the aqueous layer extracted with EtOAc (2 x 25 mL); the combined organic layer was washed with brine (3 x 25 mL), dried ($MgSO_4$), and concentrated to give 735 mg crude product. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 216 mg (55%) **276** as a clear oil. R_f (8:2 hexanes : ethyl acetate) = 0.33.

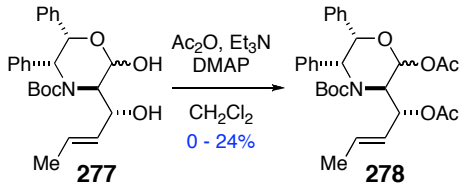




A solution of **276** (57 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C was treated with DIBAL (0.65 mL, 0.65 mmol, 1 M in PhMe) and the solution stirred 35 min at -78 °C, then quenched with H_2O (1 drop) and allowed to warm to ambient temperature. The solution was adsorbed onto Florisil (0.5 g), concentrated, and flushed through a silica

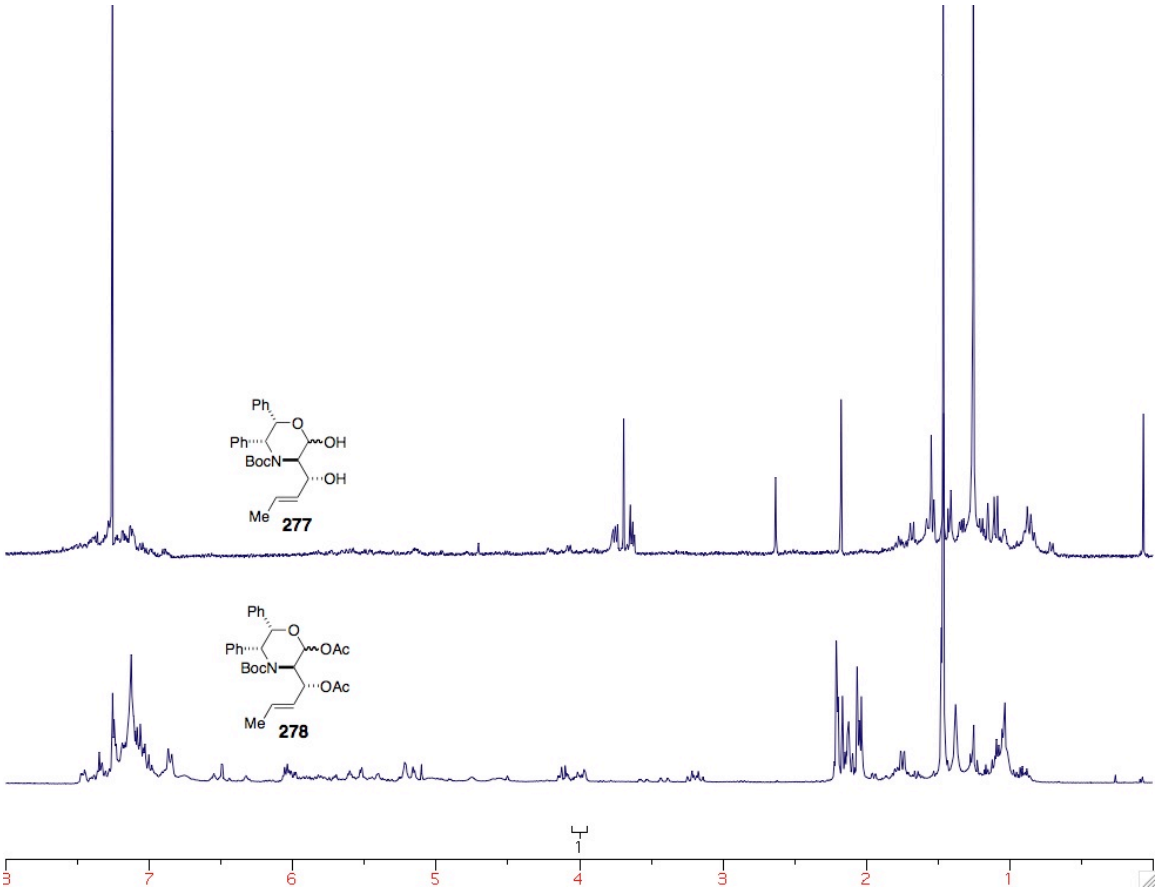
plug with EtOAc. Evaporation in vacuo yielded 11 mg (19%) **277**. R_f (7:3 hexanes : ethyl acetate) = 0.0.

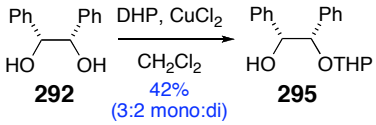




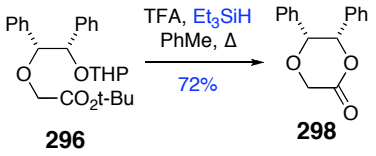
A solution of **276** (239 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) at -78 °C was treated with DIBAL (2.8 mL, 2.8 mmol, 1 M in PhMe) and the solution stirred 1 h at -78 °C, then quenched with H_2O (several drops) and allowed to warm to ambient temperature. The mixture was filtered and the filtrate rinsed with brine (2 x 15 mL), dried (Na_2SO_4), and concentrated in vacuo to give 143 mg crude **277**. The material was redissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C, then treated with Et_3N (0.14 mL, 1.0 mmol) and Ac_2O (0.10 mL, 1.1 mmol). The solution was stirred 20 h at ambient temperature and concentrated to

give 244 mg yellow oil. Flash chromatography (8:2 hexanes : ethyl acetate) gave 69 mg (24%) **278**. R_f (8:2 hexanes : ethyl acetate) = 0.33.

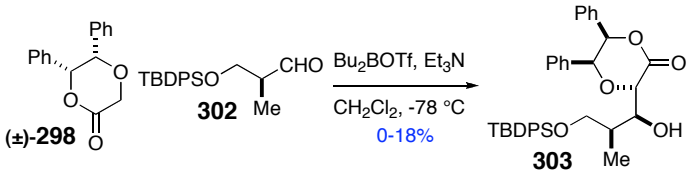




A solution of *meso*-hydrobenzoin (2.1423 g, 10.0 mmol) and copper (II) chloride (202 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was treated with dihydropyran (0.91 mL, 10.0 mmol) and stirred 2 h; the resultant green solid was diluted with CH_2Cl_2 (45 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers washed with brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo to give 2.142 g white powder. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 755 mg (25%) **295** and 645 mg (17%) of bis-THP product.

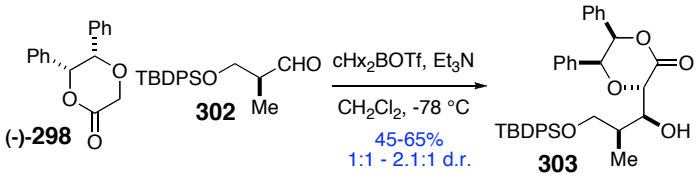


A solution of **296** (427 mg, 1.04 mmol), TFA (0.025 mL, 0.32 mmol), and Et_3SiH (0.165 mL, 1.03 mmol) in PhMe (4 mL) was refluxed under a condenser for 24 h at 120 °C, then cooled to ambient temperature and diluted with saturated aqueous $NaHCO_3$ (6 mL). The aqueous layer was extracted with EtOAc (10 mL) and the combined organic layers dried (Na_2SO_4) and evaporated in vacuo to give 360 mg of orange-brown oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 190 mg (72%) **298** as colorless oil.



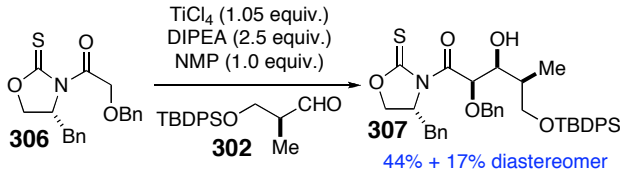
A solution of **298** (4.8 mg, 0.019 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was treated with Bu_2BOTf (36 µL, 0.036 mmol, 1 M in CH_2Cl_2) and Et_3N (7.4 µL, 0.053 mmol) to produce a pale yellow solution that was stirred 10 min at 0 °C and cooled to -78 °C. A solution of **302** (6.8 mg, 0.021 mmol) in CH_2Cl_2 (0.5 mL) was added via canula to produce a colorless solution that was stirred 45 min at -78 °C, warmed to 0 °C over 30 min, and quenched with pH 7 phosphate buffer (0.025 M) and allowed to warm to ambient temperature. The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic extracts dried (Na_2SO_4) to give 13.5 mg yellow oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 2 mg (18%) **303**.

CMB278

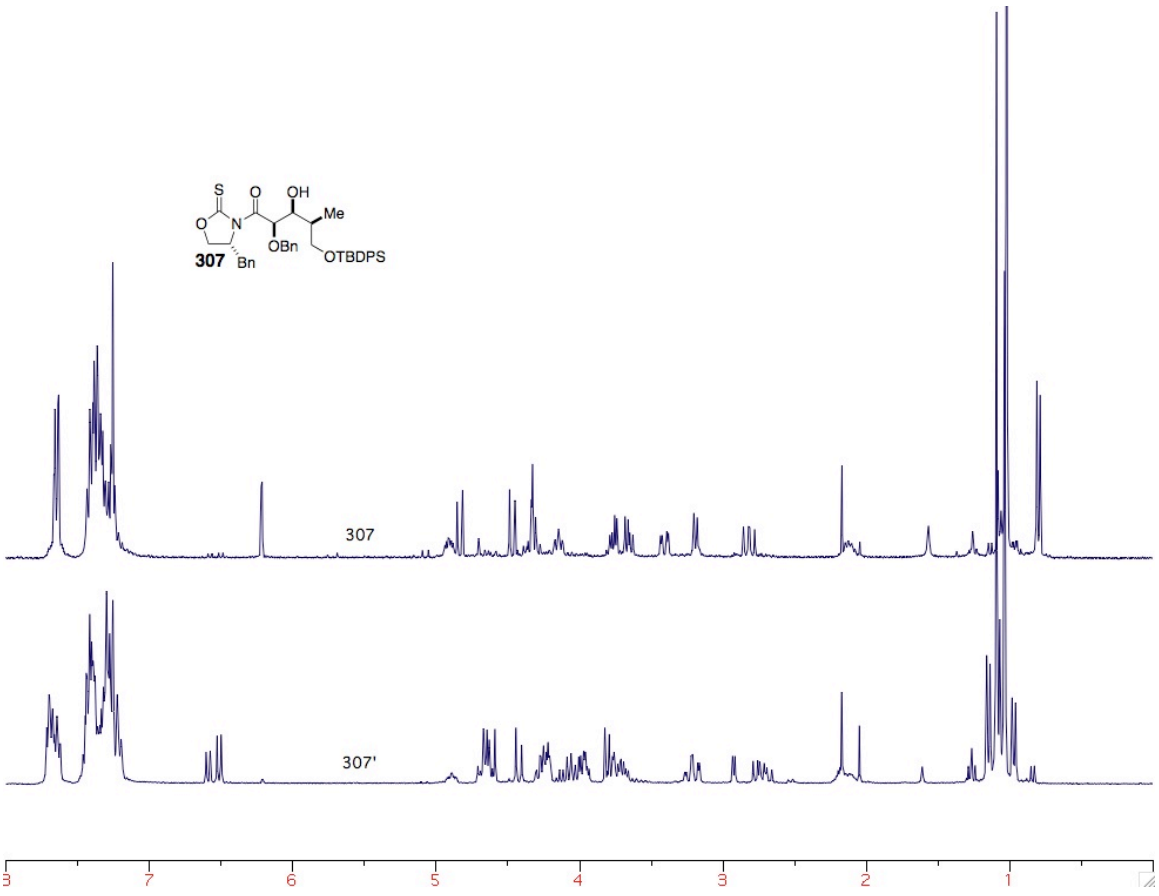


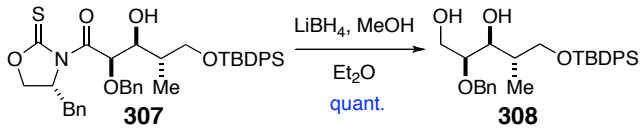
To a solution of lactone CMB420 (50.2 mg, 0.20 mmol) in CH_2Cl_2 in a 25-mL round-bottom flask at -78 °C was added Et_3N dropwise over 1 min and the solution stirred 5 min at -78 °C. Dicyclohexylboron triflate (0.61 mL, 0.60 mmol, 0.98 M in CH_2Cl_2) was

added dropwise over 3 min and the solution stirred 2.3 h at -78 °C. A solution of aldehyde (94 mg, 0.29 mmol) in CH_2Cl_2 (2 mL + 2 mL rinse) was added via canula and the combined solution stirred 2 h at -78 °C, then quenched with pH 7 phosphate buffer (1.0 mL, 0.0025 M), MeOH (0.2 mL), and 30% aqueous H_2O_2 (0.1 mL). The mixture was warmed to ambient temperature with stirring, then diluted with Et_2O (38 mL) and washed with saturated aqueous $NaHCO_3$ (2.5 mL). The aqueous layer was back-extracted with Et_2O (3 x 20 mL) and the combined organic layers washed with 10% HCl (5 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and evaporated to give 160 mg of colorless oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 31 mg (27%) of CMB426B, 32 mg (28%) of CMB426C, and 12 mg (10%) of mixed fractions. NMR spectra were too messy for analysis. CMB426B: HRMS (FAB+) calcd. for $C_{36}H_{41}O_5Si$ ($M+H^+$) (*m*/*z*): 581.2723, found (*m*/*z*): 581.2712. CMB426C: HRMS (FAB+) calcd. for $C_{36}H_{41}O_5Si$ ($M+H^+$) (*m*/*z*): 581.2723, found (*m*/*z*): 581.2722.

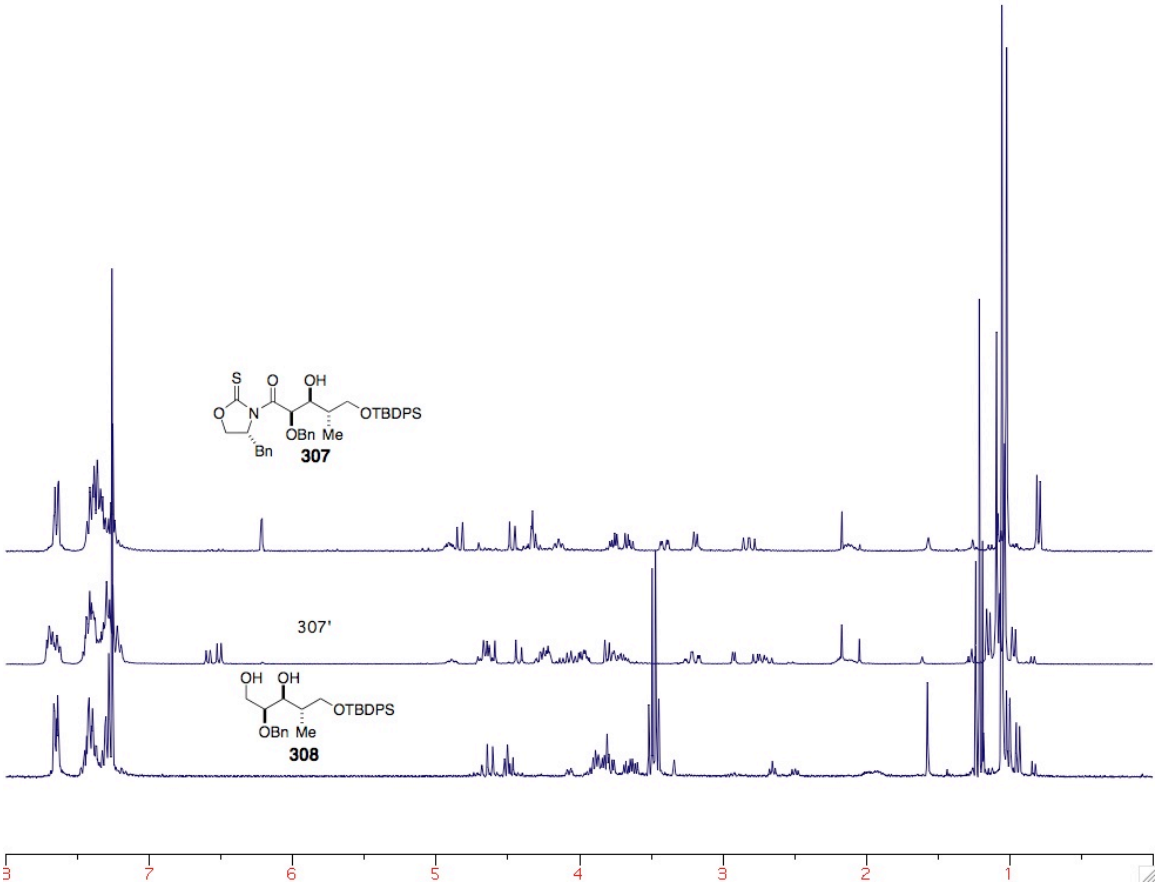


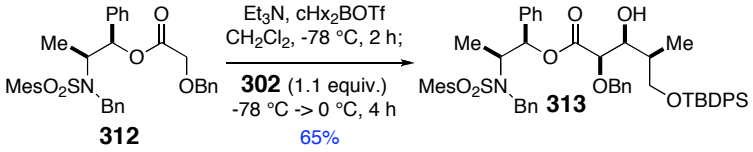
A solution of **306** (706 mg, 2.07 mmol) in CH_2Cl_2 (21 mL) at -78 °C was treated with $TiCl_4$ (0.24 mL, 2.19 mmol) and the solution stirred 15 min at -78 °C. DIPEA (0.90 mL, 5.17 mmol) was added and the solution stirred 2.5 h at -78 °C; *N*-methylpyrrolidinone (0.20 mL, 2.07 mmol) was added and the solution stirred 20 min at -78 °C. A solution of **302** (1.620 g, 4.96 mmol) in CH_2Cl_2 (5 mL + 5 mL rinse) was added via canula and the combined solution stirred 2 h at -78 °C and 2 h at -40 °C, then quenched with half-saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers dried (Na_2SO_4) and evaporated in vacuo to give 2.621 g crude product. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 601 mg (44%) **307** and 236 mg (17%) of its diastereomer.





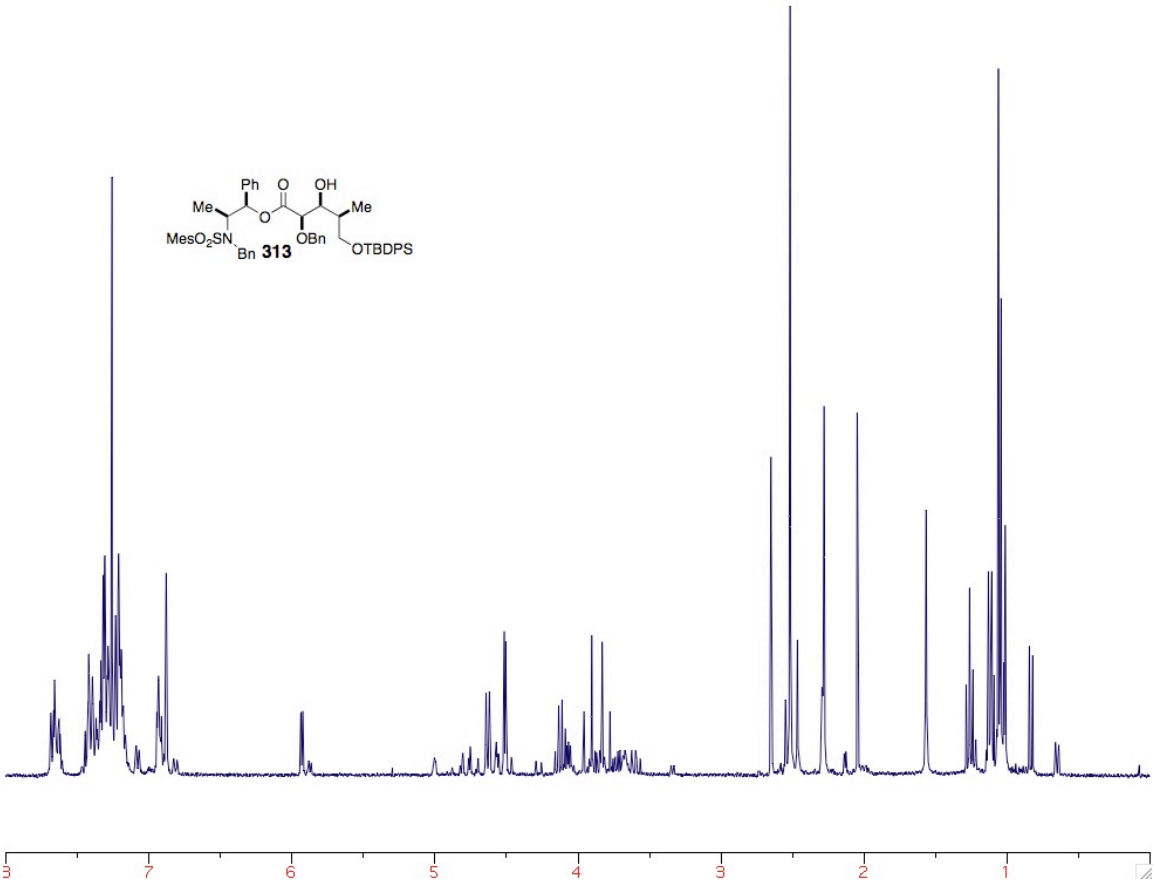
A solution of **307** (236.8 mg, 0.35 mmol) in Et_2O (3.6 mL) at 0 °C was treated with solid $LiBH_4$ (10.0 mg, 0.46 mmol) and MeOH (0.02 mL, 0.49 mmol); the solution was stirred 15 min at 0 °C, causing bubbling, and 2 h at ambient temperature, then quenched with 14% aqueous NaOH (3 mL) and stirred an additional 30 min. The layers were separated and the aqueous layer back-extracted with Et_2O (5 mL); the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo and on pump to yield 160-180 mg (quant) **308** as a pale yellow oil that was carried on without purification.

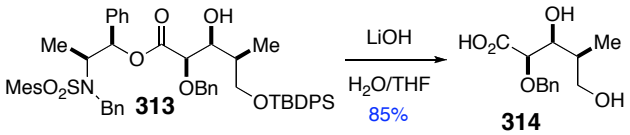




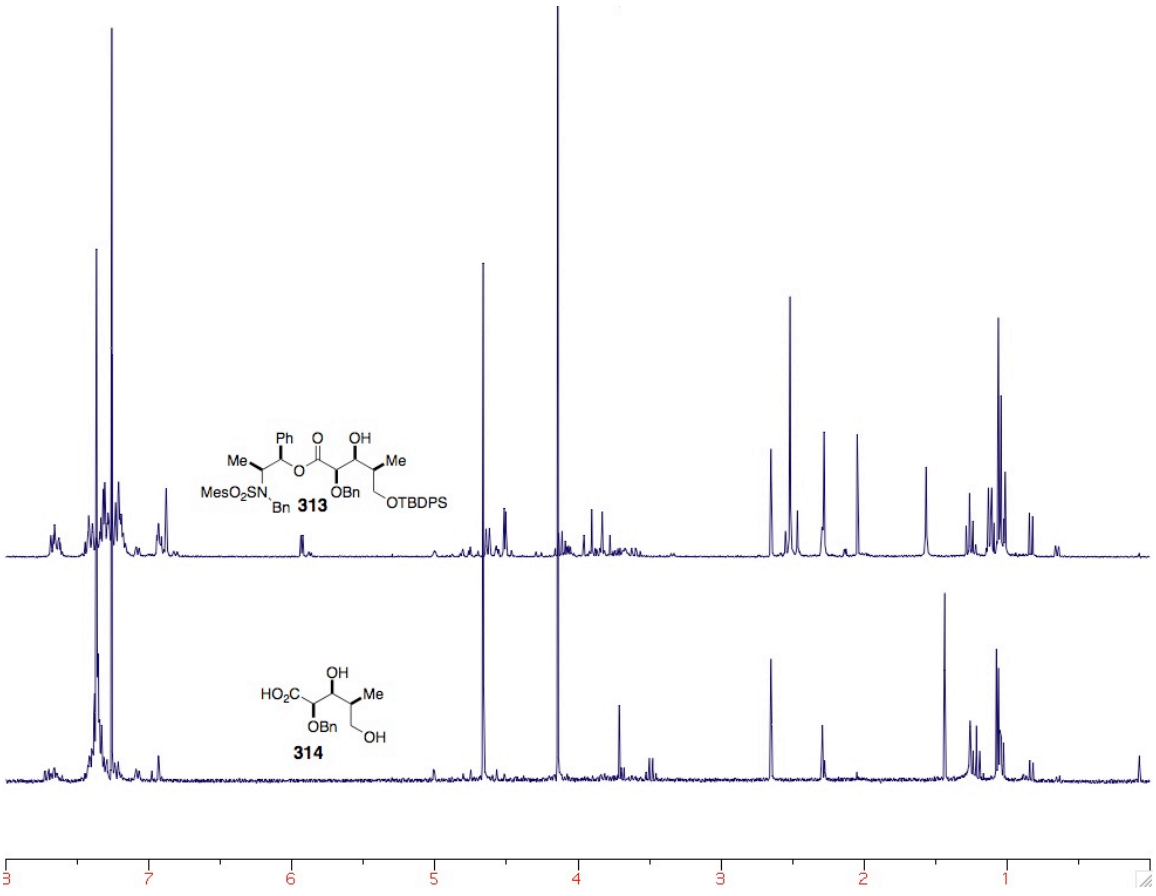
A solution of **312** (99.4 mg, 0.20 mmol) in CH_2Cl_2 (15 mL) at -78 °C was treated dropwise over 1 min with Et_3N (0.07 mL, 0.50 mmol) and the solution stirred 5 min; dicyclohexylboron triflate (0.60 mL, 0.59 mmol, 0.98 M in CH_2Cl_2) was added dropwise over 5 min and the solution stirred 3.5 h at -78 °C. A solution of **302** (95.7 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) was added and the combined solution stirred 2 h at -78 °C and 2 h at 0 °C, then quenched with pH 7 phosphate buffer (1.0 mL, 0.0025 M), MeOH (1.0 mL), and 30% aqueous H_2O_2 (0.5 mL). The quenched solution was allowed to warm to ambient temperature overnight, then diluted with CH_2Cl_2 (75 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was back-extracted with Et_2O (20 mL) and the combined organic layers washed with 10% aqueous HCl (10 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo to give 249 mg yellow oil. Flash

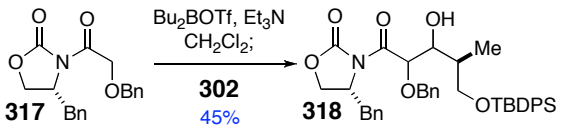
chromatography (8:2 hexanes : ethyl acetate) yielded 101 mg (65%) **313**. R_f (8:2 hexanes : ethyl acetate) = 0.47.





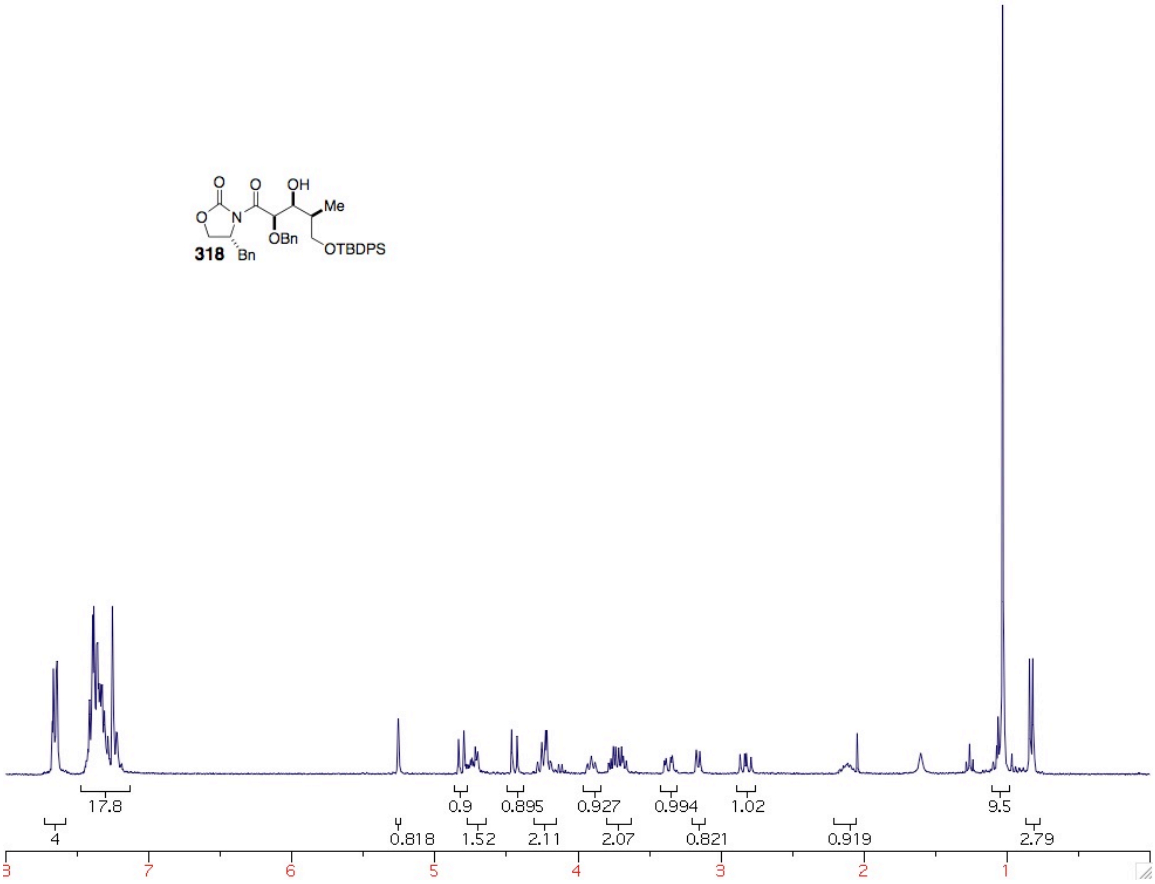
A solution of **313** (46.1 mg, 0.051 mmol) in H_2O (1 mL) and THF (2 mL) at 0 °C was treated with LiOH • H_2O (10.8 mg, 0.25 mmol) and the solution stirred 4 h at 0 °C and 4 h at ambient temperature, then diluted with Et_2O (5 mL) and H_2O (2 mL). The aqueous layer was adjusted to pH 1-2 (1 M HCl) and extracted with Et_2O (4 x 5 mL); the combined acidic organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give 11 mg (85%) **314**.

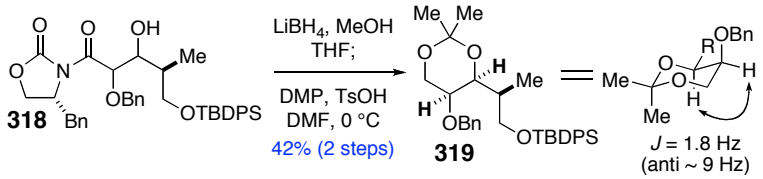




To a stirred solution of **317** (200.6 mg, 0.617 mmol) in CH_2Cl_2 (2.0 mL) in a 10-mL round-bottom flask at -78 °C were added Bu_2BOTf (0.62 mL, 0.62 M, 1 M in CH_2Cl_2) and DIPEA (0.11 mL, 0.63 mmol) dropwise via syringe and the yellow solution stirred 1 h at -78 °C. A solution of **302** (273.3 mg, 0.837 mmol) in CH_2Cl_2 (1 mL + 1 mL rinse) was added via canula from a 50-mL round-bottom flask and the combined solution stirred 90 min at ambient temperature, then cooled to 0 °C and quenched with pH 7 phosphate buffer (0.0025 M, 0.60 mL), MeOH (3.17 mL), and 30% aqueous H_2O_2 (0.70 mL). The solution was allowed to warm to ambient temperature over 1 h and diluted with H_2O and CH_2Cl_2 (10 mL ea.); the aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layers washed with brine (10 mL), dried (Na_2SO_4), and evaporated to give 401 mg of pale yellow oil. Flash chromatography (8:2 hexanes : ethyl acetate)

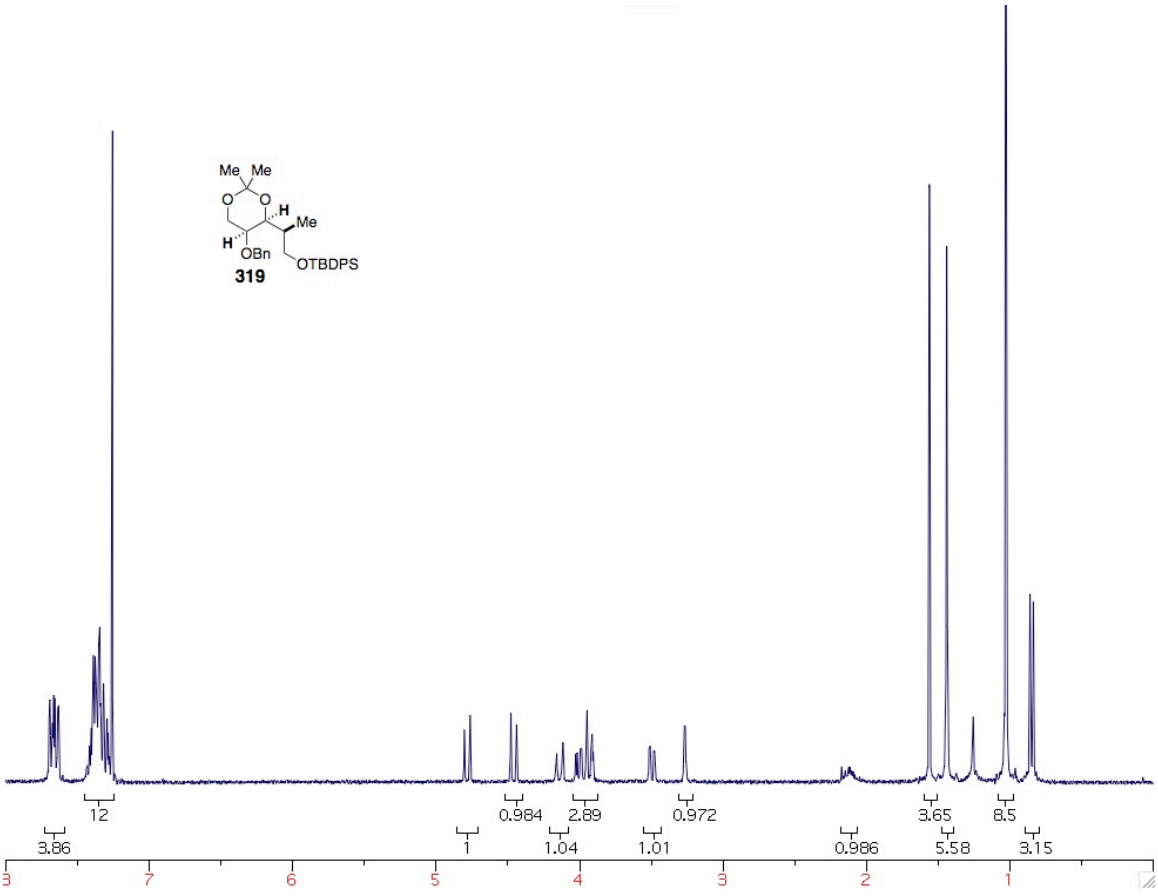
yielded 180.2 mg (45%) **318** as a pale yellow oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.71-7.59 (d, 4 H, Ar H), 7.46-7.21 (m, 16 H, Ar H), 5.26 (s, 1 H, OH), 4.82 (1/2 ABq, 1 H, J = 11.4 Hz), 4.73 (m, 1 H, N-CH), 4.44 (1/2 ABq, 1 H, J = 11.4 Hz), 4.23 (m, 2 H, ox. O-CH_2), 3.91 (d, 1 H, J = 9.6 Hz, BnO-H), 3.73 (ABm, 2 H, CH_2-OTBDPS), 3.37 (1/2 ABq, 1 H, J = 13.5, 5.2 Hz, ox. CH_2-Ph), 3.16 (m, 1 H, CH-OH), 2.83 (1/2 ABq, 1 H, J = 13.3, 9.4 Hz, ox. CH_2Ph), 2.12 (m, 1 H, CH-Me), 1.03 (s, 9 H, ^{t}Bu), 0.83 (d, 3 H, J = 6.8 Hz, CH_3-CH). HRMS (FAB+) calcd. for $C_{39}H_{46}NO_6Si$ ($M+H^+$) (m/z): 652.3094, found (m/z): 652.3097.

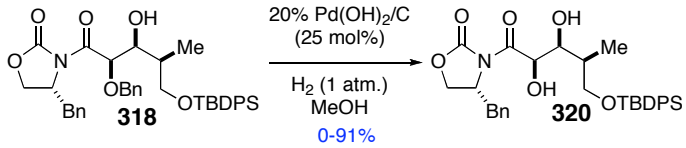




A stirred solution of **318** (56.5 mg, 0.058 mmol) in THF (0.5 mL) was treated with $LiBH_4$ (4.0 mg, 0.18 mmol) and MeOH (0.005 mL, 0.12 mmol) and the solution stirred 25 h,

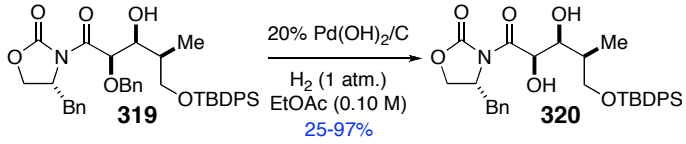
then treated with Rochelle's salt and Et_2O (1 mL each). The solution was stirred 2 h and diluted with H_2O and Et_2O (5 mL each); the aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic extracts washed with brine (5 mL), dried (Na_2SO_4), and evaporated in vacuo to give 44.5 mg oil. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 22.2 mg (80%) **319** as a colorless oil slightly contaminated with oxazolidinone.



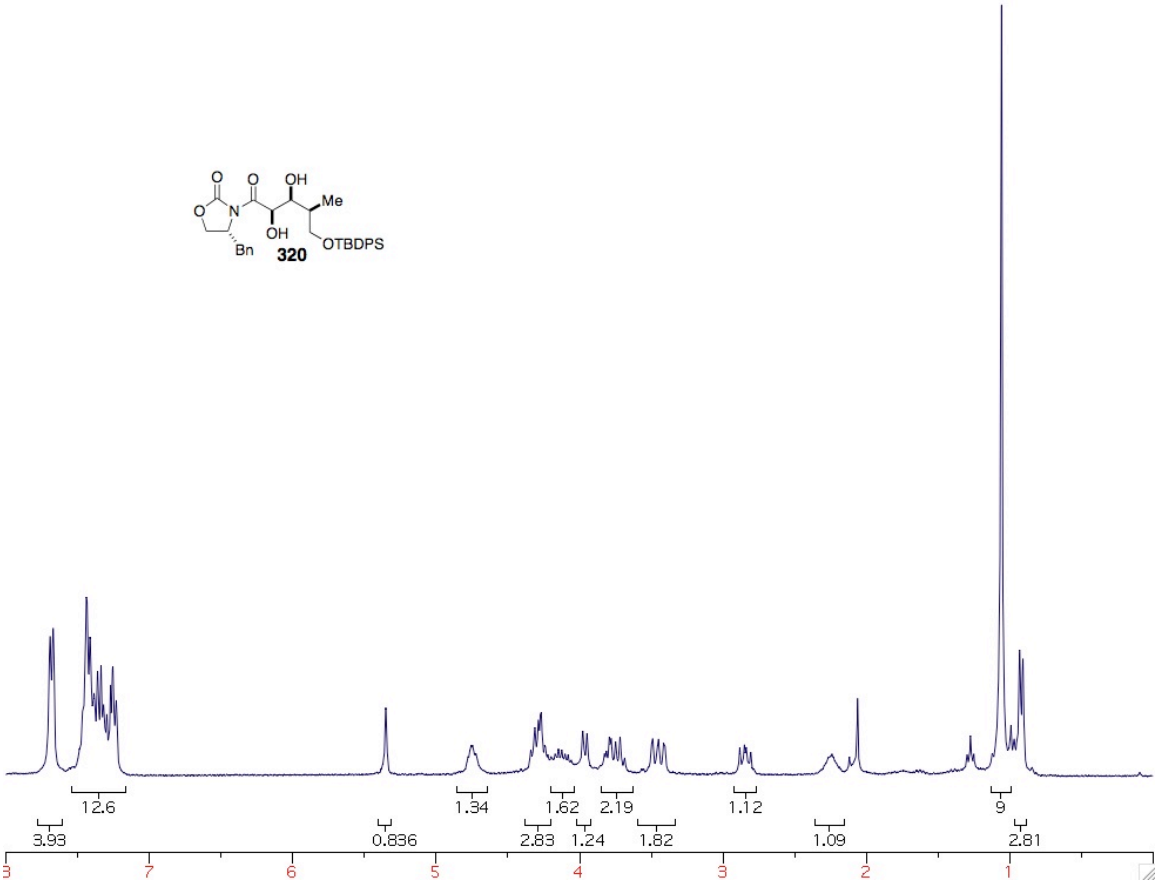


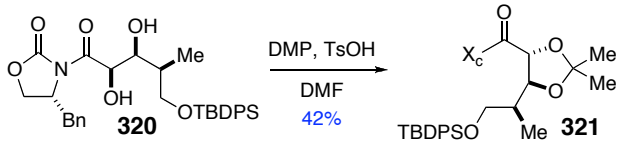
A solution of **319** (54.4 mg, 0.083 mmol) in MeOH (1.67 mL) was treated with 20% palladium hydroxide on carbon (10.9 mg, 0.020 mmol) and stirred 24 h under an H_2 balloon; the solution was filtered through a pad of Celite and evaporated in vacuo to give 42.8 mg (91%) **320** as a colorless oil used without further purification.

CMB588/630

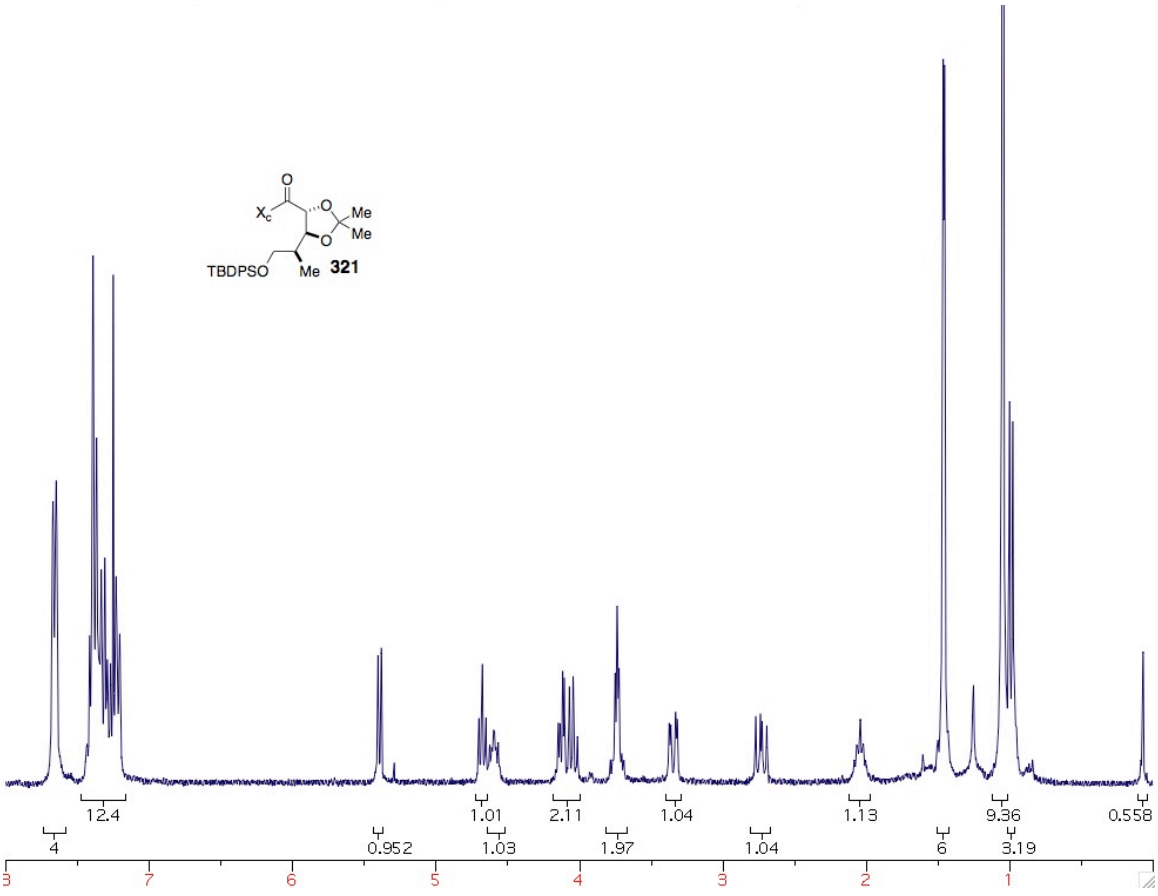


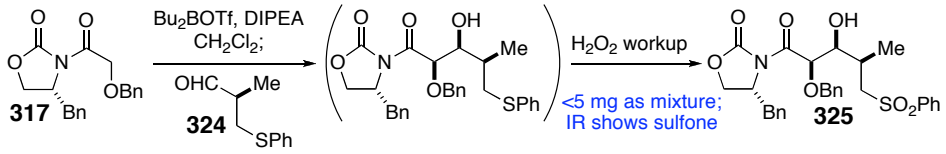
A solution of **319** (65.2 mg, 0.100 mmol) in EtOAc (1.0 mL) was treated with 20% palladium hydroxide on carbon (53.4 mg, 0.100 mmol) and stirred 24 h under an H_2 balloon; the solution was filtered through a pad of Celite and evaporated in vacuo to give 54.5 mg (97%) **320** as a colorless oil pure by NMR. R_f (9:1 hexanes : ethyl acetate) = 0.14. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.73-7.63 (m, 4 H), 7.52-7.18 (m, 12 H), 5.35 (s, 1 H), 4.76 (m, 1 H), 4.41-3.37 (m, 9 H), 2.85 (m, 1 H), 2.25 (m, 1 H), 1.06 (s, 9 H), 0.92 (d, 3 H, J = 6.9 Hz).



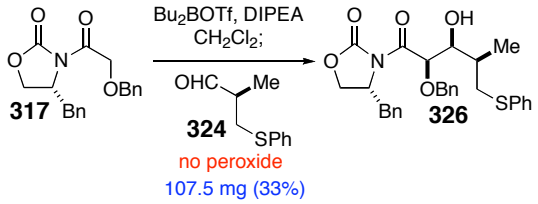


A solution of **320** (44.2 mg, 0.079 mmol) in acetone (0.395 mL) was treated with 2,2-dimethoxypropane (0.08 mL, 0.65 mmol) and TsOH • H_2O (1.5 mg, 0.0079 mmol) and stirred 24 h, then neutralized with Et_3N (0.05 mL). The mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 25 mL), and the combined organic extracts were dried and evaporated in vacuo to give 57.1 mg crude product. Flash chromatography (9:1 hexanes : ethyl acetate) yielded 20.0 mg (42%) **321**. R_f (9:1 hexanes : ethyl acetate) = 0.26. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.70-7.61 (m, 4 H), 7.46-7.18 (m, 12 H), 5.39 (d, 1 H, J = 6.9 Hz), 4.68 (t, 1 H, J = 6.9 Hz), 4.64-4.55 (m, 1 H), 4.16-4.02 (m, 2 H), 3.74 (m, 2 H), 3.34 (1/2ABqd, 1 H, J = 13.2, 3.3 Hz), 2.74 (1/2ABqd, 1 H, J = 13.2, 9.6 Hz), 2.04 (m, 1 H), 1.46 (2s, 6 H), 1.05 (s, 9 H), 0.99 (d, 3 H, J = 6.9 Hz).

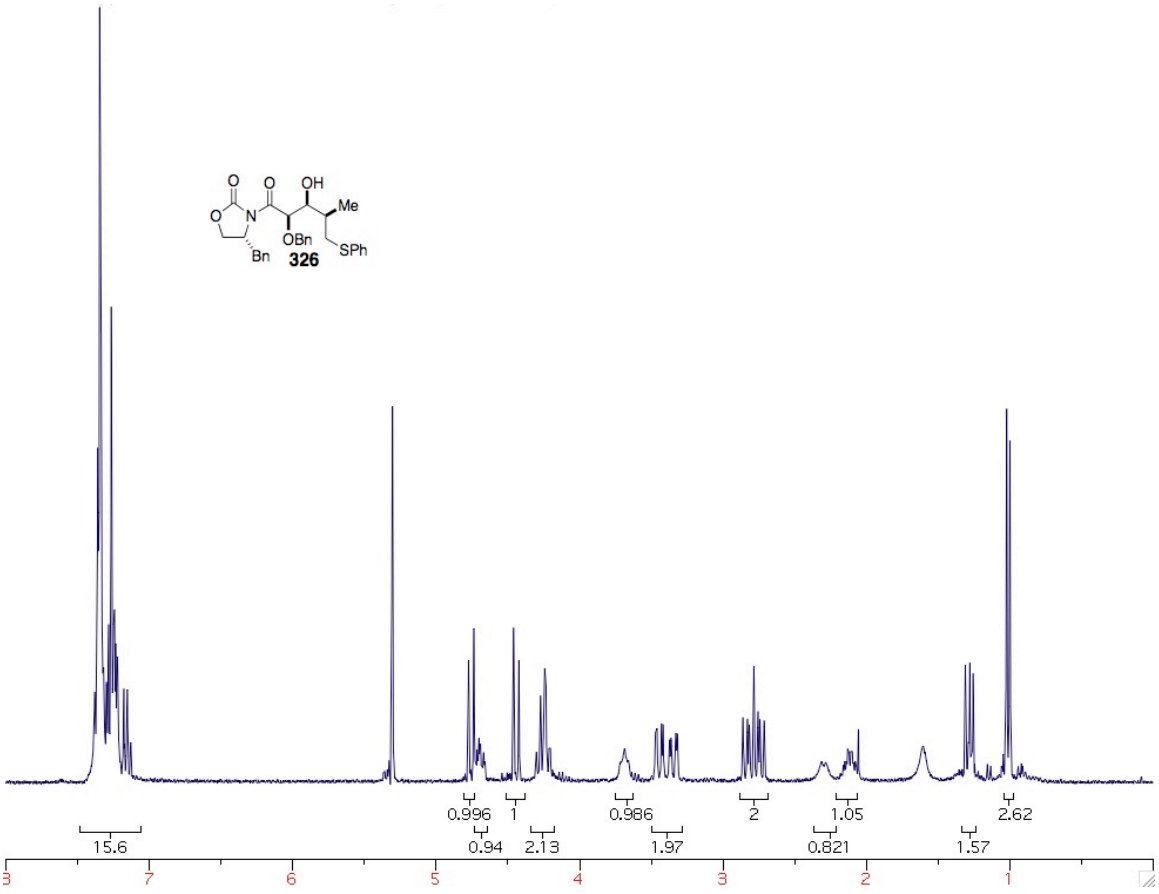


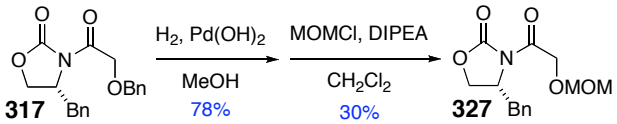


A solution of **317** (203.5 mg, 0.625 mmol) in CH_2Cl_2 (2.0 mL) was treated dropwise via syringe with Bu_2BOTf (0.69 mL, 0.69 mmol, 1 M in CH_2Cl_2) and DIPEA (0.12 mL, 0.69 mmol) and the solution stirred 70 min at -78 °C. A solution of **324** (147.7 mg, 0.82 mmol) in CH_2Cl_2 (1.0 mL + 1.0 mL) was added via syringe and the cooling bath removed; the solution was stirred 2 h 5 min at ambient temperature and quenched with pH 7 phosphate buffer (0.61 mL, 0.0025 M), MeOH (3.2 mL), and 30% aqueous H_2O_2 (0.70 mL), then stirred 7 d. The colorless solution was diluted with H_2O and CH_2Cl_2 (10 mL each) and the aqueous layer was extracted with CH_2Cl_2 (10 mL); the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and evaporated in vacuo to give 256 mg colorless oil. Flash chromatography (8:2 to 1:1 hexanes : ethyl acetate) yielded >80 mg unreacted **317** and 6 mg **325** as a mixture of compounds.



A solution of **317** (206.8 mg, 0.636 mmol) in CH_2Cl_2 (2.0 mL) was treated via syringe with Bu_2BOTf (0.66 mL, 0.66 mmol, 1 M in CH_2Cl_2) and DIPEA (0.115 mL, 0.66 mmol) and the solution stirred 75 min at -78 °C. A solution of **324** (118.1 mg, 0.655 mmol) in CH_2Cl_2 (1.2 mL) was added via canula and the cooling bath removed; the solution was stirred 90 min and quenched with half-saturated aqueous NH_4Cl (3 mL), then stirred 16 h and diluted with H_2O and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and evaporated in vacuo to give 382.3 mg crude product. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 107.5 mg (33%) **326**. R_f (8:2 hexanes : ethyl acetate) = 0.09. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.41-7.12 (m, 16 H), 4.75 (1/2ABq, 1 H, J = 11.1 Hz), 4.73-4.65 (m, 1 H), 4.44 (1/2ABq, 1 H, J = 11.1 Hz), 4.24 (m, 2 H), 3.68 (m, 1 H), 3.44 (1/2ABqd, 1 H, J = 12.6, 3.3 Hz), 3.34 (1/2ABqd, 1 H, J = 13.2, 3.3 Hz), 2.87-2.70 (m, 2 H), 2.30 (m, 1 H), 2.12 (m, 1 H), 1.28 (m, 2 H), 1.01 (d, 3 H, J = 6.9 Hz).

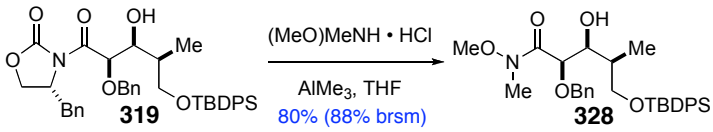




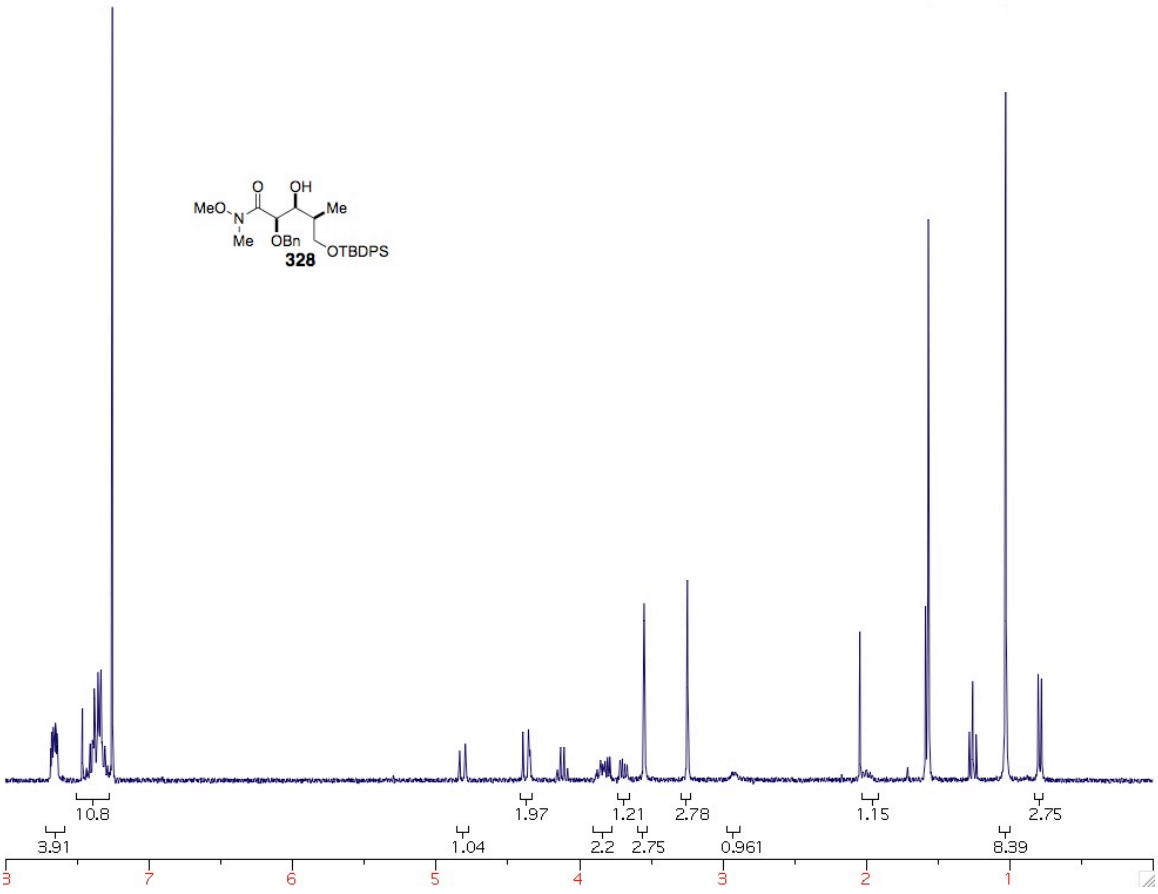
A solution of **317** (1.0037 g, 3.08 mmol) in MeOH (13.2 mL) was charged with 20% $Pd(OH)_2/C$ (409.7 mg, 0.77 mmol) and stirred 4 h under an H_2 balloon, then filtered through a pad of Celite. The filtrate was evaporated to give 564 mg (78%) alcohol.

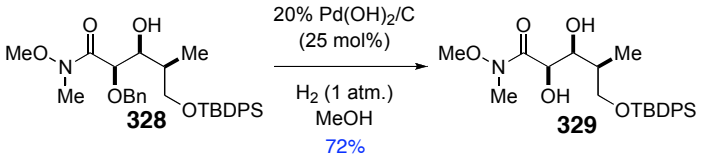
To a stirred solution of alcohol (287 mg, 1.22 mmol) in Et_2O (2.24 mL) and DMF (0.56 mL) at 0 °C was added NaH (64.0 mg, 1.60 mmol) portionwise and the solution stirred 30 min while warming to ambient temperature. The solution was recooled to 0 °C and stirred 25 min; MOMCl (0.12 mL) was added via syringe and the solution stirred 16 h while allowed to warm to ambient temperature. The solution was recooled to 0 °C, then quenched with MeOH (1.0 mL) and diluted with H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the organic extracts washed with brine (10 mL),

dried (Na_2SO_4), and evaporated in vacuo to give 277 mg oil. Flash chromatography (7:3 to 1:1 hexanes : ethyl acetate) yieled 103 mg (30%) **327**.

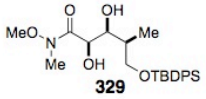


A mixture of Weinreb salt (2.44 g, 25.0 mmol) in THF (4.5 mL) in a 50-mL flame-dried round-bottom flask at -33 °C was treated with $AlMe_3$ (13 mL, 26 mmol, 2 M in toluene) and the mixture stirred 15 min while warming to ambient temperature, eventually producing a homogeneous solution. The solution was recooled to -33 °C and a solution of **319** (651.9 mg, 1.00 mmol) in THF (4.5 mL) was added via canula; the combined solution was stirred 4 h at 0 °C and 24 h at 3 °C, then canulated into a stirring mixture of CH_2Cl_2 and saturated aqueous Rochelle's salt (1:1, 60 mL). This mixture was stirred 24 h at ambient temperature, then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give 0.93 g crude product; flash chromatography (7:3 hexanes : ethyl acetate) yielded 435.5 mg (81%) **328**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.7-7.63 (m, 4 H), 7.47-7.28 (m, 11 H), 4.80 (1/2ABq, J = 11.8 Hz), 4.38 (m, 2 H), 3.89-3.78 (m, 2 H), 3.70 (1/2ABqd, J = 9.9, 4.67 Hz), 3.55 (s, 3 H), 3.25 (s, 3 H), 2.92 (m, 1 H), 2.00 (m, 1 H), 1.03 (s, 9 H), 0.79 (d, 3 H, J = 6.8 Hz). HRMS (FAB^+) calc'd for $C_{31}H_{42}NO_5Si$ ($M+H^+$) (*m/z*): 536.2832; found (*m/z*): 536.2832.

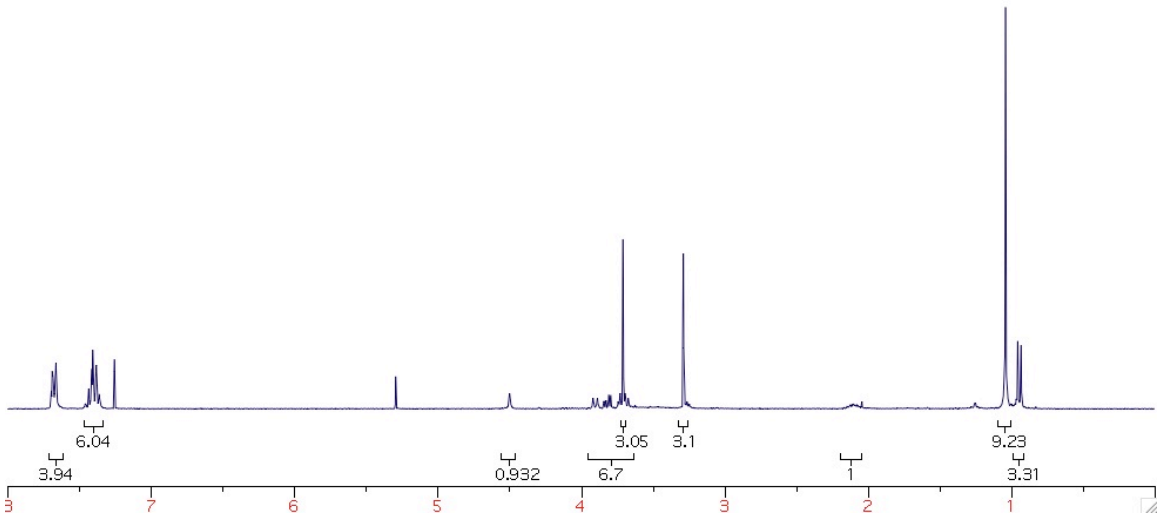


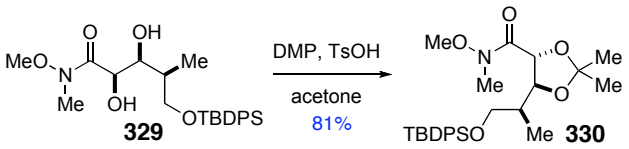


A mixture of **328** (110.6 mg, 0.206 mmol) and 20% $Pd(OH)_2/C$ (111.1 mg, 0.209 mmol) in MeOH (1.5 mL) was stirred 17 h under an H_2 balloon, then filtered through a pad of Celite and evaporated in vacuo to give 90 mg colorless oil. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 66.0 mg (72%) **329** as a whitish solid. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.70-7.62 (m, 4 H), 7.47-7.34 (m, 6 H), 4.50 (s, 1 H), 3.95-3.65 (m, 4 H), 3.71 (s, 3 H), 3.29 (s, 3 H), 2.11 (m, 1 H), 1.04 (s, 9 H), 0.95 (d, 3 H, J = 6.6 Hz).



329





329 **330**

A solution of **328** (278.9 mg, 0.521 mmol) in MeOH (5 mL) in a 50-mL round-bottom flask was treated with 20% $Pd(OH)_2/C$ (109.3 mg, 0.157 mmol), then stirred 24 h under an H_2 balloon. The mixture was filtered through Celite and evaporated to give 195.3 mg crude **329**, which was dissolved in acetone (5.2 mL) and treated with 2,2-dimethoxypropane (0.32 mL, 2.6 mmol) and recrystallized *p*-toluenesulfonic acid (13.5 mg, 0.08 mmol). This solution was stirred overnight, quenched with Et_3N (0.05 mL), and diluted with H_2O (10 mL); the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the organic extracts were dried (Na_2SO_4) and evaporated to give 189.7 mg of crude product. Flash chromatography (8:2 hexanes : ethyl acetate) yielded 135.5 mg (54%) **330** as a colorless oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.7-7.64 (m, 4 H), 7.44-7.33 (m, 6 H), 4.67-4.44 (m, 2 H), 3.77 (1/2ABqd, J = 9.9, 4.2 Hz), 3.72 (s, 3 H), 3.66 (1/2ABqd, J =

9.9, 6.1 Hz), 3.22 (s, 3 H), 1.96 (m, 1 H), 1.44-1.38 (m, 6 H), 1.04 (s, 9 H), 0.97 (d, 3 H, *J* = 6.9 Hz). HRMS (FAB$^+$) calc'd for $C_{27}H_{40}NO_5Si$ (M+H$^+$) (*m/z*): 486.2676; found (*m/z*): 486.2670.

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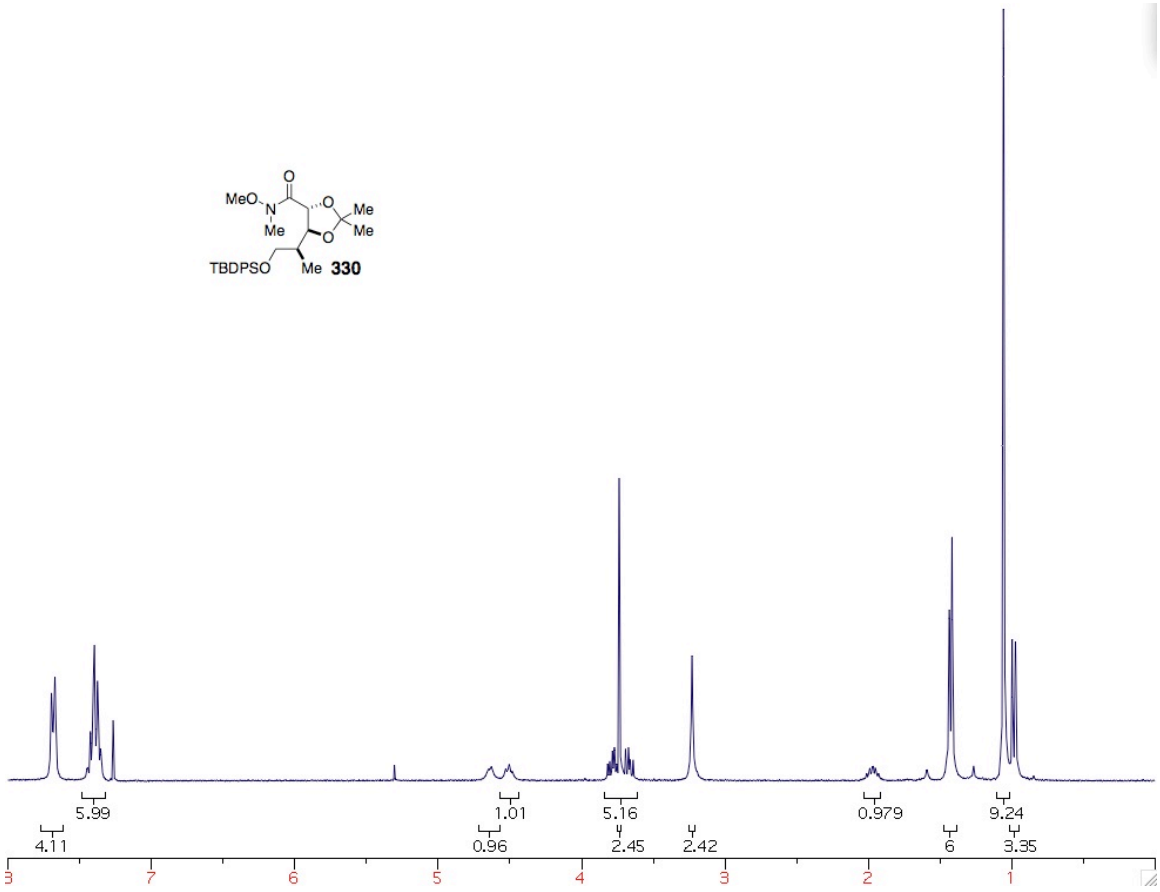
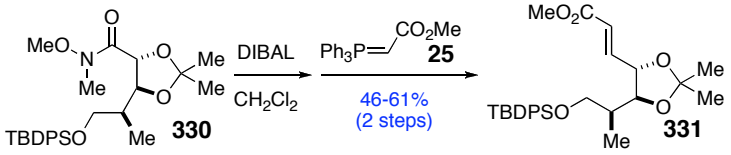
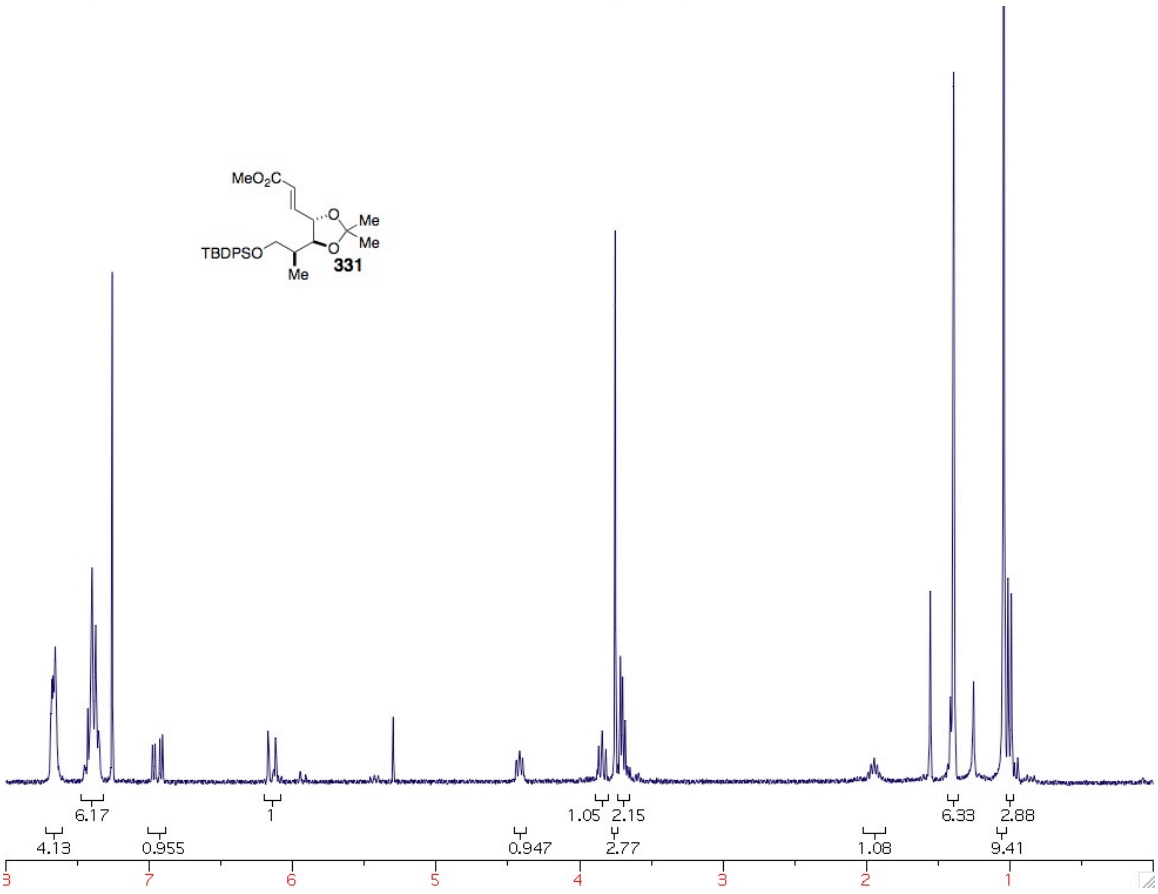
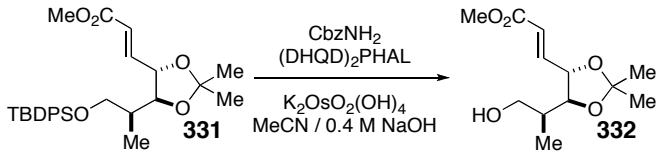




A solution of **330** (285.8 mg, 0.588 mmol) in Et_2O (6.0 mL) at -78 °C was treated with DIBAL (0.62 mL, 0.62 mmol, 1 M in hexanes) and the solution stirred 2 h at -78 °C, then quenched with saturated aqueous NH_4Cl (0.56 mL). The mixture was filtered and the filter cake rinsed with Et_2O (5 mL); the filtrate was evaporated in vacuo to give 228.3 mg (91%) aldehyde. The aldehyde was dissolved in CH_2Cl_2 (5 mL) along with **25** (343.7 mg, 1.03 mmol) and the solution stirred overnight, then evaporated in vacuo. Flash chromatography (9:1 hexanes : ethyl acetate) yielded 172.4 mg (61%) **331** as a pale

yellow oil. R_f (9:1 hexanes : ethyl acetate) = 0.44. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.69-7.63 (m, 4 H), 7.48-7.33 (m, 6 H), 6.94 (1/2ABqd, 1 H, J = 15.6, 5.7 Hz), 6.14 (1/2ABqd, 1 H, J = 15.6, 1.5 Hz), 4.42 (m, 1 H), 3.84 (m, 1 H), 3.75 (s, 3 H), 3.73-3.64 (m, 2 H), 1.95 (m, 1 H), 1.39 (2s, 6 H), 1.04 (s, 9 H), 1.00 (d, 3 H, J = 7.2 Hz).



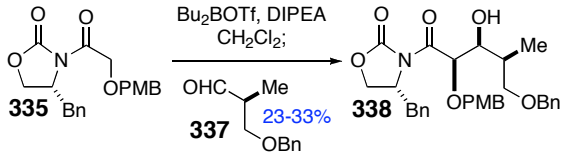


In a 1-mL HPLC vial 0.40 M NaOH (0.11 mL) was treated with $K_2OsO_2(OH)_4$ (3.1 mg) and the mixture stirred to dissolve, turning purple.

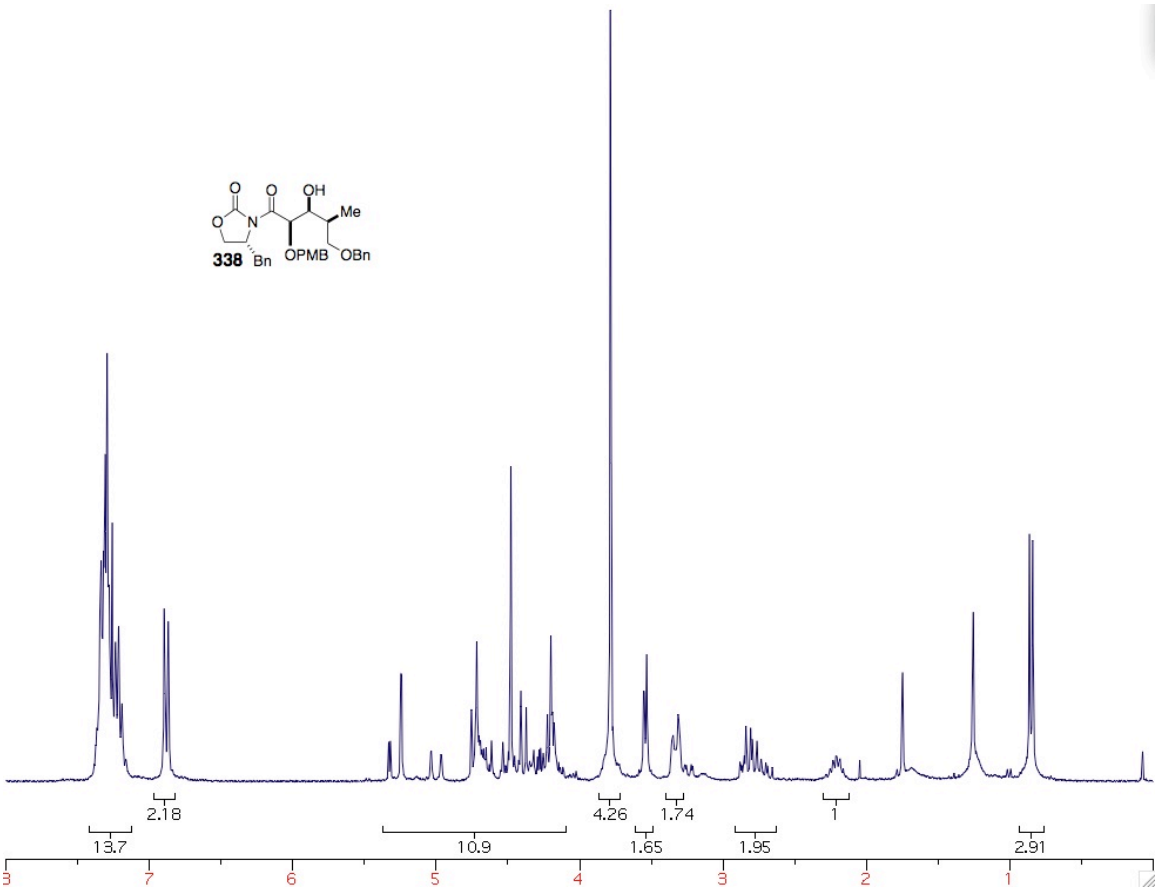
In a 5-mL round-bottom flask 0.40 M NaOH (1.47 mL) was treated with benzyl carbamate (98.8 mg) and MeCN (0.74 mL) and the solution stirred 10 min; the hood lights were turned out and the flask immersed in an ambient-temperature H_2O bath. To the flask *tert*-butyl hypochlorite (0.073 mL) was added via syringe.

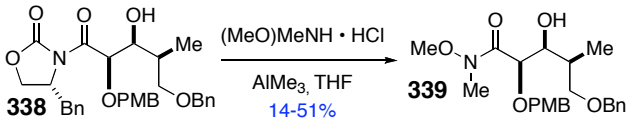
In a 5-mL round-bottom flask **331** (70.9 mg, 0.147 mmol) and $(DHQD)_2PHAL$ (8.2 mg) were dissolved in MeCN (0.74 mL).

To the carbamate solution were added sequentially the alkene solution and the osmate solution. Each flask was rinsed with MeCN (0.05 mL) and the combined solution was stirred 6 h. The reaction mixture was treated with sodium sulfite (210.8 mg) and stirred 45 min. The hood lights were turned on and the mixture extracted with EtOAc (4 x 1.05 mL); the combined organic extracts were washed with H_2O and brine (1.05 mL each), dried (Na_2SO_4), filtered, and evaporated in vacuo to give 143.3 mg crude product. Flash chromatography (7:3 hexanes : ethyl acetate) yielded **332**. R_f (7:3 hexanes : ethyl acetate) = 0.43.



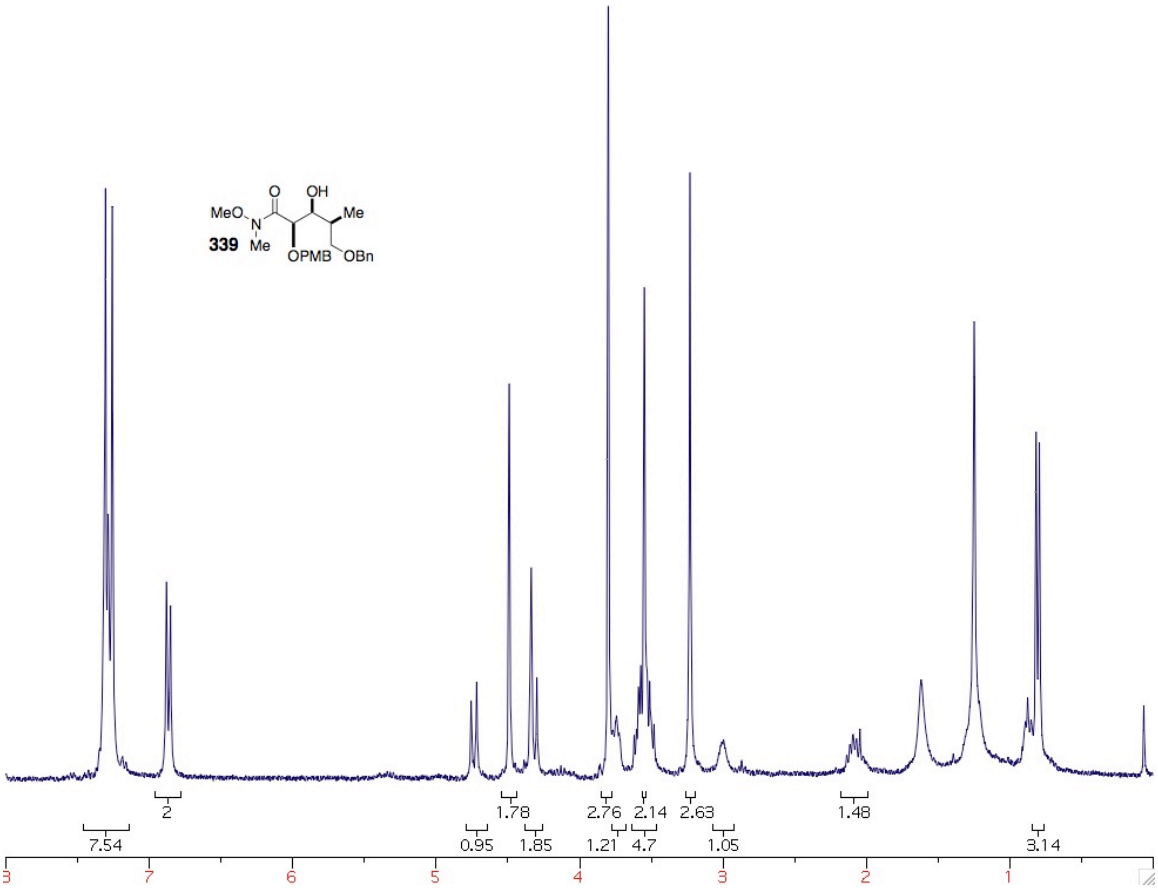
To a stirred solution of **335** (199.9 mg, 0.562 mmol) in CH_2Cl_2 (2.8 mL) at -78 °C were added Bu_2BOTf (0.62 mL, 0.62 M, 1 M in CH_2Cl_2) and DIPEA (0.11 mL, 0.63 mmol) dropwise via syringe and the yellow solution stirred 70 min at -78 °C. A solution of **337** (70.0 mg, 0.393 mmol) in CH_2Cl_2 (2.8 mL) was added via canula and the combined solution stirred 10 h at ambient temperature, then cooled to 0 °C and quenched with pH 7 phosphate buffer (0.0025 M, 0.56 mL), MeOH (1.65 mL), and 30% aqueous H_2O_2 (1.95 mL). The solution was allowed to warm to ambient temperature over 1 h and diluted with H_2O and CH_2Cl_2 (20 mL each); the aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers washed with brine (20 mL), dried (Na_2SO_4), and evaporated to give 287.1 mg of pale yellow oil. Flash chromatography (7:3 hexanes / ethyl acetate) yielded 94.3 mg (45%) **338** as a pale yellow oil. ^1H NMR δ (300 MHz, $CDCl_3$): 7.39-7.15 (m, 14 H), 6.92-6.87 (m, 2 H), 5.27 (1/2ABqd, 1 H, J = 23.7, 1.8 Hz), 4.77-4.12 (m, 9 H), 3.79 (s, 3 H), 3.55 (m, 2 H), 3.33 (m, 2 H), 2.91-2.65 (m, 2 H), 2.21 (m, 1 H), 0.85 (d, 3 H, J = 6.9 Hz). HRMS (FAB+) calcd. for $C_{31}H_{35}NO_7Na$ ($M+Na^+$) (*m*/*z*): 556.2311, found (*m*/*z*): 556.2272.

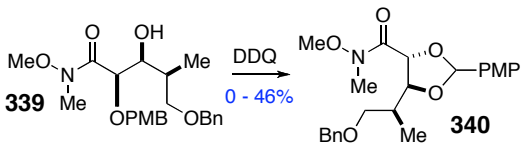




To a stirred mixture of Weinreb salt (1.46 g, 15 mmol) in THF (2.6 mL) in a 25-mL round-bottom flask at -33 °C was added $AlMe_3$ (7.5 mL, 2 M in toluene) and the mixture allowed to warm to ambient temperature over 15 minutes with stirring. The solution was then re-cooled to -33 °C and a solution of **338** (318.9 mg, 0.598 mmol) in THF (2.8 mL) was added via canula; the combined solution was stirred 5.5 h at 0 °C to 15 °C, then added via canula to a stirred mixture of CH_2Cl_2 and saturated aqueous Rochelle's salt (15 mL each). The solution was stirred 16 h and extracted with CH_2Cl_2 (2 x 20 mL); the combined organic extracts were dried (Na_2SO_4) and evaporated to give 360 mg crude product. Flash chromatography (7:3 to 1:1 hexanes : ethyl acetate) yielded 127.8 mg (51%) **339** as a milky oil. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.37-7.23 (m, 8 H), 6.93-6.82 (d, 2 H), 4.74 (1/2ABq, 1 H, J = 11.7 Hz), 4.49 (s, 2 H), 4.32 (1/2ABq, 1 H, J = 11.7 Hz;

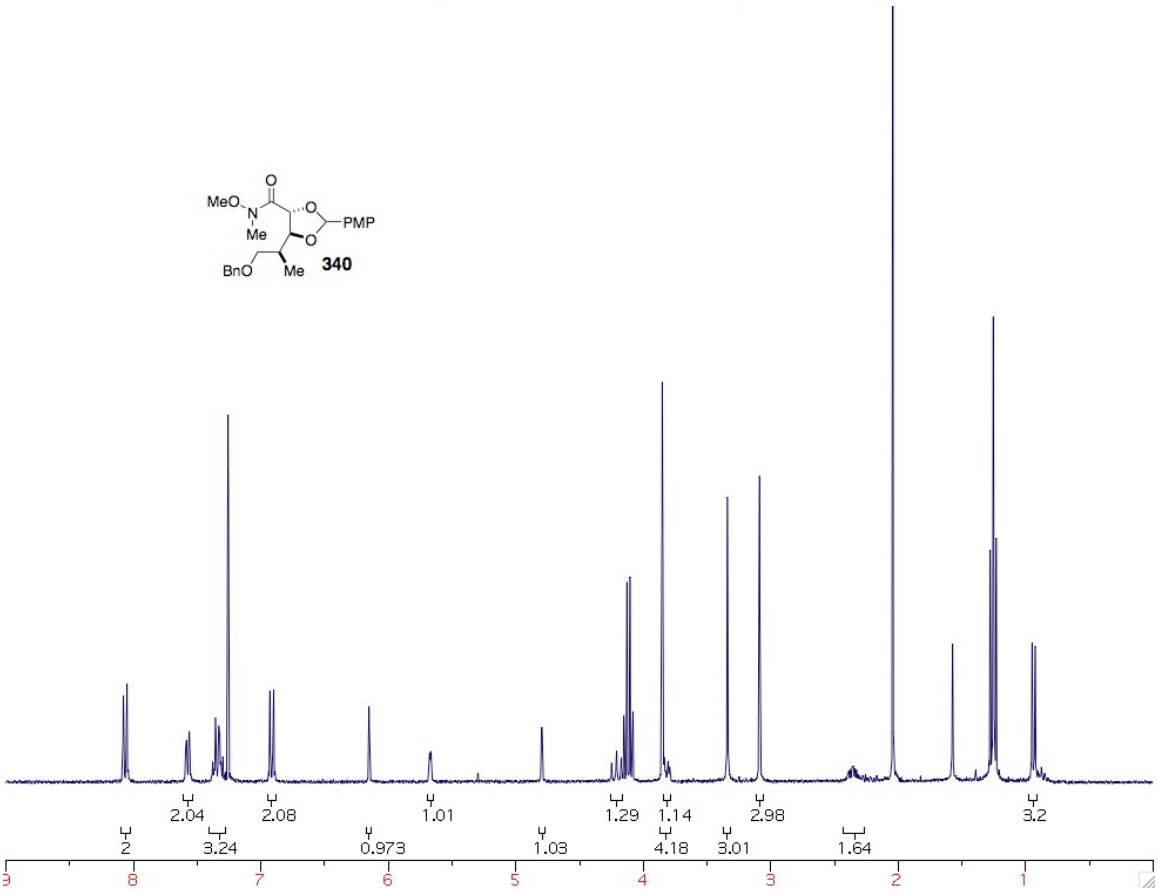
overlap with s, 1 H), 3.80 (s, 3 H), 3.74 (br m, 1 H), 3.63-3.47 (m, 2 H), 3.55 (s, 3 H), 3.23 (s, 3 H), 3.00 (br m, 1 H), 2.16-2.03 (m, 1 H), 0.81 (d, 3 H, J = 6.8 Hz).

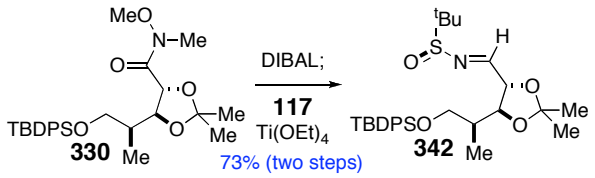




A mixture of **339** (17.2 mg, 0.041 mmol) and powdered molecular sieves (21.5 mg) in CH_2Cl_2 in a vial was treated with DDQ (14.4 mg, 0.063 mmol) and the reddish solution stirred 20 h, then filtered through a pad of neutral alumina. The pad was eluted with 9:1 CH_2Cl_2 : MeOH (10 mL) and the filtrate evaporated to give 19.6 mg crude product. Flash chromatography (7:3 hexanes : ethyl acetate) yielded 7.9 mg (46%) of **340** and 4.8 mg (28%) of recovered **339**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.07 (d, 2 H, J = 8.9 Hz), 7.60-7.55 (m, 2 H), 7.40-7.29 (m, 3 H), 6.92 (d, 2 H, J = 8.9 Hz), 6.15 (s, 1 H, acetal CH), 5.67 (d, 1 H, J = 3.3 Hz), 4.80 (d, 1 H, J = 1.0 Hz), 4.21 (t, 1 H, J = 11.4 Hz), 3.85 (s, 3 H,

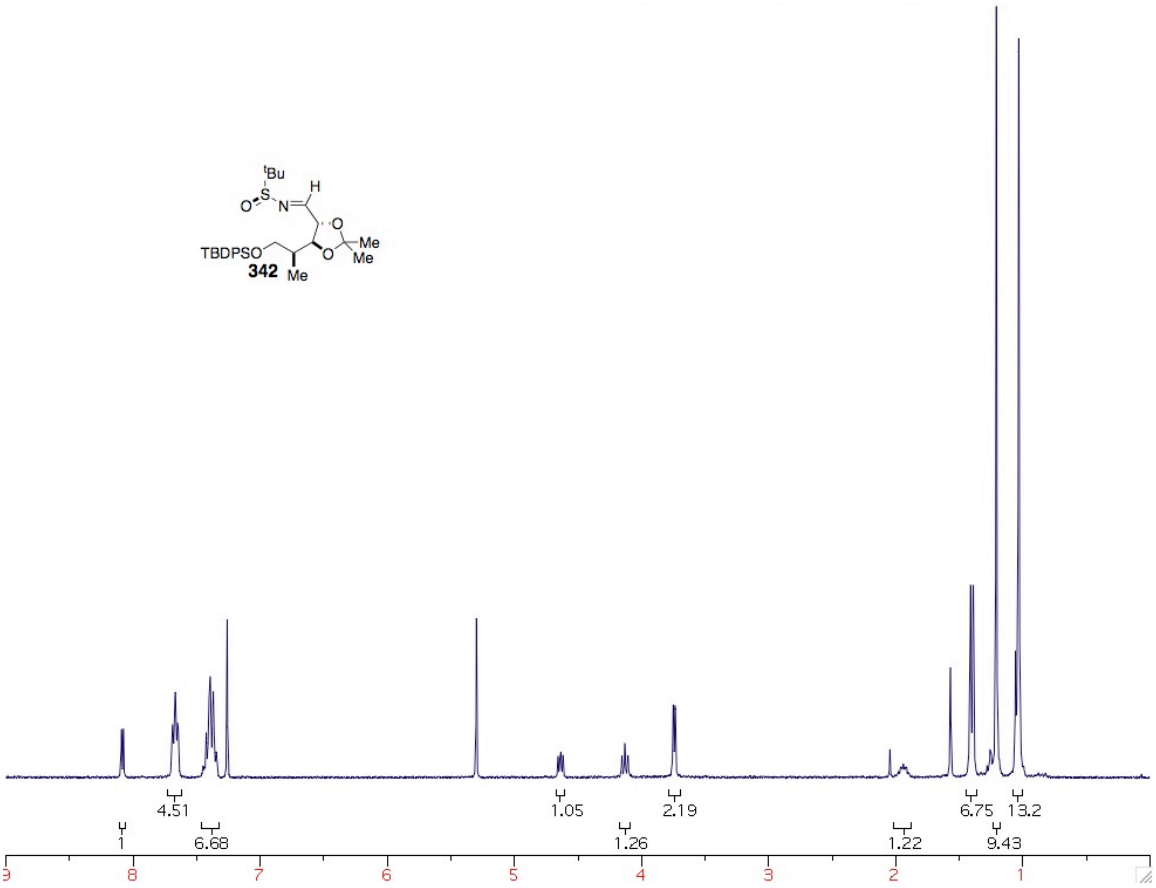
OMe), 3.82 (1/2 ABqd, 1 H, J = 12.1, 3.2 Hz), 3.34 (s, 3 H, PMB OMe), 3.09 (s, 3 H, NMe), 2.35 (m, 1 H, α-Me CH), 0.94 (d, 3 H, J = 7.1 Hz, Me).

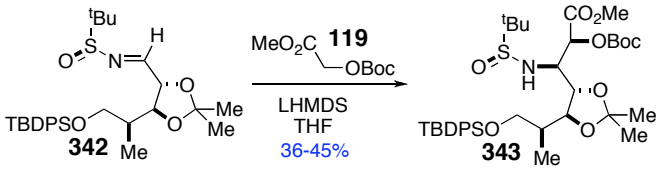




A mixture of **330** (35.5 mg, 0.083 mmol) and **117** (11.1 mg, 0.092 mmol) in CH_2Cl_2 (2.1 mL) was treated with $Ti(OEt)_4$ (0.088 mL, 0.59 mmol) and stirred 6 h 15 min at ambient temperature, then cooled to 0 °C and treated with ice water (0.46 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts washed with brine (10 mL), then dried (Na_2SO_4) and evaporated. Flash chromatography (9:1 hexanes : ethyl acetate) yielded 32.0 mg (73%) product. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.08 (d, 1 H, J = 4.8 Hz), 7.70-7.64 (m, 4 H), 7.46-7.33 (m, 6 H),

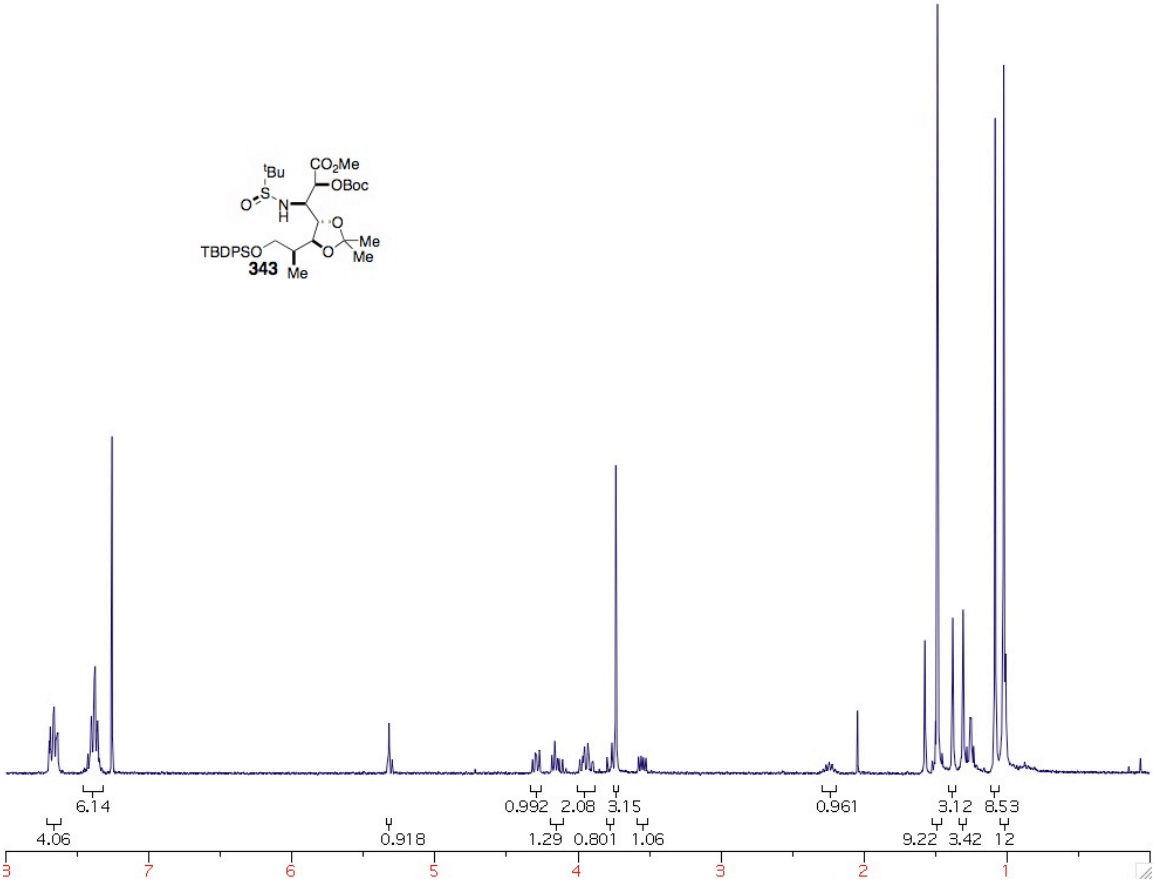
4.66-4.61 (m, 1 H), 3.74 (m, 2 H), 1.94 (m, 1 H), 1.40 (2 s, 6 H), 1.21 (s, 9 H), 1.03 (s overlapping d, 12 H).

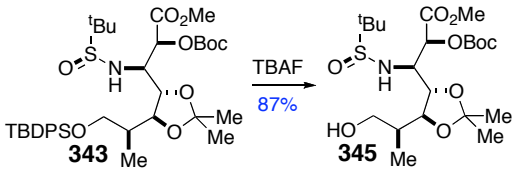




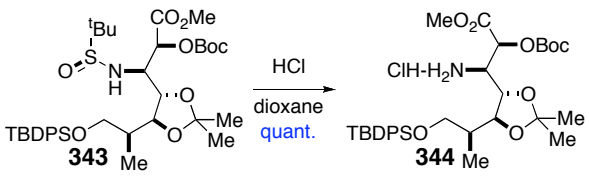
A solution of **119** (46.4 mg, 0.244 mmol) in THF (0.72 mL) in a 4-mL vial at -78 °C was treated with LHMDS (0.25 mL, 0.25 mmol) and stirred 1 h at -78 °C; a solution of **342** (32.0 mg, 0.060 mmol) in THF (0.18 mL) was added via syringe and the combined solution stirred 90 min at -78 °C, then quenched with saturated aqueous NH_4Cl (1.8 mL), diluted with H_2O (2 mL), and extracted with EtOAc (2 x 4 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give 42.4 mg crude product; flash chromatography (3:1 hexanes : ethyl acetate) yielded 19.5 mg (45%) **343**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.73-7.62 (m, 4 H), 7.48-7.32 (m, 6 H), 5.32 (d, 1 H, J = 2.0 Hz),

4.33-4.27 (m, 1 H), 4.19-4.09 (m, 1 H), 4.0-3.88 (m, 2 H), 3.80-3.75 (m, 1 H), 3.74 (s, 3 H), 3.55 (m, 1 H), 2.25 (m, 1 H), 1.49 (s, 9 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.08 (s, 9 H), 1.02 (d, 3 H, J = 6.8 Hz), 1.02 (s, 9 H).

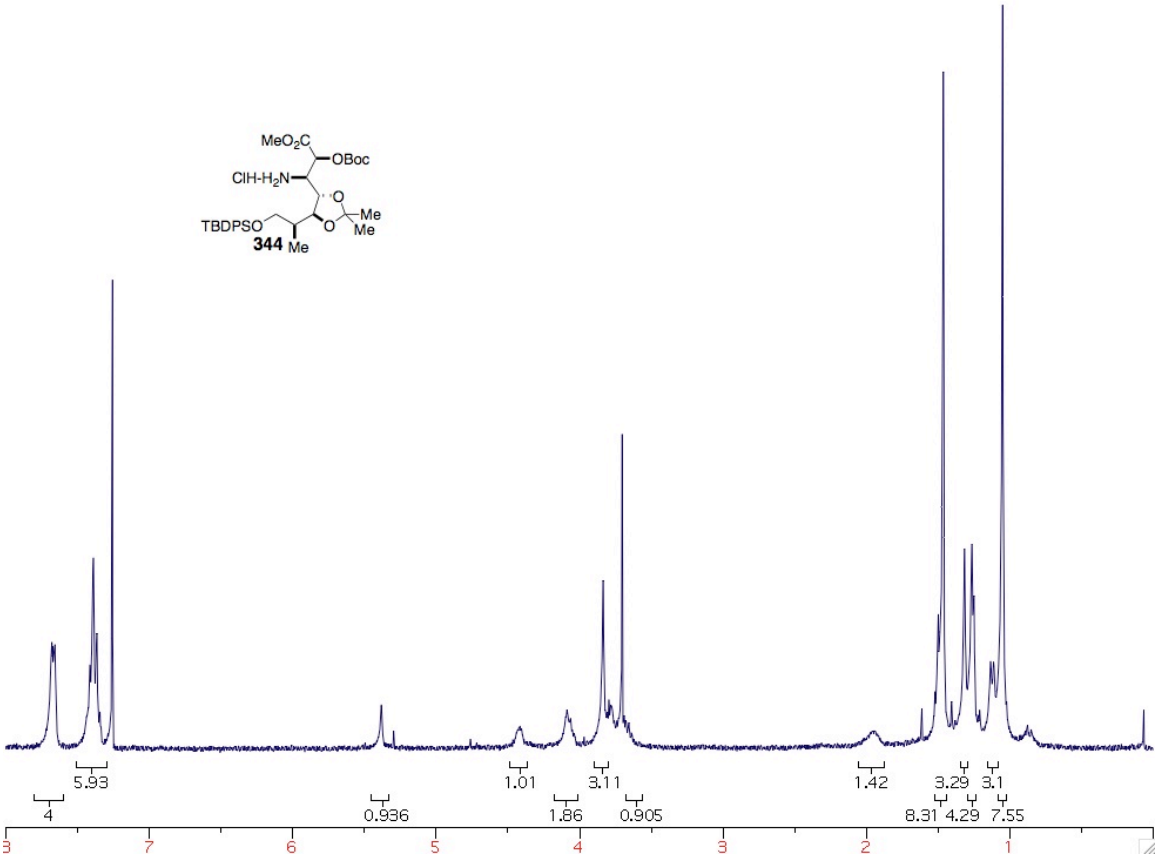


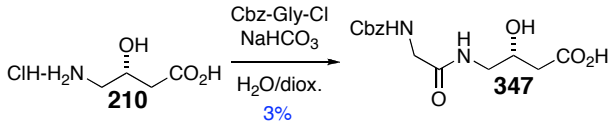


A solution of **343** (53.8 mg, 0.111 mmol) in THF (1.10 mL) was treated with TBAF (0.14 mL, 1 M in THF, 0.14 mmol) and stirred 6 h; the solution was evaporated, and flash chromatography gave 23.9 mg (87%) **345**.



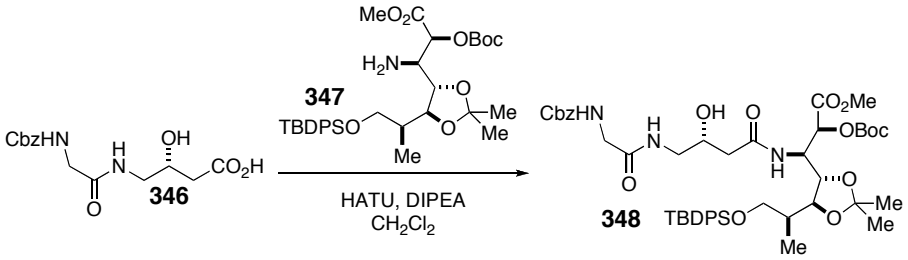
A solution of **343** (7.7 mg, 0.0107 mmol) in dioxane (0.116 mL) was treated with HCl (4 M in dioxane, 0.06 mL) and stirred 10 min; TLC indicated disappearance of starting material, so the mixture was evaporated and subjected to hi-vac to give 6.9 mg (99%) **344**. ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.70-7.63 (m, 4 H), 7.44-7.34 (m, 6 H), 5.39 (br s, 1 H), 4.42 (m, 1 H), 4.09 (m, 2 H), 3.84 (s, 3 H), 3.56 (m, 1 H), 1.96 (m, 1 H), 1.46 (s, 9 H), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.12 (d, 3 H, J = 6.2 Hz), 1.05 (s, 9 H).



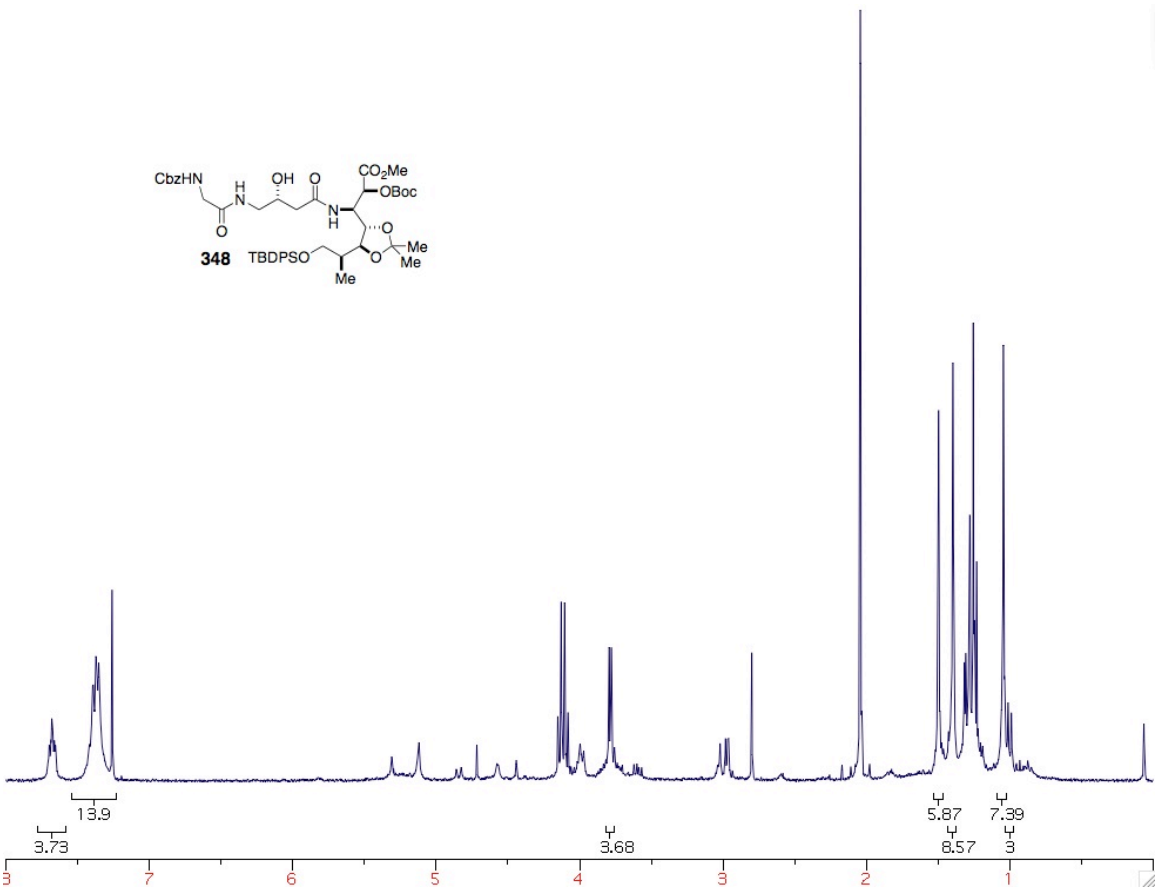


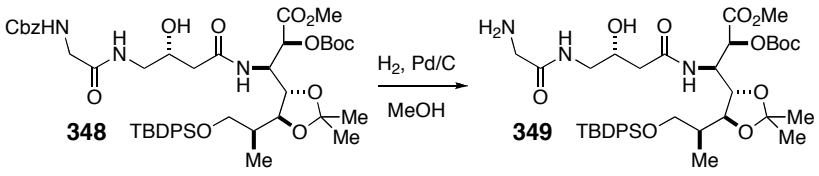
A solution of Cbz-glycine (245.7 mg, 1.17 mmol) in CH_2Cl_2 (3.7 mL) in a 10-mL pear-shaped flask at 0 °C was treated dropwise with oxalyl chloride (0.10 mL, 1.18 mmol) and DMF (0.01 mL, 0.12 mmol), producing bubbling; the combined solution was stirred 90 min at ambient temperatre. Direct addition of **210** (70.0 mg, 0.59 mmol), followed by dropwise addition of Et_3N (0.31 mL, 2.22 mmol), gave a color change from yellow to

dark brown. The mixture was stirred 3 h, then treated with 2 M HCl (5 mL); the aqueous layer was separated and extracted with CH_2Cl_2 and EtOAc (5 mL each). The combined organic extracts were dried (Na_2SO_4) and evaporated to give 107.0 mg of brown oil after hi-vac overnight. Flash chromatography (9:1 CH_2Cl_2:MeOH) gave 5.8 mg (3%) **347** used without further purification.



A mixture of **346** (5.8 mg, 0.019 mmol), **347** (9.7 mg, 0.016 mmol), and HATU (7.6 mg, 0.020 mmol) in CH_2Cl_2 (0.08 mL) at 0 °C was treated with DIPEA (0.005 mL, 0.028 mmol) and stirred 3 h at ambient temperature. The solution was diluted with EtOAc (4 mL) and washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine (4 mL each); the organic layer was dried (Na_2SO_4) and evaporated to give 21.7 mg **348** as a yellow oil used without further purification.





A mixture of **348** (21.7 mg, 0.016 mmol) and 5% Pd/C (5.1 mg, 0.0024 mmol) in MeOH (0.20 mL) was stirred 13 h under an H_2 balloon, then filtered through a tiny pad of Celite and evaporated in vacuo to give 9.5 mg (78% from **346**) **349** as colorless oil.