DISSERTATION

THE TOTAL SYNTHESIS OF (-)-PARAHERQUAMIDE A

Submitted by

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In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY JIANHUA CAO ENTITLED THE TOTAL SYNTHESIS OF (-)-PARAHERQUAMIDE A BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Adviser

Department Head

ABSTRACT OF DISSERTATION

THE TOTAL SYNTHESIS OF (-)-PARAHERQUAMIDE A

The first stereocontrolled total synthesis of (-)-paraherquamide A is described in 48 chemical steps. The synthesis is a convergent one, starting from ethyl glycinate, ethyl acrylate and vanillin. The longest linear route is 35 steps. Vanillin was acetylated and nitrated to provide nitrovanillins (**94** and **95**). These were converted to the azalactones, hydrolyzed to the α–ketocarboxylic acids, oxidatively decarboxylated to acids **99** and **108**. Compound **99** was reductively cyclized to oxindoles **100**, which was then demethylated to give pure oxindole **101**. The oxindole was regioselectively prenylated, epoxidized, and subjected to a key seven-membered ring forming procedure to provide the unique dioxepin **104**. Compound **104** was reduced to indole **105** and indoline **106** which was converted to **105** by reaction with DDQ. Indole **105** was protected and subjected to a Mannich reaction to afford the gramine derivative **60**. The Michael adduct **150** from ethyl glycinate and ethyl acrylate was protected, intramolecularly condensed and reduced with Baker's yeast to give *cis*-β-hydroxy proline ester **129**. Stereoselective α-alkylation of **129**, protection, deprotection, bromoacetyl amide formation, aminolysis, cyclization and dimethoxycarbonylation provided diketopiperazine (DKP) **91**. DKP **91** was alkylated with compound **60** to provide indoles **303** and **304**, which were then individually decarbomethoxylated to afford four separable diastereomers *anti*-**305** (**305E/Z**) and *syn*-**306** (**306E/Z**). These four diastereomers were individually converted to the corresponding S_N2' substrates through lactim ether formation, protection of the indole nitrogen, deprotection, allylic chloride formation and TBS ether formation. S_N2' cyclization of these four S_N2' substrates individually provided the same product **327**.

Cyclization of lactim ether **327**, ring opening of the lactim ether moiety and ring closure afforded DKP **338**. Selective amide group reduction of **338**, N-methylation, MOM ether deprotection, oxidation, bis-deprotection by TFA provided indole-ketone **344**. Oxidative spirooxidation of **344** followed by dehydration gave ketone-olefin **43**. Stereoselective methyl addition to **43** afforded (-)-paraherquamide A.

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Dr. Tomas Glinka and coworkers in the Williams group laid a basic foundation for this project by finishing the total synthesis of (-)-brevianamide B. Dr. Tim Cushing and Professor Juan. F. Sanz-Cervera beautifully finished the synthesis of (+)-paraherquamide B, which serves as a more solid foundation for this work. Their input into this project was invaluable.

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I wish to extend a special thanks to all of my colleagues past and present in the Williams group. Bob Kause and John Clark spent some time helping me make the oxindole precursors, and their support was very helpful.

Finally, I would like to thank Professor Robert M. Williams for his support and guidance as my advisor. His intellectual and creative input are the key to the success of this work.

Table of Contents

List of Abbreviations

Ac_2O	acetic anhydride
AcOH	acetic acid
Bn	benzyl
BOC	tert-butoxycarbonyl
$(BOC)_2O$	di-tert-butyl dicarbonate
BSTFA	bis(trimethylsilyl)trifluoroacetamide
Bz	benzoyl
18-C-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
Collidine	2,4,6-trimethylpyridine
m-CPBA	meta-chloroperbenzoic acid
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCU	1,3-dicyclohexylurea
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DKP	diketopiperazine
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMEA	dimethylethyl amine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
HMPA	hexamethylphosphoramide
im	1-imidazolyl
LDA	lithium diisopropylamine
2,6-Lutidine	2,6-dimethylpyridine
MeOH	methanol
MOM	methoxymethyl
Ms	methanesulfonyl(mesylate)
MTPI	methyl triphenoxyphosphonium iodide
NCS	N-chlorosuccinimide
pMB	p-methoxybenzyl
PPTS	pyridinium p- toluenesulfonate
PTLC	preparative thin layer chromatography
pv	pivaloyl
Py	pyridine
TBDMS	tert-butyldimethylsilyl
t-BDMSCl	tert-butyldimethylsilyl chloride
t-BDMSOTf	tert-butyldimethylsilyl trifluoromethanesulfonate
TBAF	tetrabutylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
t-BuOH	tert-butanol
Tf	trifluoromethanesulfonate
TFAA	trifluoroacetic anhydride

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
TS	toluenesulfonyl

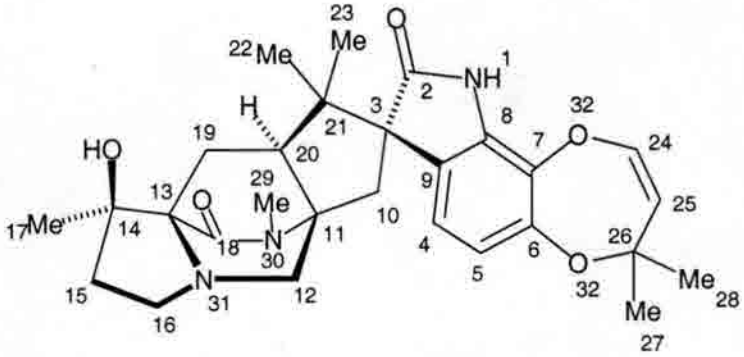
CHAPTER ONE

INTRODUCTION

1.1 Background and Significance

Paraherquamide A (**1**), a toxic metabolite, was first isolated from the mold *Penicillium paraherquei* in 1980 by Yamazaki and Okuyama.[1] Relevant data (NMR, IR, UV, MS) was obtained, including a single crystal X-ray structural analysis that firmly established the structure and relative stereochemistry of this molecule. In 1989 an investigation by researchers at Merck Sharp & Dohme[2] conclusively established the absolute configuration of paraherquamide A (Scheme 1).

Scheme 1

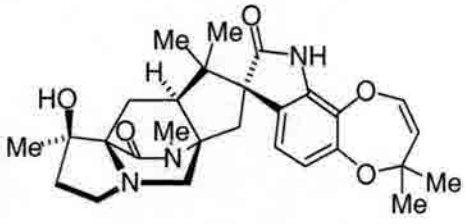


1, (-)-paraherquamide A

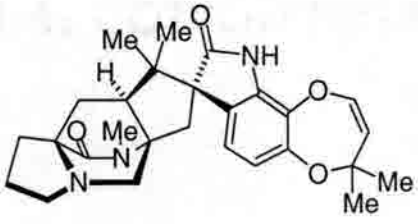
In 1990 a group at Merck isolated paraherquamide A (**1**) and six structurally related compounds (paraherquamides B-G) from the fermentation broth of *Penicillium charlesii* (ATCC 20841).[3] A similar group from SmithKline Beecham discovered paraherquamide A (**1**) and three of the six previously mentioned paraherquamides from an organism found in the soil of Kemer, Turkey.[4] This strain was later identified as a *Penicillium* species. The growing interest in paraherquamide A (**1**) (and the other paraherquamides) has resulted

from the discovery of its potent anthelmintic activity.[5] After this revelation, paraherquamide A (**1**) was intensively studied, in an attempt to elucidate both the chemical and pharmacological properties of this molecule. To date, a number of patents relating to the culture and isolation have been published (Scheme 2).

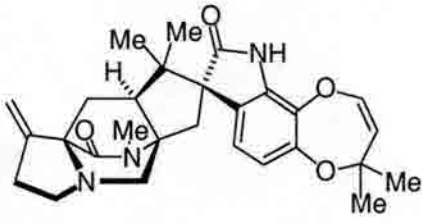
Scheme 2



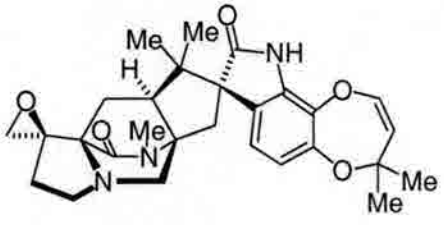
1, (-)-paraherquamide A



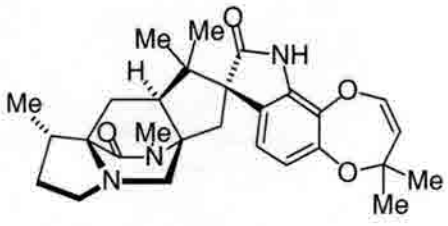
2, (-)-paraherquamide B



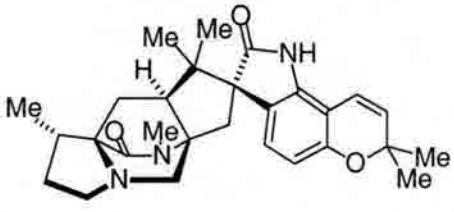
3, (-)-paraherquamide C



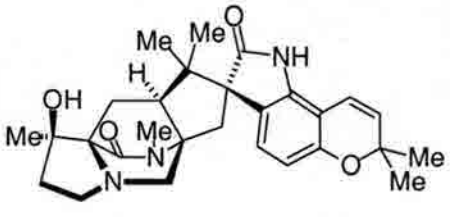
4, (-)-paraherquamide D



5, (-)-paraherquamide E



6, (-)-paraherquamide F



7, (-)-paraherquamide G

The importance of a new antinematodal (anthelmintic) agent cannot be overstated. Helminths or intestinal nematodes infect large numbers of livestock world wide and result in sickness or death of the host animal. This devastation on the farmer or stock owner is immeasurable. It not only causes financial loss, but also increased human suffering. This is particularly painful to those people who depend entirely on their animals for sustenance. Today, there are essentially three classes of broad spectrum anthelmintics: the benzimidazoles, the levamisoles/morantel and the avermectins/milbemycins. Unfortunately, the first two groups have lost much of their original anthelmintic activity because of the resistance built up by the helminths.[6] More recently, the third group has also started to lose effectiveness against various parasites.[7] Paraherquamide A and the other paraherquamides represent a brand new class of antiparasitic agents. They could play a large role in supplanting or complementing the anthelmintics currently on the market.

1.2 Physical-Chemical and Structural Characteristics

Yamazaki and Okuyama[1] reported the following characteristics of paraherquamide A (**1**): colorless prisms, mp = 244-247 °C (decomposition); $[\alpha]_D^{22}$ = - 28° (c = 0.43, CH_3OH); $C_{28}H_{35}N_3O_5$ (M + m/e 493); UV λ max (EtOH) nm (ε): 226 (32400), 260 (6100), 290 (1600); IR (KBr) 3510, 3430, 3245, 1714, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (3H, s); 1.10 (3H, s); 1.45 (6H, s); 1.85 (1H, d, J = 15 Hz); 1.77-2.40 (5H, m); 2.55 (1H, d, J = 11 Hz); 2.58 (1H, s, D_2O exch.); 2.67 (1H, d, J = 15 Hz); 2.93-3.25 (2H, m); 3.03(3H, s); 3.58 (1H, d, J = 11 Hz); 4.87 (1H, d, J = 8 Hz); 6.30 (1H, d, J = 8 Hz); 6.64 (1H, d, J = 8 Hz); 6.78 (1H, d, J = 8 Hz); 8.33 (1H, s, D_2O exch.). A Dragendorf test gave a positive color. Crystals were grown in ethyl acetate and an X-ray diffraction pattern was obtained which established the relative stereochemistry. Later, workers at Merck & Company published data from ^1H NMR spectra taken in CD_2Cl_2 and $(CD_3)_2CO$. They also reported data from a ^{13}C NMR spectrum in CD_2Cl_2. They made the carbon and proton assignments from these spectra and also a one-bond ^{13}C-^1H chemical shift correlation experiment (HETCOR); ^1H NMR (400 MHz) (CD_2Cl_2) δ 0.84 (3H, s, 23-

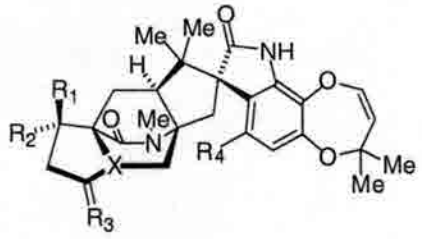
H); 1.08 (3H, s, 22-H); 1.41 (3H, s, 27-H); 1.43 (3H, s, 28-H); 1.56 (3H, s, 17-H); 1.75 (1H, dd, J = 10.5, 12.5 Hz, 19-Hβ); 1.77 (1H, dd, J = 10.8, 10.8 Hz, 19-Hα); 1.80 (1H, m, 15-Hα); 1.97 (1H, d, J = 15.6 Hz, 10-Hβ); 2.18 (1H, d, J = 16.1 Hz, 10-Hα); 2.66 (1H, br s, D_2O exch, 14-OH); 2.96 (1H, ddd, J = 2.0, 10.3 Hz, 20-H); 2.99 (3H, s, 29-H); 3.17 (1H, m, 16-Hβ); 3.58 (1H, d, J = 10.8 Hz, 12-Hβ); 4.90 (1H, d, J = 6.8 Hz, 25-H); 6.32 (1H, d, J = 7.8 Hz, 24-H); 6.68 (1H, d, J = 7.3 Hz, 5-H); 6.84 (1H, d, J = 7.3 Hz, 4-H); 7.5 (1H, br s, D_2O exch, 1-H), (proton assignments as numbered according to Chemical Abstracts) (Scheme 1). They reported a UV λ max (methanol) of 225 nm (logε = 4.50) and a Rf value of 0.51 using Whatman KC18F reverse phase TLC: methanol/H_2O (8/2). Mass spectral data was also reported; $C_{28}H_{35}N_3O_5$ 493 m/e M+ (493) (165) (163). They found paraherquamide A (**1**) soluble in methanol, ethyl acetate, acetone, and dimethylsulfate but essentially insoluble in water. Paraherquamide A responded to iodine and 50% H_2SO_4. Workers at SmithKline Beecham performed similar work including a 2D, ^1H, ^{13}C and COSY NMR experiment and obtained the same structural assignments as the Merck group. The absolute configuration for paraherquamide A (**1**) was established via an X-ray crystal analysis of a bromine atom-containing semi-synthetic analog. The Merck workers performed detailed spectroscopic work (COSY, HETCOR, NOE, MS) on the other paraherquamides (C-G) and obtained the structures shown in Scheme 2. They reported similar spectral characteristics for all seven compounds. As would be expected, the only major change in the NMR spectra stemmed from the signals contained on the proline ring (except for paraherquamides E-F). The chemical shifts of the other signals were quite close This can be gleaned from a perusal of the proton NMR spectral data of paraherquamide A and B. The conclusions reached by the Merck group, were independently confirmed by the SmithKline workers for paraherquamides A and E-G. They concluded that the relative stereochemistry must be the same for all seven analogs. The Merck group also reported that the absolute stereochemistry for the other six products was the same as for paraherquamide A (**1**).

1.3 Relatives of the Paraherquamides

The paraherquamides are structurally very similar to the marcfortines (A-C), and the brevianamides (A-B))Scheme 3). Marcfortines A,[8] B and C were isolated from *Penicillium roqueforti* (strain B26) in 1980 by Polonsky.[9] The similarities between the paraherquamides and the marcfortines is striking. The only difference between paraherquamide B (**2**) and marcfortine A is that marcfortine A contains a pipecolic residue instead of a proline unit. The marcfortine structures were solved by X-ray diffraction. Patterns were obtained for both marcfortines A and C. This data confirmed that the paraherquamides and marcfortines have the same relative stereochemistry. As would be expected, the published NMR data for marcfortine A is similar to that of the paraherquamides (A-E). Similarly, marcfortine C has the identical pyran ring system as in paraherquamides F and G (and similar NMR characteristics), but marcfortine B and C lack the N-methyl group found in marcfortine A and all the paraherquamides. The paraherquamides also have structural features reminiscent of the brevianamides.[10] (+)-Brevianamide B (**11b**) is similar to the paraherquamides in that it contains the same proline moiety as well as the bicyclo [2.2.2] ring structure. Interestingly, the bicyclo [2.2.2] ring system of (+)-brevianamide A (**11a**) possesses the opposite absolute configuration relative to (+)-brevianamide B, the paraherquamides and marcfortines (Scheme 3). In addition, other paraherquamide relatives such as sclerotamide (**8f**),[11] aspergamide A (**10a**) and B (**10b**),[12] VM55596 (**8a**), VM55587 (**8b**), SB203105 (**8c**), SB200437 (**8d**), VM55595 (**8e**), and VM55599 (**12**),[13a,b] asperparaline A and VM55598 (**13a**),[14] as well as SB202327 (**13b**) have been described.

The paraherquamides, marcfortines, brevianamides, aspergamides and asperparaline belong to a large group of natural products containing a diketopiperazine moiety, produced from the condensation of two amino acid subunits. This group includes such notable toxins as the echinulins, gliotoxins and the sporidesmins.

Scheme 3

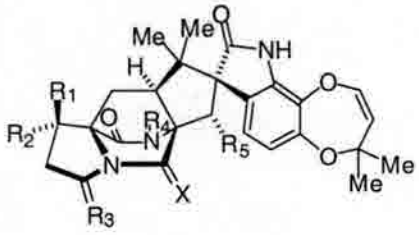


8a, VM55596, R_1 = OH, R_2 = Me, R_3 = H_2, X = N^+-O^-, R_4 = H

8b, VM55597, R_1 = OH, R_2 = Me, R_3 = H_2, X = N, R_4 = H

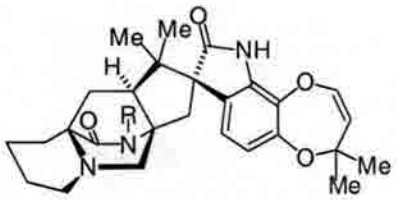
8c, SB203105, R_1 = H, R_2 = Me, R_3 = H_2, X = N, R_4 = OH

8d, SB200437, R_1 = H, R_2 = Me, R_3 = H_2, X = N, R_4 = H



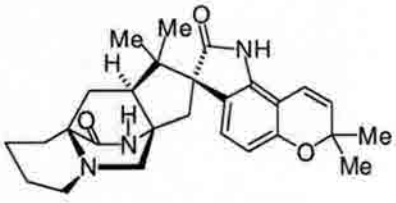
8e, VM55595, R_1 = H, R_2 = Me, R_3 = H_2, X = H_2, R_4 = H

8f, , sclerotamide, R_1 = R_2 = R_3 = H_2 = R_4 = H, X = O

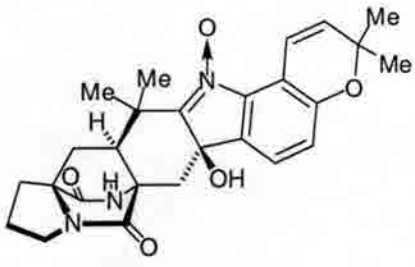


9a, (-)-marcfortine A, R = Me

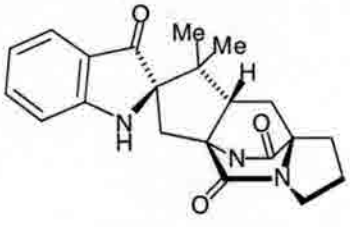
9b, (-)-marcfortine B, R =H



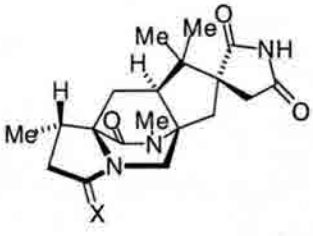
9c, (-)-marcfortine C



10a, aspergamide A

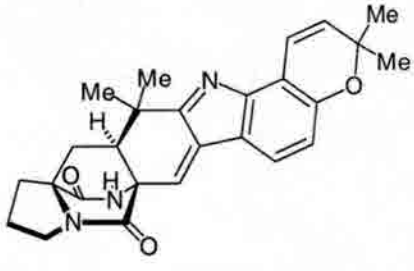


11a, (+)-brevianamide A

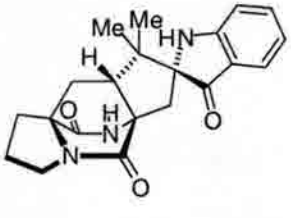


13a, asperparaline A (X = H_2)
aspergillimide (VM55598)

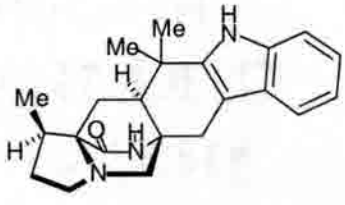
13b, SB202327 (X = O)



10b, aspergamide B



11b, (+)-brevianamide B



12, VM55599

1.4 Pharmacology

Originally, paraherquamide A was tested on a simple animal model (gerbils). The results showed that paraherquamide A (**1**) has strong activity against a benzimidazole- and avermectin-resistant helminth (*Trichustiogylus colubriformis*). Paraherquamide A (**1**) was well-tolerated by the gerbils even at a high dose (200 mg kg^{-1})[5] (Table 1).

Table 1

Efficacy of paraherquamide A against immature *Trichstrongylus colubriformis* in gerbils and a comparison to some other anthelmintics.

Treatment	Dosage (mg/kg)	Number of Animals	Efficacy %
Placebo	-	8	-
Paraherquamide A	200	3	100
	100	3	100
	50	3	100
	6.25	5	100
	3.12	4	99.7
	1.56	3	98.1
	0.78	3	96.5
	0.39	3	66.3
Thiabendazole	200	3-6	85
	100	3-6	72.3
	50	3-6	44.1
Levamisole hydrochloride	6.25	3-6	100
	3.125	3-6	80.3
	1.562	3-6	40.7
Avermectin A_1a	0.125	3-6	99.4
	0.0625	3-6	79.3
	0.0312	3-6	57.4
Avermectin A_2a	0.125	3-6	99.8
	0.0625	3-6	90.1
	0.0312	3-6	55.9
Avermectin B_1a	0.0312	3-6	100
	0.0156	3-6	75.4
	0.0078	3-6	18.8
Avermectin B_2a	0.0312	3-6	100
	0.0156	3-6	95
	0.0078	3-6	75.7

A subsequent animal study was performed on various nematode-infected sheep. Seven different species, larval and adult, were presented to the sheep including an

avermectin-resistant strain (*Haemochus contortus*) and an avermectin/benzimidazole-resistant strain (*Trichostrongylus colubriformis*). Paraherquamide A (**1**) showed good activity against these organisms, in doses ranging from 2.00-0.25 mg of paraherquamide A per kg of sheep body weight. In almost all cases the efficacy was 99% or greater; however, **1** was ineffective against *Oesophagostomum columbianum* (zero percent efficacy at the 0.25 mg kg^{-1} level). Another study demonstrated the safety and efficacy of paraherquamide A in cattle. Calves were infected with nine different species of nematode larvae and then treated with paraherquamide A at doses ranging from 4 mg kg^{-1} to 0.5 mg kg^{-1}. The only nematode that was not affected was C. *punctata* (zero percent efficacy at the 0.5 mg kg^{-1} level). The other eight parasites were killed with >95% efficacy at the 1.0 mg kg^{-1} level. It was reported that the calves suffered no ill effects. Problems arose when **1** was fed to dogs at doses much lower than those used on calves and sheep. The mixed breed dogs showed acute toxicity reactions[15] and because of this, a toxicity profile was undertaken comparing paraherquamide A (**1**) to avermectin using mice as the animal vector.[16] It was concluded that not only is paraherquamide A more toxic than avermectin but it has a different mode of toxicity. The mice fed paraherquamide A suffered respiratory distress followed by death. In contrast, the mice fed avermectin suffered ataxia, coma and then death.

A Merck group performed a study[17] that reported a membrane binding site of paraherquamide A (**1**) in a membrane preparation from *Caenohabditis elegans* . This was done by synthesizing [^{3}H] paraherquamide (^{3}H incorporated at position 24)[18] and incubating it with membranes obtained from macerated *C. elegans* worms. A Scatchard plot analysis of the binding data pointed to one particular high affinity binding site for paraherquamide A. The dissociation constant K_d = 263 μM was found that compared favorably with 268 μM obtained from a kinetic binding study. This value $k_{-1}/k1 = K_d$ was found by examining the effect of excess unlabeled paraherquamide A (**1**) incubated with the ^{3}H paraherquamide A membrane complex and measuring the rate of decline of the [^{3}H] paraherquamide over time (giving k_{-1} = 1.1 min^{-1}). The specificity of paraherquamide A to

this binding site was also examined. Various analogs of paraherquamide A were tested to see how well they inhibited paraherquamide A binding. While none of the analogs bound as strongly to this site as paraherquamide A itself, there was an almost one-to-one correlation between the binding and the motility assay (Ec50 ug/mL) for *C.elegans*, indicating that this binding site is indeed the active site for biological activity. Another experiment was done to determine if the membrane binding site of paraherquamide A is the same as that for other anthelmintic agents. While all of the compounds tested showed antinematode activity, only the phenothiazine analogs had any specific inhibitory effects at the paraherquamide A binding site. This was an interesting result indicating that both types of compounds interact at a common or close binding site. The mode of action of phenothiazine is not known, though it does possess both anthelmentic and antiprotozoal activity. The Merck group concluded that paraherquamide A interacts (interferes) with a specific ligand-receptor that could be the same as for the phenothiazines. The nature of this site remains to be determined.

The Merck group did extensive semi-synthetic work in modifying paraherquamide A. They reported making over 100 different analogs of this compound. Unfortunately, paraherquamide A was the most active. Additionally, of the natural paraherquamides, paraherquamides A (**1**) is the most active (Table 2).

Table 2

Antinematodal activity of the natural paraherquamides against *C.elegans*.

Compound	**LD_{50} (μg/mL)**
(-)-paraherquamide A (**1**)	2.5
(-)-paraherquamide B (**2**)	100
(-)-paraherquamide C (**3**)	40
(-)-paraherquamide D (**4**)	160
(-)-paraherquamide E (**5**)	6
(-)-paraherquamide F (**6**)	65
(-)-paraherquamide G (**7**)	20

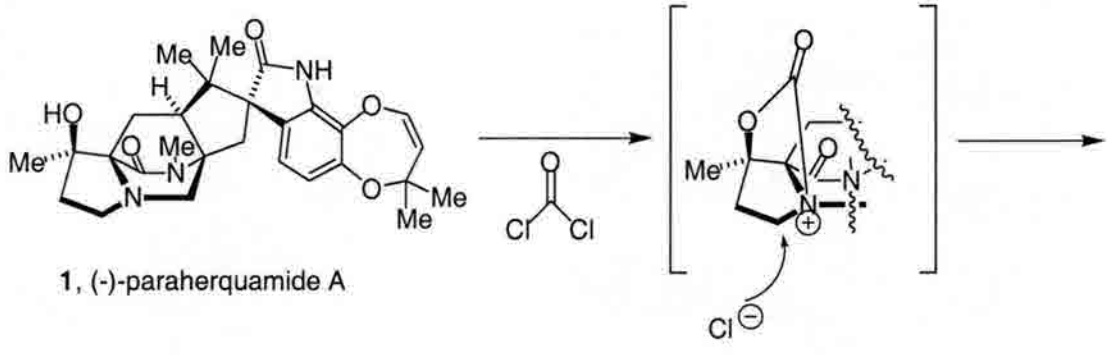
1.5 Chemical Modification of (-)-Paraherquamide A

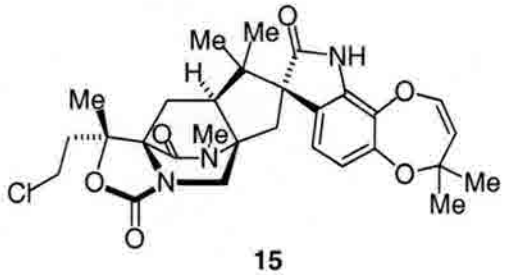
1.5.1 Merck's Modification

As part of a program directed at searching for more potent and less toxic antiparasitic analogs of (-)-paraherquamide A, Blizzard and coworkers at Merck Sharp & Dohme investigated the chemical properties of (-)-paraherquamide A by modifying its chemical structure at different positions. The following is a brief review of the chemistry done by the researchers at Merck towards (-)-paraherquamide A. The chemical properties of (-)-paraherquamide A will provide key information for our design of a synthetic plan towards (-)-paraherquamide A.

Blizzard et al., [19] (Scheme 4) treated **1** with phosgene and quenched the reaction with MeOH, expecting to provide the methyl carbonate, but instead, several by-products were obtained. By quenching with aqueous base instead of MeOH, they produced the cyclic carbamate **15**.

Scheme 4



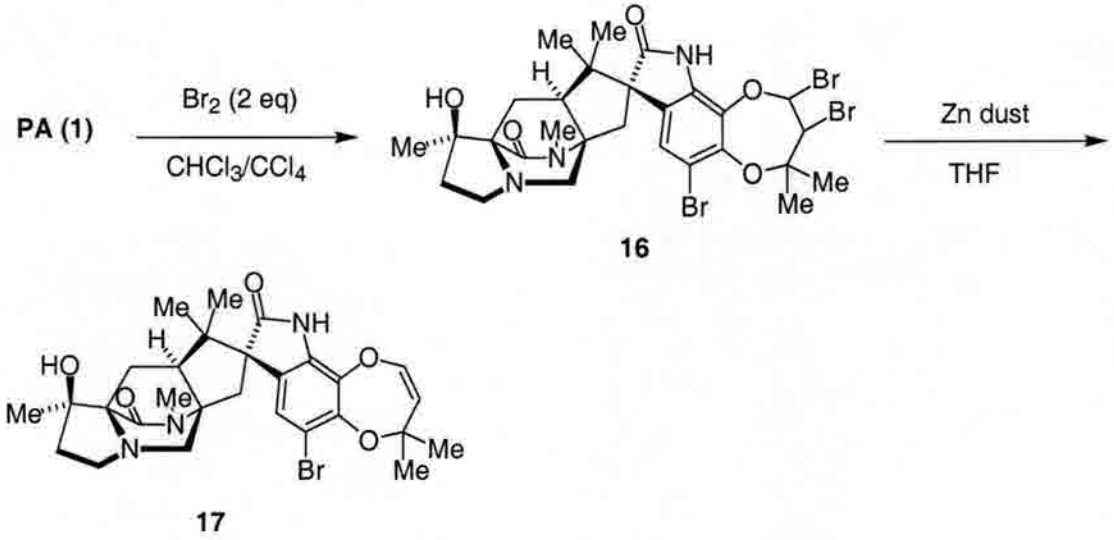


This interesting product (**15**) was presumably formed by chloride ion induced opening of a strained, reactive intermediate **14**, which is believed to be formed by attack of the tertiary nitrogen at the initially produced chloroformate, since paraherquamide analogs

lacking the C-14 hydroxyl group did not undergo ring cleavage under identical reaction conditions.

5-Bromoparaherquamide A (**17**) was prepared by treating **1** with two equiv. of bromine followed by zinc reduction of the intermediate tribromide **16** (Scheme 5). When four equiv. of Br_2 was allowed to react with **1**, and then followed by zinc dust reduction, compounds **17** and **18** were formed. Compound **18** was first treated with KH to form the amide anion and alkoxide. Subsequent addition of t-BuLi resulted in halogen-metal exchange, and the incipient carbon anion was quenched with H_2O to provide **19**. The structure of **19** was confirmed by chemical correlation. Platinum-catalyzed air oxidation of paraherquamide A also afforded compound **19** (Scheme 6).

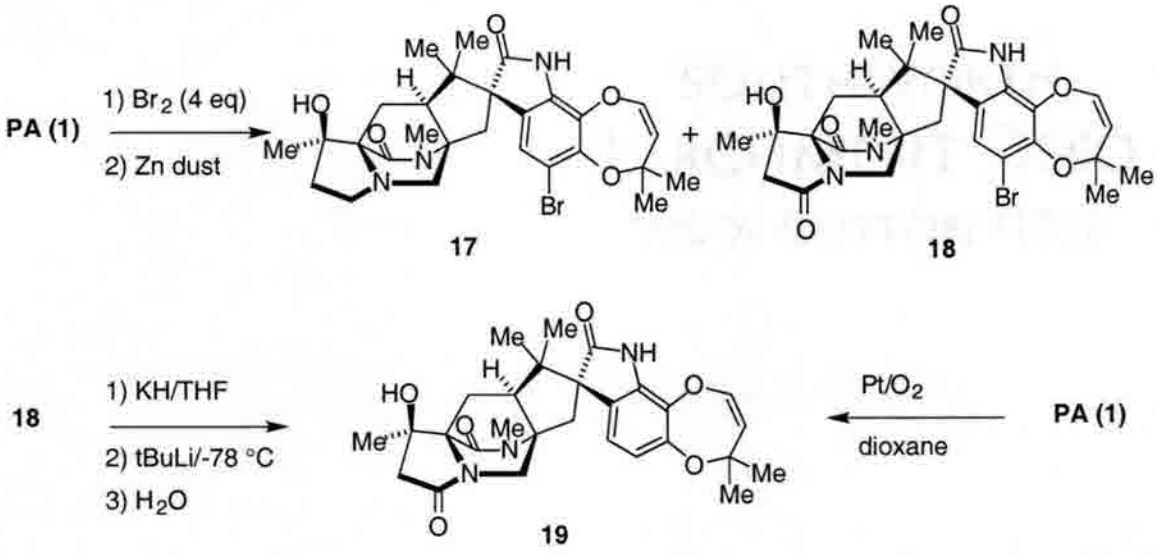
Scheme 5



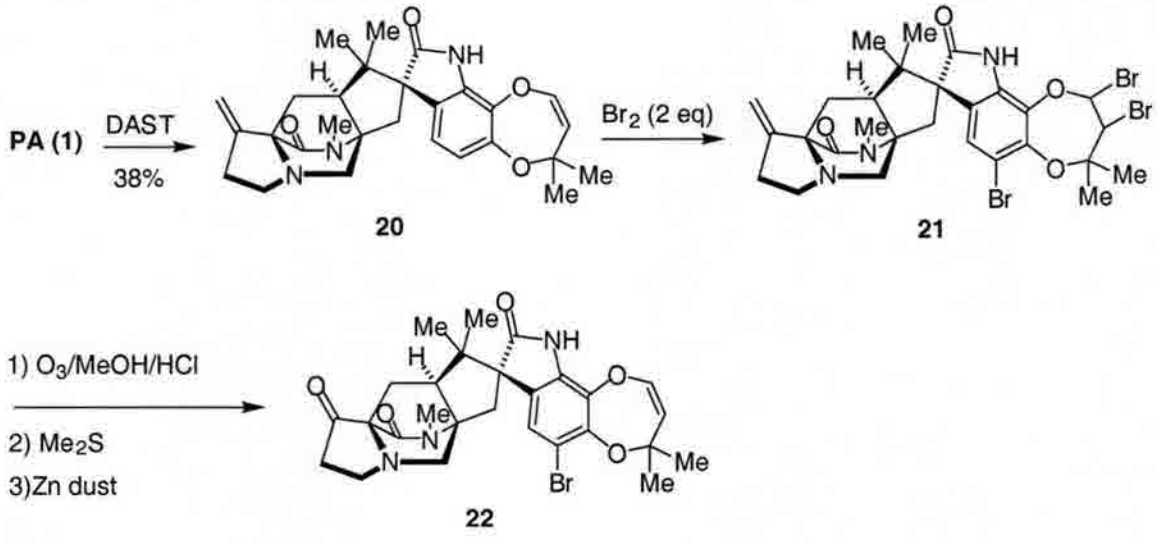
Blizzard and coworkers[20] reported that when **1** was reacted with DAST, the major product formed was the *exo*-olefin **20** in 38% yield (Scheme 7). Bromination of **20** using two equiv. of bromine selectively added to the enol ether double bond and the 5-position of the oxindole instead of the C-14 *exo*-double bond due to their different reactivities. The tribromide **21** was synthesized in order to protect the enol ether double bond in the ozonolysis step. Ozonolysis of **21** in acidic methanol solution (to protonate the tertiary

amine) with dimethyl sulfide workup followed by zinc dust reduction afforded the desired ketone **22**.

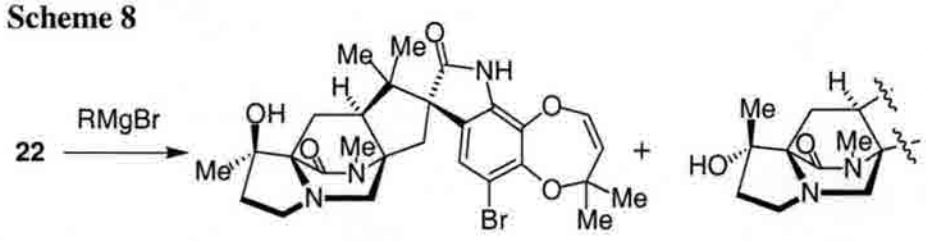
Scheme 6



Scheme 7



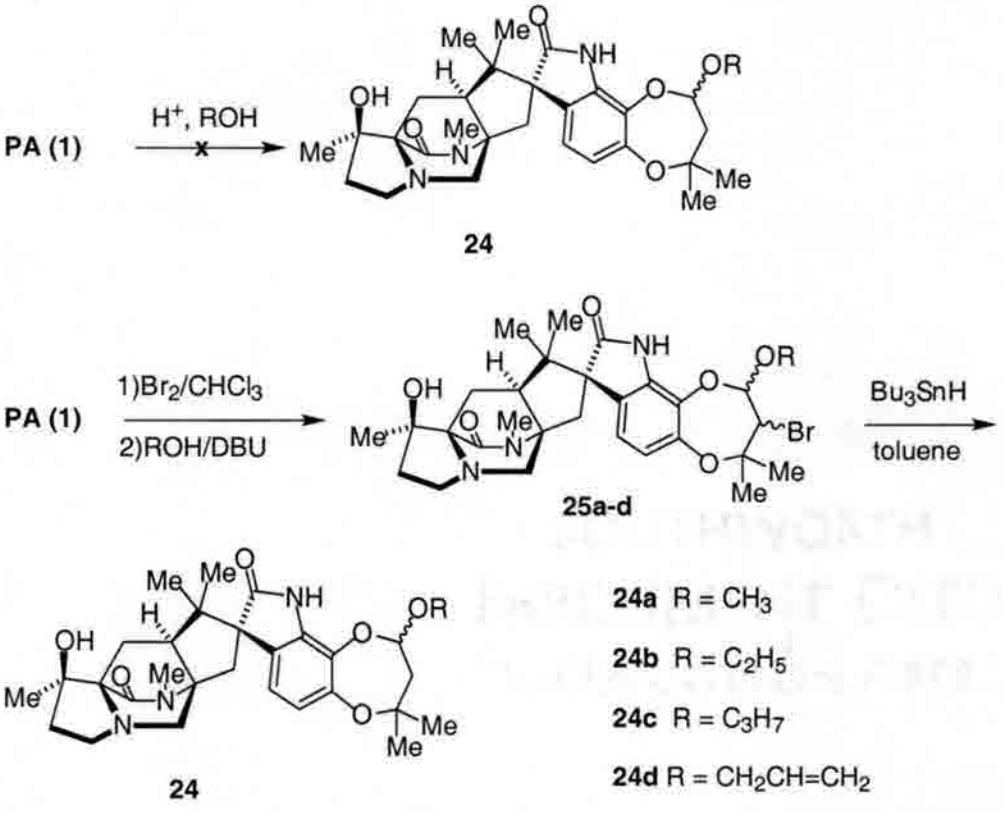
Scheme 8



23a **23b**

23a/23b	
R = CH_3	1/2
R = CH_2CH_3	3/1
R = CH_2Ph	0/100

Scheme 9



24a R = CH_3

24b R = C_2H_5

24c R = C_3H_7

24d R = $CH_2CH{=}CH_2$

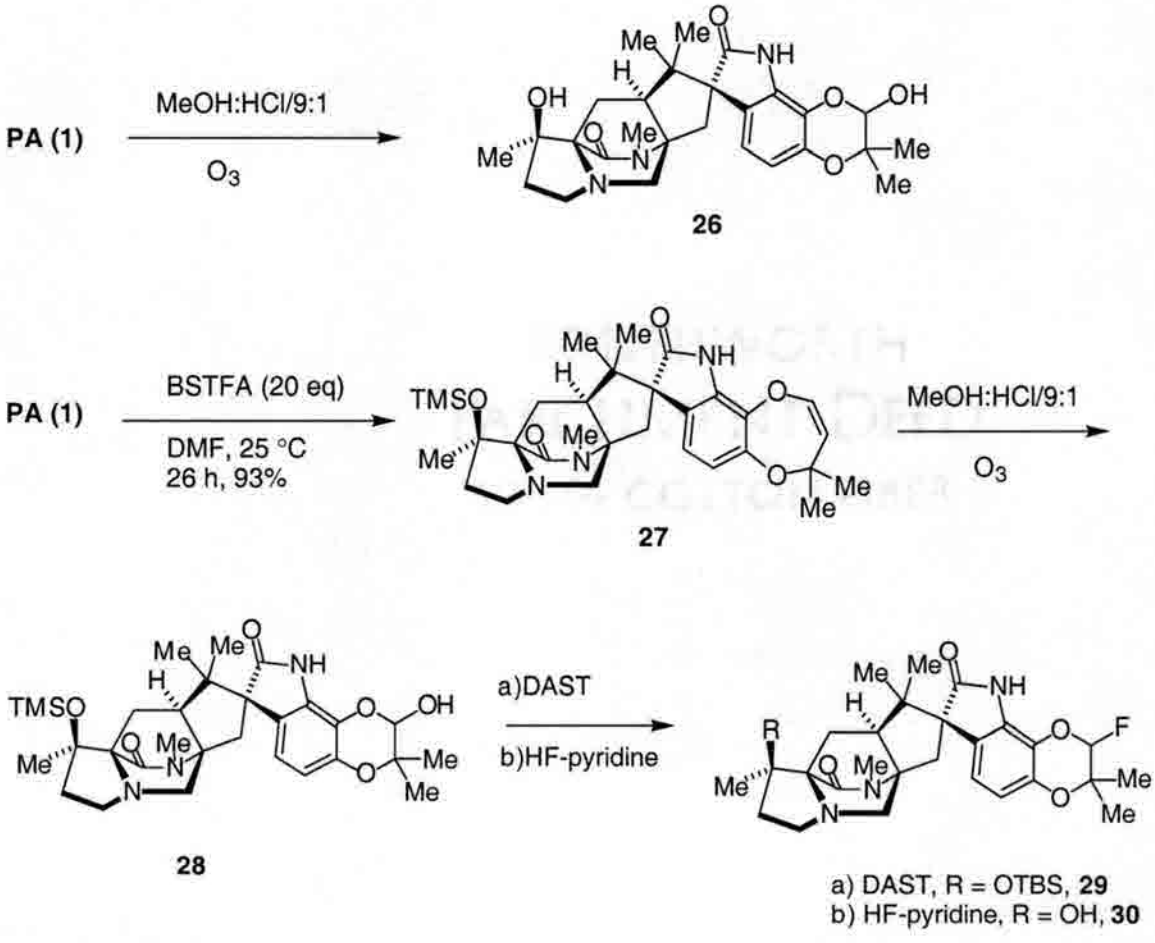
When ketone **22** was treated with $NaBH_4$, epimeric adducts **23a** and **23b** (R=H) were obtained in a 40:60 ratio, with **23a** being the desired epimer (Scheme 8). Methylmagnesium bromide addition to **22** provided a 1:2 ratio of products while ethylmagnesium bromide gave a 3:1 ratio of products, favoring the desired isomer.

However, introduction of a benzyl group formed only **23b** with the *epi*-stereochemistry at C-14.

Blizzard and coworkers[21] studied the chemical behavior of the vinyl ether double bond in PA (**1**). Acid-catalyzed alcohol addition to the olefin failed to provide the desired product **24**. By using an indirect two-step approach, compounds **24a-24d** were obtained. Selective addition of bromine to PA **1** gave the dibromide intermediates, which were treated with DBU/ROH to produce the alkoxy analogs **25a-25d**. Reductive debromination with Bu_3SnH led to the ketal analogs **24a-24d** (Scheme 9).

As outlined in Scheme 10, Blizzard et al. also explored ozonolysis of the vinyl ether as a source of new analogs.

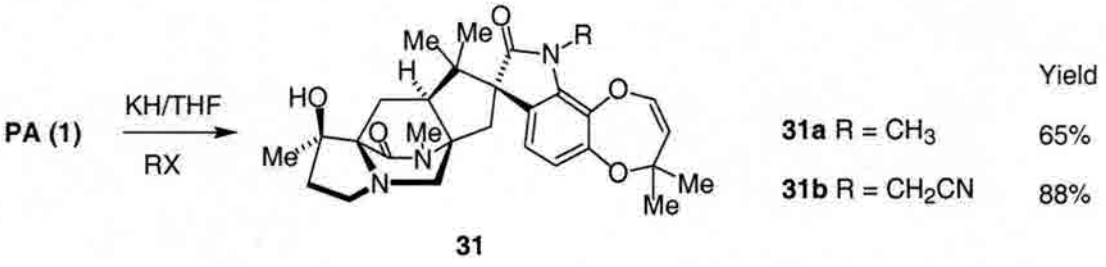
Scheme 10



Brief treatment (5 min) of a solution of PA (**1**) in acidic methanol with ozone at –78 °C followed by $(CH_3)_2S$ workup cleanly afforded compound **26**. However, ozonolysis of **1** in MeOH gave a mixture of products, presumably due to oxidation of the free tertiary amine. The 14-O-trimethylsilyl PA **27**, made by reaction of **1** with BSTFA, was treated with ozone to provide hemiketal **28**. Reaction of **28** with DAST resulted in the formation of fluoride **29**, and deprotection with HF/pyridine/THF afforded the fluoride compound **30** (Scheme 10).

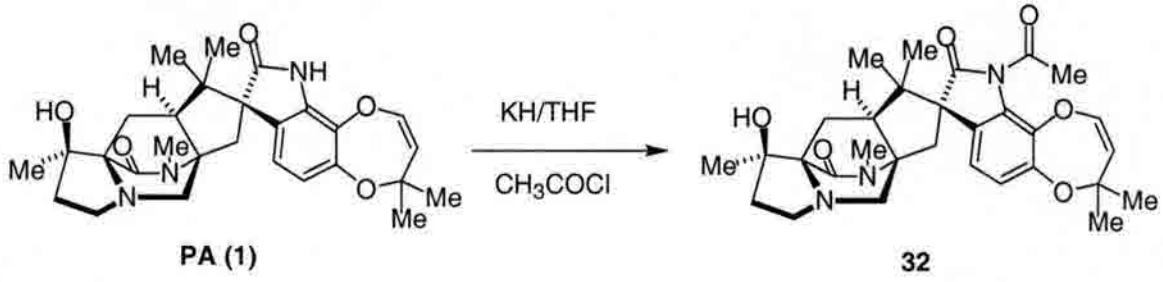
The same Merck group led by Blizzard[22] attempted to introduce substitutents at the C-14-O position. They found that under all the conditions they tried, the 1-NH group was significantly more reactive than the C-14-OH group toward electrophiles. For example, reaction of **1** with excess KH in THF (25 °C, 2h) followed by addition of CH_3I (10 eq, 5 min) afforded 1-N-methyl-PA **31a** as the major product (65%) along with a small amount of the 1-N, 14-O-bis alkylated product. None of the 14-O-methyl analog was observed (Scheme 11).

Scheme 11



They also found that the amide nitrogen could be selectively acylated (Scheme 12) to give product **32**.

Scheme 12

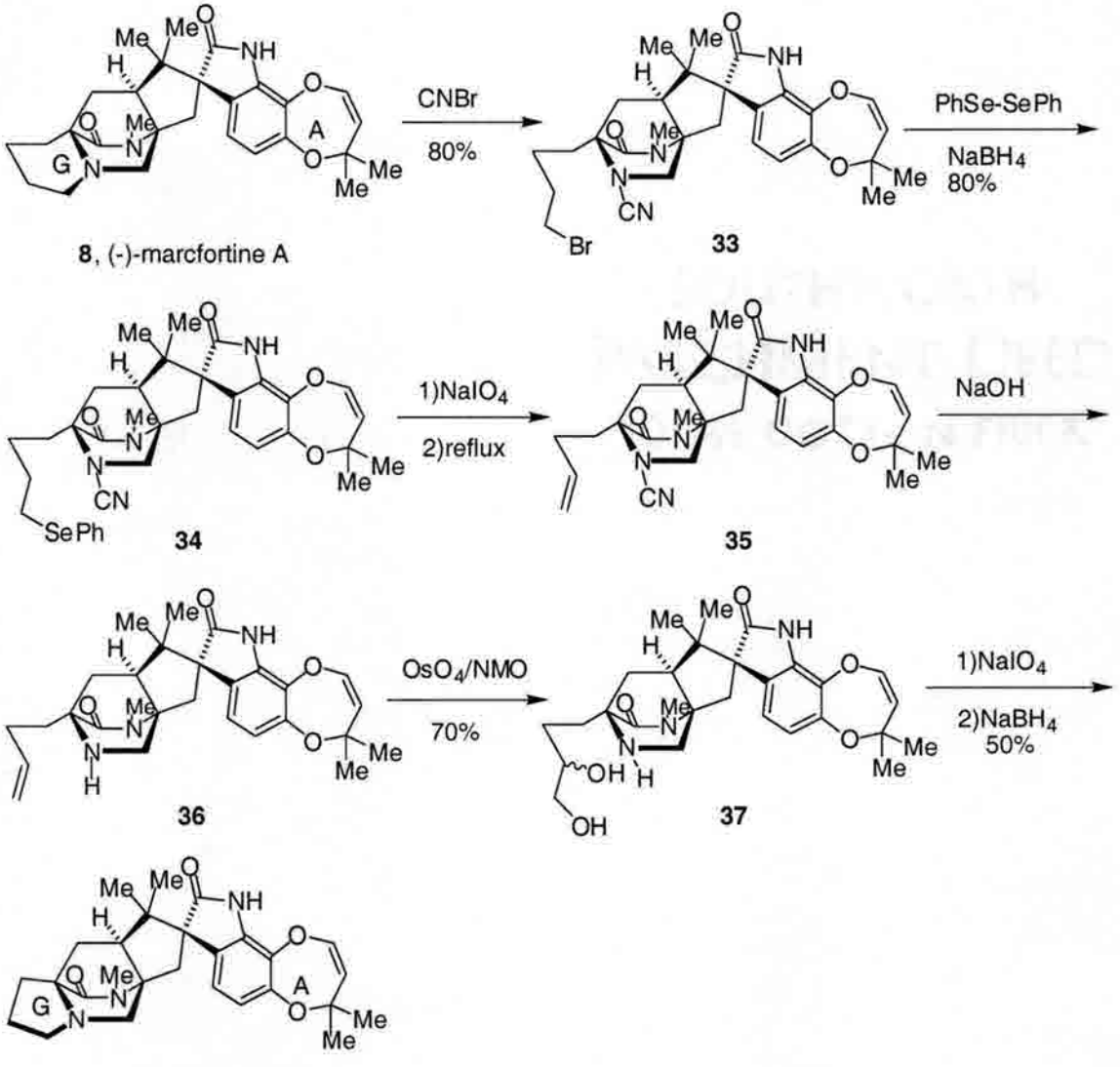


1.5.2 Pharmacia and Upjohn's Modification

The First Formal Synthesis of (-)-Paraherquamide A

In 1997, Lee and Clothier[23] at Pharmacia and Upjohn reported the first formal synthesis of (-)paraherquamide A from (-)-paraherquamide B (Scheme14 and 15), which came from the conversion of marcfortine A (Scheme 13). Marcfortine A, reported by Polonsky et al.,[8] is a fungal metabolite of *Penicillium roqueforti* and is structurally related to paraherquamide B, the sole difference occurring in ring G. Paraherquamide B contains a five-membered G-ring, and the G-ring of marcfortine A is six-membered. Opening the G-ring of marcfortine A, oxidatively removing one carbon atom, and reclosing the ring was expected to give paraherquamide B. This approach was accomplished in six steps as depicted in Scheme 13. Von Braun reaction of **8** with cyanogen bromide provided bromide **33**, which was converted to selenide **34** in the presence of diphenyl diselenide and $NaBH_4$. Oxidation of **34** with $NaIO_4$ followed by elimination of the resulting selenol in refluxing benzene gave alkene **35**. Hydrolysis of alkene **35** produced compound **36** that under osmylation conditions, provided diol **37** (70%). Cleavage of the diol with $NaIO_4$ followed by reductive amination gave (-)-paraherquamide B. (-)-Paraherquamide B and (-)-paraherquamide A both have the same stereochemistry, but paraherquamide A also has a tertiary alcohol moiety at the C-14 position. The formal synthesis of (-)-paraherquamide A was completed in seven steps starting with (-)-paraherquamide B according to the synthetic pathway illustrated in Scheme 14 and 15.

Scheme 13



8, (-)-marcfortine A

33

34

35

36

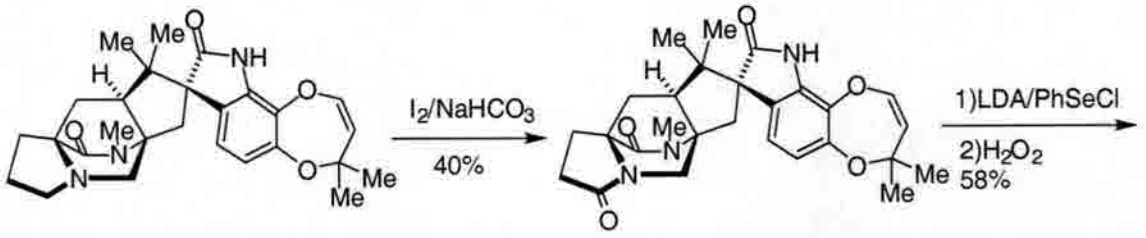
37

2, (-)-paraherquamide B

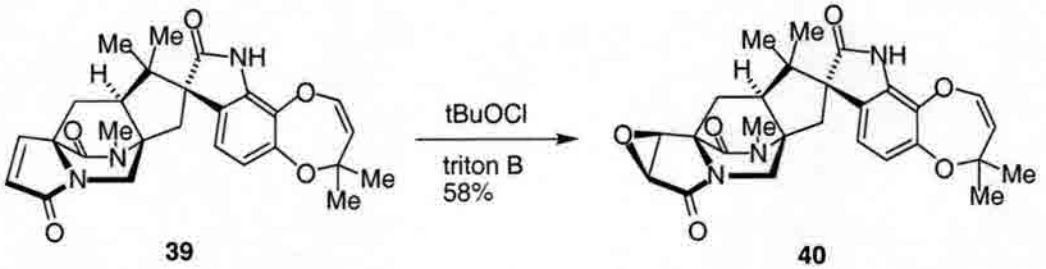
Oxidation of paraherquamide B with $I_2/NaHCO_3$ gave lactam **38**. The α,β-unsaturated lactam **39** was formed by treatment of **38** with LDA/PhSeCl followed by H_2O_2 oxidation (58%). Stereoselective epoxidation followed by epoxide ring-opening with SmI_2 provided alcohol **41**. Selective reduction of one of the amide groups in **41** with LAH gave **42**, which was then oxidized to the C-14 ketone **43** (71%). A slightly modified procedure (THF, 3 M MeMgBr in ether, 50% yield based on recovered starting material) relative to the original method (CH_2Cl_2, 2 M MeMgBr in THF) by the Merck group was used to

introduce the methyl group and resulted in almost exclusively the desired isomer with only a trace amount of epimer.

Scheme 14

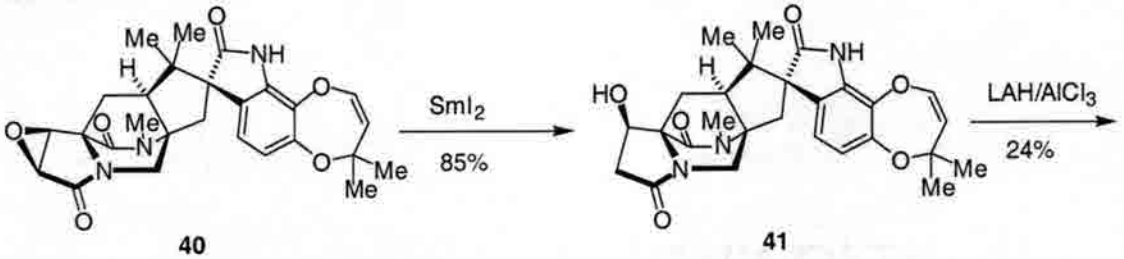


2, (-)-paraherquamide B **38**

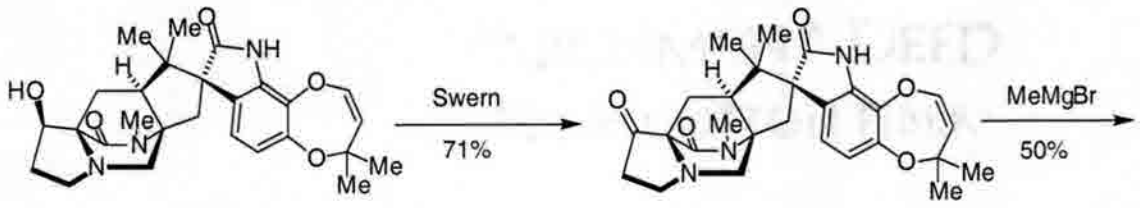


39 **40**

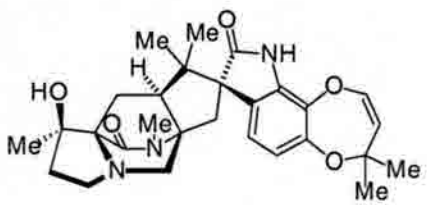
Scheme 15



40 **41**



42 **43**

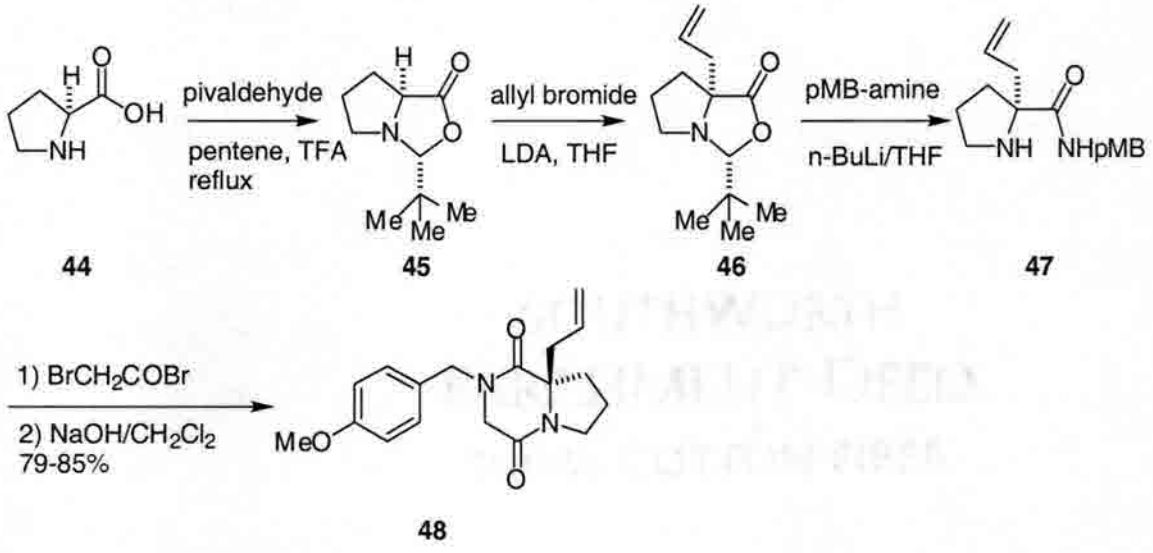


1, (-)-paraherquamide A

1.6 The Total Synthesis of (-)-Brevianamide B

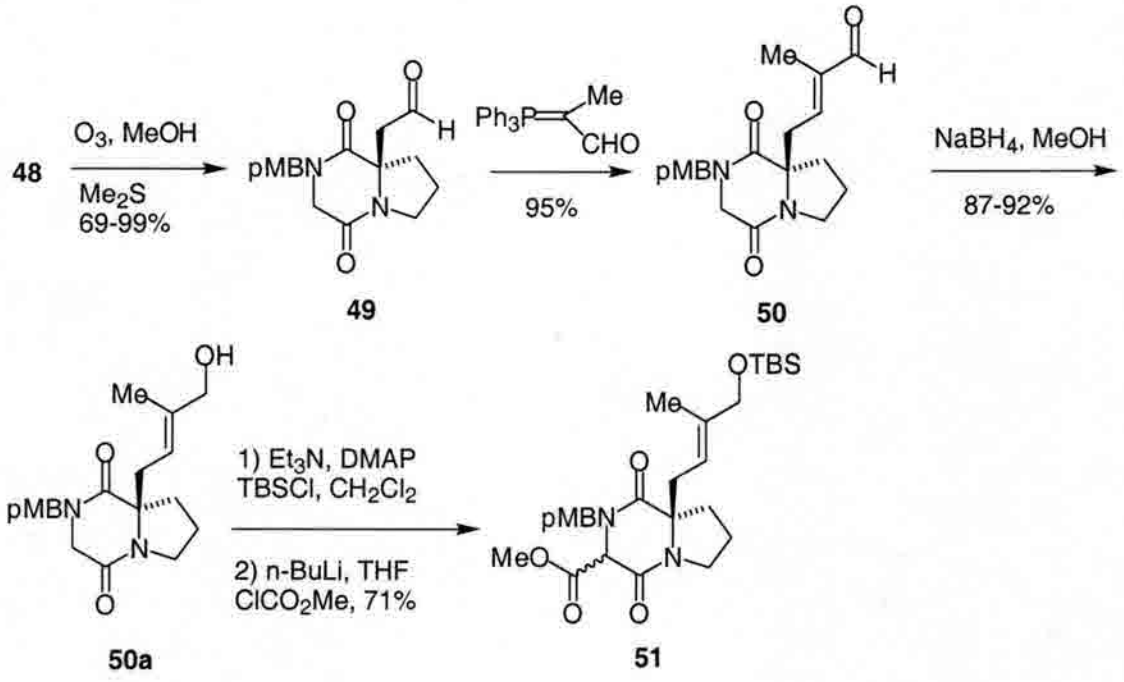
In 1988 Williams et al.[24] completed the total synthesis of (-)-breviamide B in 20 steps from L-proline based on a model study developed by the same group [25] (Scheme 16). The formation of **47** from L-proline (**44**) was based on the procedure developed by Seebach[26]. Proline was condensed with pivaldehyde to give aminal **45**, which was stereospecifically alkylated with allylic bromide to provide **46**. Ring-opening of **46** by the preformed amide anion afforded amide **47**. Reaction of **47** with bromoacetyl bromide and subsequent cyclization provided diketopiperazine **48**. Ozonolysis of **48** (dimethylsulfide work-up) followed by a Wittig reaction gave aldehyde **50** (Scheme 17). Reduction of the aldehyde to the corresponding alcohol followed by TBS ether protection and further introduction of the methoxycarbonyl group provided the key intermediate **51**.

Scheme 16



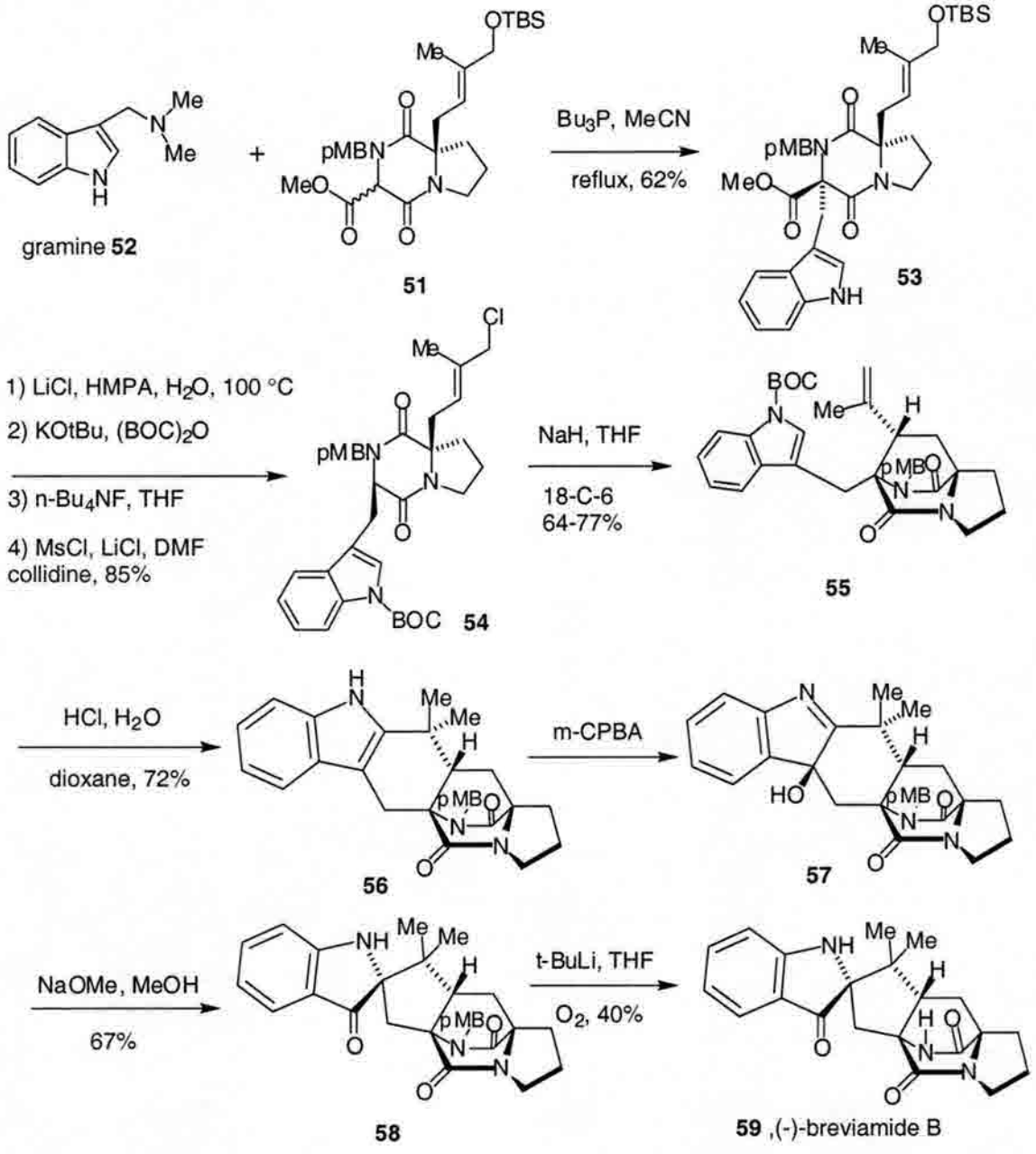
44 **45** **46** **47** **48**

Scheme 17



Compound **51** was treated with gramine in the presence of Bu_3P in refluxing CH_3CN to give only the *syn*-diastereomer **53** (Scheme 18). Decarbomethoxylation, protection of the indole nitrogen as the t-BOC derivative, deprotection of the TBS ether moiety, and allylic chloride formation (MgCl, LiCl, DMF collidine, 85%) led to the S_N2' precursor **54**. Intramolecular S_N2' cyclization of **54** was best carried out in refluxing THF with 18-C-6 and NaH to provide the *anti*-isomer **55**. Treatment of compound **55** with HCl in dioxane induced electrophilic cyclization to give indole **56**. Oxidation of **56** with m-CPBA resulted in the formation of hydroxy indolenine **57**, which was immediately treated with NaOMe in MeOH to effect a stereoselective pinacol-type rearrangement, yielding the rdesired indoxyl **58**. Removal of the *para*-methoxy benzyl group in **58** provided (-)-brevianamide B (**59**) in 40% yield.

Scheme 18

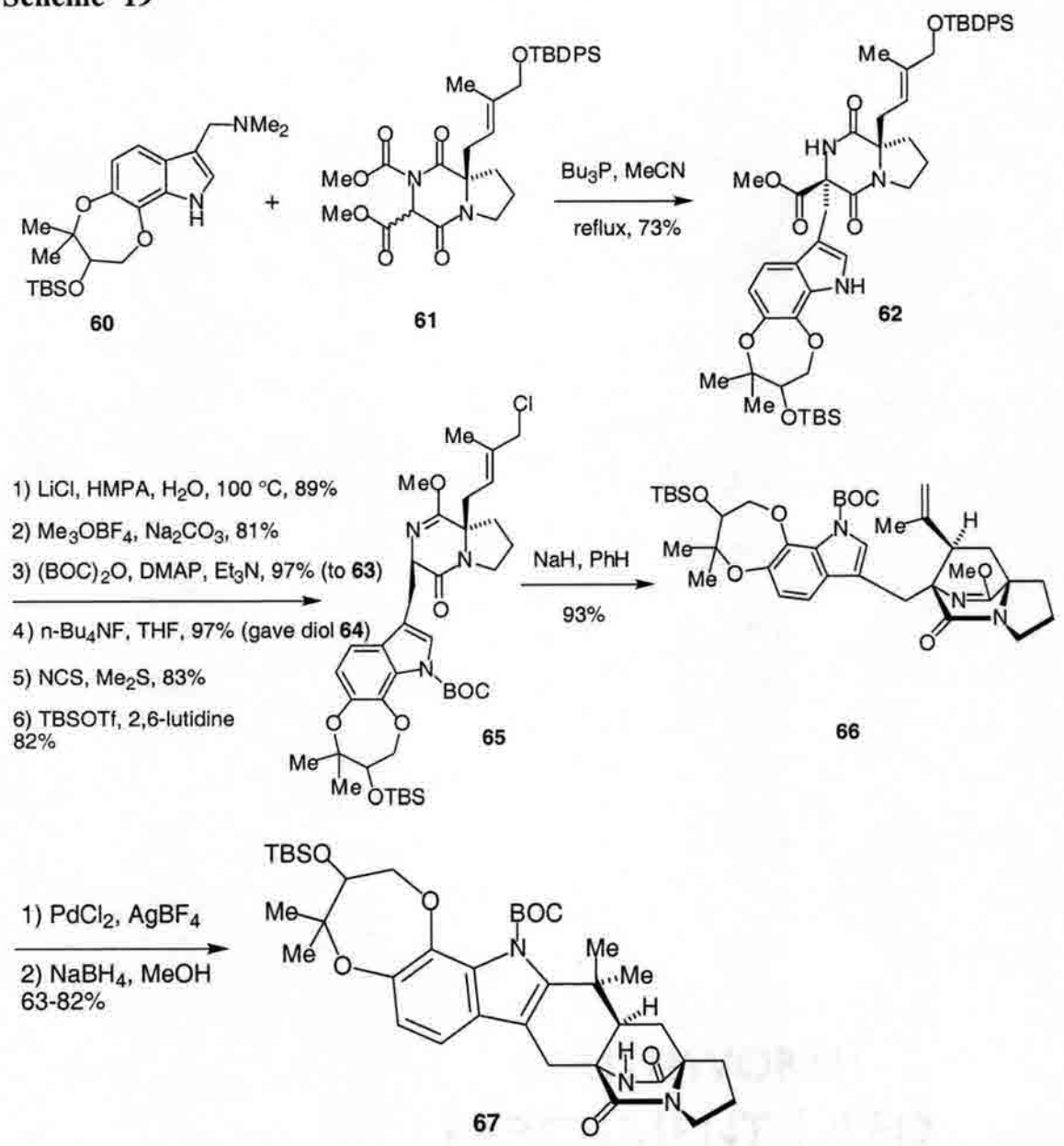


1.7 Total Synthesis of (+)-Paraherquamide B

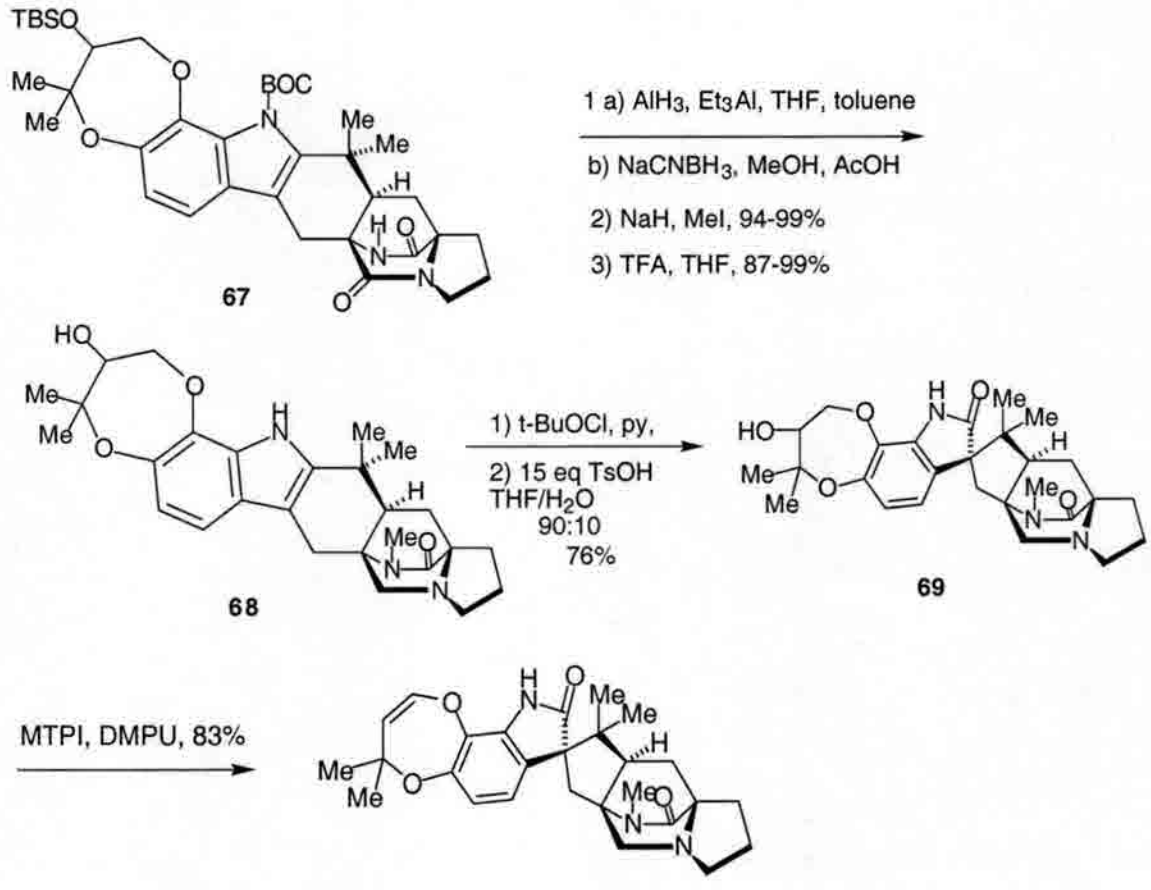
In 1993, Cushing, Sanz-Cervera and Williams [27a,b] finished the total synthesis of (+)-paraherquamide B in 42 chemical steps. This synthesis was a convergent one, which coupled two key pieces together using the same Somei/Kametani reaction used during the synthesis of (-)-brevianamide B.

The synthetic approach after the Somei/Kametani coupling step is shown in Scheme 19. Gramine derivative **60** was coupled with diketopiperazine **61** by catalysis with 0.5 equiv. of Bu_3P to give the *syn*-stereoisomer **62** in 73% yield. Decarbomethoxylation, lactim ether formation, indole nitrogen protection with $(BOC)_2O$/DMAP in CH_2Cl_2 and removal of both TBS ether protecting groups gave diol **64**. Conversion of the allylic alcohol to the allylic chloride under Corey-Kim conditions followed by reprotection of the secondary alcohol as its t-butyldimethylsilyl ether, led to the precursor **65** for the key S_N2' reaction. Compound **65** was treated with NaH in refluxing benzene to give the cyclization product **66** in a stereoselective fashion. Stoichiometric Pd(II)-mediated reaction followed by reduction with $NaBH_4$ provided the heptacyclic product **67**. Selective reduction of the tertiary amide, N-methylation, and subsequent deprotection of both the N-t-BOC and the t-butyldimethylsilyl ether gave the indole-alcohol **68**. Oxidative Pinacol-type rearrangment of **68** afforded oxindole **69**. Dehydration of **69** was effected with MTPI in DMPU to give paraherquamide B in 83% yield.

Scheme 19


NMe2
Me
Me
TBSO
60
+
OTBDPS
Me
MeO
MeO
61
Bu3P, MeCN
reflux, 73%
OTBDPS
Me
HN
MeO
NH
62
Me
Me
OTBS
1) LiCl, HMPA, H2O, 100 °C, 89%
2) Me3OBF4, Na2CO3, 81%
3) (BOC)2O, DMAP, Et3N, 97% (to 63)
4) n-Bu4NF, THF, 97% (gave diol 64)
5) NCS, Me2S, 83%
6) TBSOTf, 2,6-lutidine
82%
Cl
Me
MeO
BOC
65
NaH, PhH
93%
TBSO
BOC
Me
H
MeO
66
1) PdCl2, AgBF4
2) NaBH4, MeOH
63-82%
67

Scheme 20



2a, (+)-paraherquamide B

1.8 The Synthetic Strategy towards (-)-Paraherquamide A

Our synthetic strategy is based on the success of the synthetic approaches to (-)-breviamide B and (+)-paraherquamide B. The key intermediate for our synthesis of (-)-paraherquamide A is similar to the key intermediates used in the (-)-breviamide B and (+)-paraherquamide B work. This intermediate is diketopiperazine **70** (Scheme 21).

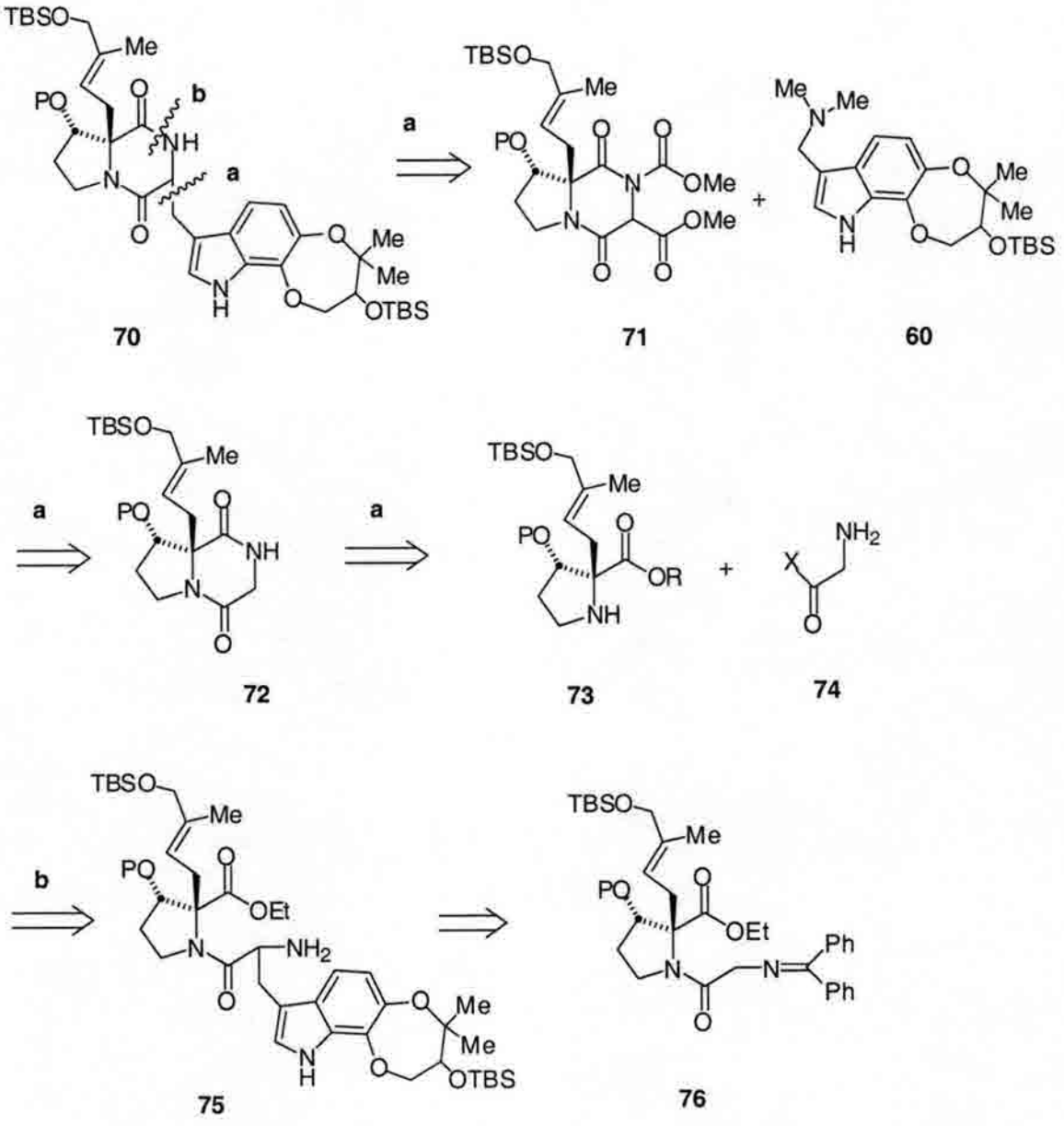
According to the retrosynthetic design for (-)-paraherquamide A shown in Scheme 21, compound **70** can be constructed in two different ways. The first approach is to connect bond **a** between the two fragments **71** and **60** using the same Somei/Kametani coupling reaction found in the (-)-breviamide B and (+)-paraherquamide B syntheses. Cyclic dipeptide formation between **73** and **74** should provide **72**, and **71** will be obtained upon further functionalization of **72**. The second approach is the disconnection of bond **b**,

and this will lead to an acyclic dipeptide **75**, which can come from the coupling between diphenyl imine compound **76** and gramine derivative **60** (Scheme 21). The retrosynthetic analysis and the synthetic details for compounds **73** and **76** will be discussed in Chapter 2.

Our final retrosynthetic analysis of paraherquamide A is summarized in Scheme 22. (-)-Paraherquamide A contains a tertiary methyl alcohol moiety at the C-14 position, and paraherquamide B lacks this structural feature at the C-14 position. In order to carry out the synthesis of paraherquamide A, there are different and challenging problems that we need to carefully consider. First, we need to find a way to asymmetrically synthesize the chiral intermediate **73** in a practical and efficient manner, and then further transform **73** into diketopiperazine **71**. Second, when do we introduce the tertiary methyl alcohol functionality at C-14? If we decide to introduce this moiety as a secondary alcohol and convert it into the tertiary methyl alcohol at the final stage of the synthesis, what kind of protecting group will we need to use for the secondary alcohol? Third, and most importantly, will the newly introduced functional group at the C-14 position affect the stereochemistry at the S_N2' reaction step and at the Pinacol-type rearrangement step (both steps create a new chiral center)?

In our retrosynthetic plan, we have decided to put a protected secondary alcohol at the C-14 position instead of the tertiary methyl alcohol. During the final stage of our synthesis, the protected hydroxy group at the C-14 position will be deprotected and oxidized to provide a ketone. Methyl addition to the ketone should lead straightforwardly to the tertiary methyl alcohol.

Scheme 21

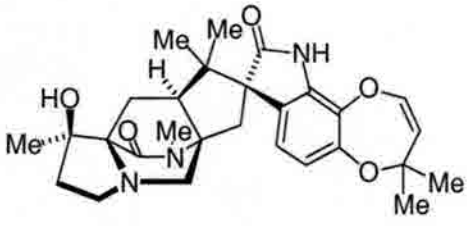


There are four reasons for this particular synthetic plan. First, we want to ensure that the group at the C-14 position is sterically as small as possible, in order to mimic the steric situation at the C-14 position of (+)-paraherquamide B. (+)-Paraherquamide B has two hydrogens at this position. If we place the tertiary alcohol at the C-14 position, and protect this alcohol, the groups at the C-14 position will be quite large. Second, from the chemical modification studies of (-)-paraherquamide A, we know that the tertiary alcohol moiety at the C-14 position of paraherquamide A is very unreactive, and therefore

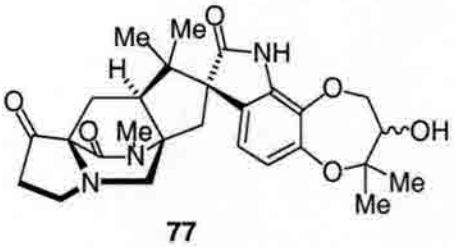
protection of this alcohol will be difficult. Third, construction of the methyl alcohol will use the known reaction of methylmagnisum bromide addition to a ketone group. This reaction should be feasible in terms of yield, stereoselectivity and scale. Merck's procedure for the methylmagnesium bromide addition to the C-14 ketone group gave products in a ratio of 1:2, favoring the wrong stereoisomer. The modified procedure of Upjohn provided almost exclusively the desired isomer in 50% yield. At the early stage of a long synthesis, any low yield and/or poor diastereoselectivity in a single step will be a disaster to the whole project. Finally, the formation of the ketone at the final stage of our synthesis will provide us with a handle to make different analogs of paraherquamide A (PA). Interestingly, when Lee and Clother published the first formal synthesis of (-)-paraherquamide A (Scheme 14 and 15) in 1997, they used the same synthetic strategy at the last two steps (from **42** to **43**, then to PA) that we plan to use.

The first synthetic plan for (-)-paraherquamide A proposed by Professor Williams is illustrated in Scheme 23. Comparison of this synthetic route with our actual final synthesis of (-)-paraherquamide A shows that the two are very similar.

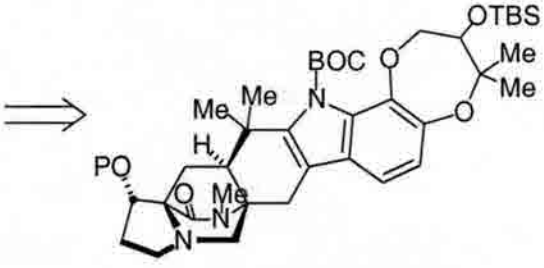
Scheme 22 The Retrosynthetic Analysis of (-)-Paraherquamide A



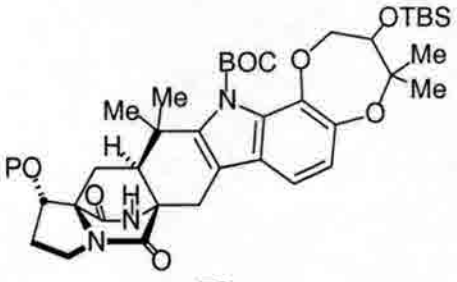
1, (-)-paraherquamide A



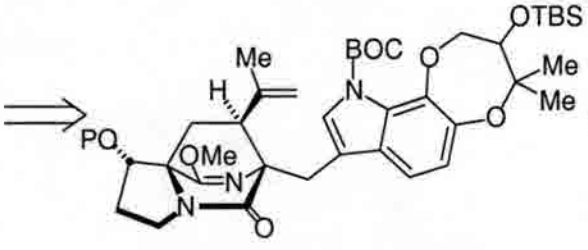
77



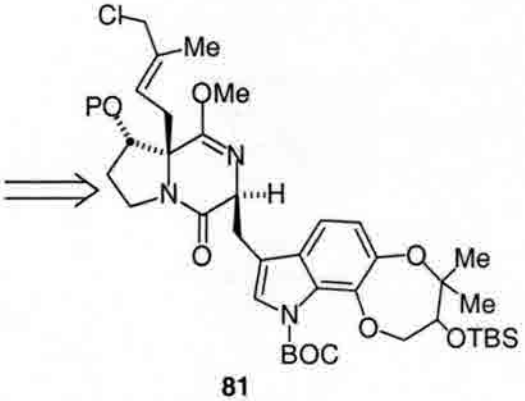
78



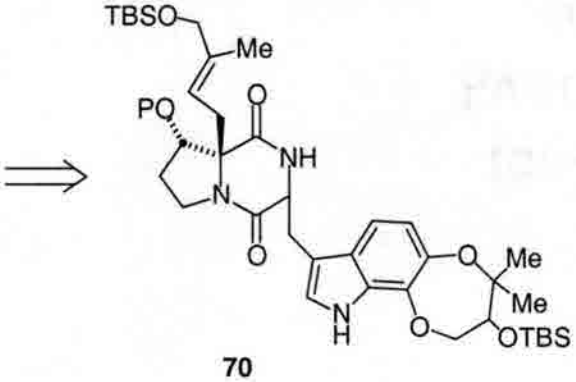
79



80

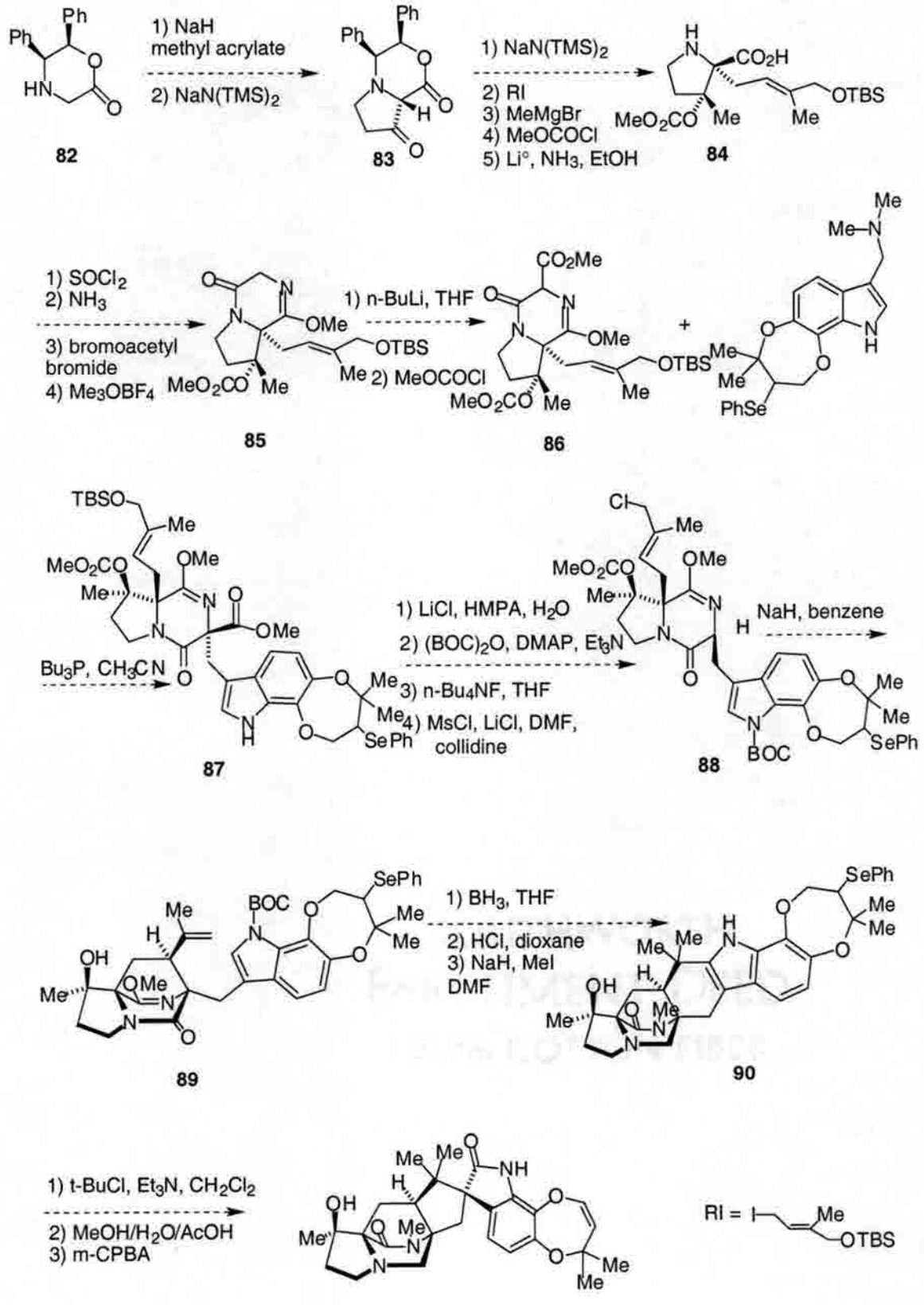


81



70

Scheme 23



1, (-)-paraherquamide A

CHAPTER TWO

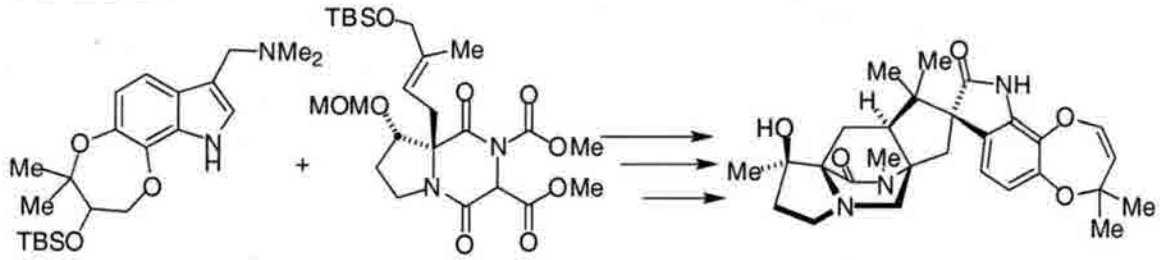
THE TOTAL SYNTHESIS OF (-)-PARAHERQUAMIDE A

2.1 The Improved Large Scale Synthesis of the Dioxepin-indole of Paraherquamide A

2.11 Introduction

Dioxepin-indole **60** is one of the two key intermediates required for our proposed synthesis of (-)-paraherquamide A (Scheme 24).

Scheme 24

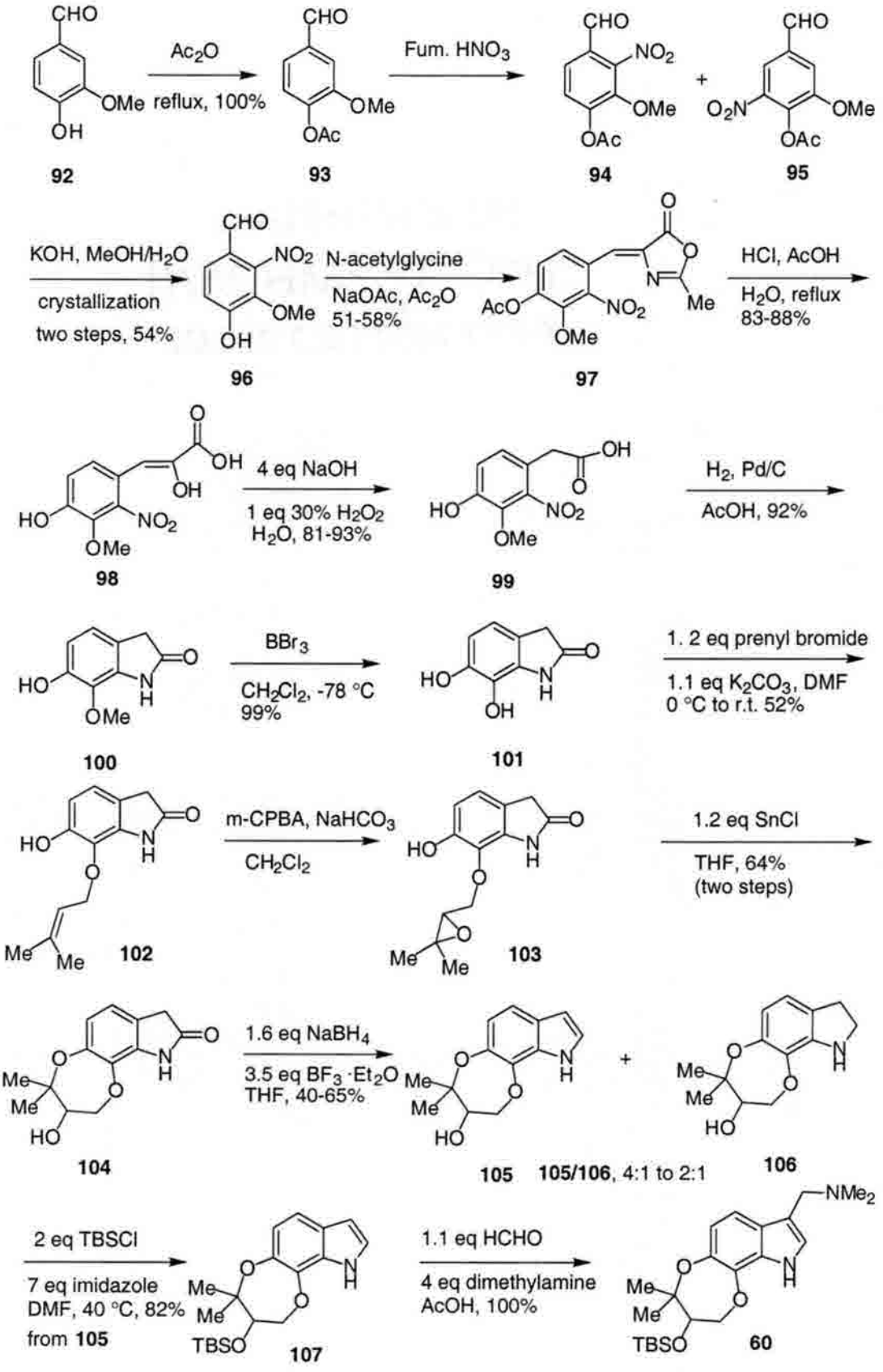


60 **91** **1**, (-)-paraherquamide A

In the course of the (+)-paraherquamide B synthesis,[27a,b] Tim Cushing synthesized **60** in fourteen chemical steps (Scheme 25). Developing a synthetic approach to make compound **60** on a large scale (30-40 grams) practically and efficiently is critical for the successful synthesis of (-) paraherquamide A since the proposed synthetic approach would require an additional 21 steps starting from the coupling between **60** and **91**.

Cushing made a tremendous effort in discovering the above approach for the construction of **60**, which was successfully used for the synthesis of (+)-paraherquamide B. There are several advantages in the above synthetic approach to compound **60**. There are no column chromatographies necessary until the purification of compound **102**. Most of the chemical steps do not require special equipment and give reproducible results.

Scheme 25

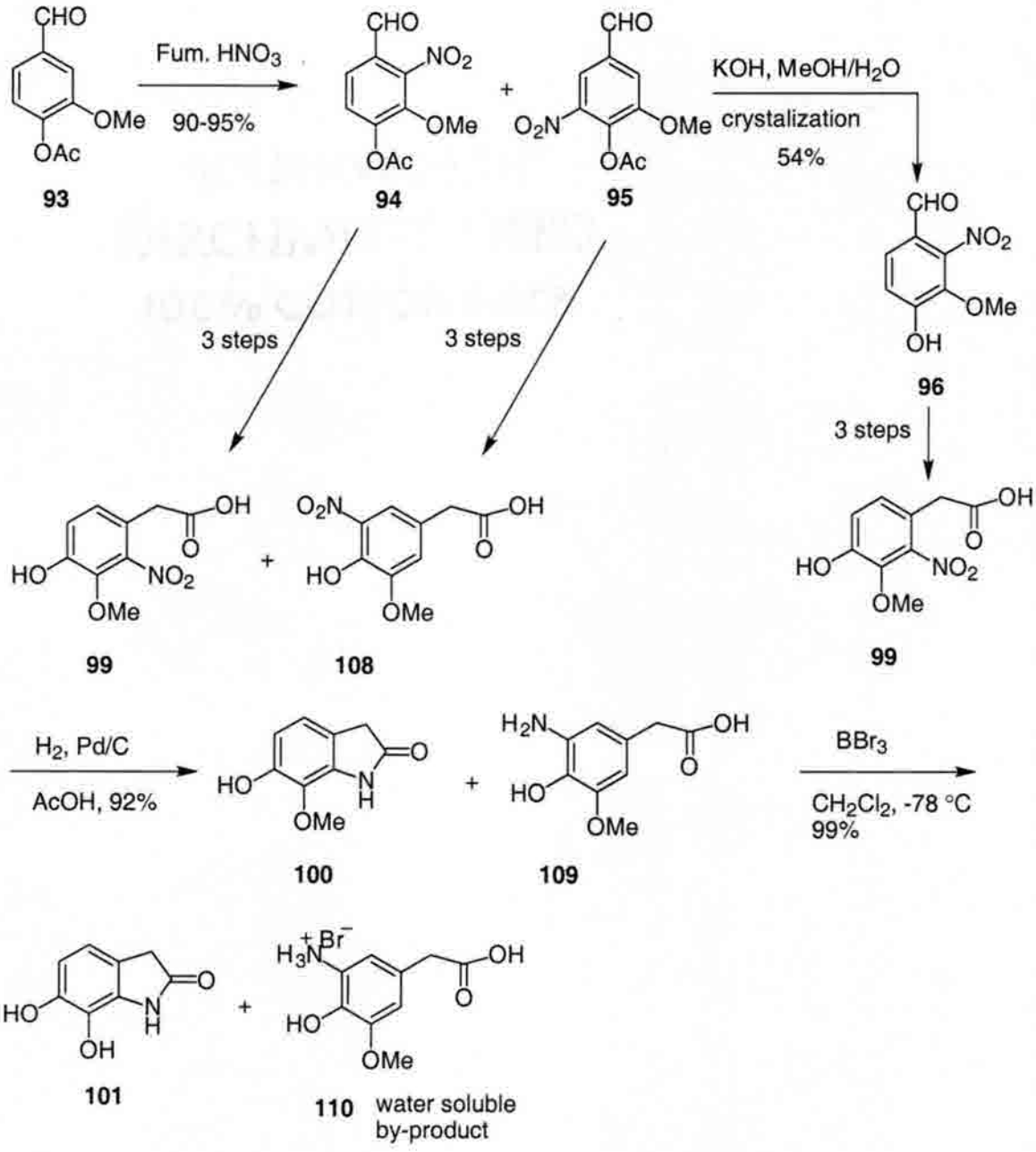

CHO
OMe
OH
92
Ac2O
reflux, 100%
CHO
OMe
OAc
93
Fum. HNO3
CHO
NO2
OMe
OAc
94
+
CHO
O2N
OMe
OAc
95
KOH, MeOH/H2O
crystallization
two steps, 54%
CHO
NO2
OMe
OH
96
N-acetylglycine
NaOAc, Ac2O
51-58%
O
O
N
AcO
NO2
Me
OMe
97
HCl, AcOH
H2O, reflux
83-88%
O
OH
OH
HO
NO2
OMe
98
4 eq NaOH
1 eq 30% H2O2
H2O, 81-93%
OH
O
HO
NO2
OMe
99
H2, Pd/C
AcOH, 92%
HO
O
N
H
OMe
100
BBr3
CH2Cl2, -78 °C
99%
HO
O
N
H
OH
101
1. 2 eq prenyl bromide
1.1 eq K2CO3, DMF
0 °C to r.t. 52%
HO
O
N
H
O
Me
Me
102
m-CPBA, NaHCO3
CH2Cl2
HO
O
N
H
O
Me
Me
103
1.2 eq SnCl
THF, 64%
(two steps)
Me
Me
O
N
H
HO
104
1.6 eq NaBH4
3.5 eq BF3·Et2O
THF, 40-65%
Me
Me
O
N
H
HO
105
105/106, 4:1 to 2:1
+
Me
Me
O
N
H
HO
106
2 eq TBSCl
7 eq imidazole
DMF, 40 °C, 82%
from 105
Me
Me
O
N
H
TBSO
107
1.1 eq HCHO
4 eq dimethylamine
AcOH, 100%
NMe2
Me
Me
O
N
H
TBSO
60

However, there are also some disadvantages which exist in this synthetic route, creating an obstacle for quick and efficient large-scale synthesis of **60**. Therefore, I have further optimized our synthetic route towards compound **60**, and in the following sections, I will discuss the details of these improvements.

2.12 The Synthesis of Dioxepin-Indole 60 Optimized from 14 Steps to 13 Steps

As shown in Scheme 25, vanillin (**92**) was acetylated with acetic anhydride to provide acetate **93**, which was then treated with fuming nitric acid to afford **94**, the desired regioisomer, and **95**, the undesired isomer, in a ~10:1 ratio. TLC showed that **94** had a lower R_f and **95** had the exact same R_f as the starting material **93**. Flash column chromatography was used to give a nice separation of **94** and **95**. However, in the course of our (-)-paraherquamide A synthesis, more than 6.3 kg of the nitro-substituted acetate **94** and **95** was needed, and flash column chromatography is not the optimal method for separating large amounts of **94** and **95**. The original method used to separate compounds **94** and **95** is as follows: the mixture of **94** and **95** was hydrolyzed in a solution of KOH/MeOH/H_2O to give the phenoxide mixture, which was then neutralized with HCl to provide free phenol **96** and the phenol corresponding to **95**. The two phenol isomers were then taken up in EtOH at 23 °C. The resulting mixture, due to the high solubility of **96** and the low solubility of the by-product phenol, was filtered to give a filtrate containing almost pure phenol **96**. This filtrate was concentrated, and the residue was recrystallized in water to give the pure product **96**.

Scheme 26



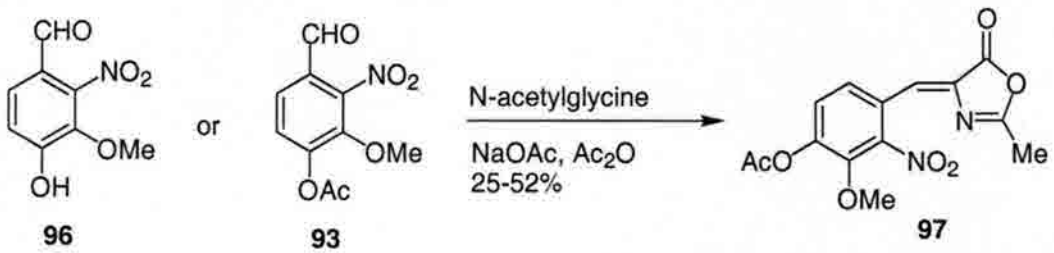
A comparison of our new improved approach and the originl approach is outlined in Scheme 26. The new approach avoids the KOH/MeOH/H_2O hydrolysis step and the crude product recrystallization process. Instead, it directly used the mixture of nitro-acetaldehydes **94** and **95**. After a three-step transformation, **94** provided the desired acid **99**, and **95** provided the undesired acid **108**. The next step is the hydrogenation of the nitro group to

the corresponding amine at 80 °C in acetic acid. Compound **99** cyclized into oxindole **100**, but **108** was simply reduced to amino acid **109**, which cannot undergo the intramolecular cyclization reaction due to geometric restriction. Demethylation of **100** and **109** using BBr_3 at -78 °C in CH_2Cl_2 provided oxindole **101** and acid **110**. The work-up procedure for this reaction requires quenching the reaction mixture with water, and produced hydrobromic acid (HBr). The resulting HBr reacted with the amino group of **110**, forming a water soluble salt. In contrast, compound **101** was insoluble in CH_2Cl_2 (the reaction solvent). Filtration of the acidic mixture and washing the solid product pad (**101**) with water provided a very pure solid product **101**. ^1H NMR and TLC showed that intermediate **101** had the same purity as the batches which were made by the old approach. The advantages of this new approach were significant. The yield of **96** increases from 54% to more than 80% (**94**). Considering that over 6.3 kg of **94** and **95** has been used, removing the KOH/MeOH/H_2O hydrolysis step and the recrystallization process lowers the cost of making **60**, increases the overall yield, and more importantly saves time.

2.13 Synthetic Investigation of the Transformation of Nitro-Aldehyde 93 to Azalactone 97

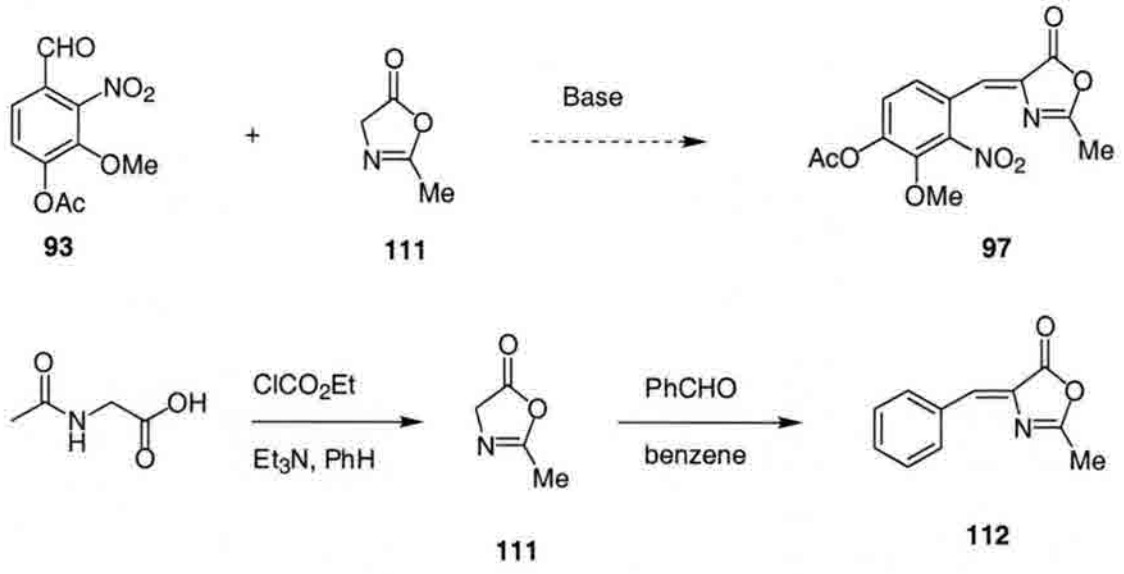
The synthesis of azalactone **97** from **93** or **96** takes eight days and the yields are not reproducible. The yield ranges from 25-52% (Scheme 27).

Scheme 27



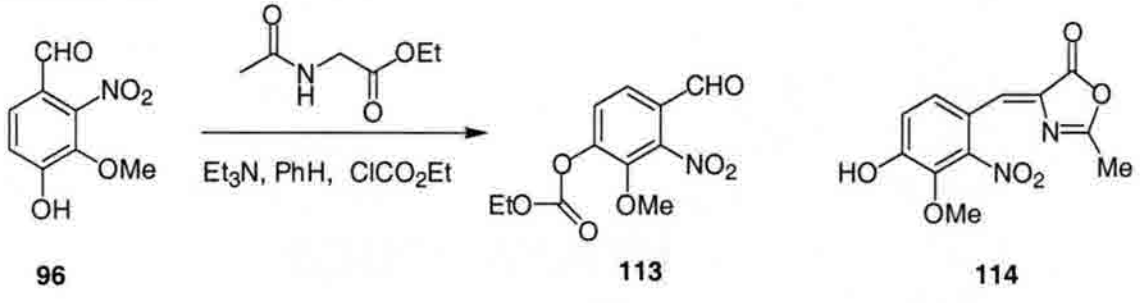
From a retrosynthetic point of view, azalactone **97** can also be made from aldehyde **93** and azalactone **111** (Scheme 28).

Scheme 28



Mukerjee and coworkers[28] reported a very similar reaction which is depicted in Scheme 29. These researchers started with N-acetylglycine and treated it with $ClCO_2Et$ and Et_3N to give azalactone **111**, which coupled with benzaldehyde in situ to provide the α,β-unsaturated azalactone **112**. According to the above procedure, aldehyde **96** was treated with ethyl N-acetylglycinate and $ClCO_2Et$ in the presence of Et_3N. However, none of the desired product **114** was formed. The only product was the ethyl carbonate **113** (Scheme 29).

Scheme 29

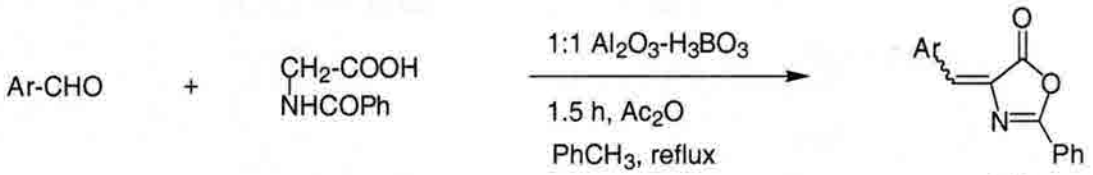


We believe that if N-acetylglycine was used instead of ethyl N-acetyl glycinate, the desired azalactone **114** might be formed because the N-acetyl-glycine could be activated by

$ClCO_2Et$ to form a mixed anhydride which will be a much better leaving group than the ethyl ester and therefore facilitate cyclization to azalactone **111**.

In 1998, Das and coworkers[29] reported an interesting synthesis of azalactone **116** (Scheme 30). A variety of aromatic aldehydes were treated with glycine derivative **115** in the presence of $1:1/Al_2O_3$-H_3BO_3 and provided **116** in very good yields (81-91%). The reaction time was short, and the work-up was easy. This protocol should be a feasible method to make **97**.

Scheme 30

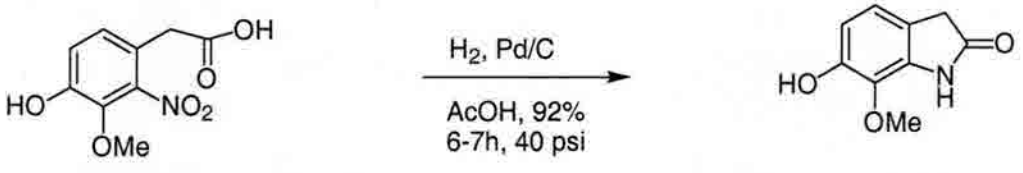


115 **116**

2.14 Different Approaches for the Synthesis of Oxindole 100 from Nitrophenyl Acetic Acid 99

The reaction conditions illustrated in Scheme 31 are the original ones used for the synthesis of (+) paraherquamide B. It is a very good method in terms of reaction set-up, work-up and yield.

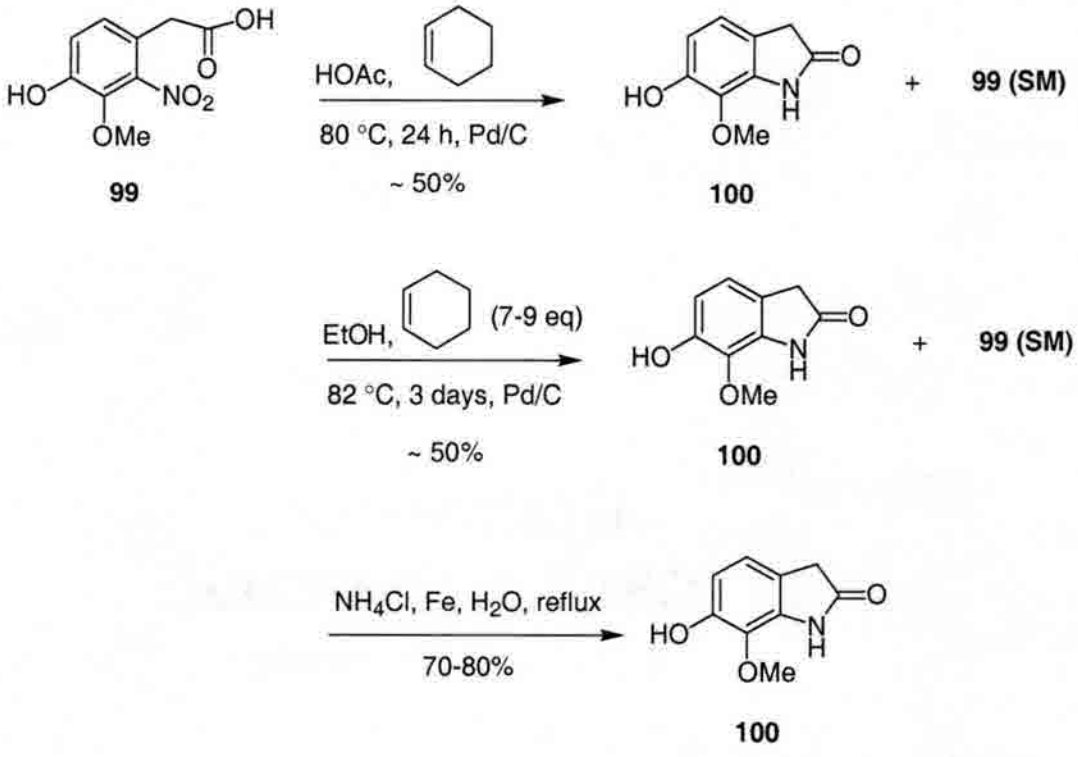
Scheme 31



99 **100**

The only disadvantage is that only 23 grams of **99** can be used in each batch because the hydrogenation is a heterogeneous reaction. Too much starting material will give by-products that are only partially reduced, and the product will not be pure. The following three different methods were attempted (Scheme 32) in order to solve the scale-up problem, but none of them proved to be as good as the original method.

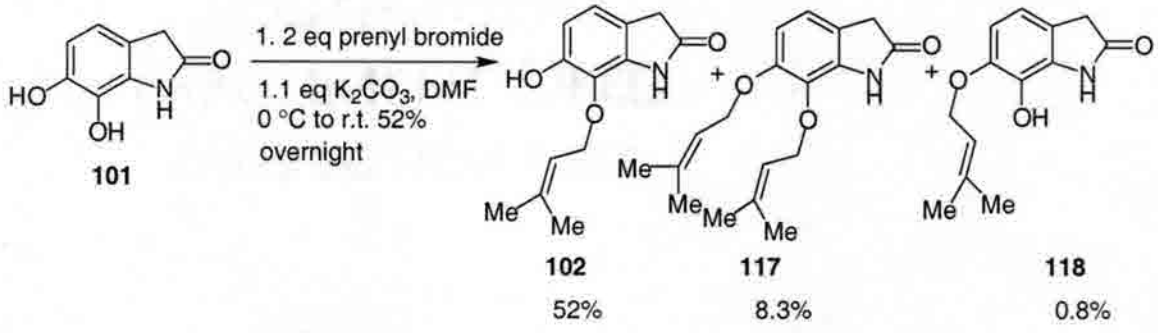
Scheme 32



For the catalytic hydrogen transfer reduction, two conditions were used. One used HOAc as the solvent while the other used EtOH as the solvent and was heated at reflux for 3 days. Both methods gave the desired compound **100**, but there was always some starting material **99** remaining no matter how long the reaction was run and how many equivalents of cyclohexene were used. The third method involved the mild NH_4Cl/Fe reflux condition. This reaction has been run several times, and the yield was between 70-80%. The drawbacks are the lower yield and the work-up is more complex and time consuming.

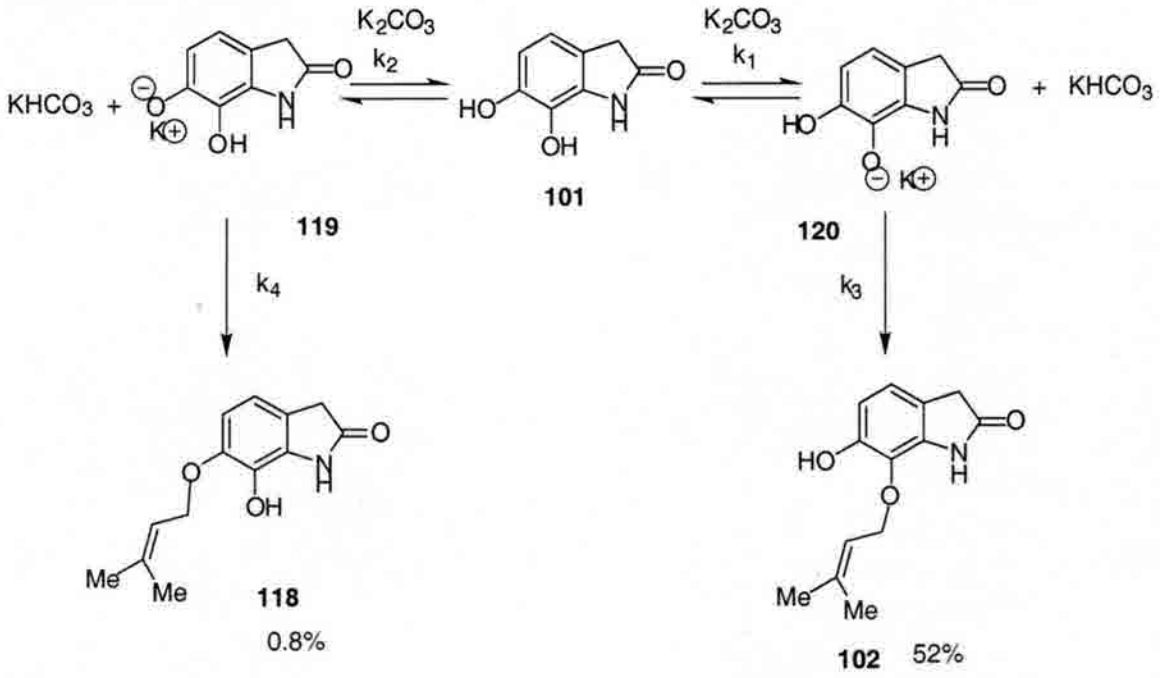
2.15 Investigation of the Selective 7-Hydroxy Prenylation Reaction of 6,7-Dihydroxy Oxindole 101

Scheme 33



The reaction shown in Scheme **33** is the original conditions to synthesize the desired compound **102**. Two by-products **117** and **118** were formed. The drawback for this reaction is that the R_fs of **102**, **117** and **118** are very close, and the separation is very difficult. The reason for the selective prenylation of the 7-hydroxy position is due to the ortho alkylcarbonylamino group which has a net electron-withdrawing effect ($\sigma > 0.14$).[30] This electron-withdrawing effect applies to both hydroxy groups, but the effect at the 7-hydroxy group is greater than at the 6-hydroxy group. Therefore, the acidity of the 7-hydroxy moiety is larger than that of the 6-hydroxy moiety.

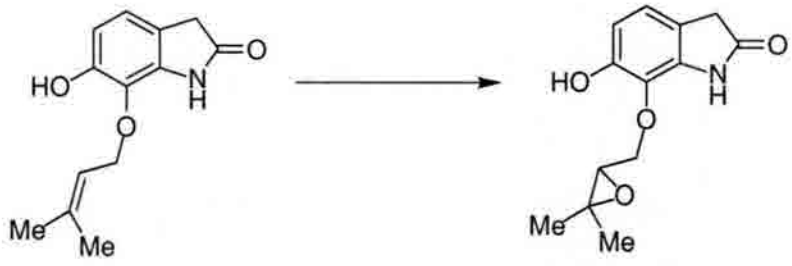
Scheme 34



As diagrammed in Scheme 34, k_1 and k_2, the rate constants for each product-determining steps, are smaller than k_3 and k_4. Compounds **119**, **101**, **120** are in equilibrium with each other. Anion **120** is more stable than anion **119** (acidity difference), therefore $k_1 > k_2$, which in turn determines the ratio of products. In my own investigation of this reaction, employing Na_2CO_3 as the base makes no difference. However, when Cs_2CO_3 is used, both yield and selectivity of **102** are slightly higher. For the separation of compounds **102, 117** and **118**, phenols **102** and **118** have a free phenol group while **117** does not have a free phenol group. Using a basic extraction, the phenoxide salts of **102** and **118** should stay in the aqueous layer. The separated aqueous layer containing **102** and **118** can be acidified to give back **102** and **118** as the free forms. This removal of by-product **117** made the flash column purification much easier, and this proved to be successful. The mixture of **102, 117** and **118** was treated with 1 N NaOH (3 times) and the separated aqueous portion acidified with 0.8 M H_2SO_4 to afford a mixture of only **102** and **118**, which were separated by a short flash column chromatography.

2.16 Epoxidation Investigation of Olefin-Containing Oxindole 102

Scheme 35



102 **103**

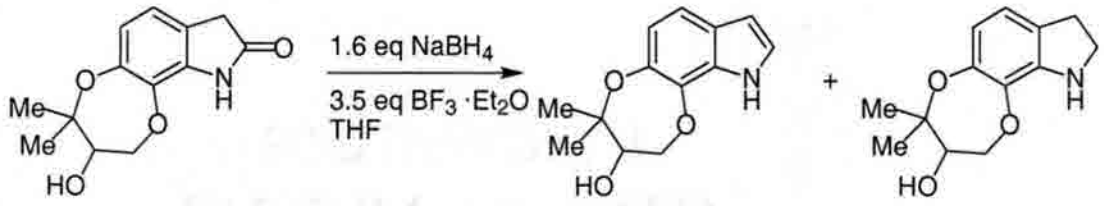
The original epoxidation of olefin **102** with m-CPBA was very fast, but the yield was moderate, usually around 64% yield. An undesired six membered ring by-product formed which resulted from the intramolecular hydroxy attack of the epoxide at the less-substituted carbon. The by-product formation is promoted by factors such as the presence of acid, strong base and water. A summary of the conditions which were examined is collected in Table 3. According to the results in Table 3, entry JC-384 gave the best result. Magnesium sulfate was added to remove any water which promotes the by-product formation.

Table 3

Entry	Solvent	Conditions, 0°C	Results	Yield(%)
JC-379	CH_2Cl_2	once mCPBA(1eq)/$NaHCO_3$(1eq) ,1h twice mCPBA(1eq)/$NaHCO_3$,2h	some byproduct, mainly desired	64
JC-381	CH_2Cl_2/H_2O	once mCPBA(1eq)/$NaHCO_3$(1.5eq) ,1h twice mCPBA(1eq)/$NaHCO_3$(1.5eq) ,>2h	byproduct +SM+product	not calculated
JC-382	CH_2Cl_2/H_2O No $NaHCO_3$	once mCPBA(1eq)/$NaHCO_3$(1eq) ,1h twice mCPBA(1eq)/$NaHCO_3$(1eq) ,>2h	byproduct +SM+product	not calculated
JC-384	CH_2Cl_2 $NaHCO_3$,$MgSO_4$	once mCPBA(1eq)/$NaHCO_3$(1eq) ,1h twice mCPBA(1eq)/$NaHCO_3$(1eq) ,3h		87
JC-386	CH_2Cl_2 $NaHCO_3$,$MgSO_4$	mCPBA(2.5eq)/$NaHCO_3$(5eq) ,35min then,SM, 1h		54.6
JC-387	CH_2Cl_2 $NaHCO_3$,$MgSO_4$	mCPBA(2.5eq)/$NaHCO_3$(5eq) ,35min $MgSO_4$,filtered,then,SM+$NaHCO_3$(1eq)		50

2.17 Investigation of the Reduction of Oxindole 104 to Indole 105 and Indoline 106

Scheme 36



104 **105** **106**

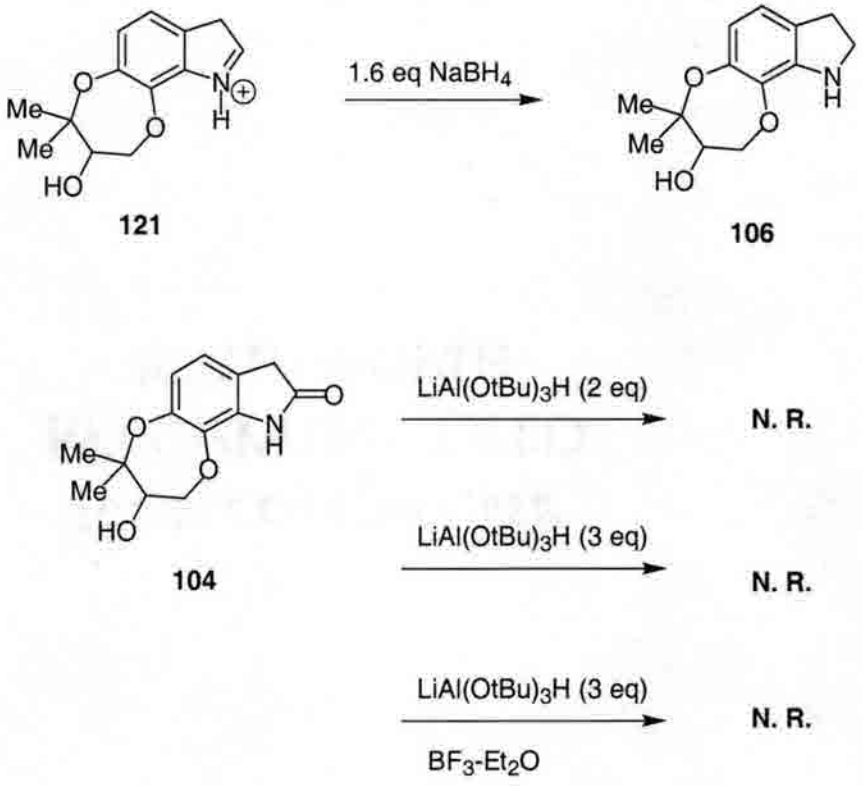
105/106, 4:1 to 2:1

When oxindole **104** is treated with $BF_3{\cdot}Et_2O$ and $NaBH_4$ in THF, there are two products formed. Indole **105** is the desired compound and indoline **106** is the undesired compound (Scheme 36). This reaction developed by Cushing is a very challenging one, considering the very restricted requirement of the reducing agent and the substrate being an N-unsubstituted oxindole. When other reducing agents (1.0 M BH_3 in THF) were used, there was no reaction. Unfortunately, the ratio of **105/106** can vary in different batch reactions from 4:1 to 2:1. Since this reaction is the 12th step of a 14 step synthesis, the loss of compound **106** as a by-product is a very big problem. Indoline **106** is presumably formed from the reduction of iminium **121** with excess $NaBH_4$ (Scheme 37).

Therefore, we believed that minimizing the amount of reducing agent would be helpful for maximizing the formation of the desired indole **105**. $LiAl(OtBu)_3H$ has been examined as the reducing agent since each molecule of $LiAl(OtBu)_3H$ can only contribute one hydride as the reducing agent. Unfortunately, there was no reaction occurring for different equivalents of $LiAl(OtBu)_3H$ alone or in combination with $BF_3{\cdot}Et_2O$. For the $BF_3{\cdot}Et_2O/NaBH_4$ reducing condition, the real mechanism of this reaction is still not clear. One possibility is that the actual reducing agent is BH_3, which can be formed in situ from the reduction of $BF_3{\cdot}Et_2O$ with $NaBH_4$. Another possibility is that the Lewis acid properties of $BF_3{\cdot}Et_2O$ activate the oxindole to reduction and $NaBH_4$ or a similar species

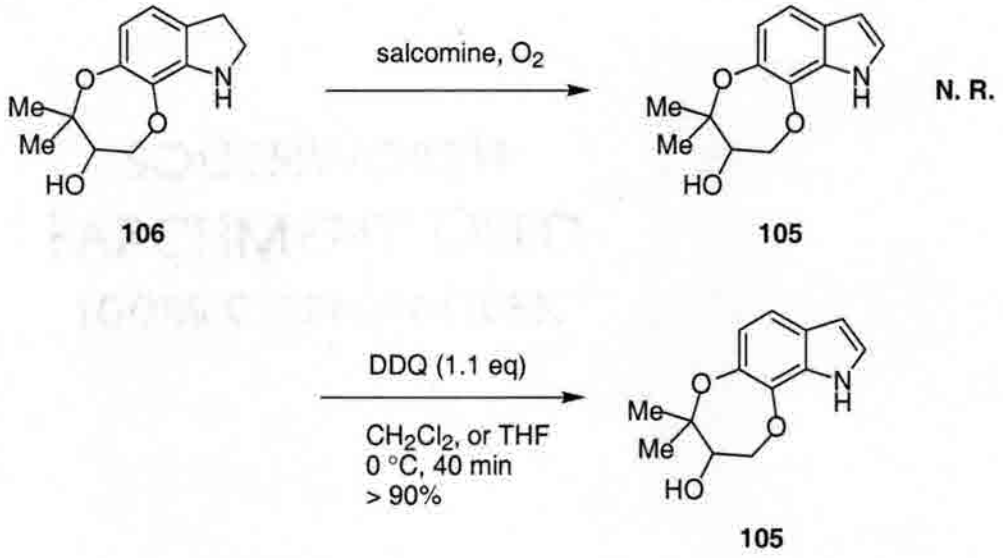
actually does the reduction. During the $LiAl(OtBu)_3H$ experiment, the oxindole amide hydrogen may react with the hydride of $LiAl(OtBu)_3H$, giving off H_2 to yield an amide anion-aluminum salt, which is inert to further reduction.

Scheme 37



The question remains, can we find a way to convert **106** to **105** and solve this problem in an indirect manner? Tim Cushing treated **106** with salcomine, bubbling O_2 through the reaction solution, but unfortunately, no reaction occurred. There are some reports in the literature[31] mentioning that DDQ can oxidize an indoline to an indole but no reaction conditions are reported. When a solution of **106** in CH_2Cl_2 was treated with solid DDQ, the color of the solution changed instantly. After 10-15 min, all the starting material **106** was converted into the desired compound **105**. On a small scale, when CH_2Cl_2 was used as a solvent, the yield was quantitative. On a large scale, THF is the best solvent, and the reaction usually gives greater than 90% yield (Scheme 38).

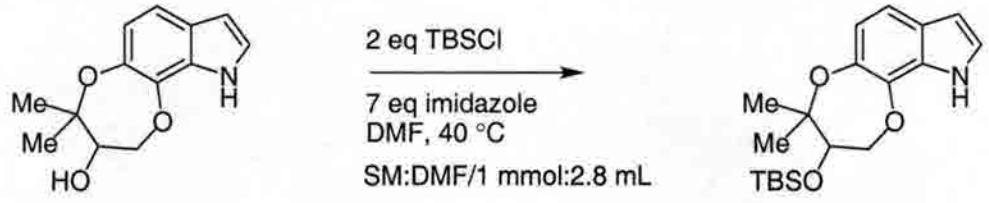
Scheme 38



106 **105** **105**

2.18 Optimization Investigation of the t-Butyldimethylsilylation Reaction of Hydroxyindole 105

Scheme 39

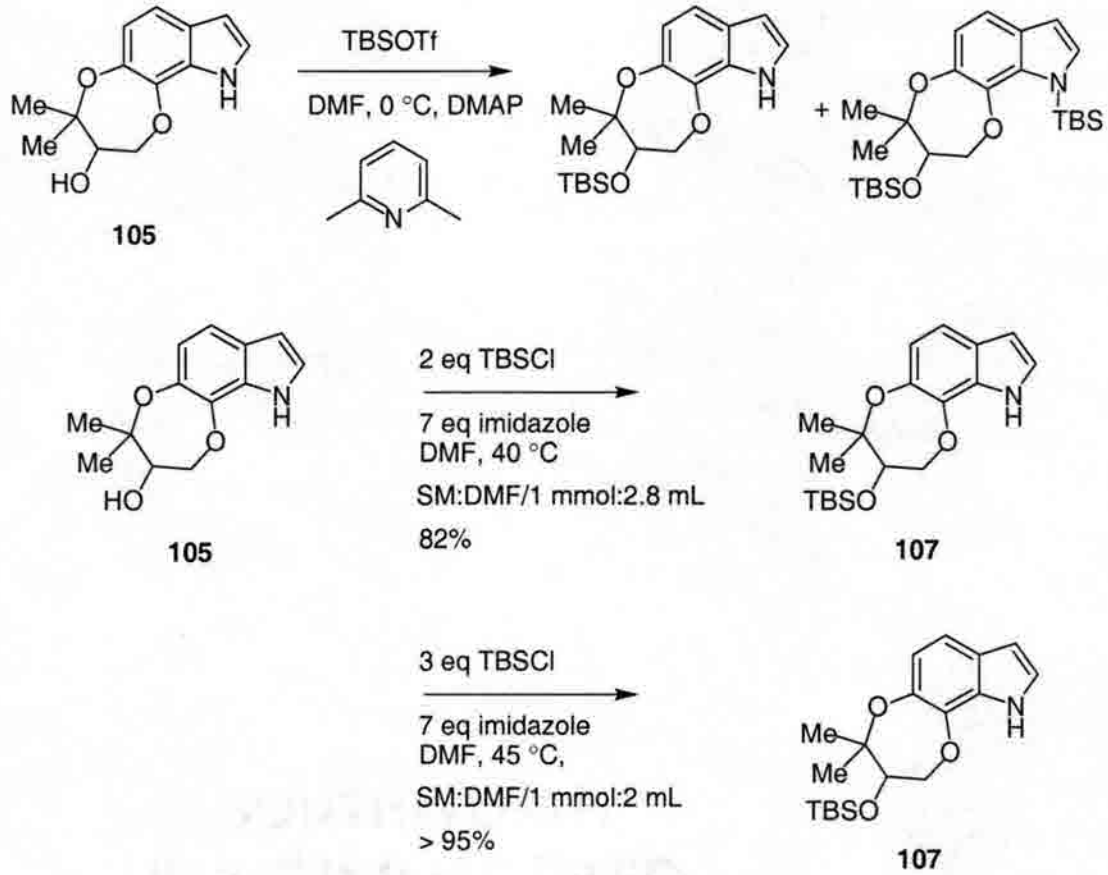


105 **107**

Tim Cushing found that when **105** was treated with TBSCl and imidazole in DMF at 23 °C, the reaction was very slow, because the secondary hydroxy group of **105** is adjacent to a gemdimethyl substituted carbon. When the mixture was warmed to 40 °C and TBSCl (2 eq) and imidazole (7 eq) were used, the yield was 82%. Initially, when I repeated this reaction on a small scale, there was always starting material remaining and the reaction was very slow. The yield is about 40%. TBSOTf is a more reactive silylating

reagent and reacts with indole **105** to give very little desired product. TLC shows many products including the N,O-double silylation product. (Scheme 40).

Scheme 40



It has been shown that TBS ether formation of hindered alcohols is very sensitive to the concentration of the reactants. Therefore, if we increase the equivalents of TBSCl and decrease the amount of DMF used, the yield will be higher. The optimized conditions found are: TBSCl (3 eq), imdazole (7 eq) and at 45 °C with SM:DMF/1 mmol:2 mL. The latter provides product **107** with greater than 95% yield.

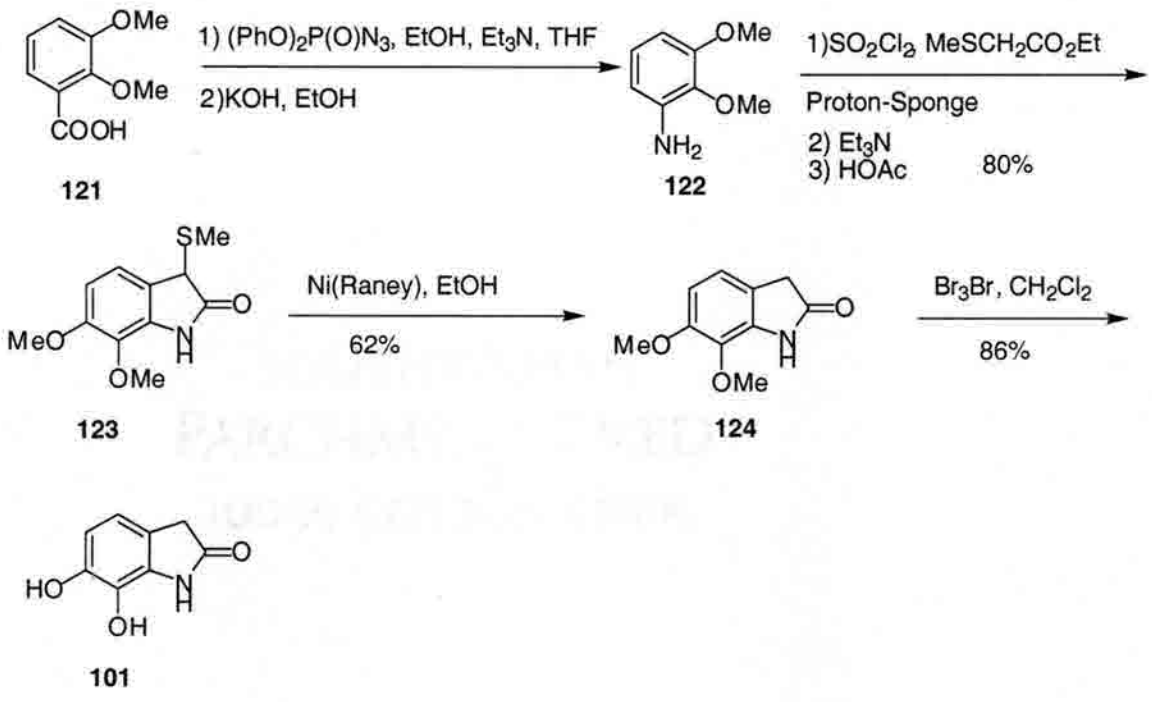
2.19 McWhorter's Route to 6,7-Dihydroxyindole 101

In 1996 McWhorter and Savall[32] reported a short and efficient synthesis of 6,7-Dihydroxyindole (**101**) (Scheme 41) which was the intermediate for the synthesis of dioxepin-indole sub-unit (**60**) (Scheme 25). They used the methodology of Gassman and co-workers to form **101** in four steps with an overall yield of 35% from a commercially available starting material 2,3-dimethoxybenzoic acid (**121**).

2,3-Dimethoxybenzoic acid (**121**) was converted to 2,3-dimethoxyaniline by the Yamada modification of the Curtius rearrangement followed by hydrolysis of the resulting urethane (Scheme 41). 2,3-Dimethoxyaniline (**122**) was converted to 3-(methylthio)-6,7-dimethoxyoxindole (**123**) by means of a modified Gassman oxindole synthesis. Ethyl methylthioacetate was chlorinated with sulfuryl chloride and reacted with 2,3-dimethoxyaniline (**122**) in the presence of 1,8-bis(dimethylamino)naphthylene to produce an azasulfonium salt, which was in turn treated with triethylamine to bring about the rearrrangement of the azasulfonium ylide to afford the ethyl ester of 2-amino-3,4-dimethoxy-a-(methylthio)benzeneacetic acid. This acic was treated with acetic acid to yield oxindole (**123**) in 80% overall yield. This oxindole (**123**) was desulfurized with Raney nickel to give 6,7-dimethoxyoxindole (**124**) in 62% yield. 6,7-Dimethoxyoxindole (**124**) was demethylated with BBr_3 in CH_2Cl_2 to produce of 6,7-Dihydroxyindole (**101**) in 86% yield.

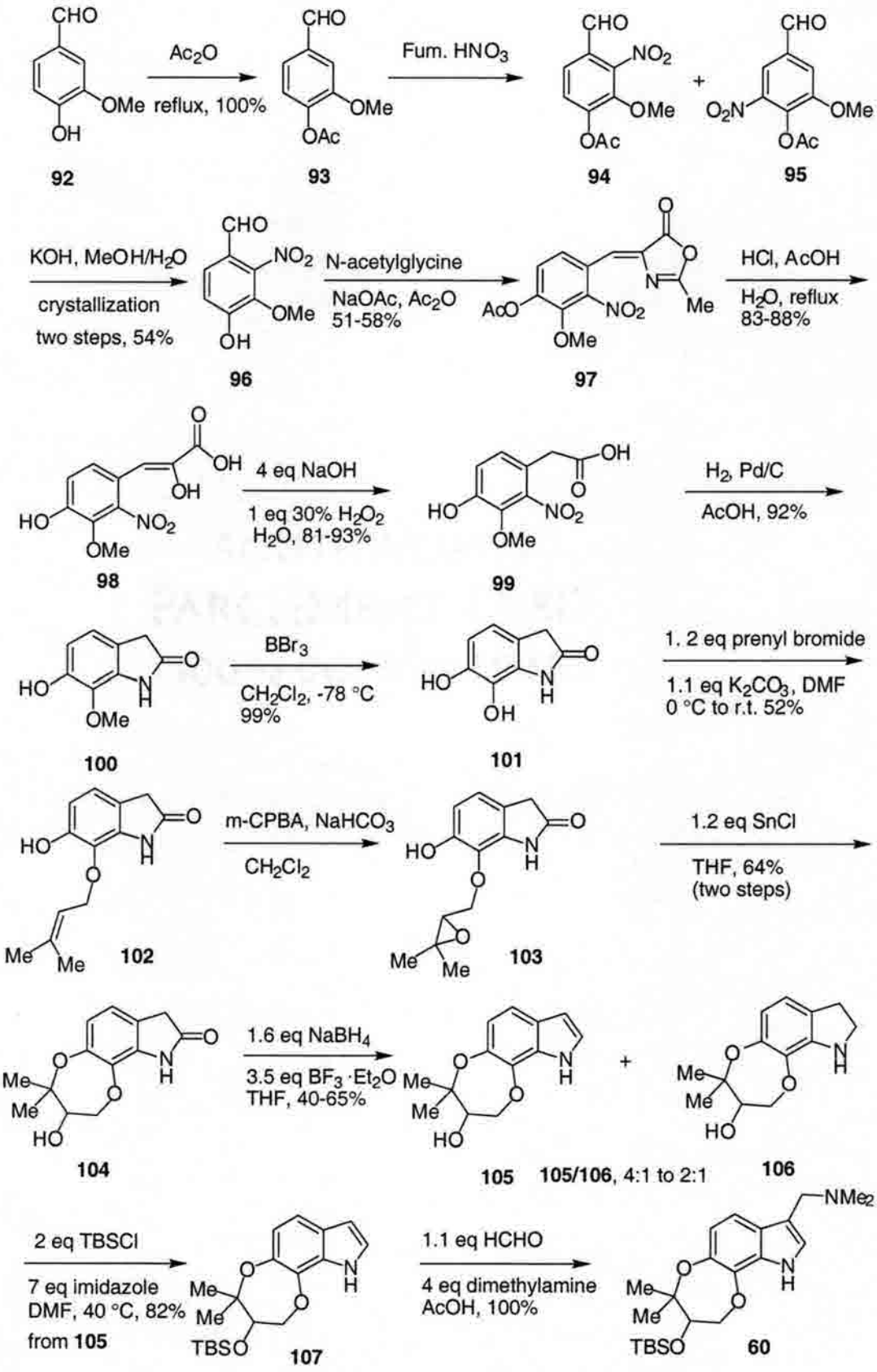
The McWhorter's route is short and give overall high yield. This approach may be the optimal method for the synthesis of dihydroxyindole (**101**). However, the experimental part of this work only demonstrated relatively small scale synthesis. In Cushing's route to oxyindole **101**, each step except the hydrogenation one can be carried out on about hundred gram-scale without chromatography purification and provides ~40 grams of 6,7-dihydroxyindole (**101**) in a single run. According to our experience, if we need to make 30-40 grams of compound **60**, about 200 grams of 6,7-dihydroxyindole (**101**) is required.

Scheme 41

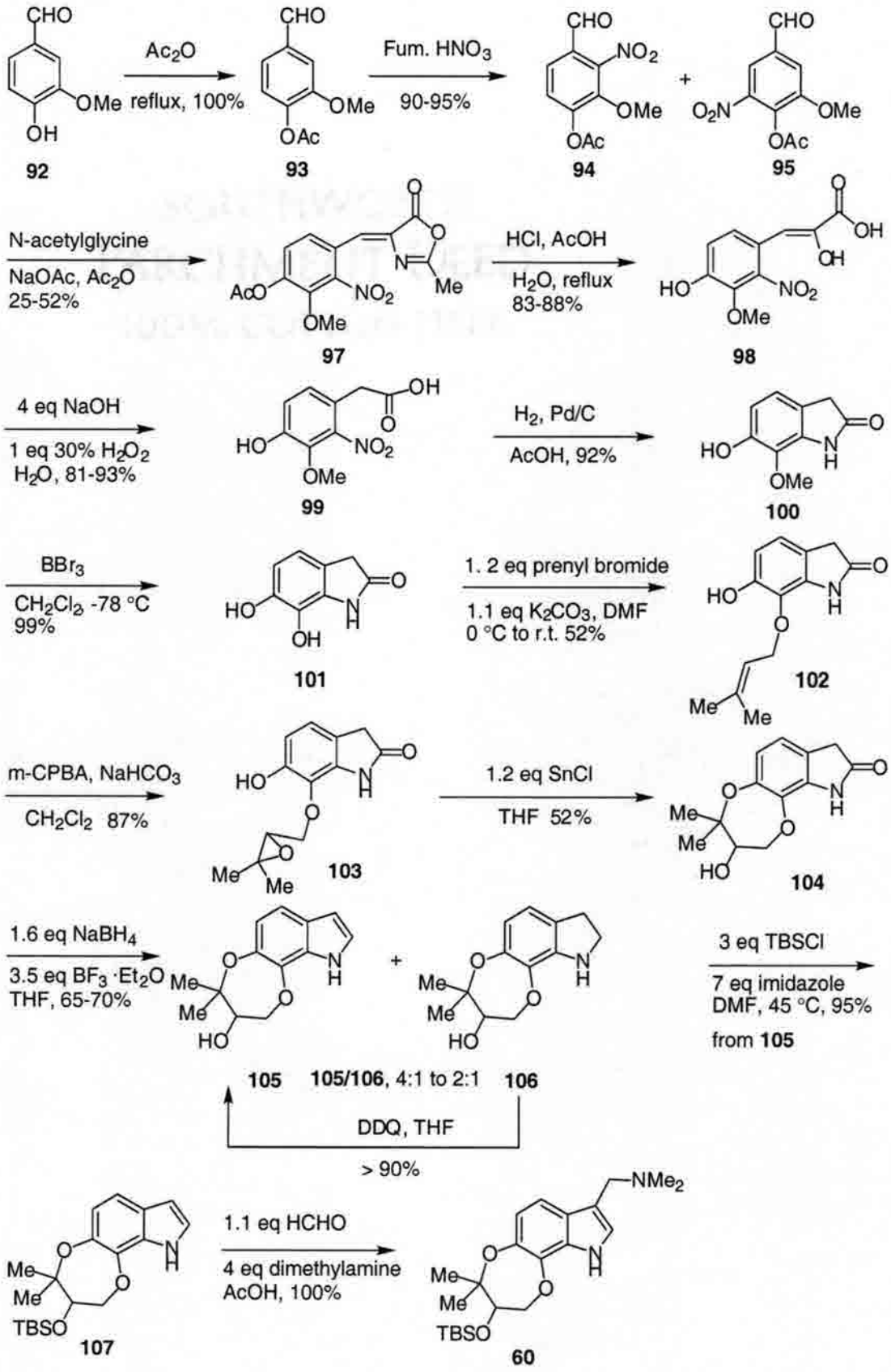


121 **122** **123** **124** **101**

Scheme 42 Cushing's Synthetic Route to Dioxepin-indole 60



Scheme 43 The Improved Synthesis of Dioxepin-indole Subunit 60

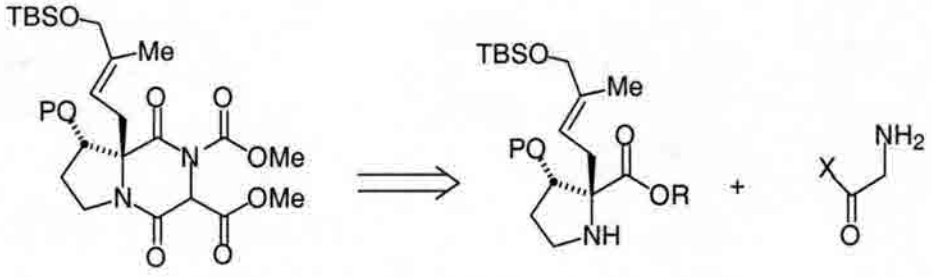


2.2 The Synthesis of Diketopiperazine Subunit

According to the retrosynthetic plan for (-)-paraherquamide A illustrated in Scheme21, the coupling between diketopiperazine (DKP) subunit **71** and the dioxepin-indole subunit **60** can lead to the synthesis of compound **70**. Here we will discuss the synthesis of DKP **71**.

2.21 Retrosynthetic Analysis of the Proline Derivative 125

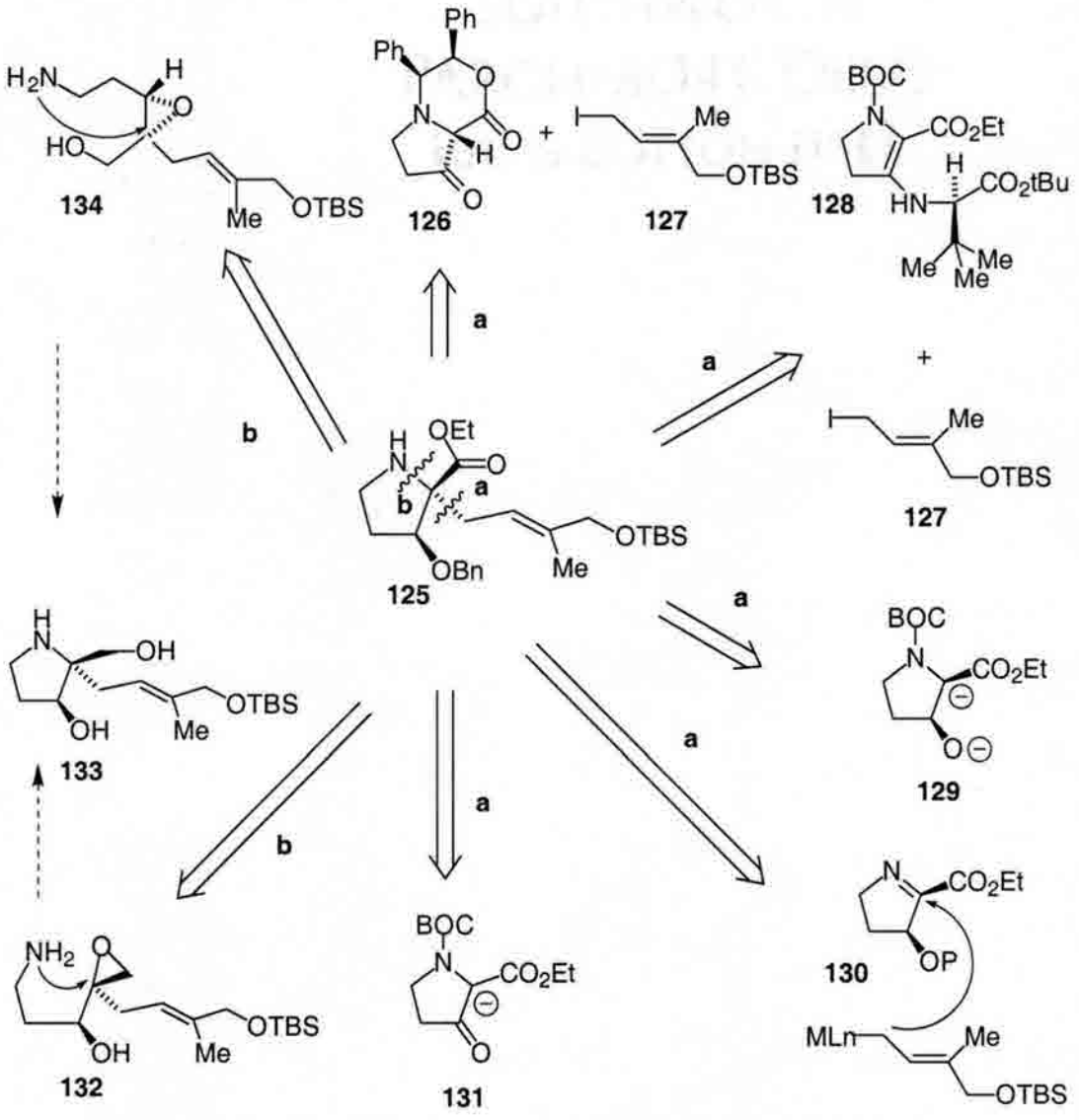
DKP **71** and its analogs can be synthesized from proline derivative **125** (a representative of compound **73**, P = Bn) and glycine derivative **74**. The benzyl ether group at the β-position of the proline ring in compound **125** was our first generation protecting group. The synthetic route using intermediate **125** with the benzyl ether protecting group did not lead to the successful synthesis of (-)-paraherquamide A. The successful route used a MOM ether as the protecting group. In order to present the research results in a logical way, we chose compound **125** as the example in our retrosynthetic analysis (Scheme 44).



71 **73** **74**

Basically, there are two different places where we can disconnect the bonds in compound **125** from a retrosynthetic point of view. One position is bond **a**, and the other is bond **b**. Each of them can lead to either racemic or asymmetric syntheses of the proline subunit **125**. The details of our investigation of the synthetic approaches to **125** depicted in Scheme 44 will be discussed in the following sections.

Scheme 44

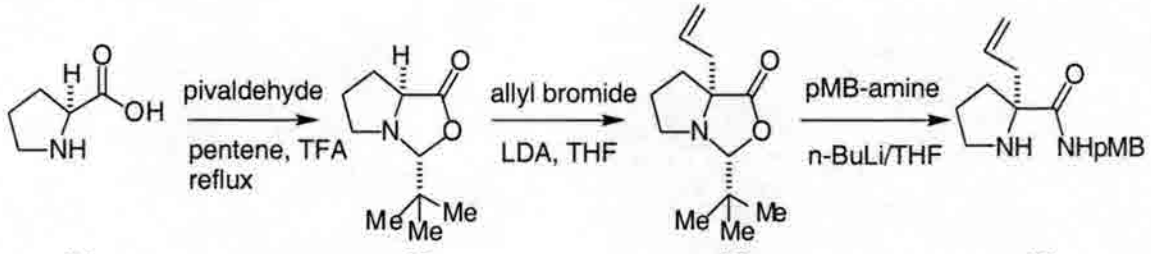


2.22 Known Synthetic Methods Related to Proline Subunit 125

In 1983, Seebach and coworkers[26] developed a method to make optically active α-substituted proline derivatives (Scheme 45). The enolate formed from aminal **45** reacted with a variety of alkylating reagents to produce the α-substituted aminal **46** and its analogs. These products can only be hydrolytically cleaved with 15%-48% HBr at refluxing temperature to give the α-substituted proline derivative. Compound **46** and its analogs react with lithium amide to give the α-substituted amide **47** and its analogs. They also

found that the enolate formed from **45** only reacted with activated alkylating reagents. Comparing the α-substituted proline derivatives made by Seebach's method with the required compound **125**, which has the β-benzyl ether group, the acid-labile TBS ether group and double bond, obviously this method can not be used to synthesize this intermediate of (-)-paraherquamide A.

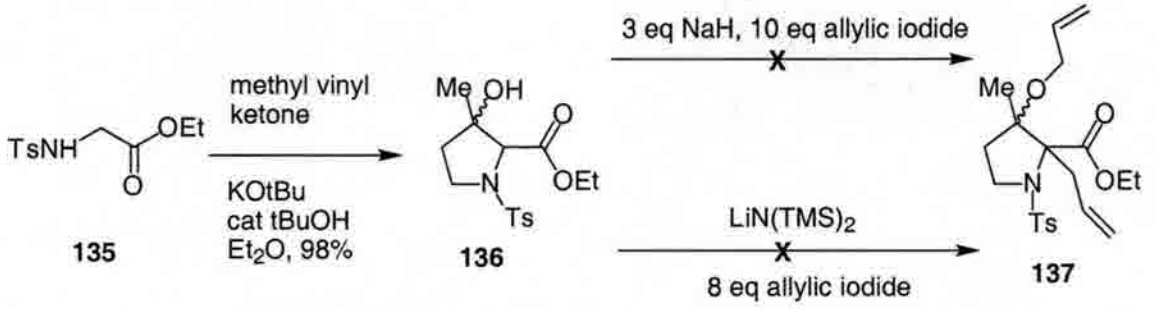
Scheme 45



44 **45** **46** **47**

The initial Ph.D. project of Cushing[33] in the Williams group was to synthesize (-)-paraherquamide A. He investigated the racemic synthesis of analogs of **125**, and the results are outlined below (Scheme 46). A mixture of diastereomers **136**, synthesized from the Michael addition of **135** to methyl vinyl ketone, was treated with different bases and an excess of allyl iodide. Cushing hoped to alkylate both the α-C position and the tertiary alcohol at the same time, since an allyl ether protecting group can be easily removed. In spite of his efforts, this approach was unsuccessful due to there being no α-alkylation. Apparently, the proline derivative **136** is sterically too congested for the reaction to take place.

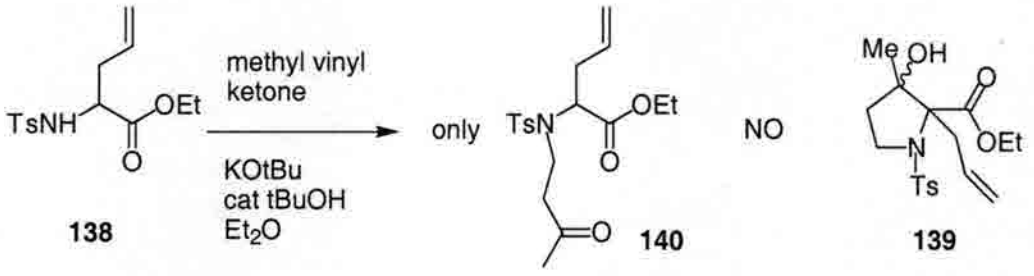
Scheme 46



135 **136** **137**

To avoid this problem, he thought it might be easier to incorporate the allyl group prior to the cyclization. Compound **138** was made from 2-amino-4-pentenoic acid in two steps in 66% yield and was subjected to the same cyclization conditions as ester **135**, however none of the desired compound **139** was found. The only material isolated was the N-alkylated derivative **140** (Scheme 47).

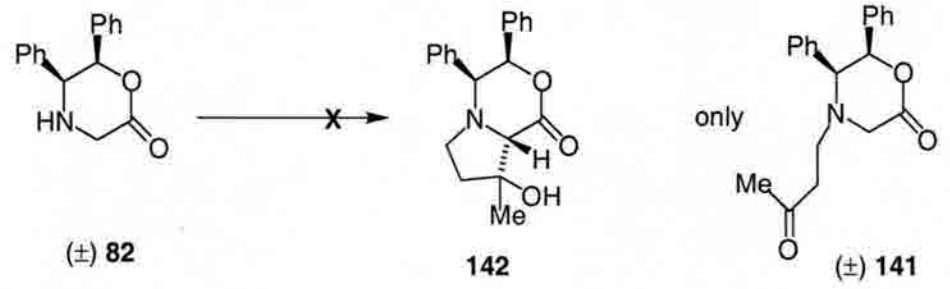
Scheme 47



138 **140** **139**

The attempted alkylation of racemic oxazolone **82** with methyl vinyl ketone gave ketone **141**, and none of the cyclization product **142** was formed (Scheme 48).

Scheme 48



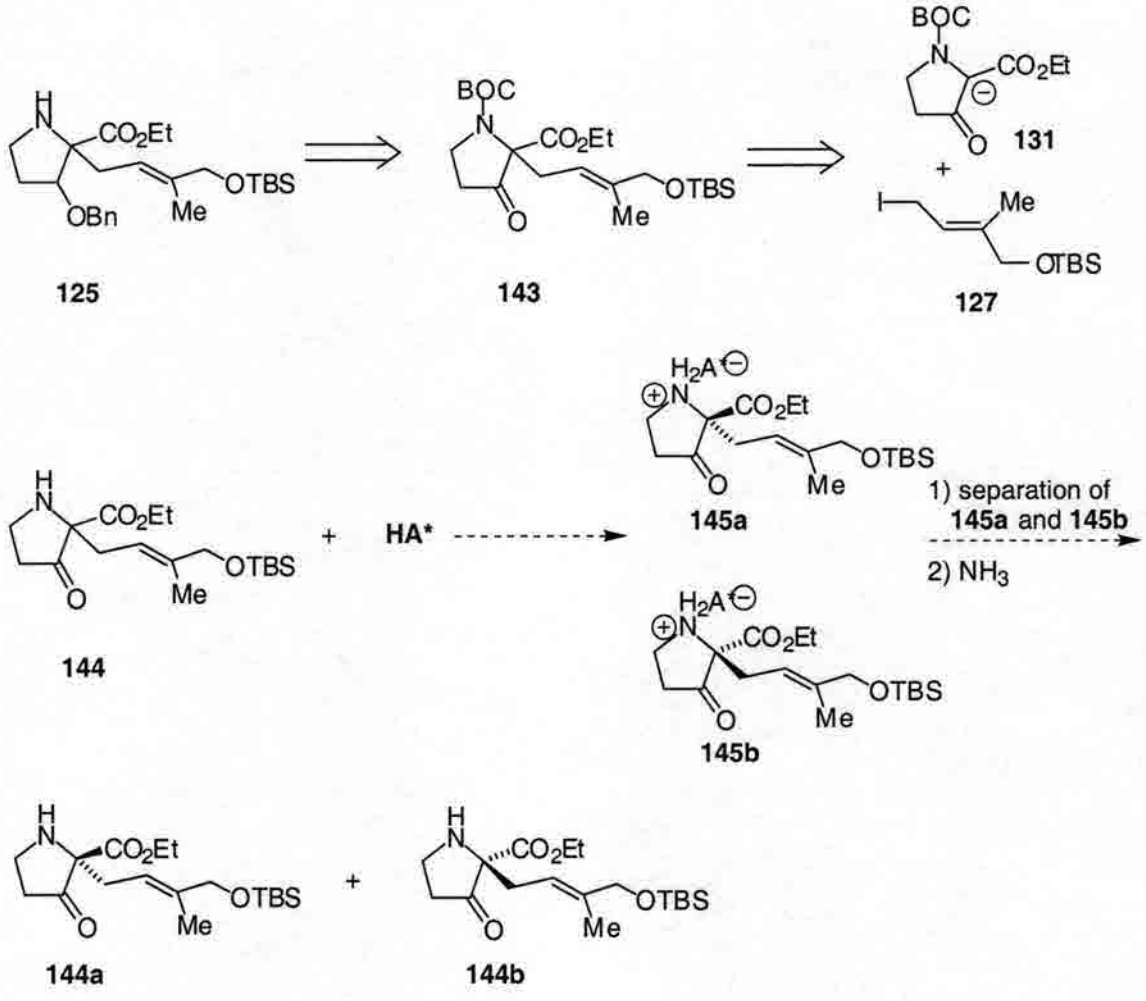
(±) **82** **142** (±) **141**

2.23 Racemic Synthesis of Proline Subunit 125

Our goal was the stereocontrolled asymmetric synthesis of (-)-paraherquamide A. Two methods relating to the synthesis of proline subunit **125** are reviewed in section 2.22. Although these methods can provide us with important information, none of them can be used for the synthesis of compound **125**. Basically, there is no known synthetic method available for the construction of this type of compound. Generally, developing a racemic synthetic method should be easier than developing an asymmetric one. According to this idea, we decided to carry out a racemic synthesis of **125** and then use **125** as an

intermediate to further make DKP **71** (P = Bn). This racemic approach can give us very useful information and guidelines for the asymmetric synthesis of compound **125**. The retrosynthetic analysis of racemic proline subunit **125** is shown in Scheme 49.

Scheme 49.

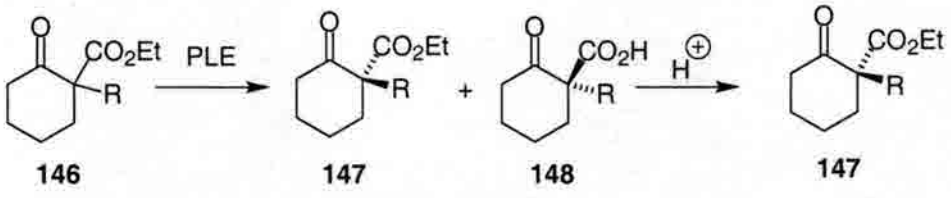


Compound **125** can be obtained from ketone **143** through the reduction of the ketone to the corresponding alcohol, protection of the alcohol as the benzyl ether followed by deprotection of the N-t-BOC group. If the enolate, formed from β-ketoester **131**, undergoes alkylation with iodide **127**, it will provide the α-substituted β-ketoester **143**. Theoretically, this racemic approach can also be used to make the optically active proline derivatives **144a** and **144b**. β-Ketoester **144** can be treated with a chiral organic acid

HA* to provide a mixture of diastereomeric salts of **145a** and **145b**. Separation of **145a** and **145b** and subsequent neutralization with ammonia will provide the optically active compounds **144a** and **144b**.

Westermann and coworkers[34] reported a method which used pig liver esterase (PLE) to affect a kinetic resolution of α-alkyl-β-ketoester **146** (Scheme 50). In a pH 8 phosphate buffer media and at 20 °C, PLE hydrolyzed one of the enantiomers of compound **146** much faster than the other one. After a certain period of time (depending on different substrates, the required time is different), the reaction was quenched and work-up provided the optically active α-alkyl-β-ketoester **147**. Theoretically, the α-alkyl-β-ketoester **143** or **144** can also be used to undergo a PLE-catalyzed kinetic resolution to provide the required optically active α-alkyl-β-ketoester, which can then be utilized for the synthesis of (-)-paraherquamide A.

Scheme 50



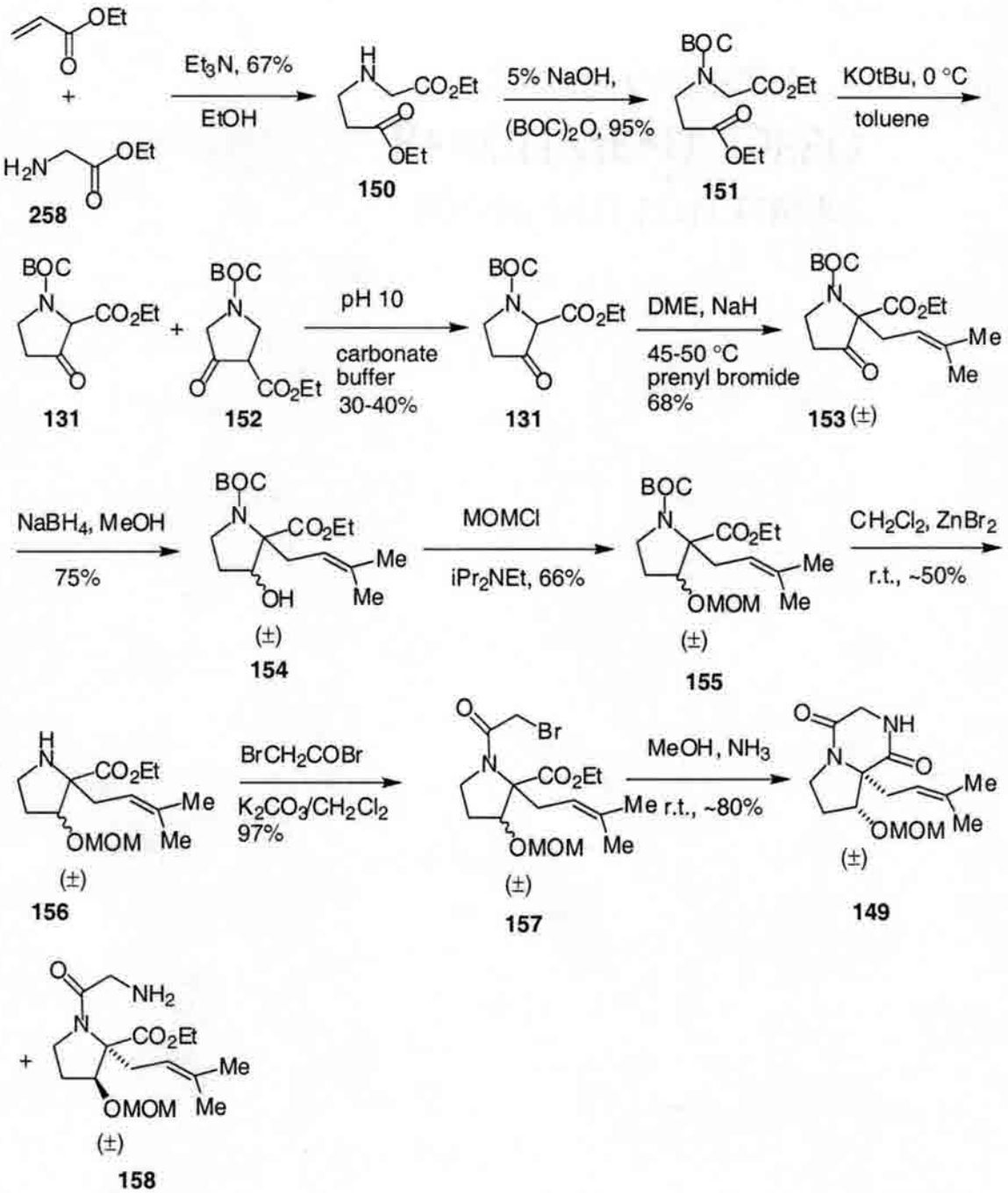
146 **147** **148** **147**

Condition: pH 8, phosphate buffer, 20 °C

R	ee%
CH_3	99
C_3H_7	70
C_4H_9	99
$PhCH_2$	no reaction after 48 h

At the initial stage of the racemic synthesis, optimization of the synthesis of allyl iodide derivative **127** was not our top priority. Our focus is to quickly find a route for the synthesis of proline derivative **125** and its analogs and further convert them into the corresponding diketopiperazines (DKP). Prenyl bromide is a commercially available reagent and structurally similar to allylic iodide derivative **127**. Therefore, prenyl bromide

Scheme 51

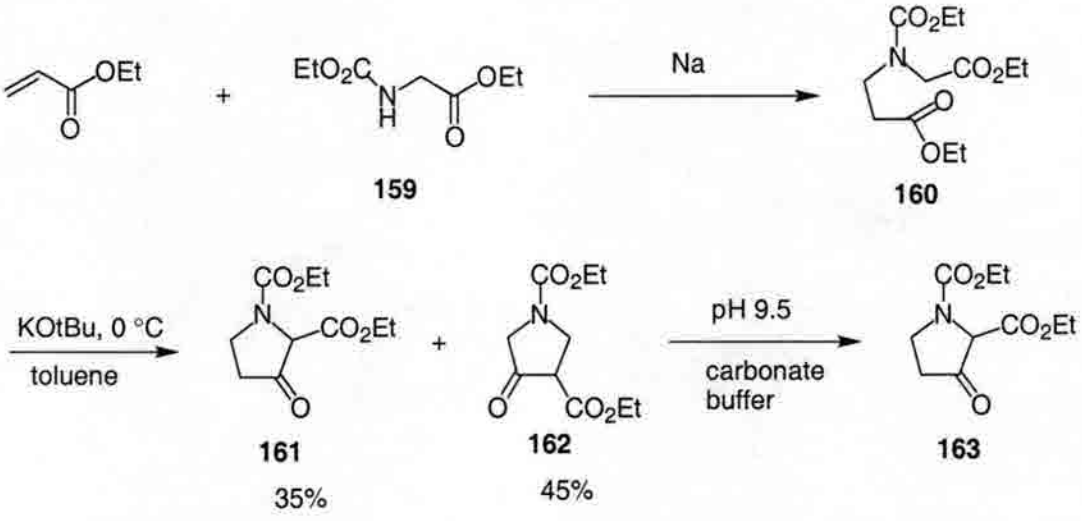


was used as the alkylation reagent for β-ketoester **131**. A model synthetic study for α-prenyl-β-methoxylmethyl ether diketopiperazine **149** is depicted in Scheme 51.

At the time when compound **131** was our target, there was no known method for its preparation of **131**. Rapport et al.[35] in 1964 reported a similar synthesis of compound

163 (Scheme 52). Compound **160** has an ethyl carbamate protecting group at the nitrogen. When **160** was treated with KOtBu in toluene at 0 °C, two regioisomers **161**

Scheme 52



and **162** were formed. The synthesis of **163** used a more complex route than the one shown in Scheme 51 for our synthesis of **131**. We proposed a Michael addition and N-t-BOC protection approach. In order to successfully synthesize (-)-paraherquamide A, these two steps should be feasible in terms of yield, scale and require no flash column chromatography. Michael addition of ethyl glycinate to ethyl acrylate in the presence of EtOH and Et_3N provided **150** in 67% yield, and this was the best condition among eight different conditions examined. Compound **150** can be made on a several hundred gram-scale using vacuum distillation as the purification process. t-BOC protection of **150** gave **151** in 95% yield which again was purified by vacuum distillation. Dieckman condensation of **151** by treatment with KOt-Bu in toluene at 0 °C (a slightly modified condition of Rapport) provided the desired isomer **131** and the by-product **152**, which were separated by extracting **152** with pH 10 sodium carbonate buffer. The principle of this separation is as follows: because of the steric interaction between N-t-BOC group at the N-1 position and the ethoxycarbonyl group at the C-2 position of compound **131**, it is not easy to form an enolate for **131** under pH 10 condition, and therefore it can not be extracted by the sodium carbonate buffer. For compound **152**, there is no 1,2-interaction as in compound

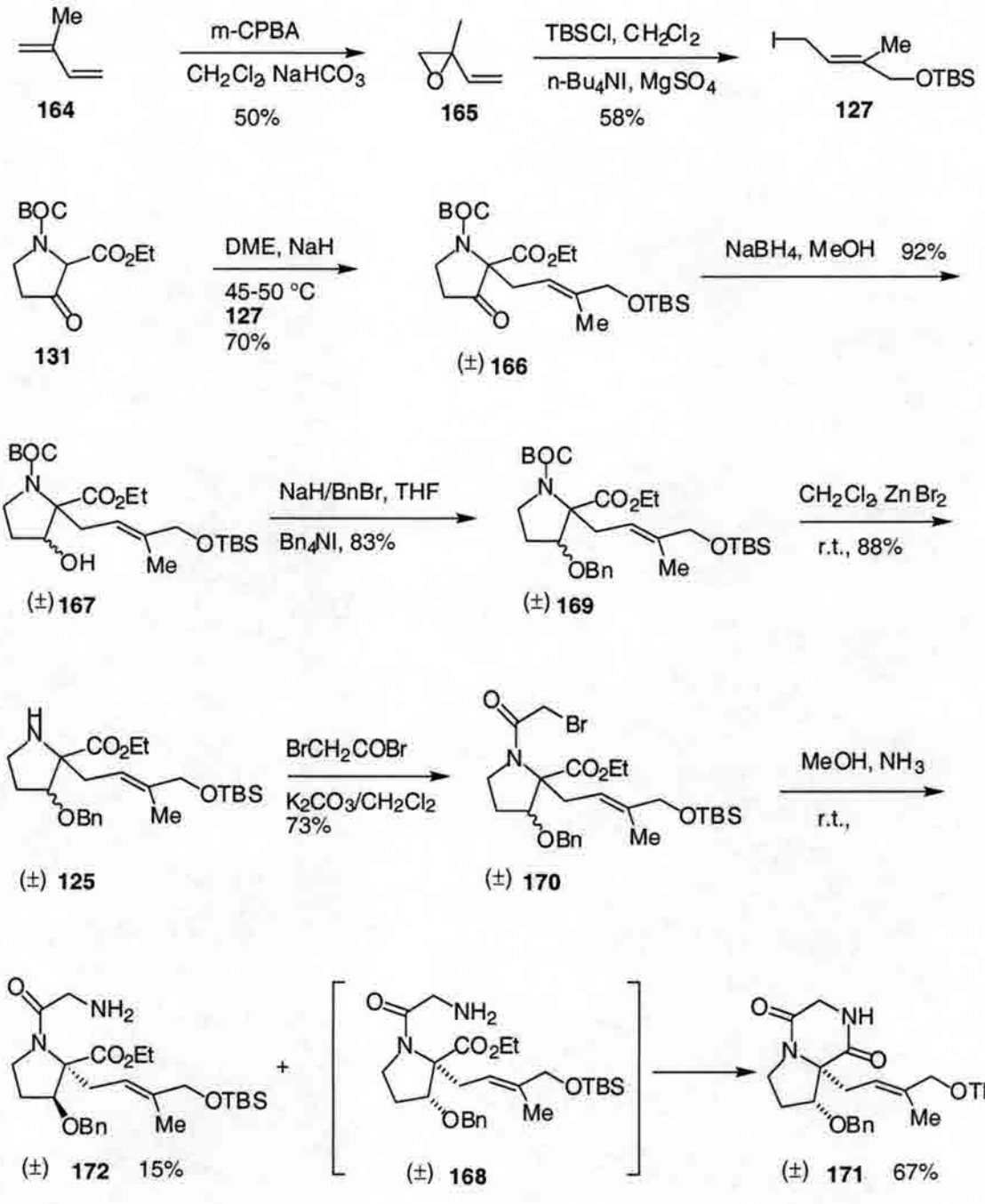
131, and the β-ketoester moiety can be easily deprotonated and reacted with pH 10 carbonate buffer to form an enolate which is water soluble. A lot of effort was invested to run this reaction successfully on a large scale in a practical manner. The purified intermediate **131** (distilled) still contained some starting material **151** and was used as a mixture in the following alkylation step as well as in the Baker's yeast reduction procedure which will be discussed at a later stage. Six different conditions were examined for the alkylation, and the reaction conditions (NaH/DME, 45–50 °C) was the best one to provide **153**. Several conditions were examined for the deprotection of the N-t-BOC group in **153**, including TFA/CH_2Cl_2 (at 0 °C or room temperature), 3.28 N HCl/EtOAc (at 0 °C or room temperature) and $ZnBr_2/CH_2Cl_2$, but only TFA/CH_2Cl_2 conditions provided the desired compound in about 10% yield. We decided to reduce the ketone moiety and protect the formed alcohol before deprotecting the N-t-BOC group, in hopes of solving this problem. Ketone ester **153** was treated with $NaBH_4$ in MeOH to provide **154** as a diastereomeric mixture, which was reacted with MOMCl to afford methoxymethyl ether **155** in 66% yield. There are three reasons that we chose the methoxymethyl ether as our protecting group. First, it can withstand many different reaction conditions required during the synthesis of (-)-paraherquamide A (the benzyl ether protecting group may be even better than the methoxymethyl ether in terms of stability). Second, the methoxymethyl ether can be introduced easily, and third, it can be deprotected under mild conditions. The protocol ($ZnBr_2/CH_2Cl_2$) developed by Nigam et al.[36] can be used to selectively deprotect a secondary amine t-BOC group in the presence of a primary amine t-BOC group in a mild and almost neutral manner. When **155** was treated with $ZnBr_2/CH_2Cl_2$ at room temperature, the desired amine **156** was obtained in 50% yield. At the later stage of this project when the optimal work-up procedure was used, usually greater than 95% yield can be obtained for other similar substrates. Compound **156** was then treated with bromoacetyl bromide to give **157** in 97% yield under Schotten-Baumann condition. Displacement of the bromine with ammonia in methanol solution followed by in-situ cyclization of the amino-

ester intermediate provided racemic *trans*-DKP**149**. The *cis*-(ester group and MOM ether group are in a *cis*-relationship) compound **158** could not cyclize to give the corresponding DKP compound. A possible explanation will be discussed later.

After the successful synthesis of DKP **149**, the real synthetic target **171** was made following a similar route (Scheme 53). Epoxide **165**, commercially available or made from the epoxidation of isoprene by m-CPBA, was treated with n-Bu_4NI and TBSCl to provide iodide **127** as a ~5/1 mixture of E/Z isomers in 58% yield. Alkylation of **131** by treatment with NaH and iodide **127** afforded **166**, which was then reduced to the alcohol with $NaBH_4$ followed by benzyl ether formation to give intermediate **169** as a diastereomeric mixture. Bromide **170** was obtained from **169** through a two-step process involving the deprotection of the N-t-BOC group by $ZnBr_2$ (in CH_2Cl_2) followed by bromoacetate formation. Aminolysis of the bromide **170** with a solution of NH_3 in MeOH gave the *trans* -isomer DKP **171** and the *cis*-isomer aminoester compound **172**. DKP **171** was produced from the cyclization of the in situ formed *trans* amino ester compound. However, the cyclization of aminoester **172** to the corresponding DKP requires much stronger conditions, and therefore **172** was obtained as an aminoester.

The synthetic approach to racemic DKP **171** was completed in 12 steps. The majority of the transformations proceed in very good yield and under mild classical conditions. We not only learned that racemic **125** can be made from the alkylation approach of proline β-ketoester **131**, but also that this alkylated compound can be transformed into DKP **171**, a proposed key intermediate for the synthesis of paraherquamide A.

Scheme 53

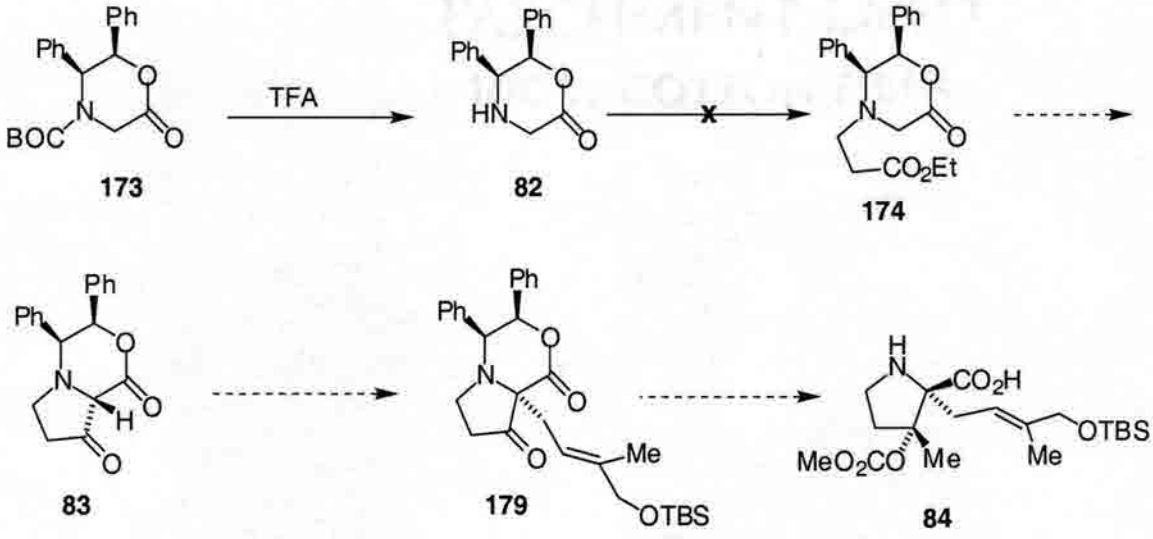

Me
164
m-CPBA
CH_2Cl_2 $NaHCO_3$
50%
165
TBSCl, CH_2Cl_2
n-Bu_4NI, $MgSO_4$
58%
Me
OTBS
127
BOC
CO_2Et
131
DME, NaH
45-50 °C
127
70%
(±) 166
$NaBH_4$, MeOH 92%
OH
(±) 167
NaH/BnBr, THF
Bn_4NI, 83%
OBn
(±) 169
CH_2Cl_2, $ZnBr_2$
r.t., 88%
(±) 125
$BrCH_2COBr$
K_2CO_3/CH_2Cl_2
73%
Br
(±) 170
MeOH, NH_3
r.t.,
NH_2
(±) 172 15%
(±) 168
NH
(±) 171 67%

2.24 Asymmetric Synthesis of Proline Subunit 125

2.24.1 Lactone Alkylation Approach

We first investigated the lactone (**83**) alkylation approach illustrated in Scheme 54.

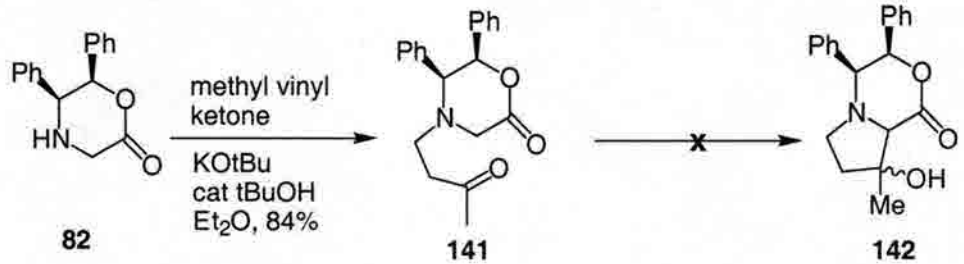
Scheme 54



173 **82** **174** **83** **179** **84**

Williams lactone **173**, discovered in the Williams group for the synthesis of α-amino acids, was treated with TFA to provide amine **82**. Theoretically, Michael addition of **82** to methyl acrylate or reaction with β-halogen propionate should provide **174**. We examined a variety of Michael acceptors, various bases, different temperatures, and solvents, but none of these reactions gave the desired compound. It is presumably the sterically hindered environment which renders this secondary amine less nucleophilic. The only successful Michael addition reaction is shown in Scheme 55. Compound **141** was formed by the reaction of **82** with methyl vinyl ketone, but the subsequent aldol reaction to form **142** did not occur.

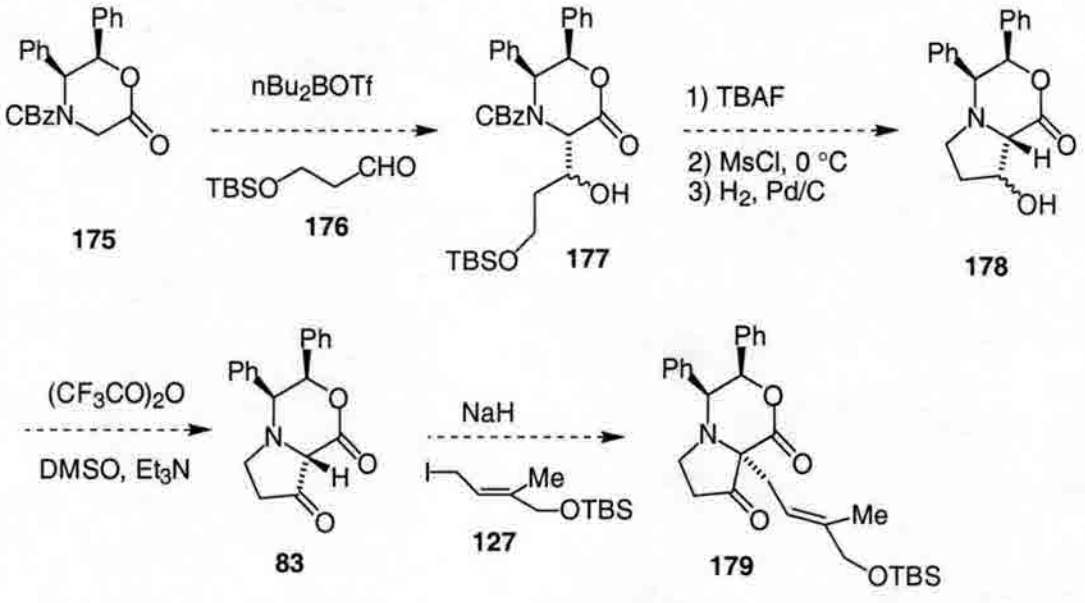
Scheme 55



82 **141** **142**

An alternative synthetic plan is depicted in Scheme 56. but did not have time to investigate this approach. Addition of the boron enolate formed from CBz-lactone **175** to aldehyde **176** can provide alcohol **177**. This type of reaction is presented in a paper published by Miller et al.[37] Alcohol **177** is then treated with TBAF to provide a diol which can be selectively mesylated at the primary alcohol. Deprotection of the N-CBz group and in situ cylization of the amino mesylate intermediate will afford alcohol **178**. Oxidation of **178** should provide compound **83**, and a similar reaction was done by myself for a different substrate in good yield. Finally, the α-alkylation of **83** with iodide **127** is expected to give the desired compound **179**.

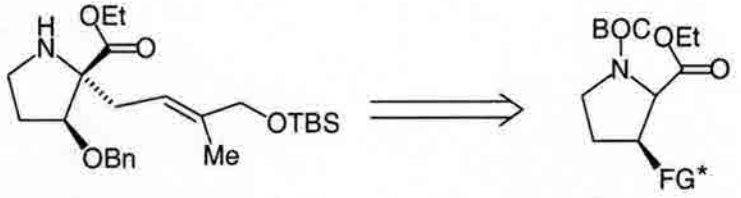
Scheme 56



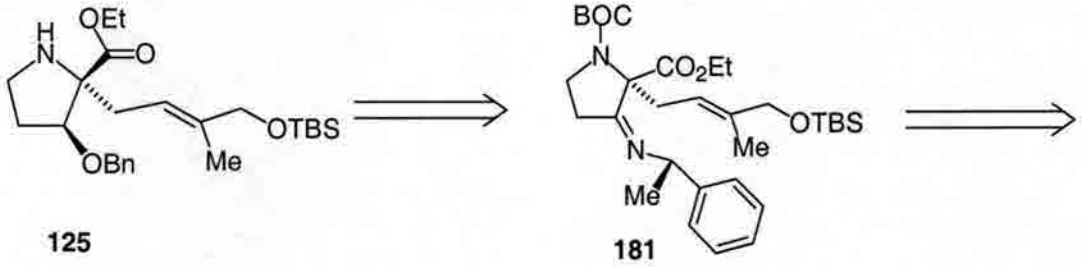
2.24.2 Asymmetric α-Alkylation of Proline β-Ketoester via Chiral Enamine Intermediate

According to the retrosynthetic analysis, a chiral nonracemic compound **125** can be synthsized from the α-alkylation of compound **180** in which there is a chiral functional group (FG*) introduced at the β-position of the proline ring (Scheme 57). Based on this idea, a chiral enamine moiety was introduced at the β-position of **180** which is an equivalent of **182**, an intermediate formed from the chiral enamine **183** with $LiN(TMS)_2$.

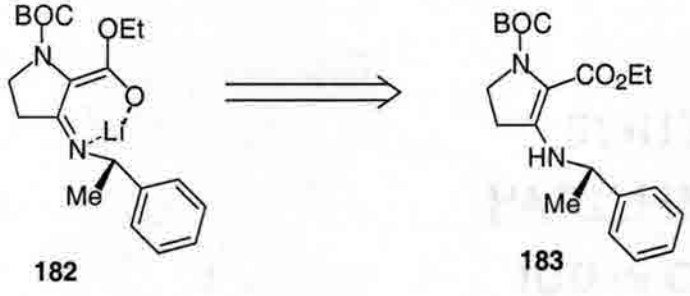
Scheme 57



125 FG* = a chiral functional group **180**



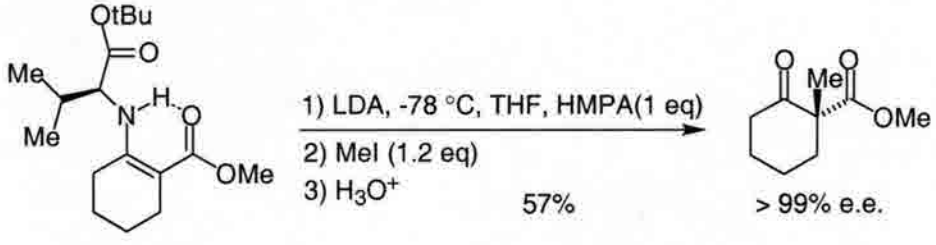
125 **181**



182 **183**

In 1984, Koga and coworkers[38] developed methodology for the asymmetric alkylation of α-alkyl-β-ketoesters to form α,α-dialkyl-β-ketoesters by using enamine **184** as the chiral intermediate. One of their substrate was the cyclohexanone ester derivative **184** (Scheme 58). The bases, solvents, solvent/cosolvent ratio, alkylating reagents and reaction temperature all affect the diastereoselectivity of the products.

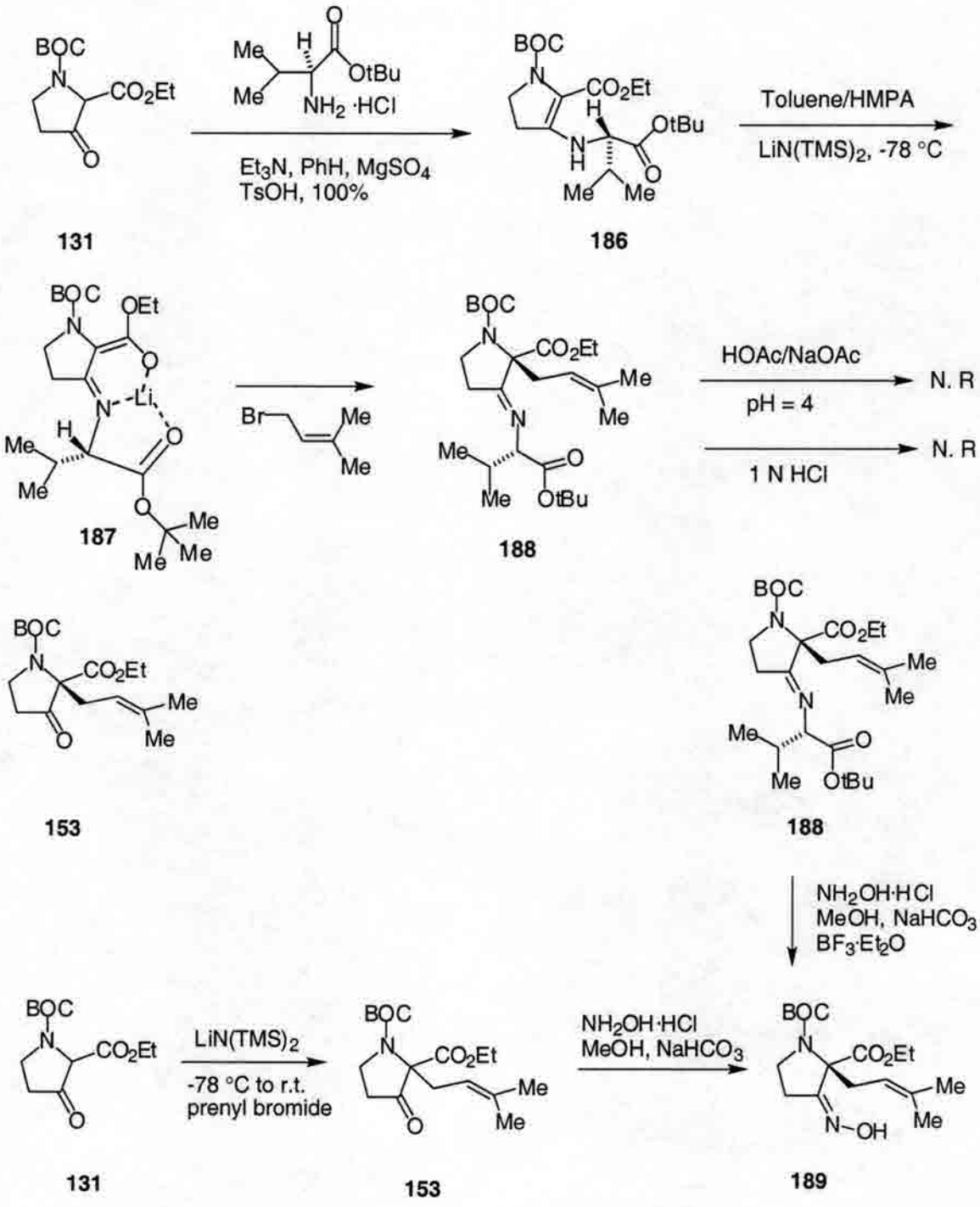
Scheme 58



184 **185**

At first we proposed to use α-methyl benzyl amine as the chiral auxiliary in compound **183**. After Koga and coworker's paper was considered, we decided to follow their protocol. The synthetic investigation towards chiral nonracemic **189** is diagrammed in Scheme 59. β-Ketoester **131** was condensed with S-valine t-butyl ester by using Et_3N, TsOH, $MgSO_4$ in refluxing benzene to provide **186** in almost quantitative yield. Enamine **186** is not very stable. When purified by silica gel chromatography, compound **186** decomposes to starting material. Even when stored at room temperature for 1-2 days, **186** decomposes slowly. A solution of **186** in toluene/HMPA at –78 °C was treated with $LiN(TMS)_2$ followed by addition of prenyl bromide providing a mixture of several compounds on TLC. After preparative TLC purification, one of the major spots was obtained as an oil. ^1H NMR indicated that it contained all the required peaks corresponding to the desired compound **188**. Due to the presence of rotamers and/or possible diastereomers, the ^1H NMR is very complex, and interpretation was difficult. The stereochemistry of **188** was assigned arbitrarily. Surprisingly, when **188** was treated with HOAc/NaOAc (pH 4) or 1 N HCl, typical conditions[39] for the cleavage of an imine, no reaction took place. However, when **188** was condensed with hydroxylamine catalyzed by $BF_3 \cdot Et_2O$, oxime **189** was formed very cleanly. The racemic version of **189**, was also synthesized through a two-step process from **131**. It turned out that both of these products from two different routes showed the same mobility on TLC and the same ^1H NMR. The approach shown in Scheme 59 demonstrates that the β-ketoester alkylation method through a chiral enamine intermediate can result in the asymmetric synthesis of α-alkyl-β-substituted proline derivatives. There are several drawbacks which prevent this method from being used in the real synthesis of (-)-paraherquamide A. First, enamine **186** is not stable enough to be stored for even two days. Second, the diastereoselectivity of the asymmetric alkylation product depends on too many factors, and this is not good news for an asymmetric synthesis, especially on large scale. Third, imine **188** is too stable to be hydrolyzed into the corresponding ketone.

Scheme 59

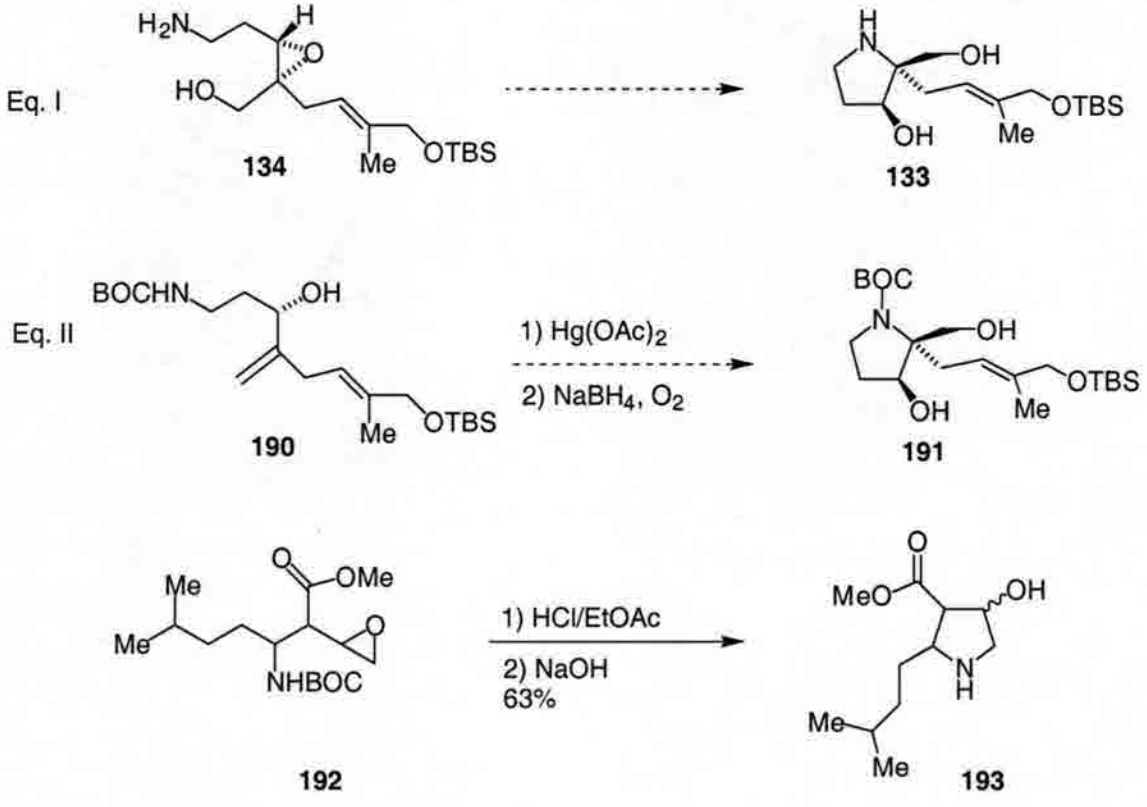

BOC
CO2Et
Me
H
OtBu
Me
NH2 ·HCl
Et3N, PhH, MgSO4
TsOH, 100%
Toluene/HMPA
LiN(TMS)2, -78 °C
131
186
OEt
Li
187
Br
Me
HOAc/NaOAc
pH = 4
1 N HCl
N. R
188
153
NH2OH·HCl
MeOH, NaHCO3
BF3·Et2O
LiN(TMS)2
-78 °C to r.t.
prenyl bromide
189
N-OH

2.24.3 Intramolecular Epoxide Opening-Amination Approach and Intramolecular Amido-Mercuration Approach

These two approaches have some similarity and are discussed here in the same section. For the intramolecular epoxide opening-amination approach (Eq I), there is one literature example published in 1993.[40] (Scheme 60). The N-t-BOC protected epoxide **192** was treated with HCl to remove the t-BOC group and gave the corresponding amine hydrochloric acid salt. Neutralization with NaOH allowed the free amino group to attack the epoxide and provided pyrrolidine **193**.

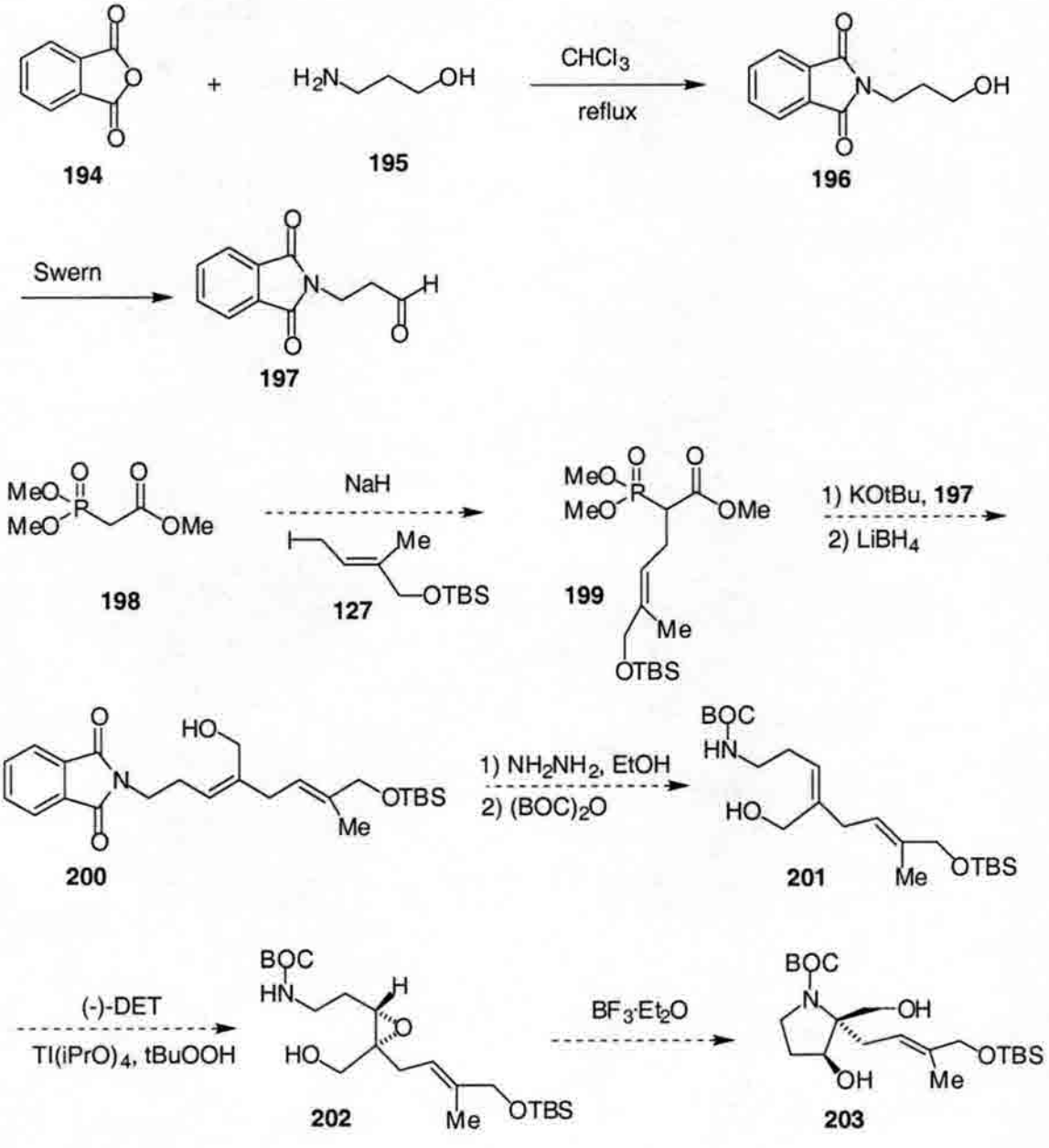
The synthetic plan for chiral nonracemic compound **203** is outlined in Scheme 61. The synthesis of aldehyde **197** and ester **199** should be straightforward. The coupling reaction between **197** and **199** (Horner-Emmons reaction) [41,42,43] should proceed without any problem. The only uncertainty is the olefin E/Z selectivity. The required isomer **200** is the Z configuration, and there are several factors which influence the E/Z selectivity.

Scheme 60



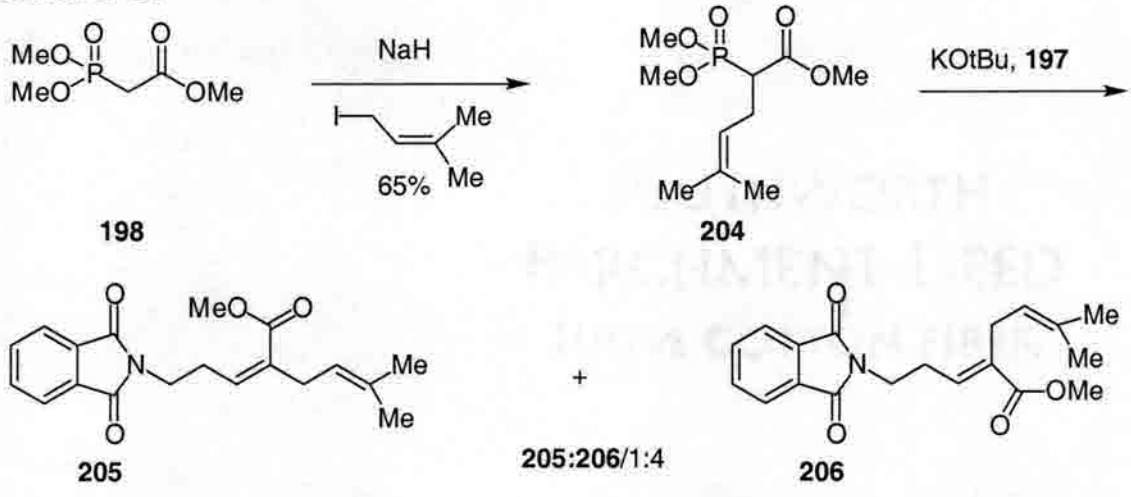
By examining all the possible factors, the desired Z isomer **200** can be obtained as the major isomer. Imidate cleavage with hydrazine followed by protection of the nitrogen as its t-BOC derivative will provide compound **201**. Sharpless epoxidation using (-)-DET can give epoxide **202**, which is then treated with $BF_3{\cdot}Et_2O$ to induce cyclization on the epoxide and provide the desired diol **203**.

Scheme 61



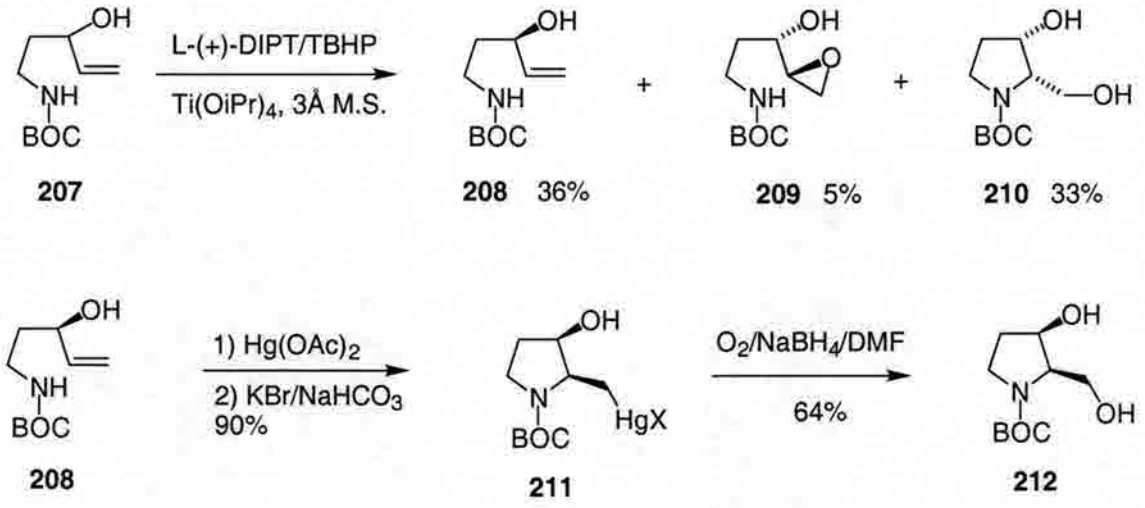
A model study was carried out and is summarized in Scheme 61 and 62. A solution of **194** and **195** in $CHCl_3$ was refluxed to provide alcohol **196** which was then oxidized to aldehyde **197**. Compound **204** was obtained in 65% yield from the alkylation of **198** by the treatment of NaH in DMF. Horner-Emmons reaction between **204** and **197** gave a mixture of **205** and **206** in a 1:4 ratio. The required Z isomer **205** was the minor isomer. Since this approach has too many steps and the set-up for the Sharpless epoxidation reaction is not very convenient[44], this is therefore not the best approach for the total synthesis of paraherquamide A. We decided to dismiss this approach. With further optimization, a practical but longer synthetic route based on this intramolecular epoxide opening-amination approach might prove feasible.

Scheme 62



In Eq II (Scheme 60), a similar strategy using an intramolecular amido-mercuration approach to build diol **191** is depicted. Takahata and coworkers[45] reported a similar case (Scheme 63) in 1997.

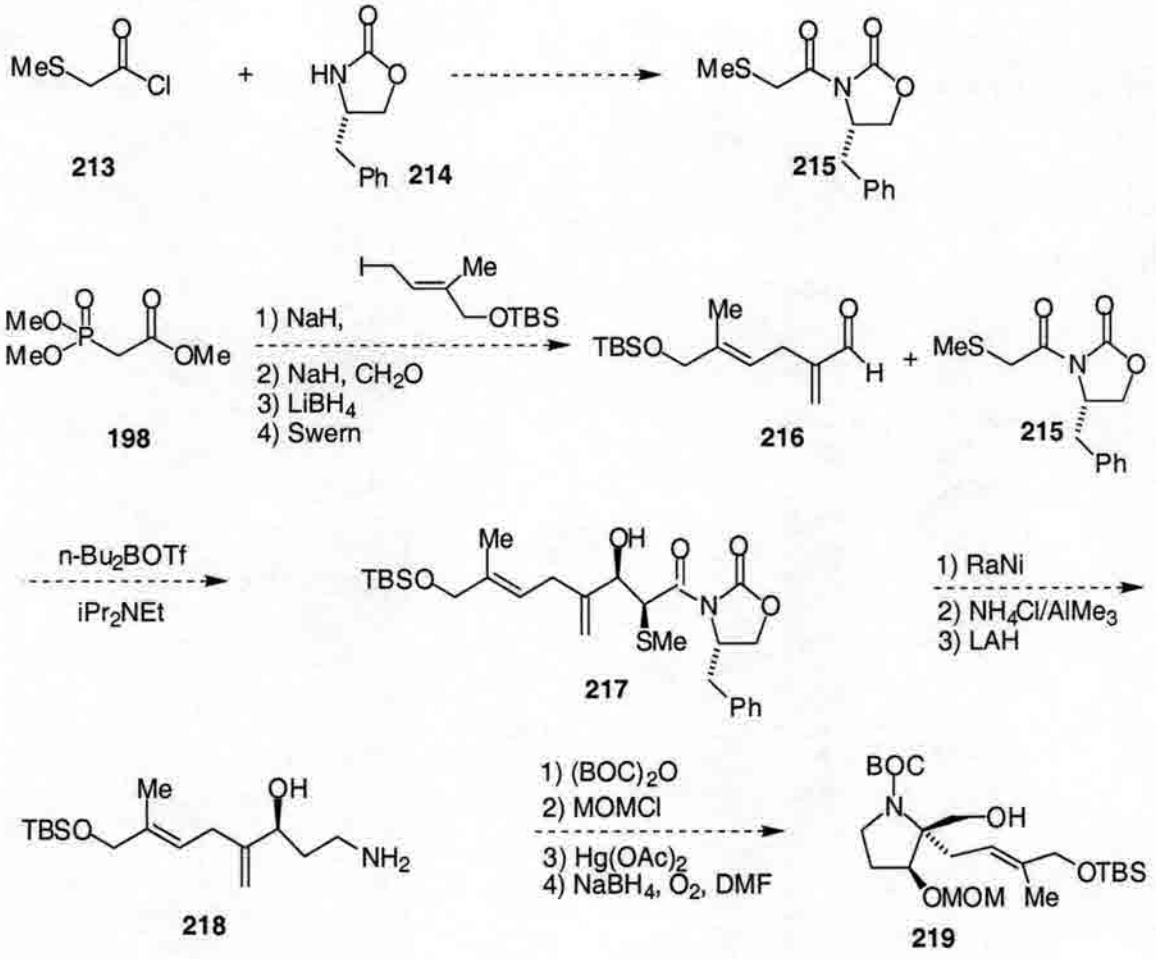
Scheme 63



Sharpless kinetic resolution of racemic alcohol **207** provided the optically active compounds **208** (36%) and **210** (33%). Olefin **208** was subsequently used for the intramolecular amido-mecuration reaction to give intermediate **211** followed by work-up with $O_2/NaBH_4$ in DMF to provide diol **212** in 64% yield. According to this idea, a synthetic plan for compound **219** is illustrated in Scheme 64.

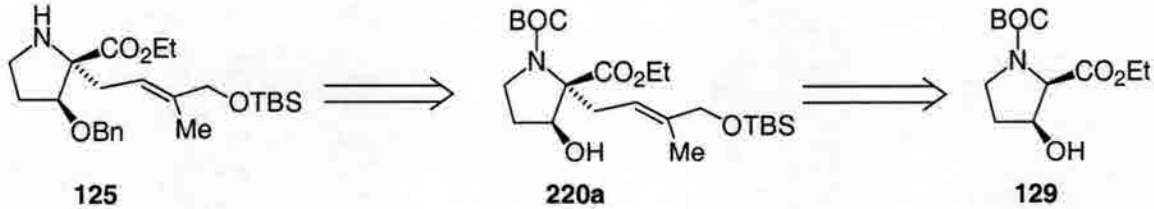
The synthesis of aldehyde **216** will follow normal procedures and should have no problems. The addition of boron enolate, formed from Evans oxazalone **215**, to aldehyde **216** is expected to give alcohol **217**. The transformation of **217** to amino alcohol **218** follows a similar four-step process[46]. The last three steps follow the procedure developed by Takahata and coworkers[45] as shown in Scheme 63. Due to the success of the α-alkylation of cis-β-hydroxy proline ester **129**, we did not attempt to investigate this plan.

Scheme 64



2.24.4 α-Alkylation Approach of β-Hydroxy Proline Ester 129

Scheme 65

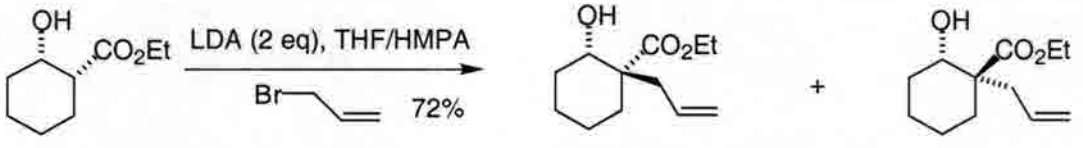


The retrosynthetic analysis of this approach is illustrated in Scheme 65. Amino ester **125** can be obtained from alcohol **220a** by several functional group transformations. These transformations were done previously during the racemic series synthesis. Aminoester **125** can be used to synthesize the corresponding diketopiperazine (DKP)

which was designed to be the key intermediate for the total synthesis of (-)-paraherquamide A. The methodology which remains to be developed is the α-alkylation of cis-β-hydroxyproline ethylester **129**. By using this method, compound **220a** and analogs can be made. The idea for the stereoselective α-alkylation of ester **129** is as follows: when the dianion of compound **129** reacts with alkylating reagents, the alkoxide at the β-position of **129** will induce the incoming alkyl group *anti*-to the alkoxide due to the 1,2-induction and therefore provide the desired stereoisomer **220a**. The regioselectivity issue, whether α-C or β-O alkylation occurs, can be answered only by experimental result. However, from literature reports,[52,53] the ratio of polar aprotic solvent in a co-solvent reaction media has a profound effect on the ratio of C/O alkylations.

A literature search found reports by Frater and coworkers,[47,48] in which the investigation of α-alkylation of chiral cis-ethyl-2-hydroxy-cyclohexanecarboxylate **221** (Scheme 66) was carried out. The *cis* (**222**) and *trans* (**223**) compounds were obtained in a 94.5/5.5 ratio with a combined 72% yield. The conditions are as follows: to a LDA (2.5 eq) solution at –50 °C in THF was added a solution of **221** in THF, and the reaction mixture was stirred at –15 °C for 10 min to give a dianion solution of **221**. At this time, a mixture of allylic bromide in HMPA (4.2 eq) was added to the above dianion solution. After the reaction mixture was stirred for 30 min at 32 °C, it was quenched with a NH_4Cl solution followed by normal work-up to provide **222** and **223** in 72% yield.

Scheme 66



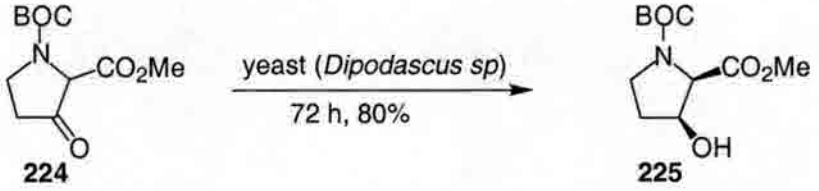
221 **222** **223**

First, we needed to make chiral nonracemic proline ester **129**. Three different groups have reported the synthesis of **129** through yeast-mediated bio-transformation (Scheme 67). The method[49] in Eq I gave **225** in 80% yield with >99% e.e., but the yeast

Dipodascus sp was not available. Sibi et al.[50] (Eq II) used the CBz substrate **226** and immobilized baker's yeast as the reducing reagent to synthesize the corresponding CBz-alcohol in 85% yield (I repeated this reaction in 40% yield). CBz cleavage (Pd/C, H_2) and in-situ protection of the amine using $(BOC)_2O$ gave **129** in 90% yield. For the immobilized baker's yeast reduction conditions, the work-up process was much easier than the normal yeast conditions. The only drawbacks are the low yield of this reaction and the extra protection step needed to make **129**. The method[51] we used for the synthesis of (-)-paraherquamide A is shown in Eq III. Although it gave **129** in 90% e.e., it usually provides **129** in high yields (80-83%) on a large scale.

Scheme 67

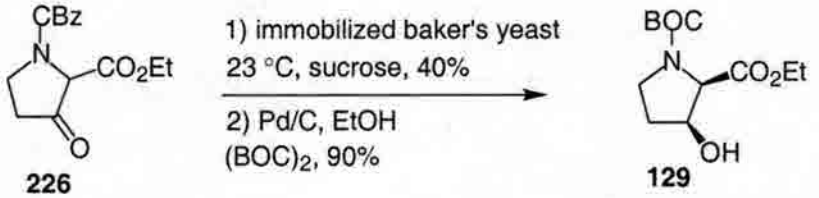
Eq. I



224 **225**

>99% e.e.

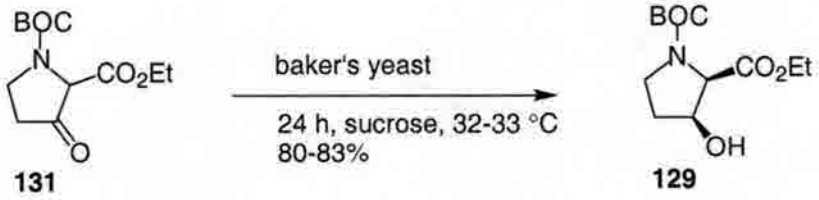
Eq. II



226 **129**

95% e.e.

Eq. III



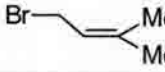
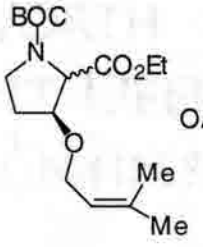
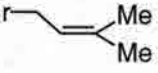
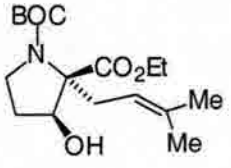
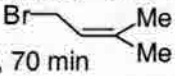
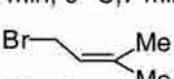
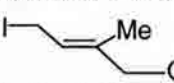
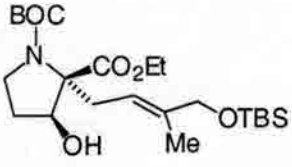
131 **129**

90% e.e.

Table 4 tabulates the results of our study of the α-alkylation reaction. First, we have used prenyl bromide as our model alkylating reagent. When the same reaction conditions as reported by Frater was used, only the O-alkylation product was produced. We believe this result was due to the excess molar equivalents of HMPA used. When the

quantity of HMPA used was 10 eq or 8.4 eq again only O-alkylation occurred. Once the molar equivalents of HMPA was lowered to 2.3 eq or 1 eq, the desired α-C-alkylation product was obtained in 73% yield, and only a minor amount of O-alkylation was produced. For entry 5, the real allylic iodide derivative **127** was the alkylating reagent, and the desired product **220a** was obtained in 45-70% yield. Employing $NaN(TMS)_2$ as the base did not give any desired product. Other polar apotic solvents such as DMPU and TMEDA were also examined. DMPU was not as good as HMPA in terms of yield, and for TMEDA there was no reaction. In summary, we found that the absence of HMPA produced no alkylation reaction while an excess of HMPA gave only O-alkylation product.

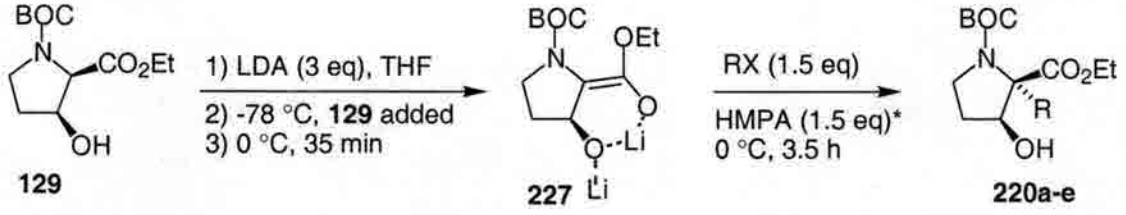
Table 4

Entry	Conditions	Results
1	THF:HMPA (3:1), $NaN(TMS)_2$ -78 °C,1 h; 0 °C,1 h 	 OA = O-alkylation
2	THF, LDA,SM, -50 °C -15 °C,15 min; 0 °C,15 min -10 °C,  + HMPA (2.3 eq) 23-30 °C,70 min	 + OA major minor
3	THF, LDA, SM, -50 °C -15 °C,15 min; 0 °C,15 min -10°C,  + HMPA (10 eq) 23-30 °C, 70 min	OA only
4	THF, LDA,SM, -50 °C, 3-4 min -10 °C,15 min; 0 °C,7 min 0 °C,  + HMPA (8.4 eq) 23-30 °C, 60 min	OA only
5	THF, LDA,SM, -50 °C -15 °C,15 min; 0 °C,5 min -35 °C,  + HMPA (1 eq) 0 °C, 50 min; r t, 4 h	 + OA 45-70% 3-4%

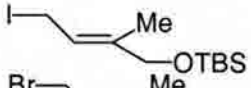
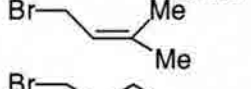
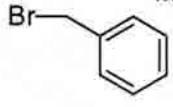
1) LDA is the required base
2) Reverse addition of starting material is required
3) No HMPA, no reaction
   Too much HMPA, only O-alkylation
   1-3 eq is good for C-alkylation
4) HMPA is the best solvent
5) Only one diastereomer is formed

Scheme 68

Simplified conditions for the formation of compound **220a**



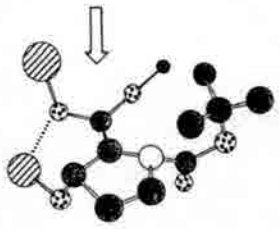
*different batches of **129** required distinct equiv. of HMPA ranging from 1.5, 4.5, 9.7 to 13.7 eq.

Entry	RX	% Yield
a		70%
b		73%
c		53%
d	I-CH3	57%
e		49%

After the successful synthesis of **220a** and **220b**, we decided to extend this methodology to other activated or nonactivated alkylating reagents. The results are shown in Scheme 68. Compounds **220c-e** were obtained in good yield. The simplified condition was used only for the large scale synthesis of **220a**. The difference between the two conditions is in the procedure for forming the dianion while the work-up is the same. The simplified condition (LDA in THF at -78 °C, addition of **129** in THF, then at 0 °C for 35 min) to form the dianion of **129** is much simpler than the old one. Therefore, the simplified condition to form the dianion can also be used for the α-alkylation of other alkylating agents. In each case, only one diastereomer was formed, and little or no O-monoalkylated or O-, C-dialkylated by-products were produced. These highly stereoselective alkylation reactions all proceeded with net retention of configuration giving a single diastereomer as

evidenced by ^{1}H NMR and other analytical data including the X-ray analysis of **220e** (Figure 1) and the ^{1}H NMR of the t-BOC-deprotected derivative of compound **220a**. The relative and absolute stereochemistry of the alkylation products was rigorously secured through a single crystal X-ray analysis for **220e** (Figure 1). Chemical correlation was used to determine the relative and absolute stereochemistry of **220a** (Scheme 69). We also attempted to use a NOE method to determine the relative stereochemistry of all the α-alkylated products, but the results were inconclusive. The relative, and thus, absolute stereochemistry was assigned based on similarities in nmr spectroscopic characteristics and optical rotation.

The dianion **227** derived from **129** is expected to have a concave shape due to a Li-coordinated bicyclic [4.3.0] ring system geometry. Alkylation from the convex face opposite the alkoxy substituent is the expected (and observed) diastereofacial bias.



The chemical correlation method used for the absolute and relative stereochemistry determination of **220a** is outlined in Scheme 69. Barton deoxygenation of **220a** through a two-step process provided ester **229**, which was then treated with $ZnBr_2$ to remove the N-t-BOC group followed by reaction with bromoacetyl bromide to afford bromide **231**. Aminolysis of **231** and in-situ cyclization resulted in DKP **232**. Aldehyde **233**, a known compound synthesized during the synthesis of (+)-paraherquamide B, was converted to DKP **235**, an enantiomer of **232**. DKP **232** and **235** have the exact same ^{1}H NMR, IR and mobility on TLC. These facts indicate that DKP **232** and **235** have the same relative stereochemistry. DKP **232** has an optical rotation of $[\alpha]^{D}_{25}$ = +51.4 (c 0.36, EtOAc) and DKP **235** has an optical rotation of $[\alpha]^{D}_{25}$ = -62.5 (c 0.39, EtOAc). These opposite

optical rotations indicate that DKP **232** and **235** are enantiomers. Since DKP **232** is contaminated with a very minor amount of the Z isomer, we can not use the optical rotation of **232** to calculate its enantiomeric excess.

Scheme 69

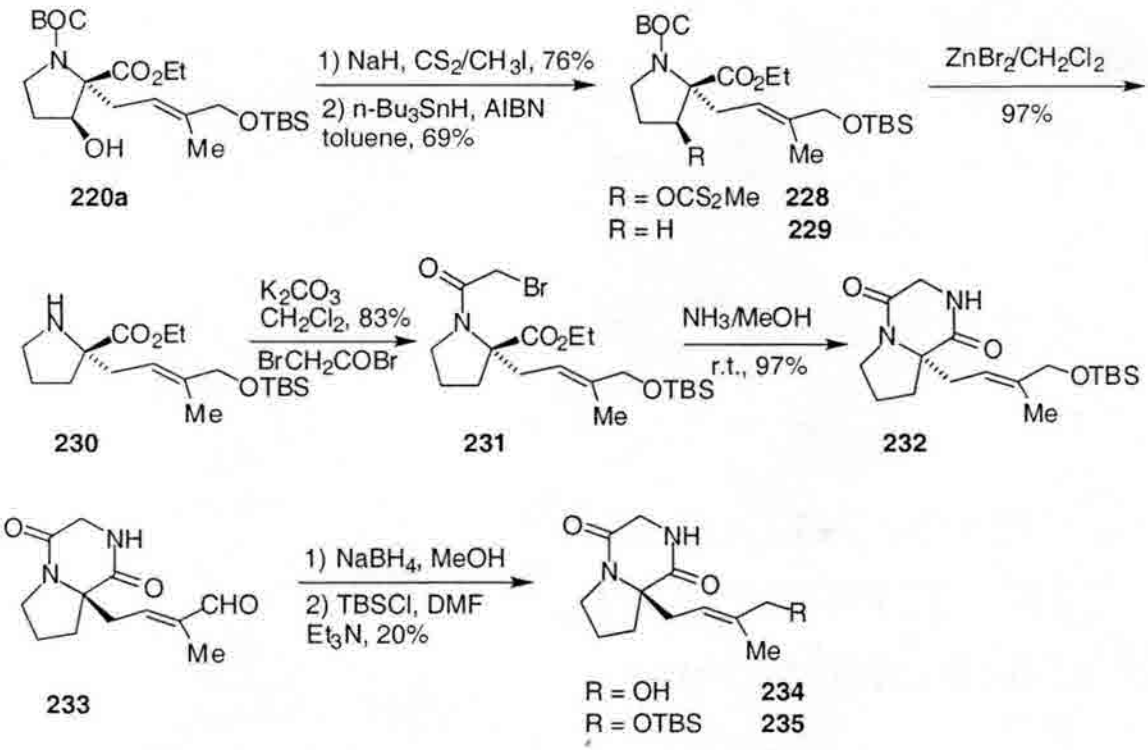
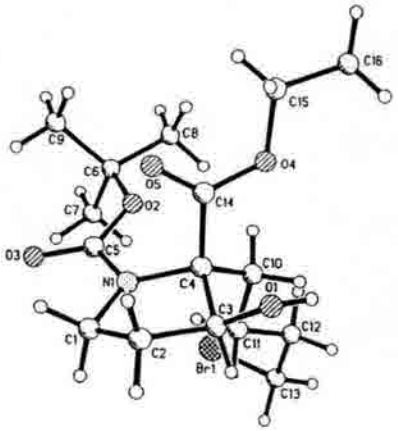


Figure 1 The molecular structure of **220e** through X-ray analysis



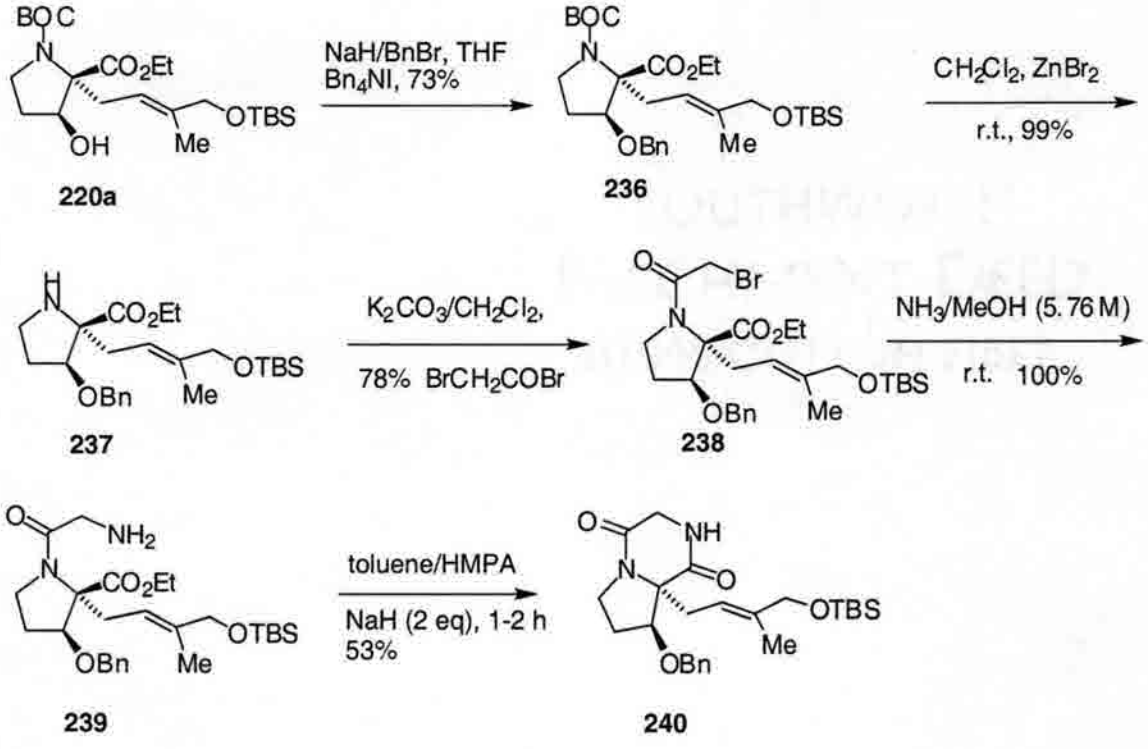
Herein we will discuss the issue of α-alkylation diastereoselectivity in more detail. In Scheme 70, chiral nonracemic DKP **240** was synthesized from compound **220a**. In the aminolysis step (**238** to **239**), the amino ester compound **239** did not cyclize to give DKP **240** because it is the *cis*-isomer. However, the corresponding *trans*-isomer, which was made in the synthesis of the racemic series of compounds, can cyclize to give the corresponding DKP **171** (Scheme 72) under the aminolysis conditions. The ^{1}H NMR of DKP **171** is very unique. For all the aminolysis reactions, the measured ^{1}H NMRs of **239** and its analogs showed no formation of DKP **171** and its analogs. Based on these results, it was concluded that no *trans*-isomer was formed in the α-alkylation step. Since the process of producing the dianion of compound **129** did not touch the hydroxy-attached chiral center at the β-position of **129** and only one stereoisomer was formed, the enantiomeric excess of all the α-alkylated products should be the same as that of **129** (>90% ee).

The total synthesis of paraherquamide A required large scale synthesis of **220a**. There was a very interesting and unique phenomenon discovered during this large scale synthesis of **220a**. The first batch of compound **129** was synthesized on a 1.5 gram scale and was used to develop the α-alkylation methodology. For this batch of **129**, 1.4 equivalents of HMPA were found to be sufficient to make the alkylation reaction take place. If greater than four equivalents of HMPA were used, only the O-alkylation product was observed. The second batch of compound **129** was made on a 5 gram scale. The exact same conditions were used for the alkylation, but no reaction occurred and only starting material was recovered. After two weeks of investigation, it was discovered that 4.5 equivalents or more of HMPA were needed to make the alkylation reaction successful. Interestingly, the remaining **129** of the first batch only required 1.4 equivalents of HMPA in the same alkylation reaction. The third batch of **129** was synthesized on a 30 gram scale, and 13.7 equivalents of HMPA were found to be necessary for the alkylation procedure. The ^{1}H NMR, IR ,TLC and specific optical rotation of these three batches of **129** were

identical. For the second batch of **129**, this compound was repurified by distillation or column chromatography. However, the alkylation still required 4.5 equivalents or more of HMPA and showed no difference from the non-repurified same batch of **129**. The reason[54] for this phenomenon is still not clear. We also found that the yield of a 3 gram versus 2 gram scale reaction of **129** were the same and the recovered starting material did not undergo the alkylation.

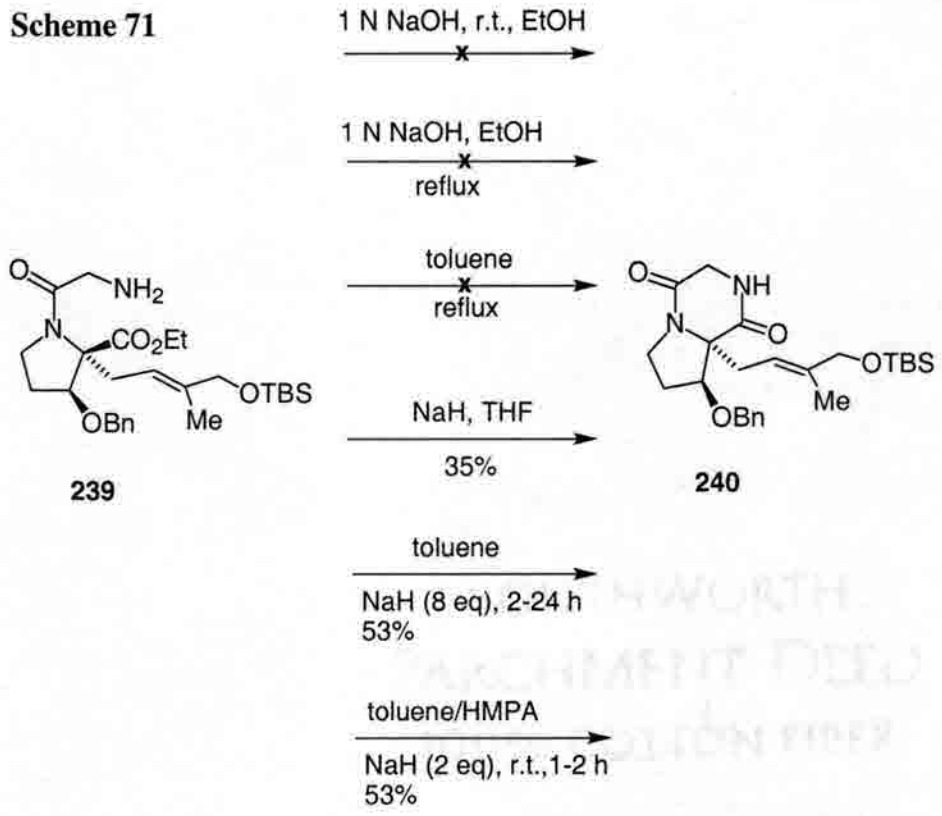
With enough **220a** in hand, DKP **240** was synthesized from **220a** according to the route shown in Scheme 70. Protection of the secondary alcohol of **220a** as the benzyl ether (73%), and subsequent deprotection of the N-t-BOC group with $ZnBr_2$ (99%) followed by treatment with bromoacetyl bromide provided bromide **238** (78%). Aminolysis of **238** was accomplished by the syringe pump-mediated addition of **238** in MeOH to an ammonia solution in MeOH (5.76 M) to avoid the formation of by-products such as the secondary and tertiary amines.

Scheme 70



The amide formation step turned out to be quite difficult. In Scheme 71, the reaction conditions examined are illustrated. When toluene or EtOH was used as the solvent under room temperature or reflux, there was no reaction. DKP **240** was obtained in about 35% yield with the addition of NaH in THF. Toluene was a superior solvent compared to THF, and the yield was 53-60%. However, there were some disadvantages for the toluene/NaH (8 eq) conditions. This reaction was not reproducible. Sometimes it was complete in 2 h, and sometimes there was no reaction even after 24 h. Eight equivalents of NaH were definitely required. The difficulty of this intramolecular amidation reaction lies in the steric-hindrance of the α,α-disubstituted ethyl ester. There are two ways to overcome this problem. One approach was to activate the RNH^- anion and to render it more nucleophilic. The other approach was to activate the ester group by Lewis acid coordination to the carbonyl oxygen, hence increasing the electrophilicity of the carbonyl group. The RNH^- anion activation can be achieved by using HMPA or any other polar aprotic solvents which coordinate the sodium cation. Another alternative was to use Weinreb's[55] aluminum amide to convert the ester to the corresponding amide. When three equivalents of HMPA were added, the amidation reaction proceeded very quickly and was finished within 2 h. Only two equivalents of NaH were needed to give a 53% yield, and this reaction was reproducible on a large scale.

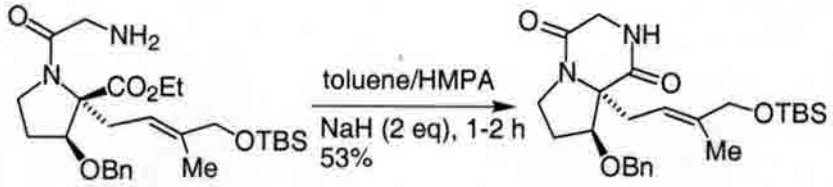
Scheme 71



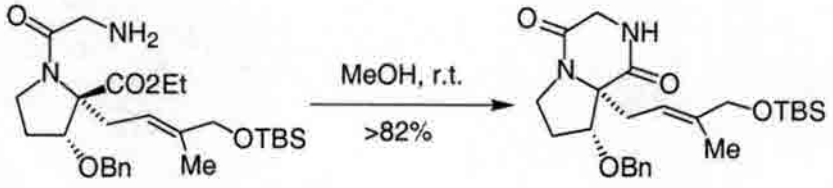
There was an interesting observation regarding the DKP formation from the corresponding amino ester (for example **239** to **240**). Several examples of this amide formation reaction are shown in Scheme 72.

Amino ester **239** (*cis*) has a diastereomer **168** (*trans*) that can be cyclized in MeOH at room temperature to provide (±) DKP **171** in >82% yield. In comparison, the *cis*-isomer **239** requires much stronger reaction conditions for cyclization. Compounds **241** and **149a** exhibit the same behavior. We decided to spend some time investigating this phenomenon, and hoped to find an answer which will help us to understand more about this reaction and hopefully improve the yield of the *cis*-isomer cyclization.

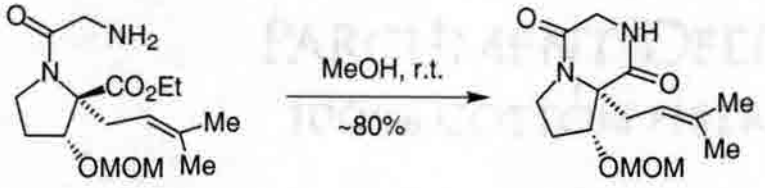
Scheme 72



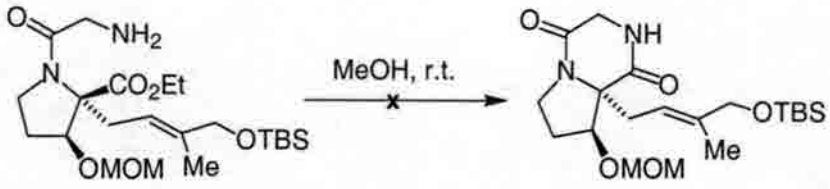
239 **240**



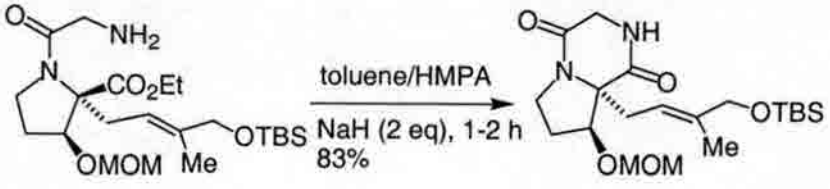
(±) **168** (±) **171**



(±) **149a** (±) **149**

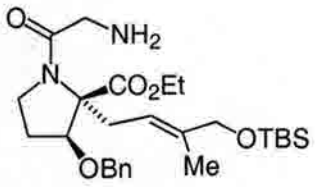


241 **242**

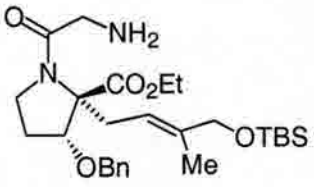


241 **242**

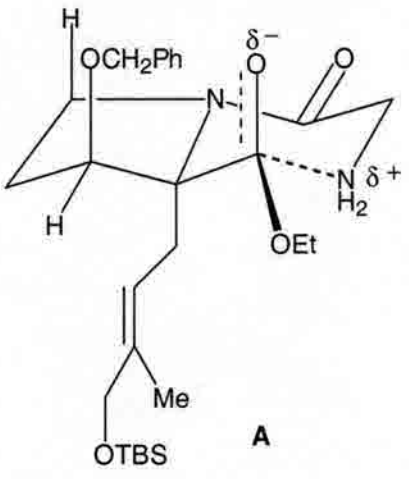
Figure 2



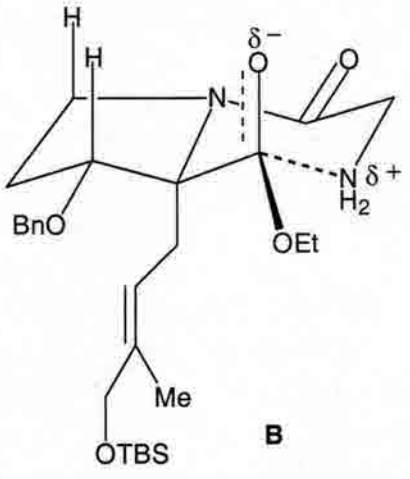
Cis **239**



Trans **168**



A

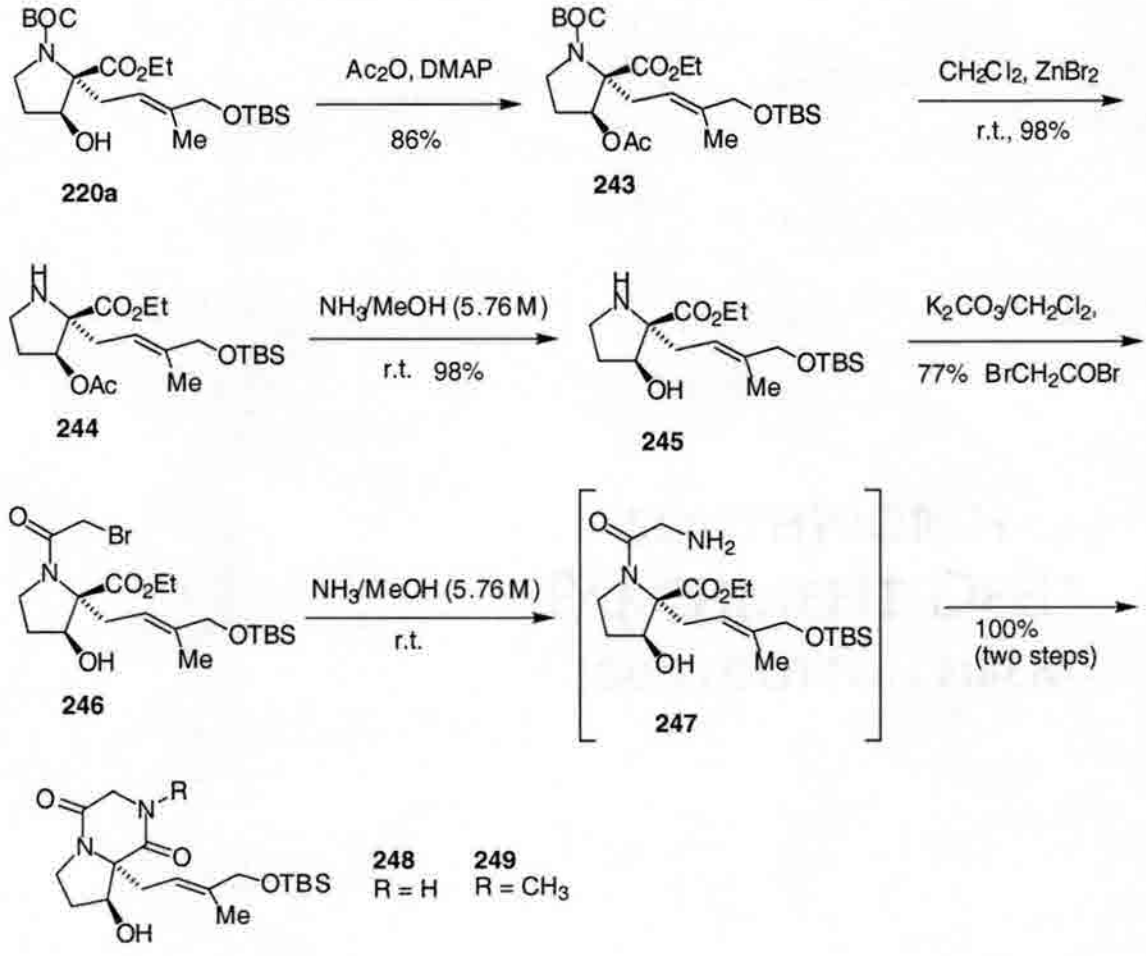


B

A and **B** are the two transition state models for *cis*-**239** and *trans*-**168** respectively (Figure 2). For the *cis*-compound, the transition state adopts a half chair-chair conformation (**A**). The large allylic group is in an axial position, and benzyl ether is also in an axial position. The carbonyl oxygen has a partial negative charge and the amino group has a partial positive charge. Due to the strong 1,3-axial-axial interaction between the benzyl ether group and hydrogen as well as the carbonyl group, the activation energy E_A* for cyclization is higher than that of E_B*. For *trans*-**168**, the transition state structure **B** has a lower activation energy E_B* because the benzyl ether group is in the equatorial position. Therefore, the cyclization of the *cis*-isomer **239** is more difficult than that of *trans*-isomer **168**. According to this model, if we change the protecting group at the β-position to a smaller one, the amide formation should be easier. Hydroxy bromide **246** was made from **220a** in four steps (Scheme 73). **220a** reacted with acetic anhydride catalyzed by DMAP to give acetate **243**. Deprotection of the N-t-BOC group with $ZnBr_2$ followed by another deprotection of the acetate moiety with NH_3/MeOH provided hydroxy amine **245**.

Treatment of **245** with one equivalent of bromoacetyl bromide under basic conditions afforded hydroxy bromide **246** in good yield. Aminolysis of **246** gave amine **247**, which was cyclized in-situ in a solution of NH_3/MeOH to afford DKP **248** in almost quantitative yield. Bromide **246** was also treated with a solution of CH_3NH_2 in MeOH and DKP **249** was obtained in >95% yield. In Scheme 72, the formation of DKP **242** (83%), which has a smaller MOM ether protecting group at the β-position, was also much easier than that of compound **239**. Therefore, the difficulty in cyclization of the *cis*-amino esters to the corresponding DKPs is in the order of $PhCH_2O$ > MOMO > OH. These facts support the transition model drawn in Figure 2.

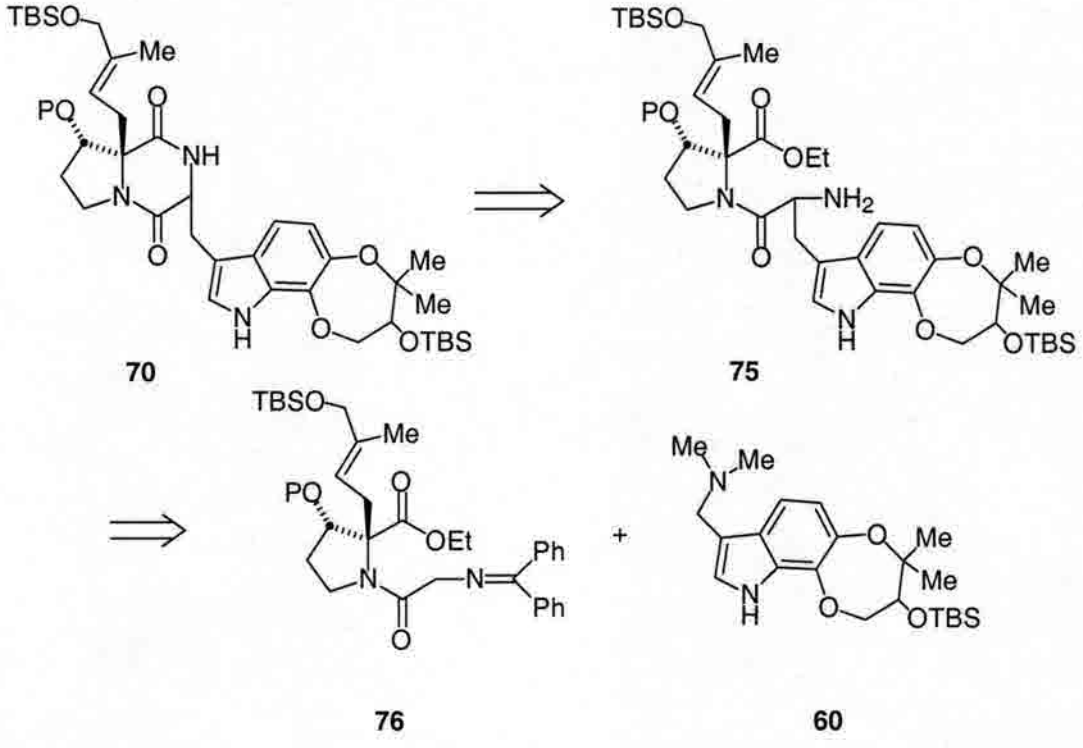
Scheme 73



2.3 Two Connecting Methods between the Indole-dioxepin Subunit and Proline Derivatives

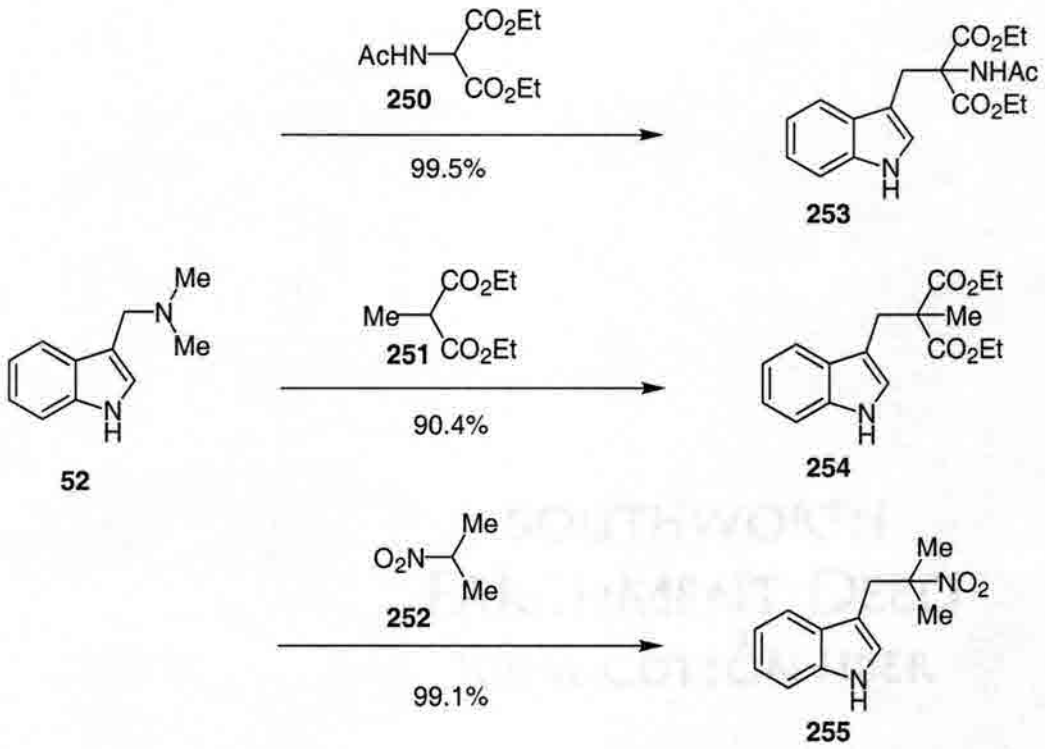
According to the synthetic strategy to access (-)-paraherquamide A, there were two methods envisioned for the connection of the indole-dioxepin subunit and the proline derivative. One approach was the dipeptide cyclization to the DKP (section 2.31), and the other was the Somei/Kametani coupling method. In this section, these two methods will be discussed in detail.

2.31 Dipeptide Cyclization to Diketopiperazine Method



Retrosynthetically, indole derivative **70** can be obtained from the cyclization of dipeptide **75**. The coupling between compounds **60** and **76**, and subsequent functional group transformations can provide intermediate **75**. In fact, the coupling reaction between compounds **60** and **76** is the reaction which constructs the tryptophan derivative (right hand side amino acid of **75**). The best available method is the one developed by Somei and Kametani et al.[56,57] in 1981 (Scheme 74).

Scheme 74

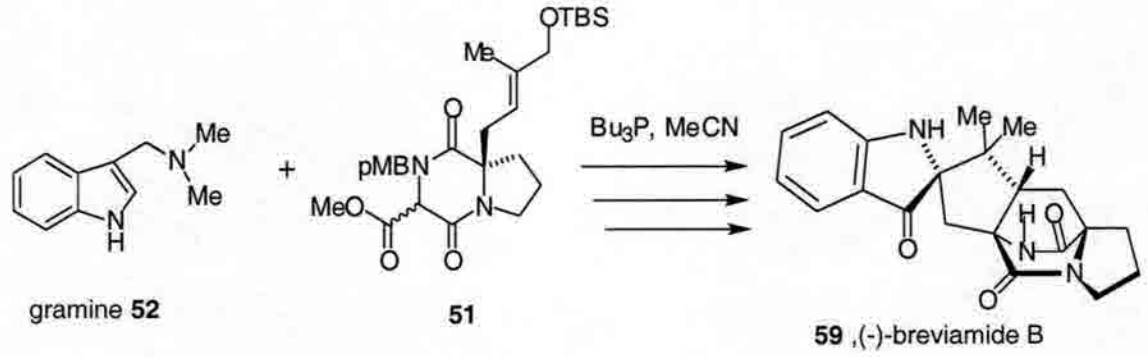


Condition: n-Bu_3P, CH_3CN, reflux, 4 h

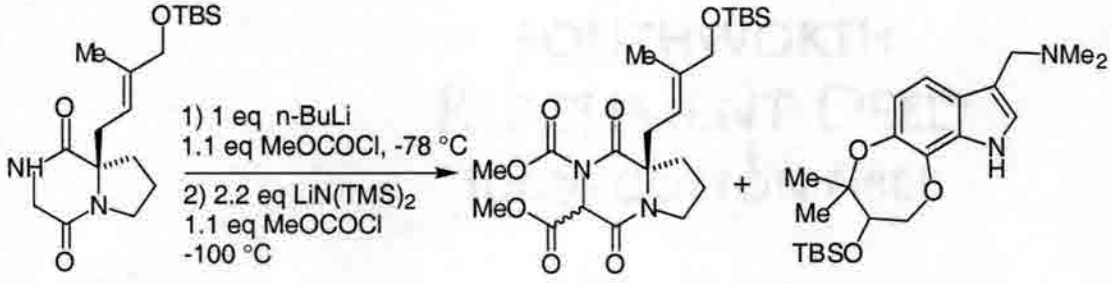
The malonates **250** and **251** and the nitro compound **252** were coupled with gramine **52** in the presence of Bu_3P in refluxing CH_3CN to provide a variety of α-substituted tryptophan derivatives or nitro indole **255**. For the Somei/Kametani reaction, a relatively strong carbon acid (pKa < 12) substrate (such as malonates **250** and **251**, or nitro compound **252**) is required. These substrates have two electron-withdrawing groups or an electron-withdrawing nitro group. Based on this method, (-)-brevianamide B and (+)-paraherquamide B were synthesized in the Williams group (Scheme75). In order to synthesize a suitable substrate for the Somei/Kametani type coupling reaction, two electron-withdrawing groups must be attached to the same carbon. Compound **61**was considered a reasonable substrate, and it was made from **256** by a two-step process. After the coupling

step, one of the electron-withdrawing groups must be removed to in order to make the tryptophan-type derivative. The whole process involves four steps.

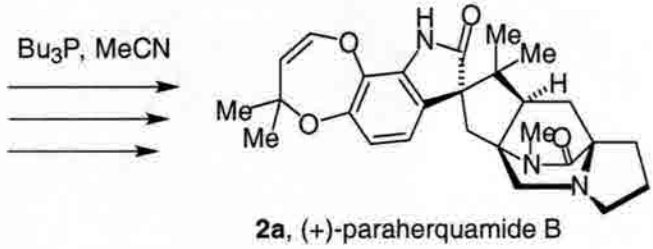
Scheme 75



gramine **52** **51** **59** ,(-)-breviamide B



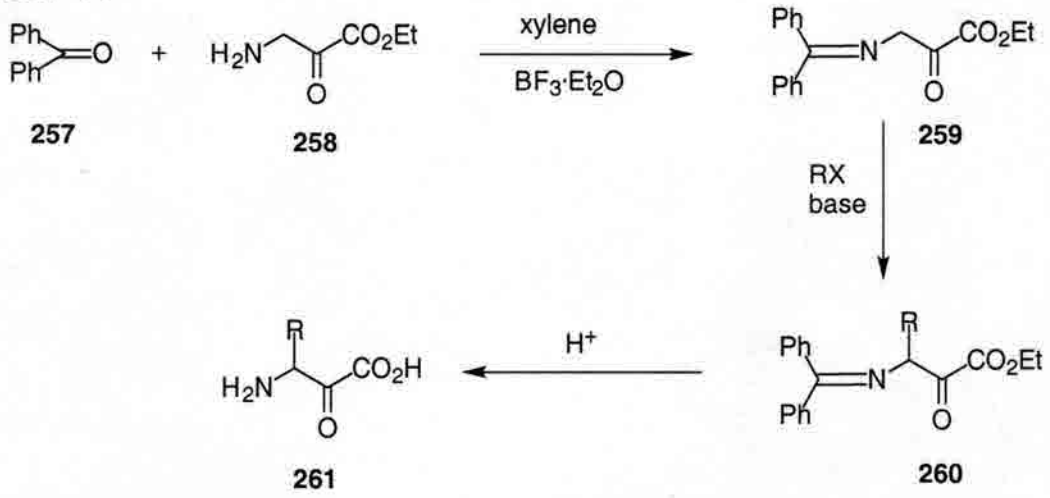
256 **61** **60**



2a, (+)-paraherquamide B

Can we find a substrate that has a relatively high pKa but will still couple with gramine derivatives to afford tryptophan-type compounds? Based my own experience with amino acids, imine protected glycine ester may be an appropriate substrate worth examining. In 1978, O'Donnell and coworkers[58] developed a methodology for synthesizing racemic α-amino acids from the stable Schiff base **259**[59] derived from glycine ethyl ester and benzophenone (Scheme 76).

Scheme 76

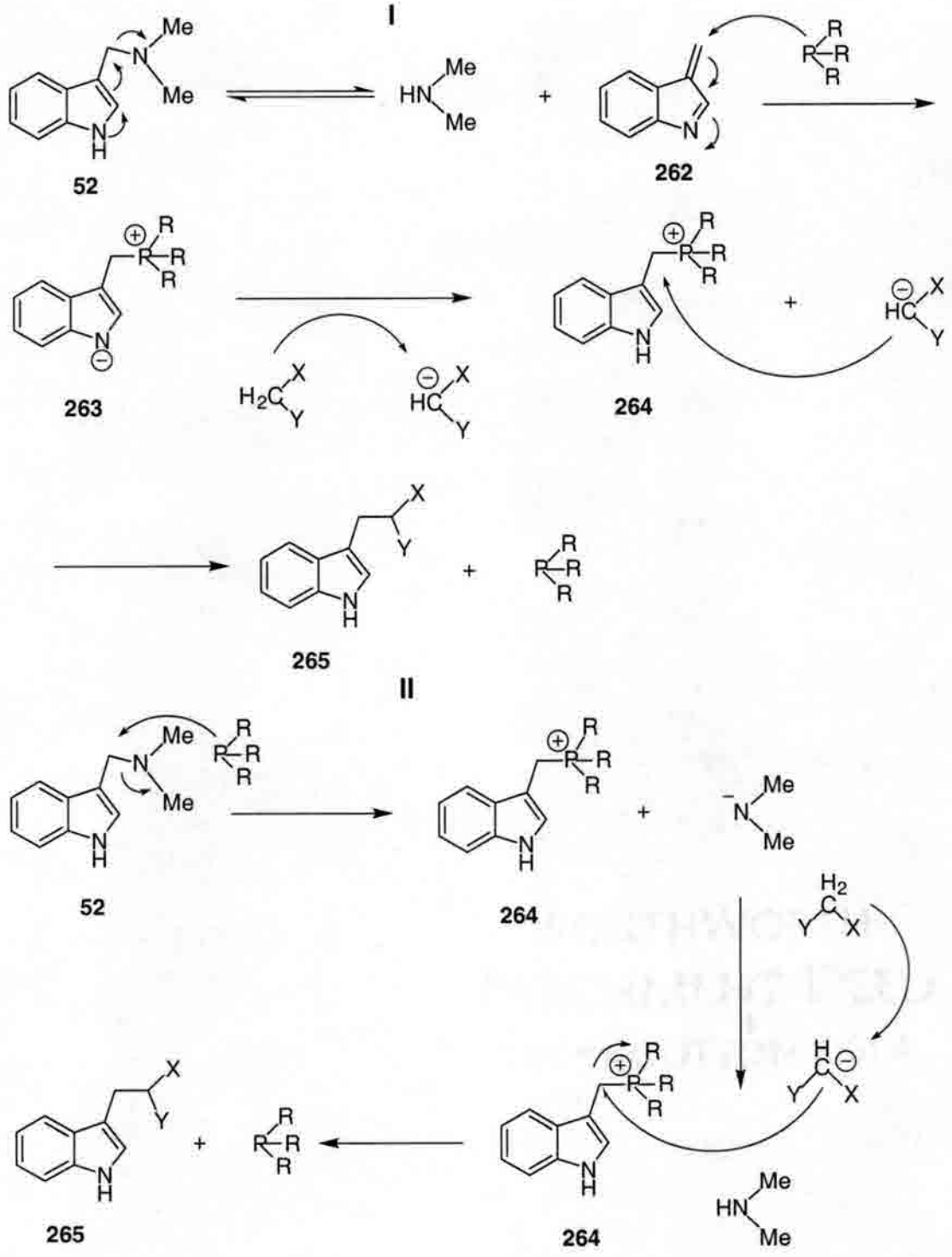


Tryptophan and its analogs are α-amino acids. The pKa of imine ester **259** is 18.8.[59] Several related syntheses of tryptophan and derivatives was found through extensive literature search. Some researchers used lithium enolate to react with the gramine methiodide[60,61]. Others [62,63] have used compound **259** in an alkylation reaction with gramine methiodide under phase transfer catalysis conditions.

The possible mechanism (**I**) of the Somei/Kametani reaction is shown in Scheme 77. Under refluxing CH_3CN, gramine is in equilibrium with dimethylamine and **262** which can be attacked by the catalyst Bu_3P to provide anion **263**. Anion **263** can act as a base to abstract a proton from a relatively acidic carbon acid H_2CXY to form the carbanion intermediate HC^-XY. S_N2 reaction at the α-carbon of **264** provides the coupling product **265** and returns the catalyst Bu_3P. Another possible mechanism (**II**) in Scheme 77 shows some difference from the first one. In order to propagate this catalytic cycle, **263** must be a stronger base than anion HC^-XY or very close. The pKa value for the deprotonation of indole is 16.97.[64] The pKa of **259** is 18.8. These two pKa valves are very close. There is a good chance for imine **259** to undergo the Somei/Kametani reaction, because, in different solvent systems, the pKas of different substrates will respond differently. When imine **259** was treated with gramine under Bu_3P catalysis in refluxing CH_3CN, the desired coupling product (**266**) was obtained in 80% yield (Scheme 78).

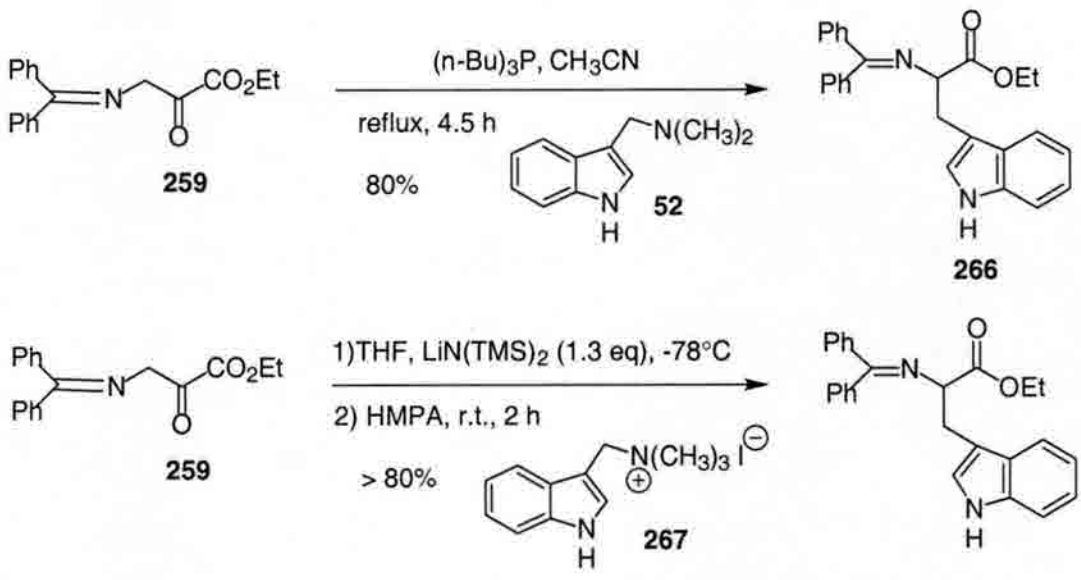
Scheme 77

Somei/Kametani Reaction



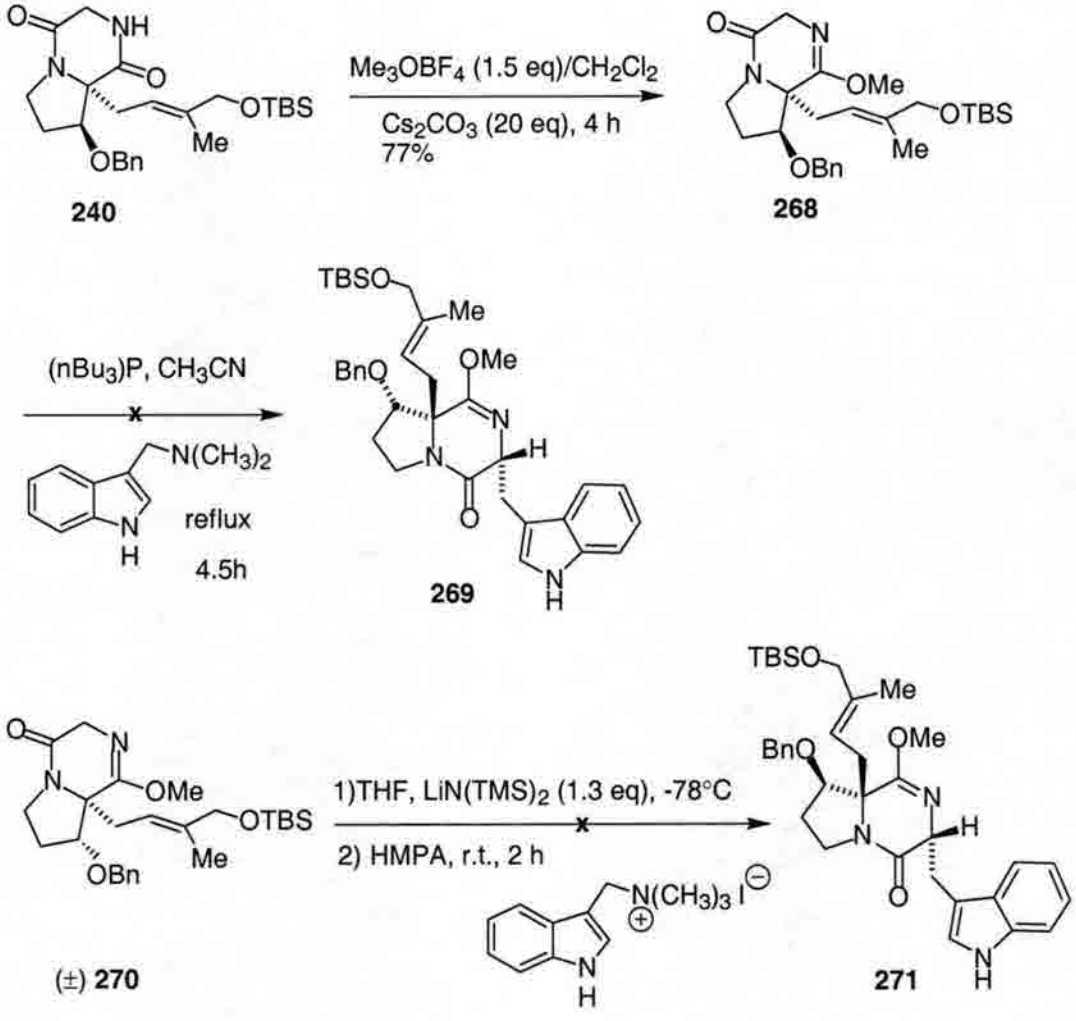
Another method, the alkylation of the enolate formed from imine **259** and $LiN(TMS)_2$ with gramine methiodide also provided **266** in >80% yield (Scheme 78).

Scheme 78



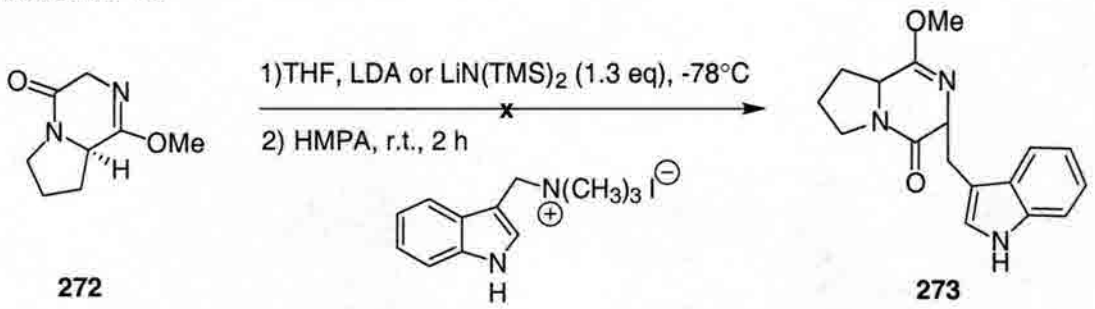
Based on the successful synthesis of **266**, lactim ether **268**, obtained from amide **240** in 77% yield (Scheme 79), was treated with gramine under Somei/Kamatani condition, but no reaction occurred. Lactim ether **270**, a racemic diastereomer of **268**, was treated with the base $LiN(TMS)_2$ and gramine methiodide and produced no coupling product. Other bases such as NaH, LDA and additives such as 15-C-5 were also used, but only the starting material lactim ether **268** or **270** were recovered. In a comparison of the pKa between **268** and **259**, certainly the pKa of **268** is greater than that of **259**. This pKa difference may reach the critical point such that the Bu_3P-catalyzed reaction cycle can not occor. The reason for the lack of coupling between lactim ether **268** or **270** with gramine methiodide in the presence of strong base is still not clear.

Scheme 79



Initially, we reasoned that the anion was too stable and the lactim ether substrate was too hindered for reaction to occur. A much simple lactim ether **272** (Scheme 80), synthesized from proline, was treated with the same basic conditions. Although no starting material remained, no desired coupling product **273** was formed.

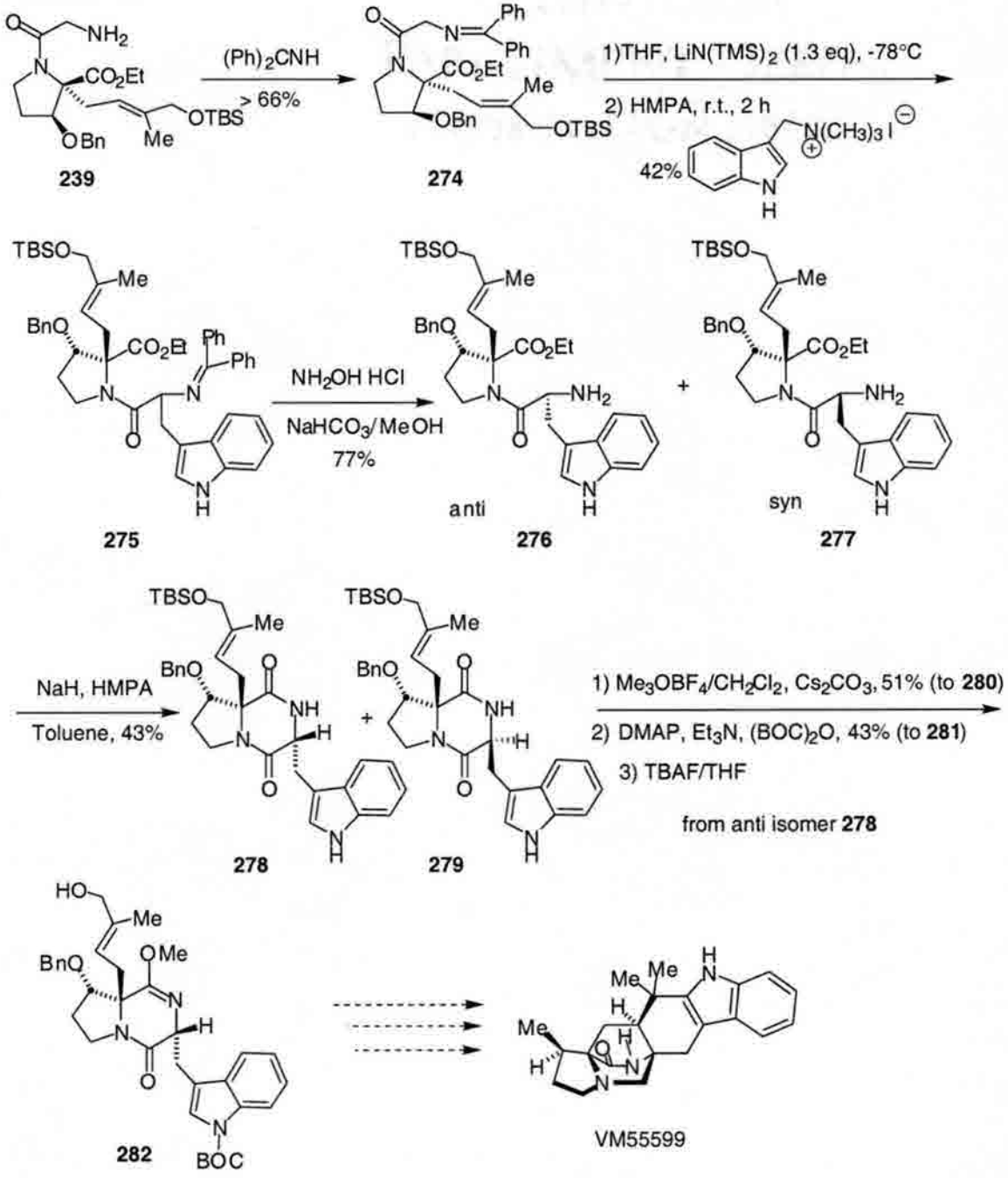
Scheme 80



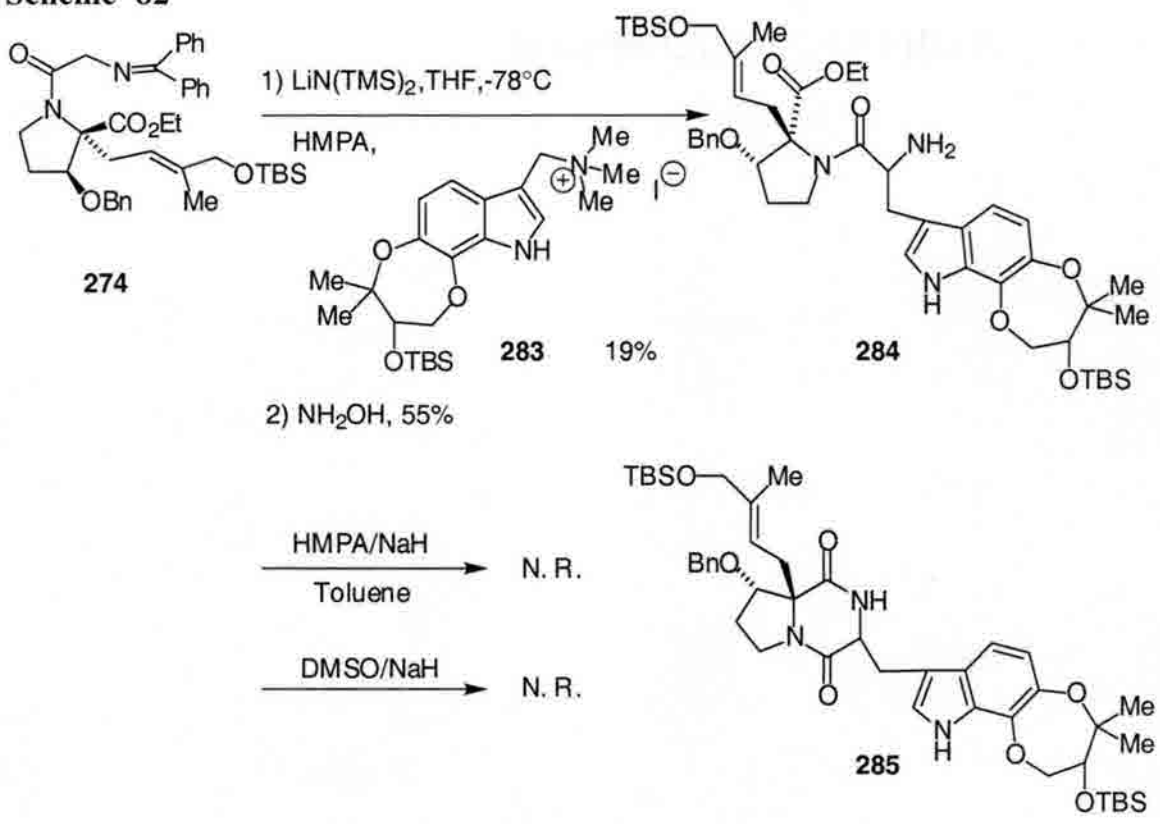
Next, we decided to synthesize compound **70** by alkylation of compound **76** with gramine derivative **60** before ring closure to the DKP system. First, a model study was carried out (Scheme 81). Primary amine **239** was reacted with diphenyl imine[65,66] to give the proline derivative **274**. Compound **274** was treated with $LiN(TMS)_2$ in THF/HMPA at –78 °C, and then gramine methiodide was added at room temperature. After 2 h, the desired product **275** was obtained as a diastereomeric mixture in 42% yield. The *anti*-and *syn*-free amines **276** and **277** were obtained by deprotection of the diphenylimine with hydroxylamine.[67,68] Compounds **276** and **277** were treated with NaH in toluene/HMPA repectively to give the *anti*-isomer **278** and the *syn*-isomer **279**. The major *anti*-isomer **278** was converted into the lactim ether **280** followed by protection of the indole nitrogen as its t-BOC derivative, and TBAF-promoted t-butyldimethylsilyl ether deprotection to give lactim ether-alcohol **282**. Compound **282** was a proposed intermediate for the stereocontrolled asymmetric synthesis of VM55599[13a,b], a structurally similar alkaloid to (-)-paraherquamide A. The approach shown here is a new method for the coupling reaction between a complex proline derivative and a tryptophan in order to form a diketopiperazine like **278** and **279**. For the formation of **275**, the Somei/Kametani reaction condition was also used on substrate **274**, but the desired compound **275** was obtained in lower yield with a longer reaction time. The stereochemical assignment for amines **276/277** and diketopiperazines **278/279** were based on similar intermediates made during the synthesis of breviamide B, (+)-paraherquamide B, and Kishi/Hutchison's work[70]. The *syn*-DKP **279** is more polar (lower Rf) and *anti*-DKP **278** is less polar (high Rf). The relative

polarity of the *syn* and *anti* diastereomers are the same as those of the corresponding proline–containing diketopiperazines (DKP). Westly and coworkers[71] found that of various DKPs, the *syn*-isomer is the most polar, and the *anti*-isomer was the least polar on the TLC system. Additional evidence supporting these structural assignments will be discussed in the actual synthesis of (-)-paraherquamide A.

Scheme 81



Scheme 82



Following the synthetic route of the model system, the synthetic approach to (-)-paraherquamide A was devised as shown in Scheme 82. Gramine derivative **60** reacted with methyl iodide in THF to provide **283** in almost quantitative yield. Diphenyl imine derivative **274** was treated with $LiN(TMS)_2$ at –78 °C in a solvent system of THF/HMPA to provide the enolate intermediate, which was coupled with **283** to give a diphenyl imino dipeptide in 19% yield. Deprotection of the diphenyl imino group with hydroxylamine produced amine **284** in 55% yield. Compound **284** was then subjected to the standard cyclization conditions successfully used in the other diketopiperazine-forming reactions (HMPA/toluene/NaH, at room temperature or reflux), but there was no reaction. Other conditions such as DMSO/NaH were also tried, and again there was no reaction. The only difference between amine **284**, and amine **276** (*anti*-isomer), is that **284** has a t-butyldimethylsilyl (TBS) ether protected dioxepin ring fused to the indole ring. First, we believed that the TBS group was quite large, and this may force the molecule (**284**) to adopt a stable conformation that can not cyclize to the desired diketopiperazine. When the

intermediate without the TBS ether protecting group was treated with the same cyclization conditions, no reaction occurred. Due to the difficult cyclization reaction and the low yield (19%) coupling reaction between compounds **274** and **283**, the cyclic dipeptide formation approach from the acyclic dipeptide was abandoned.

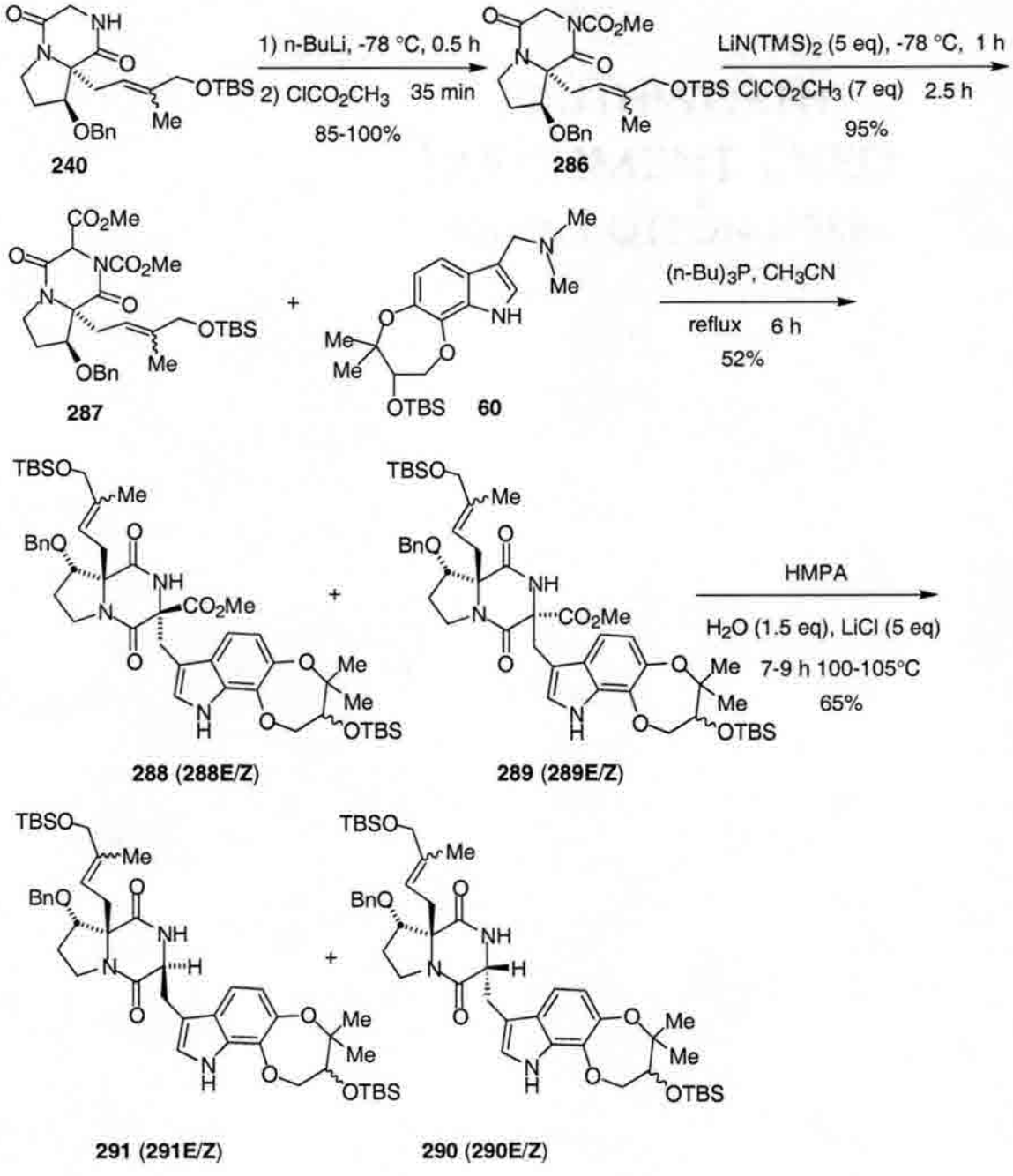
2.32 The Coupling between Benzyl Ether Substituted DKP and Gramine Derivative via Somei/Kametani Coupling Reaction

Benzyl ether substituted DKP **240** is the first candidate to undergo the Somei/Kametani coupling reaction. At the initial stage of planning for the synthesis of (-)-paraherquamide A, both benzyl ether and MOM ether protecting groups were carefully examined (including their stability towards all possible reaction conditions and the method of introducing and removing them). The benzyl ether group became our first choice due to its ease of introduction, stability to a variety of reaction conditions and its unique and neutral deprotection method. The only disadvantage of this protecting group is its steric bulkiness relative to the hydrogen atom found in (+)-paraherquamide B, and we want the protecting group to be as small as possible in order to mimic the steric environment of the intermediates used in the synthesis of (+)-paraherquamide B. The synthetic approach using benzyl ether DKP **240** is illustrated in Scheme 83.

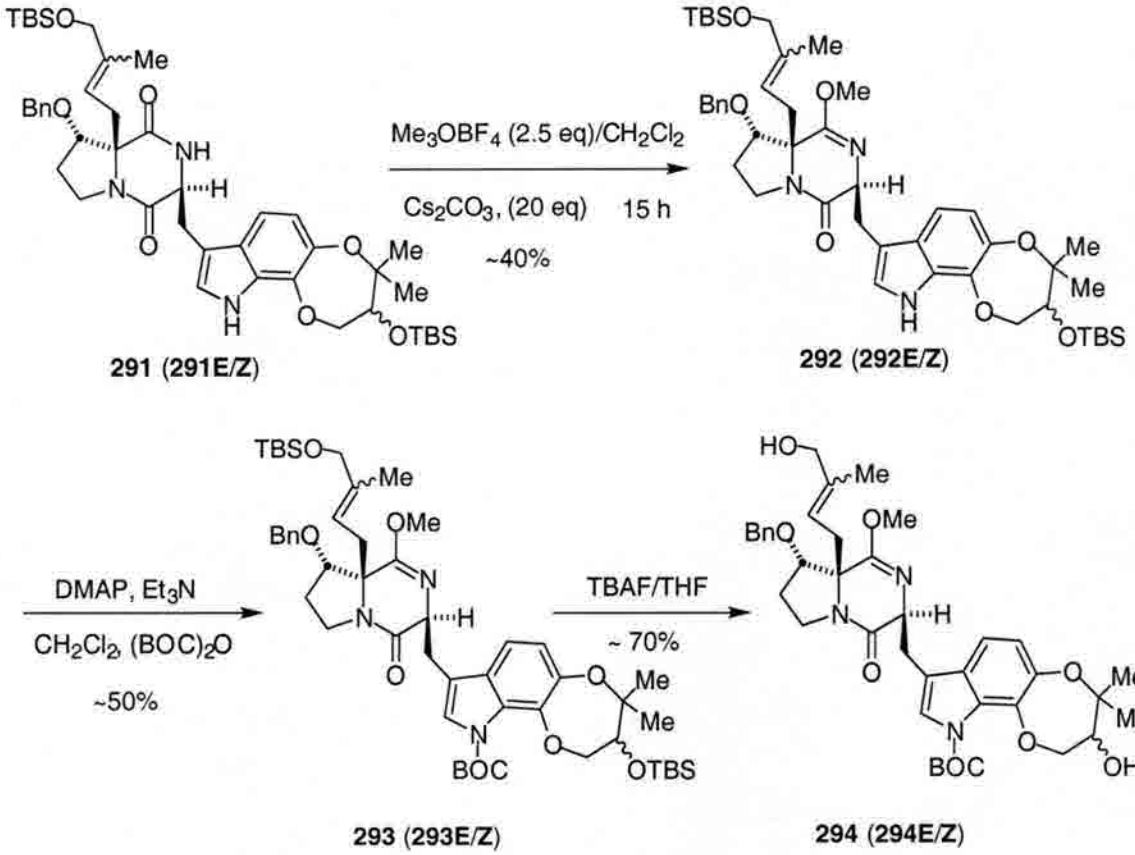
The amide nitrogen of **240** was protected with a methoxycarbonyl group to provide **286** in 85-100% yield. When **286** was treated with $LiN(TMS)_2$ (5 eq) at –78 °C and reacted with methyl chloroformate (7 eq), a second methoxycarbonyl group was introduced at the α-position of the glycine moiety in **286** to give **287** with the newly created chiral center as a single stereoisomer (as a mixture of E/Z isomers) which was confirmed by ^1H and ^{13}C NMR. Compound **287** was then reacted with gramine derivative **60** in the presence of Bu_3P (in refluxing CH_3CN for 6 h, 52%) to provide the *syn*-isomer **288** (a mixture of four diastereomers, E/Z and R/S) and the *anti*-isomer **289** (a mixture of four diastereomers) in a 3.3:1 ratio. The stereochemical assignment of **288** and **289** was based on their mobilities on TLC, the major less polar compound **288** possessing the *syn*-

configuration (but the allylic group is *anti* to the large indole ring, so **288** is less polar) and the minor more polar compound **289** being the *anti*-configuration.

Scheme 83



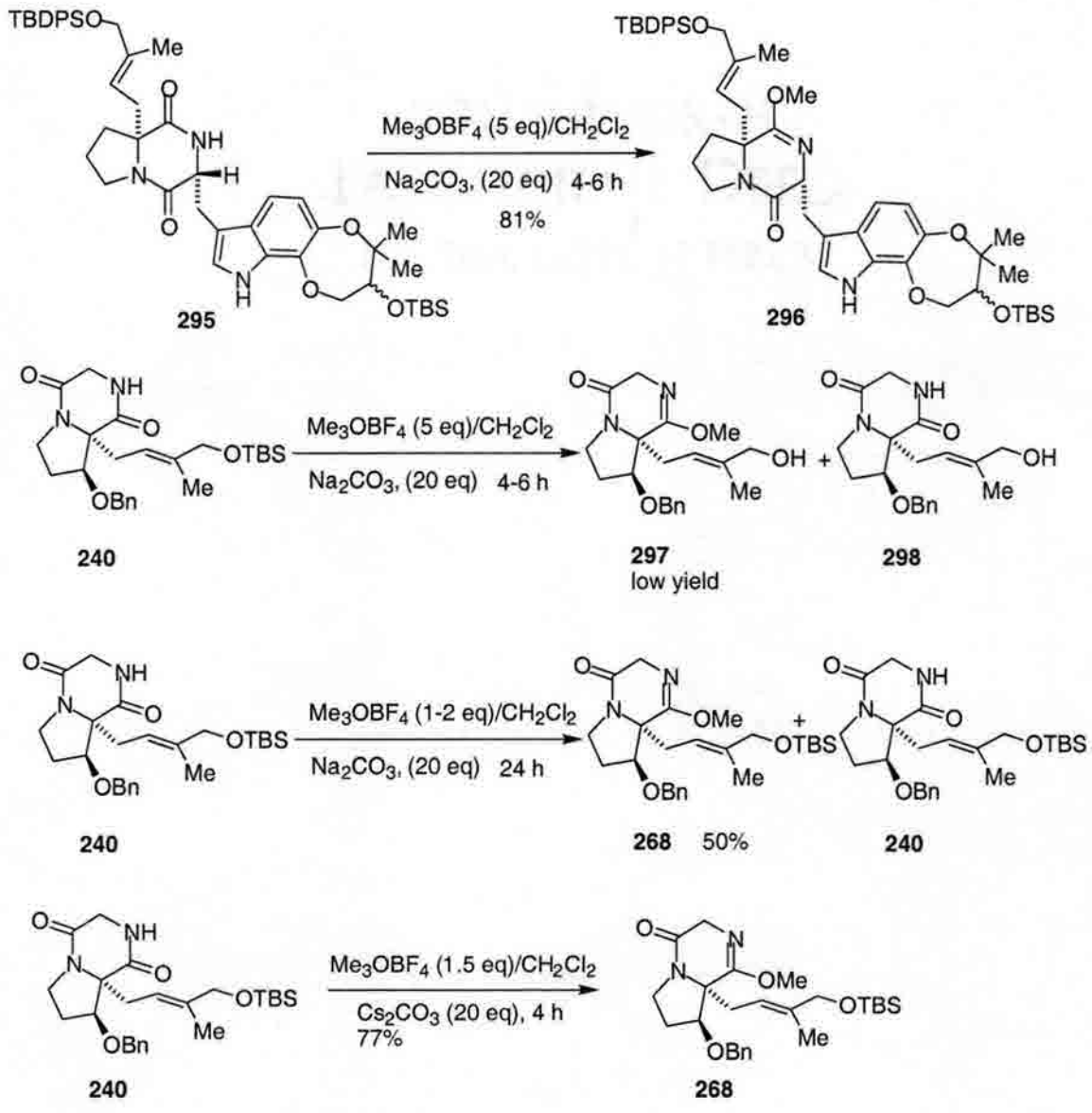
Scheme 84



Although compound **288** was a mixture of four diastereomers and the ^{1}H and ^{13}C NMR were complex, the high resolution mass spectrum (HRMS, FAB^{+}) displayed the correct molecular mass. Both *syn*-and *anti*-isomers **288** and **289** smoothly underwent decarbomethoxylation [HMPA, H_2O (1.5 eq), LiCl (5 eq), 100-105 °C, 7-9 h] respectively to provide DKP **290** and **291** in a 1:1.6 ratio in 65% yield. The same result can be obtained for this reaction if a mixture of **288** and **289** were used. The stereochemical assignment of **290** and **291** were again based on their mobilities on TLC, the major more polar compound **291** possessing the *syn*-configuration, and the minor less polar compound **290** being the *anti*-configuration. The *syn*-isomer **291** was then treated with Me_3OBF_4 (2.5 eq) [CH_2Cl_2, Cs_2CO_3 (20 eq)] to give a spot on TLC which had the exact same R_f as the starting material **291** (Scheme 84). Several solvent systems were used (including EtOAc:hexane, CH_2Cl_2:MeOH and CH_2Cl_2:Et_2O), but we did not achieve

any separation for the possible products and the starting material. ^{1}H NMR indicated that the spot was a mixture of desired lactim ether **292**, starting material **291** (**292**:**291**/~1:0.6) and some amide N-methylation product. Compound **291** was also treated with Me_3OBF_4 (5.0 eq) [CH_2Cl_2, Na_2CO_3 (20 eq)], under the condition used successfully in the synthesis of (+)-paraherquamide B. However, the results were even worse. Considering the E/Z isomers, this spot is a mixture of twelve components. The subsequent protection of the indole nitrogen was accomplished by the reaction of **292** with $(BOC)_2O$ (DMAP, CH_2Cl_2, Et_3N) in about 50% yield. Since the starting material was a mixture, the obtained **293** was also a mixture of the desired O-methylation and N-methylation compounds. Deprotection of both TBS ether groups with TBAF provided **294** as a mixture of many compounds. ^{1}H NMR and MS showed the product mixture contained the desired compound. Clearly, the lactim ether formation step was a major problem and can not be used in the total synthesis. Apparently, the Me_3OBF_4 reagent is the best choice[72] for this kind of transformation. Other reagents such as Me_2SO_4 are too harsh for the sensitive indole and lactim ether moiety and employing Me_2SO_4 may also produce amide N-methylation products[73]. Usually, the N- and O-methylation products are inseparable or very close in mobility on TLC. From our experience of working with the lactim ether formation reaction using Me_3OBF_4, the results strongly depend on the substrate. Usually you can obtain the desired product quickly in moderate to very good yield with trace amount of starting material remaining and no N-methylation. At other times, there is always a certain amount of starting material remaining no matter how many equiv. of Me_3OBF_4 are used and how long the reaction is run. If these substrates contain functional groups which are labile to Me_3OBF_4, too much Me_3OBF_4 and longer reaction time will usually cause the starting material or product to decompose. Some typical reaction conditions are listed in Scheme 85.

Scheme 85



During the synthesis of (+)-paraherquamide B, **296** was obtained from **295** in 81% yield under the conditions of Me_3OBF_4 (5 eq) and Na_2CO_3 (20 eq) in CH_2Cl_2 for 4-6 h. When the same conditions was applied to compound **240**, the obtained products were the desilylated **240** (**298**) and desilylated lactim ether **297** in low yield, and if less Me_3OBF_4 (1-2 eq) was used, there was starting material remaining even after 24 h. We finally found that Cs_2CO_3 was a much better buffering reagent than Na_2CO_3. Compound **240** smoothly underwent lactim ether formation with 1.5 equiv. of Me_3OBF_4 and Cs_2CO_3

(20 eq) in CH_2Cl_2 within 4 h in 77% yield, with only a trace amount of starting material remaining. Compound **280** was obtained in 51% yield without starting material remaining (Scheme 81). There are several factors that may be responsible to the better performance (high yield, much less cleavage of TBS-ether functional group, less favoring the formation of N-methylation product) for Cs_2CO_3. HBF_4, produced during the formation of lactim ether functional group, is the cause for the cleavage of TBS-ether group. Cs_2CO_3 is a much stronger base than Na_2CO_3 and can quickly react with HBF_4. Therefore the cleavage of TBS-ether group is decreased dramatically. The proton at the amide group can be pulled away much easier by Cs_2CO_3 and this may be responsible for the higher yield of the desired product. The Cs^+ ion has a larger radius than Na^+ ion. The oxygen anion in the O^--Cs^+ ion pair is looser than that in O^--Na^+ ion pair. Therefore the oxygen anion in the former is harder and reacts fast with a harder reagent like Me_3OBF_4, favoring the formation of O-methylation product.

2.33 The Coupling between the MOM Ether Substituted DKP and Gramine Derivative via Somei/Kametani Coupling Reaction

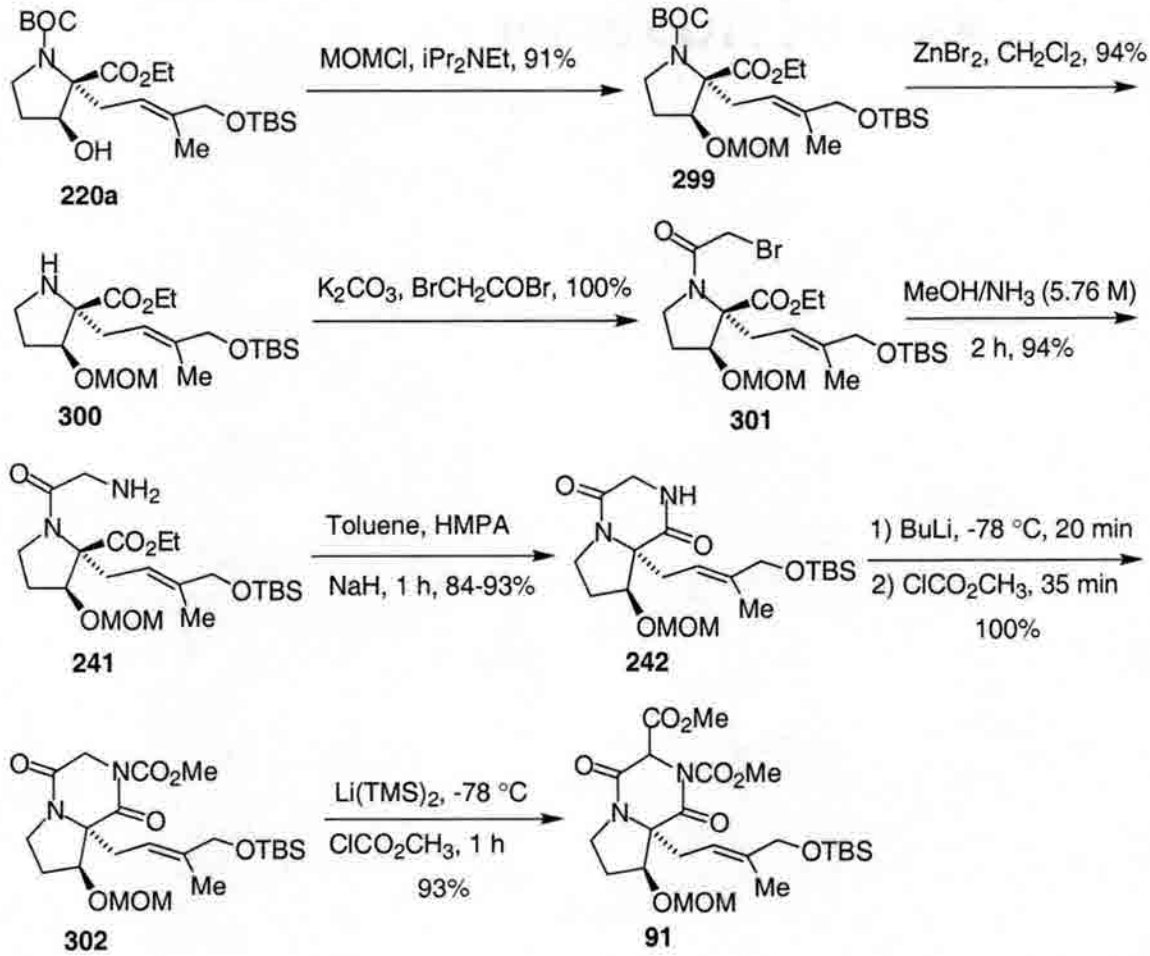
The Successful Synthesis of (-)-Paraherquamide A

At this point, due to the failed lactim ether transformation of **291** to **292**, we decided to examine the MOM ether-protected substrates **305/306** (Scheme 87). Our reasoning was that the MOM ether group is more polar than the benzyl ether group, and the corresponding lactim ether product may have a different R_f from the starting material. Also the lactim ether formation reaction using Me_3OBF_4 usually varies with different substrates, and changing to a different substrate may produce a better result.

The MOM ether protected diketopiperazine **91** was synthesized from **220a** (Scheme 86). Treatment of alcohol **220a** with MOMCl and iPr_2NEt in CH_2Cl_2 provided the MOM ether ester **299** in 91% yield, which was then reacted with $ZnBr_2$ in CH_2Cl_2 to give amino ester **300** in 94% yield. Subsequent reaction of **300** with bromoacetyl bromide afforded bromide **301** in quantitative yield. Aminolysis of **301** with ammonia in MeOH

(5.76 M) provided the amino ester **241** in 94% yield. The resulting compound **241** was converted into the MOM ether DKP **242** in 84-93% yield. Amide nitrogen protection was carried out by treatment of **242** with n-BuLi at -78 °C followed by addition of methyl chloroformate to give **302**, and further introduction of a second methoxycarbonyl group (THF, $LiN(TMS)_2$, -78 °C, $ClCO_2CH_3$, 1 h) resulted in the desired MOM ether protected DKP **91** as a mixture of E:Z isomers, with the newly created chiral center as a single stereoisomer.

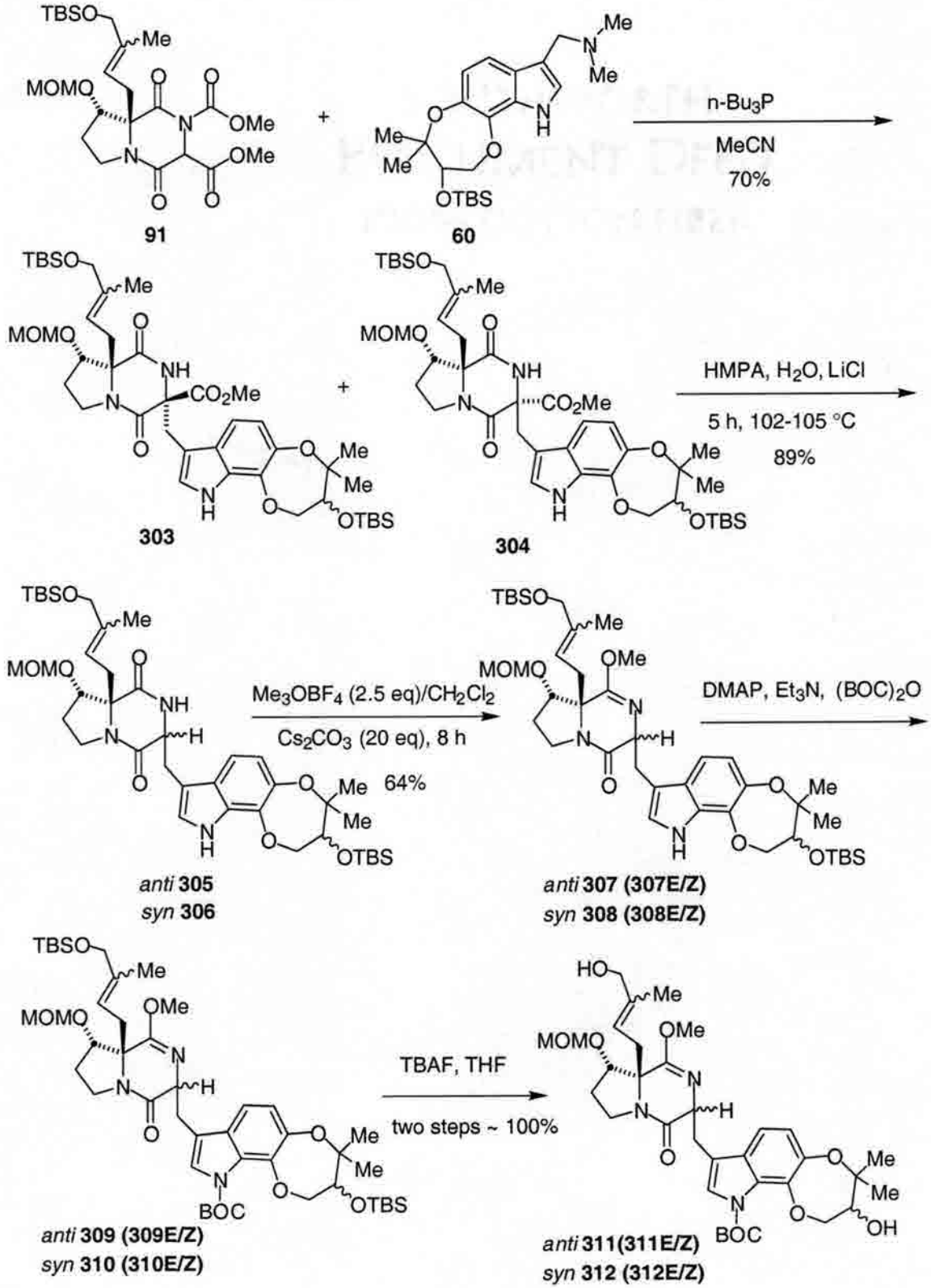
Scheme 86



At this point, we were ready for the coupling reaction (Scheme 87). The Somei/Kametani reaction between compounds **60** and **91** provided the *syn*-isomer **303** (high R_f, as a mixture of four diastereomers) and the *anti*-isomer **304** (lower R_f, as a mixture of four diastereomers) in a 3.1:1 ratio in 70% yield. Decarbomethoxylation of

303 and **304** were carried out respectively to give, with the same results, four separable diastereomers **305Z**, **305E**, **306Z** and **306E** in a combined 89% yield, and each of these is a mixture of two diastereomers (epimeric at the dioxepin 2° alcohol carbon). This reaction was reproducibly run on a 1 g scale. If more than 1 g of **303** or **304** was used, or the external reaction temperature was greater than 104-105 °C, or the reaction lasted longer than 5 h, a by-product was formed in 20% yield. This by-product was deprotection of only the primary TBS ether moiety. One can convert the by-product into the desired product by standard TBS ether formation protocol. In order to ensure the right amount of water (1.5 eq) was added, a stock solution of water in HMPA was always used. Next, we were ready to test the important key lactim ether-forming reaction. Compounds **306E/Z** underwent lactim ether formation smoothly to provide the desired compound **308E/Z** in 57-64% yield (86% yield based on recovered **306E/Z**) under the conditions of Me_3OBF_4 (2.5 eq) and Cs_2CO_3 (20 eq) in CH_2Cl_2 for 8 h or overnight with about 30% starting material remaining. There was neither N-methylation, nor TBS ether cleavage observed. The desired product has a mobility higher than the starting material, and therefore the reaction process can be monitored by simple TLC. The advantage for this reaction is that the remaining starting material can be easily separated on a short flash column and can be recycled to give the desired lactim ether. This reaction has been run on a 1.5 g scale without problem. Literature precedent[74] reveals that the stability of the MOM ether group is marginal to Me_3OBF_4 and may be cleaved. Fortunately, all four substrates **305E/Z** and **306E/Z** are stable to Me_3OBF_4 when used individually or as a mixture of **305E/Z** or **306E/Z**.

Scheme 87

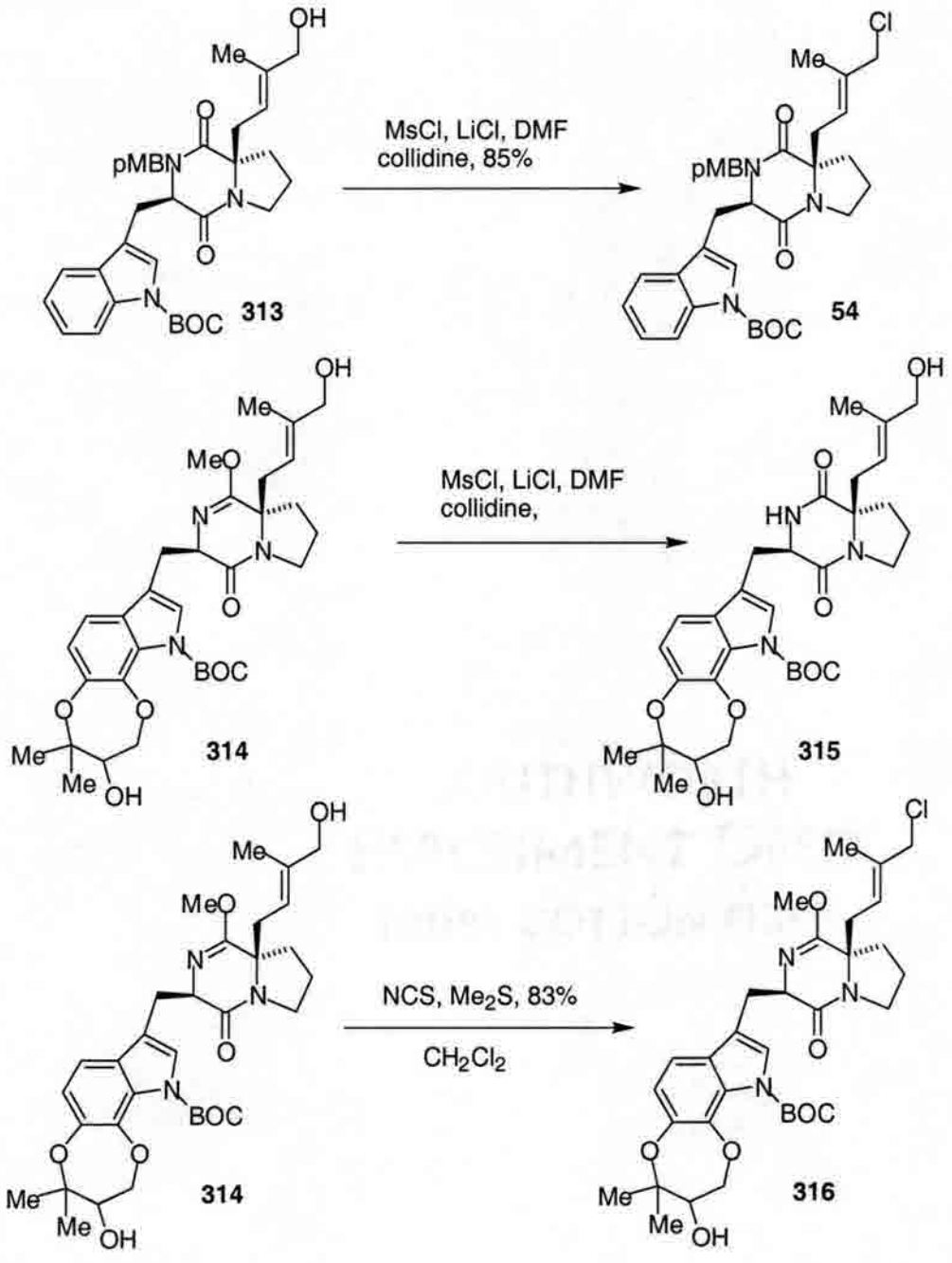

TBSO
Me
MOMO
OMe
OMe
91
60
n-Bu3P
MeCN
70%
303
304
HMPA, H2O, LiCl
5 h, 102-105 °C
89%
Me3OBF4 (2.5 eq)/CH2Cl2
Cs2CO3 (20 eq), 8 h
64%
DMAP, Et3N, (BOC)2O
anti 305
syn 306
anti 307 (307E/Z)
syn 308 (308E/Z)
TBAF, THF
two steps ~ 100%
anti 309 (309E/Z)
syn 310 (310E/Z)
anti 311(311E/Z)
syn 312 (312E/Z)

Herein we wish to discuss the stereochemical assignment of the lactim ether isomers **307E/Z** and **308E/Z**. We previously assigned our proline-containing DKP compounds based on their mobility on TLC. The *anti*-isomer is less polar and the *syn*-isomer is more polar by TLC. For compounds **307E/Z** (formed from **305E/Z**), we assign them as the *anti*-isomers. The ^{1}H NMRs of these *anti*-isomers have a distinct difference with those of the *syn*-isomers **308E/Z**. The methyl peaks of the MOM group are at 3.06 and 3.18 ppm for the two diastereomers of **307E** and at 3.04 and 3.17 ppm for the two diastereomers of **307Z**. However, the methyl peaks of the MOM group are at 3.31 ppm (3H, s) for the *syn*-isomers **308E/Z**. The methyl peaks of *anti*-isomer **307E/Z** appear at a higher field than that of *syn*-isomers **308E/Z**. This observation can be explained by their structural difference. The methyl group of the MOM ether in the *anti*-isomers **307** (**307E/Z**) is on the same face and close to the dioxepin-indole ring, and is shielded by the dioxepin-indole ring. Therefore, they appear at higher field. For the *syn*-isomer **308E/Z**, the dioxepin-indole ring is on the opposite face to the MOM ether group, and the methyl group of MOM ether is not shielded by the dioxepin-indole ring and appears at a lower field at 3.31 ppm. This phenomena appears for all the compounds (prior to S_N2') containing the lactim ether moiety. In summary, the stereochemical assignments for the DKP intermediates based on the their TLC mobility are correct and consistent with the ^{1}H NMR evidence.

Protection of the indole nitrogen for **307** and **308** was straightforward and provided the corresponding products in >95% yield (Scheme 87). Usually, **308E/Z** were converted directly to diols **312E** and **312Z** by a two-step one pot process in 95~100% yield. Sometimes more than 5 equiv. of TBAF were needed to completely convert **310** to **312** when the reaction was conducted on a 1 g scale. In the decarbomethoxylation step, *anti*-isomers **305Z** and **305E** can be separated easily by flash column chromatography. However, the separation of the *syn*-isomers **306E** and **306Z** was much more difficult.

Instead, they were converted to the diols **312E/Z**, and these two compounds can be separated by radial chromatography on a 1 g scale.

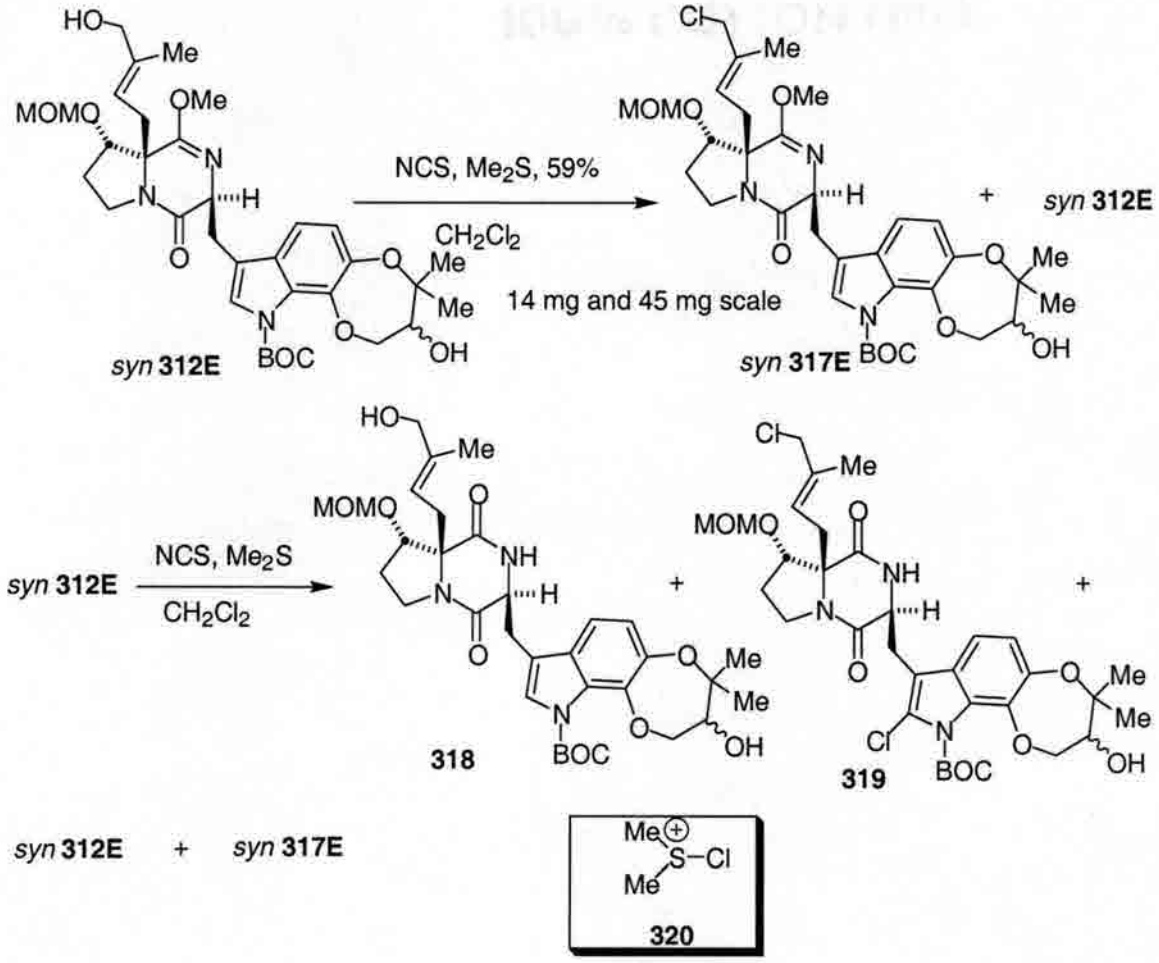
Scheme 88



The allylic chloride formation step, such as the formation of **317** or **316**, is one of the most difficult transformations in both the synthesis of (+)-paraherquamide B and (-)-paraherquamide A (Scheme 88). During the synthesis of (-)-brevianamide B, the Meyers

procedure[75] (DMF, MsCl, LiCl, Collidine) was used successfully for the synthesis of **54** from **313** (Scheme 88). However, for (+)-paraherquamide B intermediate **314**, the same procedure only led to the lactim ether-cleaved product **315**. Cushing also tried several alternative routes to synthesize **316**, but they all failed. Finally, this problem was solved by embracing the procedure of Corey[76], essentially a modified Corey-Kim oxidization but without the base. Compound **316** was obtained in 81% yield (based on recovered starting material).

Scheme 89



Here is a quote about using the Corey-Kim procedure from Cushing's thesis " however, this reaction was somewhat problematic. It was extremely sluggish. On a large

scale it had to be stirred all day at –23 °C and then placed in the freezer (~ -35 °C) and stirred for an additional period. If the reaction mixture was placed in the freezer one more night total decomposition would result ".

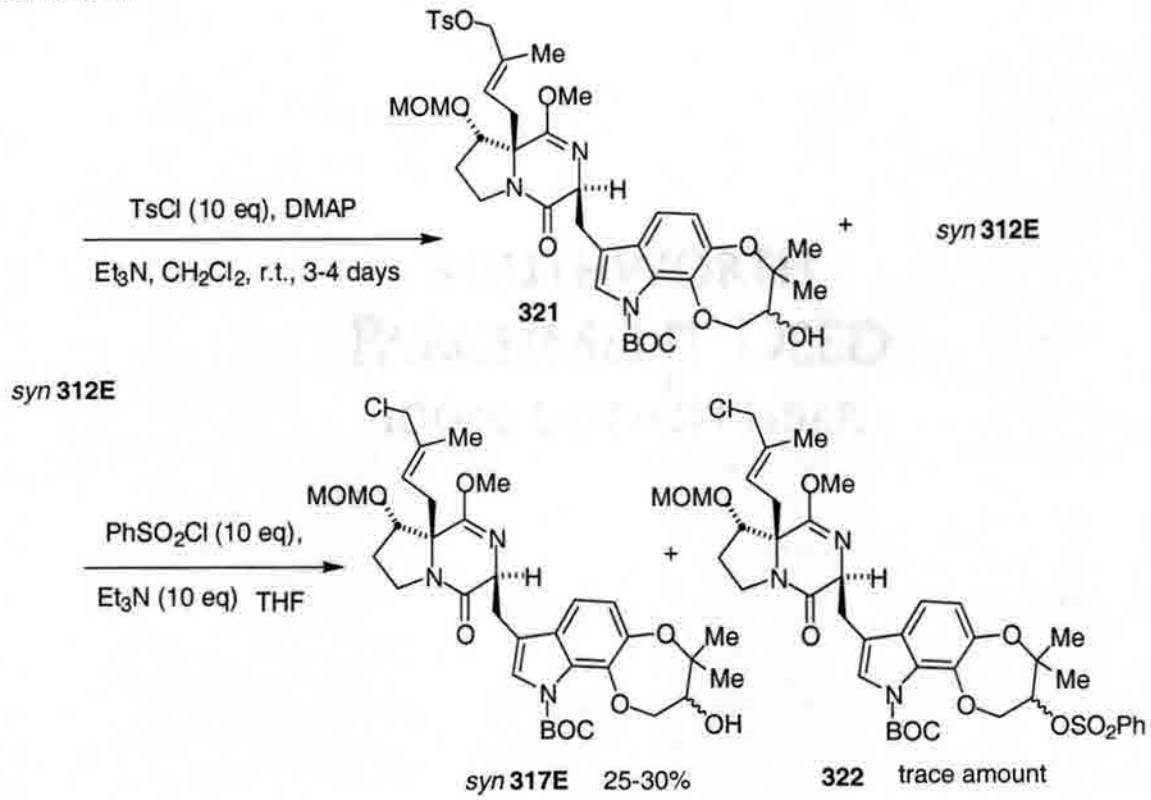
When the same Corey-Kim procedure was used for diol **312E** (Scheme 89), there were two reactions which gave good results (14 mg and 45 mg scale). For all other cases, small or large scale, a complex mixture was produced including the starting material, the lactim ether moiety-cleaved starting material **318**, the desired product **317E** and an unusual dichloro intermediate **319**. A yellow-orange oily mixture was always obtained without exception. Compound **319** was presumably formed from the reaction of the highly electron-rich indole moiety with the intermediate **320**. The structure of **319** was rigorously confirmed by ^{1}H NMR, IR and HRMS. We also purified the NCS by recrystallization from H_2O, AcOH or benzene and redistilled DMS from sodium. However, compound **319** was always produced as a nearly inseparable spot on TLC from the desired compound **317E**.

At this point, for this type of diol, the sensitive functionalities such as t-BOC group, electron-rich indole and lactim ether, the allylic chloride formation proved to be a major obstacle. We decided to do a methodology investigation. According to a literature procedure[77], diol **312E** was treated with TsCl, DMAP and Et_3N in CH_2Cl_2 for 3-4 days at room temperature, in hopes of producing the allylic chloride **317E** (Scheme 90). Instead, the product obtained was the tosylate **321** and about half of the starting material was recovered. Phenyl sulfonate was expected to be more reactive and be displaced by chloride anion more easily to generate the allylic chloride. Diol **312E** was reacted with $PhSO_2Cl$ (10 eq) and Et_3N (10 eq) in THF to provide the desired allylic chloride **317E** in 25-30% yield with a trace amount of **322** formed. Although this reaction went from spot to spot, for some unknown reason, the yield was low. At this time, we had depleted our supply of compound **312E** and had 240 mg of **312Z**, which was then used as the starting material for studying the allylic chloride-forming reaction. From our previous examples,

we knew that the allylic phenylsulfonate is not stable and can be displaced by the Cl^- in THF. The allylic mesylate is even less stable and may be used as an intermediate to synthesize the desired allylic chloride. The first example of this idea was conducted by treating **312Z** with MsCl (2 eq) and Et_3N (4 eq) in CH_2Cl_2 for 24 h at room temperature. Work-up gave two products, one is the allylic chloride-mesylate **323**, the other is the desired allylic chloride **317Z** in a 11:1 ratio. In order to decrease the formation of **323**, less MsCl (1 eq) and Et_3N (2 eq) in CH_2Cl_2 (at 0 °C for 10 h, then r.t. for 24 h) were used, and gave a mixture of **317Z/312Z** in a 29:22 ratio in 75% yield based on the recovered starting material **312Z**.

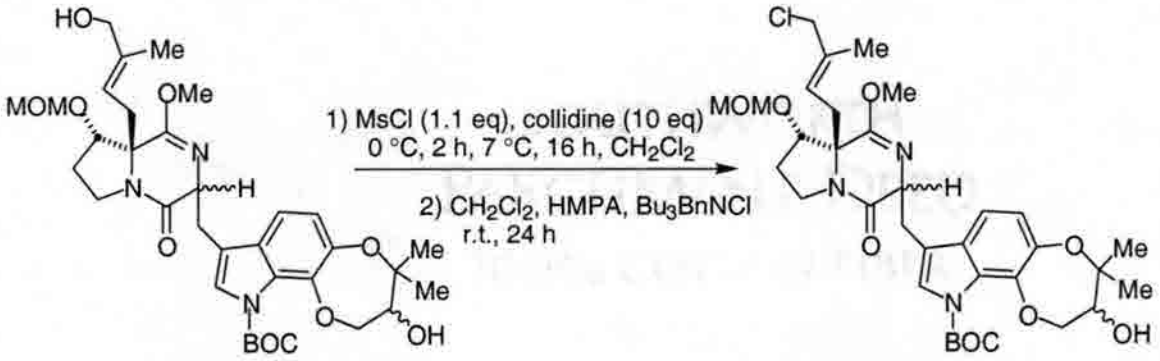
Due to the by-product **323** formation, we did a literature search in order to solve this selective mesylation problem. In 1998, Burke et al.[78] published a paper entitled " Selective Mesylation of Vicinal Diols: A Systematic Case Study." In this paper, they stated " It is known that the reaction of methanesulfonyl chloride with Et_3N results in a very reactive sulfene intermediate, which is unlikely to be kinetically selective. The increased selectivity observed with Hunig's base can be attributed to its lower basicity, thus generating less of the reactive sulfene intermediate." We modified their best conditions to test diol substrate **312E** (Scheme 91). The base was changed from Et_3N to a large excess of a more hindered base collidine, the reaction was run at 0 °C and at low concentration (0.05 M), in hopes of decreasing the formation of the by-product dimesylate.

Scheme 90


TsO
Me
MOMO
OMe
N
H
O
TsCl (10 eq), DMAP
Et3N, CH2Cl2, r.t., 3-4 days
+
syn 312E
321
BOC
OH
Me
Cl
PhSO2Cl (10 eq),
Et3N (10 eq) THF
OSO2Ph
syn 317E 25-30%
322 trace amount
condition*
syn 312Z
323
OMs
syn 317Z
condition* MsCl (2 eq), Et3N (4 eq) CH2Cl2, r.t., 24 h
MsCl (1 eq), Et3N (2 eq)
CH2Cl2, 0 °C, 10 h
r.t., 24 h
75%
syn 317Z + syn 312Z 29:22
MsCl (1.5 eq), Et3N (3 eq)
CH2Cl2, r.t., 24 h
syn 317Z + syn 323 45:60

To a solution of **312E** in CH_2Cl_2 at 0 °C was added collidine (10 eq) and MsCl (1.1 eq), and the reaction mixture was stirred at 0 °C for 2 h and at 7 °C for 17 h, the desired allylic mesylate-OH was obtained in >90% yield, and the by-product bis mesylate in only 7% yield. Displacement of the mesylate by the Cl^- formed in-situ proceeded very slowly at 0.05 M concentration in CH_2Cl_2. This reaction should be faster if HMPA or DMF or an external Cl^- source such as Bu_3BnNCl were added because this is an ionic reaction and can be accelerated by the addition of a polar solvent. When the mesylate solution in CH_2Cl_2 was concentrated to half volume and HMPA (5.7 eq) and Bu_3BnNCl (4 eq) were added, the desired allylic chloride was produced in 90% yield in 24 h without any cleavage of the lactim ether moiety which occurred with the Meyers procedure. This procedure always gave the product as a nice white foam. The above method is a simple, practical and reproducible way to synthesize the allylic chloride compounds which have labile founctionalities.

Scheme 91

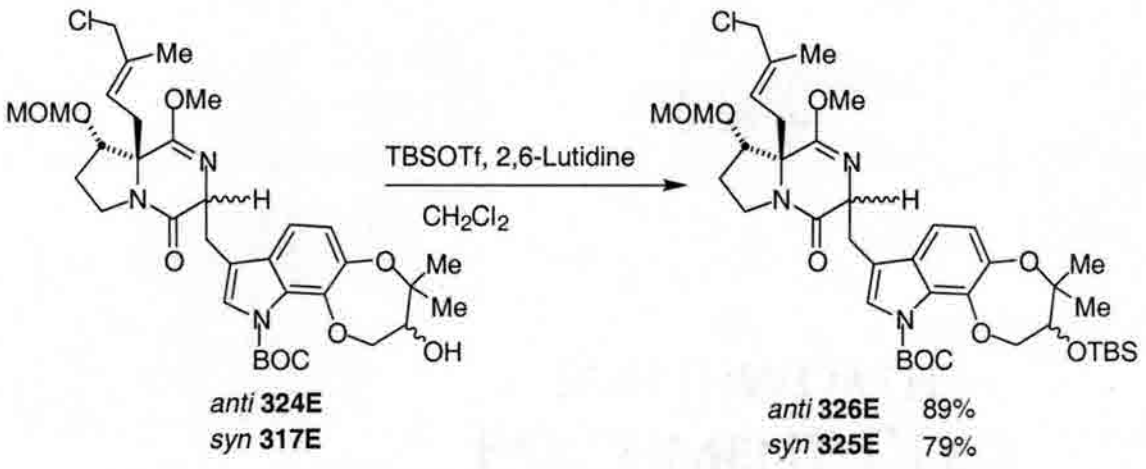


anti **311E**
syn **312E**

anti **324E** 77%
syn **317E** 90%

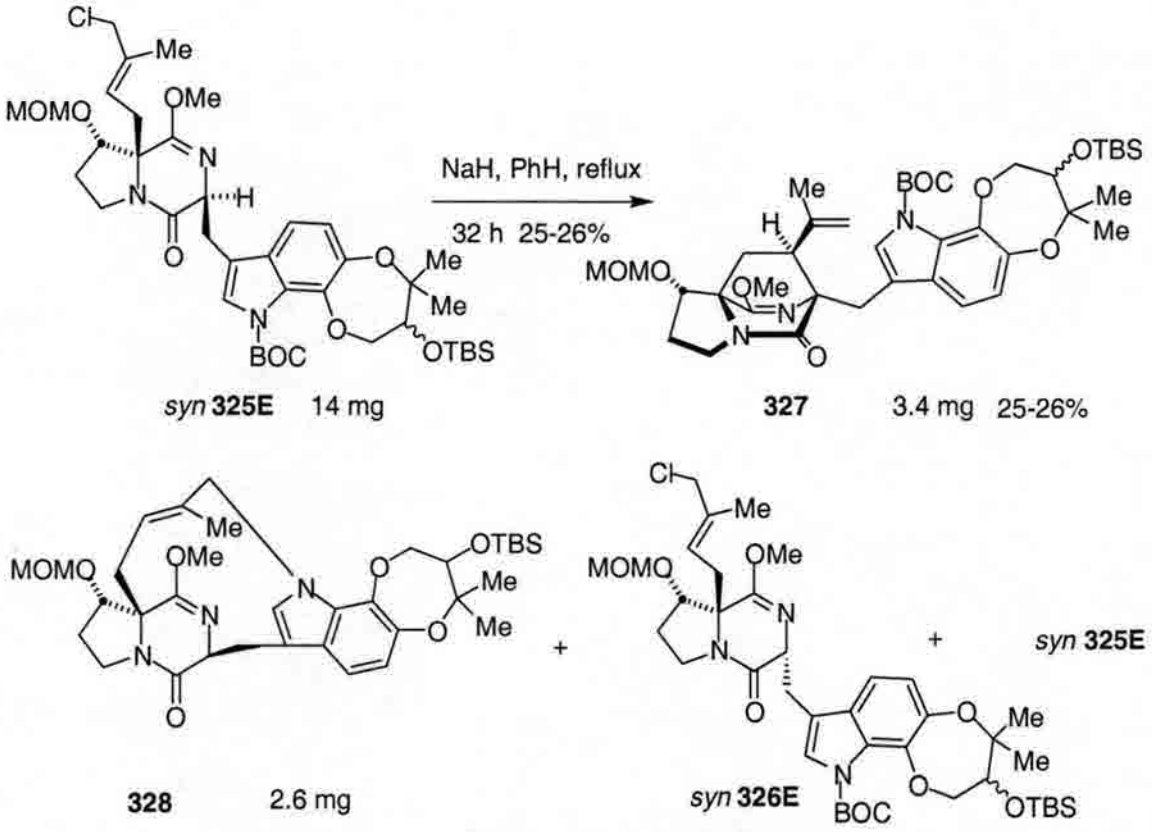
The secondary alcohols of the desired allylic chlorides were carefully reprotected with t-butyldimethylsilyl triflate to furnish the key S_N2' cyclization substrate **325E/Z** (*syn* series) and **326E/Z**.(*anti* series) (Scheme 92).

Scheme 92



S_N2' substrate **325E** (14 mg) was treated with NaH (20 eq) in refluxing benzene for 32 h (Scheme 93). Three products were obtained and less than 1 mg **325E** was recovered. Compound **327** is the desired product and macrocyclization compound **328** is the undesired product, which was formed from intramolecular alkylation of the indole nitrogen. The t-BOC group at the indole nitrogen is more labile than a t-BOC group of a normal alkyl amine under basic conditions and therefore was cleaved by extraneous hydroxide in the reaction. Compound **326E** is the diastereomer of **325E**, and this material was formed by epimerization of the stereogenic center adjacent to the lactim ether double bond. The above reaction was very sluggish and provided the desired product in very low yield (25-26%). During the synthesis of paraherquamide B, chloride **65** was treated with NaH (20 eq) in refluxing benzene and the desired product **66** was obtained in 93% yield after 6-8 h with no macrocyclization by-product formed (Scheme 19). The only difference between compound **65** and **325E** is that **325E** has a MOM ether group at the C-3 position of the proline ring, which results in a large change in reactivity. Since the MOM ether group of **325E** is on the α-face and the indole moiety is on the β-face of the diketopiperazine ring, these two groups are on opposite sides of the DKP ring and block the NaH from pulling the proton from the reactive site; therefore the reaction is very sluggish.

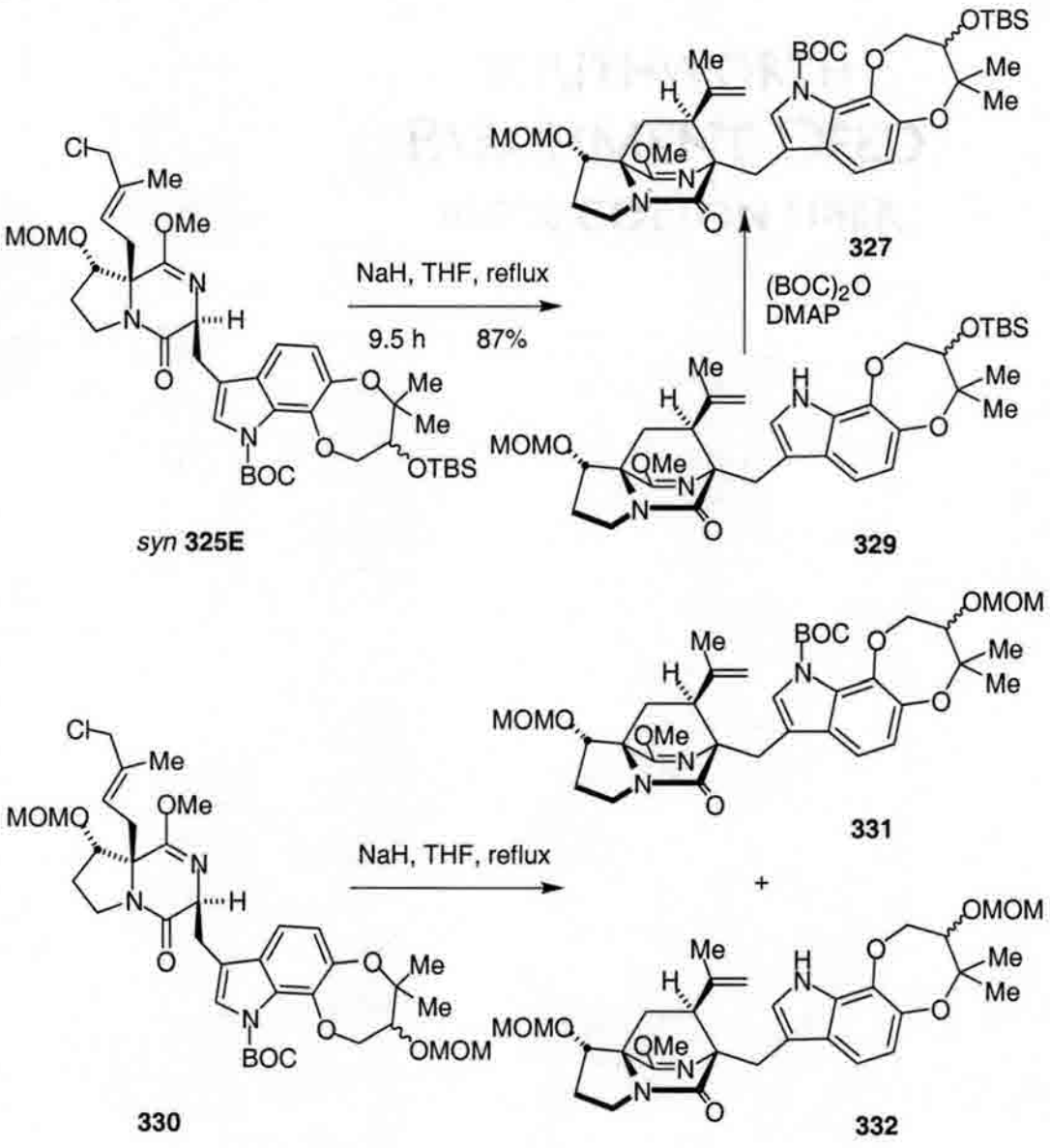
Scheme 93



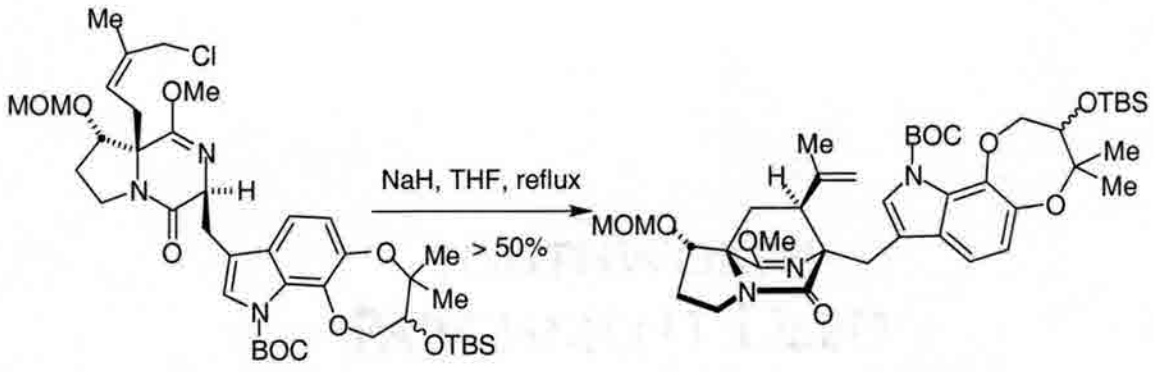
One possible explanation may be as follows: NaH in benzene may not exist as a monomer but as a cluster. This will make it difficult for the NaH to reach the reactive site. A possible solution is to use THF as the solvent to disassociate the cluster of NaH. When **325E** was treated with NaH in refluxing THF for 6 h, the desired product was obtained in 65% yield with no starting material left and no macro-cyclization by-product (Scheme 94). When this reaction was run on a large scale, the desired product was obtained in >87% yield. Occasionally , if the reaction takes longer than 9 h and is contaminated with moisture, compound **329** was obtained, which can then be converted back to **327** very easily. Bis-MOM ether compound **330** was also synthesized from **317E** in 90% yield. Under NaH/PhH conditions, there was no desired product **331** formed, and there was a tiny bit of decomposition of compound **330**. Once the solvent was changed to

THF, the reaction underwent cyclization very quickly to give the desired product **331** and some **332**.

Scheme 94



Scheme 95



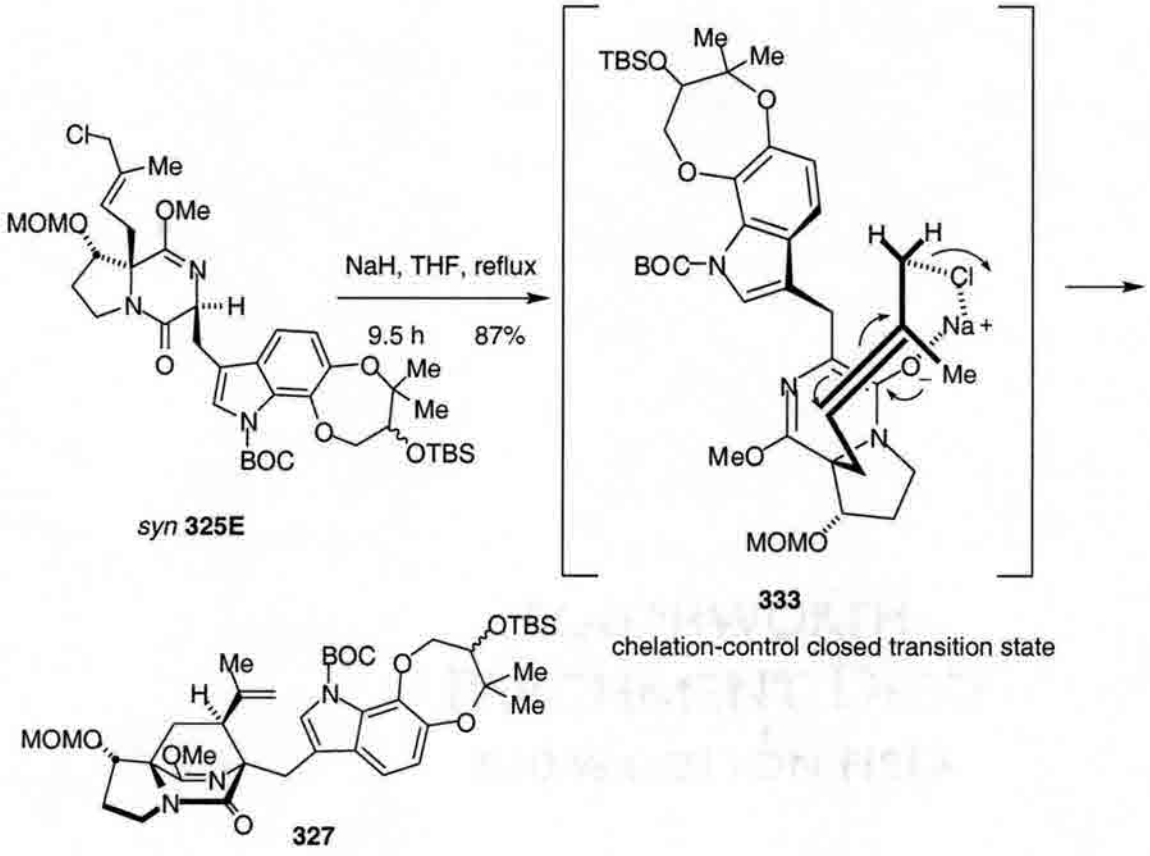
325Z **327**

Interestingly, **325Z**, the Z-isomer, and the Z-isomer of similar analogs have never been subjected to the S_N2' cyclization previously. In this case, **325Z** provided the desired cyclization product with exclusively *syn*-stereochemistry (*syn* refers to isopropenyl group and the proline nitrogen in compound **327**) identical to the E-somers (Scheme 95). Fortunately, for both *syn*-series compounds **325** and *anti*-series compounds **326**, the MOM ether group at the β-position of the proline ring did not affect the stereoselectivity of the newly created chiral center, and the result is the same as for paraherquamide B. The purity of the newly created stereogenic center was rigorously confirmed by ^1H and ^{13}C NMR.

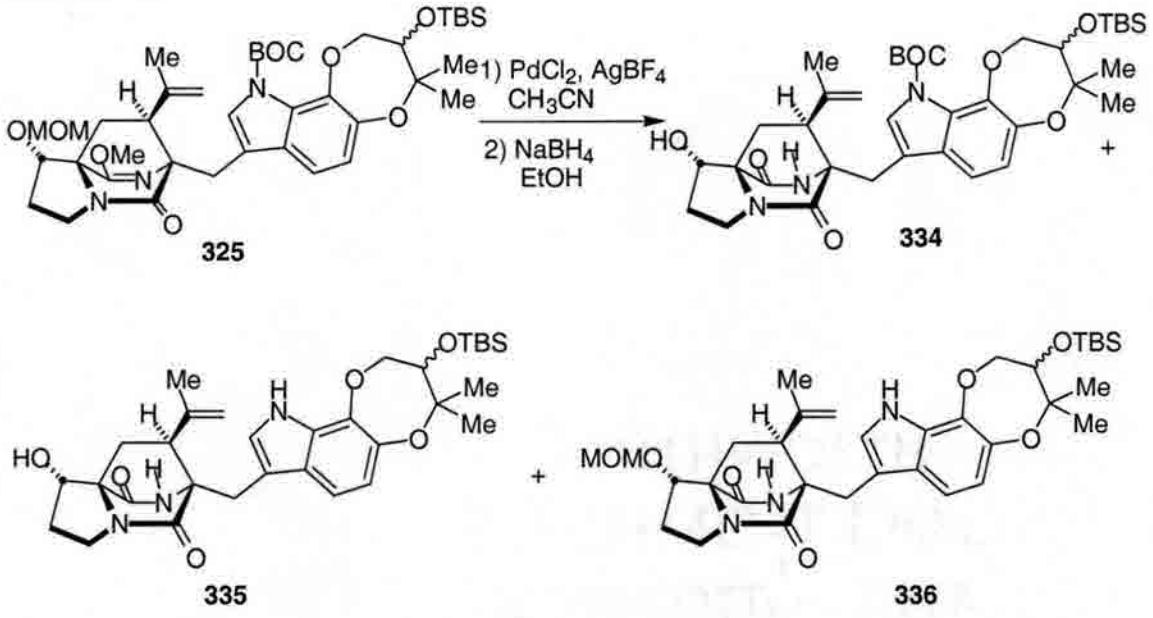
The high degree of facial selectivity observed in the cyclization from *syn*-**325E** to **327** is quite interesting and warrants some comments. It is generally accepted that S_N2' reactions favor a *syn* orientation (i.e., the incoming nucleophile attacks the π–electrons from the same face as the departing leaving group, polarizing the π–system in the proper orientation for a backside displacement on the C-Cl bond). In the synthesis of (-)-brevianamide B Williams et al.[24] found that in a polar aprotic solvent (DMF or in the presence of 18-C-6), the major product was the *exo*-(*anti*) structure, while in a nonpolar solvent (benzene) the *endo*-(*syn*) product predominated. In the synthesis of (+)-paraherquamide B, the *syn*-S_N2' product was formed exclusively in the presence of NaH under reflux in benzene. The stereochemistry outcome of the S_N2' cyclization can be

explained by whether the transition state possesses a chelation-control closed structure or not. In the presence of DMF or 18-C-6, the chelation-control closed structure (transition state) (like **333**) was forced to open to form a *exo*-open transition state structure, that would lead to the formation of *anti*-product, while in the presence of benzene or THF the chelation-control closed structure (transition state) can exist and would lead to the formation of the *syn*-product (Scheme 96).

Scheme 96

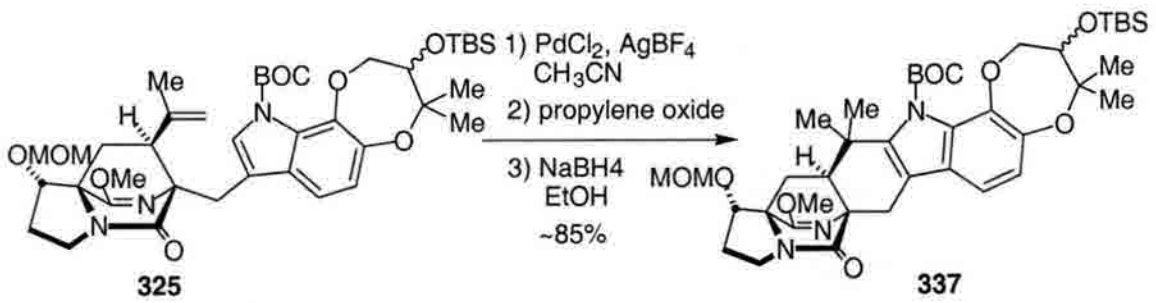


Scheme 97



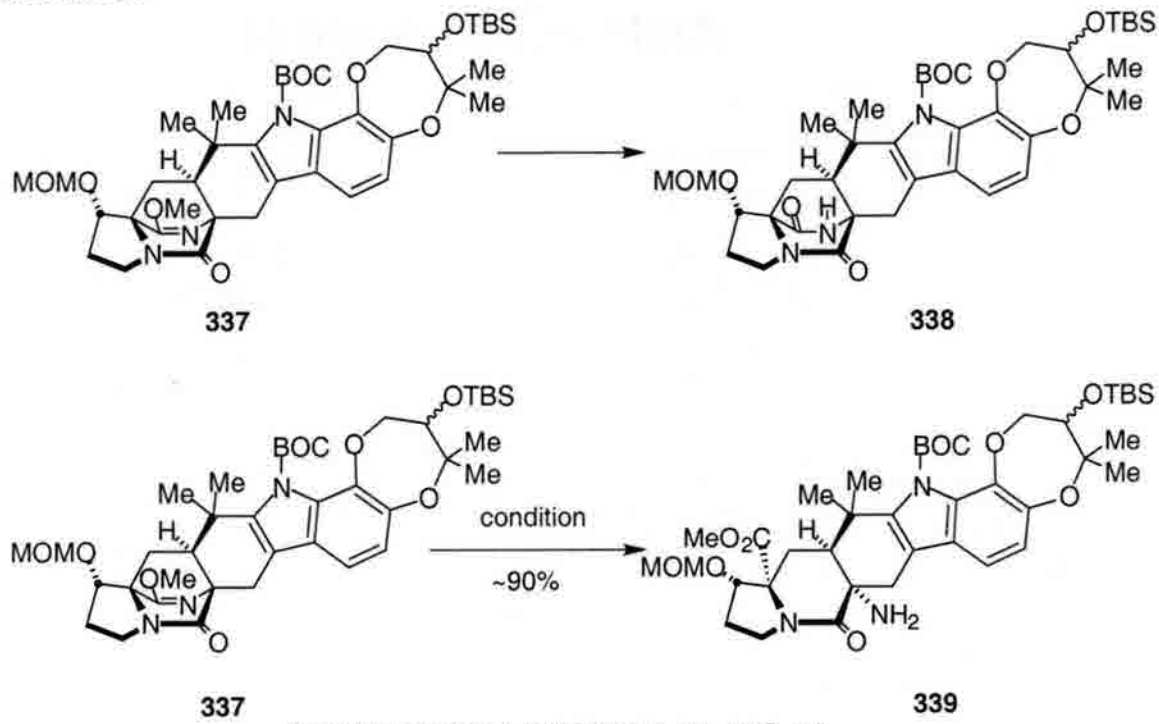
When the successful cyclization procedure used for the corresponding paraherquamide B intermediate was applied to olefin **325**, the reaction gave a lot of spots on TLC (Scheme 97). There was no desired cyclized product **337** formed. Each of the spots were separated, and the ^{1}H NMR indicated that they were most likely the deprotected products **334**, **335** and **336** produced by the HBF_4 formed in-situ. When the more eletrophilic Pd reagent $[Pd(CH_3CN)_4](BF_4)_2$ was stirred with **325** in CH_3CN for two days at room temperature, no reaction occurred. Based on the information of the separated products from the $PdCl_2$-$AgBF_4$ mediated reaction, obviously the products were produced by an acid formed in-situ (most likely HBF_4). To prevent this from happening, a base should be added to neutralize the HBF_4. Et_3N is not a proper choice because it will reduce Pd^{2+} to Pd° medal as indicated by Trost et al.[79] 2,6-Lutidine, a hindered base in which the α-carbon of the nitrogen has no hydrogen, was added to the reaction mixture, but only starting material was recovered. Finally, when 54 equiv. of propylene oxide were added, the desired cyclization product **337** was obtained in good yield (on a 50 mg scale, 66% yield; on a 201 mg scale, 85% yield) (Scheme 98).

Scheme 98



The transformation of lactim ether **337** to lactam **338** in a practical manner turned out to be very difficult (Scheme 99). Two procedures (LiCl, HMPA, H_2O, and Bu_3BnNCl, 60 °C)[80] and [NCS, $(CH_3)_2S$, 0 °C to r.t., CH_2Cl_2][81] were able to provide the desired product **338**, but these reactions gave complex mixtures and the yield was low, and were often not reproducible. Other conditions like 1 N HCl in THF (1:1), or 1 N HCl in THF (1:6), or PPTS in EtOH gave a complex mixture which contained some of the amino ester **339**.

Scheme 99



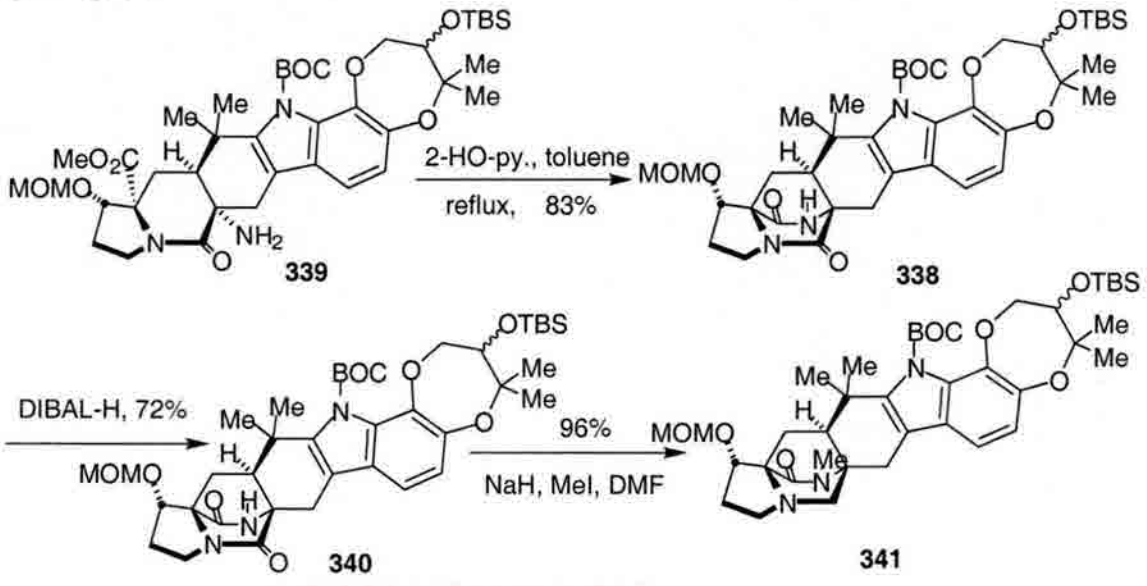
Condition: THF:0.1 N HCl aq/12.5:1, 0 °C, 1 h

At this point, I had to leave Colorado State University to work at Schering-Plough Corporation, New Jersey. At the same time, Dr. Hidekazu Tsujishima joined this project. He worked on the rest of this total synthesis work till the finish of the total synthesis of (-)-paraherquamide A.

However, when THF:0.1 N HCl/12.5:1 was used for compound **337**, the desired amino ester **339** were obtained in high yield. Reformation of the diketopiperazine **338** was accomplished by refluxing **339** in toluene catalyzed with 2-hydroxypyridine to provide **338** in 83% yield (Scheme 100).

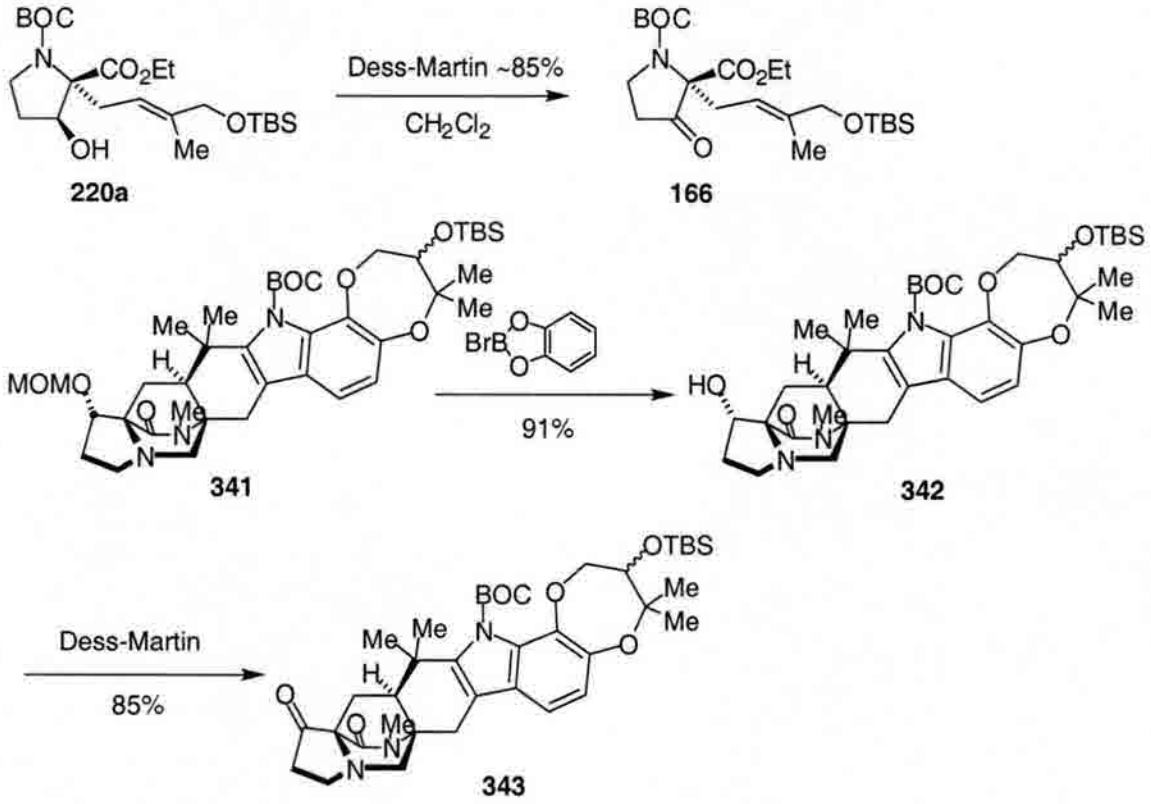
In the paraherquamide B synthesis, AlH_3-Me_2NEt[85] complex and Et_3Al were used to carry out the reduction in 64-71%. However, making this alane complex reagent and subsequent titration were time-consuming and not convenient. In the total synthesis of (±)-gelsemine by Fukuyama et al.[82], they reported the selective reduction of a tertiary amide in the presence of a secondary amide using DIBAL-H in 82% yield. Regioselective reduction of the tertiary amide of **338** following the same procedure of Fukuyama proceeded cleanly with DIBAL-H in toluene to give tertiary amine **340** in 72% yield. N-Methylation of the secondary amide in **340** (NaH, MeI in DMF, 96%) afforded intermediate **341** (Scheme 100).

Scheme 100

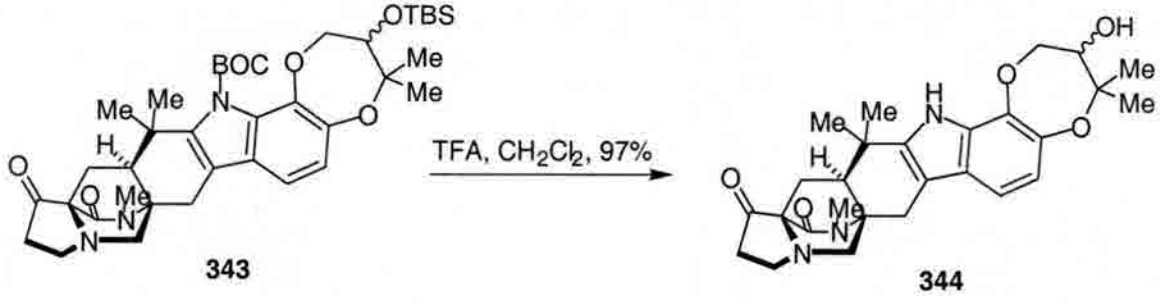


Selective deblocking[83] of the MOM ether protecting group in **341** (bromocatecholborane, 6 eq, in CH_2Cl_2, at °C) gave **342** in 91% yield (Scheme 101). This secondary alcohol was oxidized with Dess-Martin periodinane to afford compound **343** in 85% yield. In order to ensure that the oxidation of this hindered secondary alcohol would be successful, during the early stage of this project, a model study was conducted and the desired ketone **166** was obtained from **220a** in >85% yield (Scheme 101).

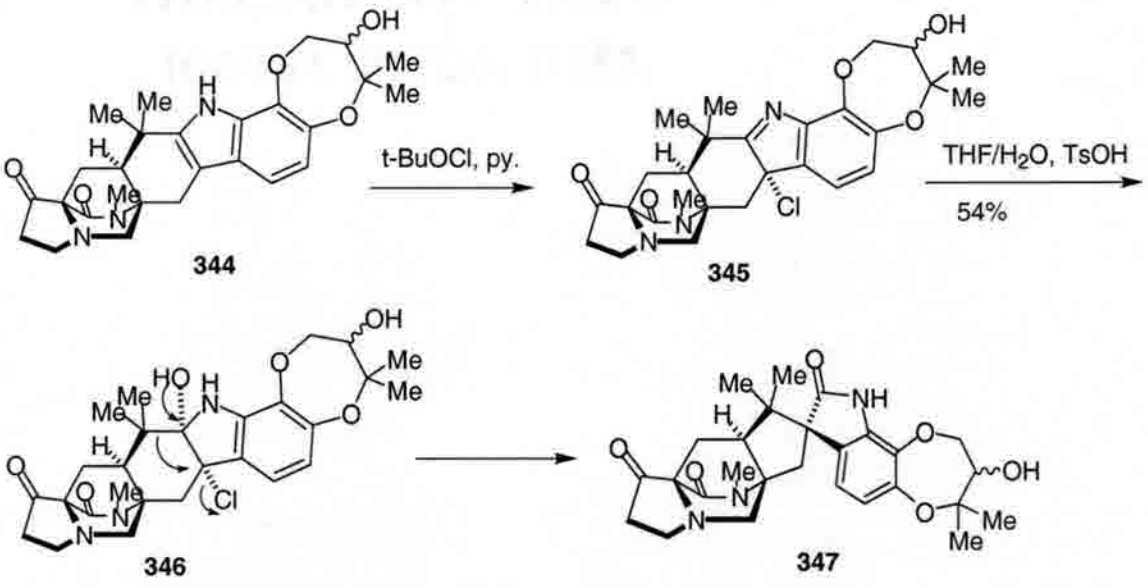
Scheme 101



Scheme 102



Scheme 103

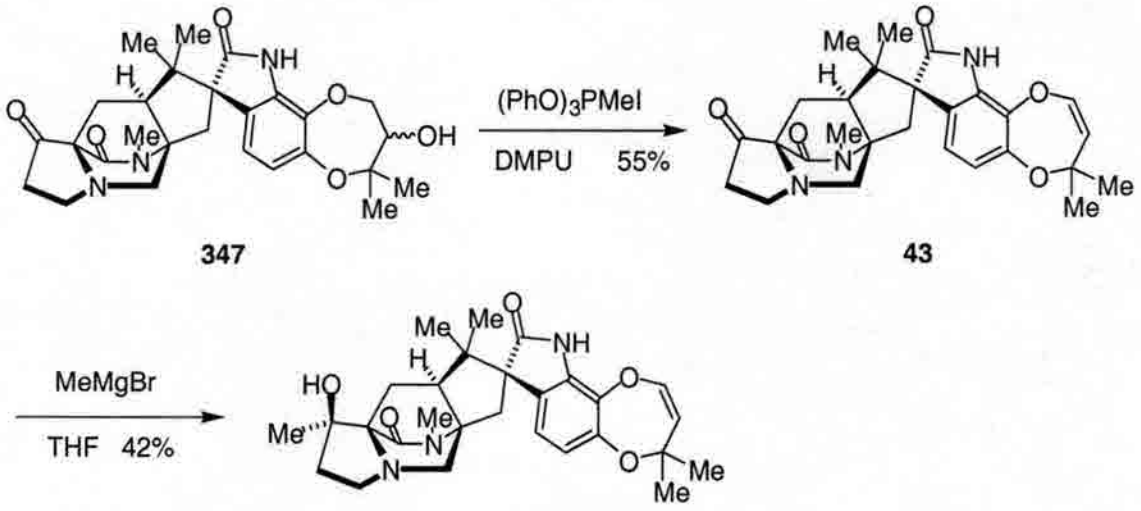


Deblocking of both protecting groups of **343** (510 eq of TFA in CH_2Cl_2) gave keto-alcohol **344** in 97% yield (Scheme 102). The oxidative spirooxidation was accomplished by a two-step oxidation/rearrangement process (Scheme 103). Chloroindolenine **345** was obtained by treatment of **344** at –15 °C with a complex of pyridine and t-BuOCl. Hydration of the chloroindolenine **345** in a relatively less polar solvent system (90% THF/10% H_2O) with 5 equiv. of TsOH affected rearrangement to oxindole **347** in 54% yield. It was found necessary to rigorously remove all of the pyridine solvent prior to the Pinacol-type rearrangement. It is assumed that the chlorination of **344** proceeds from the least hindered face of the indole giving the α-chloroindolenine **345**. The hydration of the imine functionality interestingly, must also occur from the same α-face which is *syn*-to the relatively large chlorine atom furnishing the *syn*-chlorohydrin **346** which subsequently rearranges stereospecifically to the desired spiro-oxindole **347**.

The final dehydration was affected with MTPI in DMPU[84] to provide 14-keto-(-)-paraherquamide A **43** in 55% yield (Scheme 104). This material proved to be identical to the semi-synthetic intermediate prepared by Lee[23] at Pharmacia-Upjohn by ^{1}H nmr,

HRMS and mobility on TLC. The final step, that involves methylmagnisum bromide addition to ketone **43** followed the same procedure that was successfully used by Lee[23] at Pharmacia-Upjohn to give (-)-paraherquamide A as the exclusive product (Scheme 104) (the C-14 epimer was not detected) in 42% yield that was identical in all respects (^{1}H nmr, ^{13}C nmr, ir, exact mass, mobility on TLC). The synthetic sample recrystallized from ether has m.p. 250 °C (decomp.) and $[\alpha]_D^{25}$ = -22 (c = 0.2 MeOH). A sample of natural paraherquamide A recrystallized from ether under the same conditions rendered a sample with m.p. 250 °C (decomp.) and $[\alpha]_D^{25}$ = -21 (c = 0.2 MeOH). The final synthetic paraherquamide A upon recrystallization from ether is ~optically pure.

Scheme 104



2.4 Summary of the Total Synthesis of (-)-Paraherquamide A

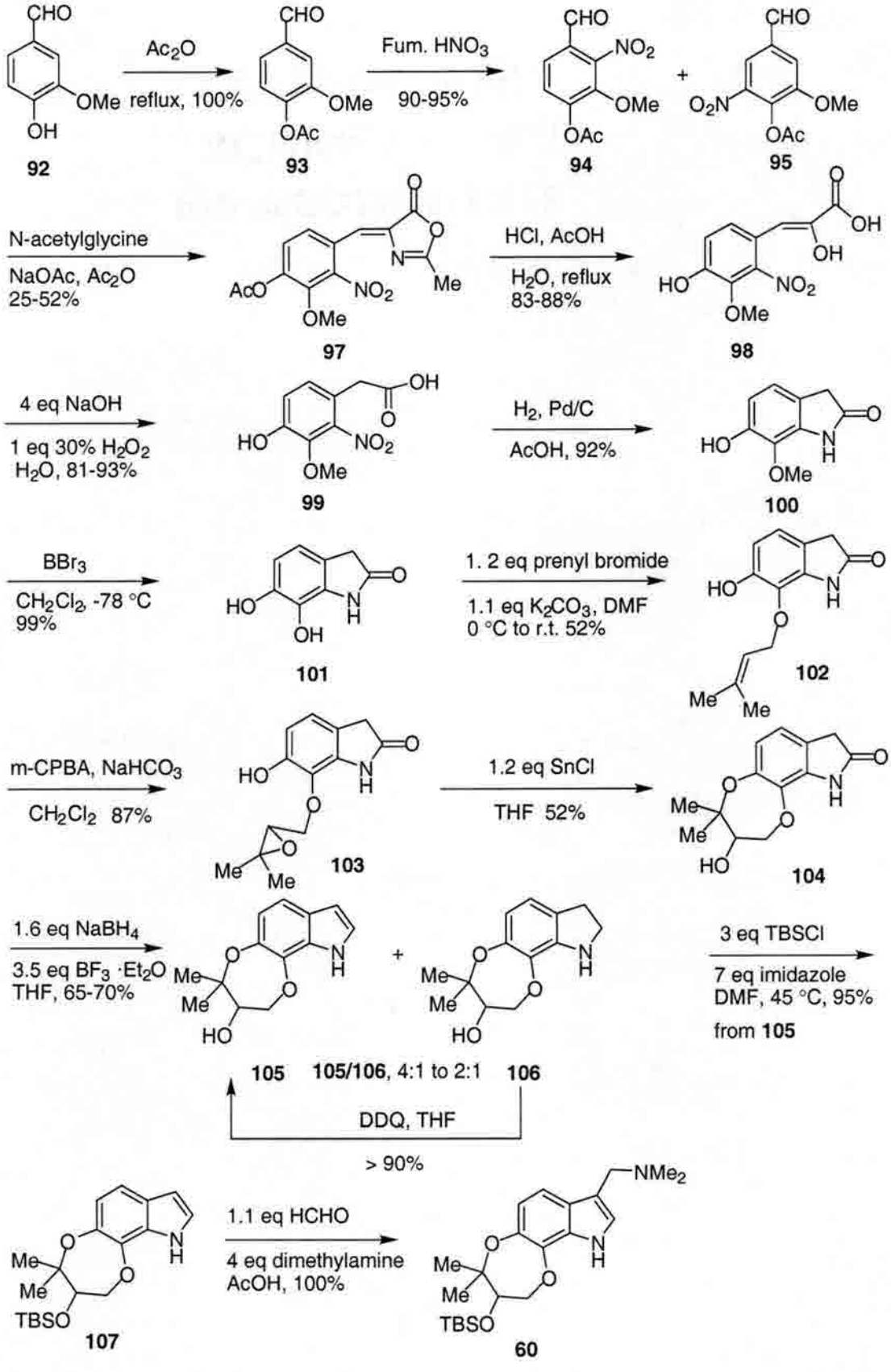
The first stereocontrolled total synthesis of (-)-paraherquamide A was completed in 48 chemical steps. This synthesis is a convergent one, starting from ethyl glycinate, ethyl acrylate and vanillin. The longest linear route is 35 steps.

Dioxepin-indole **60**, one of the key intermediates, was synthesized in 13 steps from 4 kg of vanillin according to a known synthetic approach. Five different steps of this synthesis were optimized by way of increasing the yield of products, avoiding unnecessary chemical transformations and simplifying purification procedure. Key features of these optimizations include: the synthetic route was shortened from 14 to 13 steps by avoiding a basic hydrolysis step and the following recrystallization procedure; a simplified purification procedure for the prenynation reaction of compound **101**; the yield of the epoxidation of **102** was increased to 85% from 64%; the over-reduced indoline **106** was converted to the desired indole **105** in almost quantitative yield; and finally, the yield of a hindered alcohol t-butyldimethylsilylation reaction was increased to 95% from 82%.

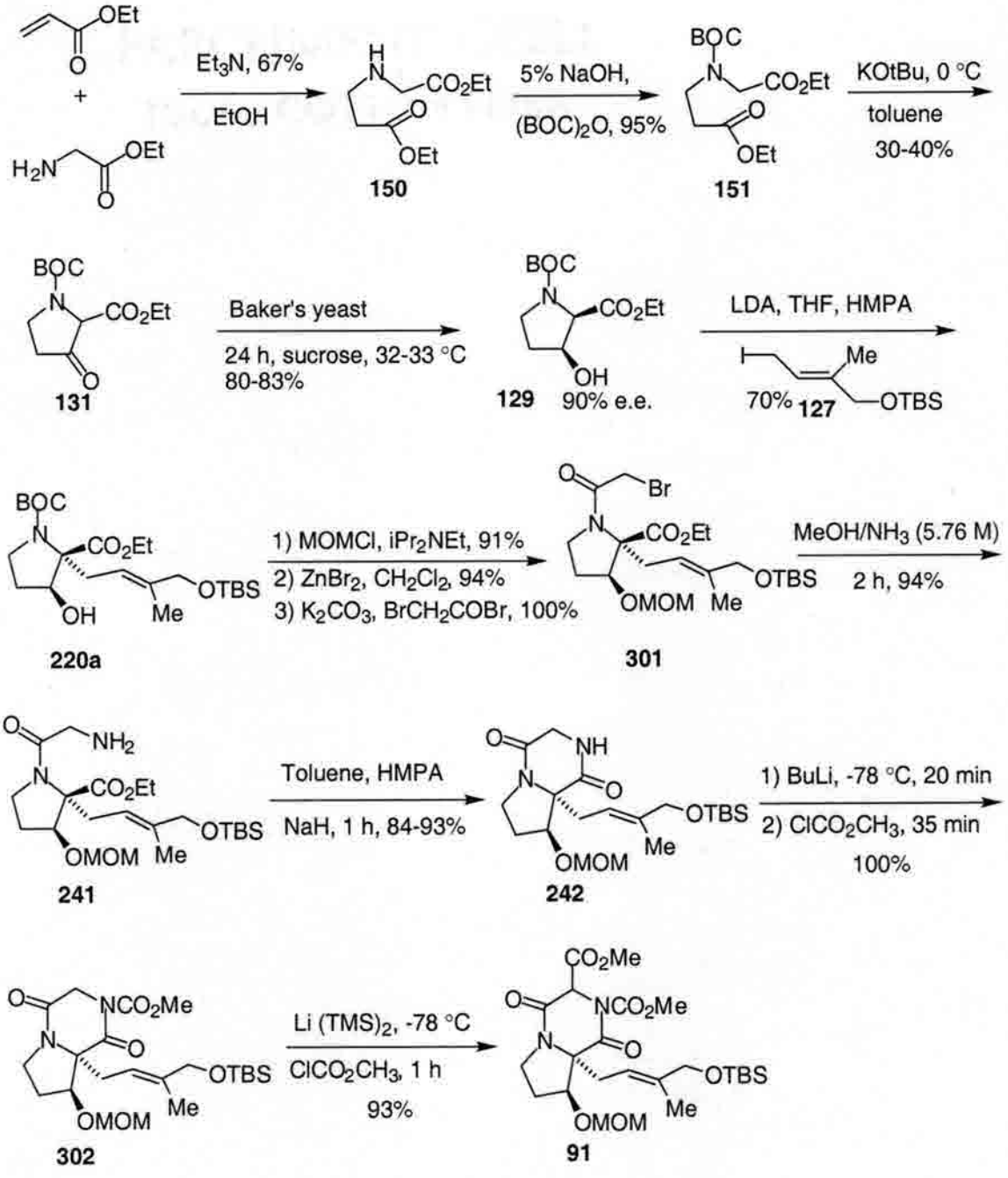
Both racemic and asymmetric synthetic methods were developed to synthesize α-substituted β-hydroxy proline derivatives (**219a-e**). This compound was further transformed to DKP **91**, the other key intermediate for the synthesis of paraherquamide A. The direct α-alkylation of β-hydroxy proline ester **129** produced only one diastereomer, and this method demonstrated convenience and simplicity without the need for additional protection of **129**. Other novel features are as follows: a complex DKP **91** and compound **60** were coupled together by using the Somei/Kametani reaction; a MOM ether protected substrate was converted to the lactim ether by using optimized conditions to overcome this often problematic transformation; a unique, convenient and mild allylic chloride formation procedure was found for the synthesis of compound **317** and its analogs ; a high yielding entirely stereoselective S_N2' reaction was carried out in THF not only for the E-isomeric allylic chloride, but also, for the first time, the Z isomer; a unique Pd(II)-mediated cyclization reaction through addition of propylene oxide to neutralize the

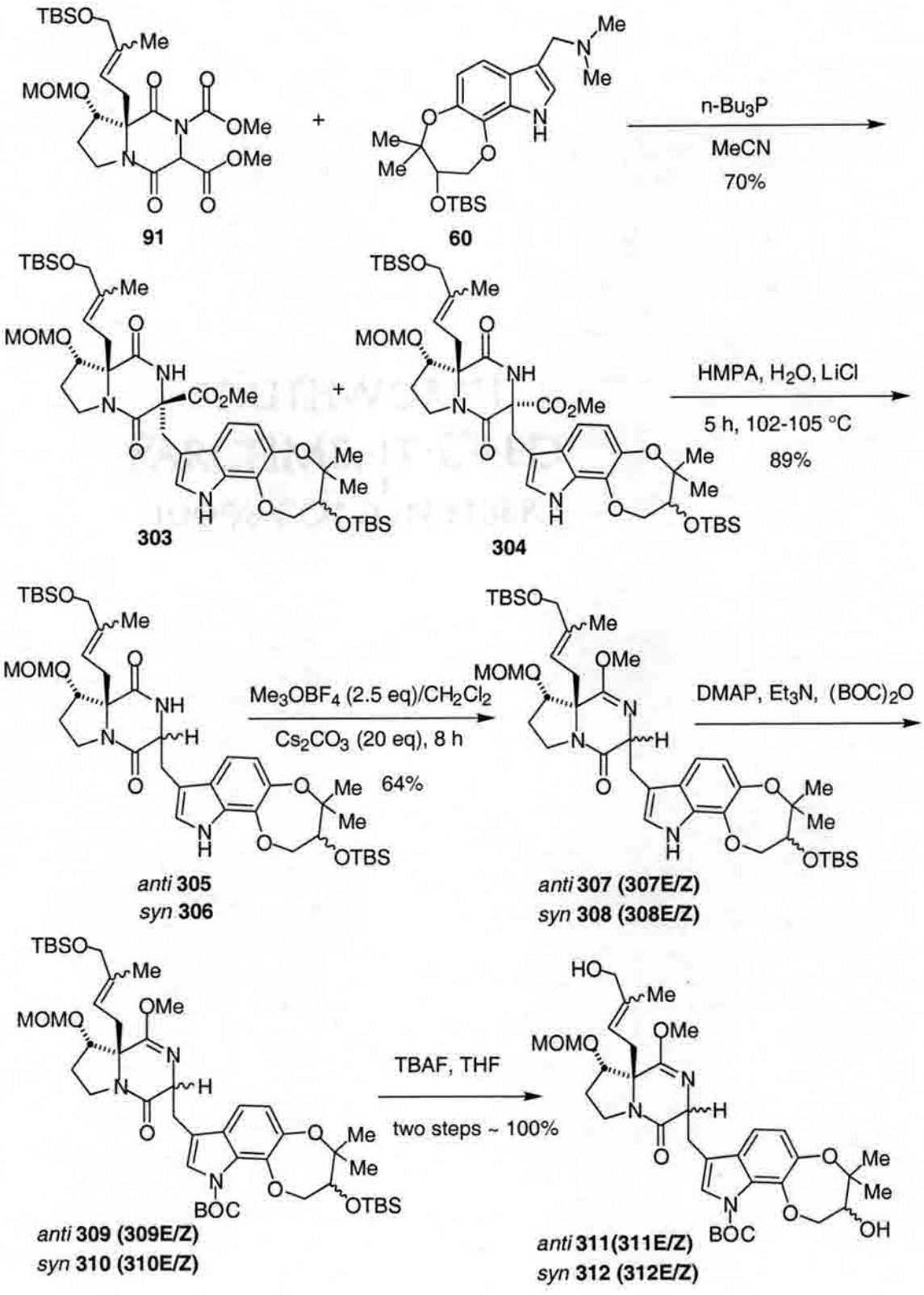
in-situ formed acid; and a mild acidic condition for cleavage of the lactim ether without cleaving other acid-labile protecting groups.

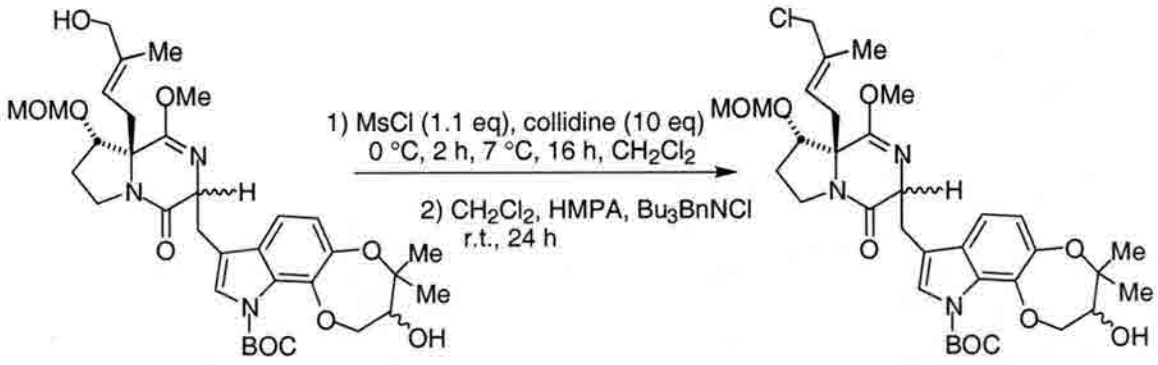
Scheme 105 The Improved Synthesis of Dioxepin-indole Subunit 60



Scheme 106 Completion of the Paraherquamide A Synthesis

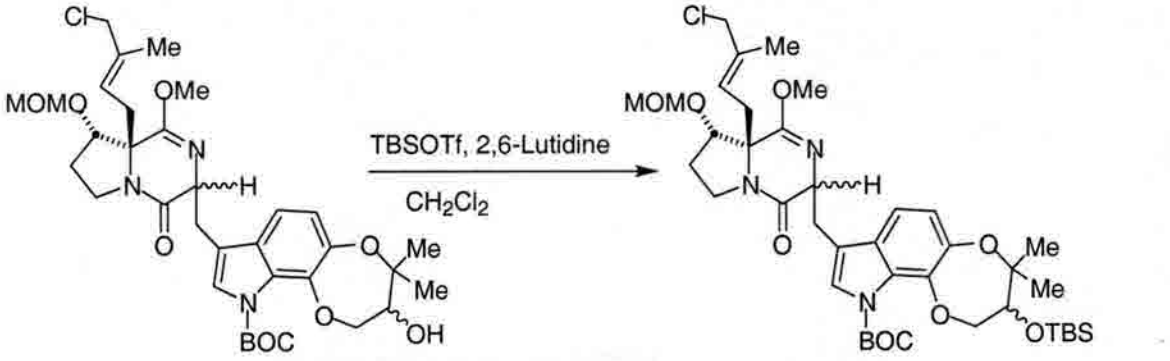



TBSO
Me
MOMO
O
N
OMe
OMe
O
O
91
+
Me
N
Me
Me
O
N
H
O
Me
OTBS
60
n-Bu3P
MeCN
70%
TBSO
Me
MOMO
O
NH
CO2Me
N
O
303
+
TBSO
Me
MOMO
O
NH
CO2Me
N
O
304
HMPA, H2O, LiCl
5 h, 102-105 °C
89%
Me
Me
OTBS
anti 305
syn 306
Me3OBF4 (2.5 eq)/CH2Cl2
Cs2CO3 (20 eq), 8 h
64%
OMe
anti 307 (307E/Z)
syn 308 (308E/Z)
DMAP, Et3N, (BOC)2O
BOC
anti 309 (309E/Z)
syn 310 (310E/Z)
TBAF, THF
two steps ~ 100%
HO
OH
anti 311(311E/Z)
syn 312 (312E/Z)



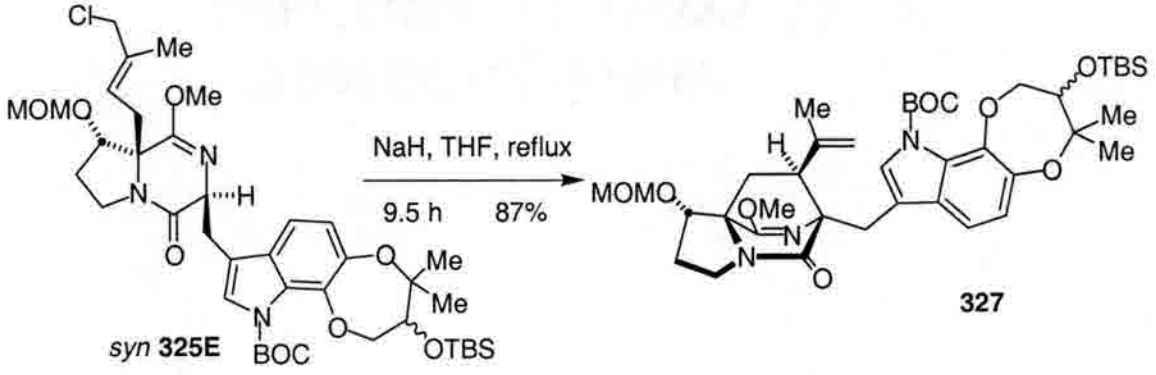
anti **311E**
syn **312E**

anti **324E** 77%
syn **317E** 90%



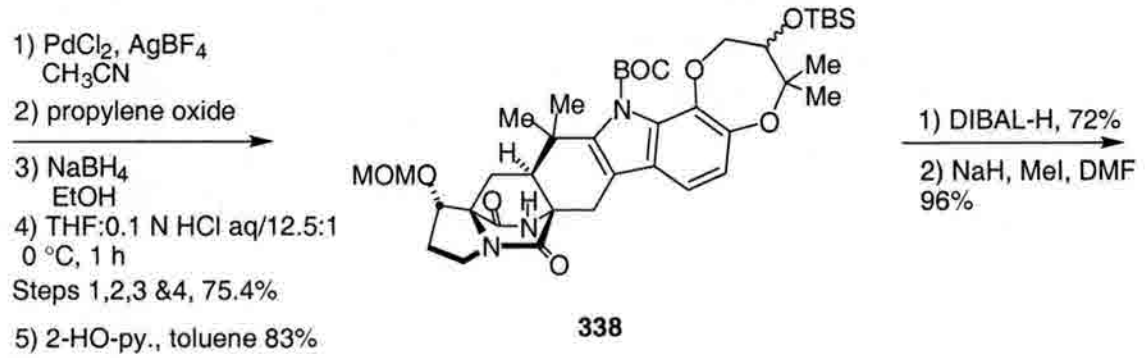
anti **324E**
syn **317E**

anti **326E** 89%
syn **325E** 79%

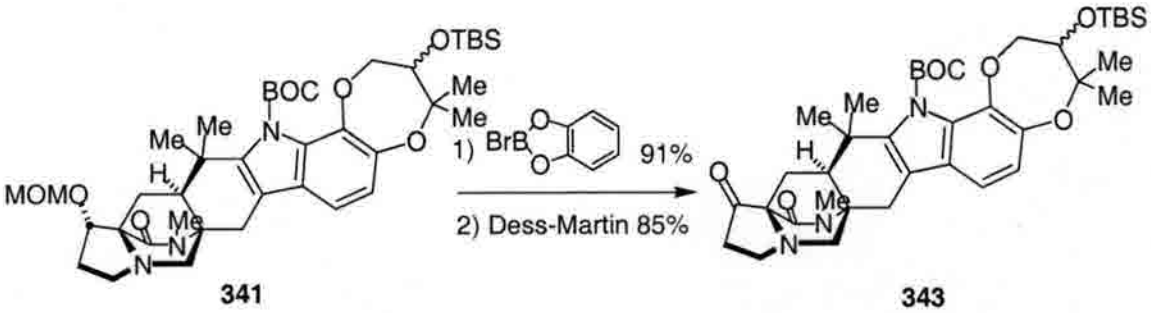


syn **325E**

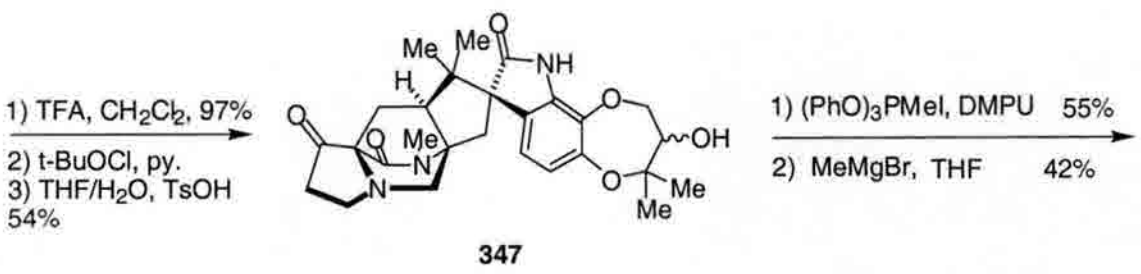
327



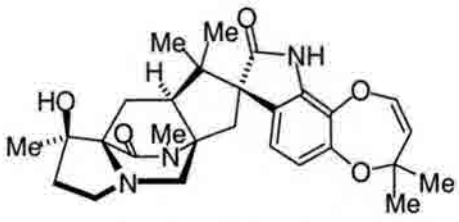
338



341 **343**



347



1 (-)-paraherquamide A

CHAPTER THREE

EXPERIMENTAL

General information

^{1}H and ^{13}C NMR were acquired using either a Bruker WP-270SY 270 MHz or a Bruker AC300P or Varian JS-300 NMR spectrometer. The chemical shifts are given in parts per million (ppm) downfield from TMS at δ 0.0 ppm or relative to residual $CHCl_3$ at δ 7.24 ppm. IR spectra were recorded on a Perkin-Elmer 1600 FT IR as thin films from CH_2Cl_2 or $CDCl_3$. Both low and high resolution mass spectra were obtained from Colorado State University. Elemental analysis were from M-H-W Laboratories, Phoenix Arizona. Optical rotations were recorded on Perkin-Elmer 24 polarimeter at a wavelength of 589 nm using a 1.0 decimeter cell of 1.0 mL total volume.

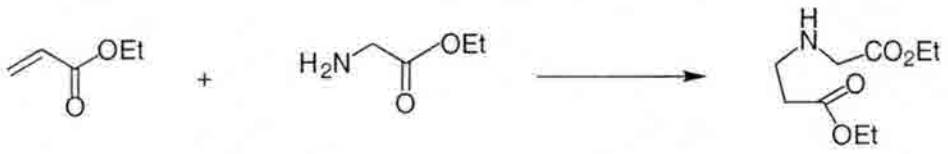
Chromatography

Flash column chromatography was performed with silica gel grade 60 (230-400 mesh). Radial chromatography was performed with a Harrison Research Chromatotron model 7924 using E.Merck silica gel 60 PF-254 containing gypsum and one, two or four millimeter plates were used as needed. Preparative thin layer chromatography (PTLC) was carried out with Merck Kieselgel 60 F_{254} precoated glass plates (20 x 20 cm x 0.25 mm). These plates were also used as a qualitative indicator for reaction completion, with ultraviolet light and heating with a solution of 5-7 % phosphomolybdic acid in 95% ethanol. Additional visualization stains (I_2/vanillin) were occasionally used.

Reagents and solvents

Unless otherwise noted materials were obtained from commercially available sources and used without further purification. Tetrahydrofuran and diethyl ether were

distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Methylene chloride, triethylamine, pyridine, acetonitrile, toluene, benzene, and diisopropylamine were distilled from calcium hydride under a nitrogen atmosphere. DMF and HMPA were dried over 3 Å molecular sieves for 1 week prior to use. The molecular sieves were activated by heating to 200 °C at 1 mm Hg for 4 h in a round bottom flask. NCS was recrystallized from benzene or acetic acid. LiCl and $AgBF_4$ are hydroscopic and were handled quickly. Me_3OBF_4 was stored in a freezer and weighed in the air without problem. After each use, Me_3OBF_4 was placed on the vacuum line and filled with nitrogen or argon. A stock solution of water in HMPA was used for the decarbomethoxylation reaction. A mesyl chloride stock solution in CH_2Cl_2 was used for the allylic chloride formation reaction. Zinc chloride was dried by heating to 210 °C for 4 h under vacuum in a flask.



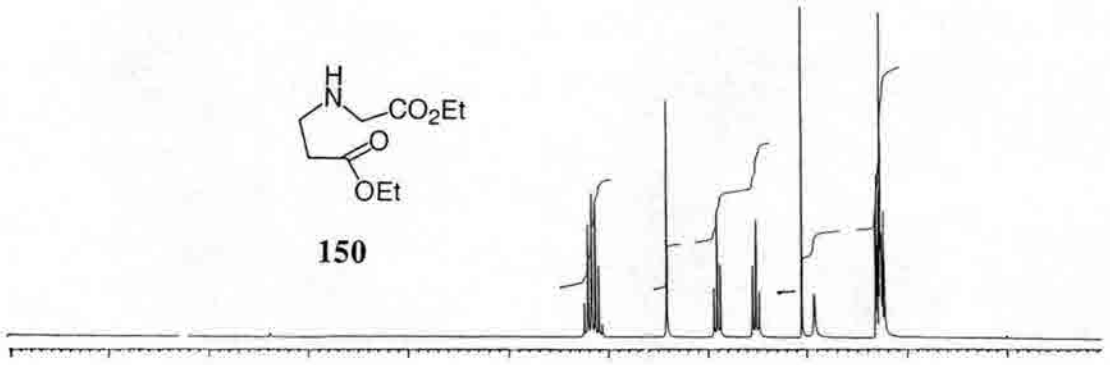
150

β-Alanine, N-(2-ethoxy-2-oxoethyl)-, ethyl ester (150)

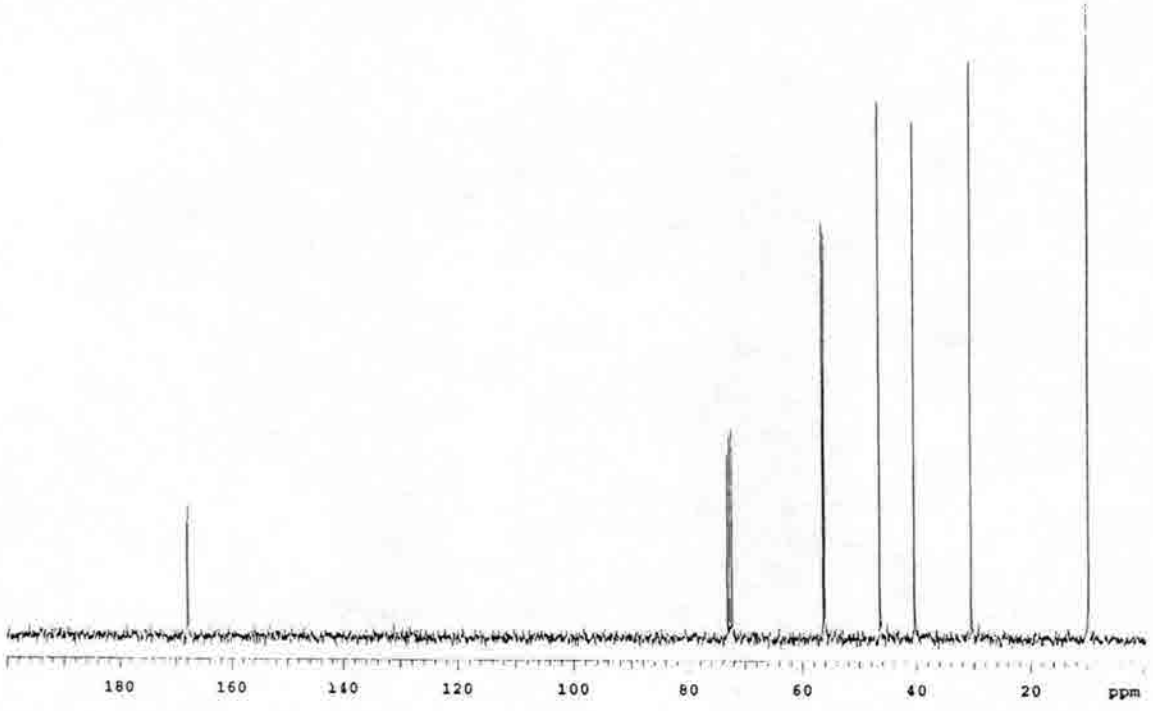
To a stirred solution of ethyl glycinate hydrochloride salt (100.5 g, 720 mmol, 1.0 eq) in 95% ethanol (1650 mL) at room temperature was added ethyl acrylate (79.3 g, 793 mmol, 1.1 eq) followed by triethyl amine (73.3 g, 720 mmol, 1 eq). The mixture was stirred at room temperature for 2-3 days. TLC (hexane:EtOAc:MeOH/4:2:1) was used to monitor the reaction. After the reaction was completed, the reaction mixture was concentrated, and water was added. The product was extracted with EtOAc, and the combined organic solution was washed with brine (3 times), dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by vacuum distillation (104-108 °C/0.6-1 mmHg) to afford 111 g (76%) of **150** as a colorless oil (lit., [51])

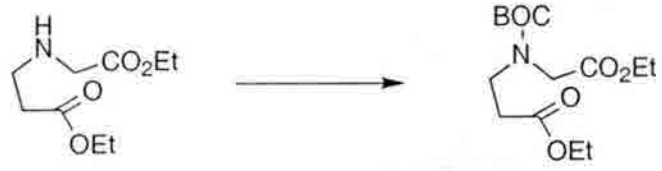
^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22-1.31 (6H, m), 1.92 (1H, broad, s), 2.50 (2H, t, J = 6.6 Hz), 2.90 (2H, t, J = 6.6 Hz), 3.41 (2H, s), 4.07-4.25 (4H, m)

IR (NaCl, film) 3338, 2982, 2937, 2910, 1732, 1465, 1371, 1888 cm^{-1}



150





150 **151**

β-Alanine, N-[(1,1-dimethylethoxy)carbonyl]-N-(2-ethoxy-2-oxoethyl), ethyl ester (151)

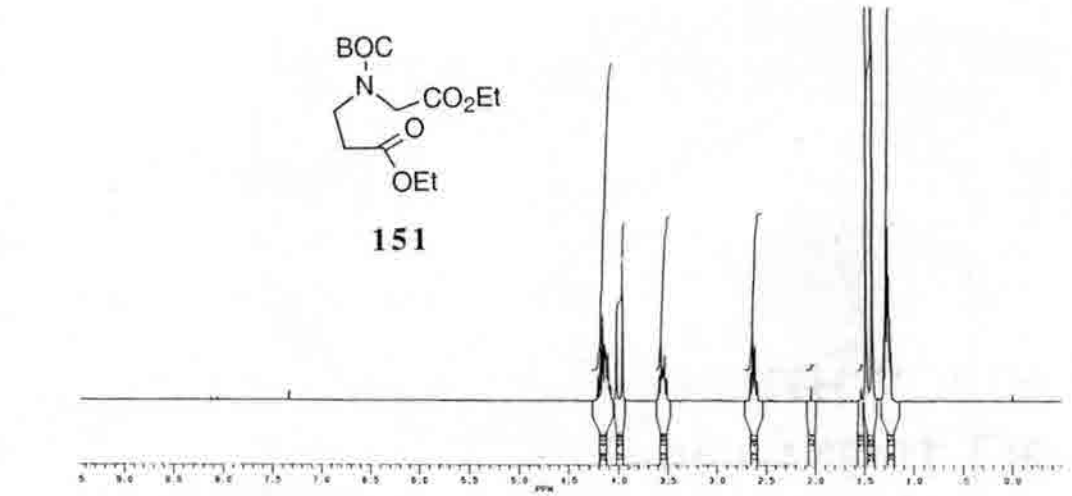
To a stirred solution of **150** (17.6 g, 86.8 mmol, 1 eq) in $CHCl_3$ (190 mL) at 0 ℃ was added $(BOC)_2O$ (25.9 g, 119 mmol, 1.37 eq) followed by 5% NaOH (190 mL). The reaction mixture was stirred at 0 ℃ for about 1 h and at room temperature for 10 h. TLC (hexane:EtOAc/4:1) was used to monitor the reaction. The reaction mixture was extracted with $CHCl_3$. The organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to provide 50 g of a crude oil. Purification of the product by vacuum distillation (123-128 °C/0.15 mmHg) afforded 23.5 g (90-95%) of **151** as a colorless oil (lit., [50,51])

^1H NMR (200 MHz, $CDCl_3$) δ 1.21-1.33 (6H, m), 1.40-1.53 (9H, m), 2.59-2.70 (2H, m), 3.49-3.60 (2H, m), 3.95-4.05 (2H, s), 4.08-4.30 (4H, m)

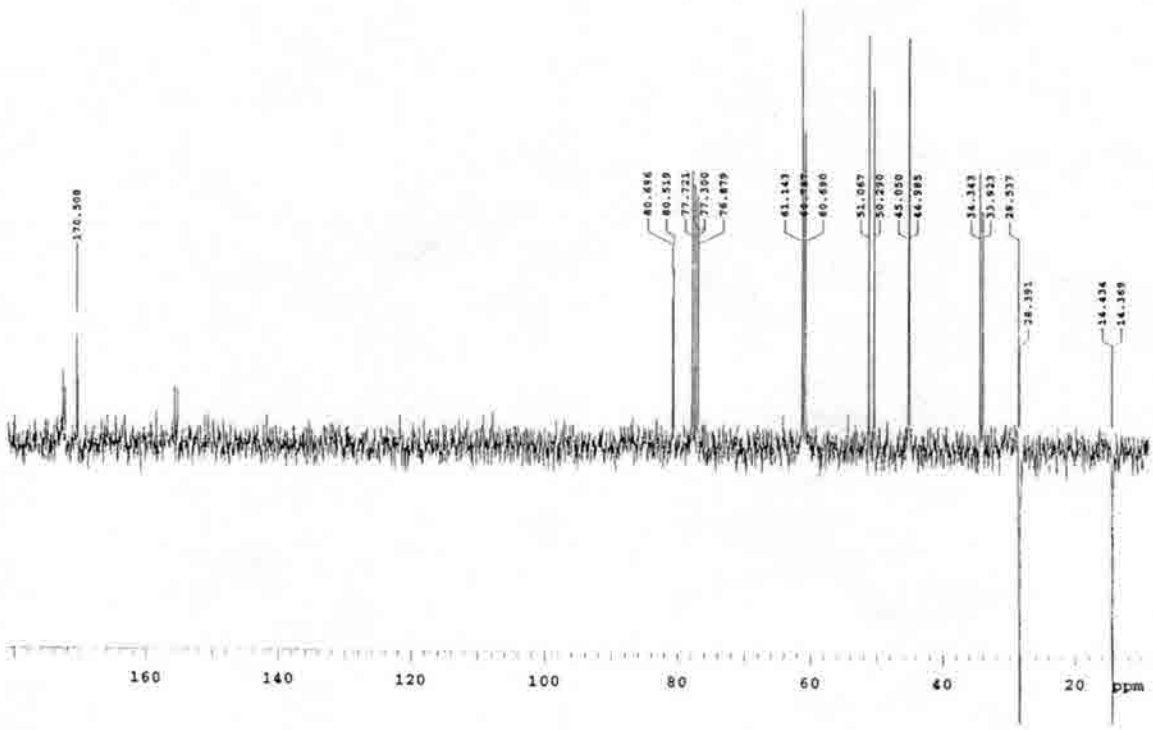
^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.9, 172.6, 170.8, 170.6, 156.0, 155.5, 80.6, 80.5, 61.1, 60.7, 60.6, 51.0, 50.2, 45.0, 44.9, 34.3, 33.9, 28.5, 28.3, 14.4, 14.3.

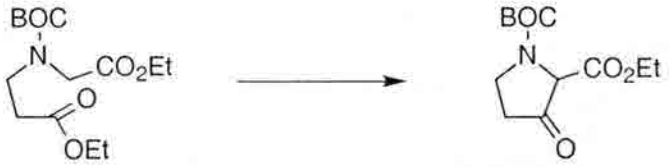
IR (NaCl, film) 2978, 2938, 1743, 1702, 1462, 1367, 1030 cm^{-1}

FAB HRMS m/e 304.1760 ($C_{14}H_{25}NO_6$ + H requires 304.1760)


BOC
N
CO2Et
O
OEt

151


170.508
80.696
80.519
77.721
77.390
76.479
61.143
60.690
51.067
50.290
45.050
44.985
34.343
33.923
28.337
28.391
14.434
14.369
160
140
120
100
80
60
40
20
ppm



151 **131**

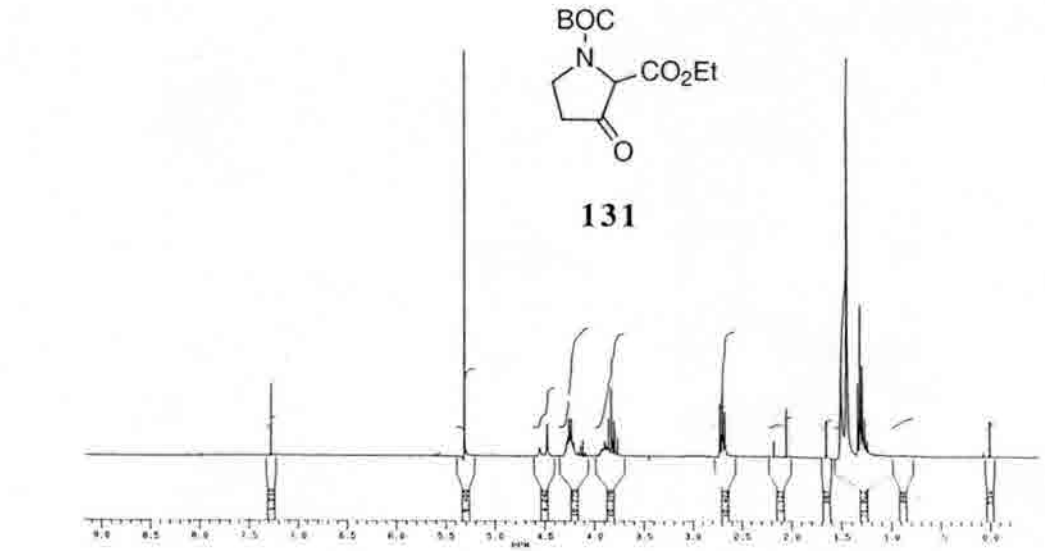
1,2-Pyrrolidinedicarboxylic acid, 3-oxo-, 1-(1,1-dimethylethyl) 2-ethyl ester (131)

A suspension of KO^{t}Bu (24.48 g, 218.0 mmol, 1.5 eq) in toluene (580 mL) was cooled to 0 °C by means of an external ice-NaCl bath (-6 °C to -8 °C) and was stirred vigorously by a mechanic stirrer. A solution of **151** (44.8 g, 145.6 mmol, 1 eq) in toluene (80 mL) was added via cannula over 12 min. After the reaction mixture was stirred at 0 °C for 85 min, it was quenched with acetic acid (16 mL) (in one portion) followed by a cold solution of $NaH_2PO_4.H_2O$ (80 g) in H_2O (800 mL). The upper organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (500 mL, 300 mL). The combined organic solution was washed with pH 7 phosphate buffer (2 × 150 mL), dried over Na_2SO_4, filtered and concentrated to give 36 g of an oil. Toluene (800 mL) was added to the above crude oil, and the resulting solution was washed with pH 10 sodium carbonate buffer (5 × 400 mL), followed by water (1 × 200 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford 16 g of a reddish oil. The product was purified by Kugelrohr distillation (125-145 °C/2-3 mmHg) to yield 14.0 g (37.4%) of **131** as a colorless oil (lit., [50,51]). TLC solvent system was hexane:EtOAc:MeOH/ 5:2:0.5.

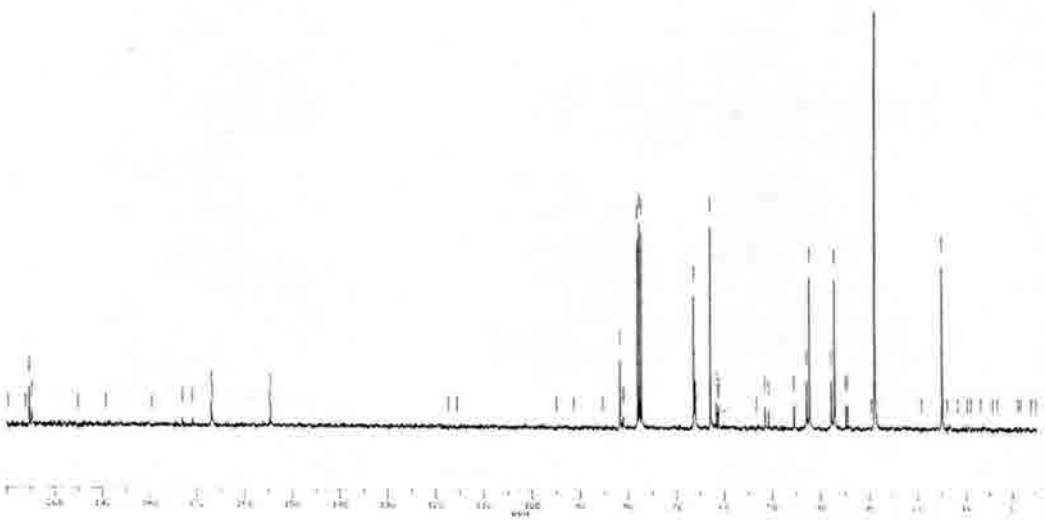
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, m), 1.40-1.50 (9H, m), 2.65-2.71 (2H, m), 3.75-3.95 (2H, m), 4.20-4.30 (2H, m), 4.45-4.55 (1H, m).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 205.3, 204.8, 166.9, 166.7, 154.7, 81.7, 66.4, 66.0, 62.7, 42.8, 42.2, 37.7, 37.0, 34.7, 34.3, 28.8, 14.8.

IR (NaCl, film) 2978, 2930, 1771, 1738, 1704, 1391, 1160 cm^{-1}



131



131 **129**

1,2-Pyrrolidinedicarboxylic acid, 3(S)-hydroxy, 1-(1,1-dimethylethyl) 2(R)-ethyl ester (129)

To a 6-L Erlenmeyer flask, immersed in a water bath, was added in succession, **131** (34.15 g, 0.132 mol, 1 eq), sucrose (513 g) and distilled water (2731 mL). The mixture was stirred until the sucrose dissolved, after which dry Baker's yeast (341 g, Red Star^{R}) was added. After the reaction mixture was stirred at 32 °C to 33 °C for 24 h, it was centrifuged. The aqueous layer was separated and extracted with ether (4 times). The combined extracts were dried over Na_2SO_4 and concentrated to give an oil. Purification of the product by flash column chromatography (hexane:EtOAc /4:1 then 2:1) gave 28.7 g (84%) of **129** as a pure oil (lit., [50,51]). Both ^{1}H and ^{19}F NMR spectra of the derived Mosher's ester of **129** indicated an enantiomeric excess of *ca* .90% (Knight et al.[51]).

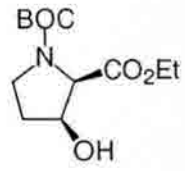
^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28-1.35 (3H, m), 1.45-1.50 (9H, m), 1.95-2.18 (2H, m), 3.30 (1H, broad, s), 3.42-3.55 (1H, m), 3.55-3.65 (1H, m), 4.15-4.25 (2H, m), 4.30-4.42 (1H, m), 4.55-4.65 (1H, m).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.6, 170.5, 154.4, 154.0, 80.2, 80.1, 72.2, 71.3, 64.0, 63.5, 61.0, 44.3, 43.8, 32.6, 32.0, 28.4, 28.2, 14.3, 14.2.

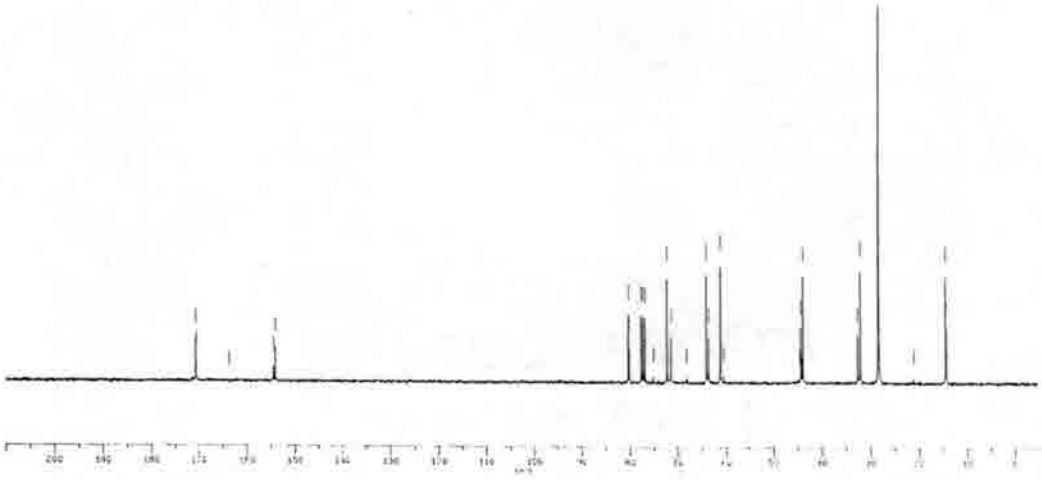
IR (NaCl, film) 3449, 2982, 2958, 2899, 1742, 1702, 1420, 1358, 1211, 1194 cm^{-1}.

$[\alpha]^{25}_{D}$ + 19.0 (c 1.21, CH_2Cl_2). lit., [51] $[\alpha]^{27}_{D}$ + 18.2 (c 1.45, CH_2Cl_2).

Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.41; H, 7.93; N, 5.15.



129



165 **127**

Silane, (1,1-dimethylethyl)[(E)-(4-iodo-2-methyl-2-butenyl)oxy]dimethyl (127)

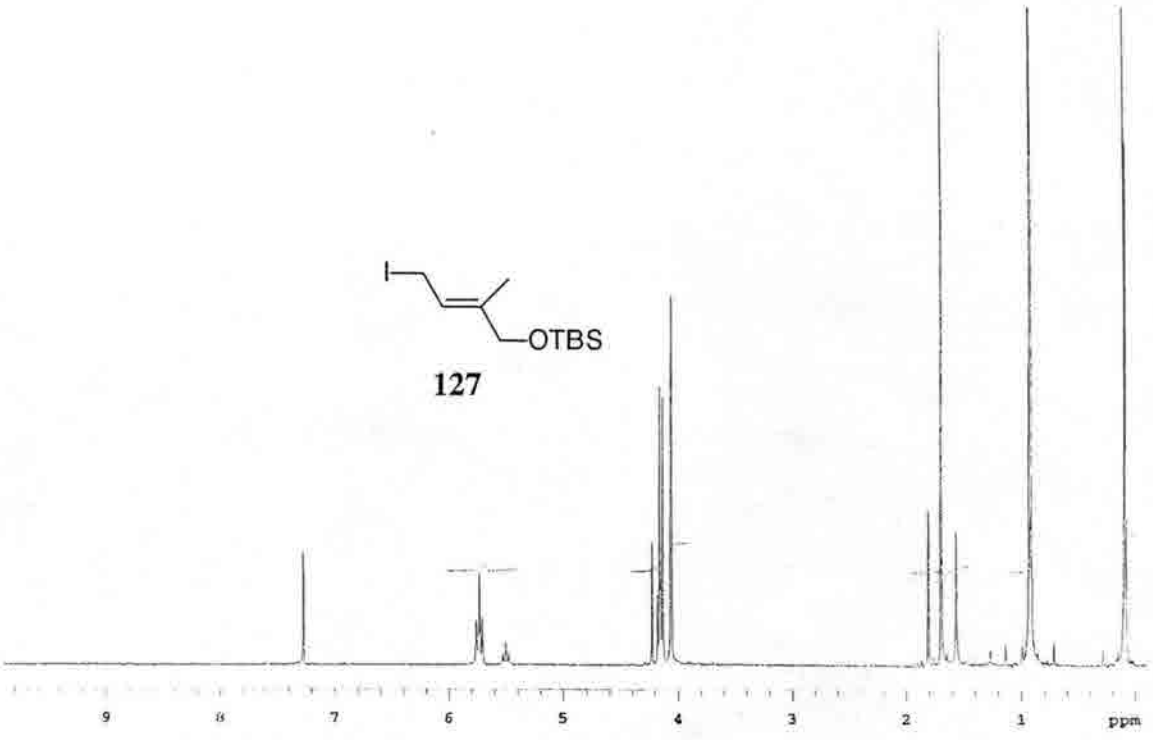
To a stirred solution of **165** (4.70 g, 50.3 mmol, 1 eq), at 0 °C, in CH_2Cl_2 (87.5 mL) was added $MgSO_4$ (3.0 g), *t*-butyldimethylsilyl chloride (7.43 g, 49.3 mmol, 0.98 eq) and tetrabutylammonium iodide (22.25 g, 60.30 mmol, 1.2 eq). The reaction mixture was allowed to warm to room temperature and stirred for 27 h. The solvent was removed *in vacuo* , and hexane was added. The resulting suspension was filtered, and the solid pad was washed with hexane. The filtrate was concentrated and purified by Kugelrohr distillation (80-90 °C/0.1 mmHg) to give 9.33 g (58%) of an isomeric mixture of the E (**127**) and the Z isomer (a colorless liquid, as an E:Z/6.4:1 mixture).

Data of the E/Z mixture:

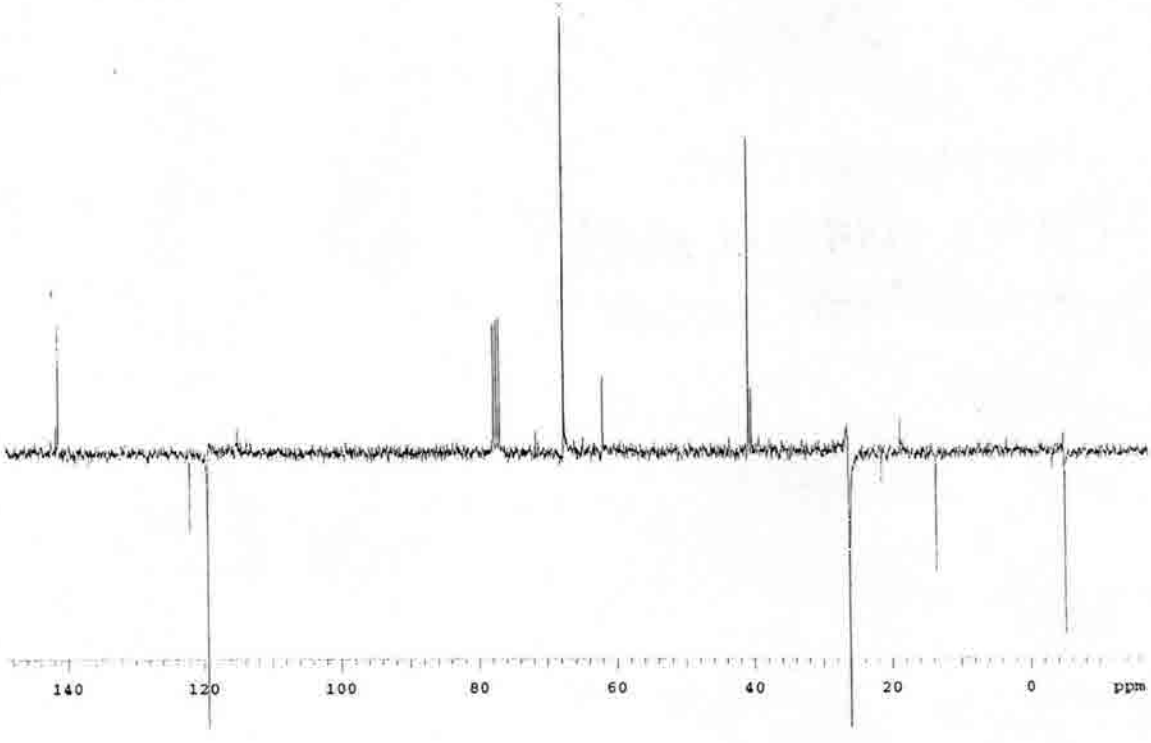
^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, m), 0.89 (9H, m), 1.65-1.82 (3H, s), 4.05 (2H, s), 4.12-4.31 (2H, m), 5.65-5.75 (1H, m).

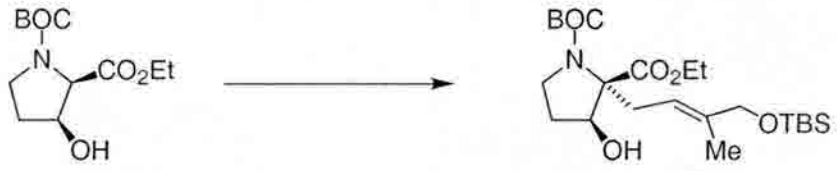
^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 141.6, 141.2, 121.9, 119.3, 67.4, 61.8, 40.5, 40.1, 26.0, 25.8, 21.3, 18.5, 13.4, -5.2.

IR (NaCl, film) 2956, 2930, 2886, 2857, 1472, 1463, 1389, 1362, 1254, 1147, 1115, 1078, 1006, 837 cm^{-1}.



127





129 **220a**

1,2-Pyrrolidinedicarboxylic acid, 2(R)-[E-4-[[(1,1-dimethylethyl) dimethyl silyl]oxy]-3-methyl-2-butenyl]-3(S)-hydroxy-,1-(1,1-dimethylethyl),2-ethyl ester (220a)

To a stirred solution of diisopropylamine (2.38 g, 25.8 mmol, 3.25 eq) in THF (7.5 mL) at 0 °C under N_2 was added CH_3Li (25.8 mL, 1.0 M in THF, 25.8 mmol, 3.25 eq) over 8 min. The resulting brown solution was stirred at 0 °C for 20 min and then cooled to -78 °C. A solution of **129** (2.02 g, 7.80 mmol, 1 eq) in THF (12.5 mL + 2.5 mL rinse) was added via cannula over 7 min. The reaction mixture was stirred at -78 °C for an additional 3 min and at 0 °C for 50 min, then recooled to -78 °C. A solution of allylic iodide derivative (4.56 g, 14.0 mmol, 1.8 eq) in HMPA (19.0 g, 106 mmol, 13.7 eq) was introduced in one portion to the above vigorously stirred solution. The reaction was allowed to proceed at 0 °C for a further 2 h before being quenched with EtOAc and saturated NH_4Cl solution. The mixture was extracted with EtOAc (3 times), and the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a liquid. TLC system (hexane:EtOAc:MeOH/5:3:0.5) was used to monitor the reaction. Purification by flash column chromatography (hexane:EtOAc/4:1) provided 2.08 g (58%) of an isomeric mixture of the E (**220a**) and the Z isomer (a colorless oil, as an E:Z/4.3:1 mixture). On a scale of 1.68 g, 2.04 g product was obtained (70%).

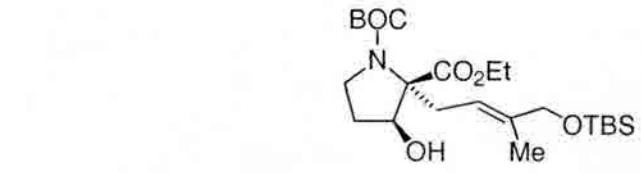
Data of the E/Z mixture:

^1H NMR (300 MHz, $CDCl_3$) δ 0.01–0.02 (6H, m), 0.85 (9H, s), 1.17-1.26 (3H, m), 1.32-1.41 (9H, m), 1.37-1.70 (3H, m), 1.89-1.98 (2H, m), 2.50 (1H, broad, s), 2.74-2.88 (2H, m), 3.14-3.19 (1H, m), 3.60-3.77 (1H, m), 3.94 (2H, s), 4.02-4.22 (3H, m), 5.25-5.29 (1H, m).

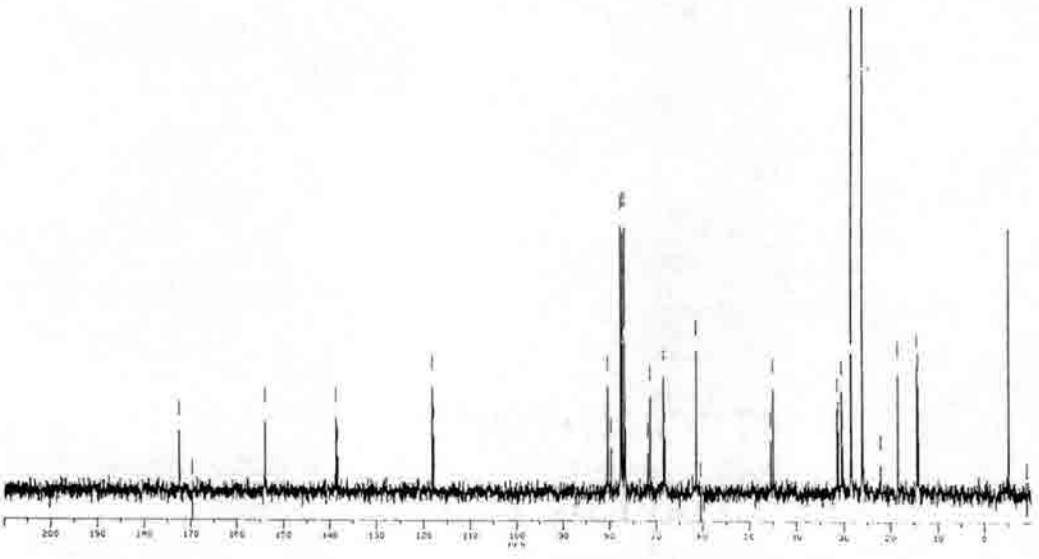
^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.3, 153.8, 138.6, 138.2, 118.1, 117.7, 80.4, 79.6, 76.8, 76.5, 71.7, 71.2, 68.4, 68.1, 61.3, 45.4, 44.9, 31.4, 31.1, 30.4, 30.2, 28.5, 28.4, 26.0, 22.0, 18.5, 14.4, 14.3, 14.1, 14.0, -5.1.

IR (NaCl, film) 3449, 2977, 2955, 2928, 2857, 1739, 1703, 1391, 1367, 1251, 837, 774 cm^{-1}

Anal. Calcd. for $C_{23}H_{43}NO_6Si$: C, 60.36; H, 9.47; N, 3.06. Found: C, 60.17; H, 9.30; N, 3.05.



220a



129 **220d**

1,2-Pyrrolidinedicarboxylic acid, 3(S)-hydroxy-2(R)-methyl-, 1-(1,1-dimethylethyl) 2-ethyl ester (220d)

To a stirred solution of diisopropylamine (113 mg, 1.20 mmol, 3 eq) in THF (0.2 mL) at 0 °C under N_2 was added CH_3Li (1.32 mL, 1.0 M in THF, 1.32 mmol) over 3 min. After the solution was stirred at 0 °C for 15 min and cooled to -50 °C, a solution of **129** (104 mg, 0.40 mmol, 1 eq) in THF (0.4 mL) was added via cannula over 3 min. The temperature was raised to –10 °C and held for 25 min, then at 0 °C for 5 min and lowered to –35 °C to –40 °C. A solution of methyl iodide (87 mg, 0.60 mmol, 1.5 eq) in HMPA (100 mg, 0.56 mmol, 1.4 eq) was added by syringe in one portion. After the reaction mixture was stirred at 0 °C for 1.5 h, at room temperature for 24 h and at 35 °C for 20 h, it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The organic solution was washed with brine (4 x 10 mL), dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by preparative TLC (hexane:EtOAc:MeOH/5:3:0.5) to give 54 mg (57%, based on 15 mg of recovered **129**) of **220d** as a colorless oil.

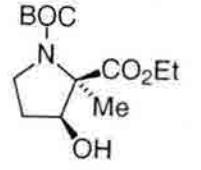
^1H NMR (300 MHz, $CDCl_3$) δ 1.18-1.26 (3H, m), 1.36-1.41 (9H, m), 1.52-1.56 (3H, m), 1.89-1.96 (1H, m), 2.00-2.08 (1H, m), 2.83 (1H, broad, s), 3.33-3.14 (1H, m), 3.65-3.71 (1H, m), 4.05-4.21 (3H, m).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.3, 154.1, 81.1, 80.4, 80.0, 79.8, 69.1, 61.5, 31.4, 30.8, 28.6, 28.5, 22.6, 21.6,14.4.

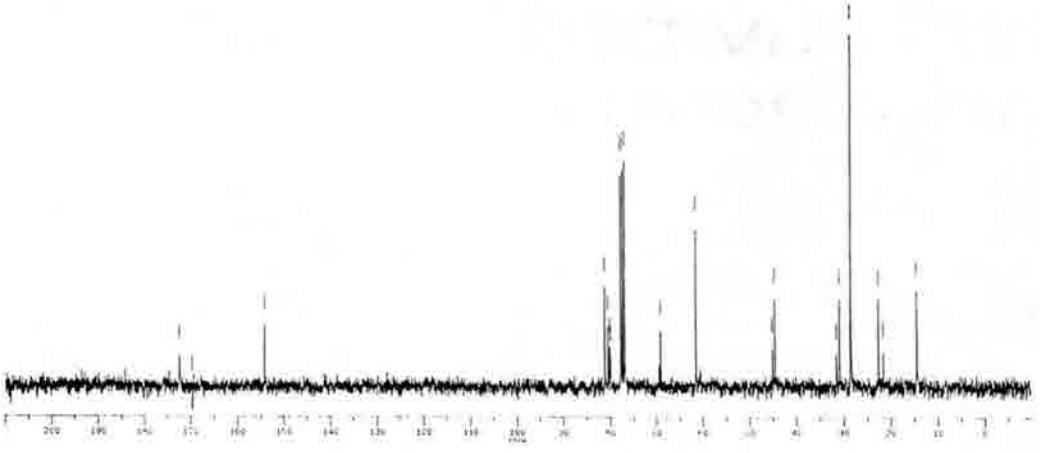
IR (NaCl, film) 3443, 2980, 2936, 1746, 1731, 1698, 1391, 1167, 1094 cm^{-1}.

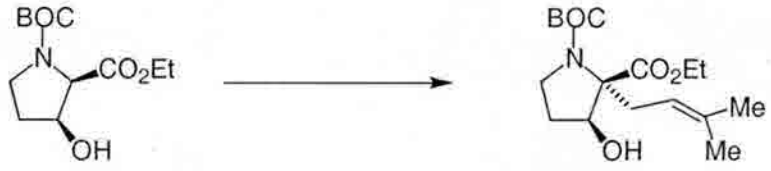
$[\alpha]^{25}_D$ -3.9 (c 0.54, EtOAc)

Anal. Calcd. for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.92; H, 8.28; N, 5.05.



220d





129 **220b**

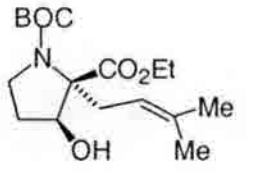
1,2-Pyrrolidinedicarboxylic acid, 3(S)-hydroxy-2(R)-(3-methyl-2-butenyl)-1-(1,1-dimethylethyl) 2-ethyl ester (220b)

To a stirred solution of diisopropylamine (113 mg, 1.2 mmol, 3 eq) in THF (0.2 mL) at 0 °C under N_2 was added CH_3Li (1.32 mL, 1.0 M in THF, 1.32 mmol, 3.24 eq) over 3 min. After the solution was stirred at 0 °C for 15 min and cooled to -50 °C, a solution of **129** (104 mg, 0.4 mmol, 1 eq) in THF (0.4 mL) was added via cannula over 3 min. The reaction temperature was raised to –10 °C and held for 25 min, then at 0 °C for 5 min and lowered to –35 °C to –40 °C. A solution of prenyl bromide (91 mg, 0.60 mmol, 1.5 eq) in HMPA (100 mg, 0.56 mmol, 1.38 eq) was added by syringe in one portion. After the reaction mixture was stirred at 0 °C for 2.5 h, and at room temperature for 2 h, it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The organic solution was washed with brine (4 x 10 mL), dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by preparative TLC (hexane:EtOAc:MeOH/5:3:0.5) to provide 98.4 mg (73.4%) of **220b** as a colorless oil.

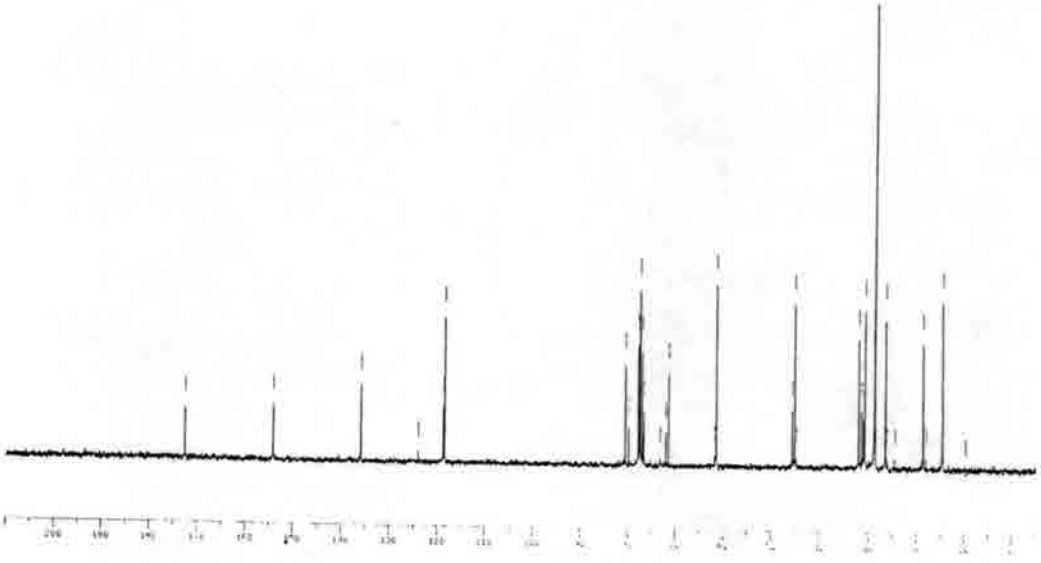
^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.29 (3H, m), 1.34-1.37 (9H, m), 1.53-1.65 (6H, m), 1.84-2.01 (2H, m), 2.70-2.91 (3H, m), 3.10-3.19 (1H, m), 3.57-3.77 (1H, m), 4.03-4.19 (3H, m), 4.92-4.94 (1H, m).

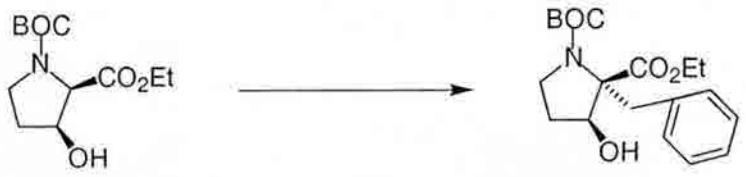
^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.4, 172.3, 154.1, 154.0, 135.9, 135.8, 118.7, 118.4, 80.5, 79.7, 76.5, 71.9, 71.461.4, 45.6, 45.0, 31.8, 31.3, 30.9, 30.6, 28.6, 28.5, 26.4, 26.3, 18.5, 18.3, 14.5, 14.4. IR (NaCl, film) 3447, 2972, 2930, 2873, 1743, 1699, 1668, 1391, 1170, 1137 cm^{-1}. $[\alpha]^{25}_D$ -48.2 (c 0.98, EtOAc).

Anal. Calcd. for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.19; H, 9.03; N, 4.27.



220b

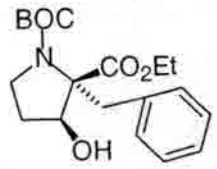




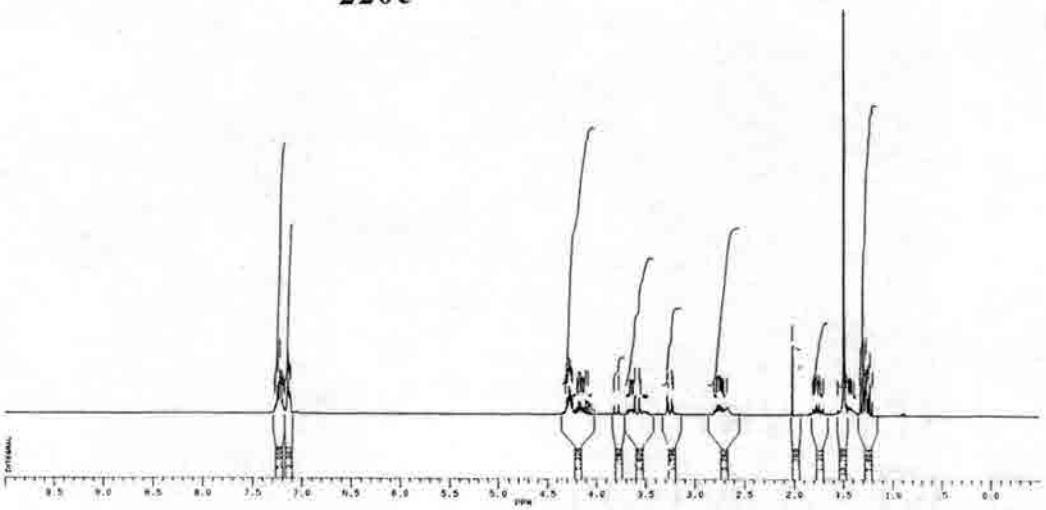
129 **220c**

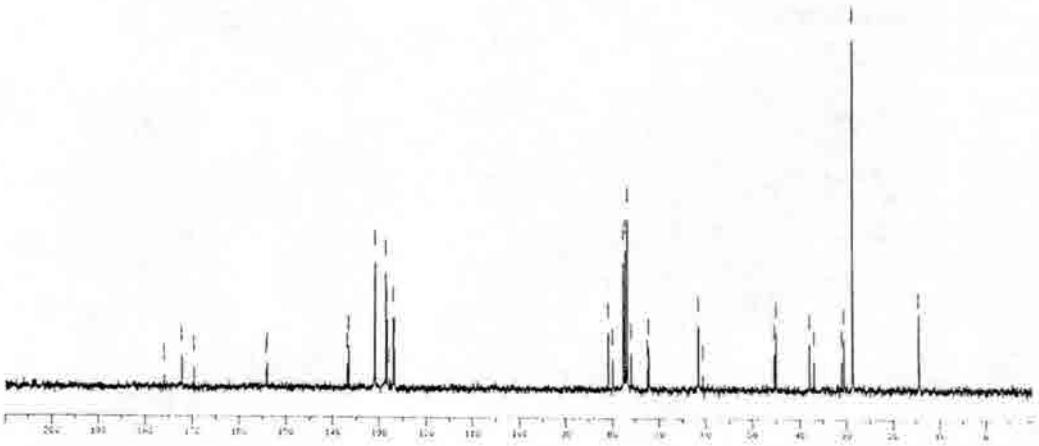
1,2-Pyrrolidinedicarboxylic acid, 3(S)-hydroxy-2(R)-(phenylmethyl)-, 1-(1,1-dimethylethyl) 2-ethyl ester (220c)

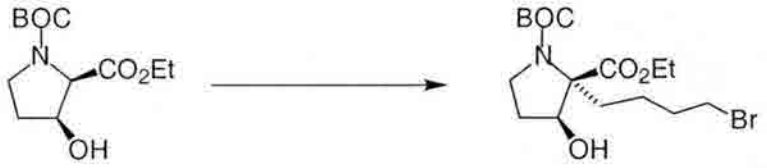
To a stirred solution of diisopropylamine (113 mg, 1.2 mmol, 3 eq) in THF (0.2 mL) at 0 °C under N_2 was added CH_3Li (1.32 mL, 1.0 M in THF, 1.32 mmol, 3.3 eq) over 3 min. After the solution was stirred at 0 °C for 15 min and cooled to -50 °C, a solution of **129** (104 mg, 0.4 mmol, 1 eq) in THF (0.4 mL) was added via cannula over 3 min. The reaction temperature was raised to –10 °C and held for 25 min, then at 0 °C for 5 min and lowered to –35 °C to –40 °C. A solution of benzyl bromide (109 mg, 0.64 mmol, 1.6 eq) in HMPA (100 mg, 0.56 mmol, 1.4 eq) was added by syringe in one portion. After the reaction mixture was stirred at 0 °C for 1.5 h, and at room temperature for 50 h, it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The organic solution was washed with brine (4 x 10 mL), dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by preparative TLC (hexane:EtOAc:MeOH/5:3:0.5) to provide 64 mg (53%, based on 15 mg of recovered **129**) of **220c** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.31 (3H, m), 1.38-1.46 (1H, m), 1.48 (9H, s), 1.69-1.80 (1H, m), 2.66 (1H, broad, s), 2.70-2.80 (1H, m), 3.22-3.27 (1H, m), 3.54-3.81 (2H, m), 4.11-4.19 (1H, m), 4.23-4.31 (2H, m), 7.11-7.27 (5H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.1, 169.5, 154.2, 153.9, 136.8, 136.5, 130.9, 130.8, 128.5, 128.3, 126.9, 126.7, 80.8, 79.9, 75.9, 72.5, 72.2, 61.6, 60.6, 45.3, 45.0, 37.8, 36.8, 30.9, 30.5, 28.6, 14.46, 14.41. IR (NaCl, film) 3446, 3085, 3062, 3030, 2979, 2881, 1732, 1693, 1681, 1392, 1367, 1167 cm^{-1}.Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.15; H, 7.69; N, 3.87. $[\alpha]^{25}_D$ -77.6 (c 0.59, EtOAc).



220c





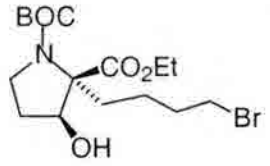


129 **220e**

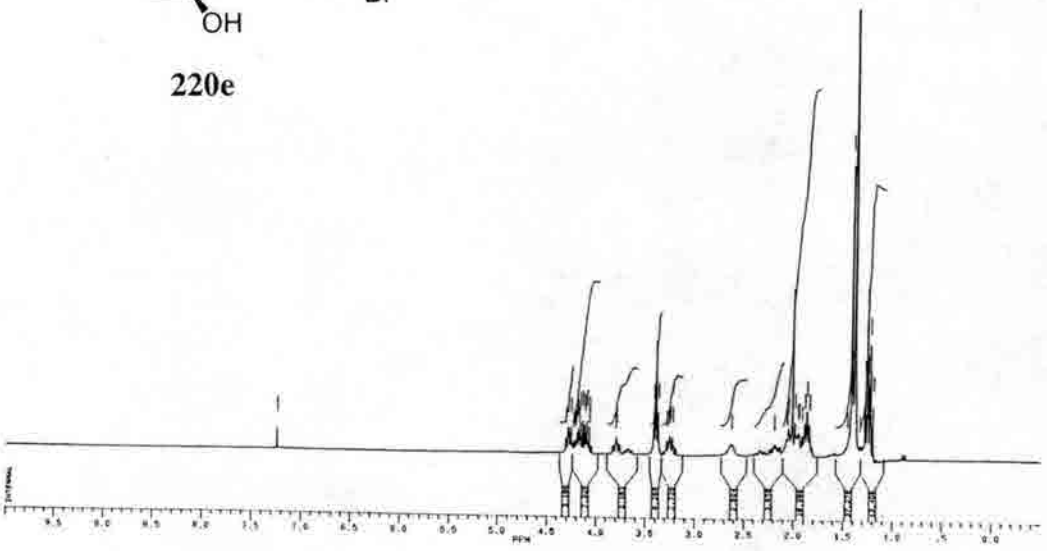
1,2-Pyrrolidinedicarboxylic acid, 2(R)-(4-bromobutyl)-3(S)-hydroxy-, 1-(1,1-dimethylethyl) 2-ethyl ester (220e)

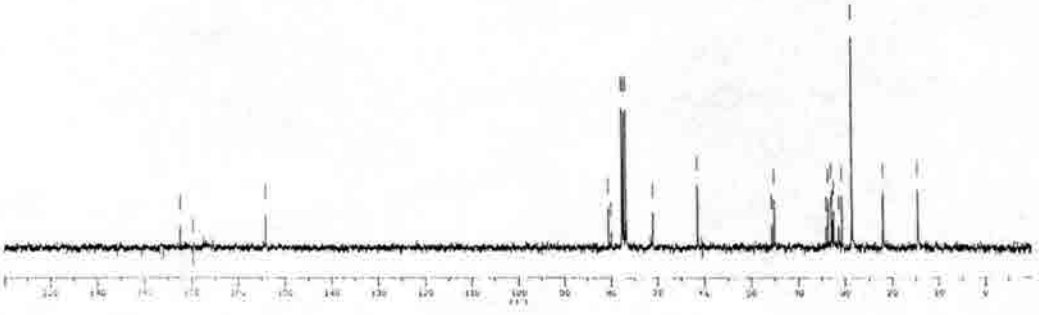
To a stirred solution of diisopropylamine (113 mg, 1.2 mmol, 3 eq) in THF (0.2 mL) at 0 °C under N_2 was added CH_3Li (1.32 mL, 1.0 M in THF, 1.32 mmol, 3.3 eq) over 3 min. After the solution was stirred at 0 °C for 15 min and cooled to -50 °C, a solution of **129** (104 mg, 0.40 mmol, 1 eq) in THF (0.4 mL) was added via cannula over 3 min. The reaction temperature was raised to –10 °C and held for 25 min, then at 0 °C for 5 min and lowered to –35 °C to -40 °C. A solution of 1,4-dibromobutane (130 mg, 0.6 mmol, 1.5 eq) in HMPA (100 mg, 0.56 mmol, 1.4 eq) was added by syringe in one portion. After the reaction mixture was stirred at 0 °C for 1 h, and at room temperature for 19 h, it was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (4 x 10 mL), dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by preparative TLC (hexane:EtOAc/1:1) to provide 54 mg (49%, based 16 mg of recovered **129**) of **220e** as a colorless oil.

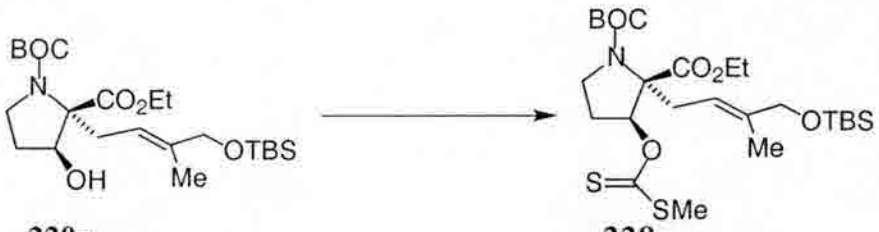
^1H NMR (300 MHz, $CDCl_3$) δ 1.21–1.24 (3H, m), 1.28–1.40 (2H, m), 1.32–1.40 (9H, m), 1.83-2.40 (7H, m), 2.62 (1H, broad, s), 3.22-3.28 (1H, m), 3.38 (1H, t, J = 6.5 Hz), 3.65-3.75 (1H, m), 4.06-4.22 (2H, m), 4.24-4.30 (1H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.3, 154.0, 80.5, 79.9, 76.8, 76.6, 71.0, 61.4, 45.5, 45.0, 34.0, 33.6, 32.9, 32.7, 32.4, 31.2, 30.6, 28.5, 22.1, 21.9, 14.4. IR (NaCl, film) 3438, 2973, 2934, 2875, 1735, 1696, 1672, 1383, 1366, 1246, 1168, 772 cm^{-1}. $[\alpha]^{25}_D$ -22.8 (c 0.54, EtOAc). Anal. Calcd. for $C_{16}H_{28}BrNO_5$: C, 48.74; H, 7.16; N, 3.55. Found: C, 48.90; H, 7.31; N, 3.60.



220e







220a **228**

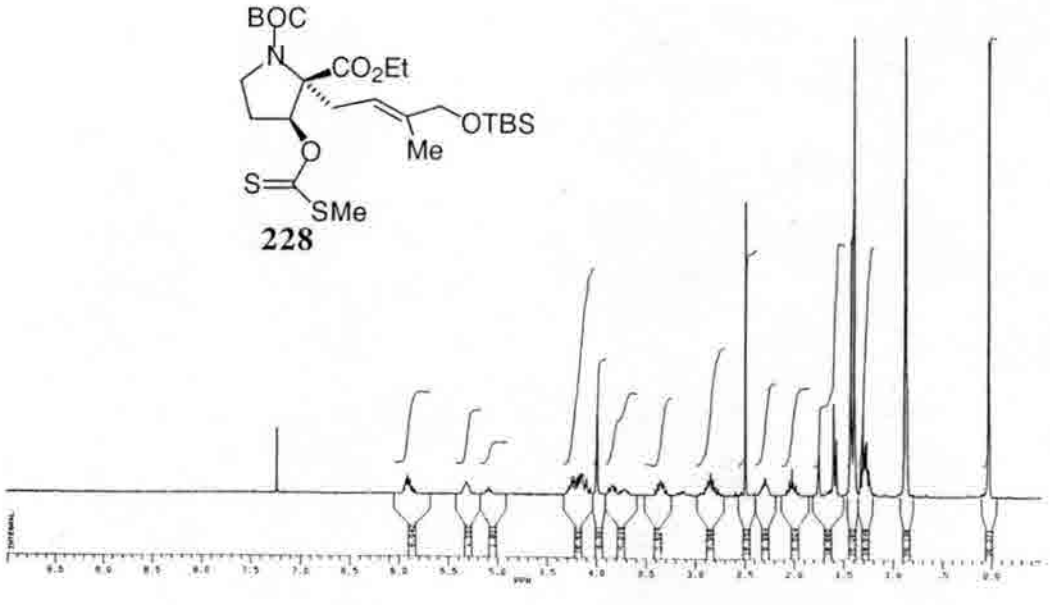
1,2-Pyrrolidinedicarboxylic acid,2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethyl silyl]oxy]-3-methyl-2-butenyl]-3(S)-[(methylthio)thioxomethoxy]-, 1-(1,1-dimethylethyl) 2-ethyl ester (228)

To a solution of **220a** (92 mg, 0.2 mmol, 1 eq) in THF (3 mL) at 0 °C was added 60% NaH (17 mg, 0.42 mmol, 2.1 eq) under Ar. After 15 min, CS_2 (126 mg, 1.66 mmol, 8.3 eq) was added to the reaction mixture, producing a deep red solution. After 20 min, methyl iodide (454 mg, 3.2 mmol, 16 eq) was added to the above solution in one portion. The resulting mixture was allowed to warm to room temperature slowly. After 8.5 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 x 30 mL). The organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of the product by radial chromatography (hexane:EtOAc/12:1) gave 86 mg (79%) of an isomeric mixture of the E (**228**) and the Z isomer (a colorless oil, as an E:Z/~3:1 mixture).

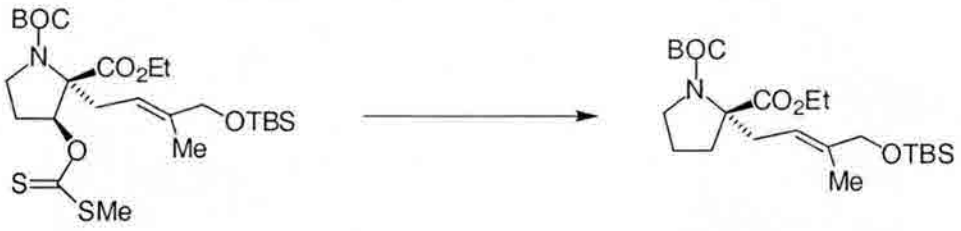
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.89 (9H, m), 1.25-1.35 (3H, m), 1.40-1.50 (9H, m), 1.60-1.75 (3H, m), 2.00 (1H, m), 2.30 (1H, m), 2.50 (3H, s), 2.75-2.90 (1H, m), 3.30-3.42 (1H, m), 3.68-3.90 (1H, m), 4.00 (2H, s), 4.05-4.25 (3H, m), 5.05-5.35 (1H, m), 5.85-5.95 (1H, m).

IR (NaCl, film) 2979, 2958, 2931, 2851, 1744, 1701, 1390, 836, 775 cm^{-1}.



228



228 **229**

1,2-Pyrrolidinedicarboxylic acid,2(S)-[(E)-4-[[(1,1-dimethylethyl)dimethyl silyl]oxy]-3-methyl-2-butenyl]-, 1-(1,1-dimethylethyl) 2-ethyl ester (229)

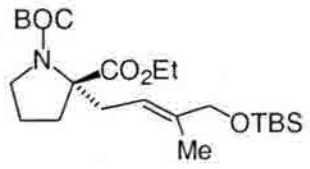
To a solution of AIBN (56.0 mg, 0.341 mmol, 0.86 eq) in toluene (20 mL) was added Bu_3SnH (892 mg, 3.06 mmol, 8 eq) via syringe under Ar, and the reaction mixture was heated to reflux. A solution of **228** (209 mg, 0.383 mmol, 1 eq) in toluene (10 mL) was added dropwise over 20 min. After 4.5 h, the solvent was removed *in vacuo* , and the residue was purified by radial chromatography (hexene:EtOAc/12:1) to yield 115 mg (69%) of an isomeric mixture of the E (**229**) and the Z isomer as a colorless oil.

There were occasions of obtaining pure E isomer by radial chromatography purification method.

Data of the E isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00-0.02 (6H, m), 0.85-0.90 (9H, m), 1.20-1.30 (3H, m), 1.35-1.45 (9H, m), 1.55-1.62 (3H, m), 1.70-1.90 (2H, m), 1.90-2.00 (2H, m), 2.60-2.90 (2H, m), 3.25-3.40 (1H, m), 3.50-3.70 (1H, m), 4.00 (2H, s), 4.05-4.20 (2H, m), 5.35 (1H, m).

IR (NaCl, film) 2954, 2928, 2855, 1738, 1699, 1388, 1251, 1169, 836 cm^{-1}



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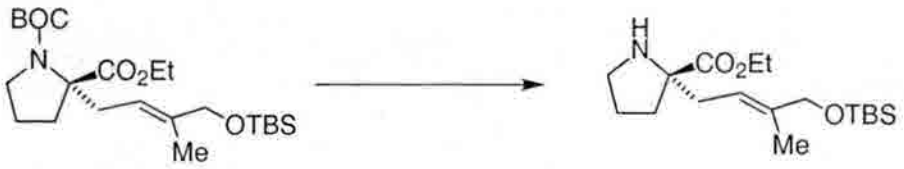


229 **230**

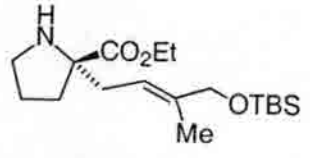
D-Proline, 2(S)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-, ethyl ester (230)

To a suspension of zinc bromide (53 mg, 0.24 mmol, 4 eq) in CH_2Cl_2 (1 mL) at room temperature was added a solution of **229** (22.7 mg, 0.051 mmol, 1 eq) in CH_2Cl_2 (600 μL + 1 mL rinse) via cannula over 2 min. After 7 h, the reaction mixture was quenched with pH sodium 10 carbonate buffer and extracted with EtOAc (2 x 15 mL). The aqueous layer was filtered through a Celite pad, and the filtrate was extracted with EtOAc (3 x 10 mL). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 19.5 mg (100%) of an isomeric mixture of the E (**230**) and the Z isomer as a colorless oil that was used without further purification.

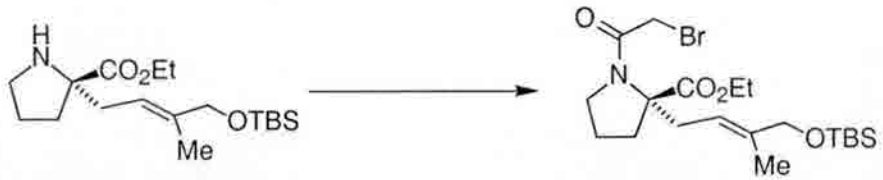
Data of the E isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.86 (9H, s), 1.20-1.40 (1H, m), 1.22 (3H, t, J = 4.4 Hz), 1.57 (3H, s), 1.60-1.80 (3H, m), 2.15 (1H, m), 2.30 (1H, dd, J = 7.5, 14.4 Hz), 2.55 (1H, dd, J = 7.5, 14.4 Hz), 2.94 (2H, t, J = 6.6 Hz), 3.96 (2H, s), 4.10 (2H, q, J = 4 Hz), 5.34 (1H, m).

IR (NaCl, film) 2957, 2855, 1731, 1253, 1180, 835 cm^{-1}.



230



230 **231**

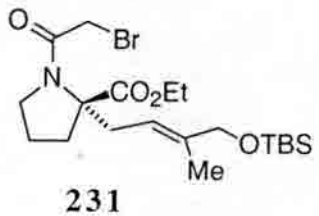
D-Proline, 1-(bromoacetyl)-2(S)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl] oxy]-3-methyl-2-butenyl]-, ethyl ester (231)

To a solution of **230** (65 mg, 0.19 mmol, 1 eq) in CH_2Cl_2 (1 mL) at 0 °C was added 0.5 M K_2CO_3 in water (572 μL, 0.286 mmol, 1.5 eq) followed by bromoacetyl bromide (57.9 mg, 0.286 mmol, 1.5 eq). After 5 h, the reaction mixture was quenched with water and extracted with EtOAc (3 x 10 mL). The organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 74 mg (83%) of an isomeric mixture of the E (**231**) and the Z isomer (a colorless oil, as an E:Z/3:1 mixture) that was used without further purification.

Data of the E isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.87 (9H, s), 1.23 (3H, t, J = 7.2 Hz), 1.58 (3H, s), 2.02 (4H, m), 2.70 (1H, dd, J = 8.4, 15 Hz), 3.13 (1H, dd, J = 6.6, 15 Hz), 3.50-3.60 (1H, m), 3.73 (1H, d, J = 7.5 Hz), 3.75 (1H, d, J = 7.5 Hz), 3.75 (1H, m), 3.97 (2H, s), 4.15 (2H, q, J = 7.2 Hz), 5.31 (1H, m).

IR (NaCl, film) 2951, 2853, 1738, 1654, 1439, 1412, 1209, 1108, 836 cm^{-1}.



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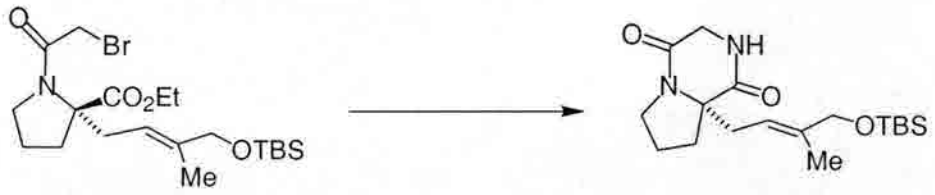


231 **232**

Pyrrolo[1,2-a]pyrazine-1,4-dione, 8a(S)-[(E)-4-[[(1,1dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]hexahydro (232)

A solution of **231** (35.0 mg, 0.076 mmol, 1.0 eq) in 2.59 M/NH_3 in MeOH (2.4 mL, 6.21 mmol, 82 eq) was stirred at room temperature for 28 h. The solvent and excess ammonia were removed *in vacuo* and a solid residue. EtOAc was added, and the resulting suspension was filtered. The filtrate was concentrated to give 26 mg (97%) of an isomeric mixture of the E (**232**) and the Z isomer as a colorless oil.

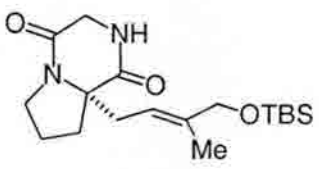
Data of the E isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 1.56 (3H, s), 1.98-2.00 (2H, m), 2.13-2.18 (2H, m), 2.47 (1H, dd, J = 8.4, 16 Hz), 2.59 (1H, dd, J = 8.4, 16 Hz), 3.45-3.55 (1H, m), 3.73 (1H, 1/2ABq, J = 16.8 Hz), 3.70-3.82 (1H, m), 3.95 (2H, s), 4.12 (1H, 1/2ABq, J = 16.8 Hz), 5.50 (1H, m), 6.00 (1H, broad, s).

IR (NaCl, film) 3241, 2952, 2927, 2857, 2892, 1667, 1445, 1254, 1107 cm^{-1}.

$[\alpha]^{D}_{25}$ = +51.4 (c 0.36, EtOAc).

For compound **235**, the enantiomer of **232**, $[\alpha]^{D}_{25}$ = -62.5 (c 0.39, EtOAc).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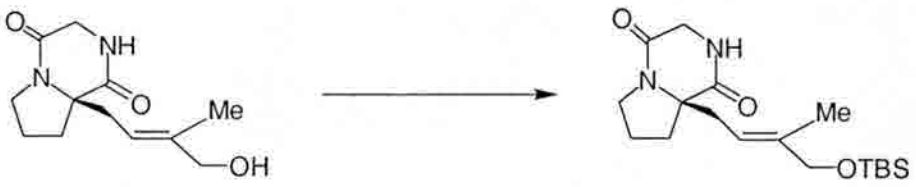


234 **235**

Pyrrolo[1,2-a]pyrazine-1,4-dione,8a(R)-[(E)-4-[[(1,1dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]hexahydro (235)

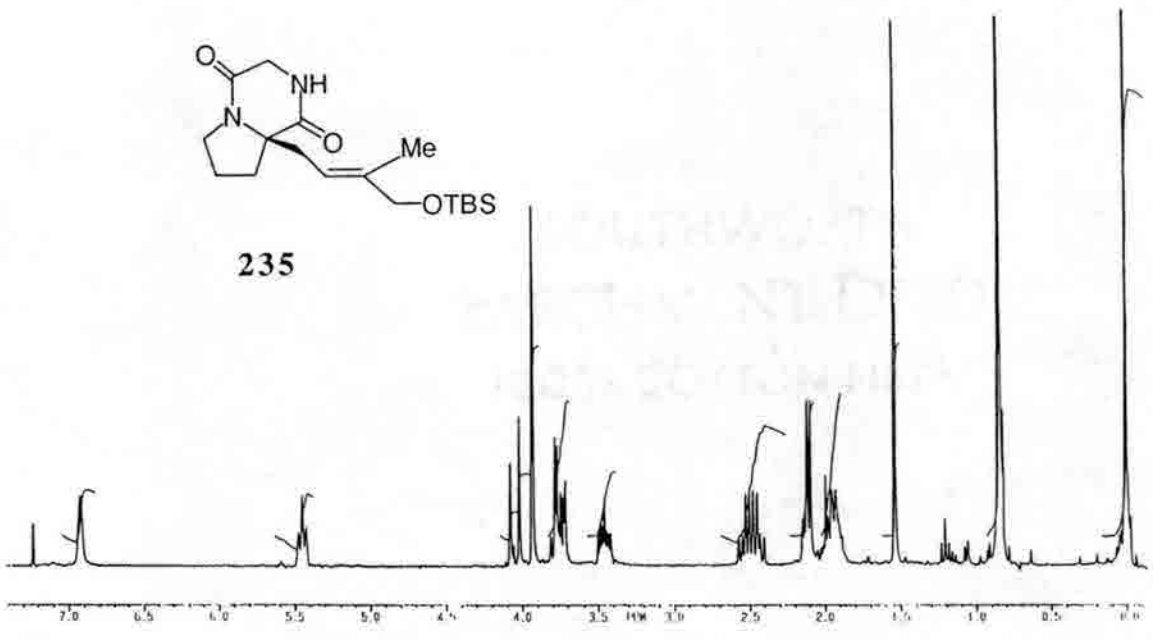
To a solution of **234** (130 mg, 0.546 mmol, 1 eq) in DMF (1.5 mL) at 0 °C was added *t*-butyldimethylsilyl chloride (124 mg, 0.819 mmol, 1.5 eq) followed by Et_3N (83.5 mg, 0.819 mmol, 1.5 eq). After 3 h, saturated NH_4Cl solution was added and the reaction mixture was extracted with EtOAc (3 x 15 mL). The organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a crude oil 176 mg. The product was purified by preparative TLC (EtOAc:MeOH/7:1) to afford 39 mg (20%) of **235** as a colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 1.56 (3H, s), 1.98-2.0 (2H, m), 2.13-2.18 (2H, m), 2.47 (1H, dd, *J* = 8.4, 16 Hz), 2.59 (1H, dd, *J* = 8.4, 16 Hz), 3.45-3.55 (1H, m), 3.73 (1H, 1/2ABq, *J* = 16.8 Hz), 3.70-3.82 (1H, m), 3.95 (2H, s), 4.12 (1H, 1/2ABq, *J* = 16.8 Hz), 5.50 (1H, m), 6.00 (1H, broad, s).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.3, 163.5, 140.3, 116.1, 67.8, 46.7, 45.2, 35.9, 34.8, 26.0, 20.4, 18.4, 13.7, 5.2.

IR (NaCl, film) 3241, 2952, 2857, 1667, 1445, 1254, 1107 cm^{-1}.

$[\alpha]^D_{25}$ = -62.5 (c 0.39, EtOAc).



235

220a **236**

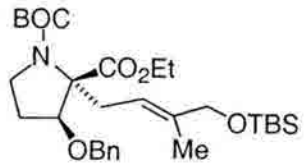
1,2-Pyrrolidinedicarboxylic acid, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, 1-(1,1-dimethylethyl) 2-ethyl ester (236)

To a suspension of 60% NaH (35.2 mg, 0.880 mmol, 1.5 eq) in THF (3 mL) at room temperature was added a solution of **220a** (91 mg, 0.20 mmol, 1 eq) in THF (8 mL) via cannula. After 5 min, Bu_4NI (91.3 mg, 0.234 mmol, 0.4 eq) and benzyl bromide (154 mg, 0.88 mmol, 1.5 eq) were added. The reaction mixture was stirred 2.5 h, quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC to give 80 mg (73%) of an isomeric mixture of the E (**236**) and the Z isomer (a colorless oil, as an E:Z/~2.3:1 mixture).

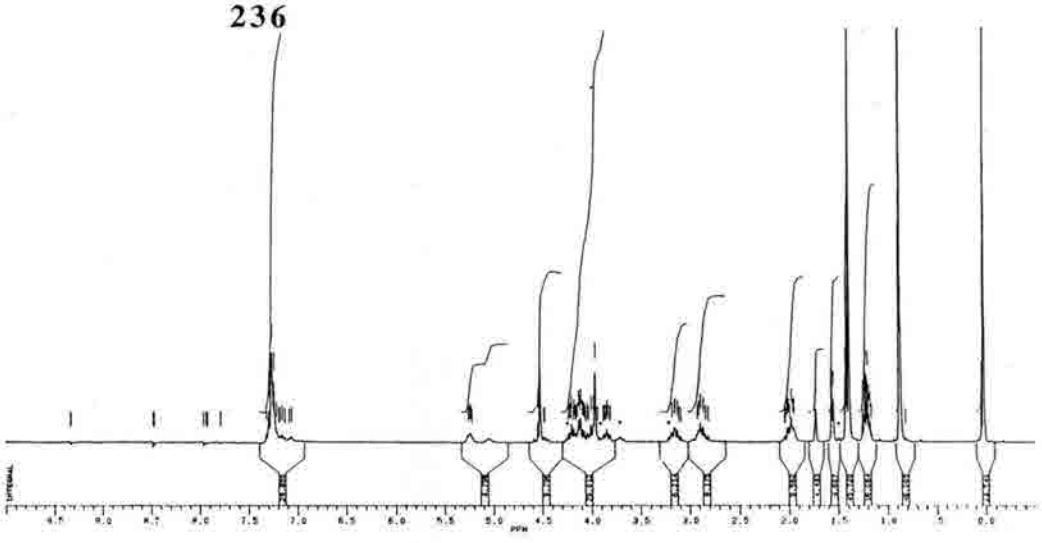
Data of the E/Z mixture:

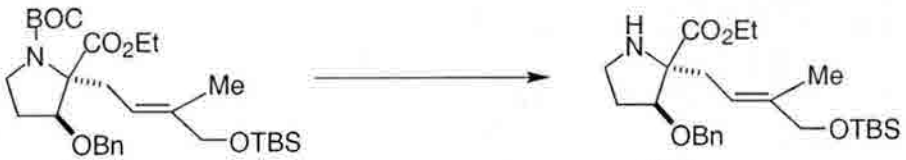
^1H NMR (270 MHz, $CDCl_3$) δ 0.01 (6H, m), 0.86 (9H, m), 1.22 (3H, m), 1.38-1.42 (9H, m), 1.54-1.72 (3H, m), 2.00 (2H, m), 2.85 (2H, m), 3.12-3.18 (1H, m), 3.80-3.93 (1H, s), 3.95 (2H, s), 4.05-4.23 (3H, m), 4.47-4.54 (2H, m), 5.05-5.25 (1H, m), 7.06-7.31 (5H, m).

IR (NaCl, film) 3066, 3030, 2976, 2954, 2885, 2857, 1737, 1705, 1696, 1392, 1250, 1112, 836, 774 cm^{-1}.



236





236 **237**

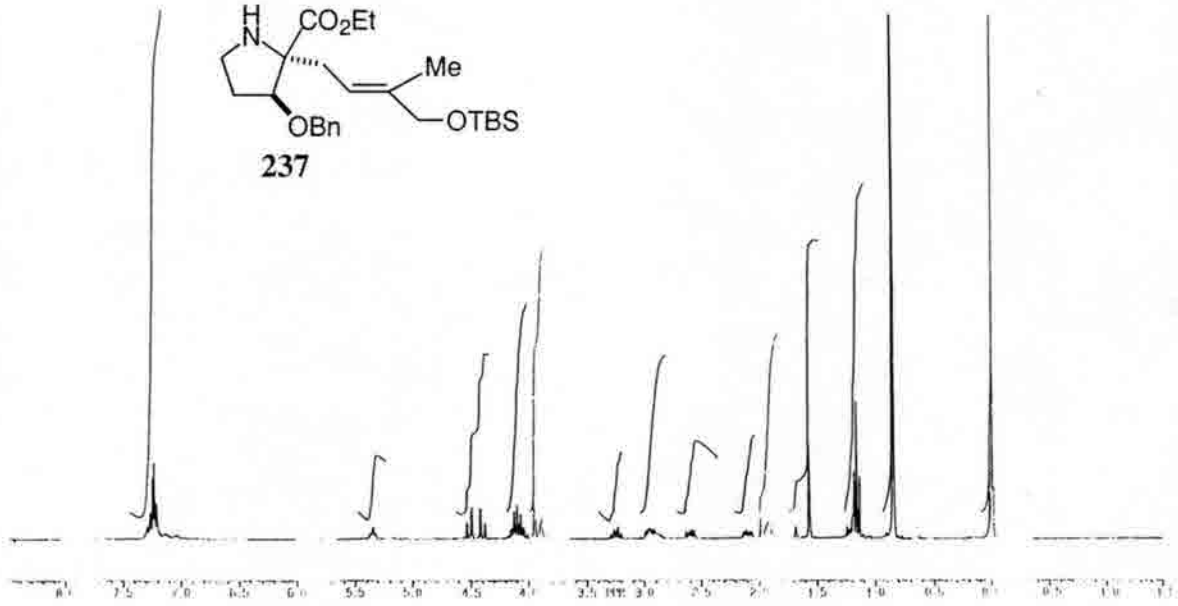
D-Proline, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, ethyl ester (237)

To a suspension of zinc bromide (568 mg, 2.40 mmol, 2.5 eq) in CH_2Cl_2 (11.4 mL) at room temperature was added a solution of **236** (550 mg, 1.0 mmol, 1 eq) in CH_2Cl_2 (10 mL) via cannula over 2 min. After 20 h, the reaction mixture was quenched with pH 10 sodium carbonate buffer and extracted with ether (90 mL, 50 mL, 2 x 40 mL). The combined ether solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 441 mg (99%) of an isomeric mixture of the E (**237**) and the Z isomer (a colorless oil, as an E:Z/2.3:1 mixture) that was used without further purification.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.85 (9H, s), 1.16 (3H, t, J = 7.2 Hz), 1.56 (3H, s), 1.89-1.94 (2H, m), 2.01-2.15 (1H, m), 2.52-2.65 (1H, m), 2.90 (1H, br, s), 2.95-2.96 (1H, m), 3.23 (1H, m), 3.94 (2H, s), 4.04-4.12 (1H, m), 4.08 (2H, q, J = 7.2 Hz), 4.41 (1H, 1/2 ABq, J = 12 Hz), 4.50 (1H, 1/2 ABq, J = 12 Hz), 5.34-5.35 (1H, m), 7.21-7.29 (5H, m).

IR (NaCl, film) 3358, 3064, 2951, 2857, 1732, 1457, 1250, 1112, 1067, 837 cm^{-1}



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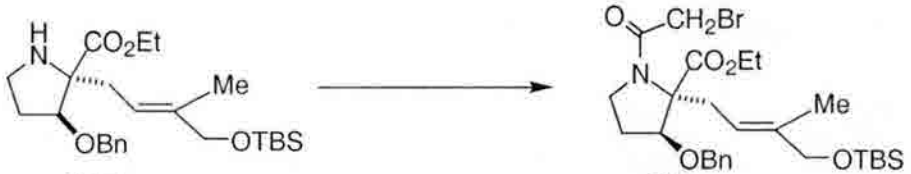


237 **238**

D-Proline,1-(bromoacetyl)-2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, ethyl ester (238)

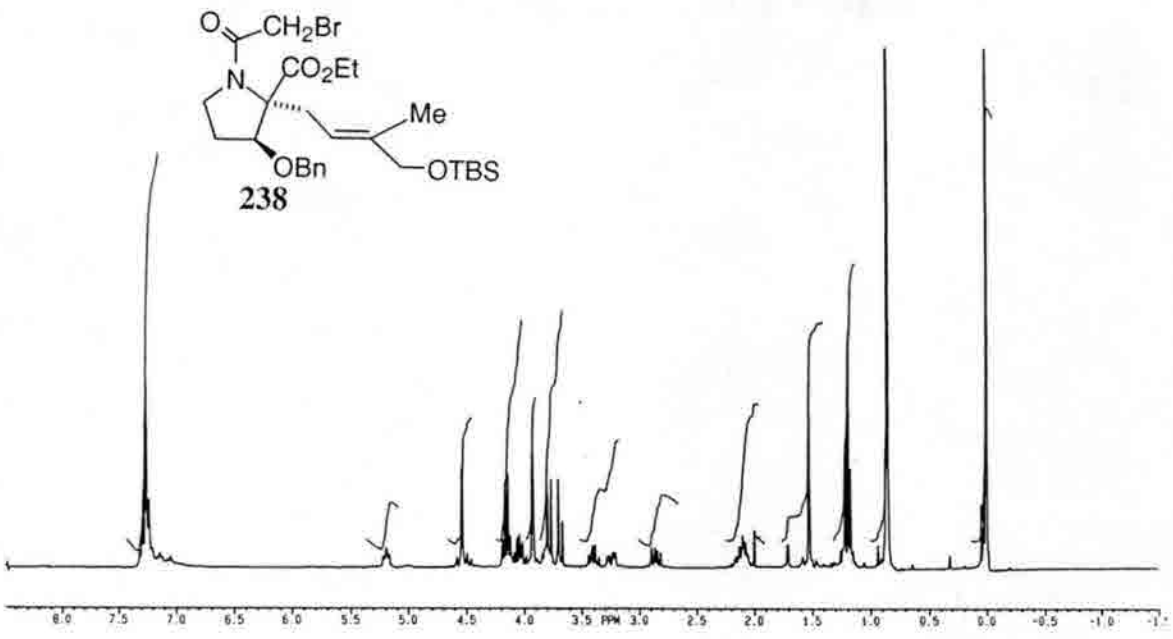
To a solution of **237** (441 mg, 0.980 mmol, 1 eq) in CH_2Cl_2 (20 mL) at 0 °C was added 0.5 M K_2CO_3 solution in water (3.3 mL, 1.65 mmol, 1.68 eq) followed by bromoacetyl bromide (408 mg, 2.00 mmol, 2 eq). After 6 h, the reaction mixture was quenched with water and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by radial chromatography (hexane:EtOAc/12:1 then 3:1) to gave 435 mg (78%) of an isomeric mixture of the E (**238**) and the Z isomer as a colorless oil.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.86 (9H, s), 1.18 (3H, m), 1.52 (3H, s), 2.00-2.15 (2H, m), 2.80-2.90 (1H, m), 3.18-3.28 (1H, m), 3.35-3.45 (1H, m), 3.65-3.70 (1H, m), 3.65-3.85 (1H, m), 3.80-3.85 (1H, m), 3.95 (2H, s), 4.00-4.10 (1H, m), 4.10-4.20 (2H, m), 4.50-4.60 (2H, m), 5.20 (1H, m), 7.25 (5H, m).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.1, 164.7, 138.8, 137.8, 128.8, 128.5, 127.6, 117.2, 82.4, 72.5, 72.1, 68.1, 61.3, 46.9, 29.8, 29.4, 27.4, 26.0, 18.4, 14.3, 14.0,-5.1.

IR (NaCl, film) 3089, 3064, 3032, 2955, 2930, 2855, 1738, 1659, 1651, 1435, 1413, 1249, 1109, 1069, 1029, 837, 776, 737 cm^{-1}.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N
CO2Et
Me
OBn
OTBS
238
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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5 PPM 3.0
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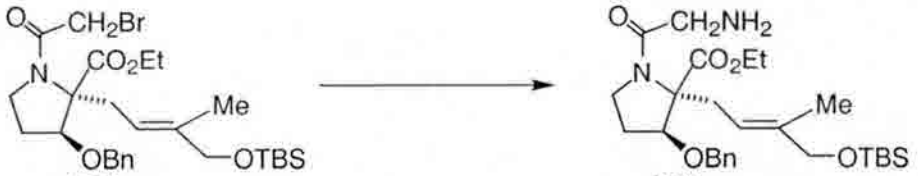
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0



238 **239**

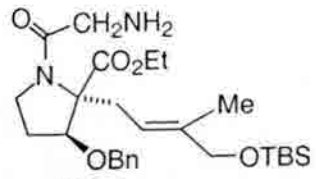
D-Proline, 1-(aminoacetyl)-2(R)-[E-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, ethyl ester (239)

A solution of **238** (435 mg, 0.74 mmol, 1.0 eq) in NH_3/MeOH (15 mL, 2.59 M, 37 mmol, 50 eq) was stirred at room temperature for 6 h. The solvent and excess ammonia were removed *in vacuo* and gave a solid residue. EtOAc was added, and the resulting suspension was filtered. The filtrate was concentrated to give 387 mg (100%) of an isomeric mixture of the E (**239**) and the Z isomer (a colorless oil, as an E:Z/2.3:1 mixture) that was used without further purification.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.86 (9H, s), 1.20 (3H, m), 1.55 (3H, s), 2.10 (2H, m), 2.85-2.95 (1H, m), 3.10-3.20 (1H, m), 3.30-3.40 (1H, m), 3.70-4.00 (5H, m), 4.00-4.10 (1H, m), 4.10-4.25 (2H, m), 4.52 (2H, s), 5.20 (1H, m), 5.50 (2H, br s), 7.40 (5H, m).

IR (NaCl, film) 3200, 3087, 3062, 2952, 2852, 1737, 1667, 1455, 1360, 1252, 1108, 1070, 836 cm^{-1}.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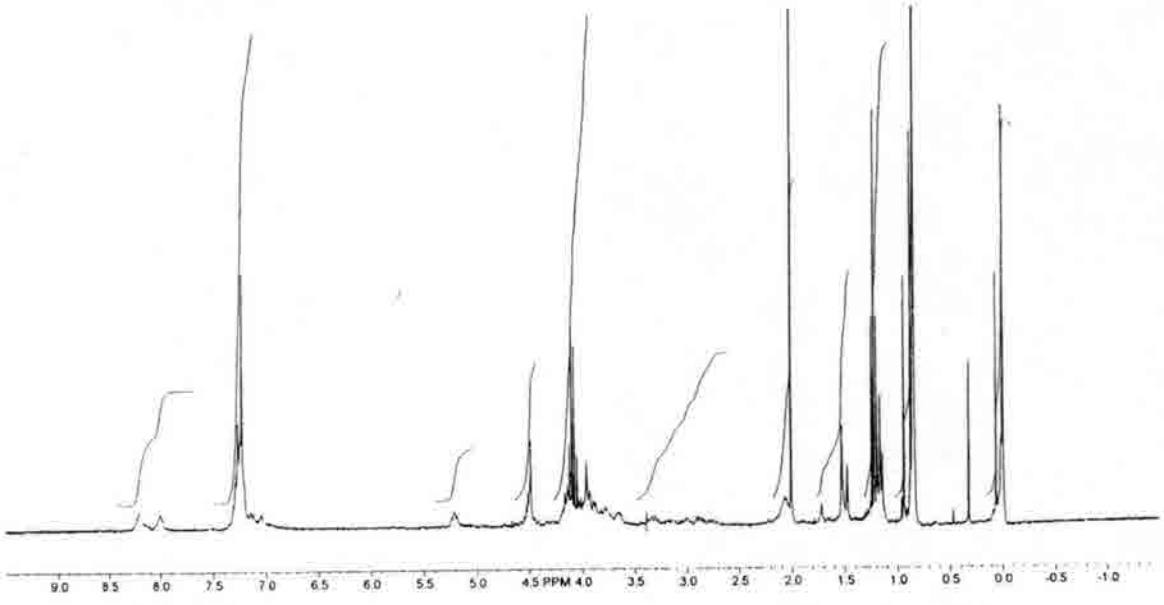
N
CO2Et
Me
OBn
OTBS

239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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
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3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

239 **240**

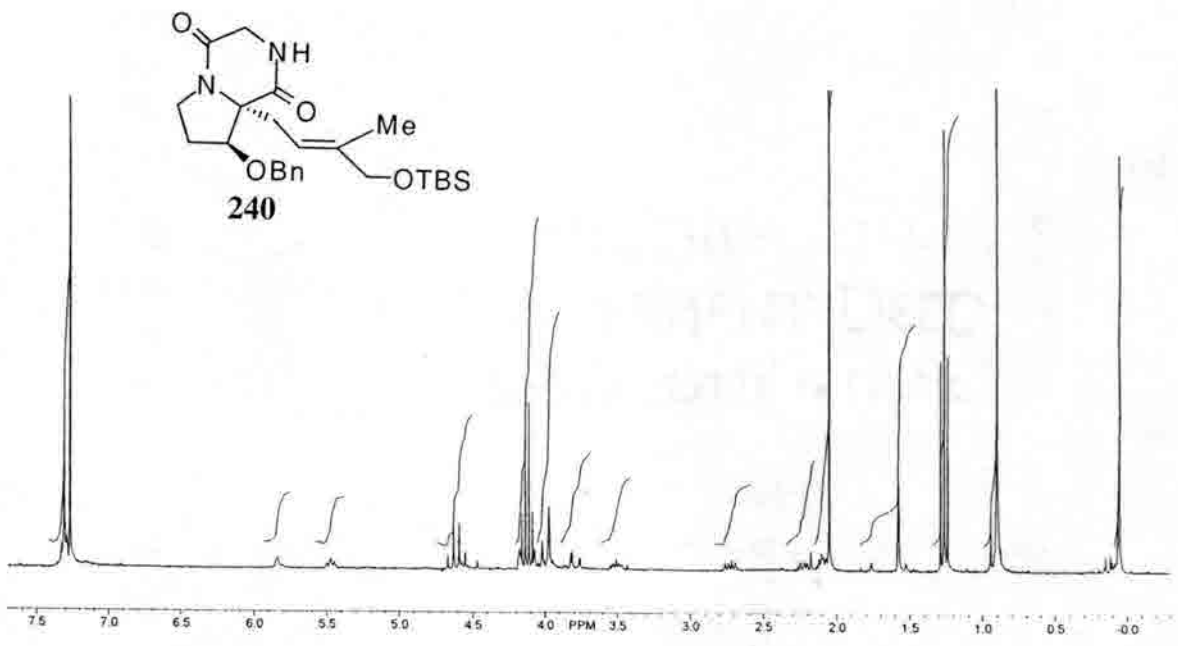
Pyrrolo[1,2-a]pyrazine-1,4-dione, 8a(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl] oxy]-3-methyl-2-butenyl]hexahydro-8(S)-(phenylmethyloxy) (240)

To a solution of **239** (197 mg, 0.388 mmol, 1 eq) in toluene (6 mL) at room temperature was added 60% NaH (64.0 mg, 1.56 mmol, 4 eq) followed by HMPA (200 μL). After 3.5 h, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with EtOAc (4 x 10 mL). The organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to give an oil. The product was purified by preparative TLC (EtOAc:MeOH/10:1) to gave 93.5 mg (53%) of an isomeric mixture of the E (**240**) and the Z isomer (a colorless oil, as an E:Z/8:1 mixture).

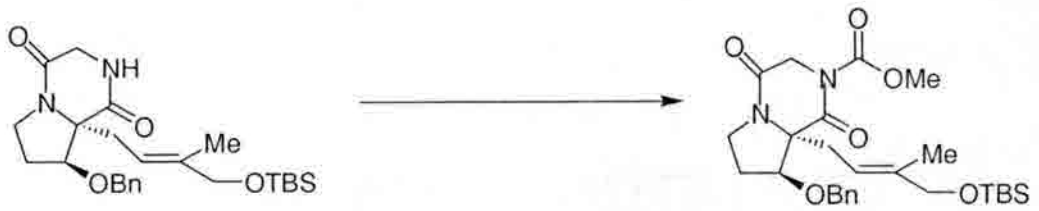
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.86 (9H, s), 1.56 (3H, s), 2.00-2.15 (2H, m), 2.16-2.25 (1H, m), 2.68-2.78 (1H, m), 3.50 (1H, m), 3.75-3.85 (1H, m), 3.96 (2H, s), 3.90-4.00 (1H, m), 4.00-4.20 (2H, m), 4.50-4.70 (2H, m), 5.50 (1H, m), 5.82 (1H, s, br) 7.40 (5H, m).

IR (NaCl, film) 3229, 3063, 2955, 2932, 2858, 1692, 1682, 1667, 1455, 1321, 1252, 1110, 1068, 837, 775, 755 cm^{-1}.



240



240 **286**

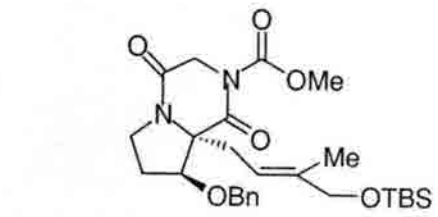
Pyrrolo[1,2-a]pyrazine-2-carboxylic acid, 8a(R)-[(E)-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]hexahydro-1,4-dioxo-8(S)-(phenylmethyloxy), 2-methyl ester (286)

To a solution of **240** (140 mg, 0.306 mmol, 1 eq) in THF (3.82 mL) at -78°C was added n-BuLi (1.6 M in hexane) (229 μL, 0.37 mmol, 1.2 eq) over 2 min under Ar. After 0.5 h, methyl chloroformate (31.7 mg, 0.336 mmol, 1.1 eq) was added over 1 min. After the reaction mixture was stirred for 35 min, it was diluted with a mixture of EtOAc (5 mL) and NH_4Cl (8 mL) solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 159.4 mg (100%) of an isomeric mixture of the E (**286**) and the Z isomer (a colorless oil, as an E:Z/8:1 mixture) that was used without further purification.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.85 (9H, s), 1.51-1.71 (3H, s), 2.06 (2H, dd, *J* = 2.1, 6.6 Hz), 2.18 (1H, dd, *J* = 8.1, 13.8 Hz), 2.74 (1H, dd, *J* = 8.1, 13.8 Hz), 3.49 (1H, dd, *J* = 6.6, 9 Hz), 3.85 (3H, s), 3.92 (2H, s), 3.90-4.00 (1H, m), 4.26 (1H, 1/2ABq, *J* = 17.1 Hz), 4.16 (1H, dd, *J* = 2.1 Hz), 4.38 (1H, 1/2ABq, *J* = 17.1 Hz), 4.50 (1H, 1/2ABq, *J* = 11.7 Hz), 4.57 (1H, 1/2ABq, *J* = 11.7 Hz), 5.41 (1H, dd, *J* = 8.1 Hz), 7.20-7.30 (5H, m).

IR (NaCl, film) 3065, 3031, 2955, 2853, 1784, 1733, 1668, 1435, 1377, 1285, 1258, 1230, 1107, 1070, 835, 777, 742 cm^{-1}.


O
O
N
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N
O
Me
OBn
OTBS

286

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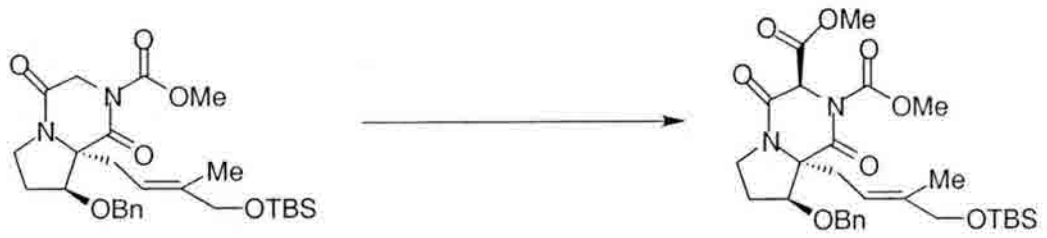


286 **287**

Pyrrolo[1,2-a]pyrazine-2,3(1H)(S)-dicarboxylic acid, 8a(R)-[(E)-4-[[(1,1-dimethyl ethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]hexahydro-1,4-dioxo-8(S)-(phenyl methyloxy)-, 2,3-dimethyl ester (287)

To a solution of **286** (137.4 mg, 0.2663 mmol, 1 eq) and methyl chloroformate (176 mg, 1.86 mmol, 7 eq) in THF (2 mL) at -78°C was added $LiN(TMS)_2$ (1.33 mL, 1.0 M in THF, 1.33 mmol, 5 eq). After 2.5 h, the reaction mixture was diluted with EtOAc at –78 °C, quenched with saturated NH_4Cl solution, and extracted with EtOAc (2 x 10 mL). The combined organic solution was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to give 145 mg (95%) of an isomeric mixture of the E (**287**) and the Z isomer (a colorless oil, as an E:Z/8:1 mixture) that was used without further purification.

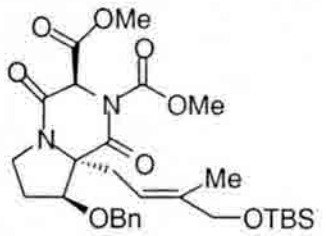
Data of the E/Z mixture:

^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.85 (9H, s), 1.56 (3H, s), 2.01-2.07 (2H, m), 2.59 (2H, dd, J = 7.5, 14.4 Hz), 3.42-3.50 (1H, m), 3.73 (3H, s), 3.86 (3H, s), 3.95 (2H, s), 4.00-4.10 (1H, m), 4.20 (1H, dd, J = 2.1, 2.7 Hz), 4.49 (1H, 1/2ABq, J = 11.7 Hz), 4.54 (1H, 1/2ABq, J = 11.7 Hz), 5.5 (1H, m), 7.20-7.30 (5H, m).

^{13}C NMR (75.47 MHz, $CDCl_3$) 165.0, 140.4, 138.0, 128.4, 127.8, 127.6, 115.4, 84.1, 74.4, 72.1, 68.1, 55.2, 54.8, 35.4, 26.6, 26.0, 18.5, 13.9, -5.1.

IR (NaCl, film) 3034, 2955, 2858, 1789, 1756, 1692, 1434, 1258, 1200, 1109, 1072, 836 cm^{-1}.

FAB HRMS m/e 573.2628 ($C_{29}H_{42}N_2O_8Si$ + H requires 573.2632)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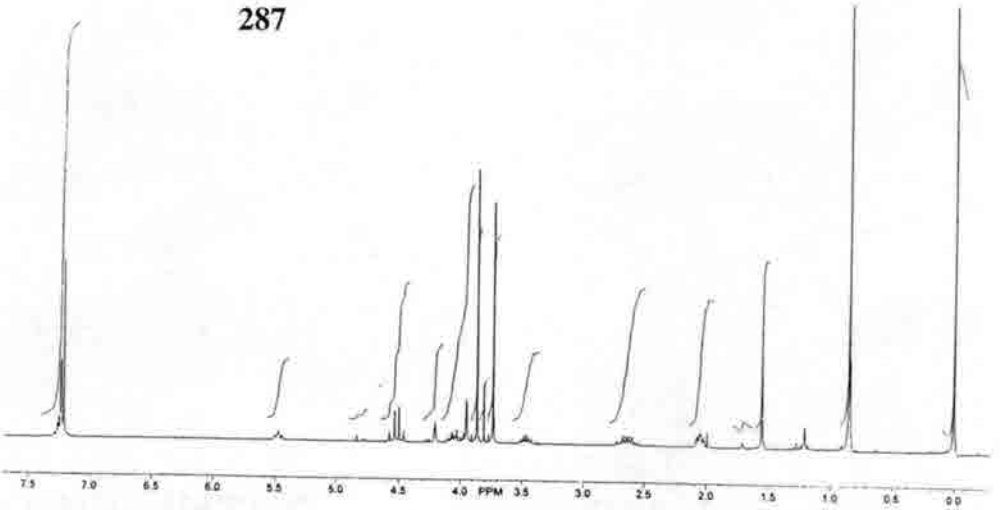
OBn
OTBS

287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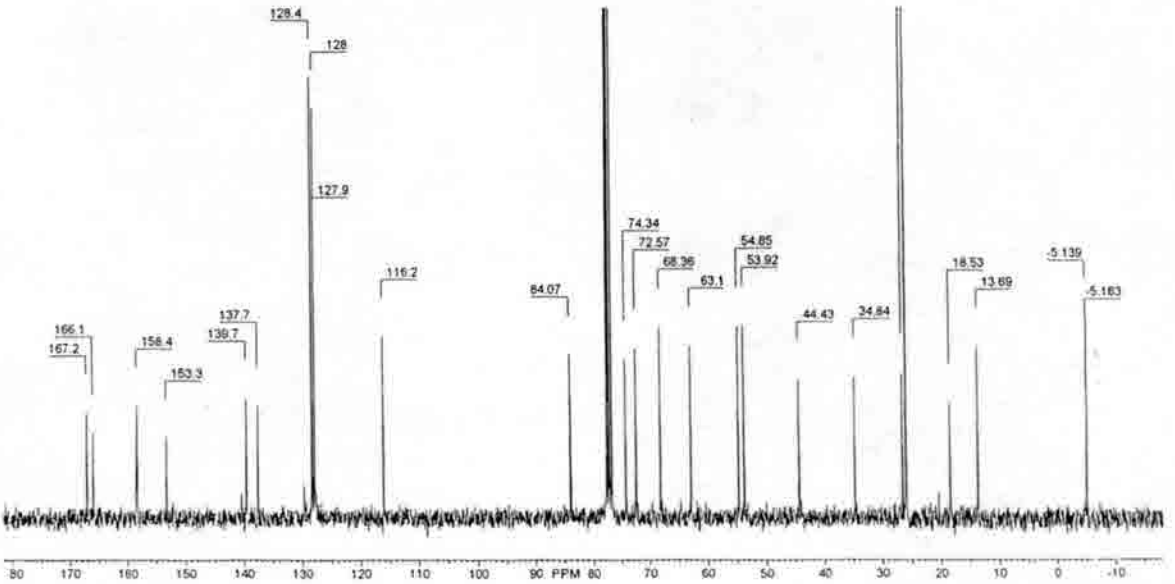
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-5.163
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167.2
158.4
153.3
137.7
139.7
80
170
160
150
140
130
120
110
100
90 PPM 80
70
60
50
40
30
20
10
0
-10

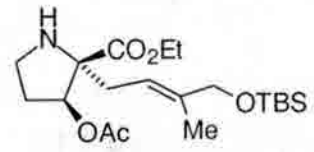
D-Proline, 3(S)-(acetyloxy)-, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3 methyl-2-butenyl], ethyl ester (244)

To a suspension of zinc bromide (552 mg, 2.45 mmol, 2.5 eq) in CH_2Cl_2 (14 mL) at room temperature was added a solution of **243** (450 mg, 0.90 mmol, 1 eq) in CH_2Cl_2 (14 mL + 3 mL rinse) via cannula over 2 min. After the reaction mixture was stirred overnight, it was quenched with pH 10 sodium carbonate buffer (140 mL) and extracted with Et_2O (3 × 40 mL). The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated to give 352 mg (98%) of an isomeric mixture of the E (**244**) and the Z isomer as a colorless oil. The product was used in the next step without further purification.

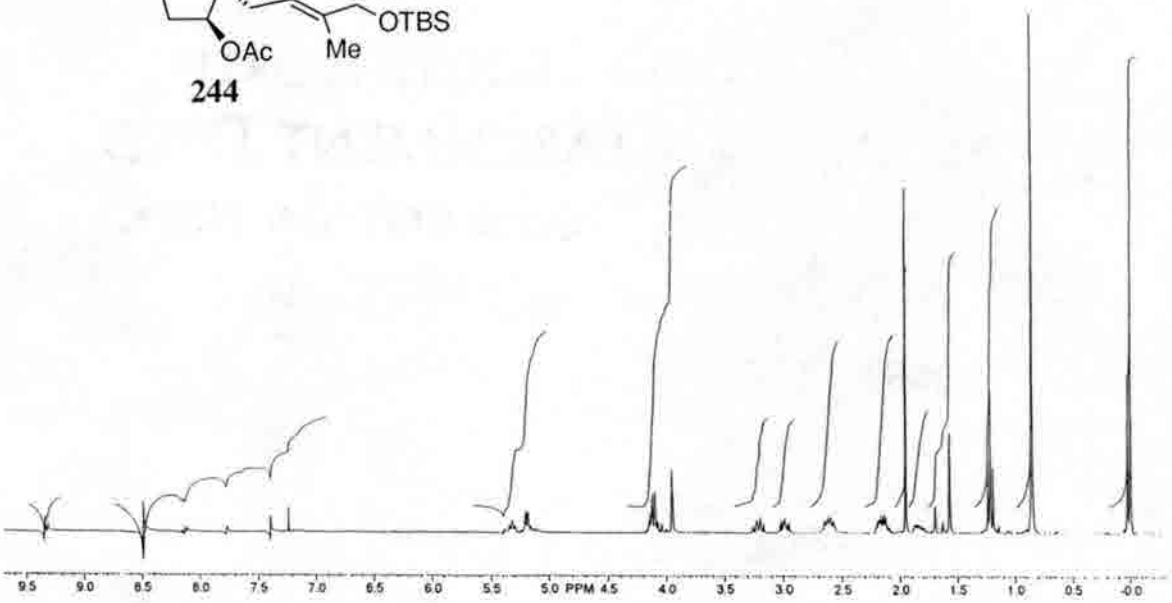
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.22-1.28 (3H, m), 1.61 and 1.74 (total 3H, s), 2.00 (3H, s), 2.20-2.32 (2H, m), 2.60-2.70 (2H, m), 3.00-3.10 (1H, m), 3.20-3.30 (1H, m), 3.99 (2H, s), 4.08-4.18 (2H, m), 5.20-5.40 (2H, m).

IR (NaCl, film) 3361, 2925, 2853, 1742, 1364, 1239, 1073, 835 cm^{-1}.


H
N
CO2Et
OTBS
OAc
Me

244


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0 PPM 4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

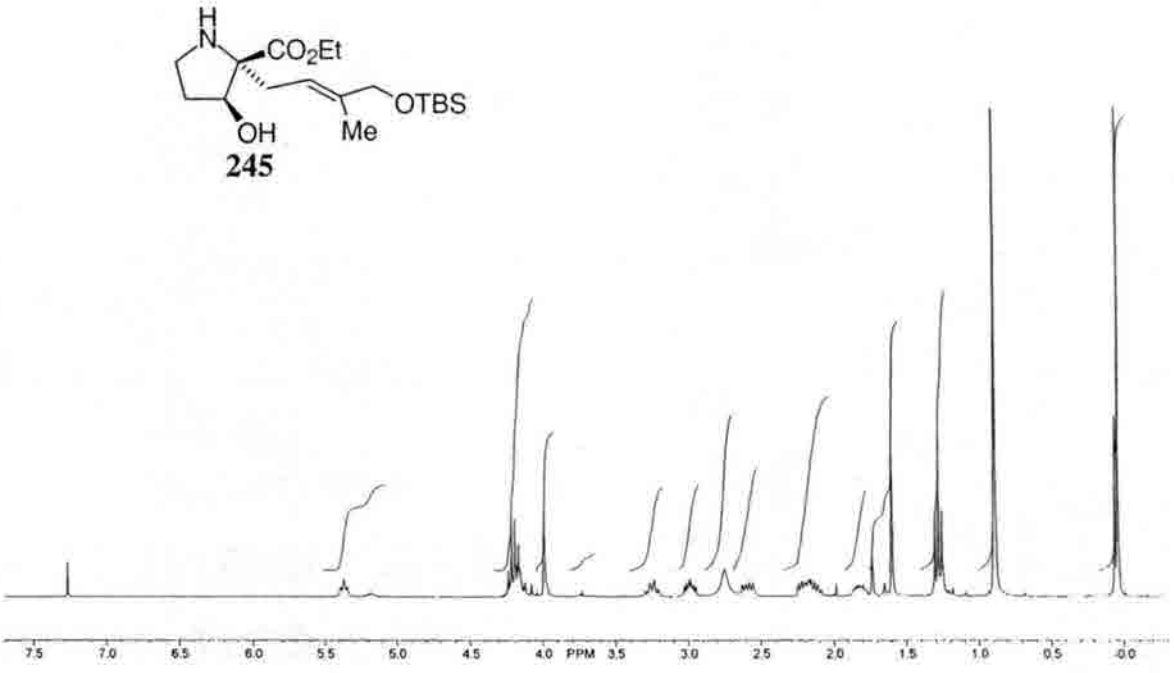
D-Proline, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl] -3(S)-hydroxy, ethyl ester (244)

A solution of **244** (541 mg, 1.35 mmol, 1 eq) in NH_3/MeOH (63.3 mmol, 5.76 M, 11 mL, 47 eq) was stirred at room temperature for 21 h. The reaction mixture was concentrated to give 473 mg (98%) of an isomeric mixture of the E (**245**) and the Z isomer as a colorless oil that was used in the next step without further purification.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.89 (9H, s), 1.20-1.30 (3H, m), 1.60 and 1.75 (total 3H, s), 1.75-1.90 (1H, m), 2.10-2.25 (2H, m), 2.55-2.65 (1H, m), 2.75 (2H, br s), 3.00 (1H, m), 3.20-3.30 (1H, m), 3.95 (2H, s), 4.10-4.25 (3H, m), 5.15-5.40 (1H, m).

IR (NaCl, film) 3360, 2955, 2858, 1738, 1732, 1251, 1072, 837 cm^{-1}.


H
N
CO2Et
OTBS
OH
Me
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

245

245 **246**

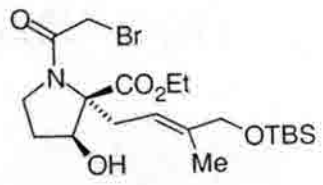
D-Proline, 1-(bromoacetyl)-2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-hydroxy-, ethyl ester (246)

To a solution of **245** (473 mg, 1.32 mmol, 1 eq) in CH_2Cl_2 (26 mL) at 0 °C was added 0.5 M K_2CO_3 solution in water (3.97 mL, 1.98 mmol, 1.5 eq) followed by bromoacetyl bromide (294 mg, 1.45 mmol, 1.1 eq). After 3 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (1 × 20 mL). The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give 490 mg (77%) of an isomeric mixture of the E (**246**) and the Z isomer (a colorless oil, as an E:Z/16:1 mixture) that was used in the next step without further purification.

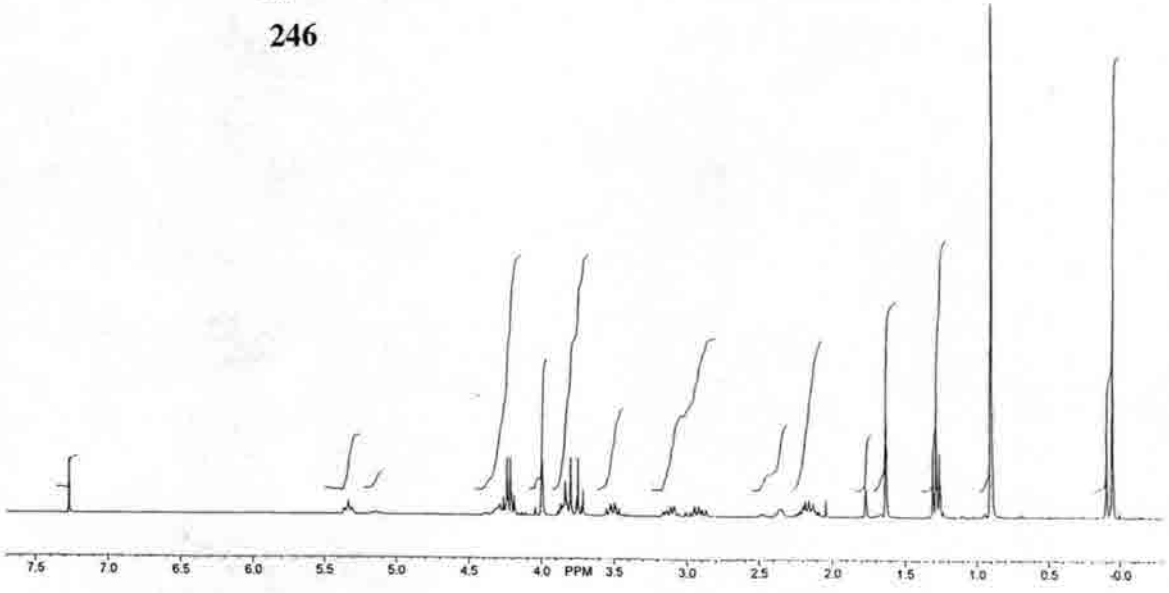
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.90 (9H, s), 1.25-1.35 (3H, m), 1.62 and 1.78 (total 3H, s), 2.10-2.25 (2H, m), 2.30-2.50 (1H, br s), 2.85-3.20 (2H, m), 3.50 (1H, m), 3.70-3.90 (3H, m), 4.00 (2H, s), 4.20-4.30 (3H, m), 5.10-5.40 (1H, m).

IR (NaCl, film) 3421, 2956, 2930, 2858, 1737, 1640, 1443, 1252, 1070, 839 cm^{-1}.


O
Br
N
CO2Et
OTBS
OH
Me

246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7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
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1.0
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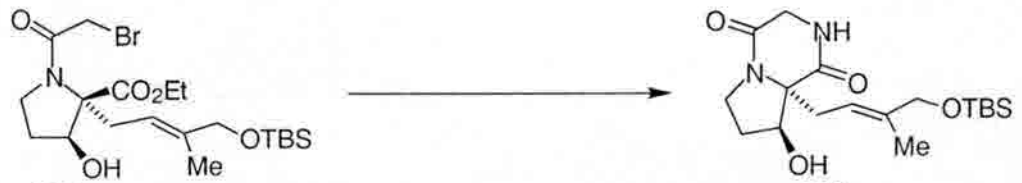
0.0



246 **248**

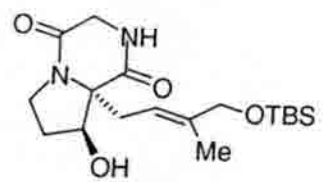
Pyrrolo[1,2-a]pyrazine-1,4-dione, 8a(R)-[(E)-4-[[(1,1-dimethylethyl) dimethylsilyl] oxy]-3-methyl-2-butenyl]hexahydro-8(S)-hydroxy (248)

A solution of **246** (478 mg, 1 mmol, 1 eq) in NH_3/MeOH (25 mL, 5.76 M, 144 mmol, 144 eq) was stirred at room temperature for 10 h. The solvent was removed under reduced pressure. EtOAc was added to the residue, and the resulting suspension was filtered. The filtrate was concentrated to give 368.5 mg (100%) of an isomeric mixture of the E (**248**) and the Z isomer (a colorless oil, as an E:Z/16:1 mixture) that was used in the next step without further purification.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.90 (9H, s), 1.25 (3H, s), 1.95-2.04 (1H, m), 2.12-2.27 (1H, m), 2.23 (1H, ddd, *J* = 7.2, 7.8, 13.8 Hz), 2.5 (1H, ddd, *J* = 7.2, 7.2, 13.8 Hz), 2.83 (1H, br s), 3.47-3.55 (1H, m), 3.74 (1H, d, *J* = 17.8 Hz), 3.92 (2H, s), 3.88-3.95 (1H, m), 4.03 (1H, 1/2ABq, *J* = 17.8 Hz), 4.35-4.72 (1H, m), 5.42(1H, dd, *J* = 7.8, 8.4 Hz), 6.46 (1H, d, *J* = 3.3 Hz).

IR (NaCl, film) 3258, 2953, 2931, 2859, 1674, 1650, 1455, 1322, 1254, 838 cm^{-1}.



248

220a **299**

1,2-Pyrrolidinedicarboxylic acid, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy] -3-methyl-2-butenyl]-3(S)-(methoxymethoxy)-, 1-(1,1-dimethylethyl), 2-ethyl-diester (299)

To a solution of **220a** (9 g, 1.69 mmol, 1 eq) in CH_2Cl_2 (50.4 mL) at 0 °C was added diisopropylethylamine (13.08 g, 98.46 mmol, 5 eq) followed by methoxymethyl chloride (8.14 g, 98.46 mmol, 5 eq). The reaction mixture was allowed to warm to 23 °C over 1 h and after 26 h, it was quenched with saturated $NaHCO_3$ (300 mL) and extracted with Et_2O. The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give an oil. TLC solvent system (hexane:EtOAc:MeOH/5:2: 0.5) was used to monitor the reaction. Purification of the product by flash column chromatography (hexane:EtOAc/6:1) afforded 9 g (91.2%) of an isomeric mixture of the E (**299**) and the Z isomer (a colorless oil, as an E:Z/3.3:1 mixture).

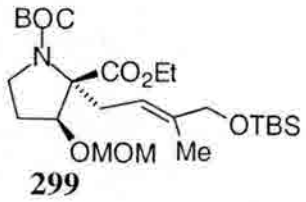
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04-0.11 (6 H, m), 0.901, 0.907 and 0.913 (total 9 H, s), 1.22-1.32 (3 H, m), 1.41, 1.44 and 1.45 (total 9 H, s), 1.63, 1.67 and 1.77 (total 3 H, s), 1.98-2.11 (2 H, m), 2.74-2.99 (2 H, m), 3.04-3.27 (1 H, m), 3.337 and 3.344 (total 3 H, s), 3.68-3.91 (1 H, m), 4.02 (2 H, s), 4.04-4.32 (3 H, m), 4.59 (1 H, 1/2ABq, J = 6.9 Hz), 4.62 (1 H, 1/2ABq, J = 6.9 Hz), 5.07 (1/5 H, m), 5.24-5.34 (4/5 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 171.6, 171.62, 153.7, 139.0, 138.5, 138.1, 120.0, 118.0, 117.6, 96.5, 96.4, 96.2, 82.6, 82.2, 81.1, 70.6, 70.1, 69.9, 68.5, 68.1, 62.0, 61.9, 61.0, 55.7, 45.7, 45.2, 31.1, 30.0, 29.5, 29.0, 28.9, 28.5, 28.4, 21.7, 14.5, 14.0, -5.1, -5.2.

IR (NaCl, film) 2957, 2852, 1739, 1701, 1391 cm^{-1}.

FAB HRMS m/e 502.3217 ($C_{25}H_{47}NO_7Si$+ H requires 502.3200)


BOC
N
CO2Et
OTBS
OMOM
Me

299

7
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4
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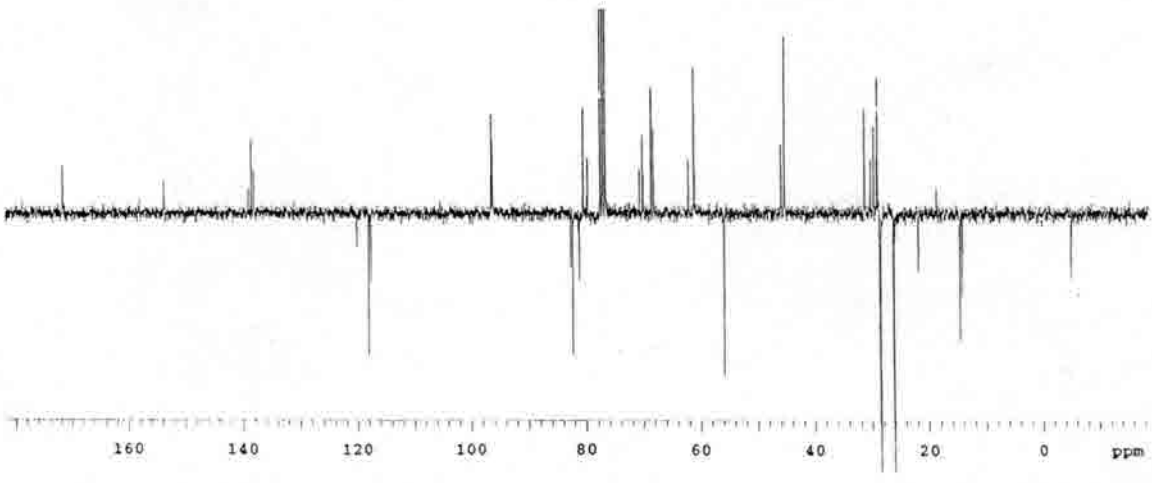
1
ppm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40
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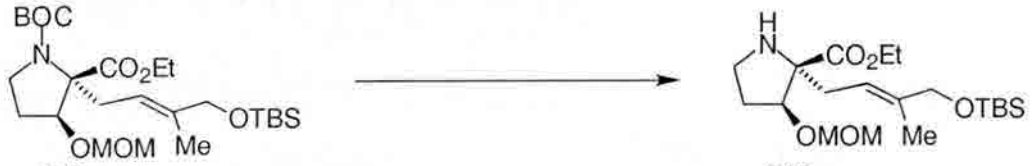
ppm



299 **300**

D-Proline,2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(methoxymethoxy)-, ethyl ester (300)

To a suspension of zinc bromide (11.0 g, 48.8 mmol, 2.7 eq) in CH_2Cl_2 (205 mL) at 23 °C was added a solution of **299** (9.0 g, 17.95 mmol, 1 eq) in CH_2Cl_2 (180 mL + 25 mL rinse) via cannula under Ar. After the reaction mixture was stirred at 23 °C for 24 h, it was checked by TLC (hexane:EtOAc:MeOH/5:2:0.5), and all the starting material had gone. The reaction mixture was poured into a flask containing pH 10 sodium carbonate buffer (2 L) and extracted with Et_2O (1300 mL, 800 mL, 700 mL). The combined Et_2O solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 6.8 g (94.4%) of an isomeric mixture of the E (**300**) and the Z isomer (a colorless oil, as an E:Z/3.5:1 mixture) that was used in the next step without further purification.

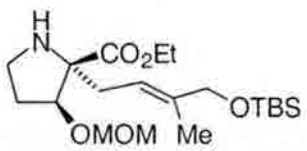
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.042, 0.044 and 0.07 (total 6 H, s), 0.87-0.94 (9 H, m), 1.27 (3 H, t, J = 7.2 Hz), 1.63 and 1.74 (total 3 H, br s), 1.91-2.11 (2 H, m), 2.12-2.25 (1 H, m), 2.67 (1 H, dd, J = 14.4, 7.8 Hz), 2.74-3.14 (2 H, m), 3.24-3.43 (1 H, m), 3.35 (3 H, s), 4.00 (2 H, br s), 4.05-4.30 (3 H, m), 4.60 (1 H, 1/2ABq, J = 6.9 Hz),), 4.63 (1 H, 1/2ABq, J = 6.9 Hz), 5.21 (2/7 H, m), 5.39 (5/7 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 172.9, 138.4, 138.0, 120.3, 118.9, 100.1, 95.6, 83.5, 74.4, 68.7, 62.1, 61.29, 61.25, 55.7, 44.6, 44.5, 35.3, 35.0, 31.8, 26.1, 21.5, 18.5, 14.3, 14.0, -5.1, -5.2.

IR (NaCl, film) 3360, 2953, 2891, 1739, 1250, 1182, 1040, 836 cm^{-1}.

FAB HRMS m/e 402.2665 ($C_{20}H_{39}NO_5Si$ + H requires 402.2675)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N
CO2Et
OTBS
OMOM
Me

300

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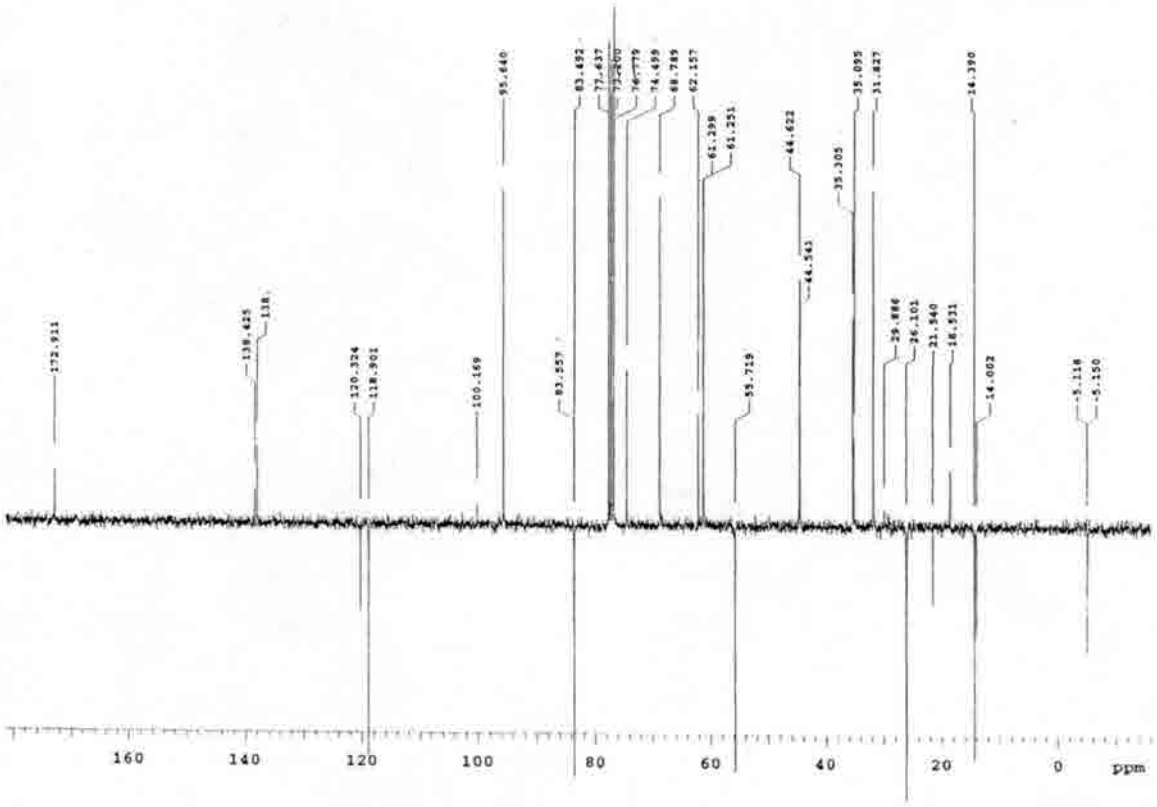
6
5
4
3
2
1
0
ppm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68.789
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61.399
61.251
55.719
44.622
44.543
35.305
35.095
31.827
29.886
26.101
21.540
18.531
14.390
14.002
-5.118
-5.150
160
140
120
100
80
60
40
20
0
ppm

300 **301**

D-Proline,1-(bromoacetyl)-2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(methoxymethoxy), ethyl ester (301)

To a stirred solution of **300** (3.40 g, 8.48 mmol, 1 eq) in CH_2Cl_2 (155 mL) at 0 °C was added 0.5 M K_2CO_3 solution in water (43 mL, 21.2 mmol, 2.5 eq) followed by bromoacetyl bromide (34.8 g, 16.9 mmol, 2 eq). After 2.5 h, the reaction mixture was quenched with saturated $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give 4.4 g (100%) of an isomeric mixture of the E (**301**) and the Z isomer (a colorless oil, as an E:Z/3.5:1 mixture) that was used in the next step without further purification.

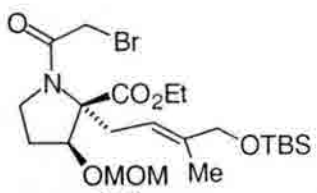
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 and 0.08 (total 6 H, br s), 0.91 (9 H, s), 1.27 and 1.28 (total 3 H, t, J = 7.2 Hz), 1.64 and 1.77 (total 3 H, s), 2.14-2.25 (2 H, m), 2.78-2.91 (1 H, m), 3.12-3.53 (2 H, m), 3.357 and 3.363 (total 3 H, s), 3.74 and 3.75 (total 1 H, 1/2ABq, J = 10.8 Hz), 3.83 and 3.85 (total 1 H, 1/2ABq, J = 10.8 Hz), 4.00 (2 H, br s), 4.07-4.27 (3 H, m), 4.64 (2 H, s), 5.05 (1/3 H, m), 5.26 (2/3 H, m).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.1, 164.8, 164.7, 139.7, 138.9, 119.5, 117.0, 96.5, 96.4, 81.0, 80.7, 71.7, 71.6, 68.2, 61.9, 61.4, 55.8, 30.1, 29.9, 29.6, 27.3, 26.1, 21.8, 18.5, 14.2, 14.0, -5.0.

IR (NaCl, film) 2955, 2893, 1747, 1650, 1416, 1249, 839, 776 cm^{-1}.

FAB HRMS m/e 522.1727 ($C_{22}H_{40}BrNO_6Si$ + H requires 522.1709).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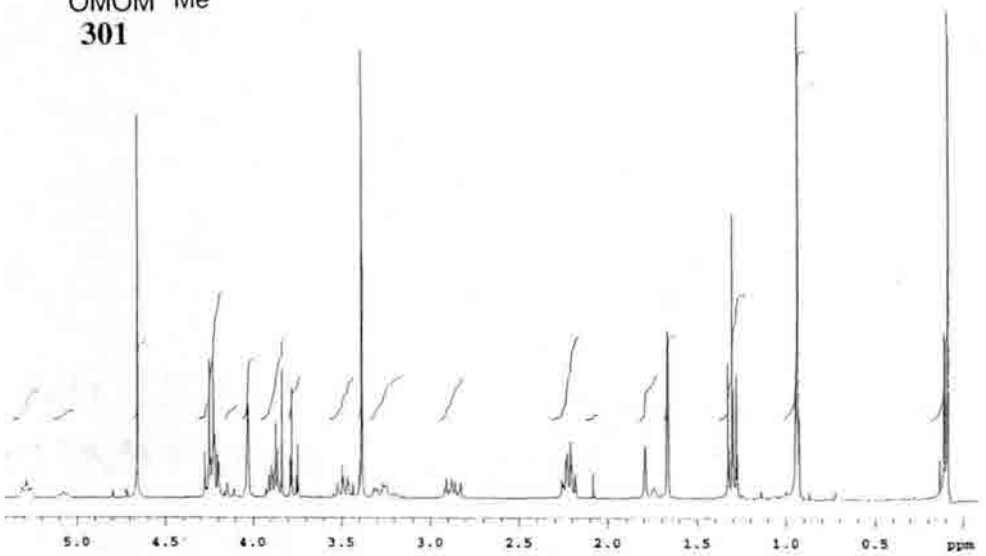
Br
N
CO2Et
OTBS
OMOM
Me

301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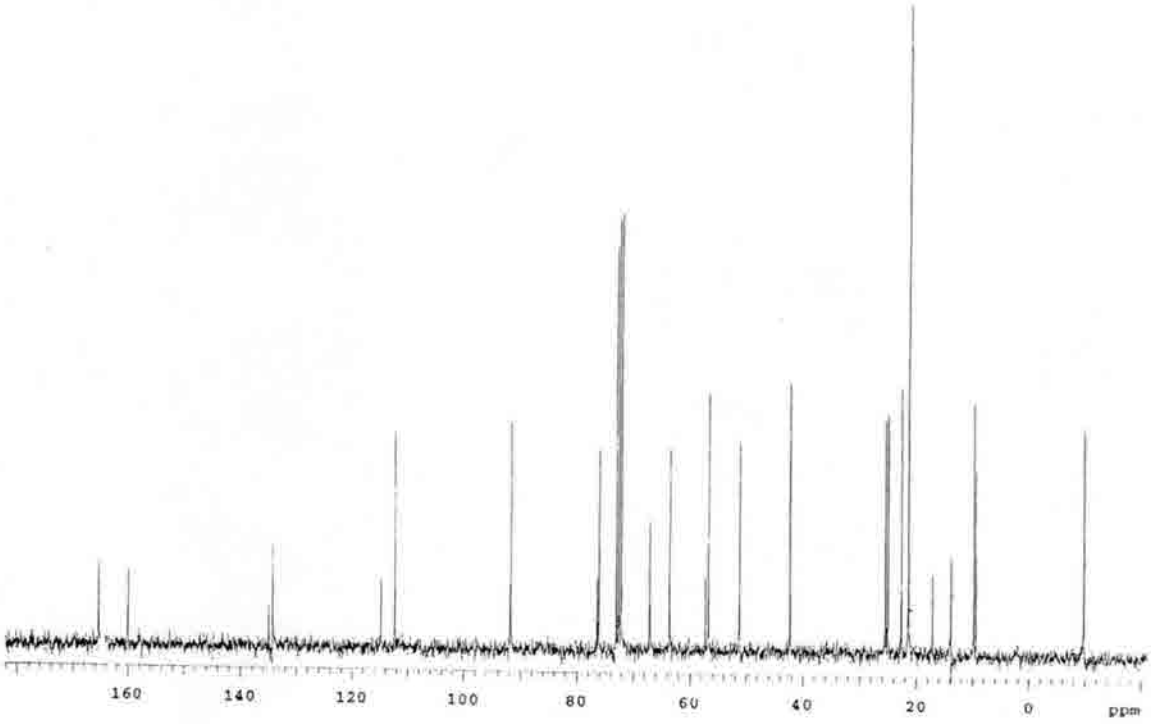
1.5
1.0
0.5
ppm


160
140
120
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80
60
40
20
0
ppm

301 **241**

D-Proline,1-(aminoacetyl)-2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(methoxymethoxy), ethyl ester (241)

To a stirred solution of **301** (6.66 g, 12.77 mmol, 1 eq) in CH_3OH (296 mL) at 23 °C was added NH_3/MeOH (165 mL, 5.76 M, 950 mmol, 75 eq) over 1 min. After 2 h, the solvent and excess ammonia were removed under reduced pressure. EtOAc (600 mL) was added to the residue followed by saturated $NaHCO_3$ (600 mL) and 1 N NaOH (60 mL) solutions. The organic layer was separated, and the aqueous layer was extracted with EtOAc (1 × 200 mL). The combined organic solution was washed with brine (2 × 200 mL), dried over Na_2SO_4 and concentrated to give 5.49 g (94%) of an isomeric mixture of the E (**241**) and the Z isomer (a colorless oil, as an E:Z/3.5:1 mixture) that was used in the next step without further purification.

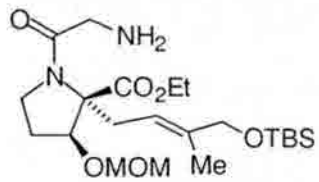
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00-0.10 (6 H, m), 0.87 and 0.89 (total 9 H, s), 1.15-1.33 (3 H, m), 1.51-1.80 (3 H, m), 1.99-2.28 (2 H, m), 2.60-2.95 (1 H, m), 2.95-3.86 (8 H, m), 3.90-4.06 (2 H, m), 4.06-4.45 (3 H, m), 4.50-4.76 (2 H, m), 4.90-5.50 (1 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 170.2, 169.8, 168.6, 163.3, 162.5, 140.7, 139.2, 138.9, 138.5, 117.2, 116.8, 114.9, 96.3, 96.33, 96.1, 80.8, 80.5, 79.9, 72.8, 72.5, 71.9, 68.1, 67.6, 61.9, 61.3, 61.1, 56.0, 55.8, 48.2, 46.2, 45.1, 43.2, 34.6, 30.3, 30.0, 27.1, 26.0, 25.8, 18.4, 14.3, 14.0, 13.7, -3.4, -5.1, -5.2.

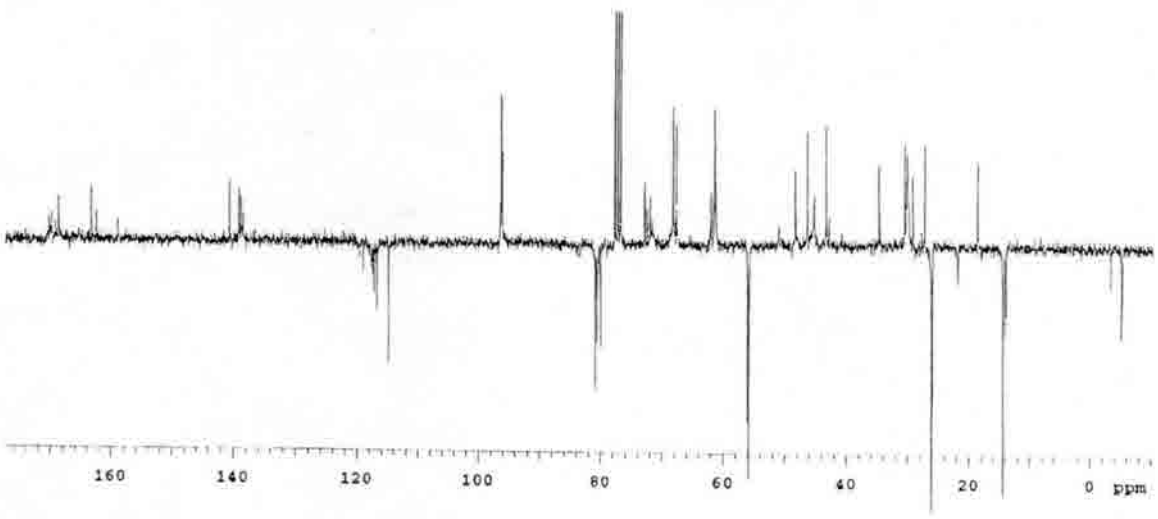
IR (NaCl, film) 3474, 3316, 3060, 2951, 2843, 1745, 1652, 1454, 1252, 1045, 838, 774 cm^{-1}.

FAB HRMS m/e 459.2908 ($C_{22}H_{42}N_2O_6Si$ + H requires 459.2890)


O
NH2
N
CO2Et
OTBS
OMOM
Me

241

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


160
140
120
100
80
60
40
20
0
ppm

241 **242**

Pyrrolo[1,2-a]pyrazine-1,4-dione, 8a(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl] oxy]-3-methyl-2-butenyl]hexahydro-8(S)-(methoxy methoxy) (242)

To a stirred solution of **241** (2.74 g, 5.98 mmol, 1 eq) in toluene (70 mL) at 23 °C was added 60% NaH (710 mg, 17.9 mmol, 3 eq) over 5 min followed by HMPA (5.5 mL). After 75 min, the reaction mixture was added dropwise to a saturated NH_4Cl solution (300 mL). The mixture was extracted with EtOAc (300, 200, 100 mL). The combined organic solution was washed with brine (3 × 260 mL), dried over Na_2SO_4 and concentrated to give an oil. Purification of the product by flash column chromatography (EtOAc) provided 2.06 g (84%) of an isomeric mixture of the E (**242**) and the Z isomer (a colorless oil, as an E:Z/~3:1 mixture).

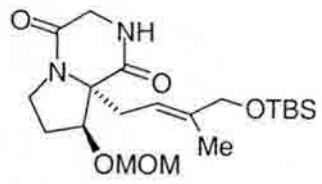
Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 and 0.04 (total 6 H, s), 0.88 (9 H, s), 1.56 and 1.74 (total 3 H, s), 2.02-2.32 (3 H, m), 2.60-2.76 (1 H, m), 3.34 and 3.35 (total 3 H, s), 3.51 (1 H, m), 3.72-3.85 (1 H, m), 3.89-4.07 (2 H, m), 3.96 (2 H, br s), 4.26-4.33 (1 H, m), 4.58 and 4.59 (total 1 H, 1/2ABq, J = 7.2 Hz), 4.70 (1 H, 1/2ABq, J = 7.2 Hz), 5.19 (1/3 H, m), 5.44 (2/3 H, m), 6.44-4.72 (1 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 168.9, 163.5, 141.8, 140.8, 117.5, 115.0, 96.2, 80.9, 72.9, 67.7, 61.6, 56.1, 46.3, 43.4, 34.7, 34.6, 27.2, 26.1, 21.8, 18.5, 13.9, -5.0, -5.1.

IR (NaCl, film) 3237, 2955, 2855, 1694, 1638, 1639, 1053, 1323, 1252, 1112, 1064, 835, 775 cm^{-1}.

FAB HRMS m/e 413.2475 ($C_{20}H_{36}N_2O_5Si$ + H requires 413.2471)


O
NH
N
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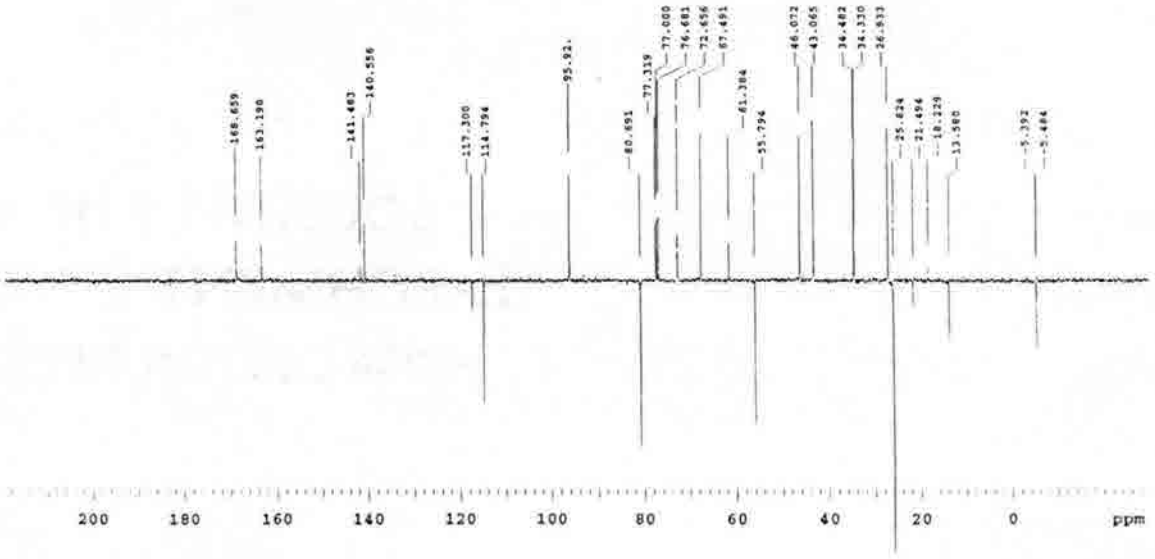
OTBS
Me
OMOM

242

9
8
7
6
5
4
3
2
1
ppm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43.065
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25.824
21.494
18.229
13.580
-5.392
-5.484
200
180
160
140
120
100
80
60
40
20
0
ppm

242 **91**

Pyrrolo[1,2-a]pyrazine-2,3(1H)-dicarboxylic acid, 8a(R)-[(E)-4-[[(1,1-dimethyl ethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]hexahydro-1,4-dioxo-8(S)-(methoxy methoxy)-, 2,3-dimethyl ester (91)

To a stirred solution of **242** (5.02 g, 12.17 mmol, 1 eq) in THF (192 mL) at –78 °C under Ar was added n-BuLi (1.1 M in hexane) (14.4 mL, 15.83 mmol, 1.3 eq) over 6 min. When the addition of n-BuLi was almost over, the reaction mixture changed to brown, and then was stirred for an additional 10 min. Methyl chloroformate (1.49 g, 15.8 mmol, 1.3 eq) was added over 3 min. After 40 min, the reaction was complete (TLC system EtOAc:MeOH/10:1) and the reaction mixture was stirred for an additional 10 min. At this time, methyl chloroformate (4.60 g, 48.7 mmol, 4 eq) was added by syringe to the above reaction mixture at –78 °C over 2 min, followed by $LiN(TMS)_2$ (60.8 mL, 6o.8 mmol, 1.0 M in THF, 5 eq) over 8 min. After the reaction mixture was stirred for 70 min (TLC system EtOAc), it was quenched with EtOAc (400 mL) and saturated NH_4Cl solution (800 mL). The EtOAc layer was separated, and the aqueous layer was extracted with EtOAc (2 × 400 mL). The combined organic solution (red color) was washed with brine (3 × 500 mL), dried over Na_2SO_4 and concentrated to give a red oil. Purification of the product by flash column chromatography (EtOAc) gave 6.0 g (93.4%) of an isomeric mixture of the E (**91**) and the Z isomer (a colorless oil, as an E/Z mixture).

Data of the E/Z mixture:

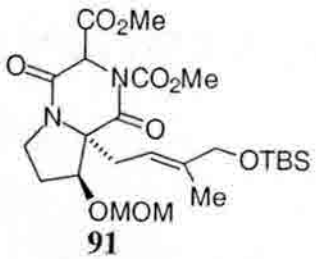
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (6 H, s), 0.89 and 0.90 (total 9 H, s), 1.53, 1.58 and 1.75 (total 3 H, br s), 1.84-2.35 (2 H, m), 2.44-2.80 (2 H, m), 3.345 and 3.348 (total 3 H, s), 3.35-3.69 (2 H, m), 3.86 (3 H, s), 3.90 (3 H, s), 3.91-4.15 (3 H, m), 4.35 and 4.37

(total 1 H, br s), 4.572 and 4.575 (total 1 H, 1/2ABq, J = 7.2 Hz), 4.65 (1 H, 1/2ABq, J = 7.2 Hz), 5.23 (1/3 H, m), 5.43 (2/3 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 167.1, 165.8, 158.4, 158.42, 140.2, 139.8, 118.0, 116.0, 113.5, 96.2, 96.1, 81.7, 81.0, 74.1, 74.0, 68.3, 67.3, 63.2, 61.8, 67.3, 56.2, 54.8, 54.0, 44.4, 44.2, 34.9, 34.6, 27.3, 27.0, 26.1, 21.9, 21.2, 18.5, -5.0.

IR (NaCl, film) 2955, 2857, 1793, 1749, 1680, 1434, 1375, 1222, 1035, 838, 779 cm^{-1}.

FAB HRMS m/e 529.2592 ($C_{24}H_{40}N_2O_9Si$ + H requires 529.2581)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OTBS
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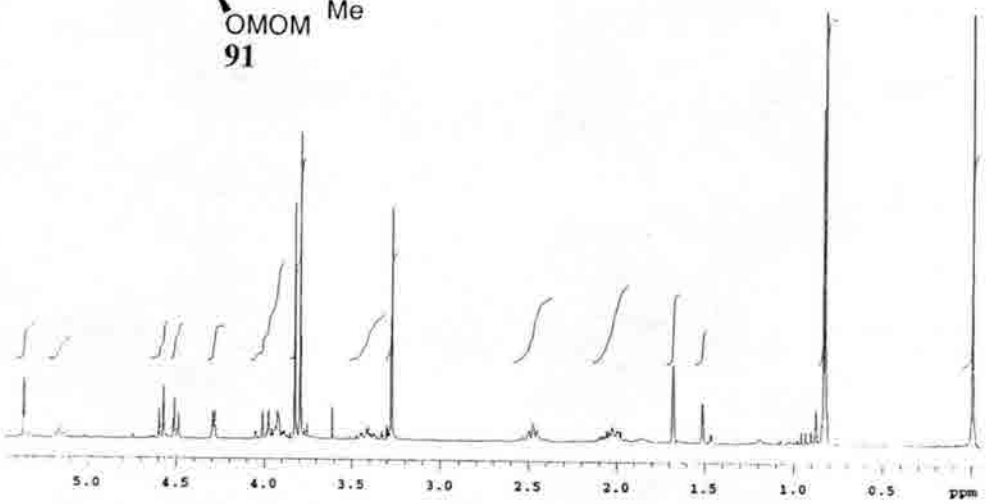
OMOM

91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2.0
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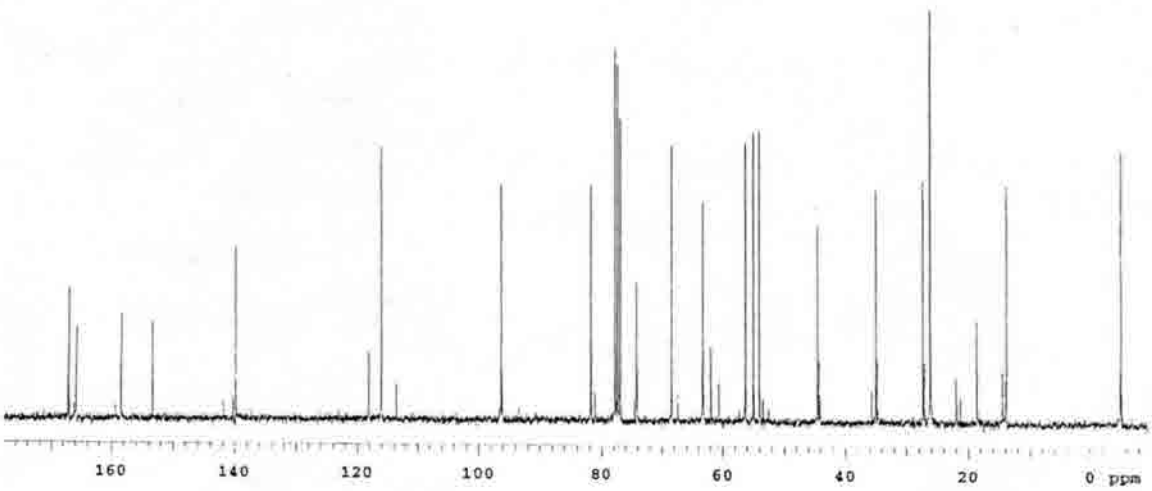
1.0
0.5
ppm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80
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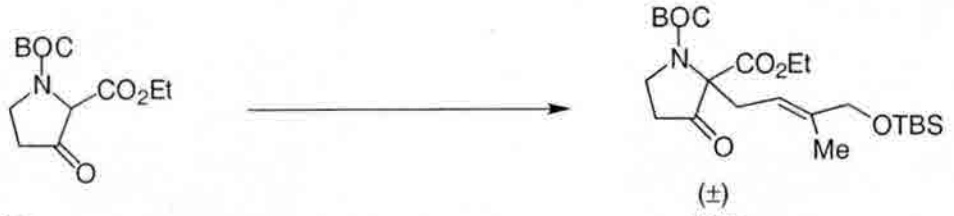


131 (±) 166

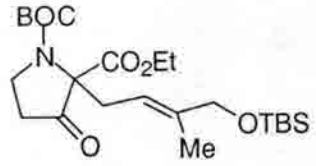
1,2-Pyrrolidinedicarboxylic acid, 3-oxo-, 2(R/S)-[(E)-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl], 1-(1,1-dimethylethyl) 2-ethyl ester (166)

To a suspension of 60% NaH (88 mg, 2.2 mmol, 1.1 eq) in DME (5 mL) at 0 °C was added a solution of **131** (514 mg, 2.0 mmol, 1 eq) in DME (1 mL). After 10 min, t-butyldimethylsilylether substituted prenyl iodide (915 mg, 3.10 mmol, 1.4 eq) was added. After the reaction mixture was stirred at 23 °C for 30 min and at 41 °C for 17 h, it was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Purification of the product by radial chromatography (hexane:EtOAc/25:1) provided 637 mg (70%) of an isomeric mixture of the E (**166**) and the Z isomer (a colorless oil, as an E:Z/10.3:1 mixture).

Data of the E/Z mixture:

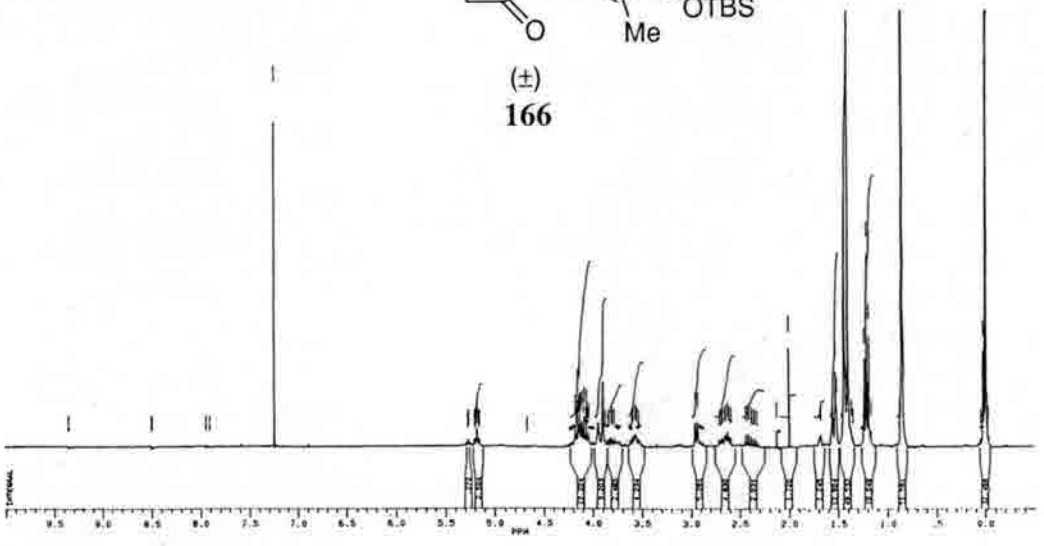
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01-0.05 (6H, m), 0.83-0.87 (9H, m), 1.16-1.23 (3H, m), 1.35-1.43 (9H, m), 1.51-1.56 and 1.68 (total 3H, m), 2.29-2.45 (1H, m), 2.25-2.71 (1H, m), 2.85-2.97 (2H, m), 3.53-3.60 (1H, m), 3.78-3.87 (1H, m), 3.90-3.94 (2H, m), 4.05-4.21 (2H, m), 5.14-5.47 (total 1H, m).

IR (NaCl, film) 2974, 2928, 2856, 1769, 1738, 1707, 1389, 1251, 1109, 835, 769 cm^{-1}.



(±)

166



(±) **166** (±) **167**

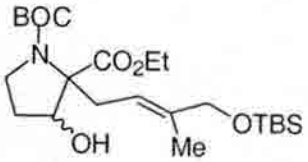
1,2-Pyrrolidinedicarboxylic acid, 2(R/S)-[(E)-4-[[(1,1-dimethylethyl)dimethyl silyl]oxy]-3-methyl-2-butenyl]-3(R/S)-hydroxy-,1-(1,1-dimethylethyl) 2-ethyl ester (167)

To a stirred solution of **166** (303 mg, 0.666 mmol, 1 eq) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (103 mg, 2.66 mmol, 4 eq) over 10 min. After 7 h, the reaction mixture was quenched with 0.25 M $KHSO_4$ solution (0.6 mL). The solvent was removed under reduced pressure. Water was added to the residue followed by aqueous $KHSO_4$ solution until the acidity of the mixture reached pH 2-3. The product was extracted with $CHCl_3$ (4 × 30 mL). The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give a colorless oil. Preparative TLC purification of the product (hexane:EtOAc:MeOH/5:2:0.5) provided 280 mg (92%) of an isomeric mixture of the E (**167**) and the Z isomer as a colorless oil.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.89 (9H, s), 1.20-1.30 (3H, m), 1.35-1.45 (9H, m), 1.50-1.65 (3H, m), 1.65-1.80 (1H, m), 2.05-2.15 (1H, m), 2.30-2.70 (1H, m), 2.70-2.90 (1H, m), 3.30-3.70 (2H, m), 3.95 (2H, s), 4.05-4.20 (3H, m), 4.25-4.50 (1H, m), 5.25-5.50 (1H, m).

IR (NaCl, film) 3426, 2976, 2892, 1731, 1738, 1698, 1673, 1391, 1366, 1252, 1174, 837.



(±)

167

(±) **167** (±) **169**

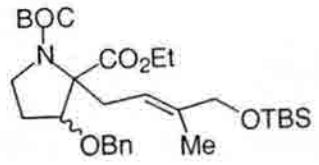
1,2-Pyrrolidinedicarboxylic acid, 2(R/S)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-methyl-2-butenyl]-3(R/S)-(phenylmethoxy)-, 1-(1,1-dimethylethyl) 2-ethyl ester (169)

To a suspension of 60% NaH (36.7 mg, 0.90 mmol, 1.5 eq) in THF (4 mL) at 23 °C under Ar was added a solution of **167** (280 mg, 0.612 mmol, 1 eq) in THF (7 mL) via cannula. After 5 min, Bu_4NI (95.4 mg, 0.25 mmol, 0.4 eq) and benzyl bromide (157 mg, 0.919 mmol, 1.5 eq) were added. After the reaction mixture was stirred for 20 h, it was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give an oil. Purification of the product (hexane:EtOAc/14:1) by radial chromatography provided 276 mg (83%) of an isomeric mixture of the E (**169**) and the Z isomer as a colorless oil.

Data of the E/Z mixture:

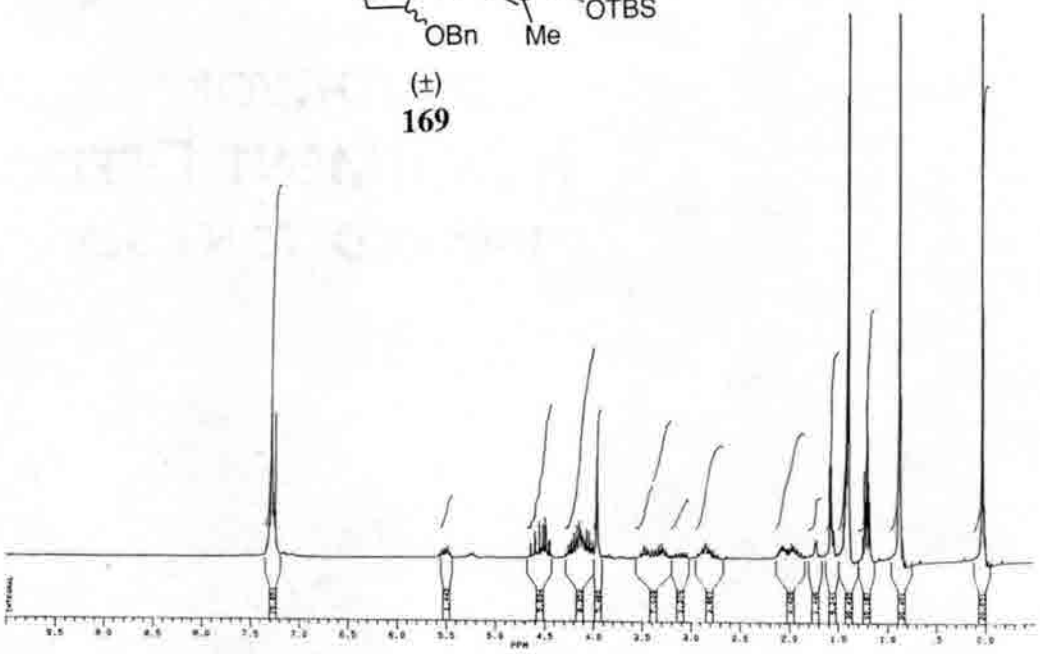
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, m), 0.88 (9H, m), 1.15-1.23 (3H, m), 1.40 (9H, m), 1.54 (3H, m), 1.82-2.12 (2H, m), 2.72-3.17 (2H, m), 3.21-3.50 (2H, m), 4.05 (2H, s), 4.00-4.29 (3H, m), 4.45-4.65 (2H, m), 5.45-5.57 (1H, m), 7.22-7.35 (5H, m).

IR (NaCl, film) 3032, 2976, 2885, 1738, 1697, 1390, 1366, 1249, 1177, 1108, 836 cm-1.



(±)

169



(±) **169** (±) **125**

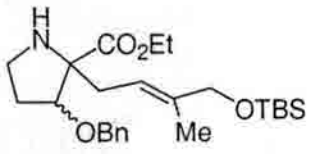
D-Proline, 2(R/S)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(R/S)-(phenylmethyloxy)-, ethyl ester (125)

To a suspension of zinc bromide (320 mg, 1.42 mmol, 2.8 eq) in CH_2Cl_2 (5 mL) at 23 °C under Ar was added a solution of **169** (279 mg, 0.51 mmol, 1 eq) in CH_2Cl_2 (5 mL) via cannula. After 15h, the reaction mixture was quenched with pH 10 sodium carbonate buffer (40 mL) and extracted with Et_2O (4 times). The combined ether solution was washed with brine, dried over Na_2SO_4 and concentrated to provide 200 mg (88%) of an isomeric mixture of the E (**125**) and the Z isomer (a colorless oil, as an E:Z/7.5:1 mixture) that was used in next step without further purification

Data of the E/Z mixture:

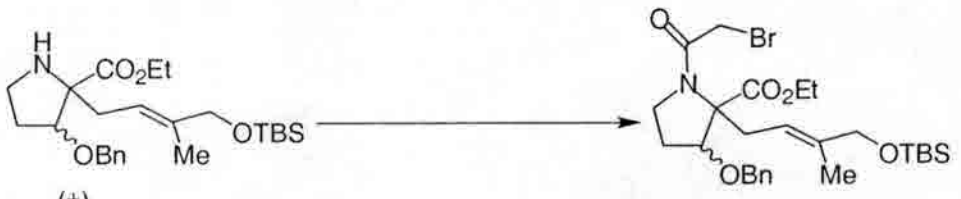
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.89 (9H, s), 1.15-1.25 (3H, m), 1.54 and 1.70 (total 3H, s), 1.86-1.96 (2H, m), 2.50-2.75 (3H, m), 2.90-3.15 (2H, m), 3.95 (2H, s), 4.05-4.18 (3H, m), 4.55-4.65 (2H, m), 5.30-5.40 (1H, m), 7.20-7.35 (5H, m).

IR (NaCl, film) 3354, 3087, 3060, 2953, 2854, 1732, 1462, 1251, 1183, 1111, 1067, 837, 735 cm^{-1}.



(±)

125



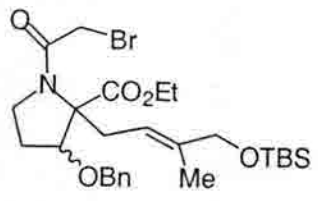
D-Proline,1-(bromoacetyl)-2(R/S)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(R/S)-(phenylmethyloxy)-, ethyl ester (170)

To a solution of **125** (200 mg, 0.447 mmol, 1 eq) in CH_2Cl_2 (9 mL) at 0 °C was added 0.5 M K_2CO_3 solution in water (1.34 mL, 0.67 mmol, 1.5 eq) followed by bromoacetyl bromide (136 mg, 0.67 mmol, 1.5 eq). After 6 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Purification of the product (hexane:EtOAc/12:1 then 3:1) by radial chromatography provided 184 mg (73%) of an isomeric mixture of the E (**170**) and the Z isomer (a colorless oil, as an E:Z/8.2:1 mixture).

Data of the E/Z mixture:

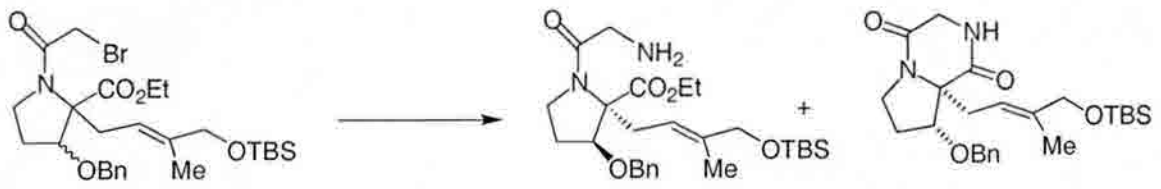
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.89 (9H, s), 1.20-1.30 (3H, m), 1.52 and 1.72 (total 3H, s), 2.10-2.25 (2H, m), 2.75-2.85 (1H, m), 3.10-3.20 (1H, m), 3.50-3.65 (2H, m), 3.70 (2H, s), 3.95 (2H, s), 4.05-4.20 (3H, m), 4.45-4.50 (1H, m), 4.60-4.65 (1H, m), 5.50 (1H, m), 7.40-7.60 (5H, m).

IR (NaCl, film) 3089, 3065, 3030, 2955, 2855, 1739, 1660, 1440, 1441, 1250, 1111, 1063, 838, 776.



(±)

170



(±) **170** (±) **172** (±) **171**

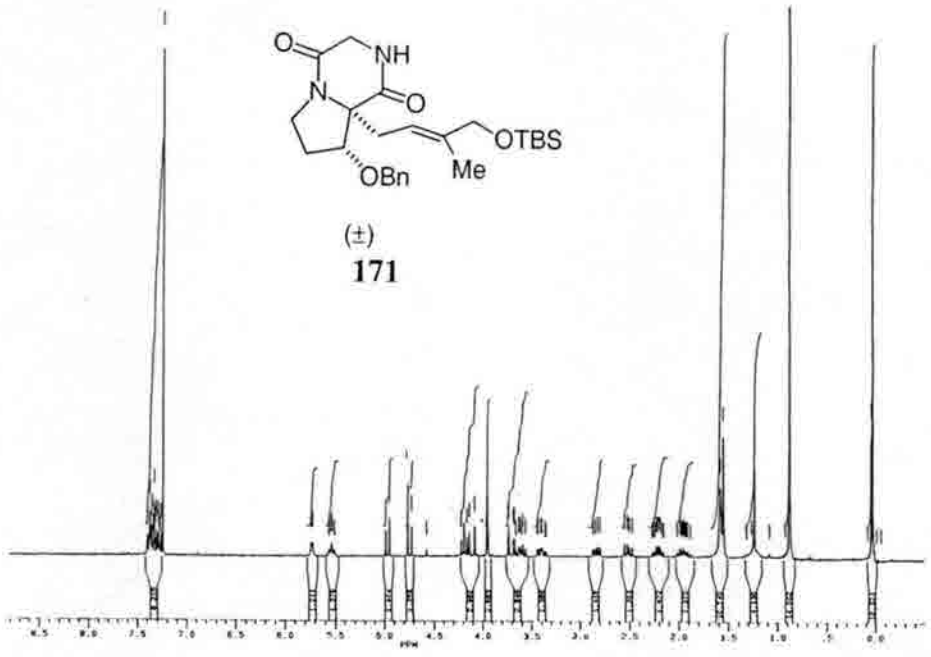
(±)-Pyrrolo[1,2-a]pyrazine-1,4-dione,8a(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl] oxy]-3-methyl-2-butenyl]hexahydro-8(R)-(phenylmethyloxy) (171)

A solution of **170** (156.4 mg, 0.275 mmol, 1 eq) in NH_3/MeOH (4 mL, 2.59 M, 10.36 mmol, 38 eq) was stirred at 23 °C for 24 h. The solvent and excess ammonia were removed *in vacuo* and gave a solid residue. EtOAc was added, and the resulting suspension was filtered. The filtrate was concentrated to give 136.3 mg of a crude oil. Preparative TLC purification of the product (EtOAc:MeOH/10:1) provided 85.0 mg (67%) of an isomeric mixture of the E (**171**) and the Z isomer as a colorless oil and 20 mg (14.4%) of an isomeric mixture of the E (**172**) and the Z isomer as a colorless oil.

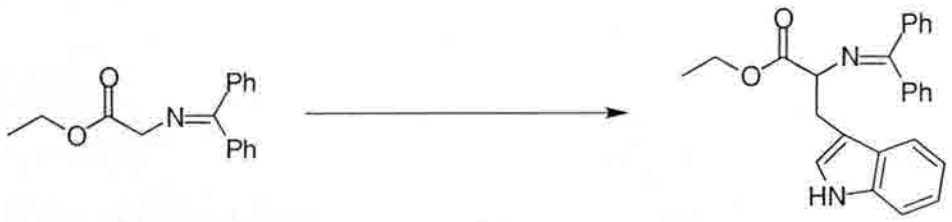
Data of **171** (E isomer):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.89 (9H, s), 1.55 (3H, s), 1.88-2.01 (1H, m), 2.15-2.26 (1H, m), 2.51 (1H, dd, *J* = 8.7, 14.4 Hz), 2.83 (1H, dd, *J* = 7.5, 14.4 Hz), 3.35-3.44 (1H, m), 3.55-3.65 (1H, m), 3.71 (1H, dd, *J* = 3.9, 16.8 Hz), 3.94 (2H, s), 4.10 (1H, d, *J* = 16.8 Hz), 4.18 (1H, dd, *J* = 8.7, 8.7 Hz), 4.73 (1H, 1/2ABq, *J* = 12 Hz), 4.96 (1H, 1/2ABq, *J* = 12 Hz), 5.50-5.56 (1H, m), 5.72 (1H, d, *J* = 3.6 Hz), 7.28-7.40 (5H, m).

IR (NaCl, film) 3233, 3088, 3029, 2954, 2854, 1681, 1661, 1434, 1256, 1111, 837, 776 cm^{-1}.



(±)
171



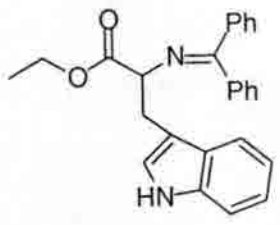
259 **266**

DL-Tryptophan, N-(diphenylmethylene)-, ethyl ester (266)

To a flask charged with **259** (267 mg, 1.0 mmol, 1 eq) and gramine (194 mg, 1.1 mmol, 1.1 eq) was added CH_3CN (21 mL) and Bu_3P (101 mg, 0.5 mmol, 0.5 eq). The reaction mixture was refluxed for 11.5 h. TLC (hexane:EtOAc/4:1) was used to monitor the reaction. The solvent was removed under reduced pressure and the residue was purified by radial chromatography (hexane:EtOAc/10:1 then 5:1) to provide 280 mg (80%, based on 16 mg of recoverd **259**) of **266** as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, t, J = 4.2 Hz), 3.25 (1H, dd, J = 8.7, 14.7 Hz), 3.46 (1H, dd, J = 4.8, 14.7 Hz), 4.10-4.20 (2H, m), 4.39 (1H, dd, J = 4.8, 8.4 Hz), 6.50-7.60 (15H, m), 8.12 (1H, br, s).

IR (NaCl, film) 3405, 3053, 2981, 2926, 1732, 1618, 1442, 1289 cm^{-1}.



266

239 **274**

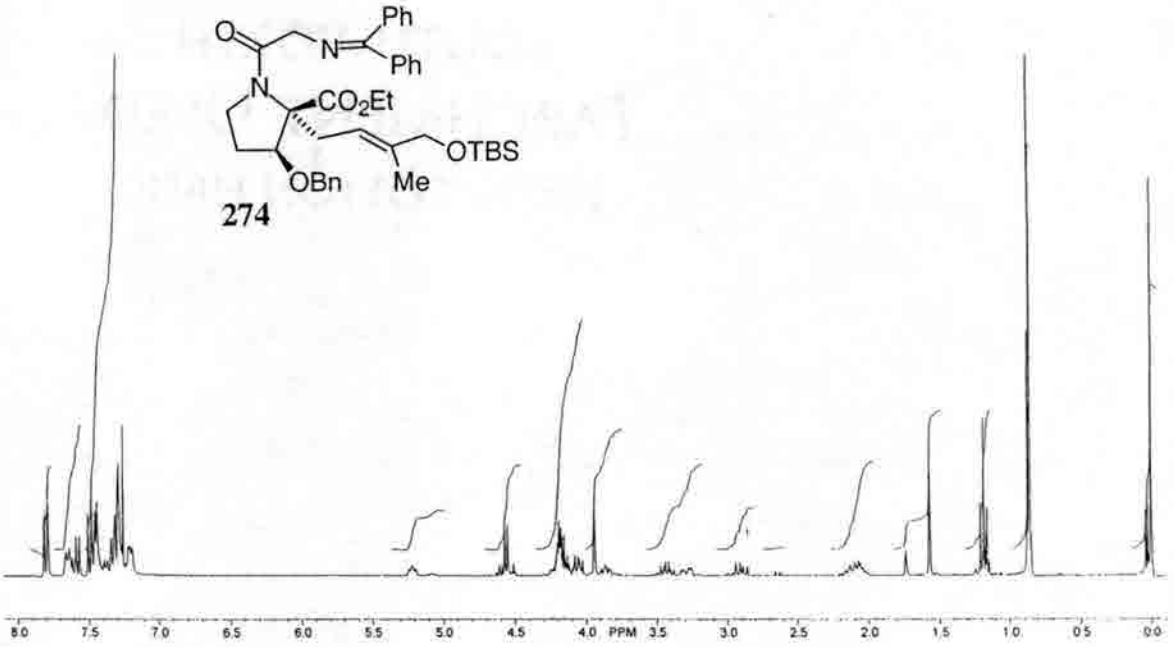
D-Proline, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-1-[N-(diphenylmethylene)amino]acetyl l-, 3(S)-(phenylmethyloxy)-, ethyl ester (274)

To a solution of **239** (50.4 mg, 0.10 mmol, 1 eq) in CH_2Cl_2 (1 mL) at 23 °C was added diphenylimine (50.4 mg, 0.28 mmol, 2.8 eq), producing a white cloudy mixture. After the reaction mixture was stirred at 23 °C for 15.5 h, it was concentrated. Preparative TLC (EtOAc:hexane/1:1) purification of the product provided 44 mg (>66%) of an isomeric mixture of the E (**274**) and the Z isomer as a colorless oil.

Data of the E/Z mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, m), 0.89 (9H, m), 1.20 (3H, m), 1.55 (3H, s), 2.00-2.20 (2H, m), 2.80-2.95 (1H, m), 3.20-3.50 (2H, m), 3.80-3.90 (1H, m), 3.95 (2H, s), 4.00-4.25 (5H, m), 4.50-4.65 (2H, m), 5.00-5.30 (1H, m), 7.20-7.80 (15H, m).

IR (NaCl, film) 3061, 3030, 2954, 2929, 2853, 1731, 1650, 1417 cm^{-1}.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CO2Et
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OBn
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PPM
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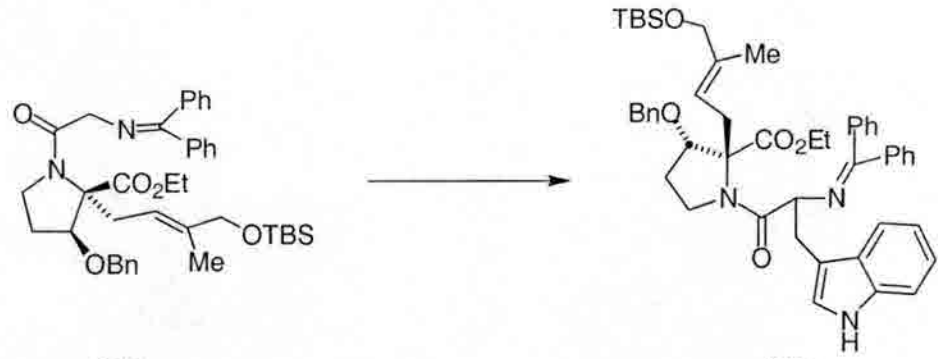
1.5
1.0
0.5
0.0

274



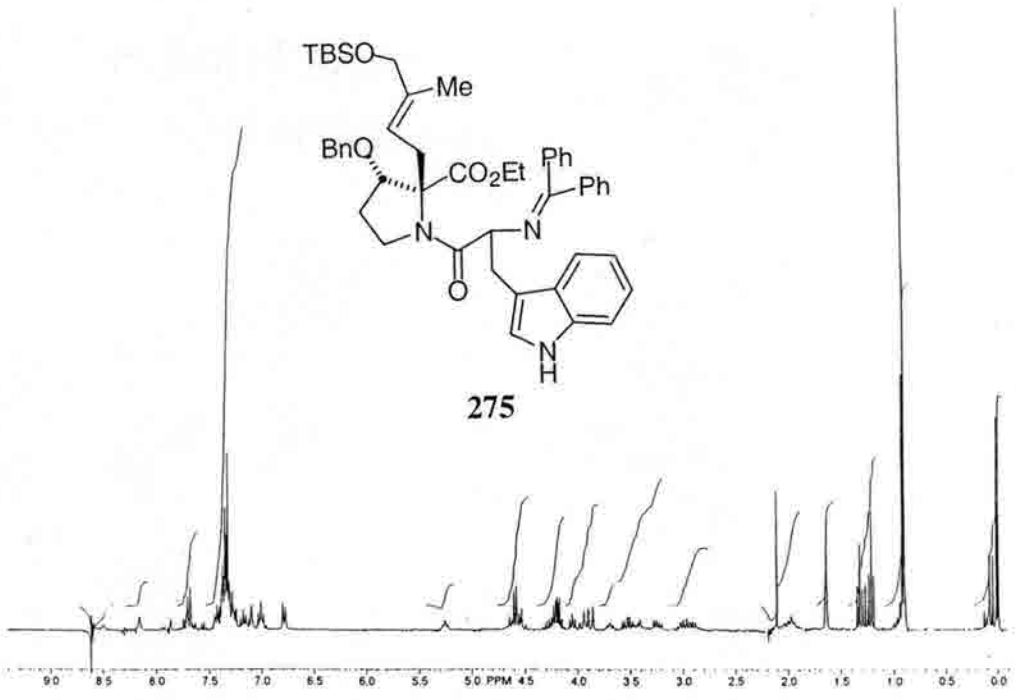
274 **275**

D-Proline, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, 1-DL-[N-(diphenylmethylene)]tryptophyl, ethyl ester (275)

To a solution of **274** (179 mg, 0.268 mmol, 1 eq) in THF (4 mL) at –78 °C under Ar was added $LiN(TMS)_2$(348 μL, 0.348 mmol, 1.3 eq). After 30 min, HMPA (192 mg, 1.07 mmol, 4 eq) was added. The reaction mixture was allowed to warm to 23 °C over 10 min, and gramine methyl iodide salt (92.8 mg, 0.29 mmol, 1.1 eq) was added in one portion. After 4 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (hexane:EtOAc/12:1) purification of the product gave 89 mg (42%).of a diastereomeric mixture **275** as a colorless oil (pure E isomer).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01-0.10 (6H, m), 0.86-0.92 (9H, m), 1.15-1.30 (3H, m), 1.62 (3H, s), 1.80-2.10 (2H, m), 2.85-3.05 (2H, m), 3.20-3.70 (4H, m), 3.80-4.00 (3H, m), 4.10-4.25 (3H, m), 4.50-4.70 (2H, m), 5.25 (1H, m), 6.80-7.20 (20H, m), 8.2 (1H, br s).

IR (NaCl, film) 3302, 3058, 2958, 2926, 2858, 1739, 1729, 1651, 1455, 1252, cm^{-1}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Me
BnO
CO2Et
Ph
Ph
N
N
O
N
H
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8.5
8.0
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6.5
6.0
5.5
5.0 PPM
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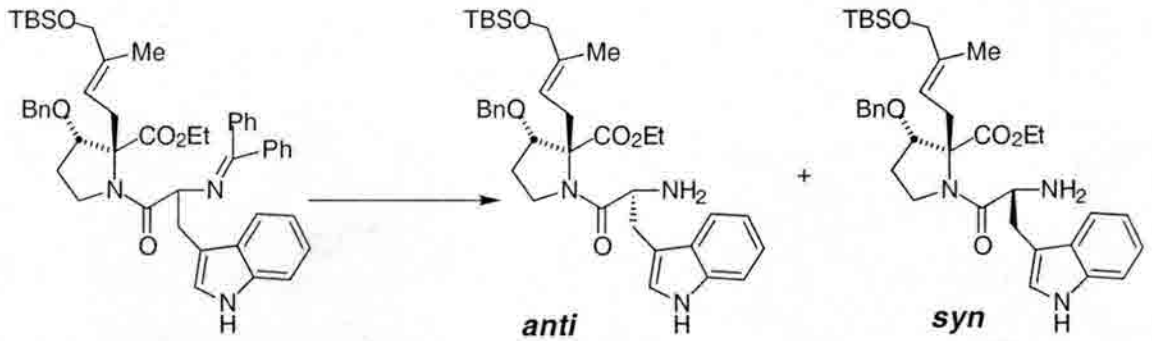
1.5
1.0
0.5
0.0

275



D-Proline, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, 1-D-tryptophyl, ethyl ester (276)

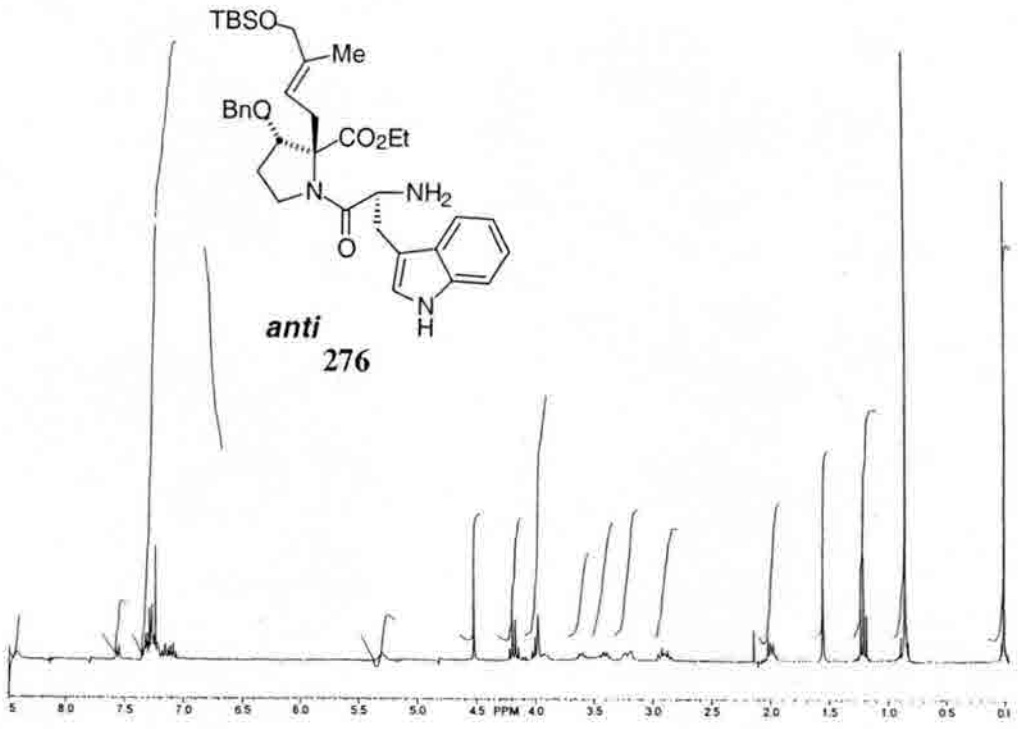
D-Proline, 2(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3(S)-(phenylmethyloxy)-, 1-L-tryptophyl, ethyl ester (277)

To a solution of **275** (40 mg, 0.05 mmol, 1 eq) in CH_2Cl_2 (1.2 mL) at 23 °C was added $NaHCO_3$ (30 mg, 0.35 mmol, 7.1 eq) followed by $NH_2OH{\cdot}HCl$ (26.4 mg, 0.38 mmol, 7.6 eq). After 9 h, the reaction mixture was filtered, and the filtrate was concentrated to give an oil. Preparative TLC (CH_2Cl_2:MeOH/15:1) purification of the product provided 16 mg (50%) of **276** (a white foam, as a single *anti*/E isomer) and 8.4 mg (26.4%)of **277** (a white foam, as a single *syn*/E isomer) (total yield 77%)

Data of *anti*/E isomer (**276**):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.85 (9H, s), 1.15-1.25 (3H, m), 1.55 (3H, s), 1.90-2.00 (2H, m), 2.80-2.95 (2H, m), 3.10-3.25 (2H, m), 3.35-3.65 (3H, m), 3.97 (2H, s), 3.85-4.00 (2H, m), 4.10-4.20 (2H, m), 4.50 (2H, s), 7.10-7.35 (9H, m), 7.60 (1H, m), 8.4 (1H, br s).

IR (NaCl, film) 3355, 3284, 3069, 2985, 2854, 1738, 1650, 1455, 1361, 1248, 1105, 1056, 858 cm^{-1}.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BnO
CO2Et
N
NH2
O
N
H
anti
276
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7.5
7.0
6.5
6.0
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5.0
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2.0
1.5
1.0
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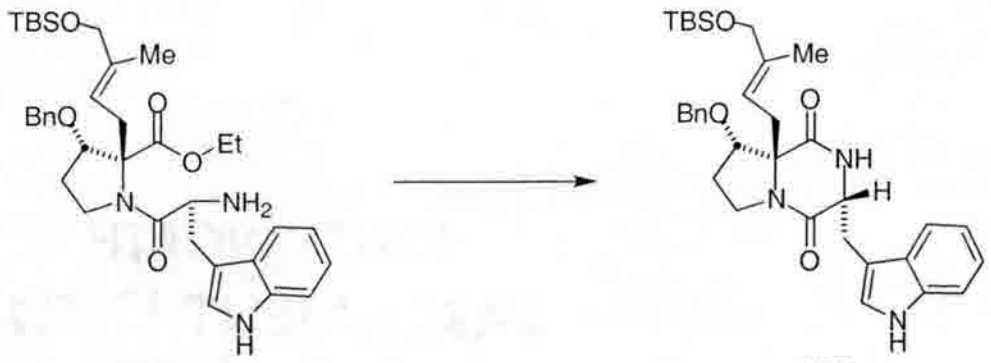
0.1



276 **278**

Pyrrolo[1,2-a]pyrazine-1,4-dione, 8a(R)-[E-4-[[(1,1-dimethylethyl)dimethylsilyl] oxy]3-methyl-2-butenyl]hexahydro-3(R)-(1H-indol-3-ylmethyl)-8(S)-(phenylmethyloxy) (278)

To a stirred solution of **276** (15.0 mg, 0.024 mmol, 1 eq) in toluene (600 μL) was added 60% NaH (7.6 mg, 0.19 mmol, 8 eq) followed by HMPA (300 μL). After 2 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (EtOAc:hexane/4:1) purification of the product provided 6 mg (43%) of **278** (a colorless oil, as a single *anti*/E isomer)

Data of **278**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.02 (3H, s), 0.89 (9H, s), 1.55 (3H, s), 2.10-2.25 (3H, m), 2.77 (1H, dd, *J* = 15, 7.8 Hz), 2.95 (1H, dd, *J* = 10.2, 15 Hz), 3.45-3.55 (1H, m), 3.61 (1H, dd, *J* = 4.5, 15 Hz), 3.94 (2H, s), 4.00-4.13 (1H, m), 4.17 (1H, m), 4.32 (1H, dd, *J* = 3.6, 9.9 Hz), 4.57 (1H, 1/2ABq, *J* = 11.4 Hz), 4.64 (1H, 1/2ABq, *J* = 11.8 Hz), 5.40 (1H, d, *J* = 9 Hz), 5.72 (1H, br s), 6.90-7.54 (10H, m), 7.9 (1H, br s).

IR (NaCl, film) 3039, 3360, 3286, 2954, 2857, 1682, 1649, 1434, 1253, 1108 cm^{-1}.


TBSO
Me
BnO
O
NH
H
N
O
N
H

278

80
75
70
65
60
55
50
45 PPM 40
35
30
25
20
15
10
05
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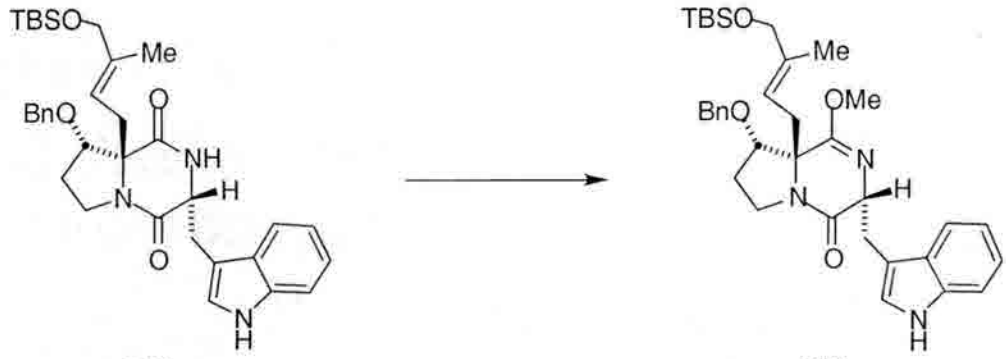


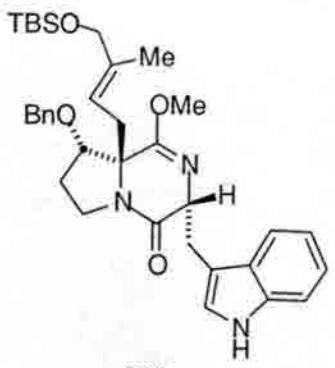
278 **280**

Pyrrolo[1,2-a]pyrazin-4(3H)-one, 8a(R)-[(E)-4-[[(1,1-dimethylethyl)dimethylsilyl] oxy]-6,7,8,8a-tetrahydro- 3(R)-[(indol-3-yl)methyl]-1-methoxy-8(S)-(phenylmethyloxy) (280)

To a solution of **278** (23.0 mg, 0.039 mmol, 1 eq) in CH_2Cl_2 (1 mL) at 23 °C was added Cs_2CO_3 (255 mg, 0.78 mmol, 20 eq) followed by Me_3OBF_4 (14.1 mg, 0.095 mmol, 2.35 eq) under Ar. After 24 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (EtOAc:hexane/1:1) purification of the product provided 12 mg (51%) of **280** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (6H, m), 0.88 (9H, s), 1.55 (3H, s), 2.05-2.16 (3H, m), 2.48 (1H, dd, J = 7.8, 12 Hz), 3.42 (3H, m), 3.66 (3H, s), 3.94 (2H, s), 3.90-4.00 (3H, m), 4.23-4.38 (2H, m), 5.30 (1H, m), 6.89 (1H, m), 7.00-7.40 (9H, m), 7.65 (1H, m).

IR (NaCl, film) 3295, 3064, 2931, 1697, 1651, 1456, 1436, 1102, 1069, 839, 739 cm^{-1}.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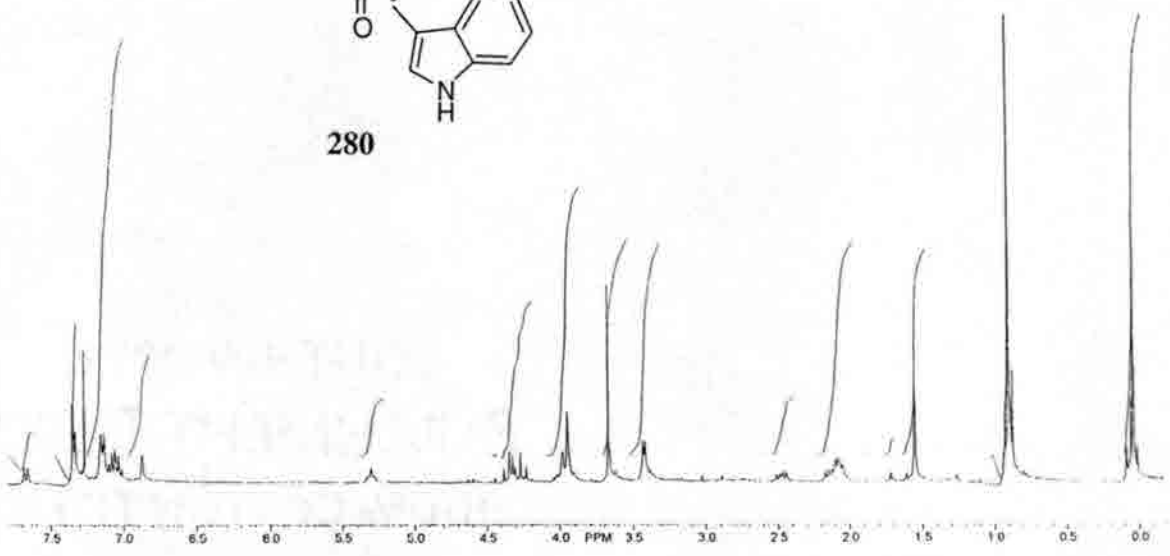
OMe
BnO
N
H
N
O
N
H

280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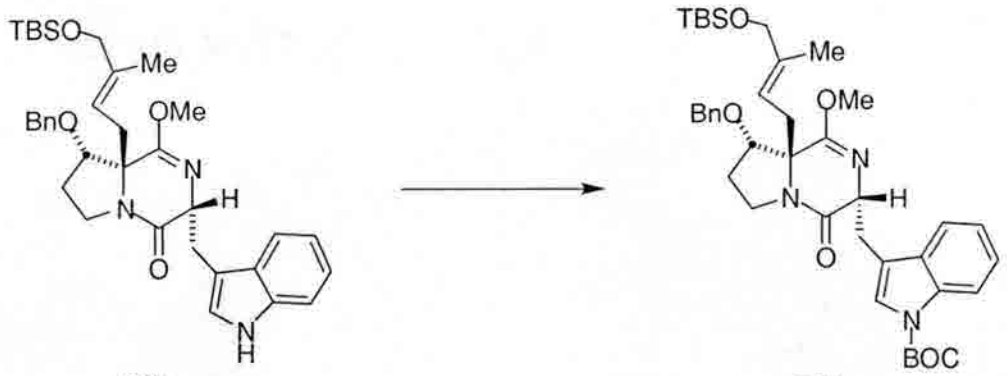


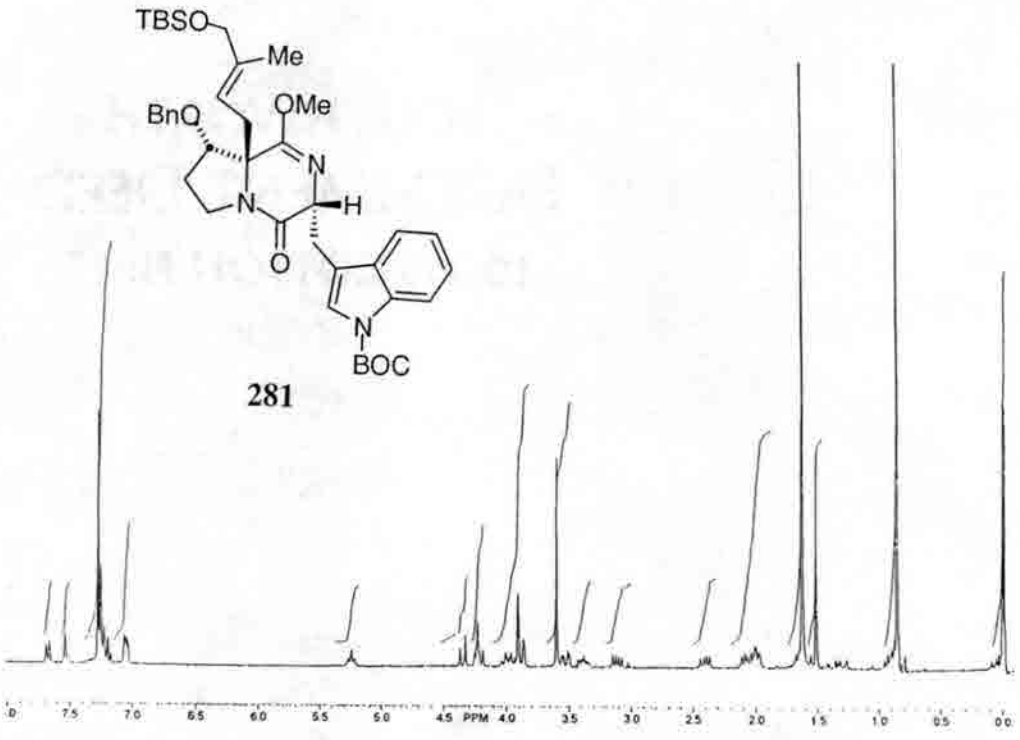
280 **281**

3-[[8aR-[(*E*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(phenylmethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3R-yl]methyl]-indole-1-carboxylic acid, 1,1-dimethylethyl ester (281)

To a stirred solution of **280** (10.0 mg, 0.0166 mmol, 1 eq) in CH_2Cl_2 (200 μL) at 23 °C was added triethylamine (1.8 mg, 0.08 mmol, 1.1 eq), DMAP (2.0 mg, 0.0166 mmol, 1.0 eq) and $(BOC)_2O$ (11.4 mg, 0.049 mmol, 3.0 eq). After 2 h, the reaction mixture was quenched with NH_4Cl solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (EtOAc:hexane/1:1) purification of the product provided 5 mg (43%) of **281** as a colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.51 (3H, s), 1.62 (9H, s), 1.96-2.11 (3H, m), 2.40 (1H, dd, J = 9.3, 14.7 Hz), 3.07-3.14 (1H, m), 3.30-3.45 (1H, m), 3.50 (1H, dd, J = 4.2, 14.4 Hz), 3.60 (3H, s), 3.85 (1H, m), 3.90 (2H, s), 3.96-4.03 (1H, m), 4.19-4.37 (3H, m), 5.24 (1H, m), 7.03-7.06 (2H, m), 7.18-7.27 (5H, m), 7.53 (1H, s), 7.65-7.68 (1H, m), 8.00-8.10 (1H, m).

IR (NaCl, film) 2930, 2857, 1732, 1694, 1650, 1372, 1254, 1159, 1090, 1069 cm^{-1}.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H
O
N
BOC
281
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6.0
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4.5 PPM 4.0
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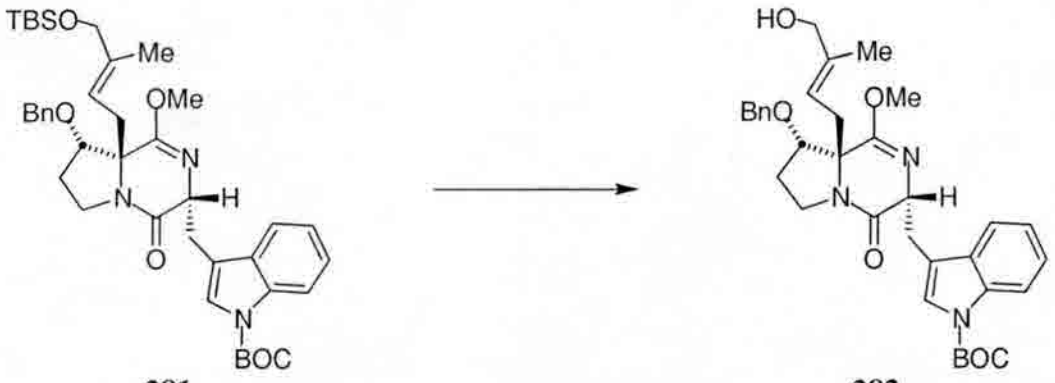


281 **282**

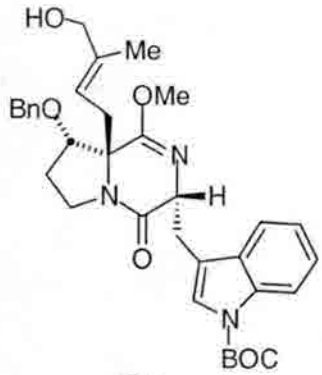
3-[[8aR-[(*E*)-4-(hydroxy)-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(phenylmethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3R-yl]methyl]-indole-1-carboxylic acid, 1,1-dimethylethyl ester (282)

A solution of **281** (5.0 mg, 7.1×10^{-3} mmol, 1 eq) and TBAF (11μL, 1.1×10^{-2} mmol, 1.0 M in THF, 1.5 eq) in THF (150 μL) was stirred at 23 °C for 2 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give **282** as an oil (yield, unknown)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (3H, s), 1.63 (9H, s), 1.95-2.10 (3H, m), 2.35-2.45 (1H, m), 3.10-3.20 (1H, m), 3.35-3.45 (1H, m), 3.50-3.60 (1H, m), 3.60 (3H, s), 3.78-3.85 (1H, m), 3.91 (3H, s), 3.90-4.00 (1H, m), 4.10-4.40 (2H, m), 5.25-5.30 (1H, m), 7.00 (1H, s), 7.20-7.50 (6H, m), 7.40-7.50 (1H, m), 7.65-7.75 (1H, m), 7.95-8.05 (1H, m).

IR (NaCl, film) 3387, 2964, 2935, 1730, 1710, 1651, 1371, 1253 cm^{-1}.

FAB HRMS m/e 588.3072 ($C_{34}H_{41}N_3O_6$ + H requires 588.3073)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BnO
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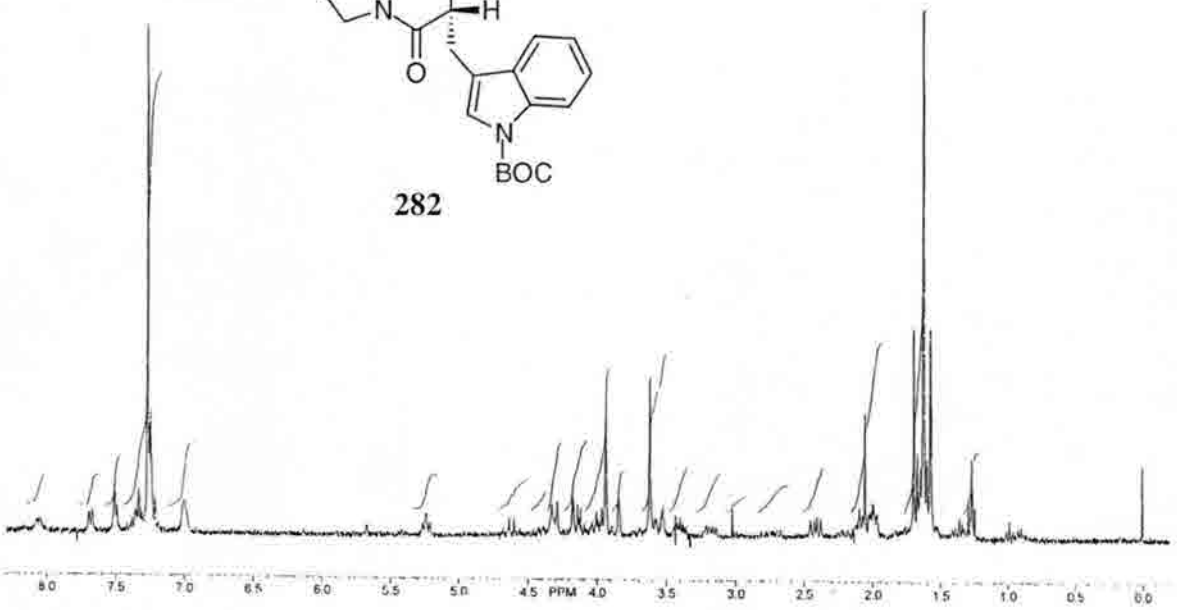
N
H
O
N
BOC

282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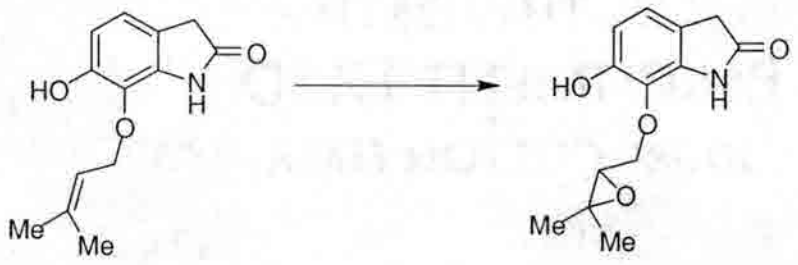
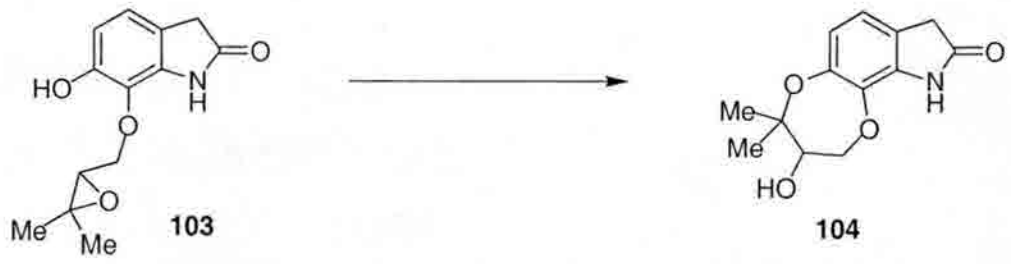


102 **103**

(±)-1,3-Dihydro-7-[3,3-dimethyloxiranyl)methoxy]-6-hydroxy-2*H*-indol-2-one (103)

To a solution of m-CPBA (8 g, 46.3 mmol, 1.4 eq) in CH_2Cl_2 (250 mL) at 0 °C was added $NaHCO_3$ (4.87 g, 59 mmol, 1.8 eq) and $MgSO_4$ (10 g). A solid of **102** (7.6 g, 32.6 mmol, 1 eq) was added to the reaction mixture in one portion. After 1 h, $NaHCO_3$ (5 g, 60 mmol, 1.85 eq) and m-CPBA (8 g, 46.3 mmol, 1.4 eq) were added to the reaction mixture. After 1.5 h, the reaction mixture was filtered, and the solid pad was washed with $CHCl_3$. The filtrate was washed twice with a mixture solution of 5% $NaHCO_3$ (100 mL) with 10% $Na_2S_2O_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic solution was washed with brine (1 x 400 mL), dried over Na_2SO_4 and concentrated to give 7.1 g (87%) of **103** as a black foam. The crude product was used without further purification.

Epoxide **103** is a known compound. Analytical data: lit. [33].



(±)-3,4,8,10-Tetrahydro-3-hydroxy-4,4-dimethyl-2*H*,9H-[1,4]dioxepino[2,3-g]indole-9-one (104)

$SnCl_4$ (3.94 mL, 33.6 mmol, 1.2 eq) was added dropwise to a flame-dried flask charged with anhydrous THF (400 mL) at 0 °C. After 20 min, a solution of **103** (7.1 g, 28.5 mmol, 1 eq) in THF (65 mL) was added to the reaction mixture via cannula over 7 min to give a gray mixture. The ice-bath was removed and the reaction mixture was stirred at room temperature for 2.5 h. Approximately one-half of the solvent was removed under reduced pressure and the remaining solution poured into a separatory funnel containing saturated $NaHCO_3$ (400 mL) and water (200 mL), which was then exhaustively extracted with CH_2Cl_2 (3 x 500 mL). The combined organic solution was washed with brine (1 x 600 mL), dried over Na_2SO_4 and concentrated to give 7.0 g of **104** as a black solid. The crude product was purified by flash column chromatography (EtOAc:Hexane/3:1) to yield 3.7 g (52%) of **104** as a reddish solid.

Epoxide **104** is a known compound. Analytical data: lit. [33].

106 **105**

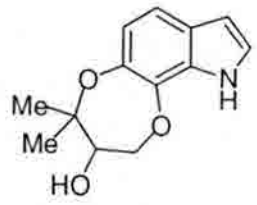
(±)-3-Hydroxy-4,4-dimethyl-3,4,10-trihydro-2*H*-[1,4]dioxepino[2,3-g]indole (105)

To a solution of **106** (2.9 g, 12.3 mmol, 1 eq) in THF (230 mL) at 0 °C was added DDQ (3.48 g, 16.7 mmol, 1.36 eq) over 2-3 min. After 20 min, the reaction mixture was concentrated and EtOAc was added to the residue. The EtOAc solution was washed with 1 N NaOH (1 x 200 mL), brine (2 x 150 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (EtOAc:Hexane/1:1) to yield 2.6 g (91%) of **105** as a white purplish solid.

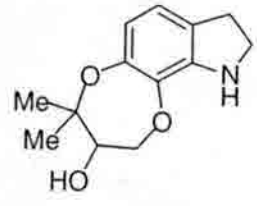
Epoxide **105** is a known compound. Analytical data: lit. [33].

Data for **106**:

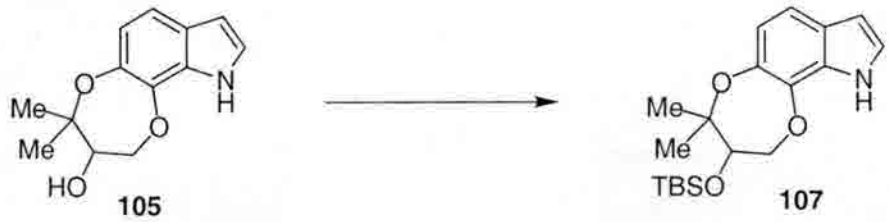
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.58 (3H, s), 3.04 (2H, t, J = 8.1 Hz), 3.61 (2H, t, J = 8.1 Hz), 3.65 (1H, m), 4.09 (1H, d, J = 12 Hz), 4.21 (1H, dd, J = 12, 4.2 Hz), 6.36 (1H, d, J = 8.1 Hz), 6.73 (1H, d, J = 8.1 Hz).



105



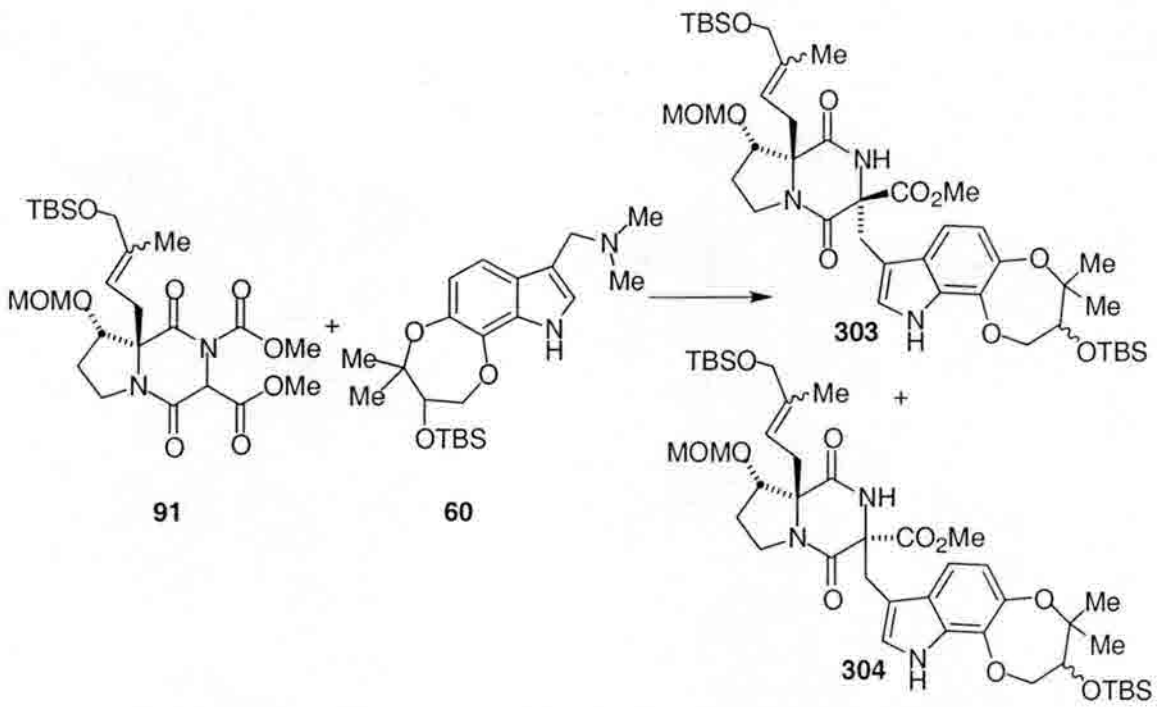
106



(±)-3-[[1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-3,4,10-trihydro-2H-[1,4]dioxepino[2,3-g]indole (107)

A solution of **105** (2.68 g, 11.5 mmol, 1 eq), imidazole (5.13 g, 75.4 mmol, 6.6 eq) and TBSCl (4.88 g, 32.3 mmol, 2.81 eq) in DMF (22.6 mL) was heated at 44-45 °C for 24 h. The reaction mixture was quenched with saturated NH_4Cl solution (200 mL) and extracted with EtOAc (3 x 70 mL). The combined EtOAc solution was washed with brine (200 mL), dried over Na_2SO_4 and concentrated to give a white solid. The crude product was purified by flash column chromatography (EtOAc:Hexane/1:6) to yield 3.9 g (98%) of **107** as a white solid.

Epoxide **107** is a known compound. Analytical data: lit. [33].



3-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8aR-[(*E/Z*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-octahydro-8S-(methoxymethoxy)-1,4-dioxo-pyrrolo[1,2-*a*]pyrazine-3R-carboxylic acid, methyl ester (303)

3-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8aR-[(*E/Z*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-octahydro-8S-(methoxymethoxy)-1,4-dioxo-pyrrolo[1,2-*a*]pyrazine-3S-carboxylic acid, methyl ester (304)

To a flame-dried 1-L flask charged with **91** (6.0 g, 11.35 mmol, 1 eq), gramine derivative **60** (5.04 g, 12.5 mmol, 1.1 eq) and molecular sieves (4 Å, 6.5 g) under Ar was added CH_3CN (340 mL, anhydrous). The reaction mixture was stirred at 23 °C for 10 min and then Bu_3P (1.59 g, 7.95 mmol, 0.7 eq) was added in one portion. After the reaction mixture was refluxed for 4 h, the solvent was removed under reduced pressure to give 12 g of a foamy solid. Purification of the products by flash column chromatography (hexane:EtOAc/2.5:1, 2:1 then EtOAc) gave 5.0 g (53%) of **303** (a white foam, as a high

R_f *syn* isomer) and 1.6 g (17%) of **304** (a white foam, as a lower R_f *anti* isomer). The combined yield was 70%.

Data of *syn* isomer (**303**) (mixture of four diasteromers)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 and 0.04 (total 6 H, s), 0.12-0.19 (total 6 H, s), 0.88 and 0.91 (total 18 H, s), 1.11-1.17 (3 H, m), 1.46 and 1.48 (total 3 H, s), 1.55 and 1.68 (total 3 H, s), 1.82-2.19 (3 H, m), 2.20-2.36 (1 H, m), 2.46-2.63 (1 H, m), 3.22-3.60 (2 H, m), 3.23, 3.29, 3.31 and 3.75 (total 3 H, s), 3.71, 3.73, 3.74 and 3.32 (total 3 H, s), 3.79-4.28 (7 H, m), 4.41-4.50 (1 H, m), 4.53-4.62 (1 H, m), 5.11 (3/5 H, m), 5.34 (2/5 H, m), 6.11, 6.13 and 6.16 (total 1 H, s), 6.75 and 6.76 (total 1 H, d, J = 8.4 Hz), 6.97-7.02 (1 H, m), 7.06 (1 H, d, J = 8.4 Hz), 8.25 and 8.27 (total 1 H, br s).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 169.6, 169.63, 167.3, 166.9, 161.9, 141.9, 141.6, 140.3, 139.6, 137.0, 136.8, 129.2, 129.1, 125.9, 125.8, 123.7, 117.9, 117.8, 116.5, 116.53, 113.1, 113.15, 108.3, 95.9, 95.8, 80.9, 80.6, 80.5, 76.3, 76.2, 73.1, 71.6, 68.4, 66.9, 66.8, 61.6, 55.9, 53.6, 44.2, 43.9, 34.1, 33.8, 28.4, 28.1, 27.2, 27.1, 26.0, 25.8, 21.8, 19.6, 19.0, 18.5, 18.0, 13.7, -4.0, -4.6, -5.1.

IR (NaCl, film) 3310, 2954, 2857, 1742, 1676, 1438, 1251, 1091, 837, 776 cm^{-1}.

FAB HRMS m/e 829.4377 ($C_{42}H_{67}N_3O_{10}Si_2$ requires 829.4365)

Anal. Calcd. For $C_{42}H_{67}N_3O_{10}Si_2$ C, 60.76; H, 8.13; N, 5.06. Found: C, 60.58; H, 7.96; N, 5.13

Data of *anti* isomer (**304**) (mixture of four diasteromers)

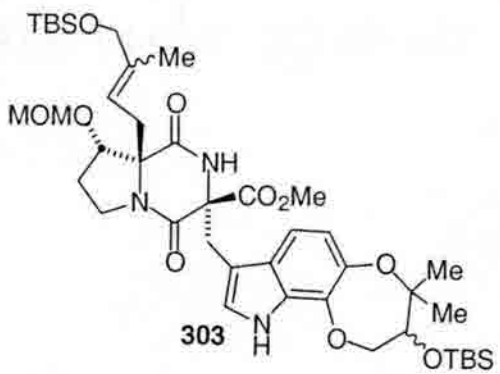
^{1}H NMR (300 MHz, $CDCl_3$) δ -0.11-0.20 (12 H, m), 0.78-0.95 (18 H, m), 1.09 and 1.12 (total 3 H, s), 1.47 (3 H, s), 1.54-1.80 (3 H, m), 1.80-2.80 (4 H, m), 3.29 (3 H, s), 3.21-3.58 (2 H, m), 3.65-4.75 (11 H, m), 4.52 (1 H, 1/2ABq, J = 6.9 Hz), 4.62 (1 H, 1/2ABq, J = 6.9 Hz), 5.07-5.52 (1 H, m), 6.32-6.52 (1 H, m), 6.70-6.81 (1 H, m), 6.90-7.03 (1 H, m), 7.05 -7.19 (1 H, m), 8.35, 8.39 and 8.46 (total 1 H, br s)

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 168.8, 168.7, 166.5, 166.4, 162.5, 141.6, 141.5, 139.6, 139.4, 136.8, 129.1, 129.0, 126.0, 124.5, 117.8, 116.1, 116.0, 113.8, 108.6, 95.6,

80.6, 80.2, 76.3, 73.1, 73.0, 72.9, 72.94, , 71.6, 68.0, 61.7, 55.9, 55.8, 53.5, 43.8, 35.2, 35.0, 33.8, 33.6, 29.8, 28.4, 28.3, 27.4, 26.0, 25.8, 19.3, 19.1, 18.5, 18.0, 13.9, 13.8, -4.0, -4.6, -5.1, -5.3.

IR (NaCl, film) 3285, 2950, 2855, 1751, 1678, 1662, 1442, 1254, 1091, 1044, 840, 777 cm^{-1}.

FAB HRMS m/e 829.4360 ($C_{42}H_{67}N_3O_{10}Si_2$ requires 829.4365)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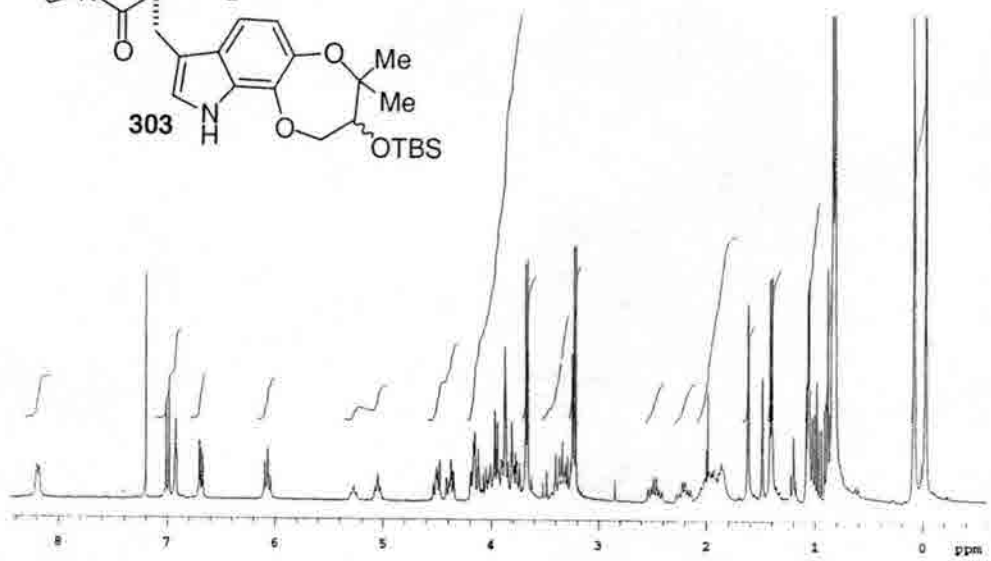
MOMO
O
NH
N
CO2Me
O
O
Me
Me
N
H
O
OTBS

303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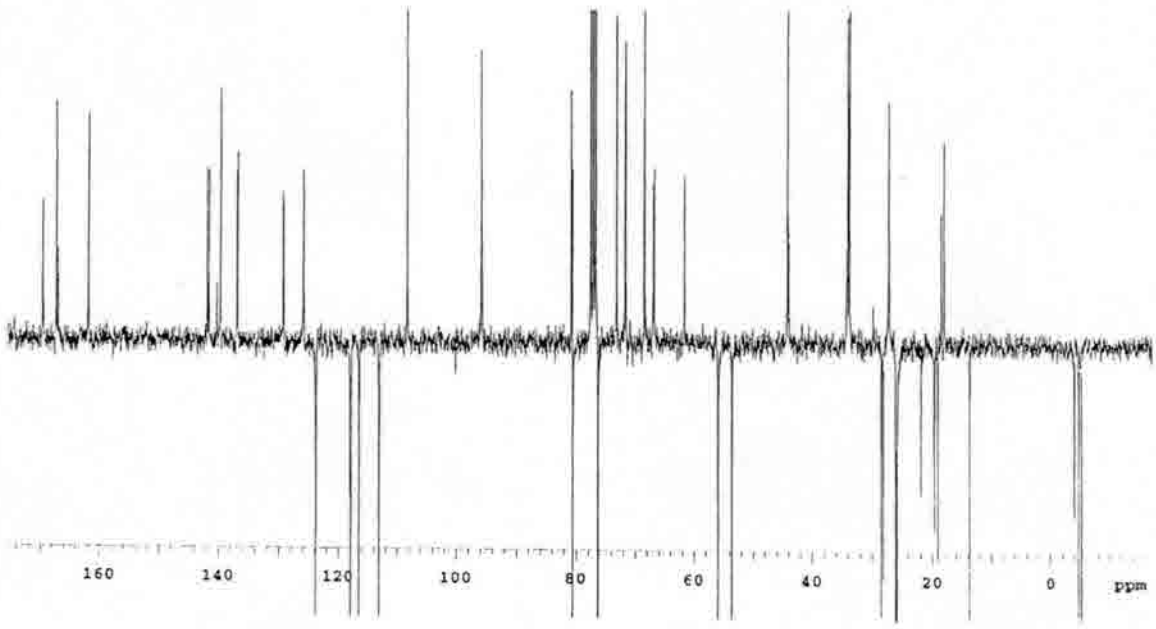
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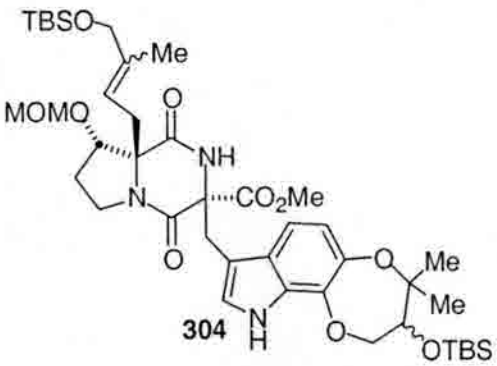
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O
NH
N
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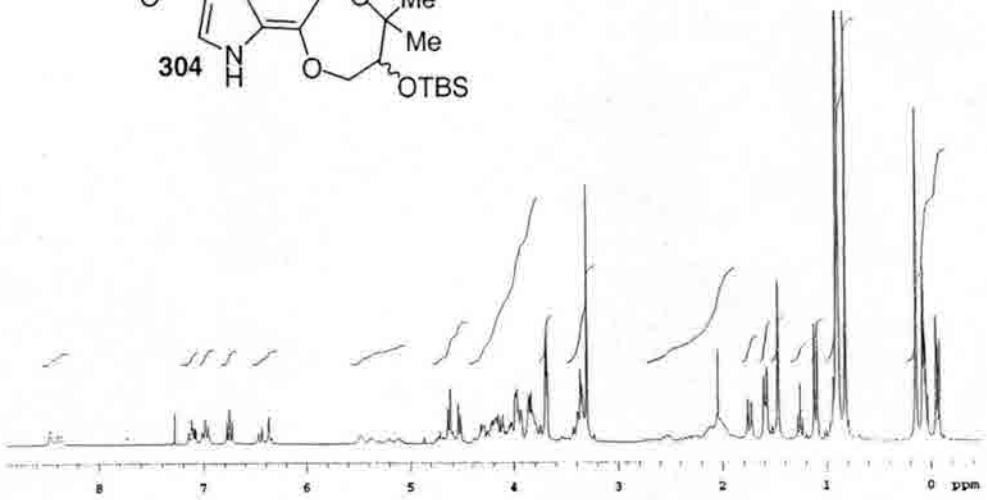
O
O
Me
Me
N
H
O
OTBS

304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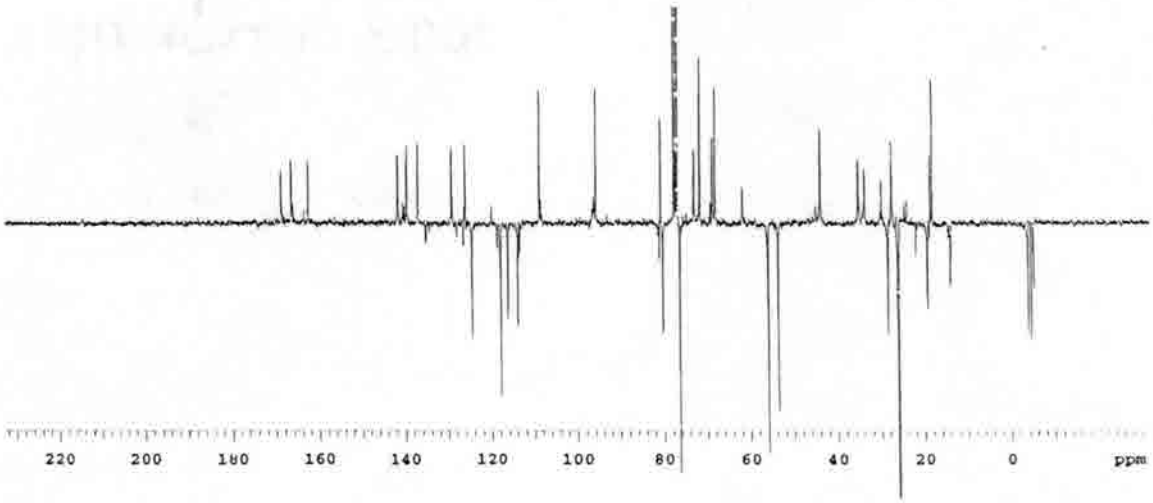
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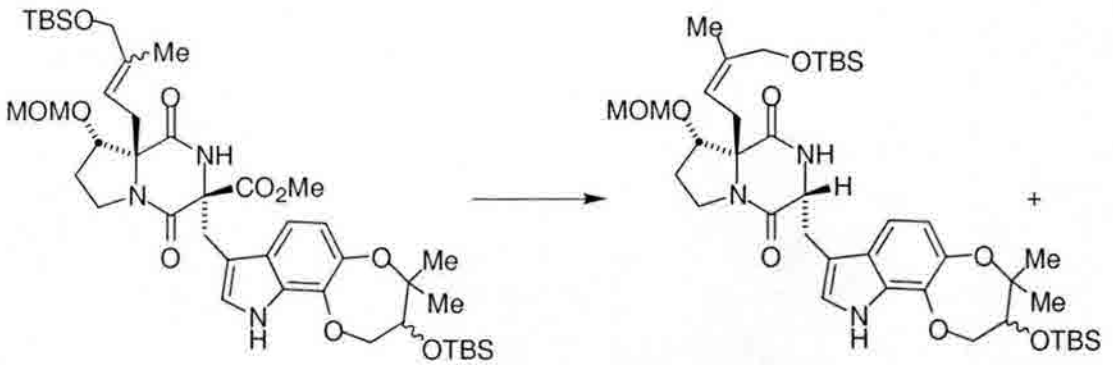
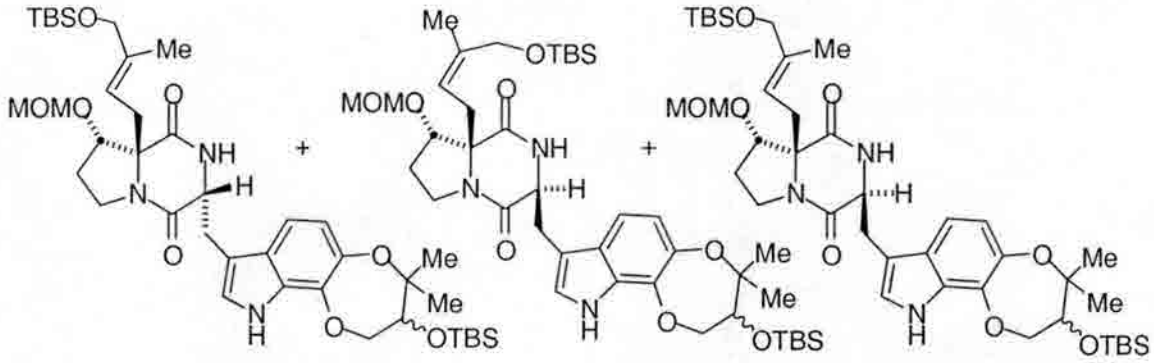


303 **305Z**



305E **306Z** **306E**

3R-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8aR-[(*Z*)-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]-hexahydro-1,4-dioxo-8S-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine (305Z)

3R-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8aR-[(*E*)-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]-octahydro-1,4-dioxo-8S-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine (305E)

3S-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8aR-[(*Z*)-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]-hexahydro-1,4-dioxo-8S-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine (306Z)

3S-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indol-8-yl]methyl]-8aR-[(*E*)-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3-methyl-2-butenyl]-octahydro-1,4-dioxo-8S-(methoxymethoxy)-pyrrolo[1,2-*a*]pyrazine (306E)

To a 50-mL flask charged with **303** (1.0 g, 1.20 mmol, 1 eq) and LiCl (260 mg, 6.02 mmol, 5 eq) under Ar was added a solution of H_2O (32.5 mg, 1.81 mmol, 1.5 eq) in HMPA (9.32 mL). After the reaction mixture was heated on an oil bath at 104-105 °C for 5 h, it was cooled to 23 °C and poured into a 250-mL Erlenmeyer flask containing EtOAc (70 mL) and saturated NH_4Cl solution (60 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined extracts were washed with brine (6 × 50 mL), dried over Na_2SO_4, filtered and concentrated to give a white foam. Purification of the products by radial chromatography (EtOAc:hexane/2:1) provided 280 mg (30%) of a diastereomeric mixture of the *anti*/Z (**305Z**) and the *anti*/E (**305E**) isomer as a white foam and 545 mg (59%) of a diastereomeric mixture of the *syn*/Z (**306Z**) and the *syn*/E (**306E**) isomer as a white foam. The combined yield was 89%.

The analytical samples of *anti*/Z, *anti*/E, *syn*/Z and *syn*/E were obtained through careful separation of the products by flash column chromatography (hexane:EtOAc/2:1, 1:1 then EtOAc)

Data of *anti*/Z isomer (**305Z**) (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03-0.17 (12H, m), 0.88 (9H, s), 0.92 (9H, s), 1.14 and 1.16 (3H, s), 1.49 (3H, s), 1.70 (3H, s), 2.06-2.30 (4H, m), 2.58-2.66 (1H, m), 2.82 (1H, dd, J = 3.3 Hz, J = 11.4 Hz), 3.37 (3H, s), 3.41-3.59 (2H, m), 3.69-3.75 (1H, m), 3.86-4.06 (6H, m), 4.61 (1H, 1/2ABq, J = 6.9 Hz), 4.73 (1H, 1/2ABq, J = 6.9 Hz), 5.16 (1H, m), 5.67 (1H, m), 6.77 (1H, d, J = 8.4 Hz), 7.03 (1H, s), 7.08 (1H, d, J = 8.4 Hz), 8.16 (1H, br s).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 168.3, 166.1, 165.6, 142.1, 141.5, 141.4, 140.5, 140.4, 137.2, 134.8, 129.9, 129.7, 125.7, 125.1, 124.8, 119.7, 117.8, 115.4, 115.3, 112.9, 110.8, 96.5, 96.3, 96.2, 80.96, 80.90, 76.3, 73.6, 73.5, 71.8, 67.7, 67.8, 61.6, 56.0, 54.4, 54.3, 44.1, 43.3, 34.5, 29.9, 28.6, 28.4, 27.5, 26.7, 26.0, 25.9, 21.7, 19.5, 19.3, 18.8, 18.5, 18.1, 13.8, -3.9, -4.6, -5.1.

IR (NaCl, film) 3366, 2955, 2929, 2893, 2856, 1681, 1445, 1251, 1221, 1090, 1042, 837 cm^{-1}.

FAB HRMS m/e 771.4286 ($C_{40}H_{65}N_3O_8Si_2$ requires 771.4310)

Data of *anti*/E isomer (**305E**) (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01, 0.02, 0.15 and 0.16 (total 12 H, s), 0.87 (9 H, s), 0.91 (9 H, s), 1.14 (3 H, s), 1.49 (3 H, s), 1.53 and 1.54 (total 3 H, s), 1.90-2.31 (4 H, m), 2.67 (1 H, br dd, *J* = 14.7, 8.4 Hz), 2.85 (1 H, dd, *J* = 14.7, 11.4 Hz), 3.12-3.77 (3 H, m), 3.37 (3 H, s), 3.81-4.10 (4 H, m), 4.18-4.38 (2 H, m), 4.60 (1 H, 1/2ABq, *J* = 6.9 Hz), 4.72 (1 H, 1/2ABq, *J* = 6.9 Hz), 5.40 (1 H, br t, J = 6.9 Hz), 5.70 (1 H, br s), 6.76 (1 H, d, *J* = 8.4 Hz), 7.02 and 7.03 (total 1 H, br s), 7.09 (1 H, d, *J* = 8.4 Hz), 8.17 (1 H, br s)

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 168.2, 165.5, 142.0, 141.9, 140.5, 137.1, 129.8, 129.7, 125.0, 125.03, 123.1, 117.8, 117.7 115.4, 115.2, 112.96, 112.90, 110.87, 110.82, 96.1, 80.85, 80.80, 76.3, 73.5, 71.7, 67.88, 67.81, 56.0, 54.5, 54.4, 43.3, 34.5, 29.8, 28.8, 28.7, 28.39, 28.35, 26.0, 25.8, 19.4, 19.3, 18.4, 18.0, 13.7, -4.0, -4.6, -5.1, -5.2.

IR (NaCl, film) 3366, 2955, 2929, 2894, 2857, 1681, 1445, 1251, 1107, 1043, 837, 776 cm^{-1}.

FAB HRMS m/e 771.4286 ($C_{40}H_{65}N_3O_8Si_2$ requires 771.4310)

Anal. Calcd. for $C_{40}H_{65}N_3O_8Si_2$: C, 62.22; H, 8.48; N, 5.44. Found: C, 62.40; H, 8.48; N, 5.34

Data of *syn*/Z isomer (**306Z**) (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.15 and 0.17 (6H, s), 0.91 and 0.93 (9H, s), 1.14 (3H, s), 1.49 (3H, s), 1.87 (3H, s), 2.07-2.28 (2H, m), 2.70-2.88 (2H, m), 3.30 (3H,

s), 3.37-3.47 (2H, m), 3.55-3.63 (1H, m), 3.85-4.00 (2H, m), 4.16 (2H, s), 4.20-4.30 (4H, m), 4.54 (1H, 1/2ABq, J = 7.2 Hz), 4.62 (1H, 1/2ABq, J = 7.2 Hz), 5.28 (1H, m), 5.74 (1H, br, s), 6.79 (1H, d, J = 8.4 Hz), 7.01 (1H, s), 7.16 (1H, d, J = 8.4 Hz), 8.16 (1H, br, s).

IR (NaCl, film) 3297, 2955, 2857, 1681, 1651, 1445, 1252, 1221, 1092, 1049, 837, 776 cm^{-1}.

FAB HRMS m/e 777.4318 ($C_{40}H_{65}N_3O_8Si_2$ requires 777.4310)

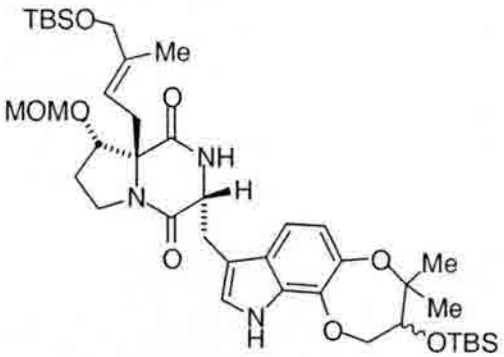
Data of *syn*/E isomer (**306E**) (mixture of two diastereomers):

^1H NMR (300 MHz, $CDCl_3$) δ 0.01-0.18 (12 H, m), 0.85-0.95 (18 H, m), 1.13 and 1.14 (total 3 H, s), 1.48 (3 H, s), 1.63 and 1.86 (total 3 H, br s), 2.00-2.26 (3 H, m), 2.61-2.99 (2 H, m), 3.30 (3 H, s), 3.35-3.63 (2 H, m), 3.82-4.01 (2 H, m), 4.05-4.35 (6 H, m), 4.54 and 4.55 (1 H, 1/2ABq, J = 6.9 Hz), 4.61 and 4.62 (1 H, 1/2ABq, J = 6.9 Hz), 5.20-5.57 (1 H, m), 5.65-5.86 (1 H, m), 6.74-6.82 (1 H, m), 6.98-7.05 (1 H, m), 7.12-7.19 (1 H, m), 8.13-8.26 (1 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) (mixture of four diastereomers) δ 166.5, 165.7, 141.8, 140.0, 139.9, 137.0, 129.6, 124.9, 123.3, 118.7, 117.7, 117.6, 116.0, 113.1, 110.9, 110.8, 95.4, 80.6, 80.7, 76.2, 73.0, 71.6, 68.0, 61.7, 57.3, 57.2, 55.8, 43.2, 33.5, 32.4, 28.3, 27.0, 26.0, 25.8, 21.9, 19.2, 18.5, 18.0, -4.0, -4.7, -5.1, -5.2.

IR (NaCl, film) 3297, 2955, 2857, 1681, 1651, 1445, 1252, 1221, 1092, 1049, 837, 776 cm^{-1}.

FAB HRMS m/e 771.4318 ($C_{40}H_{65}N_3O_8Si_2$ requires 771.4310)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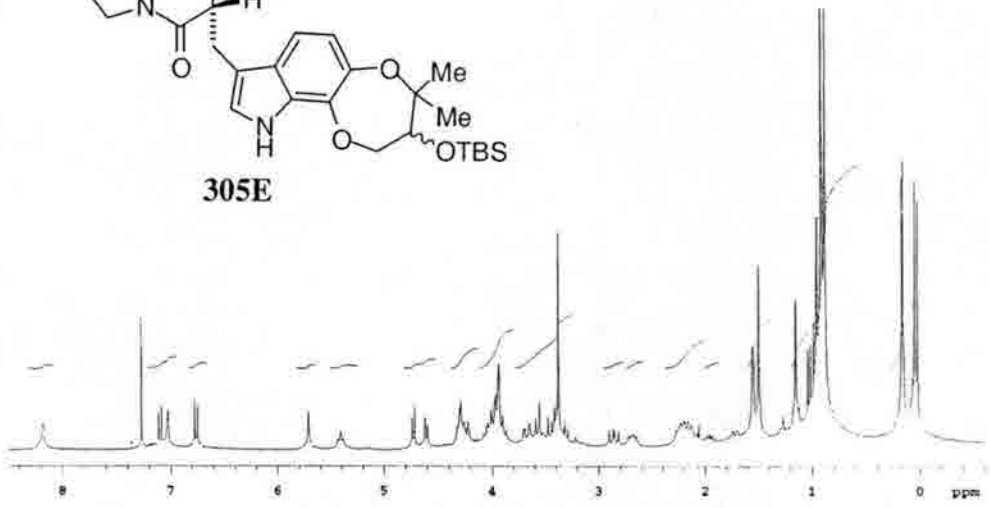
OTBS

305E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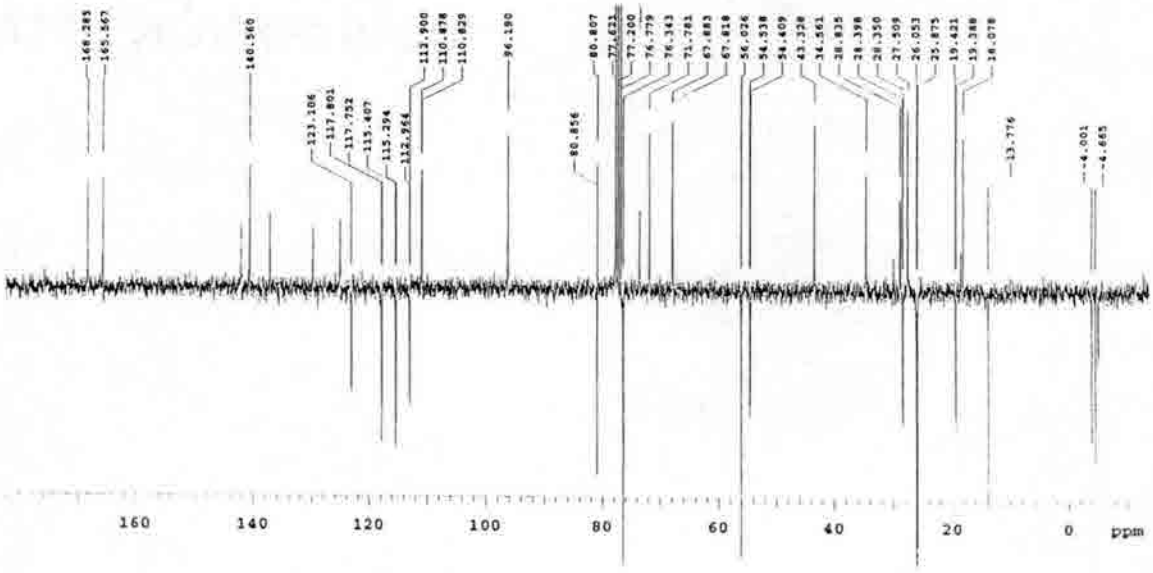
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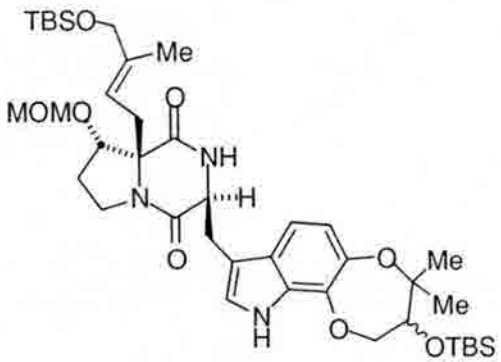
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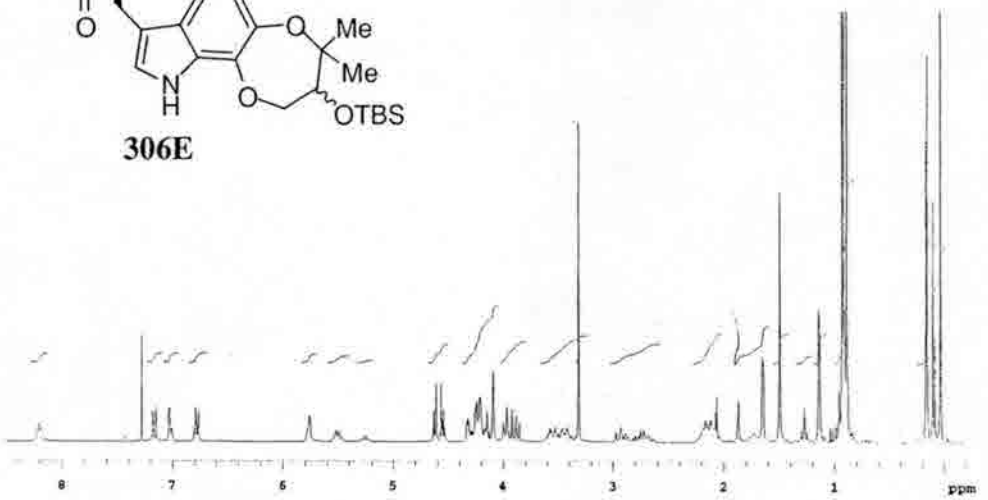
306E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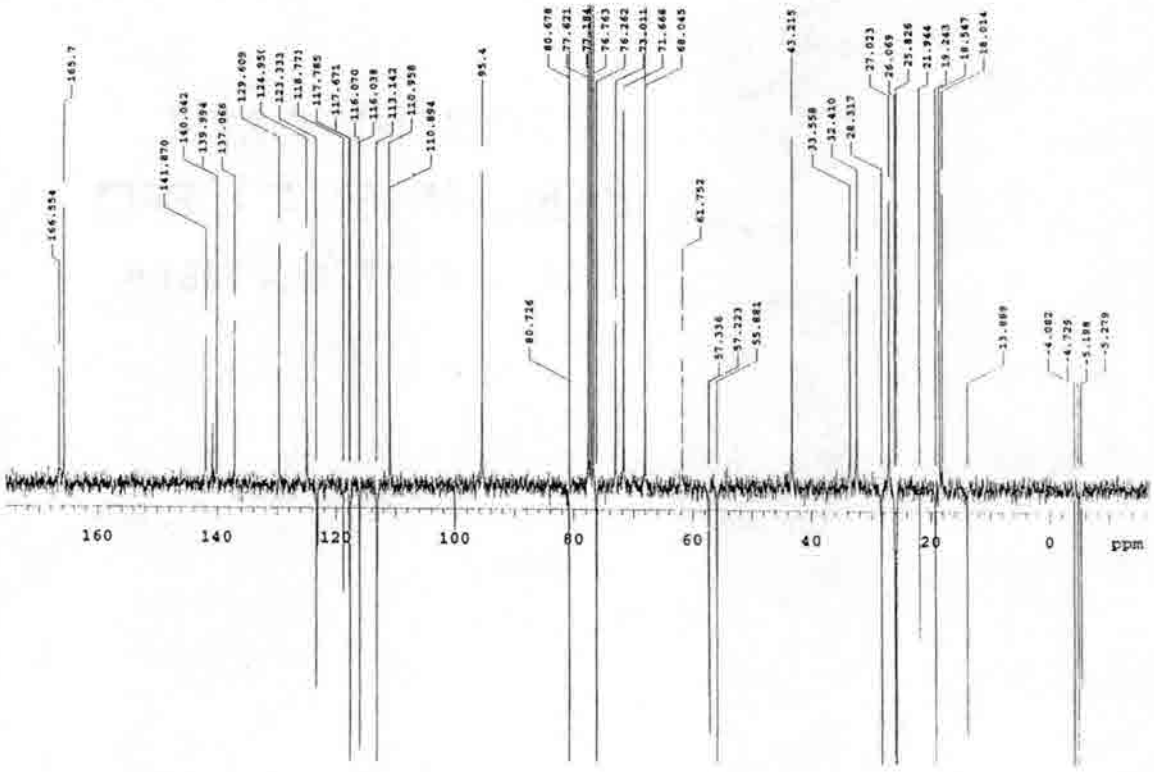
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71.668
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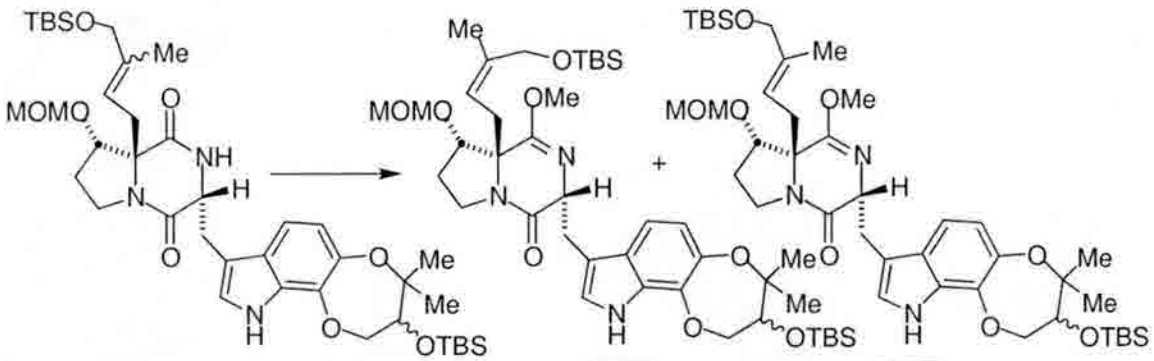


305 **307Z** **307E**

Pyrrolo[1,2-a]pyrazin-4(3H)-one, 3R-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8aR-[(*Z*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-6,7,8,8a-tetrahydro-1-methoxy-8S-(methoxymethoxy) (307Z)

Pyrrolo[1,2-a]pyrazin-4(3H)-one, 3R-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8aR-[(*E*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-6,7,8,8a-tetrahydro-1-methoxy-8S-(methoxymethoxy) (307E)

To a flask charged with **305** (45.0 mg, 58.3 μmol, 1 eq), Cs_2CO_3 (380 mg, 1.16 mmol, 20 eq) and Me_3OBF_4 (21.5 mg, 0.145 mmol, 2.5 eq) under Ar was added CH_2Cl_2 (1.93 mL). After the reaction mixture was stirred at 23 °C for 10 h, it was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a white foam. Preparative TLC (hexane:EtOAc:MeOH/5:2:0.5) purification of the products gave 8.3 mg (18%) of **307Z** (a white foam, as a high R_f *anti*/Z isomer) and 21.3 mg (46.5%) of **307E** (a white foam, as a lower R_f *anti*/E isomer). The combined yield was 65%.

Data of *anti*/Z isomer (**307Z**) (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 and 0.13-0.15 (total 12H, s), 0.87-0.90 (total 18H, s), 1.06 and 1.39 (total 3H, s), 1.44 and 1.48 (total 3H, s), 1.72 (3H, s), 1.82-2.10 (total 3H, m), 2.37-2.47 (total 1H, m), 3.00 and 3.14 (total 3H, s), 3.31-3.50 (total 3H, m), 3.61 and

3.63 (total 3H, s), 3.75-4.30 (total 10H, m), 5.05 and 5.22 (total 1H, m), 6.67 and 6.70 (total 1H, s), 6.98 and 7.01 (total 1H, d, J = 5.1 Hz), 7.24-7.29 (total 1H, m), 7.94-7.95 (1H, d, J = 5.1 Hz).

IR (NaCl, film) 3320, 2958, 2862, 1707, 1643, 1466, 1361, 1249, 1089, 837 cm^{-1}.

FAB HRMS m/e 786.4507 ($C_{41}H_{67}N_3O_8Si_2$ + H requires 786.4544).

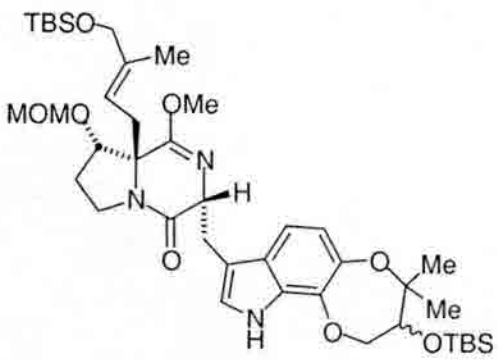
Data of *anti*/E isomer (**307E**) (mixture of two diastereomers):

^1H NMR (300 MHz, $CDCl_3$) δ 0.012, 0.018, 0.025 and 0.030 (total 6 H, s), 0.14 and 0.15 (total 6 H), 0.88, 0.89, 0.90 and 0.91 (total 18 H, s), 1.07 and 1.13 (total 3 H, s), 1.45 and 1.48 (total 3 H, s), 1.52 (3 H, s), 1.82-2.16 (3 H, m), 2.41 (1 H, m), 3.03 and 3.16 (total 3 H, s), 3.26-3.52 (3 H, m), 3.62 and 3.64 (total 3 H, s), 3.71-4.32 (10 H, m), 5.19-5.29 (1 H, m), 6.69 (1 H, d, J = 8.4 Hz), 6.99 and 7.03 (total 1 H, d, J = 2.1 Hz), 7.27 and 7.29 (1 H, d, J = 8.4 Hz), 7.93 and 7.95 (1 H, br s).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 169.1, 169.12, 141.4, 141.0, 139.9, 136.7, 136.6, 128.8, 127.6, 127.2, 123.1, 123.0, 116.4, 116.3, 115.9, 114.7, 114.5, 113.8, 113.5, 95.5, 94.9, 80.5, 80.2, 79.7, 79.5, 76.6, 71.7, 71.6, 71.4, 71.3, 68.16, 68.11, 61.0, 60.7, 55.6, 55.5, 42.0, 41.9, 33.5, 33.51, 29.1, 28.9, 28.7, 28.1, 27.7, 26.1, 25.9, 19.7, 18.7, 18.5, 18.1, 13.7, -3.8, -3.9, -4.5, -5.1.

IR (NaCl, film) 3320, 2958, 2862, 1707, 1643, 1446, 1254, 1217, 1105, 1041, 839, 775 cm^{-1}.

FAB HRMS m/e 785.4462 ($C_{41}H_{67}N_3O_8Si_2$ requires 785.4466)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O
OTBS

307E

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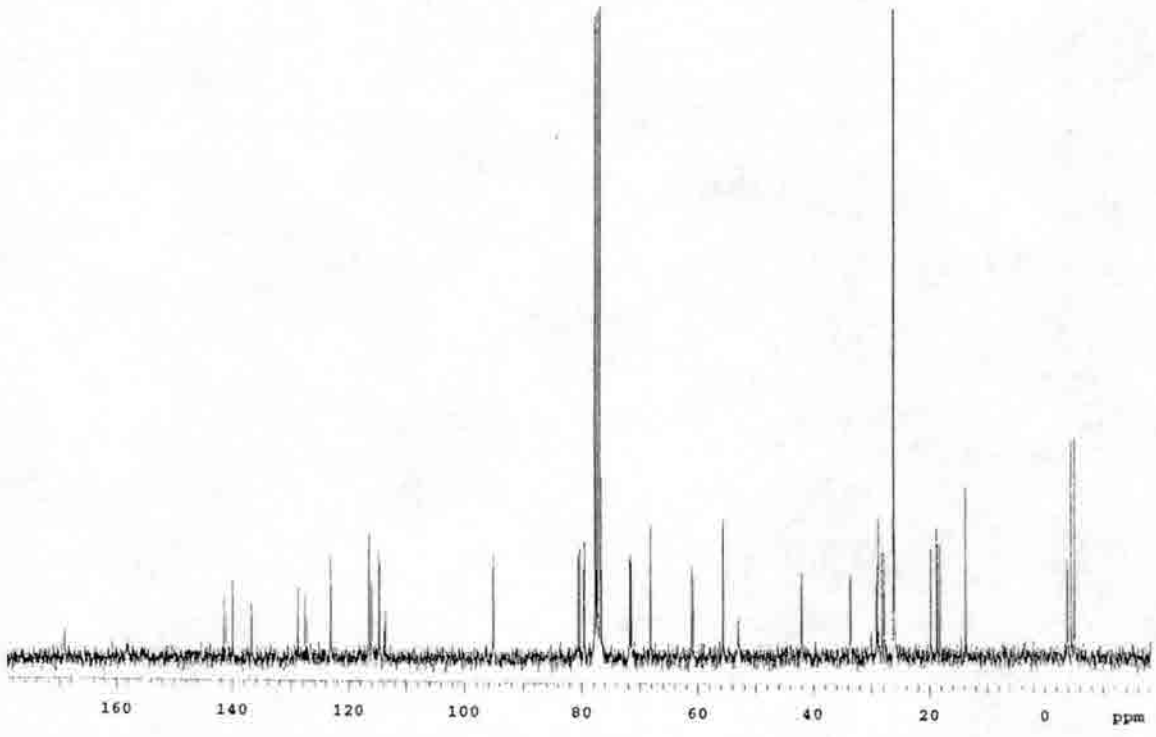
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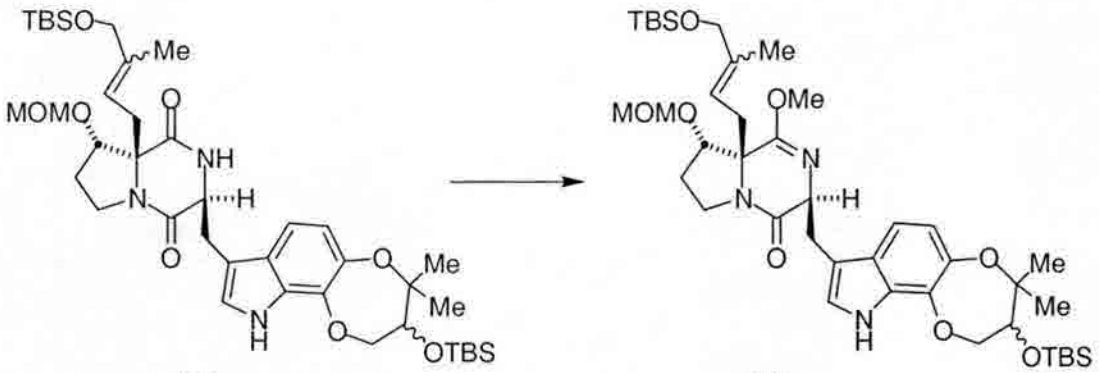


306 **308**

Pyrrolo[1,2-a]pyrazin-4(3H)-one, 3S-[[3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2H,10H-[1,4]dioxepino[2,3-g]indol-8-yl]methyl]-8aR-[(*E/Z*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-6,7,8,8a-tetrahydro-1-methoxy-8S-(methoxymethoxy) (308)

To a flask charged with **306** (1.50 g, 1.94 mmol, 1 eq), Cs_2CO_3 (9.50 g, 29.1 mmol, 15 eq) and Me_3OBF_4 (863 mg, 5.83 mmol, 3 eq) was added CH_2Cl_2 (65 mL). After the reaction mixture was stirred at 23 °C for 11 h, it was quenched with H_2O (120 mL), and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to give 1.60 g of a foamy solid. The product was purified by flash column chromatography (EtOAc:hexane/1:1) to give 877 mg of **308** (57%, 86% based on the recovered 500 mg of a mixture of starting material and product)

Data of **308** (mixture of four diasteromers):

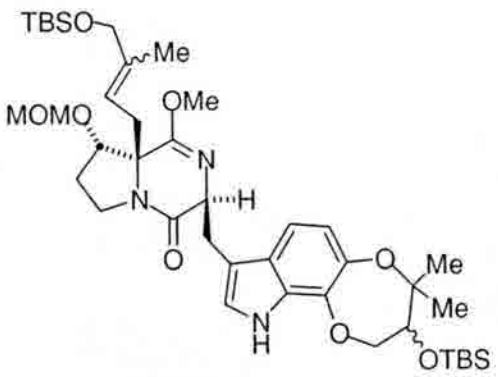
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00-0.18 (12 H, m), 0.87, 0.88, 0.90 and 0.91 (total 18 H, s), 1.07 and 1.10 (total 3 H, s), 1.47 and 1.48 (total 6 H, s), 1.51-2.03 (4 H, m), 3.04-3.16 (1 H, m), 3.20-3.51 (2 H, m), 3.28 (3 H, s), 3.70 (3 H, br s), 3.74-3.86 (1 H, m), 3.90-4.23 (6 H, m), 4.37-4.47 (1 H, m), 4.53 (2 H, s), 5.15-5.29 (1 H, m), 6.72 (1 H, d, J = 8.4 Hz), 7.06-7.11 (1 H, m), 7.20 and 7.21 (1 H, d, J = 8.4 Hz), 8.05 (1 H, br s).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 169.8, 158.5, 141.5, 141.4, 139.6, 139.3, 138.5, 138.3, 136.8, 128.9, 129.0, 126.4, 122.6, 119.3, 116.8, 114.2, 114.1, 113.9, 113.6, 94.9,

80.4, 80.3, 79.5, 71.6, 70.79, 70.73, 62.8, 62.7, 61.6, 55.7, 52.7, 42.2, 33.6, 33.2, 31.6, 28.5, 28.3, 27.1, 26.0, 25.8, 21.8, 19.2, 18.8, 18.4, 18.0, 13.5, -3.9, -4.6, -5.2.

IR (NaCl, film) 3327, 2956, 2855, 1694, 1644, 1448, 1252, 1087, 1042, 836 cm^{-1}.

FAB HRMS m/e 786.4525 ($C_{41}H_{67}N_3O_8Si_2$ + H requires 786.4544)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308

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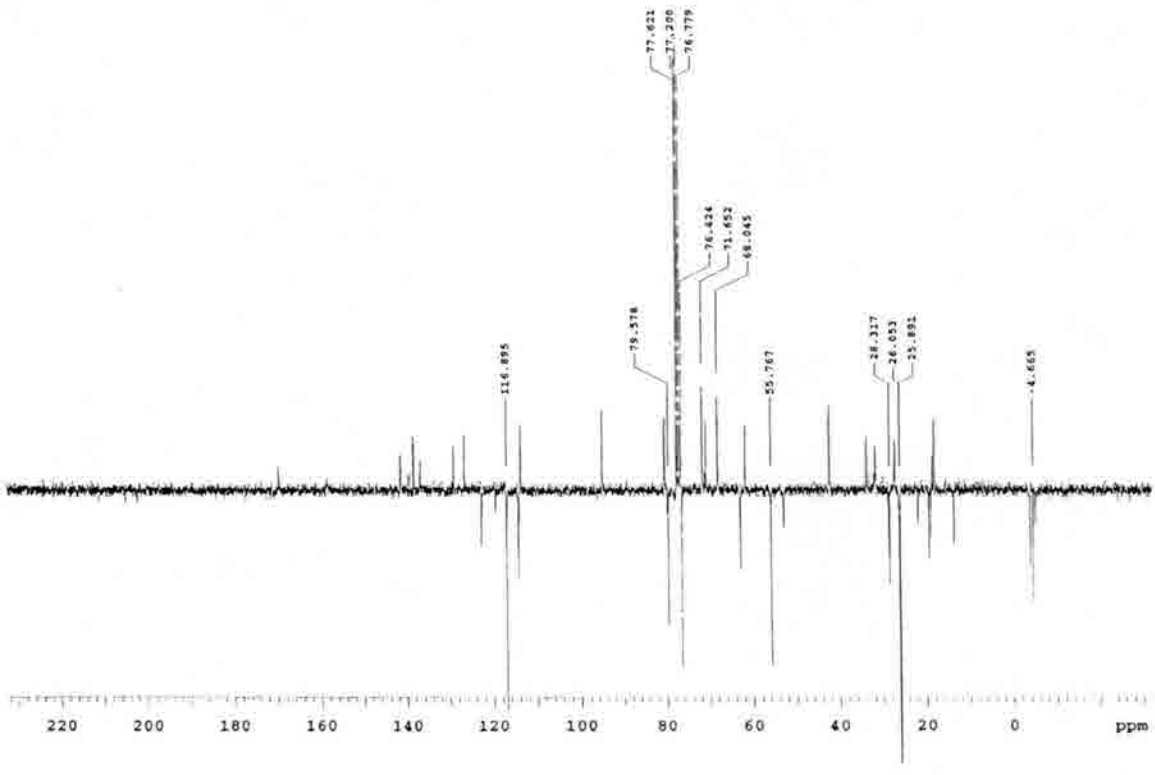
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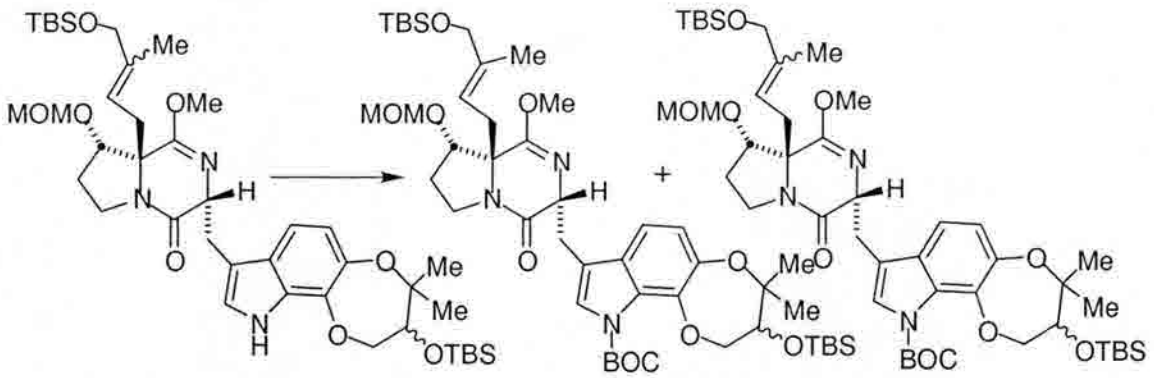


307 **309E** **309**

8-[[8aR-[(*E*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3R-yl]methyl]-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (309E)

To a solution of **307** (300 mg, 0.382 mmol, 1 eq) in CH_2Cl_2 (3.74 mL) at 0 °C was added triethylamine (42.3 mg, 0.419 mmol, 1.1 eq), DMAP (46.6 mg, 0.381 mmol, 1 eq) and $(BOC)_2O$ (250 mg, 1.15 mmol, 3.0 eq). After the reaction mixture was stirred at 0 °C for 6 h, the solvent was removed, and the residue was purified by radial chromatography (hexane:EtOAc/3:1) to provide 120 mg of **309** (a white foam, as a mixture of the *anti*/E and the *anti*/Z isomer) and 208 mg of **309E** (a white foam, as an *anti*/E isomer). The combined yield was 97%

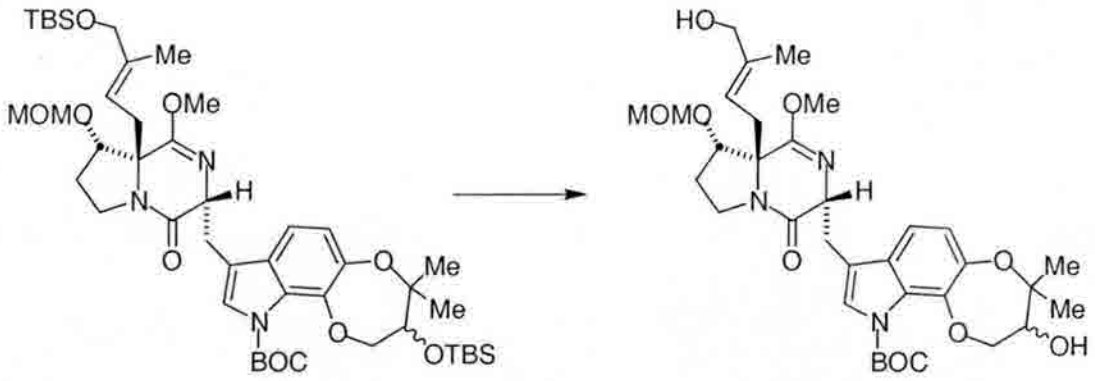
Data of *anti*/E isomer (**309E**) (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.008, 0.014, 0.018 and 0.024 (total 6 H, s), 0.14, 0.15 and 0.16 (total 6 H, s), 0.87, 0.88, 0.90 and 0.91 (total 18 H, s), 1.06 and 1.10 (total 3 H, s), 1.48 and 1.49 (total 3 H, s), 1.52 (3 H, br s), 1.595 and 1.598 (total 9 H, s), 1.76-1.95 (1 H, m), 1.97-2.13 (2 H, m), 2.35-2.48 (1 H, m), 3.02 and 3.15 (total 3 H, s), 3.18-3.48 (3 H, m), 3.55 and 3.61 (total 3 H, s), 3.70-4.06 (4 H, m), 3.93 (2 H, br s), 4.09-4.31 (4 H, m), 5.17-5.27 (1 H, m), (1 H, m), 6.85 (1 H, d, J = 8.4 Hz), 7.22-7.32 (2 H, m).

^{13}C NMR (75 MHz, $CDCl_3$) δ: -5.1, -4.6, -3.65, -3.58, 13.7, 18.2, 18.6, 18.7, 19.1, 26.0, 26.1, 27.7, 28.4, 28.6, 28.9, 33.5, 42.0, 52.7, 55.4, 55.6, 60.3, 60.7, 68.0, 68.1, 71.1, 71.2, 76.2, 79.0, 79.2, 80.3, 82.39, 82.44, 94.6, 114.9, 115.8, 116.7, 116.9, 119.1, 126.9, 127.0, 127.7, 131.1, 131.4, 139.9, 140.2, 140.3, 145.76, 145.85, 149.1, 158.0, 168.8, 169.2.

IR (NaCl, film) 2953, 2892, 1749, 1700, 1649, 1494, 1435, 1250, 1257, 1085 cm^{-1}.

FAB HRMS m/e 886.5069 ($C_{46}H_{75}N_3O_{10}Si_2$ + H requires 886.5069)



309E **311E**

8-[[8aR-[(*E*)-4-hydroxy-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3R-yl]methyl]-3R/S-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (311E)

To a solution of **309E** (190 mg, 0.214 mmol, 1 eq) in THF (2.6 mL) at 23 °C was added TBAF (0.70 mL, 1.0 M in THF, 0.70 mmol, 3.3 eq). After 11 h, the reaction mixture was quenched with water (55 mL) and extracted with EtOAc/Et_2O (1/1) (three times). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. The product was purified by radial chromatography (hexane:EtOAc/1:2) to provide 132 mg (94%) of **311E** as a white foam

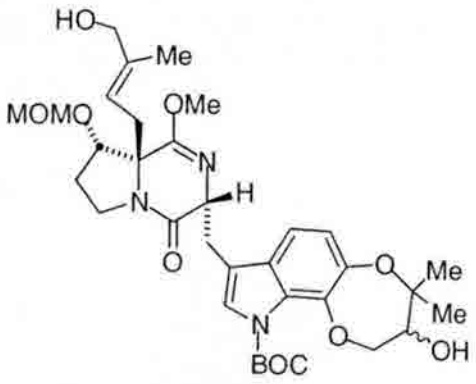
Data of **311E** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 and 1.21 (total 3 H, s), 1.55 and 1.57 (total 3 H, s), 1.591 and 1.594 (total 12 H, s), 1.77-1.97 (1 H, m), 1.98-2.16 (1 H, m), 2.44 (1 H, m), 3.01-3.12 (1 H, m), 3.04 and 3.15 (total 3 H, m), 3.20-3.44 (4 H, m), 3.49-3.67 (1 H, m), 3.52 and 3.61 (total 3 H, s), 3.75-4.38 (8 H, m), 3.95 (2 H, s), 5.22 (1 H, m), 6.88 (1 H, d, J = 8.4 Hz), 7.22-7.30 (2 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 168.9, 158.0, 148.8, 146.0, 140.5, 131.3, 131.1, 127.9, 127.8, 127.0, 126.8, 118.7, 116.4, 115.3, 115.2, 94.6, 94.4, 82.5, 82.4, 79.9, 79.8, 79.1, 78.7, 75.6, 71.1, 70.8, 70.7, 67.9, 60.5, 60.1, 55.4.

IR (NaCl, film) 3406, 2980, 2883, 1745, 1696, 1634, 1439, 1435, 1367, 1251, 1155, 1043, 966, 917 cm^{-1}.

FAB HRMS m/e 658.3328 ($C_{34}H_{47}N_3O_{10}$ + H requires 658.3339)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BOC
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311E

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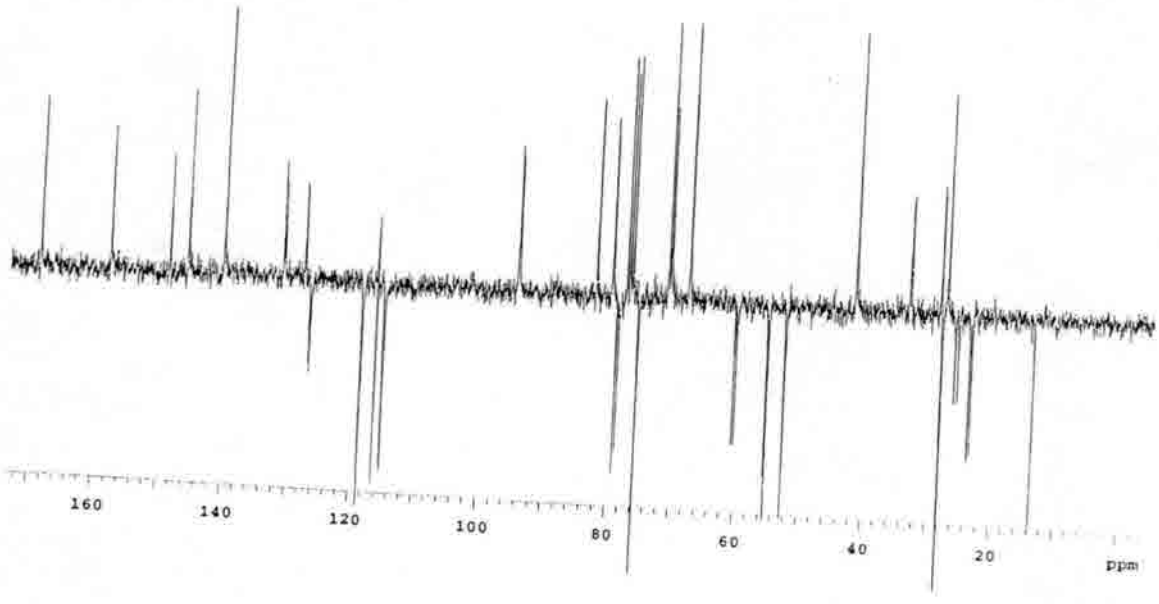
ppm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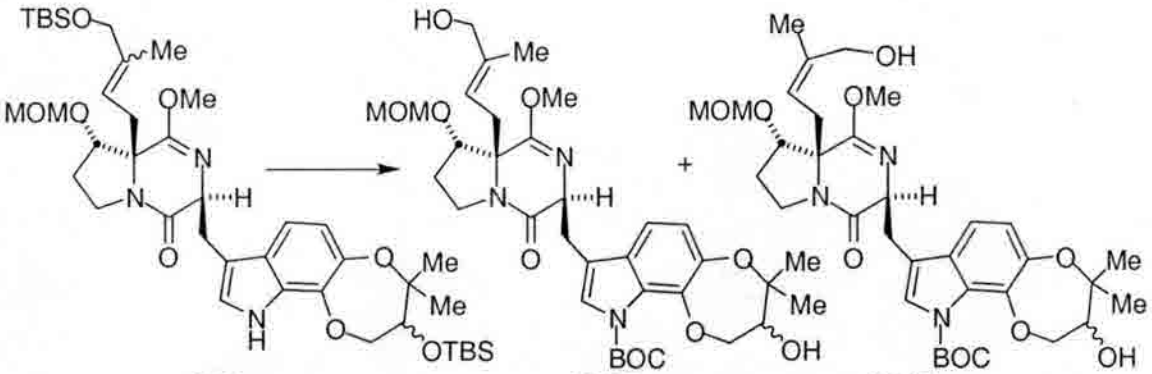


308 **312E** **312Z**

8-[[8aR-[(*E*)-4-hydroxy-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3S-yl]methyl]-3R/S-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (312E)

8-[[8aR-[(*Z*)-4-hydroxy-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3S-yl]methyl]-3R/S-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (312Z)

To a solution of **308** (877 mg, 1.12 mmol, 1 eq) in CH_2Cl_2 (8 mL) at 0 °C under Ar was added triethylamine (124 mg, 1.22 mmol, 1.1 eq), DMAP (136 mg, 1.10 mmol, 1.0 eq) and $(BOC)_2O$ (730 mg, 3.34 mmol, 3.1 eq). After 4 h, the reaction mixture was concentrated under reduced pressure. THF (0.8 mL) and TBAF (2.84 mL, 1.0 M in THF, 2.84 mmol, 2.47 eq) were added to the above residue at 23 °C. After 16 h, additional TBAF (1.70 mL, 1.70 mmol, 1.48 eq) was added. The reaction mixture was stirred for 2 h, and then a third aliquot of TBAF (1.0 mL, 1.0 mmol, 0.87 eq) was added. The reaction was allowed to proceed for a further 10 h before being quenched with H_2O (400 mL). TLC (EtOAc:MeOH/10:1) was used to monitor the reaction. The mixture was extracted with EtOAc/ether (2/1) (3 × 200 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a foamy solid. The products were purified by radial chromatography (hexane:EtOAc/1:2) to provide 550 mg of **312E** (a white foam, as

a high R_f *syn*/E isomer) and 240 mg of **312Z** (a white foam, as a lower R_f *syn*/Z isomer). The combined yield was 100%.

Data of **312E** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 and 1.22 (total 3 H, s), 1.54-1.59 (6 H, m), 1.61 (9 H, s), 1.74-2.19 (4 H, m), 2.93-3.23 (2 H, m), 3.25-3.41 (2 H, m), 3.29 and 3.30 (total 3 H, s), 3.58 (1 H, br s), 3.70 (3 H, s), 3.80-3.95 (2 H, m), 4.00-4.17 (2 H, m), 4.23-4.35 (2 H, m), 4.42 (1 H, m), 4.54 and 4.55 (total 2 H, s), 4.71 and 5.03 (total 1 H, m), 6.91 and 6.92 (total 1 H, d, J = 8.4 Hz), 7.21 (1 H, d, J = 8.4 Hz), 7.35 and 7.39 (total 1 H, s).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 169.6, 169.3, 159.2, 158.4, 148.8, 146.6, 146.5, 141.0, 139.0, 138.8, 130.5, 130.4, 128.5, 126.9, 126.8, 119.5, 119.4, 118.2, 117.9, 117.1, 116.8, 115.1, 95.0, 94.8, 83.0, 80.2, 80.1, 75.8, 71.0, 70.9, 68.4, 68.3, 62.2, 61.8, 52.8, 52.7, 42.8, 42.3, 34.2, 33.8, 30.9, 28.2, 27.1, 26.4, 26.0, 23.6, 23.3, 14.3, 13.9.

IR (NaCl, film) 3416, 1750, 1693, 1636, 1493, 1368, 1157, 757 cm^{-1}.

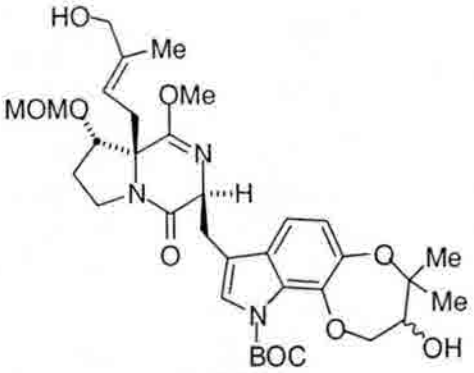
FAB HRMS m/e 657.3263 ($C_{34}H_{47}N_3O_{10}$ requires 657.3261)

Data of **312Z** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 and 1.21 (total 3H, s), 1.53 and 1.54 (total 3H, s), 1..60 (total 9H, s), 1.77 (total 3H, s), 1.90-2.15 (total 3H, m), 2.83-2.95 (2H, m), 3.28 and 3.29 (total 3H, s), 3.21-3.41 (total 3H, m), 3.59 (1H, br s), 3.67 and 3.68 (total 3H, s), 3.83 and 3.97 (total 2H, m), 4.01-4.15 (total 2H, m), 4.27-4.28 (total 2H, m), 4.37-4.42 (total 1H, m), 4.530 and 4.539 (total 2H, s), 5.05 (1H, m), 6.91 (1H, d, J = 8.4 Hz), 7.18 (2H, d, J = 8.4 Hz), 7.37 and 7.39 (total 1H, s).

IR (NaCl, film) 3420, 2977, 2945, 1750, 1699, 1635, 1368, 1154, 1037 cm^{-1}.

FAB HRMS m/e 657.3234 ($C_{34}H_{47}N_3O_{10}$ requires 657.3261)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312E

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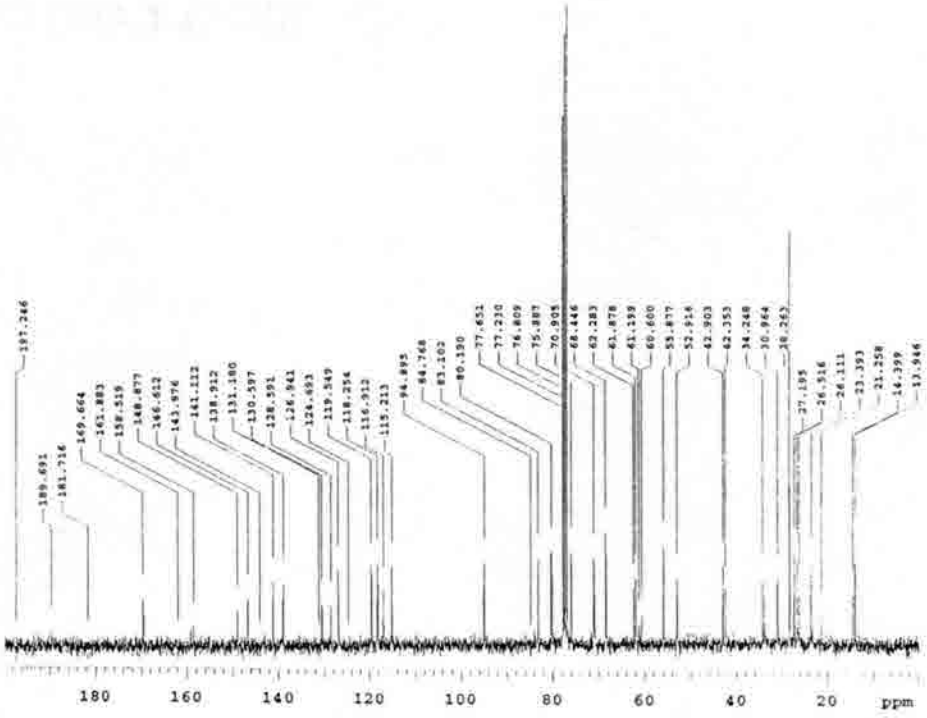
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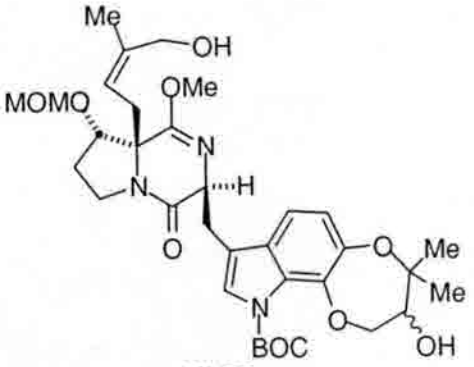
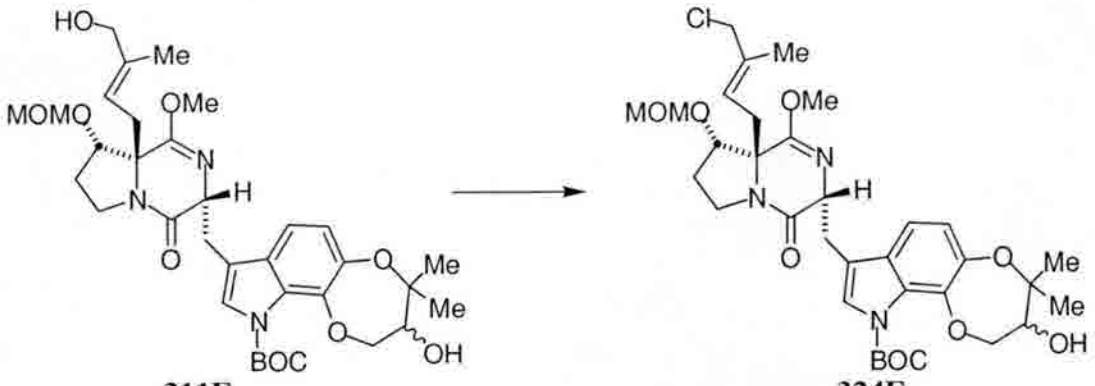


312Z



311E **324E**

8-[[8aR-[(*E*)-4-chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3R-yl]methyl]-3R/S-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (324E)

To a solution of **311E** (55.0 mg, 0.084 mmol, 1 eq) in CH_2Cl_2 (1.5 mL) at 0 °C was added collidine (101 mg, 0.84 mmol, 10 eq) followed by dropwise addition of MsCl (110 μL, 0.607 M MsCl in CH_2Cl_2, 0.092 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 3.5 h and at 7 °C for 14 h. TLC (CH_2Cl_2:MeOH/18:1) showed that the starting material had reacted and that the desired allylic mesylate and by-product bis mesylate (minor) were formed. At this time, the reaction mixture was concentrated and CH_2Cl_2 (675 μL) was added followed by HMPA (84.8 mg, 0.453 mmol, 5.4 eq). After the reaction mixture was stirred at 23 °C for 24 h, $Bn(Bu)_3NCl$ (104 mg, 0.32 mmol, 4 eq) was added, and the mixture was stirred at 23 °C for an additional 6 h. TLC (hexane:EtOAc/1:1) showed that the reaction was finished. The reaction mixture was concentrated and extracted with (EtOAc/Et_2O) (2/1). The combined extracts were washed with 0.005 N HCl in water (5 × 35 mL), washed with brine (once), dried over Na_2SO_4 and concentrated to give 60 mg of a while foam. Preparative TLC (CH_2Cl_2:MeOH/25:1) purification of the products gave 43 mg (77%) of **324E** as a white foam

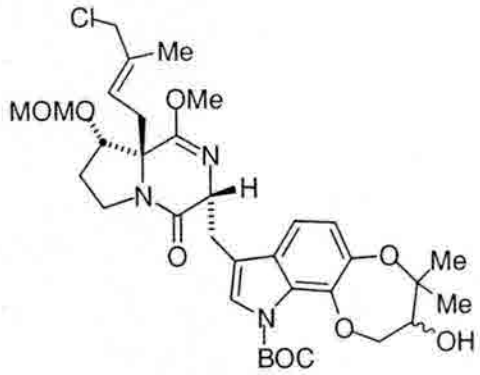
Data of **324E** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 and 1.21 (total 3 H, s), 1.53 and 1.56 (total 3 H, s), 1.58 and 1.59 (total 9 H, s), 1.67 (3 H, br s), 1.78-2.15 (4 H, m), 2.38-2.51 (1 H, m), 3.03-3.65 (4 H, m), 3.04-3.14 (total 3 H, s), 3.51 and 3.61 (total 3 H, s), 3.77-4.36 (7 H, m), 3.92 (2 H, s), 5.26-5.38 (1 H, m), 6.87 (1 H, d, J = 8.4 Hz), 7.21-7.29 (2 H, m).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 168.5, 157.7, 157.6, 148.9, 146.2, 140.7, 140.6, 137.1, 131.5, 131.1, 128.1, 128.0, 127.1, 126.9, 122.2, 118.9, 118.7, 116.7, 116.5, 115.4, 115.3, 94.7, 94.6, 82.6, 82.5, 80.0, 79.9, 79.2, 78.8, 75.8, 71.0, 71.03, 70.9, 70.8, 60.6, 60.0, 55.5, 55.3, 52.69, 52.7, 51.4, 42.0, 33.9, 33.8, 28.5, 28.4, 28.2, 27.5, 26.4, 26.0, 23.4, 23.2, 14.4.

IR (NaCl, film) 3419, 2978, 2894, 1745, 1698, 1645, 1436, 1158, 1037, 733 cm^{-1}.

FAB HRMS m/e 676.2992 ($C_{34}H_{46}N_3O_9Cl$ + H requires 676.2992)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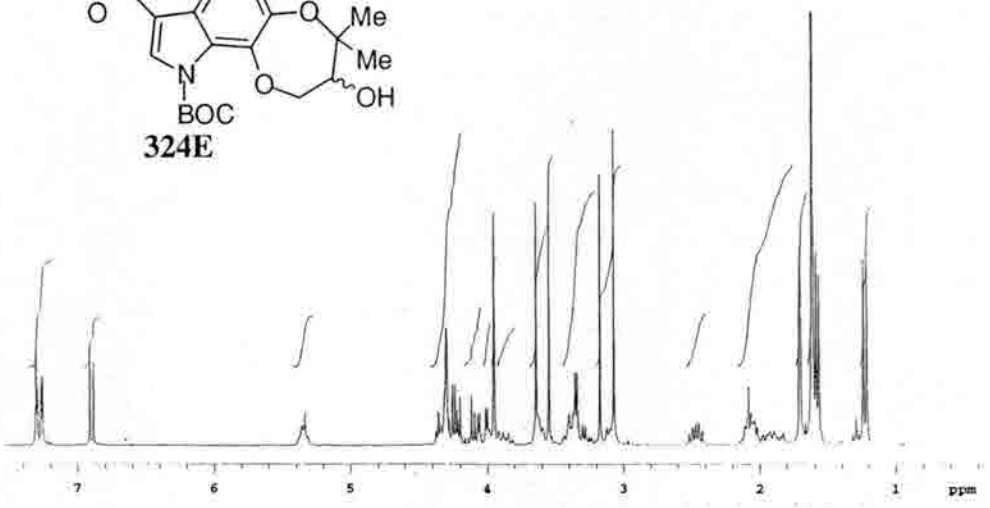
BOC

324E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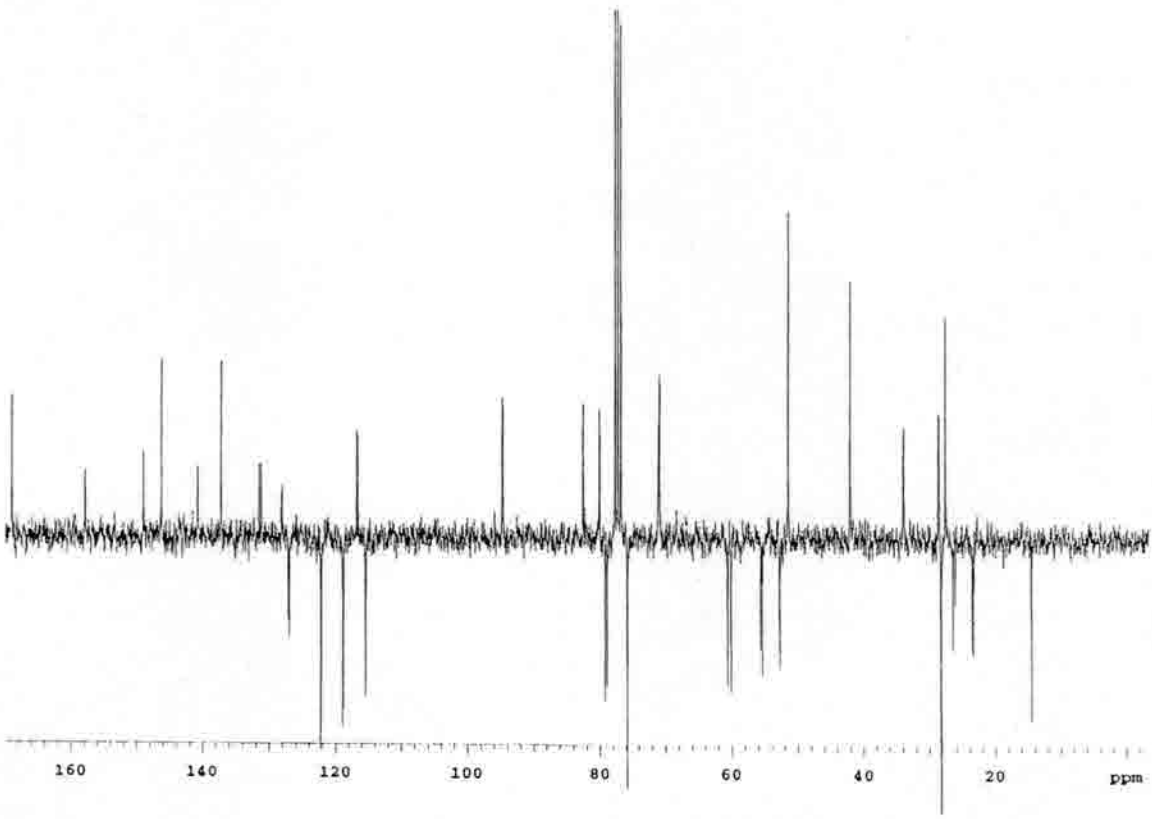
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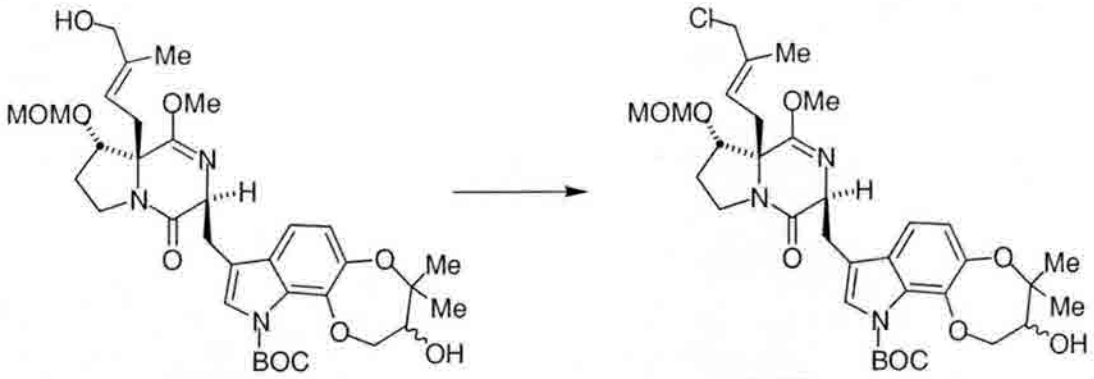


312E **317E**

8-[[8aR-[(*E*)-4-chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3S-yl]methyl]-3R/S-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (317E)

To a solution of **312E** (100 mg, 0.152 mmol, 1 eq) in CH_2Cl_2 (2.7 mL) at 0 °C was added collidine (183 mg, 1.52 mmol, 10 eq) followed by dropwise addition of MsCl (275 μL, 0.607 M in CH_2Cl_2, 0.167 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 2 h and at 7 °C for 17 h. The reaction mixture was concentrated and CH_2Cl_2 (1.35 mL) was added followed by HMPA (155 mg, 0.863 mmol, 5.7 eq). After the reaction mixture was stirred at 23 °C for 22 h, $Bn(Bu)_3NCl$ (189 mg, 0.61 mmol, 4 eq) was added, and the mixture was stirred at 23 °C for an additional 5 h. The reaction mixture was concentrated and extracted with (EtOAc/Et_2O) (2/1). The combined extracts were washed with 0.005 N HCl in water (4 × 70 mL, 1 × 15 mL), washed with brine (once), dried over Na_2SO_4 and concentrated to give 119 mg of a while foam. Preparative TLC (CH_2Cl_2:MeOH/18:1) purification of the products gave 90 mg (90%, based on recovered 2 mg of **312E**) of **317E** as a white foam and 8 mg (7%) of by-product chloride-mesylate **323E** as a white foam.

Data of **317E** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 and 1.21 (total 3 H, s), 1.57 and 1.58 (total 3 H, s), 1.61 (9 H, s), 1.69 (3 H, br s), 1.78-1.95 (1 H, m), 1.96-2.11 (2 H, m), 2.12-2.33 (1 H, m),

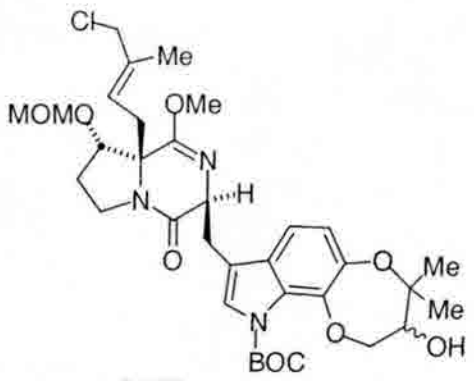
2.84 (1 H, dt, J = 14.4, 9.3 Hz), 3.02-3.14 (1 H, m), 3.21-3.43 (2 H, m), 3.295 and 3.299 (total 3 H, s), 3.56-3.64 (1 H, m), 3.66 and 3.67 (total 3 H, s), 3.93 (2 H, s), 4.10-4.25 (2 H, m), 4.25-4.33 (2 H, m), 4.38 (1 H, m), 4.55 (2 H, ABq), 5.22 and 5.29 (total 1 H, br t, J = 7.5 Hz), 6.92 (1 H, d, J = 8.4 Hz), 7.19 and 7.27 (total 1 H, d, J = 8.4 Hz), 7.42 and 7.43 (total 1 H, s).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 169.5, 158.1, 157.8, 148.8, 146.6, 141.1, 136.1, 136.0, 130.3, 128.47, 128.40, 126.8, 122.97, 122.90, 119.4, 117.0, 116.8, 114.9, 94.8, 82.9, 80.1, 80.0, 79.6, 79.5, 75.7, 70.9, 70.7, 61.8, 55.8, 52.8, 51.5, 42.3, 33.9, 33.8, 31.5, 31.4, 28.2, 27.1, 27.0, 26.4, 23.4, 23.3, 14.4.

IR (NaCl, film) 3234, 2982, 2941, 1751, 1699, 1643, 1370, 1036 cm^{-1}.

FAB HRMS m/e 675.2920 ($C_{34}H_{46}N_3O_9Cl$ requires 675.2922)

Anal. Calcd. for $C_{34}H_{46}N_3O_9Cl$: C, 60.39; H, 6.85; N, 6.21. Found: C, 60.52; H, 6.74; N, 5.98.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317E

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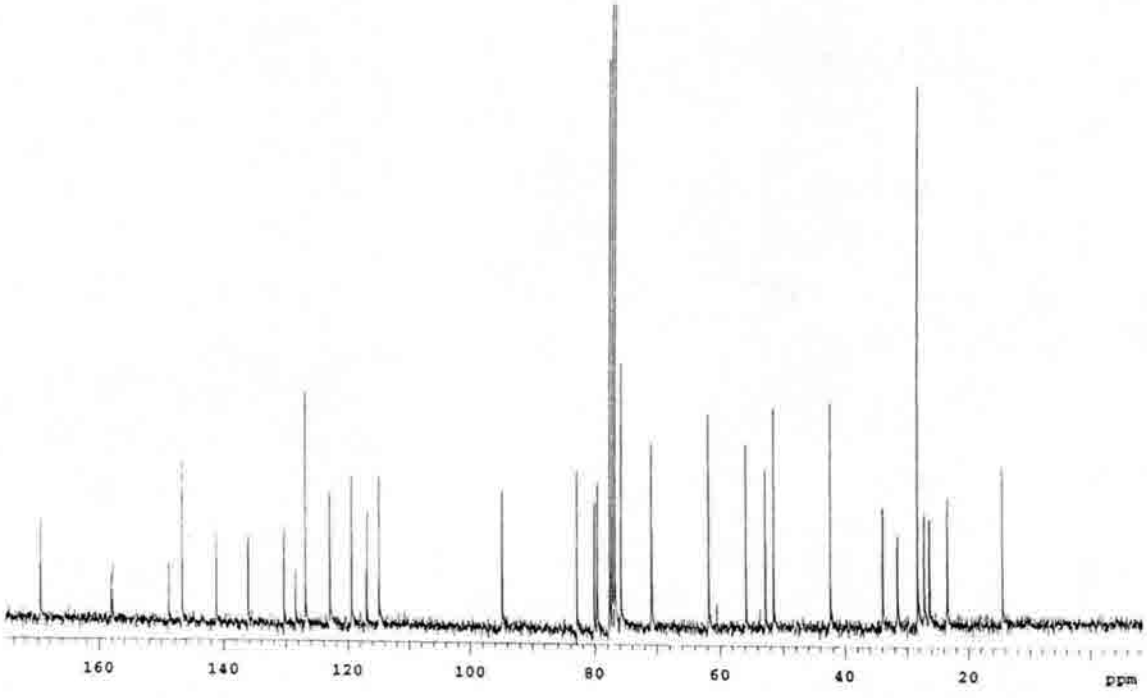
ppm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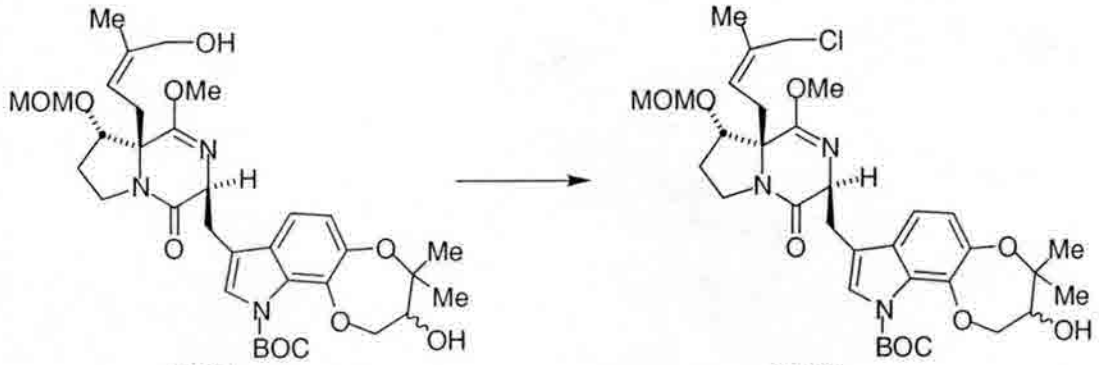


312Z **317Z**

8-[[8aR-[(*Z*)-4-chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3S-yl]methyl]-3R/S-3,4-dihydro-3-hydroxy-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (317Z)

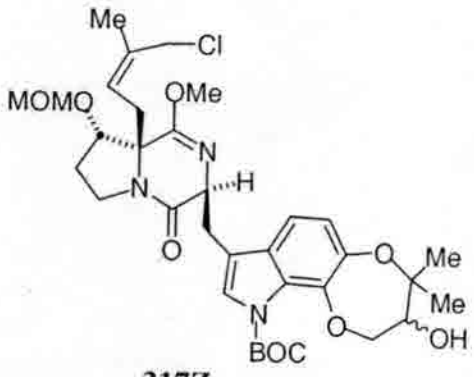
To a solution of **312Z** (60.0 mg, 91.2×10^{-3} mmol, 1 eq) in CH_2Cl_2 (1.5 mL) at 0 °C were added triethylamine (18.9 mg, 0.182 mmol, 2 eq) followed by dropwise addition of MsCl (150 μL, 0.607 M in CH_2Cl_2, 91.2×10^{-3} mmol, 1 eq). After the reaction mixture was stirred at 0 °C for 11 h and at 23 °C for 3 h, it was concentrated and extracted with (EtOAc/Et_2O) (2/1). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Preparative TLC (CH_2Cl_2:MeOH/25:1) purification of the product gave 29 mg (75% yield, based on 22.6 mg of recovered **317Z**) of **317Z** as a white foam.

Data of **317Z** (mixture of two diastereomers):

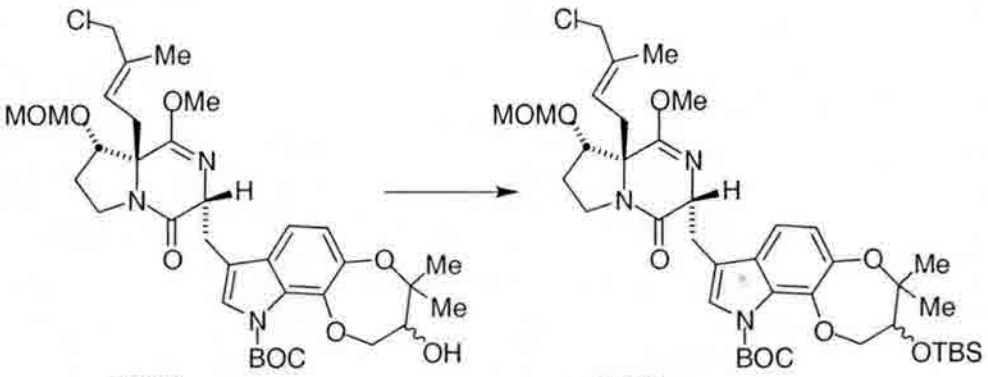
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.21 (total 3H, s), 1.56-1.57 (total 3H, s), 1.61 (total 9H, s), 1.84 (total 3H, s), 1.90-2.20 (total 3H, m), 2.32-2.45 (total 1H, m), 2.71-2.88 (total 1H, m), 3.02-3.18 (total 1H, m), 3.29-3.30 (total 3H, s), 3.23-3.41 (2H, m), 3..57-3.61 (1H, m), 3.66-3.68 (total 3H, s), 3.93-3.97 (2H, m), 4.10-4.39 (total 5H, m), 4.54-4.55 (2H, s), 5.20 (total 1H, m), 6.92 (1H, d, J = 8.4 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.43 (total 1H, s).

IR (NaCl, film) 3407, 2979, 2929, 1747, 1698, 1643, 1493, 1369, 1046 cm^{-1}.

FAB HRMS m/e 676.2994 ($C_{34}H_{46}N_3O_9Cl$ + H requires 676.2922)



317Z



324E **326E**

8-[[8aR-[(*E*)-4-chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3R-yl]methyl]-3R/S-[[(1,1-dimethyl ethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (326E)

To a solution of **324E** (40.0 mg, 59.2×10^{-3} mmol, 1 eq) and 2,6-lutidine (12.7 mg, 0.118 mmol, 2 eq) in CH_2Cl_2 (1.18 mL) at 0 °C under Ar was slowly added t-butyldimethylsilyl trifluoromethanesulfonate (23.4 mg, 0.183 mmol, 2 eq). After 3.5 h, additional 2,6-lutidine (12.7 mg, 0.118 mmol, 2 eq) and t-butyldimethylsilyl trifluoromethane-sulfonate (23.4 mg, 0.183 mmol, 2 eq) were added, and the reaction was allowed to stir for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a foamy solid. Preparative TLC (hexane:EtOAc/1:1) purification of the product gave 41.5 mg (89%) of **326E** as a white foam.

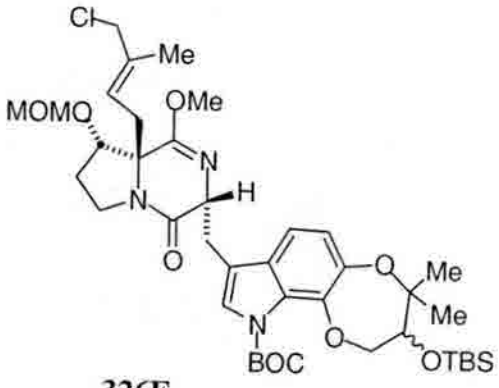
Data of **326E** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.135, 0.140 and 0.148 (total 6 H, s), 0.89 and 0.90 (total 9 H, s), 1.05 and 1.10 (total 3 H, s), 1.47 and 1.48 (total 3 H, s), 1.59 (9 H, s), 1.65-1.69 (3 H, m), 1.81-1.93 (1 H, m), 1.96-2.11 (2 H, m), 2.37-2.49 (1 H, m), 3.00 and 3.13 (total 3 H, s), 3.18-3.40 (3 H, m), 3.53 and 3.60 (total 3 H, s), 3.73-4.26 (7 H, m), 3.92 (2 H, s), 4.27-4.35 (1 H, m), 5.28-5.36 (1 H, m), 6.84 (1 H, d, J = 6.3 Hz), 7.18-7.28 (2 H, m).

^{13}C NMR (APT) (100.6 MHz, $CDCl_3$) δ 171.3, 168.9, 168.8, 157.8, 157.7, 149.1, 145.9, 145.2, 137.1, 131.3, 131.0, 127.7, 127.6, 127.0, 126.9, 122.26, 122.2, 119.1, 116.6, 116.5, 114.84, 114.80, 94.6, 82.3, 82.4, 80.2, 79.0, 78.8, 76.17, 76.14, 71.07, 71.02, 60.6, 60.5, 60.1, 55.5, 55.3, 53.6, 52.7, 51.4, 42.0, 41.9, 33.9, 33.8, 28.7, 28.6, 28.4, 28.2, 27.5, 25.9, 21.2, 19.0, 18.5, 18.0, 14.4, 14.3, -3.71, -3.79, -4.7.

IR (NaCl, film) 2953, 2894, 1749, 1701, 1652, 1491, 1369, 1247, 1159 cm^{-1}.

FAB HRMS m/e 790.3854 ($C_{40}H_{60}N_3O_9SiCl$ + H requires 790.3865)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326E

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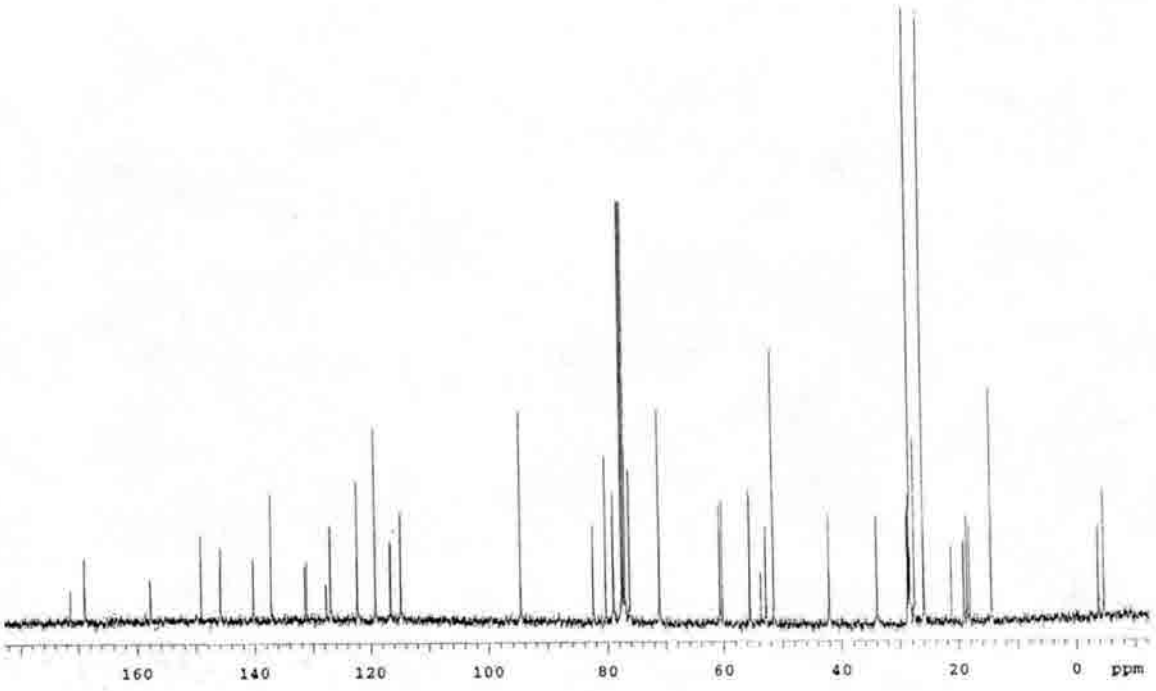
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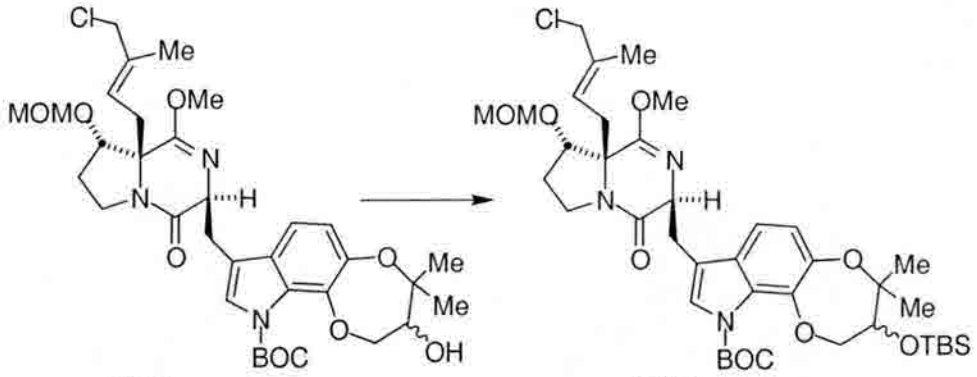


317E **325E**

8-[[8aR-[(*E*)-4-chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3S-yl]methyl]-3R/S-[[(1,1-dimethyl ethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (325E)

To a solution of **317E** (152 mg, 0.225 mmol, 1 eq) and 2,6-lutidine (48.2 mg, 0.45 mmol, 2 eq) in CH_2Cl_2 (4.4 mL) at 0 °C under Ar was slowly added t-butyldimethylsilyl trifluoromethanesulfonate (88.6 mg, 0.450 mmol, 2 eq). After 4 h, additional 2,6-lutidine (48.2 mg, 0.45 mmol, 2 eq) and t-butyldimethylsilyl trifluoromethanesulfonate (88.6 mg, 0.450 mmol, 2 eq) were added, and the reaction was allowed to proceed for a further 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a foamy solid. Purification of the product by flash column chromatography (hexane:EtOAc/1:1) gave 140 mg (79%) of **325E** as a white foam.

Data of **325E** (mixture of two diastereomers):

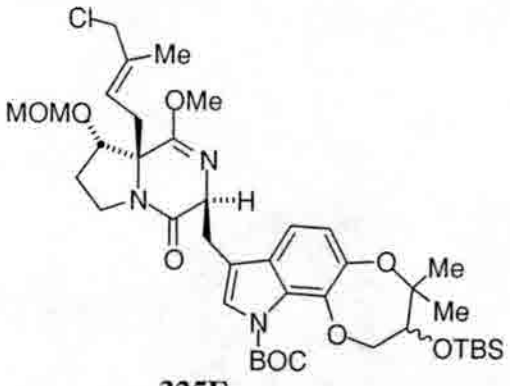
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 and 0.15 (total 6 H, s), 0.89 (9 H, s), 1.07 and 1.09 (total 3 H, s), 1.48 (3 H, br s), 1.60 (9 H, s), 1.66 (3 H, s), 1.77-1.91 (1 H, m), 1.93-2.26 (3 H, m), 2.78-2.96 (1 H, m), 3.282 and 3.284 (total 3 H, s), 3.20-3.42 (2 H, m), 3.65 and 3.66 (total 3 H, s), 3.71-3.84 (1 H, m), 3.91-3.98 (1 H, m), 3.92 (2 H, br s), 4.08-4.23 (3 H, m), 4.35-4.41 (1 H, m), 4.50-4.57 (2 H, ABq), 5.20 and 5.29 (total 1 H, br t, J = 7.5

Hz), 6.89 (1 H, d, J = 8.4 Hz), 7.15 and 7.16 (total 1 H, d, J = 8.4 Hz), 7.40 and 7.41 (total 1 H, s).

^{13}C NMR (APT) (100.6 MHz, $CDCl_3$) δ 169.5, 158.1, 157.8, 149.0, 148.9, 146.22, 146.2, 140.6, 136.1, 135.9, 130.1, 127.9, 126.7, 122.93, 122.98, 119.7, 116.9, 114.2, 94.8, 82.8, 80.3, 79.6, 76.0, 71.1, 70.7, 70.6, 61.8, 61.7, 55.7, 52.7, 51.4, 42.3, 34.0, 33.9, 31.5, 31.4, 28.7, 28.6, 28.2, 27.2, 27.1, 25.9, 18.5, 18.6, 18.0, 14.4, -3.9, -4.7.

IR (NaCl, film) 2955, 2855, 1749, 1699, 1644, 1433, 1368, 1252, 1157, 1087, 856, 835.

FAB HRMS m/e 790.3853 ($C_{40}H_{60}N_3O_9SiCl$ + H requires 790.3865)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325E

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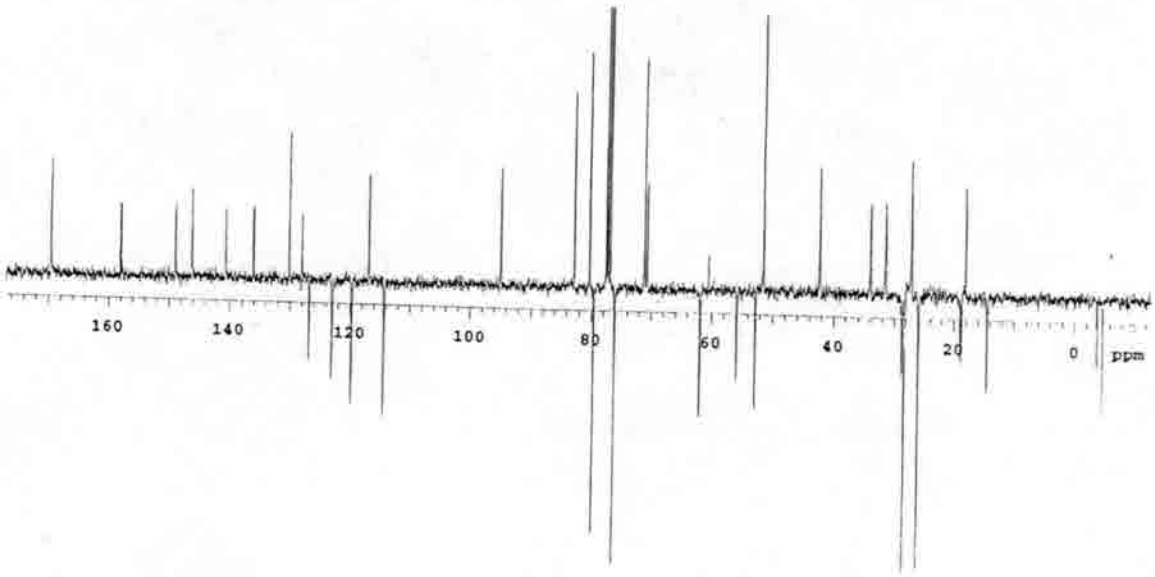
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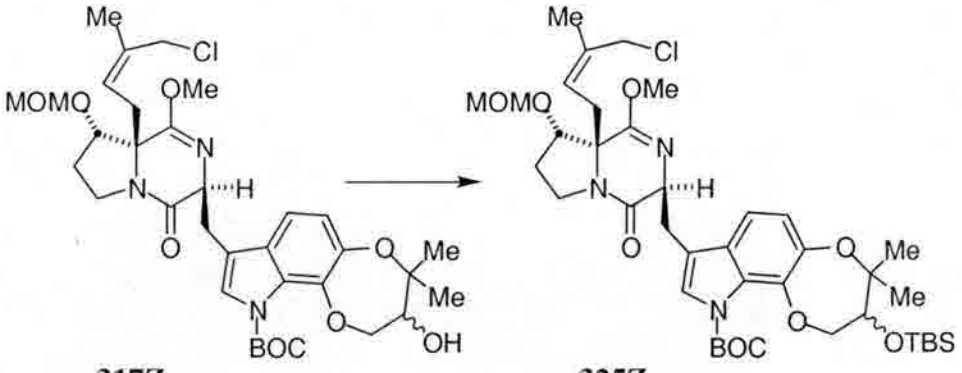


317Z **325Z**

8-[[8aR-[(*Z*)-4-chloro-3-methyl-2-butenyl]-3,4,6,7,8,8a-hexahydro-1-methoxy-8S-(methoxymethoxy)-4-oxopyrrolo[1,2-*a*]pyrazin-3S-yl]methyl]-3R/S-[[(1,1-dimethyl ethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-2*H*,10*H*-[1,4]dioxepino[2,3-*g*]indole-10-carboxylic acid, 1,1-dimethylethyl ester (325Z)

To a solution of **317Z** (17.5 mg, 25.9×10^{-3} mmol, 1 eq) and 2,6-lutidine (5.5 mg, 51.8×10^{-3} mmol, 2 eq) in CH_2Cl_2 (500 μL) at 0 °C under Ar was slowly added t-butyldimethylsilyl trifluoromethanesulfonate (10.2 mg, 51.8×10^{-3} mmol, 2 eq). After 2 h, additional 2,6-lutidine (5.5 mg, 51.8×10^{-3} mmol, 2 eq) and t-butyldimethylsilyl trifluoromethane-sulfonate (10.2 mg, 51.8×10^{-3} mmol, 2 eq) were added, and the reaction was allowed to proceed for a further 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Purification of the product by flash column chromatography (hexane:EtOAc/2:1) gave 15.4 mg (75%) of **325Z** as a white foam.

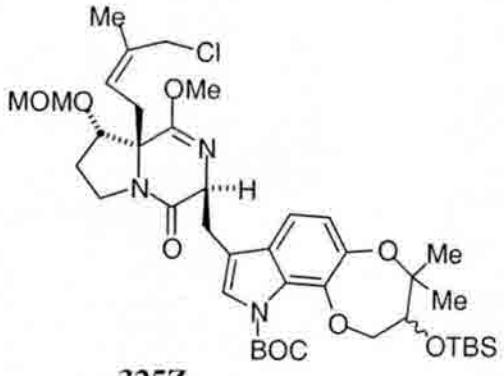
Data of **325Z** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 and 0.16 (total 6H, s), 0.91 (9H, s), 1.07 and 1.09 (total 3H, s), 1.49-1.50 (total 3H, s), 1.62-1.67 (total 9H, s), 1.83 (total 3H, s), 1.90-2.10 (total 3H, m), 2..20-2.42 (total 1H, m), 2.71-2.92 (total 1H, m), 3.29-3.30 (total 3H, s), 3.35-3.41 (total 2H, m), 3.65-3.67 (total 3H, s), 3.76-3.83 (total 1H, m), 3.93-3.98 (total

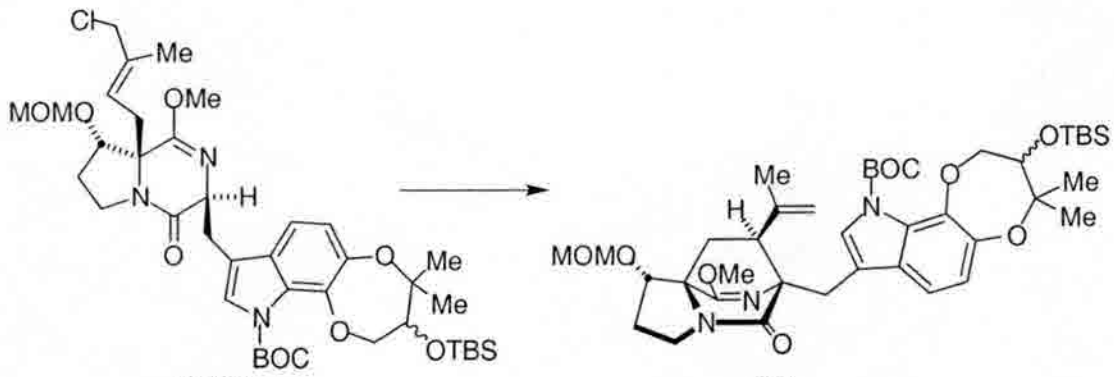
3H, m), 4.14-4.21 (total 3H, m), 4.34-4.39 (total 1H, m), 4.54 and 4.55 (total 2H, s), 5.2 (1H, m), 6.91-6.94 (1H, d, J = 8.4 Hz), 7.16-7.19 (1H, d, J = 8.4 Hz), 7.43 (total 1H, s).

IR (NaCl, film) 2957, 2860, 1749, 1701, 1700, 1652, 1491, 1370, 1253, 1156, 1088, 1039 cm^{-1}.

FAB HRMS m/e 789.3782 ($C_{40}H_{60}N_3O_9SiCl$ requires 789.3782)



325Z



3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-8-[[3,4,7,8-tetrahydro-1-methoxy-8S-(methoxymethoxy)-10S-(1-methylethenyl)-4-oxo-6H-3,8aR-ethanopyrrolo[1,2-a]pyrazin-3S-yl]methyl]- 2*H*,10*H*-[1,4]dioxepino[2,3-*g*] indole-10-carboxylic acid, 1,1-dimethylethyl ester (327)

To a suspension of anhydrous ether washed NaH (79.0 mg, 3.24 mmol, 20 eq) in THF 100 mL) was added solid **325E** (128 mg, 0.162 mmol, 1 eq) under Ar. After the reaction mixture was gently refluxed for 9.5 h, it was added dropwise to a flask containing H_2O (100 mL) and EtOAc (35 mL). The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give an oil which contained mostly the desired SN'_2 product **327** and some minor SN'_2 product (**329**) with the N-tBOC group removed. The above mixture was dissolved in CH_2Cl_2 (4 mL). Triethylamine (2.54 mg, 0.025 mmol, 0.16 eq), DMAP (2.8 mg, 0.023 mmol, 0.14 eq) and $(BOC)_2O$ (15 mg, 0.069 mmol, 0.42 eq) were added to the above mixture solution at 0 °C under Ar. After 3 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give an oil. The crude product was purified by radial chromatography (EtOAc:hexane/1:2 then 1:1) to provide 107 mg of **327** (87%) as a white foam.

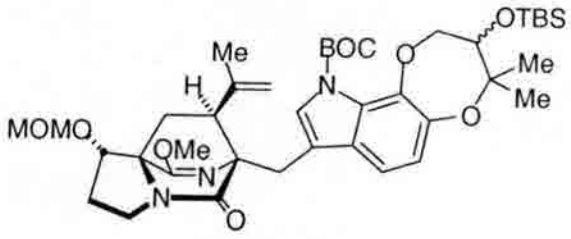
Data of **327** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 and 0.16 (total 6 H, s), 0.90 (9 H, s), 1.09 and 1.10 (total 3 H, s), 1.39-1.49 (1 H, m), 1.49 (3 H, s), 1.61 (9 H, s), 1.64 (3 H, s), 1.98-2.06 (1 H, m), 2.08-2.24 (2 H, m), 2.44-2.54 (1 H, m), 3.02-3.12 (1 H, m), 3.33-3.42 (1 H, m), 3.42 and 3.43 (total 3 H, s), 3.52-3.72 (2 H, m), 3.69 and 3.61 (total 3 H, s), 3.75-3.87 (1 H, m), 3.93-4.00 (1 H, m), 4.15-4.24 (1 H, m), 4.29-4.36 (1 H, m), 4.62-4.91 (4 H, m), 6.856 and 6.861 (total 1 H, d, J = 8.4 Hz), 7.32 and 7.39 (total 1 H, d, J = 8.4 Hz), 7.47 and 7.56 (total 1 H, s).

^{13}C NMR (APT) (100.6 MHz, $CDCl_3$) δ 171.5, 171.2, 170.2, 149.1, 145.79, 143.8, 143.5, 140.2, 140.1, 131.5, 127.9, 127.6, 119.1, 116.26, 116.2, 115.8, 96.7, 82.4, 80.2, 79.0, 76.1, 71.6, 71.10, 69.3, 69.0, 66.53, 66.5, 66.0, 56.0, 54.6, 54.56, 48.9, 48.6, 41.5, 36.9, 31.4, 28.7, 28.2, 26.9, 26.8, 25.9, 19.7, 18.8, 18.7, 18.0, -3.7, -4.7.

IR (NaCl, film) 2950, 2892, 1749, 1677, 1633, 1474, 1368, 1248, 1156, 1089, cm^{-1}.

FAB HRMS m/e 754.4099 ($C_{40}H_{59}N_3O_9Si$ + H requires754.4094)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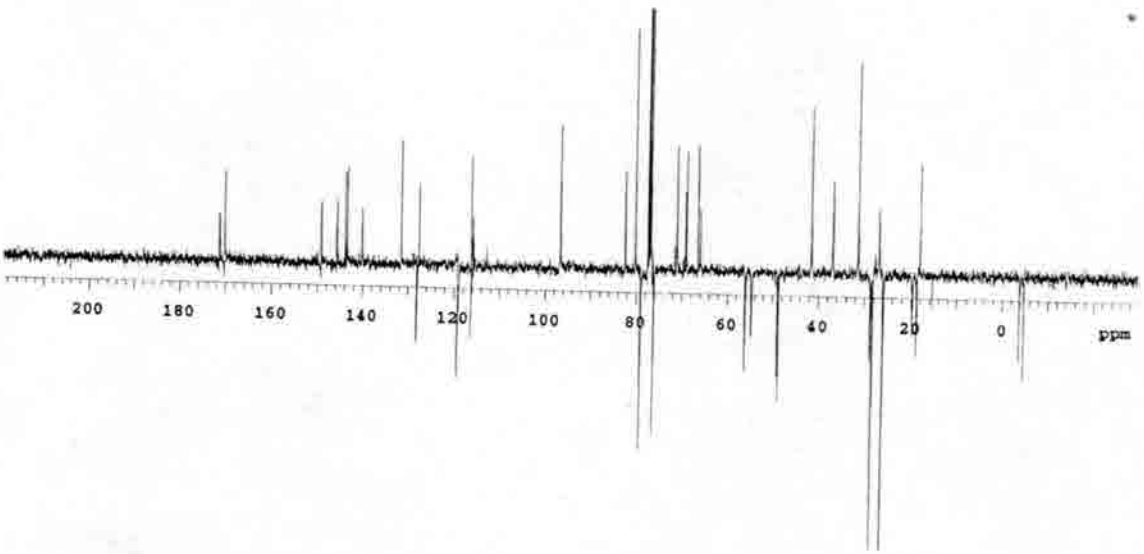
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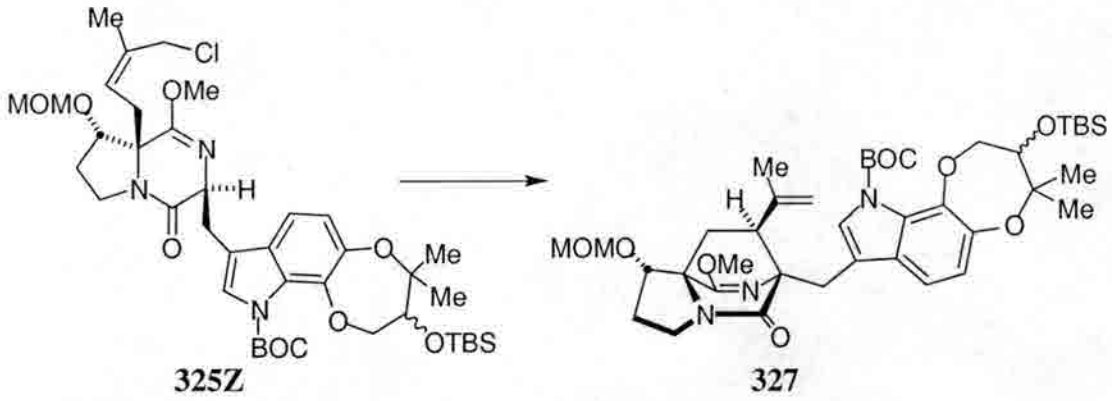
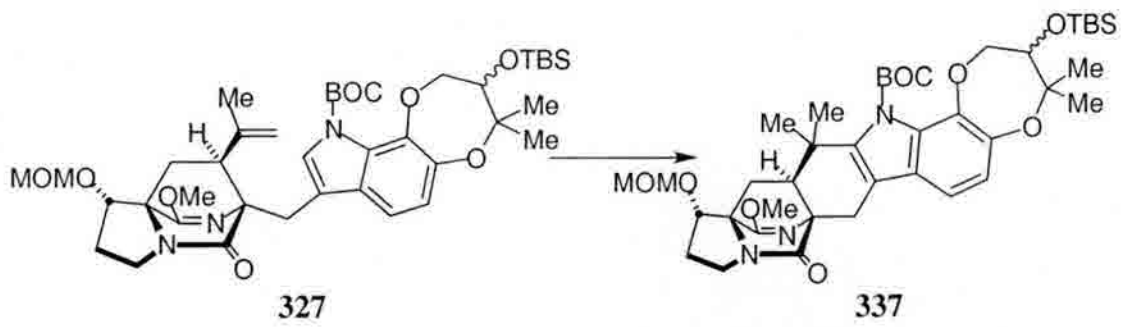


3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4-dihydro-4,4-dimethyl-8-[[3,4,7,8-tetrahydro-1-methoxy-8S-(methoxymethoxy)-10S-(1-methylethenyl)-4-oxo-6H-3,8aR-ethanopyrrolo[1,2-a]pyrazin-3S-yl]methyl]- 2*H*,10*H*-[1,4]dioxepino[2,3-*g*] indole-10-carboxylic acid, 1,1-dimethylethyl ester (327)

To a suspension of anhydrous ether washed NaH (24.6 mg, 1.03 mmol, 24 eq) in THF (2.8 mL) was added solid **325Z** (33.8 mg, 0.043 mmol, 1 eq) under Ar. After the reaction mixture was gently refluxed for 11.5 h, it was added dropwise to a flask containing H_2O (20 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (CH_2Cl_2:MeOH/18:1) purification of the product gave 16 mg (50%) of **327** as a white foam.



327 337

(8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-17-methoxy-13S-(methoxymethoxy)-4,4,15,15-tetramethyl-9-oxo-9H,11H-8a,13a-(nitrilomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (337)

To a flask charged with $AgBF_4$ (40.0 mg, 0.205 mmol, 3.1 eq)[1] and $PdCl_2$ (55.0 mg, 0.310 mmol, 4.68 eq) was added CH_3CN (2.25 mL) at room temperature under Ar. After 6.5 h, propylene oxide (207 mg, 3.56 mmol, 53.6 eq) was added and the mixture was stirred for 15 min. **327** (50.0 mg, 0.066 mmol, 1 eq) was added in one portion as a solid and produced a deep red color immediately. After the reaction mixture was stirred at room temperature for 40 h[2] and then cooled to 0 °C, absolute ethanol (1.68 mL) was added. $NaBH_4$ (30 mg, 0.793 mmol, 12 eq) was added portionwise over 45 min, yielding a black solid and a colorless clear solution. The mixture was stirred for an additional 40 min and filtered. The filtrate was concentrated, and EtOAc was added to the residue. The resulting solution was washed with 0.01 N HCl in water followed by brine, dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (hexane:EtOAc:MeOH/5:3:0.5) purification of the crude product gave 32.8 mg (66%) of **337** as a white foam (201 mg scale, 85% yield).

1. $AgBF_4$ is hydroscopic and should be handled quickly.

2. After 40 h reaction, TLC (hexane:EtOAc:MeOH/5:3:0.5) showed there was no **327** left.

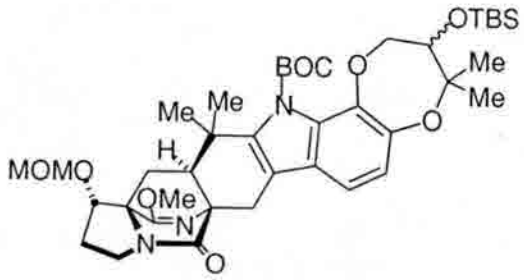
Data of **337** (mixture of two diastereomers):

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 and 0.14 (total 6 H, s), 0.90 and 0.91 (total 9 H, s), 1.10 and 1.20 (total 3 H, s), 1.23 and 1.26 (total 3 H, s), 1.33-1.35 (total 3 H, s), 1.47 and 1.49 (total 3 H, s), 1.58 ad n1.60 (total 9 H, s), 1.73 (1 H, dd, *J* = 12.9, 4.2 Hz), 1.94-2.07 (1 H, m), 2.11-2.32 (3 H, m), 3.00-3.10 (1 H, m), 3.34-3.76 (3 H, m), 3.47 (3 H, s), 3.83 (3 H, s), 3.83-3.96 (2 H, m), 4.04-4.19 (1 H, m), 4.43 (1 H, m), 4.75 (1 H, d, *J* = 7.2 Hz), 4.86 (1 H, d, *J* = 7.2 Hz), 6.80 and 6.81 (total 1 H, d, *J* = 8.1 Hz), 7.06-7.07 (1 H, d, *J* = 8.1 Hz).

^{13}C NMR (APT) (75.47 MHz, $CDCl_3$) δ 171.7, 170.7, 153.6, 143.4, 143.3, 139.5, 139.3, 138.6, 138.1, 129.3, 129.2, 125.7, 125.6, 118.7, 118.1, 113.1, 113.0, 110.8, 96.8, 84.4, 84.2, 80.7, 80.2, 79.1, 76.3, 72.1, 71.4, 67.0, 65.3, 56.0, 54.6, 49.1, 49.0, 41.6, 40.5, 37.0, 32.0, 31.6, 28.8, 28.6, 28.0, 27.5, 27.3, 26.9, 20.5, 20.4, 19.5, 19.1, 18.0, -3.9, -4.0, -4.7, -4.8.

IR (NaCl, film) 2975, 2956, 2897, 1745, 1682, 1633, 1369, 1047, 837 cm^{-1}.

FAB HRMS m/e 753.4034 ($C_{40}H_{59}N_3O_9Si$ requires 753.4020)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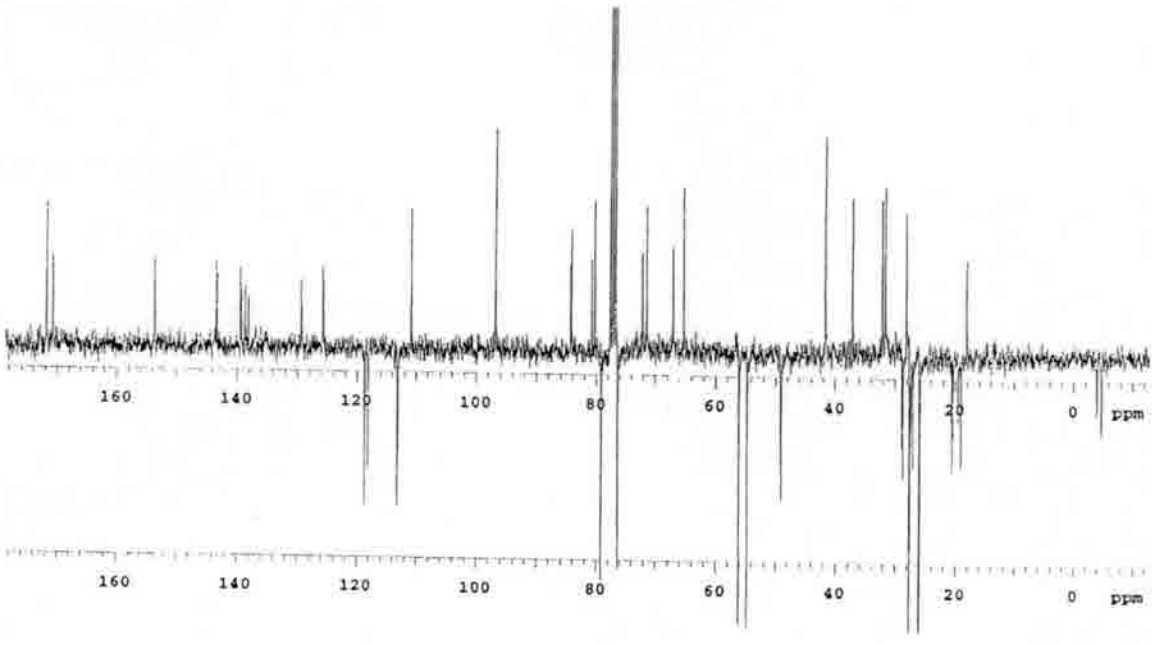
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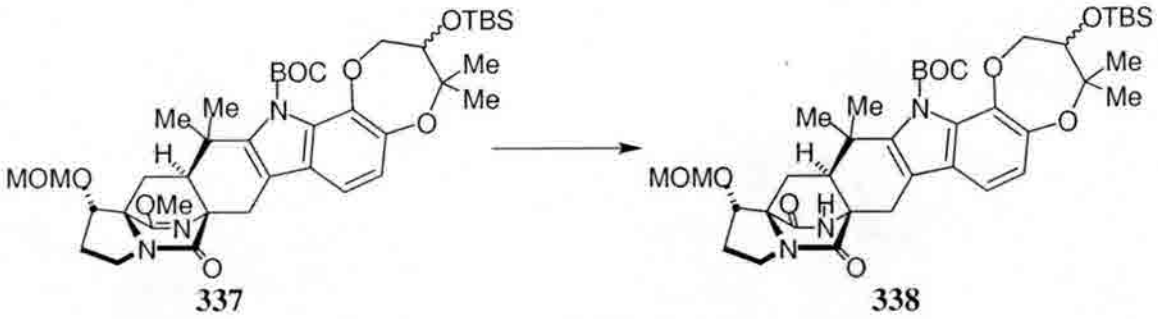


8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-13S-(methoxymethoxy)-4,4,15,15-tetramethyl-9,17-dioxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (338)

To a mixture of **337** (4.0 mg, 5.3×10^{-3} mmol, 1 eq), LiCl (12.0 mg, 0.028 mmol, 53 eq) and $BnBu_3NCl$ (2.0 mg, 5.3×10^{-3} mmol, 1.3 eq) was added a solution of H_2O (1.1 mg, 0.058 mmol, 11 eq) in HMPA (300 μL). After the reaction mixture was stirred at 60 °C for 24 h, it was quenched with H_2O and extracted with EtOAc. The combined extracts were washed with brine (5 times), dried over Na_2SO_4 and concentrated to give an oil. Preparative TLC (CH_2Cl_2:MeOH/10:1) purification of the product provided 1 mg of **338** and 2 mg of recovered starting material.

Data of **338** (mixture of two diastereomers):

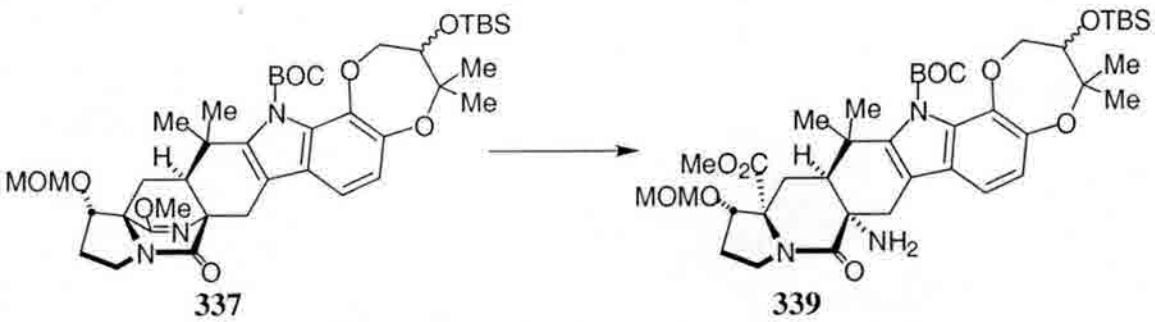
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 and 0.14 (total 6 H, s), 0.90 and 0.91 (total 9 H, s), 1.10 and 1.21 (total 3 H, s), 1.25 and 1.27 (total 3 H, s), 1.36 and 1.37 (total 3 H, s), 1.47 and 1.49 (total 3 H, s), 1.59 and 1.61 (total 9 H, s), 1.89 (1 H, dd, J = 13.2, 4.8 Hz), 2.14-2.29 (2 H, m), 2.34 (1 H, dd, J = 13.2, 10.2 Hz), 2.52-2.65 (2 H, m), 3.48 (3 H, s), 3.58-4.17 (5 H,m), 4.05-4.21 (1 H, m), 4.44 (1 H, m), 4.78 (1 H, 1/2ABq, J = 7.2 Hz), 5.00 (1 H, 1/2ABq, J = 7.2 Hz), 5.94 (1 H, br s), 6.81 and 6.83 (total 1 H, d, J = 8.4 Hz), 6.999 and 7.007 (total 1 H, d, J = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 168.2, 153.3, 153.2, 143.6, 143.4, 139.5, 139.3, 138.7, 138.0, 129.3, 129.1, 125.1, 124.9, 119.0, 118.3, 112.7, 112.5, 108.5, 97.4, 84.8, 84.6, 81.0, 80.4, 79.2, 76.3, 72.4, 71.5, 68.53, 68.48, 59.7, 56.1, 51.2, 51.1, 42.5, 36.7,

31.5, 31.2, 28.9, 28.7, 27.6, 27.0, 26.7, 26.0, 25.9, 25.1, 20.2, 20.0, 19.7, 19.1, 18.13, 18.09, -3.9, -4.0, -4.6, -4.8.

IR (NaCl, film) 3246, 2929, 2855, 1747, 1694, 1493, 1367, 1256, 1156, 1092, 1039, 839 cm^{-1}.

FAB HRMS m/e 739.3848 ($C_{39}H_{57}N_3O_9Si$ requires 739.3864)



337 339

8aS-amino-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8a,9,12,13,14aS,15-octahydro-13S-(methoxymethoxy)-4,4,15,15-tetramethyl-9-oxo-2*H*,8*H*-[1,4]dioxepino[2,3-*a*]indolizino[6,7-*h*]carbazole-13aR,16(11*H*,14*H*)-dicarboxylic acid, 16-(1,1-dimethylethyl), 13a-methyl ester (339)

To a solution of crude **337** (a product from $PdCl_2/AgBF_4$ mediated cyclization reaction, 201 mg scale) in THF (25 mL) at 0 °C was added 0.1 M HCl in water (2 mL), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C, quenched with saturated $NaHCO_3$ in water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by Preparative TLC on silica gel (CH_2Cl_2:MeOH/20:1) to give 155.2 mg (two steps, 75.4%) of **339** as a white foam.

Data for **339** (mixture of two diastereomers)

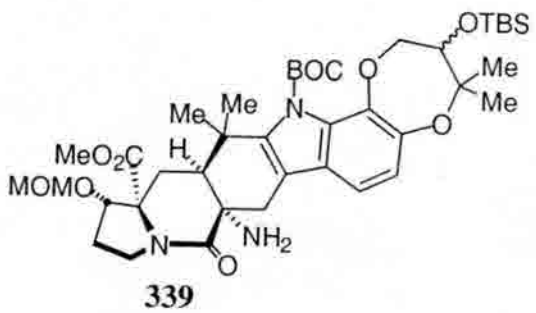
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11, 0.12 and 0.13 (total 6 H, s), 0.89 and 0.91 (total 9 H, s), 1.08 and 1.17 (total 3 H, s), 1.47 and 1.48 (total 3 H, s), 1.54 and 1.55 (total 3 H, s), 1.62 and 1.64 (total 9 H, s), 1.77 and 1.78 (total 3 H, s), 1.88-2.15 (3 H, m), 2.24-2.41 (1 H, m), 2.78 (1 H, d, J = 16.8 Hz), 2.86 (1 H, dd, J = 16.8, 2.1 Hz), 3.16 (1 H, br d, J = 13.8 Hz), 3.35 (3 H, s), 3.63-3.96 (5 H, m), 3.83 (3 H, s), 4.13 (1 H, m), 4.64 (2 H, ABq), 6.78 and 6.79 (total 1 H, d, J = 8.4 Hz), 6.88 (1 H, d, J = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 171.2, 153.4, 143.4, 139.0, 138.9, 138.6, 138.1, 129.1, 129.0, 125.7, 125.6, 118.8, 118.3, 112.4, 107.21, 107.17, 96.3, 84.9, 84.7, 83.5, 80.8, 80.4, 76.3, 76.2, 72.0, 71.5, 69.7, 69.6, 57.8, 56.0, 52.9, 50.24, 50.17, 43.8, 36.0,

33.7, 33.6, 31.2, 30.7, 30.5, 28.9, 28.6, 27.6, 27.2, 27.0, 26.0, 25.9, 19.4, 19.2, 18.1, -3.9, -4.0, -4.7, -4.8.

IR (NaCl, neat) 2954, 2930, 2891, 2861, 1743, 1644, 1496, 1438, 1368, 1251, 1232, 1155, 1115, 1091, 1050, 838, 776 cm^{-1}.

FAB HRMS m/e 772.4222 ($C_{40}H_{62}N_3O_{10}Si$ + H requires 772.4204)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NH2
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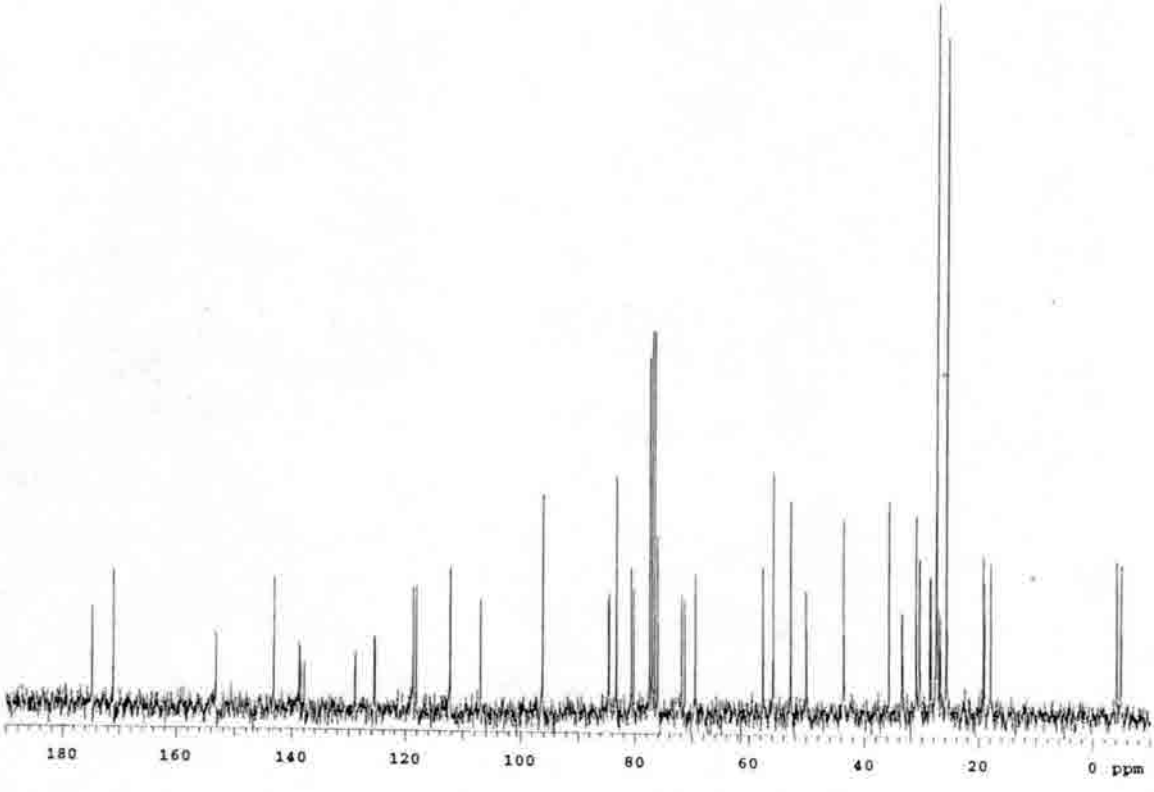
ppm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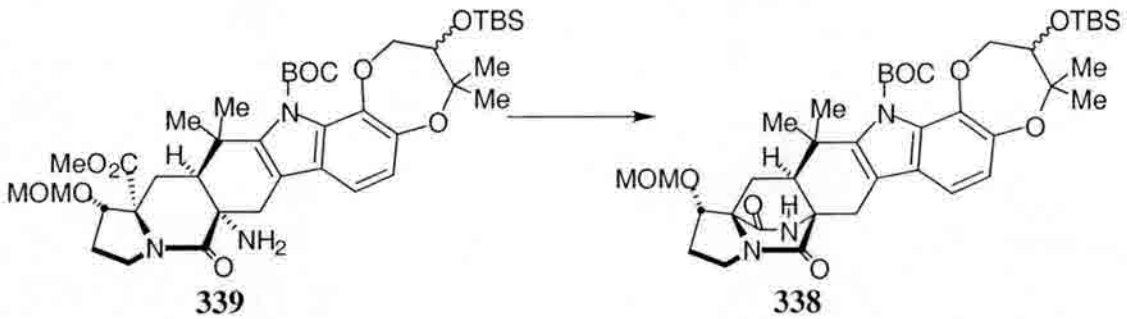


8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-13S-(methoxymethoxy)-4,4,15,15-tetramethyl-9,17-dioxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (338)

To a solution of **339** (155.2 mg, 0.201 mmol, 1 eq) in toluene (6.7 mL) was added 2-hydroxypyridine (20.8 mg, 0.219 mmol, 1.1 eq). After the reaction mixture was heated at 120 °C for 2 h, it was concentrated in vacuo, and the residue was purified by preparative TLC on silica gel (hexane:EtOAc:MeOH/5:10:1) to give 124.0 mg (83.4%) of **338** as a white foam.

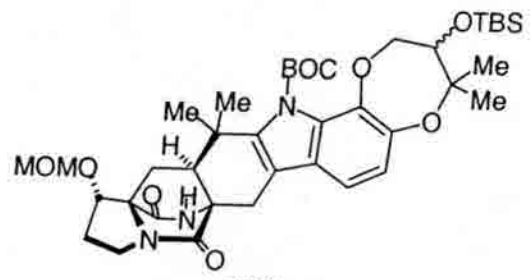
Data for **338** (mixture of two diastereomers)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 and 0.14 (total 6 H, s), 0.90 and 0.91 (total 9 H, s), 1.10 and 1.21 (total 3 H, s), 1.25 and 1.27 (total 3 H, s), 1.36 and 1.37 (total 3 H, s), 1.47 and 1.49 (total 3 H, s), 1.59 and 1.61 (total 9 H, s), 1.89 (1 H, dd, J = 13.2, 4.8 Hz), 2.14-2.29 (2 H, m), 2.34 (1 H, dd, J = 13.2, 10.2 Hz), 2.52-2.65 (2 H, m), 3.48 (3 H, s), 3.58-4.17 (5 H,m), 4.05-4.21 (1 H, m), 4.44 (1 H, m), 4.78 (1 H, 1/2ABq, J = 7.2 Hz), 5.00 (1 H, 1/2ABq, J = 7.2 Hz), 5.94 (1 H, br s), 6.81 and 6.83 (total 1 H, d, J = 8.4 Hz), 6.999 and 7.007 (total 1 H, d, J = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 168.2, 153.3, 153.2, 143.6, 143.4, 139.5, 139.3, 138.7, 138.0, 129.3, 129.1, 125.1, 124.9, 119.0, 118.3, 112.7, 112.5, 108.5, 97.4, 84.8, 84.6, 81.0, 80.4, 79.2, 76.3, 72.4, 71.5, 68.53, 68.48, 59.7, 56.1, 51.2, 51.1, 42.5, 36.7, 31.5, 31.2, 28.9, 28.7, 27.6, 27.0, 26.7, 26.0, 25.9, 25.1, 20.2, 20.0, 19.7, 19.1, 18.13, 18.09, -3.9, -4.0, -4.6, -4.8.

IR (NaCl, film) 2954, 2930, 2891, 2861, 1743, 1644, 1496, 1438, 1368 cm^{-1}.

FAB HRMS m/e 739.3848 ($C_{39}H_{57}N_3O_9Si$ requires 739.3864)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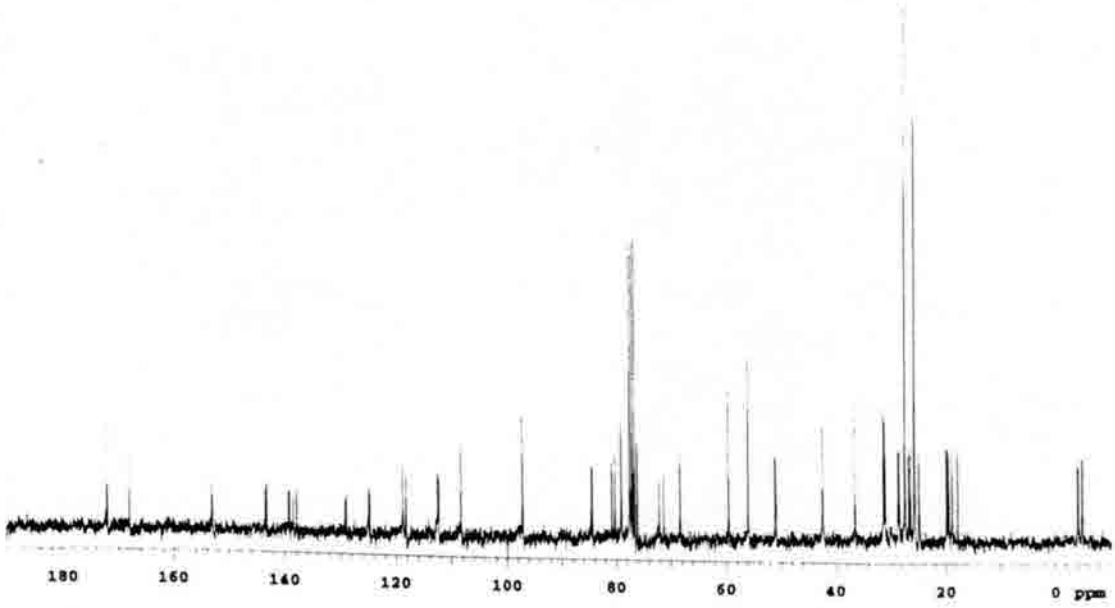
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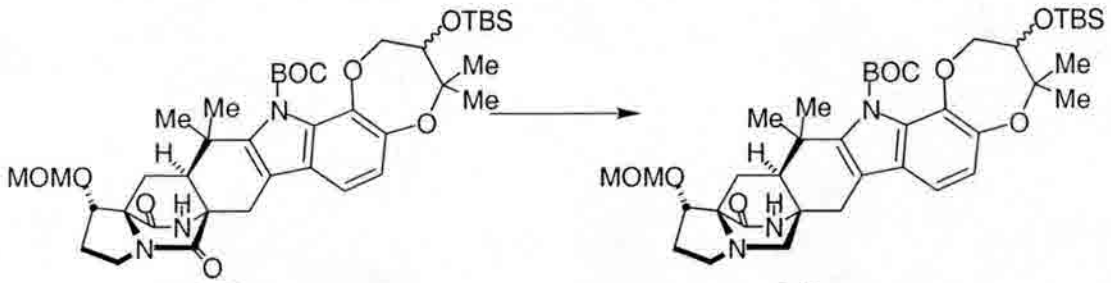


338 340

(8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-13S-(methoxymethoxy)- 4,4,15,15,-tetramethyl-17-oxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (340)

To a solution of **339** (32.8 mg, 0.044 mmol, 1 eq) in CH_2Cl_2 (2.2 mL) at 0 °C was added DIBAL-H (0.22 mL, 0.22 mmol, 1.0 M in toluene, 5 eq). After the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h, additional DIBAL-H (0.14 mL, 0.14 mmol, 1.0 M in toluene, 3.2 eq) was added. After the reaction mixture was stirred at 0 °C for 1 h, and at room temperature for 1 h, it was cooled to 0 °C, quenched with saturated NH_4Cl (aq.), and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC on silica gel (developed twice with hexane:EtOAc:MeOH /5:3:0.5) to give 23.3 mg (72.1 %) of **340** as a white foam.

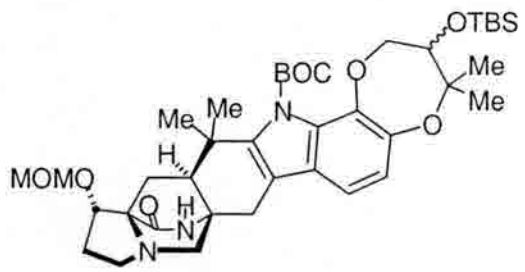
Data for **340** (mixture of two diastereomers)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.115, 0.119 and 0.137 (total 6 H, s), 0.90 and 0.91 (total 9 H, s), 1.14 and 1.18 (total 3 H, s), 1.40 and 1.41 (total 3 H, s), 1.48 (3 H, s), 1.56 (3 H, s), 1.62 and 1.64 (total 9 H, s), 1.84 (1 H, dd, *J* = 13.2, 4.2 Hz), 2.10-2.52 (6 H, m), 2.73 (1 H, 1/2ABq, *J* = 15.6 Hz), 2.82 (1 H, 1/2ABq, *J* = 15.6, 1.8 Hz), 3.19 (1 H, td, *J* = 8.7, 5.4 Hz), 3.44-3.50 (1 H, m), 3.45 (3 H, s), 3.74-3.97 (2 H, m), 4.03 (1 H, t, *J* = 9.0 Hz), 4.16 (1 H, td, J = 11.7, 3.3 Hz), 4.79 (2 H, s), 5.95 (1 H, br s), 6.81 and 6.82 (total 1 H, d, *J* = 8.4 Hz), 6.92 (1 H, d, *J* = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 153.4, 153.3, 143.5, 141.3, 141.2, 138.7, 138.3, 129.4, 125.1, 125.0, 118.9, 118.5, 112.06, 112.01, 108.1, 108.0, 96.9, 85.0, 84.9, 81.4, 81.0, 80.7, 76.4, 76.3, 72.3, 71.7, 64.3, 59.9, 56.3, 55.7, 52.8, 47.9, 35.8, 35.7, 30.4, 30.1, 29.04, 28.93, 28.7, 28.6, 28.5, 27.7, 26.0, 22.1, 22.0, 19.7, 19.5, 18.2, -3.8, -4.0, -4.6, -4.7.

IR (NaCl, neat) 2937, 2932, 2902, 2855, 1748, 1693, 1682, 1496, 1446, 1369, 1308, 1253, 1234, 1155, 1111, 1092, 1052, 992, 914, 838, 776, 732 cm^{-1}.

HRMS (FAB) *m/z* calcd for $C_{39}H_{60}N_3O_8Si$ $(M+H)^+$ 726.4150, found 726.4168.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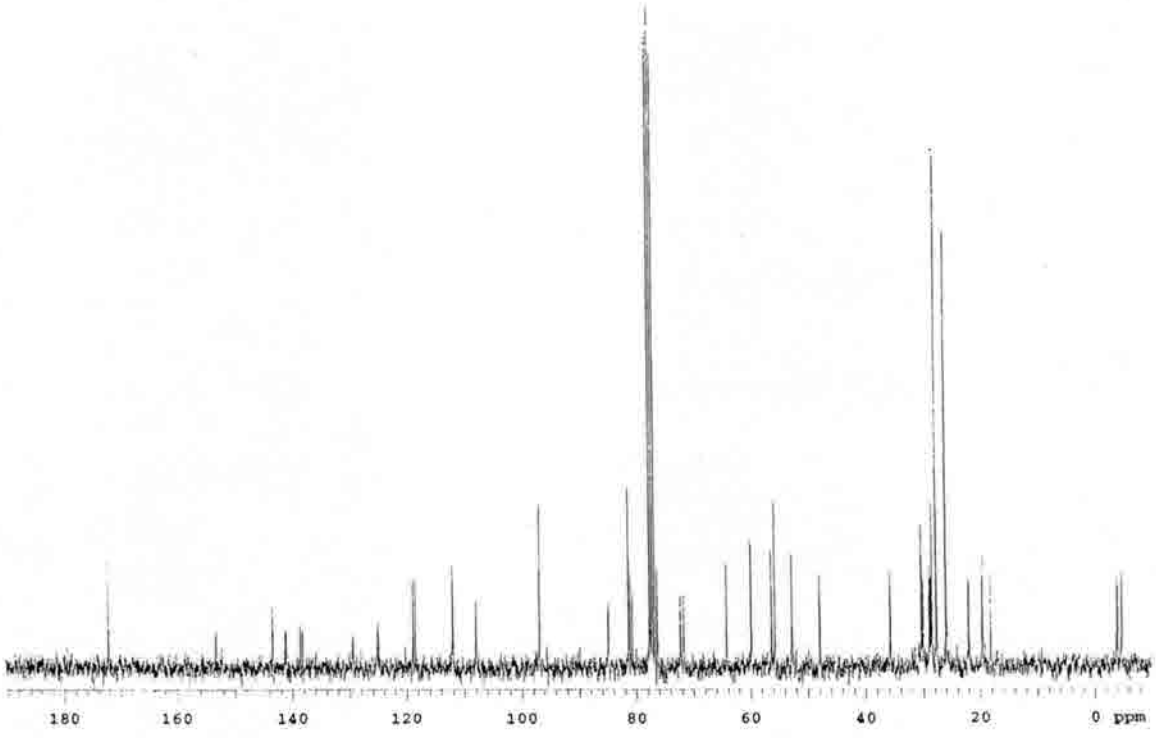
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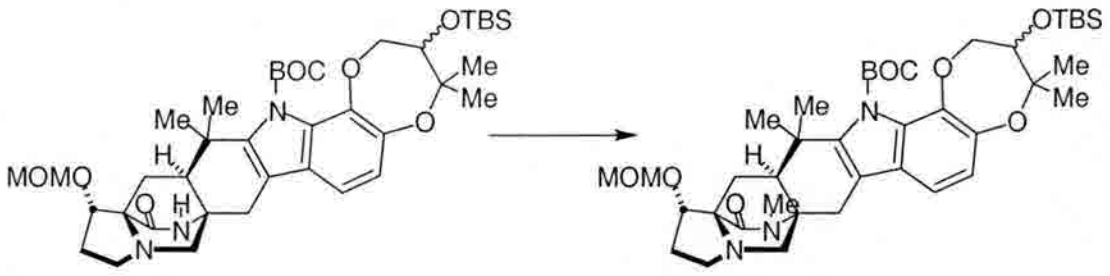


340 **341**

(8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-13S-(methoxymethoxy)- 4,4,15,15,18-pentamethyl-17-oxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (341)

To a solution of **340** (37.8 mg, 0.052 mmol, 1 eq) in DMF (1.7 mL) at 0 °C was added NaH (43.1 mg, 1.08 mmol, 60% oil dispersion, 20 eq). After 15 min, MeI (159 mg, 1.12 mmol, 22 eq) was added. After the reaction mixture was stirred at 0 °C for 1 h, and at room temperature for 1 h, it was quenched with saturated NH_4Cl (aq.), and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (hexane:EtOAc:MeOH/5:10:1) to provide 36.9 mg (95.8%) of **341** as an amorphous solid.

Data for **341** (mixture of two diastereomers)

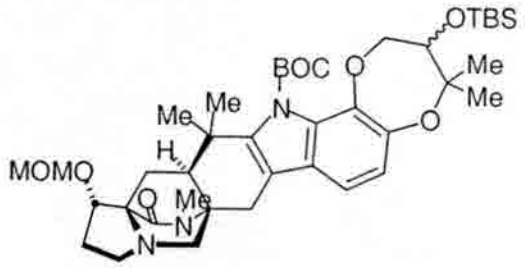
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 and 0.14 (total 6 H, s), 0.90 and 0.91 (total 9 H, s), 1.16 and 1.19 (total 3 H, s), 1.40 and 1.41 (total 3 H, s), 1.49 (3 H, s), 1.58 and 1.60 (total 3 H, s), 1.62 and 1.64 (total 9 H, s), 1.78-1.88 (1 H, m), 2.05-2.44 (6 H, m), 2.73-2.82 (1 H, m), 3.07 (3 H, s), 3.12-3.24 (2 H, m), 3.34-3.42 (1 H, m), 3.45 (3 H, s), 3.76-4.04 (3 H, m), 4.09-4.20 (1 H, m), 4.77 (1H, 1/2ABq, J = 6.9 Hz), 4.80 (1H, 1/2ABq, J = 6.9 Hz), 6.82 and 6.83 (1 H, d, J = 8.4 Hz), 6.96 (1 H, d, J = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 153.3, 143.5, 141.0, 140.8, 138.7, 138.3, 129.7, 129.5, 125.3, 125.1, 118.8, 118.4, 111.9, 108.4, 108.2, 96.8, 84.9, 84.8, 81.7, 81.0, 80.7,

76.4, 76.3, 72.2, 71.8, 63.4, 60.0, 58.4, 55.6, 53.1, 47.0, 46.9, 36.2, 36.1, 29.8, 29.0, 28.8, 28.7, 28.3, 28.2, 27.7, 25.9, 24.7, 22.6, 22.5, 19.6, 19.5, 18.1, -3.8, -4.0, -4.66, -4.72.

IR (NaCl, neat) 2955, 2932, 2896, 2857, 1747, 1677, 1496, 1368, 1252, 1233, 1154, 1116, 1091, 1052, 838.

HRMS (FAB) *m/z* calcd for $C_{40}H_{62}N_3O_8Si$ $(M+H)^+$ 740.4306, found 740.4391.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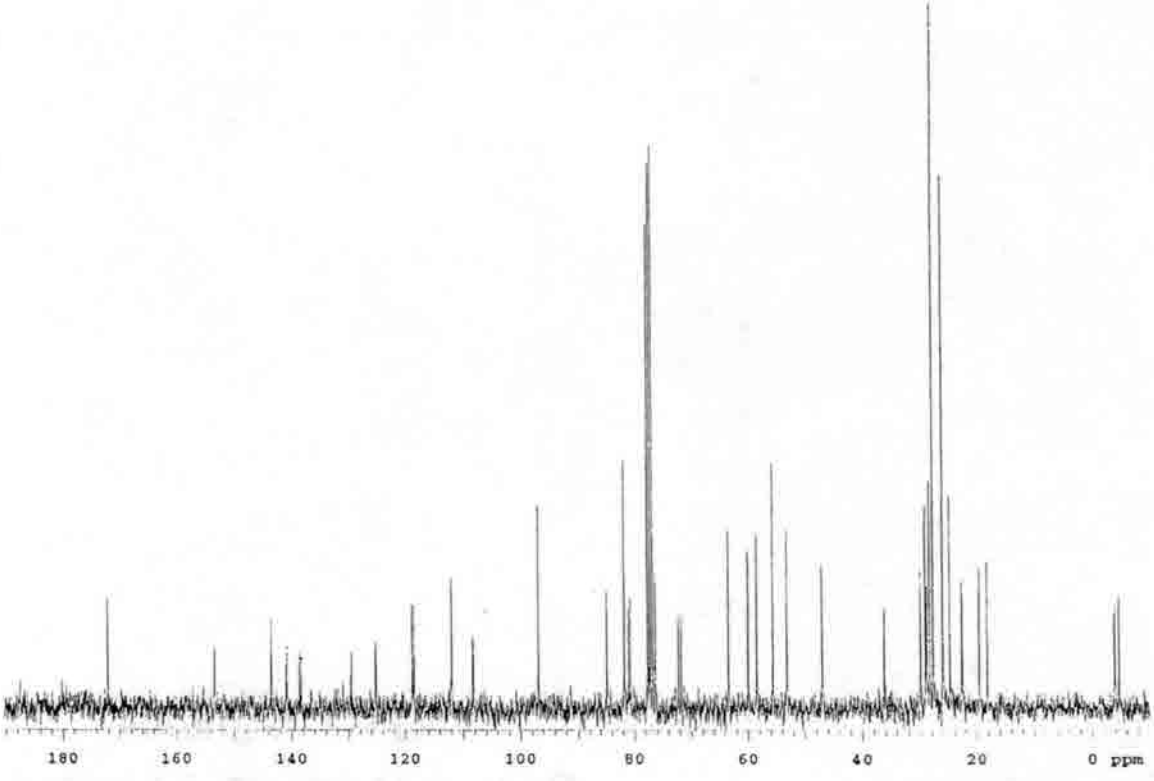
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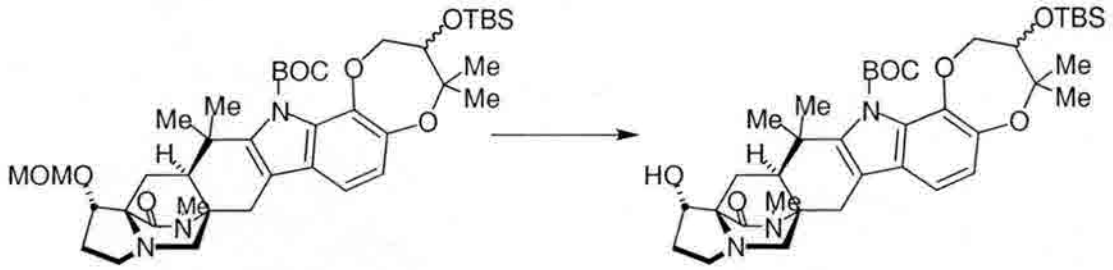


341 **342**

(8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro-13S-hydroxy- 4,4,15,15,18-pentamethyl-17-oxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (342)

To a solution of **341** (36.9 mg, 0.050 mmol, 1 eq) in CH_2Cl_2 (2.5 mL) at 0 °C was added bromocatecholborane (1.5 mL, 0.30 mmol, 0.2 M in CH_2Cl_2, 6 eq). After the reaction mixture was stirred at room temperature for 0.5 h, it was quenched with 10% NaOH (aq.) (3 mL), and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (hexane:EtOAc:MeOH/5:3:0.5) to give 31.5 mg (90.8%) of **342** as an amorphous solid.

Data for **342** (mixture of two diastereomers)

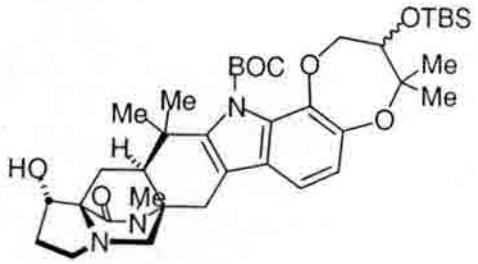
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 and 0.14 (total 6 H, s), 0.90 and 0.91 (total 9 H, s), 1.15 and 1.19 (total 3 H, s), 1.41 and 1.49 (total 3 H, s), 1.58 (3 H, s), 1.62 and 1.64 (total 9 H, s), 1.82-2.06 (2 H, m), 2.13-2.45 (5 H, m), 2.79 (1 H, dd, J = 15.6, 1.8 Hz), 3.09 (3 H, s), 3.10-3.15 (1 H, m), 3.20 (1 H, d, J = 15.6 Hz), 3.43 (1 H, d, J = 9.9 Hz), 3.73- 3.97 (2 H, m), 4.04-4.23 (2 H, m), 5.405 and 5.408 (total 1 H, dd, J = 11.4 Hz), 6.83 and 6.84 (total 1 H, d, J = 8.4 Hz), 6.96 (1 H, d, J = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 153.4, 153.3, 143.6, 140.8, 140.7, 138.7, 138.4, 129.7, 129.6, 125.2, 125.1, 118.9, 118.5, 111.9, 108.0, 107.8, 85.1, 85.0, 81.1, 80.8, 77.3, 76.4, 76.3, 72.3, 71.8, 62.0, 60.2, 58.7, 53.3, 47.32, 47.27, 36.3, 36.2, 32.5, 29.7, 29.0,

28.9, 28.8, 28.7, 27.9, 27.7, 26.01, 25.98, 24.7, 22.8, 22.7, 19.6, 18.2, -3.8, -4.0, -4.6, -4.7.

IR (NaCl, neat) 3407, 2954, 2932, 2858, 1747, 1644, 1496, 1445, 1390, 1369, 1253, 1233, 1155, 1108, 1089, 838, 733 cm^{-1}.

HRMS (FAB) *m/z* calcd for $C_{38}H_{58}N_3O_7Si$ $(M+H)^+$ 696.4044, found 696.4032.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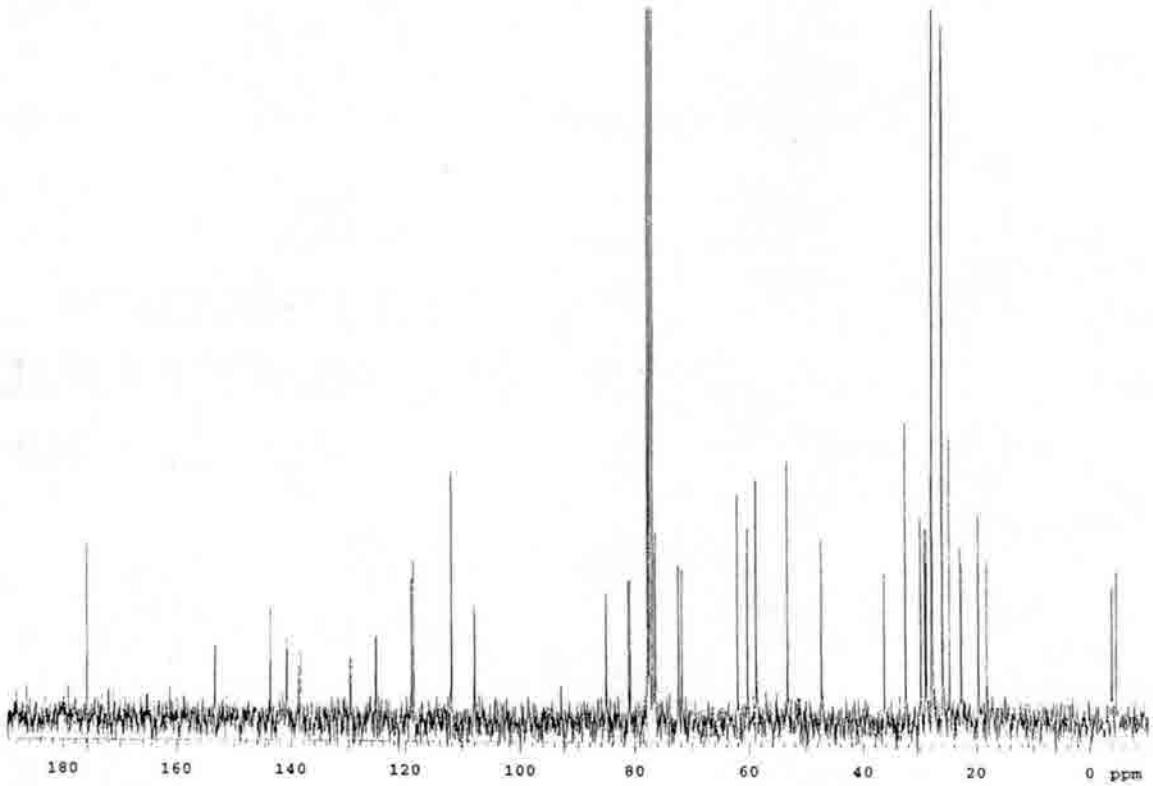
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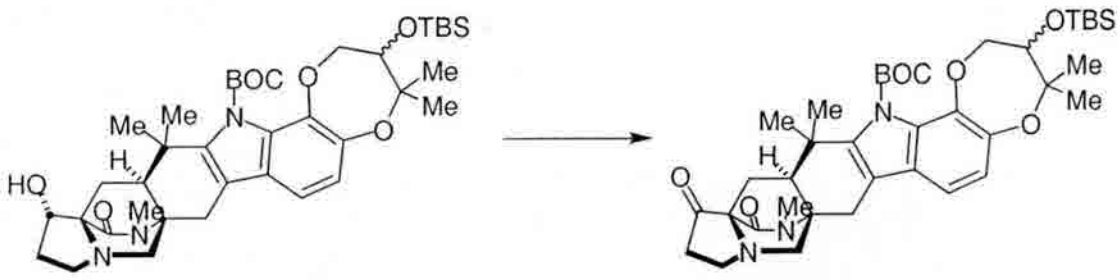


342 **343**

(8aS,13aS,14aS)-3R/S-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,4,8,12,13,14,14a,15-octahydro- 4,4,15,15,18-pentamethyl-13,17-dioxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole-16-carboxylic acid, 1,1-dimethylethyl ester (343)

To a stirred solution of **342** (13.2 mg, 0.019 mmol, 1 eq) in CH_2Cl_2 (1.9 mL) at room temperature was added Dess-Martin periodinane (40.7 mg, 0.0960 mmol, 5 eq). After 0.5 h, the reaction mixture was quenched with a solution of 0.5 M $Na_2S_2O_3$ in 1 M $NaHCO_3$ (aq.) (0.8 mL), and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (hexane:EtOAc:MeOH/5:3:0.5) to give 11.2 mg (85.1%) of **343** as an amorphous solid.

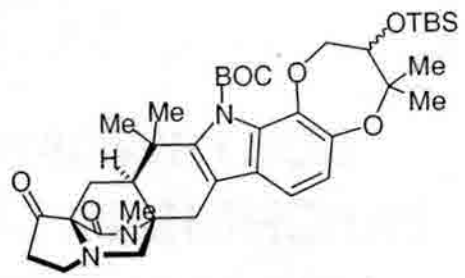
Data for **343** (mixture of two diastereomers)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 and 0.14 (total 3 H, s), 0.90 and 0.91 (total 9 H, s), 1.16 and 1.20 (total 3 H, s), 1.395 and 1.399 (total 3 H, s), 1.49 (3 H, s), 1.58 (3 H, s), 1.62 and 1.64 (total 9 H, s), 1.90-2.02 (1 H, m), 2.14-2.28 (2 H, m), 2.32 (1 H, d, J = 10.5 Hz), 2.42-2.71 (5 H, m), 2.825 and 2.833 (total 1 H, d, J = 15.3 Hz), 3.08 (3 H, d, J = 10.5 Hz), 3.19 (1 H, d, J = 15.3 Hz), 3.75-3.98 (2 H, m), 4.11-4.24 (1 H, m), 6.836 and 6.845 (total 1 H, d, J = 8.4 Hz), 6.96 (1 H, d, J = 8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ δ: 209.8, 169.9, 153.3, 153.2, 143.6, 140.8, 140.6, 138.7, 138.3, 129.7, 129.6, 125.1, 125.0, 118.9, 118.6, 111.9, 107.8, 85.1, 85.0, 81.1, 80.8, 76.4, 76.3, 72.4, 71.8, 67.6, 60.5, 57.9, 50.6, 47.1, 47.0, 36.9, 36.33, 36.28, 29.0, 28.8, 28.6, 27.8, 27.7, 26.9, 26.0, 25.0, 22.8, 22.6, 19.6, 18.1, -3.8, -4.0, -4.6, -4.7.

IR (NaCl, neat) 2956, 2930, 2855, 1760, 1748, 1670, 1496, 1252, 1233, 1157, 1139, 1112, 1092, 837 cm^{-1}.

HRMS (FAB) *m/z* calcd for $C_{38}H_{56}N_3O_7Si$ $(M+H)^+$ 694.3888, found 694.3870.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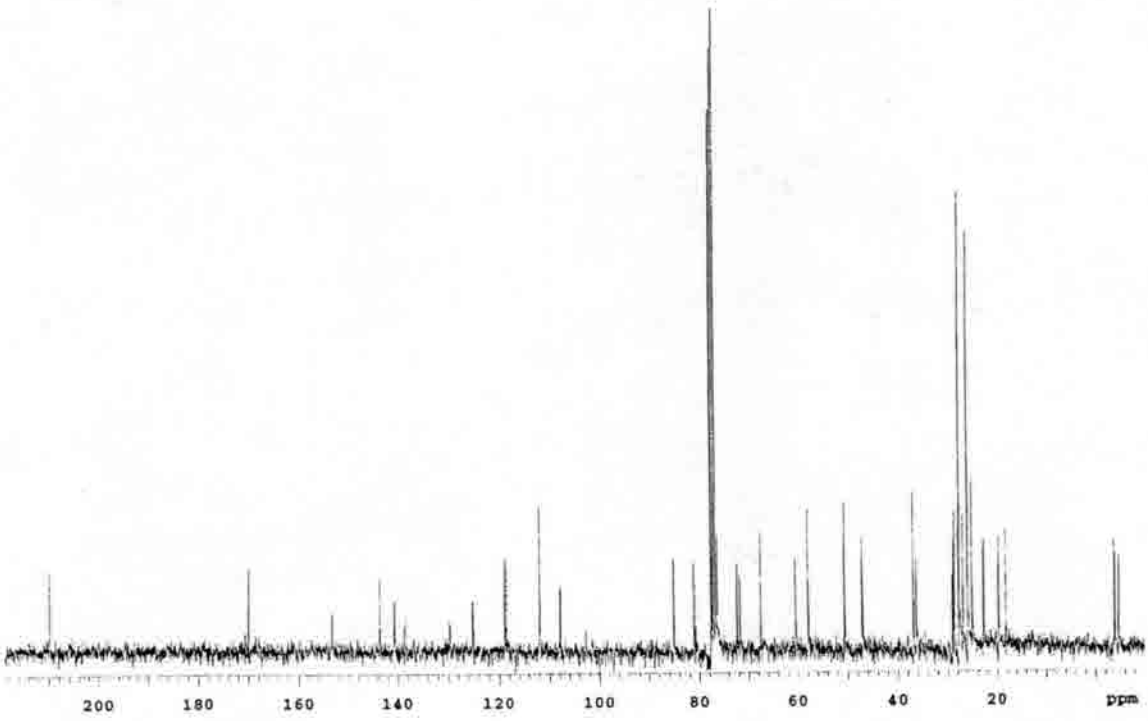
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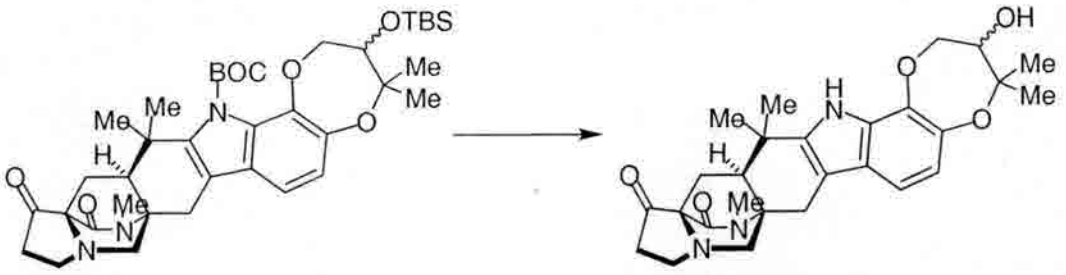


343 **344**

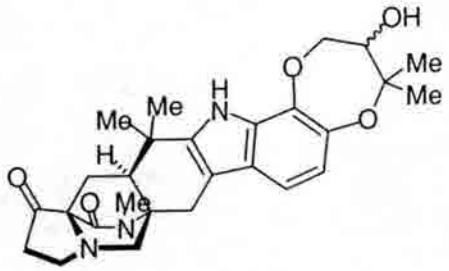
(8aS,13aS,14aS)-3R/S-hydroxy-3,4,8,12,13,14,14a,15-octahydro- 4,4,15,15,18-pentamethyl-13,17-dioxo-9H,11H-8a,13a-(iminomethano)-2H,16H-[1,4]dioxepino[2,3-a]indolizino[6,7-h]carbazole (344)

To a solution of **343** (26.2 mg, 0.038 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added TFA (2.22 g, 19.5 mmol, 513 eq). After the reaction mixture was stirred at 0 °C for 2 h and at room temperature for 3 h, it was quenched with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (hexane:EtOAc:MeOH/5:25:1) to give 17.5 mg (96.7%) of **344** as an amorphous solid.

Data for **344** (mixture of two diastereomers)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 and 1.26 (total 3 H, s), 1.33 and 1.36 (total 3 H, s), 1.41 and 1.44 (total 3 H, s), 1.568 and 1.574 (total 3 H, s), 1.88-2.00 (1 H, m), 2.16-2.28 (2 H, m), 2.35 (1 H, d, J = 10.2 Hz), 2.40-2.72 (3 H, m), 2.87 and 2.88 (total 1 H, d, J = 15.0 Hz), 3.03-3.08 (1 H, m), 3.10 (3 H, s), 3.22 and 3.24 (total 1 H, d, J = 15.0 Hz), 3.29-3.39 (1 H, m), 3.55 and 3.58 (total 1 H, d, J = 10.2 Hz), 3.66 (1 H, dt, J = 11.4, 3.0 Hz), 4.22 (1 H, dd, J = 11.7, 4.2 Hz), 4.35 (1 H. dd, J = 11.7, 3.9 Hz), 6.79 and 6.80 (total 1 H, d, J = 8.4 Hz), 7.04 (1 H, d, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 169.9, 142.3, 142.2, 140.2, 137.6, 129.6, 125.2, 116.93, 116.86, 112.8, 104.9, 79.9, 76.0, 71.3, 67.5, 61.3, 58.4, 58.3, 50.8, 45.3, 45.2, 34.89, 34.85, 30.9, 30.8, 27.9, 26.7, 26.3, 26.1, 25.2, 25.1, 24.9, 23.8, 23.7. IR (NaCl, neat): 3374, 2970, 2932, 1759, 1654, 1507, 1474, 1397, 1364, 1232, 1136, 1096, 1065, 1048, 1025 cm^{-1}.

HRMS (FAB) *m/z* calcd for $C_{27}H_{34}N_3O_5$ $(M+H)^+$ 480.2498, found 480.2478.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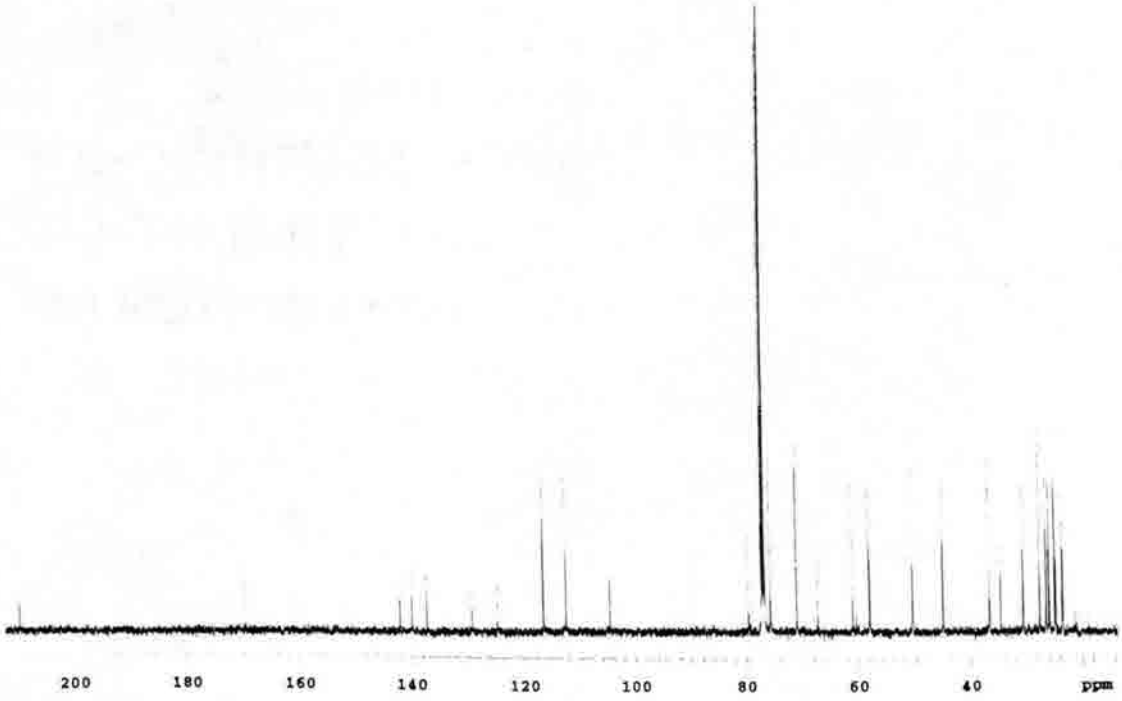
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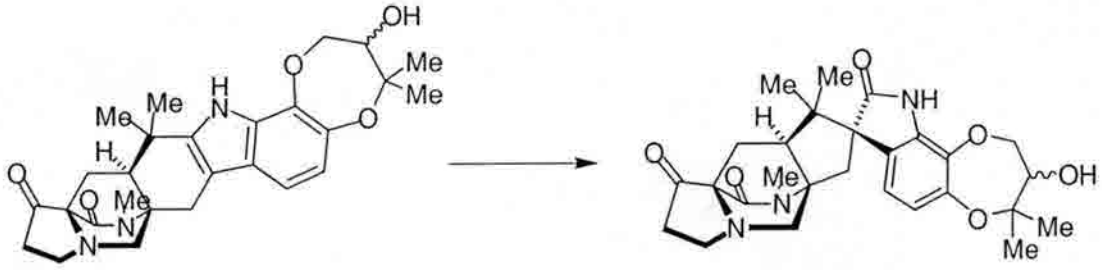


344 347

2,2',3,3',8'aS,9'-hexahydro-3R/S-hydroxy-4,4,8',8',11'-pentamethyl-spiro[4H,8H-[1,4]dioxepino[2,3-g]indole-8,7'R(8'H)-[5H,6H-5aS,9aR](iminomethano)[1H]-cyclopent[f]indolizine]-1',9,10'(10H)-trione (347)

To a solution of **344** (9.8 mg, 0.021 mmol, 1 eq) in pyridine (0.4 mL) at -15 °C was added ^{t}BuOCl (0.31 mL, 0.031 mmol, 0.1 M in CH_2Cl_2, 1.5 eq). After 2 h, the reaction mixture was concentrated in vacuo, and the trace amount of pyridine was removed azeotropically with benzene. To the above residue dissolved in THF (1.8 mL) and H_2O (0.2 mL) was added $TsOH{\cdot}H_2O$ (18.4 mg, 0.102 mmol, 5 eq). After the mixture was refluxed for 0.5 h, it was cooled to room temperature, quenched with a mixture of EtOAc and 0.5 M K_2CO_3 (aq.), and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (CH_2Cl_2:MeOH/20:1) on silica gel (developed three times) to give 5.5 mg (54.4%) of **347.**

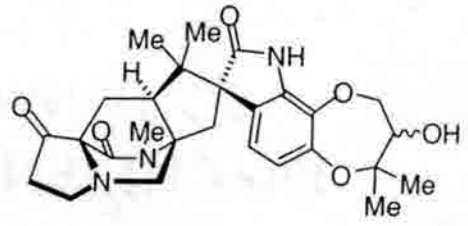
Data for **347** (mixture of two diastereomers)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 and 0.86 (total 3 H, s), 1.08 and 1.09 (total 3 H, s), 1.26 and 1.29 (total 3 H, s), 1.53 and 1.55 (total 3 H, s), 1.56-1.64 (1 H, m), 1.81 and 1.90 (total 1 H, d, J = 15.3 Hz), 2.21 (1 H, t, J = 11.4 Hz), 2.37-2.76 (5 H, m), 2.98-3.46 (3 H, m), 3.09 and 3.10 (3 H, s), 3.62-3.78 (2 H, m), 4.08-4.30 (2 H, m), 6.62 and 6.66 (total 1 H, d, J = 8.1 Hz), 6.78 and 6.81 (total 1 H, d, J = 8.1 Hz), 7.72 and 7.94 (total 1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 182.5, 182.3, 168.7, 148.4, 148.1, 136.4, 136.2, 133.7, 133.6, 125.6, 121.1, 117.3, 116.8, 81.1, 80.9, 77.4, 75.6, 71.5, 71.3, 70.3, 66.3,

63.3, 60.1, 52.54, 52.46, 50.0, 46.4, 46.2, 37.2, 36.9, 36.7, 29.9, 26.1, 25.9, 25.6, 24.6, 24.3, 23.9, 20.7.

IR (NaCl, neat) 3421, 2975, 2936, 1762, 1705, 1653, 1498, 1464, 1418, 1390, 1330, 1212, 1194, 1149, 1112, 1065 cm^{-1}.

HRMS (FAB) *m/z* calcd for $C_{27}H_{34}N_3O_6$ $(M+H)^+$ 496.2448, found 496.2447.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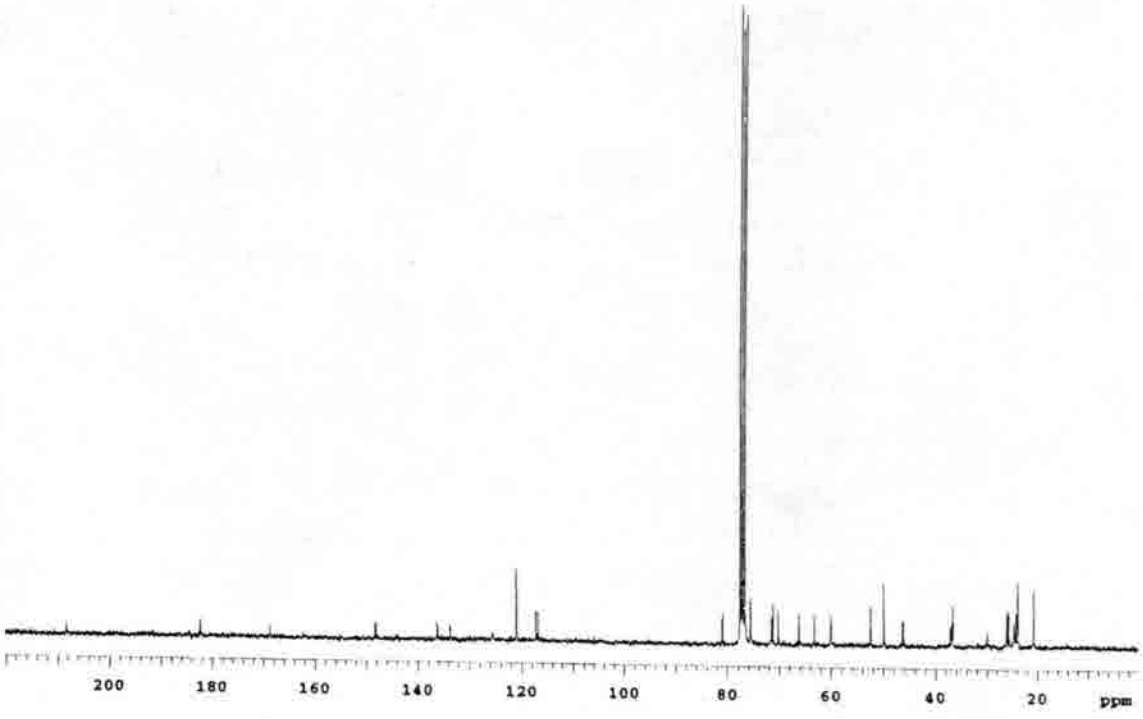
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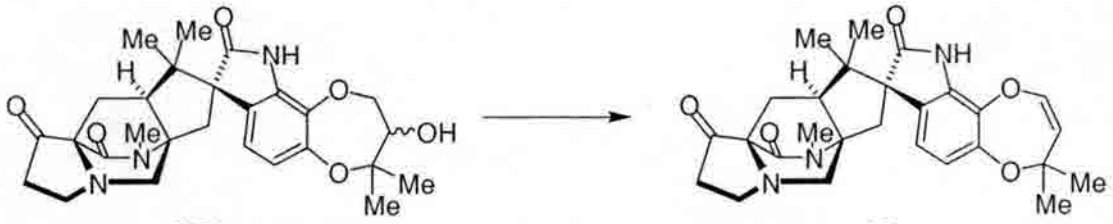


347 43

2',3',8'aS,9'-tetrahydro-4,4,8',8',11'-pentamethyl-spiro[4H,8H-[1,4]dioxepino[2,3-g]indole-8,7'R(8'H)-[5H,6H-5aS,9aR](iminomethano)[1H]cyclopent[f]indolizine]-1',9,10'(10H)-trione (43)

To a solution of **347** (6.6 mg, 0.0133 mmol, 1 eq) in DMPU (0.27 mL) at room temperature was added methyltriphosphonium iodide (30.3 mg, 0.0669 mmol, 5.0 eq) After the reaction mixture was stirred for 21 h, it was quenched with 1 M KOH (aq.), stirred for 10 min, and then 1 M HCl (aq.) was added. The reaction mixture was extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (CH_2Cl_2:MeOH/10:1) to give 3.6 mg (54.8%) of **43**.

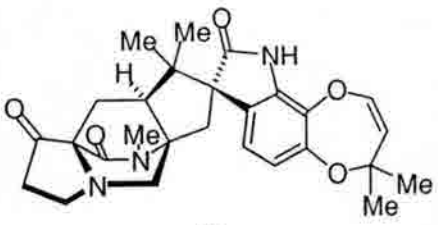
Data for **43**

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, s), 1.11 (3 H, s), 1.15 (3 H, s), 1.47 (3 H, s), 1.63 (1 H, m), 1.91 (1 H, d, *J* = 15.3 Hz), 2.22 (1 H, d, *J* = 12.6, 11.1 Hz), 2.42-2.76 (5 H, m), 3.09 (3 H, s), 3.15 (1 H, t, *J* = 10.5 Hz), 3.35 (1 H, t, *J* = 8.1 Hz), 3.76 (1 H, d, *J* = 11.4 Hz), 4.91 (1 H, d, *J* = 7.8 Hz), 6.32 (1 H, d, *J* = 7.8 Hz), 6.70 (1 H, d, *J* = 8.4 Hz), 6.83 (1 H, d, *J* = 8.4 Hz), 7.31 (1 H, br s).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.3, 182.4, 168.7, 146.3, 139.1, 135.5, 132.5, 125.0, 120.5, 117.6, 115.2, 80.0, 70.3, 66.3, 63.2, 60.0, 52.5, 49.9, 46.3, 37.0, 36.7, 30.1, 30.0, 29.9, 26.0, 24.6, 23.9, 20.7.

IR (NaCl, neat) 3226, 2927, 2853, 1762, 1702, 1654, 1502, 1466, 1387, 1328, 1190, 1112, 1047 cm^{-1}.

HRMS (FAB) *m/z* calcd for $C_{27}H_{32}N_3O_5$ $(M+H)^+$ 478.2342, found 478.2336.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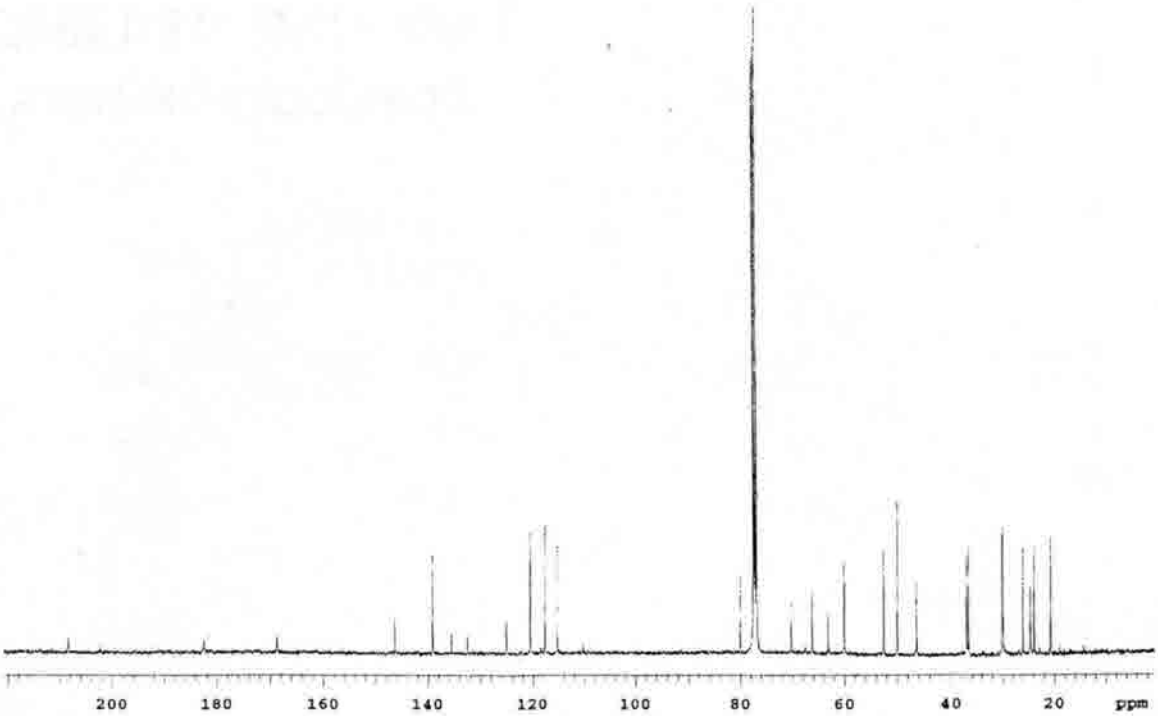
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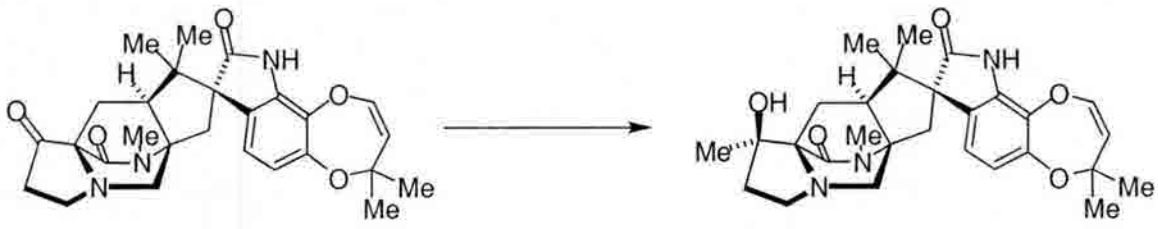


43 1, (-)-paraherquamide A

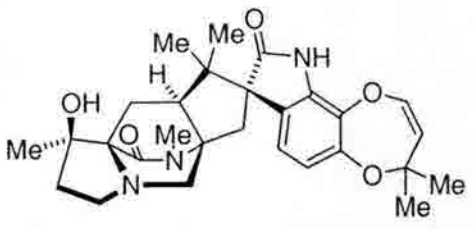
(-)-Paraherquamide A (1)

To a solution of **43** (5.3 mg, 0.011 mmol, 1 eq) in THF at – 30 °C was added MeMgBr (35 μL, 0.105 mmol, 9.5 eq, 3 M in ether). After 1 h, the reaction mixture was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 (3 times). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC on silica gel (developed five times) (hexane:EtOAc:MeOH/5:25:1) to give 2.0 mg of **(-)-paraherquamide A (1)** as an amorphous solid (42%, based on recovered 0.7 mg of starting material **43**).

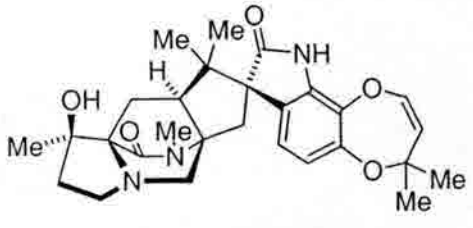
Data for **(-)-paraherquamide A (1):**

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3 H, s), 1.09 (3 H, s), 1.43 (3 H, s), 1.45 (3 H, s), 1.65 (3 H, s), 1.75-1.91 (4 H, m), 2.19-2.25 (1 H, m), 2.30-2.37 (1 H, m), 2.56 (1 H, d, *J* = 11.6 Hz), 2.64 (1 H, s), 2.69 (1 H, d, *J* = 15.2 Hz), 2.99-3.01 (1 H, m), 3.05 (3 H, s), 3.20 (1 H, m), 3.60 (1 H, d, *J* = 11.2 Hz), 4.88 (1 H, d, *J* = 8 Hz), 6.30 (1 H, d, *J* = 8 Hz), 6.68 (1 H, d, *J* = 8 Hz), 6.80 (1 H, d, *J* = 8 Hz), 7.41 (1 H, s, br).

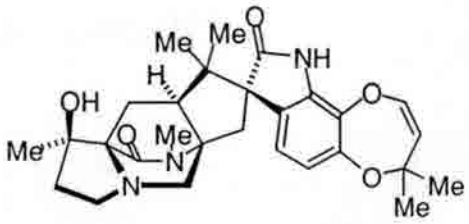
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 182.5, 171.6, 146.2, 139.2, 135.4, 132.4, 125.2, 120.6, 117.5, 115.2, 80.0, 78.2, 71.4, 65.5, 63.2, 59.4, 52.1, 51.6, 46.6, 38.2, 37.3, 30.1, 30.0, 29.9, 26.1, 24.0, 22.3, 20.6, 19.2. IR (NaCl, neat) 3409, 3212, 2972, 2934, 1703, 1654, 1328, 1193, 1047 cm^{-1}. HRMS (FAB) *m/z* calcd for $C_{28}H_{36}N_3O_5$ $(M+H)^+$ 494.2654, found. 494.2653. The synthetic sample recrystallized from ether has m.p. 250 °C (decomp.) and $[\alpha]_D^{25}$ = -22 (c = 0.2 MeOH). A sample of natural paraherquamide A recrystallized from ether under the same conditions rendered a sample with m.p. 250 °C (decomp.) and $[\alpha]_D^{25}$ = - 21 (c = 0.2 MeOH).



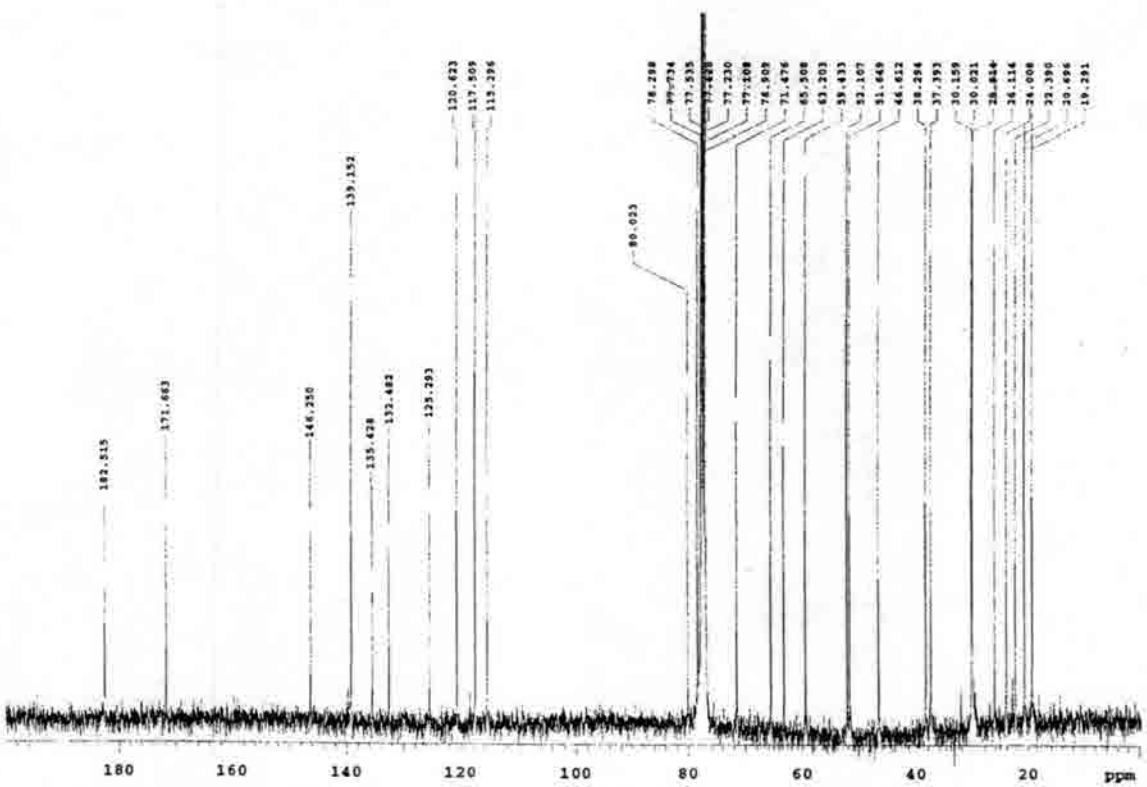
Synthetic (-)-paraherquamide A



Natural (-)-paraherquamide A from Merck & Co.



1, (-)-paraherquamide A



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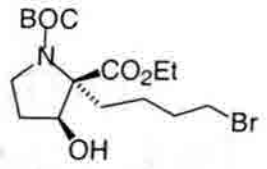
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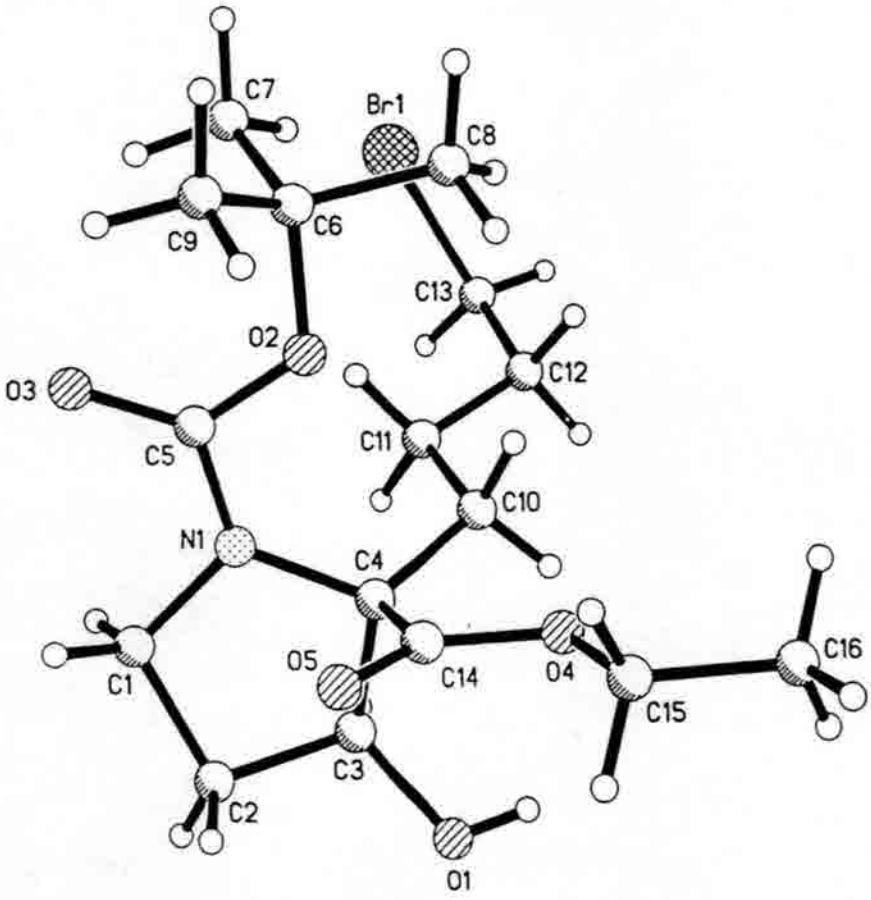
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Br1
C8
C9
C6
C13
O2
C12
O3
C5
C11
C10
N1
C4
C16
O5
C14
O4
C1
C15
C3
C2
O1

Table 1. Crystal data and structure refinement for 1.

Identification code	rw34
Empirical formula	$C_{16}H_{28}BrNO_5$
Formula weight	394.30
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.4682(11) Å alpha = 90° b = 10.3094(8) Å beta = 90° c = 19.254(2) Å gamma = 90°
Volume, Z	1879.4(3) $Å^3$, 4
Density (calculated)	1.394 Mg/m^3
Absorption coefficient	2.210 mm^{-1}
F(000)	824
Crystal size	0.20 x 0.20 x 0.22 mm
θ range for data collection	2.12 to 25.01°
Limiting indices	$-1 \le h \le 11$, $-1 \le k \le 12$, $-1 \le l \le 22$
Reflections collected	2540
Independent reflections	2357 (R_{int} = 0.0507)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2357 / 0 / 208
Goodness-of-fit on F^2	0.819
Final R indices [I>2σ(I)]	R1 = 0.0486, wR2 = 0.1124
R indices (all data)	R1 = 0.0837, wR2 = 0.1253
Absolute structure parameter	0.00(2)
Largest diff. peak and hole	0.630 and -0.395 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	1323(6)	10697(5)	1391(2)	22(1)
O(1)	2055(5)	13496(4)	351(2)	31(1)
O(2)	1616(5)	8698(4)	997(2)	30(1)
O(3)	331(5)	9032(4)	1981(2)	33(1)
O(4)	1830(4)	10900(4)	-449(2)	27(1)
O(5)	-184(5)	11002(5)	169(2)	34(1)
Br(1)	6223(1)	8116(1)	2155(1)	70(1)
C(1)	591(7)	11681(7)	1805(3)	32(2)
C(2)	714(6)	12915(6)	1373(3)	30(2)
C(3)	2049(7)	12690(6)	951(3)	25(2)
C(4)	2045(7)	11218(6)	780(3)	20(2)
C(5)	1037(7)	9429(6)	1493(3)	26(2)
C(6)	1573(7)	7257(6)	1021(3)	31(2)
C(7)	2259(7)	6781(7)	1685(4)	42(2)
C(8)	2454(9)	6893(8)	393(3)	53(2)
C(9)	57(7)	6798(8)	959(4)	49(2)
C(10)	3556(6)	10729(6)	660(3)	23(2)
C(11)	4406(6)	10496(7)	1316(3)	27(2)
C(12)	5941(7)	10139(7)	1146(4)	38(2)
C(13)	6806(8)	9742(8)	1766(4)	49(2)
C(14)	1100(8)	11022(6)	141(3)	26(2)
C(15)	1034(8)	10748(8)	-1080(3)	38(2)
C(16)	2029(9)	10684(11)	-1672(4)	62(3)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(5)	1.350(8)	N(1)-C(1)	1.464(8)
N(1)-C(4)	1.463(8)	O(1)-C(3)	1.423(7)
O(2)-C(5)	1.335(8)	O(2)-C(6)	1.488(7)
O(3)-C(5)	1.223(7)	O(4)-C(14)	1.336(7)
O(4)-C(15)	1.438(7)	O(5)-C(14)	1.217(8)
Br(1)-C(13)	1.917(8)	C(1)-C(2)	1.525(9)
C(2)-C(3)	1.520(8)	C(3)-C(4)	1.554(9)
C(4)-C(14)	1.534(9)	C(4)-C(10)	1.535(9)
C(6)-C(9)	1.516(10)	C(6)-C(8)	1.515(9)
C(6)-C(7)	1.515(9)	C(10)-C(11)	1.517(8)
C(11)-C(12)	1.535(9)	C(12)-C(13)	1.505(9)
C(15)-C(16)	1.481(10)		

C(5)-N(1)-C(1)	119.8(5)	C(5)-N(1)-C(4)	124.5(5)
C(1)-N(1)-C(4)	113.9(5)	C(5)-O(2)-C(6)	122.0(5)
C(14)-O(4)-C(15)	117.2(5)	N(1)-C(1)-C(2)	104.1(5)
C(3)-C(2)-C(1)	103.2(5)	O(1)-C(3)-C(2)	110.4(5)
O(1)-C(3)-C(4)	113.4(5)	C(2)-C(3)-C(4)	105.1(5)
N(1)-C(4)-C(14)	108.9(5)	N(1)-C(4)-C(10)	115.9(5)
C(14)-C(4)-C(10)	112.3(5)	N(1)-C(4)-C(3)	100.9(5)
C(14)-C(4)-C(3)	107.5(5)	C(10)-C(4)-C(3)	110.5(5)
O(3)-C(5)-O(2)	125.8(6)	O(3)-C(5)-N(1)	123.1(6)
O(2)-C(5)-N(1)	111.1(5)	O(2)-C(6)-C(9)	109.6(6)
O(2)-C(6)-C(8)	102.0(6)	C(9)-C(6)-C(8)	112.4(6)
O(2)-C(6)-C(7)	109.7(6)	C(9)-C(6)-C(7)	111.8(6)
C(8)-C(6)-C(7)	110.9(6)	C(11)-C(10)-C(4)	114.9(5)
C(10)-C(11)-C(12)	111.2(5)	C(13)-C(12)-C(11)	114.2(6)
C(12)-C(13)-Br(1)	113.1(5)	O(5)-C(14)-O(4)	123.5(6)
O(5)-C(14)-C(4)	123.3(6)	O(4)-C(14)-C(4)	113.1(6)
O(4)-C(15)-C(16)	108.8(6)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
N(1)	19(3)	25(3)	23(3)	-1(2)	4(3)	-2(3)
O(1)	29(2)	28(3)	36(3)	6(2)	4(2)	2(2)
O(2)	39(3)	22(2)	29(3)	1(2)	5(2)	-5(2)
O(3)	31(3)	35(3)	33(3)	6(2)	8(2)	-2(2)
O(4)	21(2)	37(3)	24(2)	-2(2)	-5(2)	3(2)
O(5)	21(3)	43(3)	39(3)	4(2)	-5(2)	1(2)
Br(1)	40(1)	79(1)	91(1)	50(1)	-6(1)	9(1)
C(1)	28(3)	40(4)	28(3)	-5(3)	4(3)	5(4)
C(2)	20(3)	29(4)	41(4)	-6(4)	-1(3)	0(3)
C(3)	19(3)	25(4)	32(4)	3(3)	0(3)	-1(3)
C(4)	19(4)	23(4)	19(3)	2(3)	3(3)	1(3)
C(5)	23(4)	37(4)	19(3)	7(3)	1(4)	3(4)
C(6)	42(4)	19(4)	30(4)	3(3)	0(4)	-11(3)
C(7)	43(4)	27(4)	56(5)	8(4)	-6(4)	-2(4)
C(8)	89(6)	29(4)	41(4)	-8(4)	20(4)	-2(5)
C(9)	48(4)	38(5)	62(5)	8(4)	-27(4)	-13(5)
C(10)	19(3)	21(3)	30(4)	0(3)	2(3)	-1(3)
C(11)	20(3)	27(4)	34(4)	4(3)	-3(3)	5(3)
C(12)	26(4)	49(5)	39(4)	17(4)	3(4)	2(4)
C(13)	27(4)	58(5)	63(5)	9(5)	-6(4)	-7(4)
C(14)	30(4)	13(3)	34(4)	5(3)	-3(4)	-1(4)
C(15)	33(4)	56(5)	25(4)	-5(4)	-8(4)	3(4)
C(16)	52(5)	101(8)	34(4)	-7(5)	-9(4)	19(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1C)	2796(5)	13362(4)	122(2)	47
H(1A)	1048(7)	11791(7)	2264(3)	38
H(1B)	-412(7)	11441(7)	1876(3)	38
H(2A)	-117(6)	13025(6)	1066(3)	36
H(2B)	808(6)	13689(6)	1673(3)	36
H(3A)	2892(7)	12897(6)	1244(3)	31
H(7A)	3235(7)	7097(7)	1707(4)	63
H(7B)	2257(7)	5831(7)	1691(4)	63
H(7C)	1730(7)	7109(7)	2085(4)	63
H(8A)	3422(9)	7208(8)	457(3)	79
H(8B)	2046(9)	7287(8)	-24(3)	79
H(8C)	2465(9)	5947(8)	341(3)	79
H(9A)	-470(7)	7055(8)	1375(4)	74
H(9B)	39(7)	5851(8)	914(4)	74
H(9C)	-379(7)	7191(8)	548(4)	74
H(10A)	3511(6)	9907(6)	394(3)	28
H(10B)	4064(6)	11370(6)	370(3)	28
H(11A)	3967(6)	9786(7)	1586(3)	33
H(11B)	4392(6)	11289(7)	1606(3)	33
H(12A)	5939(7)	9418(7)	806(4)	46
H(12B)	6400(7)	10894(7)	922(4)	46
H(13A)	6731(8)	10422(8)	2127(4)	59
H(13B)	7810(8)	9679(8)	1627(4)	59
H(15A)	382(8)	11490(8)	-1140(3)	46
H(15B)	466(8)	9942(8)	-1058(3)	46
H(16A)	1497(9)	10583(11)	-2106(4)	94
H(16B)	2664(9)	9942(11)	-1612(4)	94
H(16C)	2584(9)	11486(11)	-1692(4)	94

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	0	0	334	338	7	2	9	0	138	103	24	1	3	1	419	424	7	8	7	1	97	110	54	4	1	2	578	646	20
4	0	0	966	979	25	3	9	0	171	173	20	2	3	1	709	757	19	9	7	1	143	145	32	5	1	2	653	641	15
6	0	0	143	124	15	4	9	0	0	17	1	3	3	1	384	386	7	-8	8	1	39	62	39	6	1	2	381	398	11
8	0	0	299	296	14	5	9	0	44	41	43	4	3	1	257	259	7	-7	8	1	109	121	42	7	1	2	221	223	12
10	0	0	193	189	21	6	9	0	23	29	22	5	3	1	67	63	40	-6	8	1	134	164	29	8	1	2	191	205	17
1	1	0	404	425	8	7	9	0	26	17	26	6	3	1	498	481	13	-5	8	1	257	258	14	9	1	2	131	142	27
2	1	0	835	794	26	0	10	0	235	218	15	7	3	1	111	113	28	-4	8	1	170	153	19	10	1	2	275	267	15
3	1	0	456	440	19	1	10	0	178	187	14	8	3	1	111	126	32	-3	8	1	268	268	12	11	1	2	76	61	75
4	1	0	137	135	7	2	10	0	101	98	44	9	3	1	124	125	32	-2	8	1	185	178	17	-1	2	2	523	514	12
5	1	0	81	54	16	3	10	0	23	76	22	10	3	1	238	220	19	-1	8	1	338	323	6	0	2	2	490	524	16
6	1	0	749	734	14	4	10	0	58	47	58	-10	4	1	42	39	42	0	8	1	167	129	15	1	2	2	568	600	15
7	1	0	178	179	10	5	10	0	81	60	80	-9	4	1	138	140	29	1	8	1	306	284	10	2	2	2	905	896	20
8	1	0	254	245	9	6	10	0	0	12	1	-8	4	1	354	350	10	2	8	1	176	162	17	3	2	2	1029	946	22
9	1	0	61	39	60	1	11	0	0	40	1	-7	4	1	111	120	29	3	8	1	256	260	12	4	2	2	605	667	19
10	1	0	307	325	10	2	11	0	8	36	7	-6	4	1	137	114	19	4	8	1	150	152	21	5	2	2	497	467	9
11	1	0	74	57	73	3	11	0	0	35	1	-5	4	1	156	137	15	5	8	1	229	217	16	6	2	2	108	90	21
0	2	0	495	468	11	4	11	0	0	56	1	-4	4	1	856	820	24	6	8	1	146	159	26	7	2	2	263	257	11
1	2	0	971	963	22	0	12	0	0	29	1	-3	4	1	17	42	16	7	8	1	146	135	28	8	2	2	302	301	12
2	2	0	250	252	5	1	12	0	134	141	25	-2	4	1	234	234	7	8	8	1	36	62	35	9	2	2	247	258	15
3	2	0	493	499	13	2	12	0	0	12	1	-1	4	1	494	459	9	-7	9	1	148	150	31	10	2	2	0	5	1
4	2	0	102	127	15	1	0	1	200	202	3	0	4	1	473	446	8	-6	9	1	130	154	35	11	2	2	158	163	30
5	2	0	179	186	11	2	0	1	1884	1836	24	1	4	1	472	439	20	-5	9	1	225	219	18	-1	3	2	748	720	18
6	2	0	77	88	35	3	0	1	933	910	26	2	4	1	244	240	7	-4	9	1	142	162	26	0	3	2	433	434	11
7	2	0	280	263	11	4	0	1	686	627	11	3	4	1	31	29	31	-3	9	1	245	250	15	1	3	2	816	796	18
8	2	0	241	242	14	5	0	1	738	742	16	4	4	1	850	859	21	-2	9	1	109	120	32	2	3	2	97	98	13
9	2	0	336	344	12	6	0	1	36	28	35	5	4	1	151	137	16	-1	9	1	130	138	17	3	3	2	672	680	19
10	2	0	0	10	1	7	0	1	330	321	7	6	4	1	93	107	31	0	9	1	14	27	13	4	3	2	343	335	9
11	2	0	0	32	1	8	0	1	276	277	8	7	4	1	104	122	31	1	9	1	119	115	19	5	3	2	500	503	12
1	3	0	1036	1027	14	9	0	1	244	239	10	8	4	1	334	338	20	2	9	1	26	111	26	6	3	2	281	280	10
2	3	0	455	522	14	10	0	1	45	11	44	9	4	1	157	147	23	3	9	1	252	246	14	7	3	2	431	435	8
3	3	0	266	269	6	11	0	1	33	32	33	10	4	1	68	34	68	4	9	1	143	157	25	8	3	2	128	131	27
4	3	0	499	488	12	-11	1	1	141	145	24	-10	5	1	122	123	42	5	9	1	205	232	20	9	3	2	132	138	29
5	3	0	225	235	11	-10	1	1	177	188	16	-9	5	1	138	115	29	6	9	1	141	164	31	10	3	2	133	154	35
6	3	0	443	435	12	-9	1	1	97	90	27	-8	5	1	120	100	32	7	9	1	157	152	29	-1	4	2	1020	944	22
7	3	0	425	409	17	-8	1	1	247	246	10	-7	5	1	118	134	28	-6	10	1	73	57	72	0	4	2	491	476	11
8	3	0	242	269	14	-7	1	1	447	433	7	-6	5	1	433	439	12	-5	10	1	130	103	35	1	4	2	966	922	23
9	3	0	231	219	17	-6	1	1	359	352	7	-5	5	1	172	172	15	-4	10	1	72	122	72	2	4	2	237	228	7
10	3	0	44	89	44	-5	1	1	403	386	6	-4	5	1	117	124	19	-3	10	1	178	168	21	3	4	2	375	405	10
0	4	0	743	704	19	-4	1	1	158	152	6	-3	5	1	393	373	10	-2	10	1	47	85	47	4	4	2	0	22	1
1	4	0	713	705	34	-3	1	1	986	942	15	-2	5	1	546	520	13	-1	10	1	155	143	16	5	4	2	284	292	9
2	4	0	8	26	7	-2	1	1	769	725	27	-1	5	1	838	783	15	0	10	1	16	17	16	6	4	2	359	349	10
3	4	0	72	77	25	-1	1	1	624	633	32	0	5	1	183	178	7	1	10	1	165	165	15	7	4	2	117	122	27
4	4	0	224	210	9	0	1	1	371	390	16	1	5	1	850	814	16	2	10	1	85	89	63	8	4	2	37	47	37
5	4	0	596	558	12	1	1	1	698	694	29	2	5	1	487	509	13	3	10	1	149	166	26	9	4	2	245	236	17
6	4	0	234	219	11	2	1	1	766	724	12	3	5	1	373	362	8	4	10	1	116	136	39	10	4	2	163	155	28
7	4	0	291	295	11	3	1	1	881	924	84	4	5	1	110	133	21	5	10	1	130	106	35	-1	5	2	277	275	7
8	4	0	66	36	66	4	1	1	167	165	7	5	5	1	120	138	23	6	10	1	106	61	53	0	5	2	319	292	10
9	4	0	163	162	24	5	1	1	355	361	7	6	5	1	449	448	8	-4	11	1	60	87	59	1	5	2	218	212	10
10	4	0	24	5	23	6	1	1	345	342	6	7	5	1	125	143	27	-3	11	1	17	22	16	2	5	2	247	252	8
1	5	0	1524	1461	18	7	1	1	404	410	16	8	5	1	91	105	47	-2	11	1	138	155	32	3	5	2	430	443	9
2	5	0	217	223	8	8	1	1	239	238	9	9	5	1	133	135	32	-1	11	1	65	64	64	4	5	2	372	369	7
3	5	0	484	482	8	9	1	1	135	120	18	10	5	1	137	148	36	0	11	1	107	79	27	5	5	2	103	127	28
4	5	0	144	133	14	10	1	1	168	166	17	-9	6	1	205	191	21	1	11	1	89	73	38	6	5	2	189	190	15
5	5	0	399	425	9	11	1	1	152	161	21	-8	6	1	112	125	37	2	11	1	114	139	40	7	5	2	129	152	26
6	5	0	259	256	11	-11	2	1	125	115	42	-7	6	1	257	243	13	3	11	1	0	12	1	8	5	2	115	77	31
7	5	0	239	248	15	-10	2	1	77	99	77	-6	6	1	174	157	18	4	11	1	100	92	55	9	5	2	194	203	22
8	5	0	0	19	1	-9	2	1	285	278	14	-5	6	1	255	273	12	-2	12	1	81	48	81	10	5	2	137	145	36
9	5	0	49	34	49	-8	2	1	235	235	13	-4	6	1	323	326	10	-1	12	1	95	102	40	-1	6	2	414	398	13
10	5	0	99	102	61	-7	2	1	438	425	8	-3	6	1	243	228	10	0	12	1	35	63	35	0	6	2	561	538	12
0	6	0	38	53	37	-6	2	1	104	98	22	-2	6	1	88	79	25	1	12	1	103	103	36	1	6	2	426	396	11
1	6	0	256	238	6	-5	2	1	552	544	12	-1	6	1	432	415	6	2	12	1	60	50	60	2	6	2	220	206	10
2	6	0	110	121	19	-4	2	1	593	628	17	0	6	1	284	264	5	0	0	2	179	209	5	3	6	2	300	288	9
3	6	0	418	425	11	-3	2	1	229	222	6	1	6	1	417	393	6	1	0	2	839	824	9	4	6	2	625	640	8
4	6	0	83	73	35	-2	2	1	131	120	9	2	6	1	53	75	53	2	0	2	464	476	12	5	6	2	263	253	11
5	6	0	95	92	34	-1	2	1	657	664	48	3	6	1	222	217	10	3	0	2	82	73	15	6	6	2	47	57	47
6	6	0	141	158	22	0	2	1	892	891	26	4	6	1	324	308	9	4	0	2	889	873	22	7	6	2	104	115	37
7	6	0	277	265	13	1	2	1	737	757	12	5	6	1	268	265	11	5	0	2	294	276	7	8	6	2	208	230	18
8	6	0	106	90	39	2	2	1	120	111	9	6	6	1	148	142	20	6	0	2	302	289	10	9	6	2	146	180	33
9	6	0	49	69	49	3	2	1	185	195	9	7	6	1	215	221	16	7	0	2	254	257	11	-1	7	2	144	155	18
1	7	0	51	15	50	4	2	1	582	615	17	8	6	1	153	145	26	8	0	2	328	341	10	0	7	2	114	117	26
2	7	0	407	423	9	5	2	1	561	558	16	9	6	1	187	173	23	9	0	2	0	16	1	1	7	2	158	160	16
3	7	0	15	22	15	6	2	1	91	93	27	-9	7	1	167	167	28	10	0	2	110	86	40	2	7	2	309	292	9
4	7	0	186	182	15	7	2	1	434	417	10	-8	7	1	104	101	45	11	0	2	116	123	47	3	7	2	207	194	13
5	7	0	39	10	39	8	2	1	203	215	16	-7	7	1	109	66	36	-11	1	2	103	79	58	4	7	2	130	110	22
6	7	0	209	224	17	9	2	1	256	268	15	-6	7	1	186	183	19	-10	1	2	255	248	17	5	7	2	83	115	54
7	7	0	0	19	1	10	2	1	106	107	46	-5	7	1	162	171	19	-9	1	2	96	119	43	6	7	2	237	250	15
8	7	0	195	189	21	11	2	1	103	120	57	-4	7	1	153	147	18	-8	1	2	201	214	16	7	7	2	167	175	23
9	7	0	0	17	1	-10	3	1	209	212	21	-3	7	1	415	402	8	-7	1	2	182	180	15	8	7	2	213	196	19
0	8	0	499	480	13	-9	3	1	128	139	30	-2	7	1	65	68	65	-6	1	2	402	391	7	9	7	2	61	100	60
1	8	0	126	104	16	-8	3	1	136	138	25	-1	7	1	285	286	10	-5	1	2	680	664	18	-1	8	2	258	257	12
2	8	0	123	88	23	-7	3	1	132	126	22	0	7	1	352	351	6	-4	1	2	675	629	16	0	8	2	430	413	9
3	8	0	185	189	17	-6	3	1	519	516	10	1	7	1	284	282	12	-3	1	2	269	265	8	1	8	2	269	277	12
4	8	0	278	272	12	-5	3	1	55	58	55	2	7	1	105	104	26	-2	1	2	1213	1189	18	2	8	2	100	75	33
5	8	0	75	31	75	-4	3	1	274	255	7	3	7	1	389	407	10	-1	1	2	529	523	44	3	8	2	76	73	65
6	8	0	108	124	39	-3	3	1	403	400	11	4	7	1	131	130	22	0	1	2	1074	1042	31	4	8	2	301	300	11
7	8	0	0	18	1	-2	3	1	715	771	20	5	7	1	158	161	21	1	1	2	443	475	25	5	8	2	182	202	20
8	8	0	226	224	21	-1	3	1	398	406	9	6	7	1	183	189	19	2	1	2	1158	1139	18	6	8	2	63	70	62
1	9	0	14	37	14	0	3	1	1327	1260	30	7	7	1	77	27	76	3	1	2	249	272	8	7	8	2	49	41	48

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
8	8	2	132	121	35	0	4	3	413	438	12	7	0	4	274	269	11	0	7	4	346	320	8	10	2	5	165	188	27
-1	9	2	42	66	41	1	4	3	408	417	12	8	0	4	357	337	14	1	7	4	351	340	8	-1	3	5	254	264	7
0	9	2	31	70	31	2	4	3	242	244	7	9	0	4	105	103	38	2	7	4	287	306	10	0	3	5	407	387	10
1	9	2	101	88	37	3	4	3	342	319	8	10	0	4	20	55	20	3	7	4	192	178	14	1	3	5	251	239	6
2	9	2	200	190	17	4	4	3	458	474	11	11	0	4	157	150	32	4	7	4	207	184	14	2	3	5	486	519	9
3	9	2	63	53	63	5	4	3	236	232	12	-11	1	4	93	92	78	5	7	4	0	71	1	3	3	5	718	733	18
4	9	2	126	145	30	6	4	3	111	110	24	-10	1	4	195	190	21	6	7	4	317	329	12	4	3	5	154	164	13
5	9	2	220	230	18	7	4	3	213	208	15	-9	1	4	162	161	22	7	7	4	169	183	23	5	3	5	365	362	10
6	9	2	176	158	23	8	4	3	350	361	16	-8	1	4	83	106	52	8	7	4	86	85	86	6	3	5	371	384	9
7	9	2	73	77	73	9	4	3	82	102	81	-7	1	4	449	426	10	9	7	4	119	99	42	7	3	5	223	211	14
-1	10	2	149	157	25	10	4	3	152	134	30	-6	1	4	249	248	10	-1	8	4	37	40	37	8	3	5	167	156	20
0	10	2	0	29	1	-1	5	3	457	447	8	-5	1	4	637	621	15	0	8	4	77	80	51	9	3	5	163	202	25
1	10	2	153	148	24	0	5	3	307	276	7	-4	1	4	399	367	9	1	8	4	61	4	60	10	3	5	156	157	27
2	10	2	29	28	29	1	5	3	456	450	9	-3	1	4	540	546	13	2	8	4	140	163	22	-1	4	5	630	608	13
3	10	2	138	140	29	2	5	3	560	552	13	-2	1	4	586	597	15	3	8	4	169	157	18	0	4	5	381	423	12
4	10	2	0	54	1	3	5	3	408	411	7	-1	1	4	980	994	13	4	8	4	192	194	16	1	4	5	624	601	14
5	10	2	111	104	44	4	5	3	101	102	23	0	1	4	699	690	11	5	8	4	192	178	19	2	4	5	49	60	49
6	10	2	84	72	84	5	5	3	276	297	11	1	1	4	936	966	26	6	8	4	0	37	1	3	4	5	626	641	17
-1	11	2	114	139	41	6	5	3	266	284	14	2	1	4	547	556	14	7	8	4	139	133	30	4	4	5	229	237	9
0	11	2	0	20	1	7	5	3	78	81	60	3	1	4	550	563	16	8	8	4	111	70	48	5	4	5	158	169	16
1	11	2	154	140	27	8	5	3	89	85	57	4	1	4	339	331	6	-1	9	4	285	301	14	6	4	5	73	53	54
2	11	2	76	88	75	9	5	3	170	179	26	5	1	4	637	633	15	0	9	4	62	91	62	7	4	5	236	238	14
3	11	2	50	53	50	10	5	3	110	103	51	6	1	4	254	256	10	1	9	4	283	281	12	8	4	5	181	186	19
4	11	2	68	72	68	-1	6	3	423	427	10	7	1	4	437	410	8	2	9	4	218	213	16	9	4	5	195	199	21
-1	12	2	27	60	27	0	6	3	469	435	15	8	1	4	63	79	63	3	9	4	292	307	13	10	4	5	96	110	61
0	12	2	0	10	1	1	6	3	421	425	10	9	1	4	102	114	39	4	9	4	45	47	44	-1	5	5	584	553	15
1	12	2	108	69	49	2	6	3	128	132	17	10	1	4	153	185	28	5	9	4	77	103	76	0	5	5	378	357	11
2	12	2	53	18	53	3	6	3	303	320	9	11	1	4	107	105	54	6	9	4	57	68	56	1	5	5	535	527	14
1	0	3	776	797	11	4	6	3	314	316	9	-1	2	4	706	789	22	7	9	4	85	101	85	2	5	5	341	356	9
2	0	3	1423	1585	20	5	6	3	214	218	15	0	2	4	540	597	16	-1	10	4	63	49	63	3	5	5	118	105	18
3	0	3	755	818	22	6	6	3	144	140	21	1	2	4	786	806	20	0	10	4	176	193	22	4	5	5	55	48	55
4	0	3	278	277	7	7	6	3	156	160	22	2	2	4	194	193	7	1	10	4	69	20	69	5	5	5	207	208	13
5	0	3	42	47	42	8	6	3	144	141	27	3	2	4	478	510	12	2	10	4	93	84	54	6	5	5	123	135	26
6	0	3	392	352	10	9	6	3	27	78	27	4	2	4	616	628	17	3	10	4	147	124	26	7	5	5	242	228	14
7	0	3	308	287	10	-1	7	3	303	284	11	5	2	4	413	403	13	4	10	4	65	78	65	8	5	5	81	120	80
8	0	3	93	76	38	0	7	3	94	81	28	6	2	4	338	325	13	5	10	4	71	72	71	9	5	5	192	172	23
9	0	3	294	325	14	1	7	3	286	286	9	7	2	4	316	310	10	6	10	4	27	43	27	-1	6	5	330	311	9
10	0	3	231	241	18	2	7	3	435	435	14	8	2	4	222	204	14	-1	11	4	0	22	1	0	6	5	33	9	33
11	0	3	122	87	43	3	7	3	181	185	15	9	2	4	125	111	31	0	11	4	85	90	84	1	6	5	292	291	8
-11	1	3	86	108	86	4	7	3	165	184	18	10	2	4	190	168	22	1	11	4	0	2	1	2	6	5	316	299	8
-10	1	3	138	123	30	5	7	3	48	36	47	-1	3	4	680	667	18	2	11	4	89	46	73	3	6	5	218	196	11
-9	1	3	250	219	15	6	7	3	53	26	53	0	3	4	840	789	21	3	11	4	23	45	22	4	6	5	144	142	19
-8	1	3	338	340	14	7	7	3	193	199	19	1	3	4	688	679	14	4	11	4	0	53	1	5	6	5	169	178	18
-7	1	3	323	309	9	8	7	3	116	116	37	2	3	4	289	303	9	-1	12	4	91	126	90	6	6	5	113	112	30
-6	1	3	256	251	10	9	7	3	74	41	73	3	3	4	323	337	11	0	12	4	81	112	80	7	6	5	130	124	29
-5	1	3	510	522	15	-1	8	3	189	186	15	4	3	4	312	302	7	1	12	4	117	121	47	8	6	5	42	66	42
-4	1	3	398	372	10	0	8	3	88	42	40	5	3	4	288	311	9	1	0	5	467	505	7	9	6	5	63	98	62
-3	1	3	639	656	17	1	8	3	220	226	14	6	3	4	86	30	34	2	0	5	556	624	20	-1	7	5	175	166	15
-2	1	3	545	530	16	2	8	3	308	303	11	7	3	4	156	169	19	3	0	5	485	499	14	0	7	5	381	368	8
-1	1	3	588	610	51	3	8	3	107	105	32	8	3	4	257	249	14	4	0	5	142	146	13	1	7	5	104	127	27
0	1	3	1047	995	17	4	8	3	0	14	1	9	3	4	185	199	22	5	0	5	555	548	16	2	7	5	99	110	28
1	1	3	537	603	11	5	8	3	254	250	14	10	3	4	83	89	83	6	0	5	357	348	11	3	7	5	124	143	25
2	1	3	509	511	14	6	8	3	220	192	17	-1	4	4	179	192	9	7	0	5	282	283	11	4	7	5	390	390	10
3	1	3	621	630	14	7	8	3	177	165	24	0	4	4	591	570	13	8	0	5	26	10	26	5	7	5	387	382	11
4	1	3	328	389	13	8	8	3	78	98	78	1	4	4	176	189	9	9	0	5	0	59	1	6	7	5	178	164	20
5	1	3	565	543	13	-1	9	3	209	209	16	2	4	4	537	552	16	10	0	5	238	217	18	7	7	5	96	114	49
6	1	3	213	209	11	0	9	3	161	152	20	3	4	4	414	447	11	-10	1	5	107	70	47	8	7	5	191	203	23
7	1	3	303	299	11	1	9	3	253	230	14	4	4	4	32	26	32	-9	1	5	13	73	13	-1	8	5	238	249	13
8	1	3	328	320	11	2	9	3	150	182	23	5	4	4	400	389	7	-8	1	5	286	278	13	0	8	5	243	248	13
9	1	3	247	232	15	3	9	3	125	85	28	6	4	4	590	568	15	-7	1	5	260	269	12	1	8	5	257	256	12
10	1	3	154	140	27	4	9	3	89	88	53	7	4	4	149	147	22	-6	1	5	222	222	13	2	8	5	405	402	9
11	1	3	59	70	59	5	9	3	107	90	41	8	4	4	92	97	46	-5	1	5	297	283	8	3	8	5	213	223	15
-1	2	3	1163	1185	19	6	9	3	11	64	10	9	4	4	130	132	32	-4	1	5	569	556	12	4	8	5	102	104	36
0	2	3	743	800	20	7	9	3	65	78	64	10	4	4	167	163	28	-3	1	5	745	722	17	5	8	5	96	118	44
1	2	3	1167	1170	19	-1	10	3	92	102	50	-1	5	4	149	146	12	-2	1	5	375	356	8	6	8	5	120	135	36
2	2	3	473	472	10	0	10	3	130	166	30	0	5	4	710	680	20	-1	1	5	504	502	28	7	8	5	106	142	46
3	2	3	517	496	13	1	10	3	125	111	31	1	5	4	99	100	20	0	1	5	715	708	23	8	8	5	0	42	1
4	2	3	336	343	8	2	10	3	94	66	50	2	5	4	120	119	16	1	1	5	546	561	15	-1	9	5	75	121	75
5	2	3	209	218	13	3	10	3	0	78	1	3	5	4	152	157	14	2	1	5	340	333	7	0	9	5	297	268	15
6	2	3	203	186	12	4	10	3	97	108	52	4	5	4	458	449	14	3	1	5	769	772	18	1	9	5	122	110	28
7	2	3	111	110	27	5	10	3	124	102	38	5	5	4	167	164	16	4	1	5	576	604	14	2	9	5	0	16	1
8	2	3	392	381	14	6	10	3	0	82	1	6	5	4	134	142	24	5	1	5	295	295	8	3	9	5	98	118	40
9	2	3	180	183	20	-1	11	3	112	73	43	7	5	4	157	182	20	6	1	5	232	249	13	4	9	5	216	221	17
10	2	3	43	39	42	0	11	3	88	106	73	8	5	4	208	235	18	7	1	5	252	256	12	5	9	5	51	54	50
11	2	3	105	75	57	1	11	3	98	79	53	9	5	4	44	70	43	8	1	5	319	304	11	6	9	5	39	14	38
-1	3	3	338	332	10	2	11	3	135	123	32	10	5	4	0	39	1	9	1	5	44	65	43	7	9	5	28	73	28
0	3	3	338	328	9	3	11	3	79	102	79	-1	6	4	257	260	9	10	1	5	42	81	41	-1	10	5	0	24	1
1	3	3	323	333	7	4	11	3	0	73	1	0	6	4	291	298	8	-1	2	5	534	636	16	0	10	5	163	177	24
2	3	3	730	747	21	-1	12	3	59	69	58	1	6	4	273	273	8	0	2	5	262	297	8	1	10	5	0	12	1
3	3	3	348	333	8	0	12	3	152	144	32	2	6	4	444	436	13	1	2	5	552	631	16	2	10	5	178	155	22
4	3	3	463	431	11	1	12	3	84	62	83	3	6	4	104	99	23	2	2	5	465	486	12	3	10	5	13	37	13
5	3	3	307	315	10	0	0	4	610	624	17	4	6	4	365	378	12	3	2	5	227	210	7	4	10	5	0	65	1
6	3	3	385	390	8	1	0	4	1318	1283	11	5	6	4	220	209	14	4	2	5	419	415	7	5	10	5	30	72	30
7	3	3	285	290	12	2	0	4	75	79	16	6	6	4	227	238	14	5	2	5	510	489	12	6	10	5	127	125	40
8	3	3	183	183	17	3	0	4	275	267	6	7	6	4	175	196	21	6	2	5	463	457	11	-1	11	5	124	93	37
9	3	3	299	292	13	4	0	4	84	91	20	8	6	4	113	121	39	7	2	5	309	306	10	0	11	5	139	74	31
10	3	3	203	190	21	5	0	4	788	736	19	9	6	4	103	90	48	8	2	5	166	160	20	1	11	5	61	77	60
-1	4	3	415	410	12	6	0	4	88	88	28	-1	7	4	319	352	18	9	2	5	33	35	33	2	11	5	40	33	40

Table 6. Observed and calculated structure factors for 1 Page 3

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
3	11	5	87	105	87	6	6	6	419	409	13	10	2	7	205	220	23	2	0	8	521	476	13	0	7	8	171	144	17
4	11	5	0	15	1	7	6	6	178	170	20	-1	3	7	376	401	11	3	0	8	830	817	23	1	7	8	326	323	10
0	0	6	236	218	7	8	6	6	171	180	25	0	3	7	67	84	27	4	0	8	218	205	10	2	7	8	100	121	32
1	0	6	622	666	12	9	6	6	118	152	46	1	3	7	398	415	13	5	0	8	143	142	17	3	7	8	255	255	13
2	0	6	145	137	9	-1	7	6	331	341	9	2	3	7	318	314	7	6	0	8	195	195	14	4	7	8	217	218	15
3	0	6	663	677	18	0	7	6	339	331	9	3	3	7	222	242	9	7	0	8	756	750	21	5	7	8	284	303	14
4	0	6	378	403	10	1	7	6	379	373	8	4	3	7	417	428	13	8	0	8	73	97	73	6	7	8	93	84	51
5	0	6	637	663	18	2	7	6	77	89	49	5	3	7	350	345	8	9	0	8	139	114	30	7	7	8	254	271	16
6	0	6	200	176	12	3	7	6	214	229	14	6	3	7	124	107	23	10	0	8	107	61	48	8	7	8	70	31	69
7	0	6	155	158	20	4	7	6	170	169	18	7	3	7	275	286	13	-10	1	8	101	88	53	-1	8	8	421	422	9
8	0	6	69	94	68	5	7	6	128	129	20	8	3	7	90	69	50	-9	1	8	248	251	16	0	8	8	0	32	1
9	0	6	151	152	26	6	7	6	110	88	35	9	3	7	194	196	21	-8	1	8	0	55	1	1	8	8	377	385	10
10	0	6	45	32	45	7	7	6	79	97	79	10	3	7	115	72	43	-7	1	8	160	157	20	2	8	8	39	68	38
-10	1	6	0	39	1	8	7	6	0	51	1	-1	4	7	566	561	14	-6	1	8	233	225	12	3	8	8	213	207	16
-9	1	6	284	259	14	-1	8	6	193	210	16	0	4	7	396	406	12	-5	1	8	356	344	8	4	8	8	0	55	1
-8	1	6	234	222	14	0	8	6	104	106	35	1	4	7	561	584	15	-4	1	8	150	149	14	5	8	8	106	133	42
-7	1	6	337	330	10	1	8	6	232	215	14	2	4	7	181	171	11	-3	1	8	433	457	12	6	8	8	67	51	66
-6	1	6	325	310	8	2	8	6	209	211	15	3	4	7	571	566	10	-2	1	8	598	568	13	7	8	8	120	137	43
-5	1	6	382	374	11	3	8	6	323	315	11	4	4	7	92	67	29	-1	1	8	67	87	17	-1	9	8	91	73	48
-4	1	6	149	142	13	4	8	6	41	69	40	5	4	7	172	178	16	0	1	8	421	413	8	0	9	8	94	80	48
-3	1	6	662	652	17	5	8	6	127	130	29	6	4	7	180	191	17	1	1	8	66	82	18	1	9	8	116	98	35
-2	1	6	638	649	18	6	8	6	0	14	1	7	4	7	214	221	16	2	1	8	571	545	15	2	9	8	211	214	18
-1	1	6	707	759	19	7	8	6	178	168	24	8	4	7	156	161	23	3	1	8	448	446	12	3	9	8	227	238	17
0	1	6	126	138	7	8	8	6	120	158	44	9	4	7	196	176	21	4	1	8	202	195	10	4	9	8	23	26	22
1	1	6	757	784	12	-1	9	6	25	68	25	10	4	7	0	14	1	5	1	8	350	364	10	5	9	8	131	114	34
2	1	6	622	623	15	0	9	6	169	160	20	-1	5	7	197	209	11	6	1	8	223	218	13	6	9	8	97	96	70
3	1	6	655	690	18	1	9	6	0	38	1	0	5	7	139	151	15	7	1	8	120	107	27	-1	10	8	111	114	42
4	1	6	101	103	19	2	9	6	75	69	75	1	5	7	251	257	9	8	1	8	61	45	61	0	10	8	97	94	50
5	1	6	394	392	14	3	9	6	163	156	22	2	5	7	216	206	10	9	1	8	256	250	18	1	10	8	128	126	34
6	1	6	305	316	9	4	9	6	0	56	1	3	5	7	293	309	11	10	1	8	67	85	66	2	10	8	134	146	34
7	1	6	332	356	10	5	9	6	187	188	22	4	5	7	335	318	9	-1	2	8	326	337	6	3	10	8	125	116	34
8	1	6	252	244	13	6	9	6	73	52	73	5	5	7	144	122	21	0	2	8	195	203	8	4	10	8	0	52	1
9	1	6	255	261	15	7	9	6	72	87	71	6	5	7	93	120	41	1	2	8	336	366	9	5	10	8	105	82	56
10	1	6	44	47	43	-1	10	6	146	93	26	7	5	7	222	239	16	2	2	8	511	505	12	-1	11	8	0	13	1
-1	2	6	320	327	7	0	10	6	17	69	16	8	5	7	192	186	20	3	2	8	208	204	9	0	11	8	102	151	53
0	2	6	372	470	13	1	10	6	128	93	33	9	5	7	75	122	75	4	2	8	240	240	9	1	11	8	0	5	1
1	2	6	288	300	10	2	10	6	124	142	34	-1	6	7	260	244	10	5	2	8	140	137	18	2	11	8	120	101	43
2	2	6	644	661	17	3	10	6	0	20	1	0	6	7	215	199	12	6	2	8	613	585	16	3	11	8	73	78	72
3	2	6	575	594	16	4	10	6	82	80	81	1	6	7	249	240	10	7	2	8	229	235	14	1	0	9	133	138	9
4	2	6	251	258	8	5	10	6	75	94	75	2	6	7	438	429	10	8	2	8	121	142	31	2	0	9	897	860	23
5	2	6	342	325	9	-1	11	6	80	50	79	3	6	7	523	529	16	9	2	8	129	160	33	3	0	9	274	281	8
6	2	6	267	257	11	0	11	6	131	146	34	4	6	7	246	257	13	10	2	8	161	170	28	4	0	9	172	174	13
7	2	6	328	317	10	1	11	6	63	56	62	5	6	7	132	154	26	-1	3	8	373	378	9	5	0	9	389	389	10
8	2	6	110	126	34	2	11	6	142	136	33	6	6	7	399	425	18	0	3	8	1028	1009	24	6	0	9	669	729	17
9	2	6	124	138	33	3	11	6	126	130	39	7	6	7	273	291	14	1	3	8	368	372	10	7	0	9	222	194	15
10	2	6	237	242	19	4	11	6	0	82	1	8	6	7	95	71	58	2	3	8	399	394	10	8	0	9	48	10	47
-1	3	6	165	152	9	1	0	7	314	311	13	9	6	7	0	71	1	3	3	8	124	136	16	9	0	9	202	196	20
0	3	6	852	839	21	2	0	7	615	664	17	-1	7	7	232	223	12	4	3	8	496	487	12	10	0	9	181	177	24
1	3	6	213	202	8	3	0	7	704	634	16	0	7	7	274	282	11	5	3	8	192	190	14	-10	1	9	49	67	48
2	3	6	631	615	16	4	0	7	53	10	52	1	7	7	241	228	12	6	3	8	166	172	18	-9	1	9	74	56	73
3	3	6	426	437	11	5	0	7	377	371	7	2	7	7	337	334	10	7	3	8	176	183	19	-8	1	9	157	156	24
4	3	6	655	657	14	6	0	7	89	77	34	3	7	7	286	296	11	8	3	8	197	217	19	-7	1	9	99	97	37
5	3	6	84	95	32	7	0	7	224	206	14	4	7	7	204	235	16	9	3	8	119	168	38	-6	1	9	385	402	10
6	3	6	227	209	13	8	0	7	79	84	65	5	7	7	138	143	25	10	3	8	55	50	55	-5	1	9	153	152	18
7	3	6	267	258	12	9	0	7	175	183	21	6	7	7	90	87	52	-1	4	8	272	281	8	-4	1	9	550	548	16
8	3	6	296	283	12	10	0	7	183	205	25	7	7	7	229	242	18	0	4	8	60	64	60	-3	1	9	175	160	11
9	3	6	54	55	53	-10	1	7	0	39	1	8	7	7	89	96	89	1	4	8	279	283	10	-2	1	9	132	142	13
10	3	6	49	47	49	-9	1	7	222	207	18	-1	8	7	53	36	52	2	4	8	482	508	16	-1	1	9	136	138	9
-1	4	6	299	303	7	-8	1	7	372	347	10	0	8	7	83	68	50	3	4	8	132	126	17	0	1	9	667	687	12
0	4	6	42	36	41	-7	1	7	352	348	11	1	8	7	0	34	1	4	4	8	191	212	13	1	1	9	114	133	10
1	4	6	267	294	8	-6	1	7	79	51	40	2	8	7	85	107	51	5	4	8	159	148	18	2	1	9	133	146	16
2	4	6	464	475	11	-5	1	7	392	386	7	3	8	7	88	122	46	6	4	8	206	213	15	3	1	9	119	118	17
3	4	6	198	198	10	-4	1	7	755	742	22	4	8	7	188	187	19	7	4	8	166	179	21	4	1	9	568	556	16
4	4	6	234	238	10	-3	1	7	484	437	11	5	8	7	20	35	20	8	4	8	189	205	20	5	1	9	165	154	16
5	4	6	141	144	19	-2	1	7	556	511	14	6	8	7	141	156	30	9	4	8	0	49	1	6	1	9	396	393	9
6	4	6	453	439	11	-1	1	7	343	355	7	7	8	7	62	67	62	-1	5	8	202	188	11	7	1	9	100	125	37
7	4	6	215	224	15	0	1	7	1128	1128	16	-1	9	7	193	195	18	0	5	8	364	372	12	8	1	9	186	190	19
8	4	6	185	161	18	1	1	7	333	363	35	0	9	7	305	296	12	1	5	8	183	165	13	9	1	9	62	62	61
9	4	6	58	66	57	2	1	7	532	520	13	1	9	7	182	207	20	2	5	8	330	331	9	10	1	9	24	59	23
10	4	6	170	168	29	3	1	7	494	465	11	2	9	7	148	146	24	3	5	8	161	144	15	-1	2	9	74	83	29
-1	5	6	223	211	9	4	1	7	704	675	20	3	9	7	156	147	23	4	5	8	373	384	12	0	2	9	177	180	12
0	5	6	588	543	11	5	1	7	378	368	8	4	9	7	166	143	24	5	5	8	228	241	14	1	2	9	135	147	13
1	5	6	216	213	10	6	1	7	0	65	1	5	9	7	92	51	59	6	5	8	303	320	12	2	2	9	503	491	10
2	5	6	306	312	8	7	1	7	346	352	10	6	9	7	47	78	47	7	5	8	222	222	17	3	2	9	546	515	11
3	5	6	300	309	8	8	1	7	341	353	11	-1	10	7	91	65	57	8	5	8	316	324	14	4	2	9	222	217	11
4	5	6	562	565	14	9	1	7	190	210	22	0	10	7	149	118	26	9	5	8	53	113	52	5	2	9	267	250	12
5	5	6	144	166	20	10	1	7	53	28	53	1	10	7	96	60	53	-1	6	8	552	531	14	6	2	9	141	144	20
6	5	6	88	90	41	-1	2	7	554	523	13	2	10	7	112	103	42	0	6	8	0	14	1	7	2	9	381	401	11
7	5	6	140	127	24	0	2	7	143	154	11	3	10	7	72	95	71	1	6	8	542	534	14	8	2	9	181	196	20
8	5	6	70	121	69	1	2	7	499	562	16	4	10	7	53	79	52	2	6	8	127	143	22	9	2	9	63	69	63
9	5	6	0	34	1	2	2	7	706	743	16	5	10	7	69	91	68	3	6	8	60	64	59	10	2	9	148	127	32
-1	6	6	171	164	14	3	2	7	327	316	8	-1	11	7	128	122	38	4	6	8	42	41	41	-1	3	9	389	394	12
0	6	6	179	175	12	4	2	7	250	241	11	0	11	7	102	121	51	5	6	8	181	176	18	0	3	9	70	89	35
1	6	6	128	129	18	5	2	7	359	319	9	1	11	7	111	129	48	6	6	8	67	58	66	1	3	9	402	384	9
2	6	6	446	439	13	6	2	7	545	563	12	2	11	7	119	90	40	7	6	8	0	41	1	2	3	9	533	483	16
3	6	6	259	252	10	7	2	7	178	174	17	3	11	7	0	75	1	8	6	8	48	123	47	3	3	9	314	309	10
4	6	6	132	162	22	8	2	7	162	168	22	0	0	8	193	195	8	9	6	8	73	62	73	4	3	9	227	238	11
5	6	6	210	217	15	9	2	7	50	95	50	1	0	8	535	550	9	-1	7	8	311	310	11	5	3	9	240	236	12

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
6	3	9	168	148	18
7	3	9	252	253	14
8	3	9	182	190	21
9	3	9	137	130	32
-1	4	9	384	414	7
0	4	9	180	184	12
1	4	9	408	421	11
2	4	9	302	300	8
3	4	9	239	258	11
4	4	9	223	216	12
5	4	9	370	378	9
6	4	9	167	174	20
7	4	9	63	42	62
8	4	9	128	151	32
9	4	9	120	100	39
-1	5	9	593	575	14
0	5	9	418	421	8
1	5	9	579	570	10
2	5	9	257	237	10
3	5	9	134	141	20
4	5	9	262	243	12
5	5	9	361	360	10
6	5	9	346	350	11
7	5	9	190	197	19
8	5	9	109	108	44
9	5	9	193	162	24
-1	6	9	179	171	15
0	6	9	208	198	13
1	6	9	184	191	15
2	6	9	251	263	12
3	6	9	256	257	12
4	6	9	99	105	46
5	6	9	252	269	14
6	6	9	160	166	22
7	6	9	60	108	60
8	6	9	44	35	44
-1	7	9	84	71	47
0	7	9	144	145	22
1	7	9	41	67	40
2	7	9	205	206	15
3	7	9	185	197	18
4	7	9	285	318	13
5	7	9	142	128	27
6	7	9	0	65	1
7	7	9	115	91	40
8	7	9	146	188	34
-1	8	9	152	118	22
0	8	9	271	266	13
1	8	9	138	123	24
2	8	9	166	167	20
3	8	9	226	245	16
4	8	9	63	50	62
5	8	9	56	68	56
6	8	9	172	188	25
7	8	9	81	87	80
-1	9	9	149	157	26
0	9	9	120	132	34
1	9	9	163	160	23
2	9	9	125	141	33
3	9	9	54	44	54
4	9	9	130	147	32
5	9	9	150	140	31
6	9	9	78	80	77
-1	10	9	117	114	41
0	10	9	63	68	62
1	10	9	134	128	34
2	10	9	91	126	63
3	10	9	140	112	33
4	10	9	113	102	44
-1	11	9	111	107	51
0	11	9	0	39	1
1	11	9	80	95	80
2	11	9	0	10	1
0	0	10	490	514	12
1	0	10	248	239	8
2	0	10	431	394	12
3	0	10	424	423	10
4	0	10	188	189	13
5	0	10	171	163	16
6	0	10	140	167	23
7	0	10	154	157	22
8	0	10	191	195	20
9	0	10	152	165	29
10	0	10	0	26	1
-10	1	10	116	56	49
-9	1	10	218	207	19
-8	1	10	239	251	17
-7	1	10	169	195	21
-6	1	10	149	152	21
-5	1	10	302	283	10
-4	1	10	220	209	11
-3	1	10	263	269	9
-2	1	10	569	569	12
-1	1	10	422	438	8
0	1	10	235	243	13
1	1	10	432	452	35
2	1	10	600	594	14
3	1	10	257	255	9
4	1	10	174	188	14
5	1	10	323	312	14
6	1	10	172	181	17
7	1	10	191	196	18
8	1	10	228	234	17
9	1	10	223	199	19
10	1	10	15	60	15
-1	2	10	275	313	9
0	2	10	468	484	14
1	2	10	292	304	12
2	2	10	435	426	11
3	2	10	153	157	14
4	2	10	338	340	9
5	2	10	244	235	12
6	2	10	131	140	24
7	2	10	78	63	78
8	2	10	139	129	27
9	2	10	122	148	40
-1	3	10	168	148	13
0	3	10	178	195	12
1	3	10	138	136	15
2	3	10	195	224	12
3	3	10	72	68	42
4	3	10	469	451	12
5	3	10	192	199	16
6	3	10	369	367	10
7	3	10	139	145	26
8	3	10	314	333	14
9	3	10	132	104	35
-1	4	10	314	298	11
0	4	10	61	94	60
1	4	10	301	295	9
2	4	10	583	603	12
3	4	10	203	206	12
4	4	10	96	128	33
5	4	10	0	36	1
6	4	10	257	253	13
7	4	10	117	166	34
8	4	10	116	83	37
9	4	10	113	58	45
-1	5	10	281	274	10
0	5	10	194	191	13
1	5	10	274	278	10
2	5	10	128	107	21
3	5	10	323	318	10
4	5	10	254	266	12
5	5	10	181	173	18
6	5	10	69	55	68
7	5	10	133	114	28
8	5	10	79	113	78
9	5	10	97	104	61
-1	6	10	355	343	10
0	6	10	0	4	1
1	6	10	369	365	9
2	6	10	47	73	46
3	6	10	356	358	10
4	6	10	283	284	12
5	6	10	239	208	16
6	6	10	165	162	23
7	6	10	241	238	17
8	6	10	55	35	55
-1	7	10	400	400	10
0	7	10	105	92	33
1	7	10	361	360	10
2	7	10	51	41	50
3	7	10	273	266	13
4	7	10	118	88	30
5	7	10	232	242	17
6	7	10	115	100	40
7	7	10	50	44	49
-1	8	10	122	129	30
0	8	10	125	138	28
1	8	10	132	132	27
2	8	10	163	157	22
3	8	10	168	167	22
4	8	10	0	22	1
5	8	10	246	248	17
6	8	10	84	43	83
-1	9	10	188	206	21
0	9	10	126	119	31
1	9	10	230	209	17
2	9	10	113	117	39
3	9	10	103	106	45
4	9	10	118	87	37
5	9	10	122	94	39
-1	10	10	0	61	1
0	10	10	186	208	23
1	10	10	31	54	31
2	10	10	171	166	26
3	10	10	99	22	58
4	10	10	150	129	31
0	11	10	123	137	42
1	0	11	0	52	1
2	0	11	191	187	11
3	0	11	225	236	10
4	0	11	45	40	45
5	0	11	470	503	11
6	0	11	384	368	11
7	0	11	51	25	51
8	0	11	74	80	73
9	0	11	176	158	25
-9	1	11	35	29	34
-8	1	11	170	157	23
-7	1	11	225	233	15
-6	1	11	220	221	15
-5	1	11	178	160	16
-4	1	11	174	156	15
-3	1	11	93	84	27
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0	1	11	109	105	13
1	1	11	337	338	12
2	1	11	162	154	14
3	1	11	142	131	16
4	1	11	178	156	14
5	1	11	152	164	19
6	1	11	214	212	14
7	1	11	236	255	15
8	1	11	197	166	19
9	1	11	40	48	40
-1	2	11	268	283	9
0	2	11	344	387	8
1	2	11	240	264	10
2	2	11	236	228	10
3	2	11	259	243	10
4	2	11	232	232	12
5	2	11	286	273	11
6	2	11	65	111	65
7	2	11	128	130	30
8	2	11	58	46	57
9	2	11	177	165	25
-1	3	11	459	458	13
0	3	11	247	242	10
1	3	11	473	456	10
2	3	11	295	282	9
3	3	11	393	391	8
4	3	11	65	64	65
5	3	11	232	219	14
6	3	11	246	256	14
7	3	11	0	28	1
8	3	11	101	86	45
9	3	11	154	131	29
-1	4	11	314	317	9
0	4	11	377	396	9
1	4	11	346	354	10
2	4	11	99	135	29
3	4	11	95	88	32
4	4	11	214	222	14
5	4	11	210	192	15
6	4	11	75	77	75
7	4	11	276	284	15
8	4	11	89	90	67
9	4	11	0	71	1
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0	5	11	256	262	11
1	5	11	111	115	25
2	5	11	250	258	12
3	5	11	106	103	30
4	5	11	271	254	12
5	5	11	260	273	13
6	5	11	202	185	18
7	5	11	0	21	1
8	5	11	118	114	41
-1	6	11	180	185	17
0	6	11	97	93	36
1	6	11	157	176	21
2	6	11	212	209	14
3	6	11	47	56	46
4	6	11	195	209	16
5	6	11	47	56	47
6	6	11	163	150	23
7	6	11	155	131	28
8	6	11	225	218	21
-1	7	11	207	201	16
0	7	11	177	177	19
1	7	11	201	206	16
2	7	11	117	122	31
3	7	11	254	268	14
4	7	11	203	225	19
5	7	11	84	94	84
6	7	11	28	56	28
7	7	11	32	80	32
-1	8	11	131	145	29
0	8	11	100	103	40
1	8	11	175	168	21
2	8	11	285	289	14
3	8	11	197	185	20
4	8	11	130	136	32
5	8	11	142	148	32
6	8	11	146	177	32
-1	9	11	140	126	30
0	9	11	102	91	46
1	9	11	157	120	26
2	9	11	67	94	66
3	9	11	127	130	34
4	9	11	131	157	35
5	9	11	78	98	77
-1	10	11	141	138	31
0	10	11	41	88	40
1	10	11	109	113	48
2	10	11	93	27	65
3	10	11	173	161	27
0	0	12	458	463	13
1	0	12	199	197	8
2	0	12	111	105	22
3	0	12	83	116	36
4	0	12	382	374	9
5	0	12	126	102	25
6	0	12	44	82	44
7	0	12	15	46	15
8	0	12	113	125	40
9	0	12	27	6	27
-9	1	12	0	53	1
-8	1	12	88	132	80
-7	1	12	211	207	17
-6	1	12	193	204	17
-5	1	12	181	158	17
-4	1	12	283	269	11
-3	1	12	183	169	14
-2	1	12	300	304	9
-1	1	12	228	222	13
0	1	12	130	130	12
1	1	12	233	223	18
2	1	12	269	272	9
3	1	12	194	188	13
4	1	12	297	275	10
5	1	12	182	158	17
6	1	12	212	225	16
7	1	12	203	204	18
8	1	12	142	132	29
9	1	12	99	33	55
-1	2	12	379	361	9
0	2	12	211	228	12
1	2	12	402	395	7
2	2	12	193	168	13
3	2	12	369	324	9
4	2	12	252	265	12
5	2	12	281	279	12
6	2	12	219	218	16
7	2	12	263	266	17
8	2	12	187	190	22
9	2	12	35	6	34
-1	3	12	380	368	9
0	3	12	159	150	15
1	3	12	355	354	15
2	3	12	305	298	9
3	3	12	159	138	17
4	3	12	162	159	19
5	3	12	137	128	25
6	3	12	215	211	16
7	3	12	79	65	79
8	3	12	106	105	45
9	3	12	61	50	60
-1	4	12	279	286	11
0	4	12	64	93	63
1	4	12	279	271	10
2	4	12	256	248	11
3	4	12	253	234	12
4	4	12	158	164	20
5	4	12	173	179	19
6	4	12	165	136	22
7	4	12	113	111	40
8	4	12	53	77	52
-1	5	12	273	278	12
0	5	12	225	221	13
1	5	12	291	277	11
2	5	12	73	74	73
3	5	12	352	358	13
4	5	12	74	73	74
5	5	12	73	98	73
6	5	12	130	179	32
7	5	12	124	133	37
8	5	12	112	93	45
-1	6	12	269	259	13
0	6	12	51	65	50
1	6	12	244	242	13
2	6	12	155	175	21
3	6	12	312	283	11
4	6	12	126	97	29
5	6	12	141	135	29
6	6	12	0	64	1
7	6	12	117	143	42
-1	7	12	99	101	40
0	7	12	158	172	22
1	7	12	136	133	25
2	7	12	80	116	72
3	7	12	139	142	26
4	7	12	120	115	33
5	7	12	103	108	50
6	7	12	156	149	27
7	7	12	140	172	35
-1	8	12	117	98	35
0	8	12	260	254	15
1	8	12	103	125	40
2	8	12	0	77	1
3	8	12	146	140	28
4	8	12	183	196	23
5	8	12	50	78	49
6	8	12	24	31	23
-1	9	12	61	44	61
0	9	12	306	317	15
1	9	12	0	43	1
2	9	12	179	182	24
3	9	12	74	70	73
4	9	12	152	190	31
-1	10	12	0	28	1
0	10	12	132	147	37
1	10	12	0	31	1
2	10	12	175	129	27
1	0	13	511	493	10
2	0	13	35	50	34
3	0	13	297	291	10
4	0	13	65	73	64
5	0	13	65	48	65
6	0	13	167	142	20
7	0	13	187	169	19
8	0	13	96	106	57
9	0	13	81	91	81
-9	1	13	171	186	28
-8	1	13	0	38	1
-7	1	13	169	173	23
-6	1	13	75	110	75
-5	1	13	228	232	15
-4	1	13	143	121	21
-3	1	13	297	293	10
-2	1	13	31	66	31
-1	1	13	340	345	7
0	1	13	74	51	26
1	1	13	340	342	24
2	1	13	72	60	54
3	1	13	320	311	9
4	1	13	134	113	23
5	1	13	228	222	14
6	1	13	111	99	33
7	1	13	162	155	23
8	1	13	45	27	45
9	1	13	165	168	28
-1	2	13	365	339	10
0	2	13	270	282	10
1	2	13	346	331	8
2	2	13	234	233	12
3	2	13	322	319	11

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
4	2	13	49	34	49	2	1	14	299	289	10	-3	1	15	116	98	26	-4	1	16	96	100	43	-1	2	17	123	115	29
5	2	13	82	55	55	3	1	14	61	47	61	-2	1	15	254	246	13	-3	1	16	209	209	16	0	2	17	449	468	12
6	2	13	26	35	26	4	1	14	114	111	28	-1	1	15	325	317	8	-2	1	16	263	225	13	1	2	17	92	98	46
7	2	13	0	76	1	5	1	14	83	67	55	0	1	15	105	70	21	-1	1	16	169	176	13	2	2	17	94	135	43
8	2	13	153	114	28	6	1	14	104	121	38	1	1	15	308	315	21	0	1	16	397	407	8	3	2	17	61	80	60
9	2	13	171	155	28	7	1	14	0	37	1	2	1	15	254	250	15	1	1	16	165	185	15	4	2	17	254	236	15
-1	3	13	212	210	13	8	1	14	90	76	71	3	1	15	130	120	25	2	1	16	243	227	13	5	2	17	156	169	28
0	3	13	115	100	25	-1	2	14	127	138	22	4	1	15	109	103	34	3	1	16	171	197	19	6	2	17	71	51	70
1	3	13	246	232	11	0	2	14	79	72	48	5	1	15	177	172	20	4	1	16	26	101	26	7	2	17	0	41	1
2	3	13	241	235	12	1	2	14	110	109	28	6	1	15	151	148	25	5	1	16	0	33	1	-1	3	17	259	265	14
3	3	13	172	136	17	2	2	14	53	65	53	7	1	15	139	139	31	6	1	16	179	198	22	0	3	17	0	29	1
4	3	13	126	154	26	3	2	14	251	231	12	8	1	15	75	92	75	7	1	16	77	51	76	1	3	17	277	271	13
5	3	13	235	226	14	4	2	14	200	198	16	-1	2	15	295	299	11	8	1	16	95	52	69	2	3	17	77	109	76
6	3	13	125	142	31	5	2	14	50	30	50	0	2	15	11	29	10	-1	2	16	367	362	10	3	3	17	100	89	39
7	3	13	148	117	28	6	2	14	146	135	25	1	2	15	308	307	11	0	2	16	290	284	12	4	3	17	29	60	29
8	3	13	84	13	84	7	2	14	116	146	37	2	2	15	0	85	1	1	2	16	346	342	11	5	3	17	105	127	49
-1	4	13	141	139	22	8	2	14	65	44	64	3	2	15	168	180	20	2	2	16	159	150	20	6	3	17	165	171	27
0	4	13	536	536	14	-1	3	14	308	309	11	4	2	15	232	224	14	3	2	16	94	126	44	7	3	17	54	39	53
1	4	13	128	119	23	0	3	14	183	157	16	5	2	15	235	250	16	4	2	16	230	234	15	-1	4	17	168	166	22
2	4	13	116	108	28	1	3	14	369	341	9	6	2	15	127	147	33	5	2	16	112	122	38	0	4	17	134	167	27
3	4	13	103	80	33	2	3	14	71	30	71	7	2	15	39	68	38	6	2	16	78	51	78	1	4	17	168	177	22
4	4	13	336	339	11	3	3	14	450	441	9	8	2	15	49	63	48	7	2	16	116	119	44	2	4	17	0	59	1
5	4	13	69	93	68	4	3	14	143	134	22	-1	3	15	76	59	76	-1	3	16	267	263	13	3	4	17	73	90	72
6	4	13	184	176	20	5	3	14	148	152	24	0	3	15	77	84	76	0	3	16	108	130	33	4	4	17	117	89	36
7	4	13	63	87	63	6	3	14	126	100	30	1	3	15	101	74	34	1	3	16	256	244	13	5	4	17	44	80	43
8	4	13	133	151	34	7	3	14	132	114	33	2	3	15	223	241	15	2	3	16	148	146	23	6	4	17	51	60	50
-1	5	13	45	75	45	8	3	14	0	8	1	3	3	15	127	75	26	3	3	16	144	153	24	-1	5	17	211	204	18
0	5	13	185	196	17	-1	4	14	217	218	15	4	3	15	209	211	17	4	3	16	101	66	41	0	5	17	128	107	30
1	5	13	66	86	66	0	4	14	0	53	1	5	3	15	50	106	49	5	3	16	150	139	27	1	5	17	179	207	22
2	5	13	301	301	11	1	4	14	231	233	14	6	3	15	192	178	20	6	3	16	72	43	71	2	5	17	222	197	18
3	5	13	105	119	34	2	4	14	68	49	67	7	3	15	76	87	75	7	3	16	113	94	44	3	5	17	177	189	22
4	5	13	182	198	18	3	4	14	334	318	11	8	3	15	128	114	39	-1	4	16	195	174	17	4	5	17	129	95	35
5	5	13	91	84	55	4	4	14	8	22	7	-1	4	15	41	42	40	0	4	16	33	63	33	5	5	17	141	93	33
6	5	13	220	223	19	5	4	14	133	137	29	0	4	15	437	437	14	1	4	16	152	154	23	-1	6	17	81	80	80
7	5	13	17	61	16	6	4	14	70	40	70	1	4	15	58	38	58	2	4	16	186	195	19	0	6	17	40	61	40
8	5	13	117	86	44	7	4	14	53	75	52	2	4	15	132	134	25	3	4	16	115	95	34	1	6	17	46	55	46
-1	6	13	214	215	15	8	4	14	31	35	31	3	4	15	81	85	69	4	4	16	116	120	36	2	6	17	144	143	30
0	6	13	141	158	24	-1	5	14	104	90	34	4	4	15	183	183	20	5	4	16	201	186	21	3	6	17	111	104	44
1	6	13	210	201	16	0	5	14	197	198	17	5	4	15	70	60	70	6	4	16	81	81	80	4	6	17	117	97	41
2	6	13	159	151	21	1	5	14	97	86	40	6	4	15	145	113	28	7	4	16	141	121	35	5	6	17	158	164	33
3	6	13	0	46	1	2	5	14	44	64	44	7	4	15	0	65	1	-1	5	16	188	185	19	-1	7	17	120	143	41
4	6	13	206	199	18	3	5	14	299	303	12	-1	5	15	32	77	32	0	5	16	213	213	17	0	7	17	48	66	47
5	6	13	116	88	34	4	5	14	0	45	1	0	5	15	106	79	35	1	5	16	178	183	21	1	7	17	132	132	35
6	6	13	119	111	40	5	5	14	191	165	20	1	5	15	83	81	60	2	5	16	199	178	19	2	7	17	77	80	76
7	6	13	74	32	74	6	5	14	89	81	70	2	5	15	47	20	47	3	5	16	51	76	51	3	7	17	117	107	42
-1	7	13	184	164	19	7	5	14	138	142	35	3	5	15	120	106	31	4	5	16	0	27	1	-1	8	17	118	104	44
0	7	13	285	286	13	-1	6	14	127	119	28	4	5	15	101	84	42	5	5	16	118	122	41	0	8	17	0	32	1
1	7	13	157	154	23	0	6	14	0	75	1	5	5	15	139	138	31	6	5	16	52	19	51	1	8	17	126	98	40
2	7	13	252	256	15	1	6	14	83	81	54	6	5	15	129	126	35	-1	6	16	180	192	21	0	0	18	100	55	40
3	7	13	116	113	36	2	6	14	0	66	1	7	5	15	0	51	1	0	6	16	193	184	21	1	0	18	24	10	24
4	7	13	98	117	51	3	6	14	104	72	40	-1	6	15	231	222	16	1	6	16	217	213	19	2	0	18	107	94	36
5	7	13	109	127	46	4	6	14	99	119	47	0	6	15	306	339	14	2	6	16	240	241	17	3	0	18	130	140	29
6	7	13	113	120	44	5	6	14	194	194	21	1	6	15	235	249	16	3	6	16	61	98	61	4	0	18	177	151	22
-1	8	13	213	199	18	6	6	14	0	73	1	2	6	15	128	88	30	4	6	16	68	89	68	5	0	18	73	55	73
0	8	13	202	200	19	7	6	14	140	155	35	3	6	15	211	201	18	5	6	16	54	62	53	6	0	18	0	4	1
1	8	13	186	180	22	-1	7	14	69	81	69	4	6	15	99	127	49	-1	7	16	117	126	40	-6	1	18	122	79	38
2	8	13	126	114	33	0	7	14	182	197	21	5	6	15	75	85	75	0	7	16	348	360	19	-5	1	18	0	41	1
3	8	13	39	31	39	1	7	14	53	59	52	6	6	15	83	82	82	1	7	16	138	128	30	-4	1	18	111	88	38
4	8	13	63	100	62	2	7	14	238	240	17	-1	7	15	60	99	59	2	7	16	166	163	26	-3	1	18	93	124	48
5	8	13	104	114	55	3	7	14	55	49	54	0	7	15	156	150	26	3	7	16	51	76	51	-2	1	18	161	144	22
-1	9	13	183	177	23	4	7	14	146	122	29	1	7	15	144	128	29	4	7	16	207	221	22	-1	1	18	102	109	26
0	9	13	73	55	73	5	7	14	135	174	35	2	7	15	157	171	26	-1	8	16	0	30	1	0	1	18	206	190	18
1	9	13	170	169	26	6	7	14	130	135	39	3	7	15	101	103	52	0	8	16	123	88	40	1	1	18	73	90	43
2	9	13	0	52	1	-1	8	14	115	111	39	4	7	15	45	89	45	1	8	16	26	19	26	2	1	18	179	141	20
3	9	13	128	133	36	0	8	14	251	262	17	5	7	15	136	120	34	2	8	16	117	83	43	3	1	18	115	133	36
4	9	13	78	49	77	1	8	14	71	105	70	-1	8	15	153	108	28	3	8	16	67	73	66	4	1	18	65	95	65
-1	10	13	55	75	55	2	8	14	241	239	18	0	8	15	141	146	32	1	0	17	286	273	9	5	1	18	56	48	55
0	10	13	109	81	54	3	8	14	94	95	62	1	8	15	125	121	36	2	0	17	169	207	20	6	1	18	95	68	62
1	10	13	114	85	46	4	8	14	310	294	15	2	8	15	69	50	69	3	0	17	46	45	46	-1	2	18	135	127	27
0	0	14	0	37	1	5	8	14	51	53	50	3	8	15	28	103	28	4	0	17	82	81	81	0	2	18	27	21	27
1	0	14	145	152	13	-1	9	14	0	24	1	4	8	15	69	59	69	5	0	17	132	125	31	1	2	18	171	149	21
2	0	14	240	237	12	0	9	14	0	30	1	-1	9	15	113	141	50	6	0	17	42	59	42	2	2	18	183	220	20
3	0	14	126	120	24	1	9	14	77	14	76	0	9	15	20	28	20	7	0	17	0	8	1	3	2	18	155	146	25
4	0	14	402	400	10	2	9	14	186	178	25	1	9	15	125	124	41	-7	1	17	96	74	67	4	2	18	71	86	71
5	0	14	165	168	21	3	9	14	0	21	1	2	9	15	0	74	1	-6	1	17	75	80	75	5	2	18	80	55	79
6	0	14	112	96	34	1	0	15	88	97	25	0	0	16	443	404	9	-5	1	17	54	51	54	6	2	18	0	28	1
7	0	14	0	54	1	2	0	15	242	219	13	1	0	16	183	161	12	-4	1	17	144	153	26	-1	3	18	163	181	23
8	0	14	239	251	18	3	0	15	0	31	1	2	0	16	208	210	16	-3	1	17	139	85	24	0	3	18	0	39	1
-8	1	14	69	74	69	4	0	15	255	267	14	3	0	16	166	174	20	-2	1	17	93	103	44	1	3	18	215	197	17
-7	1	14	81	50	80	5	0	15	164	165	22	4	0	16	169	137	20	-1	1	17	136	156	17	2	3	18	68	62	68
-6	1	14	118	136	34	6	0	15	55	121	55	5	0	16	39	12	38	0	1	17	67	133	59	3	3	18	88	98	60
-5	1	14	37	52	37	7	0	15	123	99	36	6	0	16	0	44	1	1	1	17	144	170	16	4	3	18	165	171	25
-4	1	14	126	109	26	8	0	15	0	47	1	7	0	16	0	13	1	2	1	17	138	121	24	5	3	18	15	60	15
-3	1	14	73	57	73	-6	1	15	97	86	59	8	0	16	122	104	41	3	1	17	106	67	35	6	3	18	125	78	38
-2	1	14	303	304	10	-7	1	15	158	141	26	-8	1	16	44	47	44	4	1	17	169	168	21	-1	4	18	84	61	83
-1	1	14	128	124	15	-6	1	15	149	142	26	-7	1	16	0	64	1	5	1	17	59	68	59	0	4	18	28	32	28
0	1	14	82	69	26	-5	1	15	187	184	19	-6	1	16	203	194	20	6	1	17	0	82	1	1	4	18	116	81	37
1	1	14	131	107	15	-4	1	15	116	111	30	-5	1	16	8	28	7	7	1	17	99	58	55	2	4	18	85	71	72

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
3	4	18	128	108	34	0	1	19	289	280	14	2	5	19	183	153	24	-1	3	20	0	16	1	1	2	21	107	107	47
4	4	18	30	73	30	1	1	19	66	64	65	3	5	19	106	125	52	0	3	20	153	134	28	2	2	21	56	54	56
5	4	18	114	92	43	2	1	19	64	18	63	4	5	19	84	85	84	1	3	20	13	15	13	3	2	21	53	41	52
-1	5	18	137	94	30	3	1	19	155	110	25	-1	6	19	125	131	40	2	3	20	38	35	37	4	2	21	54	23	54
0	5	18	121	120	36	4	1	19	39	97	39	0	6	19	94	70	67	3	3	20	135	109	35	-1	3	21	63	84	62
1	5	18	108	99	44	5	1	19	0	58	1	1	6	19	136	119	35	4	3	20	0	41	1	0	3	21	140	138	34
2	5	18	127	134	34	6	1	19	0	15	1	2	6	19	80	55	79	-1	4	20	64	35	63	1	3	21	77	70	76
3	5	18	35	33	34	-1	2	19	39	17	39	3	6	19	90	56	89	0	4	20	99	78	55	2	3	21	49	35	49
4	5	18	125	125	39	0	2	19	50	146	49	0	0	20	0	53	1	1	4	20	72	32	71	3	3	21	107	84	49
5	5	18	34	69	33	1	2	19	0	29	1	1	0	20	171	198	16	2	4	20	0	29	1	-1	4	21	109	82	48
-1	6	18	106	95	48	2	2	19	0	32	1	2	0	20	0	1	1	3	4	20	91	76	83	0	4	21	32	58	32
0	6	18	189	160	23	3	2	19	66	13	66	3	0	20	126	123	36	4	4	20	0	72	1	1	4	21	94	85	83
1	6	18	92	89	67	4	2	19	122	107	38	4	0	20	0	45	1	-1	5	20	61	50	61	2	4	21	92	60	91
2	6	18	94	88	60	5	2	19	0	77	1	5	0	20	65	76	64	0	5	20	103	126	58	0	0	22	73	65	73
3	6	18	36	43	35	6	2	19	106	122	54	-5	1	20	99	77	61	1	5	20	0	49	1	1	0	22	126	86	26
4	6	18	107	128	54	-1	3	19	143	150	27	-4	1	20	72	5	71	2	5	20	78	19	78	2	0	22	0	47	1
-1	7	18	102	88	60	0	3	19	63	36	62	-3	1	20	78	84	78	3	5	20	87	77	87	3	0	22	122	123	42
0	7	18	69	28	69	1	3	19	99	143	48	-2	1	20	43	39	42	1	0	21	78	49	54	-2	1	22	63	70	63
1	7	18	101	90	59	2	3	19	128	120	33	-1	1	20	66	100	65	2	0	21	43	62	42	-1	1	22	101	85	34
2	7	18	110	107	51	3	3	19	113	72	40	0	1	20	0	42	1	3	0	21	0	42	1	0	1	22	95	82	39
1	0	19	225	203	11	4	3	19	82	81	81	1	1	20	86	85	37	4	0	21	21	14	21	1	1	22	56	88	56
2	0	19	193	185	20	5	3	19	70	46	70	2	1	20	0	40	1	-4	1	21	90	75	89	2	1	22	0	70	1
3	0	19	169	165	25	-1	4	19	119	102	38	3	1	20	140	101	32	-3	1	21	143	123	32	-1	2	22	61	36	60
4	0	19	0	4	1	0	4	19	170	142	24	4	1	20	0	10	1	-2	1	21	75	29	75	0	2	22	80	69	80
5	0	19	47	46	47	1	4	19	115	91	39	5	1	20	95	69	74	-1	1	21	130	124	23	1	2	22	61	46	60
6	0	19	74	108	74	2	4	19	112	112	43	-1	2	20	133	128	31	0	1	21	0	27	1	2	2	22	0	18	1
-6	1	19	0	18	1	3	4	19	99	98	53	0	2	20	91	22	64	1	1	21	131	127	26	-1	3	22	0	22	1
-5	1	19	95	55	62	4	4	19	147	65	31	1	2	20	177	136	23	2	1	21	0	24	1	0	3	22	84	18	83
-4	1	19	104	105	46	5	4	19	81	62	81	2	2	20	62	80	61	3	1	21	151	121	30	1	3	22	0	17	1
-3	1	19	149	119	26	-1	5	19	126	119	36	3	2	20	57	23	57	4	1	21	40	64	40						
-2	1	19	0	8	1	0	5	19	85	50	85	4	2	20	71	27	71	-1	2	21	106	103	46						
-1	1	19	80	55	39	1	5	19	144	123	31	5	2	20	15	14	15	0	2	21	93	41	62						

Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5441-5444, 1996

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Studies on the Total Synthesis of Paraherquamide A. Stereocontrolled, Asymmetric Synthesis of α-Alkyl-β-Hydroxyproline Derivatives

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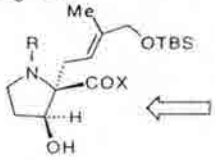
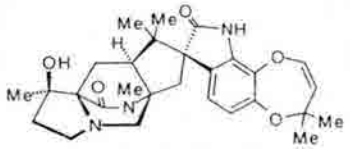
Summary: The dianion formed from 3(S),2(R)-3-hydroxyproline ethyl ester (5) with LDA, can be alkylated with a variety of alkyl halides with net retention of configuration to give the corresponding α-alkylated-β-hydroxyproline esters (6) in good yield. Copyright © 1996 Elsevier Science Ltd

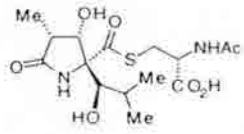
Substituted proline derivatives are widely found as constituents of natural products.[1] For example, the microbial products paraherquamide A (1)[2] and lactacystin (2)[3] contain densely functionalized α-substituted-β-hydroxyproline moieties. As part of a general program[4] aimed at developing new methods to access α-substituted amino acids in high optical purity, we have examined the enolate alkylation of 3(S), 2(R)-3-hydroxyproline ethyl ester (5) which is readily available from racemic 3-ketoproline by Baker's yeast reduction as described by Cooper, Gallagher and Knight.[5] More specifically, ongoing work in these laboratories on the total synthesis of paraherquamide A,[6a] mandated access to a β-functionalized α-prenylated proline derivative corresponding to **1**.



1



2, Paraherquamide A



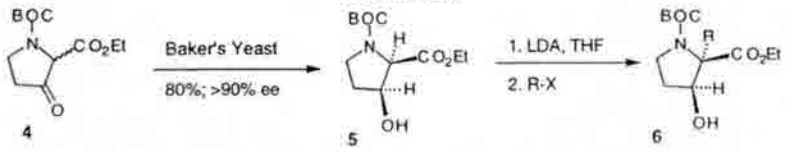
3, Lactacystin

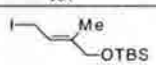
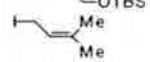
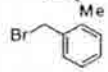
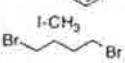
There are no general synthetic methods available for the synthesis of optically active α-substituted-β-hydroxyproline derivatives. Seebach[7] has developed a useful method to α-alkylate proline via formation of the corresponding bicyclic pivaldehyde aminal, followed by enolate alkylation which, proceeds with net retention of configuration; subsequent vigorous hydrolysis of the hindered, α-alkylated bicyclic aminal, provides the corresponding α-substituted proline derivatives in high enantiomeric excess.

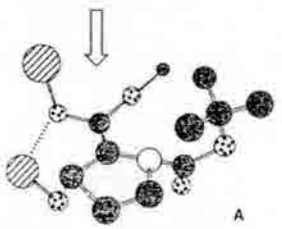
N-Boc-3(S), 2(R)-3-Hydroxyproline ethyl ester (5),[5] made by Baker's yeast reduction of N-Boc-3-ketoproline ethyl ester (4) in >90% ee, was treated with 3 equivalents of LDA at -10°C in THF to form the corresponding alkoxy enolate dianion. The subsequent alkylation was performed by cooling the mixture to -30°C and a mixture of alkyl halide (1.5 eq) and HMPA (1.4 eq) was added. The reaction was allowed to warm to 0 °C and then to 25 °C for 4 hours up to 1-2 days depending on the specific alkyl halide. Following

standard work-up and extraction of the organic-soluble product, the α-alkylated products **6a-e** (Scheme 1) were purified by silica gel chromatography and were obtained in moderate-good yields. In each case, only one diastereomer was formed, and little or no O-mono-alkylated or O-,C-dialkylated by-products were produced.

Scheme 1



Entry	RX	% YIELD of 6
a		70%
b		73%
c		53%
d		57%
e		49% (X-RAY)



For **6c**, **6d**, and **6e**, only the desired C-alkylation product was obtained, and there was no evidence for the production of O-alkylation products. For **6a** and **6b**, there was less than 1-2% of the corresponding O-alkylation products which, were easily removed by chromatography.

These highly stereoselective alkylation reactions all proceeded with net retention of configuration giving single diastereoisomers as evidenced by ^{1}H nmr. The relative stereochemistry of alkylation was rigorously secured through a single crystal X-ray analysis for **6e** (Figure 1). The absolute and relative stereochemistry of **6a** was secured by chemical correlation.[6] The relative and thus, absolute stereochemistry for all alkylation products **6a-e** was assigned based on similarities in nmr spectroscopic characteristics and optical rotation.

The dianion derived from **5** (see structure **A**[8]) is expected to have a concave shape due to the Li-coordinated bicyclo[4.3.0] ring system geometry; alkylation from the convex face opposite the alkoxy substituent is the expected (and observed) diastereofacial bias.

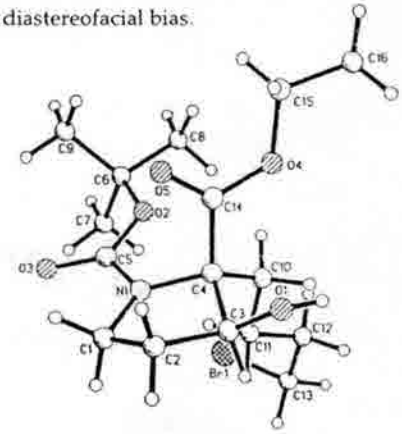


Figure 1. X-ray Structure for **5e**. Spheres are of fixed, arbitrary radius.

General experimental procedure: A solution of **5** (104 mg, 0.4 mmol) in THF (0.4 mL) was cannulated over a period of 2 min. to a magnetically stirred solution of LDA (1.2 mmol, 0.8M solution in THF) at -50°C. The reaction mixture was stirred at -10 °C for 25 min., and then at 0 °C for 5 min. followed by the dropwise addition of a solution of alkylating reagent (0.6 mmol) in HMPA (0.56 mmol) at -30 °C over a period of 2 min. The mixture was stirred at 0°C for about 1 h; the ice bath was then removed and the mixture was allowed to continue stirring at room temperature for 4 h (**6a** and **6b**) or 48h (**6c-e**). The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc (3 x 15 mL), washed with brine (5 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (eluted with hexane:EtOAc:MeOH, 5:3:0.5) to afford **6a-e**.[9-13]

It is noteworthy that, neither β-elimination nor significant O-alkylation attended these transformations. Further, the convenience and simplicity of performing the alkylations directly on substrate **5** without the need for additional protection[6,7] or manipulation should render this approach a highly attractive and general method for synthesizing functionalized pyrrolidine derivatives. The application of this methodology to the total synthesis of paraherquamide A (*via* **6a**), lactacystin and related substituted proline derivatives and pyrrolizidine alkaloids is under active investigation in these laboratories.

Acknowledgment. This work was supported by the National Science Foundation (CHE 9320010) and (in part) by the National Institutes of Health. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS and the Colorado State University Agricultural Experiment Station (USDA SAES Western Project W-122) for partial support of this work.

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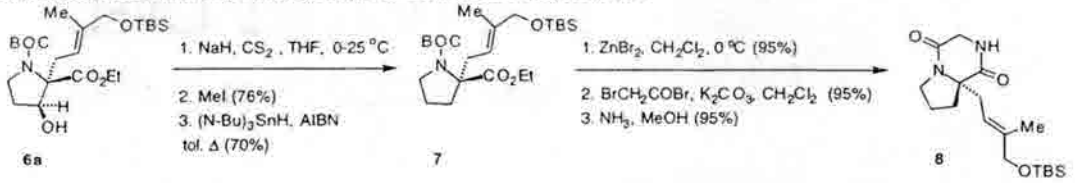
6. (a) Cushing, T.D.; Sanz-Cervera, J.F.; Williams, R.M., *J.Am.Chem.Soc.* **1996**, *118*, 557; The absolute stereochemistry of the overall process was further corroborated by the conversion of **6a** into the bicyclic substance **8** which (as the enantiomer) was previously converted into (+)-paraherquamide B, a substance whose absolute stereochemistry has been confirmed (see ref. 6a); see also: (b) Williams, R.M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J.K., *J.Am.Chem.Soc.* **1990**, *112*, 808:



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8. Structure **A** was minimized and rendered on CSC Chem 3D Plus™.

9. Data for **6a**, colorless oil, yield (70%), $[\alpha]_D^{25}$ -32.2 (C, 0.74, EtOAc). IR(neat): 3449, 2977, 2955, 2928, 2857, 1739, 1703, 1391, 1367, 1251, 837, 774. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01-0.02(6H, m), 0.83-0.84(9H, m), 1.17-1.26(3H, m), 1.32-1.41(9H, m), 1.37-1.70(3H, m), 1.898-1.98(2H, m), 2.74-2.88(2H, m), 3.14-3.19(1H, m), 3.60-3.77(1H, m), 3.94(2H, s), 4.02-4.22(3H, m), 5.25-5.29(1H, m). ^{13}C NMR (75.47MHz, $CDCl_3$) δ -5.1, 14.0, 14.1, 14.3, 14.4, 18.5, 22.0, 26.0, 28.4, 28.5, 30.2, 30.4, 31.1, 31.4, 44.9, 45.4, 61.3, 68.1, 68.4, 71.2, 71.7, 76.5, 76.8, 79.6, 80.4, 117.7, 118.1, 138.2, 138.6, 153.8, 172.3. Anal. Calcd. for $C_{23}H_{43}NO_6Si$: C, 60.36; H, 9.47; N, 3.06. Found: C, 60.17; H, 9.30; N, 3.05. (reaction scale: 1.67 g of 5).

10. Data for **6b**, colorless oil, yield (73%), $[\alpha]_D^{25}$ -48.2 (C, 0.98, EtOAc). IR(neat): 3447, 2972, 2930, 2873, 1743, 1699, 1668, 1391, 1170, 1137. ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.22-1.29(3H, m), 1.34-1.37(9H, m), 1.53-1.65(6H, m), 1.84-2.01(2H, m), 2.70-2.91(3H, m), 3.10-3.19(1H, m), 3.57-3.77(1H, m), 4.03-4.19(3H, m), 4.92-4.94(1H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 18.3, 18.5, 26.3, 26.4, 28.5, 28.6, 30.6, 30.9, 31.3, 31.8, 45.0, 45.6, 61.4, 71.4, 71.9, 76.5, 79.7, 80.5, 118.4, 118.7, 135.8, 135.9, 154.0, 154.1, 172.3, 172.4. Anal. Calcd. for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.19; H, 9.03; N, 4.27. (reaction scale: 312 mg of 5).

11. Data for **6c**, colorless oil, yield (53%), $[\alpha]_D^{25}$ -77.6 (C, 0.59, EtOAc). IR(neat): 3446, 3085, 3062, 3030, 2979, 2881, 1732, 1693, 1681, 1392, 1367, 1167. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.31(3H, m), 1.38-1.46(1H, m), 1.48(9H, s), 2.66(1H, broad), 2.70-2.80(1H, m), 3.22-3.27(1H, m), 3.54-3.81(2H, m), 4.11-4.19(1H, m), 4.23-4.31(2H, m), 7.11-7.27(5H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.41, 14.46, 28.6, 30.5, 30.9, 36.8, 37.8, 45.0, 45.3, 60.6, 61.6, 72.2, 72.5, 75.9, 79.9, 80.8, 126.7, 126.9, 128.3, 128.5, 130.8, 130.9, 136.5, 136.8, 153.9, 154.2, 169.5, 172.1. Anal. Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.15; H, 7.69; N, 3.87. (reaction scale: 104 mg of 5).

12. Data for **6d**, colorless oil, yield (57%), $[\alpha]_D^{25}$ -3.9 (C, 0.54, EtOAc). IR(neat): 3443, 2980, 2936, 1746, 1731, 1698, 1391, 1167, 1094. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18-1.26(3H, m), 1.36-1.41(9H, m), 1.52-1.56(3H, m), 1.89-1.96(1H, m), 2.00-2.08(1H, m), 2.83(1H, broad), 3.33-3.14(1H, m), 3.65-3.71(1H, m), 4.05-4.21(3H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.4, 21.6, 22.6, 28.5, 28.6, 30.8, 31.4, 61.5, 69.1, 79.8, 80.0, 80.4, 81.1, 154.1, 172.3. Anal. Calcd. for $C_{13}H_{23}NO_5$: C. 57.13; H, 8.48; N, 5.12. Found: C, 56.92; H, 8.28; N, 5.05. (reaction scale: 104 mg of 5).

13. Data for **6e**, white powder, yield (49%), $[\alpha]_D^{25}$ -22.8 (C, 0.54, EtOAc). IR(neat): 3438, 2973, 2934, 2875, 1735, 1696, 1672, 1383, 1366, 1246, 1168, 772. ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.21-1.24(3H, m), 1.28-1.40(2H, m), 1.32-1.40(9H, m), 1.83-2.18(6H, m), 2.62(1H, broad), 3.22-3.28(1H, m), 3.36-3.41(1H, t J=6.5Hz), 3.65-3.75(1H, m), 4.06-4.22(2H, m), 4.24-4.30(1H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.4, 21.9, 22.1, 28.5, 30.6, 31.2, 32.4, 32.7, 32.9, 33.6, 34.0, 45.0, 45.5, 61.4, 71.0, 76.6, 76.8, 79.9, 80.5, 154.0, 172.3. Anal. Calcd. for $C_{16}H_{28}BrNO_5$: C, 48.74; H, 7.16; N, 3.55. Found: C, 48.90; H, 7.31; N,3.60. (reaction scale 104 mg of 5).

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Asymmetric Synthesis of 2,6-Diamino-6-(hydroxymethyl)pimelic Acid: Assignment of Stereochemistry

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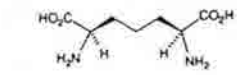
Abstract: The asymmetric synthesis of (2*S*,6*R*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**17**) and (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**) has been accomplished. Sequential enolate alkylation of (5*S*,6*R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**9**) with 1-iodo-3-butene and bromomethyl methyl ether gave the α,α-disubstituted lactone in ~100% de; subsequent ozonolysis gave the quaternary aldehyde **19**. Aldol condensation with the enol borane of (5*S*,6*R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**9**) gave the dilactone **20**. Barton deoxygenation, reductive cleavage of the oxazinones, and demethylation gave (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**). Synthesis of the 2*S*,6*R* isomer followed the same protocol, only starting with (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**5**). Comparison of these two amino acids reveals that the 2*S*,6*S* isomer **4** is the constituent of natural *N*-[2,6-diamino-6-(hydroxymethyl)pimel-1-yl]-L-alanine (**3**), a natural antibiotic produced by *Micromonospora chalcea*.

Introduction

2,6-Diaminopimelic acid (**1**, DAP) is an important, naturally occurring amino acid biosynthesized in bacteria and higher plants.[1] L,L- and *meso*-DAP serve as the penultimate biosynthetic precursors of the essential amino acid L-lysine. *meso*-DAP functions as a cross-linking constituent of virtually all Gram-negative and some Gram-positive bacterial peptidoglycans, and also serves to anchor various membrane-associated macromolecules, such as lipoprotein, to the cell wall. Recognition of the pivotal roles DAP plays in microbial metabolism[2] and cell wall structure has resulted in an increased level of interest in possible means to selectively disrupt the DAP biosynthetic pathway. A flurry of recent papers[3] on the synthesis of DAP and, more significantly, structural analogues of DAP that can function as substrate-based inhibitors of key biosynthetic transformations attests to the potential importance of the DAP/lysine pathway as a viable target for antibiotic design. Recent studies in several laboratories demonstrate that a number of compounds that inhibit the formation or metabolism of 2,6-diaminopimelic acid in bacteria possess antibiotic activity.[4] Since mammals lack the diaminopimelate pathway and require L-lysine in their diet,[5] specific inhibitors of the enzymes along this route are potential antimicrobial agents that should display low mammalian host toxicity.

Despite the apparent simplicity of this amino acid, there exist no stereochemically unambiguous syntheses of *meso*-DAP nor asymmetric synthesis of L,L-DAP. Two very recent exceptions



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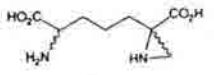

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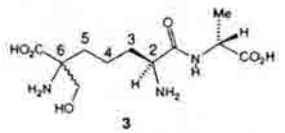

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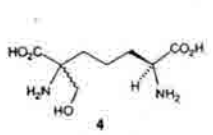

4

are the synthesis of β-fluoro DAP by Vederas and Gelb[6a] and β-hydroxy DAP by Bold and associates.[6b] The potential importance of inhibiting the DAP pathway through the design and synthesis of functionalized DAP analogues renders this class of amino acids an attractive and worthy synthetic problem. A recent example is the (stereorandom) preparation of the aziridino DAP **2** that was shown[7] to be a potent inhibitor of L,L-DAP epimerase and exhibits antimicrobial activity. In this paper, we report a stereochemically unambiguous asymmetric synthesis of two stereoisomers of the only known natural DAP homologue, 2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**).[8]

N-[2,6-Diamino-6-(hydroxymethyl)pimel-1-yl]-L-alanine (**3**) was isolated from the culture extracts of a microorganism identified as *Micromonospora chalcea* by the Shionogi Co. in Japan.[8] The dipeptide **3** exhibits limited antimicrobial activity against *Escherichia coli* on a synthetic medium, and this activity is synergistically enhanced by several cell wall synthesis inhibitors such as penicillin G, phosphonomycin, cycloserine, chloro-D-alanine, macarbomycin, and cephaloridine.

The structure of **3** was determined by spectroscopic methods and chemical degradation.[8] The natural substance was assumed to be a dipeptide composed of an unknown amino acid and alanine. This was established by hydrolysis and subsequent analysis of the hydrolysate by an automatic amino acid analyzer. Specific optical rotation and ORD spectra proved that the alanine isolated from the hydrolysate has the L configuration. Elemental analysis indicated that the molecular formula of the unknown amino acid is $C_8H_{16}N_2O_5$. Furthermore, ^1H and ^{13}C NMR spectroscopic data

(1) Patte, J.-C. In *Amino Acids: Biosynthesis and Genetic Regulation*; Hermann, K. M., Somerville, R. L., Eds.; Addison-Wesley: Reading, MA, 1983; pp 213–218.

(2) Certain bacteria bypass the L,L form of DAP by means of *meso*-DAP D-dehydrogenase: (a) Bartlett, A. T. M.; White, P. J. *J. Gen. Microbiol.* **1985**, *131*, 2145. (b) Misono, H.; Ogasawara, M.; Nagasaki, S. *Agric. Biol. Chem.* **1986**, *50*, 2729.

(3) (a) Berges, D. A.; Dewolf, W. E., Jr.; Dunn, G. L.; Grappel, S. F.; Newman, D. J.; Taggart, J. J.; Gilvarg, C. *J. Med. Chem.* **1986**, *29*, 89. (b) Berges, D. A.; DeWolf, W. E., Jr.; Dunn, G. L.; Newman, D. J.; Schmidt, S. J.; Taggart, J. J.; Gilvarg, C. *J. Biol. Chem.* **1986**, *261*, 6160. (c) Kelland, J. G.; Arnold, L. D.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1986**, *261*, 13216. (d) Girodeau, J.-M.; Agouridas, C.; Masson, M.; Pineau, R.; LeGoffic, F. *J. Med. Chem.* **1986**, *29*, 1023. (e) Lam, L. K. P.; Arnold, L. D.; Kalantar, T. H.; Kelland, J. G.; Lane-Bell, P. M.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1988**, *263*, 11814. (f) Baumann, R. J.; Bohme, E. H.; Wiseman, J. S.; Vaal, M.; Nichols, J. S. *Antimicrob. Agents Chemother.* **1988**, *32*, 1119. (g) Bohme, E. H.; Gerhart, F.; Higgins, W. U.S. Patent 4,7300,006, 1988.

(4) See also references in: Lin, Y.; Myhrman, R.; Schrag, M. L.; Gelb, M. H. *J. Biol. Chem.* **1988**, *263*, 1622.

(5) Jouanneau, J.; Stragier, P.; Bouvier, J.; Patte, J.-C.; Yaniv, M. *Eur. J. Biochem.* **1985**, *146*, 173 and references therein.

(6) (a) Gelb, M. H.; Lin, Y.; Pickard, M. A.; Song, Y.; Vederas, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4932. (b) Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 497.

(7) Gerhart, F.; Higgins, W.; Tardif, C.; Ducep, J.-B. *J. Med. Chem.* **1990**, *33*, 2157.

(8) Shoji, J.; Hinoo, H.; Kato, T.; Nakauchi, K.; Matsuura, S.; Mayama, M.; Yasuda, Y.; Kawamura, Y. *J. Antibiot.* **1981**, *34*, 374.

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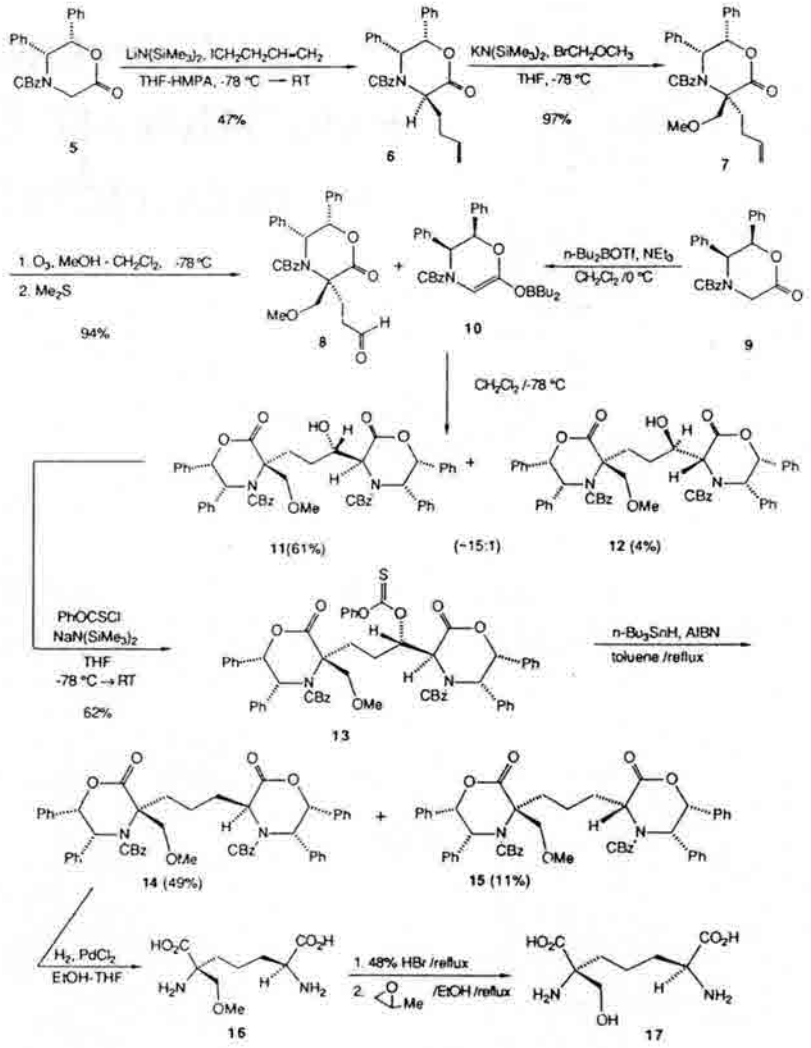
Scheme I



suggested that the unknown amino acid should be 2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**). This was further corroborated by chemical degradation. Amino acid **4** was acetylated with acetic anhydride in a dilute sodium bicarbonate solution, and then treated sequentially with $NaIO_4$ in a dilute alkaline solution followed by oxidation with $KMnO_4$; subsequent hydrolysis furnished L-α-aminoadipic acid. Thus, the new amino acid proved to be 2,6-diamino-6-(hydroxymethyl)pimelic acid with the L configuration at the C-2 stereogenic center. Employment of the Scheinblatt method[9] established the connectivity shown in **3**. However, the relative and absolute stereochemistry at C-6 remained unknown.

In spite of the weak biological activity exhibited by **3**, we decided to synthesize this natural product in a stereochemically unambiguous manner. In this way, we hoped to be able to assign the stereochemistry at C-6 and develop methodology that would be generally applicable to the 2,6-diaminopimelic acid (DAP) family of amino acids. In addition, **4** and stereoisomeric derivatives would appear to be ideal precursors for unambiguously preparing all individual stereoisomers of the biologically active aziridine **2**.

(9) Scheinblatt, M. *J. Am. Chem. Soc.* **1966**, *88*, 2845.

Results and Discussion

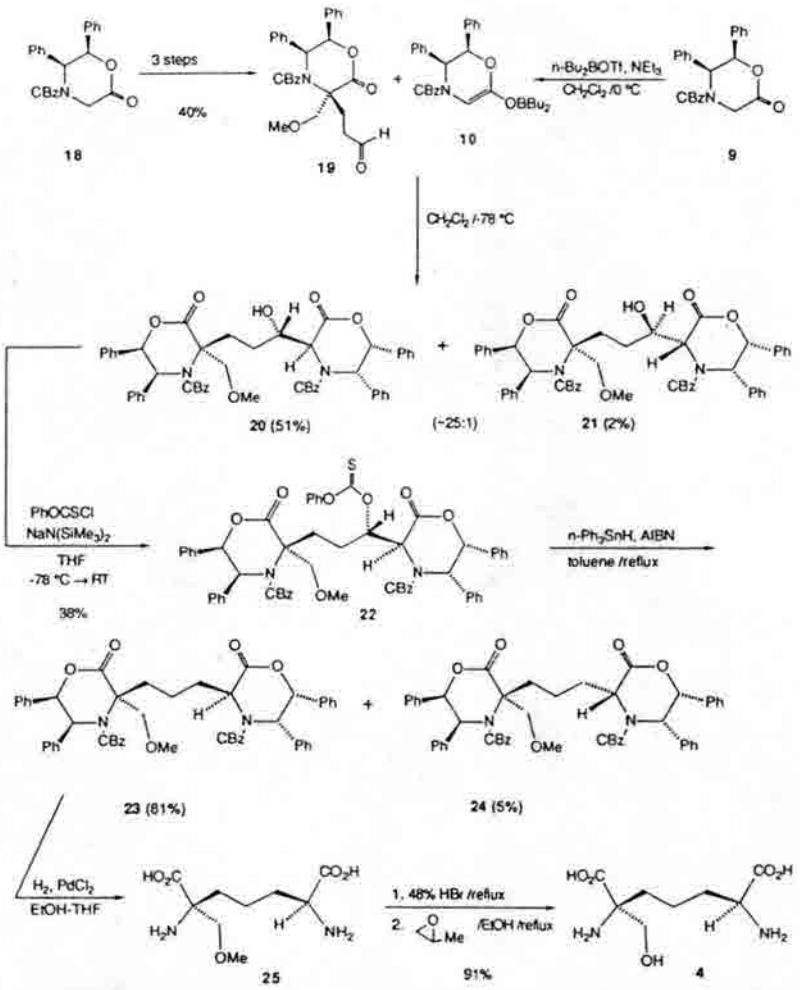
We have previously reported[10] on the utility of the diphenyloxazinones **5** as versatile templates from which both electrophilic[11] and nucleophilic[12] C–C bond-forming strategies can be employed to access a variety of nonproteinogenic α-amino acids. In selecting a strategy to accomplish the key coupling of two optically pure glycinates to a three-carbon tether, we examined a variety of C–C

(10) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

(11) (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (c) Sinclair, P. J. Ph.D. Thesis, Colorado State University, Fort Collins, CO, 1987. (d) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021. (e) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482. (f) Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425. (g) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. (h) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.

(12) (a) Williams, R. M.; Im, M.-N. *Tetrahedron Le.*. **1989**, *29*, 6075. (b) Details of dialkylations of **5** and **9** and the X-ray crystal structure of a dialkylation product (from **9**, alkylating sequentially with methyl iodide and benzyl bromide) will be published elsewhere: Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.*, in press.

Scheme II



bond-forming reactions between two oxazinones, one carrying the activated three-carbon tether and the other, unsubstituted. Attempted enolate couplings to various 3′-halo derivatives all met with complete failure. Similarly, attempted electrophilic couplings between metallo-alkynylated[11f] substrates also failed to give the desired homologations. Finally, we found that employment of the enol borane aldol couplings reported by Miller[13] on these oxazinone systems proved to be effective. Initially, we attempted to synthesize the 2*S*,6*R* isomer. As shown in Scheme I, the commercially available[14] lactone **5** was treated with homoallyl iodide in the presence of lithium bis(trimethylsilyl)amide to give the homoallyloxazinone **6** in 47% yield. After extensive experimentation, it was found that enolate alkylation of **6** could be carried out in high yield by the following procedure. To a solution of **6** in THF at −78 °C was added potassium bis(trimethylsilyl)amide; after 5 min, bromomethyl methyl ether was added. The (methoxymethyl)homoallyloxazinone **7** was obtained in 97% yield (~100% de) after chromatography. We could not detect any of the epimeric alkylation product in the crude reaction mixture by ^{1}H NMR analysis. Approach of the electrophile to the least hindered face of the enolate has been corroborated[12h] through single-crystal X-ray analysis of a related dialkylation on **5**. The homologated oxazinone **7** was ozonized and then quenched with dimethyl sulfide to afford the aldehyde **8** in 94% yield.

Preparation of the boron enolate of **9** according to Miller[13] followed by aldol condensation with the aldehyde **8** gave the β-hydroxy dilactone **11** (61%) as the major product and **12** (4%) as the minor product. It is assumed that the relative stereochemistry of the minor diastereomer **12** at the α-position is syn to the two phenyl rings (*R*) because of the characteristic[11c] relative difference in chemical shifts of methine protons at the benzylic positions of the oxazinone ring. For the anti diastereomer **11**, the difference in chemical shift (Δδ) for the benzylic methines in the monosubstituted lactone ring is 1.26 ppm while Δδ for the syn diastereomer **12** is 0.47 ppm. This assignment is based on the additional assumption that both the syn and anti diastereomers have similar chemical shift differences for the methines in the quaternary lactone system. These relative chemical shift differences are in accord with empirical observations first discussed by Sinclair.[11c] Although ultimately unimportant for the synthesis of **4**, the diastereoselectivity of the aldol condensation appears to be excellent. Out of a total of four possible diastereoisomers, only two were observable in the crude reaction mixture. The small vicinal coupling constants (~1.9 Hz) for the C-2/C-3 (DAP numbering) methines for each diastereomer (**11** and **12**) are in

(13) Reno, D. S.; Lotz, B. T.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 827.

(14) Lactones **5** and **9** are commercially available from Aldrich Chemical Co.; **5**: catalog # 33, 185-6; **9**: catalog # 33, 187-2.

accord with the anti selectivity observed by Miller[13] in related aldolizations.

Next, we examined reductive functional transformation of the β-hydroxy group to obtain the requisite deoxygenation product. This proved to be very difficult since this alcohol moiety is very hindered and is prone to α,β-elimination. Many attempts at activating the hydroxyl for hydride displacement resulted in either no reaction or α,β-dehydrogenation.[15]

After examining a multitude of reductive activation possibilities, we established conditions to prepare a Barton reaction[16] precursor. As shown in Scheme I, treatment of the alcohol **11** with phenyl chlorothionoformate in the presence of sodium bis(trimethylsilyl)amide furnished the thionoformate **13** in 62% yield. Standard procedures[17] to prepare phenyl thionoformates afforded either the α,β-unsaturated lactone or unreacted starting material, depending on the reaction conditions. Several attempts to prepare other Barton reaction precursors failed, leading to no reaction. Among several bases examined (nBuLi, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$), sodium bis(trimethylsilyl)amide gave the best result for the conversion of **11** to **13**.

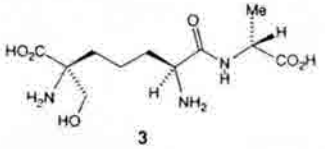
The reduction of **13** with tributyltin hydride in the presence of AIBN in refluxing toluene provided the deoxygenated product **14** in 60% yield along with an epimer **15** in 15% yield (major:minor ~5:1). Formation of the unexpected minor isomer **15** can be explained mechanistically as follows: the initially formed secondary β-radical from tin hydride removal of the thionoformate is quenched with tributyltin hydride to afford the major diastereomer **14**. However, a more stable tertiary radical at the α-position of the monosubstituted lactone can be formed by two pathways: (1) 1,2-hydrogen migration of the β-radical, or (2) abstraction of the α-hydrogen in the initially formed dilactone **14** by the secondary β-radical or from a stannane radical. Hydrogen-atom transfer from tributyltin hydride to the putative tertiary radical is expected to proceed from the least hindered face (anti to the phenyl rings), leading to the minor product **5**. It is unlikely that 1,2 hydrogen atom migration occurs because this process is not allowed by orbital symmetry theory. The latter explanation is therefore the most plausible.

Finally, **14** was smoothly converted into (2*S*,6*R*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**17**). Dilactone **14** was hydrogenated to give the amino acid **16**, which was directly converted into **17** in 95% yield by demethylation in refluxing 48% HBr and subsequent scavenging of HBr with propylene oxide in refluxing ethanol.

Measurement of the specific optical rotation of **17** indicates that the 6*R* stereochemistry is not that of the natural amino acid $[\alpha]^{25}_D$ +22.5° (*c* 0.6, 5 N HCl), lit.[8] $[\alpha]^{25}_D$ +8.1 ± 1.0° (*c* 0.506, 5 N HCl)]. Since the stereochemistry at C-2 of the natural product had been assigned by the oxidative degradation to L-α-aminoadipic acid, preparation of the 2*S*,6*S* isomer starting with the antipodal lactone **18** (Scheme II) was carried out.

Following the identical protocol used to prepare **7**, the antipodal quaternary lactone aldehyde **19** was prepared. As shown in Scheme II, aldol condensation of **10** with **19** provided the hydroxy dilactone **20** as the major diastereomer (51%) plus **21** as the minor isomer (2%). Again, as in the case above for **11** and **12**, excellent diastereoselectivity in the aldol reaction was observed. The vicinal coupling constants for the C-2/C-3 system were 0 and 2.4 Hz for **20** and **21**, respectively. We could not detect the corresponding anti (aldol) diastereomers in the crude reaction mixture by NMR analysis. Both sets of aldolizations support a Zimmerman–Traxler chair-type transition state predominantly from the face of the oxazinone anti to the two phenyl rings with the aldehyde methine oriented toward the inside of the oxazinone ring. The major isomer **20** was converted into the thionoformate **22** by the method described above for **13**. The reduction of **22** with tributyltin hydride gave the dilactone **23** (60%), and the minor syn isomer **24** was obtained in 10% yield. Employment of triphenyltin hydride instead of tri-*n*-butyltin hydride enhanced the yield of reduction, giving the major isomer **23** in 81% yield and the minor isomer **24** in 5%. Catalytic hydrogenolysis and demethylation produced (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**) in 91% overall yield from **23**. Measurement of the specific rotation of synthetic **4** demonstrates that the natural product possesses the 2*S*,6*S* relative and absolute stereochemistry $[[\alpha]^{25}_D$ +7.1° (*c* 0.55, 5 N HCl) lit.[8] $[\alpha]^{25}_D$ +8.1 ± 1.0° (*c* 0.506, 5 N HCl)]. The synthetic amino acid **4** proved to be identical (^{1}H NMR, TLC) with an authentic sample of **4** obtained from hydrolytic cleavage[18] of the natural product **3** obtained from Shionogi & Co. Since the diastereochemical purity of **19** is ca. 100% de, the enantiomeric purity of the synthetic amino acid **4** is similarly ca. 100% ee.

Thus the complete stereostructure for the natural dipeptide **3** is (2*S*,6*S*)-*N*-(2,6-diamino-6-(hydroxymethyl)pimel-1-yl)-L-alanine:



3

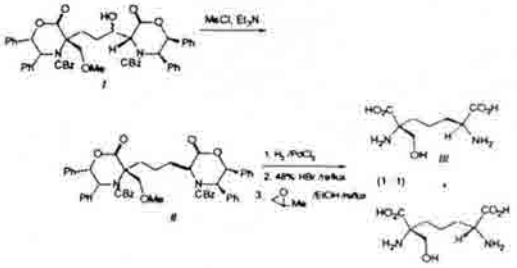
We have examined the biological activity of both amino acids **4** and **17** against nine microorganisms (*Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Candida albicans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae*, and *Seratia marcescens*) and find that neither compound displays significant antimicrobial activity up to 1 mg/mL.

In summary, we have developed an asymmetric and stereochemically defined construction of an α-functionalized diaminopimelic acid system and have assigned, through total synthesis, the stereochemistry at the quaternary center of the natural product **3**. The availability[14] of both optical antipodes of the oxazinone systems renders this chemistry adaptable to preparing all possible diastereoisomers of substances based on the DAP skeleton in optically pure form. Efforts to extend this methodology to construct other functionalized DAP systems, particularly those with potential antimicrobial activity, are being pursued in these laboratories and will be reported on in due course.

Experimental Section

General Information. ^{1}H NMR spectra were obtained on the following instruments: Brucker WP-200SY 200-MHz spectrometer, Brucker WP-270S 270-MHz spectrometer, or Brucker AC 300-MHz spectrometer. ^{19}F NMR spectra were recorded on the Brucker WP-200 SY 200 MHz spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on

(15) The reaction of i with mesyl chloride in the presence of triethylamine and subsequent treatment with excess triethylamine furnished the alkene ii. Unfortunately, sequential hydrogenation, hydrolytic deprotection of the methyl ether, and scavenging of acid with propylene oxide produced the amino acids iii and iv as a 1:1 *mixture* of diastereomers.



(16) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

(17) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. **1983**, *105*, 4059.

(18) Natural **3** was hydrolyzed and separated according to the procedure detailed in reference 8 to provide an authentic comparison sample of **4**.

Perkin-Elmer 1600 Series FTIR and are reported as λ_{max} in cm^{-1}. Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at wavelength 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1 mL. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specified temperature and the concentration (c) given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are accurate to within the calculated values by ±0.4%. High-resolution mass spectra were carried out by Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska—Lincoln, Lincoln, NE. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel glass plates. Visualization on TLC was achieved with ultraviolet light, an I_2 developing chamber, and/or heating of TLC plates submerged in a 5% solution of phosphomolybdic acid in 95% ethanol. Preparative chromatography was performed by the following methods. Column chromatography was performed with Merck silica gel grade 60, 230–400 mesh, 60 Å. Radial chromatography was done on 1-, 2-, and 4-mm silica gel plates using E. Merck silica gel 60 PF-254 containing gypsum on a Harrison Research Chromatotron Model 7924. Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dry methylene chloride and carbon tetrachloride were obtained by distillation over CaH_2. DMF and HMPA were dried over activated 4-Å molecular sieves. All moisture-sensitive reactions were carried out in glassware that was flame-dried under high vacuum (0.5–2.0 mmHg) and then purged with N_2. The term "concentrated" refers to solvent removal using a Buchi Rotavapor. The amino acids furnished crude from the hydrogenation were always obtained in greater than the theoretical amount due to a certain fraction of HCl salt resulting from the $PdCl_2$ catalyst. To ascertain the exact amount of amino acid by weight in the residue, the mixture was dissolved in D_2O with a known amount of terleucine (purity titrated against ultrapure acetamide), and ^1H NMR integration of a well-resolved resonance of the amino acid against the nine-proton singlet of terleucine was carried out, averaged, and calculated to give the adjusted chemical yields.

(3*S*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3′-butenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (6). To a stirred solution of **5** (3 g, 7.744 mmol, 1 equiv) and 4-iodobutene (4.2 mL, 39.35 mmol, 5.1 equiv) in warm THF (90 mL) and HMPA (9 mL) was added lithium bis(trimethylsilyl)amide (13.9 mL, 13.9 mmol, 1.8 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 10 min the dry ice bath was removed. After an additional 1 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 1.59 g (46.5%) of **6** as a white solid. The antipode was obtained from **9** in 48.5% yield. Data for **6**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.18–2.31 (4 H, m), 4.81–5.16 (5 H, m), 5.27 (1 H, d, J = 2.93 Hz), 5.77–5.95 (1 H, m), 6.22 (1 H, d, J = 3.02 Hz), 6.54–6.59 (2 H, m), 7.02–7.24 (13 H, m); IR (NaCl, CH_2Cl_2) 1747, 1704 cm^{-1}; mp 146–147 °C; $[\alpha]^{25}_D$ +44.1° (c 0.49, CH_2Cl_2), antipode (from **9**) −45.2° (c 0.42, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.17; N, 3.17. Found: C, 76.07; H, 6.36; N, 3.20.

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3′-butenyl)-3-(methoxymethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7). To a stirred solution of **6** (1.1 g, 2.49 mmol, 1 equiv) in THF (15 mL) was added potassium bis(trimethylsilyl)amide (8.9 mL, 12.46 mmol, 5 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 5 min bromomethyl methyl ether (2 mL, 24.9 mmol, 10 equiv) was added to the reaction mixture at −78 °C. After an additional 50 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 1.17 g (96.7%) of **7** as a colorless oil. The antipode was obtained in 88.5% yield. Data for **7**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.29–1.43 (1 H, m), 1.51–1.70 (1 H, m), 2.09–2.38 (2 H, m), 3.32 (3 H, s), 3.64 (1 H, $^1/_2$ AB q, J = 9.76 Hz), 4.37 (1 H, $^1/_2$ Ab q, J = 9.79 Hz), 4.65–4.79 (2 H, m), 5.15 (1 H, $^1/_2$ AB q, J = 12.31 Hz), 5.24 (1 H, $^1/_2$ AB q, J = 12.07 Hz), 5.41–5.64 (1 H, m), 5.72 (1 H, d, J = 3.32 Hz), 6.35 (1 H, d, J = 3.28 Hz), 7.07–7.31 (15 H, m); IR (NaCl, CH_2Cl_2) 1746, 1702 cm^{-1}; $[\alpha]^{25}_D$ −49.4° (c 0.35, CH_2Cl_2), antipode +48.7° (c 0.39, CH_2Cl_2); exact mass (FAB) calcd for $C_{30}H_{31}NO_5Li$ 492.236228, found 492.2381.

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(2′-carbonylethyl)-3-(methoxymethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8). Ozone was bubbled through a solution of **7** (316 mg, 0.651 mmol, 1 equiv) in MeOH–CH_2Cl_2 (10 mL, 1:1) until the solution turned blue (ca. 5 min). Nitrogen gas was then passed through the reaction mixture to remove excess ozone until the solution became colorless. The resulting solution was quenched with excess dimethyl sulfide. After 15 h the reaction mixture was concentrated and separated by radial chromatography on silica gel to afford 319 mg (96%) of **8** as a colorless oil. The antipode **19** was obtained in 94% yield. Data for **8**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.69–1.84 (1 H, m), 1.95–2.10 (1 H, m), 2.28–2.60 (2 H, m), 3.32 (3 H, s), 3.68 (1 H, $^1/_2$ AB q, J = 9.79 Hz), 4.38 (1 H, $^1/_2$ AB q, J = 9.81 Hz), 5.14 (1 H, $^1/_2$ AB q, J = 12.35 Hz), 5.24 (1 H, $^1/_2$ AB q, J = 12.35 Hz), 5.72 (1 H, d, J = 3.40 Hz), 6.35 (1 H, d, J = 3.44 Hz), 7.14–7.32 (15 H, m), 9.32 (1 H, s); IR (NaCl, CH_2Cl_2) 1745, 1722 (shoulder), 1701 cm^{-1}; $[\alpha]^{25}_D$ −79.9° (c 1.2, CH_2Cl_2), antipode **19** +80.4° (c 0.7, CH_2Cl_2); exact mass (FAB) calcd for $C_{29}H_{30}NO_6$ 488.207314 (M^+ + H), found 488.2070.

Aldol Adducts 11 and 12. To a stirred solution of **9** (445 mg, 1.15 mmol, 1 equiv) in CH_2Cl_2 (8 mL) was added dibutylboron triflate (2.3 mL, 2.30 mmol, 2 equiv, 1 M solution in CH_2Cl_2) followed by the addition of triethylamine (320 mL, 2.30 mmol, 2 equiv) at 0 °C. After 20 min the reaction mixture was cooled to −78 °C and a CH_2Cl_2 (11 mL) solution of aldehyde **8** (1.12 g, 2.297 mmol, 2 equiv) was added to it. After 30 min the reaction mixture was quenched with phosphate buffer solution (0.025 M, pH 6.9) and poured into water. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 613 mg (61%) of **11** as a white solid and 41 mg (4%) of **12** as a white solid.

11: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.32–1.55 (2 H, m), 2.36–2.47 (2 H, m), 3.34 (3 H, s), 3.65 (1 H, $^1/_2$ AB q, J = 9.86 Hz), 3.89–3.99 (1 H, m), 4.38 (1 H, $^1/_2$ AB q, J = 9.74 Hz), 4.52 (1 H, d, J = 1.89 Hz), 4.89 (1 H, $^1/_2$ AB q, J = 12.66 Hz), 4.98 (1 H, $^1/_2$ AB q, J = 12.52 Hz), 5.11 (1 H, $^1/_2$ AB q, J = 12.47 Hz), 5.18 (1 H, d, J = 3.21 Hz), 5.23 (1 H, $^1/_2$ AB q, J = 12.39 Hz), 5.56 (1 H, d, D_2O exch, J = 5.23 Hz), 5.63 (1 H, d, J = 3.59 Hz), 6.36 (1 H, d, J = 3.50 Hz), 6.44 (1 H, d, J = 3.14 Hz), 6.52 (2 H, d, J = 6.76 Hz), 6.93–7.34 (28 H, m); IR (NaCl, CH_2Cl_2) 3474, 1749, 1704 cm^{-1}; mp 123–125 °C; $[\alpha]^{25}_D$ −7.9° (c, 0.92, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{53}H_{50}N_2O_{10}$: C, 72.76; H, 5.76; N, 3.20. Found: C, 72.94; H, 6.02; N, 3.02.

12: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.41–1.59 (2 H, m), 1.96–2.11 (1 H, m), 2.39–2.55 (1 H, m), 3.35 (3 H, s), 3.54 (1 H, $^1/_2$ AB q, J = 9.78 Hz), 3.63–3.71 (1 H, m), 3.91 (1 H, d, D_2O exch, J = 4.79 Hz), 4.33 (1 H, $^1/_2$ AB q, J = 9.82 Hz), 4.58 (1 H, d, J = 1.96 Hz), 5.11 (1 H, $^1/_2$ AB q, J = 12.31 Hz), 5.13 (1 H, $^1/_2$ AB q, J = 12.43 Hz), 5.20 (1 H, $^1/_2$ AB q, J = 12.39 Hz), 5.22 (1 H, $^1/_2$ AB q, J = 12.33 Hz), 5.61 (2 H, d, J = 3.23 Hz), 6.08 (1 H, d, J = 3.29 Hz), 6.31 (1 H, d, J = 3.31 Hz), 7.07–7.39 (30 H, m); IR (NaCl, CH_2Cl_2) 3483, 1746, 1702 cm^{-1}; mp 101–103 °C; $[\alpha]^{25}_D$ +11.1° (c 0.56, CH_2Cl_2); exact mass calcd for $C_{53}H_{51}N_2O_{10}$ (M^+ + H) 875.35453, found 875.3521.

Phenyl Thionoformate 13. To a solution of **11** (237 mg, 0.271 mmol, 1 equiv) in THF (4 mL) was added phenyl chlorothionoformate (187 mL, 1.352 mmol, 5 equiv) followed by addition of sodium bis(trimethylsilyl)amide (298 mL, 0.298 mmol, 1.1 equiv, 1 M solution in THF) at −78 °C. After 10 min the dry ice bath was removed. After further reaction for 3 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 170 mg (62%) of **13** as a labile white solid. This compound was used directly after purification for the subsequent tin hydride reaction. Data for **13**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.50–1.76 (2 H, m), 2.22–2.65 (2 H, m), 3.35 (3 H, s), 3.66 (1 H, $^1/_2$ AB q, J = 9.56 Hz), 4.38 (1 H, $^1/_2$ AB q, J = 9.83 Hz), 4.94 (1 H, d, J = 1.66 Hz), 4.94 (1 H, $^1/_2$ AB q, J = 12.46 Hz), 5.03 (1 H, $^1/_2$ AB q, J = 12.79 Hz), 5.17 (1 H, $^1/_2$ AB q, J = 12.31 Hz), 5.30 (1 H, $^1/_2$ Ab q, J = 12.27 Hz), 5.31 (1 H, d, J = 3.15 Hz), 5.75 (1 H, d, J = 3.32 Hz), 5.77–5.85 (1 H, m), 6.00 (1 H, d, J = 3.21 Hz), 6.37 (1 H, d, J = 3.34 Hz), 6.56 (2 H, d, J = 6.84 Hz), 6.97–7.46 (33 H, m); IR (NaCl, CH_2Cl_2) 1754, 1704 cm^{-1}.

Reduction Products 14 and 15. To a solution of **13** (170 mg, 0.168 mmol, 1 equiv) in toluene (5 mL) was added AIBN (5.5 mg, 0.033 mmol, 0.2 equiv) followed by addition of tributyltin hydride (90 μL, 0.335 mmol, 2 equiv). The resulting solution was brought to reflux. After 3 h the toluene was evaporated off and the residue was separated by column chromatography on silica gel to afford 71 mg (49%) of **14** as a white solid and 16 mg (11%) of **15** as a white solid.

14: ^1H NMR (220 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.01–1.18 (1 H, m), 1.22–1.38 (1 H, m), 1.79–2.03 (2 H, m), 2.11–2.25 (1 H, m), 2.35–2.48 (1 H, m), 3.33 (3 H, s), 3.64 (1 H, $^1/_2$ AB q, J = 9.78 Hz), 4.37 (1 H, $^1/_2$ AB q, J = 9.78 Hz), 4.55 (1 H, dd, J = 9.69 Hz, J = 4.62 Hz), 4.90 (1 H, $^1/_2$ AB q, J = 12.71 Hz), 4.99 (1 H, $^1/_2$ AB q, J = 12.75

Hz), 5.13 (1 H, $^1/_2$ AB q, J = 12.33 Hz), 5.19 (1 H, d, J = 3.32 Hz), 5.22 (1 H, $^1/_2$ AB q, J = 12.25 Hz), 5.66 (1 H, d, J = 3.48 Hz), 6.08 (1 H, d, J = 3.03 Hz), 6.35 (1 H, d, J = 3.45 Hz), 6.50–6.54 (2 H, m), 7.01–7.34 (28 H, m); IR (NaCl, CH_2Cl_2) 1748, 1704 cm^{-1}; mp 99–101 °C; $[\alpha]^{25}_D$ −16° (c 0.5, CH_2Cl_2); exact mass (FAB) calcd for $C_{53}H_{50}N_2O_9Li$ 865.367 637, found 865.3675.

15: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.64–1.02 (3 H, m), 1.31–1.46 (1 H, m), 1.70–1.85 (1 H, m), 2.06–2.21 (1 H, m), 3.29 (3 H, s), 3.52 (1 H, $^1/_2$ AB q, J = 9.77 Hz), 4.24 (1 H, dd, J = 9.66 Hz, J = 4.33 Hz), 4.27 (1 H, $^1/_2$ AB q, J = 9.83 Hz), 5.02 (2 H, s), 5.07 (1 H, $^1/_2$ AB q, J = 12.74 Hz), 5.18 (1 H, $^1/_2$ AB q, J = 12.34 Hz), 5.62 (1 H, d, J = 3.54 Hz), 5.83 (1 H, d, J = 2.76 Hz), 5.88 (1 H, d, J = 2.76 Hz), 6.29 (1 H, d, J = 3.48 Hz), 7.03–7.43 (30 H, m); IR (NaCl, CH_2Cl_2) 1748, 1704 cm^{-1}; mp 114–116 °C; $[\alpha]^{25}_D$ −20.6° (c 0.6, CH_2Cl_2); exact mass (FAB) calcd for $C_{53}H_{50}N_2O_9Li$ 865.367 637, found 865.3662.

(2*S*,6*R*)-2,6-Diamino-6-(hydroxymethyl)pimelic Acid (17). To a solution of **14** (66 mg, 0.077 mmol, 1 equiv) in THF and EtOH (3 mL, 1:1) was added palladium chloride (41 mg, 0.231 mmol, 3 equiv). The reaction mixture was hydrogenated at 50 psi for 48 h. The mixture was then purged with nitrogen and filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo. The crude product **16** was dissolved in 48% HBr and refluxed for 3 h. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 16 mg (95%) of **17** as a white solid: ^{1}H NMR (300 MHz, D_2O, vs DSS) δ 1.26–1.45 (2 H, m), 1.65–1.90 (4 H, m), 3.66 (1 H, $^1/_2$ AB q, J = 11.90 Hz), 3.74 (1 H, m), 3.80 (1 H, $^1/_2$ AB q, J = 11.80 Hz); ^{13}C NMR (69.73 MHz, D_2O) δ (DSS) 21.3, 34.3, 56.8, 66.8, 68.7, 176.4, 176.6; IR (ZnS, H_2O) 3435, 3119, 1618 cm^{-1}; mp 220–230 °C dec, $[\alpha]^{25}_D$ +22.5° (c 0.6, 5 N HCl); exact mass calcd for $C_8H_{17}N_2O_5$ (M + H^+) 221.11375, found 221.1137.

Aldol Adducts 20 and 21. To a solution of **9** (407 mg, 1.05 mmol, 1 equiv) in CH_2Cl_2 (8 mL) was added dibutylboron triflate (2.1 mL, 2.1 mmol, 2 equiv, 1 M solution in CH_2Cl_2) followed by addition of triethylamine (293 μL, 2.1 mmol, 2 equiv) at 0 °C. After 20 min the reaction mixture was cooled to −78 °C and a CH_2Cl_2 (10 mL) solution of **19** (1.024 g, 2.1 mmol, 2 equiv) was added to it. After 30 min the reaction mixture was quenched with a phosphate buffer solution (pH 6.9) and poured into water. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 465 mg (50.6%) of **20** as a white solid and 17 mg (2%) of **21** as a white solid.

20: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.34–1.69 (2 H, m), 2.19–2.64 (2 H, m), 3.34 (3 H, s), 3.64–3.71 (1 H, m), 3.91–4.02 (1 H, m), 4.40 (1 H, $^1/_2$ AB q, J = 9.87 Hz), 4.66 (1 H, s), 4.98 (2 H, s), 5.11 (1 H, $^1/_2$ AB q, J = 12.38 Hz), 5.13 (1 H, d, J = 3.16 Hz), 5.22 (1 H, $^1/_2$ AB q, J = 12.58 Hz), 5.40 (1 H, d, D_2O exch, J = 5.22 Hz), 5.64 (1 H, d, J = 3.64 Hz), 6.34 (1 H, d, J = 3.43 Hz), 6.42 (1 H, d, J = 3.04 Hz), 6.55–6.58 (2 H, m), 6.91–7.37 (28 H, m); IR (NaCl, CH_2Cl_2) 3477, 1749, 1704 cm^{-1}; mp 92–94 °C; $[\alpha]^{25}_D$ +3.6° (c 0.94, CH_2Cl_2); exact mass calcd for $C_{53}H_{51}N_2O_{10}$ (M^+ + H) 875.354 53, found 875.3508.

21: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.27–1.45 (1 H, m), 1.58–1.76 (1 H, m), 2.05–2.41 (2 H, m), 3.31 (3 H, s), 3.56 (1 H, $^1/_2$ AB q, J = 9.70 Hz), 3.52–3.63 (1 H, m), 3.99 (1 H, d, D_2O exch, J = 6.70 Hz), 4.33 (1 H, $^1/_2$ AB q, J = 9.75 Hz), 4.47 (1 H, d, J = 2.39 Hz), 5.06 (1 H, $^1/_2$ AB q, J = 12.64 Hz), 5.17 (2 H, s), 5.18 (1 H, $^1/_2$ AB q, J = 12.22 Hz), 5.57 (1 H, d, J = 3.49 Hz), 5.60 (1 H, d, J = 3.60 Hz), 6.02 (1 H, d, J = 3.45 Hz), 6.30 (1 H, d, J = 3.47 Hz), 7.02–7.33 (30 H, m); IR (NaCl, CH_2Cl_2) 3488, 1747, 1704 cm^{-1}; mp 105–107 °C; $[\alpha]^{25}_D$ +56.9° (c 0.36, CH_2Cl_2).

Phenyl Thionoformate 22. To a solution of **20** (400 mg, 0.457 mmol, 1 equiv) in THF (4 mL) was added phenyl chlorothionoformate (316 μL, 2.284 mmol, 5 equiv) followed by addition of sodium bis(trimethylsilyl)amide (503 μL, 0.503 mmol, 1.1 equiv, 1 M solution in THF) at −78 °C. After 3 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by colu chromatography on silica gel to afford 174 mg (38%) of **22** as a wh solid and 135 mg (34%) of unreacted **22**: ^{1}H NMR (200 MH DMSO-d_6, 393 K, vs TMS) δ 1.41–1.59 (1 H, m), 1.76–1.95 (1 H, n 2.36–2.61 (2 H, m), 3.35 (3 H, s), 3.66 (1 H, $^1/_2$ AB q, J = 9.77 H 4.39 (1 H, $^1/_2$ AB q, J = 9.70 Hz), 5.00 (2 H, s), 5.08 (1 H, $^1/_2$ AB J = 12.32 Hz), 5.09 (1 H, d, J = 1.70 Hz), 5.24 (1 H, $^1/_2$ AB q, J 12.44 Hz), 5.31 (1 H, d, J = 3.15 Hz), 5.71 (1 H, d, J = 3.54 Hz), 5. (1 H, m), 6.01 (1 H, d, J = 3.09 Hz), 6.37 (1 H, d, J = 3.40 Hz), 6. (2 H, d, J = 6.74 Hz), 6.98–7.44 (33 H, m); IR (NaCl, CH_2Cl_2) 174 1705 cm^{-1}.

Reduction Products 23 and 24. To a solution of **22** (155 mg, 0.1 mmol, 1 equiv) in toluene (5 mL) was added AIBN (8 mg, 0.049 mm 0.3 equiv) followed by addition of triphenyltin hydride (269 mg, 0.7 mmol, 5 equiv). The resulting solution was brought to reflux. After 2 h the toluene was removed under reduced pressure and the residue w separated by column chromatography on silica gel to afford 107 m (81%) of **23** as a white solid and 7 mg (5%) of **24** as a white soli

23: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.09–1.2 (2 H, m), 1.88 (2 H, q, J = 7.67 Hz), 2.30 (2 H, t, J = 8.07 Hz), 2.5 (3 H, s), 3.65 (1 H, $^1/_2$ AB q, J = 9.87 Hz), 4.37 (1 H, $^1/_2$ AB q, J 9.78 Hz), 4.58 (1 H, t, J = 6.43 Hz), 4.98 (2 H, s), 5.10 (1 H, $^1/_2$ A q, J = 12.31 Hz), 5.19 (1 H, d, J = 2.99 Hz), 5.20 (1 H, $^1/_2$ AB q, = 12.42 Hz), 5.63 (1 H, d, J = 3.36 Hz), 6.10 (1 H, d, J = 3.02 Hz 6.35 (1 H, d, J = 3.40 Hz), 6.51–6.55 (2 H, m), 6.98–7.29 (28 H, m IR (NaCl, CH_2Cl_2) 1750, 1705 cm^{-1}; mp 98–100 °C; $[\alpha]^{25}_D$ −8.8° (c 0.5 CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd fo $C_{53}H_{50}N_2O_9$: C, 74.11; H, 5.87; N, 3.26. Found: C, 74.18; H, 6.04; N 3.08. Exact mass (FAB) calcd for $C_{53}H_{50}N_2O_9Li$ 865.367637, foun 865.3670.

24: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.66–0.8 (2 H, m), 1.01–1.14 (1 H, m), 1.28–1.42 (1 H, m), 1.96 (2 H, t, J = 8.2 Hz), 3.30 (3 H, s), 3.53 (1 H, $^1/_2$ AB q, J = 9.75 Hz), 4.25 (1 H, t, . = 4.61 Hz), 4.27 (1 H, $^1/_2$ AB q, J = 9.72 Hz), 5.02 (1 H, $^1/_2$ AB q J = 12.87 Hz), 5.08 (1 H, $^1/_2$ AB q, J = 12.51 Hz), 5.11 (1 H, $^1/_2$ AB q, J = 12.86 Hz), 5.19 (1 H, $^1/_2$ AB q, J = 12.58 Hz), 5.61 (1 H, d, . = 3.56 Hz), 5.84 (1 H, d, J = 3.29 Hz), 5.86 (1 H, d, J = 3.32 Hz), 6.25 (1 H, d, J = 3.49 Hz), 7.01–7.39 (30 H, m); IR (NaCl, CH_2Cl_2) 1749 1705 cm^{-1}; mp 88–90 °C; $[\alpha]^{25}_D$ +12.9° (c 0.22, CH_2Cl_2).

(2*S*,6*S*)-2,6-Diamino-6-(hydroxymethyl)pimelic Acid (4). To a solution of **23** (73 mg, 0.085 mmol, 1 equiv) in THF and EtOH (3 mL, 1:1) was added palladium chloride (90 mg, 0.508 mmol, 6 equiv). The reaction mixture was hydrogenated at 50 psi for 48 h. The mixture was then purged with nitrogen and filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo. The crude product was dissolved in 48% HBr and refluxed for 3 h. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 17 mg (91%) of **4** as a white solid. This material proved to be indistinguishable by ^{1}H NMR and TLC from the authentic amino acid obtained by hydrolysis of natural **3** provided by Shionogi & Co. Data for **4**: ^{1}H NMR (300 MHz, D_2O, vs DSS) δ 1.29–1.39 (1 H, m), 1.43–1.57 (1 H, m), 1.62–1.90 (4 H, m), 3.64 (1 H, $^1/_2$ AB q, J = 11.69 Hz), 3.65 (1 H, m), 3.89 (1 H, $^1/_2$ AB q, J = 11.83 Hz); ^{13}C NMR (67.93 MHz, D_2O) δ DSS 21.7, 33.2, 34.6, 57.4, 66.7, 68.6, 176.4, 176.9; IR (ZnS, H_2O) 3395, 3109, 1614 cm^{-1}; mp 235–245 °C dec, lit.[8] mp 240–250 °C dec; $[\alpha]^{25}_D$ +7.1° (c 0.55, 5 N HCl), lit.[8] +8.1 ± 1.0° (c 0.506, 5 N HCl).

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