ABSTRACT

THE TOTAL SYNTHESIS OF INDOLOCARBAZOLE NATURAL PRODUCTS K252c, (+)-K252a, (+)-RK-286c, (+)-MLR-52, (-)-TAN-1030a, AND (+)-STAUROSPORINE

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The total syntheses of indolocarbazoles K252c, (+)-K252a, (+)-RK-286c, (+)-MLR-52, (-)-TAN-1030a, and (+)-staurosporine are described. The syntheses are focused around three main themes: 1) the utilization of rhodium carbenoid chemistry for the formation of C-C bonds; 2) Lewis Acid mediated [1,2] alkyl rearrangements; and, 3) general efficiency in the construction of complex natural products.

A synthesis of the aglycon portion of the indolocarbazoles is described, wherein Rh (II) mediated C-C bond formation precedes electrocyclization and dehydration to form **4a-e** from **73** and **132a-e** in a single step. A novel rhodium initiated Claisen-α-ketol rearrangement was developed as the key step in the asymmetric synthesis of the K252a carbohydrate (i.e., **97**). Finally, a highly stereoselective (moderately regioselective) cyclofuranosylation protocol followed by amide deprotection produced K252a (**2**).

For the preparation of the pyranosylated indolocarbazoles (i.e., **1** and **6-8**) a stereoselective ring expansion of aldehyde (+)-**170** afforded ketone (+)-**171** which served as the key intermediate for the synthesis of (+)-staurosporine (**1**) and **6-8**. An interesting oxidative ring contraction of (+)-**171** to (+)-**147** provides an alternative synthesis of (+)-K252a.

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To My Family

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LIST OF ABBREVIATIONS

Ac	Acetyl, acetate
AIBN	2,2'-Azobisisobutyronitrile
aq.	Aqueous
app.	Apparent
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
BOM	Benzyloxymethyl
bp	Boiling point
br	Broad
n-Bu	*n*-Butyl
t-Bu	*tert*-Butyl
calcd	Calculated
cat.	Catalytic amount
CI	Chemical ionization
CSA	Camphorsulfonic acid
d	doulet
dec.	Decomposition
DAG	Diacyl glycerol
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMB	3,4-Dimethoxybenzyl
1,2-DME	1,2-Dimethoxyethane (glyme)
DMF	*N,N*-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EI	Electron impact
equiv	Equivalent
Et	Ethyl
FAB	Fast atom bombardment
h	hour
HMPA	Hexamethylphosphoric triamide

HPLC	High performance liquid chromatography
hν	light
Hz	Hertz
IP_3	D-*myo*-inositol-1,4,5-triphosphate
IR	Infrared (spectrum)
L-Selectride	Lithium tri-*sec*-butylborohydride
m	Multiplet or medium
m	Mass
m-CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
min	minutes
mol	Mole
mp	Melting point
Ms	Mesyl (methanesulfonyl)
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
[O]	Oxidation
p-BrBz	*p*-Bromobenzoyl
PDC	Pyridinium dichromate
Ph	Phenyl
PhH	Benzene
PIP_2	L-α-Phosphatidyl-D-*myo*-inositol-4,5-biphosphate
PKC	Protein kinase C
PMB	*p*-Methoxybenzyl
PPA	Polyphosphoric acid
ppm	Parts per million
PPSE	Polyphosphoric acid trimethylsilyl ester
Py	Pyridine
s	Singlet or strong
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

THP	Tetrahydropyranyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl (tosyl)
TsOH	*p*-Toluenesulfonic acid
w	Weak
z	Charge
Δ	Heat at reflux

CHAPTER ONE

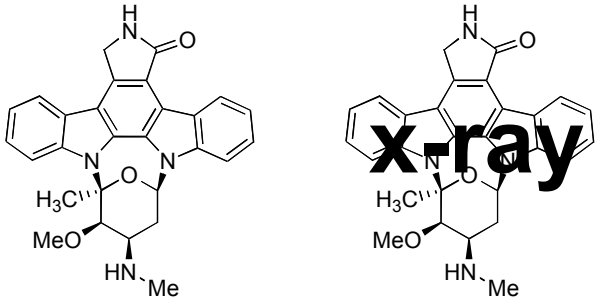
The First Twenty Years of Indolocarbazole Natural Products Chemistry

1.1 Background and Introduction.

1.1.1 Isolation and Biological Activity.

In 1977 Ō mura and co-workers reported that a novel alkaloid, isolated from *Streptomyces staurosporeus*, possessed strong hypotensive properties as well as broad spectrum antifungal activity.[1] The structure of this alkaloid, originally named AM-2282 (**1**), was elucidated by single crystal X-ray analysis, and shown to possess an indolocarbazole subunit wherein the two indole nitrogens are bridged by glycosyl linkages (see Figure 1.1.1).[2] Following the structure elucidation, AM-2282 was renamed staurosporine (**1**), and became the first of over 50 compounds to be characterized in this new family of alkaloids, possessing the novel indolo[2,3-a]carbazole subunit.[3]

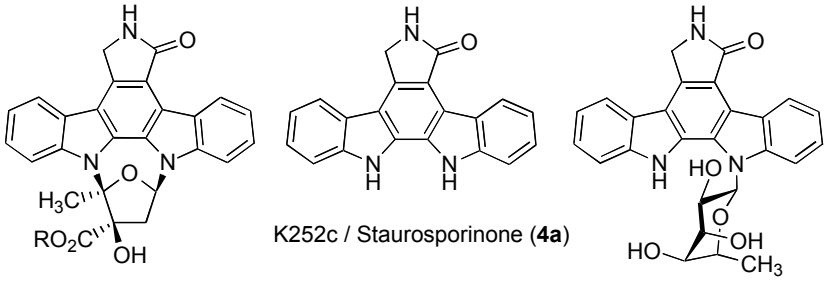
Figure 1.1.1



(+)-Staurosporine (**1**)

In 1985 Sezaki reported the isolation and structure of the first example of a furanosylated indolocarbazole, SF-2370 (**2**).[4] A year later Kase described the isolation and complete structure elucidation of K252a (**2**), a compound identical to that isolated by Sezaki, along with three structurally related compounds K252b-d (**3-5**) as shown in Figure 1.1.2.[5]

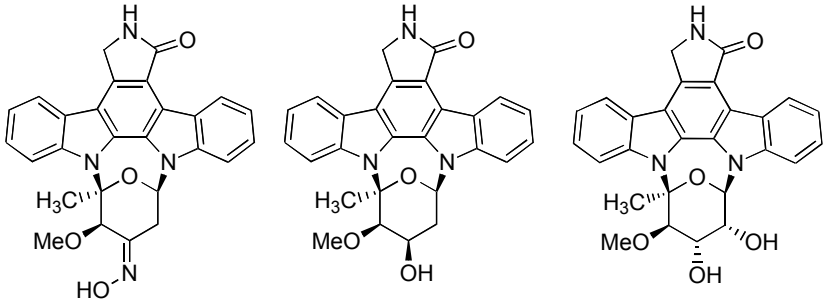
Figure 1.1.2



Kase found these compounds to be potent inhibitors of protein kinase C (PKC), with K252a possessing the greatest inhibitory power (IC_{50} = 32nM). In the same year Tamaoki reported that staurosporine also inhibits PKC but with a slightly higher affinity (IC_{50} = 2.7nM).[6] Following the discovery of potent kinase inhibitory activity, the indolocarbazoles rapidly became the focus of several investigations that have revealed their potential as chemotherapeutics against cancer,[7] Alzheimer's disease,[8] and other neurodegenerative disorders.[9]

Following the isolation of staurosporine and the K252 compounds, many new indolocarbazoles have been discovered and found to possess a wide range of structural features as well as biological profiles. In 1989, Tsubotani described the isolation and structure determination of TAN-1030a (**6**), a compound having macrophage activating properties.[10] TAN-1030a, along with many interesting minor metabolites, has been independently isolated by Fredenhagen, from the staurosporine producing strain *Streptomyces longisporoflavus*.[11]

Figure 1.1.3

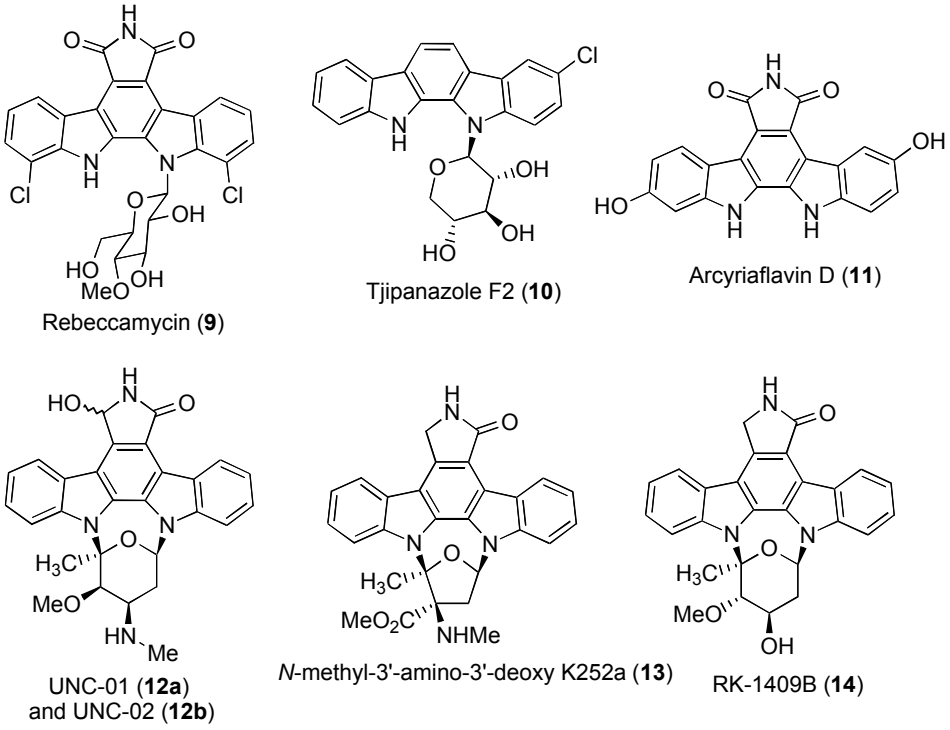


Isono reported the discovery of the μM PKC inhibitor RK-286c (**7**), a minor metabolite produced along with staurosporine by *Streptomyces sp. RK-286* in approximately a 1:4 ratio.[12] In 1994 McAlpine reported the isolation and structure of MLR-52 (**8**), a very minor metabolite co-produced with staurosporine by *Streptomyces sp. AB 1869R-359* (1:375) possessing immunosuppressive activity (IC_{50}=1.9 nM).[13]

As illustrated in Figure 1.1.4, the indolocarbazoles isolated to date are a structurally diverse family of natural products. The various types of aglycons can be classified into four groups. These include: A) the parent indolo[2,3-a]carbazole nucleus, such as that found in tjipanazole F2 (**10**); B) an imide, as in rebeccamycin (**9**) and arcyriaflavin D (**11**); C) hydroxy lactams, as in the UNC compounds (e.g., **12a,b**); and, D) simple lactams, such as those found in **13** and RK-1409B (**14**). In all of these aglycon types, substitution (i.e., halides, ethers, phenols) at various positions on the aromatic heterocycle has been observed. Another source of the diversity of these compounds is the manner in which the aglycon is attached to the carbohydrate portion. Again this mode of attachment can be classified into four sub-groups. These include: A) compounds possessing no carbohydrate, such as **11**; B) molecules having a single indole *N*-glycosidic linkages as in **9** and **10**; C) pyranosylated indolocarbazoles with two indole *N*-glycosidic linkages (e.g., **12a,b** and **14**); and, D) furanosylated

indolocarbazoles with two indole *N*-glycosidic linkages (e.g., **13**). The synthetically most challenging sub-groups of indolocarbazoles are the cyclofuranosylated [e.g., K252a(**2**)] and cyclopyranosylated [e.g., staurosporine(**1**)] congeners.

Figure 1.1.4

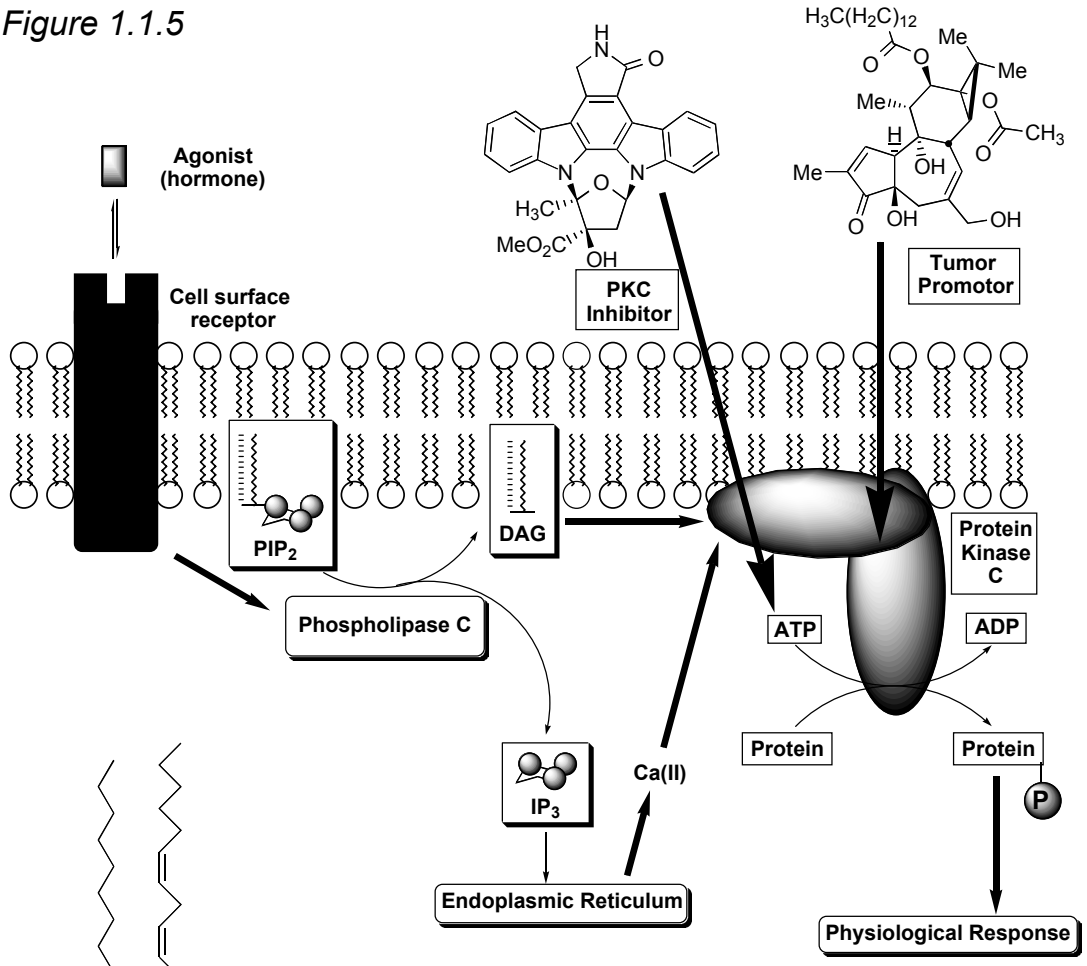


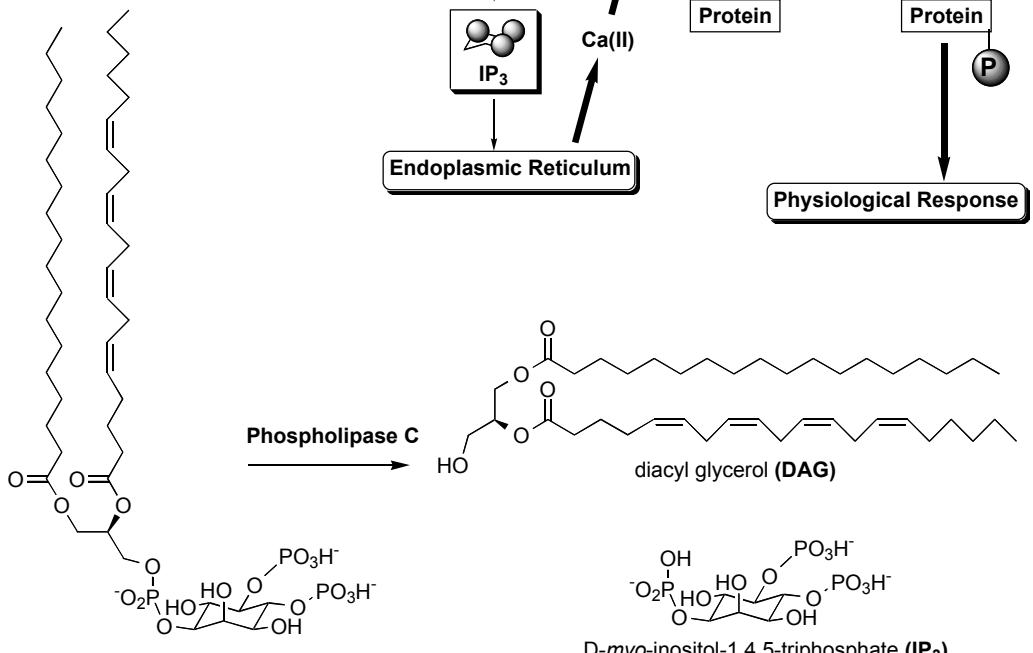
1.1.2 The Importance of Protein Kinase C Inhibitors.

1.1.2.1 Introduction: What is PKC and How Does It Function?

Protein kinase C (PKC) is a family comprised of at least eight serine/threonine specific kinases that are approximately 77 kD in size. The importance of PKC in regulating signal transduction pathways and ultimately cellular response has been well-established.[14] Activation of PKC occurs through a series of events that begins with specific binding of an extracellular agonist to a cell surface receptor. This binding event results in activation of phospholipase C which then cleaves inositol triphosphate (IP_3) from phosphatidylinositol-4-5-biphosphate (PIP_2) and leaves behind a molecule of 1,2-diacylglycerol (DAG) in the membrane (see Figure 1.1.5). Binding of the liberated IP_3 to intracellular receptors in the endoplasmic reticulum initiates the release of Ca(II) into the cytosol. The released Ca(II) in conjunction with DAG activates membrane associated PKC which, in turn effects ATP-dependent catalytic phosphorylation of serine/threonine residues on substrate proteins. Phosphorylation ultimately results in various cellular responses by modifying the function of rate limiting enzymes and regulatory proteins implicated in numerous metabolic pathways.

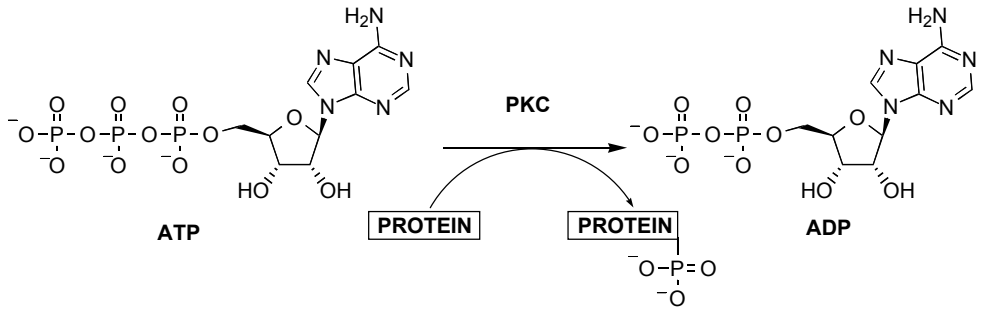
Figure 1.1.5





L-α-Phosphatidyl-D-*myo*-inositol-4,5-biphosphate **(PIP_2)**

D-*myo*-inositol-1,4,5-triphosphate **(IP_3)**



1.1.2.2 The Indolocarbazoles

The indolocarbazoles K252a and staurosporine, which are the most powerful PKC inhibitors isolated to date, presumably act by occupying the ATP binding site and thereby prevent protein phosphorylation. Unfortunately, this mode of PKC binding results in the relatively non-selective inhibition of several kinases. The preparation of indolocarbazole derivatives possessing selectivity toward specific malfunctioning kinases associated with a disease state would be a solution; thus, an efficient and general synthetic route to the indolocarbazoles is desirable.

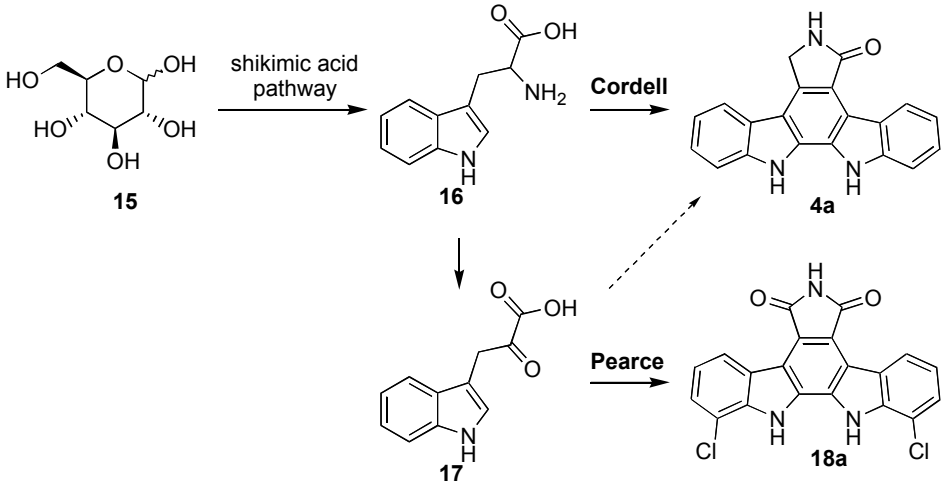
1.2 Biosynthesis of Indolocarbazoles.

1.2.1 Biogenesis of the Indolocarbazole Nucleus.

In 1988, Cordell and Pearce independently reported the first direct studies of indolocarbazole biosynthesis.[15,16] These investigations focused on staurosporine (**1**) and rebeccamycin (**9**), respectively. Through feeding experiments using L-[5-^{3}H]tryptophan, L-[β-^{14}C]tryptophan, and DL-[α-^{13}C]tryptophan, both groups independently concluded that the aglycon portions of the natural products were derived from two intact tryptophan units with a slight preference for incorporation of the L stereoisomer. Recent work by Cordell has shown that in fact the tryptophan (**16**) utilized in the aglycon biosynthesis is produced by *Streptomyces staurosporeus* from D-glucose (**15**), presumably via the shikimic acid pathway.[17] Furthermore, through a feeding experiment with $(^{15}NH_4)_2SO_4$, the imide nitrogen in rebeccamycin was not obtained from

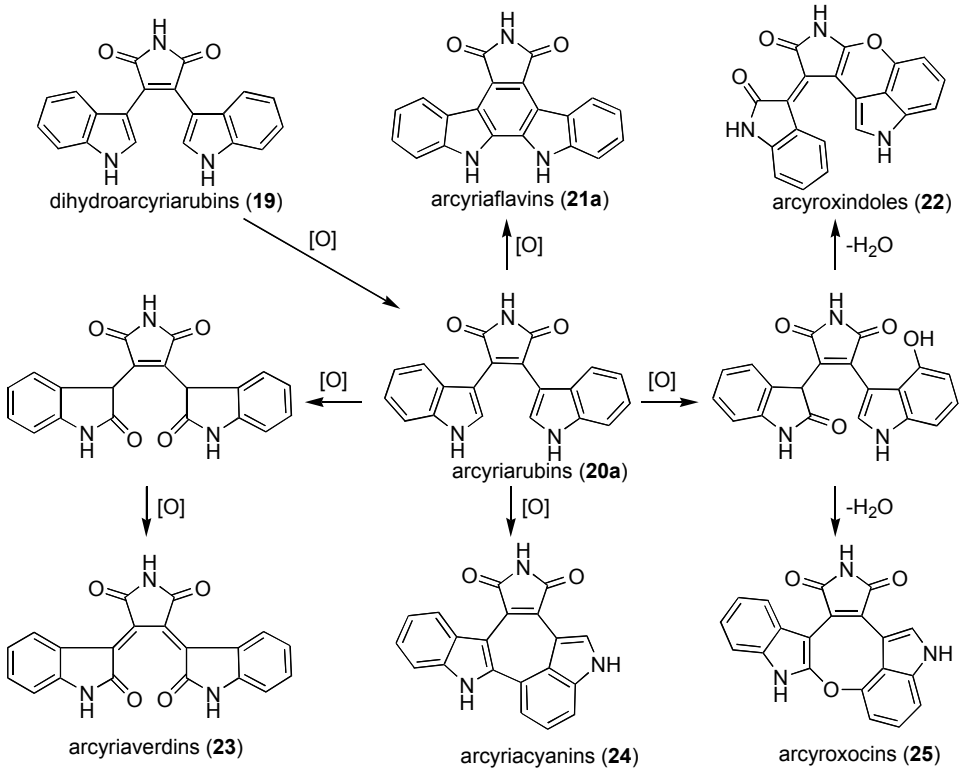
tryptophan. Pearce suggests the intermediacy of 3-indolepyruvic acid (**17**), since the conversion of **16** to **17** is precedented (see Scheme 1.2.1).

Scheme 1.2.1



As shown in Scheme 1.2.2, Steglich suggested an interesting biosynthetic scheme for the *Arcyria bis*-indolylmaleimide fungal metabolites, a class of alkaloids structurally related to the indolocarbazoles.[18] Synthetic derivatives of these natural products have been utilized as intermediates in numerous indolocarbazole synthetic approaches (*vide infra*). The proposed biosynthesis begins with the dihydroarcyriarubins (**19**), presumably derived from tryptophan, which upon oxidation to the maleimide lead to the arcyriarubins (**20a**). As the proposed common biosynthetic intermediate, oxidative cyclization of the arcyriarubins (**20a**) would lead to 7-oxo-staurosporinone derivatives known as the arcyriaflavins (**21a**) or to the arcyriacyanins (**24**). Alternative oxidative pathways lead to the arcyriaverdins (i.e., **20a**→**23**), arcyroxindoles (i.e., **20a**→**22**), and the arcyroxocins (i.e., **20a**→**25**).

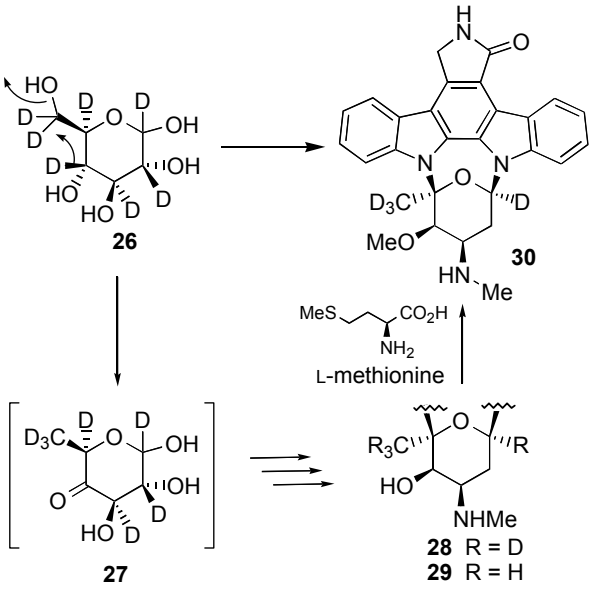
Scheme 1.2.2



1.2.2 Biosynthesis of Indolocarbazole Carbohydrates

The carbohydrate precursor to rebeccamycin has been shown to be D-glucose and the *O*-methyl group is derived from L-methionine. Likewise, the staurosporine carbohydrate unit is derived from D-glucose and the *N*- and *O*-methyl groups arise from L-methionine. Interestingly, the results from a feeding experiment employing [U-$^2H_7$]-D-glucose (**26**) suggest a dehydration event occurs at C-6 of glucose wherein a C-4 to C-6 (glucose) hydrogen transfer affords the fully labeled 2'-CD_3 staurosporine (**26**→**27**→**28**→**30**, see Scheme 1.2.3).

Scheme 1.2.3



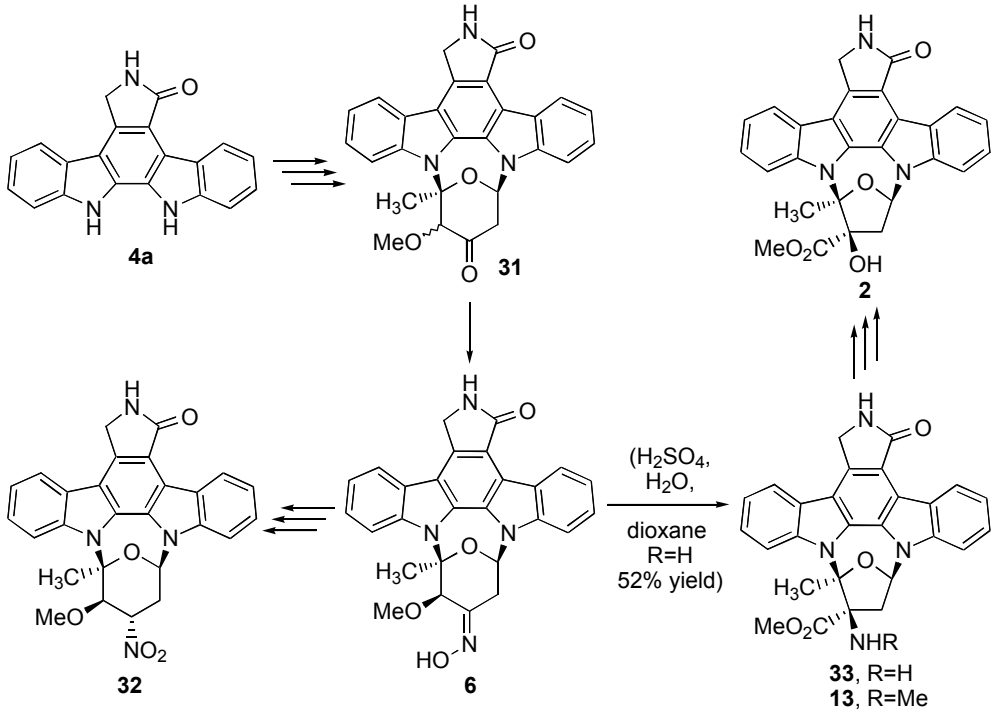
Hoehn reported the isolation of **29** from a blocked mutant (M14) of the staurosporine producing strain *Streptomyces longosporoflavus*.[19] By co-fermentation and bioconversion studies it was found that *O*-methylation is the last step in staurosporine biosynthesis, thus **29** is the direct precursor to staurosporine.

1.2.3 Fredenhagen's Proposed K252a Biosynthesis.

Over the past two years Fredenhagen has reported the isolation of a number of interesting minor metabolites (e.g., **31**, **32**, and **13**) along with the major isolate, staurosporine, from *Streptomyces longisporoflavus*.[20] In analyzing these molecules a proposed biosynthetic scheme has been set forth, including the biosynthesis of K252a (see Scheme 1.2.4). Central to Fredenhagen's postulate is the oxime TAN-1030a (**6**), which is presumably derived from methoxy ketone **31**. It is thought that oxidation of oxime **6** leads to nitro derivative **32**, while a series of events including ring contraction leads ultimately

to K252a (e.g., **6**→**33**→**2**). The interesting ring contraction of oxime **6** to amine **33** has been demonstrated in the laboratory (conditions in parenthesis).[21]

Scheme 1.2.4

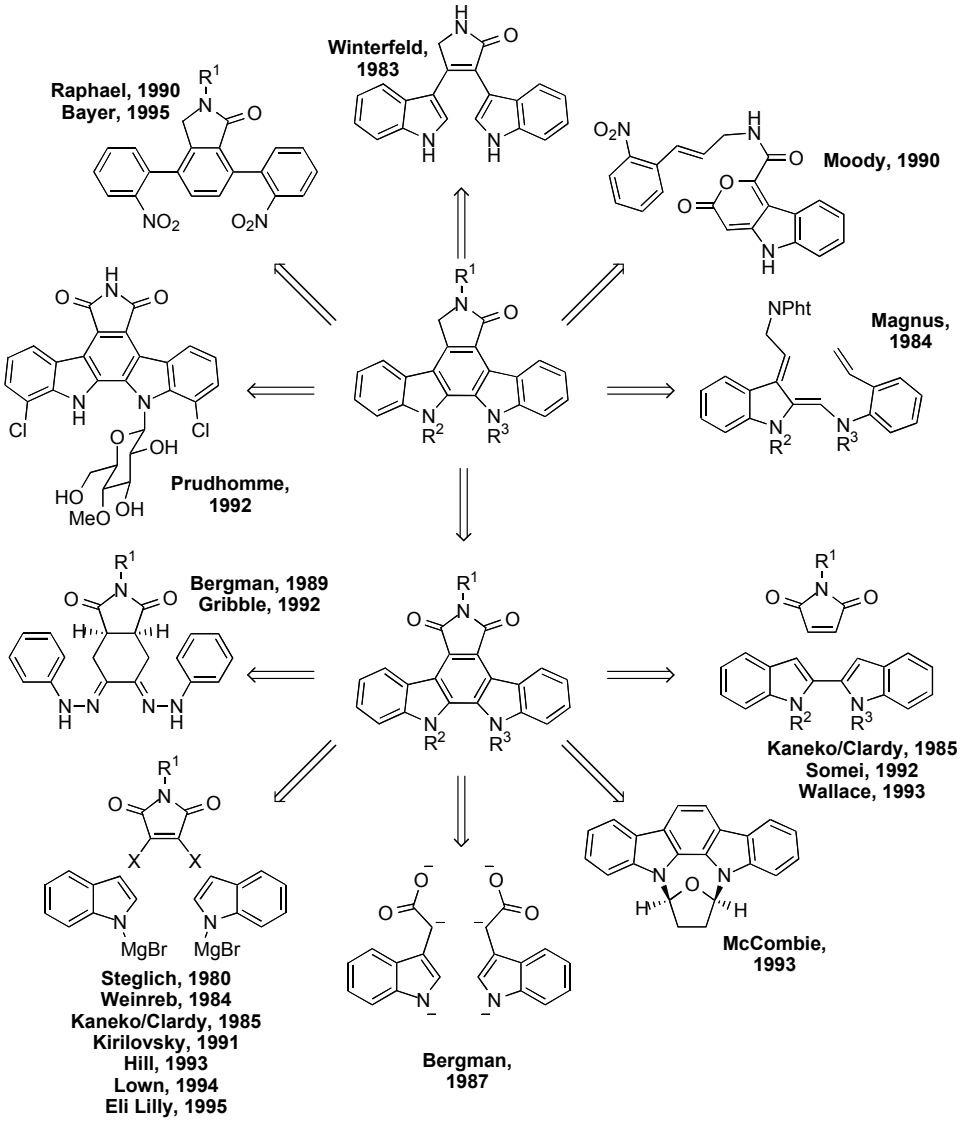


1.3 Synthetic Studies

1.3.1 Syntheses of the Indolo[2,3-a]carbazole Nucleus.

A number of approaches to the synthesis of the indolo[2,3-a]carbazole nucleus have been described and are summarized in Scheme 1.3.1 based on the key bond formations, type of structure synthesized (aglycon), and research group. In the following section each method is presented in greater detail.

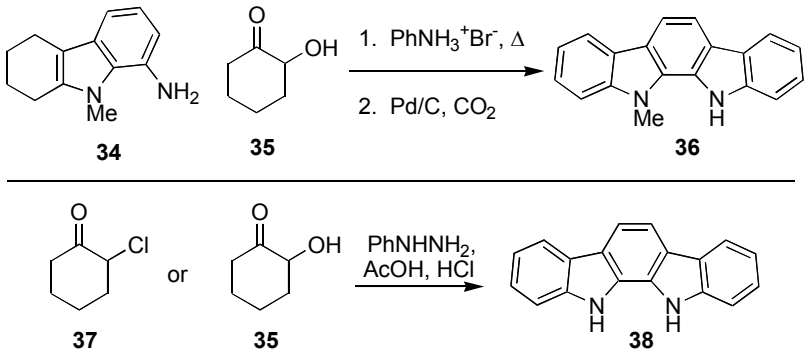
Scheme 1.3.1



1.3.1.1 Early Indolocarbazole Efforts.

The synthesis of indolocarbazole **36**, a derivative of the parent indolo[2,3-a]carbazole (**38**), was accomplished in 1956, long before the isolation of staurosporine.[22] Tomlinson reported that the condensation of tetrahydrocarbazole **34** with acyloin **35** followed by dehydrogenation produced the indolocarbazole **36**, but that attempts to access the parent structure via an analogous approach failed. Subsequent to this result, Bhide,[23] Mann,[24] and later Moldenhauser[25] developed a double Fischer indolization of **37** or **35** to provide upon oxidation indolocarbazole **38** directly.

Scheme 1.3.2

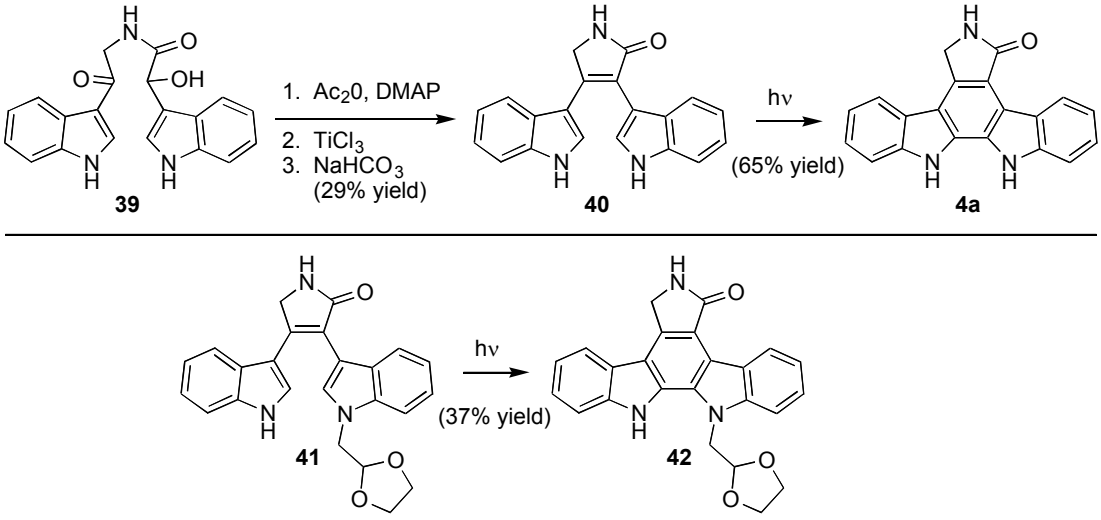


1.3.1.2 Winterfeld's Approach to Staurosporinone.[26,27]

Interest in the indolo[2,3-a]carbazoles waned until 1977 with the discovery of Staurosporine (**1**). In 1983 Winterfeld disclosed pioneering work in the revitalized indolocarbazole area by describing the first synthesis of K252c (**4a**, Scheme 1.3.3). The preparation of lactam **40** was accomplished by intramolecular aldol reaction of ketoamide **39** followed by titanium-mediated deoxygenation. Photolysis of **40** resulted in an oxidative photocyclization that forged the indolocarbazole **4a**. This reaction has been subsequently utilized by numerous groups for constructing the 2,2'-bis-indole bond. Winterfeld recently

reported a modified version of this approach which allows access to a regioselectively modified staurosporinone (e.g., **41**→**42**, Scheme 1.3.3).

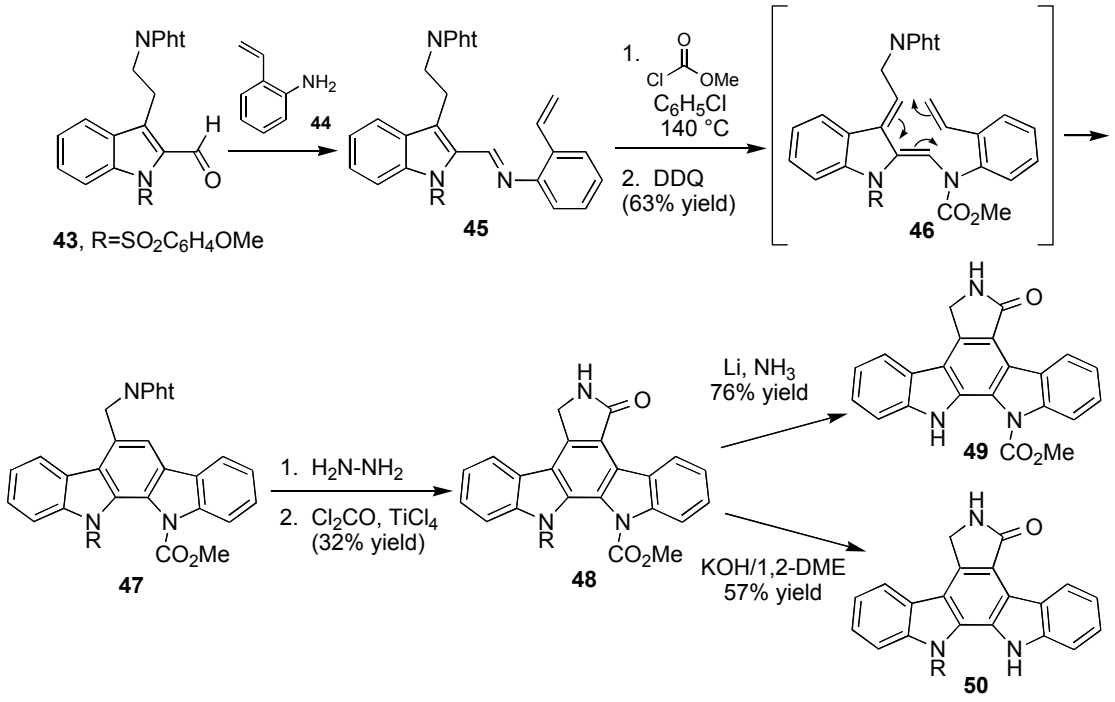
Scheme 1.3.3



1.3.1.3 Magnus' Approach.[28]

Shorly after Winterfeld's report, Magnus and Weinreb published two approaches to selectively protected staurosporinones. Magnus described an intramolecular Diels-Alder cycloaddition of indole-2,3-quinidomethane **46** as the key step in his approach to staurosporinone (see Scheme 1.3.4). Acylation of imine **45**, readily prepared by condensation of tryptamine derivative **43** with 2-aminostyrene (**44**), produced indole-2,3-quinidomethane **46** (*in situ*) and initiated an efficent intramolecular Diels-Alder reaction. Oxidative work-up with DDQ then furnished indolocarbazole **47**. Removal of the phthalimide protecting group on **47** followed by acylation afforded bis-protected staurosporinone **48**. Interestingly, the indoles could be selectively deprotected (e.g., **48**→**49** or **48**→**50**, Scheme 1.3.4) to potentially allow for the regioselective introduction of a carbohydrate moiety.

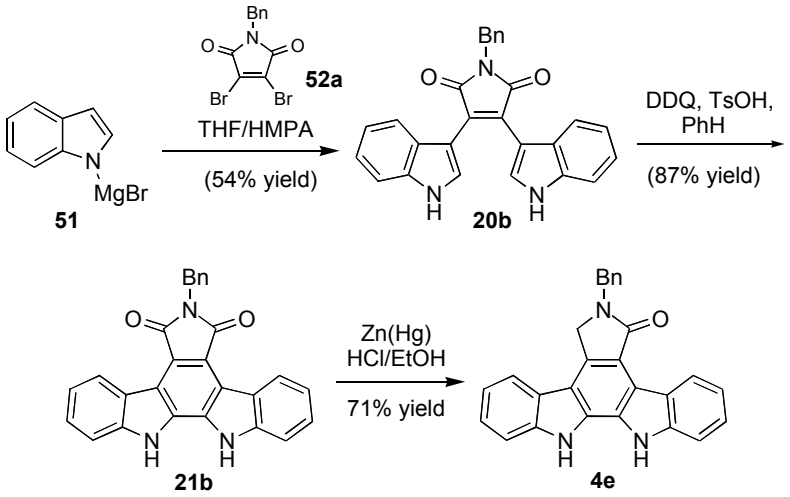
Scheme 1.3.4



1.3.1.4 The Weinreb Approach.[29]

Weinreb utilized a protocol for the preparation of bis indolyl maleimides developed by Steglich to provide maleimide **20b** from indole-Grignard **51** and imide **52a**. Oxidative cyclization of **20b** with DDQ gave *N*-benzyl imide **21b** and provides an alternative to Winterfeldt's photochemical cyclization. Finally, desymmetrization of **21b** was accomplished by Clemmensen reduction to afford lactam **4e**.

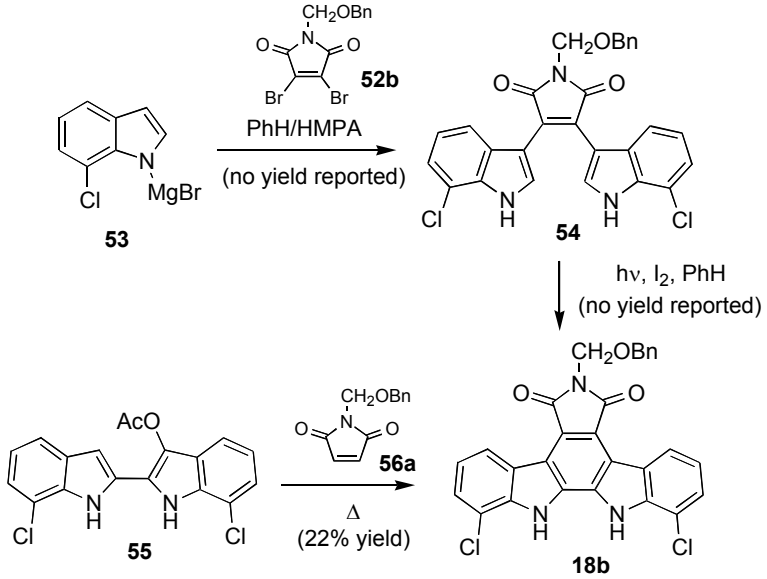
Scheme 1.3.5



1.3.1.5 The Kaneko/Clardy Approach.[30]

In 1985 Kaneko and Clardy also utilized a variation of the Steglich methodology to provide protected maleimide **54** (Scheme 1.3.6). Photocyclization of **54** produced a selectively protected aglycon of rebeccamycin (**18b**). In addition, they utilized a [4+2] cycloaddition of biindole **55** and imide **56a** to prepare the same compound.

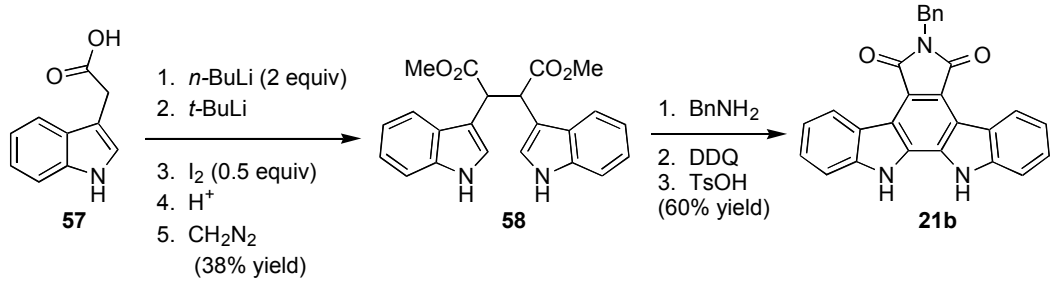
Scheme 1.3.6



1.3.1.6 Bergman's First Approach.[31]

These early reports were followed by a flurry of others. Bergman described an interesting biomimetic synthesis of indolocarbazole **21b**, wherein an iodine mediated trianion dimerization of indole acetic acid (**57**) to furnish diester **58** serves as the key feature (see Scheme 1.3.7). Subsequent oxidative cyclization using the conditions of Weinreb provided **21b**.

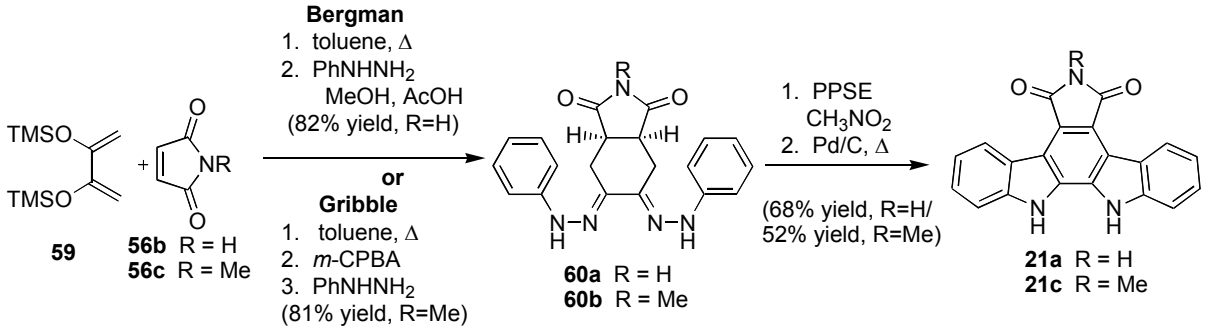
Scheme 1.3.7



1.3.1.7 The Bergman and Gribble Methods.[32]

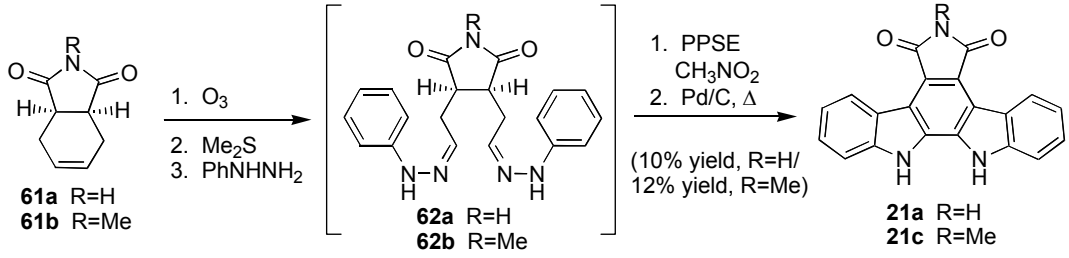
Bergman and Gribble, in a variant of the Bhide and Mann syntheses of indolo[2,3-a]carbazole (**38**, see Scheme 1.3.2), independently developed an approach to imides **21a,c** which relies on the double Fischer-indolization of osazone **60**. As demonstrated by Bergman, this process allows facile

Scheme 1.3.8



preparation of numerous analogues by alteration of the imide protecting group and type of hydrazine used in osazone formation. Additionally, Gribble has reported a short, albeit modest yielding, synthesis of **21a,c** (R=H, Me) from commercially available tetrahydrophthalimide **61a,b** in only two steps (see Scheme 1.3.9).

Scheme 1.3.9



61a R=H
61b R=Me

62a R=H
62b R=Me

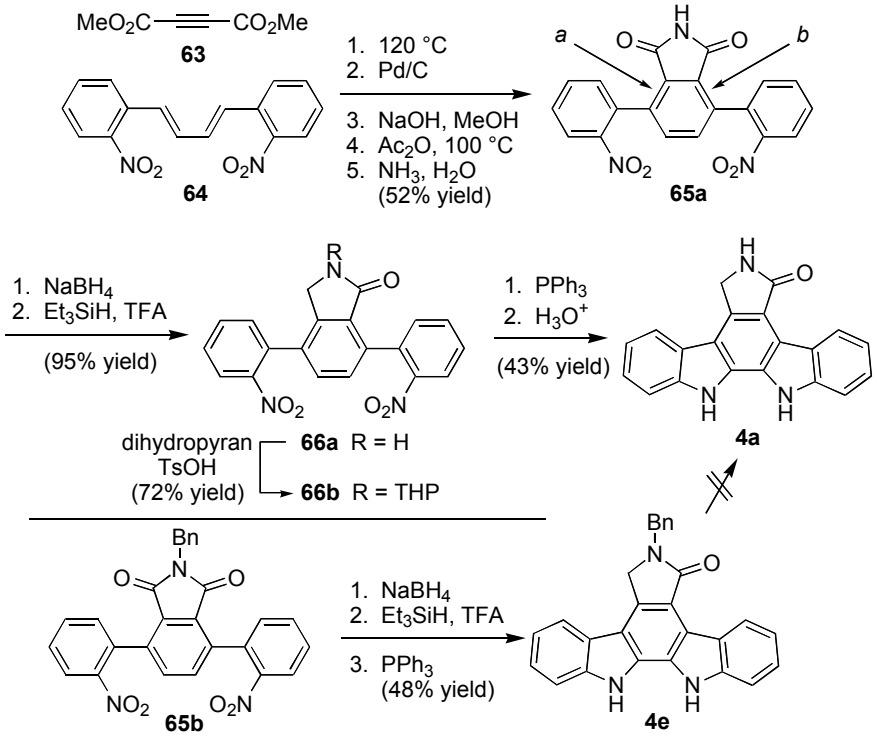
21a R=H
21c R=Me

1.3.1.8 Raphael's Approach.[33]

In 1990 Raphael and Moody reported two new staurosporinone syntheses, both of which were based on Diels-Alder methodology and nitrene insertion chemistry. Raphael utilized an intermolecular Diels-Alder reaction to forge bonds *a* and *b* (Scheme 1.3.10). Reaction of numerous dienophiles with diene **64** following dehydrogenation afforded triaryl products such as **65a** and **65b**. In an initial attempt, **65b** was reduced and cyclized in good yield to afford lactam **4e**, a compound previously prepared by Weinreb and Bergman. Importantly, Raphael described the frustration of having to devise a new strategy because the benzyl protecting group was resistant to cleavage under all conditions attempted. Thus, **65a** was prepared from dimethyl acetylenedicarboxylate (**63**) by Diels-Alder reaction with diene **64** followed by aromatization, anhydride formation, and aminolysis. A high yielding reduction with $NaBH_4/Et_3SiH$ produced lactam **66a** which, unfortunately, formed an inseparable complex of **4a** and triphenylphosphine oxide upon nitrene cyclization.

Thus, protection of lactam **66a** followed by deoxygenation and hydrolysis ultimately led to staurosporinone (**4a**).

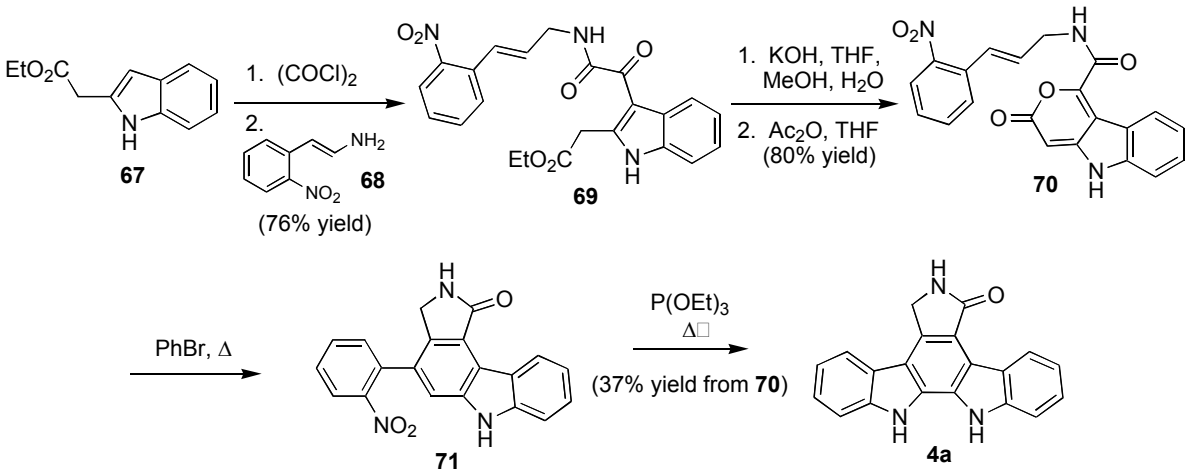
Scheme 1.3.10



1.3.1.9 The Moody Approach.[34]

The Moody synthesis centered on the utilization of pyranoindolone **70** to control an intramolecular Diels-Alder reaction with subsequent aromatization to carbazole **71** by loss of CO_2 and air oxidation. Nitrene formation by deoxygenation with triethylphosphite afforded K252c (**4a**). Interestingly, intermediate **71** provides an opportunity to differentiate the indole nitrogens and, as in the Magnus approach (see Section 1.3.1.3), again could allow for regioselective introduction of a carbohydrate.

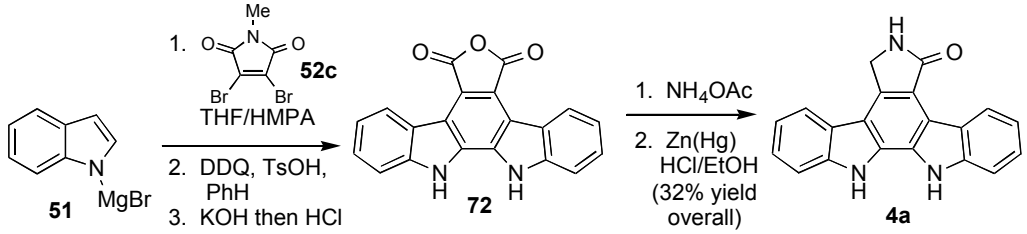
Scheme 1.3.11



1.3.1.10 The Kirilovsky Modification of the Weinreb Method.

Simple modification of Weinreb's oxidative cyclization approach to indolocarbazole **4e** (see Section 1.3.1.4) via anhydride **72** followed by aminolysis and reduction allowed for the preparation of K252c (**4a**, see Scheme 1.3.12).[35]

Scheme 1.3.12

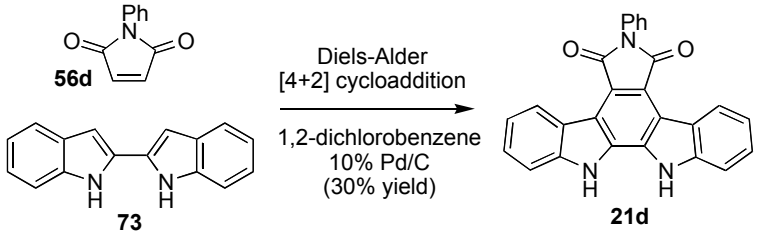


1.3.1.11 The [4+2] Cycloaddition Approach.

Since the pioneering work of Kaneko and Clardy, a number of groups have investigated the [4+2] cycloaddition of biindoles (**73**) with various dienophiles. Outlined in Scheme 1.3.13, this direct method has met with very limited success (yields range between 0-30%). The highest yields to date have been reported by Somei (e.g., **56d**+**73**→**21d**), and are highly dependent on

reaction conditions and substrates.[36] Wallace[37] and Bergman[38] have also reported many difficulties associated with this approach, and even attempts to lock the biindole substrate into an s-cis configuration by either a carbonyl or ethyl bridge have met with modest success.

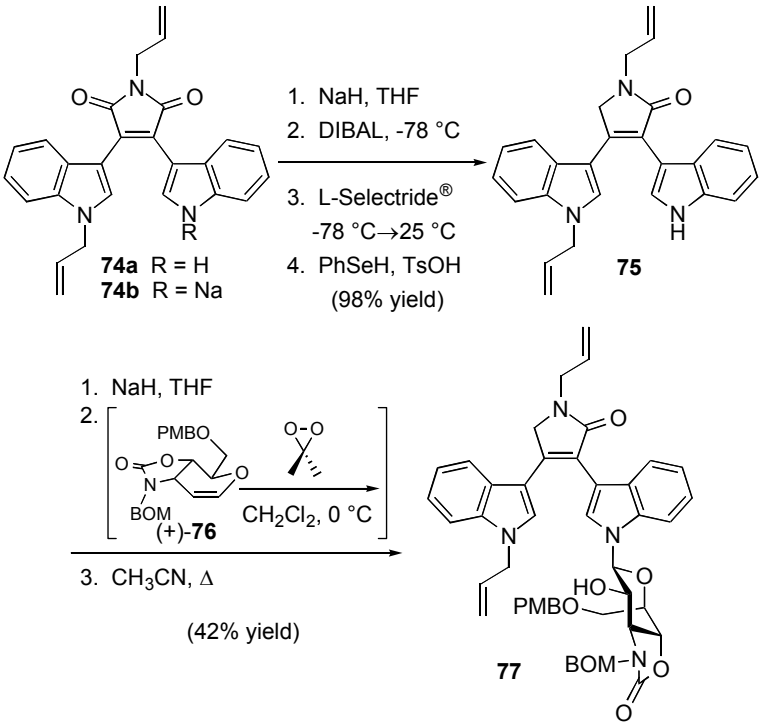
Scheme 1.3.13



1.3.1.12 The Danishefsky Approach.[39]

The goal of the total synthesis of rebeccamycin and staurosporine guided Danishefsky in his approach to the synthesis of the indolocarbazole nucleus. In general, the approach relied on glycoslyation of bis-indolyl maleimide intermediates, followed by a photocyclization similar to that employed by Winterfeld (Section 1.3.1.2). Danishefsky also attempted to reduce maleimide intermediates selectively to allow for stepwise, regioselective formation of the indole-*N*-glycosidic linkages. Reasonable success was achieved using the indole anion (e.g., **74b**) as an electron donating substituent to relay information to the imide portion of the molecule (see Scheme 1.3.14, **74a**→**75**). However, the ultimate utilization of this regioselective strategy (i.e., staurosporine synthesis) was unsuccessful due to the susceptibility of lactams such as **75** and **77** to oxidize under basic conditions coupled with problems of protecting group incompatibility.

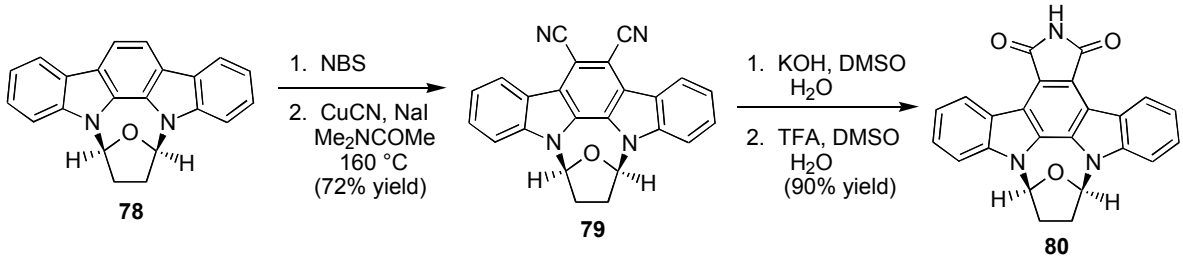
Scheme 1.3.14



1.3.1.13 McCombie's Approach.[40]

Influenced by the desire to prepare indolocarbazole analogs for biological testing, McCombie developed a novel method for introducing the imide moiety into the basic indolo[2,3]carbazole skeleton (Scheme 1.3.15). Two step cyanation of furanosylated indolocarbazole **78** was followed by hydrolysis to imide **80**. This approach proved amenable to the preparation of numerous structural analogs.

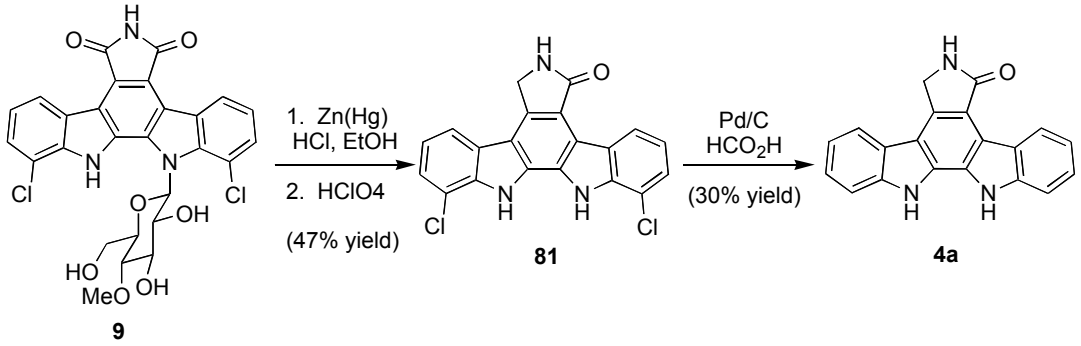
Scheme 1.3.15



1.3.1.14 The Prudhomme Degradation.[41]

Prudhomme has developed a simple degradation of rebeccamycin (**9**) to staurosporinone (**4a**). Imide reduction followed by carbohydrate cleavage afforded **81**, which upon dechlorination in the presence of palladium gave rise to K252c (**4a**, see Scheme 1.3.16).

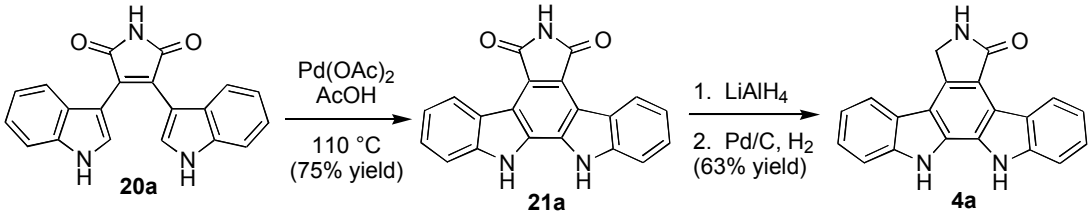
Scheme 1.3.16



1.3.1.15 Recent Modifications.

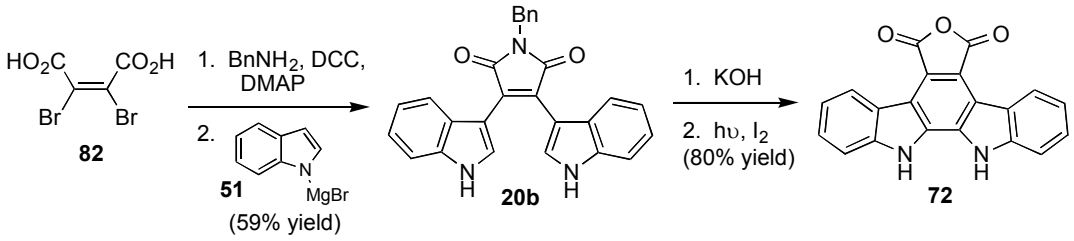
Recently, a number of improved procedures and modified syntheses of indolocarbazole **4a** based on one or more of the above strategies have appeared. Hill reported the palladium-mediated cyclization of maleimide **20a** to afford imide **21a**, which was reduced using $LiAlH_4$ followed by treatment with

Scheme 1.3.17

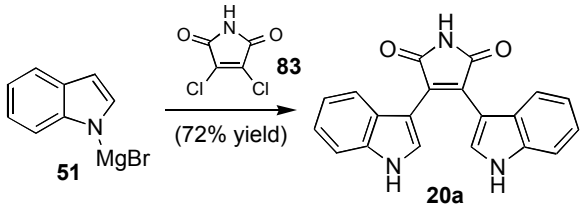


palladium to complete the synthesis of **4a** (Scheme 1.3.17).[42] Lown reported the sequence shown in Scheme 1.3.18,[43] which improves the Kirilovsky synthesis of anhydride **72**, and Lilly's process division has improved the preparation of maleimide **20a** by employing dichloromaleimide (**83**, see Scheme 1.3.19).[44]

Scheme 1.3.18

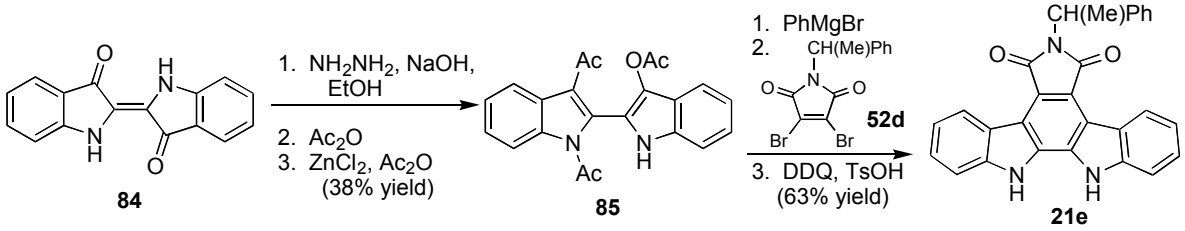


Scheme 1.3.19



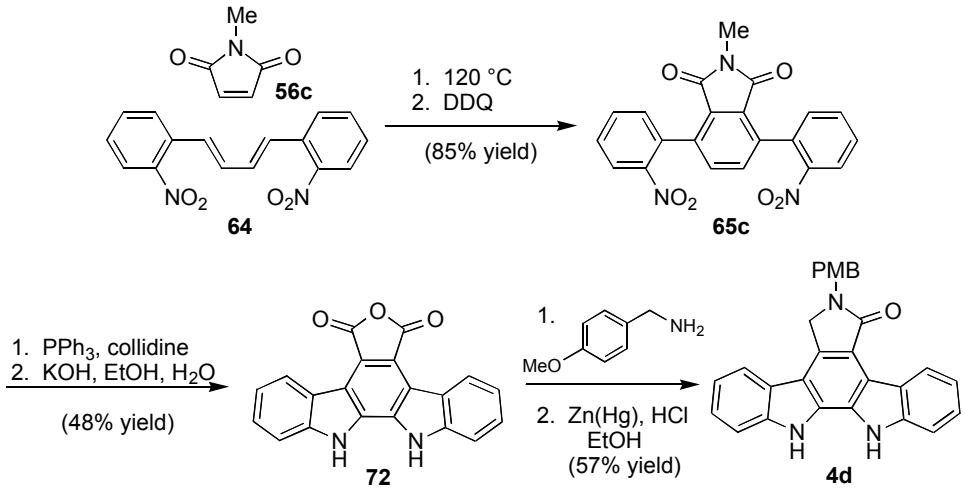
In an alternative approach, Sasaki and Sekimizu reported the novel coupling of **85** and **52d** for the preparation **21e** (Scheme 1.3.20).[45] Biindole **85** is prepared in three steps by reduction of indigo (**84**), making this approach amenable to large-scale synthesis.

Scheme 1.3.20



Finally a group at Bayer reported a modification of the Raphael approach to afford **4d** (Scheme 1.3.21).[46]

Scheme 1.3.21



1.3.2 The Synthesis of Carbohydrates for Indolocarbazole Synthesis.

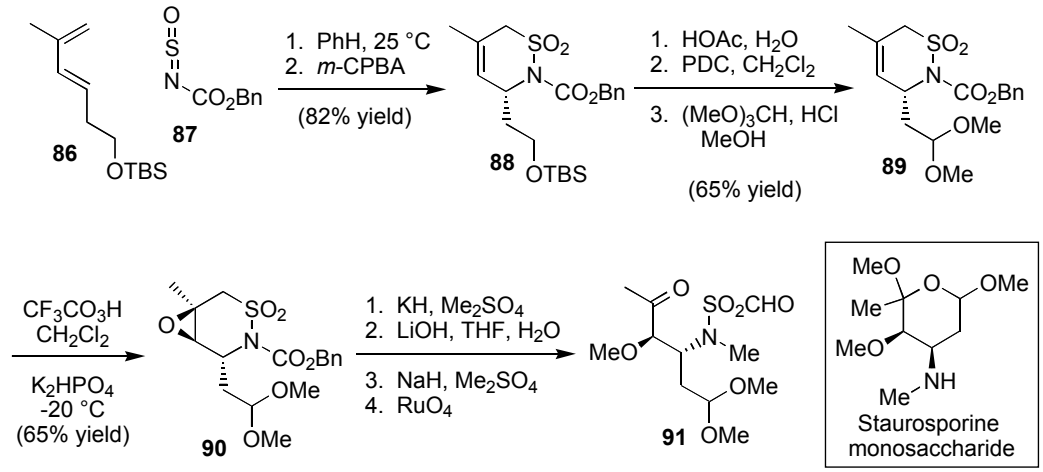
Prior to this investigation, only a limited number of approaches had been developed for the synthesis of complex carbohydrate intermediates slated for use in the total synthesis of K252a (**2**) or staurosporine (**1**). These approaches are summarized below.

1.3.2.1 Weinreb's Preparation of the Staurosporine Monosaccharide.[29]

In 1984 Weinreb reported the synthesis of the aminohexose portion of staurosporine via an *N*-sulfinyl Diels-Alder [4+2] cycloaddition. As shown in Scheme 1.3.22, cycloaddition of diene **86** and benzyl sulfinylcarbamate (**87**) formed a mixture of diastereomeric sulfoxides which were oxidized to the sultam (**88**) and then converted to acetal **89**. Olefin **89** was diastereoselectively

epoxidized with trifluoroperacetic acid to **90**. Hydrolytic-reductive opening of epoxide **90** followed by olefin cleavage afforded keto-acetal **91**, a suitable synthon for the staurosporine carbohydrate.

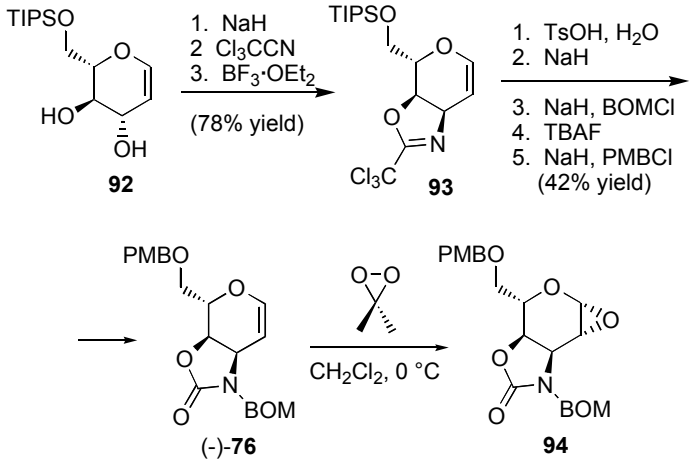
Scheme 1.3.22



1.3.2.2 Danishefsky's Staurosporine Glycal Precursor.[39b]

In the first total synthesis of staurosporine, Danishefsky utilized glycal epoxide **94** as the glycosyl donor. Glycal **92**, a derivative of L-glucal, was converted to oxazoline **93** by a modified Schmidt reaction. Conversion to oxazolidinone **76** proceeded under standard conditions, and finally treatment with Murry's reagent provided the glycal epoxide (**94**, Scheme 1.3.23).

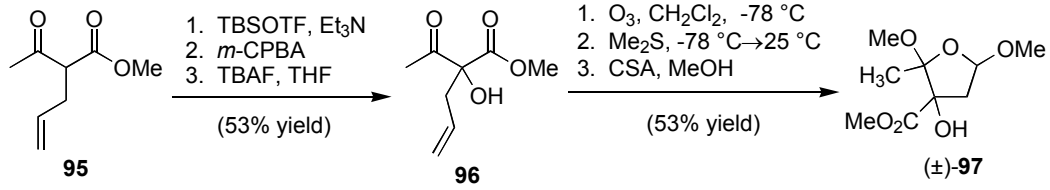
Scheme 1.3.23



1.3.2.3 The Bayer Synthesis of the K252a Carbohydrate.[46]

Subsequent to our publication of the total synthesis of K252a, a group at Bayer reported their synthesis of the K252a carbohydrate. Rubottom oxidation of acetoacetate **95** followed by reductive ozonolysis and acid mediated cyclization produced the racemic dimethoxy furanose [(±)-**97**].

Scheme 1.3.24



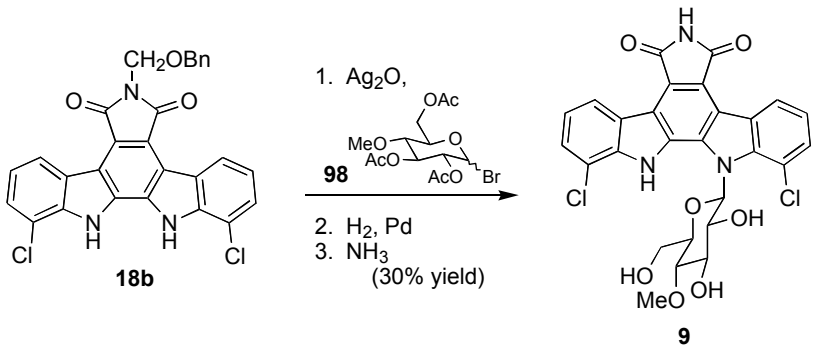
1.3.3 Methods Describing the Combination of Carbohydrate and Indolocarbazole.

1.3.3.1 Synthesis of Indolocarbazoles Possessing a Single Indole-*N*-glycosidic Linkage.

1.3.3.1.1 The Kaneko/Clardy Synthesis of Rebeccamycin.[30]

The first example in the literature of a coupling reaction between an indolocarbazole and a complex carbohydrate was carried out by Kaneko and Clardy in their synthesis of the antitumor indolocarbazole glycoside rebeccamycin (see Scheme 1.3.25). Koenigs-Knorr coupling of aglycon **18b** with bromo pyranose **98** occured in the presence of Ag_2O to form rebeccamycin (**9**) in 30% yield, upon deprotection of the imide and carbohydrate.

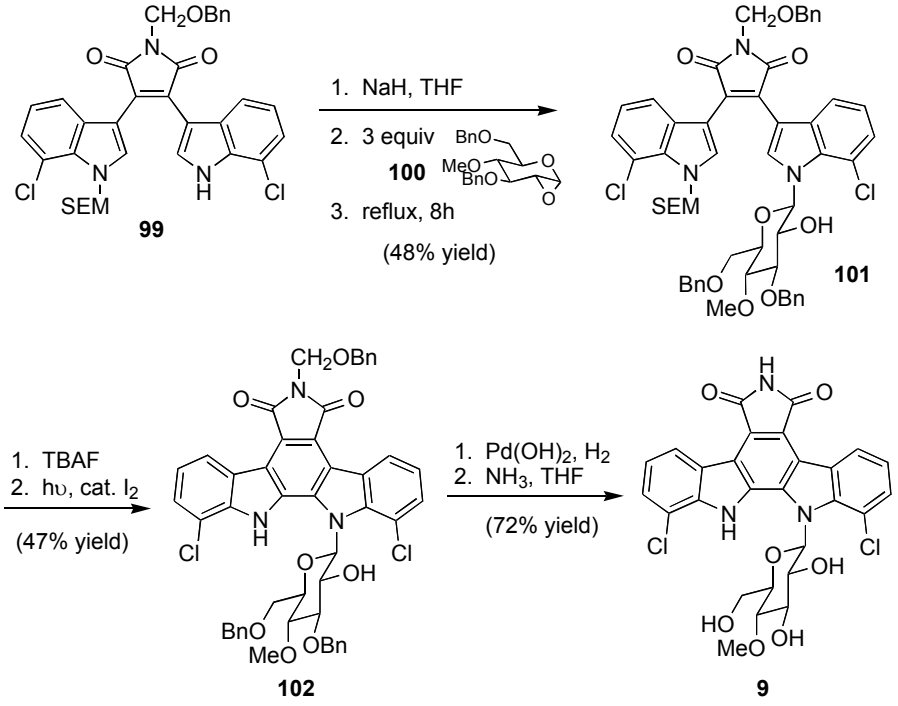
Scheme 1.3.25



1.3.3.1.2 The Danishefsky Synthesis of Rebeccamycin.[39a]

In 1993 Danishefsky reported the application of glycal epoxide chemistry to the synthesis of indolocarbazoles by developing the method to include the preparation of indole-*N*-glycosides and improving the synthesis of

Scheme 1.3.26

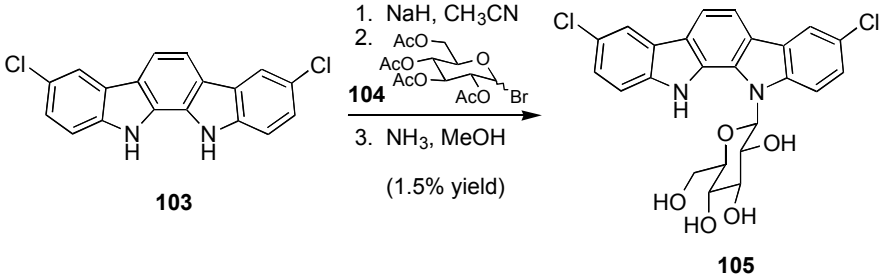


rebeccamycin (**9**). It was found that indoles were stronger glycosyl acceptors than indolocarbazoles. Thus, base induced coupling of selectively protected maleimide **99** with epoxide **100** furnished glycoside **101** in 48% yield. Deprotection of the SEM group, photocyclization, careful hydrogenolysis with Pearlman's catalyst, and finally ammonolysis (i.e., **101**→**102**→**9**, Scheme 1.3.26) yielded rebeccamycin (**9**) in 34% yield.

1.3.3.1.3 The Bonjouklian/Moore Synthesis of Tjipanazole E and Van Vranken's Synthesis of (+)-Tjipanazole F2.

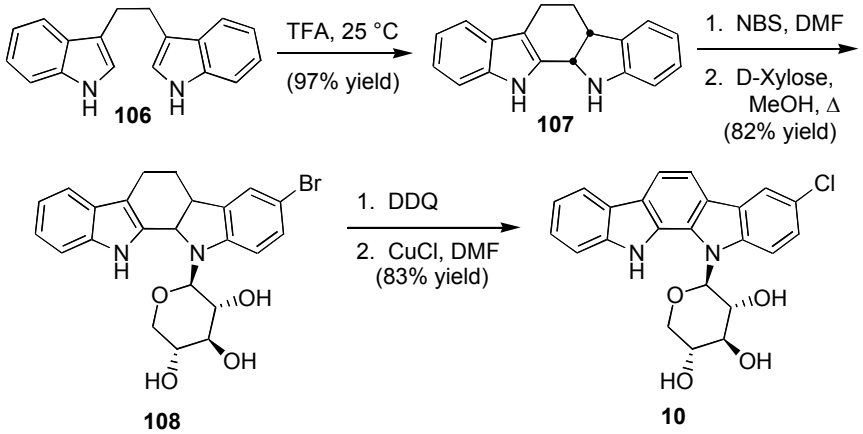
Total synthesis of tjipanazole E (**105**) was accomplished by Bonjouklian and Moore by base-mediated glycosidation of dichloroindolocarbazole **103** with bromo pyranose **104**.[47]

Scheme 1.3.27



Recently, Van Vranken developed an interesting and selective method for dissymmetric tjipanizole synthesis (see Scheme 1.3.28).[48] Acid-mediated cyclization of bis-indole **106** provided the indoloindoline **107**, which was selectively brominated and glycosylated to afford glycoside **108** as a 1:1 mixture of diastereomers. Oxidation of **108** with DDQ followed by halogen exchange provided (+)-tjipanazole F2 (**10**).

Scheme 1.3.28

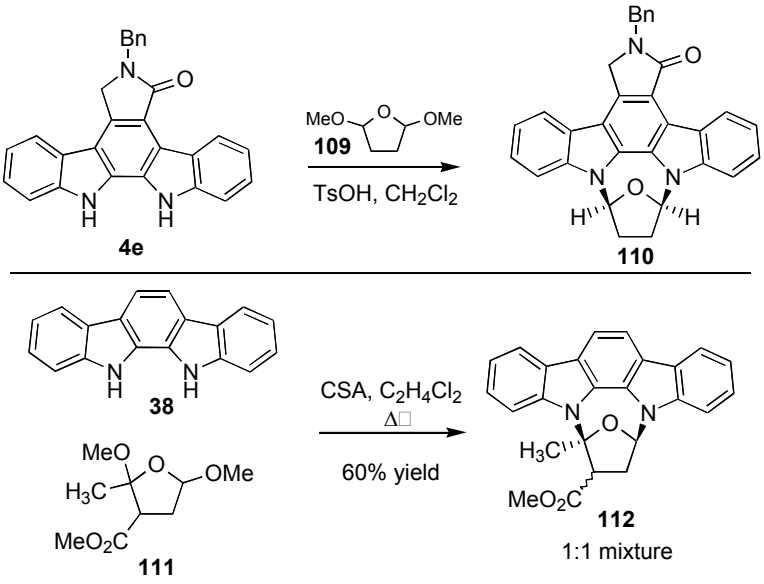


1.3.3.2 Synthesis of Indolocarbazoles Possessing a Double Indole-*N*-glycosidic Linkage.

1.3.3.2.1 Weinreb/McCombie Glycosidation Studies.[29,40]

The earliest preparation of an indolocarbazole possessing a double indole-*N*-glycosidic linkage was reported by Weinreb in a model investigation. Furan **109** was coupled to aglycon **4e** under acid catalysis. This

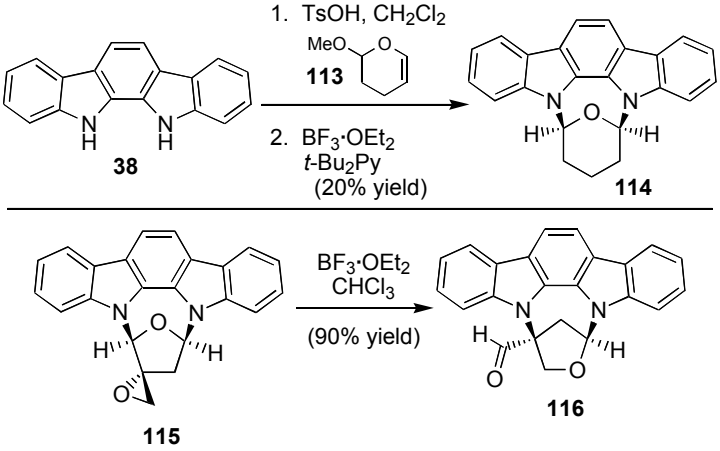
Scheme 1.3.29



cycloglycosidation approach was more fully investigated by McCombie, who discovered that improved yields could be obtained by slow addition of the carbohydrate to the indolocarbazole in dichloroethane at reflux. Importantly, McCombie investigated the coupling of more fully functionalized carbohydrates with indolocarbazoles. Although early reports suggested that the coupling remained a high yielding process, carbohydrates such as **111** resulted in the formation of a 1:1 mixture of diastereomers (**112**).

For the pyranosylation of the indolocarbazole nucleus, a two step acid-catalyzed procedure was also developed by McCombie, but resulted in only moderate yields (e.g., **38**+**113**→**114**, Scheme 1.3.30).[49] Finally, an attempt to access this class of compounds by ring expansion of a furanosylated indolocarbazole led to skeletal rearrangement rather than the desired pinacol rearrangement (e.g., **115**→**116**).[50]

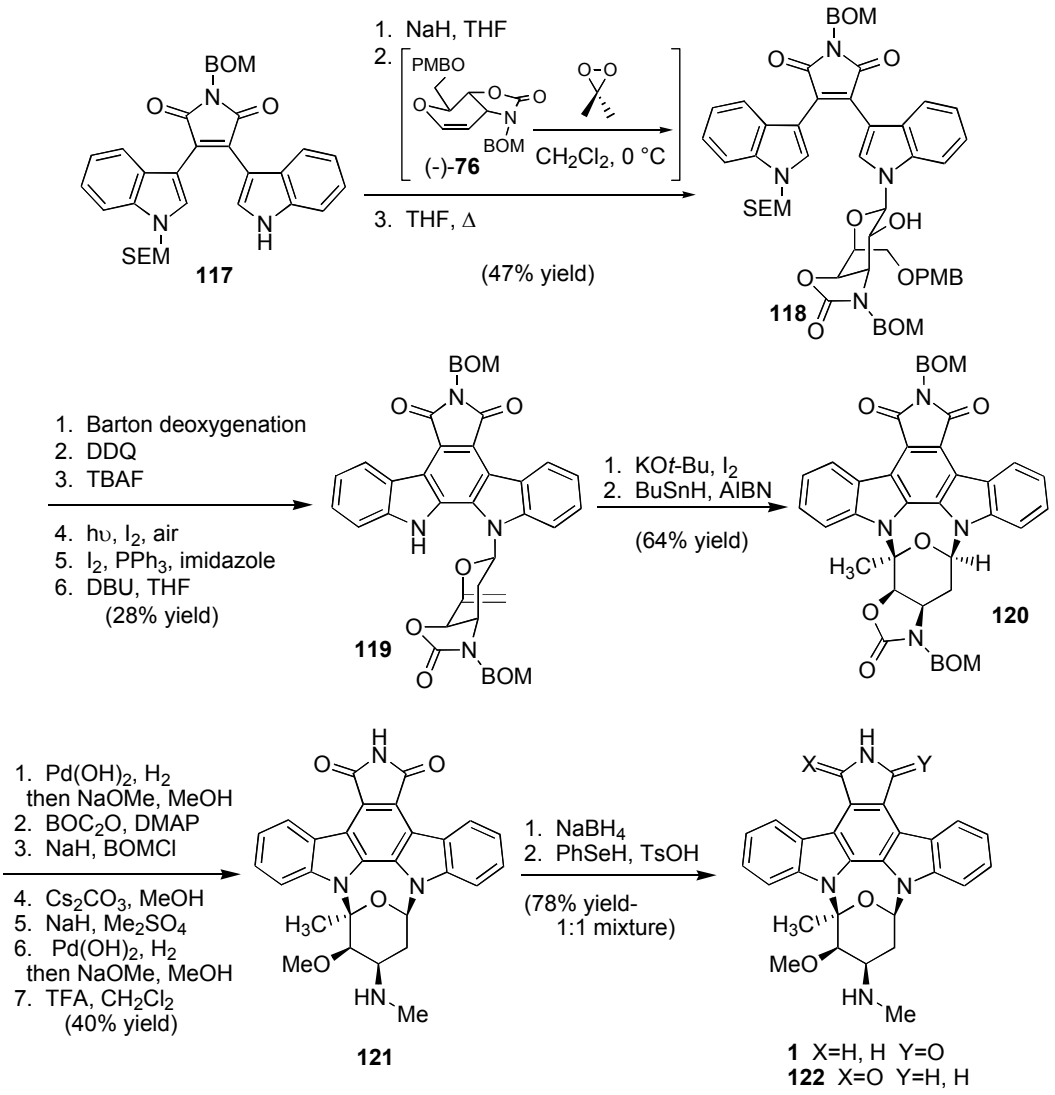
Scheme 1.3.30



1.3.3.2.2 The Danishefsky Synthesis of (+)- and (-)-Staurosporine.

As part of his pioneering effort in the development of glycal epoxide chemistry, Danishefsky devised an approach to staurosporine.[39b] Specifically, epoxidation of glycal (-)-**76** and reaction with maleimide **117** formed one of the indole *N*-glycosidic linkages. Cyclization of maleimide **118** and exo glycal formation set the stage for the critical second glycosidation. Treatment of olefin **119** with iodine and *t*-BuOK followed by radical dehalogenation provided the pyranosylated indolocarbazole **120** in 64% yield. Protecting group removal and methylation were achieved as shown in Scheme 1.3.31 (i.e., **120**→**121**). Finally, reduction of imide **121** provided a 1:1 mixture of **1** and **122**.

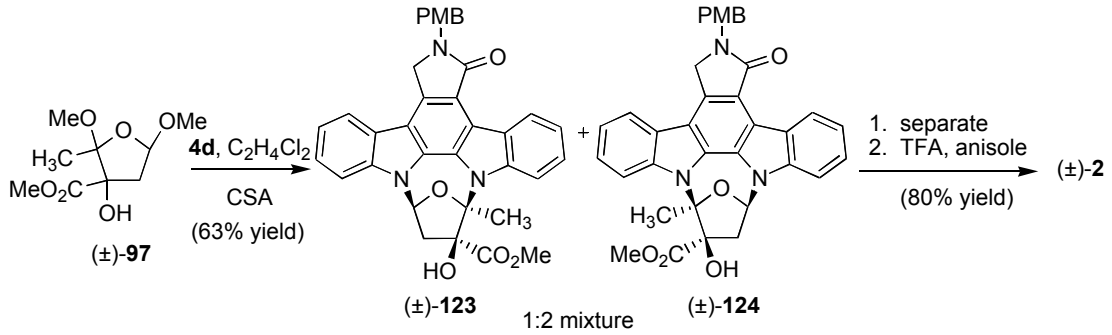
Scheme 1.3.31



1.3.3.2.3 The Bayer Synthesis of (±)-K252a.[46]

Subsequent to publication of our synthesis, a group at Bayer reported an identical approach to K252a. Cycloglycosidation of protected aglycon **4d** and furanose (±)-**97** formed a 2:1 mixture of stereoselectively formed regioisomeric indolocarbazoles (±)-**124** and (±)-**123**. Deprotection of the major regioisomer by treatment with TFA produced (±)-K252a (**2**).

Scheme 1.3.32



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CHAPTER TWO

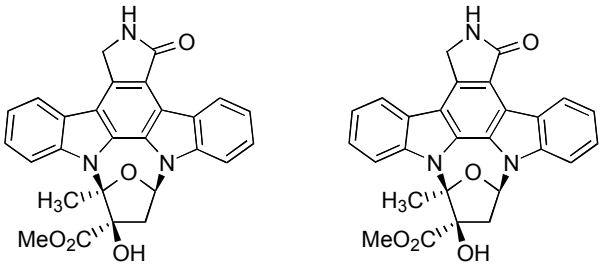
The Design and Implementation of an Efficient Synthetic Approach to Furanosylated Indolocarbazoles: The Total Synthesis of (+)- and (-)-K252a.

2.1 Background.

2.1.1 Introduction.

In 1994, nearly 17 years after Ō mura's discovery of staurosporine (**1**), we embarked on a journey into the total synthesis of indolocarbazole natural products. K252a was chosen as an initial target, owing to the interesting bis-*N*-furanosyl attachment to the aglycon moiety, its potent biological activity, and its relatively unexplored chemistry as compared to staurosporine. As described in Chapter 1, K252a (**2**) was isolated in 1985 independently by Sezaki (originally named SF-2370)[1] and a year later by Kase.[2] Kase described the complete structure elucidation of K252a by single crystal X-ray analysis (Figure 2.1.1) as well as the ability of **2** to inhibit PKC with nanomolar affinity (IC_{50} = 32nM).

Figure 2.1.1

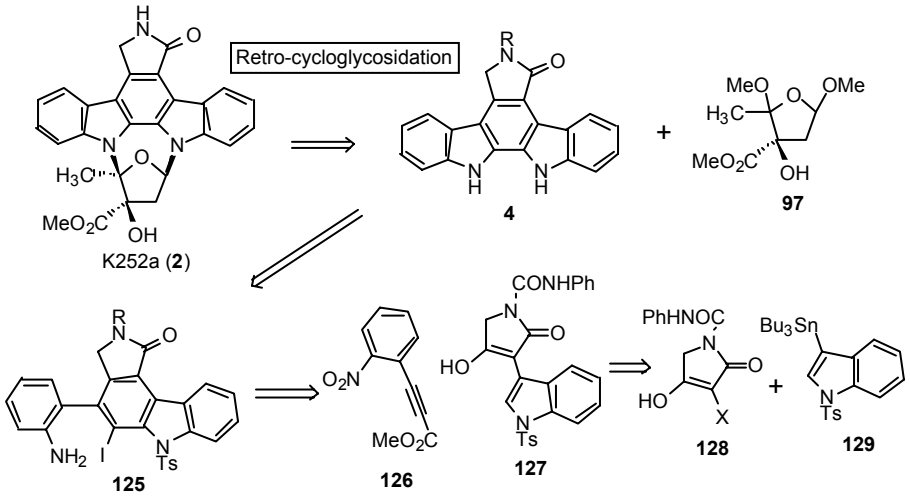


(+)-K252a (**2**)
(a.k.a. SF2370)

2.1.2 K252a Retrosynthetic Analysis.

In planning a synthesis of K252a, the single-step cycloglycosidation developed by Weinreb and McCombie (Section 1.3.3.2.1)[3] was viewed as the most efficient approach (i.e., **2**⇒**4**+**97**, Scheme 2.1.1), especially if the regio- and stereochemical issues associated with coupling a fully functionalized furanose could be addressed. Thus, the synthetic design was based on this most simplifying disconnection and the preparations of a selectively protected aglycon (e.g., **4**) and an appropriate furanose (e.g., **97**) were considered. Although one of the known approaches to **4** could possibly have been modified so as to deliver protected derivatives, the development of a novel protocol was sought that would be both efficient and amenable to installing a variety of protecting groups at the lactam nitrogen. The latter was viewed as a particularly important design feature given the likelihood of having to screen the suitability of several protecting groups.[4]

Scheme 2.1.1

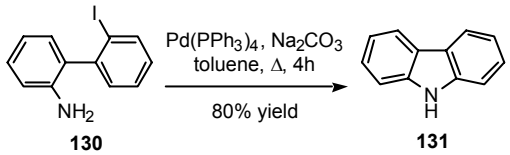


2.2 Synthesis of K252c and Aglycons 4b-e.

2.2.1 Synthesis of K252c (4a): A First Generation Approach.

With several design features in mind, a first generation strategy toward aglycon **4** emerged (Scheme 2.1.1). This approach called for late stage cyclo-furanosylation (e.g., **4**+**97**→**2**) and palladium mediated C-N bond formation in the carbazole synthesis (e.g., **125**→**4**). Diels-Alder cycloaddition of indole-pyrrolidone **127** with acetylene **126** was envisioned to be the first critical step. As a prelude to this approach, the carbazole forming reaction was investigated rather extensively in a model system. In accord with Kosugi's protocol, a tin amide (R-NH-$SnBu_3$) was initially explored as the substrate;[5] however, under certain conditions ring closure occurred in the absence of tin.[6] Thus, carbazole could be produced in up to 80% yield (e.g., **130**[7]→**131**, Scheme 2.2.1) using $Pd(PPh_3)_4$ (1.1 equiv), Na_2CO_3 in toluene at reflux for 4 hours. Reactions employing catalytic amounts of Pd (5 mol%) resulted in the formation of carbazole (ca. 60%) but only after prolonged reaction periods (5 d).[8]

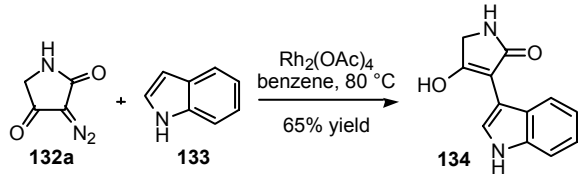
Scheme 2.2.1



130 **131**

Having established the feasibility of forming a carbazole using Kosugi's reaction, efforts turned toward preparing the actual substrate (**4**) and investigating an approach to diene **127** that called for coupling of stannyl indole **129**[9] to a halopyrrolidone **128** (X = Br, I).[10] Unable to effect the Stille coupling of **128** and **129**, alternative strategies were considered. Particularly interesting was a report from 1935 describing the preparation of ethyl 3-indoleacetate via coupling of indole with ethyldiazoacetate in the presence of Cu metal.[11] In investigating this as an approach to diene **127**, known diazotetramic acid **132a**[12] was found to undergo smooth conversion to the elusive diene **134** when exposed to $Rh_2(OAc)_4$ and indole (**133**) in benzene at reflux (65% yield, Scheme 2.2.2).[13]

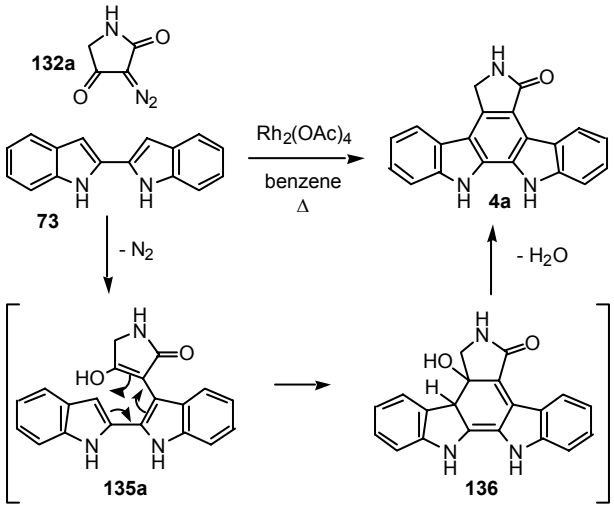
Scheme 2.2.2



132a **133** **134**

Difficulties encountered in advancing diene **134** to carbazole **125** by a Diels-Alder strategy led to a re-evaluation of the approach. Eventually it was recognized that a similar diazo addition reaction, using 2,2'-biindole as substrate, might produce a product that, upon electrocyclization/dehydration, would furnish K252c directly (e.g., **132a**+**73**→**4a**, Scheme 2.2.3).[14]

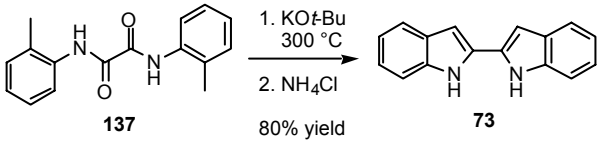
Scheme 2.2.3



2.2.2 Synthesis of K252c (4a), Second Generation Approach.

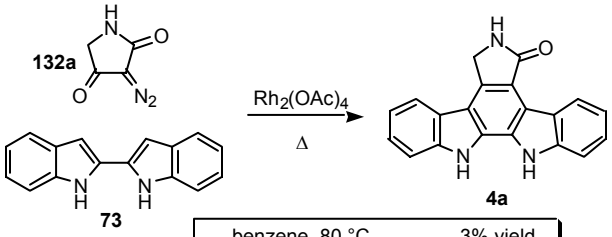
In accord with the revised plan, 2,2'-biindole (**73**) was prepared from oxaltoluidide **137** via a double Madelung cyclization, according to an excellent procedure recently published by Bergman (Scheme 2.2.4).[14f] Initial attempts to

Scheme 2.2.4



implement this revised approach by reacting diazo lactam **132a** with biindole **73** under conditions identical to those used for the preparation of diene **134** produced trace amounts of a substance possessing ^{1}H-NMR resonances in accord with K252c. Given this glimmer of hope, considerable effort was expended optimizing the reaction conditions. Guided by the observation of what appeared to be benzene C-H insertion products and the fact that biindole **73** appeared only sparingly soluble in benzene, several non-reactive solvents

Scheme 2.2.5



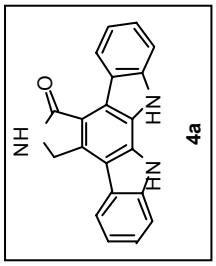
benzene, 80 °C	3% yield
pinacolone, 120 °C sealed tube degassed with N_2	25% yield

were screened. In the event, solvents typically employed in rhodium carbenoid reactions (i.e., chloroform, methylene chloride, hexafluorobenzene, 1,2-dichloroethane, xylenes, toluene and chlorobenzene) were ineffective at dissolving the substrate. However, when less traditional solvents such as ethyl acetate and acetone were employed, a striking increase in the amount of substrate solubility was noticed along with an appreciable increase (3%∅15%) in the production of aglycon **4a**. Reasoning that the carbenoid may be interacting unfavorably with the medium (e.g., carbonyl ylide formation), the use of more sterically encumbered carbonyl containing solvents was explored . In addition, the observation that exposure to air resulted in darkening of the reaction mixture led to implementation of more rigorous deoxygenation methods. In the end, changing the solvent to pinacolone and degassing with N_2 prior to conducting the reaction in a sealed tube at 120 °C had a profound effect on the yield of K252c (now isolated in 25% yield, see Figure 2.2.1).

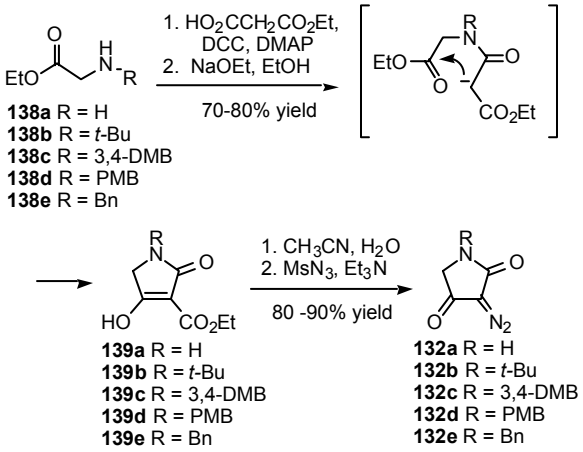
2.2.3 Further Successful Carbenoid Additions to 2,2'-Biindole, Completion of 4b-e.

As shown in Scheme 2.2.6, a series of diazo compounds were prepared by the procedure used to produce diazolactam **132a**. Thus, *N*-substituted glycine esters **138b-e**[15] were exposed to DCC/DMAP-promoted coupling with ethyl

hydrogen malonate followed by Dieckmann cyclization (NaOEt/EtOH) to produce lactams **139b-e**. A single-pot decarboethoxylation/diazo-transfer reaction was effected by heating ester **139b-e** in wet acetonitrile and then treating the cooled reaction mixture (0 °C) with MsN_3 and triethylamine.[12] The overall process involves a single purification step, can be conveniently carried out on a 20 g scale, and results in an approximate 50% overall yield of diazo lactams **132b-e** from **138b-e**.

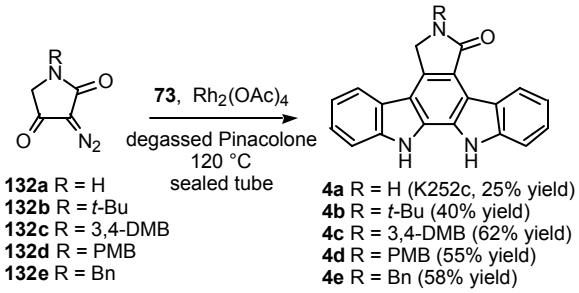


Scheme 2.2.6



With ample quantities of lactams **132b-e** and biindole **73** readily available, the optimized reaction conditions were applied. Delightfully, introduction of the amide protecting group appeared to influence the yield favorably, particularly in substrates possessing benzyl type protecting groups (Scheme 2.2.7). The optimized sequence is highlighted by preparation of the 3,4-dimethoxybenzyl protected aglycon **4c**, which was produced in 62% yield (50% overall yield for the 3 steps from *o*-toluidine)!

Scheme 2.2.7

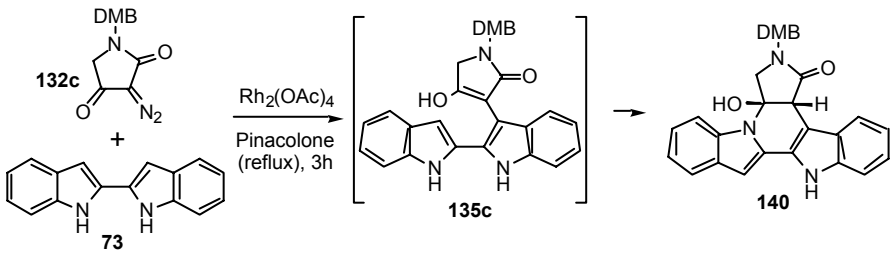


132a R = H
132b R = *t*-Bu
132c R = 3,4-DMB
132d R = PMB
132e R = Bn

4a R = H (K252c, 25% yield)
4b R = *t*-Bu (40% yield)
4c R = 3,4-DMB (62% yield)
4d R = PMB (55% yield)
4e R = Bn (58% yield)

In the initial studies, reactions had been performed on approximately 100 mg of biindole **73** in a sealed tube at elevated temperature using 10 mol% $Rh_2(OAc)_4$ and 3-4 equiv of the diazo lactam (i.e., **132c**). For the purposes of the K252a synthesis this scale was quite suitable; however, since extending this effort to staurosporine was expected to require multigram quantities of aglycon **4c**,[16] optimization efforts were continued. To this end, the reaction was attempted at atmospheric pressure and reduced stoichiometry of the Rh(II) catalyst and diazo substrate. In the event, reaction of biindole **73**, diazo lactam **132c** (1:1 mol equiv), and $Rh_2(OAc)_4$ (1.0 mol%) in degassed pinacolone at reflux for 8h produced a 36% yield of protected aglycon and 50% unreacted biindole (72% yield based on recovered starting material). Typically this reaction was run on 4.0 g of biindole **73** and produced 2.9 g of indolocarbazole **4c**. In the course of developing this improved large-scale procedure, a second isolable product was observed (ca. 5-10% yield) which, upon either heating in xylenes at reflux or exposure to CSA, undergoes quantitative conversion to **4c**. Tentatively assigned as hemiaminal **140** based on spectral evidence, this product likely forms from the initial adduct (**135c**) and supports the stepwise process outlined in Scheme 2.2.3.

Scheme 2.2.8

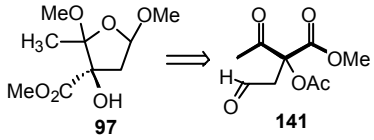


2.3 The Synthesis of (±)-K252a.

2.3.1 Preparation of the K252a Carbohydrate (±)-13.

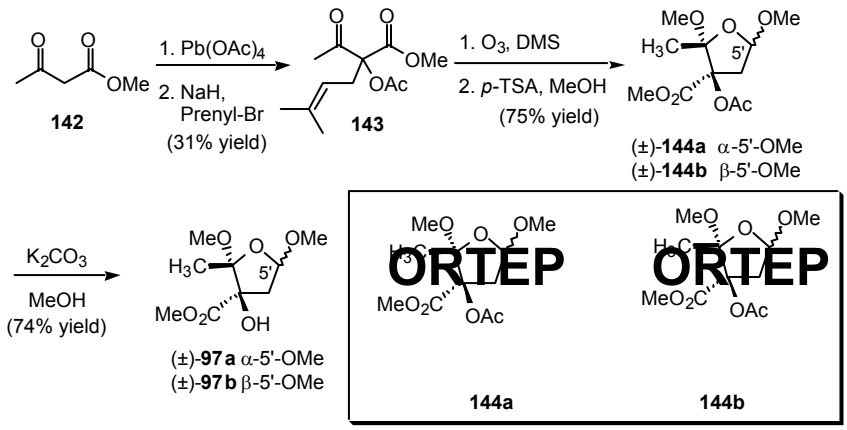
Prior to this investigation, there were no reported syntheses of the K252a carbohydrate. Viewing furanose (±)-**97** in an open chain form reveals keto-aldehyde **141** and clearly presents methyl acetoacetate as an exploitable

Scheme 2.3.1



intermediate. Thus, an initial approach to carbohydrate (±)-**97** began with the $Pb(OAc)_4$-mediated oxidation of methyl acetoacetate (**142**)[17] followed by prenylation to produce olefin **143** (31% yield). Surprisingly, reductive ozonolysis and acid-promoted ring closure produced only two of the expected four diastereomeric furanose products. Single crystal X-ray analysis

Scheme 2.3.2



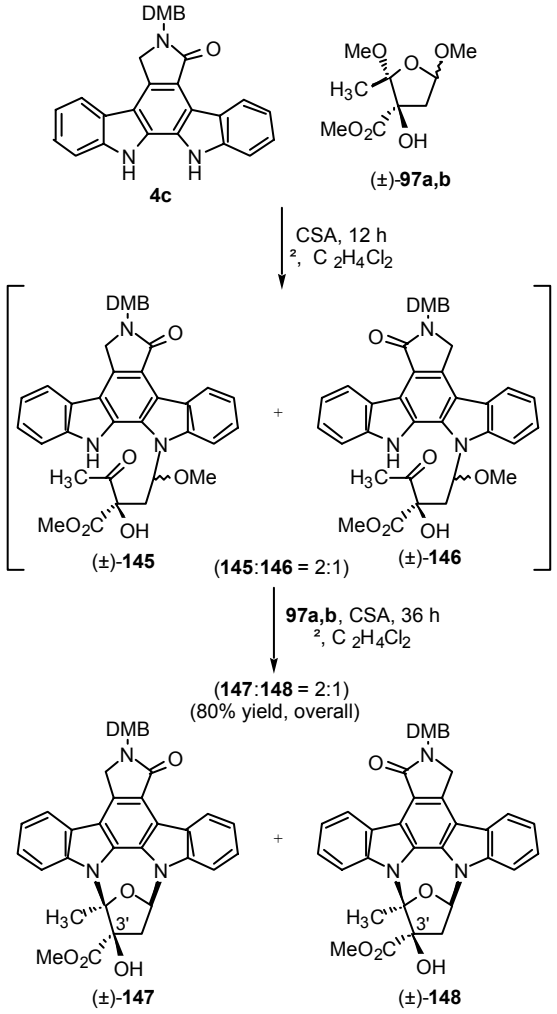
unambiguously established the structures to be C(5') epimers **144a** and **144b**. Removal of the acetate provided the cycloglycosidation substrate (±)-**97**. Although not useful in the asymmetric synthesis, this approach was amenable to scale-up and allowed rapid access to gram quantities of the furanose mixture.

2.3.2 Cyclofuranosylation of Aglycon 4c.

With ample quantities of the K252a carbohydrate and protected aglycons in hand, investigation of the key cycloglycosidation commenced. In an initial attempt, the coupling reaction was performed with K252c and furanose (±)-**97** in the presence of CSA as catalyst. The result was formation of a complex mixture comprised in-part of products derived from lactam alkylation, thus prompting the exploration of the amide protected aglycon series (**4b-e**).[18] Given that strong evidence in the literature suggested a simple benzyl group would be resistant to cleavage, it was reasonable to proceed with the 3,4-dimethoxy benzyl protected aglycon **4c**. In the event, slow addition of carbohydrate (±)-**97** (2 equiv, 24 h) to a solution of indolocarbazole **4c** and CSA (0.1 equiv) in 1,2-dichloroethane at reflux rapidly produced a quaternary mixture [(±)-**145** and (±)-**146**, *vide infra*] which, quite remarkably, upon prolonged heating was reduced to a 2:1 binary

mixture. Following isolation and characterization, the products were determined to be the regioisomeric furanosylated indolocarbazoles (±)-**147** and (±)-**148**; thus, this reaction proceeds stereoselectively such that the C(3') hydroxyl is oriented syn to the indolocarbazole moiety.[19] Furthermore, the major regioisomer corresponded to the protected K252a derivative (±)-**147**.[20]

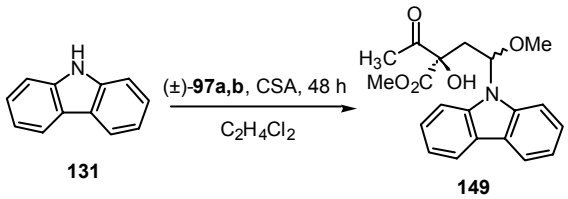
Scheme 2.3.3



In an effort to understand the surprising and remarkable stereoselectivity of this reaction, an attempt was made to isolate and characterize the components of the initially formed quaternary mixture. Despite numerous crystallization and

chromatographic attempts, the mixture was only separable into two fractions. Isolated in a 2:1 ratio, these fractions were each found to contain a 1:1 mixture of what appeared spectroscopically to be open chain monoaminoacetal diastereomers **145** and **146**.[21] To support this structural assignment, the coupling of furanose (±)-**97** with carbazole (**131**) was investigated. Under identical conditions (CSA, $C_2H_4Cl_2$, 83 °C) this reaction was found to produce a separable binary mixture wherein each component possesses spectral properties consistent with an open chain monoaminoacetal diastereomer (i.e., **149**, Scheme 2.3.4).[22]

Scheme 2.3.4

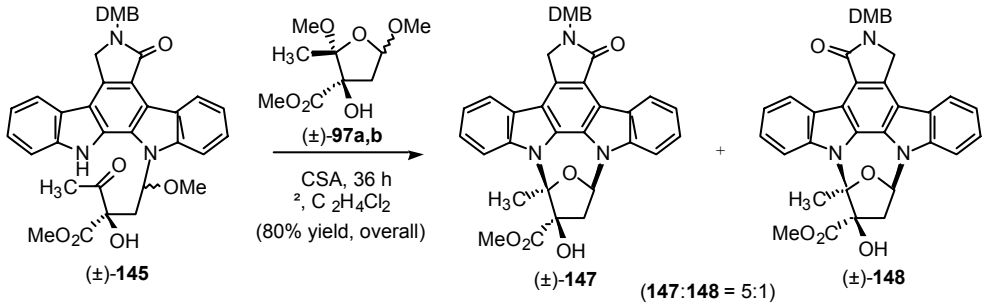


131 **149**

Satisfied with the structures assigned to ketones **145** and **146**, the reactivity of the isolated major diastereomeric pair (i.e., **145**) and the derived product (±)-**147** was explored. In the event, re-exposure of **145** to the cycloglycosidation conditions produced a 5:1 ratio of furanosylated indolocarbazoles **147** and **148**, respectively (see Scheme 2.3.5), whereas (±)-**147** remained unchanged under similar conditions; thus, the regioselectivity observed in the initial cycloglycosidation does not necessarily reflect the thermodynamic stability of regioisomeric monoaminoacetal diastereomers **145** and **146**. With regard to stereochemical outcome, the intermediacy of open chain ketones **145** and **146** indicates that the observed selectivity is not determined in the initial step and must be the result of either a kinetic preference

in the formation of the furanose oxocarbenium ion or the stability of the possible products to the reaction conditions.[23]

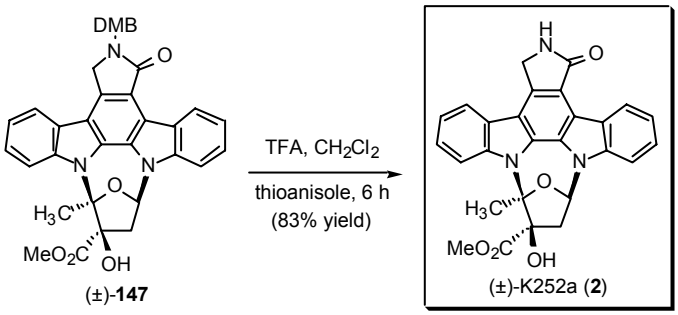
Scheme 2.3.5



2.3.3 Completion of The Synthesis of (±)-K252a.

At this stage, removal of the amide protecting group was all that remained for the completion of the synthesis.[24] Given that the glycosidic linkages had proven quite stable to acid, conditions originally refined by Steglich for the removal of 2,4-DMB groups from peptides were explored.[25,26] Thus, exposure of (±)-**147** to TFA and thioanisole (cation scavenger)[27,28] in CH_2Cl_2 at 25 °C for a period of 6 h resulted in the clean production of (±)-**2**. The latter compound proved spectroscopically identical to a sample of the natural material.[29]

Scheme 2.3.6

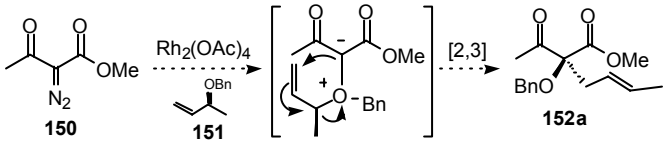


2.4 Asymmetric Synthesis of the K252a Carbohydrate Precursor [(-)-152b].

2.4.1 The Rhodium (II)-Mediated Tandem Claisen-α-Ketol Rearrangement.

Having established furanose **97** to be a suitable synthetic intermediate, attention was turned toward completing an asymmetric synthesis. Although recent work by Enders indicated that a chiral auxiliary controlled version of the synthesis of olefin **143** would likely be an effective solution to the difficult task of producing the requisite enantio-enriched tertiary alcohol,[30] a different course was chosen wherein a similar intermediate (i.e., **152a**) was envisioned to arise via [2,3]-rearrangement of a chiral carbenoid-derived allyloxonium ion (e.g., **150**+**151**→**152a**, Scheme 2.4.1).[31,32,33] Unfortunately, investigations with benzyl ether **151** and diazoester **150** produced intractable mixtures.

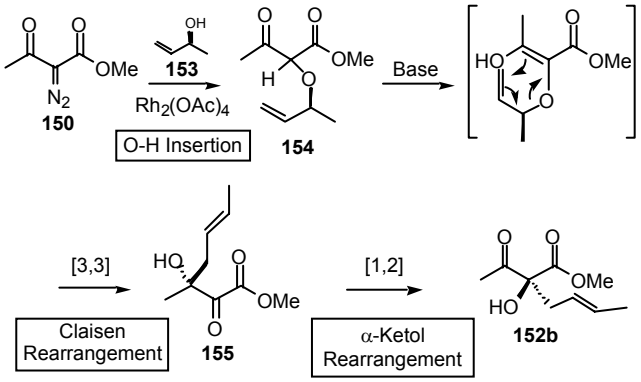
Scheme 2.4.1



Undaunted, alternatives were considered and soon a revised plan was developed wherein carbenoid-mediated O-H insertion of a chiral allylic alcohol

served as the primary event. In this scenario, ketone **152b** was envisioned to arise from the insertion product, an α-allyloxy ketone (e.g., **154**), via a tandem [3,3]/[1,2]-rearrangement protocol. From the work of Koreeda, deprotonation of

Scheme 2.4.2

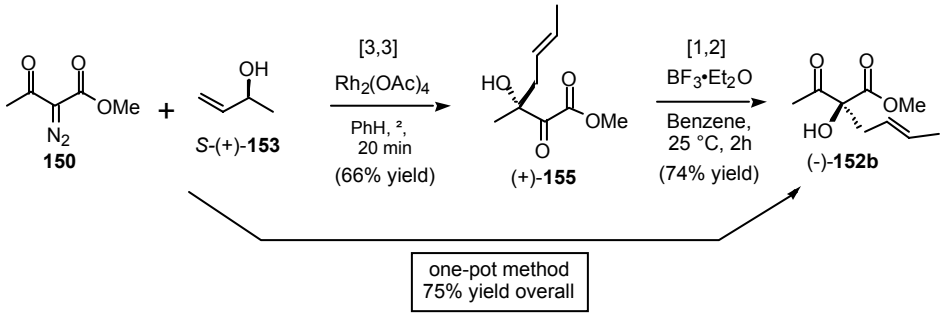


154 was expected to induce [3,3]-rearrangement and produce α-keto ester **155**,[34] a compound that appeared well suited for subsequent Lewis acid promoted [1,2]-allylic migration.[35] While the bond construction was reasonably well-precedented, the issue of stereoselectivity remained speculative. However, given the plethora of rearrangement conditions and Lewis acids, there appeared ample opportunity to influence the stereochemical outcome.

In anticipation of isolating α-allyloxy ether **154**, diazoketoester **150** was subjected to rhodium-catalyzed decomposition in the presence of *S*-(+)-1-buten-3-ol (**153**).[36] In the event, complete consumption of diazoester **150** was observed after only 20 minutes at reflux in benzene. Proton NMR analysis of the crude reaction indicated the clean formation of a product similar to ketoester **154**; however, the characteristic methyl ketone singlet appeared at 1.5 ppm instead of the expected 2.2 ppm. Clearly the allyloxy or allyloxonium ylide intermediate had undergone [3,3]-sigmatropic rearrangement to alcohol (+)-**155** (66% yield).

Completion of the tandem rearrangement protocol was achieved by exposing ketone (+)-**155** to BF_3•Et_2O which promoted a clean [1,2]-allyl migration to furnish alcohol (-)-**152b** in 74% yield. In subsequent studies, improved yields were obtained by conducting the tandem rearrangement in one pot. Thus, introducing an equivalent of BF_3•Et_2O into the cooled [3,3] reaction allows isolation of (-)-**152b** in an overall yield of 75%.[37]

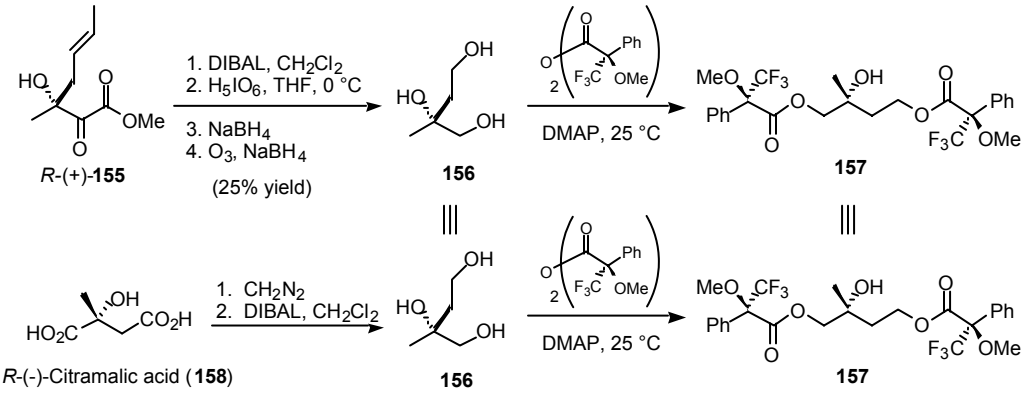
Scheme 2.4.3



2.4.2 Chemical Correlation of Esters (+)-155 and (-)-152b.

With an approach firmly established, a chemical correlation study was initiated to confirm both the sense and degree of asymmetric induction for the tandem rearrangement. Analysis of the purified products from both the [3,3] (i.e., (+)-**155**) and [1,2] (i.e., (-)-**152b**) rearrangements via ^{1}H-NMR in the presence of $Eu(hfc)_3$ gave the first indication that each step was proceeding with a high degree of stereoselectivity.[38] Conversion of ketoester (+)-**155** to triol **156**[39] as outlined in Scheme 2.4.4, followed by comparison of the derived

Scheme 2.4.4



bis Mosher ester (**157**) to samples prepared from *S*-(+)- and *R*-(-)-citramalic acid (**158**) established that *S*-(+)-1-buten-3-ol (**153**, 98% ee) had furnished ketoester *R*-(+)-**155** (95% ee, see Figure 2.4.1).

Figure 2.4.1

^{1}H NMR (500 MHz, benzene-d_6) comparison

of bis-Mosher esters **157** derived from:

top; *R*-(-)-citramalic acid (**158**)

middle; *R*-(+)-**155** □ *S*-(+)-1-buten-3-ol (**153**)

bottom; *S*-(+)-citramalic acid (**158**)

Stereoselectivity in the [1,2]-shift was established by degradation of alcohol (-)-**152b** to diester *R*-(-)-**160**[40] followed by DIBAL reduction and ^{1}H-NMR analysis of the corresponding bis Mosher ester (**161**). While the Mosher ester analysis established an ee of 92% (see Figure 2.4.2), the observation of *R*-(-)-**160** in the degradation proved the absolute stereochemistry in alcohol (-)-**152b** as *S*.

Scheme 2.4.5

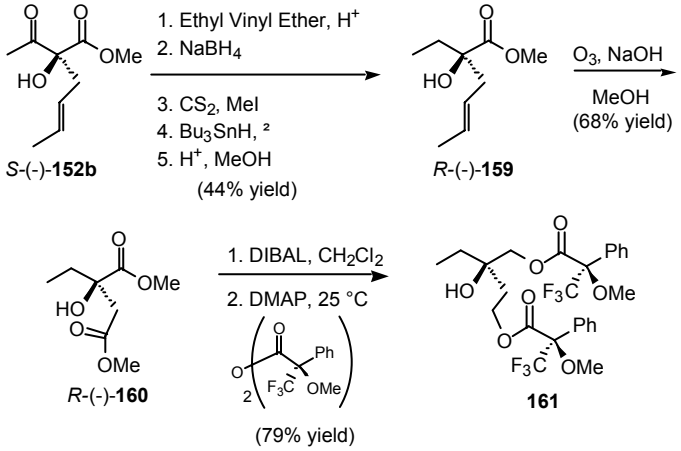
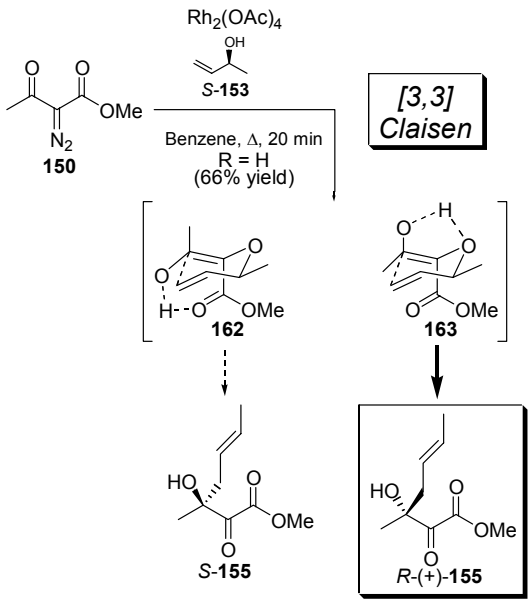


Figure 2.4.2

2.4.3 Stereochemical Rationale for the Tandem Claisen-α-Ketol Rearrangement.

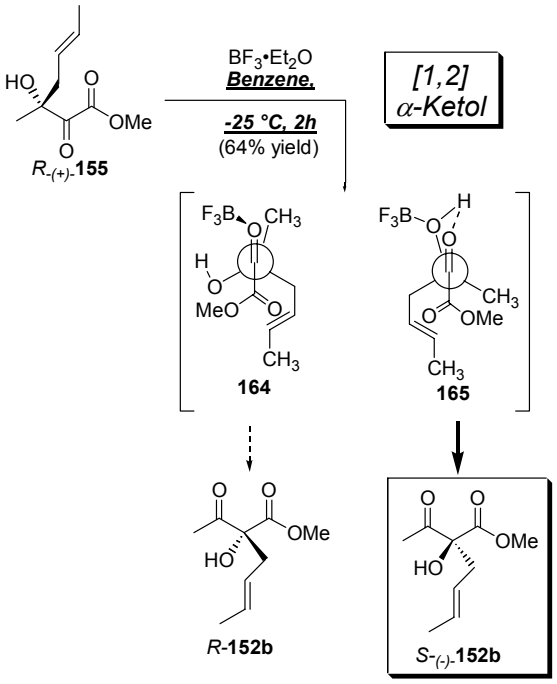
In the absence of rhodium, the sense of asymmetric induction observed in the Claisen rearrangement would normally be attributed to the intermediacy of a chair transition state possessing a Z-enol and an equatorial methyl (i.e., **163**). Thus, for the purposes of predicting the stereochemical outcome of the Rh (II)-mediated Claisen rearrangement, the predominating pathway shown in Scheme 2.4.6 can be viewed as a functioning mnemonic. However, unpublished results of Derek A. Pflum in these laboratories suggest the apparent involvement of rhodium, hence this rationalization may eventually require refinement.

Scheme 2.4.6



The stereochemical outcome of the the α-ketol rearrangement suggests a syn-periplanar relationship between the hydroxyl and carbonyl oxygens in the reactive conformer (i.e., **165**, Scheme 2.4.7). Since BF_3•Et_2O is unable to form a chelate, its role, if any, in enforcing this transition structure is not obvious. One possibility is that complexation to the hydroxyl makes the alcohol proton more available for intramolecular transfer to the carbonyl, confining the transition state to a chelation-like conformation (see Scheme 2.4.7).

Scheme 2.4.7



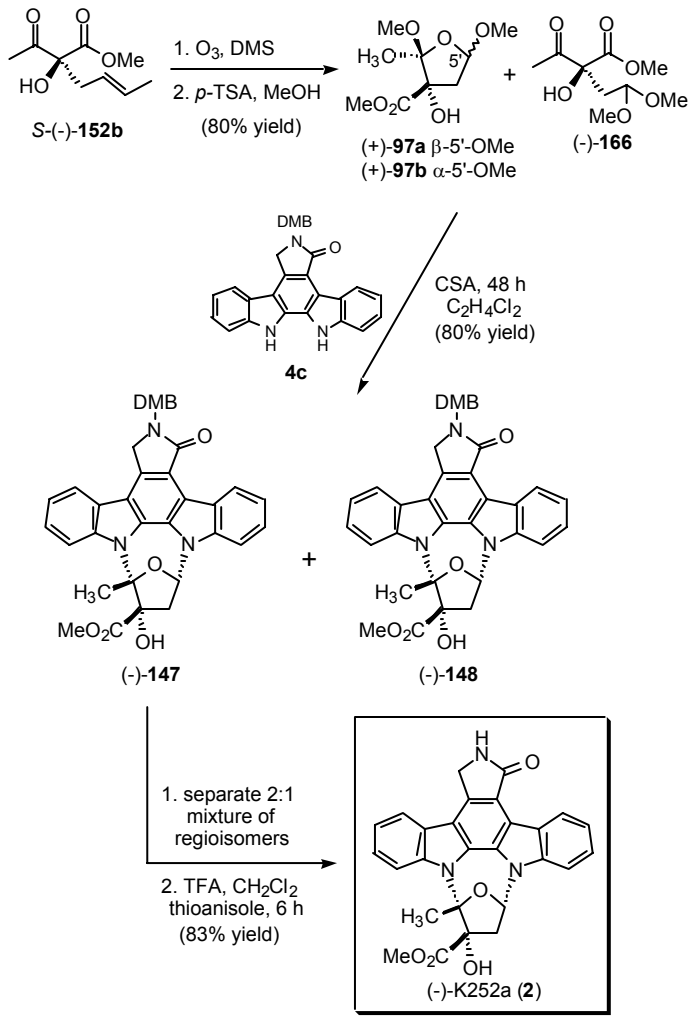
2.5 Completion of (+)- and (-)-K252a.

2.5.1 The Synthesis of (-)-K252a: Determination of Absolute Stereochemistry of (+)-K252a.

Having established the sense and degree of asymmetric induction in the preparation of alcohol (-)-**152b**, the asymmetric synthesis of furanose **97** proceeded. In contrast to olefin **143**, reductive ozonolysis of (-)-**152b** followed by acetal formation provided a ternary mixture. Characterization of the purified products indicated the reaction had produced methyl ketone (-)-**166** in addition to

the expected furanoses (+)-**97a** and (+)-**97b** (Scheme 2.5.1). The additional component proved to be of no consequence as exposure of aglycon **4c** to the ternary mixture (i.e., (+)-**97a**,**b**, and (-)-**166**) under the standard cycloglycosidation conditions produced the expected regioisomeric mixture of furanosylated indolocarbazoles (-)-**147** and (-)-**148** in yields comparable to that observed in the racemic series. Removal of the 3,4-DMB group in lactam (-)-**147** produced (-)-K252a, the enantiomer of the natural product. This observation, in conjunction with the stereochemical assignments made in the course of the degradation study (*vide supra*), allowed the absolute configuration of natural K252a to be established as depicted in (+)-**2** (see Figure 2.1.1).

Scheme 2.5.1

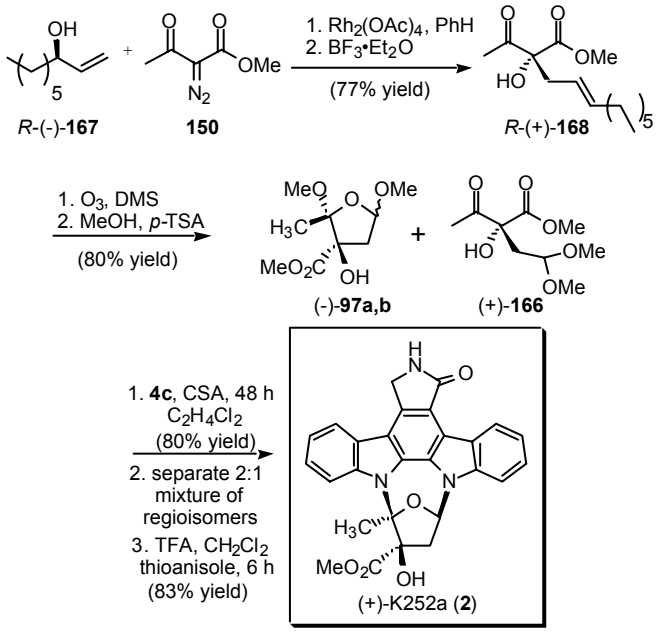


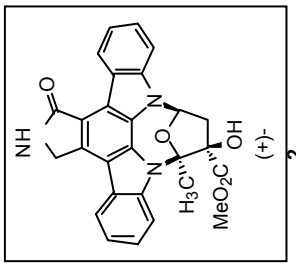
2.5.2 The Total Synthesis of (+)-K252a.

To access (+)-K252a (**2**) the absolute stereochemistry of the starting allylic alcohol in the carbohydrate synthesis was altered . In this series, handling of the allylic alcohol and early intermediates was facilitated by employing the less volatile *R*-(-)-1-nonene-3-ol (**167**)[33] as an initial substrate. Thus, exposure of *R*-(-)-**167** to diazoester **150** and catalytic $Rh_2(OAc)_4$ (PhH, 80 °C, 20 min), followed by introduction of $BF_3•Et_2O$ to the cooled reaction mixture furnished alcohol (+)-**168** in 77% yield (see Scheme 2.5.2). Ozonolysis of olefin (+)-**168** followed by acid-mediated cyclization produced the expected carbohydrate mixture (i.e., (-)-

97a,b/(+)-**166**) in 80% yield.[41] Cycloglycosidation of indolocarbazole **4c** with (-)-**97a,b**/(+)-**166** produced regioisomers (+)-**147** and (+)-**148**, which upon chromatographic separation and deprotection produced (+)-**2**, a compound identical in all respects to the natural material (see Figure 2.5.1).

Scheme 2.5.2





2.5.3 Conclusion.

The total synthesis of K252a (**2**) was completed by developing new rhodium carbenoid chemistry in the preparation of aglycon **4** and furanose **97**. The total synthesis required only twelve steps from commercially available materials, with a longest linear sequence of seven steps and an overall yield of

21% from ethyl glycinate. The remarkable stereo- and regioselective cycloglycosidation served as the cornerstone of the approach and its efficiency prompted the pursuit of staurosporine (**1**) and other pyranosylated indolocarbazoles.[16]

2.6 Experimental Section.

2.6.1 Material and Methods.

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl

ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled from calcium hydride. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and $BF_3 \bullet OEt_2$ were purchased from the Aldrich Chemical Co. in Sure/Seal□ containers and used without further purification. All other commercially obtained reagents were used as received.

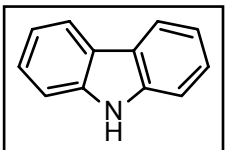
Unless stated otherwise all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography (silica) was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. In general, the chromatography guidelines reported by Still were followed.[42]

All melting points were obtained on a Haacke-Buchler variable temperature melting point apparatus (model: MFB 595 8020) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on Bruker AM-500 or Bruker WM-250 spectrometers. Chemical shifts are reported relative to internal Me_4Si (^1H and ^{13}C, δ 0.00 ppm) or chloroform (^1H, δ 7.27 ppm, ^{13}C, δ 77.0 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Microanalyses were performed by Atlantic Microlab (Norcross, GA). Single-crystal X-ray analyses were performed by Dr. Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column, or a Rainen Dynamax SD-200 system with a Rainen Microsorb 80-120-C5 column. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

The determination of enantiomeric excess by Mosher ester derivatization involved esterification of the corresponding alcohols with *R*-(+)-MTPA (DCC, CH_2Cl_2) followed by purification and 500 MHz ^1H NMR analysis in benzene-d_6. Where possible an identical analysis was performed employing a racemic mixture of alcohols.

2.6.2 Preparative Procedures:

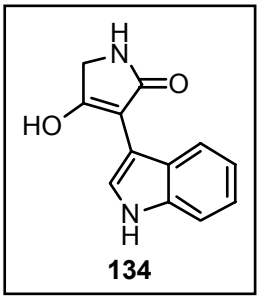
Preparation of Carbazole (131).



131

Carbazole (131). A mixture of iodide **130** (0.10 g, 0.34 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (0.43 g, 0.37 mmol, 1.1 equiv) and Na_2CO_3 (40 mg, 0.38 mmol, 1.1 equiv) in toluene (1.7 mL) was heated to reflux for 2 h. The reaction mixture was then cooled and evaporated to a residue. Flash chromatography (20:80:1 acetone:hexanes:Et_3N eluent) provided carbazole **131** (44 mg, 80% yield) as a white solid.[43]

Preparation of Indolepyrollidone 134.

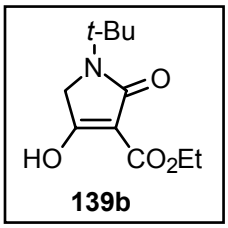


134

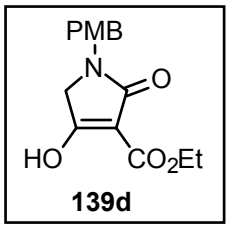
Indolepyrollidone 134. A mixture of indole (**133**) (1.40 g, 12.0 mmol, 3.0 equiv), diazo lactam **132a** (0.5 g, 4.0 mmol, 1.0 equiv) and $Rh_2(OAc)_4$ (35 mg, 0.08 mmol, 0.02 equiv) in benzene (50 mL) was heated to reflux for 18 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to a brown residue which was dissolved in EtOAc (100 mL) and extracted with 1N NaOH solution (150 mL). The aqueous layer was then acidified to pH 1 with 1 N HCl and extracted with EtOAc (3 x 100 mL). The combined organic layers were

washed with H_2O (150 mL), brine solution (150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a crude solid which was recrystallized from EtOAc/heptane to afford diene **134** (549 mg, 65% yield) as a white powder: mp 220-225 °C (dec.); IR (thin film/NaCl) 3405.3 (br m), 2957.0 (m), 2928.3 (s), 2857.7 (m), 1656.6 (s), 1541.3 (w), 1457.1 (m), 1382.8 (s), 1320.9 (m), 1241.6 (w), 1095.5 (w), 746.3 (m) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 10.23 (br s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.05 (app.t, *J* = 7.8 Hz, 1H), 6.97 (app.t, *J* = 7.4 Hz, 1H), 6.42 (br s, 1H), 4.00 (s, 2H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 174.3, 164.2, 135.6, 126.0, 123.6, 121.8, 120.4, 117.8, 110.8, 106.0, 101.2, 45.0; high resolution mass spectrum (CI) *m/z* 215.0805 [calcd for $C_{12}H_{11}N_2O_2$ (M+H) 215.0821].

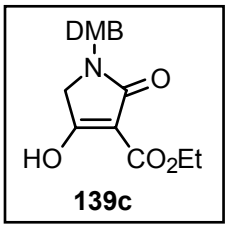
Preparation of tetramic acids 139b-e.



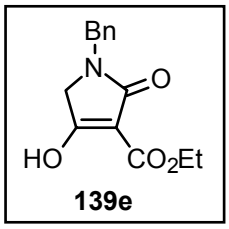
139b



139d



139c



139e

General method for the preparation of tetramic acids 139b-e. To a stirred solution of ester **138** (47.4 mmol, 1.0 equiv) in CH_2Cl_2 (95 mL) at 0 °C was added a solution of ethyl hydrogen malonate (6.26 g, 47.4 mmol, 1.0 equiv) in CH_2Cl_2 (38 mL), followed by a solution of 1,3-dicyclohexylcarbodiimide (9.9 g, 48.0 mmol, 1.01 equiv) and DMAP (290 mg, 2.37 mmol, 0.05 equiv) in CH_2Cl_2 (20 mL). The mixture was stirred at 0 °C for 15 min and allowed to warm to ambient temperature while stirring for an additional 2 h. After this time the solid urea by-product was removed by filtration. The filtrate was washed with H_2O (80 mL), dried over $MgSO_4$, filtered, and evaporated to a yellow semi-solid. To this was added acetone (30 mL) and the insoluble precipitate again removed via filtration. The filtrate was concentrated *in vacuo* to a yellow oil and used in the next step without further purification.

To a solution of NaOEt/EtOH prepared from sodium metal (1.09 g, 47.4 mmol) and absolute EtOH (31 mL) was added a solution of the crude diester in benzene (200 mL) over 5 min. The resulting mixture was brought to reflux for 6.5 h. The reaction mixture was allowed to cool to room temperature and then diluted with H_2O (100 mL). The layers were separated and the benzene layer further extracted with H_2O (2 x 80 mL). The aqueous layers were combined and

residual EtOH was removed *in vacuo*, followed by careful acidification to pH 1 with conc. HCl at 0 °C. The resultant white precipitate was filtered and dried with a slow stream of N_2 gas to give lactams **139b-e** as white powders.

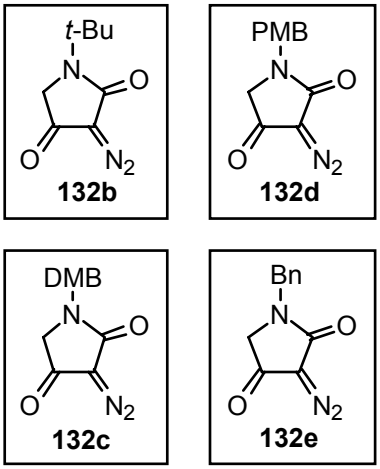
139b. The above procedure was followed using ester **138b** (7.54 g) to afford lactam **139b** (7.53 g, 70% yield): mp 155-157 °C (dec., EtOH/CH_2Cl_2); IR (thin film/NaCl) 2973.8 (br m), 2933.0 (m), 2526.6 (br m), 1707.4 (s), 1590.3 (s), 1429.7 (s), 1388.7 (m), 1222.3 (m), 1179.3 (w), 1052.1 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 315 K) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 1.33 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 305 K) δ 177.8, 167.6, 162.5, 98.3, 58.9, 52.9, 47.9, 27.5, 14.2; high resolution mass spectrum (EI) *m/z* 227.1155 [calcd for $C_{11}H_{17}NO_4$ (M^+) 227.1158]; Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16; found: C, 58.08; H, 7.50; N, 6.23.

139c. The above procedure was followed using ester **138c** (12.00 g) to afford lactam **139c** (12.6 g, 83% yield): mp 154-156 °C (EtOH/CH_2Cl_2); IR (thin film/NaCl) 2937.5 (br m), 2839.5 (w), 2612.4 (br w), 1704.0 (s), 1611.8 (s), 1514.9 (s), 1418.9 (s), 1254.7 (m), 1141.9 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.89 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 6.70 (dd, *J* = 1.5, 8.1 Hz, 1H), 4.37 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.8, 167.3, 162.0, 148.8, 148.0, 130.0, 119.8, 111.9, 111.5, 97.8, 59.0, 55.5, 55.4, 49.0, 44.1, 14.3; high resolution mass spectrum (EI) *m/z* 321.1209 [calcd for $C_{16}H_{19}NO_6$ (M^+) 321.1212]; Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.46; found: C, 59.93; H, 5.92; N, 4.36.

139d. The above procedure was followed using ester **138d** (10.6 g) to afford lactam **139d** (11.1 g, 80% yield): mp 198-200 °C (dec., EtOH/CH_2Cl_2); IR (thin film/NaCl) 2982.1 (m), 2925.0 (m), 2841.1 (w), 2593.8 (br w), 1703.9 (s), 1609.7 (s), 1512.0 (m), 1447.1 (s), 1247.0 (s), 1038.6 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.12 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 4.37 (s, 2H), 4.13 (q, *J* = 6.8 Hz, 2H), 3.79 (s, 2H), 3.72 (s, 3H), 1.20 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.7, 167.3, 162.0, 158.4, 129.6, 128.9, 114.0, 97.8, 59.0, 55.0, 48.9, 43.7, 14.3; high resolution mass spectrum (EI) *m/z* 291.1107 [calcd for $C_{15}H_{17}NO_5$ (M^+) 291.1107]; Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81; found: C, 61.70; H, 5.86; N, 4.73.

139e.[15b] The above procedure was followed using ester **138e** (9.15 g) to afford lactam **139e** (8.79 g, 71% yield): mp 152-154 °C (dec., EtOH/CH_2Cl_2); IR (thin film/NaCl) 2980.0 (m), 2929.8 (m), 1707.3 (s), 1447.1 (s), 1255.0 (m), 1139.4 (m), 1045.4 (m), 933.6 (w), 797.0 (m), 703.0 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.18-7.33 (comp m, 5H), 4.45 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 2H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.4, 167.7, 162.1, 137.8, 128.6, 127.1, 97.4, 58.9, 49.4, 44.3; high resolution mass spectrum (EI) *m/z* 261.0997 [calcd for $C_{14}H_{15}NO_4$ (M^+) 261.1101]; Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; found: C, 64.18; H, 5.75; N, 5.44.

Preparation of Diazo lactams 132b-e.



Diazo lactams 132b-e. A solution of ester **139** (33.5 mmol, 1.0 equiv) and H_2O (1mL) was heated to reflux in CH_3CN (1.5 L) for 2 h. The volume of CH_3CN was reduced to approximately 35% the original volume (ca. 560 mL) *in vacuo*. The solution was cooled to 0 °C and treated sequentially with MsN_3 (8.12 g, 67.0 mmol, 2.0 equiv) in CH_3CN (168 mL) via addition funnel followed by Et_3N (9.34 mL, 67.0 mmol, 2.0 equiv) in CH_3CN (96 mL). After 15 min the ice bath was removed and the dark orange solution was allowed to warm to 25 °C, stirred for an additional 2 h, and concentrated *in vacuo*. The dark orange residue was dissolved in a minimum of EtOAc and filtered through a pad of silica gel (EtOAc eluent). The filtrate was washed once with 1N NaOH solution, dried over $MgSO_4$, filtered and concentrated to give **132b-e** as yellow solids, which were recrystallized from acetone/hexanes.

132b. The above procedure was followed using ester **139b** (7.60 g) to afford diazo lactam **132b** (4.85 g, 80% yield): mp 83-85 °C (dec.); IR (CCl_4) 2980.8 (s), 2123.4 (s), 1718.8 (m), 1689.4 (s), 1441.6 (m), 1390.5 (s), 1347.9 (m), 1262.6 (w), 1224.3 (s), 1177.3 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 161.7, 66.7, 55.7,

53.3, 28.0; high resolution mass spectrum (CI) *m/z* 182.0929 [calcd for $C_8H_{12}N_3O_2$ (M+H) 182.0930]; Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19; found: C, 53.06; H, 6.15; N, 23.17.

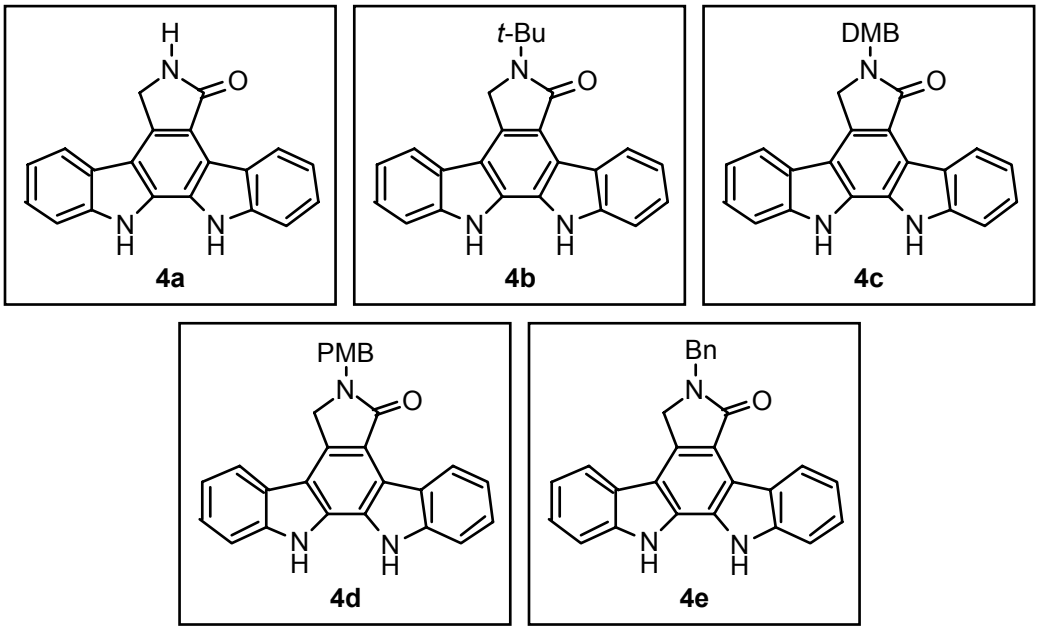
132c. The above procedure was followed using ester **139c** (10.75 g) to afford diazo lactam **132c** (8.29 g, 90% yield): mp 145-147 °C (EtOAc); IR (CCl_4) 2960.7 (br w), 2925.8 (br w), 2126.1 (s), 1695.2 (s), 1515.1 (m), 1451.2 (w), 1401.1 (m), 1355.5 (m), 1227.8 (m), 1186.6 (w), 1159.4 (w), 1024.5 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.79 (s, 1H), 4.53 (s, 2H), 3.88 (s, 6H), 3.71 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 161.7, 149.5, 149.0, 127.7, 120.8, 111.3, 111.2, 66.0, 56.0, 55.9, 53.9, 46.5; high resolution mass spectrum (CI) *m/z* 276.0981 [calcd for $C_{13}H_{14}N_3O_4$ (M+H) 276.0984]; Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27; found: C, 56.81; H, 4.81; N, 15.36.

132d. The above procedure was followed using ester **139d** (9.75 g) to afford diazo lactam **132d** (7.22 g, 88% yield): mp 91-93 °C (EtOAc); IR (CCl_4) 2926.3 (br w), 2841.5 (w), 2129.8 (s), 1693.9 (s), 1613.3 (w), 1511.7 (m), 1458.8 (m), 1401.9 (s), 1361.2 (m), 1243.4 (m), 1223.0 (m), 1174.1 (m), 1040.0 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.51 (s, 2H), 3.77 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 161.6, 159.4, 129.6, 127.2, 114.3, 65.9, 55.2, 53.8, 46.0; high resolution mass spectrum (CI) *m/z* 246.0885 [calcd for $C_{12}H_{12}N_3O_3$ (M+H) 246.0879].

132e. The above procedure was followed using ester **139e** (8.74 g) to afford diazo lactam **132e** (6.54 g, 86% yield): mp 87-88 °C (EtOAc); IR (CCl_4) 3072.1 (w), 3033.8 (m), 2922.9 (m), 2867.6 (w), 2124.0 (s), 1695.7 (s), 1447.8

(s), 1405.1 (s), 1358.2 (s), 1230.3 (s), 1187.6 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.25 (comp m, 5H), 4.60 (s, 2H), 3.70 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5, 161.7, 135.1, 128.9, 128.1, 128.1, 65.8, 53.8, 46.5; high resolution mass spectrum (CI) *m/z* 219.0779 [calcd for $C_{11}H_{10}N_3O_2$ (M+H) 216.0773]; Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53; found: C, 61.47; H, 4.27; N, 19.53.

Preparation of Indolocarbazoles 4a-e.



Indolocarbazoles 4a-e. Method A. A mixture of 2,2'-biindole (**73**) (200 mg, 0.86 mmol, 1.0 equiv), diazo tetramic acid **132a-e** (2.2 mmol, 2.5 equiv), $Rh_2(OAc)_4$ (38 mg, 0.086 mmol, 0.1 equiv) and pinacolone (8.6 mL) in a pressure tube fitted with a rubber septum was degassed with a stream of N_2 for 1 h. The septum was removed and the tube was flushed with N_2, sealed, and placed into a pre-heated sand bath (120 °C). After 6 h the tube was removed

from the sand bath, allowed to cool to room temperature, and carefully opened. After removing the solvent *in vacuo*, the residue was dissolved in EtOAc (15 mL), washed with 1N NaOH (15 mL) solution, and dried over $MgSO_4$. Filtration and removal of the solvent was followed by flash chromatography (1:1 EtOAc:hexanes eluent) to provide **4a-e** as pale yellow solids.

4a. The above procedure was followed using diazo lactam **132a** (275 mg) to afford indolocarbazole **4a** (67 mg, 25% yield): mp >330 °C (dec., EtOAc/hexanes); IR (thin film/NaCl) 3343.7 (m), 3306.5 (w), 1645.7 (s), 1454.1 (s), 1389.3 (m), 1348.5 (m), 1329.9 (m), 1316.6 (w), 1277.0 (m), 1260.7 (w), 1050.7 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.40 (br s, 1H), 11.20 (br s, 1H), 9.23 (d, *J* = 7.9 Hz, 1H), 8.35 (br s, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.47 (app.t, *J* = 7.6 Hz, 1H), 7.42 (app.t, *J* = 7.4 Hz, 1H), 7.30 (app.t, *J* = 7.4 Hz, 1H), 7.22 (app.t, *J* = 7.5 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.4, 139.2, 139.1, 132.9, 127.8, 125.4, 125.2, 125.0, 125.0, 122.8, 122.6, 121.1, 119.9, 118.9, 118.9, 115.6, 114.1, 111.9, 111.3, 45.3; high resolution mass spectrum (EI) *m/z* 311.1061 [calcd for $C_{20}H_{13}N_3O$ (M^+) 311.1059].

***nat*-K252a (4a):**[2] mp >300 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 11.38 (br s, 1H), 9.24 (d, *J* = 7.9 Hz, 1H), 8.49 (br s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.48 (br t, 1H), 7.44 (br t, 1H), 7.31 (br t, 1H), 7.24 (br t, 1H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 139.3, 139.2, 133.0, 128.0, 125.4, 125.2, 125.1, 125.1, 123.0, 122.7, 121.2, 120.0, 120.0, 119.0, 115.7, 114.2, 112.0, 111.4, 45.4.

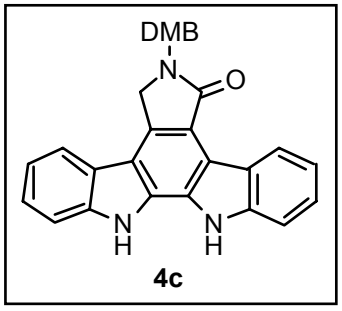
4b. The above procedure was followed using diazo lactam **132b** (400 mg) to afford indolocarbazole **4b** (126 mg, 40% yield): mp >300 °C (dec., EtOAc/hexanes); IR (thin film/NaCl) 3485.3 (br m), 3456.0 (br m), 3343.1 (br s), 3249.7 (br m), 2979.7 (m), 1654.4 (w), 1600.5 (s), 1578.2 (s), 1465.8 (w), 1446.5 (m), 1385.0 (s), 1364.0 (m), 1335.9 (w), 1225.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.45 (br s, 1H), 11.29 (br s, 1H), 9.24 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.47 (app.t, *J* = 7.5 Hz, 1H), 7.41 (app.t, *J* = 7.5 Hz, 1H), 7.30 (app.t, *J* = 7.5 Hz, 1H), 7.21 (app.t, *J* = 7.5 Hz, 1H), 5.13 (s, 2H), 1.65 (s, 9H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 169.9, 139.2, 139.0, 129.9, 127.6, 125.4, 125.3, 124.9, 122.7, 122.4, 122.0, 121.2, 119.7, 118.8, 115.1, 113.6, 111.8, 111.2, 101.9, 53.6, 48.1, 27.8; high resolution mass spectrum (FAB) *m/z* 368.1764 [calcd for $C_{24}H_{22}N_3O_1$ (M+H) 368.1763].

4c. The above procedure was followed using diazo lactam **132c** (605 mg) to afford indolocarbazole **4c** (257 mg, 62% yield): mp >202 °C (dec., EtOAc); IR (thin film/NaCl) 3487.5 (br s), 3352.0 (br s), 3232.0 (br s), 3022.3 (m), 1579.1 (s), 1571.2 (s), 1517.7 (s), 1462.9 (s), 1399.3 (m), 1262.7 (m), 1237.6 (s), 1142.0 (w), 1016.8 (w), 741.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.50 (br s, 1H), 11.35 (br s, 1H), 9.28 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.45 (app.t, *J* = 6.9 Hz, 1H), 7.44 (app.t, *J* = 7.1 Hz, 1H), 7.26 (app.t, *J* = 7.1 Hz, 1H), 7.25 (app.t, *J* = 7.1 Hz, 1H), 7.02 (s, 1H), 6.92 (s, 2H), 4.94 (s, 2H), 4.82 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 169.2, 148.9, 148.1, 139.1, 139.0, 130.6, 130.0, 127.7, 125.3, 124.9, 124.9, 124.8, 122.6, 122.3, 120.7, 119.9, 119.7, 118.8, 118.2, 115.4, 113.8, 112.3, 112.1, 111.7, 111.1, 55.5, 49.3, 45.4; high resolution mass spectrum (FAB) *m/z* 462.1813 [calcd for $C_{29}H_{24}N_3O_3$ (M+H) 462.1818].

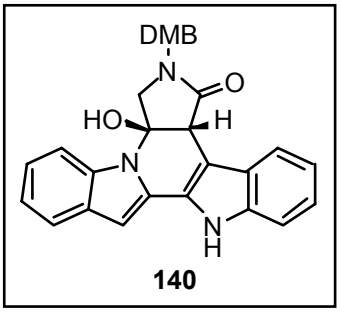
4d. The above procedure was followed using diazo lactam **132d** (539 mg) to afford indolocarbazole **4d** (204 mg, 55% yield): mp 190-200 °C (dec., acetone); IR (thin film/NaCl) 3429.3 (br s), 3351.3 (br s), 2912.4 (m), 1609.7 (s), 1580.3 (s), 1512.0 (s), 1465.5 (s), 1402.1 (w), 1250.6 (s), 1238.4 (s), 1177.3 (m), 1030.8 (w), 748.9 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.53 (br s, 1H), 11.37 (br s, 1H), 9.28 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.47 (app.t, *J* = 7.0 Hz, 1H), 7.45 (app.t, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.28 (app.t, *J* = 7.9 Hz, 1H), 7.26 (app.t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 4.94 (s, 2H), 4.83 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 169.2, 158.4, 139.1, 139.0, 130.0, 129.9, 128.9, 127.7, 125.3, 124.9, 124.8, 122.6, 122.2, 120.7, 119.7, 118.8, 118.2, 115.4, 113.9, 113.8, 111.7, 111.1, 54.9, 49.2, 45.0; high resolution mass spectrum (FAB) *m/z* 432.1699 [calcd for $C_{28}H_{22}N_3O_2$ (M+H) 432.1712].

4e. The above procedure was followed using diazo lactam **132e** (473 mg) to afford indolocarbazole **4e** (200 mg, 58% yield). This material was identical to that prepared by Moody.[44]

Preparation of Indolocarbazole 4c and 140.



4c



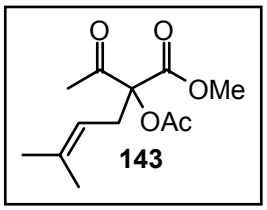
140

Indolocarbazole 4c and isolation of 140. Method B. A mixture of biindole **73** (4.0 g, 17.2 mmol, 1.0 equiv), diazo lactam **132c** (4.74 g, 17.2 mmol, 1.0 equiv), $Rh_2(OAc)_4$ (76 mg, 0.17 mmol, 0.01 equiv) and pinacolone (210 mL), in a 3-neck round bottom flask fitted with a reflux condenser was degassed with a stream of N_2 for 2 h. The reaction mixture was then heated to reflux for 8 h. The mixture was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. Flash chromatography (1:1 EtOAc:hexanes eluent) afforded unreacted **73** (2.0 g, 50% yield) as a pale yellow powder and indolocarbazole **4c** (2.9 g, 36% yield; 72% yield based on recovered **73**) as a white solid.

When heating was prematurely discontinued (3 h) and the reaction mixture was worked up in the fashion described above, **73** (1.92 g) and **4c** (1.15 g) were isolated, along with hemiaminal **140** (644 mg) as a yellow foam: IR (thin film/NaCl) 3323.5 (br m), 2935.8 (w), 2829.1 (w), 1676.6 (s), 1514.6 (s), 1439.5 (m), 1327.1 (m), 1260.9 (s), 1236.1 (m), 1023.7 (m), 745.3 (s) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 10.87 (br s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.16 (td, *J* = 1.0, 7.4 Hz, 1H), 7.03-7.12 (comp m, 3H), 6.87 (s, 1H), 6.69 (s, 2H), 6.65 (s, 1H), 6.58 (s, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.43 (s, 1H), 4.32 (d, *J* = 14.8 Hz, 1H), 3.97 (d, *J* = 10.1 Hz, 1H), 3.65 (s, 3H), 3.39 (d, *J* = 10.2 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.3, 150.0, 149.1, 138.6, 137.2, 130.5, 129.2, 127.2, 127.1, 123.3, 122.6, 121.9, 121.0, 121.0, 120.4, 120.3, 113.6,

112.0, 111.5, 111.4, 110.9, 103.8, 97.5, 87.6, 57.8, 55.5, 54.9, 53.2, 45.5; high resolution mass spectrum (EI) *m/z* 479.1845 [calcd for $C_{29}H_{25}N_3O_4$ (M^+) 479.1845].

Preparation of Acetoacetate 143.

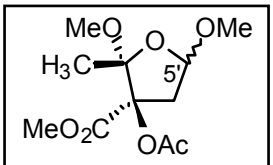


143

Acetoacetate 143. A suspension of sodium hydride (5.55 g 60% dispersion in mineral oil, 139 mmol, 1.01 equiv) in dioxane (135 mL) was treated dropwise with a solution of methyl 2-methylcarbonyloxy-3-oxobutanoate[17] (24.1 g, 138 mmol, 1.0 equiv) in dioxane (27 mL) over a period of 45 minutes. The mixture was stirred (overhead stirrer) for an additional 45 minutes at 20 °C. Prenylbromide (15.95 mL, 138 mmol, 1.0 equiv) was added over 25 minutes, and the mixture warmed to reflux for 20 minutes. After cooling to room temperature, the mixture was poured into 1.1 L H_2O containing acetic acid (7.9 mL, 138 mmol, 1.0 equiv). This mixture was extracted with ether (1 x 600 mL; 3 x 300 mL). The organic layer was washed with H_2O (500 mL), saturated NaCl solution (500 mL), and dried over $MgSO_4$. The solvent was evaporated and the reaction mixture distilled (bp 80-85 °C, 0.2 mm Hg) to provide olefin **143** as a colorless oil (28.53 g, 85% yield): IR (thin film/NaCl) 2997.1 (w), 2955.7 (m), 2929.3 (m), 2917.9 (m), 2859.7 (w), 1747.6 (s), 1436.7 (m), 1370.9 (m), 1255.6 (s), 1229.9 (s), 1176.1 (m), 1072.3 (m), 1016.3 (m), 926.0 (w), 809.0 (w), 769.4 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (t, J = 7.4 Hz, 1H), 3.75 (s, 3H), 2.88 (app.t, J = 6.3 Hz, 2H),

2.32 (s, 3H), 2.17 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 169.3, 167.5, 136.7, 115.2, 87.3, 52.5, 32.5, 26.6, 25.6, 20.3, 17.5; high resolution mass spectrum (CI) *m/z* 243.1233 [calcd for $C_{12}H_{19}O_5$ (M+H) 243.1232].

Preparation of Acetates (±)-144a,b.



(±)-**144a** α-5'-OMe
(±)-**144b** β-5'-OMe

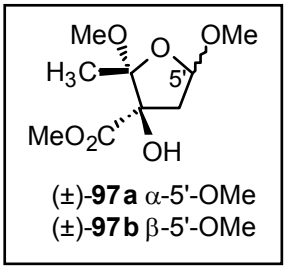
Acetates (±)-144a,b. A solution of olefin **143** (2.91 g, 12.0 mmol, 1.0 equiv) and a trace of sudan red 7B dye in a mixture of THF (65 mL) and MeOH (13 mL) was cooled to -78 °C and treated with O_3 until the dye was completely discolored (about 6 minutes). The mixture was purged with argon for 10 minutes at -78 °C and dimethylsulfide (40 mL) was added at that temperature. The reaction was brought to 0 °C with an ice bath which was allowed to thaw (0-20 °C) over a period of 3 h. The solvent was removed and the crude product dissoved in MeOH (20 mL). After addition of trimethylorthoformate (6.6 mL, 60.0 mmol, 5.0 equiv) and *p*-toluenesulfonic acid (22.8 mg, 0.12 mmol, 0.01 equiv) the mixture was heated to reflux for 1 hour. After cooling to room temperature, the solvent was evaporated *in vacuo.* Flash chromatography (20% EtOAc/hexanes eluent) provided a mixture of diastereomeric acetates **144a,b** (2.36 g, 75% yield) as a colorless oil. The diastereomers could be separated using HPLC (4:4:1

hexanes:CH_2Cl_2:EtOAc eluent). Crystals suitable for X-ray analysis were obtained by crystallization from EtOAc/hexanes.

144a: mp 106-107 °C; IR (thin film/NaCl) 2996.6 (w), 2953.1 (m), 2917.3 (m), 2837.2 (w), 1759.8 (s), 1741.3 (s), 1463.1 (m), 1378.4 (m), 1348.0 (w), 1311.3 (m), 1278.8 (s), 1251.9 (s), 1224.5 (m), 1192.1 (m), 1169.9 (s), 1132.0 (s), 1101.1 (s), 1070.5 (m), 1022.0 (s), 980.9 (m), 918.6 (m), 889.0 (w), 863.4 (w), 829.6 (w), 808.9 (w), 753.7 (w), 739.6 (w), 673.5 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.11 (app.t, *J* = 5.7 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 3H), 3.27 (s, 3H), 3.15 (dd, *J* = 5.3, 15.3 Hz, 1H), 2.57 (dd, *J* = 6.2, 15.3 Hz, 1H), 2.10 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 167.3, 108.8, 104.9, 88.4, 56.4, 52.5, 48.6, 39.2, 20.8, 15.0; high resolution mass spectrum (CI) *m/z* 231.0866 [calcd for $C_{10}H_{15}O_6$ (M-CH_3OH+H) 231.0869].

144b: mp 58-59 °C; IR (thin film/NaCl) 2998.2 (m), 2952.9 (s), 2977.7 (m), 2838.7 (m), 1760.0 (s), 1739.9 (s), 1434.2 (s), 1376.6 (s), 1315.4 (m), 1274.9 (s), 1254.2 (s), 1230.8 (s), 1190.3 (s), 1164.1 (s), 1129.0 (s), 1108.3 (s), 1084.9 (s), 1071.4 (s), 1045.3 (m), 1022.8 (s), 976.9 (m), 957.2 (s), 937.9 (m), 910.7 (m), 858.0 (w), 825.8 (w), 811.9 (w), 785.4 (w), 741.3 (w), 686.3 (w), 656.7 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (dd, *J* = 1.9, 6.5 Hz, 1H), 3.73 (s, 3H), 3.40 (s, 3H), 3.33 (dd, *J* = 6.5, 15.2 Hz, 1H), 3.25 (s, 3H), 2.19 (dd, *J* = 1.9, 15.2 Hz, 1H), 2.11 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 167.7, 109.0, 104.1, 86.4, 55.9, 52.5, 48.6, 39.1, 20.9, 15.8; high resolution mass spectrum (CI) *m/z* 231.0870 [calcd for $C_{10}H_{15}O_6$ (M-CH_3OH+H) 231.0869].

Preparation of Esters (±)-97a,b.



(±)-**97a** α-5'-OMe
(±)-**97b** β-5'-OMe

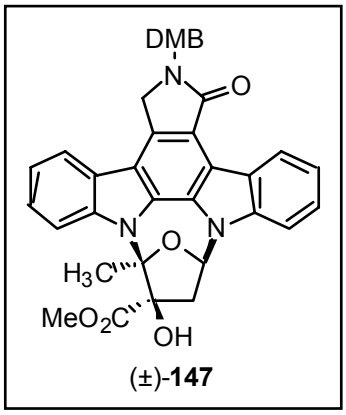
Esters (±)-97a,b. A solution of acetates **144a,b** (1.31 g, 5.00 mmol) in MeOH (50 mL) was treated with K_2CO_3 (1.04 g, 7.52 mmol, 1.5 equiv). The mixture was stirred for 2 hours at 20 °C. After evaporation of solvent *in vacuo* the residue was dissolved in Et_2O and filtered through silica gel (Et_2O eluent) to afford a mixture of hydroxyfuranoses (±)-**97a,b** (814 mg, 74% yield) as a colorless oil. The mixture of diastereomers could be separated by HPLC (2:2:1 hexanes:CH_2Cl_2:EtOAc eluent).

(±)-97a: mp 63-64°; IR (thin film/NaCl) 3487.0 (m), 2994.8 (w), 2953.8 (m), 2834.5 (w), 1749.3 (s), 1728.9 (s), 1442.6 (m), 1379.1 (m), 1361.4 (w), 1347.5 (w), 1332.6 (w), 1269.1 (m), 1238.6 (m), 1201.7 (s), 1181.8 (m), 1156.8 (m), 1125.4 (s), 1096.1 (s), 1081.2 (s), 1044.0 (s), 1018.5 (m), 976.5 (m), 947.1 (m), 928.5 (m), 896.3 (m), 866.8 (w), 834.3 (m), 802.5 (m), 754.1 (m), 684.5 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (app.t, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 3.27 (s, 3H), 3.18 (d, J = 2.0 Hz, 1H), 2.85 (ddd, J = 2.0, 5.3, 14.3 Hz, 1H), 2.34 (dd, J = 6.2, 14.3 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 109.9, 105.5, 84.5, 56.5, 53.0, 49.1, 40.5, 14.5; high resolution mass spectrum (CI) *m/z* 189.0758 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0763].

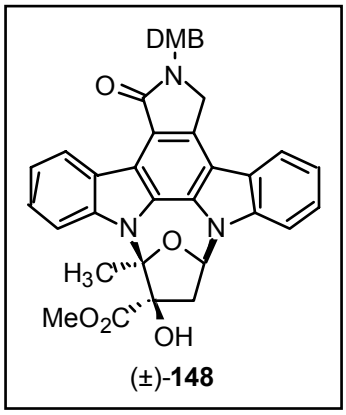
(±)-97b: mp 81-82°; IR (thin film/NaCl) 3484.5 (m), 2994.3 (w), 2951.4 (m), 2833.9 (w), 1748.1 (m), 1729.6 (s), 1443.7 (m), 1378.9 (m), 1347.9 (w),

1283.8 (m), 1270.1 (m), 1239.5 (m), 1200.9 (m), 1182.0 (m), 1164.5 (m), 1126.6 (s), 1095.4 (m), 1082.3 (m), 1046.6 (m), 1020.4 (m), 978.9 (m), 959.2 (m), 948.3 (m), 926.7 (m), 901.5 (m), 868.9 (w), 838.5 (w), 802.4 (w), 756.0 (m), 684.4 (w), 672.8 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 0.9, 5.7 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 3.36 (s, 1H), 3.25 (s, 3H), 3.03 (dd, *J* = 5.7, 14.1 Hz, 1H), 2.06 (dd, *J* = 0.7, 14.1 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 110.6, 103.9, 83.2, 55.6, 52.6, 49.3, 40.6, 15.8; high resolution mass spectrum (FAB) *m/z* 189.0767 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0763].

Preparation of Indolocarbazoles (±)-147 and (±)-148.



(±)-**147**



(±)-**148**

Indolocarbazoles (±)-147 and (±)-148. A stirred solution of aglycon **4c** (1.00 g, 2.17 mmol, 1.0 equiv) and camphorsulfonic acid (50 mg, 0.22 mmol, 0.1 equiv) in 1,2-dichloroethane (72 mL) was heated to reflux and treated over 24 h with a solution of furanoses (±)-**97a,b** (0.95 g, 4.32 mmol, 2.0 equiv) in 1,2-dichloroethane (50 mL). After an additional 24 h, the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (50 mL), and washed with 10% $NaHCO_3$ solution (50 mL). The organic layer was dried with Na_2SO_4

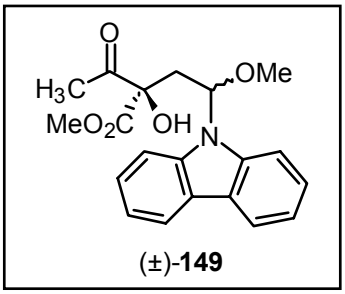
and evaporated *in vacuo*. Flash chromatography (1:1 EtOAc/hexanes eluent) provided a 2:1 mixture of indolocarbazoles (±)-**147** and (±)-**148** (1.07 g, 80% yield). Separation of the regioisomers (±)-**147** and (±)-**148** was achieved with either preparative TLC (60:1 70% CH_2Cl_2/hexanes:MeOH, 3 elutions) or by HPLC (190:10:1 CH_2Cl_2:EtOAc:MeOH eluent).

(±)-147: mp >250° (dec.); IR (thin film/NaCl) 3279.7 (br m), 3012.1 (m), 2952.1 (m), 2930.1 (m), 2850.1 (w), 1732.2 (m), 1646.2 (s), 1590.4 (m), 1513.7 (s), 1460.2 (s), 1260.3 (s), 1139.5 (s), 1028.1 (m), 744.5 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.26 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.92 (app.t, *J* = 8.0 Hz, 2H), 7.49 (app.t, *J* = 7.7 Hz, 1H), 7.47 (app.t, *J* = 7.8 Hz, 1H), 7.32 (app.t, *J* = 7.9 Hz, 1H), 7.30 (app.t, *J* = 8.1 Hz, 1H), 7.15 (dd, *J* = 5.2, 6.9 Hz, 1H), 7.02 (s, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.35 (s, 1H), 5.02 (d, *J* = 17.8 Hz, 1H), 4.97 (d, *J* = 17.8 Hz, 1H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.82 (d, *J* = 15.5 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.39 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.00 (dd, *J* = 4.7, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 168.6, 148.9, 148.2, 139.8, 136.7, 130.4, 130.0, 128.2, 125.3, 125.3, 124.8, 123.9, 123.8, 122.4, 120.9, 120.2, 119.8, 119.3, 118.9, 115.6, 114.6, 114.2, 112.3, 112.1, 108.8, 99.3, 84.8, 55.5, 52.4, 49.5, 45.4, 42.4, 22.6; high resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for $C_{36}H_{32}N_3O_7$ (M+H) 618.2240].

(±)-148: mp 260-270° (dec.); IR (thin film/NaCl) 3462.3 (br m), 3014.0 (m), 2952.3 (m), 2925.1 (m), 2849.7 (m), 1730.8 (s), 1645.0 (m), 1514.7 (m), 1455.6 (s), 1403.9 (m), 1348.5 (m), 1312.6 (m), 1257.2 (s), 1235.0 (s), 1138.1 (s), 1068.8 (m), 1027.3 (m), 750.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.54 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* =

8.5 Hz, 1H), 7.50 (app.t, *J* = 7.5 Hz, 1H), 7.45 (app.t, *J* = 7.5 Hz, 1H), 7.30 (app.t, *J* = 7.5 Hz, 1H), 7.29 (app.t, *J* = 7.6 Hz, 1H), 7.14 (dd, *J* = 5.0, 7.2 Hz, 1H), 7.01 (d, *J* = .71 Hz, 1H), 6.92 (app.t, *J* = 8.2 Hz, 1H), 6.92 (dd, *J* = 1.1, 8.4 Hz, 1H), 6.34 (br s, 1H), 4.98 (d, *J* = 17.9 Hz, 1H), 4.95 (d, *J* = 17.9 Hz, 1H), 4.84 (d, *J* = 15.1 Hz, 1H), 4.80 (d, *J* = 15.1 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.40 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.05 (dd, *J* = 4.8, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 168.9, 149.0, 148.2, 139.7, 136.8, 130.4, 126.2, 126.1, 125.4, 125.1, 124.9, 124.3, 122.0, 121.3, 120.2, 119.8, 119.2, 118.7, 116.3, 113.9, 113.8, 112.3, 112.1, 109.4, 99.3, 84.9, 84.8, 55.5, 52.4, 49.0, 45.4, 42.5, 22.8; high resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for $C_{36}H_{32}N_3O_7$ (M+H) 618.2240].

Preparation of Ketone (±)-149.



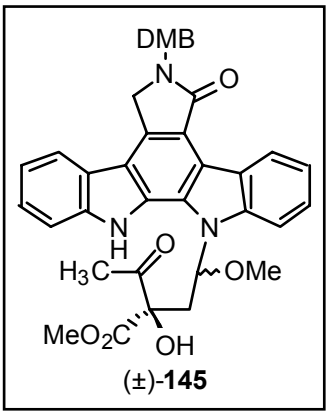
(±)-**149**

Ketone (±)-149. To a solution of furanoses (±)-**97a,b** (230 mg, 1.00 mmol, 1.0 equiv) and carbazole (**131**) (167 mg, 1.00 mmol, 1.0 equiv) in 10 mL 1,2-dichloroethane was added camphorsulfonic acid (23.0 mg, 0.10 mmol, 0.10 equiv) and the mixture was heated to reflux for 10 hours. Removal of solvent followed by flash chromatography (20% EtOAc/hexanes eluent) afforded a mixture (1:1) of diastereomeric ketones (±)-**149** (274 mg, 77% yield). The first

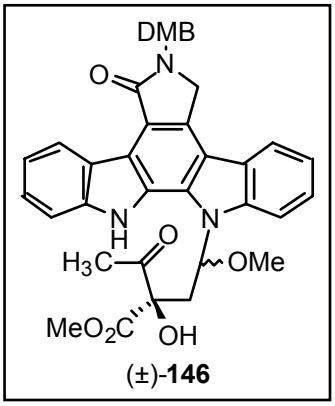
compound to elute was **Diastereomer I**: IR (thin film/NaCl) 3451.2 (m), 3057.5 (w), 3046.5 (w), 2997.5 (w), 2950.2 (m), 2828.5 (w), 1746.5 (s), 1722.2 (s), 1627.3 (w), 1600.2 (m), 1483.6 (s), 1453.7 (s), 1356.2 (m), 1320.9 (s), 1274.8 (m), 1239.6 (s), 1226.0 (s), 1198.9 (m), 1174.5 (m), 1155.5 (m), 1139.3 (s), 1112.1 (m), 1068.7 (m), 1036.2 (m), 1003.7 (m), 979.2 (m), 935.9 (w), 900.6 (m), 843.7 (m), 797.5 (w), 754.3 (s), 727.2 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 2H), 5.92 (dd, *J* = 4.4, 8.8 Hz, 1H), 4.68 (s, 1H), 3.40 (s, 3H), 3.25 (dd, *J* = 8.8, 14.8 Hz, 1H), 3.12 (s, 3H), 2.64 (dd, *J* = 4.4, 14.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 170.1, 139.1, 125.8, 123.7, 120.2, 119.8, 110.5, 83.4, 81.9, 55.7, 53.0, 38.7, 24.5; high resolution mass spectrum (FAB) *m/z* 355.1411 [calcd for $C_{20}H_{21}NO_5$ (M^+) 355.1420].

The second compound to elute was **Diastereomer II**: IR (thin film/NaCl) 3466.3 (w), 3058.7 (w), 2996.6 (w), 2950.7 (w), 2930.0 (w), 2847.2 (w), 2828.3 (w), 1723.7 (s), 1624.3 (w), 1598.7 (m), 1486.6 (m), 1451.0 (s), 1361.8 (m), 1323.5 (m), 1272.6 (m), 1239.4 (m), 1224.1 (s), 1196.1 (m), 1183.3 (m), 1157.8 (m), 1142.5 (m), 1101.7 (m), 1061.0 (m), 1030.4 (w), 1004.9 (w), 933.5 (w), 902.9 (w), 844.3 (w), 823.9 (w), 801.0 (w), 755.1 (s), 724.5 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 4H), 7.25 (t, *J* = 7.3 Hz, 2H), 5.97 (dd, *J* = 4.1, 9.1 Hz, 1H), 4.54 (s, 1H), 3.89 (s, 3H), 3.36 (dd, *J* = 9.1, 14.5 Hz, 1H), 3.17 (s, 3H), 2.33 (dd, *J* = 4.1, 14.5 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 171.4, 139.6, 125.9, 123.7, 120.3, 119.8, 110.6, 83.5, 81.8, 56.1, 53.5, 38.7, 24.2; high resolution mass spectrum (FAB) *m/z* 355.1411 [calcd for $C_{20}H_{21}NO_5$ (M^+) 355.1420].

Preparation of Ketones (±)-145 and (±)-146.



(±)-**145**



(±)-**146**

Ketones (±)-145 and (±)-146. A stirred solution of aglycon **4c** (250 mg, 0.54 mmol, 1.0 equiv) and camphorsulfonic acid (12.5 mg, 0.054 mmol, 0.1 equiv) was heated to reflux in 1,2-dichloroethane (18 mL) and treated over 30 min with a solution of furanoses (±)-**97a,b** (0.24 g, 1.1 mmol, 2.0 equiv) in dichloroethane (12 mL). After an additional 45 min at reflux the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (25 mL), and washed with 10% $NaHCO_3$ solution (20 mL). The organic layer was dried with Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (1:1 EtOAc:hexanes eluent) provided a 2:1 mixture of indolocarbazoles (±)-**145** and (±)-**146** (260 mg, 74% yield). Separation of the regioisomers (±)-**145** and (±)-**146** was achieved using either preparative TLC (1:20:20 MeOH:CH_2Cl_2:hexanes, 3 elutions) or HPLC (190:10:1 CH_2Cl_2:EtOAc:MeOH eluent).

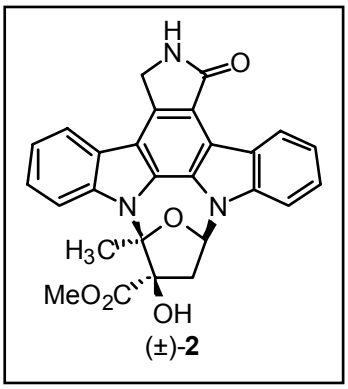
The first diastereomeric mixture to elute was minor regioisomer (±)-**146**: IR (thin film/NaCl) 3388.2 (br m), 2928.3 (s), 1731.6 (s), 1668.6 (s), 1592.9 (m), 1514.7 (m), 1454.4 (s), 1121.4 (m), 1025.5 (m), 753.1 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.08 (br s, 1H), 9.98 (br s, 1H), 9.58 (app.t, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 7.7 Hz, 2H), 7.70 (d, *J* = 4.7 Hz, 1H), 7.68 (d, *J* = 4.8 Hz, 1H), 7.50-7.62 (comp m, 6H), 7.41 (app.t, *J* = 7.6 Hz, 2H), 7.35 (app.t, *J* = 7.4 Hz, 2H), 6.99 (m,

4H), 6.89 (s, 1H), 6.87 (s, 1H), 6.28 (dd, *J* = 3.8, 9.8 Hz, 1H), 6.22 (dd, *J* = 4.6, 8.9 Hz, 1H), 4.97 (s, 4H), 4.90 (app.t, *J* = 17.1 Hz, 4H), 4.59 (s, 1H), 4.50 (s, 1H), 4.07 (s, 3H), 3.89 (s, 6H), 3.86 (s, 6H), 3.49 (dd, *J* = 9.9, 14.5 Hz, 1H), 3.45 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.33 (dd, *J* = 8.9, 14.8 Hz, 1H), 2.45 (s, 3H), 2.42 (dd, *J* = 4.5, 14.8 Hz, 1H), 2.13 (dd, *J* = 4.0, 14.6 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 202.9, 171.5, 170.2, 170.0, 149.4, 148.5, 139.9, 139.6, 139.5, 139.5, 130.4, 129.6, 129.6, 126.8, 126.7, 126.4, 126.4, 126.0, 125.9, 125.7, 125.6, 125.4, 123.3, 123.3, 123.2, 121.3, 121.2, 121.1, 120.8, 120.4, 120.2, 120.1, 118.4, 118.4, 116.3, 116.3, 111.2, 111.2, 110.9, 110.7, 110.6, 109.5, 109.3, 83.6, 83.6, 82.0, 81.8, 56.8, 56.6, 56.0, 55.9, 53.9, 53.6, 49.6, 46.4, 40.5, 24.9, 23.9; high resolution mass spectrum (EI) *m/z* 649.2422 [calcd for $C_{37}H_{35}N_3O_8$ (M^+) 649.2424].

The second diastereomeric mixture to elute was major regioisomer (±)-**145**: IR (thin film/NaCl) 3381.1 (br m), 3009.5 (w), 2942.3 (m), 2841.8 (w), 1725.6 (s), 1668.7 (s), 1513.6 (s), 1454.9 (s), 1409.8 (m), 1248.9 (m), 1144.3 (m), 1027.5 (m), 752.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 10.15 (br s, 1H), 9.68 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 3.8 Hz, 1H), 7.92 (d, *J* = 3.8 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.51-7.58 (comp m, 4H), 7.41 (app.t, *J* = 7.7 Hz, 2H), 7.34 (app.t, *J* = 7.3 Hz, 2H), 6.99 (m, 4H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.30 (dd, *J* = 3.8, 10.0 Hz, 1H), 6.26 (dd, *J* = 4.6, 8.9 Hz, 1H), 4.98 (d, *J* = 14.9 Hz, 1H), 4.98 (d, *J* = 14.9 Hz, 1H), 4.93 (d, *J* = 15.0 Hz, 1H), 4.92 (d, *J* = 15.0 Hz, 1H), 4.89 (s, 4H), 4.61 (s, 1H), 4.51 (s, 1H), 4.06 (s, 3H), 3.89 (s, 6H), 3.89 (s, 6H), 3.47 (s, 3H), 3.46 (s, 3H), 3.43-3.45 (m, 1H), 3.41 (s, 3H), 3.28 (dd, *J* = 9.0, 14.8 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, *J* = 4.7, 14.7 Hz, 1H), 2.12 (s, 3H), 2.09 (dd, *J* = 3.8, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 203.0, 171.7, 170.4, 170.1, 149.3, 148.5, 139.7, 139.5, 139.4, 139.4,

131.5, 130.4, 127.9, 127.7, 126.8, 126.8, 126.2, 125.9, 125.9, 125.6, 125.5, 125.0, 124.6, 124.4, 123.8, 123.7, 122.8, 122.8, 121.0, 121.0, 120.8, 120.7, 120.4, 120.4, 119.2, 119.1, 115.7, 115.7, 111.8, 111.6, 111.2, 111.1, 110.9, 108.5, 108.3, 107.3, 83.4, 83.4, 82.1, 81.9, 56.7, 56.4, 56.0, 55.9, 53.7, 53.7, 49.5, 46.4, 40.4, 40.4, 25.0, 23.9; high resolution mass spectrum (EI) *m/z* 649.2415 [calcd for $C_{37}H_{35}N_3O_8$ (M^+) 649.2424].

Preparation of (±)-K252a (2).

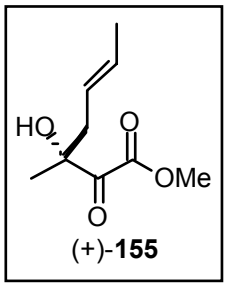


(±)-**2**

(±)-K252a (2). To a stirred solution of indolocarbazole (±)-**147** (17.0 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (1.4 mL) at 25 °C was added thioanisole (0.16 mL, 1.36 mmol, 50 equiv) followed by 2,2,2-trifluoroacetic acid (1.4 mL). The solution was stirred for 6 h, followed by dropwise addition of 2.0 mL saturated $NaHCO_3$ solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH:CH_2Cl_2:hexanes, 3 elutions) to afford (±)-K252a [**2**, 10.8 mg, 83% yield] as a pale yellow solid: mp 264-267° (dec.); IR (thin film/NaCl) 3309.6 (br m), 3053.5 (m), 2952.6 (m), 2851.9 (m), 1735.8 (s), 1675.4 (s), 1590.0 (m), 1458.6 (s), 1396.4 (m), 1313.7 (s), 1258.8 (m), 1138.8 (m), 877.3 (w) cm^{-1}; ^1H NMR

(500 MHz, DMSO-d_6) δ 9.20 (d, *J* = 7.9 Hz, 1H), 8.63 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.47 (comp m, 2H), 7.35 (app.t, *J* = 7.4 Hz, 1H), 7.28 (app.t, *J* = 7.4 Hz, 1H), 7.14 (dd, *J* = 5.0, 7.2 Hz, 1H), 6.34 (s, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.92 (s, 3H), 3.38 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.01 (dd, *J* = 4.9, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 171.8, 139.9, 136.8, 133.0, 128.3, 125.6, 125.4, 125.1, 124.2, 123.9, 122.6, 121.3, 120.4, 119.6, 119.5, 115.8, 114.8, 114.6, 109.1, 99.4, 85.0, 85.0, 52.7, 45.5, 42.5, 22.8; high resolution mass spectrum (FAB) *m/z* 468.1561 [calcd for $C_{27}H_{22}N_3O_5$ (M+H) 468.1559].

Preparation of Ketone (+)-155.

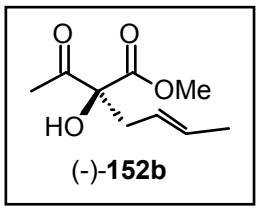


(+)-**155**

Ketone (+)-155. A stirred solution of methyl 2-diazo-3-oxobutanoate (**150**) (2.13 g, 15.0 mmol, 1.0 equiv), alcohol (*S*)-(+)-**153**[36] (1.3 mL, 15.0 mmol, 1.0 equiv) $Rh_2(OAc)_4$ (66.3 mg, 0.15 mmol, 0.01 equiv) in benzene (75 mL) was immersed into a preheated (100-110 °C) oil bath. The mixture was heated under reflux for 20 minutes. After cooling the mixture to room temperature, the solvent was carefully evaporated (0 °C) *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) afforded ketone (+)-**155** (1.84 g, 66% yield) as a colorless oil: bp 65-67 °C (0.35 mm Hg); $[\alpha]^{20}_D$ +14.65° (*c* 1.08, $CHCl_3$); IR (thin

film/NaCl) 3521.0 (m), 3028.5 (w), 2981.5 (m), 2957.1 (m), 2937.9 (m), 2919.9 (m), 2857.4 (w), 1742.6 (s), 1726.1 (s), 1452.3 (m), 1437.5 (m), 1376.0 (w), 1361.2 (w), 1289.1 (m), 1250.1 (m), 1192.6 (w), 1145.8 (w), 1116.3 (w), 1081.5 (w), 1060.1 (w), 1032.1 (s), 971.9 (m), 920.3 (w), 861.6 (w), 844.7 (w), 814.4 (w), 722.7 (w), 663.1 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (m, 1H), 5.35 (m, 1H), 3.88 (s, 3H), 3.28 (br s, 1H), 2.68 (dd, *J* = 7.0, 14.0 Hz, 1H), 2.42 (dd, *J* = 7.7, 14.0 Hz, 1H), 1.66 (d, *J* = 6.42 Hz, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 162.7, 130.9, 123.5, 78.3, 52.5, 42.2, 24.1, 17.8; high resolution mass spectrum (CI) *m/z* 187.0966 [calcd for $C_9H_{15}O_4$ (M+H) 187.0970].

Preparation of Ketone (-)-152b.

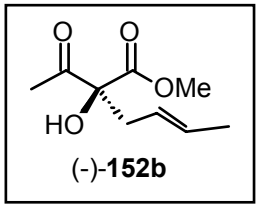


(-)-**152b**

Ketone (-)-152b. A solution of ketone (+)-**155** (3.35 g, 18.0 mmol, 1.0 equiv) in benzene (180 mL) was treated with BF_3•OEt_2 (2.21 mL, 18.0 mmol, 1.0 equiv), stirred for 2 hours at 25 °C, and the solvent was carefully evaporated (0 °C) *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) provided ketone (-)-**152b** (2.49 g, 74% yield) as a colorless oil: $[\alpha]^{20}_D$ -32.13° (*c* 1.08, $CHCl_3$); IR (thin film/NaCl) 3476.1 (m), 3031.2 (w), 3009.6 (w), 2956.2 (m), 2921.4 (w), 2857.5 (w), 1746.9 (s), 1721.9 (s), 1437.4 (m), 1357.9 (m), 1271.0 (m), 1224.2 (m), 1195.9 (m), 1183.2 (m), 1141.0 (m), 1108.5 (m), 1076.9 (w), 1052.8 (w), 994.6 (w), 972.4 (m), 861.8 (w), 816.7 (w), 798.3 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.32 (m, 1H), 4.17 (s, 1H), 3.80 (s, 3H), 2.77

(dd, *J* = 6.6, 14.3 Hz, 1H), 2.63 (dd, *J* = 7.6, 14.3 Hz, 1H), 2.28 (s, 3H), 1.65 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 170.8, 130.5, 122.9, 83.8, 53.1, 38.5, 24.7, 17.9; high resolution mass spectrum (CI) *m/z* 187.0969 [calcd for $C_9H_{15}O_4$ (M+H) 187.0970].

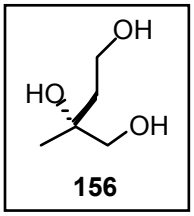
Preparation of Ketone (-)-152b. Single-pot method.



(-)-**152b**

Ketone (-)-152b. Single-pot method. A stirred solution of methyl 2-diazo-3-oxobutanoate (**150**) (427 mg, 3.00 mmol, 1.0 equiv), alcohol (*S*)-(+)-**153**[36] (0.286 mL, 3.3 mmol, 1.1 equiv) $Rh_2(OAc)_4$ (13 mg, 0.03 mmol, 0.01 equiv) in benzene (15 mL) was immersed into a preheated (100-110 °C) oil bath. The mixture was heated to reflux for 20 minutes, cooled to room temperature, treated with BF_3•OEt_2 (0.46 mL, 3.74 mmol, 1.25 equiv), and stirred for 2 hours at 25 °C. The entire reaction mixture was poured onto a silica column and chromatographed (20% pentane/Et_2O eluent) to provide ketone (-)-**152b** (418 mg, 75% yield) as a colorless oil.

Preparation of Triol 156.



156

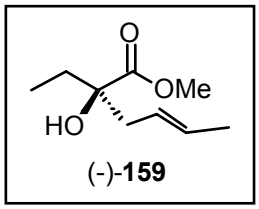
Triol 156.[39] To a cooled (0 °C) solution of ketone (+)-**155** (1.56 g, 8.38 mmol, 1.0 equiv) in CH_2Cl_2 (84 mL) was added DIBAL-H (6.72 mL, 37.69 mmol, 4.5 equiv) in a dropwise fashion over a period of 8 minutes. After stirring for 10 minutes at 0 °C the ice bath was removed, the mixture warmed to 25 °C, and stirred for 30 minutes. The reaction was quenched with EtOAc (10 mL) followed by MeOH (5 mL). A saturated solution of sodium potassium tartrate (80 mL) was added and the mixture was stirred vigorously for 1.5 hours. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, a crude oil (845 mg) was obtained and used in the next step without further purification.

To a cooled solution (0 °C) of the above oil (845 mg) in THF (74 mL) was added a solution of H_5IO_6 (1.20 g, 5.26 mmol) in H_2O (1.5 mL). After 20 minutes at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirred for 40 minutes. An excess of $NaBH_4$ (250 mg, 6.6 mmol, 5.0 equiv) was added followed by 1M HCl (3 mL). After the vigorous reaction had ceased, the reaction mixture was extracted with EtOAc and the organic layers dried with $MgSO_4$. Evaporation of the filtrate produced a colorless oil which was filtered through silica gel (5% MeOH/CH_2Cl_2 eluent) to afford an oil (349 mg) which was used in the subsequent reaction without further purification.

A solution of the derived oil (349 mg) in a cooled (-78 °C) mixture of CH_2Cl_2 (15 mL) and MeOH (3 mL) was treated with O_3 until the solution turned a

pale blue (5-6 minutes). The mixture was purged with argon before an excess of $NaBH_4$ (250 mg, 6.6 mmol, 5.0 equiv) was added at -78 °C. After warming to ambient temperature the mixture was concentrated *in vacuo*. Flash chromatography (10% MeOH/CH_2Cl_2 eluent) provided triol (*R*)-**156** (245 mg, 25% yield over 3 steps).

Preparation of Ester (-)-159.



(-)-**159**

Ester (-)-159. To a solution of alcohol (-)-**152b** (382 mg, 2.05 mmol, 1.0 equiv) in ethylvinylether (1.4 mL) at 0 °C was added 2,2,2-trifluoroacetic acid (8.7 μL). The mixture was warmed to reflux for 24 hours. During that time ethylvinylether (1.4 mL) was added twice to replace evaporated solvent. The reaction mixture was cooled to 25 °C and quenched by adding Et_3N (45 μL). The mixture was partitioned between Et_2O (4 mL) and H_2O (0.4 mL). The organic layer was separated and washed with H_2O (0.5 mL), saturated NaCl solution (0.5 mL), dried over $MgSO_4$, and concentrated to afford an oil (538 mg) which was used in the next step without further purification.

To a cooled solution (0 °C) of the derived oil (538 mg) in MeOH (10 mL) was added $NaBH_4$ (58 mg, 6.1 mmol). The reaction mixture was stirred for 2 hours at 0 °C, quenched by addition of H_2O (136 μL) and then partitioned between H_2O (3 mL) and Et_2O (30 mL). The organic layer was dried over

$MgSO_4$ and concentrated to provide an oil (490 mg) which was used without further purification.

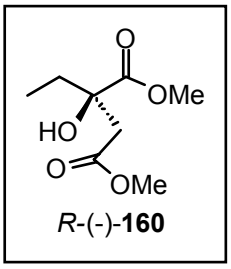
To a cooled solution (-78 °C) of the derived oil (490 mg) in THF (17.8 mL) was added $KN(SiMe_3)_2$ (9.4 mL, 0.4 M in toluene, 3.8 mmol). The mixture was stirred for 5 minutes and treated with CS_2 (1.2 mL, 20.0 mmol) followed by iodomethane (1.2 mL, 20.0 mmol). After 10 minutes at -78 °C the reaction was warmed to 0 °C, quenched with saturated NH_4Cl solution (15 mL), and diluted with CH_2Cl_2 (120 mL). The organic layer was washed with H_2O (30 mL), saturated NaCl solution (30 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford an oil (659 mg) that was used without further purification.

A solution of *n*-Bu_3SnH (1.53 mL, 5.69 mmol) and AIBN (62 mg, 0.39 mmol) in benzene (22.3 mL) was heated to reflux and treated dropwise with a solution of the crude oil obtained above (659 mg) in benzene (3.7 mL) over 10 min. The reflux was continued for an additional hour, then allowed to cool to room temperature. The solvent was evaporated and the residue filtered through silica gel (0∅5% EtOAc/hexanes gradient eluent) to provide an oil (469 mg).

A solution of the derived oil (469 mg) in THF (20 mL) was treated with 1N HCl (2 mL). The mixture was stirred at 25 °C for 15 minutes, the solvent was evaporated, and the residue partitioned between CH_2Cl_2 (133 mL) and H_2O (67 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 67 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide a yellow oil which was purified by flash chromatography (5% EtOAc/hexanes eluent) to provide ester (-)-**159** as a pale yellow oil (153 mg, 44% yield over 5 steps):**.** $[\alpha]^{20}_D$ -8.53° (*c* 1.06, $CHCl_3$); IR (thin film/NaCl) 3530.1 (w), 3028.8 (w), 2962.2 (m), 2955.8 (m), 2936.6 (m), 2922.8 (m), 2880.7 (w), 2855.8 (w), 1733.9 (s), 1459.2 (m), 1378.4 (w), 1339.5 (w), 1293.4 (w), 1243.1 (s), 1211.6 (s), 1152.5 (s), 1068.7 (m), 1019.8 (m), 970.7 (m), 871.4 (w), 805.1 (w),

749.2 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.83 (m, 1H), 5.37 (m, 1H), 3.76 (s, 3H), 3.12 (s, 1H), 2.40 (dd, *J* = 7.3, 13.8 Hz, 1H), 2.31 (dd, *J* = 7.1, 13.8 Hz, 1H), 1.78 (m, 1H), 1.67 (m, 1H), 1.65 (d, *J* = 6.3 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 129.6, 124.7, 78.0, 52.4, 42.4, 31.6, 18.0, 7.8; high resolution mass spectrum (CI) *m/z* 173.1177 [calcd for $C_9H_{17}O_3$ (M+H) 173.1178].

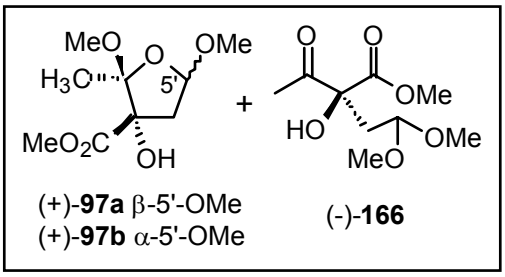
Preparation of Diester (-)-160.



R-(-)-**160**

Diester (-)-160.[40] A cooled solution (-78 °C) of olefin (-)-**159** (153 mg) in CH_2Cl_2 (4.3 mL) and 2.5 N NaOH (1.2 mL) in MeOH, was treated with O_3 until the solution turned pale blue. Diethylether (14 mL) and H_2O (14 mL) were added and the reaction mixture was allowed to warm to 25 °C followed by extraction with Et_2O (3 x 60 mL). After evaporation of the solvent the crude product was filtered through a pad of silica gel (20% EtOAc/hexanes) to afford diester (-)-**160** as a colorless oil (74 mg, 44% yield, $[\alpha]^{20}_D$ -13.88°(*c* 1.03, $CHCl_3$).

Preparation of Esters (+)-97a,b and Ketone (-)-166.



(+)-**97a** β-5'-OMe
(+)-**97b** α-5'-OMe

(-)-**166**

Esters (+)-97a,b and Ketone (-)-166. A solution of olefin (-)-**152b** (1.31 g, 7.0 mmol, 1.0 equiv) and a trace of sudan red 7B dye in MeOH (45 mL) was cooled to -78 °C and treated with O_3 until the dye was completely discolored (about 3 minutes). The mixture was purged with argon for 10 minutes at -78 °C and dimethylsulfide (20 mL) was added at that temperature. The dry-ice cold bath was replaced with an ice bath which was allowed to thaw (0-20 °C) over a period of 3 hours. The solvent was removed *in vacuo* and the crude product dissoved in benzene (45 mL). After addition of *p*-toluenesulfonic acid (20 mg, 0.11 mmol, 0.015 equiv) and MeOH (12 mL) the mixture was stirred at 25 °C for 17 hours followed by evaporation of the solvent *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) afforded a mixture of diastereomeric furanoses (+)-**97a,b** and ketone (-)-**166** (1.23 g, 80% yield). The diastereomers could be separated using HPLC. In a first run (2:2:1 hexanes:CH_2Cl_2:EtOAc eluent) a mixture of alcohols (+)-**97b** and (-)-**166** was eluted first followed by furanose (+)-**97a** which was isolated in its pure form as a colorless oil. The two component mixture was separated using a different system (10% *i*-propanol/hexanes eluent). The first compound to elute was furanose (+)-**97b**, followed by ketone (-)-**166**, both as colorless oils.

(+)-97a: mp 63-64°; $[\alpha]^{20}_D$ + 9.66° (*c* 1.03, $CHCl_3$); IR (thin film/NaCl) 3480.7 (m), 2995.0 (w), 2953.3 (m), 2914.2 (w), 2835.1 (w), 1726.7 (s), 1443.2

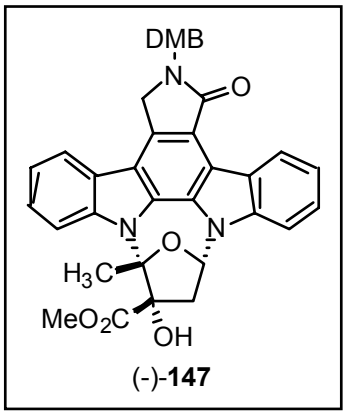
(m), 1377.9 (m), 1348.2 (w), 1278.2 (s), 1239.0 (m), 1228.0 (m), 1200.4 (m), 1181.6 (w), 1165.1 (s), 1127.6 (s), 1114.3 (s), 1092.2 (m), 1084.5 (m), 979.6 (m), 957.5 (m), 948.7 (m), 927.8 (m), 901.5 (m), 871.9 (w), 840.9 (w), 802.9 (w), 755.5 (m), 673.0 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (app.t, *J* = 5.7 Hz, 3H), 3.79 (s, 3H), 3.47 (s, 3H), 3.36 (d, *J* = 1.6 Hz, 1H), 3.27 (s, 3H), 2.84 (ddd, *J* = 1.6, 5.2, 14.3 Hz, 1H), 2.34 (dd, *J* = 6.2, 14.3 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 109.8, 105.3, 84.4, 56.3, 52.8, 49.0, 40.4, 14.5; high resolution mass spectrum (CI) *m/z* 189.0764 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0763].

(+)-97b: mp 81-82°; $[\alpha]^{20}_D$ + 112.13° (*c* 1.06, $CHCl_3$); IR (thin film/NaCl) 3495.1 (m), 2995.3 (m), 2953.2 (s), 2917.2 (s), 2848.3 (m), 1747.1 (s), 1463.7 (m), 1439.3 (m), 1379.1 (m), 1355.2 (w), 1263.5 (s), 1200.0 (s), 1182.1 (m), 1156.1 (m), 1121.8 (s), 1086.1 (s), 1043.7 (m), 1019.3 (m), 973.6 (m), 949.3 (m), 929.7 (m), 892.2 (m), 864.6 (w), 833.7 (m), 802.7 (m), 750.6 (m), 685.5 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 0.6, 5.8 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 3.38 (br s, 1H), 3.25 (s, 3H), 3.03 (dd, *J* = 5.8, 14.2 Hz, 1H), 2.06 (d, *J* = 14.2 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 110.5, 103.8, 83.1, 55.5, 52.6, 49.2, 40.5, 15.2; high resolution mass spectrum (CI) *m/z* 189.0771 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0764].

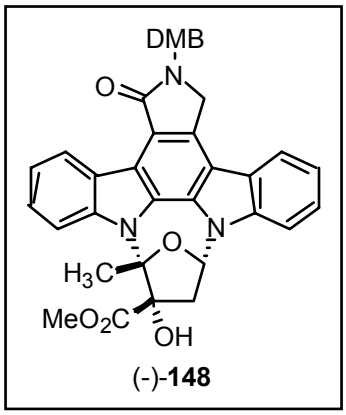
(-)-166: $[\alpha]^{20}_D$ - 20.25° (*c* 0.97, $CHCl_3$); IR (thin film/NaCl) 3450.0 (m), 2988.3 (m), 2953.5 (s), 2915.0 (s), 2849.2 (s), 1746.0 (s), 1722.3 (s), 1457.5 (m), 1436.4 (m), 1386.7 (m), 1275.0 (m), 1245.2 (m), 1198.0 (m), 1178.1 (m), 1142.1 (s), 1121.0 (s), 1063.3 (s), 1014.2 (w), 998.1 (w), 974.4 (w), 907.4 (w), 830.6 (w), 755.1 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.50 (s, 1H), 4.50 (dd, *J* = 4.8, 6.7 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.29 (s, 3H), 2.43 (dd, *J* = 4.8, 14.5 Hz, 1H),

2.39 (dd, *J* = 6.7, 14.5 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 170.8, 102.0, 81.8, 54.9, 53.8, 53.2, 38.4, 24.5; high resolution mass spectrum (FAB) *m/z* 189.0777 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0776].

Preparation of Indolocarbazoles (-)-147 and (-)-148.



(-)-**147**



(-)-**148**

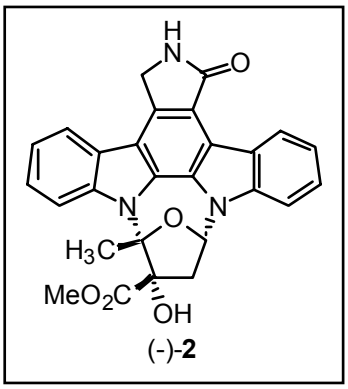
Indolocarbazoles (-)-147 and (-)-148. A stirred solution of aglycon **4c** (1.00 g, 2.17 mmol, 1.0 equiv) and camphorsulfonic acid (50 mg, 0.22 mmol, 0.1 equiv) in 1,2-dichloroethane (72 mL) was heated to reflux and treated over 24 h with a solution of alcohols (+)-**97a,b** and (-)-**166** (0.95 g, 4.32 mmol, 2.0 equiv) in 1,2-dichloroethane (50 mL). After an additional 24 h, the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (50 mL), and washed with 10% $NaHCO_3$ solution (50 mL). The organic layer was dried with Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (1:1 EtOAc/hexanes eluent) provided a 2:1 mixture of indolocarbazoles (-)-**147** and (-)-**148** (1.07 g, 80% yield). Separation of the regioisomers (-)-**147** and (-)-**148** was achieved with either preparative TLC (60:1 70% CH_2Cl_2/hexanes:MeOH, 3 elutions) or by HPLC (190:10:1 CH_2Cl_2:EtOAc:MeOH eluent).

(-)-147: mp >250° (dec.); $[\alpha]^{20}_{D}$ -17° (*c* 0.1, MeOH); IR (thin film/NaCl) 3279.7 (br m), 3012.1 (m), 2952.1 (m), 2930.1 (m), 2850.1 (w), 1732.2 (m), 1646.2 (s), 1590.4 (m), 1513.7 (s), 1460.2 (s), 1139.5 (s), 1028.1 (m), 744.5 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.92 (app.t, *J* = 8.0 Hz, 2H), 7.49 (app.t, *J* = 7.7 Hz, 1H), 7.47 (app.t, *J* = 7.8 Hz, 1H), 7.32 (app.t, *J* = 7.9 Hz, 1H), 7.30 (app.t, *J* = 8.1 Hz, 1H), 7.15 (dd, *J* = 5.2, 6.9 Hz, 1H), 7.02 (s, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.35 (s, 1H), 5.02 (d, *J* = 17.8 Hz, 1H), 4.97 (d, *J* = 17.8 Hz, 1H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.82 (d, *J* = 15.5 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.39 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.00 (dd, *J* = 4.7, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 168.6, 148.9, 148.2, 139.8, 136.7, 130.4, 130.0, 128.2, 125.3, 125.3, 124.8, 123.9, 123.8, 122.4, 120.9, 120.2, 119.8, 119.3, 118.9, 115.6, 114.6, 114.2, 112.3, 112.1, 108.8, 99.3, 84.8, 55.5, 52.4, 49.5, 45.4, 42.4, 22.6; high resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for $C_{36}H_{32}N_3O_7$ (M+H) 618.2240].

(-)-148: mp 260-270° (dec.); $[\alpha]^{20}_{D}$ -13° (*c* 0.1, MeOH); IR (thin film/NaCl) 3462.3 (br m), 3014.0 (m), 2952.3 (m), 2925.1 (m), 2849.7 (m), 1730.8 (s), 1645.0 (m), 1514.7 (m), 1455.6 (s), 1403.9 (m), 1348.5 (m), 1312.6 (m), 1257.2 (s), 1235.0 (s), 1138.1 (s), 1068.8 (m), 1027.3 (m), 750.3 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.50 (app.t, *J* = 7.5 Hz, 1H), 7.45 (app.t, *J* = 7.5 Hz, 1H), 7.30 (app.t, *J* = 7.5 Hz, 1H), 7.29 (app.t, *J* = 7.6 Hz, 1H), 7.14 (dd, *J* = 5.0, 7.2 Hz, 1H), 7.01 (d, *J* = .71 Hz, 1H), 6.92 (app.t, *J* = 8.2 Hz, 1H), 6.92 (dd, *J* = 1.1, 8.4 Hz, 1H), 6.34 (br s, 1H), 4.98 (d, *J* = 17.9 Hz, 1H), 4.95 (d, *J* = 17.9 Hz, 1H), 4.84 (d, *J* = 15.1 Hz, 1H), 4.80 (d, *J* = 15.1 Hz, 1H), 3.92 (s, 3H), 3.74

(s, 3H), 3.71 (s, 3H), 3.40 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.05 (dd, *J* = 4.8, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 168.9, 149.0, 148.2, 139.7, 136.8, 130.4, 126.2, 126.1, 125.4, 125.1, 124.9, 124.3, 122.0, 121.3, 120.2, 119.8, 119.2, 118.7, 116.3, 113.9, 113.8, 112.3, 112.1, 109.4, 99.3, 84.9, 84.8, 55.5, 52.4, 49.0, 45.4, 42.5, 22.8; high resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for $C_{36}H_{32}N_3O_7$ (M+H) 618.2240].

Preparation of (-)-K252a (2).

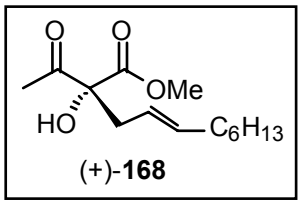


(-)-**2**

(-)-K252a (2). To a stirred solution of indolocarbazole (-)-**147** (17.0 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (1.4 mL) at 25 °C was added thioanisole (0.16 mL, 1.36 mmol, 50 equiv) followed by 2,2,2-trifluoroacetic acid (1.4 mL). The solution was stirred for 6 h, followed by dropwise addition of 2.0 mL saturated $NaHCO_3$ solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH:CH_2Cl_2:hexanes, 3 elutions) to afford (-)-K252a [**2**, 10.3 mg, 82% yield] as a pale yellow solid: mp 263-265° (dec.); $[\alpha]^{20}_D$ -39°; *c* 0.1, MeOH; IR (thin film/NaCl) 3309.4 (br m), 3055.3 (m), 2952.6 (m), 2851.9 (m), 1735.8 (s), 1675.4 (s), 1458.6 (s), 1396.4 (m), 1313.7 (s), 1258.8 (m), 1138.8 (m), 877.3 (w) cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (d, *J* = 7.9 Hz, 1H), 8.63 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.47 (comp m, 2H), 7.35 (app.t, *J* = 7.4 Hz, 1H), 7.28 (app.t, *J* = 7.4 Hz, 1H), 7.14 (dd, *J* = 5.0, 7.2 Hz, 1H), 6.34 (s, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.92 (s, 3H), 3.38 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.01 (dd, *J* = 4.9, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 171.8, 139.9, 136.8, 133.0, 128.3, 125.6, 125.4, 125.1, 124.2, 123.9, 122.6, 121.3, 120.4, 119.6, 119.5, 115.8, 114.8, 114.6, 109.1, 99.4, 85.0, 85.0, 52.7, 45.5, 42.5, 22.8; high resolution mass spectrum (FAB) *m/z* 468.1561 [calcd for $C_{27}H_{22}N_3O_5$ (M+H) 468.1559].

Preparation of Ketone (+)-168.

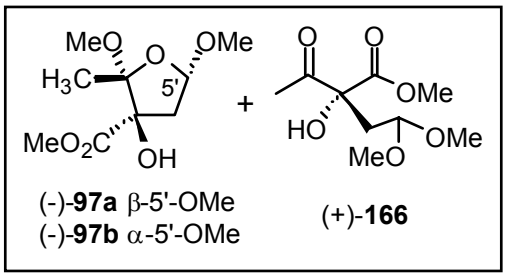


(+)-**168**

Ketone (+)-168. A stirred solution of methyl 2-diazo-3-oxobutanoate [(**150**) 10 g, 70.4 mmol, 1.0 equiv], (*R*)-(-)-nonen-3-ol[33] [(**167**) 10.8 g, 75.9 mmol, 1.1 equiv], and $Rh_2(OAc)_4$ (19 mg, 0.04 mmol, 0.0006 equiv) in benzene (235 mL) was immersed into a preheated (100-110 °C) oil bath. The mixture was heated at reflux for 20 min, cooled to room temperature, treated with BF_3•OEt_2 (10.8 mL, 85.2 mmol, 1.21 equiv), and stirred for 2 hours at 25 °C. The entire reaction mixture was poured onto a flash column and chromatographed (10% EtOAc/hexanes eluent) to provide ketone (+)-**168** (13.9 g, 77% yield) as a colorless oil: $[\alpha]^{20}_D$ +19.41° (*c* 1.03, $CHCl_3$); IR (thin film/NaCl) 3788.3 (m),

2954.9 (s), 2926.7 (s), 2871.3 (m), 2855.5 (s), 1746.6 (s), 1723.2 (s), 1456.5 (m), 1436.1 (m), 1378.2 (m), 1356.0 (m), 1272.5 (m), 1226.5 (s), 1194.1 (m), 1143.0 (m), 1114.0 (m), 972.6 (m), 797.1 (w), 725.5 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (m, 1H), 5.30 (m, 1H), 4.20 (s, 1H), 3.79 (s, 3H), 2.78 (dd, *J* = 6.7, 14.3 Hz, 1H), 2.64 (dd, *J* = 7.6, 14.3 Hz, 1H), 2.28 (s, 3H), 1.97 (q, *J* = 7 Hz, 2H), 1.31-1.23 (m, 8H), 0.88 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 170.8, 136.2, 121.6, 83.9, 53.1, 38.6, 32.4, 31.5, 29.0, 28.6, 24.7, 22.4, 13.9; high resolution mass spectrum (CI) *m/z* 257.1745 [calcd for $C_{14}H_{25}O_4$ (M+H) 257.1753].

Preparation of Esters (-)-97a,b and Ketone (+)-166.



Esters (-)-97a,b and Ketone (+)-166. A solution of ketone (+)-**168** (10.6 g, 41.4 mmol) and a trace of sudan red 7B dye in MeOH (450 mL) was cooled to -78 °C and treated with O_3 until the dye was completely discolored (about 30 minutes). The mixture was purged with argon for 10 minutes at -78 °C and dimethylsulfide (200 mL) was added at that temperature. The dry-ice cold bath was replaced with an ice bath which was allowed to thaw (0-20 °C) over a period of 3 hours. The solvent was removed *in vacuo* and the crude product dissoved in benzene (450 mL). After addition of *p*-toluenesulfonic acid (200 mg, 1.1 mmol, 0.015 equiv) and MeOH (120 mL) the mixture was stirred at 25 °C for 17 hours

followed by evaporation of the solvent *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) afforded a mixture of diastereomeric furanoses (-)-**97a,b** and ketone (+)-**166** (7.3 g, 80% yield). The diastereomers could be separated using HPLC. In a first run (2:2:1 hexanes:CH_2Cl_2:EtOAc eluent) a mixture of alcohols (-)-**97b** and (+)-**166** was eluted first followed by furanose (-)-**97a** which was isolated in its pure form as a colorless oil. The two component mixture was separated using a different system (10% *i*-propanol/hexanes eluent). The first compound to elute was furanose (-)-**97b**, followed by ketone (+)-**166**, both as colorless oils.

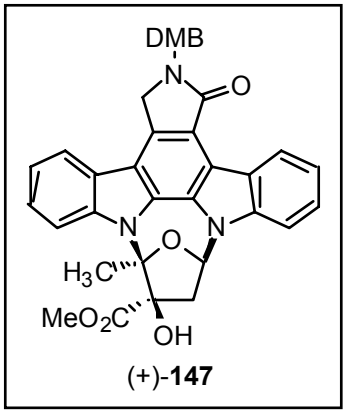
(-)-**97a**: mp 63-64 °C (EtOAc); $[\alpha]^{20}_D$ -9.00° (*c* 1.16, $CHCl_3$); IR (thin film/NaCl) 3486.7 (m), 2994.8 (m), 2954.8 (m), 2918.0 (m), 2836.2 (m), 1732.7 (s), 1442.6 (m), 1378.3 (m), 1346.6 (w), 1276.5 (s), 1243.0 (m), 1229.7 (m), 1199.7 (m), 1183.0 (m), 1165.4 (s), 1126.7 (s), 1115.6 (s), 1086.6 (s), 1049.2 (s), 1020.2 (s), 980.1 (m), 956.6 (m), 626.1 (m), 902.6 (m), 870.2 (w), 840.2 (w), 803.0 (w), 754.6 (m), 673.3 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (app.t, *J* = 5.7 Hz, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.36 (br s, 1H), 3.27 (s, 3H), 2.84 (dd, *J* = 5.3, 14.3 Hz, 1H), 2.34 (dd, *J* = 6.2, 14.3 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 109.9, 105.4, 84.5, 56.4, 52.8, 49.0, 40.5, 14.5; high resolution mass spectrum (CI) *m/z* 189.0773 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0763].

(-)-**97b**: mp 81-82 °C (EtOAc); $[\alpha]^{20}_D$ -122.55° (*c* 1.10, $CHCl_3$); IR (thin film/NaCl) 3496.4 (m), 2998.9 (m), 2953.3 (m), 2915.1 (m), 2836.9 (m), 1748.9 (s), 1732.9 (s), 1440.3 (m), 1379.3 (m), 1334.7 (w), 1261.7 (s), 1200.7 (s), 1182.7 (m), 1156.9 (s), 1122.5 (s), 1098.5 (s), 1086.5 (s), 1044.3 (m), 1021.1 (m), 975.9 (s), 948.6 (m), 930.7 (m), 893.9 (m), 865.4 (m), 834.9 (m), 802.2 (m),

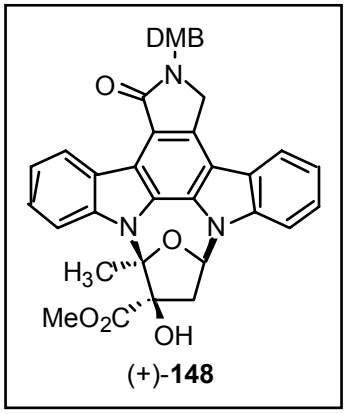
750.9 (m), 685.7 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (d, *J* = 5.8 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 3.25 (s, 3H), 3.03 (dd, *J* = 5.8, 14.1 Hz, 1H), 2.05 (d, *J* = 14.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 110.5, 103.8, 83.1, 55.5, 52.5, 49.2, 40.5, 15.7; high resolution mass spectrum (CI) *m/z* 189.0778 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0763].

(+)-**166**: $[\alpha]^{20}_D$ +19.55° (*c* 1.12, $CHCl_3$); IR (thin film/NaCl) 3452.5 (m), 2993.2 (m), 2954.6 (m), 2934.2 (m), 2917.5 (m), 2848.4 (m), 2838.2 (m), 1748.7 (s), 1723.1 (s), 1437.8 (m), 1359.7 (m), 1275.8 (m), 1245.7 (m), 1198.5 (m), 1178.2 (m), 1144.7 (s), 1124.4 (s), 1065.4 (s), 1015.7 (m), 997.3 (m), 905.2 (m), 829.6 (w), 802.0 (w), 756.0 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.51 (br s, 1H), 4.50 (dd, *J* = 4.9, 6.6 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.29 (s, 3H), 2.43 (dd, *J* = 4.9, 14.6 Hz, 1H), 2.38 (dd, *J* = 6.6, 14.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 170.8, 102.0, 81.8, 54.9, 53.8, 53.2, 38.4, 24.5; high resolution mass spectrum (FAB) *m/z* 189.0775 [calcd for $C_8H_{13}O_5$ (M-CH_3OH+H) 189.0763].

Preparation of Indolocarbazoles (+)-147 and (+)-148.



(+)-**147**



(+)-**148**

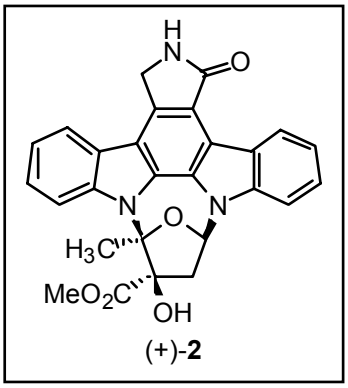
Indolocarbazoles (+)-147 and (+)-148. A stirred solution of aglycon **4c** (1.00 g, 2.17 mmol, 1.0 equiv) and camphorsulfonic acid (50 mg, 0.22 mmol, 0.1 equiv) in 1,2-dichloroethane (72 mL) was heated to reflux and treated over 24 h with a solution of alcohols (-)-**97a,b** and (+)-**166** (0.95 g, 4.32 mmol, 2.0 equiv) in 1,2-dichloroethane (50 mL). After an additional 24 h, the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (50 mL), and washed with 10% $NaHCO_3$ solution (50 mL). The organic layer was dried with Na_2SO_4 and evaporated *in vacuo*. Flash chromatography (1:1 EtOAc/hexanes eluent) provided a 2:1 mixture of indolocarbazoles (+)-**147** and (+)-**148** (1.07 g, 80% yield). Separation of the regioisomers (+)-**147** and (+)-**148** was achieved with either preparative TLC (60:1 70% CH_2Cl_2/hexanes:MeOH, 3 elutions) or by HPLC (190:10:1 CH_2Cl_2:EtOAc:MeOH eluent).

(+)-**147:** mp >250 °C (dec., MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ +15° (*c* 0.1, MeOH); IR (thin film/NaCl) 3279.7 (br m), 3012.1 (m), 2952.1 (m), 2930.1 (m), 2850.1 (w), 1732.2 (m), 1646.2 (s), 1590.4 (m), 1513.7 (s), 1460.2 (s), 1260.3 (s), 1139.5 (s), 1028.1 (m), 744.5 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.26 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.92 (app.t, *J* = 8.0 Hz, 2H), 7.49 (app.t, *J* = 7.7 Hz, 1H), 7.47 (app.t, *J* = 7.8 Hz, 1H), 7.32 (app.t, *J* = 7.9 Hz, 1H), 7.30 (app.t, *J* = 8.1

Hz, 1H), 7.15 (dd, *J* = 5.2, 6.9 Hz, 1H), 7.02 (s, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.35 (s, 1H), 5.02 (d, *J* = 17.8 Hz, 1H), 4.97 (d, *J* = 17.8 Hz, 1H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.82 (d, *J* = 15.5 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.39 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.00 (dd, *J* = 4.7, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6, 168.6, 148.9, 148.2, 139.8, 136.7, 130.4, 130.0, 128.2, 125.3, 125.3, 124.8, 123.9, 123.8, 122.4, 120.9, 120.2, 119.8, 119.3, 118.9, 115.6, 114.6, 114.2, 112.3, 112.1, 108.8, 99.3, 84.8, 55.5, 52.4, 49.5, 45.4, 42.4, 22.6; high resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for $C_{36}H_{32}N_3O_7$ (M+H) 618.2240].

(+)-**148:** mp 260-270 °C (dec., MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ +13° (*c* 0.1, MeOH); IR (thin film/NaCl) 3462.3 (br m), 3014.0 (m), 2952.3 (m), 2925.1 (m), 2849.7 (m), 1730.8 (s), 1645.0 (m), 1514.7 (m), 1455.6 (s), 1403.9 (m), 1348.5 (m), 1312.6 (m), 1257.2 (s), 1235.0 (s), 1138.1 (s), 1068.8 (m), 1027.3 (m), 750.3 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.50 (app.t, *J* = 7.5 Hz, 1H), 7.45 (app.t, *J* = 7.5 Hz, 1H), 7.30 (app.t, *J* = 7.5 Hz, 1H), 7.29 (app.t, *J* = 7.6 Hz, 1H), 7.14 (dd, *J* = 5.0, 7.2 Hz, 1H), 7.01 (s, 1H), 6.92 (app.t, *J* = 8.2 Hz, 1H), 6.92 (dd, *J* = 1.1, 8.4 Hz, 1H), 6.34 (br s, 1H), 4.98 (d, *J* = 17.9 Hz, 1H), 4.95 (d, *J* = 17.9 Hz, 1H), 4.84 (d, *J* = 15.1 Hz, 1H), 4.80 (d, *J* = 15.1 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.40 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.05 (dd, *J* = 4.8, 14.0 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.6, 168.9, 149.0, 148.2, 139.7, 136.8, 130.4, 126.2, 126.1, 125.4, 125.1, 124.9, 124.3, 122.0, 121.3, 120.2, 119.8, 119.2, 118.7, 116.3, 113.9, 113.8, 112.3, 112.1, 109.4, 99.3, 84.9, 84.8, 55.5, 52.4, 49.0, 45.4, 42.5, 22.8; high resolution mass spectrum (FAB) *m/z* 618.2240 [calcd for $C_{36}H_{32}N_3O_7$ (M+H) 618.2240].

Preparation of (+)-K252a (2).



(+)-**2**

(+)-K252a (2). To a stirred solution of indolocarbazole (+)-**147** (17.0 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (1.4 mL) at 25 °C was added thioanisole (0.16 mL, 1.36 mmol, 50 equiv) followed by 2,2,2-trifluoroacetic acid (1.4 mL). The solution was stirred for 6 h, followed by dropwise addition of 2.0 mL saturated $NaHCO_3$ solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH:CH_2Cl_2:hexanes, 3 elutions) to afford (+)-K252a [**2**, 10.8 mg, 84% yield] as a pale yellow solid: mp 264-267 °C (dec., acetone); $[\alpha]^{20}_D$ +40° (*c* 0.1, MeOH); IR (thin film/NaCl) 3309.6 (br m), 3053.5 (m), 2952.6 (m), 2851.9 (m), 1735.8 (s), 1675.4 (s), 1590.0 (m), 1458.6 (s), 1396.4 (m), 1313.7 (s), 1258.8 (m), 1138.8 (m), 877.3 (w) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.20 (d, *J* = 7.9 Hz, 1H), 8.63 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.47 (comp m, 2H), 7.35 (app.t, *J* = 7.4 Hz, 1H), 7.28 (app.t, *J* = 7.4 Hz, 1H), 7.14 (dd, *J* = 5.0, 7.2 Hz, 1H), 6.34 (s, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.92 (s, 3H), 3.38 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.01 (dd, *J* = 4.9, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.9, 171.8, 139.9, 136.8, 133.0, 128.3, 125.6, 125.4, 125.1, 124.2, 123.9, 122.6,

121.3, 120.4, 119.6, 119.5, 115.8, 114.8, 114.6, 109.1, 99.4, 85.0, 85.0, 52.7, 45.5, 42.5, 22.8; high resolution mass spectrum (FAB) *m/z* 468.1561 [calcd for $C_{27}H_{22}N_3O_5$ (M+H) 468.1559].

(+)-*nat*-K252a (2):[2] mp 262-273 °C (dec.); $[\alpha]^{20}_D$ +52° (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, *J* = 7.9 Hz, 1H), 8.64 (br s, 1H), 8.05 (d, 7.8H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.49 (br t, 1H), 7.49 (br t, 1H), 7.36 (br t, 1H), 7.29 (br t, 1H), 7.15 (dd, *J* = 4.9, 7.4 Hz, 1H), 5.04 (d, *J* = 17.3 Hz, 1H), 5.00 (d, *J* = 17.3 Hz, 1H), 3.94 (s, 3H), 3.41 (dd, *J* = 7.4, 14.0 Hz, 1H), 2.16 (s, 3H), 2.04 (dd, *J* = 4.9, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 171.7, 139.8, 136.8, 132.9, 128.3, 125.6, 125.4, 125.0, 124.1, 123.9, 122.6, 121.2, 120.4, 119.5, 119.4, 115.8, 114.7, 114.6, 109.0, 99.3, 85.0, 84.9, 52.6, 45.4, 42.5, 22.8.

2.7 Notes and References.

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([15]) Protected glycine esters **138b-e** were prepared according to known literature procedures, see: a) Mannich, C.; Kuphal, R. *Chem. Ber*. **1912**, *45*, 314. b) Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225.

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([18]) In the actual course of events, these studies paralleled our efforts to optimize the preparation of aglycons **4a-e**.

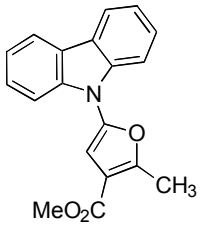
([19]) The stereochemical assignment was initially based on the chemical shift similarities of the methyl ester singlet. McCombie has reported a 0.5 ppm chemical shift difference in the ^{1}H-NMR between α and β ester signals in

ester **112**; however, no such difference was observed in indolocarbazoles **147** and **148**.

([20]) Ultimately, the regio- and stereochemical outcome of the cycloglycosidation was deduced from the fact that the major isomer produces the natural product.

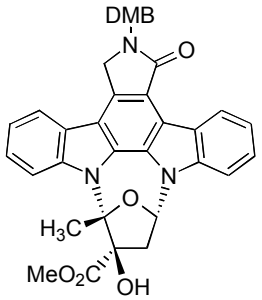
([21]) The regioisomeric nature of intermediates (±)-**145** and (±)-**146** was determined based on the characteristic free N-H chemical shift difference in the ^{1}H-NMR.

([22]) Initially, attempts to cycloglycosidate aglycon **4c** with acetates (±)-**144a,b** failed. This result was clarified upon isolation of furan **i** in 53% yield following reaction of carbazole **131** with acetates (±)-**144a,b**.



i

([23]) Of particular importance to this issue is the stability of the unobserved diastereomer (i.e., **ii**) to the reaction conditions. Unfortunately, the stereoselectivity observed in this reaction made this question impossible to address. However, in a closely related model system the corresponding diastereomer proved stable to these conditions (see Chapter 3).



ii

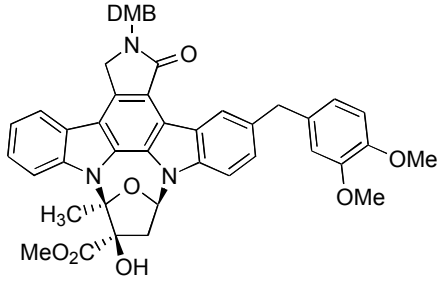
([24]) Aglycons **4b**,**4d**, and **4e** could be cycloglycosidated with similar results, however only the products arising from **4d** were successfully deprotected.

([25]) Weygand, F.; Steglich, W.; Bjarnason, J.; Akhtar, R.; Khan, N. M. *Tetrahedron Lett.* **1966**, *29*, 3483.

([26]) More recently, substituted benzyl amides have been utilized in the tirandamycin area and the 3,4-DMB group was successfully used in a synthesis of the tetrapyrrole pigment precursor porphobilinogen, see: a) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P. *J. Am. Chem. Soc.* **1985**, *107*, 1777. b) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5219. c) Jones, M. I.; Froussios, C.; Evans, D. A. *J. Chem. Soc., Chem. Comm.* **1976**, 472.

([27]) The well known tendency of indolocarbazoles to undergo Friedel-Crafts reactions necessitated using a large excess of scavenger. For examples of this Friedel-Crafts reactivity, see: a) Nakanishi, S.; Yamada, K.; Iwahashi, K.; Kuroda, K.; Kase, H. *Mol. Pharmacol*. **1990**, *37*, 482. b) Yamada, R.; Sasaki, K.; Ō mura, S. *Chem. Abstr.* **1991**, *115*, 92688.

([28]) In the absence of a cation scavenger an appreciable amount of indolocarbazole **iii** is formed along with (±)-K252a (**2**).



iii

([29]) We graciously thank the Bayer Corporation for a sample of *nat*-(+)-K252a.

([30]) For a recent example describing the use of RAMP and SAMP hydrazones in the alkylation of β-ketoesters, see: Enders, D.; Zamponi, A.; Schäfer, T.; Nübling, C.; Eichenauer, H.; Demir, A. S.; Raabe, G. *Chem. Ber.* **1994**, *127*, 1707.

([31]) Several excellent reviews have appeared, see: a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

([32]) For a recent review of the [2,3]-Wittig rearrangement, see: Nakai, T.; Mikami, K. *Organic Reactions* **1994**, *46*, 105.

([33]) The Sharpless kinetic resolution protocol provides a convenient means of accessing a variety of allylic alcohols of very high optical purity, see: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

([34]) a) Koreeda, M.; Luengo, J. *J. Am. Chem. Soc.* **1985**, *107*, 5572. b) Examples of both [2,3]- and [3,3]-rearrangement of α-allyloxy ketones have been reported, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423 and references therein.

([35]) For a leading reference to the Lewis acid catalyzed α-ketol rearrangement, see: Crout, D. H. G.; Rathbone, D. L. *J. Chem. Soc., Chem. Commun.* **1987**, 290.

([36]) This material was prepared from *S*-(-)-ethyl lactate, see: Klingler, F. D.; Psiorz, M. German Patent DE-4219510-C1, 1993. Mosher ester analysis (500 MHz ^{1}H NMR) of derived allylic alcohol establish an optical purity of 98% ee.

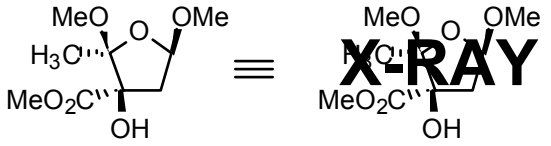
([37]) The dramatic increase in yield over the two step procedure is attributed to the difficulties of isolating the somewhat volatile intermediate ketone (+)-**155**.

([38]) These studies were performed simultaneously in the racemic series.

([39]) Triol **156** has been prepared previously from citramalic acid and is of known absolute configuration, see: Gill, M.; Smrdel, A. F. *Tetrahedron Asymmetry* **1990**, *1*, 453.

([40]) Diester **160** has been prepared previously and is of known absolute stereochemistry, see: Spencer, H. K.; Khatri, H. N.; Hill. R. K. *Bioorganic Chem.* **1976**, *5*, 177.

([41]) Upon large scale preparation of (-)-**97** a third furanose diastereomer (**iv**) was detected as a minor by-product. The structure of **iv** was unambiguously assigned by X-ray analysis.



iv

([42]) Still, W. C.; Kahn, M.; Nitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

([43]) The material obtained proved identical to a sample purchased from Aldrich chemical company.

([44]) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. J. Org. Chem. **1992**, *57*, 2105.

APPENDIX ONE: SYNTHETIC SUMMARY FOR K252c (4a) AND (+)-K252a (2)

Figure A.1.1 The Synthesis of K252c (**4a**) and Aglycon **4c**.

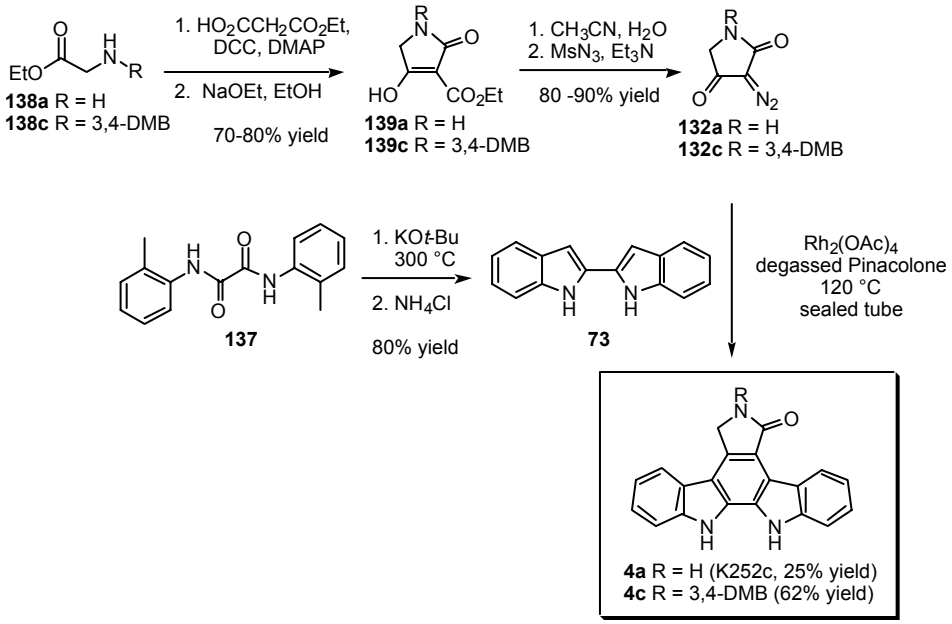
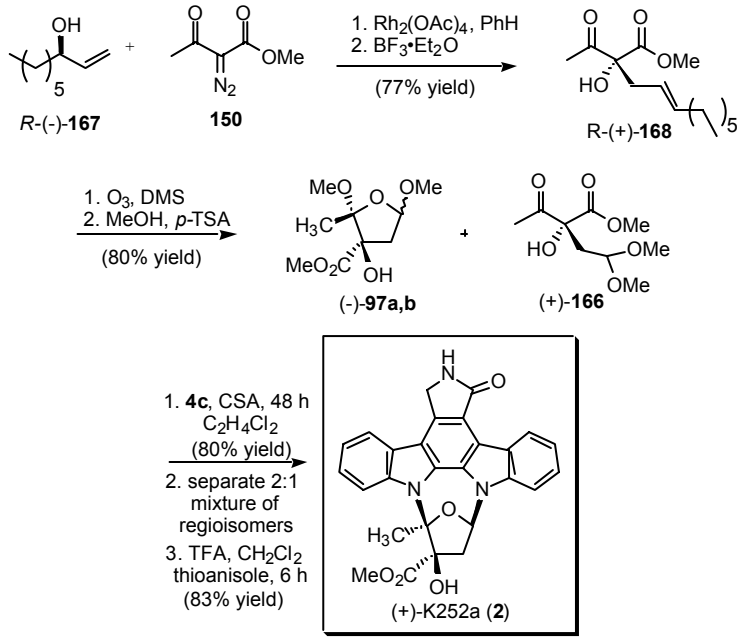
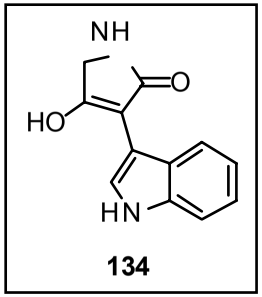


Figure A.1.2 The Synthesis of (+)-K252a (**2**).



APPENDIX TWO: SPECTRA RELEVANT TO CHAPTER TWO

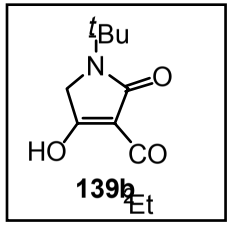


134

Figure A.2.1

Figure A.2.2 Infrared Spectrum (thin film/NaCl) of compound **134.**

Figure A.2.3 ^{13}C NMR (62.5 MHz, DMSO-d_6) of compound **134**.

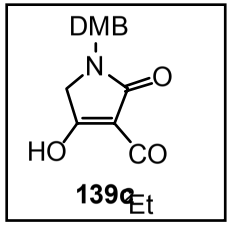


139b

Figure A.2.4

Figure A.2.5 Infrared Spectrum (thin film/NaCl) of compound **139b.**

Figure A.2.6 ^{13}C NMR (125 MHz, DMSO-d_6, 305 K) of compound **139b**.

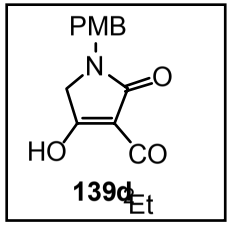


139c

Figure A.2.7

Figure A.2.8 Infrared Spectrum (thin film/NaCl) of compound **139c.**

Figure A.2.9 ^{13}C NMR (125 MHz, DMSO-d_6) of compound **139c**.

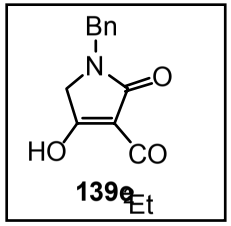


139d

Figure A.2.10

Figure A.2.11 Infrared Spectrum (thin film/NaCl) of compound **139d.**

Figure A.2.12 ^{13}C NMR (125 MHz, DMSO-d_6) of compound **139d**.

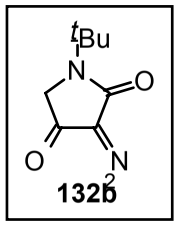


139e

Figure A.2.13

Figure A.2.14 Infrared Spectrum (thin film/NaCl) of compound **139e.**

Figure A.2.15 ^{13}C NMR (125 MHz, DMSO-d_6) of compound **139e**.

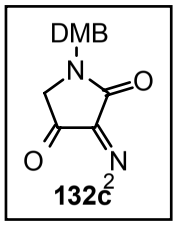


132b

Figure A.2.16

Figure A.2.17 Infrared Spectrum (CCl_4) of compound **132b.**

Figure A.2.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **132b**.

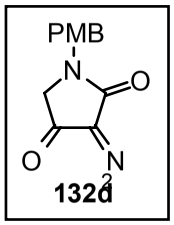


132c

Figure A.2.19

Figure A.2.20 Infrared Spectrum (CCl_4) of compound **132c.**

Figure A.2.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **132c**.

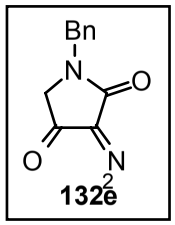


132d

Figure A.2.22

Figure A.2.23 Infrared Spectrum (CCl_4) of compound **132d.**

Figure A.2.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **132d**.

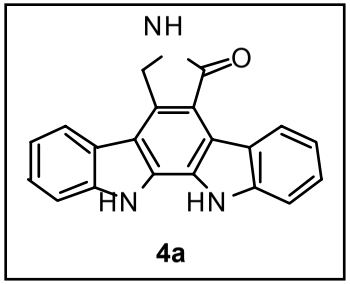


132e

Figure A.2.25

Figure A.2.26 Infrared Spectrum (CCl_4) of compound **132e.**

Figure A.2.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **132e**.

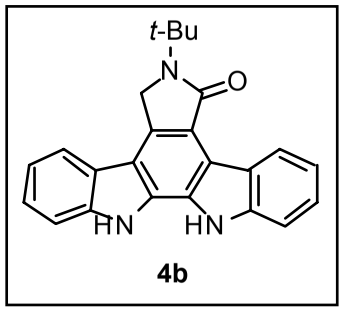


4a

Figure A.2.28

Figure A.2.29 Infrared Spectrum (thin film/NaCl) of compound **4a.**

Figure A.2.30 ^{13}C NMR (125 MHz, DMSO-d_6) of compound **4a**.

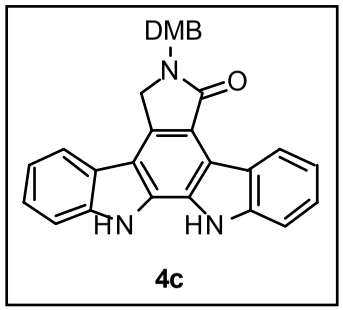


4b

Figure A.2.31

Figure A.2.31 Infrared Spectrum (thin film/NaCl) of compound **4b.**

Figure A.2.33 ^{13}C NMR (62.5 MHz, DMSO-d_6) of compound **4b**.

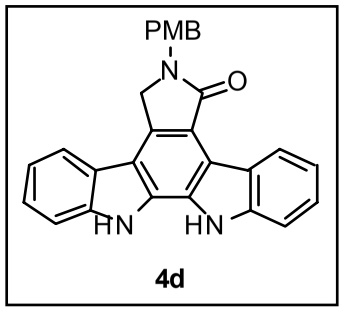


4c

Figure A.2.34

Figure A.2.35 Infrared Spectrum (thin film/NaCl) of compound **4c.**

Figure A.2.36 ^{13}C NMR (62.5 MHz, DMSO-d_6) of compound **4c**.

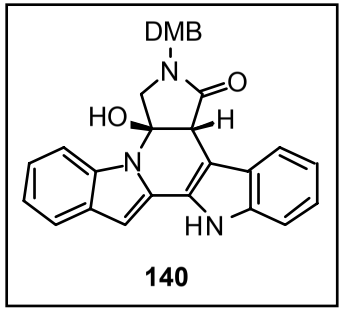


4d

Figure A.2.37

Figure A.2.38 Infrared Spectrum (thin film/NaCl) of compound **4d.**

Figure A.2.39 ^{13}C NMR (62.5 MHz, DMSO-d_6) of compound **4d**.

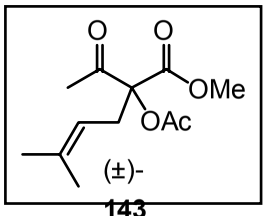


140

Figure A.2.40

Figure A.2.41 Infrared Spectrum (thin film/NaCl) of compound **140.**

Figure A.2.42 ^{13}C NMR (125 MHz, acetone-d_6) of compound **140**.

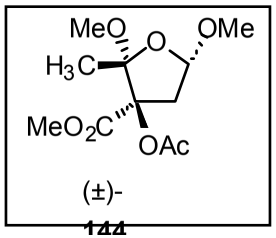


(±)-**143**

Figure A.2.43

Figure A.2.44 Infrared Spectrum (thin film/NaCl) of compound (±)-**143.**

Figure A.2.45 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**143**.



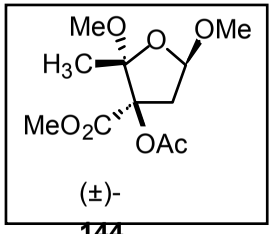
(±)-

144

Figure A.2.46

Figure A.2.47 Infrared Spectrum (thin film/NaCl) of compound (±)-**144a.**

Figure A.2.48 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**144a**.



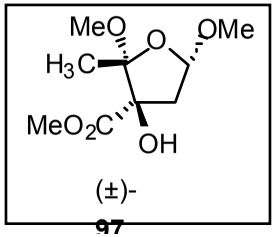
(±)-

144

Figure A.2.49

Figure A.2.50 Infrared Spectrum (thin film/NaCl) of compound (±)-**144b.**

Figure A.2.51 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**144b**.



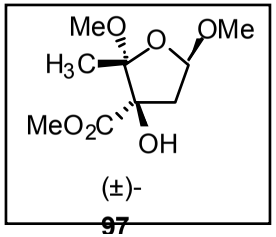
(±)-

97

Figure A.2.52

Figure A.2.53 Infrared Spectrum (thin film/NaCl) of compound (±)-**97a.**

Figure A.2.54 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**97a**.



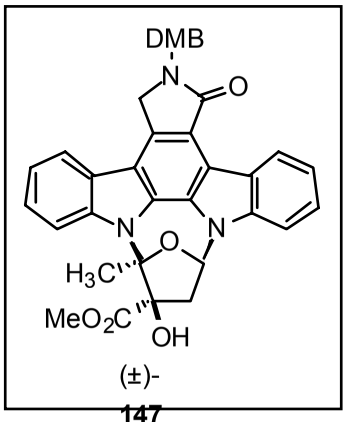
(±)-

97

Figure A.2.55

Figure A.2.56 Infrared Spectrum (thin film/NaCl) of compound (±)-**97b.**

Figure A.2.57 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**97b**.



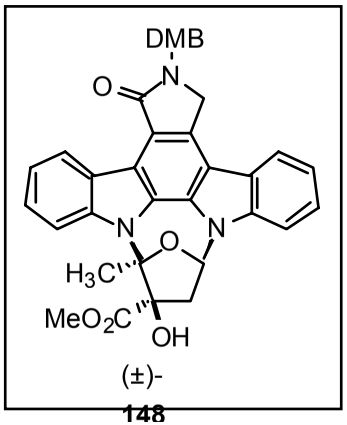
(±)-

147

Figure A.2.58

Figure A.2.59 Infrared Spectrum (thin film/NaCl) of compound (±)-**147.**

Figure A.2.60 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**147**.



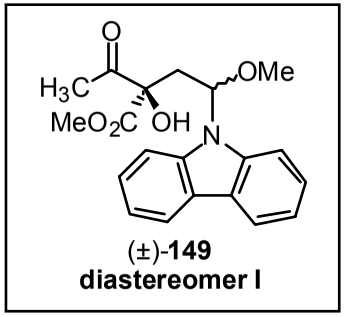
(±)-

148

Figure A.2.61

Figure A.2.62 Infrared Spectrum (thin film/NaCl) of compound (±)-**148.**

Figure A.2.63 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**148**.

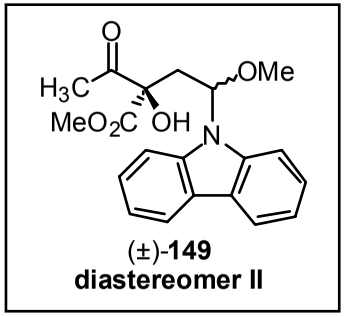


(±)-**149**
diastereomer I

Figure A.2.64

Figure A.2.65 Infrared Spectrum (thin film/NaCl) of compound (±)-**149.**

Figure A.2.66 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**149**.

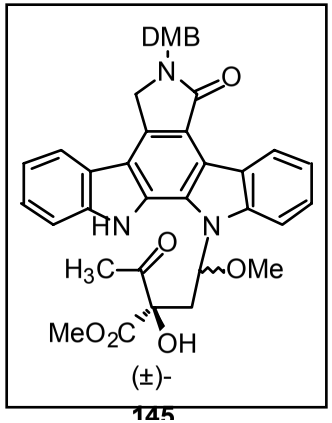


(±)-**149**
diastereomer II

Figure A.2.67

Figure A.2.68 Infrared Spectrum (thin film/NaCl) of compound (±)-**149.**

Figure A.2.69 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**149**.



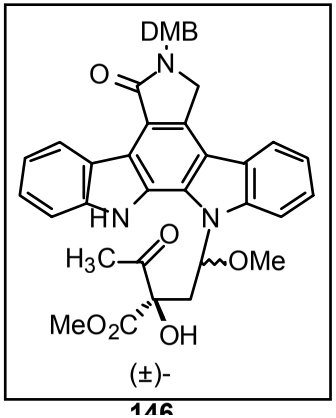
(±)-

145

Figure A.2.70

Figure A.2.71 Infrared Spectrum (thin film/NaCl) of compound (±)-**145.**

Figure A.2.72 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**145**.



(±)-

146

Figure A.2.73

Figure A.2.74 Infrared Spectrum (thin film/NaCl) of compound (±)-**146.**

Figure A.2.75 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**146**.

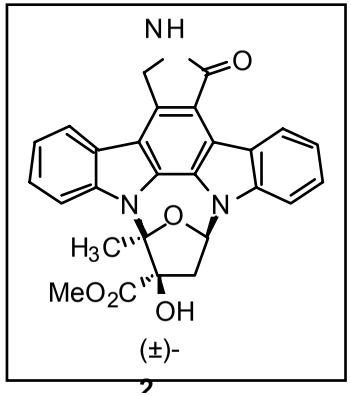
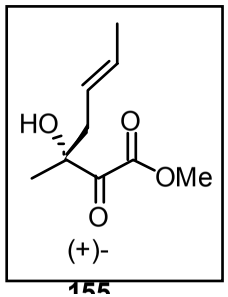


Figure A.2.76

Figure A.2.77 Infrared Spectrum (thin film/NaCl) of compound (±)-**2.**

Figure A.2.78 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**2**.



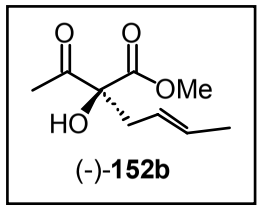
(+)-

155

Figure A.2.79

Figure A.2.80 Infrared Spectrum (thin film/NaCl) of compound (+)-**155.**

Figure A.2.81 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**155**.

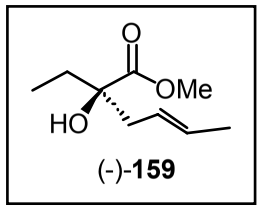


(-)-**152b**

Figure A.2.82

Figure A.2.83 Infrared Spectrum (thin film/NaCl) of compound (-)-**152b.**

Figure A.2.84 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**152b.**



(-)-**159**

Figure A.2.85

Figure A.2.86 Infrared Spectrum (thin film/NaCl) of compound (-)-**159.**

Figure A.2.87 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**159.**

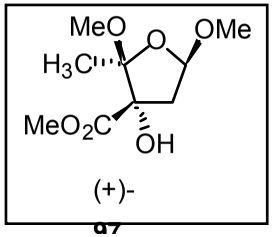
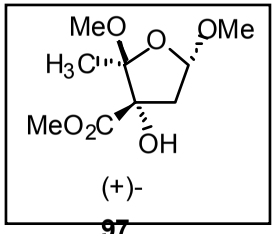


Figure A.2.88

Figure A.2.89 Infrared Spectrum (thin film/NaCl) of compound (+)-**97a.**

Figure A.2.90 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**97a**.



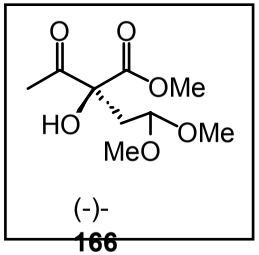
(+)-

97

Figure A.2.91

Figure A.2.92 Infrared Spectrum (thin film/NaCl) of compound (+)-**97b.**

Figure A.2.93 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**97b**.

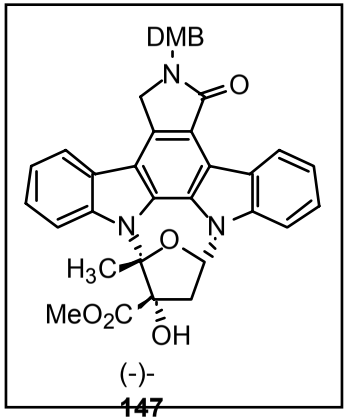


(-)-
166

Figure A.2.94

Figure A.2.95 Infrared Spectrum (thin film/NaCl) of compound (-)-**166.**

Figure A.2.96 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**166**.

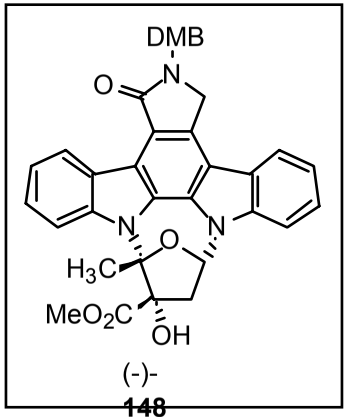


(-)-
147

Figure A.2.97

Figure A.2.98 Infrared Spectrum (thin film/NaCl) of compound (-)-**147.**

Figure A.2.99 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (-)-**147**.

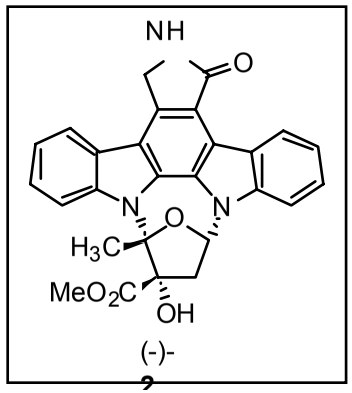


(-)-
148

Figure A.2.100

Figure A.2.101 Infrared Spectrum (thin film/NaCl) of compound (-)-**148.**

Figure A.2.102 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (-)-**148**.

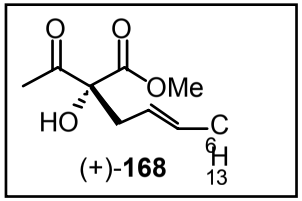


(-)-

Figure A.2.103

Figure A.2.104 Infrared Spectrum (thin film/NaCl) of compound (-)-**2.**

Figure A.2.105 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (-)-**2**.

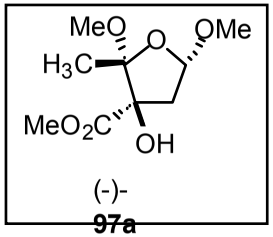


(+)-**168**

Figure A.2.106

Figure A.2.107 Infrared Spectrum (thin film/NaCl) of compound (+)-**168.**

Figure A.2.108 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**168.**

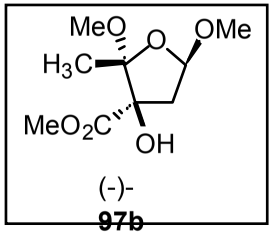


(-)-
97a

Figure A.2.109

Figure A.2.110 Infrared Spectrum (thin film/NaCl) of compound (-)-**97a.**

Figure A.2.111 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**97a**.

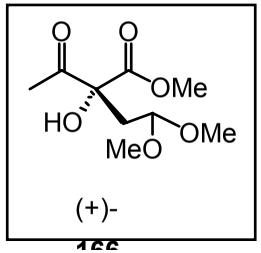


(-)-
97b

Figure A.2.112

Figure A.2.113 Infrared Spectrum (thin film/NaCl) of compound (-)-**97b.**

Figure A.2.114 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**97b**.



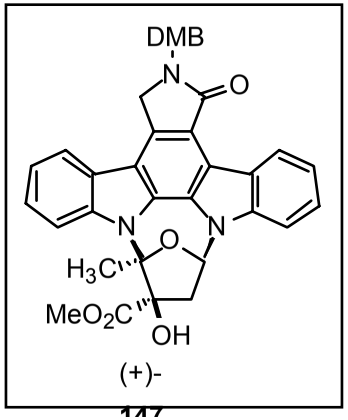
(+)-

166

Figure A.2.115

Figure A.2.116 Infrared Spectrum (thin film/NaCl) of compound (+)-**166.**

Figure A.2.117 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**166**.



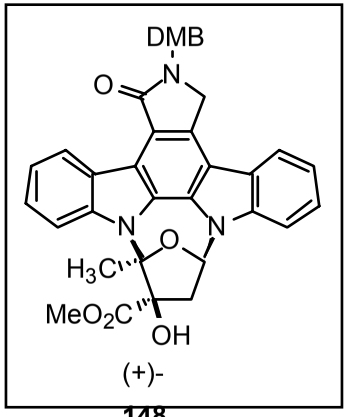
(+)-

147

Figure A.2.118

Figure A.2.119 Infrared Spectrum (thin film/NaCl) of compound (+)-**147.**

Figure A.2.120 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**147**.



(+)-

148

Figure A.2.121

Figure A.2.122 Infrared Spectrum (thin film/NaCl) of compound (+)-**148.**

Figure A.2.123 ^{13}C NMR (62.5 MHz, DMSO-d_6) of compound (+)-**148**.

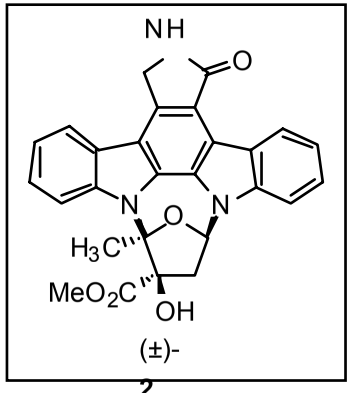


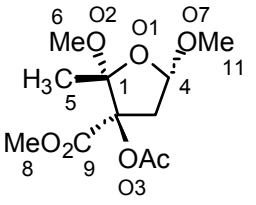
Figure A.2.124

Figure A.2.125 Infrared Spectrum (thin film/NaCl) of compound (+)-**2.**

Figure A.2.126 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**2**.

APPENDIX THREE: X-RAY CHRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER TWO

X-RAY CHRYSTALLOGRAPHY REPORT FOR FURANOSE (±)-**144a**



(X-ray Numbering)

≡

(±)-**144a**

A. Crystal Data

Empirical Formula.....$C_{11}H_{18}O_7$

Formula Weight 262.26

Crystal Color/Habit .....colorless plate

Crystal Dimensions (mm) .....0.10 X 0.18 X 0.22

Crystal System .....monoclinic

No. Reflections Used for Unit

Cell Determination (2_ range).....25(15.4 - 20.7°)

Omega Scan Peak Width

at Half-height 0.21

Lattice Parameters:

a .....7.752 (5)Å

b .....21.447 (4)Å

c .....8.243 (3)Å

ß .....104.88 (4)°

V .....1325 (1)Å^3

Space Group .....$P2_1/a$ (#14)

Z value.....4

Dcalc ..... 1.315 g/cm^3

F000 560

μ(MoKα) 1.03 cm-1

B. Intensity Measurements

Diffractometer ..... Rigaku AFC5S

Radiation ..... MoKα (λ= 0.71069 Å)

Temperature ..... 23 °C

Attenuators ..... Zr foil (factors: 2.3, 5.3, 11.7)

Take-off Angle ..... 6.0°

Detector Aperture ..... 6.0 mm hor./6.0 mm vert.

Crystal to Detector Distance ..... 285 mm

Scan Type ω-2θ

Scan Rate ..... 6.0°/min in ω (2 rescans)

Scan Width ..... (1.57 + 0.30 tanθ)°

2θmax ..... 50.0°

No. of Reflections Measured:

Total : 2599

Unique: ..... 2417 (Rint = .046)

Corrections ..... Lorentz-polarization

Decay (-7.60% decline)

C. Structure Solution and Refinement

Structure Solution ..... Direct Methods

Refinement ..... Full-matrix least-squares

Function Minimized ..... $\sum w (|Fo| - |Fc|)^2$

Least-squares Weights ..... $4Fo^2/s^2(Fo^2)$

p-factor 0.03

Anomalous Dispersion ..... All non-hydrogen atoms

No. Observations (I>3.00s(I)) 884

No. Variables 163

Reflection/Parameter Ratio.....5.42

Residuals: R; Rw 0.042; 0.046

Goodness of Fit Indicator 1.38

Max Shift/Error in Final Cycle 0.00

Maximum Peak in Final Diff. Map ..... 0.16 e-/Å^3

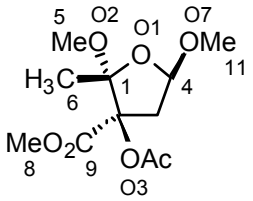
Minimum Peak in Final Diff. Map .....-0.16 e-/Å^3

Positional parameters and B(eq) for furanose (±)-**144a**

atom	x	y	z	B(eq)
O1	0.1039(4)	0.0971(1)	0.1315(4)	3.7(1)
O2	0.3557(4)	0.0683(1)	0.0421(4)	4.1(2)
O3	0.3498(4)	0.1393(2)	0.4305(4)	3.6(1)
O4	0.5196(5)	0.2250(2)	0.4962(4)	5.5(2)
O5	0.6482(4)	0.1639(2)	0.1791(4)	5.1(2)
O6	0.6719(4)	0.1021(2)	0.4028(4)	4.2(2)
O7	0.0336(4)	0.1724(2)	-0.0825(4)	4.9(2)
C1	0.2843(6)	0.0780(2)	0.1818(6)	3.5(2)
C2	0.3819(6)	0.1380(2)	0.2645(5)	3.0(2)
C3	0.2792(6)	0.1884(2)	0.1527(6)	4.0(2)
C4	0.0924(6)	0.1625(2)	0.0902(6)	3.6(2)
C5	0.2976(7)	0.0211(2)	0.2917(6)	4.8(3)
C6	0.2607(8)	0.0251(3)	-0.0811(7)	6.2(3)

C7	0.4271(7)	0.1864(3)	0.5341(6)	4.2(3)
C8	0.3765(7)	0.1817(3)	0.6978(7)	5.9(3)
C9	0.5822(6)	0.1373(2)	0.2758(6)	3.6(2)
C10	0.8639(6)	0.1001(3)	0.4247(7)	5.6(3)
C11	-0.1523(8)	0.1593(3)	-0.1459(7)	6.0(3)
H1	0.2780	0.2258	0.2144	4.7
H2	0.3300	0.1965	0.0615	4.7
H3	0.0145	0.1827	0.1455	4.4
H4	0.2582	0.0312	0.3885	5.8
H5	0.2248	-0.0112	0.2309	5.8
H6	0.4181	0.0074	0.3248	5.8
H7	0.1411	0.0389	-0.1229	7.4
H8	0.3167	0.0227	-0.1708	7.4
H9	0.2614	-0.0149	-0.0313	7.4
H10	0.4296	0.2150	0.7692	7.0
H11	0.2504	0.1840	0.6776	7.0
H12	0.4174	0.1431	0.7502	7.0
H13	0.9167	0.0739	0.5169	6.7
H14	0.8891	0.0842	0.3257	6.7
H15	0.9115	0.1410	0.4459	6.7
H16	-0.2195	0.1867	-0.0954	7.2
H17	-0.1857	0.1651	-0.2642	7.2
H18	-0.1753	0.1174	-0.1204	7.2

X-RAY CHRYSTALLOGRAPHY REPORT FOR FURANOSE (±)-**144b**



(X-ray Numbering)

≡

(±)-**144b**

A. Crystal Data

Empirical Formula.....$C_{11}H_{18}O_7$

Formula Weight 262.26

Crystal Color/Habit ..... colorless cut block

Crystal Dimensions (mm) .....0.38 X 0.40 X 0.45

Crystal System .....monoclinic

No. Reflections Used for Unit

Cell Determination (2_ range).....8(16.7 - 21.8°)

Omega Scan Peak Width

at Half-height 0.20

Lattice Parameters:

a .....8.625 (3)Å

b .....22.44 (1)Å

c .....8.157 (2)Å

ß .....118.87 (2)°

V .....1382 (2)Å^3

Space Group .....$P2_1/a$ (#14)

Z value.....4

Dcalc ..... 1.260 g/cm^3

F000 560

μ(MoKα) 0.99 cm-1

B. Intensity Measurements

Diffractometer ..... Rigaku AFC5S

Radiation ..... MoKa (λ = 0.71069 Å)

Temperature ..... 23 °C

Attenuators ..... Zr foil (factors: 2.3, 5.3, 11.7)

Take-off Angle ..... 6.0°

Detector Aperture ..... 6.0 mm hor./6.0 mm vert.

Crystal to Detector Distance ..... 285 mm

Scan Type ω-2θ

Scan Rate ..... 8.0°/min in ω (2 rescans)

Scan Width ..... (1.68 + 0.30 tanθ)°

2θmax ..... 49.8°

No. of Reflections Measured:

Total 4006

Unique: ..... 1914 (Rint = .060)

Corrections ..... Lorentz-polarization

Decay (-55.00% decline)

C. Structure Solution and Refinement

Structure Solution ..... Direct Methods

Refinement ..... Full-matrix least-squares

Function Minimized ..... $\sum w (|Fo| - |Fc|)^2$

Least-squares Weights ..... $4Fo^2/\sigma^2(Fo^2)$

p-factor 0.03

Anomalous Dispersion ..... All non-hydrogen atoms

No. Observations (I>3.00s(I)) 1136

No. Variables 163

Reflection/Parameter Ratio.....6.97

Residuals: .....R; Rw 0.055; 0.065

Goodness of Fit Indicator 2.36

Max Shift/Error in Final Cycle 0.00

Maximum Peak in Final Diff. Map ..... 0.40 e-/Å^3

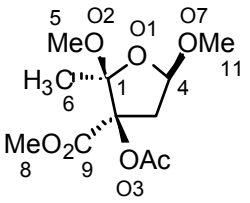
Minimum Peak in Final Diff. Map .....-0.28 e-/Å^3

Positional parameters and B(eq) for furanose (±)-**144b**

atom	x	y	z	B(eq)
O1	0.1799(3)	0.6087(1)	-0.0760(4)	3.9(1)
O2	0.4497(4)	0.5739(1)	0.1627(3)	3.9(1)
O3	0.3938(3)	0.6817(1)	-0.1812(4)	3.8(1)
O4	0.5464(5)	0.6648(2)	-0.3393(5)	5.5(2)
O5	0.7139(4)	0.5665(2)	0.0072(5)	5.6(2)
O6	0.7313(4)	0.6623(2)	0.0910(4)	5.0(1)
O7	0.0270(4)	0.5902(1)	-0.3940(4)	4.7(1)
C1	0.3606(5)	0.6218(2)	0.0424(5)	3.5(2)
C2	0.4416(5)	0.6238(2)	-0.0935(5)	3.1(2)
C3	0.3411(6)	0.5735(2)	-0.2282(5)	3.8(2)
C4	0.1643(5)	0.5702(2)	-0.2242(6)	3.6(2)
C5	0.3740(7)	0.5531(2)	0.2766(6)	5.3(2)
C6	0.3716(6)	0.6785(2)	0.1480(6)	4.8(2)

C7	0.4575(6)	0.6972(2)	-0.3007(6)	4.3(2)
C8	0.4014(8)	0.7593(3)	-0.3736(7)	6.2(3)
C9	0.6452(6)	0.6134(2)	0.0049(6)	4.1(2)
C10	0.9274(7)	0.6539(3)	0.1758(8)	7.4(3)
C11	-0.1452(7)	0.5760(3)	-0.4187(7)	7.3(3)
H1	0.3213	0.5824	-0.3507	4.6
H2	0.4043	0.5371	-0.1871	4.6
H3	0.1422	0.5304	-0.2012	4.3
H4	0.3736	0.5847	0.3539	6.4
H5	0.2560	0.5400	0.1979	6.4
H6	0.4426	0.5210	0.3529	6.4
H7	0.4923	0.6881	0.2289	5.7
H8	0.3165	0.7101	0.0615	5.7
H9	0.3129	0.6728	0.2199	5.7
H10	0.4461	0.7865	-0.2717	7.5
H11	0.4467	0.7692	-0.4556	7.5
H12	0.2758	0.7615	-0.4396	7.5
H13	0.9642	0.6224	0.2646	8.8
H14	0.9561	0.6443	0.0802	8.8
H15	0.9861	0.6896	0.2364	8.8
H16	-0.1584	0.5929	-0.3194	8.8
H17	-0.2333	0.5917	-0.5347	8.8
H18	-0.1578	0.5339	-0.4184	8.8

X-RAY CHRYSTALLOGRAPHY REPORT FOR FURANOSE (-)-**iv.**



(X-ray Numbering)

≡

iv

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula.....$C_9O_6H_{16}$

Formula Weight 220.22

Crystal Color/Habit ..... colorless cut block

Crystal Dimensions (mm) .....0.34 X 0.44 X 0.48

Crystal System .....triclinic

No. Reflections Used for Unit

Cell Determination (2θ range).....25(17.3 - 33.8°)

Omega Scan Peak Width at Half-height 0.22

Lattice Parameters:

a .....7.619 (8)Å

b .....9.66 (1)Å

c .....7.595 (8)Å

α .....91.3 (1)°

ß .....98.6 (1)°

γ.....99.24 (9)°

V.....545 (2)$Å^3$

Space Group .....P_{-1} (#2)

Z value 2

Dcalc ..... 1.342 g/cm^3

F000 236

μ(MoKα) 1.06 cm-1

B. Intensity Measurements

Diffractometer ..... Rigaku AFC5S

Radiation ..... MoKα (λ = 0.71069 Å)

Temperature ..... 23 °C

Attenuators ..... Zr foil (factors: 2.3, 5.3, 11.7)

Take-off Angle ..... 6.0°

Detector Aperture ..... 6.0 mm hor./6.0 mm vert.

Crystal to Detector Distance ..... 285 mm

Scan Type ω-2θ

Scan Rate ..... 8.0°/min in ω (2 rescans)

Scan Width ..... (1.68 + 0.30 tanθ)°

2θmax ..... 50.0°

No. of Reflections Measured

Total: 2069

Unique: ..... 1912 (Rint = .036)

Corrections ..... Lorentz-polarization

Decay (-15.00% decline)

C. Structure Solution and Refinement

Structure Solution ..... Direct Methods

Refinement ..... Full-matrix least-squares

Function Minimized ..... $\sum w (|Fo| - |Fc|)^2$

Least-squares Weights ..... $4Fo^2/\sigma^2(Fo^2)$

p-factor 0.02

Anomalous Dispersion.....All non-hydrogen atoms

No. Observations (I>3.00s(I)) 1377

No. Variables 200

Reflection/Parameter Ratio.....6.89

Residuals:.....R; Rw 0.038; 0.043

Goodness of Fit Indicator 2.01

Max Shift/Error in Final Cycle 0.00

Maximum Peak in Final Diff. Map ..... 0.18 e-/Å^3

Minimum Peak in Final Diff. Map .....-0.18 e-/Å^3

Positional parameters and B(eq) for furanose (-)-**iv**.

atom	x	y	z	B(eq)
O1	0.7759(2)	0.7060(1)	0.2591(2)	3.15(6)
O2	0.8680(2)	0.9476(1)	0.2391(2)	3.46(6)
O3	1.2136(2)	0.9218(2)	0.2951(2)	4.19(7)
O4	1.1137(2)	0.5579(2)	0.2443(2)	4.83(8)
O5	1.2615(2)	0.7218(2)	0.0928(2)	4.18(7)
O6	0.7471(2)	0.7810(2)	0.5486(2)	4.21(7)
C1	0.8948(3)	0.8113(2)	0.1882(3)	2.91(8)
C2	1.0833(3)	0.7997(2)	0.2951(3)	3.10(8)
C3	1.0350(3)	0.7611(3)	0.4778(3)	3.9(1)
C4	0.8369(3)	0.7002(3)	0.4472(3)	3.5(1)
C5	0.6925(4)	0.9798(3)	0.1801(5)	4.8(1)
C6	0.8694(4)	0.7869(3)	-0.0111(3)	3.7(1)

C7	1.1541(3)	0.6786(2)	0.2101(3)	3.3(1)
C8	1.3270(5)	0.6127(4)	-0.0001(5)	5.6(1)
C9	0.5627(5)	0.7261(5)	0.5454(5)	6.5(2)
H1	1.114(3)	0.698(2)	0.539(3)	4.1(5)
H2	1.055(3)	0.845(2)	0.555(3)	3.6(5)
H3	0.807(3)	0.599(2)	0.473(3)	4.0(5)
H4	0.679(4)	1.009(3)	0.068(5)	8(1)
H5	0.596(4)	0.909(3)	0.191(4)	7.2(8)
H6	0.676(4)	1.052(4)	0.256(4)	9(1)
H7	0.960(3)	0.853(2)	-0.060(3)	4.2(5)
H8	0.894(3)	0.691(3)	-0.047(3)	4.3(5)
H9	0.745(3)	0.797(2)	-0.060(3)	4.4(5)
H10	1.166(4)	0.984(3)	0.332(4)	6.7(8)
H11	1.219(4)	0.557(3)	-0.071(4)	7.3(8)
H12	1.409(5)	0.660(4)	-0.079(5)	11(1)
H13	1.391(6)	0.564(5)	0.086(6)	13(1)
H14	0.512(5)	0.786(4)	0.618(5)	10(1)
H15	0.497(5)	0.707(4)	0.429(6)	10(1)
H16	0.555(5)	0.633(4)	0.583(5)	12(1)

CHAPTER THREE

The Design and Implementation of an Efficient Synthetic Approach to Pyranosylated Indolocarbazoles: The Total Synthesis of (+)-RK286c, (+)-MLR-52, (+)-Staurosporine, and (-)-TAN-1030a.

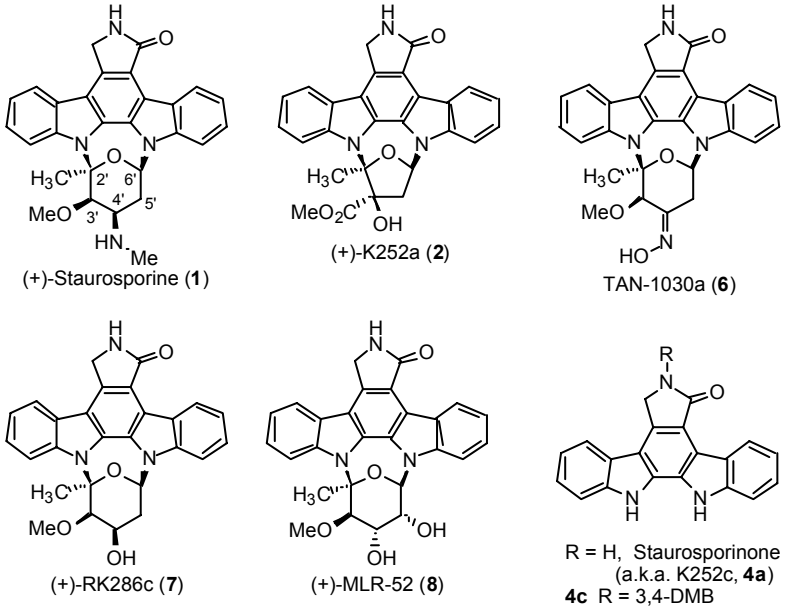
3.1 Background.

3.1.1 Introduction.

Having achieved the total synthesis of (+)-K252a (**2**) with remarkable efficiency (see Chapter 2), it was reasonable to consider extending the effort to the pyranosylated congeners illustrated in Figure 3.1.1 (i.e., **1** and **6**-**8**). The first and perhaps most notable pyranosylated indolocarbazole, staurosporine (**1**), was isolated from *streptomyces* sp. AM-2282 and subsequently found to affect a wide variety of biological functions.[1] Because of its challenging structure and the sheer notoriety of the molecule, **1** became the main focus; however, a number of other pyranosylated congeners were targeted with the hope of developing a general strategy for the synthesis of these alkaloids. Isolated In 1990, (+)-RK286c (**7**) was found to be a weak inhibitor of protein kinase C as compared to staurosporine (**1**) but comparable in its platelet aggregation inhibitory activity.[2] One year prior to this, TAN-1030a (**6**) was identified and shown to activate macrophage functions in mice.[3] Finally, in 1994 researchers at Abbott disclosed the isolation of the μM PKC inhibitor (+)-MLR-52 (**8**) and reported that it

possessed potent *in vitro* immunosuppressive activity (IC_{50} = 1.9±0.2 nM) similar to FK-506 (IC_{50} = 0.39±0.12 nM), cyclosporine (IC_{50} = 2.5±0.8 nM) and staurosporine (IC_{50} = 1.3±0.2 nM).[4]

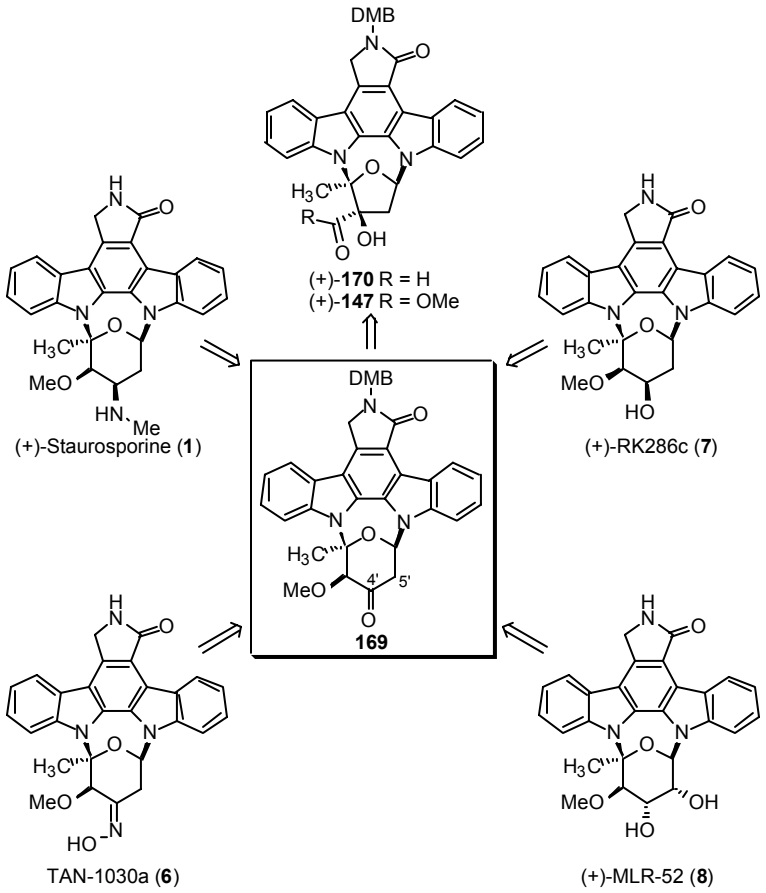
Figure 3.1.1



3.1.2 Retrosynthetic Analysis: The Development of a Ring Expansion Approach to the Pyranosylated Indolocarbazoles.

The notion of extending the K252a synthesis to staurosporine first arose upon discovering that the absolute stereochemistry at C(2') and C(5') in K252a was identical to that found in staurosporine's C(2') and C(6'). Given that cycloglycosidations akin to that employed in the synthesis of K252a (**2**) had failed in the pyranosylated series[5] and guided (or perhaps misguided) by the possible biosynthetic implications of converting a K252a congener to staurosporine, approaches were considered that involved the ring expansion of

Scheme 3.1.1



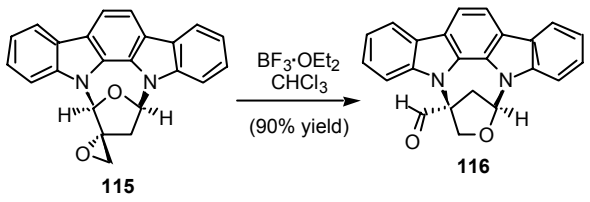
a furanosylated intermediate. Noting the striking structural homology of pyranosylated indolocarbazoles **1** and **6-8**, a strategy was envisioned that would allow access to these congeners via a common intermediate. Specifically, α-methoxy ketone **169** was viewed as an ideal intermediate wherein the stereogenic centers common among **1** and **6**-**8** are in place and flexibility for stereocontrolled functionalization at C(4') and C(5') is maintained (Scheme 3.1.1). Thus, reduction of ketone **169** at C(4') from the convex face would provide RK286c (**7**), reductive amination would produce staurosporine (**1**), and β-elimination of either a C(4')-amine (via Cope elimination) or -hydroxyl (via Martin's sulfurane or Burgess dehydration) followed by dihydroxylation would produce MLR-52 (**8**). Furthermore, conversion of ketone **169** to the corresponding oxime would lead to TAN-1030a (**6**). Critical to the development

of this approach was the recognition that ketone **169** might be accessed from aldehyde **170** via a Tiffaneu-Demyanov like ring expansion (Scheme 3.1.1). Aldehyde **170** was in turn envisioned to be readily available via reduction of ester (+)-**147**, the penultimate intermediate in the synthesis of K252a.

3.1.3 Regio- and Stereochemical Issues of Ring Expansion.

In designing this ring expansion approach, issues of regio- and stereochemical outcome were considered as well as the known propensity of similar systems to undergo skeletal rearrangement (i.e., **115**→**116**, Scheme 3.1.2).[5] As shown in Scheme 3.1.3, the planned ring expansion could occur

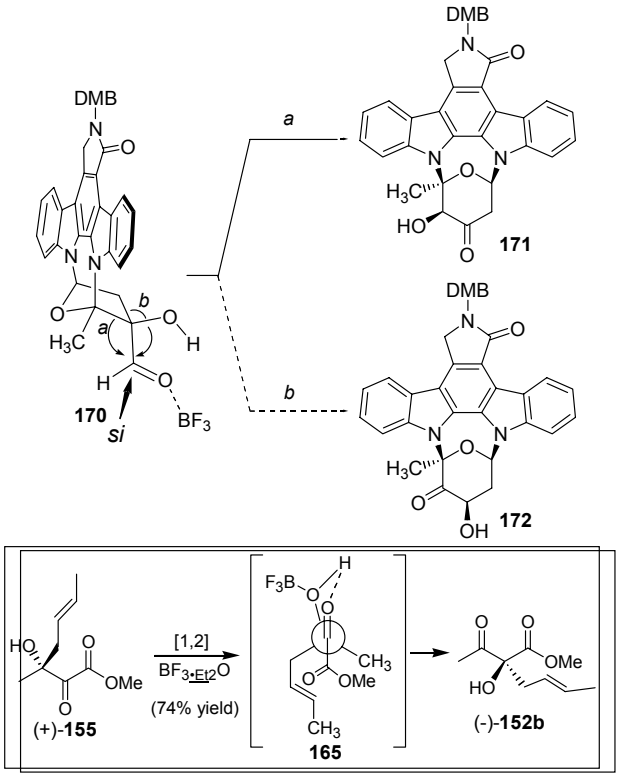
Scheme 3.1.2



with migration of either bond *a* or bond *b* of aldehyde **170** to produce regioisomeric hydroxy ketones **171** or **172**, respectively. Reasoning that bond *a*, being the more substituted linkage, would have a higher migratory aptitude, production of ketone **171** was anticipated. In addition, it was postulated that the stereochemical outcome, that is migration of bond *a* to either the *re* or *si* face of the aldehyde, would be in accord with that observed in the α-ketol rearrangement of ketoalcohol **155** wherein a syn-periplanar orientation of the hydroxyl and carbonyl oxygens was shown to be operative (e.g., **155**→**165**→**152b**). Thus, bond *a* was expected to migrate to the si face of the aldehyde producing a

product (**171**) which possesses both the regio- and stereochemistry needed for further advancement to staurosporine.

Scheme 3.1.3



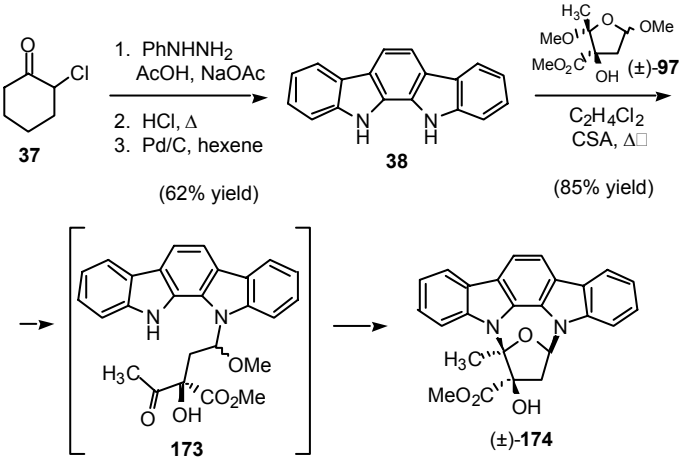
3.2 Ring Expansion-Model Studies.

3.2.1 Preparation of Desamido K252a (174) and Diastereomer 178.

3.2.1.1 Synthesis of Indolo[2,3-a]carbazole.

Given that the optimization of the production of protected aglycon **4c** was still in progress, ring expansion efforts were initiated in a model system wherein indolo[2,3-a]carbazole (**38**) replaced **4c**. This indolocarbazole core was readily prepared by slight modification of the known procedures (Scheme 3.2.1) which allowed easy preparation on large scale (10 g of **38** produced in a single run).[6]

Scheme 3.2.1

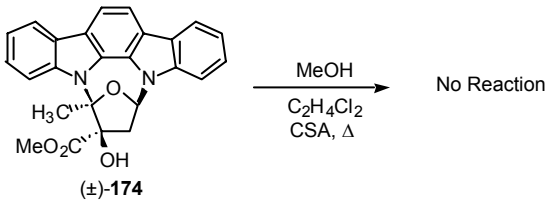


3.2.1.2 Glycosidation Studies.

Importantly, bis-cycloglycosidative coupling of aglycon **38** to furanose (±)-**97** (CSA,$C_2H_4Cl_2$, 86 °C)[7] proved highly stereoselective, producing furanosylated indolocarbazole (±)-**174** as the only isolable product in 85% yield. As in previous studies using aglycon **4c** as substrate, the reaction proceeded through an

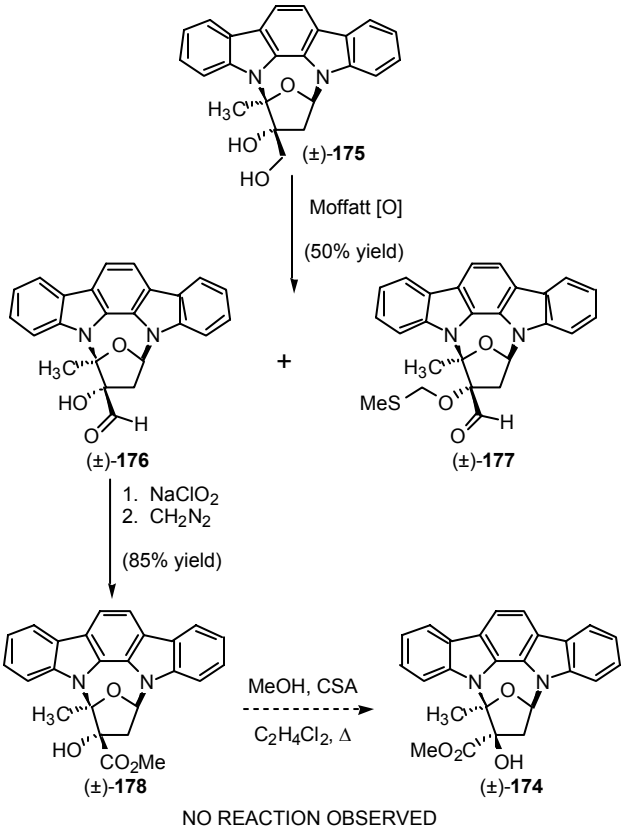
inseparable mixture of diastereomeric mono-aminoacetals (**173**), and the product (**174**) proved stable upon reexposure to glycosylation conditions wherein MeOH is added in place of furanose (±)-**97**.

Scheme 3.2.2



Although the irreversibility of this reaction suggested that the observed stereoselectivity results from a kinetic preference, definitive proof of this required independent preparation of the unobserved diastereomer [(±)-**178**]. The latter was readily accessed with aid from the McCombie group at Schering-Plough who provided a sample of diol (±)-**175**, a precursor to this product. Exposure of (±)-**175** to Moffatt oxidation[8] produced aldehyde (±)-**176** and the corresponding MTM-ether (±)-**177**. The former was converted to ester (±)-**178** via chlorite oxidation and methylation (CH_2N_2).[9] As with (±)-**174**, isomeric ester (±)-**178** proved stable to the conditions of glycosidation in the presence of added furanose [(±)-**97**] or MeOH; thus, if an appreciable amount of isomer **178** had been formed in the coupling of aglycon **38** with carbohydrate **97**, it would have been observed.

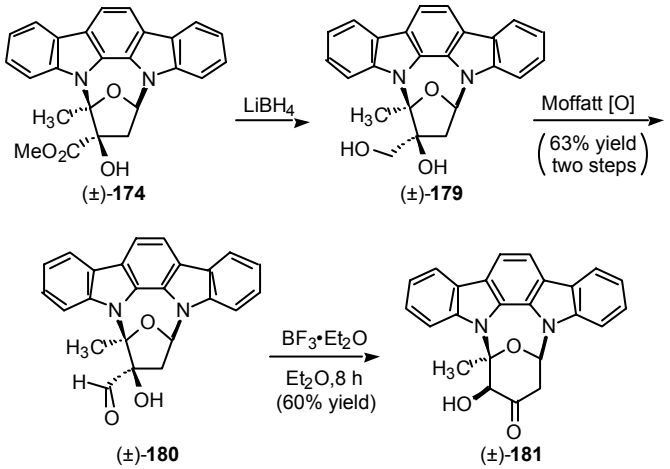
Scheme 3.2.3



3.2.2 Ring Expansion of Aldehyde (±)-180.

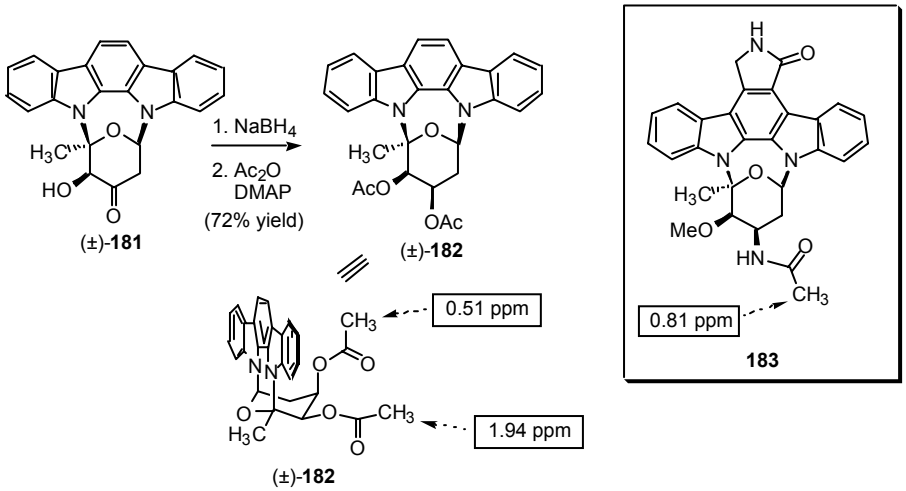
Having explored the preparation of indolocarbazole (±)-**174** in some detail, the stage was set for ring expansion by conversion of ester (±)-**174** to aldehyde (±)-**180** via a two-step protocol involving $LiBH_4$ reduction and Moffatt oxidation (63% yield, two steps). Upon exposure to BF_3•OEt_2 in Et_2O, the derived aldehyde [(±)-**180**] underwent slow conversion to a single new product that was found to be spectroscopically accordant with ketone (±)-**181**. Further structural proof was obtained by the ^{1}H-NMR chemical shift difference of the

Scheme 3.2.4



C(3') and C(4') acetate methyl groups in diacetate (±)-**182**, obtained from ketone (±)-**181** by reduction with $NaBH_4$ followed by treatment with Ac_2O and DMAP. The dramatic shielding of the C(4') acetate is analogous to that observed by Tsubotani for acetamide **183**,[3a] and is consistent with a chair conformation wherein the C(4') substituent resides in the axial position and is proximal to the aromatic heterocycle (see Scheme 3.2.5).

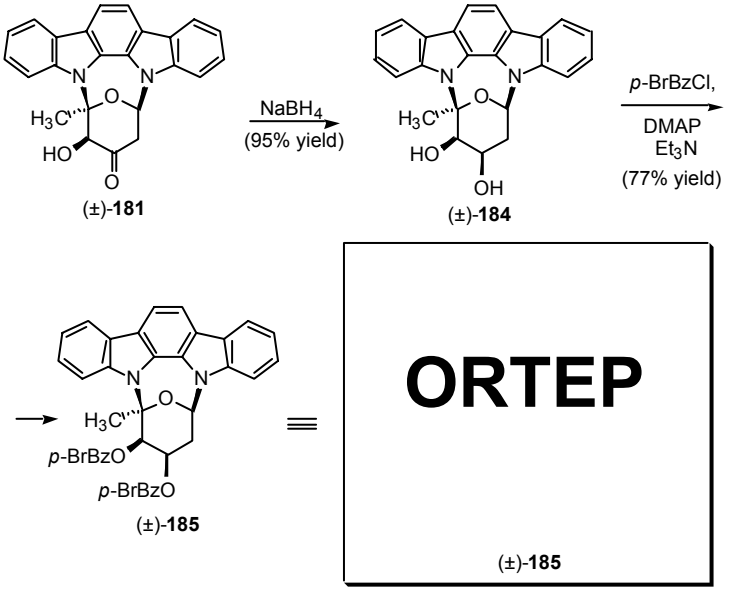
Scheme 3.2.5



Eventually, the structure was unambiguously secured by single crystal X-ray analysis of indolocarbazole (±)-**185**, the product of bis-*p*-bromo benzoylation

of diol (±)-**184**. Importantly, this X-ray structure, coupled with information obtained from the ^{1}H-NMR of ketone (±)-**181**, established that ring expansion furnishes the regio- and stereochemistry needed for the preparation of pyranosylated natural products **1** and **6**-**8** and reduction reactions en route to these compounds could be expected to occur from the exposed convex face.

Scheme 3.2.6

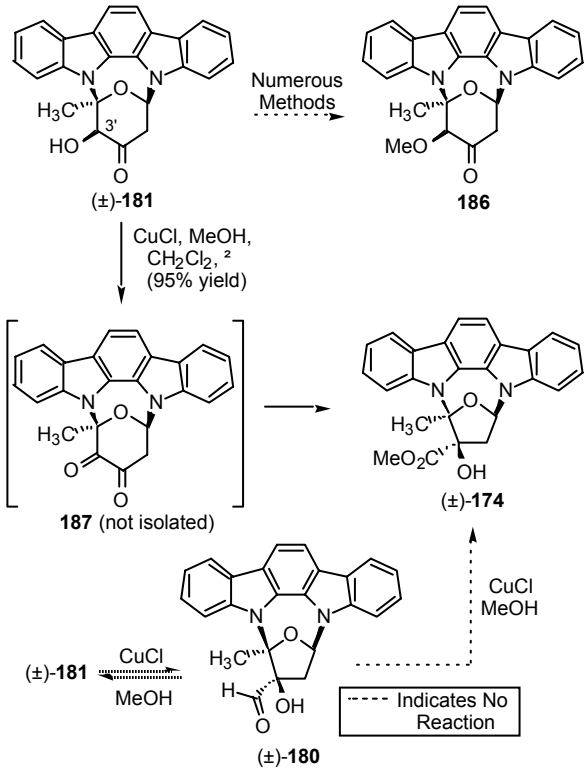


3.2.3 An Unexpected Oxidative Ring Contraction of (±)-181.

To complete the model investigation, attempts were made to access the key intermediate (**186**) by methylating the C(3') hydroxyl in pyranose (±)-**181**. Surprisingly, under numerous methylation conditions, this seemingly simple transformation failed.[10] However, in the course of these efforts CuCl in MeOH was inadvertently found to promote a very facile and stereoselective oxidative ring contraction of ketone (±)-**181** to ester (±)-**174** (95% yield). In an attempt to discern the mechanism it was found that aldehyde (±)-**180** remains unchanged upon exposure to the CuCl reaction conditions; thus, this reaction likely proceeds

by oxidation of keto-alcohol (±)-**181** to diketone **187** followed by stereoselective benzylic acid rearrangement to furanose (±)-**174** (Scheme 3.2.7).[11]

Scheme 3.2.7

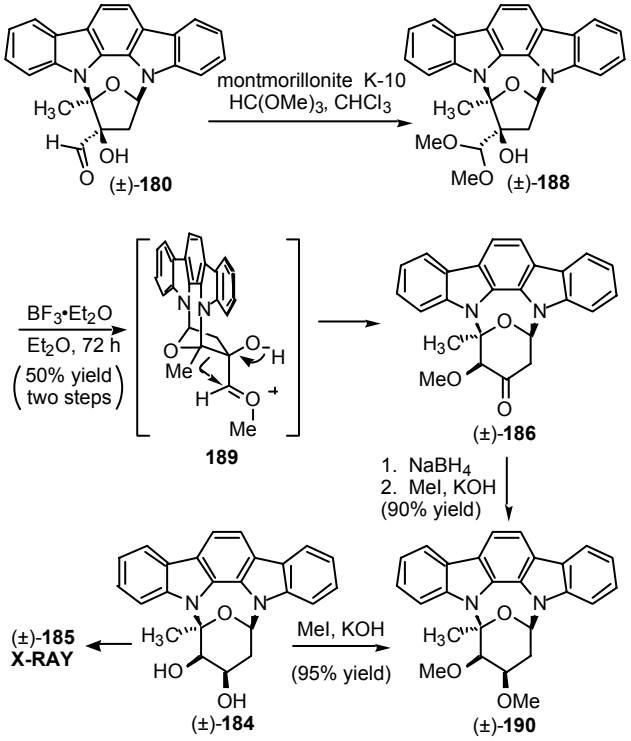


3.2.4 Ring Expansion of Dimethyl Acetal (±)-188.

To circumvent the troublesome alkylation, an alternative method was developed wherein the methyl group is installed prior to a ring expansion. This transformation was envisioned as proceeding through oxocarbenium ion **189** (Scheme 3.2.8). To orchestrate this event, aldehyde (±)-**180** was converted to the corresponding dimethyl acetal **188** with $CH(OMe)_3$ and montmorillonite clay K-10. Removal of the clay by filtration followed by solvent exchange with Et_2O and exposure of the crude product[12] to BF_3•OEt_2 led to the slow formation of new compound.[13] After 24 h at ambient temperature, the product was isolated and

found to be spectroscopically accordant with the elusive α-methoxy ketone (±)-**186**. To provide unambiguous proof of structure, a chemical correlation to the X-ray structure obtained on diester (±)-**185** was implemented. As shown in Scheme 3.2.8, reduction of ketone (±)-**186** with $NaBH_4$ followed by methylation produced diether (±)-**190**. An identical sample was independently prepared prepared by methylation of diol (±)-**184**, the benzoylation substrate for (±)-**185.**

Scheme 3.2.8

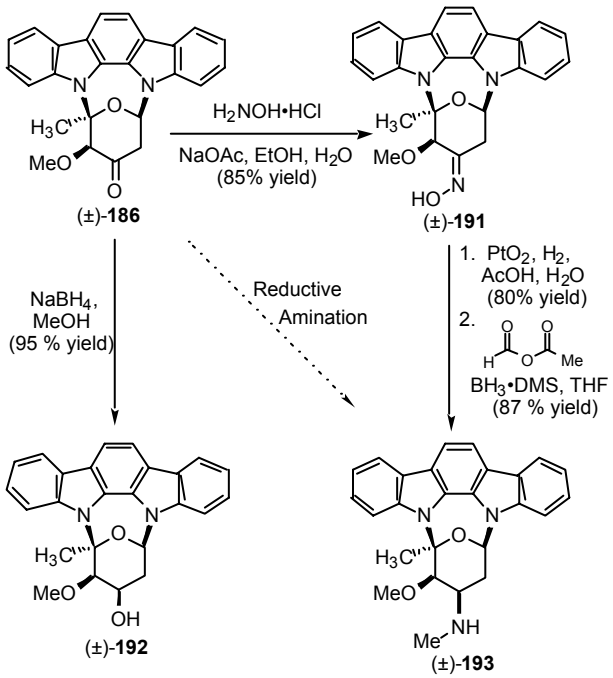


3.2.5 Completion of the Model Investigation.

Having accessed common intermediate **186**, a synthesis of the desamido analogs of staurosporine (**1**) and congeners **6**-**8** was at hand. Thus, desamido TAN-1030a [(±)-**191**] and RK286c [(±)-**192**] were prepared by reaction of ketone (±)-**186** with hydroxylamine hydrochloride in the presence of NaOAc and reduction with $NaBH_4$, respectively (Scheme 3.2.9). Attempts to prepare

desamido staurosporine [(±)-**193**] by direct reductive amination of ketone (±)-**186** failed; however, a three step protocol beginning with oxime formation followed by reduction and monomethylation proved quite effective in delivering amine (±)-**193** (59% yield, three steps).

Scheme 3.2.9

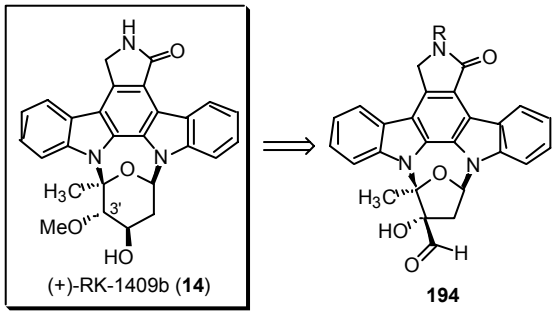


3.2.6 Mechanistic Considerations of Ring Expansion.

In the final stages of the model investigation, efforts were directed toward RK-1409b (**14**), the C(3') isomer of RK286c.[14] Based on previous experiences in the synthesis of ketones (±)-**181** and (±)-**186**, it was reasonable that **14** would be available from aldehyde **194**, the C(3') epimer of (+)-**170**, via ring expansion through a transition state possessing a syn-periplanar relationship between the

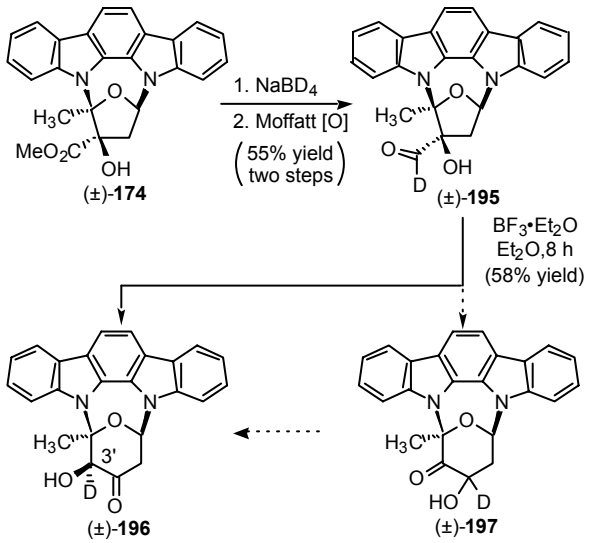
hydroxyl and carbonyl moieties (i.e., **198**, Scheme 3.2.12).

Scheme 3.2.10



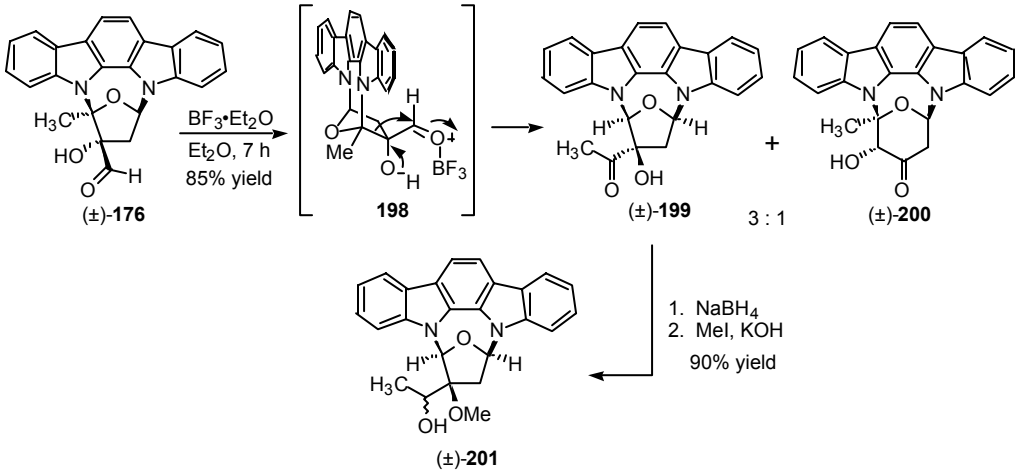
Recognizing that this hypothesis was based on the assumption that the product in the model ring expansion [(±)-**181**] was not a thermodynamic trap but had been produced directly from aldehyde (±)-**180**, the rearrangement chemistry of the latter compound was probed by employing deuterated aldehyde **195** as the substrate. Thus, reduction of ester (±)-**174** with $NaBD_4$ followed by Moffatt oxidation afforded aldehyde (±)-**195** (92% deuterium incorporation) which, when exposed to the standard ring expansion conditions, formed ketone (±)-**196** with over 90% D-incorporation at C(3'). This observation provided evidence that ketone (±)-**196** is the direct product from ring expansion and does not arise via epimerization of C(3') or tautomerization of the corresponding regioisomeric hydroxyketone **197** (Scheme 3.2.11).

Scheme 3.2.11



Turning to the synthesis of desamido RK-1409b, aldehyde (±)-**176** (*vide supra*) was exposed to BF_3•OEt_2 and surprisingly resulted in the formation of two products (3:1 mixture), wherein the minor component was identified as the desired hydroxy ketone (±)-**200**. The major component possessed spectral properties in accord with ketone (±)-**199**, the product of an acetal exchange

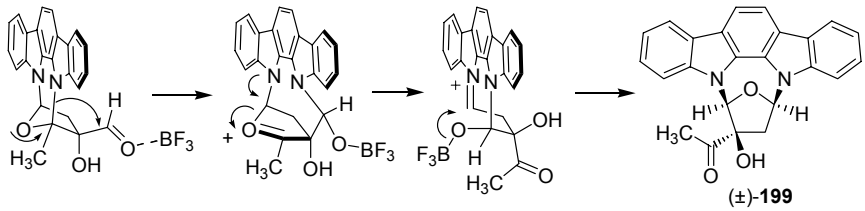
Scheme 3.2.12



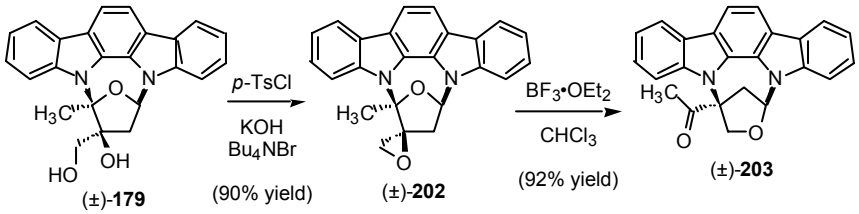
(Scheme 3.2.13). As a further proof of structure, ketone (±)-**199** was methylated and reduced to provide a 2.7:1 mixture of diastereomeric alcohols [(±)-**201**], wherein the presence of two 3H doublets (1.01 and 0.97 ppm respectively)

clearly indicated the reduction product of a methyl ketone (i.e., **199**). A plausible mechanism for acetal exchange is shown in Scheme 3.2.13 and is reminiscent of McCombie's attempted ring expansion of epoxide **115** (Scheme 3.1.2). In these laboratories epoxide (±)-**202**, prepared from diol (±)-**179**, was found to undergo analogous conversion to ketone (±)-**203** when exposed to BF_3•OEt_2 (Scheme 3.2.14).

Scheme 3.2.13



Scheme 3.2.14

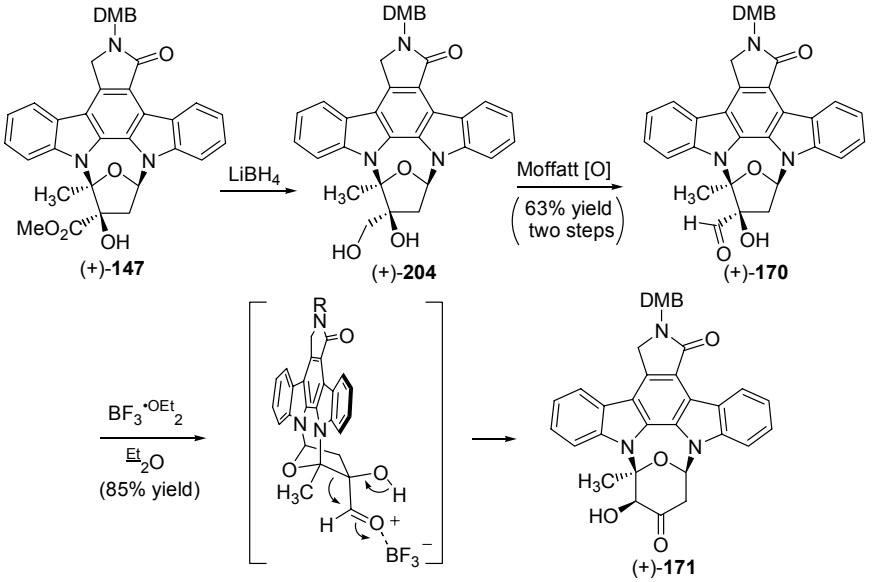


3.3 The Total Synthesis of (+)-RK-286c, (+)-MLR-52, (+)-Staurosporine, and TAN-1030a.

3.3.1 Ring Expansion Studies in the Natural System.

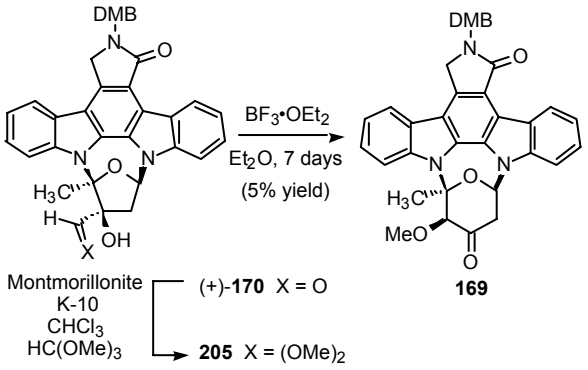
With the rather extensive preliminary investigation complete, the effort advanced to the synthesis of pyranosylated indolocarbazoles **1** and **6-8**. Thus, multigram quantities of indolocarbazole (+)-**147** were prepered via the previously developed 11 step sequence.[15] To set the stage for ring expansion, ester (+)-**147** was subjected to the $LiBH_4$ reduction/Moffatt oxidation protocol developed in the model study. In the event, ring expansion substrate (+)-**170** was produced in good yield (Scheme 3.3.1). In accord with previous studies, ring expansion was attempted on both aldehyde (+)-**170** and the corresponding dimethyl acetal **205**; the latter was prepared by treatment of (+)-**170** with $CH(OMe)_3$ in the presence of montmorillonite clay K-10.

Scheme 3.3.1



Delightfully, exposure of an ether suspension of aldehyde (+)-**170** to BF_3•OEt_2[16] followed by filtration provided ketone (+)-**171** as a pure white powder in 85% isolated yield! In contrast, ring expansion of dimethyl acetal **205** was much slower and, after one week, produced only a trace amount (5% yield) of a compound spectroscopically consistent with methoxy ketone **169**.[17]

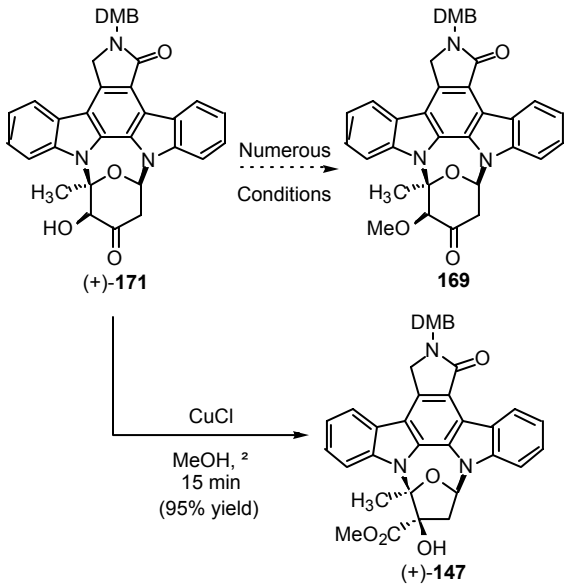
Scheme 3.3.2



3.3.2 Regioselective Monomethylation. Completion of the Synthesis of RK-286c and MLR-52.

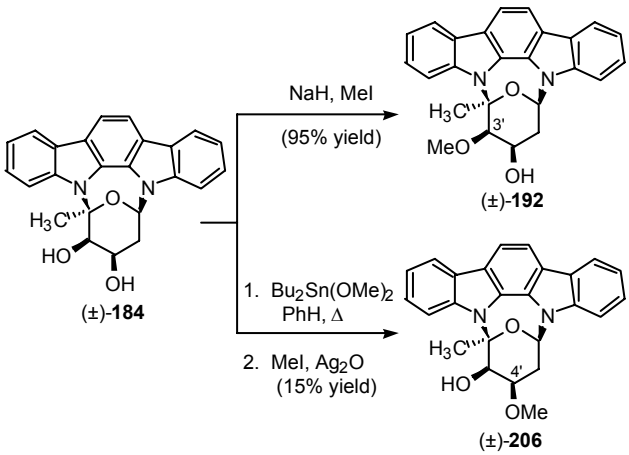
The inability to effectively advance acetal **205** resulted in a study to re-address the C(3') methylation that had proved problematic in the original model investigation. Unfortunately, the reactivity of ketone (+)-**171** toward methylation was found to be identical in all respects to the model α-hydroxy ketone [(+)-**181**], including the interesting oxidation/ring contraction reactivity that, in this particular system, marks an alternative approach to K252a [e.g., (+)-**171**$\rightarrow$(+)-**147**]. Forced into advancing (+)-**171**, the model system was again utilized, this time to explore other methods for functionalizing ketone (±)-**181**.

Scheme 3.3.3



Initially, methods for the selective alkylation of diol (±)-**184** were investigated. This effort led to the discovery of complementary methylation reactions that are promoted by either NaH/MeI, which produced the desired C(3') ether [(±)-**192**], or [$Bu_2Sn(OMe)_2$]/MeI, which furnished the C(4') ether [(±)-**206**] via the corresponding stannylene.

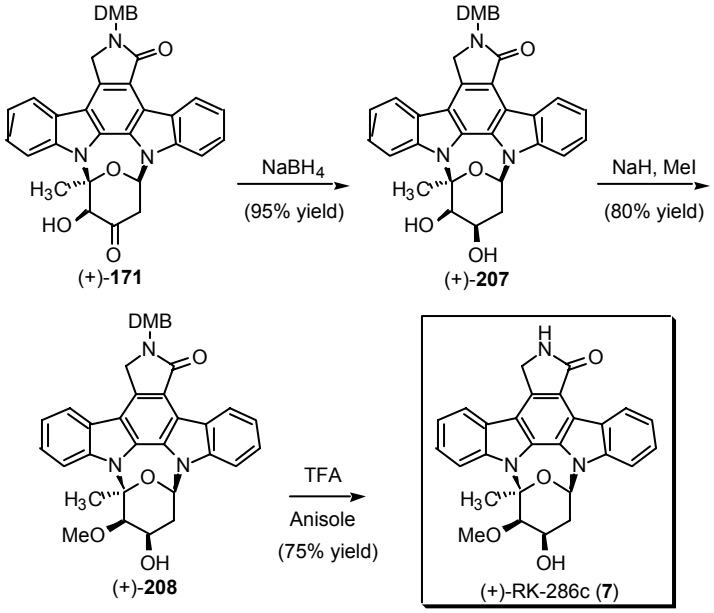
Scheme 3.3.4



As illustrated in Scheme 3.3.5, application of the reduction/selective alkylation sequence also proved effective in the natural series to furnish ether

(+)-**208** from hydroxyketone (+)-**171**. Cleavage of the DMB protecting group by treatment of ether (+)-**208** with TFA in anisole afforded synthetic (+)-RK286c (**7**) in 75% yield.

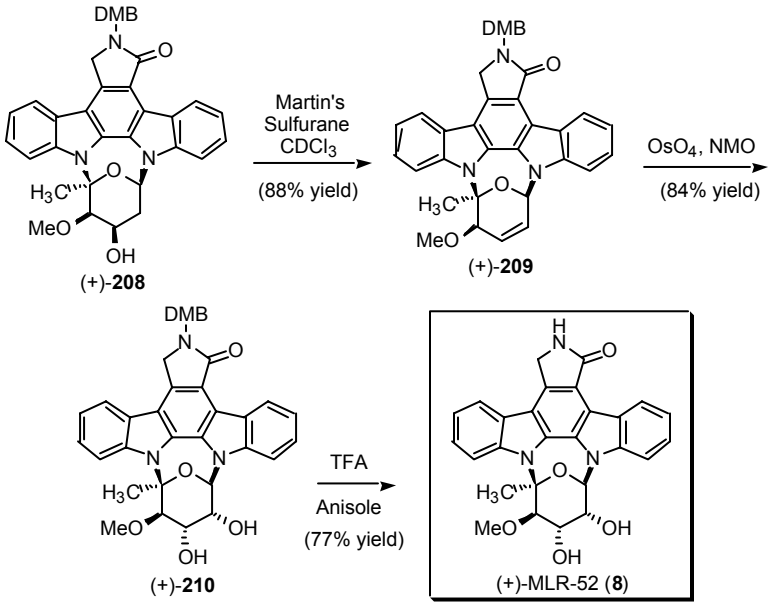
Scheme 3.3.5



Dehydration of alcohol (+)-**208** with Martin's sulfurane cleanly furnished olefin (+)-**209**, which was stereoselectively dihydroxylated in the presence of

OsO_4/NMO to give glycol (+)-**210**. Deprotection of diol (+)-**210** produced (+)-MLR-52 (**8**) in 77% yield.

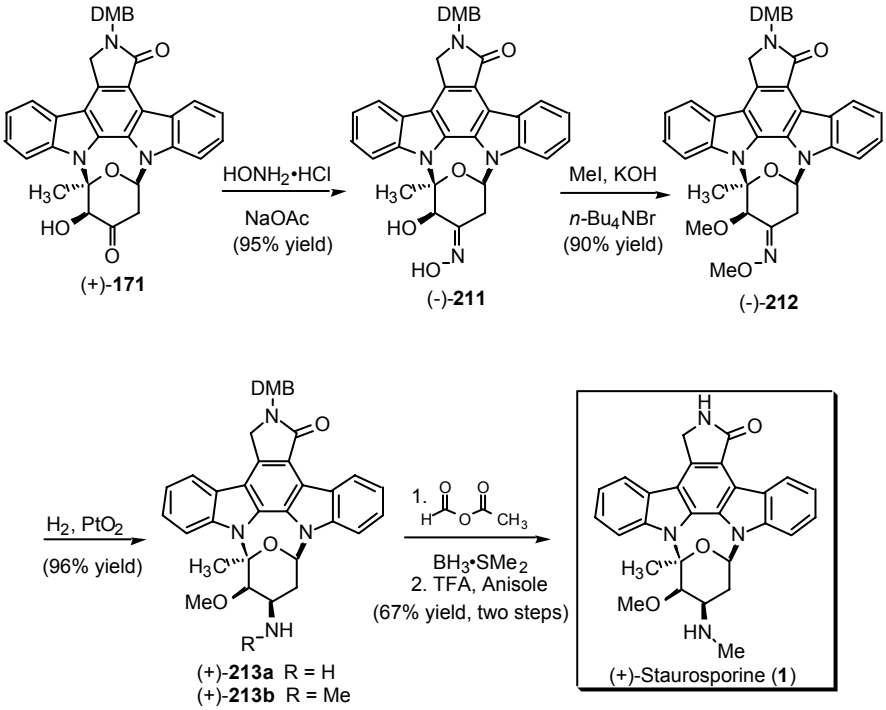
Scheme 3.3.6

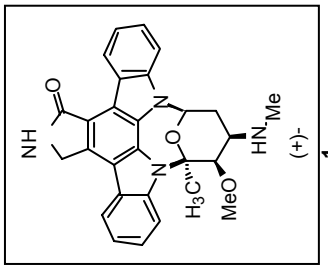


3.3.3 The Synthesis of Staurosporine and TAN-1030a.

Attempts to access the staurosporine and TAN-1030a systems via approaches that involved oxidation of alcohol (+)-**208** failed and prompted the return to ketone (+)-**171**. Thus, treatment of (+)-**171** with hydroxylamine hydrochloride produced oxime (-)-**211** in 95% yield. In contrast to ketone (+)-**171** bis-methylation of oxime (-)-**211** under phase transfer conditions (MeI, KOH, and Bu_4NBr in THF) occurred cleanly to afford bis-ether (-)-**212** and set the stage for a stereoselective reduction (H_2/PtO_2) that furnished amine (+)-**213a**.[3] Mono-methylation and deprotection then afforded (+)-staurosporine (**1**) in 67% yield (two steps) which proved identical in all respects to a sample of **1** prepared in the Danishefsky laboratories (see Figure 3.3.1).

Scheme 3.3.7

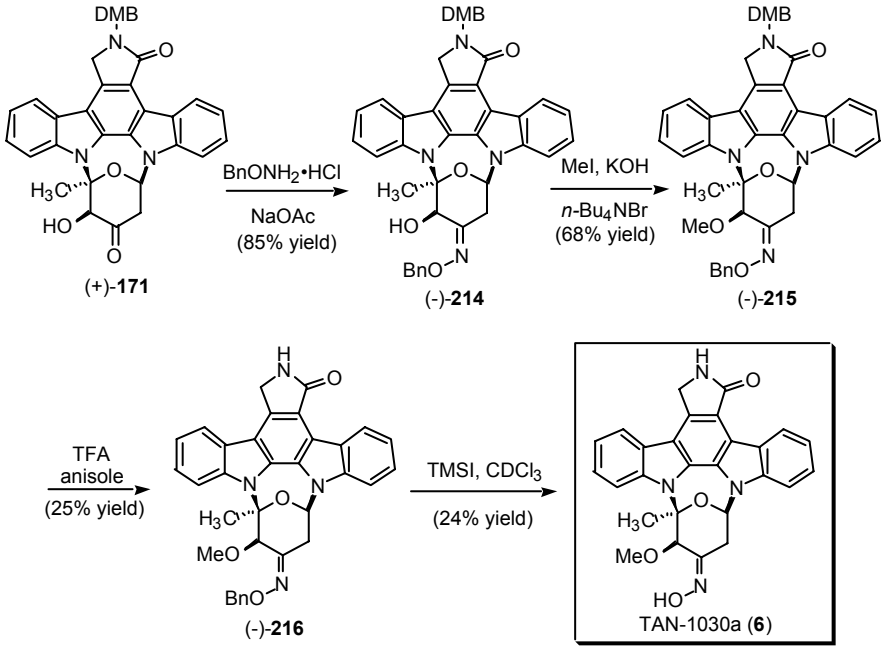




The final target, TAN-1030a (**6**), required the introduction of a selectively protected oxime ether due to the instability of the free oxime to strong acid.[18] Thus treatment of ketone (+)-**171** with *O*-benzyl hydroxylamine hydrochloride followed by MeI, KOH, and Bu_4NBr produced ether (-)-**215**. Removal of the DMB

group from (-)-**215** (TFA/anisole) followed by treatment of the derived amide (-)-**216** with iodotrimethylsilane afforded synthetic TAN-1030a (**6**) in 24% yield.

Scheme 3.3.8



3.4 Conclusion.

In summary, a ring expansion protocol was developed which allows the transformation of a furanosylated indolocarbazole to a pyranosylated derivative suited for advancement to numerous natural products. Specifically, ring expansion of aldehyde (+)-**170** proceeds in a stereo- and regioselective manner

to ketone (+)-**171** in 85% yield. Ketone (+)-**171** is a common intermediate in the synthesis of TAN-1030a (**6**, 18 steps from ethyl glycinate), (+)-RK286c (**7**, 17 steps), (+)-MLR-52 (**8**, 19 steps), and (+)-staurosporine (**1**, 19 steps). In addition, the unique oxidative benzylic acid rearrangement of ketone (+)-**171** to ester (+)-**147** may have important biosynthetic implications.

3.5 Experimental Section.

3.5.1 Material and Methods.

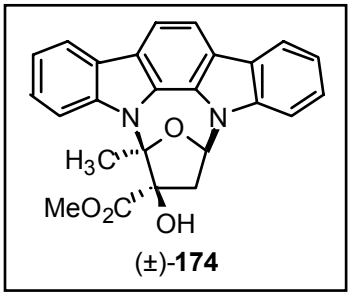
Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled from calcium hydride. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal□ containers and used without further purification. All other commercially obtained reagents were used as received.

Unless stated otherwise all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography (silica) was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. In general, the chromatography guidelines reported by Still were followed.[19]

All melting points were obtained on a Haacke-Buchler variable temperature melting point apparatus (model: MFB 595 8020) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-500 or Bruker WM-250 spectrometers. Chemical shifts are reported relative to internal Me_4Si (^{1}H and ^{13}C, δ 0.00 ppm) or chloroform (^{1}H, δ 7.27 ppm, ^{13}C, δ 77.0 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Microanalyses were performed by Atlantic Microlab (Norcross, GA). Single-crystal X-ray analyses were performed by Dr. Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column, or a Rainen Dynamax SD-200 system with a Rainen Microsorb 80-120-C5 column. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

3.5.2 Preparative Procedures.

Preparation of Ester (±)-174.

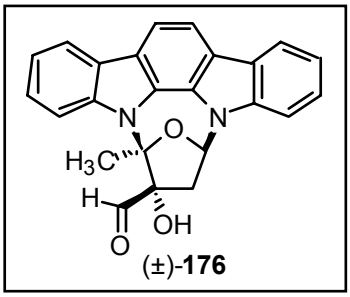


(±)-**174**

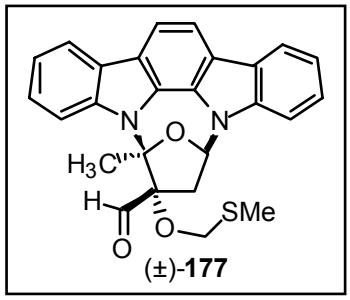
Ester (±)-174, Method A. To a suspension of indolo[2,3-a]carbazole[6] (**38**) (1.0 g, 3.9 mmol, 1.0 equiv) in 1,2-dichloroethane (130 mL) was added furanose (±)-**97**[7] (1.8 g, 8.2 mmol, 2.1 equiv) and CSA (100 mg, 0.43 mmol, 0.11 equiv). After heating at reflux for 48 h, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (100mL), and washed with 10% $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and chromatographed on silica gel (3:1 hexanes:EtOAc eluent) to afford indolocarbazole (±)-**174** (1.37 g, 85% yield) as a yellow solid: mp 235-236 °C; IR (thin film/NaCl) 3501.3 (br m), 3047.5 (m), 3006.7 (m), 2950.6 (m), 1729.4 (s), 1640.2 (m), 1568.1 (m), 1441.1 (s), 1305.9 (s), 1230.3 (s), 1128.1 (s), 740.0 (s) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.18 (app.t, *J* = 6.6 Hz, 1H), 8.18 (app.t, *J* = 5.4 Hz, 1H), 8.00 (m, 2H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.44 (td, *J* = 0.9, 7.6 Hz, 1H), 7.38 (td, *J* = 1.0, 7.9 Hz, 1H), 7.26 (app.t, *J* = 6.9 Hz, 1H), 7.25 (app.t, *J* = 7.1 Hz, 1H), 7.10 (dd, *J* = 4.9, 7.3 Hz, 1H), 5.18 (s, 1H), 3.99 (s, 3H), 3.44 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.21 (s, 3H), 2.19 (dd, *J* = 4.9, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.1, 140.8, 138.1, 127.7, 127.0, 125.6, 125.6, 125.5, 125.4, 121.6, 121.5, 121.2, 120.5, 120.4, 120.3, 115.0, 113.1, 112.8, 109.6, 99.9, 86.1, 86.0, 53.3, 43.2, 23.3; high resolution mass spectrum (EI) *m/z* 412.1419 [calcd for $C_{25}H_{20}N_2O_4$ (M^+) 412.1423].

Ester (±)-174, Method B. To a solution of ketone (±)-**181** (100 mg, 0.26 mmol) in 1:1 MeOH/CH_2Cl_2 (14 mL) was added copper (I) chloride (700 mg, 7.1 mmol, 27 equiv) and the mixture warmed to reflux for 6 h. Solvent was removed *in vacuo* and the resulting residue subjected to silica gel chromatography (2:1, hexane:EtOAc) to afford ester (±)-**174** (102 mg, 95% yield) as a colorless solid (mp 235-239 °C).

Preparation of Thioether (±)-177 and Aldehyde (±)-176.



(±)-**176**



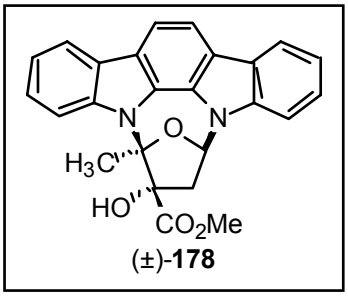
(±)-**177**

Thioether (±)-177 and Aldehyde (±)-176. To a stirred solution of diol (±)-**175** (100 mg, 0.26 mmol, 1.0 equiv) in 1:1 benzene:DMSO (1.8 mL) was added pyridinium trifluoroacetate (50 mg, 0.26 mmol, 1.0 equiv) followed by 1,3-dicyclohexylcarbodiimide (161 mg, 0.78 mmol, 3.0 equiv). The flask was quickly sealed with a septum, evacuated, and flushed with N_2 (3 x). The heterogeneous mixture was stirred for 7 h until reaction was complete as indicated by TLC. Benzene (4 mL) was added to the mixture and the 1,3-dicyclohexylurea (DCU) precipitate was filtered. The filtrate was washed with H_2O (3 x 10 mL), and the combined aqueous layers were back extracted with CH_2Cl_2 (3 x 15 mL). All organic layers were combined, dried over Na_2SO_4, and evaporated to an oily residue. A minimum amount of acetone (1 mL) was added to precipitate the

remaining DCU. Filtration and evaporation gave a yellow oil. Flash chromatography (3:1 hexanes/EtOAc eluent) afforded two products. The first compound to elute was thioether (±)-**177** (15 mg, 13% yield) as a yellow foam: IR (thin film/NaCl) 3050.3 (w), 2922.7 (m), 2848.1 (w), 1725.3 (m), 1641.9 (m), 1570.4 (m), 1446.9 (s), 1302.6 (m), 1227.0 (m), 1009.4 (m), 745.1 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.16 (app.t, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.46-7.50 (comp m, 3H), 7.40 (app.t, *J* = 8.3 Hz, 1H), 7.29-7.33 (m, 2H), 7.04 (dd, *J* = 4.4, 7.2 Hz, 1H), 4.87 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 3.23 (dd, *J* = 7.3, 15.5 Hz, 1H), 2.80 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 137.7, 136.9, 126.5, 126.4, 125.3, 125.1, 124.7, 124.5, 121.4, 121.1, 120.8, 120.6, 120.4, 119.8, 113.1, 112.4, 112.2, 108.1, 102.3, 93.6, 86.3, 70.9, 35.4, 22.9, 14.6; high resolution mass spectrum (EI) *m/z* 442.1350 [calcd for $C_{26}H_{22}N_2O_3S$ (M^+) 442.1351].

The second compound to elute was aldehyde (±)-**176** (54 mg, 50% yield) as a white solid: mp 153-155 °C; IR (thin film/NaCl) 3426.4 (br m), 3049.7 (w), 2925.4 (m), 2853.1 (m), 1715.6 (m), 1640.0 (m), 1446.7 (s), 1302.8 (s), 1133.8 (s), 744.5 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.16 (app.t, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.24-7.49 (m, 6H), 7.08 (app.t, *J* = 5.8 Hz, 1H), 4.31 (br s, 1H), 2.71 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 137.2, 136.9, 126.5, 126.4, 125.4, 125.2, 124.5, 124.2, 121.5, 120.9, 120.8, 120.6, 120.5, 119.9, 113.2, 112.2, 111.9, 108.1, 102.2, 88.0, 86.6, 42.6, 22.0; high resolution mass spectrum (EI) *m/z* 382.1313 [calcd for $C_{24}H_{18}N_2O_3$ (M^+) 382.1317].

Preparation of Ester (±)-178.

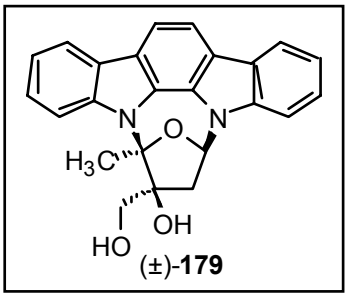


(±)-**178**

Ester (±)-178. A solution of aldehyde (±)-**176** (100 mg, 0.263 mmol, 1.0 equiv) in DMSO (10 mL) was treated sequentially with a saturated solution of NaH_2PO_4 that had been acidified to pH 2 with 1 N HCl (2.0 mL) and a solution of $NaClO_2$ (200 mg, 2.21 mmol, 8.4 equiv). The mixture was stirred for 10 min and then treated with CH_2N_2 in Et_2O until a yellow color persisted. The reaction mixture was diluted with H_2O (5 mL), extracted with Et_2O (3 x 10 mL), and the combined organic extracts dried over Na_2SO_4. Flash chromatography (1:1 EtOAc:hexanes eluent) provided ester (±)-**178** (92 mg, 85% yield) as a yellow foam: IR (thin film/NaCl) 3492.7 (br m), 3011.6 (m), 2951.6 (m), 2926.5 (m), 2851.6 (w), 1726.5 (s), 1640.2 (w), 1569.0 (w), 1440.8 (s), 1306.6 (s), 1230.9 (m), 1138.6 (s), 1093.4 (m), 743.4 (s) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.20 (app.t, *J* = 7.3 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.45 (app.t, *J* = 7.5 Hz, 1H), 7.39 (app.t, *J* = 8.4 Hz, 1H), 7.26 (app.t, *J* = 7.4 Hz, 2H), 7.23 (dd, *J* = 4.5, 7.5 Hz, 1H), 5.54 (s, 1H), 3.04 (dd, *J* = 7.5, 14.9 Hz, 1H), 2.96 (s, 3H), 2.81 (dd, *J* = 4.7, 14.7 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 138.0, 137.0, 127.0, 126.2, 125.0, 124.9, 124.8, 124.5, 121.4, 120.8, 120.7, 120.3, 119.9, 119.7, 112.7, 112.1, 111.6, 108.2, 102.0, 85.9, 83.7, 53.4, 42.8, 21.9; high

resolution mass spectrum (CI) *m/z* 413.1498 [calcd for $C_{25}H_{21}N_2O_4$ (M+H) 413.1501].

Preparation of Diol (±)-179.

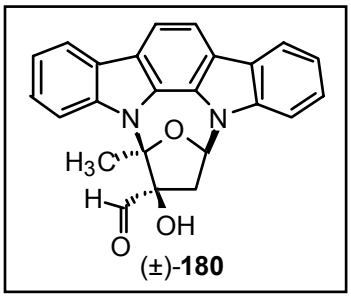


(±)-**179**

Diol (±)-179. To a stirred room temperature solution of ester (±)-**174** (1.0 g, 2.43 mmol, 1.0 equiv) in THF (24 mL) was added $LiBH_4$ (106 mg, 4.87 mmol, 2.0 equiv). After 20 min, the solvent was removed *in vacuo* to provide a white solid which was cooled to 0 °C and treated with 1.0 N HCl (50 mL). The suspension was stirred for 15 min and then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4. Flash chromatography (1:1 hexanes:EtOAc eluent) afforded diol (±)-**179** (815 mg, 87% yield) as a white solid: mp >190 °C (dec.); IR (thin film/NaCl) 3416.8 (br s), 3052.9 (m), 3010.5 (m), 2955.4 (w), 1732.7 (w), 1640.9 (m), 1568.5 (m), 1492.6 (m), 1459.0 (s), 1441.4 (s), 1309.0 (s), 1233.1 (s), 1031.9 (s), 741.0 (s) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.18 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 2H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.42 (app.t, *J* = 7.6 Hz, 1H), 7.36 (app.t, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.6 Hz, 1H), 7.23 (app.t, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 5.2, 7.4 Hz, 1H), 4.57 (s, 1H), 4.18 (app.t, *J* = 5.9 Hz, 1H), 4.06 (dd, *J* = 5.4, 11.1 Hz, 1H), 3.90 (dd, *J* = 7.1, 11.1 Hz, 1H), 3.30 (dd, *J* = 7.6, 13.8 Hz,

1H), 2.23 (dd, *J* = 5.1, 13.8 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 140.2, 137.4, 127.6, 126.3, 125.4, 125.0, 124.6, 124.6, 120.7, 120.6, 119.9, 119.5, 114.6, 112.2, 112.0, 108.8, 100.1, 84.2, 83.8, 65.5, 40.6, 21.5; high resolution mass spectrum (EI) *m/z* 384.1472 [calcd for $C_{24}H_{20}N_2O_3$ (M^+) 384.1474].

Preparation of Aldehyde (±)-180.

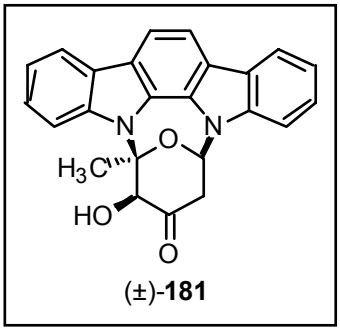


(±)-**180**

Aldehyde (±)-180. To a stirred solution of diol (±)-**179** (500 mg, 1.3 mmol, 1.0 equiv) in 1:1 benzene:DMSO (8.7 mL) was added pyridinium trifluoroacetate (250 mg, 1.3 mmol, 1.0 equiv) followed by 1,3-dicyclohexylcarbodiimide (810 mg, 3.9 mmol, 3.0 equiv). The flask was quickly sealed with a septum, evacuated, and flushed with N_2 (3 x). The heterogeneous mixture was stirred for 7 h until reaction was complete as indicated by TLC. Benzene (15 mL) was added to the mixture and the 1,3-dicyclohexylurea (DCU) precipitate was filtered. The filtrate was washed with H_2O (3 x 20 mL), and the combined aqueous layers were back extracted with CH_2Cl_2 (3 x 30 mL). All organic layers were combined, dried over Na_2SO_4, and evaporated to an oily residue. A minimum amount of acetone (2 mL) was added to precipitate the remaining DCU. Filtration and evaporation gave a yellow oil, which was purified by flash chromatography (3:1

hexanes:EtOAc eluent) to afford aldehyde (±)-**180** (373 mg, 73% yield, 63% yield 2 steps) as a yellow powder: mp >225 °C (dec.); IR (thin film/NaCl) 3486.7 (br m), 3054.6 (m), 3007.7 (m), 2945.3 (m), 2843.4 (w), 1723.9 (m), 1641.8 (m), 1568.6 (m), 1458.7 (m), 1441.1 (s), 1309.2 (s), 1232.5 (s), 1128.8 (m), 1004.2 (m), 741.7 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.99 (app.t, *J* = 7.3 Hz, 2H), 7.78 (s, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.29 (app.t, *J* = 7.4 Hz, 1H), 7.24 (app.t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.17 (app.t, *J* = 7.9 Hz, 1H), 7.15 (app.t, *J* = 7.2 Hz, 1H), 6.59 (dd, *J* = 5.0, 7.4 Hz, 1H), 3.08 (s, 1H), 2.76 (dd, *J* = 7.6, 14.6 Hz, 1H), 1.99 (s, 3H), 1.83 (dd, *J* = 5.0, 14.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 139.3, 136.9, 126.3, 126.3, 125.1, 124.7, 124.1, 121.2, 121.1, 120.8, 120.3, 120.3, 119.9, 113.1, 112.9, 112.2, 108.0, 97.7, 87.7, 84.0, 39.7, 23.0; high resolution mass spectrum (EI) *m/z* 382.1319 [calcd for $C_{24}H_{18}N_2O_3$ (M^+) 382.1317].

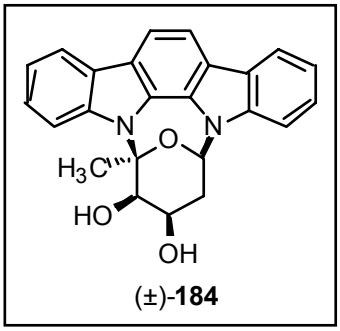
Preparation of Hydroxy ketone (±)-181.



(±)-**181**

Hydroxy ketone (±)-181. A suspension of aldehyde (±)-**180** (75 mg, 0.196 mmol, 1.0 equiv) in Et_2O (5.0 mL) was treated with BF_3•OEt_2 (27 μL, 0.220 mmol, 1.1 equiv),and stirred vigorously for 6 h. After addition of CH_2Cl_2 (25 mL) to solubilize the suspension, the resulting solution was evaporated onto SiO_2 (100 mg) and chromatographed (2:1 hexanes:EtOAc eluent) to provide ketone (±)-**181** (45 mg, 60% yield) as a white powder: mp 235-239 °C (dec.); IR (thin film/NaCl) 3328.6 (br m), 3048.0 (w), 2923.7 (m), 2852.1 (w), 1731.4 (s), 1637.4 (m), 1441.5 (s), 1395.3 (m), 1312.0 (s), 1130.1 (m), 740.8 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.7 Hz, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.43 (app.t, *J* = 7.7 Hz, 1H), 7.39 (app.t, *J* = 7.8 Hz, 1H), 7.32 (app.t, *J* = 7.4 Hz, 1H), 7.28 (app.t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 3.55 (dd, *J* = 7.5, 14.3 Hz, 1H), 3.49 (d, *J* = 6.5 Hz, 1H), 2.99 (d, *J* = 14.4 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 140.2, 136.3, 126.4, 125.7, 125.4, 125.1, 124.8, 124.6, 121.4, 120.8, 120.4, 120.2, 119.8, 115.2, 112.7, 112.4, 112.1, 107.9, 100.3, 84.0, 81.6, 44.7, 29.5; high resolution mass spectrum (EI) *m/z* 382.1315 [calcd for $C_{24}H_{18}N_2O_3$ (M^+) 382.1317].

Preparation of Diol (±)-184.

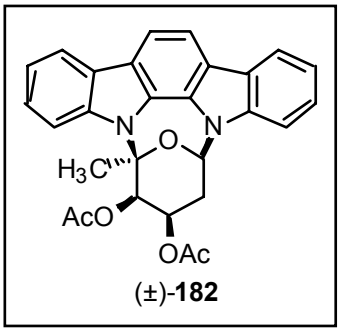


(±)-**184**

Diol (±)-184. To a stirred room temperature solution of ketone (±)-**181** (100 mg, 0.26 mmol, 1.0 equiv) in 1:1 MeOH: CH_2Cl_2 (10 mL) was added $NaBH_4$ (27 mg, 0.70 mmol, 2.7 equiv). After 5 min solvent was removed under reduced pressure to afford a white solid which was cooled to 0 °C and then treated with 1.0 N HCl (10 mL). After 5 min at 0 °C, the mixture was warmed to room temperature, stirred for 15 min at 25 °C, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried with Na_2SO_4 and chromatographed (2:1 hexanes:EtOAc eluent) to afford diol (±)-**184** (95 mg, 95% yield) as a white solid: mp 235-238 °C (dec.); IR (thin film/NaCl) 3529.6 (br m), 3043.9 (m), 2930.2 (w), 1642.5 (m), 1564.1 (m), 1445.1 (s), 1314.4 (s), 1230.1 (m), 1129.9 (m), 1073.3 (m), 739.3 (s), 694.3 (m) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.16 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.40 (app.t, *J* = 7.6 Hz, 1H), 7.31 (ddd, *J* = 1.3, 7.0, 11.4 Hz, 1H), 7.24 (app.t, *J* = 7.3 Hz, 1H), 7.17 (app.t, *J* = 7.2 Hz, 1H), 6.71 (dd, *J* = 1.0, 5.8 Hz, 1H), 4.21 (m, 1H), 3.99 (dd, *J* = 3.3, 9.1 Hz, 1H), 3.59 (br s, 1H), 2.80 (d, *J* = 13.6 Hz, 1H), 2.74 (ddd, *J* = 3.0, 5.7, 14.9 Hz, 1H), 2.63 (ddd, *J* = 1.0, 3.3, 15.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 139.4, 136.1, 127.5, 126.6, 125.2, 124.2, 123.8, 123.7, 119.9, 119.1, 118.8, 118.5, 118.3, 115.1, 111.3, 110.5, 108.7, 92.2, 79.5, 73.3,

64.0, 34.4, 29.5; high resolution mass spectrum (EI) *m/z* 384.1469 [calcd for $C_{24}H_{20}N_2O_3$ (M^+) 384.1474].

Preparation of Bis-Acetate (±)-182.

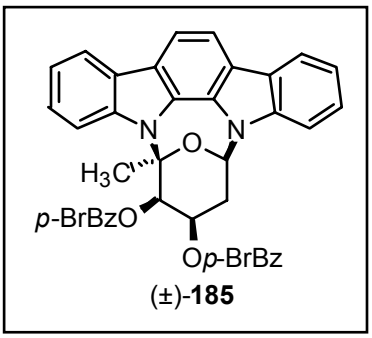


(±)-**182**

Bis-Acetate (±)-182. A solution of diol (±)-**184** (25 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (0.7 mL) was treated with Et_3N (0.03 mL, 0.22 mmol, 3.0 equiv) followed by Ac_2O (0.012 mL, 0.13 mmol, 2.0 equiv) and DMAP (1 mg, 0.007 mmol, 0.1 equiv), and stirred for 15 min. The solution was diluted with H_2O (1.0 mL) and extracted with CH_2Cl_2 (3 x 2 mL). Organic layers were combined, dried over Na_2SO_4, and evaporated to a residue which was purified by flash chromatography to provide bis-acetate (±)-**182** (25 mg, 76% yield) as a white solid: mp 147-150°; IR (thin film/NaCl) 3049.5 (br w), 3016.3 (br w), 2937.3 (w), 1747.0 (s), 1641.9 (w), 1443.8 (m), 1311.9 (m), 1230.9 (s), 1214.7 (s), 1069.0 (m), 741.6 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (app.t, *J* = 7.0 Hz, 2H), 7.93 (d, *J* = 13.7 Hz, 1H), 7.90 (d, *J* = 13.7 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.44 (app.t, *J* = 7.6 Hz, 1H), 7.25-7.37 (comp m, 4H), 6.70 (d, *J* = 5.4 Hz, 1H), 5.43 (d, *J* = 3.0 Hz, 1H), 5.34 (dd, *J* = 3.2, 6.4 Hz, 1H), 2.71 (ddd, *J* = 3.2, 5.5, 15.2 Hz, 1H), 2.59 (dd, *J* = 3.8, 15.2 Hz, 1H), 2.37 (s, 3H), 1.94 (s, 3H), 0.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 169.6, 139.1, 136.1, 127.5, 126.5, 126.0, 124.8,

124.7, 124.1, 120.5, 120.3, 119.9, 119.7, 119.6, 119.4, 113.6, 112.1, 111.1, 107.8, 90.2, 79.6, 73.1, 63.2, 32.0, 30.0, 20.7, 19.1; high resolution mass spectrum (EI) *m/z* 468.1684 [calcd for $C_{28}H_{24}N_2O_5$ (M^+) 468.1685].

Preparation of Bis *p*-bromobenzoate (±)-185.

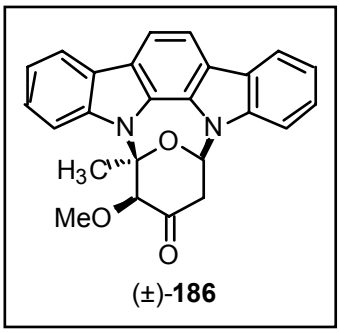


(±)-**185**

Bis *p*-bromobenzoate (±)-185. Diol (±)-**184** (30 mg, 0.078 mmol, 1.0 equiv), *p*-bromobenzoyl chloride (36 mg, 0.164 mmol, 2.1 equiv), Et_3N (23 μL, 0.164 mmol, 2.1 equiv), and 4-dimethylaminopyridine (2 mg, 0.016 mmol, 0.1 equiv) were heated to reflux in CH_2Cl_2 (1.0 mL) for 10 min. The reaction mixture was adsorbed onto SiO_2 and chromatographed (2:1 hexanes:EtOAc eluent) to afford diester (±)-**185** (45 mg, 77% yield) as a white solid which when crystallized from $CHCl_3$/MeOH provided crystals suitable for X-ray analysis: mp 198-200 °C; IR (thin film/NaCl) 3044.9 (w), 2928.5 (w), 1725.4 (s), 1642.6 (w), 1589.4 (s), 1398.4 (m), 1258.6 (s), 1230.5 (m), 1091.8 (br s), 1009.9 (s), 844.4 (w), 739.5 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 9.3 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.44 (app.t, *J* = 8.4 Hz, 1H), 7.42 (app.t, *J* = 7.5 Hz, 1H), 7.30 (s, 4H), 7.27 (m, 1H), 7.26 (app.t, *J* = 8.2 Hz, 1H), 7.21 (app.t, *J* = 7.4 Hz, 1H), 7.10 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 5.5 Hz, 1H), 6.08 (d, *J* = 8.3 Hz, 2H), 5.85 (m, 1H),

5.84 (s, 1H), 2.94 (ddd, *J* = 3.6, 5.7, 15.4 Hz, 1H), 2.78 (dd, *J* = 2.8, 15.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.8, 138.6, 136.3, 131.8, 131.6, 131.1, 130.5, 129.0, 127.8, 127.1, 127.0, 126.8, 126.0, 125.0, 124.6, 124.5, 121.0, 120.7, 120.2, 120.0, 119.8, 119.8, 114.1, 112.5, 111.5, 107.7, 90.0, 79.6, 73.3, 63.7, 32.4, 30.2; high resolution mass spectrum (EI) *m/z* 748.0214 [calcd for $C_{38}H_{26}N_2O_5Br_2$ (M^+) 748.0208].

Preparation of Methoxy ketone (±)-186.

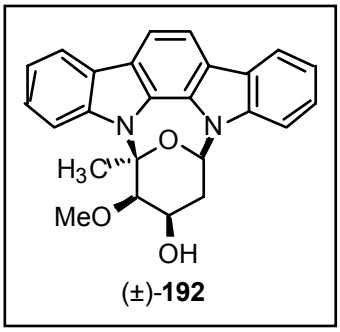


(±)-**186**

Methoxy ketone (±)-186. Montmorillonite clay K-10 (1.2 g) was mixed with trimethylorthoformate (1.78 mL, 16.3 mmol, 14.8 equiv) and immediately rinsed (3 mL $CHCl_3$) into a stirred solution of aldehyde (±)-**180** (414 mg, 1.1 mmol, 1.0 equiv) in $CHCl_3$ (11 mL). After approximately 0.5 h formation of the dimethyl acetal **188** was complete as indicated by TLC (3:1 hexanes:EtOAc). The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in diethyl ether (110 mL) under N_2 and treated with BF_3•OEt_2 (2.85 mL, 23.1 mmol, 21.0 equiv). The resultant mixture was stirred for 4 days at 25 °C. After this time, Et_3N (6.1 mL) and CH_2Cl_2 (100 mL) were added and the product was adsorbed onto silica gel *in vacuo*. Flash chromatography (2:1 hexanes:EtOAc eluent) provided methoxy ketone (±)-**186**

(214 mg, 50% yield) as a yellow solid: mp 275-280 °C (dec.); IR (thin film/NaCl) 3046.6 (br m), 3003.8 (br w), 2927.9 (m), 2835.6 (m), 1736.6 (s), 1640.5 (m), 1565.8 (m), 1492.7 (m), 1442.9 (s), 1311.5 (s), 1144.3 (m), 1126.1 (s), 740.2 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.21 (d, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.46 (td, *J* = 1.0, 7.4 Hz, 1H), 7.37 (td, *J* = 1.1, 7.7 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.30 (app.t, *J* = 7.6 Hz, 1H), 7.23 (app.t, *J* = 7.4 Hz, 1H), 5.02 (s, 1H), 3.94 (dd, *J* = 7.2, 13.7 Hz, 1H), 3.39 (s, 3H), 2.62 (d, *J* = 13.9 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.8, 139.4, 135.7, 125.0, 124.8, 124.5, 124.1, 124.0, 120.0, 119.8, 119.4, 119.2, 114.9, 112.1, 111.3, 109.2, 99.0, 88.2, 84.4, 58.9, 45.4, 29.2; high resolution mass spectrum (EI) *m/z* 396.1474 [calcd for $C_{25}H_{20}N_2O_3$ (M^+) 396.1474].

Preparation of Alcohol (±)-192.



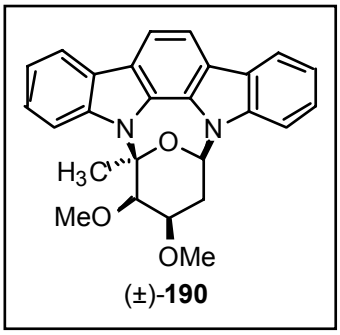
(±)-**192**

Alcohol (±)-192. Method A. To a stirred solution of ketone (±)-**186** (12 mg, 0.03 mmol, 1.0 equiv) in 1:1 MeOH: CH_2Cl_2 (1.0 mL) was added $NaBH_4$ (3 mg, 0.08 mmol, 2.7 equiv) at room temperature. After 5 min the solvent was removed *in vacuo* to afford a white solid which was cooled to 0 °C and treated with 1.0 N HCl (1 mL). After 5 min at 0 °C, the mixture was warmed to room

temperature, stirred for 15 min at 25 °C, and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried with Na_2SO_4 and chromatographed (2:1 hexanes:EtOAc eluent) to afford alcohol (±)-**192** (12 mg, 95% yield) as a white solid: mp 340-344 °C (dec.); IR (thin film/NaCl) 3528.3 (br m), 3048.1 (m), 3000.2 (m), 2928.4 (m), 1643.7 (m), 1564.8 (m), 1493.3 (m), 1445.1 (s), 1344.4 (m), 1311.6 (s), 1231.2 (s), 1109.5 (br s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.7 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.39 (td, *J* = 1.0, 8.1 Hz, 1H), 7.35 (ddd, *J* = 0.14, 7.1, 8.4 Hz, 1H), 7.25 (m, 3H), 6.54 (d, *J* = 5.6 Hz, 1H), 4.34 (m, 1H), 3.66 (d, *J* = 3.0 Hz, 1H), 3.53 (s, 3H), 2.71 (dd, *J* = 3.5, 14.9 Hz, 1H), 2.45 (m, 1H), 2.30 (s, 3H), 1.66 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 136.6, 128.3, 127.2, 126.5, 126.2, 124.8, 124.4, 123.9, 120.5, 120.3, 119.6, 119.3, 114.9, 112.1, 110.9, 107.6, 90.6, 83.1, 79.7, 60.5, 57.4, 33.7, 29.9; high resolution mass spectrum (EI) *m/z* 398.1633 [calcd for $C_{25}H_{22}N_2O_3$ (M^+) 398.1630].

Alcohol (±)-192. Method B. To a stirred suspension of NaH (6.1 mg of a 60% dispersion in mineral oil, 0.15 mmol, 1.1 equiv) in THF (1.0 mL) was added a solution of alcohol (±)-**184** (55 mg, 0.143 mmol, 1.0 equiv) in THF (5 mL). The resulting mixture was stirred for 10 min with the visible evolution of gas and for an additional 15 min thereafter. Addition of MeI (9.0 μL, 0.15 mmol, 1.1 equiv) produced a single product as evidenced by TLC (5:1 hexanes:acetone). After approximately 50 min the reaction was quenched by the sequential addition of 1.0 N HCl (1.0 mL) and H_2O (2.0 mL). Extraction of the solution with CH_2Cl_2 (3 x 10 mL), drying over Na_2SO_4, evaporation to a residue *in vacuo*, and chromatography (5:1 hexanes:acetone eluent) provided methyl ether (±)-**192** (42 mg, 70% yield) as a yellow foam.

Preparation of Bis Methyl ether (±)-190.

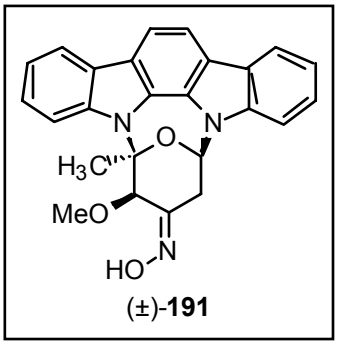


(±)-**190**

Bis Methyl ether (±)-190, Method A. A stirred room temperature solution of alcohol (±)-**192** (19 mg) in DMSO (3 mL) was treated with excess MeI (5-10 equiv) and KOH (5-10 equiv) for 5 min. After this time, the reaction was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, and evaporated. Purification by flash chromatography (1:1 hexanes:EtOAc eluent) provided bis-methyl ether (±)-**190** (20 mg, 95% yield) as a yellow solid: mp 218-224 °C (dec.); IR (thin film/NaCl) 3048.0 (m), 3003.5 (m), 2930.1 (m), 2829.9 (m), 1642.3 (m), 1565.2 (m), 1492.8 (w), 1460.9 (s), 1444.8 (s), 1396.0 (s), 1314.4 (s), 1230.2 (s), 1118.9 (s), 1035.8 (m), 740.7 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 7.0 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.41 (app.t, *J* = 7.3 Hz, 1H), 7.32 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.28 (app.t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.20 (app.t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 5.1 Hz, 1H), 3.99 (dt, *J* = 3.0, 6.4 Hz, 1H), 3.75 (d, *J* = 2.9 Hz, 1H), 3.52 (s, 3H), 2.85 (ddd, *J* = 0.9, 3.9, 15.0 Hz, 1H), 2.38 (s, 3H), 2.33 (ddd, *J* = 2.7, 5.5, 14.9 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 136.3, 127.7, 126.6, 126.0, 124.9, 124.2, 124.0, 120.5, 119.6, 119.2, 119.0, 114.6, 111.4, 111.2, 107.3, 91.3, 84.3, 80.0, 68.6, 57.5, 55.7, 30.3, 29.9; high resolution mass spectrum (EI) *m/z* 412.1784 [calcd for $C_{26}H_{24}N_2O_3$ (M^+) 412.1787].

Bis Methyl Ether (±)-35, Method B. A stirred room temperature solution of diol (±)-**184** (20 mg) in DMSO (3 mL) was treated with excess MeI (5-10 equiv) and KOH (5-10 equiv) for 5 min. After this time, the reaction was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, and evaporated. Purification by flash chromatography (1:1 hexanes:EtOAc eluent) provided bis-methyl ether (±)-**190** (19 mg, 93% yield) as a yellow solid.

Preparation of Oxime (±)-191.

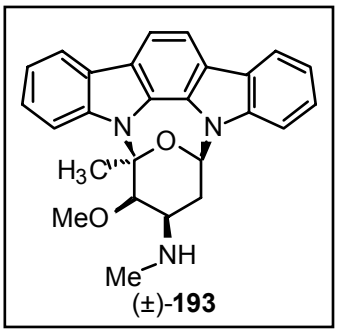


(±)-**191**

Oxime (±)-191. A suspension of ketone (±)-**186** (30 mg, 0.08 mmol, 1.0 equiv), hydroxylamine hydrochloride (17 mg, 0.24 mmol, 3.0 equiv), and NaOAc (20 mg, 0.24 mmol, 3.0 equiv) in 50% aqueous EtOH (2.0 mL) was heated gently to reflux for 30 min. After cooling to room temperature, the solvent was removed *in vacuo* and the derived residue was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to provide oxime (±)-**191** (27 mg, 85% yield) as a yellow powder: mp >280 °C (dec.); IR (thin film/NaCl) 3249.5 (br m), 2918.3 (s), 2848.4 (s), 1728.1 (m), 1640.2 (m), 1443.1 (s), 1398.1 (m), 1312.0 (m), 1124.5 (s), 740.7 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.17 (d, J = 7.8 Hz, 1H),

8.13 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.44 (app.t, *J* = 7.6 Hz, 1H), 7.34 (app.t, *J* = 7.7 Hz, 1H), 7.27 (app.t, *J* = 7.5 Hz, 1H), 7.20 (app.t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 5.5 Hz, 1H), 4.70 (s, 1H), 3.61 (d, *J* = 14.1 Hz, 1H), 3.42 (s, 3H), 2.97 (dd, *J* = 5.7, 14.3 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.3, 139.3, 135.9, 126.0, 125.1, 124.9, 124.6, 124.2, 124.0, 120.0, 119.6, 119.4, 119.1, 119.1, 115.0, 111.8, 111.0, 109.1, 95.9, 83.7, 82.2, 58.3, 29.7, 28.4; high resolution mass spectrum (EI) *m/z* 411.1582 [calcd for $C_{25}H_{21}N_3O_3$ (M^+) 411.1583].

Preparation of Amine (±)-193.



(±)-**193**

Amine (±)-193. A mixture of oxime (±)-**191** (20 mg, 0.049 mmol, 1.0 equiv) and PtO_2 (5 mg) in a 60% aqueous acetic acid (6.0 mL) was placed in a flasked capped with a H_2 filled balloon. The reaction was monitored by TLC (1:1 hexanes:EtOAc) and upon completion (2 h) was filtered through celite. The filtrate was evaporated *in vacuo* and the residue was dissolved in 1.0 N HCl (4.0 mL) and washed with EtOAc (1 x 4.0 mL). The aqueous layer was rendered basic with 3.0 N NaOH and then extracted with EtOAc (3 x 5.0mL). The

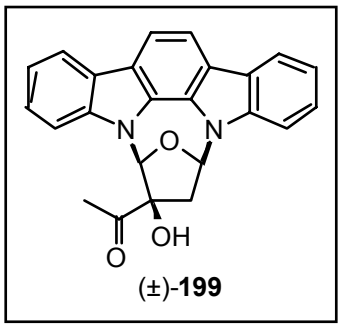
combined organic layers were dried over Na_2SO_4 and evaporated to a residue which was used without further purification.

An analytical sample of the derived primary amine could be obtained by preparative TLC of the above residue (5% MeOH/CH_2Cl_2 eluent): mp >225 °C (dec.); IR (thin film/NaCl) 3373.6 (br w), 3048.2 (br w), 2926.7 (br m), 2851.2 (br w), 1641.4 (m), 1563.9 (m), 1492.2 (m), 1459.0 (s), 1444.2 (s), 1314.0 (s), 1231.1 (s), 1110.2 (s), 741.3 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.43 (app.t, *J* = 7.6 Hz, 1H), 7.38 (app.t, *J* = 7.6 Hz, 1H), 7.27 (m, 3H), 6.55 (dd, *J* = 1.0, 5.5 Hz, 1H), 3.71 (d, *J* = 3.7 Hz, 1H), 3.65 (br m, 1H), 3.41 (s, 3H), 2.64 (dt, *J* = 5.3, 14.6 Hz, 1H), 2.58 (ddd, *J* = 1.1, 3.4, 14.4 Hz, 1H), 2.3 (s, 3H), 1.24 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 136.8, 126.8, 126.1, 125.8, 124.9, 124.6, 124.2, 120.6, 120.5, 119.8, 119.7, 119.5, 119.4, 114.7, 112.2, 111.4, 108.0, 91.2, 84.0, 80.3, 57.6, 42.7, 34.5, 29.7; high resolution mass spectrum (EI) *m/z* 397.1789 [calcd for $C_{25}H_{23}N_3O_2$ (M^+) 397.1790].

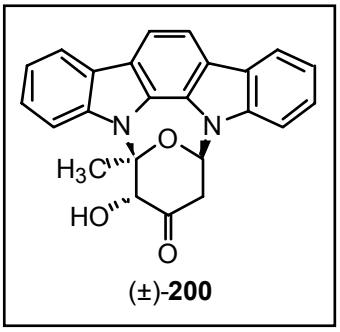
The derived residue was dissolved in THF (2.0 mL) and treated with an excess of formic acetic anhydride (3 equiv, prepared by treatment of 1.0 equiv acetic anhydride with 1.2 equiv formic acid followed by reflux for 2 h) in THF. TLC analysis showed rapid formation of a less polar substance. The solvent was evaporated with a stream of N_2 followed by high vacuum (ca. 1 torr) for 15 min. The derived residue was dissolved in THF (2.0 mL), cooled to 0 °C, and treated with BH_3•DMS (61 μL of a 2.0 N solution in toluene). The solution was heated to reflux for 2 h and then cooled to 0 °C. Methanolic HCl (4.0 mL) was added and the solution was refluxed for an additional hour. After cooling to room

temperature, volatiles were removed *in vacuo* leaving a solid residue to which was added 1.0 N NaOH (1.5 mL). The mixture was extracted with EtOAc (3 x 3.5 mL) and the combined organic layers were dried over Na_2SO_4. Purification of the residue by flash chromatography (10% MeOH/CH_2Cl_2 eluent) provided methyl amine (±)-**193** (14 mg, 70% yield 2 steps) as a white powder: mp 238-242 °C (dec.); IR (thin film/NaCl) 3344.1 (w), 3043.9 (m), 3000.7 (m), 2929.4 (m), 2850.6 (m), 2796.2 (m), 1642.5 (m), 1562.9 (m), 1442.1 (s), 1396.0 (m), 1341.5 (m), 1311.0 (s), 1232.2 (s), 1111.4 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.44 (td, *J* = 1.0, 7.7 Hz, 1H), 7.39 (ddd, *J* = 1.3, 7.1, 8.4 Hz, 1H), 7.31 (app.t, *J* = 7.7 Hz, 1H), 7.27 (app.t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.51 (dd, *J* = 1.3, 6.1 Hz, 1H), 3.83 (d, *J* = 3.5 Hz, 1H), 3.30 (s, 3H), 3.29 (dd, *J* = 4.1, 4.7 Hz, 1H), 2.63 (ddd, *J* = 1.5, 4.7, 14.5 Hz, 1H), 2.38 (ddd, *J* = 4.0, 6.1, 14.6 Hz, 1H), 2.34 (s, 3H), 1.69 (s, 3H), 0.84 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 136.6, 128.2, 127.3, 126.0, 124.7, 124.2, 123.8, 120.3, 120.0, 119.5, 119.2, 119.0, 119.0, 114.2, 111.7, 110.8, 107.5, 91.3, 84.0, 80.5, 57.5, 50.8, 33.4, 30.6, 29.7; high resolution mass spectrum (EI) *m/z* 411.1944 [calcd for $C_{26}H_{25}N_3O_2$ (M^+) 411.1947].

Preparation of Ketones (±)-199 and (±)-200.



(±)-**199**



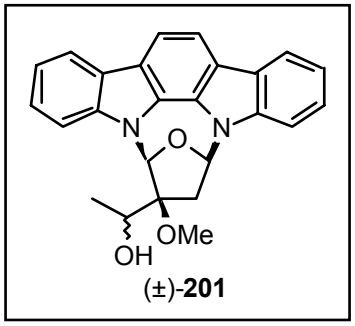
(±)-**200**

Ketones (±)-199 and (±)-200. To a suspension of aldehyde (±)-**176** (56 mg, 0.147 mmol, 1.0 equiv) in Et_2O (15.0 mL) was added BF_3•OEt_2 (20 μL, 0.161 mmol, 1.1 equiv). The mixture was stirred vigorously for 7 h and then treated with CH_2Cl_2 (25 mL) to solubilize the suspension. The resulting solution was adsorbed onto silica *in vacuo* and chromatographed (3:1 hexanes:EtOAc eluent) to provide two products. The first compound to elute, hydroxy ketone (±)-**200** (12 mg, 21% yield), was isolated as a yellow foam: IR (thin film/NaCl) 3461.9 (br m), 2924.5 (m), 1731.8 (s), 1570.7 (m), 1447.5 (m), 1389.4 (m), 1307.5 (s), 1227.4 (s), 1133.2 (s), 747.2 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.8 Hz, 1H), 8.17 (d, *J* = 4.7 Hz, 1H), 7.98 (s, 2H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.45-7.51 (comp m, 2H), 7.32-7.40 (comp m, 3H), 6.79 (dd, *J* = 4.8, 6.1 Hz, 1H), 5.13 (s, 1H), 3.65 (s, 1H), 3.41 (dd, *J* = 6.3, 15.9 Hz, 1H), 3.36 (dd, *J* = 4.7, 15.9 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 138.4, 137.2, 126.2, 125.9, 125.8, 125.5, 125.4, 125.3, 121.8, 121.2, 120.9, 120.6, 120.5, 120.4, 113.2, 112.8, 111.7, 108.2, 99.6, 83.8, 78.9, 42.6, 23.7; high resolution mass spectrum (EI) *m/z* 382.1319 [calcd for $C_{24}H_{18}N_2O_3$ (M^+) 382.1317].

The second compound to elute, ketone (±)-**199** (36 mg, 64% yield), was isolated as a white solid: mp >230 °C (dec.); IR (thin film/NaCl) 3458.1 (br m),

3053.6 (w), 2924.4 (m), 2855.9 (m), 1706.1 (s), 1655.1 (m), 1568.7 (m), 1447.9 (s), 1404.9 (s), 1342.9 (s), 1036.7 (m), 747.1 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 315 K) δ 8.19 (d, *J* = 7.9 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.45 (app.t, *J* = 7.6 Hz, 1H), 7.44 (app.t, *J* = 8.2 Hz, 1H), 7.36 (dd, *J* = 3.0, 7.5 Hz, 1H), 7.24-7.28 (m, 2H), 6.93 (s, 1H), 6.71 (s, 1H), 2.81 (dd, *J* = 7.5, 14.7 Hz, 1H), 2.47 (dd, *J* = 2.8, 14.8 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 206.0, 137.5, 137.0, 125.3, 124.9, 124.9, 124.3, 124.0, 123.9, 120.3, 120.3, 120.2, 119.7, 119.7, 119.5, 112.3, 112.2, 109.5, 109.4, 93.0, 87.8, 87.6, 42.8, 26.7; high resolution mass spectrum (EI) *m/z* 382.1312 [calcd for $C_{24}H_{18}N_2O_3$ (M^+) 382.1317].

Preparation of Diastereomeric Alcohols (±)-201.



(±)-**201**

Diastereomeric Alcohols (±)-201. To a mixture of ketone **199** (20 mg, 0.05 mmol, 1.0 equiv), MeI (86 μL, 1.4 mmol, 28 equiv), and powdered KOH (31 mg, 0.55 mmol, 10.5 equiv) in THF (5.0 mL) was added *n*-Bu_4NBr (3 mg, 0.01 mmol, 0.2 equiv). The mixture was stirred under N_2 for 30 min, solvent was removed *in vacuo*, and the residue was filtered through a pad of silica gel (3:1

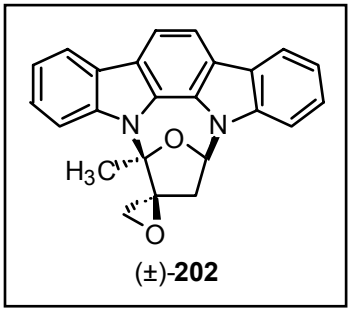
hexanes:EtOAc eluent) to afford a colorless residue used without further purification.

To a solution of the derived residue in 1:1 MeOH: CH_2Cl_2 (5.0 mL) was added $NaBH_4$ (10 mg, 0.27 mmol, 5.3 equiv) at room temperature. After 5 minutes solvent was removed under reduced pressure to afford a white solid, to which was added 1.0 N HCl (2 mL) on an ice bath. After 5 min at 0 °C, the mixture was warmed to room temperature, stirred for 15 min at 25 °C, and extracted with CH_2Cl_2 (3 x 2mL). The combined organic layers were dried with Na_2SO_4 and purified by preparative TLC (1% MeOH/CH_2Cl_2 eluent) to afford two diastereomeric products. The less polar alcohol (±)-**201 diastereomer I** (5 mg, 25% yield) was obtained as a yellow foam: IR (thin film/NaCl) 3510.6 (br m), 2928.1 (m), 2851.1 (m), 1649.8 (m), 1449.4 (s), 1400.3 (s), 1303.2 (s), 1223.4 (s), 1079.2 (m), 747.6 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.8 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.46-7.52 (comp m, 2H), 7.29-7.34 (comp m, 2H), 7.02 (dd, *J* = 3.7, 7.5 Hz, 1H), 6.82 (s, 1H), 3.81 (s, 3H), 3.10-3.14 (m, 1H), 2.88 (dd, *J* = 7.6, 15.6 Hz, 1H), 2.10 (br d, *J* = 8.9 Hz, 1H), 1.85 (dd, *J* = 3.8, 15.6 Hz, 1H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.1, 125.6, 125.0, 125.0, 124.9, 124.8, 124.3, 121.1, 121.0, 120.8, 120.2, 119.9, 112.6, 112.6, 111.0, 108.2, 92.9, 89.1, 87.3, 69.3, 53.2, 39.4, 18.6; high resolution mass spectrum (EI) *m/z* 398.1630 [calcd for $C_{25}H_{22}N_2O_3$ (M^+) 398.1630].

The more polar alcohol (±)-**201 diastereomer II** (13 mg, 65% yield) was obtained as a yellow foam: IR (thin film/NaCl) 3450.1 (br m), 3544.7 (br m), 3051.9 (w), 1651.8 (m), 1567.2 (m), 1403.4 (s), 1339.1 (s), 1301.7 (s), 1073.5 (s), 746.7 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 3.4 Hz, 1H), 8.16 (d, *J* = 3.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* =

8.2 Hz, 1H), 7.46-7.52 (comp m, 3H), 7.30-7.35 (comp m, 2H), 7.03 (dd, *J* = 3.1, 7.7 Hz, 1H), 6.67 (s, 1H), 3.67 (s, 3H), 3.57 (q, *J* = 6.2 Hz, 1H), 2.98 (dd, *J* = 7.8, 15.7 Hz, 1H), 2.33 (dd, *J* = 3.1, 15.7 Hz, 1H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.3, 126.0, 125.1, 125.1, 124.9, 124.7, 121.1, 120.8, 120.8, 120.5, 120.2, 119.8, 112.8, 112.4, 109.3, 108.4, 92.1, 89.9, 87.5, 68.4, 52.1, 37.5, 18.9; high resolution mass spectrum (EI) *m/z* 398.1630 [calcd for $C_{25}H_{22}N_2O_3$ (M^+) 398.1630].

Preparation of Epoxide (±)-202.

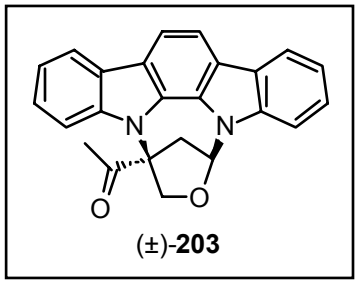


(±)-**202**

Epoxide (±)-202. To a solution of diol (±)-**179** (100 mg, 0.26 mmol, 1.0 equiv) and *p*-toluene sulfonyl chloride (52 mg, 0.27mmol, 1.05 equiv) in THF (2.6 mL) was added powdered KOH (36 mg, 0.65 mmol, 2.5 equiv) followed by *n*-Bu_4NBr (8 mg, 0.03 mmol, 0.1 equiv). The reaction mixture was stirred for 1 h, and solvent was removed *in vacuo*. Purification by flash chromatography (3:1∅1:1 hexanes:EtOAc) provided epoxide (±)-**202** (86 mg, 90% yield) as a white solid: mp >260 °C (dec.); IR (thin film/NaCl) 3049.6 (w), 3010.0 (w), 2947.3 (br w), 1638.2 (m), 1567.7 (m), 1445.6 (s), 1347.0 (m), 1307.5 (s), 1225.4 (m), 1026.0 (m), 744.9 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (app.t, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.5 Hz,

1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.45 (app.t, *J* = 7.6 Hz, 1H), 7.36 (app.t, *J* = 7.7 Hz, 1H), 7.28 (app.t, *J* = 8.2 Hz, 1H), 7.24 (app.t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 6.0 Hz, 1H), 3.28 (dd, *J* = 6.1, 14.9 Hz, 1H), 3.23 (d, *J* = 3.8 Hz, 1H), 2.98 (d, *J* = 4.2 Hz, 1H), 2.41 (s, 3H), 1.90 (d, *J* = 14.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.4, 136.5, 126.8, 125.2, 125.1, 124.9, 123.9, 120.4, 120.2, 120.1, 119.9, 119.6, 119.5, 112.6, 111.7, 111.6, 109.3, 96.7, 84.7, 66.5, 50.4, 37.4, 24.6; high resolution mass spectrum (EI) *m/z* 366.1363 [calcd for $C_{24}H_{18}N_2O_2$ (M^+) 366.1368].

Preparation of Ketone (±)-203.

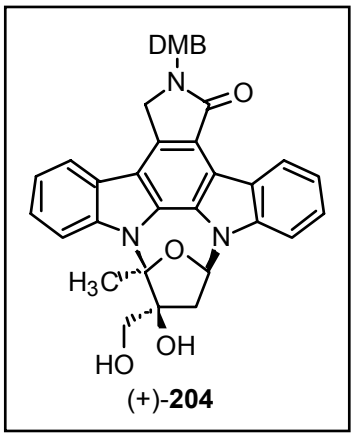


(±)-**203**

Ketone (±)-203. A solution of epoxide (±)-**202** (50 mg, 0.14 mmol, 1.0 equiv) in $CDCl_3$ (13.7 mL) was treated with BF_3•OEt_2 (18μL, 0.15 mmol, 1.05 equiv) and stirred at room temperature for 15 h. Following removal of solvent *in vacuo*, flash chromatography provided ketone (±)-**203** (47 mg, 92% yield) as a white solid: mp 180-183°; IR (thin film/NaCl) 3420.6 (br w), 3051.0 (w), 2924.3 (w), 1927.2 (w), 1717.8 (s), 1638.0 (m), 1568.9 (m), 1446.0 (s), 1347.6 (s), 1310.8 (s), 1219.7 (s), 1071.7 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.30-7.47 (comp m, 4H), 7.16 (d, *J* = 8.4 Hz,

1H), 6.69 (d, *J* = 7.4 Hz, 1H), 4.89 (d, *J* = 9.7 Hz, 1H), 4.01 (dd, *J* = 0.9, 9.8 Hz, 1H), 3.17 (d, *J* = 13.6 Hz, 1H), 2.97 (dd, *J* = 7.5, 13.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 138.6, 138.6, 127.1, 125.6, 125.3, 125.3, 124.5, 121.8, 121.6, 120.7, 120.5, 120.4, 120.3, 113.0, 112.7, 109.5, 108.3, 83.1, 75.7, 71.9, 45.6, 27.6; high resolution mass spectrum (EI) *m/z* 366.1363 [calcd for $C_{24}H_{18}N_2O$ (M^+) 366.1368].

Preparation of Diol (+)-204.

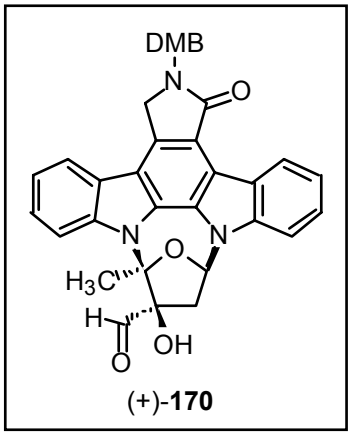


(+)-**204**

Diol (+)-204. To a stirred room temperature solution of ester (+)-**147** (150 mg, 0.243 mmol, 1.0 equiv) in THF (2.5 mL) was added $LiBH_4$ (12 mg, 0.535 mmol, 2.3 equiv) After 20 min the solvent was removed *in vacuo* and the derived white residue was cooled to 0 °C and treated with 1.0 N HCl (10.0 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4 and chromatographed (1:1 hexanes:EtOAc eluent) to afford diol (+)-**204** (127 mg, 89% yield) as a white solid: mp >225 °C (dec.); $[\alpha]^{20}_D$ +112° (*c* 0.1, MeOH); IR (thin film/NaCl) 3343.8 (br m), 3001.5 (w), 2950.7 (m), 2926.1 (m), 1647.4 (s), 1588.0 (m), 1514.4 (m),

1459.7 (s), 1422.2 (m), 1399.6 (m), 1312.4 (m), 1138.0 (s), 744.7 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.25 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.48 (app.t, *J* = 7.6 Hz, 1H), 7.43 (app.t, *J* = 7.8 Hz, 1H), 7.29 (app.t, *J* = 7.1 Hz, 1H), 7.28 (app.t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 7.96 (dd, *J* = 5.2, 7.2 Hz, 1H), 6.94 (s, 2H), 5.33 (s, 1H), 5.06 (t, *J* = 5.6 Hz, 1H), 5.02 (d, *J* = 17.7 Hz, 1H), 4.95 (d, *J* = 17.6 Hz, 1H), 4.85 (d, *J* = 15.9 Hz, 1H), 4.85 (d, *J* = 15.7 Hz, 1H), 3.85-3.81 (comp m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.14 (dd, *J* = 7.6, 13.7 Hz, 1H), 2.15 (s, 3H), 1.94 (dd, *J* = 4.8, 13.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 148.9, 148.1, 140.0, 136.7, 130.5, 130.2, 128.7, 125.4, 125.3, 124.6, 124.3, 123.8, 122.4, 120.9, 120.0, 119.8, 119.2, 118.5, 115.2, 114.9, 114.0, 112.1, 111.8, 108.7, 100.2, 83.5, 64.7, 55.5, 55.5, 49.6, 45.4, 40.2, 40.1, 21.3; high resolution mass spectrum (FAB) *m/z* 590.2289 [calcd for $C_{35}H_{32}N_3O_6$ (M+H) 590.2291].

Preparation of Aldehyde (+)-170.

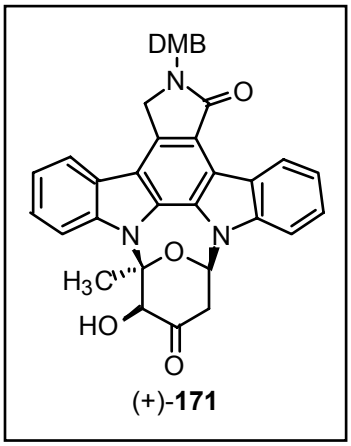


(+)-**170**

Aldehyde (+)-170. To a stirred solution of diol (+)-**204** (395 mg, 0.67 mmol, 1.0 equiv) in 1:1 benzene:DMSO (4.6 mL) was added pyridinium trifluoroacetate (130 mg, 0.67 mmol, 1.0 equiv) followed by 1,3-dicyclohexylcarbodiimide (415 mg, 2.01 mmol, 3.0 equiv). The flask was quickly sealed with a septum, evacuated, and flushed with N_2 (3 x). The heterogeneous mixture was stirred for 9 h at room temperature until reaction was complete as indicated by TLC. Benzene (5.0 mL) was added to the mixture and the 1,3-dicyclohexylurea (DCU) precipitate was filtered. The filtrate was washed with H_2O (3 x 5.0 mL) and the combined aqueous layers were back extracted with CH_2Cl_2 (3 x 10.0 mL). All organic layers were combined, dried over Na_2SO_4, and evaporated to give an oily residue. A minimum amount of acetone (2 mL) was added to precipitate the remaining DCU. Filtration and evaporation afforded a yellow oil, which was chromatographed (2:1∅1:1 hexanes:EtOAc eluent) to furnish aldehyde (+)-**170** (280 mg, 71% yield, 63% yield 2 steps) as a yellow powder: mp >205 °C (dec.); $[\alpha]^{20}_D$ +48° (*c* 0.1, MeOH); IR (thin film/NaCl) 3253.9 (br m), 3010.7 (m), 2953.6 (m), 2934.0 (m), 2833.9 (s), 1734.0 (s), 1646.2 (s), 1614.7 (w), 1589.9 (m), 1514.1 (m), 1399.1 (s), 1275.7 (m), 1138.4 (s), 1024.8 (m), 745.1 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.31

(d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.50 (app.t, *J* = 8.1 Hz, 1H), 7.47 (app.t, *J* = 8.2 Hz, 1H), 7.32 (app.t, *J* = 8.1 Hz, 2H), 7.17 (dd, *J* = 7.2, 4.8 Hz, 1H), 7.04 (s, 1H), 6.94 (d, *J* = 9.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.57 (br s, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.98 (d, *J* = 17.7 Hz, 1H), 4.87 (d, *J* = 15.2 Hz, 1H), 4.83 (d, *J* = 15.2 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.24 (dd, *J* = 7.6, 14.0 Hz, 1H), 2.22 (s, 3H), 2.00 (dd, *J* = 4.5, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 202.2, 168.7, 148.9, 148.1, 139.9, 136.9, 130.4, 130.2, 128.2, 125.5, 125.1, 123.9, 123.9, 122.5, 121.1, 120.4, 119.9, 119.6, 119.1, 115.8, 114.6, 114.4, 112.1, 111.8, 109.0, 98.7, 86.8, 84.3, 55.5, 55.5, 49.6, 45.5, 39.4, 22.7; high resolution mass spectrum (FAB) *m/z* 588.2135 [calcd for $C_{35}H_{30}N_3O_6$ (M+H) 588.2135].

Preparation of Ketone (+)-171.

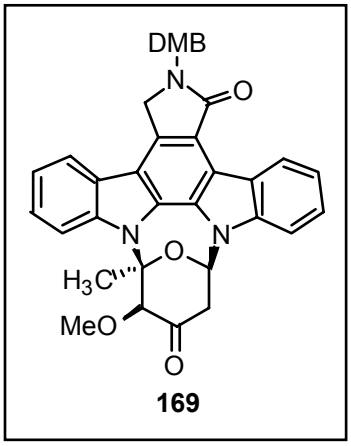


(+)-**171**

Ketone (+)-171. To a suspension of aldehyde (+)-**170** (100 mg, 0.170 mmol, 1.0 equiv) in Et_2O (17.0 mL) was added BF_3•OEt_2 (23 μL, 0.187 mmol, 1.1 equiv). The mixture was stirred vigorously for 12h at 25-30 °C and then treated with additional BF_3•OEt_2 (23 μL, 0.187 mmol, 1.1 equiv). After 12 h at

the same temperature the reaction mixture was filtered to provide ketone (+)-**171** (85 mg, 85% yield) as a white powder: mp >220 °C (dec.); $[\alpha]^{20}_{D}$ +83° (*c* 0.1, DMSO); IR (thin film/NaCl) 3300.0 (br s), 2999.5 (br m), 2848.6 (m), 1728.9 (m), 1665.5 (s), 1503.3 (m), 1451.2 (s), 1406.8 (m), 1132.8 (s), 1021.9 (m), 750.6 (s) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, 310 K) δ 9.35 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.53 (app.t, *J* = 7.6 Hz, 1H), 7.43 (app.t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 6.6 Hz, 1H), 7.35 (app.t, *J* = 7.5 Hz, 1H), 7.29 (app.t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 6.93 (s, 2H), 6.12 (d, *J* = 5.1 Hz, 1H), 5.23 (d, *J* = 4.5 Hz, 1H), 4.96 (s, 2H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.81 (d, *J* = 15.1 Hz, 1H), 3.97 (dd, *J* = 6.7, 14.1 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.66 (d, *J* = 14.1 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 201.1, 168.6, 148.9, 148.1, 140.3, 136.0, 130.4, 129.8, 126.9, 125.6, 125.5, 124.9, 124.0, 123.6, 122.8, 120.7, 120.4, 119.9, 119.9, 118.8, 115.9, 115.1, 114.3, 112.1, 111.8, 109.2, 100.5, 84.4, 80.0, 55.5, 55.5, 49.6, 45.4, 44.9, 29.4; high resolution mass spectrum (FAB) *m/z* 588.2135 [calcd for $C_{35}H_{30}N_3O_6$ (M+H) 588.2135].

Preparation of Methoxy Ketone 169.

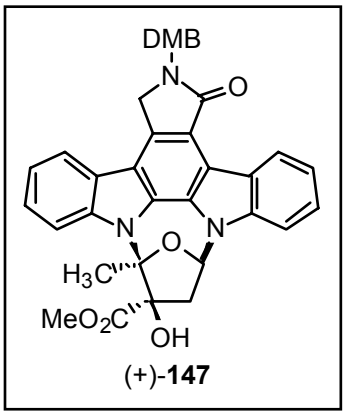


169

Methoxy Ketone 169. Montmorillonite clay K-10 (160 mg) was mixed with trimethylorthoformate (0.25 mL, 2.25 mmol, 15.0 equiv) and immediately transfered to a stirred solution of aldehyde (+)-**170** (90 mg, 0.15 mmol, 1.0 equiv) in $CHCl_3$ (0.6 mL). After 0.5 h the reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in Et_2O (15 mL) under an inert atmosphere, treated with BF_3•OEt_2 (0.39 mL, 3.15 mmol, 21.0 equiv), and stirred for 7 days at 25 °C. The reaction was diluted with CH_2Cl_2 (10 mL), adsorbed onto silica gel *in vacuo*, and chromatographed (1:1 hexanes:ethyl acetate eluent) to provide methoxy ketone **169** (6 mg, 5% yield) as a yellow residue: ^{1}H NMR (500 MHz, DMSO-d_6, 320 K) δ 9.35 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.53 (app.t, *J* = 7.6 Hz, 1H), 7.44 (app.t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 6.7 Hz, 1H), 7.35 (app.t, *J* = 7.5 Hz, 1H), 7.30 (app.t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 6.93 (s, 2H), 5.04 (s, 1H), 4.96 (s, 2H), 4.85 (d, *J* = 15.3 Hz, 1H), 4.81 (d, *J* = 14.7 Hz, 1H), 3.98 (dd, *J* = 6.8, 14.1 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.42 (s, 3H), 2.66 (d, *J* = 14.2 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 315 K) δ 200.0, 168.6, 148.9, 148.1, 139.9, 136.0, 130.4, 129.8, 126.8, 125.6, 125.5, 125.0, 124.9, 123.9, 123.6, 122.8,

120.8, 120.5, 120.0, 119.9, 118.9, 115.5, 115.2, 114.3, 112.2, 111.8, 109.1, 99.3, 88.0, 84.5, 58.9, 55.5, 49.5, 45.4, 29.4.

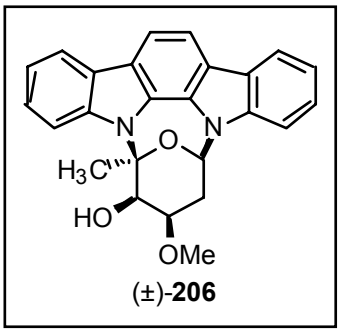
Preparation of Ester (+)-147.



(+)-**147**

Ester (+)-147. To a solution of ketone (+)-**171** (10 mg, 0.017 mmol, 1.0 equiv) in 1:1 MeOH/CH_2Cl_2 (1.0 mL) was added Copper (I) chloride (30 mg, 0.30 mmol, 17.8 equiv), and the mixture warmed to reflux for 15 min. Solvent was removed *in vacuo* and the resulting residue subjected to flash chromatography (1:1 hexanes:EtOAc) to afford ester (+)-**147** (10 mg, 95% yield) as a colorless solid that possessed spectral properties identical to material prepared previously in these laboratories.

Preparation of Ether (±)-206.

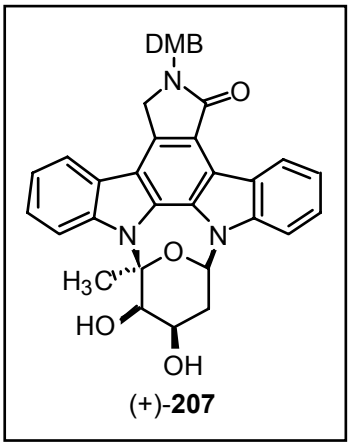


(±)-**206**

Ether (±)-206. A solution of diol (±)-**184** (38 mg, 0.10 mmol, 1.0 equiv) and $Bu_2Sn(OMe)_2$ (25 μL, 0.11 mmol, 1.1 equiv) in benzene (5.0 mL) was heated to reflux with azeotropic removal of H_2O (Dean-Stark apparatus) for 1 h. The solvent was removed *in vacuo*, followed by addition of CH_3CN (5.0 mL), MeI (6.8 μL, 0.11 mmol, 1.1 equiv), and Ag_2O (25 mg, 0.11, 1.1 equiv). The resulting mixture was heated at reflux over 4 h, diluted with H_2O (3 mL), and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4 and purified by flash chromatography (5:1 hexanes:acetone) to provide recovered diol (±)-**184** (8 mg) and ether (±)-**206** (6 mg, 15% yield) as a yellow solid: mp 213-217 °C (dec.); IR (thin film/NaCl) 3535.7 (br w), 3413.5 (w), 2963.2 (m), 2924.4 (s), 2853.7 (m), 1437.1 (m), 1314.6 (s), 735.0 (m) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.18 (d, *J* = 7.0 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.42 (app.t, *J* = 7.3 Hz, 1H), 7.30 (app.t, *J* = 8.4 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.17 (app.t, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 4.7 Hz, 1H), 4.27 (dd, *J* = 3.3, 10.0 Hz, 1H), 3.80 (m, 2H), 2.88 (ddd, *J* = 1.3, 3.6, 15.4 Hz, 1H), 2.58 (ddd, *J* = 2.8, 5.5, 15.4 Hz, 1H), 2.34 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 140.5, 137.0, 128.5, 126.6, 125.1, 125.1, 124.5, 120.7, 119.9, 119.8, 119.5, 115.7, 112.1, 111.4, 108.9, 93.3, 80.6, 74.7, 74.6, 74.1, 55.5, 30.1;

high resolution mass spectrum (EI) *m/z* 398.1630 [calcd for $C_{25}H_{22}N_2O_3$ (M^+) 398.1630].

Preparation of Diol (+)-207.

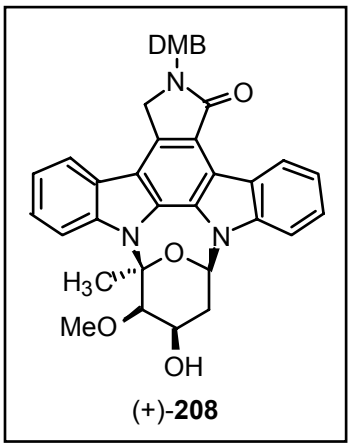


(+)-**207**

Diol (+)-207. To a stirred room temperature solution of ketone (+)-**171** (85 mg, 0.15 mmol, 1.0 equiv) in 1:1:2 MeOH:CH_2Cl_2:$CHCl_3$ (20.0 mL), was added $NaBH_4$ (20 mg, 0.53 mmol, 3.5 equiv). After 5 min, solvent was removed *in vacuo* and the residual white solid was cooled to 0 °C and treated with 1.0 N HCl (10 mL) at 0 °C. The mixture was stirred for 15 min at 25 °C and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried with Na_2SO_4 and chromatographed (1:1 hexanes:EtOAc eluent) to afford alcohol (+)-**207** (81 mg, 95% yield) as a white solid: mp 174-176 °C (dec.); $[\alpha]^{20}_D$ +37° (*c* 0.1, MeOH); IR (thin film/NaCl) 3355.5 (br m), 2922.9 (m), 2847.8 (m), 1654.5 (s), 1501.5 (w), 1449.3 (s), 1254.5 (s), 1136.8 (s), 1025.7 (m), 747.1 (s) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.53 (d, *J* = 7.9 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.46 (app.t, *J* = 7.2 Hz, 1H), 7.36 (app.t, *J* = 7.9 Hz, 1H), 7.29 (app.t, *J* = 7.4 Hz, 1H), 7.22 (app.t, *J* = 7.4 Hz, 1H), 7.08 (s,

1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 5.1 Hz, 1H), 4.95 (d, *J* = 17.1 Hz, 1H), 4.90 (d, *J* = 17.1 Hz, 1H), 4.89 (d, *J* = 15.2 Hz, 1H), 4.85 (d, *J* = 15.2 Hz, 1H), 4.24 (d, *J* = 8.5 Hz, 1H), 4.23 (br s, 1H), 4.14 (d, *J* = 8.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.64 (br s, 1H), 2.76 (d, *J* = 15.1 Hz, 1H), 2.65 (d, *J* = 15.1 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.4, 150.6, 149.7, 141.2, 137.7, 132.0, 130.7, 130.4, 127.6, 127.1, 125.8, 125.3, 125.0, 124.3, 121.5, 121.0, 120.6, 120.0, 119.8, 116.6, 116.0, 115.0, 112.8, 108.9, 93.3, 80.6, 74.7, 65.4, 56.1, 50.4, 46.6, 35.4, 30.4; high resolution mass spectrum (FAB) *m/z* 590.2289 [calcd for $C_{35}H_{32}N_3O_6$ (M+H) 590.2291].

Preparation of Alcohol (+)-208.

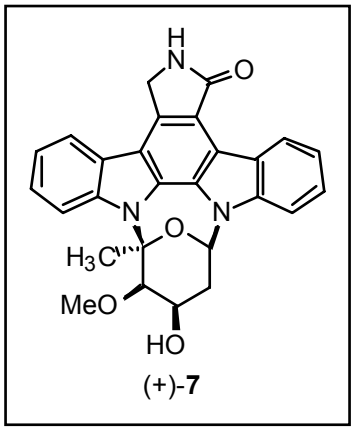


(+)-**208**

Alcohol (+)-208. To a stirred suspension of NaH (14 mg, 0.58 mmol, 4.2 equiv) in THF (1.0 mL) was added a solution of alcohol (+)-**207** (81 mg, 0.138 mmol, 1.0 equiv) in THF (7 mL). The resulting mixture was stirred for 10 min with the visible evolution of gas, and for an additional 15 min thereafter. Addition of MeI (9.5 μL, 0.15 mmol, 1.1 equiv) produced a single product by TLC (2.5:1 hexanes:acetone). After approximately 50 min the reaction was quenched by

addition of 1.0 N HCl (1.0 mL) followed by 2.0 mL H_2O. Extraction of the solution with CH_2Cl_2 (3 x 10 mL), drying over Na_2SO_4 and evaporation furnished a residue which was purified by flash chromatography (2.5:1 hexanes:acetone eluent) to provide methyl ether (+)-**208** (67 mg, 80% yield) as a yellow solid: mp >235 °C (dec.); $[\alpha]^{20}_D$ +48° (*c* 0.1, MeOH); IR (thin film/NaCl) 3423.7 (br m), 2923.2 (s), 2848.1 (m), 2636.2 (m), 1647.2 (s), 1514.3 (m), 1462.9 (s), 1258.0 (m), 1235.3 (m), 1136.9 (m), 1026.9 (w), 743.3 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.48 (app.t, *J* = 7.6 Hz, 1H), 7.41 (app.t, *J* = 7.2 Hz, 1H), 7.38 (app.t, *J* = 7.2 Hz, 1H), 7.28 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.95 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 5.8 Hz, 1H), 4.96 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.84 (d, *J* = 16.7 Hz, 1H), 4.79 (d, *J* = 16.6 Hz, 1H), 4.38 (d, *J* = 2.6 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.71 (d, *J* = 2.6 Hz, 1H), 3.57 (s, 3H), 2.76 (dd, *J* = 3.1, 15.1 Hz, 1H), 2.50 (br d, *J* = 14.7 Hz, 1H), 2.3 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 315 K) δ 170.3, 149.6, 148.7, 140.1, 136.8, 130.8, 129.4, 127.0, 126.4, 125.3, 124.8, 124.3, 123.7, 120.7, 120.4, 120.2, 120.0, 119.6, 116.0, 115.5, 114.5, 111.6, 111.5, 107.1, 90.7, 83.2, 79.5, 60.6, 57.4, 56.1, 56.0, 49.9, 46.5, 33.6, 30.1; high resolution mass spectrum (FAB) *m/z* 604.2449 [calcd for $C_{36}H_{34}N_3O_6$ (M+H) 604.2448].

Preparation of (+)-RK286c (7).



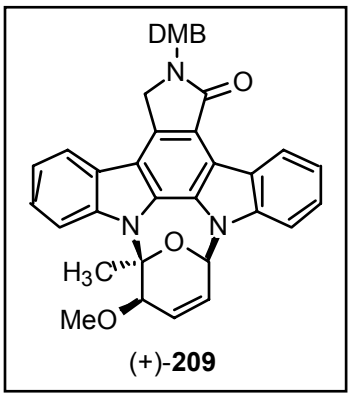
(+)-**7**

(+)-RK286c (7). To a stirred solution of ether (+)-**208** (10 mg, 0.017 mmol, 1.0 equiv) in anisole or thioanisole (80 μL) was added TFA (0.5 mL). After the reaction had proceeded to completion as evidenced by TLC (ca. 24 h), H_2O (1.0 mL) was added and the derived mixture extracted with CH_2Cl_2 (3 x 5mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue which was purified by preparative TLC (5% MeOH/CH_2Cl_2) to provide (+)-RK-286c (**7**, 6 mg, 75% yield) as a pale white powder: mp >255 °C (dec.); $[\alpha]^{20}_D$ +41.1° (*c* 0.18, EtOAc); IR (thin film/NaCl) 3354.0 (br m), 2920.4 (s), 2851.6 (m), 1677.2 (s), 1636.0 (m), 1585.3 (m), 1456.2 (s), 1352.8 (s), 1318.7 (s), 1231.7 (m), 1117.3 (m), 743.8 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.27 (d, *J* = 7.9 Hz, 1H), 8.47 (br s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.45 (app.t, *J* = 7.4 Hz, 1H), 7.40 (app.t, *J* = 7.5 Hz, 1H), 7.26 (app.t, *J* = 7.5 Hz, 2H), 6.78 (d, *J* = 5.3 Hz, 1H), 4.95 (d, *J* = 17.6 Hz, 1H), 4.89 (d, *J* = 17.7 Hz, 1H), 4.25 (br s, 1H), 4.17 (br s, 1H), 3.83 (d, *J* = 2.7 Hz, 1H), 3.41 (s, 3H), 2.60 (ddd, *J* = 3.2, 5.6, 14.8 Hz, 1H), 2.41 (dd, *J* = 3.3, 14.8 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.3, 139.7, 136.1, 129.5, 125.5, 124.7, 124.1, 123.9,

122.6, 120.6, 119.5, 118.9, 118.6, 115.7, 108.6, 90.9, 82.3, 79.5, 58.8, 56.4, 45.3, 33.9, 29.9; high resolution mass spectrum (FAB) *m/z* 454.1766 [calcd for $C_{27}H_{24}N_3O_4$ (M+H) 454.1767].

(+)-*nat*-RK286c (7):[2] mp >265 °C (dec.); $[\alpha]^{20}_D$ +45.3° (*c* 0.22, EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (d, *J* = 7.5 Hz, 1H), 8.45 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.95 (dd, *J* = 1.0, 7.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.46 (ddd, *J* = 1.0, 7.6, 8.4 Hz, 1H), 7.41 (ddd, *J* = 1.0, 7.6, 8.0 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.77 (dd, *J* = 1.0, 5.1 Hz, 1H), 4.97 (d, *J* = 16.8 Hz, 1H), 4.89 (d, *J* = 16.8 Hz, 1H), 4.27 (m, 1H), 4.17 (d, *J* = 3.6 Hz, 1H), 3.84 (d, *J* = 3.8 Hz, 1H), 3.42 (s, 3H), 2.61 (m, 1H), 2.41 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 139.7, 136.1, 132.0, 129.5, 126.2, 125.5, 124.7, 124.1, 123.9, 122.6, 120.6, 119.6, 118.9, 118.6, 115.7, 114.0, 113.5, 108.5, 90.9, 82.3, 79.5, 58.8, 56.5, 45.4, 29.8, 29.0.

Preparation of Olefin (+)-209.

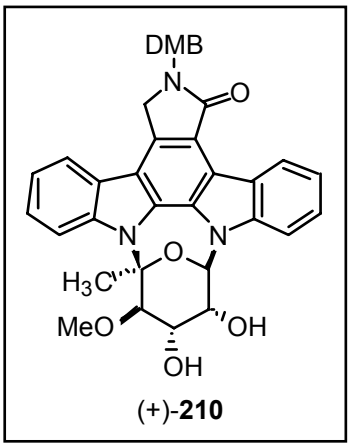


(+)-**209**

Olefin (+)-209. To a stirred solution of ether (+)-**208** (112 mg, 0.186 mmol, 1.0 equiv) in $CDCl_3$ (2.0 mL) was added Martin's sulfurane (187 mg, 0.28

mmol, 1.5 equiv). The reaction rapidly proceeded to a less polar product as evidenced by TLC and after 20 min was complete. Solvent was evaporated and the residue subjected to flash chromatography (2:1 hexanes:EtOAc eluent) to provide olefin (+)-**209** (96 mg, 88% yield) as a white solid: mp 185-187 °C; $[\alpha]^{20}_{D}$ +36° (*c* 0.1, MeOH); IR (thin film/NaCl) 2920.5 (s), 2851.5 (s), 1709.8 (m), 1674.3 (s), 1589.0 (m), 1513.7 (m), 1457.5 (s), 1222.9 (m), 1026.6 (m), 745.3 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, 315 K) δ 9.31 (d, *J* = 7.9 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.50 (td, *J* = 1.0, 7.34 Hz, 1H), 7.43 (app.t, *J* = 7.8 Hz, 1H), 7.31 (app.t, *J* = 7.0 Hz, 1H), 7.28 (app.t, *J* = 7.1 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.02 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.09 (d, *J* = 10.4 Hz, 1H), 5.77 (dt, *J* = 2.3, 10.4 Hz, 1H), 4.95 (s, 2H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.81 (d, *J* = 15.1 Hz, 1H), 4.48 (d, *J* = 1.4 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.9, 150.5, 149.7, 141.3, 137.4, 131.8, 131.2, 130.5, 127.7, 127.1, 126.4, 126.2, 125.5, 125.3, 124.3, 121.5, 121.2, 121.1, 120.5, 120.4, 118.0, 117.1, 115.9, 112.8, 112.8, 109.1, 91.5, 80.8, 78.8, 57.7, 56.0, 56.0, 50.5, 46.5, 28.0; high resolution mass spectrum (FAB) *m/z* 586.2343 [calcd for $C_{36}H_{32}N_3O_5$ (M+H) 586.2342].

Preparation of Diol (+)-210.

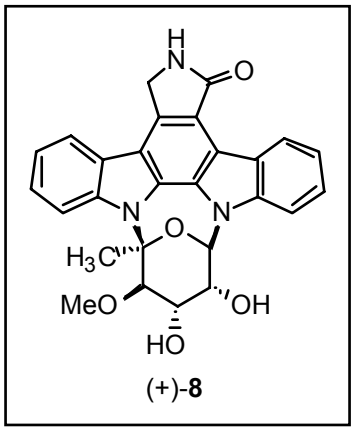


(+)-**210**

Diol (+)-210. To a stirred solution of 4-methylmorpholine-*N*-oxide (6 mg, 0.05 mmol, 1.2 equiv) and OsO_4 (0.6 mL of a 2.5% solution in *t*-BuOH, 0.05 mmol, 1.2 equiv) in 4:1 acetone:H_2O (2 mL) was added a solution of olefin (+)-**209** (25 mg, 0.043 mmol, 1.0 equiv) in acetone (1 mL). The reaction was monitored by TLC, and after 16 h had proceeded to completion. At this time, $NaHSO_3$ (100 mg) in H_2O (1.0 mL) was added and the resulting black solution was stirred for 20 min, filtered, and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, evaporated to a residue, and purified by flash chromatography (1:1 hexanes:EtOAc eluent) to provide diol (+)-**210** (23 mg, 84% yield) as a white powder: mp 227-230 °C; $[\alpha]^{20}_D$ +17° (*c* 0.1, MeOH); IR (thin film/NaCl) 3411.2 (br m), 2929.3 (m), 2849.4 (w), 2656.3 (m), 1590.0 (m), 1514.0 (m), 1461.2 (s), 1350.9 (m), 1273.6 (s), 1127.1 (s), 1025.0 (m), 743.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.36 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.55 (app.t, *J* = 7.6 Hz, 1H), 7.45 (app.t, *J* = 7.7 Hz, 1H), 7.35 (app.t, *J* = 7.5 Hz, 1H), 7.29 (app.t, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 2H), 6.59 (d, *J* = 1.6 Hz, 1H), 6.13 (d, *J* = 3.8 Hz, 1H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.99 (d, *J* = 17.8 Hz, 1H), 4.95

(d, *J* = 17.8 Hz, 1H), 4.83 (s, 2H), 4.12 (d, *J* = 10.1 Hz, 1H), 4.12 (dd, *J* = 2.3, 3.8 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 3.55 (ddd, *J* = 2.3, 6.1, 10.1 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 148.9, 148.1, 140.3, 136.5, 130.4, 129.9, 127.8, 125.7, 125.0, 124.7, 123.5, 122.7, 120.8, 120.2, 119.9, 119.9, 118.7, 115.5, 114.8, 114.1, 112.0, 111.7, 108.8, 95.6, 87.3, 83.1, 71.7, 65.6, 61.6, 55.5, 55.5, 49.6, 45.5, 29.0; high resolution mass spectrum (FAB) *m/z* 620.2390 [calcd for $C_{36}H_{34}N_3O_7$ (M+H) 620.2397].

Preparation of (+)-MLR-52 (8).



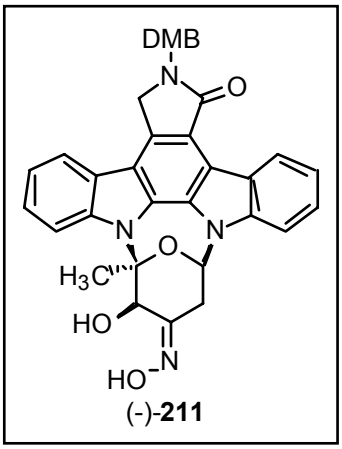
(+)-**8**

(+)-MLR-52 (8). To a stirred solution of diol (+)-**210** (10 mg, 0.016 mmol, 1.0 equiv) in anisole or thioanisole (80 μL) was added TFA (0.5 mL). The reaction was monitored by TLC, and after 16 h had proceeded to completion. The reaction mixture was treated with H_2O (1.0 mL) and then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue. Purification by preparative TLC (5% MeOH/CH_2Cl_2) provided (+)-MLR-52 (**5**, 6 mg, 77% yield) as a white solid: mp >260 °C (dec.); $[\alpha]^{20}_D$ +65° (*c* 0.1, MeOH);

IR (thin film/NaCl) 3348.5 (br m), 2922.9 (s), 2851.9 (m), 1638.2 (s), 1586.6 (m), 1455.5 (s), 1373.5 (m), 1336.6 (m), 1320.8 (m), 1275.0 (m), 1224.7 (m), 1200.3 (w), 1119.5 (s), 740.8 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.31 (d, *J* = 7.9 Hz, 1H), 8.61 (br s, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.53 (app.t, *J* = 7.5 Hz, 1H), 7.45 (td, *J* = 0.8, 7.7 Hz, 1H), 7.32 (app.t, *J* = 7.4 Hz, 1H), 7.32 (app.t, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 1.6 Hz, 1H), 6.12 (d, *J* = 4.0 Hz, 1H), 5.06 (d, *J* = 5.9 Hz, 1H), 4.99 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 17.5 Hz, 1H), 4.13 (d, *J* = 10.3 Hz, 1H), 4.12 (dd, *J* = 1.6, 2.6 Hz, 1H), 3.62 (s, 3H), 3.56 (ddd, *J* = 2.6, 6.2, 10.3 Hz, 1H), 3.28 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.8, 140.2, 136.4, 132.6, 127.8, 125.8, 125.5, 124.8, 124.6, 123.6, 122.7, 120.9, 120.1, 119.7, 119.3, 115.4, 114.9, 114.3, 108.7, 95.6, 87.2, 83.1, 71.7, 65.6, 61.6, 45.4, 29.0; high resolution mass spectrum (FAB) *m/z* 470.1717 [calcd for $C_{27}H_{24}N_3O_5$ (M+H) 470.1716].

(+)-*nat*-MLR-52 (8):[4] mp 263-268 °C; $[\alpha]^{20}_D$ +68° (*c* 0.093, MeOH); ^1H NMR (not reported MHz, DMSO-d_6) δ 9.31 (br d, *J* = 8.1 Hz, 1H), 8.01 (br d, *J* = 7.7 Hz, 1H), 7.98 (br d, *J* = 8.8 Hz, 1H), 7.64 (br d, *J* = 8.4 Hz, 1H), 7.54 (br dd, *J* = 7.0, 8.4 Hz, 1H), 7.45 (br dd, *J* = 7.0, 8.8 Hz, 1H), 7.29 (br dd, *J* = 7.0, 8.1 Hz, 1H), 7.27 (br dd, *J* = 7.0, 7.7 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 4.99 (d, *J* = 17.9 Hz, 1H), 4.95 (d, *J* = 17.9 Hz, 1H), 4.16 (dd, *J* = 1.8, 2.6 Hz, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 3.62 (s, 3H), 3.57 (dd, *J* = 2.6, 10.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (not reported MHz, DMSO-d_6) δ 171.8, 140.2, 136.4, 132.6, 127.8, 125.8, 125.5, 124.8, 124.6, 123.6, 122.8, 120.9, 120.1, 119.7, 119.2, 115.5, 114.9, 114.3, 108.7, 95.6, 87.3, 83.1, 71.7, 65.6, 61.6, 45.4, 29.0.

Preparation of Oxime (-)-211.

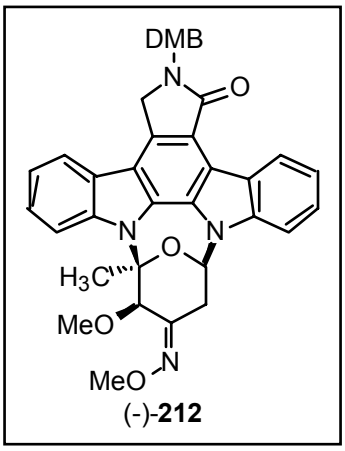


(-)-**211**

Oxime (-)-211. A suspension of ketone (+)-**171** (100 mg, 0.17 mmol, 1.0 equiv), hydroxylamine hydrochloride (165 mg, 2.38 mmol, 14.0 equiv), and NaOAc (167 mg, 2.04 mmol, 12 equiv) in 80% aqueous EtOH (35.0 mL) was heated gently to reflux for 30 min. Following cooling to room temperature, the sovent was removed *in vacuo*, and the residue purified by flash chromatography (1:1 hexanes:EtOAc eluent) to provide oxime (-)-**211** (98 mg, 95% yield) as a yellow powder: mp >270 °C (dec.); $[\alpha]^{20}_{D}$ -18° (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 3324.0 (br m), 2995.0 (w), 2911.3 (m), 1660.0 (s), 1589.7 (m), 1513.5 (s), 1461.1 (s), 1417.9 (m), 1399.0 (m), 1349.2 (s), 1315.5 (m), 1260.0 (s), 1234.6 (m), 1124.4 (m), 1027.2 (m), 741.7 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.34 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.51 (app.t, *J* = 7.6 Hz, 1H), 7.42 (app.t, *J* = 7.9 Hz, 1H), 7.32 (app.t, *J* = 7.7 Hz, 1H), 7.28 (app.t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 6.3 Hz, 1H), 7.03 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 5.56 (m, 2H), 4.97 (d, *J* = 18.1 Hz, 1H), 4.93 (d, *J* = 16.9 Hz, 1H), 4.85 (d, *J* = 15.0 Hz, 1H), 4.45 (d, *J* = 15.0 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.61 (d, *J* = 13.9 Hz, 1H), 3.01 (dd, *J* = 5.8, 14.3 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-

d_6) δ 168.8, 148.9, 148.1, 147.4, 140.2, 136.1, 130.5, 129.6, 128.1, 125.4, 125.3, 124.7, 124.6, 123.6, 122.8, 120.5, 120.1, 119.9, 119.6, 118.5, 116.0, 114.8, 113.9, 112.1, 111.9, 108.9, 97.4, 82.0, 74.9, 55.5, 55.5, 49.5, 45.5, 29.6, 28.6; high resolution mass spectrum (FAB) *m/z* 603.2238 [calcd for $C_{35}H_{31}N_4O_6$ (M+H) 603.2244].

Preparation of Methyl Ether (-)-212.

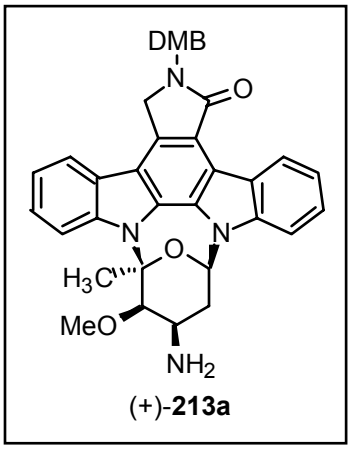


(-)-**212**

Methyl Ether (-)-212. To a mixture of oxime (-)-**211** (90 mg, 0.15 mmol, 1.0 equiv), MeI (88 μL, 1.42 mmol, 9.5 equiv), and powdered KOH (88 mg, 1.58 mmol, 10.5 equiv) in THF (15 mL) was added *n*-Bu_4NBr (10 mg, 0.03 mmol, 0.2 equiv). The mixture was stirred under N_2 for 30 min, solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (1:1 hexanes:EtOAc eluent) to provide methyl ether (-)-**212** (85 mg, 90% yield) as a yellow powder: mp >270 °C (dec.); $[\alpha]^{20}_D$ -22° (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 2998.0 (w), 2926.3 (m), 1674.1 (s), 1590.0 (m), 1513.7 (s), 1460.9 (s), 1418.2 (m), 1397.9 (s), 1349.4 (s), 1316.2 (s), 1262.1 (m), 1225.6 (m), 1044.3 (m), 743.5 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 345 K) δ 9.36 (d, *J* = 8.0 Hz,

1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.51 (app.t, *J* = 7.6 Hz, 1H), 7.44 (app.t, *J* = 7.8 Hz, 1H), 7.33 (app.t, *J* = 7.2 Hz, 1H), 7.30 (app.t, *J* = 7.1 Hz, 1H), 7.04 (s, 1H), 7.02 (d, *J* = 5.6 Hz, 1H), 6.97 (d, *J* = 9.4 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 4.97 (s, 2H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.85 (d, *J* = 15.7 Hz, 1H), 4.76 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.54 (d, *J* = 14.4 Hz, 1H), 3.45 (s, 3H), 3.16 (dd, *J* = 5.9, 14.4 Hz, 1H), 3.14 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.7, 148.9, 148.1, 147.3, 139.8, 136.1, 130.4, 129.5, 128.0, 125.4, 125.3, 124.7, 124.6, 123.6, 122.7, 120.6, 120.2, 119.9, 119.6, 118.6, 115.5, 114.9, 113.8, 112.2, 112.0, 108.9, 96.1, 83.3, 82.0, 60.8, 58.4, 55.5, 55.5, 49.5, 45.4, 30.4, 28.5; high resolution mass spectrum (FAB) *m/z* 631.2564 [calcd for $C_{37}H_{35}N_4O_6$ (M+H) 631.2557].

Preparation of Amine (+)-213a.



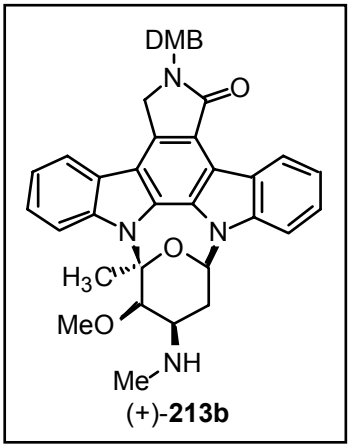
(+)-**213a**

Amine (+)-213a. A mixture of methyl ether (-)-**212** (85 mg, 0.13 mmol, 1.0 equiv) and PtO_2 (28 mg) in a 60% aqueous acetic acid (15.0 mL) was place in a flask capped with a H_2 filled balloon. The reaction was monitored by TLC (1:1

hexanes:EtOAc) and upon completion was filtered through celite. The filtrate was evaporated and the residue dissolved in CH_2Cl_2 (40 mL) and washed with 1.0 N NaOH (8.0 mL). The aqueous layer was back-extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layers were dried over Na_2SO_4, and evaporated to a residue (79 mg) which was typically used in the next step without further purification.

An analytically pure sample of primary amine could be obtained by preparative TLC (5% MeOH/CH_2Cl_2 eluent) of the above residue to afford amine (+)-**213a** as a yellow powder: mp >275 °C (dec.); $[\alpha]^{20}_D$ +14.3° (*c* 0.14, $CHCl_3$); IR (thin film/NaCl) 3414.7 (br w), 2920.8 (s), 2851.7 (s), 1733.7 (w), 1672.8 (s), 1636.0 (w), 1588.1 (m), 1513.5 (s), 1352.7 (s), 1259.3 (s), 1136.7 (m), 744.2 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 310 K) δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.51 (app.t, *J* = 7.6 Hz, 1H), 7.42 (app.t, *J* = 8.2 Hz, 1H), 7.40 (app.t, *J* = 7.5 Hz, 1H), 7.30 (app.t, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 9.4 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 4.9 Hz, 1H), 4.98 (d, *J* = 14.9 Hz, 1H), 4.92 (d, *J* = 14.9 Hz, 1H), 4.87 (d, *J* = 16.7 Hz, 1H), 4.82 (d, *J* = 16.7 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75 (m, 2H), 3.46 (s, 3H), 2.63 (m, 2H), 2.32 (s, 3H), 1.27 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 315 K) δ 170.2, 149.6, 148.7, 140.1, 137.0, 130.8, 129.6, 129.5, 127.0, 126.2, 125.4, 124.7, 124.5, 123.8, 120.8, 120.5, 120.2, 120.2, 119.6, 116.0, 115.4, 114.6, 111.6, 111.6, 107.4, 91.3, 84.2, 80.2, 57.5, 56.1, 56.1, 49.9, 46.5, 42.6, 34.6, 30.0; high resolution mass spectrum (FAB) *m/z* 603.2229 [calcd for $C_{36}H_{35}N_4O_5$ (M+H) 603.2610].

Preparation of Methyl Amine (+)-213b.

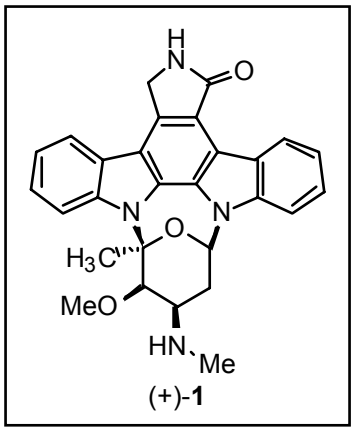


(+)-**213b**

Methyl Amine (+)-213b. A solution of amine (+)-**213a** (79 mg) in THF (2.0 mL) was treated with formic acetic anhydride in THF (1.3 μL of a 1.3 M solution in THF, 0.17 mmol, 1.3 equiv, prepared by treatment of 1.0 equiv acetic anhydride with 1.2 equiv formic acid followed by reflux for 2 h). After TLC analysis showed complete formation of a less polar substance, a stream of N_2 followed by high vacuum (ca. 1 torr for 15 min) was used to evaporate the solvent. The resultant residue was dissolved in THF (1.3 mL), cooled to 0 °C, and treated with BH_3•DMS (193 μL of a 2.0 N solution in toluene, 0.39 mmol, 3.0 equiv). The solution was heated to reflux for 2 h, cooled to 0 °C, and treated with methanolic HCl (1.0 mL) in excess MeOH (1.3 mL). The derived solution was then heated to reflux for an additional hour. After cooling, the volatiles were removed *in vacuo*, and residual boron was removed by repetative dissolution of the solids in MeOH followed by evaporation *in vauco* (5 x 5.0 mL). The remaining residue was treated with CH_2Cl_2 (7.0 mL) and 1.0 N NaOH (5.0 mL). The biphasic mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 7.0 mL). The combined organic layers were dried over Na_2SO_4, evaporated, and purified by flash chromatography (5% MeOH/CH_2Cl_2 eluent) to furnish methyl amine (+)-**213b** [80 mg, 91% yield, 2 steps from (-)-**212**] as a

yellow solid: mp 225-230 °C (dec.); $[\alpha]^{20}_{D}$ +22° (*c* 0.1, MeOH); IR (thin film/NaCl) 2954.1 (m), 2915.1 (m), 1673.2 (s), 1635.8 (m), 1462.7 (s), 1399.0 (s), 1352.6 (s), 1258.7 (m), 1136.5 (m), 1026.9 (m), 745.2 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 320 K) δ 9.55 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.48 (td, *J* = 1.0, 7.5 Hz, 1H), 7.39 (td, *J* = 1.0, 7.4 Hz, 1H), 7.38 (app.t, *J* = 7.3 Hz, 1H), 7.27 (m, 2H), 7.01 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.57 (dd, *J* = 1.4, 6.0 Hz, 1H), 4.98 (d, *J* = 14.9 Hz, 1H), 4.91 (d, *J* = 14.9 Hz, 1H), 4.84 (s, 2H), 3.92 (d, *J* = 3.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.37 (dd, *J* = 3.8, 7.7 Hz, 1H), 3.33 (br s, 3H), 2.72 (ddd, *J* = 1.3, 4.6, 14.5 Hz, 1H), 2.46 (m, 1H), 2.35 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 149.3, 148.4, 139.6, 136.7, 130.6, 130.4, 129.3, 127.1, 126.6, 125.1, 124.5, 124.3, 123.5, 120.7, 120.4, 120.0, 119.8, 119.1, 115.5, 114.9, 114.0, 111.2, 111.2, 107.0, 91.2, 83.9, 80.2, 57.5, 56.0, 55.9, 50.7, 49.9, 46.4, 33.2, 30.1, 29.9; high resolution mass spectrum (FAB) *m/z* 617.2764 [calcd for $C_{37}H_{37}N_4O_5$ (M+H) 617.2764].

Preparation of (+)-Staurosporine (1).



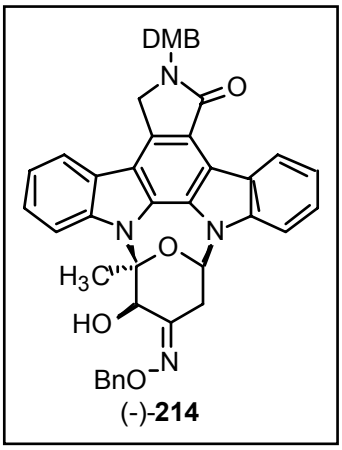
(+)-**1**

(+)-Staurosporine (1). To a stirred solution of methyl amine (+)-**213b** (10 mg, 0.016 mmol, 1 equiv) in anisole or thioanisole (80 μL) was added TFA (0.5 mL). The sluggish reaction was monitored by TLC and after 48 h had proceeded to completion. The reaction mixture was diluted with H_2O (1.0 mL), adjusted to pH 10 with 5.0 N NaOH, and extracted with CH_2Cl_2 (3 x 5mL). The combined organic layers were dried over Na_2SO_4, and evaporated to a pale yellow residue which was purified by preparative TLC (5% MeOH/CH_2Cl_2 eluent) to provide (+)-staurosporine (**1**, 6 mg, 70% yield) as a yellow powder: mp 273-280 °C (dec.); $[\alpha]^{20}_D$ +35° (*c* 0.1, MeOH); IR (thin film/NaCl) 3316.6 (m), 2925.0 (m), 2850.8 (m), 1678.7 (s), 1636.2 (m), 1584.2 (m), 1457.5 (s), 1352.2 (s), 1316.7 (s), 1281.3 (m), 1115.5 (m), 744.8 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.49 (app.t, *J* = 7.6 Hz, 1H), 7.43 (app.t, *J* = 7.7 Hz, 1H), 7.37 (app.t, *J* = 7.5 Hz, 1H), 7.33 (app.t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 5.6 Hz, 1H), 6.33 (br s, 1H), 5.05 (d, *J* = 15.8 Hz, 1H), 5.01 (d, *J* = 15.8 Hz, 1H), 3.89 (br s, 1H), 3.42 (s, 3H), 3.37 (d, *J* = 3.2, 1H), 2.76 (dd, *J* = 3.9, 14.7 Hz, 1H), 2.41 (br d, *J* = 15.4 Hz, 1H), 2.37 (s, 3H), 1.59 (br s, 1H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 139.8, 136.7, 132.2, 130.8, 126.6, 125.0, 124.6, 124.2, 123.4, 120.6, 120.0, 119.8, 115.3, 114.1, 106.9, 91.1, 84.2, 80.1, 57.2, 50.4, 45.9, 33.3, 30.3, 30.1;

high resolution mass spectrum (FAB) *m/z* 467.2085 [calcd for $C_{28}H_{27}N_4O_3$ (M+H) 467.2083].

(+)-*nat*-Staurosporine (1):[1] mp 270 °C (dec.); $[\alpha]^{25}_D$ +35° (*c* 1.0, MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.42 (t, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.81 (br s, 1H), 6.52 (d, *J* = 5.2 Hz, 1H), 4.99 (AB, 2H), 3.86 (d, *J* = 3.6 Hz, 1H), 3.37 (s, 3H), 3.33 (t, *J* = 3.6 Hz, 1H), 2.71 (dd, *J* = 3.6, 14.7 Hz, 1H), 2.39 (ddd, *J* = 3.6, 5.2, 14.7 Hz, 1H), 2.33 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (90.8 MHz, $CDCl_3$) δ 173.6, 139.7, 136.6, 132.2, 130.7, 128.3, 127.1, 125.0, 124.6, 124.1, 123.4, 120.6, 119.9, 119.7, 118.4, 115.3, 115.1, 114.0, 106.9, 91.1, 84.1, 80.1, 57.3, 50.4, 46.0, 33.3, 30.1, 30.0.

Preparation of Alcohol (-)-214.

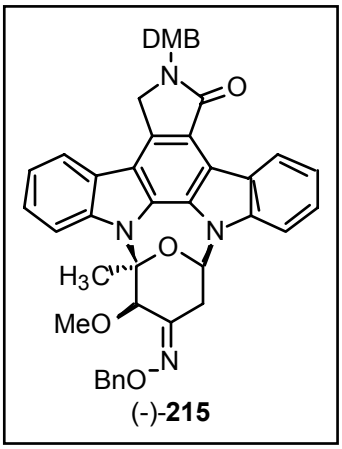


(-)-**214**

Alcohol (-)-214. A suspension of ketone (+)-**171** (75 mg, 0.128 mmol, 1.0 equiv), *O*-benzyl hydroxylamine hydrochloride (290 mg, 1.8 mmol, 14.0 equiv), and NaOAc (126 mg, 1.5 mmol, 12 equiv) in 80% aqueous EtOH (15.0 mL) was heated gently to reflux for 30 min. After cooling to room temperature, sovent was removed *in vacuo*, and the residue purified by flash chromatography (2:1∅1:1 hexanes:EtOAc eluent) to provide oxime ether (-)-**214** (75 mg, 85% yield) as a yellow foam: $[\alpha]^{20}_{D}$ -20° (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 3486.2 (br m), 3005.6 (br m), 1671.4 (s), 1513.9 (s), 1349.8 (m), 1317.2 (m), 1225.0 (m), 1026.8 (s), 745.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.41 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.51 (app.t, *J* = 7.6 Hz, 1H), 7.40 (app.t, *J* = 7.8 Hz, 1H), 7.34 (app.t, *J* = 7.6 Hz, 1H), 7.26 (app.t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 5.3 Hz, 1H), 7.06 (s, 1H), 6.93-6.98 (comp m, 2H), 6.80 (app.t, *J* = 7.3 Hz, 1H), 6.75 (app.t, *J* = 7.4 Hz, 2H), 6.13 (d, *J* = 7.4 Hz, 2H), 5.99 (br s, 1H), 4.88-5.03 (m, 4H), 4.75 (d, *J* = 14.9 Hz, 1H), 4.56 (d, *J* = 13.7 Hz, 1H), 4.33 (d, *J* = 13.7 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.68 (m, 1H), 3.12 (dd, *J* = 5.5, 14.1 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 150.1, 148.9, 148.1, 140.3, 137.5, 136.1, 130.6, 129.6, 128.0, 127.5, 126.5, 125.7, 125.6, 125.5, 124.7, 123.6, 123.0, 120.7, 120.2,

120.0, 119.8, 118.7, 115.9, 115.1, 113.9, 112.0, 111.8, 109.1, 97.7, 82.3, 74.8, 74.0, 55.5, 55.4, 49.6, 45.5, 30.8, 28.8; high resolution mass spectrum (EI) *m/z* 692.2633 [calcd for $C_{42}H_{36}N_4O_6$ (M^+) 692.2635]

Preparation of Ether (-)-215.

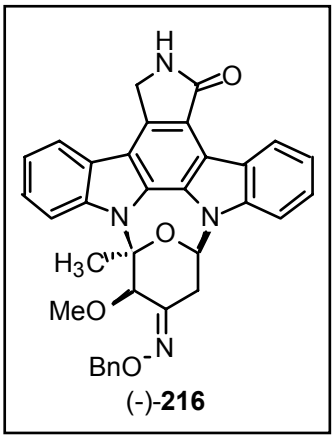


(-)-**215**

Ether (-)-215. To a mixture of oxime ether (-)-**214** (67 mg, 0.10 mmol, 1.0 equiv), MeI (30 μL, 0.48 mmol, 4.8 equiv), and powdered KOH (33 mg, 0.59 mmol, 5.9 equiv) in THF (10 mL) was added *n*-Bu_4NBr (6 mg, 0.02 mmol, 0.2 equiv). The mixture was stirred under N_2 for 30 min, solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (2:1∅1:1 hexanes:EtOAc eluent) to provide methoxy oxime ether (-)-**215** (53 mg, 68% yield) as a yellow powder: mp >230 °C (dec.); $[\alpha]^{20}_D$ -36° (*c* 0.1, CH_2Cl_2); IR (thin film/NaCl) 3002.9 (br m), 2931.6 (m), 2835.8 (m), 1672.1 (s), 1591.0 (m), 1514.2 (s), 1460.9 (s), 1398.9 (m), 1350.5 (s), 1317.2 (s), 1027.4 (s), 746.1 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.39-7.51 (m, 3H), 7.25-7.29 (m, 2H), 6.94-7.07 (m, 5H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 5.4 Hz, 1H), 6.51 (d, *J* = 7.4 Hz, 2H),

4.97 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 14.9 Hz, 1H), 4.78 (s, 2H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.39 (s, 1H), 4.29 (d, *J* = 11.7 Hz, 1H), 3.90 (d, *J* = 14.1 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.47 (s, 3H), 2.88 (dd, *J* = 5.6, 14.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 149.3, 148.4, 146.7, 140.3, 136.5, 136.3, 130.4, 129.7, 128.8, 128.0, 127.6, 127.4, 126.9, 125.5, 125.4, 124.8, 124.6, 124.0, 120.9, 120.4, 120.2, 119.4, 116.3, 115.2, 114.8, 111.2, 111.0, 107.5, 96.4, 84.9, 82.6, 75.8, 59.0, 55.9, 55.8, 49.7, 46.3, 31.1, 29.4; high resolution mass spectrum (EI) *m/z* 706.2783 [calcd for $C_{43}H_{38}N_4O_6$ (M^+) 706.2791].

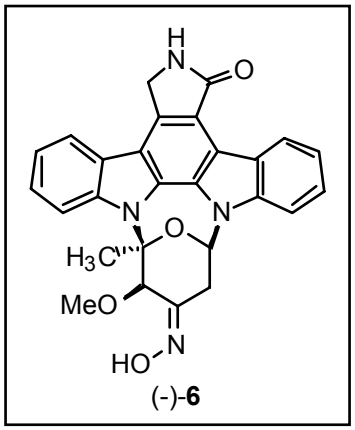
Preparation of Amide (-)-216.



Amide (-)-216. To a stirred solution of ether (-)-**215** (50 mg, 0.071 mmol, 1.0 equiv) in anisole (385 μL, 50 equiv) was added TFA (0.71 mL). The reaction was monitored by TLC, and after 24 h had proceeded to completion. The reaction mixture was diluted with H_2O (1.0 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue, which was

purified by preparative TLC (5% MeOH/CH_2Cl_2) to provide amide (-)-**216** (10 mg, 25% yield) as a white foam: $[\alpha]^{20}_D$ -8° (*c* 0.1, $CHCl_3$); IR (thin film/NaCl) 3241.0 (br m), 3059.8 (m), 2848.9 (m), 1679.7 (s), 1455.7 (s), 1395.3 (m), 1316.1 (s), 1226.1 (m), 1125.0 (m), 742.2 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.28-7.82 (comp m, 5H), 7.09 (app.t, *J* = 7.4 Hz, 1H), 7.00 (app.t, *J* = 7.5 Hz, 2H), 6.73 (dd, *J* = 1.4, 5.5 Hz, 1H), 6.62 (br s, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 4.94 (d, *J* = 10.5 Hz, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.41 (s, 1H), 4.28 (d, *J* = 11.7 Hz, 1H), 3.92 (dd, *J* = 1.6, 14.0 Hz, 1H), 3.49 (s, 3H), 2.89 (dd, *J* = 5.6, 14.0 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 146.6, 140.3, 136.5, 136.4, 132.7, 129.3, 128.0, 127.6, 127.5, 126.8, 125.6, 125.4, 124.9, 124.7, 123.9, 120.8, 120.6, 120.5, 116.4, 115.3, 114.8, 107.5, 96.5, 85.0, 82.7, 75.9, 59.0, 46.1, 31.1, 29.7, 29.4; high resolution mass spectrum (EI) *m/z* 556.2105 [calcd for $C_{34}H_{28}N_4O_4$ (M^+) 556.2111].

Preparation of (-)-TAN-1030a (6).



(-)-**6**

(-)-TAN-1030a (6). A solution of amide (-)-**216** (9 mg, 0.02 mmol, 1.0 equiv) in $CDCl_3$ (3.0 mL) was treated with iodotrimethylsilane (0.3 mL) and stirred for 48 h at room temperature. Following addition of MeOH (3.0 mL) and stirring for 30 min, the solvent was removed *in vacuo* leaving a deep red residue which was dissolved in CH_2Cl_2 (3 mL) and washed with an aqueous 10% $Na_2S_2O_7$ solution (3 x 2 mL). The pale yellow organic layer was dried over Na_2SO_4 and purified by preparative TLC (5% MeOH/CH_2Cl_2 eluent) to provide TAN-1030a (**6**, 2 mg, 24% yield) as a white foam: $[\alpha]^{20}_D$ -4° (*c* 0.1, $CHCl_3$); IR (thin film/NaCl) 3410.2 (br m), 3059.8 (m), 2848.9 (m), 1680.0 (s), 1456.1 (s), 1419.4 (m), 1348.4 (s), 1316.1 (s), 1124.9 (m), 742.2 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.43 (br s, 1H), 9.28 (d, *J* = 7.9 Hz, 1H), 8.57 (br s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.49 (app.t, *J* = 7.6 Hz, 1H), 7.43 (app.t, *J* = 7.7 Hz, 1H), 7.28-7.32 (comp m, 2H), 7.05 (d, *J* = 5.4 Hz, 1H), 4.95 (s, 2H), 4.75 (s, 1H), 3.62 (d, *J* = 14.2 Hz, 1H), 3.42 (s, 3H), 3.01 (dd, *J* = 5.7, 14.3 Hz, 1H), 2.47 (s, 3H).

***nat*-TAN-1030a (6):**[3] mp 290-295 °C (dec.); $[\alpha]^{20}_{D}$ 0° (*c* 0.5, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.31 (d, *J* = 7.8 Hz, 1H), 8.58 (s, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.50 (t, 1H), 7.44 (t, 1H), 7.32 (t, 1H), 7.32 (t, 1H), 7.04 (d, *J* = 5.2 Hz, 1H), 4.96 (s, 2H), 4.73 (s, 1H), 3.63 (d, *J* = 14.0 Hz, 1H), 3.43 (s, 3H), 3.01 (dd, *J* = 5.2, 14.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.8, 145.1, 139.8, 136.0, 132.3, 128.0, 125.6, 125.2, 124.6, 124.6, 123.8, 122.9, 120.7, 120.1, 119.5, 119.2, 115.6, 115.0, 114.0, 108.9, 96.2, 83.6, 82.2, 58.3, 45.3, 29.7, 28.6.

3.6 Notes and References

(1) a) Ō mura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275. b) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397.

([2]) Takahashi, H.; Osada, H.; Uramoto, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 168.

([3]) For the isolation and structure determination of TAN-1030a, see: a) Tanida, S.; Takizawa, M.; Takahashi, T.; Tsubotani, S.; Harada, S. *J. Antibiot.* **1989**, *42*, 1619. b) Tsubotani, S.; Tanida, S.; Harada, S. *Tetrahedron* **1991**, *47*, 3565.

([4]) McAlpine, J. B.; Karwowski, J. P.; Jackson, M.; Mullally, M. M.; Hochlowski, J. E.; Premachandran, U.; Burres, N. S. *J. Antibiot.* **1994**, *47*, 281.

([5]) Shankar, B. B.; McCombie, S. W.; Kirkup, M. P.; Viet, A. Q.; Puar, M. S.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 5685.

([6]) a) Bhide, G. V.; Tikotkar, N. L.; Tilak, B. D. *Chem. Ind.* **1957**, 363. b) Mann, F. G.; Willcox, T. J. *J. Chem. Soc.* **1958**, 1525. c) Moldenhauer, W.; Simon, H. *Chem. Ber.* **1969**, *102*, 1198.

([7]) Furanose (±)-**97** can be prepared as described in Chapter 2

([8]) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.

([9]) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

([10]) Attempted methylation resulted in either no reaction, or in the presence of bases the production of **i**.

([11]) Attempts to prepare diketone **187** by direct oxidation of hydroxy ketone (±)-**181** have been unsuccessful.

([12]) Dimethyl acetal **188** proved difficult to isolate and was subject to rapid hydrolysis upon attempted purification.

([13]) In addition to the new product, a small amount of (±)-**181** was also observed. The latter is likely the result of partial hydrolysis and rearrangement.

([14]) Koshino, H.; Osada, H.; Amano, S.; Onose, R.; Isono, K. *J. Antibiot.* **1992**, *45*, 1428.

([15]) For the synthesis of K252a, see Chapter 2.

([16]) The reaction proceeded sluggishly and required stirring at 25-30 °C for 24 h, noticeably longer than in the model system.

([17]) With this substrate, decomposition of the starting material to intractable materials competes with product formation.

([18]) Recently Fredenhagen has reported the effect of H_2SO_4 on TAN-1030a, see: Fredenhagen, A.; Peter, H. H. *Tetrahedron* **1996**, *52*, 1235.

([19]) Still, W. C.; Kahn, M.; Nitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

APPENDIX FOUR: SYNTHETIC SUMMARY FOR (+)-RK286c, (+)-MLR-52, (+)-STAUROSPORINE, AND (-)-TAN-1030a

Figure A.4.1 The Synthesis of (+)-RK286c (**7**) and (+)-MLR-52 (**8**).

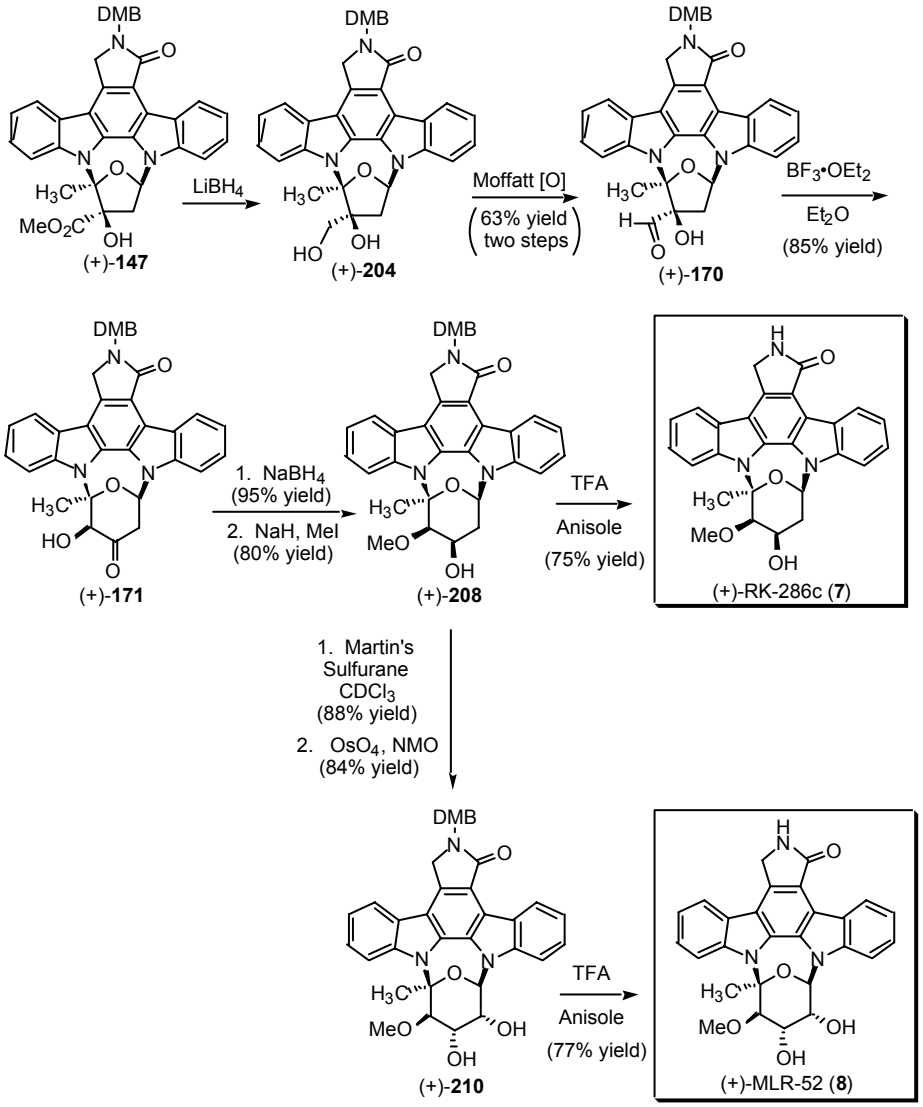


Figure A.4.2 The Synthesis of (+)-Staurosporine (**1**).

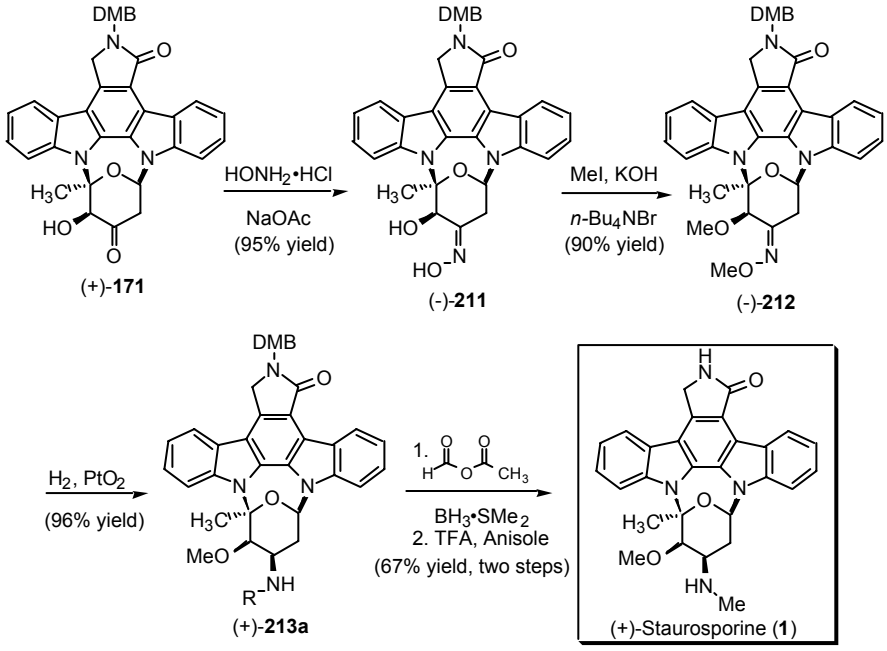
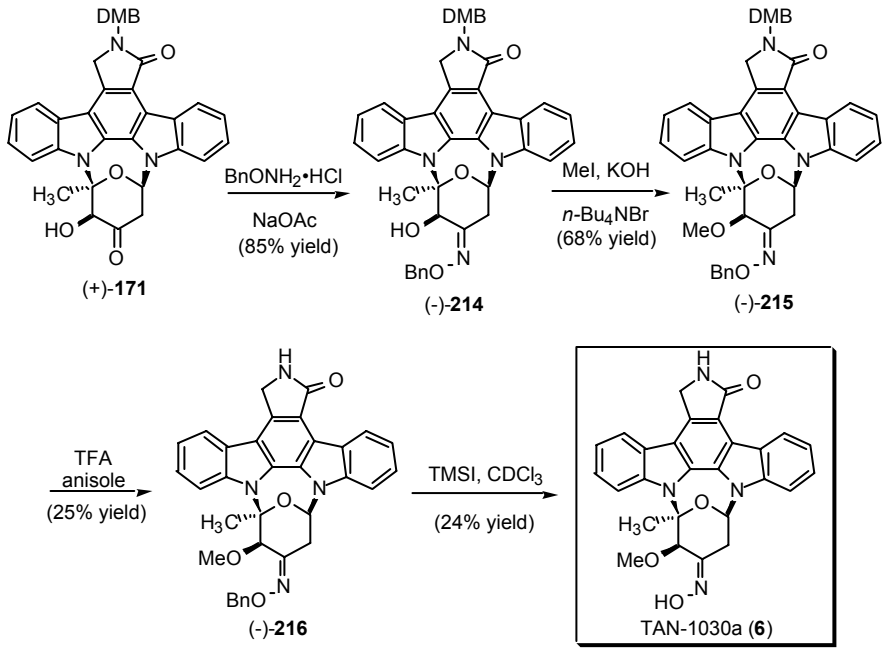
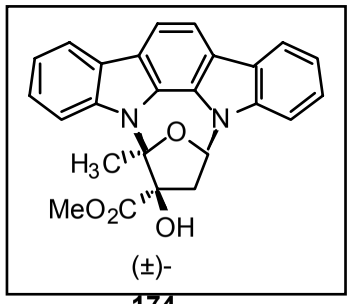


Figure A.4.3 The Synthesis of (-)-TAN-1030a (**6**).



APPENDIX FIVE: SPECTRA RELEVANT TO CHAPTER THREE



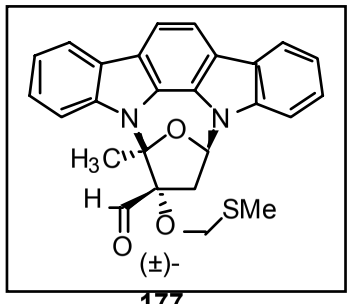
(±)-

124

Figure A.5.1

Figure A.5.2 Infrared Spectrum (thin film/NaCl) of compound (±)-**174.**

Figure A.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**174**.

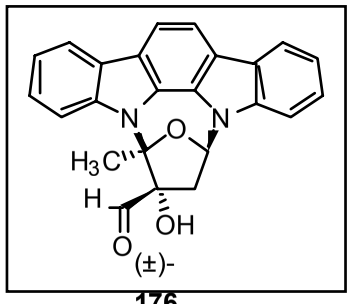


177

Figure A.5.4

Figure A.5.5 Infrared Spectrum (thin film/NaCl) of compound (±)-**177.**

Figure A.5.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**177**.

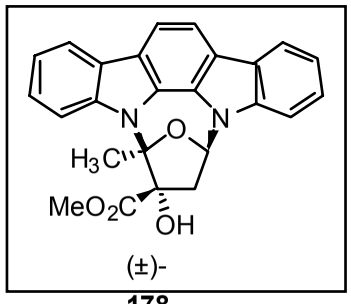


176

Figure A.5.7

Figure A.5.8 Infrared Spectrum (thin film/NaCl) of compound (±)-**176.**

Figure A.5.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**176**.



(±)-

178

Figure A.5.10

Figure A.5.11 Infrared Spectrum (thin film/NaCl) of compound (±)-**178.**

Figure A.5.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**178**.

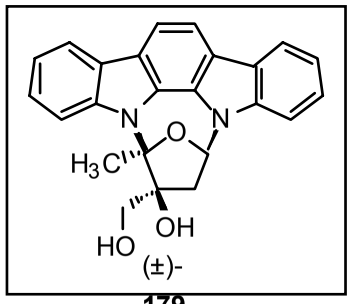


Figure A.5.13

Figure A.5.14 Infrared Spectrum (thin film/NaCl) of compound (±)-**179.**

Figure A.5.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**179**.

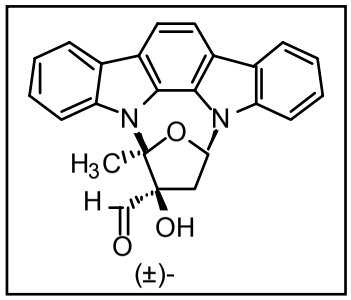
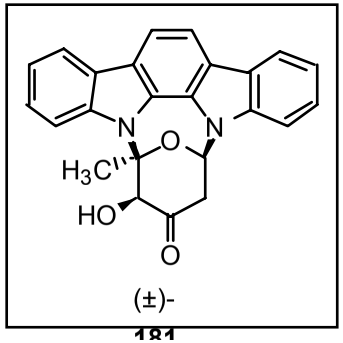


Figure A.5.16

Figure A.5.17 Infrared Spectrum (thin film/NaCl) of compound (±)-**180.**

Figure A.5.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**180**.



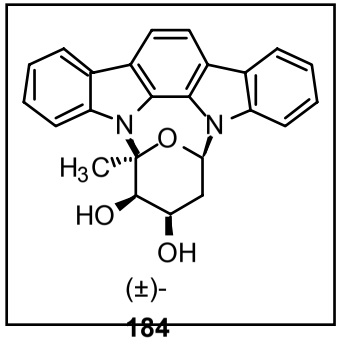
(±)-

181

Figure A.5.19

Figure A.5.20 Infrared Spectrum (thin film/NaCl) of compound (±)-**181.**

Figure A.5.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**181**.



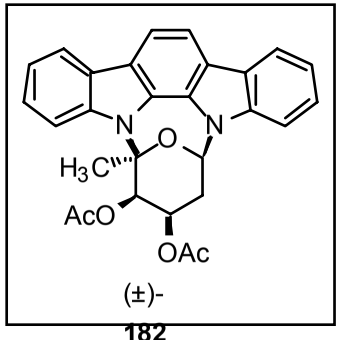
(±)-

184

Figure A.5.22

Figure A.5.23 Infrared Spectrum (thin film/NaCl) of compound (±)-**184.**

Figure A.5.24 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**184**.



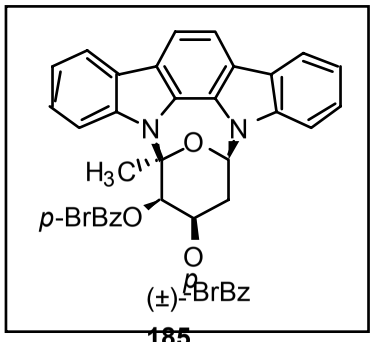
(±)-

182

Figure A.5.25

Figure A.5.26 Infrared Spectrum (thin film/NaCl) of compound (±)-**182.**

Figure A.5.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**182**.

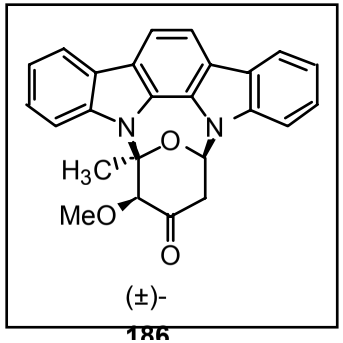


(±)-**185**

Figure A.5.28

Figure A.5.29 Infrared Spectrum (thin film/NaCl) of compound (±)-**185.**

Figure A.5.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**185**.



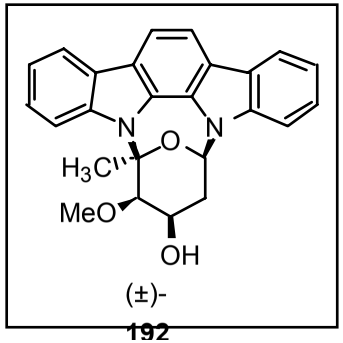
(±)-

186

Figure A.5.31

Figure A.5.32 Infrared Spectrum (thin film/NaCl) of compound (±)-**186.**

Figure A.5.33 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**186**.



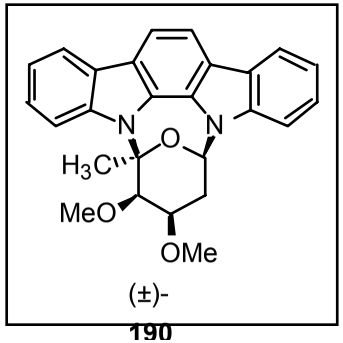
(±)-

192

Figure A.5.34

Figure A.5.35 Infrared Spectrum (thin film/NaCl) of compound (±)-**192.**

Figure A.5.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**192**.



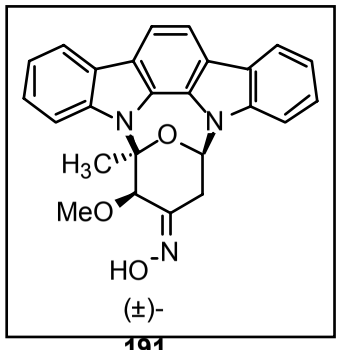
(±)-

190

Figure A.5.37

Figure A.5.38 Infrared Spectrum (thin film/NaCl) of compound (±)-**190.**

Figure A.5.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**190**.



(±)-

191

Figure A.5.40

Figure A.5.41 Infrared Spectrum (thin film/NaCl) of compound (±)-**191.**

Figure A.5.42 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**191**.

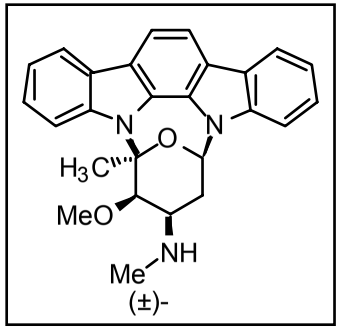
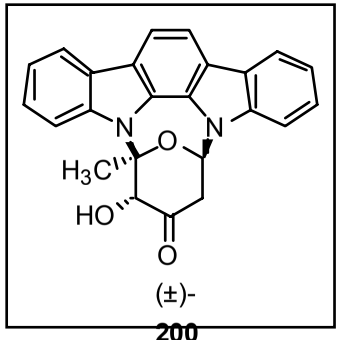


Figure A.5.43

Figure A.5.44 Infrared Spectrum (thin film/NaCl) of compound (±)-**193.**

Figure A.5.45 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**193**.



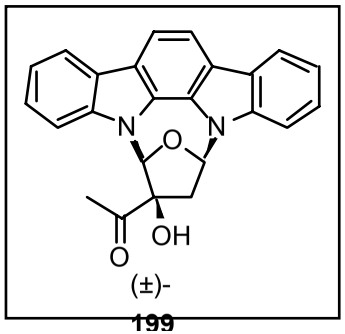
(±)-

200

Figure A.5.46

Figure A.5.47 Infrared Spectrum (thin film/NaCl) of compound (±)-**200.**

Figure A.5.48 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**200**.



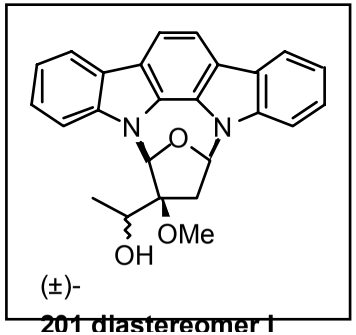
(±)-

199

Figure A.5.49

Figure A.5.50 Infrared Spectrum (thin film/NaCl) of compound (±)-**199.**

Figure A.5.51 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**199**.



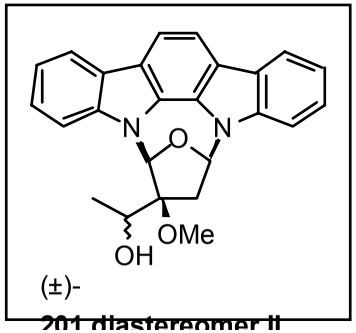
(±)-

201 diastereomer I

Figure A.5.52

Figure A.5.53 Infrared Spectrum (thin film/NaCl) of compound (±)-**201.**

Figure A.5.54 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**201**.



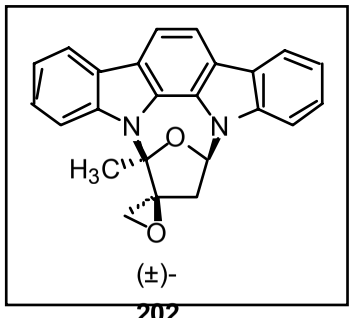
(±)-

201 diastereomer II

Figure A.5.55

Figure A.5.56 Infrared Spectrum (thin film/NaCl) of compound (±)-**201.**

Figure A.5.57 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**201**.



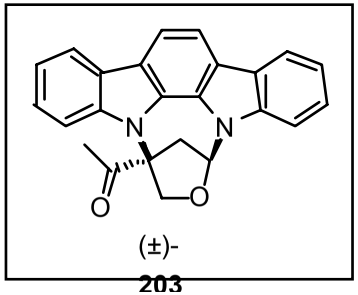
(±)-

202

Figure A.5.58

Figure A.5.59 Infrared Spectrum (thin film/NaCl) of compound (±)-**202.**

Figure A.5.60 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (±)-**202**.

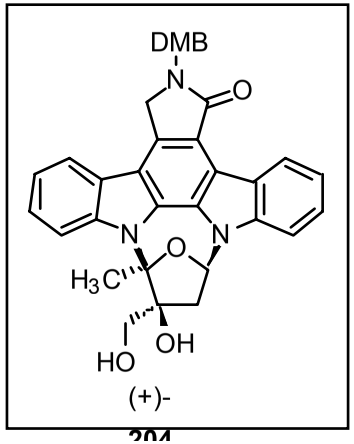


(±)-**203**

Figure A.5.61

Figure A.5.62 Infrared Spectrum (thin film/NaCl) of compound (±)-**203.**

Figure A.5.63 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**203**.



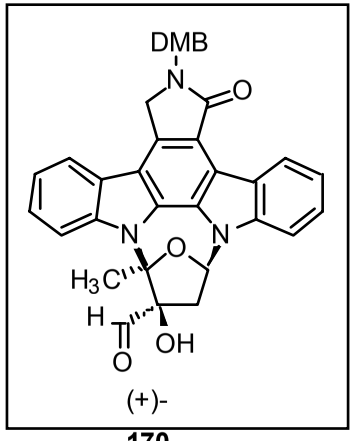
(+)-

204

Figure A.5.64

Figure A.5.65 Infrared Spectrum (thin film/NaCl) of compound (+)-**204.**

Figure A.5.66 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**204**.



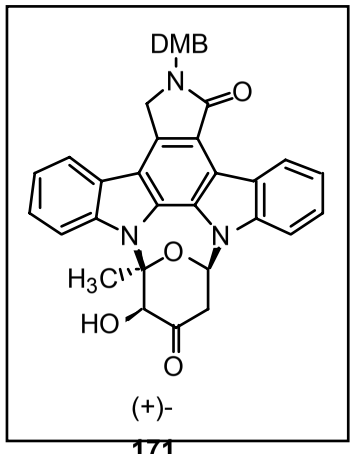
(+)-

170

Figure A.5.67

Figure A.5.68 Infrared Spectrum (thin film/NaCl) of compound (+)-**170.**

Figure A.5.69 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**170**.



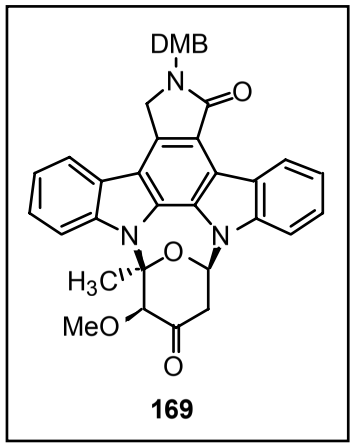
(+)-

171

Figure A.5.70

Figure A.5.71 Infrared Spectrum (thin film/NaCl) of compound (+)-**171.**

Figure A.5.72 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**171**.

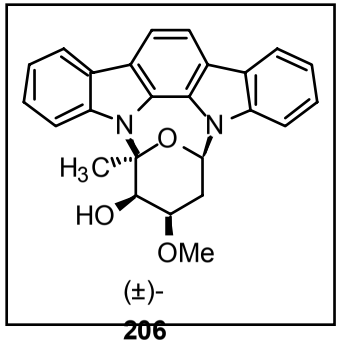


169

Figure A.5.73

Figure A.5.74 Infrared Spectrum (thin film/NaCl) of compound **169.**

Figure A.5.75 ^{13}C NMR (125 MHz, DMSO-d_6, 315 K) of compound **169**.



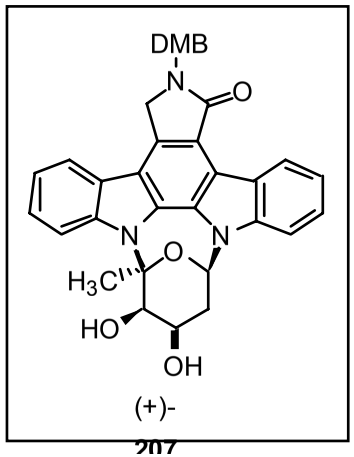
(±)-

206

Figure A.5.76

Figure A.5.77 Infrared Spectrum (thin film/NaCl) of compound (±)-**206.**

Figure A.5.78 ^{13}C NMR (125 MHz, acetone-d_6) of compound (±)-**206**.



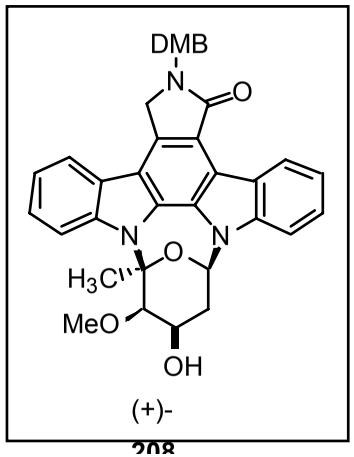
(+)-

207

Figure A.5.79

Figure A.5.80 Infrared Spectrum (thin film/NaCl) of compound (+)-**207.**

Figure A.5.81 ^{13}C NMR (125 MHz, acetone-d_6) of compound (+)-**207**.



(+)-

208

Figure A.5.82

Figure A.5.83 Infrared Spectrum (thin film/NaCl) of compound (+)-**208.**

Figure A.5.84 ^{13}C NMR (125 MHz, $CDCl_3$, 315 K) of compound (+)-**208**.

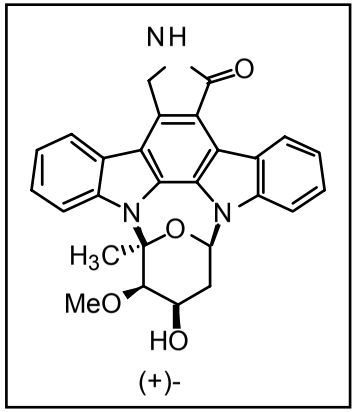
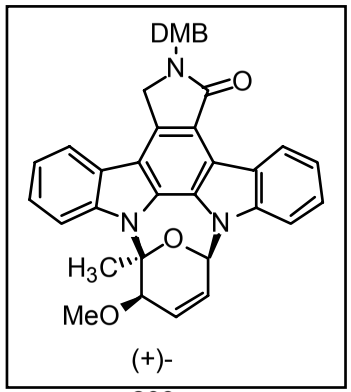


Figure A.5.85

Figure A.5.86 Infrared Spectrum (thin film/NaCl) of compound (+)-**7.**

Figure A.5.87 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**7**.



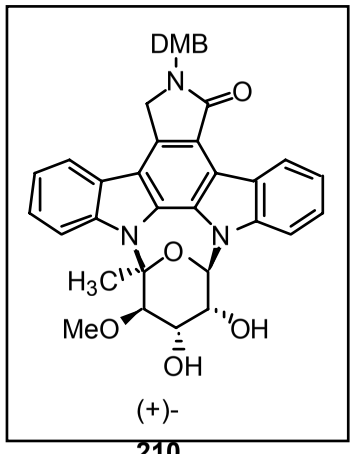
(+)-

209

Figure A.5.88

Figure A.5.89 Infrared Spectrum (thin film/NaCl) of compound (+)-**209.**

Figure A.5.90 ^{13}C NMR (125 MHz, acetone-d_6) of compound (+)-**209**.



(+)-

210

Figure A.5.91

Figure A.5.92 Infrared Spectrum (thin film/NaCl) of compound (+)-**210.**

Figure A.5.93 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**210**.

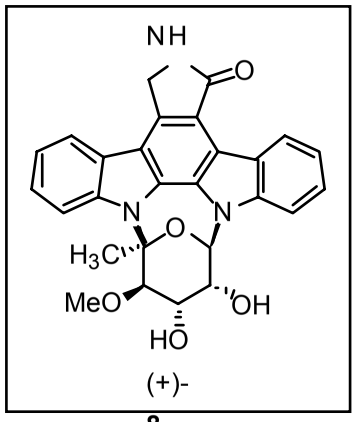
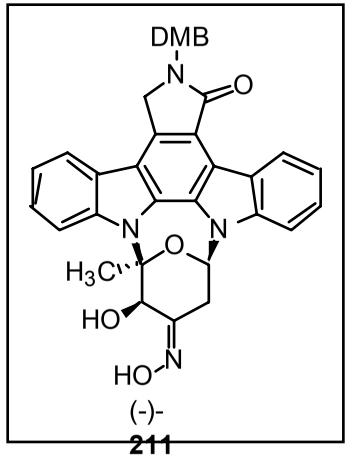


Figure A.5.94

Figure A.5.95 Infrared Spectrum (thin film/NaCl) of compound (+)-**8.**

Figure A.5.96 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (+)-**8**.

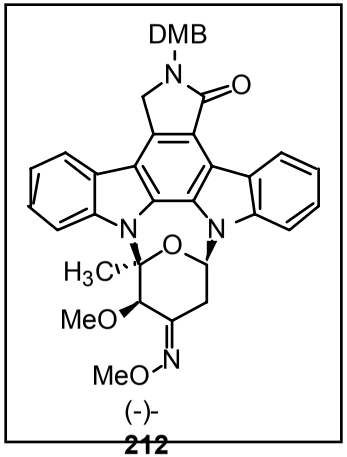


(-)-
211

Figure A.5.97

Figure A.5.98 Infrared Spectrum (thin film/NaCl) of compound (-)-**211.**

Figure A.5.99 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (-)-**211**.

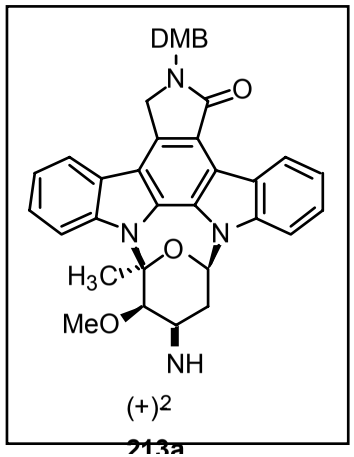


(-)-
212

Figure A.5.100

Figure A.5.101 Infrared Spectrum (thin film/NaCl) of compound (-)-**212.**

Figure A.5.102 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (-)-**212**.



(+)2

213a

Figure A.5.103

Figure A.5.104 Infrared Spectrum (thin film/NaCl) of compound (+)-**213a.**

Figure A.5.105 ^{13}C NMR (125 MHz, $CDCl_3$, 315 K) of compound (+)-**213a**.

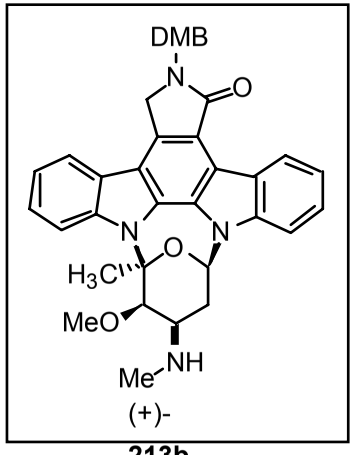


Figure A.5.106

Figure A.5.107 Infrared Spectrum (thin film/NaCl) of compound (+)-**213b.**

Figure A.5.108 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**213b**.

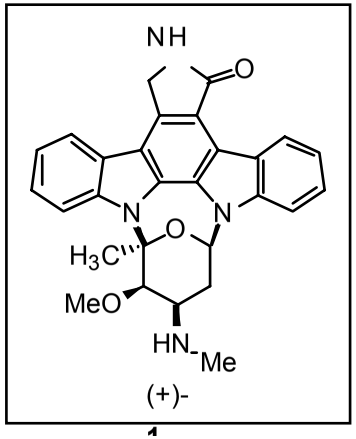
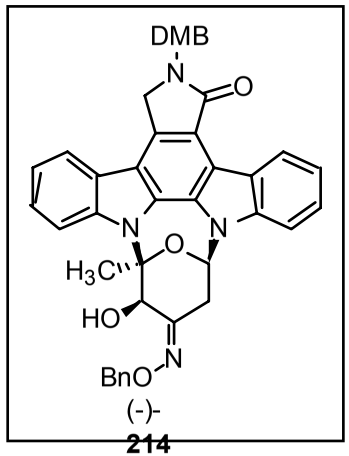


Figure A.5.109

Figure A.5.110 Infrared Spectrum (thin film/NaCl) of compound (+)-**1.**

Figure A.5.111 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (+)-**1**.

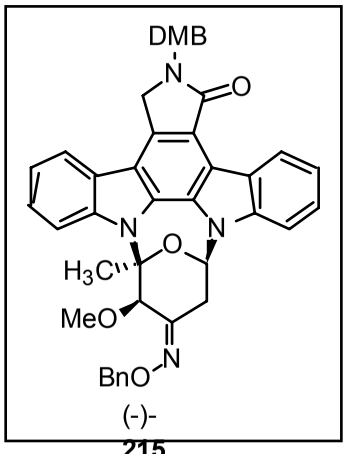


(-)-
214

Figure A.5.112

Figure A.5.113 Infrared Spectrum (thin film/NaCl) of compound (-)-**214.**

Figure A.5.114 ^{13}C NMR (125 MHz, DMSO-d_6) of compound (-)-**214**.

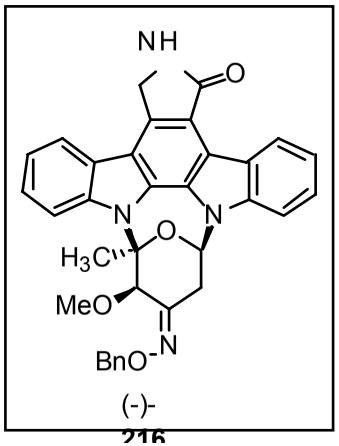


(-)-**215**

Figure A.5.115

Figure A.5.116 Infrared Spectrum (thin film/NaCl) of compound (-)-**215.**

Figure A.5.117 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**215**.



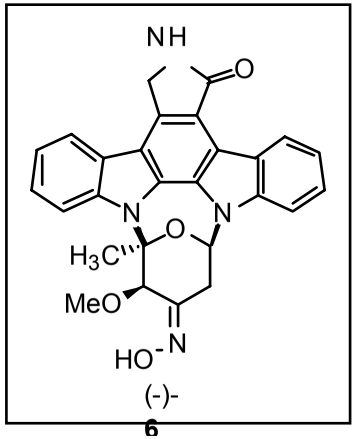
(-)-

216

Figure A.5.118

Figure A.5.119 Infrared Spectrum (thin film/NaCl) of compound (-)-**216.**

Figure A.5.120 ^{13}C NMR (125 MHz, $CDCl_3$) of compound (-)-**216**.

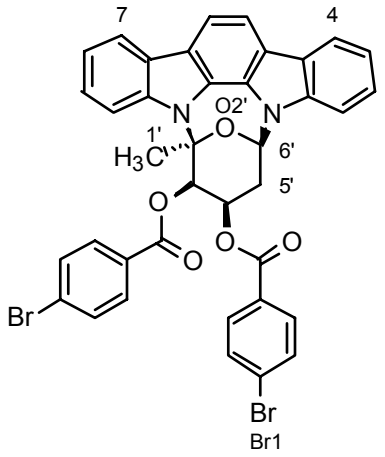


(-)-**6**

Figure A.5.121

APPENDIX SIX: X-RAY CHRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER TWO

X-RAY CHRYSTALLOGRAPHY REPORT FOR INDOLOCARBAZOLE (±)-**185**



(X-ray Numbering)

≡

(±)-**185**

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula.....$C_{38.5}H_{26}N_2O_{6.5}Br2$

Formula Weight 780.45

Crystal Color/Habit .....colorless needle

Crystal Dimensions (mm) .....0.08 X 0.11 X 0.30

Crystal System .....monoclinic

No. Reflections Used for Unit

Cell Determination (2θ range).....25(10.2-18.0□)

Lattice Parameters:

a .....30.141 (5)Å

b .....15.689 (2)Å

c .....14.803 (3)Å

β ..... 91.45 (2)°

V ..... 6998 (3)Å^3

Space Group ..... C2/c (#15)

Z value 8

Dcalc ..... 1.481 g/cm^3

F000 3144

μ(MoKα) 23.41 cm-1

B. Intensity Measurements

Diffractometer ..... Enraf-Nonius CAD-4

Radiation ..... MoKα (λ = 0.71069 Å)

Temperature ..... 23°C

Attenuator ..... Zr foil (factor = 20.4)

Take-off Angle ..... 2.8°

Detector Aperture ..... 2.0-2.5 mm hor/2.0 mm vert.

Crystal to Detector Distance ..... 21 cm

Scan Type ω-2θ

Scan Rate ..... 1.0 - 16.5°/min (in omega)

Scan Width ..... (0.95 + 0.83 tanθ)°

2θmax ..... 52.6°

No. of Reflections Measured

Total: 7660

Unique: ..... 7369 (Rint = .041)

Corrections ..... Lorentz-polarization

Absorption

(trans. factors: 0.72 - 1.51)

Decay (-27.00% decline)

C. Structure Solution and Refinement

Structure Solution .....Direct Methods

Refinement ..... Full-matrix least-squares

Function Minimized.....Σ w (&Fo& - &Fc&)^2

Least-squares Weights.....4Fo^2/σ^2(Fo^2)

p-factor 0.03

Anomalous Dispersion.....All non-hydrogen atoms

No. Observations (I>3.00σ(I)).....2877

No. Variables 436

Reflection/Parameter Ratio.....6.60

Residuals:.....R; Rw 0.077; 0.080

Goodness of Fit Indicator 4.61

Max Shift/Error in Final Cycle 0.00

Maximum Peak in Final Diff. Map .....1.21 e-/Å^3

Minimum Peak in Final Diff. Map .....-1.23 e-/Å^3

Positional parameters and B(eq) for indolocarbazole (±)-**185**

atom	x	y	z	B(eq)
Br1	0.40970(6)	0.3656(1)	0.2089(1)	5.95(8)
Br2	0.51935(5)	0.7625(2)	0.6198(1)	8.0(1)
O1	0.2819(2)	0.7003(4)	0.3297(4)	2.5(3)
O2	0.3088(3)	0.6663(5)	0.4695(5)	3.9(4)
O2'	0.2427(2)	0.8807(4)	0.2135(4)	2.3(3)
O3	0.3263(2)	0.8463(5)	0.3919(4)	2.7(3)

O4	0.3024(3)	0.8720(5)	0.5334(5)	3.0(3)
N11	0.3181(3)	0.8396(5)	0.2080(5)	2.5(4)
N12	0.2267(3)	0.7433(5)	0.1596(5)	2.4(4)
C1	0.1527(4)	0.6739(8)	0.1322(7)	3.5(6)
C1'	0.2939(4)	0.9828(7)	0.2587(8)	3.2(5)
C2	0.1312(4)	0.6120(8)	0.0805(8)	3.8(6)
C2'	0.2843(4)	0.8870(6)	0.2577(7)	2.5(5)
C3	0.1547(5)	0.5632(7)	0.0199(8)	4.1(7)
C3'	0.2811(3)	0.8535(7)	0.3578(6)	2.3(5)
C4	0.1995(4)	0.5732(7)	0.0079(7)	3.1(6)
C4A	0.2223(4)	0.6356(6)	0.0592(6)	2.4(5)
C4B	0.2670(4)	0.6646(7)	0.0641(6)	2.5(5)
C4'	0.2568(3)	0.7695(7)	0.3681(6)	2.6(5)
C5	0.3064(4)	0.6382(7)	0.0213(7)	3.2(5)
C5'	0.2122(4)	0.7770(7)	0.3203(7)	3.0(5)
C6	0.3452(4)	0.6778(8)	0.0426(7)	3.1(5)
C6A	0.3465(4)	0.7457(7)	0.1060(7)	2.6(5)
C6B	0.3820(4)	0.7979(7)	0.1409(7)	3.0(5)
C6'	0.2148(3)	0.8098(7)	0.2236(7)	2.5(5)
C7	0.4266(4)	0.802(1)	0.1208(9)	4.6(7)
C8	0.4526(4)	0.860(1)	0.165(1)	5.5(8)
C9	0.4352(4)	0.915(1)	0.2277(9)	4.3(7)
C10	0.3910(4)	0.9142(8)	0.2495(8)	3.6(6)
C10A	0.3637(4)	0.8560(8)	0.2036(7)	3.0(5)
C11	0.3067(4)	0.6529(7)	0.3893(8)	2.8(5)
C11A	0.3075(3)	0.7724(7)	0.1485(6)	2.5(5)
C11B	0.2683(3)	0.7311(6)	0.1268(6)	2.0(4)

C12	0.3316(3)	0.5845(7)	0.3432(7)	2.5(5)
C12A	0.1980(4)	0.6851(6)	0.1196(7)	2.5(5)
C13	0.3614(4)	0.5361(8)	0.3948(8)	3.3(6)
C14	0.3847(4)	0.4703(8)	0.354(1)	4.2(7)
C15	0.3773(4)	0.4559(7)	0.2634(9)	3.5(6)
C16	0.3494(4)	0.5036(8)	0.2121(8)	3.6(6)
C17	0.3258(4)	0.5687(7)	0.2510(7)	3.1(5)
C18	0.3313(4)	0.8527(7)	0.4834(7)	2.7(5)
C19	0.3779(4)	0.8341(7)	0.5133(7)	2.8(5)
C20	0.3913(4)	0.8571(8)	0.6000(7)	3.7(6)
C21	0.4342(5)	0.8375(9)	0.6300(9)	4.4(7)
C22	0.4620(4)	0.797(1)	0.575(1)	4.9(7)
C23	0.4499(5)	0.772(1)	0.490(1)	5.2(7)
C24	0.4071(4)	0.7938(9)	0.4581(8)	4.3(6)
O5	0.0452(5)	0.135(1)	0.230(1)	10.1(4)
O6	-0.018(1)	0.063(2)	0.096(2)	13(1)
C25	-0.014(3)	0.086(5)	0.201(5)	20(3)
H1	0.1371	0.7074	0.1746	4.2
H2	0.1003	0.6030	0.0866	4.5
H3	0.1392	0.5212	-0.0147	4.9
H4	0.2147	0.5387	-0.0340	3.8
H5	0.3055	0.5933	-0.0218	3.8
H6	0.3717	0.6600	0.0149	3.7
H7	0.4387	0.7651	0.0770	5.5
H8	0.4834	0.8628	0.1525	6.6
H9	0.4543	0.9553	0.2569	5.1
H10	0.3797	0.9515	0.2939	4.3

H11	0.2954	1.0031	0.1984	3.9
H12	0.2709	1.0117	0.2888	3.9
H13	0.3214	0.9931	0.2895	3.9
H14	0.2664	0.8955	0.3923	2.8
H15	0.2526	0.7586	0.4304	3.1
H16	0.1988	0.7222	0.3188	3.6
H17	0.1944	0.8151	0.3535	3.6
H18	0.1857	0.8281	0.2066	3.0
H19	0.3659	0.5478	0.4574	3.9
H20	0.4051	0.4362	0.3882	5.1
H21	0.3460	0.4925	0.1492	4.4
H22	0.3058	0.6023	0.2155	3.7
H23	0.3715	0.8858	0.6385	4.5
H24	0.4438	0.8529	0.6894	5.3
H25	0.4696	0.7402	0.4537	6.2
H26	0.3984	0.7808	0.3975	5.1

APPENDIX SEVEN: NOTEBOOK CROSS-REFERENCE

NOTEBOOK CROSS-REFERENCE

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound a folder name is given (i.e., BMS3-091) which corresponds to an archived characterization folder hard copy, as well as a folder stored on a ZIP disk. For each spectrum a notebook number (i.e., BMS3), a spectrum letter (i.e., C), and a page number (i.e., 091) is given. All notebooks , spectral data, and diskettes are stored in the Wood archives.

Compounds Appearing in Chapter One

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
134	BMS3-091	BMS3B.091	BMS3C.091	BMSMOD
139b	BMS8-043	BMS8A.043	BMS8B.043	BMS8-043
139c	BMS8-051	BMS8A.051	BMS8B.051	BMS8-051
139d	BMS8-049	BMS8C.049	BMS8B.049	BMS8-049
139e	BMS8-061	BMS8A.061	BMS8B.061	BMS8-061
132b	BMS5-113	BMS5A.113	BMS5B.113	BMSV-113
132c	BMS5-111	BMS5A.111	BMS5B.111	BMSV-111
132d	BMS4-241	BMS4A.241	BMS4B.241	BMSIV-241
132e	BMS5-081	BMS5A.081	BMS5B.081	BMSV-81
4a	BMS8-057	BMS8A.057	BMS8D.057	BMS8-057
4b	BMS5-149	BMS5A.149	BMS5B.149	BMSV-121
4c	BMS5-143	BMS5A.143	BMS5B.143	BMSV-129
4d	BMS4-247	BMS4C.247	BMS4Z.247	BMSIV-247

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
140	BMS6-301	BMS6A.301	BMS6B.301	VI301Z
(±)-**143**	HJD-166	HJD1H.166	HJD1C.166	HJDI166I
(±)-**144a**	HJD-189A	HJDIH1.189	HJDIC1.189	HJD189I1
(±)-**144b**	HJD-189B	HJDIH2.189	HJDIC2.189	HJD189I2
(±)-**97a**	BMS4-117B	BMS4H2.117	BMS4C2.117	BMS117i2
(±)-**97b**	BMS4-117A	BMS4H1.117	BMS4C1.117	BMS117I1
(±)-**147**	BMS4-227A	BMS4A.227	BMS4B.227	BMSIV-227A
(±)-**148**	BMS4-227B	BMS4C.227	BMS4D.227	BMSIV-227B
(±)-**149-d-I**	HJD-293a	HJDIH1.293	HJDIC5.293	HJD293I1
(±)-**149-d-II**	HJD-293b	HJDIH2.293	HJDIC6.293	HJD293I2
(±)-**145**	BMS8-075B	BMS8N.075	BMS8P.075	BMS8-75B
(±)-**146**	BMS8-075A	BMS8B.075	BMS8C.075	BMS8-75A
(±)-**2**	BMS4-231	BMS4A.231	BMS4B.231	BMSIV-231
(+)-**155**	HJD-256	HJDIH.256	HJDIC.256	HJDi256i
(-)-**152b**	HJD-258	HJDIH.258	HJDIC.258	HJDI258i
(-)-**159**	HJD-279	HJDIH.279	HJDIC.279	HJDi262i
(+)-**97a**	HJD-259B	HJDIH3.259	HJDIC3.259	HJD259i2
(+)-**97b**	HJD-285A	HJDIH1.285	HJDIC1.285	HJD285i1
(-)-**166**	HJD-285B	HJDIH2.285	HJDIC2.285	HJD285i2
(-)-**147**	SNG3-051B	SNG3D.051	SNG3C.051	SNG3b-051
(-)-**148**	SNG3-051C	SNG3F.051	SNG3E.051	SNG3c-51
(-)-**2**	SNG3-051A	SNG3I.051	SNG3H.051	SNG3a-51
(+)-**168**	HJD2-026	HJD2H1.026	HJD2C.026	HJDii026

Compound	Folder	^{1}H NMR	^{13}C NMR	IR

(-)-**97a**	HJD2-027C	HJD2H3.027	HJD2C3.027	HJD027i3
(-)-**97b**	HJD2-027A	HJD2H1.027	HJD2C1.027	HJD027i1
(+)-**166**	HJD2-027B	HJD2H2.027	HJD2C2.027	HJD027i2
(+)-**147**	BMS5-141a	BMS5A.141	BMS5Z.141	BMSV-141A
(+)-**148**	BMS5-141B	BMS5C.141	BMS5D.141	BMSV-141B
(+)-**2**	BMS5-153a	BMS7A.137	BMS7B.137	BMSV-153

Compounds Appearing in Chapter Three

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
(±)-**174**	BMS5-301	BMS5A.301	BMS5B.301	BMSV301
(±)-**177**	BMS7-171B	BMS7M.171	BMS7N.171	BMS7-171
(±)-**176**	BMS7-171A	BMS7A.171	BMS7B.171	BMS8-067
(±)-**178**	BMS9-117	BMS9A.999	BMS9C.117	BMSIX117
(±)-**179**	BMS6-111	BMS6A.111	BMS6B.111	BMSVI-111
(±)-**180**	BMS6-033	BMS6A.033	BMS6B.033	BMSVI-033
(±)-**181**	BMS6-041	BMS6A.041	BMS6B.041	BMSVI041
(±)-**184**	BMS5-239	BMS5A.239	BMS5B.239	BMSV239C
(±)-**182**	BMS6-103	BMS6A.103	BMS6B.103	BMSVI103
(±)-**185**	BMS5-259	BMS5A.259	BMS5B.259	BMSV259
(±)-**186**	BMS6-083	BMS6A.083	BMS6B.083	BMSVI139
(±)-**192**	BMS6-109	BMS6A.109	BMS6B.109	BMSVI109
(±)-**190**	BMS6-105	BMS6A.105	BMS6B.105	BMSVI105

Compound	Folder	^{1}H NMR	^{13}C NMR	IR

(±)-**191**	BMS6-059	BMS6D.059	BMS6E.059	BMSVI059
(±)-**193**	BMS6-213	BMS6B.213	BMS6C.213	BMSVI213
(±)-**200**	BMS8-069	BMS8B.069	BMS8C.069	BMS8-069
(±)-**199**	BMS7-177	BMS7A.177	BMS7C.177	BMS7-177
(±)-**201-d-I**	BMS8-065A	BMS8B.065	BMS8X.065	BMS8-65A
(±)-**201-d-II**	BMS8-065B	BMS8M.065	BMS8N.065	BMS8-65B
(±)-**202**	BMS8-093	BMS8A.093	BMS8B.093	BMS8-093
(±)-**203**	BMS8-095	BMS8A.095	BMS8B.095	BMS8-095
(+)-**204**	BMS7-069	BMS7B.187	BMS7D.187	VII187Z
(+)-**170**	BMS7-189	BMS7A.189	BMS7B.189	VII189Z
(+)-**171**	BMS7-197	BMS7B.197	BMS7C.197	VII271Z
169	BMS7-235	BMS7A.235	BMS7B.235	BMS7-235
(±)-**206**	SNG3-255	SNG3A.255	SNG3B.255	SNG255
(+)-**207**	BMS7-247	BMS7A.247	BMS7B.247	VII261Z
(+)-**208**	BMS7-259	BMS7A.259	BMS7B.259	VII253Z
(+)-**7**	BMS7-263	BMS7A.263	BMS7D.263	VII263Z
(+)-**209**	BMS7-279	BMS7H.279	BMS7C.279	VII279Z
(+)-**210**	BMS8-031	BMS8B.031	BMS8C.031	VII303Z
(+)-**8**	BMS7-277	BMS7A.277	BMS7B.277	VIII33Z
(-)-**211**	BMS7-201	BMS7A.201	BMS7B.201	BMS7-225
(-)-**212**	BMS7-215	BMS7B.215	BMS7D.215	VII221Z
(+)-**213a**	BMS7-223	BMS7A.223	BMS7B.223	VII219Z
(+)-**213b**	BMS7-237	BMS7C.237	BMS7D.237	VII237Z

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
(+)-**1**	BMS7-233	BMS7A.233	BMS7C.233	VII233Z

(-)-**214**	BMS9-093	BMS9C.093	BMS9D.093	IX-093
(-)-**215**	BMS9-095	BMS9A.095	BMS9B.095	IX-095
(-)-**216**	BMS9-101	BMS9A.101	BMS9B.101	IX-101
(-)-**6**	BMS8-111	BMS8G.111	--------	VIII-111

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ABOUT THE AUTHOR

The author Brian M. Stoltz was born on November 12, 1970 in Philadelphia, Pennsylvania and was the second son (behind Kurt) of Doris Ann and Vincent James Stoltz, Jr. The Stoltz family lived in Havertown, PA where Brian attended Manoa Elementary School, Haverford Junior High School and eventually Haverford Senior High School. In 1978, Brian's sister was born (Megan), and proceeded to brighten the lives of the family as a whole. In that same year the family visited relatives during a four week tour of Germany.

During Brian's childhood and adolescence, two passions were born which continue with him to this day; baseball and music. He played baseball for such teams as the Hilltop Cougars and Blue Jays and later for the Grünwald Jesters, champions of the Bavarian Baseball League. In early attempts to create music, Brian learned to play the French horn and trombone; however, following in his father's footsteps, soon took up the guitar and later found his true calling behind a kit of drums. He has performed in such bands as; The Wondabouts, The Spectacles, the HJHS and HHS Jazz/Rock Ensembles, The NYC Free Library, Das Würm, Ickyporosis, A Comedy of Worms, New Home, The Beanwhistles, Steel Toe, Slides Rule, Radio Bikini, Fervent Rosegarden, The Skangsters, The Skangsters USA, Not for Resale, and his most enjoyable and successful band, Banana Posse.

Brian attended college at Indiana University of Pennsylvania in Indiana, PA, and graduated Summa Cum Laude with a B.S. in chemistry and a B.A. in German. During his college years, Brian spent a year in Germany where he attended Ludwig Maximilians Universität in München. He also attended a nearby language institute where he met his wife Erna Knolmar. Upon returning to the states Brian began to work under the direction of John T. Wood in Indiana, and eventually moved to New Haven, CT where he earned his Ph.D. from Yale University. In January of 1998 Brian will move north to Boston, where he has accepted a postdoctoral position in the laboratories of Professor E. J. Corey at Harvard University.