DISSERTATION

CONCISE SYNTHESES OF NOTOAMIDES B–E

AND

STEPHACIDIN A

Submitted by

Alan Whitfield Grubbs

Department of Chemistry

In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Summer 2008

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WE HEREBY RECOMMENED THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ALAN WHITFIELD GRUBBS ENTITLED CONCISE SYNTHESES OF NOTOAMIDES B – E AND STEPHACIDIN A BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT OF DISSERTATION

CONCISE SYNTHESES OF NOTOAMIDES B–E

AND STEPHACIDIN A

Presented herein are concise syntheses of the cytotoxic alkaloids notoamides B-E. A highly convergent synthesis is outlined from commercially available 6-hydroxy indole and naturally derived L(-)-Proline or L(-)-cis-3-hydroxy Proline . Also presented is a 16 step synthesis of (±)-11-*epi*-norgeamide B and finally a concise 17 step synthesis of stephacidin A. The synthesis of each member of the norgeamide and notoamide family of natural products is proposed via the tunable activation or deactivation of the 1,7-dihydropyrano[2,3-g]indole ring system in order to exploit a mild Pinacol-type rearrangement en-route to notoamides A-C and norgeamides A and B, or the prevention thereof, to allow access to the pyrroloindole scaffold of norgeamides C and D or notoamide D.

Alan Grubbs

Department of Chemistry

Colorado State University

Fort Collins, CO 80523

Summer 2008

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List of Abbreviations

Ac_2O	acetic anhydride
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyldicarbonate
Bn	benzyl
BnBr	benzyl bromide
Bu_2BOTf	dibutylboron trifluoromethan sulfonate
^{i}BuOCOCl	isobutylchloroformate
BzCl	benzoyl chloride
Cbz	benzyoxycarbonyl
CbzCl	benzylchloroformate
DEAD	diethyl azodicarboxylate
Dess-Martin Periodinane	triacetoxy *o*-iodobenzoic acid
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobuytlaluminum hydride
DIC	N,N-diisopropylcarbodiimide
DMAP	4-(dimethylamino)-pyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 *H*)-pyrimidinone
DMS	dimethylsulfide

dr	diastereomeric ratio
EDCI	ethyl-dimethylaminopropylcarbodiimide hydrochloride
er	enantiomeric ratio
Et_3N	triethylamine
EtOAc	ethyl acetate
HOAc	acetic acid
HOAt	1-hydroxyazabenzotriazole
HOBt	1-hydroxybenzotriazole
IBX	*o*-iodoacetic acid
Im	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium *N*,*N*-diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*m*-chloroperbenzoic acid
MeCN	acetonitrile
MOMCl	chloromethyl methyl ether
MsCl	methane sulfonyl chloride
MsOH	methane sulfonic acid
NaHMDS	sodium bis(trimethylsilyl)amide
nOe	nuclear Overhauser effect
NMM	*N*-methylmorpholine
NMO	4-methyl morpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone

Pd / C	palladium on carbon
$PdCl_2(dppf)xCH_2Cl_2$	dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium
$Pd_2(dba)_3xCHCl_3$	tris(dibenzylideneacetone)dipalladium
Ph	phenyl
PhH	benzene
PhMe	toluene
PPTS	pyridinium *p*-toluenesulfonate
$^{i}Pr_2NEt$	diisopropylethylamine
TBAF	tetrabutyl ammonium fluoride
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyl dimethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFOH	trifluoromethane sulfonic acid
THF	tetrahydrofuran
TIPSCl	triisopropylsilyl chloride
TPAP	*tetra*-*N*-propylammonium perruthenate
TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluenesulfonic acid

Chapter 1: Introduction

1.1 Fungal Isolates

1.1.1 General Considerations

Marine natural products chemistry, born early in the 1970's, has blossomed over the past few decades into one of the most vibrant fields in chemistry today.[1] Studies of marine toxins have been dominated primarily by Japanese researchers[2-5] with highlights such as the 1981 X-ray crystallographic study of brevetoxin B (**1**) (Figure 1) isolated from the dinoflagellate (*Gymnodinium breve*),[6] and ciguatoxin (**2**), the principal toxic constituent in ciguateric seafood poisoning, identified in 1989 from material extracted from Pacific moray eels *(Gymnothorax javanicus*).[3] More recently, maitotoxin (**3**), the largest and possibly most lethal non-proteinaceous toxin was identified from the marine dinoflagellate *Gambierdiscus toxicus*, using modern methods of structural elucidation, isolation, characterization and synthesis all working together toward structural elucidation (Figure 2).[4,7]

Figure 1. Highlights in marine natural products chemistry.

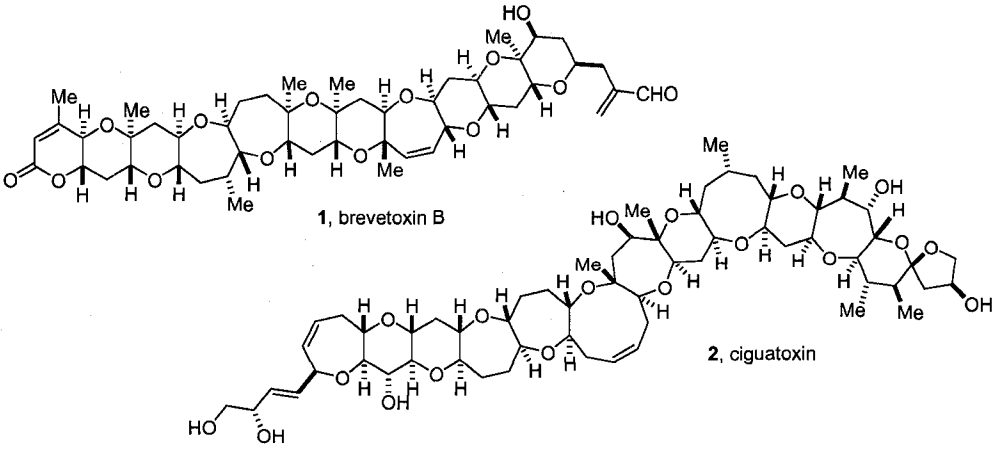
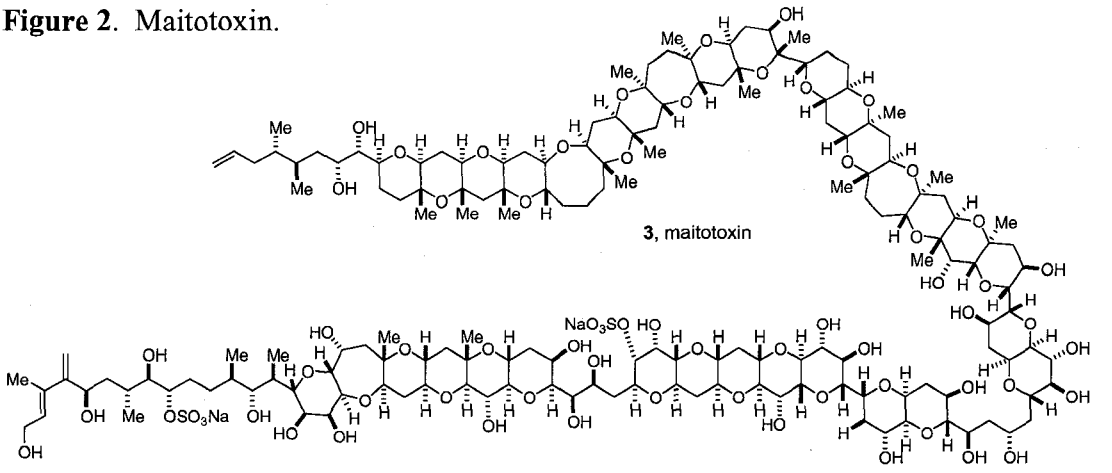


Figure 2. Maitotoxin.



Today, the success of marine natural products chemistry for drug discovery, including the identification, isolation, structural elucidation, synthetic derivatization and biological profiling of compounds from natural sources, depends highly on the originality of the chemical structures and the assigned biological activity.[8] Of particular interest in this field is the exploitation of biotechnological advances to help supply reasonable quantities of natural products while minimizing damage to our fragile aquatic environments.

1.1.2 Cold-Water Marine Fungi

Ideally suited to this kind of investigation are cold-water marine fungi amenable to laboratory cultivation. As the world-wide marine environment represents 32 of 33 animal phyla with more than 50% of the phyla being exclusively marine, it can be concluded that the taxonomic diversity is larger in the sea than on land.[8]

There are at least 550 species of marine fungi,[9] most of which are decomposers of dead organic matter. Some are parasites causing diseases in fish, shellfish, seaweed and sponges. Some form associations with algae forming terrestrial and marine lichens.

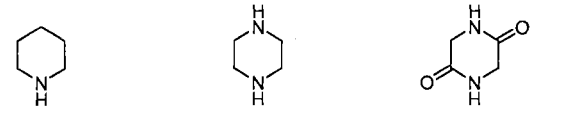
These structures may be found as thick, dark-brown / black or even orange patches on wave-splashed zones on rocky shores. As such, these organisms are highly evolved natural laboratories, each capable of synthesizing vast numbers of active natural products.

Aiding in the identification of these active natural products are HPLC-based nitrogen detectors.[10-12] Using this kind of instrumentation, huge concentrates of fermentation broths can be screened rapidly for nitrogen-containing molecules. Further analysis of these initial "hits" can identify fractions containing biologically active, nitrogen containing molecules.[8]

1.1.3 Anthelminthics / Antinematodal Compounds

Piperazines (**5** and **6**) were originally named because of their chemical similarity with piperidine (**4**), a constituent of piperine in the black pepper plant, *Piper nigrum*, (Figure 3).[13-18]

Figure 3. The diketopiperazine ring.

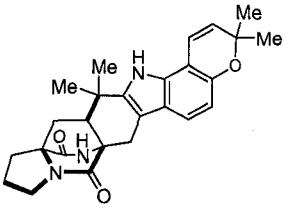


4 **5** **6**

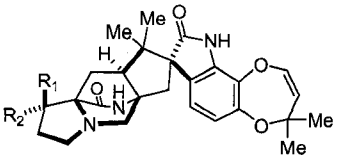
A central feature of many natural products is the diketopiperazine (DKP) ring (**6**), which formally is the union of two glycine residues into the most simple cyclic di-peptide. Piperazine (**5**) was first introduced as an anthelmintic in 1953.[19-25] A large number of piperazine-containing compounds have anthelmintic action. The mode of

action of anthelmintic drugs is generally through paralyzing parasites, which allows the host body to easily remove or expel the invading organism.[19-25] The stephacidin[26-35] and paraherquamide[36-40] families of natural products both display anthelmintic activity and are similar in that they appear to be biosynthetically derived from tryptophan, proline and isoprene (Figure 4). Furthermore, they contain the same oxidized indole ring system consisting of a pyran or dioxepine ring, and a diketopiperazine derived, tricyclic core (Figure 2).

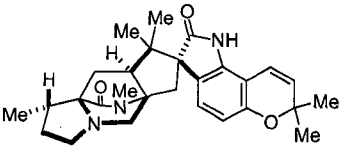
Figure 4. Anthelmintic peptides.



7, stephacidin A



8, paraherquamide A, R_1 = OH, R_2 = Me
9, paraherquamide B, R_1 = H, R_2 = H



10, paraherquamide F

Stephacidin A (**7**), isolated from a fungal species found in an Indian clay sample,[26-35] differs from paraherquamide F (**10**)[36-40] in that it lacks the oxindole feature and the β-methyl substituent of the proline ring. Due to the fascinating modes of action and interesting structural features, these compounds have been the subject of intense synthetic efforts.

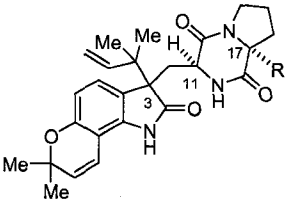
The norgeamides[8,29] described below are structurally similar to the compounds above and represent an extremely new group of natural products whose mode of action and methods of synthesis are yet to be disclosed in the familiar bodies of scientific literature.

1.2 The Norgeamides

1.2.1 Isolation and Structure Determination

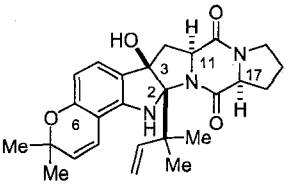
In 2005, the Hans-Knöll Institute reported the isolation of a new class of indole alkaloids[8] from a strain of cold water *Aspergillius* fungi isolated in the North Sea. The norgeamides A-D (**11-15**)[8] are structurally similar to stephacidin A (**7**)[32] and paraherquamide F (**10**)[36] in that they also all appear to be biosynthetically derived from tryptophan, proline and isoprene (Figure 5).[37] Furthermore, **11-15** contain the same oxidized indole ring system consisting of a pyran ring.

Figure 5. The norgeamides.

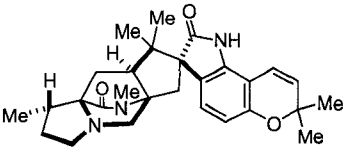


11, norgeamide A: R = OMe
12, norgeamide B: R = OH

15, des-methoxy-norgeamide A: R = H



13, norgeamide C: R = H
14, norgeamide D: R = OH



10, paraherquamide F

The norgeamides, though, structurally lack carbon connectivity between the reverse prenyl unit at C3 and the diketopiperazine (DKP) ring system C11 and C17. As observed in paraherquamides F (**10**), the carbons of the reverse prenyl group help form the bridged [2.2.2]diazooctane ring system common to this family of fungal metabolites isolated from *Aspergillius* and *Penicillium* sp. On the other hand, norgeamides A (**11**) and B (**12**) contain the 2-oxindole subunit of paraherquamide F (**10**), but lack the connectivity between the reverse prenyl group at C3 and the DKP ring. Moreover, the stereochemistry of the C3 quaternary center was not resolved during isolation and remains to be

elucidated. A reasonable assumption however, is that the stereochemistry at C3 of **11** and **12** mimics the stereochemistry of similar compounds with a known configuration at C3, such as paraherquamide F (**10**). Additionally, the α-position of the proline ring (C17) has been oxidized introducing a methoxy substituent for **11** and a hydroxyl group for **12**. The functionalization of C17 proves to be a formidable synthetic challenge due to the inherent lability of these compounds to decomposition[41] in the presence of acid to afford an *N*-acyliminium ion.[42-44] With regard to norgeamides C (**13**) and D (**14**), the indole ring has been oxidized to afford a pyrrolindole ring system.[45-47] In a similar manner to **11** and **12**, norgeamide D (**14**) has been oxidized at C17 introducing a hydroxy substituent.

1.2.2 Biological Activity

As for the biological activity of the norgeamides, all have been found to inhibit the growth of a variety of cancer cell lines with different efficacies.[8] Norgeamide A (**11**) was reported to be the most potent inhibitor of cell growth with observed values of 50-98% inhibition. Norgeamide B (**12**), which only differs from **11** by the substitution at C17, was 20-30% less effective at inhibiting cell growth. Norgeamides C (**13**) and D (**14**), were the poorest inhibitors of the family of alkaloids with only 33-60% inhibition observed (Table 1). Based on the preliminary data, it is feasible to say that the C17 substituent is important for biological activity. However, the exact mode of action and biochemical target for the norgeamides has yet to be determined.

Table 1. Antiproliferative effects of norgeamides A-D on a human tumor cell line panel.

Values indicate % inhibition of cell growth at a compound concentration of 10mg/ml; (- / - no inhibition, defined as less than 30%).[8]

A549	77%	55%	- / -	- / -
CAKI-1	80%	37%	- / -	- / -
DU-145	89%	47%	39%	33%
HT-29	89%	56%	35%	41%
MDA-MB-231	95%	49%	34%	- / -
K562	50%	- / -	60%	40%
SK-MEL-2	95%	42%	- / -	33%
SK-OV-3	98%	- / -	33%	- / -

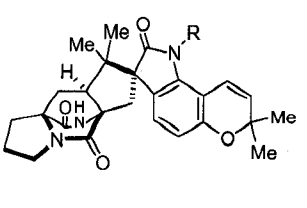
A549	lung carcinoma	MDA-MB-231	breast carcinoma
CAKI-1	kidney carcinoma	K562	myeloid leukemia
DU-145	prostate carcinoma	SK-MEL-2	melanoma
HT-29	colon carcinoma	SK-OV-3	ovary adenocarcinoma

1.3 The Notoamides

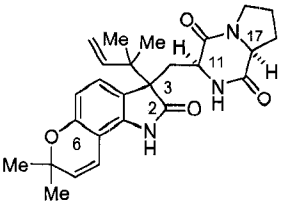
1.3.1 Isolation and Structure Determination

Around the same time period during which the norgeamides were revealing themselves as new and potent natural products, a surprisingly similar group of natural products were under investigation by a group of researchers at Kanazawa University in the Graduate School of Natural Sciences and Technology in Japan.[48] Tsukamoto and co-workers reported in August, 2006 the isolation and characterization of four new natural products named notoamides A-D (**16-19** (Figure 6). Notoamide A (**16**) and B (**17**) are structurally similar to paraherquamide F[36] (**10**, Figures 4 and 5), bearing the fused bicyclo[2.2.2]diazaoctane bridged bicycle and a 1,7-dihydropyrano[2,3-g]indole ring system.

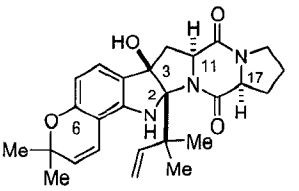
Figure 6: The notoamides and norgeamides.



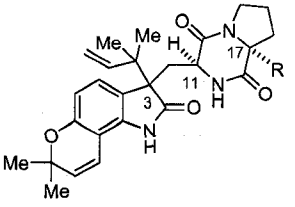
16, notoamide A: R = OH
17, notoamide B: R = H



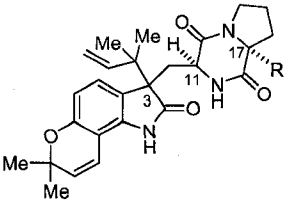
18, notoamide C



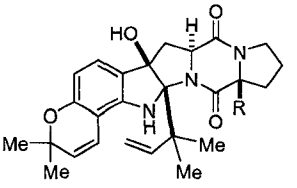
19, notoamide D



11, norgeamide A: R = OMe
12, norgeamide B: R = OH



15, des-methoxy-
norgeamide A: R = H



13, norgeamide C: R = H
(As reported by Sattler et. al.)[8]
14, norgeamide D: R = OH

Notoamide C (**18**), structurally comparable to norgeamides A (**11**) and B (**12**), bears all of the structural features of **16** and **17**, however lacks the oxidation at C17. Notoamide D (**19**) bears the pyrano indole as observed in norgeamide C (**13**) however bears a *cis*-diketopiperazine whereas **13**, is reported to possess the *trans*-diketopiperazine. The relationship between notoamide D (**19**) and norgeamide C (**13**), will be discussed in detail in the pages that follow.

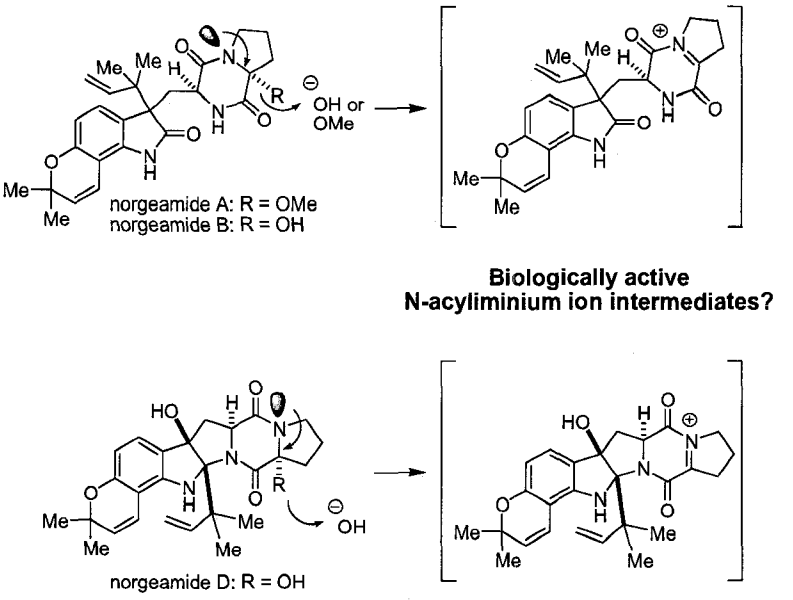
1.3.2 Biological Activity of the Notoamides

The notoamides are an extremely new class of natural products and as such have only begun to be probed for biological activity. Preliminary data, however, suggest that notoamides A-D have very limited biological activity. An assay testing for cytotoxicity was performed using four cell lines, HeLa, L1210, KB and A549.[49-52] Notoamide D was inactive against each cell line and notoamides A-C showed only moderate cytotoxicity.[50] An assay probing neurite outgrowth activity and proteosome inhibition showed notoamides A-D to be completely inactive.[51,52] Again, screens for cell cycle inhibition, or inhibition of p53-HDM2 interaction, showed notoamides A-D completely inactive.[49] Finally, insecticidal activity against silkworm larvae showed notoamides A-D inactive.

1.3.3 Proposed Mode of Action

A model of biological activity vs. structural features quickly points to the oxidation state of the L-proline residue and specifically the oxidation state of C17. The chemistry of N-acyliminium ions is well precedented and pervasive throughout the chemical literature.[42-44] Assuming that an N-acyliminium ion is a reactive intermediate leading to the observed biological activity (Figure 7), then only compounds bearing either the C17 hydroxyl group or the C17 methyl ether are at the required oxidation state to generate an N-acyliminium ion and thus render the compound biologically active. This is the observed trend in the biological activity of both the norgeamides and notoamides and may very likely be an avenue to fully characterize the general mode of action of each class of compounds.

Figure 7: N-acyliminium ion formation.



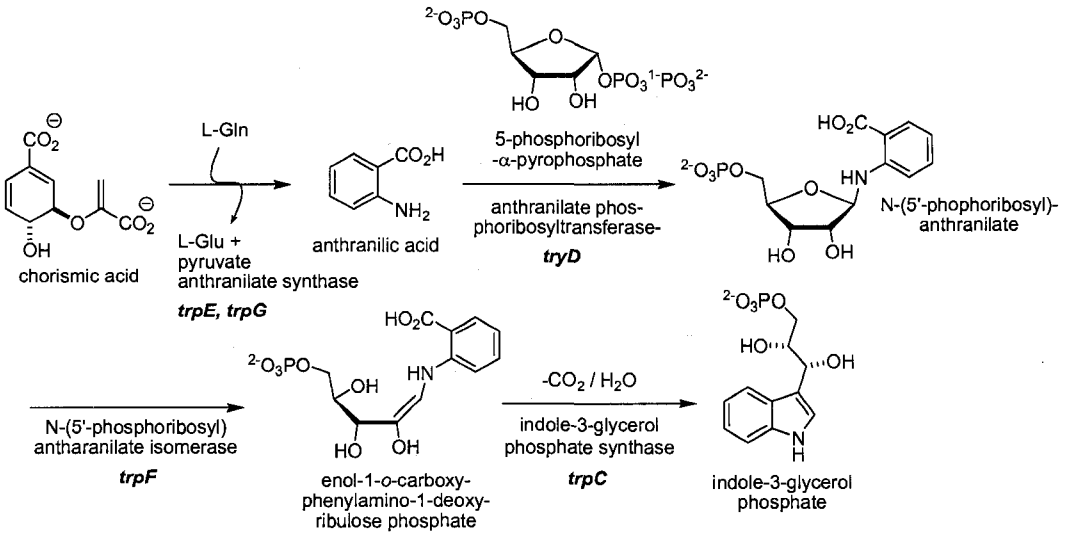
The differential activity of norgeamides A and B could be explained by the relative rates of N-acyliminium ion formation with each compound passing through the same biologically active intermediate. This argument would predict that norgeamide A forms the N-acyliminium ion more readily and that norgeamides B and D should be less active than norgeamide A. These predictions are consistent with all experimental details. The complete mode of action and further biological studies of the norgeamides and the notoamides are currently under investigation in our laboratories.

1.4 Biosynthetic Considerations

1.4.1 Biosynthesis of L-typtophan

The aromatic amino acids, including phenylalanine, tyrosine, and tryptophan are derived biosynthetically from the shikimate pathway.[53-56] L-Tryptophan is constructed from a branch point in the shikimic acid pathway.[53-56] Thus, chorismic acid is transaminated with L-glutamine as the nitrogen donor to afford anthranilic acid (Scheme 1).

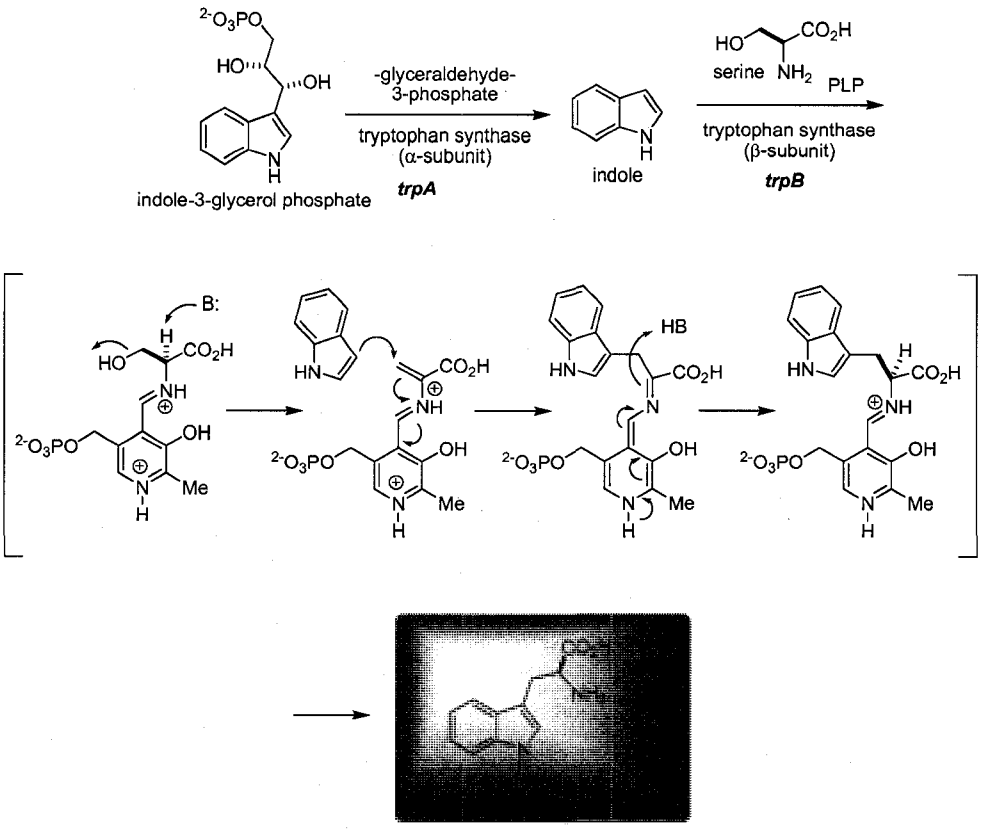
Scheme 1. Biosynthesis of L-tryptophan.



Anthranilic acid is then enzymatically condensed with 5-phosphoribosyl-α-pyrophosphate to form N-(5'-phosphoribosyl)-anthranilate from which two carbons of the indole ring will be constructed. Cleavage of the furan ring is then facilitated via an Amadori-type rearrangement, catalyzed by N-(5'-phosphoribosyl)-anthranilate isomerase, to afford enol-1-carboxyphenylamino-1-deoxyribulose phosphate. Indole-3-

glycerol phosphate synthase then effects the decarboxylation and dehydration giving indole-3-glycerol phosphate. Indole-3-glycerol phosphate is the penultimate substrate which is fed into the tryptophan synthase complex (Scheme 2). Cleavage of the last C-C bond to form indole is mediated by tryptophan synthase and involves protonation of the indole 2,3-double bond followed by loss of glyceraldehyde-3-phosphate. The final assemblage of L-tryptophan occurs in a channeling sequence mediated by two separate domains of tryptophan synthase whereby indole made in the α-subunit is passed down or "channeled" to the β-subunit where final installation of the hydrophilic serine unit is accomplished.[53-56]

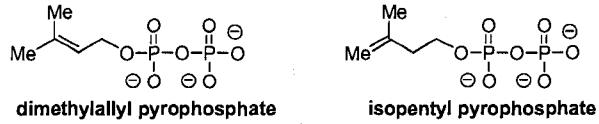
Scheme 2. Biosynthesis of L-tryptophan.



1.4.2 Biosynthesis of the Isoprene Unit: The Mevalonate Pathway

The five-carbon isoprene skeleton constitutes a ubiquitous biosynthetic building block. Nature uses two basic precursors (DMAPP and IPP, Figure 8) to functionalize a wide array of secondary metabolites where the "prenyl" or "reverse prenyl" substituent constitutes ethers, amines and 5-carbon extensions (Figure 8).[54-56]

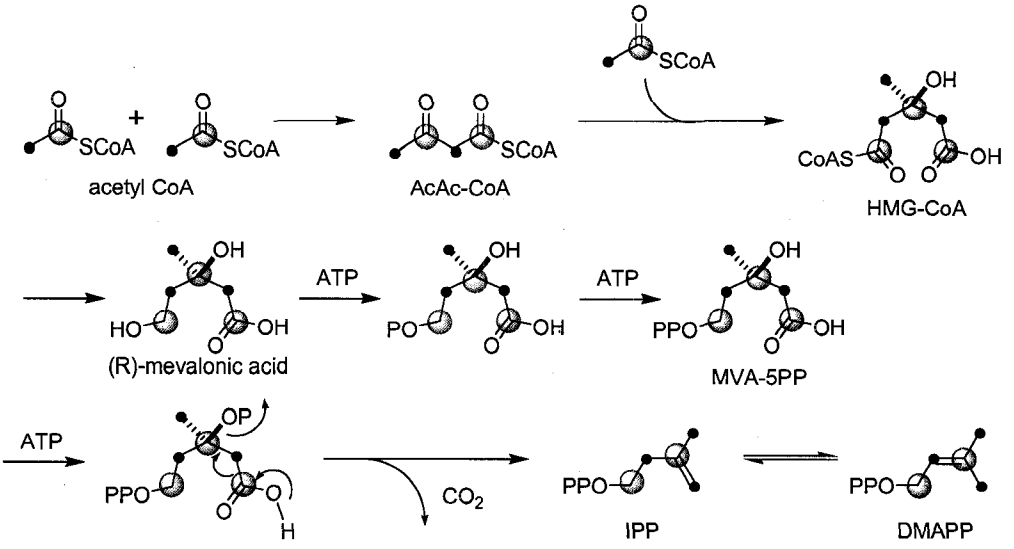
Figure 8. The isoprene building blocks.



To date two distinct biosynthetic pathways are known to produce both DMAPP and IPP.[57-62] Shown below is the classical mevalonic acid pathway (Scheme 3.) A discussion of both pathways and a commentary on the evolutionary origin of both pathways can be found in a review by Williams and Stocking, and references therein.[53] The mevalonic acid pathway begins with the Claisen-type condensation of two acetyl-CoA units to form the four-carbon skeleton, acetoacetyl-CoA. A third equivalent of CoA is then added in an aldol-type reaction giving, after hydrolysis of the thiol esters, hydroxymethylglutaryl CoA (HMG-CoA). HMG-CoA is then reduced by a net four electrons to mevalonic acid and is then subsequently phosphorylated to mevalonic acid 5-pyrophosphate (MVA-5PP). This substrate is finally phosphorylated to give the five carbon isoprenoid, isopentenyl pyrophosphate (IPP). IPP is then isomerized to DMAPP by an isomerase.

The carbon distribution in the product can be traced via labeled acetyl-CoA (Scheme 3, green circles).[53,57-62]

Scheme 3. Classical mevalonic acid pathway using 1,2-doubly labeled acetate.



The classical mevanlonate pathway has long been recognized as one of the key primary metabolic pathways leading to the formation of the branched five-carbon skeleton of the isoprene building blocks, isopentenyl pyrophosphate and dimethylallyl pyrophosphate.[54-56] The compounds described herein are built in nature from these simple precursors to develop the complex scaffolds that give rise to biologically active natural products. Williams, et al. have shown that the isoprene units of the paraherquamides are derived from mevalonate.

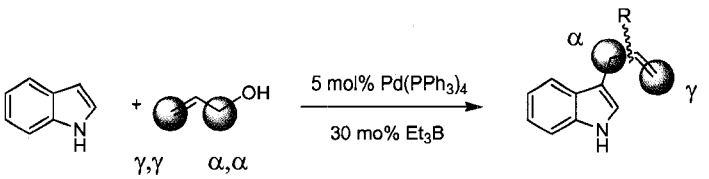
1.5 Previous Synthetic Achievements

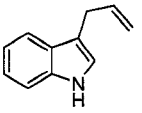
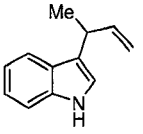
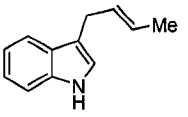
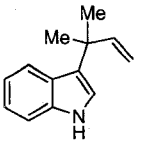
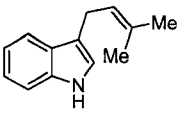
Although the norgeamides and the notoamides are new and recently published natural products, they possess striking structural features that have held the attention of synthetic chemists for many years. The following is a chronological discussion of synthetic methodology that has been applied to the synthesis of the main structural features present in the norgeamides and notoamides.

1.5.1 Tamaru's Triethylborane Promoted Allylation of Indoles with Allyl Alcohols.

Recently a powerful method to access 3-alkyl indoles was reported by Tamaru and co-workers.[63-66] Their investigations centered on the reactivity of indoles as nucleophiles and π-allylpalladium species as electrophiles.[67-72] Recent observations have shown that Pd(0) species in the presence of catalytic Et_3B promotes allylic alcohols to undergo both N-allylation and C-allylation of active methylene compounds.[63-66] Tamaru's work showed for the first time that the Pd-Et_3B system works nicely for the selective C3 allylation of indoles (Table 2) to provide 3-allylindoles in excellent yields.

Table 2. Allylation of indole with allyl alcohols.



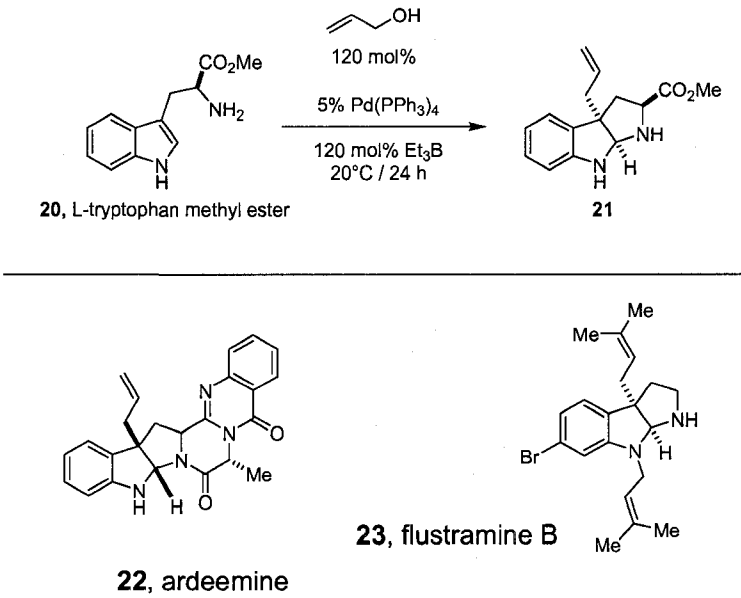
reaction	alcohol	time (h)	Products: % Yield	
1		12		80-85%
2 γ–Me		20	 30	 48
3 α–Me		20	34	46
4 γ,γ–Me_2		24	 75	 0
5 α,α–Me_2		24	86	9

Reaction conditions: Indole (1.0 mmol), allyl alcohol (1.0 mmol in rxns 1-3, 3.0 mmol in rxns 4-5), $Pd(PPh_3)_4$ (5 mol%), and Et3B (1N solution in hexane; 0.3 mmol in rxns 1-3, 2.4 mmol in rxns 4-5) in THF (2.5mL) at 50°C under N_2.

Initial results showed that the parent allyl alcohol, as well as α and γ-methyl alcohols are reactive. Reactions are typically complete within 20 hours at 50°C in the presence of 30 mol% Et_3B and 100 mol% allyl alcohol to provide cleanly the desired allyl indoles in near quantitative yield. The uniform mixture of products in runs 2 and 3 suggest a common intermediate, most likely a π-allylpalladium species.[63-66] Entries 4 and 5 provide more mechanistic detail and allow formation of α,α-, and γ,γ-dimethyl alcohols found commonly in many natural products. Although more reluctant, the C3-reverse prenyl indole was generated in 75-86% yield by increasing the amount of both the

required alcohol (300mol %) and Et_3B (240mol %). Encouraged by these results the authors examined the allylation of L-tryptophan methyl ester (Figure 9). Under identical conditions, selective alkylative amination upon the indole 2,3-double bond took place and provided pyrroloindole **21** as a single diastereomer in ~73-76% isolated yield without protection of either of the two nitrogens.

Figure 9. Stereoselective synthesis of pyrroloindole frameworks.

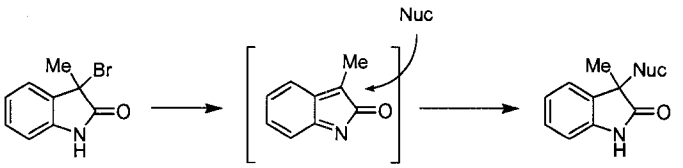


The synthetic utility of this methodology has far reaching implications including the synthesis of natural products bearing a pyrroloindole ring system such as ardeemine (**22**)[73-75] and flustramine B (**23**).[76-80]

1.5.2 Funk's C(3) Reverse Prenylation: Total Synthesis of (±)-Flustamines A and C

In December of 2004 Funk and Fuchs[78,79] reported an elegant approach to the installation of the C3 reverse prenyl group. Funks' reverse prenylation studies drew upon the seminal observations of Hinman and Bauman[81] who reported the base promoted substitution reactions of 3-bromo-3-methylindolin-2-one (**24**) with hetero nucleophiles (Table 3). The intermediacy of 3-methyl-2-one (**25**) was not advanced in that report.

Table 3. Nucleophilic attack at C3.



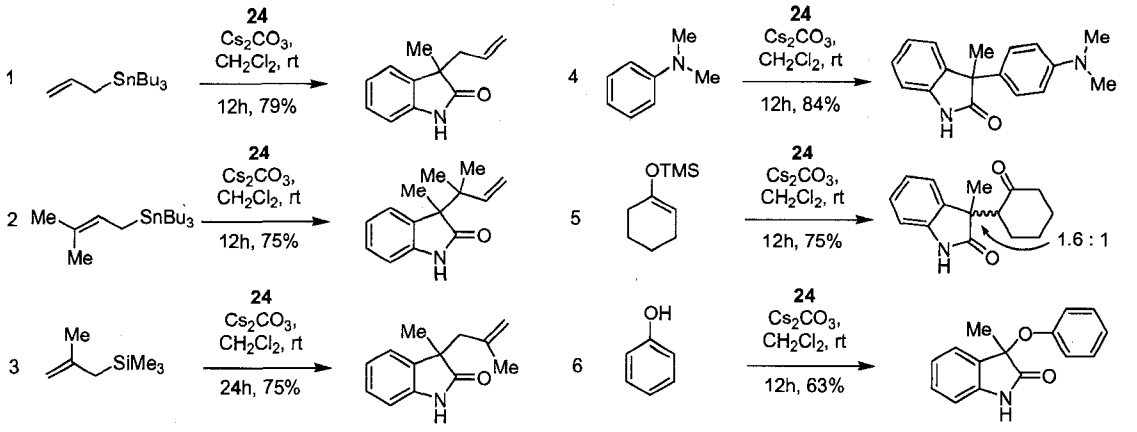
24 **25, 3-methylindol-2-one** **26**

Nuc	conditions	yield
OH	$NaHCO_3$, H_2O *t*-BuOH, 22h, rt	84%
OMe	$NaHCO_3$, H_2O MeOH, 3d, rt	85%
SC_6H_5	NaOH, HSC_6H_5 *t*-BuOH, 15min, rt	48%
NC_5H_{10}	Et_2O, HNC_5H_{10} 1.5h, rt	91%

Funk's group looked to explore carbon nucleophile variants of the substitution reaction as a means to introduce the C3 reverse prenyl unit common to many natural products. The initial investigations focused on the intermolecular reaction of various nucleophiles with 3-bromo-3-methylindolin-2-one (**24**, Table 4), using previously reported conditions (Cs_2CO_3, CH_2Cl_2, rt).[82] Allyl stannanes (entries 1 and 2) and methallyltrimethylsilane (entry 3) cleanly provided the 3-allyl-substituted oxindoles. Among others, electron rich

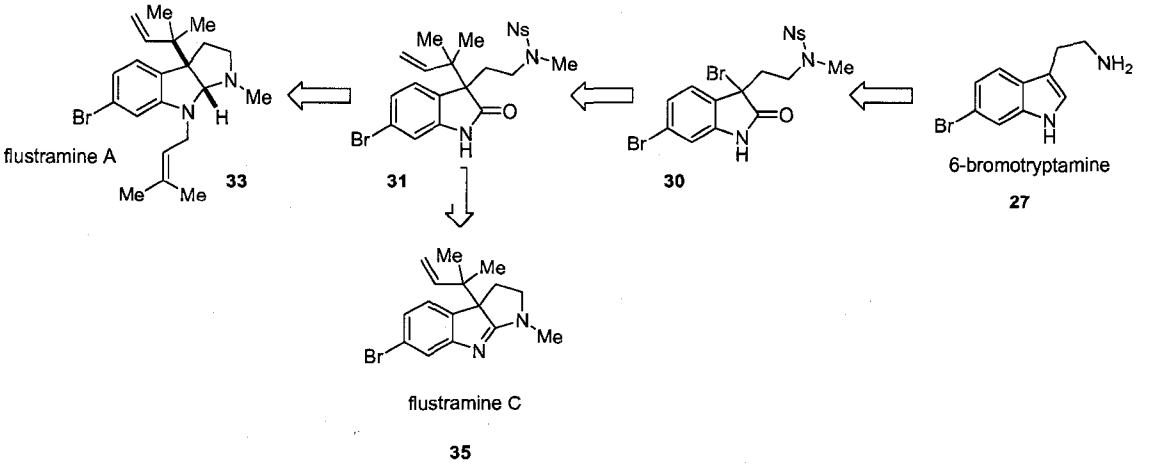
aromatic compounds such as N,N-dimethylaniline (entry 4) and N-methylpyrrole also served as competent nucleophiles along with silyl enol ethers, enamide functionalities, and phenolic derivatives (entries 5 and 6).

Table 4. Intramolecular Addition of (Nuc) to 3-bromo-3-methylindolin-2-one (**24**).

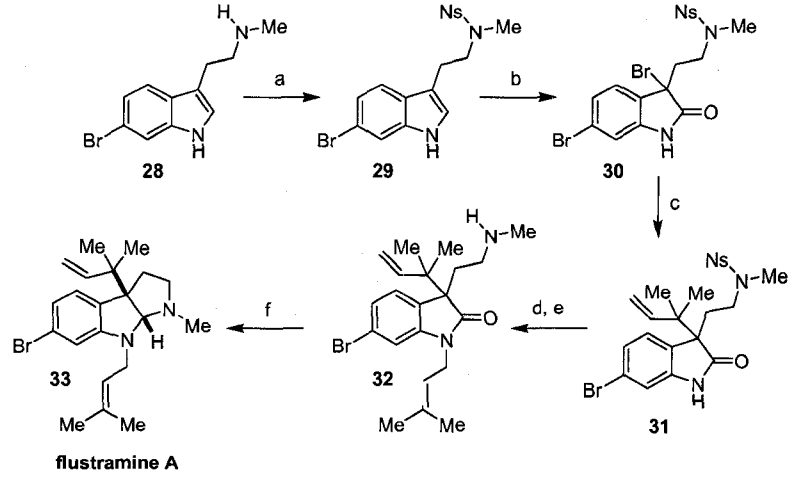


Of particular interest to natural product synthesis were entries 1 and 2 providing 3-allyl substituted oxindoles. With this methodology set in place Funk initiated a synthesis of flustramines A and C (Figure 10).[76-80]

Figure 10. Funk's Retrosynthesis of the Flustramines.



To begin the synthesis, previously reported N-methyl-6-bromotryptamine[83] (**28**), was treated with 4-nitrobenzenesulfonyl chloride in the presence of Et_3N and DMAP to afford the N-methyl-N-Nosyl amine **29**. Using a procedure reported first by Hinman and Bauman,[81] 6-bromoindole **29** was converted to 3-alkyl-3-bromoindolin-2-oxindole **30** by treatment with NBS in cold THF thus arriving at a substrate similar to those reported in the original model study (Scheme 4).



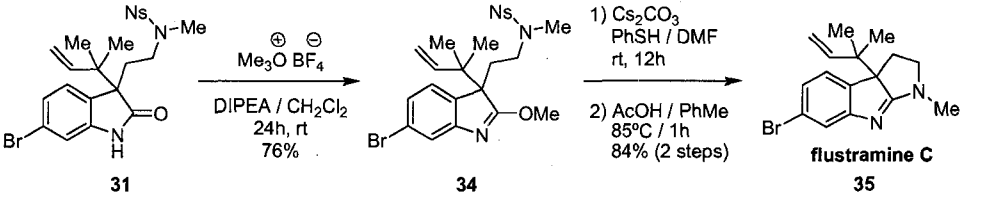
Scheme 4. a) 4-nitrobenzenesulfonyl chloride, Et_3N, DMAP, CH_2Cl_2, (75%). b) NBS, THF, *t*-BuOH, H_2O, (83%). c) Tributyl(3-methyl-2-butenyl)tin, Cs_2CO_3, CH_2Cl_2, rt, (74%). d) NaH, THF, dimethylallylbromide, (83%). e) Cs_2CO_3, PhSH, DMF, rt, 12h, (88%). f) alane, THF, reflux 2h, (62%).

Treatment of the 3-bromoindolin-2-one **30** with cesium carbonate in the presence of tributyl(3-methyl-2-butenyl)tin cleanly provided the desired indolin-2-one **31**. *N*-Alkylation of **31** with dimethylallyl bromide and subsequent deprotection of the secondary amine according to the protocol of Fukuyama[84] proved to be uneventful. Reduction of the resulting amine **32** with 2.5 equivalent of alane led to formation of flustramine A (**33**) as the minor product along with a substantial amount of the fully reduced indoline by-product resulting from reduction of the intermediate iminium ion

(4 : 1) ratio. Fortunately, flustramine A could be obtained as the major product (3 : 1) by employing only 1.1 equivalent alane and diluting the reaction mixture by > 200%.

Utilizing again the C(3) reverse prenyl indolinone **31**, a divergent route provided access to flustramine C (**35**, Scheme 5). To that end, treatment of **31** with Meerwein's salt[85] provided the cyclic imidate **34**. Suprisingly, removal of the nosylamide functionality of compound **34** under the aforementioned Fukuyama conditions[84] afforded none of the desired amidine. However (±)-flustramine C was ultimately obtained by simply heating the crude deprotected amine in toluene with an equivalent of acetic acid.[76-80]

Scheme 5. Synthesis of (±)Flustramine C.



Funk's synthesis of flustramines A and C[76-80] demonstrated the diverse utility of the 3-methylindole-2-one functionality as a means to introduce the C(3) reverse prenyl unit into a natural product scaffold. The observation that 3-alkyl-3-bromoindolin-2-ones undergo base-promoted reactions with a variety of nucleophiles significantly expanded the initial studies of Hinman and Bauman.[81]

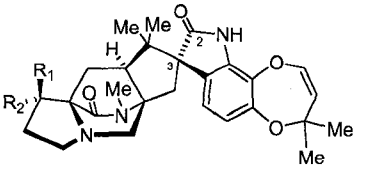
1.5.3 The *Spiro*-Oxindole: Williams' Synthesis of Paraherquamide A.

The paraherquamides (Figure 11, **8-10**),[36-40] are an unusual family of fungal natural products which contain a bicyclo[2.2.2]diazaoctane core structure, a *spiro*-oxindole and a substituted proline moiety. The parent member, paraherquamide A (**8**), was first isolated from cultures of *Penicillium paraherquei* by Yamazaki and co-workers in 1981.[86] Since then, paraherquamides B-G, VM55595, VM55596 and VM55597, SB203105 and SB200437, and sclerotamide have been isolated from various *Penicillium* and *Aspergillus* species.[87] Marcfortines A-C (**36-38**)[88-94] are structurally similar to **8** and **9**, but contain a pipecolic acid unit in place of L-proline. Also closely related are VM55599 (**39**), avrainvillamide (CJ-17,665)[26-30,95] and the most recently isolated members of this family, stephacidins A and B.[28,30,32,34] Many of these compounds contain a 2,3-disubstituted indole in place of the *spiro*-oxindole (Figure 11, **38, 39**). Brevianamide B (**40**),[96-101] which contains a *spiro*-indoxyl rather than a *spiro*-oxindole, and the asperparalines,[98,102-106] which contain a *spiro*-succinimide, are also structurally comparable.

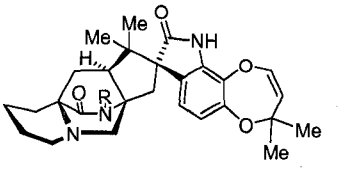
Paraherquamide A (**8**), as described in a recent total synthesis in the Williams group,[86,107-111] bears a masked C(3) reverse prenyl group. Whereas in norgeamides A and B (Figure 5) the C(3) reverse prenyl group is not connected to any neighboring carbons, the C(3) reverse prenyl group in paraherquamide A (**8**) appears to have undergone a proposed biosynthetic Diels-Alder reaction[108,112-117] to generate the unusual bicycle[2.2.2]diazaoctane core. A key reaction in the completion of paraherquamide A is a carbon-carbon bond migration from C2 to C3 via a Pinacol-type rearrangement to effect

the equivalent of C(3) reverse prenylation and concomitant introduction of the *spiro*-oxindole.

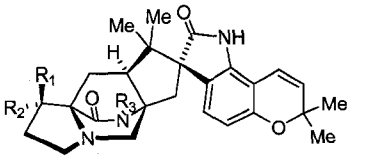
Figure 11. The paraherquamides and related compounds.



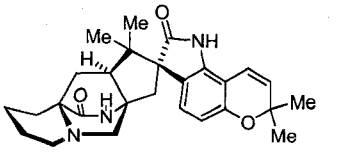
8, paraherquamide A, R_1 = OH, R_2 = Me
9, paraherquamide B, R_1 = H, R_2 = H



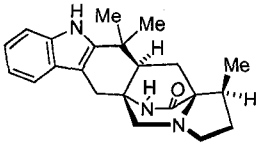
36, marcfortine A, R = Me
37, marcfortine B, R = H



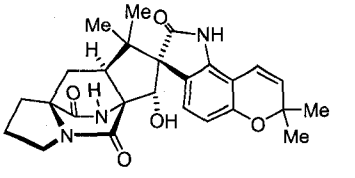
10, paraherquamide F
R_1 = H, R_2 = Me, R_3 = Me



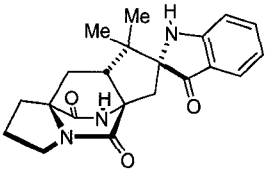
38, marcfortine C



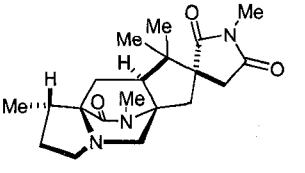
39, VM55599



41, sclerotiamide



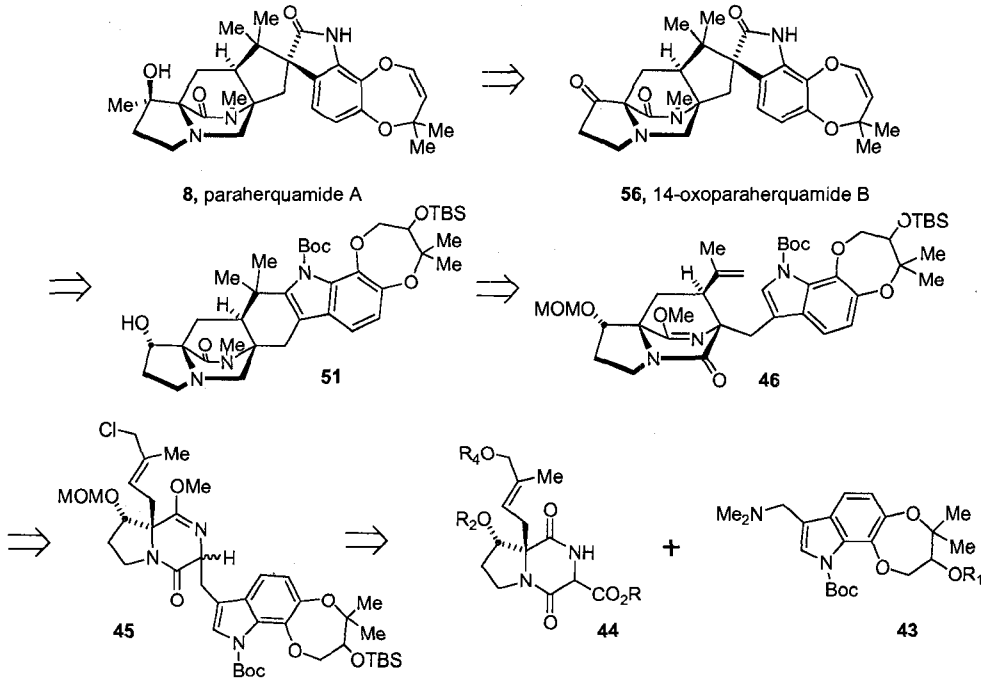
40b, brevianamide B



42, asperparaline A

Key steps in the synthesis include the union of suitably functionalized indole **43** and diketopiperazine **44** through a Somei-Kametani coupling[118,119] to obtain compound **45**. An intramolecular S_N2' cyclization followed by palladium-mediated closure to C2 of the indole moiety, and finally oxidation and rearrangement of the 2,3-disubstituted indole affords the spiro-oxindole, 14-oxoparaherquamide B (Figure 12), which is converted to paraherquamide A (**8**) via addition of methyl Grignard.

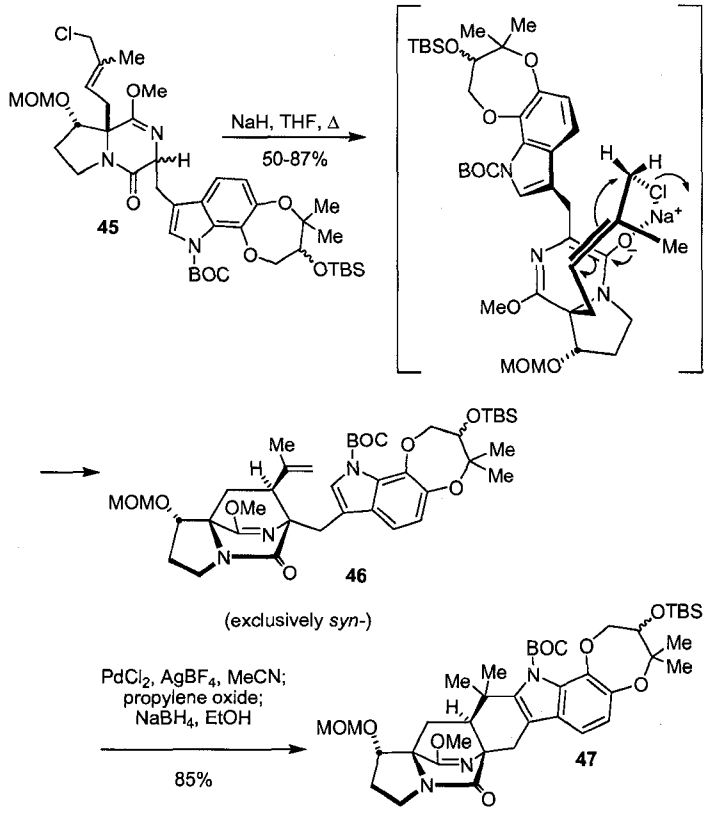
Figure 12. Williams' Retrosynthetic Plan for Paraherquamide A.



A critical step in Williams' and Cao's synthesis is the masked-C3-reverse prenylation event. This C-C bond forming reaction was set up via the preparation of compound **45**. (Scheme 6). Thus, compound **45** was treated with NaH in THF to afford the desired S_N2' cyclization product **46**.

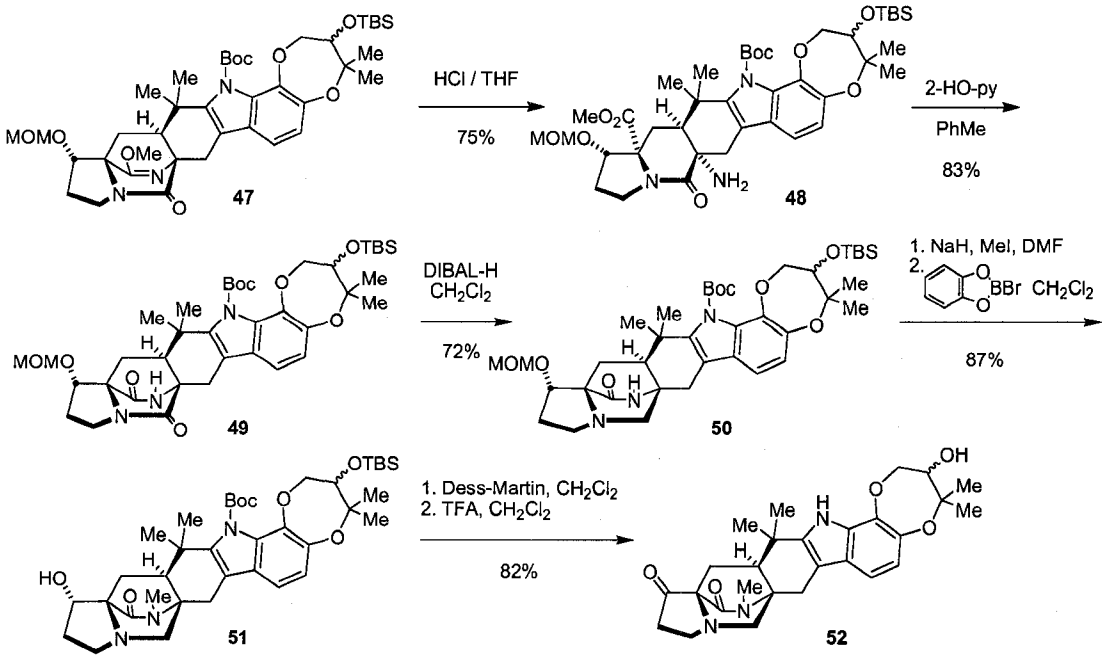
It was proposed that the reaction which is conducted in a nonpolar solvent like THF, proceeds via a tight, intramolecular ion-pair driven cyclization ("closed" transition state)[120,121] as shown in Scheme 6, to provide exclusively the *syn*-isomer. The final ring was then closed with $PdCl_2$ and $AgBF_4$ using propylene oxide as an acid scavenger, followed by $NaBH_4$ to reduce the incipient heptacyclic σ-palladium adduct.[122]

Scheme 6. Diastereoselective intramolecular S_N2' cyclization.



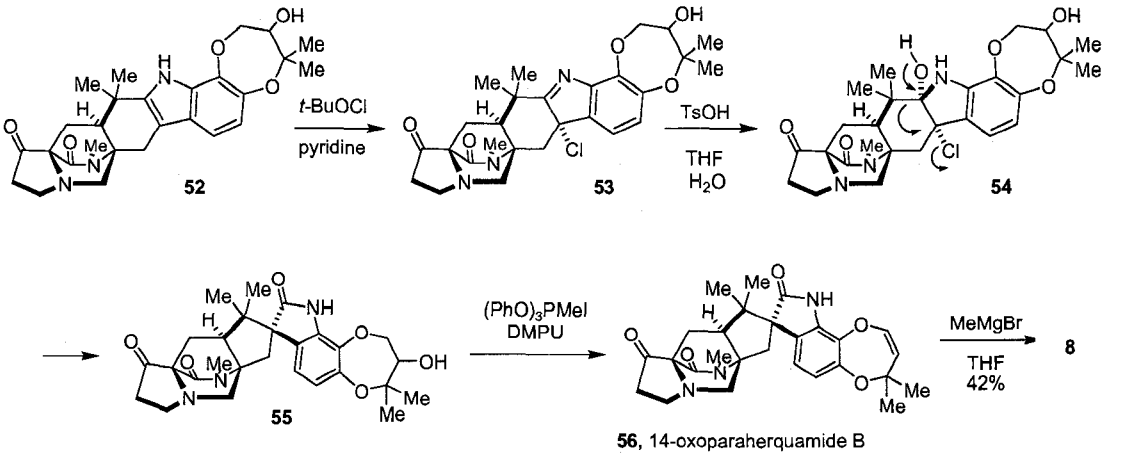
The lactim ether **47** could not be converted directly to the amide; However use of 0.1N aq. HCl in THF gave the corresponding ring-opened methyl ester **48** which could be closed uneventfully to the bicyclo[2.2.2]diazaoctane **49** by treatment of the amine **48** with catalytic 2-hydroxypyridine in refluxing toluene (Scheme 7).

Scheme 7. Williams' synthesis of paraherquamide A.



At this point a chemoselective reduction of the tertiary amide over the secondary amide was performed by treatment of **49** with diisobutylaluminum hydride (DIBAL-H) in dichloromethane. *N*-methylation of the secondary amide proceeded smoothly followed by cleavage of the MOM ether with bromocatecholborane.[123] The secondary alcohol of fragment **51** was oxidized with Dess-Martin periodinane.[124,125] Removal of the *N*-*t*-BOC group and TBS ether with TFA gave ketone **52** (Scheme 8). The final critical oxidative spirocyclization of the 2,3-disubstituted indole was effected by a two-step procedure. Treatment of **52** with *tert*-butyl hypochlorite[126] in pyridine provided a labile 3-chloroindolenine, from which it was found necessary to rigorously remove, by azeotroping with benzene, all of the pyridine prior to the next step. Pinacol-type rearrangement with TsOH in aqueous THF then generated the desired *spiro*-oxindole **55**.

Scheme 8. Spirocyclization and Total Synthesis of Paraherquamide A.



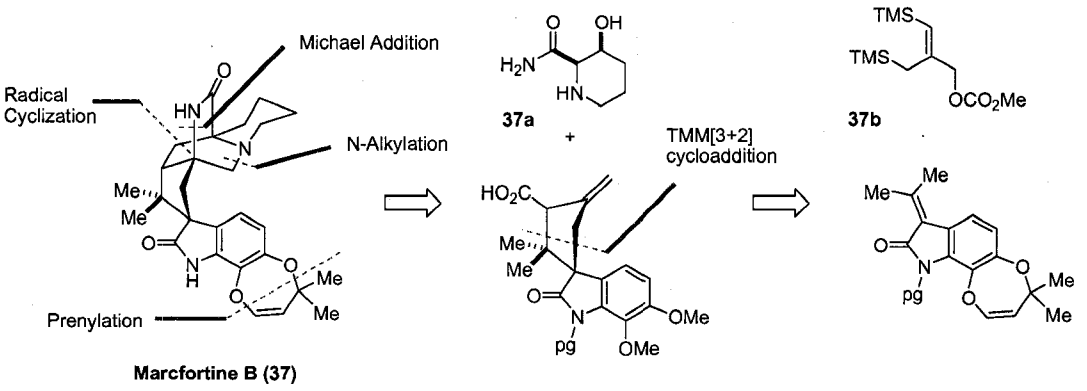
Previous investigations in the Williams group showed that the use of sterically hindered bases gave the best stereoselectivity during the chlorination reaction. The assumption was that the addition of chlorine to **52** proceeds via the least-hindered face of the indole giving chloroindolenine **53**. Hydration of the transient chloroindolenine occurs from the same face to generate the *syn*-chlorohydrin **54**, which subsequently rearranges stereospecifically to the desired spiro-oxindole **55**. Paraherquamide A was thus obtained after dehydration of the final secondary alcohol with methyltriphenoxyphosphonium iodide followed by addition of methyl magnesium bromide to the ketone group of **56**.

1.5.3 The *Spiro*-Oxindole: Trost's Synthesis of (±)-Marcfortine B.

Trost's synthesis of marcfortine B (**37**) employs a carboxylative trimethylene-methane (TMM) [3+2]-cycloaddition methodology (Figure 12a). The strained, bicyclo[2.2.2]diazaoctane core would be assembled by an alkylation of 2-

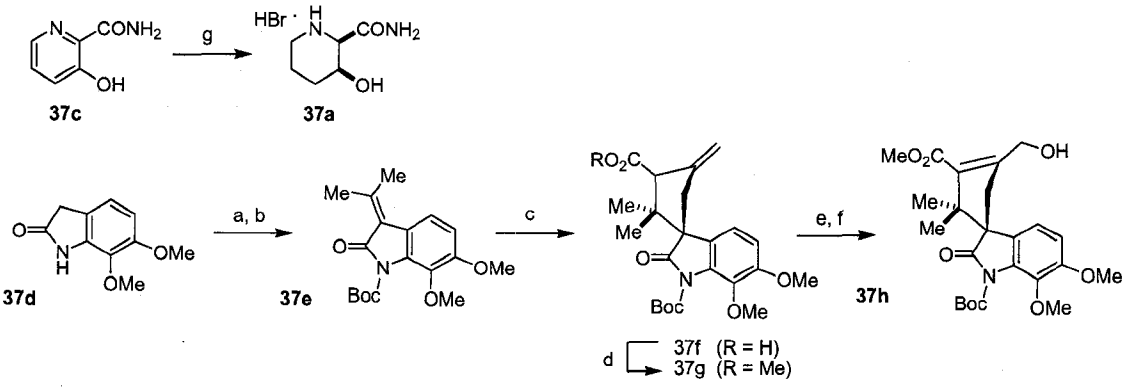
hydroxypipecolic amide (**2**), followed by an intramolecular Michael addition and a radical cyclization.

Figure 12a. Trost's Retrosynthetic Analysis.



Trost's TMM-acceptor **37e** is accessible from the known oxindole **37d** (Scheme 8a). Thus treatment of **37d** with acetone and HCl at ambient temperature gave the desired olefin which was subsequently treated with Boc_2O and DMAP to protect the oxindolic nitrogen. Treatment of **37e** with TMM-donor **37b** in the presence of catalytic palladium acetate and triisopropyl phosphite gave the desired spiro-oxindole **37f**. Methylester formation followed by epoxidation and treatment with DBU gave allylic alcohol **37h** as a single diastereomer.

Scheme 8a. Synthesis of allylic alcohol **37h**.



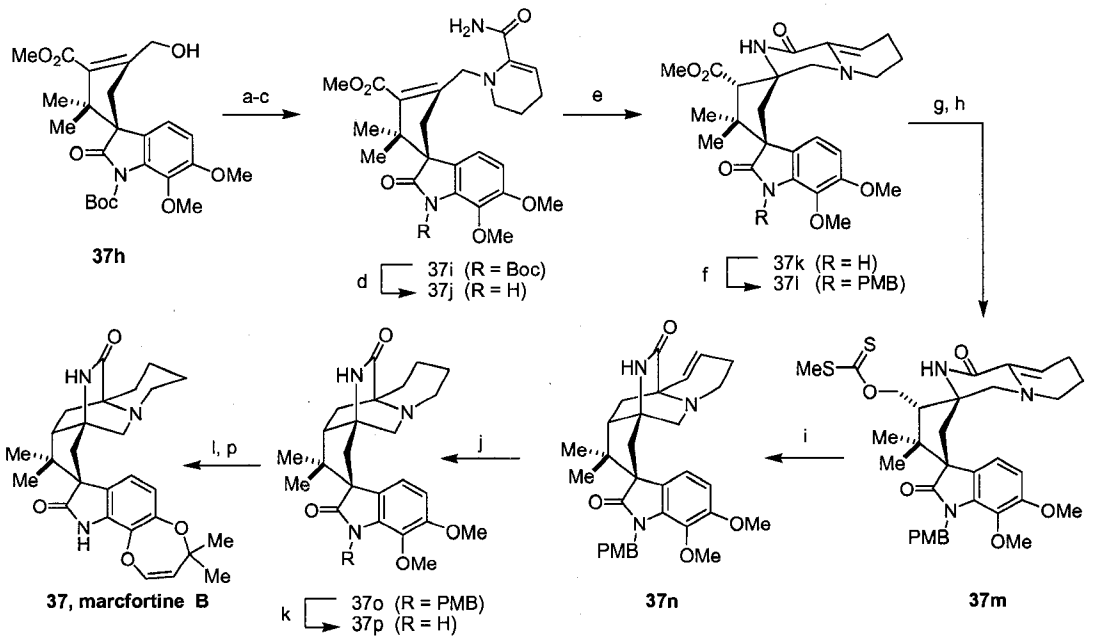
Conditions: (a) acetone, HCl, room temp, 70%; (b) Boc_2O, DMAP, NEt_3, CH_2Cl_2, 85%; (c) **37b**, 5% PdOAc, 35% $P(Oi\text{-}Pr)_3$, toluene, reflux; (d); Me_2SO4, K_2CO_3, acetone, reflux, 93% over two steps; (e) *m*CPBA, CH_2Cl_2, 0 °C, 89%; (f) DBU, THF, 0 °C to room temp, 72%; (g) 100 bar H_2, cat.Rh/Al_2O_3, aq HBr pH 3, 65 °C, quant.

At this point the allylic alcohol **37h** was activated as the mesylate followed by displacement of the newly formed mesylate with piperidine **37a** giving the desired coupled product whose secondary alcohol was eliminated again by activation as the mesylate and treatment with triethylamine to afford the α,β-unsaturated amide **37i** (Scheme 8b). Finally, removal of the Boc group of **37i** was effected using tintetrachloride to afford the Michael addition precursor **37j**.

Treatment of the free oxindole **37j** with potassium hexamethyldisilazide afforded the Michael adduct **37k** as a single diastereomer in quantitative yield. The authors propose aromatic shielding of the re-face as a means to explain the observed selectivity, which leads to selective protonation of the latent enolate by the amide hydrogen to afford the desired trans-relationship of ester **37k**. Due to poor solubility of ester **37k**, a re-protection step was employed to afford the PMB derivate **37l**. Chemoselective reduction of the ester with DIBAL gave the primary alcohol which was subsequently converted into

xanthate ester **37m** using standard procedures. Xanthate **37m** was treated with AIBN and 20% tributyltin hydride in refluxing benzene to afford a carbon-centered radical which closed to form the desired bicyclo[2.2.2]diazaoctane core. This transformation suffered an unexpected elimination event to form exclusively olefin **37n,** which necessitated reduction using Crabtree's catalyst to afford **37o**. Finally, deprotection of the PMB group with TFA / anisole gave the free oxindole **37p**. The final steps in the synthesis included the cleavage of the methyl ethers, mono-prenylation at the 7 position of the oxindole with prenyl bromide, epoxidation and endo-cyclization to form the 7-membered ring, and finally, elimination of the secondary alcohol to afford marcfortine B.

Scheme 8b. Completion of marcfortine B.

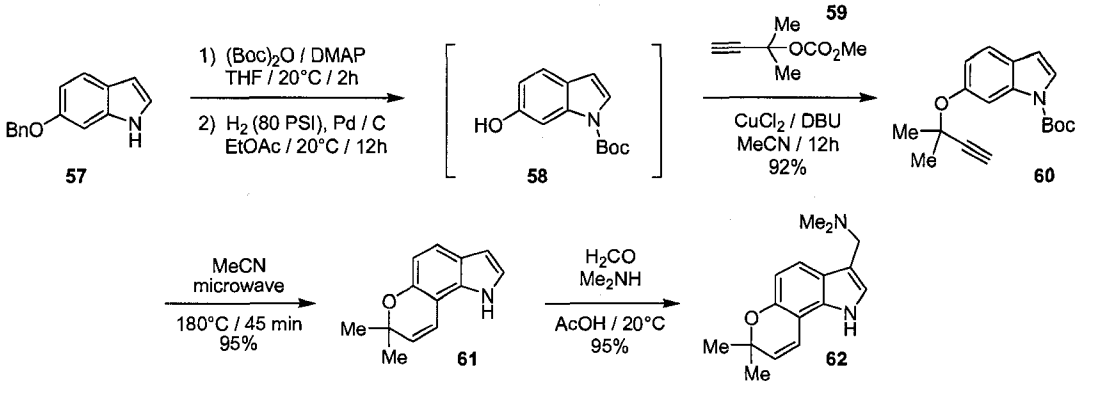


Conditions: (a) MsCl, NEt_3, CH_2Cl_2, 0 °C; (b) **37a**, NEt_3, DMSO, room temp; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C, then DBU, 84% over three steps; (d) $SnCl_4$, EtOAc, room temp, 89%; (e) KHMDS, THF, 0 °C to room temp, quant.; (f) PMBCl, Bu_4NI, K_2CO_3, acetone, reflux, 95%; (g) DIBAL, CH_2Cl_2, 0 °C, 86%; (h) KHMDS, THF, CS_2, -78 °C to room temp, then MeI, 75%; (i) 170% AIBN, 20% Bu_3SnH, C6H6, reflux, 61%; (j) 50 bar H_2, 15% Crabtree's catalyst, CH_2Cl_2, 89%; (k) TFA, anisole, reflux, 91%; (l) BBr_3, CH_2Cl_2, 0 °C; (m) prenylbromide, KI, Cs_2CO_3, acetone/H_2O 10:1, 62% over two steps; (n) *m*CPBA, $CHCl_3$, 0 °C to room temp, then aq $NaHSO_3$; (o) $SnCl_4$, dioxane, room temp; (p) $MeP(OPh)_3I$, DMPU, room temp, 42% over three steps.

1.5.4 Williams' S_N2' Mediated Synthesis of (+)-Stephacidin A.

Williams (+)-stephacidin A synthesis begins with commercially available 6-benzyloxy indole **57** (Scheme 9). Treatment of **57** with $(Boc)_2O$ in the presence of catalytic DMAP gave the N-tert-butoxycarbonyl derivative which was directly hydrogenated at 80 psi to afford 6-hydroxy indolic derivative **58**. Intermediate **58** was directly alkylated with carbonate **59** in the presence of DBU and catalytic $CuCl_2$ in 92% overall yield after 3 steps. The ether **60** was subjected to microwave irradiation in MeCN for 15 min at 180°C to achieve not only the thermal Claisen rearrangement but also thermolytic cleavage of the Boc protecting group. Conversion of indole **61** to gramine **62** was conducted under standard conditions using aqueous formaldehyde and dimethylamine in acetic acid as solvent.

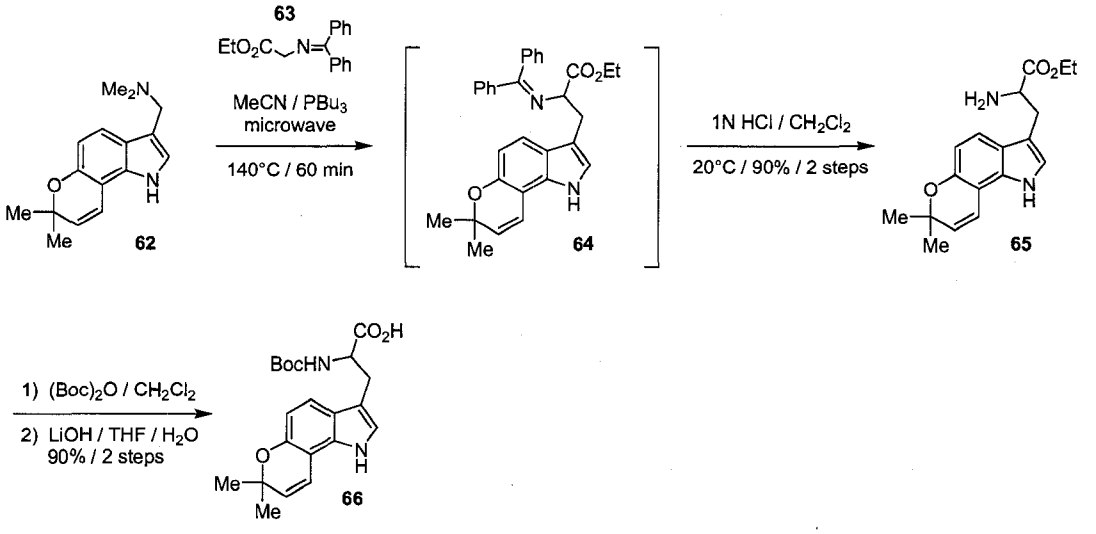
Scheme 9: Synthesis of pyranoindolic tryptophan **66**.



Coupling of gramine **62** to the commercially available benzophenone imine of glycine **63** was also effected using microwave irradiation in MeCN in the presence of catalytic PBu_3 (30min, 130°C) to afford imine **64**, which after removal of the benzophenone protecting group with 1N HCl, afforded the amino ester **65** in 90% over the two steps (Scheme 10).

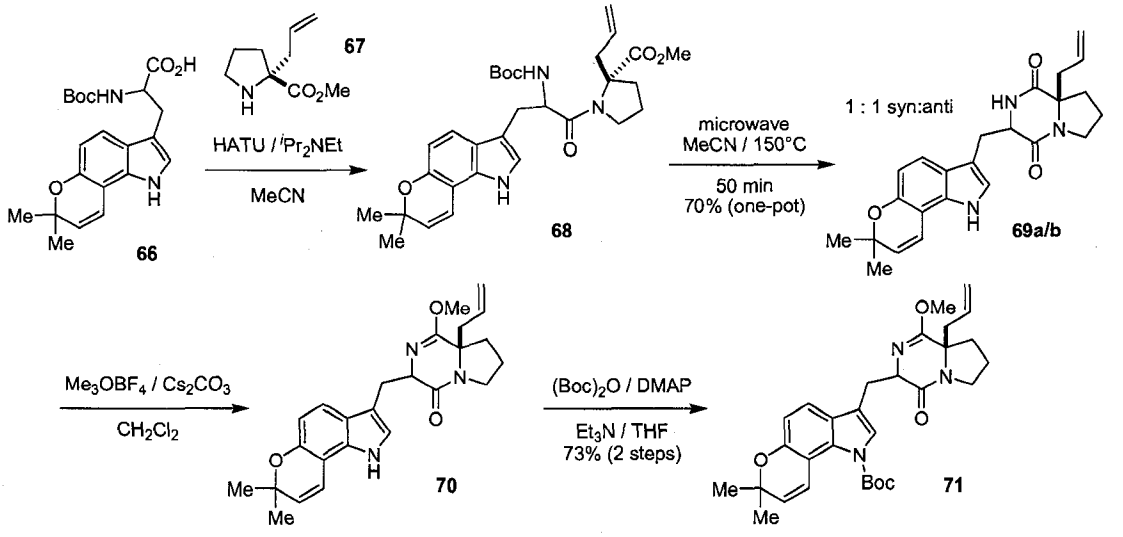
Chemoselective introduction of the Boc protecting group onto the primary amine of **65** followed by saponification using LiOH produced the N-Boc acid **66** in excellent yield over the two steps.

Scheme 10: Somei-Kametani Coupling and acid formation.



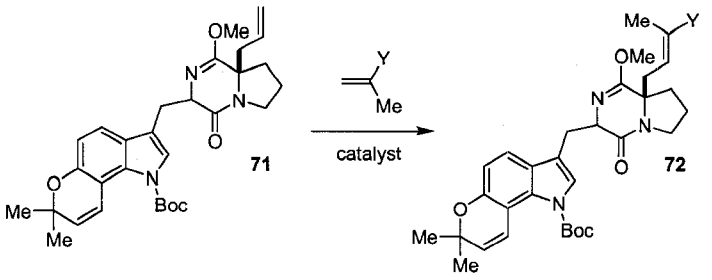
Coupling of commercially available allyl proline methyl ester **67** to tryptophan acid **66** was completed using HATU in the presence of the $^{i}Pr_2NEt$ (Scheme 11). Heating the crude coupled reaction mixture containing **68** by microwave for 50 min at 150°C effected thermal removal of the Boc protecting group followed by concomitant cyclization to the desired diketopiperazine **69a/b** as a 1 : 1 mixture of diastereomers that were separated by flash silica gel chromatography in 70% yield. Introduction of the lactim ether protecting group onto the amides **69a/b** by employing Me_3OBF_4 in the presence of Cs_2CO_3 and subsequent Boc protection of the indolic nitrogen provided key substrate **71** poised for a cross-metathesis reaction.

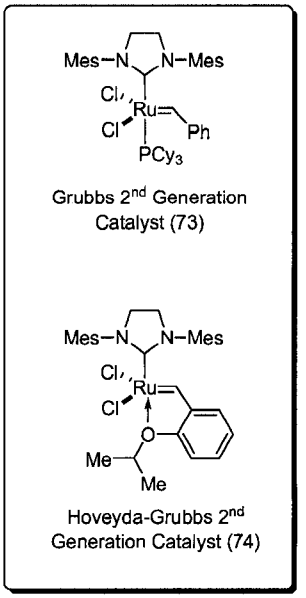
Scheme 11: Formation of the diketopiperazine.



Attempts to convert the terminal olefin of **71** to the requisite allyl chloride **72** (Y = CH_2Cl) using Grubbs' 2nd generation catalyst (**73**) and commercially available 3-chloro-2-methyl-2-propene failed to produce the desired product leaving much of the starting olefin **71** unchanged (Scheme 12). Alternatively, cross-metathesis of **71** with methacrolein using catalytic **73** in refluxing CH_2Cl_2 for 24 hr readily afforded the aldehyde **75** (Y = CHO) in 65% yield with 20% recovered starting material. Unfortunately, additional quantities of the catalyst **73** had to be added during the reaction raising the catalyst loading from the initial 5 mol % to 20 mol %. Using the Hoveyda derivative of the Grubbs 2nd generation catalyst (**73**), the catalyst loading was reduced back to 5 mol % and the yield for **75** (Y = CHO) was increased to 70% with 10% of **74** after 48 hr of reflux. Finally, heating olefin **71** with methacrolien in the presence of 5 mol % of **74** in CH_2Cl_2 at 100°C for 45 min generated the aldehyde **75** (Y = CHO) in 73% with 10% recovered starting material.

Scheme 12: Cross metathesis results.



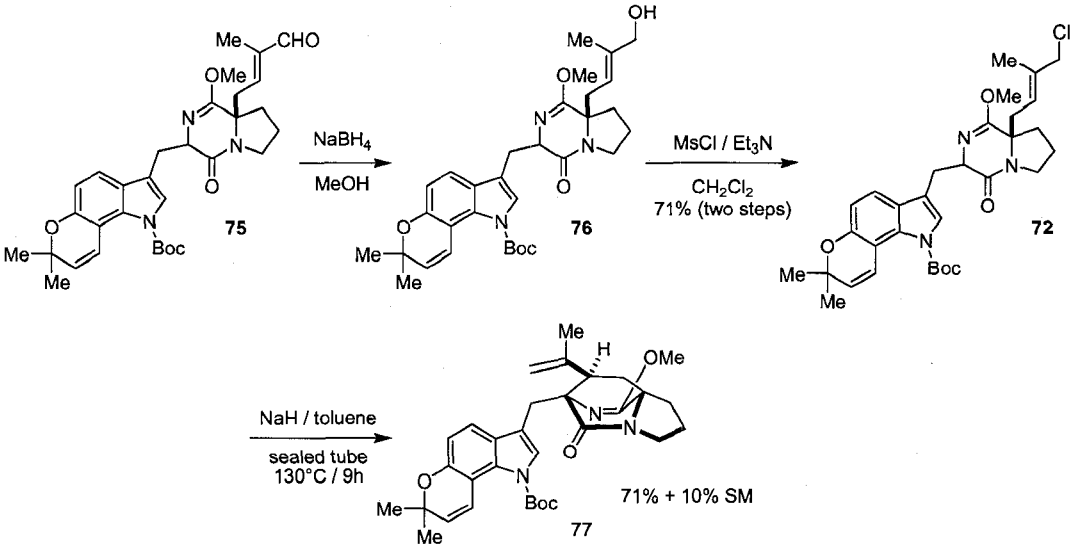


Y	Catalyst	Conditions	Yield of 75
$-CH_2Cl$	**73** (5 mol%)	CH_2Cl_2 / reflux / 24h	Recovered **71**
-CHO	**73** (5-20 mol%)	CH_2Cl_2 / reflux / 24h	65% + 20% **71**
-CHO	**74** (5 mol%)	CH_2Cl_2 / reflux / 48h	70% + 10% **71**
-CHO	**74** (5 mol%)	CH_2Cl_2 / 100°C Microwave / 45 min	73% + 10% **71**

Upon successful cross-metathesis, the reduction of aldehyde **75** was performed using $NaBH_4$ in MeOH to afford the allylic alcohol **76**. After a series of failed chlorination reactions (MsCl, LiCl, etc.), the desired allyl chloride **72** was finally accessed by slow addition of MsCl / TEA to a 0°C solution of the allylic alcohol in CH_2Cl_2 followed by slow warming to 20°C over 12 hr (Scheme 13). Cyclization of the allyl chloride **72** under standard S_N2' conditions was then explored. Exposure of **72** to 20 equiv. of NaH in toluene followed by refluxing for 30 hr afforded the desired bridged bicycle **77** in 60% yield and as a single stereoisomer, which presumably arises through a chelate-controlled closed-transition state. However, the length of the reaction time was less than desirable.

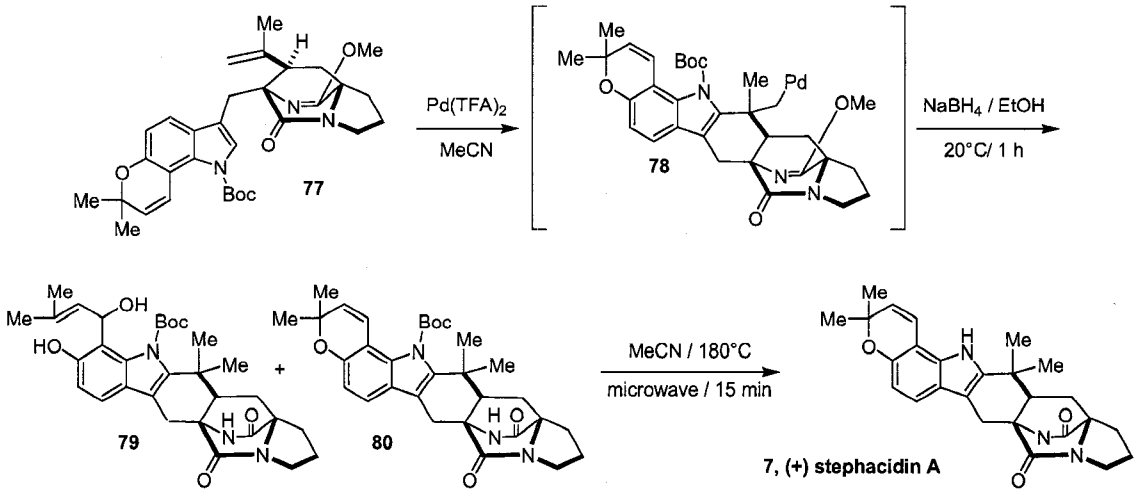
Ultimately, heating of **72** with NaH in toluene at 130°C for 9 hr produced the desired product **77** in an improved 71% yield with recovered starting allyl chloride **72**.

Scheme 13. Formation of the [2.2.2] bridged bicycle.



With the formation of the bridged bicycle complete, the task remained to form the heptacyclic ring system as well as to remove the lactim ether and Boc protecting groups. Closure to the heptacycle was achieved using a one-pot, two step procedure developed by Trost and employed in the synthesis of paraherquamides A and B. Thus, exposure of **77** to 5 equiv. of $Pd(TFA)_2$ in MeCN at 20°C rapidly formed the alkyl palladium intermediate **78** (Scheme 14). The reaction was then diluted with EtOH and exposed to $NaBH_4$ and subsequently quenched with 1N HCl to afford **79** and **80** as an inseparable mixture in a 1.6 : 1 ratio. Heating the mixture of **79** and **80** in MeCN via microwave irradiation at 180°C for 15 min afforded (+)-stephacidin A.

Scheme 14: Completion of the total synthesis of (+)-stephacidin A.



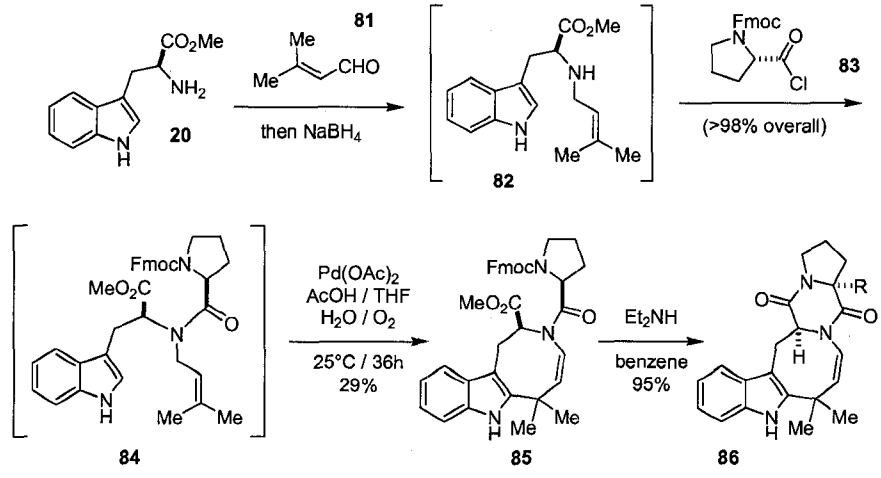
1.5.5 The *Spiro*-indoxyl: Corey's Synthesis of (+)-Austamide.

In June of 2002, E.J. Corey and P.S. Baran reported a very elegant palladium-mediated indole to dihydroindoloazocine cyclization.[127-130] This work, following in the footsteps of Kishi and Hutchison,[127-130] provided the first enantioselective total synthesis of (+)-austamide (**89**). Embedded in this work is an excellent example of the formation of a *spiro*-indoxyl group.

Corey's synthesis is shown in Scheme 15. Using readily available (L)-Tryptophan methyl ester as starting material, the corresponding N-prenylated amino acid was generated by amination of 3-methyl-2-butenal in CH_2Cl_2 using 4 Å molecular sieves followed by reduction with $NaBH_4$ in methanol. Removal of the solvent and reaction with Fmoc-(S)-prolyl chloride **83** in CH_2Cl_2 at 23°C gave the coupled amide **84** which again was isolated by simply removing the solvent. This material was treated with 1 eq.

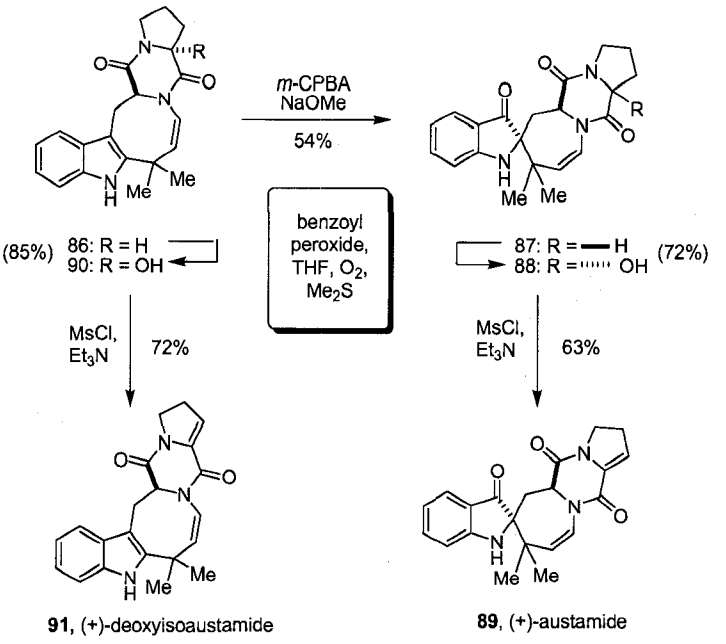
$Pd(OAc)_2$ in 1:1:1 THF / H_2O / AcOH at 23°C under 1 atm O_2 for 36h. These conditions afforded after flash chromatography on silica gel the desired indolazocine **85** in 29% yield. The Fmoc group was removed under standard conditions followed by thermal cyclization in refluxing benzene to afford diketopiperazine **86** in 95% yield.

Scheme 15. Enantioselective total synthesis of (+)-austamide.



At this point Corey's synthesis intersects with the pioneering work of Kishi and Hutchison.[127-130] In an unprecedented and completely chemoselective radical-initiated α-hydroxylation reaction, both Corey and Kishi introduce the required oxidation at the proline residue (Scheme 10).

Scheme 16. Radical initiated α-hydroxylation / *spiro*-indoxyl formation.



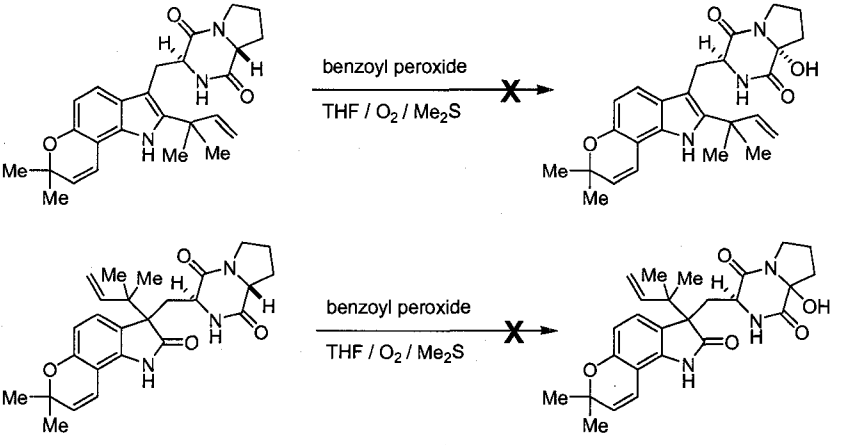
The total synthesis of (+)-austamide was accomplished by first epoxidation of the indole 2,3-double bond in **86** with *m*-CPBA followed by C-O bond cleavage to afford a 3-hydroxy indolenine intermediate. Subsequent rearrangement of the 3-hydroxy indolenine subunit via a pinacol-type ring contraction gave indoxyl **87** in 54% yield. This material was then selectively oxidized at the proline subunit using benzoyl peroxide under 1 atm O_2 followed by reduction with dimethylsulfide to afford α-hydroxy **88** in 72% based on recovered **87**. It is noteworthy to point out that the conversion of **87** to **88** takes place with inversion of configuration while the oxidation of **86** to **90** occurs with retention of configuration. The synthesis was completed via a final elimination step mediated by methane sulfonyl chloride in the presence of Et_3N. Alternatively, (+)-deoxyisoaustamide **91** was generated by direct oxidation of the proline residue **86** under the same radical-initiated α-hydroxylation protocol followed by elimination. Investigations into the

complete mechanism of the α-hydroxylation reaction and the palladium mediated ring closure are currently underway in the Corey group.

Note:

At first glance the benzoyl peroxide / O_2 / Me_2S oxidation of the proline subunit in **86** or **87** appears to be a general reaction that might have applications in the total synthesis of many α-hydroxy proline bearing natural products. This assumption was the basis for a sizeable body of research within these pages in our efforts to synthesize norgeamides A and B. We have since found that this oxidation is not general and most likely a conformation dependent process operative only in cyclic compounds **86** and **87**. Our approach towards these molecules now focuses on pre-installation of the required oxidation state of the proline subunit to access the α-hydroxy group through more conventional and general methodology (Figure 13).

Figure 13. Failed α-hydroxylation



1.5.6 Conclusions and Goals

The natural products described above all bear similar functionality and share a pattern of reactivity unique to *spiro*-oxindole and *spiro*-indoxyl alkaloids. Although the mode of action of the paraherquamides and similar molecules is not yet completely characterized, advances in the synthesis of related molecules continue to piece together complex hidden machinery.

Described in the following pages are two entirely new classes of compounds whose isolation and characterization have only begun to be divulged. The norgeamides and notoamides are new families of natural products bearing many of the structural features of the paraherquamides, stephacidins, and marcfortines.

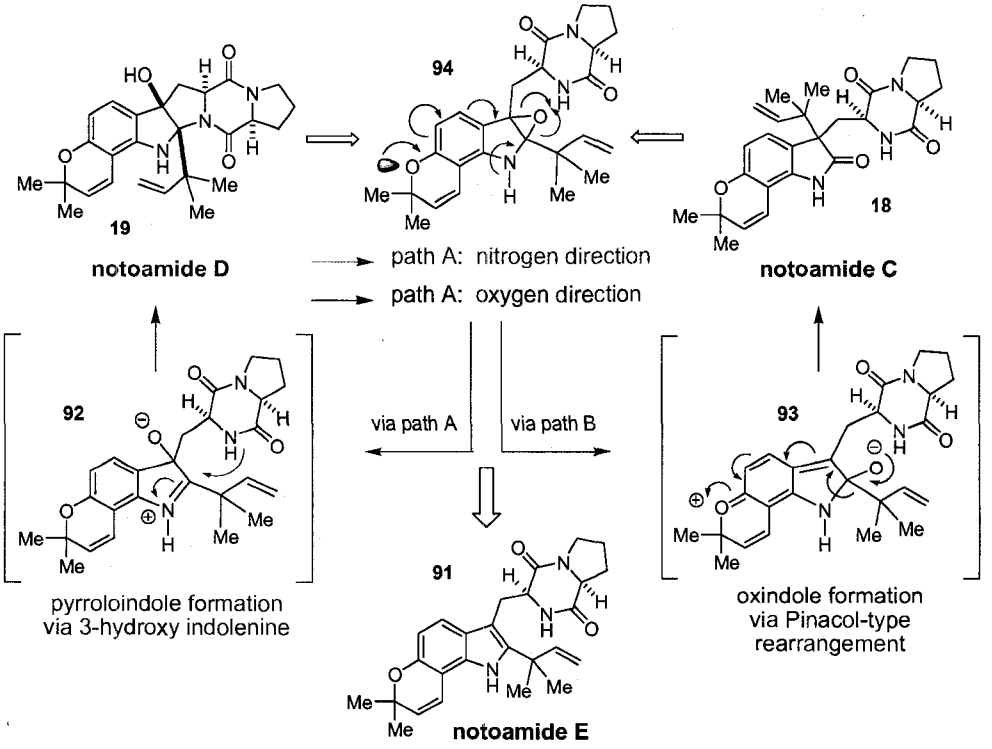
The research herein seeks to uncover new methodology and achieve the total synthesis of each member of the norgeamide and notoamide families of natural products. In doing so we hope to contribute to an understanding of the molecular features that lead to biological activity and help resolve the yet unsettled mechanism of action.

Chapter 2: Total Synthesis of Notoamides C and D

2.1 Retrosynthetic Analysis of Notoamides C and D

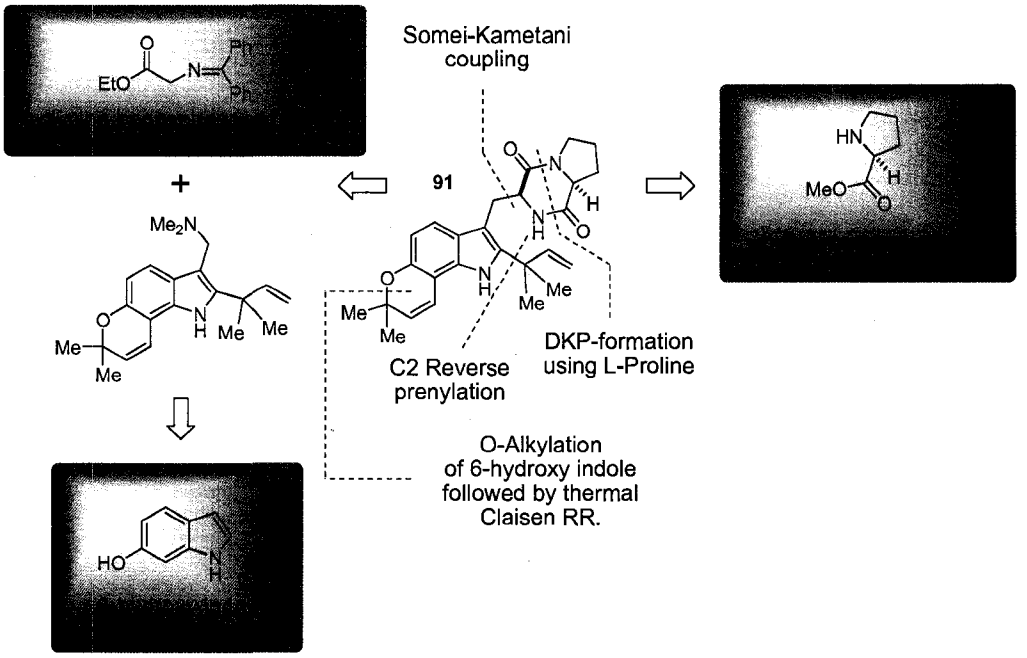
Our initial target, considering the synthesis of the notoamides, was notoamide D (**19**). Previous work on similar molecules suggested that epoxidation of the indole 2,3-double bond in proposed natural product, notoamide E (**91**), would afford a 3-hydroxyindolenine intermediate **92** which would readily be trapped by the exposed amide nitrogen (Figure 14, purple arrows) to produce notoamide D (**19**). Another possibility, that was not immediately considered, would be the oxygen directed generation of a *pseudo-para*-quinone methide[131,132] **93** that could undergo the proposed pinacol-type rearrangement shown below to generate notoamide C (**18**, Figure 14, blue arrows).

Figure 14. Oxygen vs. nitrogen directed epoxide fragmentation.



Epoxide **94** would in turn be derived from a potential natural product, notoamide E (**91**), bearing the natural L-configuration at both amino acid residues. Our retrosynthesis of notoamide C or D is then simplified to a high yielding and concise synthesis of notoamide E (**91**, Figure 15).

Figure 15. Notoamide E: Retrosynthetic Analysis



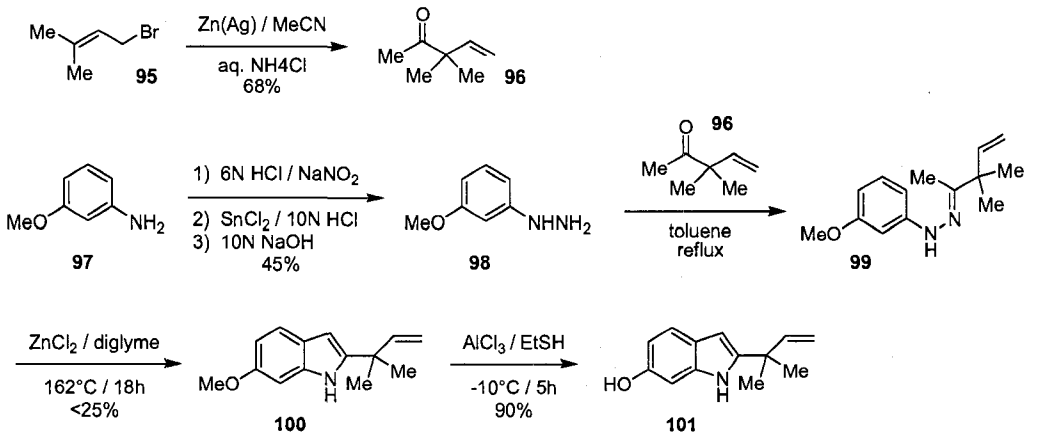
An examination of the diketopiperazine ring quickly identifies L-proline and an L-tryptophan analog as the two required constituents. Indole is a widely used precursor to tryptophan derivatives which suggests 6-hydroxy indole as a logical starting material leaving only a phenolic O-alkylation and a C2-reverse prenylation sequence to fully functionalize the left hand portion of the molecule. The stereochemistry of the tryptophan derivative mimics that of natural L-tryptophan and thus any synthetic plan

must include either the development of an enantioselective amino acid synthesis favoring the natural L-configuration or a strictly racemic amino acid synthesis that would dependably afford a maximum yield of 50% of the desired enantiomer. Given a fairly rigid time constraint, we favored the latter racemic route leaving for a second generation synthesis the burden of an asymmetric amino acid protocol. The Somei-Kametani coupling[118,119] of 3-dimethylaminomethyl indoles would serve as an ideal template to access both the R and desired S amino acid configuration. After coupling with L-proline ethyl ester and closure to a diketopiperazine, the separation of the desired naturally configured dipeptide (**91**) could be accomplished, which after oxidation should generate either notoamide D and 2,3-epi-notoamide D (Figure 14, purple arrows), or notoamide C and 3-epi-notoamide C (Figure 14, blue arrows).

2.2 C3 Reverse Prenylation.

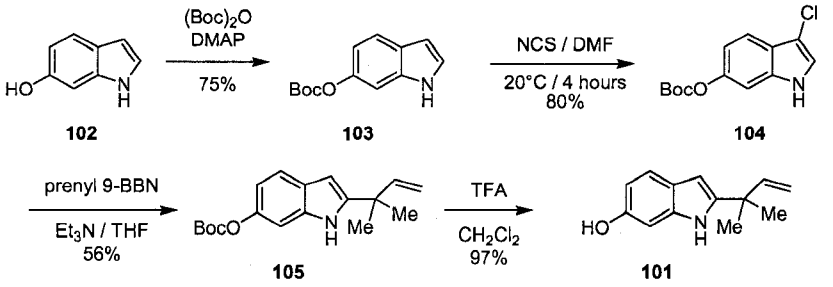
The first challenge in the synthesis of the tryptophan derivative was the development of a high-yielding C2 reverse prenylation sequence. Previous work in the Williams group[36] had afforded a tedious and low-yielding synthesis of indole **101** (Scheme 17). Historically, weeks, if not months, were required to painstakingly prepare the components of a Fisher-Indole synthesis that yielded a 1 : 1 mixture of the 4- and 6-methoxyindoles that after careful separation provided the desired 6-methoxy indole **100** in less than 25%. Adding to the difficulty of the synthesis is the unpleasant methyl ether cleavage in the presence of $AlCl_3$ and ethanethiol to afford the phenolic derivative **101** in varying yields and purity.

Scheme 17. Williams / Cox Synthesis of C2 reverse prenyl, 6-hydroxy indole.



Foreseeing the need for consistent, multi-gram quantities of indole **101**, a more direct synthesis was proposed drawing from a report in 2001 by Tatsuta in which 3-chloroindoles were reverse prenylated at C2 of indole with prenyl 9-BBN.[133] To this end, the hydroxyl group of commercially available 6-hydroxyindole **102** was protected as its Boc carbonate to form indole **103** (Scheme 18). Indole **103** was then chlorinated using NCS to afford the 3-chloroinole **104** in good yield. Pleasingly, compound **104** readily reacted with prenyl 9-BBN[134] to afford the C2 reverse prenyl indole **105** in 60-70% yield. We believe the electron withdrawing nature of the carbonate is vital for the success of this reaction in that electron rich variants of **104** (i.e. silyl ethers, and alkyl ethers) proved extremely sluggish in the chlorination reaction and failed to produce any of the desired prenylated indole.

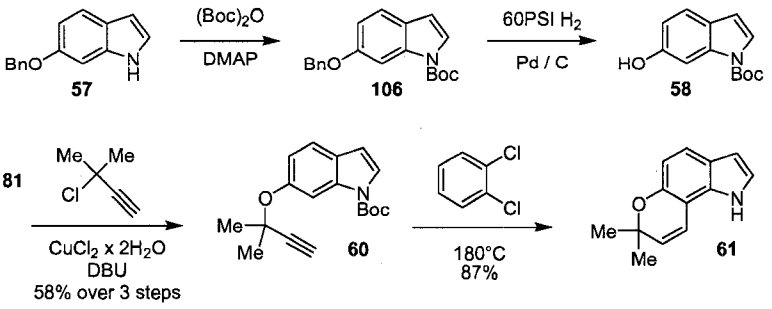
Scheme 18. Alternative synthesis of indole **101.**



Finally, removal of the Boc carbonate of **105** with TFA produced the previously reported 6-hydroxy-2-reverse prenyl indole **101** obtained by the Fisher indole route. Our new route to indole **101** affords the desired product in 4 steps and 41% overall yield and excellent purity in comparison to the previous route requiring 5 steps to afford 7% of the desired product after a very laborious series of purification events.

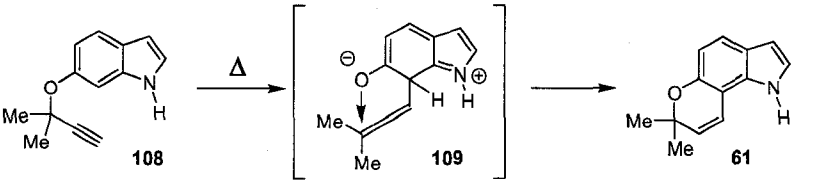
At this point the O-alkylation of 6-hydroxyindole **101** was investigated. Previous work had suggested that the phenolic oxygen could be alkylated using $CuCl_2$ x $2H_2O$. The procedure for alkylation of the similar 6-hydroxy indole **58** (Scheme 19), included a protection step of the indole nitrogen. Thus the nitrogen of commercially available 6-benzyloxy indole **57** was protected with $(Boc)_2O$ and subsequently hydrogenated to afford N-boc-6-hydroxy indole **58**.

Scheme 19. Synthesis of pyrano indole.



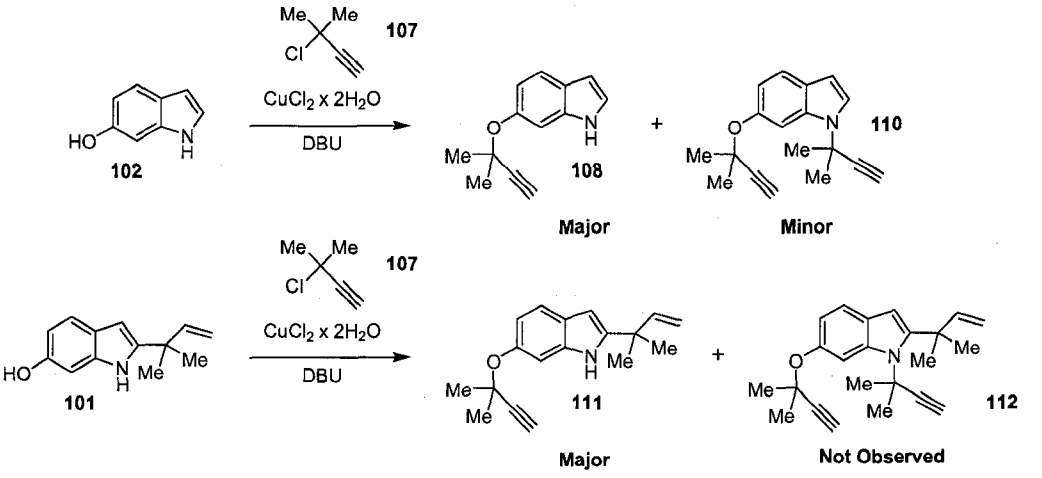
The phenolic oxygen of **58** was then alkylated with 3-chloro-3-methylbut-1-yne **107** in the presence of $CuCl_2$ x $2H_2O$ to afford ether **60** in 58% over the 3 steps on multi-gram scale. Finally, simply heating compound **60** in *o*-dichlorobenzene at 180°C cleanly effected the aromatic Claisen cyclization as well as Boc cleavage to afford the desired pyrano indole **61** in 87% yield. Amazingly, this thermal Claisen cyclization occurs completely regioselectively to afford the 6,7-pyrano indole over the regioisomer, the 5,6-pyrano indole. This selectivity arises most likely from the electron rich nature of the 7 position due to two adjacent *ortho*-directing groups (Figure 16). The mechanism of this rearrangement proceeds most likely through cleavage of the O-C bond to generate allene **109**, which closes to the observed pyran via cyclization and re-aromatization.

Figure 16. Regioselective thermal Claisen rearrangement.



In our system, the process of Boc-protection was not needed for two obvious reasons: 1) Introduction of the reverse prenyl group at C2 all but shuts down any reactivity of the indole nitrogen (Figure 16). As a result, very few protecting groups can be installed after reverse prenylation at C2. 2) Protection of the indole nitrogen of **58** was needed in Scheme 19 because the exposed nitrogen would facilitate over-alkylation with chloride **107** (Scheme 20). So not only does the the reverse prenyl group at C2 block functionalization of the indole nitrogen, but also it serves as an internal blocking group to prevent over alkylation in the $CuCl_2$ x $2H_2O$ reaction.

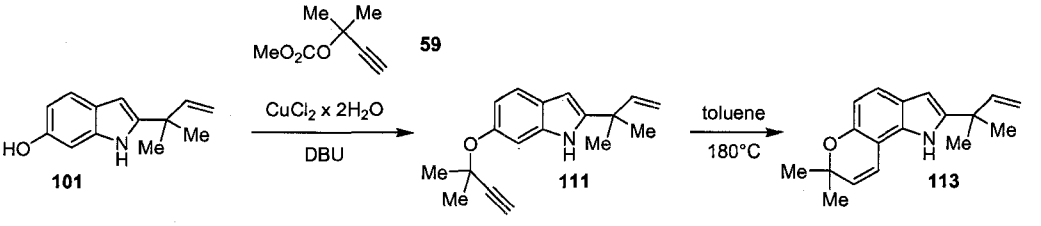
Scheme 20. $CuCl_2$ x $2H_2O$ mediated over-alkylation.



2.3 Somei-Kametani Coupling

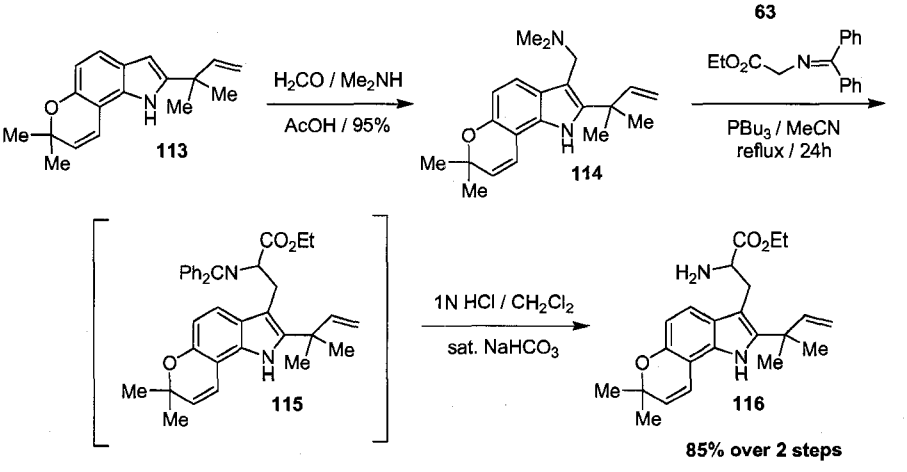
Our synthesis of indole **113** (Scheme 21) begins with the alkylation of phenol **101**. A major improvement in the alkylation of **101** was reported first by Godfrey and co-workers[135] and then used again in Baran's synthesis of stephacidin A.[32] Where chloride **107** (Scheme 20) gave mixed results, methyl carbonate **59**[26] (Scheme 21) afforded a much more consistent and higher yielding alkylation than the corresponding tertiary chloride. The yield of this alkylation depends highly on the nature of the leaving group.[26] Thus carbonate **59** prepared in one step from the corresponding alcohol and methylchloroformate, served as an excellent electrophile in the $CuCl_2$ x $2H_2O$ reaction.

Scheme 21. 2nd Generation Synthesis of Inodole **113**.



Treatment of phenol **101** with carbonate **59** in the presence of $CuCl_2$ x $2H_2O$ and DBU afforded ether **111** in >80% yield. We then looked to replace the cumbersome *o*-dichlorobenzene reaction and quickly found that simply heating **111** in toluene at 180°C effected complete conversion to the desired pyran **113**. This simple solvent exchange greatly improved throughput by eliminating a difficult process needed to completely remove excess *o*-dichlorobenzene solvent. Preparation of the required tryptophan derivative then began using standard conditions to prepare Somei-Kametani substrate **116** using standard procedure (Scheme 22).[29]

Scheme 22. Synthesis of Amino Ester **116**.



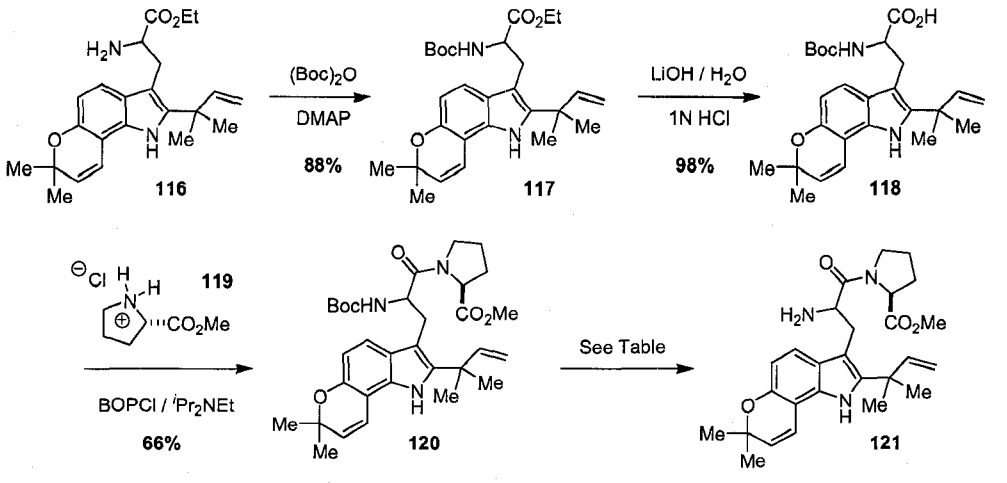
Thus upon treatment of indole **113** with a pre-mixed solution of formaldehyde and dimethylamine in 0°C acetic acid as solvent, previously reported indole **114** was isolated after neutralization of excess acetic acid with solid NaOH. Somei-Kametani coupling of **114** and commercially available ethylglycine benzophenone imine **63** afforded the desired product **115** along with 0.5-1.0 eq. PBu_3. Instead of a troublesome and precarious isolation of benzophenone imine **115** the entire reaction mixture, after the Somei-

Kametani coupling, was directly concentrated and partitioned between CH_2Cl_2 and 1N HCl. This mildly acidic and biphasic reaction mixture served to quickly hydrolyze the benzophenone imine **115** which after a basic work-up provided the desired free amine **116** which was easily separated from the byproducts of two separate reactions. In doing so we had completed our desired racemic amino acid synthesis. A template had been established for research into further asymmetric amino acid syntheses and we now could investigate the formation of the right hand fragment of notoamide C.

2.4 Total Synthesis of Notoamide E

Our first approach was to protect the amino acid nitrogen with a robust protecting group such as an N-Boc derivative (Scheme 23). The proposed Boc group would be stable to the future coupling conditions and would provide a product isolable on silica gel after hydrolysis under standard conditions (LiOH, NaOH, THF, H_2O). To this end, aminoester **116** was protected as the N-Boc-carbamate under standard conditions to afford carbonate **117** in good yield. Standard hydrolysis using LiOH and H_2O at 0°C provided exclusively the desired Boc-protected amino acid **118**. To our delight, coupling of commercially available L-proline ethyl ester took place uneventfully using the coupling reagent BOPCl[136] in the presence of N,N-diisopropyl ethylamine to afford dipeptide **120**. Interestingly, both the reaction rate and reaction yield were vastly improved by avoiding BOPCl available from Aldrich and freshly preparing the reagent in-house. The freshly prepared material could be stored for months assuming the reagent was dried overnight under high vacuum prior to use.

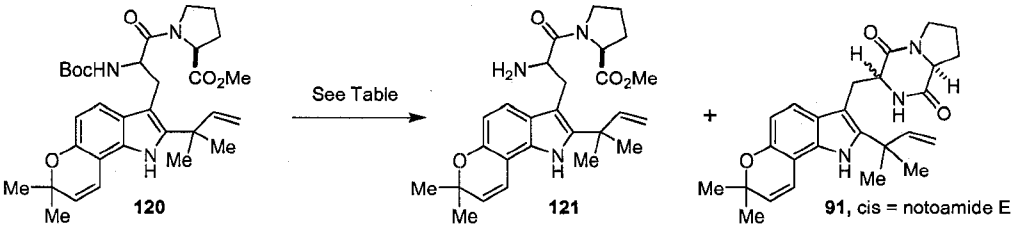
Scheme 23. Initial approach to notoamide E.



At this point all that remained to produce notoamide E was the removal of the N-Boc carbamate and subsequent thermal DKP formation. This process, unsuprisingly, turned out to be completely inconsistent with the stability of the recently formed pyran ring. All standard N-Boc deprotection attempts failed, returning either completely unreacted starting material or a complex reaction mixture due to decomposition of the pyran ring (Table 5).

Thermal removal of the Boc-group was completely ineffective leaving only unreacted starting material. Typical methods for removal of N-Boc indole derivates such as BBr_3 in CH_2Cl_2 at –78°C gave mixtures of baseline decomposition products as well as unreacted starting material. Also widely used $ZnBr_2$ in CH_2Cl_2 led to complete decomposition at any temperature. After numerous other attempts at Boc removal (Table 5), we were drawn to conditions used in Baran's synthesis of Austamide (Scheme 15), where the required diketopiperazine was formed under similar conditions using the amine base labile N-Fmoc protecting group.[127]

[p-Table 5. Failed attempts at Boc removal and DKP formation.

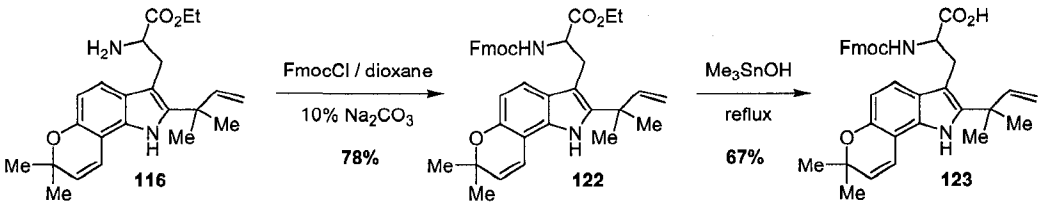


Conditions	% **120**	%**121**	%**91**	%decomp
toluene / 180°C	100	0	**0**	0
BBr_3 / CH_2Cl_2 / -78°C	50	0	**0**	50
$ZnBr_2$ / CH_2Cl_2 / 20°C	0	0	**0**	100
TBSOTf / 2,6-lutidine	90	0	**0**	10
AcCl / MeOH	90	0	**0**	10
TFA / CH_2Cl_2	0	0	**0**	100
3N HCl / dioxane	100	0	**0**	0

After experiencing poor results with Boc removal, protection of aminoester **116** was achieved using FmocCl in dioxane in the presence of an equal volume of 10% Na_2CO_3 (Scheme 24). Hydrolysis of **122** posed another problem in that our previously employed hydrolysis conditions, (LiOH, THF, H_2O), completely removed the Fmoc protecting group. At this point we looked to Nicolau's trimethyltin hydroxide hydrolysis[1] developed in their synthesis of thiostrepton.[2-4] Amazingly, complete hydrolysis of ethyl

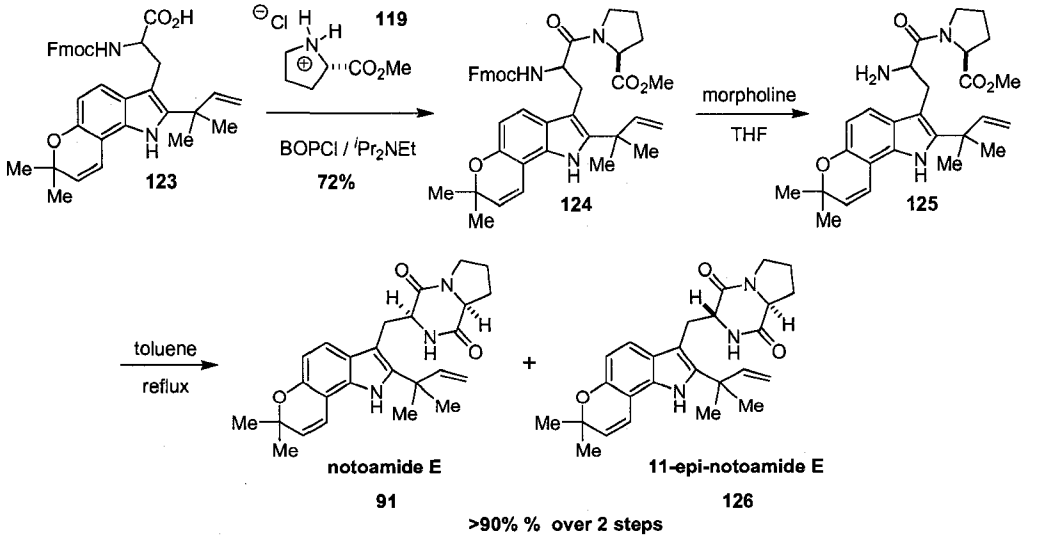
ester **122** was accomplished using 10 eq. trimethyltin hydroxide in refluxing dichloroethane without any cleavage of the sensitive Fmoc protecting group.

Scheme 24. Trimethyltin hydroxide mediated hydrolysis.



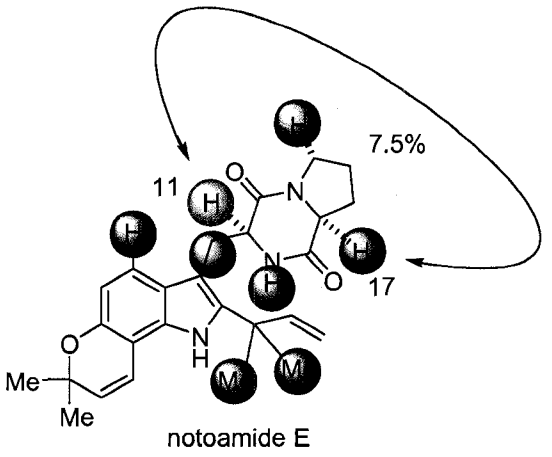
Finally, coupling of acid **123** with commercially available L-proline ethyl ester took place uneventfully using the coupling reagent BOPCl, in the presence of N,N-diisopropyl ethylamine (Scheme 25).

Scheme 25. Synthesis of notoamide E and 11-epi-notoamide E.



Isolation of dipeptide **124** was accomplished after a challenging separation of latent dibenzofulvene formed as **123** and **124** slowly decomposed under the reaction conditions. The primary amine **125** was then isolated after treatment with morpholine and then repeated distillation from toluene. The final closure of amine **125** to notoamide E and 11-epi-notoamide E was effected by refluxing amine **125** in toluene for 3 hours. Notoamide E and 11-epi-notoamide E were separated from dibenzofulvene by flash chromatography on silica gel. Finally, notoamide E and 11-epi-notoamide E were separated by PTLC to obtain each diastereomer in good yield. The stereochemistry of the diketopiperazine (trans vs. cis) was assigned by nOe observations (Figure 17).

Figure 17. Assignment of notoamide E by nOe.

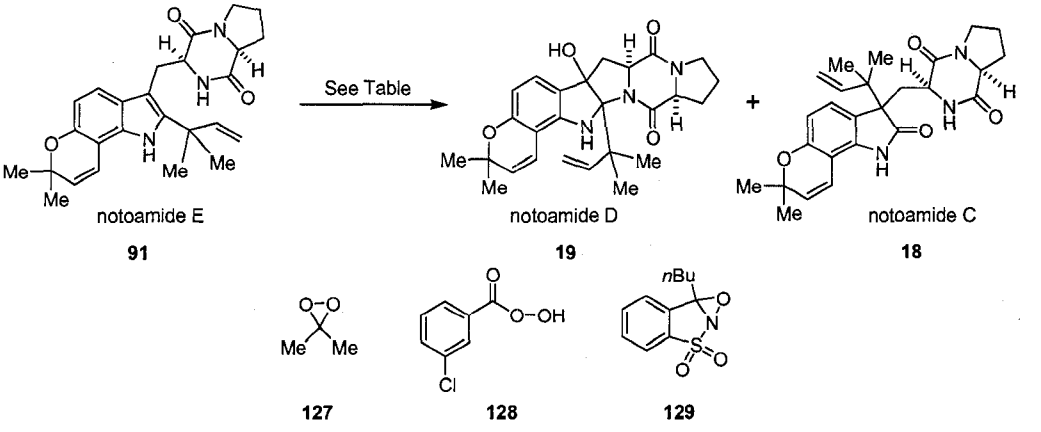


Irradiation of H11 (red) gave rise to the indicated nOe enhancements (blue) with the relative and absolute configuration of the diketopiperazine indicated by the double arrows.

2.5 Total Synthesis of Notoamides C and D

With the correct stereochemistry established at the diketopiperazine we sought to synthesize notoamide D. However, under a variety of oxidation conditions a number of counterintuitive observations were seen (Table 6).

Table 6. Oxidation of the 2,3-double bond in notoamide E.



Entry	Reagent	Conditions	Results
1	**127**	THF / acetone / -78°C	s.m. + decomposition + trace **18**
2	**128**	CH_2Cl_2 / Na_2HPO_4 / -78°C	s.m. + decomposition + trace **18**
3	**128**	CH_2Cl_2 / Na_2HPO_4 / -78°C *Inverse addition*	s.m. + decomposition + trace **18**
4	**O_2**	methanol / O_2 / light *methylene blue or rose bengal (sensitizers)*	s.m. + decomposition + trace **18**
5	**129**	CH_2Cl_2 / 20°C / 24 hours	90% **18** 10% **19**

Treatment of notoamide E **91** with a variety of oxidants gave almost no trace of the desired product notoamide D (Table 6, entries 1-4). Analysis by 1H NMR showed starting material and decomposition and a trace product showing presence of the indole

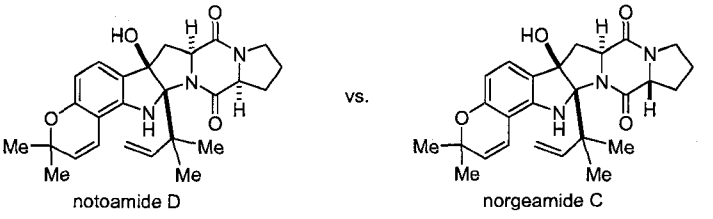
nitrogen and a dramatic downfield chemical shift (~6ppm to ~14ppm) of the amide N-H proton. A thorough analysis of the oxidation products was only accomplished after a very clean oxidation was observed using Davis' saccharin derived oxaziridine **129**.[5,6] Oxidation under these conditions gave cleanly two diasereomers varying in configuration at C3. Further analysis as well as comparison with natural notoamide C, confirmed the major reaction products as notoamide C and 3-epi-notoamide C, with trace amounts of the target compound notoamide D and 2,3-epi-notoamide D (Table 6, entry 5).

Although we had not anticipated the Pinacol rearrangement (Figure 14), we were delighted to confirm path B as the operative mechanism of oxidation to provide cleanly two natural products with the major products confirmed to be notoamide C and 3-epi-notoamide C.

2.6 Structural Revision of Norgeamide C

One last problem we wanted to investigate was the relationship of the recently published norgeamide C and our synthetic notoamide D (Figure 18).

Figure 18. Notoamide D vs. norgeamide C.

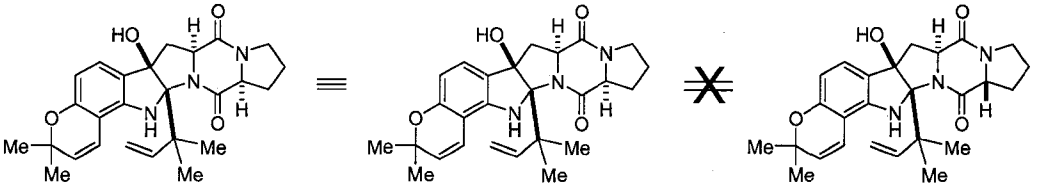


The structure of norgeamide C, recently published by the Hans-Knöll institute, bears a remarkably similar skeleton as notoamide D. In fact, our initial research toward both the

notoamides and the norgeamides began with non-natural D-proline to mimic the configuration found in norgeamide C. The proposed *trans*-relative configuration of the diketopiperazine was very intriguing due to the presence of the non-natural amino acid, D-proline. Spectral data obtained from the Hans- Knöll institute included norgeamides A-D all obtained in $CDCl_3$. Alternatively, all spectral data obtained for notoamides A-D were obtained in acetone-D_6. After many failed attempts to synthesize norgeamide C we began to question the assignment of the *trans*-diketopiperazine.

Finally a resolution to this issue came about by simply obtaining a spectrum of synthetic notoamide D in $CDCl_3$. In fact, comparison of synthetic notoamide D in $CDCl_3$ with natural norgeamide C showed two completely superimposable spectra at all points, thereby proving the misassignment of norgeamide C (Figure 19).

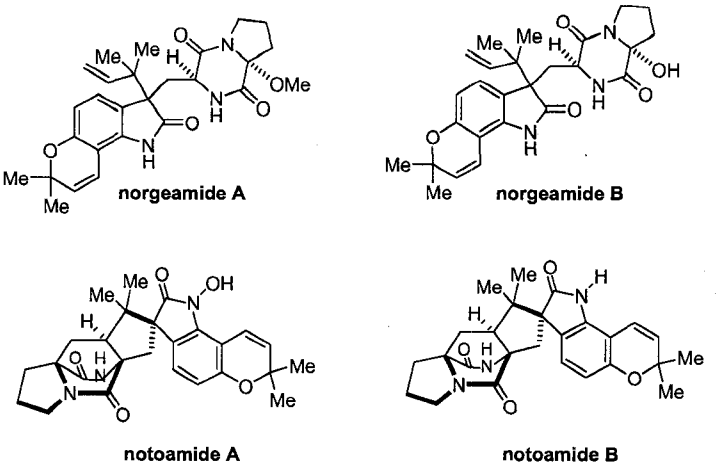
Figure 19. Structural revision of norgeamide C.



With a more solid understanding of the reactivity of the oxidation-Pinacol rearrangement mechanism we now turn our attention to a more complex series of natural products, norgeamides A and B and notoamides A and B (Figure 20).

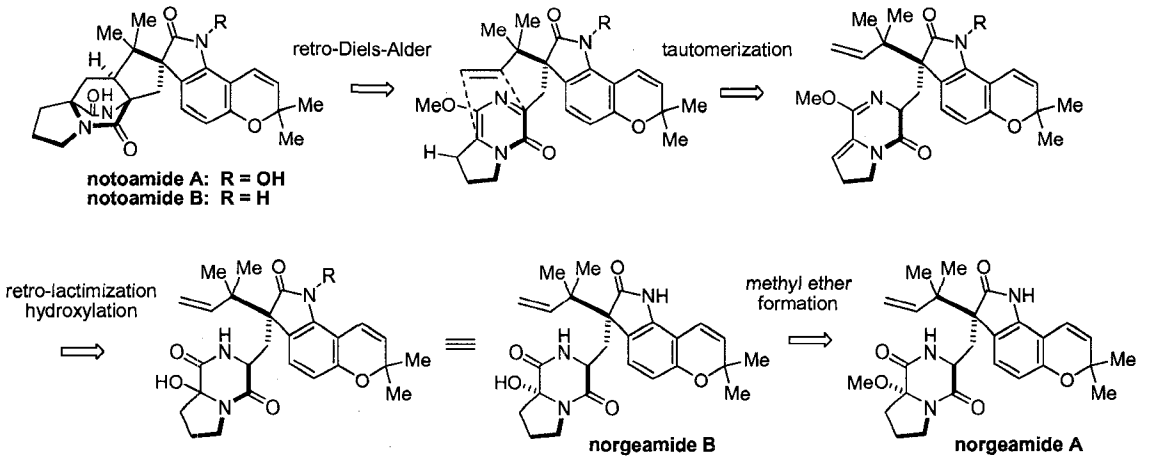
2.7 Similarities Between the Notoamides and the Norgeamides

Figure 20. Norgeamides A and B and notoamides A and B.



Norgeamides A and B and notoamides A and B (Figure 20) all bear the same oxidation state at the diketopiperazine. Norgeamide A and norgeamide B exhibit this oxidation at C2 of the proline ring where norgeamide A bears a methyl ether and norgeamide B bears the α-hydroxy proline derivative. Notoamides A and B share the same oxidation state as norgeamides A and B however the nature of the oxidation is not as apparent. Notoamides A and B bear the same oxidation state through the following disconnection sequence (Figure 20).

Figure 21. Norgeamide and Notoamide Similarities



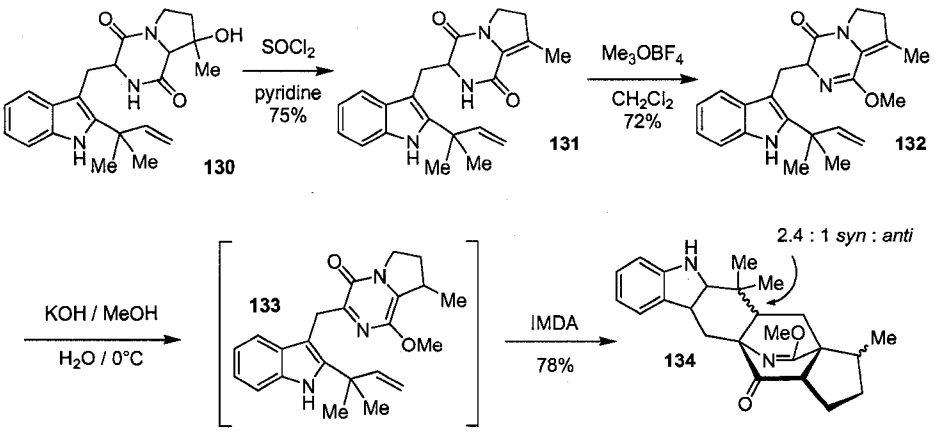
An obvious route to norgeamide B follows the previously reported work of Kishi and Hutchison.[7] However, upon subjection of our synthetic 17-epi-notoamide C to Kishi's conditions, no oxidation was observed (Figure 13). In fact, even using a large excess of benzoyl peroxide in refluxing THF, the 1H NMR of the starting material looked identical to reactions run at reflux for 24 and 48 hours without any sizeable decomposition. Additionally, using an excess of the oxaziridine **129** at reflux shows a clean Pinacol rearrangement of however no additional oxidation was observed.

Chapter 3. Studies Toward the Total Synthesis of Norgeamides A and B

3.1 Retrosynthesis of Norgeamides A and B.

Without a direct method to oxidize C17 of notoamide C, we turned to a more conventional approach. Based on a previous total synthesis of VM55599, accomplished by Williams and Stocking in October, 2000[8], we sought to synthesize compound **136** (Figure 22). Williams and Stocking's synthesis of VM55599 addressed the same oxidation problem via the putative Diels-Alder precursor **133** (Scheme 26).

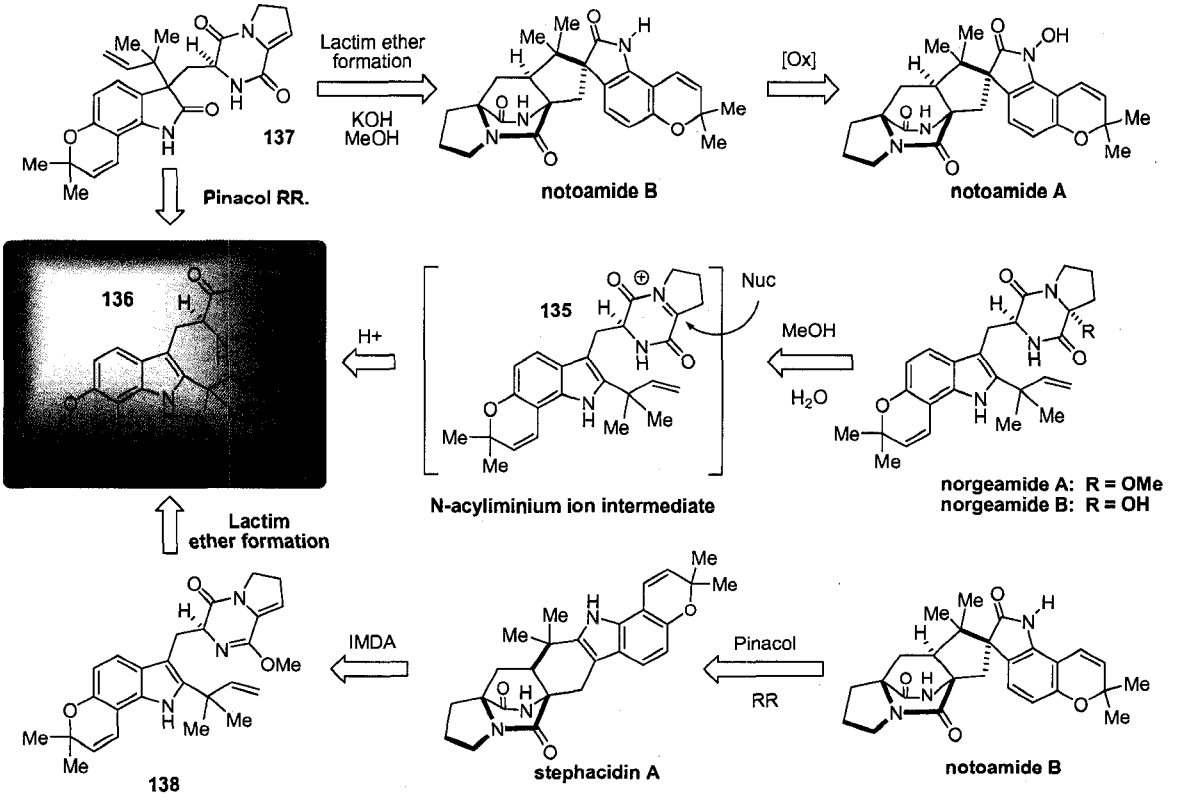
Scheme 26. Williams and Stocking's synthesis of VM55599.



Williams and Stocking coupled 3-methyl-3-hydroxy proline in a manner similar to our coupling reaction (Scheme 25). Dehydration was then effected in the presence of thionyl chloride in pyridine to afford as a single regio-isomer, enamide **131**. Subsequent treatment of **131** with trimethyloxonium tetrafluoroborate in dichloromethane provided the azadiene **132** in good yield. Treatment of azadiene **132** with KOH in aqueous methanol effected tautomerization to the labile incipient azadiene **133** which

spontaneously underwent intramolecular Diels-Alder (IMDA) cycloaddition at room temperature to give a mixture of four possible cycloadducts in 78% yield. With a very similar strategy in mind, we derive our retrosynthesis of notoamides A and B and norgeamides A and B from a common precursor **136** (Figure 22). Consequently, intermediate **138** should also provide a very concise route to stephacidin A, notoamide A, and notoamide B.

Figure 22. Retrosynthetic analysis of norgeamides, notoamides and stephacidin A.



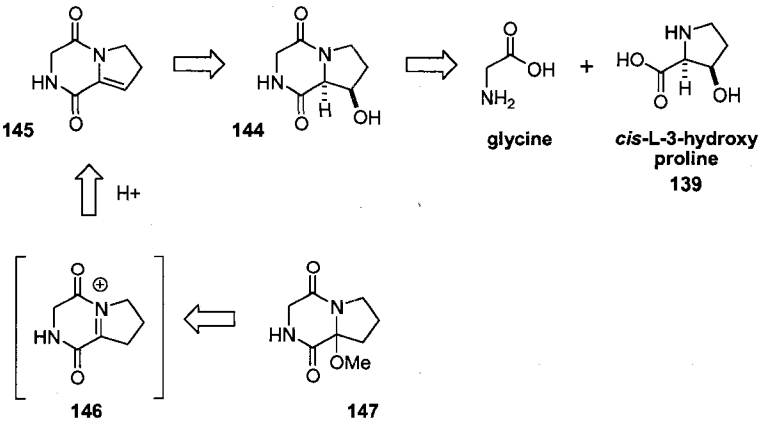
Generation of enamide **136** and subsequent lactim ether formation would give azadiene **138**. Treatment of azadiene **138** with KOH in methanol should afford stephacidin A through an intramolecular Diels-Alder cyclization and notoamide B after Pinacol

rearrangement. Similarly, direct Pinacol rearrangement of enamide **136** should give **137** which after treatment with KOH / MeOH should give notoamide B via the proposed intramolecular Diels-Alder cyclization. After another oxidation event, notoamide A should be afforded. Finally, generation of an N-acyliminium ion from enamide **136** (Figure 22), in the presence of an acidic methanol solution should form norgeamide A (methanol adduct) and / or norgeamide B (water adduct).

3.2 First Generation Model System: The N-Acyl Iminium Ion.

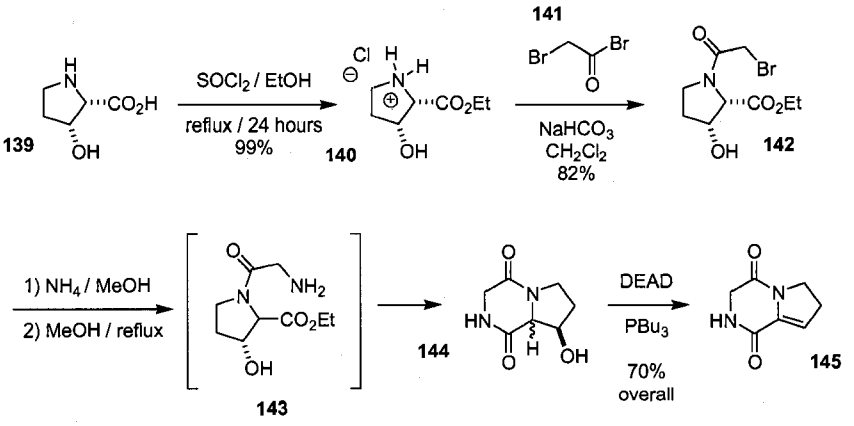
Before attempting to generate intermediate **136**, a much more simple model system was proposed to explore the potential to eliminate water to form enamide **145** and to assess the potential of compound **145** to form N-acyliminium ion **146**. The most simple model system would fundamentally be the union of glycine and *cis*-3-hydroxy-L-proline (**139**) to form intermediate **144** which could undergo elimination to form enamide **145** (Figure 23).

Figure 23. Enamide model system.



Using a very similar strategy, *cis*-L-3-hydroxy proline ethyl ester (**140**) was acylated under Schotten-Baumann conditions using bromoacetyl bromide (**141**, Scheme 27). In a one-pot two step procedure bromide **142** was converted to enamide **145** by first amination with NH_4 in ammonia, followed by elimination of the secondary alcohol under Mitsunobu conditions. Isolation of alcohols **143** and **144** were avoided due to their extreme polarity and water solubility. Although the amination sequence occurred with complete racemization of proline, alcohol **144** was isolated and reacted directly under the Mitsunobu conditions directly to afford **145** in good yield. Thus, *cis*-L-3-hydroxy proline was converted without chromatography in 3 steps and 70% overall yield to enamide **145**.

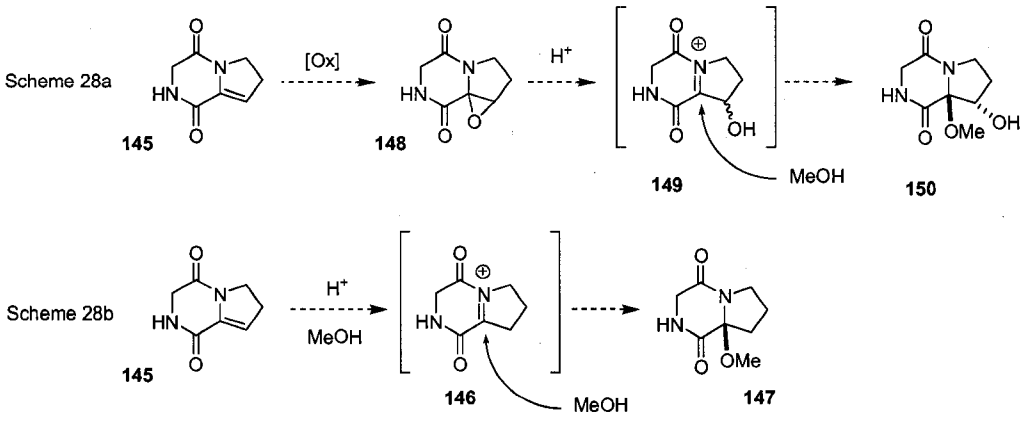
Scheme 27. 1st generation model system: N-acyliminium ion formation.



At this point we looked to two different oxidation strategies. One possibility would be to directly oxidize the double bond to an epoxide which, in the presence of methanol, should genereate 3-hydroxy ether **150** via N-acyliminium ion **149** (Scheme 28a). A more direct approach would be to generate N-acyliminium ion **146** (Scheme 28b) under highly acidic

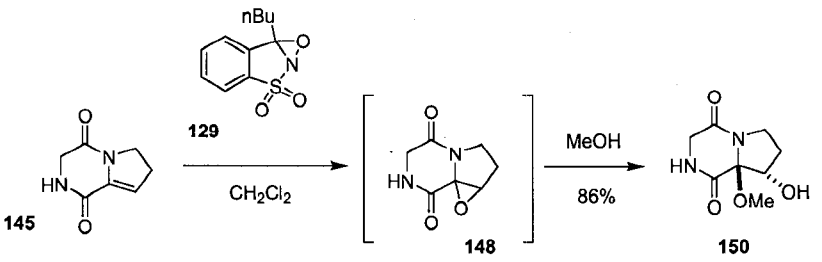
conditions and subsequently trap the incipient electrophile with methanol to afford methyl ether **147**.

Scheme 28. Methanolation of N-acyliminium ion.



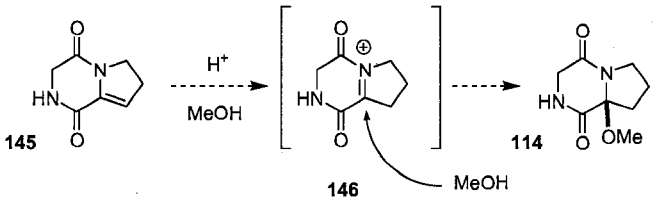
Following Scheme 20a, enamide **145** was stirred in CH_2Cl_2 with oxaziridine **129**, used earlier for our key Pinacol rearrangement. To our surprise, epoxidation was facile and simply removing the solvent and refluxing the newly formed epoxide in methanol generated the desired 3-hydroxy-2-methyl ether **150** (Scheme 29). Although we had accomplished the generation of the methanol adduct, this method would require a sensitive deoxygenation procedure in our full system.

Scheme 29. Epoxidation / methanolysis via oxaziridine **129**.



Given the anticipated difficultly in the deoxygenation reaction, we looked at a series of acids in order to assess the required pH to directly generate an N-acyliminium ion under the most mildly acidic conditions possible (Table 7). A typical procedure included using 4 eq. of the specified acid in methanol. Each reaction was run 24 hours at 20°C and then again for another 24 hours at reflux in methanol. The results of these experiments are summarized in Table 7. Initial experimentation showed little or no reactivity in almost every case at 20°C. However, after treatment of **145** with acids with pKa = < -8.0 at 20°C modest reactivity was observed. To our delight the reaction proceeded with near complete conversion at reflux at pKa = < -8.0. We then had found a very narrow range in pKa (pKa = -8.0 to –14.0) under which we could generate an N-acyliminium ion. We were happy however to observe that upon generation, the N-acyliminium ion, intermediate **148** would readily accept methanol.

Table 7. pKa of the acid vs. N-acyliminium ion formation.



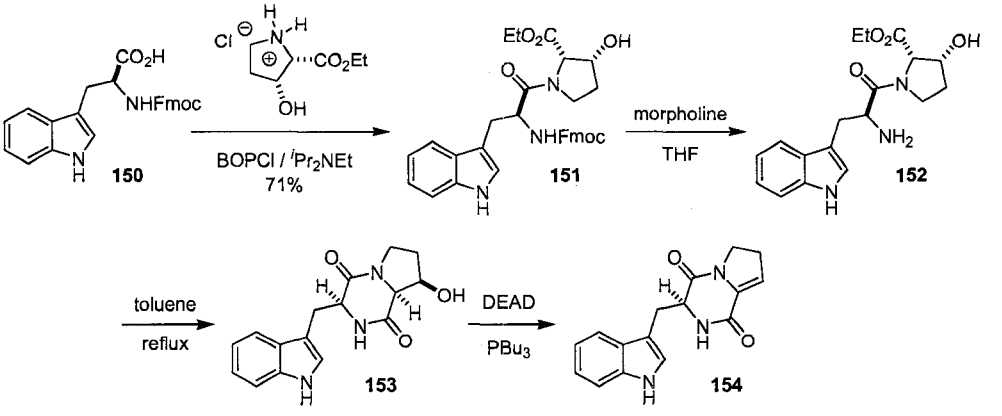
Acid (in Methanol)	% **147** at 20°C	%**147** after 24 hours at reflux	pKa =
PPTS	0	0	--
p-TsOH	0	0	--
MsOH	0	0	-0.6
HNO_3	0	0	-1.3
citric	0	0	> 1.0
$HClO_4$	**trace**	**>80%**	**-10**
TfOH	**20%**	**>80%**	**-14**
conc. aq. HCl	**20%**	**>80%**	**-8.0**

We were now in a position to extend our model system to answer a more compelling question. Would a tryptophan derivative survive the harsh, acidic conditions required to generate the N-acyliminium ion? To answer this question the following model system was employed (Scheme 30). This new model system had two objectives: 1) Determine the fate of L-tryptophan in the presence of acids at pKa = < -8.0 in methanol and 2) Pilot the chemistry required to build diketopiperazine **154** and ultimately, **136**. The answers to these questions would help in a decision to commit time and material to the construction of the complete natural product precursor.

3.3 Second Generation Model System: Stability of L-Tryptophan

Having already developed the peptide coupling sequence for L-proline (Scheme 25), our synthesis of the L-tryptophan model system was straightforward. Thus N-Fmoc-L-tryptophan was coupled to 3-hydroxyproline ethyl ester in good yields with BOPCl as the coupling reagent. Removal of the Fmoc protecting group mediated by morpholine was facile at 20°C to afford the transient amine **152** which underwent cyclization to diketopiperazine **153** after a short time at reflux in toluene.

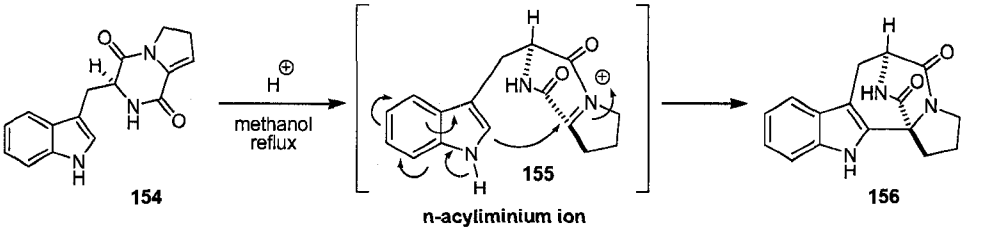
Scheme 30. Model system derived from L-tryptophan and *cis*-L-3-hydroxy proline.



Again, the secondary alcohol was eliminated in the presence of diethylazodicarboxylate (DEAD) and tributylphosphine to afford enamide **154** in good yield. We then had only to establish a pattern of reactivity in acidic methanol. Therefore **154** was treated with methanolic $HClO_3$, TfOH and conc. aq. HCl (Scheme 31). At first glance, a curious observation was made. It appeared that enamide **154** was completely unreactive under each condition. The product co-eluted and showed the exact retention on silica gel as the

starting material. Unwilling to accept that such a small modification to the model system in Table 7 would yield a completely unreactive intermediate, NMR data was obtained to establish this observation unambiguously. A very interesting observation resulted from the new data. As it turns out, compound **154** was very reactive under the proposed conditions, however the C2 carbon of the tryptophan moiety served as an internal nucleophile over the potential addition of methanol (Scheme 31).

Scheme 31. Stereospecific N-acyl Pictet-Spengler cyclization.



Thus treatment of **154** with acids of pKa < -8.0 in methanol formed an N-acyliminium ion which spontaneously undergoes the observed stereospecific N-acyl Pictet-Spengler cyclization to generate the proline derived diazabicyclo[3.2.2]nonanedione **156**. Compound **156** is among a very interesting class of molecules presently under investigation at the Novartis Institute of Research in Basel, Switzerland.[9] For our purposes, **156** provided valuable information. Emerging from this reaction were a few important points. First, we knew we were in fact generating the desired N-acyliminium ion and that the L-tryptophan residue did not decompose under the reaction conditions. Second, the intramolecular C2 nucleophile attacked the transient N-acyliminium ion at a much greater rate than intermolecular addition of methanol (albeit a large excess of methanol). Third, blocking C2 should prevent the observed pathway assisting in the

competitive and desired addition of methanol. Not surprisingly, we, and nature, have a pre-fabricated blocking group at C2, the well known C2 reverse prenyl substituent.

3.4 Thoughts on Nature's Use of the C2 Reverse Prenyl Group.

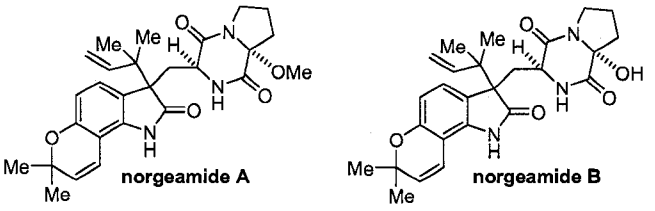
The observations in the previous pages raise some interesting questions. Does nature employ the C2 reverse prenyl group to insure the intermolecular reactivity one would expect for biological activity? Is there inherent stability brought to tryptophan analogs bearing a C2 reverse prenyl group? What other groups are found at C2 of similar natural products and do these groups serve the same purpose? Does the Pinacol rearrangement from C2 to C3 block both positions from intramolecular interactions? Answers to these questions are at the heart of the goals of this project.

Chapter 4. Total Synthesis of (±)-11-epi-Norgeamide A

4.1 Methanolation of N-Acyliminium Ions

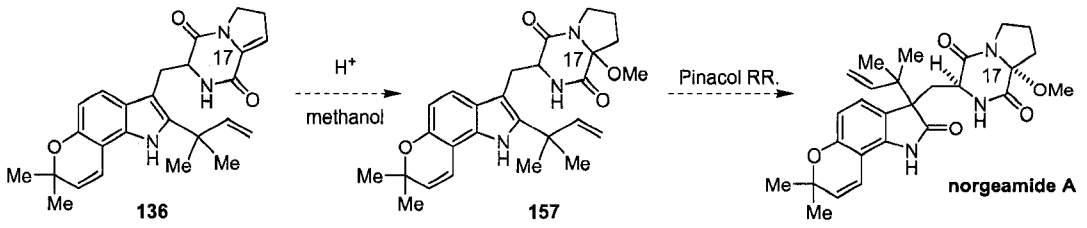
We now embark on a synthetic journey with a full set of tools and a fundamental understanding of multiple modes of reactivity. Surely, the total synthesis of norgeamides A and B (Figure 24) will cross paths with many of the reactive manifolds uncovered along the road leading us to this new challenge.

Figure 23. Norgeamides A and B.



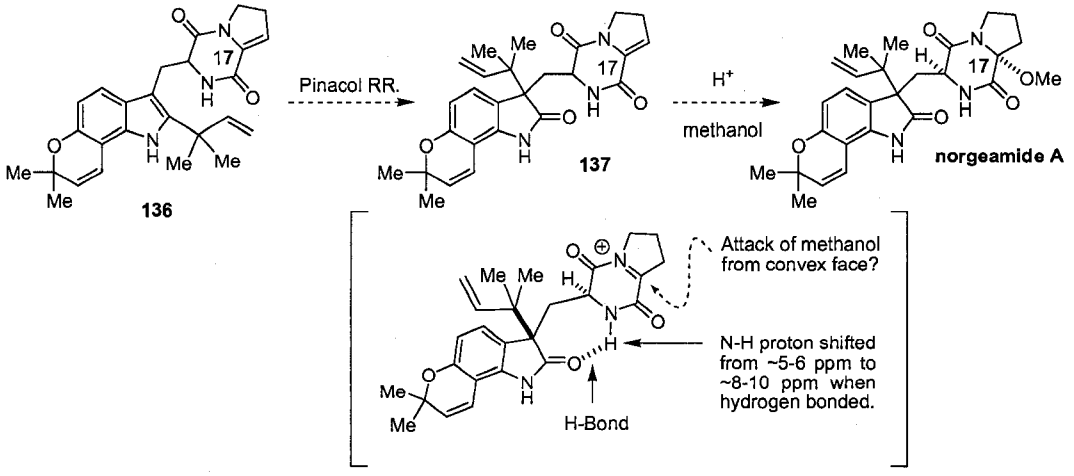
We face two possible crossroads in deciding where to introduce methanol and / or water into the difficult C17 position of the norgeamides. One possible route would mimic exactly both model systems and seek to introduce methanol before a potential Pinacol-rearrangement (Scheme 32). We face at this juncture the possibility that the methyl ether might not survive the Pinacol rearrangement. Also at hand is the required facial selectivity of the methanol addition to generate the *cis*-orientation of norgeamide A.

Scheme 32. Addition of methanol before the Pinacol rearrangement.



Another possibility is to effect the Pinacol rearrangement first, and then finish the total synthesis with the addition of methanol (Scheme 33). This possibility opens up another stereochemical issue. We know from 1H NMR experiments that a strong hydrogen bond likely exists between the oxindole carbonyl and the amide N-H bond in **137** thus shifting the N-H proton resonance downfield by 3-4 ppm. Perhaps it is this rigid conformation that helps direct the addition of methanol to the observed *cis*-orientation in notoamide A.

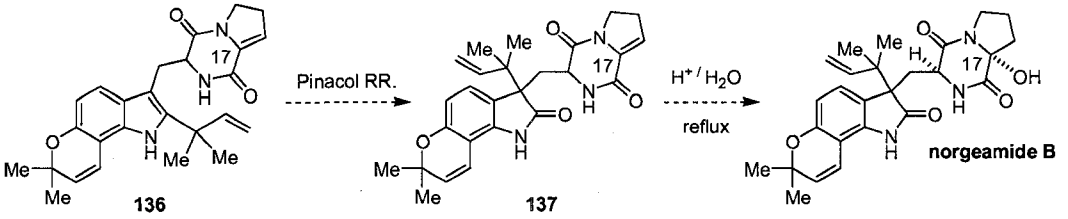
Scheme 33. Hydrogen bonding as a route to direct methanol addition.



4.2 Hydration of N-Acyliminium ions

Another question to be answered is whether or not water would add to the N-acyliminium ion if water were used in place of methanol? This would be the obvious route to norgeamide B (Scheme 34) and if norgeamide B were formed stereoselectively or with a higher degree of conversion, then norgeamide B itself would be the obvious precursor to norgeamide A. The following synthesis seeks to answer these questions.

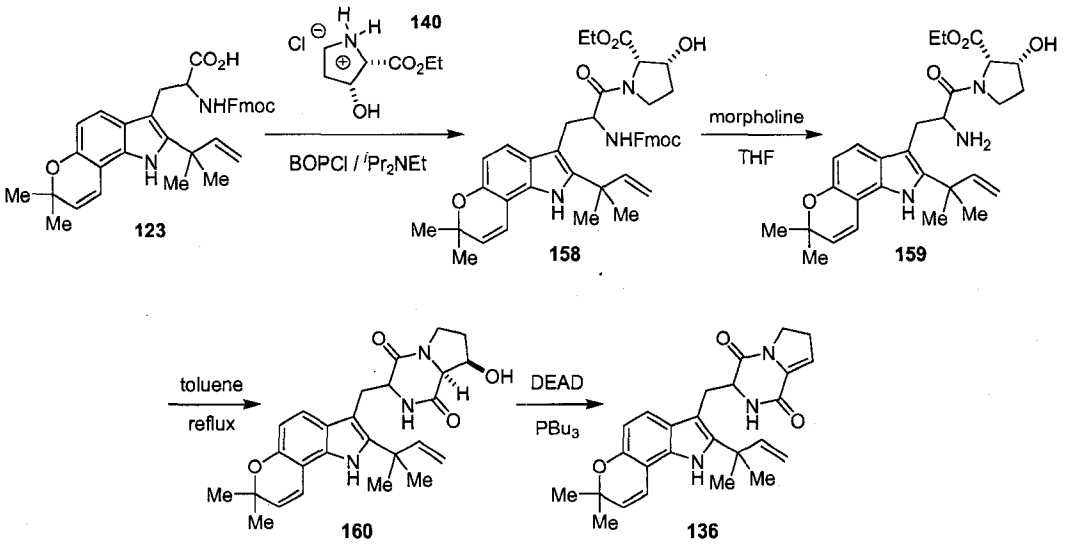
Scheme 34. Hydration of N-acyliminium ion to form norgeamide B.



We now turn our attention back to our amino acid **123** and follow the coupling methodology employed in our synthesis of notoamide C and D (Table 6). Thus coupling of previously reported N-Fmoc amino acid **140** (Scheme 35) with cis-3-hydroxy proline, as depicted in our L-tryptoptophan pilot system, gave the corresponding dipeptide in 60-70% yield.

4.3 Synthesis of (±)-17-epi-Norgeamide A

Scheme 35. Toward the total synthesis of norgeamides A and B.

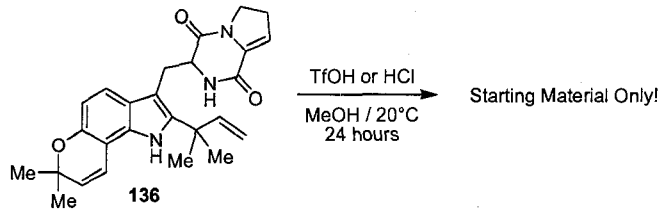


Amine base mediated elimination of the Fmoc protecting group proceeded smoothly to afford amino alcohol **159** which cyclized thermally in refluxing toluene to afford diketopiperazine **160**. Again, Mitsunobu elimination gave the desired enamide **136** after separation from residual diethylazodicarboxylate.

We now sought to effect the key N-acyliminium ion formation with the hopes of trapping it with methanol (Scheme 36). Thus, enamide **136** was treated with 4 eq. TfOH or 4 eq. conc. HCl in methanol and stirred overnight at ambient temperature. To our surprise, the starting material was completely unreactive to the reaction conditions. This negative result had important implications: 1) Our target molecule **136** was stable to an extremely acidic methanolic environment at 20°C. 2) Our next task was to gently warm the

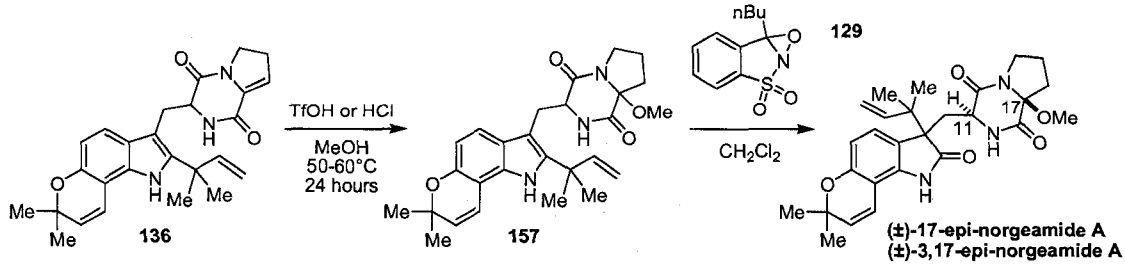
solution and assess the rate of decomposition vs formation of a potential N-acyliminium ion and addition of methanol.

Scheme 36. Temperature dependence of N-acyliminium ion chemistry.



Not surprisingly, treating the same compound **136** again with 4 eq. TfOH or conc. HCl in methanol at reflux for 24 hours gave almost complete baseline decomposition. However if one holds the reaction at just under the boiling point of methanol (50-60°C), a substantial amount of the desired methanol adduct is formed (Scheme 37). Also encouraging was the tolerance of the newly formed ether to oxidation via oxaziridine **129** and subsequent Pinacol rearrangement. Unfortunately, further data confirmed that we had generated the undesired *trans*-DKP, thus affording (±)-17-epi norgeamide A and (±)-3,17-epi norgeamide A.

Scheme 37. Synthesis of (±)-3-epi-norgeamide A and (±)-3,17-epi-norgeamide A.

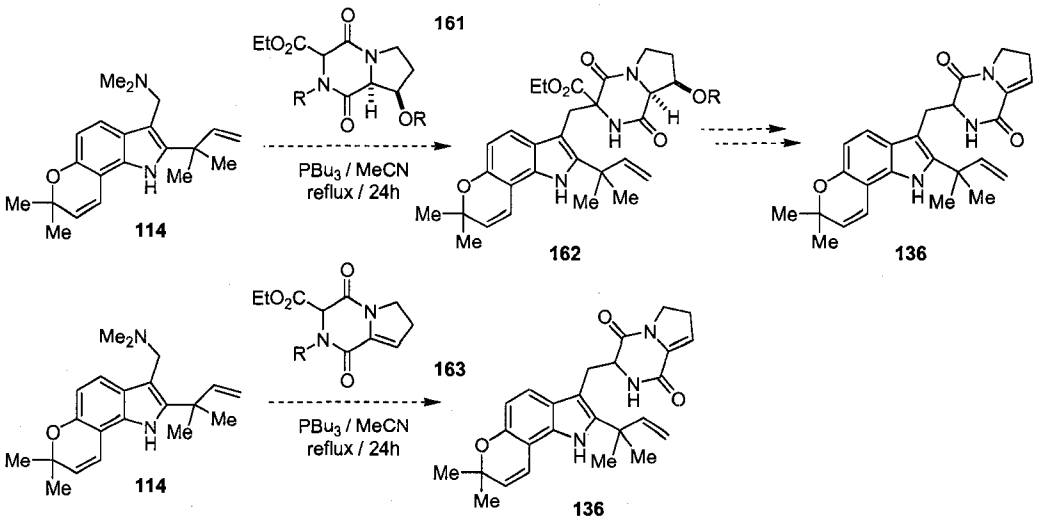


Further efforts toward the total synthesis of norgeamide A include the potential epimerization of C11 or pursuing the pinacol rearrangement first and subsequent addition of methanol based on the proposed convex-face attack outlined in Scheme 33.

4.4 Coupling of the Preformed DKP – Failed Attempts

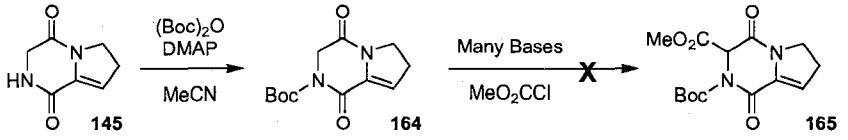
Our synthesis of (±)-11-epi-Norgeamide A (Scheme 37), outlined in the previous chapter, is convergent in that two amino acid components come together through a peptide coupling to form the required diketopiperazine at the required oxidation state to generate our key intermediate enamide **136**. Our approach to compound **136** currently utilizes the BOPCl mediated coupling of Fmoc amino acid **123** with 3-hydroxy proline **(140)**. This peptide coupling obviously requires that a racemic amino acid be generated via a Somei-Kametani coupling of pyrano indole **114** with benzophenone imine **63** (Scheme 22). The resulting primary amine is then protected as the Fmoc derivative **122** which is finally hydrolyzed to afford the desired coupling partner **123**. A much more direct route to the target enamide **136** would utilize preformation of the DKP and functionalization to a suitable Somei-Kametani intermediate such as compound **161** or **163** (Scheme 38). A route such as this was our initial approach, however both compound **161** and **163** proved to be extremely stubborn even after a comprehensive synthetic effort. Our first approach toward compound **136** began with L(-)-cis-3-hydroxy proline (Scheme 27 and 39). However the only manipulation achieved with compound 145 was the introduction of the N-Boc group on the secondary nitrogen using $(Boc)_2O$, MeCN and DMAP (Scheme 39).

Scheme 38: Preformation of the DKP.



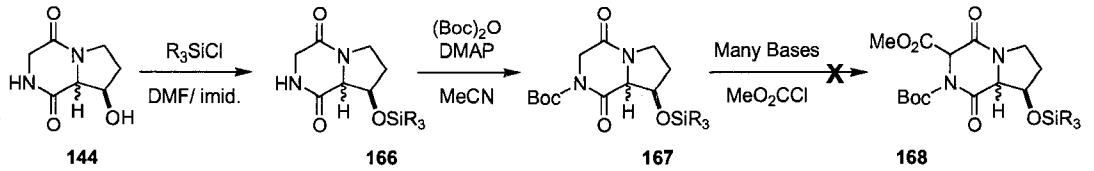
Further manipulation of enamide **164** proved virtually impossible. All attempts to introduce the required carbomethoxy group required for the Somei-Kametani reaction (Compound **161** or **163**) failed. This simple molecule would accept no further manipulation. Our only conclusion is that compounds like **145** and **164** are very stable and inaccessible sterically to any further functionalization.

Scheme 39: Carbomethoxylation Attempts.



Further attempts to access compound **136** included the manipulation of **144** via the introduction of silicon based oxygen protecting groups (Scheme 40). Again, each attempt to access the Somei-Kametani substrate met with failure for apparently similar reasons.

Scheme 40: Further carbomethoxylation attempts.

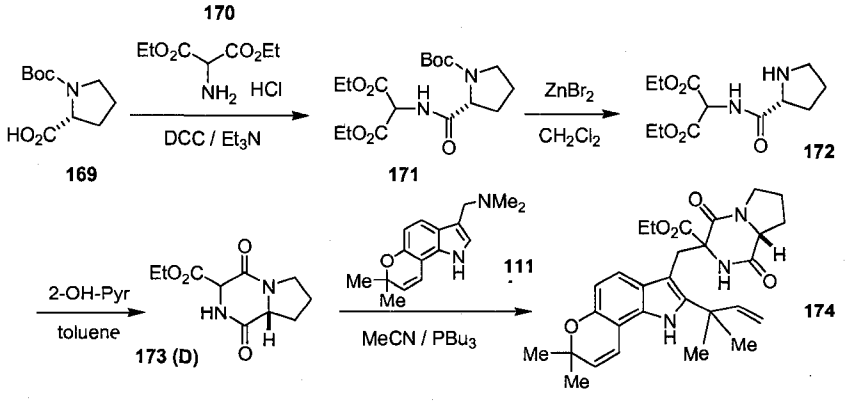


Again, only the Boc carbonate could be made from amide **166**. Smaller nitrogen protecting groups, such as the methyl carbonate, could not be prepared using common methods.

4.5 Synthesis of 17-epi-Notoamide E

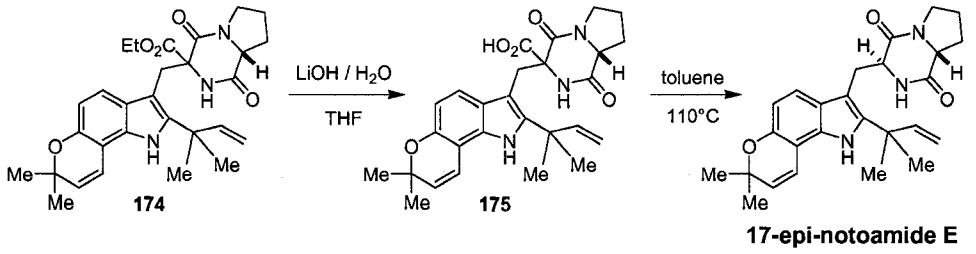
The failure of both of the above routes was completely unexpected due to a previous synthesis of 17-epi-notoamide E derived from D-proline. Using a variation of the DKP formation starting from diethylaminomalonate (**170**), the fully saturated analog of **161** or **163** was synthesized and coupled via the Somei-Kametani procedure without incident (Scheme 41).

Scheme 41: 17-epi-notoamide E.



Thus treatment of D-Boc-Pro-OH with diethylaminomalonate HCl in the presence of dicyclohexylcarbodiimide (DCC) produced the coupled product **171** in good yields. Lewis acidic Zinc Bromide mediated the Boc removal to afford free amine **172** which cyclized to the desired DKP in the presence of catalytic 2-hydroxy pyridine. Without further protection of the amide nitrogen, **173** underwent the Somei-Kametani coupling to afford the coupled product **174** as a 1 :1 mixture of diastereomers. After a short exposure to a basic hydrolytic environment (LiOH, H_2O, THF), the ester was completely saponified which after acidification with 1N HCl produced acid **175** in good yields (Scheme 42). Simply refluxing acid **175** in toluene for 3 hours effected complete decarboxylation which pleasingly protonated exclusively to generate the more stable *trans*-DKP (17-epi-notoamide E).

Scheme 42. Synthesis of 17-epi-notoamide E.

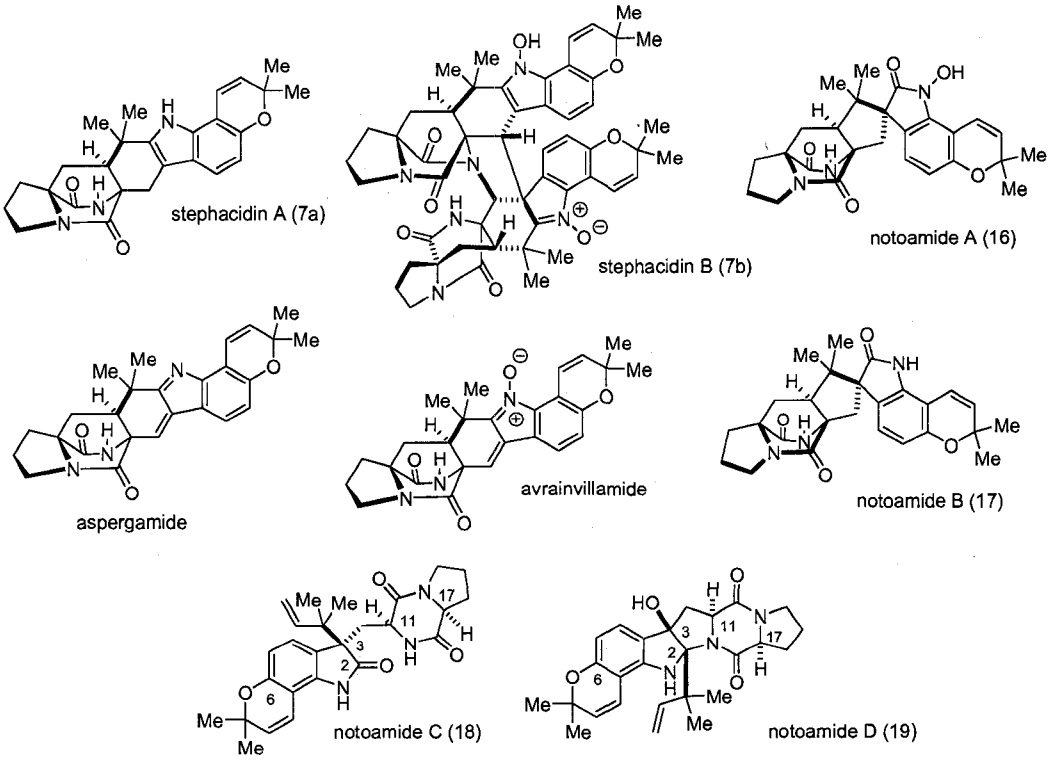


Chapter 5. Total Syntheses of Stephacidin A and Notoamide B

5.1 Synthesis of Stephacidin A.

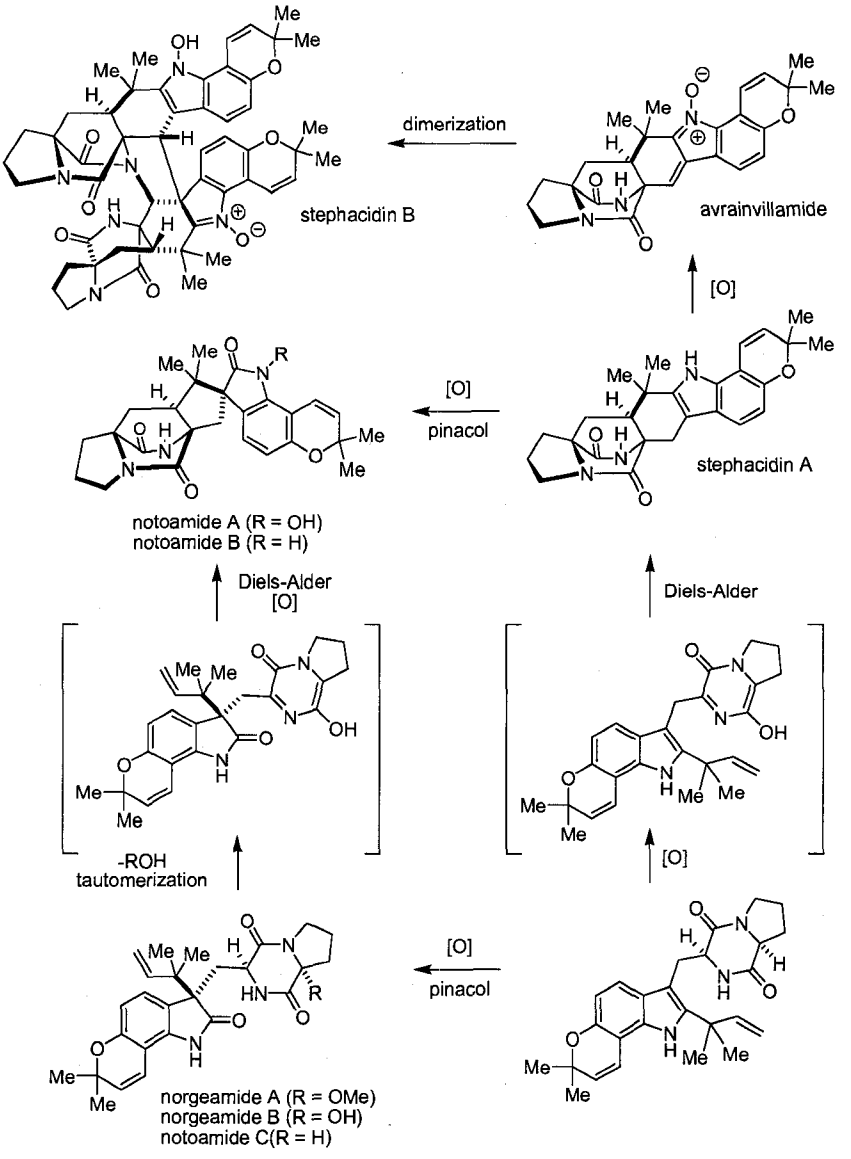
As mentioned in Figure 22, our synthesis of notoamide E places us very close synthetically to two very important natural products, stephacidin A and notoamide B (Figure 24). Based on their structural similarities and their origin from the genus *Aspergillus*, it is quite interesting to contemplate some reasonable biogenetic relationships between the stephacidins and notoamides.

Figure 24. Structures of the stephacidins, notoamides and avrainvillamide.



A plausible biosynthetic pathway interrelating these compounds is outlined in Scheme 43. Previous studies from our laboratory[10-12] as well as those of Birch[13] and Sammes[14] suggest that the bicyclo[2.2.2]diazaoctane core of these alkaloids likely arises in nature *via* a biosynthetic intramolecular Diels-Alder construction. Thus, one could imagine a [4+2] cycloaddition reaction of the compound **91**-derived azadiene **176** with the reverse prenyl group directly furnishing stephacidin A (**7**). Stephacidin A (**7**) would appear to be an obvious and important biosynthetic precursor to avrainvillamide, stephacidin B (**178**), and notoamides A (**16**) and B (**17**). It has already been suggested that stephacidin A (**7**) undergoes a net four-electron oxidation to the unsaturated nitrone avrainvillamide (**177**), which in turn spontaneously dimerizes to stephacidin B (**178**).[15] The latter process has been experimentally corroborated by Myers and Baran.[16,17] Notoamide B (**17**) may simply arise from the plausible precursor (**91**) through two plausible pathways: (1) oxidation and tautomerization to azadiene **176** followed by intramolecular Diels-Alder cycloaddition to give stephacidin A (**7**) and subsequent oxidative ring contraction to the spirooxindole; alternatively (2): oxidation and rearrangement to oxindoles such as notoamide C (**18**) and/or further oxidation to norgeamide A (**11**) or B (**12**), elimination/tautomerization to produce azadiene **179** that could then be trapped by the isoprenyl group to afford notoamide B (**17**).

Scheme 43: Postulated biosynthetic relationships.

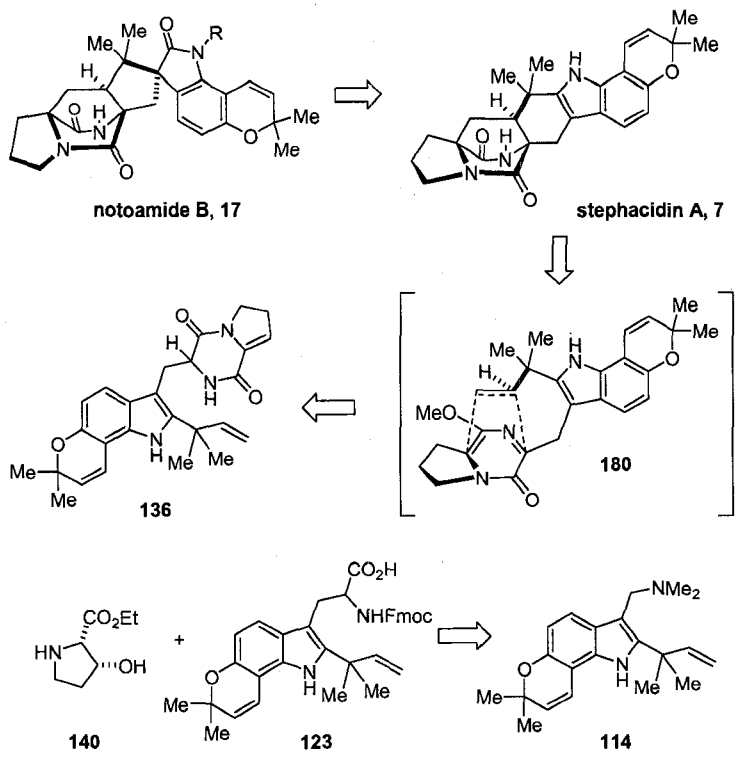


Intrigued by the possible biosynthetic relationships between these families of alkaloids, along with their unique biological activity, we have explored their total synthesis with the objective of fashioning isotopically labelled substances for ongoing biosynthetic investigations. A retrosynthetic analysis (Scheme 44) envisaged the

spirooxindole of notoamide B (**17**) to arise from a stereoselective oxidative ring contraction of the C(8)-C(20) fused indole of stephacidin A (**7**). A biomimetic intramolecular Diels-Alder reaction of the azadiene **176** with the isoprene residue should proceed preferentially to produce the desired *syn*-relative stereochemistry at the C(6)-C(22) ring fusion required to access stephacidin A (**7**). Our laboratory has previously reported related biomimetic Diels-Alder cyclizations[8,18,19] which culminated in the total synthesis of the fungal metabolite VM55599[8] and brevianamide B. Based on previous experiments with similar substrates, it seemed unlikely that azadiene **176** would be stable, and therefore could be generated from enamide **136** via lactim ether formation, followed by a base-induced tautomerization.

Finally, enamide **136** should be available through coupling of tryptophan derivative **123** with *cis*-3-hydroxy-L-proline ethyl ester (**140**), followed by Fmoc removal, concomitant diketopiperazine formation, and dehydration. Tryptophan derivative **123** is readily available from the corresponding gramine **114** and has been recently synthesized in our group on gram-scale.[20]

Scheme 44: Notoamide B, retrosynthesis.

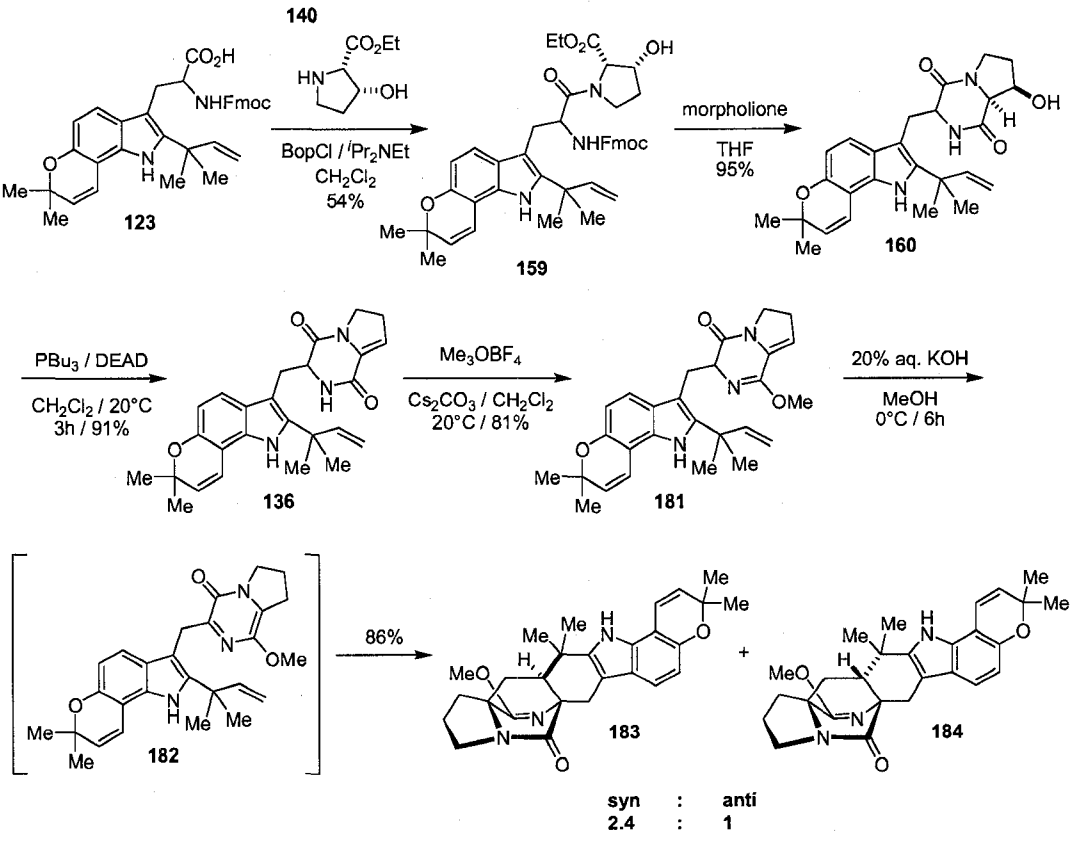


Our synthesis commenced with a coupling of *cis*-3-hydroxy-L-proline ethyl ester hydrochloride (**140**)[21] and acid **123** in the presence of BOPCl to afford amide **159** (Scheme 45) as an inseparable 1:1 mixture of diastereomers in 54% yield. Varying amounts of starting material (25% - 35%) were recovered in this coupling reaction, and it appeared to be more sluggish than an analogous coupling of **123** with the parent *S*-proline methyl ester hydrochloride as reported in our total synthesis of notoamides C and D. Subjecting peptide **159** to a solution of morpholine in THF at room temperature effected removal of the *N*-Fmoc group and a concomitant cyclization of the resultant amine onto the ethyl ester to provide diketopiperazine **160** as a separable mixture of diastereomers. Both diastereomers were then found to undergo a smooth Mitsunobu-type elimination

(PBu_3, DEAD) to afford the enamide **136** (see Scheme 44) that was treated with Me_3OBF_4 and Cs_2CO_3 to cleanly provide the desired lactim ether **181** in good yield.

We next directed our attention toward the key cycloaddition reaction and the completion of the total synthesis of stephacidin A. We were delighted to find that treatment of lactim ether **181** with 20% aqueous KOH in MeOH (0 °C - rt, 6 h) effected tautomerization to the intermediate azadiene **182**, which spontaneously suffered intramolecular Diels-Alder cycloaddition to produce cycloadducts **183** and **184** as a 2.4 : 1 mixture of diastereomers favoring the desired *syn*-stereoisomer. Interestingly, the intermediate azadiene **182** is a metastable substance that could be observed by both thin layer chromatography and ^1H NMR analysis. During the reaction, lactim ether **181** (R_f = 0.75, EtOAc) disappeared within 1.5 h by TLC and azadiene **182** (R_f = 0.25, EtOAc) appeared. This TLC spot then slowly disappeared giving rise to cycloadducts **183** and **184** (R_f ~ 0.4, EtOAc). The azadiene intermediate **182** was also observable by ^1H NMR spectroscopy through treatment of lactim ether **181** with KOD in CD_3OD/D_2O in an NMR tube.

Scheme 45: Construction of the stephacidin A ring system via an intramolecular Diels-Alder cycloaddition.



The tentative stereochemical assignment for cycloadduct **183** was confirmed upon its transformation to racemic stephacidin A (**7**). Thus, treatment of **183** with 0.1 M HCl (3 equiv) in THF (0 °C, 5 min) effected cleavage of the lactim ether to the corresponding secondary amide affording stephacidin A (**7**) in 96% yield (Scheme 46). All ^{1}H and ^{13}C NMR spectral characteristics of synthetic stephacidin A (**7**) were identical to those reported (d^6-DMSO and $CDCl_3/CD_3OD$, 1:1).[22,23] Interestingly, this reaction appears to proceed through the ring-opened aminoester **185** which spontaneously cyclizes to stephacidin A during workup. Aminoester **185**, which could be observed by thin layer

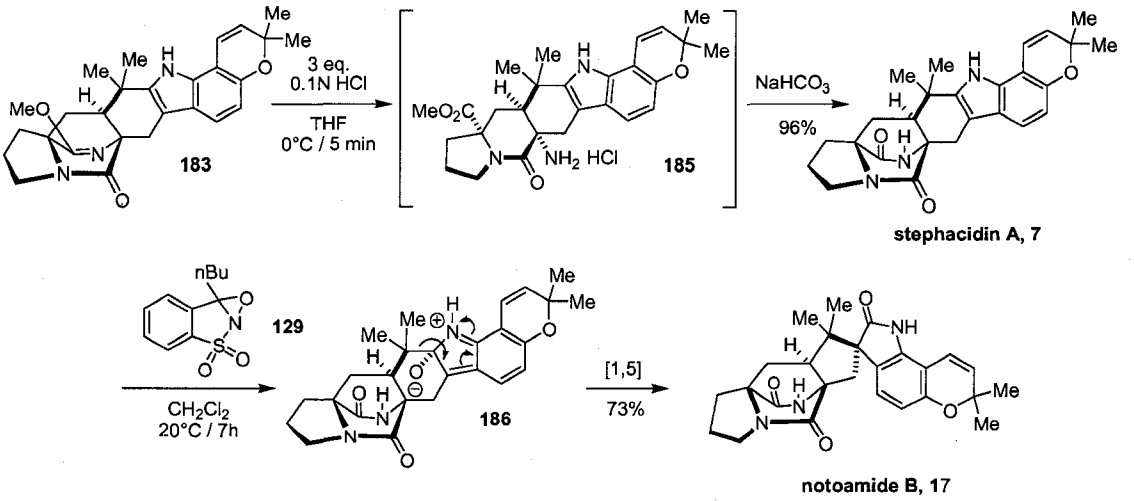
chromatography (R_f = 0.12, 10% MeOH/CH_2Cl_2) slowly disappeared upon concentration of the reaction mixture giving rise to stephacidin A (R_f = 0.68, 10% MeOH/CH_2Cl_2). Our laboratory has also observed similar ring-opened aminoester intermediates in the total synthesis of VM55599.[8]

5.2 Synthesis of Notoamide B.

With stephacidin A in hand, we directed our attention to the stereoselective oxidation and pinacol rearrangement of **7** to notoamide B (**17**). Indeed, we were pleased to find that treatment of stephacidin A with excess oxaziridine **129**[6,24] in CH_2Cl_2 cleanly provided notoamide B (**17**) as a single product in 73% yield. The stereochemical result can be rationalized by epoxidation of the 2,3-disubstituted indole from the less-hindered α-face, followed by ring opening of the incipient epoxide to the 2-alkoxyindole intermediate **186**. A subsequent α-face ring contraction by a [1,5] sigmatropic shift successfully furnishes **17** as a single diastereomer. Once again, all ^1H and ^{13}C NMR spectral properties (d^6-acetone) were identical to those published by Tsukamoto and coworkers. It might be further noted that the deployment of oxaziridine **129** for the one-step conversion of a 2,3-disubstituted indole to the corresponding *spiro*-oxindole is an unprecedented and potentially highly useful transformation. Standard methods for effecting such an oxidative ring contraction have been known for many years and typically involve treatment of the indole substrate with *t*-butyl hypochlorite to give a 3-choloroindolenine that must be hydrated to a *syn*-chlorohydrin and subsequently rearranged to the *spiro*-oxindole.[25-31] Additional applications of this mild and direct oxindole-forming reaction are currently being explored.

In conclusion, we have completed a concise biomimetic total synthesis of stephacidin A (**7**) via an intramolecular azadiene Diels-Alder reaction in seventeen steps and 5.4% overall yield from commercially available 6-hydroxyindole. In addition, we have also effected the biomimetic oxidation of stephacidin to the closely related fungal metabolite notoamide B (**17**). This work underscores the low activation barriers inherent in this specific class of azadiene IMDA reactions that have been strongly implicated in the construction of the bicyclo[2.2.2]diazaoctane core ring system common to the paraherquamide/stephacidin/notoamide family of prenylated indole alkaloids. Further studies to experimentally corroborate the biogenetic relationship between the notoamides and stephacidins as well as the validity of the proposed biosynthetic intermediates (Scheme 43) are currently under investigation and will be disclosed in due course.

Scheme 46: Synthesis of stephacidin A and notoamide B.

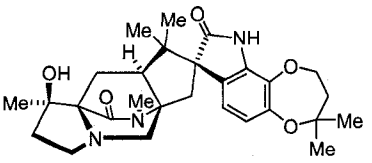


5.2 Synthesis of Versicolamide B.

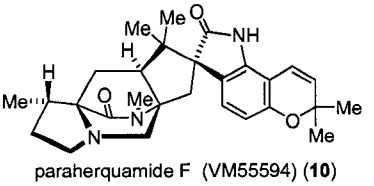
Our synthesis of notoamide B (Scheme 46) intrinsically offers a synthesis of versicolamide B (**207**)[32] (Scheme 47c) via the 2.4 : 1 selectivity of the IMDA reaction. Prenylated indole alkaloids containing as a structural core the bicyclo[2.2.2]diazaoctane ring system now number more than thirty-eight family members. These natural substances, produced by various genera of fungi, in particular *Aspergillus* sp. and *Penicillium* sp., among others, exhibit a range of interesting structural and stereochemical features. Significantly, a myriad of biological activities are displayed within this family including insecticidal, anti-tumor, anthelmintic, calmodulin inhibitory, and anti-bacterial activities. Structurally, these substances arise from the oxidative condensation of one or two isoprene units, tryptophan and another cyclic amino acid residue, such as proline, β-methylproline or pipecolic acid. With respect to the relative stereochemistry within the core bicyclo[2.2.2]diazaoctane ring system, all of the known members of the paraherquamides, stephacidins, asperparalines and notoamides have been shown to possess the *syn*-stereochemistry while only the brevianamides (**40a-b,** Figure 11, Scheme 47a) have been shown to possess the *anti*-relative configuration (Schemes 47b). The *syn-/anti-* relationship refers to the relative stereochemistry between the C-19 stereogenic center (sclerotiamide numbering) and the cyclic amino acid residue (proline, β-methylproline, or pipecolic acid (Scheme 47b). This reveals that in the oxidative cyclization process(es) to construct this core ring system biosynthetically, both faces of the isoprene-derived dienophile participate in the ring-forming process. But until now,

this stereochemical divergence was cleanly separated between the brevianamides and all other members of this growing family of natural products.

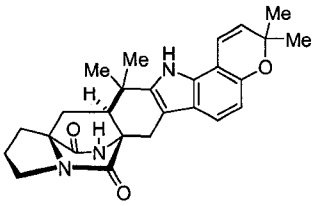
Scheme 47a. Structures of several members of the paraherquamide, stephacidin, and brevianamide families of prenylated indole alkaloids.



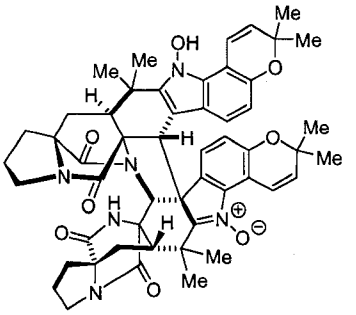
(-)-paraherquamide A (**8**)



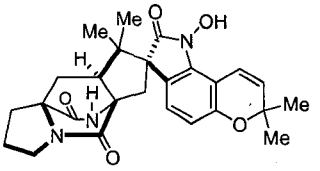
paraherquamide F (VM55594) (**10**)



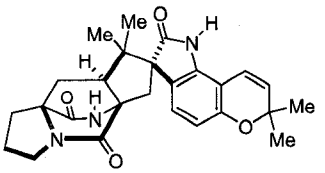
(+)-stephacidin A (**7a**)



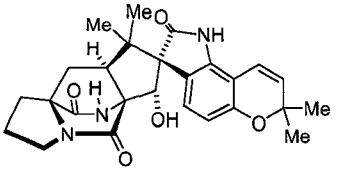
(-)-stephacidin B (**7b**)



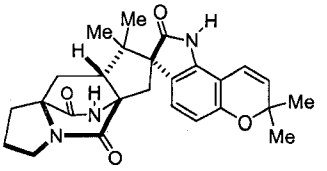
(-)-notoamide A (**16**)



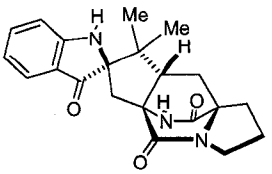
(-)-notoamide B (**17**)



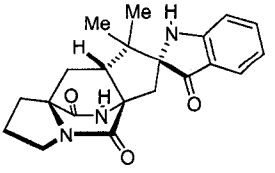
(-)-sclerotiamide (**41**)



versicolamide B (**207**)

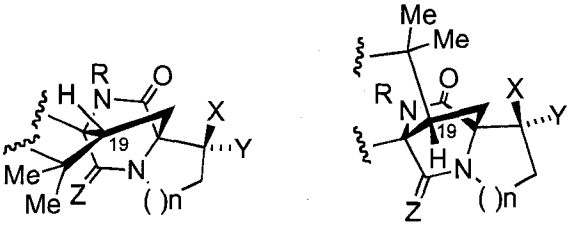


(-)-brevianamide A (**40a**)



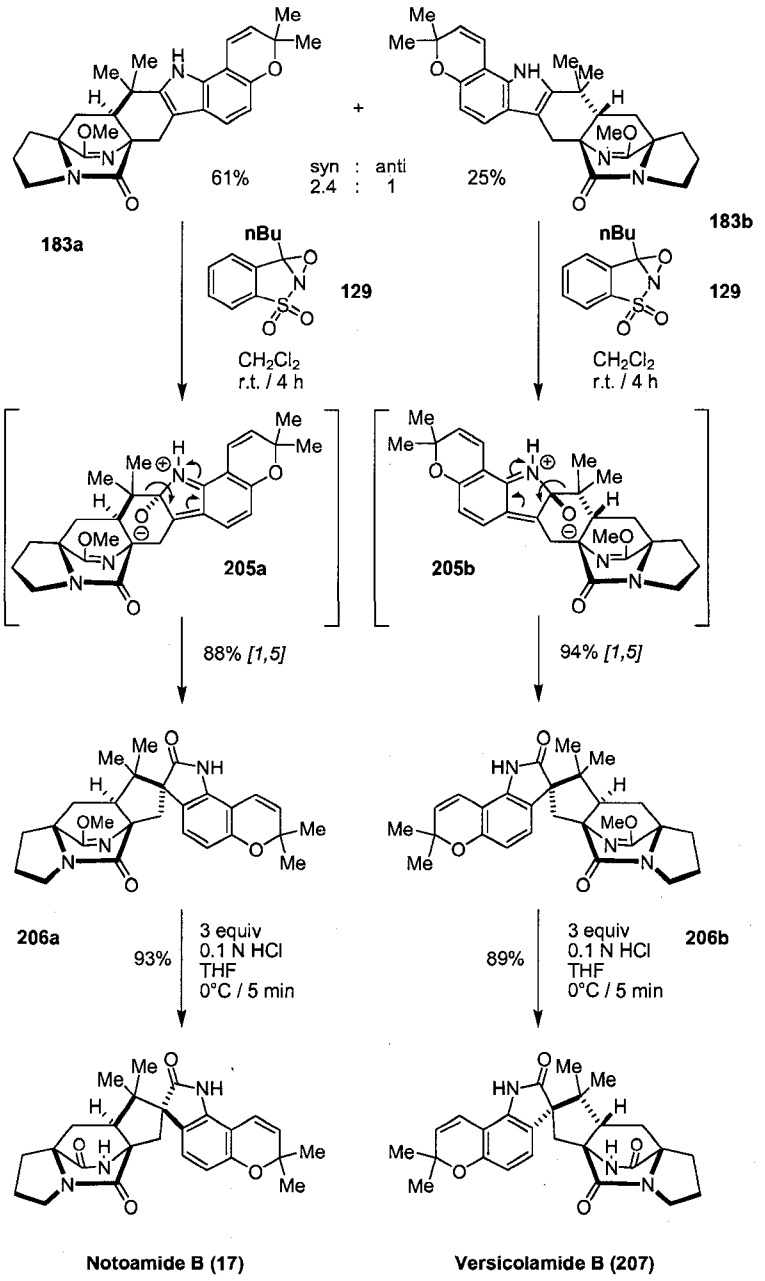
(-)-brevianamide B (**40b**)

Scheme 47b. Syn- and anti-relative configurations at C-19 of the bicyclo[2.2.2]diazaoctane ring system (sclerotiamide numbering).



Our synthesis of versicolamide B (**207**) represents a confirmatory biomimetic total synthesis of the first member of the paraherquamide-stephacidin family to possess the rare *anti*-relative stereochemistry within the bicyclo[2.2.2]diazaoctane ring system. For this natural product, a minor metabolite of *Aspergillus versicolor* NRRL 35600, we propose the new name versicolamide B (**207**). Based on CD spectra (Appendix X), we have assigned the absolute configuration to this metabolite, and have concluded that it possesses the *ent*-configuration with respect to the bicyclo[2.2.2]diazaoctane core. Surprisingly and as striking, we have also isolated (-)-stephacidin A and (+)-notoamide B from *Aspergillus versicolor* NRRL 35600 *and conclude that these substances are produced as the corresponding antipodes to what has been previously described for these natural products.*

Scheme 47c. Synthesis of Versicolamide B.



The production of this metabolite by *A. versicolor* suggests that the putative biosynthetic IMDA construction that leads to the major metabolites within the producing organism may suffer some stereochemical "leakage" with respect to the facial selectivity of addition to the reverse isoprene moiety anchored at the indole 2-position. Based on our observations, it is reasonable to anticipate that stereochemically related members of this family may be produced by other fungi, albeit in trace amounts. The surprising stereochemical paradox posed by the existence of versicolamide B along with the opposite enantiomers of stephacidin A and notoamide B demand explanation on biogenetic grounds and constitute a major thrust of our ongoing work. Studies to further establish the relationship of these and simpler precursor metabolites in the biosynthesis of this family of agents are under investigation in these laboratories.

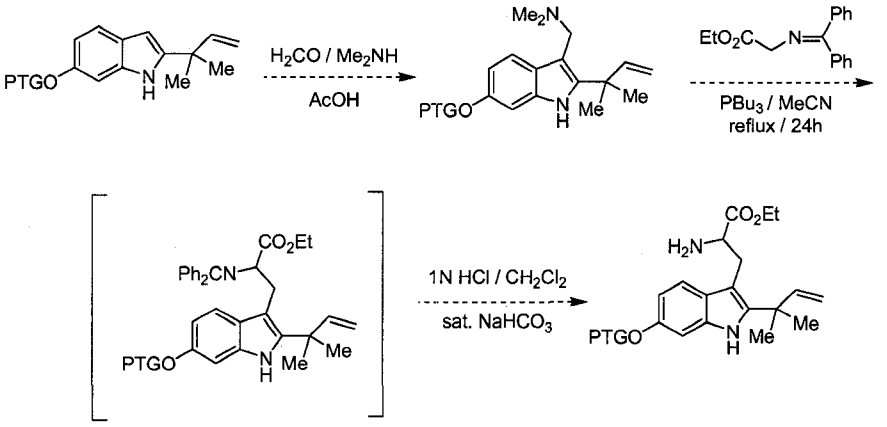
Chapter 6. Toward a Late Installation of the Pyran

6.1 The Carbonate Route.

An alternative approach to the natural products like the norgeamides and the notoamides involves a late installation of the sensitive pyran ring. As we have seen, the pyran presents a significant challenge synthetically due to its capricious instability in the presence of acids (Scheme 14, page 33). An interesting solution to this problem would be to use a robust protecting group on 6-hydroxy indole (Figure 25) that would allow for the development of the norgeamide and notoamide scaffold prior to installation of the

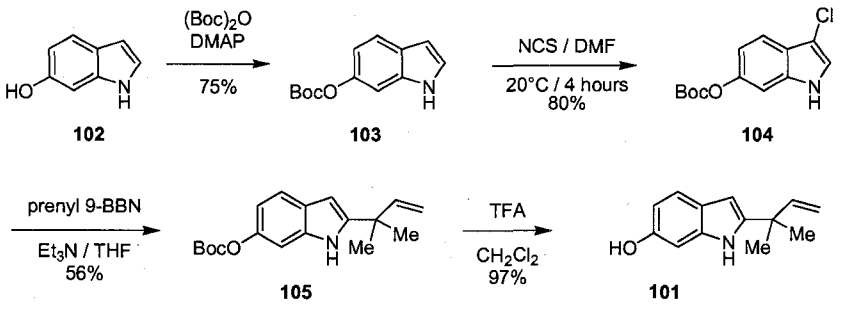
pyran ring. This approach would avoid any complications that arise as a result of the instability of the pyran ring and leave for a final sequence of steps, the pyran closure.

Figure 25. Late installation of the pyran.



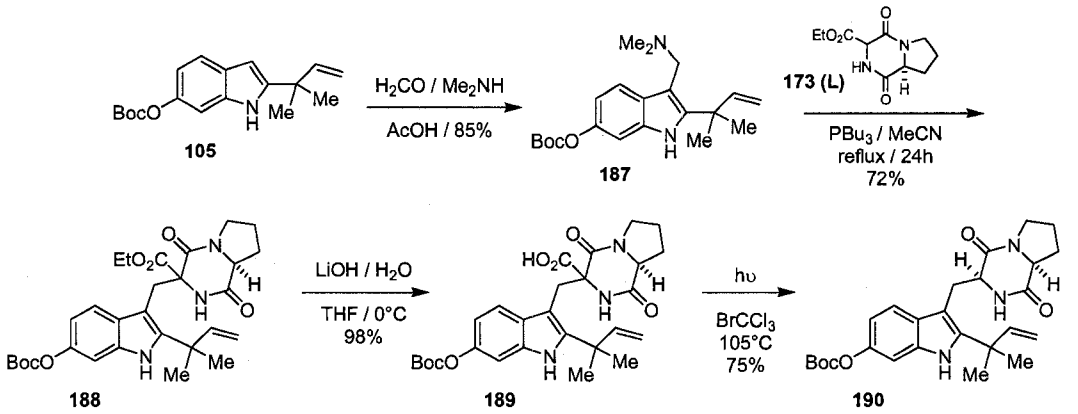
An ideal protecting group this approach would obviously need to survive all the conditions present in figure 25. If we now take a look back at our initial reaction to install the reverse prenyl group, an obvious oxygen protecting group emerges (Scheme 47).

Scheme 47. Alternative synthesis of indole **101**.



Remember that our original synthesis relied on the electron-withdrawing nature of the Boc-protecting group in compound **103** to promote both the chlorination to compound **104** and reverse prenylation to compound **105**. An obvious protecting group then for a late installation of the pyran ring would be the Boc group found in indole **105**. To investigate this possibility, compound **105** was subjected to the following reaction sequence (Scheme 48). Amazingly, repeating the exact reaction conditions that gave rise to compound **166** (Scheme 41) also produced the corresponding ester **188** without any apparent difficulty associated with the Boc carbonate protecting group. Thus upon treatment of indole **105** with a pre-mixed solution of formaldehyde and dimethylamine in 0°C acetic acid as solvent, indole **187** was isolated after neutralization of excess acetic acid with solid $NaHCO_3$. Somei-Kametani coupling of **187** and the previously mentioned diketopiperazine **173** afforded the desired product **188** along with 0.5-1.0 eq. PBu_3. Careful hydrolysis of the resulting ester **188** at 0°C for 30 minutes afforded the desired acid **189** which, like compound **175** (Scheme 42), underwent facile decarboxylation and subsequent protonation to afford compound **190** as a single diastereomer.

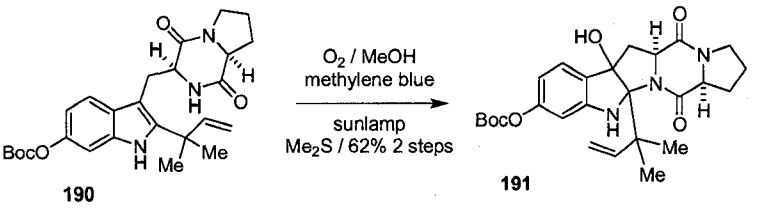
Scheme 48. Elaboration of compound **105** to diketopiperazine **190**.



6.2 Toward pre-Notoamide D and pre-Notoamide C.

With the target compound in hand, we had only to subject the newly formed diketopiperazine **190** to standard oxidation conditions to generate the desired pyrroloindole. To that effect, compound **190** was oxidized using the protocol described in Corey and Baran's synthesis of okaramine N. Therefore compound **190** was dissolved in methanol and stirred under an atmosphere of oxygen in the presence of light via a sunlamp. We were pleased at this point to discover that the desired oxidation had occurred and we had established a new route to the scaffold of the norgeamides and notoamides centering on a late installation of the pyran ring (Scheme 49).

Scheme 49. Oxidation to pyrroloindole **191**.

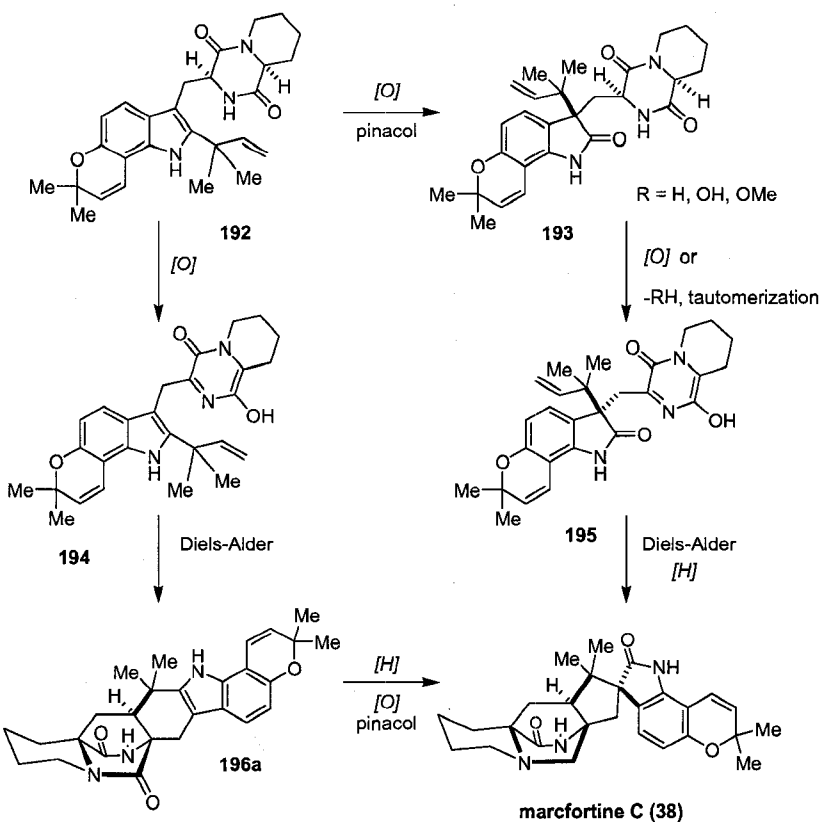


Chapter 7. Synthesis of (±)-Marcfortine C

7.1 Synthesis of (±)-Marcfortine C – Biosynthetic Considerations

A final application of our IMDA / Pinacol-type rearrangement is shown below in our synthesis of marcfortine C (**38**, Scheme 53).[33] Retrosynthetically, it was envisaged that marcfortine C (**38**) could arise from compound **196a** (Scheme 50) *via* a chemoselective reduction of the tertiary amide over the secondary amide of the diketopiperazine, followed by a well-precedented stereoselective oxidative ring contraction of the C(9)-C(21) fused indole. A biomimetic intramolecular Diels-Alder reaction of the azadiene **197** with the isoprene residue should proceed preferentially to produce the desired *syn*-relative stereochemistry at the C(7)-C(23) ring fusion required to access marcfortine C (**38**, Scheme 51). In addition to the stephacidin A/notoamide B synthesis, our laboratory has previously reported related biomimetic Diels-Alder cyclizations, which culminated in the total synthesis of the fungal metabolites VM55599 and brevianamide B. Based on our experiences with similar substrates, it seemed unlikely that azadiene **194** (Scheme 50) would be stable, and therefore a functional equivalent (**197**) would be generated from enamide **198** via lactim ether formation, followed by a base-induced tautomerization (Scheme 51). Herein, we detail implementation of this strategy to the biomimetic total synthesis of marcfortine C which has not hitherto succumbed to total synthesis.

Scheme 50. Postulated Biosynthesis of Marcfortine C.

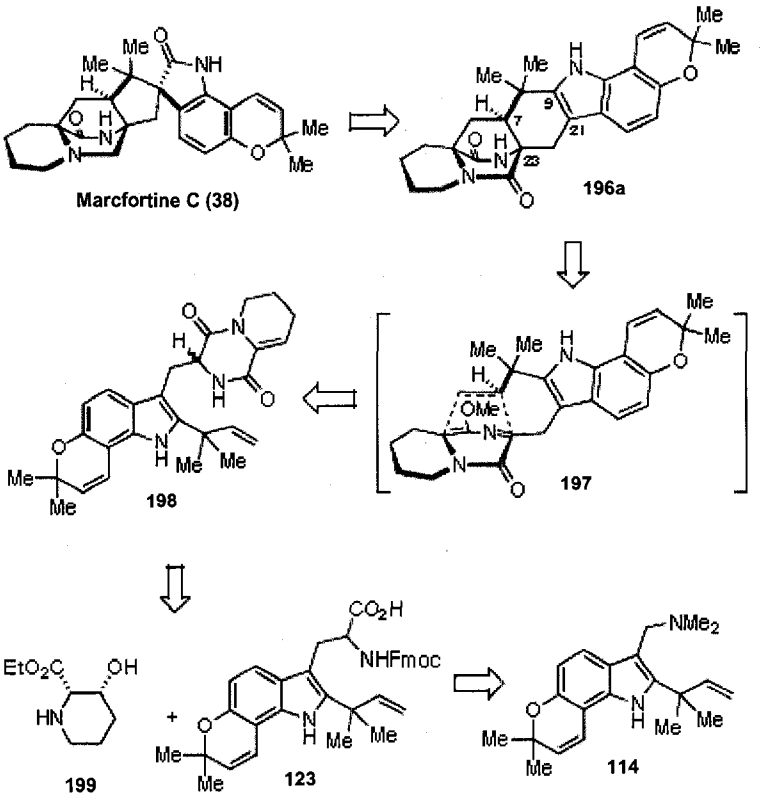


Our plan mandated the construction of the key enamide **198** (Scheme 51), which should be available through coupling of tryptophan derivative **123** with *cis*-3-hydroxypipecolic acid ethyl ester (**199**), followed by Fmoc removal, concomitant diketopiperazine formation, and dehydration. Tryptophan derivative **123** is readily available from the corresponding gramine **114** and has been recently synthesized in our group on gram-scale. Our synthesis commenced with a coupling of *cis*-3-hydroxy pipecolic acid ethyl ester (**199**) and *d,l*-acid **123** in the presence of BOP and $^{i}Pr_2NEt$ to afford amide **200** (Scheme 52) as an inseparable mixture of diastereomers in 77% yield. Subjecting peptide **200** to a solution of morpholine in THF at room temperature effected removal of the *N*-

Fmoc group and a concomitant cyclization of the resultant amine onto the ethyl ester to provide diketopiperazine **201**, once again produced as an inseparable and inconsequential mixture of diastereomers. As previously described in our stephacidin A synthesis, we had planned to eliminate the alcohol of compound **201** under Mitsunobu conditions to afford enamide **198**. Following lactim ether formation and a KOH-induced tautomerization, azadiene **197** (Scheme 51) would then undergo the desired cycloaddition reaction to construct the desired bicyclo[2.2.2]diazaoctane core. However, upon subjection of alcohol **201** to our standard elimination conditions (PBu_3, DEAD, CH_2Cl_2, room temperature), only a small amount of enamide **198** (~15%) was obtained, along with large amounts of recovered starting material. In an effort to thermally force the Mitsunobu reaction to completion, we were surprisingly pleased to find that heating alcohol **201** with excess PBu_3 and DEAD to 40 °C for 20 h, not only effected the anticipated dehydration, but the incipient enamide **198** spontaneously underwent enolization and tautomerization directly furnishing the desired intramolecular [4+2] aza-Diels-Alder reaction that smoothly provided cycloadducts **196a** and **196b** as a 2.4 : 1 mixture diastereomers favoring the desired *syn*-stereoisomer. This amazing one-pot transformation must produce azadiene **194** *in situ*, which then undergoes the subsequent cycloaddition reaction to produce cycloadducts **196a** and **196b**. We currently have no experimental data with which to speculate about the possible roles the tributylphosphine, DEAD, or the diethyl 1,2-hydrazinedicarboxylate by-product may have in this fortuitous sequence. It was found, however, that resubjecting enamide **198** (isolated from a room temperature Mitsunobu reaction) to the same reaction conditions (PBu_3, DEAD, CH_2Cl_2)

at 40 °C did produce varying amounts of cycloadducts **196a** and **196b** albeit in diminished yields (25-45%).

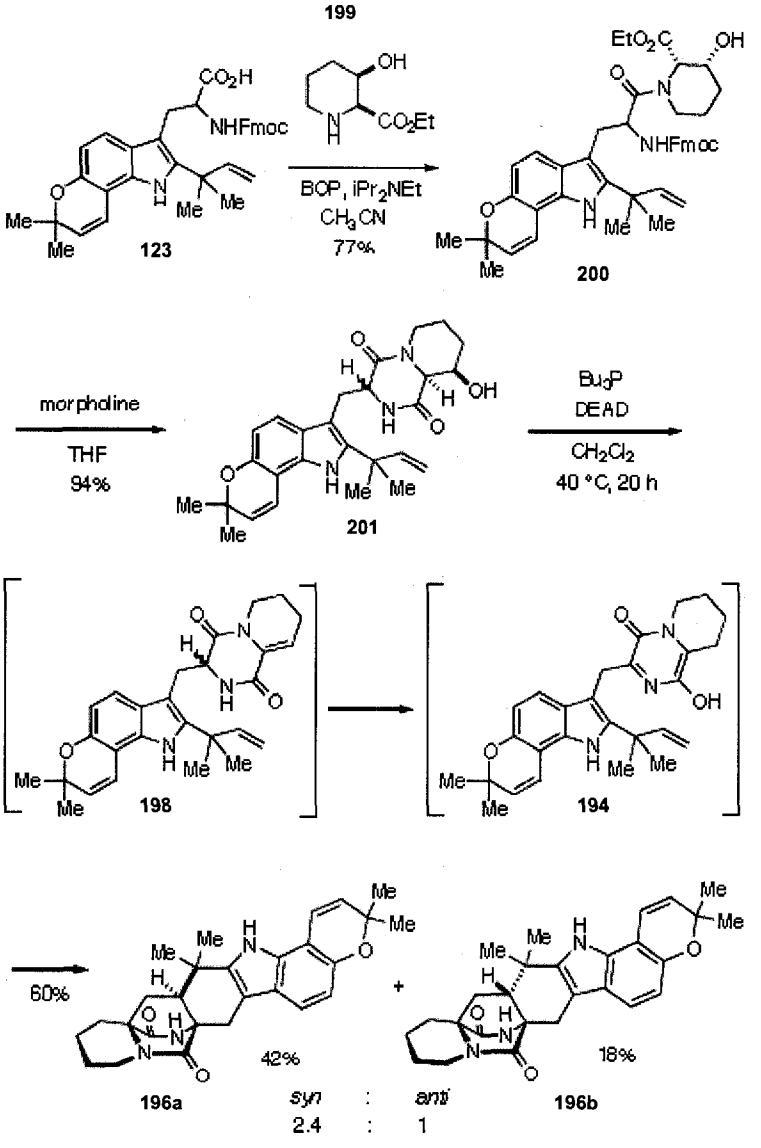
Scheme 51. Biomimetic retrosynthesis of marcfortine C.



To our knowledge, this is the first example of such a cycloaddition reaction wherein the putative azadiene species (**194**) is generated with a free hydroxyl residue. The facility with which putative azadiene species **194** was generated under these conditions was striking and provides support for the possible intermediacy of such a species in the biological construction of this ring system within this family of secondary metabolites.

The tentative stereochemical assignment for *syn*-cycloadduct **196a** was confirmed by its transformation to racemic marcfortine C (**38**).

Scheme 52. Construction of the marcfortine C ring system via an intramolecular Diels-Alder cycloaddition.

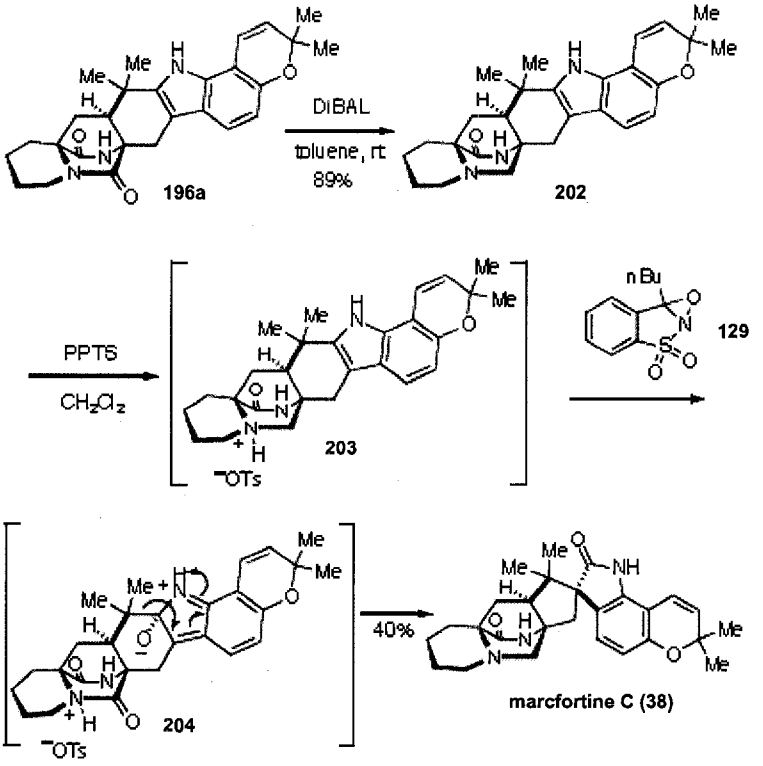


Thus, selective reduction of the tertiary amide over the secondary amide was accomplished by treatment of **196a** with excess DIBAL-H (20 equiv) to provide amine **202** in 89% yield (Scheme 53). We have previously been successful in effecting the desired oxidation/pinacol rearrangement in the total synthesis of notoamide B (**17**) by employing oxaziridine **129**. In the case at hand, however, **202** contains a tertiary amine that can be easily oxidized by the oxaziridine. To circumvent this inherent problem, we surveyed a variety of acids that would be acidic enough to protonate the tertiary amine and render it unreactive toward oxidizing agents, but still be compatible with the sensitive oxaziridine reagent. We were pleased to find that pyridinium tosylate (PPTS) met both criteria. Thus, treatment of amine **202** with 1.25 equiv. of PPTS for 15 min at room temperature effected protonation to the amine salt **203**, which was then treated with excess oxaziridine **129** in CH_2Cl_2 to effect the desired stereoselective oxidation and pinacol rearrangement to produce marcfortine C (**38**) as a single diastereomer in 40% yield, along with recovered starting material (25%). The stereochemical result can be rationalized by epoxidation of the 2,3-disubstituted indole from the less hindered α-face, followed by ring opening of the incipient epoxide to the 2-alkoxyindole intermediate **204**. A subsequent α-face ring contraction by a [1,5] sigmatropic shift successfully furnishes **38** as a single diastereomer. All 1H and 13C NMR spectral properties were identical to those published by Polonsky and coworkers. In addition, the synthetic material was identical by mobility on TLC and 1H nmr to an authentic specimen kindly provided by Prof. David Miller of Carleton University, Canada. Once again, the deployment of oxaziridine **129** for the one-step conversion of a 2,3-disubstituted indole to the corresponding *spiro*-oxindole has proven to be a highly useful transformation that

provides a mild alternative to the standard methods that have been utilized over the years for effecting such a transformation.

7.2 Synthesis of (±)-Marcfortine C – Biomimetic Total Synthesis

Scheme 53. Completion of marcfortine C.



In conclusion, we have completed a concise biomimetic total synthesis of marcfortine C (**38**) via an intramolecular azadiene Diels-Alder reaction in 15 steps and 2.4% overall yield from commercially available 6-hydroxyindole. This work underscores the low activation barriers inherent in this specific class of azadiene IMDA reactions that have

been strongly implicated in the construction of the bicyclo[2.2.2]diazaoctane core ring system common to the paraherquamide/stephacidin/marcfortine family of prenylated indole alkaloids. Significantly, enamide species such as **198** provide a provocative new venue for generating the hitherto elusive azadiene species **194** which has been strongly implicated as a biosynthetic intermediate. Further studies to experimentally corroborate the biosynthesis of this family of fungal metabolites are under investigation and will be reported in due course.

7.3 Synthetic Summary and Conclusions

Concise syntheses of notoamides B-E, stephacidin A, versicolamide B and marcfortine C have been achieved. In the wake of these syntheses many important clues and questions that penetrate deeply into the fundamental mode of action by which these and similar natural products manifest their biological activity have been clarified. Through the synthesis of notoamide E we have established a versatile intermediate that undoubtedly will serve as a valuable precursor to many natural products related to the notoamides, norgeamides and stephacidins. Notoamide E is also posed for studies using isotopically labeled derivates for ongoing biosynthetic investigations that will ultimately contribute to a more clear understanding of nature's machinery used in the construction of many known and yet to be discovered natural products.

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Chapter 8: Experimental Section

8.1 General Considerations

Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using flame-dried glassware. Dichloromethane, diisopropylamine, triethylamine, and *N,N*-diisopropylethylamine were distilled from CaH_2 immediately prior to use. Tetrahydrofuran, diethylether, toluene, and dimethylformamide were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves. Flash chromatography was performed on Merk silica gel Kieselgel 60 (230-400 mesh) from EM science with the indicated solvent. Alkyllithium reagents were standardized in THF with diphenylacetic acid as the acid and indicator.[1]

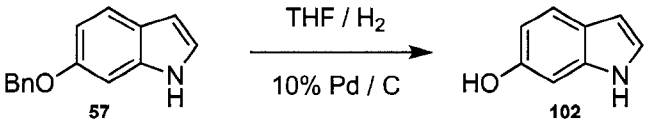
^{1}HNMR spectra were recorded on Varian 300, 400, or 500 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances are reported relative to $CHCl_3$, DMSO-d_5, HOD, or HD_2COD using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), coupling constant(s) (*J* in Hz), integral].[2,3] ^{13}CNMR spectra were recorded at 75, 100, or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak, except those in D_2O which are referenced to methanol.[2]

Infrared spectra were recorded on a Nicolet Avatar 320-FT IR spectrometer. All absorptions are reported in cm^{-1} relative to polystyrene (1601 cm^{-1}). Spectra that were recorded 'neat' refer to a thin film of pure liquid on NaCl plates. Spectra were also recorded as films deposited from $CDCl_3$ (dep. $CDCl_3$) or CH_2Cl_2 (dep. CH_2Cl_2) solutions on NaCl plates followed by solvent evaporation. Peaks reported in the IR spectrum are described using the following conventions: w = weak, m = medium, s = strong, vs = very strong, sh = shoulder, and br = broad.

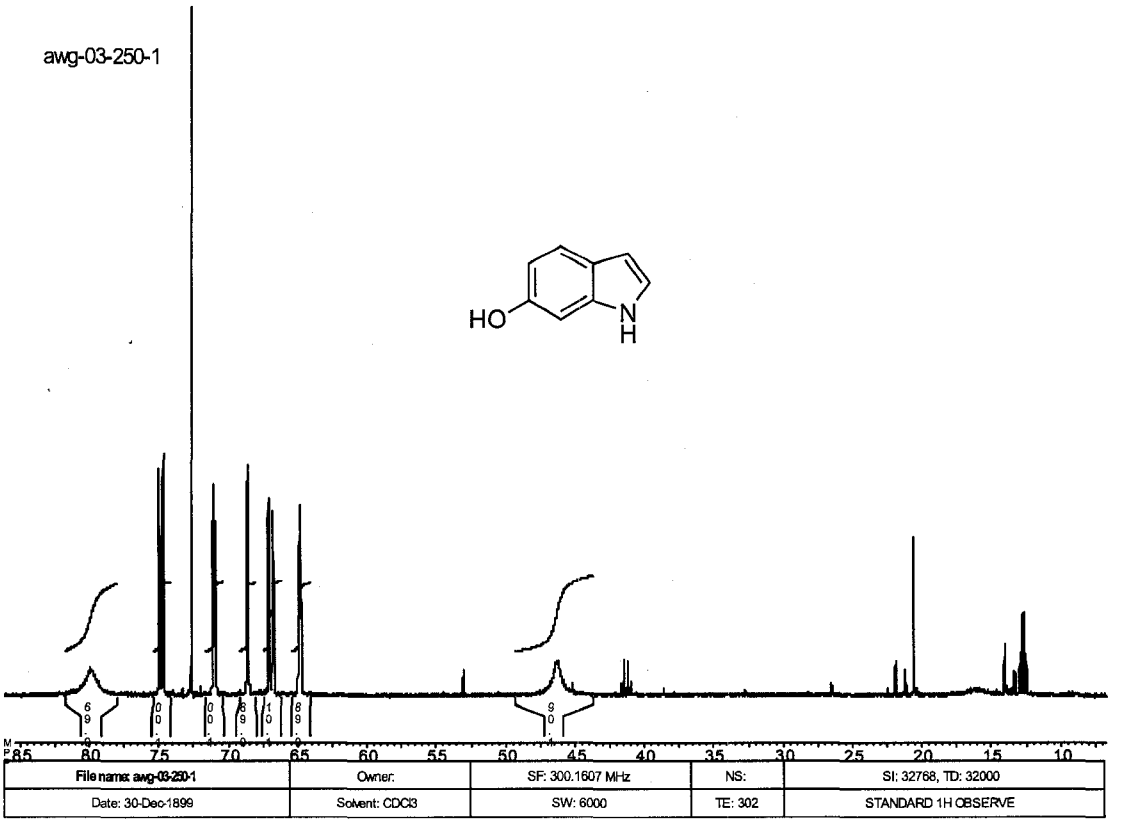
Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec. Optical rotations were obtained with a 2 mL, 1 dm cell on a Rudolf Research Autopol III polarimeter operating at 589 nm. $CHCl_3$ was distilled from $CaCl_2$ for optical rotations where indicated. HPLC data was obtained on a Waters 600 HPLC system Interfaced with Varian Dynamax Integration software using the indicated column and eluent conditions. Melting points are uncorrected.

8.2 Experimental procedures

1*H*-indol-6-ol (102)



6-benzyloxy indole **57** (10g, 44.8mmol) was dissolved in 300ml THF. Oxygen was purged from the system by gentle bubbling of argon through the solvent mixture for 5min. The solution was then charged with 10% palladium on carbon (10g, 1 wt / wt **57**). The reaction was stirred under a balloon of hydrogen for 24h and then purged again by gentle bubbling of argon. The mixture was filtered through a pad of celite and then directly concentrated to afford the desired 6-hydroxy indole (5.90g, 99%) as a pink crystalline solid (mp 140–143°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (1H, bs), 6.47-6.51 (1H, m), 6.70 (1H, dd, J = 2.3 Hz, J = 8.5 Hz), 6.86 (1H, d, J = 2.2 Hz), 7.11 (1H, dd, J = 2.5 Hz, J = 3.2 Hz), 7.49 (1H, d, 8.4 Hz), 8.00 (1H, bs).



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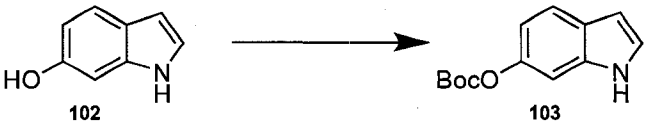
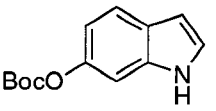
***tert*-Butyl 1H-indol-6-yl carbonate (103).**



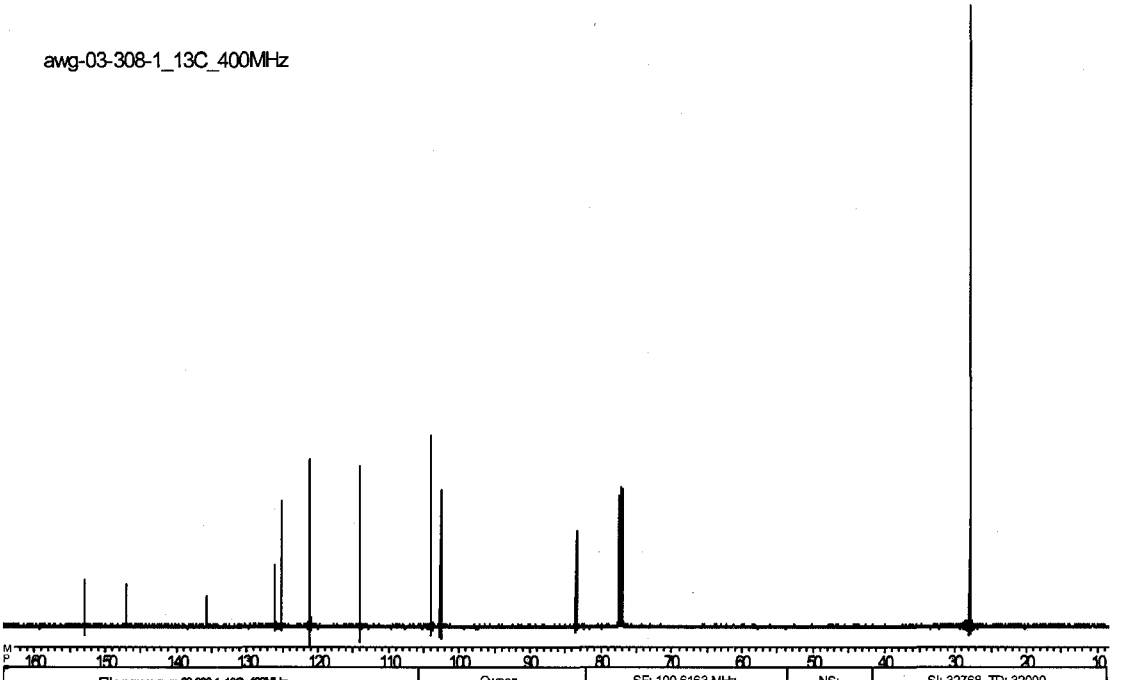
102 103

To a 100 mL round bottom flask, di-*tert*-butyl dicarbonate (3.00 g, 13.7 mmol) was added to a -10°C solution of commercially available 6-hydroxyindole (102, 3B Medical, 1.82 g, 13.7 mmol) in MeCN (55 mL). The solution was then charged with 4-dimethylaminopyridine (17.0 mg, 0.14 mmol) and the reaction mixture was allowed to warm to 20°C over 24 hours and concentrated directly. The crude material was passed through a short column of silica eluting with 1:1 EtOAc: hexanes to produce a white solid. The solid was recrystallized from 10% EtOAc / hexanes to give the indole **103** (2.38 g, 75% yield) as a white crystalline solid (mp 140–143°C). IR (Thin Film) 3413, 2977, 1751, 1455, 1396, 885, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9 H), 6.50-6.52 (m, 1H), 6.91 (dd, J = 8.4, 2.0 Hz, 1H), 7.17 (dd, J = 3.2, 3.1 Hz, 1H), 7.19-7.20 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 8.15 (br. s, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 152.95, 146.96, 135.66, 126.03, 125.19, 121.14, 114.09, 103.99, 102.65, 83.49, 27.95; HRMS (FAB+): Calc. for $C_{13}H_{15}O_3N$ (*m/z*) 233.1052; found (*m/z*) 233.1049.

awg-03-308-1_400MHz



awg-03-308-1_13C_400MHz



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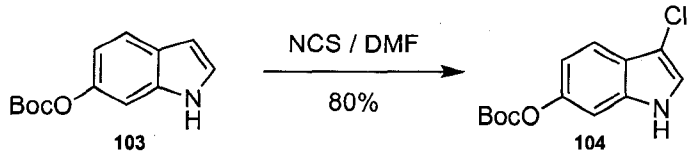
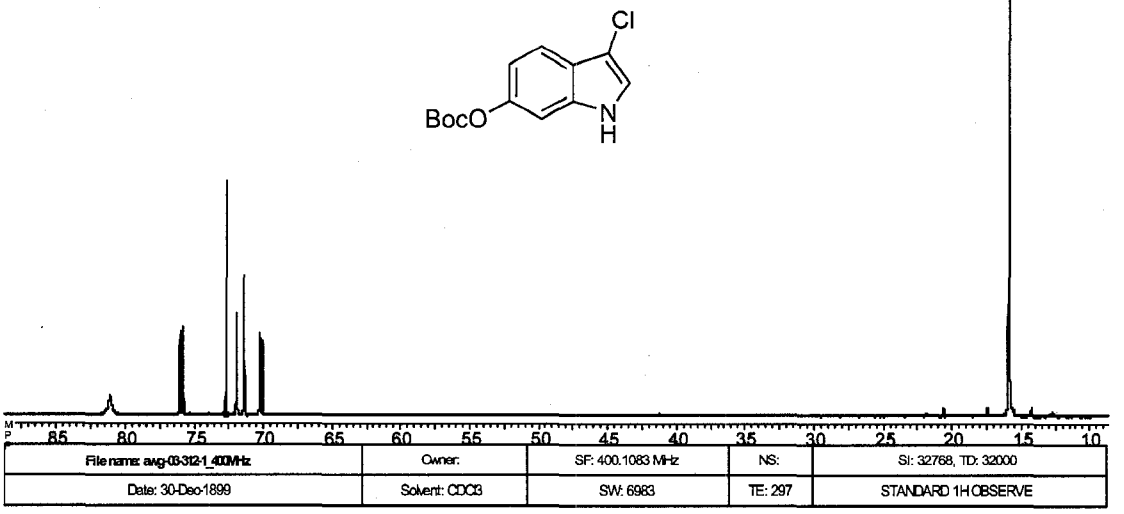
***tert*-Butyl-3-chloro-1*H*-indol-6-yl carbonate (104).**



To a 50 mL round bottom flask, indole **103** (500 mg, 2.14 mmol), was dissolved in DMF (10 mL) at 20°C and charged with *N*-chlorosuccinimide (286 mg, 2.14 mmol). The reaction was stirred at ambient temperature for 2 hours and then charged with brine (10 ml). The mixture was extracted with EtOAc (2 x 50ml) and the combined organics were washed with H_2O (20 ml), brine (20 ml), and dried over Na_2SO_4 and concentrated. The crude oil was purified by flash silica gel chromatography (1:4 EtOAc: hexanes) to give the 3-chloroindole (**104**) (460 mg, 80% yield) as a crystalline solid (mp 125-127 °C). IR (Thin Films) 3368, 2980, 1735, 1626, 1454, 1141, 1003, 882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 7.01 (dd, J = 8.4, 2.0 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 2.4, 0.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 8.11 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.68, 147.90, 134.84, 123.61, 121.76, 119.05, 115.01, 106.85, 104.50, 83.79, 27.95; HRMS (FAB+) Calc. for $C_{13}H_{14}O_3NCl$, 267.0662; found, 267.0657.

awg-03-312-1_400MHz



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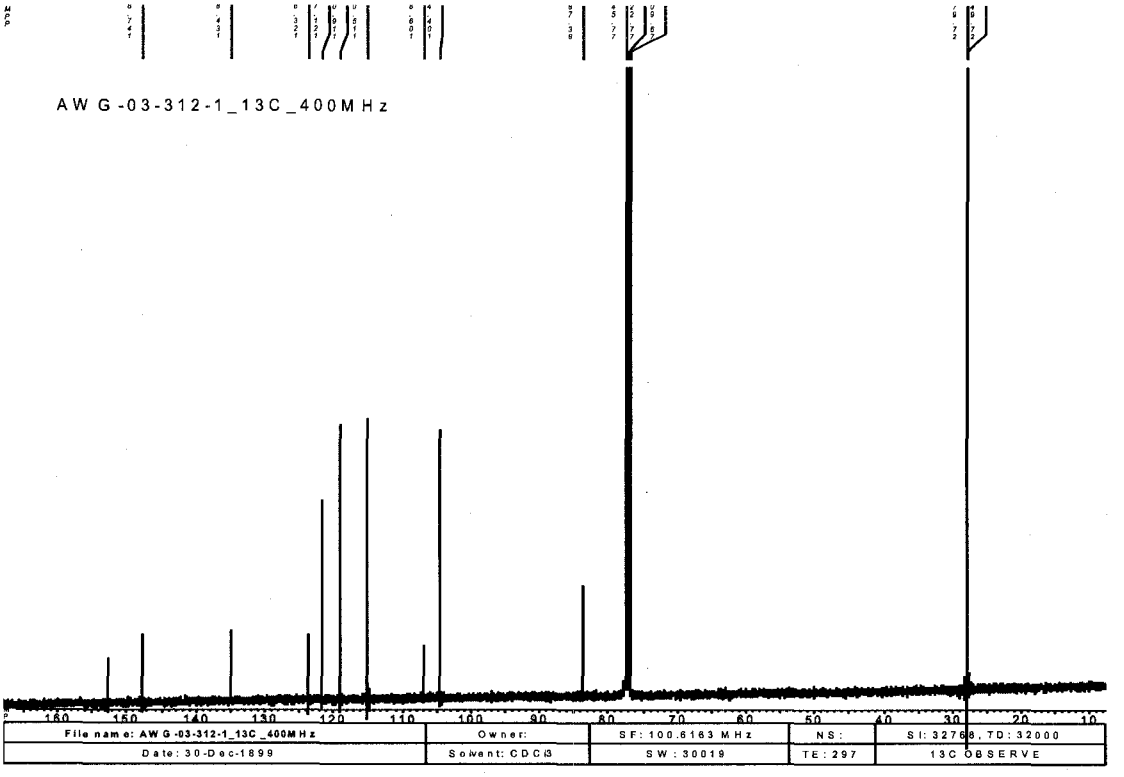
AWG-03-312-1_13C_400MHz



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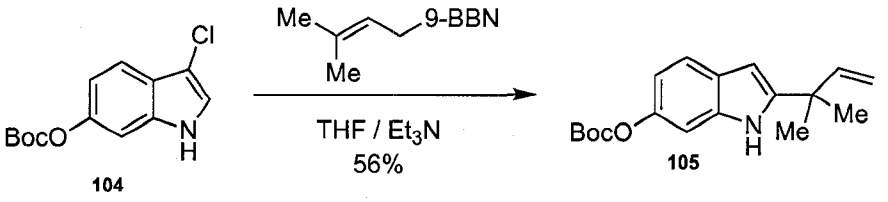
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 297	13C OBSERVE

***tert*-Butyl 2-(2-methylbut-3-en-2-yl)-1H-indol-6-yl carbonate (105).**



To a 25 mL round bottom flask, Et_3N (337 mg, 3.33 mmol) was added to chloroindole **104** (446 mg, 1.67 mmol) in THF (9 mL). The ethereal solution was stirred at 20°C for 10 min and then prenyl-9-BBN (633 mg, 3.33 mmol) was added via syringe. The reaction mixture was stirred at ambient temperature for 12 h. The volatile organics were then removed in vacuo and the resulting crude product was purified by flash silica gel chromatography (1:9 EtOAc : hexane) to afford indole **105** (282 mg, 56 %) as an amber oil. IR (Thin Film) 3384, 2972, 2932, 1755, 1735, 1458, 1141, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl^3$) δ 1.46 (s, 6H), 1.58 (s, 9H), 5.09 (dd, J = 6.0, 1.2 Hz, 1H), 5.13 (br. s, 1H), 6.01 (dd, J = 18.0, 10.4 Hz, 1H), 6.29 (dd, J = 3.2, 2.0 Hz, 1H), 6.89 (dd, J = 8.4, 0.8 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.89 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl^3$) δ 152.91, 146.77, 146.54, 146.13, 135.78, 126.73, 120.53, 113.83, 112.55, 103.49, 98.13, 83.36, 38.43, 27.96, 27.56; HRMS-FAB: [M+H]+ calcd for $C_{18}H_{24}NO_3$, 302.1756; found, 302.1742.

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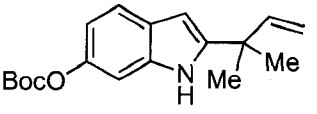

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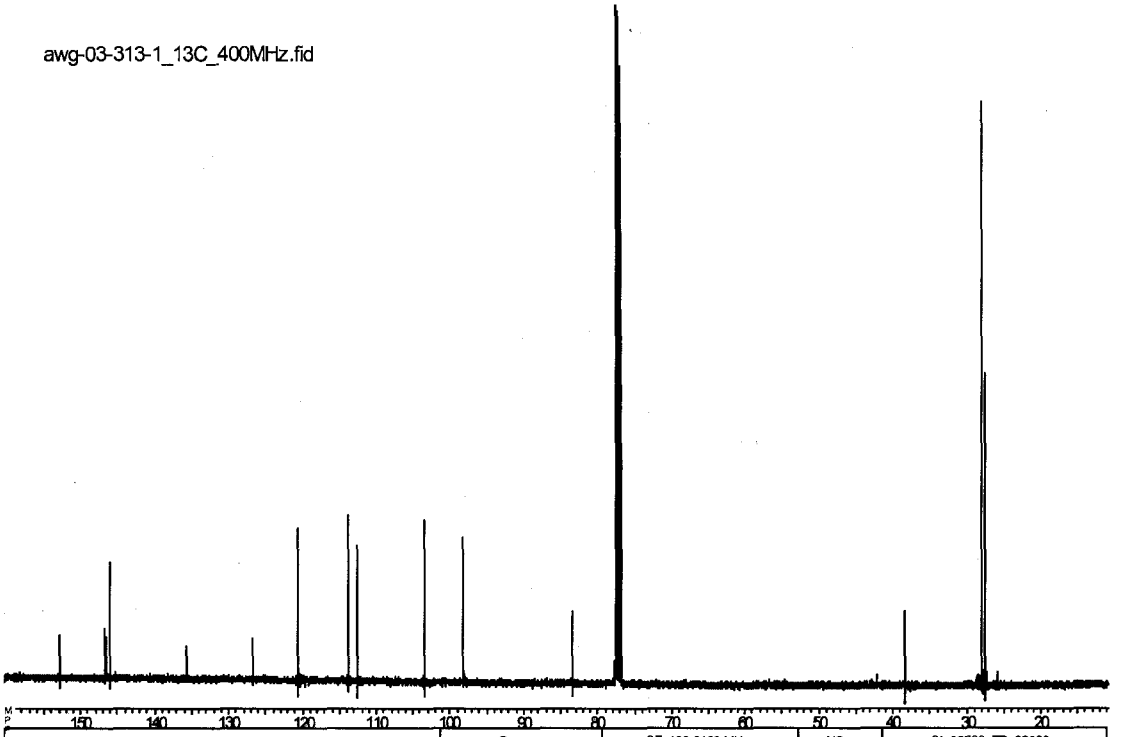

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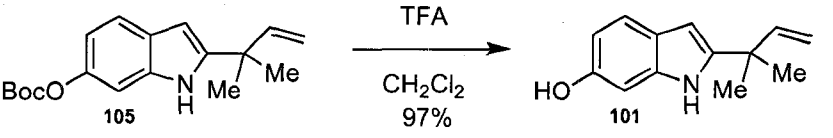
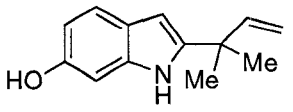
2-(2-methylbut-3-en-2-yl)-1H-indol-6-ol (101).



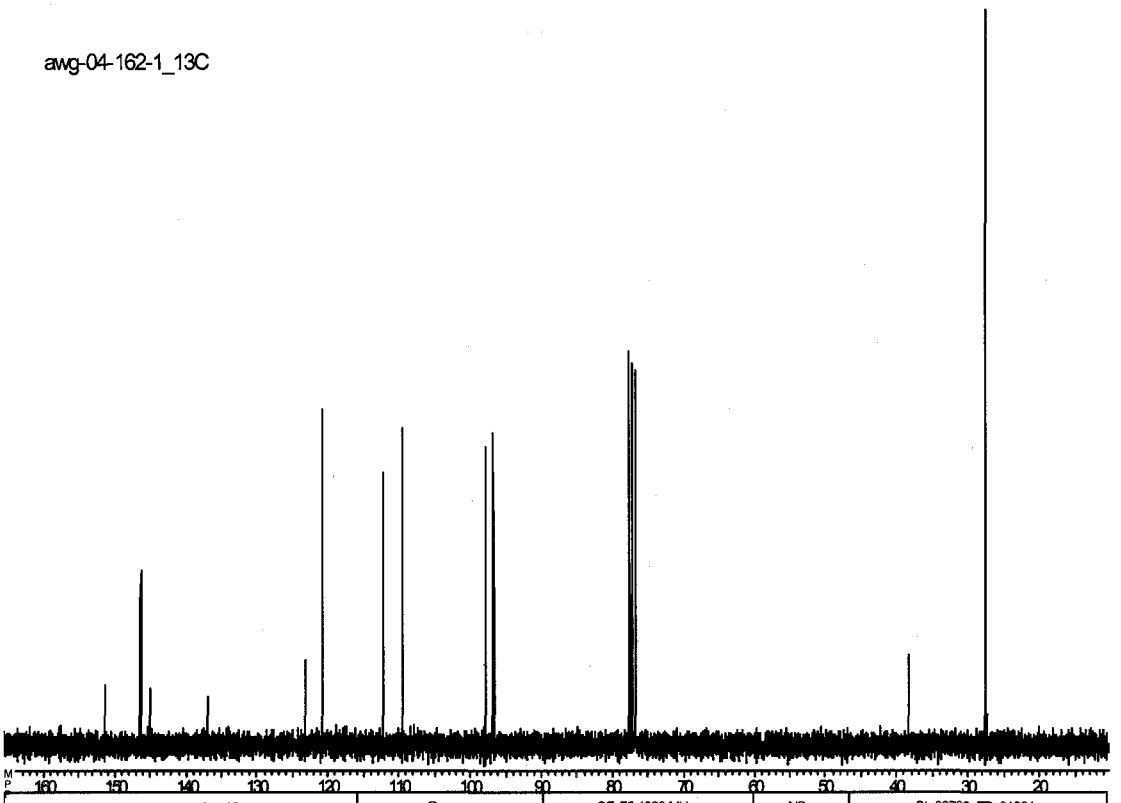
To a 10 mL round bottom flask, *O*-Boc indole **105** (72 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and the reaction mixture was cooled in an ice bath. TFA (533 mg, 4.67 mmol) was then added via a syringe and the reaction mixture was warmed with stirring to 20°C. After 1h, the reaction mixture was cooled to 0°C and saturated aqueous $NaHCO_3$ was slowly added until the solution was basic. The organic layer was separated from the biphasic solution and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and the volatile organics removed under reduced pressure to afford the desired phenol **101** (47 mg, 97 %) as a solid (mp 130–134 °C, 130-131 °C). IR (NaCl, neat) 3419, 2968, 1628, 1462, 1352, 1228, 1156, 918, 807 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 6H), 5.13 (m, 2H), 5.33 (bs, 1H), 6.04 (dd, J = 10.4 Hz, J = 17.6Hz, 1H), 6.25 (d, J = 1.8 Hz, 1H), 6.67 (dd, J = 2.7 Hz, J = 8.4 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.79 (bs, 1H). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ 27.7, 38.5, 97.0, 97.9, 109.6, 112.3, 120.9, 123.1, 136.9, 145.0, 146.3, 151.3; HRMS-FAB: [M+H]+ calcd for $C_{13}H_{15}NO$, 201.1154; found, 201.1154.

awg-04-162-1



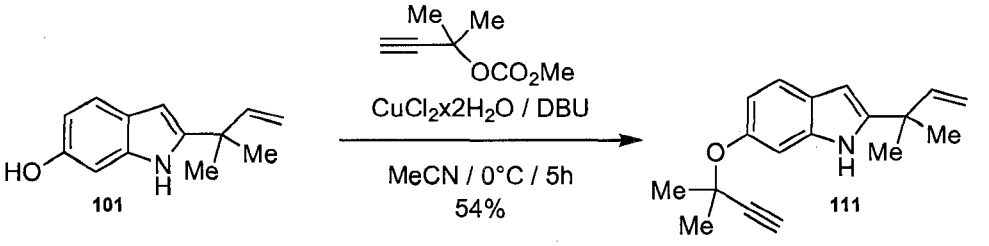
File name: awg-04-162-1	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 31994
Date: 30-Dec-1899	Solvent: CDCl3	SW: 5995	TE: 302	STANDARD 1H OBSERVE

awg-04-162-1_13C



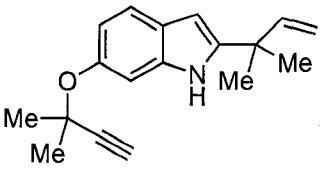
File name: awg-04-162-1_13C	Owner:	SF: 75.4826 MHz	NS:	SI: 32768, TD: 31984
Date: 30-Dec-1899	Solvent: CDCl3	SW: 22936	TE: 302	13C OBSERVE

2-(2-methylbut-3-en-2-yl)-6-(2-methylbut-3-yn-2-yloxy)-1*H*-indole (111)



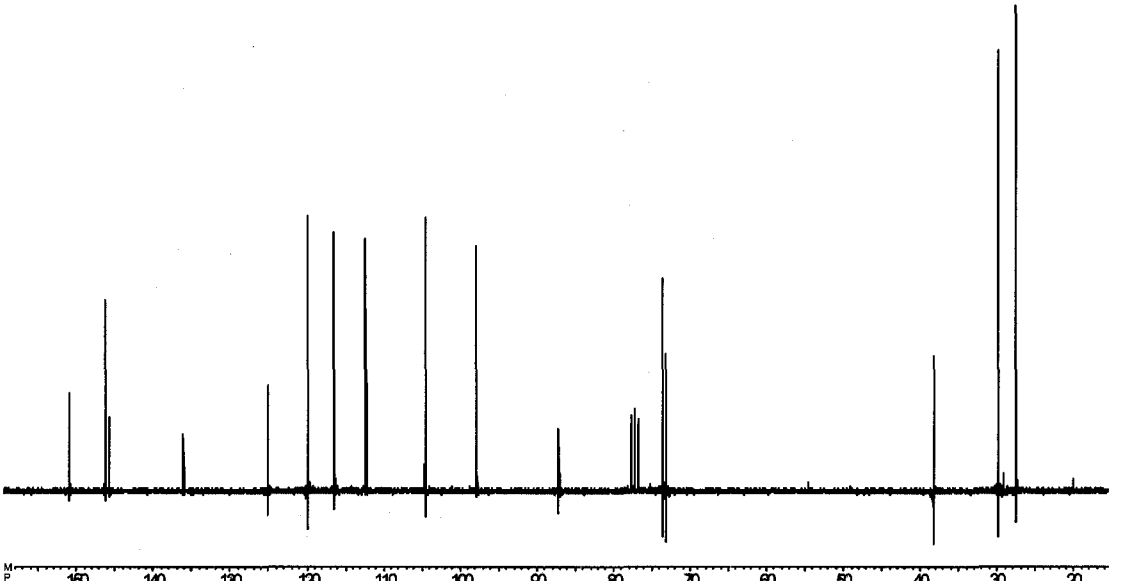
To a 0°C solution of phenol **101** (3.12g, 15.5mmol) in 100ml MeCN was added $CuCl_2x2H_2O$ (3.0mg, 0.1mol%). The solution was stirred at 0°C for 5 min and then charged with the methyl carbonate (6.61g, 46.5mmol). The mixture was stirred for an additional 15 min at 0°C and then charged dropwise with DBU (7.08g, 46.5mmol). The mixture was allowed to warm to 20°C overnight and then charged with a 10% citric acid solution. The mixture was charged with 500ml EtOAc, stirred vigorously, and then separated from the aqueous phase. The resulting organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The crude oil was purified by flash chromatography (10% EtOAc / hexanes) to afford 2.24g (54%) of **111** as an amber oil. IR (NaCl, neat): 3428, 3361, 3295, 2970, 2934, 2111, 1622, 1456, 1239, 1132, 976, 885, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (6H, s), 1.66 (6H, s), 2.56 (1H, s), 5.15 (2H, m), 6.06 (1H, dd, J = 10.5 Hz, J = 17.4 Hz), 6.28 (1H, dd, J = 0.6 Hz, J = 2.1Hz), 6.96 (1H, dd, J = 2.1Hz, J = 8.7Hz), 7.24 (1H, d, J = 1.8Hz), 7.42 (1H, d, J = 8.4 Hz), 7.83 (1H, bs). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ 27.7, 30.0, 38.5, 73.2, 73.6, 87.2, 97.9, 104.6, 112.3, 116.4, 119.9, 125.1, 136.1, 145.7, 146.3, 150.9; HRMS-FAB: [M+H]+ calcd for $C_{18}H_{21}NO$, 267.1623; found, 267.1621.

awg-04-165-1



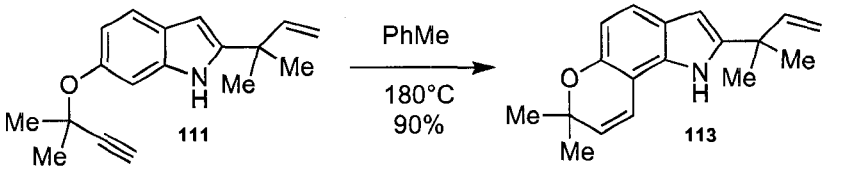
File name: awg-04-165-1	Owner:	SF: 300.1574 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	RJC33 Fractions 10-14 21Sep01

awg-04-165-1_13C



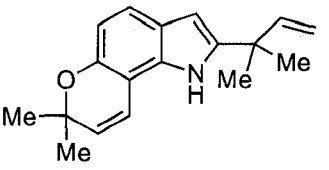
File name: awg-04-165-1_13C	Owner:	SF: 75.4826 MHz	NS:	SI: 32768, TD: 31984
Date: 30-Dec-1899	Solvent: CDCl3	SW: 22936	TE: 302	13C OBSERVE

7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indole (113)



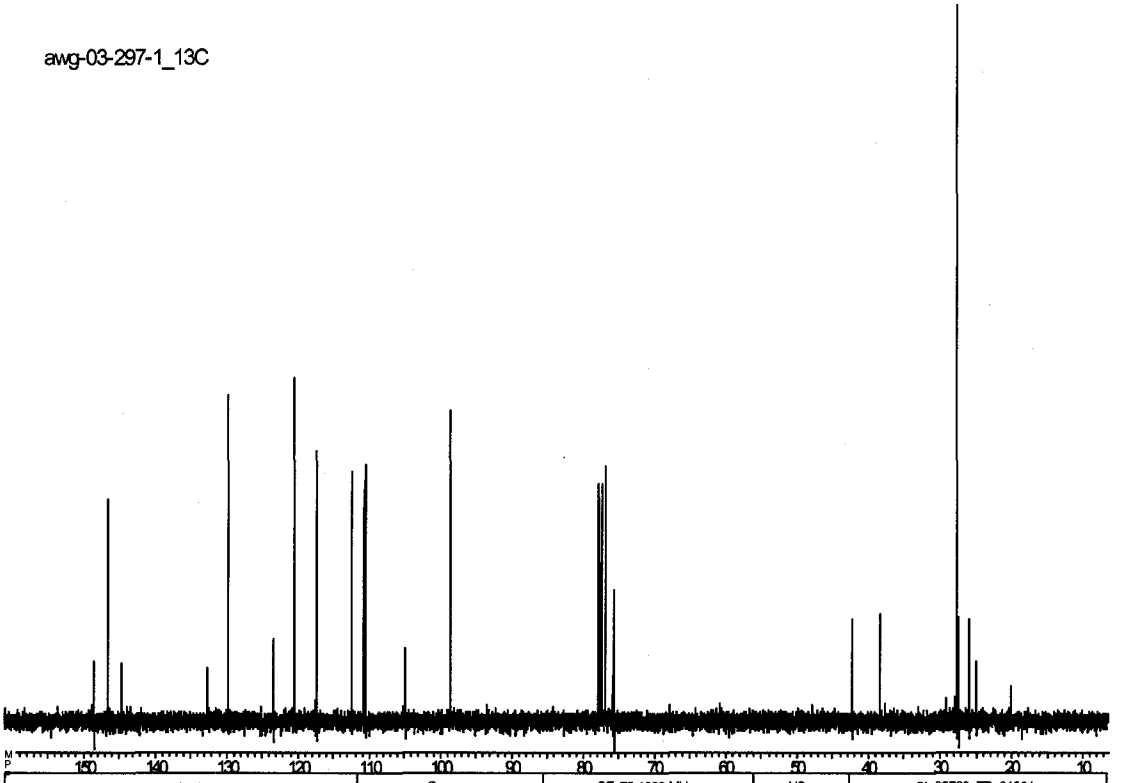
A 100ml ChemGlass sealed tube was charged with indole **111** (1.68g, 6.28mmol) and 20ml freshly distilled toluene. The mixture was sealed and heated to 180°C for 5 hours and cooled to 20°C. The mixture was concentrated directly and then charged with 20ml EtOAc and concentrated. The mixture was charged again with 50ml CH_2Cl_2 and concentrated to afford 1.51g (90%) of the title compound **113** as amber crystals (mp 155–156 °C). IR (NaCl, neat) 3381, 2975, 2931, 1637, 1437, 1361, 1218, 1154, 921, 809, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (6H, s), 1.48 (6H, s), 5.14 (2H, m), 5.66 (1H, d, J = 9.6Hz), 6.05 (1H, dd, J = 10.5 Hz, J = 17.4 Hz), 6.23 (1H, d J = 2.1 Hz), 6.59 (1H, d, J = 9.6 Hz), 6.64 ((1H, d, J = 8.4 Hz), 7.29 (1H, d, J = 9.3 Hz), 7.68 (1H, bs). ^{13}C NMR (74.47 MHz) ($CDCl_3$) δ 27.7, 38.5, 75.8, 98.6, 104.9, 110.6, 112.4, 117.3, 120.4, 123.3, 129.6, 132.5, 144.6, 146.3, 148.4; HRMS-FAB: [M+H]+ calcd for $C_{18}H_{21}NO$, 267.1623; found, 267.1627.

awg-03-297-1



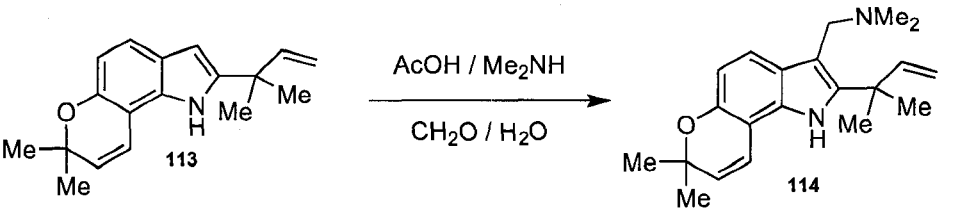
File name: awg-03-297-1	Owner:	SF: 300.1574 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	RJC36 Fractions 3-12 30Sep01

awg-03-297-1_13C



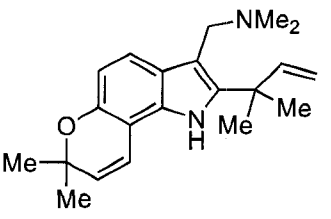
File name: awg-03-297-1_13C	Owner:	SF: 75.4826 MHz	NS:	SI: 32768, TD: 31984
Date: 30-Dec-1899	Solvent: CDCl3	SW: 22936	TE: 302	13C OBSERVE

(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)-*N*,*N*-dimethylmethanamine (114)



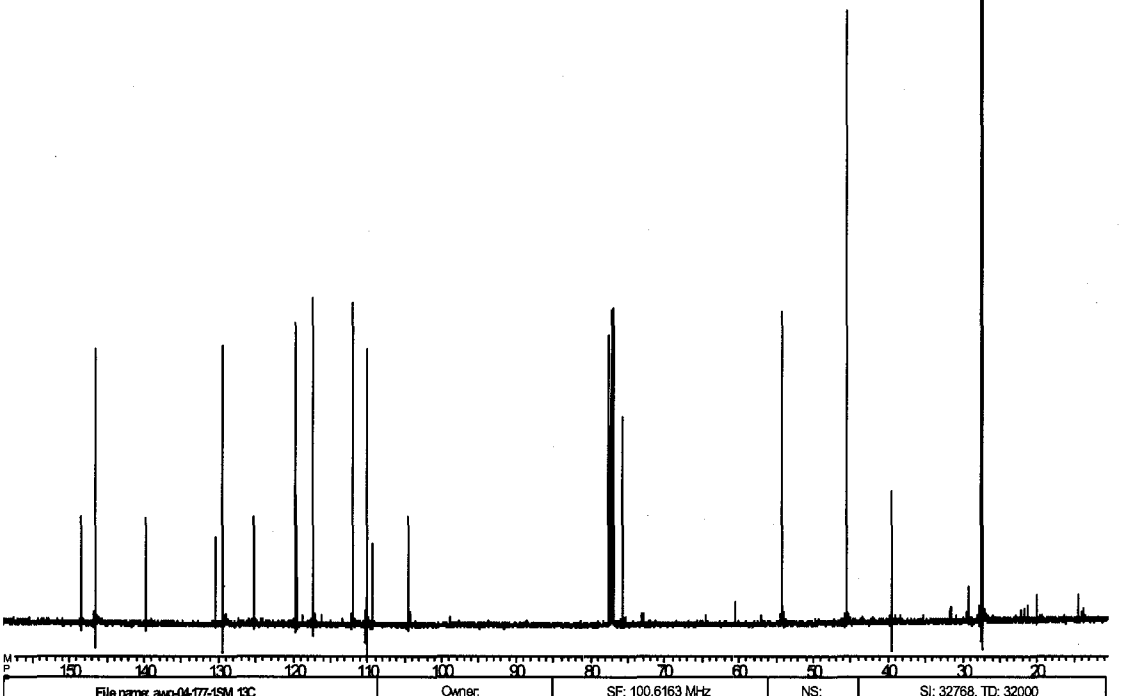
A clean dry round bottom flask was charged with 40% dimethylamine, 40% solution in H_2O (603mg, 13.4mmol) and cooled to 0°C. The mixture was then charged slowly with 14.0ml acetic acid. The mixture was stirred until the acetic acid began to crystallize and then was charged with formaldehyde, 37% solution in H_2O (110mg, 3.67mmol). The mixture was allowed to warm to 20°C for 15min and then the entire mixture was poured into a flask containing indole **113** (893mg, 3.34mmol). The mixture was allowed to warm to 20°C overnight and then was quenched with 1N NaOH. The mixture was charged with EtOAc and mixed thoroughly. The organic layer was washed with water, brine and dried over Na_2SO_4, filtered and concentrated to afford 1.07g (99%) of compound **114** as an amber oil that was used without further purification in the next reaction.). IR (NaCl, neat) 3387, 2973, 2810, 2760,1639, 1443, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (6H, s), 1.57 (6H, s), 2.22 (6H, s), 3.54 (2H, s), 5.14-5.22 (2H, m), 5.64 (1H, d, J = 9.6 Hz), 6.17 (1H, dd, J = 10.7 Hz, J = 17.6 Hz), 6.56 (1H, d, J = 9.9 Hz), 6.63 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 8.4 Hz), 7.68 (1H, bs). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 27.3, 27.6, 39.5, 45.6, 54.1, 75.7, 104.5, 109.4, 110.1, 112.0, 117.3, 119.5, 125.4, 129.4, 130.4, 139.7, 146.5, 148.4; HRMS-FAB: [M+H]+ calcd for $C_{21}H_{28}N_2O$, 324.2202; found, 324.2207.

awg-03-298-1



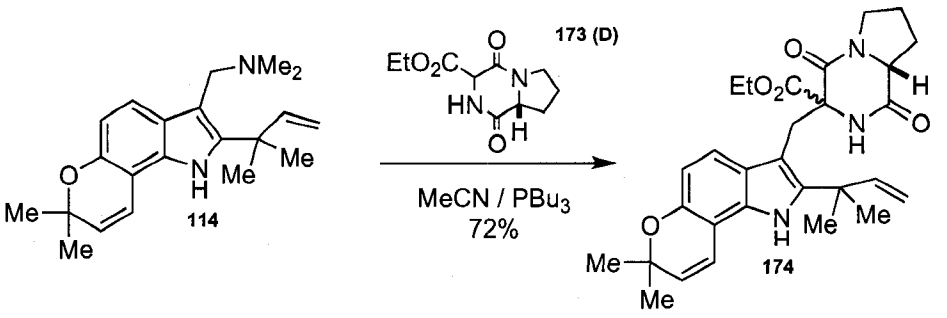
File name: awg-03-298-1	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 8000	TE: 302	RJC294 Crude 25Sep02

awg-04-177-1SM_13C



File name: awg-04-177-1SM_13C	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

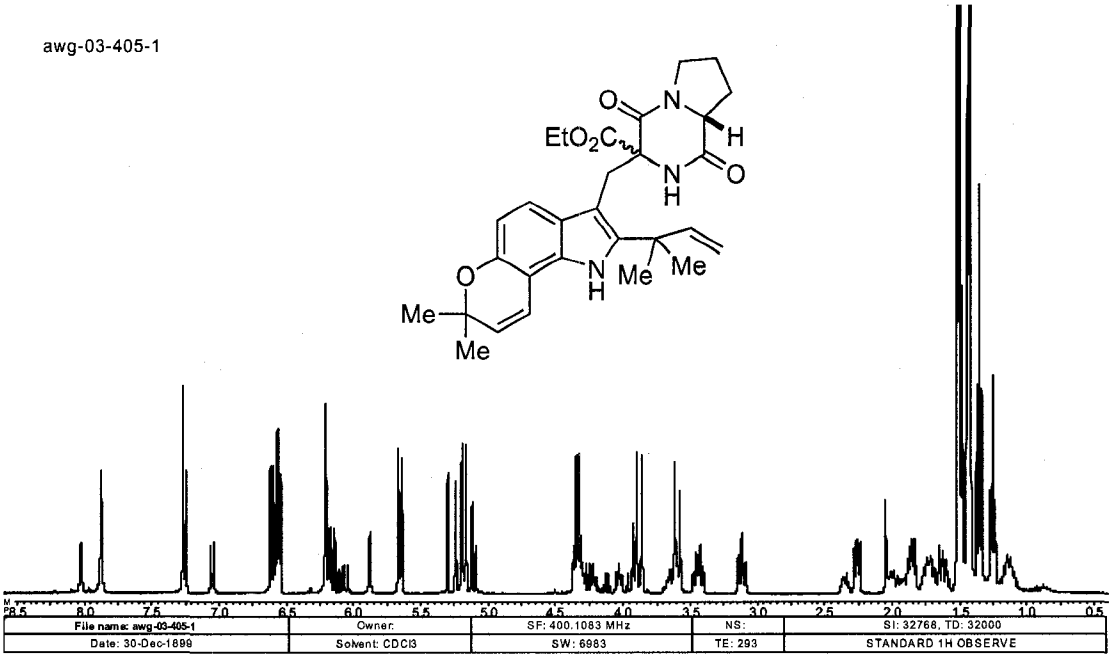
(*R*)-ethyl 3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)methyl)-1,4-dioxo-octahydropyrrolo[1,2-*a*]pyrazine-3-carboxylate (174)



A solution of pyranoindole **114** (363mg, 1.12mmol), and diketopiperazine **173** (278mg, 1.23mmol), in 11ml MeCN was charged at 20°C with PBu_3 (113mg, 0.559mmol). The mixture was heated to reflux for 24h and then directly concentrated. The crude oil was purified by flash chromatography (5% MeOH, CH_2Cl_2) to afford 378mg (72%) of the desired product **174** as a 7:3 mixture of diastereomers. IR (NaCl, neat) 3338, 2975, 2924, 2872, 2247, 1898, 1738, 1666, 1440, 1251, 1120, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08-1.20 (1H, m), 1.27 (0.9H, t, J = 6.8 Hz), 1.35 (2.1H , t, J = 6.8 Hz), 1.62-1.65 (6H, m), 1.52-1.68 (6H, m), 1.57-2.05 (4H, m), 2.26 (0.7H, dd, J = 10.8 Hz, J = 6.4Hz), 2.32-2.39 (0.3H, m), 3.12 (0.7H, t, J = 10.4 Hz), 3.64 (0.7H, m), 3.59 (0.7H, ½ ABq, J = 15.2 Hz), 3.60-3.67 (0.6H, m), 3.88 (0.7H, ½ ABq, J = 15.6Hz), 3.90-3.97 (0.6H, m), 4.03 (0.3H, m), 4.20-4.37 (2H, m), 5.09-5.30 (2H, m), 5.88 (0.3H, bs), 6.08 (0.3H, dd, J = 17.2, J = 10.8 Hz), 6.18 (0.7H, dd, J = 17.6 Hz, J = 10.8 Hz), 6.21 (0.7H, bs,), 6.54-6.62 (2H, m), 7.05 (0.3H, d, J = 8.8 Hz), 7.26 (0.7H, d, J = 8.8 Hz), 7.88 (0.7H, bs.), 8.03 (0.3H, bs.). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.1, 14.3, 21.2, 21.5, 22.7, 27.2, 27.3, 27.5, 27.7, 28.1, 28.1, 28.2, 28.2, 28.7, 28.8, 29.3, 32.9, 39.4, 39.7, 45.7, 46.4, 57.9, 59.3, 60.5, 63.1, 63.3, 64.9, 68.9, 75.7, 75.8, 103.4, 104.3, 104.3, 104.8, 110.3,

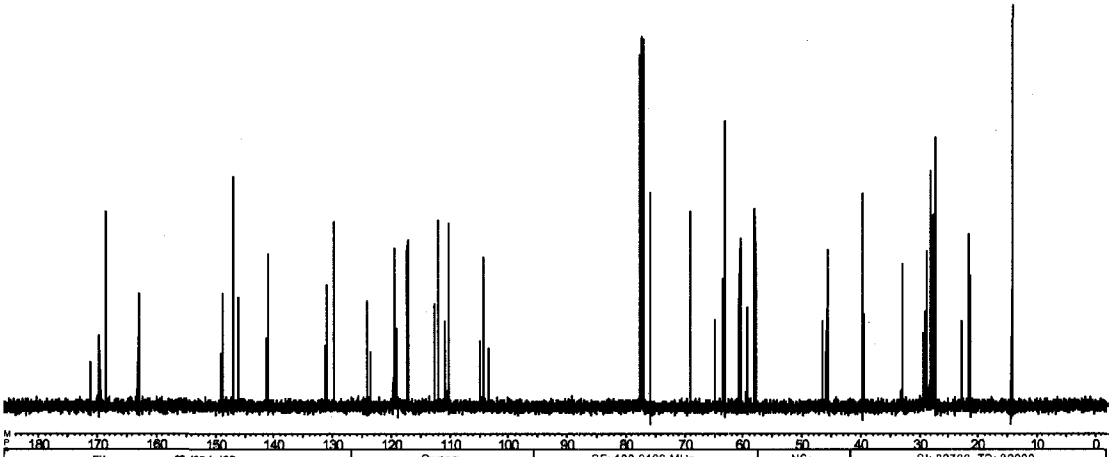
110.6, 112.0, 112.5, 117.1, 117.2, 119.0, 119.5, 123.7, 124.1, 129.7, 130.8, 131.2, 141.0, 141.4, 146.0, 146.9, 148.8, 149.0, 163.0, 163.1, 168.6, 169.6, 171.4; HRMS-FAB: [M+H]+ calcd for $C_{29}H_{35}N_3O_5$, 505.2577; found, 505.2600.

awg-03-405-1



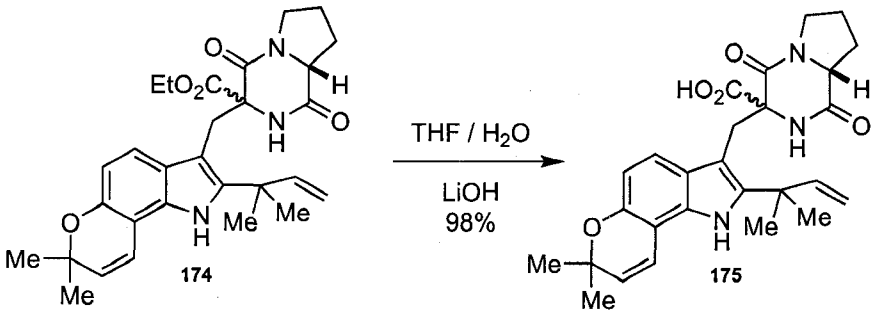
File name: awg-03-405-1	Owner:	SF: 400.1083 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6983	TE: 293	STANDARD 1H OBSERVE

awg-03-405-1_13C



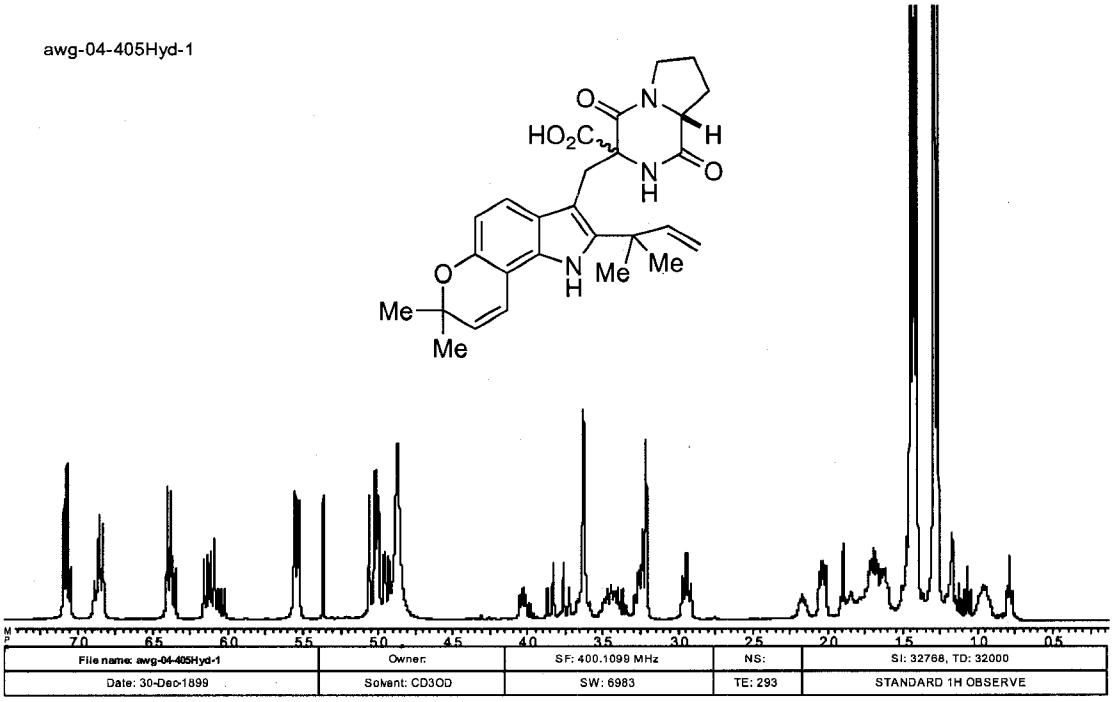
File name: awg-03-405-1_13C	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 293	13C OBSERVE

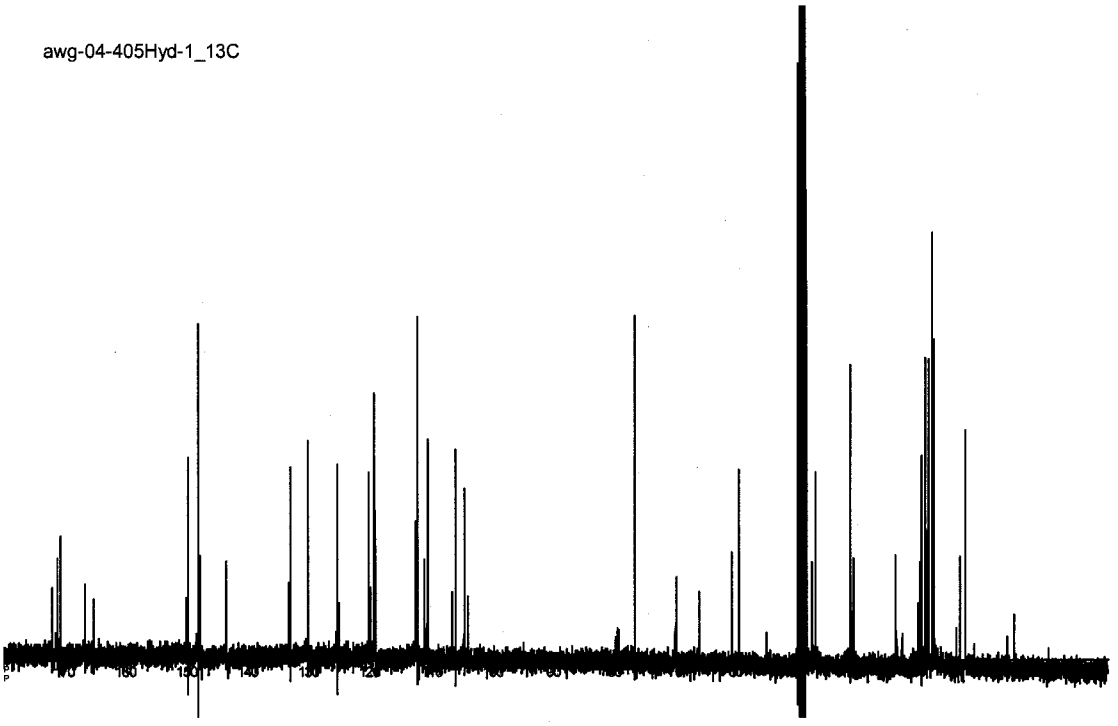
(*R*)-3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)methyl)-1,4-dioxo-octahydropyrrolo[1,2-*a*]pyrazine-3-carboxylic acid (175)



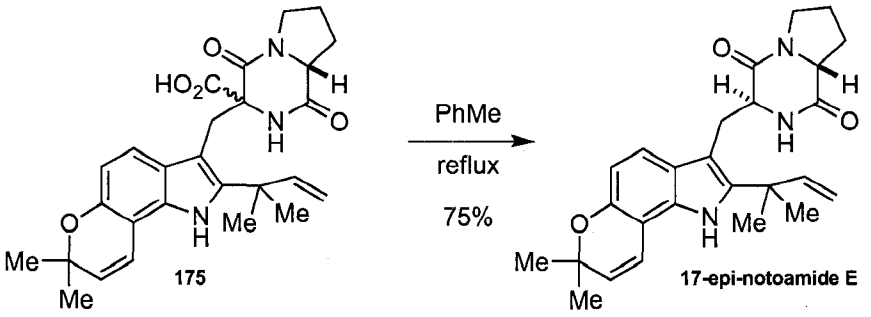
Ethyl ester **174** (560mg, 1.10mmol) was dissolved in 28ml THF and cooled to 0°C. The solution was then charged with 28ml H_2O and then LiOH (265mg, 11.1mmol). The mixture was allowed to warm to 20°C overnight and then brought carefully to pH = 4-6 with the addition of 1N HCl. The solution was then partitioned between EtOAc and brine. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated to afford acid **175** as a white foam (523mg, 99%).). IR (NaCl, neat) 3360, 2975, 2916, 1746, 1680, 1676, 1636, 1446, 1222 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.96-1.11 (0.7H, m), 1.23 (0.7H, m), 1.33-1.35 (6H, m), 1.47-1.50 (6H, m), 1.65-1.78 (2H, m), 1.81-1.98 (0.6H, m), 2.09 (0.7H, dd, J = 11.2 Hz, J = 6.0 Hz), 2.19-2.25 (0.3H, m), 3.00 (0.7H, t, J = 10.8 Hz), 3.27-3.57 (2H, m), 3.69 (1.4H, s), 3.80 (0.3H, d, J = 15.6 Hz), 3.91 (0.3H, d, J = 15.6 Hz), 4.07-4.11 (0.3H, m), 4.92-5.12 (4H, m), 5.42 (0.3H, bs), 5.60 (1H, d, J = 10.0 Hz), 6.11 (0.3H, dd, J = 17.6 Hz, J = 10.8 Hz), 6.18 (0.7H, dd, J = 17.6 Hz, J = 10.8 Hz), 6.42 (0.3H, d, J = 8.4 Hz), 6.45 (0.7H, d, J = 8.4 Hz), 6.89-6.95 (1H, m), 7.10-7.15 (1H, m). ^{13}C NMR (100 MHz) (CD_3OD) δ 22.5, 23.41, 27.5, 27.8, 27.9, 28.5, 28.8, 28.9, 29.1, 29.7, 29.8, 30.2, 33.8, 40.7, 41.1, 47.0, 47.4, 54.92, 59.5, 59.6, 60.6, 66.2, 69.9, 76.5, 76.6, 79.0, 79.4, 79.6, 79.7, 104.0, 104.6, 106.0, 106.4, 110.6,

111.1, 112.3, 112.5, 119.1, 119.2, 119.9, 120.1, 125.0, 125.4, 130.1, 130.2, 133.0, 133.4, 143.4, 143.6, 147.8, 148.1, 148.2, 149.7, 150.0, 165.2, 166.6, 170.5, 171.2, 172.0; HRMS-FAB: [M+H]+ calcd for $C_{27}H_{31}N_3O_5$, 477.2264; found, 477.2263.

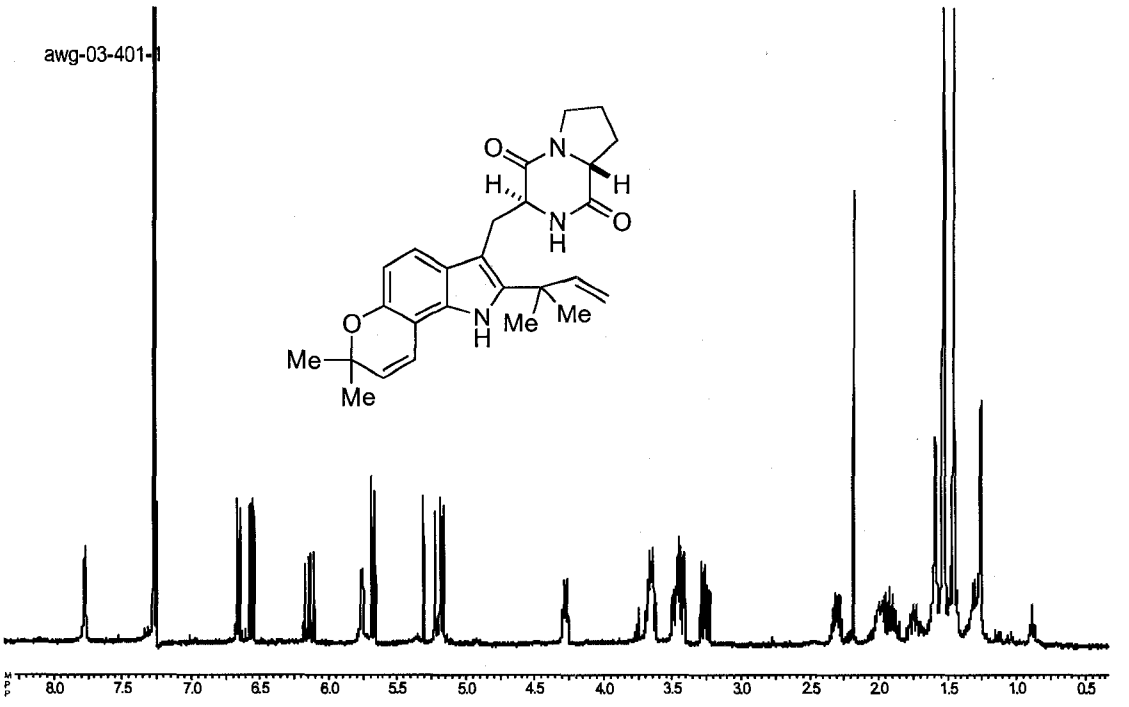




(3*S*,8a*R*)-3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)methyl)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (17-epi-notoamide E)



Acid **175** (111mg, 0.231 mmol) was suspended in 11ml dry toluene and brought to reflux for 1 hour. The mixture was then cooled back to 20°C and concentrated to am amber residue. The crude material was purified by PTLC (5% MeOH, CH_2Cl_2) to afford the *trans*-diketopiperazine (**17-epi-notoamide E**) (98mg, 91%) as a single diastereomer. IR (NaCl, neat) 3338, 2975, 2931, 1658, 1456, 1120, 916, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (6H, s), 1.53 (6H, s), 1.86-2.04 (2H, m), 2.27-2.34 (1H, m), 3.27 (1H, dd, J = 14.8, J = 9.2 Hz), 3.41-3.50 (2H, m), 3.62-3.68 (1H, m), 4.26-4.29 (1H, m), 5.17 (1H, d, J = 10.4 Hz), 5.20 (1H, d, J = 17.6 Hz), 5.68 (1H, d, J = 10.0), 5.76 (1H,d, J = 3.2 Hz), 6.14 (1H, dd, J = 17.6 Hz, J = 10.4 Hz), 6.56 (1H, d, J = 10.0 Hz), 6.66 (1H, d, J = 8.6 Hz), 7.27 (1H, d, J = 8.0 Hz), 7.77 (1H, bs), . ^{13}C NMR (100 MHz) ($CDCl_3$) δ 27.3, 27.6, 39.5, 45.6, 54.1, 75.7, 104.5, 109.4, 110.1, 112.0, 117.3, 119.5, 125.4, 129.4, 130.4, 139.7, 146.5, 148.4; HRMS-FAB: [M+H]+ calcd for $C_{21}H_{28}N_2O$, 324.2202; found, 324.2207.


awg-03-401-1
O
N
H
H
N
H
O
O
N
H
Me
Me
Me
Me
8.0
7.5
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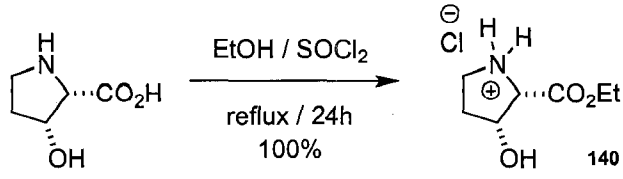
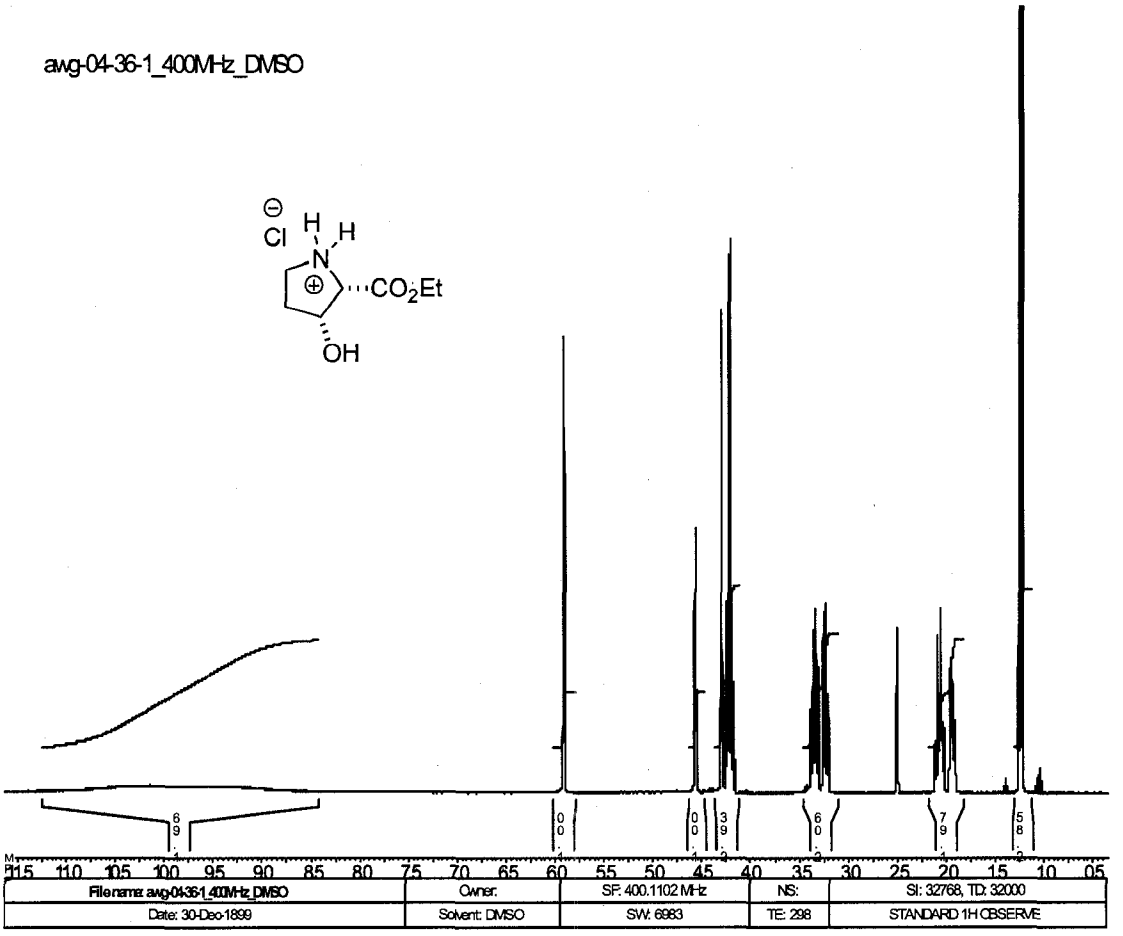
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

(2*S*,3*R*)-2-(ethoxycarbonyl)-3-hydroxypyrrolidinium chloride (140)



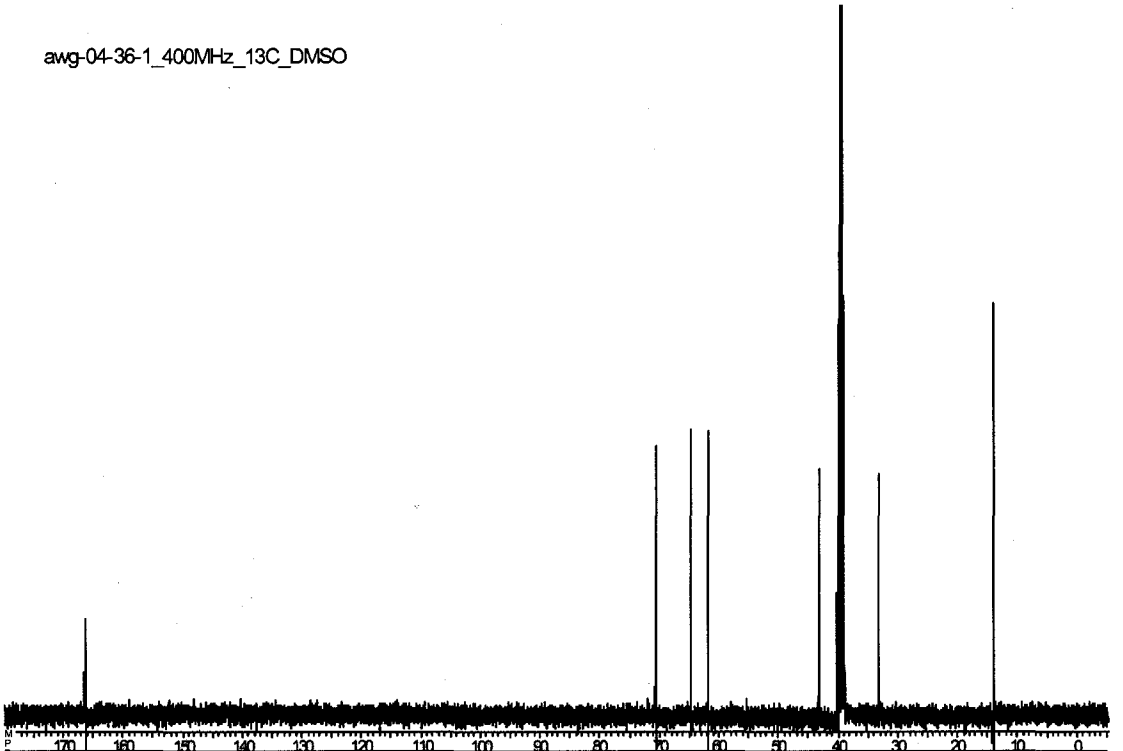
A 500ml R.B. flask was charged with 150ml of 200 proof ethanol. The solution was charged slowly at 25°C with thionyl chloride (5.44g, 45.7mmol, 1.2eq). The mixture was stirred at 25°C for 10min then charged with *cis*-3-hydroxy-L-Proline (5.0g, 38mmol, 1.0eq). The clear solution was refluxed 24h and then concentrated directly to afford a white crystalline solid. The solids were charged with an additional 150ml ethanol and concentrated again to afford the product in >99% yield. M.P. (200-202°C) ^{1}H NMR (400 MHz, DMSO-D_6) δ 1.24 (3H, t, J = 7.0 Hz), 1.88-1.98 (1H, m), 2.00-2.13 (1H, m), 3.18-3.40 (2H, m), 4.21 (2H, m), 4.29 (1H, d, J = 4.10 Hz), 4.56 (1H, dd, J = 3.95 Hz, J = 7.15 Hz), 5.91 (1H, d, J = 4.10 Hz), 9.87 (2H, bs). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.0, 33.1, 43.2, 61.8, 64.7, 70.6, 166.32; HRMS-FAB: [M+H]+ calcd for $C_7H_{14}N_1O_3$, 160.0974; found, 160.0981.

awg-04-36-1_400MHz_DMSO



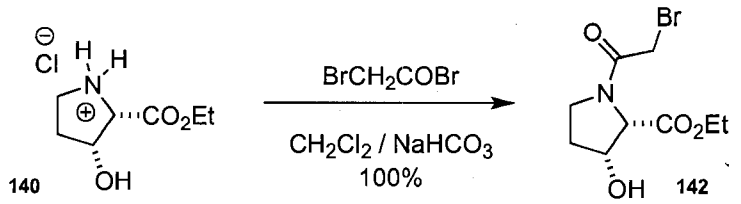
File name: awg-04-36-1_400MHz_DMSO	Owner:	SF: 400.1102 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-36-1_400MHz_13C_DMSO



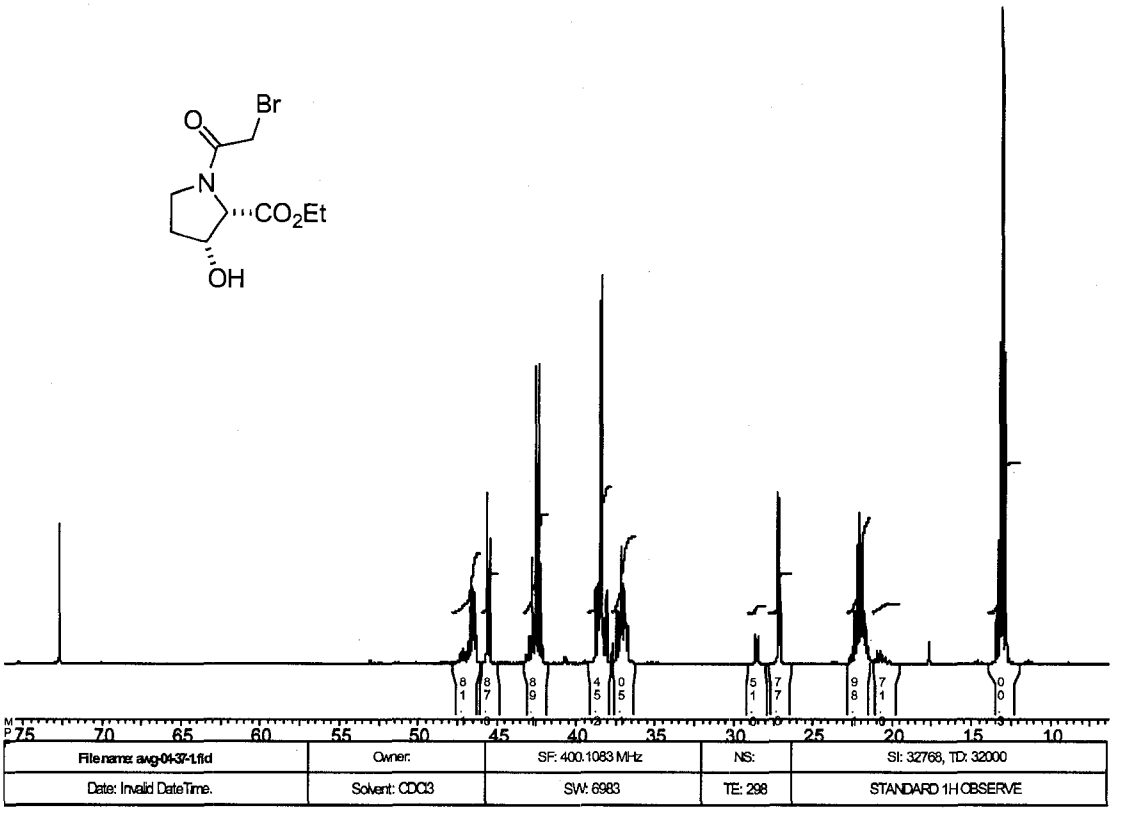
File name: awg-04-36-1_400MHz_13C_DMSO	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 30019	TE: 298	13C OBSERVE

(2*S*,3*R*)-ethyl 1-(2-bromoethanoyl)-3-hydroxypyrrolidine-2-carboxylate (142)



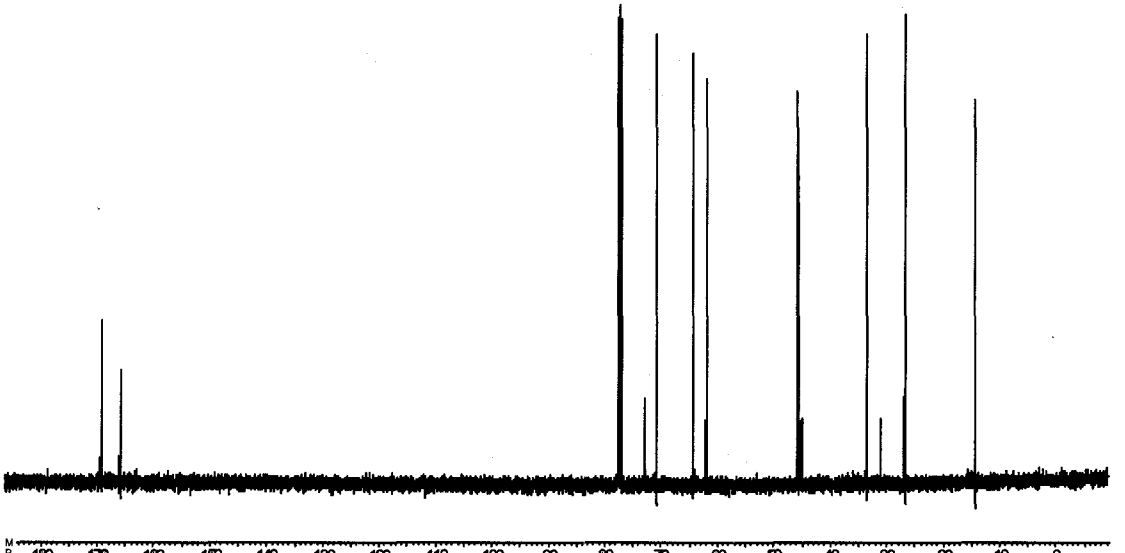
A 500ml R.B. flask was charged with ester **140** (7.27g, 37.2mmol, 1.0eq). The mixture was then charged with 145ml CH_2Cl_2 and cooled to 0°C. The mixture was then charged slowly with 145 sat. aq. $NaHCO_3$ (additional solid $NaHCO_3$ may be added to quench residual $SOCl_2$) and stirred at 0°C for an additional 30min. The reaction was then charged slowly at 0°C with bromoacetyl bromide (7.5g, 37.2mmol, 1.0eq). The resulting mixture was allowed to warm to 20°C over 24 hours. The lower organic layer was separated. The aqueous layer was extracted with EtOAc (4x 145ml) and the organics combined and dried over Na_2SO_4, and concentrated to furnish 9.4g of the water soluble product **142** as a white crystalline solid in 90% yield. M.P. (96-100°C); IR (NaCl, neat) 3416, 2982, 1739, 1641, 1448, 1190, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (1: 5 mixture of rotamers) δ 1.30 (3H, t, J = 7.0 Hz), 2.00-2.40 (0.17H, m), 2.14-2.29 (1.89H, m), 2.72 (0.77H, d, J = 5.3 Hz), 3.64-3.76 (1.5H, m), 3.79-3.90 (2.5H, m), 4.24 (2H, dd, J = 7.1 Hz, J = 14.4 Hz), 4.55 (1H, d, J = 6.6 Hz), 4.61-4.78 (1H, m). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.4, 26.7, 26.9, 31.0, 33.5, 45.0, 45.6, 61.7, 62.2, 64.2, 70.8, 72.8, 165.9, 169.0, 169.5; HRMS-FAB: [M+H]+ calcd for $C_9H_{15}N_1O_4Br_1$, 280.0184; found, 280.0174.

awg-04-37-1



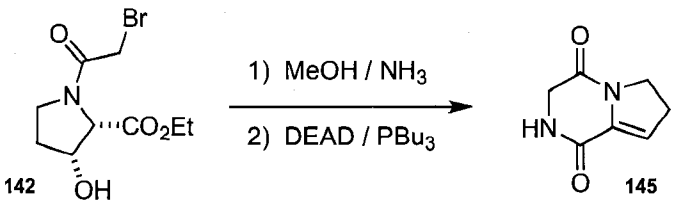
File name: awg-04-37-1.fid	Owner:	SF: 400.1083 MHz	NS:	SI: 32768, TD: 32000
Date: Invalid DateTime.	Solvent: CDCl3	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-37-4_13C_400MHz



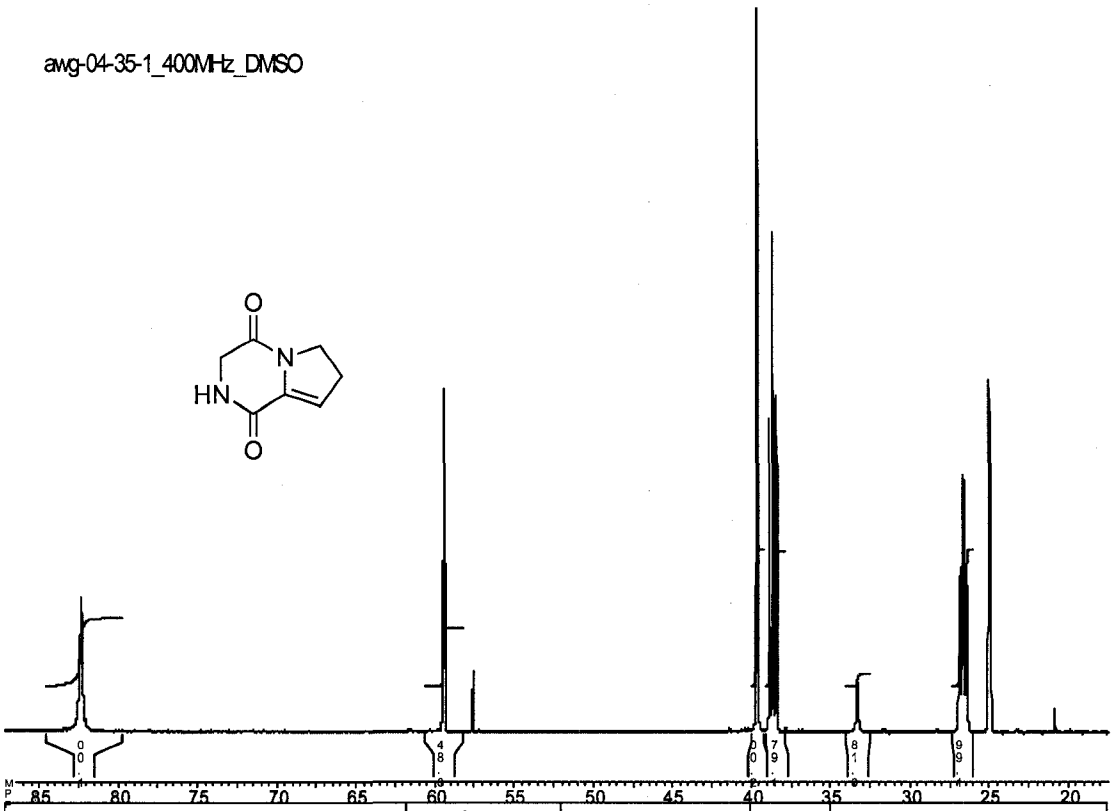
File name: awg-04-37-4_13C_400MHz	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

2,3,6,7-tetrahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (145)



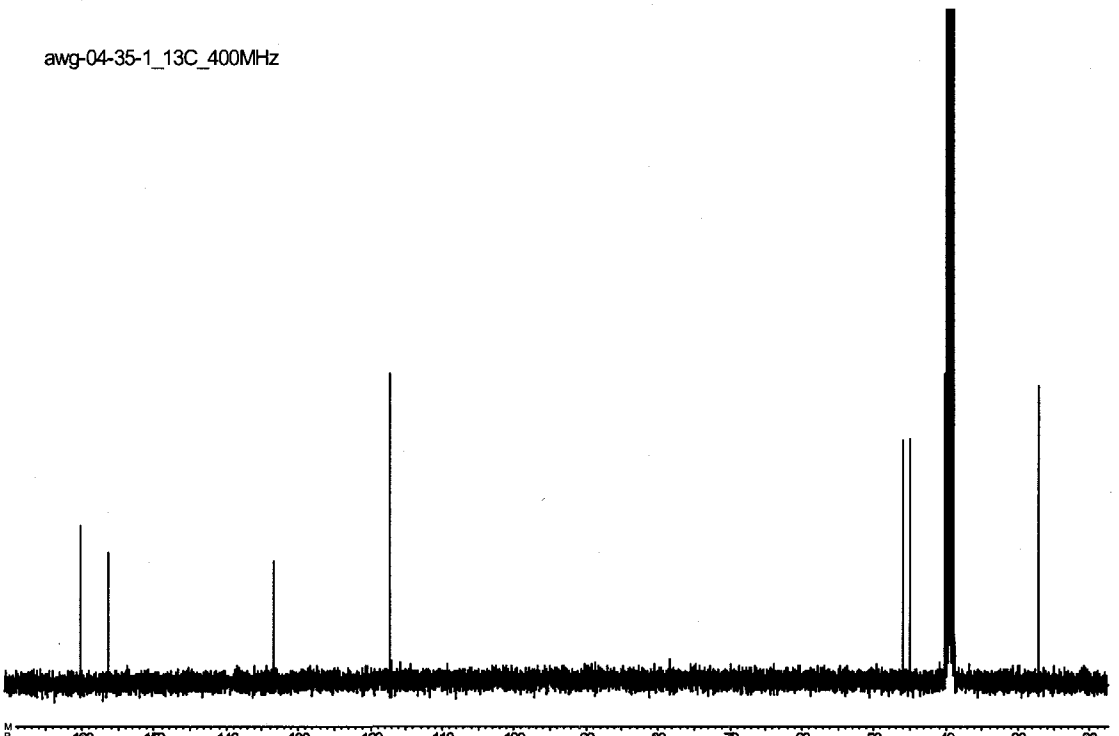
Bromide **142** (780mg, 2.78mmol) was treated with NH_4 (ca. 7N in methanol, 20ml, 0.14mol) at 20°C under argon. The mixture was stirred overnight and then directly concentrated. The crude mixture was charged again with fresh methanol and concentrated. The resulting solids were reslurried in CH_2Cl_2 at 20°C and charged with DEAD (1.6g, 9.19mmol), followed by dropwise addition PBu_3 (1.86g, 9.19mmol). The mixture was stirred at 20°C for an additional 5h and then partitioned between 1N NaOH and EtOAc. The organic layer was separated and then washed with 1N HCl, H_2O, brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (5% MeOH, CH_2Cl_2) to afford the desired product **145** (358mg, 85%). IR (NaCl, neat) 3191, 1665, 1646, 1455, 1313 cm^{-1}; ^1H NMR (400 MHz, DMSO-D_6) δ 2.66 (1H, t, J = 9.38 Hz), 2.67 (1H, t, J = 9.16 Hz), 3.86 (2H, t, J = 8.95 Hz), 3.96 (2H, s), 5.94 (1H, t, J = 2.98 Hz), 8.24 (1H, bs). ^{13}C NMR (100 MHz) (DMSO-D_6) δ 27.2, 45.0, 46.0, 117.1, 133.4, 156.4, 160.1; HRMS-FAB: [M+H]+ calcd for $C_7H_9N_2O_2$, 153.0664; found, 153.0664.

awg-04-35-1_400MHz_DMSO



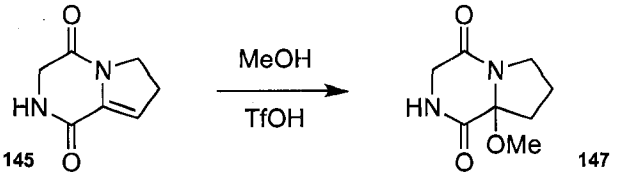
File name: awg-04-35-1_400MHz_DMSO	Owner:	SP: 400.1102 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-35-1_13C_400MHz



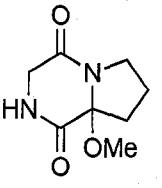
File name: awg-04-35-1_13C_400MHz	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 30019	TE: 298	13C OBSERVE

8a-methoxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (147)



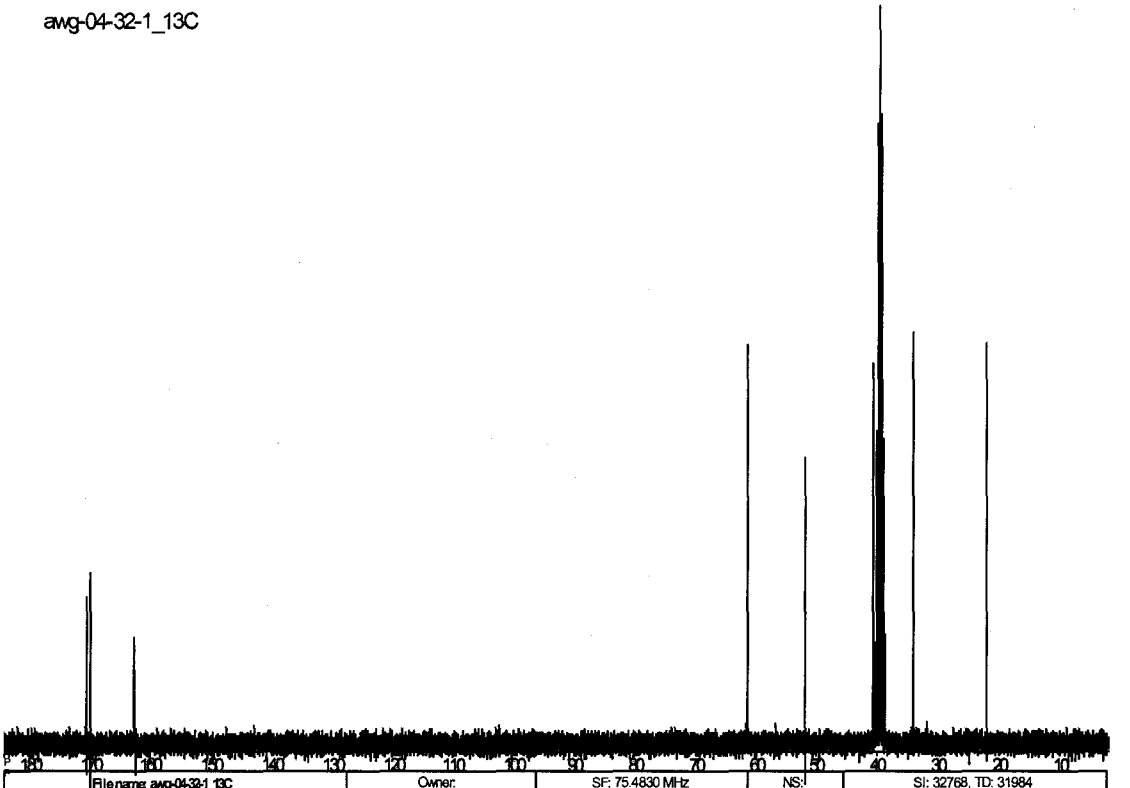
Diketopiperazine **145** (319mg, 2.1mmol) was dissolved in MeOH at 0°C and charged with trifluoromethanesulfonic acid (1.26g, 8.4mmol). The mixture was brought to reflux for 24h and then cooled back to 20°C and quenched by the addition of sat. aq. $NaHCO_3$. The basic solution was extracted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4 and concentrated to a clear oil. The crude product was purified by flash chromatography (50% EtOAc / hexanes) to afford product **147** as a light green oil (317mg, 82%). ^1H NMR (300 MHz, DMSO-D_6) δ 1.81-1.96 (2H, m), 2.62-2.75 (2H, m), 3.63 (3H, s), 3.90 (2H, d, J = 6.22 Hz), 3.93-4.01 (2H, m), 8.65 (1H, t, J = 5.86). ^{13}C NMR (75.5 MHz) (DMSO-D_6) δ 21.9, 34.1, 40.57, 51.8, 61.4, 162.6, 170.0, 170.4; HRMS-FAB: [M+H]+ calcd for $C_8H_{13}N_2O_3$, 185.0926; found, 185.0921.

awg-04-32-1



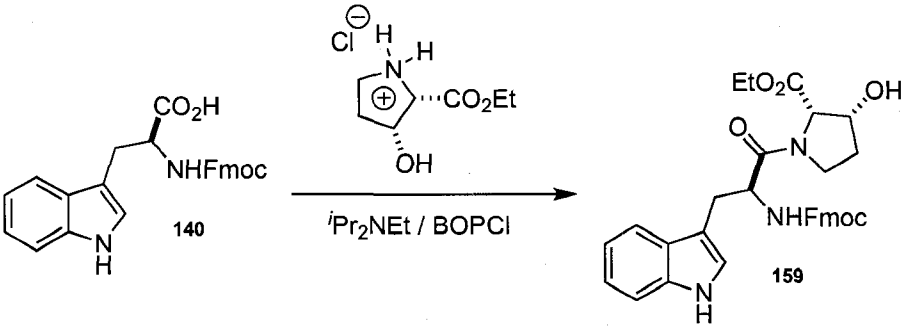
Filename: awg-04-32-1	Owner:	SF: 300.1621 MHz	NS:	SI: 32768, TD: 31994
Date: 30-Dec-1899	Solvent: DMSO	SW: 5995	TE: 302	STANDARD 1H OBSERVE

awg-04-32-1_13C



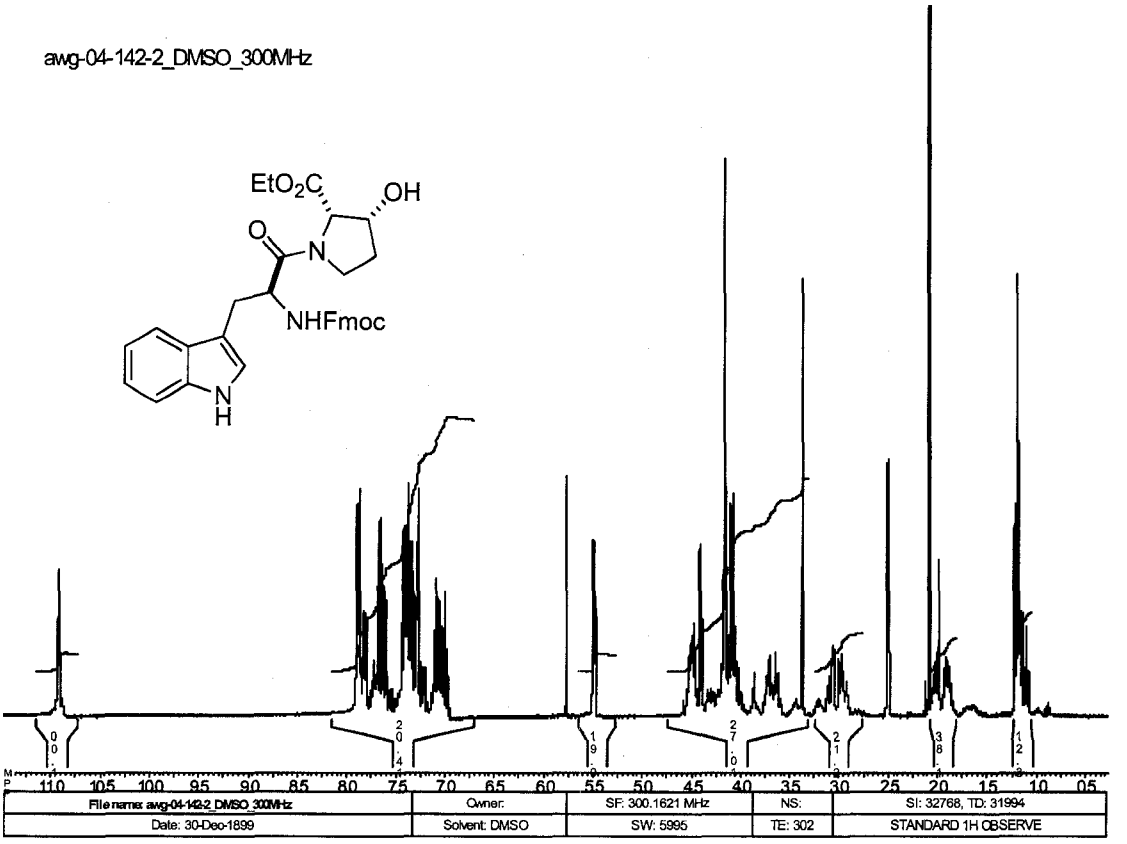
Filename: awg-04-32-1_13C	Owner:	SF: 75.4830 MHz	NS:	SI: 32768, TD: 31984
Date: 30-Dec-1899	Solvent: DMSO	SW: 22936	TE: 302	13C OBSERVE

(2*S*,3*R*)-ethyl 1-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(1*H*-indol-3-yl)propanoyl)-3-hydroxypyrrolidine-2-carboxylate (159)



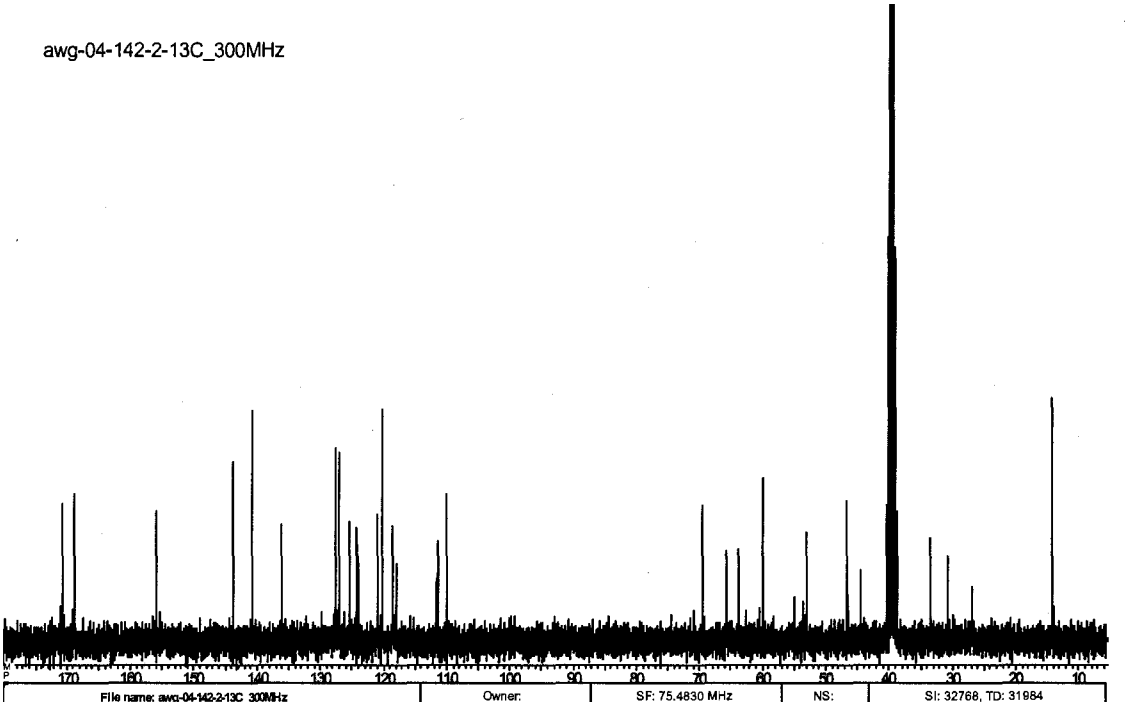
To a solution of Fmoc-Tryp-OH (500mg, 1.17mmol) in 15ml CH_2Cl_2 was added solid HCl salt **140** (344mg, 1.76mmol). The mixture was charged at 20°C with $^{i}Pr_2NEt$ (530mg, 4.1mmol) and then BopCl (450mg, 1.76mmol). The resulting solution was stirred overnight at ambient temperature and then partitioned between 10% citric acid and EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (5% MeOH / CH_2Cl_2) to afford (474mg, 71%) of the desired coupled product **159** as a white foam. ^1H NMR (300 MHz, DMSO-D_6) δ 1.19 (3H, t, J = 6.9 Hz), 1.79-2.12 (2H, m), 2.80-3.27 (2H, m), 3.54-4.61 (10H, m), 5.48 (1H, d, J = 3.7 Hz), 6.82-8.07 (14H, m), 10.92 (1H, s). ^{13}C NMR (75.5 MHz) (DMSO-D_6) δ 14.2, 26.8, 30.7, 33.4, 44.5, 46.6, 53.1, 60.0, 63.7, 65.7, 70.0, 110.0, 118.0, 118.5, 120.1, 120.9, 124.1, 125.3, 125.4, 127.1, 127.7, 136.1, 140.7, 143.8, 155.9, 168.7, 170.4; HRMS-FAB: [M+H]+ calcd for $C_{33}H_{34}N_3O_6$, 568.2448; found, 568.2450.

awg-04-142-2_DMSO_300MHz



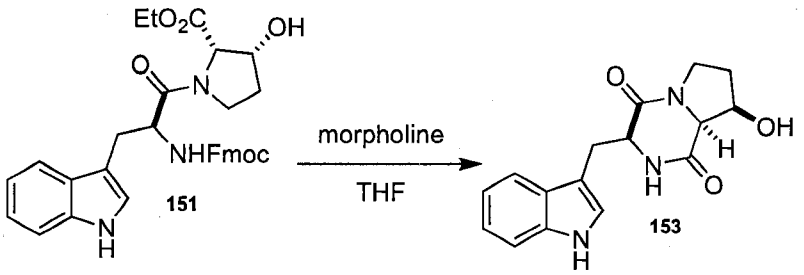
File name: awg-04-142-2_DMSO_300MHz	Owner:	SF: 300.1621 MHz	NS:	SI: 32768, TD: 31994
Date: 30-Dec-1899	Solvent: DMSO	SW: 5995	TE: 302	STANDARD 1H OBSERVE

awg-04-142-2-13C_300MHz



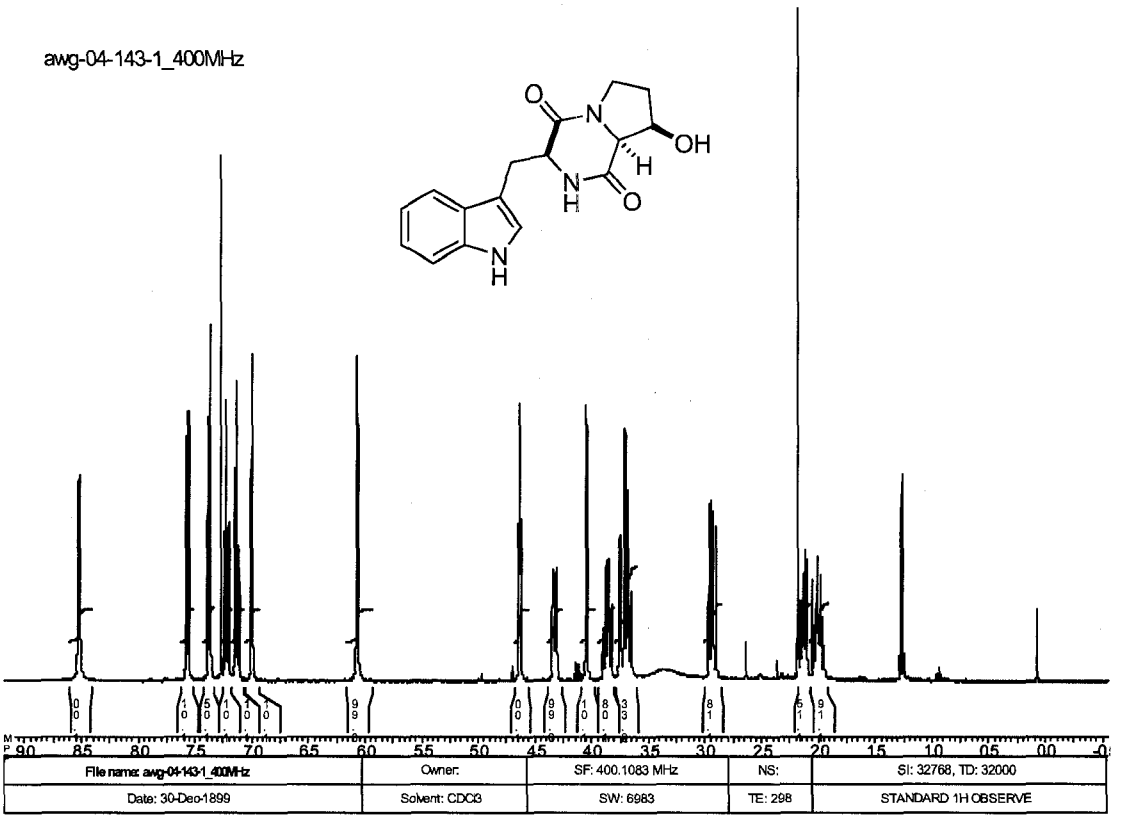
File name: awg-04-142-2-13C_300MHz	Owner:	SF: 75.4830 MHz	NS:	SI: 32768, TD: 31984
Date: 30-Dec-1899	Solvent: DMSO	SW: 22936	TE: 302	13C OBSERVE

(3*S*,8*R*,8a*S*)-3-((1*H*-indol-3-yl)methyl)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (153)



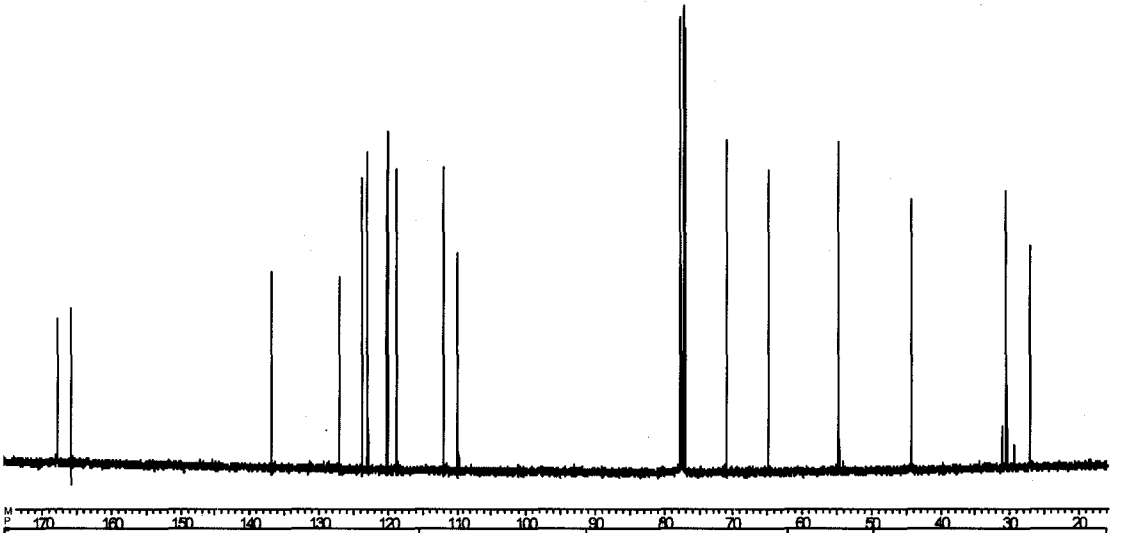
Fmoc peptide **151** (937mg, 1.65mmol) was dissolved in 50ml THF at 20°C and charged with 10ml morpholine. The reaction was stirred overnight at ambient temperature and then concentrated directly. The mixture was charged with 100ml toluene and concentrated again. This process was repeated ~3x until no morpholine was present by NMR. The products was passed through a plug of silica (10% MeOH / CH_2Cl_2) to afford the cyclized compound **153** (484mg, 89%) as a tan foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93-2.07 (1H, m), 2.13 (1H, dd, J = 7.4 Hz, J = 13.8 Hz), 2.93 (1H, dd, J = 10.7 Hz, J = 15.2 Hz), 3.66-3.77 (2H, m), 3.81-3.91 (1H, m), 4.05 (1H, s), 4.33 (1H, d, J = 8.9 Hz), 4.63 (1H, t, J = 3.4 Hz), 6.07 (1H, bs), 7.00 (1H, d, J = 1.9 Hz), 7.13 (1H, dt, J = 7.9 Hz), 7.22 (1H, dt, J = 7.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.57 (1H, d, J = 7.9 Hz), 8.52 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 27.0, 30.5, 44.2, 54.7, 64.8, 71.0, 109.8, 111.8, 120.1, 122.9, 123.7, 126.9, 136.9, 165.7, 167.9; HRMS-FAB: [M+H]+ calcd for $C_{16}H_{18}N_3O_3$, 300.1348; found, 300.1334.

awg-04-143-1_400MHz



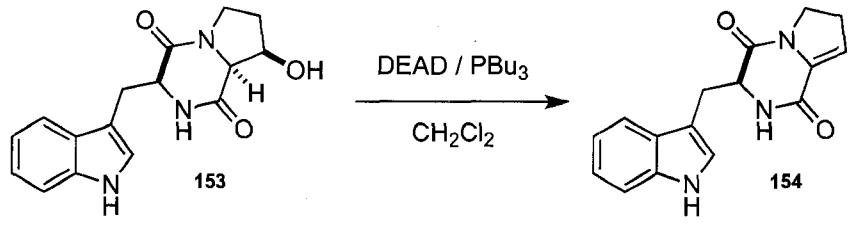
File name: awg-04-143-1_400MHz	Owner:	SF: 400.1083 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-143-1_13C_400MHz



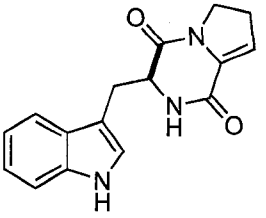
File name: awg-04-143-1_13C_400MHz	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

(*S*)-3-((1*H*-indol-3-yl)methyl)-2,3,6,7-tetrahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (154)



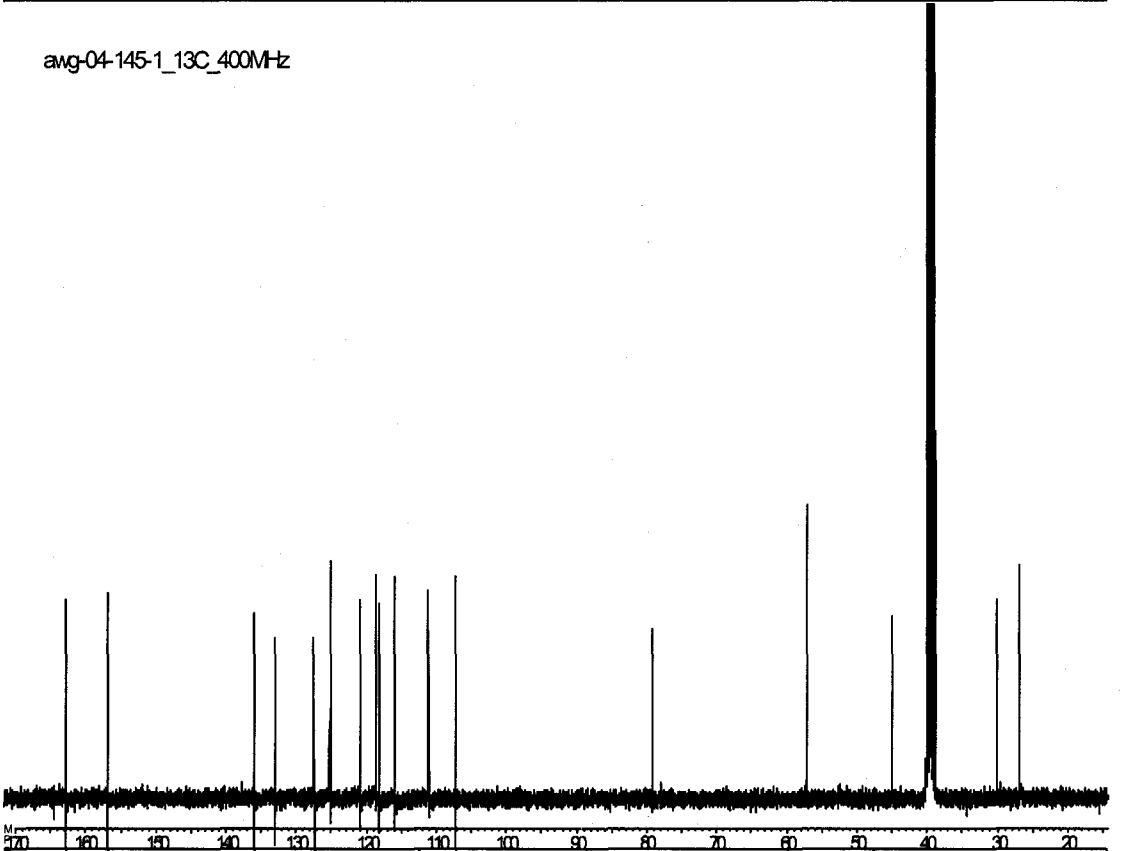
To a solution of the alcohol **153** (464mg, 1.55mmol) in 23ml CH_2Cl_2 at 25°C was added diethyazodicarboxylate (540mg, 3.10mmol). The mixture was stirred 10min and then charged with tributylphosphine (627mg, 3.10mmol). The mixture was stirred fir 3 hours at 20°C and then partitioned between 10% citric acid and EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated to a crude oil. The crude mixture was purified by flash chromatography (20-50% EtOAc / hexanes) to afford the desired product **154** (401mg, 92%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.96 (1H, m), 2.67-2.39 (1H, m), 2.99 (1H, dd, J = 4.7 Hz, J = 14.5 Hz), 3.29-3.43 (2H, m), 3.54-3.65 (1H, m), 4.28-4.33 (1H, m), 5.45 (1H, t, J = 2.9 Hz), 6.90-6.98 (2H, m), 7.03 (1H, t, J = 7.89 Hz), 7.28 (2H, d, J = 7.6 Hz), 7.46 (2H, d, J = 7.6 Hz), 10.87 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 26.8, 30.1, 44.9, 57.3, 79.2, 107.3, 111.1, 115.9, 118.1, 118.7, 120.8, 125.2, 127.5, 133.0, 136.0, 156.9, 162.8; HRMS-FAB: [M+H]+ calcd for $C_{16}H_{16}N_3O_2$, 282.1243; found, 282.1243.

awg-04-145-1_400MHz



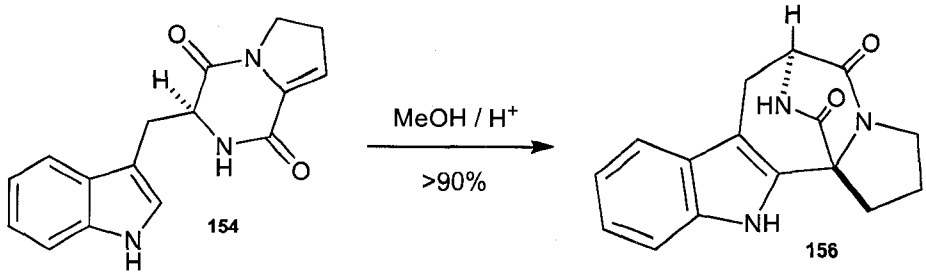
File name: awg-04-145-1_400MHz	Owner:	SP: 400.1102 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-145-1_13C_400MHz



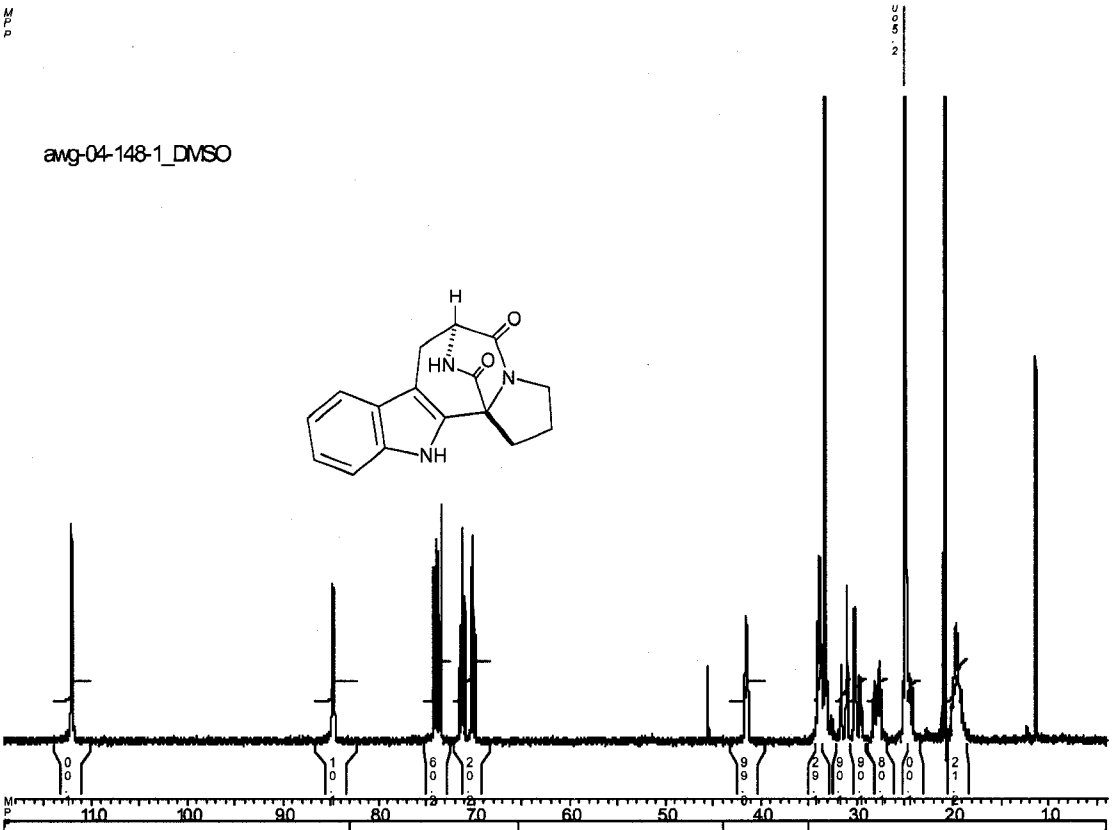
File name: awg-04-145-1_13C_400MHz	Owner:	SP: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 30019	TE: 298	13C OBSERVE

Tricycle (156)



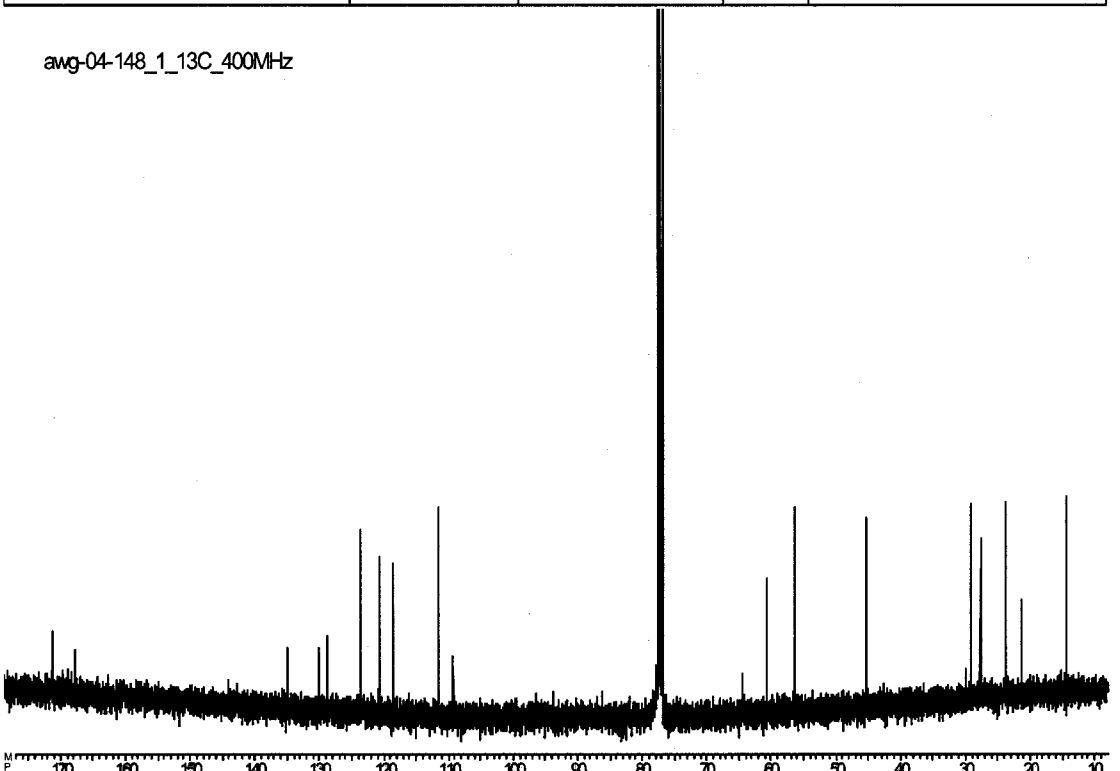
A mixture of enamide **154** (100mg, 0.355mmol) in 50ml MeOH was added trifluoromethane sulfonic acid (213mg, 1.42mmol). The resulting mixture was heated to reflux for 24h and then cooled back to 20°C. The mixture was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by PTLC (50% EtOAc / hexanes) to afford (98mg, 98%) of tricycle **156** as a thin film. ^1H NMR (300 MHz, DMSO-D_6) δ 1.83-2.04 (2H, m), 2.39-2.54 (1H, m), 2.73,-2.85 (1H, m), 2.99 (1H, dd, ½ ABq, J = 4.7 Hz, J = 17.1 Hz), 3.14 (1H, dd, ½ ABq, J = 2.0 Hz, J = 17.2 Hz), 3.35-3.44 (2H, m), 4.12-4.20 (1H, m), 7.01 (1H, t, J = 7.9 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.39 (2H, dd, J = 8.0 Hz, J = 15.3 Hz), 8.48 (1H, d, J = 5.1 Hz), 11.21 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.4, 21.3, 23.7, 27.7, 29.1, 45.3, 56.4, 60.6, 109.2, 111.6, 118.5, 120.7, 123.5, 128.7, 130.2, 134.9, 167.7, 171.2; HRMS-FAB: [M+H]+ calcd for $C_{16}H_{16}N_3O_2$, 282.1243; found, 282.1229.

awg-04-148-1_DMSO



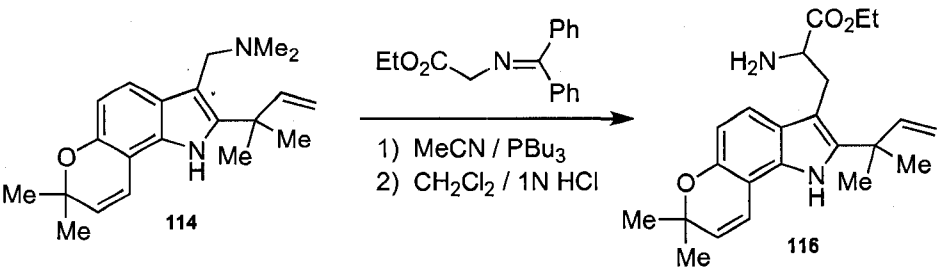
Filename: awg-04-148-1_DMSO	Owner:	SF: 300.1621 MHz	NS:	SI: 32768, TD: 31994
Date: 30-Dec-1899	Solvent: DMSO	SW: 5995	TE: 302	STANDARD 1H OBSERVE

awg-04-148_1_13C_400MHz

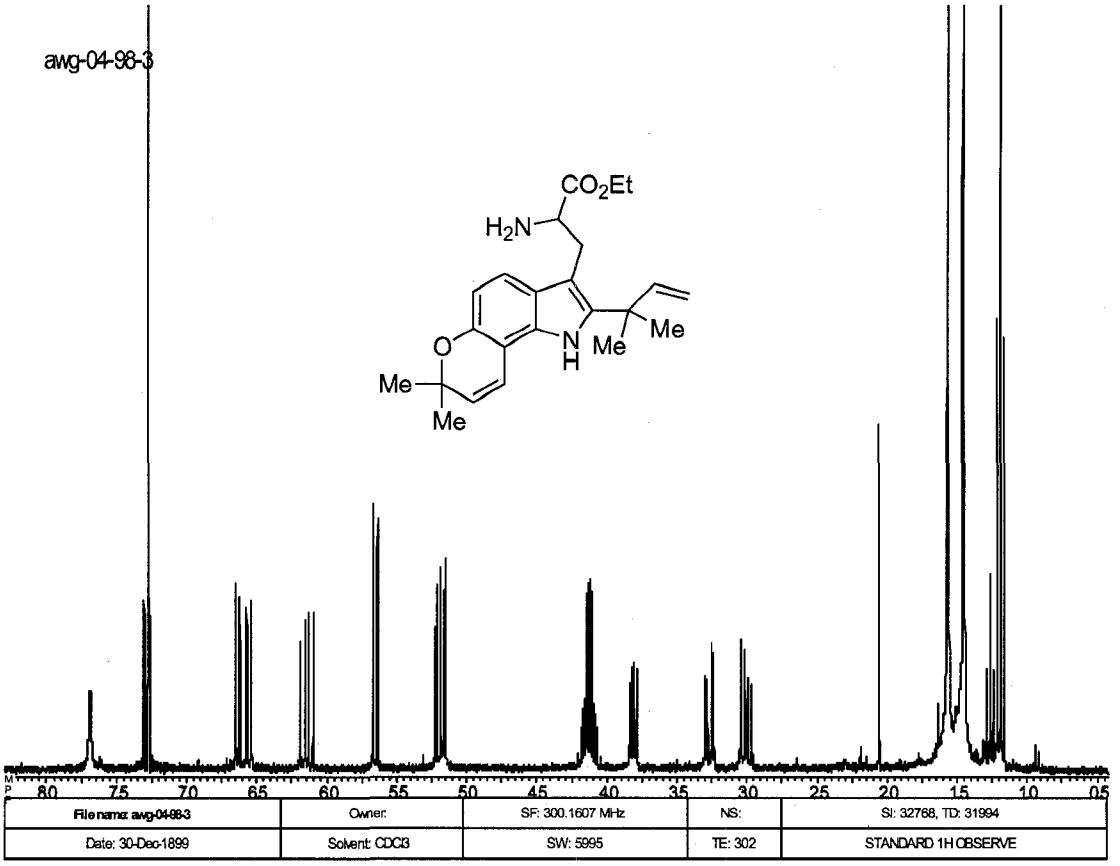


Filename: awg-04-148_1_13C_400MHz	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

Ethyl 2-amino-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)propanoate (116)

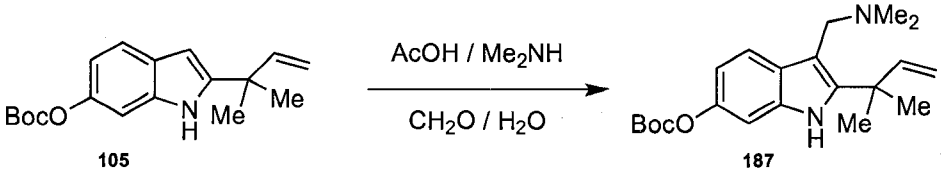


A mixture of gramine **114** (645mg, 2.0mmol) and glycine benzophenone imine **63** (531mg, 2.0mmol) in 20ml MeCN was charged at 20°C with tributylphosphine (405mg, 2.0mmol). The mixture was heated to reflux 24 h and then cooled back to 20°C and concentrated directly. The crude mixture was partitioned between CH_2Cl_2 and 1N HCl and stirred at 20°C for an additional 24h. The mixture was then charged with Et_3N until basic and then charged with an additional 100ml sat. $NaHCO_3$. The aqueous layer was extracted 3X with EtOAc, washed with brine and dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (5-10% MeOH / CH_2Cl_2) to afford the desired amino ester **116** (712mg, 92%) as an amber oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.45 (8H, s), 1.57 (6H, s), 3.00 (1H, dd, ½ ABq, J = 9.6 Hz, J = 14.4 Hz), 3.27 (1H, dd, ½ ABq, J = 5.05 Hz, J = 14.3 Hz), 3.82 (1H, dd, J = 5.2 Hz, J = 9.5 Hz), 4.04-4.22 (2H, m), 5.16 (1H, dd, J = 0.9 Hz, J = 2.6 Hz), 5.20 (1H, dd, J = 1.05 Hz, J = 9.45 Hz), 5.66 (1H d, J = 9.7 Hz), 6.15 (1H, dd, J = 10.5 Hz, J = 17.5 Hz), 6.56 (1H, d, J = 9.7 Hz), 6.60 (1H, d, J = 8.3 Hz), 7.29 (1H, d, J = 8.3 Hz), 7.69 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.4, 21.3, 23.7, 27.7, 29.1, 45.3, 56.4, 60.6, 109.2, 111.6, 118.5, 120.7, 123.5, 128.7, 130.2, 134.9, 167.7, 171.2; HRMS-FAB: [M+H]+ calcd for $C_{16}H_{16}N_3O_2$, 282.1243; found, 282.1229.



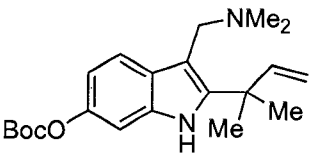
Filename: awg-04-98-3	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 31994
Date: 30-Dec-1899	Solvent: CDCl3	SW: 5995	TE: 302	STANDARD 1H OBSERVE

***tert*-butyl-3-((dimethylamino)methyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-6-yl carbonate (187)**



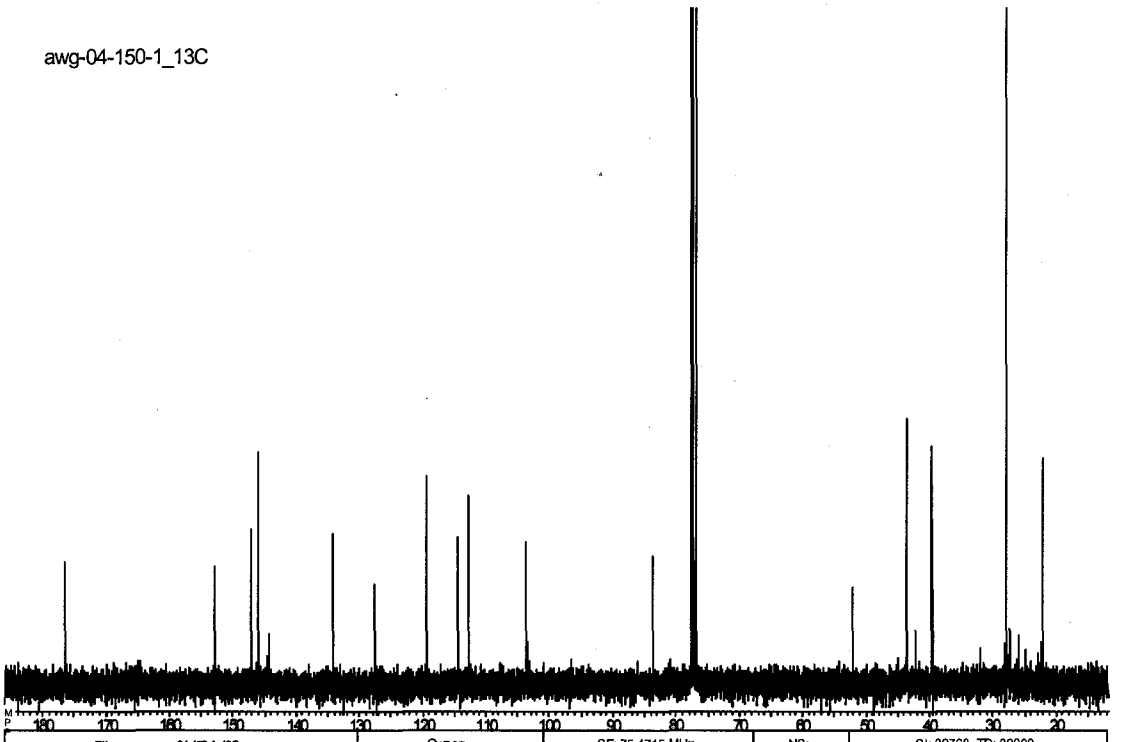
A clean dry round bottom flask was charged with 40% dimethylamine, 40% solution in H_2O (7.23g, 64.1mmol) and cooled to 0°C. The mixture was then charged slowly with 73ml acetic acid. The mixture was stirred until the acetic acid began to crystallize and then was charged with formaldehyde, 37% solution in H_2O (1.43g, 17.6mmol). The mixture was allowed to warm to 20°C for 15min and then the entire mixture was poured into a flask containing indole **105** (4.83g, 16.0mmol). The mixture was allowed to warm to 20°C overnight and then was quenched with 0°C (ice water) 1N NaOH. The mixture was charged with EtOAc and mixed thoroughly. The organic layer was washed with water, brine and dried over Na_2SO_4, filtered and concentrated to afford 5.68g (99%) of **187** as an amber oil that was used without further purification in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (6H, s), 1.58 (9H, s), 2.54 (6H, s), 4.14 (2H, s), 5.19 (1H, dd, J = 0.8 Hz, J = 5.3 Hz), 5.24 (1H, dd, J = 0.8 Hz, J = 1.7 Hz), 6.18 (1H, dd, J = 10.4 Hz, J = 17.7), 6.95 (1H, dd, J = 2.1 Hz, J = 8.6 Hz), 7.16 (1H, d, J = 2.1 Hz), 7.66 (1H, d, J = 8.7 Hz), 8.54 (1H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.1, 27.8, 27.9, 39.6, 43.6, 43.7, 83.6, 103.4, 103.8, 112.8, 114.4, 119.4, 127.5, 134.2, 144.5, 146.0, 147.0, 152.8; HRMS-FAB: [M+H]+ calcd for $C_{21}H_{31}N_2O_3$, 359.2335; found, 359.2323.

awg-04-150-2



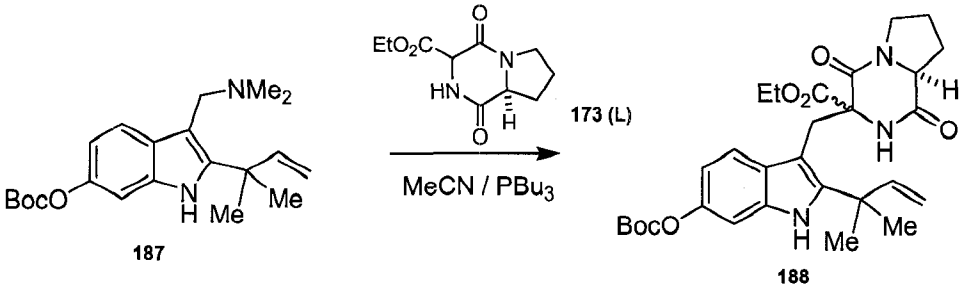
File name: awg-04-150-2	Owner:	SF: 300.1164 MHz	NS:	SI: 65536, TD: 32784
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 298	STANDARD 1H OBSERVE

awg-04-150-1_13C



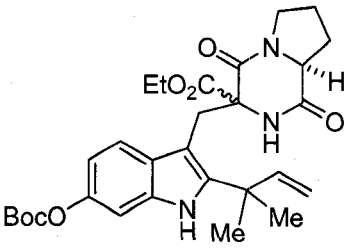
File name: awg-04-150-1_13C	Owner:	SF: 75.4715 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 20000	TE: 298	13C OBSERVE

(*R*)-ethyl 3-((6-(*tert*-butoxycarbonyloxy)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)methyl)-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-3-carboxylate (188)



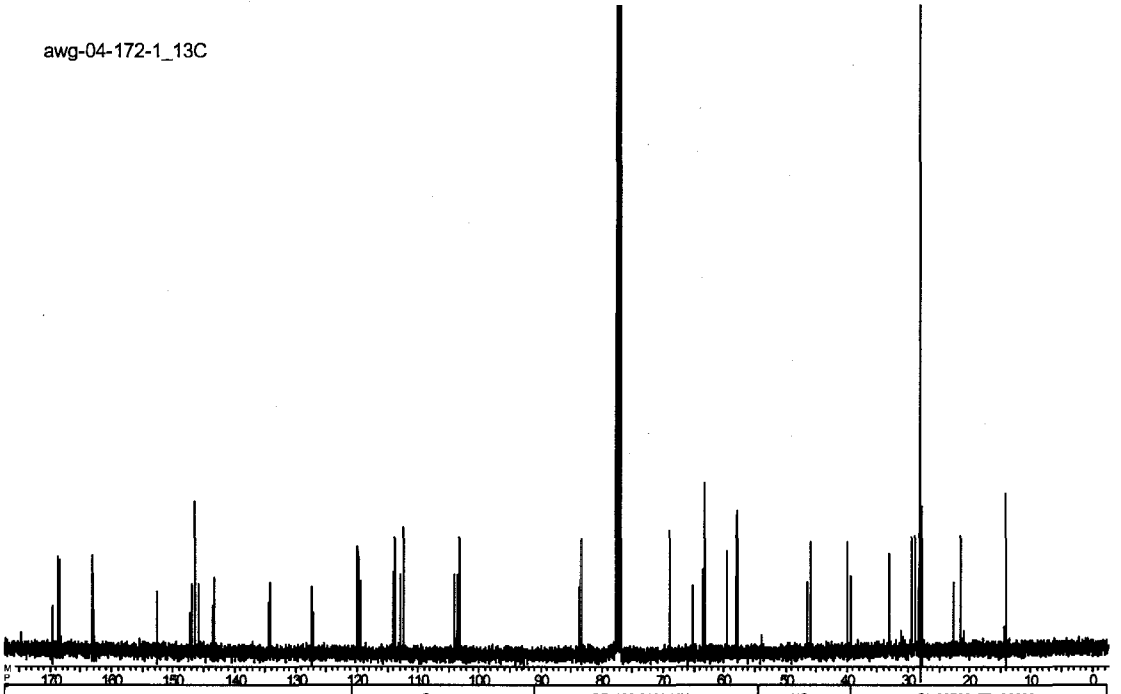
A solution of gramine **187** (5.32g, 14.8mmol), and diketopiperazine **173** (3.36g, 1.48mmol), in 160ml MeCN was charged at 20°C with PBu_3 (3.0g, 14.8mmol). The mixture was heated to reflux for 24h and then directly concentrated. The crude oil was purified by flash chromatography (50-100% EtOAc / hexanes) to afford 6.42g (75%) of the desired product as a 1 : 1.6 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.38 (3H, t, J = 7.1 Hz), 1.51 (3H, s), 1.53 (3H, s), 1.57 (9H, s), 1.59-1.76 (2H, m), 1.79-1.91 (1H, m), 2.12 (1H, dd, J = 6.1 Hz, J = 10.9 Hz), 2.99-3.13 (1H, m), 3.35-3.51 (1H, m), 3.61 (1H, d, ½ ABq, J = 15.2 Hz), 3.96 (1H, d, ½ ABq, J = 15.2 Hz), 4.32-4.42 (2H, m), 5.17-5.27 (2H, m), 6.08 (1H, s), 6.17 (1H, dd, J = 10.5 Hz, J = 17.5 Hz), 6.87 (1H, dd, J = 2.2 Hz, J = 8.6 Hz), 7.09 (1H, d, J = 2.0 Hz), 7.51 (1H, d, J = 8.6 Hz), 8.00 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.18, 14.22, 21.43, 22.47, 27.8, 27.9, 28.0, 28.1, 28.8, 28.9, 29.5, 33.1, 39.5, 39.8, 45.9, 46.5, 56.0, 59.4, 63.3, 63.4, 69.0, 83.5, 103.2, 103.3, 104.0, 112.3, 113.0, 113.7, 114.1, 103.2, 103.3, 103.7, 104.0, 112.3, 113.0, 113.7, 114.1, 119.4, 119.9, 127.1, 127.4, 134.1, 134.4, 143.3, 143.6, 145.7, 146.5, 147.0, 147.2, 152.6, 163.0, 168.5, 168.8, 169.7; HRMS-FAB: [M+H]+ calcd for $C_{29}H_{37}N_3O_7$, 539.2632; found, 539.1709.

awg-03-356-1



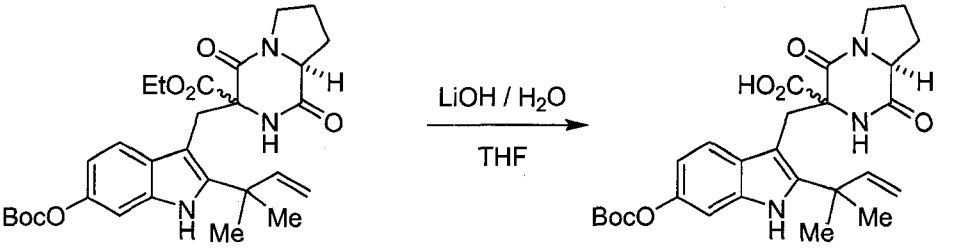
File name: awg-03-356-1	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	STANDARD 1H OBSERVE

awg-04-172-1_13C



File name: awg-04-172-1_13C	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

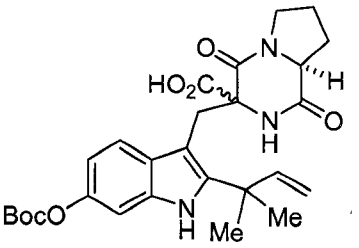
(*R*)-3-((6-(*tert*-butoxycarbonyloxy)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)methyl)-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-3-carboxylic acid (189)



188 **189**

To a 0°C solution of ester **188** (303mg, 0.562mol) in 15ml THF and 15ml H_2O was added LiOH (134mg, 5.62mmol). The solution was stirred 30min at 0°C and then slowly brought to pH = 4-6 by the dropwise addition of 1N HCl. The acidic mixture was diluted with brine, extracted 2X with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated to afford (281mg, 98%) of the desired acid as a white foam and product **189** as a 1 : 1.6 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.08-1.23 (1H, m), 1.52 (6H, d, J = 6.2 Hz), 1.57 (9H, s), 1.46-1.64 (1H, m), 1.83-1.96 (1H, m), 2.08-2.18 (1H, m), 3.04-3.18 (1H, m), 3.51-3.69 (1H, m), 3.72 (2H, s), 5.23 (1H, dd, J = 0.7 Hz, J = 8.9 Hz), 5.28 (1H, d, J = 1.5 Hz), 6.12 (1H, dd, J = 10.6 Hz, J = 17.2 Hz), 6.85 (1H, s), 6.91 (1H, dd, J = 2.1 Hz, J = 8.7 Hz), 7.12 (1H, d, J = 2.0 Hz), 7.44 (1H, d, J = 8.6 Hz), 8.17 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.18, 14.22, 21.43, 22.47, 27.8, 27.9, 28.0, 28.1, 28.8, 28.9, 29.5, 33.1, 39.5, 39.8, 45.9, 46.5, 56.0, 59.4, 63.3, 63.4, 69.0, 83.5, 103.2, 103.3, 104.0, 112.3, 113.0, 113.7, 114.1, 103.2, 103.3, 103.7, 104.0, 112.3, 113.0, 113.7, 114.1, 119.4, 119.9, 127.1, 127.4, 134.1, 134.4, 143.3, 143.6, 145.7, 146.5, 147.0, 147.2, 152.6, 163.0, 168.5, 168.8, 169.7; HRMS-FAB: [M+H]+ calcd for $C_{27}H_{34}N_3O_7$, 512.2397; found, 512.2399.

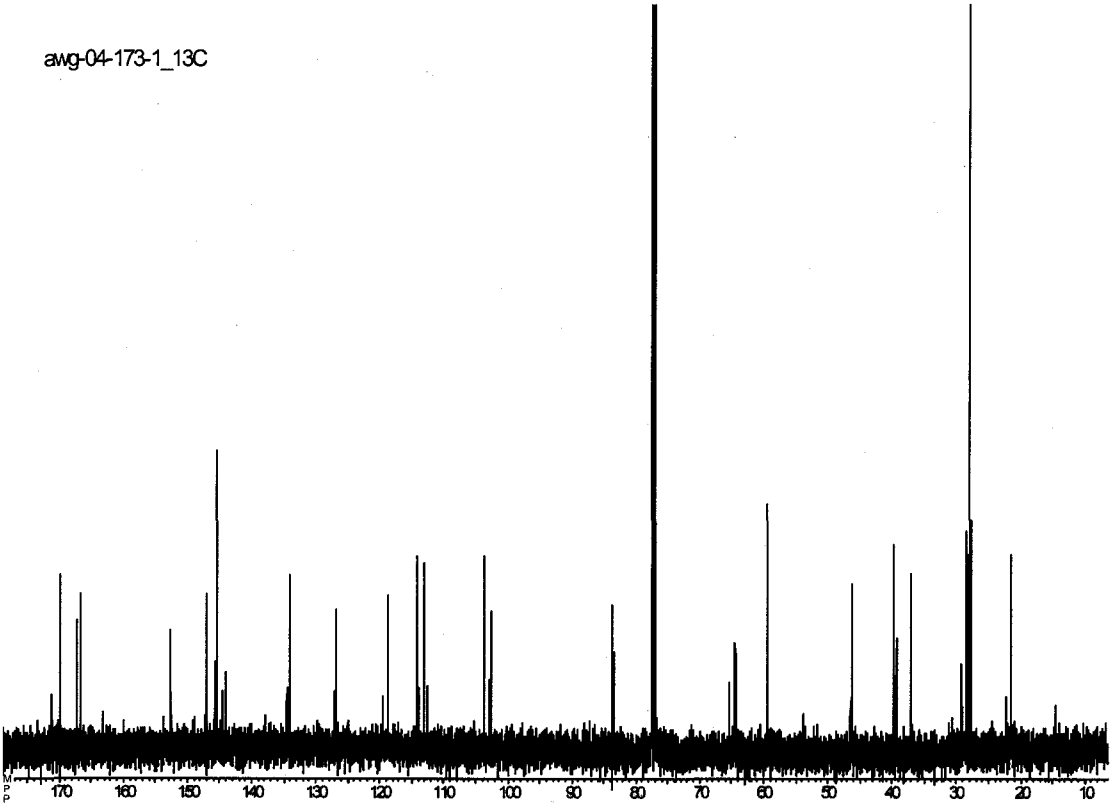
awg-03-360-1



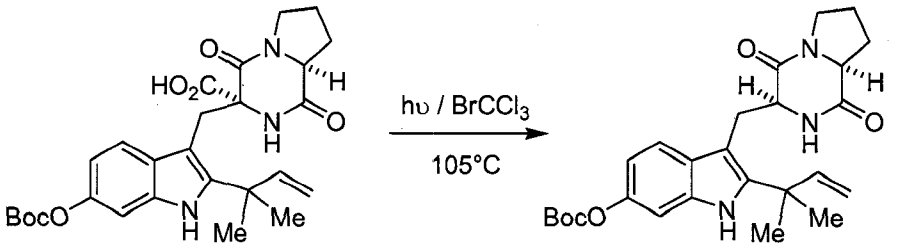
189

File name: awg-03-360-1	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	STANDARD 1H OBSERVE

awg-04-173-1_13C



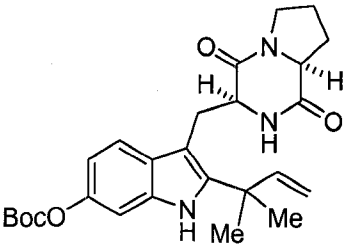
***tert*-butyl 3-(((3*S*,8a*R*)-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-6-yl carbonate (190)**



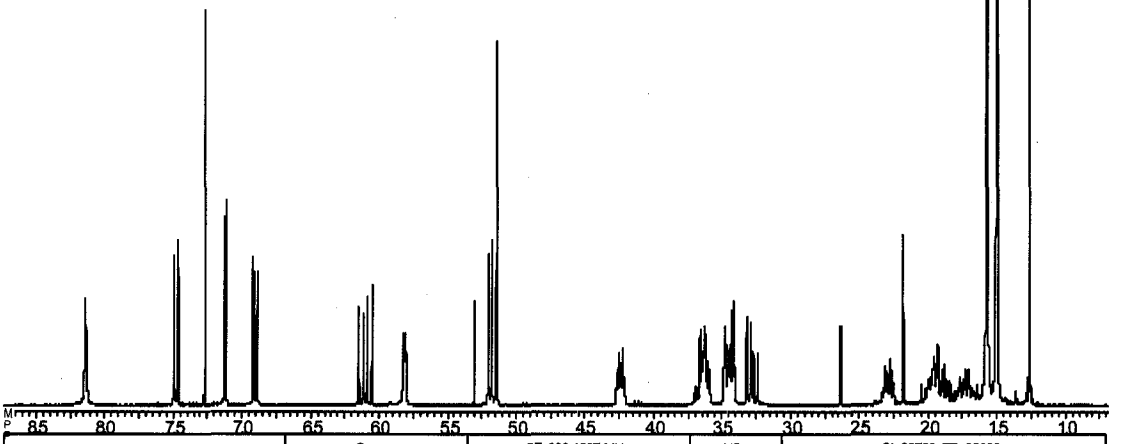
189 **190**

Acid **189** (251mg, 0.491mmol) was charged with 50ml $BrCCl_3$ in the presence of a sunlamp and heated to 105°C for 1 hour. The resulting mixture was cooled back to 20°C and concentrated directly. The crude residue was purified by PTLC (5% MeOH / CH_2Cl_2) to afford the desired product **190** (198mg, 86 %) as a single diastereomer. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (6H, s), 1.57 (9H, s), 1.62-2.07 (3H, m), 2.22-2.36 (1H, m), 3.28 (1H, dd, J = 9.2 Hz, J = 14.7 Hz), 3.39-3.50 (2H, m), 3.57-3.73 (2H, m), 4.20-4.29 (1H, m), 5.14 (1H, s), 5.19 (1H, dd, J = 0.95Hz, J = 7.35 Hz), 5.81 (1H, d, J = 4.0 Hz), 6.10 (1H, dd, J = 10.6 Hz, J = 17.2 Hz), 6.89 (1H, d, J = 2.2 Hz), 6.92 (1H, d, J = 2.2 Hz), 7.12 (1H, d, J = 2.2 Hz), 7.48 (1H, d, J = 8.7 Hz), 8.14 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 22.1, 27.9, 28.0, 29.2, 30.0, 39.3, 45.7, 58.4, 58.8, 83.6, 103.7, 105.2, 112.2, 113.9, 119.1, 127.0, 134.2, 142.5, 146.1, 146.9, 152.8, 166.0, 168.8; HRMS-FAB: [M+H]+ calcd for $C_{26}H_{33}N_3O_5$, 467.2420; found, 467.2425.

awg-03-sm-1

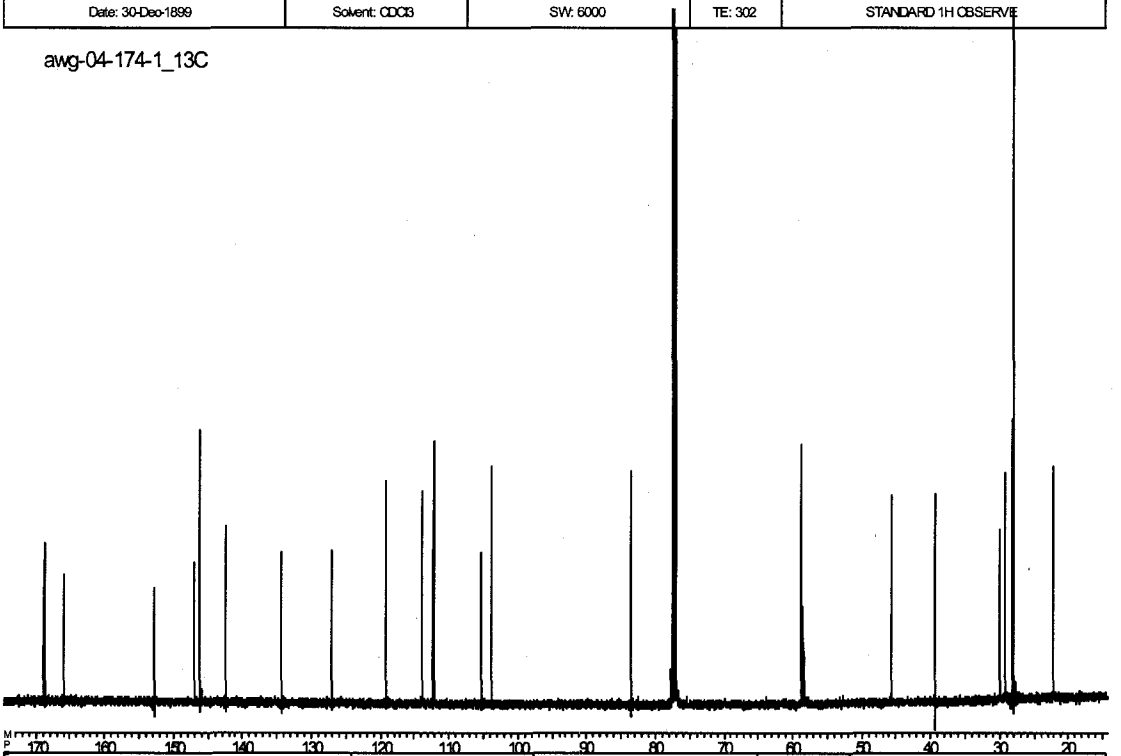


190



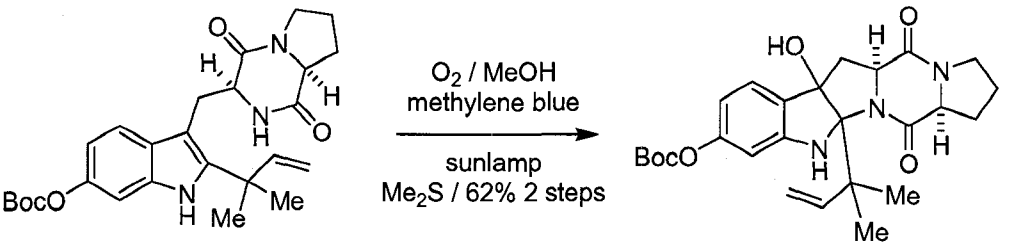
File name: awg-03-sm-1	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	STANDARD 1H OBSERVE

awg-04-174-1_13C



File name: awg-04-174-1_13C	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

Pyrroloindole (191)

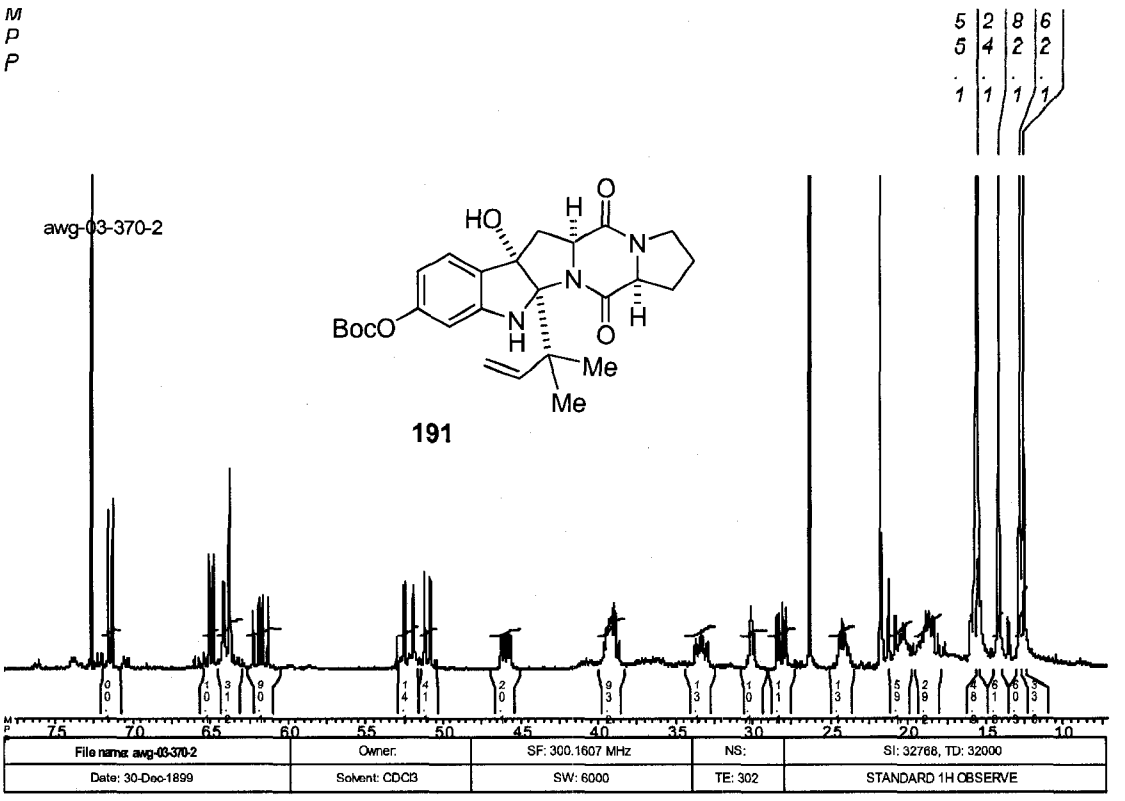


190 **191**

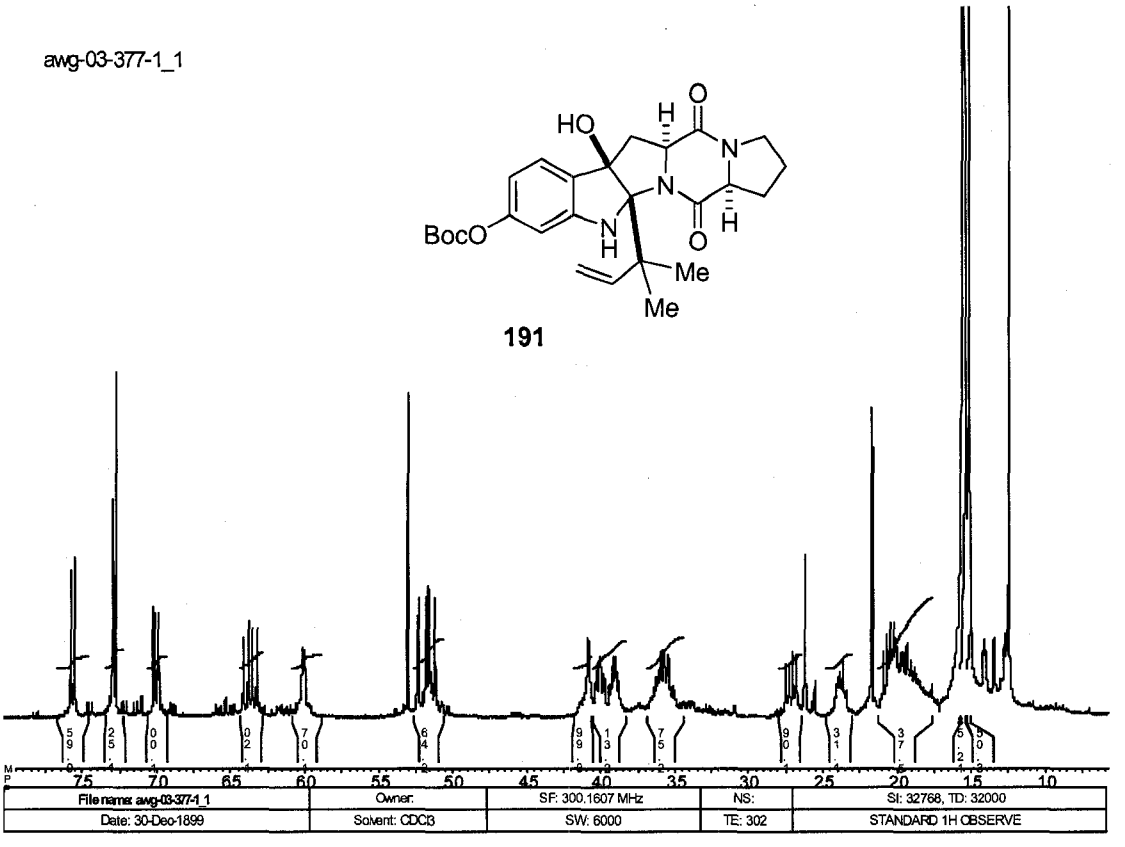
Compound **190** (56mg, 0.043mmol) was dissolved in 50 ml MeOH and charged with trace methylene blue as a photosensitizer. The reaction was stirred under an atmosphere of O_2 at 0°C for 24 hours in the presence of light provided by a sunlamp. The reaction was then charged with excess dimethylsulfide (1 ml). After warming to 20°C the reaction was concentrated directly and purified by PTLC to afford the product **191** as a 1 : 1 mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) (*cis*-syn diastereomer) δ 1.29 (3H, s), 1.42 (3H, s), 1.56 (9H, s), 1.81-1.95 (3H, m), 1.99-2.11 (1H, m), 2.37-2.48 (1H, m), 2.82 (1H, dd, J = 5.75 Hz, J = 12.8 Hz), 3.01 (1H, bs), 3.29-3.39 (1H, m), 3.86-3.98 (2H, m), 4.55-4.64 (1H, m), 5.12 (1H , dd, J = 1.2 Hz, J = 10.9 Hz), 5.22 (1H, dd, J = 1.2 Hz, J = 17.7 Hz), 6.18 (1H, dd, J = 0.8 Hz, J = 17.6 Hz), 6.38 (1H, d, J = 2.0 Hz), 6.42 (1H, s), 6.50 (1H, dd, J = 2.2 Hz, J = 8.0 Hz), 7.15 (1H, d, J = 8.0 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 22.1, 27.9, 28.0, 29.2, 30.0, 39.3, 45.7, 58.4, 58.8, 83.6, 103.7, 105.2, 112.2, 113.9, 119.1, 127.0, 134.2, 142.5, 146.1, 146.9, 152.8, 166.0, 168.8; HRMS-FAB: [M+H]+ calcd for $C_{29}H_{35}N_3O_5$, 505.2577; found, 505.2600.

^{1}H NMR (300 MHz, $CDCl_3$) (*cis*-anti diastereomer) δ 1.52 (3H, s), 1.55 (12H, s), 1.75-2.13 (4H, m), 2.28-2.48 (1H, m), 2.65-2.78 (1H, dd, J = 6.75 Hz, J = 14.3 Hz), 3.48-3.69 (2H, m), 3.84-4.00 (1H, m), 3.95-4.05 (1H, m), 4.10 (1H, s), 5.14 (1H, d, J = 10.6 Hz), 5.20 (1H, d, J = 17.4 Hz), 6.00 (1H, d, J = 4.0 Hz), 6.37 (1H, dd, J = 10.6 Hz, J = 17.6 Hz), 7.00 (1H, dd, J = 2.05 Hz, J = 8.05 Hz), 7.30 (1H, d, J = 2.2 Hz), 7.56 (1H, d, J = 8.1 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 22.1, 27.9, 28.0, 29.2, 30.0, 39.3, 45.7, 58.4, 58.8, 83.6, 103.7, 105.2, 112.2, 113.9, 119.1, 127.0, 134.2, 142.5, 146.1, 146.9, 152.8, 166.0, 168.8; HRMS-FAB: [M+H]+ calcd for $C_{29}H_{35}N_3O_5$, 505.2577; found, 505.2600.

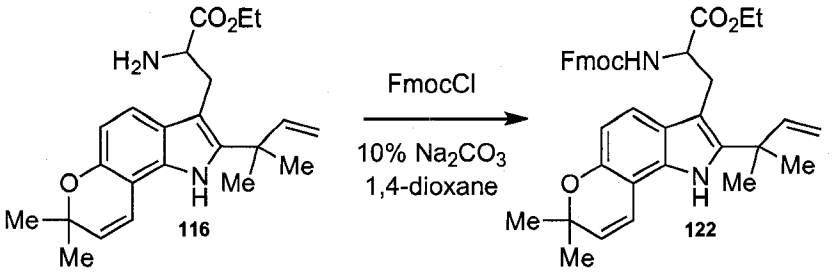


File name: awg-03-370-2	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	STANDARD 1H OBSERVE



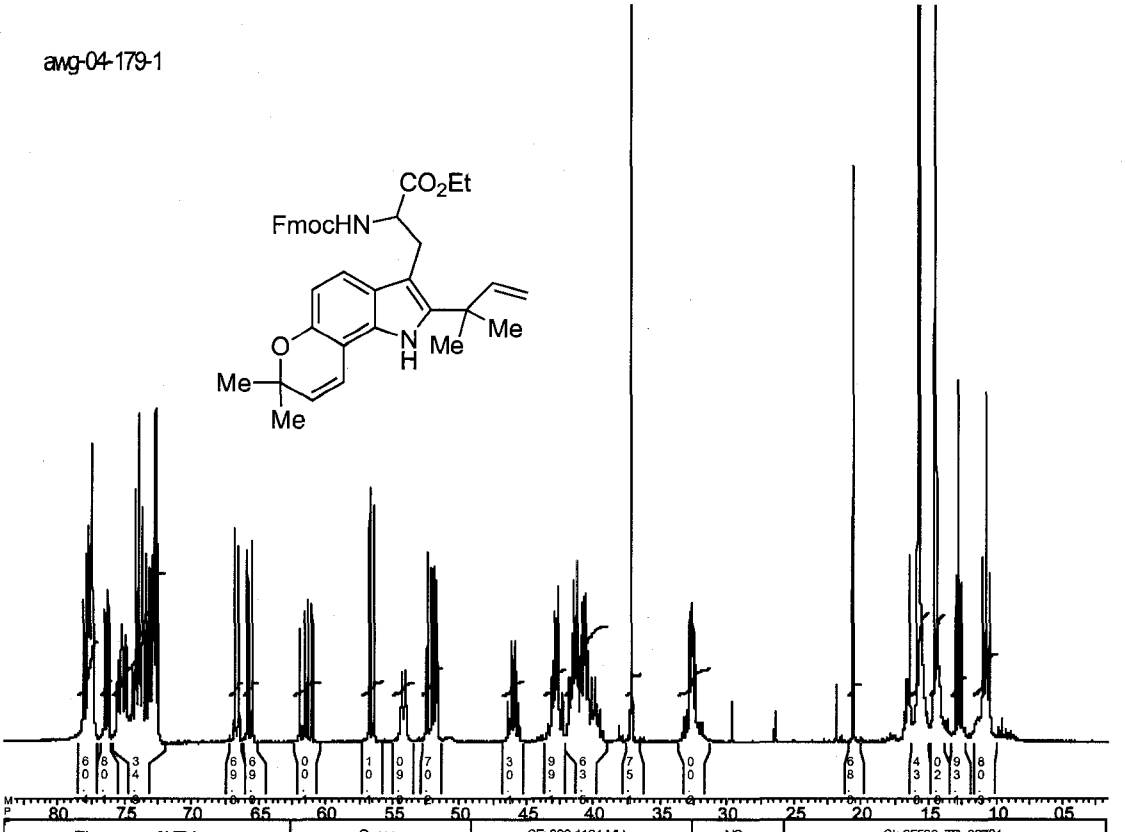
File name: awg-03-377-1_1	Owner:	SF: 300.1607 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 302	STANDARD 1H OBSERVE

Ethyl-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)propanoate (122)



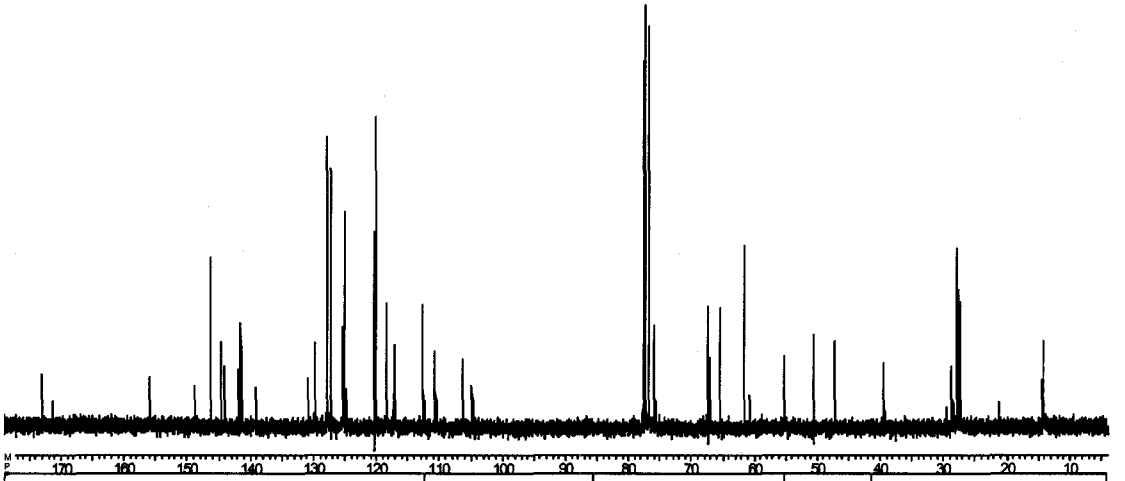
To a solution of aminoester **116** (184mg, 0.048mmol) in 740μL 1,4-dioxane at 0°C was added 1.50 ml 10% sodium carbonate. The mixture was stirred 5min at 0°C then charged with FmocCl (137mg, 0.053mmol) followed by an additional 1.50 ml 1,4-dioxane. The solution was stirred at 0°C for 2 hours and for an additional 14 hours at 20°C. The mixture was extracted 3X with ethyl acetate, dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (20-50% EtOAc / hexanes) to afford the desired amino ester **122** (252mg, 87%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, t, J = 7.2 Hz), 1.45 (6H, s), 1.58 (6H, s), 3.15-3.36 (2H, m), 3.93-4.21 (5H, m), 4.22-4.35 (2H, m), 4.51-4.68 (1H, m), 5.13-5.28 (2H, m), 5.41 (1H, d, J = 8.0 Hz), 5.65 (1H, d, J = 9.7 Hz), 6.14 (1H, dd, J = 10.4 Hz, J = 17.4 Hz), 6.56 (1H, d, J = 9.8 Hz), 6.66 (1H, d, J = 8.5 Hz), 7.19-7.59 (5H, m), 7.63 (1H, d, J = 7.3 Hz), 7.70-7.85 (4H, m). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.0, 14.4, 27.5, 27.9, 28.6, 39.4, 47.2, 50.5, 55.3, 60.6, 61.6, 65.4, 67.1, 67.3, 75.8, 104.7, 106.3, 110.5, 112.5, 117.1, 118.5, 120.1, 120.3, 124.7, 124.9, 125.3, 125.4, 127.2, 127.3, 127.8, 129.8, 130.7, 139.2, 141.4, 141.7, 144.1, 144.5, 146.3, 148.8, 155.9, 171.4, 172.9; HRMS-FAB: [M+H]+ calcd for $C_{38}H_{40}N_2O_5$, 604.2937; found, 604.2913.

awg-04-179-1



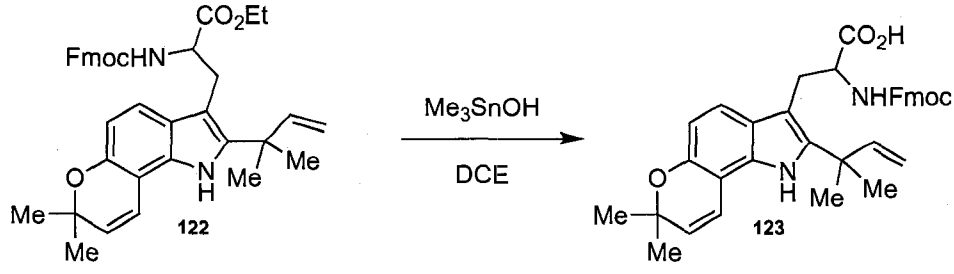
File name: awg-04-179-1	Owner:	SF: 300.1164 MHz	NS:	SI: 65536, TD: 32784
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 298	STANDARD 1H OBSERVE

awg-04-179-1_13C_300MHz



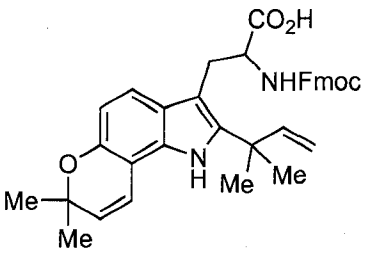
File name: awg-04-179-1_13C_300MHz	Owner:	SF: 75.4715 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 20000	TE: 298	13C OBSERVE

2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)propanoic acid (123)



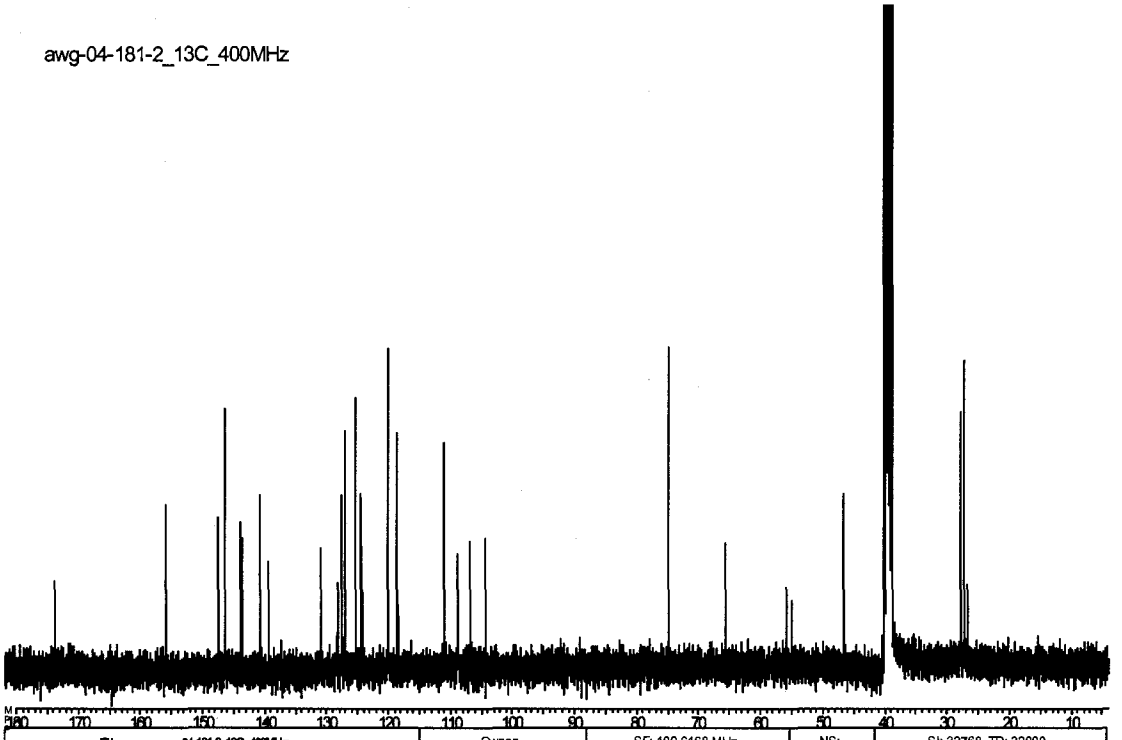
Fmoc aminoester **122** (1.03g, 1.7mmol) was dissolved in 100ml 1,2-dichloroethane and then charged with trimethyltin hydroxide (1.53g, 8.5mmol). The mixture was heated to reflux until TLC showed a complete reaction (8-10hours). The mixture was concentrated in vacuo, and the resulting mixture dissolved in ethyl acetate. The organic layer was washed with 5% HCl, brine, dried over sodium sulfate and concentrated. The crude material was purified by flash chromatography (5-10% MeOH / CH_2Cl_2) to afford the desired amino acid **123** (762mg, 84%) as an amber oil. ^{1}H NMR (400 MHz, DMSO-D_6) δ 1.34 (6H, d, J = 10.3 Hz), 1.49 (6H, s), 2.96 (1H, dd, J = 8.7 Hz, J = 14.7 Hz), 3.28 (1H, dd, J = 5.8 Hz, J = 14.5 Hz), 4.08-4.21 (3H, m), 4.98-5.08 (2H, m), 5.67 (1H, d, J = 9.8Hz), 6.18 (1H , dd, H = 10.6 Hz, J = 17.4 Hz), 6.43 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 9.8 Hz), 7.23-7.45 (5H, m), 7.59-7.69 (3H, m), 7.87 (2H, d, J = 7.7 Hz), 10.01 (1H, s), 12.28 (1H, bs). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 26.8, 27.2, 27.3, 27.9, 46.5, 54.9, 55.9, 65.7, 75.0, 104.4, 106.8, 108.8, 111.0, 118.5, 120.1, 124.4, 125.3, 127.1, 127.6, 128.3, 140.0, 140.6, 143.7, 143.8, 146.3, 147.4, 155.8, 173.7; HRMS-FAB: [M+H]+ calcd for $C_{36}H_{37}N_2O_5$, 577.2702; found, 577.2674.

awg-04-181-1_400MHz



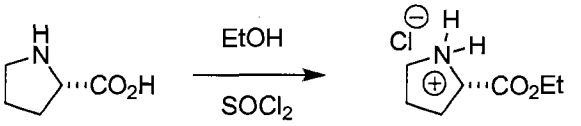
File name: awg-04-181-1_400MHz	Owner:	SF: 400.1102 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-181-2_13C_400MHz



File name: awg-04-181-2_13C_400MHz	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 30019	TE: 298	13C OBSERVE

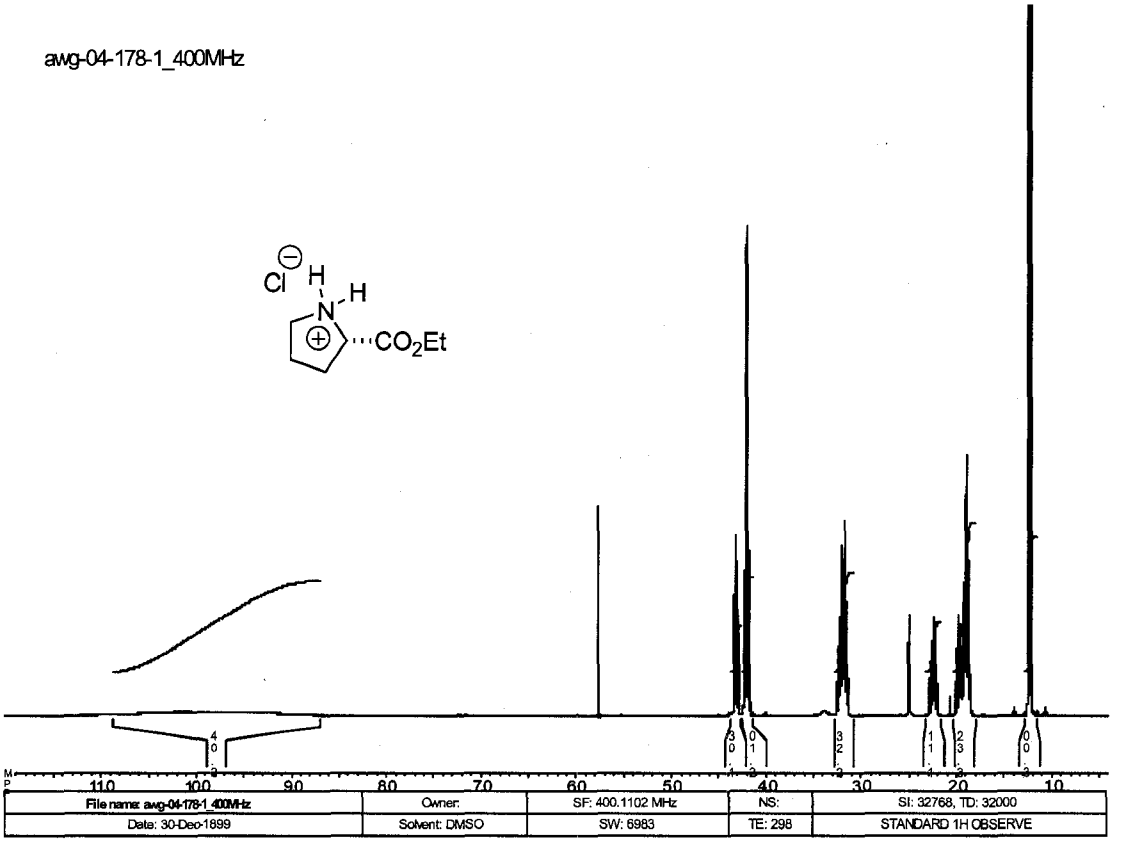
(*S*)-2-(ethoxycarbonyl)pyrrolidinium chloride (119)



L-Proline 119

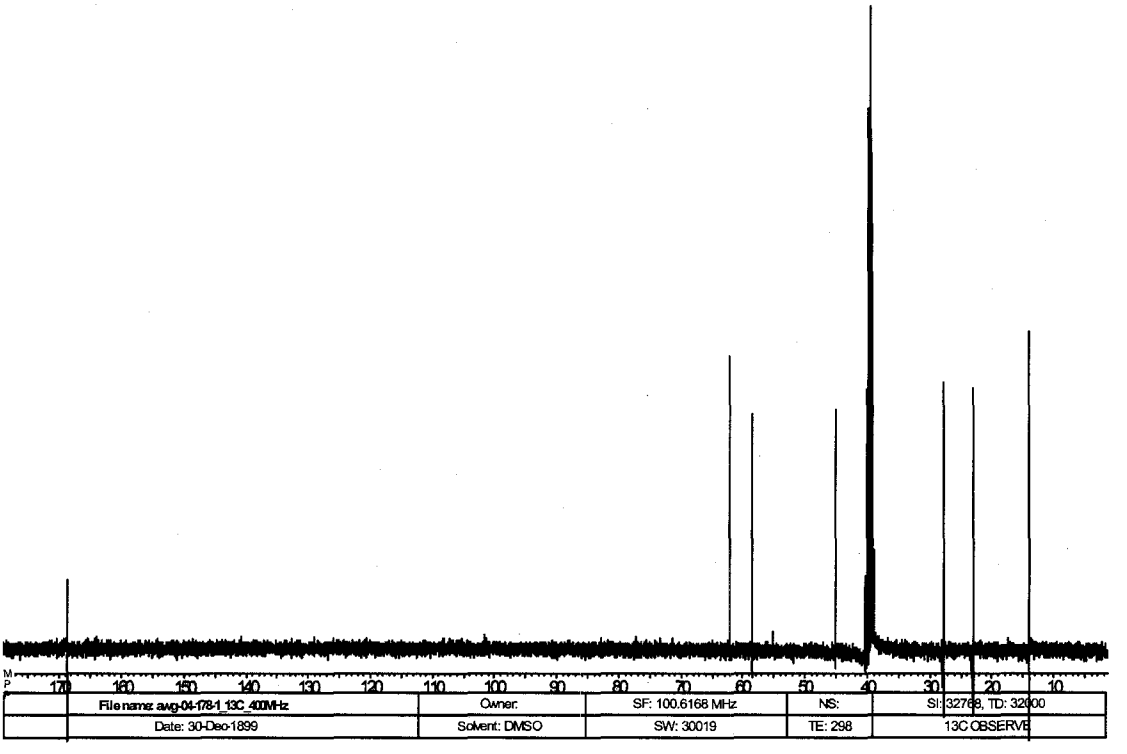
A clean, dry 500ml flask was charged with 150ml absolute ethanol. The solution was cooled to 0°C and then charged dropwise with thionyl chloride (6.2g, 52.0mmol). The reaction was allowed to warm to 20°C over 1 hour and then charged with solid L(-)-Proline (5g, 43.4mmol). The mixture was heated to reflux 24 hours and then concentrated directly. The mixture was charged with 150ml toluene and concentrated. An additional 150ml of toluene was added and the mixture was concentrated again. The resulting solids were charged with 150ml ethyl acetate and concentrated. Again, the mixture was charged with 150ml dichloromethane and concentrated and then dried 24 hours over high vacuum to afford (7.3g, 99%) of the desired salt **119** as a clear oil. ^{1}H NMR (400 MHz) (DMSO-D_6) δ 1.23 (3H, t, J = 7.3 Hz), 1.82-2.04 (3H, m), 2.18-2.31 (1H, m), 3.09-3.28 (2H, m), 4.20 (2H, q, J = 7.03 Hz, J = 14.28 Hz), 4.29-4.35 (1H, m), 8.54-10.85 (2H, bs). ^{13}C NMR (100 MHz) (DMSO-D_6) δ 13.9, 23.1, 27.8, 45.1, 58.4, 62.0, 168.7; HRMS-FAB: [M+H]+ calcd for $C_7H_{14}N_1O_2$, 144.1025; found, 144.0836.

awg-04-178-1_400MHz



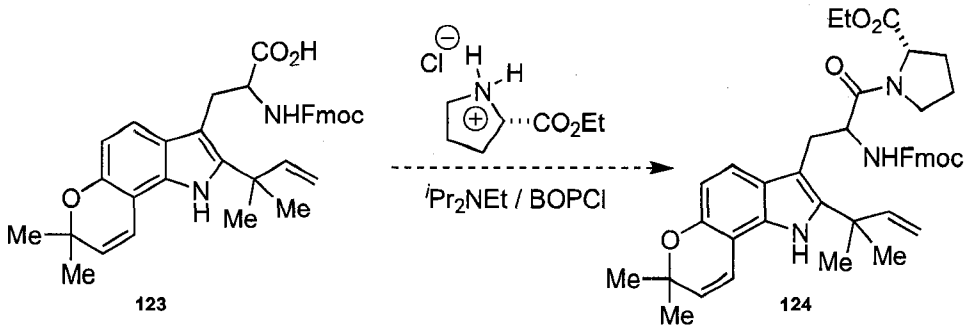
File name: awg-04-178-1_400MHz	Owner:	SF: 400.1102 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-178-1_13C_400MHz



File name: awg-04-178-1_13C_400MHz	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: DMSO	SW: 30019	TE: 298	13C OBSERVE

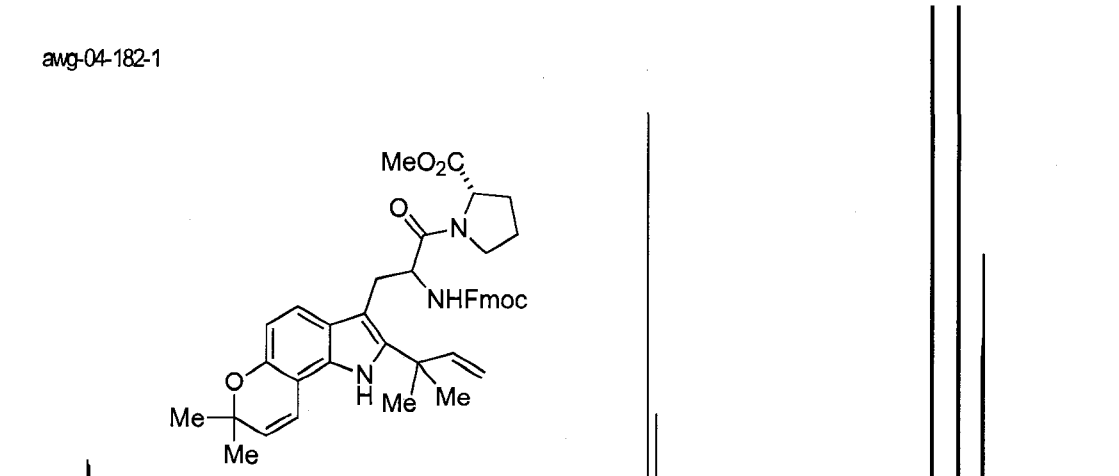
(2*S*)-ethyl 1-(2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)propanoyl)pyrrolidine-2-carboxylate (124)

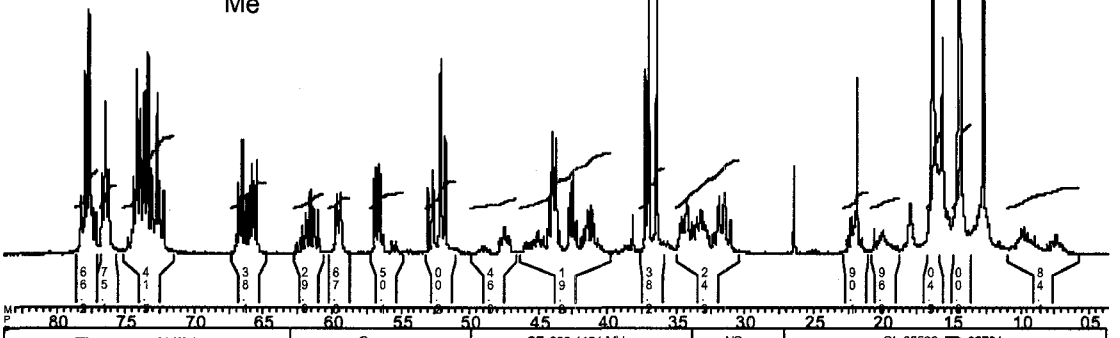


To a solution of acid **123** (100mg, 0.0173mmol) in 5.0ml CH_2Cl_2 was added solid L(-)-Proline ethyl ester hydrochloride (43mg, 0.026mmol). The mixture was charged at 0°C with $^{i}Pr_2NEt$ (79mg, 0.067mmol) and then BopCl (66mg, 0.026mmol). The resulting solution was stirred overnight at ambient temperature and then partitioned between 10% citric acid and EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (20-50% EtOAc / hexanes) to afford (73mg, 61%) of the desired coupled product **124** as a white foam. ^1H NMR (300 MHz, $CDCl_3$) (complex mixture of diastereomers) δ 1.44 (6.53H, s), 1.63 (5.86H, s), 1.85-2.07 (0.73H, m), 2.10-2.30 (1.18H, m), 3.02-3.52 (3.76H, m), 1.06 (1.06H, s), 3.70 (0.41H, s), 3.72 (0.41H, s), 3.81 (0.18H, s), 4.01-4.30 (1.91H, m), 4.31-4.63 (2.26H, m), 4.66-4.98 (0.69H, m), 5.13-5.29 (2H, m), 5.49-5.73 (1.14H, m), 5.89-6.02 (0.82H, m), 6.06-6.29 (0.98H, m), 6.50-6.73 (1.95H, m), 7.18-7.50 (5.51H, m), 7.64 (1.64H, t, J = 7.0 Hz), 7.70-7.85 (2.86H, m). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.2, 24.2, 25.1, 27.2, 27.3, 27.4, 27.8, 27.9, 28.8, 29.2, 29.5, 29.9, 30.2, 30.9, 40.0, 32.0, 34.0, 46.7, 47.2, 47.3, 52.4, 52.8, 53.1, 53.6, 53.9, 58.6, 59.1, 59.2, 67.0, 67.1,

67.2, 69.7, 75.7, 75.8, 104.5, 104.6, 104.8, 106.3, 106.4, 110.5, 110.6, 112.3, 112.7, 112.8, 117.2, 118.6, 119.0, 119.2, 120.1, 124.5, 124.7, 125.4, 125.5, 127.2, 127.8, 129.7, 129.9, 130.0, 130.2, 130.8, 139.4, 139.5, 141.5, 143.9, 144.0, 144.2, 144.3, 145.6, 145.7, 146.7, 148.8, 155.4, 155.7, 156.0, 170.9, 171.3, 171.6, 172.2, 172.5, 172.6; HRMS-FAB: [M+H]+ calcd for $C_{42}H_{46}N_3O_6$, 688.3387; found, 688.3369.

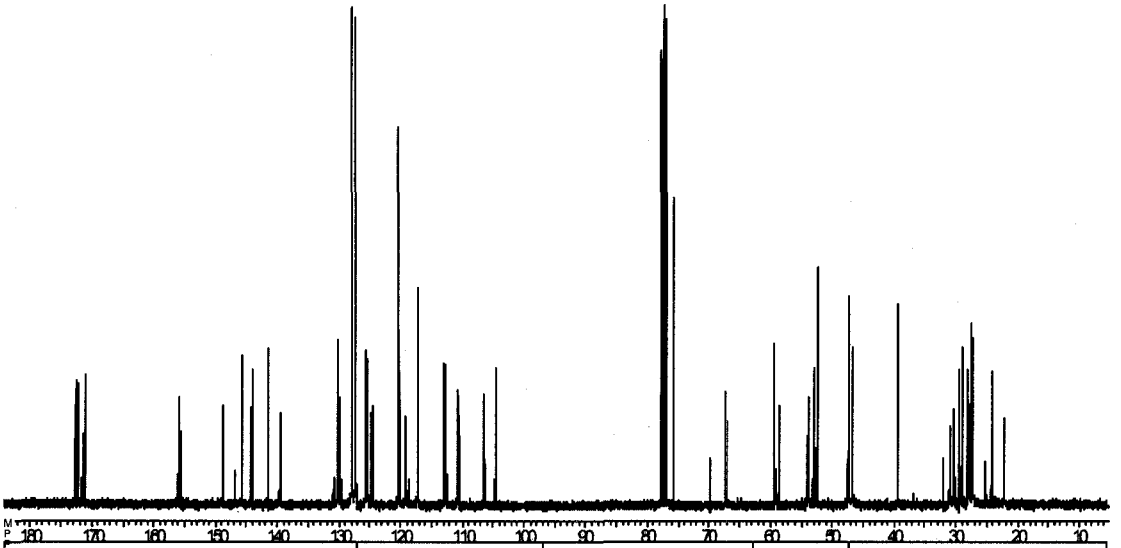
awg-04-182-1





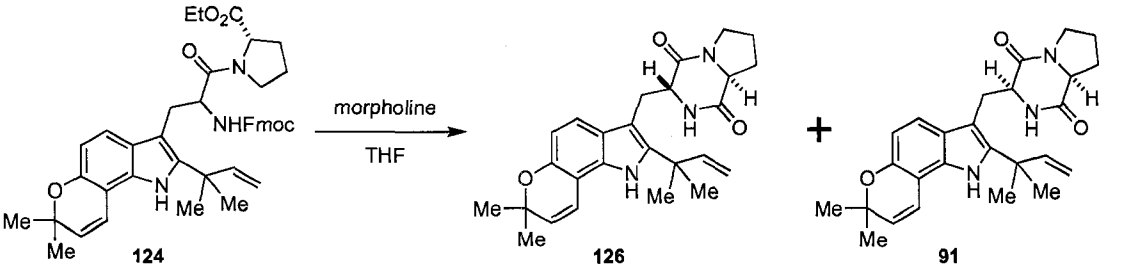
File name: awg-04-182-1	Owner:	SF: 300.1164 MHz	NS:	SI: 65536, TD: 32784
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6000	TE: 298	STANDARD 1H OBSERVE

awg-04-182-1_13C



File name: awg-04-182-1_13C	Owner:	SF: 75.4715 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 20000	TE: 298	13C OBSERVE

(3*S*,8a*S*)-3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)methyl)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (126), and notoamide E (91).



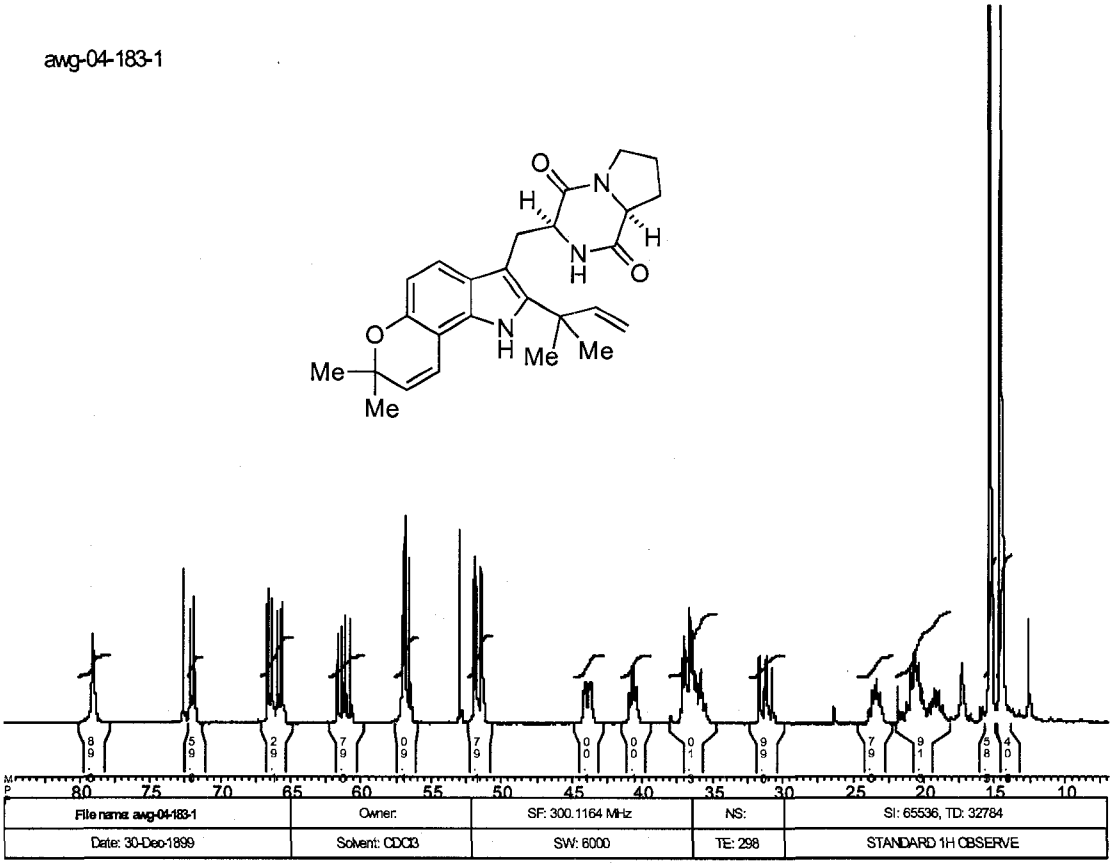
To a solution of peptide **124** (100mg, 0.0145mmol) in 10ml THF was added 1.0 ml morpholine. The solution was stirred 5 hours at 20°C and then warmed to 66°C for an additional hour. The mixture was concentrated directly and charged with 100ml EtOAc. The resulting mixture was concentrated and purified by flash chromatography (20-100% EtOAc / hexanes then 10% MeOH / CH_2Cl_2), to afford a crude mixture of the desired product as a 1 : 1 mixture of diastereomers. The crude material was further purified by PTLC (0-5% MeOH / CH_2Cl_2) to afford cleanly the *cis* and *trans* diastereomers (cis, 25mg, 40%), (trans, 22mg, 35%).

^{1}H NMR (***cis*-diastereomer, notoamide E**) (300 MHz, $CDCl_3$) δ 1.46 (6H, s), 1.54 (6H, s), 1.81-2.20 (3H, m), 2.27-2.41 (1H, m), 3.12 (1H, dd, J = 11.7 Hz, J = 15.3 Hz), 3.51-3.75 (3H, m), 4.00-4.12 (1H, m), 4.33-4.44 (1H, m), 5.10-5.21 (2H, m), 5.67 (1H, d, J = 9.7 Hz), 5.70 (1H, bs), 6.13 (1H, dd, J = 10.4 Hz, J = 17.5 Hz), 6.58 (1H, d, J = 9.7 Hz), 6.65 (1H, d, J = 8.5 Hz), 7.21 (1H, d, J = 8.5 Hz), 7.91 (1H, bs). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.8, 26.1, 27.5, 27.6, 28.1, 28.6, 39.2, 45.6, 55.1, 59.4, 76.0, 105.1, 105.2, 111.1, 112.8, 117.0, 118.2, 123.9, 130.2, 131.0, 140.1, 146.0, 149.1, 166.0, 169.5; HRMS-FAB: [M+H]+ calcd for $C_{26}H_{32}N_3O_3$, 434.2444; found, 434.2422.

$[\alpha]_D^{25}$ = -43.8 (c=0.5, CH_2Cl_2)

^{1}H NMR (*trans*-diastereomer) (300 MHz, $CDCl_3$) δ 1.45 (6H, s), 1.52 (6H, s), 1.62-2.05 (4H, m), 2.21-2.37 (1H, m), 3.26 (1H, dd, J = 9.0 Hz, J = 14.6 Hz), 3.35-3.52 (2H, m), 3.55-3.76 (2H, m), 4.22-4.31 (1H, m), 5.15 (1H, d, J = 4.4 Hz), 5.19 (1H, d, J = 11.7 Hz), 5.66 (1H, d, J = 9.9 Hz), 5.84 (1H, d, J = 3.7 Hz), 6.13 (1H, dd, J = 10.6 Hz, J = 17.5 Hz), 6.58 (1H, d, J = 9.7 Hz), 6.64 (1H, d, J = 8.4 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.87 (1H, bs). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.1, 27.5, 28.0, 28.2, 29.2, 30.0, 39.3, 45.7, 58.4, 58.7, 75.9, 104.8, 105.7, 110.8, 112.0, 117.0, 118.9, 123.7, 130.0, 130.9, 140.2, 146.4, 148.9, 166.0, 168.8; HRMS-FAB: [M+H]+ calcd for $C_{26}H_{32}N_3O_3$, 434.2444; found, 434.2422.

awg-04-183-1



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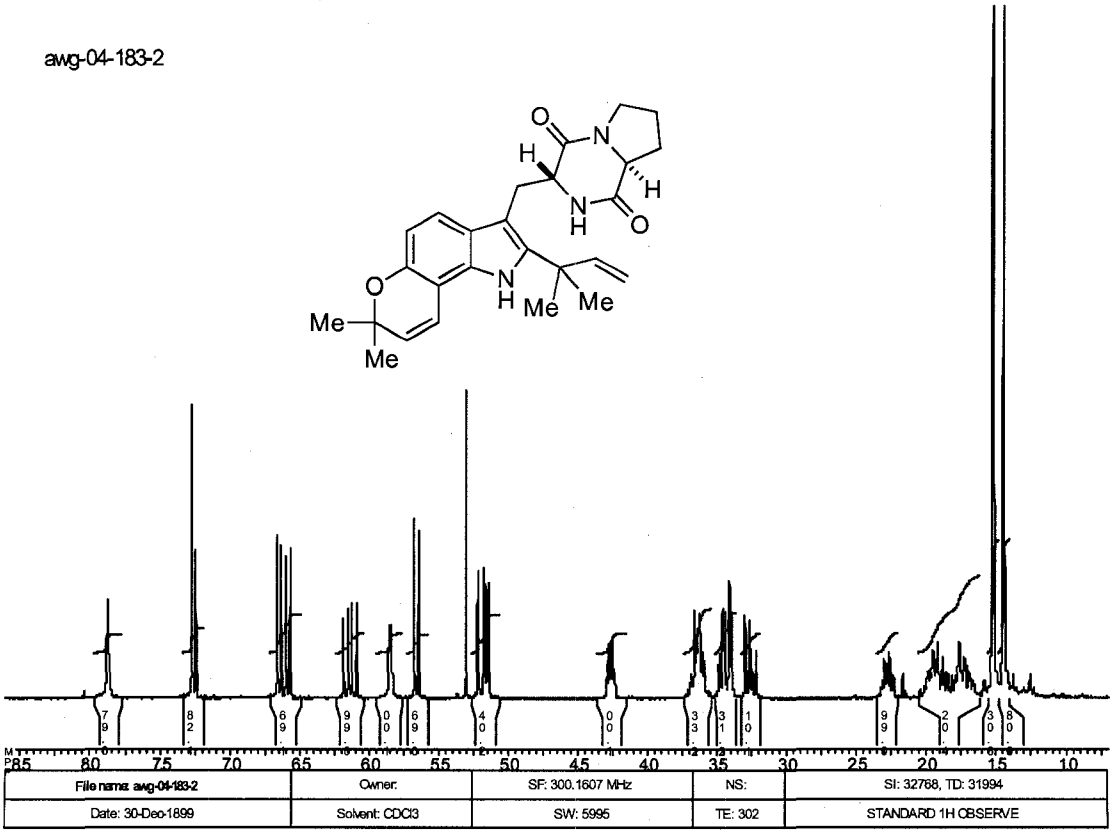
awg-04-183-2



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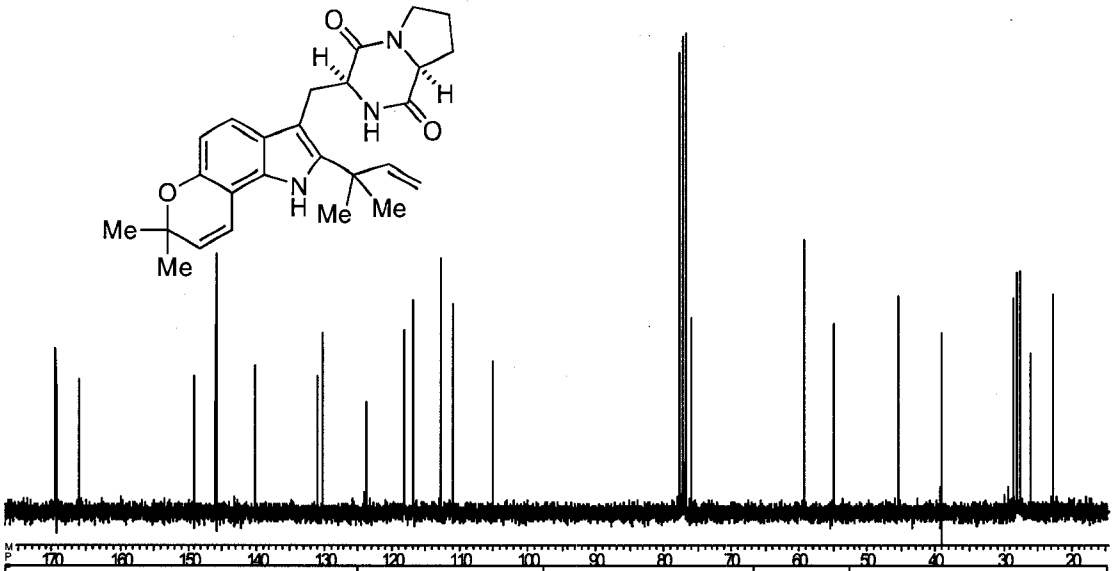
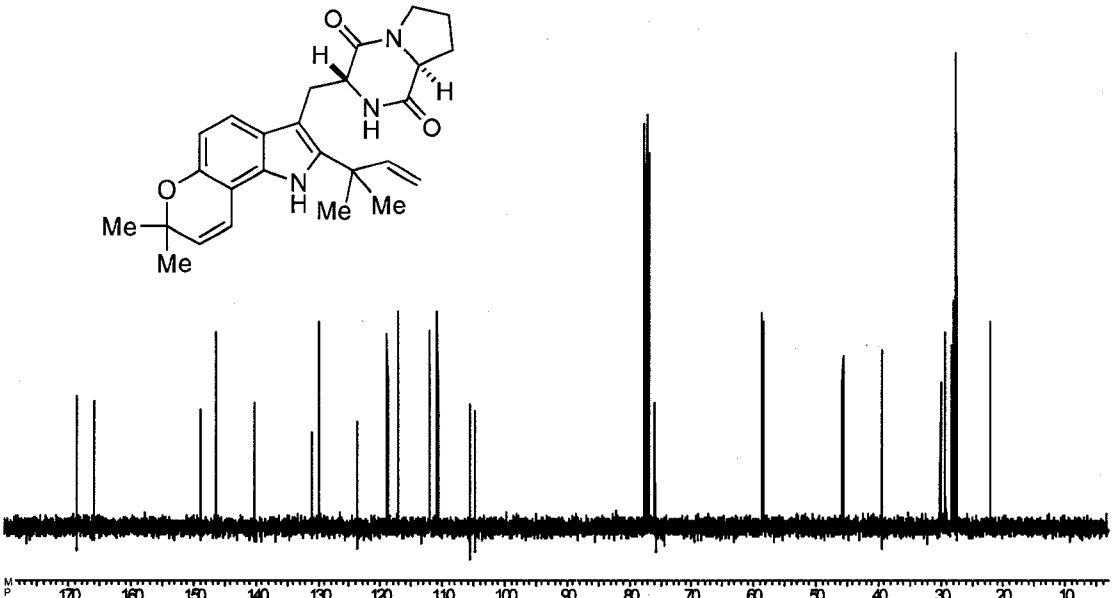
Date: 30-Dec-1899	Solvent: CDCl3	SW: 5995	TE: 302	STANDARD 1H OBSERVE

awg-04-183-1_13C



File name: awg-04-183-1_13C	Owner:	SF: 75.4715 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 20000	TE: 298	13C OBSERVE

awg-04-183-2_13C



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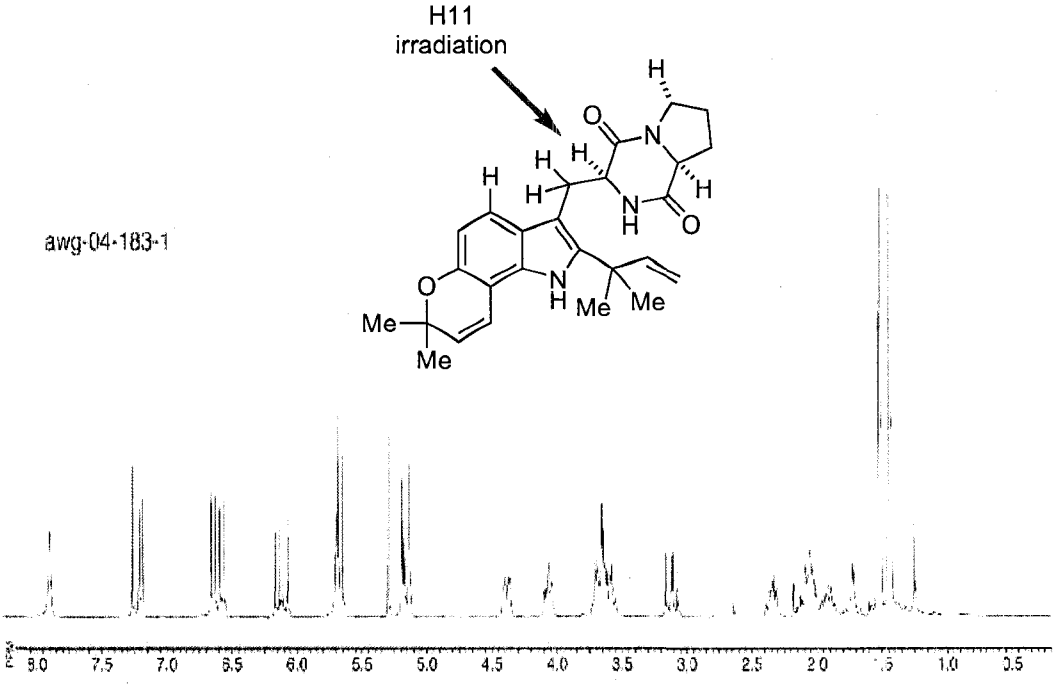
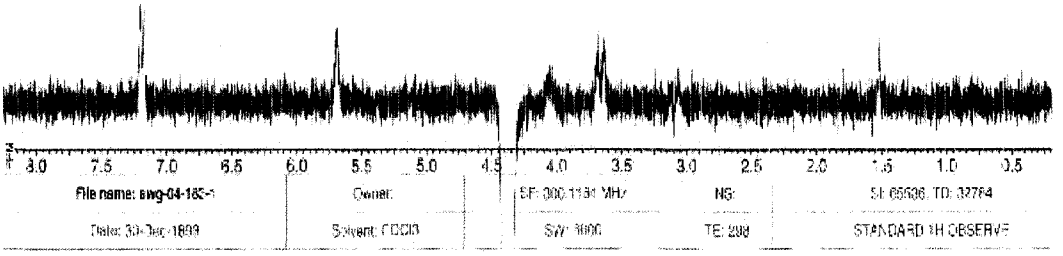
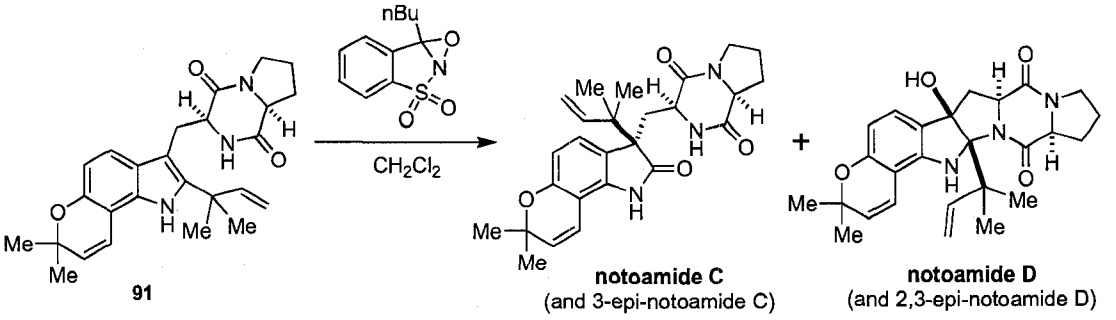
Date: 30-Dec-1899	Solvent: CDCl3	SW: 22936	TE: 302	13C OBSERVE



awg-04-183-1_nOe



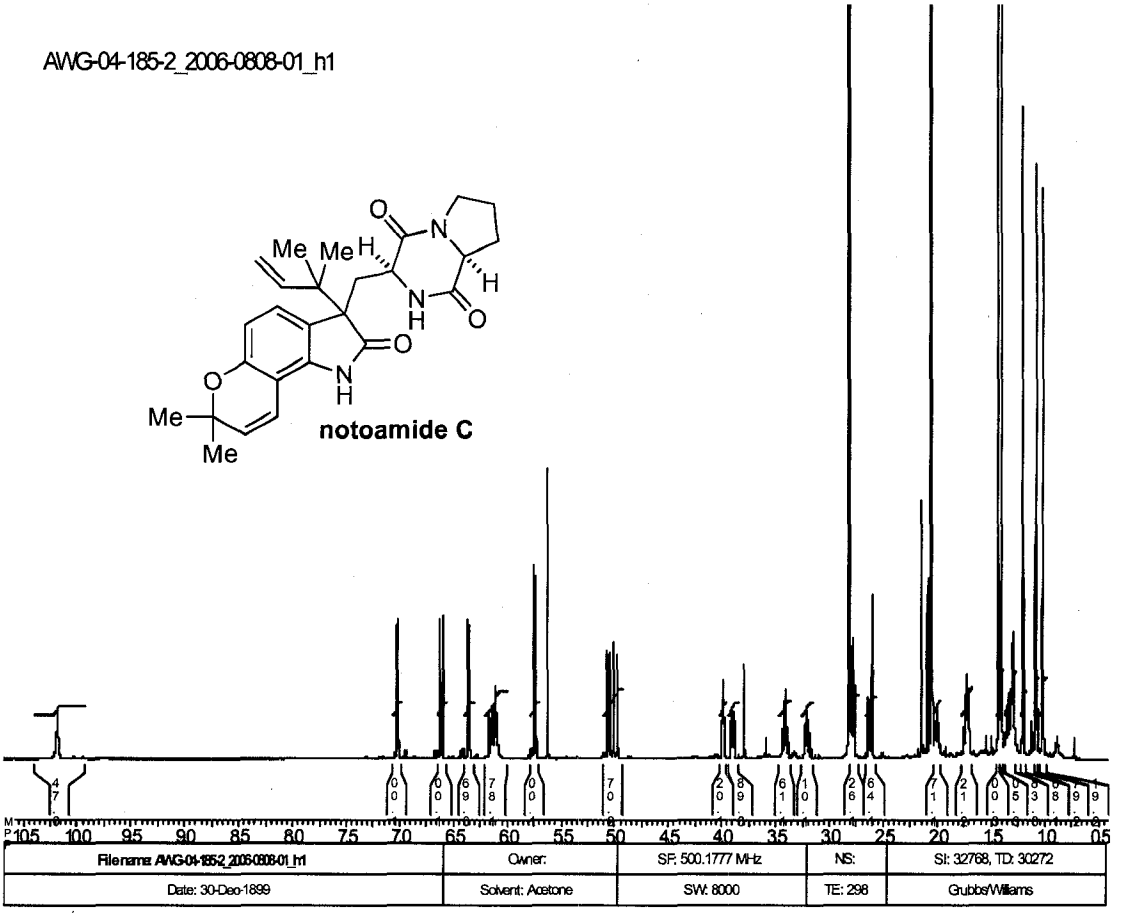
Notoamides C and D



Compound **91** (**notoamide E**) (24mg, 0.0554mmol), in 2.4ml CH_2Cl_2 was charged at 20°C with oxaziridine **129** (26mg, 0.11mmol). The mixture was slowly concentrated under a gentle stream of argon to ½ the original volume. The reaction was then sealed with a rubber stopper, and left to stir for 24 hours. The reaction was then directly concentrated and the crude residue purified by flash chromatography to afford (±), notoamide C. The mixture was further purified by PTLC to afford cleanly notoamide C (7mg, 28%) and C3-epi-notoamide C (12mg, 48%), (76% overall yield). ^{1}H NMR (notoamide C) (500 MHz, acetone-D_6) δ 1.01 (3H, s), 1.08 (3H, s), 1.40 (3H, s), 1.43 (3H, s), 1.68-1.77 (2H, m), 1.96-2.07 (1H, m), 2.58-2.65 (1H, m), 2.75-2.83 (2H, m), 3.17-3.25 (1H, m), 3.37-3.45 (1H, m), 3.37-3.45 (1H, m), 3.90 (1H, ddd, J = 1.6 Hz, J = 6.6 Hz, J = 10.2 Hz), 3.96-4.01 (1H, m), 4.99 (1H, dd, J = 1.3 Hz, J = 17.6 Hz), 5.05 (1H, dd, J = 1.3 Hz, J = 10.9 Hz), 5.74 (1H, d, J = 10.1 Hz), 6.10 (1H, bs), 6.14 (1H, dd, J = 10.8 Hz, J = 17.6 Hz), 6.35 (1H, d, J = 8.3 Hz), 6.61 (1H, d, J = 10.0 Hz), 7.02 (1H, d, J = 8.3 Hz), 10.19 (1H, s). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.8, 26.1, 27.5, 27.6, 28.1, 28.6, 39.2, 45.6, 55.1, 59.4, 76.0, 105.1, 105.2, 111.1, 112.8, 117.0, 118.2, 123.9, 130.2,

131.0, 140.1, 146.0, 149.1, 166.0, 169.5; HRMS-FAB: [M+H]+ calcd for $C_{26}H_{32}N_3O_4$, 450.2393; found, 450.2378.

^{1}H NMR (C3-epi-notoamide C) (500 MHz, acetone-D_6) δ 1.07 (3H, s), 1.12 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.72-2.00 (3H, m), 2.07-2.16 (2H, m), 3.12 (1H, d, J = 14.6 Hz), 3.30-3.37 (1H, m), 3.39-3.48 (1H, m), 3.97 (1H, t, J = 7.8 Hz), 5.03 (1H, dd, J = 1.4 Hz, J = 17.4 Hz), 5.09 (1H, dd, J = 1.3 Hz, J = 10.9 Hz), 5.78 (1H, d, J = 10.0 Hz), 6.11 (1H, dd, J = 10.8 Hz, J = 17.4 Hz), 6.30 (1H, bs), 6.41 (1H, d, J = 8.1 Hz), 6.65 (1H, d, J = 9.8 Hz), 6.94 (1H, d, J = 8.3 Hz), 9.97 (1H, s). ^{13}C NMR (125 MHz) ($CDCl_3$) δ 22.1, 22.9, 23.3, 17.8, 28.3, 28.8, 30.7, 32.1, 43.0, 46.1, 53.3, 58.2, 59.4, 76.8, 106.1, 110.1, 114.2, 117.7, 122.3, 126.8, 131.6, 139.7, 144.3, 154.0, 165.8, 170.4, 183.0; HRMS-FAB: [M+H]+ calcd for $C_{26}H_{32}N_3O_4$, 450.2393; found, 450.2378.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notoamide C
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Owner:
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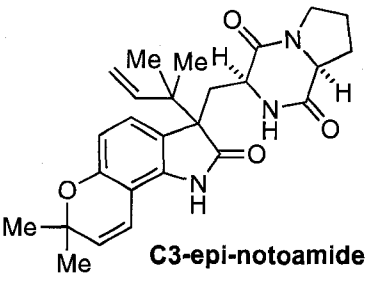
NS:
SI: 32768, TD: 30272
Date: 30-Dec-1899
Solvent: Acetone
SW: 8000
TE: 298
Grubbs/Williams

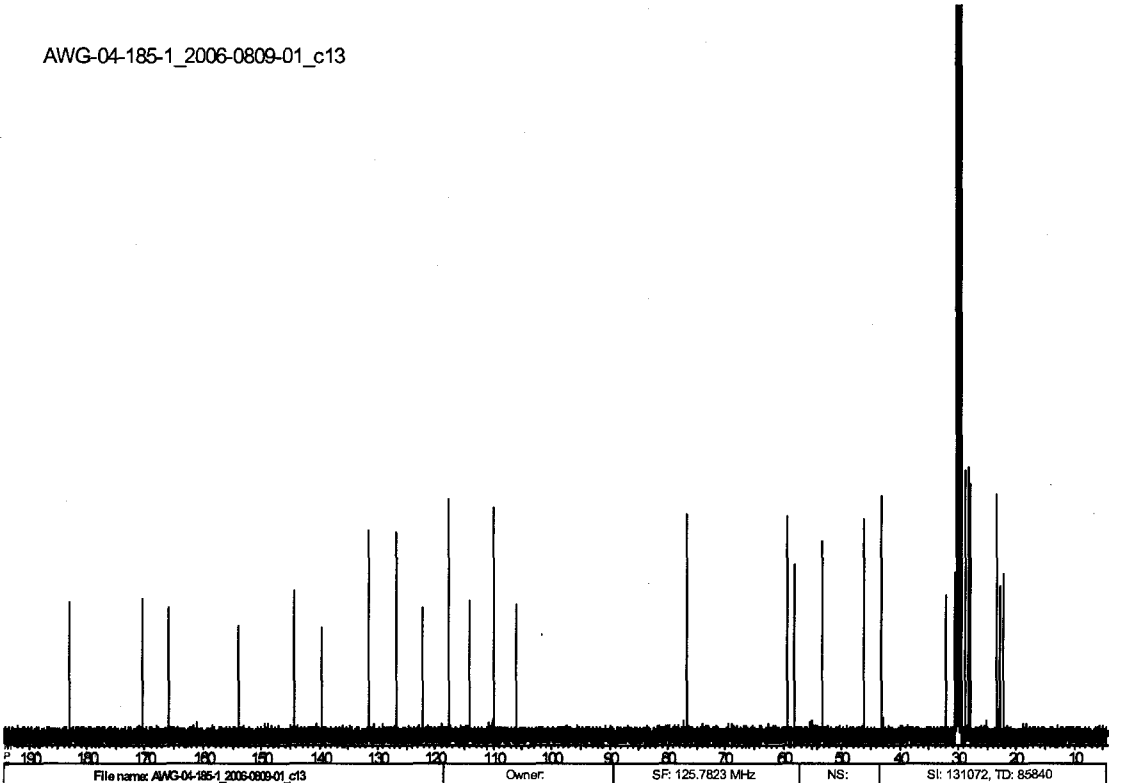
AWG-04-185-1_2006-0809-01_h1



C3-epi-notoamide C

File name: AWG-04-185-1_2006-0809-01_h1	Owner:	SF: 500.1777 MHz	NS:	SI: 32768, TD: 30272
Date: 30-Dec-1899	Solvent: Acetone	SW: 8000	TE: 298	Grubbs/Williams

AWG-04-185-1_2006-0809-01_c13



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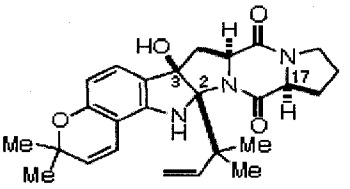
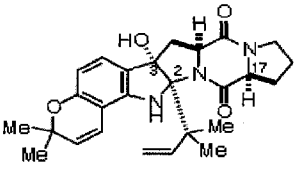


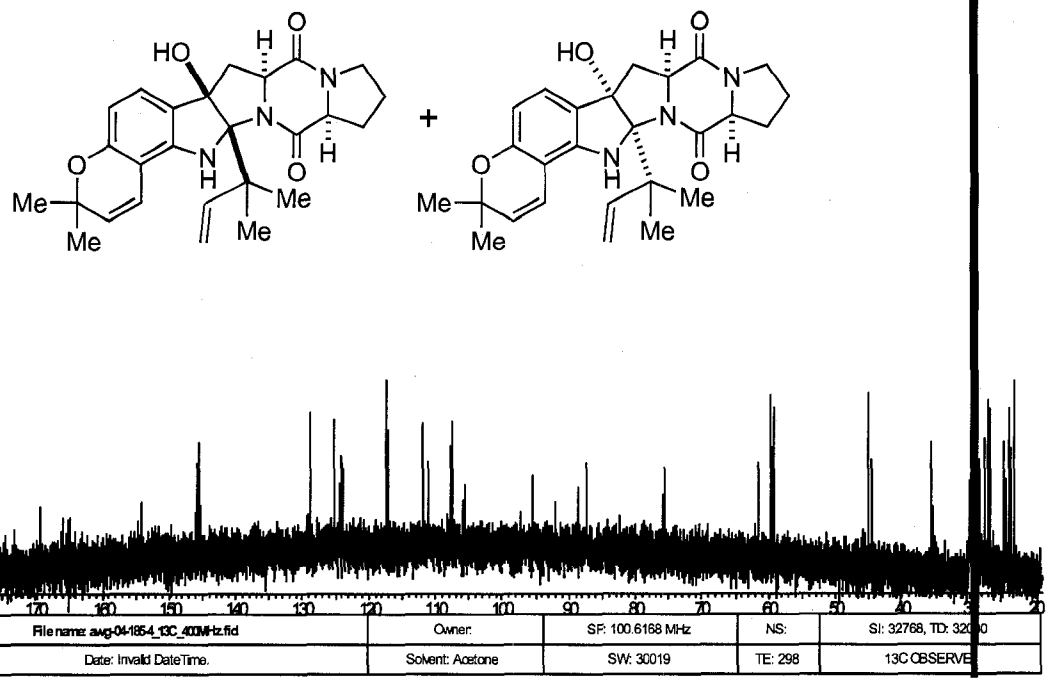
notoamide D (**4**)

STANDARD ^{1}H OBSERVE
Desktop08August\awg-04-185-6_400MHz
November 27, 2006 10:55 AM



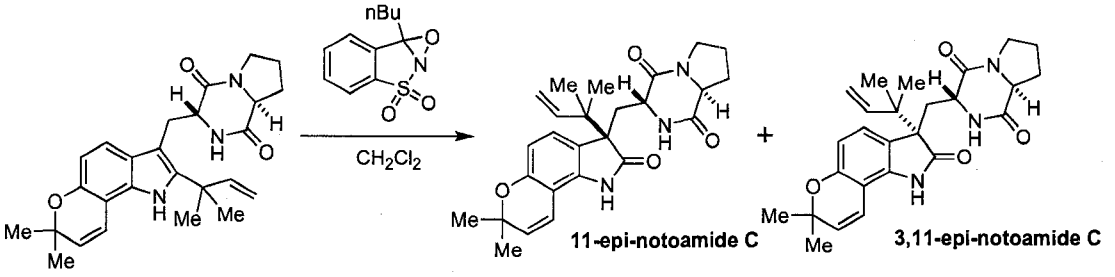
2,3-*epi*-notoamide D

awg-04-185-4_13C_400MHz.fid



File name: awg-04-185-4_13C_400MHz.fid	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: Invalid DateTime.	Solvent: Acetone	SW: 30019	TE: 298	13C OBSERVE

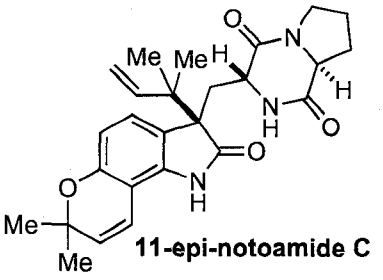
11-epi-notoamide C and 3,11-epi-notoamide C



11-epi-notoamide E (22mg, 0.0507mmol), in 2.2ml CH_2Cl_2 was charged at 20°C with oxaziridine **129** (19mg, 0.0760mmol). The mixture was slowly concentrated under a gentle stream of argon to ½ the original volume. The reaction was then sealed with a rubber stopper, and left to stir for 24 hours. The reaction was then directly concentrated and the crude residue purified by flash chromatography to afford 11-epi-notoamide C and 3,11-epinotoamide C. The mixture was further purified by PTLC to afford cleanly **11-epi-notoamide C** (8mg, 35%) and **3,11-epi-notoamide C** (6mg, 26%), (61% overall yield). ^{1}H NMR (**11-epi-notoamide C**) (400 MHz, acetone-D_6) δ 0.97 (3H, s), 1.05 (3H, s), 1.41 (3H, s), 1.42 (3H, s), 1.52-1.71 (2H, m), 1.78-1.91 (1H, m), 1.93-2.02 (1H, m), 2.53 (1H, dd, ½ ABq, J = 7.1 Hz, J = 14.5 Hz), 2.65 (1H, dd, ½ ABq, J = 3.65 Hz, J = 14.4 Hz), 2.74-2.84 (1H, m), 3.07-3.19 (1H, m), 3.37-3.50 (1H, m), 3.90-3.96 (1H, m), 4.98 (1H, dd, J = 1.3 Hz, J = 17.5 Hz), 5.05 (1H, dd, J = 1.5 Hz, J = 10.9 Hz), 5.76 (1H, d, J = 10.0 Hz), 6.06 (1H, dd, J = 10.9 Hz, J = 17.7 Hz), 6.38 (1H, dd, J = 0.6 Hz, J = 8.1 Hz), 6.60 (1H, dd, J = 0.7 Hz, J = 10.0 Hz), 6.86 (1H, d, J = 8.1 Hz), 7.17 (1H, s), 10.39 (1H, s). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 21.1, 21.3, 21.6, 27.3, 33.8, 42.6, 44.7, 55.6, 55.7, 57.1, 76.0, 78.3, 105.3, 108.1, 113.2, 117.0, 120.4, 127.7, 130.4, 139.9, 143.6, 153.2, 164.6, 167.7, 181.4.

^{1}H NMR (**3,11-epi-notoamide C**) (400 MHz, acetone-D_6) δ 1.05 (3H, s), 1.17 (3H, s), 1.41 (3H, s), 1.50 (3H, s), 1.72-1.91 (3H, m), 2.17-2.30 (2H, m), 2.54-2.64 (1H, m), 3.22-3.48 (3H, m), 4.21-4.29 (1H, m), 5.04 (1H, dd, J = 1.25 Hz, J = 10.9 Hz), 5.82 (1H, d, J = 9.8 Hz), 6.11 (1H, dd, J = 10.8 Hz, J = 17.4 Hz), 6.48 (1H, d, J = 8.1 Hz), 6.67 (1H, d, J = 9.8 Hz), 7.02 (1H, d, J = 8.1 Hz), 8.44 (1H, s), 11.19 (1H, s). ^{13}C NMR (100 MHz) (acetone-D_6) δ 22.3, 22.33, 23.0, 27.7, 28.9, 34.8, 43.1, 46.2, 56.7, 57.0, 58.8, 76.8, 107.5, 110.0, 114.4, 118.5, 120.6, 126.7, 130.9, 139.7, 144.2, 154.1, 166.6, 172.3, 184.6, 209.4.

awg-04-184-2_400MHz



11-epi-notoamide C

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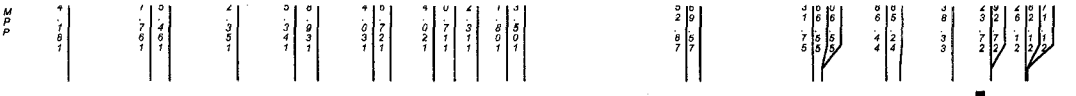
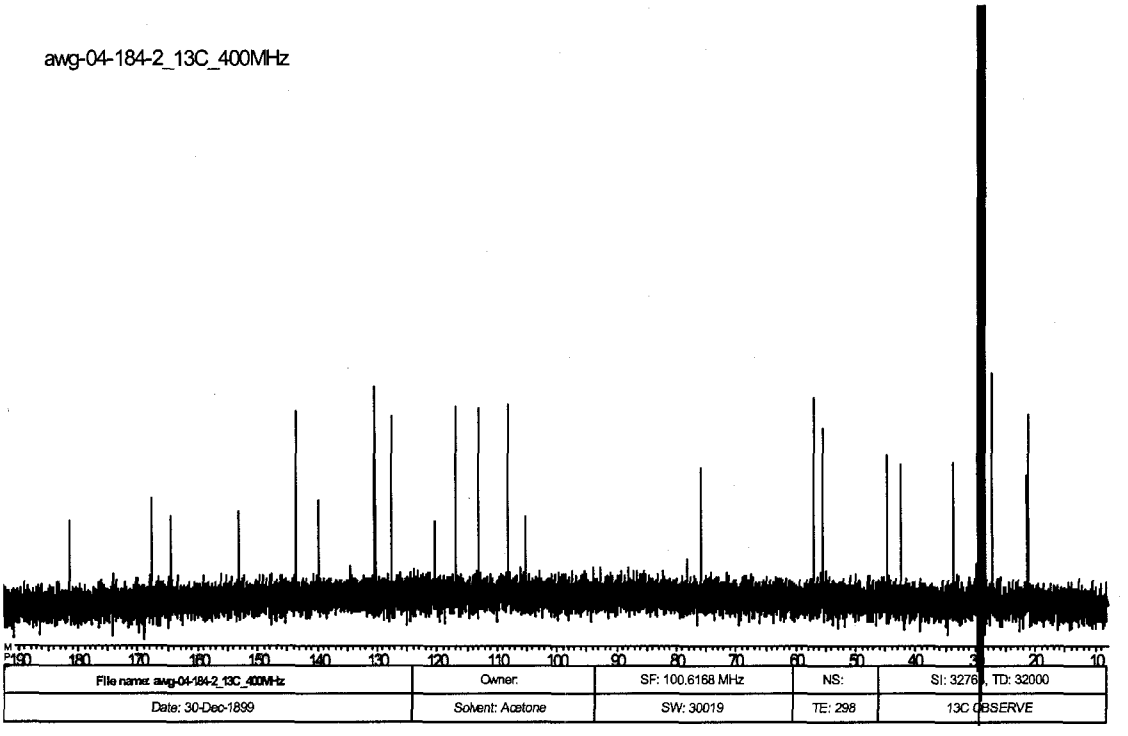
Date: 30-Dec-1899	Solvent: Acetone	SW: 6983	TE: 298	STANDARD 1H OBSERVE

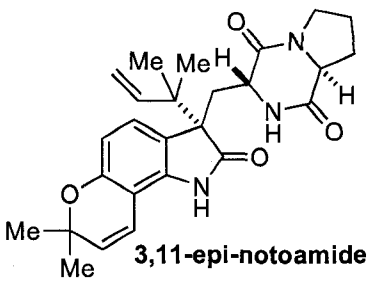


awg-04-184-2_13C_400MHz



File name: awg-04-184-2_13C_400MHz	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: Acetone	SW: 30019	TE: 298	13C OBSERVE

awg-04-184-1_400MHz



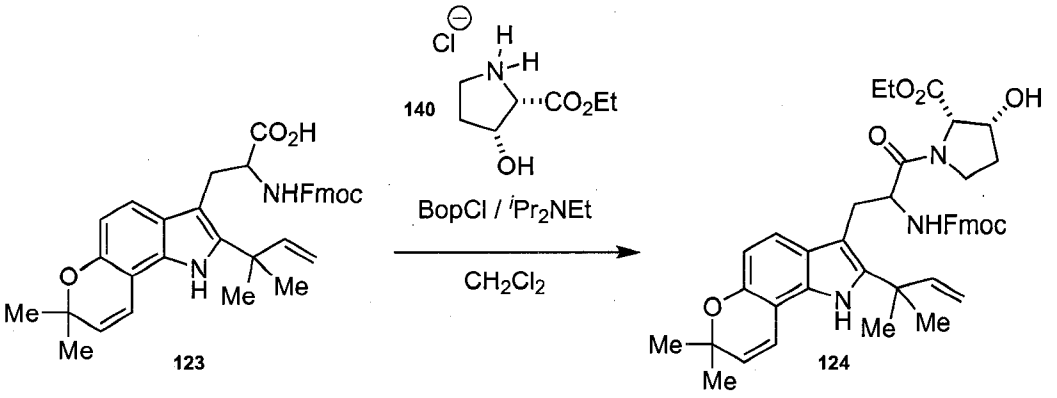
3,11-epi-notoamide C

File name: awg-04-184-1_400MHz	Owner:	SF: 400.1104 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: Acetone	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-184-1_13C_400MHz

File name: awg-04-184-1_13C_400MHz	Owner:	SF: 100.6168 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: Acetone	SW: 30019	TE: 298	13C OBSERVE

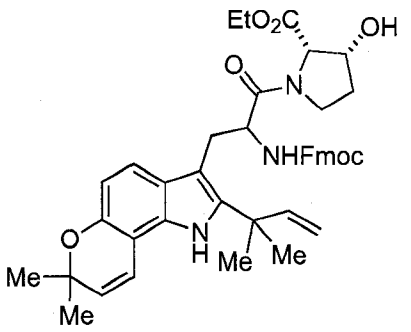
(2*S*,3*R*)-ethyl 1-(2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-*g*]indol-3-yl)propanoyl)-3-hydroxy-pyrrolidine-2-carboxylate (124)



To a solution of acid **123** (144mg, 0.323mmol) in 6.0 ml CH_2Cl_2 was added solid cis-3-hydroxy-L-proline ethyl ester hydrochloride **140** (95.0mg, 0.484mmol). The mixture was charged at 20°C with $^{i}Pr_2NEt$ (146mg, 1.13mmol). The mixture was stirred for ~ 1 hour until all solids dissolved and then BopCl (417mg, 1.64mmol) was added. The resulting solution was stirred overnight at ambient temperature and then partitioned between 10% citric acid and EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (20-50% EtOAc / hexanes) to afford (144mg, 62%) of the desired coupled product as a white foam. ^1H NMR (400 MHz, $CDCl_3$) (complex mixture of diastereomers) δ 1.02-1.20 (3.2H, m), 1.39-1.49 (7.44H, m), 1.51-1.64 (11.6H, m), 3.15-3.34 (1.95H, m), 3.92-4.03 (0.78H, m), 4.04-4.19 (3.50H, m), 4.22-4.34 (2.32H, m), 4.39 (0.2H, d, J = 7.3 Hz), 4.55-4.63 (1H, m), 5.16-5.24 (2H, m), 5.39 (1H, d, J = 8.1 Hz), 5.66 (1H, d, J = 9.8 Hz), 6.14 (1H, dd, J = 10.7 Hz, J = 17.3 Hz), 6.55 (1H, d, J = 9.8 Hz), 6.65 (1H, d, J = 8.5 Hz), 7.22-7.45 (9.82H, m), 7.48-7.57 (2.19H, m), 7.58-7.66 (0.66H, m), 7.67-7.83 (4.29H, m).

^{13}C NMR (100 MHz) ($CDCl_3$) δ 14.0, 14.4, 21.3, 22.9, 27.5, 27.6, 27.87, 27.92, 27.94, 28.7, 31.8, 39.4, 50.6, 53.6, 55.3, 60.6, 61.6, 65.4, 67.1, 67.6, 75.8, 104.7, 106.3, 110.6, 112.5, 117.1, 118.5, 120.1, 120.3, 124.9, 125.3, 125.4, 127.2, 127.3, 127.8, 129.8, 139.2, 141.4, 144.0, 144.1, 146.3, 148.8, 155.9, 170.6, 170.9, 172.9; HRMS-FAB: [M+H]+ calcd for $C_{42}H_{46}N_3O_6$, 688.3387; found, 688.3369.

awg-04-186-1_400MHz

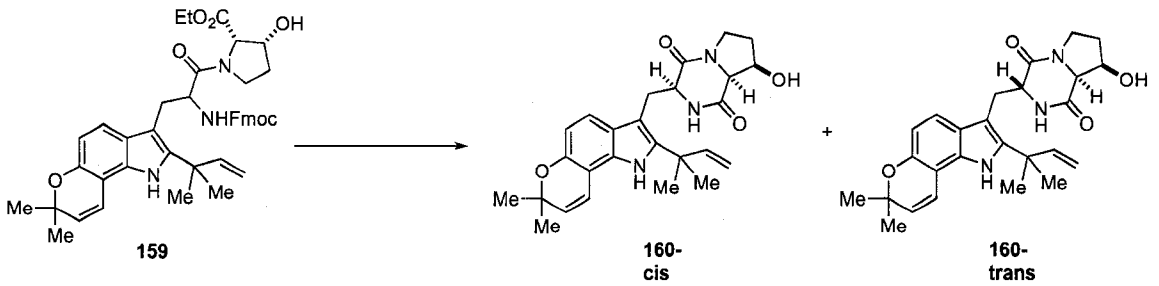


File name: awg-04-186-1_400MHz	Owner:	SF: 400.1083 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 6983	TE: 298	STANDARD 1H OBSERVE

awg-04-186-1_13C

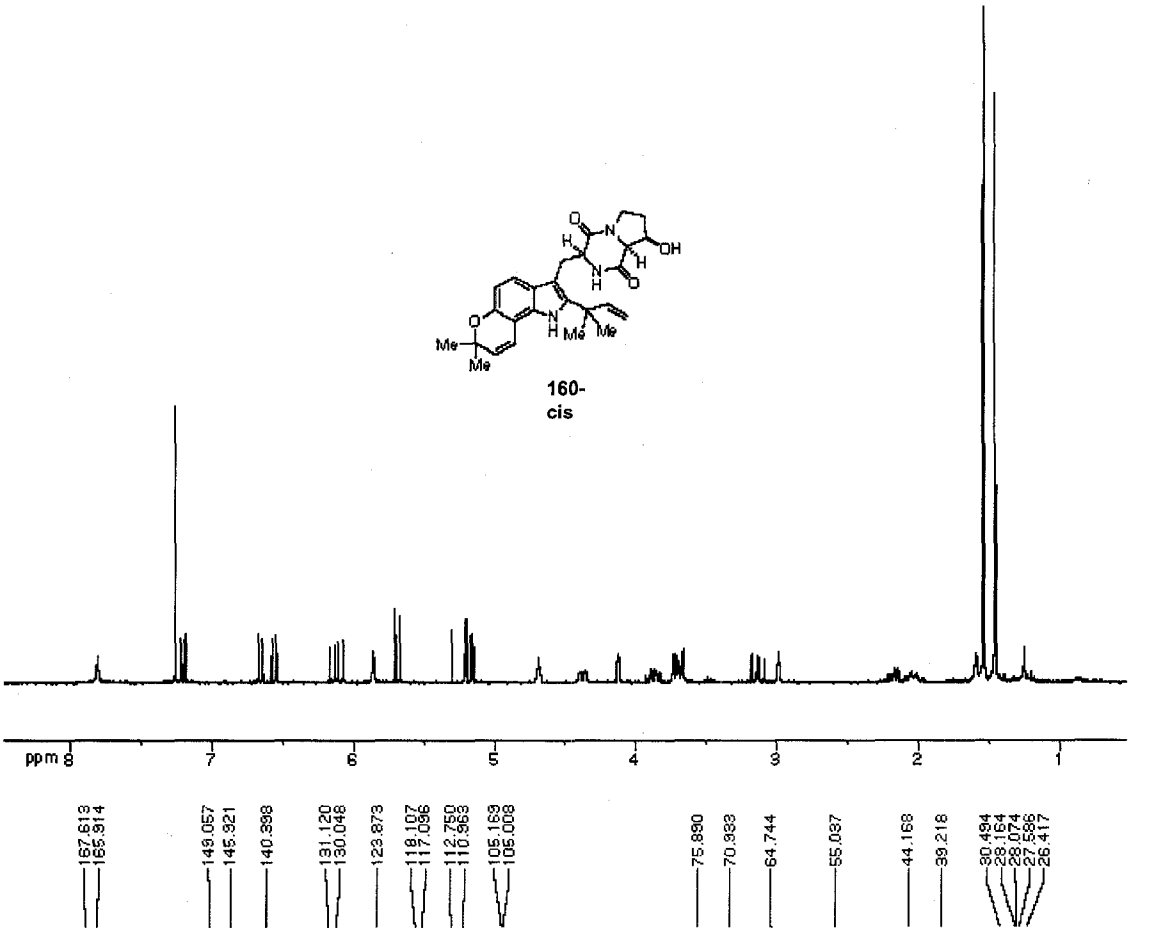
File name: awg-04-186-1_13C	Owner:	SF: 100.6163 MHz	NS:	SI: 32768, TD: 32000
Date: 30-Dec-1899	Solvent: CDCl3	SW: 30019	TE: 298	13C OBSERVE

(2S,3R)-ethyl-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-g]indol-3-yl)propanoyl)-3-hydroxy-pyrrolidine-2-carboxylate (159)



To a solution of amide **159** (500 mg, 0.70 mmol) in THF (28 mL) at rt was added morpholine (7 mL). The mixture was stirred at rt for 2 h. The resulting solution was concentrated to afford diketopiperazine **160** as a 1 : 1 mixture of diastereomers (298 mg, 95%). The mixture was separated by silica gel chromatography (MeOH : CH_2Cl_2, 3 : 97) for characterization purposes; Top diastereomer (**160-cis**) (Rf = 0.3, MeOH : CH_2Cl_2, 3 : 97) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6 H), 1.54 (s, 6 H), 2.04 (m, 1 H), 2.18 (dd, *J* = 7.7, 13.6 Hz, 1 H), 2.99 (s, 1 H), 3.13 (dd, *J* = 11.7, 15.3 Hz, 1 H), 3.65 - 3.75 (m, 2 H), 3.87 (m, 1 H), 4.12 (br t, *J* = 2.6 Hz, 1 H), 4.37 (br d, *J* = 11.7 Hz, 1 H), 4.69 (br t, *J* = 3.9 Hz, 1 H), 5.17 (d, *J* = 10.4 Hz, 1 H), 5.18 (d, *J* = 17.6 Hz, 1 H), 5.68 (d, *J* = 9.8 Hz, 1 H), 5.86 (s, 1 H), 6.12 (dd, *J* = 10.4, 17.6 Hz, 1 H), 6.56 (d, *J* = 9.8 Hz, 1 H), 6.65 (d, *J* = 8.5 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 1 H), 7.81 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 26.4, 27.6, 28.1, 28.2, 30.5, 39.2, 44.2, 55.0, 64.7, 70.9, 75.9, 105.0, 105.2, 111.0, 112.7, 117.1, 118.1, 123.9, 130.0, 131.1, 140.4, 145.9, 149.1, 165.9, 167.6; Bottom diastereomer (**160-trans**) (Rf = 0.25, MeOH : CH_2Cl_2, 3 : 97) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 6 H),

1.50 (s, 3 H), 1.51 (s, 3 H), 1.81 (m, 1 H), 2.03 (dd, J = 7.8, 13.9 Hz, 1 H), 2.84 (s, 1 H), 3.24 (dd, J = 8.7, 14.7 Hz, 1 H), 3.42 (dd, J = 4.1, 14.7 Hz, 1 H), 3.52 (br t, J = 11.6 Hz, 1 H), 3.60 (d, J = 3.1 Hz, 1 H), 3.82 (m, 1 H), 4.26 (p, J = 4.1 Hz, 1 H), 4.56 (t, J = 3.6 Hz, 1 H), 5.16 (dd, J = 1.0, 10.5 Hz, 1 H), 5.18 (dd, J = 1.0, 17.5 Hz, 1 H), 5.66 (d, J = 9.7 Hz, 1 H), 5.97 (d, J = 3.7 Hz, 1 H), 6.11 (dd, J = 10.5, 17.5 Hz, 1 H), 6.54 (d, J = 9.7 Hz, 1 H), 6.64 (d, J = 8.5 Hz, 1 H), 7.24 (d, J = 8.5 Hz, 1 H), 7.78 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 27.5, 27.6, 28.0, 28.1, 29.9, 30.0, 39.3, 44.3, 58.4, 63.9, 70.9, 75.9, 104.7, 105.4, 110.7, 112.0, 117.1, 118.9, 123.8, 130.0, 130.9, 140.4, 146.4, 148.9, 166.4, 167.6; IR (neat) 3357, 2970, 2928, 1652 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{26}H_{32}N_3O_4$ 450.2393, found 450.2372.


160-
cis
ppm 8
7
6
5
4
3
2
1
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165.914
149.057
145.321
140.398
131.120
130.048
123.873
118.107
117.096
112.750
110.963
105.169
105.008
75.890
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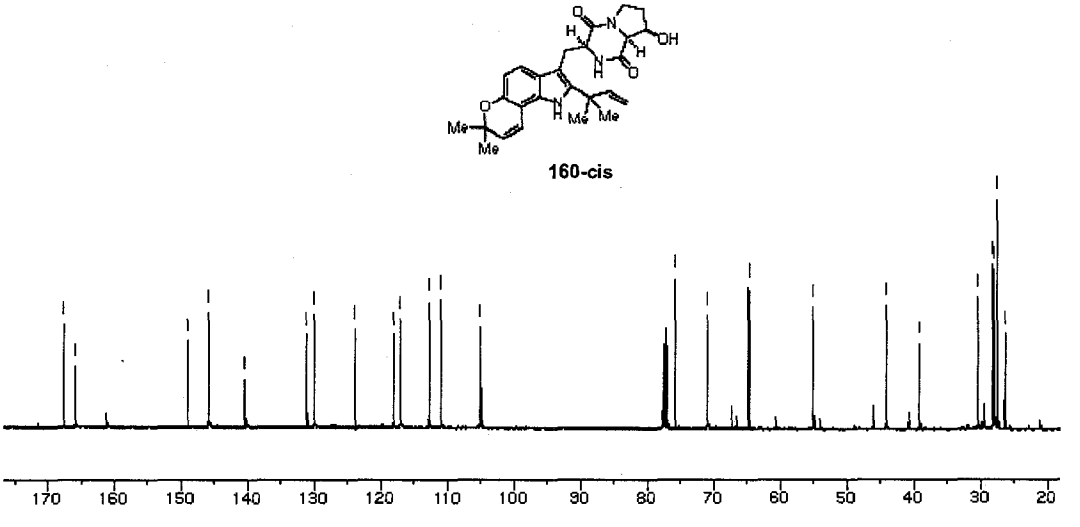
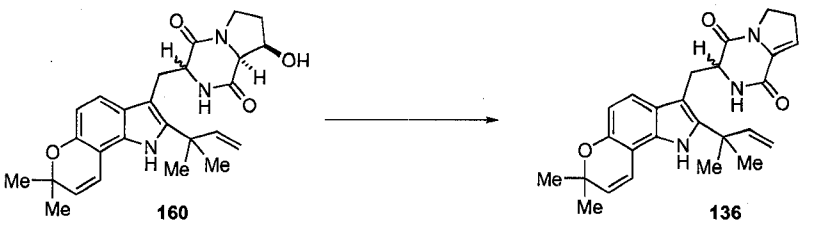
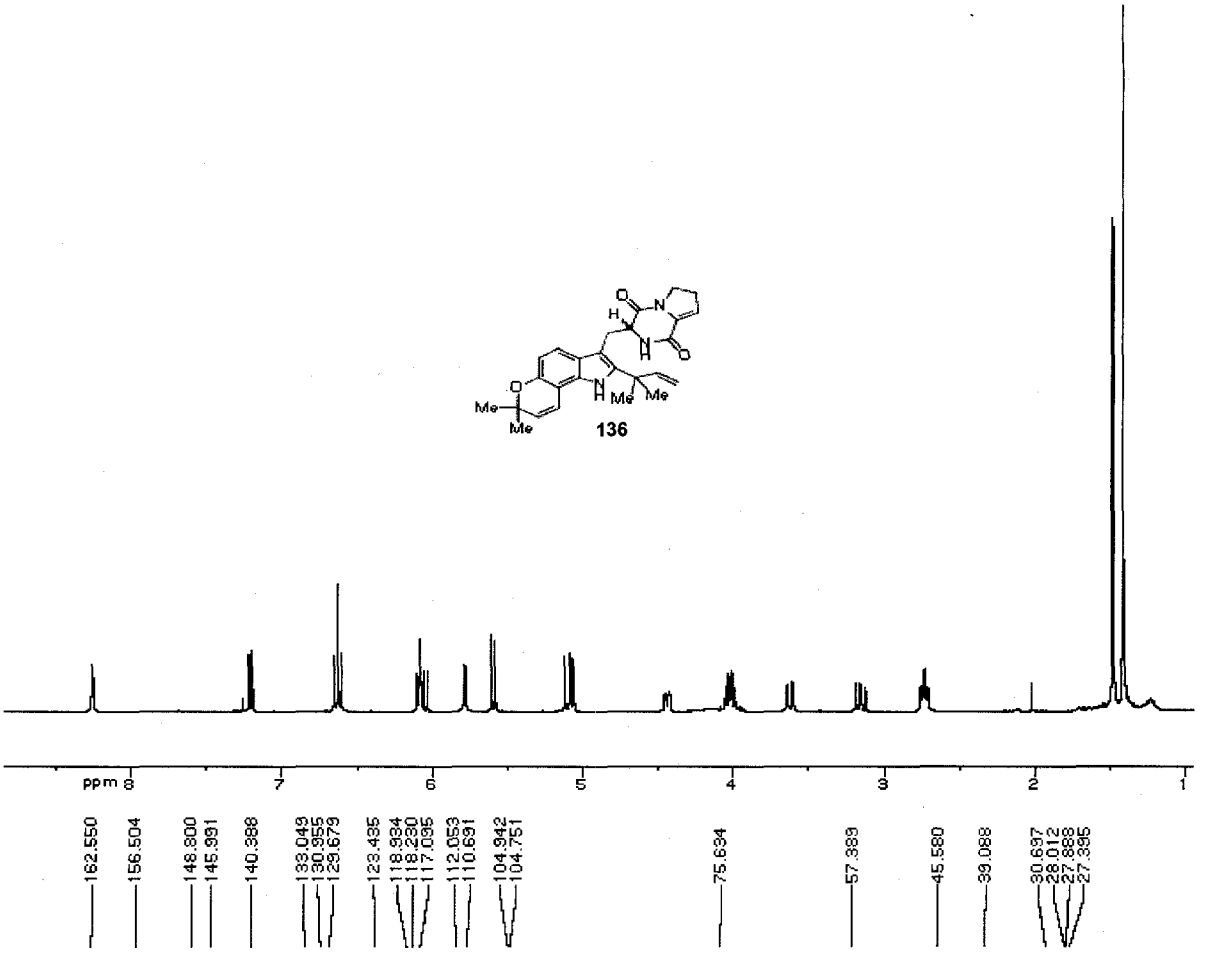
64.744
55.087
44.168
39.218
30.494
28.164
28.074
27.586
26.417


160-cis
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-g]indol-3-yl)methyl)-2,3,6,7-tetrahydropyrrolo[1,2-a]pyrazine-1,4-dione (136)



To a solution of alcohols **160** (175 mg, 0.39 mmol) in CH_2Cl_2 (6.5 ml) at rt was added DEAD (154 μl, 0.97mmol). The mixture was stirred at rt for 10 min and PBu_3 (243 μl, 0.97mmol) was then added. The solution was stirred at rt for 3 h. The resulting mixture was quenched with 10% aqueous citric acid and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate : hexane, 1 : 1 to 3 : 1) afforded enamide **136** as a colorless oil (153 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 6 H), 1.51 (s, 6 H), 2.76 (dt, *J* = 3.0, 9.0 Hz, 2 H), 3.15 (dd, *J* = 11.2, 14.5 Hz, 1 H), 3.64 (dd, *J* = 3.7, 14.5 Hz, 1 H), 4.00 - 4.09 (m, 2 H), 4.45 (br d, *J* = 11.2 Hz, 1 H), 5.12 (d, *J* = 10.5 Hz, 1 H), 5.13 (d, *J* = 17.4 Hz, 1 H), 5.63 (d, *J* = 9.7 Hz, 1 H), 5.71 (s, 1 H), 6.09 (dd, *J* = 10.5, 17.4 Hz, 1 H), 6.11 (t, *J* = 3.0 Hz, 1 H), 6.59 (d, *J* = 9.7 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 8.27 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 27.4, 27.9, 28.0, 30.7, 39.1, 45.6, 57.4, 75.6, 104.7, 104.9, 110.7, 112.1, 117.1, 118.2, 118.9, 123.4, 129.7, 131.0, 133.0, 140.4, 146.0, 148.8, 156.5, 162.5; IR (neat) 3359, 2969, 1676, 1644 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{26}H_{30}N_3O_3$ 432.2287, found 432.2273.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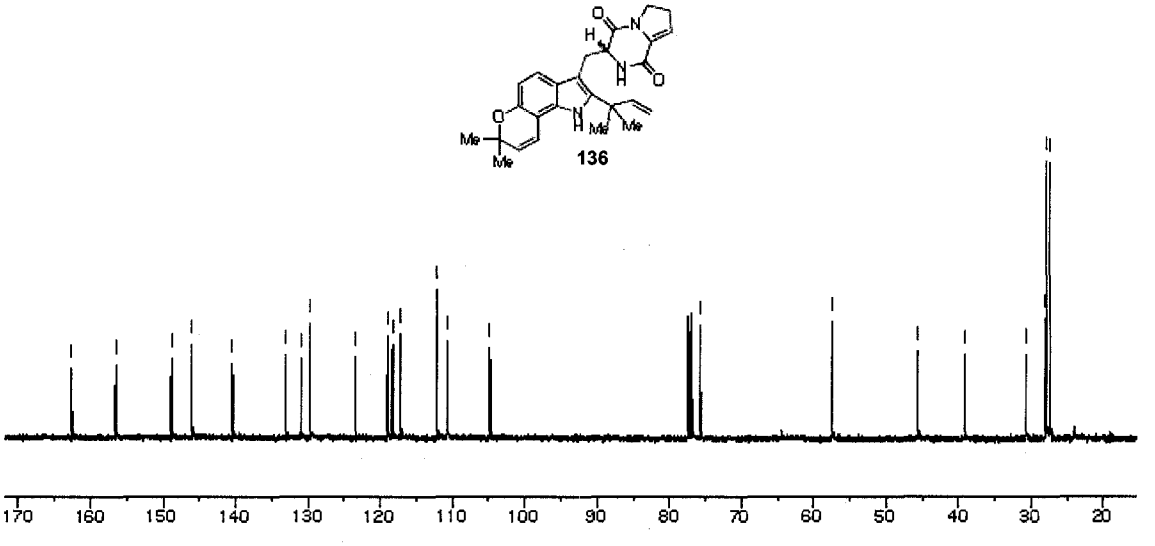
27.395


136
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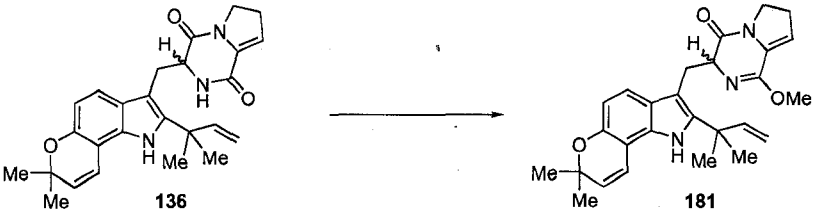
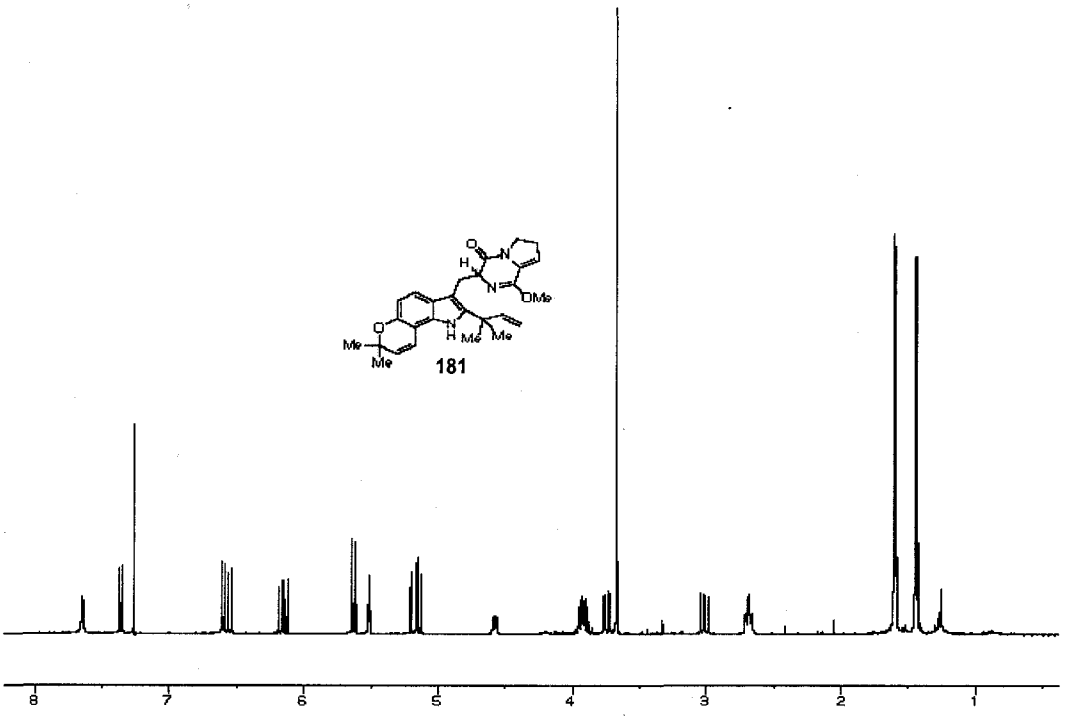
140
130
120
110
100
90
80
70
60
50
40
30
20

3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-g]indol-3-yl)methyl)-1-methoxy-6,7-dihydropyrrolo[1,2-a]pyrazin-4(3H)-one (181)



To a solution of enamide **136** (30.0 mg, 0.070 mmol) in CH_2Cl_2 (2 mL) at rt was added Cs_2CO_3 (567 mg, 1.74 mmol) and Me_3OBF_4 (51.5 mg, 0.35 mmol). The mixture was stirred at rt for 6 h. The resulting solution was quenched with iced water and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate : hexane, 1 : 1) afforded lactim ether **181** as a colorless oil (25.0 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 1.44 (s, 3 H), 1.59 (s, 3 H), 1.60 (s, 3 H), 2.68 (m, 2 H), 3.00 (dd, J = 9.4, 14.5 Hz, 1 H), 3.66 (s, 3 H), 3.74 (dd, J = 3.5, 14.5 Hz, 1 H), 3.86 - 3.96 (m, 2 H), 4.57 (br d, J = 9.4 Hz, 1 H), 5.13 (dd, J = 1.1, 10.5 Hz, 1 H), 5.17 (dd, J = 1.1, 17.4 Hz, 1 H), 5.51 (t, J = 3.0 Hz, 1 H), 5.62 (d, J = 9.7 Hz, 1 H), 6.15 (dd, J = 10.5, 17.4 Hz, 1 H), 6.54 (d, J = 9.7 Hz, 1 H), 6.59 (d, J = 8.5 Hz, 1 H), 7.35 (d, J = 8.5 Hz, 1 H), 7.63 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 27.3, 27.6, 27.9, 28.1, 31.6, 39.5, 44.5, 53.2, 64.8, 75.6, 104.4, 108.7, 109.7, 110.8, 112.0, 117.3, 120.2, 125.2, 129.3, 130.3, 130.6, 138.7, 146.5, 148.4, 151.5, 167.0; IR (neat) 3350, 2924, 1716, 1680, 1625 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{32}N_3O_3$ 446.2444, found 446.2440.


181
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7
6
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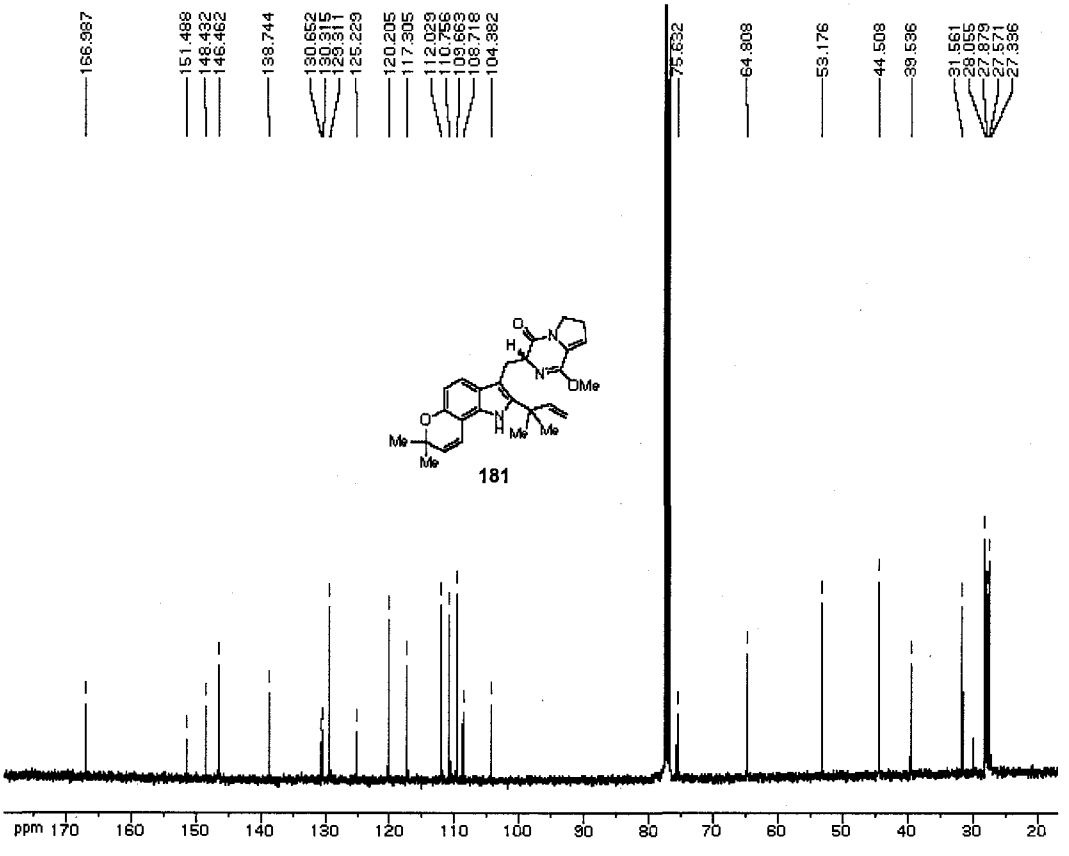
4
3
2
1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75.632
64.808
53.176
44.508
39.536
31.561
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27.571
27.336
181
ppm 170
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80
70
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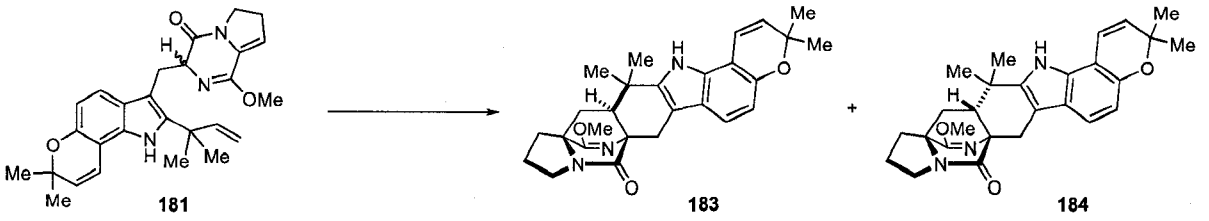
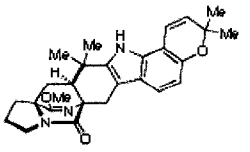
50
40
30
20

Diels-Alder Adducts (22) and (23)

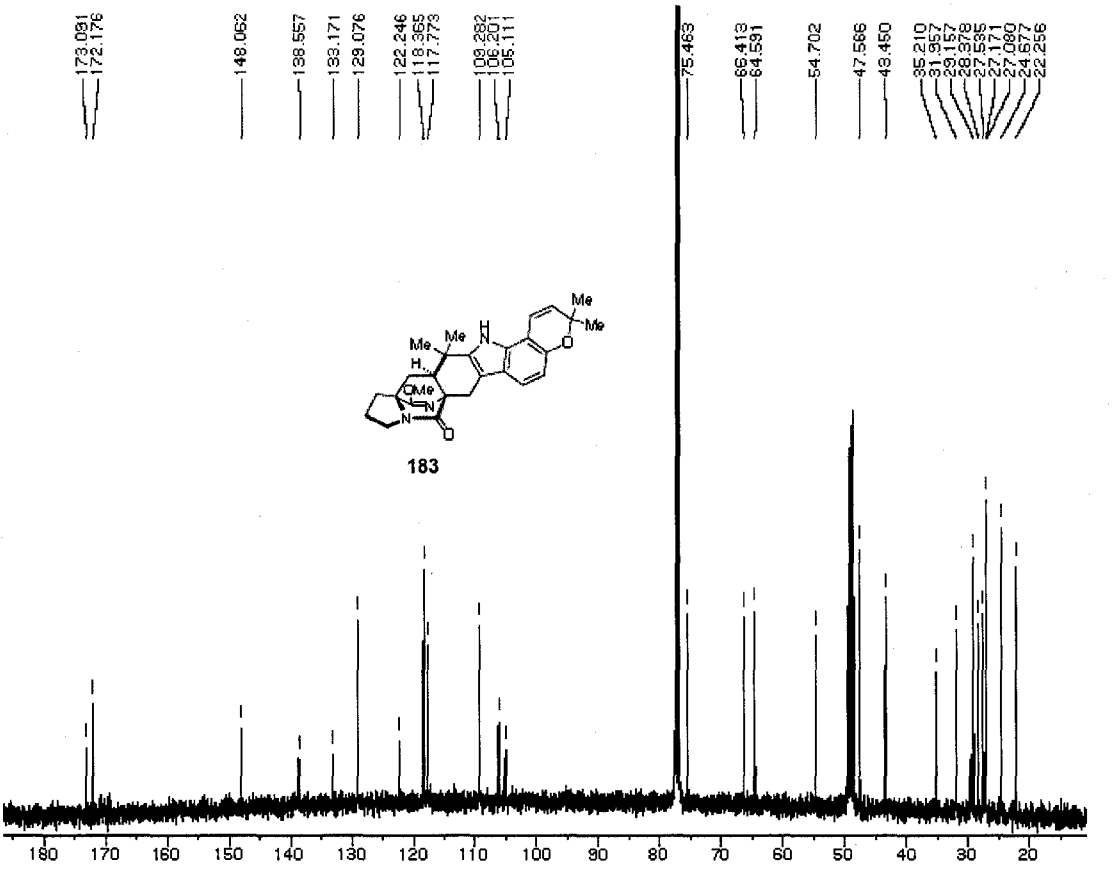


To a solution of lactim ether **181** (25.0 mg, 0.056 mmol) in MeOH (4 mL) at 0 °C was added 20% aqueous KOH (1 mL). The mixture was slowly warmed to rt over 1 h and stirred for 6 h. The resulting solution was neutralized to pH 7 with dropwise addition of saturated aqueous KH_2PO_4. The solution was diluted with H_2O and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (MeOH : CH_2Cl_2, 3 : 97) afforded *syn* cycloadduct **183** as a colorless oil (15.3 mg, 61%) along with *anti* cycloadduct **184** as a colorless oil (6.3 mg, 25%); *syn* Cycloadduct **183**: ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD, 8 : 1) δ 0.97 (s, 3 H), 1.21 (s, 3 H), 1.35 (s, 6 H), 1.73 (dd, J = 4.9, 12.9 Hz, 1 H), 1.84 - 1.98 (m, 4 H), 2.18 (dd, J = 4.9, 10.2 Hz, 1 H), 2.59 (m, 1 H), 2.97 (d, J = 16.0 Hz, 1 H), 3.25 (m, 1 H), 3.38 (m, 1 H), 3.72 (s, 3 H), 3.78 (d, J = 16.0 Hz, 1 H), 5.53 (d, J = 9.7 Hz, 1 H), 6.52 (d, J = 8.3 Hz, 1 H), 6.65 (d, J = 9.7 Hz, 1 H), 7.18 (d, J = 8.3 Hz, 1 H), 8.92 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$: CD_3OD, 8 : 1) δ 22.3, 24.7, 27.1, 27.2, 27.5, 28.4, 29.2, 32.0, 35.2, 43.4, 47.6, 54.7, 64.6, 66.4, 75.5, 105.1, 106.2, 109.3, 117.8, 118.4, 122.2, 129.1, 133.2, 138.6, 148.1, 172.2, 173.1; IR (neat) 3336, 2921, 1663 cm^{-1}; FAB-HRMS (M^+) calcd for $C_{27}H_{31}N_3O_3$ 445.2365, found 445.2353. *anti* Cycloadduct **184**: ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.16 (s, 3 H), 1.26 (s, 3 H), 1.44 (s, 3 H), 1.45 (s, 3 H), 1.81 (dd, J = 4.1, 12.7

Hz, 1 H),1.89 - 2.05 (m, 4 H), 2.33 (dd, J = 4.1, 9.6 Hz, 1 H), 2.67 (m, 1 H), 3.23 (d, J = 17.2 Hz, 1 H), 3.43 - 3.53 (m, 2 H), 3.70 (s, 3 H), 3.86 (d, J = 17.2 Hz, 1 H), 5.65 (d, J = 9.6 Hz, 1 H), 6.57 (d, J = 9.6 Hz, 1 H), 6.65 (d, J = 8.4, 1 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.56 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 24.9, 25.4, 26.2, 27.4, 27.5, 28.7, 29.3, 33.7, 35.1, 43.7, 45.9, 54.4, 64.3, 67.5, 75.6, 105.0, 106.9, 110.0, 117.4, 119.1, 123.0, 129.6, 132.9, 138.5, 148.7, 170.6, 172.3; IR (neat) 3286, 2967, 1662, 1635 cm^{-1}; FAB-HRMS (M^+) calcd for $C_{27}H_{31}N_3O_3$ 445.2365, found 445.2372.



183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47.566
43.450
35.210
31.957
29.157
28.378
27.595
27.171
27.080
24.677
22.256
Me
Me
Me
Me
H
OMe
N
N
O
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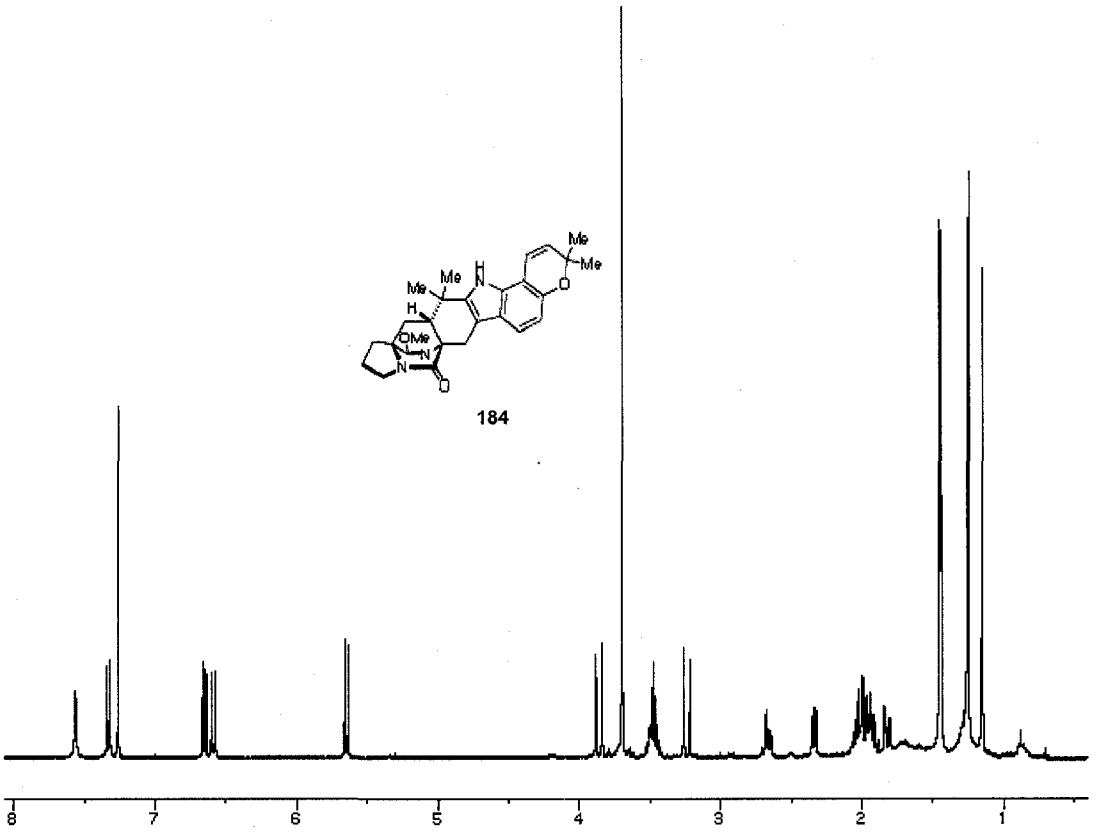
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H
OMe
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N
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O
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8
7
6
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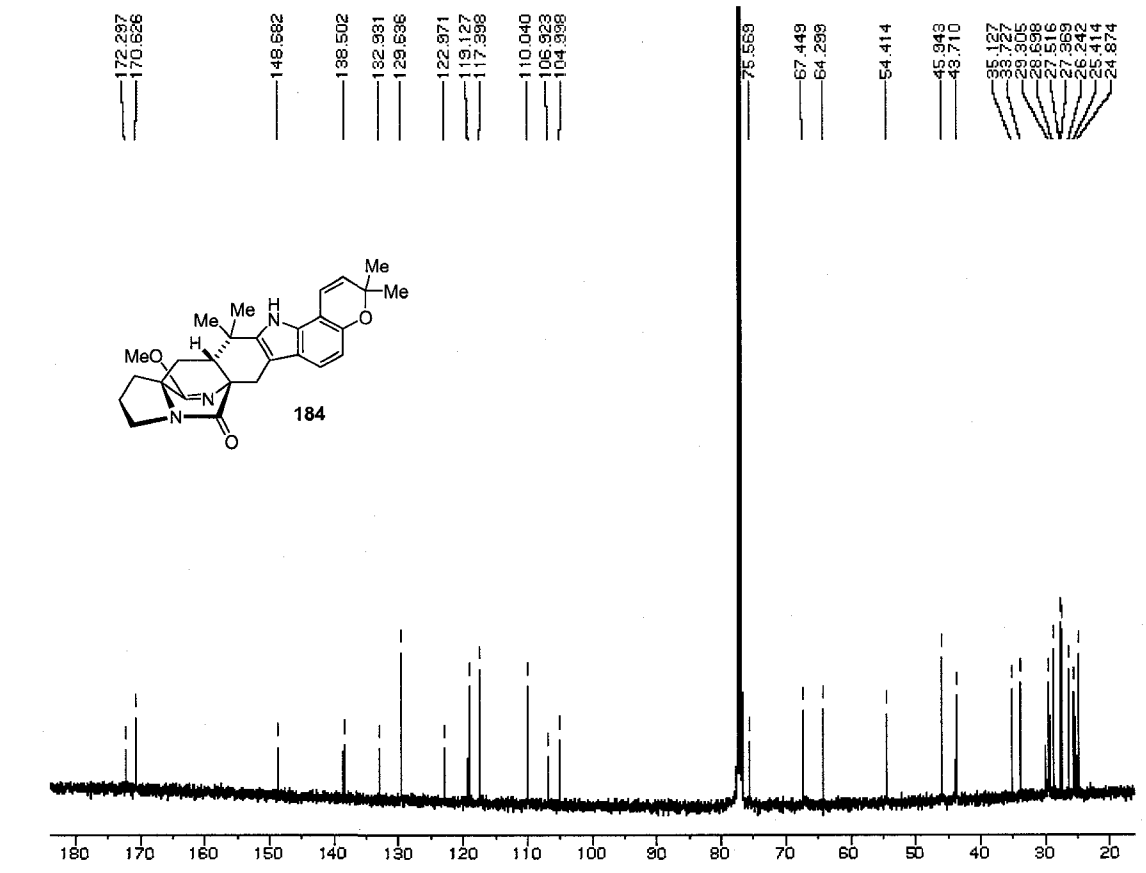
2
1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27.369
26.242
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Me
Me
Me
Me
H
N
O
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N
N
O
184
180
170
160
150
140
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120
110
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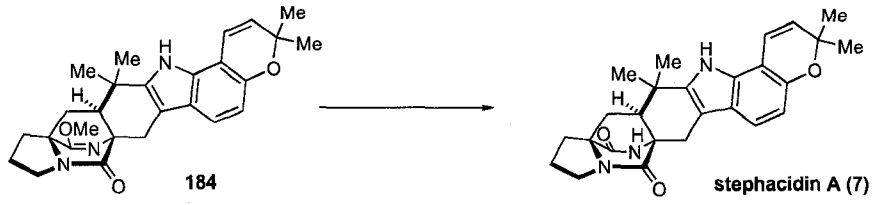
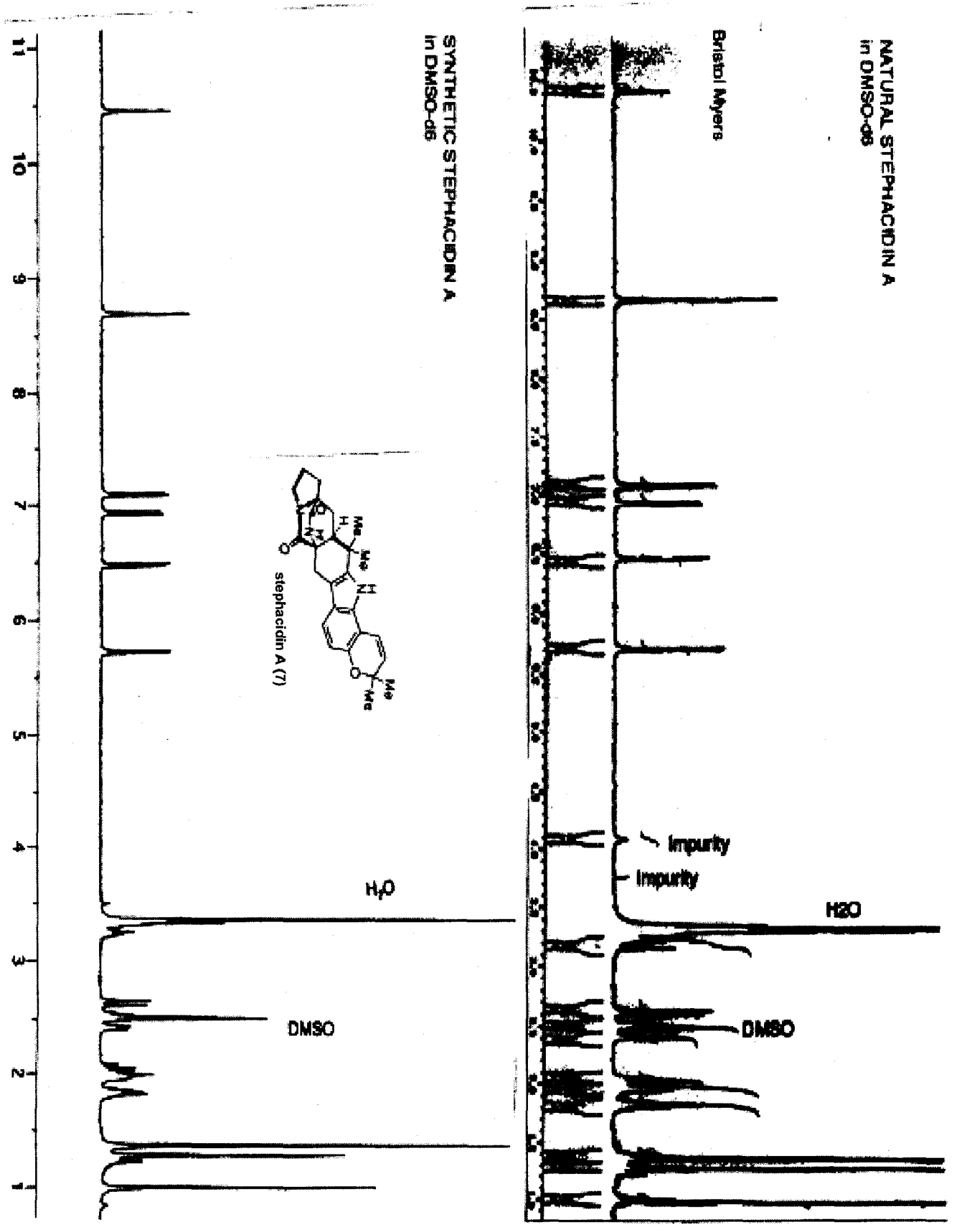
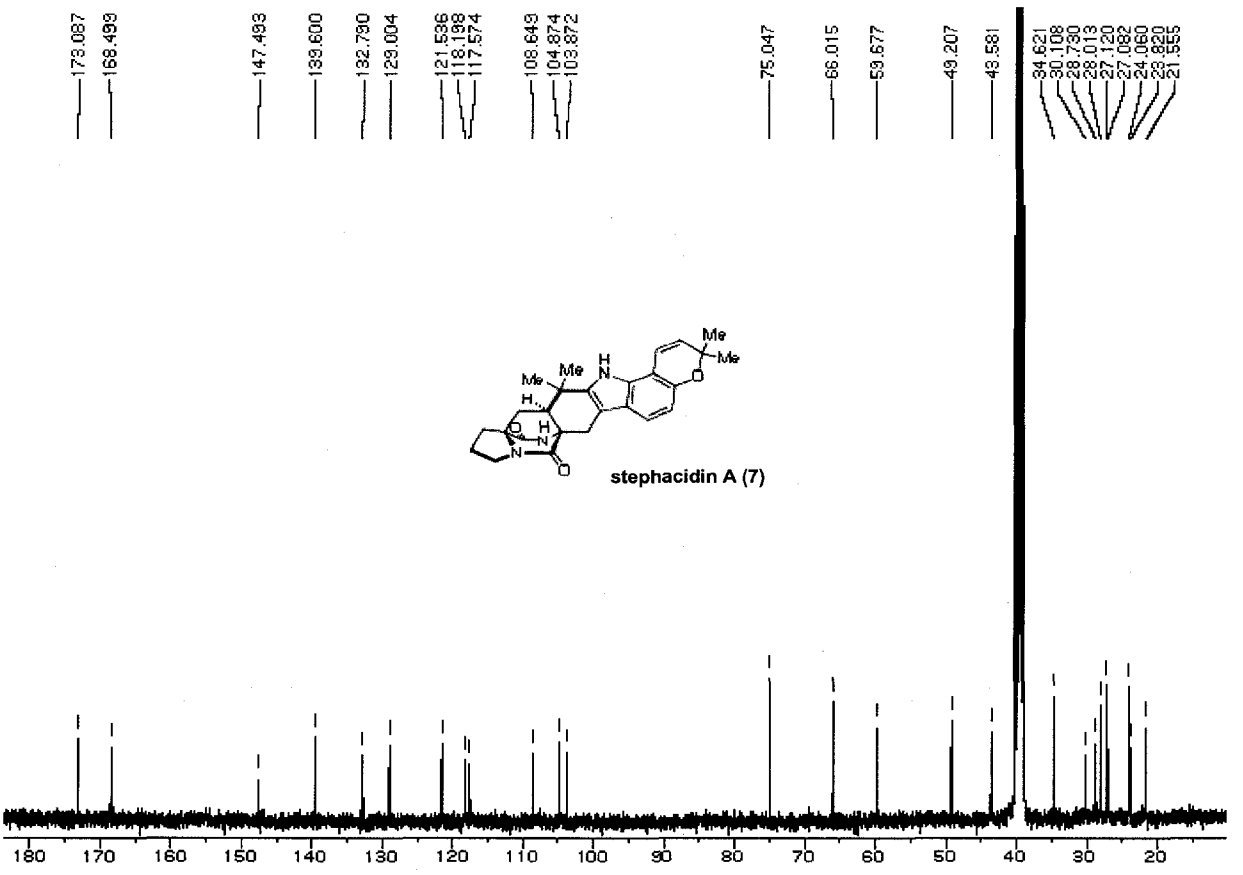
80
70
60
50
40
30
20

Stephacidin A (7)

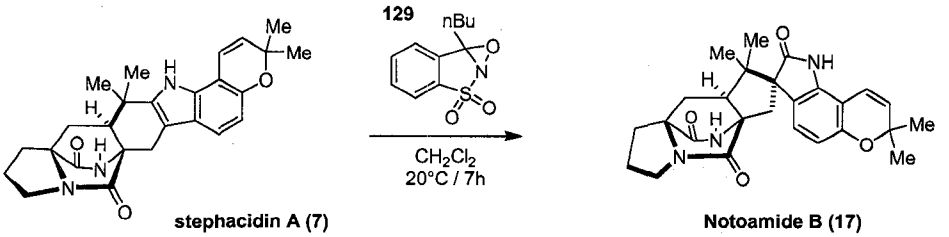


To a solution of lactim ether **184** (14.0 mg, 0.031 mmol) in THF (3.1 mL) at 0 °C was added 0.1 M aqueous HCl (943 μL). The mixture was stirred at 0 °C for 5 min. The resulting solution was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. The resulting residue was triturated with hexanes to afford stephacidin (**7**) as a white solid (13.1 mg, 96%); ^{1}H NMR (400 MHz, d^6-DMSO) δ 0.95 (s, 3 H), 1.23 (s, 3 H), 1.31 (s, 3 H), 1.32 (s, 3 H), 1.74 - 1.84 (m, 2 H), 1.88 - 1.97 (m, 2 H), 2.00 (dd, J = 9.9, 14.0 Hz, 1 H), 2.37 (dd, J = 4.9, 9.9 Hz, 1 H), 2.48 (m, 1 H), 2.58 (d, J = 15.6 Hz, 1 H), 3.20 (m, 1 H), 3.26 (m, 1 H), 3.29 (d, J = 15.6 Hz, 1 H), 5.67 (d, J = 9.8 Hz, 1 H), 6.42 (d, J = 8.3 Hz, 1 H), 6.88 (d, J = 9.8 Hz, 1 H), 7.04 (d, J = 8.3 Hz, 1 H), 8.64 (s, 1 H), 10.40 (s, 1 H); ^{13}C NMR (100 MHz, d^6-DMSO) δ 21.6, 23.8, 24.1, 27.08, 27.12, 28.0, 28.7, 30.1, 34.6, 43.6, 49.2, 59.7, 66.0, 75.0, 103.9, 104.9, 108.7, 117.6, 118.2, 121.5, 129.0, 132.8, 139.6, 147.5, 168.5, 173.1; IR (neat) 3324, 2924, 1696, 1674 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{26}H_{30}N_3O_3$ 432.2287, found 432.2282.

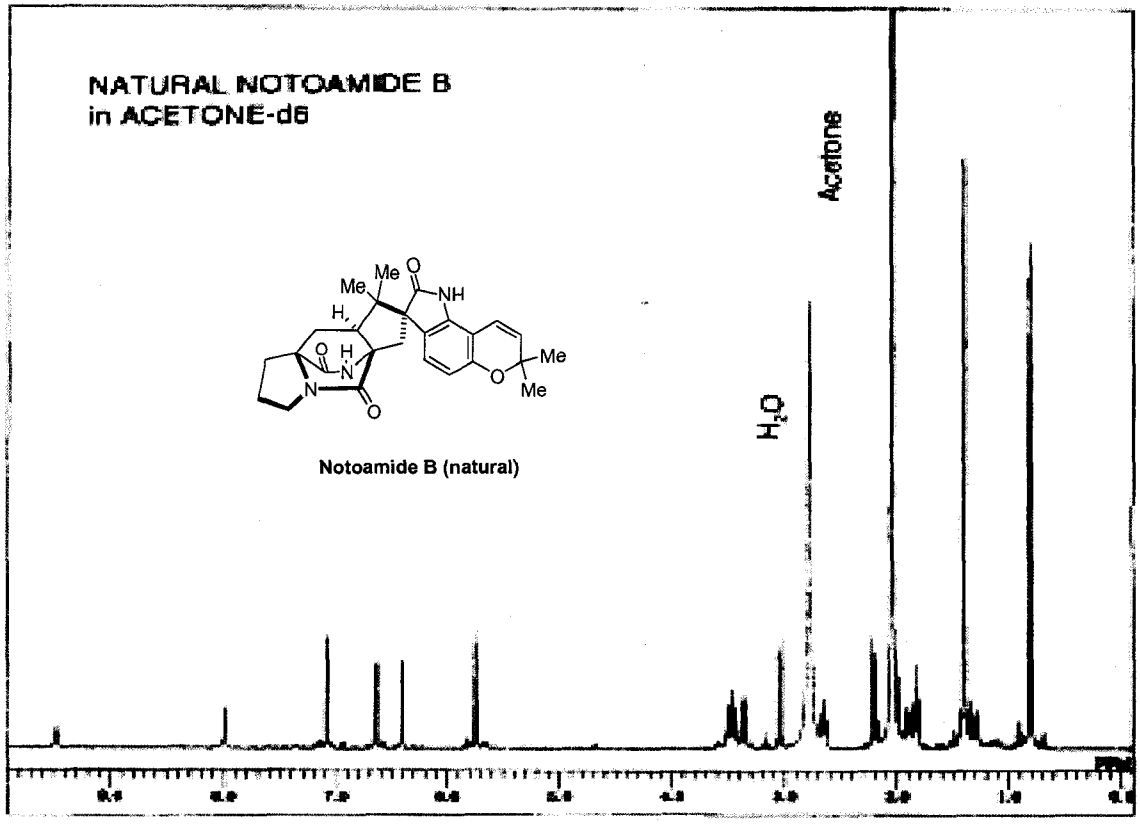

NATURAL STEPHACIDIN A
in DMSO-d6
Bristol Myers
Impurity
Impurity
H2O
DMSO
SYNTHETIC STEPHACIDIN A
in DMSO-d6
stephacidin A (7)
H2O
DMSO

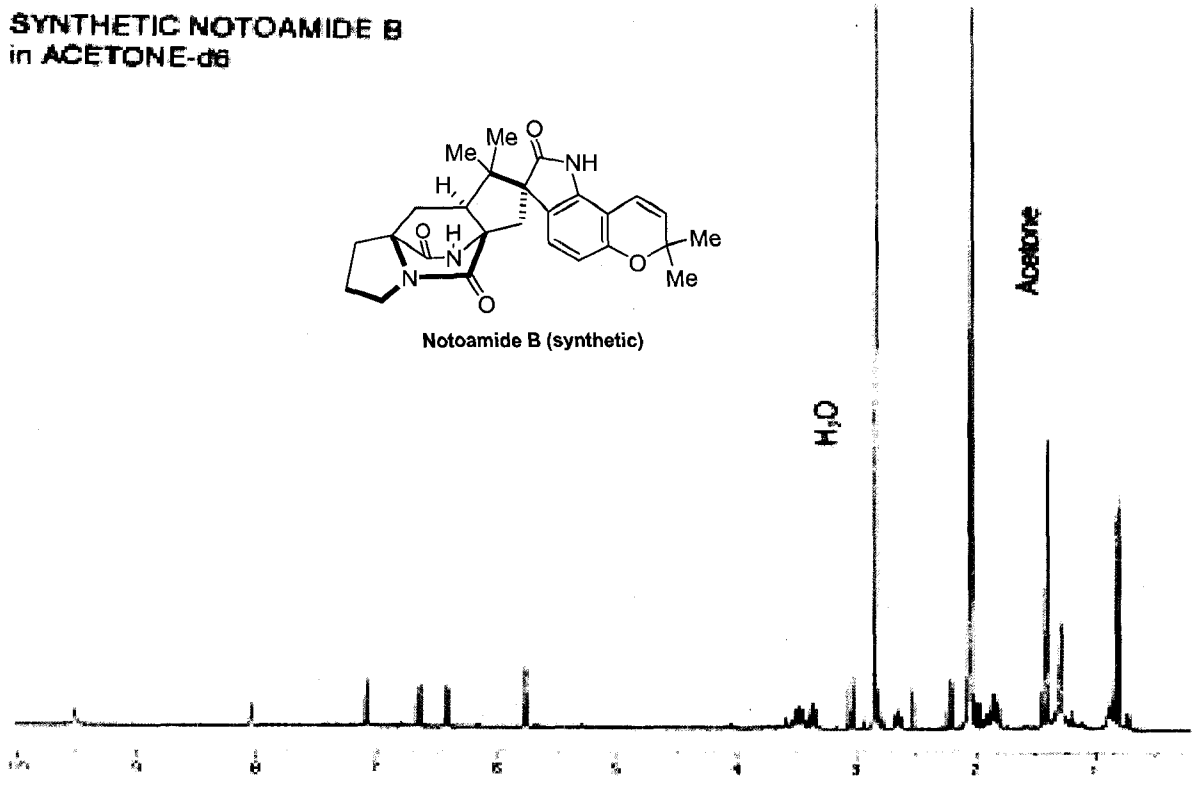

173.087
168.493
147.493
139.600
132.780
129.004
121.536
118.198
117.574
108.643
104.874
103.872
75.047
66.015
59.677
49.207
43.581
34.621
30.108
28.730
28.013
27.120
27.082
24.060
23.820
21.555
Me
Me
Me
Me
H
H
O
N
N
O
stephacidin A (7)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

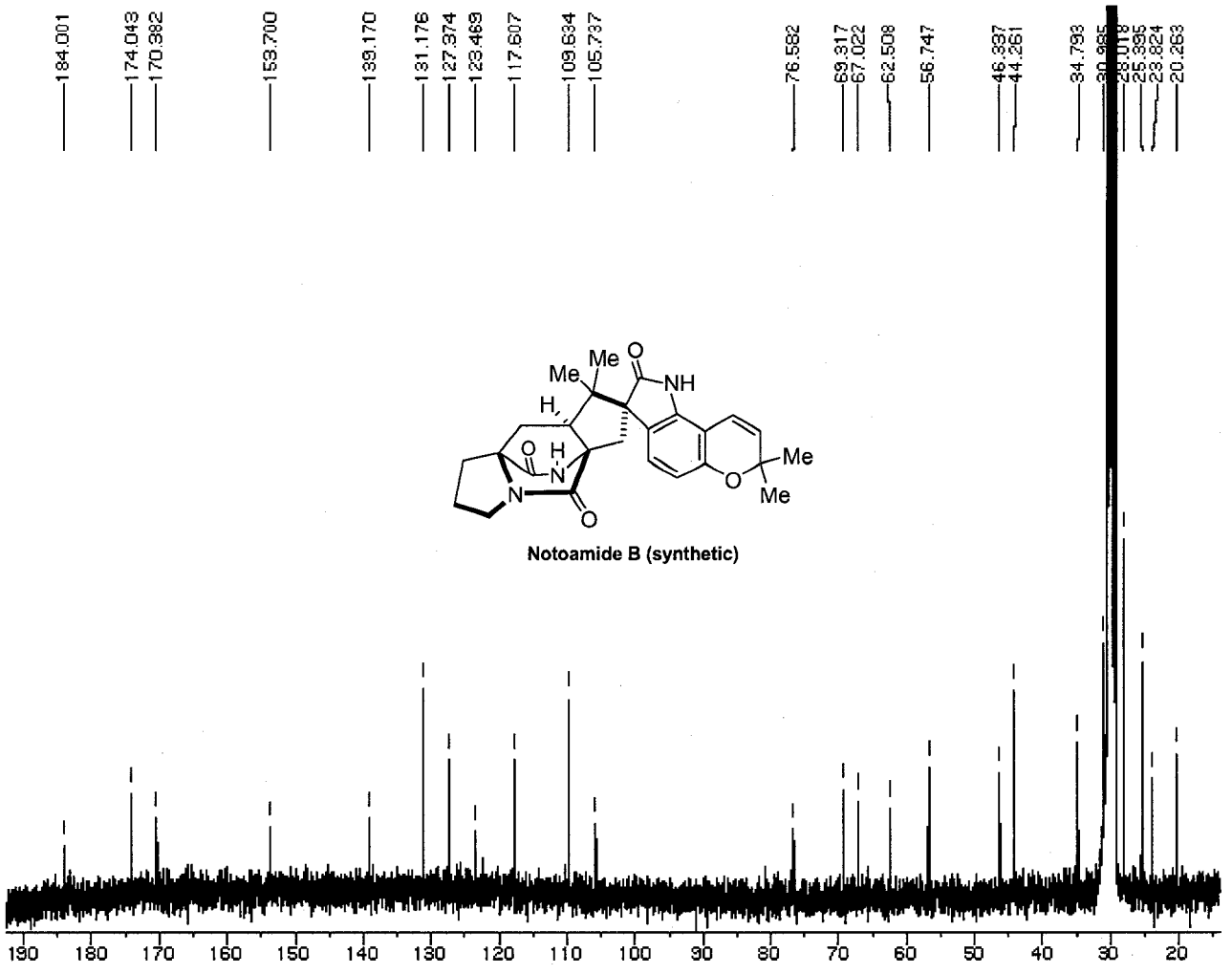
Notoamide B (17)



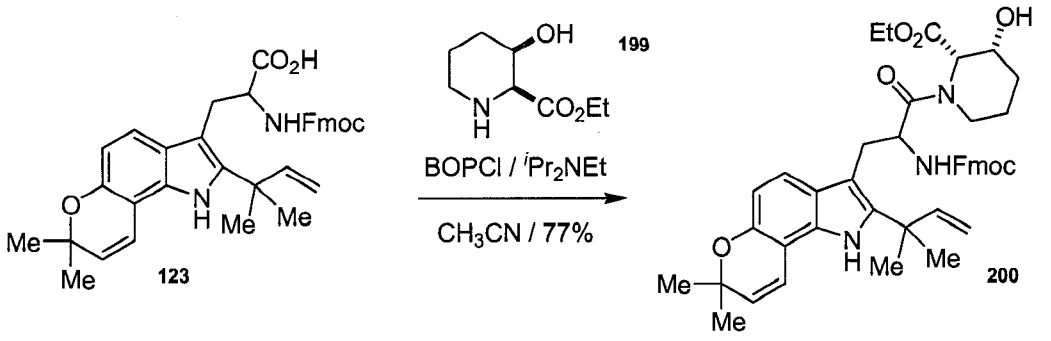
To a suspension of stephacidin A (**7**) (5.0 mg, 0.012 mmol) in CH_2Cl_2 (1.5 mL) at rt was added oxaziridine **129** (8.3 mg, 0.035 mmol). The mixture was stirred at rt for 16 h until all solids were dissolved. The resulting solution was placed directly on a column of silica gel and eluted with CH_2Cl_2, followed by MeOH : CH_2Cl_2 (5 : 95) to afford notoamide B (**17**) (Rf = 0.4, MeOH : CH_2Cl_2, 5 : 95) as a thin film (3.8 mg, 73%); ^{1}H NMR (400 MHz, d^6-acetone) δ 0.80 (s, 3 H), 0.83 (s, 3 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 1.80 - 2.02 (m, 5 H), 2.21 (d, *J* = 14.4 Hz, 1 H), 2.65 (m, 1 H), 3.04 (d, *J* = 14.4 Hz, 1 H), 3.36 (dd, *J* = 8.3, 10.3 Hz, 1 H), 3.42 - 3.54 (m, 2 H), 5.75 (d, *J* = 9.9 Hz, 1 H), 6.41 (d, *J* = 8.5 Hz, 1 H), 6.64 (d, *J* = 9.9 Hz, 1 H), 7.08 (d, *J* = 8.5 Hz, 1 H), 8.02 (br s, 1 H), 9.50 (br s, 1 H); ^{13}C NMR (100 MHz, d^6-acetone) δ 20.3, 23.8, 25.4, 28.0, 31.0, 34.8, 44.3, 46.3, 56.7, 62.5, 67.0, 69.3, 76.6, 105.7, 109.6, 117.6, 123.5, 127.4, 131.2, 139.2, 153.7, 170.4, 174.0, 184.0; IR (neat) 3225, 2923, 1696, cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{26}H_{30}N_3O_4$ 448.2236, found 448.2226.


NATURAL NOTOAMIDE B
in ACETONE-d6
Acetone
H2O
Notoamide B (natural)


SYNTHETIC NOTOAMIDE B
in ACETONE-d6
Acetone
H2O
Notoamide B (synthetic)


184.001
174.043
170.382
153.700
139.170
131.176
127.374
123.469
117.607
109.634
105.737
76.582
69.317
67.022
62.508
56.747
46.337
44.261
34.793
30.985
28.018
25.395
23.824
20.263
Me
Me
H
O
NH
O
H
N
N
O
Me
O
Me
Notoamide B (synthetic)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

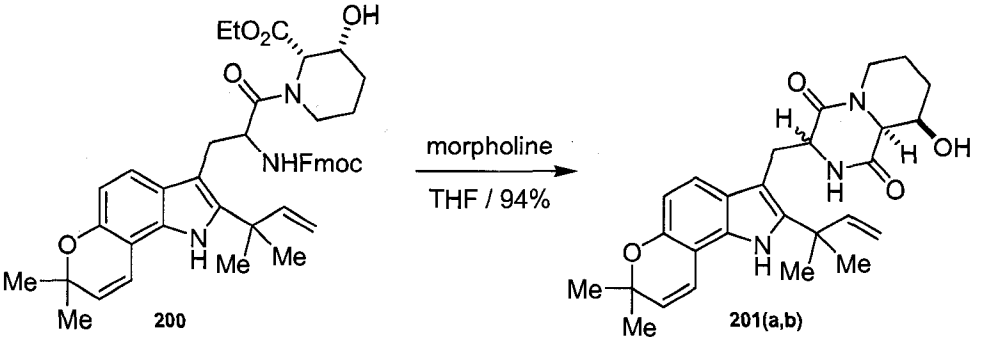
(2S,3R)-ethyl-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-(7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-g]indol-3-yl)propanoyl)-3-hydroxy-piperidine-2-carboxylate (200)



To a solution of acid **123**, (230 mg, 0.40 mmol) in CH_3CN was added HATU (228 mg, 0.60 mmol), $^iPr_2NEt$ (209 μL, 1.20 mmol), and *cis*-3-hydroxypipecolic acid ethyl ester (**199**) successively at rt. The mixture was stirred at rt for 3 h. The resulting solution was quenched with 1 M aqueous HCl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate : hexane, 2 : 3) afforded amide **200** as a mixture of diastereomers and amide rotamers (225 mg, 77%); 1H NMR (400 MHz, CDCl3) δ 1.12 - 1.24 (m, 3 H), 1.40 (s, 3 H), 1.45 (s, 3 H), 1.64 (s, 3 H), 1.66 (s, 3 H), 1.70-1.77 (m, 2 H), 2.20 (m, 1 H), 2.75 (m, 1 H), 3.08 - 3.47 (m, 4 H), 3.72 (m, 1 H), 4.05 - 4.29 (m, 3 H), 4.33 - 4.49 (m, 3 H), 5.05 (m, 1 H), 5.21 (d, J = 10.4 Hz, 1 H), 5.27 (d, J = 17.4 Hz, 1 H), 5.65 (d, J = 9.7 Hz, 1 H), 6.00 (d, J = 8.1 Hz, 1 H), 6.26 (dd, J = 10.4, 17.4 Hz, 1 H), 6.58 (d, J = 9.7 Hz, 1 H), 6.67 (m, 1 H), 7.25 - 7.45 (m, 5 H), 7.60 - 7.65 (m, 2 H), 7.70 - 7.80 (m, 2 H), 7.95 (s, 1 H); 13C NMR (100 MHz, CDCl3) δ 13.9, 14.1, 14.2, 21.9, 22.3, 26.6, 27.4, 27.5, 27.6, 27.8, 29.3, 29.5, 29.6, 30.8, 30.9, 38.9, 39.2, 42.8, 43.1, 47.2, 50.8, 51.2, 53.9, 55.6, 59.1, 61.7, 62.0,

67.9, 68.0, 68.4, 75.6, 104.7, 105.5, 105.8, 110.7, 110.8, 112.5, 112.8, 117.0, 117.2, 118.7, 120.0, 125.0, 125.1,125.2, 127.1, 127.8, 129.8, 130.0, 130.2, 130.3, 139.1, 139.6, 141.3, 143.82, 143.88, 143.9, 145.6, 146.4, 148.8, 155.4, 155.6, 170.4, 170.8, 172.2, 172.7; IR (neat) 3370, 2972, 1720, 1638 cm-1; FAB-HRMS (MH+) calcd for $C_{44}H_{50}N_3O_7$ 732.3649, found 732.3622.

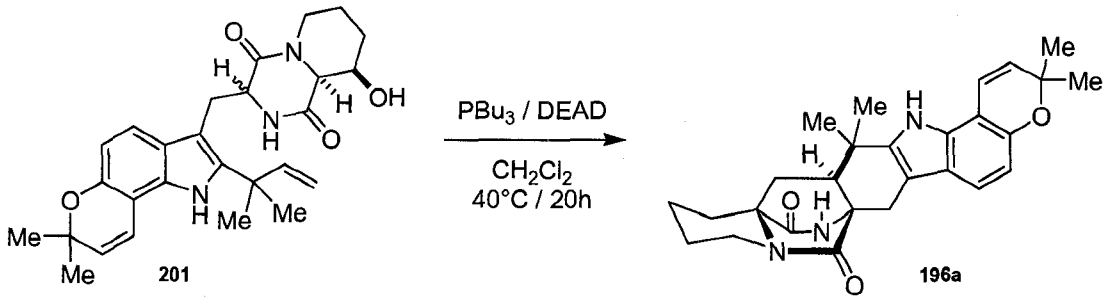
(8R,8aS)-3-((7,7-dimethyl-2-(2-methylbut-3-en-2-yl)-1,7-dihydropyrano[2,3-g]indol-3-yl)methyl)-8-hydroxy-octahydronaphthalene-1,4-dione (201)



To a solution of amide **200** (225mg, 0.31 mmol) in THF (12 mL) at rt was added morpholine (3 mL). The mixture was stirred at rt for 2 h. The resulting solution was concentrated to afford the crude diketopiperazine **201** as a mixture of diastereomers. The inseparable mixture of diastereomers was purified by silica gel chromatography (ethyl acetate) to afford diketopiperazines **201 a** and **b** as a yellow gum (134 mg, 94%); 1H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.41 (s, 3 H), 1.47 (s, 3 H), 1.50 (s, 3 H), 1.68 (m, 1 H), 1.85 - 1.96 (m, 2 H), 2.50 (m, 1 H), 2.63 (m, 1 H), 3.06 (**a**) (dd, J = 11.4, 14.4 Hz, 1 H), 3.25 (**b**) (dd, J = 11.4, 14.4 Hz, 1 H), 3.66 (dd, J = 2.9, 14.4 Hz, 1 H), 3.80 (**a**)

(s, 1 H), 3.85 (**b**) (s, 1 H), 4.25 (m, 1 H), 4.39 (m, 1 H), 4.67 (m, 1 H), 5.09 - 5.15 (m, 2 H), 5.62 (**b**) (d, J = 9.7 Hz, 1 H), 5.63 (**a**) (d, J = 9.7 Hz, 1 H), 5.80 (**a**) (s, 1 H), 5.90 (**b**) (s, 1 H), 6.07 (**a**) (dd, J = 10.4, 17.4 Hz, 1 H), 6.09 (**b**) (dd, J = 10.4, 17.4 Hz, 1 H), 6.58 (d, J = 9.7 Hz, 1 H), 6.61 (d, J = 8.5 Hz, 1 H), 7.18 (**a**) (d, J = 8.5 Hz, 1 H), 7.30 (**b**) (d, J = 8.5 Hz, 1 H), 7.95 (**b**) (s, 1 H), 8.00 (**a**) (s, 1 H); 13C NMR (100 MHz, $CDCl_3$) δ 18.6 (**a**), 18.8 (**b**), 27.4, 27.5, 27.9, 28.0, 30.0 (**a**), 31.2 (**a**), 31.4 (**b**), 31.6 (**b**), 39.1 (**a**), 39.2 (**b**), 42.6 (**b**), 42.9 (**a**), 54.3 (**a**), 55.9 (**b**), 62.9 (**b**), 63.6 (**a**), 66.1 (**b**), 66.8 (**a**), 75.7, 104.7 (**b**), 104.9 (**a**), 105.2 (**a**), 105.9 (**b**), 110.7 (**a**), 110.8 (**b**), 112.2 (**a**), 112.4 (**b**), 117.0, 118.5 (**a**), 118.9 (**b**), 123.6 (**a**), 124.2 (**b**), 129.7 (**b**), 129.9 (**a**), 130.8 (**b**), 130.9 (**a**), 139.9 (**b**), 140.4 (**a**), 146.0 (**a**), 146.1 (**b**), 148.7 (**b**), 148.8 (**a**), 165.4 (**a**), 165.5 (**b**), 166.1 (**a**), 166.3 (**b**); IR (neat) 3365, 2971, 2930, 1674, 1641 cm-1; FABHRMS (M+) calcd for $C_{27}H_{33}N_3O_4$ 463.2471, found 463.2474.

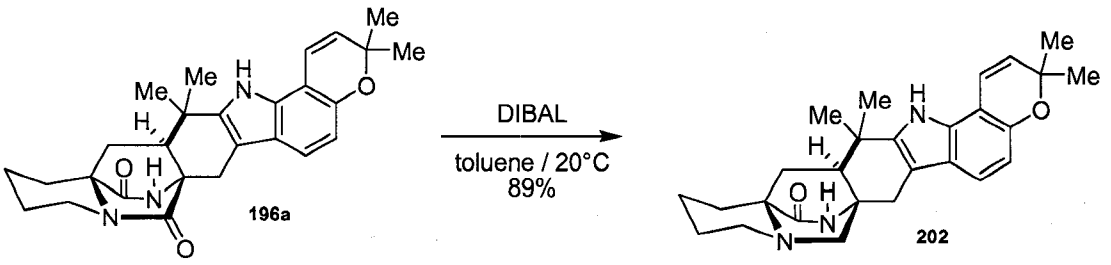
Cycloadduct 196a.



To a solution of alcohols **201(a,b)** (55 mg, 0.12 mmol) in CH_2Cl_2 (12 mL) at rt was added DEAD (112 μL, 0.71 mmol). The mixture was stirred at rt for 5 min and PBu_3 (178 μL, 0.71 mmol) was then added. The solution was heated to 40 °C for 20 h. The resulting mixture was concentrated. Purification by silica gel chromatography (ethyl acetate : hexane, 1 : 1) afforded cycloadducts **196a(syn)** and **196b(anti)** as a 2.4 : 1 crude mixture of diastereomers. This mixture was further separated by preparative TLC (MeOH : CH_2Cl_2, 3 : 97) to afford *syn* cycloadduct **196a** as a colorless oil (22.4 mg, 42%) along with *anti* cycloadduct **196b** as a colorless oil (9.4 mg, 18%); *Syn* Cycloadduct **196a**: 1H NMR (400 MHz, $CDCl_3$ - CD_3OD, 10 : 1) δ 1.00 (s, 3 H), 1.25 (s, 3 H), 1.37 (s, 6 H), 1.58 - 1.69 (m, 5 H), 1.92 (dd, J = 10.3, 13.8 Hz, 1 H), 2.02 (dd, J = 5.0, 13.8 Hz, 1 H), 2.38 (m, 1 H), 2.43 (dd, J = 5.0, 10.3 Hz, 1 H), 2.59 (d, J = 15.5 Hz, 1 H), 3.30 - 3.37 (m, 2 H), 3.64 (d, J = 15.5 Hz, 1 H), 5.57 (d, J = 9.8 Hz, 1 H), 6.54 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 9.8 Hz, 1 H), 7.15 (d, J = 8.4 Hz, 1 H), 8.99 (s, 1 H); 13C NMR (100 MHz, $CDCl_3$) δ IR (neat) cm-1; FAB-HRMS (MH+) calcd for $C_{27}H_{32}N_3O_3$, found . *Anti* Cycloadduct **196b**: 1H NMR (400 MHz, $CDCl_3$ - CD_3OD, 10 : 1) δ 1.17 (s, 3 H), 1.25 (s, 3 H), 1.37 (s, 3 H), 1.38 (s, 3 H), 1.55 - 1.70 (m, 5 H), 1.75 (dd, J = 3.0, 13.0 Hz, 1 H),

2.12 (dd, J = 3.0, 10.3 Hz, 1 H), 2.21 (dd, J =10.3, 13.0 Hz, 1 H), 2.37 (m, 1 H), 2.79 (d, J = 17.7 Hz, 1 H), 3.45 (m, 1 H), 3.73 (d, J = 17.7 Hz, 1 H), 4.11 (m, 1 H), 5.59 (d, J = 9.8 Hz, 1 H), 6.56 (d, J = 8.4 Hz, 1 H), 6.68 (d, J = 9.8 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 1 H), 9.12 (s, 1 H); 13C NMR (100 MHz, $CDCl_3$) δ IR (neat) cm-1; FABHRMS (MH+) calcd for $C_{27}H_{32}N_3O_3$, found.

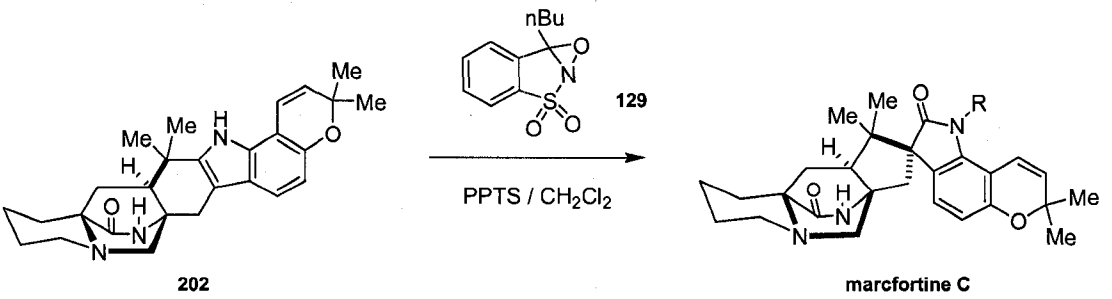
Amine (202).



To a solution of diketopiperazine **196a** (11.8 mg, 0.027 mmol) in toluene (5.3 mL) at 0 °C was added DIBAL (1.0 M in toluene, 530 μL, 0.53 mmol). The mixture was slowly warmed to rt and stirred at rt for 3 h. The resulting solution was quenched by the slow addition of solid $Na_2SO_4 \cdot 10H_2O$ (500 mg). The mixture was stirred for an additional hour at rt. The resulting mixture was filtered through a fritted glass funnel to remove the solid and subsequently washed with ethyl acetate and concentrated. Purification by silica gel chromatography (MeOH : CH_2Cl_2, 5 : 95) afforded amine **202** as a colorless oil (10.1 mg, 89%); 1H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3 H), 1.43 (s, 3 H), 1.45 (s, 6 H), 1.50 - 1.82 (m, 6 H), 1.88 (d, J = 8.1 Hz, 1 H), 2.02 - 2.31 (m, 3 H), 2.65 (m, 1 H), 2.69 (d, J = 15.4 Hz, 1 H), 2.85 (d, J = 15.4 Hz, 1 H), 3.50 - 3.65 (m, 2 H), 5.68 (d, J = 9.9 Hz, 1 H),

6.05 (s, 1 H), 6.60 (d, J = 9.9 Hz, 1 H), 6.64 (d, J = 8.4 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 1 H), 7.72 (s, 1 H); 13C NMR (100 MHz, $CDCl_3$) δ IR (neat) cm-1; FAB-HRMS (MH+) calcd for $C_{27}H_{34}N_3O_2$.

Marcfortine C.



202 marcfortine C

To a solution of amine **202** (9.0 mg, 0.021 mmol) in CH_2Cl_2 (2 mL) at rt was added PPTS (6.6 mg, 0.026 mmol). The mixture was stirred at rt for 15 min. To the resulting solution was added oxaziridine **129** (20.0 mg, 0.083 mmol) and the reaction mixture was stirred at rt for 18 h. The resulting solution was placed directly on a column of silica gel and eluted with CH_2Cl_2, followed by MeOH : CH_2Cl_2 (5 : 95 then 10 : 90) to afford marcfortineC (**3**) (Rf = 0.4, MeOH : CH_2Cl_2, 10 : 90) as a thin film (3.7 mg, 40%) along with recovered starting material **202** (2.2 mg, 25%); 1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 1.12 (s, 3 H), 1.44 (s, 3 H), 1.45 (s, 3 H), 1.55 - 1.85 (m, 6H), 1.93 (d, J = 15.3 Hz, 1 H), 2.13 (br d, J = 11.2 Hz, 1H), 2.26 (d, J = 15.3 Hz, 1 H), 2.42 (m, 1 H), 2.45 (d, J = 11.2 Hz, 1 H), 2.68 (br d, J = 11.2 Hz, 1 H), 3.11 (t, J = 10.1 Hz, 1 H), 3.65 (m, 1 H), 3.70 (d, J = 11.2 Hz, 1 H), 5.72 (d, J = 9.9 Hz, 1 H), 6.40 (d, J = 9.9 Hz, 1 H), 6.42 (d, J = 8.2 Hz, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 7.40 (s, 1 H), 9.18 (s, 1 H); 13C NMR (100 MHz, $CDCl_3$) δ IR (neat) 3298, 2923, 1672, 1601 cm-1; FAB-HRMS (MH+) calcd for $C_{27}H_{34}N_3O_3$ 448.2600, found 448.2608.

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[2] *NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities*. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**; *62*(21); 7512-7515.

[3] *A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy.* Hoye, T.R.; Hansen, P.R.; Vyvyan, J.R. *J. Org. Chem.* **1994**; *59*(15); 4096-4103.

[4] for examples of tertiary amide rotamer separation on chiral stationary phases see: Clayden, J.; Pink, J.H, *Angew. Chem. Int. Ed. Eng.***1998**, 1937-1939.

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[6] *The Role of Glutathione in the Toxicity of a Novel Cyanobacterial Alkaloid Cylindrospermopsin in Cultured Rat Hepatocytes.* Runnegar, M. T.; Kong, S. M.; Zhong, Y. Z.; Ge, J. L.; Lu, S. C. *Biochem. Biophys. Res. Comm.* **1994**, *201*, 235-241.

[7] *Enzymatic method for quantitative determination of nanogram amounts of total and oxidized glutathione: Applications to mammalian blood and other tissues.* Tietze, F. *Anal. Biochem.* **1969**, *27*, 502-522.

Appendix 1: Publications

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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 9013–9016

Concise syntheses of the 1,7-dihydropyrano[2,3-*g*]indole ring system of the stephacidins, aspergamides and norgeamides

Alan W. Grubbs, Gerald D. Artman, III and Robert M. Williams*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA
University of Colorado Cancer Center, Aurora, CO 80045, USA

Received 16 June 2005; revised 18 October 2005; accepted 21 October 2005
Available online 8 November 2005

Abstract—Three approaches towards the synthesis of the 1,7-dihydropyrano[2,3-*g*]indole ring system of the stephacidins, paraherquamides and norgeamides have been investigated. The first involves a tandem nitrene insertion/aromatic Claisen rearrangement. The second consists of a more conventional approach from commercially available 6-benzyloxyindole. The third approach is a revised synthesis of the 2-prenylated pyrano indole necessary for a biomimetic Diels–Alder approach towards the stephacidins, aspergamides and the norgeamides.
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Fungi continue to be a rich source of complex and unprecedented indole alkaloids with a wide range of biological activity. As is often the case, the indole ring is oxidized to produce a variety of functionalized heterocyclic ring systems. In particular, the 1,7-dihydropyrano[2,3-*g*]indole ring system has recently been observed in several novel alkaloids. For example, the aspergamides A (**1**) and B (**2**) were isolated from *Aspergillus ochraceus* by Zeek and co-workers, who elucidated their structures using NMR experiments (Fig. 1).[1] Both were characterized by a bicyclo[2.2.2]diazaoctane bridged bicycle and a 1,7-dihydropyrano-[2,3-*g*]indole ring system. Furthermore, aspergamide A (**1**) exhibits a unique α-hydroxy nitrone moiety, whereas aspergamide B (**2**) is the dehydrated imine congener. Structurally related to the aspergamides, avrainvillamide (CJ-17,665, **3**) also contains a [2.2.2] bridged bicycle and the pyrano indole ring system, in addition to an unprecedented vinyl nitrone moiety, which had previously not been observed in this family.[2]

In addition to the aspergamides and avrainvillamide, a German institute cultivated four alkaloids containing the aforementioned indole ring system from a marine fungus growing in the North Sea.[3] The norgeamides A-D (**4**–**7**) are unique, in that they do not contain the bridged diazaoctane observed in related alkaloids. Instead, norgeamides A (**4**) and B (**5**) are comprised of a pyrano 2-oxindole moiety bearing a reverse prenyl group at C3, one of the two quaternary centers present in these compounds. An oxidized diketopiperazine (DKP) unit harbors the remaining quaternary center at C17. Alternatively, norgeamides C (**6**) and D (**7**) find the reverse prenyl group at C2 of a pyrroloindole ring system and a hydroxyl group at C3. Preliminary biological assays of the norgeamides reveal that norgeamide A (**4**) to be the most cytotoxic against several carcinoma cell lines.[3]

However, the most intriguing alkaloid recently isolated containing the pyrano indole ring system is stephacidin B (**9**). Isolated by Bristol-Meyers Squibb (BMS) from the fungus *A. ochraceus* WC76466,[4] the stephacidins A (**8**) and B (**9**) both displayed in vitro cytotoxicity against a panel of carcinoma cell lines with **9** being five- to thirty-fold more cytotoxic than **8** possessing a high affinity for testosterone-dependent prostate LNCaP cancer cells. However, the cytotoxicity of stephacidin B (**9**) is eclipsed by its unprecedented structure, which was determined using NMR experiments and X-ray crystallography. Stephacidin B contains fifteen rings, nine stereogenic centers and two pyrano indole rings and was proposed to be a dimer of **3**.[5] The unique structure, cytotoxicity and biosynthetic relationships between

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* Corresponding author. Tel.: +1 970 491 6747; fax: +1 970 491 3944; e-mail: rmw@chem.colostate.edu

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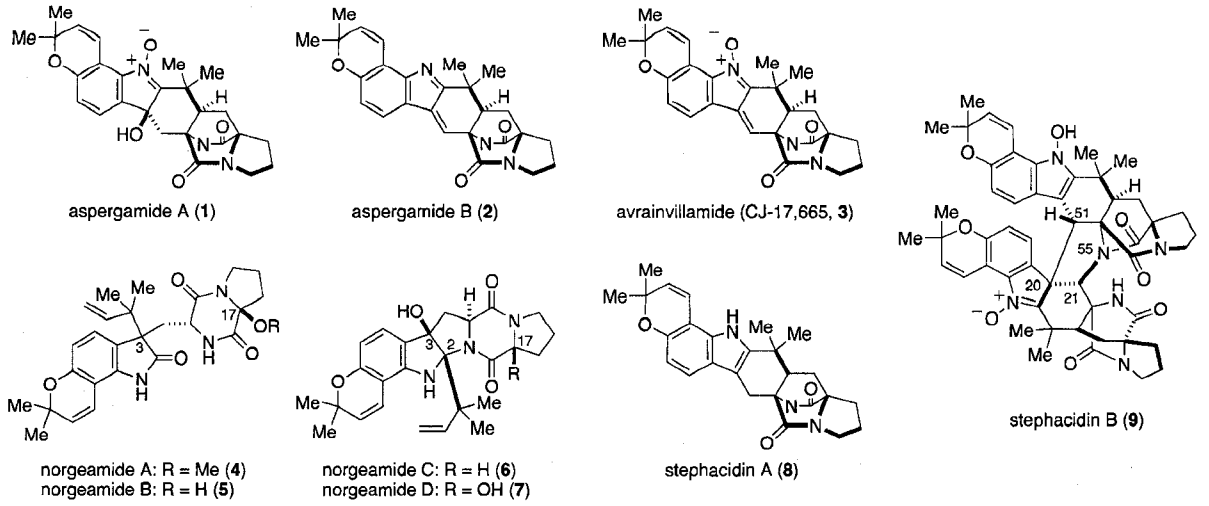
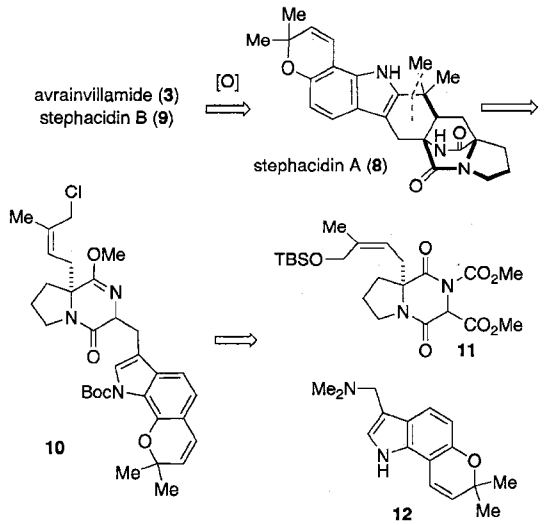


Figure 1. Recently isolated alkaloids containing a 1,7-dihydropyrano[2,3-*g*]indole ring system.

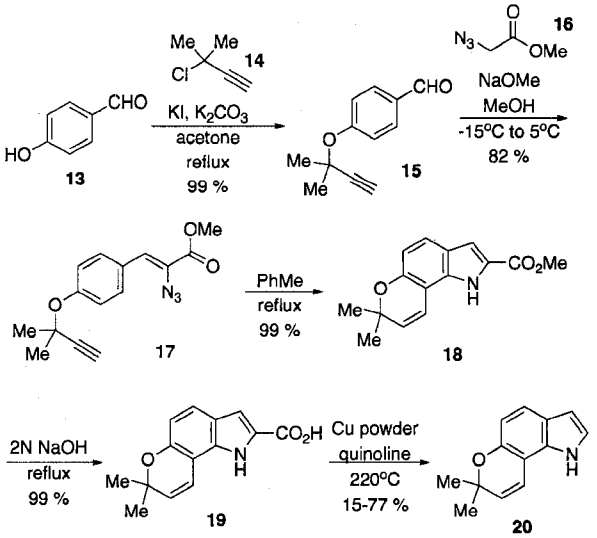
these alkaloids have recently resulted in intense synthetic interest including the first total synthesis of avrainvillamide (**3**) and stephacidin B (**9**) by Myers,[6] and more recently, Baran's revised total synthesis of stephacidin A (**8**) en route to stephacidin B (**9**).[7]

Our laboratory has a rich history with respect to similar alkaloids containing many of the structural features highlighted in **Figure 1**.[8] We developed the first intramolecular S_N2' approach for the preparation of the [2.2.2]diazaoctane ring system found in these alkaloids that was employed in asymmetric total syntheses of brevianamide B, paraherquamide B and paraherquamide A.[8] Retrosynthetically, we envisioned that stephacidin A (**8**) could be oxidized[7] to afford avrainvillamide (**3**) and stephacidin B (**9**, Scheme 1). In turn, **4** would be accessed from lactim ether **10** via displacement of the allylic chloride in an S_N2' fashion to produce the bridged bicycle and subsequent cyclization at C2 of the indole would produce the cyclohexyl ring of **8**. It was envisioned that the lactim ether **10** can be accessed from a coupling of the known diketopiperazine **11** and previously unknown gramine **12**.

Since we were endeavoring to access two alkaloids from a common intermediate, it was necessary to develop a concise, high yielding synthesis of gramine **12** for the S_N2' approach. To this end, we were drawn to the elegant nitrene insertion/Claisen rearrangement chemistry developed by Moody for the synthesis of allyl substituted indoles.[9,10] Thus, 4-hydroxybenzaldehyde (**13**) was alkylated with 3-chloro-3-methyl-1-butyne (**14**) using KI and K_2CO_3 in refluxing acetone affording the ether aldehyde **15** in excellent yield (Scheme 2).[11] Condensation of the aldehyde **15** with methyl azidoacetate[9,10] (**16**) cleanly afforded the conjugated azide **17** in good yield. Generation of the nitrene from **17** in refluxing toluene facilitated formation of the indole formation via CH insertion and, additionally, the pyran ring was formed



Scheme 1. An S_N2' retrosynthetic approach towards the stephacidins.



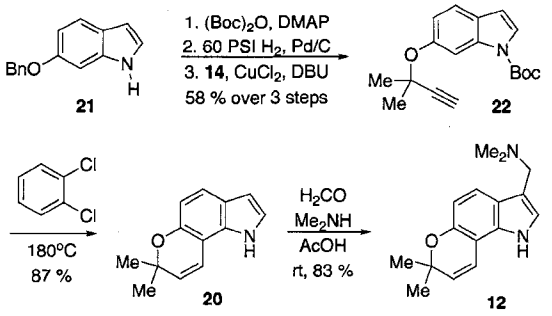
Scheme 2. Synthesis of indole **20** via a Claisen/nitrene insertion.

under these conditions through a Claisen cyclization[12] to produce compound **18** in excellent yield and as a single regioisomer. Subsequent saponification of methyl ester **18** to acid **19** was uneventful. However, decarboxylation of **19** proved to be capricious with yields of the desired indole **20** ranging from 15% to 77%. Unfortunately, an exhaustive effort with various forms of copper, additives and solvents failed to provide consistency to this key transformation.

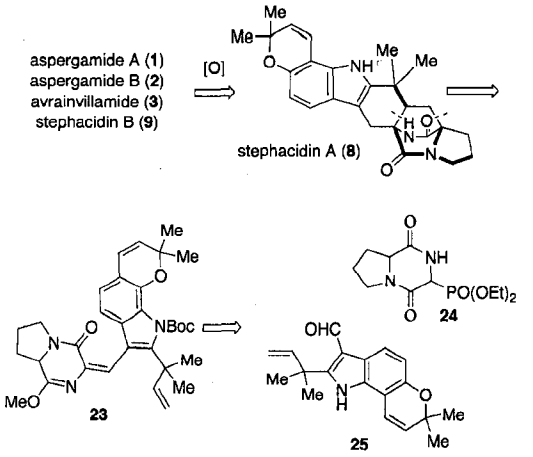
Alternatively, a more direct approach to gramine **12** was realized from commercially available 6-benzyloxyindole (**21**, Scheme 3).[13] Protection of the indole nitrogen of **21** with $(Boc)_2O$, followed by debenzylation and alkylation of the resulting crude phenol with the previously employed chloride **14** afforded aryl ether **22** in 58% over the three steps on a multigram scale.[12b] Finally, heating of alkyne **22** in *o*-dichlorobenzene cleanly effected the aromatic Claisen cyclization as well as Boc cleavage to afford the desired pyrano indole **20** in 87% yield. Finally, conversion of indole **20** to the desired gramine **12** was accomplished using standard conditions in 83% yield.

More recently, our laboratory has reported the synthesis of isotopically labelled putative biosynthetic intermediates in this family of alkaloids and feeding experiments describing the biosynthetic pathway towards these bridged bicycle alkaloids.[8,14–16] A substantial body of evidence suggests that the biosynthetic formation of the bicyclo[2.2.2]diazaoctane core is accomplished via a Diels–Alder reaction. To this end, we have developed a secondary, biomimetic approach towards these alkaloids (Scheme 4). In the case of the stephacidins, the bridged diazaoctane of stephacidin A (**8**) can be disconnected retrosynthetically to afford **23**. Further disconnection of the Diels–Alder precursor **23** generates the DKP **24** and the prenylated indole **25.**

We recently reported the synthesis of prenylated indole **25** via a Fisher indole strategy.[12b] Unfortunately, the key Fisher ring formation step exhibited poor regioselectivity generating a ~1:1 mixture of the 4- and 6-methoxyindoles, thereby limiting the throughput of material for further manipulation. In order to overcome the deficiencies of the Fisher route, we were drawn to a report by Tatsuta in which 3-chloroindoles can be reverse prenylated at C2 of indole with prenyl 9-BBN.[17] To this end, the hydroxyl group of commercially available 6-



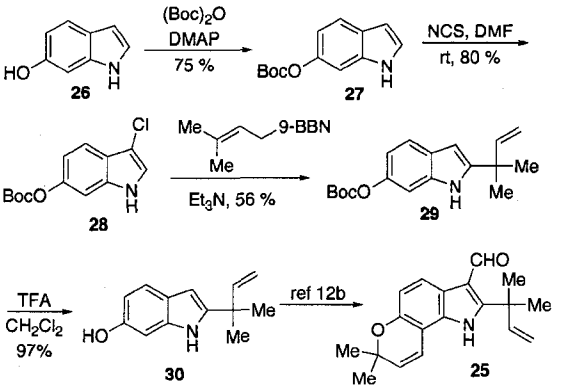
Scheme 3. Synthesis of gramine 12 from 6-benzyloxyindole (**21**).



Scheme 4. A Diels–Alder approach towards the stephacidins.

hydroxyindole[18] (**26**) was protected as its Boc carbonate to form indole **27** in 75% yield (Scheme 5). Indole **27** was then chlorinated using NCS to afford the 3-chloroindole **28** in good yield. Pleasingly, compound **28** readily reacted with prenyl-9-BBN[19] to afford 2-prenylated indole **29** in 56% yield. We believe that the electron-withdrawing nature of the carbonate is vital for the success of this reaction in that electron-rich protected variants of **28** (i.e., silyl ethers and alkyl ethers) failed to produce any of the desired prenylated indole. Finally, removal of the Boc carbonate of **29** with TFA produced the previously synthesized 6-hydroxy-2-prenyl indole **30** obtained by the Fisher indole approach. Indole **30** was converted to the pyrano indole **25** according to our previous report[12b] in three steps, thereby providing the necessary indole for our biomimetic approach in a more concise and regioselective manner.

In conclusion, we have described the synthesis of our key gramine **12** by two different strategies. The first route proved to be capricious and failed to afford the desired indole precursor in high yield. The second route produced the desired gramine **12** in only five steps and in 41% overall yield. Furthermore, we have revised our synthesis of the prenylated indole **25** via a boron-mediated reverse prenylation reaction, thereby providing multigram quantities of **25**, regioselectively. These



Scheme 5. Synthesis of 2-reverse prenylated indole **25.**

substances should find broad utility in the preparation of the stephacidins, aspergamides and norgeamides as well as for the preparation of isotopically labelled biosynthetic intermediates for biosynthetic studies, which are currently being pursued in our laboratories.

Acknowledgements

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Supplementary data

The supplementary data is available with the paper at ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.112.

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Biomimetic Alkaloid Synthesis

A Concise Total Synthesis of the Notoamides C and D**

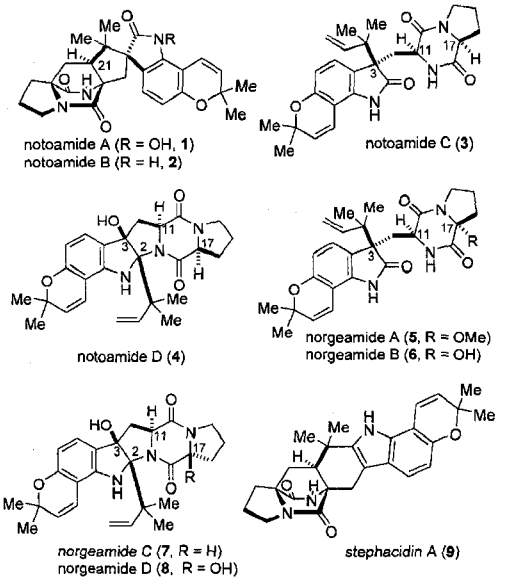
*Alan W. Grubbs, Gerald D. Artman, III, Sachiko Tsukamoto, and Robert M. Williams**

Dedicated to Professor David A. Evans on the occasion of his 65th birthday

The past several years have seen an explosion of new metabolites that are isolated from fungi and have interesting biological activities. Our research group has a rich history in the synthesis[1] and elucidation of the biosynthesis[2] of fungal metabolites derived from tryptophan, isoprene, proline, and proline derivatives.[3] Recently, two research groups have reported structurally related alkaloids that were isolated from two different strains of fungi, cultivated from marine environments. Tsukamoto and co-workers recently isolated four new prenylated indole alkaloids named the notoamides A–D (**1**–**4**, Scheme 1), along with the known alkaloids sclerotiamide and stephacidin A (**9**), from a marine strain of *Aspergillus* sp. cultivated from the common mussel, *Mytilus edulis*.[4] The structures of the notoamides A–D contain a pyranoindole ring system similar to those found in the stephacidins[5,6] and several paraherquamides.[7] In addition, notoamide A (**1**) and B (**2**) possess the bridged [2.2.2]diazaoctane ring system commonly found in the paraherquamide and stephacidin family. Interestingly, the nitrogen atom of the 2-oxindole moiety of notoamide A is oxidized to the *N*-hydroxy group. The notoamides C (**3**) and D (**4**) lack the bridged bicycle of **1** and **2**, and **4** contains the pyrrroloindole ring system.[8] The notoamides A–C exhibit moderate cytotoxicity against a panel of cancer cell lines but notoamide D shows no such activity.

In 2005, a related alkaloid family, the norgeamides (**5**–**8**, Scheme 1), was reported by researchers at the Hans–Knöll Institute.[9] These compounds were isolated from a strain of cold water *Aspergillius* fungi growing in the North Sea[9] and bear a striking resemblance to **3** and **4**. However, the distinguishing feature of the norgeamides is that the α position of the proline ring (at C17) has a methoxy substituent for norgeamide A (**5**) and a hydroxy group for norgeamide B (**6**) and D (**8**). As for the biological activity of the norgeamides, all have been found to inhibit the growth of a variety of cancer cell lines with different efficacies. Norgeamide A (**5**) was reported to be the most potent inhibitor of cell growth with observed values of 77–98% inhibition. Norgeamide B (**6**), which only differs from **5** in the substitution at the C17 position, was 20–30% less effective at inhibiting cell growth. The norgeamides C (**7**) and D (**8**) were the poorest inhibitors of this family of alkaloids with only 34–41% inhibition being observed. In comparison with the notoamides, it is reasonable to assume that the oxidation state of the proline ring system is vital for biological activity.

From a biosynthetic standpoint, one could envision a single biosynthetic pathway encompassing the notoamides and the norgeamides. To this end, a key starting substrate for this family, as well as for the stephacidins and several paraherquamide derivatives, would be substance **11** (Scheme 2). A single oxidation of **11** would generate the pyrroloindole ring system of **4**. It is particularly intriguing that



Scheme 1. Structures of the notoamides, norgeamides, and stephacidin A.

[*] A. W. Grubbs, Dr. G. D. Artman, III, Prof. R. M. Williams
Department of Chemistry, Colorado State University
Fort Collins, CO 80523 (USA)
E-mail: rmw@chem.colostate.edu
Prof. R. M. Williams
The University of Colorado Cancer Center
Aurora, CO 80045 (USA)
Fax: (+1) 970-491-3944
Homepage: http://rwindigo1.chm.colostate.edu/
Prof. S. Tsukamoto
Graduate School of Natural Science and Technology
Kanazawa University, Kakuma-machi, Kanazawa 920-1192 (Japan)
Fax: (+81) 76-264-6241
E-mail: sachiko@p.kanazawa-u.ac.jp

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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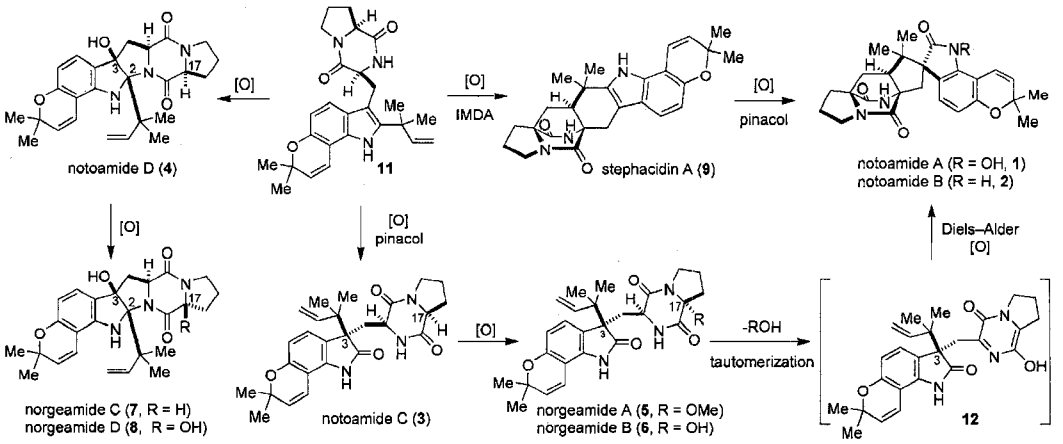
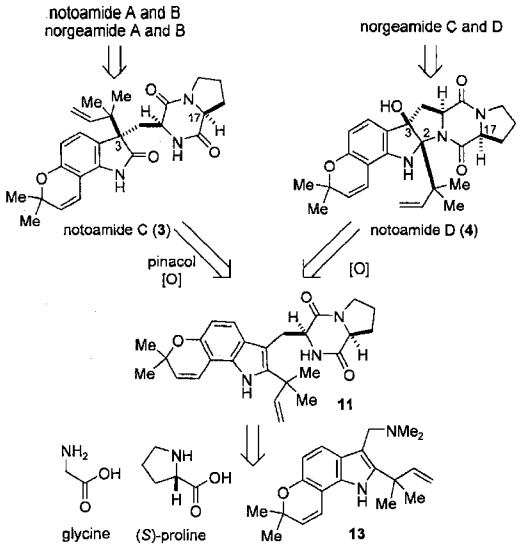


Scheme 2. Postulated biosynthetic relationships between the alkaloids.

4 is structurally identical to **7** except for the reported stereochemistry at the C17 position. A second oxidation of **11** would introduce the hydroxy group at the C17 position of **8**. As for the remaining alkaloids, oxidation and pinacol rearrangement of **11** would afford **3**, which, after oxidation at the C17 position, would give **5** and **6**. Interestingly, alkaloids **5** and **6** exist in the correct oxidation state to serve as substrates for a biosynthetic intramolecular Diels–Alder (IMDA) reaction, in which the elimination of MeOH or water from **5** and **6**, respectively, followed by tautomerization, would generate the putative azadiene **12**. Cycloaddition of the isoprenyl moiety of **12** could generate the bridged bicyclic core of **1** and **2**. Subsequent oxidation of the nitrogen atom of **2** would complete the biosynthesis of **1**. Alternatively, an oxidation and IMDA sequence from the key precursor **11** would directly generate stephacidin A (**9**), which, upon indole oxidation and Pinacol-type rearrangement, would generate **2**.

The possible biosynthetic relationship between the notoamides and the norgeamides with respect to the stephacidins and notoamides A/B, along with their biological activity, has stimulated us to explore their total synthesis. Retrosynthetically, we envisioned a convergent biomimetic synthesis of the notoamides C and D, and the norgeamides from **11** (Scheme 3). Oxidation and pinacol rearrangement of **11** would generate the 2-oxindole observed in notoamides A–C and the norgeamides A and B. Alternatively, oxidation of **11** and trapping with the tryptophyl amide would assemble the pyrroloindole system of **4** and provide a synthetic intermediate to explore conditions for epimerization to **7**, as well as for the oxidation at the C17 position to **8**. We anticipated that the key common intermediate **11** would be readily available from (*S*)-proline, glycine, and the gramine derivative **13**, which was recently synthesized by our group on a gram scale.[10]

Our synthesis began with a coupling of the gramine **13** with the benzophenone imine of glycine **14** by using a method reported by the research groups of Somei and Kametani,[11] which after hydrolysis afforded the amino ester **15** (75%, Scheme 4). Introduction of the Fmoc group onto the amine of **15** followed by saponification of the ethyl ester with trimethyltin hydroxide according to conditions reported by



Scheme 3. Retrosynthetic plan.

Nicolaou et al.[12] afforded the acid **16** (74% yield from **15**). Coupling of the commercially available (*S*)-proline ethyl ester hydrochloride (**17**) with the acid **16** in the presence of BOPCl proceeded without problems, and the intermediate *N*-Fmoc peptide was deprotected and cyclized in the presence of morpholine to afford **11** and the 11-*epi* diastereomer which were readily separable by chromatography. Oxidation of the C2=C3 bond of the indole proved to be troublesome under numerous conditions, but was finally achieved using the oxaziridine[13] **19** to afford notoamide C (**3**, 28%) and 3-*epi*-notoamide C (**20**, 48%) as the major products (76% combined), along with a minor amount of notoamide D (**4**) and 2,3-*epi*-notoamide D (10% combined).

To the best of our knowledge, this oxidation is a new and direct method for the conversion of 2,3-disubstituted indoles into oxindoles, a well-known conversion, but one that is classically performed stepwise by treatment of the indole with

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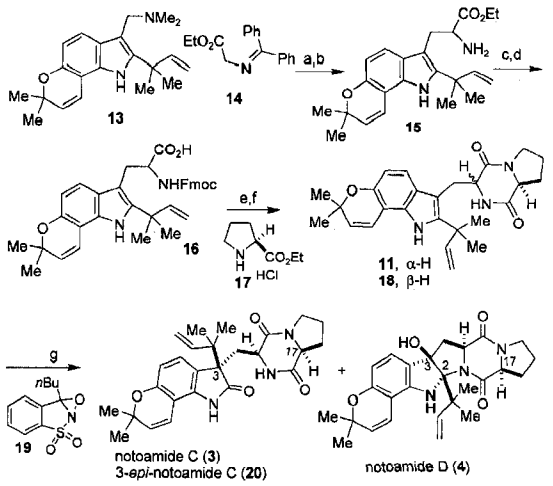
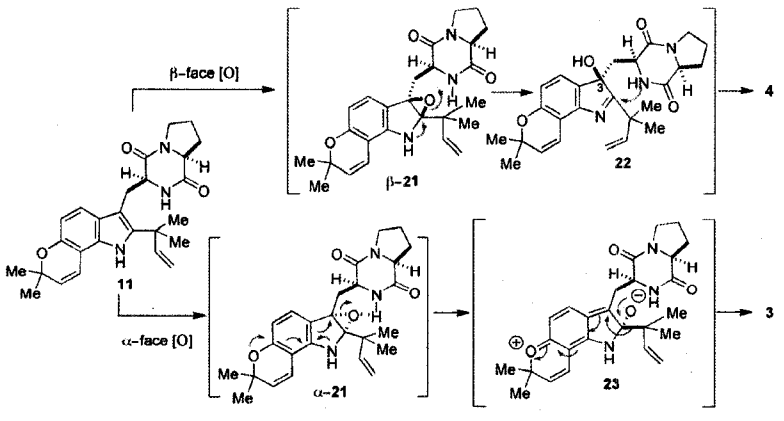


Scheme 4. Total synthesis of notoamide C (**3**), 3-*epi*-notoamide (**20**), and notoamide D (**4**). Reagents and conditions: a) nBu$_3$P, CH_3CN, reflux; b) 1 N HCl, CH_2Cl_2 (75% over 2 steps); c) FmocCl, 10% Na_2CO_3, 1,4-dioxane; d) Me_3SnOH, $ClCH_2CH_2Cl$ (74% over 2 steps); e) BOPCl, DIPEA (61%); f) morpholine, THF; **11** (40%) and **18** (35%); g) **19**, CH_2Cl_2; **3** (28%), **20** (48%), **4**, and 2,3-*epi*-notoamide (10% combined). BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DIPEA = *N*,*N*-diisopropylethylamine, Fmoc = 9-fluorenylmethyloxycarbonyl.

tert-butylhypochlorite to yield an unstable 3-chloroindolenine, followed by hydration to the corresponding *cis*-chlorohydrin, and pinacol-type rearrangement.[14,15] Interestingly, we had anticipated that direct oxidation of the C2=C3 bond of the indole would greatly favor formation of notoamide D. In this context, it is significant that notoamides C and D are isolated in roughly equal amounts from the fungi.[4] To rationalize why the oxindole species are formed as the dominant products, consideration of the mechanism of this oxidation/rearrangement proved insightful. Oxidation of the C2=C3 bond of 2,3-disubstituted indole derivatives is a well-precedented transformation.[14] We had anticipated that opening of the incipient β-2,3-epoxyindole β-**21** (Scheme 5) would occur through participation of the indole nitrogen atom to generate the usual 3-hydroxyindolenine species **22**, which would be trapped by the tryptophyl amide nitrogen atom and thus would generate the pyrroloindole of **4**. However, consideration of the electron-rich nature of the indolopyranyl ring system of **11** revealed that the alternative rupture of the putative epoxide at C3 (shown for α-**21**, Scheme 5), facilitated by participation of the pyranyl oxygen atom and the indole nitrogen atom, could generate the pseudo-*para*-quinone methide species **23**. Subsequent β-face migration of the reverse-prenyl group from C2 to C3 (from **21**-α) would quench the quinone methide and the 2-oxindole of **3** would be produced as the major product. The dominance of the latter pathway reveals an unexpectedly large electronic influence of the pyranyl oxygen atom.

From a biosynthetic perspective, the oxidation of **11** must occur from both the α and β faces of the C2=C3 indole bond to accommodate the relative stereochemical differences between notoamide D (which must arise through β-face oxidation) against notoamides A, B, and C (which all arise from α-face oxidation of the same putative precursor **11**). Our attempts to model the competing conformations and transition states for this oxidation reaction have failed to provide a convincing rationale for the minor facial selectivity observed in the synthetic oxidation of **11** to **3** and its epimer **20**. Further experimental and computational data will be required to gain more understanding of this interesting stereochemical bias.

To obtain additional insight into the delicate electronic control of these two competing pathways, we decided to introduce an electron-withdrawing group onto the oxygen substituent at C6 with the expectation that this would attenuate the ring-opening at the C3 position and shunt ring-opening of the epoxide predominantly at the C2 position via the 3-hydroxyindolenine species, thereby favoring the formation of the pyrroloindole ring system of notoamide D (**4**). To this end, the *O*-Boc-protected prenylated indole **24** was converted into the gramine **25** in high yield (Scheme 6). Coupling of **25** with the known diketopiperazine **26** under the conditions reported by the research groups of Somei and Kametani afforded the ethyl ester **27**. Hydrolysis of **27** to the acid **28** followed by decarboxylation afforded **29** as a single diastereomer. Exposure of **29** to three equivalents of **19** in CH_2Cl_2 for three days at room temperature gave no detectable reaction. On the other hand, exposure of **29** to molecular oxygen in the presence of methylene blue afforded the pentacycles **30** and **31** as a mixture of diastereomers with no detectable oxindole products corresponding to **3**. These results thus demonstrate the vital role the electronic nature of the indole ring system plays in controlling these two distinct pathways. Further investigations into the mechanistic aspects of this unique transformation are underway.



Scheme 5. Proposed biosynthetic conversion of **11** into **3** and **4**.

In conclusion, we have achieved a concise, biomimetic synthesis of notoamides C (**3**) and D (**4**) through an

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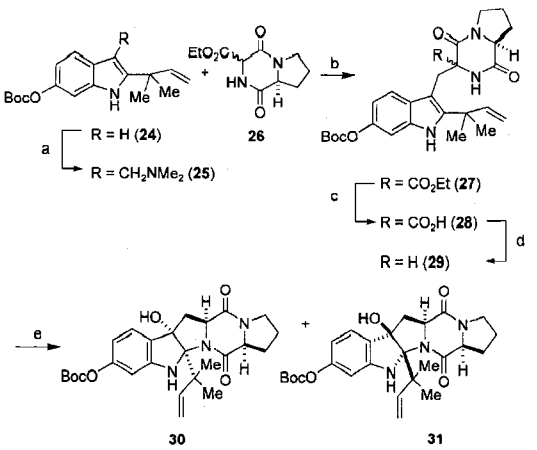

Scheme 6. Reagents and conditions: a) CH_2O, Me_2NH, AcOH, RT (85%); b) **26**, nBu_3P, CH_3CN, reflux (72%); c) LiOH, THF, H_2O, RT (98%); d) *hv*, $BrCCl_3$, 105°C (75%); e) 1. *hv*, O_2, MeOH, methylene blue, 0°C; 2. Me_2S, 62% over 2 steps.

oxidation of the proposed biosynthetic precursor **11**. The synthesis is readily adaptable to the incorporation of both stable and radioisotopic labels through the formaldehyde-based construction of the relevant gramine derivatives which will prove useful in future biosynthetic studies. In addition, we have found that the electronic properties of the indole ring greatly influences the regiochemistry of oxidation of the C2=C3 indole bond, thus resulting in either the pyrroloindole or the oxindole species.

The co-occurrence of the notoamides A–D along with stephacidin A and sclerotiamide[16] as metabolites from a strain of *Aspergillus* sp. cultivated from the common mussel, *Mytilus edulis* suggests two distinct biosynthetic pathways that interrelates these species; either the sequence from **11** through notoamide C to notoamide B and finally to notoamide A, or alternatively, oxidative conversion of **11** into stephacidin A, through notoamide B and then into notoamide A appears equally plausible. The oxidation of the piperazinedione nucleus of notoamide C to a putative azadiene species, necessary for an IMDA cyclization that would construct the bicyclo[2.2.2]diazaoctane ring system, remains an interesting, but as yet untested biogenesis. Some insight into these two distinct pathways can be gleaned from ab initio calculations reported by Domingo et al. on the IMDA reactions of azadiene species such as **12**.[17] These studies indicate a 4–7 kcal mol^{-1} energy difference in the transition states greatly favoring formation of the 21-*epi*-notoamide B Diels–Alder adduct. These calculations are supported thus far by experiments using simpler, yet structurally related systems.[18] Based on these data, we currently favor the latter path to notoamides A and B through stephacidin A. It might be further anticipated that the metabolites corresponding to the norgeamides A and B can arise from the interception (hydration/methanolysis) of such azadiene species, they could be biosynthetically equivalent or actual precursors to such azadiene species, and might further be expected to be co-metabolites (yet to be detected) with the notoamides. Further studies are currently being conducted to address these biogenetic interrelationships.

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Biomimetic Alkaloid Synthesis

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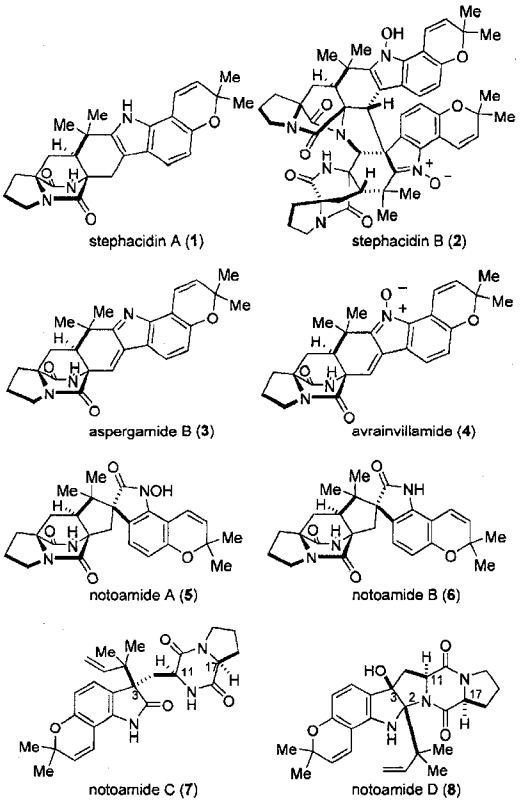
A Concise, Biomimetic Total Synthesis of Stephacidin A and Notoamide B**

*Thomas J. Greshock, Alan W. Grubbs, Sachiko Tsukamoto, and Robert M. Williams**

Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Marine organisms, particularly fungi, are abundant sources of biologically active natural products that possess complex and diverse ring systems. Prenylated indole alkaloids such as the paraherquamides[1] and brevianamides[2] are fungal metabolites whose synthesis and biogenetic origin have been extensively investigated.[3] Recently, several other structurally related prenylated indole alkaloids have been discovered from marine environments. Stephacidin A (**1**) and B (**2**) were isolated from the fungal strain *Aspergillus ochraceus* WC76466 and were shown to exhibit potent in vitro cytotoxicity against various human tumor cell lines (Scheme 1).[4] Stephacidin B (**2**) was found to be especially potent against testosterone-dependent prostate LNCaP cells (IC_{50} = 60 nM).[4] More importantly, the cytotoxic effects of these substances are not mediated by p53, mdr, bcl2, tubulin, or topoisomerase II, which is indicative of a novel mechanism of action.[4] The stephacidins possess remarkably similar structural features to those of the cytotoxic marine alkaloid, avrainvillamide (**4**), which had previously been isolated from *Aspergillus* sp.[5]

Very recently, Tsukamoto and co-workers[6] have reported the isolation of four new indole alkaloids, the notoamides A–D (**5–8**), from the marine-derived fungal strain *Aspergillus* sp. separated from the common mussel, *Mytilus edulis* obtained in the Sea of Japan. The notoamides A–C showed moderate



Scheme 1. Structures of the stephacidins, notoamides, and avrainvillamide.

cytotoxicity against a panel of tumor cell lines, while notoamide D was virtually inactive. Like stephacidins A and B, the notoamides possess a sensitive indolopyran ring system and a tryptophan/proline-derived bicyclo[2.2.2]diazaoctane embedded in their core. As a result of their inherent biological activity and structurally diverse ring systems, this family of prenylated indole alkaloids have become the subject of intense synthetic endeavors, including the first total synthesis of avrainvillamide (**4**) and stephacidin B (**2**) by Myers and Herzon,[7] and more recently stephacidin A (**1**) en route to avrainvillamide (**4**) and stephacidin B (**2**) by Baran and co-workers.[8] Our research group has extensively studied both the synthesis and biosynthesis of prenylated indole alkaloids of this family,[3] and in the preceding Communication reported the first biomimetic synthesis of

[*] Dr. T. J. Greshock, A. W. Grubbs, Prof. R. M. Williams
Department of Chemistry
Colorado State University
Fort Collins, CO 80523 (USA)
and
University of Colorado Cancer Center
Aurora, CO 80045 (USA)
Fax: (+1) 970-491-3944
E-mail: rmw@chem.colostate.edu
Homepage: http://rwindigo1.chm.colostate.edu/
Prof. S. Tsukamoto
Graduate School of Natural Science and Techlology
Kanazawa University
Kakuma-machi, Kanazawa 920-1192 (Japan)

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

InterScience
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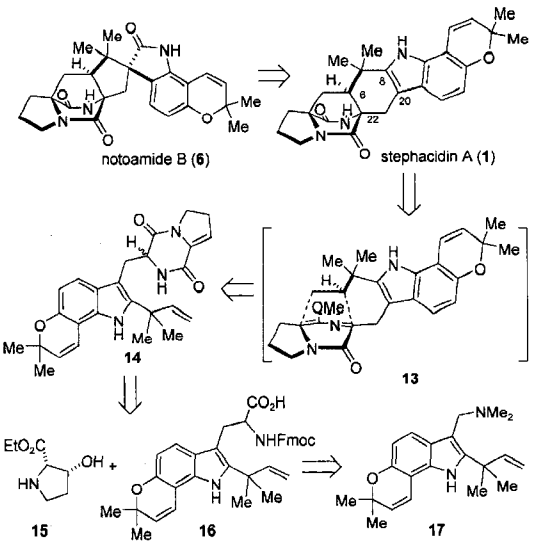
the notoamides C (**7**) and D (**8**).[9] Herein, we report the application of a general biomimetic strategy to the concise total synthesis of stephacidin A (**1**) and notoamide B (**6**).

Based on their structural similarities and their origin from the genus *Aspergillus*, it is quite interesting to contemplate some reasonable biogenetic relationships between the stephacidins and notoamides. A plausible biosynthetic pathway that interrelates these compounds is outlined in Scheme 2. Previous studies from our research group,[3] as well as those of the research groups of Birch[10] and Sammes,[11] suggest that the bicyclo[2.2.2]diazaoctane core of these alkaloids is likely to arise in nature from a biosynthetic intramolecular Diels–Alder (IMDA) reaction. Thus, one could imagine a [4+2] cycloaddition reaction of azadiene **10** (derived from **9**), which contains the reverse prenyl group, and which would directly furnish stephacidin A (**1**). Compound **1** would appear to be a clear and important biosynthetic precursor to avrainvillamide (**4**), stephacidin B (**2**), and notoamide A (**5**) and B (**6**). It has already been suggested that **1** undergoes an overall four-electron oxidation to the unsaturated nitrone **4**, which in turn spontaneously dimerizes to **2**.[12] The latter process has been experimentally corroborated by the research groups of Myers and Baran.[7,8] Notoamide B (**6**) may simply arise from the precursor **9** through two plausible pathways: 1) oxidation and tautomerization to the azadiene **10**, followed by an IMDA cycloaddition to give **1** and subsequent oxidative ring contraction to the spirooxindole; or 2) oxidation and rearrangement to oxindoles such as notoamide C (**7**) and/or further oxidation to norgeamide A (**11a**) or B (**11b**), elimination/tautomerization to produce the azadiene **12**, which could then be trapped by the isoprenyl group to afford **6**.

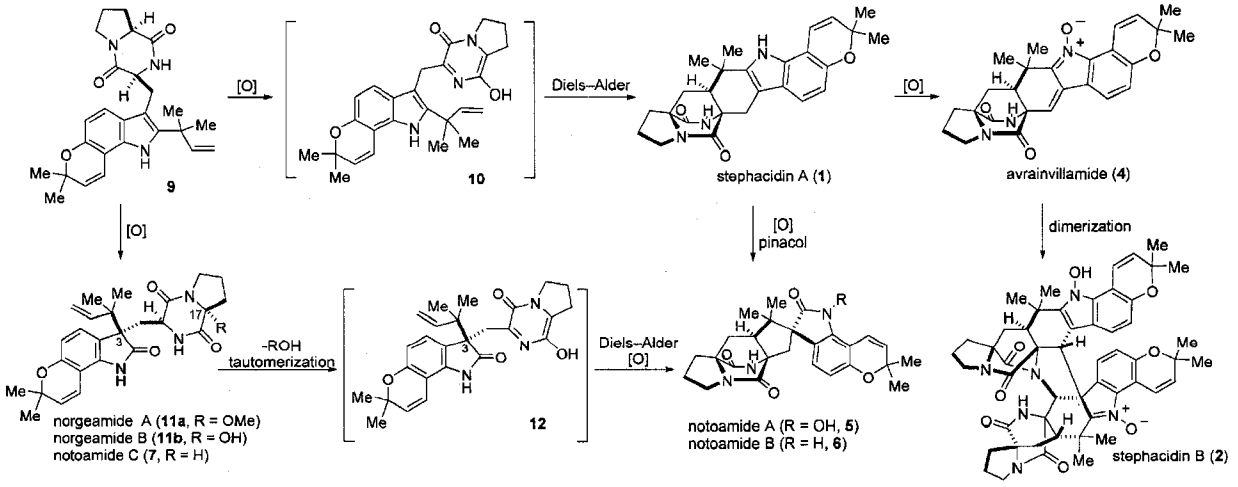
Intrigued by possible biosynthetic relationships between these families of alkaloids, along with their unique biological activities, we have explored their total synthesis with the objective of forming isotopically labeled substances for ongoing biosynthetic investigations. In the retrosynthetic analysis (Scheme 3), we envisaged that the spiroxindole of **6** could arise from a stereoselective oxidative ring contraction



Scheme 3. Retrosynthetic analysis. Fmoc = 9-fluorenylmethyloxycarbonyl.

of the C8–C20 fused indole of **1**. A biomimetic IMDA reaction of the azadiene **13** with the isoprene residue should proceed preferentially to produce the desired *syn* relative stereochemistry at the C6–C22 ring fusion required to access **1**. Our research group has previously reported related biomimetic Diels–Alder cyclizations,[3a,13] which culminated in the total synthesis of the fungal metabolite VM55599[13b] and brevianamide B. Based on previous experiments with similar substrates, it seemed unlikely that azadiene **13** would be stable, and therefore could be generated from enamide **14** through lactim ether formation, followed by a base-induced tautomerization.

Finally, enamide **14** should be available from coupling of the tryptophan derivative **16** with *cis*-3-hydroxy-L-proline



Scheme 2. Postulated biosynthetic relationships between the alkaloids.

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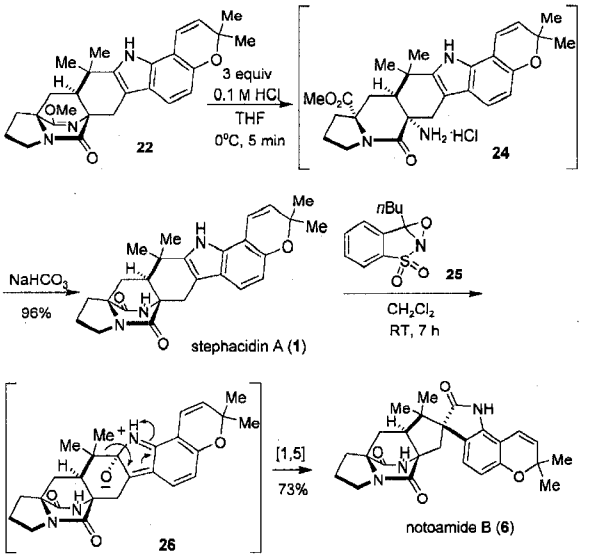
ethyl ester (**15**), followed by removal of the Fmoc group, concomitant diketopiperazine formation, and dehydration. Compound **16** is readily available from the corresponding gramine **17**, and has been recently synthesized in our group on gram scale.[9,14]

Our synthesis commenced with the coupling of the L-proline derivative **15**[15] and acid **16** in the presence of BOPCl to afford amide **18** in 54% yield as an inseparable 1:1 mixture of diastereomers (Scheme 4). Various amounts of starting material (25%–35%) were recovered, and the reaction appeared more sluggish than an analogous coupling of **16** with the parent (*S*)-proline methyl ester hydrochloride as reported in the preceding Communication.[9] Peptide **18** was subjected to a solution of morpholine in THF at room temperature to effect removal of the Fmoc group and a concomitant cyclization of the resultant amine onto the ethyl ester provided diketopiperazine **19** as a separable mixture of diastereomers. Both diastereomers were then found to undergo a smooth Mitsunobu-type elimination (PBu_3, DEAD) to afford the enamide **14**, (Scheme 3) which was treated with Me_3OBF_4 and Cs_2CO_3 to provide the desired lactim ether **20** cleanly in good yield.

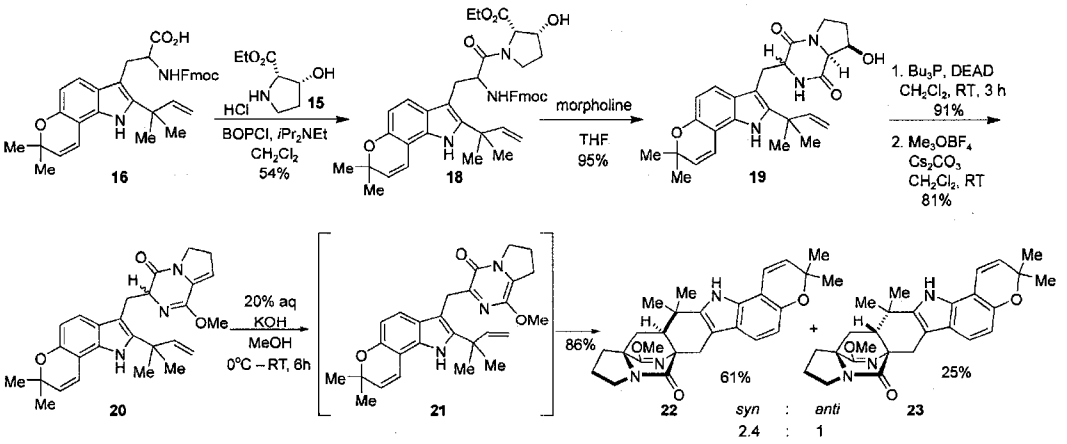
We next directed our attention toward the key cycloaddition reaction and the completion of the total synthesis of stephacidin A. We were delighted to find that treatment of **20** with 20% aqueous KOH in MeOH effected tautomerization to the intermediate azadiene **21**, which spontaneously suffered IMDA cycloaddition to produce the cycloadducts **22** and **23** as a 2.4:1 mixture of diastereomers favoring the desired *syn* stereoisomer. Interestingly, the intermediate azadiene **21** is a metastable substance that could be observed by both TLC and ^{1}H NMR analysis. During the course of the reaction, the lactim ether **20** ($R_f = 0.75$, EtOAc) disappeared within 1.5 h, as evident by TLC, and the azadiene **21** ($R_f = 0.25$, EtOAc) appeared. Then, the azadiene slowly disappeared, as evident by TLC, and the cycloadducts **22** and **23** ($R_f \approx 0.4$, EtOAc) appeared. The azadiene intermediate **21** was also observable by ^{1}H NMR spectroscopy through treatment of **20** with KOD in CD_3OD/D_2O in an NMR tube.

The tentative stereochemical assignment for cycloadduct **22** was confirmed upon its transformation to racemic stephacidin A (**1**). Thus, treatment of **22** with HCl in THF effected cleavage of the lactim ether to afford, through the corresponding secondary amide, stephacidin A (**1**) in 96% yield (Scheme 5). All ^{1}H and ^{13}C NMR spectroscopic data for



Scheme 5. Synthesis of stephacidin A and notoamide B.

synthetic stephacidin A (**1**) corresponded with those reported previously ([D_6]dimethylsulfoxide and $CDCl_3/CD_3OD$, 1:1).[4] Interestingly, this reaction appears to proceed through the ring-opened amino ester **24**, which spontaneously cyclizes to **1** during workup. Amino ester **24**, which could be observed by TLC ($R_f = 0.12$, 10% $MeOH/CH_2Cl_2$), slowly disappeared on concentration of the reaction mixture to give rise to **1** ($R_f = 0.68$, 10% $MeOH/CH_2Cl_2$). Our research group also encountered similar ring-opened amino ester intermediates in the total synthesis of VM55599.[13b]



Scheme 4. Construction of the ring system of **1** by using an IMDA cycloaddition. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DEAD = diethyl azodicarboxylate.

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With stephacidin A (**1**) in hand, we directed our attention to the stereoselective oxidation and pinacol rearrangement of **1** to notoamide B (**6**). Indeed, we were pleased to find that treatment of **1** with excess oxaziridine **25**[16] in CH_2Cl_2 cleanly provided **6** as a single product in 73% yield. The stereochemistry of the transformation can be rationalized by the epoxidation of the 2,3-disubstituted indole occurring from the less-hindered α face, followed by ring opening of the incipient epoxide to the 2-alkoxyindole intermediate **26**. A subsequent α-face ring contraction by a [1,5] sigmatropic shift successfully furnished **6** as a single diastereomer. Again, all ^1H and ^{13}C NMR spectroscopic data ([D_6]acetone) corresponded to those reported by Tsukamoto and co-workers.[6] Furthermore, the use of oxaziridine **25** for the one-step conversion of a 2,3-disubstituted indole into the corresponding spirooxindole is an unprecedented and potentially highly useful transformation. Standard methods for effecting such an oxidative ring contraction have been known for many years and typically involve treatment of the indole substrate with *tert*-butyl hypochlorite to give a 3-chloroindolenine that must be hydrated to a *syn*-chlorohydrin that subsequently undergoes a rearrangement to the spirooxindole.[17,18] Additional applications of this mild and direct reaction to form oxindoles are currently being explored.

In conclusion, we have completed a concise biomimetic total synthesis of stephacidin A (**1**) in 17 steps and 5.4% overall yield from the commercially available 6-hydroxyindole by using an azadiene IMDA reaction. In addition, we have also effected the biomimetic oxidation of stephacidin A (**1**) to the closely related fungal metabolite notoamide B (**6**). This study underscores the low activation barriers inherent in this specific class of azadiene IMDA reactions that have been strongly implicated in the construction of the bicyclo-[2.2.2]diazaoctane core ring system that is common to the paraherquamide/stephacidin/notoamide family of prenylated indole alkaloids. Further studies to experimentally corroborate the biogenetic relationship between the notoamides and stephacidins, as well as the validity of proposed biosynthetic intermediates, such as **1**, **7**, and **9–12** (Scheme 2) are currently under investigation and will be disclosed in due course.

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Concise, biomimetic total synthesis of *d,l*-marcfortine C

Thomas J. Greshock,[a] Alan W. Grubbs[a] and Robert M. Williams[a,b,*]

[a]*Department of Chemistry, Colorado State University, Fort Collins, CO 80523, United States*
[b]*University of Colorado Cancer Center, Aurora, CO 80045, United States*

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We wish to dedicate this paper to Professor Victor Snieckus on the occasion of his 70th birthday

Abstract—A biomimetic total synthesis of the fungal metabolite marcfortine C utilizing an intramolecular Diels–Alder reaction is described. In addition, a key stereoselective oxaziridine-mediated oxidation/pinacol rearrangement of indole **24** was used to complete the total synthesis.
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1. Introduction

Fungi produce an exhausting abundance of biologically active natural products possessing complex and diverse ring systems. Prenylated indole alkaloids such as the paraherquamides,[1] brevianamides,[2] stephacidins,[3] and notoamides[4] are fungal metabolites whose synthesis and biogenetic origin have been extensively investigated, in our laboratory and that of others.[5] These fungal metabolites are all believed to arise biogenetically from tryptophan, isoprene, and proline and derivatives of proline.[5] Significantly, a myriad of biological activities are displayed within this family including insecticidal, anti-tumor, anthelminthic, and anti-bacterial, among others. Another sub-class in this family of prenylated indole alkaloids, the marcfortines (**1–3**) (Fig. 1), were isolated from *Penicillium roqueforti* in 1980 by Polonsky and co-workers.[6] These metabolites are uniquely derived from pipecolic acid rather than a proline derivative. Like many of the paraherquamides, the marcfortines, as well as several of their derivatives, have proven to possess potent anti-parasitic and anthelminthic activity.[7]

Common structural features of these compounds include a sensitive indolopyran or dioxepin ring system and a tryptophan/proline-derived (or, in the case of the marcfortines, pipecolic acid) bicyclo[2.2.2]diazaoctane embedded in their core. Due to their inherent biological activity and structurally diverse ring systems, this family of prenylated indole alkaloids has become the subject of intense synthetic endeavors. Recent work in this family includes the total synthesis of avrainvillamide and stephacidin B by Myers,[8] and more recently stephacidin A (**4**) enroute to avrainvillamide and stephacidin B by Baran and co-workers.[9] Our laboratory has extensively studied both the synthesis and biosynthesis of prenylated indole alkaloids of this family,[5] and has recently reported the biomimetic total syntheses of

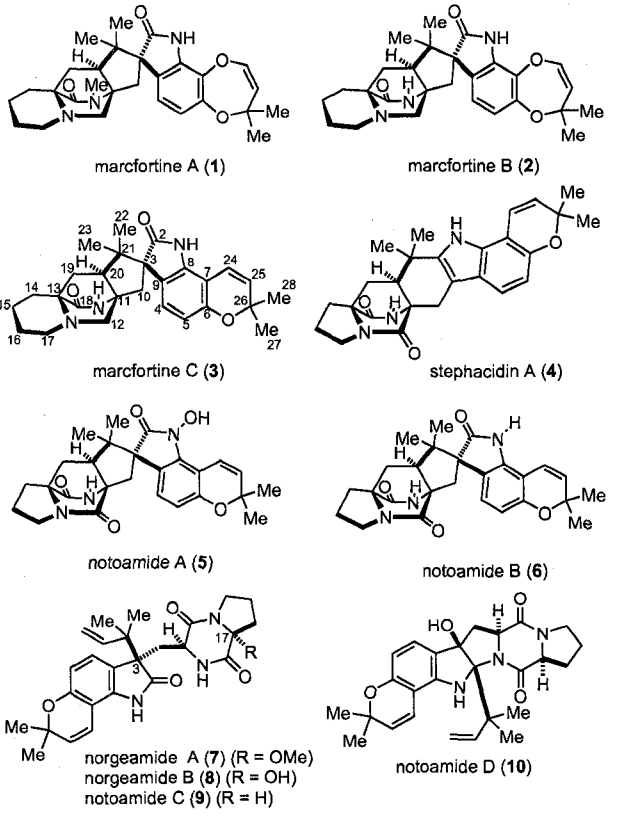

Figure 1. Structures of the marcfortines and various prenylated indole alkaloids.

Keywords: Marcfortine; Diels–Alder; Indole; Natural product; Azadiene.
* Corresponding author. Tel.: +1 970 491 6747; fax: +1 970 491 3944; e-mail: rmw@chem.colostate.edu

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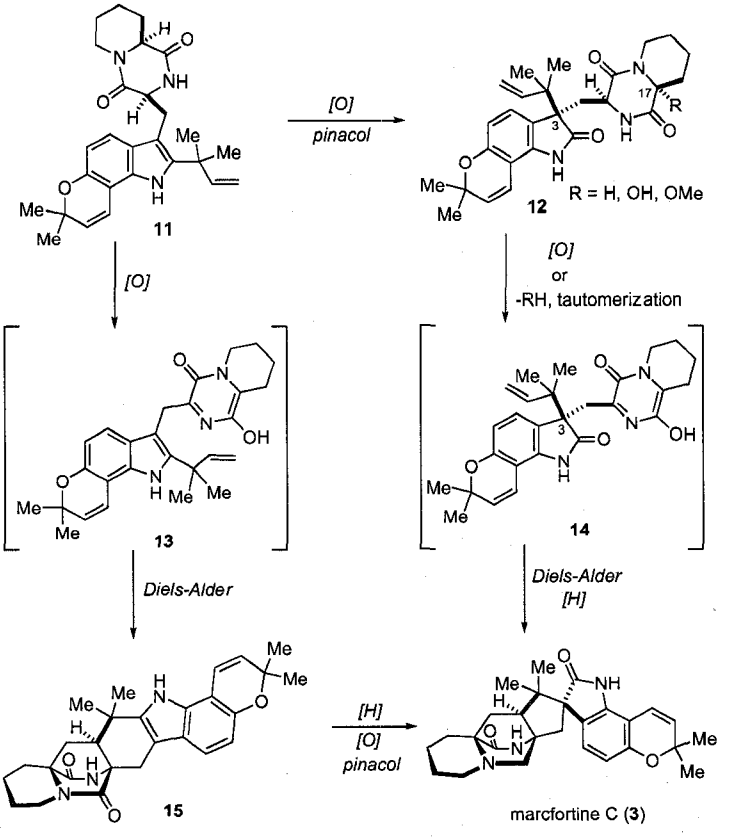
notoamides B (**6**), C (**9**), and D (**10**), as well as stephacidin A (**4**) (Fig. 1).[10] We now wish to report the application of a general biomimetic strategy to the first concise total synthesis of marcfortine C (**3**).

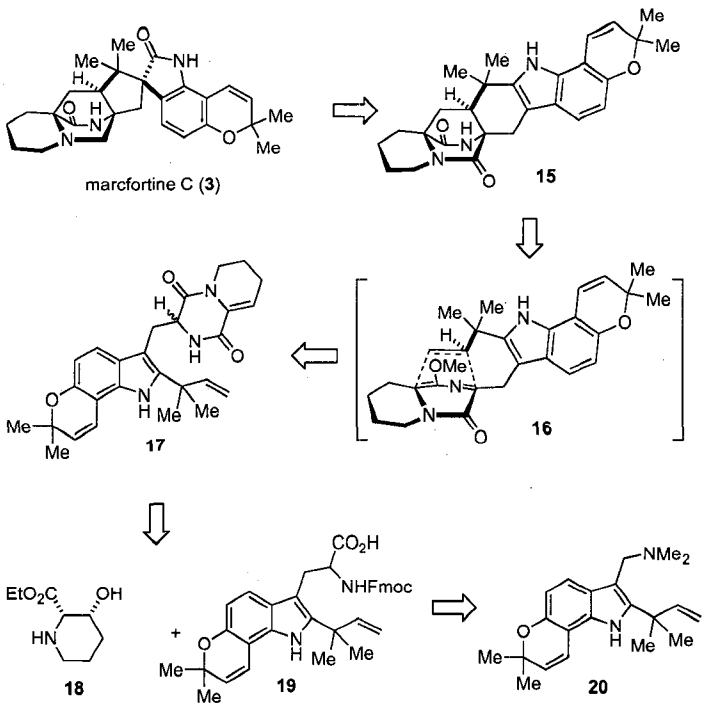
Previous disclosures from our laboratory[5] as well as those of Birch[11] and Sammes[12] have suggested that the core bicyclo[2.2.2]diazaoctane ring system that is characteristic of this family of alkaloids likely arises in Nature via a biosynthetic intramolecular Diels–Alder construction. While [4+2] cycloaddition reactions are perhaps the most powerful tool for rapid construction of highly functionalized six-membered rings in synthetic chemistry, there are relatively few examples of natural products that have been rigorously proven to arise via a biological Diels–Alder reaction, despite a multitude of proposed biogeneses. We have recently proposed some interesting biogenetic relationships between the stephacidins and notoamides[10] in which an intramolecular [4+2] hetero-Diels–Alder cycloaddition is the key transformation in linking natural products such as notoamide C (**9**) and norgeamides A (**7**) and B (**8**) to the core bicyclo-[2.2.2]diazaoctane ring system embodied in notoamides A (**5**) and B (**6**) as well as stephacidin A (**4**) and furthermore avrainvillamide and stephacidin B.

We have also contemplated a parallel biosynthetic relationship enroute to the fungal metabolite marcfortine C (**3**); two plausible biosynthetic pathways to marcfortine C (**3**) are outlined in **Scheme 1**. Thus, a [4+2] cycloaddition reaction of compound **11**-derived azadiene **13** with the reverse prenyl group serving as the dienophile, would directly establish the bicyclo[2.2.2]diazaoctane core. Following a selective reduction of the tertiary amide of the diketopiperazine, a subsequent oxidative ring contraction to the spiro-oxindole would give rise to marcfortine C (**3**). Alternatively, initial oxidation and rearrangement of indole **11** would produce the pipecolic acid-derived spiro-oxindole **12**, analogous to the natural proline-derived congener notoamide C (**12**, R=H) or norgeamides A (**12**, R=OMe) and B (**12**, R=OH). Following an oxidation of (R=H) or an elimination/tautomerization (R=OMe, OH) of spiro-oxindole **12**, the resulting azadiene **14** could then be trapped by the proximal isoprenyl group to directly afford marcfortine C (**3**), following reduction of the tertiary amide. We currently prefer the former pathway proceeding through **13** as the spiro-6 IMDA reaction in such systems has intrinsic facial bias favoring the natural *syn*-relative stereochemistry at C-20 although both pathways merit complete experimental evaluation.[5]

Based on our recent successful deployment of a biomimetic Diels–Alder cycloaddition reaction in the total synthesis of stephacidin A enroute to the first biomimetic total synthesis of notoamide B,[10b] we were compelled that a similar strategy could be employed to complete the first total synthesis of the prenylated indole alkaloid marcfortine C. Retrosynthetically, it was envisaged that marcfortine C (**3**) could arise from compound **15** (Scheme 2) via a chemoselective reduction of the tertiary amide over the secondary amide of the diketopiperazine, followed by a well precedented[10]



Scheme 1. Postulated biosyntheses of marcfortine C.



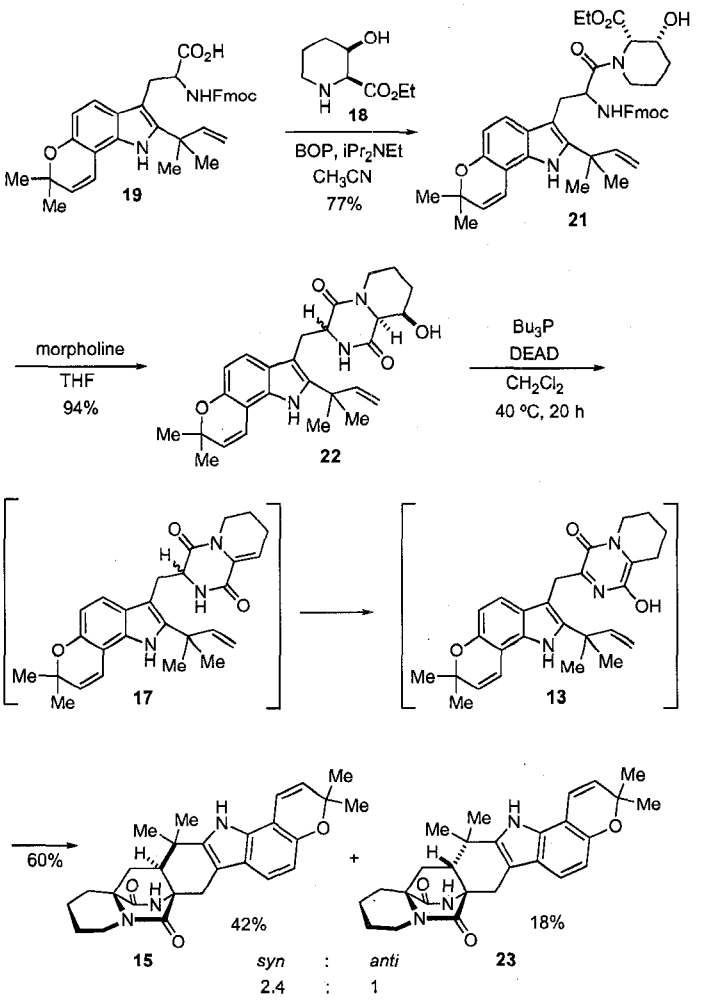
Scheme 2. Biomimetic retrosynthesis of marcfortine C.

stereoselective oxidative ring contraction of the 2,3-disubstituted indole. A biomimetic intramolecular Diels–Alder reaction of the azadiene **16** with the isoprene residue should proceed preferentially to produce the desired *syn*-relative stereochemistry at the C11–C20 ring fusion required to access marcfortine C (**3**). In addition to the stephacidin A/notoamide B synthesis, our laboratory has previously reported related biomimetic Diels–Alder cyclizations,[5a,13] which culminated in the total synthesis of the fungal metabolites VM55599[13b] and brevianamide B.[13c] Based on our experiences with similar substrates, it seemed unlikely that azadiene **13** would be stable, and therefore a functional equivalent (**16**) would be generated from enamide **17** via lactim ether formation, followed by a base-induced tautomerization. Herein, we detail implementation of this strategy to the biomimetic total synthesis of marcfortine C, which has not hitherto succumbed to total synthesis.

2. Results and discussion

Our plan mandated the construction of the key enamide **17**, which should be available through coupling of tryptophan derivative **19** with *cis*-3-hydroxypipecolic acid ethyl ester (**18**), followed by Fmoc removal, concomitant diketopiperazine formation, and dehydration. Tryptophan derivative **19** is readily available from the corresponding gramine **20** and has been recently synthesized in our group on gram-scale.[10a,14]

Our synthesis commenced with a coupling of *cis*-3-hydroxypipecolic acid ethyl ester (**18**)[15] and *d,l*-acid **19** in the presence of BOP and *i*-Pr_2NEt to afford amide **21** (Scheme 3) as an inseparable mixture of diastereomers in 77% yield. Subjecting peptide **21** to a solution of morpholine in THF at room temperature effected removal of the *N*-Fmoc group and a concomitant cyclization of the resultant amine onto the ethyl ester to provide diketopiperazine **22**, once again produced as an inseparable and inconsequential mixture of diastereomers. As previously described in our stephacidin A synthesis,[10b] we had planned to eliminate the alcohol of compound **22** under Mitsunobu conditions to afford enamide **17** (Scheme 3). Following lactim ether formation and a KOH-induced tautomerization, azadiene **16** (see Scheme 2) would then undergo the desired cycloaddition reaction to construct the desired bicyclo[2.2.2]diazaoctane core. However, upon subjection of alcohol **22** to our standard elimination conditions (PBu_3, DEAD, CH_2Cl_2, room temperature), only a small amount of enamide **17** (~15%) was obtained, along with large amounts of recovered starting material. In an effort to thermally force the Mitsunobu reaction to completion, we were surprisingly pleased to find that heating alcohol **22** with excess PBu_3 and DEAD to 40 °C for 20 h, not only effected the anticipated dehydration, but the incipient enamide **17** spontaneously underwent enolization and tautomerization directly furnishing the desired intramolecular [4+2] aza-Diels–Alder reaction that smoothly provided cycloadducts **15** and **23** as a 2.4:1 mixture of diastereomers favoring the desired *syn*-stereoisomer. This amazing one-pot transformation must produce azadiene **13** in situ, which then undergoes the subsequent cycloaddition reaction to produce cycloadducts **15** and **23**. We currently have no experimental data with which to speculate about the possible roles the tributylphosphine, DEAD, or the diethyl 1,2-hydrazinedicarboxylate by-product may have in this fortuitous sequence. It was found, however, that re-subjecting enamide **17** (isolated from a room temperature Mitsunobu reaction) to the same reaction conditions (PBu_3, DEAD, CH_2Cl_2) at 40 °C did produce varying amounts of cycloadducts **15** and **23** albeit in diminished yields (25–45%). To our knowledge, this is the very first example of

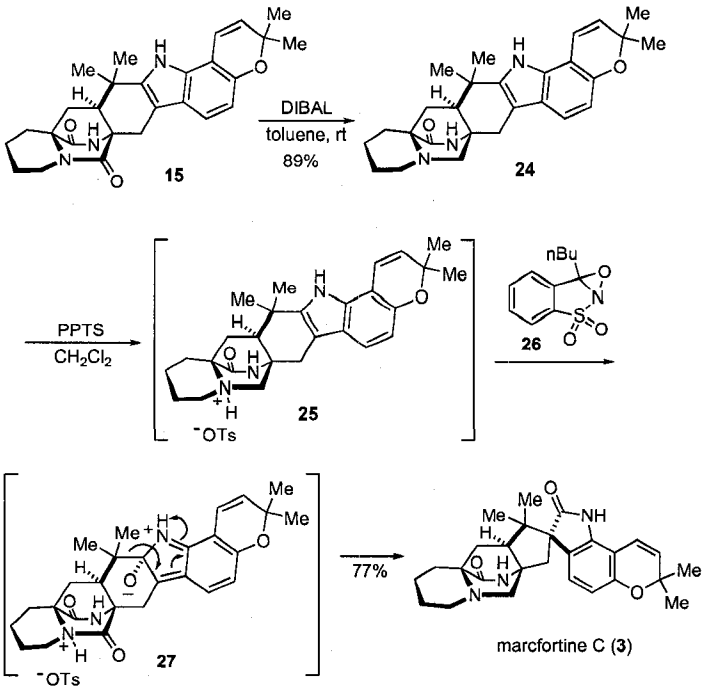


Scheme 3. Construction of the marcfortine C ring system via an intramolecular Diels–Alder cycloaddition.

such a cycloaddition reaction wherein the putative azadiene species (**13**) is generated with a free hydroxyl residue. The facility with which putative azadiene species **13** was generated under these conditions was striking and provides provocative support for the possible intermediacy of such a species in the biological construction of this ring system within this family of secondary metabolites.

The tentative stereochemical assignment for *syn*-cycloadduct **15** was confirmed by its transformation to racemic marcfortine C (**3**). Thus, selective reduction of the tertiary amide over the secondary amide was accomplished by treatment of **15** with excess DIBAL-H (20 equiv) to provide amine **24** in 89% yield (Scheme 4). We have previously been successful in effecting the desired oxidation/pinacol rearrangement in the total synthesis of notoamide B (**6**)[10b] by employing oxaziridine **26**.[16] In the case at hand, however, **24** contains a tertiary amine that can be easily oxidized by the oxaziridine, an incompatibility issue borne out experimentally in this specific case. To circumvent this inherent problem, we surveyed a variety of acids that would be acidic enough to protonate the tertiary amine and render it unreactive toward oxidizing agents, but still be compatible with the sensitive oxaziridine reagent. We were pleased to find that pyridinium *para*-toluene sulfonate (PPTS) met both criteria. Thus, treatment of amine **24** with 1.25 equiv of PPTS for 15 min at room temperature allowed for protonation to the amine salt **25**, which was then treated with excess oxaziridine **26** in CH_2Cl_2 to effect the desired stereoselective oxidation and pinacol rearrangement to produce marcfortine C (**3**) as a single diastereomer in 77% yield. The stereochemical result can be rationalized by epoxidation of the 2,3-disubstituted indole from the less hindered α-face, followed by ring opening of the incipient epoxide to the 2-alkoxyindole intermediate **27**. A subsequent α-face ring contraction by a [1,5]-sigmatropic shift successfully furnishes **3** as a single diastereomer.

The ^1H and ^{13}C NMR spectral properties of the synthetic material were identical to those published by Polonsky and co-workers.[6b] In addition, the synthetic material was identical by mobility on TLC and ^1H NMR to an authentic specimen kindly provided by Prof. David Miller of Carleton University, Canada. Once again, the deployment of oxaziridine **26** for the one-step conversion of a 2,3-disubstituted indole to the corresponding spiro-oxindole has proven to be a highly useful transformation that provides a mild alternative to the standard methods that have been utilized over the years for effecting such a transformation.[17,18]



Scheme 4. Conversion of **15** to marcfortine C.

3. Conclusion

In conclusion, we have completed a concise biomimetic total synthesis of marcfortine C (**3**) via an intramolecular azadiene Diels–Alder reaction in 15 steps and 3.7% overall yield from commercially available 6-hydroxyindole and constitutes the first total synthesis of this alkaloid.[19] This work underscores the low activation barriers inherent in this specific class of azadiene IMDA reactions that have been strongly implicated in the construction of the bicyclo-[2.2.2]diazaoctane core ring system common to the paraherquamide/stephacidin/marcfortine family of prenylated indole alkaloids. Significantly, enamide species such as **17**, provide a provocative new venue for generating the hitherto elusive azadiene species **13**, which have been strongly implicated as biosynthetic intermediates. Further studies to experimentally corroborate the biosynthesis of this family of fungal metabolites are under investigation and will be reported in due course.

4. Experimental

4.1. General methods

Unless otherwise noted, all materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using flame-dried glassware. Dichloromethane, acetonitrile, and tetrahydrofuran were degassed with argon and dried through a solvent purification system (J.C. Meyer of Glass Contour) prior to use. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh) from EM science with the indicated solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or 400 MHz spectrometer as indicated. For all NMR spectra, δ values are given in parts per million and J values are given in hertz. Infrared spectra were recorded on a Nicolet Avatar 320-FTIR spectrometer. Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec.

4.1.1. Amide (21). To a solution of acid **19**[10a,14] (230 mg, 0.40 mmol) in CH_3CN was added HATU (228 mg, 0.60 mmol), *i*-Pr_2NEt (209 μL, 1.20 mmol), and *cis*-3-hydroxypipecolic acid ethyl ester (**18**)[15] successively at rt. The mixture was stirred at rt for 3 h. The resulting solution was quenched with 1 M aqueous HCl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate–hexane, 2:3) afforded amide **21** as a mixture of diastereomers and amide rotamers (225 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.24 (m, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.64 (s, 3H), 1.66 (s, 3H), 1.70–1.77 (m, 2H), 2.20 (m, 1H), 2.75 (m, 1H), 3.08–3.47 (m, 4H), 3.72 (m, 1H), 4.05–4.29 (m, 3H), 4.33–4.49 (m, 3H), 5.05 (m, 1H), 5.21 (d, J=10.4 Hz, 1H), 5.27 (d, J=17.4 Hz, 1H), 5.65 (d, J=9.7 Hz, 1H), 6.00 (d, J=8.1 Hz, 1H), 6.26 (dd, J=10.4, 17.4 Hz, 1H), 6.58 (d, J=9.7 Hz, 1H), 6.67 (m, 1H), 7.25–7.45 (m, 5H), 7.60–7.65 (m, 2H), 7.70–7.80 (m, 2H), 7.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 14.2, 21.9, 22.3, 26.6, 27.4, 27.5, 27.6, 27.8, 29.3, 29.5, 29.6, 30.8, 30.9, 38.9, 39.2, 42.8, 43.1, 47.2, 50.8, 51.2, 53.9, 55.6, 59.1, 61.7, 62.0, 67.9, 68.0, 68.4, 75.6, 104.7, 105.5, 105.8, 110.7, 110.8, 112.5, 112.8, 117.0, 117.2, 118.7, 120.0, 125.0, 125.1, 125.2, 127.1, 127.8, 129.8, 130.0, 130.2, 130.3, 139.1, 139.6, 141.3, 143.82, 143.88, 143.9, 145.6, 146.4, 148.8, 155.4, 155.6, 170.4, 170.8, 172.2, 172.7; IR (neat) 3370, 2972, 1720, 1638 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{44}H_{50}N_3O_7$ 732.3649, found 732.3622.

4.1.2. Diketopiperazine (22). To a solution of amide **21** (225 mg, 0.31 mmol) in THF (12 mL) at rt was added morpholine (3 mL). The mixture was stirred at rt for 2 h. The resulting solution was concentrated to afford the crude diketopiperazine **22** as a mixture of diastereomers. The inseparable mixture of diastereomers was purified by silica gel chromatography (ethyl acetate) to afford diketopiperazines **22a** and **b** as a yellow gum (134 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.41 (s, 3H), 1.47 (s, 3H), 1.50 (s, 3H), 1.68 (m, 1H), 1.85–1.96 (m, 2H), 2.50 (m, 1H), 2.63 (m, 1H), 3.06 (**a**) (dd, J=11.4, 14.4 Hz, 1H), 3.25 (**b**) (dd, J=11.4, 14.4 Hz, 1H), 3.66 (dd, J=2.9, 14.4 Hz, 1H), 3.80 (**a**) (s, 1H), 3.85 (**b**) (s, 1H), 4.25 (m, 1H), 4.39 (m, 1H), 4.67 (m, 1H), 5.09–5.15 (m, 2H), 5.62 (**b**) (d, J=9.7 Hz, 1H), 5.63 (**a**) (d, J=9.7 Hz, 1H), 5.80 (**a**) (s, 1H), 5.90 (**b**) (s, 1H), 6.07 (**a**) (dd, J=10.4, 17.4 Hz, 1H), 6.09 (**b**) (dd, J=10.4, 17.4 Hz, 1H), 6.58 (d, J=9.7 Hz, 1H), 6.61 (d, J=8.5 Hz, 1H), 7.18 (**a**) (d, J=8.5 Hz, 1H), 7.30 (**b**) (d, J=8.5 Hz, 1H), 7.95 (**b**) (s, 1H), 8.00 (**a**) (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (**a**), 18.8 (**b**), 27.4, 27.5, 27.9, 28.0, 30.0 (**a**), 31.2 (**a**), 31.4 (**b**), 31.6 (**b**), 39.1 (**a**), 39.2 (**b**), 42.6 (**b**), 42.9 (**a**), 54.3 (**a**), 55.9 (**b**), 62.9 (**b**), 63.6 (**a**), 66.1 (**b**), 66.8 (**a**), 75.7, 104.7 (**b**), 104.9 (**a**), 105.2 (**a**), 105.9 (**b**), 110.7 (**a**), 110.8 (**b**), 112.2 (**a**), 112.4 (**b**), 117.0, 118.5 (**a**), 118.9 (**b**), 123.6 (**a**), 124.2 (**b**), 129.7 (**b**), 129.9 (**a**), 130.8 (**b**), 130.9 (**a**), 139.9 (**b**), 140.4 (**a**), 146.0 (**a**), 146.1 (**b**), 148.7 (**b**), 148.8 (**a**), 165.4 (**a**), 165.5 (**b**), 166.1 (**a**), 166.3 (**b**); IR (neat) 3365, 2971, 2930, 1674, 1641 cm^{-1}; FAB-HRMS (M^+) calcd for $C_{27}H_{33}N_3O_4$ 463.2471, found 463.2474.

4.1.3. Cycloadduct (15). To a solution of alcohols **22** (55 mg, 0.12 mmol) in CH_2Cl_2 (12 mL) at rt was added DEAD (112 μL, 0.71 mmol). The mixture was stirred at rt for 5 min and PBu_3 (178 μL, 0.71 mmol) was then added. The solution was heated to 40 °C for 20 h. The resulting mixture was concentrated. Purification by silica gel chromatography (ethyl acetate–hexane, 1:1) afforded cycloadducts **15** and **23** as a 2.4:1 crude mixture of diastereomers. This mixture was further separated by preparative TLC (MeOH–CH_2Cl_2, 3:97) to afford *syn*-cycloadduct **15** as a colorless oil (22.4 mg, 42%) along with *anti*-cycloadduct **23** as a colorless oil (9.4 mg, 18%); *syn*-cycloadduct **15**: ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD, 10:1) δ 1.00 (s, 3H), 1.25 (s, 3H), 1.37 (s, 6H), 1.58–1.69 (m, 5H), 1.92 (dd, J=10.3, 13.8 Hz, 1H), 2.02 (dd, J=5.0, 13.8 Hz, 1H), 2.38 (m, 1H), 2.43 (dd, J=5.0, 10.3 Hz, 1H), 2.59 (d, J=15.5 Hz, 1H), 3.30–3.37 (m, 2H), 3.64 (d, J=15.5 Hz, 1H), 5.57 (d, J=9.8 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.64 (d, J=9.8 Hz, 1H), 7.15 (d, J=8.4 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, 10:1) δ 17.4, 21.4, 21.9, 24.7, 26.1, 26.98, 27.00, 28.0, 32.0, 34.7, 39.0, 48.3, 58.8, 59.7, 75.5, 104.1, 105.3, 109.3, 117.7, 117.9, 121.8, 129.1, 133.2, 138.8, 148.1, 172.4, 174.1; IR (neat) 3300, 2917, 1685 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{32}N_3O_3$ 446.2438, found 446.2433. *anti*-Cycloadduct **23**: ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD, 10:1) δ 1.17 (s, 3H), 1.25 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.55–1.70 (m, 5H), 1.75 (dd, J=3.3, 13.5 Hz, 1H), 2.12 (dd, J=3.3, 10.3 Hz, 1H), 2.21 (dd, J=10.3, 13.5 Hz, 1H), 2.37 (m, 1H), 2.79 (d, J=17.7 Hz, 1H), 3.45 (m, 1H), 3.73 (d, J=17.7 Hz, 1H), 4.11 (m, 1H), 5.59 (d, J=9.8 Hz, 1H), 6.56 (d, J=8.4 Hz, 1H), 6.68 (d, J=9.8 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, 10:1) δ 17.7, 21.6, 23.7, 24.5, 26.3, 27.1, 27.4, 28.7, 33.6, 34.6, 39.6, 44.8, 59.9, 60.3, 75.6, 103.4, 105.3, 109.8, 117.5, 118.0, 122.1, 129.5, 133.2, 138.9, 148.4, 171.1, 173.3; IR (neat) 3300, 2917, 1686 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{32}N_3O_3$ 446.2438, found 446.2437.

4.1.4. Amine (24). To a solution of lactam **15** (11.8 mg, 0.027 mmol) in toluene (5.3 mL) at 0 °C was added DIBAL (1.0 M in toluene, 530 μL, 0.53 mmol). The mixture was slowly warmed to rt and stirred at rt for 3 h. The resulting solution was quenched by the slow addition of solid $Na_2SO_4 \cdot 10H_2O$ (500 mg). The mixture was stirred for an additional hour at rt. The resulting mixture was filtered through a fritted glass funnel to remove the solid and subsequently washed with ethyl acetate and concentrated. Purification by silica gel chromatography (MeOH–CH_2Cl_2, 5:95) afforded amine **24** as a colorless oil (10.1 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.44 (s, 3H), 1.45 (s, 6H), 1.49–1.64 (m, 3H), 1.75–1.90 (m, 4H), 2.05 (d, J=11.0 Hz, 1H), 2.07 (m, 1H), 2.19 (m, 1H), 2.25 (dd, J=3.0, 11.8 Hz, 1H), 2.67 (m, 1H), 2.70 (d, J=15.4 Hz, 1H), 2.87 (d, J=15.4 Hz, 1H), 3.54 (d, J=11.0 Hz, 1H), 5.67 (d, J=9.7 Hz, 1H), 6.25 (s, 1H), 6.61 (d, J=9.7 Hz, 1H), 6.64 (d, J=8.4 Hz, 1H), 7.14 (d, J=8.4 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 21.5, 24.5, 26.0, 27.5, 30.7, 30.9, 31.4, 34.1, 34.5, 46.8, 55.4, 55.7, 58.3, 60.9, 75.7, 104.9, 105.2, 110.2, 117.2, 118.0, 121.7, 130.0, 132.9, 139.4, 148.9, 175.0; IR (neat) 3311, 2931, 1673 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{34}N_3O_2$ 432.2646, found 432.2643.

4.1.5. Marcfortine C (3). To a solution of amine **24** (14.0 mg, 0.032 mmol) in CH_2Cl_2 (3.2 mL) at rt was added PPTS (10.2 mg, 0.041 mmol). The mixture was stirred at rt for 20 min. To the resulting solution was added oxaziridine **26** (31.1 mg, 0.13 mmol) and the reaction mixture was stirred at rt for 18 h. The resulting solution was placed directly on a column of silica gel and eluted with CH_2Cl_2, followed by MeOH–CH_2Cl_2 (5:95, then 10:90) to afford marcfortine C (**3**) (R_f=0.4, MeOH–CH_2Cl_2, 10:90) as a white solid (11.2 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.12 (s, 3H), 1.44 (s, 3H), 1.45 (s, 3H), 1.55–1.85 (m, 7H), 1.93 (d, J=15.3 Hz, 1H), 2.13 (br d, J=11.2 Hz, 1H), 2.26 (d, J=15.3 Hz, 1H), 2.42 (m, 1H), 2.45 (d, J=11.2 Hz, 1H), 2.68 (br d, J=11.2 Hz, 1H), 3.11 (t, J=10.1 Hz, 1H), 3.70 (d, J=11.2 Hz, 1H), 5.72 (d, J=9.9 Hz, 1H), 6.40 (d, J=9.9 Hz, 1H), 6.42 (d, J=8.2 Hz, 1H), 6.90 (d, J=8.2 Hz, 1H), 7.40 (s, 1H), 9.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, three drops CD_3OD) δ 20.6, 20.7, 24.0, 25.7, 27.8, 28.0, 30.9, 31.4, 39.9, 46.3, 54.2, 54.6, 61.0, 61.1, 61.3, 62.4, 76.3, 105.4, 109.4, 116.4, 121.5, 125.6, 130.9, 137.7, 152.9, 177.2, 184.5; IR (neat) 3298, 2923, 1672, 1601 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{34}N_3O_3$ 448.2600, found 448.2608.

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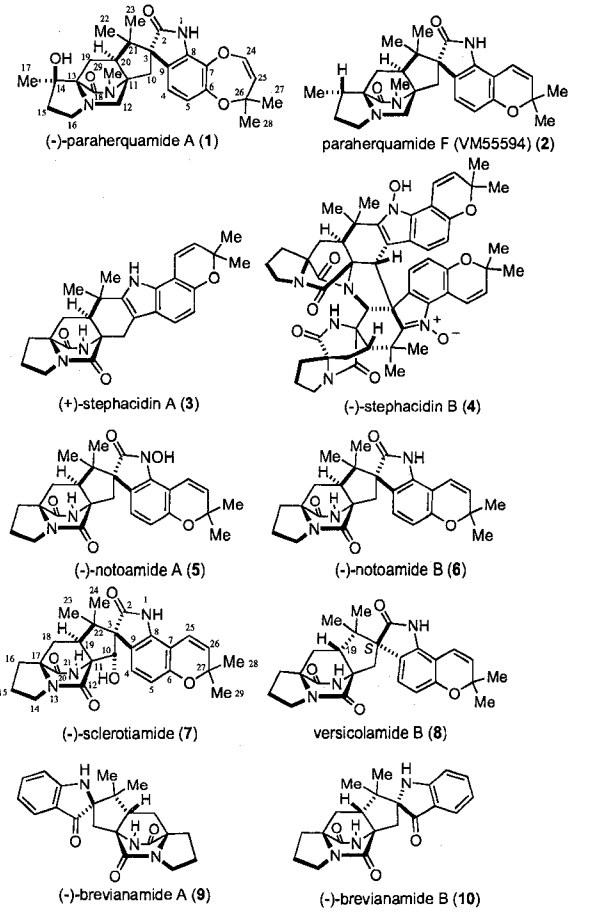
Isolation, Structure Elucidation, and Biomimetic Total Synthesis of Versicolamide B and the Isolation of Antipodal (-)-Stephacidin A and (+)-Notoamide B from *Aspergillus versicolor*

*Thomas J. Greshock,[1] Alan W. Grubbs,[1] Ping Jiao,[2] Donald T. Wicklow,[3] James B. Gloer,[2] and Robert M. Williams,[1,4]**

Prenylated indole alkaloids containing as a structural core, the bicyclo[2.2.2]diazaoctane ring system, now number more than thirty-eight family members. These natural substances, produced by various genera of fungi, in particular *Aspergillus* sp. and *Penicillium* sp., among others, exhibit a range of interesting structural and stereochemical features. Significantly, a myriad of biological activities are displayed within this family including insecticidal, anti-tumor, anthelmintic, calmodulin inhibitory, and anti-bacterial activities. Structurally, these substances arise from the oxidative condensation of one or two isoprene units, tryptophan and another cyclic amino acid residue, such as proline, β-methylproline or pipecolic acid. With respect to the relative stereochemistry within the core bicyclo[2.2.2]diazaoctane ring system, all of the known members of the paraherquamides (**1**, **2**)/stephacidins (**3**, **4**)/asperparalines and notoamides (**5**, **6**) have been shown to possess the *syn*-stereochemistry while only the brevianamides (**9**, **10**) have been shown to possess the *anti*-relative configuration (Schemes 1 and 2). The *syn-/anti-* relationship refers to the relative stereochemistry between the C-19 stereogenic center (sclerotiamide numbering) and the cyclic amino acid residue (proline, β-methylproline, or pipecolic acid; Scheme 2). This reveals that in the oxidative cyclization process(es) to construct this core ring system biosynthetically, that both faces of the isoprene-derived dienophile participate in the ring-forming process, but until now, this stereochemical divergence was cleanly separated between the brevianamides and all other members of this growing family of natural products. Herein, we describe the isolation, structure elucidation, and confirmatory biomimetic total synthesis of the first member of the paraherquamide-stephacidin family to possess the rare *anti*-relative stereochemistry within the bicyclo[2.2.2]diazaoctane ring system. This natural product (**8**), a minor metabolite of *Aspergillus versicolor* NRRL 35600, we propose the new name versicolamide B. Based on CD spectra, we have assigned the absolute configuration to this metabolite, and have concluded that it possesses the *ent*-configuration with respect to the bicyclo[2.2.2]diazaoctane core. Surprisingly and as striking, we have also isolated (-)-stephacidin A and (+)-notoamide B from *Aspergillus versicolor* NRRL 35600 *and conclude that these substances are produced as the corresponding antipodes to what has been previously described for these natural products.* The provocative biogenetic implications of these stereochemical findings are discussed herein.

Previous studies from our laboratory[1] as well as those of Birch[2] and Sammes[3] suggest that the bicyclo[2.2.2]diazaoctane core of these alkaloids likely arises in Nature *via* a biosynthetic intramolecular Diels-Alder construction. We have recently completed the total synthesis of several prenylated indole alkaloids containing the common bicyclo[2.2.2]diazaoctane ring system *via* biogenetically inspired intramolecular Diels-Alder cycloaddition reactions,[1a,4] including brevianamide B, stephacidin A, marcfortine C and the recently discovered fungal metabolite notoamide B (Scheme 1).[4,5] We demonstrate herein that this general strategy was easily amendable to the total synthesis of versicolamide B and provided unambiguous structural and relative stereochemical corroboration fort his stereochemically unique natural product.



Scheme 1. Structures of several members of the paraherquamide/stephacidin/brevianamide family of prenylated indole alkaloids.

[1] [*] Dr. T. J. Greshock, A. W. Grubbs, Prof. Robert M. Williams*
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523 (USA)
Fax: +1-970-491-3944
E-mail: rmw@lamar.colostate.edu
website: http://rwindigo1.chm.colostate.edu/
[2] *Department of Chemistry, University of Iowa, Iowa City, Iowa 52242*
[3] *Mycotoxin Research Unit, Agricultural Research Service, National Center for Agricultural Utilization Research, USDA, Peoria, Illinois 61604*
[4] The University of Colorado Cancer Center, Aurora, Colorado 80045 (USA)

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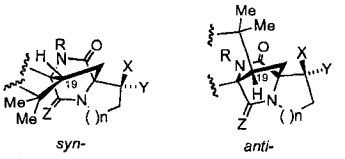
Supporting Information Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. *Syn-* and *anti-*relative configurations at C-19 of the bicyclo[2.2.2]diazaoctane ring system (sclerotiamide numbering).

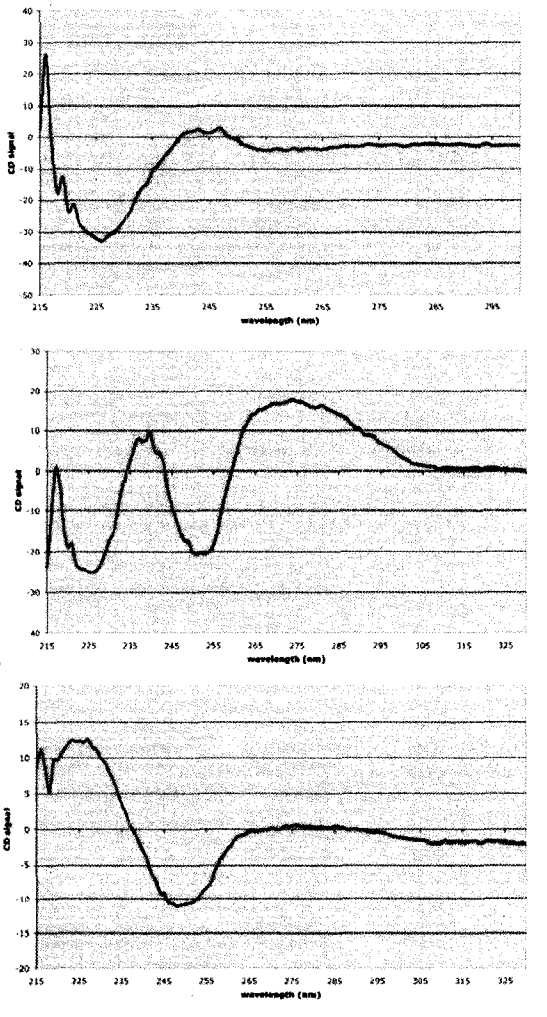
The isolate of *A. versicolor* was obtained from a basidioma of *Gandoderma australe* collected in a Hawaiian forest, and was selected for investigation as part of a project targeting mycoparasitic and fungicolous fungal isolates as sources of new bioactive natural products.[6] This isolate was cultured by solid-substrate fermentation on rice, and the crude extract of these cultures showed significant antiinsectan activity. Five "known" compounds (sterigmatocystin, brevianamide F, stephacidin A, norgeamide D, and notoamide B) were obtained from this extract. The structures of four of the known compounds were confirmed by comparison of their NMR and MS data with literature values,[7] while the structure of notoamide B was independently assigned because the report describing this metabolite[5] had not yet appeared in the literature. Sterigmatocystin was a major component, and appears to be responsible for most of the antiinsectan activity of the crude extract.

The molecular formula of an additional minor component (versicolamide B; **8**) was established as $C_{26}H_{29}N_3O_4$ (14 unsaturations) on the basis of NMR and HRESIMS data. Analysis of ^1H, ^{13}C, and DEPT NMR data (Table 1) revealed that **8** is a member of the paraherquamide class of fungal metabolites. The presence of the 1,2,3,4-tetrasubstituted aromatic ring fused with an oxygen-containing six-membered ring was indicated by HMBC correlations of H-4 to C-6, C-7, and C-8; of H-5 to C-6, C-7, and C-9; of H-25 to C-6, C-7, C-8, C-27, C-28, and C-29; and of H-26 to C-7, C-27, C-28, and C-29. The remaining three oxygen atoms of the molecular formula were attributed to three carbonyl signals (δ_C 183.5, 173.5, 170.2), which must all correspond to amide carbons, leading to the assignment of two exchangeable proton signals at δ_H 9.49 and 7.72 as amide NH protons. HMBC correlations of the NH proton at δ_H 9.49 (H-1) to C-3, C-8 and C-9, and of H-4 to C-3, revealed the presence of an indolinone system. The shift of the C-2 carbonyl at δ_C 183.5 is consistent with its placement in the pyrrolidone ring as shown.[1a,8]

The bicyclo[2.2.2.]diazaoctane system and the C-13–C17 pyrrolidine ring were similarly assigned by analysis of 1D and 2D NMR data. The amide proton at δ_H 7.72 (H-21) showed correlations to C-10, and to quaternary sp^3 carbons C-11 and C-17, which were consistent with its assignment as the amide NH associated with carbonyl carbon C-20 at δ_C 173.5. The methine proton H-19 was coupled to H_2-18 to form an isolated $CHCH_2$ unit, which was incorporated as shown based on HMBC correlations. The linkage between the indolinone ring and the bicyclo[2.2.2.]diazaoctane system via a five-membered ring was established by HMBC correlations of the isolated methylene protons (H_2-10) to C-2, C-3, C-11, and C-12; of H-19 to C-11, C12, C-18, C-23, and C-24; of amide proton H-21 to C-10, C-11, and C-17; and of H_2-18 to C-11, C-17, C-19, and C-20. Further HMBC correlations of H_2-10 to C-3, C-22, C-11, and the two amide carbonyl carbons C-2 and C-12 supported its location as shown. All shift assignments were made by detailed analysis of 2D NMR data, and are consistent with structure **8**.

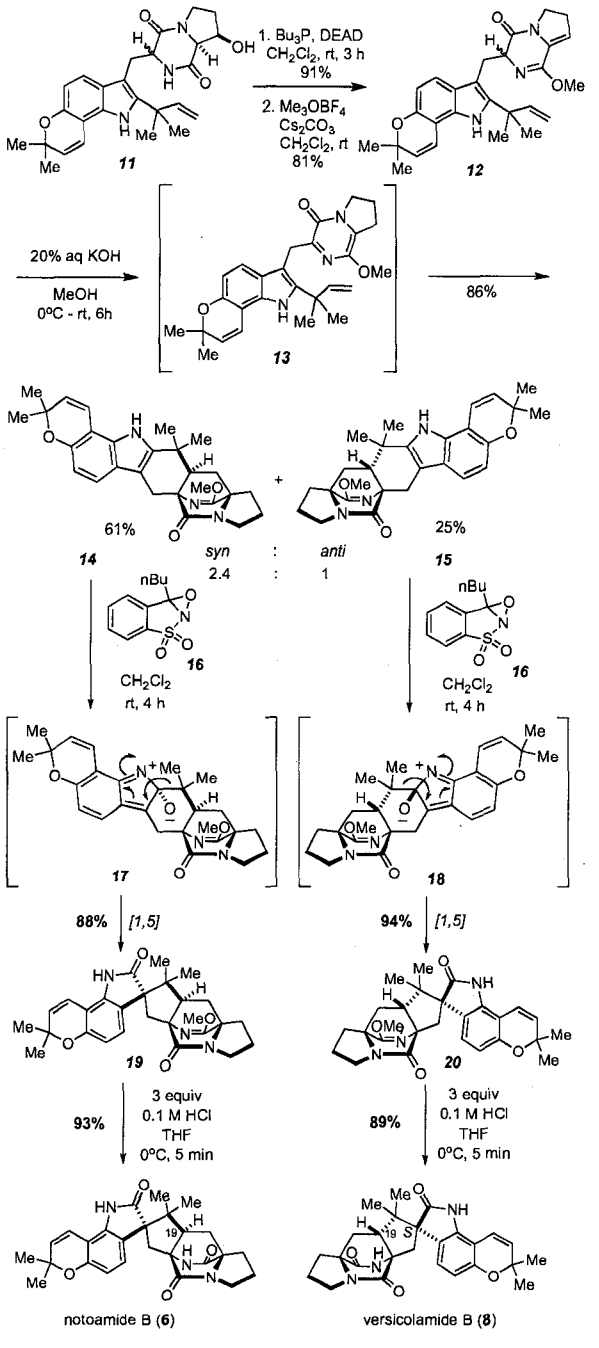
The relative configuration of **8** was assigned on the basis of NOESY data. Key NOESY correlations between H-4, H-10β, H_3-24, H-18β, and H-21 indicated that N-21, H-10β, and H_3-24 are on the same face of the cyclopentane ring and are spatially close to aromatic proton H-4, leading to assignment of the relative configuration of spirocenter C-3 as shown. NOESY interactions between H-19, H-10α, H-18α, and H_3-23 placed the bridgehead proton H-19 on the opposite face of the cyclopentane ring, requiring an *anti*-relationship between H-19 and the C-20 amide bridge in the bicyclo[2.2.2.]diazaoctane ring system in **8**, which is unprecedented among the paraherquamides, but has been reported for the brevianamides.[1a] The structure of **8** differs from the known compound sclerotiamide, originally reported from *Aspergillus sclerotiorum*,[8a] by lacking the 10-OH group and possessing the opposite relative configuration at C-19.

CD spectroscopy has been utilized as a method to assign absolute configuration for *spiro*-oxindole alkaloids.[9] The Cotton effect at 250-350 nm is considered to be an indication of the configuration at *spiro*-stereogenic center C-3.[9a,b] The CD spectra of **8** and the (+)-notoamide B isolated from *A. versicolor* both show a positive Cotton effect at the *spiro*-oxindole absorbance region around 280 nm, suggesting the same 3*S*-configuration for each compound, in agreement with the configuration previously assigned for synthetic, *ent*-(+)-paraherquamide B (Scheme 3). Correspondingly, the absolute configuration of compound **8** is proposed as shown. Of further interest, was the surprising observation that, the stephacidin A and notoamide B samples isolated from *A. versicolor* possess *the opposite absolute configurations* to that previously reported. These assignments were based on examination of the CD spectra and optical rotation values of these substances (Scheme 3).



Scheme 3. CD spectra of *Aspergillus versicolor* NRRL 35600 isolates: (A) *ent*-(-)-stephacidin A; (b) *ent*-(+)-notoamide B; (c) versicolamide B. All CD spectra were recorded in 1:1 CH_2Cl_2:MeOH.

Baran and co-workers, have previously reported in their elegant total synthesis of stephacidin A, optical rotation data and CD spectra of natural (+)-stephacidin A obtained from Professor Fenical's laboratory and corroborating data on synthetic (+)-stephacidin A.[10a] In addition, these workers recorded mirror-image CD spectra for natural (+)- stephacidin A and synthetic (-)-stephacidin A.[10c]



Scheme 4. Synthesis of *d,l*-**6** and *d,l*-**8**. Structures are depicted with the correct relative and absolute configuration fort the natural materials isolated from *Aspergillus versicolor* NRRL 35600; all substances after **11** are produced in racemic form.

The optical rotation data for the natural samples derived from *Aspergillus versicolor* NRRL35600 utilized in this study are as follows: *ent*-stephacidin A $[\alpha]_D$ = -32 (c = 0.05, CH_2Cl_2-MeOH; 1:1) lit. $[\alpha]_D$ = +61.5 (c=0.26, 1:1 CH_2Cl_2/MeOH);[10] *ent*-notoamide B $[\alpha]_D$ = +102 (c = 0.05 MeOH) lit. $[\alpha]_D$ = -118 (c= 0.064, MeOH).[5] We have further determined that the (-)-stephacidin A sample collected from *Aspergillus versicolor* is optically pure by chiral HPLC. These data, along with the CD spectra recorded, rigorously support the surprising fact that *Aspergillus versicolor* NRRL35600 produces the opposite enantiomers of stephacidin A and notoamide B to that obtained from the related fungi *Aspergillus ochraceus* WC76466 and the marine-derived *Aspergillus* sp.

The structure and relative stereochemistry of versicolamide B was corroborated through a biomimetic, racemic total synthesis. Our synthesis of **8** commenced with a Mitsonobu-type elimination (PBu_3, DEAD) of the recently prepared alcohol **11**[4] to afford an intermediate enamide which was then treated with Me_3OBF_4 and Cs_2CO_3 to cleanly provide the desired lactim ether **12** in good yield (Scheme 4).

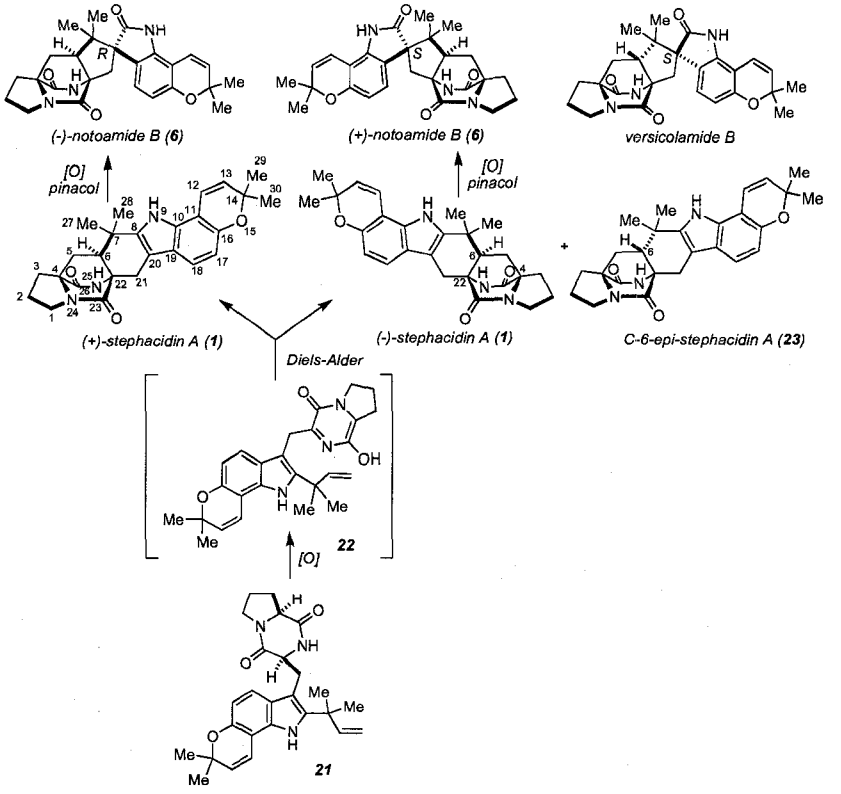
With lactim ether **12** in hand, we were ready to try the key biomimetic cycloaddition reaction. As recently reported, treatment of lactim ether **12** with 20% aqueous KOH in MeOH (0 °C - rt, 6 h) effected tautomerization to the intermediate azadiene **13**, which spontaneously suffered intramolecular Diels-Alder cycloaddition to produce cycloadducts **14** and **15** as a 2.4 : 1 mixture of diastereomers favoring the *syn*-stereoisomer. Interestingly, the intermediate azadiene **13** is a metastable substance that could be observed by both thin layer chromatography and ^1H NMR analysis. During the reaction, lactim ether **12** (R_f = 0.75, EtOAc) disappeared within 1.5 h by TLC analysis and azadiene **13** (R_f = 0.25, EtOAc) appeared. This TLC spot then slowly disappeared giving rise to cycloadducts **14** and **15** (R_f ~ 0.4, EtOAc). The azadiene intermediate **13** was also observable by ^1H NMR spectroscopy through treatment of lactim ether **12** with KOD in CD_3OD/D_2O in an NMR tube.

The tentative stereochemical assignment for cycloadducts **14** and **15** were confirmed upon their transformation to racemic notoamide B (**6**) and versicolamide B (**8**), respectively. We recently reported that notoamide B (**6**) could be prepared *via* lactim ether cleavage of *syn*-cycloadduct **14** giving rise to stephacidin A, which was then subjected to a stereoselective oxidation and pinacol-type rearrangement to cleanly produce notoamide B (**6**).[4] This protocol however proved problematic for the completion of versicolamide B (**8**) from the corresponding *anti*-cycloadduct **15**. The intermediate indole derived from cleavage of the lactim ether of **15** was found to be unstable when exposed to the atmosphere and underwent a facile ring-opening/hydrolysis of the diketopiperazine to produce the corresponding amino acid.

We therefore decided to perform the oxidation/pinacol rearrangement to the *spiro*-oxindole prior to cleavage of the methyl lactim ether. Indeed, we were pleased to find that treatment of cycloadducts **14** and **15** with excess oxaziridine **16**[11] in CH_2Cl_2 cleanly provided the desired *spiro*-oxindoles **19** and **20**, respectively. The stereochemical result of these oxidative rearrangements can be rationalized by considering that epoxidation of the 2,3-disubstituted indoles **14** and **15** occurs from the less-hindered α-face, followed by ring-opening of the incipient epoxides to their respective 2-alkoxyindole intermediates **17** and **18**. A subsequent α-face ring contraction by a [1,5] sigmatropic shift successfully furnishes **19** and **20**, each as a single diastereomer. Finally, the lactim ethers of both **19** and **20** were uneventfully cleaved by treatment with 0.1 M HCl (3 equiv) in THF (0 °C, 5 min) to successfully provide notoamide B (**6**) and versicolamide B (**8**), respectively. The biomimetic synthesis of versicolamide B was thus completed in eighteen steps and 1.8% overall yield and notoamide B was completed in eighteen steps and 4.2% overall yield, both from commercially available 6-hydroxyindole. All ^1H and ^{13}C NMR spectral properties were identical to those of natural notoamide B (**6**) and versicolamide B (**8**) corroborating the relative stereochemical assignment based on nmr as discussed above.

The discovery of versicolamide B and the co-isolates (-)-stephacidin A and (+)-notoamide B, adds another intriguing twist to the emerging picture on the biogenesis of these alkaloids. Some possible biosynthetic relationships are depicted in Scheme 5. In this

view, notoamide E (**21**) is envisioned to be the key biosynthetic progenitor. Oxidation and tautomerization of **21** would yield the key azadiene species **22** that can, in principle, suffer cycloaddition to produce four stereoisomers: stephacidin A (as the (+)- and (-)-enantiomers) and C-6-*epi*-stephacidin A (also as the (+)- and (-)-enantiomers; only one is shown). Oxidation of the 2,3-indolic moiety of (-)-stephacidin A to the corresponding *spiro*-oxindole produces (+)-notoamide B. Similar face-selective oxidation of C-6-*epi*-stephacidin A would produce versicolamide B. What is most curious, is the enantio-facial divergence of this presumed cycloaddition in the different species of *Aspergillus* that have been demonstrated to produce stephacidin A. Thus far, (-)-stephacidin A, is the enantiomer produced in *Aspergillus ochraceus* WC76466[7c] and the marine-derived *Aspergillus* sp. reported by Tsukamoto and co-workers.[5] The isolation of (-)-stephacidin A and it's presumed oxidation metabolite (+)-notoamide B in the same stereochemical series, but distinct from that reported from these other species of *Aspergillus*, is striking. If the proposed IMDA-based biogenesis is correct, this would mandate that each species of fungus evolved a means to select for the production of one enantiomeric cycloadduct (ie., stephacidin A); either through manipulation of the pre-cyclization conformers of putative azadiene **22**; or perhaps through selective catabolism of one enantiomer from an initially produced racemate. The latter seems less plausible as we have confirmed the optical purity of the (-)-stephacidin A here and Baran has previously confirmed the optical purity of (+)-stephacidin A. [10] The existence of versicolamide B as a co-metabolite with (-)-stephacidin A and (+)-notoamide B, is even more perplexing since, the bicyclo[2.2.2]diazaoctane core of this metabolite is *pseudo*-enantiomeric to that of these co-metabolites (but corresponds to that of (+)-stephacidin A). Does this occur through the selection of two of the four possible transition state stereochemistries accessible to **22**? We are currently preparing isotopically labeled substrates to further penetrate this fascinating and apparent stereochemical paradox.



Scheme 5. Some possible biosynthetic relationships.

In summary, the first member of the larger paraherquamide family of prenylated indole alkaloids that contains the *anti*-relative configuration in the bicyclo[2.2.2]diazaoctane ring system has been isolated and the structure of this substance, named versicolamide B, has been rigorously elucidated through spectroscopic means and total synthesis.

The production of this metabolite by *A. versicolor* suggests that the putative biosynthetic IMDA construction that leads to the major metabolites within the producing organism may suffer some stereochemical "leakage" with respect to the facial selectivity of addition to the reverse isoprene moiety anchored at the indole 2-position. Based on our observations, it is reasonable to anticipate that stereochemically related members of this family may be produced by other fungi, albeit in trace amounts. The surprising stereochemical paradox posed by the existence of versicolamide B along with the opposite enantiomers of stephacidin A and notoamide B demand explanation on biogenetic grounds and constitute a major thrust of our ongoing work. Studies to further establish the relationship of these and simpler precursor metabolites in the biosynthesis of this family of agents are under investigation in these laboratories.

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Appendix 2: Research Proposal

"Synthesis of new 10 and 11 membered nitrogen bearing heterocycles derived from naturally occurring cyclic amino acids."

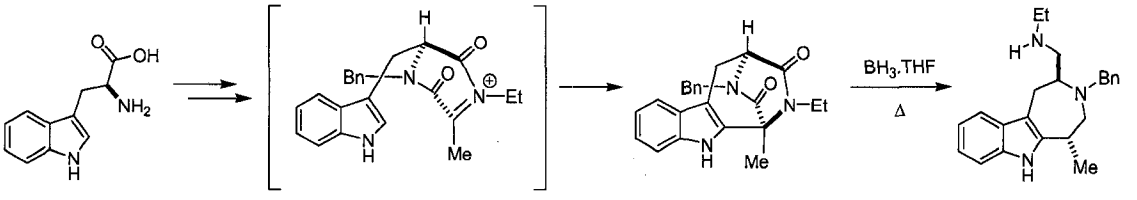
Alan Grubbs
Colorado State University
Department of Chemistry

Abstract: The purpose of this research will be to explore new reactions that will exploit an N-acyl Pictet-Spengler reaction[1,2] in combination with a stereoselective Borane-THF reduction to access complex 10 and 11 membered nitrogen heterocycles derived from naturally occurring cyclic amino acids. Specifically this research will target 1) An N-acyl Pictet-Spengler reaction of cyclic dipeptides derived from L-tryptophan or L-phenylalanine, in combination with L-*cis*-3-hydroxy proline or L-*cis*-3-hydroxy pipecolic acid.

Background and significance:

Recently an article by a group at Novartis in Basel, Switzerland reported the stereoselective transformation of L-typtophan (**1**) derived indole diaza-bicyclo[3.2.2]nonedione **3** to azepinoindole **4** (Figure 1).[3] This report drawing on the initial studies of Ottenheijm and co-workers[4,5] and more recently Mortier and co-workers[6], describes the formation of indole diazabicycle[3.2.2]nonedione via an N-acyl Pictet-Spengler reaction of intermediate **2**.

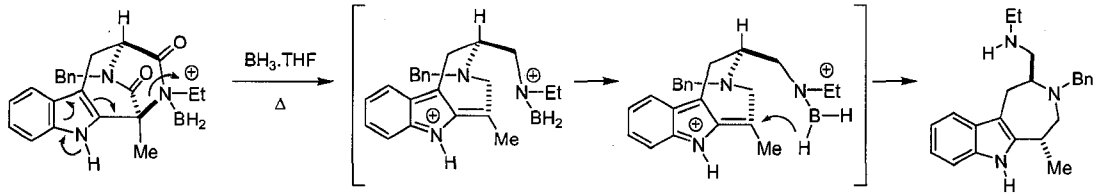
Figure 1: Pictet-Spengler reaction and BH_3·THF reduction.



1 **2** **3** **4**

The reduction step (**3** → **4**), is proposed to occur via cleavage of the C-N bond in **5** via formation of a borate complex which undergoes stereoselective BH_3·THF reduction[7,8] via intermediate **7** (Scheme 1). Some important observations can be drawn from the experimental details.

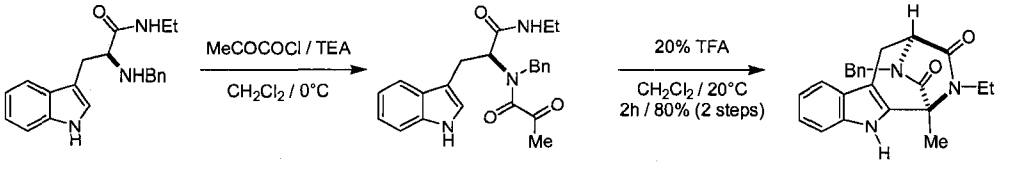
Scheme 1: BH_3·THF directed stereoselective reduction.



5 **6** **7** **4**

The mechanism of the reaction depends on an electron rich amino acid such as L-tryptophan for both the reactivity of the Pictet-Spengler reaction and the formation of intermediate **6**. One limitation of the existing methodology can be seen from an examination of the synthesis of compound **3** (Scheme 2). The ethyl amide of N-benzyl-L-tryptophan was acylated with pyruvyl chloride to generate N-acyliminium ion precursor **9**. This methodology limits the product 4 to compounds generated from methyl of alkyl pyruvyl chlorides.

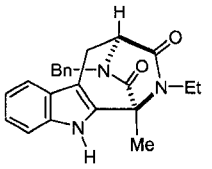
Scheme 2: Synthesis of compound **3** via pyruvyl chloride.



8 **9** **3**

Specific Aims: The goal of our research is to create a new and novel approach to structures such as compound **3** that bear a linker between the methyl and ethyl group (Figure 2). This approach would have some very interesting consequences in subjection of the newly formed cycles **10** and **11** to the BH_3·THF reduction.

Figure 2: L-proline and L-pipecolic acid derived tricycles.



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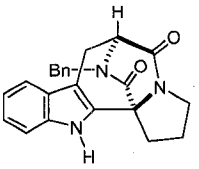

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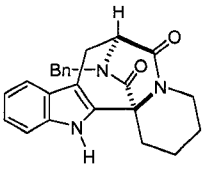
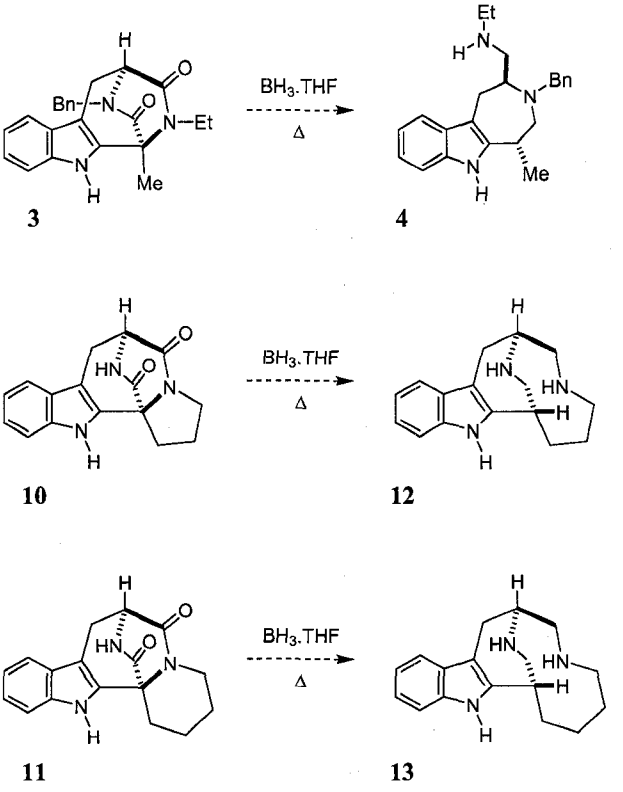


11

The reduction of compound **4** (cleavage of the C-N bond), is a ring cleavage event. In other words, breaking the C-N bond destroys the 6-membered ring leaving only a 7-membered ring in **4**. In our examples the cleavage the C-N bond should result in the formation of a new 10 or 11 membered ring (Figure 3). Moreover, formation of the reported borate complex, should deliver hydride from stereoselectively if not stereospecifically to afford the indicated stereochemistry at the benzylic position.

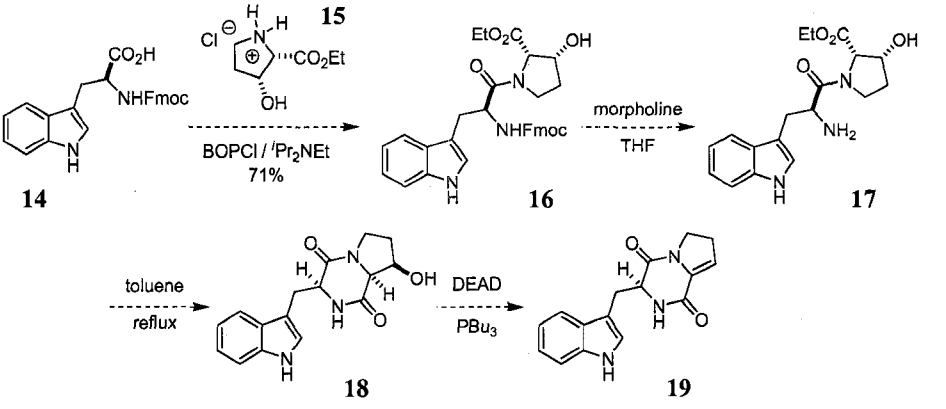
Figure 3: Ring Expansion Reactions.



Research Methods and Design:

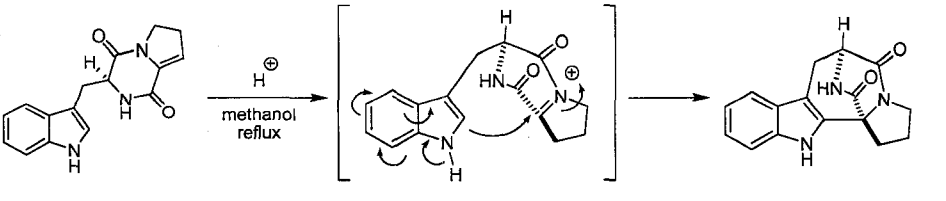
The following synthetic scheme is proposed for the synthesis of compounds **10** and **11**. Coupling of Fmoc protected L-tryptophan **14** with *cis*-3-hydroxy-L-proline[9-12] **15** under standard peptide coupling conditions should afford dipeptide **16**. Removal of the Fmoc group of **16** should expose primary amine **17** which should cyclizes to afford diketopiperazine **18**. Elimination of the secondary alcohol in **18** should generate N-acyliminium ion precursor **19**.

Scheme 3: Synthesis of compound **10**.



Compound **19** should form N-acyliminium ion **20** which, like compound **2** (Figure 1), would be subject to the N-acyl Pictet-Spengler reaction to form **10** (Scheme 4). Analogously, any β-hydroxy amino acid should follow the chemistry in scheme 10. The same chemical sequence in scheme 10 will be repeated to generate compound **11** (Figure 3), with the exception being the replacement of L-*cis*-3-hydroxy proline for L-*cis*-3-hydroxy pipecolic acid.

Scheme 4: N-acyl Pictet-Spengler Reaction



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US, 1999, p 39 pp , Cont -in-part of U S Ser No 474,135, abandoned.

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Appendix 3: Studies Toward the Total Synthesis of Okaramine B.

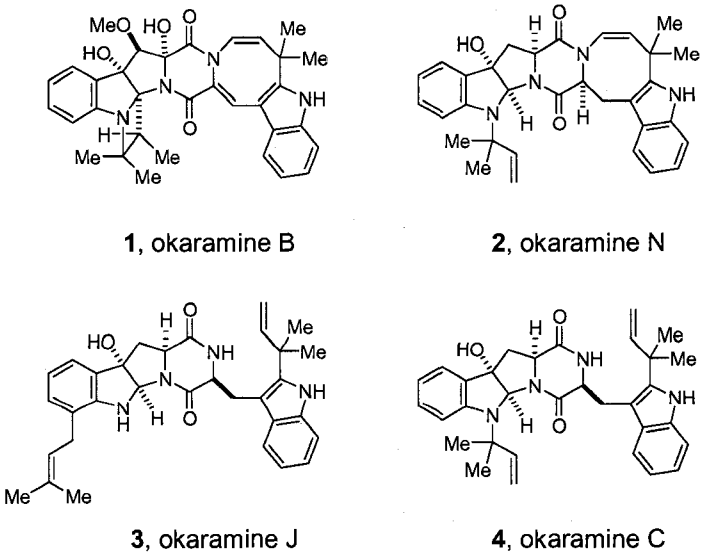
Chapter 1: Introduction

1.1 The Okaramines

1.1.1 Isolation and Structure Determination

Okaramine B (**1**), was isolated in 1989 by Hayashi and co-workers from cultures of *Penicillium simplicissimum* (ATCC 90288) on okara, the insoluble residue of whole soybean (Figure 1).[1] The okaramine family of natural products[1-8] include 18 heptacyclic or octacyclic alkaloids (Figure 14), each with varying degrees of oxidation around a common diketopiperazine core.

Figure 1. Okaramines B, N, J and C.



1.1.2 Biological Activity

Okaramine B (**1**), the most biologically active of the family, exhibited potent insecticidal activity against the 3rd instar larvae of silkworm (LD_{50} = 0.2$\mu g/g$ diet), while others in the family at reduced oxidation states showed little or no biological activity (Table 1).

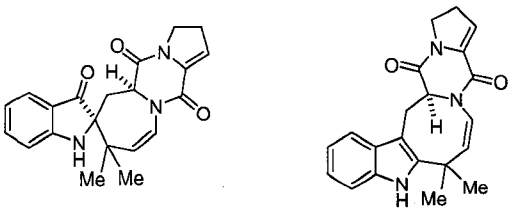
Table 1: Biological Activity.

Compound	LD_{50}(ug/g diet)	Compound	LD_{50}(ug/g diet)
Okaramine B	0.2	Okaramine J	>100
Okaramine C	8	Okaramine N	>100

* The insecticidal activities of okaramines against the 3rd instar larvae of silkworm

Interest in the synthesis and biological activity of related compounds can be traced back to studies of toxigenic fungi isolated from strains of *Aspergillus ustus*. These fungi are important because they commonly infect corn products in early stages of processing. Further studies resulted in the isolation of active compounds produced by these fungi, (+)-austamide (**5**) and (+)-deoxyisoaustamide (**6**) (Figure 2). Similarly, the okaramines are produced by a fungus that infects raw materials produced in the tofu industry.

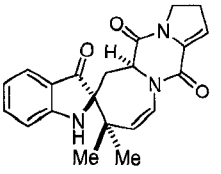
Figure 2: Austamide and 12,13-dihydro-12-hydroxyaustamide.



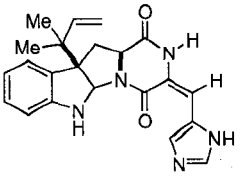
5, (+)-austamide **6**, (+)-deoxyisoaustamide

Okaramine B (**1**) bears some unique structural features that play important roles in the overall biological activity. Composed of 8 fused rings surrounding 5 contiguous stereocenters, okaramine B presents itself as a challenging synthetic target. To date, no synthetic achievement of any portion of okaramine B has been reported. Complicating the potential total synthesis is the unique azetidine ring found in no other natural products. This strained 4 membered heterocycle bearing 3 methyl groups and 2 stereocenters at the junction of a fragile pyrroloindole is the heart of the synthetic challenge. Also posing a daunting synthetic challenge is the sensitive 8 membered azocinoindole ring bearing a bis-enamide functional group. No azocinoindole ring at this oxidation state has ever been synthesized. Many related natural products have held the attention of organic chemists for many years (Figure 3).

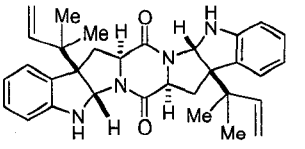
Figure 3. Related natural products.



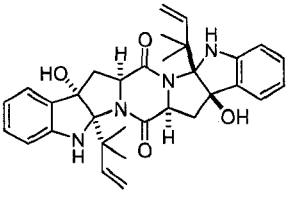
5, (+)-austamide
Corey; **2002**
Kishi; **1979**



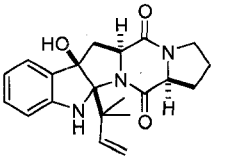
7, isoroquefortine C
Joullie, M. M.; **2002**



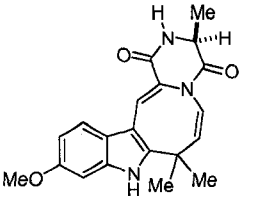
8, amouromine
Danishefsky, S. J.;
1994,1999



9, gypsetin
Danishefsky, S. J.;
1995, 1999



10, brevianamide E
Danishefsky, S. J.; **1999**
Kametani, T.; **1980**

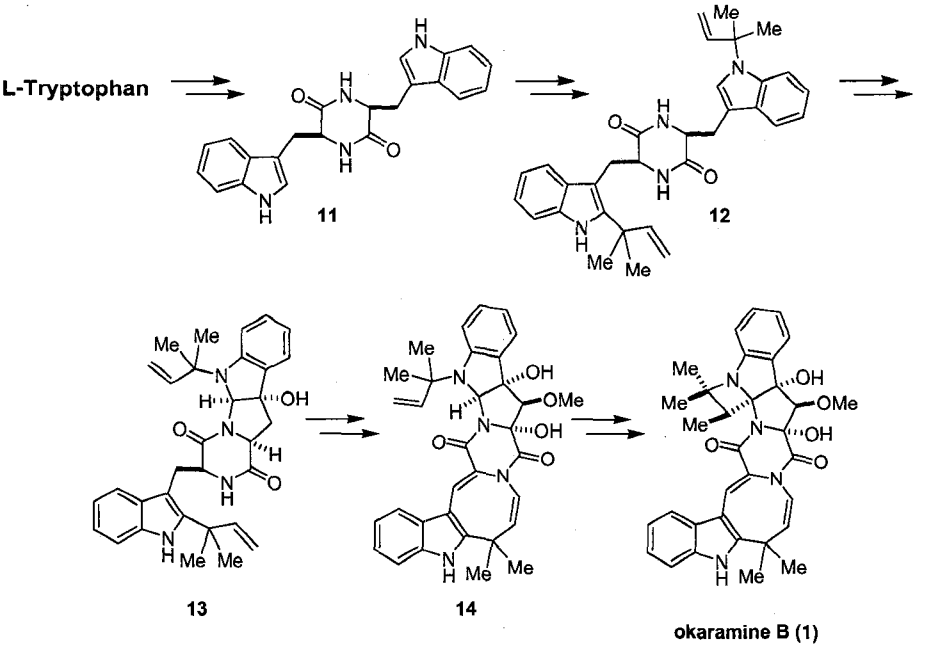


11, cycloechinulin

1.1.3. Biosynthesis of Okaramine B

Each member of the okaramine family of natural products (Figure 4), is derived biosynthetically from two L-tryptophan molecules. The union of two L-tryptophan molecules through a DKP linkage gives the symmetric and unfunctionalized dimer **11**. Through two reverse prenylation events, one at C2 of **12** and the other on the opposite indole nitrogen, generates the acyclic precursors to both the future azocinoindole ring and the azetidine ring in **15**. After a series of oxidation events and formation of the 8-membered azocinoindole, compound **14** stands as likely precursor to okaramine B. A final ring closure through an undetermined mechanism converts **14** to the natural product **1**.

Figure 4: Okaramine biosynthesis.



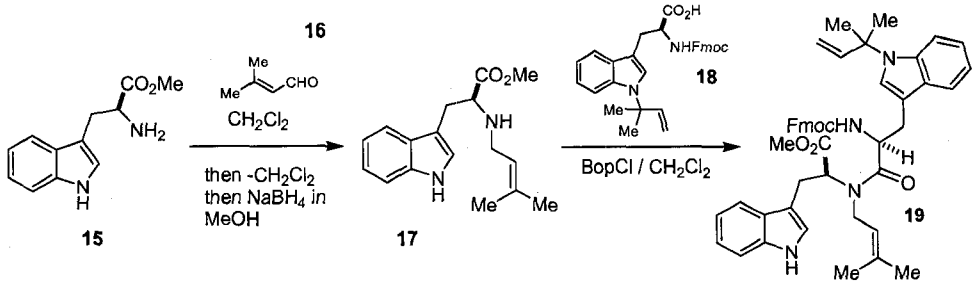
1.1.4. Previous Synthetic Achievements

To date only 3 of the 18 naturally occurring okaramine natural products have been synthesized.[9-11] A detailed examination of each synthesis highlights some of the difficulties that face the total synthesis of okaramine B while at the same time showcasing existing methodology available to access some of the main structural features of the more complex members of the family.

1.1.5 Baran and Corey's Synthesis of Okaramine N.

Baran's synthesis of Okaramine N begins, much like natures synthesis, with two molecules of L-tryptophan (Scheme 1). Thus, the bottom half of okaramine N was constructed using a reductive amination of L-tryptophan methylester (**15**) in methanol with aldehyde **16** to afford a transient imine which was reduced in-situ to the desired allylamine **17** which was coupled without further purification in the presence of BopCl to indole **18** after removal of methanol.

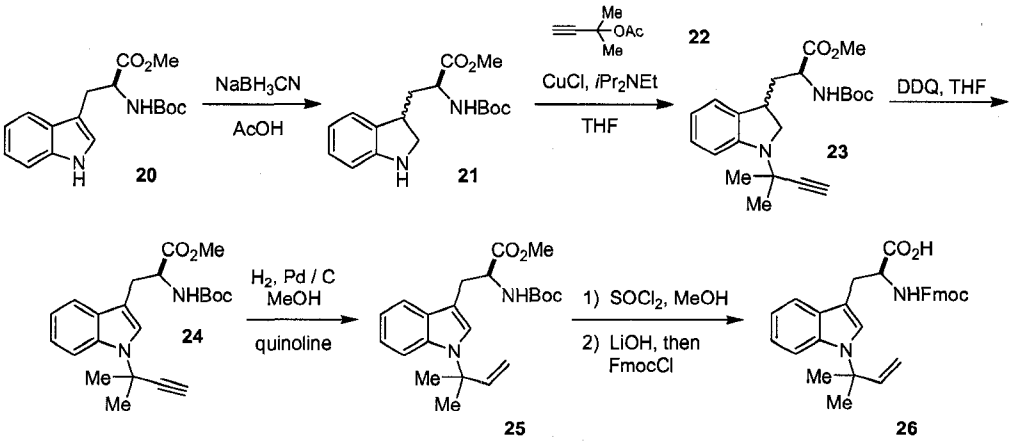
Scheme 1: Top and Bottom Fragments of Okaramine N.



Indole **18**, prepared also from commercially available N-Boc-L-Tryptophan methyl ester was readily available on large scale from a 3-step reduction, alkylation, oxidation sequence (Scheme 2). Treatment of N-Boc-L-Tryptophan methyl ester with $NaBH_3CN$ in AcOH reduced the indole 2,3-double bond to form known dihydroindole **21** which was alkylated via a copper-catalyzed reaction with 2-acetoxy-2-methyl-3-butyne (**22**) to afford compound **23** which was re-oxidized in the presence of DDQ to afford N-reverse prenyl indole **24**. Partial reduction of **24** using H_2, Pd / C, in methanol containing quinoline, gave the desired compound minus a few protecting group manipulations.

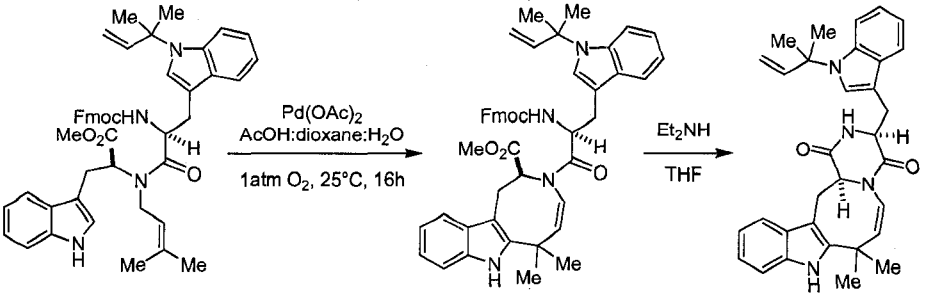
Finally compound **26** was prepared by removal of the Boc-group, hydrolysis of the remaining methyl ester and acylation of the free nitrogen under Schotten-Baumann conditions to provide Fmoc amino acid **26** (Scheme 2).

Scheme 2: Preparation of the N-reverse prenylated fragment of okaramine N.



With both halves of okaramine in place, a method applied to the austamide family of petacyclic dihydroindoloazocine alkaloids was employed to generate the delicate azocinoindole ring (Scheme 3). Thus, treatment of **19** with 1 equivalent of $Pd(OAc)_2$ in 1 : 3.5 : 1 acetic acid-dioxane-water at 23°C for 16 hours provided **27** in 38% isolated yield (44% yield based on recovered starting material). Despite the presence of two indole subunits in **19**, only the N-unsubstituted unit reacted and only 8-membered ring formation was observed. Exposure of **27** to excess diethylamine in THF resulted in Fmoc cleavage and cyclization to form diketopiperazine **28**.

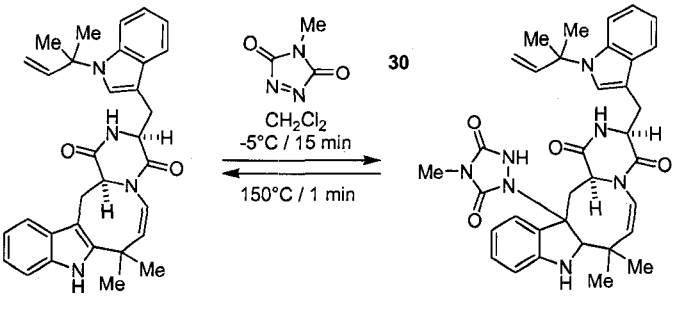
Scheme 3: Palladium mediated cyclization.



19 27 28

At this point the two indole subunits of **28** could both be oxidized under previously reported photooxidation conditions. In fact, the lower, unsubstituted indole ring reacted faster with O_2 across the indole 2,3-double bond. This problem lead to the development of new method to protect the indole 2,3-double bond to remove the reactivity of the lower indole ring and isolate the less reactive, mono-substituted, N-*tert*-prenyl indole ring system.

Scheme 4: Protection of the indole 2,3-double bond.

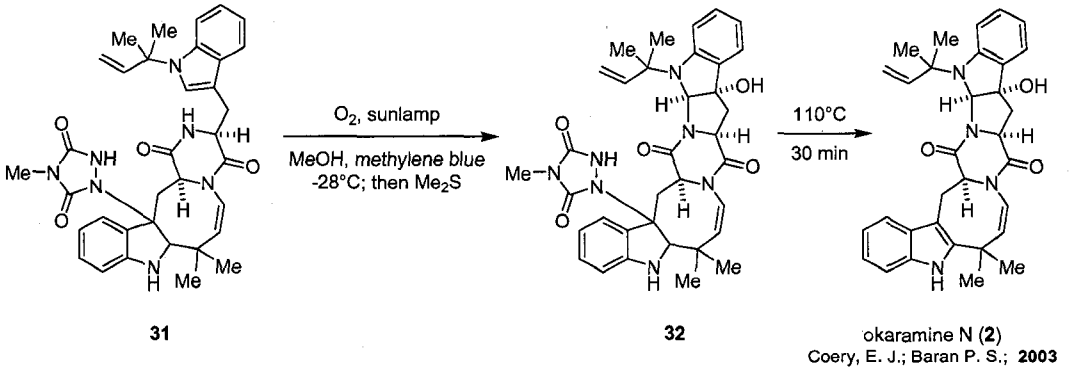


28 31

Amazingly, treatment of **28** with the commercially available "ene" reaction reagent N-methyltriazolinedione (MTAD, **30**) in CH_2Cl_2 at -5°C for 10 min afforded exclusively the

ene product at C3 of the lower unsubstituted indoleazocine subunit (Scheme **4**). Additionally, reversion back to the original indole system could be achieved via thermolysis of the ene reaction product. Finally, photooxidation of **31** was accomplished (methylene blue as a photosensitizer) in methanol via irradiation with a sunlamp followed by reduction of the resulting product by Me_2S afforded the hydroxylated octacycle **32** cleanly. Thermolysis of the mixture at 110°C followed by chromatographic isolation furnished okaramine N (**2**) in 70% yield from **28** based on recovered **31** (ca, 50%, due to incomplete photooxidation).

Scheme 5: Completion of okaramine N.



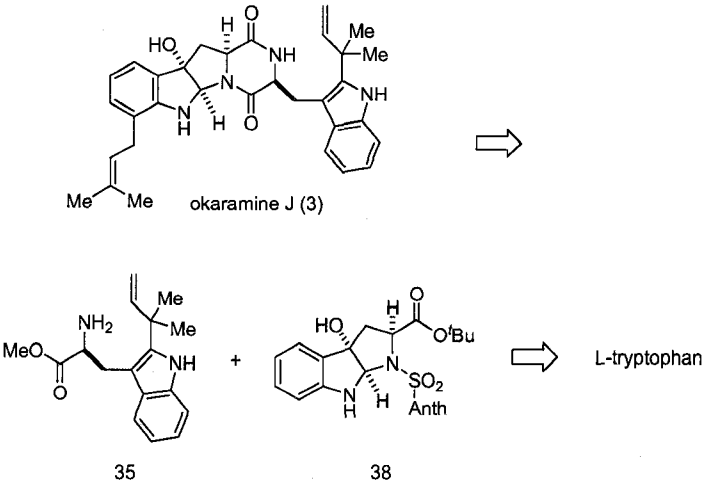
1.2.5 Ganesan's Synthesis of (+)-Okaramine J.

Ganesan's synthesis of okaramine J features a facile Aza-Claisen rearrangement. A closer look at the following rearrangement underscores the relative ease with which the reverse prenyl group migrates from nitrogen to carbon. In the synthesis of okaramine J, this rearrangement was exploited. The synthesis of okaramine congeners that retain the

N-reverse prenyl group must address the tendency for this migration to occur and prevent this non-desired reaction pathway.

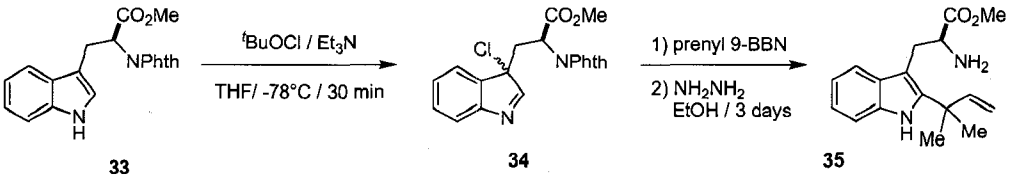
Ganesan's retrosynthesis takes advantage of two previously existing fragments **35** and **38** derived from L-tryptophan reported first by Danishefsky in the total synthesis of himastatin, gypsetin, and brevianamide E (figure 5).[12-17]

Figure 5: Ganesan's retrosynthesis.



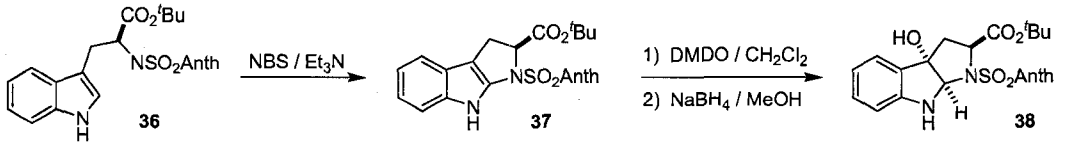
Referring back to Danishefsky's synthesis of gypsetin[13], fragment **35** was prepared from N-phthaloyltryptophan methyl ester **33** (Scheme **6**). Treatment of **33** with tert-butylhypochlorite and triethylamine led to the formation of the unstable 3-chloroindolenine **34**. Addition of freshly prepared prenyl 9-BBN[18] to this intermediate led to the desired C2 reverse prenyl compound **35**. Further removal of the N-phthaloyl group was facilitated via hydrazinolysis in ethanol at ambient temperature for 3 days.

Scheme 6: Danishefsky's reverse prenylation procedure.



The synthesis of fragment **38** reported in the synthesis of himistatin[15] began with an N-anthracenosulfonyl group in the *tert*-butyl ester of L-tryptophan (Scheme 7). Conversion of sulfonamide **36** to pyrroloindole **37** was accomplished via the transient 3-bromoindolenine generated by treatment of **36** with NBS in the presence of triethylamine. Further oxidation of the indole 2,3-double bond with dimethyl dioxirane (DMDO), followed by reduction with sodium borohydride in methanol furnished indolenine **38** in 75% over 2 steps.

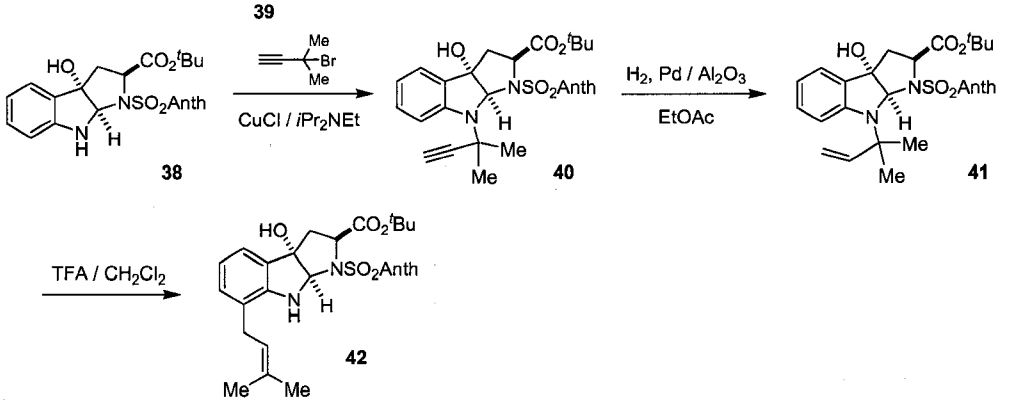
Scheme 7: Danishefky's NBS oxidation protocol.



With both fragments in hand, the stage was set to elaborate known compound **38** to the N-reverse prenyl derivative through alkylation and reduction (Scheme 8). Thus treatment of **38** with bromide **39** in the presence of catalytic CuCl and Hunigs base afforded the N-alkyl derivative **40** in 55% yield (39% recovered sm). The resulting alkyne **40** was surprisingly stable to standard Lindlar reduction which led to the use of a more active

catalyst, 20 wt. % Pd / Al_2O_3, H_2, EtOAc. The *tert*-butyl ester of **42** was then deprotected with TMSOTf buffered with 2,6-lutidine. Suprisingly, the TMSOTf deprotection sequence was accompanied by rearrangement of the N-reverse prenyl group to the C7 prenylated analog. Alternate conditions (TFA) also produced the rearrangement leaving the *tert*-butyl ester intact. The authors propose a charge accelerated aza-Claisen rearrangement similar to that originally proposed by Carnahan and Hurd.[19] Also proposed is a strong Thorpe-Ingold effect[20-23] placing the vinyl group in the desired conformation away from the bulky sulfonamide and by the inductively electron-withdrawing nature of the other functionality present in the hexahydro[2,3-*b*]pyrroloindole.

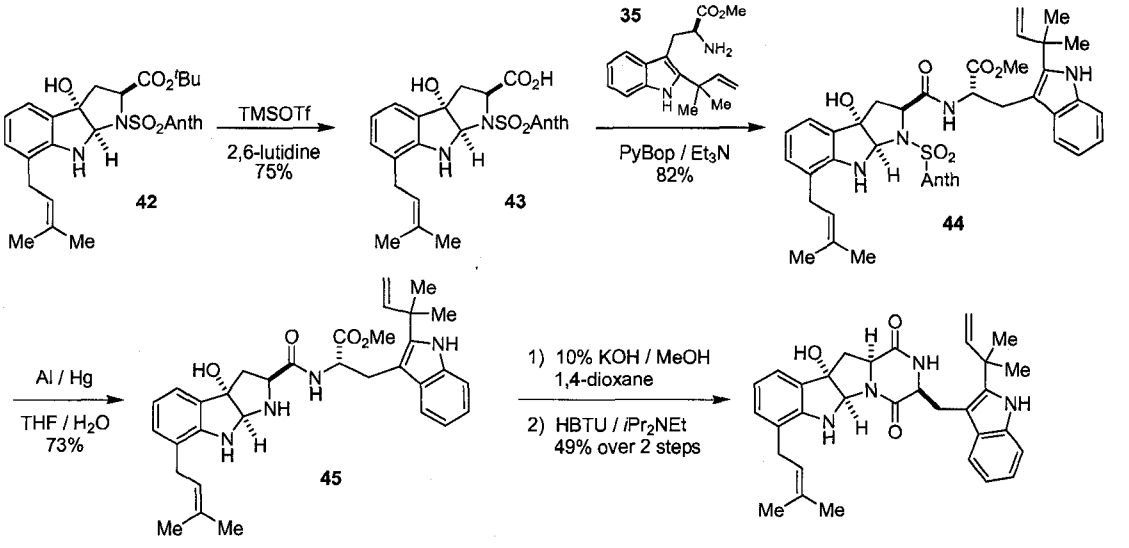
Scheme 8: Charge accelerated aza-Claisen reaction.



It is interesting to note that the original target of Ganesan's group was the total synthesis of okaramine C (Figure 1). However this effort was thwarted upon observation of the facile aza-Claisen rearrangement. The formation of **42** did present itself as an intermediate suitable for the serendipitous synthesis of okaramine J (Scheme 9). To that

end the *tert*-butyl ester of **42** was removed with TMSOTf in the presence of 2,6-lutidine to afford acid **43**. Coupling of the free acid with amine **35** afforded the desired dipeptide **44** in good yield. Reductive removal of the anthracenylsulfonamide protecting group afforded the DKP precursor **45**, which cyclized to the desired DKP only after hydrolysis of the methyl ester and subsequent treatment with standard peptide coupling conditions. This sequence led to the formation of (+)-okaramine J in 49% yield.

Scheme 9: Total synthesis of okaramine J.

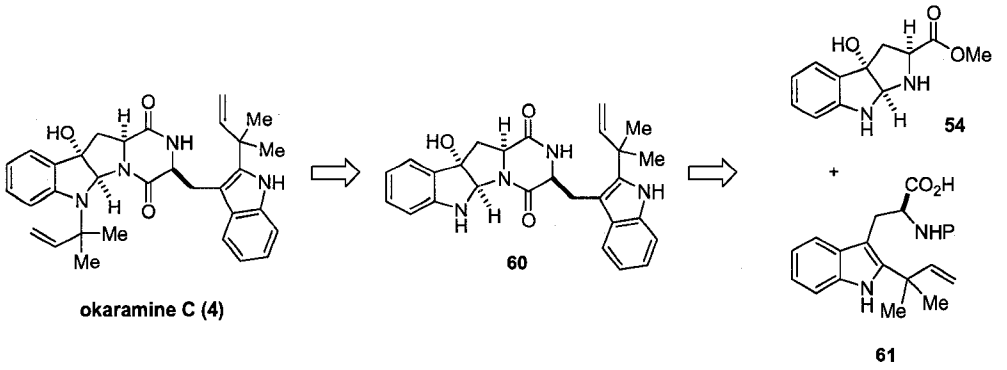


1.2.6 Ley's Synthesis of (+)-Okaramine C.

Okaramine C, at first sight, appears to be the simplest target within the okaramine family of natural products. As such, this compound was the original of Ganesan in the previously described synthesis above. Highlighted in the Ganesan's work toward

okaramine C was the facile charge accelerated aza-Claisen rearrangement that prevented a direct approach to okaramine C and serendipitously offered a route to okaramine J. Ley's entire approach toward okaramine C involved the suppression of the aza-Claisen rearrangement through a late installation of the N-reverse prenyl group. The retrosynthetic plan is then very similar to Ganesan's synthesis with the exception being the reverse prenylation event introduced as the last step in the sequence (Figure **6**).

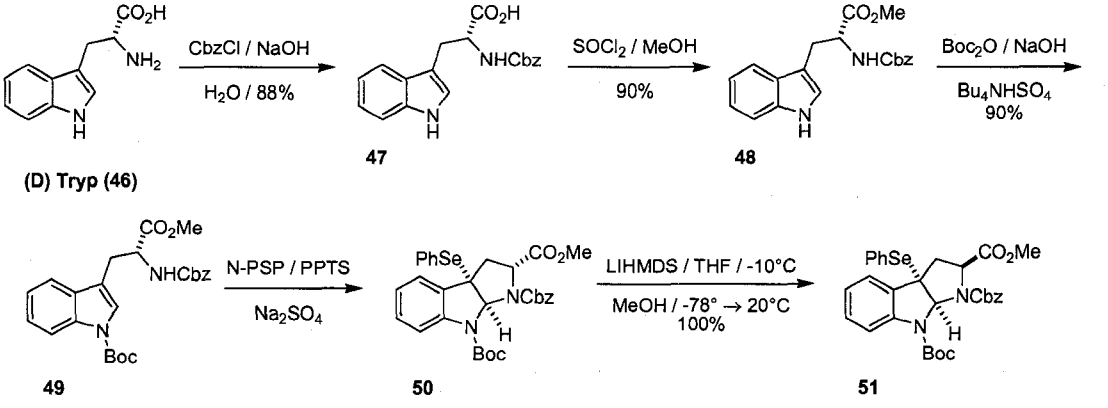
Figure 6: Ley's retrosynthetic plan.



With this strategy in mind, Ley, like Ganesan, would utilize the previously reported C2 reverse prenylated analog **61**. A new synthesis however would be required for the pyrroloindole **54**. Utilizing an selenation / oxidation strategy, intermediate **54** was prepared from D-tryptophan **46** (Scheme 10). Thus Cbz protection of **46** followed by formation of the methyl ester and Boc protection of the indolic nitrogen afforded **49** in 71% yield over 3 steps. Treatment of **49** with N-(phenylseleno)phthalimide (*N*-PSP) resulted in seleno-cyclized pyrroloindole **50** as a single diastereomer in 89% yield. The stereochemistry of the amino ester **50** was reversed completely from the non-natural D-conformation to the natural L-conformation using an epimerization protocol in the

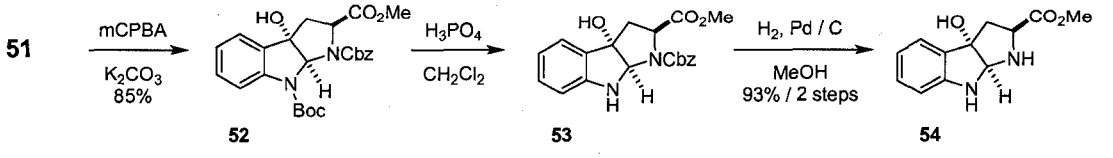
presence of LiHMDS and methanol to afford naturally configured amino ester **51** (Scheme 10).

Scheme 10: Selenation / Oxidation / Epimerization.



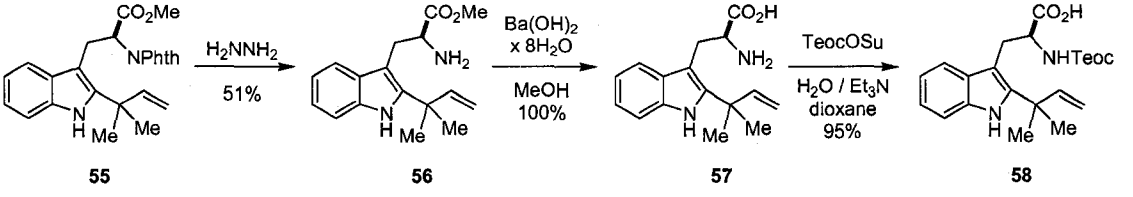
Oxidative deselenation of **51** was effected on addition of wet *m*CPBA giving the corresponding alcohol **52** in 92% yield bearing the same stereochemistry as the original selenide **51** (Scheme 11). Removal of the N-Boc protecting group proved somewhat troublesome however using a new and mild procedure reported by a group at Pfizer[24] the deprotection was achieved followed by hydrogenolysis of **53** to afford the desired pyrroloindole **54** in an overall yield of 50% over 8 steps.

Scheme 11: Oxidative deselenation.



With the left-hand fragment successfully completed, again, Danishefsky's intermediate **55** was used as a starting point. To this end, the phthalimide group was removed in the presence of hydrazine followed by ester hydrolysis facilitated by barium hydroxide in methanol (Scheme 12). Substitution of the robust phthalimide group with the fluoride labile Teoc group allowed for standard peptide coupling of fragment **58** and **54** which cyclized concomitantly to diketopiperazine **59** upon removal of the Teoc group. The use of the Teoc group was necessary due to over-reduction that occurred upon removal of the Cbz analog or racemization that occurred upon removal of the Fmoc analog using amine bases.

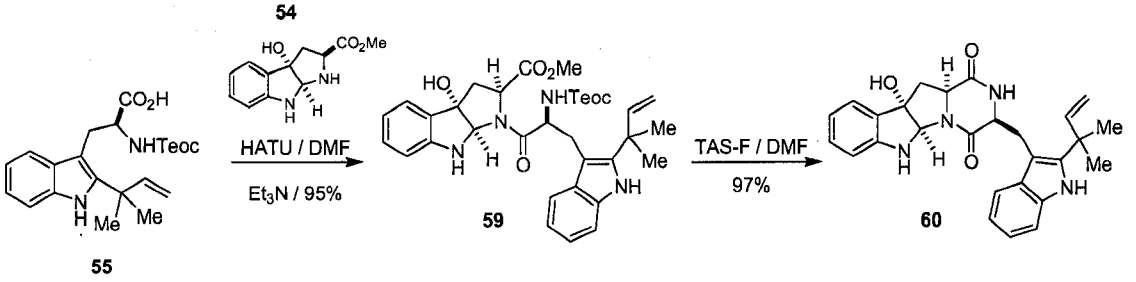
Scheme 12: Protecting group manipulation.



55 **56** **57** **58**

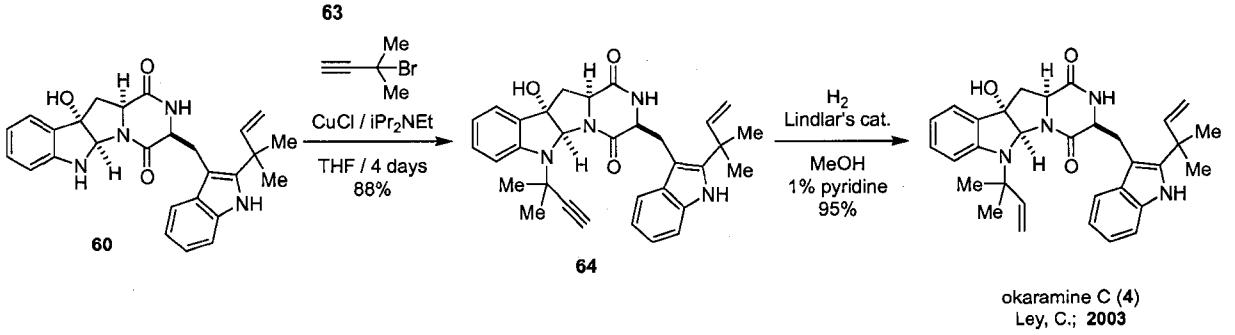
Thus compound **58** was coupled to acid **54** was mediated by o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), followed by deprotection with tris(dimethylamino)sulfur(trimethylsilyl) difluoride (TAS-F), which was accompanied by cyclization to DKP **60** with loss of methanol (Scheme **13**).

Scheme 13: Peptide coupling and DKP formation.



At this point most known methods for installation of the reverse prenyl group on the anilinic nitrogen failed[10], however subjection of **60** to the corresponding alkynyl bromide in the presence of copper(I) chloride effected the transformation relatively smoothly. Under these conditions the desired alkyne **64** could be isolated in 70% yield along with 20% unreacted starting material (Scheme **14**).

Scheme XX: The late-stage reverse prenylation: Synthesis of okaramine C.



1.2.7 Conclusions and Goals.

The syntheses outlined above share many common synthetic approaches. Also embedded in each synthesis are carefully crafted reaction pathways that exploit or

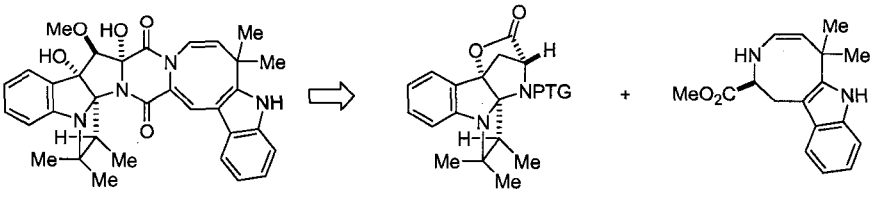
circumvent the natural reactivity of the okaramine backbone. It is only through careful consideration of each approach that a meaningful proposal can be made that ultimately will lead to the total synthesis of the most complex member of the family, okaramine B. The complexity of the okaramines increases with oxidation state, number of rings, and number of stereocenters. The following pages describe attempts to synthesize okaramine B. Each synthetic approach was designed around the installation of the sensitive azetidine ring. The goal of this work aims to highlight potential pitfalls of certain disconnection patterns and to summarize a body of work that may lead to a biomimetic series of transformations to address the late installation of the azetidine ring present in okaramine B.

Chapter 2: Toward Okaramine B

2.1 Azetidine formation by carbon-nitrogen bond formation: The vinyl indole approach

Our initial approach to okaramine B utilized a disconnection sequence (Figure **7**) that completely separated the left and right hand fragments into a compact pyrroloindole bearing the key azetidine moiety and the azocinoindole **66** previously reported by Corey and Baran.[10]

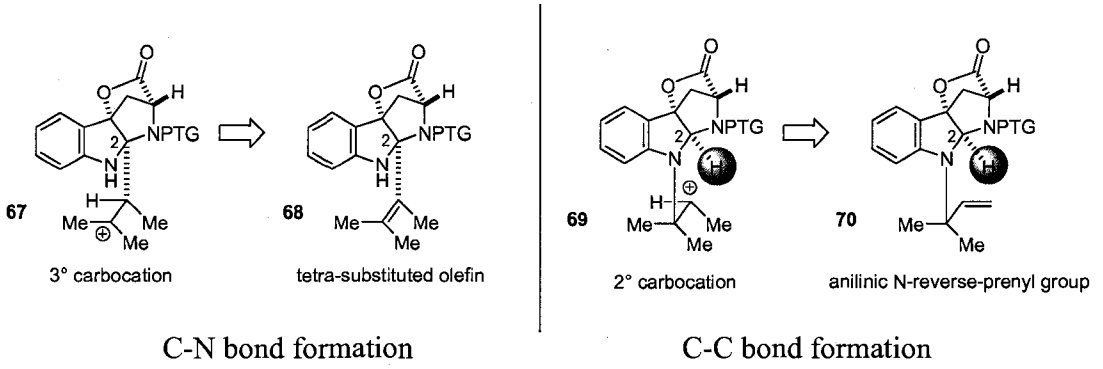
Figure XX: Retrosynthesis via the Spiro-Lactone.



Okaramine (1) 65 66

With this strategy in mind, the problem of the highly oxidized pyrroloindole **66** bearing all of the stereochemical elements could be isolated. Upon the successful completion of **65** a number of possible peptide coupling strategies could be envisioned to join the known fragment **66** and unite the left and right hand fragments of okaramine B. The pyrroloindole bearing oxidation at C3 has been historically constructed in a manner similar to Danishefsky,[13] or Corey and Baran[10]. Following this precedent, and excluding the possibility of an unprecedented 2 + 2 cycloaddition, the azetidine can be formed by formation of the C-C bond or the C-N bond as shown (Figure **8**).

Figure XX: Azetidine Formation Strategies.

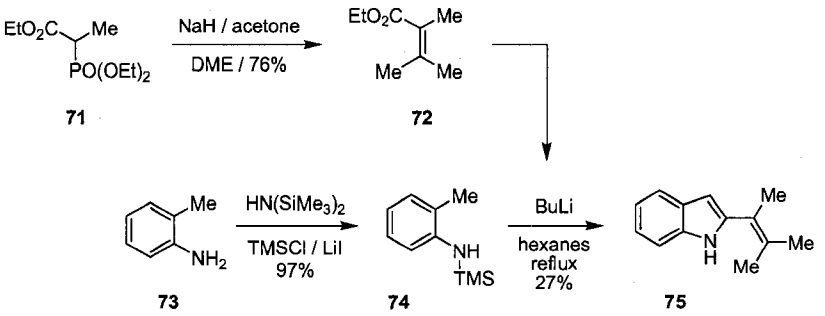


Without a direct method in hand to functionalize the C2 C-H bond (69-70, green) in order to generate a carbon centered radical or anion, a route was chosen to install all 3 methyl groups of the azetidine via tetra-substituted olefin **68** which could serve as a precursor to cation **67** en-route to the requisite azetidine. Although a direct route to functionalize the C2 C-H bond was not initially in hand, one intrinsically promising

aspect of the C-C bond formation route is that the N-reverse prenylation sequence now has a strong precedent.[9,11]

Our C-N bond formation approach begins with a C2 vinyl indole process first described by Smith and Co-workers.[25] Therefore the requisite ester **72** was constructed from the H.W.E. reaction of phosphonate **71** and acetone to afford **72** in 76% after vacuum distillation (Scheme **15**). The dianion of TMS-protected *o*-toluidine was generated in refluxing hexanes in the presence of n-BuLi to afford after cooling, a bright orange solid that was charged with preformed ester **72**.[26,27] After ketone formation and subsequent Peterson olefination, the desired previously reported vinyl indole **75** was obtained as a dark crystalline solid.[25]

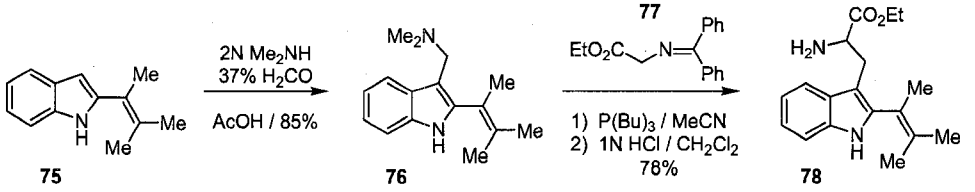
Scheme 15: The Vinyl Indole Process.



Compound **75** was then treated with aqueous dimethylamine in the presence of formaldehyde using acetic acid as solvent to afford, after neutralization with NaOH, the precursor to a Somei-Kametani reaction (Scheme 16). The second nitrogen of the future pyrroloindole was then introduced as its benzophenone imine by reaction with indole **76** with benzophenone imine **77**[28] using catalytic tributylphosphine in refluxing acetonitrile.

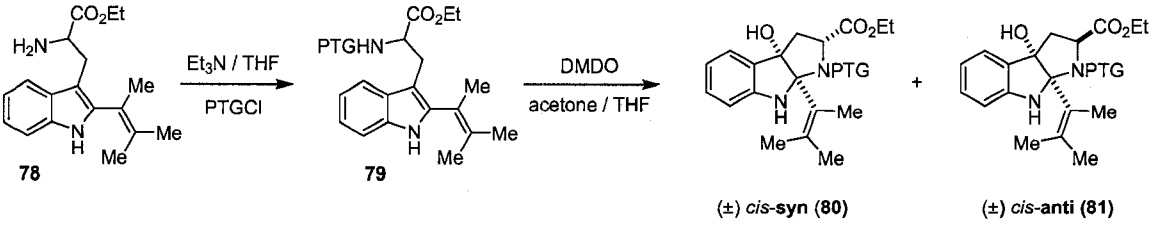
The transient imine was directly hydrolyzed in 1N HCl to afford, after neutralization with triethylamine and aq. $NaHCO_3$, the desired amino ester **78**.

Scheme 16: Elaboration to the amino acid.



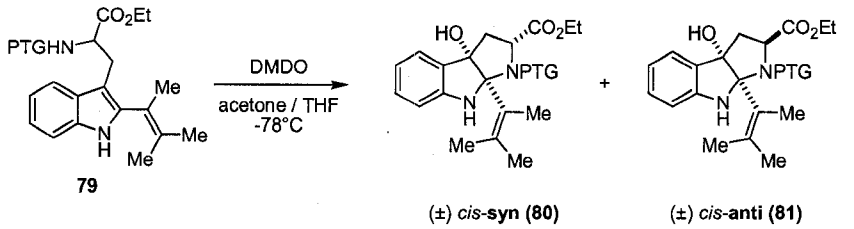
At this point a series of protecting groups were installed on the amino acid nitrogen in anticipation of mixed stereoselectivity upon oxidative cyclization. Thus the general scheme was was followed anticipating the potential (±) cis-syn **(80)** or (±) cis-anti (**81**) stereoisomers (Scheme 17).

Scheme 17: Towards the *spiro*-lactone.



As anticipated, the nature of the protecting group has a strong influence on the stereochemical outcome. Fortunately, a series of protecting groups screened by Danishefsky for a similar system[29,30], provided a suitable protecting group to obtain almost exclusively the desired (±) *cis*-syn product (Table 2).

Table 2: Effects of N-protection on Pyrroloindole Stereochemistry.

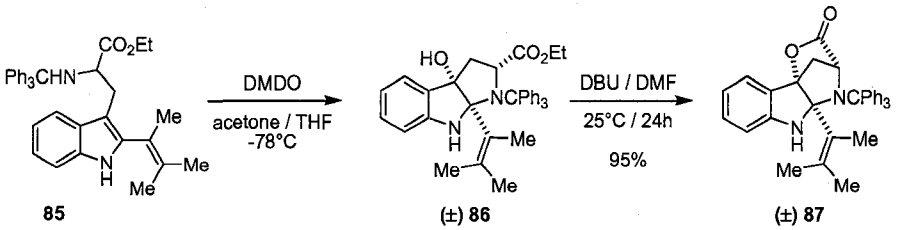


(±) *cis*-**syn (80)** (±) *cis*-**anti (81)**

PTG =	**(80) vs (81)**	**% Yield**
Cbz (82)	**1 : 1**	**82**
Boc (83)	**1.3 : 1**	**93**
SO_2Anth (84)	**3.7 : 1**	**74**
CPh_3 (85)	**> 99 : 1**	**86**

With access to reasonable quantities of the *cis*-syn product **86** (Scheme 18), we were pleased to find that simply treating hydroxyl ester **86** with DBU in THF effected complete esterification to afford *spiro*-lactone **87** with the desired *syn*-relationship at all three stereocenters (Scheme **18**).

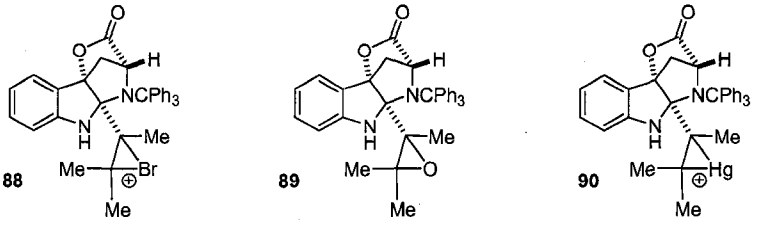
Scheme 18: Stereoselective oxidative cyclization followed by *spiro*-lactonization.



The proposed advantages of compound **87** were that only the two intended functional groups to react were exposed for further manipulation. The hydroxy ester **86** was protected as the corresponding lactone and the other nitrogen was blocked with the trityl

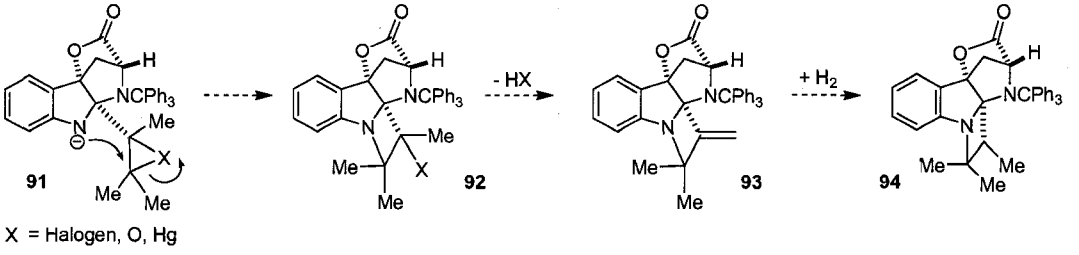
group. This, in theory, exposed only the anilinic nitrogen and the pendant olefin for azetidination attempts. Some of the proposed intermediates en-route to a future azetidine were cation precursors (Figure 9).

Figure 9: Proposed azetidine precursors.



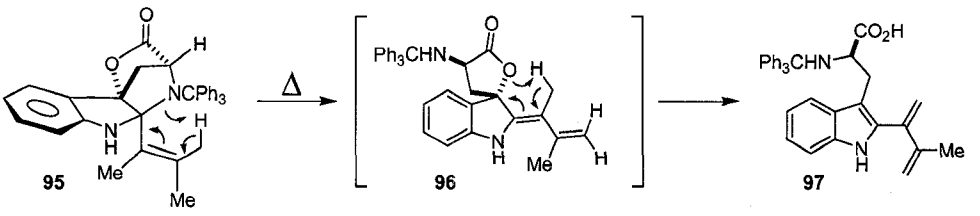
Upon capture of cyclic intermediates **88-90** via the anilinic nitrogen, the leaving group after a 4-*exo*-cyclization would be poised for subsequent elimination and finally hydrogenation to generate the third methyl group around the azetidine (Scheme **19**).

Scheme 19: Proposed azetidination, elimination and hydrogenation.



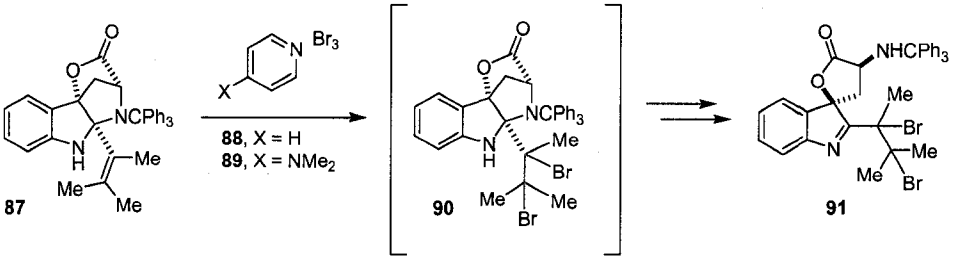
Unfortunately, all attempts to functionalize **95** (Figure **10**), were thwarted due to an unexpected background decomposition pathway. Thus even prolonged exposure of **95** to heat promoted the "ene" decomposition pathway leading to diene **96** and then acid **97** (Figure 10).

Figure 10: Decomposition pathway.



Adding to the difficulty of functionalizing **87** was the unexpected lability of the pyrrolodindole in generation of imine **91** (Figure **10**). Thus even mild treatment of **87** with pyridinium tribromide (**88**) or 4-dimethylamino pyridinium tribromide (**89**) not only effected the desired bromination of the double bond but any trace acid protonated the nitrogen bearing the trityl group which promoted the generation of *spiro*-indolenine **91** which prevented the isolation of pyrroloindole **90**.

Figure 10: The *spiro*-indolenine.

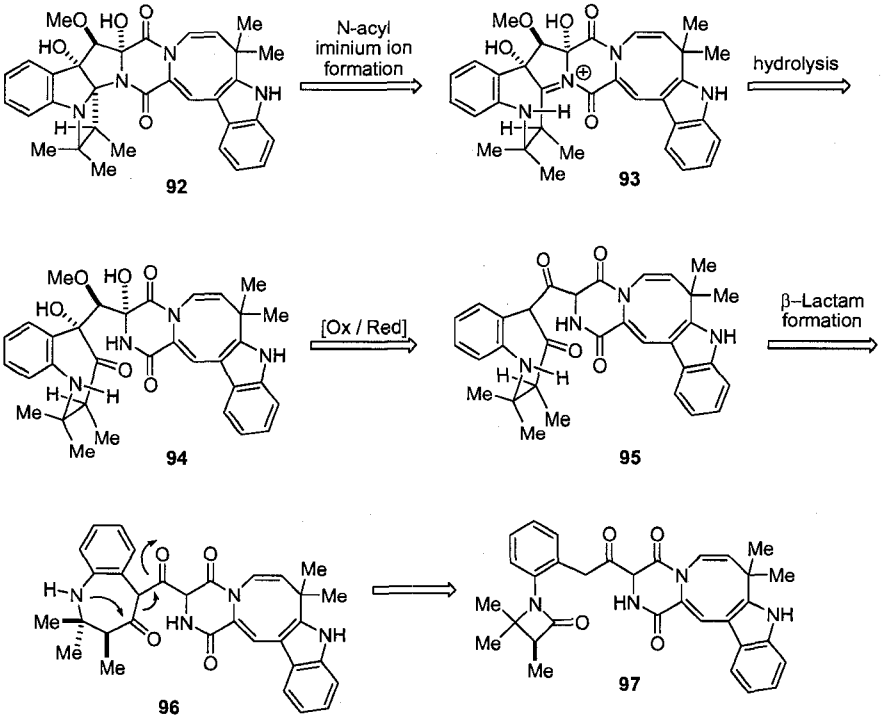


Due to the array of difficulty encountered with the C-N bond forming approach including the unexpected decomposition pathway outlined in Figure **10**, and the instability of pyrroloindole **90**, the C-N bond forming approach was abandoned in favor of a more biomimetic disconnection pattern.

2.2 The β-Lactam Approach.

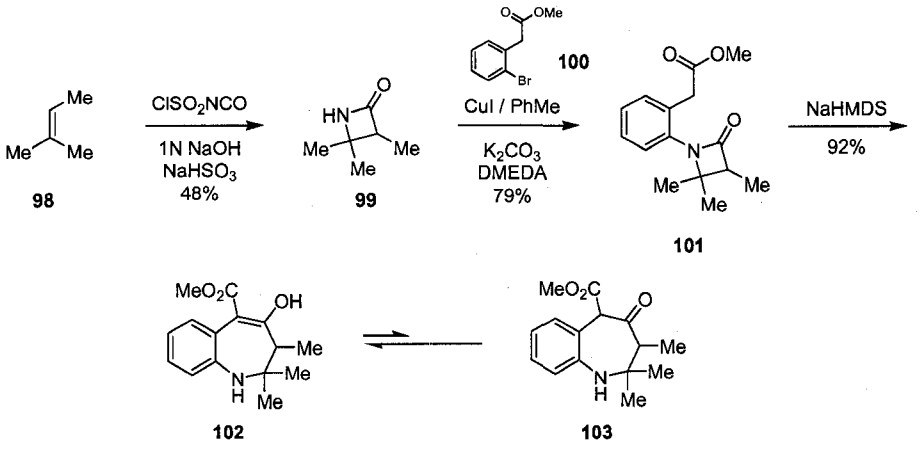
An interesting and biomimetic disconnection sequence was proposed by Prof. Dave Evans (Figure **12**). This retrosynthetic analysis follows are very logical series of well precedented reactions, however, it too fails due to unforeseeable patterns of reactivity. The proposal begins through disconnection of azetidine **92** via generation of the N-acyl iminium ion **93**. Hydrolysis of the iminium ion leads to trimethyl dihydro benzo azepinone **94**. After removing two levels of oxidation and introducing one reduction step we arrive at a more simple azepinone, compound **96**. The 7-membered ring can be reduced to a simple N-phenyl β-lactam **97**, through a retro-enolate addition. This proposed plan reduces our initial synthetic target to an analog of compound **97**.

Figure 12: Prof. Evans Retrosynthetic Analysis.



With this strategy in mind, β-lactam **101** was targeted (Scheme **20**). Thus treatment of 2-methyl-2-butene was treated with chlorosulfonyl isocyanate followed by hydrolysis with 1N NaOH in the presence of sodium hydrogen sulfate to produce, after vacuum distillation, β-lactam **99**. Compound **99** was then coupled to arylbromide **100**[31] using conditions recently reported in the Buchwald group.[32] In a manner similar to our retrosynthetic analysis, the enolate of ester **101** was generated using NaHMDS which attacked the adjacent carbonyl of the β-lactam to afford the enol tautomer **102** as expected.

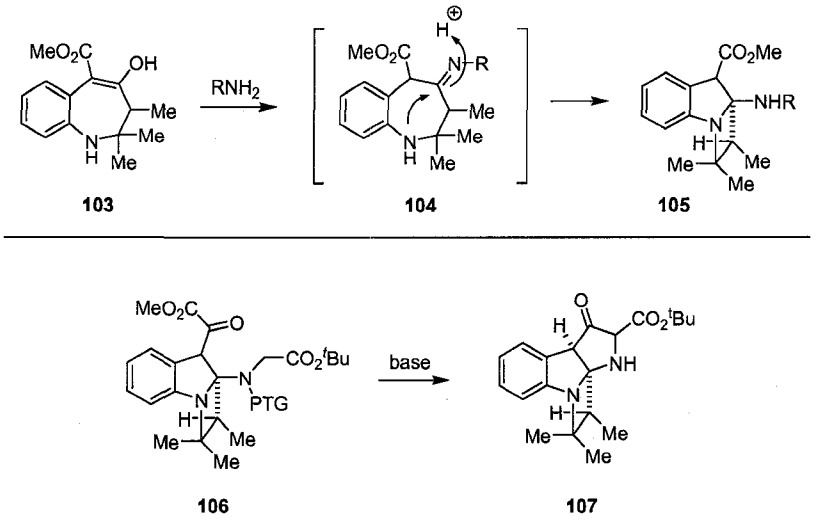
Scheme 20: Buchwald amidation and ring expansion.



Following the original proposal in Figure 12 we envisioned the generation of imine **104** which as proposed would suffer attack from the anilinic nitrogen of **104** through a ring contraction event to form the desired tricycle **105** (Figure 13). If the proposed imine formed, then tricycle **106** could be formed from a suitably protected glycine derivative

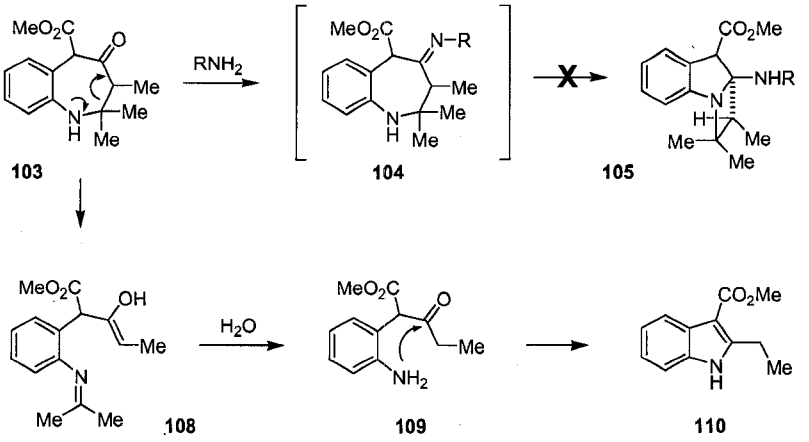
which could undergo further facially selective Deickmann cyclization to install the fourth ring which would be readily poised for further elaboration to a diketopiperazine.

Figure 13: Aminal Formation.



Although the proposed Deickmann cyclization appeared reasonable at the onset, an unexpected reaction prevented the desired transformation at the expense of a ring opening reaction that ultimately generated 2-ethyl indole **110** (Scheme 21). Thus treatment of azepine **103** with various amines under anhydrous conditions gave only imine **108** through a retro-Mannich fragmentation. Further hydrolysis of the incipient imine and condensation gave after tautomerization, 2-ethyl indole **110**. An obvious conclusion is that the observed retro-Mannich fragmentation will occur well in advance of a trans-annular ring contraction to form tricycle **105**.

Scheme 21: The Retro-Mannich Fragmentation.



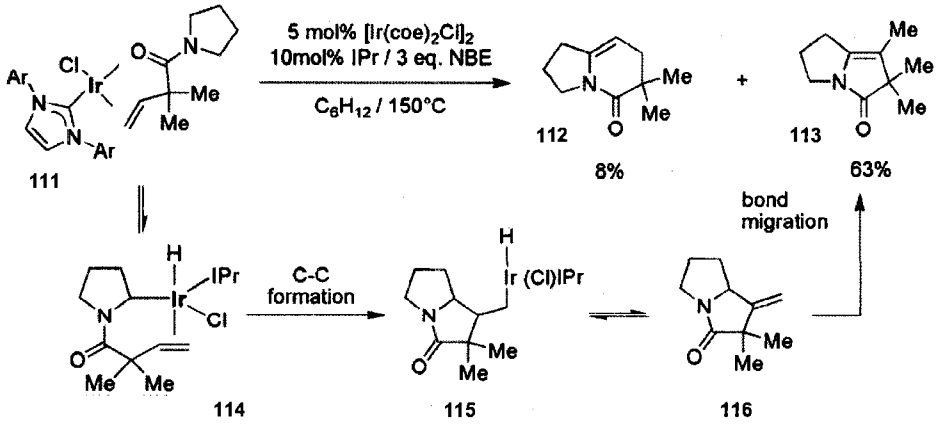
2.3 A Biomimetic Approach to Okaramine B.

A final attempt toward okaramine B and specifically the azetidine functionality incorporates many of the lessons learned in past approaches and syntheses. Some of these guidelines suggest that formation of the carbon-nitrogen bond of the azetidine ring should occur first through well precedented N-reverse prenylation reactions.[9] Also well precedented is an early formation of the pyrroloindole ring system[9,10,29,30] which also serves as a concise method to also introduce the oxidation required at C3. These observations together with the fact that any biomimetic synthesis must start from L-tryptophan, lead toward a compilation of known reactions and reagents to define a final approach toward okaramine B outlined below (Scheme 24).

One of the issues facing this potential route is the lack of background and tools available to functionalize a key carbon-hydrogen bond in okaramine B. Fortunately some precedent does exist and may be the straw that will ultimately break the back of okaramine B. Recently C-H activation methodology has emerged as an increasingly well

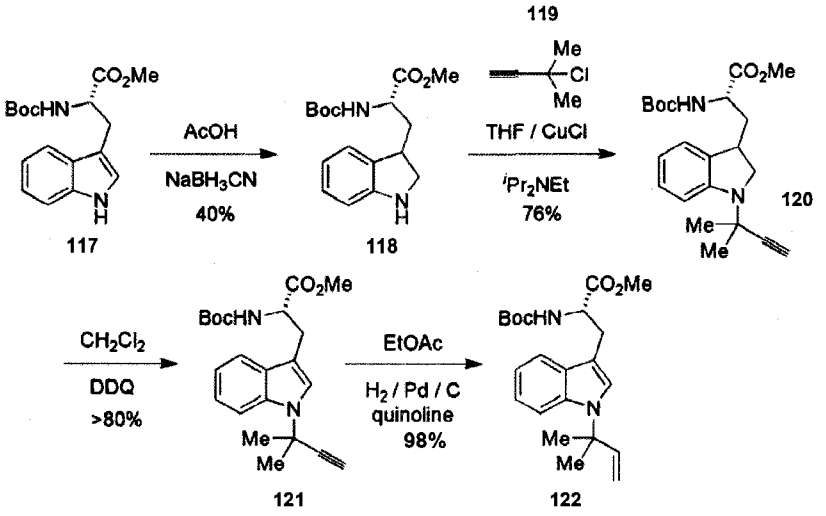
defined science and has found utility in many complicated syntheses. A reaction of particular interest was reported in 2004 by Sammes and Co-workers. In the mentioned report a C-H bond similar to the C-H bond required for azetidination in okaramine B was activated and used to form 5 and 6 membered rings (Scheme 22). Two important functional group relationships were necessary for the observed reactivity. First, the outlined Iridium complex requires pre-complexation to both an amide carbonyl and a terminal, monosubstituted double bond, consequently, appended to a geminal dimethyl group. The nature of this complexation brings the Iridium complex proximal to an activated C-H bond alpha to the mentioned amide nitrogen. Next, insertion, transmetallation, elimination, and finally bond migration ultimately closes to form the desired ring system. This general scheme will be the basis for Iridium mediated C-H activation as a means of azetidine formation in okaramine B.

Scheme 22: Iridium Mediated C-H activation.



Our final approach toward okaramine B begins as mentioned previously with a biomimetic synthesis starting from L-tryptophan. Using the known Gribble reduction / alkylation / oxidation sequence, N-Boc-L-tryptophan methyl ester was treated with sodium cyanoborohydride in the presence of AcOH to produce known indoline **118**[33] (Scheme 23). Alkylation with chloride **119** mediated by copper(I) chloride gave indoline **120** which was then oxidized back to the indole and subjected to Lindlar reduction to produce previously reported N-reverse prenyl indole **122**.[10]

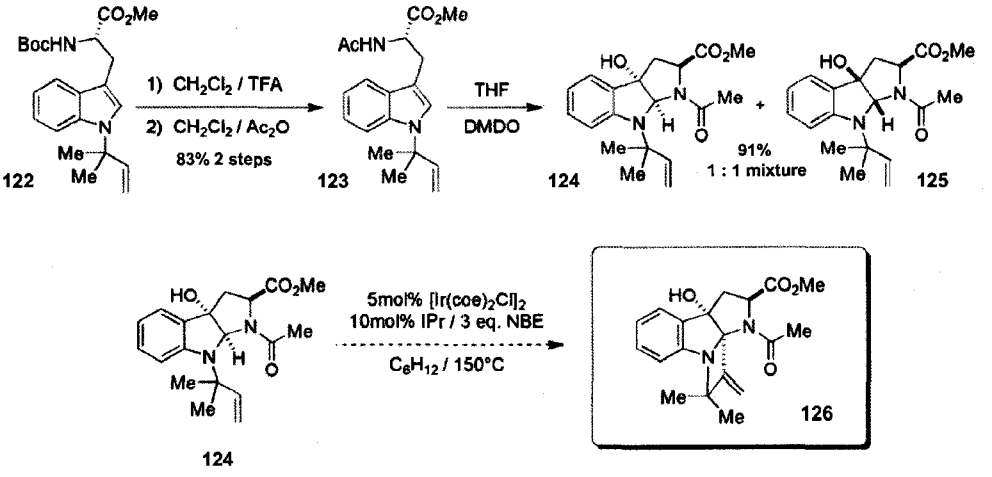
Scheme 23: N-Reverse Prenylation Sequence.



At this point the Boc-carbonate protecting group on the primary nitrogen was exchanged for an acetate group. Although this seems like a useless transformation, it has a specific purpose (Scheme 24). As mentioned before in the Sammes C-H activation protocol (Scheme 22), the coordination of Iridium requires both coordination to a double bond and coordination to a proximal amide carbonyl. Our protecting group exchange serves to mimic this known catalyst configuration. Treatment of the newly formed acetamide with

DMDO gave a 1 : 1 mixture of diastereomeric pyrroloindoles **124** and **125**. The desired cis-anti compound **124** was separated by PTLC.

Scheme 24: Functional group exchange and DMDO oxidation.



Although the key reaction has yet to be executed it is possible that our system will mimic that reported Sammes. Thus coordination to both the terminal double bond and amide carbonyl in **127** should place the Iridium complex in a position next the C-H bond alpha to the amide nitrogen (Scheme **25**). Should this insertion take place, transmetallation similar to the Sames system would give azetidine **128** which upon elimination would afford compound **129**. With no further bond migration possible, an oxygen directed hydrogenation event would deliver hydrogen from the convex face to install stereospecifically the third methyl group.

Scheme 25: Azetidine formation via C-H activation.

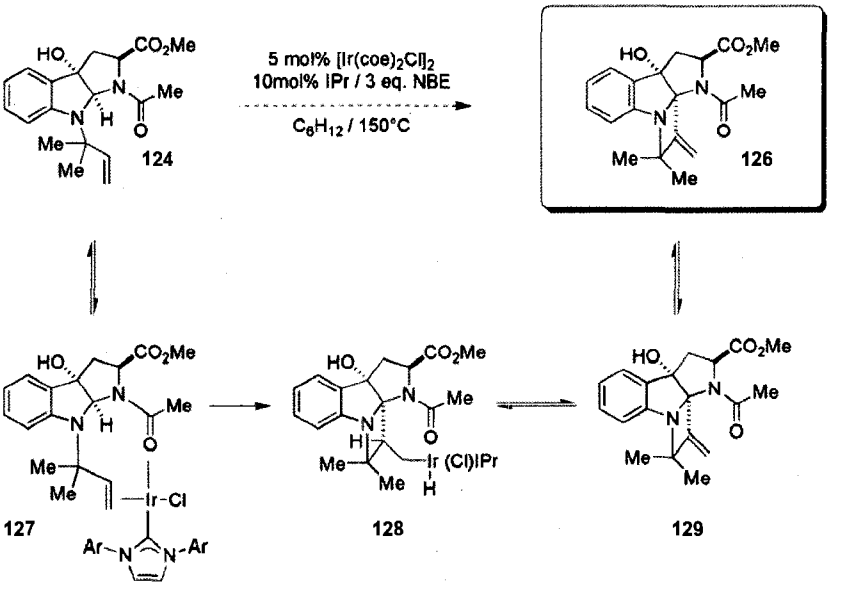
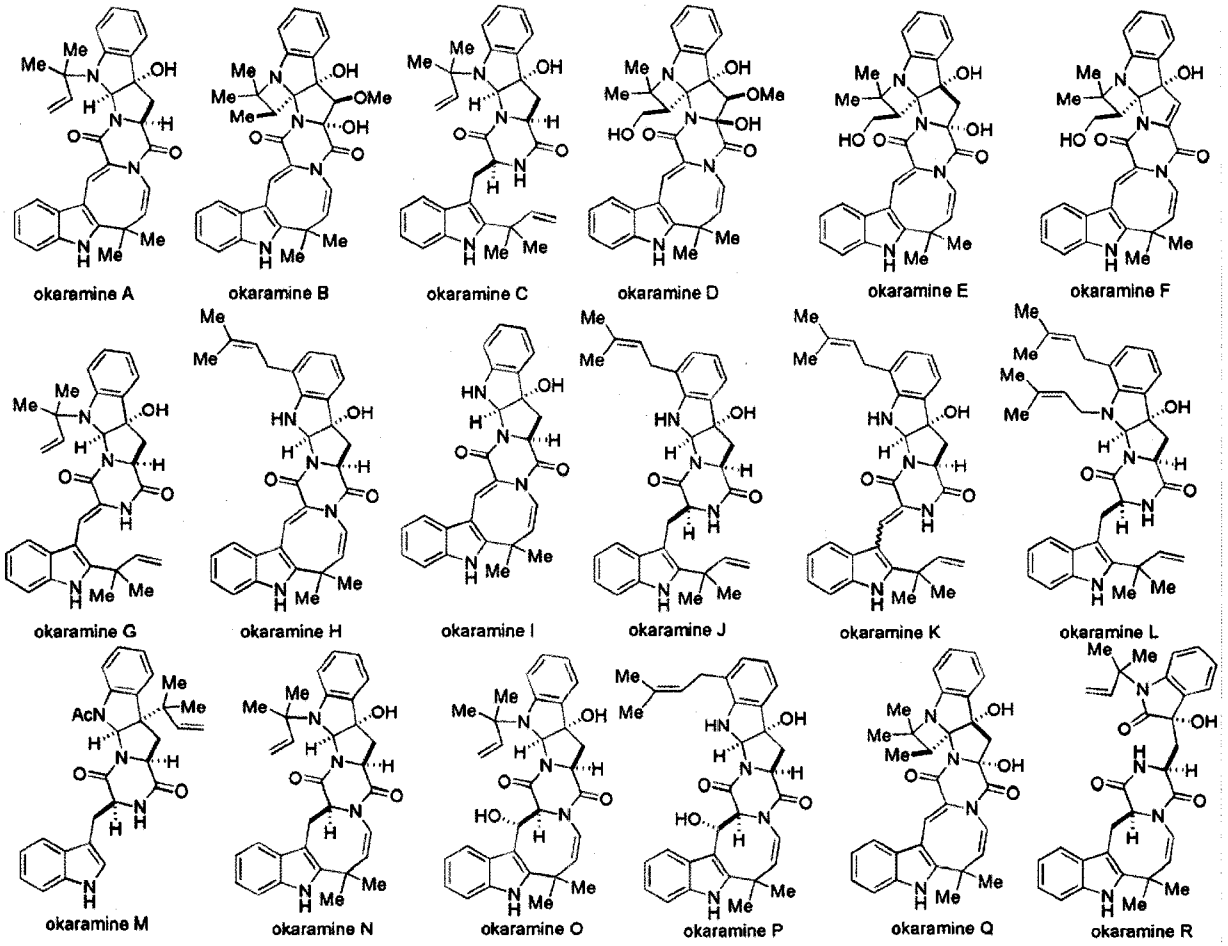


Figure 14: The Okaramines



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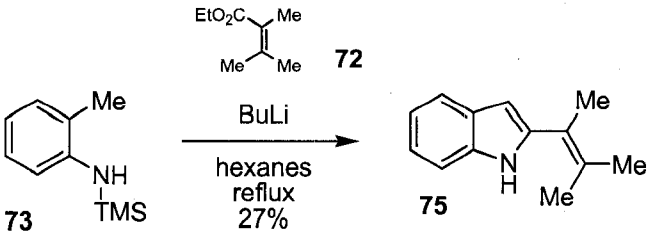
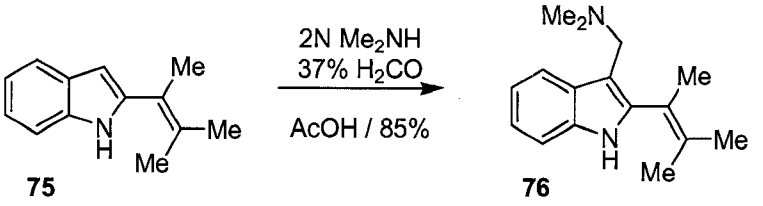
Experimental Procedures: Toward okaramine B

2-(3-methylbut-2-en-2-yl)-1H-indole (75)



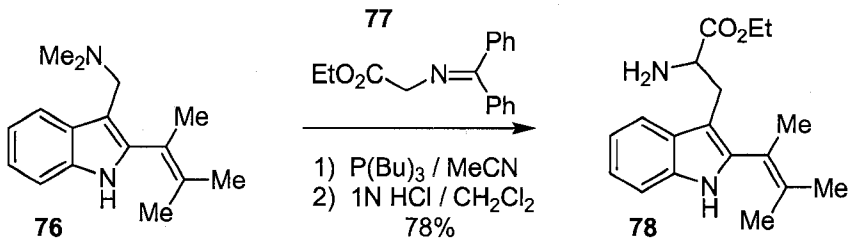
To a mixture of TMS-protected toluidine (**73**) (12.6g, 70.3mmol) in 630ml hexanes was added butyllitium (100ml, 155.0mmol) at 20°C. The mixture was heated to reflux for 6 hours and then cooled to 20°C over 2 hours and cool further to -10°C in an ice-acetone bath. In a separate flask cool a mixture of ester (**72**) (10.0g, 70.3mmol) in 200ml THF to -78°C. Transfer the orange solution containing **73** via cannula to the solution of ester **72** keeping the temperature <50°C. Stir the resulting solution 1 hour at -78°C and then warm to ~50°C before pouring the entire mixture slowly into a cold reservoir of H_2O. Discard the aqueous layer and wash with H_2O, brine and dry over Na_2SO_4, and concentrate. The resulting mixture was dissolved in CH_2Cl_2 and filtered through a pad of silica gel and then concentrated and crystallized from pentane to afford indole **75** as dark crystals (1.9g = 15% yield). (mp 140–143°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88-1.91 (bs, 3H), 1.91-1.96 (m, 3H), 2.05-2.09 (m, 3H), 6.34-6.38 (m, 1H), 7.08 (0.15H, d, J = 1.1 Hz), 7.09-7.11 (0.44H, m), 7.11-7.14 (0.69H, m), 7.15-7.17 (0.45H, m), 7.18 (0.19H, d, J = 1.3 Hz), 7.31-7.38 (1H, m), 7.56-7.62 (1H, m), 7.80-8.04 (1H, bs); HRMS (FAB+): Calc. for $C_{13}H_{15}N_1$ (*m/z*) 185.1204; found (*m/z*) 185.1211.

N,N-dimethyl(2-(3-methylbut-2-en-2-yl)-1H-indol-3-yl)methanamine (76)



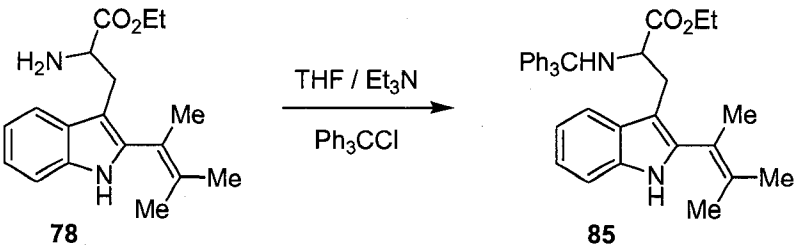
A clean dry round bottom flask was charged with dimethylamine (9.3ml, 18.6mmol), as a 40% solution in H_2O and cooled to 0°C. The mixture was then charged slowly with 1.87g acetic acid. The mixture was stirred until the acetic acid began to crystallize and then was charged with formaldehyde (411mg, 13.7mmol) as a 37% solution in H_2O. The mixture was allowed to warm to 20°C for 15min and then the entire mixture was poured into a flask containing indole **75** (2.30g, 12.4mmol). The mixture was allowed to warm to 20°C overnight and then was quenched with 1N NaOH. The mixture was charged with EtOAc and mixed thoroughly. The organic layer was washed with water, brine and dried over Na_2SO_4, filtered and concentrated to afford 1.75g (58%) of compound **78** as an amber oil that was used without further purification in the next reaction.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, m), 1.86 (3H, m), 1.99 (3H, m), 2.21 (6H, m), 3.46 (2H, s), 7.03-7.20 (2H, m), 7.24-7.32 (1H, m), 7.64-7.73 (1H, bs), 7.76 (1H, d, J = 7.7 Hz); HRMS-FAB: [M+H]+ calcd for $C_{16}H_{22}N_2$, 242.1783; found, 242.1794.

Ethyl 2-amino-3-(2-(3-methylbut-2-en-2-yl)-1H-indol-3-yl)propanoate (78)



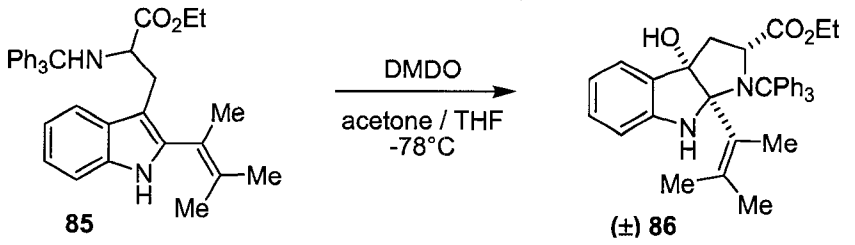
A mixture of gramine **76** (645mg, 2.0mmol) and glycine benzophenone imine **77** (531mg, 2.0mmol) in 20ml MeCN was charged at 20°C with tributylphosphine (405mg, 2.0mmol). The mixture was heated to reflux 24 h and then cooled back to 20°C and concentrated directly. The crude mixture was partitioned between CH_2Cl_2 and 1N HCl and stirred at 20°C for an additional 24h. The mixture was then charged with Et_3N until basic and then charged with an additional 100ml sat. $NaHCO_3$. The aqueous layer was extracted 3X with EtOAc, washed with brine and dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (5-10% MeOH / CH_2Cl_2) to afford the desired amino ester **78** (712mg, 78%) as an amber oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, J = 7.2 Hz), 1.34-1.55 (2H, bs), 1.64 (3H, s), 1.86 (3H, s), 2.00 (3H, s), 2.76-2.87 (1H, dd, J = 14.1, 9.0 Hz), 3.13-3.23 (1H, dd, J = 14.1, 4.9 Hz), 3.78-3.85 (1H, dd, J = 9.1, 4.9 Hz), 4.03-4.23 (2H, m), 7.06-7.20 (2H, m), 7.28-7.34 (1H, m), 7.56-7.62 (1H, m), 7.74-7.93 (1H, bs); HRMS-FAB: [M+H]+ calcd for $C_{18}H_{24}N_2O_2$, 300.1838; found, 300.1822.

Ethyl 3-(2-(3-methylbut-2-en-2-yl)-1H-indol-3-yl)-2-(tritylamino)propanoate (85)



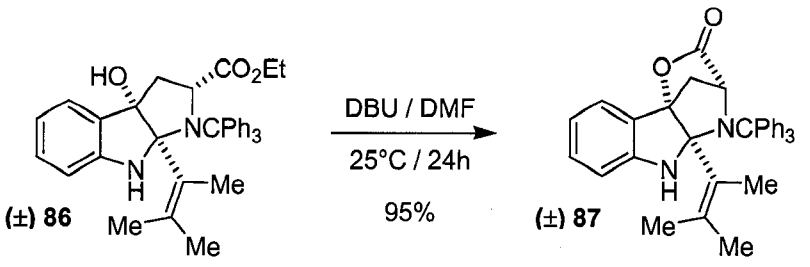
Amine **78** (425mg, 1.42mmol) was dissolved in 8.5 ml THF at 20°C and charged with triphenylmethyl chloride (394mg, 1.42mmol). The solution was then charged slowly with triethylamine (215mg, 2.12mmol). The mixture was allowed to stir at 20°C for 72 hours and then charged directly with brine. The mixture was diluted with EtOAc before removing the lower aqueous layer. The organic layer was washed with water, brine, filtered and dried over Na_2SO_4, filtered and concentrated. The product was purified by silica gel chromatography (50% EtOAc / hexanes) to afford the title compound **85** (437mg, 57). ^{1}HNMR (300MHz, $CDCl_3$) δ 1.59 (3H, s), 1.80 (3H, s), 1.96 (3H, s), 2.85 (1H, bs), 3.12-3.27 (2H, m), 2.95-3.11 (2H, m), 3.53 (1H, t, J = 7.5 Hz), 6.96-7.22 (11H, m), 7.22-7.32 (1H, m), 7.39-7.49 (7H, m), 7.64 (1H, bs); HRMS-FAB: [M+H]+ calcd for $C_{37}H_{38}N_2O_2$, 542.2933; found, 542.2933.

Pyrroloindole (86)



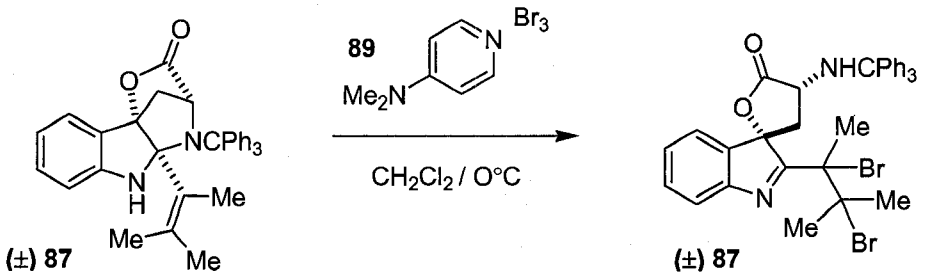
Compound **85** (400mg, 0.74mmol) was dissolved in 16ml THF and cooled to -78°C. A distilled solution of dimethyldioxirane in acetone (DMDO, ~25ml) was condensed into the stirred solution of ester **85**. The mixture was slowly warmed to -20°C at which point the DMDO began to reflux. The mixture was held at reflux for 20min and then concentrated directly. The crude mixture was purified directly by silica gel chromatography (20-100% EtOAc / hexanes) to afford the title compound as a mixture of enantiomers (68mg, 63% Yield). %).). ^{1}HNMR (300MHz, DMSO-D6) δ 0.73 (3H, t, *J* = 6.8 Hz), 1.49 (3H, s), 1.60 (3H, s), 1.82-1.92 (1H, m), 1.98 (3H, s), 2.21-2.45 (2H, m), 2.84-3.01 (2H, m), 6.96-7.35 (19H, m); MS (FAB) *m/z* (rel intensity) HRMS m/z calcd for $C_{37}H_{38}N_2O_3$ 559.2966, found 559.2961.

Lactone (87)



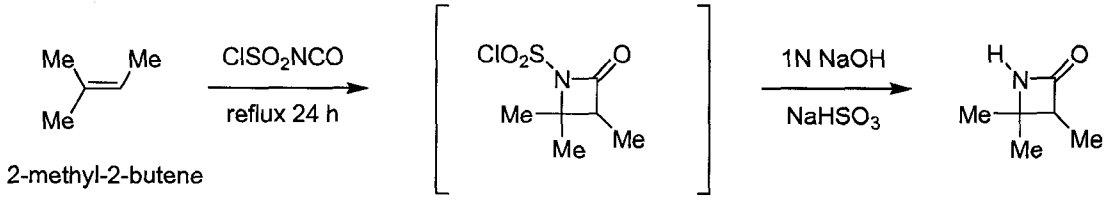
Ester (±) **86** (1.54g, 3.15mmol) was dissolved in 40.0 ml DMF and charged dropwise with DBU (1.2ml, 8mmol). The mixture was stirred at ambient temperature 1 hour and then cooled to 0°C and then poured in 500ml ice/H_2O. The mixture was extracted with Et_2O (5 X 200ml) and concentrated. The residue was filtered through a silica plug (100% CH_2Cl_2), and then purified by flash chromatography (30%EtOAc:hexanes) to give 1.54g of a yellow oil (96% yield). ^{1}HNMR (300MHz, $CDCl_3$) δ 1.20-1.34 (1H, dd, J = 12.9, 8.4 Hz), 1.61 (3H, bs), 1.84 (3H, bs), 1.88 (1H, dd, J = 12.8, 8.4 Hz), 1.92 (3H, bs), 2.81-2.92 (1H, bs), 3.85-3.98 (1H, m), 6.80-6.87 (1H, d, J = 7.1 Hz), 7.09 (1H, t, J = 7.5 Hz), 7.15-7.36 (10H, m), 7.40-7.48 (1H, d, J = 7.3 Hz), 7.52-7.61 (6H, m); MS (FAB) *m/z* (rel intensity). HRMS m/z calcd for $C_{35}H_{32}N_2O_2$ 512.2464, found 512.2475.

Spirolactone (91)



A cold 0°C solution of lactone **(±) 87** (1.10g, 2.145mmol) in 55ml CH_2Cl_2 was charged slowly with 4-dimethylaminopyridinium tribromide **89** (764mg, 2.145mmol). The mixture was stirred for 30min at 0°C and then concentrated directly and purified by silica gel chromatography or quenched with aq. $NaHCO_3$, or quenched with sat. aq. Brine. All work-up methods produced exclusively imino lactone (±) **87** (1.43g, 99%).). ^{1}HNMR (300MHz, $CDCl_3$) δ 1.32-1.43 (1H, dd (methylene), J = 13.6, 9.2 Hz), 2.19 (3H, s), 2.26 (3H, s), 2.29 (3H, s), 2.85 (1H, bs), 2.94-3.06 (1H, dd (methylene), J = 13.6, 11 Hz), 3.81-3.97 (1H, m), 6.69-7.62 (19H, m); MS (FAB) *m/z* (rel intensity). HRMS m/z calcd for $C_{35}H_{32}Br_2N_2O_2$ 673.0876, found 673.0888.

3,4,4-trimethylazetidin-2-one (99)



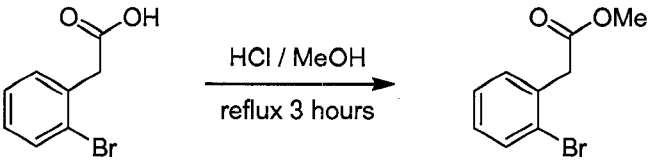
2-methyl-2-butene

98

99

Compound **98** (2-methyl-2-butene) (4.0g, 57.0mmol) was dissolved in 20ml Et_2O and cooled to 0°C. The mixture was then charged with chlorosulfonylisocyanate (4.0g, 28.5mmol) and refluxed overnight. The reaction was then cooled back to 0°C and charged with 2N NaOH. The mixture was then charged EtOAc, washed with H_2O, brine, dried over Na_2SO_4 and concentrated directly to afford 655mg of the transient chlorosulfonic acid as a yellow oil (20% yield). The mixture was then charged with 1N NaOH and then neutralized with solid $NaHSO_3$. The mixture was then charged EtOAc, washed with H_2O, brine, and dried over Na_2SO_4 and concentrated directly to afford the title compound **99,** 655mg of a yellow oil (20% yield). ^{1}HNMR (300MHz, $CDCl_3$) δ 5.96 (1H, bs), 3.20-3.31 (1H, dd, J = 15.4, 7.32 Hz), 1.74 (3H, s), 1.62 (3H, s), 1.26-1.32 (1H, d, J = 7.5 Hz). HRMS-FAB: [M+H]+ calcd for $C_6H_{11}N_1O_1$, 113.0841; found, 113.0852.

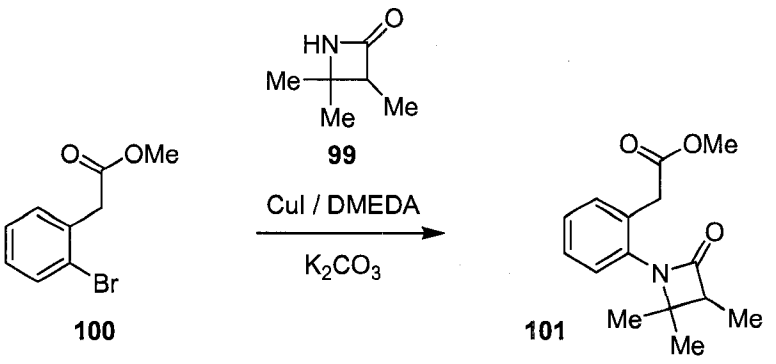
Methyl 2-(2-bromophenyl)acetate (100)



100

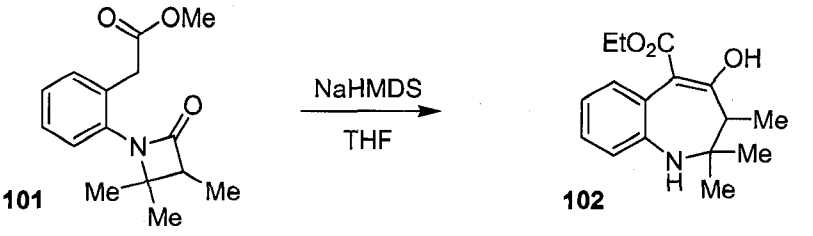
2-(Bromo-phenyl) acetic acid (76.6 g, 356 mmol) and catalytic concentrated HCl (2mL) in methanol (500 mL) were heated under reflux for 2.5 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The resulting product was diluted with diethyl ether (250 mL) and then washed with a saturated aqueous NaHCO3 solution (250 mL) and saturated aqueous NaCl solution (250 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 81.3 g (99%) of clear oil (See Reference 31).

Methyl 2-(2-(2,2,3-trimethyl-4-oxoazetidin-1-yl)phenyl)acetate (101)



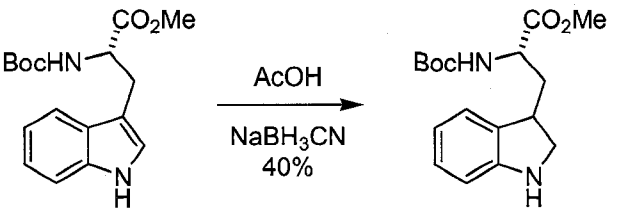
Ester **100** (12.25g, 53.5mmol) and **99** (6.05g, 53.5mmol) were dissolved in 123 ml toluene in a sealed tube at 20°C and and charged with K_2CO_3 (15.0g, 107.0mmol) and CuI (509mg, 2.68mmol). The mixture was stirred 20 min at 20°C and then charged with DMEDA (472mg, 5.35mmol). The reaction changed color slightly and then was closed into the sealed tube and heated to 150°C for 24h. The reaction was concentrated directly and then purified by silica gel chromatography (20-50% EtOAc / hexanes) to afford the title compound **101** (5.87g = 42% Yield).). ^{1}HNMR (300MHz, $CDCl_3$) δ 1.23 (3H, d, *J* = 7.5 Hz), 1.32 (3H, s), 1.45 (3H, s), 2.87-3.12 (1H, m), 3.62 (3H, s), 3.69, (2H, s), 7.00-7.36 (4H, m). HRMS-FAB: [M+H]+ calcd for $C_6H_{11}N_1O_1$, 113.0841; found, 113.0852.

(Z)-ethyl 4-hydroxy-2,2,3-trimethyl-2,3-dihydro-1H-benzo[b]azepine-5-carboxylate (102)



To a solution of ester **101** (7.1g, 27.2mmol), in 355ml THF was added at 0°C a 2N solution of NaHMDS (30ml, 60.0mmol) slowly. The mixture was then allowed to warm to 20°C over 2 hours and then cooled back to 0°C. The solution was poured into a cold solution of 10% brine and then charged with EtOAc. The organic layer was separated and washed 3X with brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography to afford compound **102** (6.48g, 91% yield).). ^{1}HNMR (300MHz, $CDCl_3$) δ 1.08 (3H, d, J = 7.0 Hz), 1.25 (3H, s), 1.29 (3H, s), 2.34-2.45 (1H, m), 3.78 (3H, s), 6.81-6.96 (1H, m), 7.02-7.44 (4H, m), 13.52 (1H, s). HRMS-FAB: [M+H]+ calcd for $C_{16}H_{21}N_1O_3$, 275.1521; found, 275.1514.

(2S)-methyl 2-(tert-butoxycarbonyl)-3-(indolin-3-yl)propanoate (118)



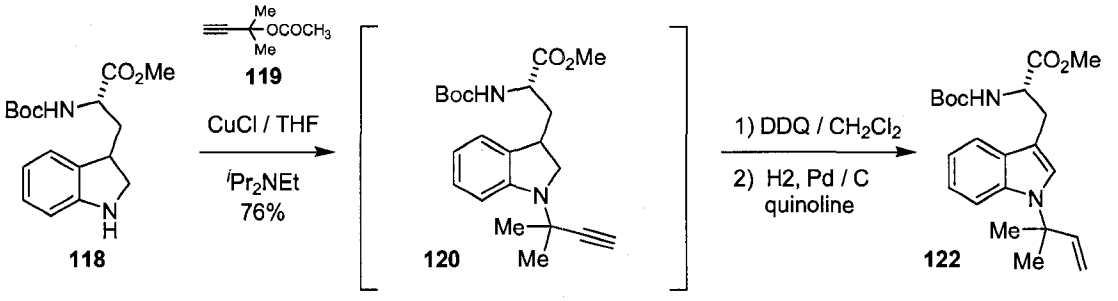
117 **118**

To a solution of (S)-*N*-Boc-tryptophan methyl ester (1.84g, 5.78 mmol) in acetic acid (28 mL) at 0 °C was added $NaBH_3CN$ (3.63g, 57.8 mmol). After addition, the reaction vessel was allowed to warm to room temperature. After 12 h, the crude material was diluted with water and CH_2Cl_2 (150 mL each). Using 1 *N* aq. NaOH, the pH of the mixture was brought to > 12. The organic layer of the resulting mixture was isolated and washed twice with water (200 mL) then once with brine (200 mL). The solution was dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 6:1 to 1:1) yielded a 1:1 mixture (1.11g, 60% yield) of diastereomers whose spectral characteristics were identical to those reported in the literature.[10,33]

6a (αS, γS). R_f = 0.37 in 40% EtOAc/hexanes; IR (KBr) 3013, 2907, 2848, 1743, 1711, 1608, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, *J* = 7.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 5.20 (d, *J* = 8.5 Hz, 1H), 4.44 (td, *J* = 7.5, 7.0 Hz, 1H), 3.73 (m, 1H), 3.71 (s, 3H), 3.34 (m, 1H), 3.22 (m, 1H), 2.29 (dt, *J* = 13.5, 6.0 Hz, 1H), 1.85 (dt, *J* = 14.0, 8.0 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 155.2, 151.0, 131.5, 127.8, 124.0, 118.7, 118.6, 109.6, 80.0, 53.6, 52.2, 38.8, 37.4, 28.3; LRMS (CI), *m/z* (%): 320 (M^+, 53), 265 (32), 247 (10), 221 (22), 202 (35), 159 (18), 132 (75), 117 (100); HRMS (CI^+): calcd $C_{17}H_{24}N_2O_4$: 320.1739; found 320.1736. Anal. calcd for $C_{17}H_{24}N_2O_4$: C, 63.72; H, 7.55; N, 8.75. Found C, 63.59; H, 7.50; N, 8.69.

6b (αS, γR). R_f = 0.46 in 40% EtOAc/hexanes; IR (KBr) 3010, 2955, 2848, 1741, 1710, 1608, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.0 Hz, 1H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 5.21 (d, *J* = 8.5 Hz, 1H), 4.40 (td, *J* = 5.0, 4.0 Hz, 1H), 3.74 (m, 1H), 3.72 (s, 3H), 3.35 (m, 1H), 3.30 (t, *J* = 8.5, 7.0 Hz, 1H), 2.03 (m, 2 H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 155.4, 151.2, 131.6, 127.7, 123.5, 118.5, 109.5, 79.9, 52.9, 52.3, 51.9, 38.6, 37.4, 28.2; LRMS, CI, *m/z* (%): 321 (MH^+, 100), 320 (93), 265 (45), 247 (11), 221 (47), 202 (31), 159 (17), 132 (51); HRMS (CI^+): calcd $C_{17}H_{24}N_2O_4$: 320.1739; found 320.1736; Anal. calcd for $C_{17}H_{24}N_2O_4$: C, 63.72; H, 7.55; N, 8.75. Found C, 63.51; H, 7.53; N, 8.55.

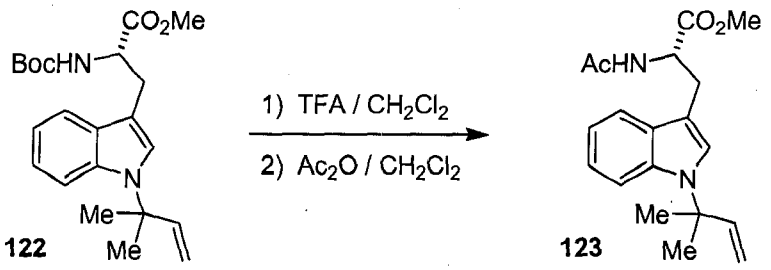
(S)-methyl 2-(tert-butoxycarbonyl)-3-(1-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoate (122)[10]



A solution of indoline **118** (742mg, 2.32 mmol) in THF (8 mL) was charged with CuCl (23mg, 0.23 mmol). The suspension was stirred for 5 min after which diisopropylethylamine (0.44 mL, 2.55 mmol) was added over 1 min. Again, the suspension was allowed to stir for 5 min after which 2-acetoxy-2-methyl-3-butyne (**119**) (0.35 mL, 2.78 mmol) was added over 2 min. The suspension was heated at reflux for 8 h after which it was filtered through a pad of Celite. The crude material was purified by flash column chromatography (SiO_2, hexanes:EtOAc 6:1 to 4:1) to furnish 851 mg (95% yield) of the propargyl indoline. This intermediate (851 mg, 2.20 mmol) was dissolved in CH_2Cl_2 (11 mL) and cooled to 0 °C. DDQ (525 mg, 2.31 mmol) was then added in one portion and the reaction was allowed to stir for 20 min. The crude material was passed through a pad of Celite and diluted with EtOAc before being washed sequentially with 10% aq. $NaHCO_3$ (twice, 100 mL), water (twice, 50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), the solvent removed in vacuo, and the residue dissolved in a solution of MeOH/quinoline (10:1, 8 mL total volume). A catalytic amount of 10% Pd/C was added and hydrogen bubbled though the solution until the reduction was complete (3 h). The crude material was passed through a pad of Celite and

diluted with EtOAc (20 mL) before being washed sequentially 10% aq. H_2SO_4 (twice, 50 mL), water (twice, 50 mL), and brine (50 mL). The organic layer was dried (Mg_2SO_4), the solvent removed in vacuo, and the residue purified by flash column chromatography (SiO_2, hexanes/ether 3:1) to furnish 744 mg (87% yield from the propargyl indoline) of **9**: yellow viscous oil; R_f = 0.66 (silica gel, hexanes/EtOAc, 2:1); $[\alpha]_D$ = +93 (c 0.47, MeOH) ; IR (neat) ν_{max} 3371, 2977, 1743, 1711, 1499, 1456, 1365, 1242, 1200, 1163, 1017, 739 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 2 H) 7.48 (d, *J* = 8 Hz, 1 H), 7.13 – 7.07 (m, 3 H), 6.13 (dd, *J* = 17.5, 11 Hz, 1 H), 5.21 (d, *J* = 11 Hz, 1 H), 5.16 (d, *J* = 17.5 Hz, 1 H), 5.05 (bd, *J* = 8.0 Hz, 1 H), 4.65 (bdd, *J* = 13, 5.5 Hz, 1 H), 3.68 (s, 3 H), 3.28 (dd, *J* = 14.5, 5.5 Hz, 1 H), 3.23 (dd, *J* = 14.5, 5.5 Hz, 1 H), 1.73 (s, 6 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 155.2, 144.0 (2 C), 123.8, 120.8, 118.9, 118.8, 113.8 (2 C), 113.5 (2 C), 108.1, 58.9, 54.3, 52.1, 28.3 (3 C), 28.1, 27.9 (2 C); MS (APCI+) 329 ($M + H^+$); HRMS (ESI-MS) calcd. for $C_{21}H_{23}N_3O_2H^+$ [$M + H^+$] 387.2284, found 387.2292.

(S)-methyl 2-acetamido-3-(1-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoate (123)



Compound **122** (4.9g, 12.6mmol) was dissolved in 100ml CH_2Cl_2 at 20°C and charged with 25ml TFA. The reaction was stirred overnight at 20°C and then cooled to 0°C. The reaction was charged slowly with Et_3N until basic and then charged further with sat. aq. $NaHCO_3$. The mixture was charged with EtOAc and the aqueous layer was separated. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to afford the free amino ester as a brown oil. The oil was redissolved in 100ml CH_2Cl_2 and charged slowly with 10ml Ac_2O. The reaction was concentrated directly and purified by silica gel chromatography to afford the desired acetate **123** (3.43g, 83% over 2 steps).). ^{1}HNMR (300MHz, $CDCl_3$) δ 1.74 (6H, s), 1.98 (3H, s), 3.31 (2H, t, J = 4.76), 4.92-5.00 (1H, m), 5.16 (1H, d, J = 27.47), 5.21 (1H, d, J = 20.88), 5.99 (1H, bd, J = 20.88), 6.14 (1H, dd, J = 17.2, 10.6), 7.07 (1H, s), 1.08-7.16 (2H, m), 7.45-7.56 (2H, m). HRMS-FAB: [M+H]+ calcd for $C_{19}H_{24}N_2O_3$, 328.1787; found, 328.1781.